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Comparison of Prediction Models for a Dual-Hormone Artificial Pancreas ⋆

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Abstract: In this paper we compare the performance of five different continuous time transfer function models used in closed-loop model predictive control (MPC). These models describe the glucose-insulin and glucose-glucagon dynamics. They are discretized into a state-space description and used as prediction models in the MPC algorithm. We simulate a scenario including meals and daily variations in the model parameters. The numerical results do not show significant changes in the glucose traces for any of the models, excepted for the first order model. From the present study, we can conclude that the second order model without delay should provide the best trade-off between sensitivity to uncertainties and practical usability for in vivo clinical studies.

Keywords: Type 1 Diabetes, Artificial Pancreas, Model Predictive Control

1. INTRODUCTION

In people with type 1 diabetes (T1D), the immune system destroys the insulin-producing β-cells in the islets of Langerhans in the pancreas. This condition leads to a deficiency in endogenous insulin production, which is manifested by significant metabolic disturbances including elevated blood glucose levels (i.e. hyperglycemia). To keep the glucose level under control and avoid the long term complications associated with hyperglycemia, people with T1D have to administer exogenous insulin. Nowadays, patients are treated either by Multiple Daily Injections of insulin (MDI) or by Continuous Subcutaneous Insulin Infusion (CSII) using an insulin pump. These therapies are usually titrated empirically by the patient and his/her physician. To a large extent, the efficiency of the treatment is dependent on the patient's decisions on insulin dosing.

For more than 50 years, scientists have been trying to replace the patient's decisions by an automated closed-loop insulin delivery system, known as Artificial Pancreas (AP). Various control strategies have been investigated and tested. Yet, a popular approach with promising results is MPC (Turksoy et al. (2014); Magni et al. (2009)). An important component of the MPC is the choice of the model used to compute predictions. Several models used for modeling and/or control can be found in the literature. For instance, Kirchsteiger et al. (2011) used a third order transfer function with an integrator, van Heusden et al. (2012) used a third order discrete transfer function model and Percival et al. (2010) applied a first order transfer function with a time delay and an integrator. In our previous work, we used a second order transfer function model, see Boiroux et al. (2012); Bátora et al. (2015). All these models have been validated on simulations and/or clinical studies. However, some of these models may not be suitable as prediction models in an AP using MPC.

One way to reduce the risk of hypoglycemia is to incorporate glucagon as a safety hormone in the AP. Results from Herrero et al. (2013a); Russell et al. (2014); Bátora et al. (2014) show, that a dual-hormone AP (i.e. AP with insulin and glucagon) has the potential to increase the safety of the glucose control and provide a tighter regulation without increasing risk of hypoglycemia. Fig. 1 shows a possible AP setup, including the CGM sensor, a smartphone used for monitoring and control, and the insulin and glucagon pumps.

The purpose of the present paper is to discuss the importance of the prediction model in the model predictive control (MPC) algorithm. We use a control strategy allowing both administration of insulin and glucagon. We state and compare five different transfer function models on 30-hour simulations with meals and variations in the model parameters reflecting the Circadian rhythm for three virtual patients.

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

2. SIMULATION MODEL

The model proposed by Herrero et al. (2013b) simulates the effects of subcutaneously administered insulin and glucagon, as well as the effect of meal intakes. This model presents an extension to the minimal model of plasma glucose and insulin kinetics by employing a glucagon action resulting in glucose production, a subcutaneous insulin absorption model and the gastrointestinal absorption model proposed by Hovorka et al. (2004). We augment this model with a model for glucose transport from plasma to interstitial tissues introduced by Breton and Kovatchev (2008).

2.1 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 $G(t)$ [mg/dl] is the plasma glucose concentration, $I(t)$ [μU/dl] is the plasma insulin, and $N(t)$ [pg/dl] the plasma glucagon concentration. $X(t)$ [min^{-1}] and $Y(t)$ [min^{-1}] represent the insulin and glucagon action on glucose production.

2.2 Gastrointestinal Absorption Model

The model incorporates a two-compartment gastrointestinal absorption subsystem suggested by Hovorka et al. (2004)

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

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

$D_1(t)$ describes the glucose in the first compartment and $D_2(t)$ is the glucose in the second compartment.

2.3 Subcutaneous Insulin Absorption Model

The model employs a linear model of subcutaneous insulin absorption

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

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

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

$S_1(t)$ and $S_2(t)$ represent a two-compartment absorption model of subcutaneously administered insulin.

2.4 Subcutaneous Glucagon Absorption Model

Herrero *et al.* Herrero et al. (2013b) use the same model structure as in case of insulin to model subcutaneous glucagon absorption

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

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

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

$Z_1(t)$ and $Z_2(t)$ represent a two-compartment absorption of subcutaneously administered glucagon.

2.5 Model Parameters

In our simulations, we use separate sets of time-varying parameters originally identified from 3 patients to reproduce the Circadian rhythm. We use the model together with the identified time-varying parameters to compare the performance of the different prediction models. The detailed description and the numerical values of the model parameters can be found in Herrero et al. (2013a).

2.6 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 to generate the CGM measurement data with a non-Gaussian sensor noise from the plasma glucose concentration (Breton and Kovatchev (2008)).

3. MODELING OF GLUCOSE-INSULIN DYNAMICS

In this section, we introduce several prediction models for subcutaneous (sc) glucose, $y(t)$. The model has a deterministic part describing the effect of sc injected insulin and glucagon, $u(t)$, and a stochastic part describing the effect of other unknown factors.

Even the most simple physiological models for people with T1D, such as the minimal model developed by Bergman et al. (1981), may be difficult to identify, as shown in Pillonetto et al. (2003). Using a low-order linear model to describe the glucose-insulin and glucose-glucagon dynamics can overcome this limitation.

Transfer function models We compare continuous-time transfer functions of the form

$$Y(s) = Y_D(s) + Y_S(s) = G(s)U(s) + H(s)E(s) \quad (5)$$

$Y_D(s)$ represents the deterministic part and $Y_S(s)$ the stochastic part. The term $G(s)U(s)$ in (5) models the

Table 1. Continuous-time insulin and glucagon transfer functions.

Order	Insulin t.f. $G_I(s)$	Glucagon t.f. $G_G(s)$
1st order + delay	$\frac{K_I}{(\tau_I s+1)}e^{-\theta_I s}$	$\frac{K_G}{(\tau_G s+1)}e^{-\theta_G s}$
2nd order	$\frac{K_I}{(\tau_I s+1)^2}$	$\frac{K_G}{(\tau_G s+1)^2}$
2nd order + delay	$\frac{K_I}{(\tau_I s+1)^2}e^{-\theta_I s}$	$\frac{K_G}{(\tau_G s+1)^2}e^{-\theta_G s}$
3rd order	$\frac{K_I}{(\tau_I s+1)^3}$	$\frac{K_G}{(\tau_G s+1)^3}$
3rd order + delay	$\frac{K_I}{(\tau_I s+1)^3}e^{-\theta_I s}$	$\frac{K_G}{(\tau_G s+1)^3}e^{-\theta_G s}$

effects of the manipulated variables $U(s)$ (insulin and glucagon) on the output (glucose). Thus, the deterministic part $Y_D(s)$ can be reformulated as

$$Y_D(s) = [G_I(s)\ G_G(s)] \begin{bmatrix} U_I(s) \\ U_G(s) \end{bmatrix} \tag{6a}$$

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

$G_I(s)$ and $G_G(s)$ represent the transfer functions from insulin/glucagon to glucose. $U_I(s)$ and $U_G(s)$ are the Laplace transforms of the insulin injection, $u_I(t)$, and the glucagon injection, $u_G(t)$.

The term $H(s)E(s)$ in (5) is a stochastic part representing the (unknown) process and measurement noises and other plant-model mismatches to model the effect of sc injected insulin and sc injected glucagon on sc glucose. Here, we consider first, second and third order models. The different transfer functions used in this paper are listed in Table 1.

Parameter identification For all the transfer function models, the gains K_I and K_G, the time constants τ_I and τ_G, and the time delays θ_I and θ_G are identified by least-square fitting of the insulin and glucagon impulse responses. The insulin and glucagon boluses sizes are 0.1U and 1μg, respectively. Fig. 2 illustrates the impulse response of each model for a 0.1U insulin bolus for the five considered models. A similar result has been observed for the glucagon impulse response (not shown).

Due to the fact that the glucose level returns to its initial value after a bolus, models including an integrator cannot be identified, and are therefore not included in this study. Also, we assume the time constants to be equal in the second and third order models. This choice has been motivated by the following reasons. Firstly, identifying more than one time constant does not improve the fitting. Other research groups reached a similar conclusion, see e.g. Kirchsteiger et al. (2011). Secondly, having more than one time constant would be impractical for real clinical studies where the parameters are obtained from patient-specific parameters, such as body weight, basal insulin, insulin sensitivity factor or insulin action time.

4. STOCHASTIC MODEL

We discretize the transfer functions (5) in the form

$$y(t) = \frac{B_I(q^{-1})}{A_I(q^{-1})}u_I(t) + \frac{B_G(q^{-1})}{A_G(q^{-1})}u_G(t) + \frac{C(q^{-1})}{D(q^{-1})}\varepsilon(t) \tag{7}$$

with a sampling time of 5 minutes. Similarly to the continuous-time transfer function (5), the model (7) has

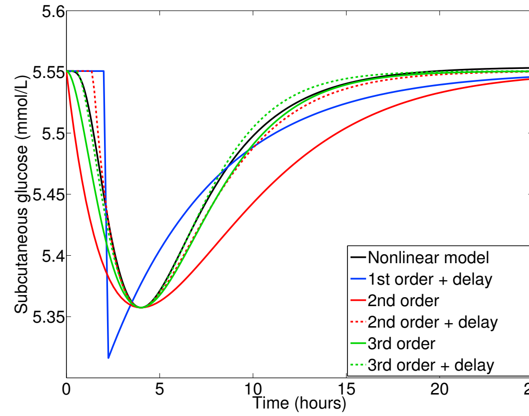

Fig. 2. Impulse response of each model on glucose for a 0.1U insulin bolus

a deterministic part describing the effects of insulin injections $u_I(t)$, the effects of glucagon injections $u_G(t)$ and the 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 $C(q^{-1}) = 1+c_1q^{-1}+c_2q^{-2}$ and $D(q^{-1}) = A_I(q^{-1})$. c_1 and c_2 are determined from clinical data for one real patient (Duun-Henriksen et al. (2012)). They are $c_1 = 1.62$ and $c_2 = 0.68$. This turns the model (7) into the following autoregressive moving average model with exogenous input (ARMAX)

$$\bar{A}(q^{-1})y(t) = \bar{B}_I(q^{-1})u_I(t) + \bar{B}_G(q^{-1})u_G(t) + \bar{C}(q^{-1})\varepsilon(t) \tag{8}$$

$\bar{A}(q^{-1}) = A_I(q^{-1})A_G(q^{-1})$, $\bar{B}_G(q^{-1}) = B_G(q^{-1})A_I(q^{-1})$, $\bar{B}_I(q^{-1}) = B_I(q^{-1})A_G(q^{-1})$, $\bar{C}(q^{-1}) = C(q^{-1})A_G(q^{-1})$.

4.1 Realization and predictions

We can represent the ARMAX model (8) as the following discrete-time state space model in innovation form

$$x_{k+1} = Ax_k + B_i u_{i,k} + B_g u_{g,k} + K\varepsilon_k \tag{9a}$$

$$y_k = Cx_k + \varepsilon_k \tag{9b}$$

The innovation of the discrete-time state space model (9) is

$$\varepsilon_k = y_k - C\hat{x}_{k|k-1} \tag{10}$$

and the corresponding predictions are

$$\hat{x}_{k+1|k} = A\hat{x}_{k|k-1} + B\hat{u}_{k|k} + K\varepsilon_k \tag{11a}$$

$$\hat{x}_{k+1+j|k} = A\hat{x}_{k+j|k} + B\hat{u}_{k+j|k}, \quad j = 1,\dots,N-1 \tag{11b}$$

$$\hat{y}_{k+j|k} = C\hat{x}_{k+j|k}, \qquad j = 1,\dots,N \tag{11c}$$

The innovation (10) and the predictions (11) constitute the feedback and the predictions in the model predictive controller described in the next section.

5. MODEL PREDICTIVE CONTROL

In this section we describe the linear MPC responsible for the insulin and glucagon infusion. The controller uses a relay with hysteresis to avoid simultaneous injections of insulin and glucagon and oscillations around a single relay level. The switching strategy is discussed in Bátora et al. (2014) and is based on the current estimate of the output $\hat{y}_{k|k-1}$.

The innovation (10) provides the feedback from the CGM to the controller. We consider hard constraints on the inputs (insulin or glucagon) and soft constraints on the output (glucose level).

5.1 Micro-Bolus Insulin Controller Design

At each time sample the controller computes the insulin micro-bolus infusion rate by solving the constrained convex quadratic program

$$\min_{\{u_{I;j},\eta_{j+1}\}_{j=0}^{N-1}} \phi \tag{12a}$$

$$\begin{aligned}
s.\ t.\ & \hat{x}_{k+1|k} = A\hat{x}_{k|k-1} + B_1 u_{I;k|k} + Ke_k & & (12b)\\
& \hat{y}_{k+1|k} = C\hat{x}_{k+1|k} & & (12c)\\
& \hat{x}_{k+1+j|k} = A\hat{x}_{k+j|k} + B_1 u_{I;k+j|k} \quad j\in\mathcal{N}_1 & & (12d)\\
& \hat{y}_{k+1+j|k} = C\hat{x}_{k+1+j|k} \quad j\in\mathcal{N}_1 & & (12e)\\
& u_{I;\min} \leq u_{Ik+j-1|k} \leq u_{I;\max} \quad j\in\mathcal{N}_0 & & (12f)\\
& \hat{y}_{k+j|k} \geq y_{\min} - \hat{\eta}_{k+j|k} \quad j\in\mathcal{N}_0 & & (12g)\\
& \hat{y}_{k+j|k} \leq y_{\max} + \hat{\eta}_{k+j|k} \quad j\in\mathcal{N}_0 & & (12h)\\
& \hat{\eta}_{k+j|k} \geq 0 \quad j\in\mathcal{N}_0 & & (12i)
\end{aligned}$$

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

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

We use a prediction and control horizon of 24 hours ($N = 288$). 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 (13) penalizes the glucose deviations from the setpoint, $r_{k+1+j|k}$, as well as violations of the output soft constraints (12g)-(12h). The asymmetric soft constraint bounds, $y_{\min}$ and $y_{\max}$ correspond to 4 mmol/L and 10 mmol/L. The slack variables η_{j+1} are used to penalize the soft constraint violation, which is subject to heavy penalty with $\gamma = 100$. The regularization term $\lambda_I \|\Delta u_{I;k+j|k}\|^2$ ensures smooth control by tempering the controller aggressiveness. $\lambda_I = 600/u_{1\,b}$ is individualized by the patient-specific basal rate, $u_{I;b}$, which maintains a steady state 5.5 mmol/L. The computed insulin infusion profile represents deviations from the constant basal infusion rate $u_{I;b}$. Thus, the micro-bolus insulin controller operates in the range $[-u_{I;b}, u_{I;\max}]$.

Algorithm Modifications To enhance safety the algorithm includes a time-varying reference signal when the glucose concentration is above the target. Furthermore, a set of security rules limits the maximal insulin infusion rate, $u_{I;\max}$, depending on the current glucose level. A detailed description of the modifications can be found in Bátora et al. (2014).

5.2 Mealtime Bolus Calculation

The insulin mealtime bolus calculation utilizes information about the insulin-to-carbohydrate ratio IC (U/g) and the meal size (g). We estimate the IC from the insulin sensitivity factor and the patients response to a defined amount of carbohydrates ingested. We compute the bolus size in the following way

$$Bolus = \eta \frac{CHO}{1/IC} \tag{14}$$

CHO (g) is the amount of carbohydrates ingested. To prevent insulin overdose, we choose $\eta = 0.7$ regardless of the current glucose level.

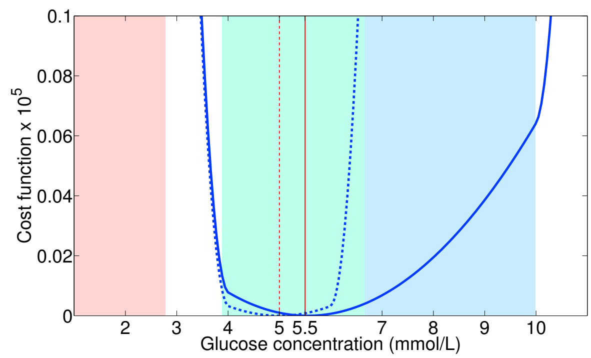

Fig. 3. The asymmetric cost functions for insulin and glucagon.

5.3 Glucagon Controller Design

The glucagon MPC uses the same structure as the MPC that manipulates the insulin micro-bolus infusion (12b)-(12i) with control vector u_G and vector B_G corresponding to the glucagon infusion. The objective function is

$$\phi = \frac{1}{2}\sum_{j=0}^{N-1} \|\hat{y}_{k+1+j|k} - r_{k+1+j|k}\|^2 + \lambda_G \|\Delta u_{G;k+j|k}\|^2 + \gamma\|\hat{\eta}_{k+1+j|k}\|^2 \tag{15}$$

We do not restrict the maximal glucagon infusion rate (12f). Soft constraints (12g)-(12h) prevent hypoglycemia as well as overshooting the target glucose level due to 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 glucagon infusion rate uses $\lambda_G = 0.1$ to prevent sudden variations and unnecessary administration of glucagon. The asymmetric cost functions for insulin (13) and glucagon (15) are plotted in Fig. 3.

6. SIMULATION RESULTS AND DISCUSSION

We compare the five transfer function models introduced in Table 1 for the three patients identified in Herrero et al. (2013b). The model parameters change throughout the day and reflect the intra-patient variability. We simulate a 30-hour scenario including three major meals and one snack. The meal sizes are adjusted according to the body weight of the subject. We consider the nominal case where the parameters in the transfer function (gains, time constants and time delays) are correctly estimated for the morning (5:00 - 12:00). We use the same CGM noise realization for each of the five models for comparison purposes.

6.1 Qualitative analysis of the glucose, insulin and glucagon traces for patient 3

Fig. 4 depicts the glucose, insulin and glucagon traces for the five models for patient number 3. The glucose traces do not show any substantial difference for the second and third order models. However, slightly more severe hypoglycemia and slower recovery occur for the first order model.

For the first order model, the switching timings between insulin and glucagon differ from the other models. The CGM noise sequences are identical for all the models. However, the inaccuracy of the output estimates for the first order model explains such a difference (data not shown).

It can also be noticed that the third order models have more abrupt variations in the insulin and glucagon traces. Increasing the penalty parameter on insulin variation in the objective function (13) would only partially solve this issue, as the predictions are more sensitive to noise.

Nevertheless, the deterministic part in (7) does not take into account all the uncertainties, such as the process and measurement noises, uncertainty in meal size or model-patient mismatches. Addressing these uncertainties adequately could benefit to the overall performance of the controller.

The second order model without delay performs similarly compared to the third order models. The second order with delay avoids hypoglycemia after dinner (i.e. in the time 18:00 - 21:00) and can reduce the postprandial hyperglycemia after dinner. Therefore, it seems to be slightly superior to the other models in terms of the controller performance for this specific patient and scenario.

6.2 Quantitative analysis for all patients

Table 2 shows the time spent in target, in hypo- and in hyperglycemia along with the total amount of administered basal insulin and glucagon for each virtual patient and each model.

All prediction models perform similarly. In terms of time spent in hypoglycemia, the second order and the third order models without delays perform the best, at the expense of a larger amount of administered glucagon. The first order model spends the largest time in hypoglycemia.

In terms of time spent in euglycemia, the second order models on average outperform the other ones. However, it is important to notice that the difference is small. The third order models use by far the least amount of insulin.

From the Table 2 and the traces shown in Fig. 4, we can conclude that the second order with delay offers a slightly better performance than the other models.

However, a model with delay requires the identification of an extra parameter (the time delay). In practice, this parameter is difficult to obtain without conducting an impulse response experiment. Third order models are more sensitive to the effects of uncertainties. The first order model with delay has a slower response to glucose variations, leading to longer hypoglycemic events. From this, we can conclude that the second order model without delay should provide the best trade-off between the overall performance and the use in a clinical practice.

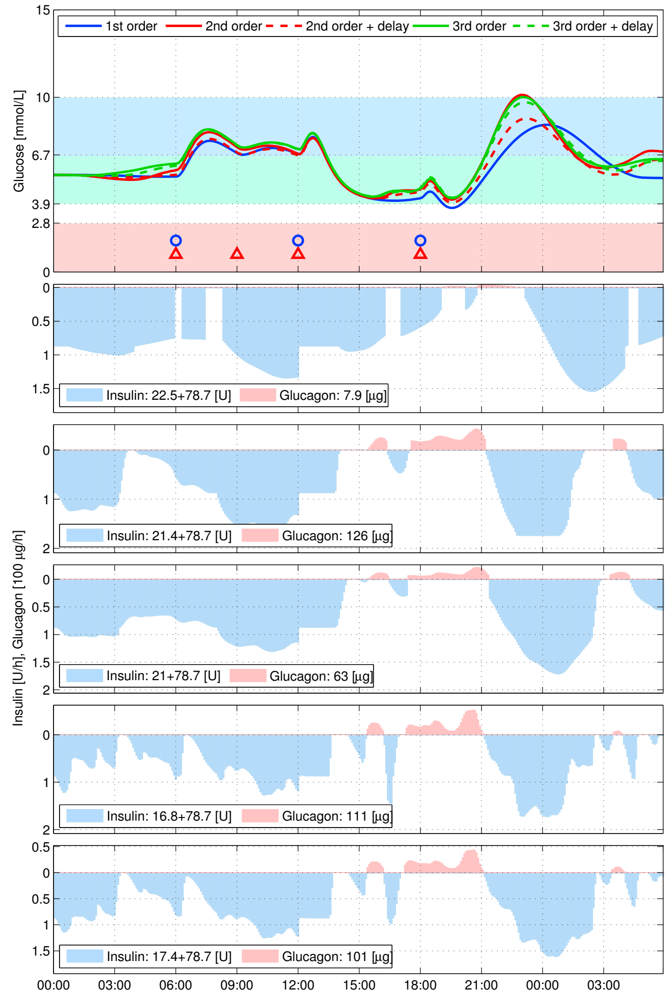

Fig. 4. Comparison of the bi-hormonal control strategy for all the transfer function models in the nominal case. From top to bottom: Glucose trace, Insulin and glucagon traces for the first order model with delay, the second order model, the second order model with delay, the third order model, and the third order model with delay. Red triangles: Meal. Blue circles: Bolus

7. CONCLUSION

This paper presents a qualitative and quantitative comparison of the performance of five prediction models for three virtual patients with T1D. The numerical results suggest that the performance of the controller is almost not affected by the choice of the prediction model. Even models fitting the impulse response poorly are able to provide a fairly good glycemic control. On the other hand, models specifically designed for modeling may not perform optimally when it comes to closed-loop control. Therefore, one of the most important criteria in the choice of the prediction model is the implementation *in vivo*.

Table 2. Summary of the experiment, no mismatch

		1st order + delay	2nd order	2nd order + delay	3rd order	3rd order + delay
Patient 1	$G > 10$ mmol/L (%)	0.00	0.00	0.00	0.00	0.00
	$8 \leq G \leq 10$ mmol/L (%)	7.50	7.78	7.50	8.89	7.78
	$3.9 \leq G \leq 8$ mmol/L (%)	92.50	92.22	92.50	91.11	92.22
	$G < 3.9$ mmol/L (%)	0.00	0.00	0.00	0.00	0.00
	Total basal insulin administered (U)	8.33	7.63	8.15	5.42	6.78
	Total glucagon administered (μg)	0.00	48.47	7.97	28.85	17.77
Patient 2	$G > 10$ mmol/L (%)	0.00	0.00	0.00	0.00	0.00
	$8 \leq G \leq 10$ mmol/L (%)	6.39	6.67	6.39	6.94	6.67
	$3.9 \leq G \leq 8$ mmol/L (%)	88.89	91.67	89.72	91.95	91.39
	$G < 3.9$ mmol/L (%)	4.72	1.66	3.89	1.11	1.94
	Total basal insulin administered (U)	12.19	10.12	12.18	9.12	10.91
	Total glucagon administered (μg)	0.00	48.94	10.64	42.25	28.91
Patient 3	$G > 10$ mmol/L (%)	0.00	1.39	0.00	0.00	0.00
	$8 \leq G \leq 10$ mmol/L (%)	5.83	8.33	6.39	12.22	11.67
	$3.9 \leq G \leq 8$ mmol/L (%)	91.11	90.28	93.61	87.78	88.33
	$G < 3.9$ mmol/L (%)	3.06	0.00	0.00	0.00	0.00
	Total basal insulin administered (U)	22.54	21.43	21.03	16.84	17.40
	Total glucagon administered (μg)	7.92	126.27	63.22	111.21	101.42

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