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Abstract

The control design of an artificial pancreas, a hot research topic in diabetology, is tackled via the newly introduced model-free control and its corresponding "intelligent" proportional controller, which were already quite successful in many concrete and diverse situations. It results in an insulin injection for type 1 diabetes which displays via constant references a good nocturnal/fasting response, but unfortunately a poor postprandial behavior due to long hyperglycemia. When a variable reference is introduced, that switches between a constant one, when glycemia is more or less normal or moderate, and an exponential decay reference path, when a high glycemia rate indicates a meal intake, the results *in silico*, which employ real clinical data, become excellent. We obtain a bolus-shaped insulin injection rate during postprandial phases. The hyperglycemic peaks are therefore lowered a lot.

Keywords Type 1 diabetes, artificial pancreas, control algorithms, model-free control, intelligent proportional controller, variable reference trajectory, algebraic estimation techniques.

1 INTRODUCTION

Type-1 diabetes mellitus (*T1DM*), or *insulin-dependent diabetes*, is a chronic disease that results from the autoimmune destruction of the insulin-producing beta cells in the pancreas (see, *e.g.*, [3], and the references therein). A *functional insulin therapy* (*FIT*) is a most effective pedagogical treatment (see, *e.g.*, [26], and the references therein) where exogenous insulin is injected, or infused subcutaneously via a pump, according to the patient's everyday life.

Rapid technological advancements justify the research of an *artificial pancreas*, *i.e.*, of an automated device which consists of:

- a blood glucose sensor, or a *continuous glucose monitor* (*CGM*),
- an insulin pump,
- a control algorithm for injecting the appropriate insulin dose.

Most diverse control techniques have been proposed and often tested *in silico*, *i.e.*, via computer simulators. See, *e.g.*, [6, 9, 12, 14, 33, 51] for reviews. Obtaining a suitable mathematical modeling is therefore an essential issue (see, *e.g.*, the previous reviews, and [1, 10, 34]). Like in many concrete applications, PID control (see, *e.g.*, [12, 37, 39, 49]) and model-based predictive control (see, *e.g.*, [13, 25, 31, 35, 41]) are quite often encountered (see, *e.g.*, [24]).[1] They are however far from being completely satisfactory:

1. Although PIDs do not require a precise mathematical model, their tuning (see, *e.g.*, [2, 40]) may be extremely difficult and quite sensitive to "disturbances" like meals or stress.

2. The reference trajectory which is connected to model-based predictive control (see, *e.g.*, [7, 23, 42]) is a most attractive and useful feature. It is however paid by the need of a mathematical modeling and by cumbersome optimization procedures.

Let us also mention [43] which presents a wearable, automated, bihormonal, bionic pancreas that improved mean glycemic levels, with less frequent hypoglycemic episodes.

Our purpose is to show that the new *model-free control* (MFC) [16], which has already been successfully applied in many concrete and diverse situations (see [16, 29, 38], and the references therein), might get closer to a real artificial pancreas. As a matter of fact the benefits of this control algorithm are numerous:

- As for PIDs there is no need of any mathematical modeling, which is anyway extremely difficult to write down in the case of diabetes, and, more generally, for biological systems.

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[1] Other mathematical techniques have also been investigated, like delay differential equations and partial differential equations (see, *e.g.*, [36], and the references therein).

- Contrarily to PIDs the tuning of the corresponding *intelligent* controller is straightforward.
- This controller, which may be easily implemented on a cheap programmable device [27], is moreover quite robust with respect to disturbances and system modifications.
- Our feedforward standpoint, *i.e.*, the choice of a reference trajectory, is similar to what is done in flatness-based control (see [17, 18], and [32, 45]). Contrarily to predictive control, optimal control becomes pointless.

An excellent description of the tremendous advantages of a model-free setting is provided by the following citation, which is extracted from Section 1.4.3 in [5], where a machine learning viewpoint is developed:
Model-free methods, in either open-loop or closed-loop systems, have some advantages over their model-based counterparts. ... One problem with the model-based methods is that they need an accurate model, and building such a model usually requires special and costly physiological studies of the processes involved in glucose regulation. However, model-free control algorithms rely solely on the "simple" type of data that patients normally collect. Another problem with the model-based methods is their dependence on a patient specific model. Thus any modification to a component of the mathematical model will require the parameters of the model-based method to be re-calculated. ... We believe model-free methods are an important avenue of research that has not been exploited to its full advantage by the diabetes community.

Our contributions, which seem to be quite new in the huge, and, sometimes, old literature on automated pancreas, might be summarized as follows:

1. The design of a fully automated intelligent controller for blood glucose (BG) regulation including postprandial phase.
2. The design of an *ad hoc* time-varying glycemic reference trajectory, based on the results of [37]. It is modified to reproduce an artificial insulin bolus, *i.e.*, regular to rapid-acting insulin dose, when meals are taken.
3. This variable reference yields a postprandial bolus-shaped injection rate which is more effective in handling hyper peaks of glycemia.
4. Clinical data are used to test the design.

Our paper is organized as follows. Model-free control and the corresponding controllers are briefly reviewed in Section 2. Section 3 and 4 present respectively the virtual patient simulator, and the system constraints and limitations. Implementation issues are discussed in Section 5. Promising simulation results are displayed in Section 6. Concluding remarks are given in Section 7.

2 Model-free control and intelligent controllers[2]

2.1 The ultra-local model Replace the unknown global description by the *ultra-local model*:

$$\boxed{\dot{y} = F + \alpha u} \tag{2.1}$$

where

- the control and output variables are respectively u and y,
- the derivation order of y is 1 like in most concrete situations,
- $\alpha \in \mathbb{R}$ is chosen by the practitioner such that αu and $\dot{y}$ are of the same magnitude.

The following explanations on F might be useful:

- F is estimated via the measure of u and y,
- F subsumes not only the unknown system structure but also any perturbation.

2.2 Intelligent controllers The loop is closed by *intelligent proportional controller*, or *iP*,

$$\boxed{u = -\frac{F - \dot{y}^* + K_P e}{\alpha}} \tag{2.2}$$

where

- $y^\star$ is the reference trajectory,
- $e = y - y^\star$ is the tracking error,
- K_P is the usual tuning gain.

Combining Equations (2.1) and (2.2) yields:

$$\dot{e} + K_P e = 0$$

where F does not appear anymore. The tuning of K_P becomes therefore quite straightforward. This is a major benefit when compared to the tuning of "classic" PIDs (see, *e.g.*, [2, 40], and the references therein), which

- necessitate a "fine" tuning in order to deal with the poorly known parts of the pant,
- exhibit a poor robustness with respect to "strong" perturbations and/or system alterations.

See Figure 1 for the corresponding block diagram.

REMARK 2.1. *See [16] for academic comparisons with classic PIDs, and [21] for a concrete one.*

REMARK 2.2. *See [16] for the connection with the classic integral-proportional (PI) controllers.*

REMARK 2.3. *See [22, 30] for a slightly different presentation of model-free control. See [16] for other references.*

[2] See [16] for more details.

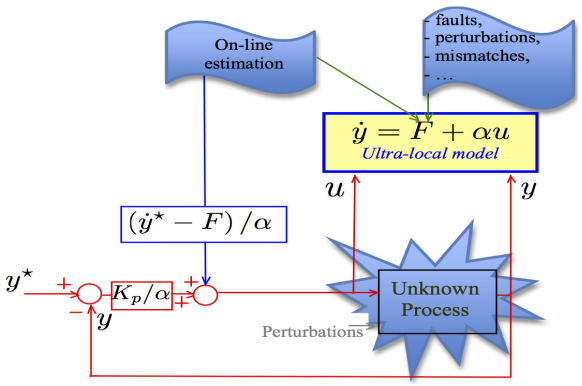

Figure 1: MFC block diagram .

2.3 Estimation of F The calculations below stem from new estimation techniques (see [19, 20], and [46]).

2.3.1 First approach The term F in Equation (2.1) may be assumed to be "well" approximated by a piecewise constant function F_{est}. Rewrite then Equation (2.1) in the operational domain (see, *e.g.*, [50]): $sY = \frac{\Phi}{s} + \alpha U + y(0)$, where Φ is a constant. We get rid of the initial condition $y(0)$ by multiplying both sides on the left by $\frac{d}{ds}$: $Y + s\frac{dY}{ds} = -\frac{\Phi}{s^2} + \alpha\frac{dU}{ds}$. Noise attenuation is achieved by multiplying both sides on the left by s^{-2}. It yields in the time domain the realtime estimate, thanks to the equivalence between $\frac{d}{ds}$ and the multiplication by $-t$,

$$F_{\text{est}}(t) = -\frac{6}{\tau^3}\int_{t-\tau}^{t}[(\tau - 2\sigma)y(\sigma) + \alpha\sigma(\tau-\sigma)u(\sigma)]\,d\sigma \tag{2.3}$$

2.3.2 Second approach Close the loop with the iP (2.2):

$$F_{\text{est}}(t) = \frac{1}{\tau}\left[\int_{t-\tau}^{t}(\dot{y}^\star - \alpha u - K_P e)\,d\sigma\right] \tag{2.4}$$

REMARK 2.4. *Note the following facts:*

- *integrals* (2.3) *and* (2.4) *are low pass filters,*
- $\tau > 0$ *might be quite small,* i.e., *online estimation is achieved,*
- *the integrals may of course be replaced in practice by classic digital filters.*

3 Virtual patient

Our control algorithm is tested and evaluated *in silico* via a long-term linear time-invariant model, which was recently developed [34]: .

$$\begin{bmatrix}\dot{G}\\ \dot{I}\\ \ddot{I}\\ \dot{D}\\ \ddot{D}\end{bmatrix} = \begin{bmatrix}0 & -k_{si} & 0 & 1 & 0\\ 0 & 0 & 1 & 0 & 0\\ 0 & -\frac{1}{T_u^2} & -\frac{2}{T_u} & 0 & 0\\ 0 & 0 & 0 & 0 & 1\\ 0 & 0 & 0 & -\frac{1}{T_r^2} & -\frac{2}{T_r}\end{bmatrix}\begin{bmatrix}G\\ I\\ \dot{I}\\ D\\ \dot{D}\end{bmatrix} + \begin{bmatrix}0\\ 0\\ \frac{K_u}{V_I T_u^2}\\ 0\\ 0\end{bmatrix}u + \begin{bmatrix}0\\ 0\\ 0\\ 0\\ \frac{K_r}{V_B T_r^2}\end{bmatrix}r + \begin{bmatrix}k_l - \frac{128}{M}\\ 0\\ 0\\ 0\\ 0\end{bmatrix} \tag{3.5}$$

- $G(t)$ is the glycemia (mg/dL),
- $I(t)$ is the insulinemia (U/dL),
- $D(t)$ is the increase of glycemia due to digestion of carbohydrate (mg/dL).min^{-1},
- $u(t)$ is the insulin infusion rate (U/min),
- $r(t)$ is the carbohydrate in the meal (mg).

The parameters are given in Table 1. Recall some advantage of this modeling with respect to existing ones. It was shown, for instance in [34], that the parameters in [11] cannot be estimated from standard clinical data (CGM, injection and meal intake). Most existing models introduce, however, some apparent equilibria which are not consistent with real life. Equation (3.5), though it is linear, or, more exactly, affine, appears to be a significant scientific alternative as it displays a long-term fit with clinical data unlike other short-term predictions models such as [8, 28]. Fundamental concrete quantities can be deduced from Equation (3.5), that are not found in [8, 11, 28]. Let us mention here:

- The basal rate: it is the constant insulin infusion rate that maintains glycemia at a constant value during fasting.
- The insulin sensitivity factor (ISF): it corresponds to the glycemic drop per unit of extra insulin when the basal infusion rate is correctly set.
- Raise: it is the glycemic increase due to the digestion of 15g of carbohydrate (CHO) while a basal insulin rate is infused. Note that insulinemia is then at equilibrium.
- U/P: additional insulin units, above the infused basal rate, per portion of CHO required to steer glycemia back to its initial level prior to digestion.

The parameters of the simulator are identified on the model thanks to the data provided by the *Centres hospitaliers universitaires (CHU) de Nantes et Rennes*[3] (see Table 2). After the identification process there is still a modeling error (including measurement fluctuations) between the model output and the corresponding CGM data. This error signal is computed for each subject and added to the model. In this manner, the clinical CGM data are reconstructed for each case to simulate the corresponding *virtual patient*. Furthermore, it allows a better comparison with the open-loop control as the CGM record of FIT controlled glycemia can now be reconstructed by the simulator.

[3] Nantes and Rennes University-Hospital Centers.

Table 1: Definitions of the parameters.

Parameters	Definition	Units
M	Patient weight	kg
ksi	Insulin sensitivity	$(mg/U)min^{-1}$
T_u	Time constant of insulinemia dynamics	min
V_i	$2.5 * M$ insulin distribution volume	dl
K_u/V_i	Static gain	min/dl
T_r	Characteristic time constant	min
V_B	0.65 *M Blood volume	dl
k_r/V_B	Static gain	min/dl
$k_l - 128/M$	The constant increase of glycemia resulting from liver and brain activity	$(mg/dl)min^{-1}$

Table 2: Parameters' values of the virtual patients.

Parameters	IF2	IF3	BE
M	72	94	73.5
ksi	197	274	186
T_u	122	88	59
K_u/V_i	10/180=0.0556	15/235= 0.0621	10/183.75=0.0541
T_r	183	49	38
k_r/V_B	0.11/46.8=0.0024	0.1248/61.1= 0.002	0.13/47.775=0.0028
$k_l - 128/M$	1.94−1.778=0.1582	$1.72 - 0.0136 = 0.358$	1.91-1.7415=0.171

4 Constraints and limitations

For a non-diabetic subject during fasting/nocturnal period, where $r = 0$, G is maintained steady with respect to liver production and brain consumption of glucose ($k_l - \frac{128}{M}$) in normal range by a basal (equilibrium) level of $u = u_{eq}$ and hence basal insulinemia I_b. In the T1DM case the main challenge is that with a very low constant rate ($u < u_{eq}$) during fasting/nocturnal conditions G diverges. It is due to the continuous liver glucose production resulting in fasting hyperglycemia [44]. It yields $\dot{G} > 0$.

Thus, for an insulin-dependent diabetic, the control objective is to maintain G within the interval $[70, 120]$ mg/dL relatively fast. Two main constraints are emphasized:

- hypoglycemic limit of 70 mg/dL,
- the input is nonnegative ($u \geq 0$).

Insulin infusion rate cannot be reversed once it is spread out in the blood stream. If BG drops into hypoglycemia, the only possible control is to shut off the insulin pump temporarily and to have some carbohydrates to raise BG back to euglycemia, *i.e.*, to a normal level of sugar in the blood. Therefore, the system is *externally* positive [15].

5 Control implementation

The first step in the design is to define the reference input to the controller. The time-varying reference trajectory which was introduced in [37] for the purpose of PID switching control, is modified in order to be utilized here:

$$G_{\text{ref}}(t) = \begin{cases} (G(t^s) - G^*) \exp^{-\frac{t-t^s}{\tau_{\text{ref}}}} + G^* & \text{if } G(t) > G^* \\ G_r & \text{if } G(t) \leq G^* \end{cases}$$

- t^s is the switching time,
- τ_{ref} is a design parameter,
- G_r is the constant set point, G^* is the switching threshold.

The following properties hold:

1. The time-varying trajectory starts decaying directly at $G(t^s)$.
2. The switching threshold G^* is set to 140 mg/dL while $G_r = 120$ mg/dL to avoid hypoglycemia.
3. t^s is the switching/reset time: to re-start the trajectory if $(t - t^s) > 45$ min and $\dot{G} > 0$ (BG is still increasing).

When G is above the postprandial hyperglycemia level ($G \geq$ 140mg/dL), the controller switches from a constant reference $G_r = 120$ mg/dL to an exponential-decay trajectory initiated at $G_{\text{ref}}(t) = G(t_s)$. It settles eventually at G_r. The resulting discontinuity produces an impulsive control due to $\dot{e}$ that appears in the iP control law. This bolus-shaped insulin rate permits to have a fast response in order to regulate G towards the normal level and to avoid extended postprandial hyperglycemia.

The control will first be designed and tested on IF2 subject, the parameters are specified as follows:

- $\tau = nT_s$, where T_s is the sampling time, and $n \geq 1$ is an integer,
- $T_s = 1$ min, $n = 30$, $\tau = 30$ min for smooth estimation,
- $\tau_{\text{ref}} = 5$ min,
- since G responds inversely to the control variable, α is negative and: $\alpha^{-1} = -0.07$.
- K_P is tuned individually aiming to have a minimum number of hypoglycemic events.

Once they are designed, the parameters τ, τ_{ref}, α are kept constant. Only K_P is adjusted per patient for an optimal performance. The closed-loop design, with constant or variable reference, will be compared to the open-loop FIT therapy with the same meal protocol.

6 Simulation results

The proportional gain is set respectively to 0.023 and to 0.018 for the fixed set point and for the variable reference trajectory (see Section 5). Figure 2 displays the difference between the two strategies in the postprandial phase. Postprandial peaks are reduced by (25 ± 23) mg/dL. IF2 has a one-day fasting phase, *i.e.*, a non-glucidic regime, during which our control algorithm has a much better performance than the open-loop FIT control with a fasting hyperglycemia time lapse greater than 11 hours (see Figure 2b). This design is tested on the two other virtual patients IF3 and BE

as shown in Figures 3 and 4. The simulator is considered as a black box where the model parameters and meals are all unknown. The proportional gain is scaled to $K_P = 0.0065$ and 0.01 for IF3 and BE respectively for variable-reference control. These values represent the upper bound with minimum hypoglycemic episodes during the simulated period. Tables 3, 4 and 5 present simulation statistics for open and closed-loop control, including a conventional iP controller with a constant reference trajectory. Hyperglycemia is then reduced in time. Hypoglycemia remains small. The sudden one-minute drop in Figure 3b at t = 12.6 h of ΔBG = 29 mg/dL is too fast to be the response to a bolus or an overdose. It might be a measurement issue. An unavoidable hypoglycemia episode follows. It happens for all three controllers.

The frequent initialization of the exponential decay reference path appeared as a series of consecutive impulsive insulin rates. These bolus-shaped rapid pulses are infused only when a postprandial phase is detected, *i.e.*, BG $\geq$ 140 mg/dL, positive rate. It yields an *Ersatz*, *i.e.*, a replacement, for the missing pre-meal boluses. The postprandial peaks under closed-loop insulin administration occur more often than under FIT control. It might be due to the FIT injections anticipatory character, *i.e.*, the boluses are infused before meals as shown in Figures 2, 3 and 4 (parts d and e). For the fully automatic control, meals are unknown disturbances. As a result, G grows until the retarded plasma insulin reaches its peak (see Figures 2c, 3c, 4c). The insulin absorption rate is slow. According to the American Diabetes Association (ADA), the minimum insulin onset[4] is 15 minutes. It takes about 60 minutes to reach its peak with a minimum overall duration of 2-4 hours.

Our control design is tested on three different virtual patients: IF2, IF3, and BE. They are stable diabetics according to the *Mean Amplitude Glycemic Excursion* (MAGE) index. Unstable or *brittle diabetics*[5] are not included in this study. Severe BG swings from hyper to hypoglycemia, as a matter of fact, are hard to control and usually need extensive care.

The following two achievements summarize the benefits of our approach:

1. When postprandial phase is detected, artificial rapid insulin bolus are produced.

2. The overall BG mean value is improved and postprandial peaks are lowered.

[4]It is the time lapse before insulin reaches the bloodstream and begins lowering blood glucose.

[5]T1DM is an intrinsically unstable condition. The terminology *brittle diabetes* corresponds to an instability, causing life disruption, or prolonged hospitalization [47].

Table 3: IF2 simulation statistics for FIT and iP: constant and variable references.

Parameters	IF2		
	FIT	iP	iP-Vref
$Max\,(G)$ mg/dL	268.9	298	263.52
$Min\,(G)$ mg/dL	75.11	60.37	54.34
$Max\,(hyper.period(x_1 > 200))$ h	11.35	6.77	4.32
$Mean\,(G)$ mg/dL	169.25	163.28	144.19
$Standard\ Deviation\,(G)$ mg/dL	51.56	63.24	51.05
$Mean\,(u)$ U/h	2.85	2.66	2.52
$Max\,(hypo.\ episode)$h	---	0.5	0.58

Table 4: IF3 simulation statistics for FIT and iP: constant and variable references.

Parameters	IF3		
	FIT	iP	iP-Vref
$Max\,(G)$ mg/dL	183.4	316.62	287.14
$Min\,(G)$ mg/dL	42.25	48.02	47.85
$Max\,(hyper.period(x_1 > 200))$ h	---	5.08	3.03
$Mean\,(G)$ mg/dL	91.26	169.63	150.11
$Standard\ Deviation\,(G)$ mg/dL	30.52	56.13	53.3
$Mean\,(u)$ U/h	2.6	2.56	2.44
$Max\,(hypo.\ episode)$h	5.33	0.33	0.33

Table 5: BE simulation statistics for FIT and iP: constant and variable references.

Parameters	BE		
	FIT	iP	iP-Vref
$Max\,(G)$ mg/dL	287.7	274.59	264.67
$Min\,(G)$ mg/dL	66.05	71.16	76.69
$Max\,(hyper.period(x_1 > 200))$ h	3.33	2.57	2.3
$Mean\,(G)$ mg/dL	156.4	155.81	150.41
$Standard\ Deviation\,(G)$ mg/dL	46.2	52.86	47.9
$Mean\,(u)$ U/h	2.72	2.76	2.64
$Max\,(hypo.\ episode)$h	0.5	---	---

7 Conclusion

Let us emphasize once again the following features of our intelligent proportional controller:

- a most promising *in silico* behavior,
- the few parameters which need to be calibrated are easy to tune,
- the implementation on cheap programmable devices is straightforward.

Some *fault accommodations* may also be easily handled via this setting (see [16], and [29] for a concrete application).[6] Some other future investigations should also be added:

- test the controller on UVa/Padova simulator [11],
- apply it on a large cohort of diabetics,
- compare it with other control schemes,
- relate K_P with a known characteristic of the patient like the body mass.

Model-free control yields a quite elementary control synthesis, whereas questions stemming from computer simulations remain most complex. This fact, which was already mentioned in [16], where several other references

[6]This important topic seems to have been neglected to some extent. See however [48].

are provided, might be an "epistemological break" (*rupture épistémologique* in French) in the sense of Bachelard [4].

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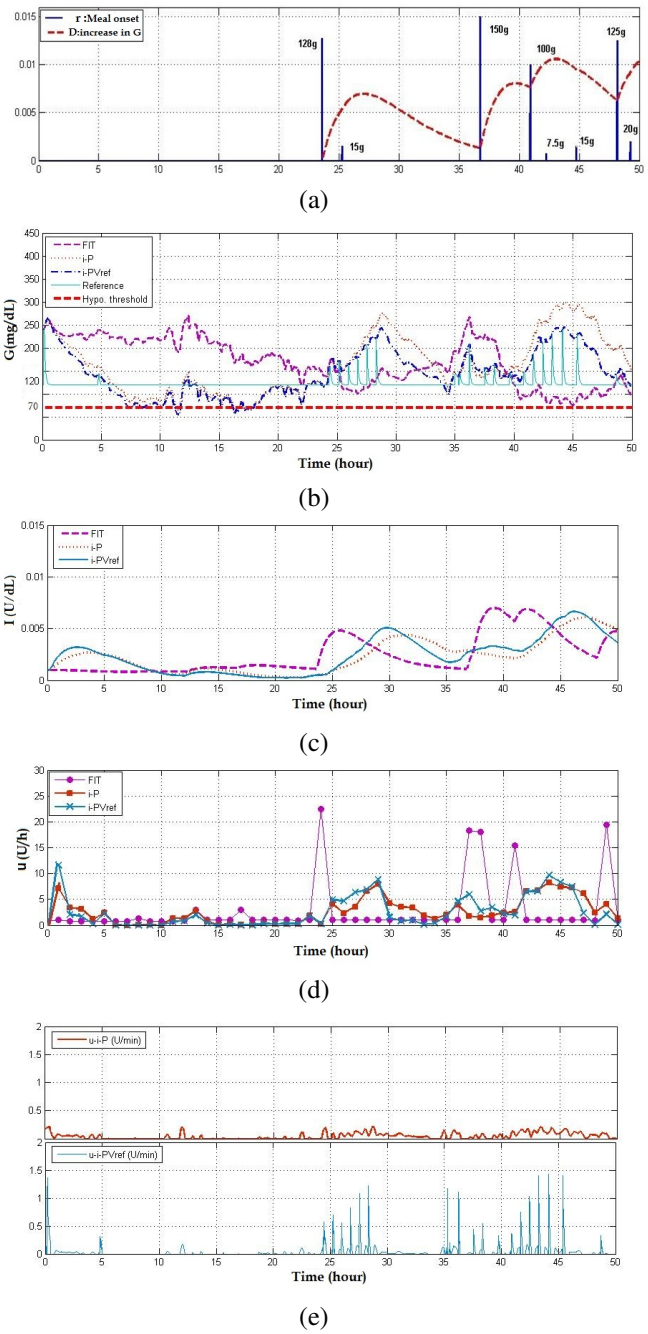
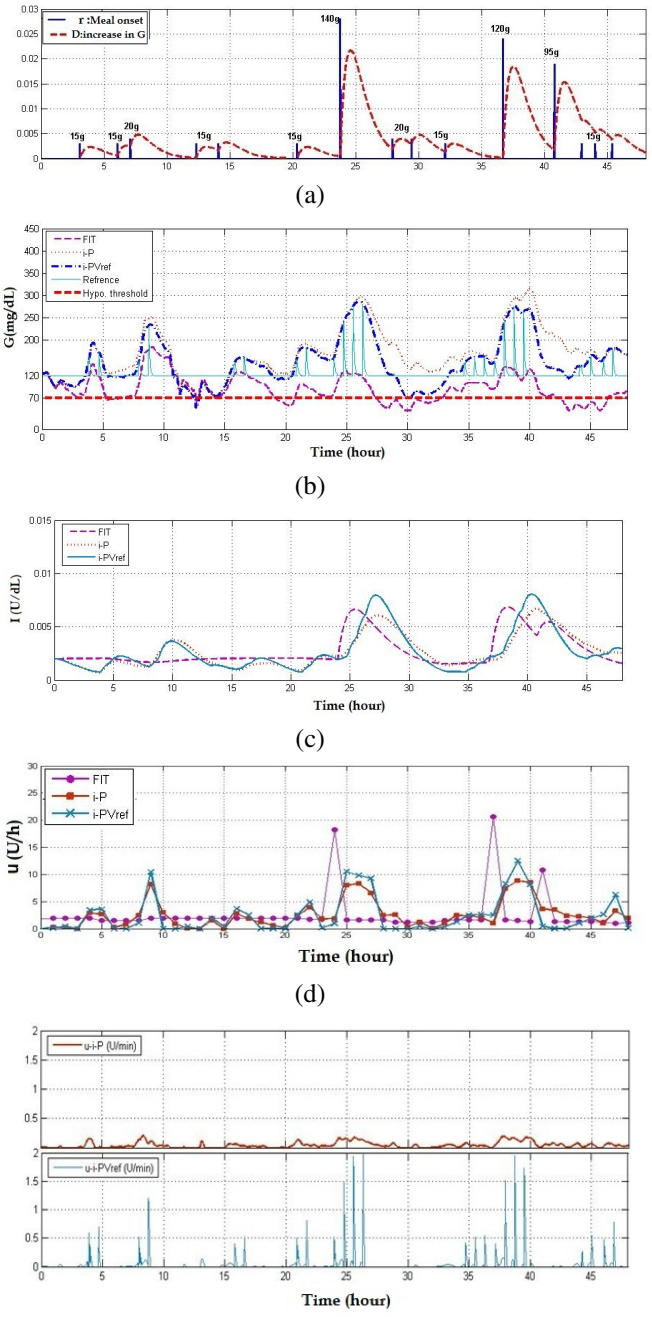


Figure 2: IF2 response for FIT, where $K_p = 0.023$ or 0.018. (a): Meal intake and the corresponding increase of BG. (b): BG behavior. (c): Insulinemia. (d): The integral of the control rate per hour. (e): Controlled insulin injection minute rate.



(a)

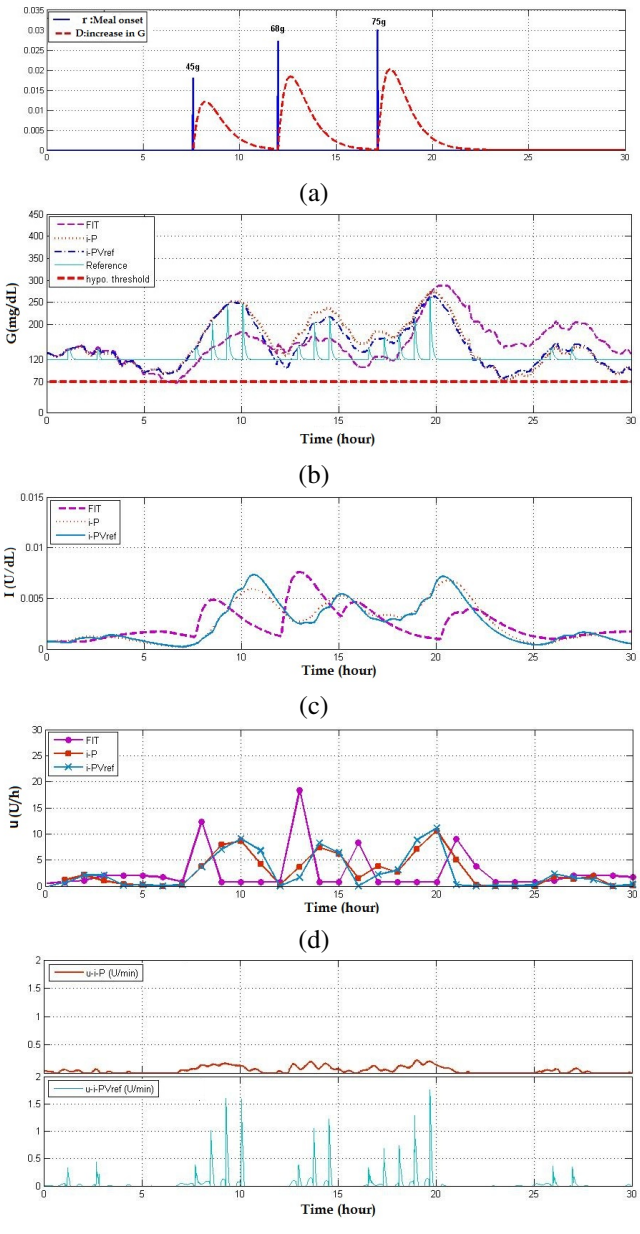
(b)

(c)

(d)

(e)

Figure 3: IF3 response for FIT, where $K_p = 0.021$ or 0.0065. (a): Meal intake and the consequent increase of BG. (b): BG behavior. (c): Insulinemia. (d): The integral of the control rate per hour. (e): Controlled insulin injection minute rate.



(a)

(b)

(c)

(d)

(e)

Figure 4: BE response for FIT, where $K_p = 0.029$ or 0.01. (a): Meal intake and the consequent increase of BG. (b): BG behavior. (c): Insulinemia. (d): The integral of the control rate per hour. (e): Controlled insulin injection minute rate.