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, $60 \sim 110$ mg/dl or, equivalently, $3.33 \sim 6.11$ 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.

Keywords: artificial pancreas; diabetes; physiological model; modeling and identification; control of physiological and clinical variables; T2DM; insulin-resistance; IVGTT

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 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, treatment with metformin), the possibility to early treat 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 hypoglycemic episodes.

This note investigates the design of intra-venous insulin infusions for T2DM patients by exploiting mathematical models of the glucose-insulin system at different levels. 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. The use of a comprehensive model of the glucose-insulin system to validate an insulin infusion therapy designed according to a different, compact and more easy-to-handle model has been adopted also 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 may be thought of as an elementary firing unit), each one

reacting to the common glucose signal independently from the others. The motivation for the use of this new comprehensive model stems from the fact that this 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 *silico* paradigm to represent the 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 by 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 feasible parameter values (Palumbo et al. (2007)).

The model is composed of two compartments, describing the variation in time of plasma glucose (G compartment) and plasma insulin concentrations (I compartment) following an IVGTT.

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:

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

with initial conditions:

$$\begin{aligned} G(t) &= G_b \quad \forall t \in (-\infty, 0), \quad G(0) = G_b + G_\Delta, \\ &\text{where } G_\Delta = \frac{D_g}{V_g}. \end{aligned} \tag{2}$$

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:

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

with initial condition:

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

The novelty that this model had introduced, however, 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, in such a way 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, respectively, Eq. (1) and (3). 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 the previous works Palumbo and De Gaetano (2010); De Gaetano et al. (2013)) has been the first 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 (that is, when insulinemic signal acquires the same frequency of the glycemic signal) when a patient undergoes different I.V. glucose patterns with different frequency (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 condition and finally 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 is the same, each unit reacts differently to glycemia, and these heterogeneous performances yield the characteristic insulin responses to different stimuli.

The pancreas is composed of a collection of *firing units* [1], each one described by three equations. A firing unit, namely unit n, releases at time t^* its stored packet of insulin $J_n(t^*)$ [pmol/kgBW] whenever the circulating glycemia exceeds a given sensitivity value, that is a threshold $B_n(t)$ [mM], whose time-course is in general different for each unit. As soon as the controller fires, its threshold

[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).

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 again reaches 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 glycemias: 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 extracted from a given (usually lognormal) distribution.

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

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

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:

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

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:

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

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

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

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]:

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

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 made on the virtual patient;
(2) estimate 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 in order that the glucose profile coming from the *compact model* where the insulin kinetics in (3) is replaced with

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

mimics 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 in 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 have been 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 worths noticing how the insulin-sensitivity parameter $K_{xgI} \simeq 4.3 \times 10^{-5}$ min^{-1}pM^{-1} (see eq. (1)) closely

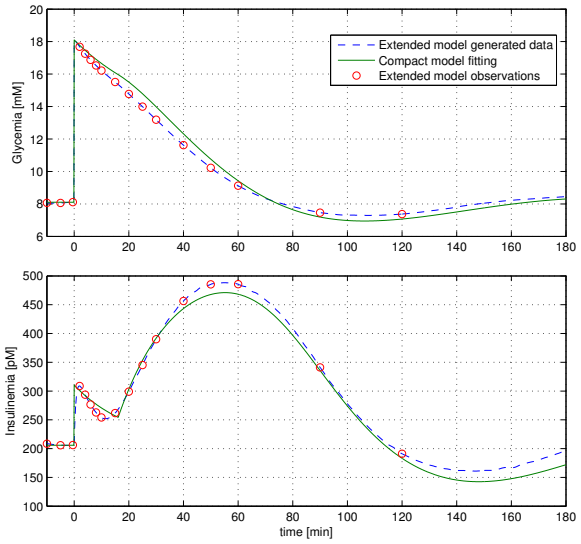

Fig. 1. Generated virtual T2DM patient's IVGTT (dashed blue line) with the *extended model*, whose observations (red circles) are used to fit both glycemia and insulinemia equations of the *compact model*, respectively (1) and (3) (continuous green lines).

estimates the original "generating" parameter $k_2 \simeq 4.2 \times 10^{-5}$ min^{-1}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, ranging [2] from a T2DM patient (4.2×10^{-5} min^{-1}pM^{-1}) to an NGT patient (14×10^{-5} min^{-1}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 as a mathematical tool exploited 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 coming from an IVGTT run on the NGT subject. The goodness of the fitting 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

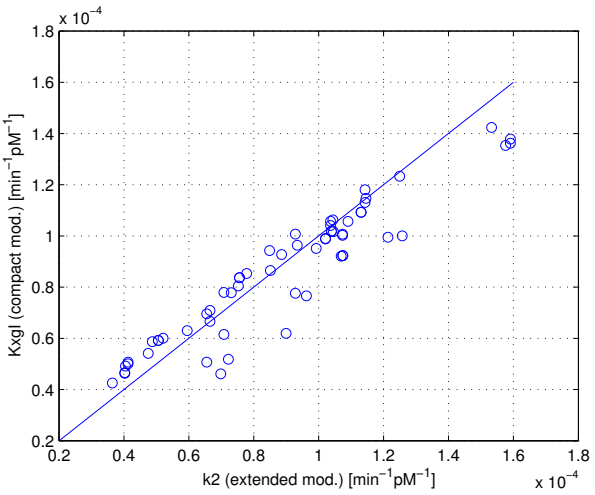

Fig. 2. Sixty simulated IVGTTs have been generated from the *extended model* from different virtual patients, ranging from NGT to T2DM. Then, the *compact model* has been fitted to every generated dataset. The insulin-sensitivity values for the two models for each patient are shown to lay close to the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

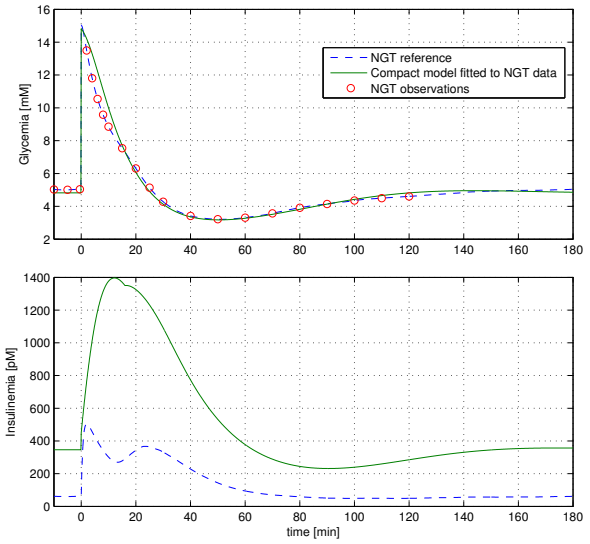

Fig. 3. Reference NGT patient's glycemia and insulinemia (dashed blue lines). NGT glycemia observations (red circles). Results of the fitting of the *compact model* with the controlled insulin equation (10) (continuous green line).

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 (and 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

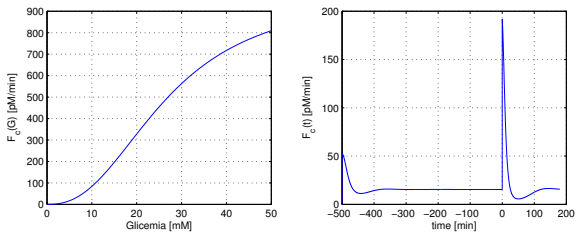

Fig. 4. External supplementary insulin function F_c depending on glycemia levels (left panel). F_c function (actual insulin external infusion) over time for the T2DM patient under study (right panel).

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 substantially 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 class [3]:

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

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.

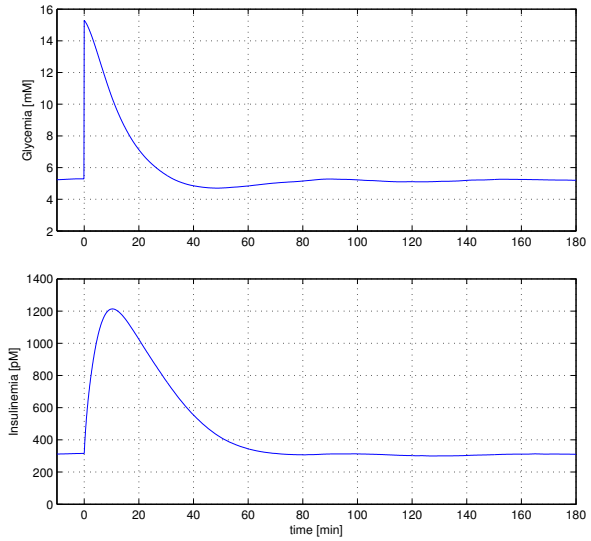

Fig. 5. Application of the external infusion control function (9) with the parameters in Tab. 2 to the virtual T2DM patient undergone an IVGTT.

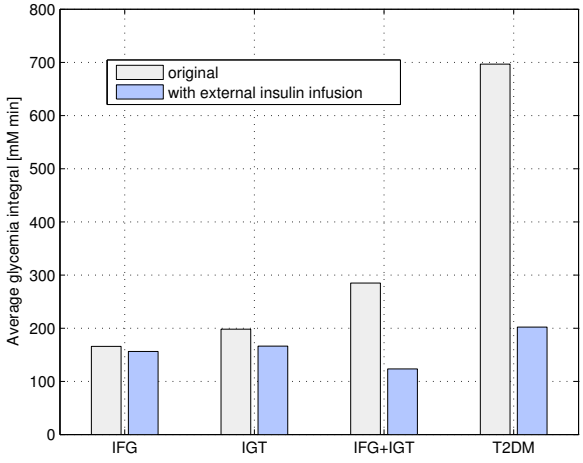

Fig. 6. Application of the controller calibrated for the virtual T2DM patient to other diseased virtual patients (IFG, IGT, IFG+IGT). The cost function for each class is (11).

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 it 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 (actual or simulated, as in this case) 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.

REFERENCES

Chiu, H.K., Tsai, E.C., Juneja, R., Stoever, J., Brooks-Worrell, B., Goel, A., and Palmer, J.P. (2007). Equivalent insulin resistance in latent autoimmune diabetes in adults (lada) and type 2 diabetic patients. *Diabetes research and clinical practice*, 77(2), 237–244.

Dalla Man, C., Rizza, R., and Cobelli, C. (2007). Meal simulation model of the glucose insulin system. *IEEE Transactions on Biomedical Engineering*, 54(10), 1740–1749.

De Gaetano, A., Gaz, C., Gori Giorgi, C., and Palumbo, P. (2013). An islet population model of pancreatic insulin production. In *Decision and Control (CDC), 2013 IEEE 52nd Annual Conference on*, 3355–3360. doi: 10.1109/CDC.2013.6760396.

De Gaetano, A., Gaz, C., Palumbo, P., and Panunzi, S. (2015). A unifying organ model of pancreatic insulin secretion. *PLoS ONE*, 10(11), 1–34. doi: 10.1371/journal.pone.0142344.

Després, J.P., Lamarche, B., Mauriège, P., Cantin, B., Dagenais, G.R., Moorjani, S., and Lupien, P.J. (1996). Hyperinsulinemia as an independent risk factor for ischemic heart disease. *New England Journal of Medicine*, 334(15), 952–958.

Ferrannini, E., Buzzigoli, G., Bonadonna, R., Giorico, M.A., Oleggini, M., Graziadei, L., Pedrinelli, R., Brandi, L., and Bevilacqua, S. (1987). Insulin resistance in essential hypertension. *New England Journal of Medicine*, 317(6), 350–357.

Grodsky, G. (1972). A threshold distribution hypothesis for packet storage if insulin and its mathematical modeling. *Journal of Clinical Investigation*, 51.

Groop, L. (1999). Insulin resistance: the fundamental trigger of type 2 diabetes. *Diabetes, obesity and metabolism*, 1(s1), 1–7.

Kincaid-Smith, P. (2004). Hypothesis: obesity and the insulin resistance syndrome play a major role in end-stage renal failure attributed to hypertension and labelled hypertensive nephrosclerosis'. *Journal of hypertension*, 22(6), 1051–1055.

Mari, A., Tura, A., Gastaldelli, A., and Ferrannini, E. (2002). Assessing insulin secretion by modeling in multiple-meal tests: role of potentiation. *Diabetes*, 51.

Meigs, J.B. (2003). Epidemiology of the insulin resistance syndrome. *Current diabetes reports*, 3(1), 73–79.

Palumbo, P. and De Gaetano, A. (2010). An islet population model of the endocrine pancreas. *Journal of Mathematical Biology*, 61.

Palumbo, P., Panunzi, S., and De Gaetano, A. (2007). Qualitative behavior of a family of of delay-differential equations models of the glucose-insulin regulatory system. *Discrete Contin Dyn Syst Ser B*, 7(2), 399–424.

Palumbo, P., Pizzichelli, G., Panunzi, S., Pepe, P., and De Gaetano, A. (2014). Model-based control of plasma glycemia: Tests on populations of virtual patients. *Mathematical Biosciences*, 257, 2–10.

Panunzi, S., De Gaetano, A., and Mingrone, G. (2010). Advantages of the single delay model for the assessment of insulin sensitivity from the intravenous glucose tolerance test. *Theoretical Biology and Medical Modelling*, 7(1), 9. doi:10.1186/1742-4682-7-9. URL `http://dx.doi.org/10.1186/1742-4682-7-9`.

Panunzi, S., Palumbo, P., and De Gaetano, A. (2007). A discrete single delay model for the intra-venous glucose tolerance test. *Theor Biol Med Model*, 4(35).

Pørksen, N., Juhl, C., Hollingdal, M., Pincus, S., Sturis, J., Veldhuis, J., and Schmitz, O. (2000). Concordant induction of rapid in vivo pulsatile insulin secretion by recurrent punctuated glucose infusions. *Am J Physiol Endocrinol Metab*, 278.

Simon, C., Brandenberger, G., and Follenius, M. (1987). Ultradian oscillations of plasma glucose, insulin and C-peptide in man during continuous enteral nutrition. *Journal of Clinical Endocrinology and Metabolism*.

Sturis, J., Pugh, W., Tang, J., Ostrega, D., Polonski, J., and Polonski, K. (1994). Alterations in pulsatile insulin secretion in the zucker diabetic fatty rat. *Am. J. Physiol.*, 267, E250–E259.

Toschi, E., Camastra, S., Sironi, A., Masoni, A., Gastaldelli, A., Mari, A., Ferranini, E., and Natali, A. (2002). Effect of acute hyperglycemia on insulin secretion in humans. *Diabetes*, 51(Suppl.1), S130–S133.