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AN INSULIN SCALING ALGORITHM IN A CONTROL SYSTEM BASED ON RISK MINIMIZATION OF HYPO- AND HYPERGLYCEMIA

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ABSTRACT

Current insulin therapy for patients with type 1 diabetes often results in high variability in blood glucose concentration and may cause hyperglycemia (high glucose level>10 mmol/L) and hypoglycemic (low blood glucose level< 3.8 mmol/L) episodes. Closing the glucose control loop with a fully automated control system improves the quality of life for insulin-dependent type-1 diabetic patients. This paper presents a closed loop control system that is based on minimization of the risk of the future hypo or hyperglycemicepisodes. The blood glucose level is predicted after 60 minutes using recurrent neural network (RNN), and the fuzzy logic controller (FLC) calculates the insulin dose according to previous setting for patient. The controller tunes the insulin infusion rate to minimize the predicted risk of hypo- or hypoglycemica. The system is tested and evaluated using a simulated diabetic patient model with three meal challenges, and direct performance measures are measured for the resulted controlled blood glucose (BG). Our results indicated that, using our controller can control the blood glucose level without any recorded hyperglycemia even if the scheduled meals are increased by 10%. A mild hyperglycemic episode was recorded when a meal is 35% more thanthe scheduled meal, but it continues for short time (around 2 Hours, where it is dangerous to be continued for few days or weeks) then the glucose returned to the target range. All the direct performance measures for the controlled blood glucose with our controller is within the standard levels that are mentioned in literature.

KEY WORDS

Insulin Pump, Hypoglycemia, Hyperglycemia, Blood Glucose Prediction, Fully Automated Control, Recurrent Neural Network (RNN), Fuzzy Logic Controller (FLC).

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INTRODUCTION:

A closed-loop artificial pancreas has the potential to simultaneously reduce the risks of hypo- and hyperglycemia while also enabling individuals with type 1 diabetes mellitus to maintain a normal lifestyle [1]. In these closed-loop systems, patients must use subcutaneous insulin injection or continuous insulin infusion, combined with infrequent blood glucose measurements, to regulate their blood glucose concentration and reduce the risks of hypo- and hyperglycemia. The self-monitoring requires a considerable effort and is a constant reminder of their disease. These systems work as an artificial pancreas, and can continuously monitor the glucose level and infuse the insulin that is appropriate to the meal size or the current blood glucose level. The controller is customized once on the scheduled meals of the patient. If the patient eats meals that are out of regime, the controller injects the insulin based on the predicted and measured glucose regardless of meal size. There are many problems in using closed loop blood glucose control systems, we will mention two of them that are in our scope. One of them is that these systems are dependent on patients to feed information about their basal insulin and the meal sizes, which sometimes cause errors in fault meal size calculation. The other problem facing any BG control system is avoiding the hypoglycemia especially during the sleeping hours. Our proposed system will focus on the problem of hypoglycemia, it works on minimization of risk of hypoglycemia that could happen now and in the future. We simulated our program on an artificial patient in many situations (eating scheduled meals, fault estimated meals and a large meal consumption situation), and we proved that our controller can regulate the BG without any recorded hypoglycemia. It also can avoid hypoglycemia during sleeping hours.

Due to the limitations on infusing the diabetic patient with high insulin dose (control action) that can decrease the glucose level suddenly and the patient could enter hypoglycemic episode during the two hours of the insulin action, Proportional Integral Controller (PID) [2] in a closed loop control system is unable to achieve the constraints in the control action (insulin infusion rate). This inability further limits thepotential of PID for success in closed-loop controlling of type-1 diabetic patients' glucose without necessitate manual inputs of maximum accepted insulin dose. When the minimally invasive subcutaneous glucose measurement and subcutaneous insulin delivery are considered, significant delays in predicting blood glucose concentration and delivering insulin to the blood stream introduce additional challenges to the control problem. Predictive framework of the model-based controllers provides a powerful tool not only to deal with time-delays in the system but also to evaluate the future effects of a meal challenge and thus achieving disturbance rejection.

This paper presents a proposed control strategy for decreasing the risk of hypoglycemia. The strategy is based on using continuousglucose measuring sensor, control strategy to calculate the appropriate insulin infusion rate based on the predicted glucose values for the next 60 minutes, and insulin pump to infuse the decided dose [3]. The controller is customized once upon a time in the starting to each patient, after that, the patient will not need to enter any data because the controller reacts with the continuous glucose measurements and glcose prediction. Our controller addresses the issues of the irreversible insulin action (i.e. wrong high infused insulin cannot be corrected using the

insulin dose scaling algorithm which predicts the risk of the decided insulin dose on BG after 3 hours which is the time to reach the peak of insulin effect in the blood.

CLOSED LOOP CONTROL SYSTEM

Our controller addresses the asymmetric glycemic risk, which is the risk of low versus high BG levels and the inability to actively raise the BG level. It uses an offline patient's model that is used to predict any hypoglycemic event that can occur from the decided insulin dose, and then the controller will decrease the insulin dose even if hyperglycemia is the result of this decreasing in insulin.

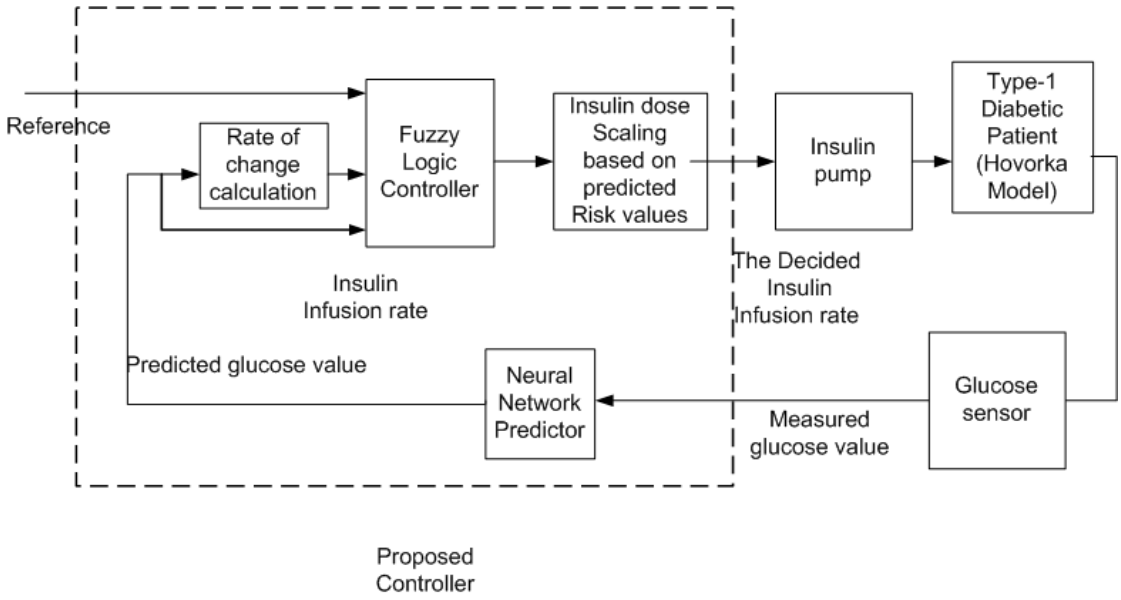


Fig. 1. The proposed complete closed loop control system for type-1 diabetic patient

The proposed Nonlinear Model Predictive Control (NMPC) in a closed loop system is shown in Fig. 1. It consists of the following elements:

1. RNN: which is used as a nonlinear predictor to predict the future glucose concentration. we need the neural network that can predict for longer prediction horizons to compensate for the delays in the system [4], RNN achieves root mean square error 1.32 for 1 hour prediction horizon, as stated in [4].
2. FLC: it receives the predicted glucose value and its rate of change as inputs and decides the appropriate insulin infusion rate according to its inputs and the fuzzy rules [5].
4. Insulin dose scaling algorithm: to adjust the insulin dose (outputs of the FLC) according to the predicted risk of hypo or hyperglycemia that could happen from the decided insulin dose.

RNN GLUCOSE PREDICTION MODEL

The prediction model is designed to support the proposed closed loop control system that will need to predict the future glucose values to determine the needed insulin bolus. The

RNN [4] is used as a nonlinear glucose prediction model, the inputs to the RNN is the previous 40 glucose values that obtained from the glucose sensor. The output of RNN is the predicted glucose value. This RNN can predict up to 20 future values of glucose concentration (100 minutes). The evaluation of this prediction model was done in [4], the best predictions obtained after 60 minutes with RMSE 1.32 mmol/L.

FUZZY LOGIC CONTROLLER (FLC)

The FLC is used in our control system as an optimizer (control law) to determine the appropriate insulin dose based on the predicted blood glucose concentration. The FL controller is structured with a Mamdani-type fuzzy architecture. The controller has two input variables and one output. The two input variables are the predicted plasma glucose concentration G(t) and its rate of change dG(t)/dt. The output variable of the controller is the insulin infusion rate. The membership functions of all variables are structured according to some modifications in the membership functions that are mentioned in [5]. The range of the input and output variables and the names of the membership functions for these variables are given in Tables 1 and 2, respectively. The two-dimensional inference engine (or decision matrix) processes the BG and its rate of change fuzzy input variables into an output fuzzy variable by means of IF-THEN rules that are predefined. The decision matrix is composed by experienced clinicians. Table (3) shows the decision matrix or IF-THEN rules that are used in the construction of the FLC. As shown in table (3), this FLC has 24 rules. The FLC is structured with a Mamdani type fuzzy architecture.

Table 1. Characteristics of input variable

Input Variable	Interval	Membership functions							
Blood glucose concentration (BG) mmol/L	[0 - 16]	Negative Big (NB) [0,2.5, 3.026]	Neg. Medium (NM) [2.05,3, 4.5]	Neg. small (NS) [3.07, 4.51, 4.55]	Normal NOM [4.5,4.71, 5.1]	Positive Small (PS) [4.5,5,8]	Pos. Med. (PM) [5,8, 10.01]	Pos. Big (PB) [8, 10.1, 12]	Pos. Large (PL) [10,12,>12]
Blood glucose rate of change (BG_R) mmol/L/min.	[-0.4, 0.4]	Negative [-0.4, 0]			Zero [-0.055, 0 , 0.055]		Positive [0, 0. 4]		

Table 2. Characteristics of the output variable (insulin infusion rate)

Output Variable	interval	Membership functions							
Insulin infusion rate	[6.5-66.66]	Neg. big (NB)	Neg. Medium (NM)	Neg. Small (NS)	Zero (Z) [16.32 ,	Pos. Small (PS)	Pos. Medium (PM)	Pos. Big (PB)	Pos. Large (PL)

mU/min.		[6.606, 9.255, 11.9]	[9.255, 11.9, 16.32]	[11.9, 16.32, 20.74]	20.74, 26.03]	[20.74, 26.03, 32.21]	[26.03, 32.21, 43.69]	[32.21, 43.69, 55.18]	[43.69, 55.18, 66.66]

Table3. The IF-THEN rules of the FLC

	BG_R		
BG	**Negative**	**Zero**	**Positive**
PL	PL	PL	PL
PB	PB	PB	PB
PM	PM	PM	PB
PS	Z	PS	PB
NOM	Z	Z	Z
NS	NB	NS	Z
NM	NB	NM	NM
NB	NB	NB	NB

RISK MINIMIZATION COST FUNCTION

The first step in calculating the risk index is to calculate a function of the blood glucose readings called *f* (BG) using Equation (1):

$$f(BG) = 1.509 * [(\ln(18 * BG))^{1.084} - 5.381] \quad (1)$$

Where the BG readings are in mmol/L. Then the BG risk function is calculated using Eq. (2)

$$r(BG) = 10\text{x}f^2(BG) \quad (2)$$

Fig. 2 presents the plot of the *r(BG)* for the whole BG range that can be measured by the Continuous Glucose Monitoring (CGM) sensor [1.1:33.3mmol/L] [6].

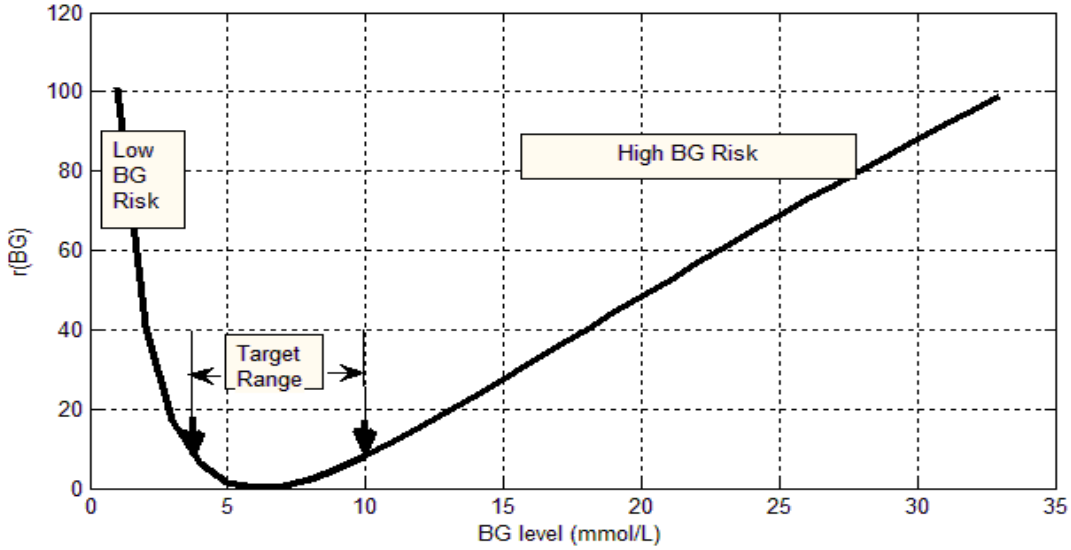


Fig. 2. The blood glucose risk function *r(BG)* plotted over the standard BG scale.

The function r(BG) ranges from 0 to 100. Its minimum value is achieved at BG = 6.25 mmol/L, a safe BG reading, while its maximum is reached at the extreme ends of the BG scale (the scale of the function starts from very low BG and ends at very high BG with risk 100 for both). Thus, r(BG) can be interpreted as a measure of the risk associated with a certain BG level. Due to the curve shown in Fig. 2, the target range shows that, the maximum acceptable blood glucose risk is 7.793 at 10 mmol/L.

HOVORKA MODEL OF TYPE-1 DIABETIC PATIENT

The glucoregulatory model, as described by Hovorka [7, 8], represents the input–output relationship between subcutaneous insulin infusion as input and intravenous glucose concentration as output. Hovorka model includes three subsystems: glucose, insulin and insulin action subsystems [7]. The insulin subsystem has three differential equations and represents the absorption of short-acting insulin (Lispro) and the plasma insulin concentration. The insulin action subsystem models the effects of insulin on glucose disposal, glucose transfer from accessible to inaccessible compartments and endogenous glucose production, which is defined as glucose production from the liver pursuant to the conversion glycogen depots into glucose. The glucose subsystem has two differential equations, which is the most important part of the model that represents the blood glucose concentrations in the accessible and inaccessible compartments. Glucose absorption, which is a fundamental process affecting postprandial, depends on the time required to reach maximum carbohydrate absorption [7]. The equations of this model are described in [8].

INSULIN DOSE SCALING BASED ON PREDICTED RISK VALUES

This algorithm is based on calculating the risk of using the calculated insulin dose on the glucose of the diabetic patient for the next 3 hours (the duration of insulin acting in the blood [9]). The diabetic patient here is represented by Hovorka model [8]. The algorithm is shown in Fig. 3.

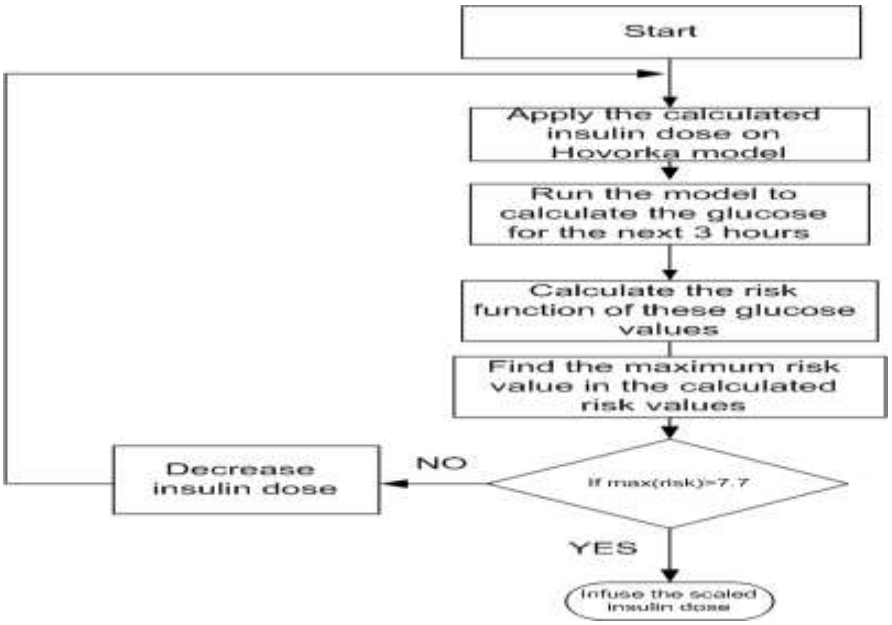


Fig. 3. Insulin Dose Scaling Based On Predicted Risk Values

EVALUATION OF THE PROPOSED CONTROLLER:

To evaluate the proposed controller, we run a simulation program with a virtual (simulated) patient (using Hovorka model [8]) and a controller that calculates the required insulin infusion rate. The simulated patient's parameters are as indicated in [8]. The patient is 45 kg weight, the simulation time is 24 hours with three meals: Breakfast at 9:30 AM, lunch at: 1:30 PM, dinner at 5:15 PM. The evaluation of the proposed controller is performed in two scenarios:

First scenario:

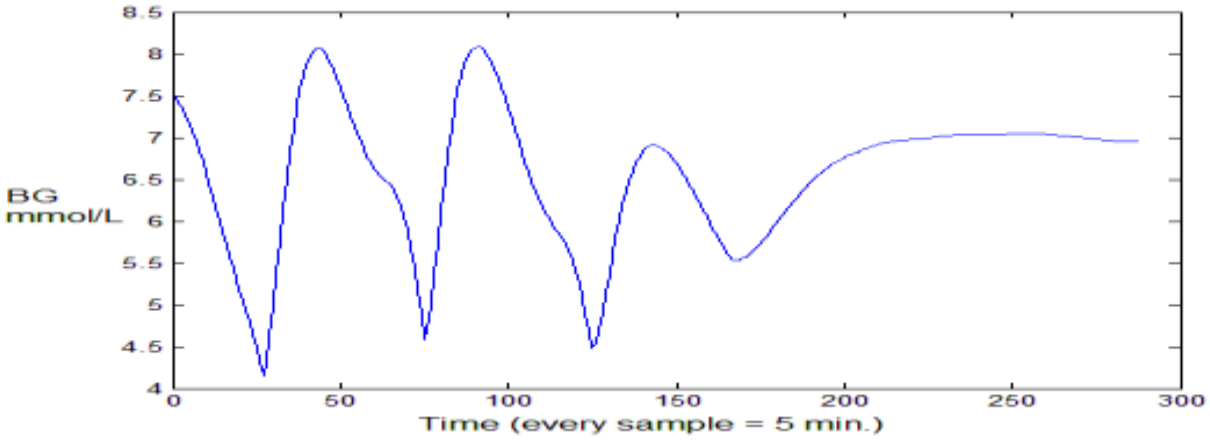
In this scenario, there is a simulation of the normal patient's day, when the patient eats the scheduled meals. We also simulate faulty meals according to faults in carbohydrate counting (±10%). The BG concentrations of this scenario are shown in Fig. 4. The controller is tested here using direct performance measures that are used in UVa/Padova Metabolic Simulator [10]. These measures calculate the percentage of time that the patient spent in: severe hypoglycemia ("sh", BG<=2.77mmol/L), hypoglycemia ("mh", 2.77<BG<=3.88mmol/L), normo-glycemia ("TBG", 3.88<BG<=10), hyperglycemia ("MH", 10<BG<=16.66), and severe hyperglycemia ("SH", BG>16.66). The values of: mean or average BG (AVBG), pre- meal BG ("PRBG" is the average glucose during 60 minutes period prior to meal times) and post- meal BG ("POBG" is the average glucose over 60 minutes after one hour of a given meal) are also calculated. These direct performance parameters are shown in table 4.

Second Scenario

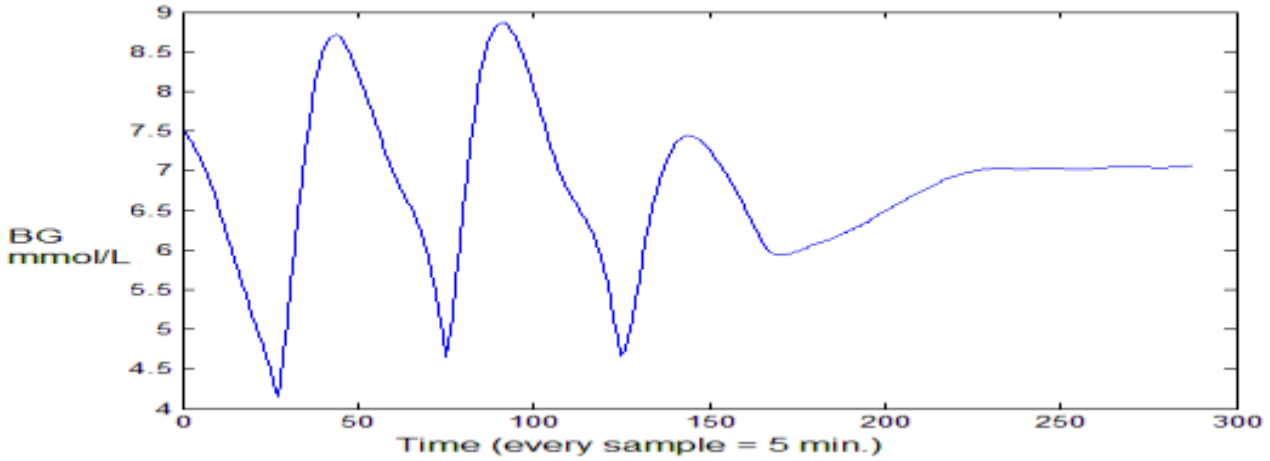
In this scenario, there is a simulation of large meal consumption (out of regime). This is simulated by 35% increase the largest meal size (second meal). The BG concentrations of this scenario are shown in Fig. 5.

RESULTS AND DISCUSSION:

The simulation results of using our proposed controller in the first scenario as shown in Fig.4 shows that, there isn't any recorded hypoglycemic episodes during the whole day and sleeping hours. The glucose level during sleeping hours is stable around 7mmol/L. Table 4 shows that the direct performance measures for the controlled BGusing our controller is comparable within the standard values, the patient spends 100% of time in normo-glycemia when scheduled or ±10% meals are eaten.



(a)



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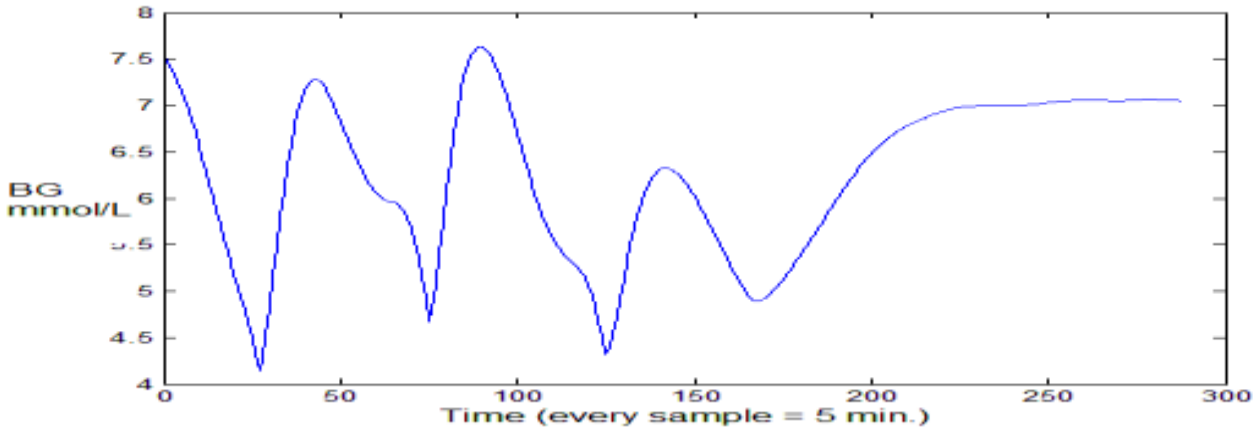

(c)

Fig. 4.The BG concentration for (a) normal scheduled meals, (b) 10% increase in scheduled meals, (c) 10% decrease in scheduled meals (the time unit in horizontal axis is 5 minutes).

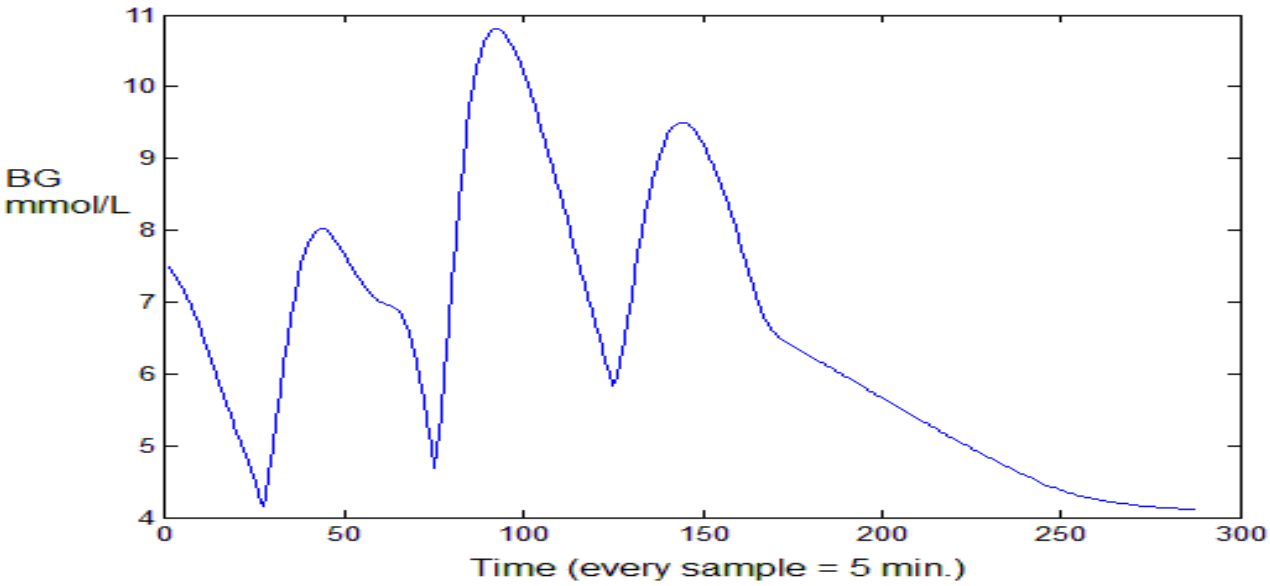

Fig. 5. The BG concentration for 35% increase in scheduled meals (the time unit in horizontal axis is 5 minutes)

Table 4. Direct performance measures for the first evaluation scenario compared with the standard values mentioned in [11].

Case	AVBG	% of Time in TBG	% of Time In mh	% Time In sh	% Time In MH	% Time In SH	POBG mmol/L	PRBG mmol/L
Scheduled meals	6.557	100	0	0	0	0	7.0573	6.4630
%10 increase	6.908	100	0	0	0	0	7.5689	6.8858
10% decrease	6.257	100	0	0	0	0	6.6549	6.1245
Standard values	6.944	98.82	0.62	0	0.56	0	8.33	6.611

Fig. 5 shows that, when patient eats large meal (35% increase), the patient goes in mild hyperglycemic episode after the second increased meal, but this happened for short time (2 hours). The glucose shouldn't decrease suddenly because it is dangerous and

because of the insulin kinetics in the blood [11]. Entering the patient into successive hyper and hypoglycemic episodes is very dangerous on his members.

CONCLUSION

According to the simulated results, our proposed automatic control system can control the BG of type-1 diabetic without any recorded hypoglycemic episodes. It doesn't need data entry from the patient about the meals every day. Its settings could be done once on the parameters of patient and his scheduled meals, the patient can eat without notification but within limits. As the meals get larger, as the postprandial value of hyperglycemic value gets larger but it gets under control within appropriate time. The system can also alarm at high and low levels of predicted glucose level. The system is proposed with continuous blood glucose measuring subcutaneous (under skin) sensor, and subcutaneous infusion pump to be less invasive. Subcutaneous measurement and infusion can be done with small devices that are fixed in the patient's cloths without affecting his life.

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