A contraction theory approach to observer-based controller design for glucose regulation in type 1 diabetes

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Abstract—Artificial Pancreas has evolved to be effective in regulating the blood glucose in the safe range of 70-180 mg/dl in type 1 diabetic patients. However, the high intra-patient variability, as well as exogenous meal disturbances, pose serious challenges. Moreover, the unavailability of insulin sensors in Artificial Pancreas adds to the difficulty. In the present work, a subcutaneous model of type 1 diabetes (T1D) is considered for observer-based controller design in the framework of contraction analysis. A variety of realistic multiple-meal scenarios for different virtual T1D patients have been investigated and results are presented.

I. INTRODUCTION

Deficiency of insulin is prominent in type 1 diabetes patients (T1DPs) due to auto-immune destruction of the insulin-secreting $\beta$-cells in the pancreas. It results in prolonged elevated glucose levels (> 180 mg/dl) in the blood plasma, termed as hyperglycemia [1]. Thus the T1DPs have to rely upon insulin therapy in terms of multiple daily insulin injections to maintain normalcy in glucose level (70-180 mg/dl). In insulin therapy, dosage of insulin is manually calibrated, which requires the carbohydrate counting a priori. Any overestimation or underestimation of carbohydrate counting can lead to inappropriate insulin dosages resulting in hyperglycemic (> 180 mg/dl) and hypoglycemic (< 70 mg/dl) episodes. Hyperglycemic and hypoglycemic instances can lead to ineffective glucose management in T1DPs.

The issues as mentioned above can be addressed by the Artificial Pancreas (AP), an externally worn device equipped with a continuous insulin delivery system (insulin pump) and a glucose sensor. Among several factors, the performance of the AP is affected by uncertainty in meal absorption [2] which may cause postprandial hyperglycemia and late hypoglycemia [3]. So the existing APs often rely on additional feed-forward strategy and safety algorithms to achieve effective glucose regulation (70-180 mg/dl). The feedforward strategy requires accurate information about the carbohydrate contents of the meals to determine the insulin dosage required to compensate for the effect of the meal [4]. On the other hand, safety algorithms prevent excessive insulin infusion by estimating the existing insulin concentration in the body [5]. Thus, the focus of the current work is to achieve a tight glycemic control.

The functionality of an automated AP is broadly in state estimation and control design. A summary of a wide variety of state estimation techniques has been reported in the literature [6], where the primary drags to the success of the existing works are intra-patient variability and uncertainty in the meal absorption dynamics [7]. There are several attempts to address these issues as in [7], [8]. Still, this remains an open problem. A few robust nonlinear extended Luenberger observers have been designed in some recent studies [7], [8] for addressing intra-patient variability, but comes with some restrictive assumptions. On the other hand, algorithms like KFs [9], extended KFs and unscented KFs [10] have been used for the AP problem. The requirement of precise model, complex matrix computations forces to rethink before implementing. An observer of extended Luenberger structure is proposed in the present work. The issues related to intra-patient variability and meal disturbance are addressed in the framework of contraction analysis.

The main objectives of the current work are (i) to minimize postprandial hyperglycemia, and (ii) to avoid late hypoglycemic instances. Mainly, two variants of robust controllers, namely the $H_{\infty}$ control [11] and the sliding mode control (SMC) [12] exist in the literature pertaining to AP. The necessity of structural characterization of the uncertainty makes the practical implementation of the $H_{\infty}$ filter based controllers challenging. The chattering issues in SMC may trigger hypoglycemia during large intra-patient variability due to excessive insulin infusion. Thus, an attempt is made to devise a simple feedback control law based on contraction theory, which would be sufficient in itself to tackle these issues.

Contraction theory having evolved as a powerful analysis tool has an inherent feature of forgetting initial conditions exponentially [13]. Contraction theory is used in applications like observer design in [14]. As compared to the stability analysis of uncertain nonlinear systems in the framework of Lyapunov stability, contraction analysis offers a more relaxed framework. To deal with this, shifting of the equilibrium concerning the variability in system parameters complicates Lyapunov stability analysis, and getting a closed-form expression of equilibria in respect of parameters may not be possible [15]. This problem can be circumvented by using contraction analysis.

This article considers the IVP model in [16] for the observer and controller design. The highlights of the proposed results are as follows:

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(i) A nonlinear observer is designed for estimating the glucose and insulin concentrations based on the contraction theory approach. The unknown observer gains are computed by solving a set of linear inequalities.

(ii) The estimates are used to design a feedback control law for the glucose regulation.

(iii) The proposed strategy allows the design of observer and controller separately. Stability of overall closed loop system, is ensured using partial contraction theory.

The remainder of the paper is presented in the following sections. Section-II presents the methodology, further divided into four subsections that present the mathematical model, theoretical background, observer design, and controller design. Section-III contains the closed-loop studies’ results to show the effectiveness of design followed by concluding remarks in Section-IV.

II. METHODS

A. Mathematical model

In this section, the dynamical model of the glucose-regulatory system of T1DP is presented. Numerous mathematical models are available in the existing literature that capture the dynamics of the glucose-insulin interactions in T1DPs with varying levels of abstractions and utility, as mentioned in [17]. The complexity of these models, in terms of a large number of state variables and complicated nonlinear functions, limit their relevance to control applications. Recently, a few control-oriented subcutaneous models of T1DPs have been reported in the literature [16]. The model in [16] is adopted here due to its structural simplicity and identifiability.

1) State space representation: The Medtronic Virtual Patient (MVP) models the glucose-insulin dynamics of T1D in terms of ordinary differential equations (ODE) as

\[
\begin{align*}
\dot{x}_1 &= -p_1 x_1 - x_1 x_2 + EGP + R_a(t) \\
\dot{x}_2 &= -p_2 x_2 + p_3 x_3 \\
\dot{x}_3 &= -p_4 x_3 + p_4 x_4 \\
\dot{x}_4 &= -p_5 x_4 + p_6 u(t)
\end{align*}
\]  

(1)

where the states vector \( x = [x_1, x_2, x_3, x_4]^T \) represent the blood glucose concentration\((x_1)\) in mg/dl, the effective insulin in the blood\((x_2)\) in \( min^{-1}\), plasma insulin concentration\((x_3)\) in mU/l and the subcutaneous insulin concentration\((x_4)\) in mU/l respectively. \( u(t) \) represents the insulin infusion rate (mg/dl/min) and infused through the actuator called Continuous Insulin Infusion Pump. The parameter, \( p_1 \) denotes the glucose effectiveness, \( p_2, p_3 \), the insulin sensitivity, \( p_4 \), the time constant of the plasma insulin, \( p_5 \), the time constant of the subcutaneous insulin and \( EGP \) represents endogenous glucose production. Output \( y \) is blood glucose concentration, expressed as \( y = x_1 \) and is measurable by Continuous Glucose Monitoring(CGM) device.

The equilibrium of the system in (1) is given as,

\[
\begin{align*}
[x_1, x_2, x_3, x_4]^T &= [EGP/p_1, 0, 0, 0]^T.
\end{align*}
\]

The corresponding deviated dynamics of the system (1) is

\[
\begin{align*}
\dot{x}_{1d} &= -p_1 x_{1d} - \frac{EGP}{p_1} x_{2d} - x_{1d} x_{2d} + R_a(t) \\
\dot{x}_{2d} &= -p_2 x_{2d} + p_3 x_{3d} \\
\dot{x}_{3d} &= -p_4 x_{3d} + p_4 x_{4d} \\
\dot{x}_{4d} &= -p_5 x_{4d} + p_6 u(t).
\end{align*}
\]

(3)

where the output is expressed as \( y = x_{1d} \).

2) Meal disturbance model: This represents the dynamics of the glucose absorption in the gut and its appearance in the blood circulation following the meal intake. As in [18], it is a two-compartmental model, as provided below

\[
\begin{align*}
\dot{d}_1 &= -\frac{\delta_1}{\tau_{max}} + Bio \times Carb(t) \\
\dot{d}_2 &= -\frac{\delta_2}{\tau_{max}} - \frac{\delta_1}{\tau_{max}} d_2 \\
R_a(t) &= \frac{\delta_1}{\tau_{max}} - \frac{\delta_2}{\tau_{max}} d_2
\end{align*}
\]

(4)

where \( d_1 \) and \( d_2 \) be the amount of glucose in the first and second compartments (mg/dl), \( \tau_{max} \) is the time-to-maximum rate of appearance of glucose in the blood (min), \( t \) is the time of meal intake (min), \( Carb(t) \) denotes the ingested carbohydrates (mg/dl/min), \( Bio \) is carbohydrate bioavailability of the meal (unitless) and \( R_a(t) \) represents glucose absorption rate (mg/dl/min) in the gut. The values of the parameters are adopted from [18] as \( \tau_{max} = 43 \) min and \( Bio = 71 \).

B. Preliminaries on Contraction Theory

Contraction theory helps to characterise the temporal behaviour of trajectories w.r.t each other for a dynamical system. The system is said to be contracting if two arbitrary trajectories converge towards each other, forgetting their initial conditions. Here, we briefly present results from contraction theory, which will be used in subsequent sections and can be found in details in [19].

Consider a nonlinear dynamical system,

\[
\dot{x} = f(x),
\]

(5)

where, \( x \in \mathbb{R}^n \) is the system states, \( f(x) \) is the drift function \( f : \mathbb{R}^n \rightarrow \mathbb{R}^n \). The differential dynamics of (5) is,

\[
\delta \dot{x} = \frac{\partial f}{\partial x} \delta x = J(x) \delta x,
\]

(6)

where, \( \delta x \) is the virtual displacement of infinitesimal perturbation in \( x \), \( J(x) \) is the Jacobian matrix of \( f(x) \). The evolution of virtual displacement can be inferred using (6) as,

\[
\frac{d}{dt} (\delta x^T \delta x) = 2 \delta x^T \frac{\partial f}{\partial x} \delta x \leq 2 \lambda_{max}(J) \delta x^T \delta x
\]

(7)

where, \( \lambda_{max}(J) \) is the largest eigenvalue of the Jacobian \( J \). If \( \lambda_{max}(J) \) is strictly uniformly negative, then any infinitesimal length \( |\delta x| \) converges exponentially to zero.

A relaxed form as partial contraction analysis extends contraction analysis for convergence to a specific behavior. It has been applied to the synchronization of oscillators [13] and observer design [20].

Lemma 1. Consider a nonlinear system of the form \( \dot{x} = f(x, x) \) and assume that the auxiliary system \( a(x, a) \) virtual system \( y = f(y, x) \) is contracting to \( y \). If a particular solution of the auxiliary \( y \)-system verifies a smooth specific property, then all trajectories of the original \( x \)-system verify this property exponentially. The original system is said to be partially contracting. For proof refer [21].

The idea here is to design a virtual system that will have estimated state as a particular solution and system state as another particular solution. The salient property of contraction analysis is that it can quantify the robustness to an external perturbation.

Lemma 2. Consider that the nominal system \( \dot{x} = f(x) \) is contracting and the perturbed model \( \dot{x}_p = f(x_p) + \delta(t) \), where \( x_p \) is the perturbed state, \( \delta(t) \) be a vanishing perturbation satisfying
\[ |d(t)| \leq c_1 e^{-c_2 t} \] for some \( c_1, c_2 > 0 \) and \( t \geq 0 \). Then, there exist constants \( k_1, k_2 > 0 \) such that the following property holds \( \forall t > 0 \)
\[ |x(t) - x_p(t)| < e^{-k_1 t} (k_2 + |x_0 - z_0|) \] (8)

C. Observer Design for Artificial Pancreas

As discussed earlier, the state estimation is necessary to retrieve information of insulin concentrations in the body. A nonlinear observer of the extended Luenberger structure is considered for estimating the state variables concerning glucose and insulin concentrations in the plasma and subcutaneous compartments. The observer dynamics for the system in (1) is provided below

\[
\begin{align*}
\dot{x}_1 &= -p_1 \hat{x}_1 - \dot{x}_2 x_1 + EGP + l_1 (x_1 - x_1) \\
\dot{x}_2 &= -p_2 \dot{x}_2 + p_3 \dot{x}_3 + l_2 (\dot{x}_1 - x_1) \\
\dot{x}_3 &= -p_4 \dot{x}_3 + p_4 x_4 + l_3 (\dot{x}_1 - x_1) \\
\dot{x}_4 &= -p_5 \dot{x}_4 + u(t) + l_4 (\dot{x}_1 - x_1)
\end{align*}
\] (9)

where \( \hat{x}_i, i = 1, \ldots, 4 \) are the estimated states and \( L = [l_1, l_2, l_3, l_4]^T \) is the unknown observer gain that needs to be selected to ensure the convergence of estimated state, \( \dot{x}_1, i = 1, \ldots, 4 \) in (9) to the true states, \( x_i, i = 1, \ldots, 4 \) in (1). The existence and computation of the observer gain, \( L \) is stated in the form of following theorem.

**Theorem 1.** Consider the system dynamics in (1) and the observer in (9) with the observer gain, \( L = [l_1, l_2, l_3, l_4]^T \). The estimated states, \( \hat{x}_1 \) in (9) will converge to the true states, \( x_1 \) in (1), exponentially from arbitrary initial conditions if the observer gain \( L \) satisfies the following linear inequalities

\[-p_1 + l_1 + l_2 + l_3 + l_4 < 0, \quad -p_2 + x_1 < 0, \quad -p_3 + p_3 < 0 \] (10)

**Proof:** Let us consider a virtual system as

\[
\begin{align*}
\dot{s}_1 &= -p_1 s_1 - x_1 s_2 + EGP + l_1 (s_1 - x_1) \\
\dot{s}_2 &= -p_2 s_2 + p_3 s_3 + l_2 (s_1 - x_1) \\
\dot{s}_3 &= -p_4 s_3 + s_4 x_4 + l_3 (s_1 - x_1) \\
\dot{s}_4 &= -p_5 s_4 + u(t) + l_4 (s_1 - x_1)
\end{align*}
\] (11)

where, \( s_i, i = 1, \ldots, 4 \) are the states of virtual system which has two particular solutions. For \( s_i = x_i \), the virtual system represents the system in (1), and for \( s_i = \hat{x}_i \), it represents the observer dynamics in (9). Now, the corresponding differential dynamics of the virtual system in (11) can be obtained as

\[
\begin{bmatrix}
\delta s_1 \\
\delta s_2 \\
\delta s_3 \\
\delta s_4
\end{bmatrix} =
\begin{bmatrix}
-p_1 + l_1 & -x_1 & 0 & 0 \\
-l_2 & -p_2 & p_3 & 0 \\
l_3 & 0 & -p_4 & p_4 \\
l_4 & 0 & 0 & -p_5
\end{bmatrix}
\begin{bmatrix}
\delta s_1 \\
\delta s_2 \\
\delta s_3 \\
\delta s_4
\end{bmatrix}
\] (12)

In the compact form, the differential dynamics becomes

\[ \delta \dot{s} = J \delta s \] (13)

Hence, by Lemma 1, it can be inferred that the estimated states, \( \hat{x}_1 \) in (9) converges to the corresponding true states exponentially.

**Remark 1.** It is important to note that the inequalities in (10) involve only the information of blood glucose concentration, \( x_1 \), which is measurable. It provides less conservatism than the observer designs in [7, [23] where it is required to know the bounds of all the state variables which is difficult to get precisely.

**Remark 2.** The observer designs in [7, [23] are based on quadratic Lyapunov functions and involve linear approximations of the nonlinearity, such as Lipschitz condition [23] and one-sided quasi-Lipschitz condition. However, in the proposed result it doesn’t require any such assumptions.

1) Results of Estimation: To evaluate the performance of the observer, the estimation of the plasma glucose and plasma insulin concentration are performed for three TID subjects. A hypothetical 24 h scenario is considered with the assumption that the TID subjects receive a single meal of 70 g carbohydrate at t=10 min followed by a fasting period. The parameters are referred from Table I. The initial conditions are chosen as \( x_1 = 120 \text{ mg/dl} \), \( x_2 = 0.01 \text{ min}^{-1} \), \( x_3 = 1 \text{ mU/l} \) and \( x_4 = 1 \text{ mU/l} \). Observer gains are chosen by satisfying the inequalities in (10) while considering minimum glucose concentration \( x_1 = 0 \text{ mg/dl} \). The corresponding results of the state estimation are shown in Fig. 1. It can be observed that the convergence of the estimate \( \hat{x}_1 \) to the true state \( x_1 \) of Subject 1 is comparatively slower than Subjects 2 and 3. Results verify that the observer is capable of estimating both glucose and insulin concentrations. Next, the design of the control law based on the contraction analysis is presented.

D. Controller Design for Artificial Pancreas

The objective of control design in AP is to avoid severe hypoglycemia \( x_1 < 50 \text{ mg/dl} \). Additionally, it should ensure an automated continuous insulin delivery to minimize the risks of hyperglycemia \( x_1 > 180 \text{ mg/dl} \). Moreover, the blood glucose should be below 180 mg/dl within 1 h after meal intake. All these objectives need to be achieved utilizing the obtained state estimates in the presence of parametric uncertainty and exogenous meal disturbances.

The convergence of the estimated states to the actual states has been already established in Theorem 1. In the next step, the deviated dynamics in (3) is considered to formulate the control problem as a regulation problem. By ensuring the deviated state \( x_d \) converges to zero, the actual states converge to the equilibrium point. To achieve this objective, a feedback control law is chosen as

\[ u = K \dot{x}_d \] (14)

where, \( K = [k_1 k_2 k_3 k_4] \) is the controller gain matrix and \( \dot{x}_d = [x_{1d} \dot{x}_{2d} \dot{x}_{3d} \dot{x}_{4d}]^T \) is the estimate of the deviated state, \( x_d = [x_{1d} x_{2d}, x_{3d}, x_{4d}]^T \). The information of \( \dot{x}_d \) can be extracted from the transformation to the estimated states \( \hat{x} \) as introduced in (2) as

\[ [\dot{x}_{1d} \dot{x}_{2d} \dot{x}_{3d} \dot{x}_{4d}]^T = [\dot{x}_1 \dot{x}_2 \dot{x}_3 \dot{x}_4]^T - [EGP/p_1 0 0 0]^T. \] (15)

The estimation error is \( e = x_d - \hat{x}_d \). By substituting the control law in (14), the closed loop deviated dynamics (3) can be re-written in

\[ TABLE I: Estimated parameters for different subjects [16].

| Subjects | \( p_1 \)  | \( p_2 \)  | \( p_3 \)  | \( p_4 \)  | \( p_5 \)  | \( EGP \)  | \( p_6 \)  |
|----------|----------|----------|----------|----------|----------|-----------|----------|
| 1        | 2.20 \times 10^{-8} | 1.06 \times 10^{-8} | 8.60 \times 10^{-8} | 0.0213 | 0.0204 | 1.33 | 1.02 \times 10^{-5} |
| 3        | 3.50 \times 10^{-3} | 2.33 \times 10^{-2} | 1.079 \times 10^{-5} | 0.0143 | 0.0141 | 1.07 | 1.55 \times 10^{-5} |
| 5        | 4.33 \times 10^{-3} | 9.63 \times 10^{-3} | 1.974 \times 10^{-6} | 0.0217 | 0.0217 | 0.6 | 1.410 \times 10^{-5} |

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which further becomes
\[
\dot{x}_d = f(x_d) + BKx_d - BKe
\]
where, \( f(x_d)c_L = f(x_d) + BKx_d \) and \( d(t) = -BKx_d \). For the control law, \( u = Kx_d \), the gain matrix \( K \) needs to be designed. The gains, \( k_i, i = 1, \ldots, 4 \) in (14) are to be selected to ensure the stability of closed loop system that includes the observer states in (9) and the control law in (14). The same is presented in the form of following theorem.

**Theorem 2.** Consider the closed loop system in (17) with \( d(t) = -BKx(t) \) be the vector function satisfying \( |d(t)| \leq c_1 e^{-c_2 t} \), there exist a controller gain matrix, \( K = [k_1, k_2, k_3, k_4] \) dictated by the following relations in (18) such that \( f(x_d)c_L \) is contracting.

\[
\begin{align*}
-p_1 - x_{2d} + k_1 p_6 < 0 \\
-p_2 + k_2 p_6 + (\text{EGP}/p_1) - x_{1d} < 0 \\
-p_4 + k_3 p_6 < 0 \\
k_4 p_6 - p_5 + p_4 < 0,
\end{align*}
\]

(18)

The states of closed loop system (controller-observer put together) will exponentially converge to the equilibrium. Further, it will imply that the following relation will hold.

\[
|x_d| < e^{-\alpha_1 t}(\alpha_2 t + |x_{d0}|)
\]

(19)

where \( \alpha_1, \alpha_2 > 0 \) depend on the minimum contraction rates.

**Proof:** The proof of the above theorem is straightforward as stated below. Consider the closed loop dynamics as mentioned in (17), where

\[
f(x_d) = \begin{bmatrix} -p_1 x_{1d} + (\text{EGP}/p_1) x_{2d} - x_{1d} x_{2d} \\
-p_2 x_{2d} + p_3 x_{3d} \\
-p_4 x_{3d} + p_4 x_{4d} \\
-p_5 x_{4d} \end{bmatrix}, \quad B = \begin{bmatrix} 0 \\
0 \\
0 \end{bmatrix}
\]

The closed loop system in compact form represented as

\[
f(x_d)c_L = \begin{bmatrix} -p_1 x_{1d} + (\text{EGP}/p_1) x_{2d} - x_{1d} x_{2d} \\
-p_2 x_{2d} + p_3 x_{3d} \\
-p_4 x_{3d} + p_4 x_{4d} \\
-p_5 x_{4d} + p_6 k_1 x_{1d} + p_6 k_2 x_{2d} + p_6 k_3 x_{3d} + p_6 k_4 x_{4d} \end{bmatrix}
\]

(20)

The differential dynamics of closed loop system is in the form,

\[
\delta \dot{x}_d = J_c \delta x_d,
\]

(21)

where

\[
J_c = \begin{bmatrix}
-p_1 - x_{2d} & (\text{EGP}/p_1) - x_{1d} & 0 & 0 \\
0 & -p_2 & p_3 & 0 \\
0 & 0 & -p_4 & p_4 \\
k_1 p_6 & k_2 p_6 & k_3 p_6 & k_4 p_6 - p_5
\end{bmatrix}
\]

Similar to the observer design in II-C, the controller gain \( K \) can be selected using Lemma 1. Therefore, designed \( K \) will ensure the closed loop system \((f(x_d)_{\text{nominal}})\) to be contracting and \( e(t) \rightarrow 0 \) exponentially as the observer dynamics achieves exponential convergence. The term \( d(t) = -BKx(t) \) is treated as a decaying perturbation to the nominal system. Using Lemma 2, exponential convergence of states to the equilibrium is guaranteed as given in (19).

For the nominal system to be contracting, we need to design \( K \) such that the Jacobian \( J_c \) has negative matrix measure. Thus, the design conditions can be obtained as in (18).
Remark 2.1. The observer and controller design can be carried out separately for this nonlinear system due to a powerful property of cascaded individual contracting systems, being contracting [13]. Hence, this work is less restrictive than the other works on observer-based controller in [7], [8].

III. RESULTS

For evaluating the efficacy of the proposed observer-based control technique, a realistic daily scenario of T1D patients, where three meals of 75 g carbohydrates, a representative of breakfast, lunch, and dinner, is considered. The gains of observer and controller are chosen from proposed inequalities (10) and (18), respectively. The underlying assumption is that the AP has sufficiently fast infusion rate in comparison to the innate glucose regulation dynamics. The model, as presented in (1), is being considered to represent the T1DPs. This virtual simulation scenario is of 24 h (equivalent to 1440 min) time frame. 3 virtual T1DPs, namely, subjects 1, 3, and 5 are considered and the parameters are adopted as mentioned in Table I. 3 meals containing an equal amount of carbohydrate of 75 g are provided as breakfast, lunch, and dinner at t=10, 360, and 720 min, respectively. Simulation is assumed to start from a safe blood glucose level, and initial conditions $x_1$ of 120 mg/dl and initial conditions $x_2 = 0.01 \text{ min}^{-1}$, $x_3 = 1 \text{ mU/l}$ and $x_4 = 1 \text{ mU/l}$.

![Fig. 2: Plasma glucose concentration trajectories of (a) subject 1, (b) subject 2 and (c) subject 3 under the proposed observer-based feedback control law.](image)

In this article, to showcase the robustness of the design, the intra-patient variability is not considered explicitly. For detailed performance analysis of the proposed technique with respect to intra-patient variability, the readers can refer to [24].

IV. CONCLUSIONS

Contraction analysis is utilized for designing an observer and a controller to achieve a tight glycemic control. Extensive numerical simulations are carried out to evaluate the performance of the proposed technique for realistic scenarios. The postprandial hyperglycemic events and hypoglycemia are significantly minimized. The simple structure of the observer and control law makes it a desirable candidate for AP. The control scheme can be extended to more complicated models like the UVa Padova model, Hovorka model, etc., that consider a detailed dynamics. The design can be extended for nonlinear systems with a sampled output, which represents the actual glucose measurements done by the CGM devices in practice.

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