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Predictive Active Disturbance Rejection Control for Insulin Infusion in Patients with T1DM

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Abstract: This paper presents an active disturbance rejection control scheme to automatically regulate the glucose level in type 1 diabetic patients. Although the blood glucose system is nonlinear, in this control approach, it is represented as a linear perturbed system, whose lumped disturbance input is estimated by an Extended State Observer (ESO) and then compensated by an robust controller tuned with Quantitative Feedback Theory (QFT). The robust control scheme uses a Smith predictor for the time delay compensation and allows taking into account the inter-patient variability presented in the glucose control problem.
In order to validate the effectiveness of this approach, the controller is tested in silico on a cohort of adult patients of the UVA/Padova metabolic simulator, which has been accepted by the Food and Drug Administration (FDA). *In silico* results indicate that safe blood glucose control can be achieved by the proposed controller.

Keywords: Glucose Control, Time delay, Active Disturbance Rejection Control, Smith Predictor, Quantitative Feedback Theory (QFT), Uncertainty.

1. INTRODUCTION

Diabetes is a chronic disease in which the body either cannot produce or use appropriately insulin. This disease causes high blood sugar levels, which can damage organs, blood vessels and nerves, and it has been considered as the fifth cause of death worldwide after communicable diseases, cardiovascular diseases, cancer and injury.

According to the International Diabetes Federation (IDF), in 2015 was estimated that 415 million of people suffered diabetes and it is estimated that rise to 642 million people with aged 20-79 (uncertainty interval: 521-829 million) will suffer from this disease in 2040 (Ogurtsova et al., 2017). Due to the high social impact of this disease, the scientific community has striven to attack the problem of diabetes from different perspectives and advances have been made in areas such as mathematical model of glucose-insulin dynamics, glucose sensors, pumps for automatic infusion and control strategies for the dosage of insulin.

Glucose control has been studied for more than four decades and different solutions have been proposed. With the appearance of new technologies in glucose sensing and insulin infusion, it is now possible to act upon glucose levels using real-time measurements since the sampling period of most continuous glucose monitors (CGM) is 5 minutes or less (Patek et al., 2007). Therefore, increasing scientific and industrial effort is focused on the development of artificial pancreas systems to control insulin delivery.

In situations where the disturbance can be measured a feedforward block could be added in order to attenuate or eliminate the influence of the disturbance. However, in processes such as blood glucose regulation system, where external disturbances cannot be measured directly, an active disturbance rejection control (ADRC) can be used. This method requires the least amount of information from the plant, tolerating the uncertainty in the model. The combined effect of both external disturbances and unknown dynamics is treated as an auxiliary state, estimated using an extra dimension accounted for in a Luenbergeer-type state observer (Sira-Ramirez et al., 2018; Carreño-Zagarra et al., 2019, 2018). Once the total disturbance is estimated, it can be cancelled out in the control law, reducing a complex non-linear control problem in a simple linear invariant time.

Due to the glucose-insulin system is a time-delayed process the control design is more demanding since an additional phase lag is introduced, which limits the bandwidth and reduces the stability margin. In these cases, a greater effort of the compensator is needed to achieve the desired

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performance specifications, within the physical limits imposed by the time delay (Garcia-Sanz and Guillen, 1999). The well-known predictor of Smith has been the main method to treat such systems, since it can increase the closed-loop bandwidth by eliminating the effect of time delay in the closed-loop. The prerequisite is an accurate system model available; otherwise, the non-perfect time-delay cancellation in the loop can cause instability. Some works with Smith predictor modifications have presented excellent results (Santos et al., 2016; Rodríguez et al., 2016).

To deal simultaneously with not just one, but many performance specifications at the same time, including stability, reference tracking, disturbance rejection, actuator limitations, reduction of vibrations, noise rejection, etc. in the presence of uncertainty in the model, quantitative feedback theory (QFT) can be a powerful robust control design tool (Garcia-Sanz, 2017). In (Garcıa-Sanz et al., 2001) and (Garcia-Sanz and Guillen, 1999) a Smith Predictor based on QFT is proposed to deal with processes with large delays and uncertainty. The method is applicable in the presence of uncertainty both in the model of the minimum phase part and in the time delay.

This paper presents a methodology for the design of a feedback controller and a disturbances observer for a set of adult patients with type 1 diabetes by using the QFT technique. The study is organized as follows. The mathematical model of glucoregulatory system is presented in Section 2. Section 3 explains the proposed robust design methodology for simultaneously tuning of both observer and feedback controller. In section 4 the methodology is used to address the problem of blood glucose regulation in a set of patients with type 1 diabetes. Section 5 presents the *in-silico* results and Section 6 contains the conclusions of the work.

2. MATHEMATICAL MODEL OF GLUCO-REGULATORY SYSTEM

The most well-known model is the Bergman's model, which contains the minimal number of parameters and is widely used in physiological researches to estimate glucose effectiveness and insulin sensitivity in the Intravenous Glucose Tolerance Test (IVGTT) (Bergman et al., 1981). This model represents the response of the blood glucose concentration to an intravenous glucose tolerance test and describes the behavior of glucose concentration in plasma, $G(t)$, and insulin concentration in plasma, $I(t)$, which are connected by an insulin-effect remote compartment denoted as $I_{is}(t)$:

$$\dot{G}(t) = -p_1\left(G(t) - G_b\right) - I_{is}(t)G(t) + d(t) \tag{1}$$

$$\dot{I}_{is}(t) = -p_2 I_{is}(t) + p_3\left(I(t) - I_b\right) \tag{2}$$

$$\dot{I}(t) = -nI(t) + u(t)/V_1 \tag{3}$$

where G_b and I_b correspond to the glucose and insulin basal level, respectively. Intravenous glucose injection is define as disturbance $d(t)$ and the actuating variable is the intravenous insulin infusion rate $u(t)$. Parameter p_1 represents the rate at which glucose is removed from the plasma. p_2 and p_3 are the fractional transfer coefficients of insulin into and out of the remote compartment where insulin action is expressed. n is the fractional disappearance rate of insulin and V_1 is an assumed intravenous insulin distribution volume. Fig. 1 illustrates a schema of mass transport according to (1)-(3). The dashed line indicates the effect of one concentration on another, and the continuous lines indicate mass transports.

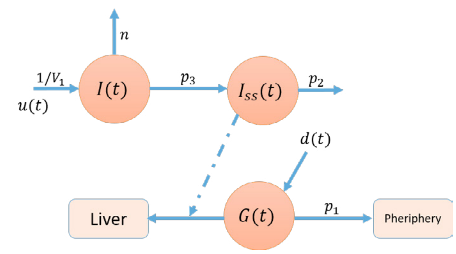

Fig. 1. Schematic representation of Bergman's minimal model

The model formulated in (Hovorka et al., 2004), describes the carbohydrates catabolism to monosaccharide taking place during meal digestion, as well as intestinal absorption. The intravenous glucose injection, represented by a two-compartment chain with identical transfer rates $1/t_{max,g}$, is given by:

$$d(t) = \frac{D_g A_g t e^{-t/t_{max,g}}}{V_g t_{max,g}^2} \tag{4}$$

being D_g the amount of carbohydrates ingested, A_g the carbohydrate bioavailability, $t_{max,g}$ the time-of-maximum appearance rate of glucose in the accessible glucose compartment and V_g is the distribution volume of the accessible compartment (glucose distribution space).

Motivated on these simple glucose-insulin models, other approaches were proposed. Recently, in (Sánchez-Peña et al., 2017) the following linear parameter-variant (LPV) model from the subcutaneous insulin delivery ($pmol/min$) to the subcutaneous glucose concentration deviation (mg/dl) is presented:

$$G_j(s) = k_j \frac{(s+z)\, e^{-15s}}{(s+p_1)\,(s+p_2)\,(s+p_3)} \tag{5}$$

where $z = 0.1501$, $p_2 = 0.0138$, $p_3 = 0.0143$ and the dominant pole p_1 is a variant parameter as a function of glucose. When considering the inter-patient variability, the model is adjusted by means of the 1800 rule (Hanas and Adolfsson, 2017), obtaining a personalized gain k indicated by k_j.

Uncertain parameters of the dynamic model are the following:

$$p_1 = [2.8, 6.8]\, 10^{-3}; \quad k = [-2.2024, -1.4343]\, 10^{-5} \tag{6}$$

3. ROBUST CONTROL APPROACH

This section presents a control approach where a disturbance observer and a robust controller to deal with the reference rejection problems are combined. This methodology focuses on uncertain time-delay systems. First, the parameters of the disturbance observer are selected, then, the robust controller for the equivalent plant (which consists of the observer and the uncertain plant) is designed by using QFT.

3.1 GPI Observer Design for Time-delay Systems

Consider the n-dimensional, time-delay smooth dynamic system:

$$\begin{aligned} f^{(n)}(t) &= K(t, f, \dot{f}, .., f^{(n-1)})u(t - t_d) + \xi(t) \\ y(t) &= c_o f + c_1 \dot{f} + ... + c_{n-1} f^{(n-1)} \end{aligned} \tag{7}$$

where t_d is the time-delay, $K(t, f, \dot{f}, .., f^{(n-1)})$ is the non-linear input gain matrix, evenly bounded, known and far from zero, y is the output of the system and the function $\xi(t)$ can be unknown and is uniformly absolutely bounded as well as all and each of its temporal derivatives to a finite order m. It is said that f is the flat output of the system described in (7), such that the input u and the output y can in turn be expressed as a linear combination of the flat output and a finite number of its derivatives, i.e., that y and u differential functions of the flat output f (Sira-Ramirez and Agrawal, 2004).

Lets consider the following extended state observer of grade $n + m$:

$$\begin{aligned} \dot{f}_0 &= f_1 + \lambda_{m+n-1}(f - f_0) \\ \dot{f}_j &= f_{j+1} + \lambda_{m+n-j-1}(f - f_0), \\ & \quad j = 1, ..., n-2 \\ \dot{f}_{n-1} &= K_0 u(t - t_d) + z_1 + \lambda_m (f - f_0) \\ \dot{z}_l &= z_{l+1} + \lambda_{m-l}(f - f_0), \quad l = 1, 2, ..., m-1 \\ \dot{z}_m &= \lambda_0 (f - f_0) \end{aligned} \tag{8}$$

where K_0 is the gain of the nominal plant. This observer is commonly called as Generalized Proportional Integral (GPI) and the disturbance estimation error can be reduced as small as desired if the observer gain parameters $\{\lambda_0, ..., \lambda_{m+n-1}\}$ are appropriately selected. The coefficients λ_j are selected such that the following polynomial in the complex variable s, is Hurwitz:

$$p_{obs}(s) = s^{m+n} + \lambda_{m+n-1} s^{m+n-1} + ... + \lambda_0 = 0 \tag{9}$$

Let $d(t)$ be the disturbance at plant input, defined as $d(t) = \xi(t)/K(t, y)$ and z_1 the estimate of such disturbance, i.e. $z_1 = \hat{d}(t)$. The transfer function between the control signal and the input disturbance estimation is given by: $u(s)/z_1(s) = -Q(s)e^{-t_d s}$, where:

$$Q(s) = \frac{\lambda_{m-1} s^{m-1} + \lambda_{m-2} s^{m-2} + ... + \lambda_0}{s^{n+m} + \lambda_{n+m-1} s^{n+m-1} + ... + \lambda_0} \tag{10}$$

By using the methodology proposed by (Kim and Wu, 2012), in order to mitigate typical peaking effects in high gain observers, the coefficient λ_0 can be chosen as:

$$\lambda_0 = \frac{T\alpha_0}{\lambda_{n+m}} \tag{11}$$

where α_0 is an arbitrary and strictly positive constant and the term $T > 0$ is known as the desired settling time or generalized time constant. The parameters $\lambda_0, \lambda_1 ... \lambda_{n+m}$ are determined by:

$$\lambda_i = \frac{T^i \alpha_0}{\alpha_{i-1}\alpha_{i-2}^2 \alpha_{i-3}^3 ... \alpha_1^{i-1} \lambda_{n+m}}, i = 1, ..., n+m-1 \tag{12}$$

$$\lambda_{n+m} = \frac{T^{n+m}\alpha_0}{\alpha_{n+m-1}\alpha_{n+m-2}^2 \alpha_{n+m-3}^3 ... \alpha_1^{n+m-1}} \tag{13}$$

From the above expressions, α_1 is the desired damping factor of the observer and it must be an adjustable constant parameter greater than 2. (Kim and Wu, 2012) proposes to calculate the remaining α_k coefficients by:

$$\alpha_k = \alpha_1 \frac{\sin\left(\frac{k\pi}{n+m}\right) + \sin\left(\frac{\pi}{n+m}\right)}{2\sin\left(\frac{k\pi}{n+m}\right)}, k = 2, ..., n+m-1 \tag{14}$$

3.2 Flat Output in Glucose-Insulin System

By considering that the linear system (5) is controllable, its flat output, f, is given by:

$$f(s) = \frac{e^{-15s}u(s)}{(s + \bar{p}_1)(s + p_2)(s + p_3)} \tag{15}$$

Therefore, the plasma glucose is determined by the flat output by means of the following expression:

$$\hat{G}(t) = \bar{k}\left(\dot{f}(t) + z f(t)\right) \tag{16}$$

where $\bar{k}$ and $\bar{p}_1$ are the average parameters of the uncertainty defined in (6), on whose basis an ADRC scheme is implemented.

Solving the expression (15) over time, its obtain:

$$\begin{aligned} f^{(3)} &= u_d - (p_1 + p_2 + p_3)\ddot{f} - \\ & (p_1 p_3 + p_1 p_2 + p_2 p_3)\dot{f} - p_1 p_2 p_3 f \end{aligned} \tag{17}$$

with $u_d(t)$ the input signal delayed, i.e. $u_d = u(t - 15)$.

Letting $\xi(t) = -(p_1 + p_2 + p_3)\ddot{f} - (p_1 p_3 + p_1 p_2 + p_2 p_3)\dot{f} - p_1 p_2 p_3 f$, the original problem is reduced to one defined on a simpler system, said to be in perturbed Brunovsky's canonical form:

$$f^{(3)} = u_d + \xi(t) \tag{18}$$

where $\xi(t)$ is the disturbance signal that includes the depreciated dynamics and the effect of glucose ingestion.

An state extended observer or GPI observer (19) is designed for the system (18), which provides simultaneous estimations of the phase variables associated with the flat output f and of the disturbance $\xi(t)$.

$$\begin{aligned} \dot{f}_0 &= f_1 + \lambda_3 (f - f_0) \\ \dot{f}_1 &= f_2 + \lambda_2 (f - f_0), \\ \dot{f}_2 &= u_d + z_1 + \lambda_1 (f - f_0) \\ \dot{z}_1 &= \lambda_0 (f - f_0) \end{aligned} \tag{19}$$

where f_0 is the estimation of the flat output f, f_1 and f_2 are the first and second derivatives of f_0 and $z_1 = \hat{\xi}(t)$ is the disturbance estimation. To guarantee an settling-time close to 5 minutes of the estimation error the observer gain parameters in (11) and (14) were set as: $T = 20$, $\alpha_0 = 1$ and $\alpha_1 = 8$. In this way the estimation error characteristic polynomial is defined by $p_{obs}(s) = s^4 + 21.85s^3 + 59.68s^2 + 23.87s + 1.194 = 0$.

3.3 Robust Smith Predictor Scheme

Consider the control based on disturbance observer (DOB) in Fig. 2. The transfer function from input disturbance to the output is given by:

$$P_{dy}(s) = \frac{[1 - Q(s)e^{-\hat{t}_d s}]P(s)e^{-t_d s}}{1 + \left[\frac{P(s)}{P_n(s)}e^{-t_d s} - e^{-\hat{t}_d s}\right]Q(s)} \quad (20)$$

where P_n is the nominal model used in the Smith Predictor and the disturbance observer.

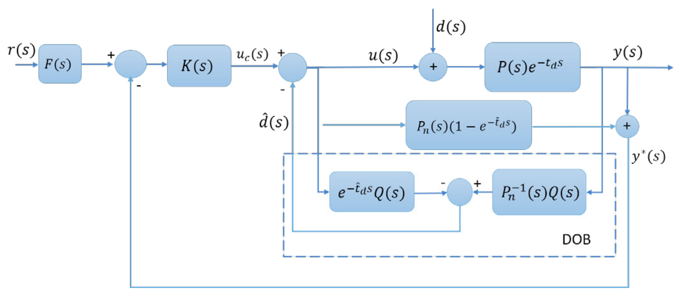

Fig. 2. Predictive disturbance observer for time-delay systems

The transfer function from controller signal to the output of the plant -which will be called equivalent plant of the system- is given by the following expression:

$$P_{eq}(s) = \frac{P(s)e^{-t_d s} + P_n(s)(1 - e^{-\hat{t}_d s})}{1 + \left[\frac{P(s)}{P_n(s)}e^{-t_d s} - e^{-\hat{t}_d s}\right]Q(s)} \quad (21)$$

$$\frac{y(s)}{y^*(s)} = \frac{e^{-t_d s}}{\left(1 - e^{-\hat{t}_d s}\right)\frac{P_n(s)}{P(s)} + e^{-t_d s}} \quad (22)$$

The diagram shown in Fig. 2 is rearranged to an equivalent structure, as shown in Fig. 3, where the expression $P_{eq}(s)$ is presented in (21), $H(s)$ is the denominator of function in (22) and $d_i(s)$ is the disturbance at equivalent plant input.

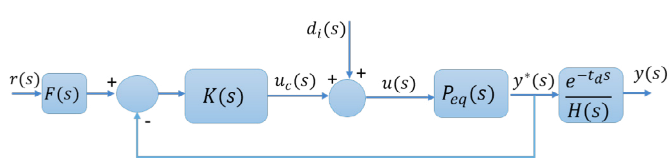

Fig. 3. Equivalent Diagram of the Smith Predictor

An analysis of the equivalent plant structure shows that, if there is no uncertainty in the model, the design of the controller can be done without considering the effect of the disturbance observer. However, if there is a model-plant mismatch, the expression $P_{eq}(s)$ is different from $P(s)$. As a consequence, the control system is affected by the uncertainty and a robust control technique must be considered.

3.4 Feedback controller design using QFT

The quantitative feedback theory (QFT) is a robust control strategy that explicitly proposes the use of feedback to reduce the effects of plant uncertainty and satisfy desired performance control specifications by using a 2-DOF control scheme. This methodology searches quantitatively for a controller that satisfies all the required performance specifications for every plant valued within the uncertain parameters set.

The reliability of the final controller depends on the adequate description of the uncertainty. If the uncertainty covers the entire operating range of the plant, a controller that complies with all QFT bounds will guarantee good performance for each possible plant. However, a large uncertainty would make it more difficult to obtain a suitable controller for the problem due there is a trade-off between the size of the uncertainty and the achievable performance of the controller (Garcia-Sanz, 2017).

The specifications set considered in this paper is given by:

Stability specification

$$\left|\frac{y^*(j\omega)}{F(j\omega)r(j\omega)}\right| = \left|\frac{K(j\omega)P_{eq}(j\omega)}{1 + K(j\omega)P_{eq}(j\omega)}\right| \le \delta_U(\omega) \quad (23)$$

where $K(j\omega)$ is the loop controller and $P_{eq}(j\omega)$ is the equivalent-plant.

The stability specification has to be achieved at every frequency of interest. This inequality imposes a maximum over-impulse in closed-loop system response. It also guarantees particular phase and gain margins, which reflects the degree of stability of the control system.

References tracking specification Two functions $T_U(\omega)$ and $T_L(\omega)$ are given, indicating upper and lower bounds for the magnitude of the closed-loop transfer function magnitude from reference to output:

$$T_L(\omega) \le \left|\frac{y^*(j\omega)}{r(j\omega)}\right| = \left|\frac{F(j\omega)K(j\omega)P_{eq}(j\omega)}{1 + K(j\omega)P_{eq}(j\omega)}\right| \le T_U(\omega) \quad (24)$$

In order to reduce the high frequency activity of the actuators and avoid possible mechanical fatigue problems, the reference tracking specifications are generally defined only for some low to mid frequencies. A practical choice is given by the following expressions (Garcia-Sanz, 2017):

$$T_U(s) = \frac{\omega_n^2/a(s+a)}{s^2 + 2\zeta\omega_n s + \omega_n^2}$$
$$T_L(s) = \frac{1}{(\tau_1 s + 1)(\tau_2 s + 1)(\tau_3 s + 1)} \quad (25)$$

where $T_U(\omega) = |T_U(j\omega)|$ and $T_L(\omega) = |T_L(j\omega)|$.

4. CONTROLLER SYNTHESIS FOR UVA/PADOVA TYPE 1 DIABETES SIMULATOR

As mentioned, the parameters of the Smith predictor and the observer of Figure 2 are set for the average adult model of the UVA/Padova. This is the nominal case. To consider the high uncertainty and intra-patient parametric variation, the quantitative feedback theory is used to satisfy the desired performance specifications. Considering the feedback control scheme of Fig. 3 and equation (21), the equivalent plant, containing the predictor, observer, dynamics of the patient, CGM sensor and insulin pump, is obtained.

As a frequency-domain methodology, QFT works with a vector of frequencies of interest. Based on the family of equivalent-plants generated from the definition of the parametric uncertainty and by inspection of the Bode diagram, the following vector of working frequencies is defined: $W = [0.0003, 0.04, 0.4, 1]$ rad/s. For the glucose regulation system, an adequate glucose level in the patient in the presence of strong disturbances due to food intake is required. Considering the benefits of the disturbance observer, robust stability and references tracking specifications can be defined for the feedback controller design.

In order to obtain a phase margin around 30.5° a $\delta_U = 1.9$ dB is set in the robust stability specification in eq. (23). For blood glucose response to meal the following references tracking specifications have been considered:

$$T_U(s) = \frac{7.744 * 10^{-5}(10s+1)}{s^2 + 0.0264s + 4.84 * 10^{-4}}$$
$$T_L(s) = \frac{0.16}{(40s+1)(50s+1)(60s+1)} \quad (26)$$

These frequency specifications correspond to a closed loop time constant between 65 and 95 minutes.

The controller design by loop-shaping is carried out on the Nichols chart. As can be seen in Fig. 4, the nominal loop transmission function $L_0(s) = K(s)P_0(s)$ satisfies all the bounds and the stability contour, where $P_0(s)$ is the nominal equivalent plant. The proposed controller satisfying all the bounds is given by the following expression:

$$K(s) = -1.2685\frac{(s+0.0075)(s+0.083)}{s(s+1.1302)} \quad (27)$$

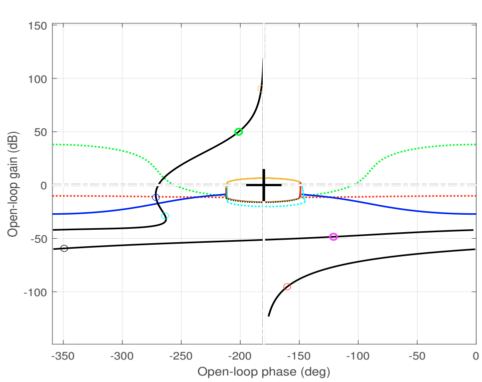

Fig. 4. Stability and tracking bounds and $L_0(s)$ design-loop shaping

Taking into account the controller $K(s)$ defined in equation (27), the reference tracking specifications presented in (24), and the equivalent plant model presented in (21), a prefilter $F(s)$ to assure that all the input/output function $FKP_{eq}/(1+KP_{eq})$ are inside the band defined by the limits $T_U(\omega)$ and $T_L(\omega)$ is designed. The prefilter obtained is the following and validation of the references tracking specification is given in Fig. 5:

$$F(s) = \frac{0.16}{2500s^2 + 70.71s + 1} \quad (28)$$

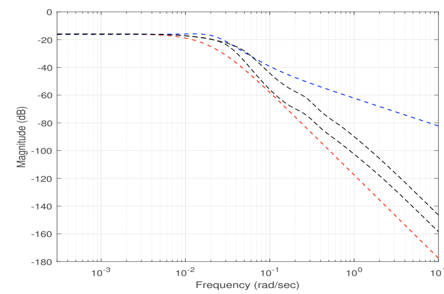

Fig. 5. Validation of tracking specifications given by (26) for $\{K, F\}$ controller from (27) and (28).

Analysis of the closed-loop stability in the frequency domain is shown in Fig. 6. The dashed line is the stability specification δ_U defined in equation (23). The solid line represent the worst case of all the possible functions $KP_{eq}/(1+KP_{eq})$ at each frequency due to the model uncertainty. The control system meets the stability specification (the solid line is below the dashed line δ_U) for all the plants within the uncertainty.

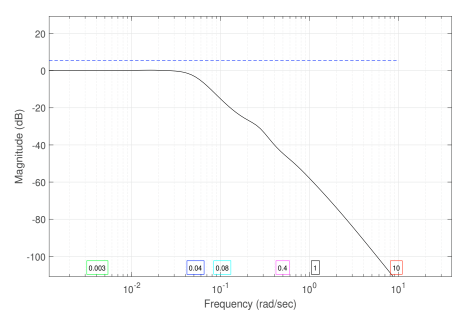

Fig. 6. Stability analysis, frequency domain: δ_U specification (dashed line), and worst case of $KP_{eq}/(1+KP_{eq})$ within the uncertain plants at each frequency (solid line).

5. IN SILICO RESULTS

Before the clinical trial, the algorithm must be rigorously tested *in silico*. Here, some results are presented considering the following: *i*) the complete *in silico* adult cohort of the 10 subject FDA accepted UVA/Padova simulator, a CGM as sensor, and a CSII pump; *ii*) all meals contain 90 g of carbohydrates; *iii*) The first meal that is shown in simulation for each *in silico* subject is dinner.

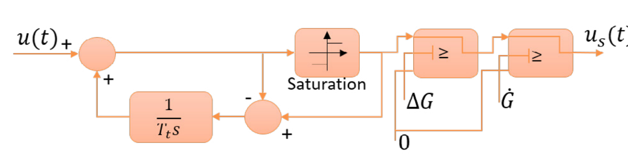

Fig. 7. Nonlinear dynamic control structure

To overcome the limitations of simple LTI controllers, the inclusion of a non-linear scheme is proposed, as shown in Fig. 7. The structure consists of an anti-windup stage with an inner-loop around the integral part for the actuator saturation. $1/T_t$ is the anti-windup gain and it has been suggested as $T_t = \sqrt{T_i T_d}$ (Åström et al., 2006), where T_i and T_d are the integral and derivative time in (27).

Also two switches are added to control insulin infusion and avoid hypoglycemic events. The first switch allows the suspension of insulin when glucose values are lower than basal glucose, i.e. $\Delta G = G(t) - G_b < 0$. The second switch is used to limit the insulin application provided by the controller only when there is a positive derivative in the measured or estimated glucose. This ensures that the pump only delivers insulin when there is an increase in glucose due to meal intake, otherwise the infusion will be suspended. Based on equations (16) and (19) the derivative of glucose can be estimated by means of the following expression:

$$\hat{\dot{G}}(t) = \bar{k}\left[f_2 + (\lambda_2 + z\lambda_3)(f - f_0) + zf_1\right] \tag{29}$$

Fig. 8 shows the results of blood glucose for the 10 adult patients. Although there are postprandial hyperglycemic events, it can be observed that in none of the cases, when the predictive active disturbance rejection control strategy is used, there are hypoglycemia levels.

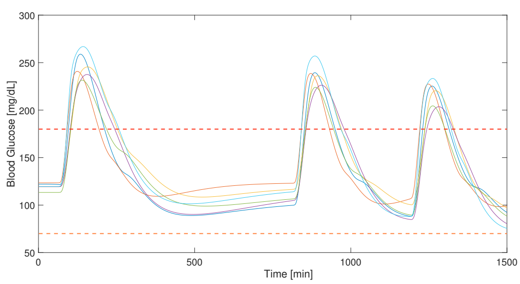

Fig. 8. Simulation results for the proposed predictive observer-based control using UVA/Padova simulator

6. CONCLUSION

In this article, the artificial pancreas problem is dealt by designing a control strategy for a set of T1DM adult patients. A linearized uncertain model is employed for designing a linear controller using loop-shaping joint to a GPI observer that estimates the states and external disturbances. A safety stage is added in order to regulate the amount of insulin once the blood glucose concentration begins to decrease. This avoids low late postprandial levels and hypoglycemic events and enables a safer closed loop control. The great advantage that was found with the proposed glucose regulation structure is the no requirement of an individualized controller design for each patient, but rather a single controller is obtained for the set of adult patients. *In silico* results showed an excellent dynamic behaviour of proposed robust controller for every patient in the presence of large amounts of glucose intake.

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