Knowledge-based Closed-loop Control of Blood Glucose Concentration in Diabetic Patients and Comparison with H_∞ Control Technique

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ABSTRACT

In this paper, fuzzy-based closed-loop controller is applied to obtain a robust controller for blood glucose regulation in type I diabetes mellitus patients. The control technique incorporates expert knowledge about treatment of disease by using Mamdani-type fuzzy logic controller to robustly stabilize the blood glucose concentration in normoglycemic level. Controller performance is considered in terms of its ability to reject the multiple meals, on an averaged nonlinear patient model. Robustness of the controller is tested over a group of patients with model parameter varying considerably from the average model. The controller provides the possibility of more accurate control of blood glucose level in the patient in spite of uncertainty in model parameters and measurement noise. The proposed controller has showed superiority over other classical control techniques. A comparative study is presented with well-known conventional H_∞ control technique. Simulation results show the superiority of the proposed scheme in terms of reference tracking, disturbance rejection, and measurement noise in comparison with other approaches.

Keywords:

Closed-loop control, Glucose-insulin model, H_∞ control technique, Insulin delivery rate, Knowledge-based control, Type I diabetic patient.

1. INTRODUCTION

Diabetes mellitus has affected a large number of patients worldwide. Type I diabetes 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 to 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 [2]. 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 [3]. Consequently, an intensive therapy is encouraged for type I diabetic patients prescribed by a continuous subcutaneous insulin infusion pump.

Control strategies of diabetes treatment can be categorized as open-loop control, semi closed-loop, and closed-loop control. Current treatment methods utilize open loop control in which physicians inject a predetermined dose of insulin subcutaneously based on three or four times daily glucose measurements, usually by an invasive method of finger prick. This method not only is painful and inconvenient but also unreliable because of approximation involved in type and the amount of insulin delivered. In semi closed-loop control, insulin infusion rate adjust according to intermittent blood glucose readings. This technique is sub-optimal and unable to accomplish the aforementioned normalization and also suffered from long sampling time problem of missing fast or inter-sample disturbances. However, closed-loop control method which acts as an artificial pancreas is the most effective way of diabetes treatment and could improve the quality of life and life expectancy of patients. Ultimately, a true artificial pancreas is a closed-loop device that enables a person with diabetes to maintain normal glucose levels by providing the right amount of insulin at the right time, just as the pancreas does in non-diabetic individuals [4].

In the near term, we expect artificial pancreases to be external devices comprising of insulin pumps, already widely available; continuous glucose monitors (CGMs), which are coming on the market now; and an appropriate control algorithm. Figure 1 shows the block diagram of a closed-loop control system of diabetic patients. In this system, the control algorithm would calculate optimal insulin delivery rate designed to keep the patient under metabolic control, and a signal would drive a mechanical pump to deliver the desired amount of insulin.

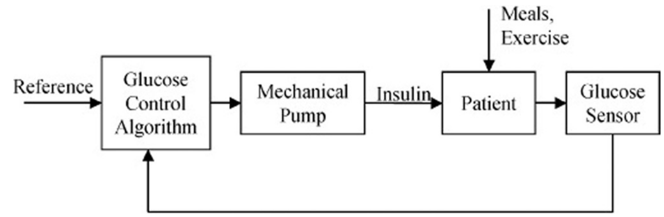

Figure 1: A closed-loop glucose control system.

Since recent advances have made programmable and variable-rate infusion pumps [5], 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. Four major sites for invasive insulin delivery are subcutaneous, intramuscular, intravenous, and intraperitoneal [6]. The subcutaneous site is the simplest and safest in long term but the absorption of insulin from subcutaneous tissue is delayed. The intramuscular site is usually preferred for people affected by brittle diabetes who have a subcutaneous barrier to insulin absorption. The intravenous has rapid delivery with negligible dead-time. The main problem of this approach is presence of the intravenous lines which may not be suitable for some patients. Intraperitoneal is the most physiological insulin delivery, though the major disadvantage is its difficult access. The recent advances have brought in non-invasive modes of insulin delivery such as transdermal and oral [6]. These modes are not painful like the invasive modes but have problems such as low skin permeability in transdermal mode and issues concerned with the oral bioavailability for the oral mode.

CGMs are devices that provide continuous "real time" readings and data about trends in glucose levels. Blood glucose monitoring devices are classified as invasive, minimally invasive, and non-invasive. Fully invasive systems can be either beside clinical devices or self-monitoring meters. Such system allows continuous monitoring, therefore increasing the amount of clinical information. System which puncture the skin are still standard techniques for home monitoring reading glucose concentration through electrochemical or optical disposable strips for finger prick blood samples [7]. Efforts have been made to reduce the level of invasiveness by decreasing the blood sample volume to a few microliters, and measuring areas of the body less sensitive to pain than fingertips, such as forearm, upper arm, or thigh. Minimally invasive measurements sample the interstitial fluid with subcutaneous sensors [8]. Even in this method, the discomfort causes difficulties to the patient's therapy. Hence, the recent researches has been focused on developing the non-invasive glucose control devices [9].

In testing the performance of the control algorithm, a virtual patient needs to be implemented by using a suitable mathematical model. It has been assumed that glucose measurements are done subcutaneously, considering that accurate sensors are available for such measurements. During the last decades, many mathematical models have been derived to describe dynamics of glucose-insulin regulatory system [10-12]. These models have ranged from linear to nonlinear with increasing the levels of complexity [13]. However, the primary drawback of these mathematical models is identifying a nominal patient to implement the model parameters. It is evident that physical characteristics vary from person to person and so different patients have different responses to the same treatment, which in turn can cause parameter variations in the system. Thus, designed controller should be robust to uncertainty in model parameters and meal disturbances.

With these mathematical models, different algorithms based on control theory have been developed to control the blood glucose level in people with diabetes. Some of these algorithms include proportional-integral-derivative [14,15] and proportional-derivative [16], that need a linearized model for the design, as well as H_∞ control technique. If linear models are employed for the patients, control algorithm like H_∞ control can guarantee some level of performance, but full robustness cannot be achieved via this algorithms. However, as far as linear control algorithms are concerned, H_∞ control offers a promising result in maintaining blood glucose regulation in diabetic patients. Some interesting result of this method can be found in [17,18]. Also, optimal control algorithms are applied for blood glucose regulation in semi closed-loop control system [19,20]. However, 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 they would not be successful in practice and failed while applying to an actual patient. A fuzzy controller to keep a normoglycemic average of blood glucose concentration was designed in [21]. Although simulation results were promising for the nominal patient, uncertainty in patient model parameters has not considered.

In the control theory, the fuzzy logic has emerged as a powerful tool to employ expert knowledge about the systems for implementing an appropriate control low [22]. Specially, the ability of expert knowledge in the fuzzy logic field has increased a lot of attention in the biomedical engineering field [23,24].

The ultimate goal of this research is to develop a consistent, robust controller for safe, predictable regulation of blood glucose levels in diabetic patients. This work employs fuzzy logic control scheme to obtain a robust feedback controller to stabilize the blood glucose concentration of type I diabetic patients around normal value, where a Mamdani-type of fuzzy controller is designed by using expert knowledge about diabetes mellitus treatment. Insensitive to typical error in commercial device and multiple meal disturbances, accuracy, robustness to model parameter variations, and appropriate settling time are main features of proposed algorithm. The text is organized as follows.

In section 2, the physiological model is introduced to show the dynamics of glucose-insulin regulatory system of human body. Section 3 includes the design of knowledge-based fuzzy logic controller. Simulation results are included in section 4. A comparative study with open-loop control and classical H_∞ algorithm is presented in section 5. Finally, the paper is closed with the interpretation and discussion of the results.

2. MATHEMATICAL MODEL OF GLUCOSE-INSULIN REGULATORY SYSTEM

Although complex models are accurate for regimen evaluation, they are not suitable for real-time control, because they require patient specific data and known glucose input. However, simple models capture essential dynamic behaviors and provide a more suitable foundation for real-time control design.

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 has been proposed as a powerful modeling approach to estimating the insulin sensitivity and the glucose effectiveness, which are very useful in the study of diabetes, and is the most popularly used model in the literature which has the following advantages [25,26]:

- 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 [26,27]:

$$\begin{aligned} &\dot{G}(t) = -p_1[G(t)-G_b] - X(t)G(t) + D(t), \quad G(0) = G_0 \\ &\dot{X}(t) = -p_2X(t) + p_3[I(t)-I_b], \quad X(0) = 0 \qquad (1) \\ &\dot{I}(t) = -n[I(t)-I_b] + \gamma[G(t)-h]^+ t + u(t), \quad I(0) = I_0 \end{aligned}$$

Where, t=0 is the glucose injection, + denotes positive reflection, and

G(t): The plasma glucose concentration at time t (mg/dl), *X(t)*: Is the generalized insulin variable for the remote compartment (min^{-1}), *I(t)*: Is the plasma insulin concentration at time t (μU/ml), G_b: Is the basal preinjection value of plasma glucose (mg/dl), I_b: Is the basal preinjection value of plasma insulin (μU/ml), p_1: Insulin-independent rate constant of glucose rate uptake in muscles, liver, and adipose tissue (per min), p_2: The rate of decrease in tissue glucose uptake ability (per min), p_3: The insulin-independent increase in glucose uptake ability in tissue per unit of insulin concentration above I_b (min^{-2}(μU/ml)), n: The first order decay rate for insulin in plasma (per min), h: The threshold value of glucose above which the pancreatic β-cells release insulin, γ: The rate of the pancreatic β-cells' release of insulin after the glucose injection and with glucose concentration above h [(μU/ml) min^{-2} (mg/dl)$^{-1}$], G_0: The theoretical glucose concentration in plasma (mg/dl) at time 0, I_0: The theoretical insulin concentration in plasma (μU/ml) at time 0.

The term $\gamma[G(t)\text{-}h]^+$ in the third equation of the model acts as an internal regulatory function that formulates the insulin secretion in the body, which does not exists in diabetic patients. The metabolic portrait of a single individual is then determined by the following parameters:

$$\text{Insulin Sensitivity: } S_I = \frac{p_3}{p_2} \qquad (2)$$

$$\text{Glucose Effectiveness: } S_G = p_1 \qquad (3)$$

Pancreatic responsiveness:

$$\varphi_1 = \frac{I_{max} - I_b}{n(G_0 - G_b)}, \qquad (4)$$
$$\varphi_2 = \gamma \times 10^4$$

Where, I_{max} is the maximum value of insulin in plasma. S_I is measured in $(\mu U/ml)^{-1}$ per minute; S_G in min^{-1} and φ_1 in $min^{-1}\mu U/ml$ per mg/dl. These factors are important indicatives of how glucose and insulin act inside that person's body.

The available clinical data indicate that the value of p_1 parameter for diabetic patient will be significantly reduced and it can be approximated as zero [20]. Model parameters and constants are adopted from [25,26] and are given in Table 1. Note that these values were calculated for a person of average weight and vary from patient to patient, which makes the design of controller a more challenging task.

$D(t)$ shows the meal glucose disturbance and can be modeled by decaying exponential function of the following form [17]:

$$D(t) = A\exp(-Bt), \quad B > 0 \qquad (5)$$

Where,t is in min and $D(t)$ is in (mg/dl/min). $u(t)$ is the exogenous insulin infusion rate. The model is simple, yet accurately represents the essential dynamics of the human glucose-insulin regulatory system. 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.

To verify the physiological model, the control input, $u(t)$, is set to zero in system (1) and the responses of a healthy person and diabetic patient are obtained. As seen in Figure 2, a healthy person's blood glucose value is stabilized in normal value in spite of meal disturbance, but a patient's glucose level remains dangerously in much more than basal value.

3. DESIGN OF THE KNOWLEDGE-BASED CONTROLLER

The block diagram of fuzzy logic controller for blood glucose regulation is shown in Figure 3.

The controller is designed with a Mamdani-type fuzzy architecture with two input linguistic variables and one output variable. The input variables are the plasma glucose level $G(t)$ and its rate of change dG/dt, and the output variable is the exogenous insulin infusion rate. The characteristics of the input and output variables are given in Tables 2 and 3, respectively. The types of membership functions applied in the design are chosen triangular membership functions for simplicity. These membership functions were selected according with the fuzzy classification of the input and output variables. The shapes of input membership functions are presented in Figure 4. The output membership function is then shown in Figure 5.

By the definition of the input and output membership functions, 21 IF-THEN rules were defined. These rules were of AND (minimum) type antecedent. The output (defuzzification method) is calculated by the CENTROID method. The linguistic rules are detailed in Table 4.

Table 1: Parameters of the model

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

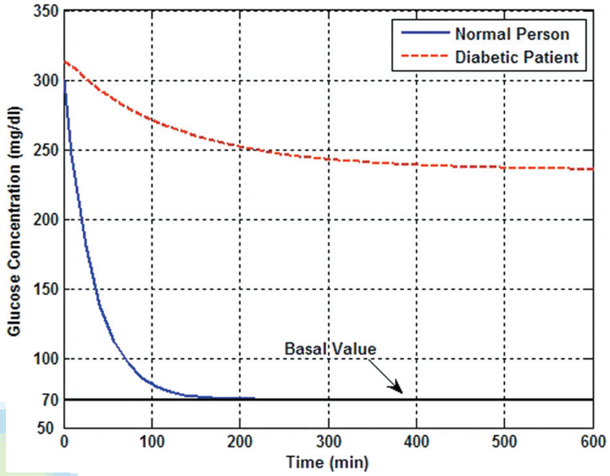

Figure 2: Healthy person and diabetic patient glucose regulatory system.

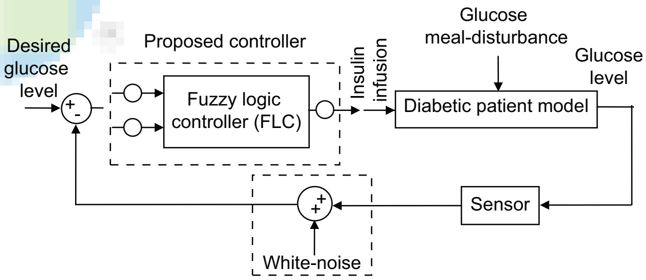

Figure 3: Fuzzy logic control block diagram.

Table 2: Characteristics of input variables

Input variables	Interval	Membership functions						
Glucose level G(t)	[40 400] mg/dl	Very low	Low	Normal	Medium	High	Very high	Extreme
Glucose deviation	[-20 20] mg/dl	Negative	Zero	Positive				

Table 3: Output variable characteristics

Output variables	Interval	Membership functions						
Insulin infusion u(t)	[-1 8] [μU/mg/min2]	Very low	Low	Normal	Medium	High	Very high	Extreme

Table 4: Fuzzy IF-THEN rules

Glucose	Glucose rate of change		
	Negative	Zero	Positive
Extreme	Extreme	Extreme	Extreme
Very high	Very high	Very high	Extreme
High	High	High	High
Medium	Medium	Medium	medium
Normal	Zero	Zero	Zero
Low	Very low	Low	Low
Very low	Very low	Very low	Very low

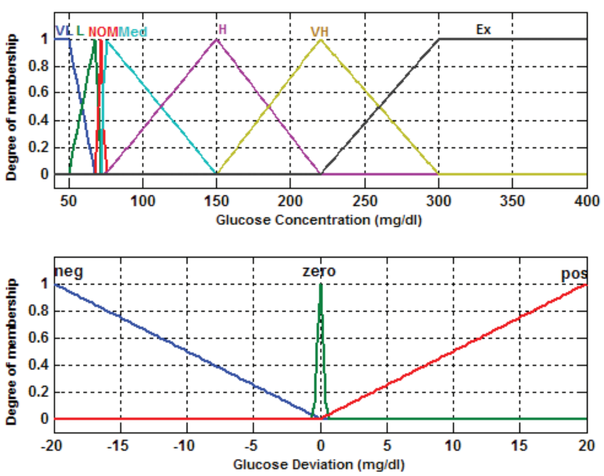

Figure 4: Input membership functions.

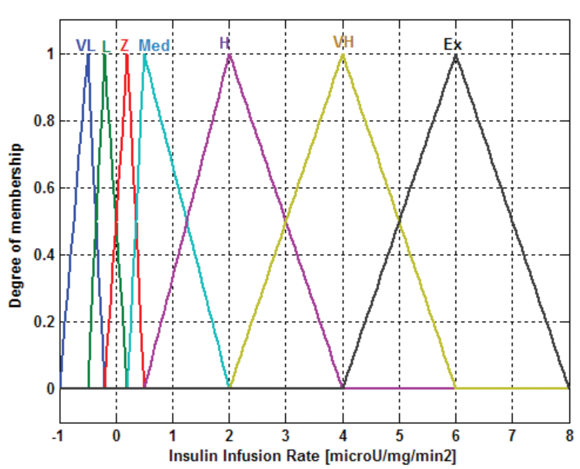

Figure 5: Output membership function.

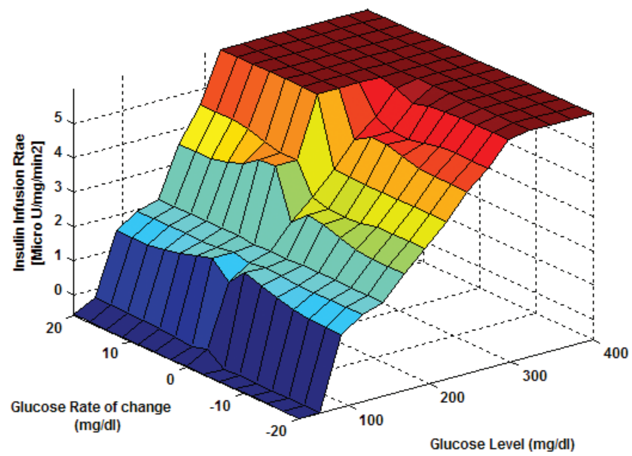

Figure 6: Control action surface.

Figure 6 shows the output surface of the controller. It is obvious that controller inputs change with the output in a piecewise linear manner.

4. SIMULATION RESULTS

4.1 Blood Glucose Closed-loop Response

In the first set of simulation designed, fuzzy logic controller is applied to virtual patient as shown in Figure 3 and blood glucose patient's response obtained in presence of meal disturbance at time t=0. As seen in Figure 7, maximum tracking error in this case is 4.51 mg/dl.

4.2 Measurement Noise

In order to consider the effect of measurement noise, a white Gaussian noise with amplitude 0.15 is applied to the system and response of blood glucose level of diabetic patient is obtained. Figure 8 demonstrates that the fuzzy logic controller remains close to normoglycemic average in presence of error in measurements.

4.3 Correction of Severe Initial State

In third set of simulations, the proposed fuzzy logic controller is applied to nonlinear patient model and severe initial state of type I diabetic patient is corrected. Figure 9 shows the simulation result of this section. Also, to check the robustness of controller to parameter variations in model, three sets of parameters for three different patients are used. As it can be seen in Figure 9, the controller is able to stabilize the patient blood glucose in suitable time period in spite of meal disturbance. Initial conditions of patient model variable are given in Table 5.

4.4 Multiple Meal Disturbances

In the next set of simulations, multiple meal disturbances is applied at time t=0 and t=360 minutes and response of controller is obtained using normal initial condition for model variables. As shown in Figure 10, proposed controller acts successfully in controlling the blood glucose level in presence of multiple meal disturbances. It is obvious that the transient responses of the different patients to the same controller are different, but in all cases, the glucose is completely stabilized at the basal level with an appropriate settling time. The controller performance demonstrates superiority of using fuzzy logic control and shows more effective results in terms of settling time and uncertainty in the model parameters, comparing with the results discussed in [20,21].

Also, Figure 11 demonstrates that closed-loop control

Table 5: Initial conditions of model variables

Parameter	Patient 1	Patient 2	Patient 3
G(0)	200	220	180
I(0)	55	50	60
X(0)	0	0	0

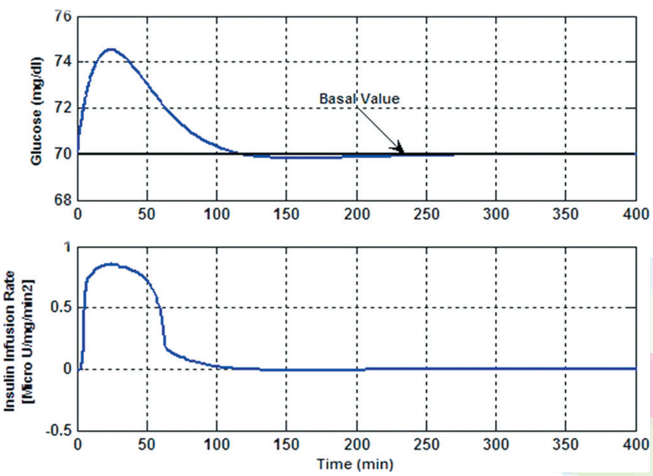

Figure 7: Closed-loop response based on fuzzy controller (a) blood glucose (b) insulin infusion rate.

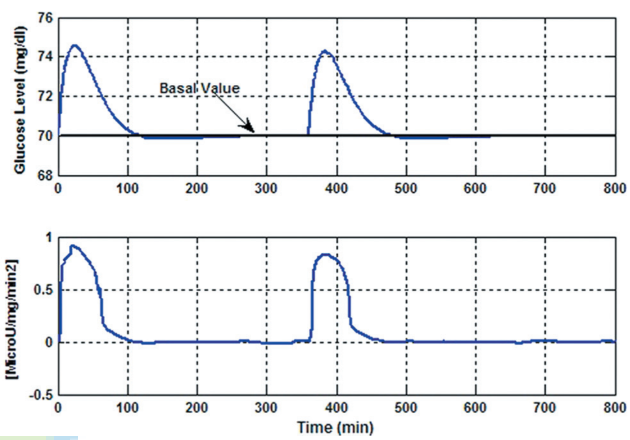

Figure 8: Closed-loop response in presence of measurement noise.

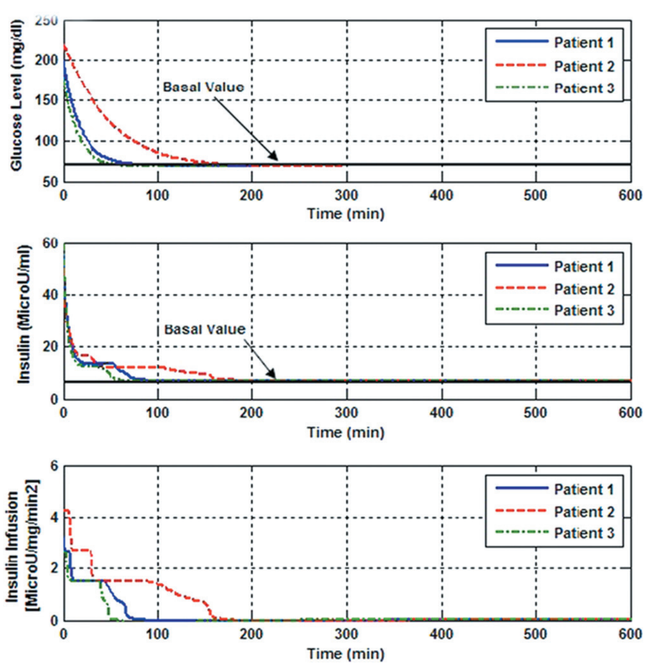

Figure 9: A severe initial state correction.

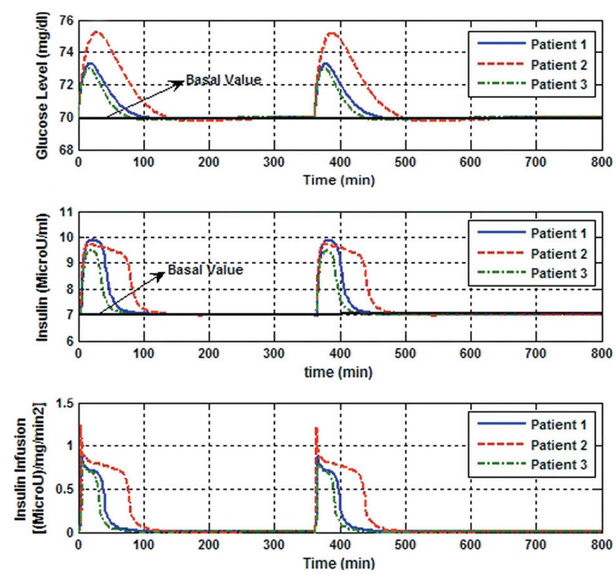

Figure 10: Blood glucose regulation under two meals, at time t=0 and t=360 minutes. (a) Plasma glucose concentration with initial state of 70 mg/dl (b) Plasma insulin concentration with initial state of 7 MicroU/ml (c) Exogenous insulin infusion rate.

works slightly better than open-loop control in terms of peak reduction and settling time. This Figure also includes a plot of the response for a normal person under the same conditions.

The values of the model parameters that have been used in implementing the controller are given in Table 6.

5. H_∞ CONTROL TECHNIQUE

Another approach to controlling blood glucose in diabetic patients is H_∞ control approach [17,18]. The goal of this control methodology is to bind the worst-case closed-loop performance of the process under study as measured by the induced-2 norm space representation. To evaluate the performance of an H_∞ controller *vs* fuzzy logic control approaches detailed here, some cases are examined. The nominal controller is compared with an H_∞ controller in terms of settling time, overshoot, and sum-square error. As shown in Table 7, fuzzy controller with 59.53% in sum squared error and 50.51% reduction in settling time acts better than H_∞ controller. Therefore fuzzy controller is superior in terms of reference tracking.

Also, Figure 12 demonstrates the response of two controllers in presence of measurement noise. As it can be seen, closed-loop control system based on fuzzy controller operates better than H_∞ control. Overall, the performance of both control algorithms is excellent.

Controller performance degrades when uncertainty is present. In order to compare the performance of two controllers, model parameters are perturbed from average value. Figure 13 shows blood glucose response with H_∞ controller (right figure) and fuzzy controller (left figure). The H_∞ controller performance in terms of glucose tracking in presence of uncertainty is superior in contrast with fuzzy logic algorithm. H_∞ controller is robust to 90% parameter variations in patient model, while fuzzy controller is almost unstable for more than 70% parameter variations.

Table 6: Parameter values

	Normal	Patient 1	Patient 2	Patient 3
p_1	0.0317	0	0	0
p_2	0.0123	0.02	0.0072	0.0142
p_3	4.92×10^{-6}	5.3×10^{-6}	2.16×10^{-6}	9.94×10^{-6}
γ	0.0039	0.005	0.0038	0.0046
n	0.2659	0.3	0.2465	0.2814
h	79.0353	78	77.5783	82.9370
G_b	70	70	70	70
I_b	7	7	7	7
G_0	291.2	220	200	180
I_0	364.8	50	55	60

Table 7: Comparison of fuzzy controller and H_∞ controller

Controller	Settling time (min)	Overshoot (mg/dl)	Sum-squared error	
H_∞	217.4	5.29	3.7919×10^3	3×10
Fuzzy logic	107.6	3.63	1.5346×10^3	3×10

6. CONCLUSION

In this work, a closed-loop control system based on fuzzy logic control for type I diabetic patients has been proposed. In order to incorporate knowledge about patient treatment, the controller is designed using a Mamdani-type fuzzy scheme. It is important to mention that the control algorithm is essence model-free. The proposed controller can successfully tolerate dynamic uncertainty in patient model while rapidly rejecting meal disturbances and tracking the constant glucose reference. Robustness was tested over a group of three patients, with model parameters varying considerably from the

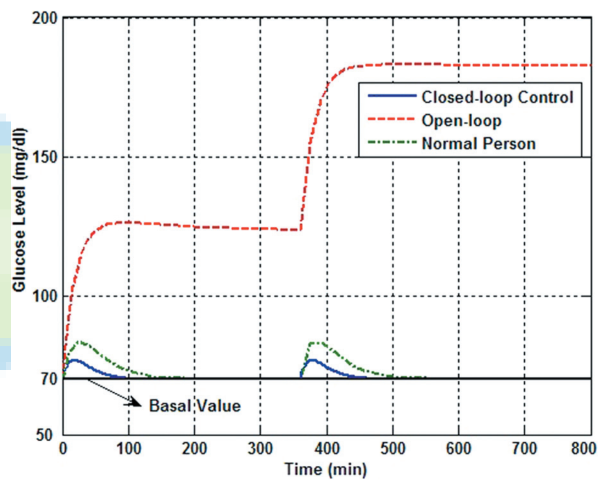

Figure 11: Comparison of feedback and open-loop glucose regulatory systems.

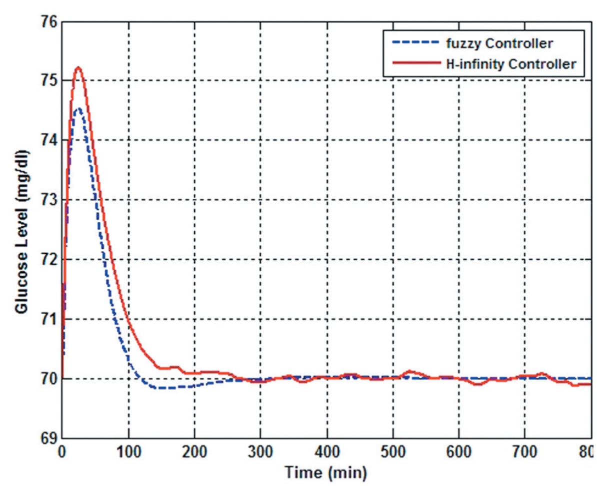

Figure 12: Performance of fuzzy controller and H_∞ controller against measurement noise.

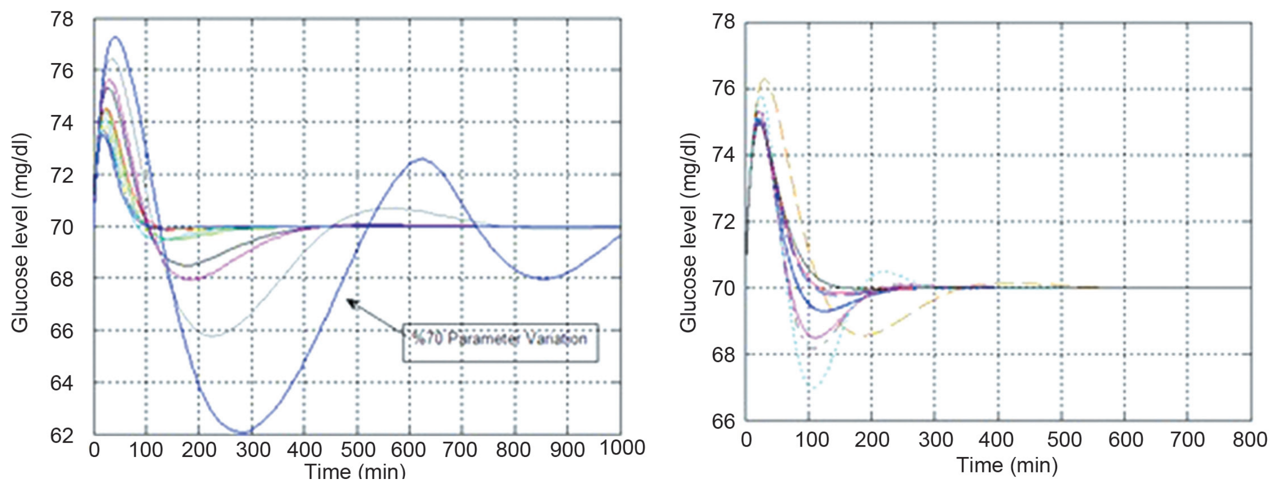

Figure 13: Performance of fuzzy controller and H_∞ controller versus uncertainty in model parameters.

averaged model. As shown in this paper, the fuzzy logic framework has the potential to synthesize expert knowledge to treat diseases. In addition, it is proved that this method has preference over other conventional techniques in blood glucose control. The fuzzy logic controller has shown to have comparable performance to the H_∞ control technique in terms of online computation. In relation to robustness to uncertainty, both controllers show good performance; however, H_∞ control is more robust than fuzzy controller. The selection of a control algorithm is clearly a multi-objective problem where fuzzy and H_∞ approaches have their individual advantages and shortcomings. The suggested scheme is expected to enhance the automation of insulin delivery in Type I diabetic patients.

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DOI: 10.4103/0377-2063.102314; Paper No JR 567_10;