

Backstepping Glycemic Control of Type 1 Diabetes for Implementation on an Embedded System

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Abstract: In this paper a nonlinear control intended for Blood glucose regulation for Type 1 Diabetes patients is considered. The control law is designed using the Lyapunov theory associated with a Kalman filter to estimate the system states. The asymptotic stability of the overall system is theoretically proven. The proposed control scheme will be implemented in a low cost embedded system. The simulation results confirm the effectiveness of the proposed control.

Keywords: Type 1 Diabetes, Blood glucose, Nonlinear control, Lyapunov method, Kalman filter, Backstepping control.

Introduction

Insulin is a hormone produced by the pancreas to regulate blood glucose in the human body. If the pancreas does not give enough or more insulin, blood glucose concentration becomes upper or lower than the recommended range. People's pancreas with Type 1 Diabetes (T1D) produces little or no insulin. They need insulin injections every day in order to control the levels of glucose in their blood. To prevent or delay the onset of microvascular (retinopathy, nephropathy) and macrovascular (myocardial ischemia, stroke) complications [5, 24], diabetes management becomes necessary.

In 2017, the American Diabetes Association (ADA) has fixed the glycemic target range (80-180) mg/dl for many non-pregnant adults with diabetes [1].

In this context emerging treatment approaches, also known as the artificial pancreas, have been developed. It is a closed-loop insulin delivery [9]. It links a continuous glucose monitor (CGM) to an insulin pump via a control algorithm, which infuses the correct dose of insulin and keeps blood glucose in the target zone (Fig. 1).

The well-known model, called Bergman Minimal Model (BMM), was developed by Bergman in 1986. The control of the blood glucose by the insulin hormone allows patients to obtain the homeostasis of glucose, according to the scheme presented in Fig. 3 [3, 19, 25].

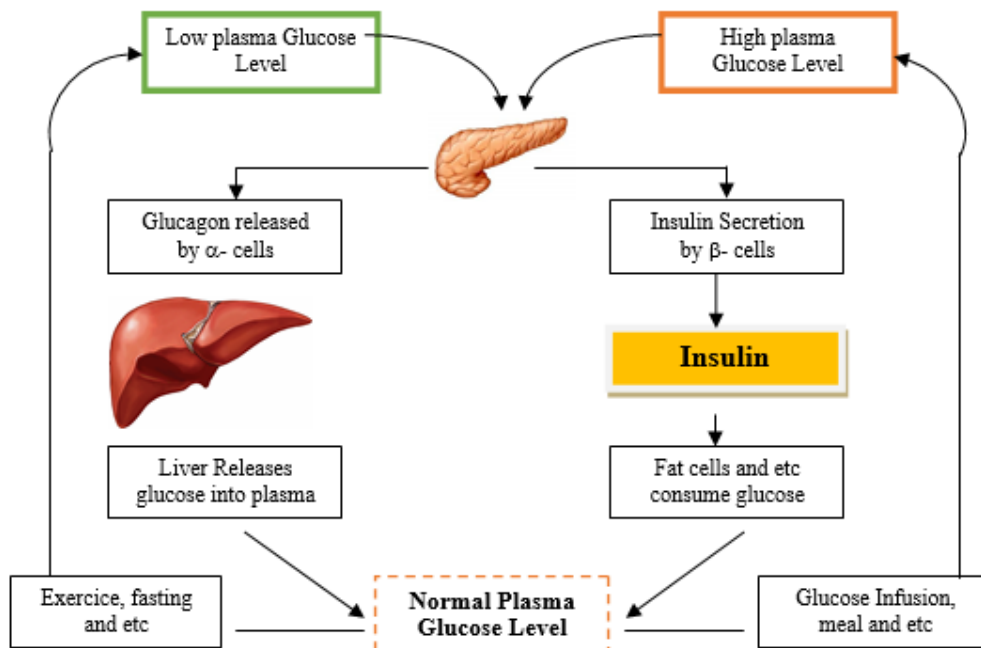


Fig. 3 Physiological glucose-insulin regulatory system

The main objective of this paper is to propose a control strategy in order to obtain a normal plasma glucose concentration (80-160) [mg/dL] for T1D.

Though Bergman’s minimal model is a non-linear system, which requires high-performance control, we opted for the non-linear backstepping, using the Lyapunov approach. This control requires some variable state (insulin X, I). It can be estimated by a Kalman filter [17]. The theory of Kalman filter can be extended to nonlinear processes, through a linearization procedure known as an “Extended Kalman filter” [28].

Modeling of glucose and insulin kinetics

The original minimal model describes how the glucose level behaves according to measured insulin data during an IVGTT (intravenous glucose tolerance test) [2, 4, 21], Fig. 4.

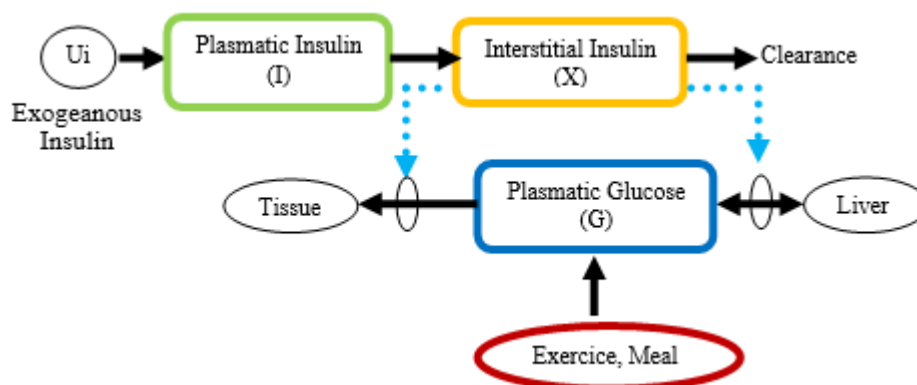


Fig. 4 Schematic illustration of BMM

Bergman's model is developed from differential equations of the first order using three state variables including: the blood glucose concentration (G), interstitial insulin (X) found between the muscle cells and is involved in the uptake of glucose into the muscles, and the plasmatic insulin concentration (I) [26, 27].

Bergman's minimal model is a one-compartment model, in which the body is described as a compartment with a basal concentration of glucose and insulin. For that purpose, we need information on these two parameters: G_b (basal glucose) and I_b (basal insulin) [12].

In case of Type 1 diabetic patients, these parameters are unknown compared to other kinds of diabetics. Plasmatic insulin moves in the interstitial tissue compartment at a rate proportional to the difference between the plasma insulin level $I(t)$, and the basal level, I_b :

- if $I(t) > I_b$ insulin enters the interstitial tissue compartment. Insulin in the interstitial tissue compartment disappears by another pathway at a rate proportional to the concentration of insulin in this compartment. However, glucose enters the plasma compartment at a rate proportional to the difference between the plasma glucose level, $G(t)$, and the basal level, G_b .
- if $G(t) < G_b$, glucose enters the plasma compartment,
- if $G(t) > G_b$, glucose leaves the plasma compartment.

Similar to insulin, Glucose disappears from the plasma compartment by another pathway at a rate proportional to the concentration of insulin in the interstitial tissue [15].

The model of a BG and insulin dynamics is represented by three differential equations as follows [3, 4, 12, 14, 25]:

$$\begin{cases} \dot{G} = -P_1 G - XG + P_1 G_B + U_g \\ \dot{X} = -P_2 X + P_3 I - P_3 I_B \\ \dot{I} = -NI + \frac{1}{V_I} U_i \end{cases}, \quad (1)$$

where $G(0) = G_b$, $I(0) = 0$ and $X(0) = 0$, the first expression of Eq. (1), describes the dynamics of the metabolism of glucose, the second expression of Eq. (1), represents the dynamics of the transport of insulin from the blood to interstitial fluid, and the last expression of Eq. (1), describes the change in insulin concentration in the blood over time.

Many researchers have tried to include the effect of physical exercise on insulin sensitivity and glucose effectiveness. In fact, some modifications on the original minimal model have been proposed. This is done by adding more equations so that the model becomes more complex [7].

System (1) can be written as follow:

$$\dot{x} = \begin{bmatrix} -P_1 & -G & 0 \\ 0 & -P_2 & P_3 \\ 1 & 0 & -N \end{bmatrix} \begin{bmatrix} G \\ X \\ I \end{bmatrix} + \begin{bmatrix} 1 & P_1 G_B & 0 \\ 0 & -P_3 I_B & 0 \\ 0 & 0 & \frac{1}{V_I} \end{bmatrix} \begin{bmatrix} U_g \\ 1 \\ U_i \end{bmatrix}. \quad (2)$$

The system (1) is non-linear and can be presented in the following general form:

$$\dot{x} = f(x, U), \tag{3}$$

with $x = [G \ X \ I]^T$; $U = [U_g \ 1 \ U_i]^T$.

Validation of the model

To test the Bergman model (1), some simulations have been done and compared to other works [12]. Fig. 5 represents the response of the BMM during three clinical tests (exogenous meal without insulin (0-500) min, insulin administration without meals (500-1000) min and fasting (1000-1500) min. Note that for all the tests; the basal glucose is set at $G_b = 200$ mg/dL and the basal insulin concentration is set at $I_b = 0$ uU/mL. All parameters are given in the Appendix.

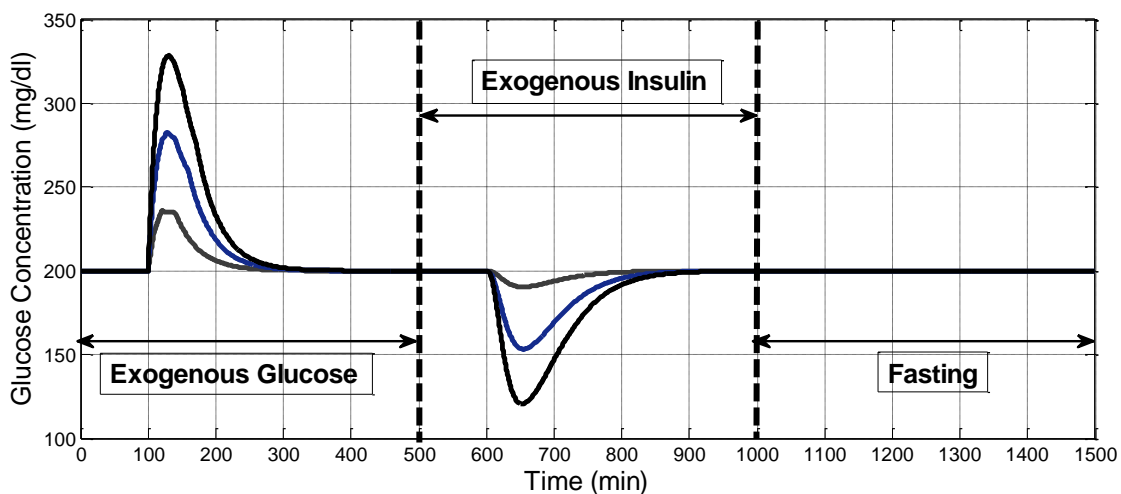


Fig. 5 Testing of the BMM

Exogenous glucose [0-500 min]

During this test, the model is excited by Fisher's function, $D(t) = A \exp(-\alpha t)$, as meal disturbance at $t = 100$ min. The objective of this test is to observe the reaction of BMM to such disturbance without exogenous insulin [11], where $A = (4, 8, 12)$ [g], and $\alpha = 0.1 \text{ min}^{-1}$.

The results show that glucose has a similar form as meal increases and then returns to its initial state within 2 hours.

In physiology, it is well known that after meal ingestion, a peak of plasma glucose concentration appears (30-60) min [22].

Exogenous insulin Administration [500-1000 min]

In the second test an exogenous insulin injection is applied on the BMM according to the next function $U_i(t) = a \exp(-bt)$, where $a = (20, 60 \text{ and } 120)$ [$\mu\text{U/mL}$] and $b = 0.1 \text{ [min}^{-1}]$.

We note that the plasmatic glucose concentration drops in regard of the plasmatic insulin concentration. For normal subjects, after meal, the peak plasma insulin level is obtained 30 to 60 minutes without exceeding 70 [$\mu\text{U/mL}$]. The insulin concentration returns to its normal values after 2 hours [22].

Fasting test [1000-1500 min]

In the last test, the plasmatic glucose concentration remains at the same initial level 200 [mg/dL]. This test is used to identify the basal insulin value of T1D.

In the treatment of T1D, it is important to identify the basal insulin value. The first role of basal insulin is to maintain blood glucose concentrations stable at its rate values. While fasting, basal insulin is needed to regulate the glucose delivered continuously by the liver and keep the plasmatic glucose levels in the normal range.

Kalman filter state variable observation

The Kalman filter is an algorithm that is paralleled with the system using its model as equations of state. It allows to reconstruct or estimate all the state variables, if the system is observable.

The comparison between the outputs of the system and Kalman filter is multiplied by the Kalman gain matrix and then added to the estimated state variables.

Discretization of Bergman model

The discretization of Bergman Model (3) using Euler approximation gives as:

$$\dot{x} = \frac{x_{k+1} - x_k}{T} = f(x, U) \Rightarrow x_{k+1} = x_k + Tf(x, U), \quad (4)$$

where T is the sampling period which must be smaller than the small time constant of the system. Using Eq. (4) and Eq. (1), we obtain the following equations:

$$\begin{cases} G_{k+1} = G_k - TP_1 G_k - TX_k G_k + TP_1 G_B + TU_g \\ X_{k+1} = X_k - TP_2 X_k + TP_3 I_k - TP_3 I_B \\ I_{k+1} = I_k - TN I_k + T \frac{1}{V_I} U_i \end{cases}, \quad (5)$$

$$\Rightarrow \begin{cases} G_{k+1} = (1 - TP_1)G_k - TX_k G_k + TP_1 G_B + TU_g \\ X_{k+1} = (1 - TP_2)X_k + TP_3 I_k - TP_3 I_B \\ I_{k+1} = (1 - TN)I_k + T \frac{1}{V_I} U_i \end{cases}. \quad (6)$$

The EKF uses the discrete model of the system as states equations. In a stochastic medium, the system (6) can be represented by:

$$\begin{cases} x_{k+1} = x_k + T.f(x, U) + w_k \\ y_k = h(x_k) + v_k \end{cases}, \quad (7)$$

where y_k is the system output and $h(x_k) = [G \ 0 \ 0]^T$.

Kalman filter algorithm

In general, EKF Algorithm has two alternate phases as follows:

Prediction phase (time update)

In this phase, the state vector is first estimated at $(k + 1)$ according of the state and of the measurements made at (k) .

$$x_{k+1} = x_k + Tf(x, U). \quad (8)$$

The covariance matrix is also computed in this phase by the following equation:

$$P_{k+1/k} = Fd_k P_{k/k} Fd_k^t + Q_k, \quad (9)$$

where Fd_k is the system Jacobian matrix.

Correction phase (measurement update)

The Kalman gain is calculated by the following equation:

$$K_{k+1} = P_{k+1/k} H_k^t (H_k^t P_{k+1/k} H_k^t + R_k)^{-1}, \quad (10)$$

where H_k is the Jacobian matrix of the output vector.

The correction of the estimated state vector is done by the Eq. (11):

$$\hat{x}_{k+1} = \hat{x}_k + K_{k+1} (y_{k+1} - H_k \hat{x}_{k+1/k})^{-1}. \quad (11)$$

In Eq. (11), we note that the difference between the output of the system and that of the EKF is multiplied by the Kalman gain, calculated in [10]. The result is then added to the state vector computed in the first phase Eq. (8).

The last equation of the correction phase consists in updating covariance matrix:

$$P_{k+1/k+1} = P_{k+1/k} - K_{k+1} H_k P_{k+1/k}, \quad (12)$$

where

$$Fd_k = \begin{bmatrix} \frac{\partial G_{k+1}}{\partial G_k} & \frac{\partial G_{k+1}}{\partial X_k} & \frac{\partial G_{k+1}}{\partial I_k} \\ \frac{\partial G_k}{\partial X_{k+1}} & \frac{\partial G_k}{\partial X_k} & \frac{\partial G_k}{\partial X_{k+1}} \\ \frac{\partial I_{k+1}}{\partial G_k} & \frac{\partial I_{k+1}}{\partial X_k} & \frac{\partial I_{k+1}}{\partial I_k} \\ \frac{\partial G_k}{\partial G_k} & \frac{\partial G_k}{\partial X_k} & \frac{\partial G_k}{\partial I_k} \end{bmatrix} = \begin{bmatrix} (1 - TP_1 - TX_k) & -TG_k & 0 \\ 0 & (1 - TP_2) & TP_3 \\ 0 & 0 & (1 - TN) \end{bmatrix};$$

$$H_k = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}; Q_k = \begin{bmatrix} Q1 & 0 & 0 \\ 0 & Q2 & 0 \\ 0 & 0 & Q3 \end{bmatrix}; R = \begin{bmatrix} R1 & 0 & 0 \\ 0 & R2 & 0 \\ 0 & 0 & R3 \end{bmatrix}$$

Control strategy

Fig. 6 illustrates a general block diagram of the suggested BG control scheme. Note that the placement of the Kalman filter to estimate the I and X states of the BG Model.

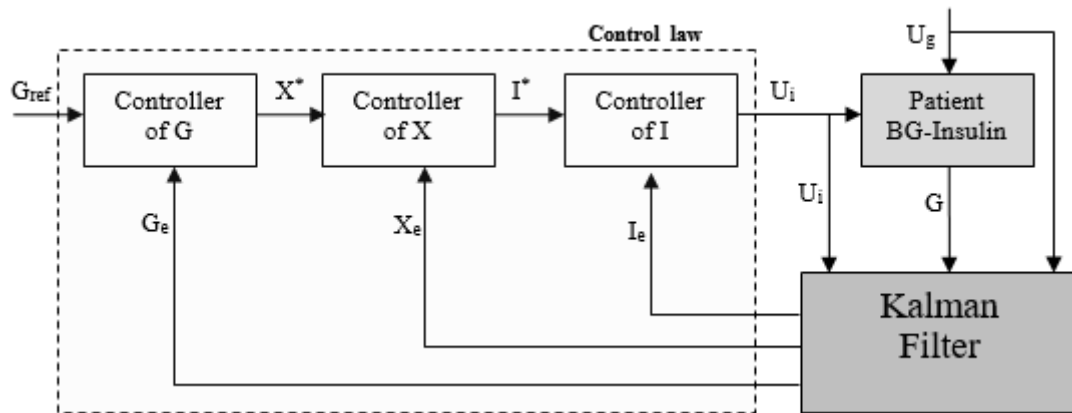


Fig. 6 Scheme of the proposed control

Backstepping of GB controller design

Nonlinear control is one of the biggest challenges in modern control theory. Nonlinear processes are difficult to control because there can be so many variations of the nonlinear behaviour. The method of Lyapunov, also known as Lyapunov’s direct method [16], is becoming increasingly recognized as having great potentiality, both for resolving nonlinear stability and performance problems. Lyapunov’s direct method is now being widely used for designing stable controllers for various fields like biomedical applications. Lyapunov function is energy-like function. This function may draw conclusions about the stability of the system without solving the set of non-linear equations.

Step 1

The controller based on the Lyapunov method is designed as slope changes of energy function which always remains negative ($\dot{V} < 0$) [16]. This energy function consists of a set of error terms. This expression provides stability condition of error terms in the presence of uncertainty and disturbance. Therefore, the tracking error and its derivative are defined as below. Let us formulate a Lyapunov function as follows:

$$V_1 = \frac{1}{2} e_1^2 > 0 \tag{13}$$

with $e_1 = (G_{ref} - G)$.

its derivative function is

$$\dot{V}_1 = (\dot{G}_{ref} - \dot{G})e_1. \tag{14}$$

Substituting Eq. (1) and Eq. (14) gives

$$\dot{V}_1 = (\dot{G}_{ref} + P_1G + XG - P_1G_B - U_g)e_1. \tag{15}$$

Eq. (15) becomes negative definite, if we define the following the virtual control law:

$$X^* = \frac{1}{G}(-\dot{G}_{ref} - P_1 G + P_1 G_B + U_g - K_1 e_1). \quad (16)$$

Indeed, Eq. (16) substituted into Eq. (15) gives the required result as:

$$\dot{V}_1 = -K_1 e_1^2 < 0 \quad (17)$$

where $K_1 > 0$ and $G \neq 0$.

Step 2

Now, we have to find the control to ensure that $X \rightarrow X^*$

$$V_2 = V_1 + \frac{1}{2} e_2^2 > 0 \quad (18)$$

with $e_2 = (X^* - X)$.

The derivate of Lyapunov function is

$$\dot{V}_2 = \dot{V}_1 + \dot{e}_2 e_2 = \dot{V}_1 + (\dot{X}^* - \dot{X}) e_2 = \dot{V}_1 + (\dot{X}^* + P_2 X - P_3 I + P_3 I_B) e_2. \quad (19)$$

Eq. (19) becomes negative definite, if we define the following virtual control law:

$$I^* = \frac{1}{P_3} (\dot{X}^* + P_2 X + P_3 I_B + K_2 e_2). \quad (20)$$

Indeed, Eq. (20) substituted into Eq. (19) gives the required result as:

$$\dot{V}_2 = \dot{V}_1 - K_2 e_2^2 < 0, \quad (21)$$

where $K_2 > 0$ and $P_3 \neq 0$.

Step 3

Now, we have to find the control to ensure that $I \rightarrow I^*$

$$V_3 = V_1 + V_2 + \frac{1}{2} e_3^2 > 0 \quad (22)$$

with $e_3 = (I^* - I)$.

The derivate of Lyapunov function is

$$\dot{V}_3 = \dot{V}_1 + \dot{V}_2 + \dot{e}_3 e_3 = \dot{V}_1 + \dot{V}_2 + (\dot{I}^* - \dot{I}) e_3 = \dot{V}_1 + \dot{V}_2 + (\dot{I}^* + NI - \frac{1}{v_I} U_i) e_3. \quad (23)$$

The Eq. (23) becomes negative definite, if we define the following the reel control law:

$$U_i^* = v_I (\dot{I}^* + NI + K_3 e_3). \quad (24)$$

Indeed, Eq. (24) substituted into Eq. (23) gives the required result as:

$$\dot{V}_3 = \dot{V}_1 + \dot{V}_2 - K_3 e_3^2 < 0. \quad (25)$$

Simulation tests and discussion

In order to validate our work, the performance of the proposed control scheme is presented via simulation results. First, the performances of the proposed Back-stepping controller are analyzed and compared with the classical PI controller. Second, the performances of Kalman observer are presented by estimations of error. The rating and parameters of the BMM are given in the appendix. Note that for all simulations given for $G_b = 200$ mg/dL, $I_b = 0$ uU/L and the initial glucose basal $G_{b0} = 200$ mg/dL.

Fig. 7 presents the carbohydrate intake within one day according to three different meals (breakfast, lunch and dinner).

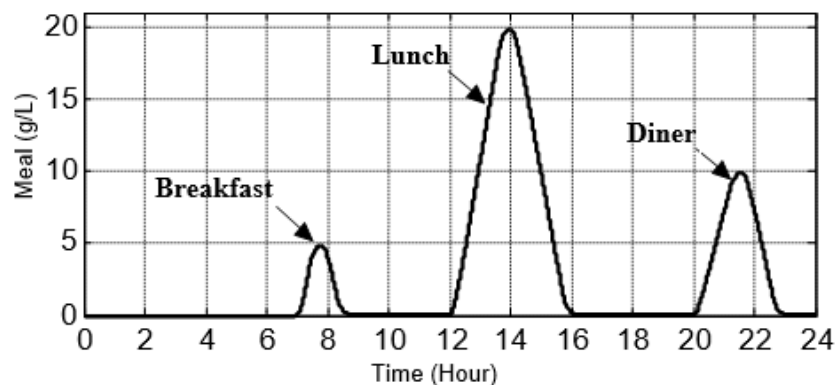


Fig. 7 Meal profile

Simulation results

Figs. 8 and 9 present the plasmatic glucose response with back-stepping and PI controller for three different periods of meals profile as shown in Fig. 7. Figs. 10-13 show the interstitial insulin and plasmatic insulin profiles with both proposed control and PI controllers. Estimations errors of plasmatic glucose, plasmatic insulin and interstitial insulin are presented in Figs. 14-16.

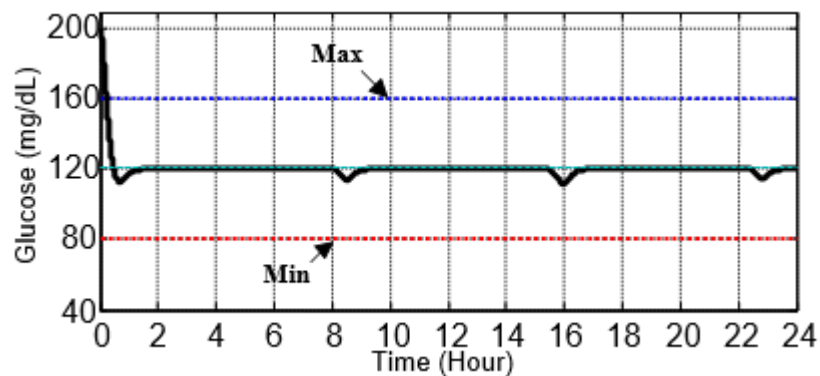


Fig. 8 Control of glucose with Lyapunov

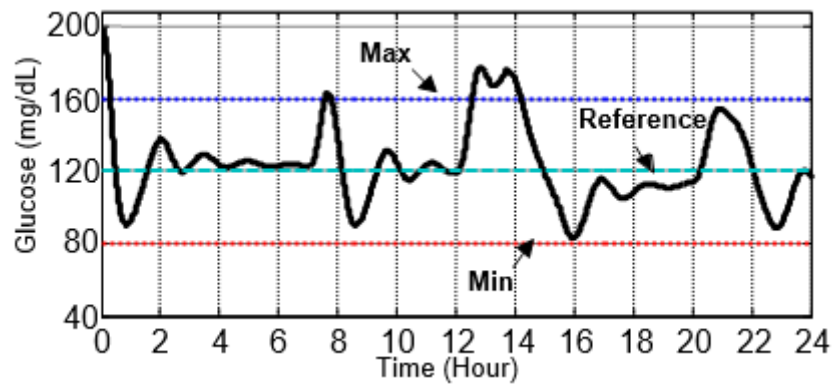


Fig. 9 Control of glucose with PI

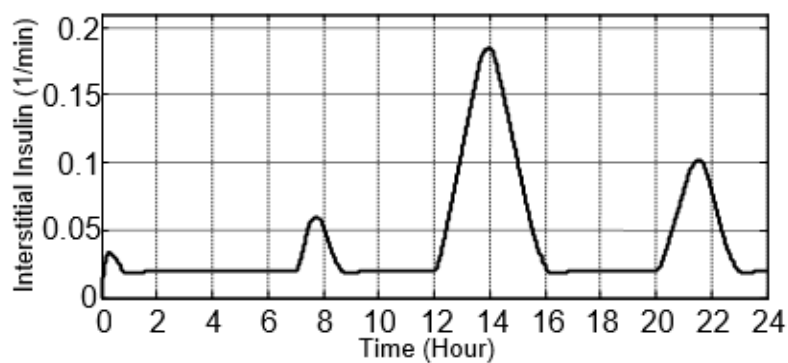


Fig. 10 Interstitial insulin (with Lyapunov)

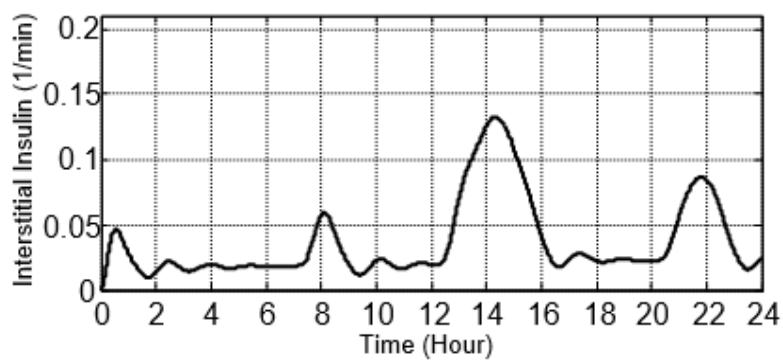


Fig. 11 Interstitial insulin (with PI)

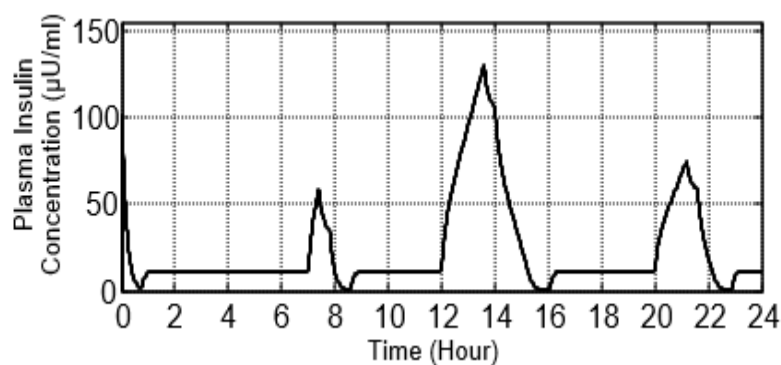


Fig. 12 Insulin (with Lyapunov)

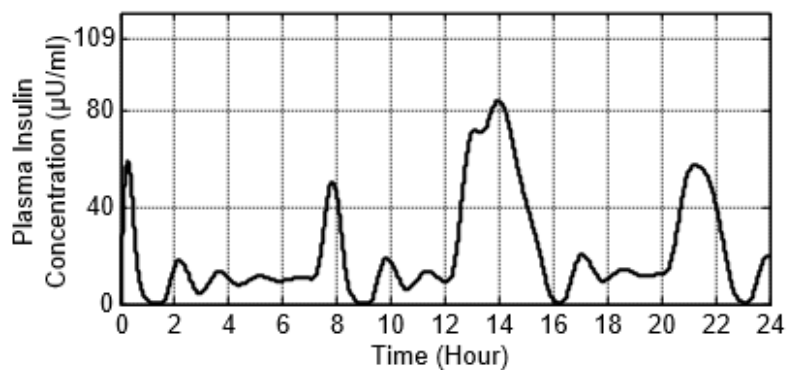


Fig. 13 Insulin (with PI)

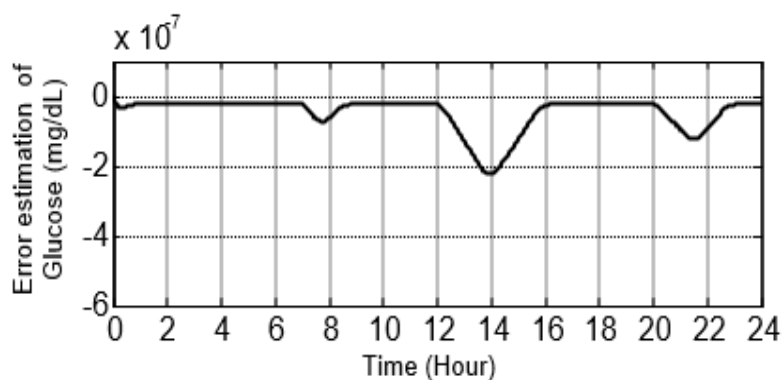


Fig. 14 Error of glucose estimation (Kalman filter)

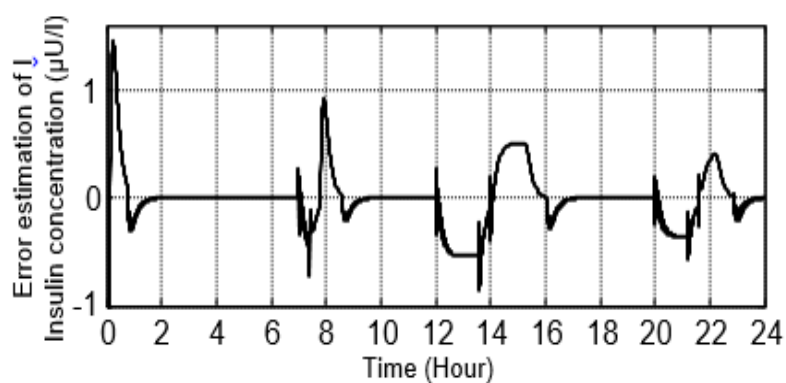


Fig. 15 Error of insulin concentration estimation (Kalman filter)

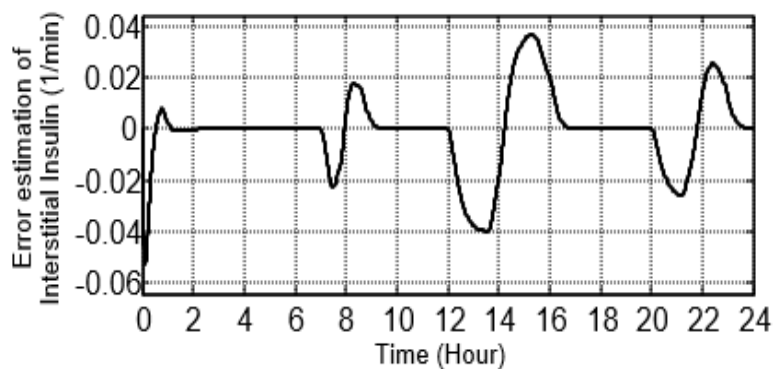


Fig. 16 Error of interstitial insulin estimation (Kalman filter)

Discussions

Fig. 8 illustrates the plasmatic glucose concentration after introducing three meals with different carbohydrate concentrations. That confirms the efficacy and stability of the proposed control system. Figs. 10 and 12 show the concentration of insulin interstitial and plasmatic insulin that the controller injects for the T1D subject to reach the target range. Comparing the performance of the proposed controller with the classical PI, we prove the efficacy and stability of Lyapunov controller.

We can observe in Figs. 14-16 that the variations of the error signals is related to meals intake. More the meal is important, more the error is larger. Besides, the results show the good performance of estimation since the errors are in a small range of variations.

Conclusion

Due to its simplicity, the Bergman minimal model is widely used to study the behavior of T1D. Besides, this model is used to design the control laws to regulate the blood glucose concentration. This is of great importance for improving methods and evaluating the effectiveness of diabetes treatment systems [18].

In this paper, a nonlinear control was proposed to improve the performance of blood glucose regulation of T1D. The Control stability is proved using a Lyapunov approach. Simulation results for different meal profiles have been shown.

This control needs some state variables of the model. To do this, Kalman filter is used. The obtained results clearly indicate successful ride-through performance of the proposed control.

Nomenclature

I	: the plasma insulin concentration, [$\mu\text{U}/\text{mL}$]
X	: the interstitial insulin, [min^{-1}]
G	: the plasma glucose concentration, [mg/dL]
P_1	: the glucose effectiveness, [min^{-1}]
P_2	: the weighted external insulin input, [min^{-1}]
P_3	: the insulin clearance, [$\text{mL}/\text{uU}\cdot\text{min}^{-2}$]
G_b	: the basal plasma glucose concentration, [mg/dL]
I_b	: Basal blood insulin concentration, [$\mu\text{U}/\text{mL}$]
N	: the transfer coefficient of insulin to interstitial compartment, [min^{-1}]
T1D	: Type 1 Diabetes
BG	: Blood Glucose
BMM	: Bergman Minimal Model
EKF	: Extended Kalman Filter
CGM	: Continuous Glucose Monitoring
FDA	: Food and Drug Administration

Appendix

Parameter	Value	Unit
P_1	0.028735	min^{-1}
P_2	0.028344	min^{-1}
P_3	$5.0353 \cdot 10^{-5}$	$\text{mL/uU} \cdot \text{min}^{-2}$
G_b	200	uU/mL
I_b	0	uU/mL
N	0.10	min^{-1}
v_i	12	L

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