Optimal Experimental Design to Estimate Insulin Response in Type 2 Diabetes

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

I. Introduction

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

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

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

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

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

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

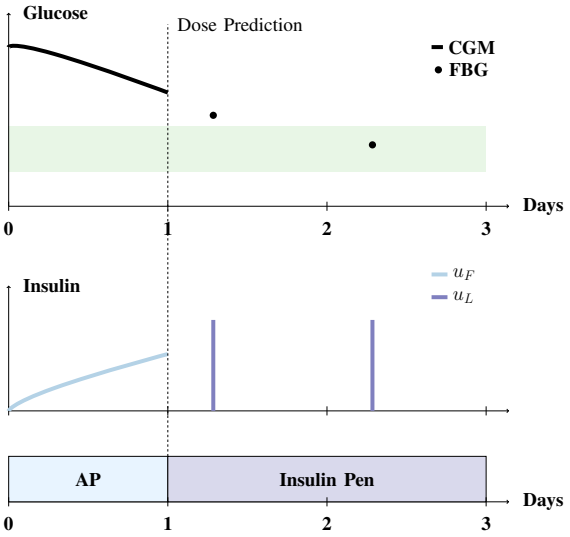

Fig. 1. A visualization of the titration solution from [7]. Data from an artificial pancreas (AP) enables the prediction of an insulin dose for injection-based therapy with long-acting insulin. In the AP period, fast-acting insulin (u_F) infusion is based on glucose measurements from a continuous glucose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

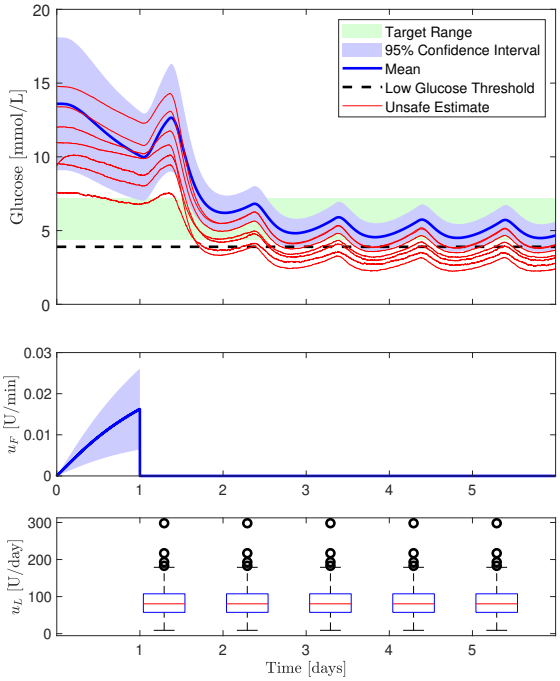

Fig. 2. Simulation results for 100 virtual people using the titration solution in [7]. During the first 24 hours, a closed-loop system gradually increases fast-acting insulin infusion and the plasma glucose drops. After 24 hours, the collected data enables parametrization of a dose-response model. The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

II. The Test Case

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

III. Methods

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

A. Design model

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

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

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

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

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

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

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

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

The system outputs discrete sensor measurements,

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

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

B. Optimal Experimental Design

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

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

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

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

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

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

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

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

where Fisher's Information matrix is defined as

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

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

$$S_y(t_k) = \left[\frac{\partial y(t_k)}{\partial \theta_1} \quad \cdots \quad \frac{\partial y(t_k)}{\partial \theta_n}\right] \quad (7)$$

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

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

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

$$\begin{aligned}
\dot{I}_{eff}(t) &= c_f \{p_3[I_p(t) + \beta G(t)] - p_3 I_{eff}(t)\} && \text{(9a)}\\
\dot{G}(t) &= [p_{GEZI} + S_I I_{eff}(t)/c_f] G(t) \\
&\quad + p_{EGP} + R_A(t). && \text{(9b)}
\end{aligned}$$

C. Decision Variable

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

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

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

D. Design Constraints

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

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

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

TABLE I

POPULATION PARAMETERS FOR THE DESIGN MODEL

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

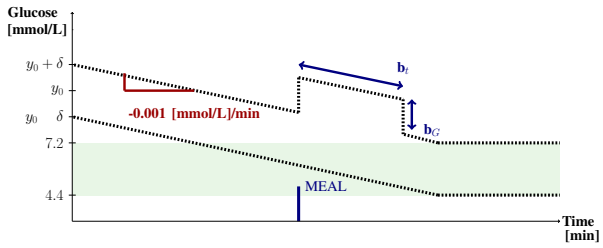

Fig. 3. Output constraints for the optimal experimental design. Over the course of the experiment, the glucose concentration must drop slowly towards the target range. We allow the glucose to fluctuate within the constraints $y_0 - 0.001 \cdot t_k - \delta \leq y_k \leq y_0 - 0.001 \cdot t_k + \delta$.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

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

E. Simulation model and implementation

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

IV. RESULTS

In this work, we investigate how optimal experimental design may improve the performance of an insulin titration algorithm for people with T2D. We solve the optimization problem in (3) to design a 24 hour long experiment to capture data for parameter identification. Fig. 4 shows the resulting experimental protocol where all design constraints are met. The first two meals (57g and 67g of carbohydrate, respectively) drive the glucose concentration to the upper bound and maximize the effect of β. The last meal is smaller,

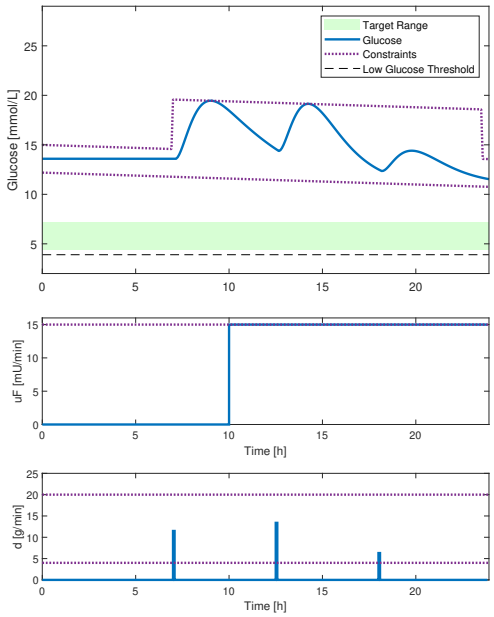

Fig. 4. The optimal experimental design for parameter estimation given the input and output constraints. Meal consumption happens over a five minute interval, hence the three meal sizes are 57g, 67g, and 31g of carbohydrates. The insulin infusion starts three hours after the first meal and remains on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

31g of carbohydrate, and lets the insulin input drive the glucose concentration closer to the lower bound emphasizing the influence of S_I. The insulin infusion resembles a step function. At 10AM, the infusion increases from 0 mU/min to 15 mU/min and remains at maximal infusion until the end of the experiment. The optimal input strategy separates different model dynamics as the insulin input increases three hours after the first meal. Fig. 5 presents the output sensitivity of each of the three estimated parameters during the experiment. The sensitivities appear to be somewhat correlated and all three are of similar absolute magnitude.

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

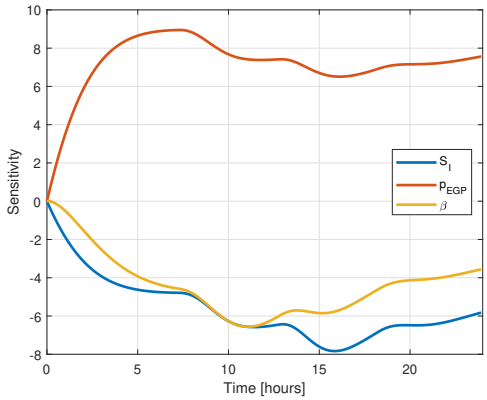

Fig. 5. The output sensitivities for the three estimated parameters over the course of the experiment. The parameters show some correlation.

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

V. Discussion

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

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

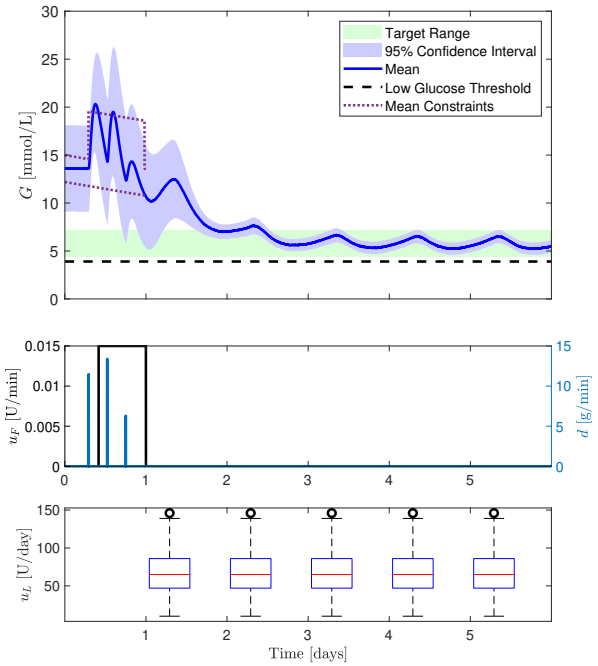

Fig. 6. Test of the experimental design on 100 virtual patients. Over the first 24 hours, we administer the optimized meal, $d(t)$, and fast-acting insulin, $u_F(t)$, inputs. Meals are consumed over 5 minute intervals. In the experiment, the mean glucose curve mildly exceeds the output constraints after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

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

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

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

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

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

VI. Conclusion

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

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