

Effective Control of Glycemia using a Simple Discrete-delay Model

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Abstract: Type-2 Diabetes Mellitus (T2DM) is a metabolic syndrome characterized by low insulin sensitivity, so that higher amounts of insulin are required in order to keep glycemia in a safe range (approximately, 60 ~ 110 mg/dl or, equivalently, 3.33 ~ 6.11 mM). Although insulin resistance and T2DM are often treated without exogenous insulin administration, the possibility to early treat pre-diabetic states or T2DM patients with insulin administration could be envisaged if the clinical need exists (e.g. surgical stress, infection). The present work introduces a possible new therapeutic insulin administration dosing approach for T2DM patients. The IVGTT glycemia and insulinemia profiles of a diseased patient are collected and, successively, its metabolic parameters are obtained by fitting a compact delay model to those data. Then a controller is designed exploiting the previous model as a tool. Finally, the tuned controller is applied to the patient as an artificial pancreas supplying external insulin administration. The results are shown on a virtual patient, whose behavior is described by a comprehensive, validated extensive model.

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1. INTRODUCTION

Insulin Resistance (IR) is a metabolic syndrome in which tissues fail to respond normally to insulin: in insulin-sensitive people the hormone, released when blood glucose levels increase, promotes glucose utilization by enhancing tissue glucose uptake by peripheral tissues and by suppressing endogenous (mainly hepatic) glucose production. Insulin resistance plays a central role in the development of Type-2 Diabetes Mellitus (T2DM); indeed people who develop T2DM usually pass through earlier stages of insulin resistance and pre-diabetic conditions (Groop (1999); Chiu et al. (2007)). Insulin resistance is also linked to a wide array of other pathophysiologic conditions including hypertension (Ferrannini et al. (1987)), hyperlipidemia, coronary heart disease (Després et al. (1996)), chronic renal failure (Kincaid-Smith (2004)). The prevalence of IR in the general population is important (around 10%) and increasing (Meigs (2003)), also due to the increase in the worldwide prevalence of obesity, which represents one of the major causes of insulin resistance. It therefore appears that an accurate measurement of the degree of IR by an easily performed test would be of great relevance. Although insulin resistance and T2DM are often treated without exogenous insulin administration (life style and dietary modifications, bariatric surgery in obese people, oral hypoglycemic agents such as metformin), the possibility of early treatment of pre-diabetic states or T2DM patients with insulin administration exists, particularly when hyperglycemia is produced by acute stress, such as

during surgical procedures. In this case it becomes critical to properly determine the exact quantity of the hormone to be supplied to maintain blood glucose levels within a normal range, without incurring dangerous hypoglycemic episodes.

This work investigates the design of intra-venous insulin infusions for T2DM patients by exploiting mathematical models of the glucose-insulin system at different levels. The process of restoring the patient's basal glycemia to a "safe range" (Huyett et al. (2015)), is accomplished by exploiting information on the response of the patient at a wide range of glycemic stimuli, such as occurs during an IVGTT experiment. On one hand we introduce a family of comprehensive models playing (by suitably changing the appropriate parameter values) the twofold role of representing a virtual T2DM patient (to be controlled) as well as a reference virtual healthy subject providing the "ideal" pancreatic insulin response to a glucose stimulus, to be reproduced in closed-loop; on the other hand a different, compact model (Panunzi et al. (2007)) is introduced to design the feedback control law in the same way as it would be used on a real patient; such a model has also been recently employed to reconstruct the continuous insulin behavior from (possibly sparse) glycemia measurements, in view of the possible use in glucose control techniques with partial information (Borri et al. (2017a,b)). A comprehensive model of the glucose-insulin system to validate an insulin infusion therapy designed according to a different, compact and more easily handled model has been also adopted in Palumbo et al. (2014), where a population

of T2DM patients provided a benchmark to evaluate a previously published feedback control law. In that case the validation had been carried out on a model (Dalla Man et al. (2007)) accepted by the Food and Drug Administration as a substitute of animal trials; here we propose a different whole body model, De Gaetano et al. (2015), mainly focused on the correct characterization of the endogenous insulin secretion, modeled by a population of simple, similar controllers, each reacting to the common glucose signal independently of the others. The motivation for the use of this new comprehensive model stems from the fact that it has been shown to faithfully reproduce a large variety of clinical experiments involving short- and long-term insulin secretion phenomena (including fast and slow glucose-insulin oscillations, entrainments to exogenous pulsatile signals, potentiation), providing an *in silico* paradigm to represent physiological endogenous insulin secretion. The feedback control law will be tuned to track the pancreatic response to an external glucose perturbation, provided by an healthy subject, simulated with the above extended model (De Gaetano et al. (2015)). The chosen virtual perturbation experiment to tune the control parameters is the Intra-Venous Glucose Tolerance Test (IVGTT), among the most affordable and commonly used perturbation procedures used to estimate insulin sensitivity.

2. REFERENCED COMPACT AND EXTENDED MODELS

2.1 Compact Model

The delay model used in the present work, henceforth *compact model*, has been shown to be able to represent well the glucose and insulin concentrations observed during an Intra-Venous Glucose Tolerance Test (IVGTT) (Panunzi et al. (2007, 2010)). Using this model it is possible to estimate the insulin sensitivity of a patient by fitting the patient’s glucose-insulin dynamics. Also, this model has been shown to admit mathematically consistent solutions with physiologically plausible parameter values (Palumbo et al. (2007)).

Let $G(t)$ and $I(t)$ be, respectively, the plasma glucose concentration [mM] and the serum insulin concentration [pM], while their distribution volumes are indicated, respectively, as V_g [L kgBW⁻¹] and V_i [L kgBW⁻¹]. The differential equation representing variation of plasma glucose concentration is:

$$\frac{dG(t)}{dt} = -K_{xg}I(t)G(t) + \frac{T_{gh}}{V_g}, \quad (1)$$

with initial conditions:

$$G(t) = G_b \quad \forall t \in (-\infty, 0), \quad G(0) = G_b + G_\Delta, \quad (2)$$

where $G_\Delta = \frac{D_g}{V_g}$.

The glucose basal concentration G_b [mM] is the glycemia level before the bolus injection, while G_Δ [mM] represents glycemia increase following the bolus. D_g [mmol kgBW⁻¹] is the intravenous dose of glucose administered at time 0 during an IVGTT experiment. The equation representing the dynamics of plasma insulin concentration I [pM] is the following:

$$\frac{dI(t)}{dt} = -K_{xi}I(t) + \frac{T_{ig,max}}{V_i} \frac{\left(\frac{G(t-\tau_g)}{G^*}\right)^\gamma}{1 + \left(\frac{G(t-\tau_g)}{G^*}\right)^\gamma}, \quad (3)$$

with initial condition:

$$I(0) = I_b + I_{\Delta G}G_\Delta, \quad (4)$$

The novelty this model introduced is in the second term of (3): it represents second-phase insulin delivery from the β -cells, and its sigmoidal shape captures the fact that, while β -cells may promptly react to abrupt changes in glycemia, their insulin production is limited, so that they are unable to substantially increase insulin secretion once already stimulated at high glycemias. The constant values T_{gh} and $T_{ig,max}$ can be directly computed from the steady state conditions of Eq. (1) and (3) respectively. See the original references for more details.

2.2 Extended Model

The mathematical model of the glucose-insulin system presented in De Gaetano et al. (2015) (on the basis of previous work, Palumbo and De Gaetano (2010); De Gaetano et al. (2013)) has been the first model of whole-body insulin secretion to provide a unified explanation of an array of diverse clinical experimental procedures. In fact, the model is able to reproduce, with the same set of (meta)parameters: the low-frequency ultradian oscillations appreciable in the insulinemic signal when a constant enteral feeding is administered to a patient (Simon et al. (1987)); the entrainment of insulinemia to glycemia when a patient undergoes different I.V. glucose patterns with different frequencies (Sturis et al. (1994)); high-frequency insulinemia oscillations triggered by I.V. administration of very small amount of glucose (Pørksen et al. (2000)); reproduction of the glycemia and two-stages-insulinemia (first and second phase) curves, upon simulated I.V. glucose administration during an IVGTT experiment. In this latter case, moreover, the model is able to mimic the clinically observable glycemia and insulinemia curves both for Normal Glucose Tolerance patients (NGT) and for different classes of morbidity, such as Impaired Fasting Glycemia (IFG), Impaired Glucose Tolerance (IGT), IFG+IGT and Type 2 Diabetes Mellitus (T2DM).

The basic paradigm of this model is that in the pancreas a multitude of similar, but not identical, independent controllers react to the sensed plasma glucose, which acts as the single “coupling” signal. While the qualitative behavior of the *firing units*¹ is the same, each unit reacts differently to glycemia, and these heterogeneous performances yield the characteristic insulin responses to different stimuli.

A firing unit (unit n) releases at time t^* its stored packet of insulin $J_n(t^*)$ [pmol/kgBW] whenever the circulating glycemia exceeds a given variable threshold value $B_n(t)$ [mM], whose time-course is in general different for each

¹ The physiological identification of the firing unit could be the β -cells scattered in the pancreatic Langerhans islet, or, by choosing a different level of model granularity, subcellular granules, or, conversely, collections of synchronized β -cells within the islets of Langerhans. For more details, see De Gaetano et al. (2015).

unit. As soon as the controller fires, its threshold abruptly increases its value and the controller enters a refractory state. From this moment onwards, the threshold value decreases exponentially. When the threshold B_n reaches again values comparable to the current glycemia, the unit n is ready to release a new packet again. The size itself of the packet of insulin depends on prevailing glycemia: in fact, the well-known phenomenon of *potentiation* occurs, that is the ability of the pancreas to respond with progressively increasing insulin amounts to identical glucose stimuli, when these are repeated in close proximity over time (Grodsky (1972); Mari et al. (2002); Toschi et al. (2002)). The variation in size of the packet of insulin (subject to potentiation) for each firing unit is described by the equation for $D_n(t)$ [pmol/kgBW] (De Gaetano et al. (2015)).

Each different firing unit n is then characterized by a triple of equations of same form ($B_n(t)$, $D_n(t)$, $J_n(t)$), but different in the operational parameters. As described in depth elsewhere (De Gaetano et al. (2015)), they are randomly sampled from a given (usually lognormal) distribution.

The *Insulin Secretion Rate* (ISR) is defined as:

$$\text{ISR}(t) = \sum_{n=1}^N J_n(t) \delta(\chi(\{G(t) < B_n(t)\})), \quad (5)$$

where $G(t)$ [mM] is the glucose plasma concentration (glycemia), χ is the characteristic function of its argument set and N is the total number of firing units. Basically, equation (5) states that the ISR at time t is given by the sum of the insulin packets fired by the units whose threshold $B_n(t)$ is below current glycemia $G(t)$. Insulin then flows to the portal vein and the liver according to:

$$\frac{dQ(t)}{dt} = -h_x Q(t) + \sum_{n=1}^N J_n(t) \delta(G(t) < B_n(t)) \quad (6)$$

where Q (pmol/kgBW) refers to the insulin amount in the portal vein/liver compartment. Then, insulin mass Q enters the plasma insulin distribution space according to the following equation:

$$\frac{dI(t)}{dt} = -k_4 I(t) + \frac{h_d Q(t)}{V_I}, \quad (7)$$

where $I(t)$ [pM] is the serum insulin concentration. Finally, glucose plasma concentration is described by:

$$\frac{dG(t)}{dt} = -k_1 \tilde{u}(G(t)) - k_2 I(t) G(t) + \frac{k_3(t)}{V_G}. \quad (8)$$

For further details, see (De Gaetano et al. (2015)).

3. DESIGNING AN ARTIFICIAL PANCREAS FOR T2DM PATIENTS

We designed a simple controller that can be implemented as an insulin pump, which computes the proper amount of insulin to be released at the current moment in order to restore glycemia of an insulin-resistant T2DM patient to safe levels. This controller aims to compensate high insulin resistance of a diseased patient with a supplementary administration of insulin, depending on glycemia levels.

Given a virtual patient, sampled from a population of T2DM built according to De Gaetano et al. (2015), the control law presented here consists in the insulin infusion therapy provided by the glycemia-dependent input function F_c [pM/min]:

$$F_c(G) = k_c \frac{G(t)^{\nu_c}}{g_{50c}^{\nu_c} + G(t)^{\nu_c}}. \quad (9)$$

This sigmoidal form has been chosen in order to mimic the behavior of the pancreas, as explicitly modeled both in the compact and extended models: in fact, the released quantity of insulin is an asymptotically increasing function of glycemia. Control parameters k_c [pM/min], ν_c [#] and g_{50c} [mM] are tuned according to the following steps:

- (1) collect glycemia and insulinemia from an IVGTT conducted on the virtual patient;
- (2) estimate the patient's physiological parameters (insulin resistance among others) by fitting the *compact model* (Sec. 2.1) to the observed glycemia and insulinemia curves;
- (3) control parameters k_c , ν_c and g_{50c} are tuned so that the glucose profile coming from the *compact model* where the insulin kinetics in (3) is replaced with

$$\frac{dI(t)}{dt} = -K_{xi} I(t) + \frac{T_{ig,max}}{V_i} \frac{\left(\frac{G(t-\tau_g)}{G^*}\right)^\gamma}{1 + \left(\frac{G(t-\tau_g)}{G^*}\right)^\gamma} + F_c(G). \quad (10)$$

mimics as closely as possible a healthy NGT subject's glycemia profile during an IVGTT, with the NGT subject provided by the extended model by properly changing the model parameters from T2DM into NGT (see De Gaetano et al. (2015));

- (4) apply the calibrated controller (which behaves as an artificial pancreas) to the virtual T2DM patient and verify its efficacy by performing another IVGTT and observing that:
 - (a) basal glycemia is decreased to a safe value G_s before injecting the glucose bolus;
 - (b) glycemia is restored to G_s after a short transient period (comparable to NGT patients) after the glucose bolus is injected.

Below the procedure is described step by step in details.

Step 1. Step 1 has been performed by sampling glycemia and insulinemia curves generated by a simulated IVGTT using the virtual patient's *extended model*. The sampling occurs at times -10 , -5 , -0.5 , 2 , 4 , 6 , 8 , 10 , 15 , 20 , 25 , 30 , 40 , 50 , 60 , 90 , 120 minutes (the glucose bolus injected at time 0). Fig. 1 reports the generated glycemia and insulinemia curves (dashed-blue lines), while the observed samples are shown as red circles.

Step 2. Both glycemia and insulinemia curves are fitted with the *compact model* and patient's parameters are estimated. The result of the fitting procedure is reported graphically in Fig. 1 (continuous green line), while the estimated parameters are reported in Table 1; parameter V_i has been kept fixed and equal to 0.25 L/kgBW (Panunzi et al. (2007)).

It is worth noticing how the insulin-sensitivity parameter $K_{xgI} \simeq 4.3 \times 10^{-5} \text{ min}^{-1} \text{ pM}^{-1}$ (see eq. (1)) closely

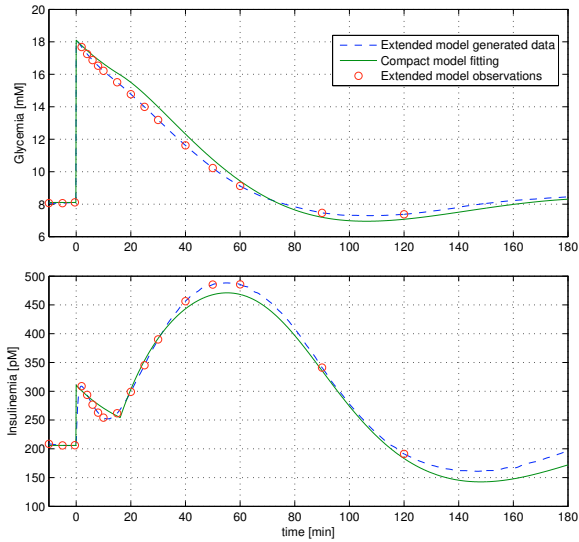


Fig. 1. Generated virtual T2DM patient’s IVGTT (dashed blue line) with the *extended model*, whose observations (red circles) are used to fit both glycemia and insulinemia equations of the *compact model*, respectively (1) and (3) (continuous green lines).

estimates the original “generating” parameter $k_2 \simeq 4.2 \times 10^{-5} \text{ min}^{-1} \text{ pM}^{-1}$ (see eq. (8) and De Gaetano et al. (2015)).

Remark 1. To verify this correspondence over a range of insulin sensitivities, we generated 60 virtual patients from the *extended model* with different insulin-sensitivity k_2 , ranging² from T2DM patient levels ($4.2 \times 10^{-5} \text{ min}^{-1} \text{ pM}^{-1}$) to perfectly normal NGT levels ($14 \times 10^{-5} \text{ min}^{-1} \text{ pM}^{-1}$). The *compact model* was then fitted to the patient simulated IVGTT glycemia and insulinemia profiles. As reported in Fig. 2, the estimated insulin-sensitivity is close to the original value. This latter result suggests that both models well represent physiological and clinical features, and fitting the *compact model* to the data generated by the *extended model* is reasonable.

Step 3. In order to estimate the controller parameters, another virtual subject is sampled from the extended model. This time the extended model parameters are set to provide an NGT subject, because it will be exploited as a healthy standard for our purposes. We stress the fact that, differently from the choice of the virtual T2DM patient (that refers to a potentially *real* patient), here the NGT subject is involved only as a mathematical tool in order to design the control law. The control parameters are set in order to (i) replicate the same basal glycemia of the NGT subject, (ii) fit the glucose profile from an IVGTT run on the NGT subject. The performance of the fit can

² The insulin sensitivity values reported for NGT and T2DM patients are taken from De Gaetano et al. (2015).

Table 1. Estimated patient’s parameters

Par.	V_g	I_Δ	τ_g	K_{xgI}	K_{xi}	γ
Val.	0.2811	10.4478	16.05	4.331E-05	0.0476	5.1519

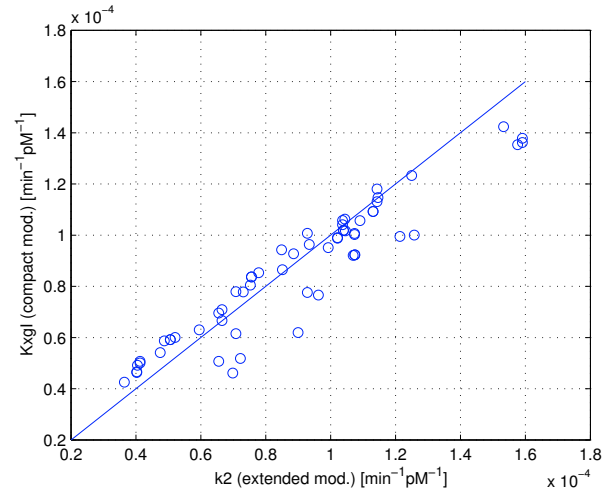


Fig. 2. Sixty simulated IVGTTs have been generated from the *extended model* from different virtual patients, ranging from NGT to T2DM. Then, the *compact model* has been fitted to every generated dataset. The insulin-sensitivity values for the two models for each patient are shown to lay close to the line $K_{xgI} = k_2$. The coefficient of determination R^2 is 0.85.

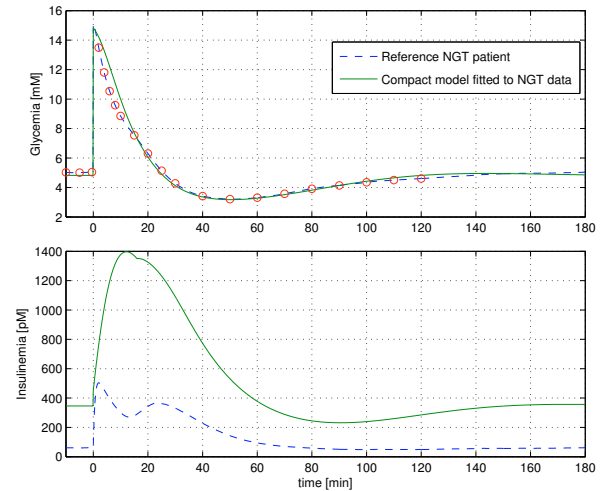


Fig. 3. Reference NGT patient’s glycemia and insulinemia (dashed blue lines). NGT glycemia observations (red circles). Results of the fitting of the *compact model* with the controlled insulin equation (10) (continuous green line).

be appreciated in Fig. 3, and the controller parameters are reported in Tab. 2. Clearly, to replicate the NGT glucose profile, much more insulin is required (as provided by the control law) with respect to the endogenous pancreatic release of the NGT subject, as it appears in the bottom panel of Fig. 3.

Table 2. Estimated controller parameters

Par.	k_c	g_{50c}	ν_c
Val.	985.75	26.67	2.42

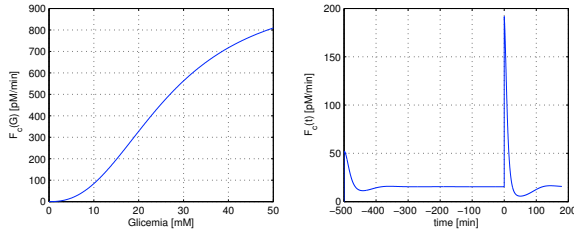


Fig. 4. External supplementary insulin function F_c depending on glycemia levels (left panel). F_c function (actual insulin external infusion) over time for the T2DM patient under study (right panel).

Fig. 4 reports in its left panel the supplementary insulin function (9) – depending on glycemia levels – according to the estimated parameters in Tab. 2, while the insulin infusion over time supplied by the controller is shown in the right panel. The initial high insulin infusion (52.21 pM/min at time $t = -500$ min) and the successive constant maintenance to 15.4 pM/min are able to restore the patient’s glycemia to normal values, as shown in Fig. 3 (green continuous line) where the T2DM patient is supposed to have a basal glycemia under therapy of 4.823 mM.

Step 4. Step 4 tests the effectiveness of the designed control law, by closing the loop on the T2DM virtual patient during a simulation involving another IVGTT on the diseased patient (this time under control). In other words, we applied the control law (9) with the parameters in Tab. 2 to the virtual T2DM patient, by modifying eq. (7) adding the control action. As shown in Fig. 5, we would expect the same (or, possibly, similar) behavior of the real/virtual patient with respect to the patient modeled in Fig. 3: nevertheless, due to possible differences between the two models (or, equivalently, between the *compact model* and reality), the behavior that we observed is slightly different. In fact, a basal value of 5.286 mM of glycemia is maintained instead of the expected level of 4.823 mM; moreover, almost no rebound is observed, and the previous basal value is restored earlier with respect to the designed behavior.

We performed a further validation for the designed artificial pancreas: we applied the same identical controller to other classes of patients, such as IFG, IGT, IFG+IGT, plus other T2DM patients. We generated IVGTTs from 6 virtual patients for each class (thus, 24 IVGTTs totally) by means of the *extended model*, with the parameters reported in De Gaetano et al. (2015). In order to evaluate the efficacy of the controller, the following cost function $C(G)$ has been computed for the average IVGTT of each class³:

$$C(G) = \int_{t=0}^{t=t_f} |G(t) - r_G| dt, \quad (11)$$

where $t_f = 120$ min and $r_G = 4.44$ mM is a chosen reference normal value (corresponding to a glycemia of 80mg/dl), in such a way that $C(G)$ increases whenever

³ Performing an average has been necessary since the *extended model* contains stochastic features, as $k_3(t)$ and, most of all, the characteristic parameters for each secretory unit, which are extracted from statistic distributions.

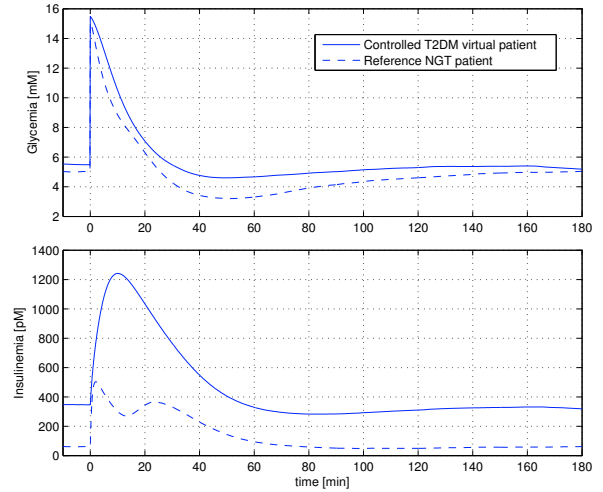


Fig. 5. Application of the external infusion control function (9) with the parameters in Tab. 2 to the virtual T2DM patient undergone an IVGTT (continuous blue line). In dashed blue line, the reference (virtual) NGT patient.

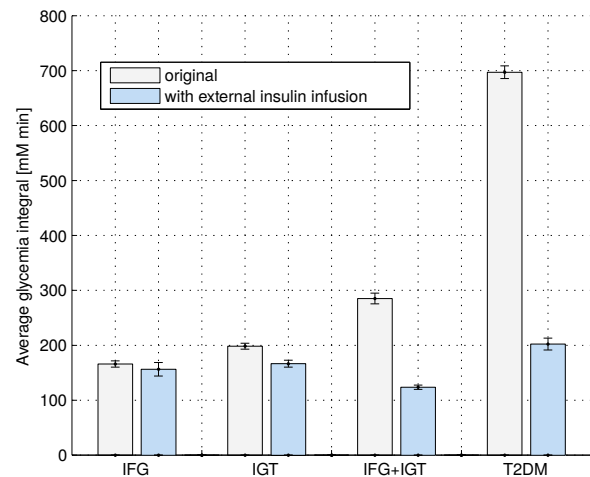


Fig. 6. Application of the controller calibrated for the virtual T2DM patient to other diseased virtual patients (IFG, IGT, IFG+IGT). The cost function for each class is (11).

glycemia exceeds or is below r_G . We evaluated function (11) applying the same controller that we calibrated for a particular T2DM patient to the other diseased classes of patients, obtaining (see Fig. 6) a progressive (with respect to worse morbidity situations) improvement of the physiological status of the patients in terms of circulating glycemia ranging in a safer interval: furthermore, it is clear that a dramatic improvement is observed for the average T2DM patient.

4. CONCLUSION

In the present work we presented a possible control law to be implemented as an artificial pancreas, in order to

supply extra insulin to overcome insulin-resistance in selected patients. The control function (with three structural parameters only) mimics the behavior of the pancreas and is calibrated for a single patient by collecting glycemia and insulinemia data from an IVGTT experiment.

The reason why we chose to calibrate the controller using data coming from an IVGTT is because this experiment is able to perturb the natural glucose-insulin system (producing transients that allow the estimation of the patient's own control parameters) and is safer, cheaper and less cumbersome than the commonly employed glucose clamp technique.

The control function presented, in order to be calibrated, is added to a previously published model of glucose-insulin system (Panunzi et al. (2007)), and this model is fitted to the retrieved IVGTT data. After calibration, the artificial pancreas is applied to the patient: the *in silico* results here presented show that a T2DM patient improves basal glycemia and, moreover, glycemia is promptly restored to safe values when a perturbation (like an IVGTT) is administered.

The present work will be further extended with a proposal of a similar therapy approach for Type-1 Diabetes Mellitus patients. Moreover, other therapies will be introduced, e.g. an optimal control approach for discrete quantities of insulin, using the commonly employed multiple insulin injections therapy.

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