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A Feedback Glucose Control Strategy for Type II Diabetes Mellitus

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***Abstract*—Type II diabetes mellitus is characterized by both insulin resistance and β-cell failure. Although patients with type II diabetes mellitus are not initially dependent on insulin, the introduction of insulin therapy becomes one of the most effective methods of attaining good glycemic control. In this work, a proportional-integral-derivative (PID) controller is implemented to maintain normoglycemia in a simulated Type II diabetic patient using a closed-loop insulin infusion pump. The simulation employs a compartment model, which represents the glucose regulatory system and includes submodels representing the absorption of subcutaneously administered short-acting insulin and gut absorption. The feedback control system returns blood glucose to normoglycemic ranges after a meal disturbance. The settling time is similar to that of a non-diabetic. These results demonstrate the potential use of control algorithms for regulation of blood glucose by insulin for Type II diabetic patients.**

I. Introduction

The prevalence of diabetes in the world is growing at an unprecedented rate and rapidly becoming a health concern. Type II diabetes mellitus is a progressive disease characterized by both insulin resistance and β-cell failure, resulting in a decline in insulin secretion and in an increase in blood glucose levels [1]. The importance of tight glycemic control has been demonstrated by results of various prospective studies in which prolonged hyperglycemia was found to be associated with an increased risk of various complications[2,3]. These complications include microvascular disorder such as sensory neuropathy, retinopathy, and nephropathy, as well as stroke, myocardial infarction, macro-vascular mortality, and all-cause mortality. In order to prevent these complications and achieve a better quality of life, effective regulation of blood glucose is essential.

Patients with Type II diabetes mellitus require insulin treatment when an appropriate combination of oral antidiabetic agent and life style changes fail to provide adequate glycemic control [4]. Insulin therapy has traditionally been divided into two major routes of application: subcutaneous insulin injection and continuous infusion of insulin. Recently, studies have demonstrated that the continuous subcutaneous insulin infusion with external pumps provided more efficacy and safety compared to the usual multiple daily injection therapy for Type II diabetic patients[4-6]. Automated control techniques can improve the functionality of biomedical systems, including disease treatments. For Type II diabetic patients being treated with continuous subcutaneous insulin infusion, the blood glucose control system is very useful and effective in Type II diabetic patients. During the past 30 years, a variety of glucose control strategies for Type I diabetic patients have been reported [7-9]. However, until now none of these studies have been applied to the regulation of blood glucose in Type II diabetes mellitus.

The proportional-integral-derivative (PID) control algorithm is known to be applicable to a wide variety of dynamic systems (automobiles, planes, liquid level systems, satellite tracking devices, etc.) [10]. A variety of PID control strategies have been developed for Type I diabetes and described in survey papers and articles [11-13]. A proportional-derivative controller has been derived with a pole assignment strategy and tested in patients [11]. Later Chee et al. (2003) proposed a PID control system based on a sliding scale approach and successfully tested said approach in patients in intensive care unit [14]. A PID control strategy is desirable for glucose control because of its ability to mimic the first and second phase responses that the pancreas β-cells use to secrete insulin [15].

Vahidi et al. (2010) recently proposed a substantial modification of the compartmental model for a category of Type II diabetic patients who are characterized by multiple abnormalities in the pancreas, body tissues and liver [16]. The proposed compartmental model by Vahidi et al. (2010) is use

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to develop a PID controller to regulate the blood glucose. In the following sections, the underlying glucose regulatory model will be described, followed by the control strategy and simulation results.

I. Modeling of Type II Diabetic Patient

A mathematical representation of the human glucose-insulin system is necessary to implement a model-based control scheme. Many approaches have been taken, starting from the initial glucose modeling work of Bolie [17]. In many of these models [18-20], the compartmental modeling approach has been used. In this approach, the body is divided into compartments representing different organs, or parts of the body, and mass balance equations are derived for each compartment. The compartmental minimal model of Bergman (1981) has been widely used in many studies [18]. More complicated compartmental models proposed by Cobelli (1983)[19] and Sorensen (1985) [20] have considered more compartments. Their application of additional compartments allow for a more accurate simulation of the physiological dynamics for Type I diabetic patients and hence a more thorough analysis of the control system for blood glucose level regulation [21,22]. Recently, models proposed for a healthy body have been modified to describe glucose-insulin interactions in type II diabetic patients [16].

In this paper, the Type II diabetic model proposed by Vahidi et al. (2010) is used. This model results from initial work by Guyton et al. which was updated by Sorensen [23]. The Sorensen model contains three main sub-models which represents blood glucose, insulin and glucagon concentrations in the body [20]. Each sub-model is divided into individual compartments representing a specific organ in the human body.

Model equations include mass balance equations over each sub-compartment for every individual compartment. Since pancreatic insulin production is a complex mechanism which cannot be described by simple mass balance equations, a separate model is considered for the pancreas. The general form of the mass balance equation on each sub-compartment is as follows:

$$VdY/dt = Q(Y_{in} - Y_{out}) + r_{source} - r_{sink} \qquad (1)$$

where V is the volume of sub-compartment; Y is the concentration of either insulin, glucose or glucagon; t is time, Q is blood flow rate, and r_{sourse} and r_{sink} are the metabolic source and sink of the material balance substance, respectively. Since the glucagon sub-model has only one compartment, blood flow rate is set to zero and the glucagon mass balance equation has only the metabolic sink and source rates.

The metabolic rate of different substances takes on the following general form:

$$r = M^{I}(t,I)M^{G}(G)M^{\Gamma}(t,\Gamma)r_{basal} \qquad (2)$$

where M^{X} represents the $X's$ multiplier which represents the regulatory effect of X substance on the metabolic rate and r_{basal} is the metabolic rate at the basal condition. As indicated in the equation, the regulatory hormonal effects of insulin and glucagon are generally time dependent. Insulin is secreted from beta cells in the pancreas in a complex mechanism. The pancreatic insulin release model used in this paper has been proposed by Vahidi (2010) [16]. Considering characters of Type II diabetic patients, the relative parameters are estimated by using available clinical data.

The controlled output for this system is the arterial glucose concentration, which is regulated by the manipulated variable, insulin infusion rate. A disturbance variable, glucose uptake from the gut compartment, is added to the model to simulate the diabetic patient ingesting a meal. The mathematical representation of the meal sub-model is described in Lehmann and Deutsch (1992) [24].

II. Math

The principles of feedback control can be exemplified using the PID controller. The controller continuously adjusts the insulin infusion rate (R_I , mU/min) by assessing glucose excursions from three viewpoints, the departure from the blood glucose concentrations of normal human (the proportional component), the area-under-curve between capillary and target glucose (the integral component), and the change in capillary glucose (the derivative component). R_I is computed as

$$R_I(t) = K_P(G_B(t) - G(t)) + K_I\int(G_B(t) - G(t))dt + K_D d(G_B(t) - G(t))/dt \qquad (3)$$

where K_P , K_I , and K_D represent weights (gains) given to the proportional, integral, and derivative components, and G and G_B represent capillary and target glucose levels, respectively. Both units of capillary and target glucose levels (G and G_B) are mg/dL . Some controllers include a subset

of components, for example, a proportional-derivative (PD) controller includes the proportional and derivative components to improve robustness. Tuning of the controller corresponds to the determination of constants K_P, K_I, and K_D. This can be achieved by an off-line assessment using, for example, pharmacokinetic modelling [25]. The constants may also be estimated from the subject's daily dose.

The goals are to reduce the hyperglycemic trajectory to as short a time as possible, to avoid hypoglycemia below 60 mg / dL and to return to and maintain normoglycemic levels within 3 hours. In clinical practice, the plasma glucose concentration is allowed to vary in a normoglycemic range. Therefore, a modified PID control strategy is proposed:

$$R_I(t) = K_P(G_B(t) - G(t))^2 + K_I \int (G_B(t) - G(t))dt + K_D d(G_B(t) - G(t))/dt \quad (4)$$

III. Results and Discussion

U The dynamic simulation for the PID controller is programmed in Matlab, with a 50g meal disturbance at t=50 minutes. The controller is tuned to values of K_P =-0.1, K_I =-500, and K_D =0, to achieve the results displayed in Fig. 1.

In Fig. 1, the meal disturbance is implemented at t=50 minutes, and the resulting trajectory with the PID response strategy plotted. For Type II diabetic patients, the initial value of blood glucose concentration is defined as 114 mg / dL. At t=50 minutes, a 50g meal disturbance is introduced. In Fig. 1 demonstrates that the PID controller is able to handle the 50g meal disturbance, with blood glucose decreasing to 92 mg / dL within 3 hours. Low blood glucose concentrations ($\leq 60 mg / dL$) in diabetic patients are dangerous, and thus the minimum value of glucose concentration is kept safely within normoglycemic ranges. The blood glucose concentration then returns to the set point level within 3 hours. The plasma insulin concentration in a healthy patient is rarely above 100 mU / l. Additionally, it is impossible to remove insulin once it has been delivered to the patient. In Fig. 1, the rate of insulin infusion is also kept in this range.

In Fig. 2, the meal disturbance is also implemented at t=50 minutes, and the modified PID control strategy who used. The controller was tuned to K_P =0.015, K_I =-1000, and K_D =0, to achieve the results displayed in Fig. 4. Compared with above simulation results, the plasma glucose concentration decreased into the normoglycemic range more quickly. The total insulin infusion amounts are also lower than the simulation in Fig. 1. Although both the glucose concentration and insulin infusion rate fluctuate after the meal

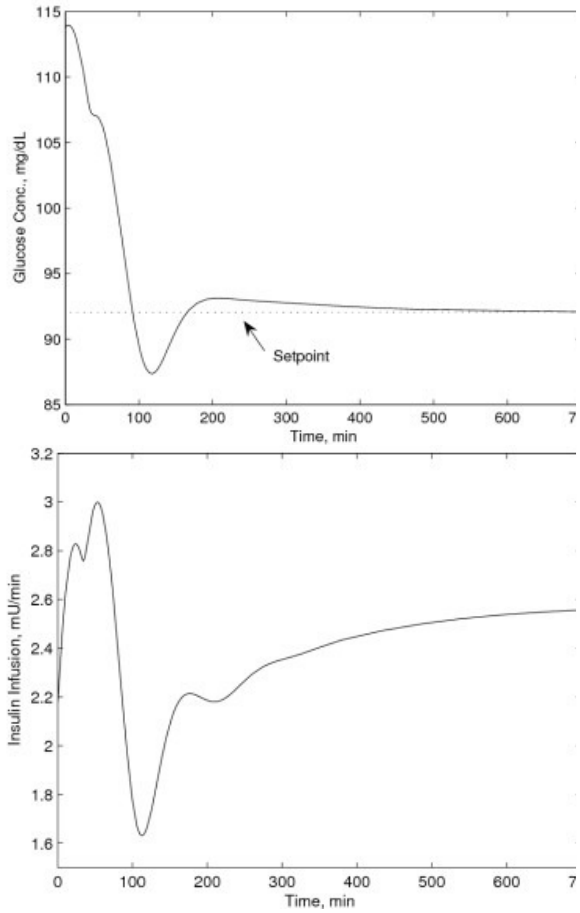

Fig. 1. Response of the initially controlled diabetic model with a 50g meal disturbance at time =50 min

disturbance, the values are still within the normal range. Therefore, considering the hyperglycemic reduction time and the insulin amount the modified PID control strategy is demonstrates an improved performance which provides a more aggressive response for larger deviations and less response for smaller deviations.

IV. Conclusions and Future Work

The PID control system is well suited to regulate glucose concentration with a meal disturbance in subjects with Type II diabetes mellitus. The simulation results demonstrate the potential use of a feedback controller to regulate blood glucose for Type II diabetic patients. charge of $81 per 100 for color reprints.

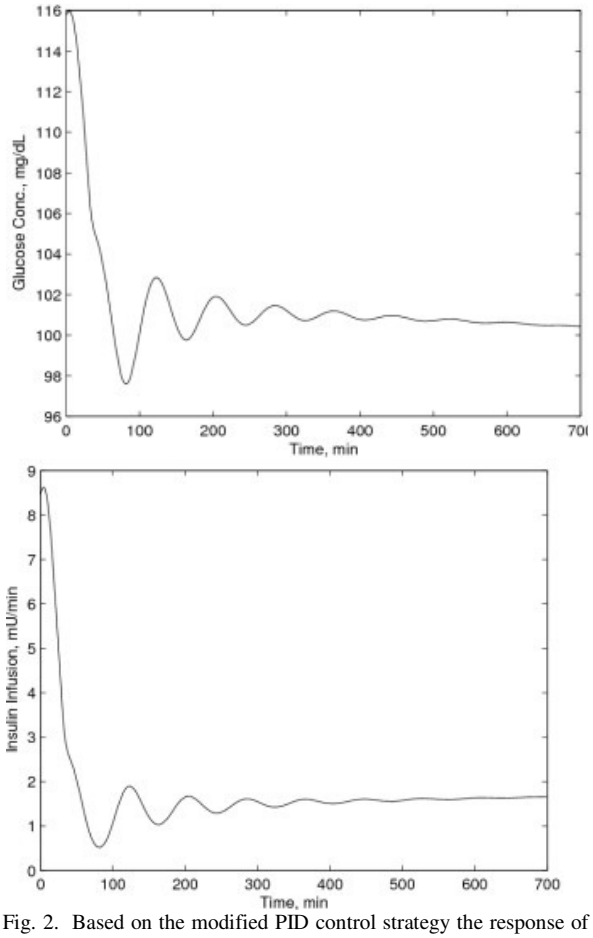

Fig. 2. Based on the modified PID control strategy the response of the initially controlled diabetic model with a 50g meal disturbance at time =50 min

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