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SIMULATION OF AN ADAPTIVE CLOSED LOOP SYSTEM FOR BLOOD GLUCOSE CONCENTRATION CONTROL

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Abstract: *The main objective of this paper is to set up an adaptive control strategy for a closed loop system to control the glucose concentration in blood by delivering variable dosage of insulin. Simulations are done using the modified Bergman's minimal model for type 1 diabetes mellitus patients. Based on this nonlinear model, an adaptive controller is proposed and tested in simulations. Good results confirm the efficiency of adaptive techniques for controlling the glycaemia level in diabetic patients, even when unexpected disturbance occurs, as having meals with different quantity of carbohydrates.*

Key words: *adaptive control, MIT rule, blood glucose concentration control, insulin to glucose model, Bergman's minimal model.*

1. Introduction

Some of the latest studies in automatic control of blood glucose concentration for type 1 diabetes mellitus (T1DM) patients are taking experiments to outpatient environment and focus on 24 hours experiments. Any automatic insulin deliver system ("artificial pancreas", the term is described in [13]) is intended to allow a routine therapy, which requires studies and solutions that prove efficient (and safe) long-term results.

Studies have been carried out at diabetes camp [22], under medical supervision, but in a more familiar environment. Also, experiments at patients' home are currently being carried out: Nimri et al. published the results of the first home study in 2013 [17]. Also, tests of closed-loop systems outside the protecting environment of the hospital are reported in [18] and [8].

During several consecutive days there are many influences over the biological parameters of the glycemic metabolism, especially for T1DM patients, as: having meals with different quantities of carbohydrates (than assumed by the patient), doing exercises and occasional effort that increase the glucose consumption, night changes in metabolism, and others.

One of the major risks of using automatic insulin deliver devices would be to run into an accidental hypoglycemia state, which for T1DM patients can lead to critical situations (dizziness, fainting, increased heart rate that could be dangerous to people with cardiac disorder and others). Recently, encouraging results towards the reduction of nocturnal hypoglycemia were reported in [18]. However, more *in silico* studies and clinical trials are considered still necessary [4].

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In control engineering, the risk of getting a hypoglycemia state caused by a wrong insulin dose imposes two design conditions:

a) to avoid large overshoot (or, even better, to set it to zero);

b) to use adaptive control algorithms which may increase the efficiency when unexpected disturbance or parameters variations may appear.

One important aspect in controlling biological processes is the large variability of parameters from one patient to another, which means that any mathematical model has major uncertainties. Even more, for a patient, those parameters could vary during a longer period of time, making any personalized model also uncertain. These aspects encourage the use of algorithms from adaptive control theory.

Probably the most used control algorithm so far in this subject is the model predictive control (please refer to the recent reviews in [15], [4], [19], [20]). In this paper, we applied the MIT rule (please refer to [1], [14], [10] for good introduction in the subject) and ran simulations using an intensively used model of the insulin-glucose dynamics.

2. Insuline-Glucose Minimal Model

The models which describe the glucose-insulin metabolism are usually complex, nonlinear models, with many parameters. However, in many cases, a simpler model with only a few parameters would be sufficient to make a good analysis. Such a model was introduced in the eighties by Bergman et al. [3] to describe the glucose dynamics during an intravenous glucose tolerance test, and was further adapted to describe insulin to glucose dynamics by Cobelli et al. [5]. The modified model is what today in known as the Bergman minimal model.

The model is described by the following three Equations:

$$\begin{aligned} \dot{G}(t) &= -[p_1 + X(t)]G(t) + p_1 G_b + m(t), \\ \dot{X}(t) &= -p_2 X(t) + p_3 I(t), \\ \dot{I}(t) &= -nI(t) + \tau u(t), \end{aligned} \tag{1}$$

where: $G(t)$ [mg/dL] is the concentration of glucose in blood; $X(t)$ [1/min] is the dynamic insulin response; $I(t)$ [mU/L] is the concentration of insulin in blood; G_b [mg/dL] is the basal level of glucose; $m(t)$ [mg/min] is the rate of exogenous glucose infusion (which can be the result of a meal); p_1, p_2, p_3, τ, n are the "plant's" parameters, defined in Table 1. Note that the parameters vary from patient to patient.

The last term in the first equation from (1) refers to any exogenous source of glucose. There are two examples: a) an intravenous glucose injection (glucose tolerance tests), or b) having a meal. After a meal, the glucose concentration raises due to the absorption of carbohydrates.

Different values for the parameters of the minimal model Table 1

Parameter	Unit	Value				
		in [7]	in [6], [2]	in [12]		
p_1	[min^{-1}]	0.0337	0	0	0	0
P_2	[min^{-1}]	0.0209	0.025	0.02	0.0072	0.0142
P_3	[$L/(mU*min^2)$]	7.5×10^{-6}	13×10^{-6}	5.3×10^{-6}	2.16×10^{-6}	9.94×10^{-6}
τ	[L^{-1}]	1/12	1 (*)			
N	[min^{-1}]	0.214	0.09	0.3	0.2465	0.2814
G_b	[mg/dL]	80	81	70	70	70

(*) The parameter is a unit conversion factor that can be equal to 1 by proper conventions over the other parameters, or can be calculated as $\tau = 1/V$, with V being the total blood volume.

To describe the glucose dynamics after a meal we considered the model proposed by Hovorka et al. [9]. The raise of glucose concentration is caused by the time varying absorption rate, described by: -

$$m(t) = \frac{D_g A_g t e^{(-t/t_{\max})}}{t_{\max}^2} \qquad (2)$$

where D_g [g] is the quantity of carbohydrates in the meal (note that its value could be uncertain), A_g = 0.8 is constant in the model, $t_{\max}$ = 40 min is the time moment when the absorption is at its peak value. The shapes of the disturbance variable for different quantities of carbohydrates are shown in Figure 1.

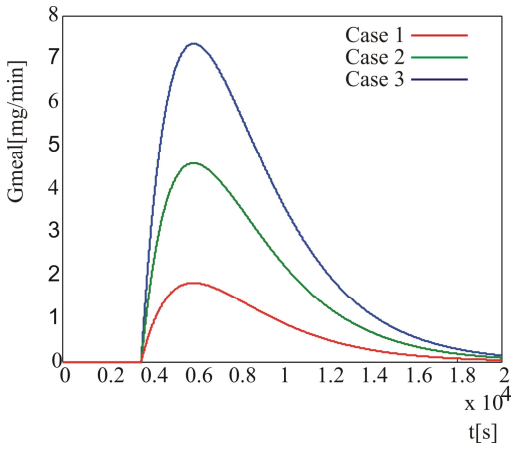

Fig. 1. *The "unexpected" disturbance: meal glucose absorbtion rate*

3. Designing an Adaptive Controller for Blood Glucose Concentration

The closed loop control system is depicted in Figure 2. The objective is to design an adaptive controller to maintain the blood glucose at a safe value (between 70 and 120 mg/dL), even if an unexpected disturbance may appear. To achieve this, a variable dose of insulin has to be injected in the blood.

For the simulations in this research, parameters of the minimal model are considered to have different values within certain ranges as follows:

$$p_1 \in (0;0.0375),$$

$$p_2 \in (0.02;0.025),$$

$$p_3 \in (0.000006;0.000013).$$

To control such a process, it is necessary to select an adaptive control law with three adjustable parameters [1], [14], [10], noted k_1, k_2, k_3, in:

$$u(t) = k_1 r(t) - k_2 y(t) - k_3 \dot{y}(t). \qquad (3)$$

To determine the proper values for the adjustable parameters in the adaptive law, the MIT rule is applied. According to this method, a reference model has to be set, which in our case should be a first-order element (to avoid the overshoot in glucose concentration; please refer to [1], [14], [10] for detailed introduction in the theory). The time constant of the reference model is set to 6480 seconds [11], [21], meaning that the chosen transfer function for the reference model is:

$$G_m(s) = \frac{b_m}{s + a_m} = \frac{1}{6480s + 1}, \qquad (4)$$

which should make the glycaemia level return to safe value in less than 3 hours. The parameters a_m = 1/6480 and b_m = 1 are chosen according to the desired time constant.

The sensitivity derivatives required by the adjustment mechanism are obtained by taking the partial derivatives of the error variable. Finally, the adjustment equations for the controller's parameters can be obtained:

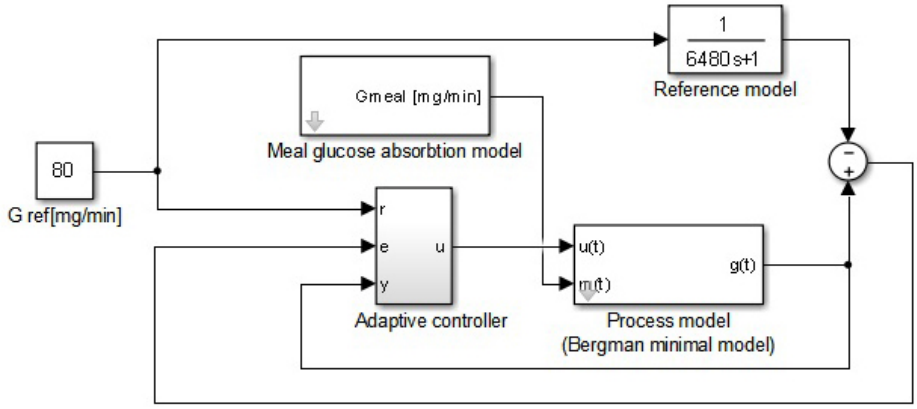

Fig. 2. *The adaptive closed loop system*

$$\frac{dk_1(t)}{dt} = -\gamma\left(\frac{1}{p+a_m}r(t)\right)e(t),$$
$$\frac{dk_2(t)}{dt} = \gamma\left(\frac{1}{p+a_m}y(t)\right)e(t), \qquad (5)$$
$$\frac{dk_3(t)}{dt} = \gamma\left(\frac{1}{p+a_m}\frac{dy(t)}{dt}\right)e(t),$$

where $e(t)$, $y(t)$, $y_m(t)$ and $r(t)$ are the standard notations in control engineering theory for the error variable, process output, reference model output (i.e. the system desired response) and reference input variable, respectively. The notation p is the differential operator and the adaptation gain γ is set to 0.1 (A good theoretical back-ground which supports the equation set (5) can be found in [1] and [10]. Also, these references stand as some of the best introduction textbooks in the adaptive control theory).

Note that the error should asymptotically lower to a small value, r even to zero. The decision on how small the error can be is influenced by the model reference, the process, and the command signal.

Three scenarios were simulated (see Figure 1):

- case 1: the patient has a meal with D_g = 10 g carbohydrates;
- case 2: the patient has a meal with D_g = 40 g carbohydrates;
- case 3: the patient has a meal with D_g = 60 g carbohydrates.

Figure 3 shows the evolution of blood glucose concentration for these three cases, when the parameters are the first set of values defined in Table 1 [7], with the adaptation gain value set to γ = 0.1.

As it can be seen in Figure 4, a perfect model is achieved [1], [14], [16], by reducing the error to zero.

In all cases the control objective was to maintain the blood glucose concentration at the value of 80 mg/dL. However, it should be mentioned that for T1DM patients higher values are accepted.

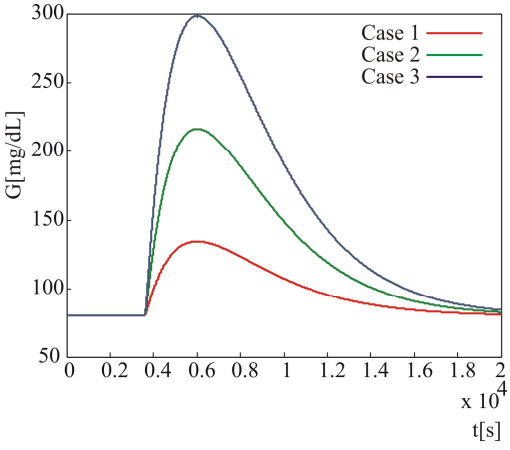

Fig. 3. *Glucose concentration in time for the simulated cases*

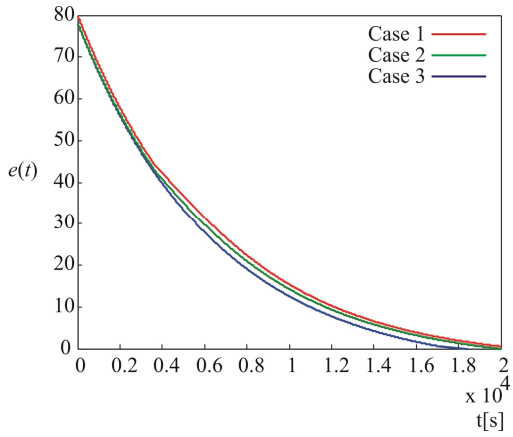

Fig. 4. *The difference* between *the glucose concentration output and reference model output*

Another important challenge was to maintain the error signal to zero, by choosing a proper reference model.

The adaptive system uses two loops: the first one, the so called the inner loop includes the classical feedback, and the second one, the so called the outer loop, was used to adjust controller parameters.

The simulations were done using a Matlab-Simulink scheme, and we considered one single meal.

4. Conclusions

In this paper, we investigated an adaptive control strategy, in order to design an efficient controller for blood glucose concentration control. The design and simulations use the nonlinear Bergman minimal model of insulin-glucose dynamics. The control objective is to maintain the blood glucose concentration within in normal range while an assumed unexpected disturbance appears. In our case, disturbances appear due to the absorption of different quantities of carbohydrates after having the meals.

Based on the simulations' results, the adaptive control strategy meets the expectations that were to return the blood glucose concentration to the initial value from before the unexpected disturbance. The stabilization time (settling time) would be within 3 hours.

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References

1. Astrom, K., Wittenmark, B.: *Adaptive Control*. USA, Addison-Wesley, 1989.
2. Bequette, B.W.: *Process Control. Modelling, Desing and Simulation*. Prentice Hall PTR, 2006.
3. Bergman, R.N., Phillips, L.S., Cobelli, C.: *Physiologic Evaluation of Factors Controlling Glucose Tolerance in Man. Measurement of Insulin Sensitivity and β-Cell Glucose Sensitivity from the Response to Intravenous Glucose*. In: Journal of Clinical Investigations **68** (1981), p. 1456-1467.
4. Caudal, A., Mulroy, M., Wagers, W., Atlas, E., Dassau, E.: *Closing the Loop*. In: Diabetes Technology & Therapeutics **17** (2015) No. 1, p. S27-S38.
5. Cobelli, C., Toffolo, G., Ferrannini, E.: *A Model of Glucose Kinetics and Their Control by Insulin, Compartmental and Noncompartmental Approaches*. In: Mathematical Biosciences **72** (1984), p. 291-315.
6. Chee, F., et al.: *Optimal H inf Insuline Injection Control for Blood Glucose Regulation in Diabetic Patients*. In: IEEE Transaction on Biomedical Engineering **52** (2005) No. 10, p. 1625-1631.

7. Chen, J., et al.: *Continuous Drug Infusion for Diabetes Therapy: A Closed Loop Control System Design*. In: EURASIP Journal on Wireless Communications and Networking (2008), p. 1-10; (2007), p. 110.
8. Doyle, F.J., Huyett, L.M., Lee, J.B., et al.: *Closed-Loop Artificial Pancreas Systems: Engineering the Algorhitms*. In: Diabetes Care **37** (2014), p. 1191-1197.
9. Hovorka, R., et al.: *Nonlinear Model Predictive Control of Glucose Concentration in Subjects with Type 1 Diabetes*. In: Physiological Measurement **25** (2004), p. 905-920.
10. Ioannou, P., Fidan, B.: *Adaptive Control Tutorial*. Society for Industrial and Applied Mathematics, USA, 2006.
11. Jensen, E.: *Modelling and Simulation of Glucose-Insulin Metabolism*. Bachelor Thesis, Technical University of Denmark, 2007.
12. Kaveh, P., Shtessel, Y.: *High Order Sliding Mode Control for Blood Control Regulation*. In: Proc. of the 2006 Int. Workshop on Variable Structure Systems, Mon A.3, Alghero, Italy, 2006, p. 11-16.
13. Klonoff, D.C.: *The Artificial Pancreas: How Sweet Engineering Will Solve Bitter Problems*. In: Journal of Diabetes Science and Technology **1** (2007) No. 1, p. 72-81.
14. Landau, I., at al.: *Adaptive Control*: *Algorithms, Analysis and Applications*. London. Springer-Verlag, 2011.
15. Lunze, K., et al.: *Blood Glucose Control Algorithms for Type-1 Diabetic Patients: A Methodological Review*. In: Biomedical Signal Processing and Control **8** (2012) No. 2, p. 107-119.
16. Monopoli, R.V.: *Model Reference Adaptive Control with an Augmented Error Signal*. In: IEEE Trans. on Automatic Control **19** (2003) No. 5, p. 474-484.
17. Nimri, R., et al.: *Night Glucose Control with MD-Logic Artificial Pancreas in Home Setting: A Single Blind, Randomized Crossover Trial-Interim Analysis*. In: Pediatric Diabetes **15** (2014) No. 2, p. 91-99.
18. Nimri, R., Phillip, M.: *Artificial Pancreas: Fuzzy Logic and Control of Glycemia*. In: Current Opinion in Endocrinology, Diabetes and Obesity **21** (2014) No. 4, p. 251-256.
19. Owens, C., at al.: *Run-to-Run Control of Blood Glucose Concentrations for People with Type 1 Diabetes Mellitus*. In: IEEE Transaction on Biomedical Engineering **53** (2006) No. 6, p. 996-1005.
20. Owren, M.: *Automatic Blood Glucose Control in Diabetes*. In: Master Thesis at Norwegian University of Science and Technology, 2009.
21. Palerm, C.: *Drug Infusion Control*: *An Extended Direct Model Reference Adaptive Control Strategy*. In: Ph.D. Thesis, Polytechnic Institute Troy, New York, 2003.
22. Phillip, M., et al.: *Nocturnal Glucose Control with an Artificial Pancreas at a Diabetes Camp*. In: The New England Journal of Medicine **368** (2013), p. 824-833.