

# Quasi-Continuous High Order Sliding Modes Controllers Applied to Glucose-Insulin Regulatory System Models

Gabriela Gallardo-Hernández, Leonid Fridman, Sergio Islas-Andrade and Yuri Shtessel

**Abstract**—This paper analyzes two glucose-insulin models for diabetic patients: by Bergman and by Hovorka. Bergman's Model is nonlinear, and has relative degree three. It offers a good approximation of the system, but omits several important physiological functions, and insulin features, that are included in Hovorka's Model. This is a nonlinear model with relative degree five. It includes most of physiological parameters of glucose system and insulin action. It has two glucose and insulin compartments. It describes in details the insulin action and the rate of appearance of subcutaneously injected insulin. An intestinal glucose absorption function is proposed to describe better the process of glucose production from ingested food. A renal excretion function is proposed in order to model kidneys filtration excretion. Hovorka's non-insulin-dependent function has been smoothed to avoid discontinuities in the system. For both models Homogeneous Quasi-Continuous Controllers of order three and five are used giving a good performance from a medical point of view.

## I. INTRODUCTION

**Motivation.** According to World Health Organization, more than 180 million people worldwide have diabetes, it represent 2% of world population, and they estimates than in 2030 it will duplicate [1]. It does not attack all world population in the same way, because there is a strong genetic influence, and some other social and economics factors [2], [3], but still a worldwide problem.

Biological models are quite complicated, since the 70's there have been several published model that have evolved [4],[5], [6],[7]. The earlier models are simple, i.e. Bergman model that only considers the insulin dependent and independent glucose uptake. Other models, like Hovorka's et al model, include more physiological functions that are obviated by other authors, i.e. renal excretion, endogenous glucose production and an insulin action subsystem. There are some improvements that can be done in the model

G. Gallardo-Hernández and L. Fridman are with Universidad Nacional Autónoma de México (UNAM), Department of Control, Engineering Faculty. C.P. 04510. México D.F. (e-mail: anagabygh@gmail.com, lfridman@servidor.unam.mx).

S. Islas-Andrade is with Centro Médico Nacional Siglo XXI Av. Cuauhtémoc 330 Col. Doctores C.P. 06725 México D.F.

Y. Shtessel is with Department of Electrical and Computer Engineering, University of Alabama in Huntsville, Huntsville, AL 35899 (e-mail: shtessel@eng.uah.edu).

L. Fridman gratefully acknowledges the financial support of this work by the Mexican CONACyT (Consejo Nacional de Ciencia y Tecnología), grant no. 56819, and the Programa de Apoyo a Proyectos de Investigación e Innovación Tecnológica (PAPIIT) UNAM, grant no. IN111208. Programa de Apoyo a Proyectos Institucionales para el Mejoramiento de la Enseñanza (PAPIME), UNAM, grant PE100907.

G Gallardo-Hernández acknowledges the financial support of this work by CONACyT, granted by the Beca Mixta program.

using our clinical experience, in the renal excretion and the intestinal absorption function.

In the matter of control the ideal is to have a simulation of pancreatic control on glucose, it is soft enough to allow the cells to avail the glucose in blood to get energy, but robust enough to support system disturbances, like high sugar meals, long fasting periods or sudden parameters changes.

Several methods have been previously employed to design feedback controller for insulin delivery, such as classical methods like proportional-integral-derivatives (PID) [8],[9], pole placement [10], which require a linearized model for the design, model predictive control (MPC) [11],[12]. In [13] there is a control based on  $H_\infty$ , it offers parameters robustness up to  $\pm 40\%$ , but the model is linearized, the operation range in a diabetic patients can vary from 60 to 400 mg/dl, so it is difficult to guarantee robustness in a so wide operation range. High Order Sliding Modes are used in [14], where parameters robustness is achieved using Bergman's model.

**Contribution.** Two models for glucose-insulin regulation are considered: by Bergman (BM) [4] and by Hovorka (HM) [7]. BM gives the best approximation that is possible to get with the less number of equations [15]. BM has relative degree three. HM offers a better physiological approximation to the system while include some functions like, renal excretion, endogenous glucose production, and a better description of insulin action. It has relative degree five. New intestinal absorption and renal excretion functions are proposed describing more adequately glucose production from meal process and glucose renal filtration, according to our clinical experience. Hovorka's non-insulin dependent glucose uptake is smoothed in order to have a totally continuous system to use high order sliding modes. Third order homogeneous quasi-continuous sliding mode control is used for BM, and fifth order is used for HM. Tracking is used in order to have a smoother control. As a result control time is adequate to medical references for normal pancreatic control even in the presence of parameters uncertainties and strong perturbations, so robustness is achieve.

## II. PHYSIOLOGICAL BACKGROUND.

Cells use glucose as a fuel and the mechanism to take advantage it is call metabolism. Cells can be classified by the way they absorb glucose, there are some cells that can absorb glucose direct and this are brain, retina and gonad cells. Others need insulin to absorb the glucose, this kind of cells represent 80% of body cells. The insulin is a hormone produced in the pancreas by Beta cells ( $\beta$  cells). This latter

glucose absorption allows body to have a hormonal control on glucose level concentration [16].

Pancreas controls glucose concentration level by two hormones. It can decrease it by secreting insulin or increase it by secreting glucagon, that is a hormone that allows the liver to liberate the glucose stored in it by glycogenolysis, this process is also known as endogenous glucose production (EGP). It is important that glucose concentration never be lower than its basal level ( $G_b = 70\text{mg/dl}$ ), otherwise it may cause permanent brain damage in a relative short time, 30 to 45 min, and this condition can derive into a coma state.

There are two types of Diabetes. Diabetes type 1 is a disease where the pancreatic cells that produce the insulin,  $\beta$  cells, are damaged and they cannot produce it anymore by autoimmune mechanisms, in such a case the glucose level is always higher than the basal and so retina, kidney and brain maybe damaged, because the blood chemistry changes [17]. The human body has the extraordinary ability to compensate the insulin function, and if glucose level exceed the threshold (180 mg/dl usually), the auxiliary systems starts to operate in order to decrease it. The first, one and most important, is the renal excretion, where the kidneys allow the glucose to be excreted by urine, but like this is not their normal operation, if the renal excretion continues for a long time the kidneys tissue will be damaged as well. It is important to notice that kidney tissue get damaged after some years of constant renal glucose excretion. Diabetes type 2 is very common, more than 80% of the patients in the world, are type 2 diabetic. In this type 2 diabetes, the insulin is not decreased at beginning; even the insulin levels are highest the normal levels. The mechanism for produce disease is first, insulin resistance, all the cells shown resistance of his receptors to take insulin, and then the insulin is higher and also blood glucose as well. With more years of followup, the Beta cells has decrease the insulin production and the glucose is higher but not the insulin.

In diabetics patients is normal that only  $\beta$  cells are damaged, and the Alpha cells ( $\alpha$  cells), that secret glucagon are intact.

The glucose-insulin regulatory system is a time variant model because the body can vary the parameters even from hour to hour. For example, when a patient exercises the glucose demand by muscles increase rapidly and it can even occur in absence of insulin and after the exercise is over the parameters go back to normal. And if the patient changes his exercise routine to a stronger one for a long period of time the basal parameters will also change.

Current medical treatment suggests three or four daily glucose measurement, with the same number of subcutaneous insulin injections [18],[19]. A good treatment includes also a strict low carbohydrates diet, and it is not always done, and this is the major disturbance of the system [3].

An approach is to close the broken pancreas insulin feedback loop outside the body and deliver it using an external actuator such as a pump [9]. This pump that acts like an artificial pancreas would include a sensor and an insulin container. The sensor provides the measurements of

the blood glucose concentration and passes the information to a feedback control system that would calculate the necessary insulin delivery rate using robust higher order sliding mode control algorithms [20], to keep the patient under metabolic control. A signal is to be sent to the insulin pump by the controller that delivers the desired amount of insulin. The pump injects insulin through a catheter placed under the patient's skin [19].

There are several kinds of glucose sensors, but the amperometric sensor has reached successful commercialization ahead of other measuring techniques. Until now the principal disadvantage is that sampling period is very low, it last 10 seconds to do a measurement [21].

### III. BERGMAN MODEL

The first analyzed model is known as Bergman's Minimal Model. It is call 'minimal' in the sense that satisfy certain validation criteria while having the smallest number of parameters [15].

$$\begin{aligned}\dot{G}(t) &= -p_1[G(t) - G_b] - X(t)G(t) \\ \dot{X}(t) &= -p_2X(t) + p_3[I(t) - I_b] \\ \dot{I}(t) &= -n[I(t) - I_b] + \gamma[G(t) - h]^+t + u(t)\end{aligned}\quad (1)$$

The "+" sign shows the positive reflection to glucose intake,  $G(t)$  is the glucose concentration in the blood plasma (mg/dl),  $X(t)$  is the insulin's effect on the net glucose disappearance, the insulin concentration in the remote compartments (1/min),  $I(t)$  is the insulin concentration in plasma at time  $t$  ( $\mu\text{U/ml}$ ),  $G_b$  represents the nominal value of glucose level, (mg/dl),  $I_b$  is the basal pre-injection level of insulin ( $\mu\text{U/ml}$ ),  $p_1$  is the insulin-independent rate constant of glucose uptake in muscles and liver (1/min),  $p_2$  is the rate for decrease in tissue glucose uptake ability (1/min),  $p_3$  is the insulin-dependent increase in glucose uptake ability in tissue per unit of insulin concentration above the basal level [ $(\mu\text{U/ml})/\text{min}^{-2}$ ],  $n$  is the first order decay rate for insulin in blood (1/min),  $h$  is the threshold value of glucose above which the pancreatic cells release insulin (mg/dl) and is the rate of the pancreatic cells' release of insulin after the glucose injection with glucose concentration above the threshold [ $(\mu\text{U/mlmin}^2)(\text{mg/dl})^{-1}$ ] [19].

The term  $\gamma[G(t) - h]^+t$  on  $\dot{I}(t)$  equation represent the normal pancreatic control of the system, because it represents the pancreas insulin secretion, but a diabetic patient who already is on insulin shots therapy does not have this natural control, so this term is considered as zero.

The system output is  $y = G(t)$ , and the input is  $u(t)$ , so it is easily see that the relative degree of the system is three.

BM is a one compartment for insulin and glucose model. It considers the effect of insulin only on glucose disappearance, but omits insulin effect on endogenous glucose production and the glucose renal excretion, functions that play an important role in the glucose regulation of diabetic type I patients. In [22] is also said that BM overestimate the

glucose the glucose effectiveness, and insulin sensitivity is underestimate, due undermodeling.

After the patient eats, the intestine absorbs the glucose to transport it to the blood and the total glucose ( $G_T$ ) is the  $G(t)$  plus the absorption. Using the function for intestinal absorption describe for Fisher [23].

$$G_T(t) = G(t) + A(t) \quad (2)$$

$$A(t) = Be^{ct} \quad (3)$$

Then the system is arranged as follows:

$$\dot{G}(t) = -p_1[G(t) - G_b] - X(t)G(t) + \dot{A}(t) \quad (4)$$

$$\dot{X}(t) = -p_2X(t) + p_3[I(t) - I_b]$$

$$\dot{I}(t) = -n[I(t) - I_b] + \gamma[G(t) - h]^+ t + u(t)$$

#### IV. HOVORKA'S MODEL

There is more complete model for the system, HM. It was developed using glucose tracers. It is a two glucose and two insulin compartments model. It considers most of glucose-insulin regulatory parameters, insulin independent and depend glucose uptake, glucose intestinal absorption, EGP, the flux between both glucose compartments. It has a insulin subsystem to describe subcutaneously insulin absorption, it means the appearance of injected insulin in blood. And an insulin action subsystem that describe insulin effect on glucose transport, glucose disposal and EGP. HM is a nonlinear model, it has relative degree five [7]. It is important to remark that a short action insulin was used to model the system.

##### A. Glucose subsystem

$$G(t) = \frac{Q_1(t)}{V_G} \quad (5)$$

$$\frac{dQ_1(t)}{dt} = - \left[ \frac{F_{01}^c}{V_G G(t)} + x_1(t) \right] Q_1(t) + k_{12}Q_2(t) - F_R + U_G(t) + EGP_0[1 - x_3(t)]. \quad (6)$$

$$\frac{dQ_2(t)}{dt} = x_1(t)Q_1(t) + [k_{12} + x_2(t)]Q_2(t) \quad (7)$$

$$F_{01}^c = \begin{cases} F_{01} & G(t) \geq 81 \text{ mg/dl} \\ F_{01}G(t)/4.5 & \text{otherwise} \end{cases} \quad (8)$$

$$F_R = \begin{cases} 0.003(G - 180)V_G & G(t) \geq 180 \text{ mg/dl} \\ 0 & \text{otherwise} \end{cases} \quad (9)$$

$$U_G(t) = \frac{D_G A_G t e^{-t/t_{max,G}}}{t_{max,G}^2} \quad (10)$$

where  $Q_1(t)$  and  $Q_2(t)$  represent the masses of glucose in the accessible and non-accessible compartments (mg),  $k_{12}$  represents the transfer rate constant form both compartments ( $\text{min}^{-1}$ ),  $G(t)$  is the glucose concentration (mg/dl), and

$EGP_0$  represents endogenous glucose production (EGP) extrapolated to the zero insulin concentration ( $\text{mg/min}$ ). is the total non-insulin dependent glucose use ( $\text{mg/min}$ ).  $F_R$  is the renal glucose clearance above the glucose threshold of  $180 \text{ mg/dl}$  ( $\text{mg/min}$ )

##### B. Insulin subsystem

Insulin absorption is described as

$$\frac{dS_1(t)}{dt} = u(t) - \frac{S_1(t)}{t_{max,I}} \quad (11)$$

$$\frac{dS_2(t)}{dt} = \frac{S_1(t)}{t_{max,I}} - \frac{S_2(t)}{t_{max,I}} \quad (12)$$

$$U_I = \frac{S_2(t)}{t_{max,I}} \quad (13)$$

$$\frac{dI(t)}{dt} = \frac{U_I}{V_I} - k_e I(t) \quad (14)$$

where  $S_1(t)$  and  $S_2(t)$  are a two compartment chain representing absorption of subcutaneously administered short-acting insulin;  $u(t)$  is the control signal, it represent the injected insulin;  $t_{max,I}$  is the time to maximum insulin absorption ( $\text{min}$ );  $U_I$  is the insulin absorption rate, appearance of insulin in plasma;  $I(t)$  represents the plasma insulin concentration;  $k_e$  is the fractional elimination rate;  $V_I$  is the volume distribution (l).

##### C. Insulin action subsystem

The insulin has three actions on glucose kinetics:

$$\frac{dx_1}{dt} = -k_{a1}x_1(t) + k_{b1}I(t) \quad (15)$$

$$\frac{dx_2}{dt} = -k_{a2}x_2(t) + k_{b2}I(t) \quad (16)$$

$$\frac{dx_3}{dt} = -k_{a3}x_3(t) + k_{b3}I(t) \quad (17)$$

$x_1, x_2, x_3$  represent the remote effects of insulin on glucose distribution/transport, glucose disposal and endogenous glucose production;  $k_{a1}, k_{a2}$  and  $k_{a3}$  represent the deactivation rate constants, and  $k_{b1}, k_{b2}$  and  $k_{b3}$  represent the activation rate constants.

The system output is  $y = G(t)$ . It is not possible to establish the relative degree of the system because  $F_{01}^c$  and  $F_R$  are discontinuous functions. To avoid this problem the smoothed functions are used, considering that in nature discontinuous functions does not exist. For  $F_R$  the  $F_{rs}$  function is proposed to describe the behavior of glucose excretion according to our clinical experience.

$$F_{01}^s = F_{01}(1 - e^{-G(t)^{2/7.5}}) \quad (18)$$

$$F_{rs} = \frac{6}{\pi} \arctan(G(t) - 180) + e \quad (19)$$

Differentiating the control appears first in the fifth derivate:

$$\begin{aligned}
G^{(5)} = & V_G^{-1} \left( -F_{01}^{c(4)} - ([k_{a1}^2 \ddot{x}_1 + (k_{b1}k_{a1} - k_{b1}k_e)] \ddot{I} \right. \\
& + k_{b1} t_{max,I} V_I^{-1} [u(t) - 2S_1(t) t_{max,I}^{-1} \\
& + 2S_2(t) t_{max,I}^{-1}] Q_1 + 4\dot{Q}_1 \ddot{x}_1 + 5\ddot{x}_1 \dot{Q}_1 \quad (20) \\
& \left. + k_{12} Q^{(4)} - F_R^{(4)} + U_G^{(4)} - EGP_0 x_3^{(4)} \right)
\end{aligned}$$

In order to simplify the implementation HM can be rewritten in state space as

$$\begin{aligned}
G(t) &= \frac{X_1}{V_G} \\
\dot{X}_1 &= -X_1 X_3 + k_{12} X_2 + EGP_0 [1 - X_5] \\
&\quad - F_{01} - F_R + U_G \\
\dot{X}_2 &= X_1 X_3 - [k_{12} + X_4] X_2 \\
\dot{X}_3 &= -k_a X_3 + k_b X_6 \\
\dot{X}_4 &= -k_a X_4 + k_b X_6 \quad (21) \\
\dot{X}_5 &= -k_a X_5 + k_b X_6 \\
\dot{X}_6 &= \frac{1}{t_{max,I}} k_{VI} X_7 - k_e X_6 \\
\dot{X}_7 &= \frac{1}{t_{max,I}} [X_8 - X_7] \\
\dot{X}_8 &= u(t) - \frac{1}{t_{max,I}} X_8
\end{aligned}$$

where glucose subsystem is represented by  $X_1$  and  $X_2$ , as  $Q_1$  and  $Q_2$ ; insulin action subsystem are  $X_3$ ,  $X_4$  and  $X_5$ , corresponding to  $x_1$ ,  $x_2$  and  $x_3$ ; insulin subsystem is denoted by  $X_6$ ,  $I(t)$ ;  $X_7$ , representing  $S_1$  and  $X_8$  is  $S_2$ .

## V. METHODOLOGY

As seen in sections one and two, there are several glucose-insulin regulatory system models, but there are some uncertainties in the parameters. Using High Order Sliding Mode Control is well suited because a robust control is needed even with all the model and parameters uncertainties and it presents less chattering than other High Order Sliding Mode Controllers [24], [25],[26].

Control must be smooth in order to let the cells absorb the glucose, so a tracking control is proposed. A standard subject was chosen to generate the tracking reference for glucose blood concentration,  $G_{ref}$ .

As human body is not an exact system, for medical proposes the goal is that after two hours of food intake, the blood glucose concentration must be under  $110mg/dl$  and above  $70mg/dl$ .

The output for both models is  $G(t)$ , the glucose blood concentration; and control signal is  $u(t)$ , the injected insulin;  $G_{ref}$  represents the desired value. Then errors is defined as:

$$\sigma = G_{ref} - G(t) \quad (22)$$

Actuator is considered as a first order system, and its dynamic is compensated by the controller.

Homogeneous Quasi-Continuous controller suggested in [27] is proposed to use. It is call Quasi-Continuous because is continuous if the produced control is a continuous function of the state variables everywhere except the  $r$ -sliding set:

$$\sigma = \dot{\sigma} = \ddot{\sigma} = \dots = \sigma^{(r-1)} = 0 \quad (23)$$

Control is represented by

$$u = -\alpha \Psi_{r-1,r}(\sigma, \dot{\sigma}, \dots, \sigma^{(r-1)}) \quad (24)$$

where

$$\Psi_{i,r} = \varphi_{i,r} / N_{i,r} \quad (25)$$

$$\varphi_{i,r} = \sigma^i + \beta_i N_{i-1,r}^{(r-i)/(r-i+1)} \Psi_{i-1,r} \quad (26)$$

$$N_{i,r} = |\sigma^i| + \beta_i N_{i-1,r}^{(r-i)/(r-i+1)} \quad (27)$$

where  $\beta_1, \dots, \beta_r$  are positive numbers, and  $\alpha > 0$ . This algorithm can easily be programmed using recursiveness. In this paper a third order controller ( $u_{BM}$ ), and a fifth order controller ( $u_{HM}$ ) are used.

$$\begin{aligned}
\varphi_{2,3} &= \dot{\sigma} + \beta_2 \left( |\dot{\sigma}| + \beta_1 |\sigma|^{2/3} \right)^{-1/2} \left( \dot{\sigma} + \beta_1 |\sigma|^{-1/3} \sigma \right) \\
N_{2,3} &= |\dot{\sigma}| + \beta_2 \left( |\dot{\sigma}| + \beta_1 |\sigma|^{2/3} \right)^{1/2} \\
u_{BM}(t) &= \alpha \frac{\varphi_{2,3}}{N_{2,3}} \quad (28)
\end{aligned}$$

$$\begin{aligned}
\varphi_{4,5} &= |\sigma^4| + \beta_4 \left[ |\ddot{\sigma}| + \right. \\
&\quad \left. \beta_3 \left( |\dot{\sigma}| + \beta_2 \left( |\dot{\sigma}| + \beta_1 |\sigma|^{4/5} \right)^{3/4} \right)^{2/3} \right]^{-1/2} \\
&\quad \left[ \ddot{\sigma} + \beta_3 \left( |\dot{\sigma}| + \beta_2 \left( |\dot{\sigma}| + \beta_1 |\sigma|^{4/5} \right)^{3/4} \right)^{-1/3} \right. \\
&\quad \left. \left( \ddot{\sigma} + \beta_2 \left( |\dot{\sigma}| + \beta_1 |\sigma|^{4/5} \right)^{-1/4} \right. \right. \\
&\quad \left. \left. \left( \dot{\sigma} + \beta_1 |\sigma|^{-1/5} \sigma \right) \right) \right] \\
N_{4,5} &= |\sigma^4| + \beta_4 \left( |\ddot{\sigma}| + \right. \\
&\quad \left. \beta_3 \left( |\dot{\sigma}| + \beta_2 \left( |\dot{\sigma}| + \beta_1 |\sigma|^{4/5} \right)^{3/4} \right)^{2/3} \right)^{1/2} \\
u_{HM}(t) &= \alpha \frac{\varphi_{4,5}}{N_{4,5}} \quad (29)
\end{aligned}$$

Simulations are made using the proposed glucose absorption function (3), for both systems. The actual sensors available are slow, so we used a sample rate of 5 samples per minute.

VI. SIMULATION

For BM the three set of parameters presented in [19] are used to prove the control robustness. For HM there is only one set of parameters presented in [7], so the parameters have been varied up to 40% in order to create other sets of parameters to prove robustness.

In the minute 100 a disturbance is induced in order to represent a normal meal.

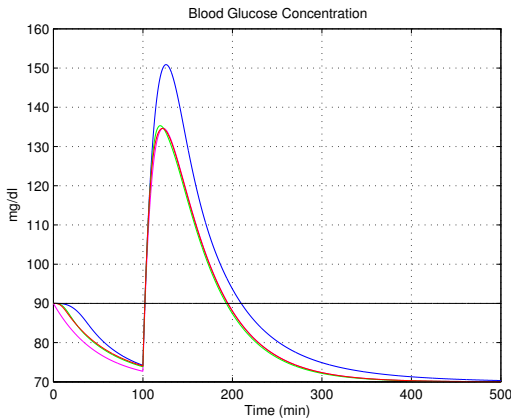


Fig. 1. Controlled BM by Quasi-Continuous of fourth order.

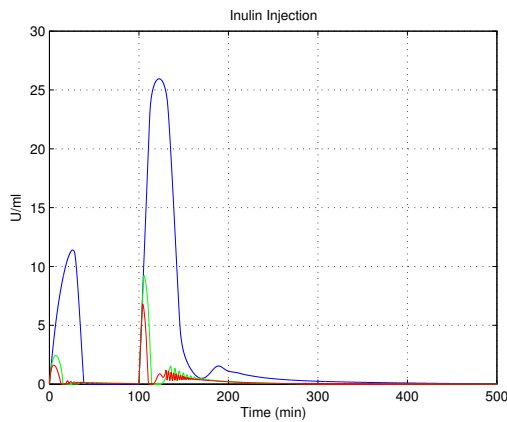


Fig. 2. Injected Insulin in BM.

As we can see the simplicity of BM give us a good comparison parameter. For HM stability es difficult to achieve, but the medical standards are accomplished, due basal glucose and insulin concentration, oscillate in the desired steady state value.

VII. CONCLUSIONS

Two models were evaluated, BM and HM. BM was the first model to offer a good approximation of the glucose-insulin regulatory system. It considers only a compartment for glucose and insulin, and the effect of insulin on glucose disappearance, and the non-insulin-dependent uptake. HM gives a better physiological accuracy. It describes most of the parameters involved in the system, and it has two

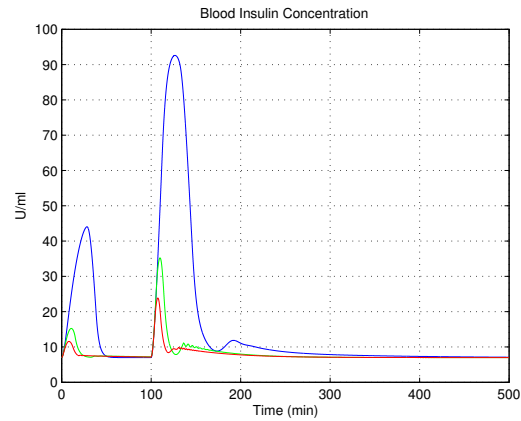


Fig. 3. Insulin Concentration in BM.

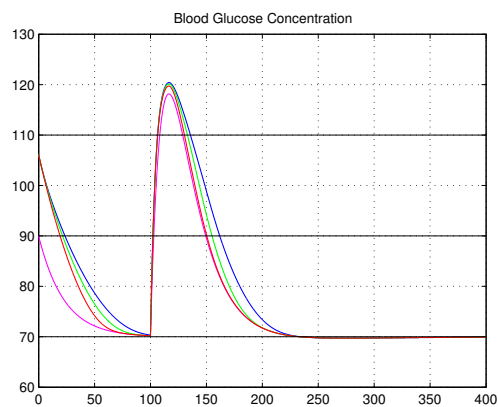


Fig. 4. Controlled HM by Quasi-Continuous of fourth order.

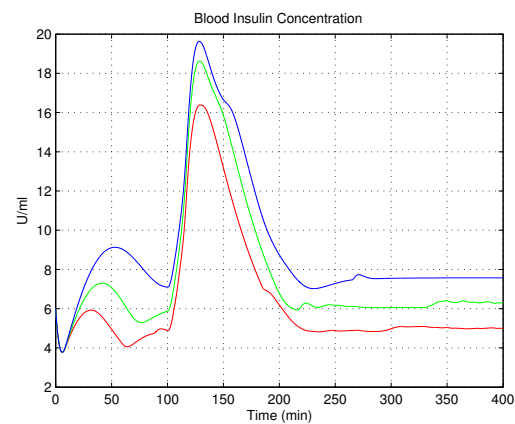


Fig. 5. Insulin Concentration in HM.

compartments of glucose and for insulin. HM considers insulin independent and dependent glucose uptake, glucose intestinal absorption, EGP, the flux between both glucose compartments. It has a insulin subsystem to describe subcutaneously insulin absorption, it means the appearance of injected insulin in blood. And an insulin action subsystem that describes insulin effect on glucose transport, glucose

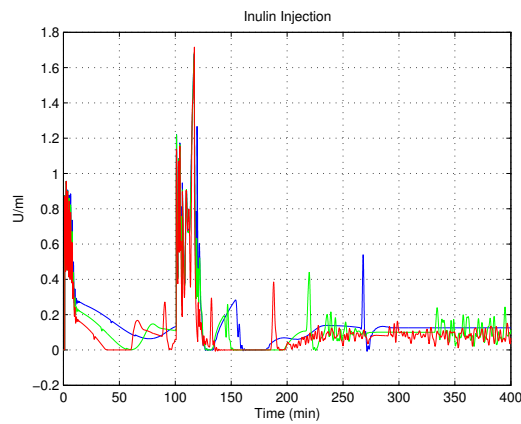


Fig. 6. Injected Insulin in HM.

disposal and EGP. HM is a nonlinear model, it has relative degree five. HM needs constant injection of insulin in order to get to the basal state. EGP and non-insulin dependent glucose use are not balanced in stable state it derives in a oscillatory behavior of glucose and insulin concentration. For future work glucagon dynamics must be considered in order represent better the stable state. As the model consider a short action insulin, the insulin dynamic es very fast.

Using our clinical experience, two functions are proposed. One renal excretion, because the kidneys excrete a nominal quantity of glucose per hour once the glucose level concentration threshold is exceed, but this quantity varies only with the spoliation of kidneys tissues and it happens after several years, of glucose filtration. The other proposed function is a modification of Fisher intestinal glucose function to describe better the rate of appearance of glucose obtained from the ingested food.

Homogenous Quasi-Continuous Controllers are used to control both models, considering 3 different patients for each model, the results are good in every case. It proves robustness even in presence of parameters uncertainties that can be induced by time variability and strong perturbation like unbalanced meals, exercise or long fasting periods and for different kinds of insulin.

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