Adaptive Control in an Artificial Pancreas for People with Type 1 Diabetes

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Abstract

In this paper, we discuss overnight blood glucose stabilization in patients with type 1 diabetes using a Model Predictive Controller (MPC). We compute the model parameters in the MPC using a simple and systematic method based on a priori available patient information. We describe and compare 3 different model structures. The first model structure is an autoregressive integrated moving average with exogenous input (ARIMAX) structure. The second model structure is an autoregressive moving average with exogenous input (ARMAX) model, i.e. a model without an integrator. The third model structure is an adaptive ARMAX model in which we use a recursive extended least squares (RELS) method to estimate parameters of the stochastic part. In addition, we describe some safety layers in the control algorithm that improve the controller robustness and reduce the risk of hypoglycemia. We test and compare our control strategies using a virtual clinic of 100 randomly generated patients with a representative inter-subject variability. This virtual clinic is based on the Hovorka model. We consider the case where only half of the meal bolus is administered at mealtime, and the case where the insulin sensitivity increases during the night. The numerical results suggest that the use of an integrator leads to higher occurrence of hypoglycemia than for the controllers without the integrator. Compared to the other control strategies, the adaptive MPC reduces both the time spent in hypoglycemia and the time spent in hyperglycemia.

Keywords: Model Predictive Control, Adaptive control, Artificial pancreas, Type 1 diabetes, Closed-loop glucose control

1. Introduction

Type 1 diabetes is a metabolic disease characterized by destruction of the insulin-producing β-cells in the pancreas. Therefore, patients with type 1 diabetes need exogenous insulin administration. However, the dosage of insulin must be done carefully. An insulin overdose may lead to low blood glucose (hypoglycemia). Hypoglycemia has immediate effects, such as seizures, coma or even death. In contrast, prolonged periods of too high blood glucose (hyperglycemia) are associated with complications such as retinopathy, neuropathy and nephropathy [1].

An increasing number of patients with type 1 diabetes apply a therapy approach based on continuous subcutaneous (sc) insulin infusion (CSII) using insulin pumps combined with continuous glucose monitoring devices (CGMs). CGMs provide frequent subcutaneous (sc) glucose measurements. The CSII pump provides a preprogrammed continuous infusion of rapid acting insulin to mitigate the endogenous glucose production (EGP) from the liver. Larger amounts of insulin are administered in relation to meals to compensate the effects of carbohydrates (CHO) intake. However, the decisions on the timing and amount of meal insulin injection as well as the profile of the EGP insulin injection are left to the patient. By automating the decisions on insulin injections, closed-loop control of the blood glucose concentration by an Artificial Pancreas (AP) has the potential to ease the life and reduce the burden and risk of complications for patients with type 1 diabetes. The first version of the AP (Biostator) was developed 40 years ago [2, 3]. It used intravenous insulin, dextrose injections, and intravenous glucose measurements. However, this setup is only usable for in-clinical studies and does not mimic everyday life of a type 1 diabetes patient. Current prototypes of the AP use the sc-sc route for glucose sensing and injection of insulin. They include a CGM, a control algorithm, and an insulin pump. Fig. 1 illustrates the principle of an AP. Even more recently, glucagon has been tested as a safety hormone [4–6], but the use of glucagon is not considered in this paper. Several research groups worked

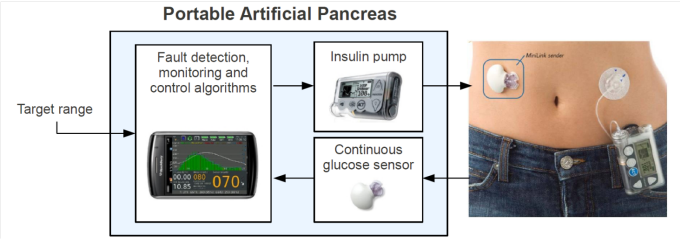

Figure 1: Closed-loop glucose control. Glucose is measured subcutaneously using a continuous glucose monitor (CGM). Insulin is dosed by an insulin pump.

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on the implementation of APs and tested their implementation with virtual patients [7–9] as well as in vivo clinical studies [10–14]. Regardless of the control algorithm used, the performance of current APs is limited by several factors: 1) the intra- and inter-patient variability; 2) the lags and delays associated to the choice of the sc-sc route for glucose monitoring and insulin administration [15]; and 3) the accuracy and reliability of the CGM.

Model Predictive Control (MPC) is one of the most commonly used methods for the AP. The main advantage of MPC is the ability to handle hard constraints on input variables and soft constraints on output variables in a systematic way. Insulin on board (IOB) constraints in the linear MPC can reduce the risk of overdosing insulin due to nonlinearities in glucose-insulin dynamics [16]. MPC can easily incorporate a feedforward-feedback mechanism that reduces the postprandial glucose peak by administering meal boluses in anticipation of meals [17, 18]. Disturbances, such as meal intake, physical exercise, stress, and illness affect the insulin needs throughout the day. Patients with type 1 diabetes usually reject the disturbance coming from meals by taking a large amount of insulin. In this procedure, it is implicitly assumed that people with type 1 diabetes can accurately estimate their meal sizes and have an accurate knowledge of their postprandial dynamics. In practice, patients typically do not have such information available [19]. Moreover, the other sources of disturbances cannot easily be measured and are usually included in a stochastic term. An adaptive control algorithm has the potential to cope with these unknown disturbances [7, 20].

This paper presents an adaptive control strategy for overnight BG stabilization. We describe an AP using a CGM for glucose feedback, an insulin pump, and a control algorithm based on MPC. The considered control strategy requires a priori available patient information for computing a subject-specific set of parameters. The required information is: The basal insulin infusion rate, the insulin sensitivity factor (also called the correction factor), and the insulin action time. We discuss MPCs based on three different structures for the stochastic part of a deterministic-stochastic input-output model. The first MPC is based on an autoregressive integrated moving average with exogenous input (ARIMAX) model. The integrator in the ARIMAX based MPC provides steady-state offset free control at the expense of a deliberate model-plant mismatch that increases the variance of the control error [21, 22]. The ARIMAX based MPC is described in [23] and tested in an overnight clinical study [11]. The key novelties in this paper are that we investigate by simulation if the integrator is needed in the MPC for an AP and introduce adaptive estimation. Therefore, the second MPC is based on an autoregressive moving average with exogenous input (ARMAX) model, i.e. a model without an integrator. This model cannot guarantee offset-free steady state control to step disturbances but provides lower control error variance [21, 22].The third MPC is based on an adaptive ARMAX model in which we use a Recursive Extended Least Square (RELS) method to estimate parameters of the moving average part. The controllers are tested and compared using a cohort of 100 virtual patients.

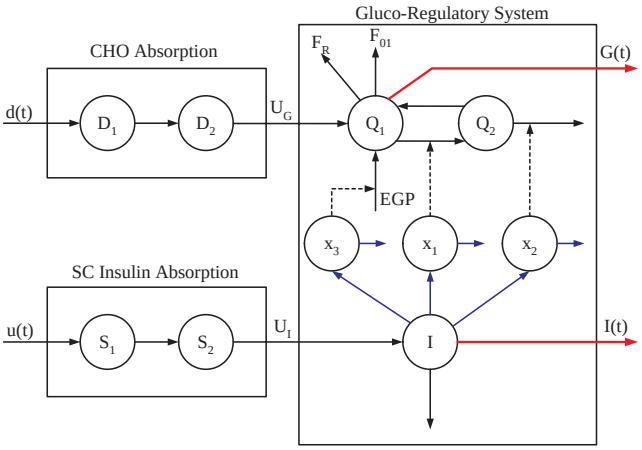

Figure 2: The Hovorka model.

The paper is structured as follows. In Section 2, we describe the model and the methods used to simulate a cohort of patients with type 1 diabetes and noise-corrupted CGM measurements. Section 3 presents a procedure for computation of the deterministic part of the model used by the MPC. The parameters in this part of the model are derived from prior patient information and are common for the three model classes. In Section 4, we introduce the stochastic models for the three different MPCs. Furthermore, we describe the realization of the deterministic-stochastic input-output models as state space models in innovation form and present the corresponding Kalman filtering and prediction equations. Section 5 presents the MPC algorithm used in the AP. The MPC is based on a state space model in innovation form and uses soft output constraints to define a zone of desirable glucose concentrations. In Section 6, we evaluate and discuss the performance of the three different controllers using a cohort of 100 virtual patients. We consider the case where half of the ideal meal bolus is administered at mealtime, and the case where the insulin sensitivity increases during the night. Conclusions are provided in Section 7.

2. Physiological models for patients with type 1 diabetes

Several physiological models have been developed to simulate virtual patients with type 1 diabetes [24–26]. They describe subcutaneous insulin transport, intake of carbohydrates through meals, and include a model of glucose-insulin dynamics.

In this paper, we use the Hovorka model to simulate patients with type 1 diabetes. Using the parameters and distributions provided in [15, 27] and [28], we generate a cohort of 100 virtual patients. The Hovorka model is illustrated in Fig. 2. Table 1 summarizes the parameters and their distributions.

2.1. CGM model

In addition, we use a CGM for glucose feedback in our controller setup. For the numerical simulations, we generate noisy CGM data based on the model and the parameters determined

Table 1: Parameters and distribution for the simulated cohort.

Parameter	Unit	Distribution
EGP_0	mmol/kg/min	$EGP_0 \sim N(0.0161, 0.0039^2)$
F_{01}	mmol/kg/min	$F_{01} \sim N(0.0097, 0.0022^2)$
k_{12}	min^{-1}	$k_{12} \sim N(0.0649, 0.0282^2)$
k_{a1}	min^{-1}	$k_{a1} \sim N(0.0055, 0.0056^2)$
k_{a2}	min^{-1}	$k_{a2} \sim N(0.0683, 0.0507^2)$
k_{a3}	min^{-1}	$k_{a3} \sim N(0.0304, 0.0235^2)$
S^f_{IT}	min^{-1}/(mU/L)	$S^f_{IT} \sim N(51.2, 32.09^2)$
S^f_{ID}	min^{-1}/(mU/L)	$S^f_{ID} \sim N(8.2, 7.84^2)$
S^f_{IE}	L/mU	$S^f_{IE} \sim N(520, 306.2^2)$
k_e	min^{-1}	$k_e \sim N(0.14, 0.035^2)$
V_I	L/kg	$V_I \sim N(0.12, 0.012^2)$
V_G	L/kg	$V_G \sim N(0.15, 0.23^2)$
τ_I	min	$\frac{1}{\tau_I} \sim N(0.018, 0.0045^2)$
τ_G	min	$\frac{1}{\ln(\tau_G)} \sim N(-3.689, 0.25^2)$
A_g	Unitless	$A_g \sim U(0.7, 1.2)$
BW	kg	$BW \sim U(65, 95)$

Table 2: Parameters for the CGM model [29].

Parameter	Value
τ_{sub}	15 min
λ	15.96
ξ	-5.471
δ	1.6898
γ	-0.5444

by [29]. This model consists of two parts. The first part describes the glucose transport from blood to interstitial tissues, which is

$$\frac{dG_{sub}}{dt} = \frac{1}{\tau_{sub}} \left(G(t) - G_{sub}(t) \right). \tag{1}$$

$G_{sub}(t)$ is the subcutaneous glucose concentration and $G(t)$ is the blood glucose concentration. The time constant τ_{sub} is associated to glucose transport from blood to subcutaneous tissues.

The second part models non-Gaussian sensor noise. The model is given by

$$e_k = 0.7(e_{k-1} + v_k), \; k \geq 1, \tag{2}$$

$$v_k \sim N_{iid}(0, 1), \tag{3}$$

$$\eta_k = \xi + \lambda \sinh\left(\frac{e_k - \gamma}{\delta} \right), \tag{4}$$

and the initial condition $e_0 \sim N_{iid}(0, 1)$. Fig. 3 provides an example of a CGM noise sequence η_k. The glucose value returned by the CGM that is used for the controller feedback is

$$G_{CGM}(t_k) = G_{sub}(t_k) + \eta_k. \tag{5}$$

3. A control relevant model of glucose-insulin dynamics

In this section, we derive a control relevant model describing the effect of sc injected insulin, $u(t)$, on the subcutaneous glucose concentration, $y(t)$. This model is the deterministic part

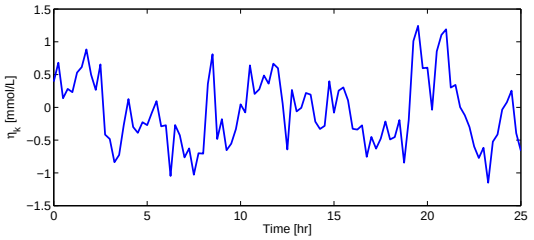

Figure 3: Example of a CGM noise realization.

of the deterministic-stochastic input-output model used by the MPCs. The deterministic part of the model is based on clinically available parameters, and turns out to give a good compromise between data requirements, performance and robustness of the resulting controller.

3.1. Choice of the deterministic model

All the physiological models listed in Section 2 contain a large number of parameters, and even the minimal model may be difficult to identify [30]. To overcome this issue, we use a low-order linear model to describe the glucose-insulin dynamics. Similar approaches have been investigated previously. Kirchsteiger *et al.* [31] used a third order transfer function with an integrator, van Heusden *et al.* [32] used a third order discrete transfer function model, and Percival *et al.* [33] applied a first order transfer function with a time delay. In this paper, we use a continuous-time second order transfer function,

$$G(s) = \frac{Y(s)}{U(s)} = \frac{K_u}{(\tau s + 1)^2}, \tag{6}$$

to model the effect of sc injected insulin on sc glucose. The gain, K_u, and the time constant, τ, are computed from known subject-specific parameters: the insulin action time and the insulin sensitivity factor (ISF).

The insulin action time and the insulin sensitivity factor are related to the response of blood glucose to an insulin bolus. If we assume that blood glucose is approximately identical to sc glucose, this is the impulse response of (6). The insulin action time is the time for blood glucose to reach its minimum. The ISF corresponds to the maximum decrease in blood glucose per unit of insulin bolus. These parameters are empirically determined by the patient and his/her physician. These parameters may vary from day to day for a given patient but give an estimate of the effect of insulin on blood glucose and sc glucose. Fig. 4 provides an illustration of the ISF and the insulin action time.

Fig. 5 depicts the impulse response for a virtual patient with type 1 diabetes and its second order approximation (6). This patient is simulated using the model developed by Hovorka *et* al. [24]. Fig. 5 illustrates that a second order model provides an acceptable approximation of a patient with type 1 diabetes.

In the temporal domain, the impulse response of (6) is described by

$$y(t) = K_u \frac{t}{\tau^2} \exp(-t/\tau). \tag{7}$$

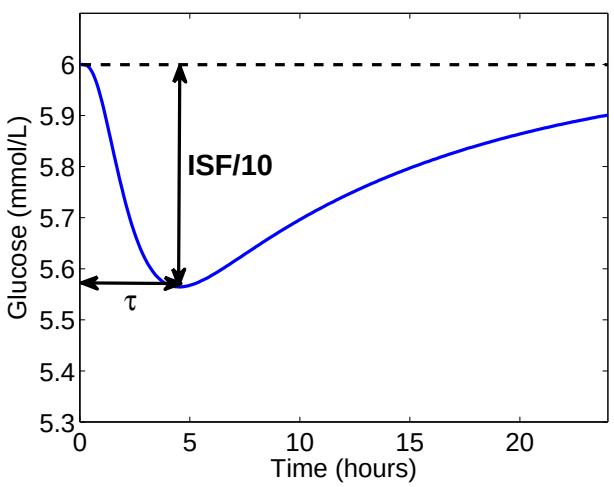

Figure 4: Impulse response for the nonlinear Hovorka model. The bolus size is 0.1U.

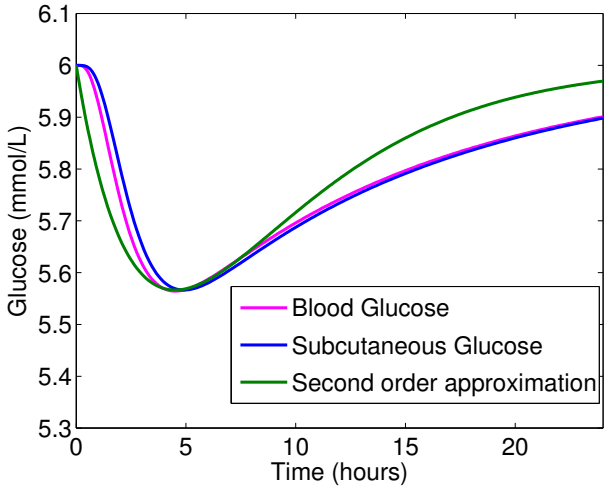

Figure 5: Impulse responses for a second order model and the nonlinear Hovorka model. The bolus size is 0.1U and the parameters for the second order model are: τ=4 hours and ISF = 0.4 mmol/L/0.1 U = 4.0 mmol/L/U.

The insulin action time corresponds to the time to reach the minimum blood glucose. Consequently, this insulin action time is equal to τ. We determine K_u using (7) and the fact that the insulin sensitivity factor is equal to the minimal blood glucose (sc glucose), $y(\tau) = -ISF$, such that

$$K_u = -\tau \exp(1) ISF. \tag{8}$$

We discretize the transfer function (6) in the form

$$y(t) = \frac{B(q^{-1})}{A(q^{-1})} u(t). \tag{9}$$

Using a zero-order-hold insulin profile, the continuous-time transfer function (6) may be used to determine the A and B polynomials in the model (9). They are

$$A(q^{-1}) = 1 + a_1 q^{-1} + a_2 q^{-2}, \tag{10a}$$
$$B(q^{-1}) = b_1 q^{-1} + b_2 q^{-2}, \tag{10b}$$

with the coefficients a_1, a_2, b_1 and b_2 computed as [34]

$$a_1 = -2\exp(-T_s/\tau), \tag{11a}$$
$$a_2 = \exp(-2T_s/\tau), \tag{11b}$$
$$b_1 = K_u(1 - \exp(-T_s/\tau)(1 + T_s/\tau)), \tag{11c}$$
$$b_2 = K_u \exp(-T_s/\tau)(-1 + \exp(-T_s/\tau) + T_s/\tau). \tag{11d}$$

T_s is the sample time.

4. A control relevant deterministic-stochastic model

In this section, we extend the deterministic discrete-time transfer function model (9) with a stochastic part that models the process noise, measurement noise, and other unknown factors affecting the glucose concentration measured by the CGM.

We assume that the model describing the glucose-insulin dynamics is in the form

$$A(q^{-1})y(t) = B(q^{-1})u(t) + C(q^{-1})F(q^{-1})\varepsilon(t). \tag{12}$$

$A(q^{-1})$ and $B(q^{-1})$ are obtained as described in Section 3. $C(q^{-1}) = 1+c_1q^{-1}+c_2q^{-2}$ is the moving average polynomial and $F(q^{-1})$ is a filter transfer function giving the resulting MPC system certain properties. When $F(q^{-1}) = 1$, the resulting model (12) is an ARMAX model. This model structure does not necessarily contain an integrator and cannot guarantee steady state offset free control to unknown step disturbances. When

$$F(q^{-1}) = \frac{1 - \alpha q^{-1}}{1 - q^{-1}}, \quad \alpha \in [0,\ 1[, \tag{13}$$

the resulting model (12) becomes an ARIMAX model. It contains an integrator in the filter that ensures steady-state offset free control to unknown step disturbances. The drawback of using the filter (13) is that it introduces a model-plant mismatch, which gives higher control error variance. When $\alpha \to 1$, $F(q^{-1}) \to 1$ and the model-plant mismatch based on the filter vanishes along with the steady-state offset free property. Based on extensive simulations for the Hovorka model with an MPC based on (12) and (13), we choose $\alpha = 0.99$.

We propose and discuss three different choices for the stochastic model in (12). The first two choices estimate the $C(q^{-1})$ polynomial based on a previous clinical study, while the last method estimates it recursively using a RELS algorithm.

4.1. Estimation in stochastic differential equations

Using the procedure introduced in [35, 36], we estimate the coefficients $C(q^{-1})$ by estimating the noise parameters, σ and r, in

$$dx(t) = (A_c x(t) + B_c u(t))dt + \sigma d\omega(t), \tag{14a}$$
$$y_k = C_c x(t_k) + v_k. \tag{14b}$$

The triple (A_c, B_c, C_c) is a realization of (6). $\omega(t)$ is a standard Wiener process. In our case, the matrix σ is time invariant and diagonal with a single identical parameter in the diagonal. The measurement noise, v_k, is normally distributed, i.e. $v_k \sim N_{iid}(0, r^2)$. We estimate σ and r using a maximum likelihood criteria for the one-step prediction error [37, 38]. By zero-order hold (zoh) discretization, design of a stationary Kalman filter, and z-transformation of the resulting state space model in innovation form, (14) may be represented as

$$y_k = G(q^{-1})u_k + H(q^{-1})\epsilon_k \tag{15}$$

with

$$G(q^{-1}) = \frac{B(q^{-1})}{A(q^{-1})} = \frac{b_1 q^{-1} + b_2 q^{-2}}{1 + a_1 q^{-1} + a_2 q^{-2}}, \tag{16a}$$

$$H(q^{-1}) = \frac{C(q^{-1})}{A(q^{-1})} = \frac{1 + c_1 q^{-1} + c_2 q^{-2}}{1 + a_1 q^{-1} + a_2 q^{-2}}. \tag{16b}$$

The parameters identified from data for a single patient are $c_1 = -1.62$ and $c_2 = 0.68$ [35, 36]. These parameters are used in the MPC based on an ARIMAX model and in the MPC based on an ARMAX model. The adaptive MPC is based on an ARMAX model for which c_1 and c_2 are estimated recursively.

The discrete-time model (15) obtained by estimation of the noise parameters, σ and r, in (14) is related to (12) by

$$\epsilon_k = F(q^{-1})\varepsilon_k. \tag{17}$$

This implies that (15) with the transfer functions (16) and the noise ϵ_k defined by (17) is equivalent to the deterministic-stochastic model (12) used by the MPC for filtering and prediction.

4.2. ARMAX model

The MPC based on an ARMAX model uses (12) with $A(q^{-1}) = 1 + a_1 q^{-1} + a_2 q^{-2}$ and $B(q^{-1}) = b_1 q^{-1} + b_2 q^{-2}$ defined from clinical available parameters, $C(q^{-1}) = 1 + c_1 q^{-1} + c_2 q^{-2}$ obtained from noise estimation in a continuous-discrete linear stochastic model fitted to data for a single patient, and $F(q^{-1}) = 1$. In this case, (12) can be expressed as the ARMAX model

$$A(q^{-1})y(t) = B(q^{-1})u(t) + C(q^{-1})\varepsilon(t), \tag{18}$$

which can be represented as a state space model in innovation form

$$x_{k+1} = Ax_k + Bu_k + K\varepsilon_k, \tag{19a}$$

$$y_k = Cx_k + \varepsilon_k, \tag{19b}$$

using the observer canonical realization

$$A = \begin{bmatrix} -a_1 & 1 \\ -a_2 & 0 \end{bmatrix}, \tag{20a}$$

$$B = \begin{bmatrix} b_1 \\ b_2 \end{bmatrix}, \tag{20b}$$

$$K = \begin{bmatrix} c_1 - a_1 \\ c_2 - a_2 \end{bmatrix}, \tag{20c}$$

$$C = \begin{bmatrix} 1 & 0 \end{bmatrix}. \tag{20d}$$

The MPC based on this ARMAX model does not guarantee offset free control and the moving average model, $C(q^{-1})$, has been identified from data for a single patient that may be different than the virtual patients generated by the Hovorka model and used to evaluate the MPCs in this study. However, the ARMAX based MPC is expected to produce lower control error variance than the MPC based on the ARIMAX model [21, 22].

4.3. ARIMAX model

The MPC based on an ARIMAX model uses (12) with $A(q^{-1}) = 1 + a_1 q^{-1} + a_2 q^{-2}$ and $B(q^{-1}) = b_1 q^{-1} + b_2 q^{-2}$ defined from clinical available parameters, $C(q^{-1}) = 1 + c_1 q^{-1} + c_2 q^{-2}$ obtained from noise estimation in a continuous-discrete linear stochastic model fitted to data for a single patient, and $F(q^{-1})$ defined by (13) using $\alpha = 0.99$. In this case, (12) can be expressed as the ARMAX model

$$\bar{A}(q^{-1})y(t) = \bar{B}(q^{-1})u(t) + \bar{C}(q^{-1})\varepsilon(t) \tag{21}$$

with

$$\begin{aligned} \bar{A}(q^{-1}) &= (1 - q^{-1})A(q^{-1}) \\ &= 1 + (a_1 - 1)q^{-1} + (a_2 - a_1)q^{-2} + (-a_2)q^{-3}, \end{aligned} \tag{22a}$$

$$\begin{aligned} \bar{B}(q^{-1}) &= (1 - q^{-1})B(q^{-1}) \\ &= b_1 q^{-1} + (b_2 - b_1)q^{-2} + (-b_2)q^{-3}, \end{aligned} \tag{22b}$$

$$\begin{aligned} \bar{C}(q^{-1}) &= (1 - \alpha q^{-1})C(q^{-1}) \\ &= 1 + (c_1 - \alpha)q^{-1} + (c_2 - \alpha c_1)q^{-2} + (-\alpha c_2)q^{-3}, \end{aligned} \tag{22c}$$

and realized as a state space model in innovation form (19) with the observer canonical state space matrices

$$A = \begin{bmatrix} -(a_1 - 1) & 1 & 0 \\ -(a_2 - a_1) & 0 & 1 \\ -(-a_2) & 0 & 0 \end{bmatrix}, \tag{23a}$$

$$B = \begin{bmatrix} b_1 \\ b_2 - b_1 \\ -b_2 \end{bmatrix}, \tag{23b}$$

$$K = \begin{bmatrix} (c_1 - \alpha) - (1 - a_1) \\ (c_2 - \alpha c_1) - (a_2 - a_1) \\ (-\alpha c_2) - (-a_2) \end{bmatrix}, \tag{23c}$$

$$C = \begin{bmatrix} 1 & 0 & 0 \end{bmatrix}. \tag{23d}$$

The key advantage of the ARIMAX model is that it guarantees steady-state offset free control for step disturbances. Its drawback is that the filter (13) introduces a model-plant mismatch that increases the variance of the controlled variables [21, 22].

4.4. Adaptive ARMAX model

In this case, we estimate the parameters c_1 and c_2 in $C(q^{-1}) = 1 + c_1 q^{-1} + c_2 q^{-2}$ at each sample time. In this way, we adapt the noise model $C(q^{-1})$ to the data but keep the deterministic model (9) fixed. Previously, adaptive control for ARMAX model structures has been considered for the control algorithm in an AP [7, 39–42]. These papers estimate the full model (12), i.e. ($A(q^{-1})$, $B(q^{-1})$, $C(q^{-1})$) with $F(q^{-1}) = 1$. However, such

estimations may for some data lead to an unstable system or a system with a positive insulin gain [43]. The key novelty for this paper is that we adaptively identify only the stochastic part, i.e. the $C(q^{-1})$ polynomial. This corresponds to keeping the deterministic part of the model fixed and adaptively estimating the Kalman filter gain.

The parameters c_1 and c_2 are estimated at each iteration using the RELS method

$$\varepsilon_k = y_k - \phi_k'\hat{\theta}_{k|k-1} - \tilde{\phi}_k'\tilde{\theta}_k, \tag{24a}$$

$$K_k = \frac{P_{k-1}\phi_k}{\mu + \phi_k' P_{k-1}\phi_k}, \tag{24b}$$

$$\hat{\theta}_{k+1|k} = \hat{\theta}_{k|k-1} + K_k\varepsilon_k, \tag{24c}$$

$$P_k = \frac{1}{\mu}\left(P_{k-1} - \frac{P_{k-1}\phi_k\phi_k' P_{k-1}}{\mu + \phi_k' P_{k-1}\phi_k}\right). \tag{24d}$$

The past innovations, ϕ_k, the estimated parameters, θ_k, the past data, $\tilde{\phi}_k$, and the fixed parameters, $\tilde{\theta}_k$, are

$$\phi_k = \begin{bmatrix}\varepsilon_{k-1} & \varepsilon_{k-2}\end{bmatrix}', \tag{25a}$$

$$\theta_k = \begin{bmatrix}c_1 & c_2\end{bmatrix}', \tag{25b}$$

$$\tilde{\phi}_k = \begin{bmatrix}y_{k-1} & y_{k-2} & u_{k-1} & u_{k-2}\end{bmatrix}', \tag{25c}$$

$$\tilde{\theta}_k = \begin{bmatrix}-a_1 & -a_2 & b_1 & b_2\end{bmatrix}'. \tag{25d}$$

P_k is the model parameters covariance matrix that we initialize with

$$P_0 = \begin{bmatrix}100 & 0\\ 0 & 100\end{bmatrix}. \tag{26}$$

Finally, μ is the forgetting factor. This parameter has an influence on the weight of previous observations. When $\mu = 1$, all the past observations are equally weighted. Small values of μ (i.e. μ close to zero) give more importance to recent observations [44]. $1/(1-\mu)$ is an approximation of the memory length (in time samples). In this paper, we use $\mu = 0.95$ such that the corresponding memory length is approximately $1/(1-0.95) = 20$ time samples, i.e. 100 minutes.

This ARMAX model, (18) with $A(q^{-1})$ and $B(q^{-1})$ individualized but fixed and $C(q^{-1})$ estimated at each sample time, provides a personalized and adaptive model for filtering and prediction of the CGM values. However, using the adaptive ARMAX model structure does not guarantee steady-state offset free control to step disturbances.

4.5. Filtering and prediction

The ARMAX model with the parameters fixed or adaptively estimated as well as the ARIMAX model may all be realized as a state space model in innovation form (19). In this section, we describe the optimal filtering and prediction of state space models in innovation form. The innovation of (19) is

$$e_k = y_k - C\hat{x}_{k|k-1} \tag{27}$$

and the corresponding predictions are [22]

$$\hat{x}_{k+1|k} = A\hat{x}_{k|k-1} + B\hat{u}_{k|k} + Ke_k, \tag{28a}$$

$$\hat{x}_{k+1+j|k} = A\hat{x}_{k+j|k} + B\hat{u}_{k+j|k}, \qquad j = 1,\ldots,N-1, \tag{28b}$$

$$\hat{y}_{k+j|k} = C\hat{x}_{k+j|k}, \qquad j = 1,\ldots,N. \tag{28c}$$

The innovation (27) and the predictions (28) constitute the feedback and the predictions in the MPCs.

5. Model Predictive Control

Control algorithms for glucose regulation in patients with type 1 diabetes must be able to handle intra- and inter-patient variability. In addition, the controller must administer insulin in such a way that hypoglycemia is avoided. Due to the nonlinearity in the glucose-insulin interaction, the risk of hypoglycemic episodes as consequence of dosing too much insulin is particularly prominent.

In this section, we describe an MPC formulation with soft output constraints and hard input constraints. This formulation is based on the individualized prediction model for glucose computed in Section 3 and the stochastic models described in Section 4. Along with other features, we introduce a modified time-varying reference signal to robustify the controller and mitigate the effect of glucose-insulin nonlinearities and model-plant mismatch in the controller action.

The MPC algorithm computes the insulin dose by solution of an open-loop optimal control problem. Only the control action corresponding to the first sample interval is implemented and the process is repeated at the next sample interval. This is called a moving horizon implementation. The innovation (27) provides feedback from the CGM, y_k. The open-loop optimal control problem solved in each sample interval is the convex quadratic program

$$\min_{\{\hat{u}_{k+j|k},\hat{v}_{k+j+1|k}\}_{j=0}^{N-1}} \quad \phi \tag{29a}$$

$$s.t. \qquad (28) \tag{29b}$$

$$u_{\min} \le \hat{u}_{k+j|k} \le u_{\max} \qquad j = 0,\ldots,N-1 \tag{29c}$$

$$\hat{y}_{k+j+1|k} \ge y_{\min} - \hat{v}_{k+j+1|k} \quad j = 0,\ldots,N-1 \tag{29d}$$

$$\hat{v}_{k+j+1|k} \ge 0 \qquad j = 0,\ldots,N-1 \tag{29e}$$

with the objective function, ϕ, defined as

$$\begin{aligned}\phi =& \frac{1}{2}\sum_{j=0}^{N-1} \|\hat{y}_{k+j+1|k} - \hat{r}_{k+j+1|k}\|_2^2 + \kappa\|\hat{v}_{k+j+1|k}\|_2^2 \\ &+ \frac{1}{2}\sum_{j=0}^{N-1} \lambda\|\Delta\hat{u}_{k+j|k}\|_2^2.\end{aligned} \tag{30}$$

N is the control and prediction horizon. We choose a prediction horizon equivalent to 10 hours, such that the insulin profile of the finite horizon optimal control problem (29) is similar to the insulin profile of the infinite horizon optimal control problem, i.e. (29) with $N \to \infty$. $\|\hat{y}_{k+j+1|k} - \hat{r}_{k+j+1|k}\|_2^2$ penalizes glucose deviation from the time-varying glucose setpoint and aims to drive the glucose concentration to 6 mmol/L. $\lambda\|\Delta\hat{u}_{k+j|k}\|_2^2$ is a regularization term that prevents the insulin infusion rate from varying too aggressively. For the simulations and the in vivo clinical studies, we set $\lambda = 100/u_{ss}^2$. The soft output constraint (29d) penalizes glucose values below 4 mmol/L. Since hypoglycemia is highly undesirable, we choose the weight on the

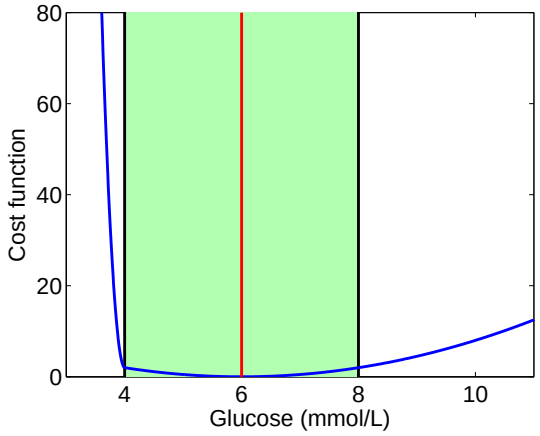

Figure 6: The penalty function $\rho = \|y - r\|_2^2 + \kappa \|\min\{y - y_{\min}, 0\}\|_2^2$.

soft output constraint to be rather high, i.e. $\kappa = 100$. Fig. 6 illustrates the penalty function.

To guard against model-plant mismatch, we modify the maximal allowable insulin injection, $u_{\max}$, and let it depend on the current glucose concentration. If the glucose concentration is low (below the target of 6 mmol/L), we prevent the controller from taking future hyperglycemia into account by restricting the maximal insulin injection. If the glucose concentration is high (4 mmol/L above the target), we increase the maximal allowable insulin injection rate. In the range 0 - 4 mmol/L above target, we allow the controller to double the basal insulin injection rate. These considerations lead to

$$u_{\max} = \begin{cases} 1.5u_{ss} & 4 \le y_k \le \infty \\ u_{ss} & 0 \le y_k \le 4 \\ 0.5u_{ss} & -\infty \le y_k \le 0 \end{cases}, \tag{31}$$

in which u_{ss} is the basal insulin infusion rate. Due to pump restrictions, the minimum insulin injection rate, $u_{\min}$, is a low value, but not exactly zero.

Ref. [45] and [7] use a time-varying glucose reference signal to robustify the controller and reduce the risk of hypoglycemic events. In this paper, we use an asymmetric time-varying glucose reference signal. The idea of the asymmetric reference signal is to induce safe insulin injections in hyperglycemic periods and fast recovery in hypoglycemic and below target periods. The asymmetric time-varying setpoint is given by

$$\hat{r}_{k+j|k}(t) = \begin{cases} y_k \exp\left(-t_j/\tau_r^+\right) & y_k \ge 0 \\ y_k \exp\left(-t_j/\tau_r^-\right) & y_k < 0 \end{cases} \qquad j = 1, \ldots, N. \tag{32}$$

Since we want to avoid hypoglycemia, we make the controller react more aggressively if the blood glucose level is below 6 mmol/L, so we choose $\tau_r^- = 15$ min and $\tau_r^+ = 90$ min. Fig. 7 provides an illustration of the time-varying reference signal.

6. Comparison of the MPC strategies for a virtual clinic

In this section, we compare the three different versions of our MPC for a cohort of 100 virtual patients. These three versions are the ARMAX formulation presented in Section 4.2, the ARIMAX formulation presented in Section 4.3, and the adaptive ARMAX model formulation presented in Section 4.4. We compare the performance of the controllers for the case where the meal is underbolused and the case where the insulin sensitivity is increased by 30% during the night. The change in insulin sensitivity is simulated by a step change in the insulin sensitivity parameters of the Hovorka model.

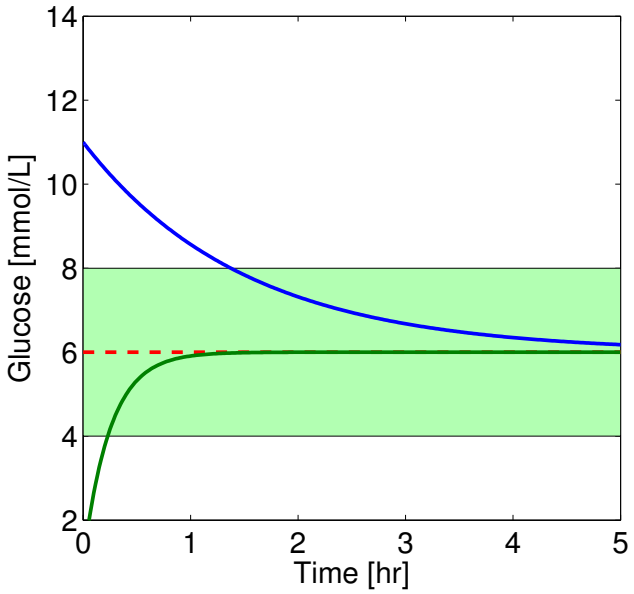

Figure 7: Time-varying reference signals for glucose above (blue curve) and below (green curve) the target of 6 mmol/L.

The ARMAX based controllers do not contain an integrator and cannot guarantee steady-state offset free control. However, the tuning of the MPCs based ARMAX models are simpler than the tuning of the MPC based on the ARIMAX model. The reason is that no artificial model-plant mismatch is introduced in the MPC based on ARMAX models, while the ARIMAX based controller deliberately include such a mismatch to ensure steady-state offset free control.

The MPC is individualized using the insulin basal rate (u_{ss}), the insulin sensitivity factor (ISF), and the insulin action time (τ) for each individual patient. In the virtual clinic, these numbers are computed from an impulse response starting at a steady state. The meal boluses are determined using a bolus calculator similar to the one presented in [46]. The glucose is provided to the controller every 5 minutes by a noise-corrupted CGM. The pump insulin infusion rate is changed every 5 minutes.

The clinical protocol for the 100 in silico patients is: 1) The patient arrives at the clinic at 17:00. The Kalman filter is activated; 2) The patient gets a 75 g CHO dinner and an insulin bolus at 18:00. We assume that the meal is rapidly consumed. The bolus size is determined to compensate the effects of the meal; 3) The closed loop starts at 22:00. In addition to the Kalman filter, the MPC is activated; 4) The patient gets a 60 g CHO breakfast and an insulin bolus at 08:00. The controller is switched off.

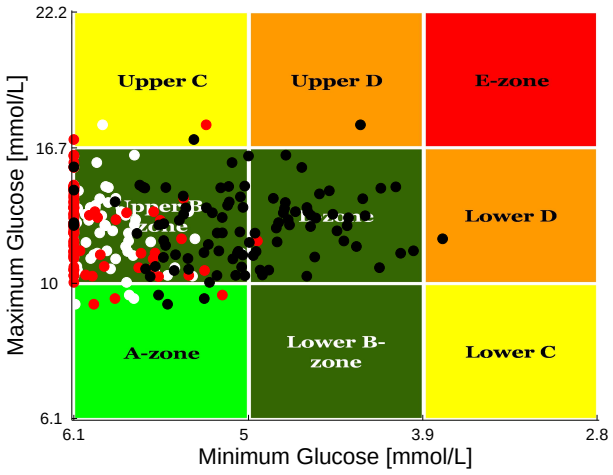

Figure 8: Control Variability Grid Analysis (CVGA) plot for the three different stochastic model structures. 50% of the meal bolus is administered at mealtime. Black: ARIMAX. Red: ARMAX. White: Adaptive ARMAX.

Table 3: Evaluation of the controller for the different control strategies in the case where only 50% of the meal bolus is administered at mealtime. The numbers show the total percentage of time spent in different glucose ranges for the 100 virtual patients during the period 22:00 - 08:00.

Glucose (mmol/L)	ARIMAX	ARMAX	Adaptive ARMAX
$G > 10$	17.8	23.9	20.8
$G > 8$	31.6	58.1	42.2
$3.9 \leq G \leq 10$	82.1	76.1	79.2
$3.9 \leq G \leq 8$	68.3	41.9	57.8
$G < 3.9$	0.1	0	0
$G < 3.5$	0	0	0

6.1. *Underbolused meal*

Fig. 8 shows the CVGA plot for the three different strategies in the case where only 50% of the meal bolus is administered at mealtime. The control strategy based on an ARIMAX model shows several cases of mild hypoglycemia due to an insulin overdose. The two control strategies based on an ARMAX model are able to avoid this undershoot. Fig. 9 shows the glucose and insulin traces for a single patient. Table 3 shows the time spent in the euglycemic range, hypoglycemia and hyperglycemia for the three different strategies. The results show that the control strategy based on an ARIMAX model structure reduce the time spent in hyperglycemia. The adaptive ARMAX model structure shows the best compromise between the time spent in euglycemia and safety concerning the risk of insulin overdose.

6.2. *Change in insulin sensitivity*

Fig. 10 shows the CVGA plot for the three different strategies for the case where the insulin sensitivity is increased by 30% during the night. Table 4 shows the time spent in the euglycemic range, hypoglycemia and hyperglycemia for the three different strategies. The control strategies based on an ARMAX model structure, i.e. the controllers without the integrator, reduce the occurrences of hypoglycemia, and avoid severe hypoglycemia (i.e. glucose values below 3.5 mmol/L). Fig. 11 provides the glucose and insulin traces for a specific patient.

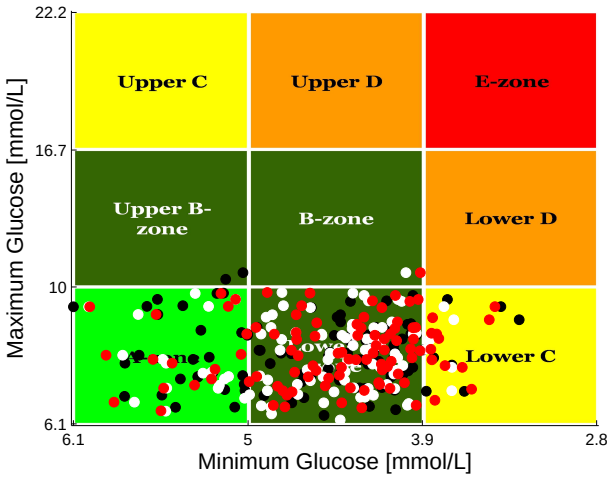

Figure 10: Control Variability Grid Analysis (CVGA) plot for the three different stochastic model structures. The insulin sensitivity is increased by 30% during the night. Black: ARIMAX. Red: ARMAX. White: Adaptive ARMAX.

Table 4: Evaluation of the controller for the different control strategies. The insulin sensitivity is increased by 30% during the night. The numbers show the total percentage of time spent in different glucose ranges for the 100 virtual patients during the period 22:00 - 08:00.

Glucose (mmol/L)	ARIMAX	ARMAX	Adaptive ARMAX
$G > 10$	<0.1	<0.1	<0.1
$G > 8$	3.2	2.5	2.2
$3.9 \leq G \leq 10$	99.1	99.4	99.7
$3.9 \leq G \leq 8$	95.9	96.9	97.5
$G < 3.9$	0.9	0.6	0.3
$G < 3.5$	0.2	0	0

7. Conclusion

This paper presents subject-specific control strategies designed for overnight stabilization of blood glucose in patients with type 1 diabetes. The controllers are tested using 100 virtual patients with a representative parameter distribution and scenarios where we simulate an underbolused meal and insulin sensitivity variation. The choice of the model structure for the stochastic part of the model is a tradeoff between offset-free control and model-plant mismatch. For the specific virtual patients and scenarios used in this paper, simulations reveal that the MPC based on the adaptive ARMAX model provides better performance than the MPC based on an ARMAX model and the MPC based on an ARIMAX model. The MPC based on the ARIMAX model has been applied in a previous clinical study.

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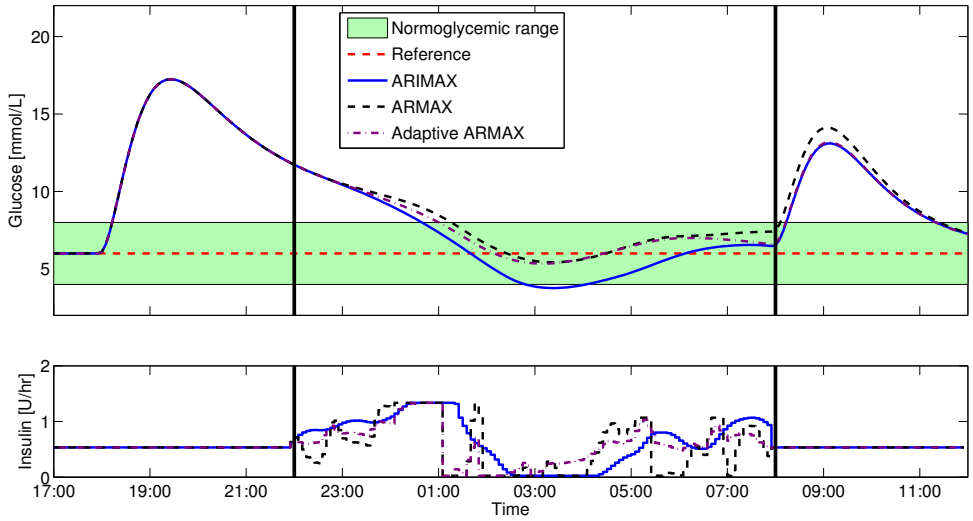

Figure 9: Glucose and insulin profiles of a specific patient for the different control strategies. The patients gets half of the optimal bolus at mealtime.

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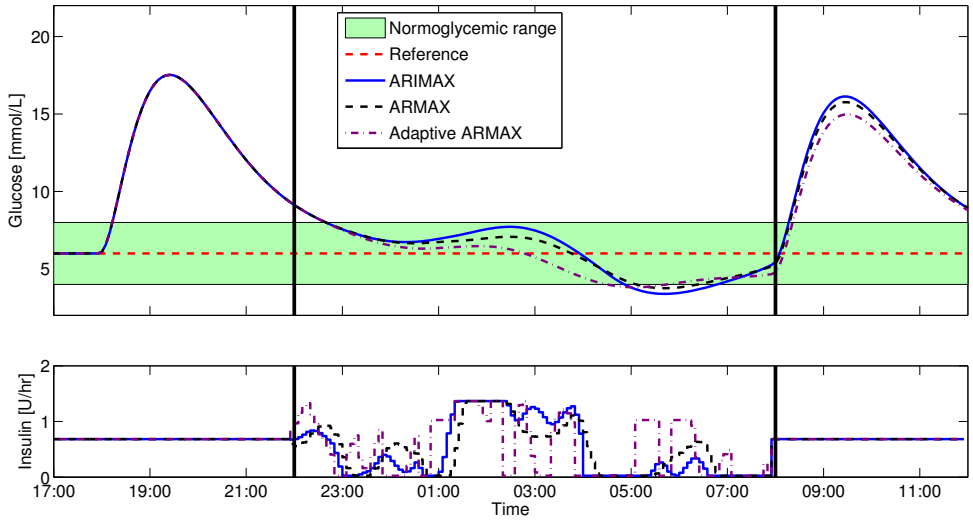

Figure 11: Glucose and insulin profiles of a specific patient for the different control strategies. The insulin sensitivity increases by 30% during the night.

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