

Variable structure robust controller design for blood glucose regulation for type 1 diabetic patients: A backstepping approach

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Abstract

Diabetes mellitus type 1 occurs when β -cells in the pancreas are destroyed by the immune system. As a result, the pancreas cannot produce adequate insulin, and the glucose enters the cells to produce energy. To elevate the glycaemic concentration, sufficient amount of insulin should be taken orally or injected into the human body. Artificial pancreas is a device that automatically regulates the level of body insulin by injecting the requisite amount of insulin into the human body. A finite-time robust feedback controller based on the Extended Bergman Minimal Model is designed here. The controller is designed utilizing the backstepping approach and is robust against the unknown external disturbance and parametric uncertainties. The stability of the system is proved using the Lyapunov theorem. The controller is exponentially stable and hence provides the finite-time convergence of the blood glucose concentration to its desired magnitude. The effectiveness of the proposed control method is shown through simulation in MATLAB/Simulink environment via comparisons with previous studies.

1 | INTRODUCTION

Diabetes type 1 is a fatal and acute disease caused either by the inability of the body to produce insulin or impaired insulin functioning, or both. It is well known that beta cells in the pancreas are the main source of insulin production.

Diabetes is increasing at a high rate. The International Diabetes Federation announced the number of diabetes patients in 2013 about 381 million in the world. According to World Health Organization (WHO), this number was increased to 422 million patients by 2014 [1]. Comparing this number with 108 million patients in 1980, it can be stated that diabetes prevalence has been doubled in adults during these years.

In 2012, diabetes was announced as the main factor of 1.5 million deaths out of 3.7 million [1]. According to CDC, in 2017, about 30.3 million people in the United States have diabetes which costs 327 billion dollars. Consequently, diabetes is considered a fatal disease and causes economic burden [2].

The tolerable range of glucose in the blood for non-diabetics is 70–130 mg/dl. This range is known as the euglycemic range [3, 4]. In hypoglycaemia, the glucose level falls under normal level, while in hyperglycaemia, the glucose is above the normal level. There are two categories of diabetes

mellitus: type 1 diabetes, insulin-dependent, is hyperglycaemia that occurs due to the destruction of beta cells in the pancreas or the failure of insulin excretion. Type 2 diabetes, which is non-insulin-dependent, occurs due to a chronic condition in which glucose level builds up into the bloodstream due to the abnormalities of insulin functions [5].

Uncontrolled diabetes, when lasts for a long time, may cause deep-rooted damages to the kidneys, heart, blood vessels, nerves [5]. Consequently, it is necessary to control blood glucose to prevent severe injuries to the body.

In type 1 diabetes, the infusion of exogenous insulin is mandatory for stabilizing the glucose level, while in type 2 diabetes, the glucose level is controlled through proper medications. The insulin injection comprises the discrete-time measurement of glycaemic concentration and exogenous injection of insulin bolus into the patient's body. Injection therapy is quite a troublesome process in which the patient has to empirically estimate the amount of required insulin and tolerate it several times a day through skin penetration.

This method of controlling diabetes is somehow open loop. Since in an open-loop controlled system, the controller does not know the level of insulin in the blood at any time, hence any disturbance that occurs during infusions, such as the

meal intake and the rate of activation, may make the system unstable. Consequently, this method is not a precise way to stabilize the blood glucose level due to its inability to achieve the desired BGC.

In the feedback control method, unlike open-loop one, the controller measures the blood insulin level at each instant, and the control command is designed properly as a function of the deviation of the blood glucose-insulin level from its desired magnitude.

It is well known that one of the advantages of a feedback controlled system is its intrinsic robustness against external disturbance and uncertainties. Consequently, a feedback control method for controlling the level of blood glucose by online feedback from continuous glucose monitoring (CGM) is of the prime interests. The emerging solution is an automated closed-loop insulin delivery system termed an artificial pancreas (AP) [6, 7].

AP is a closed-loop feedback control system that includes three individual subsystems [8]: CGM, controller, and insulin pump. The schematic of the AP mechanism is illustrated in Figure 1.

The CGM system continuously measures the insulin level, and these sensory data are then used as feedback to the controller to stabilize the system. The controller then actuates the insulin pump to inject the requisite insulin to control the blood glucose level.

To provide the continuous measurement of blood insulin with discontinuous time interval samples, the MMTT (Mixed Meal Tolerance Test), IVGTT (Intravenous Glucose Tolerance Test), and OGTT (Oral Glucose Tolerance Test) mentioned in [9] can be utilized. Stability represents the main criteria that should be considered in designing control systems. Besides stability, three main factors used to compare and evaluate the performance of the control systems are transient time, overshoot, and steady-state error.

The controller design for the AP is a challenging task due to external perturbation and various parametric variations during medication that causes the escalation of BGC in a realistic environment. This perturbation may be caused by meal intake or by burning sugar as a physical exercise. The above challenges are considered as a significant impediment in controller design for the AP mechanism. The type 1 diabetic patient can be modelled in state space by the EBMM (extended Bergamn's minimal model) [10, 11].

In [12–17], linear control techniques are applied to design AP controlled system. In [12–14], PID controller is designed for AP systems to minimize steady-state errors. However, the PID controller cannot deal with the non-linearities that exist in the EBMM. In [15, 16], fuzzy logic approach is applied to control blood glucose. The fuzzy logic control approach is a rule-based algorithm that depends on crisp input data designed by experts.

The fuzzy approach is computationally very costly and does not consider the non-linear nature of the EBMM. In [17], an LQR algorithm is applied to design a controller for type 1 diabetic patients.

The glucose-insulin dynamics are non-linear, and hence utilizing a linear controller for non-linear systems may degrade

the controller's performance and may even destabilize the system. To stabilize the non-linear system, non-linear control algorithms are a better choice.

In [18], the feedback stabilization approach is utilized to control AP; however, the stability of internal dynamics was not confirmed. In [19–22], the sliding mode control (SMC) approach is utilized to design robust controllers for AP systems in the presence of uncertainties and disturbance. However, the SMC suffers from chattering, which may result in aggressive exogenous insulin infusions leading to hypoglycemia.

In [23, 24], the fuzzy logic is combined with the SMC to control AP. However, these methods required a long settling time, and in an uncertain environment the control performance degraded and the controller suffers from chattering.

In [25], the control approach is presented based on the states-dependent Riccati equation approach. However, the controller provides acceptable results around the equilibrium and cannot provide satisfactory performance in a realistic environment.

In [26], a non-linear backstepping (BS) controller has been designed for Bergman's minimal model (BMM). In BMM, the effect of disturbance is not considered. The controller ensures boundedness of state errors, and in simulation results, there exists some steady-state error. In [27], a controller is designed for EBMM based on the BS approach. BS is a recursive feedback control approach for the stabilization of a non-linear system [28]. The controllers designed based on the BS approach require the knowledge of external disturbance and result in bounded tracking error. Moreover, the integral action is integrated with the BS technique to reduce the steady state error.

In [3], an observer-based robust controller is designed to control the blood glucose in the presence of disturbance. The controller is designed utilising the LMI approach, and the controller only ensures the boundedness of the BGC to the attractive ellipsoid.

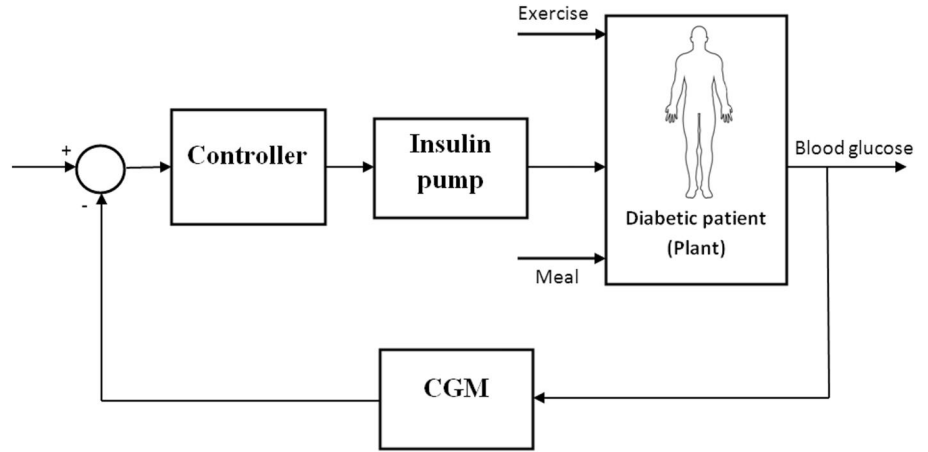
In [10, 29], the H_∞ approach is utilized to design robust controllers for AP systems. However, H_∞ controllers are of high order and fragile. In [30], the BMM is linearized at specified points, and the gain scheduling control technique is utilized to design a controller for the AP system. However, the controller only ensures local convergence.

In [31], a novel observer-based non-linear controller has been designed for EBMM. Both the observer and controller were designed in an LMI framework using feedback linearization and regional pole placement technique. The control gain was supposed to satisfy the LMI condition. Even though the system parameters were required to be known for satisfaction of the LMI condition. However, the robustness of the system to the specified range of parameter variation was shown iteratively.

In [32], the non-linear neural network SMC method was proposed for robotic systems. The controller provided bounded tracking error in the presence of uncertainties.

In this manuscript, a variable structure robust controller is designed based on the BS approach for EBMM. Recursive BS is an applicable methodology that combines the selection of a Lyapunov function with the design of a feedback system. In

FIGURE 1 Closed-loop artificial pancreas controlled system



this methodology, a design problem for the full system is divided into a series of subsystems with lower-order (even scalar) that enables the BS technique for solving stabilization problems with fewer conditions than those faced in other approaches.

The controller ensures the exponential stability of the system, which enables us to control the convergence rate of BGC in the presence of time-varying parametric uncertainties (intra-patient variability) as well as exogenous meal disturbance. The main novelties of the proposed control method are as follows:

1. Unlike [12–17] in which AP controlled system were designed utilizing linear control techniques, the controller is designed utilizing non-linear control techniques in this study, and hence the exponential stability of the system is proved mathematically using the Lyapunov theorem.
2. The controller is designed through the BS approach, and hence we control all the states regarding the EBMM. Consequently, unlike [18], the instability of the internal dynamics does not happen using the proposed approach.
3. The controller is robust against external disturbance and uncertainties in system parameters. Unlike [28] that required the knowledge of disturbance as an auxiliary state, the proposed control method does not require any knowledge about the disturbance.
4. Unlike [26–28] that provided boundedness of system states, the proposed controller ensures the exponential stability of the system, and consequently, the converging time of the system errors can be controlled by adjusting the control gains properly.
5. Unlike [31], the proposed controller does not require solving an LMI condition to compute the control gain. Moreover, the performance of the system in tracking the desired trajectory is better, since the proposed controller ensures exponential stability in the presence of uncertainties and external disturbance. However, in [31], the system states are estimated through an observer.
6. Finally, control variability grid analysis (CVGA) of 150 virtual T1D patients under the proposed control law is

carried out for the evaluation of the efficacy as well as verification of the reliability and robustness of the proposed control technique.

The rest of the study is organized as follows: In Section 2, the system is modelled in the state space, and the controller and the system errors are presented in Section 3. In Section 4, the stability of the system is analysed utilizing the Lyapunov theorem. In Section 5, the simulation results are presented, and some concluding results are presented in Section 6.

2 | MATHEMATICAL MODELLING

In this section, the system modelling is presented in state space. Bergman modelled the type 1 diabetes mellitus by a three-state non-linear mathematical model [10]:

$$\dot{x}_1 = -p_1 x_1 - x_2(x_1 + G_b) + d, \quad (1a)$$

$$\dot{x}_2 = -p_2 x_2 + p_3 x_3, \quad (1b)$$

$$\dot{x}_3 = -n(x_3 + I_b) + u(t), \quad (1c)$$

where x_1 , x_2 , x_3 represent, respectively, the glucose concentration, remote insulin concentration, and plasma insulin concentration, and the control input u is external insulin infusion rate and d represents the meal disturbance. All other parameters with their values used for simulation purposes have been listed in Table 1. The effect of meal disturbance in this model is considered to be constant.

In [11, 22], the EBMM is proposed, which incorporates the meal disturbances as a dynamical state changing with respect to time (here defined by x_4):

$$\dot{x}_1 = -p_1(x_1 - G_b) - x_1 x_2 + x_4, \quad (2a)$$

$$\dot{x}_2 = -p_2 x_2 + p_3(x_3 - I_b), \quad (2b)$$

$$\dot{x}_3 = -p_4(x_3 - I_b) + u(t), \quad (2c)$$

$$\dot{x}_4 = -p_5 x_4. \quad (2d)$$

The EBMM is more realistic compared with the BMM [11].

TABLE 1 System parameters

Parameters	Values
Glucose effectiveness factor (p_1)	0 min^{-1}
Delay in insulin actions (p_2)	0.025 min^{-1}
Patient parameters (p_3)	$0.000013 \text{ mU L}^{-1} \text{ min}^{-2}$
Insulin degradation rate (p_4)	0.021 min^{-1}
Meal disturbance (p_5)	0.05 min^{-1}
Basal plasma insulin (I_b)	4.5 mU L^{-1}
Basal plasma glucose (G_b)	4.5 m Mol L^{-1}

3 | CONTROLLER DESIGN

In this section, the control objectives are presented, and afterwards, the error systems are presented, and the controller is presented in the form of Theorem 1.

3.1 | Control objectives

Conventionally, the level of blood glucose in diabetic patients is maintained in the normal range by manual insulin intake. However, this method is not feasible during sleeping hours and is not precise. The artificial pancreas is the method that regulates BGC to its normal magnitude by automatic injection of the required insulin in the body. In AP systems, blood sugar level is monitored by sensors, and these sensory data are then used as feedback to the controller. The controller calculates the amount of required insulin and guides the insulin pump to inject that amount of insulin into patients' body.

Since the model calculated by Equations (2a)–(2d) are non-linear; hence non-linear control methods should be utilized to ensure the global stability of the system.

In this study, the BS approach is utilized to design the controller. Recursive BS is an applicable methodology that combines the selection of a Lyapunov function with the feedback system design. The controller is robust against parametric uncertainties and meal disturbance. The stability of the system is shown utilizing the Lyapunov theorem.

3.2 | Error systems and controller design

Let e_1 be calculated by

$$e_1 = x_1 - x_{1r}, \quad (3)$$

where the constant x_{1r} represents the reference magnitude of the blood glucose concentration.

Differentiating Equation (3) with respect to time and substituting Equation (2a) in the result, we obtain

$$\dot{e}_1 = -p_1(x_1 - G_b) - x_1x_2 + x_4, \quad (4)$$

where the constant reference x_{1r} represents the desired magnitude of insulin in the blood.

Let the error e_2 be calculated by

$$e_2 = x_1x_2 - e_2^*, \quad (5)$$

where

$$e_2^* = -p_1x_{1r} + p_1G_b + k_1e_1 + k_{1s} \text{sign}(e_1), \quad (6)$$

and the positive constant k_{1s} is the control gain. Considering definitions (3) and (5), Equation (4) can be rewritten as

$$\dot{e}_1 = -p_1e_1 - p_1x_{1r} + p_1G_b - e_2 - e_2^* + x_4. \quad (7)$$

Considering Equation (7), the variable e_2^* can be represented as the guiding variable to control the state e_1 .

Substituting Equation (6) in Equation (7), we obtain

$$\dot{e}_1 = -p_1e_1 - e_2 - k_1e_1 - k_{1s} \text{sign}(e_1) + x_4. \quad (8)$$

Differentiating definition (5) with respect to time, we obtain

$$\dot{e}_2 = \dot{x}_1x_2 + x_1\dot{x}_2 - \dot{e}_2^*. \quad (9)$$

Substituting Equations. (2a) and (2b) in Equation (9), we obtain

$$\dot{e}_2 = (-p_1(x_1 - G_b) - x_1x_2 + x_4)x_2 + x_1(-p_2x_2 + p_3(x_3 - I_b)) - \dot{e}_2^*. \quad (10)$$

Let us define

$$e_3 = x_1x_3 - e_3^*, \quad (11)$$

where

$$\begin{aligned} e_3^* = & \frac{1}{p_3} [(p_1(x_1 - G_b) + x_1x_2)x_2 + p_2x_1x_2 + p_3I_bx_1 \\ & - k_1(p_1 + k_1)e_1 - k_2e_2 - k_{2s}|x_2|\text{sign}(e_2) \\ & - k_1k_{1s}\text{sign}(e_1) - k_1k_{2s}\text{sign}(e_2)], \end{aligned} \quad (12)$$

and the positive constants k_1 , k_2 , k_{2s} are control gains.

Considering definition (11), Equation (10) can be rewritten as

$$\dot{e}_2 = (-p_1(x_1 - G_b) - x_1x_2 + x_4)x_2 + x_1(-p_2x_2 - p_3I_b) - \dot{e}_2^* + p_3(e_3 + e_3^*). \quad (13)$$

Considering Equation (13), it can be stated that e_3^* represents as the governing variable to control the state e_2 .

In Appendix A, it is shown that the dynamic equation governing e_2 is calculated by

$$\dot{e}_2 = (k_1 - k_2)e_2 + x_4x_2 - k_1x_4 - k_{2s}|x_2|\text{sign}(e_2) - k_1k_{2s}\text{sign}(e_2) + p_3e_3. \quad (14)$$

Differentiating Equation (11) with respect to time, we obtain

$$\dot{e}_3 = \dot{x}_1x_3 + x_1\dot{x}_3 - \dot{e}_3^*. \quad (15)$$

Substituting Equations (2a) and (2c) in Equation (15), we obtain

$$\dot{e}_3 = (-p_1(x_1 - G_b) - x_1x_2 + x_4)x_3 + x_1(-p_4(x_3 - I_b) + u) - \dot{e}_3^*. \quad (16)$$

Considering Equation (16), the term u can be regarded the governing variable to control the state e_3 . Consequently, the control input u should be designed such that the error e_3 tends to zero.

Theorem: 1 *The controller calculated by Equation (17) asymptotically stabilizes the system calculated by Equations (2a)–(2d).*

$$u = p_4(x_3 - I_b) + \frac{1}{x_1}[F - Ax_3 - k_3e_3 - k_{3s}(x_2^2 + p_3I_b + (p_1 + p_2)|x_2| + k_1(p_1 + k_1) + k_2|x_2| + p_3|x_3| + k_1k_2)\text{sign}(e_3)], \quad (17)$$

where

$$\begin{aligned} A &= -p_1(x_1 - G_b) - x_1x_2, \\ B &= -p_2x_2 + p_3(x_3 - I_b), \\ F &= \frac{1}{p_3} [((p_1 + p_2)x_2 + x_2^2 + p_3I_b)A + ((p_1 + p_2)x_1 - p_1G_b + 2x_1x_2 - k_{2s}\text{sign}(x_2)\text{sign}(e_2))B \\ &\quad + (k_1(p_1 + k_1)p_1 + k_1^2(p_1 + k_1))e_1 \\ &\quad + (k_1(p_1 + k_1) - k_2(k_1 - k_2))e_2 \\ &\quad + k_1(p_1 + k_1)(k_{1s}\text{sign}(e_1)) + k_1k_2k_{2s}\text{sign}(e_2) \\ &\quad - k_2p_3e_3 + k_2k_{2s}|x_2|\text{sign}(e_2)] \end{aligned} \quad (18)$$

In Appendix B, it is shown that the dynamic governing error \dot{e}_3 is calculated by

$$\begin{aligned} \dot{e}_3 &= x_4x_3 - \frac{1}{p_3}[x_4x_2^2 + p_3I_bx_4 + (p_1 + p_2)(x_4x_2) \\ &\quad - k_1(p_1 + k_1)(x_4) - k_2x_4x_2 + k_1k_2x_4] \\ &\quad - k_3e_3 - k_{3s}(x_2^2 + p_3I_b + (p_1 + p_2)|x_2| \\ &\quad + k_1(p_1 + k_1) + k_2|x_2| + p_3|x_3| + k_1k_2)\text{sign}(e_3). \end{aligned} \quad (19)$$

4 | STABILITY ANALYSIS

The stability of the system is analysed in this section utilizing the Lyapunov theorem.

Consider the following PD Lyapunov function

$$V = \frac{1}{2}X^T X, \quad (20)$$

where

$$X = [e_1, e_2, e_3]^T. \quad (21)$$

Differentiating Equation (20) with respect to time, we obtain

$$\dot{V} = e_1 \dot{e}_1 + e_2 \dot{e}_2 + e_3 \dot{e}_3. \quad (22)$$

Substituting Equations (8), (14), and (19) in Equation (22), we obtain

$$\begin{aligned} \dot{V} &= e_1 [-p_1e_1 - e_2 - k_1e_1 - k_{1s}\text{sign}(e_1) + x_4] \\ &\quad + e_2 [(k_1 - k_2)e_2 + x_4x_2 - k_1x_4 - k_{2s}|x_2|\text{sign}(e_2) \\ &\quad - k_1k_{2s}\text{sign}(e_2) + p_3e_3] + e_3 [x_4x_3 - \frac{1}{p_3}(x_4x_2^2 + p_3I_bx_4 \\ &\quad + (p_1 + p_2)(x_4x_2) - k_1(p_1 + k_1)(x_4) - k_2x_4x_2 + k_1k_2x_4) \\ &\quad - k_3e_3 - k_{3s}(x_2^2 + p_3I_b + (p_1 + p_2)|x_2| + k_1(p_1 + k_1) \\ &\quad + k_2|x_2| + p_3|x_3| + k_1k_2)\text{sign}(e_3)]. \end{aligned} \quad (23)$$

Considering that for any arbitrary function such as a, b , we have

$$ab \leq \frac{1}{2}(a^2 + b^2). \quad (24)$$

Considering Equation (24), we can simplify Equation (23) to obtain

$$\begin{aligned}
\dot{V} \leq & -p_1 e_1^2 + \frac{1}{2}(e_1^2 + e_2^2) - k_1 e_1^2 - k_{1s}|e_1| + |e_1||x_4| \\
& + (k_1 - k_2)e_2^2 + |e_2||x_2||x_4| - k_{2s}|x_2||e_2| \\
& + k_1|x_4||e_2| - k_1 k_{2s}|e_2| + \frac{1}{2}p_3(e_2^2 + e_3^2) \\
& + |e_3||x_4| \left[|x_3| + \frac{1}{p_3}(x_2^2 + p_3 I_b + (p_1 + p_2)|x_2| \right. \\
& \left. + k_1(p_1 + k_1) + k_2|x_2| + k_1 k_2) \right] \\
& - k_3 e_3^2 - k_{3s}(x_2^2 + p_3 I_b + (p_1 + p_2)|x_2| \\
& + k_1(p_1 + k_1) + k_2|x_2| + p_3|x_3| + k_1 k_2)|e_3|.
\end{aligned} \tag{25}$$

Considering Equation (2d), we obtain

$$x_4 = x_4(0) e^{-p_3 t} \leq x_4(0) \leq \gamma. \tag{26}$$

Consequently, we obtain

$$\begin{aligned}
\dot{V} \leq & \left(-p_1 + \frac{1}{2} - k_1 \right) e_1^2 + \left(\frac{1}{2} + (k_1 - k_2) + \frac{1}{2}p_3 \right) e_2^2 \\
& + \left(-k_3 + \frac{1}{2}p_3 \right) e_3^2 + (\gamma - k_{1s})|e_1| + (\gamma - k_{2s})|e_2||x_2| \\
& + (k_1\gamma - k_1 k_{2s})|e_2| + \gamma \left(|x_3| + \frac{1}{p_3}(x_2^2 + p_3 I_b \right. \\
& \left. + (p_1 + p_2)|x_2| + k_1(p_1 + k_1) + k_2|x_2| + k_1 k_2) \right) |e_3| \\
& - k_{3s} \left(x_2^2 + p_3 I_b + (p_1 + p_2)|x_2| + k_1(p_1 + k_1) \right. \\
& \left. + k_2|x_2| + p_3|x_3| + k_1 k_2 \right) |e_3|.
\end{aligned} \tag{27}$$

From Equation (27), it can be stated that if the control gains are selected such that

$$\begin{aligned}
k_1 & > -p_1 + \frac{1}{2}, \quad k_1 > 0, \quad k_2 > \frac{1}{2} + k_1, \\
k_3 & > \frac{1}{2}p_3, \quad k_{1s} > \gamma, \quad k_{2s} > \gamma, \quad k_{3s} > \frac{\gamma}{p_3},
\end{aligned} \tag{28}$$

then we have

$$\dot{V} \leq -\varepsilon_1 e_1^2 - \varepsilon_2 e_2^2 - \varepsilon_3 e_3^2, \tag{29}$$

where $\varepsilon_1, \varepsilon_2, \varepsilon_3$ are positive constants. Consequently, we obtain

$$\dot{V} \leq -\varepsilon |X(t)|^2, \tag{30}$$

where $\varepsilon = \min\{\varepsilon_1, \varepsilon_2, \varepsilon_3\}$.

Considering Equation (20), we have

$$V(t) = \frac{1}{2}|X(t)|^2. \tag{31}$$

Considering Equation (31), the Equation (30) can be rewritten as

$$\dot{V}(t) \leq -2\varepsilon V(t). \tag{32}$$

Integrating both sides, we obtain

$$\int_{V(0)}^{V(t)} \frac{dV}{V} \leq -\int_0^t 2\varepsilon dt, \tag{33}$$

we obtain

$$\ln\left(\frac{V(t)}{V(0)}\right) \leq -2\varepsilon t. \tag{34}$$

Consequently, we have

$$V(t) \leq V(0) e^{-2\varepsilon t}. \tag{35}$$

Considering Equation (31), we have

$$|X(t)| \leq |X(0)| e^{-\varepsilon t}. \tag{36}$$

Consequently, it can be stated that the errors $e_1(t), e_2(t), e_3(t)$ exponentially converge to zero.

Remark: From Equation (36), it can be easily observed that the convergent rate of system errors can be controlled by increasing the magnitude of control gains.

5 | SIMULATION RESULTS

In this section, to evaluate the theoretical results, the performance of the proposed controllers given by Equation (17) for glycaemic regulation in T1D patients in the presence of a high initial meal disturbance is shown in MATLAB/Simulink software. The results are compared with the PID and BS controller proposed in [27].

The proposed controller is simulated for the system that is subjected to time-varying uncertain external meal disturbances calculated by Equation (2d), known as Fisher's meal disturbance, considering that (i) the BGC must not fall below the severe hypoglycemic level ($x_1 > 50$ mg/dl), (ii) the BGC must not rise the post-prandial hyperglycemia level in the presence of external meal disturbance (iii) the control signal should be non-negative.

Similar to [18, 19], the initial conditions of plasma glucose-insulin are supposed for a patient in the state of hyperglycaemia as $x_1(0) = 200$ mg/dl, $x_2(0) = 0.001$ min⁻¹, $x_3(0) = 7$ mU/l. As mentioned previously, the BGC level for a healthy person should be 70–180 mg/dl. In the simulation, the reference range for BGC is considered to be $x_{1r} = 80$ mg/dl and the controller is designed to regulate the system BGC to

the reference level by the intravenous injection of insulin. The system parameters utilized for the simulation purpose are mentioned in Table 1, and the control gains are presented in Table 2. The results are compared with the PID and the BS controller proposed in [27]. The same data set has been chosen for each simulation to make the results comparable with each other.

The time history of BGC is shown in Figure 2, in which the result of the proposed controller is compared with those of the PID and BS controller proposed in [27], in the presence of Fisher's meal disturbance. The x -axis represents the time in seconds, and the y -axis the BGC in mg/dl. The comparisons verify that the PID controller undergoes an oscillatory response with larger undershoots/overshoots, has a very large settling time, and has some steady-state error in comparison. The BS controller response is faster compared with the PID controller. However, the BS controller ensures boundedness of system error, and moreover, the PID and BS controllers require the measurement of external disturbance. As the proposed controller provides exponential stability of the system, the rate of convergence utilising the proposed control method can be controlled, and hence the controller has a very low settling time.

TABLE 2 Controller gains

Control gains	Values
k_{1s}	0.03
k_1	0.01
k_{2s}	0.03
k_2	0.03
k_{3s}	0.03
k_3	0.07

The comparisons verify the improvement made by the proposed controller even in the presence of unknown dynamical meal disturbances. So it can be clearly observed that the performance of the PID and BS controller is not satisfactory when compared with the proposed controller in terms of oscillations, steady-state error, undershoots/overshoots, and convergence time.

Figure 2 shows that the proposed controller effectively monitors and tracks the reference level of BGC for the data of three patients very nicely without undergoing chattering and steady-state errors.

It is worth noting that the controller proposed in [27] required the knowledge of the disturbance meal (here denoted by x_4), and provided boundedness of the system errors. In this study, the controller ensures exponential stability of the system without requiring the knowledge of the external disturbance.

Figure 3 demonstrates the required insulin that should be injected as the control input. As shown in Figure 3, the first pulse in the control signal causes the BGC to fall from higher to a lower level, and then another pulse is injected by the controller to achieve the reference position. The insulin infusion rate is diminished as the BGC approaches the reference level of 80 mg/dl.

The results of the proposed controller and the PID and BS controllers presented in [27] are compared in Table 3. From the results, it can be observed that the settling time has been improved considerably in the presence of unknown external disturbance in the proposed method. This outcome was expected since the proposed controller ensures exponential stability and hence the converging time can be controlled by properly adjusting the control gains. It is worth noting that the proposed controller does not require the knowledge of external disturbance. The proposed controller leads to better tracking performance without requiring a higher amount of insulin.

It is worth highlighting that the insulin infusion rate is within acceptable limits for available insulin pumps.

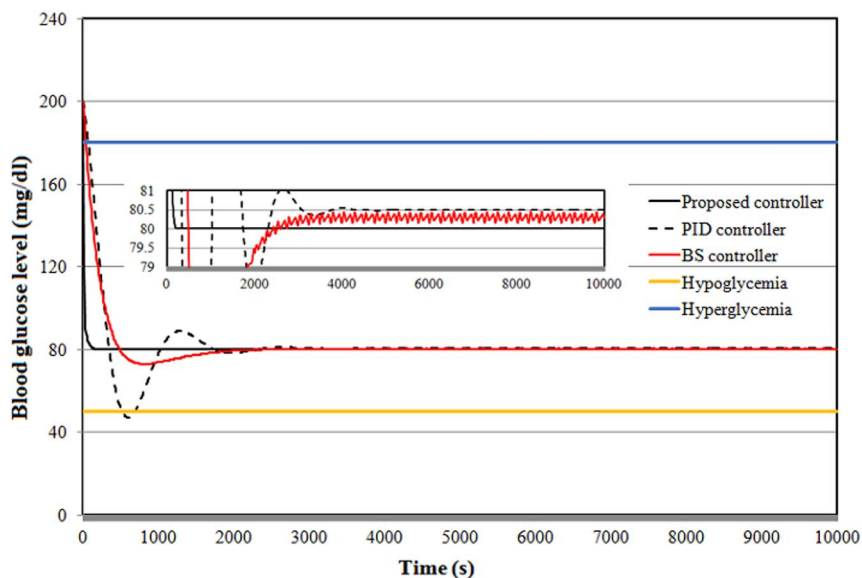


FIGURE 2 Time history of blood glucose level

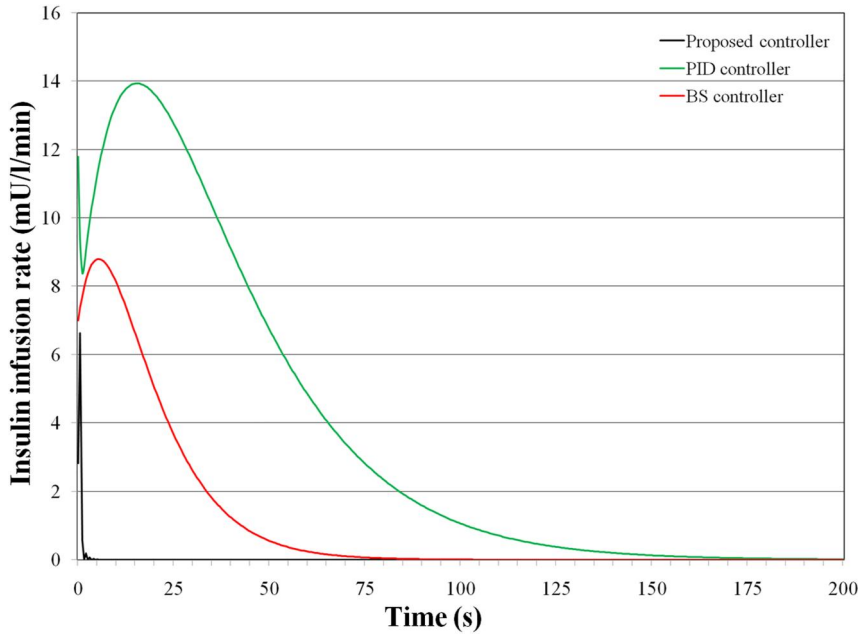


FIGURE 3 Time history of the proposed control signal

TABLE 3 Comparison of performance of controlled systems

	Proposed controller	PID controller [27]	BS controller [27]
Stability result	Asymptotic	Boundedness	Boundedness
Requiring knowledge of disturbance	×	✓	✓
Robustness to uncertainties	✓	×	×
Maximum insulin infusion rate (mU/l/min)	6.7	14	8.8
Maximum blood glucose level (mg/dl)	200	200	200
Minimum blood glucose level (mg/dl)	80.001	48	69
Steady-state error (mg/dl)	0.001	0.5	0.3
Settling time (seconds)	173	2000	1120

To evaluate the robustness of the controller in the presence of the uncertainties in system parameters and external disturbance, the controller performance is analysed for 150 different random patients with different parameters, and the control grid variability analysis (CGVA) is shown in Figure 4. The parameters of 150 patients vary in the range $\pm 30\%$ from the nominal magnitudes utilized in designing the controller. From Figure 4, it can be shown that 100% of the minimum BGC are greater than 70 mg/dl, and 90% of the maximum BGC are less than 200 mg/dl.

To evaluate the effectiveness of the proposed control method in the presence of parametric uncertainties, the proposed control method and the PID and BS control methods are simulated in the presence of 20% uncertainties in the system parameters and the results are shown in Figure 5. As shown in Figure 5, the controller proposed in this study ensures asymptotic stability in the presence of uncertainties. However, the BS and PID controller only ensure boundedness. This outcome was to be expected since the proposed controller is robust against uncertainties.

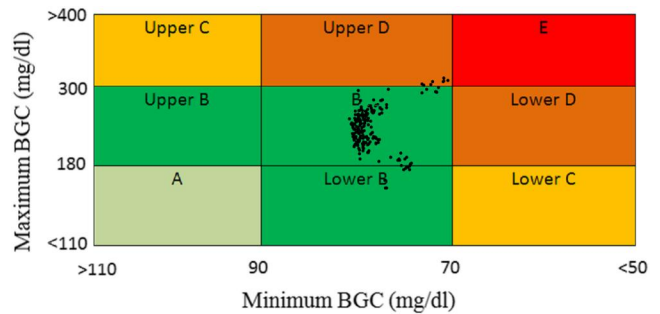


FIGURE 4 CVGA for parametric variability of $\pm 30\%$

To evaluate the effectiveness of the proposed control method in the presence of unknown disturbance, we simulate the proposed control method and the PID and BS control methods in the presence of unknown constant disturbance. A fairly high meal disturbance of $x_4(t) = 10$ mg/dl/min is considered here and the results are shown in Figure 6.

FIGURE 5 Time history of blood glucose level (robustness to 20% uncertainties in system parameters)

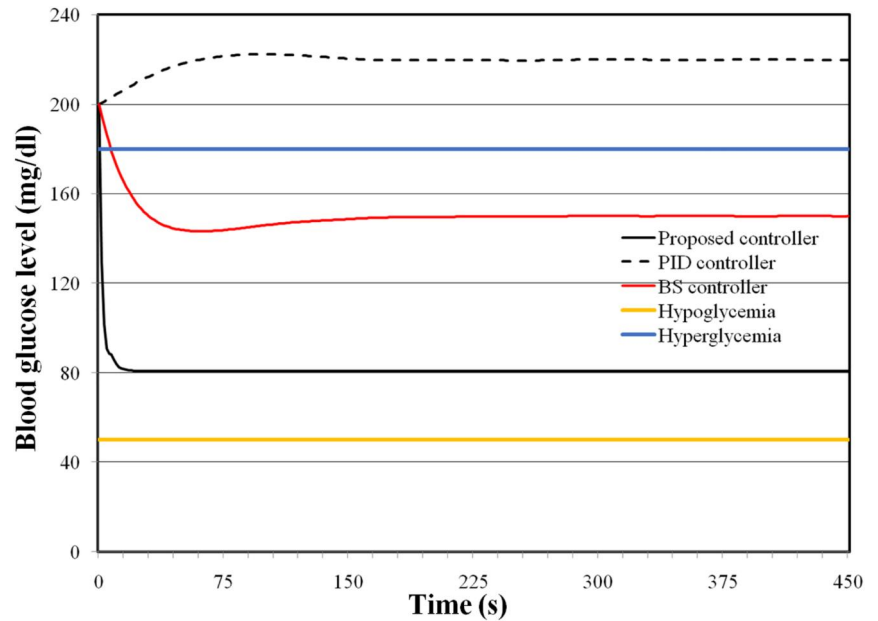
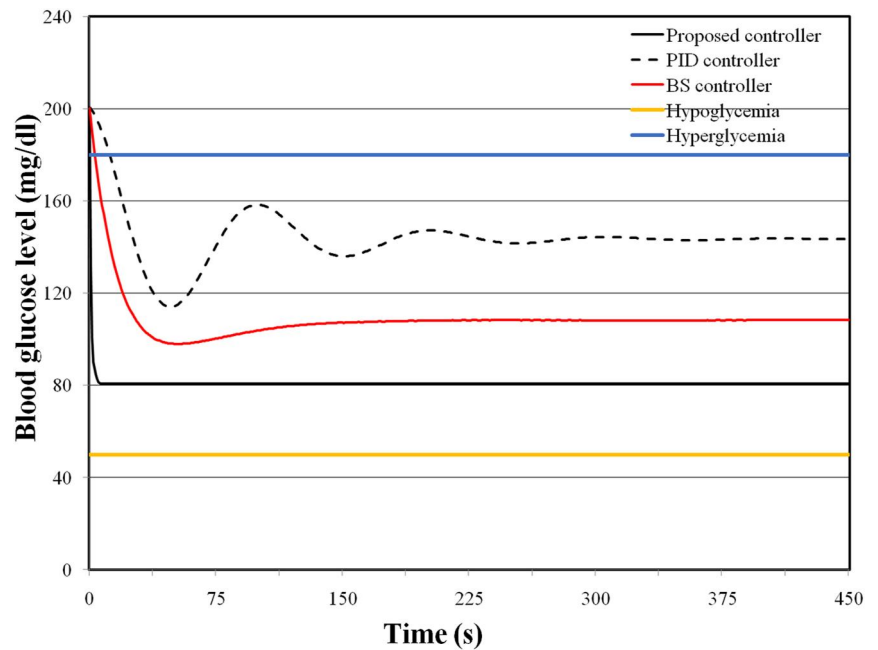


FIGURE 6 Time history of blood glucose level (robustness to unknown external disturbance)



As shown in Figure 6, the controller proposed in this study ensures asymptotic stability in the presence of unknown external disturbance. However, the BS and PID controller only ensure boundedness. This outcome was to be expected since the proposed controller is robust against external disturbance.

6 | CONCLUSION

This study proposed a new variable structure robust blood-glucose regulation methodology for an uncertain Bergman's minimal model employing a backstepping approach. The stability of the system was proved utilizing the Lyapunov theorem. The proposed controller ensures exponential stability of the

system in the presence of meal disturbances and parametric uncertainties. The simulation results verify the satisfactory performance of the proposed controller in comparison with previous related studies. Better regulation results were obtained without requiring the knowledge of external disturbance. This outcome was expected because the proposed controller provides exponential stability. The proposed controller leads to better tracking performance without requiring a higher amount of insulin. Future studies would exploit other techniques to control blood glucose in the presence of unknown disturbance and uncertainties. As a future work, adaptive control approaches [33, 34]; adaptive robust control approaches [35]; and neural network techniques [32] could be studied in the context of blood-glucose regulation.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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APPENDIX A

Differentiating Equation (6) with respect to time, we obtain

$$\dot{e}_2^* = k_1 \dot{e}_1. \quad (A1)$$

Substituting Equation (8) in Equation (A1), we obtain

$$\dot{e}_2^* = k_1(-p_1 e_1 - e_2 - k_1 e_1 - k_{1s} \text{sign}(e_1) + x_4). \quad (A2)$$

Substituting Equation (A2) in Equation (10) and considering definition (11), we obtain

$$\begin{aligned} \dot{e}_2 = & (-p_1(x_1 - G_b) - x_1 x_2 + x_4)x_2 + x_1(-p_2 x_2 - p_3 I_b) \\ & - k_1(-p_1 e_1 - e_2 - k_1 e_1 - k_{1s} \text{sign}(e_1) + x_4) \\ & + p_3(e_3 + e_3^*). \end{aligned} \quad (A3)$$

Substituting e_3^* by Equation (12) in Equation (A3), we obtain

$$\begin{aligned} \dot{e}_2 = & \underbrace{(-p_1(x_1 - G_b) - x_1 x_2)}_{\cancel{\quad}} x_2 + x_4 x_2 + \underbrace{x_1(-p_2 x_2 - p_3 I_b)}_{\cancel{\quad}} \\ & - \underbrace{k_1(-p_1 e_1 - k_1 e_1)}_{\cancel{\quad}} - \underbrace{k_1(-e_2 + x_4)}_{\cancel{\quad}} + \underbrace{k_1 k_{1s} \text{sign}(e_1)}_{\cancel{\quad}} + p_3 e_3 \\ & + \underbrace{(p_1(x_1 - G_b) + x_1 x_2)}_{\cancel{\quad}} x_2 + \underbrace{p_2 x_1 x_2}_{\cancel{\quad}} + \underbrace{p_3 I_b x_1}_{\cancel{\quad}} - \underbrace{k_1(p_1 + k_1)e_1}_{\cancel{\quad}} \\ & - \underbrace{k_2 e_2 - k_{2s} |x_2| \text{sign}(e_2)}_{\cancel{\quad}} - \underbrace{k_1 k_{1s} \text{sign}(e_1)}_{\cancel{\quad}} - \underbrace{k_1 k_{2s} \text{sign}(e_2)}_{\cancel{\quad}} \end{aligned} \quad (A4)$$

Simplifying Equation (A4), we obtain

$$\begin{aligned} \dot{e}_2 = & (k_1 - k_2)e_2 + x_4 x_2 - k_1 x_4 - k_{2s} |x_2| \text{sign}(e_2) \\ & - k_1 k_{2s} \text{sign}(e_2) + p_3 e_3. \end{aligned} \quad (A5)$$

APPENDIX B

Differentiating Equation (12) with respect to time and substituting Equations (8) and (14), we obtain

$$\begin{aligned} \dot{e}_3^* = & \frac{1}{p_3} \left[(p_1 + p_2)(\dot{x}_1 x_2 + x_1 \dot{x}_2) - p_1 G_b \dot{x}_2 + \dot{x}_1 x_2^2 \right. \\ & + 2x_1 x_2 \dot{x}_2 + p_3 I_b \dot{x}_1 - k_1(p_1 + k_1)(-p_1 e_1 - e_2 - k_1 e_1 \\ & - k_{1s} \text{sign}(e_1) + x_4) - k_2((k_1 - k_2)e_2 + x_4 x_2 - k_1 x_4 \\ & \left. - k_{2s} |x_2| \text{sign}(e_2) - k_1 k_{2s} \text{sign}(e_2) + p_3 e_3) - k_{2s} \dot{x}_2 \text{sign}(x_2) \text{sign}(e_2) \right] \end{aligned} \quad (A6)$$

Considering definition (18), the Equation (A6) can be rearranged as

$$\begin{aligned} \dot{e}_3^* = & F + \frac{1}{p_3} [x_4 x_2^2 + p_3 I_b x_4 + (p_1 + p_2)(x_4 x_2) \\ & - k_1(p_1 + k_1)(x_4) - k_2 x_4 x_2 + k_1 k_2 x_4] \end{aligned} \quad (A7)$$

Substituting \dot{e}_3^* by Equation (A7) and the control input by Equation (17) in Equation (16), we obtain

$$\begin{aligned} \dot{e}_3 = & \underbrace{(x_4 + x_4)}_{\cancel{\quad}} x_3 \quad \rightarrow \dot{e}_3^* \\ & - \left[\cancel{\frac{1}{p_3}} (x_4 x_2^2 + p_3 I_b x_4 + (p_1 + p_2)(x_4 x_2) - k_1(p_1 + k_1)(x_4) - k_2 x_4 x_2 + k_1 k_2 x_4) \right] \\ & - \cancel{x_1 p_4 (x_3 - I_b)} \\ & + \underbrace{x_1 p_4 (x_3 - I_b) + \cancel{\frac{1}{p_3}} - \cancel{A} x_3 - k_{3s} e_3 - k_{3s} (x_2^2 + p_3 I_b + (p_1 + p_2)|x_2| + k_1(p_1 + k_1) + k_2|x_2| + p_3|x_3| + k_1 k_2) \text{sign}(e_3)}_{\rightarrow x_1 u} \end{aligned} \quad (A8)$$

Consequently, we obtain

$$\begin{aligned} \dot{e}_3 = & x_4 x_3 - \frac{1}{p_3} [x_4 x_2^2 + p_3 I_b x_4 + (p_1 + p_2)(x_4 x_2) - k_1(p_1 + k_1)(x_4) - k_2 x_4 x_2 + k_1 k_2 x_4] \\ & - k_{3s} e_3 - k_{3s} (x_2^2 + p_3 I_b + (p_1 + p_2)|x_2| + k_1(p_1 + k_1) + k_2|x_2| + p_3|x_3| + k_1 k_2) \text{sign}(e_3). \end{aligned} \quad (A9)$$