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High-Order Sliding-Mode Control for Blood Glucose Regulation in the Presence of Uncertain Dynamics

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Abstract— **The success of blood glucose automatic regulation depends on the robustness of the control algorithm used. It is a difficult task to perform due to the complexity of the glucose-insulin regulation system. The variety of model existing reflects the great amount of phenomena involved in the process, and the inter-patient variability of the parameters represent another challenge. In this research a High-Order Sliding-Mode Control is proposed. It is applied to two well known models, Bergman Minimal Model, and Sorensen Model, to test its robustness with respect to uncertain dynamics, and patients' parameter variability. The controller designed based on the simulations is tested with the specific Bergman Minimal Model of a diabetic patient whose parameters were identified from an *in vivo* assay. To minimize the insulin infusion rate, and avoid the hypoglycemia risk, the glucose target is a dynamical profile.**

I. Introduction

Diabetes is a disease characterized by abnormally elevated concentration of blood glucose. To date there is no cure for it. Some diabetes cases can be treated with oral medication, but when pancreatic insulin production is impaired, diabetes has to be treated with exogenous insulin [1]. Insulin infusion via a wearable pump represents a better alternative. It improves patient quality of life, but it does not guarantee that patient remains normoglycemic because closed loop control is not yet approved in ambulatory systems. Moreover, the risk of incidental over-medication is high, and can be lethal [2]. It is important to maintain normoglycemia to reduce or avoid the long-term complications of this disease.

The glucose-insulin regulatory system is nonlinear and time variable. The most important parameters, such as insulin resistance, can be temporarily or permanently changed depending on the personal habits.

Automatic insulin infusion has been the subject of extensive research since 1960, but to date there is no algorithm approved by FDA for outpatients use. There are several research publications describing control algorithms for glucose regulation. Algorithms using methods like PID control [2], pole placement [3], feed-forward feedback [4], use linearization, and, naturally, the best results were obtained when they were tuned for a specific patient. Parameter identification is expensive and invasive. Since the system is time varying, parameter uncertainties are always present, and these kinds of control are not robust.

High Order Sliding Mode Control (HOSMC) [5] is a *black-box* oriented control i.e. it only needs knowledge of the relative degree [6] of the system and reasonable bounds of a few expressions. Thus HOSMC is an attractive alternate approach to blood glucose control. Due to its nonlinearity, it spans of the target system. Its design does not depend on parametric or system model uncertainties, which guarantees the required robustness.

There are a several known mathematical models describing the glucose-insulin regulatory system. Improved models involve additional dynamics, like renal excretion, or the impact of exercise on blood glucose disappearance, which significantly increases the model order. It is not reasonable to assure that any model considers all the phenomena involved in the glucose-insulin regulation system, and the design of a controller has to be robust with respect to uncertain dynamics that can be present in reality.

In this research a High-Order Sliding-Mode Control is designed, and it is tested in two well known mathematical models, the Bergman Minimal Model (BeM) and Sorensen Model (SoM), and it robustness with respect to unaccounted dynamics [7] is tested.

BeM is a nonlinear compartmental model and contains the fewest number of parameters that describe the glucose-insulin regulatory system with sufficient accuracy [8].

One of the most complete models is the Sorensen Model (SoM). It is composed of 24 differential equations and describes the action of each group of organs, having some influence on glucose regulation. In particular, it accounts for the glucagon effect, opposite to the insulin effect, and the glucose renal excretion, which is a defense mechanism applied when glucose exceeds a healthy threshold.

The HOSMC is designed and it is fist tested for six different *in silico*, three in each model, and its performance is compared to a PID control described in [9]. A second test is done on the BeM of an specific diabetic patient from the Metabolic Diseases Research Unit of the National Medical Center S-XXI, whose parameters were identified analyzing

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the information of a continuous glucose monitor.

Hypoglycemia could be lethal, a security restrain must be provided to avoid it. In this work the use of dynamical target profile is studied.

II. Models

A. Bergman Model

Following is the Bergman Model (BeM):

$$\begin{aligned}\dot{B}_1 &= -p_1[B_1 - G_b] - B_1 B_2,\\ \dot{B}_2 &= -p_2 B_2 + p_3[B_3 - I_b],\\ \dot{B}_3 &= -n[B_3 - I_b] + \gamma[B_1 - h]t + u(t).\end{aligned} \tag{1}$$

Here B_1, B_2 and B_3 are plasma glucose concentration, the insulin influence on glucose concentration reduction, and insulin concentration in plasma respectively. The control input $u(t)$ represents the insulin infusion rate, p_1 is the insulin-independent glucose-utilization rate, p_2 is the rate of decrease of the tissue glucose uptake ability, p_3 is the insulin-dependent increase of the glucose uptake ability. The term $\gamma[B_1 - h]t$ represents the pancreatic insulin secretion after a meal intake at $t = 0$. According with [10] the parameters p_1 and γ are assumed to be zero in order to represent the dynamic of this disease. The parameter n is the first order decay rate for insulin in blood. The parameters to simulate the BeM *in silico* patients where obtain from [11].

TABLE I
BERGMAN MINIMAL MODEL PARAMETERS

Variable	BeM1	BeM2	BeM3	Units
p_1	0	0	0	$1/min$
p_2	0.02	0.0072	0.0142	$1/min$
p_3	$5.3x10^{-6}$	$2.16x10^{-6}$	$9.94x10^{-5}$	$ml/uUmin^2$
n	0.3	0.2465	0.2814	$1/min$

The relative degree r is defined as the order of the total time derivative of σ where the input variable u explicitly appears for the first time [6]. Thus, calculating

$$B_1^{(3)} = \phi_B(B,t) - p_3 B_1 u(t) \tag{2}$$

where

$$\begin{aligned}&\phi_B(B,t) = \\ &B_1[-p_1(p_1^2 + 3p_3 I_b) - p_3 I_b(p_2 + n) - p_3\gamma[(B_1 - h)^+ t]]\\ &+B_2[-p_1^2(1 + G_b) + p_1 p_2(2G_b - 1) + 2D(p_1 + p_2)]\\ &+B_3[-2p_3(p_1 + D)] + B_1 B_2[-(p_1 + p_2)^2 - 3p_3 I_b]\\ &+B_1 B_3[p_3(3p_1 + p_2 + n)] + B_1 B_2^2[-3(p_1 + p_2)]\\ &+B_2^2(p_1 G_b + D) + 3p_3 B_1 B_2 B_3 - B_1 B_2^3\\ &+\ddot{D} + (p_1 G_b + D)(p_1^2 + 2p_3 I_b)\end{aligned} \tag{3}$$

shows that the relative degree BeM is 3.

B. Sorensen Model

SoM is a physiological model with tissue and organs compartments, 8 for glucose and 7 for insulin. It was developed writing the mass balance equation accounting for blood flow, the exchange between the compartments and metabolic processes causing addition or removal of glucose, insulin and glucagon [12]. SoM is a non-linear model of relative degree five. The original model and the detailed explanation of parameters can be found in [12]. In order to get a form comparable with BeM, SoM could be rewritten as

$$\dot{S}_1 = \frac{1}{V_H^G}(-Q_H^G S_1 + Q_L^G S_2 + S_7 - F_{RBGU})$$

$$\dot{S}_2 = \frac{1}{V_L^G}(Q_A^G S_1 + Q_G^G S_6 - Q_L^G S_2 + f_{HGP} S_8 - f_{HGU} S_3)$$

$$\dot{S}_3 = \frac{1}{\tau_1}(2\tanh(0.55 S_4^N) - S_3)$$

$$\dot{S}_4 = \frac{1}{V_L^I}(Q_A^I S_5 + Q_G^I S_{10} - Q_L^I S_4 - F_{LIC})$$

$$\dot{S}_5 = \frac{1}{V_H^I}(Q_L^I S_4 - Q_H^I S_5 + S_9 + u(t))$$

$$\dot{S}_6 = \frac{Q_G^G}{V_G^G}(S_1 - S_6) + \frac{1}{V_G^G}(F_{MEAL} - R_{GGU})$$

$$\dot{S}_7 = Q_K^G \dot{G}_K + G_P^G \dot{G}_{PV} + Q_B^G \dot{G}_{BV}$$

$$\dot{S}_8 = \frac{1}{\tau_1}(1.21 - 1.14\tanh[1.66(S_4^N - 0.89)] - S_8)$$

$$\dot{S}_9 = Q_B^I \dot{I}_B + Q_K^I \dot{I}_K + Q_P^I \dot{I}_{PV}$$

$$\dot{S}_{10} = \frac{Q_G^I}{V_G^I}(S_5 - S_{10})$$

$$\dot{S}_{11} = \frac{1}{V_C}(F_{PCR} - F_{MCC} S_{11}^N)$$

The upper index N means the normal value of the corresponding variable.

To simulate the SoM *in silico* patients the parameters were obtained from [12], but the parameters that describe patient metabolic profile were significantly changed in order to have patients with the same physiology, but different disease characteristics (Table III).

III. HOSM Controller

Quasi Continuous High-Order Sliding-Mode Control (QC-HOSMC) [13], belongs to a family of Homogeneous High Order Controllers [14], these kind of controllers are robust with respect to fast unaccounted dynamics, parameter, and

TABLE II

SORENSEN MODEL STATE SPACE VARIABLES

Variable	Description	Units
S_1	Glucose in blood	mg/dl
S_2	Glucose in liver circulation	mg/dl
S_3	Hepatic glucose uptake	mg/dl
S_4	Insulin in liver circulation	mg/dl
S_5	Insulin in blood	mg/dl
S_6	Glucose in gut circulation	mg/dl
S_7	Glucose in kidney, periphery and brain circulation	mg/dl
S_8	Hepatic glucose production	mg/dl
S_9	Insulin in kidney, brain an periphery circulation	mU/l
S_{10}	Insulin in gut circulation	mU/l
S_{11}	Glucagon secretion	pg/ml

TABLE III

SOM *in silico* PATIENTS METABOLIC PORTRAIT

Variable	Patient 5	Patient 4	Patient 6	Units
F_{BGU}	70	70	70	mg/min
F_{RBGU}	10	5	15	mg/min
R_{GGU}	20	10	11	mg/min
F^B_{PGU}	35	20.5	11	mg/min
F^B_{HGP}	155	123.5	200	mg/min
F^B_{HGU}	20	10	10	mg/min

relative degree uncertainties [7]. QC-HOSMC was chosen in this work because it produces less chattering than other HOSMC, like Nested-HOSMC.

The main design parameter for an HOSMC is the system's relative degree, then QC-HOSMC u, was chosen according to BeM relative degree 3, which is the minimum. It is important to remark that all the simulations done in research used the same QC-HOSMC, with no special retuning for any model.

$$u = -\alpha[\ddot{\sigma} + \beta_2(|\dot{\sigma}| + \beta_1|\sigma|^{2/3})^{1/2}(\dot{\sigma} + \beta_1|\sigma|^{2/3} sign\sigma)]/[|\ddot{\sigma}| + \beta_2(|\dot{\sigma}| + \beta_1|\sigma|^{2/3})^{1/2}] \quad (4)$$

σ is defined as the difference between the glucose target and the glucose measurement. The first and second derivatives of σ are calculated using finite differences [15], with a sample step $\delta = 0.2m$, consistent with an amperometric glucose sensor sample time [16]. β_1, β_2 are the controller gains.

The glucose target is usually set to a fix level [9], but in order to minimize the insulin rate, in this work a dynamical profile is considered as glucose target. It is generated by the BeM of a nondiabetic person.

IV. SIMULATION EXPERIMENTS

A. Test of the controller on in silico patients

Simulations start at a blood glucose level of 350mg/dl, representing a postprandial event of a poorly controlled diabetic patient. The controller was tested with SoM and BeM, with no special retuning. For each model three different *in silico* patients are tested.

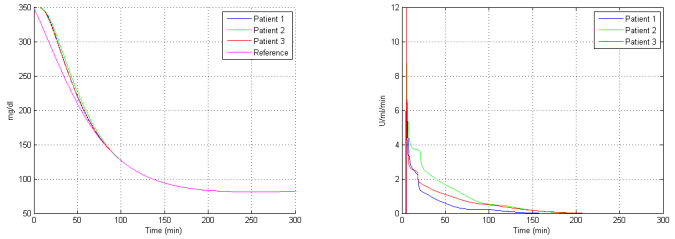

Fig. 1. (left) Glucose concentration for BeM , representing a postprandial event, controlled by a third order QC-HOSMC. There is no hypoglycemia, and normoglycemia is achieved in acceptable time ($\leq 100min$). Controller gains are the same for the three patients. (right) Insulin dose prescribed by the controller to achieve normoglycemia. Notice the different dose for each patient.

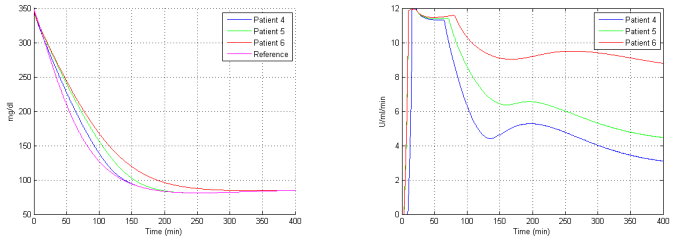

Fig. 2. (left) Glucose concentration for SoM, representing a postprandial event, controlled by the same third order QC-HOSMC, as BeM. SoM relative degree is 5, but its practical relative degree is 3. There is no hypoglycemia and normoglycemia is achieved in acceptable time ($\leq 100min$). (right) Insulin dose prescribed by the controller to achieve normoglycemia. Notice the different dose for each patient.

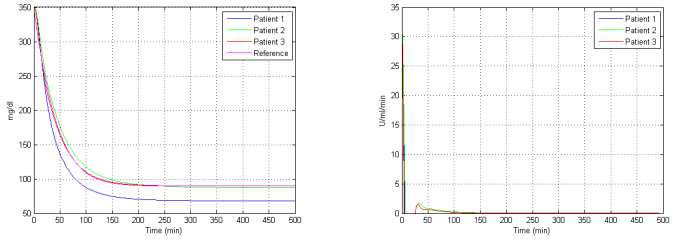

Fig. 3. (left) Glucose concentration for BeM, representing a postprandial event, controlled by PID controller. Patients 2 and 3 track the dynamic reference, but Patient 1 presents a hypoglycemia episode ($68mg/dl$. (right) Insulin dose prescribed by the PID controller. The first impulse infuse a great amount of insulin that can easily lead to a hypoglycemia episode, there is no maximal insulin infusion limit set in PID controller.

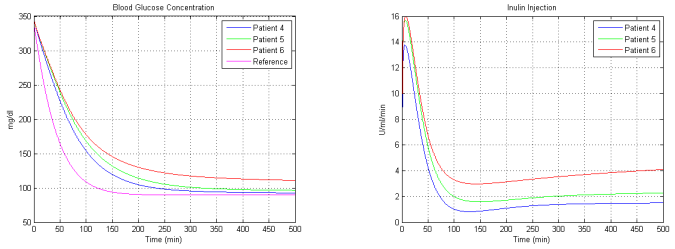

Fig. 4. (left) Glucose concentration for SoM, representing a postprandial event, controlled by PID controller. There is no hypoglycemic overshoot, but no Patient track the dynamic reference. (right) Insulin dose prescribed by the PID controller.

In fig. 1 (BeM) and fig. 2 (SoM), where QC-HOSMC

is used to control the glucose concentration, the dynamic target is reached, in aceptable time. The additional dynamics considered in SoM did not affect the performance of QC-HOSMC. It can be seen that in BeM after the basal level is achieved the model is at the stable equilibrium point; then no insulin infusion is needed to maintain the basal concentration. Since SoM considers the effect of basal insulin in glucose homeostasis, insulin infusion persist after the basal glucose concentration is reached. The QC-HOSMC automatically compensates for the additional dynamics of SoM.

In fig. 3 (BeM) and fig. 4 (SoM), where the PID controller was used, there was one hypoglycemia episode; the dynamic target was not reached for any of the *in silico* patients. In contrast to other researches PID controller has a better performance with the dynamic reference rather than when a fix reference is used. The results were compared to those of the PID controller the dynamic profile used as a glucose target minimizes the hypoglycemia risk but did not avoided hypoglycemia with the PID controller.

B. Test of the controllers on in vivo identified patient (Pa1)

As part of our ongoing clinical diabetes research the model parameters of of a patient (Pa1) were identified from *in vivo* assay using a continuos blood glucose instrument. Both controllers were tested for the specific BeM model of this patient.

Pa1 is a 65 years old diabetic patient with $BMI = 21.22kg/m^2$ using insulin therapy, and perform 1.5 hours aerobical exercise 5 times per week.

It is seen in table IV, that p_1 is not zero as it is consider for the *in silico* BeM patients. It means there is an additional dynamic not considered when the controllers were designed. It is important to remark that p_1 is the parameter associated with the insulin independent glucose uptake that is consider zero for BeM [10], but in SoM and Pa1, has an influence. In figure 5, it seen the insulin overdose prescribed by PID controller.

TABLE IV
IDENTIFIED PARAMETERS OF PA1

p_1	p_2	p_3	n
0.001	0.23	$6.3x10^{-4}$	0.16

V. CONCLUSIONS

Since the true glucose regulation model is incompletely defined know and approximate and uncertainty is always present, an ideal controller is not achievable. High-Order Sliding-Mode Control offers an optimal control solution because of insensitivity to changing dynamics, input conditions and system structure. BeM is the simplest model simulated; SoM is one of the most complete models, and, therefore, they are used to test the robustness of the HOSM controller. The controller has been tested via simulation for 6 *in silico* patients and one *in vivo* identified patient (Pa1). The results demonstrate that the additional dynamics considered in SoM and of Pa1 modeled as BeM did not affect the controller performance. The results were compared those of the PID controller. A dynamic profile used as glucose target, to minimize the risk of hypoglycemia, but it was not avoided in the PID controller.

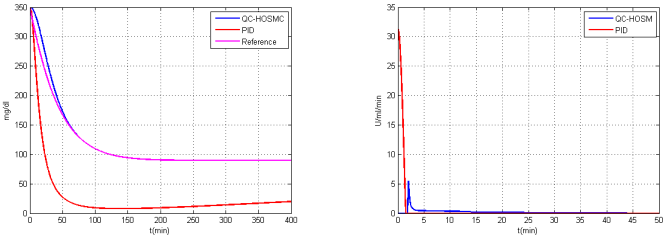

Fig. 5. (left) Glucose concentration for the *in vivo* identified patient Pa1, representing a postprandial event, controlled by QC-HOSMC and PID controller. There is no hypoglycemic overshoot for QC-HOSMC despise the additional dynamic introduced by $p_1 \neq 0$. (right) The insulin prescribed by both controllers is confined to the first 50 minutes. The dose prescribed by PID controller leads to hypoglycemia.

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