Robust μ-synthesis: towards a unified glucose control in adults, adolescents and children with T1DM

Eduardo Ruiz-Velázquez*, Julio García-Rodríguez

División de Electrónica y Computación, CUCEI-UDG,
Boulevard Marcelino García Barragán No. 1421, Olímpica, Guadalajara, Jal., C.P. 44430,
México. (email: eduardo.ruiz@cucei.udg.mx; julio.garciar@alumnos.udg.mx)

Griselda Quiroz

Universidad Autónoma de Nuevo León, FIME, Av. Universidad S/N, Ciudad
Universitaria, C.P. 66455, San Nicolás de los Garza, Nuevo León, México.
(email: griselda.quirozcm@uanl.edu.mx)

Ricardo Femat

División de Matemáticas Aplicadas, IPICYT,
Camino a la Presa San José No. 2055, Lomas Cuarta Sección, San Luis Potosí, SLP.,
C.P. 78216, México.(email: rfemat@ipicyt.edu.mx)

Abstract

Type 1 Diabetes Mellitus (T1DM) remains as a severe public health problem in a wide range of population, from children to adults. Recently, the number of diabetics worldwide and morbility rates are increasing. Therefore, emerging technologies as the artificial pancreas (AP) are directing their efforts to improve treatments and to reduce long-term complications. In this work, a cross-age control strategy is proposed to tackle the blood glucose regulation problem in people with T1DM. The contribution of this paper is focused on the blood glucose regulation in T1DM patients, at distinct ages, and it can be controlled in face to physiological uncertain parameters. In other words, a robust model-based controller is proposed via μ-synthesis technique by considering structured uncertainties in physiological meaningful parameters. The proposed controller exhibits the feasibility for blood glucose regulation in virtual diabetic children, adolescents and adults. The relevance of these parameters lies in their high

*Corresponding author

sensitivity to the solutions of a physiological mathematical model; that is, a slight parametric variation can lead to a hyperglycemic scenario. Thus, it is innovative to consider this uncertainties scheme in parameters that are directly related to the glucose dynamics. The robust control algorithm was integrated into the well-known Uva/Padova simulator for T1DM to show the technical viability of this methodology in the available three populations. The outcomes of a control variability grid analysis show that 90.9% of virtual adults are in upper B-zone and 9.09% in B-zone. Likewise for virtual adolescents, 90.9% fall in upper B-zone and 9.09% B-zone. Regarding children, 63.63% lie in upper B-zone, 27.27% B-zone and only 9.09% failure to deal with hypoglycemia. Furthermore, the results are compared to the ones obtained from $\mathcal{H}_\infty$ schemes previously reported which also were implemented in the simulator. Despite being a theoretical approach, the results reveal that the proposed cross-age control scheme could be a useful strategy in the development of real PA systems that lead to future clinical trials in humans.

Keywords: Robust controller, Structured uncertainties, μ-synthesis, Type 1 Diabetes Mellitus, Blood glucose regulation.

1. Introduction

Diabetes Mellitus (DM) is a chronic disease that affects more than 422 million adults worldwide. According to data reported by World Health Organization (WHO) in 2012 there were 1.5 million deaths worldwide directly caused by DM and it is one of the first-10 leading causes of dead both in men and women [1]. Type 1 Diabetes Mellitus (T1DM) occurs when pancreas reacts in an autoimmune way and it is no longer capable to produce enough insulin. Insulin is a hormone that allows glucose uptake by cells and tissues. In the absence of insulin, the blood blucose (BG) level can rise considerably, even fasting and especially after a meal. This increased BG level is known as hyperglycemia that can lead to serious damage in heart, blood vessels, eyes, kidneys and nerves.

Patients with T1DM require of insulin injections to maintain BG into the physiological range (70-120 mg/dL). The effectiveness of a therapy based on continuous insulin infusion was proved in the early 1990s, where the long-term complications of T1DM were considerable diminished in continuous (also called tight control) therapy in comparison with daily-injections therapy [2]. Since then, the development of continuous subcutaneous insulin infusion (CSII) systems and continuous glucose monitoring (CGM) systems was the golden goal. Both equipment are available in the market since the first decade of the 2000s, and after that, the therapy based on CSII and CGM has been validated in many clinical trials [3]. Such a therapy, also called open-loop sensor-augmented pump (SAP), diminished the time on hyperglycemia but a disadvantage is that tight control can increase the risk of hypoglycemia induced by insulin infusion. In SAP, the adjustment of insulin dosage depends on off-line recommendation of a physician, and this confronts the patient to make many decisions regarding dosage adjustments throughout the day. To face these disadvantages, the interest to develop a closed-loop therapy have been widely discussed for many years. This therapy has been called the artificial pancreas (AP) system and in addition to the CSII and the CGM systems, AP includes a closed-loop control system to resolve the online automatic dosage of insulin infusion accordingly to the current BG level.

From the point of view of automation science, the AP systems have led many technical issues that must be resolved and many control approaches have been proposed to address them. For example, Colmegna *et al.* proposed a linear parameter-varying controller switches between operation modes that are related to the hypoglycemic, hyperglycemic and glycemia scenarios [4]. These results show a significant decrease in risk episodes. Galandaci *et al.* propose a monitor which takes glucose readings and through pattern recognition technique, the control law adapts for preventing hyperglycemic episodes in the presence of disturbances as meal intake [5]. Kóvacs *et al.* use nonlinear control strategies in order to track asymptotically the output of a mathematical model that describes glucose-insulin interaction in T1DM [6]. An affine neural model is proposed in

León *et al.* that is obtained from an on-line identifier which uses a recurrent neural network. This scheme allows to synthesize an inverse optimal controller to follow the dynamics of glucose absorption of a healthy person [7]. Ruiz *et al.* develop a proposal based on $\mathcal{H}_\infty$ techniques to obtain a robust controller for blood glucose regulation. The results are good to solve a tracking problem and this contribution shows how $\mathcal{H}_\infty$ strategies are promising for T1DM problem [8]. Then, in 2009 Femat *et al.* identify the most significant frequency components in the insulin release of a healthy pancreas. These components are incorporated via transfer function in the design of a robust $\mathcal{H}_\infty$ algorithm [9]. Significant advances have been made using a variety of control strategies as insulin feedback for BG control [10], [11], [12], Model Predictive Control [13], [14], [15], robust control schemes using safety mechanisms [16], learning control strategies [17] and novel Bio-Inspired approaches [18].

Thus, sufficient theoretical evidence about the usefulness of the AP systems to solve the full automation of insulin infusion has been accumulated in the last years. In fact, clinical implementation of AP systems is now a reality and some inpatient, transitional and outpatient trials have been reported recently [19]. For example, some trials combine the closed-loop AP therapy and open-loop SAP therapy in short-time trials (48 hours) [20], or in long-time trials (two months) [21]. The closed-loop glucose controllers of the AP systems tested in outpatient, inpatient and transitional trials resolve the automation of the insulin infusion for a specific set of patients who have met the inclusion and exclusion criteria of that particular trial. Indeed, it is expected the robust μ–synthesis achieve a better performance that $\mathcal{H}_\infty$ when the feedback control is designed for a given plant, such a fact can be verified is the control problem stands for, as examples, a robot or an electromechanical system, a chemical or biochemical reactor, even for distillation process. However, the biomedical systems involve more complicated interactions and subsystems. The T1DM case is an illustrative example where the plant response can change drastically as a consequence of the cross-age. These changes can be attributable to hormonal and cellular behaviors typical of cross-age from childhood to youth and adulthood. Hence,

a unified control approach in the cross-age context is an open problem which is addressed at this contribution. Nevertheless, from the automation point of view, it could be of interest to seek for a general approach that could resolve the control problem in a wider set of patients. With this in mind, in this work we propose an approach to address such generalization focusing in one of the main inclusion criteria of the clinical trials: the age of the patients. The approach is based on a physiological model that describes the pharmacokinetics of glucose and insulin in relevant organs of the human body [22]. Other similar models also used in T1DM research are reported in [23], [24], [25]. Although the model proposed by Sorensen considers nominal parameters, a deeper study revealed that it has a subset of parameters highly sensitive to small changes which are closely linked with the glucose dynamics [26]. A structured uncertainties approach is applied to the physiological model and it characterizes the sensitive parameters reported in [26] in order to obtain a robust feedback controller via μ-synthesis technique. To evaluate the performance of the proposed controller as a cross-age strategy for the glucose regulation of T1DM patients, an *in silico* experiment was designed. The μ-synthesis controller (called K_μ) was incorporated in the Uva/Padova simulator considering the virtual population available in the academic version: 11 adults, 11 adolescents and 11 children [27], [28]. The Uva/Padova simulator also includes an insulin pump and a real continuous glucose monitoring to simulate a behavior closer to reality. Furthermore, the performance of the proposed controller was analyzed via a control variability grid analysis (CVGA), and the results were compared with those corresponding to robust control algorithms previoulsy reported [8], [9].

2. Preliminaries of μ-synthesis

2.1. Mathematical physiological modeling in T1DM

The compartmental technique has been used to model biological systems as in [22]. The model proposed by Sorensen was created by performing mass balance to describe the pharmacokinetics and pharmacodynamics interaction

of glucose, insulin and glucagon in organs of the human body. These three subsystems are coupled to form a complete system of 19 differential equations. Many researchers agree that this model is a good approximation to glucose metabolism since it includes several important physiological processes [29], [30], [31], [32].

2.2. Background of μ-structured singular value

Modeling of systems that describe biological effects, as in T1DM, is not an easy task. Mathematical models in this area contain physiological parameters which do not have a fixed value. They can be within a region or be different from person to person. A robust control design approach should then considers this model dynamics as well as parameter variations. In other words, uncertainties are always present and a system may have multiple sources of them. The problem of glucose control in T1DM could be addressed in terms of the μ-SSV[1] as follows. Consider that all the uncertainties are grouped into a single block Δ, and they can be taken out from the dynamics of the nominal plant P. Now the complete system can be rearranged in a standard configuration described in Figure 1. The aim for the generalized system is to find a stabilizing controller K for the plant P with a defined structure of uncertainties Δ.

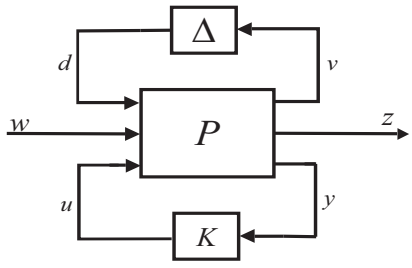

Figure 1: Generalized framework of a robust control system where P is the model of the nominal plant, Δ is the block of all the uncertainties and K is a stabilizing controller. Input signals: d is the uncertainty, input w is the reference and u is the control input. Output signals: v is the uncertainty, z stands for error or controlled outputs and y groups the measured signals.

[1]Acronym for *Structured Singular Value*.

The performance specifications of a robust system are generally based on the minimization of z with respect to w in terms of some norm, such as $\mathcal{H}_\infty$ norm, with the assumption that both are energy bounded signals. The optimization problem of finding a stabilizing controller K is achieved by minimizing the μ-SSV over a frequency range. Minimization of the μ value allows us to ensure that the robust stability and robust performance specifications are accomplished.
Let the plant P and controller K be integrated in a lower linear fractional transformation (LLFT) renamed as $M(P, K)$ as shown in Figure 2.

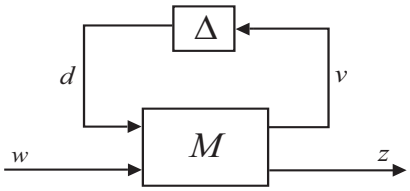

Figure 2: Generalized framework of a robust control system where M is the LLFT renamed as $M(P, K)$ and Δ is the block of all the uncertainties.

The smallest size of uncertainty that makes $(I - M(jw)\Delta(jw))$ singular at some frequency w describes how robustly stable the system is in dealing with such Δ. This measurement is the μ-SSV and the controller K is called robustly stable if μ-SSV remains small enough while the below singularity condition holds. Therefore, the following definitions are appropriate.

Definition 2.1. *Structured uncertainty* [33].
Consider two different types of matrix, with both, repeated scalar and full blocks. Let s and f be the number of repeated blocks and the number of full blocks respectively. Positive integers $r_1, \ldots, r_s$; $m_1, \ldots, m_f$ are defined to keep dimensions compatible as the i-th repeated scalar block is $r_i \times r_i$ and the j-th full block is $m_j \times m_j$. Thus, the set $\mathbf{\Delta} \subset \mathbb{C}^{n \times n}$ can be defined as:

$$\begin{aligned} \mathbf{\Delta} &= \text{diag } [\delta_1 I_{r_1}, ..., \delta_s I_{r_s}, \Delta_1, ..., \Delta_f] \\ &\quad \delta_i \in \mathbb{C},\ \Delta_j \in \mathbb{C}^{m_j \times m_j}, \end{aligned} \tag{1}$$

where

$$\sum_{i=1}^{s} r_i + \sum_{j=1}^{f} m_j = n. \tag{2}$$

This set is considered to be bounded and now written as

$$\mathbf{B\Delta} := \{\Delta : \bar{\sigma}(\Delta) < 1, \Delta \in \mathbf{\Delta}\}, \tag{3}$$

with $\bar{\sigma}(\cdot)$ the largest singular value of a matrix.

■

Definition 2.2. *The structured singular value* [33].
For $M \in \mathcal{C}^{n\times n}$ and for $\Delta \in \mathbf{\Delta}$, the structured singular value μ of M is the number $\mu^{-1}(M)$ that equals the smallest $\bar{\sigma}(\Delta)$ need to make $(I - M\Delta)$ singular, that is

$$\mu^{-1} = \min_{\Delta\in\mathbf{\Delta}} \{\bar{\sigma}(\Delta) : \det(I - M\Delta) = 0\}. \tag{4}$$

■

Correspondingly, when M is an interconnected transfer matrix as in Figure 2, the μ-SSV with respect to $\mathbf{\Delta}$ is defined as:

$$\mu(M(s)) = \sup_{w\in\mathcal{R}} \mu(M(jw)). \tag{5}$$

The system is said to be robustly stable if $\mu(M(s)) \leq 1$.

2.3. D-K iteration algorithm

The μ-SSV is a tool for the analysis of robust performance with a given controller. However, finding the controller that minimizes the μ condition is not an easy task because there is not a direct method to synthesize it. In order to guarantee robust performance is required to find the controller K such that:

$$\sup_{w\in\mathcal{R}} \mu[M(P,K)(jw)] < 1. \tag{6}$$

In other words, the objective is to solve K such that:

$$\inf_{K(s)} \sup_{w\in\mathcal{R}} \mu[M(P,K)(jw)]. \tag{7}$$

The D-K is an iterative method to find a stabilizing controller that involves the solution of the next optimization problem:

$$\inf_{K(s)} \sup_{w\in\mathcal{R}} \inf_{D\in\mathbf{D}} \bar{\sigma}[DM(P,K)D^{-1}(jw)], \tag{8}$$

where D and D^{-1} match the structure of $\mathbf{\Delta}$ and belong to $\mathbf{D}$, the matrix set that commutes with Δ. Now the requirement in (6) to find a stabilizing controller is modified as:

$$\sup_{w\in\mathcal{R}} \inf_{D\in\mathbf{D}} \bar{\sigma}[DM(P,K)D^{-1}(jw)] < 1. \tag{9}$$

The iterative method is to alternately minimize (8) for K and D. That is, reducing K in the left hand-side of (9) while keeping D fixed, and then reducing D while K is fixed. This procedure continues until requirement (9) is reached. The D-K iteration method may result in high order μ-controllers however several reduction techniques are available in [33] and [34].

3. Robust control design by μ-synthesis

The model of a biological dynamic system can be seen as a mathematical approximation of reality. Usually, such a model is proposed with nominal values for all parameters. However, these parameters may change for some systems and under certain conditions. In fact, small parametric variations can significantly affect the closed-loop performance of a control system. Robust control theory provide approaches where parameters can take values within a region, there are uncertainties or there are external disturbances. Therefore, the approach is based upon the design of a robust control law that exhibits satisfactory performance in blood glucose regulation despite parametric variations or uncertainties. The sensitivity analysis carried out by Quiroz *et al.* showed that the four metabolic parameters η_3, η_4, η_5 and η_6 are more sensitive to the solution of the model of Sorensen [26]. Physiologically, η_3 is related to the mediation of the glucagon on the hepatic glucose production. While η_4, η_5, η_6 are related to the mediation of the glucose concentration on the hepatic glucose production through the metabolic rate. These sensitive parameters are rewritten in a

mathematical structured uncertainty form as:

$$\eta_3 = \overline{\eta}_3 \left(1 + P_{\eta_3}\delta_{\eta_3}\right) \tag{10}$$

$$\eta_4 = \overline{\eta}_4 \left(1 + P_{\eta_4}\delta_{\eta_4}\right) \tag{11}$$

$$\eta_5 = \overline{\eta}_5 \left(1 + P_{\eta_5}\delta_{\eta_5}\right) \tag{12}$$

$$\eta_6 = \overline{\eta}_6 \left(1 + P_{\eta_6}\delta_{\eta_6}\right) \tag{13}$$

where $\overline{\eta}_3 \ \ldots \ \overline{\eta}_6$ are the nominal values. The terms $P_{\eta_3} = P_{\eta_4} = P_{\eta_5} = P_{\eta_6} = 0.5$ are the relative uncertainties and $\delta_{\eta_3} \ \ldots \ \delta_{\eta_6}$ are scalars satisfying $|\delta_\eta| \leq 1$. In this way, the parameters are bounded within a region and they are summarized in Table 1.

Parameter	Maximum	Nominal value	Minimum
η_3	0.195	0.390	0.585
η_4	0.710	1.420	2.130
η_5	0.705	1.410	2.115
η_6	0.310	0.620	0.930

Table 1: Bounds of the most important sensitive parameters in the model proposed by Sorensen [26].

Now, the structured uncertainties approach includes the δ terms in a diagonal matrix Δ_P as follows:

$$\Delta_P = \begin{bmatrix} \delta_{\eta_3} & & & 0 \\ & \delta_{\eta_4} & & \\ & & \delta_{\eta_5} & \\ 0 & & & \delta_{\eta_6} \end{bmatrix} \tag{14}$$

The generalized scheme in Figure 3 is used to carry out the synthesis of a robust controller via μ-synthesis technique. Therefore, a linear representation of the diabetic patient is required. Thus, a linearization of the nonlinear model described in [22] is performed to obtain linear P and P_m. In fact, the linear fractional transformation P with Δ_P integrates the T1DM model when the

input is an exogenous insulin infusion and the output is blood glucose. In the same way, P_m with Δ_{P_m} involves the plant when the input is a perturbation due to carbohydrate intake. The balanced truncation method reduces the order of plants P and P_m resulting as follows:

$$P = \frac{8.977\text{e}^{-5}s^4 - 1.749\text{e}^{-4}s^3 - 3.861\text{e}^{-4}s^2 - 7.414\text{e}^{-5}s - 1.050\text{e}^{-6}}{s^5 + 0.313s^4 + 0.039s^3 + 2.063\text{e}^{-3}s^2 + 4.545\text{e}^{-5}s + 2.844\text{e}^{-7}}, \quad (15)$$

$$P_m = \frac{-8.476\text{e}^{-4}s^4 + 7.552\text{e}^{-4}s^3 + 1.437\text{e}^{-4}s^2 + 6.331\text{e}^{-6}s + 6.76\text{e}^{-8}}{s^5 + 0.313s^4 + 0.039s^3 + 2.063\text{e}^{-3}s^2 + 4.545\text{e}^{-5}s + 2.844\text{e}^{-7}}. \quad (16)$$

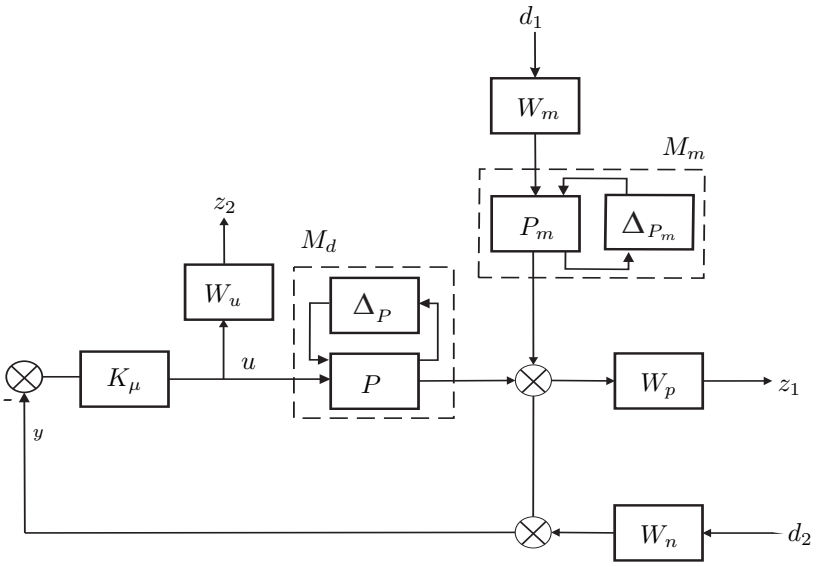

Figure 3: Generalized closed-loop structure for robust controller design. Here, W functions are called weighted transfer functions. M_d and M_m are upper LFT given by $M_d(P, \Delta_P)$ and $M_m(P_m, \Delta_{Pm})$, respectively.

The transfer function W_p is the performance weight such that its frequency content is captured to improve the performance of glycemic regulation. The meal weight W_m includes the effect by carbohydrate intake, the specific description of this weight can be found in [8] and [9]. The characterization of sensor noise

is weighted by W_n. Then, the weight transfer functions are:

$$W_p = \frac{0.8333s + 0.01}{s + 0.001}, \tag{17}$$

$$W_m = \frac{1}{3.5s + 1.5}, \tag{18}$$

$$W_n = \frac{1}{10000}. \tag{19}$$

Furthermore, the W_u function is a weight to shape the control action. In the contribution of Femat *et al.* a W_u is identified with experimental data in order to capture the pattern of insulin delivery by a healthy pancreas [9]. This weight transfer function is included to characterize the dynamics of a real pancreas. Then W_u is as follows:

$$W_u = \frac{2.38s^3 - 2.05s^2 + 4.71s - 4.09}{s^4 + 0.39s^3 + 4.27s^2 + 0.98s + 4.3}. \tag{20}$$

The generalized control plant $G(s)$ is

$$\begin{bmatrix} z_1 \\ z_2 \\ y \end{bmatrix} = G(s) \begin{bmatrix} d_1 \\ d_2 \\ u \end{bmatrix}, \tag{21}$$

and it can be expressed mathematically as:

$$\begin{bmatrix} z_1 \\ z_2 \\ y \end{bmatrix} = \left[\begin{array}{cc|c} W_p M_m W_m & 0 & W_p M_d \\ 0 & 0 & W_u \\ \hline -W_m M_m & -Wn & -M_d \end{array}\right] \begin{bmatrix} d_1 \\ d_2 \\ u \end{bmatrix}. \tag{22}$$

The instruction *dksyn* of Matlab® from MathWorks Inc. synthesizes a robust μ-controller for the generalized plant model via *D-K* iteration method. The iteration summary is shown in Table 2.

A controller of order 46 is obtained in the second iteration with the minimum gamma of 0.861 and peak μ-value of 0.808. It can be seen that for both values they no longer decrease for the next iterations. Therefore, the optimal controller that achieves the robust design specifications is the resulting in the second iteration. Likewise, an order reduction by balanced truncation is carried out

Iteration	**1**	**2**	**3**	**4**	**5**
Controller order	44	46	46	44	44
Gamma (γ)	11.266	0.861	0.871	0.880	0.881
Peak μ-value	0.790	0.808	0.812	0.816	0.816

Table 2: Summary of D-K iterations throughout μ-synthesis process provided by *dksyn* command by Matlab®.

for the robust controller [34]. The K_μ controller of order 14 is as follows:

$$\begin{aligned} K_\mu \quad = \quad & \frac{-4.399\text{e}^4 s^{13} - 8.189\text{e}^5 s^{12} - 3.027\text{e}^6 s^{11} - 6.989\text{e}^6 s^{10} - 1.355\text{e}^7 s^9}{s^{14} + 2401 s^{13} + 5.073\text{e}^4 s^{12} + 2.837\text{e}^5 s^{11} + 8.443\text{e}^5 s^{10} + 1.717\text{e}^6 s^9} \\ & \frac{-1.716\text{e}^7 s^8 - 1.679\text{e}^7 s^7 - 1.209\text{e}^7 s^6 - 3.531\text{e}^6 s^5 - 4.032\text{e}^5 s^4}{+2.570\text{e}^6 s^8 + 2.872\text{e}^6 s^7 + 2.311\text{e}^6 s^6 + 1.136\text{e}^6 s^5 + 2.901\text{e}^5 s^4} \\ & \frac{-1.836\text{e}^4 s^3 - 333.7 s^2 - 1.921 s - 2.701\text{e}^{-3}}{+2.638\text{e}^4 s^3 + 3.692\text{e}^2 s^2 + 0.709 s + 3.666\text{e}^{-4}}. \end{aligned} \tag{23}$$

This $D - K$ iteration procedure performs robust stability and robust performance analysis for the controllers synthesized in each iteration. That is, the behavior of the μ-value is evaluated in the frequency domain to verify that it remains below 1 to ensure that the closed-loop system remains robustly stable for design specifications. In Figure 4 it can be verified that the μ-value is always below 1 for frequencies from 10^{-2} to 10^1. Also, the robust performance analysis is presented in Figure 5. Similarly, the μ value is less than 1 for all frequencies in the analysis.

The global analysis carried out by Matlab® provides a final robustness report of the complete control system. Such report describes in detail that the control system achieves robust performance for the modeled uncertainty degree of this design. Likewise, it can remain robustly stable in up to 168% of the modeled uncertainty.

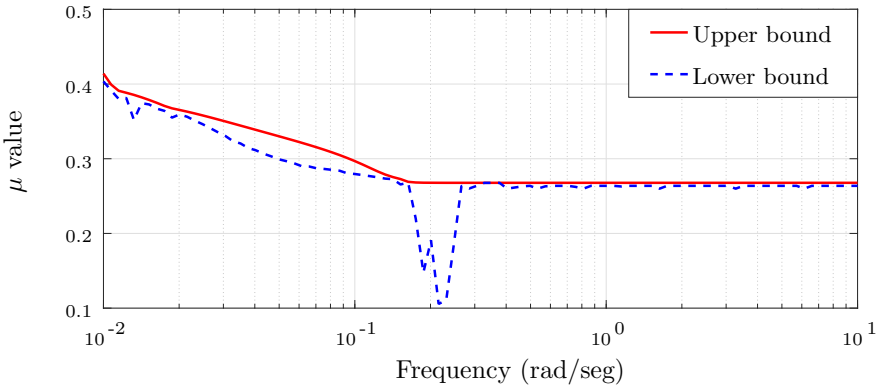

Figure 4: Robust stability analysis for the K_μ controller in the frequency domain. Solid red line and the blue dashed line are the upper and lower bounds of the robust stability analysis in terms of the μ value. Robust stability is guaranteed when such limits remain below 1 for the entire frequency range of interest. If there is a μ value greater than 1 means that the system gain can change and some modeled uncertainty can lead the system to unstable.

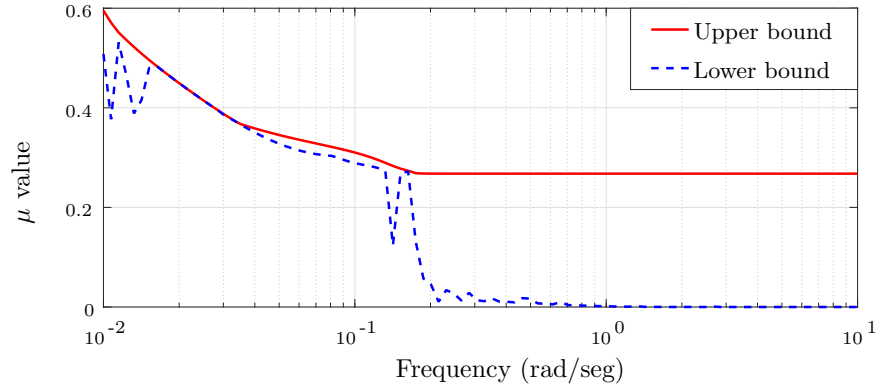

Figure 5: Robust performance analysis for the K_μ controller in the frequency domain. Solid red line and the blue dashed line are the upper and lower bounds of the robust performance analysis in terms of the μ value. Robust performance is guaranteed when such limits remain below 1 for the entire frequency range of interest. If there is a μ value greater than 1 means that the system gain can change and some modeled uncertainty can lead the system to unstable.

4. Simulation results

4.1. The Uva/Padova simulator of T1DM

Simulation environments are good tools for collecting useful data prior to *in vivo* experimentation. In 2008 the Uva/Padova Simulator was approved by the Food and Drug Administration (FDA) as a substitute to animal trials in preclinical testing of control strategies in artificial pancreas studies [27]. In 2013 the Epsilon Group launches a new version of the T1DM simulator. This release incorporates modifications to the glucose kinetics model in hypoglycemia, secretion models and action of glucagon kinetics, the real dynamics of an insulin pump, and a glucose sensor, among other improvements [28].

4.2. In silico implementation of the robust K_μ controller

In this work the K_μ controller (23) is integrated as the unique control law for glucose regulation in the 2013 version of the Uva/Padova simulator. The treatment of a diabetic patient should consider a strictly balanced diet; for this reason, a meal protocol is proposed based on a realistic amount of carbohydrate intake per day, measured in grams (gCH). The total intake for virtual adults and adolescents is 175 gCH. Likewise, for children it is 90 gCH. It is considered that these amounts are consumed in a total of 5 meals throughout the day as summarized in Table 3.

Meal protocol (gCH)	Breakfast	Snack	Meal	Dinner	Snack	Total
Time (hrs) / Population	7:00	12:00	15:00	19:00	23:00	One-day
Adults and adolescents	35	20	60	40	20	175 gCH
Children	20	5	35	25	5	90 gCH

Table 3: Proposed meal protocol for one-day of glycemic treatment.

4.3. CGM data acquisition

The BG level increases after a meal intake and then glucose is transferred to the interstitial fluid to be used as energy by cells. This physiological transfer from BG to interstitial glucose (IG) lasts approximately 20 minutes to be readable by a subcutaneous sensor. That is, the IG is delayed to the BG and the data provided by the glucose sensor have a characteristic uncertainty related to each type of sensor. In this work, the 7-day sensor of Dexcom^{TM} Inc. is selected in the Uva/Padova simulator for continuous glucose monitoring.

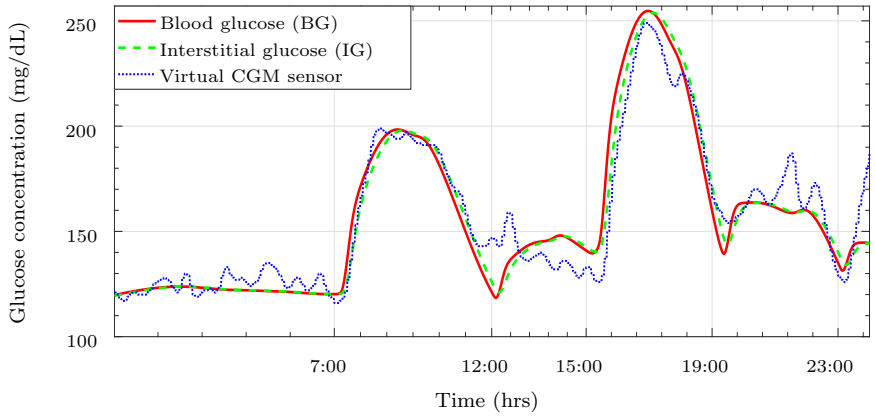

Figure 6: Blood glucose concentration of an averaged virtual adult with the meal protocol in Table 3 and insulin infusion computed by the robust K_μ controller in a closed-loop approach. Lines red and green are the glucose concentration on arterial and peripheral interstitial compartment of the physiological model, respectively. The blue line represents the blood glucose measured by the virtual CGM.

Figure 6 presents the response of the K_μ controller in a closed-loop treatment proved in the averaged model of diabetic adults and the meal protocol in Table 3. This graph displays the states of the system corresponding to BG and IG, as well as the virtual CGM signal. In fact, it must be noted that the robust control approach developed here takes the uncertain IG measurements provided by the CGM as the only feedback signal.

4.4. One meal scenario

As a first assay, the Uva/Padova simulator was configured for one meal scenario. The virtual model of the averaged adults was chosen. The amount of meal intake is 45 gCH and it is ingested at $t = 0{:}00$ hours. Similarly to the study of control theory, this scenario allows us to analyze the system behavior against a disturbance input given by carbohydrate intake. Therefore, the performance of the K_μ controller is compared with the robust $\mathcal{H}_\infty$ controllers proposed by Ruiz *et al.* in [8] and Femat *et al.* in [9], strictly under the same conditions. Reference has been set to a glycemic value of 115 mg/dL. The BG dynamics under the three control algorithms is presented in Figure 7. The treatment

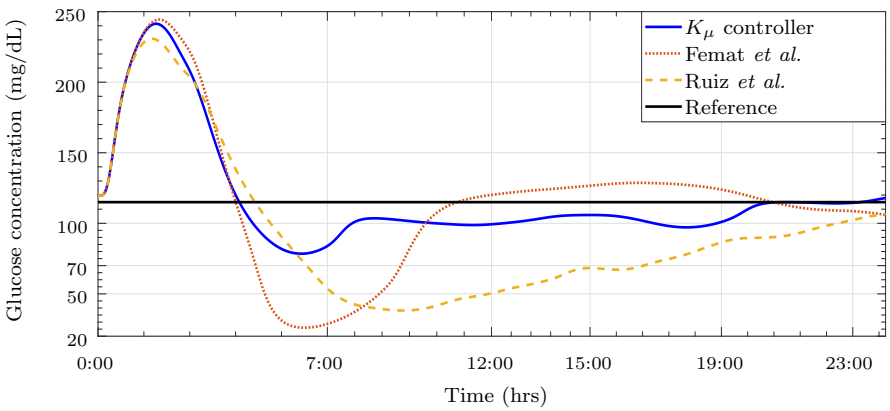

Figure 7: Comparative framework for one meal scenario by using the robust $\mathcal{H}_\infty$ controllers reported by Ruiz *et al.* in [8] and Femat *et al.* in [9] and the proposed K_μ controller.

with K_μ controller provides a maximum value of glucose of 241 mg/dL after 1:48 hours, while the minimum is 78 mg/dL after 6:12 hours of meal intake. In case of the $\mathcal{H}_\infty$ controllers, they were not able to maintain safe levels in the postprandial lapse, since the glucose falls below 50 mg/dL. This means a severe hypoglycemia episode.

4.5. Five meals scenario: A comparative framework

A virtual scenario of five meals in a 24 hour was proposed to represent daily life habits of meal ingestion. This includes three full meals and two snacks, as

previously presented in Table 3. The total amount is 175 gCH for adults and adolescents. For children this is much smaller, just 90 gCH.

4.5.1. Adults

As stated before, the performance of the K_μ controller is compared with the robust $\mathcal{H}_\infty$ controllers proposed by Ruiz *et al.* in [8] and Femat *et al.* in [9], rigorously in the same environments. The complete results for adults are presented separately for each controller in Figure 8. The left graph shows at the top subfigure, the blood glucose dynamics during 24 hours of simulation for the averaged adults model; while the bottom subfigure presents the insulin infusion rate calculated by the controller. It is worth mentioning that the reference signal was identified as the glucose curve of a healthy patient. It can be clearly seen that the three robust control algorithms are able to satisfactorily regulate the blood glucose of the averaged adults model. However, the insulin infusion calculated by K_μ controller is cleaner, without jumps or high value peaks. This control law allowed a BG minimum of 115.3 mg/dL and maximum of 235.1 mg/dL exhibiting a more convenient performance. Regarding the control variability grid analysis (CVGA), it is a method to visualize the overall performance of a control algorithm in a group of subjects. Thus, the plot is gridded in different color zones and each subject is represented by one data point. In this

Zones	**Control assessment**
A-Zone (Single A zone) X: 110-90 and Y: 110-180 mg/dL	Accurate control
B-Zone (Scattered in 3 zones) X: 90-70 and Y: 180-300 mg/dL	Benign deviations in hypo/hyperglycemia
C-Zone (Only upper and lower) X: 70-50; 110-90 and Y: 300-400; 110-180 mg/dL	Over-correction in hypo/hyperglycemia
D-Zone (Only upper and lower) X: 70-50; 90-70 and Y: 180-300; 300-400 mg/dL	Failure to deal with hypo/hyperglycemia
E-Zone (Single E zone) X: 70-50 mg/dL and Y: 300-400 mg/dL	Erroneous control

Table 4: CVGA zones provides a simultaneous visual and numerical assessment of the overall quality of glycemic regulation in the entire population of patients [35].

manner, each virtual patient is plotted taking as X-Y coordinates the minimum and the maximum of the glucose readings for the entire simulation time. The quality of a control is measured by the area in which each diabetic is located. In general, the sections are classified as in Table 4. A more detailed description of this classification is found in [35]. In order to have a more relevant comparative approach, the population of 10 adults and an averaged adult, that is, 11 virtual subjects are tested under the treatment of the three control algorithms. Figure 8 (top) demonstrates the satisfactory performance of the K_μ controller by maintaining 11 of 11 subjects in the green B-zones of benign deviations in hypo/hyperglycemia. Strictly speaking, K_μ controller achieves 90.9% patients in Upper-B and 9.09% in B-zone. In this order, the robust controller of [9] develop 63.63% in Upper-B and 18.18% in B-zone (Figure 8 middle). Likewise, the robust $\mathcal{H}_\infty$ controller of [8] obtains 45.45% in Upper-B and 18.18% in B-zone (Figure 8 bottom). Both controllers percentages are lower than the reached by the K_μ controller for the task of glycemic regulation in the population of 11 virtual adults.

4.5.2. Adolescents

Same tests are carried out for the population of 10 adolescents and a averaged adolescent, 11 virtual subjects in total. Now in Figure 9 the generalized performance of the three algorithms is shown. The behavior of the $\mathcal{H}_\infty$ controllers of [8] and [9] is quite unfeasible since both fail to maintain glycemia. Insulin overinfusion leads to scenarios below 50 mg/dL for the average adolescent. Similarly, the CVGA analysis exhibits unsatisfactory results for glucose regulation in the entire adolescents population because several patients drop in unsafe areas, that is, Lower D and Lower C (Figure 9 middle and bottom). In the case of the K_μ controller, an appropriate performance is maintained again, as seen in Figure 9 (top). The BG bounds are 80.03 mg/dL minimum and 235.7 mg/dL maximum for the averaged model. The postprandial lapse does not represent any risk at all, since the BG does not remain long at the maximum. The CVGA chart exposes 90.9% virtual subjects in Upper-B and 9.09% in B-zone.

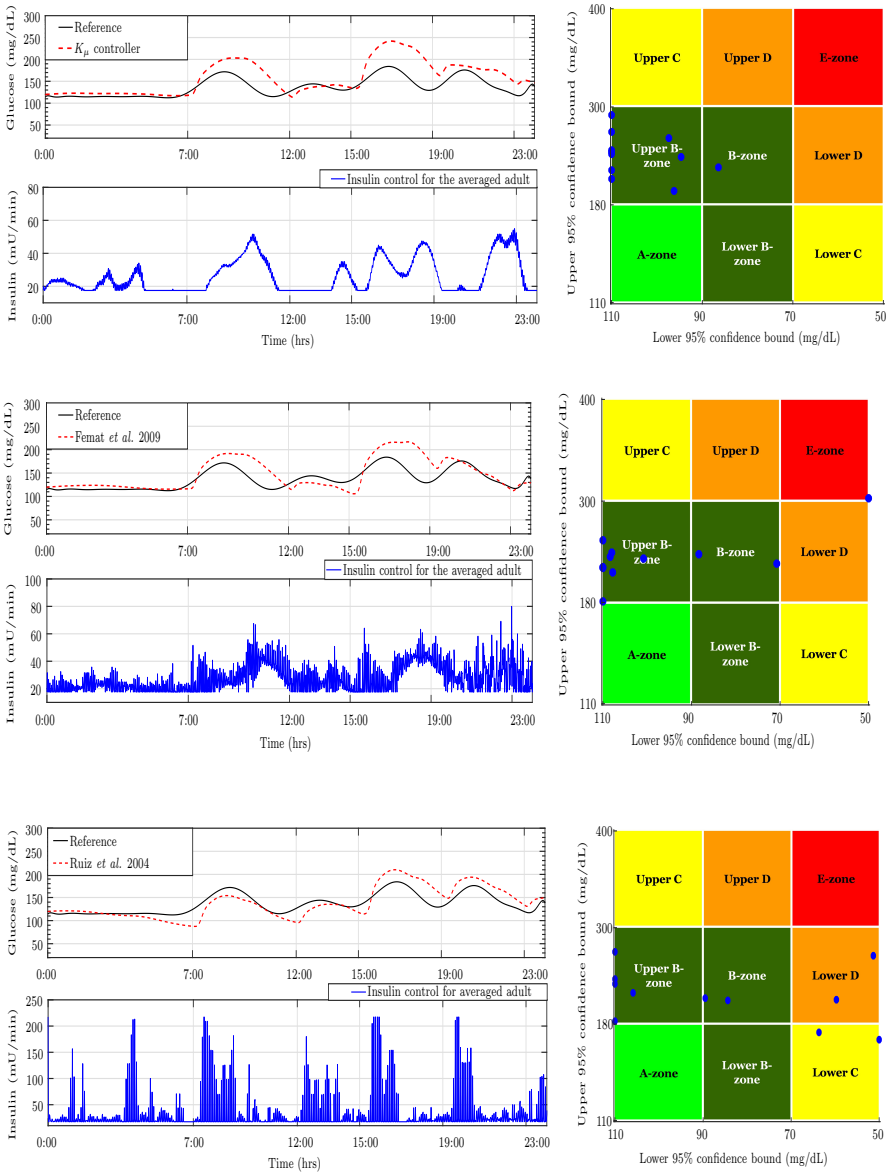

Figure 8: Results of the proposed cross-age strategy to control blood glucose in virtual adults. *Left*: closed-loop performance of the proposed K_μ controller (top) and two robust controllers reported previously (middle and bottom) in a five meals scenario. *Right*: CVGA performance chart in one-day treatment proved in 11 virtual adults.

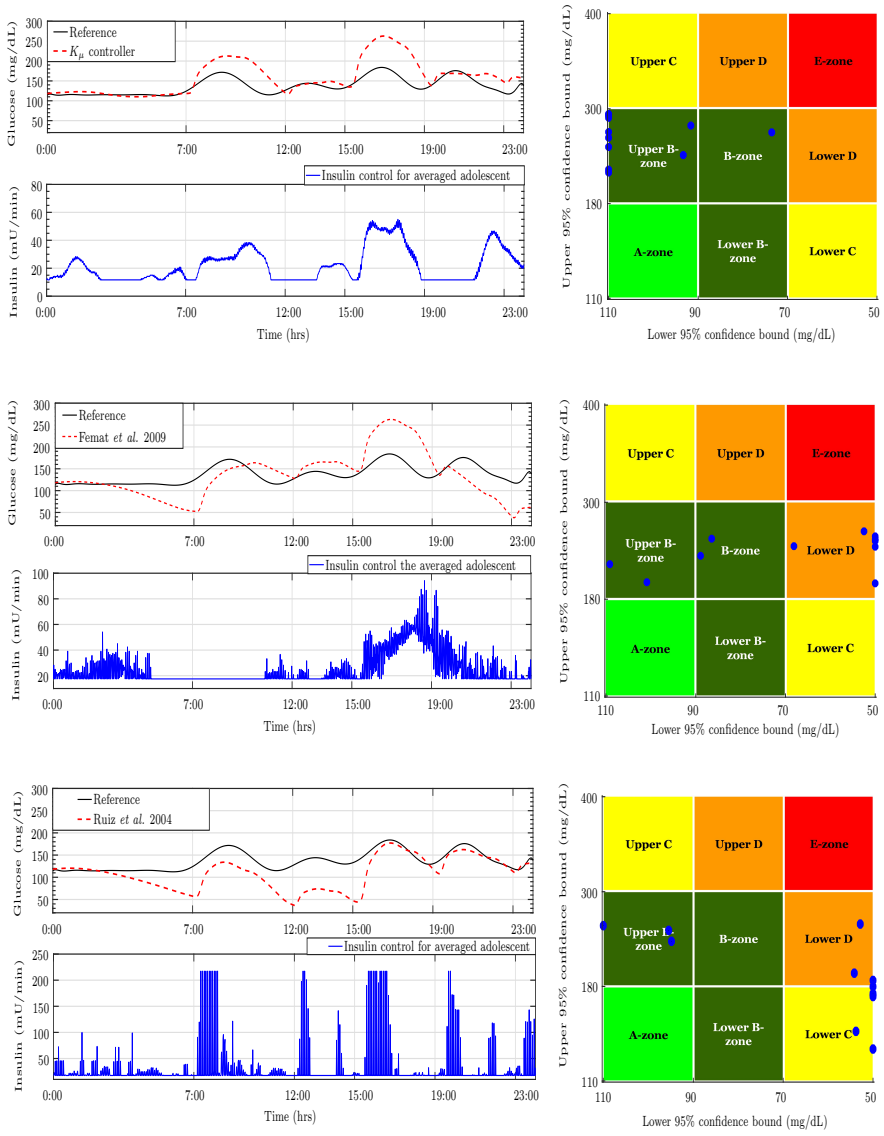

Figure 9: Results of the proposed cross-age strategy to control blood glucose in virtual adolescents. *Left*: closed-loop performance of the proposed K_μ controller (top) and two robust controllers reported previously (middle and bottom) in a five meals scenario. *Right*: CVGA performance chart in one-day treatment proved in 11 virtual adolescents.

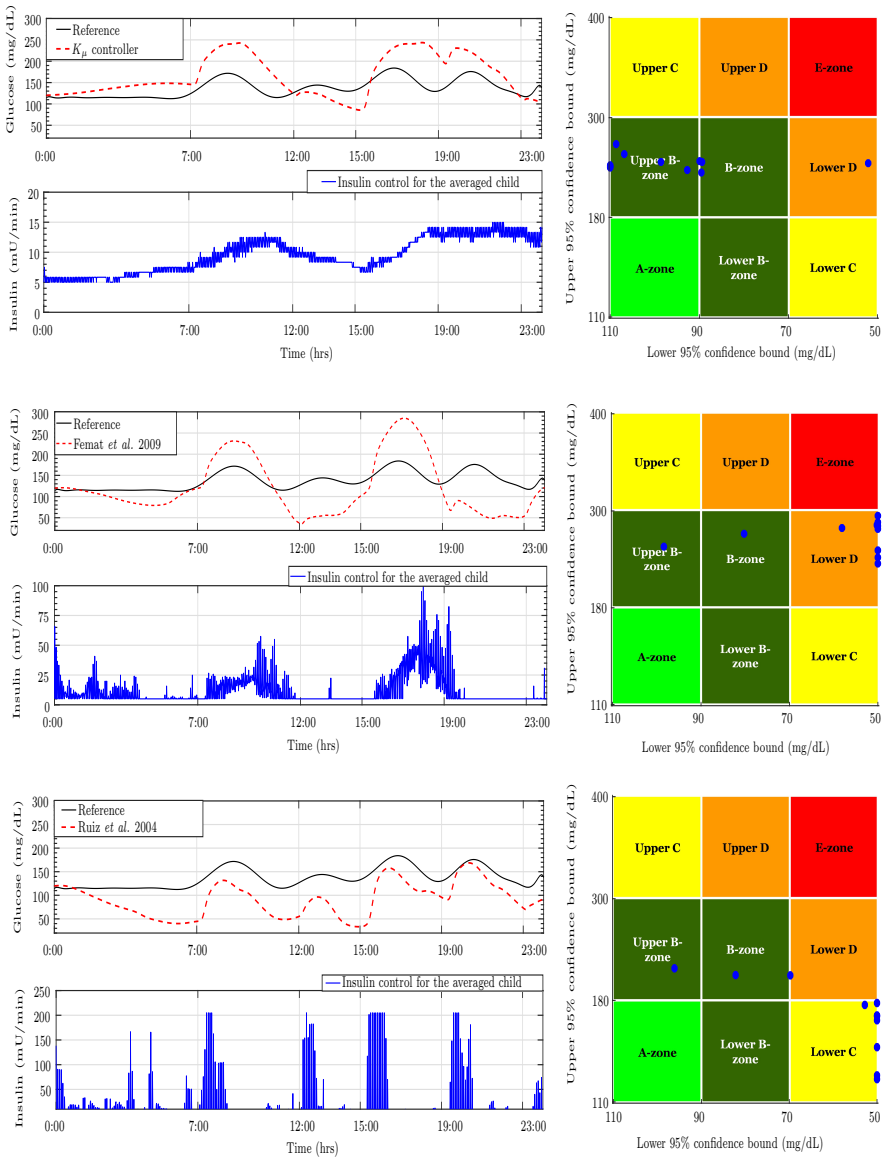

Figure 10: Results of the proposed cross-age strategy to control blood glucose in virtual children. *Left*: closed-loop performance of the proposed K_μ controller (top) and two robust controllers reported previously (middle and bottom) in a five meals scenario. *Right*: CVGA performance chart in one-day treatment proved in 11 virtual children.

4.5.3. Children

The virtual children population exhibits the most complex glucose-insulin behavior. For this reason, a slight adaptation of the basal infusion was made in all scenarios involving this population. Correspondingly in Figure 11 the results of glucose regulation in children are presented. Both $\mathcal{H}_\infty$ controllers of [9] and [8] failed to deal with the glucose regulation in an averaged model of children. The hypoglycemic lapses experienced under the treatment of [8] are evident and prolonged. The CVGA analysis shows that only 2 of 11 children can be in the green zone of benign deviations for both control algorithms (Figure 11 middle and bottom). On the other hand, the insulin administration of the K_μ controller is smooth and more appropriate. In fact, Figure 11 (top) shows an increased error in reference tracking due to the presence of high insulin sensitivity in children. However, the overall performance is acceptable because the maximum is 245 mg/dL and the minimum 78 mg/dL for the entire simulation lapse. Additionally, 7 of 11 children are placed in Upper-B which means 63.63% of glycemic effectiveness; 3 children fall in B-zone, this is 27.27% and only one child in Lower D, which means a 9.09% failure to deal with hypo/hyperglycemia as it was classified in Table 4.

4.6. 3-meal scenario

The glycemic control proposals reported in the literature which present results on the Uva/Padova simulator platform use a wide variety of combinations for meal intake and multi-day meal plans to test these control schemes. In the

Meal protocol (gCH)	Breakfast	Meal	Dinner	Total
Time (hrs) / Population	7:00	14:00	20:00	One-day
Adults	50	60	50	160 gCH
Adolescents	50	60	50	160 gCH

Table 5: One-day meal protocol for adolescents and adults reported in [4].

.

work of Colmega *et al.* [4] a LPV controller approach with switching modes is developed to deal with postprandial hyperglycemia excursions. Such controller is tested in the complete 100 virtual adult cohort of the FDA-approved Uva/Padova simulator under two different meal protocols in a 3-day scenario. Protocol #1 consists of 3 meals with a high carbohydrate content and Protocol #2 has prolonged fasting periods. In this section, the K_μ controller is tested under Protocol #1 of [4] in a single-day treatment scenario for adolescents and adults. The carbohydrate amounts intake and mealtime day are detailed in the Table 5.

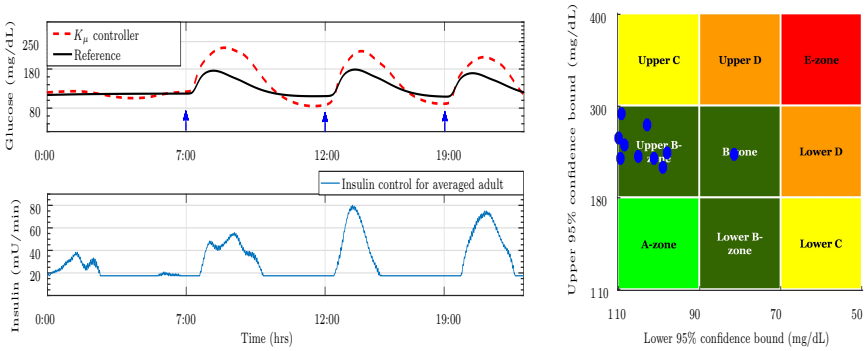

Figure 11: Results of the proposed cross-age strategy to control blood glucose in virtual adults. The blue arrows indicate the time the meal takes place. *Left*: closed-loop performance of the K_μ controller for the three meals protocol proposed in [4]. *Right*: CVGA performance chart in one-day treatment proved in 11 virtual adults.

The results of this section are presented in a similar way to those of the previous subsections. Although this new scenario has only 3 meals it can be seen in Figure 11 that K_μ controller is able to successfully regulate the averaged adult glucose in the postprandial period. In the performance for the 11 virtual adults, the CVGA analysis reveals that the majority of virtual adults are located in the Upper-B zone. In the experiments of the K_μ controller with the population of virtual adolescents an acceptable behavior is exhibited since the averaged patient can be controlled within limits similar to adults, as presented in Figure 12. Although the meal intakes of this protocol are considerably high, the K_μ

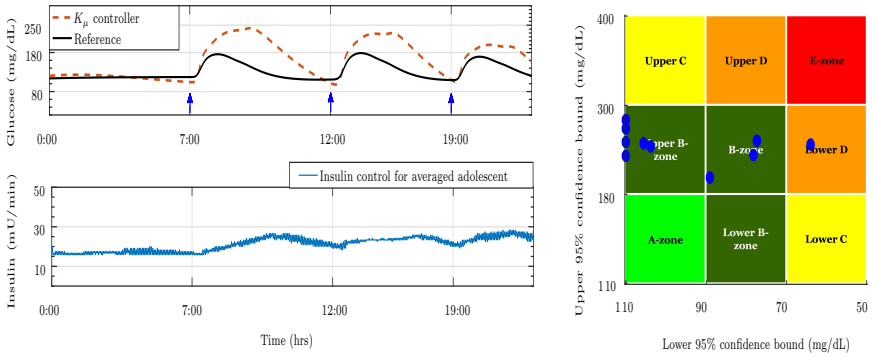

Figure 12: Results of the proposed cross-age strategy to control blood glucose in virtual adolescents. The blue arrows indicate the time the meal takes place. *Left*: closed-loop performance of the K_μ controller for the three meals protocol proposed in [4]. *Right*: CVGA performance chart in one-day treatment proved in 11 virtual adolescents.

controller can suitably supply insulin to avoid prolonged hyperglycemia lapses. However, the CVGA chart for trials with 11 adolescents illustrates that 1 subject falls into the Lower-D area of failure to deal with hypoglycemia. This is because the periods between meals are very long for this protocol #1. That is, a well-planned diet for diabetic patients should include snacks intake or intermediate meals to avoid prolonged fasting during daylight hours. In addition to proposing a cross-age strategy for glycemic control, the efforts of this work are also oriented to suggest more appropriate meal protocols for diabetic patients.

5. Conclusions

In this article, a cross-age strategy for the glucose regulation of T1DM patients is proposed. The aim is to contribute in enhancing a control scheme useful towards the implementation of AP systems. Since the T1DM is an illustrative example where the plant response can change drastically as a consequence of the cross-age. That is, a consequence of the endocrine subsystem the blood glucose metabolism changes dramatically due to hormone and cellular behaviors while the subject evolves to the adulthood. A critical issue concerns adolescence, where hormone change is dramatic. Thus, a unified control approach in

the cross-age context is an open problem which is addressed here. The characterization of the important sensitive parameters in the strategy of structured uncertainties allows us to design a robust control algorithm by μ-synthesis. Although the controller design is based on a mathematical physiological model, the validation of results in Uva/Padova simulator involves completely different models and scenarios. The underlying idea is to show feasibility of the approach based on the μ-synthesis control. The averaged glucose level under control for both the virtual adults and adolescents remain within the range of 80.03 mg/dL and 235.7 mg/dL. These results include the postprandial period, which avoid risk at all because the safe levels were robustly preserved. The CVGA charts shows the viability of μ-synthesis technique to resolve the glycemic regulation problem; this because the percentage of virtual adults and adolescents that exhibited a satisfactory glycemic control is greater than 90%. Although glycemic regulation for children is a more challenging research area, CVGA analysis provides encouraging results when the K_μ controller is tested and compared with other robust control algorithms. It is noteworthy that the K_μ controller is a low-order transfer function; thus its practical implementation could be simple and portable. This is an advantage for its future integration as closed-loop controller in AP systems.

The results presented here provide evidences about the feasibility of *in silico* implementations of $\mu-$syntesis control in AP systems. An interesting, but expected results, regards to the controller execution. As showed at the *in silico* testing, the previous $\mathcal{H}_\infty$ controllers achieve the control goal but the performance is deteriorated. On contrary, the K_μ controller tracks the reference glucose level with a lower effort. Finally, the methodology proposed here and the theoretical results using virtual patients from a standardized T1DM patient simulator, establish the foundations for further biomedical investigation regarding clinical validation of cross-age control schemes.

6. Acknowledgements

This study was supported by National Council of Science and Technology (CONACYT) in México (grant 249062, 220187 and 257120).

References

[1] World Health Organization, WHO Mortality Database [online database]. Geneva: World Health Organization. (2016). doi:http://apps.who.int/healthinfo/statistics/mortality/.

[2] The Diabetes Control and Complications Trial Research Group, *The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus*, New England Journal of Medicine 329 (14) (1993) 977–986, pMID: 8366922. doi:10.1056/NEJM199309303291401.

[3] H. Yeh, T. T. Brown, N. Maruthur, P. Ranasinghe, Z. Berger, Y. D. Suh, L. M. Wilson, E. B. Haberl, J. Brick, E. B. Bass, S. H. Golden, *Comparative effectiveness and safety of methods of insulin delivery and glucose monitoring for diabetes mellitus: A systematic review and meta-analysis*, Annals of Internal Medicine 157 (5) (2012) 336–347. doi:10.7326/0003-4819-157-5-201209040-00508.

[4] P. Colmegna, R. Sánchez-Pena, R. Gondhalekar, E. Dassau, F. Doyle, *Switched LPV Glucose Control in Type 1 Diabetes*, IEEE Transactions on Biomedical Engineering 63 (6) (2016) 1192–1200. doi:10.1109/TBME.2015.2487043.

[5] J. Galadanci, R. Shafik, J. Mathew, A. Acharyya, D. Pradhan, *A Closed-Loop Control Strategy for Glucose Control in Artificial Pancreas Systems*, in: Electronic System Design (ISED), 2012 International Symposium on, 2012, pp. 295–299. doi:10.1109/ISED.2012.76.

[6] L. Kovács, P. Szalay, B. Benyó, G. Chase, *Asymptotic output tracking in blood glucose control. A case study*, in: 2011 50th IEEE Conference on Decision and Control and European Control Conference, 2011, pp. 59–64. doi:10.1109/CDC.2011.6161400.

[7] B. S. León, A. Y. Alanís, E. N. Sanchez, F. Ornelas-Tellez, E. Ruiz-Velázquez, *Neural Inverse Optimal Control via Passivity for Subcutaneous Blood Glucose Regulation in Type 1 Diabetes Mellitus Patients*, Vol. 20, 2014, pp. 279–295. doi:10.1080/10798587.2014.891307.

[8] E. Ruiz-Velázquez, R. Femat, D. Campos-Delgado, *Blood glucose control for type 1 diabetes mellitus: A robust tracking $\mathcal{H}_\infty$ problem*, Control Engineering Practice 12 (9) (2004) 1179–1195.

[9] R. Femat, E. Ruiz-Velázquez, G. Quiroz, *Weighting Restriction for Intravenous Insulin Delivery on T1DM Patient via $\mathcal{H}_\infty$ Control*, IEEE Transactions on Automation Science and Engineering 6 (2) (2009) 239 –247. doi:10.1109/TASE.2008.2009089.

[10] W. Garcia-Gabin, E. Jacobsen, *Multilevel model based glucose control for Type-1 diabetes patients*, in: 2013 35th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), 2013, pp. 3917–3920. doi:10.1109/EMBC.2013.6610401.

[11] S. Hashimoto, C. Noguchi, E. Furutani, *Postprandial blood glucose control in type 1 diabetes for carbohydrates with varying glycemic index foods*, in: 2014 36th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, 2014, pp. 4835–4838. doi:10.1109/EMBC.2014.6944706.

[12] B. Liu, H. Ying, *Analysis of the islets-based glucose control system involving the nonlinear glucose-insulin metabolism model*, in: Information and Automation, 2015 IEEE International Conference on, 2015, pp. 2373–2378. doi:10.1109/ICInfA.2015.7279683.

[13] Y. Wang, H. Xie, X. Jiang, B. Liu, *Intelligent Closed-Loop Insulin Delivery Systems for ICU Patients*, IEEE Journal of Biomedical and Health Informatics 18 (1) (2014) 290–299. doi:10.1109/JBHI.2013.2269699.

[14] V. Bátora, M. Tárník, J. Murgaš, S. Schmidt, K. Nørgaard, N. Poulsen, J. Jørgensen, *Bihormonal control of blood glucose in people with Type 1 Diabetes*, in: Control Conference (ECC), 2015 European, 2015, pp. 25–30. doi:10.1109/ECC.2015.7330520.

[15] M. Messori, M. Ellis, C. Cobelli, P. Christofides, L. Magni, *Improved postprandial glucose control with a customized Model Predictive Controller*, in: 2015 American Control Conference (ACC), 2015, pp. 5108–5115. doi:10.1109/ACC.2015.7172136.

[16] P. Colmegna, R. Sánchez-Pena, R. Gondhalekar, E. Dassau, F. Doyle-III, *Reducing Risks in Type 1 Diabetes Using $\mathcal{H}_\infty$ Control*, IEEE Transactions on Biomedical Engineering 61 (12) (2014) 2939–2947. doi:10.1109/TBME.2014.2336772.

[17] E. Daskalaki, P. Diem, S. Mougiakakou, *Personalized tuning of a reinforcement learning control algorithm for glucose regulation*, in: 2013 35th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), 2013, pp. 3487–3490. doi:10.1109/EMBC.2013.6610293.

[18] I. Pagkalos, P. Herrero, C. Toumazou, P. Georgiou, *Bio-Inspired Glucose Control in Diabetes Based on an Analogue Implementation of a β-Cell Model*, IEEE Transactions on Biomedical Circuits and Systems 8 (2) (2014) 186–195. doi:10.1109/TBCAS.2014.2301377.

[19] H. Thabit, R. Hovorka, *Coming of age: the artificial pancreas for type 1 diabetes*, Diabetologia 59 (9) (2016) 1795–1805. doi:10.1007/s00125-016-4022-4.

[20] A. C. van Bon, Y. M. Luijf, R. Koebrugge, R. Koops, J. B. L. Hoekstra, J. H. DeVries, *Feasibility of a Portable Bihormonal Closed-Loop System to*

Control Glucose Excursions at Home Under Free-Living Conditions for 48 Hours, Diabetes Technology & Therapeutics 16 (3) (2014) 131–136, pMID: 24224750. doi:10.1089/dia.2013.0166.

[21] J. Kropff, S. Del Favero, J. Place, C. Toffanin, R. Visentin, M. Monaro, M. Messori, F. Di Palma, G. Lanzola, A. Farret, F. Boscari, S. Galasso, P. Magni, A. Avogaro, P. Keith-Hynes. B. P. Kovatchev, D. Bruttomesso, C. Cobelli, J. H. DeVries, E. Renard, L. Magni, *2 month evening and night closed-loop glucose control in patients with type 1 diabetes under free-living conditions: a randomised crossover trial*, The Lancet Diabetes & Endocrinology 3 (2) (2015) 939–947. doi:10.1016/S2213-8587(15)00335-6.

[22] J. T. Sorensen, *A physiologic model of glucose metabolism in man and its use to design and assess improved insulin therapies for diabetes*, Ph.D. thesis, Massachusetts Institute of Technology (April 1985).

[23] R. Hovorka, V. Canonico, L. J. Chassin, U. Haueter, M. Massi-Benedetti, M. Orsini Federici, T. R. Pieber, H. C. Schaller, L. Schaupp, T. Vering, et al., *Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes.*, Physiological Measurement 25 (4) (2004) 905–920.

[24] C. Dalla-Man, R. Rizza, C. Cobelli, *Meal Simulation Model of the Glucose-Insulin System*, Biomedical Engineering, IEEE Transactions on 54 (10) (2007) 1740 –1749. doi:10.1109/TBME.2007.893506.

[25] L. Magni, D. Raimondo, C. Dalla-Man, G. D. Nicolao, B. Kovatchev, C. Cobelli, *Model predictive control of glucose concentration in type 1 diabetic patients: An in silico trial*, Biomedical Signal Processing and Control 4 (4) (2009) 338 – 346, Special Issue on Biomedical Systems, Signals and Control Extended Selected papers from the IFAC World Congress, Seoul, July 2008. doi:http://dx.doi.org/10.1016/j.bspc.2009.04.003.

[26] G. Quiroz, R. Femat, *On hyperglicemic glucose basal levels in Type 1 Diabetes Mellitus from dynamic analysis*, Mathematical biosciences 210 (2) (2007) 554–575. doi:10.1016/j.mbs.2007.06.004.

[27] B. P. Kovatchev, M. Breton, C. Dalla-Man, C. Cobelli, *In silico preclinical trials: a proof of concept in closed-loop control of Type 1 diabetes*, Journal of Diabetes Science and Technology 3 (1) (2009) 44—55. doi:10.1177/193229680900300106.

[28] C. Dalla-Man, F. Micheletto, D. Lv, M. Breton, B. Kovatchev, C. Cobelli, *The UVA/PADOVA Type 1 Diabetes Simulator: New Features*, Journal of Diabetes Science and Technology 8 (1) (2014) 26–34, pMID: 24876534. doi:10.1177/1932296813514502.
URL https://doi.org/10.1177/1932296813514502

[29] L. Kóvacs, B. Kulcsar, J. Bokor, Z. Benyo, *Model-based nonlinear optimal blood glucose control of Type I diabetes patients*, in: 2008 30th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, 2008, pp. 1607–1610. doi:10.1109/IEMBS.2008.4649480.

[30] A. G. G. Hernández, L. Fridman, R. Leder, S. I. Andrade, C. R. Monsalve, Y. Shtessel, A. Levant, *High-order sliding-mode control for blood glucose regulation in the presence of uncertain dynamics*, in: 2011 Annual International Conference of the IEEE Engineering in Medicine and Biology Society, 2011, pp. 3998–4001. doi:10.1109/IEMBS.2011.6090993.

[31] L. Cantu, I. Y. Sanchez, L. Garza-Castanón, S. O. Martinez, *Feedforward compensation of exercise in diabetes*, in: 2010 18th Mediterranean Conference on Control Automation (MED), 2010, pp. 1335–1340. doi:10.1109/MED.2010.5547863.

[32] M. G. Markakis, G. D. Mitsis, V. Z. Marmarelis, *Computational study of an augmented minimal model for glycaemia control*, in: 2008 30th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, 2008, pp. 5445–5448. doi:10.1109/IEMBS.2008.4650446.

[33] Da-Wei Gu and Petko Petkov and Mihail M. Konstantinov, *Robust Control Design with Matlab®*, 2nd Edition, Advanced Textbooks in Control and Signal Processing, Springer-Verlag London, 2013.

[34] Kemin Zhou and John C. Doyle, *Essentials of Robust Control*, Prentice Hall Modular Series for Eng., Prentice Hall, 1998.
URL https://books.google.com.mx/books?id=QviHQgAACAAJ

[35] L. Magni, D. M. Raimondo, C. Dalla-Man, M. Breton, S. Patek, G. De Nicolao, C. Cobelli, B. P. Kovatchev, *Evaluating the Efficacy of Closed-Loop Glucose Regulation via Control-Variability Grid Analysis*, Journal of Diabetes Science and Technology 2 (4) (2008) 630–635, pMID: 19885239. doi:10.1177/193229680800200414.