2015 American Control Conference
Palmer House Hilton
July 1-3, 2015. Chicago, IL, USA

The Contribution of Glucagon in an Artificial Pancreas for People with Type 1 Diabetes

Vladimír Bátora [1], Marián Tárník [1], Ján Murgaš [1], Signe Schmidt [3,4], Kirsten Nørgaard [3], Niels Kjøstad Poulsen [2], Henrik Madsen [2], Dimitri Boiroux [2,4], John Bagterp Jørgensen [2]

Abstract— **The risk of hypoglycemia is one of the main concerns in treatment of type 1 diabetes (T1D). In this paper we present a head-to-head comparison of a currently used insulin-only controller and a prospective bihormonal controller for blood glucose in people with T1D. The bihormonal strategy uses insulin to treat hyperglycemia as well as glucagon to ensure fast recovery from hypoglycemic episodes. Two separate model predictive controllers (MPC) based on patient-specific models handle insulin and glucagon infusion. In addition, the control algorithm consists of a Kalman filter and a meal time insulin bolus calculator. The feedback is obtained from a continuous glucose monitor (CGM). We implement a bihormonal simulation model with time-varying parameters available for 3 subjects to compare the strategies. We consider a protocol with 3 events - a correct mealtime insulin bolus, a missed bolus and a bolus overestimated by 60%. During normal operation both strategies provide similar results. The contribution of glucagon becomes evident after administration of the overestimated insulin bolus. In a 10h period following an overbolused meal, the bihormonal strategy reduces time spent in hypoglycemia in the most severe case by almost 15% (1.5h), outperforming the insulin-only control. Therefore, glucagon contributes to the safety of an Artificial Pancreas.**

I. INTRODUCTION

The International Diabetes Federation estimates the prevalence of diabetes to be over 380 million worldwide [1]. Approximately 10% of the diabetic patients suffer from type 1 diabetes (T1D). In usual insulin therapy, patients are required to make decisions on the actual insulin dosing infused by insulin pens or pumps. However, these decisions are often based on intuition as the amount of information available to the patient is limited. Erroneous decisions may lead to insulin overdosing followed by dangerous hypoglycemic episodes. Conversely, the patient may deliberately underdose the insulin to avoid hypoglycemia at the cost of long term complications caused by insufficient diabetes compensation.

For decades, researchers have been developing an automated glucose control system, known as the artificial pancreas (AP) [2]. Continuous subcutaneous insulin infusion systems (CSII) allowed a continuous insulin dosing. Yet, the closed-loop control had a fundamental drawback in missing feedback from glucose sensing. Eventually, development of CGMs has made the idea of a closed-loop control practically achievable.

With the feedback available, various control strategies have been investigated. Among others PID control [3], adaptive control [4]–[6], and fuzzy logic control [7]. The most widely used control approach is the model predictive control (MPC) due to its ability to elegantly handle a broad range of system constraints [2], [8], [9]. Despite the progress in AP research, it remains a great challenge to overcome the difficulties in glucose regulation. Inter- and intra-patient variability, considerable lag in action time caused by subcutaneous route of insulin infusion and sensing, and CGM reliability may all compromise safety of the glucose regulation. Prevention and safe recovery from the hypoglycemic episodes are the main concerns of the AP systems.

A potential way to increase safety of these systems may be to incorporate the insulin-antagonistic pancreatic hormone, glucagon, into the control system. So far, the absence of a stable soluble glucagon formulation has been a major problem. Recently, several pharmaceutical companies revealed information about a planned release of formulations overcoming the current problems.

[10]–[12] involve glucagon in the control systems. Clinical trials in [11], as well as simulation results in [12] provide evidence that the bihormonal artificial pancreas can significantly reduce the risk and time spent in hypoglycemic episodes compared to usual insulin therapy. However, they do not provide comparison of the bihormonal AP with an insulin-only solution to distinguish the benefits of glucagon use.

In this paper, we analyze the contribution of glucagon in a blood glucose control system by means of simulation to obtain preliminary results precluding a planned clinical study. We describe a clinical protocol which will be used in the study. We provide a comparison of an MPC-based control system which employs only insulin and a bihormonal control system containing two independent MPCs for insulin and glucagon infusion. Both solutions include a pre-meal insulin bolus calculator to partly compensate the postprandial glucose peaks [13].

For the simulation purposes we use a bihormonal model presented together with its parameters for three subjects in [12]. The controller tuning is based on individual models built from patient specific data.

The paper is organized as follows. Section II describes the bihormonal model used for the simulations. Section III

[1] Faculty of Electrical Engineering and Information Technology, Slovak University of Technology, Bratislava, Slovak Republic vladimir.batora@stuba.sk

[2] Department of Applied Mathematics and Computer Science, Technical University of Denmark, Kgs. Lyngby, Denmark jbjo@dtu.dk

[3] Department of Endocrinology, Hvidovre Hospital, Denmark

[4] Danish Diabates Academy, Denmark

*This work has been supported by the Danish Diabetes Academy and the Slovak Scientific Grant Agency through grant VEGA-1/2256/12.

briefly presents the individual patient models and predictions performed by a Kalman filter and predictor. Section IV outlines the control system. Sections V and VI provide simulation results and a conclusion.

II. SIMULATION MODEL

There are numerous models describing the glucose metabolism which include the insulin and carbohydrate absorption dynamics [9], [14]. However, only few of the models incorporate glucagon and allow to simulate the effects of subcutaneously injected insulin and also glucagon [12], [15], [16]. To simulate the controlled system we use a model proposed in [12]. The model presents an extension to the minimal model of plasma glucose and insulin kinetics by employing a glucagon action on endogenous glucose production, a subcutaneous insulin absorption model and a gastrointestinal absorption model proposed by Hovorka [14]. The bihormonal model [12] is described by a system of ODEs that we introduce and explain in this section.

A. Extended Model of Glucose Kinetics

The glucose kinetics is described by a system of differential equations in the form

$$\dot{G}(t) = -[S_G + X(t) - Y(t)]G(t) + S_G G_b + \frac{D_2(t)}{t_{maxG} V} \quad (1a)$$

$$\dot{X}(t) = -p_2 X(t) + p_2 S_I [I(t) - I_b] \quad (1b)$$

$$\dot{Y}(t) = -p_3 Y(t) + p_3 S_N [N(t) - N_b] \quad (1c)$$

where G [mg/dl] is the plasma glucose concentration, I [μU/dl] is the plasma insulin, and N [pg/dl] the plasma glucagon concentration. X [min^{-1}] and Y [min^{-1}] represent the insulin and glucagon action on glucose production. S_G [min^{-1}] is the fractional glucose effectiveness describing how glucose per se promotes its disposal and inhibits its production. S_I [min^{-1}/(μU/ml)], S_N [min^{-1}/(pg/ml)] are the insulin and glucagon sensitivities. p_2 [min^{-1}] and p_3 [min^{-1}] are rate constants describing the dynamics of insulin and glucagon action. V [dl/kg] is the glucose distribution volume and $R_a(t) = D_2(t)/t_{maxG}$ [mg/min/kg] is the rate of appearance of glucose in plasma following a meal ingestion. Values with b denote the basal state.

B. Gastrointestinal Absorption Model

The model incorporates a two-compartment gastrointestinal absorption subsystem presented by Hovorka [14]

$$\dot{D}_1(t) = \frac{1}{t_{maxG}}(-D_1(t)) + A_G D_G \quad (2a)$$

$$\dot{D}_2(t) = \frac{1}{t_{maxG}}(-D_2(t) + D_1(t)) \quad (2b)$$

where $D_1(t)$ describes glucose in the first compartment, $D_2(t)$ is glucose in the second compartment, A_G [-] is the carbohydrate bioavailability. D_G [mg/kg/min] represents the intake of carbohydrates per kg of body weight.

C. Subcutaneous Insulin Absorption Model

The model employs a linear model of subcutaneous insulin absorption

$$\dot{I}(t) = -k_e I(t) + \frac{S_2(t)}{V_I t_{maxI}} \quad (3a)$$

$$\dot{S}_1(t) = u_1(t) - \frac{S_1(t)}{t_{maxI}} \quad (3b)$$

$$\dot{S}_2(t) = \frac{S_1(t) - S_2(t)}{t_{maxI}} \quad (3c)$$

where k_e [min^{-1}] describes the insulin clearance from plasma, u_1 [μU/kg/min] is the subcutaneous insulin infusion rate, V_I [ml/kg] is the distribution volume of plasma insulin, t_{maxI} [min] is the insulin absorption time constant and S_1, S_2 represent a two-compartment absorption of subcutaneously administered insulin.

D. Subcutaneous Glucagon Absorption Model

Herrero et al. [12] use the same model structure as in case of insulin to model subcutaneous glucagon absorption

$$\dot{N}(t) = -k_N N(t) + \frac{Z_2(t)}{V_N t_{maxN}} \quad (4a)$$

$$\dot{Z}_1(t) = u_2(t) - \frac{Z_1(t)}{t_{maxN}} \quad (4b)$$

$$\dot{Z}_2(t) = \frac{Z_1(t) - Z_2(t)}{t_{maxN}} \quad (4c)$$

k_N [min^{-1}] describes the glucagon clearance from plasma, u_2 [pg/kg/min] is the subcutaneous glucagon infusion rate, V_N [ml/kg] is the distribution volume of plasma glucagon, t_{maxN} [min] is the glucagon absorption time constant and Z_1, Z_2 represent a two-compartment absorption of subcutaneously administered glucagon.

E. Model Parameters

To mimic the Circadian rhythm for 3 real patients, [12] identifies separate sets of parameters corresponding to 3 time windows of day. In our simulations we use the model together with the identified time-varying parameters to compare performance of a bihormonal and an insulin-only control system.

F. Glucose Measurement

A CGM provides feedback to the controller. The sensor measures glucose concentration in the interstitial tissue, which differs from concentration in the plasma. We use a CGM model [17] to generate the CGM measurement data with a non-Gaussian sensor noise from the plasma glucose concentration.

III. PREDICTION MODEL

The model [12] is too complex to be individualized from the patient clinical data and directly used in a model based controller. In this section we develop a simple linear model of the subcutaneous glucose concentration identifiable from basic patient data. The resulting model is the basis for filtering and prediction in the model predictive control system.

A. ARMAX Model

The model has ARMAX structure with a deterministic and a stochastic part. The deterministic part describes the glucose-insulin and glucose-glucagon dynamics when insulin and glucagon are administered subcutaneously. The stochastic part accounts for unknown disturbances. Identification of the glucose-insulin dynamics using various linear models has been considered previously [6], [18]. We use second order continuous-time transfer function models in the form

$$G_I(s) = \frac{Y(s)}{U_1(s)} = \frac{K_I}{(\tau_I s+1)^2} \tag{5}$$

$$G_g(s) = \frac{Y(s)}{U_2(s)} = \frac{K_g}{(\tau_g s+1)^2} \tag{6}$$

This simple model offers a key advantage - its parameters K_I, τ_I (K_g, τ_g) can be computed directly from the available patient specific data, the insulin sensitivity factor (ISF) and the insulin action time [5]. Definition and illustration of ISF and τ_I can be found in [5]. From the time-domain impulse response of (5), $y(t) = K_I t/\tau_I^2 e^{-t/\tau_I}$, it is easy to show that the insulin action time is equal to τ_I. Consequently, $y(\tau_I) = -ISF$ and $K_I = -\tau_I e^1\ ISF$. We discretize the models (5), (6) with sampling time T_s = 5 min assuming a ZOH on the insulin and glucagon infusion rates, $u_1(t)$ and $u_2(t)$. We augment the discrete-time deterministic model with a stochastic part presented in [5]. The resulting discrete-time model can be expressed as a dual-input ARMAX model [13]

$$\bar{A}(q^{-1})y(t) = \bar{B}_1(q^{-1})u_1(t) + \bar{B}_2(q^{-1})u_2(t) + \bar{C}(q^{-1})\varepsilon(t) \tag{7}$$

The stochastic term $\bar{C}(q^{-1})\varepsilon(t)$ models effects of unknown disturbances, e.g. exercise or uncertainty of meals.

B. Filtering and Prediction

An innovation form state space realization of (7) with A, B, C, K in canonical observer form is [19], [20]

$$x_{k+1} = Ax_k + Bu_k + K\varepsilon_k \tag{8a}$$

$$y_k = Cx_k + \varepsilon_k \tag{8b}$$

x_k and y_k represent deviations from the steady-state, $u_k = [u_{1k}\ \ u_{2k}]^T$ is the control vector of the insulin and glucagon infusion rates computed at step k. We use the Kalman gain, K, identified in [5]. The gain is constant for all patients. We denote the columns of matrix B as $B = [B_1\ \ B_2]$. The Kalman filter performs state estimation and prediction with the innovation form state space model (8) as follows [20]: The innovation of (8) is $e_k = y_k - C\hat{x}_{k|k-1}$. $\hat{x}_{k|k-1}$ is a one-step prediction of the state vector x_k computed at step $k-1$. Using $\hat{x}_{k|k} = \hat{x}_{k|k-1}$, the predictions are [20]

$$\hat{x}_{k+1|k} = A\hat{x}_{k|k-1} + Bu_{k|k} + Ke_k \tag{9a}$$

$$\hat{y}_{k+1|k} = C\hat{x}_{k+1|k} \tag{9b}$$

$$\hat{x}_{k+1+j|k} = A\hat{x}_{k+j|k} + Bu_{k+j|k} \qquad j = 1,2,...N-1 \tag{9c}$$

$$\hat{y}_{k+1+j|k} = C\hat{x}_{k+1+j|k} \qquad j = 1,2,...N-1 \tag{9d}$$

The Kalman filter receives all available information including the current and future micro-bolus insulin and glucagon infusion rates as well as the current mealtime insulin bolus. Model (7) does not include a carbohydrate absorption subsystem. The innovation e_k provides feedback to the Kalman filter and predictor. When CGM measures a rise in the subcutaneous glucose concentration following a meal ingestion, the Kalman filter receives the information about meal indirectly, through this feedback.

IV. CONTROL SYSTEM

The control system consists of a micro-bolus insulin infusion controller, a glucagon infusion controller, and an insulin bolus calculator that is enabled if a meal is announced at mealtime. In the center of the system is the Kalman filter which interconnects the three elements. The filter reflects previous insulin (micro-bolus as well as mealtime bolus) and glucagon infusion in the state update and the predictions. The insulin infusion rate, $u_{1,k}$, computed at each sampling instant consists of the micro-bolus insulin infusion, $u_{1m,k}$, and the mealtime insulin bolus, $u_{1bol,k}$. $u_{1,k}$ represents a deviation from the basal infusion rate, u_{1b}, which maintains a steady state glucose concentration 5.5 mmo/L.

A. Insulin and Glucagon Controller Switching

To avoid a simultaneous infusion of both hormones we employ a simple switching logic of the insulin and glucagon controller with hysteresis. The hysteresis prevents frequent switching between the two controllers around a single glucose level. During normal operation above the hypoglycemic range, only the insulin controller is running. The glucagon controller is switched on when glucose concentration decreases under 4.5 mmol/L and simultaneously the micro-bolus insulin controller is switched off. In order to disable the glucagon injection and turn the micro-bolus insulin controller back on, the glucose concentration has to reach 5 mmol/L. We could achieve the same behavior by a single MIMO MPC, however, at the cost of a more complicated tuning and increased computational requirements to solve a more complex optimization problem.

B. Micro-Bolus Insulin Controller Design

Currently, the most successful strategy for the blood glucose control is the MPC [2], [14], [21].

1) Linear Model Predictive Controller: In this section we describe a linear MPC that is responsible for the insulin infusion. We consider both input and output constraints.

The micro-bolus insulin controller and the glucagon controller are never active simultaneously. Therefore, the insulin micro-bolus controller prediction model does not have to explicitly involve current and future glucagon infusion. Information about past glucagon injections is present in the Kalman filter state estimates and available for the micro-bolus insulin controller. Conversely, the glucagon controller does not have to explicitly involve current and future insulin infusion in its prediction model. The state estimates also contain information about the mealtime insulin boluses. Thus, direct information is not necessary for the controllers.

At each sample instant we compute the insulin micro-bolus infusion rate by solution of a constrained convex quadratic

program

$$\min_{\{u_{1mj},\eta_{j+1}\}_{j=0}^{N-1}} \phi \tag{10a}$$

$$s.\,t. \quad \hat{x}_{k+1|k} = A\hat{x}_{k|k-1} + B_1 u_{1mk|k} + Ke_k \tag{10b}$$

$$\hat{y}_{k+1|k} = C\hat{x}_{k+1|k} \tag{10c}$$

$$\hat{x}_{k+1+j|k} = A\hat{x}_{k+j|k} + B_1 u_{1mk+j|k} \quad j \in \mathcal{N}_1 \tag{10d}$$

$$\hat{y}_{k+1+j|k} = C\hat{x}_{k+1+j|k} \quad j \in \mathcal{N}_1 \tag{10e}$$

$$u_{1m\,\min} \le u_{1mk+j-1|k} \le u_{1m\,\max} \quad j \in \mathcal{N}_0 \tag{10f}$$

$$\hat{y}_{k+j|k} \ge y_{\min} - \hat{\eta}_{k+j|k} \quad j \in \mathcal{N}_0 \tag{10g}$$

$$\hat{y}_{k+j|k} \le y_{\max} + \hat{\eta}_{k+j|k} \quad j \in \mathcal{N}_0 \tag{10h}$$

$$\hat{\eta}_{k+j|k} \ge 0 \quad j \in \mathcal{N}_0 \tag{10i}$$

with $\mathcal{N}_0$={1,...,N}, $\mathcal{N}_1$={1,...,N-1} and the objective function

$$\phi = \frac{1}{2}\sum_{j=0}^{N-1} \|\hat{y}_{k+1+j|k} - r_{k+1+j|k}\|^2 + \lambda_I \|\Delta u_{1mk+j|k}\|^2 + \gamma \|\hat{\eta}_{k+1+j|k}\|^2 \tag{11}$$

We use a prediction and control horizon of 20 hours (N = 240). It has to be sufficiently long to capture the slow glucose-insulin dynamics and include the effect of all insulin on board. The objective function (11) penalizes the glucose deviations from the setpoint, $r_{k+1+j|k}$, as well as violations of the output soft constraints (10g)-(10h). The asymmetric soft constraint bounds, $y_{\min}$ and $y_{\max}$, correspond to 4 and 10 mmol/L. The soft constraint violation is subject to heavy penalty with γ = 100. The regularization term $\lambda_I \|\Delta u_{k+j|k}\|^2$ ensures smooth control by tempering the controller aggressiveness. λ_I = 600/u_{1b} is individualized by the patient-specific basal rate, u_{1b}, which maintains a steady state 5.5 mmol/L. The computed insulin infusion profile represents deviations from the constant basal infusion rate u_{1b}. Thus, the micro-bolus insulin controller operates in the range $[-u_{1b}, u_{1m\,\max}]$.

2) Algorithm Modifications: To enhance safety the algorithm includes a time-varying reference signal [5], [22] when the glucose concentration is above the target. Furthermore, a set of security rules limits the maximal insulin infusion rate, $u_{1m\,\max}$, depending on the current glucose level. A detailed description of the modifications can be found in [13].

C. Mealtime Bolus Calculation

The mealtime insulin bolus calculation requires knowledge of the insulin-to-carbohydrate ratio, IC (U/g), and the amount of carbohydrates ingested, CHO (g). We estimate the IC from the insulin sensitivity factor, ISF (mmol/L/U) and the glucose rise, ΔG_1 (mmol/L) after ingestion of a defined amount of carbohydrates, CHO_1 (g). Then, $IC = (\Delta G/CHO)/ISF$. The amount of bolus insulin is computed as

$$Bolus = CHO \cdot IC \tag{12}$$

D. Glucagon Controller Design

The glucagon MPC uses the same structure as the MPC that manipulates the insulin micro-bolus infusion (10b)-(10i) with control vector u_2 and vector B_2 corresponding to the glucagon infusion. The objective function is

$$\phi = \frac{1}{2}\sum_{j=0}^{N-1} \|\hat{y}_{k+1+j|k} - r_{g\,k+1+j|k}\|^2 + \lambda_G \|\Delta u_{2;k+j|k}\|^2 + \gamma \|\hat{\eta}_{k+1+j|k}\|^2 \tag{13}$$

We do not restrict the maximal glucagon infusion rate (10f). Naturally, the lower bound is 0. Soft constraints (10g)-(10h) prevent hypoglycemia as well as excessive glucagon administration. The lower and upper constraints correspond to 4 mmol/L and 6 mmol/L. The soft constraint violation penalty remains $\gamma = 100$. The term penalizing changes in glucagon infusion rate uses λ_G = 0.1. The glucagon MPC tracks the target 5 ($\sim r_g$=-0.5) mmol/L. Fig. 1 depicts different penalization of the glucose excursions from setpoints in the micro-bolus insulin and the glucagon MPC.

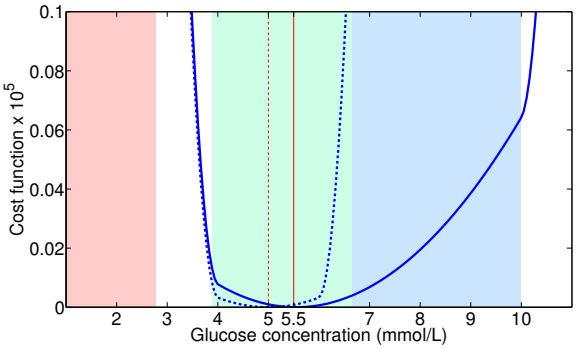


Fig. 1. Illustration of the glucose excursion penalty in the insulin (full line) and glucagon (dashed line) MPC.

V. SIMULATIONS

We compare the insulin-only and the bihormonal control strategy for the 3 subjects with daily profiles of parameters identified in [12].

A. Simulated Scenario - Simplified Clinical Protocol

For the simulation purposes we consider a simplified, and idealized 3 day protocol. The protocol includes 3 different events for each subject. In the idealized scenario, the events are executed at separate days. Physical exercise should also be included as an additional event. However, the vast majority of the available models, including the one that we are using, do not support exercise simulation. Therefore, we exclude this event from the simulation study. We assume that at the beginning of the simulation (00:00), the subjects are at steady state (5.5 mmol/L). Each event includes a meal containing 60 g of carbohydrates at 10:00. In the three consecutive events, we administer 100%, 0% and 160% of the calculated meal time insulin bolus.

B. Results

Fig. 2 illustrates the results obtained by the bihormonal and the insulin-only control strategy for Subjects 1 and 2. Tables I-IV summarize the time spent in different glucose concentration zones for each patient.

TABLE I

SUMMARY OF THE WHOLE EXPERIMENT. BIHORMONAL CONTROL.

Glucose (mmol/L)	Subject 1 [%]	Subject 2 [%]	Subject 3 [%]
$G \geq 10$	3.36	4.63	1.62
$G \geq 6.7$	13.31	11.11	10.99
$3.9 \leq G \leq 10$	96.41	93.40	98.37
$3.9 \leq G \leq 6.7$	86.46	86.92	89.00
$G \leq 3.9$	0.23	1.97	0.00
$G \leq 3.5$	0.00	1.16	0.00

TABLE II

SUMMARY OF THE WHOLE EXPERIMENT. INSULIN-ONLY CONTROL.

Glucose (mmol/L)	Subject 1 [%]	Subject 2 [%]	Subject 3 [%]
$G \geq 10$	3.36	4.40	1.62
$G \geq 6.7$	12.38	11.00	11.00
$3.9 \leq G \leq 10$	95.95	91.55	98.37
$3.9 \leq G \leq 6.7$	86.92	84.95	89.00
$G \leq 3.9$	0.69	4.05	0.00
$G \leq 3.5$	0.00	2.78	0.00

TABLE III

SUMMARY OF EVENT 3. BIHORMONAL CONTROL.

Glucose (mmol/L)	Subject 1 [%]	Subject 2 [%]	Subject 3 [%]
$G \geq 10$	0	0	0
$G \geq 6.7$	25.62	14.88	8.26
$3.9 \leq G \leq 10$	98.35	85.95	100
$3.9 \leq G \leq 6.7$	72.73	71.07	91.74
$G \leq 3.9$	1.65	14.05	0.00
$G \leq 3.5$	0.00	8.26	0.00

TABLE IV

SUMMARY OF EVENT 3. INSULIN-ONLY CONTROL.

Glucose (mmol/L)	Subject 1 [%]	Subject 2 [%]	Subject 3 [%]
$G \geq 10$	0	0	0
$G \geq 6.7$	19.01	14.05	8.26
$3.9 \leq G \leq 10$	95.04	71.07	100
$3.9 \leq G \leq 6.7$	76.03	57.02	91.74
$G \leq 3.9$	4.96	28.93	0.00
$G \leq 3.5$	0.00	19.83	0.00

1) Correct Meal Time Insulin Bolus: In case of the first event with 100% of the mealtime insulin bolus administered, both strategies ensure safe glucose control in each subject. A noteworthy difference can be seen in Subject 2 where the bihormonal control system ensures faster transition from the lower zone of euglycemia to the target. The single hormone control system is also able to avoid hypoglycemia thanks to an early suspension of the micro-bolus insulin infusion by the safety rules [13].

2) No Meal Time Insulin Bolus: In case of a missed bolus, the micro-bolus insulin controller alone is not able to compensate the postprandial glucose peaks particularly due to the strict safety rules limiting the maximal micro-bolus insulin infusion rate. On the other hand, the safety rules prevent the controller from insulin overdose. After the peak, the glucose smoothly converges to the target without any considerable undershoot.

3) Overestimated Insulin Bolus: The last event simulates a situation when the patients overestimate a meal and the algorithm administers a too large meal time insulin bolus. This may lead to insulin overdose and potential hypoglycemia. In case of Subject 3, the two strategies perform almost identically with small glucagon injections caused by the measurement noise. The situation changes with Subject 1 and 2 where the glucagon controller actively helps to bring the glucose concentration back to the target. Especially in Subject 2, the glucagon controller considerably reduces the time spent in hypoglycemia.

4) Experiment Summary: Tables I - IV provide a summary of the whole experiment and of a 10 hour window following the 3rd event with 160% of the bolus administered. In general, during normal operation both strategies provide good results. However, in case of an eventual insulin overdose, the bihormonal strategy clearly outperforms the insulin-only control. The bihormonal control reduces time spent in hypoglycemia during a 10 hour period after the meal ingestion and bolus administration by almost 16% as indicated in Table III and Table IV.

VI. CONCLUSION

This paper provides a head-to-head comparison of a bihormonal and an insulin-only control system for the blood glucose concentration in people with type 1 diabetes. The simulation results provide evidence, that in case of unexpected events, such as meal overestimation, the glucagon has large potential to mitigate effects of the insulin-induced hypoglycemia, and thus, provide additional safety compared to the insulin-only controller. The simulations do not include physical exercise. Intensive exercise may further prove the glucagon to be an efficient way to prevent hypoglycemia and ensure a fast recovery.

Due to significant variance of the parameters over time, adaptive strategies should be considered in future work. Tuning of the glucagon controller to be sufficiently aggressive, but at the same time resistant to unwanted activation caused by measurement noise is also an important challenge.

REFERENCES

[1] International Diabetes Federation, *IDF Diabetes Atlas*. Brussels, Belgium: International Diabetes Federation, 2013.

[2] C. Cobelli, E. Renard, and B. Kovatchev, "Artificial Pancreas: Past, Present, Future." *Diabetes*, vol. 60, no. 11, pp. 2672–1682, 2011.

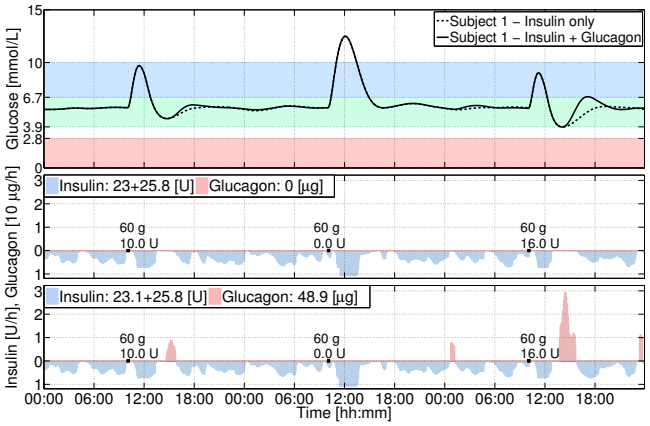
[3] G. M. Steil, C. C. Palerm, N. Kurtz, G. Voskanyan, A. Roy, S. Paz, and F. R. Kandeel, "The effect of insulin feedback on closed loop glucose control." *The Journal of Clinical Endocrinology and Metabolism*, vol. 96, pp. 1402–1408, 2011.

[4] K. Turksoy, L. Quinn, E. Littlejohn, and A. Cinar, "Multivariable adaptive identification and control for artificial pancreas systems." *IEEE Transactions on Bio-medical Engineering*, vol. 61, pp. 883–891, 2014.

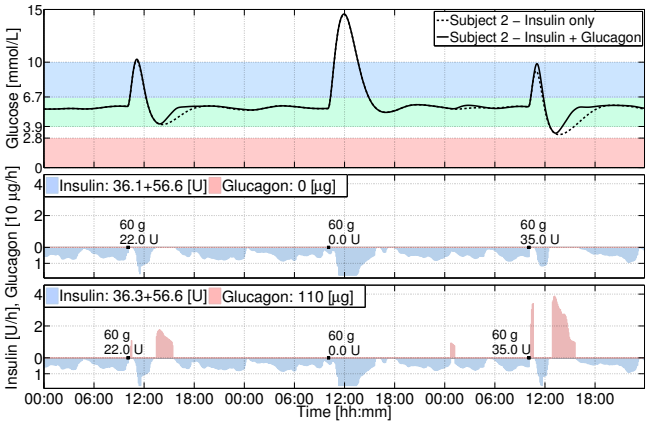
[5] D. Boiroux, A. K. Duun-Henriksen, S. Schmidt, K. Nørgaard, N. K. Poulsen, H. Madsen, and J. B. Jørgensen, "Assessment of model predictive and adaptive glucose control strategies for people with type 1 diabetes," in *The 19th IFAC World Congress*, vol. Preprints, 2014.

[6] M. Tarnik, J. Murgas, E. Miklovicova, and L. Farkas, "Adaptive control of time-delayed systems with application for control of glucose concentration in type 1 diabetic patients," in *11th IFAC International Workshop on Adaptation and Learning in Control and Signal Processing 2013, Caen, France*, vol. 11, 2013.

[7] E. Atlas, R. Nimri, S. Miller, E. A. Grunberg, and M. Phillip, "Md-logic artificial pancreas system," *Diabetes care*, vol. 33, pp. 1072–1076, 2010.

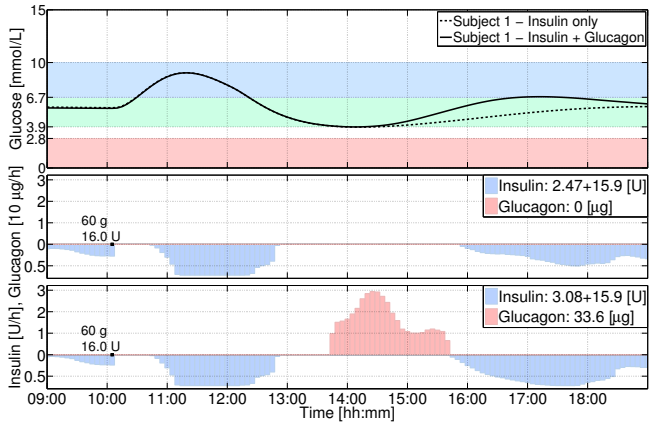


(a) Subject 1

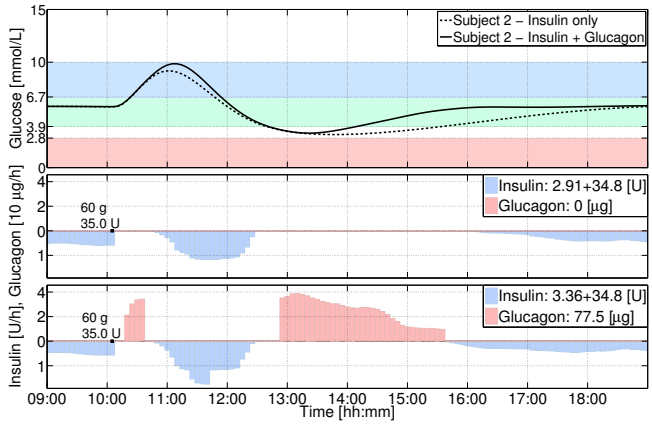


(b) Subject 2

Fig. 2. Comparison of the bihormonal control strategy (full line) and insulin-only control strategy (dashed line). In the three subsequent events, 100%, 0% and 160% of the optimal insulin meal time bolus is administered.



(a) Subject 1



(b) Subject 2

Fig. 3. Comparison of the bihormonal control strategy (full line) and insulin-only control strategy (dashed line) during event 3 where 160% of the optimal insulin meal time bolus is administered.

[8] P. Soru, G. De Nicolao, C. Toffanin, C. Dalla Man, C. Cobelli, and L. Magni, "MPC based Artificial Pancreas: Strategies for individualization and meal compensation," *Annual Reviews in Control*, vol. 36, no. 1, pp. 118–128, 2012.

[9] C. Cobelli, C. D. Man, G. Sparacino, L. Magni, G. De Nicolao, and B. P. Kovatchev, "Diabetes: Models, signals, and control." *IEEE reviews in biomedical engineering*, vol. 2, pp. 54–96, 2009.

[10] S. J. Russell, F. H. El-Khatib, D. M. Nathan, K. L. Magyar, J. Jiang, and E. R. Damiano, "Blood Glucose Control in Type 1 Diabetes With a Bihormonal Bionic Endocrine Pancreas," *Diabetes Care*, vol. 35, pp. 2148–2155, 2012.

[11] F. H. El-Khatib, S. J. Russell, D. M. Nathan, R. G. Sutherlin, and E. R. Damiano, "A bihormonal closed-loop artificial pancreas for type 1 diabetes." *Science Translational Medicine*, vol. 2, no. 27, p. 27, 2010.

[12] P. Herrero, P. Georgiou, N. Oliver, M. Reddy, D. Johnston, and C. Toumazou, "A Composite Model of Glucagon-Glucose Dynamics for In Silico Testing of Bihormonal Glucose Controllers," *Journal of Diabetes Science and Technology*, vol. 7, no. 4, pp. 941–951, 2013.

[13] V. Bátora, M. Tárnik, J. Murgaš, S. Schmidt, K. Nørgaard, N. K. Poulsen, H. Madsen, and J. B. Jørgensen, "Bihormonal model predictive control of blood glucose in people with type 1 diabetes," in *2014 IEEE Conference on Control Applications (CCA)*, 2014, pp. 1693–1698.

[14] R. Hovorka, V. Canonico, L. J. Chassin, U. Haueter, M. Massi-Benedetti, M. O. Federici, T. R. Pieber, H. C. Schaller, L. Schaupp, T. Vering, and M. E. Wilinska, "Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes," *Physiological Measurement*, vol. 25, pp. 905–920, 2004.

[15] P. S. Neelakanta, M. Leesirikul, Z. Roth, and S. Morgera, "A complex system model of glucose regulatory metabolism," *Complex Systems*, vol. 16, pp. 343–368, 2006.

[16] S. Schaller, S. Willmann, J. Lippert, L. Schaupp, T. R. Pieber, A. Schuppert, and T. Eissing, "A generic integrated physiologically based whole-body model of the glucose-insulin-glucagon regulatory system," *Pharmacometrics & Systems Pharmacology*, vol. 65, 2013.

[17] M. Breton and B. Kovatchev, "Analysis, modeling, and simulation of the accuracy of continuous glucose sensors." *Journal of diabetes science and technology*, vol. 2, pp. 853–862, 2008.

[18] K. van Heusden, E. Dassau, H. C. Zisser, D. E. Seborg, and F. J. Doyle, "Control-relevant models for glucose control using a priori patient characteristics." *IEEE Transactions on Bio-medical Engineering*, vol. 59, pp. 1839–1849, 2012.

[19] J. K. Huusom, N. K. Poulsen, S. B. Jørgensen, and J. B. Jørgensen, "Tuning SISO offset-free Model Predictive Control based on ARX models," *Journal of Process Control*, vol. 22, no. 10, pp. 1997–2007, 2012.

[20] J. B. Jørgensen, J. K. Huusom, and J. B. Rawlings, "Finite horizon MPC for systems in innovation form," *Decision and Control and European Control Conference (CDC-ECC), 2011 50th IEEE Conference on*, pp. 1896–1903, 2011.

[21] G. De Nicolao, L. Magni, C. Dalla Man, and C. Cobelli, "Modeling and control of diabetes: Towards the artificial pancreas," *Proceedings of the 18th IFAC World Congress*, vol. 18, pp. 7092–7101, 2011.

[22] M. Eren-Oruklu, A. Cinar, L. Quinn, and D. Smith, "Adaptive control strategy for regulation of blood glucose levels in patients with type 1 diabetes," *Journal of Process Control*, vol. 19, no. 8, pp. 1333–1346, 2009.