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APPLICATION OF OPTIMAL CONTROL STRATEGIES FOR PHYSIOLOGICAL MODEL OF TYPE 1 DIABETES - T1D

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Abstract. Type 1 diabetes is a serious disease that affects many children and adolescents. The disease causes the pancreas to stop producing insulin, a hormone that regulates blood sugar level. Insulin is a hormone that lowers the blood glucose concentration by catalyzing storage of glucose. In this work, the mathematical model describing the whole blood glucose-insulin system was considered where it was derived both based upon the two minimal models of Bergman's minimal model, which is primarily used to interpret an IVGTT. Our objective is to propose a therapeutic scheme adapted to the needs of the diabetic patient and this through a mathematical model describing type 1. To illustrate the obtained results using Matlab/Simulink TM, various examples are presented.

Keywords: physiological mode; type 1 diabetes mellitus; Bergman's model; glucose-insulin system; optimal control and Pontryagin's Maximum Principle.

2010 AMS Subject Classification: 93A30, 49J15.

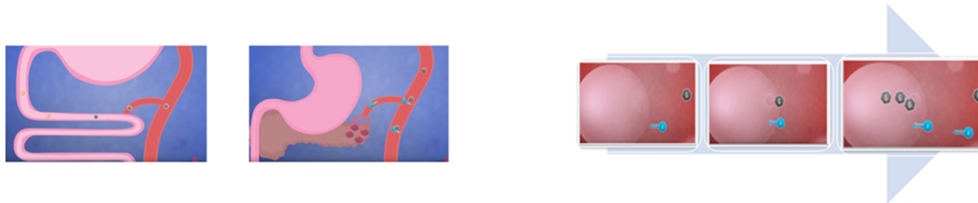
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1. INTRODUCTION

To entirely understand diabetes in first, we explain the mechanism of the use of the body's energy from food. In fact, during digestion, a large part of the supply transforms into glucose (Figure. 1a) When glucose enters the bloodstream, it moves to cells that need energy and support for absorption. The presence of glucose in the blood stimulates the production of insulin by the pancreas (Figure. 1b). Therefore, the insulin is considered as the primordial key in bringing glucose into the cells where the mechanism of glucose transformation and storage takes place. When this regulatory system does not work or when in other words enough insulin or use it properly. Then we can talk about diabetes.



(A) Pancreatic regulation of glucose homeostasis

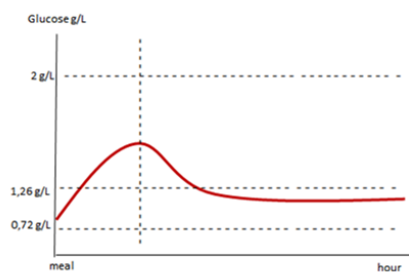
(B) Glucose-stimulated insulin secretion

FIGURE 1. Energy homeostasis body systems

The rest of the paper is organized as follows. In section 2, we present our description of diabetes. Section 3 gives a general description of our proposed method and the description of the carbohydrate metabolism model. In section 4, we illustrate by an example and numerical simulations. Finally, in section 5, we provide the conclusion.

2. DESCRIPTION OF DIABETES

Diabetes is then a disorder of the assimilation, the use and storage of sugar brought by the diet. This result by a high level of glucose within the blood called glycemia.

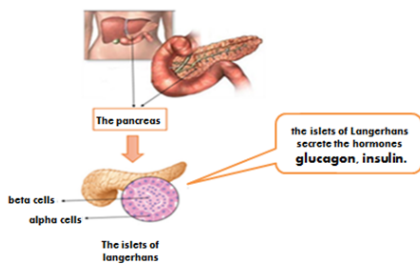


While fasting, the glycemia of a normal person is included between 0.72 and 1.26. When the glycemia is inferior than 0.72 g/l or superior than 1.26 g/l, we are then respectively speaking hypoglycemia or After a meal, glycemia may increase slightly and then return to normal state. Diabetes is then hyperglycemia when the glycemia is higher or equal to 1.26 while fasting and higher than 2 g/l during a normal day. The organ that is responsible of the regulation of the glycemia is called the pancreas.

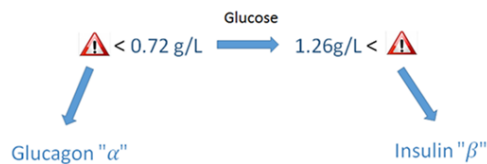
The pancreas. The pancreas is an organ located just behind the stomach. It contains small clusters of cells called islets of Langerhans which produce two hormones important for the regulation of glycemia and thus for the control of the amount of glucose in the blood (Figure. 2a). The cells at the center of the islets are called insulin secreting β cells, while the cells at the periphery of the islets called glucagon secreting α cells.

The role of these two hormones in the regulation of glucose is as follows (Figure. 2b):

- When the Glycemia is superior than 1.26 g/l or hyperglycemia, the β cells will secrete insulin. Having a hypoglycemic effect, that is to say an effect to lower the glycemia.
- When the Glycemia is inferior than 0.72g/L or hypoglycemia, the alpha cells will secrete glucagon: Having a hyperglycemic effect, that is to say an effect which will increase the glycemia.



(A) The Pancreas



(B) The role of α cells and β cells

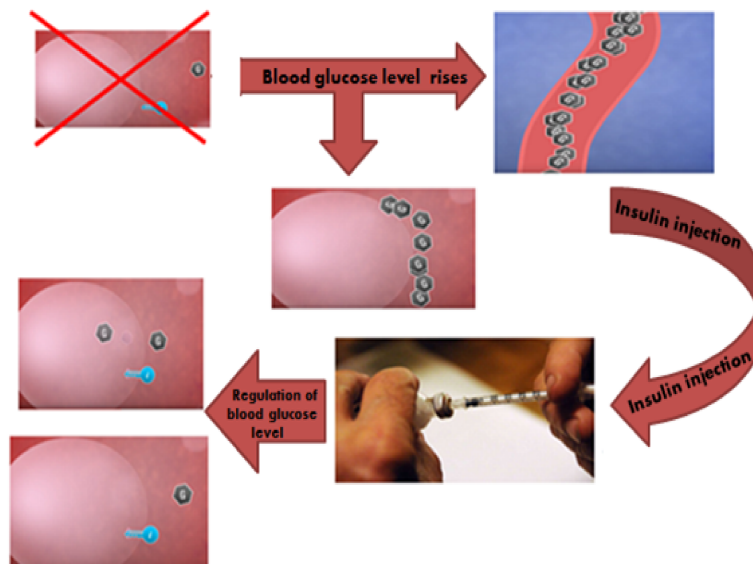
FIGURE 2. Diabetes and the pancreas

Insulin and glucagon are always working together to help the body maintaining a stable glycemia, but for people diagnosed with diabetes, this system does not work properly, because the body does not produce enough or at all insulin, or either because the body's cells are resistant

to insulin. Here we may say that diabetes is precisely a disease that comes from a flaw in the production of insulin. There are two main types diabetes, type 1 diabetes T1D which affected 10% of the diabetics, and type 2 diabetes T2D which is the most common type, affects 85%, while the remaining 5% are affected by an other type.

The type 1 diabetes, also called DID, is usually found in children, adolescents and adults for some unknown reasons. This type of diabetes is characterized by an absence of β -cells in the islet of Langerhans, thing that makes it possible to say that this type of diabetes is an autoimmune disease, it means that the immune system starts to fight its own cells.

Concerning people with this type of diabetes. The body does not langer manufacture any more insulin so the only current treatment is the contribution of this one, either in the form of injection with a syringe or a pen or with a pump portable or implantable treatment device intended to administer the insulin continuously.



For people with type 1 diabetes that's mean the tack of insulin, the glucose cannot enter cells so it accumulated within the blood which causes an abnormal increase of the level of glucose in the blood. where case the insulin injection allows the glucose to enter cells and be used as energy.

Traitement D1D. During the treatment, it is the patient who controls his disease. However, the patient relies on the subcutaneous administration of insulin, called insulin therapy, associated with a balanced diet and regular physical activity. This treatment must be for life. And The patient must himself determine the dose of insulin to be injected (Figure. 3a) according to the measurements of his glucose level In fact, the injectable insulin replaces the insulin that should be manufactured by the body, so the doctor offers an insulin regimen adapted to the patient's glycemic profile Slow insulin is used to regulate the glycemia throughout the day, while the fast insulin is used to regulate the glycemia after meals The injected insulin is divided into “necessary to live” which is the elementary insulin, and the insulin “necessary to eat” is the bolus “roundmass” of insulin. Yet, the issue here is how to properly manage basal doses of insulin.

The types of insulin used in case of intensive treatment are slow analog insulin and fast analogue (Figure. 3b).

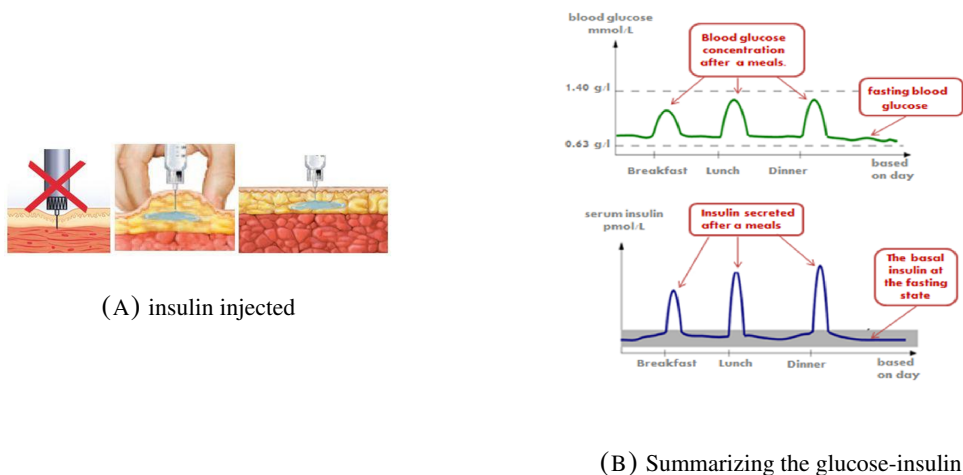


FIGURE 3. Schematic diagram traitement of D1T

3. DESCRIPTION OF THE CARBOHYDRATE METABOLISM MODEL

The minimal Bergman model. The minimal model of Bergman was developed in 1979 for intravenous glucose tolerance test (IVGTT) for nondiabetic and type II diabetic patients. It was modified for T1DM by adding a compartment for external insulin injection. Bergman's minimal model (Figure. 4) is a one compartment model, meaning that the body is described

as a compartment tank with a basal concentration of glucose and insulin. The minimal model actually contains two minimal models. One describing glucose kinetics, how blood glucose concentration reacts to blood insulin concentration and one describing the insulin kinetics, how blood insulin concentration reacts to blood glucose concentration. The two models respectively take insulin and glucose data as an input.

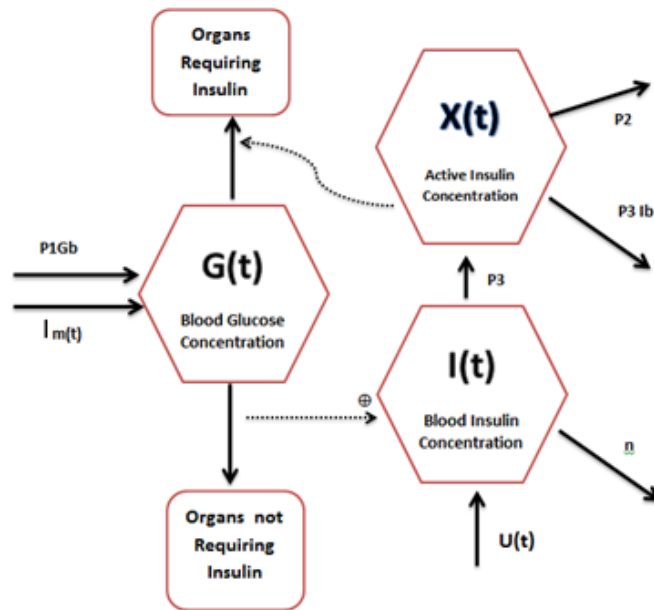


FIGURE 4. Schema of Bergman model

The Bergman model. Minimal model involves two physiological compartments : a glucose compartment and a plasma insulin compartment, which is assumed acting through a remote form to influence net glucose uptake. The glucose-insulin systems is given as follows.

$$(S) \quad \begin{cases} G'(t) = -p_1(G(t) - G_b) - X(t)G(t) + m(t) \\ X'(t) = -p_2X(t) + p_3(I(t) - I_b) \\ I'(t) = -nI(t) + U(t) \end{cases}$$

$G(t)$: Blood glucose concentration ; $I(t)$: Blood insulin concentration ; $X(t)$: The effect of active insulin. With the parameters given in the following table:

Parameter	Unit	Description
$G(t)$	[mg/dL]	Blood glucose concentration
$X(t)$	[1/min]	The effect of active insulin
$I(t)$	[mU/L]	Blood insulin concentration
G_b	[mg/dL]	Basal blood glucose concentration
I_b	[mU/L]	Basal blood insulin concentration
p_1	[1/min]	Glucose clearance rate independent of insulin
p_2	[1/min]	Rate of clearance of active insulin (decrease of uptake)
p_3	[L/(min ² mU)]	Increase in uptake ability caused by insulin.
n	[1/min]	decay rate of blood insulin
$m(t)$	[mg/dL/min]	Meal disturbance function
$U(t)$	[mu/min]	exogenous insulin

TABLE 1. The description of parameters and terms used

The Bergman model with control. The bergman model with control is introduced as follows:

$$(S_1) \quad \begin{cases} G' = -p_1(G(t) - G_b) - X(t)G(t) + (1 - u(t))m(t) \\ X' = -p_2X(t) + p_3(I(t) - I_b) \\ I' = -n(I(t) - I_b) + u(t) \end{cases}$$

and the problem is to minimize the objective functional :

$$J(u) = \int_{t_0}^{t_f} \left(\alpha G(t) + \beta I(t) - \rho X(t) + A \frac{u^2}{2} \right) dt$$

The study will be focused on examining the glucose insulin model oscillation related to food intake, and to examine their ability to simulate homeostatic glucose control.

The Pontryagin's Maximum Principle provides necessary conditions for an optimal control problem. This principle converts into a problem of minimizing the Hamiltonian,

$$H(t, G, X, I, u, \lambda) = \alpha G(t) + \beta I(t) - \rho X(t) + A \frac{u^2}{2} + \sum_{i=1}^3 \lambda_i g_i(G, X, I)$$

where

$$\begin{aligned}
H(t, G, X, I, u, \lambda) = & \alpha G(t) + \beta I(t) - \rho X(t) + A \frac{u^2}{2} \\
& + \lambda_1 (-p_1 (G(t) - G_b)) - X(t) G(t) + (1 - u(t)) (t) \\
& + \lambda_2 (-p_2 X(t) + p_3 (I(t) - I_b)) \\
& + \lambda_3 (-n(I(t) - I_b) + u(t))
\end{aligned}$$

such that

$$G' = \frac{\partial H}{\partial \lambda_1}, \quad X' = \frac{\partial H}{\partial \lambda_2}, \quad I' = \frac{\partial H}{\partial \lambda_3}, \quad \lambda_1' = -\frac{\partial H}{\partial G}, \quad \lambda_2' = -\frac{\partial H}{\partial X}, \quad \lambda_3' = -\frac{\partial H}{\partial I}$$

we obtain the following theorem:

Theorem 3.1. *Given optimal control u^* and solutions G^* , X^* and I^* of the corresponding state system, there exists adjoints satisfying the following equations:*

$$\begin{cases} \lambda_1' = \lambda_1 (X^* + p_1) - \alpha \\ \lambda_2' = \rho + \lambda_1 G^* + \lambda_2 p_2 \\ \lambda_3' = -\beta + n\lambda_3 - \lambda_2 p_3 \end{cases}$$

with transversally conditions $\lambda_1(t_f) = \eta$, $\lambda_2(t_f) = 0$ and $\lambda_3(t_f) = 0$. Moreover, the optimal control is given by:

$$\min(u_{\min}, \max(\frac{m(t)\lambda_1 - \lambda_3}{A}, u_{\min}))$$

The optimal control u can be solve from the optimality condition,

$$\frac{\partial H}{\partial u} = 0.$$

4. NUMERICAL SIMULATIONS

In this section we will present a numerical simulation to illustrate the contribution of our method Note that it is always difficult to assign a set of general settings for patients with diabetes 1 types and representing varying clinic cases. However, since the main purpose of this study is to use the optimal control theory to reduce the rate of glucose in blood, the values of the parameters found in [7] are kept and it is stated that the stability properties of the model (S_1) are stored for these parameters.

The glucose minimal model is used to interpret the glucose kinetics of an IVGTT. These interpretations are based on parameter estimation, using measured blood insulin concentrations

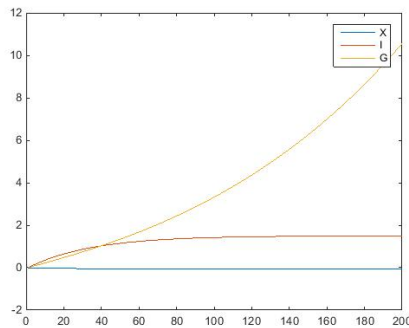
during the test as input to the model. Bergman et al. [11].

The basal values measured are $G_b = 92$ mg/dL and $I_b = 7.3$ mU/dL. By inserting the insulin data as input, and using Matlab/Simulink they derive the following parameters:

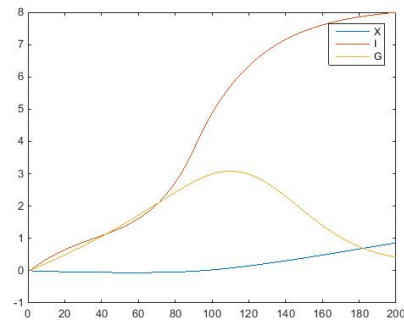
$$p_1 = 0.03082 \quad p_2 = 0.02093 \quad p_3 = 1.062 \cdot 10^{-5} \quad n = 0.3 \quad G(0) = 287 \text{ mg/dL} \quad \cdot$$

To solve numerically this problem, namely to find an optimal control u^* that maximizes the objective function $J(u)$, many methods and techniques of programming can be used. The method we chose for solving the optimality system optimally is generally known under the name of 'Forward Backward Sweep Method [8]. The optimality system is solved using an iterative method with a Runge-Kutta fourth order scheme. The state system with an initial guess is solved forward in time and then the adjoint system is solved backward in time. The iterations continue until convergence is achieved. Finally, we note that all informations about the convergence of this method is given in [7].

the figures (Figure. 5b) and (Figure. 6b) represent The influence of the control u .



(A) Bergman's model without control and $m(t) = 0$



(B) Bergman's model with control and $m(t) = 0$

FIGURE 5. The evolution the glycemia at fasting

This figure (Figure. 5) depicts the evolution the glycemia at fasting in the case without a control that means that's means in the absence of insulin the glycemia level augment highly. But in the presence of the control (Figure. 5b) we can see that glycemia has decreased from its initial condition once the control has been introduced.

this figure (Figure. 6) depicts the evolution the glycemia after a meal, in the case without a control (Figure. 6a) that means that's means in the absence of insulin and the present the meal

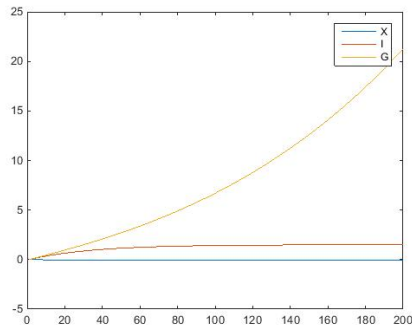
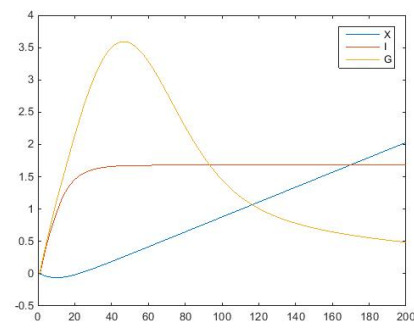
(A) Bergman's model without control and $m(t) \neq 0$ (B) Bergman's model with control and $m(t) \neq 0$

FIGURE 6. The evolution the glycemia after a meal

the glycemia ncrease slightly. But in the presence of the control we can see that glycemia has decreased (Figure. 6b) once the control has been introduced.

CONCLUSION

In this work, we proposed an effective strategy to reduce or to decrease the glycimia. The optimal control theory has been applied in the context of Bergman's model, and that includes one control representing the effort reducing the glucose by digestion, lost and . By using the Pontryagins maximum principle, the explicit expression of the optimal controls was obtained. The numerical simulation of both the systems i.e with control and without control, shows that this strategy helps to reduce the glycemia.

In morocco, we don't currently have available application adapted to the Moroccan context. So, in future work and in collaboration with the endocrinology department of the University Hospital Center UHC-Casablanca, we will try to implement our model with parameters adapted to Moroccan habits (family meal,...) using android or smartphone.

CONFLICT OF INTERESTS

The author(s) declare that there is no conflict of interests.

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