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Robust Sliding Mode Closed-loop Glucose Control with Meal Compensation in Type 1 Diabetes Mellitus ⋆

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Abstract: This work addresses the design of a robust closed-loop plasma glucose controller for Type 1 Diabetes Mellitus patients. The feedback controller is based on Sliding Mode Control (SMC) while robust feedforward boluses to compensate food intake are calculated in a robust way by means of an interval glucose predictor that minimizes the risk of hypoglycaemia. The designed controller has been validated in a virtual environment following standard protocols. The resulting control algorithm shows a considerable robustness regarding intra-patient variability in insulin sensitivity as well as an enhanced ability to handle disturbance rejection. The International Diabetes Federation guidelines for glycaemia targets in Diabetes Mellitus are fulfilled by the designed control strategy.

1. INTRODUCTION

Diabetes mellitus is a metabolic disease that is accompanied by elevated plasma glucose levels comprising all forms of acute or chronic hyperglycaemia. This is so due to the lack of insulin secretion by the β-cells in the islets of Langerhans in the pancreas (Type 1 Diabetes) or a reduction in its efficiency to promote transport of glucose into the cells (Type 2 Diabetes).

Since the Diabetes Control and Complications Trial (DCCT Research Group [1993]) euglycaemia has been established as the control objective for patients with Type 1 Diabetes, except if some contraindication exists. However, there still lacks a universal, efficient and safe system able to normalize the glucose levels of patients. The intensive insulin therapy required to achieve the glucose control objectives, based on the injection of basal and bolus insulin to "emulate" its physiological secretion, has as counteraction an increase in the risk of severe hypoglycaemia with all their consequences.

Recent advances in continuous subcutaneous (sc) glucose monitors and the generalization of the use of insulin pumps have triggered the development of the so-called artificial pancreas (Hovorka et al. [2006]). Although closed-loop control of plasma glucose has been a subject of continuous research for the last 40 years, till now no commercially available product does exist (Bequette [2005]). As insulin pumps technology is relatively mature, the primary limitations to develop such artificial pancreas are the availability of robust and precise glucose sensors and the development of reliable control algorithms.

Although several studies have demonstrated the feasibility of closed-loop insulin delivery systems (Steil et al. [2006]) no one control algorithm has shown its superiority. Several recent papers provide an overview of diabetes control strategies from the control engineering point of view, see for instance Bequette [2005], Parker et al. [2001], Hovorka [2005a], Steil et al. [2004] Doyle III et al. [2007], Hovorka [2005a], Doyle III et al. [2007], Hovorka [2005b], Galley et al. [2004], Campos-Delgado et al. [2006], Ruiz-Velazquez et al. [2004].

The main problems faced when developing control algorithms for an artificial pancreas are:

- There are many models that describe the behavior of the glucose-insulin system, from simple ones such as the so-called "minimal model" by Bergman (Bergman et al. [1979]), to very complex ones such as Sorensen's model (Sorensen [1985]); see for instance Hovorka et al. [2004], Dalla Man et al. [2007]. However, none of them can realistically describe the behavior of Type 1 Diabetes.
- Moreover, many of the model parameters are difficult or impossible to estimate for an individual. Even the simplest models present non-identifiability regions (Pillonetto et al. [2003]).
- Such a system must rely on accurate enough predictions of glycaemia. However, there exists a large intra-individual and inter-individual variability in the

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patients' behavior. Furthermore, parameters such as insulin sensitivity change along the day in individuals.
- Strong disturbances like stress, exercise or meal intake are acting on the system. In this latter case, an important source of uncertainty is the quantity of carbohydrates in the ingested food, since it is difficult to have a precise estimation of it from a mixed meal. Furthermore, it is very difficult to measure properly all these acting disturbances.

Another important limitation in the development of the artificial pancreas is that insulin delivery have the effect of lowering the glucose level and no action exist to rise it.

In this paper, a robust sliding mode closed-loop glucose controller is developed in order to guarantee safe operation regarding variability in the patient's behavior (large variations in patient's parameters like insulin sensitivity, etc.). Compensation of meal disturbances is tackled in a semi-automatic way by calculating bolus insulin doses from uncertain information by means of interval simulations (Calm et al. [2007]). This method minimizes the risk of hypoglycaemia even in case of large variations in the parameters of the patient.

Virtual patients have been widely used to test control algorithms in the field of artificial pancreas and some recent papers describe very friendly environments for such purpose (Canonico et al. [2006]). Validation protocols have also been defined for a proper validation in this context (Chassin et al. [2004]). This protocol will be followed by this work except in the case of system failures, which is out of the scope of this paper.

The paper is organized as follows: Section 2 describes the virtual patient model considered here; in Section 3, the developed closed-loop algorithm, composed of an SMC feedback loop plus an interval bolus feedforward, is designed; Section 4 presents the results and finally some conclusions are drawn in Section 5.

2. VIRTUAL PATIENT

To develop, evaluate and test the designed controller, a simulation environment is used. Simulation of an insulin therapy involves modeling subcutaneous insulin absorption, carbohydrates digestion and absorption, insulin pharmacokinetics and pharmacodynamics (PK/PD), and glucose metabolism. The relationship among these processes is shown in Figure 1.

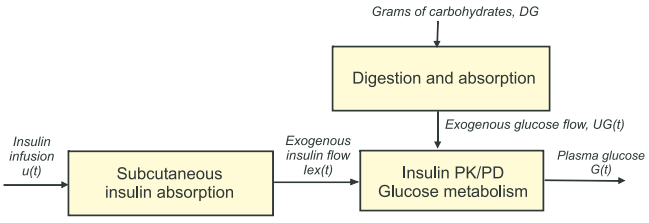

Fig. 1. Model overview.

In this work, the model presented in Hovorka et al. [2002, 2004], has been used to represent the glucose-insulin system. This model shows a good trade-off between simplicity and accuracy. Experimental validation results have been reported in the literature. Simple models are also implemented for the measurement device and for the insulin pump.

2.1 Glucose-insulin model

Carbohydrates digestion and absorption. This model describes the carbohydrates catabolism to monosaccharides (mostly glucose) taking place during meal digestion, as well as intestinal absorption. Glucose absorption rate U_G is represented by

$$U_{\mathrm{G}}(t) = \frac{D_G A_G t \exp(-t/t_{\max,G})}{t^2_{\max,G}} \tag{1}$$

being D_G the amount of carbohydrates ingested, A_G is carbohydrate bioavailability and $t_{\max,G}$ is the time-of-maximum appearance of glucose in plasma (Hovorka et al. [2004]).

Subcutaneous insulin absorption. Subcutaneous absorption of bolus and infused insulin is modelled by means of a linear two-compartmental system (Hovorka et al. [2004]):

$$\frac{\mathrm{d}S_1(t)}{\mathrm{d}t} = u(t) - \frac{S_1(t)}{t_{\max,\mathrm{I}}}, \quad \frac{\mathrm{d}S_2(t)}{\mathrm{d}t} = \frac{S_1(t)}{t_{\max,\mathrm{I}}} - \frac{S_2(t)}{t_{\max,\mathrm{I}}} \tag{2}$$

where $t_{\max,\mathrm{I}}$ is the time-to-maximum insulin absorption. The exogenous insulin flow is thus given by

$$I_{\mathrm{ex}}(t) := \frac{S_2(t)}{t_{\max,\mathrm{I}}}. \tag{3}$$

Insulin PK/PD and glucose metabolism. Insulin pharmacokinetics is considered of first order. Plasma insulin concentration, $I(t)$, is thus described as

$$\frac{\mathrm{d}I(t)}{\mathrm{d}t} = \frac{I_{\mathrm{ex}}(t)}{V_I} - k_e I(t) \tag{4}$$

where $I_{\mathrm{ex}}(t)$ is the exogenous insulin absorption rate above-described, k_e is the fractional elimination rate and V_I is the insulin distribution volume.

Plasma insulin concentration is considered to affect on glucose transport from plasma to the tissues, hepatic glucose production and peripheral glucose disposal (Hovorka et al. [2004]). These actions are modelled as first-order processes:

$$\begin{aligned}
\frac{\mathrm{d}x_1(t)}{\mathrm{d}t} &= -k_{a1}x_1(t) + k_{b1}I(t) \\
\frac{\mathrm{d}x_2(t)}{\mathrm{d}t} &= -k_{a2}x_2(t) + k_{b2}I(t) \\
\frac{\mathrm{d}x_3(t)}{\mathrm{d}t} &= -k_{a3}x_3(t) + k_{b3}I(t)
\end{aligned} \tag{5}$$

where x_1 represents the effects of insulin on glucose distribution/transport, x_2 represents the effect on glucose disposal and x_3 the effect on endogenous glucose production; k_{ai}, $i = 1, \ldots, 3$ are deactivation rate constants and k_{bi}, $i = 1, \ldots, 3$ activation rate constants. It will be considered here an alternative parametrization where $\frac{k_{b1}}{k_{a1}} =: S_{IT}$, $\frac{k_{b2}}{k_{a2}} =: S_{ID}$ and $\frac{k_{b3}}{k_{a3}} =: S_{IE}$, representing respectively insulin sensitivities to transport, disposal and endogenous glucose production.

Finally, glucose metabolism is represented as the two-compartmental system (Hovorka et al. [2004])

$$\frac{\mathrm{d}Q_1(t)}{\mathrm{d}t} = -F_{01}^c(t) - x_1(t)Q_1(t) + k_{12}Q_2(t) - \\ -F_R(t) + U_\mathrm{G}(t) + \mathrm{EGP}_0(1 - x_3(t))$$

$$\frac{\mathrm{d}Q_2(t)}{\mathrm{d}t} = x_1(t)Q_1(t) - (k_{12} + x_2(t))Q_2(t)$$

$$G(t) = \frac{Q_1(t)}{V_G}$$

where Q_1 and Q_2 represent the masses of glucose in the accessible and non-accessible compartments, k_{12} represents the transfer rate constant from the non-accessible to the accessible compartment, V_G represent the distribution volume of the accessible compartment, G is the glucose concentration and EGP_0 represents endogenous glucose production extrapolated to the zero insulin concentration. F_{01}^c is the total non-insulin-dependent glucose disposal, and F_R is the renal glucose clearance above the glucose threshold of 9 mmolL^{-1}. Contrary to Hovorka et al. [2004], these ones are modelled here by the functions:

$$F_{01}^c(t) = \frac{f_{01}}{9}(G(t) - 4.5 - \sqrt{(G(t) - 4.5)^2}\ ) + f_{01}$$

$$F_R(t) = \frac{0.003V_G}{2}(G(t) - 9 + \sqrt{(G(t) - 9)^2}\ )$$

Table 1 lists the model parameters used for the different components of the model, taken from Hovorka et al. [2002, 2004], patient n=2.

Table 1. Model parameters for patient $n = 2$.

Symbol	Value	Unit
A_G	0.8	unitless
$t_{\max,G}$	40	min
V_I	0.12	L/kg
k_e	0.138	1/min
k_{a1}	0.0157 (12)*	1/min
k_{a2}	0.0231 (27)	1/min
k_{a3}	0.0143 (6)	1/min
S_{IT}	18.7×10^{-4} (11)	min^{-1} per mUL^{-1}
S_{ID}	6.1×10^{-4} (8)	min^{-1} per mUL^{-1}
S_{IE}	379×10^{-4} (2)	mUL^{-1}
k_{12}	0.0871 (8)	1/min
f_{01}	0.0075 (2)	mmol /(kg min)
V_G	0.13 (1)	L/kg
EGP_0	0.0143 (2)	mmol /(kg min)
$t_{\max,\mathrm{I}}$	55	min

*Accuracy of a parameter estimate expressed as a fractional standard deviation (%).

The sensor is modelled as a pure time delay (t_0=10 min) with white noise,

$$G_{meas}(t) = G(t - t_0) + \epsilon \tag{6}$$

3. CLOSED-LOOP GLUCOSE CONTROLLER

3.1 Control architecture

It will be considered here that closed-loop glucose control is carried out through the sc-sc route, *i.e.* a continuous glucose monitor and an insulin pump accessing to subcutaneous tissue are considered.

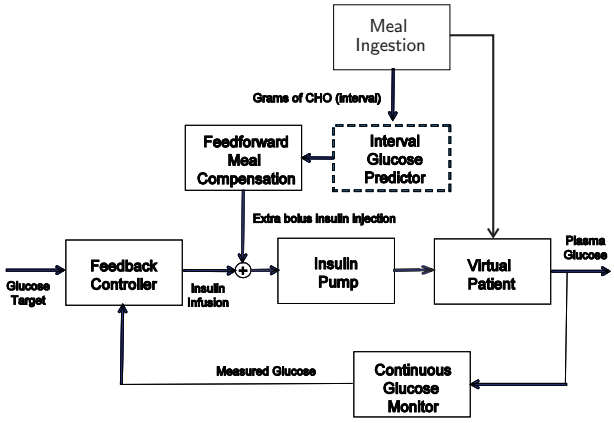

Fig. 2. Feedback-feedforward control scheme.

Control scheme will be based on a feedback-feedforward strategy. On one hand, a feedback sliding mode controller will be charged of keeping plasma glucose at its target value. On the other hand, a feedforward scheme will help this controller to face with postprandial glucose excursions from information given by the user on the meal ingested. Based on a prediction of postprandial glucose with consideration of uncertainty in patient's behavior and meal description, a bolus insulin dose will be estimated to minimize the risk of hypoglycaemia and supplied additionally by the insulin pump (see Figure 2).

3.2 Feedback sliding mode controller

Basic Concepts.- SMC is a robust and simple procedure to synthesize controllers for linear and nonlinear processes based on principles of Variable Structure Control (VSC). The design problem consists of tuning the parameters of each controller's structure and defining the switching logic. The first step in SMC is to define a surface $S(t)$, along which the process can *slide* to its desired final value. The sliding surface divides the phase plane into regions where the switching function $S(t)$ has different signs. The structure of the controller is intentionally altered as its state crosses the surface in accordance with a prescribed control law.

There are many options to choose the sliding surface. In this work, the sliding surface presented by Slotine and Li [1991] is used, consisting in the integral-differential error function

$$S(t) := \left(\frac{d}{dt} + \lambda\right)^n \int_0^t e(\tau)d\tau \tag{7}$$

where n is the system order, $e(t)$ is the tracking error between the reference and the output and λ is a tuning parameter, which helps to shape S(t). This term is selected by the designer, and determines the performance of the system on the sliding surface.

The control objective is to ensure that the controlled variable is driven to its reference value. It means that, in stationary state, $e(t)$ and its derivatives must be zero. This condition is achieved assuring that

$$\frac{dS(t)}{dt} = 0. \tag{8}$$

Once the sliding surface has been selected, attention must be turned to the design of the control law that drives the controlled variable to its reference value and satisfies (8). The SMC control law, $U(t)$, consists of a continuous part, $U_C(t)$, and a discontinuous part, $U_D(t)$, so that

$$U(t) = U_C(t) + U_D(t). \tag{9}$$

The continuous part is given by

$$U_C(t) = f(Y(t), R(t)) \tag{10}$$

where $f(\cdot)$ is a function of the controlled variable, $Y(t)$, and the reference value, $R(t)$. The discontinuous part, $U_D(t)$, generally incorporates a nonlinear element that includes the switching element of the control law. In this case a natural continuous approximation of the signum function was included to avoid the chattering problem (Zinober [1994]). This is the sigmoid-like function

$$U_D(t) = K_D \frac{S(t)}{|S(t)| + \delta}, \quad \delta > 0 \tag{11}$$

where K_D is the tuning parameter responsible for the reaching mode and δ is a tuning parameter used to reduce the chattering problem. Chattering is a nondecreasing oscillatory component of finite amplitude and frequency. It is undesirable in practical applications because it produces high control activity and also can excite high frequency dynamics ignored in the process modelling (Zinober [1994], Slotine and Li [1991]).

Controller synthesis.- For design purposes, the following second-order differential equation is used to approximate the plasma glucose-insulin relationship at a given estimated equilibrium point (I_0, G_0):

$$\alpha \frac{d^2G(t)}{dt^2} + \beta \frac{dG(t)}{dt} + G(t) + \Omega(t; D_G) = KI(t) \tag{12}$$

where $G(t)$ and $I(t)$ are deviations of plasma glucose and insulin infusion with regard to the chosen point, α, β and K are the model parameters and $\Omega(t; D_G)$ represents the disturbance on glycaemia produced by an ingestion of D_G grams of carbohydrates. For the second-order process (12), the sliding surface (7) is as follows

$$S(t) = \frac{de(t)}{dt} + \lambda_1 e(t) + \lambda_0 \int_o^t e(\tau) d\tau \tag{13}$$

where $e(t) := R(t) - G(t)$ is the error between the reference and the continuous glucose monitor output. $\lambda_0 = \lambda^2$ and $\lambda_1 = 2\lambda$ are tuning parameters.

Applying the sliding condition (8) to (13):

$$\frac{dS(t)}{dt} = \frac{d^2e(t)}{dt^2} + \lambda_1 \frac{de(t)}{dt} + \lambda_0 e(t) = 0 \tag{14}$$

and solving for the highest derivative, we obtain

$$\frac{d^2G(t)}{dt^2} = \frac{d^2R(t)}{dt^2} + \lambda_1 \frac{de(t)}{dt} + \lambda_0 e(t). \tag{15}$$

Substituting now (15) in (12) and solving for $I(t)$, in absence of perturbations, provides the continuous part of the controller using the equivalent control procedure (Utkin [1981]):

$$I_C(t) = \frac{1}{K}\Big(\alpha \frac{d^2R(t)}{dt^2} + \alpha\lambda_1 \frac{de(t)}{dt} + \alpha\lambda_0 e(t) + \beta \frac{dG(t)}{dt} + G(t)\Big). \tag{16}$$

The following criteria may be used to tune the controller,

$$\lambda_1 = \frac{\beta}{\alpha}. \tag{17}$$

Once λ_1 is chosen the initial value of λ_0 can be obtained using the relations $\lambda_0 = \lambda^2$ and $\lambda_1 = 2\lambda$. They are obtained when (13) is deduced,

$$\lambda_0 = \frac{\lambda_1^2}{4}. \tag{18}$$

However λ_0 and λ_1 can be fitted independently only restricted to obtain a stable dynamics of the sliding surface. For de discontinuous part of the controller the tuning parameters are,

$$K_D = \frac{1}{K}, \text{ and } \delta = 0.6 \tag{19}$$

Regarding the discontinuous part of the controller, the gain K_D will be selected so that $KK_D > 0$. Accordingly to the Lyapunov stability criterion (25), its value must be high enough to cancel the disturbances. In order to increase the dynamic behavior of the sliding mode controller in the hypoglycemic range a variable gain K_V has been considered, so that when the glucose is bigger than 88 mg/dL then $K_V = 1$; otherwise $K_V = K_V^*$.

Finally, with the selection of λ_1, λ_0 and replacing $\frac{dR(t)}{dt} = 0$ (Camacho et al. [2007]), $I(t)$ can be simplified. Thus, the incremental control action over the basal insulin is given by

$$I(t) = \frac{\alpha}{K}\left[\lambda_0 e(t) + \frac{G(t)}{\alpha}\right] + K_V K_D \frac{S(t)}{|S(t)| + \delta}. \tag{20}$$

The SMC controller was implemented in the virtual patient using the follow parameters $\lambda_0 = 3.2 \times 10^{-4}$, $\lambda_1 = 13.7$, $K_D = -4.9$, $\delta = 0.6$, $K_V^* = 0.5$ and the plasma glucose-insulin model with $K = -2.1$, $\alpha = 6889$ and $\beta = 166$.

Stability analysis.- To proof the reaching condition, the following Lyapunov function is first defined

$$V(t) = \frac{1}{2}S^2(t), \qquad S(t)\frac{dS(t)}{dt} < 0. \tag{21}$$

Substituting the glucose model (12) in the derived sliding surface (14):

$$\frac{dS(t)}{dt} = -\frac{1}{\alpha}\Big(KI(t) - \beta \frac{dG(t)}{dt} - G(t) - \Omega(t; D_G)\Big) - \lambda_1 \frac{dG(t)}{dt} + \lambda_0 e(t). \tag{22}$$

Substituting now in the above equation the control law (20), the derivative of sliding surface is obtained:

$$\frac{dS(t)}{dt} = \frac{1}{\alpha}\left(\Omega(t; D_G) - KK_V K_D \frac{S(t)}{|S(t)| + \delta}\right). \tag{23}$$

Stability condition is thus given by

$$\frac{1}{\alpha}\left(S(t)\Omega(t;D_G) - KK_VK_D\frac{S(t)^2}{|S(t)|+\delta}\right) < 0. \qquad (24)$$

In the above expression $\Omega(\cdot)$ is a non-negative quantity since it represents a glucose concentration value. It also holds that $KK_VK_D > 0$. Thus, for $S(t) > 0$,

$$KK_VK_D\frac{S(t)}{|S(t)|+\delta} > \Omega(t;D_G) \qquad (25)$$

must hold to get stability. This will have to be fulfilled from an estimation of the maximum expected perturbation and a proper tuning of K_D. For $S(t) < 0$, condition (24) will hold everywhere.

3.3 Feedforward meal compensation

When meal in ingested, a high rise on plasma glucose will appear. In case information is given to the system about the amount of carbohydrates contained in the meal, a feedforward scheme may be implemented to additionally infuse a bolus insulin flow. However, this must be done carefully, since an excess of insulin may induce not desirable hypoglycaemia episodes.

In this work, uncertain information on the quantity of carbohydrates supplied, D_G, and patient's peripheral and hepatic insulin sensitivities, S_{ID} and S_{IE}, are considered. An interval glucose predictor (Calm et al. [2007]) is then used to calculate a band containing all possible glucose excursions given the defined uncertainty. Based on a worst-case analysis, the bolus dose of insulin is calculated to reduce the risk of hypoglycaemia episodes, calculated as the area under 70 mg/dL (see Figure 3).

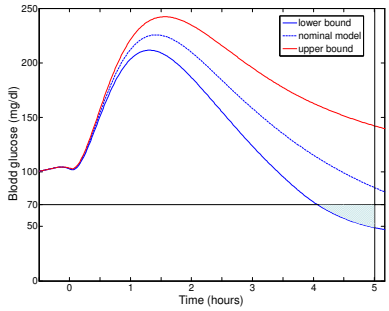

Fig. 3. Example of computation of the hypoglycaemia risk index (60 gr CHO; 6IU). Upper and lower bounds computed for 20 % variation in model parameters.

4. RESULTS

To demonstrate the feasibility of the proposed closed-loop controller, a virtual patient with nominal parameters as described in previous sections has been considered and a typical one day routine has been implemented (Steil et al. [2006]):

- Food intake: 55.1 g CHO at 8:00; 87.9 g CHO at 13:00; 69.0 g CHO at 18:00 and 45.3 g CHO at 22:00.

The controller has been tested during 36 hours comprising fasting as well as postprandial states. To consider a realistic situation, insulin sensitivity has been considered to change along the day, accordingly to clinical study described in Scheiner and Boyer [2005] in patients with age between 21 and 60 years. The sensor is modelled with white noise with zero mean and a standard deviation of 2 mg/dL, also the input of the controller is a filtered glucose measurement. A third order low pass Bessel filter with a cut frequency of 125 mHz has been chosen to filter the glucose signal. The Bessel filter maximizes the flatness of the group delay curve at zero frequency. The transition from the pass band to the stop band is much slower than for other filters, but the group delay is practically constant in the pass band. In the simulations presented here, it has been considered that the continuous glucose monitor shows a delay of 10 min. Saturation in the insulin pump range has also been considered.

Results are shown in Figure 4, for patient number 2 (taken from Hovorka et al. [2002]). It may be observed a good noise rejection and a well-behaved robustness of the controller face to changes in insulin sensitivity during the fasting state (from 0 to 8 hours and from 25 to 32 hours). No nocturnal hypoglycaemia is produced, keeping glucose in the euglycaemic range. Regarding postprandial state, the controller is also robust to insulin sensitivity changes. In this case, it may observed how the feedforward meal compensation scheme implemented, helps the feedback controller by infusing extra bolus insulin doses. The bolus dose is then complemented by the feedback controller, as it may be observed. Neither hyperglycaemic nor hypoglycaemic episodes are observed.

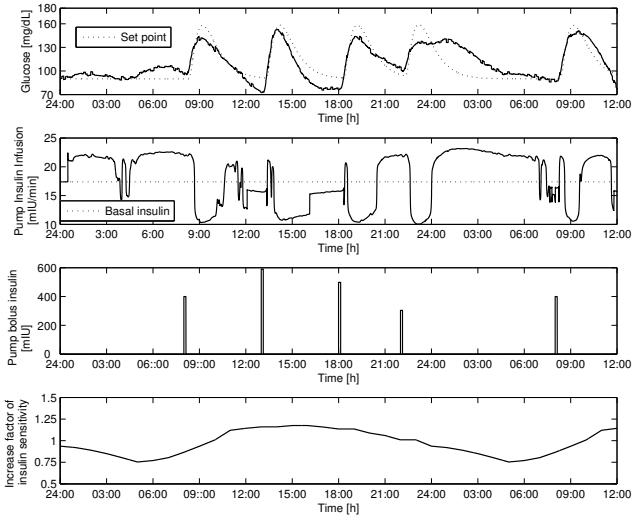

Fig. 4. Controller behavior for patient $n = 2$ in fasting and postprandial state for time-varying insulin sensitivity.

The International Diabetes Federation (IDF), in a recent publication (International Diabetes Federation [2007]) establishes as glycaemic goals for clinical management of diabetes a fasting glucose level lower than 100 mg/dL and a 2-hour postprandial glucose level lower than 140 mg/dL, with no hypoglycaemia episodes. It is also stressed

in the IDF guidelines the need to address postprandial hyperglycaemia, which has been associated to an increased risk of cardiovascular diseases among other things. It may observed in Figure 4 that these criteria are fulfilled for the designed controller in an *in silico* setting. Set point has been selected so as to follow an ideal postprandial response according to the IDF guidelines.

5. CONCLUSIONS

In this paper, a new approach to plasma glucose closed-loop control composed by a feedback sliding mode controller and a feedforward meal compensation has been presented. The feasibility of the proposed approach has been demonstrated in *in silico* trials.

The designed controller gives a very good overall performance, fulfilling the guidelines of the International Diabetes Federation on glycaemic targets. While the feedback sliding mode controller assures robustness against intra-patient variability, the feedforward bolus compensation, by means of an interval glucose predictor, helps to reach the glycaemic target by infusing an extra bolus insulin which minimizes the hypoglycaemia risk.

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