# Glucagon Administration Strategies for a Dual-Hormone Artificial Pancreas

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***Abstract*—In this paper, we describe and evaluate Model Predictive Control (MPC) algorithms for an Artificial Pancreas (AP) with both insulin and glucagon. Such a device is called a dual-hormone AP. We evaluate the performance of two different glucagon administration strategies and compare them to a strategy using insulin only that serves as a reference strategy. In all cases, the dosing of the insulin is based on the same MPC algorithm. Glucagon is included as a safety feature in the closed-loop system, and the administration of insulin is done in a non-aggressive way such that it does not anticipate glucagon administration. Insulin and glucagon are never administered simultaneously; the switch between insulin and glucagon administration is based on either a measured glucose level threshold with hysteresis or a prediction of future hypoglycemia. We simulate cases where meals are correctly bolused and not bolused, as well as cases with insulin sensitivity changes. The results indicate that both switching strategies for a dual-hormone AP reduce the time spent in hypoglycemia significantly. Moreover, the glucagon control strategy using glucose predictions in the switch allows earlier glucagon intervention and further reduces the time spent in hypoglycemia without overdosing glucagon.**

## I. Introduction

Healthy people keep the blood glucose around the target 3.5 - 8.0 mmol/L. People with type 1 diabetes (T1D) are dependent on exogenous insulin supply due to an autoimmune destruction of the insulin producing cells in the pancreas. The therapeutic target for this patient group is near-normalization of blood glucose levels via intensive insulin therapy.

Furthermore, T1D affects the glycemic counter-regulatory system. In healthy people, a too low glucose concentration (i.e. hypoglycemia) inhibits the production of insulin and stimulates the secretion of an antagonistic pancreatic hormone, glucagon. However, hypoglycemia in T1D is typically related to insulin overdosing, which suppresses the counter-regulatory mechanisms and blocks the restoration of euglycemia.

For decades, researchers have been trying to replace the usual insulin therapy by an automated closed-loop insulin delivery system that is known as the Artificial Pancreas (AP) [1]–[10]. With Continuous Glucose Monitors (CGM) available, various control strategies have been investigated and tested. The approaches with the most promising results are based on Model Predictive Control (MPC) [11]–[20]. Yet, safety of the AP remains an unresolved issue; especially when it comes to hypoglycemia prevention.

Fig. 1. The dual-hormone artificial pancreas. It includes a CGM sensor, a smartphone for control, an insulin pump and a glucagon pump.

One way to reduce the risk of hypoglycemia is to incorporate glucagon as a safety hormone in the AP. The first controller using glucagon was developed more than 30 years ago [21]. This dual-hormone AP (i.e. an AP with insulin and glucagon) was not usable in everyday life due to, among other reasons, the instability of glucagon in soluble formulation. Recently, the planned release of stable soluble glucagon analogues has raised the interest in dual-hormone APs [22]–[25]. For virtual as well as real patients with T1D, all studies using a dual-hormone AP confirm that the time spent in hypoglycemia is reduced compared to an AP using insulin only [26]–[29]. However, high doses of glucagon may have side effects including nausea and vomiting [30]. For example, Russell *et al.* [28] reported several cases of nausea and vomiting during the glucagon administration phase, although they could not relate it to high glucagon doses. Fig. 1 shows a possible dual-hormone AP setup, including the CGM sensor, a smartphone used for monitoring and control, and the insulin and glucagon pumps.

So far, the most popular control strategies for glucagon administration are proportional derivative (PD) control [26], [28], [31] and MPC [32], [33]. PD controllers have fewer parameters, but rely much more on the glucose trend (deriva-

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tive part) than on the current glucose level (proportional part). In PD control, glucagon overdose can for instance be avoided by stopping the glucagon administration beyond a certain threshold as in [26]. Conversely, MPC can use the glucose level predictions to optimize the insulin and glucagon administration in a straightforward way. In addition, MPC can incorporate soft constraints on insulin/glucagon variations or levels to improve the safety of the controller and to limit the administration of glucagon to safety purposes only. The tuning of an MPC with soft constraints and switching logic between the insulin and the glucagon controller requires some expertise in MPC. The tuning of such an MPC system with soft constraints should be based on simulations as well as the systematic and partially automatic tuning methods for MPC [34]–[39]. Therefore, even though the tuning of a controller using MPC seems more difficult than the one of a PD due to the lack of experience with a dual-hormone AP, the systematic tuning methods facilitate the tuning of the MPC considerably. At this point in time, the simulation based evaluation of controllers is partially limited as there only exist a limited number of models that describe the absorption of subcutaneous glucagon and its action on blood glucose. In this paper, we report such a model and demonstrate how it can be used for evaluation of a dual-hormone AP.

In addition, a further complication is that the action time associated with the subcutaneous route of glucagon administration impairs the performance of a dual-hormone AP. This time is shorter than the absorption time of subcutaneously administered fast acting insulin, but is longer than the absorption time of naturally secreted glucagon. A review of dual-hormone APs indicates that administering glucagon too late may reduce its efficiency to prevent hypoglycemia [40]. Therefore, one of the major challenges in a dual-hormone AP is to find a suitable strategy for when to start the glucagon administration.

The aim of this paper is to evaluate different glucagon administration strategies for the dual-hormone AP. We compare three different controllers. The first controller uses only insulin. The second controller uses a strategy based on the current glucose level to enable or disable the glucagon administration. Finally, the third controller uses the glucose predictions to enable or disable the glucagon administration.

The paper is organized as follows. Section II describes the model used for simulations, Section III introduces the prediction model used in the MPC, and Section IV describes the dual-hormone control algorithm. Sections V and VI provide the simulation results and concluding remarks.

## II. Dual-hormone Simulation Model

*In-silico* testing of a dual-hormone control algorithm requires a suitable model that is able to simulate the effects of subcutaneously administered insulin and glucagon. Until recently, the majority of mathematical models including the UVA/Padova T1D simulator [41] and the Hovorka model [42] considered only insulin in the description of the glucose regulatory system. Some of the physiology-based models incorporate also glucagon [43], [44]. These complex models have numerous parameters. Consequently, these models are not easy to individualize by adjusting the parameters.

Recently, Dalla Man *et al.* presented an extension of the UVA/Padova T1D simulator [45]. The extension contains glucagon kinetics and action. It can be used to simulate a cohort of patients. This model is an important step forward for testing of the dual-hormone AP. Its main drawback is that its parameters are not publicly available. For *simulation* purposes, we implement the model by Bergman *et al.* [46] extended with glucagon action as proposed by Herrero *et al.* [47]. Herrero *et al.* augment the minimal model of glucose kinetics with compartmental absorption models for subcutaneously administered insulin and glucagon, as well as ingested meals.

### A. Model Overview

A system of differential equations describes the extended glucose kinetics in the form [47]

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

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

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

$G(t)$ [mg/dL], $I(t)$ [$\mu$U/dL] and $N(t)$ [pg/dL] are the plasma glucose, plasma insulin and plasma glucagon concentrations, respectively. $X(t)$ [$min^{-1}$] and $W(t)$ [$min^{-1}$] describe the action of insulin and glucagon on glucose production.

Herrero *et al.* [47] employ three-compartment models with identical structure to describe the absorption of insulin and glucagon from the subcutaneous depot into the plasma. For insulin the model is [47]

$$\dot{I}(t) = -k_e I(t) + \frac{S_2(t)}{V_I t_{maxI}} \tag{2a}$$

$$\dot{S}_1(t) = u_1(t) - \frac{S_1(t)}{t_{maxI}} \tag{2b}$$

$$\dot{S}_2(t) = \frac{S_1(t) - S_2(t)}{t_{maxI}} \tag{2c}$$

$S_1(t)$ [$\mu$U/kg] and $S_2(t)$ [$\mu$U/kg] represent the insulin concentrations in the first and in the second compartment. $u_1(t)$ [$\mu$U/kg/min] is the subcutaneous insulin infusion rate per kg of body weight.

Similarly, the model describing glucagon absorption is of the form [47]

$$\dot{N}(t) = -k_N N(t) + \frac{Z_2(t)}{V_N t_{maxN}} \tag{3a}$$

$$\dot{Z}_1(t) = u_2(t) - \frac{Z_1(t)}{t_{maxN}} \tag{3b}$$

$$\dot{Z}_2(t) = \frac{Z_1(t) - Z_2(t)}{t_{maxN}} \tag{3c}$$

where $Z_1(t)$ [pg/kg] and $Z_2(t)$ [pg/kg] represent the glucagon concentrations in the first and in the second compartment. $u_2(t)$ [pg/kg/min] is the subcutaneous glucagon infusion rate per kg of body weight.

Furthermore, the model includes the two-compartment gastrointestinal absorption subsystem proposed by Hovorka *et al.* [42]

$$\dot{D}_1(t) = A_G D_G - D_1/t_{maxG} \tag{4a}$$

$$\dot{D}_2(t) = (D_1(t) - D_2(t))/t_{maxG} \tag{4b}$$

$D_1(t)$ [mg/kg] and $D_2(t)$ [mg/kg] are the glucose concentrations in the first and in the second compartment. $D_G$ [mg/kg/min] is the carbohydrate intake per kg of body weight.

Herrero *et al.* [47] identify the model parameters for 3 separate periods of a day to mimic the circadian rhythm for 3 real patients. For details about the model and its parameters together with the numerical values we refer the reader to [47].

### B. Glucose Sensor

The glucose concentration is measured by a CGM. The feedback from the CGM is a very important component of the control system. Instead of the plasma glucose concentration, CGMs measure glucose concentration in the interstitial tissue. To simulate a CGM measurement, we employ a deterministic model of the glucose transport from blood to interstitial tissue together with the sensor noise model presented by Facchinetti *et al.* [48].

## III. Prediction Model

The central part of the MPC is the prediction model. In the context of an AP, the prediction model should capture the action times and delays associated with subcutaneous insulin and glucagon administration. Ideally, the model should follow the physiological properties of the patient. However, due to the lack of easily obtainable clinical data, even the simplest physiological models for T1D (e.g. the model developed by Bergman *et al.* [46]) are difficult to identify and individualize for a particular patient [49].

Therefore, simpler linear models for predicting the blood glucose have been investigated. Kirchsteiger *et al.* [50] investigate models with integrators, van Heusden *et al.* [51] propose a third order linear transfer function model, and Percival *et al.* [52] use a first order model with a transport delay. Turksoy *et al.* [11] and Russell *et al.* [28] use high order ARX models to describe the insulin and glucagon (Russell *et al.*) dynamics.

We employ a low-order linear model to describe the effects of insulin, glucagon and other unknown factors. The model consists of a deterministic part modeling the glucose-insulin and glucose-glucagon dynamics and a stochastic part describing all unknown factors. As the meal dynamics is very uncertain, we do not consider an explicit meal model in our predictions. The continuous-time transfer function model is

$$Y(s) = Y_D(s) + Y_S(s) = G(s)U(s) + H(s)E(s) \tag{5}$$

with a deterministic part, $Y_D(s)$, and a stochastic part, $Y_S(s)$. $Y(s)$ and $U(s)$ denote the Laplace transforms of the output (the subcutaneous glucose concentration) and the inputs (the insulin and glucagon delivery). The stochastic part, $Y_S(s) = H(s)E(s)$, accounts for process and measurement noises and patient-model mismatch.

### A. The Deterministic Part of the Prediction Model

In our previous simulation study, we investigated how different deterministic parts of the prediction model affect the closed-loop performance of a dual-hormone control algorithm [53]. We considered first, second and third order linear systems with and without a transport delay. In the second and third order models, we assumed equal time constants to reduce the number of identified parameters. Using different time constants does not improve the quality of the model fit [50], [53]. The ability of the considered models to capture the insulin and glucagon dynamics varies significantly. Fig. 2 compares the responses of the linear models and the nonlinear simulation model to a defined insulin bolus [53]. We have observed similar responses for glucagon. Surprisingly, the results indicate that the choice of prediction model is not critically important for the performance of the closed-loop system. Based on these findings, we selected the second order system without a delay as the best trade-off between the overall performance and identifiability in the clinical practice.

We can express the deterministic part $Y_D(s)$ in (5) as

$$Y_D(s) = G_I(s)U_I(s) + G_G(s)U_G(s) \tag{6}$$

$G_I(s)$ and $G_G(s)$ are the transfer functions describing the effects of insulin and glucagon on glucose. $U_I(s)$ and $U_G(s)$ are the Laplace transforms of the insulin and glucagon infusion rates, $u_I(t)$ and $u_G(t)$, respectively.

*1) Individualization of the deterministic model:* The selected second order transfer functions $G_I(s)$ and $G_G(s)$ are

$$G_I(s) = \frac{K_I}{(\tau_I s + 1)^2} \tag{7a}$$

$$G_G(s) = \frac{K_G}{(\tau_G s + 1)^2} \tag{7b}$$

where $K_I$, $K_G$ and $\tau_I$, $\tau_G$ are the gains and time constants corresponding to the insulin and glucagon action on glucose. A large advantage of (7a)-(7b) compared to linear systems with different time constants or transport delay is that the parameter pairs ($K_I$, $\tau_I$) and ($K_G$, $\tau_G$) can be computed from easily accessible patient-specific data. It is evident from the impulse response of (7a) that the computation of the parameters of the glucose/insulin transfer function, $K_I$ and $\tau_I$, requires only knowledge of the insulin sensitivity factor (ISF) and the insulin action time($\tau_I$) [54]. Both ISF and insulin action time are commonly known patient parameters. On the other hand, the corresponding parameters of the glucagon action are usually not known, but they can be estimated from the response of the patient to a glucagon dose in a fairly simple manner [32].

### B. The Stochastic Part of the Prediction Model

Discretization of (5) with a sampling time of $T_s = 5$ min yields

$$y(t) = \frac{B_I(q^{-1})}{A_I(q^{-1})}u_I(t) + \frac{B_G(q^{-1})}{A_G(q^{-1})}u_G(t) + \frac{C(q^{-1})}{D(q^{-1})}\varepsilon(t) \tag{8}$$

Similarly to the continuous-time version (5), the model (8) has a deterministic part associated to the infusion of insulin, $u_I(t)$, and glucagon, $u_G(t)$, and a stochastic term $C(q^{-1})/D(q^{-1})\varepsilon(t)$. $\varepsilon(t)$ is assumed to be a white noise process. In addition, we assume that $C(q^{-1}) = 1 + c_1 q^{-1} + c_2 q^{-2}$ and $D(q^{-1}) = A_I(q^{-1})$ with $c_1 = 1.62$ and $c_2 = 0.68$ determined from clinical data for one real patient [54], [55]. Then, we can express (8) as the following ARMAX model

$$\bar{A}(q^{-1})y(t) = \bar{B}_I(q^{-1})u_I(t) + \bar{B}_G(q^{-1})u_G(t) + \bar{C}(q^{-1})\varepsilon(t) \tag{9}$$

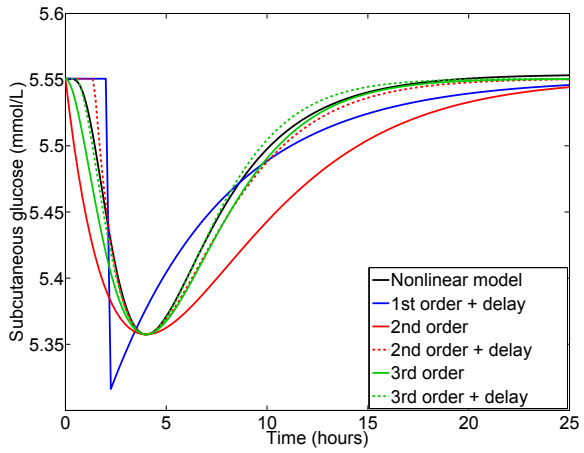


Fig. 2. Impulse responses of different linear models and the nonlinear simulation model to a 0.1U insulin bolus [53].

$\bar{A}(q^{-1}) = A_I(q^{-1})A_G(q^{-1})$, $\bar{B}_G(q^{-1}) = B_G(q^{-1})A_I(q^{-1})$, $\bar{B}_I(q^{-1}) = B_I(q^{-1})A_G(q^{-1})$, and $\bar{C}(q^{-1}) = C(q^{-1})A_G(q^{-1})$. Using an observer canonical realization, we represent the ARMAX model (9) as a discrete-time state space model in innovation form [17], [36], [54], [56], [57]

$$x_{k+1} = Ax_k + Bu_k + K\varepsilon_k \tag{10a}$$
$$y_k = Cx_k + \varepsilon_k \tag{10b}$$

with $B = [B_I\ B_G]$ and $u_k = [u_I; u_G]_k$.

### C. Kalman Filter and Predictor

The innovation of the state space model (10) is $e_k = y_k - C\hat{x}_{k|k-1}$. $\hat{x}_{k|k-1}$ represents a one-step prediction from the previous step. As the process and measurement noise are perfectly correlated, the filtering is reduced to $\hat{x}_{k|k} = \hat{x}_{k|k-1}$ and the corresponding predictions are [56]

$$\hat{x}_{k+1|k} = A\hat{x}_{k|k-1} + B\hat{u}_{k|k} + Ke_k \tag{11a}$$
$$\hat{x}_{k+1+j|k} = A\hat{x}_{k+j|k} + B\hat{u}_{k+j|k},\ j = 1,\ldots,N-1 \tag{11b}$$
$$\hat{y}_{k+j|k} = C\hat{x}_{k+j|k},\qquad j = 1,\ldots,N \tag{11c}$$

Equations (11) constitute the prediction model used in the MPC. The innovation $e_k$ provides the glucose feedback from the CGM to the control algorithm. Through the innovation, all unknown factors affecting the glucose concentration, including meal intake, enter the Kalman filter and MPC when the CGM senses the corresponding change in subcutaneous glucose.

## IV. Dual-Hormone Control Algorithm

In this section, we describe the dual-hormone control algorithm responsible for the insulin and glucagon administration. The control algorithm uses two independent MPCs to manipulate the insulin and glucagon infusion. In the following, we describe both MPCs as well as two different strategies for switching between the controllers. The first strategy utilizes the principle of relay with hysteresis to activate/deactivate the MPCs. In the second strategy, the activation is based on the Kalman filter predictions.

Even with glucagon available, the goal is to design a control algorithm that relies on manipulating the insulin infusion. It uses glucagon only as a safety feature when hypoglycemia cannot be avoided by restricting or completely suspending insulin infusion. In the controller design, we consider hard input constraints (insulin or glucagon infusion) and soft output (glucose concentration) constraints.

### A. Micro-Bolus Insulin Controller Design

At each sample instant, the controller solves the following constrained convex quadratic program to compute the insulin micro-bolus infusion rate profile

$$\min_{\{u_{I;j},\eta_{j+1}\}_{j=0}^{N-1}} \phi \tag{12a}$$
$$s.\,t. \quad \hat{x}_{k+1|k} = A\hat{x}_{k|k-1} + B_I u_{I;k|k} + Ke_k \tag{12b}$$
$$\hat{y}_{k+1|k} = C\hat{x}_{k+1|k} \tag{12c}$$
$$\hat{x}_{k+1+j|k} = A\hat{x}_{k+j|k} + B_I u_{I;k+j|k} \quad j \in \mathcal{N}_1 \tag{12d}$$
$$\hat{y}_{k+1+j|k} = C\hat{x}_{k+1+j|k} \quad j \in \mathcal{N}_1 \tag{12e}$$
$$u_{I;\min} \le u_{I;k+j-1|k} \le u_{I;\max} \quad j \in \mathcal{N}_0 \tag{12f}$$
$$\hat{y}_{k+j|k} \ge y_{\min} - \hat{\eta}_{k+j|k} \quad j \in \mathcal{N}_0 \tag{12g}$$
$$\hat{y}_{k+j|k} \le y_{\max} + \hat{\eta}_{k+j|k} \quad j \in \mathcal{N}_0 \tag{12h}$$
$$\hat{\eta}_{k+j|k} \ge 0 \quad j \in \mathcal{N}_0 \tag{12i}$$

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

$$\phi = \frac{1}{2}\sum_{j=0}^{N-1} \overbrace{\|\hat{y}_{k+1+j|k} - r_{k+1+j|k}\|^2 + \gamma\|\hat{\eta}_{k+1+j|k}\|^2}^{\text{glucose penalty function}} + \frac{1}{2}\sum_{j=0}^{N-1} \underbrace{\lambda_I \|\Delta u_{I;k+j|k}\|^2}_{\text{regularization term}} \tag{13}$$

To capture the slow glucose-insulin dynamics and the influence of all insulin on board, we use a prediction and control horizon of 24 hours ($N = 288$). In the objective function (13), the penalty related to glucose deviations includes the error of tracking the reference trajectory, $r_{k+1+j|k}$, and violations of the soft output constraints (12g)-(12h), $\hat{\eta}_{k+j|k}$. The lower and upper soft constraints, $y_{\min}$ and $y_{\max}$, corresponding to 4.5 mmol/L and 10 mmol/L are asymmetrical with respect to the target 5.5 mmol/L. The soft constraint violations are heavily penalized by $\gamma = 100$. The regularization term $\lambda_I\|\Delta u_{I;k+j|k}\|^2$ moderates the controller aggressiveness and reduces sensitivity to noise to ensure smooth control action. We individualize the algorithm using $\lambda_I$ = 600/$u_{I;b}$; $u_{I;b}$ is the patient-specific basal insulin infusion rate, which maintains a basal glucose concentration of 5.5 mmol/L. The linear MPC computes deviations from the constant basal infusion rate, $u_{I;b}$. Hence, the operating range is $[-u_{I;b}, u_{I;\max}]$.

*1) Safety Modifications:* To enhance safety of the algorithm, we employ a time-varying exponential reference signal when the glucose concentration is above the target [32], [57], [58]. When the glycemia is lower, the reference is set to the target level. Consequently

$$r_{k+j|k}(t) = \begin{cases} \hat{y}_k e^{-t/\tau_r} & \text{if } \hat{y}_k \ge 0\,\text{mmol/L} \\ 0 & \text{if } \hat{y}_k < 0\,\text{mmol/L} \end{cases} \tag{14}$$

It is important to note that $r_k$ and $\hat{y}_k$ are deviations from the target. The time constant that determines the reference trajectory is $\tau_r$ = 90 min.

To reduce the risk of hypoglycemia, we implement a set of safety rules restricting the maximal allowed insulin infusion rate, $u_{I;\max}$. $u_{I;\max}$ depends on the current estimate of the glucose level [32], i.e.

$$u_{I;\max} = \begin{cases} 1.5\,u_{I;b} & \text{if } \hat{y}_k \geq 4.5\,\text{mmol/L} \\ u_{I;b} & \text{if } 0 \leq \hat{y}_k < 4.5\,\text{mmol/L} \\ 0 & \text{if } \hat{y}_k < 0\,\text{mmol/L} \end{cases} \tag{15}$$

Furthermore, if the patient announces a meal and a prandial bolus is administered, the algorithm suspends the insulin infusion for the 3 hours following the bolus. This is motivated by our previous studies with an ideal nonlinear MPC with full knowledge of the system states, which would deliver the insulin in a similar manner, i.e. almost bolus-like insulin dose followed by a period with no insulin administration [59]–[61].

### B. Glucagon Controller Design

The glucagon MPC uses a similar structure as the MPC for insulin micro-bolus infusion, (12b)-(12i). The glucagon MPC uses 1) the control vector $u_G$ and vector $B_G$ corresponding to the glucagon infusion instead of $u_I$ and $B_I$; and 2) the objective function

$$\phi = \frac{1}{2}\sum_{j=0}^{N-1} \overbrace{\|\hat{y}_{k+1+j|k} - r_{k+1+j|k}\|^2 + \gamma\|\hat{\eta}_{k+1+j|k}\|^2}^{\text{glucose penalty function}} + \frac{1}{2}\sum_{j=0}^{N-1} \underbrace{\lambda_G \|\Delta u_{G;k+j|k}\|^2}_{\text{regularization term}} \tag{16}$$

In case of glucagon, we do not restrict the maximal allowed infusion rate (12f). However, we do impose soft constraints (12g)-(12h) to prevent hypoglycemia, but also to avoid overshooting the target glucose concentration by excessive glucagon dosing. For this purpose, we set the soft lower and the upper glucose concentration constraints to 4.5 mmol/L and 6 mmol/L. Their violation is subject to a large penalty, i.e. $\gamma = 100$. Variations in the glucagon infusion rate are penalized using the weighting coefficient $\lambda_G = 0.1$. This regularization is used to reduce the sensitivity of the glucagon infusion to measurement noise and other sources of noise.

If the patient announces a meal and the glucagon MPC is active, the control algorithm will not allow glucagon administration in a 30-minute period following the meal ingestion to avoid increasing the post-prandial hyperglycemia.

Fig. 3 illustrates the asymmetric glucose penalty functions for the insulin infusion MPC (13) and the glucagon infusion MPC (16).

### C. Switch between the Insulin MPC and the Glucagon MPC

An important aspect of a dual-hormone AP is the decision mechanism that can activate the glucagon infusion sufficiently soon to retain the glucagon efficiency, but at the same time avoid an unwanted or a too aggressive glucagon dosing.

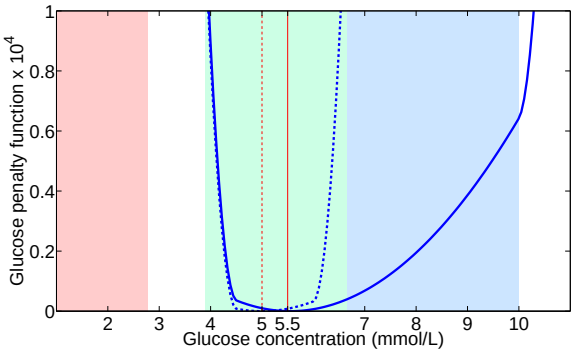


Fig. 3. The asymmetric glucose penalty functions for the insulin MPC and the glucagon MPC. The full line corresponds to the insulin MPC and the dashed line to the glucagon MPC.

The first strategy we investigate is based on relay switching with hysteresis. The glucagon controller is activated, when the measured glucose concentration decreases below 4.5 mmol/L. At the same time the insulin MPC is switched off. The insulin MPC is switched back on and the glucagon MPC is deactivated, when the measured glucose concentration rises above 5 mmol/L.

In the second strategy, the Kalman filter *predictions* determine the glucagon activation. Under normal conditions the insulin MPC is running. However, if the Kalman filter predicts future hypoglycemia at any time in the prediction horizon, the glucagon MPC is turned on and the insulin controller is switched off.

### D. Mealtime Bolus Calculation

Besides the insulin and glucagon MPCs, the control algorithm includes a bolus calculator. The prandial insulin bolus calculation utilizes information about the insulin-to-carbohydrate ratio, $IC$ (U/g), of the particular patient and the announced meal size (g). The bolus size is computed by

$$Bolus = \kappa\, CHO \cdot IC \tag{17}$$

$CHO$ (g) is the announced amount of carbohydrates. For each patient we choose an appropriate $\kappa \in [0,1]$ to prevent overdosing insulin. $\kappa$ is independent of the current glucose concentration. $\kappa$ varied from 0.5 to 1.0 in the three virtual patients. It was tuned empirically based on information about the insulin absorption time constants. For virtual patients with a slow insulin absorption, we chose a lower value of $\kappa$. However, we currently do not have any fixed and systematic rules regarding the individualization and selection of $\kappa$.

## V. Simulation Results and Discussion

We perform the simulation study for the 3 patients with time-varying parameters from [47]. The fixed daily meal regimen consists of three meals at 6:00, 12:00 and 18:00. The CHO meal sizes are: Patient 1, 85g - 85g - 110g; Patient 2, 70g - 70g - 90g; and Patient 3, 110g - 110g - 150g. The scenarios we simulate include missed prandial boluses, correct boluses when insulin sensitivity (IS) is at its nominal value, and correct boluses when IS increases by 40%. These scenarios are included to challenge the control algorithm.

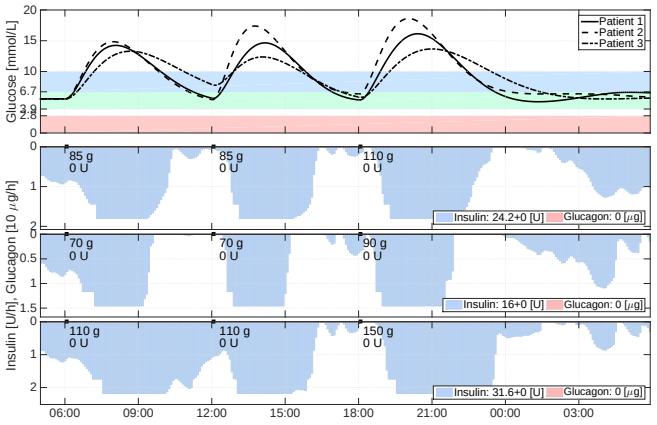


Fig. 4. Performance of the relay switching dual-hormone AP when the meals are not announced. No mealtime bolus is administered. The glucose traces are followed by the insulin and glucagon infusion profiles for the 3 patients. The legend reports the total amount of insulin (basal+bolus) and glucagon administered over 24 hours.

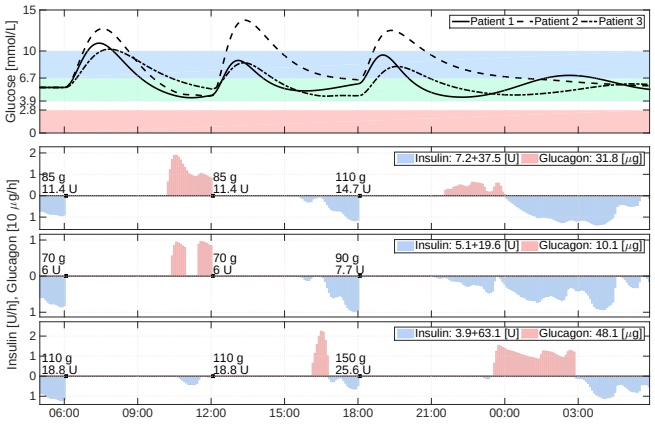


Fig. 5. Performance of the relay switching dual-hormone AP when the meals are announced at mealtime and the IS is correctly estimated.

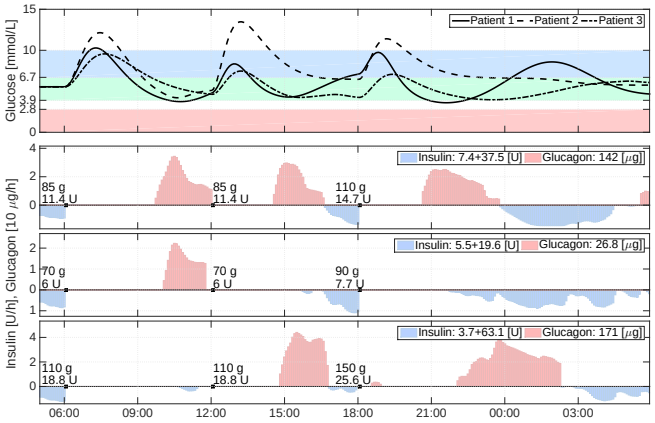


Fig. 6. Performance of the relay switching dual-hormone AP. The meals are announced at mealtime and the simulated IS is 40% larger than estimated.

### A. No Mealtime Bolus

To illustrate the ability of the controller to safely regulate the blood glucose and avoid a late postprandial insulin-induced hypoglycemia, we first simulate a scenario when no meals are announced and therefore no prandial insulin is administered. Fig. 4 shows the glucose traces along with the insulin infusion profiles for the 3 patients. Due to the strict safety rules (15), the insulin MPC cannot sufficiently compensate the postprandial glucose peaks. However, the controller provides a safely regulated process without a single hypoglycemic episode caused by insulin overdosing. As is evident from Fig. 4, the controller never uses glucagon infusion for the 3 virtual patients in the situation of a forgotten mealtime bolus.

### B. Correct Mealtime Bolus - Nominal Insulin Sensitivity

In this scenario, the control algorithm administers a correct prandial insulin bolus and the insulin sensitivity follows the nominal daily profile identified in [47]. Under these circumstances, glucagon infusion is not necessary and even the single-hormone control is able to avoid hypoglycemia, as the summarizing Table I reports. Nevertheless, the table also shows that none of the glucagon administration strategies are able to avoid glucagon infusion. In case of the relay switching, the glucagon MPC is activated each time the estimated glucose concentration falls below 4.5 mmol/L and remains active until it rises above 5 mmol/L. Activating the glucagon MPC based on predictions is prone to measurement noise, especially when the current glucose is close to the hypoglycemic range. As a result, the strategy with predictive activation of the glucagon MPC administers slightly more glucagon than the relay switching approach. Fig. 5 illustrates the situations when the control algorithm injects glucagon even though the hypoglycemia is not imminent. In this scenario, we observed similar patterns with both glucagon administration strategies.

### C. Correct Mealtime Bolus - Increased Insulin Sensitivity

Here, we simulate a scenario where the prandial boluses are estimated correctly, but the IS increases by 40%. The increased IS leads to a late postprandial hypoglycemia caused by an insulin overdose at mealtime. Moreover, during the night, the insulin infusion controller has to overcome a large patient-model mismatch. With significantly increased IS and the same bolus sizes, the controller has to inject glucagon to prevent severe hypoglycemia. Subsequent to an insulin overdose, the single-hormone controller has no means to counteract the effects of the insulin on board. Fig. 6 and Fig. 7 show the performance of the two glucagon administration strategies. Table I provides a summary and further details. The strategy using predictive activation of the glucagon MPC injects in general slightly more glucagon. Both strategies are able to completely avoid hypoglycemia for Patient 2 and 3. Accordingly, the slightly larger glucagon doses in the predictive activation strategy do not improve the glycemic control. In Patient 1, however, the predictive activation results in reducing the time spent in hypoglycemia by more than 50% compared to the relay switching at the expense of a 14% increase in the glucagon dosage.

### D. Discussion and Limitations

The simulations show that a glucagon switching strategy based on predictions allows earlier administration of glucagon

TABLE I
SUMMARY OF THE DUAL-HORMONE EXPERIMENT

| | | Normal IS | | | Increased IS | | |
|---|---|---|---|---|---|---|---|
| | | Ins. | Ins.+Gluc. Rel. | Ins.+Gluc. Pred. | Ins. | Ins.+Gluc. Rel. | Ins.+Gluc. Pred. |
| Patient 1 | $G > 10$ mmol/L (%) | 4.00 | 4.00 | 4.00 | 2.00 | 2.00 | 2.00 |
| | $8 \leq G \leq 10$ mmol/L (%) | 10.33 | 12.33 | 12.00 | 8.00 | 17.67 | 11.67 |
| | $3.9 \leq G \leq 8$ mmol/L (%) | 85.67 | 83.67 | 84.00 | 73.33 | 70.67 | 81.66 |
| | $G < 3.9$ mmol/L (%) | 0.00 | 0.00 | 0.00 | 16.67 | 9.67 | 4.67 |
| | Total basal insulin administered (U) | 7.26 | 7.22 | 7.75 | 6.81 | 7.37 | 7.72 |
| | Total glucagon administered ($\mu$g) | 0.00 | 31.78 | 50.84 | 0.00 | 141.72 | 162.47 |
| Patient 2 | $G > 10$ mmol/L (%) | 23.67 | 24.33 | 24.67 | 17.67 | 19.00 | 18.33 |
| | $8 \leq G \leq 10$ mmol/L (%) | 14.00 | 14.00 | 14.00 | 12.33 | 11.67 | 12.34 |
| | $3.9 \leq G \leq 8$ mmol/L (%) | 62.33 | 61.67 | 61.33 | 64.67 | 69.33 | 69.33 |
| | $G < 3.9$ mmol/L (%) | 0.00 | 0.00 | 0.00 | 5.33 | 0.00 | 0.00 |
| | Total basal insulin administered (U) | 5.12 | 5.15 | 5.18 | 5.47 | 5.54 | 5.55 |
| | Total glucagon administered ($\mu$g) | 0.00 | 10.05 | 12.25 | 0.00 | 26.77 | 27.89 |
| Patient 3 | $G > 10$ mmol/L (%) | 2.67 | 2.67 | 2.67 | 0.00 | 0.00 | 0.00 |
| | $8 \leq G \leq 10$ mmol/L (%) | 13.33 | 14.00 | 14.00 | 7.67 | 7.67 | 7.67 |
| | $3.9 \leq G \leq 8$ mmol/L (%) | 84.00 | 83.33 | 83.33 | 77 | 92.33 | 92.33 |
| | $G < 3.9$ mmol/L (%) | 0.00 | 0.00 | 0.00 | 15.33 | 0.00 | 0.00 |
| | Total basal insulin administered (U) | 2.92 | 3.85 | 4.40 | 2.41 | 3.74 | 3.42 |
| | Total glucagon administered ($\mu$g) | 0.00 | 48.09 | 50.66 | 0.00 | 170.71 | 191.45 |

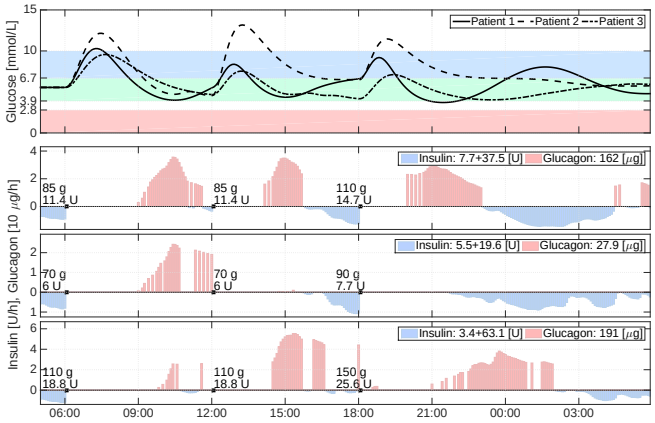


Fig. 7. Performance of the dual-hormone AP with predictive switching. The meals are announced at mealtime and the simulated IS is 40% larger than estimated.

in case of upcoming hypoglycemia. The largest improvement is obtained for Patient 1, for which the time spent in hypoglycemia is significantly reduced at the expense of a slightly increased amount of administered glucagon. Overall, the above mentioned results are consistent with the findings from Bakhtiani *et al.* [40].

However, the obtained results are limited by the simulation model and the available population size. This model does not take into consideration the interaction between insulin and glucagon. Insulin in the $\alpha$-cells has an inhibitory action on glucagon secretion. For instance, the model developed by Dalla Man *et al.* uses the plasma insulin level to mimic this action [45]. Therefore, further studies using a larger population and with different physiological models are necessary to support the results presented in this paper.

## VI. CONCLUSION

This paper presents MPC based control algorithms in a dual-hormone AP. The control system is based on an insulin infusion MPC and a glucagon infusion MPC. The glucagon infusion MPC is used as a safety controller to prevent hypoglycemia and glucagon is only administered when hypoglycemia is either measured or predicted. The paper addresses different glucagon switching strategies for a dual-hormone AP. The simulations results indicate that earlier administration of glucagon by use of a prediction approach has a positive effect on the prevention of hypoglycemia. In addition, this causes neither glucagon overdosing nor increase of the time spent in hyperglycemia. Further studies using a larger virtual population and using different simulation models, as well as in vivo studies, will be needed to validate these findings.

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