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Fixed-time synergetic control for chaos suppression in endocrine glucose–insulin regulatory system

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ABSTRACT

This paper, puts forward the control of chaos phenomena in an important endocrine glucose–insulin metabolic regulatory system. Using a robust fixed-time synergetic controller, which has been designed to regulate the plasma glycemic level in type 1 diabetic patients (T1D). In the view of the recent improvement in synergetic control algorithm, terminal attractor technique and fixed time stability. The introduced technique has the benefit of utilizing a continuous control law. In addition, the proposed control algorithm, other than being without chattering, has the advantage of being converging in finite fixed-time. Lyapunov framework is exploited to ensure the stability of the controlled system. Simulation results of the designed synergetic controller, are exhibiting the ability of the proposed control technique for rapidly achieving normoglycemia in type 1 diabetes patients and stabilizing the biological disorder in a robust manner. These features make it interesting because one of the great matters in the diabetes mellitus treatment is the search of the best controller acting as an artificial pancreas and a safe and efficient control algorithm of the plasma glucose level and control devices enhancement, which relieves the diabetic subjects.

1. Introduction

The human body needs blood glucose levels (blood sugar) maintained within a very narrow range. To make this happen two hormones are utilized insulin and glucagon which play major roles in regulating the glucose level. The pancreas secretes both these two hormones, and thus are called pancreatic endocrine hormones. The production of insulin and glucagon from the pancreas substantially determines if a patient has diabetes hyperglycemia, hypoglycemia, or other diabetes problem. Human body desires plasma glucose to be regulated in the range 70 [mg/dl] to 110 [mg/dl]. If below 70 [mg/dl] is termed "hypoglycemia". And above 180 [mg/dl] is called "hyperglycemia" (equivalent to mean "high level of glucose in the blood"). The abnormal secretion of these two hormones in humans prompts to the occurrence of diabetes type 1 or type 2. Globally, diabetes is among the main 10 reasons for death. The number of deaths due to diabetes mellitus (DM) and its complications in 2019 is estimated to be 4.2 million (IDF, 2019). Diabetes type 1 (T1D) is an autoimmune disease, characterized most seriously by pancreas β-cell failure to secret any amount of insulin to regulate the blood glycemic level within normal limit, and leading to a serious increase in blood glucose above 120 [mg/dL] (Ma, Tang, & Shen, 2018; Turksoy, Littlejohn, & Cinar, 2018), which causes long-term complications. The insulin shortage is normally treated by an external insulin source through Function Insulin Therapy or Treatment (FIT) (Amear, Raafat, & Al-Khazraji, 2019).

The blood glucose can be regulated by a closed loop controller in an automated manner, through continuously monitoring blood glucose levels and injecting the appropriate amount of insulin automatically without intervention from the patient. The artificial pancreas can realize these processes autonomously. It represents a system with an essential element is an insulin-pump empowered by an effective control technique to continuously administrates correct dose of insulin to the diabetic subject of type 1 diabetes in real time as same as a real human pancreas do. The feedback controller used must automatically calculate and adjust the insulin dose in real time to regulate blood sugar level emulating the function of a healthy biological pancreas, thus limiting the risks and time spent under a high glycemic level state. Several automatic closed loop control algorithms have been developed successfully, for example, proportional integral derivative (PID) (Gao & Wang, 2012) and H_∞ controller (Mandal & Sutradhar, 2010), both these techniques need system linearization through the design, which clearly limits the system robustness. Another control method developed in Abedini Najafabadi and Shahrokhi (2016) and Ning and Wang (2015) is the model predictive control (MPC) where the system model, is used to predict and to minimize the tracking error, by obtaining the insulin delivery rate, with a period of infusion every 10–15 [min], due

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to this a problem of hypoglycemia may occur using this type of control algorithm, which is a serious matter and can lead to death. Moreover, a precise mathematical model of the system must be employed to linearize the input–output model dynamics, which is hard to achieve in biological systems subjected to parametric variations, and are undergoing external disturbances. A learning-type model predictive control algorithm is proposed in Wang et al. (2017), and a customized model predictive control presented in Messori, Ellis, Cobelli, Christofides, and Magni (2015).

The mentioned concerns have led to turn the research to use robust techniques such as sliding mode control (SMC) algorithm characterized by their high efficiency, precise tracking, and robustness toward system dynamics uncertainties. Sliding mode control (SMC) has been used widely in robust control methods in numerous applications (Fridman, Levant, et al., 2002; Hosseinnia, Ghaderi, Mahmoudian, Momani, et al., 2010; Zhihong, Paplinski, & Wu, 1994) and among which in controlling the glucose–insulin regulatory system (Abu-Rmileh, Garcia-Gabin, & Zambrano, 2010; Hernández et al., 2013). However, in practical applications of SMC, the designer may experience undesirable oscillations having finite frequency and amplitude, which is known as chattering phenomenon. Chattering is a ruinous phenomenon because it reduces control accuracy, excites fast dynamics which were neglected in the ideal model, induces instability, and may cause severe damage and high wear of moving mechanical parts of actuators through high frequency control effort (Yu, Yu, Shirinzadeh, & Man, 2005). Several solutions have been proposed to overcome this problem, among which SMC approximations (Slotine, Li, et al., 1991), as well as the development of High Order Sliding Mode (HOSM) (Emel'Yanov, Korovin, & Levant, 1996). In Hernández et al. (2013) the HOSM approach has been employed in controlling the blood glucose level at the normal range. All these methods alleviate chattering to different degrees at expenses of added complexity and often robustness.

Another robust control technique is the synergetic control approach, based on the analytical design of aggregated regulators (ADAR) (Kolesnikov, Veselov, Kolesnikov, et al., 2000), remove chattering as a whole by the use of completely continuous control law and achieves the same level of closed loop invariance similar to the SMC. This method provides the advantages of the SMC without the chattering phenomena and its complications. The synergetic control theory has recently attracted a lot of attention, is based on the principle of directed self-organization (Ahifar, Noei, & Rahmani, 2019). System synthesis problems, i.e. finding the rules of the common goal of control processes in the complex nonlinear dynamical systems, are currently complex and infeasible in different aspects for the existed control science. Kolesnikov, the Russian scientist, proposed the essential rules of nonlinear system synthesis theory based on the synergetic realization in addition to its applications that is known as the synergetic control theory (SCT) (Kolesnikov et al., 2000). The main advantages of the synthesis procedure of the synergetic controller are, its works on the full nonlinear system and does not need any simplification or linearization of the input–output system dynamics, as required in the traditional control theory during application (Lazarević, 2015).

Chaos existed in nonlinear dynamical systems whose behavior is highly sensitive to initial conditions. Therefore, small changes in initial conditions can produce totally different time-responses (Hilborn et al., 2000). Some evidence claims that chaos exists in many biological systems both in normal and abnormal situations, e.g. brain (Baghdadi, Jafari, Sprott, Towhidkhah, & Golpayegani, 2015; Freeman & Barrie, 1994), heart (Goldberger, 1991), kidney (Jensen, Holstein-Rathlou, Leyssac, Mosekilde, & Rasmussen, 1987). Many practical research (Frandes, Timar, Timar, & Lungeanu, 2017; Li, Tuo, & Wang, 2018), proved the existence of chaos in the dynamics of the glucose–insulin regulatory system due to metabolic disorder. This is adding an extra challenge for the control algorithm to be applied to regulate the blood glucose level. This is a blind point of all the aforementioned glucose level control algorithms which are studied simple mathematical models for the glucose–insulin regulatory system and not tackled the chaos stabilization that may occur in the endocrine system. The main contributions of the paper are the following aspects: suppressing chaotic oscillation in the predator–prey based model of endocrine glucose–insulin regulatory system is investigated and to the best of the authors knowledge, no controller designed for the model yet. A synergetic controller will be designed based on its fixed time version to elaborate a robust control algorithm for regulating blood glucose levels in diabetes type 1 patients.

This paper is organized as follows. In Section 2, the mathematical model of the glucose–insulin regulatory system was introduced based on the predator–prey modeling approach, and the system dynamics investigated to reveal the system behavior which shows a chaotic state at abnormal metabolic. In Section 3, the fixed time synergetic controller preliminaries are given and the general design framework is provided. In Section 4, four simulation scenarios were provided to reveal the controller effectiveness and robustness. Then general conclusions and discussion are given in Section 5.

2. Mathematical model

Insulin and glucagon hormones support maintaining the homeostasis state, in which the status inside the human body remains constant. The pancreas keeps monitoring the blood glucose level, when it is too high, the pancreas β-cell secretes the required amount of insulin to help the body reduce the glucose level. The body cells need sugar for producing energy. However, most of them cannot utilize glucose without the existence of insulin. It gives glucose entry to the body cells. Insulin activates transmembrane receptors on the cell called insulin receptors, instructing the cells to open special gates and allow glucose entry to target cells. Low levels of insulin circulate steadily throughout the body. A spike in insulin signals to the liver that blood glucose level is also high. The liver absorbs sugar in response to the insulin spike then converts it into an energy storage molecule called glycogen. When plasma glucose levels decrease below basal level, the pancreas α-cells release glucagon triggering the lever to convert back the glycogen to glucose until normal glucose level is achieved. A schematic diagram demonstrating this process is given in Fig. 1. Based on the aforementioned process one can conceive the glucose and insulin relationship as a prey and predator nature, therefore, a continuous nonlinear model for insulin–glucose regulatory system using the prey and predator model has been presented in Shabestari, Panahi, Hatef, Jafari and Sprott (2018) and adapted here as follows:

$$\begin{cases} \dot{x}(t) &= -a_1 x + a_2 xy + a_3 y^2 + a_4 y^3 + a_5 z + a_6 z^2 \\ & \quad + a_7 z^3 + a_{20} \\ \dot{y}(t) &= -a_8 xy - a_9 x^2 - a_{10} x^3 + a_{11} y(1-y) - a_{12} \\ & \quad \cdot z - a_{13} z^2 - a_{14} z^3 + a_{21} \\ \dot{z}(t) &= a_{15} y + a_{16} y^2 + a_{17} y^3 - a_{18} z - a_{19} yz. \end{cases} \tag{1}$$

$$J = \begin{bmatrix} -a_1 + a_2 y & a_2 x + 2a_3 y + 3a_4 y^2 & a_5 + 2a_6 z + 3a_7 z^2 \\ -a_8 y - 2a_9 x - 3a_{10} x^2 & -a_8 x + a_{11}(1-2y) & -a_{12} - 2a_{13} z - 3a_{14} z^2 \\ 0 & a_{15} + 2a_{16} y + 3a_{17} y^2 - a_{19} z & -a_{18} - a_{19} y \end{bmatrix} \tag{2}$$

where $x(t)$ represents the predator population density (plasma insulinemia), $y(t)$ represents the prey population density (plasma glycemia) and $z(t)$ is the pancreatic β-cells population density. The system (1) incorporates various parameters whose values are essential in changing the system behavior. The parameters of system (1) are defined in Table 1.

The endocrine regulatory system (1) has two positive equilibrium points (0.805, 1.815, 1.319) and (0.624, 0.935, 0.877), for the parameters set in Table 2 and $a_1 = 3$. To reveal the dynamical behavior of system (1) the eigenvalues of the Jacobian matrix given in (2) evaluated at each equilibrium points that the system has. The eigenvalues are

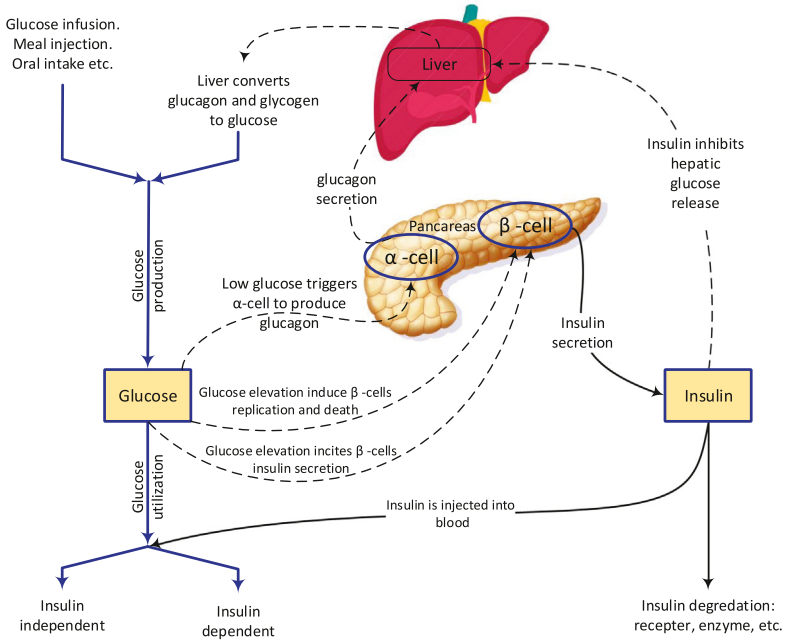

Fig. 1. Schematic diagram of glucose–insulin regulatory system.

Table 1
System (1) parameters essential rule.

Parameter	Function
$-a_1$	Insulin natural reduction rate in absence of glucose
a_2	Insulin propagation rate in presence of glucose
a_3, a_4	Insulin increasing rate in response to glucose increase
a_5, a_6, a_7	Insulin increasing rate due to β-cells secretion
$-a_8$	Insulin effect on glucose
a_9, a_{10}	Glucose reduction rate triggered by insulin secretion
a_{11}	Glucose natural growth in absence of insulin
a_{12}, a_{13}, a_{14}	Glucose reduction rate due to insulin secreted by β-cells
a_{15}, a_{16}, a_{17}	β-cells increasing rate due to glucose increase
a_{18}, a_{19}	β-cells natural decreasing rate

Table 2
System (1) parameters values.

Parameter	Value	Parameter	Value
a_1	2.04	a_{12}	1.37
a_2	0.1	a_{13}	−0.3
a_3	1.09	a_{14}	0.22
a_4	−1.08	a_{15}	0.3
a_5	0.03	a_{16}	−1.35
a_6	−0.06	a_{17}	0.5
a_7	2.01	a_{18}	−0.42
a_8	0.22	a_{19}	−0.15
a_9	−3.84	a_{20}	−0.19
a_{10}	−1.2	a_{21}	−0.56
a_{11}	0.3		

found respectively (1.3802, −1.7563 ± j7.509) and (−2.8372, 0.5262 ± j2.3472), then the two equilibrium points are saddle points.

The pathophysiology in diabetes type 1 is a destruction of β-cells in the pancreas which is the insulin-producing cell in the human body. System (1) can exhibit this disorder by varying the a_{15} which represents the rate of increase in population density of β-cells. If the a_{15} parameter is reduced, this renders the pancreas unable to secrete enough insulin for regulating the blood glucose level. According to that, system (1) exhibits chaotic behavior for small values of parameter a_{15}. It can be deduced from the bifurcation diagram Fig. 2 and Lyapunov exponents plot presented in Fig. 3 of the system (1) with respect to the

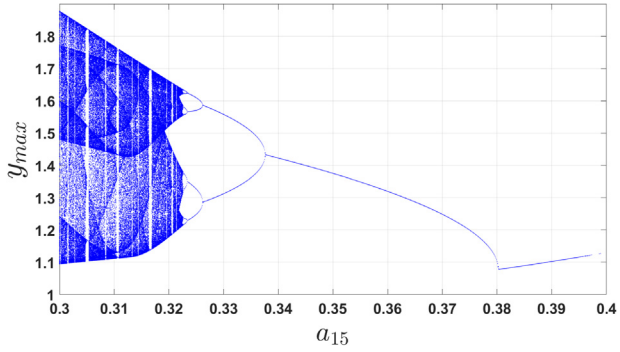

Fig. 2. Bifurcation diagram of system (1) with respect to the parameter a_{15}.

control parameter a_{15}. The mathematical model (1) shows some kind of steady state dynamics for a wide range of system parameter a_{15} but when the parameter decreases, the system behaves chaotically which is corresponding the expectation. The period doubling root to chaos is clear as an indication of the predator–prey nature of the metabolic system.

The chaotic systems have high sensitivity to initial conditions therefore, small changes in initial insulin concentration value can greatly affect glucose level response behavior of the endocrine system (1) (variable $y(t)$). It is noted that in some patients, the administration of insulin dose through an appropriate program is difficult (Shabestari, Panahi et al., 2018). Furthermore, in such patients, using a combination of exercise program, timetabled insulin therapy, and scheduled nutrition is sure inadequate in confining plasma glucose level within the healthy range. For these reasons, the interaction irregularity of the glucose–insulin cannot be ignored and must be taken into consideration (Molnar, GD, WF, & AL, 1972; Shabestari, Panahi et al., 2018).

3. Control design

Synergetic control methodology is a promising trend in control science based on the principle of directed self-organization (Kondratiev,

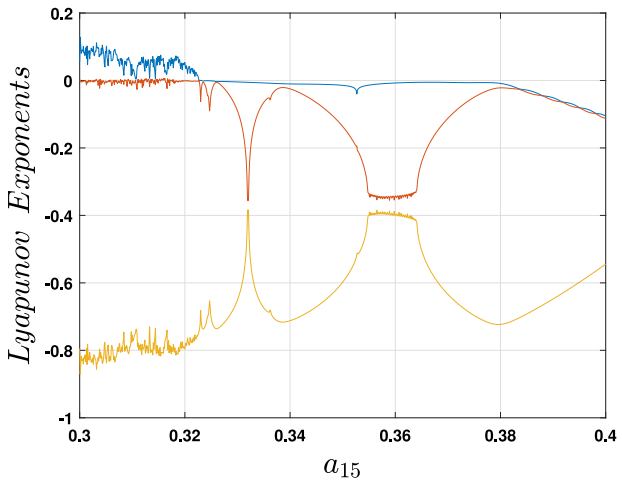

Fig. 3. The Lyapunov exponent diagram of system (1) with respect to the parameter a_{15}.

Dougal, Kolesnikov, & Veselov, 2001). The method found a particular application in nonlinear systems for solving complicated controlling problems. Synergetic control theory requires a comprehensive view of controlled system dynamic interactions between energy, matter and information being implemented using positive and negative feedback (Ahifar, Noee, & Rahmani, 2018).

The synergetic control framework is based on the foundation of expansion and contraction of the state space dynamics of the controlled system. It has a proper transient performance for the controlled system, which is an important requirement and challenge in modern controller designing in the nonlinear system control theory (Ahifar et al., 2019). Moreover, the synergetic controller is chattering free, the phenomena that restricts the practical usage of the sliding mode control theory because of its discontinuity.

The ensuing subsections, introduce the fixed-time synergetic controller that can steer aggregated macro variable to reach the specified invariant manifold within a constant upper bounded fixed-time. The controller designed to control the chaotic state in the glucose–insulin regulatory system, and effectively enhance the convergence rate of the model state variables.

3.1. Fixed-time stability theory

The control objective is to design a fixed time synergetic algorithm for system dynamics stabilization. The following required definitions are given:

Definition 1 (Ni, Liu, Liu, Hu, & Li, 2016; Wang, Liu, Liu, & Liu, 2019). Consider the following differential equation system with $x \in R$ and the nonlinear function $f(x) \in R$:

$$\dot{x} = f(x), \quad x(0) = x_0. \tag{3}$$

Assume the origin of (3) is an equilibrium point, then it is called a fixed-time stable provided that it is stable with bounded convergence time $T(x_0)$, that is $\exists T_{max} > 0$, such that: $\lim_{x_0 \to \infty}[T(x_0)] \le T_{max}$.

Lemma 1 (Ni et al., 2016; Wang et al., 2019; Zuo & Tie, 2016). *Consider the following differential equation system with $y \in R$:*

$$\dot{y} = -\alpha y^{m/n} - \beta y^{q/p}, y(0) = y_0 \tag{4}$$

where α and β are > 0, and all the parameters m, n, q, p are odd and positive numbers, satisfying $m/n > 1$, $0 < q/p < 1$. The convergence time of (4) for stabilizing to the origin is set to be $T(y_0)$, then y will converge to the origin within an upper bounded constant fixed-time $T_{max}(y)$, that is $\lim_{y_0 \to \infty}[T(y_0)] \le T_{max}(y)$, and

$$T_{max}(y) = \frac{1}{\alpha}\frac{n}{(m-n)} + \frac{1}{\beta}\frac{p}{(p-q)} \tag{5}$$

Lemma 2 (Wang et al., 2019). *Consider the following differential equation system with V is a positive definite function:*

$$\dot{V} = -\alpha_1 V^{\zeta_1} - \beta_1 V^{\zeta_2}, \quad V(0) = V_0 \tag{6}$$

where α_1, β_1 are positive real numbers, ζ_1 and ζ_2 are positive numbers such that satisfy $\zeta_1 > 1, 0 < \zeta_2 < 1$. The convergence time of V to stabilize to the origin is set to be $T(V_0)$, then V will converge to the origin within an upper bounded constant fixed-time $T_{max}(V)$, that is: $\lim_{V_0 \to +\infty}[T(V_0)] \le T_{max}(V)$ and

$$T_{max}(y) = \frac{1}{\alpha_1}\frac{1}{(\zeta_1 - 1)} + \frac{1}{\beta_1}\frac{1}{(1-\zeta_2)} \tag{7}$$

Proof. The proof of Lemma 2 is presented in Appendix A. □

3.2. Synergetic control design for the glucose–insulin regulatory system

Consider the following nonlinear system:

$$\begin{cases} \dot{x}_i &= x_{i+1}, \quad i = 1, 2, \dots, n-1 \\ \dot{x}_n &= f_n(x) + g_n(x)u \end{cases} \tag{8}$$

where $x \in R^n$ is the state variable vector of the system, $f_n(x) \in R$ represents a smooth nonlinear function describing the system dynamics, $g_n(x) \neq 0$ is the control gain function, and $u \in R$ is the input control.

In practice, the control vector, u necessary to be found based on synergetic control theory which ensures system dynamics movement from any initial state to invariant manifold and then toward the system (8) origin. The control designed is a function of special macro variable ψ which is called aggregated variables. These macro variables ψ are defined as a function of state variables of the dynamical system and should be chosen properly by designer and satisfy (Kolesnikov, 2014; Kondratiev, Santi, & Dougal, 2008):

$$T\dot{\psi} + \theta(\psi) = 0 \tag{9}$$

where T is a design parameter that specifies the convergence rate of the macro variable ψ to the invariant manifold $\psi(x,t) = 0$, and $\theta(\psi)$ is a smooth differentiable function of ψ that is chosen such that Kondratiev et al. (2008):

(1) invertible and differentiable;
(2) $\theta(0) = 0$;
(3) $\theta(\psi)\psi > 0, \forall \psi \neq 0$.

Lemma 3 (Wang et al., 2019). *If the function $\theta(\psi)$ is selected in the form of (10), then the $\theta(\psi)$ is satisfying previous conditions.*

$$\theta(\psi) = \psi^{(p_1/q_1)} + \psi^{(q_1/p_1)} \tag{10}$$

where the parameters q_1 and p_1 are odd number such that $q_1 > 0$ and $p_1 > 0$, and $0 < q_1/p_1 < 1$.

Proof. The proof of Lemma 3 is presented in Appendix B. □

Then according to Lemma 3, the aggregated macro variable dynamics can be written as follows:

$$T\dot{\psi} + \psi^{(p_1/q_1)} + \psi^{(q_1/p_1)} = 0 \tag{11}$$

Therefore, according to Lemma 1 and (11) the macro variable ψ converges in a fixed-time toward the invariant manifold $\psi(x,t) = 0$ and stays forever.

The convergence time, according to Lemma 1, is given by $T(\psi_0)$ and upper bounded by a constant, $\lim_{\psi_0\to\infty}[T(\psi_0)] \le T_{max}(\psi)$ such that:

$$T_{max}(\psi) = T\frac{(p_1+q_1)}{(p_1-q_1)}. \tag{12}$$

where p_1, q_1 and T are all design parameters selected such that the aggregated macro variable attracted to the invariant manifold as fast as required. From the viewpoint of the synergetic control theory, these parameters proportional to actions done by the forces of self-organization. Where the required self-organization speed can be obtained by appropriate selection for these parameters.

The object of the controller is to restore the state variables of the endocrine regulatory system (1) from a chaotic state to an equilibrium state and stabilize the system whole dynamics. This is will be implemented through controlling the insulin consecration as the manipulated variable, then the controlled system dynamics can be written as follows:

$$\begin{cases} \dot{x}(t) &= f_1 + u(t) \\ \dot{y}(t) &= f_2 \\ \dot{z}(t) &= f_3. \end{cases} \tag{13}$$

where

$$\begin{cases} f_1 &= -a_1x + a_2xy + a_3y^2 + a_4y^3 + a_5z + a_6z^2 \\ & \quad +a_7z^3 + a_{20} \\ f_2 &= -a_8xy - a_9x^2 - a_{10}x^3 + a_{11}y(1-y) - a_{12}z \\ & \quad -a_{13}z^2 - a_{14}z^3 + a_{21} \\ f_3 &= a_{15}y + a_{16}y^2 + a_{17}y^3 - a_{18}z - a_{19}yz. \end{cases}$$

and $u(t)$ is the injected insulin rate, with reference to the insulin basal level. let $x_1 = y - y_d$, where y is the glucose consecration level that represents the output variable of the controlled system, and y_d is the required glucose level, then the glucose dynamics can be written as follows:

$$\begin{cases} \dot{x}_1(t) &= x_2 \\ \dot{x}_2(t) &= f_4 + m_1u(t) \end{cases} \tag{14}$$

where

$$\begin{cases} f_4 &= m_1f_1 + m_2f_2 + m_3f_3 \\ m_1 &= -a_8y - 2a_9x - 3a_{10}x^2 \\ m_2 &= -a_8x + a_{11} - 2a_{11}y \\ m_3 &= -a_{12} - 2a_{13}z - 3a_{14}z^2 \end{cases}$$

Noting that the glucose concentration variable $y(t)$ has a relative degree of two with respect to control input $u(t)$, as can be observed in (14).

There are different methods to select the aggregated macro variable ψ, such that it guarantees the control objective of making the state variable of the controlled system (14) converge asymptotically to the origin, after entering the invariant manifold $\psi(x,t) = 0$. However, for the simplest method, consider the aggregated macro variable as a linear combination of the controlled system (14) states x_1 and x_2 as follows:

$$\psi = kx_1 + x_2 \tag{15}$$

where k is a positive parameter, obtains the convergence rate of the state variable of (14) to the origin. By substituting (15) into (11) and solve for the control input $u(t)$, it can be written in the following form:

$$u(t) = -\frac{1}{m_1}(f_4 + kx_2 + \frac{1}{T}(\psi^{q_1/p_1} + \psi^{p_1/q_1})) \tag{16}$$

Theorem 1. *For the system (14), if the control input is given by (16), then the selected aggregated variable (15) reaches the invariant manifold $\psi(x,t) = 0$ within a fixed-time.*

Proof. Consider the following Lyapunov candidate function V that is defined as follow:

$$V = \frac{1}{2}\psi^2 \tag{17}$$

Then the time derivative of Lyapunov function V, can be obtained as follows:

$$\begin{aligned} \dot{V} = \psi\dot{\psi} &= -\frac{1}{T}\left(\psi^{(q_1/p_1+1)} + \psi^{(p_1/q_1+1)}\right) \\ &= -\frac{1}{T}\left((2V)^{(\frac{p_1+q_1}{p_1})} + (2V)^{(\frac{p_1+q_1}{q_1})}\right) \end{aligned} \tag{18}$$

Let $W = 2V$, then (18) can be written as follows:

$$\begin{aligned} \dot{W} &= -\frac{2}{T}\left(W^{(\frac{p_1+q_1}{2p_1})} + W^{(\frac{p_1+q_1}{2q_1})}\right) \\ &= -\frac{2}{T}\left(W^{\gamma_1} + W^{\gamma_2}\right) \end{aligned} \tag{19}$$

where $\gamma_1 = \frac{p_1+q_1}{2p_1}$ and $\gamma_2 = \frac{p_1+q_1}{2q_1}$.

According to Lemma 2, and since $\gamma_1 > 1$ and $0 < \gamma_2 < 1$ in (19), then the functions W and V converge within fixed-time to zero, which forces the defined macro variable ψ to reach the invariant manifold $\psi(x,t) = 0$ within a fixed-time. The proof is completed. □

4. Simulation results

To illustrate the effectiveness of the designed controller, four scenarios have been presented. The controller parameters can be tuned using different optimization algorithms such as GA, PSO and many other methods. In this paper, the trial-and-error methodology is used to select the controller parameters, which is typically adopted by many scientific researchers. The parameters are tuned to achieve the best transient response and to satisfy the design objectives. The selected parameters are as follows $k = 5.7$, $T = 0.51$, $p_1 = 9$ and $q_1 = 7$. In the first scenario, the controller has been applied at the beginning of the simulation to stabilize the system dynamics as shown in Fig. 4, it is clear that the system dynamics move toward and settle down to the equilibrium point with good response time, the controller quickly steer the state variables movement to the invariant manifold in finite-time. Fig. 5, shows the time series of the insulin, glucose and β-cell, with proper transient response. The controller output is presented in Fig. 6 and it is chattering free and smooth signal. The glucose error is illustrated in Fig. 7. It is clear that the system reached the equilibrium in a sophisticated timing manner. The auxiliary variables x_1 and x_2 converge to the origin in a short time as shown in Fig. 8, consequently this forces the macro variable dynamics to reach the invariant manifold as it required.

The results demonstrate that even using the injected insulin as the only manipulated variable, the proposed synergetic controller successfully stabilizes the glucoregulatory system dynamics, compared to other type of controller as in Shabestari, Rajagopal, Safarbali, Jafari and Duraisamy (2018), where sliding mode controller based on integral sliding mode surface has been used to control the glucose–insulin system, the provided controller has three manipulated variables which are the insulin, glucose and the β-cells. This fact hinders the controller practical applicability and feasibility using single hormone artificial pancreas (SH-AP). On the other side, the proposed control strategy in this paper use one manipulated variable for regulating the glucose level to the normal range. This render the proposed controller more feasible to be implemented by the SH-AP for clinical applications.

In the second scenario, the system in the beginning behaves chaotically then the controller is applied at an arbitrary time point, the results of the system dynamics show that the trajectory leaves the chaos attractor and stabilizes to the equilibrium point as indicated in the red line in Fig. 9. So, even that the type 1 diabetic patient is suffering an uncontrolled glucose level which is difficult for common treatment

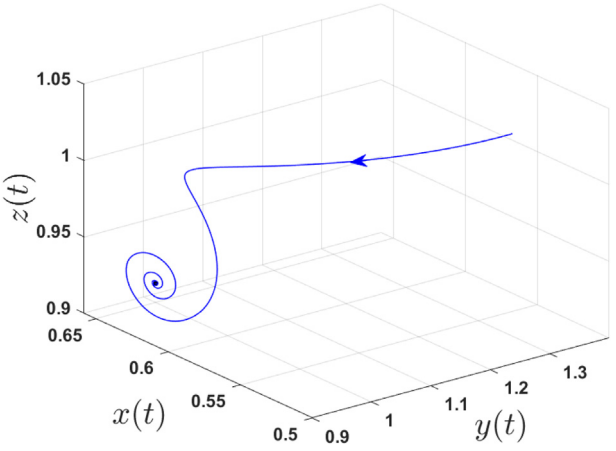

Fig. 4. System (1) phase portrait with control in action at $t = 0$.

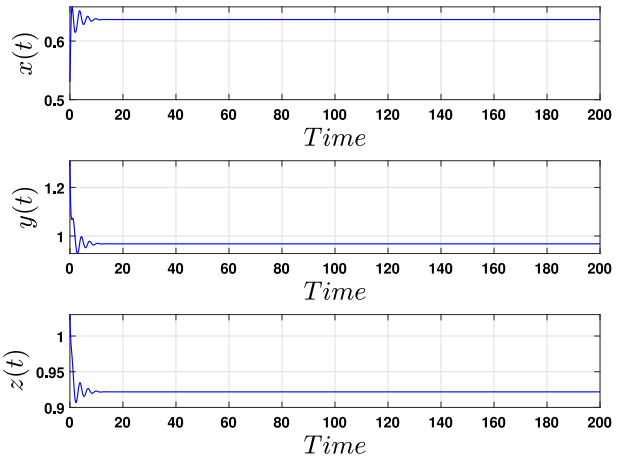

Fig. 5. Time series response of the system states with control in action at $t = 0$.

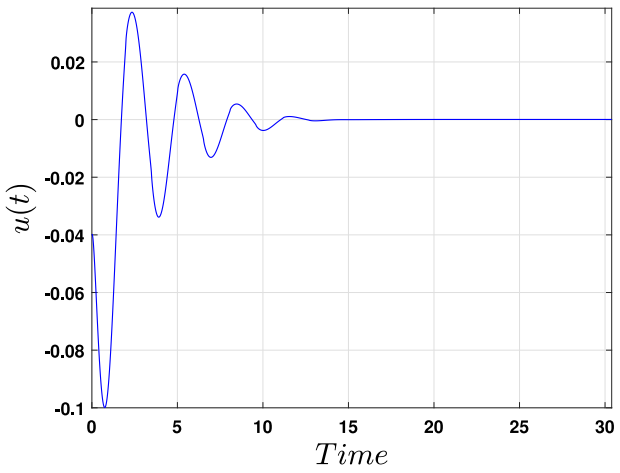

Fig. 6. The controller output signal with control in action at $t = 0$.

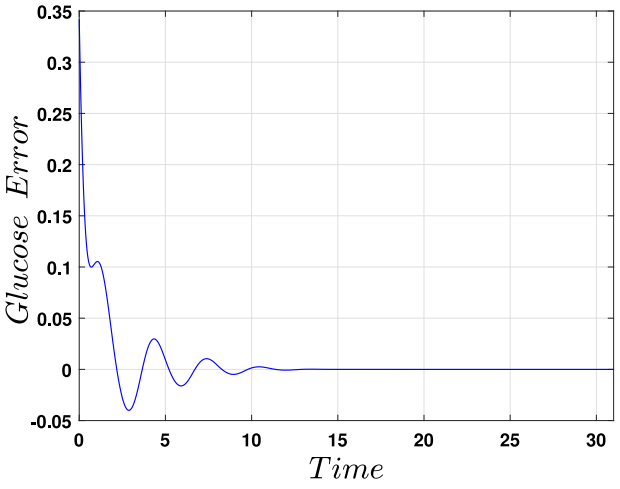

Fig. 7. Glucose error time series with control in action at $t = 0$.

methods to administrate proper insulin dose and overcome this biological disorder, the designed synergetic controller can successfully treat the disorder and confine the glucose level within a proper limit. The time series of the system variables are given in Fig. 10. The smooth output of the controller is shown in Fig. 11. The glucose error and the auxiliary variables x_1 and x_2 for the second scenario are illustrated in Figs. 12 and 13 respectively, the results reveal that the aggregated macro variable converge to the invariant manifold ultimately as fast as required. Moreover, the controller is applied on different realizations of the glucose–insulin chaotic system, to prove that the proposed approach performs well for various degrees of chaotic systems as shown in Figs. 14 and 15.

In the third scenario, to confirm the robustness of the proposed control algorithm against disturbances, the T1D patient is subjected to a three unannounced meals scenario with one unit, and one and half unit of carbohydrate (CHO). Unannounced meal mode is closer to the daily life style of the patient, and naturally, the controller synthesis for it also needs more concerns and challenges. This mismatched disturbance, can be modeled by a decaying exponential function in the following form $D(t) = A\exp(-Bt)$, $B > 0$ (Fisher, 1991). $D(t)$ represents the rate at which glucose is absorbed to the blood from the intestine, following food intake. The diabetic subject profile is shown in Fig. 16, where the meals glucose disturbances are given at time $t = 50$, $t = 100$ and $t = 150$. The figure shows the glucose concentration level and the control output. The results reveal the robustness of the proposed fixed time synergetic control algorithm against disturbances, where the blood glucose level returned to the required level within an acceptable time.

In the fourth scenario, when stressed or at emergency situation, the human body prepares itself by ensuring that enough sugar or energy is readily available. Epinephrine (commonly known as adrenaline) levels rise and more glucose is released from the liver, so that quickly increases the concentration of glucose in the blood (Kwach, Ongati, & Simwa, 2011). So, assume that the epinephrine released into the blood stream due to excitement, trauma and/or stress and let G_e be the amount of glucose production from the breakdown of glycogen due to epinephrine secretion. Then G_e increases the glucose concentration in the blood stream (Mohammed, Adamu, & Barka, 2019). G_e can be written as $G_e(t) = 0.3 \cdot [\varepsilon(t-80) - \varepsilon(t-120)]$, where ε is the unit step function. The patient profile at this situation under the proposed control algorithm is shown in Fig. 17, it is obvious that the proposed control approach successfully responds to the emergency situation effects and regulate the glucose level to the normal range.

To show the ability of the designed controller to vary the nature of the response oscillatory behavior and the convergence rate adjustment. The controller has been applied with different values for the parameter T, the results are given in Fig. 18. From Fig. 18 it is easy to find that the parameter T has opposite effect on the convergence speed and the oscillatory behavior. If T is big, the oscillator behavior be more evident. If T is small, the convergence speed can be accelerated.

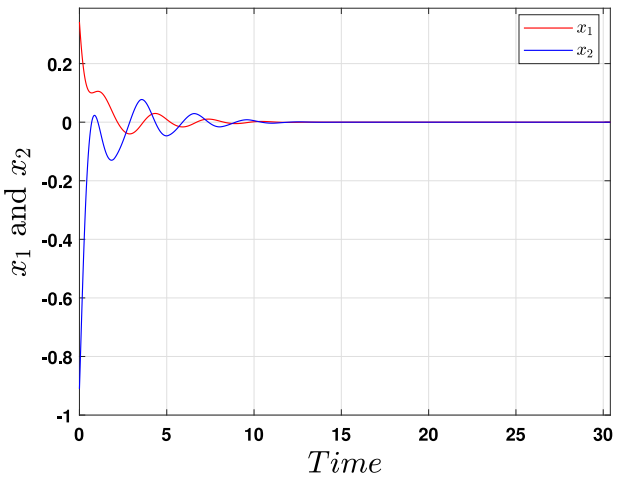

Fig. 8. The auxiliary variables time series with control in action at $t = 0$.

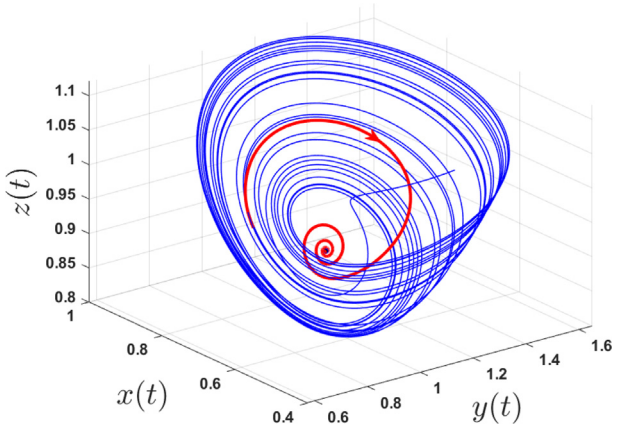

Fig. 9. System (1) phase portrait with control in action at $t = 99$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

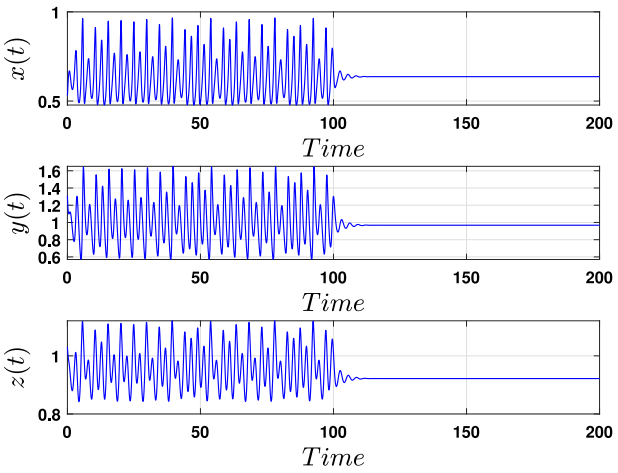

Fig. 10. Time series response of the system states with control in action at $t = 99$, where $a_{15} = 0.30$.

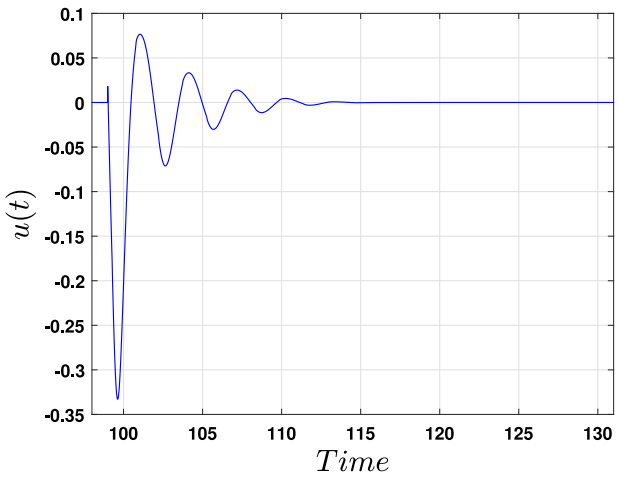

Fig. 11. The controller output signal with control in action at $t = 99$.

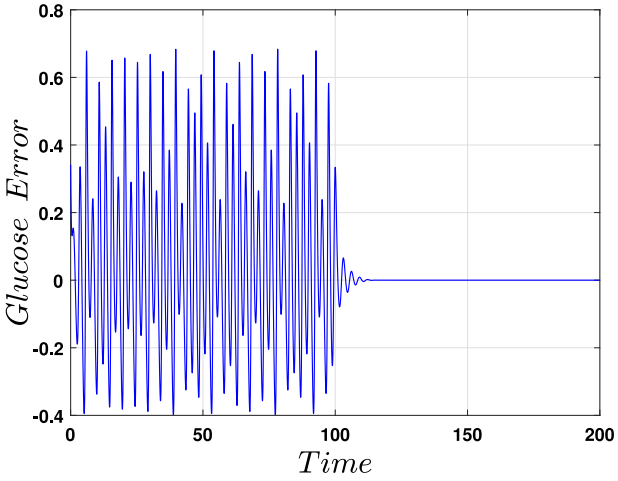

Fig. 12. Glucose error time series with control in action at $t = 99$.

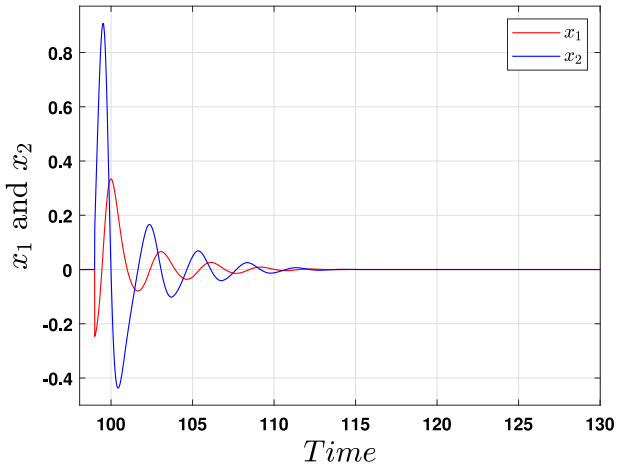

Fig. 13. The auxiliary variables time series with control in action at $t = 99$.

5. Conclusions

Chaotic oscillation suppression in the endocrine glucose–insulin regulatory system is an interesting research field for artificial pancreas development and diabetes therapy. Most of the current research works focus only on some simple endocrine regulatory models. This paper presents the investigation of the chaotic state and chaos control in a complex dynamics predatory–prey based glucose–insulin regulatory system model. Fixed-time stability theory has been exploited with the

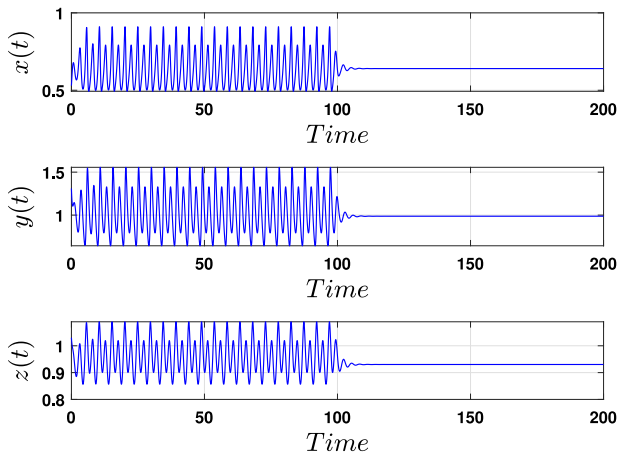

Fig. 14. Time series response of the system states with control in action at t = 99, where $a_{15} = 0.31$.

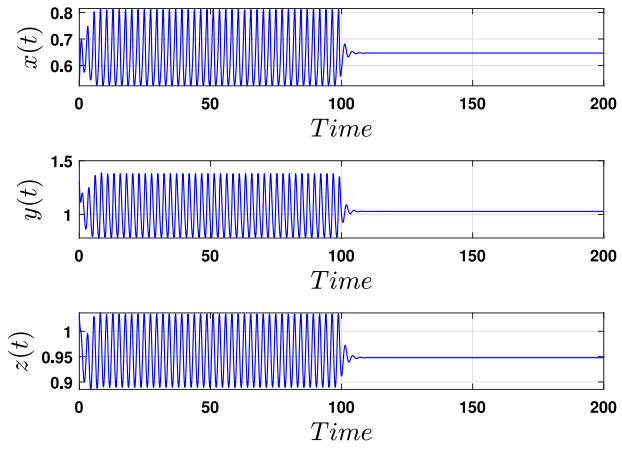

Fig. 15. Time series response of the system states with control in action at t = 99, where $a_{15} = 0.33$.

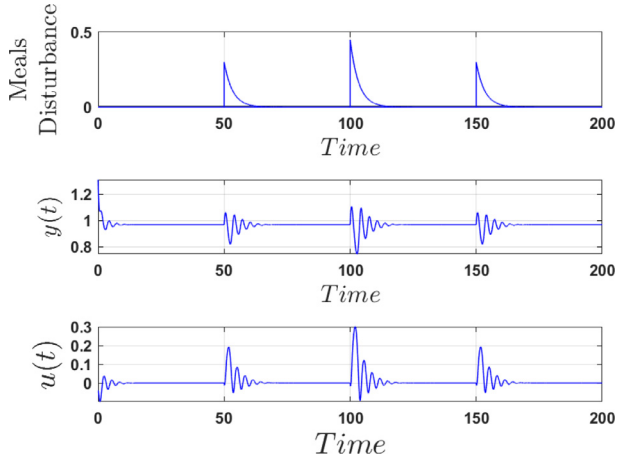

Fig. 16. The applied meals disturbances with the glucose level and the control output.

robust synergetic control method. The design of the aggregated macro variable is achieved to steer the controlled model dynamics toward the invariant manifold within a fixed-time. The convergence time is upper bounded by a constant, and not depends on the initial condition values of the system states. The convergence time can be determined by a proper selection of control parameters and can effectively accelerate

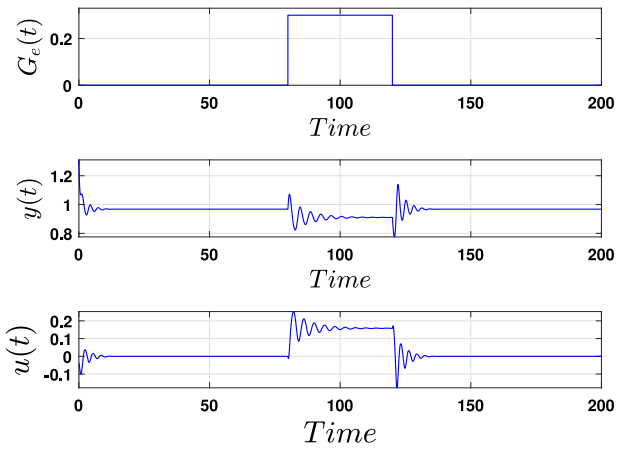

Fig. 17. Glucose production due to epinephrine secretion with the blood glucose level and the control output.

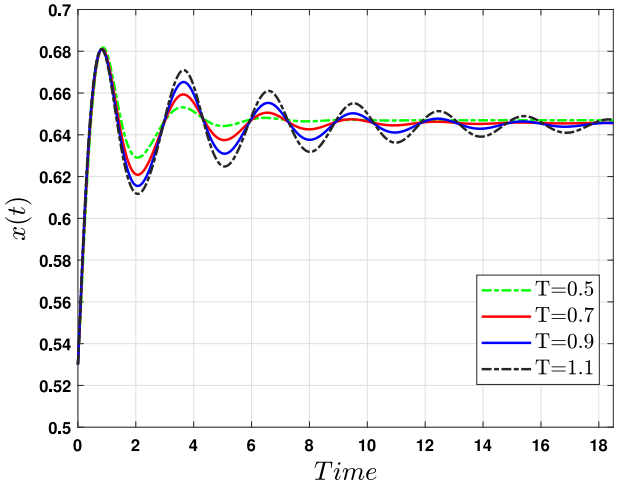

Fig. 18. Time series response of the insulin concentration with the variation of the controller parameter T and control in action at $t = 0$.

controlled system state variables convergence rate and modulate the controller aggressiveness. Four simulation scenarios have been presented to illustrate the effectiveness, superiority and robustness of the designed controller. Future work may be directed to investigate the practical implementation of the controller using artificial pancreas, and further development of the control algorithm to use bi-hormonal insulin and glucagon synthesis to tackle the problem of glucose–insulin hemostat.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Proof of Lemma 2

Proof. from (6), one can obtains that:

$$V^{-\zeta_2}\dot{V} = -\alpha V^{\zeta_1-\zeta_2} - \beta_1. \tag{20}$$

Let $r = V^{1-\zeta_2}$, then (20) can be changed to (21) as:

$$\dot{r} = (1-\zeta_2)\left(-\alpha_1 r^{1+\frac{\zeta_1-1}{1-\zeta_2}} - \beta_1\right) \tag{21}$$

The dynamic system (21) is converging from initial state r_0 to zero state in finite time $T(r_0)$. By integrating (21) as follows:

$$\frac{1}{(1-\zeta_2)}\int_{r_0}^{0}\frac{dr}{\alpha_1 r^{1+\mu}+\beta_1}=-\int_{0}^{T(r_0)}dt=-T(r_0). \tag{22}$$

where $\mu=\frac{\zeta_1-1}{1-\zeta_2}$ and then from (22), get:

$$\begin{aligned}
&\lim_{V_0\to\infty}[T(V_0)]\\
&\quad=\lim_{r_0\to\infty}[T(r_0)]\\
&\quad=\frac{1}{(1-\zeta_2)}\lim_{r_0\to\infty}\left[\int_0^{r_0}\frac{dr}{\alpha_1 r^{1+\mu}+\beta_1}\right].\\
&\quad=\frac{1}{(1-\zeta_2)}\left[\int_0^{1}\frac{dr}{\alpha_1 r^{1+\mu}+\beta_1}+\int_1^{\infty}\frac{dr}{\alpha_1 r^{1+\mu}+\beta_1}\right]\\
&\quad\le\frac{1}{(1-\zeta_2)}\left[\int_0^{1}\frac{dr}{\beta_1}+\int_1^{\infty}\frac{dr}{\alpha_1 r^{1+\mu}}\right]\\
&\quad=\frac{1}{\alpha_1}\frac{1}{(\zeta_1-1)}+\frac{1}{\beta_1}\frac{1}{(\zeta_1-2)}\\
&\quad=T_{max}(V)
\end{aligned}$$

The proof is completed. □

Appendix B. Proof of Lemma 3

Proof. (a) using (10), the derivative of $\theta(\psi)$ can be written as follows:

$$\dot{\theta}(\psi)=\frac{p_1}{q_1}\psi^{(p_1-q_1)/q_1}+\frac{q_1}{p_1}\frac{1}{\psi^{(p_1-q_1)/q_1}} \tag{23}$$

Since q_1 and p_1 are odd numbers, then (p_1-q_1) is even, therefore $\dot{\theta}(\psi)>0$, and then $\theta(\psi)$ in (10) is a monotone function. Therefore, $\theta(\psi)$ satisfies invertibility since it is monotonic function, which meets the first condition requirements.

(b) It is clear that $\theta(0)=0$ according to (10), and this is enough to prove the second condition.

(c) Using (10), the term $\theta(\psi)\psi$ can given as follows:

$$\theta(\psi)\psi=\psi^{\frac{p_1+q_1}{q_1}}+\psi^{\frac{p_1+q_1}{p_1}} \tag{24}$$

Since q_1 and p_1 are odd numbers, then their sum (p_1+q_1) is even number, therefore:

$$\theta(\psi)\psi>0,\quad \forall\psi\neq 0,$$

and this is meeting the requirements of the last condition.

The proof is completed. □

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