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Testing PFC Controller On A Well Validated *In Silico* Model of a Type I Diabetic Patient ⋆

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Abstract: Diabetes technology has been focused since three decades ago on developing the artificial páncreas through several closed-loop control algorithms linking glucose measurements and insulin delivery. This work is focused on rigorously analyzing the Predictive Functional Control (PFC) algorithm capabilities for deciding about the correct insulin dosage under everyday circumstances.
The study is done by applying the PFC in a recently developed model of the endocrine system, approved by the FDA in 2008, as a substitute to animal trial. The platform used here consists only of a limited number of patients: 10 children, 10 adolescents, and 10 adults. To realistically represent the full closed loop system, a model of a subcutaneous glucose sensor was added and the constraints related to the insulin pump was taken into account by the predictive controller.
The performance of the controller, with and without the sensor model, was evaluated by means of the Control Variability Grid Analysis (CVGA) technique and the results were satisfactory in all patients.

Keywords: Artificial Pancreas, Diabetes Technology, PFC, Virtual Patient, CVGA.

1. INTRODUCTION

Diabetes Mellitus is a disorder of the metabolism where either insufficient insulin is produced by the beta cells in the páncreas, or the body is unable to effectively utilize that insulin. As a result, glucose cannot be transported to the cells, leading to dangerously high blood glucose levels. Untreated over time, high blood glucose levels can lead to costly complications and low blood glucose can lead to death. It is a very frequent chronic disease that in the last years has reached the proportion of an epidemy. The prevalence of diabetes for all age-groups worldwide was estimated to be 7.8% in 2030 by the International Diabetes Federation (IDF Diabetes Atlas). The total number of people with diabetes is projected to rise from 171 million in 2000 to 439 million in 2030.

Nowadays, to treat this disease, diabetic patients measure their blood sugar content by pricking their fingers several times a day and inject doses of insulin accordingly. From a control point of view, this is an open loop method that tries to correct blood glucose no more than 6 times a day, usually before having a meal. The way artificial pancreas is thought is to regulate sugar content in blood in real time, just as the human pancreas would do. This could be done by means of a blood glucose sensor accurate enough to give blood glucose content in real time, an insulin pump that delivers the correct amount of insulin that the body needs, and the control algorithm, which is the responsible for calculating this amount of insulin in real time.

To date, many control algorithms have been tested. PID (proportional integral derivative) (Ramprasad et al., 2004) and MPC (model predictive control) (Hovorka et al., 2004; Magni et al., 2009) control laws are among the most well-known methodologies proposed in literature. However, model-based control strategies have been used with more encouraging outcomes in tighter regulation of blood glucose levels. The knowledge incorporated by the models in these types of controllers is what makes them more appealing. It is worth mentioning that other types of control algorithms have been tested too. For example, robust H_∞ (Parker et al., 2000).

The PFC corresponds to the family of MPC. It has been used many times in very different industrial applications with excellent results. Particularly, this type of controller has a great capacity to handle nonlinear systems, unstable and with large dead times. Moreover, PFC methodology has incorporated what is called control zone. This means that the setpoint changes ($\pm\Delta\%$ - control zone) depending on the difference of the process output and the desired value, making it more versatile. The authors have tested it before (Díaz et al., 2005) with promising results but employing the old version of Cobelli's model (Carson et al., 1982). In the present work, the usefulness of this controller is proved against a novel well validated physiological model, much better than the old one.

So, the algorithm robustness has been tested on 30 *in silico* patients based on the Food and Drug Administration (FDA)

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approved simulation environment. The full model consists of 300 patients (100 adults, 100 adolescents and 100 children) but is only available to the Juvenile Diabetes Research Foundation (JDRF) Artificial Pancreas Consortium (Kovatchev et al., 2009). First, the type 1 diabetic patient model and the sensor model are fully described. Then, the mathematics behind the control algorithm is summarized. After that, the development of the models for the controller and the adjustment of its parameters is explained. Finally, the PFC is tested with and without the *in silico* sensor, and introducing errors in the internal models showing that it is robust enough to perform successfully.

2. THE INTERACTION MODEL: GLUCOSE-INSULIN

The mathematical model used in this work to synthesize and test the controller is the one developed by Dalla Man et al. (2007) because it is one of the only ones that has been validated against clinical and experimental data and has been approved by the FDA as a substitute to animal trial in the pre-clinical testing of closed-loop control algorithms. This model allows simulating the dynamic effect of exogenous glucose and insulin dosage under different specific tests for diabetic patients and it is summarized in the following subsections.

2.1 Glucose intestinal absorption

It is modeled by a recently developed three-compartment model:

$$\dot{Q_{sto1}}(t) = -k_{gri}Q_{sto1}(t) + d(t) \quad (1)$$

$$\dot{Q_{sto2}}(t) = -k_{empt}(t, Q_{sto}(t))Q_{sto2}(t) + k_{gri}Q_{sto1}(t) \quad (2)$$

$$\dot{Q_{gut}}(t) = -k_{abs} + k_{empt}(t, Q_{sto}(t))Q_{sto2}(t) \quad (3)$$

$$Q_{sto}(t) = Q_{sto1}(t) + Q_{sto2}(t) \quad (4)$$

$$Ra(t) = fk_{abs}Q_{gut}(t)/BW \quad (5)$$

where Q_{sto} (mg) is the amount of glucose in the stomach (solid, Q_{sto1} , and liquid phase, Q_{sto2}), Q_{gut} (mg) is the glucose mass in the intestine, k_{gri} is the rate of grinding, k_{abs} is the rate constant of intestinal absorption, f is the fraction of intestinal absorption which actually appears in plasma, $d(t)$ (mg/min) is the amount of ingested glucose, BW (kg) is the body weight, Ra (mg/kg/min) is the glucose rate of appearance in plasma and k_{empt} is the rate constant of gastric emptying which is a time-varying nonlinear function of Q_{sto}:

$$k_{empt}(t, Q_{sto}(t)) = k_{max} + \frac{k_{max} - k_{min}}{2}[A(t)]; \quad (6)$$

where:

$$A(t) = \tanh[\alpha(Q_{sto}(t) - bD(t))] - \tanh[\beta(Q_{sto}(t) - dD(t))] \quad (7)$$

$$\alpha = \frac{5}{2D(t)(1-b)} \quad (8)$$

$$\beta = \frac{5}{2D(t)d} \quad (9)$$

$$D(t) = \int_{t_i}^{t_f} \mathrm{d}(t)\, dt \quad (10)$$

with t_i and t_f, respectively, start time and end time of the last meal, b, d, k_{max} and k_{min} model parameters.

2.2 Glucose subsystem

A two-compartment model is used to describe glucose kinetics:

$$\dot{G_p}(t) = EGP(t) + Ra(t) - U_{ii}(t) - E(t) - k_1 G_p(t) + k_2 G_t(t) \quad (11)$$

$$\dot{G_t}(t) = k_1 G_p(t) - U_{id}(t) - k_2 G_t(t) \quad (12)$$

$$G(t) = \frac{G_p(t)}{V_G} \quad (13)$$

with $G_p(0) = G_{pb}$, $G_t(0) = G_{tb}$, $G(0) = G_b$. Here G_p and G_t (mg/kg) are glucose masses in plasma and rapidly-equilibrating tissues, and in slowly-equilibrating tissues, respectively, G (mg/dl) is plasma glucose concentration, suffix b denotes basal state, EGP is endogenous glucose production (mg/kg/min), Ra is glucose rate of appearance in plasma (mg/kg/min), E is renal excretion (mg/kg/min), U_{ii} and U_{id} are insulin-independent and dependent glucose utilizations, respectively (mg/kg/min), V_G is the distribution volume of glucose (dl/kg), and k_1 and k_2 (min^{-1}) are rate parameters.

2.3 Glucose renal excretion

Renal excretion represents the glucose flow which is eliminated by the kidney, when glycaemia exceeds a certain threshold k_{e2}:

$$E(t) = \max(0, k_{e1}(G_p(t) - k_{e2})); \quad (14)$$

The parameter k_{e1} (1/min) represents renal glomerular filtration rate.

2.4 Endogenous glucose production

EGP comes from the liver, where a glucose reserve exists (glycogen). EGP is inhibited by high levels of glucose and insulin:

$$EGP(t) = \max(0, EGP_b - k_{p2}(G_p(t) - G_{pb}) - k_{p3}(I_d(t) - I_b)); \quad (15)$$

where k_{p2} and k_{p3} are model parameters and I_d (pmol/l) is a delayed insulin signal, coming from the following dynamic system:

$$\dot{I_1}(t) = k_i I(t) - k_i I_1(t) \quad (16)$$

$$\dot{I_d}(t) = k_i I_1(t) - k_i I_d(t) \quad (17)$$

where I (pmol/l) is plasma insulin concentration or insulinemia and k_i (1/min) is a model parameter.

2.5 Glucose utilization

Glucose utilization is made up of two components: the insulin-independent one U_{ii}, which represents the glucose uptake by the brain and erythrocytes, and the insulin-dependent component U_{id}, which depends non-linearly on glucose in the tissues:

$$U_{id}(t) = V_m(X(t))\frac{G_t(t)}{K_m + G_t(t)}; \quad (18)$$

where V_m (1/min) is a linear function of interstitial fluid insulin X (pmol/l)

$$V_m(X(t)) = V_{m0} + V_{mx}X(t); \quad (19)$$

which depends from insulinemia in the following way:

$$\dot{X}(t) = p_{2u}(I(t) - Ib) - p_{2u}X(t); \quad (20)$$

where K_m, V_{m0}, V_{mx} are model parameters, I_b (pmol/l) is the basal insulin level and p_{2U} (1/min) is called rate of insulin action on peripheral glucose.

2.6 Insulin subsystem

Insulin flow s, coming from the subcutaneous compartments, enters the bloodstream and is degradated in the liver and in the periphery:

$$\dot{I}_p(t) = m_1 I_l(t) - (m_2 + m_4) I_p(t) + s(t) \quad (21)$$

$$\dot{I}_l(t) = m_2 I_p(t) - (m_1 + m_3) I_l(t) \quad (22)$$

$$I(t) = I_p(t)/V_I \quad (23)$$

where V_I (l/kg) is the distribution volume of insulin and m_1, m_2, m_3, m_4 (1/min) are model parameters.

2.7 Subcutaneous insulin subsystem

The subcutaneous insulin subsystem is modeled here with two compartments, S_1 and S_2 (pmol/kg), which represent, respectively, polymeric and monomeric insulin in the subcutaneous tissue:

$$\dot{S}_1(t) = -(k_{a1} + k_d) S_1(t) + u(t) \quad (24)$$

$$\dot{S}_2(t) = k_d S_1(t) - k_{a2} S_2(t) \quad (25)$$

$$s(t) = k_{a1} S_1(t) + k_{a2} S_2(t) \quad (26)$$

where $u(t)$ (pmol/kg/min) represents injected insulin flow, k_d is called degradation constant, k_{a1} and k_{a2} are absorption constants.

2.8 Subcutaneous glucose subsystem

The delay of the sensor was modeled with a system of first order:

$$\dot{G_M}(t) = k_{sc} G(t) - k_{sc} G_M(t); \quad (27)$$

3. THE SUBCUTANEOUS SENSOR MODEL

In order to simulate more realistically the behaviour of a diabetic patient using an artificial pancreas (Kovatchev et al., 2009), a model of the sensor was incorporated. The *in silico* subcutaneous sensor used in the simulations is the one developed by (Breton and Kovatchev, 2008). After generating a random calibration error, the components of sensor error can be modeled as:

(1) Blood-to-interstitium glucose transport described by the equation:

$$\frac{\partial IG}{\partial t} = \frac{-1}{\tau}(IG - BG); \quad (28)$$

where IG is the interstitial and BG is plasma glucose concentration, and τ represents the time lag between the two fluids;

(2) Noise of the sensor, which is non-white (Gaussian). We therefore use ARMA process for its modeling:

$$e_1 = v_1 \quad (29)$$

$$e_n = 0.7(e_{n-1} + v_n) \quad (30)$$

with $v_n \sim \Phi(0,1)$, i.i.d.. The sensor noise is ε_n, which is driven by the normally distributed time series e_n. The parameters ξ, λ, δ, and γ are the Johnson system (SU - unbounded system) parameters corresponding to empirical noise distributions established in accuracy trials:

$$\varepsilon_n = \xi + \lambda \sinh(\frac{e_n - \gamma}{\delta}); \quad (31)$$

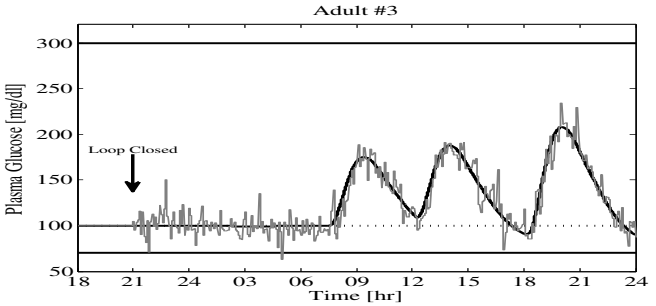

Fig. 1. Nominal scenario for adult patient. It can be seen the upper bound (300 mg/dl) and the lower bound (70 mg/dl) in accordance with the CVGA and the sensor noise superimposed in gray.

4. THE *IN SILICO* PRECLINICAL TRIAL

The performance of our controller was tested on a 1-day virtual protocol (Fig. 1) based on Patek et al. (2009). For an adult:

(1) Admit state: Patient blood glucose steady at 100 mg/dl at 18:00 Day 1.
(2) Control loop is closed at 21:00 Day 1.
(3) At 7:30 Day 2, the patient has breakfast lasting about 2 min with a carbohydrate (CHO) content of 50 grams.
(4) At approximately noon (12:00) Day 2, the patient takes a lunch meal containing 65 grams CHO. Meal duration is 15 min.
(5) At 18:00 Day 2, the patient takes a dinner meal containing 80 grams CHO. Meal duration is 15 min.

This scenario changes for adolescents and children just in the amount they eat (Adolescents: 40/50/65 grams; Children: 25/30/40 grams).

5. PREDICTIVE FUNCTIONAL CONTROL (PFC)

The PFC technique is the third generation of a family of Model Algorithmic Control. PFC basically consists of four main elements such as a process dynamic model, a reference trajectory $y_r(n)$, a self-compensation of the predicted error and a specific structure for the manipulated variable. The future error between $y_r(n)$ and the predicted output over the coincidence horizon $[H_1, H_2]$ is estimated. A self compensation is done accounting for the actual mismatch between real data and model output. The estimation of the future error at the coincidence horizon by specific kind of extrapolation, allows to improve the model prediction. Within PFC, feedforward and feedback control actions can be jointly designed and constraints are taken into account in a very natural way.

Calling the inputs of the manipulated variable $u(n)$ (insulin from the pump) and the perturbation $d(n)$ (a meal), the first order model response at the coincidence point $(n+H)$ becomes:

$$\begin{aligned} y_m(n+H) = {} & \alpha_m^H x_{mi}(n) + \alpha_d^H x_{md}(n) + \\ & \sum_{j=0}^{H-1} \alpha_m^{H-1-j} K_{mi}(1-\alpha_m) u(j+n) + \\ & \sum_{j=0}^{H-1} \alpha_d^{H-1-j} K_{di}(1-\alpha_d) d(j+n) \end{aligned} \quad (32)$$

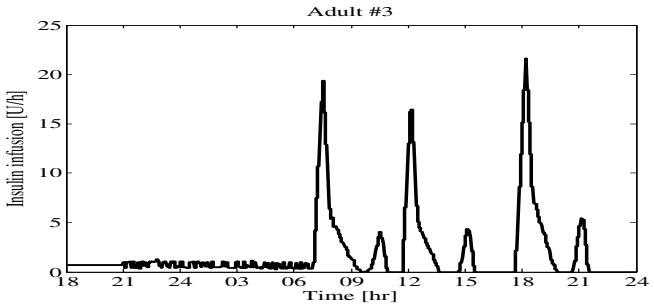

Fig. 2. External insulin infused to Adult #3.

$$u(n) = K_0\hat{\varepsilon}(n) + K_1 y_{mi}(n) + ... \quad (33)$$
$$... + K_2 y_{md}(n) + K_3 d(n) + K_4 y_m(n)$$

$$K_0 = \frac{(1-\lambda^H)}{K_{mi}(1-\alpha_m^H)} \quad (34)$$

$$K_1 = \frac{-\alpha_m^H}{K_{mi}(1-\alpha_m^H)} \quad (35)$$

$$K_2 = \frac{-\alpha_d^H}{K_{mi}(1-\alpha_m^H)} \quad (36)$$

$$K_3 = \frac{-K_{di}(1-\alpha_d^H)}{K_{mi}(1-\alpha_m^H)} \quad (37)$$

$$K_4 = \frac{1}{K_{mi}(1-\alpha_m^H)} \quad (38)$$

$$(39)$$

The reference trajectory, which is the path to the future set point, is resetted at every instant and is given by:

$$C(n+j) - y_r(n+j) = \lambda^j (C(n) - y_p(n)), 0 \leq j \leq H \quad (40)$$

$$\lambda = e^{\frac{-3T_s}{CLTR}} \quad (41)$$

where $C(n)$ is the set-point, $y_p(n)$ the real process output and λ is a parameter that represents the exponential convergence of the algorithm, and thus fixes the closed-loop behaviour. T_s is the sampling time and was considered as 5 minutes because of the sensor readings per hour.

The parameters to be tuned for the PFC are: number of coincidence points (H), closed loop time response (CLTR) of the reference trajectory, the control zone considered so that CLTR moves linearly between two extremes values recognized as $CLTR\_L$ (low) and $CLTR\_H$ (high), the transition zone [%] that set the allowed zone for the controlled variable expressed as $\pm$ $Delta$ [%] with respect to the set point value and constraints to the manipulated variable are also included by fixing maximum (U_{max}), minimum (U_{min}) and variations for it $[(dU/dt)_{max}]$.

Here just a brief summary of the PFC technic is presented. For more details about the implementation of PFC, the reader should see Richalet and O'Donovan (2009).

5.1 Models for the PFC controller

The PFC has three inputs, the glucose measurement, the glucose set point (100 mg/dl in our case) and the glucose rate of appearance into the glucose compartment (Ra). The last input is only present if the meal is announced. To avoid the nonlinearities in the stomach compartment, the model for the controller was linearized without this compartment present. As a consequence of this, the meal disturbance has to be given as a filtered response into the glucose compartment and not as a step response into the stomach compartment (Ellingsen, 2008).

To announce a meal, the mean of all model parameters for each group of patients was taken and the glucose rate of appearance of each group was saved in a matrix. Then, the controller receives a mean absorption profile. Another way of solving this problem could be detecting when a patient receives a meal as shown in Dassau et al. (2008).

In our case, the relationship between insulin infusion (manipulated variable) and blood glucose (controlled variable) is named G_{mi}. Meanwhile G_{di} refers to the relationship between exogenous glucose (Glucose rate of appearance Ra from a meal) and blood glucose. Both models were set to be first order with time delay, and their identification was done by means of a step excitation in the insulin delivery and in the meal ingestion at the nominal condition. The step used depends on the group studied. For the manipulated variable, having the information of the Total Daily Insulin (TDI [U]) consumed by each patient, the mean value of all patients was taken. For the perturbation, the $\bar{Ra} = \sum \bar{Ra}_i$ was calculated.

5.2 PFC tuning

First, the controller was adjusted to each individual patient to see the optimal performance of it. The way parameters were set is described later in this section. Then, the controller was tested over three groups of patients: 10 children, 10 adolescents, and 10 adults. A set of parameters for the PFC was proposed to each group of patients (See Table 1). These set of parameters were obtained as follows:

(1) for each patient, two first order models with time delay was proposed (the plant and the disturbance):

$$G_{mi} = \frac{K_{mi}e^{-\theta_{mi}s}}{1+T_{mi}s} \quad (42)$$

$$G_{di} = \frac{K_{di}e^{-\theta_{di}s}}{1+T_{di}s} \quad (43)$$

(2) for each patient the CLTR_L, CLTR_H, H_1 and H_2 were computed as:
- $CLTR\_L = T_{mi}/2$
- $CLTR\_H = 10T_{mi}$
- $H_1 = \theta_{mi}$
- $H_2 = \theta_{mi} + 3T_{mi}$

(3) then, the mean value of these parameters were taken for each group (children, adolescents and adults) and the rest of the parameters were fixed as shown in Table 1. The only parameter to be changed among the patients was $[(\mathrm{dU/dt})_{max}]$.

The parameter ($[(\mathrm{dU/dt})_{max}]$) represents the aggressiveness of the controller. If it is set in a low value, the response of the controller is very soft. Increasing it, the controller becomes more and more aggressive. The adopted parameters for the simulations shown in this work are included in Table 1. This table shows the parameters adopted in cases study 3 (columns 2, 3 and 4) and 4 (fifth column) as will be shown in the following section.

6. RESULTS

The Control-Variability Grid Analysis (CVGA) is a graphical representation of min/max glucose values in a population of patients either real or virtual. The CVGA provides a simultaneous

Table 1. Controller Parameters

Parameter	Children	Adolescents	Adults	Mean	Units
$CLTR\_L$,	100.5	184.5	167.5	150.8	[min]
$CLTR\_H$,	2010	3690	3350	3016.7	[min]
$Delta$,	30	30	30	30	[%]
U_{min},	0	0	0	0	[pmol/min]
U_{max},	150	150	150	150	[pmol/min]
$(\frac{dU}{dt})_{max}$,	$(\frac{dU}{dt})_{max}$	$(\frac{dU}{dt})_{max}$	$(\frac{dU}{dt})_{max}$	$(\frac{dU}{dt})_{max}$	[pmol/min^2]
K_{mi},	-1.899	-0.573	-1.283	-1.2517	[(mg/dl)/(pmol/min)]
T_{mi},	201	369	335	301.7	[min]
θ_{mi},	104	121	137.5	120.8	[min]
K_{di},	42.243	44.753	53.471	46.822	[(mg/dl)/(mg/kg/min)]
T_{di},	146	164.5	174.5	161.7	[min]
θ_{di},	7.9	6.7	6.3	6.97	[min]
H,	1	1	1	1	[dimensionless]
H_1,	104	121	137.5	120.8	[min]
H_2,	707	1228	1142.5	1025.8	[min]
T_s,	5	5	5	5	[min]

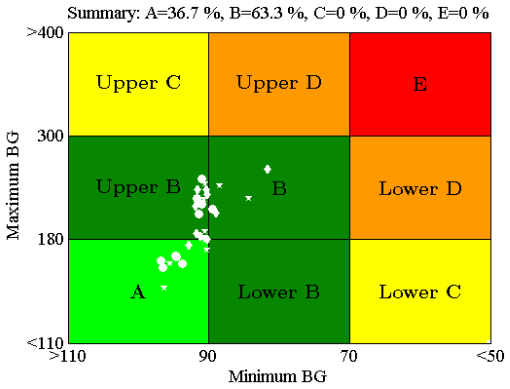

Fig. 3. CVGA (Case Study 1): circles (adults), diamonds (adolescents) and pentagrams (children).

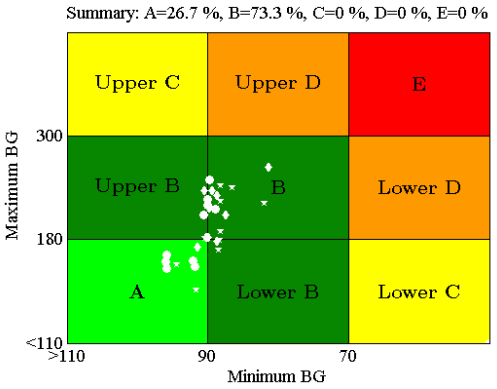

Fig. 4. CVGA without the use of the sensor model (Case Study 2): circles (adults), diamonds (adolescents) and pentagrams (children).

assessment of the quality of glycaemic regulation in all patients. As such, it has the potential to play an important role in the tuning of closed-loop glucose control algorithms and also in the comparison of their performances (Magni et al., 2008). So, it is a method for visualization of the extreme glucose excursions caused by a control algorithm in a group of subjects, with each subject represented by one data point for any given observation period. In this work, four case studies are presented:

6.1 Case Study 1

In Fig. 3 the CVGA done with the controller adjusted to each patient is presented. To differentiate among the groups, they are represented as follows: adults with circles, adolescents with diamonds, and children with pentagrams. As can be seen, everybody is in the green zone, which means that they are safe, not running major risks. In Figs. 1 and 2 the glucose and insulin profiles obtained in the nominal scenario with the PFC including the subcutaneous sensor model are reported for adult #3. There can be seen superimposed the sensor signal in gray.

6.2 Case Study 2

In another study, the CVGA without using the sensor model was done (Fig. 4). This is as if the controller received the real blood glucose content, a perfect sensor. The controller in this scenario uses the same tuning as in case study 1. It can be seen that, although everybody is in the safe zone, they have all gone closer to the lower bound (to the right - 70 mg/dl of blood glucose), where the risk of undergoing an hypoglycaemic episode is bigger. It is remarkable that Case Study 1 is misleading because it seems that the controller performed better than in this case which is just a matter of randomness (because of the sensor noise and error some patients crossed the line between zone B and A). If the influence of the sensor model is needed in depth , a different study should be done. This may lead to a Fault Diagnosis and Identification (FDI) system which gives the controller the exact quantity (Campetelli et al., 2009).

6.3 Case Study 3

In this case study, the controller parameters were adjusted to each group of patients as explained in Section 5.2. In Fig. 5 a CVGA performed with this PFC tuning is showed. It results in a poorer performance of the controller than in case study 1 but everybody is still in the safe region.

6.4 Case Study 4

Taking into account the good performance obtained hitherto, we encouraged to go even farther. In this case study, the controller parameters were set the same to all patients. The mean value of all parameters as showed in the fifth column of Table 1 was used. Then, adjusting the value of $[(dU/dt)_{max}]$ to each individual patient as done before, everybody was sent to the safety zone. This can be seen in Fig. 6. Even though the number of patients in zone A is smaller than in the other case

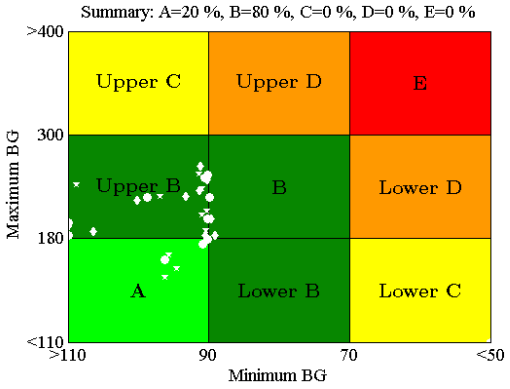

Fig. 5. CVGA using mean parameters in the controller for each group of patients (Case Study 3): circles (adults), diamonds (adolescents) and pentagrams (children).

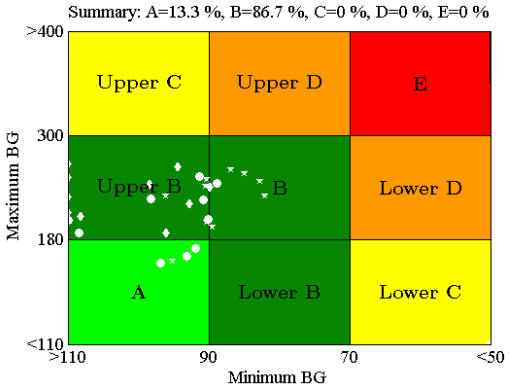

Fig. 6. CVGA using mean parameters in the controller for all patients (Case Study 4): circles (adults), diamonds (adolescents) and pentagrams (children).

studies, everybody is still in the green zone, which means that they are under control. Just to make a comparison among the different scenarios, each CVGA has the percentages at the top, showing that the case where most patients were in zone A is the first scenario studied (36.7%).

7. CONCLUSIONS

This is the first time that PFC was tested in a well-known mathematical model of the glucose-insulin system accounting for the physiological variability of different patients of different age groups. In spite of the fact that the internal model is so simplistic, the performance of the controller is more than acceptable and is similar to the results obtained by using other technologies within MPC technique (Magni et al., 2009). In Fig. 1 the evolution of a type 1 diabetic adult after the virtual protocol defined in Section 4 can be seen. The insulin infusion rate calculated by the PFC controller to keep this patient within normal glucose range is shown in Fig. 2.

It must be remarked that the PFC results very intuitive for selecting all the adjusting parameters involved in this technique. Hence, even though a more sophisticated implementation of this kind of MPC philosophy could be applied, the results obtained here demonstrate its potentiality for this type of complex problems. It has been proved that the robustness of the control algorithm is capable of dealing with inter-patient variability. Taking the same parameters within the same group of patients resulted in a very good performance of the control algorithm. So, it gives more simplicity and seems to be robust enough to be useful for a group of models corresponding to similar patients.

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