AN AUTOMATIC INSULIN INFUSION SYSTEM BASED ON H-INFINITY CONTROL TECHNIQUE

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Abstract-**This paper presents a control algorithm for a type I diabetes mellitus patient under an intensive insulin treatment. The control algorithm employs a robust H∞ controller to regulate the blood glucose level. The control scheme is based on closed-loop feedback strategy to overcome the variability in the glucose-insulin dynamics from patient to patient. Controller performance is assessed in terms of its ability to track a normoglycemic set point (70 mg/dl) in response to multiple meal disturbances resulting from food intake. Simulations results show that resulted controller are robust to 90% parameter variations from mean value on nonlinear patient model. The proposed approach can successfully regulate the blood glucose level and represents more effective results in terms of robustness to uncertainty, in comparison with other existing algorithms.**

Keywords –**Glucose regulation, Insulin Delivery rate, Robust H∞ control, Robustness, Type I Diabetes.**

I. INTRODUCTION

Type I diabetes mellitus is a disease in the glucose-insulin endocrine metabolic regulatory system, in which the body immune system destroys pancreatic beta cells, the only cells in the body that make the hormone insulin, which regulates blood glucose [1]. In normal physiology the body maintains blood glucose levels within a narrow range of 70-110 mg/dl. When a normal person is subjected to a glucose meal, the glucose concentration in plasma increases from basal value and so the pancreatic β-cells secrete insulin. The insulin in plasma is hereby increased, and the glucose uptake in muscles, liver, and tissues is raised by the remote insulin in action. This lowers the glucose concentration in plasma, implying the β-cells to secrete less insulin, from which a feedback effect arises. However, in type I diabetic patients whose pancreas does not release insulin, blood glucose level remains in much more than basal value for long period of time. When glucose level remains high for extended periods of time the patient is at risk for neuropathy, nephropathy, blindness, and other long-term vascular complications. However the result of the Diabetes Control and Complications Trial (DCCT) showed that an intensive insulin therapy can reduce the risk of developing complications [2]. Consequently, an intensive therapy is encouraged for type I diabetic patients prescribed by a continuous subcutaneous insulin infusion pump.

The current medical treatment for type I diabetes is open-loop control in which physicians inject a pre-determined dose of insulin. This method not only is painful and inconvenient but also unreliable because of approximation involved in type and the amount of insulin delivered. However, closed-loop control method which acts as an artificial pancreas includes a blood glucose sensor, insulin pump, and appropriate control algorithm (figure 1). In this system, a control algorithm processes the information of the glucose sensor in real-time, and updates the insulin injection rate by the pump.

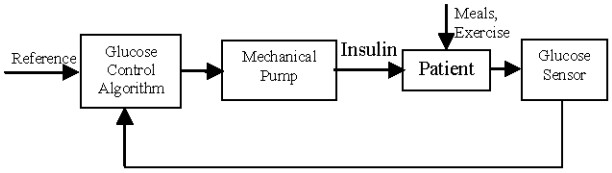

Fig. 1. Closed-loop control of diabetic patients.

Since recent advances have made available programmable and variable-rate infusion pumps [3], the feedback control system mimics the normal function of a pancreas more closely. However, creating a device which would accurately replace multiple insulin injections per day for a long period of life is not an easy task. It should be made from biocompatible materials and as small as possible. More ways to make the function of the implantable insulin pumps idea are currently under research. Current blood glucose monitoring is accomplished through invasive methods, such as, a finger prick, but the use of a non-invasive monitor would increase patient comfort and therefore compliance to the insulin therapy [4].

In testing the performance of the control algorithm a virtual patient need to be implemented using an appropriate mathematical model. During the last decades, many mathematical models have been derived to describe dynamics of glucose-insulin regulatory system [5-7]. These models have ranged from linear to nonlinear with increasing the levels of complexity [8]. Since, the parameters of these models are in general time-varying, even for a patient under a constant treatment and environment conditions. Therefore, employed controller in closed-loop system should be robust to parameters variations in model and physical disturbances like food intake.

With the availability of these mathematical models different algorithms based on control theory have been developed to optimize the insulin therapy of people with diabetes. Some of these algorithms include proportional-integral-derivative (PID) [9] and proportional-derivative (PD) [10], pole placement [11], and optimal control algorithms [12,13]. Nevertheless, the important point in most of these researches is that proposed controller has been designed with regard to mathematical model as a crisp model, and uncertainty in the model parameters has been not considered. Therefore, although these methods, would offer good responses in simulations, it is likely that it would not be successful in practice and failed while applying to an actual patient. Also, robust control using the H∞ control methodology was the topic of the paper by Kientiz and Yoneyame [14]. While meal disturbance simulations were promising for the nominal

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patient, but the controller was robust to small amount of patient uncertainty and inferences to larger patient variability would require retuning of certain controller parameters.

In control theory field, the H_∞ framework is well suited for blood glucose regulation, due to the ability to tune the controller to robustness to uncertainty while mathematically guarantying a certain degree of performance [15].

This work exploits H∞ control strategy to regulate the blood glucose level of type I diabetes mellitus patient around euglycemia with a closed-loop system. Insensitive to internal and external disturbances, accuracy, and robustness to uncertainty are the main features of proposed algorithm. The text is organized as follows. In section II the physiological model of glucose-insulin regulatory system in type I diabetes mellitus patient is introduced. Section 3 includes the synthesis of the H∞ control. Simulation results and concluding remarks are included in sections IV and V, respectively.

II. GLUCOSE-INSULIN REGULATORY SYSTEM MODEL

Models of the glucose-insulin regulatory system are categorized as either comprehensive or simple models. Comprehensive models, though they are very accurate in regimen evaluation, are generally unsuited for real-time control, requiring several time points of input to generate the insulin infusion profile. Moreover, they are not generic requiring patient-specific data and known glucose inputs. The goal of this paper is to develop a control technique based on a physiological model that capture the essential system dynamics, which do not require unavailable data, and are applicable to a wider variety of subjects. Simple models capture these essential dynamic behaviors, providing a more suitable model for real-time control design and analysis. Bergman's minimal model is the most popularly used model in the literature which has the following advantages [7]:

- to be physiologically based,
- having parameters that can be estimated with a reasonable precision,
- parameters with values that are reasonable and have physiological interpretation,
- best able to simulate the dynamics of the system with the smallest number of identifiable parameters.

The third-order model is comprised of a glucose compartment, G , a remote insulin compartment, X , and an insulin compartment, I . The remote insulin compartment mediates glucose uptake within the glucose space to the peripheral and hepatic tissues. The model equations are [18]:

$$\begin{aligned} \dot{G}(t) &= -p_1[G(t)-G_b]-X(t)G(t)+D(t) \\ \dot{X}(t) &= -p_2X(t)+p_3[I(t)-I_b] \\ \dot{I}(t) &= -n[I(t)-I_b]+\gamma[G(t)-h]^+t+u(t) \end{aligned} \quad (1)$$

with initial conditions $G(0)=G_0$, $I(0)=I_0$, and $X(0)=X_0$. The sign (+) denotes the positive reflection to glucose intake and $t = 0$ is the glucose injection time.

In the above equations $G(t)$ represents the glucose concentration in plasma at time t (mg/dl), $X(t)$ is proportional to active insulin in remote compartment and describes the time dependent effect of the insulin on the net glucose disappearance (1/min), $I(t)$ is the insulin concentration in plasma at time t (μU/ml), G_b is the basal value of plasma glucose (mg/dl), I_b is the basal value of plasma insulin (μU/ml), p_1 is the glucose effectiveness when insulin remains at the basal level (1/min), p_2 is the rate for decrease in tissue glucose uptake ability (1/min), p_3 is referred as an insulin-dependent increase in glucose uptake ability in tissue per unit of insulin concentration above I_b [$(\text{min}^{-2})(\mu\text{U/ml})^{-1}$], n is the time constant for insulin disappearance (1/min), h is the threshold value of glucose above which the pancreatic β-cells release insulin (mg/dl), and γ is the rate by which the pancreatic β-cells' release of insulin after the glucose injection and with glucose concentration above the threshold [(μU/ml) min^{-2} $(\text{mg/dl})^{-1}$]. The term $\gamma[G(t)-h]^+$ in the third equation of the model acts as an internal regulatory function that formulates the insulin secretion in the body, which does not exist in diabetic patients. The available clinical data indicates that for patients with diabetes the value of p_1 parameter is well below the normal value and it can be approximated as zero [13]. Model parameters and constants are adopted from [13,16] are given in table 1. It is worth nothing that these values were calculated for a person of average weight and vary from patient to patient which makes the glucose regulation a challenging control problem.

TABLE I
MODEL PARAMETERS

Parameter	Value
p_1	0.0316
p_2	0.0107
p_3	5.3×10^{-6}
n	0.2640
h	80.2576
γ	0.0042
G_b	70
I_b	7

The disturbance $D(t)$ is the glucose meal and can be modeled by decaying exponential function of the following form [13]:

$$D(t) = A\exp(-Bt),\ \ B>0 \quad (2)$$

Where t is in min and $D(t)$ is in (mg/dl/min). $u(t)$ is the exogenous insulin infusion rate. The controller uses a feedback loop that employs the blood glucose level G, and its derivative (dG/dt), as sensor inputs, and the exogenous insulin infusion rate $u(t)$ as the control output. The purpose is to design an appropriate control function u(t) to compensate the uncertainties and disturbances and stabilize blood glucose level of diabetic patient at basal level.

To verify the physiological model the controller output, $u(t)$ is set to zero and the response of a healthy person and diabetic patient is obtained to show the difference between their glucose regulatory systems. As seen in figure 2, a healthy person's blood glucose value is stabilized in normal

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value in spite of meal disturbance, but a patient's glucose level remains dangerously in much more than basal value.

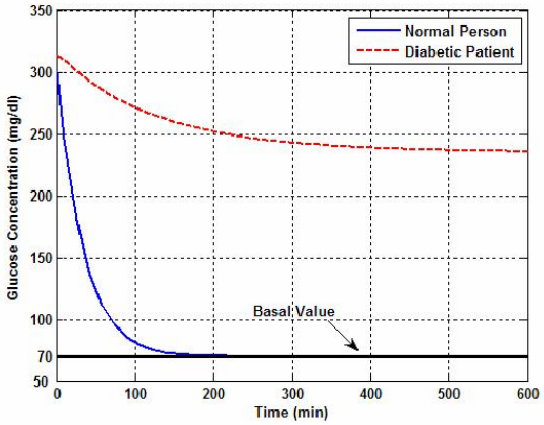

Fig. 2. Healthy person and diabetic patient glucose regulatory system.

III. CONTROLLER SYNTHESIS

A block diagram representation of the nominal $H\infty$ problem is shown in figure 3, which is compatible with dimensions of $z(t) \in R^{p}$, $v(t) \in R^{p}$, $w(t) \in R^{d}$, $u(t) \in R^{q}$. P and K are assumed to be real rational and proper transfer functions. Transfer matrix P is called generalized plant and has the following realization:

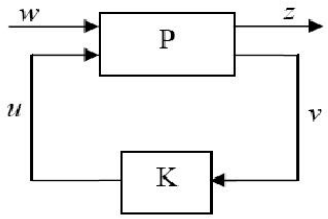

Fig 3. H_∞ synthesis problem.

$$P(s) = \left[\begin{array}{c|cc} A & B_1 & B_2 \\ \hline C_1 & D_{11} & D_{12} \\ C_2 & D_{21} & D_{22} \end{array}\right] = \left[\begin{array}{c|c} G_{11} & G_{12} \\ \hline G_{21} & G_{22} \end{array}\right] \tag{3}$$

The goal of this control methodology is to bound the worst case closed-loop performance of the process under study as measured by the induced-2 norm space representation. An H_∞ controller if one exists, minimizes $\|T_{zw}\|_\infty$ [15]. T_{zw} is the closed-loop transfer function matrix from ω to z:

$$T_{zw} = F_l(p,k) = P_{11} + P_{12}k(I - P_{22}K)^{-1}P_{21} \tag{4}$$

In order to find the controller, if exists, $P(s)$ should satisfy the following conditions:

1. (A,B) is controllable and (A,C) is detectable.
2. The matrix $\begin{bmatrix} A - j\omega I & B_2 \\ C_1 & D_{12} \end{bmatrix}$ must have the full
3. The matrix $\begin{bmatrix} A - j\omega I & B_1 \\ C_2 & D_{21} \end{bmatrix}$ must have the full rank for all ω.

Assumption 1 simply states that the linearized reduced order system must satisfy the controllability and observability criterion for linear systems based on the insulin delivery rate manipulated variable and arterial insulin concentration measurements. The second assumption guarantees a synthesized $H\infty$ controller is proper. For the system in the present study this assumptions were satisfied. The system of two Riccati equations is solved through the γ-iteration technique.

Bergman mathematical model is a nonlinear model, which become linear around steady state values to design closed-loop controller of the model. Generalized plant $P(s)$ is obtained according to block diagram in figure 3 in which G is the transfer function from blood glucose output to insulin input and G_d is transfer function corresponding meal disturbance. W's represent the weights for respective signals into the system. The generalized planet P for the blood glucose control is given by:

$$\begin{bmatrix} z_1 \\ z_2 \\ r - v \end{bmatrix} = P(s) \begin{bmatrix} d \\ n \\ u \end{bmatrix} = \begin{bmatrix} W_P G_d & 0 & W_P G \\ 0 & 0 & W_u \\ -G_d & -W_n & -G \end{bmatrix} \begin{bmatrix} d \\ n \\ u \end{bmatrix} \tag{5}$$

Where d is meal disturbance, n is measurement noise, u is insulin infusion rate by pump, z_1 represents blood glucose concentration, z_2 is control output of insulin infusion, and v is measured glucose concentration by sensor. Weight W_p is first order transfer function and is selected in a manner that $(1/|W_p|) > |SG_d|, \forall\, \omega$ in which S is sensitivity transfer function. Transfer function SG_d is a good measure for closed-loop performance in disturbance rejection. Weight W_u indicates control input weight. Sensor noise effects are given by W_n and indicate possible errors produced by glucose sensor.

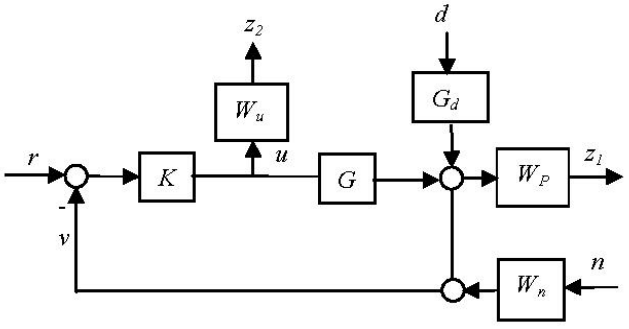

Fig. 4. Standard feedback configuration with weights.

The transfer functions G and G_d in (5) are:

$$G = \frac{-0.001548}{s^3 + 0.3063s^2 + 0.01151s + 8.92 \times 10^{-5}} \tag{5}$$

$$G_d = \frac{1}{s + 0.0316} \tag{6}$$

and the weighted transfer functions are:

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$$W_p = \frac{\frac{1}{1.2}s+1}{s+0.0001},\ W_u = 1,\ W_n = \frac{1}{10} \qquad (7)$$

IV. CLOSED-LOOP SIMULATION RESULTS

The designed controller is numerically implemented to the nonlinear physiological model of the glucose insulin system. The order of the resulted controller is forth, the gamma reaches here was γ=3.152. Figure 5 illustrates the results obtained from the simulation, using basal value of glucose and insulin concentration as initial condition. In the presence of multiple meal disturbance at time t=0 and t=360, patient's blood glucose concentration increases from target level of 70 mg/dl and then is completely stabilized at basal level in a reasonable time interval. To check the robustness of the controller three sets of parameters for three different patients are used. Although, the transient response of patients are different but in all cases the blood glucose stabilize in basal value with appropriate settling time. Also, the parameters of patient model are perturbed 90% from mean value and the closed-loop blood glucose response has been obtained. As shown in figure 6 the H∞ controller is completely robust to uncertainty in model parameters and stabilizes the blood glucose of patients in normal value.

Figure 7 demonstrates that the H_∞ controller work slightly better than a normal person in terms of peak reduction and settling time. Figure 8 also includes a plot of the response for a normal subject under the same conditions. These simulations show that a feedback scheme is the best choice for the blood glucose regulation.

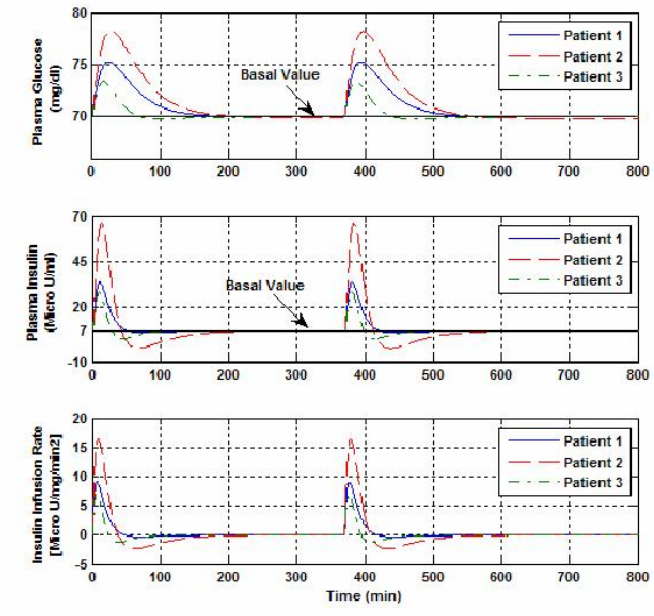

Fig 5. Closed-loop glucose regulation under two meals, at time t=0 and t=360 min. (a) Plasma glucose concentration (b) Plasma insulin concentration (c) Exogenous insulin infusion rate.

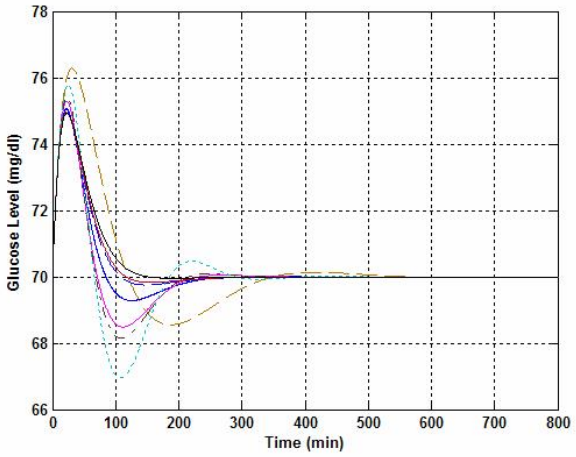

Fig 6. Closed-loop blood glucose control.

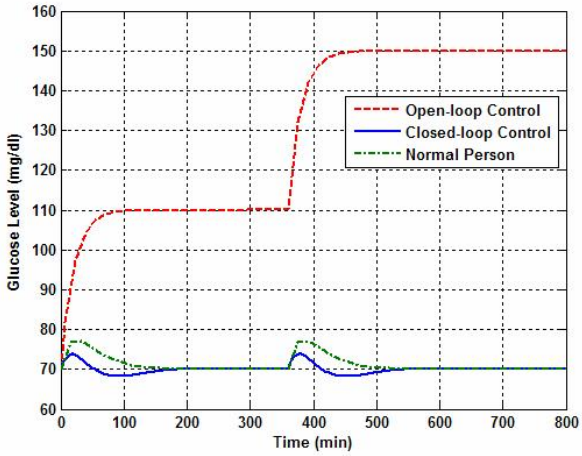

Fig 7. Comparison of feedback and open-loop glucose regulatory systems.

IV. CONCLUSIONS AND FUTURE WORKS

A. Conlusions

Diabetes management is one of important issues in the field of human regulatory systems, which is discussed in recent years. In This study, a closed-loop H_∞ controller has been developed to maintain the normoglycaemic average for diabetic patients of type I. The proposed can successfully tolerate patient variability and dynamic uncertainty while rapidly rejecting meal disturbances and tracking the constant glucose reference. Moreover, it has the potential of being implemented in a microcomputer for home treatment. Robustness was tested over a group of three patients with model parameters varying considerably from the averaged model. In addition, it is proved that this method has preference over other conventional techniques in blood glucose control. Employed control technique reported in this paper is expected to simplify insulin automatic injection mechanism and increase the quality of life, and life expectancy of diabetic patients.

A. Future Works

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Future work is conducted to the employing of the μ analysis and synthesis approach in designing a robust controller for blood glucose regulation in diabetic patients. Also, the effect of measurement noise is to be assessed and attenuated. Finally, the inclusion of an exercise regime in the overall model of the Type I diabetic patients in order to have a more realistic simulation will be considered.

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