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An adaptive back-stepping control for blood glucose regulation in type 1 diabetes

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ABSTRACT

In this paper, an adaptive back-stepping controller is designed to regulate the blood glucose in type 1 diabetics. Bergman's minimal model (BMM) is employed to mathematically model Type 1 diabetes mellitus (T1DM). Firstly, an adaptive virtual controller is designed to bring back the blood glucose level to its safe range. Then, a second adaptive controller is designed to determine the insulin intake. Controller performance and asymptotic stability of the adaptive back-stepping method is proved using Lyapunov stability theory. To verify the effectiveness of the proposed approach in tracking the desired blood glucose, simulation results have been performed. Meal disturbance to diabetes patient is also definitely described and is presented in simulation results. The results show the advantages of the proposed controller such as proper convergence time, robustness in the presence of external disturbances and uncertainties in human body parameters.

1. Introduction

Type 1 Diabetes is a prevailing, chronic disease that occurs when the immune system attacks and destroys Beta cells, producing insulin in pancreas so the body does not produce enough insulin. So, in this case glucose remains in bloodstream and over time hyperglycemia (blood glucose >200 mg/dl) damages most tissues in body. According to World Health Organization (WHO), about 425 million people suffer from diabetes that include 1 out of 11 adults. The international Diabetes Federation has predicted this number will increase to 629 million patients in 2045. China, India and America have the highest number of diabetics respectively [1]. In the beginning of the 1993, the diabetes control group reported a link between high blood glucose and cardiovascular risk. On the one hand, hypoglycemia (blood glucose lower than 60 mg/dl) can lead to medical emergency like loss of consciousness and coma that can be deadly, on the other hand, hyperglycemia can lead to serious complications such as blindness, cardiovascular disease, diabetic nephropathy, neuropathy and retinopathy [2]. Due to the cessation of insulin secretion in type 1 diabetic patients and considering that insulin is a protein, oral insulin consumption in gastric juices is attacked by strong digestive enzymes. Therefore, insulin cannot be used as a pill or a capsule and must be injected [3]. There are two common ways to inject insulin; dissociation of insulin injection which is done by different types of syringes and continuous insulin infusion which is done by a pump. Dissociation injection is not an ideal therapy for diabetes because after injection there is no feedback related to the impact of insulin on the blood glucose level. Since there are many factors like meals, exercise or individual mood affecting blood glucose directly so the blood glucose level stays higher than normal, it may be because the consumption of carbohydrate is estimated wrong. In contrast, continuous insulin infusion using an insulin pump which is programmable has the ability to leverage closed-loop control to regulate the blood glucose. This approach can regulate insulin injection rate individually for each person [4,5].

Currently, diabetic patients with insulin-dependent face a daily challenge in controlling the blood glucose concentrations manually. To avoid determining the dose of insulin manually, the use of a control method is suggested based on the continuous measurement of the blood glucose done via a sensor [6,7]. The sensor produces an electrical current proportional to the patient's blood glucose and due to the changes in blood sugar in the diabetics with the help of a closed-loop system, insulin dosage is prescribed and enters the patient's body by the insulin pump (Fig. 1). Preserving the natural level of blood glucose and obtaining insulin injection rate according to the patient's need is the main goal of controlling diabetes [8].

Closed-loop control systems for regulating the blood glucose in diabetics are performed mainly based on model and experimental data methods. For blood glucose concentration in T1DM, several control

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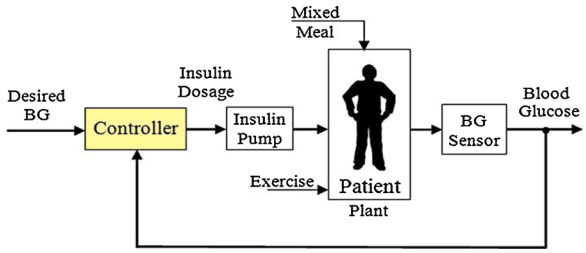

Fig. 1. Block diagram of closed loop control of blood glucose [6].

methods are available in literature. This includes Model predictive control (MPC) [9,10], PID controllers [11], smart controllers like fuzzy logic and neural networks [12,13], robust H_∞ controllers [14], sliding mode control (SMC) [15,16] and adaptive control [17]. Nonlinear models of the disease can incorporate deep knowledge and details about the disease and are more realistic and compatible to the patient's body than linear models. However, uncertainties and unknown parameters are inevitable in these models and must be taken into account when designing a controller. Thus, adaptive control method has received a surge of attention in recent decades.When there is no prior information about the bounds of unknown system parameters, adaptive control can be leveraged to reduce uncertainty. Now, back-stepping method has been noted for the design of adaptive controllers. Back-stepping is a recursive Lyapunov-based scheme that has been used for the class of strict feedback systems [18]. In [19], an adaptive back-stepping control is designed to regulate the blood glucose concentration. Considering only one unknown parameter in the system is the major drawback of the latter approach. On the other hand, SMC is a robust control method that can handle system uncertainties and disturbances. But this method requires to know some bounds on uncertainties and it has high frequency chattering in control signal. One remedy to alleviate the chattering is using the higher order SMC. In [20], high frequency chattering is minimized using super twisting SMC approach that is based on the higher order SMC. Moreover, in [21–23] a dual-hormone control scheme with SMC approaches have been proposed for avoiding sever hypoglycemia. Briefly, the disadvantages of the control strategies are some continuous oscillations and undershoot/overshoot in tracking responses.

Here, an adaptive back-stepping control strategy is designed for an uncertain nonlinear minimal model representing blood glucose regulation in type 1 diabetes mellitus patients. The purpose of this work is (i) to present an adaptive virtual controller for glucose subsystem to regulate the blood glucose concentration and (ii) to determine an adaptive actual controller (insulin injection rate) for insulin subsystem to track the virtual controller. Our proposed method is a fully adaptive control method, i.e., all parameters of the system's model have been considered unknown. Asymptotic stability of the adaptive back-stepping controller is evaluated using Lyapunov stability theory. Comparison of the proposed controller has been performed with a sliding mode control (SMC) technique and simulation results have also been discussed in detail.

The remaining of the paper has been arranged as follows: Section 2 briefly reviews mathematical model of glucose-insulin dynamics of human body. The proposed controller is presented in section 3. Simulation results have been discussed in section 4 and finally section 5 contains its conclusion.

2. Mathematical representation of glucose-insulin dynamics

Glucose-insulin system in human body acts reciprocally by feedback control signals. If low or high glucose concentrations occurs, liver and beta-cells regulate the blood glucose in body respectively by producing glucose or insulin as illustrated in Fig. 2.

Mathematical models play an important role in understanding dynamic behavior and performance of different and complex biological systems. In the context of diabetes, due to the factors affecting the disease involving complex interactions of metabolism, hereditary and environmental factors, thus mathematical models are required to consider such complexity [24].

The mathematical models may be simple/complex, deterministic/stochastic, continuous/discrete described using different differential equations. Mathematical models presented to the time domain can be arranged into different categories based on the considered physiology, complexity level of model and type of data is used in the models. Many attempts have been made to investigate the complexity of the disease performance, but there is still some inconsistency between the information obtained theoretically and mathematically. Bergman et al. (1981), Sturis and Tolic (1991), Topp et al. (2000) and Hovorka (2004) proposed ODE (ordinary differential equations) models for glucose-insulin dynamics [26,27]. Drozdov and Khanina (1995) proposed a nonlinear ODE with one delay, Li (2006), Chen and Tsai (2010) proposed a model with two delay in dynamics of glucose-insulin [28–30]. Wach et al. (1995) proposed PDE (partial differential equations) model that is adapted to enable quantitation of subcutaneous insulin imbibition following insulin injections of soluble insulin [31]. Gaetano and Arino (2000) proposed a dynamic model with IDE (integral differential equations). The models introduced in this form of differential equations are all based on insulin and glucose dynamics in IVGTT (intravenous glucose tolerance test) [32]. Along with the aforementioned researches, a simulator has been developed by the University of Padova and Virginia, USA [33]. It is a useful computational tool verified by the Food and Drug Administration (FDA) as a substitute for pre-clinical animal testing in trials of new glycemic control strategies.

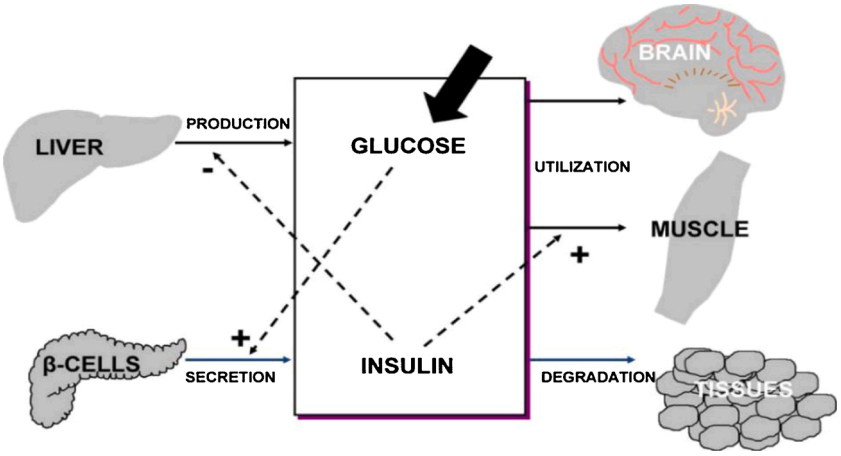

Fig. 2. Glucose regulation in human body [25].

The BMM is currently used in physiological researches in glucose metabolism and insulin regulation was proposed in the beginning of the 1980s by Bergman to interpret the glucose concentrations and plasma insulin in IVGTT. This model provides a quantitative and economical description of insulin and glucose levels in the blood sample and generally one reason for calling this model as minimal model is that a mathematical model with the minimum possible parameters is to cover the empirical data [34,35]. The BMM is made of a glucose chamber where plasma insulin acts through a delay chamber and affects glucose uptake. It includes of two parts: the first part describes the glucose plasma concentration considering dynamics of glucose uptake and independence of circulating insulin as follows

$$\dot{G}(t) = -p_1(G(t) - G_b) - X(t)G(t) + D(t) \tag{1-a}$$

$$\dot{X}(t) = -p_2X(t) + p_3(I(t) - I_b) \tag{1-b}$$

where $t = 0$ is the time that glucose enters the bloodstream, $G(t)$ represents the glucose concentration, G_b is a constant value which shows the basal plasma glucose, $X(t)$ is the insulin effect on glucose concentration reduction, $I(t)$ represents plasma insulin concentration and I_b is the basal plasma insulin concentration. Parameter p_1 is the glucose effectiveness factor, p_2 defines delay in insulin action, p_3 is the insulin-dependent rate and $D(t)$ shows a meal which is an external disturbance.

Insulin kinetics is given by (2) which describes the plasma insulin concentration as below

$$\dot{I}(t) = -n(I(t) - I_b) + \gamma(G(t) - h)^+ t \tag{2}$$

Where n shows fractional disappearance rate, h is the pancreatic target glycemia and γ defines the rate of pancreatic release of insulin after bolus. '+' sign indicates the positive reflection to glucose intake. When $(G(t) - h) > 0$, the term of $\gamma(G(t) - h)^+$ in (2) takes as an internal regulatory function that formulates the insulin emission in the body, which does not exist in diabetic patients [36].

3. Proposed controller design

Because there is no internal regulatory in diabetic patients or its inefficiency, so, it results $\gamma = 0$ in (2). Also injected insulin is regarded as an external input for the BMM, therefore Eqs. (1) and (2) can be rewritten in the following form

$$\dot{G}(t) = -p_1(G(t) - G_b) - X(t)G(t) + D(t) \tag{3}$$

$$\dot{X}(t) = -p_2X(t) + p_3(I(t) - I_b) \tag{4}$$

$$\dot{I}(t) = -n(I(t) - I_b) + u(t) \tag{5}$$

where the variable $u(t)$ is the insulin injection rate (the control input), $D(t)$ is a disturbance (the meals) which is bounded and may be defined as below

$$D(t) = \begin{cases} 0 & t < t_0 \\ A\exp(-B(t - t_0)), \ B > 0 & t \geq t_0 \end{cases} \tag{6}$$

By taking the time derivative of (4) and mixing it with (5), one can obtain

$$\ddot{X}(t) + (p_2 + n)\dot{X}(t) + p_2nX(t) = p_3u(t) \tag{7}$$

Hence, the BMM may be described as follows

$$\dot{G}(t) = -p_1(G(t) - G_b) - X(t)G(t) + D(t) \tag{8}$$

$$\ddot{X}(t) + (p_2 + n)\dot{X}(t) + p_2nX(t) = p_3u(t) \tag{9}$$

Now, a two-layer adaptive back-stepping controller is designed for the latter system to lower the blood glucose level to the safe range. In step1, a virtual control signal (a virtual concentration of infused insulin) is designed for glucose subsystem (8), to guarantee the blood glucose level goes to the basal glucose asymptotically. In step2, a real control input i.e. insulin injection rate is offered for insulin subsystem (9), such that the concentration of infused insulin converges to its virtual value computed in the step1.

3.1. Virtual adaptive controller design for glucose subsystem

According to (8), if $D(t) = 0$, by choosing the following virtual control input for $X(t)$, it can easily show that $\widetilde{G}(t)$ go to zero asymptotically.

$$X^*(t) = \frac{1}{G(t)}\left(-p_1\widetilde{G} + \alpha_1\widetilde{G} + \alpha_2\int \widetilde{G}dt\right) \tag{10}$$

in which α_1 and α_2 are positive design parameters and $\widetilde{G}$ is taken as difference between the real and the base value of $G(t)$ given below

$$\widetilde{G} = G(t) - G_b \tag{11}$$

Indeed, by applying (10) on (8), the following asymptotic stable dynamic equation for regulating glucose is found

$$\dot{\widetilde{G}} + \alpha_1\widetilde{G} + \alpha_2\int \widetilde{G}\,dt = 0 \tag{12}$$

Since parameter p_1 and also $D(t)$ are unknown, the virtual control law of (10) cannot be realized and thus the subsequent virtual control proposed for dynamic Eq. (8)

$$X_v(t) = \frac{1}{G(t)}\left(-\widehat{p}_1\widetilde{G} + \alpha_1\widetilde{G} + \alpha_2\int \widetilde{G}dt + x_r\right) \tag{13}$$

Where $\widehat{p}_1$ is an estimated value of p_1 and x_r is a robust term for compensating the effect of disturbance $D(t)$. Let $\widetilde{p}_1$ is defined as difference between the estimated and actual value of p_1 given follows

$$\widetilde{p}_1 = \widehat{p}_1 - p_1 \tag{14}$$

By replacing (13) in (8), one can get

$$\dot{\widetilde{G}} = -\alpha_1\widetilde{G} - \alpha_2\int \widetilde{G}dt + \widetilde{p}_1\widetilde{G} + D(t) - x_r \tag{15}$$

By defining vector $\boldsymbol{Z}_1 = \left[\int \widetilde{G}dt,\ \widetilde{G}\right]^T$, (15) further can be written as

$$\dot{\boldsymbol{Z}}_1 = \boldsymbol{A}_1\boldsymbol{Z}_1 + \boldsymbol{B}_1v_1 \tag{16}$$

where

$$\boldsymbol{A}_1 = \begin{pmatrix} 0 & 1 \\ -\alpha_2 & -\alpha_1 \end{pmatrix},\ \boldsymbol{B}_1 = \begin{pmatrix} 0 \\ 1 \end{pmatrix} \tag{17}$$

And

$$v_1 = \widetilde{p}_1\widetilde{G} + D(t) - x_r \tag{18}$$

Now, choose the following positive function $V_1(t)$

$$V_1(t) = \frac{1}{2}\boldsymbol{Z}_1^T\boldsymbol{P}_1\boldsymbol{Z}_1 + \frac{1}{2\gamma_{p_1}}\widetilde{p}_1^{\,2} + \frac{1}{2\gamma_\rho}\widetilde{\rho}^2 \tag{19}$$

Where γ_{p_1} and γ_ρ are positive design parameters. Here the value of meal disturbance $D(t)$ is unknown and suppose the upper limit is $|D(t)| \leq \rho_m$. The value of ρ_m is also unknown and $\widetilde{\rho}$ is taken as estimated error given by

$$\widetilde{\rho} = \rho - \rho_m \tag{20}$$

where ρ is a positive tuning parameter.

By taking the time derivative of (19) and substituting (16) into it, one can get

$$\dot{V}_1(t) = \frac{1}{2}(\boldsymbol{A}_1\boldsymbol{Z}_1 + \boldsymbol{B}_1 v_1)^T \boldsymbol{P}_1\boldsymbol{Z}_1 + \frac{1}{2}\boldsymbol{Z}_1^T\boldsymbol{P}_1(\boldsymbol{A}_1\boldsymbol{Z}_1 + \boldsymbol{B}_1 v_1) + \frac{1}{\gamma_{p_1}}\widetilde{p}_1\dot{\widehat{p}}_1 + \frac{1}{\gamma_\rho}\widetilde{\rho}\dot{\rho} \tag{21}$$

By replacing from (18) into (21), it can be arranged as

$$\dot{V}_1(t) = \frac{1}{2}\boldsymbol{Z}_1^T(\boldsymbol{A}_1^T\boldsymbol{P}_1 + \boldsymbol{P}_1\boldsymbol{A}_1)\boldsymbol{Z}_1 + \left((\boldsymbol{Z}_1^T\boldsymbol{P}_1\boldsymbol{B}_1)\widetilde{p}_1\widetilde{G} + \frac{1}{\gamma_{p_1}}\widetilde{p}_1\dot{\widehat{p}}_1\right) + \left((\boldsymbol{Z}_1^T\boldsymbol{P}_1\boldsymbol{B}_1)D(t) - (\boldsymbol{Z}_1^T\boldsymbol{P}_1\boldsymbol{B}_1)x_r + \frac{1}{\gamma_\rho}\widetilde{\rho}\dot{\rho}\right) \tag{22}$$

Since α_1 and α_2 are positive parameters, consequently matrix $\boldsymbol{A}_1$ is stable and thus for any symmetric positive definite matrix $\boldsymbol{Q}_1$, there exists a symmetric positive definite matrix $\boldsymbol{P}_1$ such that

$$\boldsymbol{A}_1^T\boldsymbol{P}_1 + \boldsymbol{P}_1\boldsymbol{A}_1 = -\boldsymbol{Q}_1 \tag{23}$$

Thus, (22) becomes

$$\dot{V}_1(t) = -\frac{1}{2}\boldsymbol{Z}_1^T\boldsymbol{Q}_1\boldsymbol{Z}_1 + \widetilde{p}_1\left((\boldsymbol{Z}_1^T\boldsymbol{P}_1\boldsymbol{B}_1)\widetilde{G} + \frac{1}{\gamma_{p_1}}\dot{\widehat{p}}_1\right) + \left((\boldsymbol{Z}_1^T\boldsymbol{P}_1\boldsymbol{B}_1)D(t) - (\boldsymbol{Z}_1^T\boldsymbol{P}_1\boldsymbol{B}_1)x_r + \frac{1}{\gamma_\rho}\widetilde{\rho}\dot{\rho}\right) \tag{24}$$

Using the following inequality

$$(\boldsymbol{Z}_1^T\boldsymbol{P}_1\boldsymbol{B}_1)D(t) \le |\boldsymbol{Z}_1^T\boldsymbol{P}_1\boldsymbol{B}_1||D(t)| \le |\boldsymbol{Z}_1^T\boldsymbol{P}_1\boldsymbol{B}_1|\rho_m \tag{25}$$

and choosing

$$x_r = \rho\ \mathrm{sgn}(\boldsymbol{Z}_1^T\boldsymbol{P}_1\boldsymbol{B}_1) \tag{26}$$

one can infer from (24)

$$\begin{aligned}\dot{V}_1(t) &\le -\frac{1}{2}\boldsymbol{Z}_1^T\boldsymbol{Q}_1\boldsymbol{Z}_1 + \widetilde{p}_1\left((\boldsymbol{Z}_1^T\boldsymbol{P}_1\boldsymbol{B}_1)\widetilde{G} + \frac{1}{\gamma_{p_1}}\dot{\widehat{p}}_1\right) + |\boldsymbol{Z}_1^T\boldsymbol{P}_1\boldsymbol{B}_1|\rho_m - \boldsymbol{Z}_1^T\boldsymbol{P}_1\boldsymbol{B}_1 x_r + \frac{1}{\gamma_\rho}\widetilde{\rho}\dot{\rho}\\ &= -\frac{1}{2}\boldsymbol{Z}_1^T\boldsymbol{Q}_1\boldsymbol{Z}_1 + \widetilde{p}_1\left((\boldsymbol{Z}_1^T\boldsymbol{P}_1\boldsymbol{B}_1)\widetilde{G} + \frac{1}{\gamma_{p_1}}\dot{\widehat{p}}_1\right) + |\boldsymbol{Z}_1^T\boldsymbol{P}_1\boldsymbol{B}_1|\rho_m - |\boldsymbol{Z}_1^T\boldsymbol{P}_1\boldsymbol{B}_1|\rho + \frac{1}{\gamma_\rho}\widetilde{\rho}\dot{\rho}\\ &= -\frac{1}{2}\boldsymbol{Z}_1^T\boldsymbol{Q}_1\boldsymbol{Z}_1 + \widetilde{p}_1\left((\boldsymbol{Z}_1^T\boldsymbol{P}_1\boldsymbol{B}_1)\widetilde{G} + \frac{1}{\gamma_{p_1}}\dot{\widehat{p}}_1\right) + \widetilde{\rho}\left(-|\boldsymbol{Z}_1^T\boldsymbol{P}_1\boldsymbol{B}_1| + \frac{1}{\gamma_\rho}\dot{\rho}\right)\end{aligned} \tag{27}$$

Making the expressions inside parentheses of (27) equal to zero, the adaptive laws are derived as

$$\dot{\widehat{p}}_1 = -\gamma_{p_1}(\boldsymbol{Z}_1^T\boldsymbol{P}_1\boldsymbol{B}_1)\widetilde{G} \tag{28}$$

$$\dot{\rho} = -\gamma_\rho|\boldsymbol{Z}_1^T\boldsymbol{P}_1\boldsymbol{B}_1| \tag{29}$$

and (27) will be simplified as

$$\dot{V}_1(t) \le -\frac{1}{2}\boldsymbol{Z}_1^T\boldsymbol{Q}_1\boldsymbol{Z}_1 \tag{30}$$

3.2. Adaptive controller design for insulin subsystem

The purpose of this part is designing an actual controller in which $X(t)$ in (9) can behave like virtual control input $X_v(t)$ in (13). For attaining this purpose, input $u(t)$ in (9) is defined as a whole system input which determines the required insulin rate to achieve the desired blood glucose level.

Rewrite (9) as

$$a\ddot{X}(t) + b\dot{X}(t) + cX(t) = u(t) \tag{31}$$

in which

$$a = \frac{1}{p_3}\ ,\ b = \frac{(p_2 + n)}{p_3}\ ,\ c = \frac{p_2\ n}{p_3} \tag{32}$$

An estimated error is defined as difference between $X(t)$ in (31) and the desired value i.e. $X_v(t)$ in (13) given follows

$$\widetilde{X}(t) = X(t) - X_v(t) \tag{33}$$

Now, an error dynamic is chosen as

$$\dddot{\widetilde{X}}(t) + \beta_1\ddot{\widetilde{X}}(t) + \beta_2\dot{\widetilde{X}}(t) = 0 \tag{34}$$

where values of β_1 and β_2 are positive design constants. According to (33), (34) is rewritten as

$$\dddot{X}(t) - \dddot{X}_v(t) + \beta_1\ddot{\widetilde{X}}(t) + \beta_2\dot{\widetilde{X}}(t) = 0 \tag{35}$$

By multiplying both sides of (35) in a and then subtracting the both sides from (31), the following control signal can be derived

$$u^*(t) = b\dot{X}(t) + cX(t) + a\left(\dddot{X}_v(t) - \beta_1\ddot{\widetilde{X}}(t) - \beta_2\dot{\widetilde{X}}(t)\right) \tag{36}$$

Since parameters a, b and c in (36) are unknown, ideal control signal (36) cannot be employed, so the subsequent control input is proposed for (31)

$$u(t) = \widehat{b}\dot{X}(t) + \widehat{c}X(t) + \widehat{a}\left(\dddot{X}_v(t) - \beta_1\ddot{\widetilde{X}}(t) - \beta_2\dot{\widetilde{X}}(t)\right) \tag{37}$$

in which $\widehat{a}$, $\widehat{b}$ and $\widehat{c}$ are the estimated values of a, b and c, respectively. In order to obtain dynamic error of the subsystem, the following obvious equation is considered

$$a\left(\dddot{\widetilde{X}}(t) + \beta_1\ddot{\widetilde{X}}(t) + \beta_2\dot{\widetilde{X}}(t)\right) = a\dddot{X}(t) - a\left(\dddot{X}_v(t) - \beta_1\ddot{\widetilde{X}}(t) - \beta_2\dot{\widetilde{X}}(t)\right) \tag{38}$$

By computing $a\dddot{X}(t)$ from (31) and substituting it into (38), it yields

$$a\left(\dddot{\widetilde{X}}(t) + \beta_1\ddot{\widetilde{X}}(t) + \beta_2\dot{\widetilde{X}}(t)\right) = -b\dot{X}(t) - cX(t) + u(t) - a\left(\dddot{X}_v(t) - \beta_1\ddot{\widetilde{X}}(t) - \beta_2\dot{\widetilde{X}}(t)\right) \tag{39}$$

Further, by replacing control input $u(t)$ from (37) into (39), it results

$$\begin{aligned}a\left(\dddot{\widetilde{X}}(t) + \beta_1\ddot{\widetilde{X}}(t) + \beta_2\dot{\widetilde{X}}(t)\right) &= -b\dot{X}(t) - cX(t) + \widehat{b}\dot{X}(t) + \widehat{c}X(t)\\ &+ (\widehat{a} - a)\left(\dddot{X}_v(t) - \beta_1\ddot{\widetilde{X}}(t) - \beta_2\dot{\widetilde{X}}(t)\right)\end{aligned} \tag{40}$$

Now, estimated error values of a, b and c are defined as follow

$$\begin{aligned}\widetilde{a} &= \widehat{a} - a\\ \widetilde{b} &= \widehat{b} - b\\ \widetilde{c} &= \widehat{c} - c\end{aligned} \tag{41}$$

As a result, (40) can be simplified as below

$$\dddot{\widetilde{X}}(t) + \beta_1\ddot{\widetilde{X}}(t) + \beta_2\dot{\widetilde{X}}(t) = \frac{1}{a}\left(\widetilde{b}\dot{X}(t) + \widetilde{c}X(t) + \widetilde{a}\left(\dddot{X}_v(t) - \beta_1\ddot{\widetilde{X}}(t) - \beta_2\dot{\widetilde{X}}(t)\right)\right) \tag{42}$$

and by denoting error vector for the subsystem as $\boldsymbol{Z}_2 = \left[\widetilde{X}(t),\ \dot{\widetilde{X}}(t)\right]^T$, (42) may be rewritten in the subsequent form

$$\dot{\boldsymbol{Z}}_2 = \boldsymbol{A}_2\boldsymbol{Z}_2 + \boldsymbol{B}_2 v_2 \tag{43}$$

where

$$\boldsymbol{A}_2 = \begin{pmatrix}0 & 1\\ -\beta_2 & -\beta_1\end{pmatrix},\ \boldsymbol{B}_2 = \begin{pmatrix}0\\ 1\end{pmatrix} \tag{44}$$

and

$$v_2 = \frac{1}{a}\left(\widetilde{b}\dot{X}(t) + \widetilde{c}X(t) + \widetilde{a}\left(\dddot{X}_v(t) - \beta_1\ddot{\widetilde{X}}(t) - \beta_2\dot{\widetilde{X}}(t)\right)\right) \tag{45}$$

Now, the following positive function is candidate for (43)

$$V_2(t) = \frac{1}{2}\boldsymbol{Z}_2^T\boldsymbol{P}_2\boldsymbol{Z}_2 + \frac{1}{2a\gamma_a}\widetilde{a}^2 + \frac{1}{2a\gamma_b}\widetilde{b}^2 + \frac{1}{2a\gamma_c}\widetilde{c}^2 \tag{46}$$

where γ_a, γ_b, γ_c are positive designing constants and $\boldsymbol{P}_2$ is a symmetric positive definite matrix. Taking time derivative of (46), it becomes

$$\dot{V}_2(t) = \frac{1}{2}\dot{\boldsymbol{Z}}_2^T\boldsymbol{P}_2\boldsymbol{Z}_2 + \frac{1}{2}\boldsymbol{Z}_2^T\boldsymbol{P}_2\dot{\boldsymbol{Z}}_2 + \frac{1}{a\gamma_a}\tilde{a}\dot{\hat{a}} + \frac{1}{a\gamma_b}\tilde{b}\dot{\hat{b}} + \frac{1}{a\gamma_c}\tilde{c}\dot{\hat{c}} \tag{47}$$

By substituting (43) in (47), one can write

$$\dot{V}_2(t) = \frac{1}{2}\boldsymbol{Z}_2^T\left(\boldsymbol{A}_2^T\boldsymbol{P}_2 + \boldsymbol{P}_2\boldsymbol{A}_2\right)\boldsymbol{Z}_2 + \left(\boldsymbol{Z}_2^T\boldsymbol{P}_2\boldsymbol{B}_2\right)v_2 + \frac{1}{a\gamma_a}\tilde{a}\dot{\hat{a}} + \frac{1}{a\gamma_b}\tilde{b}\dot{\hat{b}} + \frac{1}{a\gamma_c}\tilde{c}\dot{\hat{c}} \tag{48}$$

and also replacing (45) in the latter, it yields

$$\dot{V}_2(t) = \frac{1}{2}\boldsymbol{Z}_2^T\left(\boldsymbol{A}_2^T\boldsymbol{P}_2 + \boldsymbol{P}_2\boldsymbol{A}_2\right)\boldsymbol{Z}_2 + \frac{1}{a\gamma_a}\tilde{a}\dot{\hat{a}} + \frac{1}{a\gamma_b}\tilde{b}\dot{\hat{b}} + \frac{1}{a\gamma_c}\tilde{c}\dot{\hat{c}} + \left(\boldsymbol{Z}_2^T\boldsymbol{P}_2\boldsymbol{B}_2\right)\frac{1}{a}\left(\tilde{b}\dot{X}(t) + \tilde{c}X(t) + \tilde{a}\left(\ddot{X}_v(t) - \beta_1\dddot{\tilde{X}}(t) - \beta_2\ddot{\tilde{X}}(t)\right)\right) \tag{49}$$

Regarding to (44), since matrix $\boldsymbol{A}_2$ is stable, there are two symmetric positive definite matrices $\boldsymbol{P}_2$ and $\boldsymbol{Q}_2$, such that

$$\boldsymbol{A}_2^T\boldsymbol{P}_2 + \boldsymbol{P}_2\boldsymbol{A}_2 = -\boldsymbol{Q}_2 \tag{50}$$

Noticing (50), (49) can be simplified and rearranged as

$$\dot{V}_2(t) = -\frac{1}{2}\boldsymbol{Z}_2^T\boldsymbol{Q}_2\boldsymbol{Z}_2 + \frac{\tilde{a}}{a}\left(\frac{1}{\gamma_a}\dot{\hat{a}} + \left(\boldsymbol{Z}_2^T\boldsymbol{P}_2\boldsymbol{B}_2\right)\left(\ddot{X}_v(t) - \beta_1\dddot{\tilde{X}}(t) - \beta_2\ddot{\tilde{X}}(t)\right)\right) + \frac{\tilde{b}}{a}\left(\frac{1}{\gamma_b}\dot{\hat{b}} + \left(\boldsymbol{Z}_2^T\boldsymbol{P}_2\boldsymbol{B}_2\right)\dot{X}(t)\right) + \frac{\tilde{c}}{a}\left(\frac{1}{\gamma_c}\dot{\hat{c}} + \left(\boldsymbol{Z}_2^T\boldsymbol{P}_2\boldsymbol{B}_2\right)X(t)\right) \tag{51}$$

By defining the following adaptive laws

$$\dot{\hat{a}} = -\gamma_a\left(\boldsymbol{Z}_2^T\boldsymbol{P}_2\boldsymbol{B}_2\right)\left(\ddot{X}_v(t) - \beta_1\dddot{\tilde{X}}(t) - \beta_2\ddot{\tilde{X}}(t)\right) \tag{52}$$

$$\dot{\hat{b}} = -\gamma_b\left(\boldsymbol{Z}_2^T\boldsymbol{P}_2\boldsymbol{B}_2\right)\dot{X}(t) \tag{53}$$

$$\dot{\hat{c}} = -\gamma_c\left(\boldsymbol{Z}_2^T\boldsymbol{P}_2\boldsymbol{B}_2\right)X(t) \tag{54}$$

(48) will become

$$\dot{V}_2(t) = -\frac{1}{2}\boldsymbol{Z}_2^T\boldsymbol{Q}_2\boldsymbol{Z}_2 \tag{55}$$

3.3. Overall control system and stability analysis

Results of the two-step controller design are summarized in the following theorem.

Theorem: Consider BMM dynamic system presented by (8) and (9). Using control signal (37), robust term (26) and adaptation laws of (28), (29) and (52)-(54), tracking error of blood glucose i.e. (11) converges to zero asymptotically.

Proof: According to Eqs. (19) and (46), the following Lyapunov-like function for the whole system is proposed

$$V(t) = V_1(t) + V_2(t) \tag{56}$$

Noticing (30) and (55), time derivative of (55) results

$$\dot{V}(t) = \dot{V}_1(t) + \dot{V}_2(t) \le -\frac{1}{2}\boldsymbol{Z}_1^T\boldsymbol{Q}_1\boldsymbol{Z}_1 - \frac{1}{2}\boldsymbol{Z}_2^T\boldsymbol{Q}_2\boldsymbol{Z}_2 \tag{57}$$

By defining $\boldsymbol{Q} = \mathrm{Diag}(\boldsymbol{Q}_1, \boldsymbol{Q}_2)$ and $\boldsymbol{Z} = [\boldsymbol{Z}_1^T, \boldsymbol{Z}_2^T]^T$, (56) can be written as

$$\dot{V}(t) \le -\frac{1}{2}\boldsymbol{Z}^T\boldsymbol{Q}\boldsymbol{Z} \le -\frac{1}{2}\lambda_{min}(\boldsymbol{Q})\|\boldsymbol{Z}\|^2 \tag{58}$$

where $\lambda_{min}(\boldsymbol{Q})$ is the smallest eigenvalue of matrix $\boldsymbol{Q}$.

Regarding to (58), $\dot{V}(t) \le 0$ and since $V(t) \ge 0$, then it can result $0 \le V(t) \le V(0)$. This means $V(t)$ is bounded and decreasing and according to (55), $V_1(t)$ and $V_2(t)$ are also bounded. It consequences all right-handed variables and parameters of (19) and (46) are bounded. Thus $\boldsymbol{Z}_1$ and $\boldsymbol{Z}_2$ are bounded i.e. $\boldsymbol{Z}$ is too, in other word $\boldsymbol{Z}\varepsilon L_\infty$. By integrating from both sides of (58), it can show $\boldsymbol{Z}\varepsilon L_2$. Also, through (16) and (43), it can infer $\dot{\boldsymbol{Z}}_1$ and $\dot{\boldsymbol{Z}}_2$ and so $\dot{\boldsymbol{Z}}$ is bounded i.e. $\boldsymbol{Z}$ is uniformly continuous. Now, according to Barbalat's lemma [37], it can conclude $\lim_{t\to\infty}\boldsymbol{Z}(t) = 0$, i.e. $\lim_{t\to\infty}\tilde{\boldsymbol{G}}(t) = 0$. This completes the proof.

4. Simulation results

In this section, simulation results of the proposed closed-loop control system have been studied in MATLAB/Simulink environment. In numerical simulations, initial conditions for state variables of BMM are set to $[200050]^T$. The nominal values of parameters used in the BMM and their units are given in Table 1. In order to show robustness of the proposed controller, a meal disturbance (i.e. $D(t)$ in the BMM) is applied to the system as follows

$$D(t) = \begin{cases} 0 & t < 450 \\ \exp(-0.05(t-450)) & t \ge 450 \end{cases} \tag{59}$$

To confirm the performance of the proposed controller, it is enough

Table 1
BMM parameters in simulation.

Parameters	Normal	Patient 1	Patient 2	Units
p_1	0.0317	0	0	min^{-1}
p_2	0.0123	0.0142	0.02	min^{-1}
p_3	4.92e-06	1.54e-05	5.3e-06	$(\mu U/mL)^{-1}min^{-1}$
γ	0.0039	0	0	$(\mu U/mL)(mg/dL)^{-1}min^{-2}$
n	0.2659	0.2814	0.3	min^{-1}
h	79.035	–	–	mg/dL
B	0.05	0.05	0.05	–
G_b	80	80	80	mg/dL
I_b	7	7	7	$\mu U/mL$

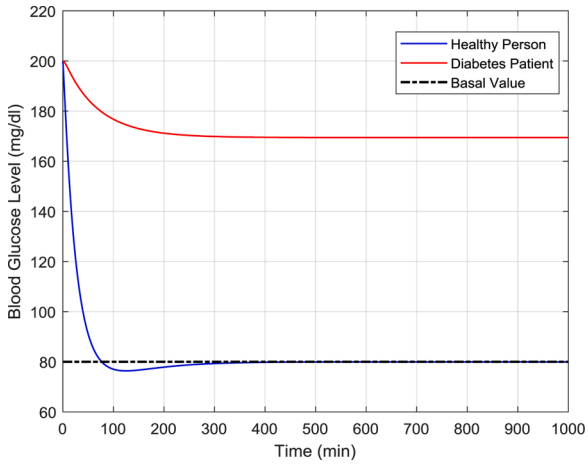

Fig. 3. Blood glucose concentration of both healthy and diabetic persons.

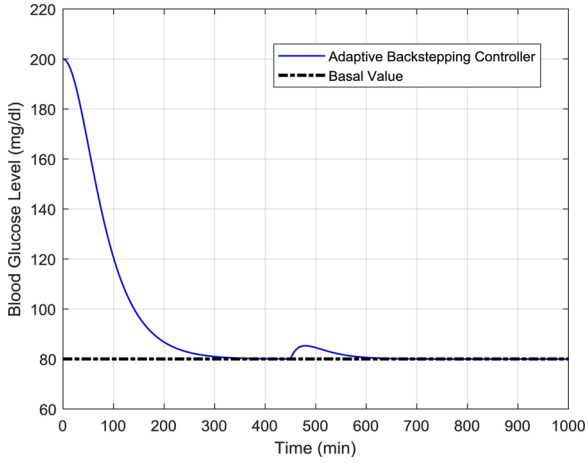

Fig. 4. Blood glucose regulation by applying adaptive backstepping controller.

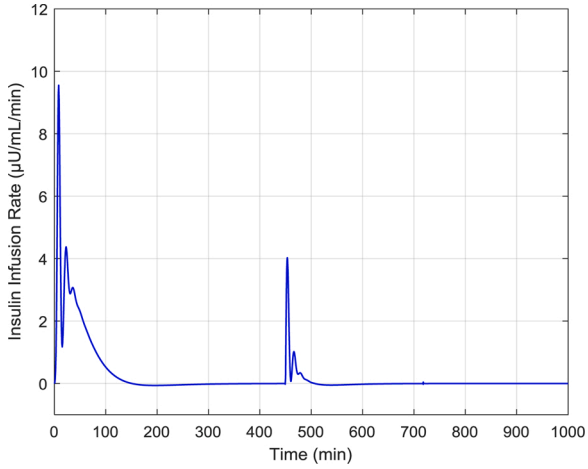

Fig. 5. Control input of adaptive backstepping approach.

to notice the blood glucose concentration of both healthy and diabetic person in the BMM (without controller) which has been indicated in Fig. 3. It is easy to see that the blood glucose value of the healthy person is finally achieved to the basal value in a short period of time, while in type 1 diabetic patient, it cannot reach to desired value. According to simulation results, the designed controller can practically control and

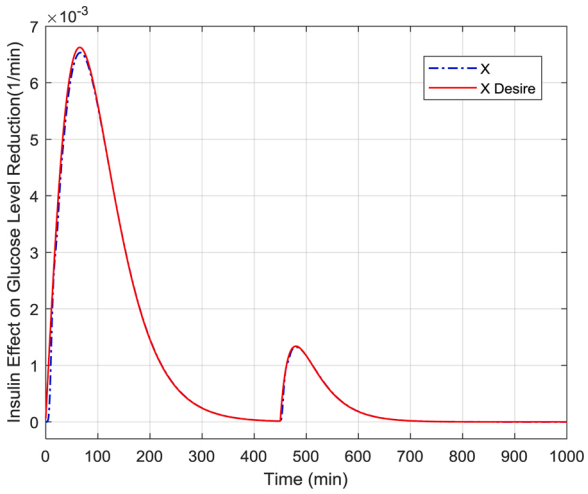

Fig. 6. Tracking of insulin effect on glucose concentration reduction with desired value.

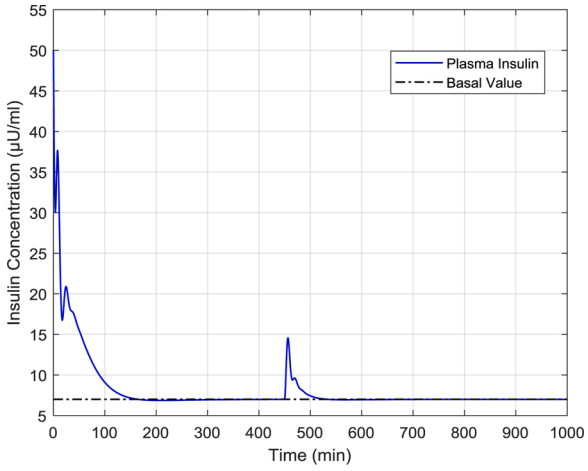

Fig. 7. Stabilization of plasma insulin concentration.

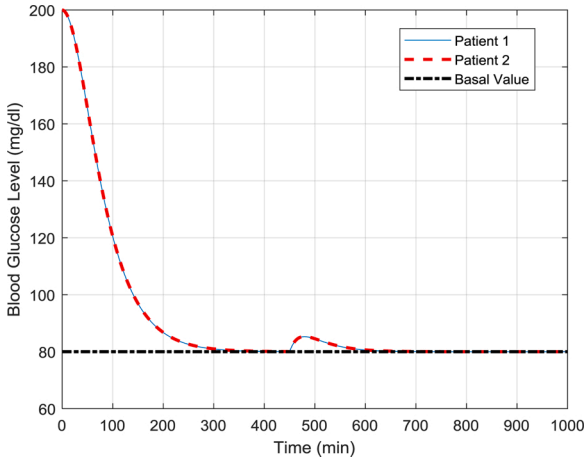

Fig. 8. Comparison of blood glucose level for the two patients.

regulate the blood glucose level of a type 1 diabetic patient. As Fig. 4 indicates, by adaptive back-stepping controller, the blood glucose can reach the base level in a proper time in spite of disturbance and unknowingness of the parameters of the model. Moreover, the dose of

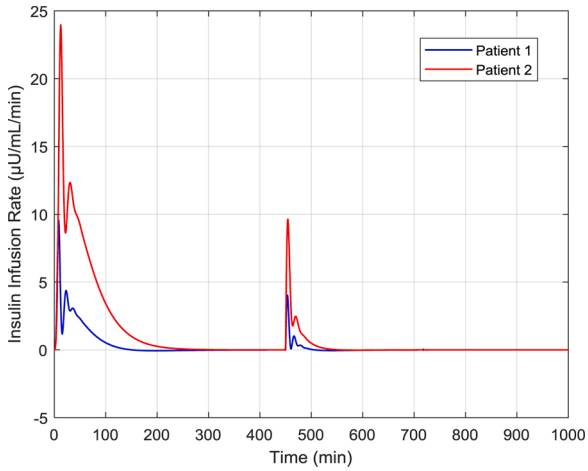

Fig. 9. Comparison of control input for the two patients.

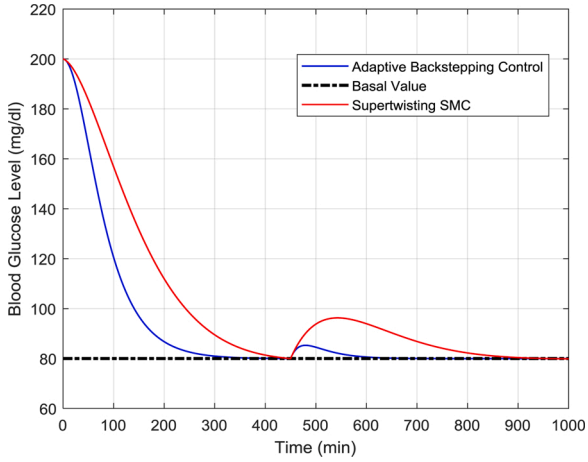

Fig. 10. Comparison of the proposed controller and super twisting SMC.

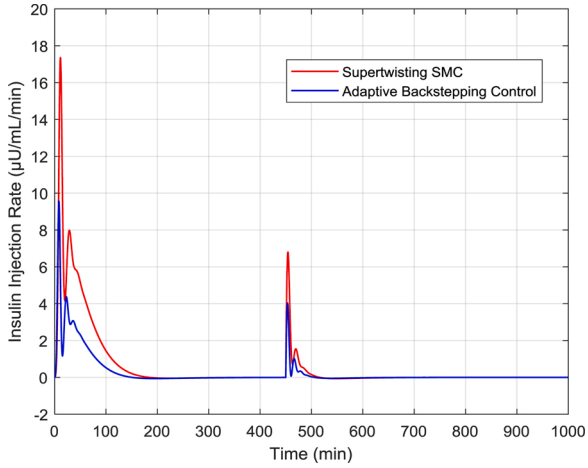

Fig. 11. Comparison of control effort of the proposed controller and super twisting SMC.

injected insulin (control input) remains in appropriate range. Fig. 5 displays the control effort used for the blood glucose regulation. Tracking of $X(t)$ (insulin effect on glucose concentration reduction) with the desired value has been shown in Fig. 6. In Fig. 7, the stabilization of plasma insulin concentration is clearly illustrated. It is obvious that the

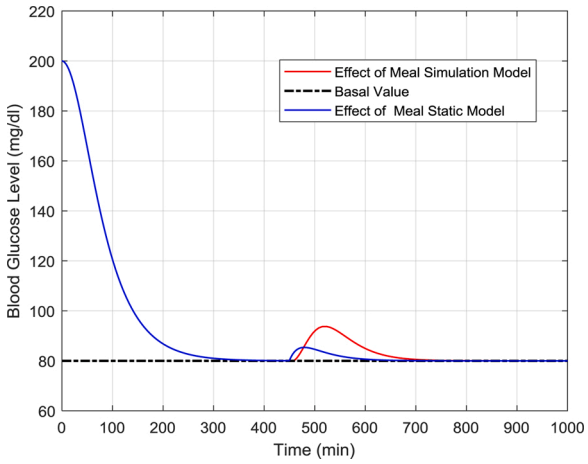

Fig. 12. Blood glucose regulation by applying different meal models.

proposed controller regulates the insulin concentration at the desired value in the presence of meal disturbance. Finally, the efficiency of the proposed controller with comparing two diabetic patients has been evaluated. Fig. 8 shows the same convergence time for the first and the second patient and Fig. 9 compares the insulin injection rate in the two patients, which shows the second patient compared to the first one needs more insulin dose.

A comparison of the proposed adaptive back-stepping controller with super twisting SMC [20] has been presented in Fig. 10. As shown, the proposed controller assures dynamic stability of the system against meal disturbance and it has a good convergence as compared with the super twisting SMC. The overall response of the proposed controller is better and it gives good results with smooth tracking and less convergence time. A comparison of control effort of the proposed method with the super twisting SMC has been depicted in Fig. 11.

In general, disturbances in diabetic human body such as physical activity, stress and meals can have great relevance in the overall performance of the blood glucose concentration. Hence, it is important that the consideration of disturbances has a physical meaning. For this reason, meal disturbance simulation model in [38] is applied to our control system. Result in the controlled blood glucose level can be seen in Fig. 12. It is clear, by applying the meal disturbance simulation model, how it eventuates in variation of blood glucose from the safe range but it finally returns to the desired level.

5. Conclusion

In this paper, it was focused on controlling blood glucose regulation in type 1 diabetes patient using the BMM. The main goal was decreasing the blood glucose to safe range and determining injected insulin dose. For this purpose, a novel adaptive back-stepping controller i.e. a two-layer adaptive control method was designed and simulated. The proposed controller assures the stability of the overall system in the presence external disturbance i.e. meal intake. In addition, in this method all parameters of the model have been considered unknown and their values have been adapted using the Lyapunov based adaptive back-stepping control approach. Simulation results showed effectiveness and robust performance of the proposed method in regulating blood glucose of type 1 diabetes patients. Also, based on the results, control effort i.e. delivered insulin to the patient remains in an appropriate range. In order to reduce the injected insulin rate, optimal design of the control input can be a good research topic as a future work.

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CRediT authorship contribution statement

Shiva Sepasi: Investigation, Visualization, Software. **Ali Akbarzadeh Kalat:** Conceptualization, Methodology, Supervision, Writing - review & editing, Validation. **Masoud Seyedabadi:** Writing - original draft, Software, Data curation.

Declaration of Competing Interest

The authors report no declarations of interest.

References

[1] International Diabetes Federation [IDF], Eighth Edition 2017, 8th edition, IDF Diabetes Atlas, 2017.
[2] Standards of medical care in diabetes—2016 abridged for primary care providers, Clin. Diabetes 34 (1) (2016) 3–21.
[3] I. Pagkalos, P. Herrero, C. Toumazou, P. Georgiou, Bio-inspired glucose control in diabetes based on an analogue implementation of a β-cell model, IEEE Trans. Biomed. Circuits Syst. 8 (2) (2014) 186–195.
[4] R.S. Parker, F.J. Doyle, J.H. Ward, N.A. Peppas, Robust H∞ glucose control in diabetes using a physiological model, AIChE J. 46 (12) (2000) 2537–2549.
[5] Y. Ramprasad, G.P. Rangaiah, S. Lakshminarayanan, Robust PID controller for blood glucose regulation in type I diabetics, Ind. Eng. Chem. Res. 43 (26) (2004) 8257–8268.
[6] A.Y. Ben Sasi, M.A. Elmalki, A fuzzy controller for blood glucose-insulin system, J. Signal Inf. Process. 04 (02) (2013) 111–117.
[7] K. Lunze, T. Singh, M. Walter, M.D. Brendel, S. Leonhardt, Blood glucose control algorithms for type 1 diabetic patients: a methodological review, Biomed. Signal Process. Control 8 (2) (2013) 107–119.
[8] Z. Trajanoski, P. Wach, Neural predictive controller for insulin delivery using the subcutaneous route, IEEE Trans. Biomed. Eng. 45 (9) (1998) 1122–1134.
[9] L. Magni, D.M. Raimondo, C. Dalla Man, G. De Nicolao, B. Kovatchev, C. Cobelli, Model predictive control of glucose concentration in type I diabetic patients: an in silico trial, Biomed. Signal Process. Control 4 (4) (2009) 338–346.
[10] H. Lee, B.W. Bequette, A closed-loop artificial pancreas based on model predictive control: human-friendly identification and automatic meal disturbance rejection, Biomed. Signal Process. Control 4 (4) (2009) 347–354.
[11] G.M. Steil, K. Rebrin, C. Darwin, F. Hariri, M.F. Saad, Feasibility of automating insulin delivery for the treatment of type 1 diabetes, Diabetes 55 (12) (2006) 3344–3350.
[12] R. Mauseth, et al., Use of a 'fuzzy logic' controller in a closed-loop artificial pancreas, Diabetes Technol. Ther. 15 (8) (2013) 628–633.
[13] J. Fernandez de Canete, S. Gonzalez-Perez, J.C. Ramos-Diaz, Artificial neural networks for closed loop control of in silico and ad hoc type 1 diabetes, Comput. Methods Programs Biomed. 106 (1) (2012) 55–66.
[14] E. Ruiz-Velázquez, R. Femat, D.U. Campos-Delgado, Blood glucose control for type I diabetes mellitus: a robust tracking H∞ problem, Control Eng. Pract. 12 (9) (2004) 1179–1195.
[15] A. Abu-Rmileh, W. Garcia-Gabin, D. Zambrano, Internal model sliding mode control approach for glucose regulation in type 1 diabetes, Biomed. Signal Process. Control 5 (2) (2010) 94–102.
[16] P. Kaveh, Y.B. Shtessel, Blood glucose regulation via double loop higher order sliding mode control and multiple sampling rate, Lect. Notes Control Inf. Sci. 375 (2008) 427–445.
[17] M. Ottavian, M. Barolo, H. Zisser, E. Dassau, D.E. Seborg, Adaptive blood glucose control for intensive care applications, Comput. Methods Programs Biomed. 109 (2) (2013) 144–156.
[18] J. Zhou, C. Wen, Adaptive Backstepping Control of Uncertain systems: Nonsmooth Nonlinearities, Interactions or Time-variations, Springer, 2008.
[19] I. Ahmad, F. Munir, M.F. Munir, An adaptive backstepping based non-linear controller for artificial pancreas in type 1 diabetes patients, Biomed. Signal Process. Control 47 (2019) 49–56.
[20] S. Ahmad, NasimUllah, N. Ahmed, M. Ilyas, W. Khan, Super twisting sliding mode control algorithm for developing artificial pancreas in type 1 diabetes patients, Biomed. Signal Process. Control 38 (September) (2017) 200–211.
[21] M. Dansa, V.H.P. Rodrigues, T.R. Oliveira, Blood glucose regulation in patients with type 1 diabetes by means of output-feedback sliding mode control, in: Ahmad Taher Azar. (Org.) (Ed.), Control Applications for Biomedical Engineering Systems, 1 ed, Elsevier, 2020, pp. 25–54.
[22] M. Dansa, V.H.P. Rodrigues, T.R. Oliveira, Bihormonal sliding Mode controller applied to blood glucose regulation in patients with type 1 diabetes, Proc. of the 22nd Int. Conference on System Theory, Control and Computing (ICSTCC), Sinaia, Romania (2018) 79–86.
[23] M. Dansa, V.H.P. Rodrigues, T.R. Oliveira, Blood glucose regulation through bihormonal Non-singular terminal sliding Mode controller, Proc. of the 15th Int. Conference on Control, Automation, Robotics and Vision (ICARCV), Marina Bay Sands, Singapore (2018) 474–479.
[24] G.M. Steil, B. Clark, S. Kanderian, K. Rebrin, Modeling insulin action for development of a closed-loop artificial pancreas, Diabetes Technol. Ther. 7 (1) (2005) 94–108.
[25] C. Cobelli, C. Dalla Man, G. Sparacino, L. Magni, G. De Nicolao, B.P. Kovatchev, Diabetes: models, signals, and control, IEEE Rev. Biomed. Eng. 2 (2009) 54–96.
[26] S. Rathee, Nilam, ODE models for the management of diabetes: a review, in: 1 (Ed.), Int. J. Diabetes Dev. 37 (2017) 4–15.
[27] R. Hovorka, et al., Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes, Physiol. Meas. 25 (4) (2004) 905–920.
[28] A. Drozdov, H. Khanina, A model for ultradian oscillations of insulin and glucose, Math. Comput. Model. 22 (2) (1995) 23–38.
[29] J. Li, Y. Kuang, C.C. Mason, Modeling the glucose-insulin regulatory system and ultradian insulin secretory oscillations with two explicit time delays, J. Theor. Biol. 242 (3) (2006) 722–735.
[30] C.L. Chen, H.W. Tsai, Modeling the physiological glucose-insulin system on normal and diabetic subjects, Comput. Methods Programs Biomed. 97 (2) (2010) 130–140.
[31] P. Wach, Z. Trajanoski, P. Kotanko, F. Skrabal, Numerical approximation of mathematical model for absorption of subcutaneously injected insulin, Med. Biol. Eng. Comput. 33 (1) (1995) 18–23.
[32] A. De Gaetano, O. Arino, Mathematical modelling of the intravenous glucose tolerance test, J. Math. Biol. 40 (2) (2000) 136–168.
[33] R. Visentin, C. Dalla Man, B. Kovatchev, C. Cobelli, The university of virginia/padova type 1 diabetes simulator matches the glucose traces of a clinical trial, Diabetes Technol. Ther. 16 (7) (2014) 428–434.
[34] G. Pacini, R.N. Bergman, MINMOD: a computer program to calculate insulin sensitivity and pancreatic responsivity from the frequently sampled intravenous glucose tolerance test, Comput. Methods Programs Biomed. 23 (2) (1986) 113–122.
[35] R.N. Bergman, L.S. Phillips, C. Cobelli, Physiologic evaluation of factors controlling glucose tolerance in man: measurement of insulin sensitivity and β-cell glucose sensitivity from the response to intravenous glucose, J. Clin. Invest. 68 (6) (1981) 1456–1467.
[36] S.F. Ali, R. Padhi, Optimal blood glucose regulation of diabetic patients using single network adaptive critics, Optim. Control Appl. Methods 32 (2) (2011) 196–214.
[37] J.J.E. Slotine, W. Li, Applied Nonlinear Control, Prentice Hall, New Jersey, 1991.
[38] C. Dalla Man, R.A. Rizza, C. Cobelli, Meal simulation model of the glucose-insulin system, IEEE Trans. Biomed. Eng. 54 (October(10)) (2007) 1740–1749.