Overnight Control of Blood Glucose in People with Type 1 Diabetes

Dimitri Boiroux [*] **Anne Katrine Duun-Henriksen** [*]
Signe Schmidt [***] **Kirsten Nørgaard** [***] **Sten Madsbad** [***]
Ole Skyggebjerg [****] **Peter Ruhdal Jensen** [**]
Niels Kjølstad Poulsen [*] **Henrik Madsen** [*]
John Bagterp Jørgensen [*]

[*] *DTU Informatics, Technical University of Denmark, Denmark*
[**] *DTU Systems Biology, Technical University of Denmark, Denmark*
[***] *Dept. of Endocrinology, Hvidovre Hospital, Denmark*
[****] *Horus ApS, Copenhagen, Denmark*

Abstract:
In this paper, we develop and test a Model Predictive Controller (MPC) for overnight stabilization of blood glucose in people with type 1 diabetes. The controller uses glucose measurements from a continuous glucose monitor (CGM) and its decisions are implemented by a continuous subcutaneous insulin infusion (CSII) pump. Based on a priori patient information, we propose a systematic method for computation of the model parameters in the MPC. Safety layers improve the controller robustness and reduce the risk of hypoglycemia. The controller is evaluated in silico on a cohort of 100 randomly generated patients with a representative inter-subject variability. This cohort is simulated overnight with realistic variations in the insulin sensitivities and needs. Finally, we provide results for the first tests of this controller in a real clinic.

1. INTRODUCTION

People with type 1 diabetes need several blood measurements and insulin injections per day to regulate their blood glucose properly. Too small doses of insulin result in high blood glucose (hyperglycemia), which has long-term complications such as nerve diseases, kidney diseases, and blindness. In contrast, too high doses lead to low blood glucose (hypoglycemia) with immediate adverse effects such as seizure, coma or even death.

Closed-loop control of blood glucose, also known as the artificial pancreas (AP), has been suggested to overcome the burden and complications associated with management of the blood glucose level in people with type 1 diabetes. An AP using subcutaneous (sc) measurements and subcutaneous delivery consists of a continuous glucose monitor (CGM), a control algorithm, and a continuous subcutaneous insulin infusion (CSII) pump. Fig. 1 illustrates the principal components of an AP. It has been a subject of interest for almost 40 years (Albisser et al. (1974)) and is still an active field of research (Cobelli et al. (2011), Nicolao et al. (2011)).

Model Predictive Control is a useful control method for the AP due to its ability to handle constraints and out-of-zone glucose levels in a systematic and proactive fashion. Prototypes of AP using MPC have been successfully tested both in silico (Magni et al., 2009) and in vivo (Hovorka et al., 2010).

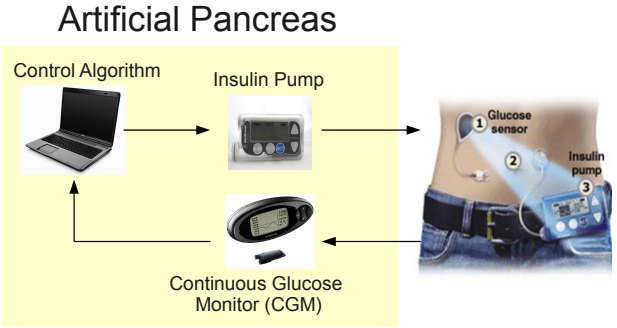

Fig. 1. Closed-loop glucose control. Glucose is measured subcutaneously using a continuous glucose monitor (CGM). Insulin is dosed by an insulin pump.

In this paper we implement an AP using a CGM for glucose feedback, an insulin pump and a control algorithm based on MPC. We present a method exploiting a priori available patient information for computing a personalized set of model parameters. In the considered setup, the patient information required by the controller is: The basal insulin infusion rate, the insulin sensitivity factor (also called the correction factor), and the insulin action time. Safety layers limit the occurrence of hypoglycemic events. The controller is tested in silico on a cohort of 100 patients. We simulate an overnight clinical trial and induce realistic variations in insulin needs. We also present glucose and

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Corresponding author: J.B. Jørgensen, jbj@imm.dtu.dk

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_{IT}^f	min^{-1}/(mU/L)	$S_{IT}^f \sim N(51.2, 32.09^2)$
S_{ID}^f	min^{-1}/(mU/L)	$S_{ID}^f \sim N(8.2, 7.84^2)$
S_{IE}^f	L/mU	$S_{IE}^f \sim N(520, 306.2^2)$
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	$\exp(V_G) \sim N(\ln(0.15), 0.23^2)$
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	$BW \sim U(65, 95)$

insulin profiles from an initial test of the controller in a real clinic.

This 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. Section 3 presents a procedure for computation of the MPC model parameters from prior patient information. Section 4 describes the controller. In Section 5 we evaluate and discuss the controller performance on a cohort of 100 patients and provide in vivo test results. Conclusions are provided in Section 6.

2. PHYSIOLOGICAL MODELS FOR PEOPLE WITH TYPE 1 DIABETES

Several physiological models have been developed to simulate virtual patients with type 1 diabetes (Hovorka et al. (2004); Bergman et al. (1981); Dalla Man et al. (2007)). 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 people with type 1 diabetes. Using the parameters and distribution provided in Hovorka et al. (2002) and Wilinska et al. (2010), we generate a cohort of 100 patients. These parameters and their distribution are summarized in Table 1.

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. The second part models non-Gaussian sensor noise.

3. PREDICTION OF SUBCUTANEOUS GLUCOSE

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. The prediction model is an autoregressive integrated moving average with exogenous input (ARIMAX) model

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

The ARIMAX model structure is used do have offset free control when the filter and predictor of this model are used in an MPC. A and B are individualized and derived from known patient information. C is identified from data for one real patient and this C is used for the cohort of virtual and real patients. This model identification technique turns out to give a good compromise between data requirements, performance and robustness of the resulting controller for the overnight study described in this paper.

3.1 Deterministic Model

All the physiological models presented in Section 2 contain a large number of parameters, and even the minimal model developed by Bergman et al. (1981) may be difficult to identify (Pillonetto et al., 2003). 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 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

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

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 (2). 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. These parameters 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.

In the temporal domain, the impulse response of (2) is described by

$$y(t) = K_u \frac{t}{\tau^2} \exp(-t/\tau) \tag{3}$$

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 (3) and the fact that the insulin sensitivity factor is equal to the minimal blood glucose (sc glucose), $y(\tau) = -ISF$, such that

$$K_u = -\tau \exp(1) ISF \tag{4}$$

Using a zero-order-hold insulin profile, the continuous-time transfer function (2) may be used to determine the A and B polynomials in the ARIMAX model (1). They are

$$A(q^{-1}) = 1 + a_1 q^{-1} + a_2 q^{-2} \tag{5a}$$
$$B(q^{-1}) = b_1 q^{-1} + b_2 q^{-2} \tag{5b}$$

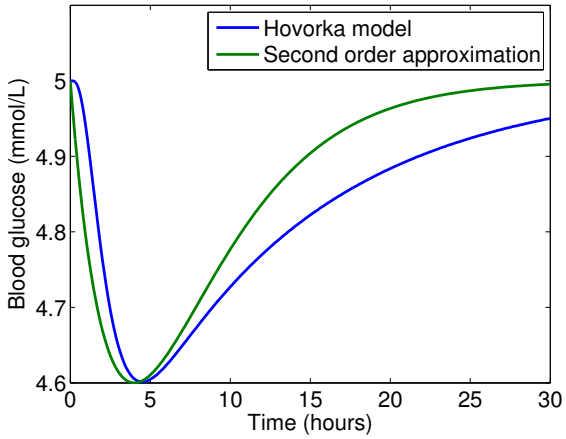


Fig. 2. Impulse responses for a second order model and the nonlinear Hovorka model. The bolus size is 0.1U and the parameters for the second order model are: τ=4 hours and $ISF = 0.4$ mmol/L/0.1 U $= 4.0$ mmol/L/U.

with the coefficients a_1, a_2, b_1 and b_2 computed as

$$a_1 = -2\exp(-T_s/\tau) \tag{6a}$$
$$a_2 = \exp(-2T_s/\tau) \tag{6b}$$
$$b_1 = K_u(1 - \exp(-T_s/\tau)(1 + T_s/\tau)) \tag{6c}$$
$$b_2 = K_u \exp(-T_s/\tau)(-1 + \exp(-T_s/\tau) + T_s/\tau) \tag{6d}$$

T_s is the sample time.

Fig 2 depicts the impulse response for a virtual patient with type 1 diabetes and its second order approximation (2). 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 patient with type 1 diabetes.

3.2 Stochastic Model

The stochastic part, $C(q^{-1})$, of the ARIMAX model (1) is assumed to be a third order polynomial of the form

$$\begin{aligned} C(q^{-1}) &= 1 + c_1 q^{-1} + c_2 q^{-2} + c_3 q^{-3} \\ &= (1 - \alpha q^{-1})(1 - \beta_1 q^{-1})(1 - \beta_2 q^{-1}) \end{aligned} \tag{7}$$

$\alpha = 0.99$ is a fixed parameter. It has been determined based on performance studies of the resulting MPC. β_1 and β_2 are determined from clinical data for one real patient (Boiroux et al., 2012).

We compute β_1 and β_2 by estimating the process and measurement noise characteristics, σ and r, in the following continuous-discrete stochastic linear model

$$dx(t) = (A_c x(t) + B_c u(t))dt + \sigma d\omega(t) \tag{8a}$$
$$y_k = h(t_k, x(t_k)) + v_k \tag{8b}$$

A_c and B_c are realizations of (2). $\omega(t)$ is a standard Wiener process. The matrix σ is time-invariant and 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 (Kristensen et al., 2004; Jørgensen and Jørgensen, 2007). By zero-order hold (zoh) discretization, Kalman filter design, and z-transformation, (8) may be represented as

$$y_k = G(q^{-1})u_k + H(q^{-1})\epsilon_k \tag{9}$$

with

$$G(q^{-1}) = B(q^{-1})/A(q^{-1}) \tag{10a}$$
$$H(q^{-1}) = \tilde{C}(q^{-1})/A(q^{-1}) \tag{10b}$$

The parameters, β_1 and β_2, in

$$\tilde{C}(q^{-1}) = (1 - \beta_1 q^{-1})(1 - \beta_2 q^{-1}) \tag{11}$$

are extracted from $H(q^{-1})$. The coefficients β_1 and β_2 computed in this way are $\beta_{1,2} = 0.81 \pm 0.16i$.

The difference equation (9) corresponding to the SDE (8) is related to the ARIMAX model (1) by

$$\epsilon_k = \frac{1 - \alpha q^{-1}}{1 - q^{-1}} \varepsilon_k \tag{12}$$

This specification introduces a model-plant mismatch. ϵ_k is white noise in (9) while (12) models ϵ_k as filtered integrated white noise. This model-plant mismatch is necessary to have offset free control in the resulting predictive control system. (12) implies that

$$C(q^{-1}) = (1 - \alpha q^{-1})\tilde{C}(q^{-1}) \tag{13}$$

such that $c_1 = -2.61$, $c_2 = 2.28$ and $c_3 = -0.67$.

3.3 Realization and Predictions with ARIMAX Models

The ARIMAX model (1) with A, B and C given by (5) and (7) may be represented as a discrete-time state space model in innovation form

$$x_{k+1} = Ax_k + Bu_k + K\varepsilon_k \tag{14a}$$
$$y_k = Cx_k + \varepsilon_k \tag{14b}$$

with the observer canonical realization

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

The innovation of (14) is

$$e_k = y_k - C\hat{x}_{k|k-1} \tag{15}$$

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

$$\hat{x}_{k+1|k} = A\hat{x}_{k|k-1} + B\hat{u}_{k|k} + Ke_k \tag{16a}$$
$$\hat{x}_{k+1+j|k} = A\hat{x}_{k+j|k} + B\hat{u}_{k+j|k}, \quad j = 1, \ldots, N-1 \tag{16b}$$
$$\hat{y}_{k+j|k} = C\hat{x}_{k+j|k}, \quad j = 1, \ldots, N \tag{16c}$$

The innovation (15) and the predictions (16) constitute the feedback and the predictions in the model predictive controller.

4. 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 administrate 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 3. 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 (15) provides feedback from the CGM, y_k, and the open-loop optimal control problem solved in each sample interval is the convex quadratic program

$$\min_{\{\hat{u}_{k+j|k},\hat{v}_{k+j+1|k}\}_{j=0}^{N-1}} \phi \tag{17a}$$

$$s.t. \quad (16) \tag{17b}$$

$$u_{\min} \leq \hat{u}_{k+j|k} \leq u_{\max} \tag{17c}$$

$$\hat{y}_{k+j+1|k} \geq y_{\min} - \hat{v}_{k+j+1|k} \tag{17d}$$

$$\hat{v}_{k+j+1|k} \geq 0 \tag{17e}$$

with the objective function ϕ defined as

$$\begin{aligned}\phi =& \frac{1}{2}\sum_{j=0}^{N-1} \|\hat{y}_{k+j+1|k} - \hat{r}_{k+j+1|k}\|_2^2 \\ &+ \lambda\|\Delta\hat{u}_{k+j|k}\|_2^2 + \kappa\|\hat{v}_{k+j+1|k}\|_2^2\end{aligned} \tag{18}$$

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 (17) is similar to the insulin profile of the infinite horizon optimal control problem, (17) 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 and the in vivo clinical studies we set $\lambda = 100/u_{ss}^2$. The soft output constraint (17d) 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. $\kappa = 100$.

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

$$u_{\max} = \begin{cases} 1.5u_{ss} & 4 \leq y_k \leq \infty \\ u_{ss} & 0 \leq y_k \leq 4 \\ 0.5u_{ss} & -\infty \leq y_k \leq 0 \end{cases} \tag{19}$$

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.

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

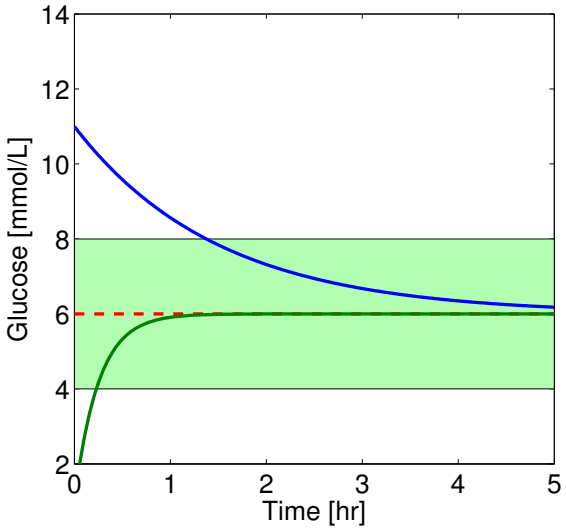


Fig. 3. Time-varying reference signals for glucose above (blue curve) and below (green curve) the target of 6 mmol/L.

$$\hat{r}_{k+j|k}(t) = \begin{cases} y_k \exp\left(-t_j/\tau_r^+\right) & y_k \geq 0 \\ y_k \exp\left(-t_j/\tau_r^-\right) & y_k < 0 \end{cases} \tag{20}$$

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 3 provides an illustration of the time-varying reference signal.

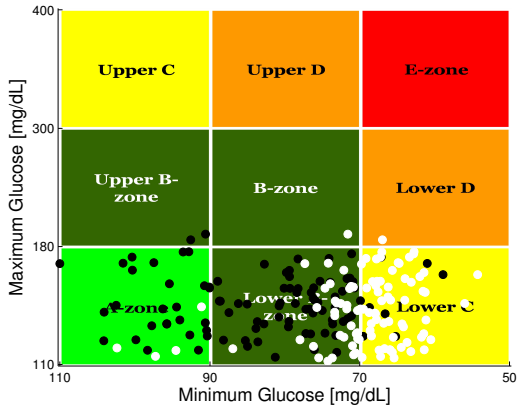
5. NUMERICAL RESULTS AND DISCUSSION

In this section we discuss the performance of the MPC for a randomly generated cohort of 100 patients. The 100 patients are generated from the probability distribution presented in Section 2. We compare the performance of the controller with simulated conventional insulin therapy in which the basal insulin infusion rate remains constant during the night. Variations in metabolism and insulin need is simulated by a sudden change in the insulin sensitivity parameters of the Hovorka model.

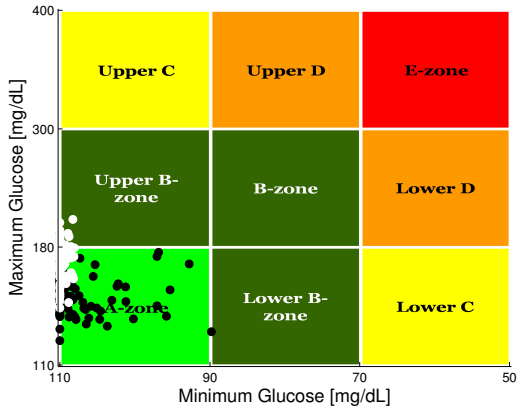
The clinical protocol for the 100 in silico patients is:

- The patient arrives at the clinic at 17:00.
- The patient gets a 75 g CHO dinner and an insulin bolus at 18:00.
- The closed loop starts at 22:00.
- The insulin sensitivity is modified by ±30% at 01:00.
- The patient gets a 60 g CHO breakfast and an insulin bolus at 08:00. The controller is switched off.

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

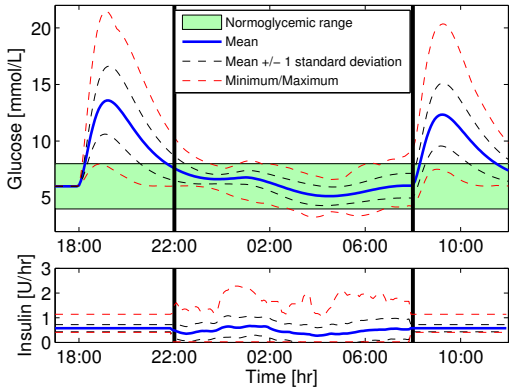


(a) Insulin sensitivity increases by 30%



(b) Insulin sensitivity decreases by 30%

Fig. 4. CVGA (Magni et al. (2008)) plot of the 100 in silico patients. White: Without MPC. Black: With MPC.



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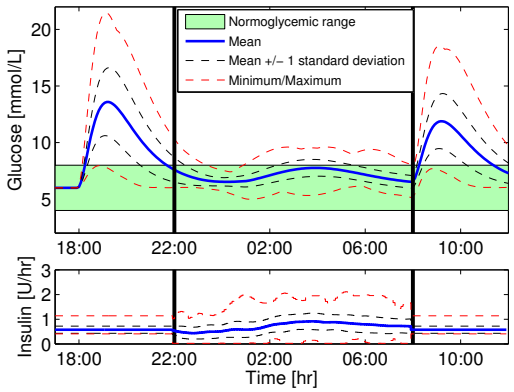

(b) Insulin sensitivity decreases by 30%

Fig. 5. Glucose and insulin profiles envelopes. Closed-loop control takes place between the 2 vertical black lines.

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 is provided to the controller every 5 minutes by a noise-corrupted CGM. The pump insulin infusion rate is changed every 5 minutes.

Fig. 4 shows the control variability grid analysis (CVGA) of the period between 22:00 and 08:00 for the case without MPC (white circles) and the case with MPC (black circles). In Fig. 4(a) we depict the case where the insulin sensitivity is increased by 30%, and in Fig. 4(b) we depict the case where the insulin sensitivity is decreased by 30%. These figures show that our control algorithm reduces the risk of nocturnal hypoglycemia. Although the improvement is less significant, they also show that it can slightly reduce the risk of nocturnal hyperglycemia. Fig. 5 depicts the mean, standard deviation and minimum/maximum blood glucose and insulin profiles for the closed-loop simulations. In the case where insulin sensitivity is increased by 30% (Fig. 4(a) and 5(a)), mild hypoglycemic events occur for some of the patients. However, no severe hypoglycemia (i.e. blood glucose concentrations below 50 mg/dL) is observed, and the choice of the tuning parameters in the controller allows for a fast recovery. In the case where insulin sensitivity is decreased by 30% (Fig. 4(b) and 5(b)), all the patients are well controlled during the study period.

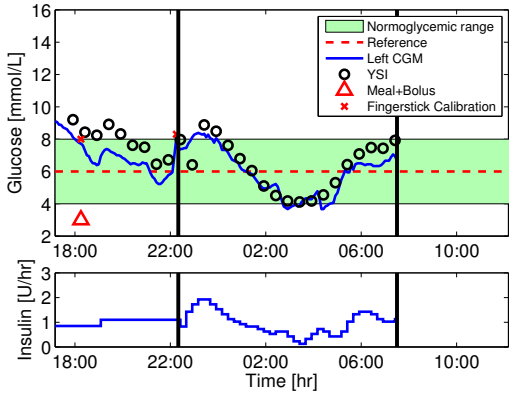

Fig. 6. Glucose and insulin profiles for an in vivo clinical study. Glucose input is provided by a CGM (blue curve). Closed-loop control takes place between the 2 vertical black lines.

Fig. 6 illustrates the glucose and insulin profiles for a real clinical test of the MPC. The glucose input is provided by a CGM (blue curve). Actual blood glucose measurements are provided by a glucose analyzer of blood samples (YSI). Although a mild hyperglycemic event occurred at approximately 23:00 and a few CGM values are below

4 mmol/L at approximately 03:00 and 04:00, this study shows the capability of the controller to stabilize blood glucose during the study night. Currently, the controller is being tested in a real clinical study.

6. CONCLUSION

This paper presents a subject-specific MPC controller designed for overnight stabilization of blood glucose in people with type 1 diabetes. The model parameters in the MPC are personalized based on easily available patient information. The main advantage of this method is its ease of implementation in real clinical studies due to the moderate model parameter requirement. The design of the controller allows for both a conservative control strategy in case of high glucose values, and a more aggressive control strategy in case of low glucose values. The controller is tested in silico on a cohort of 100 patients with temporal insulin sensitivity variations. A single test study from a real clinic is also presented. The proposed MPC is able to stabilize blood glucose overnight and reduces the risk of nocturnal hypoglycemia and hyperglycemia.

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