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An Interval Predictor–based Robust Controller for the Blood Glucose Regulation Problem

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***Abstract*—This paper contributes to designing a robust controller for the blood glucose regulation problem in patients with diabetes mellitus type–1. The proposed switching control approach is based on an interval predictor–based state–feedback, which takes into account the state and input constraints of the insulin–glucose system dynamics (Bergman minimal model), *i.e.,* positive states and input, and minimum and maximum values of the blood glucose level and the insulin infusion rate. The method deals with interpatient variabilities and unannounced food intake. Additionally, the switching structure of the control law allows us to switch off the state–feedback controller stopping the insulin injection for proper glucose level regulation. The stability analysis is based on a Lyapunov function approach and guarantees the asymptotic convergence of the blood glucose level around the desired value. The synthesis of the controller is constructive since it is in terms of linear matrix inequalities. Some simulation results, over a cohort of 4 virtual type 1 diabetes mellitus adult patients, illustrate the performance of the proposed robust controller.**

***Index Terms*—Constrained Systems, Glucose Regulation, Robust Control.**

I. Introduction

THE diabetes mellitus is a chronic disease involving a deficiency of insulin production by the pancreas. As a result, the patients suffer from hyperglycemia, an increase in blood glucose levels that, if left unattended, may lead to several health complications [1]. Diabetic patients, particularly those suffering from type–1 diabetes mellitus (T1DM), rely on external insulin ministration on a daily basis. Since the '60s, considerable research has been devoted to proposing autonomous insulin delivery systems to regulate blood glucose and keep it within the normoglycemic range (*i.e.*, 70–180 mg/dl). The goal is to avoid glucose excursions to the hyper and hypoglycemia ranges, that is, above and below the normoglycemic band. While hyperglycemia may result in a long–term problem, hypoglycemia is potentially life–threatening [2].

Autonomous insulin delivery systems rely on state–feedback control schemes and face challenging problems such as inter and intrapatient variability and unannounced food intake. Interpatient variability relates to the diverse biological characteristics of the patients; in contrast, intrapatient variability refers to the evolving physiological condition of a patient over time. Therefore, to address robustness and grant reliable performance, several robust control approaches have been considered in the literature. For instance, sliding–mode control [3], H_∞ control [4], model predictive control (MPC) [5], and linear parameter varying (LPV)–based control [6], among many others.

An additional defiance is that the model describing the glucose–insulin dynamics of the patient is a positive system, *i.e.*, the states represent concentrations of particular substances, and the control input only admits positive values. In other words, the control signal cannot reverse an insulin overdose. A possible way to address this issue is by establishing states and input constraints. In this regard, MPC is a systematic approach to face state and input constraints by solving a control optimization problem. Nonetheless, MPC demands a detailed and reliable mathematical model, which in practice is not affordable. The MPC approach has been combined with other methods to address robustness (see, *e.g.*, [7] and the references therein). Still, the computational burden is the main drawback of MPC strategies.

Apart from MPC, only a few results have coped with the positive nature of the glucose–insulin dynamics (see, *e.g.*, [8], [9], and [10]). The work in [8] proposes a Lyapunov function approach that takes into account the constraints in the input and the insulin variable. Given the cascade structure of the glucose–insulin dynamics model, insulin stabilization entails glucose stabilization. Nonetheless, hypoglycemia may occur since the glucose variable is left unconstrained. In contrast, [9] tackles the problem designing two independent discontinuous sliding–mode controllers for the glucose and insulin subsystems. Still, a continuous approximation is used and therefore the robustness is lost in practice. Instead, in [10], the authors propose a positive state–feedback control to regulate the blood glucose, constraining the insulin within a desired interval while ensuring the blood glucose value is kept above the desired value. All the previously discussed approaches assume that the full state is available and disregard the effect of food intake.

To sum up, only few works are developed respecting the natural system constraints, *i.e.,* positive states and input, and

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minimum and maximum values of the blood glucose level and the insulin infusion rate. Motivated by these issues, in this paper, we propose a robust controller for the blood glucose regulation problem in patients with T1DM. The proposed switching control approach is based on an interval predictor–based state–feedback that considers the state and input constraints of the insulin–glucose system dynamics, *i.e.,* the Bergman minimal model. Moreover, the switching structure of the control law allows us to switch off the state–feedback controller stopping the insulin injection for proper glucose level regulation. A Lyapunov function approach ensures the asymptotic convergence of the blood glucose level around the desired value. The synthesis of the controller is constructive since it is in terms of linear matrix inequalities (LMIs).

The rest of this manuscript is organized as follows. The problem statement is given in Section II. The regulation error dynamics is presented in Section III. In Section IV, we provide an interval predictor for the regulation error dynamics while the robust control design is introduced in Section V. In Section VI the simulation results are discussed. Finally, Section VII provides some concluding remarks.

Notation: For a couple of vectors $x_1, x_2 \in \mathbb{R}^n$ and a couple of matrices $A_1, A_2 \in \mathbb{R}^{n\times n}$, the relations $x_1 \leq x_2$ and $A_1 \leq A_2$ are understood in the component–wise sense. In the same sense, for a matrix $A \in \mathbb{R}^{n\times n}$, define $A^+ = \max\{0, A\}$, $A^- = A^+ - A$ and $|A| = A^+ + A^-$, similarly for a vector. For a symmetric matrix $P \in \mathbb{R}^{n\times n}$, the notation $P \prec 0$ ($P \succeq 0$) means that P is negative (nonnegative) definite. A matrix $A \in \mathbb{R}^{n\times n}$ is called Metzler when all its non–diagonal elements are nonnegative. Define the vector $\mathbf{1}_n = (1, \dots 1)^\top \in \mathbb{R}^n$. The term $\mathrm{He}(A)$ denotes $A + A^\top$, for a matrix $A \in \mathbb{R}^{n\times n}$. The set $\mathscr{E}(R, x_\star) = \{x \in \mathbb{R}^n : (x - x_\star)^\top R(x - x_\star) \leq 1\}$ is an ellipsoid centered at $x_\star \in \mathbb{R}^n$, characterized by a matrix $0 \prec R^\top = R \in \mathbb{R}^{n\times n}$.

II. Problem Statement

The insulin–glucose system dynamics, for patients with T1DM, can be represented as follows [11]

$$\dot{x}_1 = -x_1 x_2 + d(t), \tag{1a}$$
$$\dot{x}_2 = -p_2 x_2 + p_3(x_3 - I_b), \tag{1b}$$
$$\dot{x}_3 = -n(x_3 - I_b) + u(t), \tag{1c}$$

where x_1 is the glucose concentration in the blood plasma [mg/dl]; x_2 is the insulin's effect on the net glucose disappearance, the insulin concentration in the remote compartments [1/min]; x_3 is the insulin concentration in plasma at time t [μU/ml]; u is the control input, which corresponds to the insulin infusion rate; d describes the rate at which glucose is absorbed to the blood from the intestine after food intake; I_b is the basal pre–injection level of insulin [μU/ml]; p_2 is the rate for decrease in tissue glucose uptake ability [1/min]; p_3 is the insulin–dependent increase in glucose uptake ability in tissue per unit of insulin concentration above the basal level [(μU/ml)/min^2]; n is the first–order decay rate for insulin in blood [1/min]. We consider that all of the parameters and the food intake are unknown but a set of nominal, maximum, and minimum values are available.

We assume that the disturbance d can be modeled by a vanishing exponential function of the following form:

$$d(t) = b_1 e^{-b_2(t - t_{FI})}, \tag{2}$$

with some positive constants $b_1, b_2 > 0$, $t \geq t_{FI}$, and a certain food intake time $t_{FI} \geq 0$. Therefore, we have that $d \in [0, b_1]$.

This work aims to design a control law that is able to achieve a desired glucose concentration for an entire adult patient cohort, despite the interpatient variability and disturbances, and taking into account the system constraints, *i.e.,* $x_1(t) \in \mathbb{X}_1 = (70, 250)$, $x_2(t) \in \mathbb{X}_2 = [0, x_{2\max})$, $x_3(t) \in \mathbb{X}_3 = (I_{b\min}, I_{b\max})$, and $u(t) \in \mathbb{U} = [0, u_{\max}]$, for all $t \geq 0$, and for some positive values $x_{2\max}$, $I_{b\min}$, $I_{b\max}$, and $u_{\max}$.

III. Regulation Error Dynamics

Let us define the regulation errors as follows

$$e_1 = x_1 - G_d, \tag{3a}$$
$$e_2 = x_2, \tag{3b}$$
$$e_3 = x_3 - I_d, \tag{3c}$$

where G_d is the desired level of glucose [mg/dl] and I_d is the desired level of insulin [μU/ml]. Therefore, the state constraint sets are given now as follows:

$$\mathbb{E}_1 = \{e_1 \in \mathbb{R} : e_1 \in (90 - G_d, 180 - G_d)\}, \tag{4a}$$
$$\mathbb{E}_2 = \{e_2 \in \mathbb{R} : e_2 \in [0, x_{2\max})\}, \tag{4b}$$
$$\mathbb{E}_3 = \{e_3 \in \mathbb{R} : e_3 \in (I_{b\min} - I_d, I_{b\max} - I_d)\}. \tag{4c}$$

According to (1) and (3), the regulation error dynamics holds the following differential equations.

$$\dot{e}_1 = -(e_1 + G_d)e_2 + d(t), \tag{5a}$$
$$\dot{e}_2 = -p_2 e_2 + p_3 e_3 + p_3 I_{db}, \tag{5b}$$
$$\dot{e}_3 = -n e_3 - n I_{db} + u(t), \tag{5c}$$

where $I_{db} = I_d - I_b$, *i.e.,* I_{db} is the difference between the desired level of insulin and the basal pre–injection level of insulin. Note that the constraints over the error dynamics do not necessarily imply that the error must be positive, it will depend on the values G_d, I_d, $I_{b\min}$, and $I_{b\max}$, but system (1) is positive.

Let us introduce a virtual control such that

$$e_2 = \psi(e_1) = x_1^{-1} k_1 e_1, \tag{6}$$

with some $k_1 > 0$. Thus, the dynamics for e_1 satisfies

$$\dot{e}_1 = -k_1 e_1 + d(t). \tag{7}$$

It is easy to show that system (7) is Input–to–State Stable with respect to d. Define the following auxiliary variable

$$z_2 = e_2 - \psi(e_1) = e_2 - x_1^{-1}k_1e_1. \tag{8}$$

Then, based on (8), the system (5) can be rewritten as follows

$$\dot{e}_1 = -k_1e_1 - x_1z_2 + d(t), \tag{9a}$$
$$\dot{z}_2 = -p_2z_2 - p_2\psi(e_1) - \dot{\psi}(e_1) + p_3e_3 + p_3I_{db}, \tag{9b}$$
$$\dot{e}_3 = -ne_3 - nI_{db} + u(t), \tag{9c}$$

where $\dot{\psi}(e_1) = -x_1^{-1}k_1^2e_1 - k_1z_2 + x_1^{-1}k_1e_1z_2 + x_1^{-2}k_1^2e_1^2 + x_1^{-2}k_1G_dd(t)$. Therefore, the closed–loop regulation error dynamics can be given in the following form, *i.e.,*

$$\dot{\varepsilon} = A(\rho)\varepsilon + Bu + F(x_1)w(t), \tag{10}$$

where $\varepsilon = (e_1, z_2, e_3)^\top$, $w(t) = (d(t), p_3I_{db}, nI_{db})^\top$, and

$$A(\rho) = \begin{pmatrix} -k_1 & -x_1 & 0 \\ x_1^{-2}k_1(k_1G_d - p_2x_1) & -p_2 + x_1^{-1}k_1G_d & p_3 \\ 0 & 0 & -n \end{pmatrix},$$
$$B = \begin{pmatrix} 0 \\ 0 \\ 1 \end{pmatrix},\ F(x_1) = \begin{pmatrix} 1 & 0 & 0 \\ -x_1^{-2}k_1G_d & 1 & 0 \\ 0 & 0 & -1 \end{pmatrix},$$

with the unknown scheduling vector $\rho = (x_1, p_2, p_3, n)^\top$. Note that the state and input constraints for the system (10) are given now as follows:

$$\mathbb{E}_1 = \{e_1 \in \mathbb{R} : e_1 \in (90 - G_d, 180 - G_d)\}, \tag{11a}$$
$$\mathbb{Z}_2 = \{z_2 \in \mathbb{R} : z_2 \in (\underline{z}_2, \overline{z}_2)\}, \tag{11b}$$
$$\mathbb{E}_3 = \{e_3 \in \mathbb{R} : e_3 \in (I_{b\min} - I_d, I_{b\max} - I_d)\}, \tag{11c}$$
$$\mathbb{U} = \{u \in \mathbb{R} : u \in [0, u_{\max}]\}, \tag{11d}$$

where $\underline{z}_2 = -k_1(180 - G_d)/180$ and $\overline{z}_2 = x_{2\max} + k_1(G_d - 90)/90$. In addition, the state constraints can be expressed in the following polytopic way

$$\mathcal{P} = \left\{\varepsilon \in \mathbb{R}^3 | q_i^\top\varepsilon \le 1,\ i = \overline{1,6}\right\}, \tag{12}$$

where the vectors $q_i \in \mathbb{R}^3$ are $q_1 = (90 - G_d, 0, 0)^\top$, $q_2 = (0, \underline{z}_2, 0)^\top$, $q_3 = (0, 0, I_{b\min} - I_d)^\top$, $q_4 = (180 - G_d, 0, 0)^\top$, $q_5 = (0, \overline{z}_2, 0)^\top$, and $q_1 = (0, 0, I_{b\max} - I_d)^\top$. Now, we need to design a robust control law u, for system (10), such that $u(t) \in \mathbb{U} = [0, u_{\max}]$, for all $t \ge 0$, and the trajectories of regulation error dynamics converge to zero or to a region around the origin, despite the parameter uncertainties and disturbances, and taking into account the system constraints (11). Then, the idea is to design u based on an interval predictor state–feedback.

IV. Interval Predictor

Note that the matrix $A(\rho)$ can be written as follows

$$A(\rho) = \begin{pmatrix} -k_1 & 0 & 0 \\ 0 & -\bar{p}_2 & \bar{p}_3 \\ 0 & 0 & -\bar{n} \end{pmatrix}$$
$$+ \begin{pmatrix} 0 & -x_1 & 0 \\ x_1^{-2}k_1(k_1G_d - p_2x_1) & -\tilde{p}_2 + x_1^{-1}k_1G_d & \tilde{p}_3 \\ 0 & 0 & -\tilde{n} \end{pmatrix},$$

where $\bar{p}_2$, $\bar{p}_3$, and $\bar{n}$ are known nominal values for p_2, p_3, and n, respectively; while $\tilde{p}_2 = p_2 - \bar{p}_2$, $\tilde{p}_3 = p_3 - \bar{p}_3$, and $\tilde{n} = n - \bar{n}$ represent the error between the real and nominal parameter values. Therefore, there always exist a Metzler matrix $A_0 \in \mathbb{R}^{3\times3}$, and some matrices $A_i, F_j \in \mathbb{R}^{3\times3}$, for $i = \overline{1,16}$, and $j = \overline{1,2}$, for some $k, l \in \mathbb{N}_+$ such that the following equations

$$A(\rho) = A_0 + \sum_{i=1}^{16}\lambda_i(\rho)A_i,\ F(x_1) = \sum_{j=1}^{2}\lambda_j(x_1)F_j, \tag{13a}$$
$$\sum_{i=1}^{16}\lambda_i(\rho) = \sum_{j=1}^{2}\lambda_j(x_1) = 1,\ \lambda_i(\rho), \lambda_j(x_1) \in [0,1], \tag{13b}$$

hold for the system (10). Therefore, taking into account (13), the dynamics of the system (10) is given by

$$\dot{\varepsilon} = \left[A_0 + \sum_{i=1}^{16}\lambda_i(\rho)A_i\right]\varepsilon + Bu + \sum_{j=1}^{2}\lambda_j(x_1)F_jw(t). \tag{14}$$

Then, according to [12], it follows that

$$-\overline{A}\underline{\varepsilon}^- - \underline{A}\overline{\varepsilon}^+ \le \sum_{i=1}^{16}\lambda_i(\rho)A_i\varepsilon \le \overline{A}\overline{\varepsilon}^+ + \underline{A}\underline{\varepsilon}^-,$$
$$-\overline{F}\underline{w}^- - \underline{F}\overline{w}^+ \le \sum_{j=1}^{2}\lambda_j(x_1)F_jw \le \overline{F}\overline{w}^+ + \underline{F}\underline{w}^-,$$

where $\overline{A} = \sum_{i=1}^{16}A_i^+$, $\underline{A} = \sum_{i=1}^{16}A_i^-$, $\overline{F} = \sum_{j=1}^{2}F_j^+$, $\underline{F} = \sum_{j=1}^{2}F_j^-$, vectors $\underline{\varepsilon}, \overline{\varepsilon}, \underline{w}, \overline{w} \in \mathbb{R}^3$ such that $\underline{\varepsilon} \le \varepsilon \le \overline{\varepsilon}$ and $\underline{w} \le w \le \overline{w}$, respectively; and

$$F_1 = \begin{pmatrix} 1 & 0 & 0 \\ -\frac{k_1G_b}{(90)^2} & 1 & 0 \\ 0 & 0 & -1 \end{pmatrix},\ F_2 = \begin{pmatrix} 1 & 0 & 0 \\ -\frac{k_1G_b}{(180)^2} & 1 & 0 \\ 0 & 0 & -1 \end{pmatrix},$$
$$\underline{w} = \begin{pmatrix} 0 \\ \min(p_3I_{db}) \\ \min(nI_{db}) \end{pmatrix},\ \overline{w} = \begin{pmatrix} b_1 \\ \max(p_3I_{db}) \\ \max(nI_{db}) \end{pmatrix}.$$

Thus, it is possible to design the following interval predictor [13] for system (14):

$$\dot{\underline{\varepsilon}} = A_0\underline{\varepsilon} - \underline{A}\overline{\varepsilon}^+ - \overline{A}\underline{\varepsilon}^- + Bu - \underline{F}\overline{w}^+ - \overline{F}\underline{w}^-, \tag{15a}$$
$$\dot{\overline{\varepsilon}} = A_0\overline{\varepsilon} + \overline{A}\overline{\varepsilon}^+ + \underline{A}\underline{\varepsilon}^- + Bu + \overline{F}\overline{w}^+ + \underline{F}\underline{w}^-, \tag{15b}$$

with two vectors $\underline{\varepsilon}_0, \overline{\varepsilon}_0 \in \mathbb{R}^3$ such that $\underline{\varepsilon}_0 \le \varepsilon(0) \le \overline{\varepsilon}_0$ providing the interval inclusion property for the errors independently of the control, *i.e.,* $\underline{\varepsilon}(t) \le \varepsilon(t) \le \overline{\varepsilon}(t)$, for all $t \ge 0$. The previous dynamics may be represented in the following compact form

$$\dot{\zeta} = \mathcal{A}_0\zeta + \mathcal{A}_1\zeta^+ + \mathcal{A}_2\zeta^- + \mathcal{B}u + \mathcal{F}\delta, \tag{16}$$

where $\zeta = (\underline{\varepsilon}^\top, \overline{\varepsilon}^\top)^\top \in \mathbb{R}^6$, $\delta = (\underline{w}^{-\top}, \overline{w}^{+\top})^\top \in \mathbb{R}^6$, and

the system matrices given as follows

$$\mathcal{A}_0 = \begin{pmatrix} A_0 & 0 \\ 0 & A_0 \end{pmatrix},\ \mathcal{A}_1 = \begin{pmatrix} 0 & -\underline{A} \\ 0 & \overline{A} \end{pmatrix},$$
$$\mathcal{A}_2 = \begin{pmatrix} -\overline{A} & 0 \\ \underline{A} & 0 \end{pmatrix},\ \mathcal{B} = \begin{pmatrix} B \\ B \end{pmatrix},\ \mathcal{F} = \begin{pmatrix} -\overline{F} & -\underline{F} \\ \underline{F} & \overline{F} \end{pmatrix}.$$

Then, in order to stabilize the error dynamics (10), due to the interval properties of system (16), we can design a state–feedback u to take the trajectories of the system (16), and hence the trajectories of system (10), to zero or a neighborhood of the origin (see, *e.g.,* [14]).

V. Robust Control Design

The proposed control signal u possesses the following structure

$$u(t) = \begin{cases} \sigma(\bar{u}(t)), \text{ if } x_1 > G_d + \sqrt{\lambda_{\max}^{-1}(P)(u_\mu+1)}, \\ 0, \text{ else,} \end{cases} \tag{17}$$

where $0 < P \in \mathbb{R}^{6\times 6}$ is a diagonal matrix, $u_\mu = (u_{\max} - u_{\min})^3/2(u_{\max}+u_{\min})^2$, the signal $\bar{u}$ is a state–feedback control law, and the function σ is the saturation function, *i.e.,*

$$\sigma(\bar{u}) = \begin{cases} u_{\max}, & \text{if } u_{\max} \le \bar{u}, \\ \bar{u}, & \text{if } u_{\min} < \bar{u} < u_{\max}, \\ u_{\min}, & \text{if } \bar{u} \le u_{\min}. \end{cases}$$

with some given positive values $u_{\min}, u_{\max} > 0$. The state–feedback controller $\bar{u}$ is designed, based on (16), as

$$\bar{u} = K_0\zeta + K_1\zeta^+ + K_2\zeta^- + K_3\delta, \tag{18}$$

where $K_0, K_1, K_2, K_3 \in \mathbb{R}^{1\times 6}$ are the matrix gains to be designed. The following theorem provides a constructive way to design the state–feedback gains in order to ensure the convergence of the trajectories of the system (16) to a neighborhood of the origin satisfying the system constraints.

Theorem 1. *Let the state–feedback control law (17)–(18) be applied to the system (16), with $x_1(0) > G_d$. Suppose that, for some given $u_{\min}, u_{\max} > 0$, there exist two vectors $\underline{\varepsilon}_0, \overline{\varepsilon}_0 \in \mathbb{R}^3$ such that $\underline{\varepsilon}_0 \le \varepsilon(0) \le \overline{\varepsilon}_0$, diagonal matrices $0 < X_i, Q_j \in \mathbb{R}^{6\times 6}$, $0 \le R_j \in \mathbb{R}^{6\times 6}$, and some matrices $K_3, Y_l, Z \in \mathbb{R}^{1\times 6}$, for $i = \overline{0,3}$, $j = \overline{0,5}$, and $l = \overline{0,2}$; such that the following LMIs*

$$\begin{pmatrix} \beta_1 X_3 & Z^\top \\ Z & u_{\max} \end{pmatrix} \succeq 0,\ \beta_1 = \frac{u_{\max}+u_{\min}}{2u_{\max}}, \tag{19a}$$
$$\begin{pmatrix} \beta_2 X_3 & Z^\top \\ Z & u_{\min} \end{pmatrix} \succeq 0,\ \beta_2 = \frac{u_{\max}+u_{\min}}{2u_{\min}}, \tag{19b}$$
$$\Omega \preceq 0, \tag{19c}$$
$$X_3 \prec X_0 + X_1 + X_2, \tag{19d}$$

where

$$\Omega = \begin{pmatrix} \Omega_{11} & \Omega_{12} & \Omega_{13} & \Omega_{14} & \Omega_{15} & \Omega_{16} & \Omega_{17} & \Omega_{18} \\ \star & \Omega_{22} & \Omega_{23} & \Omega_{14} & \Omega_{15} & \Omega_{16} & \Omega_{17} & \Omega_{28} \\ \star & \star & \Omega_{33} & \Omega_{34} & \Omega_{35} & \Omega_{36} & \Omega_{37} & \Omega_{38} \\ \star & \star & \star & \Omega_{44} & R_4 & \Omega_{46} & 0 & 0 \\ \star & \star & \star & \star & \Omega_{55} & R_3 & 0 & 0 \\ \star & \star & \star & \star & \star & \Omega_{66} & 0 & 0 \\ \star & \star & \star & \star & \star & \star & \Omega_{77} & \Omega_{78} \\ \star & \star & \star & \star & \star & \star & \star & \Omega_{88} \end{pmatrix},$$
$$\Omega_{11} = \mathrm{He}(\mathcal{A}_0X_0 + \mathcal{B}Y_0) + Q_0,$$
$$\Omega_{12} = \mathcal{A}_1X_1 + \mathcal{B}Y_1 + X_0\mathcal{A}_0^\top + Y_0^\top\mathcal{B}^\top + R_1,$$
$$\Omega_{13} = \mathcal{A}_2X_2 + \mathcal{B}Y_2 - X_0\mathcal{A}_0^\top - Y_0^\top\mathcal{B}^\top - R_2,$$
$$\Omega_{14} = \mathcal{A}_0X_0 + \mathcal{B}Y_0,\ \Omega_{15} = \mathcal{A}_1X_1 + \mathcal{B}Y_1,$$
$$\Omega_{16} = \mathcal{A}_2X_2 + \mathcal{B}Y_2,\ \Omega_{17} = \mathcal{F} + \mathcal{B}K_3,$$
$$\Omega_{18} = \mathcal{B} - \delta(Y_0 - Z)^\top,\ \Omega_{22} = \mathrm{He}(\mathcal{A}_1X_1 + \mathcal{B}Y_1) - Q_1,$$
$$\Omega_{23} = \mathcal{A}_2X_2 + \mathcal{B}Y_2 - X_1\mathcal{A}_1^\top - Y_1^\top\mathcal{B}^\top + R_0,$$
$$\Omega_{28} = \mathcal{B} - \delta Y_1^\top,\ \Omega_{33} = -\mathrm{He}(\mathcal{A}_2X_2 + \mathcal{B}Y_2) - Q_2,$$
$$\Omega_{34} = -\Omega_{14},\ \Omega_{35} = -\Omega_{15},\ \Omega_{36} = -\Omega_{16},$$
$$\Omega_{37} = -\Omega_{17},\ \Omega_{38} = \mathcal{B} - \delta Y_2^\top,\ \Omega_{44} = -Q_3,$$
$$\Omega_{46} = -R_5,\ \Omega_{55} = -Q_4,\ \Omega_{66} = -Q_5,$$
$$\Omega_{77} = -\alpha Q,\ \Omega_{78} = -\delta K_3^\top,\ \Omega_{88} = -2\gamma,$$

are feasible for some fixed constants $\alpha, \delta, \gamma > 0$ and a matrix $Q = |\delta|^{-2}I_6$. If the state–feedback gains are designed as $K_l = Y_lX_l^{-1}$, for $l = \overline{0,2}$, and K_3; and the inequalities

$$X_0^{-1}(Q_0X_0^{-1} + 2\min(R_1X_1^{-1}, R_2X_2^{-1})) - X_1^{-1}Q_1X_1^{-1} - X_2^{-1}Q_2X_2^{-1} \ge \alpha P, \tag{20a}$$
$$P > X_3^{-1}, \tag{20b}$$
$$X_0^{-1}(Q_3X_0^{-1} - 2\min(R_4X_1^{-1}, R_5X_2^{-1})) + X_1^{-1}Q_4X_1^{-1} + X_2^{-1}Q_5X_2^{-1} \preceq \alpha X_3^{-1}, \tag{20c}$$

hold for some diagonal matrix $0 < P \in \mathbb{R}^{6\times 6}$ and the solution $(X_i, K_3, Y_l, Q_i, R_j)$, $i = \overline{0,3}$, $j = \overline{0,5}$, and $l = \overline{0,2}$, of (19)*; then, the trajectories of the system (16), starting in $\mathscr{E}(R, \zeta_\star) \setminus \mathscr{E}((u_\mu+1)^{-1}P, \zeta_\star) = \{\bar{\zeta} \in \mathbb{R}^6 : \bar{\zeta}^\top R\bar{\zeta} \le 1,\ \bar{\zeta}^\top P\bar{\zeta} > u_\mu + 1\}$, with $\bar{\zeta} = \zeta - \zeta_\star$, $\zeta_\star = \mu X_3Z^\top$, $\mu = (u_{\max}-u_{\min})/(u_{\max}+u_{\min})$, and $u_\mu = \mu^2(u_{\max}-u_{\min})/2$, asymptotically converge to the ellipsoid $\mathscr{E}((u_\mu+1)^{-1}P, \zeta_\star)$, implying that x_1 asymptotically converges to a region around G_d,* i.e., *$x_1(t) \to G_d + \sqrt{\lambda_{\max}^{-1}(P)(u_\mu+1)}$, as $t \to \infty$. Moreover, if the inequalities*

$$(q_i - \bar{\zeta}_\star)^\top \overline{R}^{-1}(q_i - \bar{\zeta}_\star) \le 1, \tag{21a}$$
$$(q_i - \underline{\zeta}_\star)^\top \underline{R}^{-1}(q_i - \underline{\zeta}_\star) \le 1, \tag{21b}$$
$$\underline{\zeta}_\star \le \zeta_\star \le \overline{\zeta}_\star,$$
$$\overline{R} = R_{22} - R_{12}R_{11}^{-1}R_{12}^\top,\ i = \overline{1,6},$$
$$\underline{R} = R_{11} - R_{12}R_{22}^{-1}R_{12}^\top,\ i = \overline{1,6},$$
$$X_3^{-1} = \begin{pmatrix} R_{11} & R_{12} \\ R_{12}^\top & R_{22} \end{pmatrix},$$

are satisfied; then, $x_1(t) \in \mathbb{X}_1$, $x_2(t) \in \mathbb{X}_2$, $x_3(t) \in \mathbb{X}_3$, and $u(t) \in \mathbb{U}$, for all $t \ge 0$.

Due to space limitations, the proof of this result is omitted.

Remark 1. *The switching mechanism introduced in (17) prevents the occurrence of hypoglycemia by cutting off the insulin injection. Otherwise, the controller $\bar{u}$ in (18), due to $u_{\min} > 0$ and the parameter uncertainties, would continue injecting insulin despite that the glucose level is at the desired value.*

A. Practical Implementation

The matrix inequality (19), proposed in Theorem 1, is linear with respect to $(X_i, K_3, Y_l, Q_i, R_j)$, $i = \overline{0,3}$, $j = \overline{0,5}$, and $l = \overline{0,2}$, if we fix some values $\alpha, \gamma > 0$. Additionally, we may maximize the volume of the ellipsoid $\mathscr{E}(R, \zeta_\star)$ in order to increase the attraction region. However, we need to verify the inequalities (20) and (21). In order to facilitate the design of the control parameters, such that the conditions of Theorem 1 are satisfied, we propose the following tuning algorithm:

Algorithm 1 Tuning Algorithm

Input: Constants $u_{\min}$ and $u_{\max}$, and vectors q_i.
Output: Controller parameters $(X_i, K_3, Y_l, Q_i, R_j)$, $i = \overline{0,3}$, $j = \overline{0,5}$, and $l = \overline{0,2}$.
1. Select $\alpha, \delta, \gamma > 0$.
2. Look for a solution $(X_i, K_3, Y_l, Q_i, R_j)$ of LMIs (19) such that $\log\{\det(X_3)\}$ is maximized:
- If the solution is feasible, go to step 3.
- Otherwise, return to step 1 and modify α, δ, and/or γ.

3. Look for a solution P of LMIs (20a) and (20b), for the feasible solution $(X_i, K_3, Y_l, Q_i, R_j)$:
- If the solution is feasible, go to step 4.
- Otherwise, return to step 1 and modify α, δ, and/or γ.

4. Verify that (20c) holds.
- If it does, fix $K_l = Y_l X_l^{-1}$, for $l = \overline{0,2}$, K_3, and the algorithm ends.
- Otherwise, return to step 1 and modify α, δ, and/or γ, and continue with the algorithm.

VI. Simulation Results

The simulations have been done in MATLAB with the Euler explicit discretization method and sampling time equal to 0.1 [s], while the solution to the given LMIs is obtained by means of SDPT3 solver, among YALMIP in MATLAB.

The proposed controller is tested in a cohort of 4 virtual T1DM adult patients, which parameters are taken from [15] and can bee seen in Table I.

Table I
Patient Parameters

Patient	p_2	p_3	I_b	n
1	4.78×10^{-2}	8.73×10^{-6}	15	0.3
2	3.13×10^{-2}	9.7×10^{-6}	3	0.22
3	6.76×10^{-2}	16.1×10^{-6}	17	0.09
4	0.69×10^{-2}	0.55×10^{-6}	81	0.13

The simulation considers a single–meal closed–loop scenario (80 [g] of carbohydrates at 5 hr in 24 hr). The proposed controller is active since the beginning of the trial. The system constraints sets are taken as $\mathbb{X}_1 = (70, 250)$, $\mathbb{X}_2 = [0, 3)$, $x_3(t) \in \mathbb{X}_3 = (3, 100)$, and $\mathbb{U} = [0, 10]$, and $u_{\min} = 0.001$, while the initial conditions are set in $x_1(0) = 160$, $x_2(0) = 0$, and $x_3(0) = 80$, for all the patients. The nominal values are $\bar{p}_2 = 3 \times 10^{-2}$, $\bar{p}_3 = 10 \times 10^{-6}$, $\bar{I}_b = 50$, and $\bar{n} = 0.1$, and hence, taking into account the patient parameters, we can establish that $p_{2\,\min} = 0.30 \times 10^{-2}$, $p_{2\,\max} = 6.8 \times 10^{-2}$, $p_{3\,\min} = 0.50 \times 10^{-6}$, $p_{3\,\max} = 19 \times 10^{-6}$, $I_{b\,\min} = 2.5$, $I_{b\,\max} = 100$, $n_{\min} = 0.08$, and $n_{\max} = 0.35$. Based on all the previous minimum and maximum values, and taking $G_d = 110$ [mg/dl], $I_d = 30$ [μU/ml], and $k_1 = 0.01$, we are able to compute all the matrices A_i, $i = \overline{1,16}$, using a convex polytopic approach.

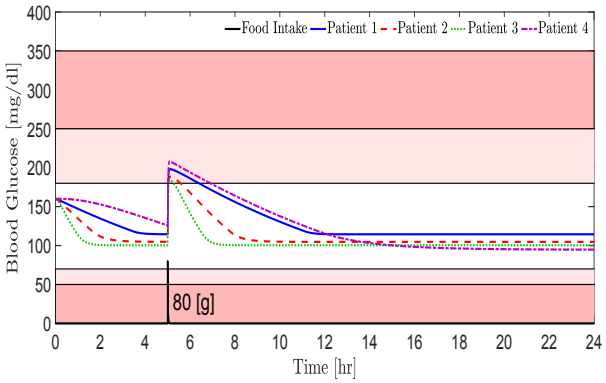

Figure 1. Blood Glucose Level

Then, we apply Algorithm 1 to tune the controller parameters selecting $\alpha = 2000$, $\delta = 0.1$, and $\gamma = 10$, and obtaining the following controller gains $K_0 = (0, 0, 0.0026, 0, 0, 0.0032)$, $K_1 = (0, 0, -0.0495, 0, -0.1322, -0.2017)$, $K_2 = (0, 0.1241, 0.2041, 0, 0, 0.0497)$, $K_3 = (0, 0, -1.0045, 0, -0.0001, 0.9876)$, and $P = \mathrm{diag}(0.0795, 0.0324, 0.0795, 0.0795, 0.0324, 0.0795)$.

Thus, the switching controller (17) is implemented to the whole cohort of patients offering the results depicted by Figs. 1, 2, and 3. The blood glucose for the 4 patients, under the same carbohydrate intake, is shown in Fig. 1. In the 4 cases, the blood glucose level is taken to the normoglycemic band (70–180 [mg/dl]) while no hypoglycemic events (<70 [mg/dl]) occur despite the carbohydrate intake. It is also clear that the blood glucose level never violates the state constraints and is always around the desired value of 110 [mg/dl]. Moreover, the proposed controller provides a minimal hyperglycemic (>180 [mg/dl]) risk, for the whole cohort. The control signals, corresponding to the infusion rate, are shown in Fig. 2, where we also see that the input constraints are not transgressed. The time evolution of the regulation errors e_1, z_2, and e_3 is presented in Fig. 3. We can see that these regulation errors satisfy $\lim_{t\to\infty} e_1(t) = e_1(t_r)$, $\lim_{t\to\infty} z_2(t) = k_1 e_1(t_r)/(G_d + e_1(t_r))$ ($\lim_{t\to\infty} e_2(t) = 0$), and $\lim_{t\to\infty} e_3(t) = -I_{db}$, respectively.

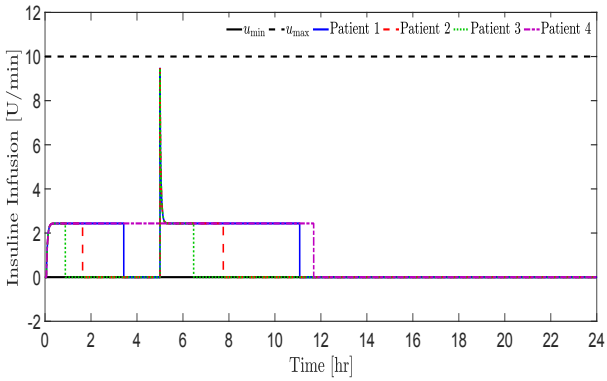

Figure 2. Insulin Infusion

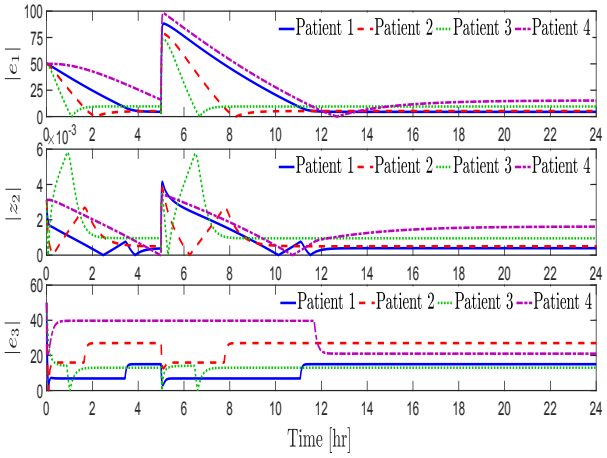

Figure 3. Regulation Errors

VII. Conclusions

In this paper, we propose a robust controller for the blood glucose regulation problem in patients with T1DM. The proposed switching control approach is based on an interval predictor–based state–feedback that considers the state and input constraints of the insulin–glucose system dynamics, *i.e.,* positive states and input, and minimum and maximum values of the blood glucose level and the insulin infusion rate. The stability analysis is based on a Lyapunov function approach, which ensures the asymptotic convergence of the blood glucose level around the desired value. The synthesis of the controller is constructive since it is in terms of LMIs. The simulation results, over a cohort of 4 virtual T1DM adult patients, demonstrate the performance of the proposed blood glucose regulation approach.

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