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Experimental Glucose Regulation with a High-Order Sliding-Mode Controller

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***Abstract*— Theoretically High-Order Sliding-Mode Controllers are well suited to perform closed loop glucose regulation because they are insensitive to parameter uncertainties and robust to unknown dynamics that may perturb the system. The implementation of the controller based on the concept of *practical relative degree* is presented. The controller was tested in Sprague-Dawley rats with steptozotocin induced diabetes. The tests demonstrated high efficacy and robustness of the controller.**

I. INTRODUCTION

Glucose is the main energy source for the body, and pancreatic β-cells are responsible for producing insulin to mediate the glucose uptake by most of the cells. If an autoimmune process destroys the β-cells the patient develops Type 1 Diabetes Mellitus (T1DM), and then insulin therapy is necessary [1]. There are also patients with Type 2 Diabetes Mellitus (T2DM) that respond better when they combine the insulin therapy with oral hypoglycemiants [2], [3].

Automatic insulin therapy for diabetic patients can improved their quality of life significantly [4]. There are several approaches reported in literature, such as Model Predictive Control [5], [6], PID [7], H_∞ [8], High-Order Sliding Mode Control (HOSMC) [9].

In particular the model predictive approach has been popularized recently by the models [10] and [11]. These models were created based on glucose tracer, and the parameters were fitted to represent a large population. This approach has had mixed results; under and overshoot are present due to inter and intra-patient variability.

Most of the models represent the glucose-insulin regulatory system as a non-linear system, with dynamic uncertainties. For example glucose consumption rate can vary during a stressful situation or when the patient performs aerobic exercise. The natural operating range of the system can vary from 40 to $500 mg/dl$ of blood glucose concentration. Meal ingestion can be considered a perturbation of the system. All these characteristics make the design of a controller to automate insulin infusion difficult.

The features of High-Order Sliding-Mode Controllers (HOSMC) make them suitable to automate the infusion. HOSMC are insensitive to parameter uncertainties [12]. It means that the same controller can be used to control any patient without special consideration of age or health status.

In [13], it was demonstrated that HOSMC are robust to unaccounted dynamics. Good performance is assured even when the model is incomplete.

This research adds, via two *in vivo* experiments, validity to the concept of practical relative degree described in [14], using a HOSMC to automate insulin infusion. Its design was based on the *practical relative degree* identified in two models, Bergman Minimal Model that is the simplest model [15], and Sorensen Model that is one of the models that considers more bio-dynamics involved in glucose-insulin regulation [16].

The *in vivo* experiments were done in two Sprague-Dawley female rats, with experimental diabetes induced by streptozotocin. It is important to note that the HOSMC is design based on human models, but it also works successfully for the rats because of its independence from parameter variations.

The study was approved by the Research Committee of the Cardiology Hospital of the Mexican Institute of Social Security and the research was conducted in accordance with the internationally accepted principles for laboratory animal use and care as found in the US guidelines (NIH publication #85-23, revised in 1985) and the Mexican guidelines (NOM-062-ZOO-1999).

II. HOSMC DESIGN

The main parameter to design an HOSMC (1), is the relative degree (r) of the system, because it determines the order of the controller [12].

$$u = -\alpha \Psi_{r-1,r}(\sigma, \dot{\sigma}, \ldots, \sigma^{r-1}) \tag{1}$$

where

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$$\Psi = \varphi_{i,r}/N_{i,r} \tag{2}$$

$$\varphi_{i,r} = \sigma^{(i)} + \beta_i N_{i-1,r}^{(r-i)/(r-i+1)} \tag{3}$$

$$N_{i,r} = |\sigma^{(i)}| + \beta_i N_{i-1,r}^{(r-i)/(r-i+1)} \tag{4}$$

$$\varphi_{0,r} = \sigma \tag{5}$$

$$N_{0,r} = |\sigma| \tag{6}$$

and σ is the error of the controller.

The relative degree (r) is only defined for linear systems, and in a simplistic way is described as the lowest order of the output derivative, which explicitly contains the control variable with a non-zero coefficient [17]. Then if system (7) is considered

$$\dot{x} = a(t,x) + b(t,x)u, \quad \sigma = \sigma(t,x) \tag{7}$$

where $x \in \mathbf{R}^n$, $u \in \mathbf{R}$ is the input, a, b and $\sigma : \mathbf{R}^{n+1} \to \mathbf{R}$ are unknown smooth functions, the order of the space (n) can be also uncertain. The output σ is measured in real time.

The relative degree (r) of the system will be determined by

$$\sigma^{(r)} = h(t,x) + g(t,x)u \tag{8}$$

where $h(t,x) = \sigma^{(r_p)}|_{v=0}, g(t,x) = \frac{\partial}{\partial v}\sigma^{(r_p)}$ are some unknown smooth functions, which can be expressed in the terms of Lie derivatives.

This number (r) is usually assumed known, and is actually the main predefined design parameter. Unfortunately its value is not always clear, because it depends on the model. Possible unaccounted-for sensors and actuators can significantly increase the relative degree, while small additive perturbations can easily lead to its lowering or even disappearance. Recent results [18], [13], [19] show that fast stable sensors and actuators, as well as small additive disturbances can be ignored causing only small degradation of the system performance. Since some parts of the system can be deliberately included in these three categories, the relative degree (RD) itself becomes a design parameter and can be varied.

It is not always easy to identify the output and input singular perturbations and negligible disturbances to simplify the model. In the case considered the human glucose-insulin regulatory system is described by at least six well-known and very different models [10], [20], [15], [16], [21] and [22]. Their relative degrees vary from 3 to 5, and no complicated model can be represented as a disturbance of a simpler case of the above. In fact, probably each model has its own discrepancies, and is not exact. A controller is needed, which would be simultaneously effective at least for the main models. The approach is to detect a Practical Relative Degree (PRD). The PRD is the lowest order of the output derivative which is explicitly affected by input step functions. A system can have a few PRDs, and each one can be used for control.

III. Identification of the Practical Relative Degree of the Glucose-Insulin Regulatory System

In order to identify the least PRD, a Heaviside step function $u = H(t - t_H)$ is applied to equation (8):

$$\sigma^{(r)} = h(t,x) + g(t,x)H(t - t_H) \tag{9}$$

If a discontinuity is observed in $\sigma^{(r)}$ at $t = t_H$, and consequently a slope change appears in $\sigma^{(r-1)}$, with the increment of $\sigma^{(r)}$ always having the same sign, then the PRD of the system is identified as r_p (see Fig. III).

The PRD identification of the glucose-insulin regulatory system was made in Bergman Minimal Model [15] and Sorensen Model [16], both models and their parameters can be seen in [14]. A Heaviside step function, $u = H(t - 15)$ was applied to both models. The robust third-order differentiator [23] was used for calculating the derivatives of the systems' response.

It is clear from Fig. 1 that the practical relative degree of Bergman Model is three, which concurs with the theoretical relative degree. One can see from Fig. 2 that for SoM the jump appears in the third derivative at $t = 15m$, and the second derivative has an inflection change. Thus, both models have the same practical relative degree $r_p = 3$, and the same controller can be applied to both models.

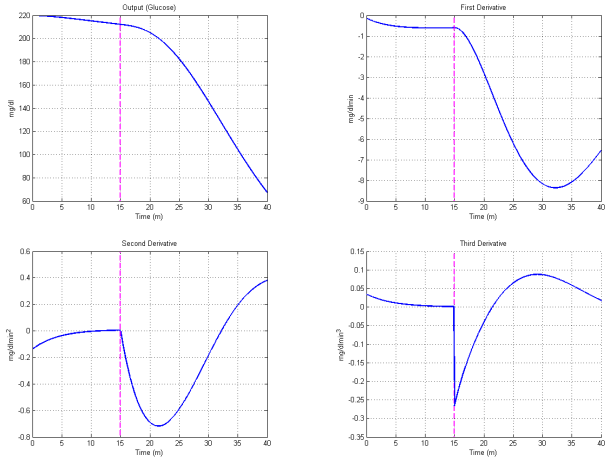

Fig. 1. Bergman Model output and its derivatives, response to a step function $u = H(t - 15)$. A jump appears in the third derivative, an abrupt change of slope is seen in the second derivative. The model's practical relative degree is clearly 3.

Based on the practical relative degree of both models the order of the controller for this system is three, and it has the form (10).

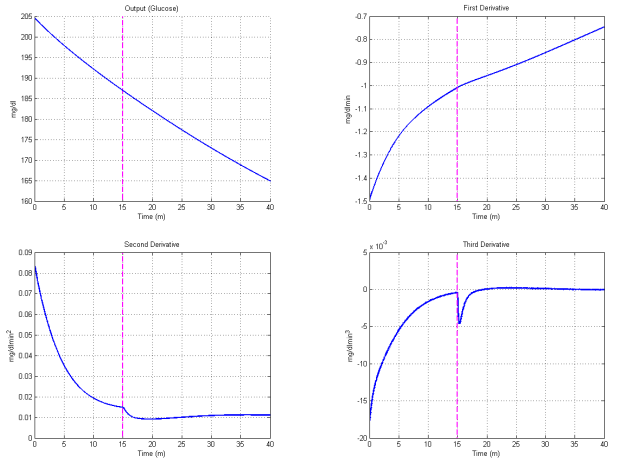

Fig. 2. Sorensen Model output and its derivatives, response to the step function $u = H(t-15)$. A jump is first seen in the third derivative, and an abrupt change of slope in the second. The practical relative degree is 3.

$$u = -\alpha[\ddot{\sigma} + \beta_2(|\dot{\sigma}| + \beta_1|\sigma|^{2/3})^{-1/2}(\dot{\sigma} + \beta_1|\sigma|^{2/3} sign\sigma)]/[|\ddot{\sigma}| + \beta_2(|\dot{\sigma}| + \beta_1|\sigma|^{2/3})^{1/2}] \quad (10)$$

IV. *In vivo* EXPERIMENT

An experimental set was designed to test the controller using the Continuous Glucose Monitor (CGM) of Medtronic (Fridley, Minnesota) to measure glucose concentration, its report rate is 5 min. The actuator was the insulin pump Medtronic 507 modified to be driven by the QC-HOSMC (10) implemented via MatLab. The communication interface was a National Instrument Card NI USB-6009. Fast-acting Aspart (Novo Norkisk, Denmark) insulin was used.

A. Experimental Diabetes

Diabetes Mellitus is the name given to a multiple group of disorders with different etiologies, characterized by an abnormal blood glucose concentration produced by impaired insulin production. Experimental Diabetes allows the analysis of the biochemical, hormonal and morphological events that take place not only during the induction of a diabetic state but also after it has taken place and during its evolution to a severe insulin deficiency or even death [1].

Experimental Diabetes can be induced surgically, by the removal of the β-cell mass or even the pancreatectomy or the injury of the ventromedial hypothalamus. It can also be induced by feeding high-fat and high-sugar diets. Chemically it can be induced by the injection of alloxan or streptozotocin. They have a cytotoxic effect on the β-cells, and leave unaffected the rest of the pancreatic cells. The effect of alloxan is reversible.

In this research diabetes was induce in two female Sprague Dawley rats by streptozotocin. If after 48 hours the streptozotocin injection the rat blood glucose concentration is higher than $200mg/dl$, then it is considered diabetic. Experimental Diabetes is comparable to Type 1 Diabetes Mellitus [1].

B. Fast-Acting Insulin

Insulin was isolated by Banting and Best in 1921, since then, several advances have been made in purification methods. The first efforts were directed to prolong the effect of the insulin to avoid the frequent patient injections. There are insulins that are slow-acting to maintain the basal concentration of insulin in blood.

The insulin used for this study is Aspart (NovoRapid) that is a fast-acting insulin analogue. It absorbs quickly into bloodstream to mimic the natural pancreatic fast secretion of insulin after meal. It is produced by recombinant DNA technology.

C. Results

Experimental Diabetes was induced to two female Sprague Dawley rats weighing 348gr and 356gr. They were maintained on a $12/12$ hours dark/light cycle with water and food *ad libitum*. Diabetes was induced by a intra-peritoneal injection of $50mg/kg$ of streptozotocin in 1 ml of acetate buffer 0.1M. pH 4.3.

*1) **Experiment 1 (Dynamic reference)**:* In this experiment a dynamic reference was used to control also the decreasing rate of the glucose concentration. The initial glucose was $599mg/dl$. The glucose concentration follows the given reference as it can be seen in figure 3. The gains of the controller were the same that where previoulsy used in [14], in a simulation study.

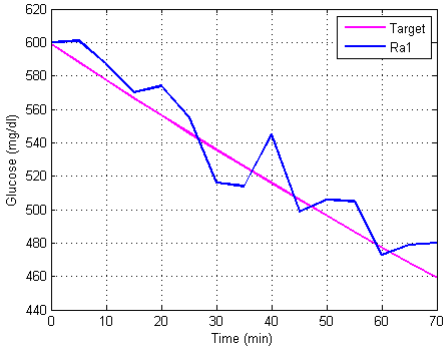

Fig. 3. **Experiment 1.** Glucose concentration of the rat with experimental diabetes. The glucose was regulated by the infusion of Aspart Insulin. The insulin dose was prescribed by the controller (10) based on the identified practical relative degree $r_p = 3$. It can be seen that glucose follows the given reference.

*2) **Experiment 2 (Fixed reference** ($80mg/dl$)**)**:* On the day of the experiment its initial glucose concentration was $312mg/dl$. The insulin dose was prescribed by the controller (10). It can be seen in Fig. 4 that the basal (normal) level of $80mg/dl$ was achieved in 55min, with no overshoot. It is very important to note that the gains of the controller (10) used in the *in vivo* experiments are the same as for the simulations [14], which shows the insensibility of the controller with respect to parameter uncertainties.

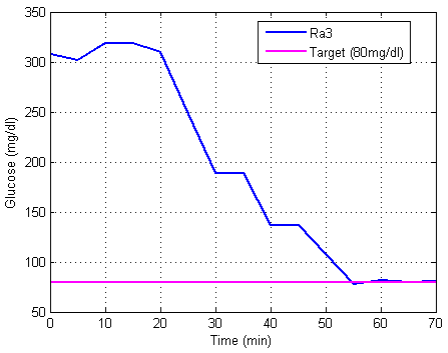

Fig. 4. **Experiment 2.** Glucose concentration of the rat with experimental diabetes. The glucose was regulated by the infusion of Aspart Insulin. The insulin dose was prescribed by the controller (10) based on the identified practical relative degree $r_p = 3$. It can be seen that glucose reaches the basal level with no insulin overshoot.

V. Conclusions

The superiority of High-Order Sliding-Mode Control (HOSMC) to automate insulin infusion is based on its independence from any model or its parameters. It is also robust with respect to unaccounted metabolic dynamics which often occur, particularly in children. This means that, the designed controller can be used for any patient with insulin therapy in spite of particular parameters due to age or body mass for example. The design of this controller was based on two classical models, Bergman Minimal Model, that is the simplest model, and Sorensen that is one of the most complete. The controller was tested *in vivo* with two rats with experimental diabetes, and there was no need to identify the particular parameters of the animal model, to tune the gains of the controller. The *in vivo* test demonstrated high efficacy and robustness of the controller. Further safety testing is planned prior use in humans subjects.

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