H_∞ control in T1DM with lactate and nocturnal adrenaline biosignals

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***Abstract*— The availability of novel technologies for exogenous insulin release and continuous glucose monitoring have increased the possibilities of developing an artificial pancreas. This contribution tackles the design of a H_∞-based controller to compensate hyperglycemia in Type 1 diabetes mellitus (T1DM) under two scenarios: exercise and nocturnal hypoglycemia. Two biosignals are integrated to the blood glucose control problem: lactate is used in exercise scenario while adrenaline releasing is used for nocturnal hypoglycemia. The effects of each scenario are represented by weighting transfer functions at the control design. Each weighting function accounts the effect of hepatic glucose production and defines separately the following relations: (a) from plasmatic glucose to lactate during exercise and (b) from plasmatic glucose to adrenaline during nocturnal hypoglycemia. Also, the controller is designed by adding a frequency restriction in control signal to incorporate frequency components by the pancreatic insulin release pattern in a healthy subject. A nonlinear physiological model, including Glucose-Insulin-Glucagon dynamics and counter-regulatory effects, is used to show the time-response of the closed-loop including actuator dynamics and parametric changes.**

Palabras clave: Blood glucose control, Controlled drug delivery, Biomedical systems.

I. Introduction

Novel technology has been well accepted in clinical applications about therapy of Type 1 Diabetes Mellitus (T1DM) (Linkeschova y Raoul, 2000; Kaufman y Gibson, 2001) via continuous subcutaneous insulin infusion (Lenhard y Reeves, 2001) or blood glucose continuous monitoring (Mastrototaro, 2000). This fact has been encouraged by the potential improvement of glucose control in T1DM patients. The success is a result of four decades of scientific and technological work directed to develop an artificial pancreas (Albisser y Leibel, 1974; kadish, 1964; Bequette, 2005). Thus, the underlying idea is to construct a feedback closed-loop approach to mimic the pancreatic insulin release of a healthy subject through the exogenous delivery of insulin and continuous monitoring of glucose (niddkd, 2006). Together with the development of insulin pump as actuator and glucose monitoring as sensor, the design of control algorithms has been tackled since early 1990s (Fisher, 1991) with the role of computing the necessary insulin to lead the blood glucose level around healthy range; namely euglycemia. This fact has opened many questions in control theory discipline.

There are many interesting issues respect to handle the blood glucose level in T1DM via closed-loop approach. One of the challenges is related to the high variability of blood glucose levels due to exogenous events (as, among others, different kind of carbohydrate load during meal, glucose uptake during exercise) or endogenous events (as changes in hepatic or renal glucose production and uptake). From the control theory viewpoint, the exogenous events can be formulated as disturbances while the endogenous ones can be seen as uncertain parameter changes. Thus, the controlled plant corresponding to the diabetic patient is a nonlinear dynamical system with parametric uncertainties and uncertain disturbance inputs. In this sense, although control design is not an easy task, this problem has been addressed mainly via four control approaches with promissory results: model-based predictive control (Hovorka, 2004), adaptable techniques (Chase y Shaw, 2005), fuzzy logic (Campos-Delgado y Hernández-Ordoñez, 2006) and H_∞ robust control (Parker y Doyle, 2000; Ruiz-Velázquez y Femat, 2004).

Respect to H_∞ approaches, the synthesis for blood glucose control is based on plant frequency response in such manner that the control design ensures closed-loop performance in the frequency interval where plant is sensitive. The controller captures the frequency components and is capable to ensure closed-loop stability in an optimal or suboptimal sense. Moreover, as parametric uncertainties are included in closed-loop, the H_∞ approach can provide robust stability and robust performance to the closed-loop. This allows to compensate effects of parameter uncertainties on the frequency response to control the plant (Parker y Doyle, 2000; Ruiz-Velázquez y Femat, 2004; Zhou y Doyle, 1998). In addition, H_∞-based approach allows to incorporate weighting functions into the controller design. Specifically, a weighting functions has been recently incorporated (Femat y Ruiz-Velázquez, 2009) such that control design captures the temporal pattern of insulin delivery from healthy pancreas.

In this contribution, a H_∞-based controller is proposed to ensure suboptimal performance and closed-loop stability

for the blood glucose level in T1DM patients. The proposed controller incorporates biosignals such that two scenarios are accounted: exercise and nocturnal hypoglycemic. Lactate concentration is used as biosignal during exercise whereas adrenaline stands for the biosignal related to nocturnal hypoglycemic. Both scenarios are very important in blood glucose control of T1DM because, on the one hand, exercise is often a therapy recommendation and, on the other, nocturnal hypoglycemic is present in patient's life because long night fasting. As summary, we propose to design a nominal H_∞ control to manage glycemia in exercise and hypoglycemic scenarios. The content of this article is as follows: Section II deals with mathematical modeling of weighting transfer functions of lactate and adrenaline for exercise and hypoglycemia. Also, the model of a frequency restriction in the control signal is presented. Section III presents the integration of the weighting transfer functions in a closed-loop system to control glycemia in exercise and hypoglycemia. Also, the design of a nominal H_∞ controller is presented, in addition to the control performance and some numerical simulations about glucose control in exercise and hypoglycemia. Finally, in the last section a discussion and some remarks are presented.

II. Transfer functions for biosignals

Towards the control synthesis, input-output identification of a transfer function for each scenario is carried out to incorporate frequency components about their interaction on carbohydrate metabolism. Thus, the metabolic signals (namely biosignals) can help us to include input-output effects in H_∞-based control schemes. In here, we consider two scenarios with the corresponding biosignals: (i) Lactate as a metabolic signal related to exercise and (ii) Adrenaline respect to nocturnal hypoglycemia. Finally, one more transfer function is shown to add insulin pattern releasing. Next, details on the transfer functions are presented and, after that, both transfer functions are used in Section 3 to incorporate frequency contents onto the H_∞ synthesis.

II-A. Exercise and lactate

Lactate is a metabolite released into the blood stream during middle-effort exercise and appears as a metabolic product when muscle cells take energy from stored glycogen (Guyton, 1991). Although the metabolic path for lactate production is a multifactorial pand complicated process, we know that blood glucose concentration is one of the stimulus for producing lactate. Such a stimulus-response effects might be used as an input-output relation to identify a transfer function. We use experimental data from the blood glucose to lactate concentrations in a healthy trained subject, which were reported in (Stuart y Kreisman, 2001), to obtain a transfer function for the glucose-lactate relation.

The classical ARX technique was used to identify a continuous transfer function assuming the glucose concentration as the input signal and lactate concentration as the output. Data were measured a with sampling about 1 minute; see Figures 1 and 5.A in (Stuart y Kreisman, 2001) for glucose and lactate data, respectively. By means of the *System Identification Toolbox* by $MatLab^{®}$, we found a fourth-order transfer function whose parameters were adjusted to find the least distance (in the sense of minimal square) between the transfer function response and the experimental data (Ljung, 1999). The resulting stable transfer function (roots: $\lambda_{L_1,L_2} = -0{,}7554 \pm 0{,}9823i$, $\lambda_{L_3} = -0{,}12$ and $\lambda_{L_4} = -0{,}0019$), called $W_L(s)$, is given in Equation (1).

$$W_L(s) = \frac{-4{,}7 \times 10^{-3} s^3 + 0{,}06 s^2 + 0{,}05 s + 5{,}1 \times 10^{-4}}{s^4 + 1{,}6 s^3 + 1{,}74 s^2 + 0{,}1 s + 8{,}3 \times 10^{-3}} \quad (1)$$

II-B. Hypoglycemia and adrenaline

The nocturnal hypoglycemic scenario arises when the blood glucose level reach 40 mg/dl. Under such a concentration, energy is depleted and body cells have not enough available energy to carry out their functions. In critical situations, nocturnal hypoglycemia could be fatal because glucose is the main source for brain energy. From this fact, a very important aim on T1DM therapy is to account or to prevent hypoglycemic scenarios. We consider the nocturnal hypoglycemic because it is an event causing clinical emergency.

As blood glucose concentration becomes lower than 70 mg/dL, the glucose hepatic production is stimulated. One of the effects of hormone adrenaline releasing is to promote the hepatic glucose production necessary to avoid long-term hypoglycemia episodes (Cryer, 2002). That is, hormone adrenaline is involved in the counter-regulatory effects of glucose homeostasis, which appears as the blood glucose control falls to hypoglycemic. Specifically, resent results show that adrenaline is released under nocturnal hypoglycemia. Now, from the control theory viewpoint, the blood glucose stimulus on the adrenaline release can be interpreted as an input-output relation. We use the experimental data reported in (Schultes, 2007) to obtain a transfer function for glucose concentration as input and adrenaline concentration as output in nocturnal hypoglycemia. Our idea is to incorporate frequency components from glucose-adrenaline relation into the control synthesis. Thus, from data presented in Figure 2.B in (Schultes, 2007), we use the *System Identification Toolbox* of $MatLab^{®}$ to propose a second-order transfer function whose parameters where selected having a minimal distance (in the sense of least squares) between the experimental data and transfer function response (Ljung, 1999). The resulting function, $W_A(s)$, is a marginal stable one (roots: $\lambda_{A_1} = 0$ y $\lambda_{A_2} = -0{,}7322$) given by:

$$W_A(s) = \frac{0{,}0778 s + 0{,}432}{s^2 + 0{,}7322 s} \quad (2)$$

II-C. Frequency restriction function

In addition to equations (1) and (2), we consider an input-output relation to restrict the frequency components of the

control signal to that contained in a temporal pattern of pancreatic insulin release by a healthy subject. The transfer function was derived in (Femat y Ruiz-Velázquez, 2009) but it is taken here for completeness.

Since insulin infusion in T1DM is desired to be closer to the healthy pancreas behavior, frequency components of the releasing pattern by pancreas is incorporated to the closed-loop. Thus, an input-output relation is derived from intravenous insulin delivery as stimulus to the blood glucose concentration as response. That is, insulin infusion stands for input while blood glucose concentration is the output for this specific transfer function. As in (Femat y Ruiz-Velázquez, 2009), we use experimental data reported in (Bergman, 1979) to proposed a fourth-order transfer function and the the parameters of the function were selected using *System Identification Toolbox* by $MatLab$® to minimize the distance between the experimental data and the function response in the sense of least square) The resulting stable transfer function (roots: $\lambda_{u_1,u_2} = -0{,}0192 \pm 1{,}6146i$ and $\lambda_{u_3,u_4} = -0{,}1758 \pm 1{,}2721i$) is given by:

$$W_u(s) = \frac{2{,}38s^3 - 2{,}06s^2 + 4{,}7s - 4{,}09}{s^4 + 0{,}39s^3 + 4{,}27s^2 + 0{,}98s + 4{,}3} \qquad (3)$$

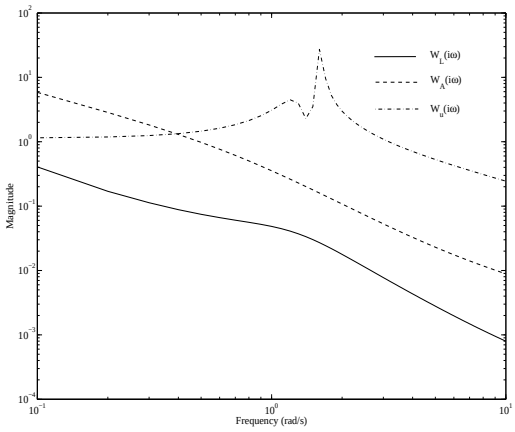

Figura 1. Frequency response of $W_L(s)$, $W_A(s)$ and $W_u(s)$.

It should be noted that the improvement of H_∞ robust performance, including $W_u(s)$, has been discussed in (Femat y Ruiz-Velázquez, 2009). As a complement, the frequency response of the three weighting transfer functions are shown in Figure 1.

III. H_∞ CONTROL FOR EXERCISE AND HYPERGLYCEMIA

The goal of controlling blood glucose concentration on T1DM patients is to handle hyperglycemia. Here, the transfer functions in previous section are added to hyperglycemia control as is shown in Figure 2. In this section, we firstly show how the complementary functions are integrated at the closed-loop to formulate the control problem. Then, the H_∞-based synthesis is discussed. Finally, the section is closed with an evaluation of the designed controller to show its capability on handle different hypoglycemic scenarios. Note there is differences with previous reports in sense the biosignaling for glucose to lactate W_L and adrenaline W_A are incorporated to account frequency components from exercise and nocturnal hypoglycemia.

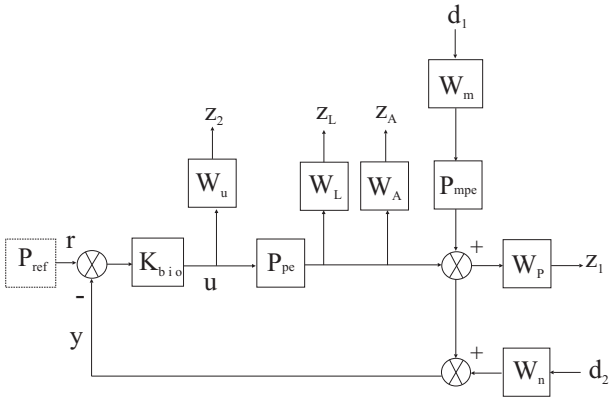

Figura 2. Block diagram for H_∞-based synthesis.

III-A. Control problem formulation

In previous control approaches (Parker y Doyle, 2000; Ruiz-Velázquez y Femat, 2004; Femat y Ruiz-Velázquez, 2009), authors addressed the hyperglycemic control by rejecting or attenuating disturbances by carbohydrate meal. Here, we formulate the disturbances rejection problem but considering effects of exercise and nocturnal hypoglycemia in the system output. Such effects are directly related to the output via the modeled weighting transfer function functions $W_L(s)$ and $W_A(s)$. The designed controller is denoted as $K_{bio}(s)$ to allude to biosignals. The description of each block in Figure 2 is as follows:

(*i*) W_L, W_A and W_u correspond to transfer functions described in Section II.

(*ii*) P_{pe} is the controlled plant and stands for a 6-th order transfer function which is derived by linearization and

posterior balanced truncation analysis of the 19-th order nonlinear physiological model proposed by Sorensen (Sorensen, 1985). The linearization was made around the unique equilibrium point of the Sorensen model reported at (Quiroz, 2007). So P_{pe} is given by Equation 4 in the top of the next page.

(*iii*) P_{mpe} (Equation 5)is a 6-th order transfer function representing the frequency contents by meal disturbance due to carbohydrate ingesta (Ruiz-Velázquez y Femat, 2004).

(*iv*) P_{ref} (Equation 6) is the following second-order model used to represent the blood glucose dynamics in a healthy subject after the ingestion of a carbohydrate load (Ruiz-Velázquez y Femat, 2004).

$$P_{pe}(s) = \frac{s^6 + 1{,}022s^5 + 0{,}339s^4 + 0{,}037s^3 + 4{,}57 \times 10^{-4}s^2 - 6{,}44 \times 10^{-5}s - 9{,}381 \times 10^{-7}}{s^6 + 1{,}022s^5 + 0{,}3391s^4 + 0{,}038s^3 + 1{,}647 \times 10^{-3}s^2 + 2{,}728 \times 10^{-5}s + 1{,}511 \times 10^{-7}} \tag{4}$$

$$P_{mpe}(s) = \frac{-1{,}403 \times 10^{-3}s^5 + 7{,}813 \times 10^{-3}s^4 + 2{,}53 \times 10^{-3}s^3 + 2{,}39 \times 10^{-4}s^2 + 7{,}948 \times 10^{-6}s + 7{,}73 \times 10^{-8}}{s^6 + 1{,}022s^5 + 0{,}339s^4 + 0{,}038s^3 1{,}647 \times 10^{-3}s^2 + 2{,}728 \times 10^{-5}s + 1{,}51 \times 10^{-7}} \tag{5}$$

$$P_{ref}(s) = \frac{3{,}51}{s^2 + 0{,}0420s + 0{,}9 \times 10^{-3}} \tag{6}$$

(v) W_n, W_m and W_p are respective transfer functions for noisy measurements, performance, and meal dynamics. They are given by:

$$W_p = \frac{0{,}88s + 0{,}01}{s + 0{,}01}\ ,\ W_n = \frac{1}{10000}\ ,\ W_m = \frac{1}{(3{,}5s + 1{,}5)}$$

As summary, the problem is worded as follows: *To solve the tracking problem with disturbances attenuation but accounting biosignals for insulin delivery, exercise, and nocturnal hypoglycemia; where system output stands for arterial glucose concentration, control input is defined as the intravenous insulin infusion, reference signal is the glucose curve tolerance of a healthy subject, and disturbances corresponds carbohydrate ingesta*.

III-B. Suboptimal H_∞ synthesis

Now we show the synthesis of the suboptimal H_∞ controller from the block diagram in Figure 2. The problem is that the arterial glucose concentration has to track the dynamics of the reference model $P_{ref}(s)$ attenuating disturbances by carbohydrate ingesta but considering exercise and nocturnal hypoglycemia. Then, a generalized plant is derived from each input signal (where u is the control signal and d_1, d_2 are perturbed signals from carbohydrate load and measurement noise, respectively) to each output signal (y is the blood glucose concentration G_H, and z_1, z_2, z_L, z_A are the output signals of the weighted functions of interest). The input and output signals of the system in Figure 2 can be related through the generalized plan via the following transfer matrix:

$$G_{bio}(s) = \left[\begin{array}{cc|c} W_pP_{mpe}W_m & 0 & W_pP_{pe} \\ 0 & 0 & W_u \\ 0 & 0 & W_LP_{pe} \\ 0 & 0 & W_AP_{pe} \\ \hline -P_{mpe}W_m & -W_n & -P_{pe} \end{array}\right] \tag{7}$$

$G_{bio}(s)$ is used for synthesis of the H_∞ control by LMI approach. After the standard iteration process via *Robust Control Toolbox* by *MatLab*®, the suboptimal problem is solved with $\gamma = 0{,}625$ by ensuring internal stability (see (Zhou y Doyle, 1998)). The resulting controller is a 23-th order one whose Hankel values are $\sigma = (0{,}74, 0{,}64, 0{,}41, 0{,}39, 0{,}23, 0{,}13, 0{,}02, 0{,}01, 0{,}002, 0{,}0004, 0{,}0003, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0)$. By inspection of σ values, the full order controller is reduced to 10-th order given by:

$$K_{bio}(s) = N_{bio}(s)/D_{bio}(s) \tag{8}$$

with $N_{bio}(s) = -38{,}97s^9 - 55{,}96s^8 - 192{,}8s^7 - 217{,}9s^6 - 252{,}9s^5 - 192{,}2s^4 - 46{,}7s^3 - 6{,}7s^2 - 0{,}203s - 1{,}298 \times 10^{-7}$ and $D_{bio}(s) = s^{10} + 48{,}14s^9 + 98{,}35s^8 + 314{,}8s^7 + 447{,}6s^6 + 565{,}4s^5 + 505s^4 + 251{,}2s^3 + 45{,}79s^2 + 2s + 1{,}3 \times 10^{-6}$. The performance for both full order controller (solid line) and the reduced (dash-dot line) $K_{bio}(s)$ is shown in Figure 3.

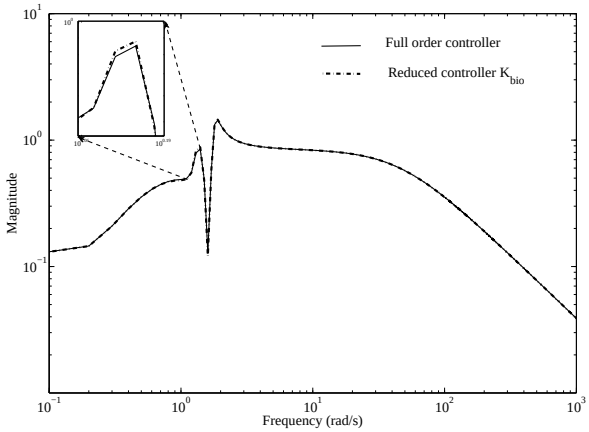

Figura 3. Frequency response of the full and reduced order controller.

It is possible to see small differences between performance of both controllers.

The closed-loop transfer function from output signal y to control signal u with full order controller is a 46-th order transfer function. Nevertheless, with the reduction, we obtain a reduced closed-loop transfer function, called $T_{yu}(s)$, given by:

$$T_{yu}(s) = \frac{NT_{yu}(s)}{DT_{yu}(s)} \tag{9}$$

where $NT_{yu}(s) = -5{,}041 \times 10^{-5}s^9 + 1{,}09 \times 10^{-4}s^8 - 1{,}3 \times 10^{-4}s^7 + 1{,}8 \times 10^{-3}s^6 + 1{,}06 \times 10^{-3}s^5 + 3{,}4 \times 10^{-3}s^4 + 2{,}08 \times 10^{-3}s^3 + 1{,}17 \times 10^{-4}s^2 + 1{,}35 \times 10^{-6}s - 3{,}31 \times 10^{-7}$ and $DT_{yu}(s) = s^{10} + 2{,}22s^9 + 7{,}78s^8 + 9{,}13s^7 + 13{,}68s^6 + 9{,}28s^5 + 4{,}24s^4 + 0{,}47s^3 + 0{,}02s^2 + 6{,}14 \times 10^{-4}s +$

$4{,}33 \times 10^{-6}$. The frequency response of full order closed-loop transfer function and the reduced $T_{yu}(s)$ is presented in Figure 4. The numerical implementation of $K_{bio}(s)$ was done using *Simulink* of *MatLab*® with the original 19-th order nonlinear Sorensen model (Sorensen, 1985) as is shown in Figure 5. Next, the control performance is evaluated in exercise and hypoglycemic scenarios via numerical simulations.

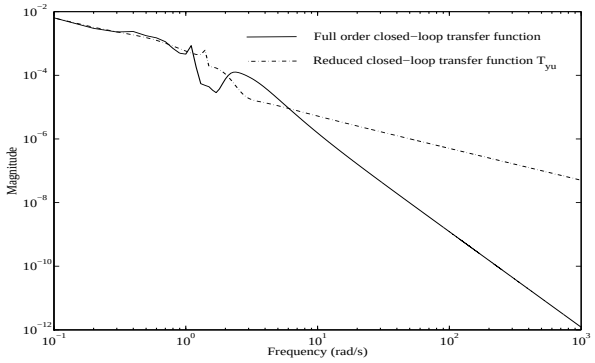

Figura 4. The closed-loop frequency response of $T_{yu}(s)$.

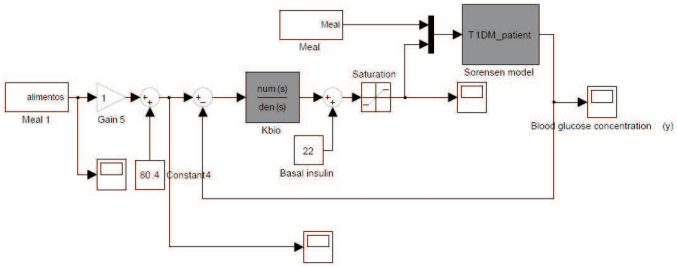

Figura 5. Numerical implementation of system in Figure 2

IV. Evaluation of K_{bio} execution

IV-A. Controlling hyperglycemia

Hyperglycemia is attenuated despite changes in parameters related to exercise and nocturnal hypoglycemia; see Figs. 6-9. In order to mimic such a glucose increment, a *positive* change (increment) in parameter related to hepatic glucose production was induced in simulation onto the nonlinear Sorensen model. The change was done according with the parametric sensitivity analysis reported in (Quiroz, 2007). That is, the most sensitive parameter to increase the glucose concentration is a metabolic parameter denoted by η_4. In order to test the execution of $K_{bio}(s)$ under exercise scenario, numerical experiments were simulated for the nominal value of η_4 and two changes equivalent to 50 % and 100 % from its nominal value, respectively. In Figure 6 under $K_{bio}(s)$ action, considering increment in parameter related to hepatic glucose production (representing exercise scenario), nominal value of $\eta_{4,0}$ is solid line, change of 50 % and 100 % on $\eta_{4,0}$ are dash-dot and dashed line, respectively. Figure 7 shows arterial insulin concentration of the Sorensen model. Now, the variation of the metabolic parameter η_6 is considered to mimic the nocturnal hypoglycemic. This parameter also is in the dynamic equation of hepatic glucose concentration but it affects the frequency component of the hyperbolic function that defines the hepatic glucose production (see Figures 5 and 7 in (Quiroz, 2007)). As in figures 6,7, the nominal value of η_6 ($\eta_{6,0}$) is considerate and the variation of 50 % and 100 % from its nominal value. The response in the blood glucose concentration under $K_{bio}(s)$ considering parametric changes in hepatic glucose production (related to nocturnal hypoglycemic scenario) is shown in Figure 9. Nominal value of $\eta_{6,0}$ is black solid line, and decreasing of 50 % and 100 % on $\eta_{6,0}$ (dash-dot and dashed line, respectively, whereas arterial insulin concentration is shown in Figure 8.

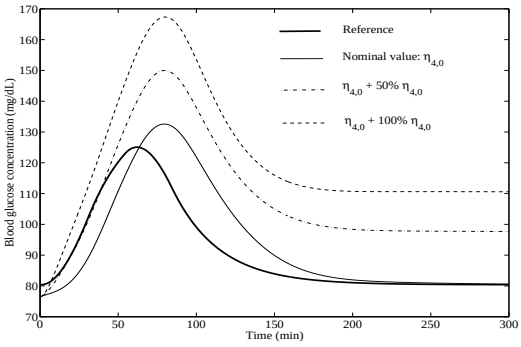

Figura 6. Blood glucose concentration during exercise scenario.

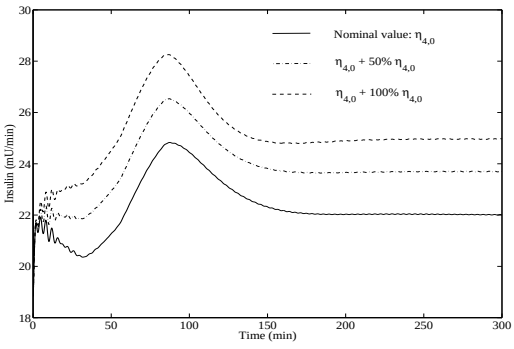

Figura 7. Control signal u in exercise scenario.

V. Concluding remarks

The numerical implementation of A suboptimal H_∞ controller $K_{bio}(s)$ is performed on the nonlinear T1DM patient and shows that: (i) under exercise scenario, $K_{bio}(s)$ avoids long-term hyperglycemic states due to the inherent increment in hepatic glucose production and (ii) at nocturnal hypoglycemic scenario, the control by $K_{bio}(s)$ is suitable to handle hyperglycemia and to reduce the hypoglycemic

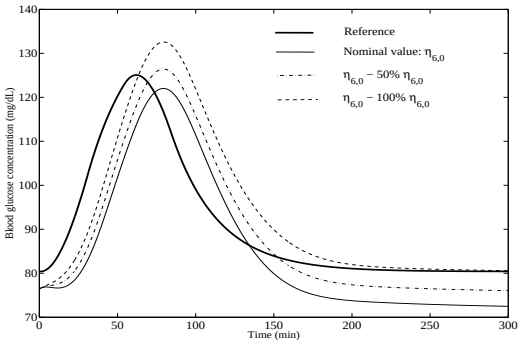

Figura 8. Blood glucose concentration during hypoglycemic scenario.

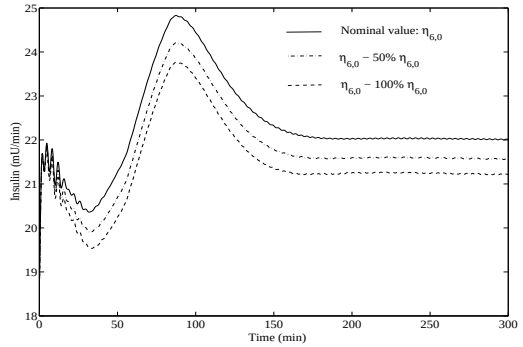

Figura 9. Control signal u in hypoglycemic scenario.

events. Finally, because of $K_{bio}(s)$ is capable of solving the tracking control problem in exercise and nocturnal hypoglycemic scenarios, incorporating the temporal pattern of pancreatic insulin release of a healthy subject, $K_{bio}(s)$ becomes a potential control algorithm to be integrate in a T1DM therapy based in artificial pancreas. However, robust H_∞ design is needed to reduce the hypoglycemic events where other biosignals induce hypoglycemia. Results on a robust approach are under progress and will be reported as soon as possible.

VI. Agradecimientos

This work was supported by CONACyT grant 48307-R.

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