RESEARCH ARTICLE OPEN ACCESS

AUTONOMOUS DRUGS OPTIMAL MANAGEMENT, PART I: OPTIMAL INSULIN REGULATION FOR TYPE 1 DIABETES USING 0/1 FIRST-ORDER AND 2/2 ORDERS COMPENSATORS COMPARED WITH A PID CONTROLLER

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Abstract:

This paper investigates the optimal insulin infusion for type 1 diabetes through the use of compensators from the second generation of control compensators. The proposed compensators are a novel 0/1 first order and 2/2 orders compensators from the second generation of control compensators. The compensators are tuned for good control system performance and optimal adjustment of the insulin infusion required to control the typ1 diabetes. The performance of the control system with the proposed compensators is compared with PID controller from the first generation of PID controllers to control the same type 1 diabetes process. A ready transfer function model for the glucose-insulin infusion process from a previous research work is used to tune the proposed compensators and present the step time response for a meal disturbance input. The characteristics of the step time responses are compared with those of the conventional PID controller. The best compensator/controller for the control of type 1 diabetes is assigned and the insulin infusion rate is investigated for three levels of the gain of the best compensator.

Keywords — **Autonomous drugs optimal management, optimal insulin regulation, PID controller, 0/1-first order compensator, 2/2 orders compensator , compensators tuning**.

I. INTRODUCTION

This is the first paper of a series of research papers oriented towards the study of autonomous drugs control aiming at increasing the efficiency of drugs use for the treatment of human body diseases. This paper deals with the control of the serum diabetes type 1 using an artificial pancreas based on feedback control of insulin infusion to the patient's body. Diabetes is an international disease resulting from increased glucose concentration in the blood (hyperglycemia) resulting in a number of symptoms such as: high thirst, blurred vision, fatigue, fruit smelling breath, breath shortness, dryness in mouth, weaknesses, comma and abdominal pain [1]. Here are some of the research efforts in presenting some aspects related to diabetes control since 2004:

Ramprasad et al. (2004) outlined that several PID controllers were assigned to specify the insulin dosage on a continuous glucose measurement basis. They stated that one of the developed PID tuning techniques was able to maintain the glucose concentration above hypoglycemic range of < 60 mg/dL [2]. Marchetti et al. (2006) proposed an improved PID control strategy for glucose control. They concluded that their proposed control strategy compared well with alternatives for meal challenges , incorrect carbohydrate meal estimate , insulin sensitivity and measurement noise [3]. Magni et al. (2008) considered the feedback control of glucose concentration in type 1 diabetic patients using insulin delivery and glucose monitoring. They used an in silico consisting of 100 patients to assess the performance of a model predictive control designed on the basis of an in silico model. They concluded that satisfactory results were obtained [4].

Elleri, Dunger and Hovorka (2011) reviewed the status of insulin delivery up to 2011 focusing on clinical evaluations of closed-loop systems. They addressed some of the dynamic systems constraints such as inaccuracies in glucose sensors, patient variability and delays [5]. Gabutti et al. (2011) outlined that rapid decrease of serum potassium concentrations during hemodialysis produces significant increase in blood pressure at the end of the session. They concluded that the risk of intra-dialysis hypotension inversely correlated to the potassium concentration in the dialysate [6].

Li et al. (2012) investigated the use of an artificial pancreas system through using a closed-loop control system to administrate the right dose of insulin for type 1 diabetes. They presented a simplified model based on Routh approximation

reduction and showed that the approximation error could be neglected. The designed a PID controller to maintain 90 mg/dL glucose concentration in subjects with type 1 diabetes. They concluded that the glucose concentration was controlled well and the risk of hypoglycemia and hyperglycemia was reduced [6]. Abadi et al. (2014) designed an optimal fuzzy-PI controller based on Mamdani-type structure for blood glucose in diabetic patients. They used the particle swarm optimization to optimate the membership functions, controller gain parameters and insulin infusion. They concluded that simulation results depicted much better accuracy and conversion speed compared with other methods. They presented graphically the glucose profiles under the fuzzy-PI control for three patients reaching a steady state value of 70 mg/dL after a time of 75, 90 and 120 min [7]. Soylu and Danisman (2016) outlined that a closed-loop insulin therapy became more important for the treatment of type 1 diabetes. They proposed three different control algorithms as a controller including: genetic algorithms based PID, artificial bee colony based PID and particle swarm optimization based PID. They implemented in silico control studies through a virtual diabetic patient based on the Stolwijk-Hardy's glucose-insulin model. They concluded that simulation results were promising in terms of regulating the daily blood glucose concentration [8]. Farahmand, Dehghani and Vafamand (2019) designed a robust controller with H∞ performance index for glucose regulation in type 1 diabetes. They employed a Takagi-Sugeno fuzzy modeling and fuzzy model -based parallel distributed compensation and non-parallel distributed compensation schemes to design a stabilizing control. THEY USED THE NONLINEAR MINIMAL bergman and Tolic models for the glucose-insulation process in type 1 diabetes. They concluded that simulation results verified the advantages of the proposed robust control techniques in maintaining the blood glucose concentration in the desired region [9].

Zahedifar and Kholajh (2022) presented an adaptive backstepping method to regulate the blood glucose induced by meals for type 1 diabetes patients. They evaluated the effectiveness of the proposed method by comparing the results of two different case studies. They concluded that the results indicated the stability of the proposed controller and the desired level of glucose concentration was tracked efficiently [10]. Sayedabadi and Kalat (2024) designed an adaptive controller to regulate the blood glucose level of type 1 diabetes while not all states of the system are measurable and with unknown parameters. They transformed the dynamic equations of the nonlinear Bergman minimal model into a companion form and presented an observer to estimate the unknown state variables and system parameters. They presented simulation results verifying the effectiveness of their proposed approach in tracking the desired blood glucose level [11]. Soleimannouri et al. (2025) presented an adaptive fuzzy controller to regulate the blood glucose type 1 diabetic patients in the presence of input saturation. They designed an anti-windup compensator to prevent the saturation problem. The concluded that the results showed a lower control effort and less convergence time for the proposed technique compared with the existing methods. Their glucose profile under control converged to 80 mg/dL (desired value) in about 400 min [12].

II. THE CONTROLLED BLOOD GLUCOSE CONCENTRATION AS A PROCESS

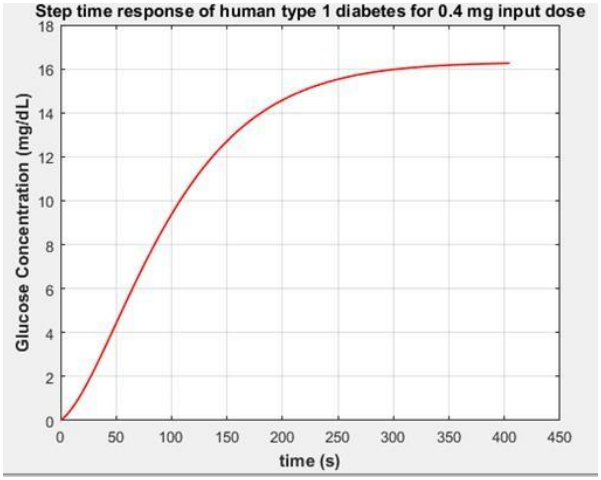
In their investigation of PID control of glucose concentration in type 1 diabetes patients, Li, et al. used a simplified 1/2 transfer function model [6]. Their model related the glucose concentration as an output and the insulin dose as an input in a process transfer function form $G_p(s)$ given by [6]:

$$G_p(s) = (0.0903s+0.0126)/(s^2+0.0339s+3.0919x10^{-4}) \quad (1)$$

The process model in Eq.1 consists of a simple zero and a quadratic pole of 0.01758 rad/min and 0.9639 damping ratio. To investigate the step time response of the glucose model in Eq.1, an insulin dose of 0.4 mg for 69 kg type 1 diabetes patient and one meal is chosen [13].

The time response profile for an input insulin dose of 0.4 mg using the glucose model of Eq.1 is shown in Fig.1 as generated by the '*step*' command of MATLAB [14].

Fig.1 Step time response of the glucose concentration.



COMMENTS:

- The human blood glucose concentration process is stable.
- Maximum overshoot: zero
- Settling time with ± 2 % tolerance: 300.72 min
- Rise time: 180.07 min

III. GLUCOSE CONCENTRATION CONTROL USING A PID CONTROLLER

- As a reference for control system characteristic comparison, a conventional PID controller from the first-generation of PID controllers is proposed to control the glucose concentration of a type 1 diabetic patient to meals as a disturbance variable by Li et al. [6].
- The authors in their work did not present the PID controller tuning nor its gain parameters. They presented the time response of the glucose control system for three successive disturbance meals starting by a 180 mg/dL concentration level [6].
- The step time response for the first meal is digitized and shown also in Fig.2.

COMMENTS:

- Maximum overshoot: zero
- Settling time with ± 2 % tolerance: 490.7 min
- Delay time: 393.5 min
- Rise time: 300.9 min
- Steady-state glucose level: 50 mg/dL

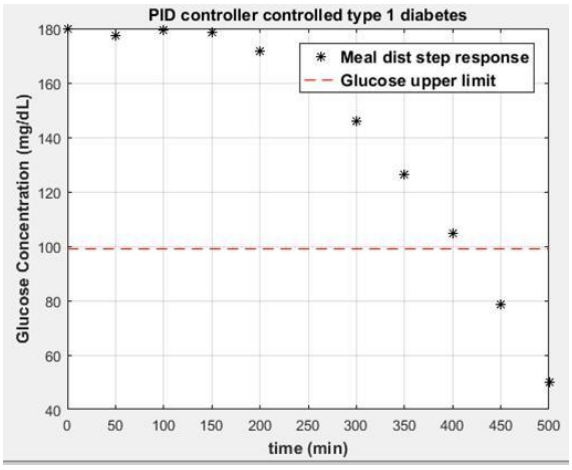


Fig.2 Glucose concentration control using a PID controller [6].

IV. GLUCOSE CONCENTRATION CONTROL USING A 0/1 FIRST-ORDER COMPENSATOR

- The 0/1 first-order compensator is a novel compensator proposed by the author as one of the second-generation control compensators presented by him since 2014. The 0/1 first-order compensator is composed of one simple pole dynamic system having a time constant T_{c1} and a compensator gain K_{c1} in the numerator of its transfer function. The compensator is located in the feedforward path of a single-loop block diagram of a linear control system just after the error detector. It has a transfer function $G_{c1}(s)$ given by:

$$G_{c1}(s) = K_{c1}/(T_{c1}s+1) \quad (2)$$

- The two gain parameters of the compensator are tuned as follows:

The process transfer function in Eq.1 is rearranged to write its numerator in a standard simple zero form as follows:

$$G_p(s) = 0.0126(7.1667s+1)/(s^2+0.0339s+3.0919x10^{-4}) \quad (3)$$

The block diagram of the proposed compensator-based control system with reference input R(s), disturbance input D(s) and controlled variable C(s) is shown in Fig.3

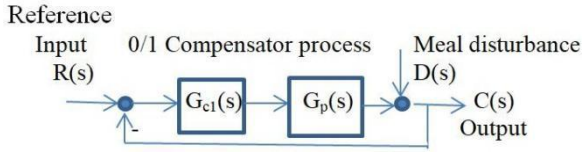


Fig.3 Block diagram of the glucose control system.

- To investigate the dynamic response of the control system to disturbance (meal) input, we set the reference input R(s) to zero. In the resulting block diagram with Dis) as input and C(s) as an output, The two elements transfer functions will be cascaded in the feedback loop of the block diagram with $G_{c1}(s)G_p(s)$ equivalent s-function.
- Now, we use the zero/pole cancellation technique [15] to cancel the zero of the process transfer function in Eq.3 with the pole of the compensator in Eq.2 giving:

$T_{c1} = 7.166 / \text{min}$ (4)

- The closed-loop transfer function of the control system incorporating the 0/1 first-order compensator can be driven using the block diagram in Fig.3 which is function only of the compensator gain K_{c1}. With few trials for good performance of the control system using the 0/1 compensator, K_{c1} was selected as:

$K_{c1} = 159$ (5)

- For a 180 mg/dL meal disturbance, the step time response of the control system is generated using the MATLAB command '*step*' [14] and shown in Fig.4.

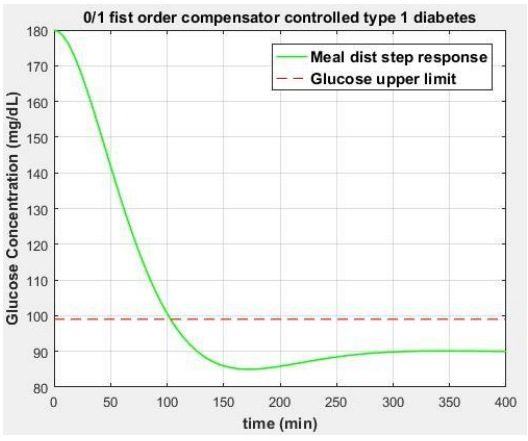


Fig.4 Glucose concentration control using a 0/1 first-order compensator.

COMMENTS:

- Maximum overshoot: 5.54 %
- Settling time with ± 2 % tolerance: 0.241.28 (compared with 490.70 min for the PID controller).
- Delay time: 61.82 min (compared with 393.50 min for the PID controller).
- Rise time: 83.19 min (com34pared with 300.90 min for the PID controller).
- Steady-state response: 89.98 mg/dL (compared with 50 mg/dL for the PID controller).

V. GLUCOSE CONCENTRATION CONTROL USING A 2/2 ORDERS COMPENSATOR

- The introduced the 2/2 orders compensator in 2014 to control a very slow second-order-like process [16]. The compensator consists of two rational quadratic zero and pole. Its transfer functions $G_{c2}(s)$ is given by [16]:

$$G_{c2}(s) = K_{c2}(s^2+2\varsigma_{z2}\omega_{z2}s+\omega_{z2}^2) / (s^2+2\varsigma_{p2}\omega_{p2}s+\omega_{p2}^2) \quad (6)$$

Where K_{c2} is its gain, (ς_{z2} and ω_{z2}) are its zero damping ratio and natural frequency and (ς_{p2} and ω_{p2}) are its pole damping ratio and natural frequency to be tuned for good control system performance as follows:

- The 2/2 orders compensator is located in the forward path of the control system block diagram replacing $G_{c1}(s)$ in Fig.3.
- Using the block diagram in Fig.3 with D(s) as input and R(s) = 0, the transfer functions $G_p(s)$ and $G_{c2}(s)$ re multiplied by each other in the feedback path of the control block diagram.
- Using the zero/pole cancellation technique [15], the quadratic pole of the process cancels the quadratic zero of the 2/2 compensator providing:

$\varsigma_{z2} = 0.9639$; $\omega_{z2} = 0.01758$ rad/min (7)

- In the quadratic zero of the 2/2 compensator, we assume that it has critical damping providing:

$\varsigma_{p2} = 1$ (8)

- With the parameters tuning in Eqs.7 and 8, the closed-loop transfer function M2(s) of the control system for disturbance input becomes:

$M_2(s) = (s^2+2\omega_{p2}s+\omega_{p2}^2) / [s^2+(2\omega_{p2}+0.0903K_{c2})s+ \omega_{p2}^2+0.0126K_{c2}]$ (9)

- There are two unknown compensator parameters in Eq.9 which have to be tuned.
- Before going to optimization techniques, a trial-and-error technique was tried first [17]. If the performance of the control system was not accepted, then optimization technique will be applied.
- The following values for K_{c2} and ω_{p2} have given excellent results using the trial-and-error approach:

$K_{c2} = 3.4$; $\omega_{p2} = 0.15$ (10)

- The transfer function in Eq.9 and the tuned controller gain in Eq.10 produce the step time response of the serum glucose concentration in response to the meal glucose generation of 180 mg/dL shown in Fig.5.

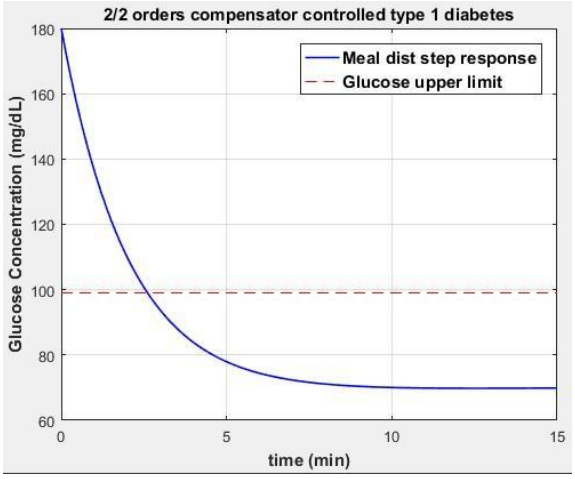


Fig.5 Glucose concentration control using a 2/2 orders compensator.

COMMENTS:

- Maximum overshoot: zero.
- Settling time with ± 2 % tolerance: 6.73 min (compared with 490.7 min for the PID controller).
- Delay time: 1.39 min (compared with 393.5 min for the PID controller).
- Rise time: 4.13 min (compared with 300.9 min for the PID controller).
- Steady-state response: 70 mg/dL (compared with 50 mg/dL for the PID controller).

VI. COMPARISON OF THE TIME-BASED CHARACTERISTICS

Graphical Comparison:

- The time-based characteristics of the control systems incorporating the controller /compensators proposed to control the serum glucose concentration are compared graphically through the step time response as depicted in Fig.6

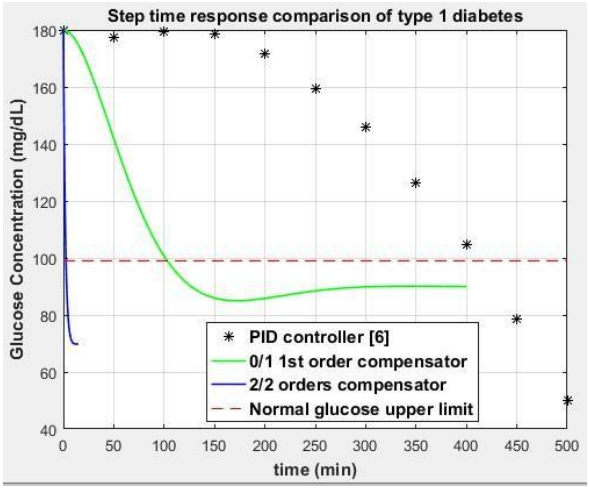


Fig.6 Graphical characteristic comparison of serum glucose control.

TABLE 1
TIME-BASED CHARACTERISTICS COMPARISON

Controller / compensators	PID controller	0/1 compensator	2/2 compensator
OS_{max} (%)	0	5.543	0
$T_{s2\%}$ (min)	490.7	241.28	6.73
T_d (min)	393.5	61.82	1.39
T_r (min)	300.9	83.19	4.13
c_{ss} (mg/dL)	50	90	70

OS_{max}: Maximum percentage overshoot.
T_d: Delay time.
T_r: Rise time.
c_{ss}: Steady-state time response.

Numerical Comparison:

- Numerical comparison for the time-based characteristics of the step time response for disturbance input of the control system with the proposed compensators is presented in Table 1 with comparison with the application of a conventional PID controller used to control the same type 1 diabetes patient.

Insulin Infusion Rate

The insulin infusion rate (IR) is defined mathematically as dI/dt where I is the insulin dose. It can be obtained from the block diagram of the control system in Fig.3 with D(s) as input, R(s) = 0 and C(s) as an output. It is the output variable of the controller assuming that the insulin pump is integrated with the compensator electronic circuit. With the 2/2 orders compensator selected as the best controller/compensators among the investigated group of controlling elements in this research work, the transfer function of the insulin rate is calculated and plotted using the step response command of MATLAB [14] for the following 2/2 compensator parameters:

ω_{p2} = 0.17 rad/min

K_{c2} = 0.02, 0.06 and 0.1

The time profile of the insulin infusion rate during the autonomous control process of type 1 diabetes is shown in Fig.7.

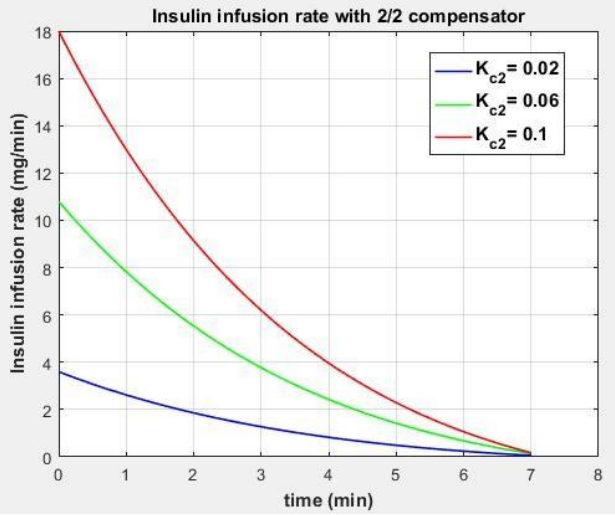


Fig.7 Insulin infusion rate with 2/2 orders compensator for type 1diabetes.

VII. CONCLUSIONS

- The research work presented in this research paper handled the first paper in a series of papers under the general title: Autonomous drugs optimal management.
- The first paper in this series dealt with the control of serum type 1 diabetes using two compensators from the second generation of control compensators compared with a PID controller from the first PID controllers.
- The proposed compensators were tuned using hybrid approach based on applying the zero/pole cancellation, critical damping of second-order dynamic systems and trial and the error approach.
- The PID controller was used in a 2012 research work to control type 1 diabetes without tuning announcement. It simulation results were used for sake of comparison with the proposed control techniques.
- The purpose of the investigated compensators was to bring down the glucose concentration due to one meal disturbance from 180 gm/dL to a value within a normal range between 70 and 100 mg/dL.
- The proposed compensators succeeded to reduce the settling time of the control system (with respect to the 2 % tolerance) to values in the range: $6.73 \leq T_{s2\%} \leq 241.28$ min compared with 490.7 min for the PID controller.
- The proposed compensators succeeded to reduce the delay time to $1.39 \leq T_d \leq 61.82$ min compared with 393.5 min for the PID controller.
- The proposed compensators succeeded to reduce the rise time to $4.13 \leq T_r \leq 83.19$ min compared with 300.9 min for the PID controller.
- The best compensator was chosen the 2/2 orders compensator based on its time-based characteristics in Table 1.
- The effect of 2/2 compensator gain K_{c2} on the insulin infusion rate was graphically illustrated for K_{c2} = 0.02, 0.06 and 0.1. The maximum infusion rate was 3.38, 10.42 and 18 mg/min respectively.
- The insulin infusion rate can be set by the control system operator to suit the type 1 diabetes individuals.
- Future work is required to set limits for the insulin infusion rate to avoid side effects and provide more safety treatment for type 1 diabetes.

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DEDICATION

Statue of Ibn al-Baytar in Spain

ABDULLAH AL-BAYTAR [18], [19]

- Arab physician, anatomist and philosopher.
- Born in Malaga of Andalus in 1197 AC.
- Died in Damascus in 1248 AC.
- He was a physician, botanist, pharmacist and scientist.
- He developed a scientific method based on empirical and experimental techniques in testing, description and identification of medical materials.
- In 1219 AC, he travelled to North Africa to collect plants.
- In 1224 AC, he was appointed as a 'Chief Herbalist' by Ayyubid 'Sultan Al-Kamil'.
- In 1227 AC, he travelled with 'Sultan Al-Kamil' to Damascus where he collected more plants from Syria.
- He wrote his famous book 'Compendium of materia medica' listing 1400 plant and their uses.
- He wrote also 'the rich in single drugs'.
- He provided chemical information on 'rosewater' and 'orangewater' and their production.
- This is why we dedicated this research work to the great pharmacist 'Ibn Al-Baytar'.