Diabetic Gastroparesis Modeling and Observer Design

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Abstract: Type 1 diabetes results from the lack of endogenous production of insulin by the pancreas. According to various references, 4% to 12% of diabetic patients are affected by gastroparesis which delays the digestion process. Gastroparesis is characterized by a constellation of gastrointestinal symptoms in association with delayed gastric emptying (GE). For the first time, a mathematical model is introduced to describe the glycemia dynamics for this significant class of patients. It is shown to yield to a nonlinear time delay model designed for estimation and control.

Keywords: Biomedical systems, Systems biology, time-delay systems, observer design, glycemia dynamics

1. INTRODUCTION

Type 1 diabetis is an auto-immune disease resulting in the lack of production of endogenous insulin by the pancreas. Insulin dependent diabetis thus requires exogenous insulin injections which are performed either manually, or through an insulin pump. A though control problem arises whose purpose is to decrease glycemia from hyperglycemia after some meal as fast as possible, but avoiding future hypoglycemia. The control has to be positive since, once injected, exogenous insulin can no more be withdrawn from the organism. Despite decades of research, the control problem is still widely open. Two mainstreams in control of glycemia are PID's and MPC (Model Predictive Control) and the latter is a special case of state feedback which requires an observer for state estimation. Observers are also used in Borri et al. (2017), Facchinetti et al. (2010), Sparacino et al. (2007) to estimate blood plasma glycemia from the intersticial glycemia measurement.

In aging diabetic patients, the evolution of this chronic disease goes together with the risk of gastroparesis, that is, with delayed gastric emptying (GE). According to various references, this results into the estimate of 12 to 20% of diabetic patients affected by gastroparesis which delays the digestion process. Gastroparesis is characterized by a constellation of gastrointestinal symptoms Shin et al. (2013).

The majority of diabetic patients – not affected by gastroparesis – are characterized by a digestion dynamics which is faster than the insulin absorbsion dynamics. This situation is the other way around for diabetic patients affected by gastroparesis. The result is that the structural properties of the respective mathematical models are dramatically different as far as positive invariant sets are concerned Farina et al. (2000).

The GE delay may be measured in clinical practice. This motivates the inclusion of a time delay in the digestion dynamics rather than increasing its response time. Thus, in this paper, a mathematical model is introduced for those diabetic patients subject to gastroparesis and it is shown that with the introduction of a time delay to model GE and of nonlinearities depending on glycemia and insulinemia, leads to a good candidate model to improve the fit to clinical data. As a consequence, the design of a delay dependent observer is appropriate for a control purpose. This is new in the area of glycemia regulation.

In Section 2, the model is detailed step by step and an additional focus is on the liver modelling. The body continously needs energy. To cope with sparse meals during the day, the liver acts as a storage device for the post prandial glucose which is not absorbed by the tissues and releases glucose, in the form of glycogen, between two meals to avoid hypoglycemia. This process is modeled by a nonlinear function depending on glycemia. Low glycemia will stimulate release of glycogen while rise in insulinemia activates storage of glucose by the liver. Section 3 is devoted to the test of (weak) observability and the observer design. Simulations results are provided in Section 4 based on some clinical data.

2. MATHEMATICAL MODELING

The glycemia/insulinemia dynamics can be decomposed into the glycemia subsytem which is fed by the blood plasma insulinemia and the glucose from the digestion subsystem. The insulinemia subsystem consists of the blood plasma compartment and the subcutaneous compartment which is subject to the controlled insulin infusion. Also the digestion process may be modeled by two compartments, the stomach and the duodenum (Magdelaine et al. (2015)). For diabetic patients who are not subject to gastroparesis, the response time of the digestion subsystem is smaller than the response time of the insulin subsystem. Patients affected by gastroparesis have a slow digestion process. A standard approach just consists in considering in this

case that the response time of the digestion subsystem is (much) larger than the response time of the insulin subsystem. This feature is acceptable for the model, but was shown to affect dramatically the control law design of insulin infusion. This motivates to distinguish between the two different populations of patients in opposition to the current control literature, where gastroparesis is not a discriminating criterion.

In order to have an overall description of the glycemia/insulinemia dynamics, we have to consider the behaviour of several quantities, and in particular of

- G - the blood plasma glycemia,
- I_p - the blood plasma insulinemia,
- I_{sc} - the subcutaneous insulinemia,
- X_s - the amount of assimilated carbohydrates that are transferred from the stomach into the duodenum,
- X_d - the amount of assimilated carbohydrates that is transferred from the duodenum to the plasma. Consequently the raise of glycemia when a meal is digested can be taken into account by adding a linear term of the form $\theta_4 X_d$ with $\theta_4 > 0$ in the glycemia dynamics.
- u - the injected insulin rate
- r - the carbohydrates absorbed through the meal

The subcutaneous insulinemia dynamics is described by the differential equation

$$\dot{I}_{sc} = -\frac{1}{\theta_3} I_{sc} + \frac{\theta_u}{V_I \theta_3} u, \tag{1}$$

where $\theta_3 > 0$ is the response time of the insulin subsystem. The dynamics of the plasma insulinemia I_p instead reads

$$\dot{I}_p = \frac{1}{\theta_3} I_{sc} - \frac{1}{\theta_3} I_p. \tag{2}$$

The glycemia dynamics can be modeled through the differential equation

$$\dot{G}(t) = -\theta_{si}(I_p(t)) I_p(t) + \theta_4 X_d(t) + \theta_1 [1 + f(G)], \tag{3}$$

where the $\theta_{si}(I_p(t))$ represents a sensitivity to insulin. When insulinemia is low, for example in case of catheter obstruction, glycemia rises and the body produces ketones to provide energy from fat. But ketosis decreases insulin sensitivity. As a consequence type 1 diabetic patients have to inject large amounts of insulin to recover both from ketosis and hyperglycemia. The θ_{si} function is approximated by

$$\theta_{si}(I_p) = \theta_2 \left[1 - 0.4 \exp(-\frac{I_p}{I^*}) \right], \tag{4}$$

$\theta_2 \theta_u / V_I > 0$ is the practical constant insulin sensitivity factor used in every day medical monitoring of diabetes. The discriminating insulinemia level I^* can be taken equal to the so-called basal rate $I_b = (\theta_1 V_I)/(\theta_2 \theta_u)$, where $\theta_1 > 0$ characterizes the glycogenolysis, i.e. the endogenous glucose release by the liver, as detailed below.

In (3), the term $\theta_1(1 + f(G))$ represents the net balance between the liver endogenous glucose release and the insulin-independent glucose consumption (e.g. by the brain).
In case of hypoglycemia, the liver endogenous glucose release increases. Similarly to Tolic et al. (2000), Sorensen (1978), $f(G)$ is defined as

$$f(G) = 2\alpha_1 \exp(-\frac{G}{G^*}). \tag{5}$$

where G^* is the limit defining hypoglycemia and is taken equal to 70 mg/dl. $\alpha_1 \geq 0$ characterizes the higher liver endogenous glucose release in case of hypoglycemia. In the simulations dispayed in Figure 2, α_1 is taken equal to 0.5 so that $f(G)$ varies from 1 to 0. When insulinemia rises, the endogenous glucose release decreases Ader et al. (1990) and the liver begins to store glucose in the form of glycogen. So that we get

$$\dot{G}(t) = -\theta_{si}(I_p) I_p(t) + \theta_4 X_d(t) + \theta_1 \left\{ 1 + 2\alpha_1 \exp\left(-\frac{G}{G^*} \right) \right\}. \tag{6}$$

At this point, considering the input X_d to be zero, one gets the minimal model during a fasting period. When carbohydrates (CHO) are ingested during a meal, then a two compartment digestion subsystem is modeled as follows. The stomach compartment is fed by the CHO input $r(t)$ (that is the meal):

$$\dot{X}_s(t) = -\frac{1}{\theta_5} X_s(t) + r(t). \tag{7}$$

The duodenum compartment dynamics is instead described by the differential equation

$$\dot{X}_d(t) = -\frac{1}{\theta_5} X_d(t) + \frac{1}{\theta_5} X_s(t - \delta), \tag{8}$$

where the gastric emptying time δ characterizing gastroparesis is displayed.
For the majority of diabetics, i.e. without gastroparesis, the response time θ_5 of the digestion subsystem is smaller than the response time θ_3 of the insulin subsystem. Besides the delay δ, the diabetic patients affected by gastroparesis are also characterized by the relationship $\theta_5 > \theta_3$ which will be assumed in the rest of this paper.

Set now $G = x_1$, $I_{sc} = x_2$, $I_p = x_3$, $X_s = x_4$ and $X_d = x_5$. Then, the complete model herein is as follows.

$$\begin{aligned}
\dot{x}_1 &= -\theta_2 x_3 + 0.4\theta_2 x_3 \exp\left(-\frac{\theta_2 \theta_u}{\theta_1 V_I} x_3 \right) \\
&\quad + \theta_1 \{ 1 + 2\alpha_1 \exp\left(-\frac{x_1}{G^*} \right) \} + \theta_4 x_5 \\
\dot{x}_2 &= -\frac{1}{\theta_3} x_2 + \frac{\theta_u}{V_I \theta_3} u \\
\dot{x}_3 &= \frac{1}{\theta_3} x_2 - \frac{1}{\theta_3} x_3 \\
\dot{x}_4 &= -\frac{1}{\theta_5} x_4 + r(t) \\
\dot{x}_5 &= -\frac{1}{\theta_5} x_5 + \frac{1}{\theta_5} x_4(t - \delta) \\
y &= x_1.
\end{aligned} \tag{9}$$

Identification result

Figure 1 displays identification results with and without delay. The model-fit was made from 17:30 to 06:00 using least square error on the output i.e. glycemia and cross-validation was made from 06:00 to 12:30.

It illustrates that taking into account the delay, and setting $\delta \neq 0$, allows to emulate better the behaviour of the glycemia. It becomes obvious in Figure 1 around time 22:30, as the simulated trajectory tracks much better the data.

The cross-validation simulates the model with the parameters obtained from the fit. Cross-validation shows that the Carbo-to-Insulin Ratio could be re-estimated for breakfast which is a typical meal with fast carbs (as at 12:30 simulated glycemia drifts from CGM data).

For alternative models, the reader is referred for instance to Cobelli et al. (2014) in which delays refer to a second phase insulin secretion and to the CGM and insulin pump technologies, to Palumbo et al. (2013) in which the tissue glucose uptake is delayed with respect to the insulin action and the insulin pancreatic secretion is delayed with respect to the glycemia action (whenever the pancreas insulin secretion is non zero), or to Reiterer et al. (2015) where no delay is considered but the essential features of the glycemia-insulinemia dynamics are modeled by linear terms as in (9).

3. OBSERVABILITY AND OBSERVER DESIGN

The measured output is the glycemia $G(t)$ in blood plasma. Elementary differentiations of $G(t)$ with respect to time show that the system is *weakly observable*, in the sense that from the knowledge of the measured output $G(t)$ and of the inputs $u(t)$ and an estimation of the ingested meal $r(t)$, one can compute the four states $(G(t), I_{sc}(t), I_p(t), X_d(t))$ at time t and the value of the fifth delayed state $X_s(t-\delta)$, for almost all values of δ.

In the present Section it is shown how to design an *ad hoc* observer to estimate the states for (9) as described above.

So, outside hypoglycemia ($x_1 >> 70$ mg/dl and $f(G) \simeq 0$), and assuming that there is no catheter obstruction ($x_2 >> 0$ and $x_3 >> 0$), and during fasting ($r = 0$, $x_4 = 0$ and $x_5 = 0$), the set of equilibria in the plane (x_1, x_3) is $\{(G, I_b)\}$ where $I_b \simeq (\theta_1 V_I)/(\theta_2 \theta_u)$ denotes the basal rate. The blood glycemia may have have any value G which is stabilized by the basal insulin infusion rate I_b as expected from medical practice.

It is easily seen that the system is in the form

$$\begin{aligned}\dot{x}(t) &= A_0 x(t) + A_1 x(t-\delta) + Pr(t) + \psi(y(t), u(t)) + \varphi(x_3(t))\\ y(t) &= Cx(t)\end{aligned}$$

with

$$A_0 = \begin{pmatrix} 0 & 0 & -\theta_2 & 0 & \theta_4 \\ 0 & -\frac{1}{\theta_3} & 0 & 0 & 0 \\ 0 & \frac{1}{\theta_3} & -\frac{1}{\theta_3} & 0 & 0 \\ 0 & 0 & 0 & -\frac{1}{\theta_5} & 0 \\ 0 & 0 & 0 & 0 & -\frac{1}{\theta_5} \end{pmatrix},$$

$$A_1 = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{1}{\theta_5} & 0 \end{pmatrix}, \qquad P = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 1 \\ 0 \end{pmatrix},$$

$$C = (1\ 0\ 0\ 0\ 0).$$

and the nonlinear terms $\varphi(x_3)$ and $\Psi(y,u)$ given by

$$\varphi(x_3) = \begin{pmatrix} 0.4\theta_2 x_3 \exp(-\frac{\theta_2 \theta_u}{\theta_1 V_I} x_3) \\ 0 \\ \vdots \\ 0 \end{pmatrix},$$

$$\psi(y(t), u(t)) = \begin{pmatrix} \theta_1 \left(1 + 2\alpha_1 \exp(-\frac{x_1}{G^*})\right) \\ \frac{\theta_u}{V_I \theta_3} u \\ 0 \\ 0 \\ 0 \end{pmatrix}.$$

Using the differential representation approach proposed in Califano et al. (2017) to deal with time–delay systems, one has to consider the differential of the dynamics, that is

$$\begin{aligned} d\dot{x}_1 &= -\frac{2\theta_1 \alpha_1}{G^*} \exp(-\frac{x_1}{G^*}) dx_1 + \theta_4 dx_5 \\ &\quad + \left[-\theta_2 + 0.4 \left(1 - \frac{\theta_2 \theta_u}{\theta_1 V_I} x_3\right) \exp(-\frac{\theta_2 \theta_u}{\theta_1 V_I} x_3) \right] dx_3 \\ d\dot{x}_2 &= -\frac{1}{\theta_3} dx_2 + \frac{\theta_u}{V_I \theta_3} du \\ d\dot{x}_3 &= \frac{1}{\theta_3} dx_2 - \frac{1}{\theta_3} dx_3 \\ d\dot{x}_4 &= -\frac{1}{\theta_5} dx_4 + dr \\ d\dot{x}_5 &= -\frac{1}{\theta_5} dx_5 + \frac{1}{\theta_5} \delta dx_4 \\ dy &= dx_1 \end{aligned}$$

and in compact form

$$\begin{aligned} d\dot{x}(t) &= (A_0 + A_1 \delta) dx(t) + P dr + \frac{\partial \psi(y(t), u(t))}{\partial y} dy \\ &\quad + \frac{\partial \psi(y(t), u(t))}{\partial u} du \\ &\quad + \frac{\partial \varphi(x_3)}{\partial x_3} dx_3 \\ dy(t) &= C dx(t) \end{aligned}$$

3.1 Observability

Setting $A(\delta) = A_0 + A_1 \delta$, in this section we will consider the observability problem assuming that there is no catheter obstruction, thus neglecting $\varphi(x_3)$. As it will be clear in the observer design later on, such an approximation does not influence the observer itself since such a nonlinearity affects only the estimation of the glycemia which is the measured variable. The observability matrix is then obtained by considering

$$\begin{aligned} dy &= C dx(t) \\ d\dot{y} &= CA(\delta) dx + C \frac{\partial \psi}{\partial y} dy \\ d\ddot{y} &= CA^2(\delta) dx + \left(CA(\delta) \frac{\partial \psi}{\partial y} + C \frac{\partial \dot{\psi}}{\partial y} \right) dy \\ &\quad + C \frac{\partial \psi}{\partial y} d\dot{y} \\ dy^{(3)} &= CA^3(\delta) dx \\ &\quad + \left(CA^2(\delta) \frac{\partial \psi}{\partial y} + CA(\delta) \frac{\partial \dot{\psi}}{\partial y} + C \frac{\partial \ddot{\psi}}{\partial y} \right) dy \\ &\quad + \left(CA(\delta) \frac{\partial \psi}{\partial y} + 2C \frac{\partial \dot{\psi}}{\partial y} \right) d\dot{y} + C \frac{\partial \psi}{\partial y} dy^{(2)} \end{aligned}$$

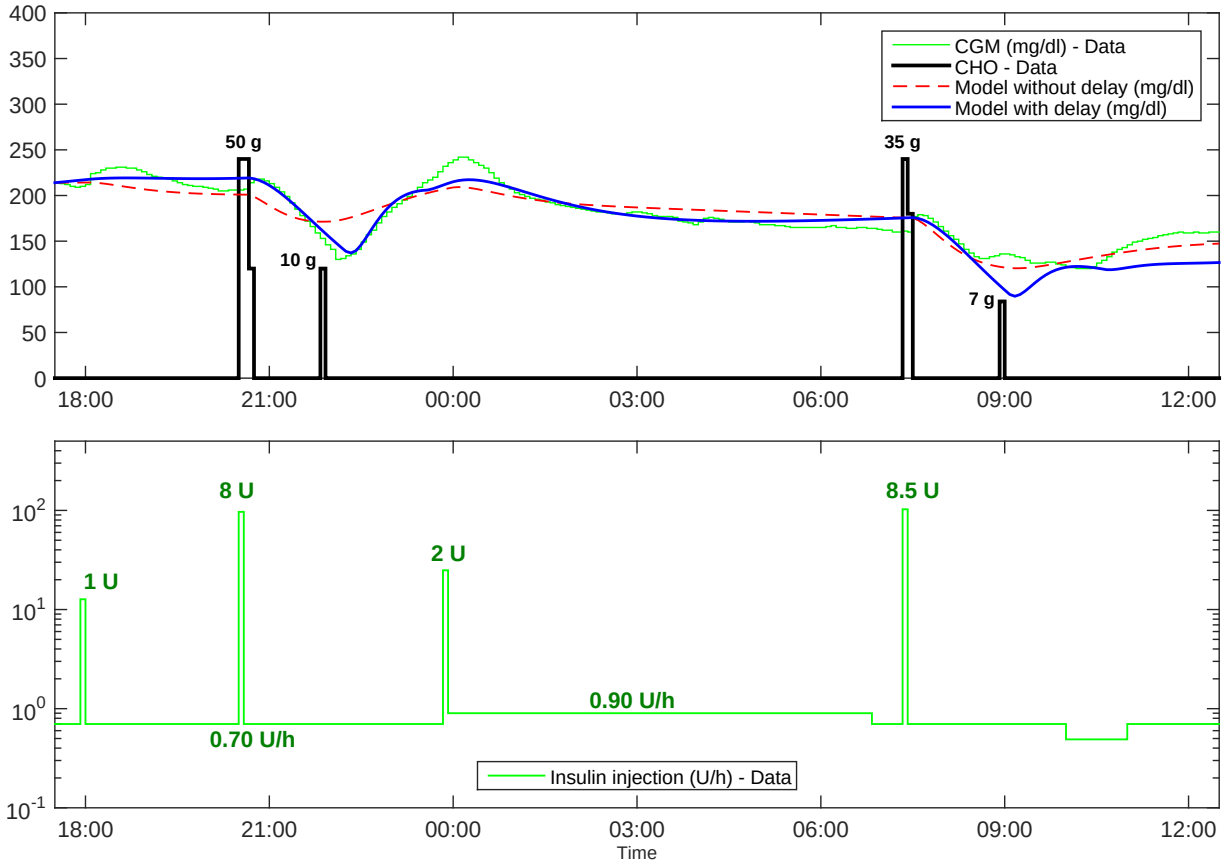

Fig. 1. Model behaviour with and without delay (from 6 pm to 12 noon next day

$$
\begin{aligned}
&dy^{(4)} = CA^4(\delta)dx \\
&+\left(CA^3(\delta)\frac{\partial \psi}{\partial y}+CA^2(\delta)\frac{\partial \dot{\psi}}{\partial y}+CA(\delta)\frac{\partial \ddot{\psi}}{\partial y}+C(\delta)\frac{\partial \dddot{\psi}}{\partial y}\right)dy \\
&+\left(CA^2(\delta)\frac{\partial \psi}{\partial y}+2CA(\delta)\frac{\partial \dot{\psi}}{\partial y}+3C\frac{\partial \ddot{\psi}}{\partial y}\right)d\dot{y} \\
&+\left(CA(\delta)\frac{\partial \psi}{\partial y}+3C\frac{\partial \dot{\psi}}{\partial y}\right)dy^{(2)}+C\frac{\partial \psi}{\partial y}dy^{(3)}
\end{aligned}
$$

Due to the structure of the output and its derivatives, observability can be checked by considering the linear matrix

$$
\mathscr{O} = \begin{pmatrix} C \\ CA(\delta) \\ CA^2(\delta) \\ CA^3(\delta) \\ CA^4(\delta) \end{pmatrix} = \begin{pmatrix} 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & -\theta_2 & 0 & \theta_4 \\ 0 & -\frac{\theta_2}{\theta_3} & \frac{\theta_2}{\theta_3} & \frac{\theta_4}{\theta_5}\delta & -\frac{\theta_4}{\theta_5} \\ 0 & 2\frac{\theta_2}{\theta_3^2} & -\frac{\theta_2}{\theta_3^2} & -2\frac{\theta_4}{\theta_5^2}\delta & \frac{\theta_4}{\theta_5^2} \\ 0 & -3\frac{\theta_2}{\theta_3^3} & \frac{\theta_2}{\theta_3^3} & 3\frac{\theta_4}{\theta_5^3}\delta & -\frac{\theta_4}{\theta_5^3} \end{pmatrix}
$$

The determinant is

$$
det(\mathscr{O}) = \frac{\theta_2^2\theta_4^2}{\theta_3\theta_5}\left(\frac{1}{\theta_5^4}-\frac{4}{\theta_3\theta_5^3}+\frac{6}{\theta_3^2\theta_5^2}-\frac{4}{\theta_3^3\theta_5}+\frac{1}{\theta_3^4}\right)\delta
$$

and is zero for $\theta_3 = \theta_5$. It follows that for $\theta_5 \neq \theta_3$ the system is weakly observable. Recall from Section 2 that we assume $\theta_5 > \theta_3$ due to gastroparesis, so there is no singularity for weak observability.

3.2 Observer design

Since the model is linear up to a nonlinear input $u(t)$ and output $y(t)$ injection, a standard observer is designed by considering a copy of the model, where the unknown input $r(t)$ is substituted by an estimation $\hat{r}(t)$ as done by the patient at every meal. That is

$$
\begin{aligned}
\dot{\xi}(t) = A_0\xi(t)+A_1\xi(t-\delta)+P\hat{r}(t)+\psi(y(t),u(t)) \\
-\tilde{K}(C\xi(t)-y(t))
\end{aligned} \tag{10}
$$

with the gain $\tilde{K}$ appropriately chosen. Accordingly, denoting by $r_e(t) = \hat{r}(t) - r(t)$, the error on the estimation of the ingested carbohydrates, the dynamics of the error $e(t) = \xi(t) - x(t)$ is linear and given by

$$
\dot{e}(t) = A_0e(t)+A_1e(t-\delta)-\tilde{K}Ce(t)+Pr_e(t) \tag{11}
$$

with $r_e(t)$ acting as an imput on the linear system. Accordingly

$$
d\dot{e} = (A_0+A_1\delta-\tilde{K}C)de+Pdr_e = \left(A(\delta)-\tilde{K}C\right)de+Pdr_e
$$

For $\tilde{K} = 0$, the eigenvalues of the matrix $A(\delta) = A_0 + A_1\delta$, are

$$\det(A(\delta)-\lambda I)=$$
$$\det\begin{pmatrix} -\lambda & 0 & -\theta_2 & 0 & \theta_4 \\ 0 & -\frac{1}{\theta_3}-\lambda & 0 & 0 & 0 \\ 0 & \frac{1}{\theta_3} & -\frac{1}{\theta_3}-\lambda & 0 & 0 \\ 0 & 0 & 0 & -\frac{1}{\theta_5}-\lambda & 0 \\ 0 & 0 & 0 & \frac{1}{\theta_5}\delta & -\frac{1}{\theta_5}-\lambda \end{pmatrix} =$$
$$-\lambda\left(\frac{1}{\theta_3}+\lambda\right)^2\left(\frac{1}{\theta_5}+\lambda\right)^2$$

which shows that the system is characterized by four negative eigenvalues and one eigenvalue in zero, so that the system is stable but not asymptotically. It is then necessary to use the gain $\tilde{K}$ to asymptotically stabilize the error dyanamics. One thus has

$$\det(A(\delta)-\tilde{K}C-\lambda I)=$$
$$\det\begin{pmatrix} -\lambda-\tilde{k}_1 & 0 & -\theta_2 & 0 & \theta_4 \\ -\tilde{k}_2 & -\frac{1}{\theta_3}-\lambda & 0 & 0 & 0 \\ -\tilde{k}_3 & \frac{1}{\theta_3} & -\frac{1}{\theta_3}-\lambda & 0 & 0 \\ -\tilde{k}_4 & 0 & 0 & -\frac{1}{\theta_5}-\lambda & 0 \\ -\tilde{k}_5 & 0 & 0 & \frac{1}{\theta_5}\delta & -\frac{1}{\theta_5}-\lambda \end{pmatrix} =$$
$$-(\lambda+\tilde{k}_1)(\frac{1}{\theta_3}+\lambda)^2(\frac{1}{\theta_5}+\lambda)^2+\tilde{k}_2\frac{\theta_2}{\theta_3}(\frac{1}{\theta_5}+\lambda)^2+$$
$$-\theta_2\tilde{k}_3(\frac{1}{\theta_3}+\lambda)(\frac{1}{\theta_5}+\lambda)^2-\tilde{k}_4\frac{\theta_4}{\theta_5}\delta(\frac{1}{\theta_3}+\lambda)^2+$$
$$+\tilde{k}_5\theta_4(\frac{1}{\theta_3}+\lambda)^2(\frac{1}{\theta_5}+\lambda),$$

where the gain matrix coefficients, $\tilde{k}_1$, $\tilde{k}_2$, $\tilde{k}_3$, $\tilde{k}_4$ and $\tilde{k}_5$ have to be chosen in order to ensure that the eigenvalues are all in the half left plane. A simple choice consists in setting $\tilde{K}=[0.1\ 0\ 0\ 0\ 0]^T$.

Remark. It should be noted that while the estimation of the system state is characterized by a linear error dynamics described by equation (11), the observer, described by equation (10) is nonlinear due to the presence of the nonlinear term $\Psi(y,u)$. □

Remark. Weak observability implies that one is able to estimate the state of the given system with some delay, for almost all values of the delays. In the present case, a stronger properties holds true which is the possibility of estimating the state with some delay for all values of the delay. □

4. IN SILICO TEST

In the present section, simulations are carried out on a diabetic patient's data who is affected by gastroparesis. The data were obtained from Nantes University Hospital. α_1 is set to 0.5, in order to take into account hypoglycemia.

In Figure 2, the estimation error on $x_2=I_{sc}$, $x_3=I_p$, $x_4=X_s$ and $x_5=X_d$ is reported. The observer is designed taking into account that the measures of the output are not continuous but discrete. The observer's inputs are:

- the measurements of the output $y(t)$ from a monitoring device (CGM) which evaluates the glycemia every 5 minutes;
- the open-loop insulin infusion $u(t)$ delivered by the pump;
- the amount of carbohydrates (CHO) in the meal $\hat{r}(t)$ estimated by the patient.

The effective amount of CHO is often different from the one estimated by the patient. In Figure 2 the amount of CHO estimated by the patient is assumed to be underestimated at 80 % of the real amount. A meal is taken around 9pm and around 8am (see Figure 1). Though the observer is designed by assuming $\varphi(x_3)=0$, the simulations are carried out the full nonlinear model. Nonetheless, the insulin pump works correctly and the basal rate is never set to zero (c.f. injections on Figure 1), $\varphi(x_3)\simeq 0$. As a matter of fact such an assumption does not affect the observer behavior, since it fortunately affects only the estimation of the glycemia which is not needed at this point.

Simulations were carried out with the following parameters which were identified from clinical data using a standard least squares method.

parameters	value
θ_1	0.32
θ_2	0.05
θ_3 (min)	70
θ_4	2.7
θ_5 (min)	22
δ (min)	95
θ_u/V_I	500

The observer was initialized with initial condition $z_0=(200,12,20,5,8)^T$. The glycemia/insulinemia model was initialized with initial condition $x_0=(214,8.75,8.75,0,0)^T$.

5. CONCLUSION

Despite very recent realizations or announcements, the design of an artificial pancreas is still an open problem. Such a reliable design will go through either a model free control or a model based control for the regulation of the blood plasma glycemia. In the latter case the design of an efficient observer is mandatory to estimate possibly all the state variables of the system. In any case, since the measured output is the intersticial glycemia and the output to be controlled is the blood glycemia, an observer will be the tool to assess the performance of the closed loop. The latter problem was left for future research in this paper as the insterticial glycemia was just assumed to be equal to the blood plasma glycemia. The model was reviewed from scratch and may be developped further. The focus was made on a significant subpopulation of diabetics as they display a very specific behavior.

The contributions is this research announcement are as follows

- A new time delay model is introduced for the subpopulation of diabetes affected by gastroparesis. From the current literature Borri et al. (2017), time-delay models have shown to be suitable to take into account external delays due to measurement devices or information processing.

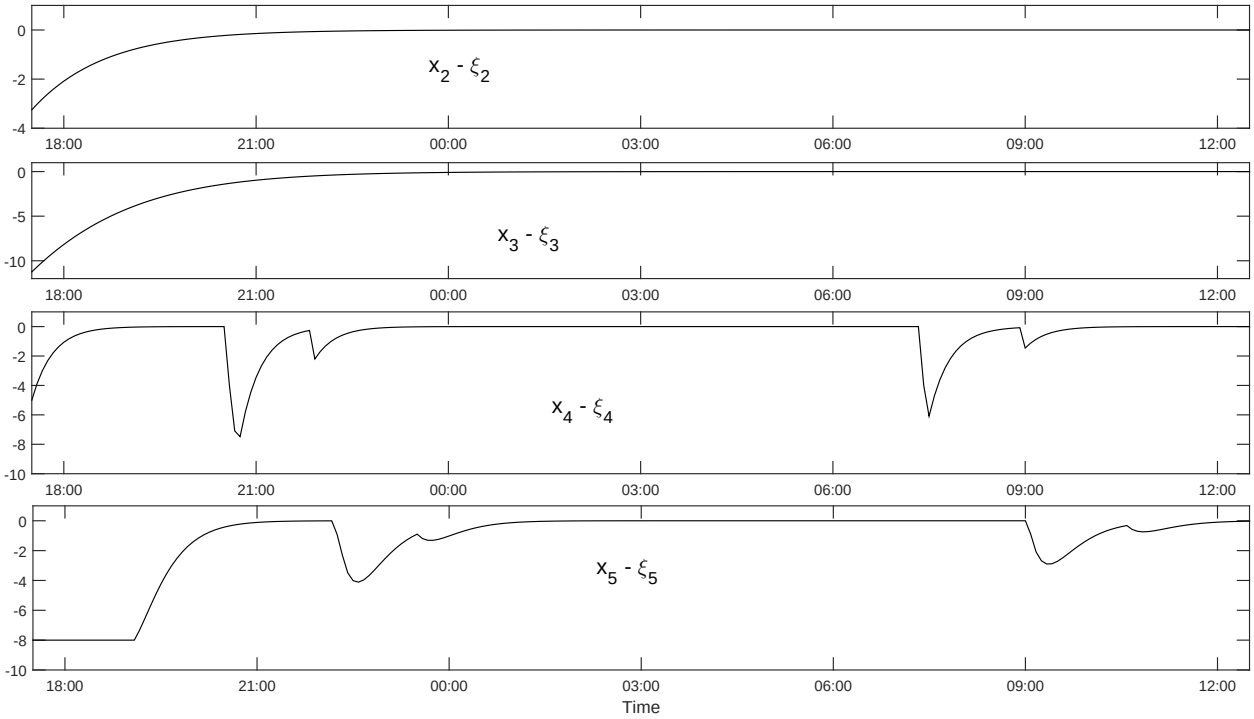

Fig. 2. Estimation Error in case of under-estimated amount of carbohydrates

In the present paper, the internal delay is inherent to the organism and may be measured through clinical tests or estimated by means of identification of a glycemic holter.

- The system is shown to be weakly observable.
- An observer is derived and tested *in silico*.

Future work concerns the use of the information obtained by the observer to automatically compute the necessary insuline quantity needed by the patient. Further perspectives include a model from the blood plasma glycemia to the intersticial glycemia as it is the latter which is directly measured by the sensor. The observer is then extended to estimate the blood plasma glycemia. Though the GE delay is measured getting through some clinical test, it is worth to estimate it in real time as done in Zheng et al. (2011).

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