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Regulation of glucose insulin metabolism using feedback linearization

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ABSTRACT

Diabetes is a chronic disease that occurs when the pancreas does not produce enough insulin, or when the body is not able to effectively use the insulin it produces. Insulin is a hormone that regulates blood sugar levels, this regulation is done by the pancreas. When this organ is damaged, the patient will have to regulate its blood sugar level themselves. This task is really painful and we will have to resort to an artificial pancreas or we will have to design a regulator which stabilizes blood sugar at its basal value. Several controls have been developed and the objective of this paper is to use input output linearization technique to regulate blood glucose levels by injecting an adequate quantity of insulin. The glucose insulin metabolism is a non-linear system whose input is the quantity of insulin to be injected and the output is the blood glucose measured in the blood. Simulations examples are given to demonstrate the usefulness of the command developed.

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1. INTRODUCTION

One of the major diseases in the Western world today is diabetes. Several million people suffer from the disease and the number is increasing. Culture is mainly due to the lifestyle in the western world, with lots of unhealthy food. Because it's a big problem, many researchers are trying to find ways to diagnose and treat disease. One approach is to design a mathematical model describing the glucose-insulin system. Diabetes is a malfunction of this system. These mathematical models can be used to diagnose, but also to create simulators to test various types of treatment. One of the mathematical models describing the glucose-insulin system with a small number of parameters is called minimal model of Bergman, it was introduced in the eighties [1]. This is the model that will be described and analyzed in this paper. To regulate the glucose level, Menani *et al*. [2] use the positive sliding mode control and Menani [3] the intelligent control is used. Ali and Padhi [4], the optimal control is used to regulate the blood glucose. Kaveh and Shtessel [5] the high order sliding mode control is applied. Another technique that means the predictive control is used by the authors in [6], [7]. The fuzzy logixc which is known that it approximate nonlinear function is used in [8] to blood glucose regulation. Chui [9], an artificial pancreas is usedand an algorithm has been developped. Seron *et al*. [10] tried to do a between several model predictive control in realistic and stochastique environment for patients of type 1 diabets. Another robust technique that means sliding mode control techniques is used in [11]. Campos-Delgado *et al*. [12], the theory of knowledge-based controllers is investigated. Meriem *et al*. [13] use the well-known backstepping technique to regulate the glucose at it's basal value. This regulation is done by injecting an amount of insuling that has been calculated using the previous technique. The insulin glucose metabolism can be regulated using the simple

adaptive control with the condition that this system is almost strictly positive real (ASPR) [14]. Karima and Mourad [15] adopts the principle of saturation that means the amounts of insulin do not take a high value. The results shows that their control laws give a good results and one see that the glucose is regulated within an acceptable time. The fuzzy logic using the mamdani concept is used in [16] where the controller in applied for three patients and the authors claim that the controller give a good result in the sense that the glucose in regulated at a natural values.

The main objective of this study is the realization of an artificial pancreas capable of providing the appropriate dose of insiline independently of the patient, so the latter can lead his life in an adequate way. This artificial pancreas is equipped with alarms in case of hyperglycemia or hypoglycemia. The description of the glucose insulin metabolism is described in [17]. Lewis *et al*. [18] gives two regulation method called the direct and indirect actions. The proportional-integral-derivative (PID) control [19] is used in glucose insulin regulation where the proportional, integral and derivative are changed in order to force the glucose concentration to be in the acceptable values. Rihan and Udhayakumar [20] uses the fractional order with time delay to regulate the glucose, the fraction order is a concept where one suppose thet the order of the system is fractional where the system order is fractional which is a more general notion than a system with integer order.

The paper is organized as follows. In section 2, one give the input output linearization. The Bergman minimal model is given in section 3. In section 4 one apply the input output (I/O) linearization to regulate the glucose level. Simulations results are given in section 5 and we end this paper with a conclusion in section 6.

2. INPUT OUTPUT LINEARIZATION

Input-output linearization is a recent control technique, it consists of linearizing a non-linear system using a state or output feedback and using a new command. This technique makes it possible to apply well-mknown linear controls to complicated and non-linear systems. Let's take the non-linear system [21].

$$\begin{cases} \dot{x} = f(x + g(x)u \\ y = h(x) \end{cases} \quad (1)$$

Where $x \in R^n$ is the state, $u \in R, y \in R$ are the input output, and suppose that the relative degree of the system is n that means the input appears in the nth derivative of the output, i.e.,

$$\dot{y} = \frac{dh(x)}{dt} = \frac{\partial h(x)}{\partial x}\frac{dx}{dt} = \frac{\partial h(x)}{\partial x}f(x) + \frac{\partial h(x)}{\partial x}g(x)u \quad (2)$$

And using the lie derivative, this expression is given by:

$$\dot{y} = L_f h(x) + L_g h(x)u \text{ with } L_g h(x) = 0 \quad (3)$$

The second derivative is given by:

$$\ddot{y} = \frac{d(L_f h(x))}{dt} = \frac{\partial (L_f h(x))}{\partial x}\frac{dx}{dt} = \frac{\partial (L_f h(x))}{\partial x}f(x) + \frac{\partial (L_f h(x))}{\partial x}g(x)u$$

Which can be written as:

$$\ddot{y} = L_f(L_f h(x)) + L_g(L_f h(x))u$$

That means:

$$\ddot{y} = L_f^2(h(x)) \text{ with } L_g(L_f h(x)) = 0$$

The (n^{th}-1) derivative is given by:

$$y^{(n-1)} = L_f^{n-1}(h(x)) \text{ with } L_g(L_f^{(n-2)}h(x)) = 0$$

And the nth derivative is given by:

$$y^{(n)} = L_f^n(h(x)) \text{ with } L_g(L_f^{(n-1)}h(x)) \neq 0$$

That means:

$$\begin{cases} y^{(i)} = L_f^i(h(x)); L_g(L_f^{(i-1)}h(x)) = 0; i = 1..n-1 \\ y^{(n)} = L_f^n(h(x)) + L_g(L_f^{(n-1)}h(x))u \end{cases} \quad (4)$$

So, if one take the transformation $\xi_i = y^{(i)}$, one have:

$$\begin{cases} \xi_1 = y \\ \dot{\xi}_1 = \dot{y} = \xi_2 \\ \dot{\xi}_2 = \ddot{y} = \xi_3 \\ . \\ \dot{\xi}_{n-1} = y^{(n-1)} = \xi_n \\ \dot{\xi}_n = y^{(n)} = L_f^n(h(x)) + L_g(L_f^{(n-1)}h(x))u = \alpha(x) + \beta(x)u = v \end{cases}$$

That means, the input output linearization is given by:

$$\begin{bmatrix} \dot{\xi}_1 \\ \dot{\xi}_2 \\ . \\ \dot{\xi}_{n-1} \\ \dot{\xi}_n \end{bmatrix} = \begin{bmatrix} 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ . & . & . & . & . \\ 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} \xi_1 \\ \xi_2 \\ . \\ \xi_{n-1} \\ \xi_n \end{bmatrix} + \begin{bmatrix} 0 \\ 0 \\ . \\ 0 \\ 1 \end{bmatrix} v; \quad y = \xi_1$$

In linear form, it is given by:

$$\dot{\xi} = A\xi + Bv; y = \xi_1 \quad (5)$$

Where:

$$\xi = [\xi_1 \quad \xi_1 \quad . \quad . \quad \xi_n]^T$$

It is well know that this form is suitable for regulation and tracking using state feedback. once the command v is synthesized, the actual command u is given by:

$$u = \frac{v-\alpha(x)}{\beta(x)} \text{ with } \beta(x) \neq 0 \quad (6)$$

In this section, one apply the I/O linearization to regulate the glucose for an illness person. This is achieved by searching the amount of insulin to be injected in order to regulate the glucose at it's basal value that means the normal value and one begin by the modelisation of the glucose insulin metabolism. Zakeri and Ozgoli [22], the authors used a state feedback controller to regulate the glucose at it's basal valur, our method is more efficient in terms of response time.

3. BERGMAN MINIMAL MODEL

There are many model of the glucose insulin system, the simple one is called minimal model of Bergman.

a. Mechanisms of blood glucose regulation

The regulation of blood sugar is given by the pancreas and the liver. The pancreas secretes two hormones:

- Glucagon is secreted by Alpha_cells
- Insulin is secreted by Beta_cells

The liver can, depending on the circumstances:

- Store glucose as glycogen when insulin levels increase
- Release glycogen in the form of glucose under the action of glucagon.

The Figure 1 [23] describe the metabolism of the glusose insulin regulation.

b. Description of the Bergman minimal model

The Bergman, minimal model is described by (7)-(9) [1].

$$\dot{G}(t) = -p_1(G(t) - G_b) - X(t)G(t) + D(t) \quad (7)$$

$$\dot{X(t)} = -p_2X(t) + p_3(I(t) - I_b) \quad (8)$$

$$\dot{I}(t) = -n(I(t) - I_b) + \gamma[G(t) - h]^+t + u(t) \quad (9)$$

$D(t)$ is a disturbance that can be modeled by a decreasing exponential function of the following form: $D(t) = A\,exp(-Bt), B > 0$, which represents

1. The meals Fisher standards [24]. $B = 0.05$
2. The effects of exercise [25]. $B = 0.11$

The description of the parameters and terms in (7) to (9) are given in the Table 1.

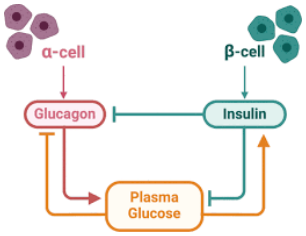

Figure 1. The know model which describe the glucose_insulin metabolism is given by R. N. Bergman

This model can be used to simulate the glucose-insulin system for a type 1 diabetic on treatment. It can be used to test the predictive controllers models [26] and as a tool in the search for an artificial pancreas. This model also adopts the problem with the minimal model of glucose.

This paragraph summarized the Bergman model, and we see that it is a nonlinear system and complex, and the feedback linearization is the robust tool to deal with such systems. Several regulation methods have been used, the only obstacle is that the Bergman model is not universal and other models exist and continue to be developed and therefore the perspective is to continue working to develop a model of insulin glucose as close as possible to the real patient.

Table 1. Parameters description and terms of the Bergman minimal model

Parameter	Unit	Description
t	min	The time
G(t)	mg/dl	concentration of glucose in the blood
G_b	mg/dl	steady state concentration of glucose in the blood.
X(t)	1/min	the effect of active insulin.
I(t)	µU/ml	The concentration of insulin in the blood.
I_b	µU/ml	steady state concentration of insulin in the blood.
I_2 (t)	µU/ml	active concentration of insulin
p_1	1/min	independent glucose disposal Speed insulin.
p_2	1/min	release rate of active insulin.
p_3	(min^{-2}) $(\mu U/ml)^{-1}$	The increase in the ability to absorb caused by insulin
n	1/min	rate of prime insulin decrease in plasma
γ	$(\mu U/ml)\ min^{-2}$ $(mg/dl)^{-1}$	release rate of insulin from pancreatic β-cells after glucose injection to the glucose concentration above the threshold
h	mg/dl	glucose threshold value which the pancreatic β - cells release insulin
u(t)	µU/ml	defines the injection of insulin and replaces the normal regulation of insulin of the body

4. GLUCOSE REGULATION USING INPUT-OUTPUT LINEARIZATION

In order to control blood glucose, we need to know the amount of insulin to inject, this operation is only possible if we know the model of glucose-insulin metabolism. Several models are known, ranging from the simplest to the most complicated. The most widespread is Bergman's model. The Bergman minimal model is given by:

$$\begin{cases} \dot{G}(t) = -p_1(G(t) - G_b) - X(t)G(t) + D(t) \\ \dot{X}(t) = -pX(t) + p_3(I(t) - I_b) \\ \dot{I}(t) = -p_4(I(t) - I_{b1}) + u(t) \end{cases} \quad (10)$$

Let's take:

$$x_1 = G(t); x_2 = X(t); x_3 = I(t) \quad (11)$$

So,

$$\begin{cases} \dot{x}_1(t) = -p_1(x_1 - G_b) - x_2x_1 + D(t) \\ \dot{x}_2(t) = -p\ _2x_2 + p_3(x_3 - I_b) \\ \dot{x}_3(t) = -p_4(x_3 - I_{b1}) + u(t) \end{cases} \quad (12)$$

The error is given by:

$$e = G(t) - G_b = x_1 - G_b \quad (13)$$

It's derivative is given by:

$$\dot{e} = \dot{x}_1 - \dot{G}_b = \dot{x}_1 = -p_1(x_1 - G_b) - x_2x_1 + D(t)$$

The second derivative is given by:

$$\ddot{e} = -p_1\dot{x}_1 - \dot{x}_2x_1 - x_2\dot{x}_1 + \dot{D}(t) = -(p_1 + x_2)\dot{x}_1 - \dot{x}_2x_1 + \dot{D}(t)$$

$$\ddot{e} = -(p_1 + x_2)[-p_1(x_1 - G_b) - x_2x_1 + D(t)] - [-px_2 + p_3(x_3 - I_b)]x_1 + \dot{D}(t)$$

The third derivative is given by:

$$\dddot{e} = -\dot{x}_2\left[-p_1(x_1 - G_b) - x_2x_1 + D(t)\right] - (p_1 + x_2)\left[-p_1\dot{x}_1 - \dot{x}_2x_1 - x_2\dot{x}_1 + \dot{D}(t)\right] - \left[-p_2\dot{x}_2 + p_3\dot{x}_3\right]x_1 + \left[-p_2x_2 + p_3(x_3 - I_b)\right]\dot{x}_1 + \ddot{D}(t)$$

That means:

$$\dddot{e} = -\dot{x}_2\left[-p_1(x_1 - G_b) - x_2x_1 + D(t)\right]$$
$$-\left(p_1+x_2\right)\left[-\left(p_1+x_2\right)\dot{x}_1 + \dot{D}(t)\right] + \left(p_1+x_2\right)\left[\dot{x}_2\, x_1\right]$$
$$+\left[p_2\dot{x}_2 - p_3\dot{x}_3\right]x_1 + \left[p_2x_2 - p_3(x_3 - I_b)\right]\dot{x}_1 + \ddot{D}(t)$$

So,

$$\dddot{e} = \dot{x}_2\left[p_1(x_1 - G_b) + x_2x_1 - D(t) + \left(p_1+x_2\right)x_1 + p_2x_1\right]$$
$$+\left(p_1+x_2\right)\left[\left(p_1+x_2\right)\dot{x}_1 - \dot{D}(t)\right]$$
$$-p_3\dot{x}_3\, x_1 + \left[p_2x_2 - p_3(x_3 - I_b)\right]\dot{x}_1 + \ddot{D}(t)$$

That means:

$$\dddot{e} = \dot{x}_2\left[p_1(x_1 - G_b) + x_2x_1 - D(t) + \left(p_1+x_2\right)x_1 + p_2x_1\right]$$
$$+\left(p_1+x_2\right)^2\dot{x}_1 - \left(p_1+x_2\right)\dot{D}(t)$$
$$-p_3\dot{x}_3\, x_1 + \left[p_2x_2 - p_3(x_3 - I_b)\right]\dot{x}_1 + \ddot{D}(t)$$

So,

$$\dddot{e} = \dot{x}_2\left[p_1(x_1 - G_b) + x_2x_1 - D(t) + \left(p_1+x_2\right)x_1 + p_2x_1\right]$$
$$+\dot{x}_1\left[\left(p_1+x_2\right)^2 + \left[p_2x_2 - p_3(x_3 - I_b)\right]\right] - \left(p_1+x_2\right)\dot{D}(t)$$
$$-p_3\left[-p_4(x_3 - I_{b1}) + u(t)\right]x_1 + \ddot{D}(t)$$

The third derivative can be written as:

$$\dddot{e} = \left[-p_2x_2 + p_3(x_3 - I_b)\right]\left[p_1(x_1 - G_b) + x_2x_1 - D(t) + \left(p_1+x_2\right)x_1 + p_2x_1\right]$$
$$+\left[-p_1(x_1 - G_b) - x_2x_1 + D(t)\right]\left[\left(p_1+x_2\right)^2 + \left[p_2x_2 - p_3(x_3 - I_b)\right]\right] - \left(p_1+x_2\right)\dot{D}(t) \quad (14)$$
$$p_3p_4(x_3 - I_{b1})x_1 - p_3u(t)x_1 + \ddot{D}(t)$$

In the form:

$$\dddot{e} = \alpha - pu(t)x_1 \quad (15)$$

Where:

$$\alpha = \left[-p_2x_2 + p_3(x_3 - I_b)\right]\left[p_1(x_1 - G_b) + x_2x_1 - D(t) + \left(p_1+x_2\right)x_1 + p_2x_1\right]$$
$$\left[-p_1(x_1 - G_b) - x_2x_1 + D(t)\right]\left[\left(p_1+x_2\right)^2 + \left[p_2x_2 - p_3(x_3 - I_b)\right]\right] - \left(p_1+x_2\right)\dot{D}(t)$$
$$p_3p_4(x_3 - I_{b1})x_1 + \ddot{D}(t)$$

Let's take the Hurwitz polynomial.

$$s^3 + \alpha_2 s^2 + \alpha_1 s + \alpha_0 \tag{16}$$

So, the differential equation:

$$\dddot{e} + \alpha_2 \ddot{e} + \alpha_1 \dot{e} + \alpha_0 e = 0 \tag{17}$$

Implies that the error $e(t)$ goes to zero and then $G(t)$ goes to G_b. From the later equation, one have:

$$\dddot{e} = -\alpha_2 \ddot{e} - \alpha_1 \dot{e} - \alpha_0 e = \alpha - pu(t)x_1 \tag{18}$$

And then the command $u(t)$ is given by:

$$u(t) = \frac{\alpha_2 \ddot{e} + \alpha_1 \dot{e} + \alpha_0 e + \alpha}{p_3 x_1} \tag{19}$$

With $pu(t) \neq 0$.

Let's take z_1, z_2 and z_3 as the poles in the feedback loop, so the characteristic polynomial is given by:

$$\begin{aligned} P(s) &= (s - z_1)(s - z_2)(s - z_3) = (s^2 - z_1 s - z_2 s + z_1 z_2)(s - z_3) \\ &= s^3 + s^2(-z_1 - z_2 - z_3) + s(z_2 z_3 + z_1 z_2 + z_1 z_3) - z_1 z_2 z_3 \\ &= s^3 + \alpha_2 s^2 + \alpha_1 s + \alpha \end{aligned} \tag{20}$$

So,

$$\begin{aligned} \alpha_0 &= -z_1 z_2 z_3 \\ \alpha_1 &= z_2 z_3 + z_1 z_2 + z_1 z_3 \\ \alpha_2 &= -z_1 - z_2 - z_3 \end{aligned} \tag{21}$$

5. SIMULATION

In the simulation, it is required that the glucose concentration tracks it's basal reference G_b=*80 mg/dl* by injecting the sufficient amount of insulin. One suppose that at *t*=250 min a perturbation is added represented by an intake of carbohydrates of the form $D(t) = A\,exp(-Bt), B > 0$. The simulation has been done over 500 min. The initial conditions are given by $p_1 = 0; p_2 = 0.025; p_3 = 0.00013$; G_b =80 mg/dl; Ib=7 µU/ml. The simulation is done over 500 min. And the roots in feedback loop are given by $z_1 = -0.1;\ z_2 = -0.2;\ z_3 = -0.3$.

Figure 2 shows the evolution of the glucose concentration of a patient and one see that the controller is able to lead the glucose to it's normal value that means G_b=*80 mg/dl* after about 100 min and just the occurrence of the perturbation, le glucose increase and return to it's basal value after 75 min. Figure 3 shows the evolution of the insulin which increase if one have a big among of glucose and return to it's basal value once the glucose is in it's basal value. Figure 4 shows controlled input which also increase if the amount of glucose is higher and settle to it's basal value if the glucose reached it's normal value that means G_b=80 mg/dl.

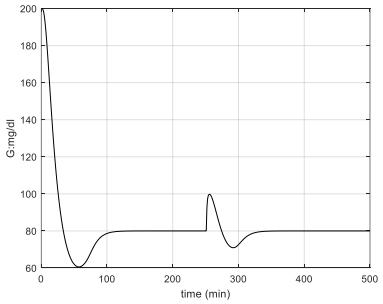

Figure 2. Glucose concentration for a patient person

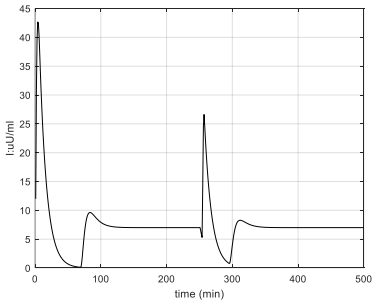

Figure 3. Concentration of insulin in the blood

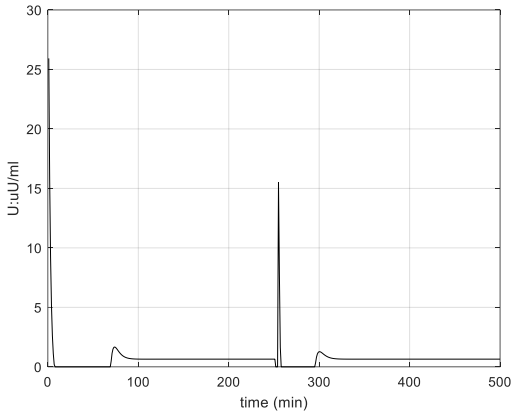

Figure 4. Command (insulin injection) to the blood glucose insulin system

6. CONCLUSION

This paper presents at first the adaptive command which will be applied for a perturbed system. The Lyapunov theory has been addressed in order the achieve a robust command against the uncertainty which is inherent in all real system. The adaptive command has been applied to control the concentration of the glucose of a patient person. The simulation results confirm the robustness of the developed controller.

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AUTHOR CONTRIBUTIONS STATEMENT

This journal uses the Contributor Roles Taxonomy (CRediT) to recognize individual author contributions, reduce authorship disputes, and facilitate collaboration.

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Abddelaziz Mourad	✓			✓				✓		✓	✓	✓	✓	✓

C : **C**onceptualization
M : **M**ethodology
So : **So**ftware
Va : **Va**lidation
Fo : **Fo**rmal analysis
I : **I**nvestigation
R : **R**esources
D : **D**ata Curation
O : Writing - **O**riginal Draft
E : Writing - Review & **E**diting
Vi : **Vi**sualization
Su : **Su**pervision
P : **P**roject administration
Fu : **Fu**nding acquisition

CONFLICT OF INTEREST STATEMENT

Authors state no conflict of interest.

DATA AVAILABILITY

- The data that support the findings of this study are available on request from the corresponding author, [Abdelaziz Mourad]. The data, which contain information that could compromise the privacy of research participants, are not publicly available due to certain restrictions.
- Derived data supporting the findings of this study are available from the corresponding author [Abdelaziz Mourad] on request.

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