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Optimal Experimental Design for System Identification in a Bi-Hormonal Intraperitoneal Artificial Pancreas

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***Abstract*— For individuals with diabetes, the intraperitoneal drug-delivery route may enable fully automated artificial pancreas technology. For such systems, the model predictive control (MPC) algorithm is favorable. However, MPC requires a reliable predictive model. In this work, we aim to design a trial protocol to collect data for identification of a bi-hormonal intraperitoneal prediction model. We apply model-based design of experiment (MBDoE) to determine the optimal input of meals, subcutaneous insulin injections, and subcutaneous glucagon injections. Based on parameters from two anesthetized pigs, we design experiments to identify parameters in awake animals. Our results demonstrate how MBDoE may be used as a planning tool when designing trial protocols. The approach may hold potential as a support tool for clinicians when personalizing control algorithms for human AP users.**

I. Introduction

Type 1 diabetes (T1D) is an autoimmune disease where the body looses its ability to secrete insulin. In some cases glucagon secretion is affected as well. Unfortunately, the two hormones are essential to maintain a healthy blood glucose level (BGL). Insulin enables cellular blood glucose uptake from the bloodstream and successively, the deposit of glucose, in the form of glycogen, inside the liver. Glucagon, the counterpart of insulin, triggers glycogenolysis, a process where stored glucose is released from the liver to raise the BGL. Without insulin to enable glucose uptake, the body generates energy for its cells in an alternative process creating toxic bi-products. Accumulation of these bi-products can be lethal. As a result, people with T1D require life-long insulin therapy to survive.

In addition to immediate survival, keeping the BGL within a tight range is crucial to avoid short- and long-term complications. However, keeping the BGL in a healthy range is no simple task. For a person with T1D, it involves constant monitoring of BGL, estimation of consumed carbohydrates and the adjustment of insulin doses in accordance with activity level and physiological variations. With the advancement of the artificial pancreas (AP), some of these tasks can be automated. An artificial pancreas consists of a continuous glucose monitor (CGM) to measure the BGL, an algorithm to calculate the needed input to drive BGL into the target range, and a pump to infuse the computed dose of insulin and possibly glucagon. Today, several commercial AP systems exist with a subcutaneous drug delivery route [1]. In such hybrid closed-loop systems, the user must estimate and announce the number of carbohydrates in a meal at the time of consumption to achieve good control. This places a significant workload on the user. Instead, delivering drugs intraperitoneally may enable fully automatic systems [2]. The intraperitoneal route of drug delivery offers faster dynamics than the subcutaneous route such that an AP control algorithm can respond in due time without meal announcements. In addition, bi-hormonal artificial pancreas systems with insulin and glucagon guards against hypoglycemic episodes and provides additional safety [3]–[6].

In several AP systems, model-based control algorithms show promising results. However, this control framework requires a personalized prediction model for each individual. Human models exist for subcutaneous systems, but for the intraperitoneal drug delivery route they remain to be identified. In previous work, we present an intraperitoneal prediction model for pigs and identify parameters in anesthetized animals using intravenous glucagon, glucose and insulin injections [7]. To obtain a system for use in awake pigs, we must re-identify a subset of parameter values. We will need a similar procedure to adapt the model to human individuals. As a first step towards clinical implementation, we aim to design a pre-clinical trial that can provide sufficient data for system identification in awake pigs. For simpler and safer data collection, we propose to excite the gluco-regulatory system through meals, and subcutaneous insulin and glucagon injections.

One approach to designing a clinical trial is optimal experimental design [8], [9]. The method offers a framework to design trial protocols that enhance the ability to estimate a selected set of model parameters [10]. Within diabetes research, the method has shown to improve glucose tolerance tests and clinical trial designs for AP studies [11]–[13] as well as in the design of therapies for type 2 diabetes (T2D) [14], [15]. In this work, we apply model-based design of experiment (MBDoE) to identify an optimal trial protocol for parameter identification. We apply parameters from two anesthetized pigs in our design model. The goal is to identify a data collection protocol to estimate four central parameters in a prediction model for awake pigs.

This paper is structured as follows. Section II introduces the model and method used to design an optimal experiment.

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In Section III, we present the computed trial protocols. We discuss the possible clinical use-case of MBDoE in Section IV and conclude on the findings in Section V.

II. Methods

A. Design model

As our design model, we use a published bi-hormonal prediction model for intraperitoneal AP systems, (1a)-(1g) [7]. To use meals as an additional input for system excitation, we augment the prediction model with a two-compartment meal model, (1h)-(1i) [16]. The augmented model consists of nine equations that describe the gluco-regulatory system,

$$\dot{x}_1(t) = -(\beta_1 + \beta_2 x_2(t) + \beta_3 x_3(t))x_1(t) + HGP_{meta} + \gamma_7(\omega) d_{EGP} + \gamma_7(\omega)\frac{x_9(t)}{\tau_m}, \quad (1a)$$

$$\dot{x}_2(t) = -x_2(t)\beta_5 + \beta_5\beta_7\gamma_1(\omega)x_4(t) - \beta_5 F_{sat}, \quad (1b)$$

$$\dot{x}_3(t) = -x_3(t)\beta_8 + \beta_8 F_{sat}, \quad (1c)$$

$$\dot{x}_4(t) = -\gamma_1(\omega)x_4(t) + \gamma_8(\omega)u(t), \quad (1d)$$

$$\dot{x}_5(t) = \beta_9(-x_5(t) + \beta_{10}x_6(t)), \quad (1e)$$

$$\dot{x}_6(t) = -\gamma_2(\omega)x_6(t) + \gamma_9(\omega)h(t), \quad (1f)$$

$$\dot{x}_7(t) = \gamma_3(\omega)x_3(t)x_1(t) - \gamma_4(\omega)\frac{HGP_{meta}}{\beta_4}, \quad (1g)$$

$$\dot{x}_8(t) = d(t)\cdot\frac{1000}{c_{MwG}} - \frac{1}{\tau_m}x_8(t), \quad (1h)$$

$$\dot{x}_9(t) = \frac{1}{\tau_m}(x_8(t) - x_9(t)), \quad (1i)$$

where

$$HGP_{meta} = \beta_4 x_5(t)\sqrt{\frac{x_7(t)}{100}}\cdot e^{-\beta_{11}x_3(t)}, \quad (1j)$$

$$F_{sat} = \beta_6\frac{\delta_{12}\gamma_5(\omega)x_4(t)}{\delta_{13} + \delta_{12}\beta_7\gamma_1(\omega)x_4(t)}. \quad (1k)$$

x_1 [mmol/L] is the plasma glucose, x_2 [U/min] is the effective insulin in the body and x_3 [U/min] is the effective insulin in the liver. x_4 [U/mL] denotes the insulin in the intraperitoneal fluid. The glucagon in the system is split between the effective glucagon in the body, x_5 [μg/min], and the glucagon in the intraperitoneal fluid, x_6 [μg/mL]. x_7 [%] is the glycogen storage level in the liver. x_8 [mmol] and x_9 [mmol] describe the absorption of meal input, $d(t)$ [g/min]. As other inputs, the system receives subcutaneous injections of insulin, $u(t)$ [U], and glucagon, $h(t)$ [μg]. HGP_{meta} [mmol/L/min] is the hepatic glucose production and F_{sat} [U] is the function to model the saturation of the hepatic first pass effect. The system outputs discrete glucose measurements,

$$y_k = x_1(t_k) + v_k, \quad (2)$$

are influenced by the measurement noise, $v_k \sim N_{iid}(0, R)$.

The model parameters are listed in Table I and have not been published previously. They were identified using the method presented in [7], for the pig experiments described in [17]. As stated in [7], the glycogen storage recharging rate, γ_3, in anesthetized pigs are very small, while as stated in [17], we experienced that the glycogen storage level refills faster in awake animal and we expect higher rate of refilling in humans. Since the method presented in this paper is planned to be used for awake animal experiments and later in humans, we used higher values for γ_3 similar to [17].

B. Optimal Experimental Design

In optimal experimental design, we aim to maximize the information content of an experimental data set to enhance the estimation of the model parameters, $\theta = \{\beta_1, \beta_2, \beta_3, \beta_4\}$. We solve an optimization problem to identify an experimental design vector, ϕ, that best excites the modelled system,

$$\min_{\phi} \quad \psi(\phi, \theta), \quad (3a)$$

$$s.t. \quad \phi = [u(t), h(t), d(t)], \quad (3b)$$

$$x(0) = x_0, \quad (3c)$$

$$\dot{x}(t) = f(t, x(t), u(t), h(t), d(t), \theta), \quad (3d)$$

$$\hat{y}_k = g(t_k, x(t_k)), \quad (3e)$$

$$0 \geq c(t, x(t), u(t), h(t), d(t), \theta). \quad (3f)$$

We approximate the dynamics of the system by the model (1) that we denote $f(\cdot)$. The discrete measurement function, $g(\cdot)$, is specified indirectly by (2), i.e. $g(t_k, x(t_k)) = x_1(t_k)$. x_0 contains the initial values for all of the N_x system states. Insulin, $u(t)$, glucagon, $h(t)$, and meals, $d(t)$, are the system inputs. The model estimates a discrete series of measurements, $\hat{y}$. Equation (3f) denotes the input and output constraints.

The cost function in Equation (3) acts on the parameter variance-covariance matrix, C_θ, which quantifies the parametric uncertainty. To improve the parameter estimates, we wish to reduce the value of C_θ. Hence, we wish to determine,

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

where ψ is the design criterion, an assigned measurement function of C_θ [10]. As an approximation of C_θ, we apply Fisher's information matrix, $I(\theta, \phi)$.

To minimize the volume of the variance ellipsoid, we apply the design criteria known as D-optimality, i.e. minimizing the determinant of the Fisher information matrix,

$$\psi_D(\phi, \theta) = \det\left(I(\theta, \phi)\right), \quad (5)$$

where Fisher's information matrix is defined as

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

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

$$S_y(t_k) = \left[\frac{\partial y(t_k)}{\partial \hat{\theta}_1} \quad \cdots \quad \frac{\partial y(t_k)}{\partial \hat{\theta}_{n_\theta}}\right]. \quad (7)$$

We normalize the n_θ parameters with respect to the (supposed) true values shown in Table I and compute S_y using central differentiation.

TABLE I

PARAMETERS FOR THE DESIGN MODEL

Parameter	Pig A	Pig B	Unit	Description
β_1	0.5264	0.2464	[min^{-1}]	Insulin-independent glucose uptake rate
β_2	0.5707	1.8443	[U^{-1}]	Insulin sensitivity rate in liver
β_3	10.9873	15.1293	[U^{-1}]	Insulin sensitivity rate in other organs
β_4	23.4194	5.8133	[mmol/L/μg]	Glucagon sensitivity of liver cells
β_5	2.9453	-	[min^{-1}]	Body response time to insulin
β_6	1	-	[U/min]	Maximum insulin clearance rate of the liver from blood
β_7	2.8116	-	[1/mL]	Coefficient in hepatic first-pass effect, representing peritoneal fluid volume
β_8	0.1215	-	[min^{-1}]	Liver response time to insulin
β_9	6.2253	-	[min^{-1}]	Liver response time to glucagon
β_{10}	1	-	[mL/min]	Coefficient (gain) in response of liver to insulin equation
β_{11}	10^{-4}	-	[unitless]	Inhibition of glucose production by effective insulin
$\gamma_1(\omega)$	$2.1818 - 0.0280\omega$	-	[min^{-1}]	Diffusion rate of insulin
$\gamma_2(\omega)$	$4.8745 - 0.0469\omega$	-	[min^{-1}]	Diffusion rate of glucagon
$\gamma_3(\omega)$	$0.0055 + 0.0393\omega$	-	[%/mmol/U]	Charging rate of glycogen storage level
$\gamma_4(\omega)$	$59.9974 - 0.7692\omega$	-	[%/mmol/μg]	Discharging rate of glycogen storage level
$\gamma_5(\omega)$	$6.1343 - 0.0786\omega$	-	[mL]	Volume of peritoneal fluid diffusing from peritoneal to portal vein
$\gamma_7(\omega)$	$202.6956/\omega$	-	[1/L]	Proportion to inverse plasma volume
$\gamma_8(\omega)$	$1/\omega$	-	[1/mL]	Inverse volume of the fluid in peritoneal that insulin dissolves in
$\gamma_9(\omega)$	$1/\omega$	-	[1/mL]	Inverse volume of the fluid in peritoneal that glucagon dissolves in
δ_{12}	1	-	[unitless]	Coefficient in hepatic first-pass effect saturation function
δ_{13}	1	-	[U/min]	Half-saturation of the insulin hepatic first-pass effect
R	0.1872	-	[mmol^2/L^2]	Covariance of CGM measurement noise [18]
ω	36	40	[kg]	Body weight
α_7	7.7792	28.9723	[%]	Initial glycogen storage level
τ_m	40	-	[min]	Meal absorption time constant [16]
c_{MwG}	180.156	-	[g/mol]	Molecular weight of glucose

C. Decision Variable

We wish to determine the decision variable ϕ,

$$\phi = \{t_I, t_H, d, I, H\} \tag{8}$$

where t_I and t_H are vectors of the injection times for n_I subcutaneous insulin injections and n_H subcutaneous glucagon injections, respectively. d lists the meal sizes for n_d meals. I and H contain the injection doses for insulin and glucagon, respectively.

D. Design Constraints

We enforce a number of constraints on the system inputs and outputs to have a safe and physiological solution to the optimization problem. Table II lists the minimal and maximal values for the inputs in ϕ, where t_{end} [hours] is the length of the experiment, and ω [kg] denotes the body weight. To account for delayed input effects, the model does not receive any inputs in the last four hours of the experiment. We determine the minimal and maximal meal sizes from the body weight of the individual. For safety, we do not allow the insulin injections to exceed 3U.

TABLE II

CONSTRAINTS

Input/Output	Min	Max	Unit
t_I	0	$t_{end} - 4$	[hours]
t_H	0	$t_{end} - 4$	[hours]
d	$\omega/3$	$\omega \cdot 1.5$	[g]
I	0	3	[U]
H	0	100	[μg]
y	3.9	10.0	[mmol/L]

TABLE III

INITIAL DESIGN VECTOR

Input		Unit
$t_I =$	[0, 1, 5]	[hours]
$t_H =$	[1, 7]	[hours]
$d =$	[$\omega/3$, $\omega/3$]	[g]
$I =$	[0, 0, 0]	[U]
$H =$	[0, 0]	[μg]

E. Simulation and implementation

We set meal times to 2 hours and 6 hours after the start of the experiment and fix the length of the experiment to 12 hours. Table III lists the initial design vector for the optimization problem. For the initial states of the design model, we assume that no insulin or glucagon has been administered immediately before the start of the experiment. Additionally, the subject is fasting prior to trial start. As a result, the initial states of the system are

$$x_0 = [y_0 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \quad \alpha_7 \quad 0 \quad 0]^T, \tag{9}$$

where $y_0 = 7$ mmol/L is the initial blood glucose level and α_7 [%] is the initial glycogen storage level.

As stated in [7], β_1, β_2, β_3, β_4, and α_7 are considered as an individual parameter that are required to be identified for each subject. In this paper, the aim is to design a simple experimental procedure to improve the identification of the parameters for the starting up a closed-loop experiments.

A low α_7 at the beginning of the experiment will lead to inadequate liver responses to glucagon in the subject. Therefore, ensuring the identifiability of β_4 (sensitivity to glucagon) requires us to confirm that the subject's glycogen storage level is sufficiently high before the experiments. This can be achieved by avoiding fasting and exercise and minimizing the use of glucagon prior to the experiments.

During the closed-loop experiments, the proposed estimator [17] will estimate the value of the α_7 based on the model parameters. Therefore, our main focus in this paper is to design an experimental procedure that maximize the accuracy of identifying β_1, β_2, β_3, and β_4.

To achieve this, a protocol outlined in Fig. 1 is devised for the initiation of the closed-loop experiments. In the proposed protocol, two meals with accompanying exercise are scheduled to initiate insulin and glucagon injections and to identify the individual parameters. The rest of the day is planed with meals and no exercises to fill up the glycogen storage level. Later, using the proposed optimal experimental design method in this paper, the dynamics of the system is excited to increase the accuracy of identifying β_1, β_2, β_3, and β_4. Additionally, the PID controller proposed in [19] could also be used to control the blood glucose prior to the parameter identification.

We assume that endogenous glucose production, d_{egp} [mmol/L/min], remains constant when the body receives no glucagon, insulin or meal input. To obtain d_{egp}, we solve a steady state problem for the glucose concentration $x_1 = 7$ mmol/L, when the model receives no inputs.

We implement the simulation and MBDoE in `Matlab R2020b`, and solve the optimization problem using `sqp`. We simulate insulin and glucagon injections as impulses and administer the meal inputs over five minutes.

III. Results

For the two pigs, we solve the optimization problem in (3) in accordance with the individual parameters, the design constraints, the initial states and the initial design vector. Figure 2 shows the resulting optimal designs.

The two designs show similar characteristics. In both cases, the glucose curve moves between the upper and lower bound of the target range over the course of the experiment. Within the first two hours, we inject insulin in maximal doses of 3U. The injections help to a reduce the glucose values throughout the experiments. To counter the decrease in BGL from insulin injections, we administer glucagon injections and meals. For both pigs, the first meal is the largest. The experiments test the glucagon effect in connection with and without insulin injections. In both protocols, we administer glucagon injections after one and eight hours. After glucagon injections, we see a reduction in the glycogen storage level.

The optimal design maximizes the output sensitivity of the four parameters we wish to estimate. Figure 3 shows the sensitivities of the four parameters over the course of the two experimental protocols. When we inject insulin, the output briefly becomes sensitive to β_2. Over the remainder of the experiments, a sensitivity to β_3 is present, however it fades over time as less insulin is active in the body. In connection with glucagon injections, we see a peak in the sensitivity to β_4. β_1 has the highest sensitivity throughout the experiment. Towards the end of the experiment, where less insulin is active and glucose levels rise due to a meal and a glucagon injection, the sensitivity to β_1 increases even further. The output is least sensitive to β_2, indicating that it may be the hardest parameter to identify from the experimental data sets.

IV. Discussion

In this paper, we compute separate trial protocols to best identify parameters in two pigs. In practice, the trial protocol would typically be generalized for the trial population rather than individually designed. The results display similar input times for glucagon and insulin injections in the two individuals, but the dose sizes differ. In Pig A, we inject 9U of insulin whilst Pig B only receives 6U despite having a higher body weight. In glucagon injections, Pig B receives almost the double amount compared to Pig A over the course of the experiment. Comparing the initial glycogen storage levels, Pig B has a higher initial amount of glycogen to release and this allows a design with larger glucagon injections. Despite the dose differences, the results hint that certain input patterns can enhance system excitation. In both designs, we inject insulin within the first two hours and we see that the first meal is the largest. We administer the first glucagon injection together with an insulin injection, and inject the second towards the end of the experiment when the insulin effect is lowest. We can apply these insights in a generalized trial protocol.

In a safety-critical system, i.e. an animal or person with diabetes, implementing an optimal protocol directly can be dangerous. When computing the protocol, we incorporate a number of assumptions into the structure of the design model and the model's parameter set. We cannot guarantee that these assumptions mirror the physical system we will perform the experiment on. Hence, a direct implementation may cause unexpected and harmful system responses. Addtionally, MBDoE results tend to depend on the initial design vector and the initial states. In most systems, many local minima exist. Hence, the solution to the optimization problem will depend on how we initialize the solver and which solver we apply. This uncertainty may make it hard to use a MBDoE framework for trial design in a highly regulated area, e.g. the medical device industry. Using grid search and slack variables when solving the optimization problem can mitigate some of these issues, improving the chance of finding an optima and making the solution less sensitive to the initial input. If used with caution, we believe that MBDoE can offer useful inputs for the trial design.

We propose to use MBDoE in an iterative fashion with inputs from subject matter experts, i.e. veterinarians or clinicians. Experts may select the initial design vector for the MBDoE, and the following optimization can assess whether a modification of the design vector leads to a higher chance of system identification. Based on the output of the MBDoE,

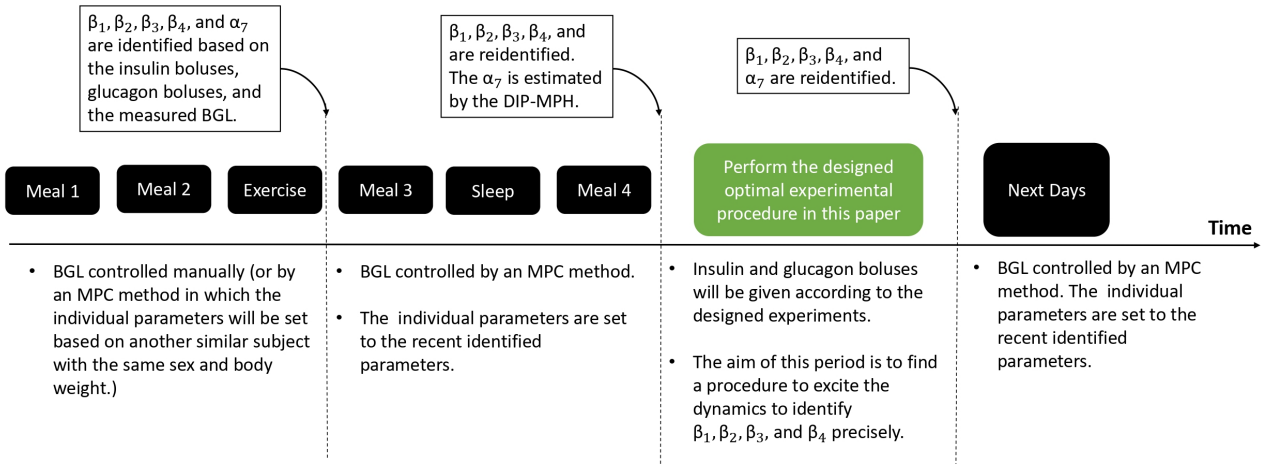
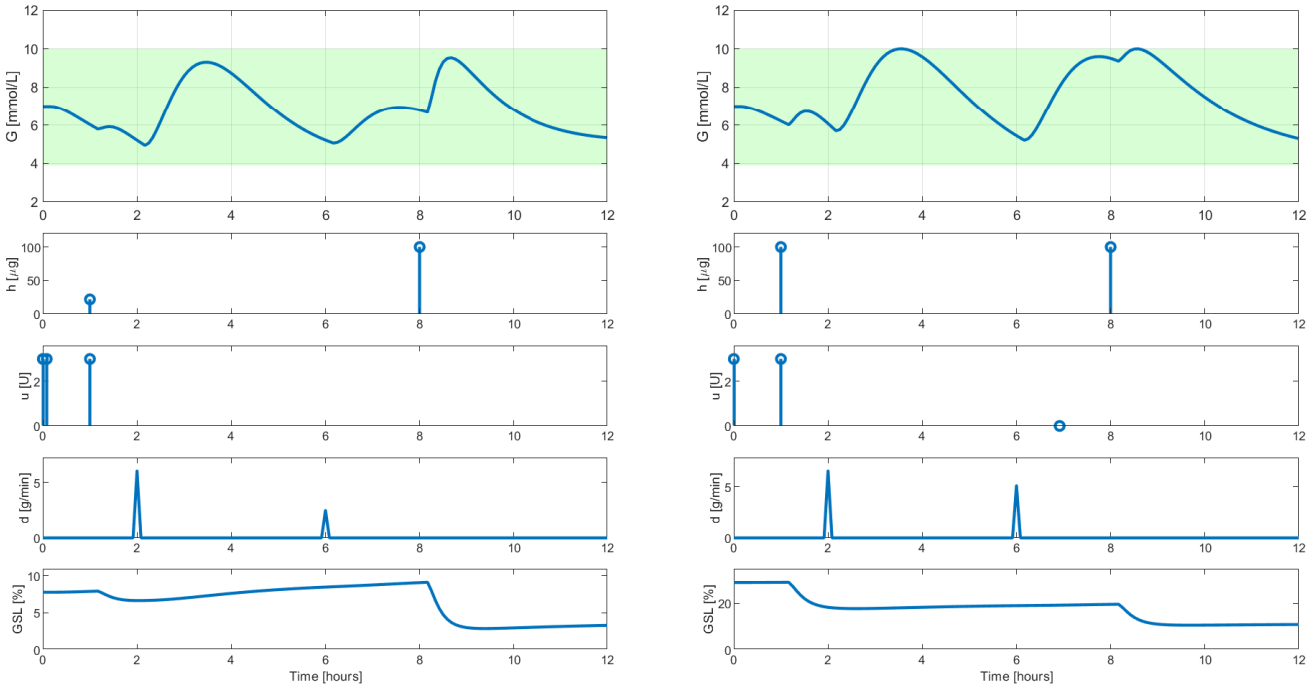


Fig. 1. An overview of the proposed structure for initiating a closed-loop experiment using the model presented in [7], the dual-hormone intraperitoneal moving horizon estimator (DIP-MHE) in [17], and the suggested optimal experimental design in this paper; MPC, model predictive control; BGL, blood glucose level.



(a) Pig A

(b) Pig B

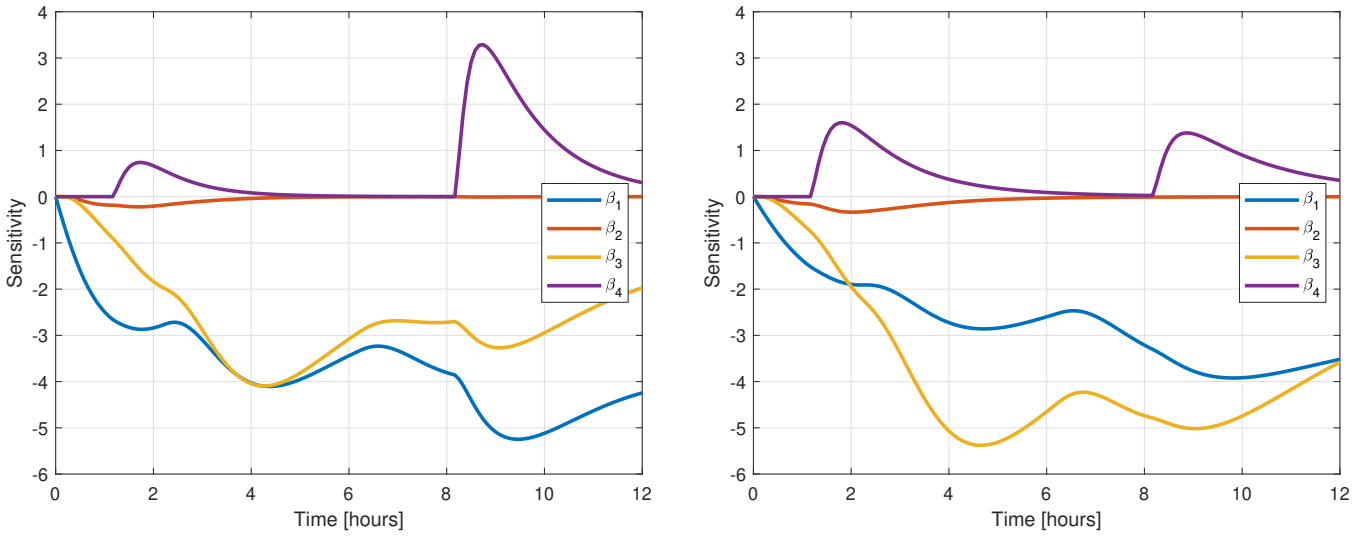
Fig. 2. Optimal design for 12 hour long experiment. G is the plasma glucose concentration. The green area shows the 3.9-10 mmol/L target range. h is the size of the glucagon injections, u denotes the dose of insulin injections, and d shows the meals absorption rate of the two meals. GSL is the glucagon storage level in the liver. The glucose curve remains within the target range and there are no system inputs in the last four hours of the experiment.

the subject matter experts can adjust the protocol to improve safety if they consider the new design concerning. The optimization may be repeated with the new design protocol. One or several iterations may be used to achieve a final protocol.

In the optimization problem's current form, no end-point constraints are placed on the glycogen storage level. Ideally, we want a high storage level at the end of experiments. If the glycogen storage level is depleted, a bi-hormonal controller will in practice be reduced to insulin-only control, since glucagon injections will not release glucose into the blood stream. In future work, we aim to add end-point constraints on the glycogen storage level in order to enable the implementation of a closed-loop system directly after parameter estimation.

V. Conclusion

In this work, we apply MBDoE to identify trial protocols to collect data for identification of a bi-hormonal intraperitoneal prediction model. For an experiment in awake pigs, we



(a) Pig A (b) Pig B

Fig. 3. Output sensitivities of the four parameters. β_1 denotes the insulin-independent glucose uptake rate. β_2 is the insulin sensitivity rate in liver. β_3 describes the insulin sensitivity rate in other organs. β_4 is the glucagon sensitivity of the liver cells.

determine the optimal input of meals, subcutaneous insulin injections, and subcutaneous glucagon injections over 12 hours. The optimized protocols for two separate animals show similar input patterns. However, due to safety requirements, a direct implementation of the design may not be applicable in a clinical setting. Still, the insights gained from a MBDoE protocol, i.e. the timing and relative sizes of inputs, may guide clinicians and veterinarians in the design of data collection protocols.

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