Model Predictive Control: Taking the Idea of Artificial Pancreas a Step forward for Diabetes Management

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***Abstract*—Biomedical sciences have experienced growing interest from mathematicians and researchers in developing mathematical models able of mimicking the physiological characteristics of human body and its processes and designing control for the medical problems. Different biomedical modeling techniques have been developed for a variety of medical problems requiring monitoring and control, which have improved lives of people with those medical problems. Diabetes is considered as one of the most important medical problem that needs attention from research community. This paper focuses on designing an advance control technique called Linear Model Predictive Control for improving glycemic regulation for type 'I' diabetic patients. The glucose-insulin dynamic model in diabetic patients discussed in this paper is a four-state nonlinear model, which is linearized before applying linear control techniques. The patient model has been investigated in the paper by presenting a comparison of Linear Model Predictive Control with Proportional Integral Derivative control and State Feedback control. The results show that our proposed scheme results in improved glycemic regulation and ensures proper check on insulin infusion rate in order to avoid both hyperglycemia and hypoglycemia. All the control techniques are simulated in MATLAB and Simulink environment.**

***Index Terms*—biomedical modeling, artificial pancreas, model predictive control, single-input-single-output, glycemic control**

I. Introduction

Diabetes is a metabolic disorder and according to reports in 2014 it has affected around 9% of adult population, in comparison with 108 million in 1980. This is nearly double prevalence of diabetes globally since 1980, rising from 4.7% to 8.5% in the adult population [1]-[3]. People with diabetes normally have higher blood glucose levels, referred as hyperglycemia. Diabetes type 'I' and type 'II' are the two main types of diabetes. Type 'I' diabetes is also called Insulin Dependent Diabetes Mellitus. It accounts for 5–10% of the patients suffering from diabetes, Type 'II' diabetes is also known as Non-Insulin Dependent Diabetes Mellitus [4]-[6]. The β-cells present in pancreas are responsible for production of insulin for blood glucose regulation in human body. Destruction of these β-cells due to any possible reason effects endogenous insulin production leading to T1D development. For keeping glucose levels under normal range and for avoiding the long-term complications which are associated with both hypoglycemia and hyperglycemia, T1D diabetics need exogenous administration of insulin. Diabetes effects the lifestyles of type 'I' diabetic person in numerous ways. Immune system destroying B-cells causes deficiency of indigenous insulin. This deficiency is fulfilled by an external source of insulin in order to maintain normal blood glucose concentration and avoid consequences of both hyperglycemia and hypoglycemia. Fig. 1 explains blood regulation in human body and shows how pancreas and liver controls the glucose-insulin metabolism in human body. Few of the symptoms present in medical literature are Polydipsia which is a very high extent thirsty state, Polyphagia which is a crunch hungry state and Polyuria which is an uncontrolled urination. Failure in regulation leads to numerous health problems which includes heart disease, kidney disease and blindness etc.
Normal range for glucose concentration ranges between 60mg/dl to 126mg/dl [7]. Glucose levels dropping below the basal glucose levels is called hypoglycemic state, whereas glucose levels rising above this basal level is termed as hyperglycemia. Considerable efforts by biomedical research community are witnessed in past decades in order to achieve tighter glycemic control by proper and risk-free automatic control process [8].

The administration of insulin infusion rate can be achieved by properly monitoring glucose levels inside the body of diabetic patient. There are some of the components of the artificial pancreas available in market in form of wearable devices, which are helping people with diabetes but they standalone do not provide a complete automatic solution to the diabetes problem. On other hand biomedical and control engineers are trying to automate the whole process and come up with a complete solution, they are yet to achieve such a success. The recent decades have witnessed development of many mathematical models describing the glucose-insulin dynamics systems in humans. This apt to coming up with an artificial pancreas as close to human pancreas as

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possible, have gained so much attention from research community over the past few decades and if researchers get close to develop such a complete and autonomous system satisfying all the results through proper trail, it surly will be life changing for diabetic people and will revolutionize the state of diabetes management.

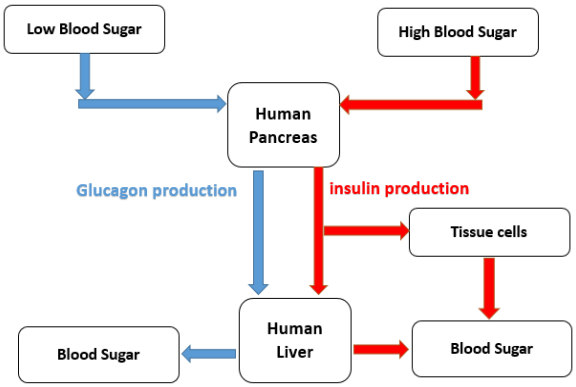

Figure 1. Blood glucose regulation in humans.

This need to come up with an artificial pancreas have accelerated the area of research in biomedical engineering focusing on diabetes management. A verity of control techniques and algorithms have been applied, investigated for achieving glycemic control in type 'I' diabetes patients. Bergman Minimal Model (MM) is the most commonly used mathematical model to describe the phenomenon of glucose-insulin dynamics in humans [9]-[15]. This basic model provided bases of the research work done in the field of diabetes management and accelerated the pace of the research dramatically. This basic 3rd Order Minimal Model developed by Richard N. Bergman and his coworkers in 1970s comprises of a set of 3 differential equations with some unidentified parameters, parameters which explains physiological process in human body. The variation in these physiological and pathological characteristics in diabetic patients leads to difference of these unknown parameters among these diabetic patients. By means of this basic version of Bergman MM and its extended versions, variety of control techniques and algorithms have been tested in order to address the glucose regulation control problem, control techniques ranging from simple linear control to complex nonlinear control techniques [16]-[24].

Fisher [16] proposed insulin infusion by means of a semi-closed loop algorithm and applied it on MM of glucose. Fisher's design was based on plasma glucose samples taken after each 3 hours. The study focused the blood glucose levels without taking some factors into consideration, i.e. insulin production rate and free plasma insulin concentration as glucose concentration increases above normal level. Furler [17] used the modified version of the glucose MM. The Insulin antibodies were added to the MM of glucose while insulin secretion was removed. Linear interpolation was used in order to calculate insulin infusion rate for the diabetic patient. Some deviations in insulin concentration and other model parameters were neglected in the study. Ibbini, Masadeh and Amer [18] verified the MM of glucose by designing a closed loop optimal control system in order to achieve glycemic control in diabetic patients. D. Boiroux and V. B´atora [19] tested results of adaptive MPC on a much complex 11th order model explaining the glucose insulin dynamics for glycemic control in diabetic patients. L. Magni [20]-[24] have applied variants of both linear and nonlinear MPC on a much complex 12th order model of which explains the glucose insulin dynamics in order to achieve better glycemic control in diabetic patients. The control techniques and algorithms developed for glucose regulation, does not provide tighter glycemic, and sometimes when catering for hyperglycemia they often suggest a value of insulin that causes glucose of lower down to a dangerous level. Which leads to a condition called hypoglycemia, which if go unnoticed can cause serious damage to a diabetic patient. Serious damage can be in the form of comma or even death in case of severe hypoglycemia. So, the main focus of the control techniques is handling such situations. In order to avoid the overdose of insulin, there is need of a control technique which can limit insulin infusion to avoid the consequences of overdosing. The control technique should take some of the state constraints and input constraints into consideration in order to avoid excess or deficiency of the insulin infusion while administering insulin for glycemic control. This paper provides a detailed comparison of a powerful adaptive control technique Linear Model Predictive Control (LMPC) with simplified control techniques like State Feedback control and Proportional-Integral-Derivative (PID) control for improved glycemic control in people with type 'I' diabetes. MPC have the capability to be considered a very promising approach for glycemic control while addressing the diabetes medical problem because of its beauty to handle constraints at input, output and states of the system. Different glucose insulin dynamic models have been exploited with linear and nonlinear MPC strategies.

Section II of the paper presents the linearized version of the extended 4th order nonlinear model of glucose inulin system, which in extension of basic 3rd Order Bergman MM, in Section III the proposed Linear Model Predictive Control technique is presented, Section IV have simulation and results of simplified linear control techniques and the proposed controller and the results are compared in the form of various figures and a table while the research paper is concluded in Section V.

II. Mathematical Modelling

Mathematical models mimicking natural phenomenon of human physiology have accelerated the nature of research in biomedical sciences. With the help of such models researchers have founds new horizons in the field of biomedical sciences and medicines. In case of diabetes medical problem, some factors like food intake, physiological and environment conditions changes glucose levels within human body significantly, it is necessary to come up with mathematical models which are able capture real dynamics for control design [9]-[15].

For simplifying the patient model for controller design and for applying simplified linear control techniques, the nonlinear MM was linearized under given operating conditions [8]. Equilibrium points were computed to be $x_0 = [859.6667,0,8,0]$ after linearizing the model. Table I shows that during fasting state the lower bond glucose levels is 80 mg/dl while the upper bond is 100 mg/dl for a normal healthy person [7].

TABLE I. CHART FOR BLOOD GLUCOSE LEVELS

Person's category	Fasting State		Postprandial
	Min Glucose (mg/dl)	Max Glucose (mg/dl)	Some 2-3 hrs after eating (mg/dl)
Hypoglycemia	-	<59	<60
Early hypoglycemia	60	79	60-70
Normal	80	100	<140
Early diabetes	101	126	140-200
Diabetic	>126	-	>200

The extension of MM of glucose-insulin has been explored for the healthy subjects, in which case pancreas secretes insulin in response to the actual glucose levels in the blood sensed by the pancreas [25]. The extended version of the glucose-insulin MM is comprised of 3 portions: first is the glucose disappearance MM, (*g* and *v*), second is the MM of insulin kinetics, (*i*) and third is the first-order pump dynamics (*w*).

$$\begin{aligned} \dot{\boldsymbol{g}}(\boldsymbol{t}) &= -[\boldsymbol{p_1} + \boldsymbol{v}(\boldsymbol{t})]\boldsymbol{g}(\boldsymbol{t}) + \boldsymbol{p_1 g_b} \\ \dot{\boldsymbol{v}}(\boldsymbol{t}) &= -\boldsymbol{p_2 v}(\boldsymbol{t}) + \boldsymbol{p_3}(\boldsymbol{i}(\boldsymbol{t}) - \boldsymbol{i_b}) \\ \boldsymbol{i}(\boldsymbol{t}) &= -\boldsymbol{n i}(\boldsymbol{t}) + \boldsymbol{\gamma}[\boldsymbol{g}(\boldsymbol{t}) - \boldsymbol{h}]\boldsymbol{t} \\ \dot{\boldsymbol{w}}(\boldsymbol{t}) &= \frac{\boldsymbol{1}}{\boldsymbol{a}}(-\boldsymbol{w}(\boldsymbol{t}) + \boldsymbol{u}(\boldsymbol{t})) \end{aligned} \tag{1}$$

where *g(t)* measured in (mg/dl) represents glucose concentration in plasma, *v(t)* measured in (min^{-1}) represents remote compartment insulin, *i(t)* measured in (µU/ml) is plasma insulin concentration, *w(t)* is the insulin infusion rate, *u(t)* represents the input insulin infusion command, i_b measured in (µU/ml) is basal insulin level, g_b measured in (mg/dl) is basal blood glucose level, *p1* measured in (1/min) is the insulin independent rate constant of glucose uptake in muscles and liver, *p2* measured in (1/min) is the rate for decrease in tissue glucose uptake ability, *p3* is the insulin-dependent increase in glucose uptake ability in tissue per unit of insulin concentration above the basal level and is measured in [(µU/ml) min $^{-2}$], *n* is the first order decay rate for insulin in blood and is measured in (1/min), *h* is the threshold value of glucose above which the pancreatic *β*−cells release insulin and is measured in (mg/dl), *γ* is the rate of the pancreatic *β*−cells release of insulin after the glucose injection with glucose concentration above the threshold and is measured in [(µU /ml min $^{-2}$ (mg/dl) $^{-1}$]. *a* represents time constant of the pump, *t* measured in (min) is the time interval after the glucose injection. The initial conditions for the system are; $g(0) = g_0$, $v(0) = 0$, $i(0) = i_0$ and $w(0) = 0$ from [24]. Change of variables into $\boldsymbol{x_1}, \boldsymbol{x_2}, \boldsymbol{x_3}, \boldsymbol{x_4}$; and (1) afterwards

$$\begin{aligned} \dot{\boldsymbol{x}}_{\boldsymbol{1}}(\boldsymbol{t}) &= -\boldsymbol{p_1 x_1}(\boldsymbol{t}) - \boldsymbol{x_1}(\boldsymbol{t})\boldsymbol{x_2}(\boldsymbol{t}) + \boldsymbol{p_1 g_b} \\ \dot{\boldsymbol{x}}_{\boldsymbol{2}}(\boldsymbol{t}) &= -\boldsymbol{p_2 x_2}(\boldsymbol{t}) + \boldsymbol{p_3 x_3}(\boldsymbol{t}) - \boldsymbol{p_3 i_b} \\ \dot{\boldsymbol{x}}_{\boldsymbol{3}}(\boldsymbol{t}) &= \boldsymbol{\gamma t x_1}(\boldsymbol{t}) - \boldsymbol{n x_3}\ (\boldsymbol{t}) + \boldsymbol{x_4}(\boldsymbol{t}) - \boldsymbol{\gamma h t} \\ \dot{\boldsymbol{x}}_{\boldsymbol{4}}(\boldsymbol{t}) &= -\frac{\boldsymbol{1}}{\boldsymbol{a}}\boldsymbol{x_4}(\boldsymbol{t}) + \frac{\boldsymbol{1}}{\boldsymbol{a}}\boldsymbol{u}(\boldsymbol{t}) \end{aligned} \tag{2}$$

The above 4th order nonlinear system has been linearized around equilibrium point (x_0, u_0) [24], becomes;

$$\dot{x} = \begin{bmatrix} -p_1 - x_2 & -x_1 & 0 & 0 \\ 0 & -p_2 & p_3 & 0 \\ \boldsymbol{\gamma t} & 0 & -n & 1 \\ 0 & 0 & 0 & -\frac{1}{a} \end{bmatrix} x + \begin{bmatrix} 0 \\ 0 \\ 0 \\ \frac{1}{a} \end{bmatrix} \mathrm{u} \tag{3}$$

$$y = [1 \quad 0 \quad 0 \quad 0]x$$

where p_1, p_2, p_3, γ, n, h, g_0 and i_0 are the given model parameters. Substituting $p_1 = 0$, $p_2 = 0.0081$, $p_3 = 0.00000401$, $i_0 = 192$, g0 = 337, $\gamma = 0.0024$, $n = 0.23$, $h = 93$, $a = 2$, $g_b = 99$, $i_b = 8$ (3) become [24].

$$A = \begin{bmatrix} 0 & -859.6667 & 0 & 0 \\ 0 & -0.0080 & 0 & 0 \\ 0.0024 & 0 & -0.2300 & 1 \\ 0 & 0 & 0 & -0.5 \end{bmatrix} \quad B = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0.5 \end{bmatrix} \tag{4}$$

$$C = [1 \quad 0 \quad 0 \quad 0]$$

Conditions for both controllability and observability were checked for the linearized model before designing PID and state feedback controllers and it was noted that system dynamics in the state space form given in (4) satisfy the conditions for both controllability and observability.

III. PROPOSED CONTROLLER: LINEAR MODEL PREDICTIVE CONTROL

In this paper a Linear Model Predicative Control (LMPC) has been derived from a linearized approximation of the full state glucose-insulin dynamic model. The linearized version of the nonlinear model is obtained as a result of the linearization of the extended nonlinear model described in [24] around an appropriate working point derived in (5) in state-space form. MPCs a general approach that provides opportunity to develop rather complex but robust control techniques and algorithms for glycemic control in type 'I' diabetics. An MPC strategy consists of two basic ingredients; a solution to an optimization problem which is model based and the receding horizon principle, in which the future input sequence moves at each point of time while optimizing a cost function $J(x,u)$ subjected to the constraints is calculated and out of whole sequence only the first control move is used for control purpose. The practice is reiterated for the next step, with subsequent translation of both prediction and control horizon. The future states and outputs can be predicated using different MPC algorithms applied for different models while addressing the diabetes problem. Multiple linear and non-linear glucose-insulin models have been discussed in [20]-[25] in both continuous and discrete domains.

The glucose-insulin dynamic system model represented in (1) can also be rewritten as:

$$\dot{x}(t) = f\big(t, x(t), u(t)\big) \tag{5}$$
$$y(t) = g(t)$$

where x = [*g, v, i, w*] and *f (...)* is derived from the model equation in (1) reported in section III. The glucose insulin system is a critical system and must have some constraints in order to avoid unwanted situation while managing diabetes. I order to achieve this objective; the glucose insulin system will be made to have the following constraints in mind.

$$x_{min} \le x \le x_{max}, \quad u_{min} \le u \le u_{max} \tag{6}$$

where x_{min} and x_{max} are lower and upper limits for state x_1(t),which represents plasma glucose concentration of the patient, while u_{min} and u_{max} represent lower and upper limits for the control input u, which represents insulin infusion rate. These are the constraints which keep glucose concentration in a safe limit providing insulin infusion in a safer way to avoid both under dosing and overdosing of insulin. Overdosing of insulin can lead to hypoglycemia, so tackling hypoglycemic events are the focus of research community working on design of artificial pancreas. For deriving an MPC control law, to maintain system state $x_1(g)$ as close to desired state r(t) as possible, following quadratic continuous time cost function was considered

$$J = \left|\left|x(t_f) - r(t_f)\right|\right|_H^2 + \int_{t_o}^{t_f} [\ \left|\left|x(t_f) - r(t_f)\right|\right|_{Q(t)}^2 + \left|\left|u(t)\right|\right|_{R(t)}^2] \, dt \tag{7}$$

where x_1(t) is the glucose state that we want to regulate, r(t) is the anticipated reference for glucose level (between 60 mg/dl and 126 mg/dl), H and Q(t) are real symmetric positive semi-definite *n* x *n* matrix while R(t) is a real symmetric positive definite *m* x *m* matrix. The elements of the matrix Q are selected to weight relative importance to $x_1(t)$ which is the glucose concentration state. With linearized plant the performance measure leads to an easy implemented optimal controller [26]. MPC generally have some independent parameters like control horizon, prediction horizon, state and input constrain, output and input weights etc. With proper choice of these parameters desired results can be achieved. Keeping input insulin infusion in a safe limit, glucose levels can be regulated. The choice of constraints on both input and constraints makes the Linear MPC a better choice for glucose regulation in type 'I' diabetes.

IV. Numerical Simulation and Results

We simulated the 4th order linearized model of glucose-insulin dynamic system of humans expressed in the state space representation in (4). Three different control techniques were applied namely PID control, State Feedback control and our proposed Linear MPC controller. The design of the PID controller was carried out by applying the root locus method at the mentioned operating points. Gains K_p, K_i, *and* K_d for PID controller are selected as [0.20791, 8.46229x10-5**,** 5.75336]. Results of PID controller are shown in Fig. 2. To make the comparison more meaningful we applied saturation function to limit input insulin infusion in case of both PID controller design and State Feedback controller. The state feedback controller is designed according to the pole locations mentioned in [26] and K = [-0.4, 4702.2 0.1 -0.7]. Results of State Feedback controller are in Fig. 3. After applying both simplified linear control techniques, we applied our proposed Linear MPC with the constraints on its input u and glucose level state $x_1(g)$. Fig. 4 shows Simulink model of the proposed Model Predictive Control strategy. Constraints on glucose state are evident from [7] that we should maintain plasma glucose concentration between 60mg/dl and 126mg/dl. Fig. 5 show the results of the proposed Linear MPC and it can be seen from the graph that our proposed Linear MPC is tracking the desired reference of glucose without violating the lower and upper limit of the basal glucose concentration mentioned in [7] and Table I. Fig. 5 shows how the Linear MPC does not go beyond the upper allowable limit of glucose concentration even if we set reference for the controller and same can be observed in Fig. 6 where Linear MPC does not violates the lower limit of the basal glucose concentration. Fig. 5-7shows how the proposed Linear MPC is satisfying all constraints on that glucose state and the insulin infusion rate. By comparing the results of all control techniques and noting rise time, settling time, peak overshoot, undershoot and the system steady state error and lower and upper bonds on the glucose levels mentioned in section I and section III, it can be easily interpreted and concluded from Table II that the proposed Linear MPC keeps the glucose levels in allowable range (60 mg/dl and 126 mg/dl) while keeping proper check on input insulin infusion rate and constraints on the glucose states to avoid positive and negative deviation from the reference value of glucose levels, which makes linear constrained MPC a better choice for a better and tighter glycemic regulation in patients with type 'I' diabetes.

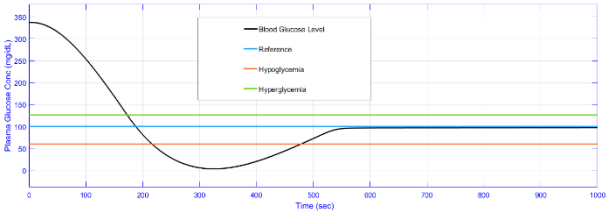

Figure 2. Plot of glucose level *g(t)* when only PID controller.

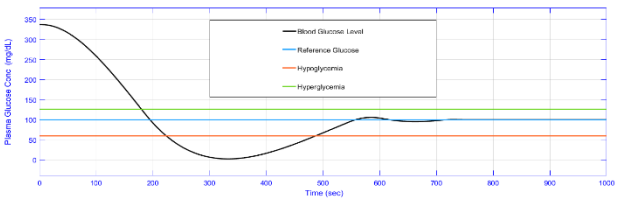

Figure 3. State feedback response of g(t).

TABLE II. COMPARISON OF LINEAR MPC WITH SIMPLE LINEAR CONTROLLERS

Control Strategy	Max conver-gence time	Overshoot Undershoot	SSE	Constraints Satisfaction
PID Controller	560s	OS, US	Yes	No
State Feedback	720s	OS	Yes	No
LMPC	95s	OS	No	Yes

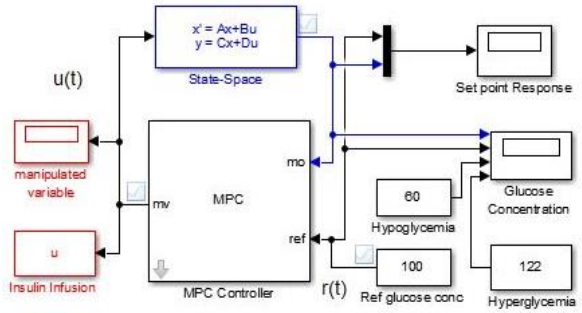

Figure 4. Model predictive control simulink model.

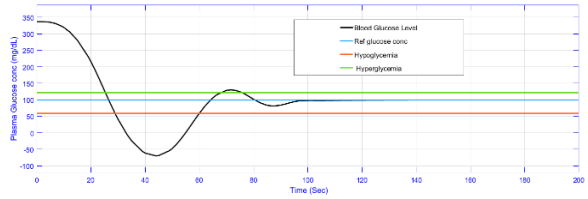

Figure 5. Linear MPC controller response of g(t).

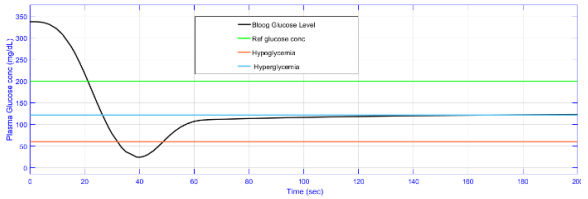

Figure 6. LMPC controller satisfying upper bond of the output constraints.

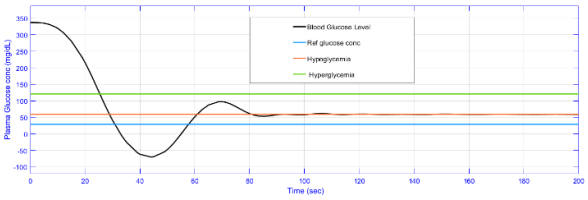

Figure 7. LMPC controller satisfying lower bond of the output constraints.

V. CONCLUSION

This paper presents an adaptive control technique called Linear Model Predictive Control for achieving tighter glycemic regulation for type 'I' diabetic patients. The performance of the proposed techniques has been examined by its qualitative and quantitative comparison with conventional linear controllers like PID and State Feedback controller for linearized 4th order extended glucose-insulin dynamic model of T1D patient. The statistical results suggest that MPC is regulating blood glucose levels very well while considering constraints on both insulin infusion and glucose levels and outperforms other simplified linear control techniques and algorithms. The simulation results indicate the dominance of the proposed controller in terms of robustness and safety to avoid undesirable consequences of both hypoglycemia and hyperglycemia.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Rahmat Ullah Safdar and Muwahida Liaquat worked on the modelling and control design; Rahmat Ullah Safdar and Muhammad Usman Akram carried out simulations and wrote the paper; Syed M. Tahir Zaidi verified the results and reviewed the manuscript; Muwahida Liaquat supervised during the course of research; all authors had approved the final version.

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