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Assessment of Model Predictive and Adaptive Glucose Control Strategies for People with Type 1 Diabetes

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Abstract: This paper addresses overnight blood glucose stabilization in people with type 1 diabetes using a Model Predictive Controller (MPC). We use a control strategy based on an adaptive ARMAX model in which we use a Recursive Extended Least Squares (RELS) method to estimate parameters of the stochastic part. We compare this model structure with an autoregressive integrated moving average with exogenous input (ARIMAX) structure, and with an autoregressive moving average with exogenous input (ARMAX) model, i.e. without an integrator. Additionally, safety layers improve the controller robustness and reduce the risk of hypoglycemia. We test our control strategies on 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 varies during the night. The simulation results demonstrate that the adaptive control strategy can reduce the risks of hypoglycemia and hyperglycemia during the night.

1. INTRODUCTION

Type 1 diabetes is a metabolic disease characterized by a destruction of the insulin-producing β-cells in the pancreas. Therefore, patients with type 1 diabetes need exogenous insulin administration in order to avoid serious damage or health issues. 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) has long-term clinical complications, such as blindness, nerve diseases or kidney diseases.

The conventional insulin therapy for people with type 1 diabetes consists of the injection of slow acting insulin once a day and rapid acting insulin several times per day, usually before mealtimes. The slow acting insulin is used to counteract the continuous glucose production from the liver. The rapid acting insulin compensates the intake of carbohydrates (CHO) during the meals. The decision on the amount of short and fast acting insulin is based on several blood glucose measurements per day.

An increasing number of patients with type 1 diabetes use an intensive and technologically advance therapy approach based on continuous glucose monitors (CGMs) and continuous subcutaneous insulin infusion (CSII) pumps instead of the conventional therapy described above. This approach can reduce the risk of complications significantly. CGMs provide more frequent subcutaneous (sc) glucose measurements. In addition, insulin pumps can be adjusted to daily variations in insulin needs.

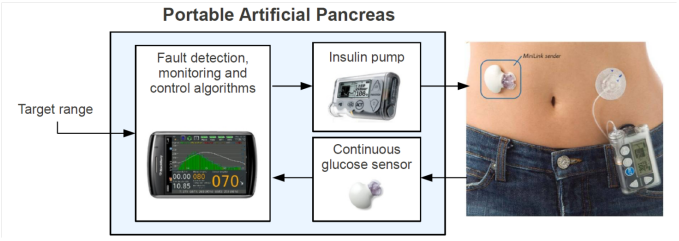

Fig. 1. Closed-loop glucose control. Glucose is measured subcutaneously using a continuous glucose monitor (CGM). Insulin is dosed by an insulin pump.

Closed-loop control of blood glucose, also known as the artificial pancreas (AP) has the potential to ease the life and reduce the burden and complications for people with type 1 diabetes. An AP consists of a CGM, a control algorithm and a CSII pump. Fig. 1 illustrates the principle of an AP. Model Predictive Control (MPC) is one of the most commonly used methods for the AP (Cobelli et al., 2009). The main advantages of MPC are the ability to handle constraints both on input and output variables in a systematic way. Prototypes of AP using MPC have been successfully tested in clinical studies (Hovorka et al., 2010; Schmidt et al., 2013).

In this paper, 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. We discuss three different model

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Table 1. Parameters for the CGM model extracted from Breton and Kovatchev (2008).

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

structures for the stochastic part. The first one is an autoregressive integrated moving average with exogenous input (ARIMAX) structure. The second one is an autoregressive moving average with exogenous input (ARMAX) model, i.e. without integrator. The third one is an adaptive ARMAX model in which we use a Recursive Extended Least Square (RELS) method to estimate parameters of the stochastic part (i.e. the MA part). The controller is tested on a cohort of 100 virtual patients.

2. PHYSIOLOGICAL MODELS FOR PEOPLE WITH TYPE 1 DIABETES

In this paper, we use the Hovorka model to simulate people with type 1 diabetes. Using the parameters and distributions provided in Hovorka et al. (2002) and Wilinska et al. (2010), we generate a cohort of 100 virtual patients.

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 by Breton and Kovatchev (2008). 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 and $G(t)$ is the blood glucose. The time constant τ_{sub} is associated to glucose transport from blood to subcutaneous tissues.

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

$$e_k = 0.7(e_{k-1} + v_k), \quad k > 0 \tag{2}$$
$$v_k \sim N_{iid}(0,1) \tag{3}$$
$$\eta_k = \xi + \lambda \sinh\left(\frac{e_k - \gamma}{\delta}\right) \tag{4}$$

with the initial condition $e_0 \sim N_{iid}(0,1)$.

The glucose value returned by the CGM is

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

The numerical values used in this paper for τ_{sub}, λ, ξ, δ and γ are shown in Table 1.

3. MODELING OF GLUCOSE-INSULIN DYNAMICS

In this section, we derive a prediction model for subcutaneous glucose, $y(t)$. The model has a deterministic part describing the effect of sc. injected insulin, $u(t)$, and a stochastic part describing the effect of other unknown factors. This model identification technique turns out to give a good compromise between data requirements, performance and robustness of the resulting controller.

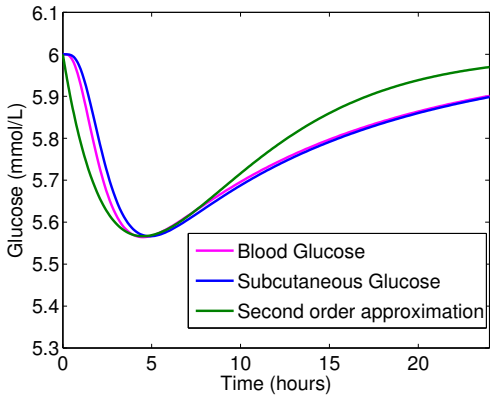

Fig. 2. Impulse responses for a second order model and the nonlinear Hovorka model. The bolus size is 0.1U and the parameters for the second order model are: τ=4 hours and ISF = 0.4 mmol/L/0.1 U = 4.0 mmol/L/U.

3.1 Choice of the deterministic model

The physiological models listed in Section 2 contain a large number of parameters, and Pillonetto et al. (2003) established that even the minimal model developed by Bergman et al. (1981) may be difficult to identify. 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. (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. 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 estimated by the patient and his/her physician. They may vary from day to day for a given patient but gives an estimate of the effect of insulin on blood glucose and sc glucose.

Fig 2 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. (2004). The figure demonstrates that a second order model provides an acceptable approximation of a virtual patient with type 1 diabetes.

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

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

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

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

The sampling time is 5 minutes.

4. STOCHASTIC MODEL

We take into account the process and measurement noise by adding a term describing the effect of unknown factors to the discrete-time model (9). We assume the model describing the glucose-insulin dynamics to be in the form

$$A(q^{-1})y(t) = B(q^{-1})u(t) + \frac{C(q^{-1})}{D(q^{-1})}\varepsilon(t) \tag{10}$$

The model (10) has a deterministic part describing the effects of insulin injections $u(t)$ and a stochastic part. We assume either $D(q^{-1}) = 1 - q^{-1}$, which turns the model (10) into an ARIMAX model or $D(q^{-1}) = 1$, which turns the model (10) into an ARMAX model.

In this section we propose and discuss three different choices for the stochastic model in (10). The two first choices estimate the $C(q^{-1})$ based on the data from a previous clinical study, while the last method estimate it recursively using a Recursive Extended Least Squares (RELS) algorithm.

4.1 ARIMAX modeling

The stochastic part, $C(q^{-1})$, of the ARIMAX model

$$A(q^{-1})y(t) = B(q^{-1})u(t) + \frac{C(q^{-1})}{1 - q^{-1}}\varepsilon(t) \tag{11}$$

is assumed to be a third order polynomial of the form

$$\begin{aligned} C(q^{-1}) &= 1 + c_1 q^{-1} + c_2 q^{-2} + c_3 q^{-3} \\ &= (1 - \alpha q^{-1})(1 - \beta_1 q^{-1})(1 - \beta_2 q^{-1}) \end{aligned} \tag{12}$$

$\alpha = 0.99$ is a fixed parameter. α has been determined based on performance studies of the resulting MPC. The choice of α is discussed in Huusom et al. (2012). β_1 and β_2 are determined from clinical data for one real patient (Duun-Henriksen et al., 2012; Boiroux et al., 2012). They are $\beta_{1,2} = 0.81 \pm 0.16i$.

The main drawback of this specification is the model-plant mismatch. However, this model-plant mismatch enables to have offset free control in the resulting predictive control system.

4.2 ARMAX modeling

The stochastic part, $C(q^{-1})$, of the ARMAX model

$$A(q^{-1})y(t) = B(q^{-1})u(t) + C(q^{-1})\varepsilon(t) \tag{13}$$

is now assumed to be a second order polynomial of the form

$$\begin{aligned} C(q^{-1}) &= 1 + c_1 q^{-1} + c_2 q^{-2} \\ &= (1 - \beta_1 q^{-1})(1 - \beta_2 q^{-1}) \end{aligned} \tag{14}$$

We use the same procedure as in Section 4.1 for computing β_1 and β_2, i.e. $\beta_{1,2} = 0.81 \pm 0.16i$. This yields

$$C(q^{-1}) = 1 - 1.62q^{-1} + 0.68q^{-2} \tag{15}$$

Unlike the ARIMAX model structure described in Section 4.1, this model structure does not ensure offset-free control. On the other hand, it does not introduce a supplementary model-plant mismatch.

4.3 Adaptive control

Here, we consider again the ARMAX model structure (13). A similar approach has been proposed by Eren-Oruklu et al. (2009).

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

$$\varepsilon_k = y_k - \phi_k' \hat{\theta}_{k|k-1} \tag{16a}$$

$$K_k = \frac{P_{k-1}\phi_k}{\mu + \phi_k' P_{k-1} \phi_k} \tag{16b}$$

$$\hat{\theta}_{k+1|k} = \hat{\theta}_{k|k-1} + K_k \left(y_k - \phi_k' \hat{\theta}_{k|k-1} \right) \tag{16c}$$

$$P_k = \frac{1}{\mu} \left(P_{k-1} - \frac{P_{k-1}\phi_k \phi_k' P_{k-1}}{\mu + \phi_k' P_{k-1} \phi_k} \right) \tag{16d}$$

ϕ_k is a vector of past observations

$$\phi_k = [y_{k-1} \ y_{k-2} \ u_{k-1} \ u_{k-2} \ \varepsilon_{k-1} \ \varepsilon_{k-2}] \tag{17}$$

θ_k is a vector of model parameters

$$\theta_k = [-a_1 \ -a_2 \ b_1 \ b_2 \ c_1 \ c_2]' \tag{18}$$

P_k is the model parameters covariance matrix. Since we want to estimate c_1 and c_2 only, we initialize it with

$$P_0 = diag(0, 0, 0, 0, 100, 100) \tag{19}$$

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. Smaller values of μ give more importance to recent observations. In this paper, we chose $\mu = 0.95$, i.e. the corresponding memory length is approximately $1/(1 - 0.95) = 20$ time samples, or 100 minutes. This model structure allows for a personalized and localized stochastic model description.

4.4 Realization and predictions

The ARIMAX model (11) and the ARMAX model (13) may be represented as a discrete-time state space model in innovation form

$$x_{k+1} = Ax_k + Bu_k + K\varepsilon_k \tag{20a}$$

$$y_k = Cx_k + \varepsilon_k \tag{20b}$$

The observer canonical realization for the ARMAX model (13) is

$$A = \begin{bmatrix} -a_1 & 1 \\ -a_2 & 0 \end{bmatrix}; \ B = \begin{bmatrix} b_1 \\ b_2 \end{bmatrix}; \ K = \begin{bmatrix} c_1 - a_1 \\ c_2 - a_2 \end{bmatrix}$$
$$C = [1 \ 0]$$

and the observer canonical realization for the ARIMAX model (11) is

$$A = \begin{bmatrix} 1 - a_1 & 1 & 0 \\ a_1 - a_2 & 0 & 1 \\ a_2 & 0 & 0 \end{bmatrix} B = \begin{bmatrix} b_1 \\ b_2 - b_1 \\ -b_2 \end{bmatrix} K = \begin{bmatrix} c_1 + 1 - a_1 \\ c_2 + a_1 - a_2 \\ c_3 + a_2 \end{bmatrix}$$
$$C = [1 \ 0 \ 0]$$

The innovation of (20) is

$$\varepsilon_k = y_k - C\hat{x}_{k|k-1} \tag{21}$$

and the corresponding predictions are (Jørgensen et al., 2011)

$$\hat{x}_{k+1|k} = A\hat{x}_{k|k-1} + B\hat{u}_{k|k} + K\varepsilon_k \tag{22a}$$
$$\hat{x}_{k+1+j|k} = A\hat{x}_{k+j|k} + B\hat{u}_{k+j|k}, \quad j = 1, \ldots, N-1 \tag{22b}$$
$$\hat{y}_{k+j|k} = C\hat{x}_{k+j|k}, \quad j = 1, \ldots, N \tag{22c}$$

The innovation (21) and the predictions (22) constitute the feedback and the predictions in the model predictive controller.

5. MODEL PREDICTIVE CONTROL

Control algorithms for glucose regulation in people with type 1 diabetes must be able to handle intra- and inter-patient variability. In addition, the controller must administer insulin in a safe way to minimize the risk of hypoglycemia. Due to the nonlinearity in the glucose-insulin interaction, the risk of hypoglycemic episodes as consequence of 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 4.2. 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 (21) provides feedback from the CGM, y_k, and the open-loop optimal control problem solved in each sample interval is the convex quadratic program

$$\min_{\{\hat{u}_{k+j|k}, \hat{v}_{k+j+1|k}\}_{j=0}^{N-1}} \quad \phi \tag{23a}$$

$$s.t. \quad (22) \tag{23b}$$
$$u_{\min} \leq \hat{u}_{k+j|k} \leq u_{\max} \tag{23c}$$
$$\hat{y}_{k+j+1|k} \geq y_{\min} - \hat{v}_{k+j+1|k} \tag{23d}$$
$$\hat{v}_{k+j+1|k} \geq 0 \tag{23e}$$

with the objective function ϕ defined as

$$\phi = \frac{1}{2}\sum_{j=0}^{N-1} \|\hat{y}_{k+j+1|k} - \hat{r}_{k+j+1|k}\|_2^2 + \lambda\|\Delta\hat{u}_{k+j|k}\|_2^2 + \kappa\|\hat{v}_{k+j+1|k}\|_2^2 \tag{24}$$

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 (23) is similar to the insulin profile of the infinite horizon optimal control problem, (23) 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. $\lambda\|\Delta u_{k+j|k}\|_2^2$ is a regularization term that prevents the insulin infusion rate from varying too aggressively. For the simulations, we set

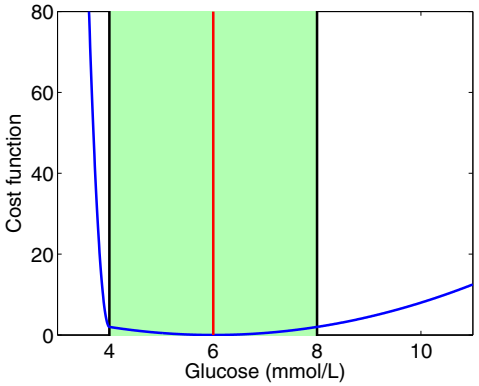

Fig. 3. The penalty function $\rho = \|y - r\|_2^2 + \kappa\|\min\{y - y_{\min}, 0\}\|_2^2$.

$\lambda = 100/u_{ss}^2$. The soft output constraint (23d) penalizes glucose values below 4 mmol/L. Since hypoglycemia is highly undesirable, we choose the weight on the soft output constraint to be rather high, i.e. $\kappa = 100$. The penalty function profile is illustrated in Fig. 3.

To prevent 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

$$u_{\max} = \begin{cases} 1.5u_{ss} & 4 \leq y_k \leq \infty \\ u_{ss} & 0 \leq y_k \leq 4 \\ 0.5u_{ss} & -\infty \leq y_k \leq 0 \end{cases} \tag{25}$$

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

Garcia-Gabin et al. (2008) and Eren-Oruklu et al. (2009) 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

$$\hat{r}_{k+j|k}(t) = \begin{cases} y_k \exp\left(-t_j/\tau_r^+\right) & y_k \geq 0 \\ y_k \exp\left(-t_j/\tau_r^-\right) & y_k < 0 \end{cases} \tag{26}$$

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.

6. COMPARISON BETWEEN ARIMAX, ARMAX AND ADAPTIVE ARMAX MODEL STRUCTURES

In this section we compare three different versions of our Model Predictive Controller on a cohort of 100 virtual

Table 2. 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

patients. These three versions are the ARIMAX formulation presented in Section 4.1, the ARMAX formulation presented in Section 4.2 and the adaptive ARMAX model formulation presented in Section 4.3. 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.

The MPC is individualized using the insulin basal rate (u_{ss}), the insulin sensitivity factor (ISF), and the insulin action time 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 Boiroux et al. (2011). The glucose level 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:

- The patient arrives at the clinic at 17:00. The Kalman filter (22) is activated.
- The patient gets a 75 g CHO dinner and an insulin bolus at 18:00.
- The closed loop starts at 22:00. In addition to the Kalman filter, the MPC is activated.
- The patient gets a 60 g CHO breakfast and an insulin bolus at 08:00. The controller is switched off.

6.1 Underbolused meal

Fig. 4 shows the Control Variability Grid Analysis (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.

Table 2 shows the time spent in the euglycemic range, hypoglycemia and hyperglycemia for the three different strategies in the case where only 50% of the meal bolus is administered at mealtime. 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.

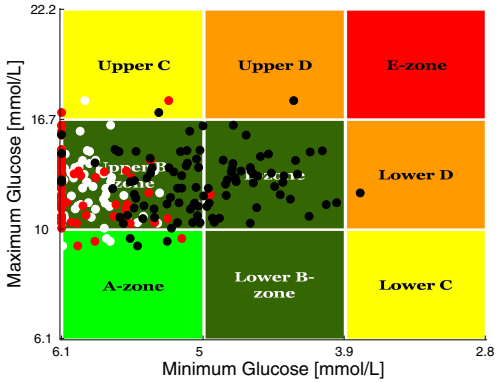

Fig. 4. Control Variability Grid Analysis (CVGA) plot for the three different stochastic model structures. 50% of the meal bolus is administered at mealtime. Black: ARIMAX. Red: ARMAX. White: Adaptive ARMAX.

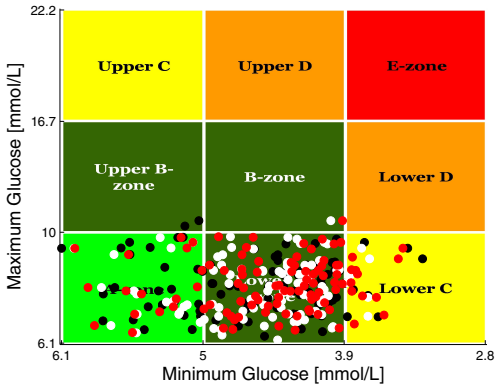

Fig. 5. Control Variability Grid Analysis (CVGA) plot for the three different stochastic model structures in the case where the insulin sensitivity is increased by 30% during the night. Black: ARIMAX. Red: ARMAX. White: Adaptive ARMAX.

6.2 Change in insulin sensitivity

Fig. 5 shows the CVGA plot for the three different strategies for the case where the insulin sensitivity is increased by 30% during the night. Table 3 shows the time spent in the euglycemic range, hypoglycemia and hyperglycemia for the three different strategies in the case where the insulin sensitivity is increased by 30% during the night. The control strategies based on an ARMAX model structure, i.e. the controllers without the integrator, reduces the occurrences of hypoglycemia, and avoid severe hypoglycemia (i.e. glucose values below 3.5 mmol/L).

7. CONCLUSION

This paper presents subject-specific control strategies designed for overnight stabilization of blood glucose in people with type 1 diabetes. This controller is tested on 100 virtual patients with a representative parameter distribution, where we simulate an underbolused meal or an insulin sensitivity variation. The choice of the model structure for the stochastic part is a tradeoff between offset-free control and model-plant mismatch. In our case, the ARMAX and

Table 3. Evaluation of the controller for the different control strategies in the case where 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

the adaptive ARMAX formulations presented in this paper have the potential to improve the controller performance, but the method would need a further investigation before being tested on real patients.

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