Control of Blood Glucose for People with Type 1 Diabetes: an in Vivo Study

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Abstract:
Since continuous glucose monitoring (CGM) technology and insulin pumps have improved recent years, a strong interest in a closed-loop artificial pancreas for people with type 1 diabetes has arisen. Presently, a fully automated controller of blood glucose must face many challenges, such as daily variations of patient's physiology and lack of accuracy of glucose sensors. In this paper we design and discuss an algorithm for overnight closed-loop control of blood glucose in people with type 1 diabetes. The algorithm is based on Model Predictive Control (MPC). We use an offset-free autoregressive model with exogenous input and moving average (ARMAX) to model the patient. Observer design and a time-varying glucose reference signal improve robustness of the algorithm. We test the algorithm in two clinical studies conducted at Hvidovre Hospital. The first study took place overnight, and the second one took place during daytime. These trials demonstrate the importance of observer design in ARMAX models and show the possibility of stabilizing blood glucose during the night.

1. INTRODUCTION

Type 1 diabetes is a disease caused by destruction of the insulin producing beta-cells in the pancreas. Therefore, patients with type 1 diabetes must rely on exogenous insulin administration in order to tightly regulate their blood glucose. Blood glucose should preferably be kept in the range 4.0-8.0 mmol/l. Long periods of high blood glucose (hyperglycemia) can lead to long-term complications like nerve diseases, kidney diseases, or blindness. However, the dosing of insulin must be done carefully, because a too high dosage of insulin may lead to a too low blood glucose (hypoglycemia). Low blood glucose has immediate effects, such as coma or even death.

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. The slow acting insulin is used to counteract the continuous glucose production from the liver. The fast acting insulin compensates the intake of carbohydrates (CHO) during the meals. The decision on the dosage of short and fast acting insulin is based on several blood glucose measurements per day.

However, an increasing number of patients with type 1 diabetes use an intensive insulin therapy based on continuous glucose monitors (CGMs) and insulin pumps instead of the conventional therapy described above. This regime can reduce the risk of complications. CGMs can provide more frequent blood glucose measurements. In addition, insulin pumps can adjust to daily variations in insulin needs.

Nevertheless, the patients still need to be constantly involved in their decisions on the insulin treatment based on their CGMs and/or fingersticks measurements. A system consisting of a CGM, an insulin pump and a control algorithm that computes the insulin dose based on glucose measurements is called an artificial pancreas. The artificial pancreas provides closed-loop control of the blood glucose by manipulation of the insulin injection. The artificial pancreas has the potential to ease the life and reduce complications for people with type 1 diabetes. Its principle is illustrated in Fig. 1. Several review papers about closed-loop control of blood glucose for people with type 1 diabetes have been published (Hovorka et al. (2006), Cobelli et al. (2011), Bequette (2011)).

Previous publications have proven that model predictive control (MPC) has great potential for design of an artificial pancreas. Magni et al. (2009) established that MPC could reduce oscillatory behaviors compared to proportional integral derivative (PID) controllers. Boiroux et al. (2010) applied open-loop constrained nonlinear optimal control. Hovorka et al. (2010) tested an MPC-based controller on children and adolescents with type 1 diabetes.

In this paper we focus on overnight blood glucose control for people with type 1 diabetes using a CGM, an insulin
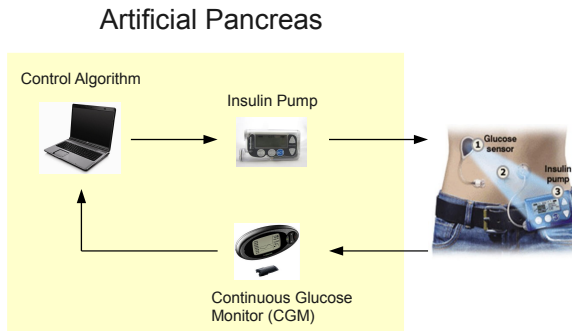
Artificial Pancreas

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

Fig. 2. Picture of the pilot trial.

pump, and a controller based on MPC. Many factors, such as meal intake, physical exercise, stress, illness, alcohol consumption etc. affect insulin needs. Also, hormone release during the night may cause elevated blood glucose in the early morning. This particular phenomenon is called the dawn phenomenon. The main goal of a closed-loop controller is to compensate these effects by adjusting the amount of injected insulin based on frequent glucose measurements coming from a CGM.

The paper is structured as following. Section 2 describes the material and methods used for the studies. We discuss the design of the controller in Section 3. Section 4 shows the results for the two clinical studies conducted at Hvidovre Hospital. Conclusions are provided in Section 5.

2. METHODS AND MATERIAL

This section describes the clinical protocol and the internally developed graphical user interface for the clinical studies.

2.1 Clinical protocol

The clinical trial consists of a randomized cross-over study including 12 patients with type 1 diabetes. The goal is to compare overnight glucose control during open-loop and closed-loop insulin administration. We investigate the cases where
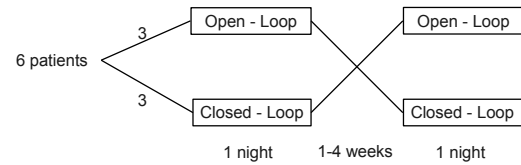

Fig. 3. Study design.

- The insulin bolus matches the evening meal (6 patients in total)
- The insulin bolus is underdosed (6 patients in total)

The study design for the 2 cases is illustrated in Fig. 3.

The scenario during the clinical studies is the following:

- The patient arrives at 16:00.
- A meal is consumed at 18:00 and an insulin bolus is administrated. The meal size is determined by the weight of the patient. The bolus size depends on the patient and the scenario (meal with the correct bolus or underbolused meal).
- The loop is closed at 22:00 (for closed-loop studies only).
- The closed-loop ends at 07:00 the following day (for closed-loop studies only).

The purpose of the first part of the study (when the insulin bolus matches the evening meal) is to validate the ability of the controller to compensate for overnight physiological changes in patients. The second part of the study (when meals are underbolused) must ensure that the controller can bring and keep blood glucose in the range 4.0-8.0 mmol/L.

The patient is equipped with 2 Dexcom Seven Plus CGMs and a Medtronic Paradigm insulin pump. The CGMs provide glucose measurements every 5 minutes. The clinician decides on the sensor used by the controller, based on the accuracy of the sensor during the days before the study. The other CGM can be used as a backup device. Insulin is administrated to the patient through small discrete insulin injections (also called microboluses) every 15 minutes.

It must be pointed out that the pump used for the trials has discrete increments of 0.025U for the microboluses, and a minimum continuous insulin injection (or basal rate) of 0.025 U/hr. The controller handles these restrictions by using hard constraints on the minimal insulin infusion rate and by rounding the suggested microbolus to the nearest 0.025U (see Section 3.6).

In addition, blood samples are taken every 30 minutes in order to measure more accurately the blood glucose (in case of prolonged period of low blood glucose, the sampling time is set to 15 minutes). The blood glucose was measured by Hemocue and after the trial by YSI. These values are not provided to the controller.

The clinician has the authority to prevent severe hypoglycemia by injection of intravenous glucose. Such a decision is based on the glucose history.
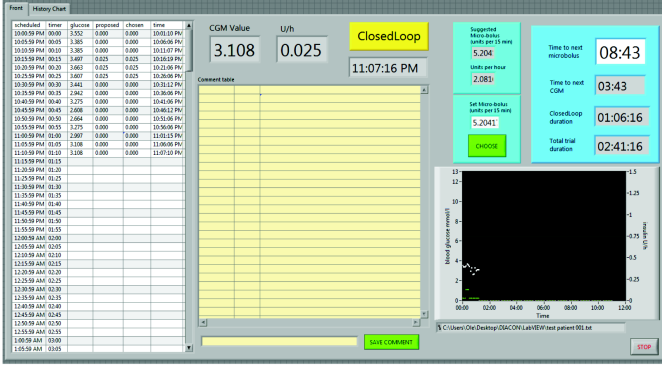
Fig. 4. Graphical User Interface screenshot

2.2 Graphical User Interface

Fig 4 provides an overview of the graphical user interface developed for the artificial pancreas. The glucose sensor provides a glucose measurement every 5 minutes. The glucose measurements are transmitted from the sensor to the software via a wireless receiver.

The graphical user interface returns a new insulin microbolus suggestion every 15 minutes. At these times, it also returns the glucose prediction and insulin prediction profiles. The decision on the insulin microbolus can be overruled if there is a safety risk for the patient. The exact time before the next microbolus suggestion is provided by the graphical user interface.

It is also possible to add comments if necessary. These comments have no influence on the microboluses computation, but are stored.

3. CONTROLLER DESIGN

This section presents the detailed description of the controller. The controller computes a discrete-time offset-free ARMAX model. This model is then used to optimize the future injections of insulin. The controller must be designed in a robust and safe way for the patient, especially regarding low blood glucose. We use here a time-varying glucose setpoint to avoid insulin overdose.

3.1 Model computation

Several research groups investigated low-order models to describe glucose-insulin dynamics. Kirchsteiger et al. (2011) used a third order transfer function, Finan et al. (2009) identified ARX models and Percival et al. (2010) applied a first order transfer function with a delay. In this paper we use a Single Input-Single Output (SISO) second order continuous-time transfer function

$$Y(s) = G(s)U(s), \quad G(s) = \frac{K}{(\tau s + 1)^2} \qquad (1)$$

The input $U(s)$ is the insulin intake and the output $Y(s)$ is the blood glucose, both expressed in terms of deviation variables from a steady state, K is the static gain and τ is the time constant. The gain and the time constant are computed from known patient-specific parameters. These parameters are the insulin action time and the insulin

sensitivity factor (ISF). They can be estimated for each individual patient by looking at the impulse response for a small insulin bolus. The insulin action time τ corresponds to the time that blood glucose takes to reach its minimum. The insulin sensitivity factor (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. However, these parameters may dramatically vary from day to day for a given patient.

The impulse response in the temporal domain of the transfer function (1) is

$$y(t) = K \frac{t}{\tau^2} \exp(-t/\tau) \qquad (2)$$

We shall now relate the insulin sensitivity factor and the insulin action time to the gain K and the time constant τ in (2). The insulin action time corresponds to the time to reach the minimum blood glucose, it is therefore equal to τ. We find K by computing the output of the impulse response (2) at its minimum, i.e. at time $t = \tau$. It gives

$$y(\tau) = -I_{SF} = \frac{K}{\tau} \exp(-1) \qquad (3)$$

Isolating K in the above equation yields to

$$K = -\tau \exp(1) I_{SF} \qquad (4)$$

The transfer function (1) can be reformulated as a discrete-time transfer function model in the form

$$y(t) = G(q^{-1})u(t), \quad G(q^{-1}) = \frac{\bar{B}(q^{-1})}{\bar{A}(q^{-1})} \qquad (5)$$

which is equivalent to

$$\bar{A}(q^{-1})y(t) = q^{-n_k}\bar{B}(q^{-1})u(t) \qquad (6)$$

$\bar{A}(q^{-1})$ and $\bar{B}(q^{-1})$ are

$$\bar{A}(q^{-1}) = 1 + \bar{a}_1 q^{-1} + \bar{a}_2 q^{-2} \qquad (7a)$$
$$\bar{B}(q^{-1}) = \bar{b}_1 q^{-1} + \bar{b}_2 q^{-2} \qquad (7b)$$

Fig 5 depicts the exact impulse response and its second order approximation for a virtual patient. This patient is simulated using the model developed by Hovorka et al. (2004). The figure demonstrates that a second order model can provide a fairly good approximation of a patient with type 1 diabetes. Current insulin, such as the Novorapid insulin documented in Nov (2002) has a similar impulse response shape, but can provide even faster action (the minimum in glucose is reached in 60-90 minutes).

3.2 Observer design for the first study

Odelson et al. (2006), Jørgensen and Jørgensen (2007) and Åkesson et al. (2008) proposed several methods for Kalman filter tuning. In our controller we use the following discrete-time, linear ARMAX model
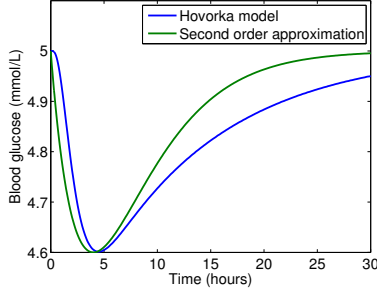
Fig. 5. Example of second order approximation compared to the exact impulse response. The bolus size is here 0.1U. The parameters are: τ=4 hours and $I_{SF} = 4$ mmol/L/U.

$$A(q^{-1})y(t) = q^{-n_k}B(q^{-1})u(t) + C(q^{-1})\varepsilon(t) \qquad (8)$$

A, B and C are polynomials, and q^{-1} is the backward shift operator. We assume that $\varepsilon(t) \sim N_{iid}(0, \sigma)$. In the first pilot study we used the following ARMAX model description

$$A(q^{-1})y(t) = B(q^{-1})u(t) + (1 - \alpha q^{-1})e(t) \qquad (9)$$

in which

$$A(q^{-1}) = (1 - q^{-1})\bar{A}(q^{-1}) \qquad (10)$$
$$B(q^{-1}) = (1 - q^{-1})\bar{B}(q^{-1}) \qquad (11)$$

The model (9) is able to provide offset-free tracking due to the integrator. The parameter $\alpha \in [0; 1]$ is a tuning parameter. $\alpha = 0$ corresponds to an integrated ARX model, while $\alpha = 1$ corresponds to an ARX model without integrator. For further details about the choice of α, see e.g. Huusom et al. (2010).

The ARX model (9) may be realized as a stationary state space model in innovation form

$$x_{k+1} = Ax_k + Bu_k + K\varepsilon_k \qquad (12)$$
$$y_k = Cx_k + \varepsilon_k \qquad (13)$$

The matrices A, B, C and K are written in the canonical form

$$
A = \begin{bmatrix} -a_1 & 1 & 0 \\ -a_2 & 0 & 1 \\ -a_3 & 0 & 0 \end{bmatrix} \quad B = \begin{bmatrix} b_1 \\ b_2 \\ b_3 \end{bmatrix}
$$
$$
K = \begin{bmatrix} -\alpha - a_1 \\ -a_2 \\ -a_3 \end{bmatrix} \quad C = \begin{bmatrix} 1 & 0 & 0 \end{bmatrix}
\qquad (14)
$$

Fig. 6 shows the glucose and insulin predictions for the first study. It can be noticed that the prediction is mostly based on the two previous observations (which show an increasing blood glucose) rather than on the global trend (which shows a decreasing blood glucose).
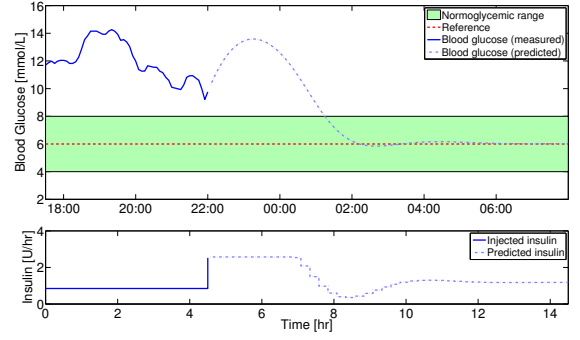

Fig. 6. Example of blood glucose prediction for the first study. It can be seen that the controller relies more on the local trend than on the global trend.

3.3 Observer design for the second study

In this section we consider the general ARMAX model (8) in which we assume

$$C(q^{-1}) = 1 + c_1 q^{-1} + c_2 q^{-2} + c_3 q^{-3} \qquad (15)$$

and

$$A(q^{-1}) = (1 - q^{-1})\bar{A}(q^{-1}) \qquad (16)$$
$$B(q^{-1}) = (1 - q^{-1})\bar{B}(q^{-1}) \qquad (17)$$

in order to preserve the offset-free control property. Therefore, the Kalman gain K in equation (14) becomes

$$
K = \begin{bmatrix} c_1 - a_1 \\ c_2 - a_2 \\ c_3 - a_3 \end{bmatrix}
\qquad (18)
$$

(the matrices A, B and C remain unchanged). The design of observer consists of setting the eigenvalues of $A - KC$. Having the eigenvalues close to 0 makes the state estimation error rapidly vanish, but on the other hand the observer will be more sensitive to noise. Having the eigenvalues close to 1 makes the observer less sensitive to noise (and therefore more relying on the global trend) but introduces a delay in the predictions. It can be shown that these eigenvalues are the roots of the polynomial

$$\chi(z) = z^3 + c_1 z^2 + c_2 z + c_3 \qquad (19)$$

$\chi(z)$ is the characteristic polynomial of $A - KC$, and the coefficients c_i, $i = 1, 2, 3$ are the same as the ones in equations (15) and (18). Let α, β_1 and β_2 be the roots of (19). We assume that $\alpha \in \mathbf{R}$, and that β_1 and β_2 are either real or complex conjugate. Furthermore, these roots must all lie inside the unit circle.

As for the first study, we fixed $\alpha = 0.99$. The choice of β_1 and β_2 has been made using data from the first pilot study. For modeling purpose, we considered the stochastic continuous-time model and measurements at discrete times, i.e.
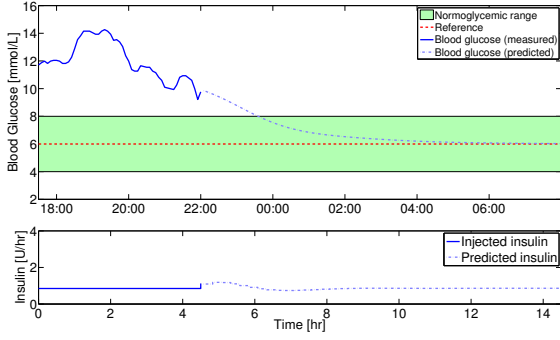
Fig. 7. Example of blood glucose prediction for the first study with the new observer. The controller is able to predict more accurately the blood glucose trend.

$$dx(t) = f(t, x(t), u(t))dt + \sigma d\omega(t) \quad (20a)$$
$$y_k = h(t_k, x(t_k)) + v_k \quad (20b)$$

$x(t)$ are the system states, $u(t)$ are the known inputs (insulin injections, meals and intravenous glucose injections) and y_k are discrete outputs (CGM measurements). The function f is a continuous-time state-space description of the transfer function (1).

We used the internally developed software "Continuous Time Stochastic Modelling" (CTSM) to estimate the variances (variance of process noise and measurement noise) with the maximum likelihood method. We took these variances to compute the predictive Kalman gain K, and hence β_1 and β_2. The computation of β_1 and β_2 yielded

$$\beta_{1,2} = 0.8078 \pm 0.1581i \quad (21)$$

These roots give

$$c_1 = -2.6056 \quad c_2 = 2.2770 \quad c_3 = -0.6708 \quad (22)$$

Fig. 7 illustrates an other example of blood glucose and insulin prediction. We have generated these prediction plots by taking the same data sequence in which we designed the observer. Unlike the previous case in Fig. 6, the controller is able to predict more accurately the blood glucose trend.

3.4 Computing the j-steps ahead predictions

If the k-th glucose measurement y_k is available, the one-step ahead prediction of the states and outputs is

$$\hat{x}_{k+1|k} = A\hat{x}_{k|k} + Bu_{k|k} + K\varepsilon_k \quad (23a)$$
$$\hat{y}_{k+1|k} = C\hat{x}_{k+1|k} \quad (23b)$$

ε_k is the innovation term

$$\varepsilon_k = y_k - C\hat{x}_{k|k-1} \quad (24)$$

In the case where the k-th glucose measurement y_k is not available, the one-step ahead prediction of the states and outputs is
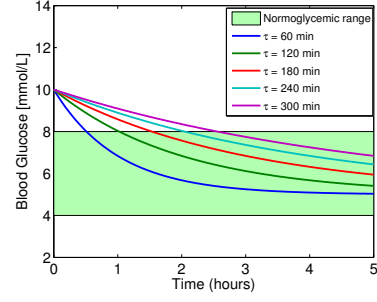

Fig. 8. Example of time-varying reference signal for different values of the time constant τ_r.

$$\hat{x}_{k+1|k} = A\hat{x}_{k|k} + Bu_{k|k} \quad (25a)$$
$$\hat{y}_{k+1|k} = C\hat{x}_{k+1|k} \quad (25b)$$

Similarly, the $j + 1$ steps ahead predictions of the states and the outputs for $j = 1, 2, ...$ are

$$\hat{x}_{k+j+1|k} = A\hat{x}_{k+j|k} + Bu_{k+j|k} \quad (26a)$$
$$\hat{y}_{k+j+1|k} = C\hat{x}_{k+j+1|k} \quad (26b)$$

3.5 Time-varying glucose setpoint

The glucose trajectory is exponentially decreasing when the blood glucose is above the target, which robustifies the controller with respect to plant-model mismatches. Consequently, the reference blood glucose is

$$\hat{r}_{k+j|k}(t) = \hat{y}_{k|k} \exp\left(-\frac{t_j}{\tau_r}\right) \quad (27)$$

The choice of the tuning parameters τ_r has an influence on the rapidness and the robustness of the controller. Small values of τ_r provide a faster return to the euglycemic range, while larger values of τ ensure a more robust control. The glucose setpoint profiles for different values of the time constant τ_r are shown in Fig. 8.

3.6 Model Predictive Control with Soft Constraints

At the time t_k, the open loop convex quadratic program solved online is

$$\min_{\{u_{k+j}, v_j\}_{j=0}^{N-1}} \phi = \frac{1}{2} \sum_{j=0}^{N-1} \|\hat{y}_{k+j+1|k} - \hat{r}_{k+j+1|k}\|_2^2 +$$
$$\lambda\|\Delta u_{k+j}\|_2^2 + \kappa\|v_{k+j}\|_2^2 \quad (28a)$$

$$s.t. \quad \hat{x}_{k+1|k} = A\hat{x}_{k|k-1} + Bu_k + Ke_k \quad (28b)$$
$$\hat{y}_{k+1|k} = C\hat{x}_{k+1|k} \quad (28c)$$
$$\hat{x}_{k+j+1|k} = A\hat{x}_{k+j|k} + Bu_k \quad (28d)$$
$$\hat{y}_{k+j+1|k} = C\hat{x}_{k+j+1|k} \quad (28e)$$
$$u_{min} \le u_{k+j} \le u_{max} \quad (28f)$$
$$G_{min} - y_{k+1} \le v_{k+j} \quad (28g)$$
$$v_j \ge 0 \quad (28h)$$

in which $\hat{x}_{k|k-1}$ and $e_k = y_k - C\hat{x}_{k|k-1}$ are given. $u_{\min}$ and $u_{\max}$ are the minimum and the maximum insulin infusion rates allowed by the pump. $\Delta u_{k+j} = u_{k+j} - u_{k+j-1}$ is the variation in the insulin infusion rate. $G_{\min}$ depicts the lower bound on blood glucose. The reference signal $\hat{r}_{k+j+1|k}$ is time-varying and its computation is given in section 3.5.

The slack variables v_j are introduced to penalize hypoglycemia. The hard input constraints (28f) limit the insulin infusion rate. The penalty term $\kappa\|v_{k+j}\|_2^2$ is used to avoid hypoglycemia and the penalty term $\lambda\|\Delta u_{k+j}\|_2^2$ prevents the insulin infusion rate from varying too aggressively.

For the study we choose $N = 120$, i.e. a 10 hour prediction horizon, and

$$u_{min} = -u_{ss} + 0.025, \quad u_{max} = u_{ss},$$
$$\lambda = \frac{10}{u_{ss}^2}, \quad \kappa = 1000 \tag{29}$$

We remind here that the input variables are deviation variables from the steady state u_{ss}. Consequently, the choice of $u_{min} = -u_{ss} + 0.025$ allows the controller to deliver the minimum basal rate (0.025U/hr), and $u_{max} = u_{ss}$ prevents the pump from overdosing the insulin. The high value of κ makes hypoglycemia undesirable.

4. STUDIES RESULTS

In this section we discuss the two studies conducted at Hvidovre Hospital on the same patient. The patient has an insulin sensitivity factor equal to 5 mmol/L/U and an insulin action time equal to 5 hours. Her basal insulin is $u_{ss} = 0.85$ U/hr.

4.1 Pilot studies results

Fig. 9 depicts the blood glucose and insulin profiles for the first pilot study. The study started at 17:30. A meal has been consumed at 18:00. An insulin overdosing led to severe hypoglycemia and an intravenous glucose injection at approximately 00:00. A microbolus decision has been overruled at 01:30.

Fig. 10 depicts the blood glucose and insulin profiles for the second pilot study. Intravenous glucose has been administrated at 10:00 and 12:00 to compensate for a too high insulin sensitivity. The sensor has to be calibrated at 12:15 and 14:45. In despite of these disturbances, the controller was able to keep the blood glucose within the range 4.0-8.0 mmol/L after the second glucose administration. In addition, the intravenous glucose is not included in the model, and therefore can be considered as an unknown disturbance. However, it can be noticed that insulin is still slightly overdosed.

5. CONCLUSION

This contribution presents a closed-loop controller for people with type 1 diabetes. We described a practical way of computing the glucose-insulin dynamics model. The controller has been tested two times on the same patient. The most noticeable difference between the two studies was the observer design. The trial results illustrated the importance of observer design in state space models in innovation form, and how modelling based on prior data can be used to design the observer. Improvements are being implemented on the controller in order to ensure a more robust control of blood glucose and avoid the observed insulin overdosing during the second pilot study.

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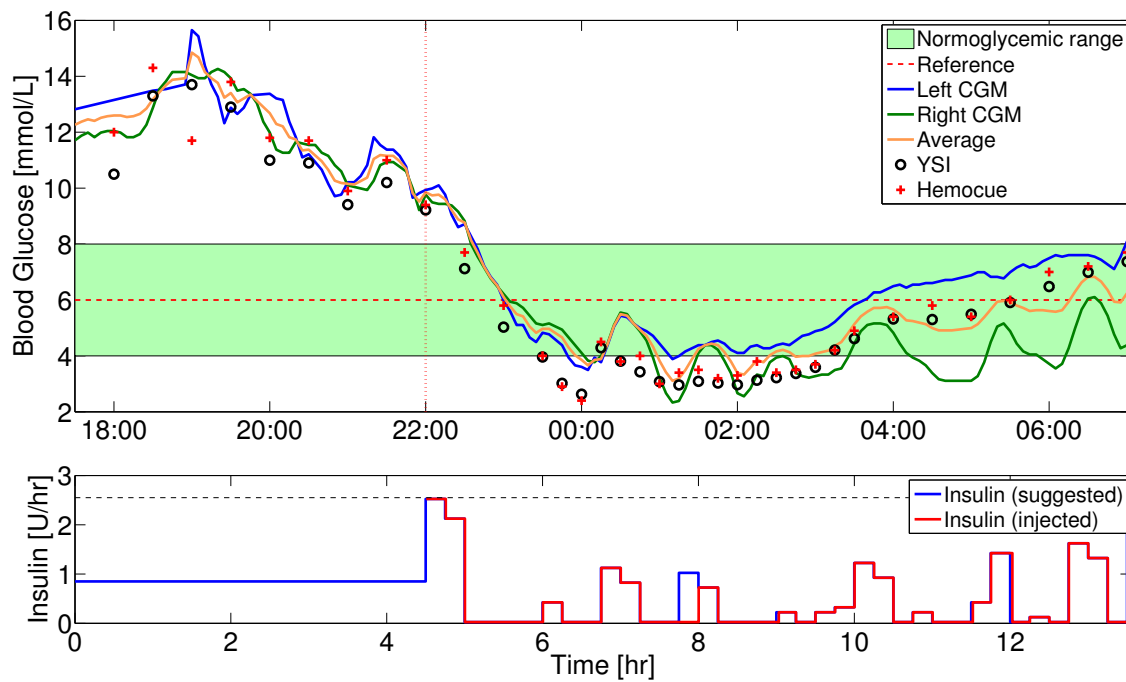
Fig. 9. Blood glucose and insulin profiles for the first pilot study. The insulin infusion rates are computed based on the right CGM (green curve).
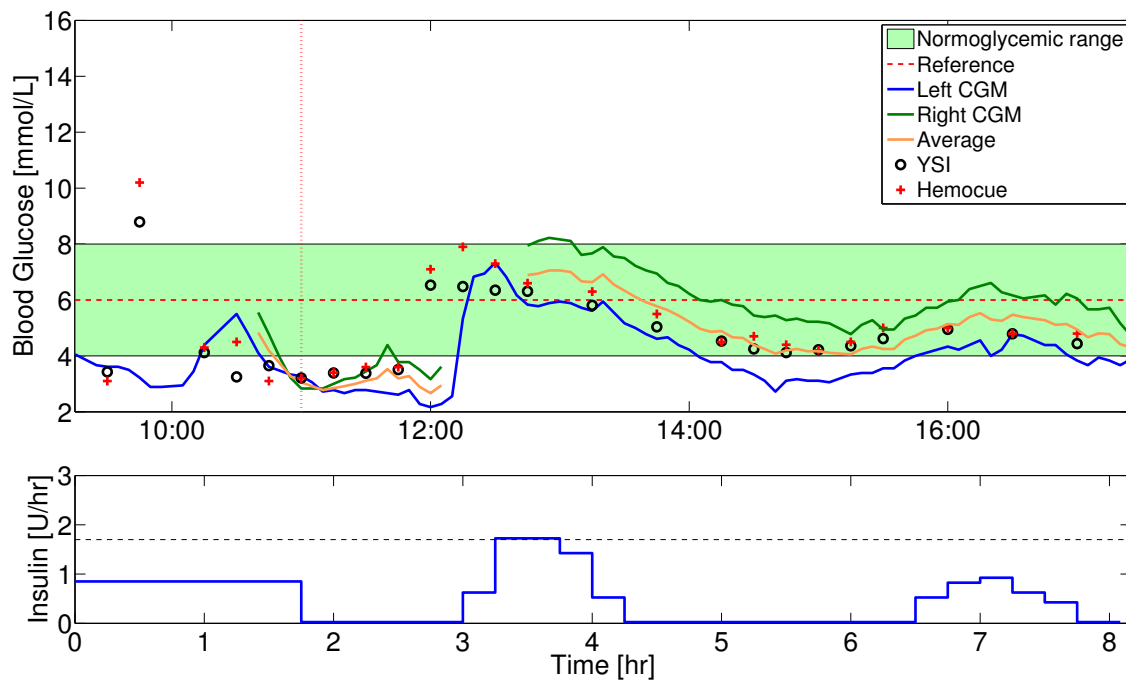

Fig. 10. Blood glucose and insulin profiles for the second pilot study. The insulin infusion rates are computed based on the left CGM (blue curve).

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