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Robust H_∞ control of glycemia in Type 2 Diabetes Mellitus via continous insulin plus Metformin ⋆

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Abstract: Several studies have shown that an adequate therapy for glycemic control in patients with type 2 diabetes mellitus (T2DM) can delay or prevent complications derived from this condition. To achieve the control objectives an adequate therapy should be performed by using insulin alone or in combination with an oral hypoglycemic agent. However, the key point of glycemic control is to determine the amount of insulin to be delivered. In order to achieve the above different strategies have been proposed, one of them is the design of feedback control algorithms. In this article a robust feedback control algorithm of glycemia in T2DM was designed. The algorithm determines the continuous insulin infusion to be delivered to maintain normoglycemia considering a combined therapy with a dose of metformin. The problem approach was to find a controller that minimized in the sense of the H_∞ norm: *i)* the difference between the glycemia of a T2DM patient and a healthy subject (tracking problem) and *ii)* the effect of disturbances due to glucose intake and noise from a glucose sensor.

Keywords: Robust control, Dynamic modelling, Closed-loop Control, Biomedical systems, Pharmacokinetic-Pharmacodynamic modelling.

1. INTRODUCTION

In a healthy human body insulin and glucagon are released into the blood in response to rising and falling glucose concentration (*i.e.* glycemia), respectively (Guyton and Hall, 2006). When these processes do not work properly and the homeostatic balance is disrupted then various pathologies can be developed. One of the most common, affecting one in eleven people in the world, is Diabetes Mellitus (DM) (Diabetes Atlas, 2015). Mainly there are two different types of DM: Type 1 diabetes mellitus (T1DM) which occurs due to a lack of insulin secretion; and Type 2 diabetes mellitus (T2DM) caused by defects in insulin secretion and insulin action (Guyton and Hall, 2006). Both are characterized by an above normal glycemia (*i.e.* hyperglycemic), which over time is responsible for the development of disabling and life-threatening health complications (Diabetes Atlas, 2015).

Although to date there is no cure for DM, several studies have shown that an adequate therapy to regulate those factors responsible for hiperglycemia in people with DM may delay or prevent the occurrence of complications and reduce the risk of mortality (Raskin et al, 2003; Jennings et al, 1991). Consequently, a glycemic control therapy is encouraged for patients with DM. According to the American Association of Clinical Endocrinologists the glycemic control objectives in DM are: *i)* maintain a fasting glycemia $<$ 110 mg/dL, and *ii)* a 2h postprandial glycemia $<$ 140 mg/dL (Handelsman et al, 2015). In order to achieve these control objectives an adequate therapy should be performed by using *i)* insulin infusion for T1DM or *ii)* insulin infusion alone or in combination with oral hypoglycaemic agents for T2DM (Handelsman et al, 2015). However, determining the dose of insulin to be delivered is not a trivial problem, since an inadequate amount can result in a dangerous decrement of glycemia (*i.e.* hypoglycemia). In consequence, the development of feedback control algorithms based on mathematical models of glycemic dynamics have been the focus of diverse research for many years (Ajmera et al, 2013).

Mainly, feedback control algorithms have been focused on glycemic control for T1DM (Aicha and Mourad, 2015; Mourad et al, 2015; Huang et al, 2012; Quiroz et al, 2011). Whereas just a few glycemic control algorithms for T2DM can be found (Ekram et al, 2012; Huang et al, 2012; Palumbo et al, 2012). One of the main challenges is the wide variety of endogenous and exogenous conditions that may affect glucose homeostasis. In this sense, the development of glycemic controllers for DMT2 robust under perturbations may be promising. Specifically, the robust control technique by H_∞ have been tested for glycemic control in DMT1 (Aicha and Mourad, 2015;

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Mourad et al, 2015; Quiroz et al, 2011). However, until our knowledge this technique has not yet been tested for DMT2.

In this article, a robust H_∞ feedback control algorithm was developed for glycemic control in T2DM. The control objective was to find a controller that maintain glycemic of a T2DM patient as close as possible to a healthy behaviour, while the effect of disturbances are reduced. To achieve the above a continuous insulin infusion has been used as control input with a single 500 mg dose of metformin.

2. A MATHEMATICAL MODEL OF GLYCEMIC DYNAMICS IN T2DM

We designed a robust H_∞ controller using the Jacobian linearization of a non-linear physiological model of glycemic dynamics in T2DM. The T2DM model was developed by a re-parametrization of a glycemic dynamics model of a nondiabetic subject taken from Alverhag and Martin (2006). The re-parameterization allows to reproduce the disturbances on glucose homeostasis that contribute to hyperglycemia in T2DM, these are: a) insulin resistance in liver and peripheral tissue, b) abnormalities in hepatic glucose uptake, and c) impaired pancreatic insulin release (DeFronzo, 2004).

2.1 Non-linear model description

The model of glycemic dynamics in T2DM is divided into compartments where principal processes of glucose regulation are carried out. As in drug modelling, a matter balance is performed in each compartment to obtain an ordinary differential equation which quantifies the solute accumulation of glucose, insulin, glucagon or incretins. In order to include the pharmacokinetic-pharmacodynamic (PK-PD) effect of Metformin a previous model developed by Stepensky et al (2004) was interconnected with the T2DM model as in Sun et al (2011). Then the set of equations of the whole model can be represented as:

$$\begin{aligned} \dot{x} &= F(x(t), u(t), d(t)), \quad x(t_0) = x_0 \\ y &= Cx \end{aligned} \tag{1}$$

where $x \in \mathbb{R}^{32\times 1}$, $C \in \mathbb{R}^{1\times 32}$, u is the control input defined as the continuous insulin infusion, $d = [d_M, d_{GE}]$, represent the model disturbances due to ingestion of 500mg oral metformin (d_M) and oral glucose intake (d_{GE}), and y stands for peripheral glycemic (*i.e.* $y = x_6$). The model in 1 is capable of emulating the glycemic response in T2DM after external perturbations such as *i)* intravenous glucose infusion, *ii)* intravenous insulin infusion, *iii)* oral glucose intake, and *iv)* a dose of 500 mg of Metformin. For a complete overview of vector field (F) and the mathematical functions representing metabolic rates of 1 refer to Appendix A and Appendix B, respectively. Appendix C contains the full list of model parameters and their nominal values, whereas the model nomenclature can be found in Appendix D.

2.2 Model linearization

For control synthesis a Jacobian linearization of 1 was performed around an operation point $[x^*, u^*, d^*]$ that represents the basal state of a healthy human body given by the the operation point of the proposed model in Alverhag and Martin (2006) when $u^* = 0$ and $d^* = [0, 0]$. Based on the above x^* has the following components:

$$\begin{aligned} x^* = [&79.45 \quad 46.79 \quad 91.32 \quad 100.44 \quad 91.32 \quad 89 \quad 86.22 \\ &89.23 \quad 91.32 \quad 15.29 \quad 15.29 \quad 21.64 \quad 10.71 \\ &13 \quad 5.35 \quad 15.29 \quad 534.6 \quad 1 \quad 0 \quad 0 \quad 1 \quad 1 \\ &0 \quad 0.31 \quad 0.25 \quad 17.78 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0]^T \end{aligned} \tag{2}$$

Following the procedure defined in W. J Rugh. (1993) the Jacobian matrices were defined as: $A = \partial F/\partial x|_{\substack{x=x^* \\ u=u^* \\ d=d^*}}$, $B_1 = \partial F/\partial u|_{\substack{x=x^* \\ u=u^* \\ d=d^*}}$, and $B_2 = \partial F/\partial d|_{\substack{x=x^* \\ u=u^* \\ d=d^*}}$. Then, the obtained linearized system was:

$$\begin{aligned} \dot{x_L} &= Ax_L + B_1 u + B_2 d, \quad x_L(t_0) = x_{L_0} \\ y_L &= Cx_L \end{aligned} \tag{3}$$

3. METHODS: ROBUST CONTROL SYNTHESIS

The H_∞ robust control synthesis presented in this paper is based on the close-loop system shown in Fig. 1 where the reference signal (ref) represent the glycemic response of a nondiabetic healthy subject and the controlled plant (P) was taken as the transfer function in frequency domain of the dynamic linear system defined in 3. The approach of control objective is to find a robust controller (K) that determines u such that y_L tracks ref as closely as possible despite d and the measured noise in data reception from the glucose sensor (d_N). In order to achieve the above, the signals u, e and the effect of d_N represented by weight functions, $W_u(s)$, $W_e(s)$ and $W_N(s)$, these were minimized in the sense of the H_∞ norm which guarantees internal stability. The weight functions were defined as a variation of the transfer functions presented in Quiroz et al (2011). The resulted transfer functions are:

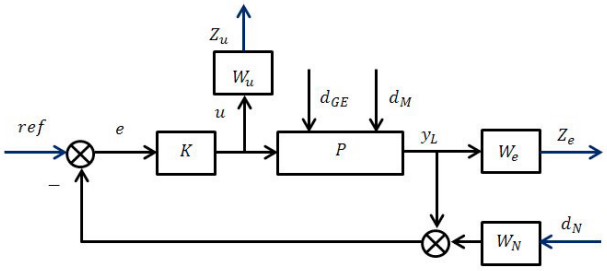

Fig. 1. Block diagram of a robust feedback control for glycemic dynamics in T2DM to solve a tracking problem considering disturbance rejection.

$$W_u(s) = [4s + 0.1]/[s + 20] \tag{4}$$

$$W_e(s) = [2s + 0.020]/[0.05s + 0.013] \tag{5}$$

$$W_N(s) = 1/10000 \tag{6}$$

The block diagram on Fig. 1 was simplified as Fig. 2 performing a linear fractional transformation (LFT) as in Zhou et al (1996). Then, the generalized plant $G(s)$ of the

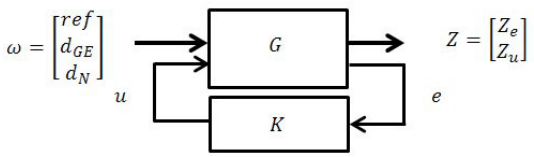

Fig. 2. Linear fractional transformation of the robust feedback control for glycemic dynamics in T2DM.

feedback control system arises from $Z = G(s)\omega$ by taking $z = [Z_e \ Z_u]^T$, $d = [ref \ d_{GE} \ d_N]^T$, and:

$$G(s) = \left[\begin{array}{ccc|c} 0 & W_e P_2 & 0 & W_e P_1 \\ 0 & 0 & 0 & W_u \\ \hline 0 & -P_2 & -W_N & -P_1 \end{array}\right] \tag{7}$$

where P_1 and P_2 represent the transfer functions of P due to inputs u and d_{GE}, respectively. From the previous discussion, the general control problem H_∞ can be formulated as follows: find a K such that $||G(s)||_\infty < \gamma$. With $\gamma < \gamma_0 := min||G(s)|| < 1$. Under this formulation, K was found by using the procedure defined in Zhou et al (1996).

4. RESULTS AND DISCUSSION

The full order controller K was derived from an iterative numerical process by using the tool *hinfsyn* of the Optimization Toolbox of MatLab®. The obtained γ value was 0.0079, ensuring robust internal stability and performance. The order of the resulted controller was 131. Nevertheless, a reduced model was obtained by means of Hankel values inspection using the *balmr* function of the Optimization Toolbox of MatLab®. The reduced controller order (K_{red}) was 7, and it is given by:

$$K_{red}(s) = \frac{num_{K_{red}}(s)}{den_{K_{red}}(s)} \tag{8}$$

where: $num_{K_{red}} = -144.1s^6 - 3035s^5 - 3478s^4 - 1136s^3 - 162.7s^2 - 6.868s - 0.05676$ and $den_{K_{red}} = s^7 + 9.884s^6 + 22.96s^5 + 26.18s^4 + 20.53s^3 + 5.496s^2 + 0.2369s + 0.001705$.

The performance of K_{red} was proved by means of numerical simulations using *Simulink* by MatLab® in closed-loop with the non-linear plant defined in 1. For simulations two different kinds of ref were taken: *i)* a dynamical reference where ref was the glycemic response of an oral glucose intake of a non-linear model that emulates glucose homeostasis in a healthy subject, and ii) a static reference where a constant glycemic of 90 mg/dl was used to represent the normoglycemic fasting state.

For dynamical reference the glycemic response of an oral glucose intake was taken from the non-linear model proposed in Alverhag and Martin (2006). Figure 3 shows a numerical simulation considering two glucose bolus of 71000 g at minute 0 and at minute 250. Whereas, at minute 0 a single metformin dose of 500 mg was given to the controlled T2DM patient. As can be seen the glycemic response of the T2DM patient with control action closely tracks the reference, while the response of the T2DM patient without control action reaches up to 150 mg/dL as a response for an oral glucose intake.

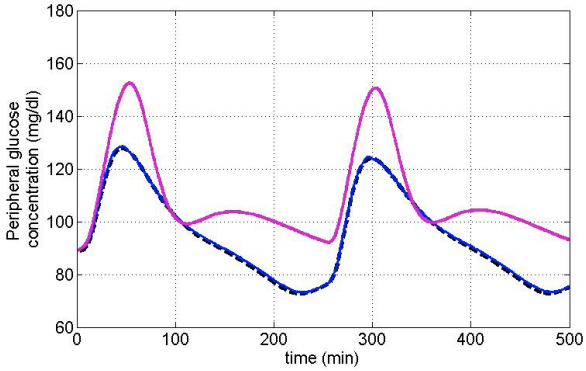

Fig. 3. The output of system 1 under action of the reduced controller (blue line) tracks the time evolution of the peripheral glycemia of a healthy human subject (doted black line). The purple line shows the output of system 1 without control action.

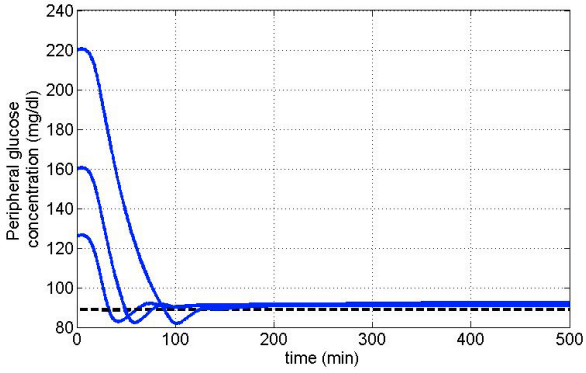

Fig. 4. The proposed controller in 8 allows us to regulate the peripheral glycemia of a T2DM patient. The blue lines represent the output of system 1 under action of the reduced controller while doted black line is a normoglycemic fasting glucose concentration.

By the other hand, Figure 4 shows that starting from the fasting stage at minute 0 a single metformin dose of 500 mg and a continuous insulin infusion were administered to the T2DM patient in order to achieve the normoglycemic fasting state at 90 mg/dl. As can be seen the closed-loop allows that the T2DM patient to reaches a normoglycemic state from a fasting state of 160mg/dL in around 50 minutes, which is a suitable time for a DM patient. Moreover, although the blood glucose level is below the reference before stabilization, it does not reaches a critical hypoglycaemic state (glycemia $<$ 70 mg/dL). After achieving stabilization, the glycemic response of the DMT2 patient is maintained with a steady state error $<$ 2 mg/dl.

5. CONCLUSION

In this paper a robust controller of glycemic in T2DM was designed by using the robust H_∞ technique. Through the use of a combined therapy of a continuous insulin and a single dose of metformin, the designed controller shows that it is capable of solving the tracking control problem whether the reference represents the dynamics of a healthy subject or a constant normoglycemic value. The control approach allowed to find a controller that is robust under

exogenous disturbances such as oral glucose intake or noise due to the glucose sensor.

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Appendix A. MODEL IN STATE SPACE

The state space variables are defined:

$x_1 = G_{BV}$	$x_9 = G_p$	$x_{17} = I_p$	$x_{25} = L$
$x_2 = G_{BI}$	$x_{10} = I_B$	$x_{18} = \Gamma^N$	$x_{26} = Q$
$x_3 = G_H$	$x_{11} = I_H$	$x_{19} = \omega$	$x_{27} = G_S$
$x_4 = G_L$	$x_{12} = I_L$	$x_{20} = \omega_G$	$x_{28} = r_{OGA}$
$x_5 = G_K$	$x_{13} = I_K$	$x_{21} = M^I_{HGP}$	$x_{29} = z_1$
$x_6 = G_{PV}$	$x_{14} = I_{PV}$	$x_{22} = M^I_{HGU}$	$x_{30} = z_2$
$x_7 = G_{PI}$	$x_{15} = I_{PI}$	$x_{23} = f_2$	$x_{31} = z_3$
$x_8 = G_G$	$x_{16} = I_G$	$x_{24} = P$	$x_{32} = z_4$

Thus, the full 32-dimension vector field is as follows:

$$\dot{x_1} = [\pi_5[x_3 - x_1] - \pi_2[x_1 - x_2]/\pi_3]/\pi_1 \quad (A.1)$$

$$\dot{x_2} = [\pi_2[x_1 - x_2]/\pi_3 - r_{BGU}]/\pi_2 \quad (A.2)$$

$$\dot{x_3} = [\pi_5 x_1 + \pi_6 x_4 + \pi_7 x_5 + \pi_8 x_6 - \pi_9 x_3 - r_{RBCU} + r_{IVG}]/\pi_4 \quad (A.3)$$

$$\dot{x_4} = [\pi_{13} x_3 + \pi_{14} x_8 + \pi_{39} x_9 - \pi_6 x_4 + r_{HGP} - r_{HGU}]/\pi_{10} \quad (A.4)$$

$$\dot{x_5} = [\pi_7[x_3 - x_5] - r_{KGE}]/\pi_{15} \quad (A.5)$$

$$\dot{x_6} = [\pi_8[x_3 - x_6] - \pi_{17}[x_6 - x_7]/\pi_{18}]/\pi_{16} \quad (A.6)$$

$$\dot{x_7} = [\pi_{17}[x_6 - x_7]/\pi_{18} - r_{PGU}]/\pi_{17} \quad (A.7)$$

$$\dot{x_8} = [\pi_{14}[x_3 - x_8] - r_{GGU} + r_{OGA}]/\pi_{19} \quad (A.8)$$

$$\dot{x_9} = \pi_{39}[x_3 - x_9]/\pi_{42} \quad (A.9)$$

$$\dot{x_{10}} = \pi_{21}[x_{11} - x_{10}]/\pi_{20} \quad (A.10)$$

$$\dot{x_{11}} = [\pi_{21} x_{10} + \pi_{32} x_{12} + \pi_{33} x_{13} + \pi_{34} x_{14} - \pi_{35} x_{11} + r_{IVI}]/\pi_{22} \quad (A.11)$$

$$\dot{x_{12}} = [\pi_{36} x_{11} + \pi_{37} x_{16} - \pi_{32} x_{12} + \pi_{38} x_{17} - r_{LIC}]/\pi_{23} \quad (A.12)$$

$$\dot{x_{13}} = [\pi_{33}[x_{11} - x_{13}] - r_{KIC}]/\pi_{24} \quad (A.13)$$
$$\dot{x_{14}} = [\pi_{34}[x_{11} - x_{14}] - \pi_{46}[x_{14} - x_{15}]/\pi_{26}]/\pi_{25} \quad (A.14)$$
$$\dot{x_{15}} = [\pi_{46}[x_{14} - x_{15}]/\pi_{26} - r_{PIC}]/\pi_{46} \quad (A.15)$$
$$\dot{x_{16}} = \pi_{37}[x_{11} - x_{16}]/\pi_{27} \quad (A.16)$$
$$\dot{x_{17}} = [\pi_{38}[x_{11} - x_{17}] + r_{PIR}]/\pi_{40} \quad (A.17)$$
$$\dot{x_{18}} = \eta_{33}[r^N_{P\Gamma R} - x_{18}]/\pi_{28} \quad (A.18)$$
$$\dot{x_{19}} = [r_{G\omega R} - r_{P\omega C}]/\pi_{41} \quad (A.19)$$
$$\dot{x_{20}} = \eta_{65} OGC_s - r_{G\omega R} \quad (A.20)$$
$$\dot{x_{21}} = [M^{I_\infty}_{HGP} - x_{21}]/\pi_{11} \quad (A.21)$$
$$\dot{x_{22}} = [M^{I_\infty}_{HGU} - x_{22}]/\pi_{11} \quad (A.22)$$
$$\dot{x_{23}} = [[M^{\Gamma 0}_{HGP} - 1]/2 - x_{23}]/\pi_{12} \quad (A.23)$$
$$\dot{x_{24}} = \eta_{35}[P_\infty - x_{24}] \quad (A.24)$$
$$\dot{x_{25}} = \eta_{41}[X - x_{25}] \quad (A.25)$$
$$\dot{x_{26}} = \eta_{42}[\eta_{43} - x_{26}] + \eta_{44} x_{24} - S \quad (A.26)$$
$$\dot{x_{27}} = OGCS - x_{27}/\pi_{44} \quad (A.27)$$
$$\dot{x_{28}} = x_{27}/[\pi_{43}\pi_{44}] - x_{28}/\pi_{43} \quad (A.28)$$
$$\dot{x_{29}} = -x_{29}(\eta_{68} + \eta_{69}) + z_O \quad (A.29)$$
$$\dot{x_{30}} = x_{29}\eta_{69} + x_{32}\eta_{70} - x_{30}\eta_{71} \quad (A.30)$$
$$\dot{x_{31}} = x_{30}\eta_{71} + x_{32}\eta_{72} - x_{31}\eta_{73} \quad (A.31)$$
$$\dot{x_{32}} = x_{31}\eta_{73} - x_{32}(\eta_{72} + \eta_{70} + \eta_{74}) \quad (A.32)$$

Appendix B. METABOLIC RATES

Glucose Subsystem rates

$$r_{BGU} = \eta_{21} \quad (B.1)$$
$$r_{RBCU} = \eta_{22} \quad (B.2)$$
$$r_{HGP} = x_{21} M^\Gamma_{HGP} M^G_{HGP} r^B_{HGP} \quad (B.3)$$
$$r_{HGU} = x_{22} M^G_{HGU} r^B_{HGU} \quad (B.4)$$
$$r_{PGU} = M^I_{PGU} M^G_{PGU} r^B_{PGU} \quad (B.5)$$
$$r_{GGU} = \eta_{23} \quad (B.6)$$
$$r^B_{HGP} = \eta_1 \quad (B.7)$$
$$r_{KGE} = \eta_{12} + \eta_{61} tanh[\eta_{13}(x_5 - \eta_{14})], x_5 < 460 \quad (B.8)$$
$$r_{KGE} = \eta_{58} + \eta_{59} x_5, x_5 >= 460 \quad (B.9)$$
$$r^B_{HGU} = \eta_{11} \quad (B.10)$$
$$r^B_{PGU} = \eta_{15} \quad (B.11)$$

Insulin Subsystem rates

$$r_{LIC} = \pi_{31}[\pi_{36} x_{11} + \pi_{37} x_{16} + \pi_{38} x_{17}] \quad (B.12)$$
$$r_{KIC} = \pi_{30}[\pi_{33} x_{11}] \quad (B.13)$$
$$r_{PIC} = x_{15}/[[1 - \pi_{29}]/\pi_{29}\pi_{34} - \pi_{26}/\pi_{46}] \quad (B.14)$$
$$r_{PIR} = S/S^N r^B_{PIR} \quad (B.15)$$
$$r^B_{PIR} = x_{11}[\pi_{35}/(1 - \pi_{31}) - \pi_{36} - \pi_{37} - (1 - \pi_{39})/(1 - \pi_{31})\pi_{34} - \pi_{21}/(1 - \pi_{31}) - \pi_{33}(1 - \pi_{30})/(1 - \pi_{31}) - \pi_{38}] \quad (B.16)$$

Glucagon Subsystem rates

$$r^N_{P\Gamma R} = M^G_{P\Gamma R} M^I_{P\Gamma R} \quad (B.17)$$
$$r_{P\Gamma C} = r_{M\Gamma C} x_{16} \quad (B.18)$$
$$r_{M\Gamma C} = \eta_{33} \quad (B.19)$$

Incretins Subsystem rates

$$r_{G\omega R} = x_{20}/\pi_{45} \quad (B.20)$$
$$r_{P\omega C} = r_{M\omega C} x_{19} \quad (B.21)$$
$$r_{M\omega C} = \eta_{64} \quad (B.22)$$

Where:

$$M^\Gamma_{HGP} = M^{\Gamma_0}_{HGP} - x_{23} \quad (B.23)$$
$$M^{\Gamma_0}_{HGP} = \eta_2 tanh[\eta_3 x_{18}] \quad (B.24)$$
$$M^G_{HGP} = \eta_4 - \eta_5 tanh[\eta_6(x_4/\eta_{48} - \eta_7)] \quad (B.25)$$
$$M^G_{HGU} = \eta_8 + \eta_{60} tanh[\eta_9(x_4/\eta_{48} - \eta_{10})] \quad (B.26)$$
$$M^I_{PGU} = \eta_{17} + \eta_{18} tanh[\eta_{19}[x_{15}/\eta_{49} - \eta_{20}] \quad (B.27)$$
$$M^G_{PGU} = x_7/\eta_{16} \quad (B.28)$$
$$M^G_{P\Gamma R} = \eta_{24} - \eta_{25} tanh[\eta_{26}(x_3/\eta_{47} - \eta_{27})] \quad (B.29)$$
$$M^I_{P\Gamma R} = \eta_{28} - \eta_{29} tanh[\eta_{30}(x_{11}/\eta_{50} - \eta_{31})] \quad (B.30)$$
$$M^{I_\infty}_{HGP} = \eta_{54} - \eta_{55} tanh[\eta_{56}(x_{12}/\eta_{51} - \eta_{57}) \quad (B.31)$$

$$M^{I_\infty}_{HGU} = \eta_{52} tanh[\eta_{53} x_{12}/\eta_{51}] \quad (B.32)$$
$$E_{gi} = (\eta_{75}(\eta_{69} x_{29})^{\eta_{76}})/(\eta^{\eta_{76}}_{77} + (\eta_{69} x_{29})^{\eta_{76}}) \quad (B.33)$$
$$E_l = (\eta_{78}(\eta_{71} x_{31})^{\eta_{79}})/(\eta^{\eta_{79}}_{80} + (\eta_{71} x_{31})^{\eta_{79}}) \quad (B.34)$$
$$E_p = (\eta_{81} x^{\eta_{81}}_{32})/(\eta^{\eta_{82}}_{83} + x^{\eta_{82}}_{32}) \quad (B.35)$$
$$S = [\eta_{45} Y + \eta_{46}[X - x_{25}]^{0^+} + \eta_{63} x_{19}] x_{26} \quad (B.36)$$
$$Y = P_\infty = X^{\eta_{40}} + \eta_{62} x_{19} \quad (B.37)$$
$$X = x_3/[\eta^{\eta_{36}}_{37} + \eta_{38} x^{\eta_{39}}_3] \quad (B.38)$$
$$z_O = \eta_{84} e^{-\eta_{85} t} - \eta_{86} e^{-\eta_{87} t} \quad (B.39)$$
$$OGC_s = [OGC_0/\eta_{66}][(t - \eta_{67})u(t - \eta_{67}) - (t - \eta_{67} - 1)u(t - \eta_{67} - 1) - (t - \eta_{67} - 4)u(t - \eta_{67} - 4) + (t - \eta_{67} - 5)u(t - \eta_{67} - 5)] \quad (B.40)$$

Appendix C. PARAMETERS

Hemodynamical parameters

$\pi_1 = 3.5$ dL	$\pi_2 = 4.5$ dL
$\pi_3 = 2.1$ L/min	$\pi_4 = 13.8$ dL
$\pi_5 = 5.9$ dL/min	$\pi_6 = 12.6$ dL/min
$\pi_7 = 10.1$ dL/min	$\pi_8 = 15.1$ dL/min
$\pi_9 = 43.7$ dL/min	$\pi_{10} = 23.5$ dL
$\pi_{11} = 25$ min	$\pi_{12} = 65$ min
$\pi_{13} = 2.5$ dL/min	$\pi_{14} = 9.6$ dL/min
$\pi_{15} = 6.6$ dL	$\pi_{16} = 10.4$ dL
$\pi_{17} = 63$ dL	$\pi_{18} = 5$ min
$\pi_{19} = 11.2$ dL	$\pi_{20} = 0.265$ L
$\pi_{21} = 0.45$ L/min	$\pi_{22} = 0.985$ L
$\pi_{23} = 1.07$ L	$\pi_{24} = 0.051$ L
$\pi_{25} = 0.735$ L	$\pi_{26} = 20$ min
$\pi_{27} = 0.945$ L	$\pi_{28} = 9930$ mL
$\pi_{29} = 0.15$	$\pi_{30} = 0.30$
$\pi_{31} = 0.40$	$\pi_{32} = 0.9$ L/min
$\pi_{33} = 0.72$ L/min	$\pi_{34} = 1.05$ L/min
$\pi_{35} = 3.12$ L/min	$\pi_{36} = 0.18$ L/min
$\pi_{37} = 0.684$ L/min	$\pi_{38} = 0.036$ L/min
$\pi_{39} = 0.5$ dL/min	$\pi_{40} = 0.07$ L
$\pi_{41} = 9.930$ L	$\pi_{42} = 1.6$ dL
$\pi_{43} = 22$ min	$\pi_{44} = 156.59$ min
$\pi_{45} = 25$ min	$\pi_{46} = 6.3$ L

Metabolic parameters

$\eta_1 = 155$ mg/min	$\eta_2 = 2.7$
$\eta_3 = 0.39$	$\eta_4 = 1.42$
$\eta_5 = 1.41$	$\eta_6 = 0.62$
$\eta_7 = 0.497$	$\eta_8 = 5.66$
$\eta_9 = 2.4$	$\eta_{10} = 1.48$
$\eta_{11} = 20$ mg/min	$\eta_{12} = 71$
$\eta_{13} = 0.011$	$\eta_{14} = 460$
$\eta_{15} = 35$ mg/min	$\eta_{16} = 86.2$ mg/dL
$\eta_{17} = 7.03$	$\eta_{18} = 6.52$
$\eta_{19} = 0.338$	$\eta_{20} = 5.82$
$\eta_{21} = 70$ mg/min	$\eta_{22} = 10$ mg/min
$\eta_{23} = 20$ mg/min	$\eta_{24} = 2.93$
$\eta_{25} = 2.10$	$\eta_{26} = 4.18$
$\eta_{27} = 0.61$	$\eta_{28} = 1.31$
$\eta_{29} = 0.61$	$\eta_{30} = 1.06$
$\eta_{31} = 0.47$	$\eta_{32} = 9.11$ mg/min
$\eta_{33} = 910$ ml/min	$\eta_{34} = 18.69$ mU/min
$\eta_{35} = 0.0482$	$\eta_{36} = 3.27$
$\eta_{37} = 132$	$\eta_{38} = 5.93$
$\eta_{39} = 3.02$	$\eta_{40} = 1.11$
$\eta_{41} = 0.931$ 1/min	$\eta_{42} = 0.00794$ 1/min
$\eta_{43} = 6.33$ U	$\eta_{44} = 0.575$ U/min
$\eta_{45} = 0.00797$ 1/min	$\eta_{46} = 0.136$ 1/min
$\eta_{47} = 91.3$ mg/dL	$\eta_{48} = 100.4$ mg/dL
$\eta_{49} = 5.3$ mU/L	$\eta_{50} = 15.2$ mU/L
$\eta_{51} = 21.6$ mU/L	$\eta_{52} = 2$
$\eta_{53} = 0.55$	$\eta_{54} = 1.21$
$\eta_{55} = 1.14$	$\eta_{56} = 1.66$
$\eta_{57} = 0.89$	$\eta_{58} = 330$
$\eta_{59} = 0.872$	$\eta_{60} = 5.66$
$\eta_{61} = 71$	$\eta_{62} = 0.003$ l/pmol
$\eta_{63} = 0.0001$ l/pmol	$\eta_{64} = 0.14$
$\eta_{65} = 0.009$	$\eta_{66} = 4$ min
$\eta_{67} = 0$ min	$\eta_{68} = 0.00188$ 1/min
$\eta_{69} = 0.00185$ 1/min	$\eta_{70} = 4.13$ 1/min
$\eta_{71} = 0.458$ 1/min	$\eta_{72} = 0.0101$ 1/min
$\eta_{73} = 0.910$ 1/min	$\eta_{74} = 0.509$ 1/min
$\eta_{75} = 0.486$	$\eta_{76} = 2$
$\eta_{77} = 431\mu$g	$\eta_{78} = 0.378$
$\eta_{79} = 5$	$\eta_{80} = 521\mu$g
$\eta_{81} = 0.148$	$\eta_{82} = 5$
$\eta_{83} = 1024\mu$g	$\eta_{84} = 63578\mu$g/min
$\eta_{85} = 0.0067$	$\eta_{86} = 63632\mu$g/min
$\eta_{87} = 0.0072$	

Appendix D. NOMENCLATURE

Variables:
G = glucose concentration
I = insulin concentration
Γ = glucagon concentration
ω = incretins concentration
ω_G = quantity of incretins in the gut above normal
r = metabolic rate
S =Secretion rate
M = Multiplier of basal metabolic rate
t = time
P =Potentiator
L =Inhibitor
Q =Labile insulin
Z_1=Metformin quantity in GI lumen
Z_2=Metformin quantity in GI wall
Z_3=Metformin quantity in liver
Z_4=Metformin quantity in periphery
f_2=Lowering effect of glucagon in HGP
G_s=Glucose quantity in stomach
OGC_s=Quantity of ingested glucose
E_{gl}=Metformin stimulation of glucose absorption in GI
E_l=Metformin inhibition of glucose production in liver
E_p=Metformin stimulation of glucose absorption in periphery
X, Y, P_∞ =Intermediate variables

First Subscript:
B =Brain
G =Gut
H =Heart and Lungs
L =Liver
P =Periphery
p =Pancreas
K =Kidney

Second Subscript:
I =Interstitial space
V =Vascular space

First Superscript:
G =Glucose model
I =Insulin model
Γ =Glucagon model
B =Basal value
N =Normalized value (divided by basal value)

Second Superscript:
0 =Initial value (normalized value as $t \to 0$)
∞ =asymptotic or final steady state value (normalized)

Metabolic rate Subscripts:
BGU =Brain glucose uptake
GGU =Gut glucose utilization
HGP =Hepatic glucose production
HGU =Hepatic glucose uptake
KGE =Kidney glucose excretion
PGU =Peripheral glucose uptake
$RBCU$ =Red blood cell glucose uptake
KIC =Kidney insulin clearance
LIC =Liver insulin clearance
PIC =Peripheral insulin clearance
IVG =Intravenous glucose infusion
IVI =Intravenous insulin infusion
OGA =Oral glucose absorption
$P\Gamma R$=Pancreatic glucagon release
$P\Gamma C$=Pancreatic glucagon clearance
$G\omega R$ =Gut incretins release
$P\omega C$ =Plasma incretins clearance
PIR =Pancreatic insulin release