

# An Adaptive Model-Based Approach to Personalized Basal Insulin Initiation in Type 2 Diabetes

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# An Adaptive Model-Based Approach to Personalized Basal Insulin Initiation in Type 2 Diabetes

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# Summary

Type 2 Diabetes is a growing global problem. Despite advancement of medication in recent years, the efficacy demonstrated in clinical trials fails to materialize in real world data and the majority of patients does not reach treatment targets. The primary reason for this discrepancy is low adherence to treatment, caused by 1) a lack of perceived need for the medication, 2) the complexity of the treatments, and 3) fear of hypoglycemia.

To address the need for support to improve glycemic outcomes, we developed and tested the feasibility of a novel concept for basal insulin initiation. The concept leverages data from diabetes management devices during insulin initiation to model dose response and estimate the dose a patient needs to reach the glycemic target. This estimated dose can be used as guidance for the remaining treatment period in combination with adaptive dose guidance algorithms. The estimated dose is expected to improve patients perceived need for insulin, reduce fear of hypoglycemia, simplify the treatment, and eventually improve adherence and outcomes.

We developed a dose response model and dose estimation method by analyzing glucose and insulin data from previous clinical trials on Insulin Degludec treatment and tested the feasibility of the dose estimation in a clinical study. Learnings from the clinical feasibility study lead us to propose two approaches to adaptive model-based dose guidance, as well as an automatic glycemic target setting method. We compared the performance with standard of care and other model-based approaches using *in silico* simulations of low adherence scenarios.

The studies suggest that dose estimation is feasible, and the adaptive dose guidance algorithms show potential for improved glycemic outcomes, even in case of low adherence to medication.

# Summary (Danish)

Type 2 Diabetes er et voksende globalt problem. På trods af nye medicinske produkter, med dokumenteret forbedret virkning i kliniske forsøg, materialiserer de samme resultater sig ikke i den virkelige verden og størstedelen af patienter opnår ikke målene fremsat for deres behandling. Den primære årsag for denne diskrepans er en lav grad af efterlevelse af behandlingen som skyldes, 1) manglende følt behov for medicin, 2) kompleksiteten af behandlingerne og 3) en frygt for hypoglykæmi.

For at adressere behovet for forbedrede glykæmiske resultater udviklede og testede vi anvendeligheden for et nyt koncept for titrering af basal insulin. Konceptet benytter data fra diabetes behandlingsudstyr under insulininitiering til at modellere dosisrespons og estimere den dosis som en patient skal bruge for at opnå sit glykæmiske mål. Denne estimerede dosis kan bruges vejledende for den resterende behandlingsperiode i kombination med adaptive, vejledende dosisalgoritmer. Den estimerede dosis forventes at forbedre patienters følte behov for insulin, reducere frygt for hypoglykæmi og simplificere behandlingen for i sidste ende at forbedre behandlingsefterlevelse og -resultater.

Vi udviklede dosisresponsmodellen og dosisestimeringsmetoden ved at analysere glukose- og insulindata fra tidligere kliniske forsøg af Insulin Degludec behandling og testede anvendeligheden af dosisestimeringen i et klinisk forsøg. Erfaringerne fra det kliniske studie over anvendeligheden ledte os til at foreslå to fremgangsmåder for adaptiv modelbaserede dosisvejledning, såvel som en automatisk glykæmisk målsætningsmetode. Vi sammenlignede resultaterne med standardbehandling og andre modelbaserede tilgange i *in silico* simulationer af lav behandlingsefterlevelse.

Studierne indikerer at dosisestimering er anvendeligt og algoritmer for adaptiv dosisvejledning udviser potentiale for forbedrede glykæmiske resultater, selv i tilfælde af lav behandlingsefterlevelse.

# Summary (Icelandic)

Sykursýki 2 er vaxandi vandamál á heimsvísu. Þrátt fyrir framfarir á sviði vísinda á síðustu árum og jákvæðar niðurstöður í klínískum rannsóknum, endurspeglast sú þróun ekki í raunveruleikanum og meirihluti sjúklinga nær ekki tilætluðum markmiðum meðferðarinnar. Algengasta orsök þessa mismunar er lág meðferðarfylgni vegna skorts á skynjaðri þörf fyrir meðhöndlun, flækjustigs meðferðarinnar og ótta við ofskömmtun.

Til að koma til móts við þörfina á bættum árangri þróuðum við og prófuðum gagnsemi nýrrar aðferðar við ákvörðun skammtastærða af hægvirku insúlíni í meðhöndlun á sykursýki 2. Við notum gögn frá blóðsykursmælingum og insúlínsprautum til að móta svörunarlíkan af fastandi blóðsykri og hægvirku insúlíni, og áætlum skammtaþörf einstaklingsins snemma í meðferðinni. Hægt er að nota þennan áætlaða skammt sem leiðarvísi fyrir meðferðartímabilið sem eftir er þar til blóðsykursmarkmiðinu er náð. Tilgangur þessarar aðferðar er að auka skynjun sjúklinga á þörf fyrir meðferð, draga úr líkum á og ótta við lágan blóðsykur og að einfalda meðferðina, sem að lokum bæta meðferðarfylgni og þar af leiðandi árangur.

Við þróuðum svörunarlíkanið útfrá blóðsykurs- og insúlíngögnum úr fyrri klínískum rannsóknum, þar sem sjúklingar voru meðhöndlaðir með Deglúdekinsúlíni. Við prófuðum einfalda útgáfu af aðferðinni, þar sem við áætlum skammtinn út frá einstaklingsmótuðu svörunarlíkani, í klínískri rannsókn. Við drógum svo lærdóm af niðurstöðunum til að auka nákvæmni skammtaáætlunarinnar. Að lokum lögðum við til tvö reiknirit til millistigsútreikninga, með möguleika á aðlögunarhæfu blóðsykursmarkmiði. Við bárum saman útkomur þessara aðferða við staðlaða meðhöndlun í *in silico* hermun.

Niðurstöður klínísku rannsóknarinnar og hermunarprófana benda til að áætlun skammtaþarfar einstaklinga sé nægilega nákvæm til að veita innsýn í meðhöndlunina, og að reikniritin geti bætt blóðsykursniðurstöður í klínískum rannsóknum sem og í raunveruleikanum, jafnvel þegar meðferðarheldni er lág.

# Preface

This thesis was prepared at the Department of Applied Mathematics and Computer Science at the Technical University of Denmark (DTU Compute) in partial fulfillment of the requirements for acquiring a Ph.D. degree. The Ph.D. study started in October 2016 and the dissertation was handed in at the end of September 2019. The project was a collaboration between the Section for Dynamical Systems at DTU Compute and the department for Device Research and Development at Novo Nordisk A/S. The project was co-funded by Innovation Fund Denmark and Novo Nordisk A/S as a part of an Industrial Ph.D. program.

The project required a multidisciplinary team of supervisors. MBA Henrik Bengtsson, Principal Specialist within Technology, was the main supervisor at Novo Nordisk A/S, and M.D., Ph.D. Morten Lind Jensen and Ph.D. Jonas Kildegaard, provided co-supervision. Associate Professor Niels Kjølstad Poulsen and Assistant Professor Dimitri Boiroux provided supervision from the Technical University of Denmark. M.D., DMSc. Kirsten Nørgaard, chief physician at Steno Diabetes Center Copenhagen, provided clinical supervision.

This thesis consists of six research papers, three technical reports and a short summary report describing the context and contributions of the research.

Lyngby, 30-September-2019

Tinna Björk Aradóttir

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The past three years have been filled with challenging and exciting experiences. During this time I have had the opportunity to travel all over the world, meet amazing colleagues, and grow personally. Although my questions at the beginning of the Ph.D. studies have partly been answered, I feel that they tend to multiply, and my interest in the topic has only increased.

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# List of publications and academic dissemination

## Scientific research publications in this thesis

1. Aradóttir, T. B., Boiroux, D., Bengtsson, H., Brockmeier, P., Kildegaard, J. P., Van Orden, B., Jørgensen, J. B. "Model for simulating fasting glucose in type 2 diabetes and the effect of adherence to treatment," *IFAC-PapersOnLine*, vol. 50, no. 1, pp. 15086-15091, 2017.

2. Aradóttir, T. B., Boiroux, D., Bengtsson, H., Poulsen, N. K. "Modelling of glucose-insulin dynamics from low sampled data," *IFAC-PapersOnLine*, vol. 51, no. 15, pp. 551-556, 2018.

3. Aradóttir, T. B., Boiroux, D., Bengtsson, H., Poulsen, N. K. "Modelling of glucose-insulin dynamics from sparse data," *Proceedings of the 40th International Engineering in Medicine and Biology Society (EMBC)*, pp. 2354-2357, 2018.

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5. Aradóttir, T. B., Mahmoudi, Z., Bengtsson, H., Jensen, M. L., Poulsen, N. K., Boiroux, D., Schmidt, S., Nørgaard, K. "A new approach to initiate insulin in type 2 diabetes – Post hoc analysis." Manuscript pending submission.

6. Aradóttir, T. B., Boiroux, D., Bengtsson, H., Jørgensen, J. B., Poulsen, N. K. "Model predictive control with sub-frequency actuation for long acting insulin treatment in type 2 diabetes," Proceedings of the 3rd IEEE Conference on Control Technology and Applications, CCTA 2019.

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## Technical reports in this thesis

8. Aradóttir, T. B., Mahmoudi, Z., Bengtsson, H., Jensen, M. L., Boiroux, D., Poulsen, N. K. "Dose response modelling in type 2 diabetes based on self-monitored blood glucose and insulin data." September 2019.

9. Aradóttir, T. B., Mahmoudi, Z., Bengtsson, H., Jensen, M. L., Boiroux, D., Poulsen, N. K. "Dose prediction based on self-measured blood glucose and insulin data: A novel approach to basal insulin titration." September 2019.

10. Aradóttir, T. B., Mahmoudi, Z., Bengtsson, H., Jensen, M. L., Boiroux, D., Poulsen, N. K. "An adaptive dose guidance approach: In silico testing in a clinical trial and real world scenario." September 2019.

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11. Mohebbi, A., Aradóttir, T. B., Johansen, A. R., Bengtsson, H., Fraccaro, M., Mørup, M. "A deep learning approach to adherence detection for type 2 diabetics," *Proceedings of 2017 39th Annual International Conference of the Ieee Engineering in Medicine and Biology Society*, IEEE, pp. 2896-2899, 2017.

12. Martinovic, B., Leth, J., Knudsen, T., Aradottir, T. B., Bengtsson, H. "Modelling the glucose-insulin system of type 2 diabetes patients using ARMAX models". Accepted for presentation at the 2019 Australian New Zealand Control Conference (ANZCC).

# Patent applications

13. Aradóttir, T. B., Bengtsson, H., Jensen, M. L., Brockmeier, P. (2018). *Metod for determining fasting glucose based on CGM data.* WO2018/228932.

14. Aradóttir, T. B., Bengtsson, H., Brockmeier, P. (2018). *Basal titration with adaptive target glucose level.* WO2018/007172.

15. Aradóttir, T. B., Bengtsson, H., Brockmeier, P., Kildegaard, J. P. (2018). *Systems and methods for adjusting a basal/bolus ratio in an insulin regimen.* WO2018/033514.

16. Aradóttir, T. B., Bengtsson, H., Brockmeier, P., Kildegaard, J. P. (2018). *Systems and methods for optimisation of a bolus insulin medicament dosage for a meal event.* WO2018/033513.

17. Aradóttir, T. B., Bengtsson, H., Brockmeier, P., Kildegaard, J. P. (2018). *Systems and methods for adjusting basal administration timing.* WO2018/036854.

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21. Bengtsson, H., Aradóttir, T. B., Brockmeier, P. (2018). *Systems and methods for analysis of insulin regimen adherence data.* WO2018/001855.

22. Bengtsson, H., Aradóttir, T. B., Brockmeier, P. (2018). *Systems and methods for analysis of insulin regimen adherence data.* WO2018/001856.

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24. Van Orden, B. W., Aradóttir, T. B., Bengtsson, H. (2018). *Starter Kit for basal rate titration.* WO2018/099912.

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27. Brockmeier, P., Bengtsson, H., Aradóttir, T. B. (2018). *Systems and methods for communicating a dose history representing an average and a variability of a distribution of medicament injections.* WO2018/060036.

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## Conference presentations

29. Aradóttir, T. B., Boiroux, D., Bengtsson, H., Brockmeier, P., Kildegaard, J. P., Van Orden, B., Jørgensen, J. B. (2017, February). *A physiological model of T2D for simulating fasting glucose levels.* Poster presented at the 10th International Conference on Advanced Technologies & Treatments for Diabetes, ATTD 2017. Paris, France.

30. Aradóttir, T. B., Boiroux, D., Bengtsson, H., Brockmeier, P., Kildegaard, J. P., Van Orden, B., Jørgensen, J. B. (2017, June). *Model for simulating fasting glucose in type 2 diabetes and the effect of adherence to treatment.* Poster presented at the 20th World Congress of the International Federation of Automatic Control, IFAC WC 2017. Toulouse, France.

31. Aradóttir, T. B., Boiroux, D., Bengtsson, H., Poulsen, N. K. (2018, July). *Modelling of glucose-insulin dynamics from low sampled data.* Oral presentation at the 18th IFAC Symposium on System Identification, SYSID 2018. Stockholm, Sweden.

32. Aradóttir, T. B., Boiroux, D., Bengtsson, H., Poulsen, N. K. (2018, July). *Modelling of glucose-insulin dynamics from sparse data.* Poster presented at the 40th International Engineering in Medicine and Biology Conference, EMBC 2018. Honolulu, Hawaii.

33. Aradóttir, T. B., Boiroux, D., Bengtsson, H., Poulsen, N. K. (2018, November). *Predictive dosing support for long acting insulin in type 2 diabetes.* Poster presented at the 18th annual diabetes technology meeting, DTM 2018. North Bethesda, Maryland.

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36. Aradóttir, T. B., Boiroux, D., Bengtsson, H., Jørgensen, J. B., Poulsen, N. K. (2019, August) *Model predictive control with sub-frequency actuation for long actinginsulin treatment in type 2 diabetes.* Oral presentation at the 3rd IEEE Conference on Control Technology and Applications, CCTA 2019. Hong Kong, China.

# Contents

Chapter 1

# Introduction

## 1.1 Context and motivation

Diabetes has become a global health problem and is now considered a pandemic. In 2017, prevalence of diabetes was 425 million worldwide and is predicted to increase by more than 200 million in the next 25 years [1]. The American Diabetes Association (ADA) estimates that the total cost, including direct and indirect cost, of diagnosed diabetes in 2017 was $327 billion in the US alone [2]. Direct costs relate to hospitalizations, medications for complications and physician office visits, anti-diabetic medicine and other diabetes supplies. Indirect costs relate to absence or inability to work, reduced productivity at work, and lost productivity due to early mortality. Despite recent improvement of diabetes medication, measured by clinically demonstrated outcomes, more than 60% of people do not reach recommended treatment targets [3].

### 1.1.1 Diabetes treatment

Diabetes is characterized by lack of balance in the glucose homeostasis. In healthy people, normoglycemia is maintained through interaction of three physiological processes; 1) hormone secretion from the pancreas, i.e., secretion of

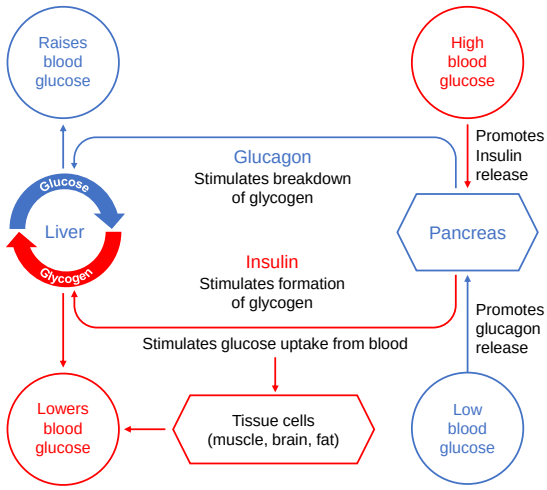


**Figure 1.1:** The glucose-insulin-glucagon homeostasis in a healthy person [1].

insulin from the $\beta$-cells and glucagon from the $\alpha$-cells, 2) glucose uptake of tissues such as muscle, brain and adipose tissue, and 3) release of stored glucose from the liver, see Figure 1.1. Type 1 diabetes (T1D) is an autoimmune disease that leads to destruction of the insulin producing $\beta$-cells. The absence of insulin results in lack of tissue utilization of blood glucose, which leads to elevated blood glucose concentration, referred to as hyperglycemia. Untreated, hyperglycemia is a life-threatening risk factor, which in the long run can cause heart disease, microvasculopathy, eyes and kidneys, foot ulcers and amputation [4]. Exogenous insulin treatment is therefore vital for treating people with T1D. On the other hand, glucose is the preferred fuel for the brain and muscles, and low blood glucose concentration, or hypoglycemia, may lead to confusion, blurred vision and seizures, as well as loss of consciousness, brain damage, or death in severe cases. Hypoglycemia due to overdosing is an acute condition and a great risk factor in insulin treatment, raising fear and insecurity amongst patients and clinicians.

Type 2 diabetes (T2D) is the most common type of diabetes, accounting for approximately 90% of cases. Although the pathophysiology of T2D is not completely known, it is a lifestyle disease where genetics are a critical component [5]. A variety of lifestyle factors increase the risk of developing T2D, where obesity is the most important, followed by physical inactivity, smoking, and alcohol consumption [5]. All these factors can cause deficiency in the glucose homeostasis, such as decreased sensitivity to insulin, which negatively impacts a large number of organs and tissues. In the long run, this leads to glucose toxicity, where

**Simple titration algorithm**

| Average pre-breakfast SMBG | Dose adjustment |
|---|---|
| >7.2 mmol/L | +2 U |
| 4.4-7.2 mmol/L | No adjustment |
| <4.4 mmol/L | -2 U |

**Table 1.1:** An example of a simple titration algorithm. The fasting glucose target varies between algorithms and should be set to ambitious or less stringent values.

insulin secretion from the pancreas and decreased insulin sensitivity worsens the glucose homeostasis further [6]. Maintaining the delicate balance of glucose homeostasis is therefore vital [7].

Due to the many factors causing and inducing worsened glycemic balance in T2D, the disease is highly heterogenous. Recently, Ahlqvist et al. [8] published results suggesting five clusters of patients with diabetes, rather than the two of T1D and T2D. In their work, people with T2D were split into four clusters, characterised by risk of complications, and level of insulin resistance and deficiency of production.

To treat T2D, the ADA recommends to start with comprehensive lifestyle changes and insulin sensitivity increasing oral anti-diabetic medications such as metformin [9]. Diabetes treatment should be reassessed every 3-6 months to avoid clinical inertia. If blood glucose concentrations remain high after treatment with oral anti-diabetic medication, other medications such as GLP-1 and eventually insulin should be added. Approximately one third of people with T2D are prescribed insulin [10]. Insulin treatment traditionally starts with basal insulin to lower fasting glucose, and may be intensified by adding bolus insulin before meals to lower post-prandial glucose. Basal insulin is titrated by starting on small doses, which are increased based on pre-breakfast self-measured blood glucose (SMBG) values, see Figure 1.2, until the clinically recommended fasting glucose target is reached [9]. The ADA recommends using a simple titration algorithm such as the one presented in Table 1.1. The general recommended target for glucose control by the ADA is $< 7\%$ hemoglobin A1c (HbA1c), corresponding to approximately 4.4-7.2 mmol/L in terms of pre-breakfast SMBG measurements. This target should however be personalized depending on risk factors including hypoglycemia, drug adverse effects, age, and comorbidities [9]. The lower the risk, the more stringent the glucose target should be set.

The U.S. Food and Drug Administration (FDA) has approved more than 40 new treatment options for T2D in the last two decades. Although these drugs show promising results in clinical trials, the change in the number of people achieving

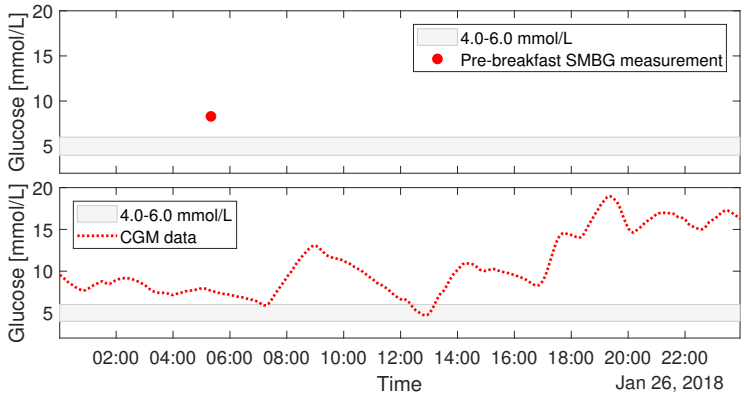


**Figure 1.2:** One day of traditional SMBG (top) data. CGM data (bottom) have been shown beneficial for treatment of T2D in terms of improved glycemic outcomes and treatment adherence, and their use is increasing.

recommended treatment goals is negligible, with only 30-50% reaching targets [11, 12]. The main reasons for this include poor medication adherence, which relates to forgetfulness, perceived need for medication, fear of hypoglycemia and lack of confidence or uncertainties regarding insulin titration [3, 12, 13]. Studies on adherence to insulin therapy have found that approximately 20-40% of injections are omitted [14–16]. Adherence is therefore a great challenge, and to reach the promising outcomes of clinical trials in the real world, this should be addressed through innovative approaches [12].

### 1.1.2 Digital health and connected devices

As with many other diseases, digital solutions and personalized medicine for diabetes are emerging [17]. Digital solutions such as the online based in-clinic platform Diasend® by Glooko, or the Glooko patient-facing app, allow users to upload data from connected devices and provide insights from glucose, insulin and activity trends and levels [18]. Such solutions can be clinician- or patient-facing, and data can be shared with other care takers if accepted by the user. Some support tools also include dose guidance. Examples of this are the Mobile Insulin Dosing System (MIDS) by Glooko, and the Diabetes Insulin Guidence System (DIGS) solution by Hygieia, which were cleared by the FDA in 2018 and 2019, respectively [19,20]. The MIDS solution allows the clinician to input dose adjustment instructions, while the DIGS algorithm uses a fuzzy logic approach,

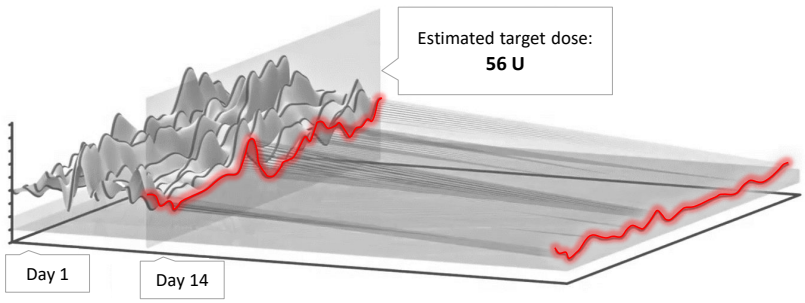


**Figure 1.3:** We test the feasibility of an algorithm that estimates the dose an individual needs, and uses this as a roadmap and input to adaptive titration.

where a set of rules from a team of clinical experts have been automized. Model based approaches to basal insulin titration include the Intelligent Dosing Systems (IDS), by Cook et al. in 2005 [21], which uses insulin and SMBG data in an adaptive learning approach to calculate a next dose to reach a desired glycemic target, and the *run-to-run* method, which has been used for titrating basal and bolus insulin in T1D [22]. All the above mentioned approaches rely on SMBG and insulin data, as well as user input glycemic targets, and provide a day-to-day guidance.

Continuous glucose monitoring (CGM) solutions have been shown beneficial for treatment of T2D in terms of improved glycemic outcomes and treatment adherence, and their use is increasing [13, 23, 24]. By measuring interstitial glucose every 5 to 15 minutes, see Figure 1.2, CGM data provide insight into glucose excursions between the traditional pre-breakfast SMBG measurements and their use is suggested to reduce patients' fear and risk of hypoglycemia [6]. A number of CGM and flash glucose monitoring devices have recently been approved by the FDA as substitutes for SMBG for dose adjustments [25–27], and recently an expert panel published a consensus on the use of CGM data to evaluate quality of treatment [28].

Other technical advances in diabetes treatment include automatic logging of insulin dose and timing, through smart insulin pens. Pens with memory function have existed for a few years, and currently several connected insulin pens are being developed and brought to market [29,30]. As with the CGM data, injection data can be displayed for the clinicians to provide reliable treatment data and treatment decisions, and has been shown to improve adherence and glycemic control [31, 32].

## 1.2 Thesis objective

As with other industries, package solutions combining mobile communication, smart devices, data clouds and advanced analytics are predicted to be a major factor in future digital success in pharma [33, 34]. In light of the need for innovative solutions to support adherence, and the recent advances in diabetes technologies, we aim to study the feasibility of a novel approach to basal insulin initiation. The concept is to use data from connected glucose and insulin devices during insulin initiation to estimate the dose needed to reach the glycemic target early in the treatment [35]. The estimated dose can be used to guide the remaining titration period and in combination with adaptive dose guidance algorithms. This concept is illustrated in Figure 1.3. The approach could fit into a package solution that supports an all-in-one digital health diabetes management system as the one in Figure 1.4. The expected implications of getting the dose guidance is reduced complexity of self treatment, improved perception of need for medication, and less fear of hypoglycemia, and thereby improved adherence.

The main objective of this work is to develop and test the feasibility of such a treatment solution from a clinical and technical perspective. The concept consists of an initial period for data capture during the initiation, followed by a second period of titration. Data captured by a CGM and insulin device during the first period are used to identify a dose response model for the individual patient which is then used in the second period for adaptive personalised dose guidance. We aim to answer the following research questions:

**Research question 1: Can a personalized dose response model be established?**

We identify the structure of the fasting glucose response to basal insulin in T2D. This model is the foundation for the personalized dose estimation. To do this we analyse glucose and insulin data from insulin naïve people with T2D initiating Insulin Degludec (IDeg) treatment, the latest long acting insulin by Novo Nordisk A/S. We adjust a previously published compartment model of insulin-glucose dynamics and identify parameters from the clinical data. For fitting the models we use continuous-time stochastic modelling with Kalman filtering and maximum likelihood for dynamic modelling, and a least squares (LSQ) approach. Given that T2D is a heterogeneous disease, we do not expect to develop one model that fits all people with T2D. However, we aim to establish a model that estimates the dose response within the time frame of insulin initiation, and can be used in dose guidance as an approximate dose need to reach the glycemic target.


**Figure 1.4:** Package solutions combining mobile communication, smart devices and analytics are predicted to be a major factor in digital success in pharma. The proposed approach could include a connected CGM and insulin pen, and support a digital health setup.

**Research question 2: Is it feasible to use a dose response model to predict the basal insulin dose needed to reach the clinically recommended fasting glucose target?**

We use the dose response model to estimate the dose an individual needs to achieve the glycemic target from an initial subset of the data and test the algorithm in a clinical feasibility study. We revise the dose estimation algorithm and compare the performance of different model identification approaches such as robust LSQ, weighted LSQ with nonlinear weighting, and LSQ with exponential forgetting, as well as a *maximum a posteriori* with a population based prior parameter distribution.

**Research question 3: How may a dose response model enable adaptive dose guidance?**

We use learnings from dose response modelling and the clinical feasibility study to propose two approaches to adaptive model based dose guidance. We incorporate an automatic glycemic target setting and compare the performance with standard of care titration algorithms and other model based approaches *in silico*.

## 1.3 Thesis structure

We aim to answer the three research questions in the following chapters and appendices:

**Research question 1**

**Chapter 2** presents our work within modelling of fasting glucose response to basal insulin in T2D. We describe the available data from clinical trials and present a brief overview of state-of-the-art physiological models of glucose-insulin dynamics in humans. We propose two models for dose response and discuss identifiability of parameters given the available data.

**Appendices A-D** present three peer-reviewed conference papers, presented and published in conference proceedings, and one technical report.

**Research question 2**

**Chapter 3** presents the procedure and results from a clinical feasibility study of a simple approach to dose estimation. We revise the dose estimation algorithm and evaluate its performance using the data from the clinical feasibility study.

**Appendices E-G** present two manuscripts on the clinical study results and ad-hoc analysis, and one technical report on algorithm revision.

**Research question 3**

**Chapter 4** presents a proposed algorithm for adaptive dose guidance. This algorithm uses the revised dose estimation approach and an adaptive glycemic target to minimize risk of hypoglycemia. We test its performance *in silico* and compare to standard of care and an alternative model based approach.

**Appendix H** presents a technical report, describing the adaptive dose guidance algorithm.

**Chapter 5** suggests the use of Model predictive control (MPC) in adaptive iterative dose guidance, and presents results from a proof of concept study. We test the performance compared to the standard of care approach *in silico*.

**Appendices I-J** present a published journal paper and a peer-reviewed conference paper, presented and published in conference proceedings. Both papers present the MPC-based adaptive dose guidance algorithm and proof-of-concept results.

**Conclusion**

**Chapter 6** summarizes our conclusion and the main contributions of this thesis, discusses issues and different approaches, and proposes future work in the field.

Chapter 2

# Dose Response

In this chapter we aim to answer the first research question, where we investigate whether a dose response model can be established. This model forms the foundation for the treatment concept and dose guidance algorithm proposed later in this thesis. We start by introducing the available clinical data for model identification from six clinical trial on IDeg initiation in T2D. We present in brief the study protocols and patient profiles, as well as characteristics of the data such as sparsity and variability. We introduce state of the art physiological models and challenges related to identification. Taking these challenges into account, we adjust one physiological model for dynamic and static identification of the most important parameters for the slow dynamics in fasting glucose and basal insulin. This chapter refers to Appendices A-D.

## 2.1 Clinical data

To characterize pharmacokinetic (PK) and pharmacodynamic (PD) profiles of medication, such as insulin, dose response studies are performed on a relatively small group of patients [36, 37]. This is traditionally done by clamping the glucose concentration to a fixed value for shorter periods of time, where the insulin is injected and glucose infused to keep blood glucose concentration steady. The

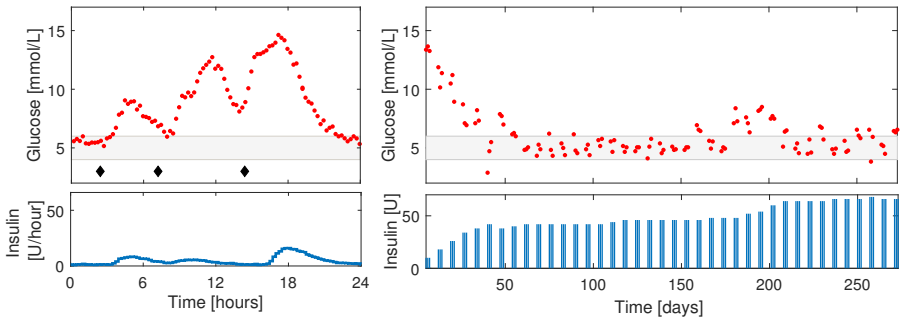


**Figure 2.1:** CGM (left) and SMBG (right) data, and corresponding insulin profiles. Post-prandial excursions following meals diamonds indicate meals. Note that the frequency of measurements is 1/5 min for CGM data and 3/7 day for SMBG data, and the timescale of hours and weeks.

average glucose infusion rates over a few hours or days, for different dose sizes, are then used to evaluate the mean dose response for the population of participants. In the current work we aim to model individual fasting glucose response to IDeg during insulin initiation, which can take up to a few months in clinical trials, rather than short term models such as in clamp studies. We therefore need data from studies with a full titration period, where the dose regimen is known, with as high adherence and frequency of glucose measurements as possible.

Although the use of CGM is increasing in the T2D segment, the availability of CGM data from controlled clinical studies over longer periods is scarce. We therefore use data from previous clinical trials of IDeg initiation in T2D, such as the data to the right in Figure 2.1. We use the data for model identification and development of a dose estimation algorithm. We therefore need to understand the patient profiles from where the data come from, the study procedures, as well as variance in the data.

The data come from six clinical trials on initiation of IDeg in 1,925 insulin naïve people with T2D, with mean (standard deviation, SD) age 57.5 (9.7) years, body weight 82.0 (19.2) kg, BMI 29.2 (5.3) kg/m$^2$ and median SMBG during the first week of 8.3 mmol/L (maximum 19.2 mmol/L) [38–43]. The trials were outpatient studies where SMBG an insulin data were home-logged three days of the week prior to a weekly dose adjustment, and most participants followed the stepwise titration algorithm in Table 2.1 (a subset of the participants adjusted doses twice weekly and measured SMBG every day). Figure 2.1 illustrates ex-

**Stepwise titration algorithm**

| Average pre-breakfast SMBG | Dose adjustment |
|---|---|
| >9.0 mmol/L | +8 U |
| 8.0-8.9 mmol/L | +6 U |
| 7.0-7.9 mmol/L | +4 U |
| 5.0-6.9 mmol/L | +2 U |
| 3.9-4.9 mmol/L | No adjustment |
| 3.1-3.8 mmol/L | -2 U |
| <3.1 mmol/L | -4 U |

**Table 2.1:** The stepwise titration algorithm has been used in clinical trials of IDeg titration [44]. The fasting glucose target varies between algorithms and can be set to ambitious or less stringent values.

amples of CGM and SMBG data. Note that the frequency of measurements is 1/5 min for CGM data and 3/7 day for SMBG data, as well as the different timescales. Notice how the SMBG data in the dataset is sparse, i.e. only data from three days are available each week.

The most widely used metrics for glucose variability are Coefficient of Variation (CV) and standard deviation (SD) [45]. CV is a relative variation of glucose to the mean, calculated by

$$CV = \frac{\sigma}{\mu} \tag{2.1}$$

where $\sigma$ is the SD of the measurements and $\mu$ is the mean. CV is measured in percentage and is thereby closely related to risk of hypoglycemia [46]. In a study on SMBG day-to-day variance in newly diagnosed individuals with T2D, glucose CV was found to be approximately 13.7% using devices with low measurement errors (expected to be higher with higher measurement errors) [47]. In order to understand the variability of the SMBG data in the data set, not caused by changes in insulin doses, we eliminate trends in the data by de-trending, see Figure 2.2. The CV is then the SD of the de-trended data. For the 1,925 participants in the dataset, we find that the median CV of SMBG is 13.2% with 10th and 90th percentiles CV of 8.0% and 20.5%, respectively. These results agree with the findings of Ollerton et al. [47].

To evaluate the performance of the dose estimation algorithms, we need to label the data with the actual dose needed to reach the glycemic target. In Appendix D we define a *target dose interval* for each participant:

**Definition 2.1** A participant's target dose interval is the range of safe and efficient insulin doses, where the corresponding fasting SMBG measurement is within the clinically recommended target. This interval is found using a simple

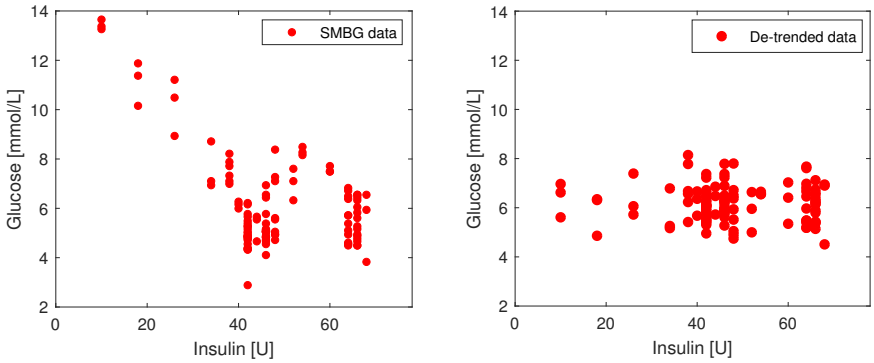


**Figure 2.2:** An example of original (left) and de-trended SMBG data (right).

titration algorithm and the ADA recommended target, see Table 1.1. A target dose is identified when the sum of three consecutive dose adjustments is equal to or within +/- 2 U. Each participant can thereby have multiple occasions of target doses as illustrated in Figure 2.3. The smallest and largest identified target doses indicate the target dose interval.

This interval includes all doses where the recommended glycemic target by the ADA is reached during the study. The results are illustrated in Figure 2.2. We observe that for each participant, a number of different dose sizes bring SMBG to the ADA recommended glycemic target over the 26-52 weeks.

### 2.1.1 Identifiability of dose response

Results from a clamp study of IDeg in 49 people with T2D indicated that the average glucose-lowering effect during a six day period increases linearly with increased dose for injections of 0.4-0.8 U/kg [37]. From these results we expect to observe a trend of decrease in SMBG with larger insulin doses given a sufficient amount of data of sufficient quality [9]. Before identifying the structure of a dose response model, we investigate whether this expected decrease in glucose with larger insulin doses is identifiable from the data. For this purpose we set up the following hypothesis in the Technical Report in Appendix D:

**Hypothesis 2.2** *The expected trend of decrease in SMBG with increased insulin is identifiable in SMBG data from clinical trials of IDeg titration in T2D.*

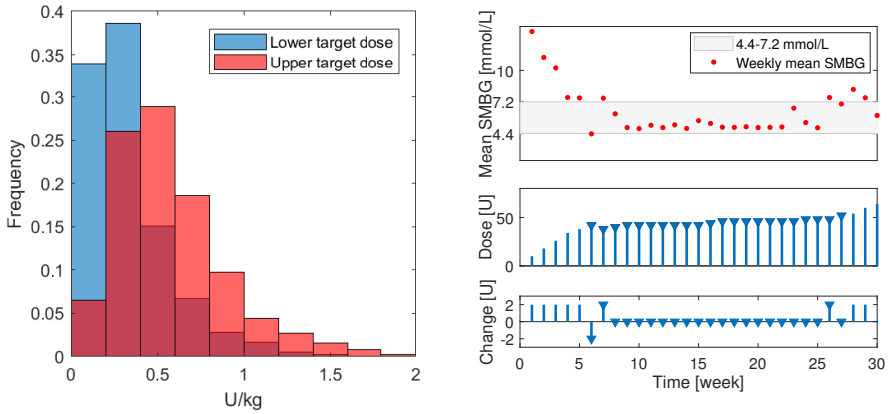


**Figure 2.3:** An example of a target dose interval identification. The top panel shows weekly average SMBG, the middle panel shows the corresponding insulin dose, and the bottom panel shows the dose adjustment as recommended by the ADA guidelines and a simple titration algorithm.

For each participant we investigate whether SMBG values, $G_i$ [mmol/L], decrease with increased insulin, $I_i$ [U/kg], i.e., whether $\beta$ is identifiable in

$$G_i = \alpha - \beta I_i + e_i, \quad e_i \sim \mathcal{N}(0, \sigma^2), \quad i = 1, 2, \ldots, n \tag{2.2}$$

where $\alpha$ [mmol/L] is glucose at zero insulin, $\beta$ [(mmol/L)/(U/kg)] is a long acting insulin sensitivity factor, and $e_i$ is white noise. To test the hypothesis, we estimate the two parameters of the model (2.2) to each individual's SMBG and insulin data. The null-hypothesis is that there is no observable decrease in SMBG with increased insulin, i.e. there is no detectable significant $\beta$ in the data.

To identify the parameters we use an ordinary LSQ approach. In brief, given a relationship between the $i$-th SMBG measurement and insulin injection on the form

$$G_i = f(I_i, \theta) + e_i \tag{2.3}$$

where $f(I_i, \theta)$ is a dose response model. The LSQ method chooses a set of parameters $\hat{\theta}$ that minimizes the sum of squared residuals

$$r = G_i - f(I_i, \hat{\theta}) \tag{2.4}$$

by

$$\hat{\theta} = \arg\min_{\theta} \sum_{i=1}^{n} r_i^2 \tag{2.5}$$

with

$$\hat{\theta} \sim \mathcal{N}(\theta, \hat{\sigma}^2 H(\theta)^{-1}) \tag{2.6}$$

where $\hat{\sigma}^2$ is the estimated noise covariance and $H(\theta)$ is the Hessian of the residuals with respect to the parameters. The Hessian can be approximatd by

$$H(\theta) \approx J(\theta)^T J(\theta) \tag{2.7}$$

with

$$J(\theta) = \begin{bmatrix} \frac{df}{d\theta_1}(t_1) & \frac{df}{d\theta_2}(t_1) & \dots & \frac{df}{d\theta_p}(t_1) \\ \frac{df}{d\theta_1}(t_2) & \frac{df}{d\theta_2}(t_2) & \dots & \frac{df}{d\theta_p}(t_2) \\ \vdots & \vdots & & \vdots \\ \frac{df}{d\theta_1}(t_n) & \frac{df}{d\theta_2}(t_n) & \dots & \frac{df}{d\theta_p}(t_n) \end{bmatrix} \tag{2.8}$$

where we have used that the Jacobian of the residuals is equal to the Jacobian of the dose response function,

$$\frac{dr_i}{d\theta} = \frac{df(I_i, \hat{\theta})}{d\theta} \tag{2.9}$$

Using the binomial sign test, we compute the probability of observing $x$ successes or more, where a model identification is successful when both estimates of $\alpha$ and $\beta$ are significantly non-zero ($p<0.05$, one-sided) and both estimates are non-negative in $n$ trials (number of participants) with the probability $p$ (50%) of successes on each trial.

We find that $\alpha$ and $\beta$ were significantly estimated for 1.740 (90%) participants and a two-sided binomial sign test of the hypothesis rejects the null hypothesis that there is no significant trend visible in the data with a $p$-value $<0.05$. The parameters are log-normally distributed with

$$\ln \begin{bmatrix} \hat{\alpha} \\ \hat{\beta} \end{bmatrix} \sim \mathcal{N}\left( \begin{bmatrix} 2.22 \\ 2.01 \end{bmatrix}, \begin{bmatrix} 0.06 & 0.07 \\ 0.07 & 0.40 \end{bmatrix} \right) \tag{2.10}$$

with mean parameter estimates

$$\hat{\alpha} = 9.21 \text{ mmol/L}, \quad \hat{\beta} = 7.46 \text{ (mmol/L)/(U/kg)} \tag{2.11}$$

and correlation between the two parameters is 0.46. We conclude that dose response is observable from the SMBG and insulin data in the six clinical studies, for approximately 90% of participants.

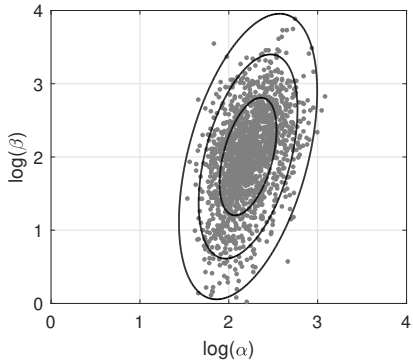


**Figure 2.4:** Parameter distribution of the model $G = \alpha + \beta I$ when fit to all participants in the data set using the robust LSQ approach.

## 2.2 Glucose-insulin dynamics in humans

### 2.2.1 Physiological models

A number of physiological models of the glucose-insulin regulatory system have been developed, including the Bergman minimal model, the Sorensen model, the Dalla man model, the Hovorka model and the Medtronic Virtual Patient model [48–52]. Such models are in general divided into submodels of insulin absorption, meal absorption and metabolic effect. Most models have few linear transition compartments for meal and insulin absorption in each submodel, and a submodel for metabolic effects of different size and complexity, see Figure 2.5. We briefly describe some of the abovementioned models in the following sections.

#### 2.2.1.1 Metabolic effect submodels

The Bergman minimal model is one of the first glucose-insulin dynamics models, published in 1981 [48]. The model is relatively simple and consists of three compartments describing the metabolic effects of insulin on glucose in healthy people. One compartment describes the glucose concentration,

$$\dot{G}(t) = [P_1 - X(t)]G(t) - P_1 G_b \tag{2.12}$$

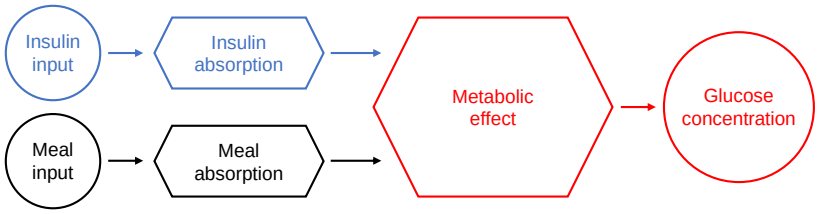


**Figure 2.5:** Physiological models of insulin-glucose dynamics in people with diabetes are in general divided into submodels of insulin absorption, meal absorption and metabolic effect.

with one metabolic parameter, $P_1$, and *basal glucose*concentration, $G_b$. $X(t)$ is the effect of insulin to lower glucose concentration, described by

$$\dot{X}(t) = P_2 X(t) + P_3 I(t), \tag{2.13}$$

with two metabolic parameters $P_2$ and $P_3$ which combined describe the insulin sensitivity by $-P_3/P_2$. The insulin secretion in healthy people following exogenous glucose intake is described in two phases. The first phase of insulin release is represented as a bolus of insulin at the time of glucose intake, and the second phase is described by

$$\dot{I}(t) = \gamma[G(t) - h]t - nI(t), \tag{2.14}$$

where $h$ is a threshold glucose concentration for insulin secretion, $\gamma$ describes the sensitivity of insulin production to glucose concentration, and $n$ is the time constant of insulin clearance. Due to its simplicity, this has been a popular model and forms the basis for many diabetes models.

The Dalla Man model is a meal-simulation model from 2007, originally developed and identified using data from healthy people and people with T2D [50]. Later the model was adjusted to T1D by substituting the insulin secretion model with subcutaneous insulin kinetics compartments, and relevant parameter adjustments. The T1D model consists of 18 compartments in total and 26 metabolic parameters, whereof 13 compartments describe the metabolic effect [53], and the model has been extended with a number of compartments in previous years [54]. The FDA accepted the T1D model to replace animal testing of closed-loop algorithms. Therefore, the model is frequently used to test dose guidance algorithms prior to clinical testing. The simulation environment can currently simulate a sequence of 24 hours with a combination of meal scenarios.

The Hovorka model is a ten compartment model with 16 metabolic parameters in total [51]. The model is a 24-hour simulation model, used for *in silico* testing of

closed-loop algorithms in T1D [55]. In brief, the glucose kinetics are described by two compartments, an accessible compartment, $Q_1$, and a non-accessible compartment, $Q_2$, by

$$\begin{aligned}\dot{Q}_1(t) &= -F_{01}^c - x_1(t)Q_1(t) + k_{12}Q_2(t) - F_R + EGP_0[1 - x_3(t)] + Ra(t)\\ \dot{Q}_2(t) &= x_1(t)Q_1(t) - [k_{12} + x_2(t)]Q_2(t)\end{aligned} \tag{2.15}$$

where $F_{01}^c$ is non-insulin dependent glucose flux, $EGP_0$ is endogenous glucose production at zero insulin, $V_G$ is distribution volume of glucose, $k_{12}$ is a transfer rate between the accessible and non-accessible glucose compartments, and $Ra(t)$ is rate of appearance of ingested carbohydrates. The insulin action submodel consists of three compartments,

$$\dot{x}_i(t) = -k_{ai}x_i(t) + k_{bi}I(t), \quad i = 1, 2, 3 \tag{2.16}$$

where the three $x_i$ compartments represent the effect of insulin on glucose distribution, glucose disposal and endogenous glucose production, and $k_{ai}$ and $k_{bi}$ are deactivation and activation constants. $I(t)$ is the insulin concentration, described by

$$\dot{I}(t) = \frac{U_I(t)}{V_I} - k_e I(t) \tag{2.17}$$

where $U_I$ is the absorption rate of subcutaneous insulin administration, $V_I$ is distribution volume of insulin and $k_e$ is an elimination rate.

The Medtronic Virtual Patient model is a six compartment model with nine metabolic parameters [52]. The model is based on the Bergman minimal model [48] and is designed to model 24-hour dynamics of insulin-glucose response in T1D for closed-loop pump control. The model was identified on ten people with T1D and Kanderian et al. [52] concluded that models for closed-loop design purposes should describe intraday variation in metabolic parameters, but that the model itself would not need to include a large number of compartments. Compared to other models, this model is therefor a simple model with fewer compartments and parameters, and one bi-linear term in the process equation. The metabolic effects submodel is described by two compartments, glucose concentration, $G$, and insulin effect on glucose, $I_{eff}$, by

$$\begin{aligned}\frac{\mathrm{d}I_{eff}}{\mathrm{d}t}(t) &= p_2\left(S_I I_p(t) - I_{eff}(t)\right)\\ \frac{\mathrm{d}G}{\mathrm{d}t}(t) &= -\left(p_{GEZI} + I_{eff}(t)\right)G(t) + p_{EGP} + R_A(t)\end{aligned} \tag{2.18}$$

where $I_p$ is the concentration of insulin in plasma, $p_2$ is an inverse time constant for delay in insulin action, $S_I$ is insulin sensitivity, $p_{GEZI}$ is an inverse time constant for the effect of glucose to eliminate glucose from plasma, $p_{EGP}$ is rate of endogenous glucose production, and $R_A$ is rate of appearance of glucose input (meals) in plasma.

#### 2.2.1.2 Meal absorption submodel

The meal absorption submodel of the Dalla Man model has three compartments, two compartments describe the transit of glucose through the stomach and intestine, $Q_{sto1}$ and $Q_{sto2}$, and one describes the gut, $Q_{gut}$,

$$\begin{aligned}
\dot{Q}_{sto1}(t) &= -k_{gri}Q_{sto1}(t) + D(t) \\
\dot{Q}_{sto2}(t) &= -k_{empt}(Q_{sto1} + Q_{sto2})Q_{sto2}(t) + k_{gri}Q_{sto1}(t) \\
\dot{Q}_{gut}(t) &= -k_{abs}Q_{gut}(t) + k_{empt}(Q_{sto1} + Q_{sto2})Q_{sto2}(t) \\
Ra(t) &= \frac{fk_{abs}Q_{gut}(t)}{BW}
\end{aligned} \tag{2.19}$$

where $k_{gri}$, $k_{abs}$ and $f$ are metabolic parameters, $D$ is the amount of ingested glucose, $BW$ is body weight and $k_{empt}$ is a rate of gastric emptying as a function of the amount of glucose in the stomach [50].

In the Hovorka model, the meal absorption model consists of two compartments, $D_1$ and $D_2$, describing the delay from ingestion to rate of appearance,

$$\begin{aligned}
\dot{D}_1(t) &= A_G D(t) - \frac{D_1(t)}{\tau_D} \\
\dot{D}_2(t) &= \frac{D_1(t)}{\tau_D} - \frac{D_2(t)}{\tau_D} \\
Ra(t) &= \frac{D_2(t)}{\tau_D}
\end{aligned} \tag{2.20}$$

where $A_G$ is the bioavailability of glucose in the meal, $D$ is the amount of ingested glucose, and $\tau_D$ is the time of maximum effect of the meal [51]. The Hovork meal submodel is used for meal absorption in other models such as, e.g., the Medtronic Virtual Patient model [52].

#### 2.2.1.3 Insulin absorption submodel

In the Dalla Man model, the insulin absorption is described in two compartments, $I_{sc1}$ and $I_{sc2}$, similar to the Hovorka meal model but with two time constants and rate of absorption from both insulin compartments,

$$\begin{aligned}
\dot{I}_{sc1}(t) &= u(t) - k_d I_{sc1}(t) + k_{a1} I_{sc1}(t) \\
\dot{I}_{sc2}(t) &= k_d I_{sc1}(t) - k_{a2} I_{sc2}(t) \\
U_I(t) &= k_{a1} I_{sc1}(t) + k_{a2} I_{sc2}(t)
\end{aligned} \tag{2.21}$$

where $k_d$, $k_{a1}$ and $k_{a2}$ are metabolic rates and $u(t)$ is the insulin administration.

The insulin submodel in the Hovorka model is similar to the meal absorption submodel, describing the absorption of fast acting insulin through two compartments, $I_1$ and $I_2$,

$$\begin{aligned} \dot{I}_1(t) &= u(t) - \frac{S_1(t)}{\tau_I} \\ \dot{I}_2(t) &= \frac{I_1(t)}{\tau_I} - \frac{I_2(t)}{\tau_I} \\ U_I(t) &= \frac{I_2(t)}{\tau_I} \end{aligned} \tag{2.22}$$

where $u(t)$ is the amount of insulin administered, and $\tau_I$ is the time to maximum insulin absorption. The Medtronic Virtual Patient model describes insulin absorption in a similar manner, however with two different time constants rather than one.

## 2.3 Dynamic dose response

We aim to investigate whether the dose response of fasting glucose to IDeg is linear during insulin titration, as IDeg clamp study results suggest, or whether another model structure is better suitable. This work is presented in Appendices A-C. As we only wish to simulate the slow dynamics of fasting glucose and basal insulin, and we have sparse data, we choose the Medtronic Virtual Patient model due to its simplicity. It has few compartments and is simple in the PD compartments with only one bi-linear term. The model is designed for simulations of T1D in insulin pump treatment with fast acting insulin. We therefore make adjustments and augmentations to model long acting insulin and endogenous insulin secretion.

### 2.3.1 Medtronic Virtual Patient model

The PK model in the Medtronic Virtual Patient model describes the concentration dynamics of subcutaneously infused insulin by

$$\frac{\mathrm{d}I_{sc}}{\mathrm{d}t}(t) = \frac{1}{\tau_1}\left(\frac{u(t)}{C_I} - I_{sc}(t)\right) \tag{2.23a}$$

$$\frac{\mathrm{d}I_p}{\mathrm{d}t}(t) = \frac{1}{\tau_2}\left(I_{sc}(t) - I_p(t)\right) \tag{2.23b}$$

with $u$ as exogenous long acting insulin, $I_{sc}$ and $I_p$ as subcutaneous and plasma insulin concentrations, and time constants $\tau_1$ and $\tau_2$. The PD model is on the form

$$\frac{\mathrm{d}I_{eff}}{\mathrm{d}t}(t) = p_2 \left(S_I I_p(t) - I_{eff}(t)\right) \tag{2.24a}$$

$$\frac{\mathrm{d}G}{\mathrm{d}t}(t) = -\left(p_{GEZI} + I_{eff}(t)\right) G(t) + p_{EGP} + R_A(t) \tag{2.24b}$$

where $I_{eff}$ is insulin effect on glucose, $p_2$ is an inverse time constant for delay in insulin action, $G$ is the glucose concentration in plasma (measurable), $S_I$ is insulin sensitivity, $p_{GEZI}$ is an inverse time constant for the effect of glucose to eliminate glucose from plasma and $p_{EGP}$ is rate of endogenous glucose production. $R_A$ is rate of appearance of glucose input (meals) in plasma,

$$R_A(t) = \frac{D(t)}{V_G \tau_m^2} t e^{-\frac{t}{\tau_m}} \tag{2.25}$$

which is represented by the two compartments in (2.20). $V_G$ is the distribution volume of glucose, $D$ is the carbohydrates consumption and $\tau_D$ is the time constant describing the delay in glucose uptake from the gut.

### 2.3.2 Insulin production augmentation

Since the Medtronic Virtual Patient model is developed for simulation of T1D, we add an endogenous insulin secretion term, $I_{endo}$, to the model by replacing $I_p$ in (2.24a) with $I_p + I_{endo}$,

$$\frac{\mathrm{d}I_{eff}}{\mathrm{d}t}(t) = p_2 S_I \left(I_p(t) + I_{endo}(t)\right) - p_2 I_{eff}(t) \tag{2.26}$$

We model the production of insulin as a linear relationship between insulin production and glucose concentration. This is similar to the second-phase insulin secretion in the Bergman minimal model, the secretion model proposed by Hovorka's group when inter-day variations are eliminated [56], as well as in the Dalla Man model when steady state is assumed. Due to the sparsity and low frequency of the data, it is fair to assume that these processes reach steady state between samples. These models all assume a threshold for insulin production. Given the sparsity of the clinical data, we aim to create a simple model, and minimize the number of parameters to estimate. We therefore assume no threshold in the fasting insulin production and set

$$I_{endo}(t) = \beta G(t) \tag{2.27}$$

| Parameter | Value | Unit |
|---|---|---|
| $C_I$ | 1.26 $10^3$ | [mL/min] |
| $p_2$ | 1.1 $10^{-2}$ | [$\text{min}^{-1}$] |
| $S_I$ | 5.5 $10^{-4}$ | [mL/$\mu$U/min] |
| $GEZI$ | 2.3 $10^{-3}$ | [$\text{min}^{-1}$] |
| $EGP$ | 1.21 | [mg/dL/min] |

**Table 2.2:** Mean parameter values from Kanderian et al. [52].

where $\beta$ is the glucose sensitivity of the insulin producing $\beta$ cells. Then we have

$$\frac{\mathrm{d}I_{eff}}{\mathrm{d}t}(t) = p_2 S_I \left(I_p(t) + \beta G(t)\right) - p_2 I_{eff}(t) \tag{2.28}$$

to substitute the insulin effect expression in (2.24a).

### 2.3.3 Long acting insulin profile

Most physiological models have been identified using data where human insulin or fast acting insulin was used. In the current work we use data from titration studies on IDeg, an ultra long acting insulin. The half-life of IDeg is approximately 25 hours which is ten times the order of half-life of fast acting insulin, and its glucose infusion rate is flat and stable over 24 hours [37]. Due to the long half-life of IDeg, insulin concentration stacks over the first days after initiating treatment or increase in doses. In general, steady state is considered reached after 4-5 half lives, but IDeg has been found to reach steady state after 2-3 days [57].

To determine the time constants $\tau_1$ and $\tau_2$ in (2.23), we assess the peak insulin concentration time from the PK curve of IDeg, where insulin concentration is stable for the first 24 hours and is detectable 96 hours after injection [58]. The curve indicates that a time constant of $\tau = \tau_1 = \tau_2 = 12$ hours is a reasonable choice in terms of peak concentration. Figure 2.6 illustrates a simulation of the Medtronic Virtual Patient model using mean parameter values published in Kanderian et al. [52], and a long acting insulin time constant of 12 hours, see Table 2.2. The figure indicates that setting the time constant $\tau$ of insulin transfer from injection site to plasma to 12 hours is a reasonable choice.

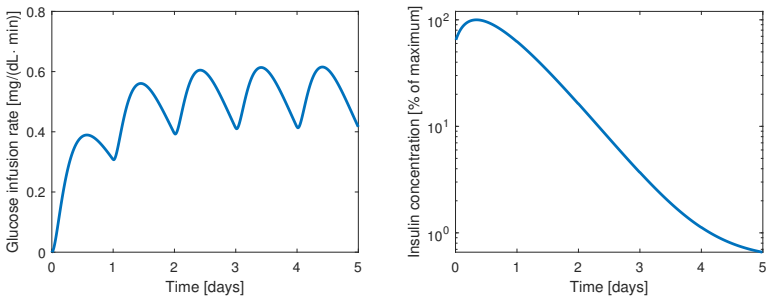


**Figure 2.6:** A simulation of glucose infusion rate (left) following daily injections using the Medtronic Virtual Patient model in (2.23)-(2.24) with $\tau_1 = \tau_2 = 12$ hours and mean parameter values from Table 2.2. The glucose infusion rate reaches steady state in approximately three days. Clearance of insulin over the following five days where no insulin is injected in the simulation (right).

### 2.3.4 Simulation of basal glucose

Given the nature and sparsity of the data, parameters related to meal excursions will not be identifiable. Therefore we set $R_A = 0$ and get the glucose dynamics equation

$$\frac{\mathrm{d}G}{\mathrm{d}t}(t) = -\left(p_{GEZI} + I_{eff}(t)\right) G(t) + p_{EGP} \tag{2.29}$$

We call this concentration, where the simulated glucose is not affected by meals the *basal glucose* and define it as follows:

**Definition 2.3** *Basal glucose*is the simulated or predicted blood glucose concentration obtained when no prandial (post meal) glucose excursions and no impact of fast acting insulin are present.

*Basal glucose*is therefore the expected lowest glucose concentration at any time of day, when a basal insulin injection has been administered. This term represents the fasting glucose, which in general can only be measured pre-meal, and is measured through pre-breakfast SMBG in practice. The full adjustet and

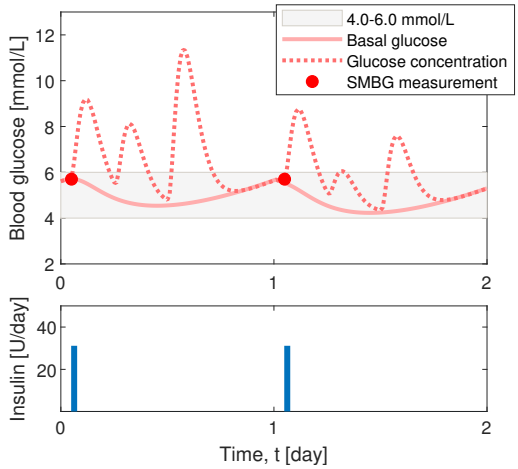


**Figure 2.7:** A simulation of glucose concentration with and without meals (top) using the adjusted Medtronic Virtual Patient model and mean parameter values from [52]. Basal insulin is injected in the morning (bottom) and three meals are ingested per day.

augmented model becomes

$$\frac{\mathrm{d}I_{sc}}{\mathrm{d}t}(t) = \frac{1}{\tau_1}\left(\frac{u(t)}{C_I} - I_{sc}(t)\right) \tag{2.30a}$$

$$\frac{\mathrm{d}I_p}{\mathrm{d}t}(t) = \frac{1}{\tau_2}\left(I_{sc}(t) - I_p(t)\right) \tag{2.30b}$$

$$\frac{\mathrm{d}I_{eff}}{\mathrm{d}t}(t) = p_2 S_I \left(I_p(t) + \beta G(t)\right) - p_2 I_{eff}(t) \tag{2.30c}$$

$$\frac{\mathrm{d}G}{\mathrm{d}t}(t) = -\left(p_{GEZI} + I_{eff}(t)\right) G(t) + p_{EGP} \tag{2.30d}$$

Figure 2.7 illustrates a simulation of two days using this model of basal glucose.

### 2.3.5 Model identification

The physiological models described in the previous section are developed for short term simulations and predictions of blood glucose. In general the time frame is up to 24 hours, and the use cases are designed for testing of closed-loop insulin pump control algorithms. Identification of these models requires data

from specific clinical tests performed in the clinic such as oral or intravenous glucose tolerance tests and clamp studies, with frequent glucose and insulin concentration measurements, see e.g. [52, 55]. In the current work, such data is not available for the relevant time frame and a large number of people with T2D.

Due to the sparsity of the data, only a subset of the parameters in the adjusted Medtronic Virtual Patient model are identifiable. We assess the value of $\tau_1$ and $\tau_2$ as described in Section 2.3.3. The augmented model has two gains, $C_I$ and $S_I$, and one proportional gain, $\beta$. We rewrite the model such tat we get one gain and one proportional gain, and the rewritten model becomes

$$\frac{\mathrm{d}\tilde{I}_{sc}}{\mathrm{d}t} = \frac{1}{\tau}u - \frac{1}{\tau}\tilde{I}_{sc} \tag{2.31a}$$

$$\frac{\mathrm{d}\tilde{I}_{p}}{\mathrm{d}t} = \frac{1}{\tau}\tilde{I}_{sc} - \frac{1}{\tau}\tilde{I}_{p} \tag{2.31b}$$

$$\frac{\mathrm{d}\tilde{I}_{eff}}{\mathrm{d}t} = p_2(\tilde{I}_p + \tilde{\beta}G) - p_2\tilde{I}_{eff} \tag{2.31c}$$

$$\frac{\mathrm{d}G}{\mathrm{d}t} = -(GEZI + \tilde{S}_I\tilde{I}_{eff})G + EGP \tag{2.31d}$$

with $\tilde{I}_{sc}$, $\tilde{I}_p$ and $\tilde{I}_{eff}$ [U/day] as rates rather than concentrations, and the two gains $\tilde{\beta}$ [U·L/mmol·day] and $\tilde{S}_I$ [1/U].

In the work presented in Appendices B and C, we propose identifying the subset of parameters, $\tilde{S}_I, EGP$ and $\tilde{\beta}$, of the model in (2.31), while keeping the other parameters constant at mean values from Table 2.2. For the model identification we use the open source Continuous Time Stochastic Modelling tooblox in R (CTSM-R) [59, 60].

Given time series data, the toolbox identifies parameters of linear and non-linear grey-box stochastic differential equation models on the form

$$dx(t) = f(x(t), u(t), \theta)dt + \sigma(u(t), \theta)dw(t) \tag{2.32a}$$

$$y(t_k) = g(x(t_k), \theta) + v_k \tag{2.32b}$$

where $x(t_0) = x_0$ is the initial condition, $\mathcal{U}_k = [u(t)]_{t_0}^{t_k}$ is the sequence of inputs, and $\mathcal{Y}_k = [y_0, y_1, \ldots, y_{k-1}, y_k]$ are the measured data. $\theta$ is the set of parameters to identify, $\sigma^2(u(t), \theta)$ is the process noise covariance matrix, $w(t)$ is standard Brownian motion and $v_k \sim N_{iid}(0, R)$ is the measurement error. The toolbox finds the set of parameters $\theta$ that maximizes the likelihood function, or the joint probability density,

$$p(x_0, \theta; \mathcal{Y}_{N_d}, \mathcal{U}_{N_d}) = \left(\prod_{k=1}^{N_d} p(y_k|\mathcal{Y}_{k-1}, \mathcal{U}_k, x_0, \theta)\right) p(y_0|x_0, \theta), \tag{2.33}$$

Here the density $p(y_k|\mathcal{Y}_{k-1}, \mathcal{U}_k, x_0, \theta)$ is the probability of a measurement $y_k$ given data up to time $k-1$, parameters $\theta$, inputs up to time $k$ and initial condition $x_0$. This density is assumed to follow a normal distribution and is found by

$$p(y_k|\mathcal{Y}_{k-1}, \mathcal{U}_k, x_0, \theta) = \frac{\exp\left(-\frac{1}{2}\varepsilon_k^T R_{k|k-1}^{-1}\varepsilon_k\right)}{\sqrt{\det(R_{k|k-1})}\left(\sqrt{2\pi}\right)^l}. \tag{2.34}$$

Here $\varepsilon_k = y_k - \hat{y}_{k|k-1}$ is the $l$-dimensional innovations and

$$\hat{y}_{k|k-1} = E[y_k|\mathcal{Y}_{k-1}, \mathcal{U}_k, x_0, \theta] \tag{2.35}$$

is the filtered measurement at time $k$ given data up to time $k-1$ using a Kalman filter, and $R_{k|k-1} = V[y_k|\mathcal{Y}_{k-1}, \mathcal{U}_k, x_0, \theta]$ is the covariance of the estimate.

Taking the negative logarithm, the software minimizes the objective function

$$\begin{aligned} -\log\left(p(x_0, \theta; \mathcal{Y}_N, y_0)\right) \propto & \frac{1}{2}\sum_{k=1}^{N}\left(\log\left(\det(R_{k|k-1})\right) + \varepsilon_k^T R_{k|k-1}^{-1}\varepsilon_k\right) \\ & + \frac{1}{2}\left(\sum_{k=1}^{N} l\right)\log(2\pi) \end{aligned} \tag{2.36}$$

We use the software to identify the parameter vector

$$\theta = \begin{bmatrix}\tilde{S}_I & EGP & \tilde{\beta} & R & \sigma_{11} & \sigma_{22} & \sigma_{33} & \sigma_{44}\end{bmatrix}^T \tag{2.37}$$

We find that the subset of parameters is identifiable from simulated and real clinical data from the data set. Since we, however, can only estimate gains and a constant input parameter, $EGP$, in a linear model, we proceed with an alternative approach in the following section.

## 2.4 Steady state dose response

The time constants in (2.31c) and (2.31d) are small compared to $\tau$ and the sampling frequency in the data. In Appendix B, we therefore assume that the two compartments $\tilde{I}_{eff}$ and $G$ reach steady state immediately following change in $\tilde{I}_p$. We propose to replace the two compartments in (2.31c) and (2.31d) with

an output function and reduce the model to

$$\frac{\mathrm{d}\tilde{I}_{sc}}{\mathrm{d}t} = \frac{1}{\tau}u - \frac{1}{\tau}\tilde{I}_{sc} \tag{2.38a}$$

$$\frac{\mathrm{d}\tilde{I}_{p}}{\mathrm{d}t} = \frac{1}{\tau}\tilde{I}_{sc} - \frac{1}{\tau}\tilde{I}_{p} \tag{2.38b}$$

$$y = \alpha + \beta\tilde{I}_{p} + \gamma\sqrt{1+\tilde{I}_{p}} \tag{2.38c}$$

where $y$ is the measured glucose concentration in plasma.

Since we only have data from the last 3 days of the week, and steady state for IDeg is reached in approximately 3 days, $\tau$ is not identifiable from the data. We therefore assume that steady state is reached between samples and identify the output function only. Assuming white error noise, and since the model is linear in the parameters and that there is no dynamics to identify, the maximum likelihood approach is equivalent to an LSQ approach. Letting $G_i$ and $I_i$ be the SMBG and insulin injection on day $i = 1, 2, \ldots, n$ for a participant in the data set, then the relationship between glucose and insulin in the output function (2.38c) may be expressed by

$$G_i = \alpha - \beta I_i - \gamma\sqrt{1+I_i} + e_i \tag{2.39}$$

where $e_i \sim \mathcal{N}(0, \sigma^2)$. From the clamp study results of IDeg, we assumed a linear relationship where the response may be expressed by

$$G_i = \alpha - \beta I_i + e_i \tag{2.40}$$

Identifying the three parameters of (2.39) may be challenging, and we therefore propose an alternative two-parameter model, on the form

$$G_i = \alpha - \gamma\sqrt{1+I_i} + e_i \tag{2.41}$$

We compare the ability of the three proposed models to fit data from each participant in the data set. We compare the fit in terms of $R^2$, a statistical measure that describes the ability of the model to explain the variance in the data. An illustration of SMBG and insulin data from one participant in the data set is illustrated in Figure 2.8, along with the three models, fit using the LSQ approach.

### 2.4.1 Model identification

The ordinary LSQ method, described in Section 2.1.1, assumes that all data points are of equal quality and that noise is normally distributed around the

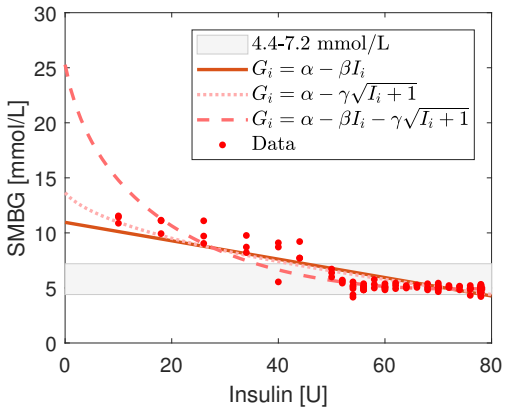


**Figure 2.8:** The three models fit to data from one participant in the data set using the LSQ approach.

mean. Considering the nature of the data, user errors may cause outliers in the data. These errors could, e.g., poorly performed measurements due to user mistake, wrong timing of the measurements etc. Therefore it may be relevant to minimize sensitivity of the parameter estimation to outliers. One way of doing this is weighted LSQ, where each residual $r_i$ has a weight term $w_i$ and we minimize

$$\hat{\theta} = \arg\min_{\theta} \sum_{i=1}^{n} w_i r_i^2 \tag{2.42}$$

with

$$\hat{\theta} \sim \mathcal{N}(\theta, \sigma^2 H^{-1}) \tag{2.43}$$

where $H(\theta)$ is the Hessian of the objective function

$$H(\theta) \approx J(\theta)^T J(\theta) \tag{2.44}$$

and $J(\theta)$ is the Jacobian of the objective function with respect to the parameters,

$$J(\theta) = \begin{bmatrix} w_1 \frac{df}{d\theta_1}(t_1) & w_1 \frac{df}{d\theta_2}(t_1) & \dots & w_1 \frac{df}{d\theta_p}(t_1) \\ w_2 \frac{df}{d\theta_1}(t_2) & w_2 \frac{df}{d\theta_2}(t_2) & \dots & w_2 \frac{df}{d\theta_p}(t_2) \\ \vdots & \vdots & & \vdots \\ w_n \frac{df}{d\theta_1}(t_n) & w_n \frac{df}{d\theta_2}(t_n) & \dots & w_n \frac{df}{d\theta_p}(t_n) \end{bmatrix} \tag{2.45}$$

Different approaches to choosing $w_i$ exist. These include, e.g., the Huber and the bisquare estimators. The Huber estimator decreases the weight linearly with distance from the mean up to a point, whereafter it is constant. The bisquare estimator which has quadratic decrease in weights with increasing distance from

the mean, and eliminates influence of points "too far away". In this work we use the bisquare weighting function for robust LSQ, with weights

$$w_i = (|u_i| < 1)(1 - u_i^2)^2 \tag{2.46}$$

where $u_i$ is the adjusted and normalized residual $r_i$ of the weighted LSQ, wich takes into account the degree by which the $i$-th residual influences the fit.

### 2.4.2 Model choice

We identify the three models from the data in the dataset and find that the ordinary LSQ is somewhat sensitive to outliers in the data. Therefore we use the robust LSQ for the model identification, where all parameters should be positive and $\alpha$ should be less than or equal to 20.0 mmol/L. The criteria for a best model fit to a participant's data are that all parameter estimates are significant (one sided $p<0.05$), and the highest $R^2$.

The results indicate that the linear model (2.40) provides the best fit for 77.2% of participants with parameter distribution

$$\ln \begin{bmatrix} \alpha \\ \beta \end{bmatrix} \sim \mathcal{N}\left( \begin{bmatrix} 2.27 \\ 2.21 \end{bmatrix}, \begin{bmatrix} 0.06 & 0.05 \\ 0.05 & 0.29 \end{bmatrix} \right) \tag{2.47}$$

and model (2.41) fits data from 17.5% of participants best with parameter distribution

$$\ln \begin{bmatrix} \alpha \\ \gamma \end{bmatrix} \sim \mathcal{N}\left( \begin{bmatrix} 2.81 \\ 2.16 \end{bmatrix}, \begin{bmatrix} 0.04 & 0.06 \\ 0.06 & 0.12 \end{bmatrix} \right) \tag{2.48}$$

For the remaining 5.3% none of the models were identified with all parameter estimates significant.

## 2.5 Summary

In this chapter we presented the dataset available for dose response model identification. We provided a brief overview of physiological models of glucose-insulin dynamics. We chose the Medtronic Virtual Patient model to base our dose response model on. Most state-of-the-art models aim to model fast dynamics with meals and fast acting insulin. However, the data presented here are sparse and include information about slow dynamics only. We therefore defined the term *basal glucose* as the lowest glucose concentration, expected when fast dynamics are omitted, i.e., meals and bolus insulin are not taken into account. After

rewriting the Medtronic Virtual Patient model for endogenous insulin production and identifiability, we presented a dynamic compartment model to simulate basal glucose. We then illustrated how the sparse data resulted in a steady state model of dose response, and concluded that the two two-parameter models fit most participants in the data set best, where the linear model was best for the majority of patients.

Chapter 3

# Clinical Feasibility of Dose Prediction

In the previous chapter we identified a model structure for the dose response during insulin initiation of 25-52 weeks. In this chapter we aim to answer research question 2 about whether this model can be used to estimate the dose needed to reach glycemic target, early in the treatment. We present the procedure and results of a clinical feasibility study, where we tested a simple dose estimation algorithm using the results from Chapter 2. We describe the clinician facing software developed for the clinical study, and discuss learnings from data. Using these learnings we revise the dose estimation algorithm, and test whether this would have performed better in the clinical study. This chapter mainly refers to Appendices E-G.

## 3.1 Dose estimation in a clinical study

Collecting SMBG data requires users to finger prick and provides a low frequency of data, traditionally from a few data points per week to one per day. To allow for the best user experience, minimize user steps during the first period of data collection, and to get a better insight into the glucose concentration throughout the day, we test the feasibility of the dose estimation concept using CGM data.

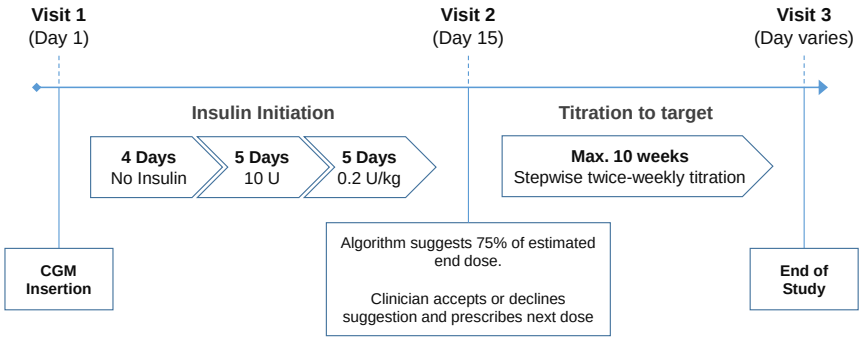


**Figure 3.1:** Clinical feasibility study procedure.

Durability of CGM devices is increasing and is currently up to approximately two weeks. Here we describe the simple dose estimation method in brief, and how we use the CGM data to determine fasting glucose. Finally we present a user interface the clinican facing software developed specifically for this clinical feasibility study.

## 3.2 A clinical feasibility study procedure

We performed a clinical study to test the clinical feasibility of a simple approach to estimating the dose needed to reach glycemic target. We tested a prototype of the concept, where a dose estimation algorithm uses data from 14 days of CGM and home-logged insulin doses during insulin initiation. The algorithm estimates the dose needed to reach the glycemic target after 14 days and proposes 75% of this dose to the clinician. The clinician then uses this estimate to guide the remaining titration period, while a traditional titration algorithm, similar to the one in Table 2.1, is used for the remaining titration. This concept is illustrated in Figure 1.3.

The study was performed at Hvidovre University Hospital and Steno Diabetes Center Copenhagen, and included eight insulin naïve people with T2D. The study procedure is illustrated in Figure 3.1 and the study devices are illustrated in Figure 3.2. A predetermined regime was followed for the first two weeks, during which the initial excitation was applied. At the second clinic visit, the dose estimation software downloaded the CGM data from Diasend® and estimated the dose needed to reach the glycemic target. 75% of this dose was proposed to the clinician as the end dose of the study. The clinician determined whether


**Figure 3.2:** The clinical study devices. Two log books for registering doses and SMBG measurements, a Dexcom® G5 CGM sensor and transmitter, and a starting kit for Tresiba® (IDeg) FlexTouch® treatment. All participants received an iPhone® 5S for receiving CGM data and sending to the Diasend® cloud.

to follow this advice, and continued the titration until target was reached with twice weekly adjustments using a stepwise titration algorithm (-4 to +8 U steps) with a fasting glucose target of 4 to 6 mmol/L. When the actual end dose was achieved, i.e., when sum of three consecutive dose adjustments was within +/-2 U, the participant was invitetd to a final visit. We set the target fasting glucose to 6 mmol/L, which is the upper target range of the titration algorithm used in the study. Patients were asked to log three SMBG measurements per day, one pre-breakfast and two later in the day. These measurements were also used for calibration of the CGM. The study is described in detail in Appendix E.

### 3.2.1 Linear dose response

In the clinical study, we incorporated a simple version of the dose estimation in the clinician facing software. We used the linear model as proposed by the results in Chapter 2, i.e.,

$$G_i = \alpha - \beta I_i + e_i, \quad i = 1, 2, \ldots, k \tag{3.1}$$

where $G_i$ represents fasting glucose of day $i$ and $I_i$ is the insulin injection taken the corresponding day. The software uses an ordinary LSQ to identify $\alpha$ and $\beta$ from 14 days of data. If both parameters are significantly identified, the software

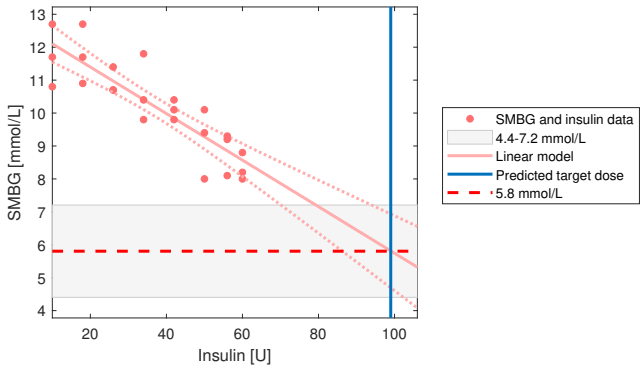


**Figure 3.3:** Dose estimation is based on the linear dose response model and an ordinary LSQ approach.

estimates the dose needed to reach a fasting glucose target $G_{target}$ by inverting the response equation,

$$\hat{I}_{target} = \frac{\alpha - G_{arget}}{\beta} \tag{3.2}$$

This concept is illustrated in Figure 3.3. In the study, 75% of this dose was proposed to the clinician. If the model is not significantly identified, the software gives an error message.

### 3.2.2 From CGM to fasting glucose

A CGM with sampling frequency 1/5 min provides up to 288 data points per day, compared to one SMBG measurement during fasting in standard of care treatment. In order to identify the response of fasting glucose to basal insulin, the only change in anti-diabetic medicine should be the size of the basal insulin dose. Then the mean change in fasting glucose is assumed to be caused, or induced, by the change in insulin dosing. To identify the response the algorithm identifies a *titration glucose level* from a day of CGM data to substitute the SMBG values:

**Definition 3.1** *Titration glucose level*, an alternative to pre-breakfast SMBG values in basal insulin titration, is the lowest average one-hour window of CGM data of each day.

The one-hour window corresponds to 12 consecutive CGM readings for a measuring frequency of 1/5 minutes. The choice of a one-hour window is assessed

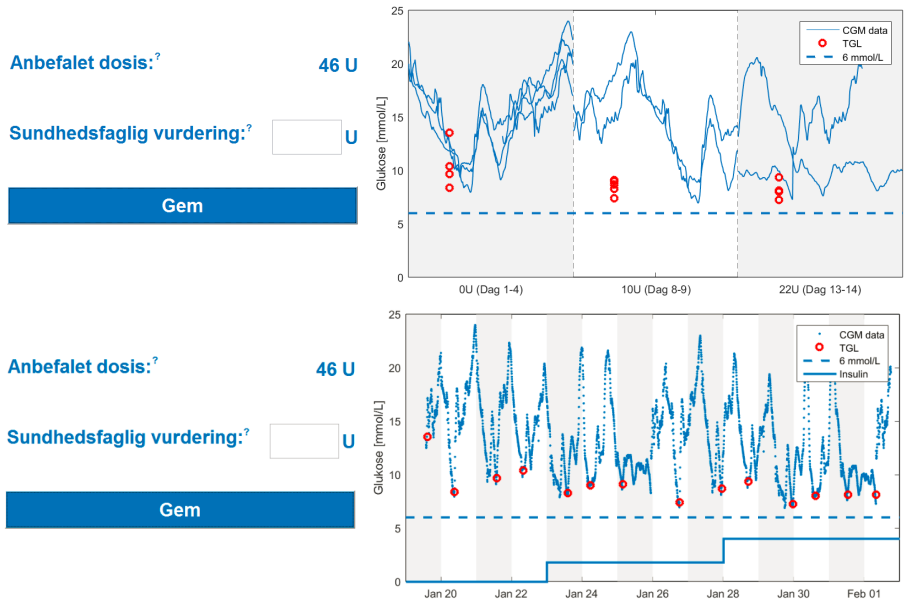


**Figure 3.4:** The graphical user interface of the clinician facing software (in danish). 75% of the estimated end dose is proposed to the clinician, where the clinican can choose to use this suggestion as a next dose, or to follow a titration algorithm. The right panels illustrate CGM and insulin data for the first 14 days, as well as the *titration glucose level*, in terms of dose sizes (top) or as a time series (bottom).

reasonable to reflect a low glucose event caused by the insulin while still being robust to noise and outliers. The dose estimation software uses the *titration glucose level* instead of pre-breakfast SMBG values, $G_i$.

### 3.2.3 A clinician facing dose estimation software

We developed the clinician facing software to estimate and communicate the end dose to the clinician, as well as to visualize the data, see Figure 3.4. To start the software, the clinician signs in with name, which is logged along with a time stamp and manually entered data. The software requests a participant ID number and checks whether this number is identical to the ID number in the CGM data file. The clinician next inputs the insulin data for the first 14 days, and requests an end dose prediction.

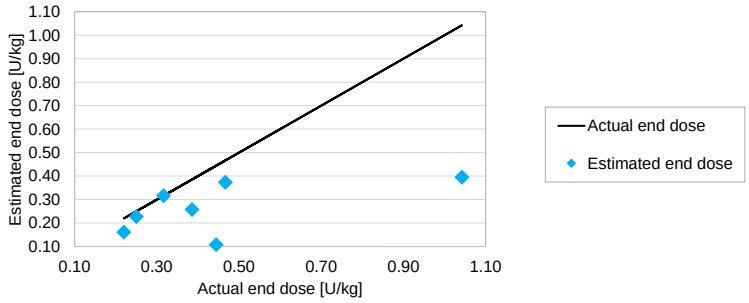


**Figure 3.5:** Results of the clinical feasibility study. The dose is underestimated in all cases and is thus considered safe. Accuracy may however be improved.

The software automatically visualizes the data in terms of dosing periods, i.e., all glucose curves where the same dose was given, are overlaid, as illustrated in the top panel of Figure 3.4. This is to visualize the decrease in glucose with increased insulin doses. The clinician can request a time series visualisation of the data instead, illustrated in the bottom panel of Figure 3.4. The markers indicate the *titration glucose level*. The clinician enters the next administered dose, which is logged by the system along with clinician name, time and insulin and CGM data.

### 3.2.4 End points and learnings

In brief, the results of the clinical feasibility study showed that estimating the dose needed to reach the target *titration glucose level* is safe. This means that that all doses estimated based on 14 days of CGM and IDeg data, were smaller than the actual study end dose. Figure 3.5 presents the primary endpoint results of the feasibility study. We observe that the accuracy of the dose predictions, when comparing to the actual end dose, the doses were underestimated with median 26.7% (range: 0.0-75.8% underestimation) and for one participant the dose prediction was not possible at two weeks.

We identified the parameters $\alpha$ and $\beta$ in the linear model, using all the data collected in the clinical study. The parameter distribution using the *titration glucose level* values, extracted from the CGM data, is

$$\ln \begin{bmatrix} \alpha \\ \beta \end{bmatrix} \sim \mathcal{N}\left( \begin{bmatrix} 2.31 \\ 2.40 \end{bmatrix}, \begin{bmatrix} 0.02 & 0.03 \\ 0.03 & 0.36 \end{bmatrix} \right) \tag{3.3}$$

The individual identified parameters for the eight participants using CGM and SMBG data are illustrated in Figure 3.6, along with the parameter distribution, (2.47), found for the large dataset in Chapter 2. We observe that the distribution from Chapter 2 is similar to what we observed using CGM data from the clinical feasibility study. Although we can not conclude from this small amount of data, the results indicate that CGM, and the extracted *titration glucose level*, agrees well with the SMBG data collected in previous clinical trials.

We found that a median of 7% (range: 2-58%) of CGM data were missing during the first two weeks, where the poorest dose estimation in terms of percentwise accuracy, occurred for the participant missing the most data. We furthermore observed that there was a delay in CGM data availability at visit 2, when the dose estimation was performed, of around 6-16 hours. This means that in the study, data for more than half a day were missing in some cases, which may have affected the accuracy of the dose estimation.

Ad hoc analyses of the CGM data indicate that the lowest glucose concentration of the day usually occurs at other time points than before breakfast, when SMBG is measured. This can be caused by, e.g., diurnal variations in insulin sensitivity, given that insulin sensitivity has previously been found to increase during the day, compared to the night and morning [61]. Figure 1.2 illustrates pre-breakfast SMBG measurements and the corresponding *titration glucose level* values in the clinical study. We observe that for most days, the *titration glucose level* is lower than the pre-breakfast SMBG, on average by 2.3 mmol/L. This difference in morning glucose and the lowest glucose of the day supports the idea of a *basal glucose* presented in Chapter 2, where we simulated the lowest expected glucose concentration throughtout the day, given no meals and other insulin injections than the once daily IDeg.

## 3.3 A revised dose estimation algorithm

We have learned that the dose estimation approach tested in the clinical feasibility study is safe (i.e. doses were not overestimated) but accuracy may be improved. In this section we use the data from the six previous clinical trials, described in Section 2.1, to revise the dose estimation approach. We compare the dose estimation performance when using ordinary, robust, weighted and a forgetting LSQ, as well as an *a posteriori* approach. We test the different approaches using the linear and the non-linear models in (2.40) and (2.41) and compare the performance in terms of safety and efficiency.

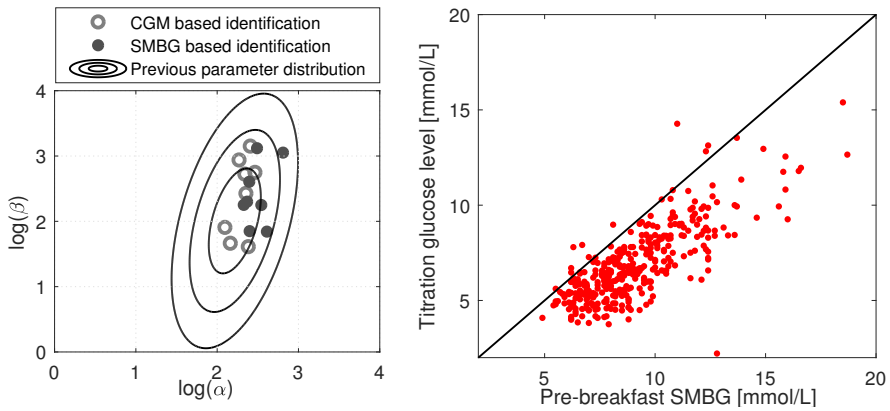


**Figure 3.6:** Parameter distribution using the full data set of the eight participants in the clinical study (left), compared to the distribution found in the large data set (2.10). *Titration glucose level* is in most cases lower than the pre-breakfast SMBG value, on average by 2.3 mmol/L (right).

### 3.3.1 Model identification

#### Non-symmetric weighted LSQ

In an MPC approach in closed-loop pump treatment, the objective function for the optimization of glucose concentration is typically non-symmetric, such that low glucose values are penalized higher than high glucose values, see e.g. [62–64]. This is done to account for the clinical severity of low glucose concentrations compared with high concentrations. We use this concept as to design a weighting function such that the weight on low SMBG values is high compared to high SMBG values. At the same time we keep in mind that insulin doses affect the glucose levels and we do not wish to eliminate information about the dose response. We therefore weigh SMBG readings compared to other SMBG readings where the same insulin dose was given. The weighting function is therefore

$$w_i = 1 - \frac{\log(G_i - \min[\mathcal{G}(I_i)] + 1)}{\log(\max[\mathcal{G}(I_i)]} \tag{3.4}$$

where $G_i$ is the i-th SMBG measurement, $I_i$ is the corresponding insulin injection, and $\mathcal{G}(I_i)$ is all SMBG measurements $G_j$ for $j = 1, 2, \ldots, n$ where $I_j = I_i$. When there is only one SMBG measurement for the corresponding insulin dose, then $\dim(\mathcal{G}(I_i)) = 1$ and $w_i = 1$.

### Forgetting LSQ

To adapt to potential changes in physiological state of the participant over the time course of the trials, we propose adding a forgetting factor to the LSQ based dose prediction. This approach assumes that the latest data points give the most accurate information about the current state of the participant. We propose using an exponential decrease with distance from the current time point counted in days,

$$w_i = \lambda^{d_i}, \quad i = 1, 2, \ldots, n \tag{3.5}$$

where $\lambda$ is the forgetting factor that determines the effective memory, $d_i$ is the distance of the data point $G_i$ from the latest data point $G_n$ in days. The effective memory of $w_i$ may be calculated by $N_d = 1/(1-\lambda)$.

### Maximum a posteriori

Instead of estimating the parameters from the current individual's data only, we may use prior information from, e.g., a similar patient group. The probability density function $p(\theta)$ for the parameters identified for a patient group can be used as a prior when identifying parameters for a new individual [60]. Bayes' rule states that the posterior probability density function of the parameters, conditioned on the new data set $\mathcal{Y}_k = [y_k, y_{k-1}, \ldots, y_1, y_0]$, is then

$$p(\theta|\mathcal{Y}_k) = \frac{p(\mathcal{Y}_k|\theta)p(\theta)}{p(\mathcal{Y}_k)} \propto p(\mathcal{Y}_k|\theta)p(\theta) \tag{3.6}$$

To maximize the likelihood of the new parameter set, given the population parameter distribution, we can maximize this posterior probability function. We previously observed that the logarithm of the parameters identified in Chapter 2 are normally distributed. We can therefore write the posterior probability density function as

$$p(\theta|\mathcal{Y}_k) \propto \left( \prod_{i=1}^{k} \frac{\exp\left(\frac{1}{2} e_i^T R_i e_i\right)}{\sqrt{\det(R_i)}(\sqrt{2\pi})^l} \right) p(y_0|\theta) \frac{\exp\left(-\frac{1}{2}\varepsilon_\theta^T \Sigma_\theta^{-1} \varepsilon_\theta\right)}{\sqrt{\det(\Sigma_\theta)}(\sqrt{2\pi})^p} \tag{3.7}$$

where $\varepsilon_\theta = \theta - \mu_\theta = \theta - E\{\theta\}$ and $\Sigma_\theta = V\{\theta\}$, $p$ is the dimension of the parameter vector, $e_i$ is the residuals of the fit with dimension $l$ and $R_i$ is the covariance of the residuals. If we condition the posterior probability on $y_0$ and take the negative logarithm, we can determine the parameter estimates by solving the optimization problem

$$\hat{\theta} = \arg\min_{\theta} \{-\log(p(\theta|\mathcal{Y}_k, y_0))\} \tag{3.8}$$

where

$$\begin{aligned} -\log\left(p(\theta|\mathcal{Y}_N, y_0)\right) =& \frac{1}{2}\sum_{i=1}^{k}\left(\log\left(\det(R_i)\right) + e_i^T R_i^{-1} e_i\right) \\ &+ \frac{1}{2}\left(\left(\sum_{i=1}^{k} l\right) + p\right)\log(2\pi) \\ &+ \frac{1}{2}\log\left(\det(\Sigma_\theta)\right) + \frac{1}{2}\varepsilon_\theta^T \Sigma_\theta^{-1}\varepsilon_\theta \end{aligned} \tag{3.9}$$

Notice that the second term in is independent of the parameters and the fit. We use a leave-one-out (LOO) approach for testing the performance of the *a posteriori* approach, and use robust LSQ to create the *a priori* distribution, as described in Appendix D.

### 3.3.2 From an identified model to a dose estimate

If the model parameters have been identified, and both are significant, we perform a dose estimation. This is similar to what we described earlier in the clinical trial software. Using the model equations of the relationship between glucose and insulin, i.e., (2.40) and (2.41), we estimate the dose needed to reach a glucose target $G_{target}$ by

$$\hat{I}_{target} = \frac{\alpha - G_{target}}{\beta} \tag{3.10}$$

for the linear model and

$$\hat{I}_{target} = \left(\frac{\alpha - G_{target}}{\gamma}\right)^2 - 1 \tag{3.11}$$

for the non-linear model. This dose estimation is then compared to the *target dose interval* identified for each participant, see Definition 2.1 and Figure 2.3. If the estimated dose is within the target dose interval, the dose is assumed to be *efficient*. If the dose is below the upper limit of the target dose interval, it is assumed to be *safe*. Otherwise the dose is overestimated and not considered safe.

In Appendix F we present the results of comparing the performance of dose estimation using the two models (2.40) and (2.41). We observed that identifiability in terms of significant parameters, the models perform similarly. However, in terms of safe and efficient dose predictions, where 1) safe estimations are all estimations smaller than the upper target dose and 2) efficient estimations are

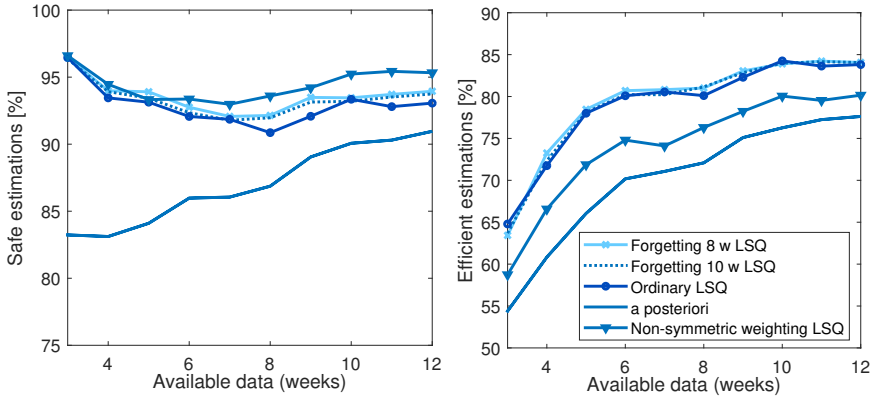


**Figure 3.7:** Frequency of safe target dose estimations (left) and efficient target dose estimations (right), tested on the full data set.

estimations within the target dose range, the linear model performs better. This is expected as the non-linear model allows for decreased response in the lower range of glucose values, and therefore the model may overestimate doses, especially when only a small subset of data are available. We therefore conclude that this model is not suitable for dose predictions.

In brief, we find that dose estimation performance is best using the forgetting LSQ approach with 8 week effective memory, see Figure 3.7. Using this approach, the model is identified for approximately 70% of participants given 18 data points (six weeks of data), whereof 93% are safe and 83% are efficient. The non-symmetric weighting function performs well with respect to safety, but not efficiency. The reason for this is it's conservative approach, i.e. doses were underestimated. The *a posteriori* approach performes well in terms of early identification of parameters, i.e., given only 9 data points (three weeks of data) the model is identified for approximately 75% of participants, and increases to over 90% given 18 data points. However, considering the number of overestimated doses, see Figure 3.7, a large number of participants would receive a dose estimate that is larger than the expected upper target dose.

### 3.3.3 CGM based dose estimation

We test the revised algorithm, i.e., the forgetting LSQ with 8 week memory, as well as the *a posteriori* approach, on the data from eight participants in the clinical feasibility study, see Figure 3.8. The accuracy is improved, with a smaller

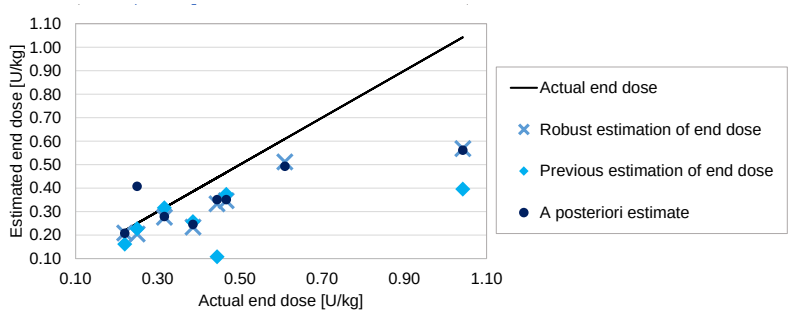


**Figure 3.8:** Results of the clinical feasibility study and the revised dose estimation approach using the forgetting LSQ with eight week memory, as well as the *a posteriori* estimation.

median error of 21.6% (range: 5.0-45.5% underestimation) for the forgetting LSQ and 22.9% (range: 46.1% underestimation to 63% overestimation) for the *a posteriori* approach, compared to 26.7% (range: 0.0-75.8% underestimation) for the simple approach in the clinical feasibility study. Using the forgetting LSQ, all doses are still underestimated and thus considered safe, and all participants would receive a dose estimate after 14 days. This is presented in Appendix G. The *a posteriori* approach overestimates the dose in one case, while otherwise performing similarly, with a slightly higher underestimation than the forgetting LSQ.

The results from the ad-hoc analysis of the data from the clinical feasibility study indicate that dose estimation using the revised algorithm and 14 days of CGM and insulin data is feasible in terms of safety and accuracy.

## 3.4 Summary

In this chapter we presented a clinical feasibility study, where we tested a simple dose estimation algorithm. The results indicate that dose estimation based on 14 days of CGM and insulin data is safe, while accuracy may be improved. We revised the dose estimation algorithm and concluded that an LSQ with an 8 week effective memory performed best. The revised algorithm improved the dose estimation when tested on the clinical feasibility study data.

This chapter further presented learnings from CGM data in the specific scenario

of IDeg initiation in insulin naïve people with T2D. We observed that pre-breakfast SMBG measurements are greater than the corresponding day's lowest one hour CGM data, which in most cases occur later in the day. This indicates that using pre-breakfast SMBG data only in insulin titration may cause In the next chapter we use the dose response model and dose estimation approach presented here, to iteratively guide day-to-day dose adjustments.

Chapter 4

# Dose Estimation-Based Guidance with Adaptive Target

In this chapter we use the dose estimation method developed in Chapter 3 as a foundation for an adaptive dose guidance algorithm. We aim to answer the third research question and propose using the uncertainty of the dose estimate to allow for safe and efficient dose adjustments without clinician and patient inputs. We furthermore propose an approach to automatic glycemic target setting to minimize risk of hypoglycemia. To evaluate the performance of the proposed algorithm, we simulate clinical trials and real world scenarios with suboptimal adhernce, and compare with safety and efficiency of standard of care and an other model based titration algorithm. This chapter mainly refers to Appendix H.

## 4.1 Iterative steps towards target

Decreased time in hyperglycemia reduces diabetes related complications such as cardiovascular disease and retinopathy. This supports fast titration to the

glycemic target. However, researchers have found a correlation between intensive treatment following prolonged periods of hyperglycemia, and increased risk of retinopathy in T1D [65]. Varadhan et al. [66] furthermore published results in 2011 indicating that rapid glycemic improvement in T2D may increase the risk of retinopathy and concluded that systematic documentation is needed for further conclusions.

Considering the results of dose prediction performance, we found that the best performing dose prediction method overestimated doses for approximately 5% of the participants given six weeks of data, or 18 data points. Furthermore, we observed that the target dose interval for each individual, in Section 2.1, included a range of doses that may not all be suitable at all times during the study. I.e., for those participants who continued increasing doses late in the study, the largest dose may be too large if administered at the beginning of insulin treatment.

We therefore do not recommend immediately administering the estimated dose, but rather taking adaptive steps towards the estimated target dose, even in the hypothetic case of a perfect dose estimation. This is in agreement with the standard of care approach and other state-of-the-art dose adjustment algorithms. In the following sections we introduce and discuss the IDS algorithm and a simple linear control strategy, both model-based iterative dose adjustment algorithms. We then propose an iterative dose guidance algorithm using the estimated end dose.

## 4.2 The Intelligent Dosing System and a linear control strategy

The IDS is an adaptive dose guidance system, published in 2004 by Cook et al. [21,67]. The IDS uses patient-specific dose response data and a mathematical model to calculate a next basal insulin dose. In brief, a linear dose response model is combined with a stochastic loop to account for individualization. A next dose, $I_{k+1}$, is the sum of the current dose, $I_k$, and a relative change in dose, $\Delta I_k$, and a stochastic loop,

$$I_{t+1} = I_t\,(1 + \Delta I_t) + Loop \tag{4.1}$$

where the relative change in dose is calculated by

$$\Delta I_k = \frac{\text{Change in level function}}{\text{Linearity function}} \tag{4.2}$$

The "Change in level function" is a relative distance in the current glucose level, $G_k$, from the desired glucose level, $G_{target}$,

$$\text{Change in level function: } \frac{G_k - G_{target}}{G_k} \tag{4.3}$$

and the "Linearity function" is drug specific describing the expected response to the drug,

$$\text{Linearity function: } 1 + \frac{I_k}{range} \tag{4.4}$$

where *range* is set to 60 mg/dL for long acting insulin, corresponding to 3.33 mmol/L. For personalization, the IDS algorithm includes a learning approach, by adding a stochastic loop that either increases or decreases the next dose, $I_{k+1}$, based on its ability to predict the current level from previous data,

$$Loop = 0.2I_k \left( \frac{\Delta\bar{G}_k - \Delta G_k}{\Delta G_k} \right) \left( 1.3^{-I_k/range} \right) \tag{4.5}$$

Here, $\Delta G_k$ is the actual change in glucose level,

$$\Delta G_k = G_k - G_{k-1} \tag{4.6}$$

and $\Delta\bar{G}_k$ is the expected change in glucose level, i.e., the difference between a predicted current glucose level, $\bar{G}_k$, and the actual previous level, $G_{k-1}$,

$$\Delta\bar{G}_k = \bar{G}_k - G_{k-1} \tag{4.7}$$

where the predicted current level is calculated by

$$\bar{G}_k = G_{k-1} \left( 1 + \frac{I_{k-1} - I_k}{I_{k-1}} \left( 1 + \frac{I_{k-1}}{range} \right) \right) \tag{4.8}$$

and the term $1.3^{-I_k/range}$ is a drug specific nonlinear response model. The stochastic loop is a learning term that allows the algorithm to adjust the dose steps depending on its ability to predict glucose response. If the expected change in glucose, $\Delta\bar{G}_k$, and the actual change in glucose, $\Delta G_k$, are equal, the stochastic loop equals zero and the calculated next dose is not changed. If the expected change is 50% lower than the the actual change, then 50% (of 20% of the current dose) is subtracted from the calculated dose.

The IDS algorithm has been criticised by Bequette et al. [68] for instability, lack of tuning abilities, and that it only allows for dose increase and not decreasing doses. Note that the stochastic loop includes a term with the actual glucose change in the denominator. This means that in some situations, e.g., when insulin is changed by small amounts leading to small changes in the glucose concentrations, this term may become close or equal to zero. We therefore only

allow the IDS algorithm to recommend dose changes until the target glucose is reached. To determine when target glucose is reached, we use the same approach as in previous work, see the definition of target glucose interval in Section 2.1. When target has been reached one time, the dose is not changed. Similar to the algorithm proposed in this work, the IDS algorithm needs an initial dose input. Therefore it relies on either a clinician or a titration algorithm for the first few steps, until a dose response is detected. In this work we use the stepwise titration algorithm in Table 2.1 for the first three dose adjustments.

Bequette et al. [68] argued that a simple linear control strategy could be used instead of the IDS, where a linear response equation is inverted and the input, $I_k$, needed to reach the desired output, $G_{target}$, is

$$I_k = I_{k-1} + \frac{1}{\beta}(G_{target} - G_k) \tag{4.9}$$

where $\beta$ is the process gain in the response model. To avoid overshooting, the add a tuning parameter $\alpha$ with values between 0 and 1 such that

$$I_k = I_{k-1} + \frac{\alpha}{\beta}(G_{target} - G_k) \tag{4.10}$$

We implement this simple linear control strategy with a tuning parameter $\alpha = 10$ mmol/L and identify $\beta$ using the robust LSQ. The approach presented in the current work uses a similar approach in that it uses a linear dose response model. This is described in the following section.

## 4.3 Iterative dose adjustments to estimated end dose

Given SMBG and insulin data, $(I_1, G_1)$, ... $(I_k, G_k)$, where $I_i = I(t_i)$ [U/kg] and $G_i = G(t_i)$ [mmol/L], we start by assuming that an estimated dose that brings fasting glucose to target, $\hat{I}_{target,k}$ [U/kg], is available at time $t_k$, with

$$I_{target,k} \sim \mathcal{N}\left(\hat{I}_{target,k}, \hat{s}_k^2\right) \tag{4.11}$$

where $\hat{I}_{target,k}$ is an estimate of the true dose, $I_{target,k}$, that brings glucose to target. The method of determining $\hat{I}_{target,k}$ is described in Chapter 3 and Appendix F. $\hat{I}_{target,k}$ is available only if both parameters of the dose response model have been identified, and $\alpha$<20.0 mmol/L, and $\beta$>0 mmol/L/(U/kg). The next recommended dose is then the smallest dose within the confidence interval of the estimated dose, i.e., the next dose, $I_{k+1}$ is calculated by

$$I_{k+1} = \hat{I}_{target,k} - t_{\alpha,k-m}\hat{s}_k \tag{4.12}$$

where $m$ is the number of parameters in the model. $t_{\alpha,k-m}$ is the Student's t inverse cumulative distribution function with $k-m$ degrees of freedom for the $(1-\alpha)$ one sided confidence interval. In this work we use the 80% one sided confidence interval, as we are only considering a lower threshold for glucose concentrations.

If the current dose is already above the lower 80% confidence interval, and the average of the last three SMBG measurements is above the lower limit of the target range, then the algorithm allows taking steps towards the mean predicted end dose, i.e.,

$$I_{k+1} = I_k + \mu(\hat{I}_{target,k} - I_k) \tag{4.13}$$

where $\mu$ determines the size of the step towards the mean. Here we set $\mu = 0.5$. If the current dose is larger than the predicted end dose, and the average of the last three SMBG measurements is above the lower target range, the dose is not changed. Otherwise, the dose is set to the lower confidence interval as in (4.12). The algorithm becomes

$$I_{k+1} = \begin{cases} I_k + \mu(\hat{I}_{target,k} - I_k) & I_k < \hat{I}_{target,k} \wedge \mathcal{G}_k > G_{min} \\ I_k & I_k > \hat{I}_{target,k} \wedge \mathcal{G}_k > G_{min} \\ \hat{I}_{target,k} - t_{\alpha,k-m}\hat{s}_k & \text{otherwise} \end{cases} \tag{4.14}$$

where $\mathcal{G}_k$ is the mean of the last three SMBG measurements at time $k$.

### 4.3.1 Moving target

The ADA recommends setting a personalized glucose target based on risk factors, including hypoglycemia, drug adverse effects, age, and comorbidities [9]. The lower the risk, the more stringent the glucose target may be set. In general, the target should be within 4.4-7.2 mmol/L.

Assuming that the SMBG measurements are normally distributed, and the distribution is independent of glucose concentration, we base the target glucose at time $t_k$, $G_{target,k}$, on the estimated variance of the measurements. Using that glucose variability and risk of hypoglycemia are closely related [36], we base the target glucose on the estimated variance of the measurements [69]. We want 90% of the measurements to be above the lower target, while the target should be within 4.4-7.2 mmol/L. We therefore set

$$G_{target,k} = \min\{G_{max}, \quad G_{min} + t_{\alpha,k-m}\hat{\sigma}_k\} \tag{4.15}$$

where $\hat{\sigma}_k$ is the estimated SD of the residuals, $G_{min} = 4.4$ mmol/L and $G_{max} = 7.2$ mmol/L. We set $\alpha = 0.1$ for a one sided 90% confidence interval.

## 4.4 Simulation study

### 4.4.1 *In silico* population

We generate an *in silico* population of patients based on the dose response models identified in Chapter 2. We validate the *in silico* population by simulating a clinical trial with the same protocol as in the dataset and compare outcomes.

We use the two dose response models, identified in previous work, and the corresponding identified parameter distributions, to create the $i$-th insulin naïve participant with T2D. Given the parameter set and model, the deterministic data for participant $i$ are calculated by

$$G_k = f(I_k, \theta) \tag{4.16}$$

We draw the *in silico* participant's body weight from $BW_i \sim \mathcal{N}(82.0, 19.2^2)$ and the SD of the fasting glucose $\sigma_{CV,i} \sim \mathcal{N}(13.9, (5.3)^2)$. We then generate glucose measurements, $\hat{G}_k$, using the dose response models and add glucose CV by

$$\hat{G}_k = G_k + v_k, \quad v_k \sim \mathcal{N}(0, G_k \sigma_{CV,i}) \tag{4.17}$$

We use this as input to the dose guidance algorithms and to evaluate their performance.

We simulate a 26 week clinical trial including 10.000 subjects with T2D, using the stepwise titration algortihm in Table 2.1 and observe that the baseline glucose, body weight, SMBG variability and target doses are similar for the clinical trial data and the simulated population, see Appendix H. Hypoglycemia is slightly overestimated in the simulations and the average of the last two week SMBG data is slightly underestimated. Due to these differences, we do not expect the results from simulations to be direct indications for absolute values of outcome measures, but rather as a way of ranking the performance of the titration algorithms with respect to hypoglycemia and glycemic outcomes at end of study.

### 4.4.2 A clinical trial scenario

Using the *in silico* environment, we now simulate a 26 week clinical trial where we compare performance of the proposed adaptive algorithm with standard of care titration algorithms in Tables 1.1 and 2.1, as well as the IDS. In this scenario we assume that all doses are administered and all dose adjustments are performed once weekly. All participants receive an initial dose of 10 U.

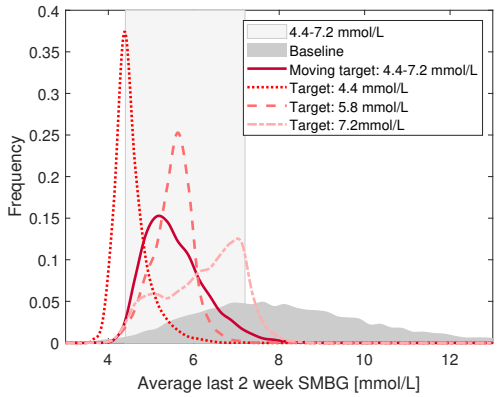


**Figure 4.1:** Frequency of average last 2 week SMBG measurements for the adaptive dose prediction algorithm in an *in silico* clinical trial.

The glycemic outcomes of the adaptive dose prediction algorithm for different fixed targets and the moving target are illustrated in Figure 4.1. Using the adaptive dose prediction approach with a fixed target of 5.8 mmol/L (middle of ADA target range) a higher frequency of participants in target at end of study is achieved with a lower frequency of hypoglycemia events than for both standard of care algorithms. Frequency of hypoglycemia events can be lowered further using a higher target or a variable target. We furthermore find that the IDS algorithm performs worse in terms of both number of participants reaching the glycemic target, and, as expected, frequency of hypoglycemia events.

### 4.4.3 A real world scenario

Studies have shown that around 40% of people with T2D reach glycemic targets [3], and that in insulin injection therapy, approximately 20-40% of injections are omitted [14–16]. We simulate a real world scenario where dose adjustments are not performed between clinic visits, and 30% of doses are omitted. In the simulation we find that if using the standard of care algorithms, the number of participants reaching the ADA target is approximately 42.2-60.2%. This is somewhat in line with the observed number of people with T2D reaching glycemic targets [3].

When comparing the performance of the algorithms in a 52 week scenario where adjustments are only performed at clinic visits every three months but all doses are administered, see Figure 4.2, we find that the model based algorithms per-

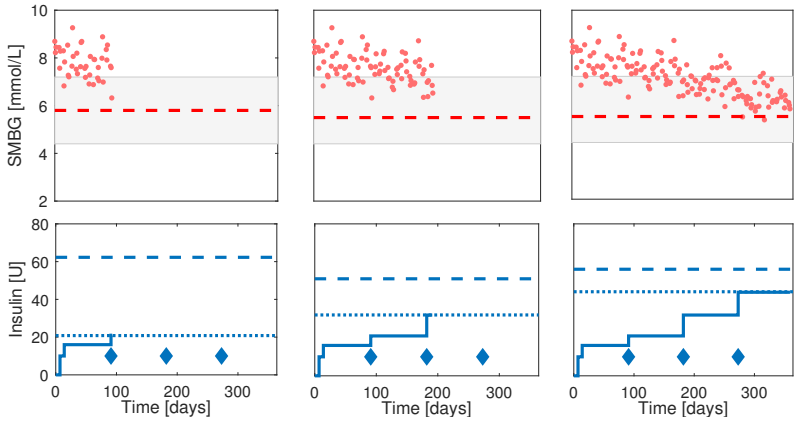


**Figure 4.2:** The adaptive dose estimation algorithm with moving target. After the first two dose adjustments, doses are adjusted at clinic visits (diamonds) only. The ADA glycemic target is indicated by the shaded area and the moving target with a dashed line (top). The predicted target dose is illustrated by a dashed line and its 80% one-sided CI in dotted lines (bottom).

form better than standard of care. The results are illustrated in Table 4.1. The adaptive dose prediction with a moving target performs best in terms of the number of participants reaching target, while lowering the frequency of hypoglycemia events. The IDS has the highest frequency of hypoglycemia events.

In the case of low adherence to injections, we do not expect all participants to reach the glycemic target. In order to reach the glycemic target, the medicine has to be administered, and an algorithm can only do part of the work. We therefore aim at showing stability in terms of low frequency of hypoglycemia, despite the poor adherence, rather than improve number of participants reaching target. We observe that with a moving target, the hypoglycemia rates can be decreased and number of people reaching targets increased, as compared to the standard of care algorithms. The IDS performs poorly in terms of hypoglycemia events.

## 4.5 Summary

Although we in previous chapters found that dose estimation is feasible in terms of safety and efficiency, we do not assume that this dose should be used as a next

**Standard of care**

| | Simple | Stepwise |
|---|---|---|
| Glycemic target | 4.0-5.0 | 4.0-5.0 |
| In ADA target | 55.3% | 77.9% |
| SMBG $<$ 3.9 mmol/L | 1.8% | 2.3% |
| SMBG $<$ 3.0 mmol/L | 0.2% | 0.3% |

**Adaptive dose estimation algorithm**

| | Dose prediction | | | |
|---|---|---|---|---|
| | Fixed target | | | Moving target |
| $G_{target}$ | 4.4 | 5.8 | 7.2 | 4.4-7.2 |
| In ADA target | 89.3% | 86.6% | 69.5% | 78.8% |
| SMBG $<$ 3.9 mmol/L | 3.4% | 1.9% | 1.8% | 1.8% |
| SMBG $<$ 3.0 mmol/L | 0.4% | 0.3% | 0.3% | 0.2% |

**Alternative model based algorithms**

| | Linear control | | IDS | |
|---|---|---|---|---|
| $G_{target}$ | 4.4 | 7.2 | 4.4 | 7.2 |
| In ADA target | 83.9% | 62.8% | 88.0% | 87.3% |
| SMBG $<$ 3.9 mmol/L | 3.2% | 2.7% | 5.4% | 5.2% |
| SMBG $<$ 3.0 mmol/L | 0.6% | 0.5% | 2.5% | 2.4% |

**Table 4.1:** Results of dose guidance algorithm comparison in a 52 week simulated real world scenario of 10.000 *in silico* participants, where doses are only adjusted at clinic visits every three months.

dose recommendation. Rather, as proposed in this chapter, the estimated dose and its uncertainty should be used to iteratively recommend a next safe dose. We proposed an approach that performs better *in silico* than standard of care and a previously published model based approach, both when adherence is perfect as well as in case of low adherence to dose adjustments and administration.

Chapter 5

# MPC-Based Guidance

In the clinical feasibility study, described in Chapter 3, we found from CGM data that glucose concentration is lower than pre-breakfast SMBG measurements at other times of day. This supports the definition of *basal glucose* concentration in Chapter 2, i.e., the glucose concentration predicted by the dynamic compartment model (2.31). In Chapter 4 we proposed an iterative dose adjustment approach using the steady state dose response model and target dose estimation. In the following chapter we propose a somewhat similar approach to the iterative algorithm in Chapter 4, but here we use the dynamic *basal glucose* model and MPC. This proposed approach has the potential to minimize the risk of hypoglycemia occurring between pre-breakfast SMBG measurements. We present in brief the concept of MPC and our application in injection treatment, and a case study to show a preliminary proof of concept. This work mainly refers to Appendices I-J.

## 5.1 Model predictive control

MPC is a control algorithm, where a model of a system is used to predict the future response of the system to a certain input, see e.g. [70]. The algorithm uses the prediction model and an optimization algorithm to determine the future input sequence, needed to reach a desired state in the system. When the

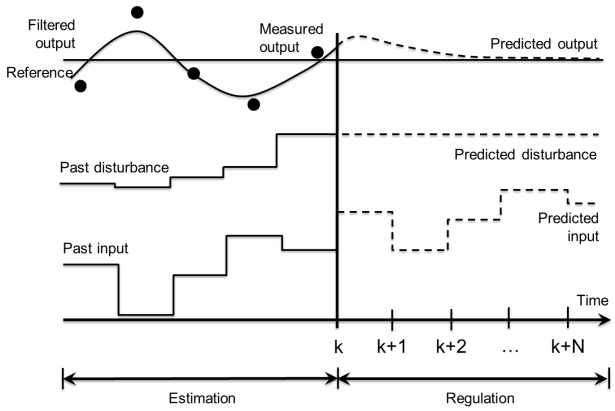


**Figure 5.1:** A conceptual illustration of model predictive control.

first input has been implemented, the response is measured and the current state of the system is estimated through, e.g., a Kalman filter. This concept is illustrated in Figure 5.1. The main advantages of MPC compared to other control algorithms such as the Linear-quadratic regulator (LQR) and proportional–integral–derivative (PID) algorithms are that 1) it incorporates physical knowledge about the system, allowing for on-line prediction of the response to the input, and 2) it allows for implementing physical and desired constraints on the inputs and outputs. MPC is used in many industries such as chemical plands and electric power systems, and has been widely used in the diabetes research field for closed-loop insulin pump treatment [62–64].

The algorithm optimizes the sequence of the next and future inputs, $u_{k+j}, j = 0, 1, \ldots, N-1$, with a receding horizon from time $t_k$ to time $t_{k+N}$, that minimize the difference of the future outputs, $y_{k+j}$, and a reference, $r_{k+j}$. The optimisation problem is in the form

$$\begin{aligned} \min_{\{u_{k+j}\}_{j=0}^{N-1}} \quad & \phi_y = \frac{1}{2}\sum_{j=1}^{N} ||(y_{k+j} - r_{k+j})||_2^2 \\ s.t. \quad & x_{k+1} = Ax_k + Bu_k + Ed_k \\ & y_k = Cx_k \\ & y_{min} \leq y_k \leq y_{max} \\ & u_{min} \leq u_k \leq u_{max} \end{aligned} \tag{5.1}$$

Here, the last two inequalities are hard upper and lower constraints on the output and input, and $x_k = \hat{x}_{k|k}$ has been estimated by a Kalman filter.

If relevant, changes in input, $\Delta u_{k+j} = u_{k+j} - u_{k+j-1}$, can be penalized, and in

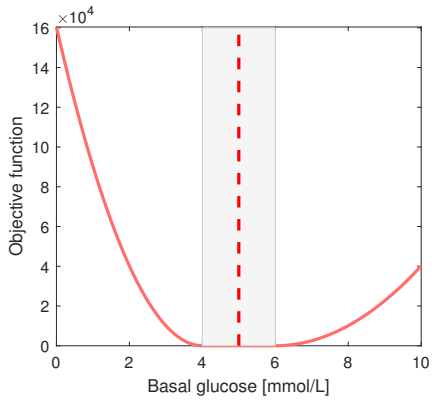


**Figure 5.2:** A non-symmetric penalty function where the weight on lower soft constraints, 4 mmol/L, is higher than on the upper soft constraints, 6 mmol/L. The reference is at 5 mmol/L.

case of physical restrictions, constrained. Soft constraints can substitute hard constraints on the output, in case of an infeasible problem. Infeasibility can occur if, e.g., a constrained output value can for some reason not be avoided, or is has already occurred and will take time to correct. An MPC minimization problem with soft output constraints and hard constraints and penalty on input changes, is on the form

$$
\begin{aligned}
\min_{\{u_{k+j},s_{k+j+1},t_{k+j+1}\}_{j=0}^{N-1}} \quad \phi_y = &\frac{1}{2}\sum_{j=1}^{N}||w_y(y_{k+j}-r)||_2^2 + \frac{1}{2}\sum_{j=0}^{N-1}||w_{\Delta u}u_{k+j}||_2^2 \\
&+\frac{1}{2}\sum_{j=1}^{N}||w_s s_{k+j}||_2^2 + \frac{1}{2}\sum_{j=1}^{N}||w_t t_{k+j}||_2^2 \\
s.t. \quad x_{k+1} =&Ax_k + Bu_k + Ed_k \\
y_k =&Cx_k \\
u_{min} \leq&u_k \leq u_{max} \\
\Delta u_{min} \leq &\Delta u_k \leq \Delta u_{max} \\
y_{min} - s_k \leq &y_k, \quad y_k \leq y_{max} + t_k \\
0 \leq &s_k, \quad 0 \leq t_k
\end{aligned}
\tag{5.2}
$$

Here, $w_y$, $w_{\Delta u}$, $w_s$ and $w_t$ represent the weighting of penalties for the different terms. By tuning the weights, low glucose can, e.g., be weighed higher in the penalty than high glucose, which has previously been done in MPC for closed-loop control of diabetes [71–73]. An example of such an objective function is

illustrated in Figure 5.2. The MPC representation in (5.1) and (5.2) assumes that the input is administered at every sample and is therefore ideal for use in closed-loop control algorithms for pump treatment in T1D and T2D, see e.g. [62–64].

## 5.2 MPC for once daily injections

In basal insulin treatment, the insulin is administered once daily, while the aim is to keep the glucose concentration between administrations in a desired range. Figure 5.3 (left) illustrates a simulation of *basal glucose* and plasma insulin, given a daily insulin dose, using the *basal glucose* model (2.31). At steady state, the glucose concentration oscillates around the reference of 5 mmol/L, and we thereby have a limit cycle rather than a fixed point, see Figure 5.3 (right). We can therefore not use the same MPC approach as for insulin pump treatment. To handle this we introduce sub-freqency actuation on the input. We define the control period, $h$, and the sampling period, $T_s$, which gives the number of samples in the control period, $m = h/T_s$. Assuming that the input is given at the first sample of each control period, we have the input sequence for $M$ control periods,

$$U_k = \begin{bmatrix} u_k & 0 & \dots & u_{k+m} & 0 & \dots & u_{k+(M-1)m} & 0 & \dots \end{bmatrix}^T \tag{5.3}$$

where $u_i$ is the input of control period $i$. This concept is illustrated in Figure 5.4.

In Appendices I-J we performed an *in silico* proof of concept study on an MPC algorithm with sub-frequency actuation, using the linearized *basal glucose* model (2.31) in the design, with disturbance modelling to detect potential changes in physiology and deviation in the data from the model [74]. The MPC has the penalty function in Figure 5.2, with soft constraints at 4.0-6.0 mmol/L, and penalizes and restricts changes in input. The non-linear *basal glucose* model was used to simulate an *in silico* patient in ten stochastic simulations. We compared its performance with the standard of care approach in Table 2.1, but with a target range of 4.0-6.0 mmol/L.

In this preliminary proof of concept study, we find that theoretically, it is possible to reach the target fasting glucose in only a few days, depending on the tuning of the weights, see Figure 5.5. This is however not necessarily desirable or feasible as 1) too rapid glycaemic control can cause some complications to worsen, e.g. retinopathy, and 2) reaching target immediately would in practice require a perfect physiological model and an accurate estimate of all parameters, which can not be expected in the real world.

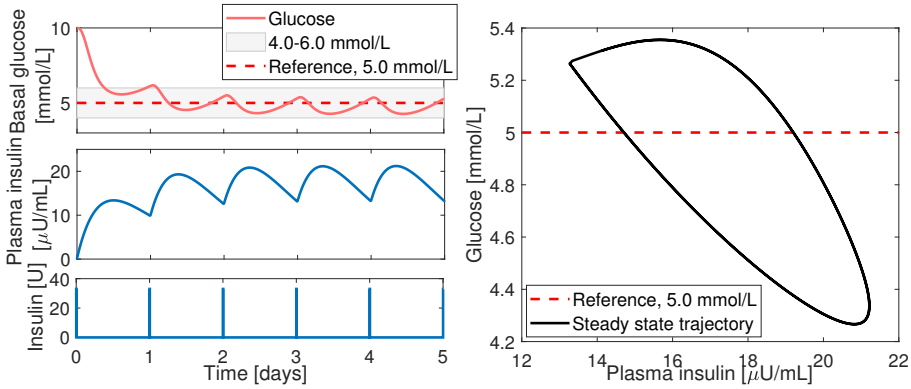


**Figure 5.3:** *Basal glucose* and insulin concentration (left) given the daily dose needed to reach the reference 5 mmol/L. After three days, an approximate steady state is reached. Evolution of *basal glucose* and plasma insulin variability for the last day (right) represents an approximate limit cycle given the constant daily dose.

Note however, more importantly, that to the right in Figure 5.5 the standard of care algorithm overtitrates the insulin, as it does not take the low glucose in the middle of day into account. This is also visible from the case where insulin sensitivity temporarily increases due to, e.g., exercise, see Figure 5.6. This preliminary proof of concept study indicates that due to the MPC algorithm's ability to predict the *basal glucose* concentrations during a day, hypoglycemia can be avoided. Compared to standard of care, which only considers the glucose concentration when it is measured, this provides improved safety.

The results indicate that the standard of care algorithm tended to recommend too high doses, if *basal glucose* values between SMBG measurements are taken into account. This is an important message, as for some patients, lower glucose levels may occur during the day rather than at night or early morning due to, e.g., diurnal fluctuations in insulin sensitivity. The results should however be considered as preliminary, as they compare the MPC to a standard of care algorithm in an idealized case, where the MPC algorithm was initiated with the true parameter values. Before drawing strong conclusions, the design model should adapt to the individual patient and be further tested *in silico*. Using one SMBG measurement to update the prediction model may be too limited, given the noise level of such data. With CGM data, more glucose data becomes available for updating the prediction model. This may furthermore be essential for identifying the *basal glucose* model, such that the difference in lowest glucose concentrations of day and night are captured for each individual.

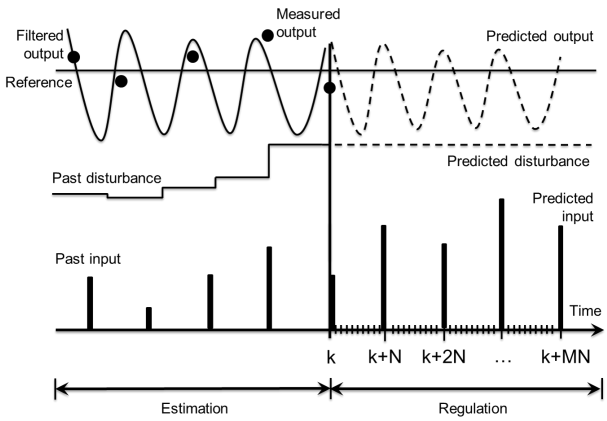


**Figure 5.4:** MPC with sub-frequency actuation

## 5.3 Summary

In this chapter we suggest using an MPC approach to iterative dose guidance. We use the dynamic compartment model of *basal glucose* to design the MPC algorithm, and test the performance in an *in silico* proof of concept study. We observe that the MPC approach has potential compared to standard of care titration algorithms during temporary or prolonged physiological changes. The main advantage is related to the ability to predict the *basal glucose*, the lowest expected glucose within a day, between the pre-breakfast SMBG measurements. The results should however be considered as indicative only, as the *in silico* simulation used the non-linear version of the design model with known parameter values. Although this proof of concept study has limitations, we believe that this work forms a basis for further research within predictive iterative dose guidance.

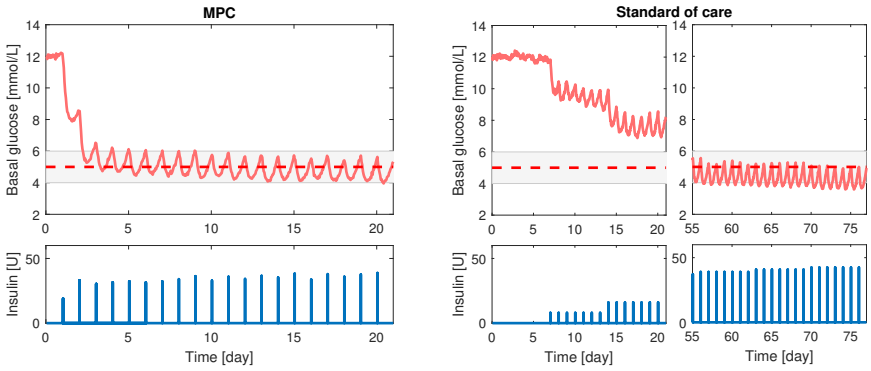


**Figure 5.5:** Insulin initiation with MPC control (left) and standard of care (right). The MPC takes into account the potential low *basal glucose* in the middle of day, while the standard of care misses the low glucose and can cause hypoglycemia.

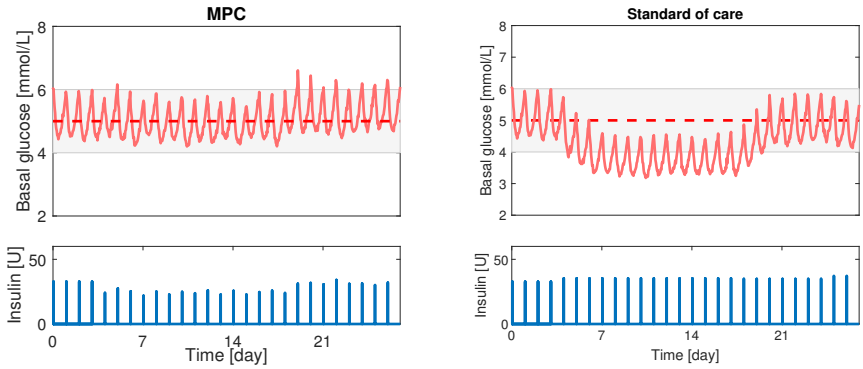


**Figure 5.6:** Insulin sensitivity temporarily increases by 30%. The MPC control (left) avoids low *basal glucose*, while the standard of care (right) does not react to the physiological changes.

Chapter 6

# Conclusion

This work proposes a novel approach to basal insulin initiation in people with T2D, using insulin and glucose data from SMBG and CGM devices. We formulated three research questions; 1) Can a personalized dose response model be established?, 2) Is it feasible to use a dose response model to predict the basal insulin dose needed to reach the clinically recommended fasting glucose target?, and 3) How may a dose response model enable adaptive dose guidance? Relating to the first research question, we proposed a linear dose response model for fasting glucose response to basal insulin. Relating to the second research question, we proposed a method for estimating the dose of IDeg from this model, needed to reach the fasting glucose target. We tested the feasibility of this approach in a clinical study. Relating to the third research question, we finally proposed two adaptive model-based approaches to iteratively reach this dose.

Results of the dose response modelling indicated that a linear model provides the best fit to IDeg response and pre-breakfast SMBG data. The parameter distribution obtained from SMBG and IDeg data from approximately two thousand T2D patients, was similar to the parameters obtained from CGM and IDeg data from the eight participants in our clinical feasibility study. As T2D is a heterogeneous disease, we do not expect this dose response model to fit all people with T2D at all times, but rather as an approximation within the time frame of insulin initiation.

For dose estimation using SMBG and IDeg data, we found that an LSQ approach with a forgetting factor of eight weeks performed best in terms of safety and efficiency. The model was identifiable for 70% of participants provided six weeks of data, where three SMBG data points were available per week. A data driven method, such as the *a posteriori* maximum likelihood approach, requires fewer data points for a significant model identification, while the frequency of dose overestimation is higher. In general, data driven approaches to dose guidance should be used with caution due to the limitations of the training data. In this work, as well as in many clinical databases with high quality data, the data were collected in clinical studies with specific inclusion criteria and protocols, where high adherence to treatment may be expected. In clinical practice, patients' characteristics and demographics, lifestyle, adherence etc. may be different than in the training data, and thereby the data driven dose guidance may not apply.

Results from the clinical feasibility study suggested that dose estimation based on two weeks of CGM and insulin data was feasible and safe. The concept relies on a number of considerations, including 1) a dose that brings the individual's fasting glucose to target exists, 2) the target dose may change over time, 3) the estimated target dose is not necessarily safe early in the treatment and should be used as a target rather than a next dose guidance, and 4) the dose estimation is specific to IDeg and may not be applicable for other basal insulins.

We proposed a dose guidance approach, where the dose estimate from glucose and insulin data, and its uncertainty, are not only communicated to the clinician or participant, but also used to suggest the next safe dose. The approach showed promising results in *in silico* studies compared to standard of care and the IDS algorithm. An adaptive glycemic target, based on variation in glucose concentration, further improved the potential of the method. We observed that the algorithm has a great potential to safely and efficiently bring fasting glucose to target in clinical trials and in a real life setting where adherence is sub-optimal. We believe that only part of the glycemic improvement potential can be indicated by *in silico* studies, as the expected implications of a final dose estimate are improved perception of need, less complexity and fear of hypoglycemia, and thereby improved adherence. This can however only be shown by real world data and not in simulations.

Using insights from the clinical feasibility study, we proposed an MPC-based dose guidance algorithm. The algorithm predicts the lowest expected glucose between pre-breakfast SMBG measurements, and optimizes the amount of IDeg administered daily to maintain glycemic control. In a preliminary proof of concept study we concluded that the MPC-based approach has a potential to improve glycemic outcomes compared to standard of care, while further studies are needed. We believe that this work forms a basis for further research.

## 6.1 Future perspectives and opportunities

This is the first work to our knowledge, where CGM data is used in automated basal insulin initiation. We presented a novel approach to using CGM data, the *titration glucose level*, which reveals low glucose concentrations outside of the traditional SMBG measuring time frame. We believe that this is a new paradigm for safer insulin treatment. In future applications, the relationship between pre-breakfast SMBG and *titration glucose level* may be identified, and used in dose guidance where CGM data is not available.

With availability of CGM data, not only does fasting glucose response to basal insulin become identifiable, but other insights such as need for bolus insulin as well. We believe that the potential for more personalization of treatment is possible from identification of patterns and dynamics in CGM and insulin data. Other indicators may be extractable from CGM data such as whether GLP-1 treatment would be more successful or should be used in combination with the basal insulin treatment.

We proposed a method of automatically determining a personalized glycemic target. The approach minimizes risk of hypoglycemia by adjusting the glycemic target based on variability in the glucose data. Extending this approach to other indicators of glycemic risk such as age, adverse effects and comorbidities, could improve safety even further.

The dose estimation method, as well as the two adaptive dose guidance approaches, are all subject to medical device regulations when used in clinical practice. Before they can be approved for release to market as software components in a medical device, clinical trials must be designed and conducted with the specific purpose of demonstrating their safety and efficacy to health authorities. Alternative black-box data driven approaches such as those developed in the machine learning space are rapidly emerging and provide useful insights when sufficient amounts and quality of data are available. The FDA recently initiated a change in the regulatory paradigm to support approval of such solutions [75]. Despite the opportunities in leveraging machine learning technologies, we believe that white-box and grey-box approaches, as presented here, will continue to play an important role in future digital health to support data collection and dose guidance, due to the simplicity and transparency of input and output, for patients and practitioners alike. And when sufficient amount of data is available for black-box approaches to prove safe, both approaches could be used complementary.

The overall concept of designing treatments based on gut microbiome, genomics and physiological, cellular, molecular or other related characteristics has re-

cently been termed Personalized Medicine. Although the practice of designing treatments based on patient characteristics is not new, recent technological developments has allowed access to data that was previously unavailable in scope and in scale. This project comprises a small yet tangible development in the area of personalized treatment since the proposed methods delivers an individualized and adaptive Insulin treatment based on a set of data that was not previously available in sufficient quality or fidelity.

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# Appendices

Appendix A

# Conference paper

## Model for simulating fasting glucose in type 2 diabetes and the effect of adherence to treatment

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# Model for Simulating Fasting Glucose in Type 2 Diabetes and the Effect of Adherence to Treatment [1]

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**Abstract:** The primary goal of this paper is to predict fasting glucose levels in type 2 diabetes (T2D) in long-acting insulin treatment. The paper presents a model for simulating insulin-glucose dynamics in T2D patients. The model combines a physiological model of type 1 diabetes (T1D) and an endogenous insulin production model in T2D. We include a review of sources of variance in fasting glucose values in long-acting insulin treatment, with respect to dose guidance algorithms. We use the model to simulate fasting glucose levels in T2D long-acting insulin treatment and compare the results with clinical trial results where a dose guidance algorithm was used. We investigate sources of variance and through simulations evaluate the contribution of adherence to variance and dose guidance quality. The results suggest that the model for simulation of T2D patients is sufficient for simulating fasting glucose levels during titration in a clinical trial. Adherence to insulin injections plays an important role considering variance in fasting glucose. For adherence levels 100%, 70% and 50%, the coefficient of variation of simulated fasting glucose levels were similar to observed variances in insulin treatment. The dose guidance algorithm suggested too large doses in 0.0%, 5.3% and 24.4% of cases, respectively. Adherence to treatment is an important source of variance in long-acting insulin titration.



*Keywords:* Biomedical systems, Diabetes, Physiological models, Medical applications, Type 2 Diabetes.

## 1. INTRODUCTION

Patients with type 2 diabetes (T2D) initiating insulin treatment typically inject long-acting insulin once daily to lower fasting glucose (FG) concentration. To determine the individual patients optimal daily dose, patients increase doses based on self-monitored blood glucose (SMBG), until the desired FG level is reached. This process is called titration, and is a delicate procedure. The effect of too little doses of insulin is hyperglycemia. Untreated hyperglycemia can cause long term complications which include cardiovascular disease, neuropathy, kidney damage and other complications. Too high doses of insulin can lead to hypoglycemia. In mild cases, hypoglycemia will cause confusion and seizures. In severe cases it may cause coma or death. The main challenges in insulin titration include complexity of regimen and dose calculations, fear of hypoglycemia, the need for frequent SMBG measurements and lack of confidence (Arnolds et al., 2013). This leads to too seldom dose adjustments and titration can take years if successful at all (Bashan et al., 2011).

To address the need for titration assistance, a number of research and industrial groups have developed automatic algorithms for dose guidance (Bergenstal et al., 2012; Cook et al., 2005; Bajaj et al., 2016). SMBG measurements have been demonstrated to be sufficient to adjust insulin dosage, provided that insulin adjustments are modest (Bergenstal et al., 2012). However, variance in SMBG not only stems from device accuracy but also biological and drug-related day-to-day variance, measuring technique and lifestyle changes. If the measured FG levels are high, the algorithms recommend an increase in insulin dose by a certain amount. Similarly, if the FG is low, the dose is decreased. The algorithms assume that the input, i.e. FG levels, is correlated with the response to the output, i.e. recommended dose. We therefore hypothesize that current titration algorithms are suboptimal with respect to high variance in glucose levels.

The motivation of this paper is to present an overview of the sources of variance in FG levels during insulin initiation and intensification, and to create a simulation model for use in development of safe and effective titration algorithms, and to evaluate the contribution of adherence in FG variance.

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In this paper, Section 2 presents a review and suggested categorization of variances in long-acting insulin titration for T2D patients. In Section 3 we suggest a model of glucose-insulin dynamics to generate a cohort of T2D patients initiating long-acting insulin treatment. In Section 4 we present the results of comparing simulation results with a clinical trial. We also evaluate the effect of adherence on safety in dose guidance. Section 5 presents a short conclusion of the methods and results.

## 2. SOURCES OF VARIANCE

A key challenge in adaptive glucose control is to determine dose sizes based on data with large day-to-day variability. Variability is caused by different factors, and some are easier to mitigate than others. Lifestyle and physiological state are closely related, and the sources of variance are therefore difficult to completely separate. Kildegaard et al. (2009) divided sources of variance in T1D into five categories; metabolic, insulin, glucose monitoring and meal variability, and lifestyle and compliance. Here we divide sources into three categories, each discussed in the following subsections; 1) metabolic variability including insulin variability, 2) variations due to lifestyle and adherence and 3) device related variability.

### *2.1 Metabolic variability*

Glucose metabolism depends on the physiological state of the body. Stress causes the release of a number of hormones that elevate glucose levels, while exercise and weight loss increase insulin sensitivity (Guthrie and Guthrie, 2009).

*Non-insulin related variability*
Research groups have previously investigated day-to-day and intraday glucose variability in patients with T2D. In a study by Ollerton et al. (1999), day-to-day FG variability in newly diagnosed T2D patients not receiving diabetes medication was approximately 14%. They also found that high levels of FG are correlated with higher glucose variance.

Studies on healthy humans have suggested that daily fluctuations in insulin sensitivity contribute to variations in glucose uptake. For instance, Gibson and Jarrett (1972) found that fall in blood sugar following doses of 0.05-0.1 IU/kg was significantly less for normal weight humans in the afternoon than in the morning. The observed difference was around 0.5-1.0 mmol/L. For obese individuals, their results suggested that this difference decreased with higher weight.

*Insulin related variability*
Basal insulin preparations act in different ways, and have different pharmacokinetic (PK) and pharmacodynamic (PD) characteristics. Some long acting insulin types crystallize subcutaneously (SC) after injection, and slowly dissolve to enter the blood stream. These insulins are prone to high day-to-day PK/PD variability due to great variability in the break-down process. Newer insulins allow less variability by forming soluble chains in the skin, which then slowly release insulin into the circulation, (Heise et al., 2012). Fig. 1 illustrates day-to-day coefficient of variation

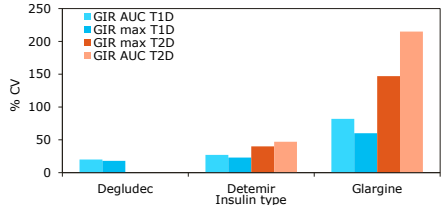


Fig. 1. Day-to-day CV in pharmacodynamics of degludec, detemir and glargine. GIR AUC and GIR max are glucose infusion rate area under the curve and maximum value (Heise et al., 2012; Klein et al., 2007).

(CV) in PD for T1D and T2D, for a number of long acting insulins on the market. For glargine, the CV is around 150% for maximum glucose infusion rate (GIR), while for detemir it is reduced to around 40%. The variations in T2D are greater than in T1D for detemir and glargine, but no data is available for degludec in T2D.

One source of variation during insulin treatment initiation is the dawn phenomenon. Extensive studies have shown that it is a frequent event across the population of T2D patients on oral treatment (Monnier et al., 2013). In a clinical trial with T2D patients on metformin only, glucose levels were monitored overnight while initiating and intensifying insulin treatment. The results showed that in non-insulin treated patients, FG levels increased overnight by approximately 20 mg/dl over 4-5 hours. However, after 6 months of insulin treatment intensification the phenomenon was eliminated (Monnier et al., 2013). Therefore its effect are only apparent early in the treatment. Degludec is ultra-long acting insulin with a half-life of over 25 hours. The long half-life causes the drug to reach steady state after 2-3 days, (Heise et al., 2015). This means that there is day-to-day variance in the FG measurements following a dose size change, and the full response to a new dose size is reached in 2-3 days. The overlap decreases random variation which, theoretically, results in a more stable treatment. Additionally, forgetting a dose is less critical than with previous drugs due to the long overlap from the previous injections (Haahr and Heise, 2014).

### *2.2 Lifestyle and adherence*

Basal insulin treatment is complex and requires extensive work from the patient. For many patients, this is a disruption of life prior to diagnosis, where they are required to manage dose calculations and daily do SMBG and injections. A study that investigated variance in glucose levels of T2D subjects on stable basal insulin doses, observed a total CV in FG of 35%. The results indicated that factors including consumption of sugars and adherence to treatment were highly correlated with FG variance, explaining 21% of the CV, (Murata et al., 2004). Furthermore, insulin sensitivity is correlated with level of activity, stress and illness, and thereby glucose levels.

*Adherence*
Adherence to treatment is essential to successful glycemic control and collecting reliable data on the level of adherence is difficult (Cramer and Pugh, 2005).

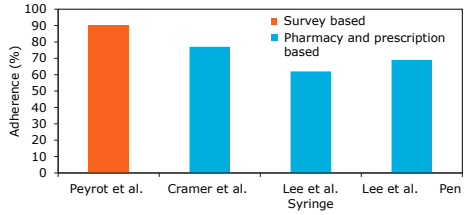


Fig. 2. Adherence measured as percentage of doses taken compared to regimen (Cramer and Pugh, 2005; Lee et al., 2006; Peyrot et al., 2012).

In a study by Peyrot et al. (2012) based on an Internet survey of physicians and diabetes patients, around 30% of patients reported insulin omission 3.3 days in the last month, and around 75% of physicians reported that their patients on average omitted basal insulin 4.3 days per month. A total rate of omission was estimated to be 3.1 days, which corresponds to approximately 90% adherence to once-daily insulin treatment. Another study used pharmacy databases and prescription data and found that insulin use was 77% of the prescribed amount. They furthermore found that significant predictors for adherence included HbA1c levels, race and treatment intensity (Cramer and Pugh, 2005). Another study on adherence based on pharmacy and clinic databases found that adherence was 62-69% based on injection device (Lee et al., 2006). Fig. 2 illustrates a summary of results from three studies using different methods to measure adherence.

*Lifestyle*
Physical activity increases insulin sensitivity. In a study where insulin sensitivity and level of physical activity in untreated T2D patients was investigated, insulin sensitivity was 8% and 25% higher for those who did some moderate and vigorous exercise than sedentary patients, respectively, (Balkau et al., 2008). This is in line with a review of studies on people with T2D, where changes in insulin sensitivity were found to be 23% - 35% after 2 weeks of aerobic training. However, the determining factor of insulin sensitivity is the total daily activity rather than time spent sedentary or doing intensive exercise (Mann et al., 2014).

In a study of FG in T2D patients on stable basal insulin doses, the relationship between variance and meal habits was investigated. No difference in CV was observed between subjects with and without regular mealtimes, or those who sometimes missed meals. CV was however greater in those who consumed more sugars (Murata et al., 2004).

### 2.3 Device related variability

Standards for accuracy of injection and measurement devices exist (ISO 11608-1:2014, ISO 15197:2013). These standards have tight ranges of accuracy, and need to be reported fulfilled before the devices go to market. However, when in the hands of health care professionals or patients in daily settings, the quality of measurements is different from what is reported in the lab.

*Glucose monitoring*
Kjome et al. (2010) compared the ISO 15197:2003 with the difference in pharmacy and patient blood glucose measurements. The limits recommended in the standard from 2003 were ±20% for glucose levels equal or over 4.2 mmol/L and ±0.83 mmol/L for lower values. They found that 5% of patients' measurements deviated by more than the recommended 20% from the pharmacy's measurements. They furthermore observed failure to comply with performance guidelines for 50% of the patients. The user errors included failure to clean hands, sampling technique, validity of sampling strips and amount of blood used.

Kildegaard et al. (2009) listed a number of similar studies, for SMBG monitors and continuous glucose monitoring (CGM) devices. They found that the percentage of measurements falling outside the ISO standard for the different monitoring devices varied from under 5% up to around 30%, and CGM measurements showed higher errors. It should be mentioned that even though CGM measurements had larger errors, they provide useful insights into glycemic trends and variations (Kildegaard et al., 2009).

*Insulin pens*
Accuracy of insulin pens as a source of variance is discussed in e.g. Kildegaard et al. (2009). Insulin pens have shown to have a CV of approximately 2%, when giving a dose of 5U. At large doses, the CV is close to or less than 1%. Heise et al. (2014) studied the impact of volume and speed of subcutaneous injections on perceived pain. They found that backflow after injection was less than 1% CV. Combined with the dosing accuracy of insulin pens, this amount of variance is not likely to be clinically relevant.

## 3. SIMULATING A COHORT OF T2D PATIENTS

We use the Medtronic Virtual Patient (MVP) model developed by Kanderian et al. (2009) and a meal subsystem described by Hovorka et al. (2004) to simulate a population of virtual T1D patients, and augment this model with an endogenous insulin production compartment to simulate T2D (Ruan et al., 2015). We introduce a method for simulating injections of long-acting insulin in a simulation model intended for pump simulations. The ambition of this model is to represent FG levels in T2D long-acting insulin treatment.

### 3.1 Type 1 diabetes model

We use two meal compartments, $D_1$ [mmol] and $D_2$ [mmol], equivalent to what is described by Hovorka et al. (2004), to describe orally ingested carbohydrates,

$$\frac{dD_1(t)}{dt} = D(t) - \frac{D_1(t)}{\tau_m}, \tag{1a}$$

$$\frac{dD_2(t)}{dt} = \frac{D_1(t)}{\tau_m} - \frac{D_2(t)}{\tau_m}. \tag{1b}$$

$\tau_m$ [min] is the peak time of absorption. $D(t)$ [mmol/min] is the amount of ingested carbohydrates per minute. Given the amount of orally ingested carbohydrates $d(t)$ [mg/min], $D(t) = A_G \frac{d(t)}{MwG}$ where $MwG = 180.1559$ [g/mol] is molar weight of glucose and $A_G$ is the unit less CHO bioavailability. We assume 100% bioavailability, $A_G = 1$.

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The MVP model is derived from the Bergman minimal model (Bergman et al., 1981). The model consists of four compartments, as described in Kanderian et al. (2009). The insulin absorption subsystem is described by two compartments, $I_{SC}$ [mU/mL] and $I_P$ [mU/mL],

$$\frac{dI_{sc}(t)}{dt} = \frac{1}{\tau_1}\frac{U(t)}{C_I} - \frac{1}{\tau_1}I_{sc}(t), \tag{2a}$$

$$\frac{dI_p(t)}{dt} = \frac{1}{\tau_2}I_{sc}(t) - \frac{1}{\tau_2}I_p(t), \tag{2b}$$

where $U(t)$ [mU/min] is the amount of infused fast acting insulin per minute, $C_I$ [mL/min] is the insulin clearance rate and $\tau_1$ and $\tau_2$ [min] are time constants of insulin flow from injection site to plasma and from plasma and out.

Insulin effect on glucose, $I_{EFF}$ [1/min], and blood glucose concentration, $G$ [mmol/L], are described by

$$\frac{dI_{eff}(t)}{dt} = p_2 S_I I_p(t) - p_2 I_{eff}(t), \tag{3a}$$

$$\frac{dG(t)}{dt} = -(GEZI + I_{eff}(t))G(t) + EGP + R_A, \tag{3b}$$

where $p_2$ [1/min] is the delay in insulin action after increase in plasma insulin. $S_I$ [mL/mU/min] represents insulin sensitivity. $GEZI$ [1/min] counts for the effect of glucose to lower endogenous glucose production at zero insulin. $EGP$ [mmol/L/min] is the endogenous glucose production rate. $V_G$ [L] is the glucose distribution volume. Rate of appearance of ingested glucose in plasma is $R_A = \frac{D_2(t)}{V_G \tau_m}$ [mmol/L/min].

### 3.2 Type 2 diabetes augmentation

Ruan et al. (2015) developed six models to describe endogenous plasma insulin concentration based on plasma glucose concentration. We use the base model which assumes constant parameters throughout the day,

$$I_{ENDO}(t) = \frac{M_I(G(t) - G_b) + M_0 G_b}{MCR_I W} \tag{4}$$

$I_{ENDO}$ [mU/L] is the endogenous plasma insulin concentration. $I_S(t)$ [mU/min] is the posthepatic insulin secretion rate. $MCR_I$ [L/kg/min] is the insulin metabolic clearance rate. $W$ [kg] is the subject's body weight. $G$ [mmol/L] is the plasma glucose concentration and $G_b$ [mmol/L] is the fasting plasma glucose concentration. $M_I$ [mU/min/(mmol/L)] is the posthepatic glucose sensitivity and $M_0$ [mU/min/(mmol/L)] is the basal glucose sensitivity.

This base model assumes a linear relationship between the rate of posthepatic insulin secretion and plasma concentration. The endogenous insulin is added to the insulin in plasma, to affect glucose concentration, so (3a) becomes

$$\frac{dI_{eff}(t)}{dt} = p_2 S_I (I_p(t) + I_{ENDO}(t)) - p_2 I_{eff}(t). \tag{5}$$

To simulate a cohort of 270 patients, we adjust insulin sensitivity and body weight of the first nine patients identified in the MVP model (Kanderian et al., 2009) and choose from the identified parameters of the T2D augmentation (Ruan et al., 2015). The parameter adjustments and choices are listed in Table 1. We use the maximum of average GIR profiles of insulin degludec in T1D and T2D to adjust insulin sensitivity, $S_I$ in the MVP model to represent T2D patients. From results by Haahr and Heise (2014), three hours after injection the maximum GIR of T2D patients is approximately 50% of the maximum GIR of the T1D patients. We choose to adjust insulin sensitivity by 30% to 70%, see Table 1. Similarly we adjust weight based on average BMI values of the patients randomized in the two studies discussed in (Haahr and Heise, 2014), and by assuming equal height of participants. Table 1 presents the body weight adjustments. Distribution volume of glucose is determined by a linear least squares fit, $V_G = aW + b$, using the parameters in Kanderian et al. (2009).

Table 1. Choice of parameter adjustments of the MVP model as defined in Kanderian et al. (2009) and chosen parameter values of the T2D augmentation from Ruan et al. (2015).

| Parameter | | Value/Adjustment |
|---|---|---|
| $S_{I,T2D}$ | [mL/mU] | $[0.3, 0.4, 0.5, 0.6, 0.7] \times S_I$ |
| $W_{T2D}$ | [kg] | $[1.1, 1.2, 1.3, 1.4, 1.5, 1.6] \times W$ |
| $MCR_I$ | [L/kg/min] | 0.013 |
| $G_b$ | [mmol/L] | 7.0 |
| $M_I$ | [mU/min/(mmol/L)] | 0.0 |
| $M_0$ | [mU/min/(mmol/L)] | 0.7 |

Ruan et al. (2015) present the parameters of complex endogenous augmentation models where parameters are assumed to change during the day. Since here the purpose of the simulation model is to use it in simulating basal insulin titration, which is based on FG measurement, we use the parameters corresponding to the night. The parameters are presented in the bottom three lines of Table 1.

### 3.3 Long-acting insulin injection

The parameters of the MVP model are fitted to simulate fast acting insulin for simulation of pump infusion. In order to simulate a long-acting insulin injection, we used the PK profile of degludec described by Heise et al. (2012) to define an infusion profile. Degludec has stable PK exposure and glucose-lowering effect over 24 hours, and is detectable in the serum for at least 120 h post-dosing. We simulate the insulin action profile of an injection, $U$, as follows,

$$u(t) = u_0 \qquad \text{if } t \le t_0, \tag{6a}$$

$$u(t) = u_0 e^{(t_0 - t)/\tau} \qquad \text{if } t > t_0, \tag{6b}$$

where $t_0$ is 12 hours, $\tau$ is 35 hours and $u_0 = U/(t_0 - t)W$.

## 4. RESULTS

### 4.1 Comparison with clinical trial data

We simulate a titration period of 26 weeks, where basal insulin dose is adjusted corresponding to the algorithm presented in Table 2. This setup is similar to a clinical trial of insulin degludec in T2D (Zinman et al., 2012). We add variance to the simulated FG by setting

$$\hat{FG}_t = FG_t + v_t, \tag{7}$$

where $\hat{FG}_t$ and $FG_t$ are simulation with and without biological noise $v_t$, respectively. In the simulations we assume a best case scenario where no insulin is omitted and biological variance is at minimum. We set $v_t \sim N(0, (0.14FG_t)^2)$

Table 2. The titration algorithm used in a titration study by Zinman et al. (2012). Dose adjustments are based on average FG of three days above target, or the lowest below target.

| FG [mmol/L] | Dose adjustment |
|---|---|
| $< 3.1$ | -4U |
| $3.1 - 3.9$ | -2U |
| $4.0 - 5.0$ | In target: no change |
| $5.1 - 7.0$ | +2U |
| $7.1 - 8.0$ | +4U |
| $8.1 - 9.0$ | +6U |
| $> 9.0$ | +8U |

since the standard deviation in untreated T2D discussed in Section 2 is 14%. Fig 3 illustrates a comparison of FG levels and the clinical trial results. Considering the two solid lines, the clinical trial results and simulation results assuming 100% adherence, both fall within one standard deviation of the other. Furthermore, the dynamics of average FG of the cohort are similar. The results indicate that the simulation results can be used to represent changes in FG over a titration period in a clinical trial with similar starting values, patient characteristics and dose guidance.

### *4.2 Effect of adherence on variability and safety*

To evaluate the effect of adherence on variations in FG and safety of dose guidance, we simulate a similar titration period as before but with different levels of adherence. From Fig. 2, adherence is reported to be between 60% and 90%. We choose to simulate three adherence levels, 50%, 70% and 100%, to represent three levels of adherence. Fig. 3 illustrates the FG values in the three adherence scenarios compared with the clinical data. To evaluate safety of dose guidance in the different scenarios, we measure:

- Number of FG measurements under 4 mmol/L ($FG < 4$) and 2.7 mmol/L ($FG < 2.7$).
- Glycemic coefficient of variation ($FG$ CV).
- Number of times where recommended dose, $U_r$, is greater than a dose that would have brought FG under 4 mmol/L, ($U_r > U_4$), and 2.7 mmol/L, ($U_r > U_{2.7}$).

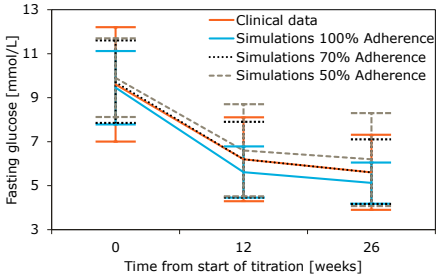


Fig. 3. Results from a clinical trial (Zinman et al., 2012) and simulations of 270 T2D patients. The results represent the same drug, the same titration algorithm, and similar inclusion criteria.

Table 3. Results from a simulated titration period of 26 weeks for adherence levels 50%, 70% and 100% (mean (standard deviation)).

| Measure | | Adherence 50% | 70% | 100% |
|---|---|---|---|---|
| $FG < 4$ | [%] | 7.7 (7.7) | 6.8 (7.1) | 4.9 (4.3) |
| $FG < 2.7$ | [%] | 0.4 (0.9) | 0.1 (0.4) | 0.0 |
| $FG$ CV | [%] | 30.1 (5.6) | 28.1 (3.7) | 21.6 (2.1) |
| $U_r > U_4$ | [%] | 24.4 (27.5) | 5.3 (13.8) | 0.0 |
| $U_r > U_{2.7}$ | [%] | 0.2 (1.1) | 0.0 | 0.0 |

The results are presented in Table 3 as the percentage of days out of 26 weeks where the events listed above occur. The results indicate a difference in FG variance of the 270 patients in the three adherence scenarios. Coefficient of variation is 21.6%(2.1%) where no doses were omitted, 28.1%(3.7%) for 70% adherence and 30.1(5.6) for 50% adherence. Similarly, the results indicate that the number of times where a recommended dose $U_r$ was larger than a dose that would lower FG below target, $U_4$. This never occurred in the perfect adherence case, but 5.3%(13.8%) and 24.4%(27.5%) of recommended doses for 70% and 50% adherence, respectively. However, there does not seem to be a difference in number of hypoglycemic events. A possible explanation could be when a too large dose is recommended but not injected, it will not cause hypoglycemia.

In the simulations of different adherence levels, we find that FG has a coefficient of variation between 20% and 30% on average. This is lower than the 35% mentioned in Section 2. It must be pointed out that this simulation only assumes 14% biological variance in FG and does not take PK/PD variance into account.

## 5. CONCLUSIONS

This paper presents a review of sources of variance in long-acting insulin treatment for T2D patients and suggests a categorization. Biological variance caused by PK/PD of insulin varies greatly between types of basal insulin. Accuracy of devices is a minor factor compared with other variance sources including biological variance and adherence to treatment. It should be noted that the group of T2D patients more heterogeneous than T1D. Categorizing sources of variability in T2D is not necessarily as simple as for T1D, as it may be different depending on the severity of the disease.

We suggest a model of glucose-insulin dynamics to generate a cohort of T2D patients initiating long-acting insulin treatment. The results indicate that the model is sufficient to simulate FG levels of T2D patients in-silico during a long-acting insulin titration period. Results from comparing dose suggestions and FG levels in different adherence scenarios indicate that dose guidance algorithms should take adherence into account to ensure safe dose guidance. We should furthermore mention that adherence is evidently crucial to reaching recommended goals in insulin treatment. We have shown that adherence is essential to safe treatment when using dose guidance algorithms.

The motivation for creating this model was to simulate FG values in T2D during a titration period. For the purpose of bolus calculations and more detailed meal

simulations, the model parameters related to carbohydrate uptake should be refined. Also the choice of endogenous insulin production model should be improved to allow daily fluctuations.

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Appendix B

# Conference paper

## Modelling of glucose-insulin dynamics from low sampled data

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# Modelling of glucose-insulin dynamics from low sampled data ⋆

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**Abstract:** In this paper we focus on modelling the glucose-insulin dynamics in the human body for the purpose of controlling the glucose level. Due to the fast dynamics in the glucose-insulin system compared to the natural sampling period (24 h) in a clinical situation, the model structure has to be adapted adequately. This results in a reduced order model with a non-linear output relation. The development of the estimation methodology is based on a simulation study with a continuous time model. The resulting model structure is used for estimating the parameters of the non-linear system, representing the slow dynamics observed from the slow and sparse sampled clinical data.



*Keywords:* System identification, reduced order models, glucose-insulin dynamics, diabetes control.

## 1. INTRODUCTION

Diabetes is a chronic condition characterized by raised levels of glucose in the blood, hyperglycemia. The condition affects more than 425 million people today and the numbers are expected to rise to 693 million by 2045 [International Diabetes Federation 2017]. Poorly managed diabetes can lead to cardiovascular diseases, lower limb amputation, blindness and kidney failure. The American Diabetes Association estimates that care for people with diabetes accounts for more than 20% of all health care expenditure in the U.S. [Petersen 2016]. Type 2 diabetes accounts for 90% of all diabetes cases. In type 2 diabetes, the elevated glucose levels are caused by inadequate production and response to the hormone insulin. As opposed to type 1 diabetes, a congenital disease with quick onset most commonly in children, type 2 diabetes is most commonly diagnosed in older adults. But with increased prevalence of obesity, less physical activity and poor diet, type 2 diabetes is becoming more common in young adults, children and adolescents.

When treating type 2 diabetes, a first attempt is through lifestyle changes. This is followed by oral medication if increased physical activity and change in diet is not adequate. When these treatments fail, insulin injections may be needed. There are two main types of insulins, long acting insulin to lower fasting glucose levels, and fast acting insulin to lower glucose levels following food intake. Standards of Medical Care in Diabetes recommend starting with long acting insulin treatment, and adding fast acting insulin if glucose values are still too high [American Diabetes Association 2017]. In this paper, we focus on treatment of type 2 diabetes with long acting insulin, specifically initiation of the long acting insulin treatment.

Initiating long acting insulin treatment is an iterative process since response to insulin is individual. Too large doses of insulin can cause low blood glucose, hypoglycemia, which in severe cases can lead to coma and even death. Health care professionals prescribe small doses and increase dose sizes over time, based on self-monitored blood glucose (SMBG), until a target glucose level is reached. SMBG measurements are glucose measurements performed by the patients by finger-pricking. Doses of long acting insulin are adjusted based on SMBG measurements performed in a fasting state, typically before breakfast. The rules by which health care professionals change dose sizes are typically represented by simple tables that do not account for the great inter-patient variability. Therefore, insulin initiation can take months to years, and in the U.S., more than 60% of type 2 diabetes patients on insulin treatment do not reach recommended treatment goals [Wong et al. 2012].

In this paper, we wish to understand the behaviour of fasting glucose in response to long acting insulin, through a physiological model of the glucose-insulin regulatory system. Physiological models of healthy humans and people with type 1 and type 2 diabetes exist. Most models are based on the Bergman minimal model [Bergman et al. 1979, Toffolo et al. 1980], but they vary in purpose and level of complexity. A number of models have been developed to simulate the regulatory system in type 1 diabetes, due to high interest in closed-loop control for this

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patient group [Kanderian et al. 2009, Hovorka et al. 2004, Dalla Man et al. 2007]. Jauslin et al. [2011] published a model for 24-hour modelling of insulin and glucose profiles in type 2 diabetes which Røge et al. [2014] used to further build a model to simulate effect of a specific type of insulin. These models are similar in that their purpose is 24-hour modelling where fast dynamics, such as increase in glucose due to meals, are well captured. In the current work we are interested in slower dynamics, as we work with fasting glucose and long acting insulin. Aradóttir et al. [2017] published a model for simulating fasting glucose during long acting insulin treatment. This model is based on a type 1 diabetes model by Kanderian et al. [2009] with an endogenous insulin production model by Ruan et al. [2015] to simulate type 2 diabetes. This model used parameters from literature, and here we wish to identify parameters from clinical data.

In Section 2 we outline the problem statement and describe important features of relevant clinical data. In Section 3 we adjust a detailed physiological model such that important parameters are identifiable from available clinical data with low sampling frequency. In Section 4 we discuss identifiability and list results from model identification based on simulated and clinical data.

## 2. STATEMENT OF THE PROBLEM

In this work we want to create a physiological model of insulin-glucose dynamics in type 2 diabetes. The purpose of this model is for control design for dose guidance in long acting insulin treatment. Such a model should have a physical interpretation, and parameter estimates based on data from a group of patients to capture variability in the patient population.

Clinical trials investigating new drugs are classified into different phases, and vary in purpose and number of participants. The first phases include only a few participants in the clinic, typically healthy volunteers, primarily aimed at testing for safety. Phase II and III studies test for efficacy and effectiveness, include hundreds or a few thousand patients and data is logged in the clinic or at home.

In Phase II and III studies on long acting insulin, glucose measuring frequency is typically one per day and sparse. The low data frequency is insufficient to identify detailed state-of-the-art models, such as the ones by Hovorka et al. [2004] or Kanderian et al. [2009]. For illustration, Figure 1 shows a four day simulation using the Kanderian et al. [2009] model, and glucose measured pre-breakfast (fasting).

Furthermore, excitation of the system in clinical trials is limited due to safety issues. Large doses of insulin can lead to hypoglycemia (too low blood glucose), a dangerous state which can lead to death. Therefore data illustrating insulin-glucose dynamics for glucose levels below 3.9 mmol/L (clinical hypoglycemia, International Hypoglycaemia Study Group [2016]) are rare.

## 3. MODEL STRUCTURE

We use the model by Kanderian et al. [2009], augmented in Aradóttir et al. [2017], as a starting point. We investigate which parameters are identifiable in long acting insulin treatment in an *in silico* setting, and finally consider whether this is applicable *in vivo*.

### 3.1 Base model

The following model, from Kanderian et al. [2009], describes insulin-glucose dynamics in type 1 diabetes in four re-named compartments, where the two-compartment meal model has been excluded,

$$\frac{dx_1}{dt} = \frac{1}{p_1}\frac{u}{p_2} - \frac{1}{p_1}x_1 \tag{1a}$$

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

$$\frac{dx_3}{dt} = p_3 p_4 x_2 - p_3 x_3 \tag{1c}$$

$$\frac{dx_4}{dt} = -(p_5 + x_3)x_4 + p_6 \tag{1d}$$

After changing units to L, U, days and mmol (respectively from mL and dL, $\mu$U, min and mg), $u$ is exogenous insulin [U/day], $x_1$ and $x_2$ denote subcutaneous and plasma insulin concentrations [U/L], respectively, $x_3$ is insulin effect [1/day] and $x_4$ is glucose concentration in plasma [mmol/L]. $p_1$ is a time constant describing transfer of insulin from the insulin delivery site, subcutaneous compartment, to plasma [day], $p_2$ is a gain describing insulin clearance [L/day], $p_3$ is an inverse time constant describing delay in insulin action following increased insulin concentration in plasma [1/day], $p_4$ is a gain describing insulin sensitivity [L/U·day], $p_5$ is an inverse time constant describing the effect of glucose at zero insulin to eliminate glucose from plasma [1/day] and $p_6$ is a contant input describing rate of endogenous glucose production [mmol/L·day].

Ruan et al. [2015] suggested a number of models for endogenous insulin production in type 2 diabetes, as a

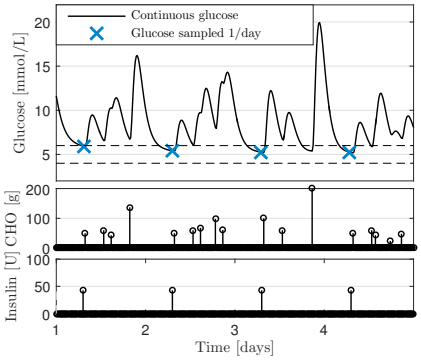


Fig. 1. Four days of simulated glucose data where carbohydrates (CHO) are ingested during the day and long acting insulin is injected bre-breakfast. The blue glucose curve indicates a full evolution of glucose concentration during the period, while the red markers indicate pre-breakfast measured glucose. The dashed lines indicate target range for fasting glucose.

Table 1. Parameter values for the base model (2). Mean (sd) for $p_2 - p_6$ as presented in Kanderian et al. [2009], and chosen or derived parameter values for $p_1$ and $p_7$.

| Parameter | Unit | Mean (Standard deviation) |
|---|---|---|
| $p_1$ * | [day] | 0.5 |
| $p_2$ | [L/day] | 1800 (760) |
| $p_3$ | [1/day] | 15.8 (6.2) |
| $p_4$ | [L/U·day] | 792 (560) |
| $p_5$ | [1/day] | 3.31 (3.17) |
| $p_6$ | [mmol/L·day] | 96.7 (63.1) |
| $p_7$ † | [U/mmol] | $1.4\times10^{-3}$ |

function of glucose concentration. The simplest model consists of two parts, a basal rate and a linear increase in production with elevated glucose levels. In this work, we assume a linear relationship between glucose and insulin production, so (1) becomes

$$\frac{dx_1}{dt} = \frac{1}{p_1}\frac{u}{p_2} - \frac{1}{p_1}x_1 \tag{2a}$$
$$\frac{dx_2}{dt} = \frac{1}{p_1}x_1 - \frac{1}{p_1}x_2 \tag{2b}$$
$$\frac{dx_3}{dt} = p_3p_4(x_2 + p_7x_4) - p_3x_3 \tag{2c}$$
$$\frac{dx_4}{dt} = -(p_5 + x_3)x_4 + p_6 \tag{2d}$$

where $p_7$ is a parameter describing glucose sensitivity of the insulin producing cells in the pancreas [U/mmol] and insulin production is assumed to increase linearly with fasting glucose. We refer to this model as the Base model.

To determine which parameters are identifiable, and for in silico data generation, we use parameter values published by Kanderian et al. [2009]. The time constant $p_1$ in this paper describes fast acting insulin, and can therefore not be used here. We choose a value for $p_1$ to roughly describe long acting insulin-glucose dynamics. The parameter describing glucose sensitivity of insulin production is a result of the other parameters, chosen such that fasting glucose has a specific value, $x_4(t=0) = x_{4,0}$. Setting the last two equations of (2) equal to zero, $x_1 = x_2 = 0$ and rewriting, we get

$$p_7 = \frac{1}{p_4x_{4,0}}\left(\frac{p_6}{x_{4,0}} - p_5\right) \tag{3}$$

which is used to determine the value for $p_7$ based on the mean values of the other parameters.

### 3.2 Modification for identifyability

The area of greatest interest is around the target glucose values, ranging from approximately 4 to 6 mmol/L. Values for $x_3$ in this area are of order 10. Typical values for $p_5$ range from an order of $10^{-5}$ to 1. We therefore neglect this inverse time constant as it is small relative to the dynamic inverse time constant $x_3$. The Base model (2) has two gains, insulin clearance rate $p_2$ and insulin sensitivity $p_4$. Considering the assumptions in Section 2, data from clinical trials will only contain insulin input, $u$, and glucose measurements, $x_4$. Therefore only one gain is identifiable.

We rewrite the model by setting $\tilde{x}_1 = x_1p_2$ [U/day], $\tilde{x}_2 = x_2p_2$ [U/day], $\tilde{x}_3 = x_3p_2/p_4$ [U/day], $\tilde{p}_7 = p_7p_2$ [U·L/mmol·day] and the modified model becomes

$$\frac{d\tilde{x}_1}{dt} = \frac{1}{p_1}u - \frac{1}{p_1}\tilde{x}_1 \tag{4a}$$
$$\frac{d\tilde{x}_2}{dt} = \frac{1}{p_1}\tilde{x}_1 - \frac{1}{p_1}\tilde{x}_2 \tag{4b}$$
$$\frac{d\tilde{x}_3}{dt} = p_3(\tilde{x}_2 + \tilde{p}_7x_4) - p_3\tilde{x}_3 \tag{4c}$$
$$\frac{dx_4}{dt} = -\tilde{p}_4\tilde{x}_3x_4 + p_6 \tag{4d}$$

where we have reduced to one gain, a ratio between the two original gains, $\tilde{p}_4 = p_4/p_2$ [1/U].

### 3.3 Discretization and model reduction

In order to determine whether the model can be reduced, we linearize the system and investigate properties of a discretization of the system. We linearize the modified model (4) such that

$$\dot{\mathbf{x}}(t) = A\mathbf{x}(t) + Bu(t), \quad \mathbf{x}(t_0) = \mathbf{x}_0$$
$$y(t) = C\mathbf{x}(t)$$

where

$$A = \begin{bmatrix} -\frac{1}{p_1} & 0 & 0 & 0 \\ \frac{1}{p_1} & -\frac{1}{p_1} & 0 & 0 \\ 0 & p_3 & -p_3 & p_3\tilde{p}_7 \\ 0 & 0 & -\tilde{p}_4x_{4,ss} & -\tilde{p}_4x_{3,ss} \end{bmatrix}$$
$$B = \begin{bmatrix} \frac{1}{p_1} & 0 & 0 & 0 \end{bmatrix}^T, \quad C = [0\ 0\ 0\ 1]$$

and $x_{4,ss}$ and $x_{3,ss}$ are steady state values. In this work we linearize around $x_{4,ss} = 5$ mmol/L. All eigenvalues of the matrix $A$ have negative real parts, and the system is asymptotically stable.

Discretizing this system yields

$$\mathbf{x}_{k+1} = A_d\mathbf{x}_k + Bu_k$$
$$y_k = C_d\mathbf{x}_k$$

where

$$\begin{bmatrix} A_d & B_d \\ 0 & I \end{bmatrix} = \exp\left(\begin{bmatrix} A & B \\ 0 & 0 \end{bmatrix}T_s\right), \quad C_d = C$$

and $T_s$ is the sampling frequency. Since in Section 2 we assume that the sampling frequency is 1/day, we investigate eigenvalues of $A_d$ for $T_s = 1$ day for the mean parameter values in Table 1. We observe that the real part of two eigenvalues are close to zero. This means that some time constants are not identifiable, and we may want to assume that two compartments reach steady state immediately. In the next section we residualize the modified model (4).

### 3.4 Residualized model

From Table 1 we observe that $1/p_3 = 0.06$ [day] which is of an order lower than $p_1$ and small compared to $T_s = 1$ day. We perform residualization for model reduction as

* $p_1$ is roughly assessed based on knowledge about long acting insulin, e.g. Heise et al. [2017] describe a half-life of approximately 24 hours.

† $p_7$ is an estimated parameter from mean parameter values. In this work we set $x_4(0) = 8$ mmol/L. This may however be chosen to fit the actual fasting glucose level at zero insulin input.

presented by Skogestad and Postlethwaite [1996], and start by assuming that the compartment $\tilde{x}_3$ reaches steady state immediately following change in $\tilde{x}_1$, $\tilde{x}_2$ and $x_4$. Setting (4c) to zero yields

$$\tilde{x}_{3,ss} = \tilde{x}_2 + \tilde{p}_7 x_4 \tag{5}$$

Inserting (5) into (4d) gives

$$\begin{aligned} \frac{dx_4}{dt} &= -\tilde{p}_4\tilde{p}_7 x_4^2 - \tilde{p}_4\tilde{x}_2 x_4 + p_6 \\ &= -(\tilde{p}_4\tilde{p}_7 x_4 + \tilde{p}_4\tilde{x}_2)x_4 + p_6 \end{aligned} \tag{6}$$

The value for $x_{2,ss}$ around the area of interest, $x_4 \in [4, 6]$ mmol/L, is $x_2 \in [21.5, 44.8]$ U/day.

Now we define a time constant in (6) such that

$$\frac{dx_4}{dt} = -\frac{x_4}{\tau} + p_6, \quad \tau = \frac{1}{\tilde{p}_4\tilde{p}_7 x_4 + \tilde{p}_4\tilde{x}_2}$$

We find that $\tau \in [0.05, 0.1]$ day which is small compared to $p_1$, the time constant in the first two compartments. Therefore we assume that $x_4$ reaches steady state immediately following change in $\tilde{x}_1$ and $\tilde{x}_2$. Setting (6) to zero gives a steady state expression for $x_4$ (after eliminating the conjugate root due to $x_4$ is a concentration and therefore $x_4 > 0$),

$$x_{4,ss} = -\frac{\tilde{p}_4\tilde{x}_2 - \sqrt{4\tilde{p}_4\tilde{p}_7 p_6 + \tilde{p}_4^2\tilde{x}_2^2}}{2\tilde{p}_4\tilde{p}_7} \tag{7}$$

and the residualized model becomes

$$\frac{d\tilde{x}_1}{dt} = \frac{1}{p_1}u - \frac{1}{p_1}\tilde{x}_1 \tag{8a}$$

$$\frac{d\tilde{x}_2}{dt} = \frac{1}{p_1}\tilde{x}_1 - \frac{1}{p_1}\tilde{x}_2 \tag{8b}$$

$$y = h(\tilde{x}_2) = -\frac{\tilde{p}_4\tilde{x}_2 - \sqrt{4\tilde{p}_4\tilde{p}_7 p_6 + \tilde{p}_4^2\tilde{x}_2^2}}{2\tilde{p}_4\tilde{p}_7} \tag{8c}$$

where $y$ is the measured glucose concentration in plasma. We refer to this model as the Residualized model. Figure 2 illustrates the output function in the area of interest (blue markers).

## 4. MODEL IDENTIFICATION

We investigate the identifiability of $\tilde{p}_4, p_6$ and $\tilde{p}_7$ in (8c) through the Fisher Information matrix. For values of $\tilde{x}_2$ in the area of interest, we observe that the Fisher information matrix is nearly singular, so we can not estimate all three parameters simultaneously.

The goal is to make a model of fasting glucose in response to long acting insulin in an area of interest, where parameters and states have a physiological meaning. Inspired by the expression in (8c), we suggest estimating $y = h(\tilde{x}_2)$ with a model of the form

$$\hat{y} = \alpha + \beta\tilde{x}_2 + \gamma\sqrt{1 + \tilde{x}_2} \tag{9}$$

where we might interpret $\alpha$ as fasting glucose at baseline [mmol/L], $\beta$ as a form of insulin sensitivity [mmol·day/U·L], and $\gamma$ contributes to describing glucose sensitivity of the insulin producing beta cells [day$^{1/2}$·mmol/L·U$^{1/2}$]. Figure 2 illustrates the output function $h(\tilde{x}_2)$ for the mean parameter values in Table 1 where $h(0) = 8$ mmol/L (blue markers). Fitting the model (9) to these points with a least squares method gives

$$\alpha = 8.89, \quad \beta = -0.003, \quad \gamma = -0.71 \tag{10}$$

The fit is illustrated with a red line in Figure 2.

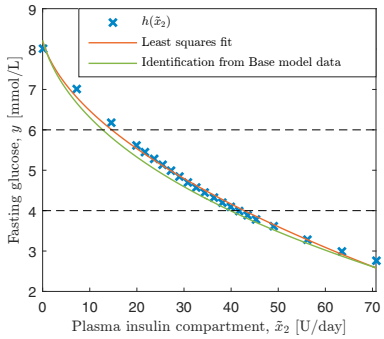


Fig. 2. Output function of the Residualized model in blue, a least squares fit of the model (9) and a fit to the data generated by Base Model in (2).

### 4.1 Parameter estimation in CTSM-R

For model identification we use CTSM-R, Continuous Time Stochastic Modelling for R, an open source platform for identifying parameters of linear and non-linear grey-box models. Given discrete time series data, CTSM-R can identify parameters of stochastic differential equations. The general model structure is a state space model on the form

$$d\mathbf{x}_t = f(\mathbf{x}_t, \mathbf{u}_t, t, \boldsymbol{\theta})dt + \boldsymbol{\sigma}(\mathbf{u}_t, t, \boldsymbol{\theta})d\mathbf{w}_t \tag{11a}$$

$$\mathbf{y}_k = h(\mathbf{x}_k, \mathbf{u}_k, t_k, \boldsymbol{\theta}) + \mathbf{e}_k \tag{11b}$$

where $\boldsymbol{\theta}$ is an $l$-dimensional set of parameters to estimate, $\theta$ is the set of parameters to identify, $\mathbf{u}_t$ is the input at time $t$, $\boldsymbol{\sigma}(\mathbf{u}_t, t, \boldsymbol{\theta})^2$ is process noise covariance matrix and $\mathbf{w}_t$ is a Brownian motion path. $\mathbf{y}_k$ is discrete observations and $\mathbf{e}_k$ is the measurement error (assumed to be white Gaussian noise). The model identification is based on maximum likelihood, where the likelihood function is the joint probability density

$$L(\boldsymbol{\theta}; \mathcal{Y}_N) = \left(\prod_{k=1}^{N} p(\mathbf{y}_k|\mathcal{Y}_{k-1}, \boldsymbol{\theta})\right) p(\mathbf{y}_0, \boldsymbol{\theta}) \tag{12}$$

where $\mathcal{Y}_k = [\mathbf{y}_k, \mathbf{y}_{k-1}, \ldots, \mathbf{y}_1, \mathbf{y}_0]$ is a sequence of measurements $\mathbf{y}_k$. CTSM-R considers stochastic differential equations that are driven by Wiener processes and so the conditional densities are approximated by Gaussian densities. A continuous-discrete extended Kalman filter is used for smoothing to determine an estimate for the measurements, $\hat{\mathbf{y}}_{k|k-1} = E[\mathbf{y}_k|\mathcal{Y}_{k-1}, \boldsymbol{\theta}]$, its covariance $\mathbf{R}_{k|k-1} = V[\mathbf{y}_k|\mathcal{Y}_{k-1}, \boldsymbol{\theta}]$, and the innovation where $\epsilon_k = \mathbf{y}_k - \hat{\mathbf{y}}_{k|k-1}$. The density is then

$$p(\mathbf{y}_k|\mathcal{Y}_{k-1}, \boldsymbol{\theta}) = \frac{\exp\left(-\frac{1}{2}\boldsymbol{\epsilon}_k^T \mathbf{R}_{k|k-1}^{-1}\boldsymbol{\epsilon}_k\right)}{\sqrt{\det(\mathbf{R}_{k|k-1})}\left(\sqrt{2\pi}\right)^l} \tag{13}$$

The software allows missing observations. CTSM-R outputs estimates for the parameters, initial conditions and noise, standard deviance of the estimates and the t-statistic, to name a few. The methods and software are described in more detail in [CTSM-R 2015].

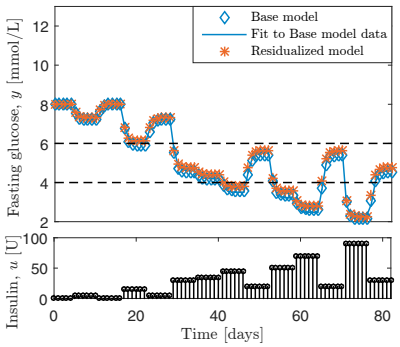


Fig. 3. Simulated glucose data. The blue diamonds indicate a simulation using the Base model, and the red stars indicate data from the Residualized model. The blue line shows the model fit estimated by CTSM-R to the Base model data.

Table 2. Parameter estimation from simulated data by the Base model.

| $\theta$ | $\theta^*$ | $\hat{\theta}$ | 95% confidence interval * | $p(>\|t\|)$ |
|---|---|---|---|---|
| $p_1$ | 0.5 | 0.55 | [0.52, 0.59] | $< 0.05$ |
| $\alpha$ | 8.9 | 9.09 | [8.98, 9.22] | $< 0.05$ |
| $\beta$ | -0.003 | 0.013 | [0.008, 0.018] | $< 0.05$ |
| $\gamma$ | -0.71 | -0.88 | [-0.93, -0.83] | $< 0.05$ |

## 5. RESULTS

### 5.1 Simulated data

We use CTSM-R to identify $p_1, \alpha, \beta$ and $\gamma$ from series of simulated data, generated from the Base model. We excite the system with a range of insulin injections such that fasting glucose levels span clinically relevant glucose concentrations; hyperglycemia ($> 6$ mmol/L), normoglycemia ($< 6$ mmol/L and $> 3.9$ mmol/L) and hypoglycemia ($< 3.9$ mmol/L). This is illustrated in Figure 3.

Table 2 shows the results from identifying the model (8a)-(8b) and (9) in CTSM-R using simulated data generated using the Base model. We observe that all parameter estimates are significant, although $\theta^*$ is not inside the confidence interval in all cases. Figure 3 illustrates the identified model in red compared to the least squares fit to the output function (8c).

### 5.2 Clinical data

In a Phase III clinical trial published by Zinman et al. [2012], 773 adult type 2 diabetes patients were initiated on insulin degludec, once daily injections. During the following months, the treatment was intensified until pre-breakfast (fasting) glucose was at a clinically recommended level. Dose sizes were adjusted once per week, based on home-logged SMPG measurements.

As mentioned in Section 2, clinical data are prone to practical issues regarding data capture and excitation. In

* Confidence intervals calculated as mean $\pm$ 1.96 $\cdot$ SD.

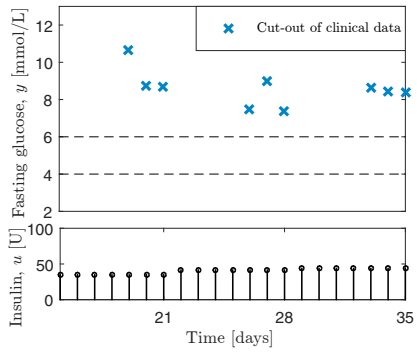


Fig. 4. A cut-out from measured clinical data for one patient in the study by Zinman et al. [2012].

the study by Zinman et al. [2012], pre-breakfast glucose was measured and logged the last three days of the week, along with the corresponding insulin dose. Figure 4 shows a 3 week cut-out from measured data for one patient in the study. This figure illustrates the sparsity of glucose data compared to the insulin data. The full data set for the patient is illustrated in Figure 5. Focus in the clinical trials that we consider relevant is not on system identification but rather on efficacy and safety of the drug. Therefore many data sets do not contain all the appropriate data for model identification. Notice that none of the measured data are lower than 4 mmol/L. The reason is that glucose levels below this value are clinically considered too low, and are therefore not frequently seen in clinical trials. This means that we can expect to only have data for $y \geq 3.9$ mmol/L.

We use CTSM-R to estimate $\alpha, \beta$ and $\gamma$ from the measured data in Figure 5. Since $p_1$ is not identifiable from the data we set $p_1 = 0.5$ days. The resulting parameter estimates, confidence intervals and p-values are listed in Table 3 and Figure 5 illustrates the model fit. We observe that all three parameter estimates are significant.

Table 3. Parameter estimation using measured clinical data from one patient.

| $\theta$ | $\hat{\theta}$ | 95% confidence interval * | $p(>\|t\|)$ |
|---|---|---|---|
| $\alpha$ | 14.6 | [12.4, 16.7] | $< 0.05$ |
| $\beta$ | 0.06 | [0.0003, 0.12] | $< 0.05$ |
| $\gamma$ | -1.52 | [-2.25, -0.79] | $< 0.05$ |

## 6. DISCUSSION

We have identified parameters of a non-linear output function using clinical data. The sampling frequency and range of values in the data are representative for what may be expected from clinical data in relevant clinical studies. This restricted us in estimating the time constant.

The interpretation of the parameters in Section 4 remains open for discussion. We mentioned that $\beta$ could be interpreted as insulin sensitivity, and that $\gamma$ could contribute to glucose sensitivity of the insulin producing beta cells.

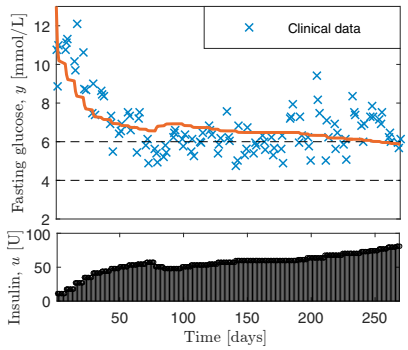


Fig. 5. Measured clinical data from Zinman et al. [2012] and model fit.

We would expect that endogenous insulin production decreases for lower values of glucose. Therefore the total glucose lowering effect of an insulin injection is lower for low values of glucose, and the output function should level off. We might therefore consider $\beta$ and $\gamma$ as a combination of insulin sensitivity of the glucose elimination and glucose sensitivity of the insulin production.

## 7. CONCLUSION

This paper suggests a model of glucose-insulin dynamics in type 2 diabetes using data of low frequency. The purpose of such a model is to simulate fasting glucose levels in long acting insulin treatment, to enable control algorithm development for dose guidance. As a starting point we used the four-compartmental physiological model for 24-hour simulations of glucose concentration following meal intake and injection of fast and long acting insulin. We investigated identifiability of parameters when the sampling period is 1 day, and reduced the model to a two-compartmental model with a non-linear output function. We use the open source software CTSM-R for model identification. All parameter estimates are significant when fitting to data simulated by the six-compartmental physiological model, as well as for the chosen set of clinical data.

Design of experiment in clinical trials remains a challenge for model identification. This work is one step of many in an iterative process to making a dynamical system of insulin-glucose dynamics in long acting insulin treatment of type 2 diabetes.

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Appendix C

# Conference paper

## Modelling of fasting glucose-insulin dynamics from sparse data

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# Modelling of fasting glucose-insulin dynamics from sparse data*

Tinna B. Aradóttir[1,2], Dimitri Boiroux[2], Henrik Bengtsson[1], Niels K. Poulsen[2]

***Abstract*— With the fast growth of diabetes prevalence, the disease is now considered an epidemic. Diabetes is characterized by elevated glucose levels, that may be treated with insulin. Tight control of glucose is essential for prevention of complications and patients' well-being.**
**In this paper we model the fasting glucose-insulin dynamics in type 2 diabetes, aiming at controlling the glucose level. Relevant clinical data are typically sparse and have a sampling period much greater than the fast dynamics in the glucose-insulin dynamics in humans. We adapt a physiological model such that important slow non-linear dynamics are identifiable and test the resulting model on deterministic simulated data and sparse, slow sampled clinical data.**

## I. INTRODUCTION

Prevalence of diabetes has grown extensively over the last years, so much that it is now considered an epidemic. The American Diabetes Association (ADA) predicts that number of diagnosed patients increases from 425 million today to 693 million by 2045 [1]. Although preventable, type 2 diabetes counts for approximately 90% of diabetes cases. The ADA estimates that 20% of health care expenditures in the United States of America are spent on care for people with diabetes [2].

In type 2 diabetes, elevated glucose levels are caused by inadequate production of insulin, reduced response to insulin, or both. High glucose levels can lead to complications in the long term such as eye damage, cardiovascular disease if not treated. However, low glucose levels can cause acute complications, in worst case coma and death. The sequence of treatment intensification in type 2 diabetes starts with lifestyle changes, to oral medication and multiple oral medications, to finally insulin injections [1]. In the current work we focus on the iterative process of initiating long acting insulin treatment of type 2 diabetes.

Response and production of insulin is individual, and therefore finding the right dose of insulin for each patient is important. In standard care, pre-breakfast self-measured blood glucose (SMBG) data are used to adjust dose sizes of long acting insulin. Due to complexity, fear of overdosing, lack of confidence and other factors, the process of finding a sufficient insulin dose can take up to years. A study in the United States of America showed that more than 60% of type 2 diabetes patients on insulin treatment do not reach recommended treatment goals [3].

In the current work we aim to model fasting glucose in response to long acting insulin. Physiological models of the glucose-insulin regulatory system in healthy and type 1 and type 2 diabetes have been published. These models vary in complexity and purpose, but are most are based on the Bergman minimal model [4], [5]. Some are designed for 24 hour simulations of glucose during meal intake and injections of fast acting insulin in type 1 diabetes [6], [7], [8] or type 2 diabetes [9]. In a paper from 2017, the model by Kanderian et al. [6] was modified to describe fasting glucose in type 2 diabetes in long acting insulin treatment. In this paper the parameters were assessed rather than found by fitting to clinical data [10]. Other groups have investigated models describing progression of type 2 diabetes [11].

In Section II in this paper we outline the problem statement. In Section III, we suggest a physiological model, which parameters can be estimated from clinical data and we briefly describe the methods used in the identification software. In Section IV we describe simulated and clinical data and finally present the results in Section V.

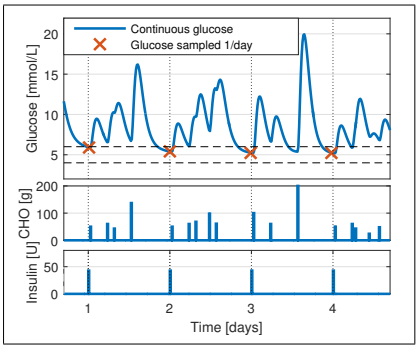


Fig. 1. Simulated glucose data (top) given carbohydrates (middle) and long acting insulin (bottom). The red markers indicate pre-breakfast SMBG. The dashed lines indicate an approximate target range for fasting glucose.

## II. STATEMENT OF THE PROBLEM

The purpose of this work is to create a physiological model of fasting glucose in response to long acting insulin in type 2 diabetes. The aim is to use this model in dose guidance control design in insulin treatment. For result interpretation purposes, such a model should have a physical interpretation.

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Parameter distributions should also be available for *in silico* simulations of the diverse type 2 diabetes population. Therefore, large scale insulin intensification studies are desirable for parameter estimation.

Parameter estimation in state of the art models of the glucose-insulin regulatory system requires high frequency data, around 1-15 minute sampling time. The top panel of Fig. 1 illustrates in blue a simulation using the model by Kanderian et al. [6], given inputs in the two lower panels. The red markers indicate measuring frequency in most large-scale clinical trials of long acting insulin. Fig. 2 illustrates how data from an insulin intensification study published by Zinman et al. [12] with 763 patients, glucose data was not only registered once per day, but also three out of seven days of the week.

Excitation of physiological systems is limited due to safety. In the case of insulin treatment, large doses of insulin can lead to coma or death, and therefore data below the desired range glucose values are rare.

Given the above limitations, we aim to modify and understand which parameters are identifiable in the state of the art models from the low sampled and sparse clinical data. Ultimately, such a model should predict fasting glucose in insulin intensification treatment of the heterogeneous type 2 diabetes patient group.

## III. METHODS

### A. A physiological model

We base this work on a model originally published by Kanderian et al. [6] on 24 hour simulations of insulin-glucose dynamics in type 1 diabetes. In [10], this model was augmented with endogenous insulin production and used to simulate fasting glucose in type 2 diabetes. After eliminating the two meal compartments from the model in [10], the model is on the form

$$\frac{dx_1}{dt} = \frac{1}{p_1}\frac{u}{p_2} - \frac{1}{p_1}x_1 \tag{1a}$$

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

$$\frac{dx_3}{dt} = p_3 p_4 (x_2 + p_7 x_4) - p_3 x_3 \tag{1c}$$

$$\frac{dx_4}{dt} = -(p_5 + x_3)x_4 + p_6 \tag{1d}$$

Here, $u$ is exogenous insulin [U/day] (input variable) and $x_4$ is glucose concentration in plasma [mmol/L] (controlled variable). $x_1$ and $x_2$ denote subcutaneous and plasma insulin concentrations [U/L] where insulin moves with time constant $p_1$ between the compartments [day]. $x_3$ is insulin effect on glucose [1/day] where $p_3$ is an inverse time constant describing delay in insulin action following increased insulin concentration in plasma [1/day]. $p_2$ is a gain describing insulin clearance [L/day] and $p_4$ is a gain describing insulin sensitivity [L/U·day]. $p_5$ is an inverse time constant describing the effect of glucose to eliminate glucose from plasma [1/day] and $p_6$ is a constant input describing rate of endogenous glucose production [mmol/L·day]. $p_7$ is a parameter added to describe endogenous insulin production, and could be interpreted as glucose sensitivity of the insulin producing cells in the pancreas [U/mmol]. Here insulin production is assumed to increase linearly with fasting glucose.

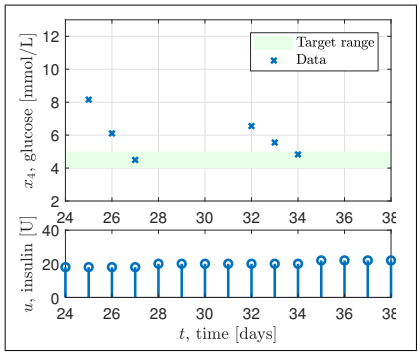


Fig. 2. A cut-out from clinical data for one patient in an insulin intensification trial [12]. The data is sparse with a sampling period of 24 hours.

### B. Model identifiability

In this paper we work with one observable variable (fasting glucose) and one input variable (insulin). We can therefore not identify both gains in (1), $p_2$ and $p_4$. Setting $\tilde{x}_1 = x_1 p_2$ [U/day], $\tilde{x}_2 = x_2 p_2$ [U/day], $\tilde{x}_3 = x_3 p_2 / p_4$ [U/day], $\tilde{p}_7 = p_7 p_2$ [U·L/mmol·day] and rewriting (1) gives

$$\frac{d\tilde{x}_1}{dt} = \frac{1}{p_1}u - \frac{1}{p_1}\tilde{x}_1 \tag{2a}$$

$$\frac{d\tilde{x}_2}{dt} = \frac{1}{p_1}\tilde{x}_1 - \frac{1}{p_1}\tilde{x}_2 \tag{2b}$$

$$\frac{d\tilde{x}_3}{dt} = p_3(\tilde{x}_2 + \tilde{p}_7 x_4) - p_3\tilde{x}_3 \tag{2c}$$

$$\frac{dx_4}{dt} = -(p_5 + \tilde{p}_4\tilde{x}_3)x_4 + p_6 \tag{2d}$$

where the gain $\tilde{p}_4$ is a ratio between the two original gains, $\tilde{p}_4 = p_4/p_2$ [1/U].

TABLE I presents mean (sd) parameter values from [6] where units are in L, U, days and mmol (respectively instead of mL and dL,U, min and mg). $p_1$ is roughly assessed based on knowledge about long acting insulins, and $p_7$ is calculated such that fasting glucose (for zero input at steady state) in (1) fulfills $x_{4,ss} = x_{4,0}$, i.e.

$$p_7 = \frac{1}{p_4 x_{4,0}}\left(\frac{p_6}{x_{4,0}} - p_5\right) \tag{3}$$

To investigate identifiability of the time constants in (2), we use the values in TABLE I. We compare the values of to the sparse sampling time in the clinical data, i.e. one measurement per day, three days prior to weekly dose

change. The typical value for $p_3$ in TABLE I is 15.8 day$^{-1}$ which corresponds to a time constant of approximately 0.06 days, and we therefore assume we can not estimate it from the clinical data. The assessed value for $p_1$ is 0.5 days and would be observable from the daily fasting glucose measurements following a change in input. Since the sparse data excludes the first four days following a dose change, $p_1$ is not observable. The typical value for $p_5$ is 3.31 day$^{-1}$ which is small compared to the term $\tilde{p}_4\bar{x}_3 \approx 15$ day$^{-1}$ in the area of interest ($x_4 \in [4,6]$). We therefore estimate $\tilde{p}_4$, $\tilde{p}_6$ as well as $\tilde{p}_7$ from simulated data using (2) using parameters in Table I and clinical data.

### C. Model identification in CTSM-R

CTSM-R, Continuous Time Stochastic Modelling for R, is an open source software for model identification. CTSM-R uses a maximum likelihood approach to identify parameters of an $l$-dimensional system of stochastic differential equations on the form

$$d\mathbf{x}_t = f(\mathbf{x}_t, \mathbf{u}_t, t, \theta)dt + \sigma(\mathbf{u}_t, t, \theta)d\mathbf{w}_t \tag{4a}$$

$$\mathbf{y}_k = h(\mathbf{x}_k, \mathbf{u}_k, t_k, \theta) + \mathbf{e}_k \tag{4b}$$

given time series data. Here, $\theta$ is the set of parameters we want to identify, $\mathbf{u}_t$ is the input at time $t$, $\sigma(\mathbf{u}_t, t, \theta)^2$ is the process noise covariance matrix and $\mathbf{w}_t$ is a Brownian motion path. $\mathbf{y}_k$ is discrete observations and $\mathbf{e}_k$ is the measurement error. The likelihood function is a joint probability density, calculated from state and covariance estimates from an extended Kalman filter,

$$L(\theta; \mathscr{Y}_N) = \left( \prod_{k=1}^{N} p(\mathbf{y}_k | \mathscr{Y}_{k-1}, \theta) \right) p(\mathbf{y}_0, \theta) \tag{5}$$

Here, $\mathscr{Y}_k = [\mathbf{y}_k, \mathbf{y}_{k-1}, \ldots, \mathbf{y}_1, \mathbf{y}_0]$ is a sequence of measurements $\mathbf{y}_k$, and the density $p(\mathbf{y}_k | \mathscr{Y}_{k-1}, \theta)$ is found by

$$p(\mathbf{y}_k | \mathscr{Y}_{k-1}, \theta) = \frac{\exp\left(-\frac{1}{2}\varepsilon_k^T \mathbf{R}_{k|k-1}^{-1} \varepsilon_k\right)}{\sqrt{\det(\mathbf{R}_{k|k-1})}\left(\sqrt{2\pi}\right)^l} \tag{6}$$

where $\hat{\mathbf{y}}_{k|k-1} = E[\mathbf{y}_k | \mathscr{Y}_{k-1}, \theta]$ is an estimate for the measurements, $\mathbf{R}_{k|k-1} = V[\mathbf{y}_k | \mathscr{Y}_{k-1}, \theta]$ is the covariance of the estimate and $\varepsilon_k = \mathbf{y}_k - \hat{\mathbf{y}}_{k|k-1}$ is the innovation.

TABLE I

PARAMETER VALUES FOR THE MODIFIED MODEL (2). MEAN (SD) FOR $p_2$ THROUGH $p_6$ ARE MEAN VALUES OF WHAT IS PRESENTED IN [6]. PARAMETER VALUES FOR $p_1$ IS ASSESSED AND $p_7$ IS CALCULATED BASED ON OTHER PARAMETERS AND AN INITIAL STATE, $x_4(0) = 8$ MMOL/L.

| | Unit | Mean (sd) |
|---|---|---|
| $p_1$ | [day] | 0.5 |
| $p_2$ | [L/day] | 1800 (760) |
| $p_3$ | [1/day] | 15.8 (6.2) |
| $\tilde{p}_4 = p_4/p_2$ | [1/U] | 0.44 (0.31) |
| $p_5$ | [1/day] | 3.31 (3.17) |
| $p_6$ | [mmol/L·day] | 96.7 (63.1) |
| $\tilde{p}_7 = p_7 p_2$ | [U·L/mmol·day] | 2.52 |

CTSM-R allows missing observations and estimates parameters, initial conditions and the measurement and process noise. Other estimates include standard deviance of the estimates and the t-statistic. More information about the methods used in the software is accessible in [13].

## IV. DATA

### A. Simulated data

Simulated data are generated from the model in (2) using the mean values of the parameters in TABLE I. We excite the system with a range of insulin injections such that fasting glucose levels span clinically relevant glucose concentrations; hyperglycemia ($> 6$ mmol/L), normoglycemia ($< 6$ mmol/L and $> 3.9$ mmol/L) and hypoglycemia ($< 3.9$ mmol/L). The blue markers in Fig. 3 indicate simulated data points.

### B. Clinical data

In this study we use data from a Phase III clinical trial, published in [12]. In this study, 773 adult type 2 diabetes patients initiated insulin degludec treatment on a once daily treatment regimen. Doses were increased weekly for up to a year, based on fasting glucose measurements. Fasting glucose was logged the last three days of the week as illustrated in Fig. 2. In clinical studies, excitation of the system is bounded by safety. The International Hypoglycaemia Study Group defines glucose levels lower than 3.0 mmol/L as clinically significant hypoglycemia and intensification algorithms used in clinical care usually control fasting glucose to a target zone, typically 4.0-5.0 mmol/L or 4.0-6.0 mmol/L [3]. Therefore we can not expect to see glucose values lower than around 3.0-4.0 mmol/L.

## V. RESULTS

### A. Fitting to simulated data

We estimate the set of parameters from simulated data where parameter values are known. We estimate $\tilde{p}_4$, $p_6$ and $\tilde{p}_7$ based on the simulated data in Fig. 3. The red line in the figure illustrates the one step prediction, and TABLE II lists the parameter estimates, $\hat{\theta}$, true values, $\theta$ and the initial parameter value $\theta_0$. All parameter estimates are significant and close to the true values. We therefore conclude that the three parameters are identifiable, and the objective function (5) seems to be convex.

TABLE II

PARAMETER ESTIMATES AND TRUE VALUES FOR THE SIMULATED DATA.

| $\theta$ | $\theta_0$ | $\theta^*$ | $\hat{\theta}$ | 95% confidence interval* | $p(>\|t\|)$ |
|---|---|---|---|---|---|
| $\tilde{p}_4$ | 10 | 0.44 | 0.438 | [0.436, 0.440] | $< 0.05$ |
| $p_6$ | 500 | 96.7 | 97.1 | [96.6, 97.5] | $< 0.05$ |
| $\tilde{p}_7$ | 10 | 2.52 | 2.51 | [2.508, 2.511] | $< 0.05$ |

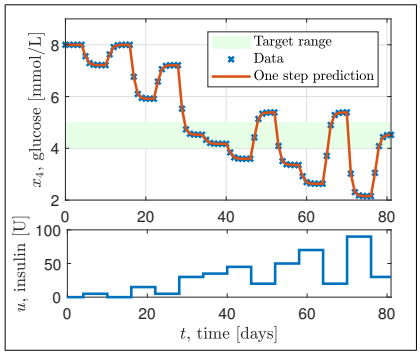


Fig. 3. Simulated glucose data using (1) (top, blue markers) given insulin input (lower panel). The red line shows the one step prediction by the model fit in TABLE II found in CTSM-R.

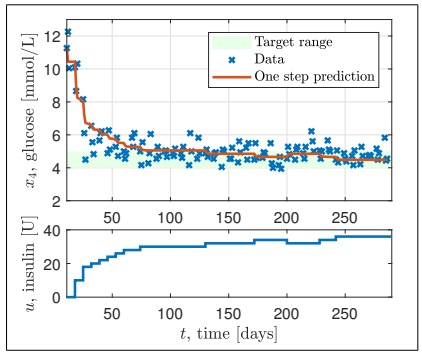


Fig. 4. Clinical glucose data from the long-acting insulin intensification trial [12] (top, blue markers) for one patient, and corresponding insulin data (bottom). The red line indicates the one step prediction by the model fit in TABLE III found in CTSM-R. The green zone in the top panel shows the target range for glucose in the clinical trial.

### B. Fitting to clinical data

Fig. 4 illustrates in blue the glucose and insulin data for one patient in the study published by Zinman et al. [12]. We use CTSM-R to estimate $\tilde{p}_4$, $p_6$ and $\tilde{p}_7$ from these data. The estimates are listed in TABLE III, and the model fit is shown in red in Fig. 4. The estimated autocorrelation function shows that there is no significant correlation between residuals up to a lag of 20, and a sign test for whiteness shows that we can not reject the null-hypothesis that residuals are continuously distributed around zero.

TABLE III
PARAMETER ESTIMATES FOR THE CLINICAL DATA.

| $\theta$ | $\hat{\theta}$ | 95% confidence interval* | $p(>\|t\|)$ |
|---|---|---|---|
| $\tilde{p}_4$ | 1.80 | [1.67, 1.94] | $< 0.05$ |
| $p_6$ | 368 | [361, 376] | $< 0.05$ |
| $\tilde{p}_7$ | 1.68 | [1.36, 2.00] | $< 0.05$ |

## VI. CONCLUSION

This work suggests that the slow dynamics of the fasting glucose-insulin system can be described with a modified version of a model of the fast glucose-insulin dynamics. We keep a number of the parameters in the four-compartment model fixed, and thereby identify important parameters describing non-linear dynamics from sparse slow sampled clinical data.

Time constants of the system are however not identifiable due to the sparsity of the data. Design of experiment is an interesting aspect in this context, with respect to data quality, system excitation and sampling frequency.

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Appendix D

# Technical report

**Dose response modelling in type 2 diabetes based on self-monitored blood glucose and insulin data**

# DOSE RESPONSE MODELLING IN TYPE 2 DIABETES BASED ON SELF-MONITORED BLOOD GLUCOSE AND INSULIN DATA

A TECHNICAL REPORT

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**ABSTRACT**

Clamp studies have shown that glucose response to insulin degludec (IDeg) in type 2 diabetes (T2D) is linear. To facilitate early identification of individual dose need we investigate the dose response during titration in insulin naïve people with T2D. We use data from six clinical trials consisting of self-monitored blood glucose (SMBG) and insulin data. We investigate whether an expected trend of decrease in SMBG values with increased insulin doses is observable from the data and whether outliers significantly affect parameter identification. We then evaluate the ability of three dose response models to describe individual dose response, two non-linear models and one linear model. The results suggest that a general trend in the data of decrease in SMBG values with increased insulin doses is observable from the data, and outliers in the data slightly affect the model identification. The linear model described the dose response best for most participants.

## 1 Introduction

New tools to support adherence and motivation of people with T2D are needed [1]. Our research group has developed an alternative approach to basal insulin initiation. As opposed to stepwise titration algorithms used in standard of care, this approach uses glucose and insulin injection data to estimate the dose needed to reach a fasting glucose target early in the treatment. The expected implications of knowing an individual's dose need, is to

improve perception of need for medication, prescription support for clinicians, and reduced fear of hypoglycemia for clinicians and people with T2D.

The aim of this report is to answer the following three research questions:

**Research question 1:** Is dose response of fasting glucose to basal insulin injections detectable from SMBG and insulin data in titration studies of insulin naïve people with T2D?

**Research question 2:** Do outliers in clinical trial data affect identification of dose response of fasting glucose to basal insulin in insulin naïve people with T2D?

**Research question 3:** What is the structure of a physiological dose response model of fasting glucose to basal insulin in insulin naïve people with T2D?

We use data from six clinical studies of insulin degludec (IDeg) including insulin naïve people with T2D. IDeg is the latest long acting insulin by Novo Nordisk A/S, markeded under the name Tresiba®. IDeg was approved by the FDA in 2015 and is used for once daily injections to lower basal glucose in both type 1 diabetes and T2D treatment.

In Section 2 we describe the clinical trial data in more detail and investigate variance in the data. In Section 3 we describe the methods used to answer the three research questions, and present the three dose response models. In Section 4 we report the results and Section 5 presents our conclusion.

## 2 Data

A number of phase 3 clinical trials on the efficacy of IDeg in T2D have been performed over the past few years [2–7]. We use data from six clinical trials on IDeg initiation, which in total included 2.155 insulin naïve T2D participants, for a duration of 26-52 weeks. A brief description of the data follows.

### 2.1 Study procedures

All six trials were out-patient studies where participants measured blood glucose before breakfast (pre-prandial) using a blood glucose monitor. SMBG and insulin data were home-logged three days of the week. The data represent the last three days prior to weekly dose adjustments. All particpiants were insulin naïve, with mean (SD) body weight of 82.0 (19.2) kg and 57.5 (9.7) years of age. Maximum baseline average SMBG values was 19.6 mmol/L, and all participants started on 10 U of basal insulin and dose adjustments followed titration algorithms, with a specified target SMBG range and dose adjustment steps. Figure 1 illustrates an example of SMBG and insulin data for one participant in the data set.

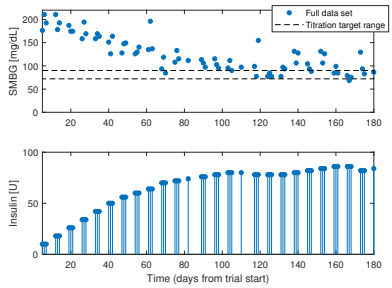


Figure 1: An example of SMBG data (upper panel) and insulin data (lower panel) for one participant.

**A simple titration algorithm with target 4.0-5.0**

| Single SMBG measurement at day of adjustment | Dose adjustment |
|---|---|
| >5.0 mmol/L | +4 U |
| 4.0-5.0 mmol/L | No adjustment |
| <3.9 mmol/L | -4 U |

**Stepwise titration algorithm with target 3.9-4.9**

| Average pre-breakfast SMBG | Dose adjustment |
|---|---|
| >9.0 mmol/L | +8 U |
| 8.0-8.9 mmol/L | +6 U |
| 7.0-7.9 mmol/L | +4 U |
| 5.0-6.9 mmol/L | +2 U |
| 3.9-4.9 mmol/L | No adjustment |
| 3.1-3.8 mmol/L | -2 U |
| <3.1 mmol/L | -4 U |

Table 1: The titration algorithms used in the six clinical studies.

The clinical trials used a titration algorithm to adjust dose sizes once weekly based on SMBG measurements. Five of the six trials used the titration algorithm to the right in Table 1 with a target range of 3.9-4.9 mmol/L. Dose adjustments were based on the mean of the last three SMBG measurements or the lowest if below target. One trial used different titration algorithms in two study arms, a simple algorithm with only two dose adjustment steps based on the lowest SMBG on the day of dose adjustment, to the left in Table 1, and a stepwise algorithm similar to the one to the right in Table 1, with a target range of 4.0-5.0 mmol/L. Left side of Figure 2 illustrates a histogram of the average SMBG during the last two weeks in the trials. We observe that most participants reach the glycemic targets recommended by the ADA of 4.4-7.2 mmol/L [8], while approximately half of the participants reached the strict target of the titration algorithms of 3.9-4.9 mmol/L. The right side of Figure 2 illustrates the frequency of final dose given in the study. Clamp studies of IDeg have shown

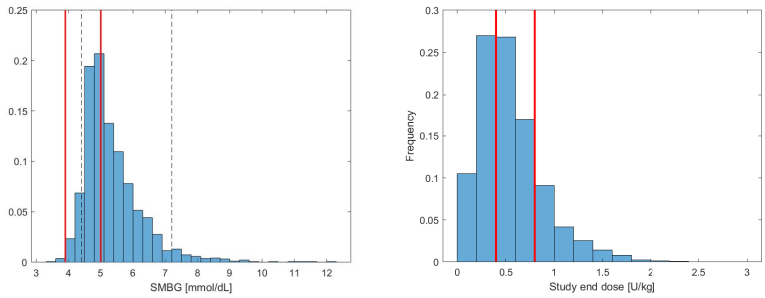


Figure 2: A histogram of the average SMBG over the last two weeks of the study duration to the left (clinical study target range in red and ADA guideline target range in black dotted line) and the study end dose to the right.

a linear response for doses in the range of 0.4-0.8 U/kg. We observe that the last study dose was above this range for approximately 20% of participants.

### 2.2 Exclusion of data

For most of the 2.155 participants in the six clinical trials, data was collected for between 25-52 weeks. For 11% of the participants, less than 25 weeks of data were available. We assume that participants with less than 25 weeks of data dropped out prematurely due to unknown reasons. We therefore excluded those from the analysis. Any unrealistic SMBG values (e.g. zero value) are eliminated from the data set. After exclusion, the data set consists of 1.925 participants with a total of 160.496 SMBG values and a corresponding insulin injection.

### 2.3 Coefficient of variation

The most widely used metrics for glucose variability are Coefficient of Variation (CV) and standard deviation. CV is a relative variation to the mean glucose value measured in percentages, and includes information about risk of hypoglycemia. CV is calculated by

$$CV = \frac{\sigma}{\mu} \tag{1}$$

where $\sigma$ is the standard deviation and $\mu$ is the mean glucose concentration. To calculate the CV of SMBG in the data set considered here, we first eliminate the trends in the data caused by insulin. We do this by subtracting the linear trend between dose sizes such that the mean of the de-trended data becomes zero. An example of SMBG and insulin data is illustrated to

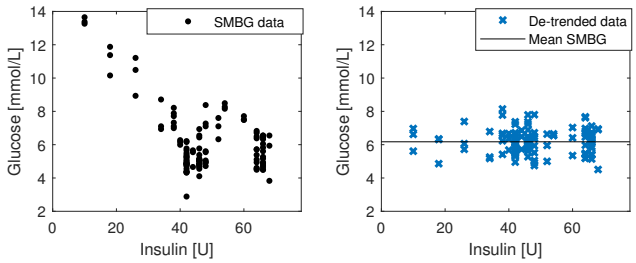


Figure 3: Example of SMBG and insulin data for one participant for a full titration period (left) and corresponding de-trended data. We observe that SMBG values take values within $\pm 2$ mmol/L for this participant.

the left in Figure 3, and the right panel shows the same data after de-trending with respect to changes in insulin. Figure 4 shows the inter-patient distribution of SMBG CV in the data set. We observe a mean CV of 13.9% (standard deviation 5.3%). A previous study on CV of SMBG measurements for people with T2D showed a CV of SMBG at around 14%, which agrees well with our observations [9].

## 3 Methods

In this section we describe the methods used for model identification. We use these methods to investigate whether the expected dose response is detectable from the data, and whether outliers in the data have a significant effect on the model identification. We finally identify parameters from three model structures and identify which model gives the best fit to the individual dose response.

### 3.1 Model identification

#### 3.1.1 Ordinary least squares

To estimate $\alpha$ and $\beta$ we use the ordinary least squares (LSQ) method, (for reference see e.g. [10]). We can write (17) for all $n$ points for an individual on matrix form,

$$y = X\theta + e \tag{2}$$

where $y = [G_1, G_2, \ldots, G_n]^T$, $X = [\mathbf{1}, x]$ with $x = [I_1, I_2, \ldots, I_n]^T$, $e = [e_1, e_2, \ldots, e_n]^T$ and $\theta = [\alpha, \beta]^T$. The ordinary LSQ estimation assumes that the residuals

$$r = y - X\hat{\theta} \tag{3}$$

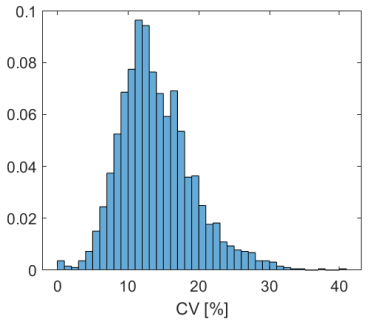


Figure 4: Distribution of CV of de-trended SMBG data for the 1.925 individuals. The 10th and 90th percentile of CV are 8.0% and 20.5%.

where $r = [r_1, r_2, \ldots, r_n]$ are normally distributed around the mean response $X\hat{\theta}$. $\hat{\theta}$ is the estimated parameters, and is found by minimizing the sum of squared residuals,

$$\hat{\theta} = \arg\min_{\theta} \sum_{i=1}^{n} r_i^2 = ||r||_2^2 = ||y - X\hat{\theta}||_2^2 \tag{4}$$

The solution is a vector, $\hat{\theta}$, which is an estimate of the unknown parameters $\theta$. By substituting the expression (3) into the 2-norm we get

$$||r||_2^2 = r^T r = \frac{1}{2}(y - X\hat{\theta})^T(y - X\hat{\theta})\hat{\theta}^T X^T X\hat{\theta} - 2\hat{\theta}^T X^T y + y^T y \tag{5}$$

We minimize this expression with respect to $\theta$ and so we take the derivative with respect to the parameters, which gives the normal equations

$$(X^T X)\hat{\theta} = X^T y \tag{6}$$

and solving for $\hat{\theta}$ gives the estimate of the unknown parameters,

$$\hat{\theta} = (X^T X)^{-1} X^T y \tag{7}$$

The distribution of the parameter estimate is

$$\hat{\theta} \sim \mathcal{N}(\theta, \sigma^2[X^T X]^{-1}) \tag{8}$$

where $\hat{\sigma}^2$ is the estimated noise covariance,

$$\hat{\sigma}^2 = \frac{1}{n - n_\theta} \sum_{i=1}^{n} r_i^2 \tag{9}$$

and $n$ and $n_\theta$ are the number of data points and parameters, respectively.

### 3.1.2 Robust least squares

In the ordinary LSQ method, we assumed that all data points were of equal quality. However, this may not be the case considering the level of variability in the SMBG data. To minimize the sensitivity of the fit to outliers and errors, we can use a weighted LSQ, where instead of minimizing the term in (4), we minimize

$$\hat{\theta} = \arg\min_{\theta} \sum_{i=1}^{n} w_i^2 r_i^2 = \frac{1}{2}||r||_2^2 = \frac{1}{2}||W(y - X\hat{\theta})||_2^2 \tag{10}$$

where $w_i$ is the weight of residual $r_i$. We can choose the weight in different ways using knowledge about the data. The normal equations become

$$(X^T W^T W X)\hat{\theta} = X^T W^T y \tag{11}$$

where $W = \text{diag}(w_1, w_2, \ldots, w_m)$ and solving for $\hat{\theta}$ gives the estimate of the unknown parameters,

$$\hat{\theta} = (X^T W^T W X)^{-1} X^T W^T y \tag{12}$$

The distribution of the parameter estimate is then

$$\hat{\theta} \sim \mathcal{N}(\theta, \hat{\sigma}^2 [X^T W^T W X]^{-1}) \tag{13}$$

Here we use the bisquare weighting for robust LSQ, which minimizes the influence of outliers on the fit. The method is iterative and gives full weight to small residuals, and zero weight to residuals larger than expected by random chance. The weights are iteratively calculated by

$$w_i = (|u_i| < 1)(1 - u_i^2)^2 \tag{14}$$

where $u_i$ is the adjusted and normalized residual $r_i$ of the weighted LSQ,

$$u_i = \frac{r_i}{K s \sqrt{1 - h_i}} \tag{15}$$

Here, $h_i$ is the leverage of residual $r_i$, i.e. the degree by which the $i$-th residual influences the fit, $K$ is a tuning constant and $s$ is the robust variance,

$$s = \frac{\text{median}(|r|)}{0.6745}, \quad K = 4.685. \tag{16}$$

The strength of the bisquare weighting is in its ability to fit the data in a similar manner as ordinary LSQ method, while eliminating the effect of outliers.

## 3.2 Observability of dose response

In a clamp study of IDeg in 49 people with T2D, Heise et al. [11] found that the glucose-lowering effect increases linearly with increased dose for injections of 0.4-0.8 U/kg. The American Diabetes Association (ADA) recommends glucose-lowering drugs such as insulin to reach glycemic targets in T2D [8]. Given a sufficient amount of data of sufficient quality, we therefore expect to observe a trend of decrease in SMBG with increase in insulin doses. To answer Research question 1, we set up the following hypothesis:

**Hypothesis 3.1** *The expected trend of decrease in SMBG with increased insulin is observable in SMBG data from clinical trials of IDeg titration in T2D.*

For each participant we investigate whether SMBG values, $G_i$ [mmol/L], decrease with increased insulin, $I_i$ [U/kg], i.e.,

$$G_i = \alpha - \beta I_i + e_i, \quad e_i \sim \mathcal{N}(0, \sigma^2), \quad i = 1, 2, \ldots, n \tag{17}$$

where $\alpha$ [mmol/L] is glucose at zero insulin, $\beta$ [(mmol/L)/(U/kg)] is long acting insulin sensitivity factor, and $e_i$ is white noise with standard deviation $\sigma$. To test the hypothesis, we estimate the two parameters of the model (17) to each individual's SMBG and insulin data. The null-hypothesis is that there is no observable decrease in SMBG with increased insulin, i.e. there is no detectable significant $\beta$ in the data. To identify the parameters we use the ordinary LSQ approach. Using the binomial sign test, we compute the probability of observing more than or equal to $x$ successes, where a model identification is successful if both estimates of $\alpha$ and $\beta$ are significantly non-zero ($p$<0.05, one-sided) in $n$ trials (number of participants) with the probability $p$ (50%) of successes on each trial. The parameter estimates have lower boundaries at zero, and $\alpha$ has an upper boundary of 20.0 mmol/L as this is the highest mean baseline SMBG observed in the dataset.

### 3.3 Dose response models

Clamp studies of IDeg have suggested the linear model structure as presented in 17. We suggest this model as the most simple dose response model. In the work in [12] we suggested a dynamic model for the physiological response of fasting glucose to basal insulin. The suggested structure of the output function is on the form

$$G_i = \alpha - \beta I_i - \gamma\sqrt{1 + I_i} + e_i, \quad e_i \sim \mathcal{N}(0, \sigma^2) \tag{18}$$

where $\alpha$ [mmol/L], $\beta$ [(mmol/L)/(U/kg)] and $\gamma$ [(mmol/L)(U/kg)$^{-\frac{1}{2}}$]. This model assumes a linear decrease in glucose with increased insulin, as the one in (17), while allowing for decreased insulin sensitivity with lower glucose values. Given the sparsity of the data and high variability, three model parameters may not be identifiable. We therefore test whether the square-root term only is able to describe the data better than the two models in (17) and (18),

$$G_i = \alpha - \gamma\sqrt{1 + I_i} + e_i, \quad e_i \sim \mathcal{N}(0, \sigma^2) \tag{19}$$

Figure 5 illustrates the three different model fits to one participant's data.

We choose the model that fits a participant's data best by the following two criteria,

1) Only considering models where all parameters are significant ($p$<0.05 one sided)
2) Calculating the coefficient of determination, $R^2$ for the remaining models and choosing the model with the highest $R^2$.

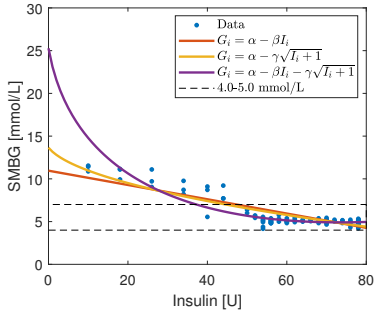


Figure 5: An illustration of the three different models and how they fit the SMBG data of one participant.

## 4 Results

### 4.1 Observability of dose response

We identify model (17) for each of the 1.925 individuals in the data set using robust LSQ. Both parameters were identified for 1.740 (90%) participants and a two-sided binomial sign test of the hypothesis rejects the null hypothesis that there is no significant trend visible in the data with a $p$<0.05. This means that with both methods we can observe a realistic and significant trend in the data, given the full data set for each participant. The parameters are log-normally distributed with

$$\ln \begin{bmatrix} \hat{\alpha} \\ \hat{\beta} \end{bmatrix} \sim \mathcal{N}\left( \begin{bmatrix} 2.22 \\ 2.01 \end{bmatrix}, \begin{bmatrix} 0.06 & 0.07 \\ 0.07 & 0.40 \end{bmatrix} \right) \tag{20}$$

In concentration values, the mean estimates for the whole population are

$$\hat{\alpha} = 9.21 \text{ mmol/L}, \quad \hat{\beta} = 7.46 \text{ (mmol/L)/(U/kg)} \tag{21}$$

and correlation between the two parameters is 0.46.

We do not obtain a realistic or significant fit to the data for 10% of participants. Figure 6 illustrates a comparison of the dose changes during the study, for those where the model identification was successful, compared to the remaining 10% of participants. We observe that the majority of the participants where identification was unsuccessful had low standard deviation of insulin doses, i.e. small changes in dose size. Due to the small changes in insulin doses, excitation is limited and the model therefore poorly identifiable.

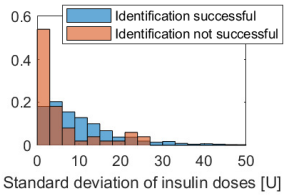


Figure 6: Frequency of insulin dose change standard deviation for the groups of participants where model identification was successful and unsuccessful. Changes in insulin doses are smaller in the group where no model was identified.

### 4.2 Sensitivity to outliers

If the ordinary LSQ is sensitive to outliers, we expect a difference in the parameter distribution than when using the robust LSQ. One-way ANOVA analysis of differences in the parameter values by identification method give $p$-values of 0.002 and 0.027 for $\alpha$ and $\beta$ respectively. This indicates that there is a difference in the mean of the baseline glucose at the 0.05 significance level, while there is not a significant difference in $\beta$ estimates. The ordinary LSQ estimates $\alpha$ (significant) and $\beta$ (non-significant) to be slightly higher than the robust LSQ.

### 4.3 Dose response models

We observed that the ordinary LSQ was slightly sensitive to outliers in the data. Therefore, we use the robust LSQ to identify $\alpha$, $\beta$ and $\gamma$. For each participant, one of the three models (or no model) is chosen as the best fit. We observe that the linear model (17) fits data from 77.2% of participants best and the two-parameter non-linear model (19) fits data from 17.5% of participants best. The full three-parameter model (18) did not have a better fit in terms of $R^2$ than the two models with two parameters. For the remaining 5.3% of participants, none of the models were identified with all parameter estimates significant.

The two models with two parameters described 94.7% of participants best. For the group of participants whose data were best described by the linear model (17), the parameter distribution is

$$\ln \begin{bmatrix} \alpha \\ \beta \end{bmatrix} \sim \mathcal{N}\left( \begin{bmatrix} 2.27 \\ 2.21 \end{bmatrix}, \begin{bmatrix} 0.06 & 0.05 \\ 0.05 & 0.29 \end{bmatrix} \right) \tag{22}$$

For the group of participants whose data were best described by the two-parameter non-linear model (19), the parameter distribution is

$$\ln \begin{bmatrix} \alpha \\ \gamma \end{bmatrix} \sim \mathcal{N}\left( \begin{bmatrix} 2.81 \\ 2.16 \end{bmatrix}, \begin{bmatrix} 0.04 & 0.06 \\ 0.06 & 0.12 \end{bmatrix} \right) \tag{23}$$

## 5 Discussion

Relating to the first research question, we found that the expected trend of decrease in fasting glucose with increased basal insulin doses was detectable from the clinical trial data for 90% of participants. We found that for the remaining 10% of participants, dose changes were limited during the study period, and thereby excitation was insufficient. We conclude that the dose response is detectable from the data.

We find that outliers in the data had a slight, but significant, effect on the model identification using an ordinary LSQ approach. We therefore used robust LSQ for parameter identification. Outliers affected the linear model fit by slightly increasing the constant of the linear model. This indicates that the outliers tended to be above the robust model fit.

Finally we compared three model structures and their ability to describe the SMBG and insulin data. These three models were chosen from clamp study observations and previous work on model identification of SMBG and insulin data. We found that the two models with two parameters described the data best. The linear and non-linear model described data from 77.2% and 17.5% of participants best, respectively.

This report presents the parameter distributions for the two models that fit the data best. We furthermore reported the distribution of SMBG CV in the data, which agreed with previously published variability data.

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Appendix E

# Manuscript

## Feasibility of a new approach to initiate insulin in type 2 diabetes

Submitted to Journal of Diabetes Science & Technology

# Feasibility of a new approach to initiate insulin in type 2 diabetes

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**Abbreviations:** (BG) blood glucose, (CGM) continuous glucose monitoring, (GCP) good clinical practice, (IDeg) Insulin Degludec, (SMBG) Self-monitored blood glucose, (T2D) type 2 diabetes

**Key words**: basal insulin, continuous glucose monitoring, degludec, dose response model, insulin initiation, type 2 diabetes

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**Figures and table count:** 1 table and 5 figures

**Abstract**

**Background:** Treatment inertia and prescription complexity are among reasons that people with type 2 diabetes (T2D) do not reach glycemic targets. This study investigated feasibility of a new approach to basal insulin initiation, where the dose needed to reach a glycemic target is estimated from two weeks of insulin and continuous glucose monitoring (CGM) data.

**Methods:** This was an exploratory single arm study with a maximum length of 84 days. Eight insulin naïve people with T2D, planning to initiate basal insulin, wore a CGM throughout the study period. A predetermined regime was followed for the first two weeks, after which the end dose was estimated. The clinician decided whether to follow this advice and continued the titration until target was reached using a twice weekly stepwise titration algorithm. The primary outcome was the comparison between the estimated and the actual end doses.

**Results:** Median age of participants was 57 years (range: 50-77 years), duration of diabetes was 16 years (range: 5-29 years) and BMI was 30.2 $kg/m^2$ (range: 22.0-36.0 $kg/m^2$). The median study end dose was 37 U (range: 20-123 U). The estimated end dose was smaller than or equal to the study end dose in all cases, with median error of 26.7% (range: 0.0-75.8% underestimation). No self-measured blood glucose values were below 70 mg/dL and no severe hypoglycemia occurred.

**Conclusion:** While accuracy may be improved, it was found safe to predict the study end dose of insulin degludec from two weeks of data.

## Background

Approximately one third of people with type 2 diabetes (T2D) are prescribed insulin (1). Insulin effectiveness in terms of lowering HbA1c in a real word setting is low, compared to clinical trial outcomes. The main reason is poor adherence to treatment, mainly caused by perceived need for medication and fear of hypoglycemia (2,3). Other reasons include lack of patient confidence in managing insulin therapy and uncertainties due to vague prescribing information from professional societies (4). The lack of adherence negatively impacts metabolic control (5), and results in over 60% of people not reaching recommended treatment targets (6). Therefore new dose guidance tools are needed to support clinicians and promote adherence and motivation of people with T2D (7).

Research groups have previously developed automated guidance systems to substitute paper-based algorithms to simplify and increase adherence to treatment, such as the Intelligent Dosing System and the Diabetes Insulin Guidance System (8,9). Both systems iteratively adjust doses based on pre-breakfast self-measured blood glucose (SMBG) to reach a fasting glucose target.

Our research group envisions that decision support tools leveraging brief use of continuous glucose monitoring (CGM), in particular in the primary care setting, will support future treatment decisions. In this context, this study evaluates an approach to rapidly identify the right insulin dose for people with T2D. The approach uses initial CGM and injection data to generate an individual dose response model. This model is then used to estimate the dose needed to reach a fasting glucose target. The expected implications of such an estimation early in the titration would be to improve perception of need for

medication, prescription support, and reduced fear of hypoglycemia. The specific aim of the study was to evaluate the feasibility of this treatment approach.

## Method

### *Design*

The study was an exploratory single arm study with variable duration, with a maximum length of 84 days. People with T2D were recruited from the outpatient clinics at Hvidovre University Hospital and Steno Diabetes Center Copenhagen, Denmark. After screening, the clinician and the participants met three times in the clinic. Phone calls were scheduled every three or four days between visits (Fig. 1). The procedure was as follows:

*Visit 1 (day 1):* The clinician introduced insulin degludec (IDeg) therapy, the CGM and a smart phone for transferring data, and demonstrated logging of insulin doses and SMBG measurements in logbooks. Participants were asked to perform three daily SMBG measurements, one before breakfast and two evenly distributed throughout the rest of the day. The SMBG measurements were used for CGM calibration.

*Insulin initiation (days 1-14):* The participants did not inject insulin during the first four days. On day five, insulin treatment was initiated with 10 U IDeg in the morning. This dose was kept unchanged for the next five days. On day 10, the clinician evaluated whether 10 U were sufficient for reaching the fasting glucose target of 72-108 mg/dL. If more insulin was needed, the daily basal insulin dose was increased to 0.2 U/kg body weight according to local standard practice guidelines.

*Visit 2 (day 15):* CGM data from the insulin initiation period were downloaded to the clinician's computer. A dose estimation algorithm estimated the study end dose and suggested 75% of this dose to the clinician. If the suggested dose was assessed safe, the participant was prescribed this dose for the next four days. If the suggested dose was lower than the dose prescribed prior to day 15, and no events of hypoglycemia had occurred, the dose was maintained during the next four days and stepwise titration should continue from the dose already reached.

*Titration to target (days 20-84):* Titration continued twice weekly according to a stepwise titration algorithm (dose change increments of -4 to +8 U) with a fasting glucose target of 72-108 mg/dL, until the study end dose was achieved, or until day 84. The study end dose was defined as the dose when the sum of three consecutive dose changes was within or equal to +/-2 U. The clinician could deviate from the titration algorithm if assessed relevant, e.g., the CGM data indicated a risk of hypoglycemia at any time of the day. The clinician determined and communicated dose changes during phone consultations.

*Visit 3 (day 84 or end of study):* When the study end dose was identified, the participant was called in for a last visit.

***Subjects***

People with T2D who planned with their physician to initiate basal insulin treatment were included. The inclusion criteria were 18-80 years of age, insulin-naïve people with HbA1c 53-100 mmol/mol (7.0-11.3%), BMI 20-40 kg/m$^2$, willing to use CGM during the study and send/receive data and dose advice to/from clinician via phone. Exclusion criteria were pregnancy, breast-feeding or intention to become pregnant, active proliferative

retinopathy or mild background retinopathy with HbA1c > 86 mmol/mol (10.0%), mean blood glucose (BG) > 270 mg/dL the week prior to screening, BG > 360 mg/dL and non-fasting ketones > 0.5 mmol/L on the screening day, conditions which made tight diabetes control undesirable, and other concomitant conditions that made participation unsuitable. No use of sulfonylurea within two weeks prior to or during the study or corticosteroids within 30 days prior to or during the study was allowed. Change in other antidiabetic medicine than basal insulin and marked change in lifestyle within 30 days prior to or during the study were not allowed.

***Devices***

All participants were provided with an insulin pen (Tresiba® FlexTouch®), a smart phone (iPhone 5S), a CGM (Dexcom G5®), and logbooks for SMBG and insulin data. The purpose of the CGM was 1) intensive data capture during the first period for dose estimation, and 2) the glucose safety alarm (alarm level set at 70 mg/dL) during the full study period. The purpose of the smart phone was to 1) receive and transfer CGM data to Diasend®, and 2) telephone consultations every three or four days. Data from the CGM and logbook entries were transferred to the study computer during visits. The clinicians had a laptop with the dose estimation algorithm.

***Algorithm***

For IDeg, the total glucose-lowering effect increases linearly with increasing doses in the range 0.4-0.8 U/kg (10). Therefore, a linear dose response model was used to estimate the study end dose based on two weeks of CGM and insulin data. The algorithm assumes that the fasting blood glucose response to long acting insulin is linear,

$$G = \alpha - \beta I \quad \text{(Equation 1)}$$

where $G$ is the fasting glucose [mg/dL] following a dose of IDeg, $I$ [U/kg], and $\alpha$ and $\beta$ are the estimated fasting glucose before initiating treatment, and sensitivity to the IDeg (Fig. 2).

The only changes in a glucose-lowering drug during the study is IDeg doses. The mean change in fasting glucose is therefore assumed to be caused or induced by the change in IDeg. To identify the response to an injection from the CGM data (288 data points per day), we define a *titration glucose level* as the lowest average one-hour window of CGM data of each day (Fig. 3). The choice of a one-hour window was assessed reasonable to reflect a low glucose event while still robust to noise and outliers. The high-level steps of the algorithm are:

1. *Titration glucose level:* The algorithm locates the lowest average one-hour window of CGM data of each day (Fig. 3).
2. *Linear dose response model:* The algorithm estimates the parameters $\alpha$ and $\beta$ in Equation 1 using a least squares approach.
3. *Estimated end dose*: The identified model is used to estimate the IDeg dose, $\hat{I}_{end}$, needed to reach a target fasting glucose, $G_{target}$, by rewriting Equation 1:

$$\hat{I}_{end} = \frac{\alpha - G_{target}}{\beta} \quad \text{(Equation 2)}$$

The target, $G_{target}$, is set to 108 mg/dL (upper limit of the fasting glucose target of the titration algorithm). If any of the parameter estimates are not significant, an error message is communicated.

***Study outcome***

The primary outcome of this feasibility study is the percentwise deviation of the estimated end dose, $\hat{I}_{end}$, from the study end dose, $I_{end}$,

$$Accuracy = \left(\frac{\hat{I}_{end} - I_{end}}{I_{end}}\right) \times 100\% \quad \text{(Equation 3)}$$

Secondary outcomes are accuracy of the estimated end dose based on SMBG data compared with the study end dose, number of participants reaching the fasting glucose target, number of titration algorithm deviations due to risk of hypoglycemia (based on evaluation of CGM data), qualitative assessment by the clinician of the participants who do not reach the fasting glucose target within 84 days: 1) frequency of participants needing additional basal insulin, and 2) frequency of participants needing additional drugs, to achieve the fasting glucose target. Number of SMBG values ≤70 mg/dL and <54 mg/dL, number of severe hypoglycemic events (defined as severe cognitive impairment requiring external assistance), time in hypoglycemia (<70 mg/dL), normoglycemia (70-180 mg/dL) and hyperglycemia (>180 mg/dL) assessed by CGM during the first and last four days of the study.

***Ethics and statistical considerations***

The study is exploratory in nature and not powered for hypothesis tests, carried out in accordance with the Helsinki Declaration and good clinical practice (GCP), and monitored by the GCP unit at Copenhagen University Hospital after approval by the Regional Scientific Ethics Committee, the Danish Medicines Agency and the Danish Data Protection Agency. The study was registered at ClinicalTrials.gov, ID: NCT03365180.

## Results

### *Demographic data*

Forty-seven participants were screened, whereof eight participants were included. Main reasons for exclusion included too high HbA1c or BMI and lack of willingness to participate. Six (75%) participants were males. Median (range) age of participants was 57 years (50-77), duration of diabetes was 16 years (5-29), HbA1c was 72 mmol/mol (64-87) or 8.8% (8.0-10.1) and BMI was 30.2 kg/$m^2$ (22.0-36.0). All participants used other anti-diabetic medicine prior to and throughout the study (2.3 on average); seven participants used metformin, five used a GLP-1 receptor agonist, four used an SGLT2-inhibitor, and two participants used DPP-4 inhibitors. Seven participants used antihypertensive drugs (2.3 on average) and seven participants used lipid-lowering drugs (1.0 on average).

### *Primary objective results*

The median (range) study end dose was 37 U (20-123) or 0.4 U/kg (0.2-1.0). The dose estimated at two weeks was smaller than or equal to the study end dose in all cases (Table 1 and Fig. 4) with median (range) 26.7% (0.0-75.8) error. One estimated end dose matched the study end dose with 0% error. An end dose estimation was not provided in one case due to unidentified response model.

The clinician prescribed the suggested dose (75% of the estimated end dose) in three out of seven recommendations. In the remaining cases, the clinician recommended following the titration algorithm. In the following weeks, the titration algorithm was used until the study end dose was reached.

***Secondary objective results***

The error of the SMBG based estimated end dose at two weeks (Fig. 4) had a median (range) deviation of 10.5% (32.8% underestimation-172.7% overestimation). The SMBG based dose suggestion at two weeks (75% of the total SMBG based estimated end dose) was greater than the study end dose in two cases.

Before initiating insulin treatment, the median (range) time below range was 0.0% (0.0-0.0), in range was 20.0% (2.0-44.7) and above range was 80.0% (55.3-98.0) during the first four days in the study (Fig. 5). Median (range) time the last four days below range was 0.0% (0.0-1.5), in range was 84.9% (66.0-99.0) and above range was 14.3% (1.0-34.0) (Fig. 5). Seven out of eight participants obtained the consensus criteria for optimal time in range with more than 70% in range and less than 4% below range (11). No SMBG values were below 54 or 72 mg/dL and no severe hypoglycemic events occurred.

The median (range) study duration was 44 days (30-84) and all participants reached the fasting glucose target within the 12 weeks. Titration algorithm deviations due to low CGM readings occurred 19 times in total. Most deviations were due to low CGM readings and were done according to the clinician's advice.

***CGM performance***

During the first two weeks, a median (range) of 7% (2-58) of CGM data were missing, whereof one participant was missing more than the 30% consensus criteria (11). The poorest dose prediction with a 75.8% underestimation was for the participant where 58% of data were missing. For the participant where dose estimation was not possible, 10% of the data were

missing. Correlation between the dose estimation error and missing data during the first two weeks was 0.51, i.e., in general the dose estimation accuracy decreases with increased missing data. In the full study period, a median (range) of 9% (1.5-17.4) of CGM data were missing. Delay in CGM data availability at visit 2 was 6-16 hours.

**Discussion**

This feasibility study demonstrates that a novel approach for insulin initiation in people with T2D based on two weeks of CGM and insulin data is feasible, and doses are not overestimated. The key results on dose estimation accuracy showed that in all participants, the estimated dose was safe, and no hypoglycemic events occurred.

Key results on time below, above and in range indicate that titration to target using this approach is feasible within the time frame of 12 weeks (Table 1 and Fig. 5). Stepwise titration algorithms with steps larger than 4 U of insulin are usually used for once weekly adjustments. Twice weekly titration was considered safe for three reasons, 1) use of CGM with hypo-alarm, 2) clinicians had access to the CGM data and frequent contact with participants, and 3) the fasting glucose target was widened from the 72-90 mg/dL often used in treat-to-target trials to 72-108 mg/dL.

We observed a correlation between missing data in the first two weeks and dose estimation performance. Some participants expressed problems with calibration, activating a new sensor, and connectivity problems between the transmitter and the smart phone. Improved new generation CGM devices solve some of these problems. Retrospective analysis of the only case where estimating the end dose was not possible at two weeks, show an 11 hour lag from CGM data. The analysis indicates that this may somewhat be mitigated

by increased outlier robustness in the dose estimation method and including the full 14 days of data.

In this study the target for the lowest glucose of the day was set to the upper limit of the fasting glucose target range. This may be too conservative, and the middle of the fasting glucose target range could be a more appropriate choice.

For the participant with the largest study end dose of 1.0 U/kg, the dose estimated at two weeks was underestimated by 62%. This is expected as for participants needing large doses to reach the fasting glucose target, the dose needed to observe a dose response is expected to be higher. Furthermore, the linear dose response was expected in the range of 0.4-0.8 U/kg. We observed a strong correlation between BMI and study end dose, which may therefore be an indicator for the dose load needed to observe a dose response.

The use of CGM was a great advantage when making dose adjustment decisions as the clinicians had information about low glucose between SMBG measurements. The clinicians furthermore had the opportunity to identify need for bolus insulin at the end of study, which would not have been possible using SMBG data only. Identification of the need for additional medication may potentially be automated in a future version.

The open CGM may have affected participants' lifestyle. If the users changed lifestyle towards more healthy diet and exercise, this would have decreased the study end dose and influenced the accuracy of the estimated end dose. However, for safety reasons, the study was designed with an open CGM and still we found the estimated end dose safe.

The study was designed to last for a maximum of 84 days. HbA1c at end of study would therefore not be reflective of the glycemic outcomes. Instead,

CGM data were used for outcome evaluation, and compared with the consensus CGM targets (11).

Standard of care titration algorithms and other dose guidance systems, such as the Intelligent Dosing System, and the Diabetes Insulin Guidance System, are iterative approaches that adjust doses on a day-by-day or week-by-week basis. The novelty of this approach is the intermittent intensive data capture and the potential to provide a roadmap for the titration. The expected implications of this are decreased fear of hypoglycemia and improved perception of need for insulin by patients, thereby improving glycemic outcomes in T2D treatment. The method can be used in combination with iterative titration approaches.

In its optimal implementation, the method requires use of connected glucose measuring devices and insulin pens and is therefore more expensive than standard of care. However, considering the high socioeconomic cost of diabetes and the great need for motivation and adherence support, the periodic use of such a solution may be economically feasible.

## Conclusions

This study was a feasibility study with eight participants, and statistical significance was not expected. The results are specific to IDeg and may therefore not apply for other insulins. The concept of a study end dose defined in this study depends on the titration method, the type of basal insulin, and the intrapatient variability in pharmacodynamic and pharmacokinetic profiles of the insulin.

To the best of our knowledge, this is the first clinical study specifically on use of CGM data to initiate basal insulin treatment in T2D, and the use of a dose response model to estimate the dose needed to reach a fasting glucose target. An optimized version of this treatment approach has the potential to

provide a roadmap of the treatment, which may facilitate understanding and perception of medication need, and reduce fear of hypoglycemia and complexity related to insulin initiation.

In this paper we have shown a method for safe estimation of the end dose of basal insulin titration in T2D. We find that the dose prediction at two weeks should be improved and are working on methods for doing this. We believe that this method will become a useful tool for initiation guidance for basal insulin. Such a system could be implemented using connected insulin pens and calibration free CGM technologies for seamless support to the clinicians and people with T2D.

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**Author disclosure statement**

T.B.A., H.B. and M.L.J. are full or part time employees of Novo Nordisk A/S. K.N. serves as adviser to Sanofi, Medtronic, Abbott and Novo Nordisk, owns shares in Novo Nordisk, has received research grants from Novo Nordisk and Roche Diabetes Care and has received fees for speaking from Medtronic, Roche Diabetes Care, Rubin Medical, Sanofi, Novo Nordisk,

Zealand Pharma and Bayer. S.S. has served on advisory boards for Roche Diabetes Care and Medtronic.

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| Participant | Baseline data HbA1c (mmol/mol) | BMI ($kg/m^2$) | Study end dose (U) | Study end dose (U/kg) | Time to end dose (days) | Estimated end dose to reach 6.0 mmol/L (U/kg) |
|---|---|---|---|---|---|---|
| 1 | 64 | 30.5 | 56 | 0.61 | 54 | none |
| 2 | 71 | 30.0 | 22 | 0.25 | 30 | 0.23 |
| 3 | 87 | 22.0 | 35 | 0.47 | 38 | 0.37 |
| 4 | 86 | 31.8 | 38 | 0.39 | 44 | 0.26 |
| 5 | 82 | 36.0 | 123 | 1.04 | 84 | 0.40 |
| 6 | 70 | 29.6 | 31 | 0.32 | 30 | 0.32 |
| 7 | 72 | 25.2 | 20 | 0.22 | 31 | 0.16 |
| 8 | 73 | 34.0 | 44 | 0.44 | 60 | 0.11 |

*Table 1: Baseline data and results for the eight participants.*

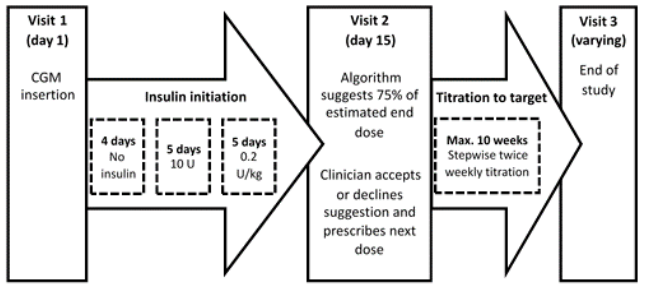


*Fig. 1: Overview of the study procedure. A predetermined regime was followed for the first two weeks. The dose prediction software suggested 75% of the estimated end dose. The clinician determined whether to follow this advice and continued the titration until target was reached. Titration continued twice weekly using a stepwise titration algorithm (-4 to +8 U steps) with target range of 72-108 mg/dL until the study end dose was achieved, or until day 84.*

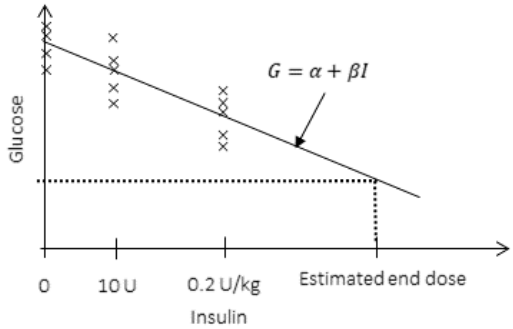


*Fig. 2: A concept illustration of the linear dose response model. The model assumed linear response of fasting glucose (x markers) to basal insulin. This model was used to estimate the end dose.*

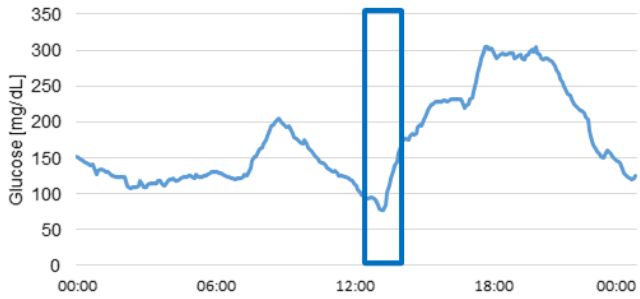


*Fig. 3: Lowest daily average one-hour CGM interval. The algorithm located the lowest average one hour of CGM data of each day. This glucose level was used to determine the dose response to the basal insulin.*

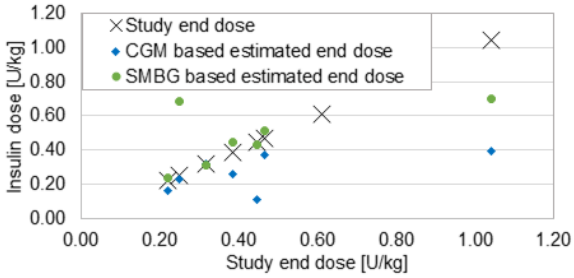


*Fig. 4: A visualization of the primary outcome. Comparison of the estimated end dose to reach 6.0 mmol/L based on insulin data, and CGM or SMBG data after two weeks, compared to the study end dose for the eight participants.*

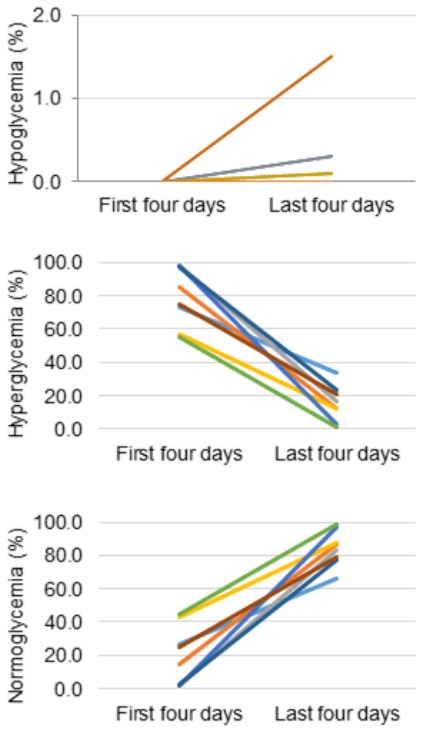


*Fig. 5: Time in hypoglycemia (below 70 mg/dL), hyperglycemia (above 180 mg/dL) and normoglycemia (between 70-180 mg/dL) during the first and last four days of the study for the eight participants, as measured by percentage of CGM data points in each range.*

Appendix F

# Technical report

**Dose prediction based on self-measured blood glucose and insulin data: A novel approach to basal insulin titration**

# DOSE PREDICTION BASED ON SELF-MEASURED BLOOD GLUCOSE AND INSULIN DATA: A NOVEL APPROACH TO BASAL INSULIN TITRATION

A TECHNICAL REPORT

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**ABSTRACT**

In basal insulin initiation in type 2 diabetes (T2D), doses are increased iteratively by small amounts until a glycemic target is reached. This can take years in practice. We investigate the feasibility of a novel approach to insulin initiation, where we predict the dose needed to reach the glycemic target early in the treatment. We use data from basal insulin initiation studies in people with T2D and a linear and nonlinear dose response model for dose estimation. To identify the model parameters, we use different least squares (LSQ) methods and a maximum a posteriori approach. Finally we compare performance with respect to safety and efficiency and find that a linear dose response model for dose estimation performs best in terms of safety and efficiency. We find that dose prediction is in general possible given six weeks of data (18 data points). We believe this approach has the potential to improve perceived need for medication and decrease complexity of treatment.

## 1 Introduction

The American Diabetes Association (ADA) predicts that prevalence of diabetes will increase by around 50% over the next 25 years, and diabetes is now considered a pandemic [1]. Approximately 30% of people with type 2 diabetes (T2D) are prescribed insulin. The

standard of care treatment approach when initiating basal insulin is a complex process. Patients use pre-breakfast self-monitored blood glucose (SMBG) and paper based algorithms, such as the one in Table 1, to determine dose adjustments. Outcomes of clinical trials in insulin treatment of T2D are not achieved in the real world, and more than 60% of patients do not meet recommended treatment goals. The main reported reason is poor treatment adherence, which mainly relates to lack of patient confidence, poor perception of need for medication, fear of hypoglycemia and vague prescription information [2–4].

In the long run, poorly controlled diabetes results in complications such as cardiovascular disease, eye damage and foot ulcers. Despite that more than 40 new drugs for treating diabetes have been approved by the FDA in the recent years, real world outcomes are not improving. Therefore, there is a need for novel and innovative approaches to assist clinicians and patients in reaching treatment targets [5].

In the recent years, computer based dose guidance algorithms for insulin treatment have been emerging. Model based approaches are used in closed-loop pump treatment with fast acting insulin, see e.g. [6–8]. This has mainly been used in treatment of type 1 diabetes, but has recently been moving to the T2D segment [8]. Two examples of dose guidance systems for basal insulin treatment in T2D are the Intelligent Dosing Systems (IDS) and Diabetes Insulin Guidance System (DIGS) [9, 10]. Both solutions provide iterative treatment guidance based on pre-breakfast SMBG data.

The aim of this work is to investigate the feasibility of a novel treatment concept, where the dose needed to reach the treatment goal is predicted early on in the treatment. This prediction may be of interest to patients and clinicians to improve perception of need for insulin and reduce complexity and fear of hypoglycemia. The concept consists of an initial period for data capture during the initiation, followed by a second period of titration. Data captured during the first period are used to estimate the dose needed to reach the glycemic target, for the individual patient. The estimated dose is used to guide the titration of the basal insulin during the second period. This approach could potentially be used in combination with iterative dose guidance approaches. The goal is to accommodate patients in reaching blood glucose targets in a safe and efficient manner.

**Simple titration algorithm**

| Average pre-breakfast SMBG | Dose adjustment |
|---|---|
| >7.2 mmol/L | +2 U |
| 4.4-7.2 mmol/L | No adjustment |
| <4.4 mmol/L | -2 U |

Table 1: Examples of simple titration algorithms. The ADA recommends to use a simple algorithm during insulin initiation, and to treat to a target of 4.4-7.2 mmol/L [1]

To investigate the technical feasibility of this treatment concept we aim to answer the following research questions:

**Research question 1:** How do we define the dose needed to reach the treatment goal?

**Research question 2:** How do we predict the dose needed to reach the treatment goal early in the treatment, while maximizing safety and efficiency?

**Research question 3:** How useful is a prediction of the dose needed to reach the treatment goal early in the treatment?

Section 2 describes the methods used to answer these questions. In Section 3 we present the results. In Section 4 we discuss the effect of changes in input data frequency and excitation, and Section 5 presents our conclusion.

## 2 Methods

In our previous work we proposed two models for describing dose response in people with T2D initiating basal insulin therapy [11]. In this work we use the same data set, and the previously developed models to test the feasibility of dose estimation early in the treatment. First we discuss and define the range of doses needed to bring fasting glucose to a glucose target. We then present different approaches to dose estimation, where we identify the dose response model using ordinary least squares (LSQ), robust LSQ, non-symmetric weighted LSQ, an LSQ with an exponential forgetting factor, as well as a maximum a posteriori approach.

### 2.1 Target dose

The main aim of this work is to identify an individual's dose response model early on in the insulin treatment, and to use the model to estimate the insulin dose needed to reach the glycemic target. To measure the performance of the dose estimation, we define an interval of safe and efficient doses for each participant. We use this interval to evaluate the safety and efficiency of the dose estimation. The standard of care guidelines by the ADA recommend lowering fasting glucose to 4.4-7.2 mmol/L, depending on the physical state of the individual [1]. This leads us to an assumption:

**Assumption 2.1** *For each participant, there exists a basal insulin dose, or a range of doses, that lowers baseline pre-breakfast SMBG to a target SMBG, and this dose is sufficient for a period of 12 months.*

This assumption forms the foundation for the treatment concept. In order for a dose estimation to be useful, we must assume that this dose size is relevant during a specific

period. We specifically indicate a time interval of 12 months as the available dataset includes data for up to 12 months.

We use SMBG and insulin data from 26-52 weeks, where three SMBG measurements were logged the last three days before a weekly dose adjustment. We previously found that the mean coefficient of variation (CV) in the SMBG data was 13.9%, with a 10th and 90th percentile of 8% and 20.5%. For a true mean SMBG value of 7.4 mmol/L (above target), the standard deviation could be as high as 1.5 mmol/L at the 90th percentile [11]. The probability of an SMBG measurement being below 7.2 mmol/L (within target) is therefore high, while the true mean glucose is above target. We should therefore avoid defining a target dose where the mean of three consecutive SMBG measurements is within the target range once, as this may be caused by stochastics rather than physiology. Considering this high level of variability in the data, we use Assumption 2.1 and the guidelines by ADA to define a target dose interval for each individual:

**Definition 2.2** *A participant's target dose interval is the range of safe and efficient insulin doses, where the corresponding fasting SMBG measurement is within the clinically recommended target. This interval is found using a simple titration algorithm and the ADA recommended target, see Table 1. A target dose is identified when the sum of three consecutive dose adjustments is equal to or within +/- 2 U. Each participant can thereby have multiple occasions of target doses. The smallest and largest identified target doses indicate the target dose interval.*

This approach is similar to the one used for defining dose convergence in a clinical trial on IDeg initiation[1]. Figure 1 illustrates an example of target dose interval identification as described in Definition 2.2. In [11] we found that model identification was slightly sensitive to outliers in the data. Definition 2.2 assumes using the mean of the last three SMBG measurements prior to dose adjustments, see Table 1. To investigate the influence of outliers on the identified target dose intervals we determine the target dose intervals based on median SMBG rather than average SMBG.

### 2.2 Target dose estimation

In the second research question of this work we aim to identify a dose estimation method, that is able to estimate the dose needed to reach the treatment target early in the treatment. Given a subset of an individual's data, from baseline at time $t_1$ to the current time $t_n$, we assume that the data ($I_1$, $G_1$), ... ($I_n$, $G_n$), where $I_i = I(t_i)$ and $G_i = G(t_i)$, can be described by

$$G_i = \phi(I_i)^T\theta + e_i \quad e_i \sim \mathcal{N}(0, \sigma^2), \quad i = 1, 2, \ldots, n \tag{1}$$

where $\theta$ is a set of parameters and $\phi(I_i)$ is the Jacobian of the dose response model at time $t_i$. The aim is to use such a dose response model to extrapolate to the desired glucose level, and

[1]Results to be published, ClinicalTrials.gov Identifier: NCT03365180

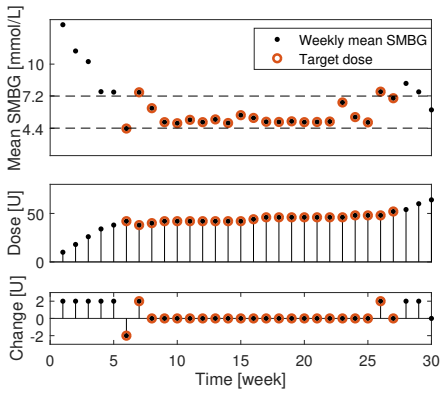


Figure 1: An example of a target dose interval identification. The top panel shows weekly average SMBG, the middle panel shows the corresponding insulin dose, and the bottom panel shows the dose adjustment as recommended by the ADA guidelines and a simple titration algorithm.

to calculate the insulin dose needed to reach this glucose level. This concept is illustrated in Figure 2.

In previous work we concluded that two models described the participants' data best [11]. The two models are the linear dose response model

$$G_i = \alpha - \beta I_i + e_i, \quad e_i \sim \mathcal{N}(0, \sigma^2), \quad i = 1, 2, \ldots, n \tag{2}$$

and the non-linear model

$$G_i = \alpha - \gamma\sqrt{I_i + 1} + e_i, \quad e_i \sim \mathcal{N}(0, \sigma^2), \quad i = 1, 2, \ldots, n \tag{3}$$

We estimate the parameters $\alpha$, $\beta$ and $\gamma$, and perform a dose estimation when

1) both parameter estimates $\alpha$ and $\beta$ (or $\gamma$) are significantly greater than zero ($p < 0.05$)
2) both parameter estimates are non-negative and $\alpha < 20.0$ mmol/L

We assume that we can extrapolate to a future insulin dose, $I_m, m > n$, and estimate the mean SMBG value, $G_m$, by

$$G_m = \alpha - \beta I_m \quad \text{or} \quad G_m = \alpha - \gamma\sqrt{I_m + 1} \tag{4}$$

Using this approach, the estimated dose needed to reach a target SMBG level, $G_{target}$, is described by

$$\hat{I}_{target} = \frac{\alpha - G_{target}}{\beta} \quad \text{or} \quad \hat{I}_{target} = \left(\frac{\alpha - G_{target}}{\gamma}\right)^2 - 1 \tag{5}$$

The dose estimates then have the distribution

$$I_{target} \sim \mathcal{N}\left(\hat{I}_{target}, \Phi^T P \Phi\right) \tag{6}$$

where $\Phi$ is the Jacobian of $\hat{I}_{target}$ with respect to the parameters,

$$\Phi = \begin{bmatrix} \frac{1}{\beta} & -\frac{\alpha - G_{target}}{\beta^2} \end{bmatrix}^T \tag{7}$$

and $P$ is the covariance of $\theta$,

$$P = \left(\sum_{i=1}^{n} \phi(I_i)^T \phi(I_i)\right)^{-1} \sigma^2 \tag{8}$$

Using this we identify the two models and estimate the target dose for each participant. We then compare the performance of the two models with respect to 1) safety, which are all dose estimations lower than or equal to an individual's upper target dose, and 2) efficiency which are all dose estimations within an individual's target dose interval. To test the quality of dose estimation and whether this is possible in general, we have the following hypothesis:

**Hypothesis 2.3** *The insulin dose needed to reach a target SMBG is predictable from a subset of SMBG and insulin data prior to reaching the target SMBG.*

To test Hypothesis 2.3, we use a two-sided sign test, and compute the probability of observing more or equal to $x$ successes where a success is counted when

1) both parameter estimates $\alpha$ and $\beta$ (or $\gamma$) significantly greater than zero ($p$<0.05)
2) both parameter estimates are non-negative and $\alpha < 20.0$ mmol/L
3) dose estimation is deemed efficient, i.e. within the target dose interval
4) the upper target dose is not reached at time of target dose estimation

in $N$ trials (number of patients) with the probability $p$ (50%) of successes on each trial using the binomial probability density function.

### 2.2.1 Least squares approaches

To estimate the parameters $\alpha$ and $\beta$ (or $\gamma$) we use a linear LSQ approach. Ordinary and weighted LSQ with biquare weights, also referred to as robust LSQ. We use the two approaches, as well as a number of modifications to the robust LSQ, with different weighting of residuals. Here we refer to [11] for the description of the ordinary and robust LSQ, but describe the modifications to the weighting of residuals, as well as a maximum a posteriori approach.

We have a dose response model, linear in the parameters, expressed on the form

$$y = X\theta + e \tag{9}$$

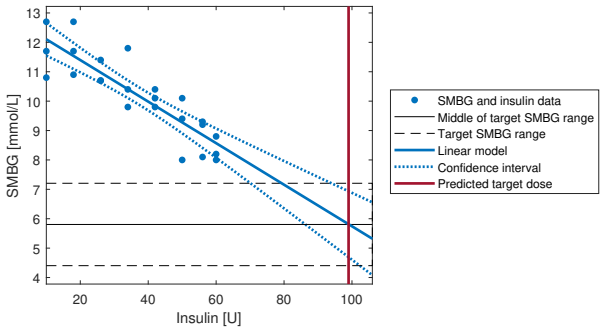


Figure 2: A visual illustration of dose estimation using a linear model.

where $y = [G_1, G_2, \ldots, G_n]^T$, $X_{ij} = \phi_j(I_i)$, $e = [e_1, e_2, \ldots, e_n]^T$, $e_i \sim \mathcal{N}(0, \sigma^2)$ and $\theta$ is a vector containing the parameters we want to identify. The residuals of the model fit $X\hat{\theta}$, where $\hat{\theta}$ are the estimated parameters of the model, are expressed by

$$r = y - X\hat{\theta} \tag{10}$$

For the weighted LSQ we have that

$$\hat{\theta} = (X^T W X)^{-1} X^T W y \tag{11}$$

where $W = \text{diag}(w_1, w_2, \ldots, w_m)$ and $w_i$ is the weight of residual $r_i$. In robust least squares, the weights are defined such that full weight is given to small residuals, while large residuals are ignored. This reduces sensitivity to outliers. One may define the weights in different ways.

**Non-symmetric weighting function**

Model predictive control has been extensively researched for closed-loop pump treatment of T1D. When designing a cost function for the opimisation of glucose values, the penalty function is typically non-symmetric, such that low glucose values are penalized higher than high glucose values, see e.g. [6–8]. This is done due to the clinical severity of low glucose concentrations compared with high concentrations. Using this as well as knowledge about outliers in the data, we can design a weighting function that favors the more reliable and important measurements. For the specific case of this work, we divide noise in the data by three origins,

$$\text{SMBG noise} = \text{Sensor noise} + \text{User errors} + \text{Biological variation} \tag{12}$$

We may assume the sensor noise to be white [12]. In the data set, the trial protocols stated that SMBG should be measured pre-breakfast to capture low glucose concentrations [11].

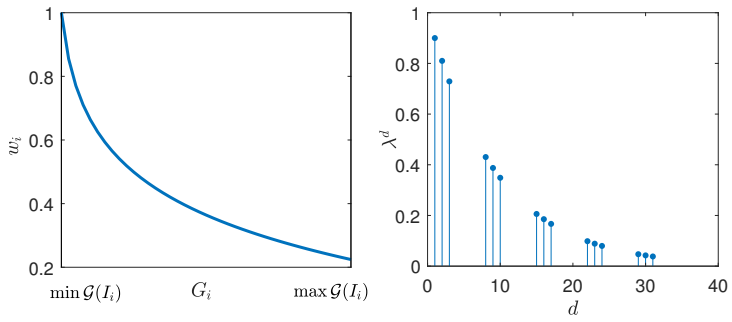


Figure 3: The left figure shows the non-symmetric weighting function of residuals in (13). The right figure shows the forgetting weights in (14) for an effective memory horizon of 10 days. Notice that only three out of seven points are illustrated. This is due to the structure of the SMBG data where only the three last values prior to a dose adjustment are available.

If a person measures SMBG at other time points by mistake, the glucose concentration is expected to be equal or higher than the actual pre-breakfast SMBG. This would in general result in an error in the SMBG measurement in the positive direction. We therefore expect that outliers caused by user errors would tend to elevate the measured glucose concentration.

Considering the user errors and severity of low glucose, we design a weighting function such that we weigh low SMBG values higher than high SMBG values. However, we should keep in mind that insulin doses affect the glucose levels and we do not wish to eliminate information about the dose response. We therefore weigh SMBG readings compared to other SMBG readings where the same insulin dose was given. The weighting function is therefore

$$w_i = 1 - \frac{\log(G_i - \min[\mathcal{G}(I_i)] + 1)}{\log(\max[\mathcal{G}(I_i)]} \tag{13}$$

where $G_i$ is the i-th SMBG measurement, $I_i$ is the corresponding insulin injection, and $\mathcal{G}(I_i)$ is all SMBG measurements $G_j$ for $j = 1, 2, \ldots, n$ where $I_j = I_i$. When there is only one SMBG measurement for the corresponding insulin dose, then $\dim(\mathcal{G}(I_i)) = 1$ and $w_i = 1$. The weighting function is illustrated to the left in Figure 3.

**Exponential forgetting factor**

If we assume that the most recent data points provide the most accurate information about the current physiological state of the patient, we can add a forgetting factor through the weights. If $w_i$ is the weight of the $i-$th neighbor to the current data point, we can make the

weights decrease exponentially with distance from the current point in days by

$$w_i = \lambda^{d_i}, \quad i = 1, 2, \ldots, n \tag{14}$$

Here, $\lambda$ is a forgetting factor that determines how much the past data points contribute to the estimation of $\theta$ and $d_i$ s the distance from the current data point $(I_i, G_i)$ in days. The relationship between the forgetting factor $\lambda$ and the effective memory horizon $N_d$ is

$$N_d = \frac{1}{1-\lambda} \tag{15}$$

and should be set to the length of the horizon where we believe the parameters are approximately constant. Figure 3 illustrates an example of the forgetting factor where $\lambda$ =0.9 and $N_d$ =10 days.

### 2.2.2 Maximum a posteriori

If we have information about the probability density function $p(\theta)$ for the parameters, we can use this as prior when identifying parameters for a new data set $\mathcal{Y}_k = [y_k, y_{k-1}, \ldots, y_1, y_0]$ [13]. Bayes' rule states that the posterior probability density function of the parameters, conditioned on the new data set, is

$$p(\theta|\mathcal{Y}_k) = \frac{p(\mathcal{Y}_k|\theta)p(\theta)}{p(\mathcal{Y}_k)} \propto p(\mathcal{Y}_k|\theta)p(\theta) \tag{16}$$

To maximize the likelihood of the new parameter set, given the population parameter distribution, we can maximize the posterior probability function. We previously observed a log-normal distribution of the parameters $\alpha$, $\beta$ and $\gamma$ [11]. We can therefore write the posterior probability density function as

$$p(\theta|\mathcal{Y}_k) \propto \left( \prod_{i=1}^{k} \frac{\exp\left(\frac{1}{2} e_i^T R_i e_i\right)}{\sqrt{\det(R_i)}(\sqrt{2\pi})^l} \right) p(y_0|\theta) \frac{\exp\left(-\frac{1}{2}\varepsilon_\theta^T \Sigma_\theta^{-1} \varepsilon_\theta\right)}{\sqrt{\det(\Sigma_\theta)}(\sqrt{2\pi})^p} \tag{17}$$

where $\varepsilon_\theta = \theta - \mu_\theta = \theta - E\{\theta\}$ and $\Sigma_\theta = V\{\theta\}$, $p$ is the dimension of the parameter vector, respectively, $e_i$ is the residuals of the fit with dimension $l$, and $R_i$ is the covariance of the residuals. If we condition the posterior probability on $y_0$ and take the negative logarithm, we can determine the parameter estimates by solving the optimization problem

$$\hat{\theta} = \arg\min_\theta \{-\log(p(\theta|\mathcal{Y}_k, y_0))\} \tag{18}$$

where

$$\begin{aligned} -\log\left(p(\theta|\mathcal{Y}_N, y_0)\right) \propto & \frac{1}{2} \sum_{i=1}^{k} \left(\log\left(\det(R_i)\right) + e_i^T R_i^{-1} e_i\right) \\ & + \frac{1}{2} \left( \left( \sum_{i=1}^{k} l \right) + p \right) \log(2\pi) \\ & + \frac{1}{2} \log\left(\det(\Sigma_\theta)\right) + \frac{1}{2} \varepsilon_\theta^T \Sigma_\theta^{-1} \varepsilon_\theta \end{aligned} \tag{19}$$

We use the leave one out (LOO) approach for testing the *a posteriori* approach, where we the robust LSQ to generate the prior distribution, as described in [11].

## 3 Results

### 3.1 Target dose

For the 1.925 patients in the dataset, we find that the lower and upper limits of the target range have a mean of 28.5 U and 49.2 U, and the length of the target dose interval has an average 20.6 U, when determined using weekly mean SMBG, see Table 2. The results indicate that, on average, the doses bringing SMBG to the target of 4.4-7.2 mmol/L changed by approximately 20U over the 26-52 weeks, or that a range of 20 U is safe and efficient for keeping SMBG in target within this time frame. To investigate the sensitivity of the method to outliers in the SMBG data, we compare the results to a target dose interval based on weekly median SMBG instead of weekly mean SMBG. If the method was sensitive to outliers, we would expect a difference in the target dose intervals. We find that the lower and upper target dose intervals, using weekly median rather than mean SMBG, are the same. We therefore conclude that the method of determining target dose interval, as described in 2.2, is not sensitive to outliers, and we use the target dose interval based on mean weekly SMBG measurements for performance evaluation.

### 3.2 Target dose prediction

To answer research questions 2 and 3 we compare the performance of the dose predictions with respect to safety, efficiency and number of identified models. Using these measures, we evaluate the number of safe, efficient and useful dose predictions each method and model provide, given three to 12 weeks of data.

The results of previous work indicate that given the full dataset for each participant, the model is significantly identified for 94.7% of participants [11]. We do therefore not expect to be able to predict a target dose for the remaining 5.3% at any time. Figure 4 illustrates the percentage of participants where the models are significantly identified given three to 12 weeks of data. There is not a difference in performance between the two models. The LSQ methods identify the models for approximately 40% of participants after three weeks, and

| | U/kg | U |
|---|---|---|
| Lower target dose | 0.33 (0.24) | 28.5 (24.5) |
| Upper target dose | 0.58 (0.33) | 49.2 (33.7) |
| Length of interval | 0.24 (0.19) | 20.6 (18.6) |

Table 2: Target dose interval results.

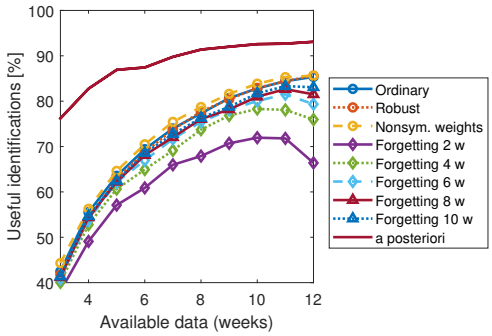


Figure 4: Percentage of cases where both parameters are significantly different from zero with the different estimation methods for the non-linear model. The results are similar for both the linear and non-linear models.

around 60-80% after eight weeks. The corresponding values for the *a posteriori* approach are 75% at three weeks, to over 90% after eight weeks.

To do a head-to-head comparison of the LSQ methods for the two models, we perform an initial comparison using the intersection set where all methods can identify the models at 3-12 weeks. The subsets include 191 and 201 of participants for the linear and non-linear models, respectively.

We observe that the performance is similar for the two models, but different for the estimation methods, see Figure 5. Considering both safety and efficiency, the best performing methods are the forgetting LSQ with effective memory of 8 and 10 weeks, and the ordinary LSQ. The weighted LSQ with non-symmetric weights performs worst with respect to efficiency. This is caused by the high weighting of the low measurements, which leads to a conservative estimate of the dose needed to reach target. We furthermore observe that the performance of the LSQ with effective memory of 2 weeks is poor in terms of useful identifications. Since the memory is short, the effective number of data points used for the identification is small and the model is therefore not identified for a small group of participants, see Figure 4. Safety and efficiency is similar to the other methods, however in the lower performance end.

We now consider the ordinary LSQ and the forgetting LSQ with 8-10 week memory, as well as the maximum a posteriori approach and compare the dose estimation performance using the full dataset, see 6. The results indicate that the safety of using the linear model is higher than for the non-linear model, independent of identification approach. Efficiency is also slightly higher when using the linear model. Note that the safety and efficiency results only reflect the quality of predictions from significantly identified models, and only 30% of

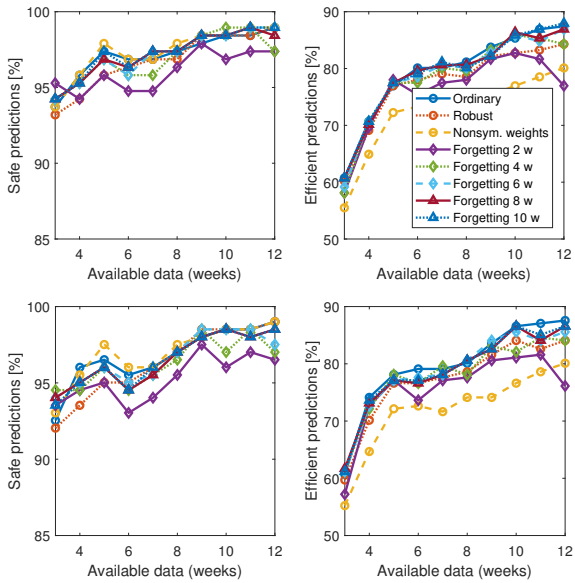


Figure 5: Head-to-head comparison of performance of linear (top) and non-linear (bottom) dose prediction using the different LSQ approaches. The left figures show the frequency of safe dose predictions and the right figures show the frequency of efficient dose predictions.

participants for the maximum a posteriori approach. Table 3 illustrates the percentage of safe and efficient dose predictions of the total population. We observe that although the *a posteriori* approach is identified for a large group of patients, the number of overestimated doses is larger than for the LSQ approach.

We investigate whether a dose prediction is in general possible early in the treatment, using Hypothesis 2.3. If a $p$-value is below the significance threshold, this indicates that the method is statistically able to perform efficient dose predictions at the given point in time. We find that the prediction is possible after six weeks for the linear model and seven weeks for the non-linear model, and from week 3 for the *a posteriori* approach.

From the results we conclude that the best model for dose prediction is the linear model. The best performing LSQ approach for model identification is the forgetting LSQ with an exponential forgetting factor and an effective memory of eight weeks. Using this approach, we may expect that given six weeks of SMBG and insulin data (18 data points), 68% of

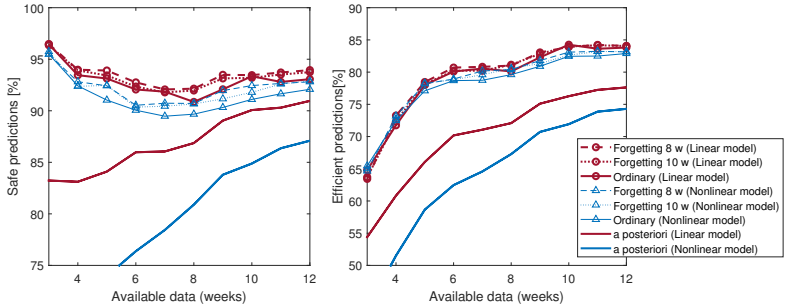


Figure 6: Frequency of safe target dose estimations (left) and efficient target dose estimations (right), tested on the full data set.

participants will receive a dose prediction, whereof 93% are safe and 80% are efficient, see Table 3. We observe that the maximum a posteriori performs well in terms of percentage of significantly identified models, while lacking in safety and efficiency. Table 3 illustrates a comparison of the best performing LSQ and maximum a posteriori. We observe that although the maximum a posteriori provides more useful identifications and a higher percentage of efficient predictions, the percentage of unsafe predictions is higher than for the LSQ approach.

**LSQ with effective memory of 8 weeks**

| Available data weeks (points) | Models identified | Safe predictions | Unsafe predictions | Efficient predictions |
|---|---|---|---|---|
| 3 (9) | 41% | 97% (39%) | 3% (1%) | 63% (26%) |
| 4 (12) | 54% | 94% (51%) | 6% (3%) | 73% (39%) |
| 5 (15) | 62% | 94% (58%) | 6% (4%) | 79% (49%) |
| 6 (18) | 68% | 93% (63%) | 7% (5%) | 80% (54%) |
| 7 (21) | 72% | 92% (66%) | 8% (6%) | 81% (58%) |

**Maximum a posteriori (Leave one out)**

| Available data weeks (points) | Models identified | Safe predictions | Unsafe predictions | Efficient predictions |
|---|---|---|---|---|
| 3 (9) | 76% | 83% (63%) | 17% (37%) | 54% (41%) |
| 4 (12) | 83% | 83% (69%) | 17% (31%) | 61% (50%) |
| 5 (15) | 87% | 84% (73%) | 16% (27%) | 66% (57%) |
| 6 (18) | 87% | 86% (75%) | 14% (24%) | 70% (61%) |
| 7 (21) | 90% | 86% (77%) | 14% (23%) | 71% (64%) |

Table 3: Performance of the best performing dose prediction algorithms using the linear model for prediction. The values in brackets indicate the percentage of the total population rather than percentage of useful identifications.

## 4 Data density and excitation

In the current data set, only three SMBG values are available per week. In clinical practice, some patients may measure SMBG every day, and this would theoretically give a better approximation of the mean pre-breakfast blood glucose. This raises a question of whether the performance of the methods tested here may improve with respect to time of identified model and quality of dose predictions.

### 4.1 Effect of higher frequency data

Assuming that the distribution of SMBG values, $G_i$, around the mean SMBG, $\hat{G}_i$, given an insulin dose size, $I_i$, then we say that the mean SMBG, given $n$ observations is

$$G_i \sim \mathcal{N}(\hat{G}_i, \sigma^2) \tag{20}$$

with

$$\mu = \frac{1}{N}\sum_{i=1}^{N} G_i \sim \mathcal{N}\left(\hat{G}_i, \frac{1}{N^2} N\sigma^2\right) \tag{21}$$

such that the variance of the mean decreases proportionally with increased number of data points. Extending this to the linear model fit gives

$$G_i = \alpha - \beta I_i + e_i = \begin{bmatrix} 1 & -I_i \end{bmatrix} \begin{bmatrix} \alpha \\ \beta \end{bmatrix} + e_i = \phi_i^T \theta + e_i \tag{22}$$

with the covariance of $\theta$

$$P = \left(\sum_{i=1}^{N} \phi_i^T \phi_i\right)^{-1} \sigma^2 = \left(\sum_{i=1}^{N} \begin{bmatrix} 1 & -I_i \\ -I_i & I_i^2 \end{bmatrix}\right)^{-1} \sigma^2 \tag{23}$$

The aim of this work is to perform a dose prediction given the parameter estimates for $\alpha$ and $\beta$. The dose estimate is calculated by

$$\hat{I}_{target} = \frac{\alpha - G_{target}}{\beta} \tag{24}$$

and has the distribution

$$I_{target} \sim \mathcal{N}\left(\hat{I}_{target}, \Phi^T P \Phi\right) \tag{25}$$

where $\Phi$ is the Jacobian of $I_{est}$. $P$ decreases proportionally with increasing $N$, i.e., going from three to seven data points per week decreases the uncertainty of the estimates from $1/3\sigma^2$ to $1/7\sigma^2$, while for six weeks this difference becomes $1/18\sigma^2$ to $1/42\sigma^2$. This difference however converges to zero with increasing number of data points.

### 4.2 Effect of excitation

Dose adjustment algorithms used in clinical practice vary in terms of glucose target range, frequency of dose adjustments, number of glucose measurements taken into considerations, and size of dose steps [4]. The algorithms used in the clinical trials considered here are ambitious in terms of a tight and low target range, and large dose steps. These large dose adjustments work in favor of the model identification as the excitation is high. Other more conservative dose adjustment algorithms would result in less excitation and thereby longer time to model identification. As an example, the ambitious algorithms can increase doses by 8U from week to week, depending on the SMBG values. Conservative algorithms adjust doses by 2U once or twice weekly, and it would therefore take two to four times longer to reach the same excitation. This would negatively impact the performance of a dose prediction in terms of time to an identified model and efficient dose predictions.

## 5 Conclusion

In this work, we found that for dose prediction, a linear model performs best with respect to safety and efficiency. Of the tested LSQ approaches, a weighted LSQ with a forgetting factor of 8-week memory, performed best with respect to time of model identification, safety and efficiency. Given 6 weeks of data (18 SMBG data points), 68% of patients would receive a dose prediction, whereof 93% of are safe predictions and 80% are within the identified individual's target dose interval.

The maximum a posteriori approach performed well in terms of number of significant model identifications and efficient dose predictions. However, the total number of overestimations was higher than for the LSQ approach. Furthermore, the maximum a posteriori approach relies on the quality of the data used for training. In general, data driven approaches, such as the maximum a posteriori, rely on the training data being well representative for the patient group using the dose guidance support. The data used here are from clinical studies with specific inclusion and exclusion criteria, and are therefore not necessarily useful for participants not fulfilling these criteria. When testing such an algorithm in the clinic, this should be taken into account.

We defined a target dose interval and found that on average, a participant's SMBG values were in range for doses varying with around 20 U. As an example, a participant's SMBG could be in range for a dose as low as 30U and as high as 50U. This may be caused by the target SMBG range being wide, i.e. 4.4-7.2 mmol/L, as well as physiological changes over time. The target dose interval, as defined here, is considered as an interval of safe and efficient doses over a period of 12 months, and this is expected to change over time. We therefore see the dose prediction treatment approach as a treatment guidance tool that should be applied intermittently when needed. This could furthermore be used in combination with iterative titration approaches.

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Appendix G

# Manuscript

## A new approach to initiate insulin in type 2 diabetes - Ad-hoc analysis

Manuscript to be submitted to Journal of Diabetes Science & Technology

# A new approach to initiate insulin in type 2 diabetes – Post hoc analysis

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**Abbreviations:** (CGM) continuous glucose monitoring, (IDeg) Insulin Degludec, (SMBG) Self-monitored blood glucose, (T2D) type 2 diabetes

**Key words**: basal insulin, continuous glucose monitoring, degludec, dose response model, insulin initiation, type 2 diabetes

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**Figures and table count:** 1 table and 1 figure

**Abstract**

**Background**: In a previous clinical study, we tested the feasibility of a new approach to basal insulin initiation in type 2 diabetes (T2D). The approach estimated the dose needed to reach a glycemic target based on two weeks of CGM and basal insulin data. The dose estimates were used in the following weeks to guide the insulin titration. The method was found to be feasible and safe. The aim of this work was to evaluate safety and accuracy of an improved dose estimation method.

**Research design and methods:** The improved method was developed using self monitored blood glucose and insulin data from 2.155 insulin naïve people with T2D initiating insulin degludec treatment over 26-52 weeks. We evaluate the performance of the method by performing a dose prediction using CGM and insulin data from the previous clinical study, and compare this to the observed study end doses.

**Results:** The mean (SD) deviation from the study end dose is 23.5% (12.7%) and 34.3% (25.5%) using the improved and previous versions, respectively. The dose estimations are underestimations in all cases. In terms of median (range), the estimation error is 21.6% (5.0-45.5%) for the improved method, which corresponds to an underestimation of 9 U (1-56 U).

**Conclusion:** Accuracy is increased and safety maintained in the improved method for predicting an end dose of insulin degludec from two weeks of CGM and insulin data. We believe that this approach is a useful tool for basal insulin initiation support in T2D.

## Background

Approximately one third of people with type 2 diabetes (T2D) rely on insulin to treat hyperglycemia (1). However, the efficacy of insulin in terms of reaching glycemic outcomes demonstrated in clinical studies is often superior to the effectiveness in the real world. In fact, more than 60% of people with T2D treated with insulin do not reach glycemic targets (2). Reasons include poor adherence to treatment due to perceived need for medication and fear of hypoglycemia, lack of patient confidence in managing insulin therapy and uncertainties due to vague prescribing information from professional societies (3–5). The poor outcomes indicate a need for new tools that support clinicians and patients through promoting adherence and motivation (6).

In a previous clinical study, we investigated the feasibility of a novel approach to basal insulin initiation (7). The approach consists of an initial period where insulin treatment is initiated and CGM and basal insulin data are captured, and a second period of basal insulin titration guided by CGM or self-measured blood glucose (SMBG). The data during the first period are used to estimate the end dose after the insulin titration. The clinician may then use the end dose estimation, provided after the first period, as a guide in the titration in the second period. The dose prediction approach may also work as a module in patient facing decision support tools, combined with, e.g., iterative dose guidance. The expected impact of the approach is to improve patients' perception of need for medication, prescription assistance for clinicians and decreased fear of hypoglycemia.

The previous clinical study included eight insulin naïve participants with T2D, who planned to start basal insulin treatment. The results showed that the

insulin degludec dose estimation two weeks after insulin initiation was safe, i.e., the dose was underestimated in all cases. The dose estimation was not possible in one case. We believe that the accuracy of the end dose estimation may be improved such that this treatment approach becomes a useful tool for decision support in basal insulin initiation.

The aim of this work is to measure the performance of an improved method for dose estimation, evaluated using data from the previous clinical feasibility study. The improved method was developed using data from clinical studies on insulin degludec titration in T2D (8–13). The data and dose prediction algorithm are briefly described in this paper.

## Research design and methods

### *Improved algorithm*

The improved dose estimation algorithm was developed using data from six clinical studies of insulin degludec titration in T2D (8–13). The dataset included 2.155 participants from Europe, N. and S. America, Asia and Africa. All six studies were out-patient studies and included insulin naïve T2D participants, for a duration of 26-52 weeks. Pre-breakfast SMBG and insulin data were home-logged the last three days prior to weekly dose adjustments. Dose adjustments followed a stepwise titration algorithm with dose adjustments from -4 U to +8 U with a target range of 3.9-4.9 or 4.0-5.0 mmol/L.

For insulin degludec, the total glucose-lowering effect increases linearly with increasing doses in the range of 0.4-0.8 U/kg (14). The estimation method

therefore assumes a linear relationship between fasting glucose and insulin, i.e., that

$$G = \alpha - \beta I \qquad \text{(Equation 1)}$$

where $G$ is the fasting glucose [mmol/L] given a dose of insulin degludec, $I$ [U], and $\alpha$ and $\beta$ are parameters that vary from individual to individual. The parameter $\alpha$ may be interpreted as the mean fasting glucose before initiating insulin treatment, and $\beta$ may be interpreted as sensitivity to the long acting insulin. The method of identifying the parameters in the linear model was improved using data from the six clinical studies. We compared performance of different least squares estimation methods, including ordinary least squares, robust least squares, non-symmetric weighted least squares, and least squares with a forgetting factor. The best performing method in terms of safety and efficacy in dose estimations is a robust least squares regression with bisquare weights and an effective memory of eight weeks through an exponential forgetting factor.

In the clinical feasibility study we have access to CGM data for a full titration period. As the estimation method was developed using SMBG data, we substitute the SMBG data points by one titration glucose level each day. Note that in the data from the feasibility study, we will have one titration glucose level for each day, while we only had three SMBG data points per week in the data set for developing the estimation method. For a more detailed description of the study design, participants and devices, see our previous work (7). The high-level steps of the algorithm used to estimate the end dose after two weeks are:

1. *Titration glucose level:* To substitute SMBG data points, used to develop the improved method, the algorithm located the lowest average one-hour window of CGM data (12 consecutive CGM readings) for each day. This is the same method as described in our previous work (7).
2. *Linear dose response regression:* The algorithm estimated the parameters $\alpha$ and $\beta$ in Equation 1. The parameters were estimated using the improved method to determine the dose response of the titration glucose level, $G$, to daily insulin injections, $I$, in Equation 1.
3. *Estimated end dose:* The linear dose response model was used to predict the number of units of basal insulin needed to reach a target glucose level, $G_{target}$. The dose response was rewritten to calculate the estimated end dose, $\hat{I}_{final}$, by

$$\hat{I}_{final} = \frac{\alpha - G_{target}}{\beta} \qquad \text{(Equation 2)}$$

The target $G_{target}$ was set to 6.0 mmol/L (upper limit of the target range of the titration algorithm). The estimated end dose was rounded to the nearest 1 U increment.

*Outcome*

The primary outcome of the previous feasibility study was the accuracy of the estimated end dose, $\hat{I}_{final}$, compared with the study end dose, $I_{final}$. Accuracy of each estimated end dose was defined as a percentage deviation of the estimated end dose vs. study end dose,

$$Accuracy = \left(\frac{\hat{I}_{final} - I_{final}}{I_{final}}\right) \times 100\% \qquad \text{(Equation 3)}$$

In this work, the accuracy of the improved dose estimation method is measured using the CGM and insulin data from the previous feasibility study. The data consisted of data from eight participants with T2D in total and are described in more detail in our previous work (7). No changes in lifestyle or anti-diabetic medicine other than insulin were allowed during the study, such that changes in fasting glucose could be related to changes in insulin dosing. The median actual end dose was 37 U (range: 20-123 U) or 0.4 U/kg (range: 0.2-1.0 U/kg). The outcome of this post hoc analysis is the comparison of accuracy of the improved estimation method and the previous study.

### *Ethics and statistical considerations*

This post hoc analysis is based on data from previously conducted studies, a) a clinical study with eight participants, conducted by the authors of this paper (7), and b) six clinical studies not conducted by the authors of this paper (8–13). The study in a) was a feasibility study and not powered for any hypothesis tests to reach statistical significance.

## Results

In terms of median (range), the error of the improved end dose prediction was 21.6% (range: 5.0-45.5%) compared to 26.7% (range: 0.0-75.8%) in the previous version (Fig. 1 and Table 1). All predictions were underestimations. In terms of insulin units, this corresponds to a median of 9 U (range: 1-56 U underestimation). The improved dose estimation method was able to predict an end dose for all eight participants based on two weeks of data. The largest error of 45.5%, or 56 U underestimation, was in the case

of the participant needing 1.0 U/kg. The expected range for linear response is 0.4-0.8 U/kg. Eliminating this participant from the results gives a median error of 18.2% (range: 5.0-39.5%) or 9 U (range: 1-15 U underestimation).

## Discussion

This paper assesses the accuracy of an improved dose estimation method for insulin degludec compared to previously published clinical study results. The algorithm used two weeks of CGM and insulin data from before and after initiating insulin treatment in the previous clinical study. The key results on performance of end dose prediction showed that accuracy was improved, while safety remained the same.

All end doses in the study, except one, were smaller than 0.8 U/kg. We observe that the accuracy is higher for this group than for the one participant with an end dose of 1.0 U/kg. In our previous work we found a strong correlation between BMI and study end dose. The participant with the high end dose had the highest weight and BMI, which may be an indicator of poor dose prediction performance. Due to the low number of participants we can however not generalize based on these data.

The end dose was underestimated in all cases. This suggests that one may consider choosing a more stringent target. With a target of 5.0 mmol/L instead of the more conservative 6.0 mmol/L used here (**Error! Reference source not found.**), the median of the absolute error reduces to 11% (range: 35.0% underestimation to 20.0% overestimation) or 4 U (range: 43 U underestimation to 7 U overestimation). Eliminating the one participant with an end dose larger than 0.8 U/kg gives a median absolute error of 11% (range: 20.0% underestimation to 11.4% overestimation) or 4 U (range: 5 U underestimation to 7 U overestimation). This indicates that it may be desirable to set the target to a more stringent value. Simultaneously, the predicted end

dose should be used as a long term goal rather than an immediate dose step, to ensure safety.

## Conclusion

This work analyzed data from a feasibility study with eight participants. Therefore, statistical significance was not expected. The results are specific to insulin degludec, and may therefore not apply for other basal insulins. As discussed in our previous work (7), the study end dose may depend on the titration method and the type of basal insulin. The end dose should be considered as a temporary definition of a dose, needed to reach glycemic outcomes. Therefore, we see this treatment approach as a solution that could be applied intermittently as a person's physiological state changes due to, e.g., lifestyle, aging, disease progression, etc.

We believe that the improved dose prediction is a useful tool for basal insulin initiation in T2D. Current approaches to basal insulin titration are iterative with day-by-day or week-by-week dose adjustments. This dose prediction approach could work as a component in a decision support tool for clinicians and patients, combined with iterative approaches, or as a standalone clinician facing digital treatment guidance tool.

The novelty of this approach is in its potential to change the paradigm of basal insulin titration. The expected implications are increased adherence to treatment. The efficacy of this approach should therefore be tested with behavioral aspects in mind and long term glycemic outcomes in a realistic treatment setting. We furthermore see a potential in using the end dose prediction in combination with iterative titration rather than a single dose adjustment. The dose prediction would in this case provide a tangible titration duration or end dose for patients and clinicians.

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T.B.A., Z.M., H.B. and M.L.J. are full or part time employees of Novo Nordisk A/S. K.N. serves as adviser to Sanofi, Medtronic, Abbott and Novo Nordisk, owns shares in Novo Nordisk, has received research grants from Novo Nordisk and Roche Diabetes Care and has received fees for speaking from Medtronic, Roche Diabetes Care, Rubin Medical, Sanofi, Novo Nordisk, Zealand Pharma and Bayer. S.S. has served on advisory boards for Roche Diabetes Care and Medtronic.

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| Participant | Baseline data HbA1c (mmol/mol) | BMI (kg/m²) | Study end dose (U) | Estimated end dose to reach 6.0 mmol/L (U) | Estimated end dose to reach 5.0 mmol/L (U) |
|---|---|---|---|---|---|
| **1** | 64 | 30.5 | 56 | 47 | 63 |
| **2** | 71 | 30.0 | 22 | 18 | 22 |
| **3** | 87 | 22.0 | 35 | 26 | 31 |
| **4** | 86 | 31.8 | 38 | 23 | 35 |
| **5** | 82 | 36.0 | 123 | 67 | 80 |
| **6** | 70 | 29.6 | 31 | 27 | 33 |
| **7** | 72 | 25.2 | 20 | 19 | 24 |
| **8** | 73 | 34.0 | 44 | 33 | 39 |

*Table 1: Baseline data and results using the improved method for end dose estimation.*

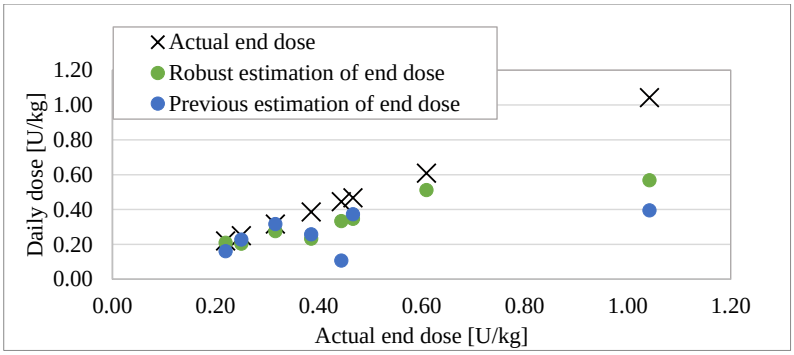


*Fig. 1: A visualization of the primary outcome. Comparison of the estimated end dose to reach 6.0 mmol/L based on insulin data, and CGM data after two weeks, compared to the study end dose for the eight participants.*

Appendix H

# Technical report

**In silico testing of a novel dose guidance approach in a real life and clinical trial setting**

# AN ADAPTIVE DOSE GUIDANCE APPROACH: IN SILICO TESTING IN A CLINICAL TRIAL AND REAL WORLD SCENARIO

A TECHNICAL REPORT

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**ABSTRACT**

Prevalence of type 2 diabetes (T2D) is rapidly increasing worldwide. Although clinical trials of insulin treatment show good results, real world outcomes are poor. This is mainly caused by lack of adherence due to complexity of the treatment. Dose need is highly individual, dose adjustments are empirical, and glycemic targets should be set by clinicians based on physiological risk. We propose an adaptive dose guidance approach with automated glycemic target setting based on glycemic variability. The algorithm uses a previously developed dose need estimation and its uncertainty to propose a next safe and efficient dose. We test the performance *in silico*, and compare to another model-based approach as well as a standard of care algorithm.

## 1 Introduction

Prevalence of diabetes is at an alarming 425 million world wide and is predicted to increase by roughly 50% over the next 25 years [1]. Approximately 90% of cases are type 2 diabetes (T2D), whereof around 30% are prescribed insulin. According to the American Diabetes Association's (ADA) standard of care, treatment with basal insulin should aim at bringing

**Simple titration algorithm**

| Average pre-breakfast SMBG | Dose adjustment |
|---|---|
| >4.9 mmol/L | +2 U |
| 3.9-4.9 mmol/L | No adjustment |
| <3.9 mmol/L | -2 U |

**Stepwise titration algorithm**

| Average pre-breakfast SMBG | Dose adjustment |
|---|---|
| >9.0 mmol/L | +8 U |
| 8.0-8.9 mmol/L | +6 U |
| 7.0-7.9 mmol/L | +4 U |
| 5.0-6.9 mmol/L | +2 U |
| 3.9-4.9 mmol/L | No adjustment |
| 3.1-3.8 mmol/L | -2 U |
| <3.1 mmol/L | -4 U |

Table 1: Examples of simple and stepwise titration algorithms. The ADA recommends to use a simple algorithm during insulin initiation. The stepwise algorithm has been used in clinical studies of insulin degludec titration [6]. The fasting glucose targets vary between algorithms and can be set to ambitious to less stringent values.

self measured blood glucose (SMBG) during fasting to 4.4-7.2 mmol/L [1]. Clinicians should choose a target glucose within this range, depending on the physiological state of the individual. For people with increased risk, such as low life expectancy, long duration of diabetes, risk of hypoglycemia, and severe comorbidities, the target should be higher than for those with lower risk. For adjusting insulin doses, the ADA recommends using a simple titration algorithm, such as the one in Table 1. Real world outcomes of diabetes treatment are poor with an alarming rate of 60% not reaching the recommended treatment targets [2]. Main reasons include poor adherence to treatment, relating to lack of confidence and poor perception of need for medication, and complexity of treatment for both patients and clinicians [2–4]. In the light of no improvements in glycemic outcomes over the last two decades, despite more than 40 new anti-diabetic drugs approved by the FDA, new tools to support clinicians and patients are needed [5].

Software based dose guidance solutions for basal insulin treatment have been emerging over the past years. Examples of solutions available in mobile apps include the Mobile Insulin Dosing System (MIDS) by Glooko, and the Diabetes Insulin Guidence System

(DIGS) solution called the d-Nav by Hygieia, both cleared by the FDA in 2018 and 2019, respectively [7]. Both solutions are automations of clinician instructions. The MIDS solution allows a clinician to input dose adjustment instructions, while the DIGS algorithm uses a fuzzy logic approach, where a set of rules from a team of clinical experts have been automized. One model based approach to basal insulin titration, referred to as the Intelligent Dosing Systems (IDS), was proposed by Cook et al. in 2005 [8]. The IDS uses insulin and SMBG data as input to a response model, and calculates a next dose to reach a desired glycemic target using adaptive learning. All these approaches rely on user input glycemic targets.

In previous work, our research group proposed a novel approach to initiation of insulin degludec (IDeg) treatment. This approach uses glucose and insulin data to predict the dose needed to reach a glycemic target early in the initiation. The expected implications of providing such a prediction are to improve perception of need for medication and reduced complexity.

In this work, we propose an adaptive titration algorithm that uses the dose prediction and its uncertainty to propose a safe and efficient next dose step. We furthermore propose a method for improved personalization, by adjusting the glycemic target based on variability in the glucose data. We compare the performance of the proposed algorithm *in silico* with standard of care and the IDS algorithms. We simulate a clinical trial scenario, where we expect adherence to be high, as well as a real world scenario with lower adherence to both insulin injections and dose adjustments. Algorithm performance is measured by frequency of participants with average two week SMBG below the 7.2 mmol/L target at end of the *in silico* study, and frequency of low SMBG measurements, with hypoglycemia defined as SMBG < 3.9 mmol/L and severe hypoglycemia events if SMBG < 3.0 mmol/L, as defined by the International Hypoglycemia Study Group [9].

Section 2 presents the proposed algorithm and state of the art titration approaches, as well as the *in silico* environment used for performance comparison. In Section 3 we present our results from simulation studies, and Section 4 presents our conclusion.

## 2 Methods

In previous work we proposed a method of predicting the dose needed to reach a glycemic target, early in basal insulin initiation [10]. Here we propose methods for using the target dose estimate for iterative dose adjustments. We furthermore propose a method for varying the glycemic target based on variability in SMBG data, and measure performance *in silico*. We compare the performance to standard of care algorithms and a previous computer based

dose guidance algorithm, the IDS. The previous work, which this work is based on, uses data from six clinical studies of IDeg initiation in T2D. Dose adjustments were performed once weekly based on three SMBG measurements, using the Stepwise titration algorithm, see Table 1. For *in silico* testing in this work, we assume a similar setup where three SMBG measurements are available per week for 25-52 weeks.

### 2.1 Iterative dose adjustments to estimated target dose

Given SMBG and insulin data, $(I_1, G_1), \ldots (I_k, G_k)$, where $I_i = I(t_i)$ [U/kg] and $G_i = G(t_i)$ [mmol/L], we start by assuming that a target dose estimation, $\hat{I}_{target,k}$ [U/kg], with standard deviation $\hat{s}_k^2$, is available at time $t_k$. The method of determining $\hat{I}_{target,k}$ is described in previous work [10]. $\hat{I}_{target,k}$ is available only if both parameters of the dose response model have been identified and are significantly different from zero. To determine the next administered dose, we use the confidence interval of the dose estimate, and recommend the smallest dose within this confidence interval. I.e., the next dose, $I_{k+1}$ is calculated by

$$I_{k+1} = \hat{I}_{target,k} - t_{\alpha,k-m}\hat{s}_k \tag{1}$$

where $k$ is the number of data points available and $m$ is the number of parameters in the model. $t_{\alpha,k-m}$ is the Student's t inverse cumulative distribution function with $k-m$ degrees of freedom for the $(1-\alpha)$ one sided confidence interval. In this work we use the 80% confidence interval.

If the current dose is already above the lower 80% confidence interval, and the average of the last three SMBG measurements is above the lower limit of the target range, then the algorithm allows taking steps towards the mean predicted target dose, i.e.,

$$I_{k+1} = I_k + \mu(\hat{I}_{target,k} - I_k) \tag{2}$$

where $\mu$ determines the size of the step towards the mean. Here we set $\mu = 0.5$.

If the current dose is larger than the predicted target dose, and the average of the last three SMBG measurements is above the lower target range, the dose is not changed. Otherwise, the dose is set to the lower confidence interval as in (1). The algorithm becomes

$$I_{k+1} = \begin{cases} I_k + \mu(\hat{I}_{target,k} - I_k) & I_k < \hat{I}_{est,k} \wedge \mathcal{G}_k > G_{lower} \\ I_k & I_k > \hat{I}_{target,k} \wedge \mathcal{G}_k > G_{lower} \\ \hat{I}_{target,k} - t_{\alpha,k-m}\hat{s}_k & \text{otherwise} \end{cases} \tag{3}$$

where $\mathcal{G}_k$ is the mean of the last three SMBG measurements. This adaptive algorithm is not a first dose calculator. Therefore, the first dose adjustments must be determined by a clinician or by another titration algorithm.

If the dose prediction is not available (due to, e.g., dose response model parameters not significantly estimated) another algorithm should be used. In this implementation we use the Stepwise titration algorithm in Table 1.

### 2.2 Moving target

The ADA recommends setting a personalized glucose target based on risk factors, including hypoglycemia, drug adverse effects, life expectancy, and comorbidities [1]. The lower the risk, the more stringent the glucose target may be set. In general, the target should be within 4.4-7.2 mmol/L. Glucose variability and risk of hypoglycemia are closely related [11]. Assuming that the SMBG measurements are normally distributed and independent of glucose concentration, we base the target glucose at time $t_k$, $G_{target,k}$, on the estimated variance of the measurements. We want 90% of the measurements to be above the lower target, while the target should be within 4.4-7.2 mmol/L. We therefore set

$$G_{target,k} = \min\left\{G_{max}, \quad G_{min} + t_{\alpha,k-m}\hat{\sigma}_t\right\} \tag{4}$$

where $\hat{\sigma}_k$ is the estimated standard deviation of the residuals at time $t_k$, $G_{min} = 4.4$ mmol/L and $G_{max} = 7.2$ mmol/l.

### 2.3 The Intelligent Dosing System

The adaptive dose guidance system, published in 2005 by Cook et al., is based on a similar idea as the method proposed here. The IDS uses patient-specific dose response data and a mathematical model to calculate a next basal insulin dose [8]. In brief, a linear dose response model is combined with a stochastic loop to account for individualization. A next dose, $I_{k+1}$, is the sum of the current dose, $I_k$, and a relative change in dose, $\Delta I_k$, and the stochastic loop,

$$I_{t+1} = I_t\left(1 + \Delta I_t\right) + Loop \tag{5}$$

where the relative change in dose is calculated by

$$\Delta I_k = \frac{\text{Change in level function}}{\text{Linearity function}} \tag{6}$$

The Change in level function is a relative distance in the current glucose level, $G_k$, from the desired glucose level, $G_{target}$,

$$\text{Change in level function: } \frac{G_k - G_{target}}{G_k} \tag{7}$$

and the Linearity function is drug specific describing the expected response to the drug,

$$\text{Linearity function: } 1 + \frac{I_k}{range} \tag{8}$$

where $range$ is set to 60 mg/dL for long acting insulin, corresponding to 3.33 mmol/L. For personalization, the IDS algorithm includes a learning approach, by adding a stochastic loop that either increases or decreases the next dose, $I_{k+1}$, based on its ability to predict the current level from previous data,

$$Loop = 0.2I_k \left( \frac{\Delta\bar{G}_k - \Delta G_k}{\Delta G_k} \right) \left( 1.3^{-I_k/range} \right) \tag{9}$$

Here, $\Delta G_k$ is the actual change in glucose level,

$$\Delta G_k = G_k - G_{k-1} \tag{10}$$

and $\Delta\bar{G}_k$ is the expected change in glucose level, i.e., the difference between a predicted current glucose level, $\bar{G}_k$, and the actual previous level, $G_{k-1}$,

$$\Delta\bar{G}_k = \bar{G}_k - G_{k-1} \tag{11}$$

where

$$\bar{G}_k = G_{k-1} \left( 1 + \frac{I_{k-1} - I_k}{I_{k-1}} \left( 1 + \frac{I_{k-1}}{range} \right) \right) \tag{12}$$

and the term $1.3^{-I_k/range}$ is a drug specific nonlinear response model. The stochastic loop is a learning term that allows the algorithm to adjust the dose steps depending on its ability to predict glucose response. If the expected change in glucose, $\Delta\bar{G}_k$, and the actual change in glucose, $\Delta G_k$, are equal, the stochastic loop equals zero and the calculated next dose is not changed. If the expected change is 50% lower than the the actual change, then 50% (of the 20% of the current dose) is subtracted from the calculated dose.

Note that the stochastic loop includes a term with the actual glucose change in the denominator. This means that in some situations, e.g., when insulin is changed by small amounts leading to small changes in the glucose concentrations, this term may become close to or equal to zero. This would cause the stochastic loop to become unstable. We therefore only allow the IDS algorithm to recommend dose changes until the target glucose is reached. To determine when target glucose is reached, we use the same approach as in previous work, see Definition 2.2 in [10]. When target has been reached, the dose is not changed.

Similar to the algorithm proposed in this work, the IDS algorithm is not a first dose calculator. Therefore it relies on either a clinician or a titration algorithm for the first few steps, until a dose response is detected. In this work we use the Stepwise titration algorithm in Table 1 for the first three dose adjustments.

### 2.4 *In silico* testing

To evaluate the safety and efficiency of the dose guidance algorithms, we perform a simulation study. We generate an *in silico* population of patients, based on the dose response

models identified from clinical trial data [12]. We validate the *in silico* population by simulating a clinical trial with the same protocol as in the dataset and compare outcomes. Finally, we perform two simulation studies to evaluate the performance of the adaptive dose prediction approach compared to standard of care algorithms and the IDS, in 1) a study evaluating safety in a clinical trial, and 2) a study evaluating safety and efficiency in a real world scenario with suboptimal adherence to treatment.

We use two dose response models, identified in previous work, and the corresponding identified parameter distributions to generate a population of *in silico* patients with T2D [12]. We create the $i$-th participant with T2D by drawing from the following distributions, according to [12]:

**Body weight [kg]:** $BW_i \sim \mathcal{N}(82.0, (19.2)^2)$

**Coefficient of variation [%]:** $\sigma_{CV,i} \sim \mathcal{N}(13.9, (5.3)^2)$

**Dose response model:**

- Linear dose response model with probability 81.5%,

$$G_t = \alpha - \beta I_t \tag{13}$$

with $G_t$ [mmol/L] and $I_t$ [U/kg] and corresponding parameter distribution

$$\ln \begin{bmatrix} \alpha \\ \beta \end{bmatrix} \sim \mathcal{N}\left( \begin{bmatrix} 2.27 \\ 2.21 \end{bmatrix}, \begin{bmatrix} 0.06 & 0.05 \\ 0.05 & 0.29 \end{bmatrix} \right) \tag{14}$$

with $\alpha$ [mmol/L] and $\beta$ [(mmol/L)/(U/kg)].

- Nonlinear dose response model with probability 18.5%,

$$G_t = \alpha - \gamma\sqrt{1 + I_t} \tag{15}$$

with $G_t$ [mmol/L] and $I_t$ [U/kg] and corresponding parameter distribution

$$\ln \begin{bmatrix} \alpha \\ \gamma \end{bmatrix} \sim \mathcal{N}\left( \begin{bmatrix} 2.81 \\ 2.16 \end{bmatrix}, \begin{bmatrix} 0.04 & 0.06 \\ 0.06 & 0.12 \end{bmatrix} \right) \tag{16}$$

with $\alpha$ [mmol/L] and $\gamma$ [(mmol/L)(U/kg)$^{-1/2}$].

We generate glucose measurements, $\hat{G}_t$, using the dose response models and add glucose coefficient of variation (CV) by

$$\hat{G}_t = G_t + v_t, \quad v_t \sim \mathcal{N}(0, G_t\sigma_{CV,i}) \tag{17}$$

We use this as input to the dose guidance algorithms and to evaluate their performance.

| | Clinical trial data | In silico population |
|---|---|---|
| N | 1.925 | 10.000 |
| Baseline glucose [mmol/L] | 8.7 (2.6) | 8.7 (2.4) |
| Body weight [kg] | 82.0 (19.2) | 82.1 (19.2) |
| Lower target dose [U] | 29 (25) | 30 (24) |
| Upper target dose [U] | 49 (34) | 53 (29) |
| CV of de-trended data [%] | 13.9 (5.3) | 12.6 (4.7) |
| Average last two week SMBG [mmol/L] | 5.3 (0.9) | 4.9 (0.6) |
| Hypoglycemia (<3.9 mmol/L) [%] | 4.5 | 4.6 |
| Severe hypoglycaemia (<3.0 mmol/L) [%] | 0.4 | 1.1 |

Table 2: Comparison of data from a clinical trial and a simulated clinical trial.

## 3 Results

In this section we validate the *in silico* population by simulating a 26 week clinical trial, similar to the clinical trials in the data set. We then use the *in silico* environment to simulate clinical trials and compare glycemic outcomes. We then simulate real world scenarios where adherence is low in terms of missed doses and dose adjustments.

### 3.1 Validation of *in silico* environment

We simulate a 26 week clinical trial including 10.000 subjects with T2D, using the Stepwise titration algortihm in Table 1. We observe that the baseline glucose, body weight, SMBG variability and target doses are similar for the clinical trial data and the simulated population, see Table 2. Hypoglycemia is overestimated in the simulations and the average of the last two week SMBG data is slightly underestimated. Due to these differences, we use the results to rank the performance of the titration algorithms with respect to hypoglycemia and average SMBG at end of study, rather than as indications for absolute values of outcome measures.

### 3.2 Performance in a clinical trial

Using the *in silico* environment, we now simulate a 26 week clinical trial where we compare performance of the proposed adaptive algorithm with standard of care titration algorithms, see Table 1, and the IDS. As we are simulating a clinical trial, we assume full adherence, i.e., all doses are administered and all dose adjustments are performed once weekly, according to the study protocol. All participants receive an initial dose of 10 U of basal insulin.

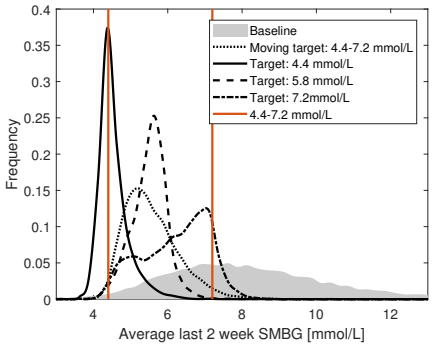


Figure 1: Frequency of average last 2 week SMBG measurements for the adaptive dose prediction algorithm in an *in silico* clinical trial.

We observe that over 26 weeks, the standard of care algorithms bring 90.8-99.5% of participants to the ADA target of 4.4-7.2 mmol/L at end of study, see Table 3. For the Stepwise algorithm, 5.2% of SMBG values are below 3.9 mmol/L and 0.6% below 3.0 mmol/L. Using the adaptive dose prediction approach with a target of 5.8 mmol/L (middle of ADA target range), we achieve a higher frequency of participants in target at end of study, with a lower frequency of hypoglycemia events. Frequency of hypoglycemia events can be lowered further using a higher target or a variable target, while the frequency of participants reaching target at end of study slightly decreases. The IDS algorithm performs worse in terms of both number of participants reaching the glycemic target, and frequency of hypoglycemia events.

The glycemic outcomes of the adaptive dose prediction algorithm for different targets are illustrated in Figure 1. Considering all three outcomes in Table 3 and the glycemic outcomes in Figure 1, the adaptive dose prediction algorithm with variable target performs best.

### 3.3 Simulation of a real world adherence scenario

In general, adherence to treatment is expected to be higher in clinical trials than in a real world scenario [5]. Insulin titration is complex and cumbersome, and often patients lack confidence in performing dose adjustments at home. Here we compare the performance of the proposed algorithm with standard of care algorithms and the IDS in a 52 week

**Standard of care**

| | Simple | Stepwise |
|---|---|---|
| Glycemic target | 4.0-5.0 | 4.0-5.0 |
| In ADA target | 90.8% | 99.5% |
| SMBG < 3.9 mmol/L | 4.2% | 5.2% |
| SMBG < 3.0 mmol/L | 0.5% | 0.6% |

**Adaptive personalized algorithms**

| | Adaptive dose prediction | | | |
|---|---|---|---|---|
| | Fixed target | | | Moving target |
| $G_{target}$ | 4.4 | 5.8 | 7.2 | 4.4-7.2 |
| In ADA target | 100% | 99.8% | 87.8% | 97.4% |
| SMBG < 3.9 mmol/L | 11.7% | 2.9% | 2.2% | 2.5% |
| SMBG < 3.0 mmol/L | 1.2% | 0.4% | 0.3% | 0.3% |

**Alternative model based algorithms**

| | Linear control | | IDS | |
|---|---|---|---|---|
| $G_{target}$ | 4.4 | 7.2 | 4.4 | 7.2 |
| In ADA target | 99.9% | 67.4% | 86.7% | 84.8% |
| SMBG < 3.9 mmol/L | 7.1% | 2.4% | 8.2% | 8.0% |
| SMBG < 3.0 mmol/L | 1.1% | 0.6% | 4.7% | 4.5% |

Table 3: Results of dose guidance algorithm comparison in a 26 week simulated clinical trial of 10.000 *in silico* participants, where doses are adjusted once weekly.

scenario where adjustments are only performed at clinic visits every three months. For illustration, Figure 2 shows an example of the adaptive dose prediction algorithm with a moving glycemic target, in this real world scenario.

Studies have shown that around 40% of people with T2D reach glycemic targets [2]. The *in silico* test of standard of care algorithms slightly overestimates the number of participants reaching the ADA target, with a rate of 55.3-77.9%, see Table 4. This is expected as we slightly underestimated average SMBG concentration at end of study in the simulations, see Table 2.

We observe that the number of participants reaching target can be increased with the adaptive algorithms. The adaptive dose prediction with a moving target increases the number of participants reaching target, while lowering the frequency of hypoglycemia events. The IDS has the highest frequency of hypoglycemia events.

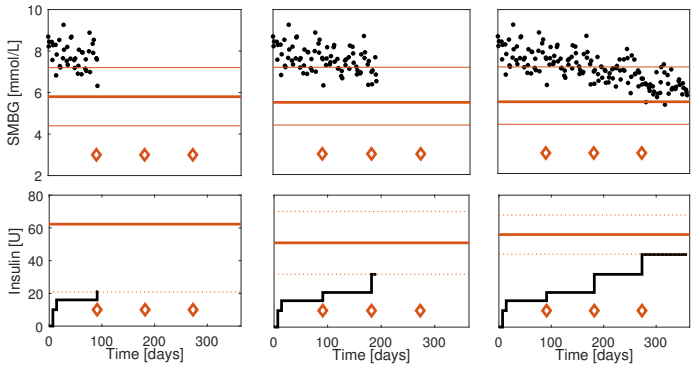


Figure 2: The adaptive dose prediction algorithm in the real world scenario with full adherence to injections. Doses are adjusted at clinic visits (diamonds) only. The ADA glycemic target is indicated by thin lines in the top and the moving target with a thick line in between. The predicted target dose is illustrated by a tick line in the bottom figures and its 80% CI in dotted lines.

Studies on adherence to insulin injection therapy have found that approximately 20-40% of injections are omitted [13–15]. We therefore test the algorithms in a scenario where doses are omitted in 30% of cases at random, and doses adjusted every three months. In the case of low adherence to injections, we do not expect all participants to reach the glycemic target. In order to reach the glycemic target, the medicine has to be administered. We therefore aim at showing stability in terms of low frequency of hypoglycemia, despite the poor adherence, rather than improve number of participants reaching target.

We observe that the number of participants reaching the ADA target decreases to 42.2-60.2% using the standard of care algorithms, see Table 5. This is somewhat in line with the observed number of people with T2D reaching glycemic targets [2]. In this scenario, we observe that with a moving target, the hypoglycemia rates can be decreased and number of people reaching targets increased, as compared to the Stepwise algorithm. Compared to the Simple titration algorithm, the number of hypoglycemia events is similar while number of people reaching targets is increased. The IDS performs poorly in terms of freqyency of hypoglycemia.

**Standard of care**

| | Simple | Stepwise |
|---|---|---|
| Glycemic target | 4.0-5.0 | 4.0-5.0 |
| In ADA target | 55.3% | 77.9% |
| SMBG < 3.9 mmol/L | 1.8% | 2.3% |
| SMBG < 3.0 mmol/L | 0.2% | 0.3% |

**Adaptive dose estimation algorithm**

| | Dose prediction | | | |
|---|---|---|---|---|
| | Fixed target | | | Moving target |
| $G_{target}$ | 4.4 | 5.8 | 7.2 | 4.4-7.2 |
| In ADA target | 89.3% | 86.6% | 69.5% | 78.8% |
| SMBG < 3.9 mmol/L | 3.4% | 1.9% | 1.8% | 1.8% |
| SMBG < 3.0 mmol/L | 0.4% | 0.3% | 0.3% | 0.2% |

**Alternative model based algorithms**

| | Linear control | | IDS | |
|---|---|---|---|---|
| $G_{target}$ | 4.4 | 7.2 | 4.4 | 7.2 |
| In ADA target | 83.9% | 62.8% | 88.0% | 87.3% |
| SMBG < 3.9 mmol/L | 3.2% | 2.7% | 5.4% | 5.2% |
| SMBG < 3.0 mmol/L | 0.6% | 0.5% | 2.5% | 2.4% |

Table 4: Results of dose guidance algorithm comparison in a 52 week simulated real world scenario of 10.000 *in silico* participants, where doses are only adjusted at clinic visits every three months.

**Standard of care**

| | Simple | Stepwise |
|---|---|---|
| Glycemic target | 4.0-5.0 | 4.0-5.0 |
| In ADA target | 42.2% | 60.2% |
| SMBG < 3.9 mmol/L | 2.0% | 4.4% |
| SMBG < 3.0 mmol/L | 0.3% | 1.4% |

**Adaptive dose estimation algorithm**

| | Dose prediction | | | |
|---|---|---|---|---|
| | Fixed target | | | Moving target |
| $G_{target}$ | 4.4 | 5.8 | 7.2 | 4.4-7.2 |
| In ADA target | 79.0% | 59.0% | 31.3% | 50.7% |
| SMBG < 3.9 mmol/L | 5.4% | 2.0% | 1.7% | 1.8% |
| SMBG < 3.0 mmol/L | 1.1% | 0.5% | 0.4% | 0.5% |

**Alternative model based algorithms**

| | Linear control | | IDS | |
|---|---|---|---|---|
| $G_{target}$ | 4.4 | 7.2 | 4.4 | 7.2 |
| In ADA target | 38.6% | 29.9% | 63.8% | 63.8% |
| SMBG < 3.9 mmol/L | 2.9% | 2.3% | 15.0% | 15.0% |
| SMBG < 3.0 mmol/L | 0.8% | 0.7% | 12.5% | 12.5% |

Table 5: Results of dose guidance algorithm comparison in a 52 week simulated real world scenario of 10.000 *in silico* participants, where 30% of doses are missed and doses are only adjusted at clinic visits every three months.

## 4 Conclusion

In this work we proposed a dose prediction algorithm for basal insulin initiation in T2D with adaptive dose steps to reach the recommended glycemic target. We furthermore introduced a moving glycemic target which uses glycemic variability to reduce risk of hypoglycemia. We compared the performance of the algorithm in *in silico* simulations of clinical trials and real world scenarios. The results indicate that performance with respect to safety and efficiency is improved with the adaptive dose prediction algorithm, as compared to standard of care algorithms and a previous computer based dose guidance algorithm. Having a moving glycemic target improved the outcomes in most cases, when considering the number of participants reaching the ADA recommended glycemic target as well as frequency of hypoglycemia.

The proposed algorithm adjusts the glycemic target within the ADA recommended 4.4-7.2 mmol/L based on variability in the SMBG data. In the Standards of Medical Care in Diabetes, the ADA recommends setting a personalized glucose target based on risk factors including hypoglycemia, drug adverse effects, age, and comorbidities [1]. The lower the risk, the more stringent the glucose target may be set. Adding other factors than the glucose variability may therefore be of interest. This could be done, e.g., through user input and could be variable as in the current implementation or fixed to a value chosen by the clinician.

These results should be considered as indicative of, and specific to, the potential of the proposed algorithm in IDeg treatment in T2D. The algorithm should be adjusted for use with other medications. When implementing the previous computer based dose guidance algorithm, the IDS, we used a published tuning constant value for long acting insulin. The performance of the IDS algorithm may be improved by fine-tuning. However, the problems discussed with instability etc. still remain.

We believe that automatic personalization of dose steps and glycemic target has the potential to improve glycemic outcomes in the real world. This adaptive dose guidance approach may be used in combination with a dose prediction, for improved perception of need for medication and improved safety, and thereby less fear of adjusting doses at home.

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Appendix I

# Conference paper

## Model predictive control with sub-frequency actuation for long acting insulin treatment in type 2 diabetes

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# Model predictive control with sub-frequency actuation for long acting insulin treatment in type 2 diabetes

Tinna B. Aradóttir[1,2], Dimitri Boiroux[1], Henrik Bengtsson[2], John B. Jørgensen[1] and Niels K. Poulsen[1]

***Abstract*— Type 2 diabetes (T2D) accounts for 90% of the diabetes patients, and more than 60% of patients on insulin fail to reach treatment targets. The main reasons include low adherence to treatment, caused by, among other reasons, complexity and fear of overdosing.**

**In insulin titration, pre-breakfast SMBG measurements are used for dose calculations. However, glucose values may be lower between the daily SMBG measurements. Not considering this may lead to over-titration. We propose a dose guidance algorithm to identify individualized optimal dosing of long acting insulin for T2D patients.**

**We use a compartment model of fasting glucose and long acting insulin dynamics in T2D to develop a model predictive control (MPC) based decision support system. To promote safety, the controller optimizes the daily dose based on predicted fasting glucose values with faster sampling than available data allows. We test the performance of the controller with respect to safety and efficacy in a simplified *in silico* environment and compare the results with standard of care dose guidance. The aim of this paper is to illustrate the importance of fast sampling in prediction between the slow input samples. This importance is observable in the results, which are indicative of the potential of such an approach.**

## I. Introduction

Diabetes has become an epidemic, and the International Diabetes Federation predicts that the number of patients will grow by 50% in the next 20 years [1]. In the United States of America, an estimated 20% of all health care expenditure are used in diabetes care [2]. The most common type of diabetes, type 2 diabetes (T2D), accounts for 90% of diabetes cases and is caused by inadequate production of and response to insulin. If not treated, long term elevated glucose concentration in the blood can lead to serious complications such as cardiovascular disease, nerve damage, foot damage and more, while too low glucose concentration can cause brain damage, coma and death in the worst case.

The Standards of Medical Care in Diabetes recommend treating T2D with oral medication and intensifying to insulin injections if necessary [3]. There are two main types of insulin, fast acting for compensating for elevated glucose following meal intake, and long acting for lowering baseline glucose concentration. In this work we focus on long acting insulin initiation and treatment.

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Long acting insulin initiation involves determining the dose needed to decrease glucose concentration to a target range, while avoiding overdosing. In standard of care, pre-breakfast self-monitoring blood glucose (SMBG) values are used to determine whether the dose of insulin should be increased or decreased based on a simple algorithm. Table I illustrates an example of such a paper based algorithm. The complexity of the dose intensification, including logging SMBG measurements and doses, calculating averages and adjusting dose size, including other issues, causes health care professionals and patients to be reluctant to insulin initiation. While more than 60% of patients do not reach the glucose targets [4], a review of studies on prevalence of hypoglycemia (low blood glucose) concluded that more than half of patients experience hypoglycemia, with an incidence of 23 events per year [5].

Extensive ongoing work has been done on dose guidance in type 1 diabetes. This work has mainly been focused on closed loop control with subcutaneous insulin infusion using MPC or other control methods [7], [8]. Some work has been done on closed loop control in T2D, e.g., in [9]. Previous work on automatic dose guidance for insulin injections in T2D includes the Intelligent Dosing System [10], where fasting SMBG data are used to generate a simple mathematical model, which is then used to calculate a new dose that brings glucose to a next (varying) therapeutic goal. Another system, the Diabetes Insulin Guidance System, uses fuzzy logic based on medical doctor decision rules and pre-breakfast SMBG data, and has been found to improve glycemic control significantly [11].

This work aims to explore the possibility of using an MPC based approach to initiating and maintaining long acting insulin treatment. A number of dynamic compartment models of type 1 diabetes and T2D exist. Most models are designed for 24 hour simulations of post-meal glucose

TABLE I

An example of a paper based insulin titration algorithm used for insulin degludec with once weekly dose adjustments [6].

| Average of last three pre-breakfast SMBG [mmol/L] | Dose adjustment |
|---|---|
| $< 3.1$ | -4U |
| $3.1 - 3.9$ | -2U |
| $4.0 - 5.0$ | In target: no change |
| $5.1 - 7.0$ | +2U |
| $7.1 - 8.0$ | +4U |
| $8.1 - 9.0$ | +6U |
| $> 9.0$ | +8U |

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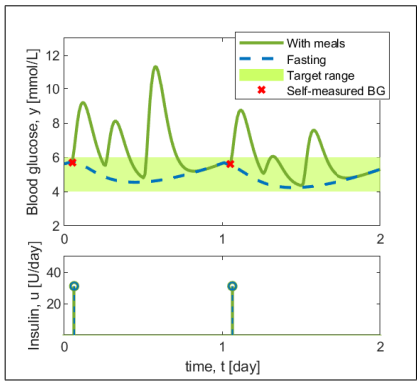


Fig. 1. Simulations of glucose concentration during two days where long acting insulin is administered pre-breakfast. The green curve illustrates how three meals per day temporarily elevate glucose concentration, the blue dotted line illustrates a simulation where no meals were given, and the red dots illustrate pre-breakfast SMBG measurements, typically used in standard of care.

dynamics rather than long term simulations of glucose to long acting insulin dynamics [12]–[15]. Specifically for T2D, the recent work by Holder-Pearson et al. aims to identify insulin sensitivity in early and progressed T2D [16], while the work in [17]–[19] aims to model fasting glucose in response to long acting insulin over an extended period of time.

In this paper we design an MPC-based dose guidance algorithm for long acting insulin treatment using a dynamic compartment model of T2D for both initiation and maintenance. Section II describes the problem statement of this paper. Section III introduces the dynamic compartment model used for simulations and design of the MPC, and describes the design of the MPC with hard and soft constraints and sub-frequency actuation. Section IV shows the results, and finally we include a discussion in Section V.

## II. Problem statement

In standard of care, dose guidance algorithms aim at bringing glucose concentrations at one time of day to a target value. This may be problematic in cases where the measured glucose does not reveal the most critical glucose concentration of the day, i.e., if lowest glucose values are not captured by the measurements. Fig. 1 illustrates this concept. Different factors contribute to variations in glucose such as insulin injections, food intake, illness, stress and exercise. In this paper we aim to design a dose guidance algorithm that predicts the lowest glucose concentrations of each day, to safely and effectively bring glucose concentrations to target.

## III. Methods

### A. Dynamic compartment model

For the purpose of simulating fasting glucose in T2D and to design the MPC, we use the model described in [18]. The model has four compartments, where the first two describe transition of long acting insulin from subcutaneous tissue to the blood, the third describes insulin effect on glucose from both endogenous and exogenous insulin, and the last compartment describes changes in glucose concentration.

Fig. 2 illustrates a model diagram with four ordinary differential equations,

$$\frac{dx_1}{dt}(t) = \frac{1}{p_1}u(t) - \frac{1}{p_1}x_1(t) \tag{1a}$$
$$\frac{dx_2}{dt}(t) = \frac{1}{p_1}x_1(t) - \frac{1}{p_1}x_2(t) \tag{1b}$$
$$\frac{dx_3}{dt}(t) = p_3[x_2(t) + p_7 x_4(t)] - p_3 x_3(t) \tag{1c}$$
$$\frac{dx_4}{dt}(t) = -[p_5 + p_4 x_3(t)]x_4(t) + p_6 \tag{1d}$$

where $u$ is exogenous long acting insulin [U/day], $x_1$ and $x_2$ denote subcutaneous and plasma insulin rates [U/day] with time constant $p_1$ [day]. $x_3$ is insulin effect on glucose [U/day] and $p_3$ is an inverse time constant for delay in insulin action [1/day]. $p_7$ describes endogenous insulin production [(U/day)/(mmol/L)] which is assumed to increase linearly with fasting glucose, similar to for example the model in [16]. $x_4$ is glucose concentration in plasma [mmol/L], $p_4$ is insulin sensitivity [1/U], $p_5$ is an inverse time constant for effect of glucose to eliminate glucose from plasma [1/day] and $p_6$ is rate of endogenous glucose production [(mmol/L)/day]. We assume here that $x_4$ is measurable, although this model does not account for the delay from plasma to subcutaneous tissue. For the purpose of this work, where insulin is dosed once daily, we do not consider this delay important to the performance. However, one may model this delay, e.g., [20].

For simulation, we use the model as described in (1). To design the MPC, we linearize the model around a point of interest, $x_{ss} = 5$ mmol/L, and the continuous time model becomes

$$\frac{dx}{dt}(t) = A_c(x(t) - x_{ss}) + B_c(u(t) - u_{ss}) \tag{2a}$$
$$y(t) = C_c(x(t) - x_{ss}) + y_{ss} \tag{2b}$$

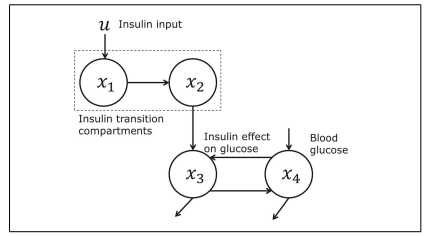


Fig. 2. A diagram of the dynamic compartment model in (1)

where

$$A_c = \begin{bmatrix} -\frac{1}{p_1} & 0 & 0 & 0 \\ \frac{1}{p_1} & -\frac{1}{p_1} & 0 & 0 \\ 0 & p_3 & -p_3 & p_3 p_7 \\ 0 & 0 & -p_4 x_{4,ss} & -(p_5 + p_4 x_{3,ss}) \end{bmatrix} \quad (3a)$$

$$B_c = \begin{bmatrix} \frac{1}{p_1} & 0 & 0 & 0 \end{bmatrix}^T, \quad C_c = \begin{bmatrix} 0 & 0 & 0 & 1 \end{bmatrix} \quad (3b)$$

We discretize the system such that

$$x_{k+1} - x_{ss} = A_s(x_k - x_{ss}) + B_s(u_k - u_{ss}) \quad (4a)$$

$$y_k - y_{ss} = C_s(x_k - x_{ss}) \quad (4b)$$

where $A_s, B_s$ and $C_s$ are found by

$$A_s = \exp\left(A_c(t)T_s\right) \quad (5a)$$

$$B_s = A_d B_c = \exp\left(A_c(t)T_s\right) B_c \quad (5b)$$

$$C_s = C_c \quad (5c)$$

assuming that the input is an impulse. We set the sampling frequency to $T_s = 1$ hour.

The blue dashed line in Fig. 1 illustrates a simulation of the non-linear model over 48 hours where two insulin injections are given at the beginning of a day. For illustration, the effect of three meals per day is shown in green, and the SMBG values in standard of care treatment in red. For simulations we use the parameter values in Table II.

### *B. Model predictive control*

We now describe the design of the linear MPC algorithm, which is based on the linearized dynamic compartment model previously described. The following descriptions assume physical variables instead of deviation variables, i.e., we set $\bar{x}_k = x_k - x_{ss}, \bar{y}_k = y_k - y_{ss}$ and $\bar{u}_k = u_k - u_{ss}$.

*1) Offset-free control:* For offset-free control, we use the method for disturbance modelling, described by Pannocchia and Rawlings [22]. We have the augmented system in discrete time,

$$\bar{x}_{k+1} = A_s\bar{x}_k + B_s\bar{u}_k + B_d\bar{d}_k \quad (6a)$$

$$\bar{d}_{k+1} = \bar{d}_k \quad (6b)$$

where $B_d$ and $C_d$ have the appropriate dimensions and ensure that the augmented system is detectable as described in [22]. We define the augmented model by

$$\xi_{k+1} = A\xi_k + Bu_k \quad (7a)$$

$$y_k = C\xi_k \quad (7b)$$

TABLE II

VALUES FOR PARAMETERS IN (1). MEAN (SD) FOR $p_2$ THROUGH $p_6$ AS IN [12]. $p_1$ IS ASSESSED FROM [21] AND $p_7$ IS CALCULATED SUCH THAT A STEADY STATE AT A DESIRED $x_4$ AT ZERO INSULIN IS REACHED.

| | Unit | Value |
|---|---|---|
| $p_1$ | [day] | 0.5 |
| $p_3$ | [1/day] | 15.8 (6.2) |
| $p_4$ | [1/U] | 0.44 |
| $p_5$ | [1/day] | 3.31 |
| $p_6$ | [mmol/L·day] | 96.7 |
| $p_7$ | [U·L/mmol·day] | 2.52 |

where

$$\xi := \begin{bmatrix} \bar{x} \\ d \end{bmatrix} \quad (8)$$

is the augmented state vector and the augmented model matrices are

$$A = \begin{bmatrix} A_s & B_d \\ 0 & I \end{bmatrix} \quad B = \begin{bmatrix} B_s \\ 0 \end{bmatrix} \quad C = \begin{bmatrix} C_s & C_d \end{bmatrix} \quad (9)$$

We determine $B_d$ and $C_d$ by trial end error,

$$B_d = \begin{bmatrix} 10^{-3} & 10^{-3} & 10^{-2} & 8 \times 10^{-2} \end{bmatrix}', \quad C_d = 0. \quad (10)$$

To estimate the disturbance, $\hat{d}$, we use a standard ordinary Kalman filter. We assume information about all states is available, except the disturbance. We do a deterministic simulation and set the process noise in the Kalman filter to $R_1 = I_{n_x} 10^{-1}$ and the measurement variance to $R_2 = 10^{-6}$.

We calculate the innovation, $e_k$ by

$$e_k = \bar{y}_k - \hat{\bar{y}}_{k|k-1} = \bar{y}_k - C\hat{\xi}_{k|k-1} \quad (11)$$

where $\bar{y}_k$ is the measured morning blood glucose and $\hat{\xi}_{k|k-1}$ is the filtered state,

$$\hat{\xi}_{k|k} = \hat{\xi}_{k|k-1} + K_k e_k \quad (12)$$

where

$$K_k = P_{k|k-1}C^T \left(CP_{k|k-1}C^T + R_2\right)^{-1} \quad (13)$$

$$P_{k|k} = (I - K_k C)P_{k|k-1}(I - K_k C)^T + K_k R_2 K_k^T \quad (14)$$

are the Kalman gain and the covariance of the estimates. The one-step prediction of the states and the data update of the covariance are computed by

$$\hat{\xi}_{k+1|k} = A\hat{\xi}_{k|k} + B\bar{u}_k \quad (15)$$

$$P_{k+1|k} = AP_{k|k}A' + R_1 \quad (16)$$

The multistep prediction, for predicting basal glucose levels between input samples, is

$$\hat{\xi}_{k+j+1|k} = A\hat{\xi}_{k+j|k} + B\bar{u}_{k+j|k} \quad j = 0, 1, \ldots, N-1 \quad (17)$$

*2) Sub-frequency actuation:* In this work we inject insulin once daily, but the glucose concentration between input samples is important. We therefore introduce sub-frequency actuation. We define $h$ as the control period (e.g., 1 day), $k$ as the sampling period (e.g., 1 hour) and $m = h/k$ as the number of intervals in the control period (e.g., 24 hours/day). If we assume that the input is given at the first interval of each control period, we set

$$\bar{U} = [\bar{u}_0, 0, \ldots, 0, \bar{u}_1, 0, \ldots, 0, \bar{u}_2, 0, \ldots]' \quad (18)$$

where $\bar{u}_i$ is the input of control period $i$. Let

$$\bar{U} = K\tilde{\bar{U}} \quad \tilde{\bar{U}} = [\bar{u}_0, \bar{u}_1, \bar{u}_2, \ldots]' \quad (19)$$

where

$$K = \begin{bmatrix} 1 & 0 & \ldots & 0 \\ \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & \ldots & 0 \\ 0 & 1 & \ldots & 0 \\ \vdots & \vdots & \vdots & \vdots \end{bmatrix} \quad (20)$$

Then the multistep prediction of the output is

$$\bar{Y}_k = \Phi\hat{\bar{\xi}}_{k|k} + \Gamma K\tilde{\bar{U}}_k \tag{21}$$

where $K\tilde{\bar{U}}_k = [\bar{u}_k, 0, 0, \ldots, \bar{u}_{k+1}, 0, 0, \ldots, \bar{u}_{k+2}, 0, 0, \ldots]'$ and $Y_k = [\hat{y}_{k|k}, \hat{y}_{k+1|k}, \hat{y}_{k+2|k}, \ldots]'$ in deviation variables or

$$Y_k - Y_{ss} = \Phi\hat{\bar{\xi}}_{k|k} + \Gamma(K\tilde{U}_k - U_{ss}) \tag{22}$$

with $K\tilde{U}_k = [u_k, 0, 0, \ldots, u_{k+1}, 0, 0, \ldots, u_{k+2}, 0, 0, \ldots]'$ and $Y_k = [\hat{y}_{k|k}, \hat{y}_{k+1|k}, \hat{y}_{k+2|k}, \ldots]'$ in physical variables and $Y_{ss} = [y_{ss}, y_{ss}, \ldots]'$ and $U_{ss} = [u_{ss}, u_{ss}, \ldots]'$. Here, $\Phi$ is the extended observability matrix, $\Gamma$ is the Toeplitz matrix,

$$\Phi = \begin{bmatrix} CA \\ CA^2 \\ \vdots \\ CA^N \end{bmatrix} \tag{23a}$$

$$\Gamma = \begin{bmatrix} CB & 0 & \ldots & 0 \\ CAB & CB & \ldots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ CA^{N-1}B & CA^{N-2}B & \ldots & CB \end{bmatrix} \tag{23b}$$

*3) Constrained MPC:* We use a standard linear MPC, as described by Maciejowski [23], while the novelty is within the application of sub-frequency actuation and basal glucose control application. We introduce a constant reference $R_k = [r, r, \ldots]'$ for the predicted output $Y_k$, soft output constraints on the output, regularization on the input $\tilde{U}_k$ and constant upper and lower hard constraints on the input, $U_{\min} = [u_{\min}, u_{\min}, \ldots]'$ and $u_{\max} = [u_{\max}, u_{\max}, \ldots]'$. We use a moving horizon, such that at sample $k$ we minimize the objective function

$$\min_{\tilde{U},T,S} \quad \phi = \phi_y + \phi_{\Delta u} + \phi_s + \phi_t \tag{24}$$

for a prediction up to sample $k+N$, where the distance of the output from the reference is penalized by

$$\phi_y = \frac{1}{2}||W_y(Y_k - R_k)||_2^2, \tag{25}$$

where $W_y = I_N \otimes \bar{W}_y$. The change in input penalty is described by

$$\phi_{\Delta u} = \frac{1}{2}||W_{\Delta u}\Delta\tilde{U}_k||_2^2 \tag{26}$$

where $\Delta\tilde{U}_k = [\hat{u}_{k+1|k} - \hat{u}_{k|k}, \hat{u}_{k+2|k} - \hat{u}_{k+1|k}, \ldots]$. We introduce upper and lower soft constraints with different weights in the linear and nonlinear terms

$$\phi_s = \frac{1}{2}||W_{s,2}S_k||_2^2 + ||W_{s,1}S_k||_1 \tag{27a}$$

$$\phi_t = \frac{1}{2}||W_{t,2}T_k||_2^2 + ||W_{t,1}T_k||_1 \tag{27b}$$

where $W_{s,2} = I_N \otimes \bar{W}_{s,2}$, $W_{s,1} = I_N \otimes \bar{W}_{s,1}$, $W_{t,2} = I_N \otimes \bar{W}_{t,2}$ and $W_{t,1} = I_N \otimes \bar{W}_{t,1}$. We penalize the slack variable at the lower boundary harder than the upper boundary. This is due to the severity and acuteness of complications from low blood glucose. The upper and lower hard constraints on the input are

$$U_{\min} \leq \tilde{U}_k \leq U_{\max} \tag{28}$$

where we set the constraints to be constant, $U_{\min} = [u_{\min}, u_{\min}, \ldots]'$, $U_{\max} = [u_{\max}, u_{\max}, \ldots]'$ and $u_{\min} = 0$ U/day and $u_{\max} = 300$ U/day. Finally, for handling the constraints we have

$$\Gamma K\tilde{U}_k - T_k \leq R_{\max} - (\Phi\hat{\bar{\xi}}_{k|k} - \Gamma U_{ss} + Y_{ss}) \tag{29a}$$

$$\Gamma K\tilde{U}_k + S_k \geq R_{\min} - (\Phi\hat{\bar{\xi}}_{k|k} - \Gamma U_{ss} + Y_{ss}) \tag{29b}$$

$$T_k \geq 0 \tag{29c}$$

$$S_k \geq 0 \tag{29d}$$

TABLE III
TUNING WEIGHT MATRICES OF THE PENALTY FUNCTION IN (24).

| In- and output change | | Lower weights | | Upper weights | |
|---|---|---|---|---|---|
| $\bar{W}_y$ | $10^{-1}$ | $\bar{W}_{s,1}$ | $10^{1}$ | $\bar{W}_{t,1}$ | $10^{-1}$ |
| $\bar{W}_{\Delta u}$ | $10^{-8}$ | $\bar{W}_{s,2}$ | $10^{1}$ | $\bar{W}_{t,2}$ | $10^{-1}$ |

The weight values are illustrated in Table III. Input changes have a low weight in the penalty function as we wish to enable the MPC to quickly control the system. We do this for illustration purposes, to show the potential of such a model based dose guidance approach. This should however be reevaluated in a clinical setting for safety, and depends highly on the quality of the model accuracy.

We now write system in the form of a quadratic program,

$$\min_{\tilde{U},T,S} \quad \phi = \frac{1}{2}\begin{bmatrix}\tilde{U}\\T\\S\end{bmatrix}_k' H \begin{bmatrix}\tilde{U}\\T\\S\end{bmatrix}_k + g'\begin{bmatrix}\tilde{U}\\T\\S\end{bmatrix}_k \tag{30a}$$

$$s.t. \quad U_{min} \leq \tilde{U}_k \leq U_{max} \tag{30b}$$

$$\Gamma K\tilde{U}_k - T_k \leq R_{\max} - (\Phi\hat{\bar{\xi}}_{k|k} - \Gamma U_{ss} + Y_{ss}) \tag{30c}$$

$$\Gamma K\tilde{U}_k + S_k \geq R_{\min} - (\Phi\hat{\bar{\xi}}_{k|k} - \Gamma U_{ss} + Y_{ss}) \tag{30d}$$

$$T_k \geq 0 \tag{30e}$$

$$S_k \geq 0 \tag{30f}$$

where the Hessian and coefficient of the linear term are

$$H = \begin{bmatrix} H_y + H_{\Delta u} & 0 & 0 \\ 0 & H_t & 0 \\ 0 & 0 & H_s \end{bmatrix} \quad g = \begin{bmatrix} g_y + g_{\Delta u} \\ g_t \\ g_s \end{bmatrix} \tag{31}$$

with the following for each of the variables

$$H_y = (W_y\Gamma K)'(W_y\Gamma K) \tag{32a}$$

$$g_y = (W_y\Gamma K)'W_y(\Phi\hat{\bar{\xi}}_{k|k} - \Gamma U_{ss} + Y_{ss} - R_k) \tag{32b}$$

$$H_s = W_{s,2}^T W_{s,2} \quad g_s = W_{s,1}e_s \tag{32c}$$

$$H_t = W_{t,2}^T W_{t,2} \quad g_t = W_{t,1}e_t \tag{32d}$$

where $e_s = e_t = [1; 1; \ldots; 1]$ such that $e_s$ and $e_t$ are of the same dimension as slack variables, $S_k$ and $T_k$, and

$$H_{\Delta u} = (W_{\Delta u}\Lambda)^T(W_{\Delta u}\Lambda) \tag{33a}$$

$$g_{\Delta u} = -(W_{\Delta u}\Lambda)^T W_{\Delta u} I_0 u_{t-1} \tag{33b}$$

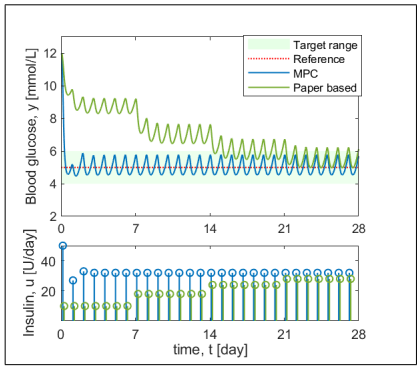


Fig. 3. Fasting glucose and insulin injections during an initiation period. The green and blue curves show a paper based dose guidance and our MPC algorithm. The green area illustrates the desired range where the soft constraints are located, and the red dotted line shows the reference.

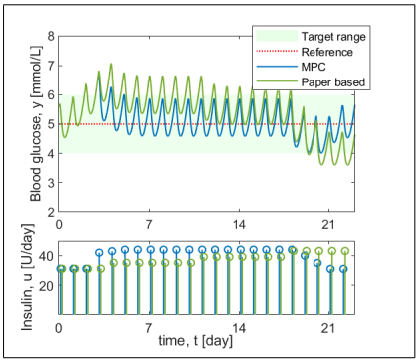


Fig. 4. Fasting glucose and insulin injections during a period of decreased insulin sensitivity. Both dose guidance algorithms increase the dose when insulin sensitivity decreases. The paper based algorithm fails to decrease the dose when insulin sensitivity returns to normal.

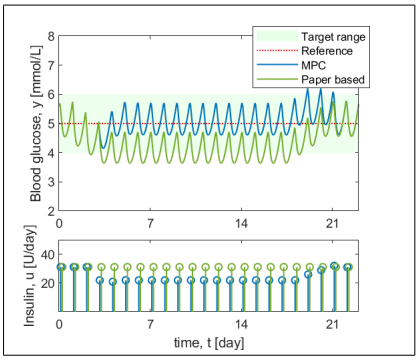


Fig. 5. Fasting glucose and insulin injections during a period of increased insulin sensitivity. The paper based dose guidance algorithm fails to decrease the doses when insulin sensitivity increases. The MPC dose guidance responds to the physiological change by temporarily decreasing the injections.

with $W_{\Delta u} = I_M \otimes \bar{W}_{\Delta u}$ and

$$\Lambda = \begin{bmatrix} I & & & \\ -I & I & & \\ & \ddots & \ddots & \\ & & -I & I \end{bmatrix} \qquad I_0 = \begin{bmatrix} I \\ 0 \\ \vdots \\ 0 \end{bmatrix} \tag{34}$$

We use the weight tuning values as in Table III. In this implementation we set $N = 168$ which corresponds to $M = 7$ days.

## IV. Results

We compare the performance of the offset-free MPC with a paper based titration algorithm, with respect to safety and efficacy. The paper based titration algorithm is illustrated in Table I, where dose adjustments are made once weekly from an average of the previous three SMBG measurements (here defined as the first glucose value of each day). We test the algorithms in simulated scenarios of insulin initiation and treatment maintenance, where parameters vary due to exercise and illness. The purpose of these tests are for concept illustration and first feasibility evaluation.

### A. Treatment initiation

We compare the performance of the two algorithms in insulin initiation. Fig. 3 illustrates a simulation of four weeks, where fasting glucose is initially $x_4(0) = 12$ mmol/L and decreases over time to the reference $r = 5$ mmol/L. The MPC clearly performs better with respect to efficacy, as fasting glucose reaches target on day 1, while paper based titration takes more than four weeks to reach the same outcomes. The MPC starts by giving a large dose, and oscillates in the input for a few days around the optimal dose. This may not be user friendly, as the changes in dose size might be confusing for a user (patient/health care professional). We might therefore consider adding hard constraints on change in input for clinical implementation. This may also solve the main problem with an aggressive MPC strategy, i.e., if the model is not accurate, or if a patient's physiological state changes rapidly.

### B. Treatment maintenance

Insulin sensitivity may change intraindividually due to illness, stress, exercise and more. We compare the performance of the two algorithms where insulin sensitivity temporarily changes by 30% over three days. When insulin sensitivity changes, we observe a similar difference as previously in performance of the two algorithms. Fig. 4 illustrates how the decrease in insulin sensitivity causes the paper based algorithm to increase the dose, without correcting the change when insulin sensitivity returns to normal. The offset-free MPC detects the change in insulin sensitivity and corrects

the administration, during the changes in insulin sensitivity. Fig. 5 illustrates a scenario where insulin sensitivity increases temporarily. Again we observe that the paper based algorithm fails to account for the low glucose values outside of the SMBG sampling time, while the offset-free MPC detects the physiological change and corrects the input.

## V. Conclusion

In this paper we have addressed the need for dose guidance in T2D long acting insulin treatment. We designed an offset-free MPC based on a dynamic compartment model of fasting glucose in T2D, and compared its performance with a paper based standard of care dose guidance algorithm in a deterministic in silico simulation. One of the main advantage of the MPC is its ability to base dose guidance on predicted glucose levels where sampling frequency high enough to capture critical values. This is in contrast to paper based algorithms that determine doses based on SMBG values only, often with a frequency of 3 times per week, without considering potential lower glucose throughout the day.

The purpose of this paper was to test the MPC algorithm in an idealized case, i.e., a case where we have access to the model parameters. In reality the algorithm could estimate parameters from continuous glucose monitoring (CGM) data and the MPC should be conservative until the model is identified. This will be addressed in future work, where we will use three months of CGM data from 8 T2D patients initiating long acting insulin treatment. We tested the two algorithms on the nonlinear model, which the MPC was derived from. This is an unrealistic and simplified *in silico* test. The message to be taken from this work is therefore not the absolute performance of the MPC, but rather that when doing basal insulin titration, the output values between inputs are important and not only at input samples. Therefore, we suggest an MPC rather than a simple paper based algorithm.

CGMs and smart administration devices are becoming more accurate and available to larger patient groups. This paves the way for development and use of more sophisticated dose guidance algorithms such as MPC than current standards of care. These algorithms have the potential to increase efficacy and safety of insulin treatment for people with T2D.

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Appendix J

# Journal paper

## Model predictive control for dose guidance in long acting insulin treatment of type 2 diabetes

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# Model predictive control for dose guidance in long acting insulin treatment of type 2 diabetes

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ABSTRACT

Approximately 90% of the people with diabetes have type 2 diabetes (T2D), and more than half of the diabetes patients on insulin fail to reach the treatment targets. The reasons include fear of hypoglycemia, complexity of treatment, and work load related to treatment intensification. This paper proposes a model predictive control (MPC) based dose guidance algorithm to identify an individual's optimal dosing of long acting insulin. We present a model for simulating the effect of long acting insulin on fasting glucose in T2D. We do this by adapting previous models such that slow and non-linear dynamics are identifiable from clinical data. For dose guidance, we use MPC with a novel approach to sub-frequency actuation, to increase safety between input samples. To test the controller, we simulate scenarios with biological variations and different levels of adherence to treatment. The results are compared to a standard of care (SOC) method in insulin dose adjustments.



## 1. Introduction

The prevalence of diabetes is predicted to increase by around 50% over the next 20 years, and diabetes is now considered a pandemic. The costs related to diabetes on a global scale are estimated to be 850 billion USD in 2017, and they are expected to increase (International Diabetes Federation, 2017). The most common type of diabetes is type 2 diabetes (T2D), accounting for 90% of the cases. Diabetes is characterized by elevated glucose levels, which if not treated can cause cardiovascular diseases and damages in e.g. nerves, eyes and feet. In T2D, lowered sensitivity to insulin, the glucose regulating hormone, causes the elevated blood glucose concentration. In most T2D patients, this implies increased production of insulin which with progression can lead to beta cell failure and eventually decreased insulin production. Recent research suggest that patients with T2D can be clustered into five subgroups characterized by the level of resistance to insulin, the level of insulin deficiency, and the risk of diabetes complications. The research suggests that different treatment regimens are suitable for different patient groups (Ahlqvist, Storm, & Karajamaki, 2018).

When treating T2D, Standards of Medical Care in Diabetes recommends initiating with lifestyle management related to diet and physical activity, and treatment by Metformin to increase the insulin sensitivity (American Diabetes Association, 2018; Dansk Selskab for Almen Medicin (DSAM), 2018). In case treatment targets are not reached, a combination with other non-insulin pharmaceuticals can be added. If glycaemic targets are still not reached, it is recommended to initiate insulin treatment. Typically, patients would start taking long acting insulin to lower fasting glucose levels, and adding fast acting insulin to compensate for elevated postprandial glucose concentrations. In insulin treatment, finding a patient's optimal dose is important. A too low dose fails to lower the blood glucose concentration adequately, which can cause complications in the long run. Too large doses can cause hypoglycemia, a state that can lead to confusion, sweating, and fainting. In the worst case, if not treated, this can lead to brain damage and coma. In this work, we focus on long acting insulin treatment for patients with T2D.

In standard of care (SOC), pre-breakfast self-measured blood glucose (SMBG) values are used to determine whether a dose should be changed to reach a target range. The decision is based on a simple algorithm, usually adding or subtracting a few units from the current dose based on an average of SMBG measurements. Despite the simplicity of the algorithm, insulin intensification is complex and a burden for patients and health care professionals. More than 60% of the patients do not reach glucose lowering targets due to reasons such as complexity, lack of

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confidence, lack of data, and fear of overdosing (Arnolds, Heise, Flacke, & Sieber, 2013). The fear of overdosing has some justification as a review of studies on the prevalence of hypoglycemia concluded that more than half of the patients experience hypoglycemia, with an incidence of 23 events per year (Edridge et al., 2015).

There is a demand for new innovative ways for diabetes treatment that improves glycaemic control for the individual patient and at the same time lowers the financial burden of diabetes for the society. Pharmaceutical, biotechnology, and information technology companies search for and develop solutions within digital health to improve treatment outcomes in a time and resource efficient manner. These include connected insulin injection devices, glucose measurement devices, such as continuous glucose monitors (CGMs), and dose guidance. Previous work using computer based dose guidance in long acting insulin treatment of T2D includes the Intelligent Dosing System and the Diabetes Insulin Guidance System (Cook et al., 2005; Donnelly, Carr, & Harper, 2015). Both systems use pre-breakfast SMBG data to adjust doses based on a mathematical model or fuzzy logic, respectively. Campos-Cornejo et al. published a run-to-run approach to insulin titration (Campos-Cornejo et al., 2010). The methods mentioned above have in common that they only consider the glucose value at the time of the measurement, and do not consider potential critical deviations between measurements. More advanced methods such as model predictive control (MPC) have mainly been used in closed-loop insulin pump treatment, especially in type 1 diabetes management (Bequette, 2013; Nath, Biradar, Balan, Dey, & Padhi, 2018; Thabit et al., 2016).

T2D is a heterogeneous disease with large variations in physiology and drug need between individuals (Færch, Hulmân, & Solomon, 2016). Intra-individual variations in lifestyle, diet, treatment adherence, and other factors related to drugs and device accuracy, cause day to day fasting glucose variability. In this work, we design an MPC based dose guidance algorithm for long acting insulin treatment in people with T2D. The dose guidance should be safe and effective during insulin initiation as well as during treatment maintenance. It should be robust to variations in glucose caused by physiological variance as well as adherence issues. The recent work in Aradóttir et al. (2017) and Aradóttir, Boiroux, Bengtsson, and Poulsen (2018a, 2018b) model the dynamics of the *basal glucose concentration* in people with T2D. We define the basal glucose concentration as the simulated or predicted blood glucose concentration obtained when no prandial (post meal) glucose excursions and no impact of fast acting insulin are present. Fig. 1 illustrates a simulation of glucose concentration during two days. The green curve indicates a simulation with meal disturbances, while the blue curve indicates a simulation without meals. We refer to the glucose without meal disturbances as basal glucose. Long acting insulin is administered in both cases as indicated in the bottom panel of the figure. These simulations conceptually illustrate that in the case of overnight fasting, the morning pre-prandial basal glucose concentration is an accurate approximation to actual morning pre-prandial glucose concentration and this concentration can be measured by a pre-breakfast SMBG (red crosses). Consequently, we use such a model for the basal glucose concentration to design a dose guidance algorithm for optimization and control of the pre-breakfast glucose concentration using long acting insulin.

The novelty of this work is the combination of methods, data and application. We use an existing physiological model of basal glucose and identify the parameters using clinical trial data of long acting insulin in T2D. We then use the concept of sub-frequency actuation in an MPC algorithm to predict in a novel way the basal glucose between insulin injections. In Section 2, we provide a brief overview of sources of glucose variations that affect glucose control. In Section 3, we introduce the physiological model that describes the basal glucose concentration in people with T2D. Furthermore, we describe our procedure for stochastic simulation using this model. Section 4 provides a description of the model identification method, and Section 5 outlines the MPC algorithm. The SOC titration algorithm is described in Section 6. Section 7 illustrates the performance of the MPC compared to the SOC algorithm with respect to efficacy and safety. We discuss the results in Section 7 and present the conclusion in Section 8.

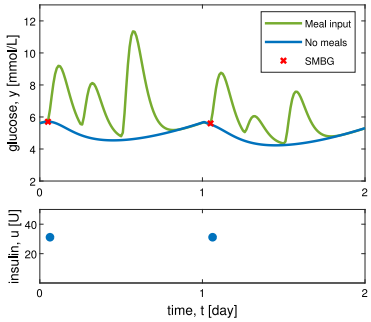


**Fig. 1.** Simulations of glucose concentration during two days with pre-breakfast long acting insulin administration. The top panel illustrates how three meals per day elevate glucose concentration (green), a simulation where no meals were given (blue), and pre-breakfast SMBG measurements (red). The bottom panel illustrates timing and volume of insulin injections.

## 2. Day to day glucose variability

The day-to-day variability in the blood glucose concentration and its response to insulin are due to many different factors. In this section, we describe metabolic variability, variability caused by lifestyle and adherence to treatment, and variability related to device accuracy.

### 2.1. Metabolic variations

Metabolic variability can be divided into drug related variability and changes in the physiological state of the body due to e.g. stress, exercise, weight loss, and more (Guthrie & Guthrie, 2009). In newly diagnosed individuals not taking medication, fasting glucose coefficient of variation (CV) is approximately 14%, and it is positively correlated with fasting glucose levels (Ollerton et al., 1999). Another study, that investigated glucose variability in individuals on stable basal insulin doses, observed a CV of 35% in fasting glucose. The study concluded that biological variability yielded a CV of approximately 14%, while factors such as adherence to treatment and consumption of sugars produced a CV of 21% (Murata, Duckworth, Shah, Wendel, & Hoffman, 2004). The dawn phenomenon is a common event across the T2D population on oral treatment. The dawn phenomenon refers to increasing glucose concentration over night by approximately 1 mmol/L (18 mg/dL). However, this phenomenon decreases and eventually disappears after initiating insulin treatment (Monnier, Colette, Dejager, & Owens, 2013). Long acting insulins have different pharmacokinetic and pharmacodynamic properties, and cause different day-to-day response variability. The CV of glucose infusion rate in clamp studies in the long and ultra long acting insulins on the market vary from 40%–150% in total between individuals and drugs (Heise, Hermanski, et al., 2012; Klein et al., 2007).

### 2.2. Variations due to lifestyle and adherence

Lifestyle, such as level of exercise, adherence to treatment, and diet, is strongly correlated with glucose levels and variability. Adherence to treatment is essential for the success of dose guidance. However, collection of reliable data on adherence is difficult (Cramer & Pugh, 2005). A number of studies based on questionnaires or pharmacy and prescription databases have found that adherence to treatment is around 60%–90% (Cramer & Pugh, 2005; Lee, Balu, Cobden, Joshi, & Pashos, 2006; Peyrot, Barnett, Meneghini, & Schumm-Draeger, 2012). Physical activity and diet affect glucose concentrations. In a study on physical activity in untreated T2D patients, insulin sensitivity was 8% and 25% higher for individuals doing moderate and vigorous exercise compared to sedentary lifestyle (Balkau et al., 2008), and insulin sensitivity can increase by 23%–35% during 2 weeks of aerobic training (Mann et al., 2014). A study of mealtimes and content effect on variability in fasting glucose showed no effect of regular mealtimes in comparison to those who sometimes missed meals. They however found that the more sugar an individual consumes, the greater the variability of the fasting glucose concentration (Murata et al., 2004).

### 2.3. Device related variability

Device related variability can be divided into two parts, accuracy of the device and errors caused by incorrect use. The ISO 15197:2013 states that 95% of measurements must be within 15% of the reference (or 15 mg/dL for glucose $<$100 mg/dL). In a study on measuring accuracy, 50% of patients made user errors and 11% of patients measured with lower accuracy than the ISO standard (Kjome, Granas, Nerhus, & Sandberg, 2010). User errors were not predictive of measuring accuracy. The reasons included unclean hands, wrong sampling technique, invalid sampling strips, and too little blood in the sample. The accuracy of insulin injection devices is high compared to the before mentioned sources of variability, with a less than 1% CV at doses larger than 5 units (Kildegaard, Christensen, & Hejlesen, 2009).

## 3. Physiological model and simulation

In this work, we base the MPC and simulations on the work presented by Aradóttir et al. (2018a). As illustrated in Fig. 1, the model describes fasting glucose in response to long acting insulin, and does not include the fast dynamics of prandial glucose excursions and the impact of fast acting insulin.

### 3.1. The medtronic virtual patient model

The insulin pharmacokinetics (PK) model that describes the concentration dynamics of exogenously administered insulin is described by

$$\frac{dI_{sc}}{dt}(t) = \frac{1}{\tau_1}\left(\frac{u(t)}{C_I} - I_{sc}(t)\right) \tag{1a}$$

$$\frac{dI_p}{dt}(t) = \frac{1}{\tau_1}\left(I_{sc}(t) - I_p(t)\right) \tag{1b}$$

with $u$ as exogenous long acting insulin, $I_{sc}$ and $I_p$ as subcutaneous and plasma insulin concentrations, and time constants $\tau_1$ and $\tau_2$.

The pharmacodynamics (PD), i.e. the effect of the plasma insulin concentration on the blood glucose concentration, is described by

$$\frac{dI_{eff}}{dt}(t) = p_2\left(S_I I_p(t) - I_{eff}(t)\right) \tag{2a}$$

$$\frac{dG}{dt}(t) = -\left(p_{GEZI} + I_{eff}(t)\right)G(t) + p_{EGP} + R_a(t) \tag{2b}$$

$I_{eff}$ is insulin effect on glucose. $p_2$ is an inverse time constant for delay in insulin action. $G$ is the glucose concentration in plasma (measurable), $S_I$ is insulin sensitivity, $p_{GEZI}$ is an inverse time constant for the effect of glucose to eliminate glucose from plasma and $p_{EGP}$ is rate of endogenous glucose production. $R_a$ is rate of appearance of glucose input (meals) in plasma. We set $R_a = 0$ as our model should not contain meal input.

This model (1)–(2) was developed in Kanderian, Weinzimer, Voskanyan, and Steil (2009) and is referred to as the Medtronic Virtual Patient (MVP) model. It describes the effect of subcutaneously administered insulin on the blood glucose concentration in people with type 1 diabetes (T1D).

#### 3.1.1. Minimal physiological model for people with T2D

We modify the MVP model such that it describes the effect of subcutaneously administered *ultra long acting insulin degludec* on the blood glucose concentration in people with *T2D*.

First, we modify the PK-model (1)

$$\frac{dI_{sc}}{dt}(t) = \frac{1}{\tau_1}\left(\frac{u(t)}{C_I} - I_{sc}(t)\right) \tag{3a}$$

$$\frac{dI_p}{dt}(t) = \frac{1}{\tau_1}\left(I_{sc}(t) - I_p(t)\right) \tag{3b}$$

such that it only has one time constant, $\tau_1$, that is chosen such that it describes the behaviour of long acting insulin.

Secondly, we model pancreatic insulin production using the simplest model from Ruan, Thabit, Wilinska, and Hovorka (2015) as

$$I_{ENDO}(t) = \frac{M_I\left(G(t) - G_b\right) + M_0 G_b}{MCR_I \cdot BW} = \beta G(t) \tag{4}$$

where we set $\beta = M_I/(MCR_I \cdot BW)$ and $M_0 = M_I$ to obtain a simple linear expression. We choose to do this to minimize the number of parameters to estimate, and given the sparsity of the data. Then we replace $I_p$ in (2a) with $I_p + I_{ENDO}$ to obtain

$$\frac{dI_{eff}}{dt}(t) = p_2 S_I\left(I_p(t) + I_{ENDO}(t)\right) - p_2 I_{eff}(t) \tag{5}$$

Thirdly, we assume fasting conditions such that $R_a(t) = 0$. Consequently, the PD part of the modified MVP model for T2D becomes

$$\frac{dI_{eff}}{dt}(t) = p_2 S_I\left(I_p(t) + \beta G(t)\right) - p_2 I_{eff}(t) \tag{6a}$$

$$\frac{dG}{dt}(t) = -\left(p_{GEZI} + I_{eff}(t)\right)G(t) + p_{EGP} \tag{6b}$$

The modified MVP model describing the effect of long acting insulin on the fasting blood glucose concentration in people with T2D is a combination of the PK-model (3) and the PD-model (6)

$$\frac{dI_{sc}}{dt}(t) = \frac{1}{\tau_1}\left(\frac{u(t)}{C_I} - I_{sc}(t)\right) \tag{7a}$$

$$\frac{dI_p}{dt}(t) = \frac{1}{\tau_1}\left(I_{sc}(t) - I_p(t)\right) \tag{7b}$$

$$\frac{dI_{eff}}{dt}(t) = p_2 S_I\left(I_p(t) + \beta G(t)\right) - p_2 I_{eff}(t) \tag{7c}$$

$$\frac{dG}{dt}(t) = -\left(p_{GEZI} + I_{eff}(t)\right)G(t) + p_{EGP} \tag{7d}$$

**Remark 1.** The PK-model (3) is linear and corresponds to a 2nd order transfer function, $I_p(s) = G_I(s)u(s)$, in the Laplace domain, where

$$G_I(s) = \frac{1/C_I}{(\tau_1 s + 1)^2} = \frac{K_I}{(\tau_I s + 1)^2} \tag{8}$$

with $K_I = 1/C_I$ and $\tau_I = \tau_1$. Assuming that the PD-model (6) is quasi-stationary, the PD-model provides the following relation between the plasma insulin concentration, $I_p(t)$, and the glucose concentration, $G(t)$,

$$\alpha(t) = p_{GEZI} + S_I I_p(t) \tag{9a}$$

$$G(t) = \frac{-\alpha(t) + \sqrt{\alpha(t)^2 + 4S_I\beta p_{EGP}}}{2S_I\beta} \tag{9b}$$

This is an example of a nonlinear static function, $G(t) = h(I_p(t))$. We notice that the inverse function, $I_p(t) = h^{-1}(G(t))$, is

$$\begin{aligned} I_p(t) &= \frac{p_{EGP} - S_I\beta G(t)^2}{S_I G(t)} - \frac{p_{GEZI}}{S_I} \\ &= \frac{p_{EGP}}{S_I}\frac{1}{G(t)} - \beta G(t) - \frac{p_{GEZI}}{S_I} \end{aligned} \tag{10}$$

The resulting model describing the effect of subcutaneously administered insulin, $u(t)$, on the blood glucose concentration, $G(t)$, is a Wiener model as the PK-model is a dynamic linear model and the PD-model can be approximated as a static nonlinear function.

### 3.1.2. Model representation

For parameter identifiability, we now rewrite (7) by setting $\tilde{I}_{sc} = I_{sc}C_I$, $\tilde{I}_p = I_p C_I$, $\tilde{I}_{eff} = I_{eff}C_I/S_I$ and $\tilde{\beta} = \beta C_I$ as in Aradóttir et al. (2018a). We get the following model representation

$$\frac{d\tilde{I}_{sc}}{dt}(t) = \frac{1}{\tau_1}\left(u(t) - \tilde{I}_{sc}(t)\right) \tag{11a}$$

$$\frac{d\tilde{I}_p}{dt}(t) = \frac{1}{\tau_1}\left(\tilde{I}_{sc} - \tilde{I}_p(t)\right) \tag{11b}$$

$$\frac{d\tilde{I}_{eff}}{dt}(t) = p_2[\tilde{I}_p(t) + \tilde{\beta}G(t)] - p_2\tilde{I}_{eff}(t) \tag{11c}$$

$$\frac{dG}{dt}(t) = -[p_{GEZI} + S_I\tilde{I}_{eff}(t)]G(t) + p_{EGP} \tag{11d}$$

where $u$ is exogenous long acting insulin [U/day], $\tilde{I}_{sc}$ and $\tilde{I}_p$ denote subcutaneous and plasma insulin rates [U/day] with time constant $\tau_1$ [day]. $\tilde{I}_{eff}$ is insulin effect on glucose [U/day] and $p_2$ is an inverse time constant for delay in insulin action [1/day]. $\tilde{\beta}$ describes endogenous insulin production [U L/mmol day] which is assumed to increase linearly with fasting glucose. $G$ is glucose concentration in plasma [mmol/L] which is assumed to be measurable, $S_I$ is insulin sensitivity [1/U], $p_{GEZI}$ is an inverse time constant for the effect of glucose to eliminate glucose from plasma [1/day] and $p_{EGP}$ is the rate of endogenous glucose production [(mmol/L)/day].

Fig. 2 is a schematic diagram of the four compartment physiological model (11). This is a system of ordinary differential equations (ODEs) in the form

$$\frac{dx}{dt}(t) = f(x(t), u(t), \theta) \tag{12}$$

where $x(t)$ is the state vector, $u(t)$ is the input, $\theta$ is the parameters, and $f$ is the glucose–insulin dynamics.

### 3.2. Simulation

For *in silico* simulations of a T2D patient, we extend (12) with a diffusion term, $\sigma dw(t)$, to obtain a system of stochastic differential equations (SDEs)

$$dx(t) = f(x(t), u(t))dt + \sigma dw(t), \quad 0 < t < T \tag{13}$$

where $u(t)$ and $f$ are defined as in (11), $\{w; t > 0\}$ is a standard Brownian motion, and the solution $x(t)$ is a random variable for each $t$. For the simulation, we solve the SDE numerically using the Euler–Maruyama method (Higham, 2001),

$$x(\tau_k) = x(\tau_{k-1}) + f(x(\tau_{k-1}), u(\tau_{k-1}))\Delta t + \sigma\Delta w_k \tag{14}$$

where

$$\Delta w_k = w(\tau_k) - w(\tau_{k-1}) \tag{15}$$

and $\Delta w_k \sim N(0, I\Delta t)$. In this work we aim at predicting basal glucose with a sampling frequency of 1 h, so $T_s = 60$ min. Now we set $\Delta t = T_s/10 = 60$ min$/10 = 6$ min and $\sigma = 2I$ which gives an SMBG CV of 14%.

Fig. 3 illustrates a stochastic simulation of basal glucose in blue compared with the deterministic simulation in green, where coefficient of variation is approximately 14% as found in the literature.

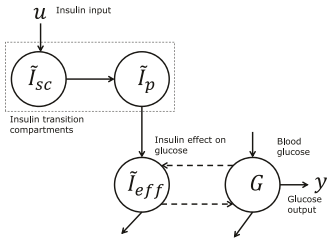


**Fig. 2.** A diagram of the four compartmental physiological model in (11).

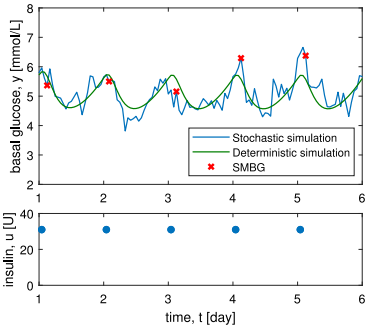


**Fig. 3.** The top panel illustrates a deterministic (green) and stochastic (blue) simulation of the basal glucose concentration. The red markers indicate SMBG measurements taken once daily. Both simulations indicate the basal glucose concentration and therefore include no meal input, i.e. $R_a = 0$. We set the process noise in the stochastic simulations such that the CV of SMBG measurements was 14%, as found in the literature.

## 4. Model identification

In previous work, we assessed and identified parameters in the transformed physiological model (11). The paper (Aradóttir et al., 2018a) furthermore discusses a number of challenges with model identification using data from clinical trials on long acting insulins. These challenges include slow and sparse sampling as well as sub-optimal excitation due to safety issues. We used data from a study by Zinman et al. (2012), which included 763 adult T2D patients initiating insulin degludec treatment on a once daily

**Table 1**
An example of a paper based insulin titration algorithm with once weekly dose adjustments (Kadowaki et al., 2017).

| Average of last three pre-breakfast SMBG [mmol/L] | Dose adjustment |
|---|---|
| <3.1 | −4U |
| 3.1–3.9 | −2U |
| 4.0–5.0 | In target: no change |
| 5.1–7.0 | +2U |
| 7.1–8.0 | +4U |
| 8.1–9.0 | +6U |
| >9.0 | +8U |

**Table 2**
Parameters for the model (11). $\tau_1$, $p_2$ and $p_{GEZI}$ are assessed or from other publications, and $S_I$, $p_{EGP}$ and $\tilde{\beta}$ are estimated from the clinical data.

| Method | | Parameter/unit | Value |
|---|---|---|---|
| Assessed | $\tau_1$ | [day] | 0.5 |
| Mean values from Kanderian et al. (2009) | $p_2$ | [1/day] | 15.8 |
| | $p_{GEZI}$ | [1/day] | 3.31 |
| Estimated | $S_I$ | [1/U] | 1.80 |
| | $p_{EGP}$ | [mmol/L day] | 368 |
| | $\tilde{\beta}$ | [U L/mmol day] | 1.68 |
| | $R$ | [mmol$^2$/L$^2$] | 1.04 |
| | $\sigma_{11}$ | [U/day] | 0.0011 |
| | $\sigma_{22}$ | [U/day] | 0.0011 |
| | $\sigma_{33}$ | [U/day] | 0.0010 |
| | $\sigma_{44}$ | [mmol/L] | 0.0010 |

treatment regimen. The daily doses were adjusted weekly for one year according to the paper based titration algorithm in Table 1. The algorithm listed in Table 1 weekly computes the dose change based on fasting glucose concentrations measured as the 3-day running average of pre-breakfast SMBG measurements.

We concluded that due to the slow sampled and sparse data set, $\tau_1$, $p_2$ and $p_{GEZI}$ were not identifiable. The time constant of the insulin moving from injection site to plasma, $\tau_1$, was assessed to be 12 h from the time to maximum glucose infusion rate (GIR) in the PD profile published in Heise, Nosek, Bøttcher, Hastrup and Haahr (2012). For the two inverse time constants of insulin effect and clearance, $p_2$, and for glucose clearance, $p_{GEZI}$, we use the mean values from the 10 patients identified by Kanderian et al. (2009). We estimated the remaining parameters, $S_I$, $p_{EGP}$ and $\tilde{\beta}$ based on data for one patient in the trial by Zinman et al. (2012). The values are listed in Table 2.

For the parameter estimation, we used the open source model identification software Continuous Time Stochastic Modelling for R (CTSM-R) (CTSM-R, 2015). We use the software to identify the parameter vector, $\theta = [S_I; p_{EGP}; \tilde{\beta}; R; \sigma_{11}; \sigma_{22}; \sigma_{33}; \sigma_{44}]$, of stochastic continuous–discrete systems in the form

$$x(t_0) = x_0 \tag{16a}$$
$$dx(t) = f(x(t), u(t), \theta)dt + \sigma(u(t), \theta)dw(t) \tag{16b}$$
$$y(t_k) = g(x(t_k), \theta) + v_k \tag{16c}$$

given the initial conditions, $x_0$, the inputs, $\mathcal{U}_k = [u(t)]_{t_0}^{t_k}$ for $k = N_d$, and the measured data $\mathcal{Y}_k = [y_0, y_1, \ldots, y_{k-1}, y_k]$. $\theta$ is the set of parameters we want to identify, $u_t$ is the input at time $t$, $\sigma^2(u_t, \theta)$ is the process noise covariance matrix, $w_t$ is standard Brownian motion and $v_k \sim N_{iid}(0, R)$ is the measurement error.

The likelihood function to be maximized is the joint probability density function

$$p(x_0, \theta; \mathcal{Y}_{N_d}, \mathcal{U}_{N_d}) = \left(\prod_{k=1}^{N_d} p(y_k|\mathcal{Y}_{k-1}, \mathcal{U}_k, x_0, \theta)\right) p(y_0|x_0, \theta), \tag{17}$$

i.e. the likelihood of a measurement sequence $\mathcal{Y}_N$ occurring, given the parameter set $\theta$ and the model (16). Here the density $p(y_k|\mathcal{Y}_{k-1}, \theta)$ is the probability of a measurement $y_k$ at time $k$, given data up to time $k-1$ and the parameter set, follows a normal distribution and is found by

$$p(y_k|\mathcal{Y}_{k-1}, \mathcal{U}_k, x_0, \theta) = \frac{\exp\left(-\frac{1}{2}\epsilon_k^T R_{k|k-1}^{-1}\epsilon_k\right)}{\sqrt{\det(R_{k|k-1})}\left(\sqrt{2\pi}\right)^l}. \tag{18}$$

Here $\epsilon_k = y_k - \hat{y}_{k|k-1}$ is the innovation, $\hat{y}_{k|k-1} = E[y_k|\mathcal{Y}_{k-1}, \mathcal{U}_k, x_0, \theta]$ is an estimate for the measurement at time $k$ given data up to time $k-1$ and $R_{k|k-1} = V[y_k|\mathcal{Y}_{k-1}, \mathcal{U}_k, x_0, \theta]$ is the covariance of the estimate.

CTSM-R estimates the parameter vector, $\theta$, initial conditions of the states, $x_0$, as well as measurement noise, $R$, and process noise, $\sigma$. Table 2 lists the identified parameters. All estimates were significant ($p < 0.01$), and the estimated initial state is

$$x_0 = \begin{bmatrix}0 & 0 & 17.6 & 10.5\end{bmatrix}^T.$$

## 5. Model predictive control

In this section we describe the MPC algorithm, which is based on a linearized and discretized version of the physiological model. We list how we avoid offset in the control strategy, then implement a Kalman filter for estimation of offset and prediction of the output. Finally we describe the MPC algorithm with hard input constraints, soft output constraints, and sub-frequency actuation. The penalty function is shaped by the soft output constraints.

### 5.1. Prediction model

The continuous–discrete-time model is in the form

$$dx(t) = f(x(t), u(t))dt + \sigma dw(t)$$
$$y(t_k) = g(x(t_k)) + v_k$$

where $dw(t) \sim N_{iid}(0, Idt)$ and $v_k \sim N(0, R)$. We linearize the model around a trajectory and the linearized model becomes

$$d(x(t) - x_{ss}(t)) = (A_c(t)[x(t) - x_{ss}(t)] + B_c[u(t) - u_{ss}(t)])dt + \sigma dw(t) \tag{19a}$$
$$y(t_k) - y_{ss}(t_k) = C_c[x(t) - x_{ss}(t)] + v_k \tag{19b}$$

where

$$A_c(t) = \begin{bmatrix} -\frac{1}{p_1} & 0 & 0 & 0 \\ \frac{1}{p_1} & -\frac{1}{p_1} & 0 & 0 \\ 0 & p_3 & -p_3 & p_3 p_7 \\ 0 & 0 & -p_4 x_{4,ss}(t) & -(p_5 + p_4 x_{3,ss}(t)) \end{bmatrix}$$
$$B_c = \begin{bmatrix}\frac{1}{p_1} & 0 & 0 & 0\end{bmatrix}^T \quad C_c = \begin{bmatrix}0 & 0 & 0 & 1\end{bmatrix}$$

and $x_{ss}(t)$ and $u_{ss}(t)$ are the current steady state vector and input values, respectively. The matrix $A_c(t)$ therefore changes at every injection sample, but is kept constant through the prediction horizon. To design the MPC we discretize the system in (19) such that

$$x_{k+1} - x_{ss} = A_d(x_k - x_{ss}) + B_d(u_k - u_{ss}) + w_k$$
$$y_k - y_{ss} = C_d(x_k - x_{ss}) + v_k$$

where $A_d$, $B_d$ and $C_d$ are found assuming impulse input and are computed by

$$A_d = \exp(A_c(t)T_s)$$
$$B_d = A_d B_c = \exp(A_c(t)T_s)\, B_c$$

$C_d = C_c$

$T_s = 1$ h is the sampling frequency. Note that $A_d$ depends on $A_c(t)$ and therefore is updated at every sample.

Further, $v_k \sim N_{iid}(0, R)$ and $w_k \sim N_{iid}(0, Q)$ where

$$\begin{bmatrix} \Phi_{11} & \Phi_{12} \\ 0 & \Phi_{22} \end{bmatrix} = \exp\left( \begin{bmatrix} -A_c(t) & \sigma\sigma^T \\ 0 & A_c(t)^T \end{bmatrix} T_s \right), \tag{20a}$$

$$Q = \Phi_{22}^T \Phi_{12}. \tag{20b}$$

**Remark 2.** This discretization assumes impulse input, while CTSM-R estimates parameters assuming zero-order-hold discretization (sampling frequency is 1/hour). We use impulse input in the controller design and simulations as this is physiologically more realistic.

### 5.2. Offset-free control

To compensate for offset in the control, due to inaccuracies in the prediction model structure, parameters or changes in physiology, we implement disturbance modelling as described by Pannocchia and Rawlings (2003). Let $\hat{x} \in \mathbb{R}^n$ be the estimated state vector, $y_k \in \mathbb{R}^{n_y}$ be the measurement, and $\hat{d} \in \mathbb{R}^{n_e}$ be the disturbance vector. We augment the system and the discrete time model becomes

$$\begin{aligned} x_{k+1} - x_{ss} &= A_{d,k}(x_k - x_{ss}) + B_d(u_k - u_{ss}) + w_k + B_e d_k \\ d_{k+1} &= d_k + \zeta_k \\ y_k - y_{ss} &= C_d(x_k - x_{ss}) + v_k + C_e d_k \end{aligned}$$

where $\zeta \sim N_{iid}(0, Q_\zeta)$, $w_k \sim N_{iid}(0, Q)$, $v_k \sim N_{iid}(0, R)$, $B_e \in \mathbb{R}^{n \times n_e}$ and $C_e \in \mathbb{R}^{n_y \times n_e}$ and their values ensure identifiability of the augmented system, i.e.

$$\text{rank} \begin{bmatrix} I - A_{d,k} & -B_e \\ C & C_e \end{bmatrix} = n + n_e \tag{21}$$

In this work we set

$$B_e = \begin{bmatrix} 1.2 & 0.2 & 0.2 & 1.2 \end{bmatrix}^T, \quad C_e = 0$$

based on trial and error, designed such that there is no direct effect of the disturbance on the output, but rather on the process. These values furthermore ensure identifiability of the augmented system, i.e. the rank in (21) is $n + n_e = 4 + 1 = 5$.

We rewrite the model in physical variables rather than deviation variables, and such the state vector is augmented with the disturbance, $\bar{x}_k := \begin{bmatrix} x_k - x_{ss} \\ d_k \end{bmatrix}$,

$$\bar{x}_{k+1} = A\bar{x}_k + B\bar{u}_k + \bar{w}_k \tag{22a}$$

$$\bar{y}_k = C\bar{x}_k + v_k \tag{22b}$$

where $\bar{y}_k = y_k - y_{ss}$, $\bar{u}_k = u_k - u_{ss}$ and

$$\bar{w}_k = \begin{bmatrix} w_k \\ \zeta_k \end{bmatrix} \sim N_{iid}\left( \begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} Q & 0 \\ 0 & Q_\zeta \end{bmatrix} \right) \tag{22c}$$

$$v_k \sim N_{iid}(0, R) \tag{22d}$$

The augmented model matrices are

$$A = \begin{bmatrix} A_d & B_e \\ 0 & I \end{bmatrix} \quad B = \begin{bmatrix} B_d \\ 0 \end{bmatrix} \quad C = \begin{bmatrix} C_d & C_e \end{bmatrix}$$

The disturbance, $d_k$, is estimated once per day, at the time when an SMBG measurement would typically be available, using a stationary ordinary discrete Kalman filter. This is described in the next section.

### 5.3. Kalman filter

The estimator used for filtering and prediction is based on the stochastic linear discrete-time state space model (22). The filtering algorithm consist of a filter that can handle missing observations and a one-step predictor. The MPC uses a multi-step prediction for computing the optimal insulin dosage.

In this work we simulate the system without measurement noise and we also design the Kalman filter using the assumption that the measurement is accurate, i.e. $R = 10^{-4}$. The process noise covariance, $\sigma$, is estimated and the scalar ratio, $\alpha = Q_\zeta / R$, is a tuning parameter that we in this work set to $10^3$. Specifically, this corresponds to $Q_\zeta = 10^{-1}$ when $R = 10^{-4}$. In this way, the process noise covariance of (22) is

$$Q_{\bar{x}} = \begin{bmatrix} Q & 0 \\ 0 & Q_\zeta \end{bmatrix}$$

where $Q$ can be computed by the expression (20) when $A_c(t)$ and $\sigma$ are available from an estimate of the stochastic process model (16).

#### 5.3.1. Measurement update (filtering)

We assume that the blood glucose concentration is measured by SMBG prior to breakfast. At these time instants, a measurement, $\bar{y}_k = y_k - y_{ss}$, is available, while at all other time instances it is not available.

When the measurement is available, the innovation, $e_k$, is computed by

$$e_k = \bar{y}_k - \hat{\bar{y}}_{k|k-1} = \bar{y}_k - C\hat{\bar{x}}_{k|k-1}$$

and the Kalman gain, $K_k$, is

$$K_k = P_{k|k-1}C^T \left( CP_{k|k-1}C^T + R \right)^{-1}$$

such that the filtered state, $\hat{x}_{k|k}$, may be computed as

$$\hat{\bar{x}}_{k|k} = \hat{\bar{x}}_{k|k-1} + K_k e_k$$

and the corresponding symmetric positive definite filtered covariance, $P_{k|k}$, is

$$\begin{aligned} P_{k|k} &= P_{k|k-1} - K_k(CP_{k|k-1}C^T + R)K_k^T \\ &= (I - K_k C)P_{k|k-1} \\ &= (I - K_k C)P_{k|k-1}(I - K_k C)^T + K_k R K_k^T \end{aligned}$$

At time instances when the measurement is not available because of non-adherence to the measurement protocol or because it is not pre-breakfast, the filtered state and covariance are updated as

$$\begin{aligned} \hat{\bar{x}}_{k|k} &= \hat{\bar{x}}_{k|k-1} \\ P_{k|k} &= P_{k|k-1} \end{aligned}$$

#### 5.3.2. One-step prediction

The one-step prediction of the states is

$$\hat{\bar{x}}_{k+1|k} = A\hat{\bar{x}}_{k|k} + B\bar{u}_k$$

and the corresponding covariance is

$$P_{k+1|k} = AP_{k|k}A^T + Q_{\bar{x}}$$

#### 5.3.3. Multi-step prediction

The multi-step predictions of the states, $\hat{\bar{x}}_{k+j|k}$, and the outputs, $\hat{\bar{y}}_{k+j|k}$, that are used by the regulator in the MPC for $j = 1, 2, \ldots, N$ are

$$\hat{\bar{x}}_{k+j+1|k} = A\hat{\bar{x}}_{k+j|k} + B\hat{\bar{u}}_{k+j|k} \quad j = 0, 1, \ldots, N-1 \tag{23a}$$

$$\hat{\bar{y}}_{k+j+1|k} = C\hat{\bar{x}}_{k+j+1|k} \quad j = 0, 1, \ldots, N-1 \tag{23b}$$

with $\hat{\tilde{u}}_{k|k} = \tilde{u}_k = u_k - u_{ss}$ when the patient adheres to the recommendation and $\hat{\tilde{u}}_{k|k} = \tilde{u}_k = u_k - u_{ss} = -u_{ss}$ when the patient does not administer insulin.

### 5.4. Constrained regulator

The principles for design of the regulator in an MPC with input constraints and soft output constraints are described in Maciejowski (2002) and Rawlings, Mayne, and Diehl (2017). A key novelty in the regulator is that it uses sub-frequency actuation that allows the insulin to be given once every 24 h, while the soft output constraints are evaluated once every hour. In optimal control such constraints are called *path constraints*.

#### 5.4.1. Prediction and sub-frequency actuation

The multi-step prediction equations (23) may by state elimination be expressed as

$$Y_k - Y_{ss} = \Phi\hat{\tilde{x}}_{k|k} + \Gamma(U_k - U_{ss}) \tag{24}$$

with $Y_k = [\hat{y}_{k+1|k}; \hat{y}_{k+2:k}; \dots; \hat{y}_{k+N|k}]$, $Y_{ss} = [y_{ss}; y_{ss}; \dots; y_{ss}]$, $U_k = [\hat{u}_{k|k}; \hat{u}_{k+1|k}; \dots; \hat{u}_{k+N-1|k}]$, and $U_{ss} = [u_{ss}; u_{ss}; \dots; u_{ss}]$. $\Phi$ is the extended observability matrix and $\Gamma$ is the Toeplitz matrix:

$$\Phi = \begin{bmatrix} CA \\ CA^2 \\ \vdots \\ CA^N \end{bmatrix} \quad \Gamma = \begin{bmatrix} CB & 0 & \dots & 0 \\ CAB & CB & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ CA^{N-1}B & CA^{N-2}B & \dots & CB \end{bmatrix}$$

The regulator is supposed to inject insulin once daily, while all basal glucose values between injections are important. Therefore, we introduce sub-frequency actuation, i.e. where input is only given at one sample in a control period. We define $h$ as the control period (e.g. 1 day), $T_s$ as the sampling period (e.g. 1 h) and $m = h/T_s$ as the number of intervals in the control period (e.g. 24 hs/day). In this work we use a moving horizon with a prediction horizon of $N = 168$ (7 days = 168 h). This corresponds to a prediction horizon of $M = 7$ control periods. This is considered a long enough horizon since given the time constant $p_1$, the drug effect reaches steady state in 2–3 days.

Assuming that the input is given at the first sample of each control period, we set

$$U_k = [u_k; 0; \dots; 0; u_{k+m}; 0; \dots; 0; u_{k+(M-1)m}; 0; \dots; 0]$$

where $u_i$ is the input of control period $i$. We define the matrix $L$ such that

$$U_k = L\tilde{U}_k$$

with

$$\begin{aligned}\tilde{U}_k &= [\tilde{u}_k; \tilde{u}_{k+1}; \tilde{u}_{k+2}; \dots; \tilde{u}_{k+M-1}] \\ &= [u_{(k+1)m}; u_{(k+2)m}; u_{(k+3)m}; \dots; u_{(k+(M-1))m}]\end{aligned}$$

and

$$L = \begin{bmatrix} 1 & 0 & \dots & 0 \\ 0 & 0 & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots \\ 0 & 1 & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots \end{bmatrix}$$

Note the indexing of $\tilde{u}$ and $u$ in $\tilde{U}_k$. We are working with two time scales where one counts control periods and the other input samples. This implies that the multi-step output prediction (24) can be expressed as

$$Y_k = \left(Y_{ss} + \Phi\hat{\tilde{x}}_{k|k} - \Gamma U_{ss}\right) + \Gamma L\tilde{U}_k = b_k + \tilde{\Gamma}\tilde{U}_k \tag{25}$$

with

$$b_k = Y_{ss} - \Gamma U_{ss} + \Phi\hat{\tilde{x}}_{k|k} \tag{26a}$$

$$\tilde{\Gamma} = \Gamma L \tag{26b}$$

#### 5.4.2. Penalty function for the blood glucose concentration

The regulator uses an output penalty and soft constraints to shape the blood glucose concentration penalty function to steer the predicted blood glucose concentration to a target zone between 4.0 and 6.0 mmol/L and with a target of 5 mmol/L (Boiroux et al., 2018, 2012, 2017). The penalty is constructed such that it highly discourages hypoglycemic blood glucose concentrations.

Deviations of the predicted blood glucose concentration, $\{\hat{y}_{k+j|k}\}_{j=1}^N$, from the target blood glucose concentration, $\{r_{k+j|k}\}_{j=1}^N$, is penalized by

$$\phi_y = \frac{1}{2}\sum_{j=1}^{N} \|W_y(\hat{y}_{k+j|k} - r_{k+j|k})\|_2^2 = \frac{1}{2}\|\bar{W}_y\,(Y_k - R_k)\,\|_2^2 \tag{27}$$

where $R_k = [r_{k+1|k}; r_{k+2|k}; \dots; r_{k+N|k}] = [r; r; \dots; r]$ with $r = 5.0$ mmol/L and $\bar{W}_y = I_N \otimes W_y$.

The $\ell_2/\ell_1$ penalty

$$\phi_s = \frac{1}{2}\sum_{j=1}^{N} \|W_{s,2}\hat{s}_{k+j|k}\|_2^2 + \sum_{j=1}^{N} \|W_{s,1}\hat{s}_{k+j|k}\|_1 \tag{28a}$$

for violation of the soft constraint

$$\hat{y}_{k+j|k} + \hat{s}_{k+j|k} \geq r_{\min,k+j|k} \qquad j = 1, 2, \dots, N \tag{28b}$$

$$\hat{s}_{k+j|k} \geq 0 \qquad j = 1, 2, \dots, N \tag{28c}$$

is used to penalize hypoglycemia and can be expressed as

$$\phi_s = \frac{1}{2}\|\bar{W}_{s,2}S_k\|_2^2 + \|\bar{W}_{s,1}S_k\|_1 \tag{29a}$$

$$Y_k + S_k \geq R_{\min,k} \tag{29b}$$

$$S_k \geq 0 \tag{29c}$$

where $R_{\min,k} = [r_{\min,k+1|k}; r_{\min,k+2|k}; \dots; r_{\min,k+N|k}] = [r_{\min}; r_{\min}; \dots; r_{\min}]$ with $r_{\min} = 4.0$ mmol/L. $\bar{W}_{s,2} = I_N \otimes W_{s,2}$ and $\bar{W}_{s,1} = I_N \otimes W_{s,1}$.

Similarly, the $\ell_2/\ell_1$ penalty

$$\phi_t = \frac{1}{2}\sum_{j=1}^{N} \|W_{t,2}\hat{t}_{k+j|k}\|_2^2 + \sum_{j=1}^{N} \|W_{t,1}\hat{t}_{k+j|k}\|_1 \tag{30a}$$

for violation of the soft constraint

$$\hat{y}_{k+j|k} - \hat{t}_{k+j|k} \leq r_{\max,k+j|k} \qquad j = 1, 2, \dots, N \tag{30b}$$

$$\hat{t}_{k+j|k} \geq 0 \qquad j = 1, 2, \dots, N \tag{30c}$$

is used to penalize hyperglycemia and can be expressed as

$$\phi_t = \frac{1}{2}\|\bar{W}_{t,2}T_k\|_2^2 + \|\bar{W}_{t,1}T_k\|_1 \tag{31a}$$

$$Y_k - T_k \leq R_{\max,k} \tag{31b}$$

$$T_k \geq 0 \tag{31c}$$

where $R_{\max,k} = [r_{\max,k+1|k}; r_{\max,k+2|k}; \dots; r_{\max,k+N|k}] = [r_{\max}; r_{\max}; \dots; r_{\max}]$ with $r_{\max} = 6.0$ mmol/L. $\bar{W}_{t,2} = I_N \otimes W_{t,2}$ and $\bar{W}_{t,1} = I_N \otimes W_{t,1}$.

In the above, $W_y$, $W_{s,1}$, $W_{s,2}$, $W_{t,1}$ and $W_{t,2}$ are weight matrices. Table 3 lists the values used in this work. The table illustrates how values below the lower soft constraints, $r_{\min} = 4.0$ mmol/L are penalized more than values above the upper soft constraints, $r_{\max} = 6.0$ mmol/L. We do this to avoid hypoglycemia. Fig. 4 illustrates the objective function $\phi = \phi_y + \phi_s + \phi_t$.

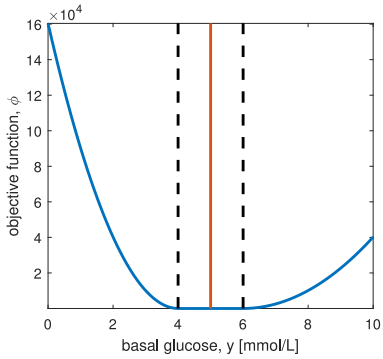


**Fig. 4.** The penalty function $\phi = \phi_y + \phi_s + \phi_t$ given parameters in Table 3, where $r_{min} = 4$ mmol/L, $r_{max} = 6$ mmol/L and $r = 5$ mmol/L.

**Table 3**
Tuning weight matrices of the penalty function $\phi = \phi_y + \phi_s + \phi_t + \phi_{\Delta u}$.

| In- and output change weights | Hypoglycemia weights ($r_{min}$) | Hyperglycemia weights ($r_{max}$) |
|---|---|---|
| $W_y$ $10^{-1}$ | $W_{s,1}$ $10^{2}$ | $W_{t,1}$ $5 \times 10^{1}$ |
| $W_{\Delta u}$ $10^{-8}$ | $W_{s,2}$ $10^{2}$ | $W_{t,2}$ $5 \times 10^{1}$ |

### 5.4.3. Regularization

Let $\Delta\tilde{U}_k = [\Delta\hat{\tilde{u}}_{k|k}; \Delta\hat{\tilde{u}}_{k+1|k}; \ldots; \Delta\hat{\tilde{u}}_{k+M-1|k}]$ such that

$$\Delta\tilde{U}_k = \Lambda\tilde{U}_k - I_0\hat{\tilde{u}}_{k-1|k} \tag{32}$$

with $\hat{\tilde{u}}_{k-1|k} = \tilde{u}_{k-1|k}$ and

$$\Lambda = \begin{bmatrix} I & & & \\ -I & I & & \\ & \ddots & \ddots & \\ & & -I & I \end{bmatrix} \qquad I_0 = \begin{bmatrix} I \\ 0 \\ \vdots \\ 0 \end{bmatrix} \tag{33}$$

Using this notation, smooth variations in the *day-to-day* variation in the long term insulin doses may be obtained using a regularization term expressed as

$$\begin{aligned} \phi_{\Delta\tilde{u}} &= \frac{1}{2}\sum_{j=0}^{M-1} \|W_{\Delta\tilde{u}}\Delta\hat{\tilde{u}}_{k+j|k}\|_2^2 = \frac{1}{2}\|\bar{W}_{\Delta\tilde{u}}\Delta\tilde{U}_k\|_2^2 \\ &= \frac{1}{2}\|\bar{W}_{\Delta\tilde{u}}\left(\Lambda\tilde{U}_k - I_0\hat{\tilde{u}}_{k-1|k}\right)\|_2^2 \end{aligned} \tag{34}$$

with $\bar{W}_{\Delta u} = I_M \otimes W_{\Delta u}$.

### 5.4.4. Input constraints

We set upper and lower hard constraints on the input at the input samples only (since the rest equals zero)

$$u_{\min} \le \hat{\tilde{u}}_{k+j|k} \le u_{\max} \quad j = 0, 1, \ldots, M-1 \tag{35}$$

We set the lower bound to $u_{\min} = 0$ U/day and the upper bound to $u_{\max} = 300$ U/day. We set the upper bound of the input to 300 U as this is the amount of insulin in one 3 ml insulin pen cartridge. We do however not expect this upper constraint on the input to become active. This may be represented as

$$\tilde{U}_{\min} \le \tilde{U}_k \le \tilde{U}_{\max} \tag{36}$$

with $\tilde{U}_{\min} = [u_{\min}; u_{\min}; \ldots; u_{\min}]$ and $\tilde{U}_{\max} = [u_{\max}; u_{\max}; \ldots; u_{\max}]$.

We also constrain the change in long acting insulin dose from day to day. This day-to-day variation is constrained by the formulation

$$\Delta\tilde{u}_{\min} \le \Delta\hat{\tilde{u}}_{k+j|k} \le \Delta\tilde{u}_{\max} \quad j = 0, 1, \ldots, M-1 \tag{37}$$

which can be expressed as

$$\Delta\tilde{U}_{\min} \le \Delta\tilde{U}_k \le \Delta\tilde{U}_{\max} \tag{38}$$

such that

$$\Delta\tilde{U}_{\min} + I_0\hat{\tilde{u}}_{k-1|k} \le \Lambda\tilde{U}_k \le \Delta\tilde{U}_{\max} + I_0\hat{\tilde{u}}_{k-1|k} \tag{39}$$

We set the upper constraints of the input change to 20 U of insulin per day. We do this to avoid oscillation in the input which in a clinical setting can be confusing to health care professionals and patients. The input should rather increase towards the optimal dose, both for simplicity and safety.

### 5.4.5. Convex quadratic program

We can state the optimization problem as a quadratic program where we optimize for the input and the two slack variables

$$\min_{\tilde{U}_k, S_k, T_k} \quad \phi = \frac{1}{2}\begin{bmatrix}\tilde{U}_k \\ S_k \\ T_k\end{bmatrix}^T H \begin{bmatrix}\tilde{U}_k \\ S_k \\ T_k\end{bmatrix} + g_k^T \begin{bmatrix}\tilde{U}_k \\ S_k \\ T_k\end{bmatrix} \tag{40a}$$

$$s.t. \quad \begin{bmatrix}\tilde{U}_{\min} \\ 0 \\ 0\end{bmatrix} \le \begin{bmatrix}\tilde{U}_k \\ S_k \\ T_k\end{bmatrix} \le \begin{bmatrix}\tilde{U}_{\max} \\ \infty \\ \infty\end{bmatrix} \tag{40b}$$

$$\begin{bmatrix}\Delta\tilde{U}_{\min} + I_0\hat{\tilde{u}}_{k-1|k} \\ R_{\min,k} - b_k \\ -\infty\end{bmatrix} \le \begin{bmatrix}\Lambda & 0 & 0 \\ \Gamma & I & 0 \\ \Gamma & 0 & -I\end{bmatrix}\begin{bmatrix}\tilde{U}_k \\ S_k \\ T_k\end{bmatrix} \tag{40c}$$

$$\begin{bmatrix}\Delta\tilde{U}_{max} + I_0\hat{\tilde{u}}_{k-1|k} \\ \infty \\ R_{\max,k} - b_k\end{bmatrix} \ge \begin{bmatrix}\Lambda & 0 & 0 \\ \Gamma & I & 0 \\ \Gamma & 0 & -I\end{bmatrix}\begin{bmatrix}\tilde{U}_k \\ S_k \\ T_k\end{bmatrix} \tag{40d}$$

where the Hessian, $H$, and the coefficient of the linear term, $g$, are

$$H = \begin{bmatrix} H_y + H_{\Delta u} & 0 & 0 \\ 0 & H_t & 0 \\ 0 & 0 & H_s \end{bmatrix} \quad g = \begin{bmatrix} g_y + g_{\Delta u} \\ g_t \\ g_s \end{bmatrix}$$

with the following for each of the control terms

$$H_y = \left(\bar{W}_y\tilde{\Gamma}\right)^T\left(\bar{W}_y\tilde{\Gamma}\right) \qquad g_y = \left(\bar{W}_y\tilde{\Gamma}\right)^T\bar{W}_y(b_k - R_k)$$
$$H_s = \bar{W}_{s,2}^T\bar{W}_{s,2} \qquad g_s = \bar{W}_{s,1}e_s$$
$$H_t = \bar{W}_{t,2}^T\bar{W}_{t,2} \qquad g_t = \bar{W}_{t,1}e_t$$

$e_s = e_t = [1; 1; \ldots; 1]$ such that $e_s$ and $e_t$ are of the same dimension as slack variables, $S_k$ and $T_k$.

The Hessian and coefficient of the linear term of the regularization term are

$$H_{\Delta u} = (\bar{W}_{\Delta\tilde{u}}\Lambda)^T(\bar{W}_{\Delta\tilde{u}}\Lambda)$$
$$g_{\Delta u} = -(\bar{W}_{\Delta\tilde{u}}\Lambda)^T\bar{W}_{\Delta\tilde{u}}I_0\hat{\tilde{u}}_{k-1|k}$$

Table 3 reports the values used in this paper.

**Remark 3.** The convex quadratic program (40) has the standard form

$$\begin{aligned} \min_x \quad & \phi = \frac{1}{2}x^THx + g^Tx \\ s.t \quad & l \le x \le u \\ & b_l \le Ax \le b_u \end{aligned}$$

i.e. the inequality in (40c)–(40d) is represented as two inequalities due to lack of space, but should be interpreted as the second inequality in this remark.

## 6. SOC titration algorithm

For comparison of the MPC algorithm to SOC treatment, we implement a titration algorithm similar to that used in phase 3 studies of insulin degludec, see e.g. the studies by Zinman et al. (target: 3.9–4.9 mmol/L) and Kadowaki et al. (target: 4.0–5.0 mmol/L) (Kadowaki et al., 2017; Zinman et al., 2012). Many different algorithms for dose guidance are used in clinical care. Most are simple paper based algorithms that adjust the dose by a few units once or twice per week based on pre-breakfast SMBG measurements. Table 1 illustrates the paper based algorithm used in a long acting insulin titration study (Kadowaki et al., 2017). Based on the average of three consecutive pre-breakfast SMBG measurements prior to a weekly dose adjustment, the dose is adjusted by $-4$ to $+8$ units. If one of the SMBG measurements is below the target, that measurement is used rather than the average.

In the simulations, each day starts at breakfast and the SMBG measurement is represented by the first glucose value of the simulated day. Furthermore, the simulations are based on no measurement noise in the SMBG pre-breakfast measurement. This is the same scenario and data point as the offset-free MPC algorithm receives as input for state and disturbance estimation. The main difference to the offset-free MPC algorithm is that the MPC algorithm adjusts the long acting insulin dosage daily, while the SOC titration algorithms administers long-acting insulin daily, but only adjusts the dose weekly. This gives a clear advantage to the MPC based algorithm. However, the purpose of this study is to demonstrate the capabilities and potential improvement of an MPC based algorithm to a widely used existing basal insulin titration algorithm. The purpose it not to perform a head-to-head comparison of the MPC based algorithm to the best possible alternative.

## 7. Results

We perform stochastic simulations with process noise such that the day to day CV in glucose at a specific time of day is approximately 14%. In order to challenge the MPC algorithm, we reduce the insulin production, identified in Section 4 such that the steady-state basal glucose at zero insulin administration, i.e. $u_{ss} = 0$, is $G_{ss} = 12.0$ mmol/L. Using (11) at steady-state, we obtain $\tilde{I}_{sc,ss} = \tilde{I}_{p,ss} = 0$ and

$$\tilde{I}_{eff,ss} = \frac{1}{S_I}\left(\frac{p_{EGP}}{G_{ss}} - p_{GEZI}\right) \tag{41}$$

such that

$$\tilde{\beta} = \frac{\tilde{I}_{eff,ss}}{G_{ss}} = 1.27 \tag{42}$$

We use this value for $\tilde{\beta}$ in the simulations along with the initial conditions

$$x_0 = x_{ss} = \begin{bmatrix}\tilde{I}_{sc,ss} & \tilde{I}_{p,ss} & \tilde{I}_{eff,ss} & G_{ss}\end{bmatrix}^T = \begin{bmatrix}0 & 0 & 15.2 & 12.0\end{bmatrix}^T$$

We compare performance of the two algorithms, initiating both at 10 U as this is in line with the prescription information of insulin degludec.

### 7.1. Insulin initiation

First we investigate the performance of the MPC compared with the SOC titration algorithm in Table 1 in an insulin initiation scenario. Fig. 5 illustrates an average curve and standard deviation of 10 simulations with the two algorithms. We observe that the MPC algorithm quickly converges to the reference of 5 mmol/L, while the titration algorithm stabilizes in around 10 weeks. Speed is however of secondary importance, while the safety of the dose guidance is of primary concern. We observe that since the SOC only uses the morning glucose values, it tends to overdose leading to glucose concentrations below 4 mmol/L. Due to its predicting capabilities, MPC avoids the low glucose values.

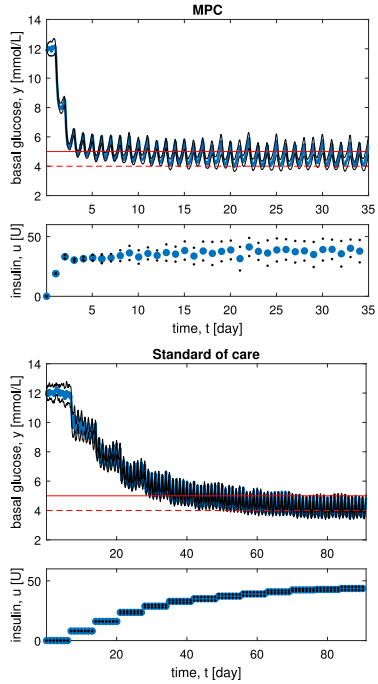


**Fig. 5.** Ten stochastic simulations of insulin initiation with MPC control (top) and SOC titration algorithm (bottom). Reaching a steady dose takes three times longer for the SOC titration algorithm. Insulin input is illustrated in U rather than U/h for simplification, using $T_s = 1$ h and zero order hold.

### 7.2. Insulin sensitivity

To investigate the sensitivity of the two algorithms to changes in physiological state of the patient, we simulate a case where the glycaemic target is reached. Figs. 6 and 7 illustrate simulations of scenarios where insulin sensitivity changes by 30% over three days and returns to normal two weeks later. The changes in physiology are not announced to the controllers. The blue and black curves indicate the mean and standard deviation of 10 stochastic simulations of the same patient parameter set. We observe that glucose values below 4 mmol/L are not avoided fully in any of the cases. However, the mean curves in the MPC simulations are within range at all times. Although both algorithms only receive one SMBG measurement per day, the MPC can predict one week ahead of glucose values with a 1 h sampling period, and thereby compensates for the low glucose occurring outside of the pre-breakfast SMBG measurements. The titration algorithm bases the calculations on one point in time only and therefore fails to react

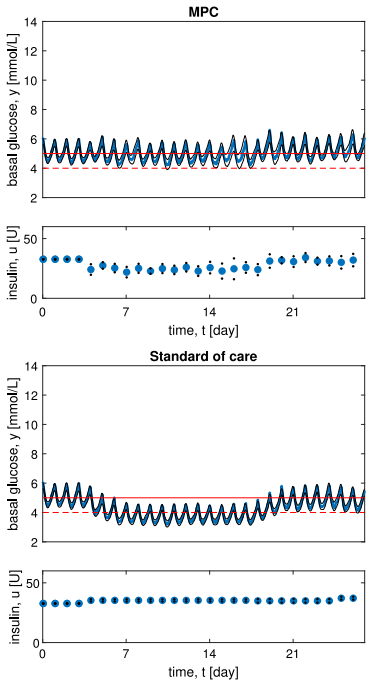


**Fig. 6.** Ten stochastic simulations of treatment where insulin sensitivity increases by 30% over days 7–9 and returns to normal on days 21–23 with MPC control (top) and SOC titration algorithm (bottom). Insulin input is illustrated in U rather than U/h for simplification, using $T_s = 1$ h and zero order hold.

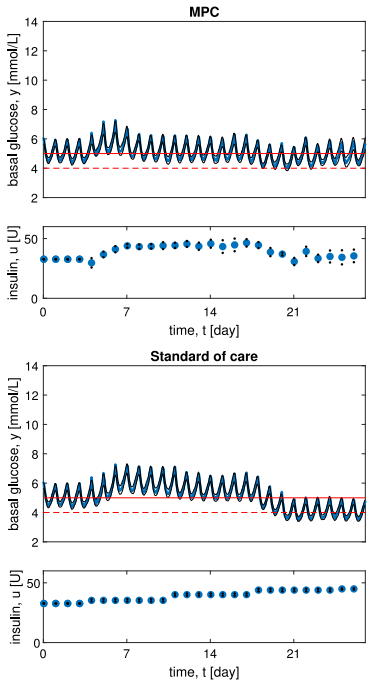


**Fig. 7.** Ten stochastic simulations of treatment where insulin sensitivity decreases by 30% over days 7–9 and returns to normal on days 21–23 with MPC control (top) and SOC titration algorithm (bottom). Insulin input is illustrated in U rather than U/h for simplification, using $T_s = 1$ h and zero order hold.

to the low glucose values occurring between samples. This is illustrated in the bottom of Figs. 6 and 7 where the titration algorithm fails to decrease the dose when insulin sensitivity increases.

### 7.3. Non-adherence by forgotten insulin administration

Finally we perform simulations of scenarios where patients forget to administer the insulin. Again, we assume that the glycaemic target is already reached. Research on adherence in type 2 diabetes has shown that an injection is omitted for some reason, including forgetting the injection, in 10%–30% of cases (Cramer & Pugh, 2005; Lee et al., 2006; Peyrot et al., 2012). We therefore perform a simulation as previously, but with injections forgotten at random in 30% of cases. The results are illustrated in Fig. 8. We observe that the SOC titration algorithm overdoses following a number of forgotten doses. The reason for this is the elevated SMBG measurements during time of non-adherence. The MPC algorithm however predicts the future glucose curves and manages to avoid the over-dosing. Considering efficacy of the two algorithms, the SOC has higher time in range than the MPC algorithm. However, since we weigh safety higher than efficacy, we conclude that the performance of the MPC algorithm is better than that of the SOC algorithm.

### 7.4. Summary

To summarize, we observe superior performance of the MPC algorithm compared to the SOC algorithm with respect to efficacy and safety. We should emphasize that this conclusion is based on the assumption that the physiological model is accurate with relatively precise parameter values.

## 8. Conclusion

This paper addresses the need for dose guidance for T2D patients initiating and maintaining long acting insulin treatment. The suggested algorithm uses MPC and a physiological model of long acting insulin and fasting glucose dynamics. When comparing efficacy and safety of our algorithm with a SOC algorithm in a simulation investigation, we observe superior performance of the MPC algorithm. Theoretically, it is possible to reach target fasting glucose in one day. This is however not desirable as too rapid glycaemic control can cause some complications to worsen, e.g. retinal disease. Furthermore, reaching target immediately would in practice require a perfect physiological model and an accurate estimate of all parameters. More importantly, MPC is able to predict the subsampled glucose concentrations during a day and avoid that any of these concentrations fall below the hypoglycemic limit. Compared to SOC, this provides both improved

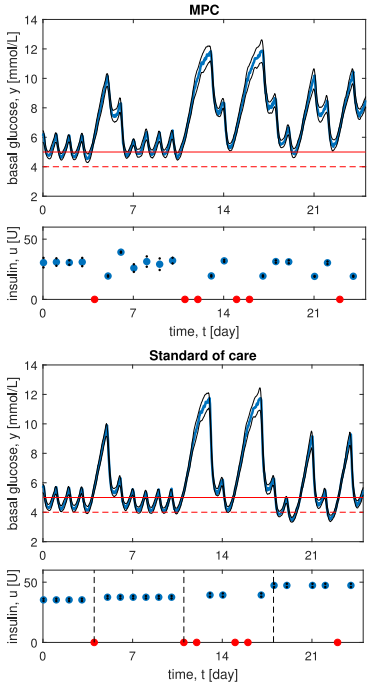


**Fig. 8.** Ten stochastic simulations of a scenario where insulin injections are forgotten in 30% of cases, indicated by red markers. The MPC algorithm (top) avoids the over-dosing observed in the SOC titration algorithm (bottom) case. The timing of SOC algorithm adjustments are indicated by the dotted lines in the bottom panel.

safety and performance. From the results, we observe that the SOC tended to overdose. The reason is that only pre-breakfast SMBG values were taken into consideration by the algorithm. For some patients, lower glucose levels may occur during the day rather than at night or early morning due to e.g. the dawn phenomenon, meals and activity. Both algorithms only receive a pre-breakfast measurement. The MPC algorithm however predicts the between samples hourly basal glucose concentration, and thereby avoids glucose levels below the target range. Opposed to the SOC algorithm, the MPC can predict the full effect of an insulin dose at steady state and therefore allow for once daily dose adjustments. However, one may wonder whether daily dose adjustments by the MPC are realistic and ideal in practice. Another approach may be to only allow for the dose adjustments on scheduled days, e.g. twice weekly, to reduce potential burden.

We aimed to compare the MPC to an SOC algorithm in an idealized case. The MPC algorithm was initiated with the true physiological parameter values, and we performed a number of stochastic simulations. The simulations considered initiation as well as treatment maintenance during insulin sensitivity changes and missed doses. In reality, such an algorithm should be initialized by adapting to the individual, ideally from CGM data, and dose adjustments should be conservative until a high accuracy is ensured. Online model identification and adaption is not in scope of this paper, but will be part of future work. Using one SMBG measurement to update the prediction model may be too limited, given the noise level of such data. With CGM data, more glucose data becomes available for updating the prediction model. In the previous simulations, we did not include sensor noise, although this is evident in the real world. We chose to simulate a simple case to keep focus on the main message of this paper.

In the comparison of the algorithms, we designed a case where insulin sensitivity changed on inconvenient days in terms of dose adjustment schedule for the SOC algorithm. A different timing in change of insulin sensitivity may improve or worsen the performance of the SOC algorithm. The reason for choosing the timing of the changes was to stress the SOC algorithm, i.e. to compare the algorithms in a worst case scenario.

For both people with T1D and T2D, the availability and accuracy of smart devices, such as CGMs, connected SMBG meters, and insulin administration devices, is increasing. This provides opportunities for development of individualized dose guidance algorithms. This work is an initial investigation of how an MPC algorithm compares to SOC paper based titration algorithms. Consequently, a natural extension of this work is to base the MPC on CGM measurements rather than SMBG measurements.

Moving forward, the linear MPC presented in this paper should be compared to nonlinear MPC as well as PID-based controllers to arrive at the right trade-off between performance and complexity. Practical issues should also be considered before moving to clinical implementation. This includes dose adjustment frequency, maximum dose size adjustments, i.e. considering safety and that oscillatory dosing may seem confusing to patients, as well as taking clinical knowledge into account to ensure safety and effectiveness. This concept of sub-frequency actuation might become the future tool for dose guidance control algorithms in long and ultra long acting insulin treatment.

## Acknowledgements

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