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Blood glucose regulation in diabetics. A flatness based nonlinear control simulation study.

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Abstract. Flat systems are a generalization of linear systems, but the techniques used for controlling flat systems are much different than many of the existing techniques for linear systems. In this paper we present the flatness-based control of blood glucose regulation in human system. A non-linear model, the Bergman Minimal Model, is used to represent the dynamics of blood regulation in humans, and because of the flatness property, the system variables can be expressed as functions of the flat output and their time derivatives and a control law is developed.

1. Introduction

In healthy people, blood glucose level is regulated by segregation of insulin in pancreas beta cells. Insulin is a hormone that activates glucose uptake in insulin sensitive cells. In Diabetes Mellitus Type I or advanced stages of Type II, the pancreas cannot segregate enough insulin to maintain blood glucose in normal level and this situation leads to hyperglycaemia, a condition given when blood glucose concentration overcomes 135 mg/dl. Diabetes Mellitus (DM) has been defined by World Health Organization (WHO) [1] as a chronic disease, which occurs when the pancreas does not produce enough insulin, or when the body cannot effectively use the insulin it produces. This leads to an increased concentration of glucose in the blood (hyperglycaemia).

Type 1 diabetes (T1DM), previously known as insulin-dependent or childhood-onset diabetes, is characterized by a lack of insulin production. Type 2 diabetes, formerly called non-insulin-dependent or adult-onset diabetes, is caused by the body's ineffective use of insulin. It often results from excess body weight and physical inactivity. Gestational diabetes is hyperglycaemia that is first recognized during pregnancy.

Traditional treatment consists in the administration of several doses of insulin day by day, in order to keep a normal blood glucose level. This therapeutic treatment, cannot avoid undetected peaks of blood

glucose. Also, the risk of hypoglycaemia, a situation where the patient can faint vanish or even go into a coma, is always present. Neither can this treatment prevent the progressive damage to the artery walls due to the effects of undetected peaks of blood glucose leading to ulterior complications such as coronary diseases, retinopathy, etc. The results of the Diabetes Control and Complications Trial (DCCT) [2] solidified the importance of continuous infusion of exogenous insulin based on mechanical pumps to the prevention of micro vascular complications of diabetes as the most effective tool to prevent complications in insulin-dependent Diabetes Mellitus [3].
Drawbacks of this approach are the skills required to operate the pump effectively and the rigid lifestyle that diabetic patients have to follow. These problems have shown the need of new developments, transparent to the user. A mechanical insulin pump, a glucose sensor and an algorithm of control conform a useful tool to sort the mentioned problems. In this work a model based control algorithm that can be integrated into an intelligent system that no requires patient doesn´t attention is presented.

2. Flatness of dynamical systems

A dynamical system is said to be flat if it is possible to find a set of variables, called the flat outputs, such that the system is (non-differentially) algebraic over the differential field generated by the set of flat outputs. Flatness was defined by Fliess et al. [4] and the word *flat* is used due to the fact that the linearizing outputs play an analogous roll as the plane coordinates in the context of the Frobenius theorem in differential geometry [5]. If the system has states $x \in \mathbb{R}^n$ and inputs $u \in \mathbb{R}^m$, then the system is flat if it is possible to find outputs $y \in \mathbb{R}^m$, $r = (r_1, \dots, r_m)^T \in \mathbb{N}^m$, of the form $y = h(x, u, \dot{u}, \dots, u^{(r)})$ such that

$$x = \varphi\left(y, \dot{y}, \dots, y^{(r)}\right) \quad (1)$$
$$u = \alpha\left(y, \dot{y}, \dots, y^{(r+1)}\right) \quad (2)$$

Flat systems are a generalization of linear systems in the sense that all linear, controllable systems are flat, but the techniques used for controlling flat systems are much different than many of the existing techniques for linear systems. Flatness is particularly well tuned for allowing one to solve the inverse dynamics problems and one builds off of that fundamental solution in using the structure of flatness to solve more general control problems. Consider a nonlinear system

$$\dot{x} = f(x, u) \quad (3)$$

where $x \epsilon R^n$ is a vector of state variables, and $u \epsilon R^m$ the input, $f(0,0) = 0$, and the rank of $\partial f / \partial u$ is equal to *m*. The system (1) is differentially (differentially independent, means that they are not related by any differential equation) flat if there exist a number m of real, analytic, scalar functions that depend on *x*, *u* and a finite number r of derivatives of *u*,

$$y_i = h\left(x, u, \dots u^{(r)}\right) \quad i = 1, \dots, m \quad (4)$$

so that the inverse of system (1), taking *u* as input and $y = (y_1, \dots, y_m)$ as output, does not have dynamics. This is, the state variables *x* and the input variables *u* can be expressed as A (n-dimensional) and B (m-dimensional) real and analytic functions of *y*

$$x = A\left(y, \dot{y}, \ddot{y}, \dots, y^{(r)}\right) \quad (5)$$
$$u = B\left(y, \dot{y}, \ddot{y}, \dots, y^{(r+1)}\right) \quad (6)$$

where the output *y* is called the flat or linearized output and r is an integer. The flat outputs have the following properties:

a. The components of *y* can be calculated from the state *x*, the inputs *u*, and a finite number of time derivatives of the later.
b. The components of *y* are differentially independent, i.e. they are not related by any differential equation.
c. The state variables *x*, the input variables *u*, and the time derivatives and functions of them can be calculated from the flat outputs *y* and a finite number of their time derivatives.

In [6] the concept of an affine flat input to a nonlinear system with a given output function is introduced. This approach can be seen as dual to the search for a flat output of a control system with a given input.
Definition.
1. The control system is said to be flat if there exists an output y = λ(x) such that the resulting SISO system

$$\begin{cases} \dot{x} = f(x) + g(x)u \\ y = \lambda(x) \end{cases} \tag{7}$$

has relative degree *n*. In that case, *y* is called a flat output of (3) defined by the output function *λ(x)*.
2. The observed system (3) is said to be flat if there exists an input vector field γ (x) such that the resulting SISO system

$$\begin{cases} \dot{x} = f(x) + \gamma(x)u \\ y = h(x) \end{cases} \tag{8}$$

has relative degree n. In that case u is called a flat input for (3) with input vector field $\gamma(x)$. Dynamics of the glucose/insulin system is represented by Bergman´s Minimal Model (BMM), a mathematical model [7] used to determinate the sensitivity of insulin action and metabolism of glucose in Intravenous Glucose Tolerance Test (IVGTT). The Bergman Minimal Model is given by the following equations

$$\dot{x_1} = -P_1 x_1 - x_2(x_1 + G_b) + D(t), \tag{9}$$
$$\dot{x_2} = -P_2 x_2 + P_3 x_3, \tag{10}$$
$$\dot{x_3} = -n(x_3 + I_b) + \frac{u(t)}{V} \tag{11}$$

Details of the model are:
x_1 = blood glucose concentration over basal value.
x_2 = remote compartment.
x_3 = blood insulin concentration over basal value.
G_b = basal blood glucose concentration.
I_b = basal blood insulin concentration.
u(t) = infusion of external insulin.
n = transference rate.
t = time.
V = plasmatic volume.
P_1=1e^{-2} min^{-1}, P_2=3.33e^{-2} mU.L^{-1}min^{-2}, and P_3 =1.$^{33e-5}$min^{-1} are patient´s dependent parameters [13].
D(t) = Perturbation due to meals.

. A flat output for the system is $y = x_1$. Substituting the flat output in (9), if *D(t)* is considered a unknown perturbation, results

$$\dot{y} = -P_1 y - x_2(y + G_b), \tag{12}$$

now, it is possible to obtain $x_2 = \frac{-P_1 y - \dot{y}}{y + G_b}$ and $\dot{x_2} = -P_2 \frac{-P_1 y - \dot{y}}{y + G_b} + P_3 x_3$. In the same way

$$x_3 = \frac{1}{P_3}\left\{\frac{(P_1\dot{y} - \ddot{y})(y + G_b) - (P_1 y - \dot{y})\dot{y}}{(y + G_b)^2} + P_2 \frac{-P_1 y - \dot{y}}{y + G_b}\right\}, \tag{13}$$

$$\dot{x}_3 = \frac{-n}{P_3}\frac{(P_1\dot{y} - \ddot{y})}{(y + G_b)} + \frac{-n}{P_3}\frac{(P_1 y - \dot{y})\dot{y}}{(y + G_b)^2} - \frac{nP_2(P_1 y - \dot{y})}{y + G_b} - nI_b + \frac{1}{V}u(t) \tag{14}$$

Isolating the control $u(t)$ from (14) , the endogenous nonlinear control u_e (15) is obtained. A supervisor control u_s (16) in closed loop is added to u_e in order to improve robustness.

$$u_e = \frac{1}{V}\left(f(y, \dot{y}, \ddot{y})\right) \tag{15}$$

$$u_s = \frac{abs(5 * G - G_b)}{5 * G - G_b} \tag{16}$$

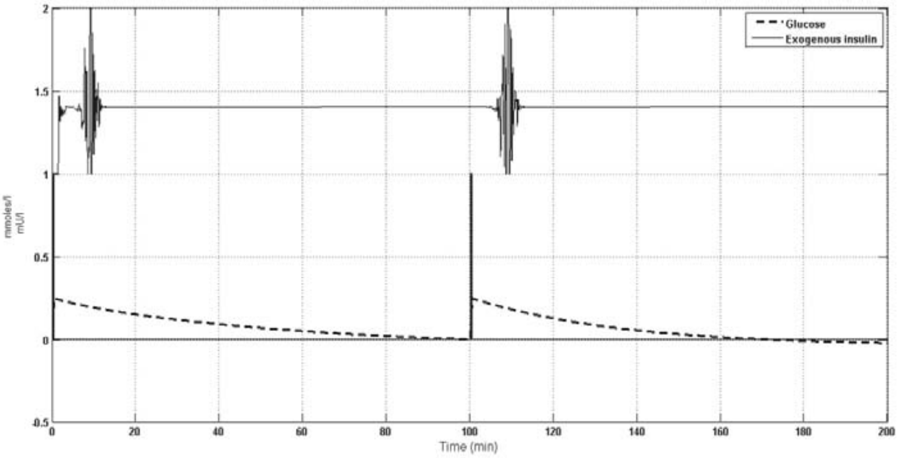

Figure 1: Blood glucose, infused insulin and perturbations at 0 and 100 minutes.

3. Results

Simulations were performed over a Matlab Simulink model. In Figure 1, a disturbance $D = 1.5 * exp(-0.05 * t)$, is added to (9) in t=0 min. and t= 100 min. to simulate a postprandial period of 200 minutes. In figure 2, similar experiences were performed over a period of 1400 minutes, approximately

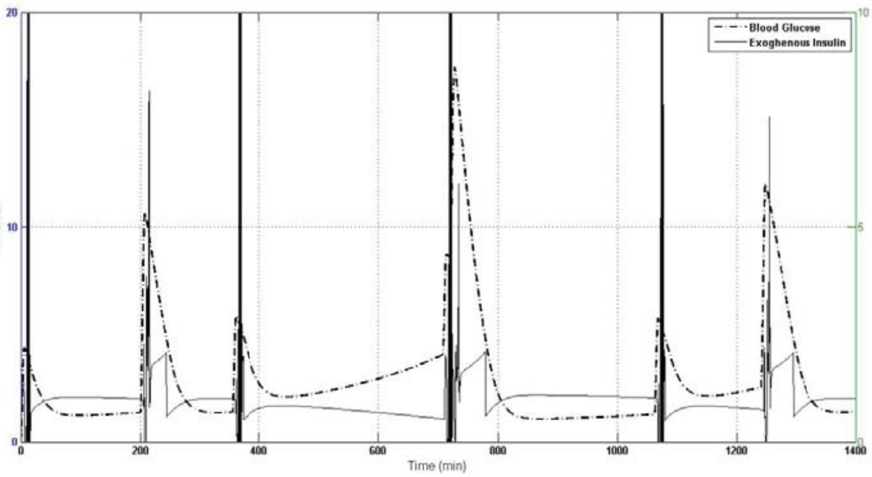

Figure 2: Blood glucose and infused insulin.

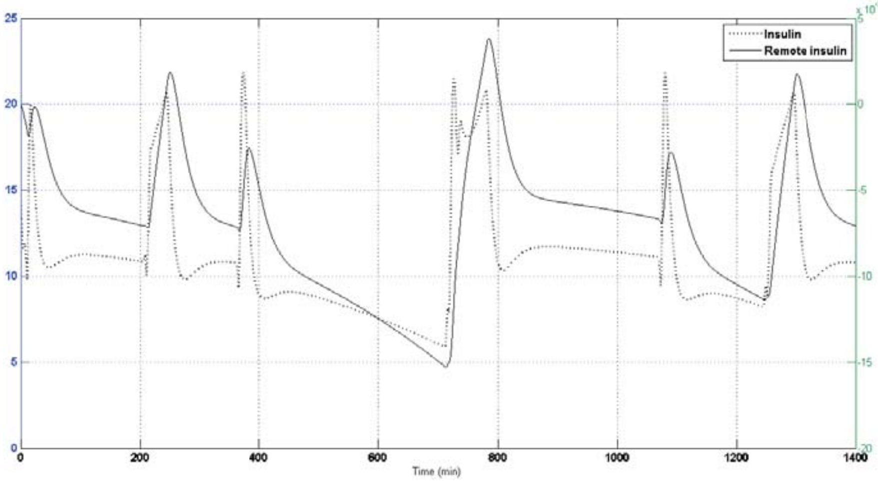

Figure 3: Blood insulin and instertitial insulin.

one day with several ingestions of carbohydrates. Two important results have been obtained:

a. Hypoglycemia, a mayor risk in glucose control, is not present. Figure 2 shows the carbohydrates ingestion, blood glucose along a day. Figure 3 show blood insulin and interstitial insulin concentration respectively. It is important to note that most of the time, interstitial insulin is below zero. This is a important indicator of lack of hypoglycemia. In others nonlinear control, for instance, based on feedback linearization (see [6],[7],[8],[9]) blood glucose is regulated but the risk of over insulin in blood is always present.

b. State observers are not need. In space state control techniques, it is assumed that all states are available. But blood glucose is the only measurable output and it is necessary to develop state observers to estimate the value of the rest of the state variables [10]. For this purpose, nonlinear observers must be developed. This can be avoided by the use of flatness control and taken blood glucose as the flat output.

As a future work, the same strategy must be adaptive and include a parameters estimation algorithm.

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