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A New Model For Endocrine Glucose-Insulin Regulatory System

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Abstract
To gain insight into complex biological endocrine glucose-insulin regulatory system where the interactions of components of the metabolic system and time-delay inherent in the biological system give rise to complex dynamics. The modeling has increased interest and importance in physiological research and enhanced the medical treatment protocols. This brief contains a new model using time delay differential equations, which give an accurate result by utilizing two explicit time delays. The bifurcation analysis has been conducted to find the main system parameters bifurcation values and corresponding system behaviors. The results found consistent with the biological experiments results.
KEYWORDS: Endocrine Regulatory System, Glucose-Insulin, Bifurcation Analysis, Modeling, Time-Delay.

I. INTRODUCTION

Diabetes Mellitus (DM) which is commonly known as diabetes is one of the most widespread chronic disease that the world face nowadays. The number of subjects with diabetes in the world is increasing continuously every year. International Diabetes Federation (IDF) estimates that 436 million people around the world live with diabetes corresponding to 1-11 of the 20-79 adult population. The figure is expected to hit the 700 million people in 2045 [1]. Diabetes in fact resulting from malfunctioning in the plasma glucose-insulin kinetics, causing abnormal high plasma sugar levels known as hyperglycemia. Moreover, due to increasing interest in the development of the artificial pancreas, the mathematical modeling of the human endocrine glucose-insulin regulatory system gained much focus and attracted more scientific research to mimic the expected mechanism of the endocrine system and determine the underlying reasons of diabetes mellitus. Knowledge of these models provide a safe and efficient control algorithm of the plasma glucose level and enhances control devices, which relieve the diabetic subjects. These reasons motivated the investigation of mathematical models, which may mimic this biological process. Thus, investigating the mathematical model is of great importance theologically and practically. Both, the theoretical investigation and numerical computation of the endocrine glucose-insulin regulatory system might enhance the medical treatment protocols and enrich the medical insight [2]. Blood glucose level is regulated through a negative feedback loop where hyperglycemia incites a rapid increase in insulin secreted from the β-cell in the pancreas. The increase in the plasma insulin level causes increased glucose uptake and decreases glucose production by the liver and leads to reduction in plasma glucose [3]. Where, this feedback loop keeps the glucose concentration in the human body within a narrow range following an overnight fast (70-109 mg/dl), and it is known that the basal blood insulin is in the range of (5-10 µU/ml) [4] and it might be in a wider range (10-40 µU/ml) during continuous enteral nutrition [5], and at meal ingestion and high glucose level reach (30-150 µU/ml) [4].

Two types of oscillation in human glucose-insulin interaction have been observed [6], with two different periods, a rapid (10-15 min) and slow or ultradian about (100-150 min). The cause of the ultradian oscillation in human body may be entirely originated by the dynamic interaction of glucose-insulin negative feedback regulatory system [6]. This oscillation already detected in human body at different physiological situations: After meal ingestion [7], glucose oral intake [8], through continuous enteral nutrition [9] and during constant glucose intravenous infusion [10]. These different oscillation patterns are given in Fig. (1) adapted from Sturis 1991 [6].
Many other biological experiments have shown that the insulin secretion from β-cell in the pancreas has an oscillatory behavior [9], where the periodic secretion of hormones are more effective than other types of stimuli such as constant or stochastic [11]. This field of vigorous interdisciplinary research came into being with the
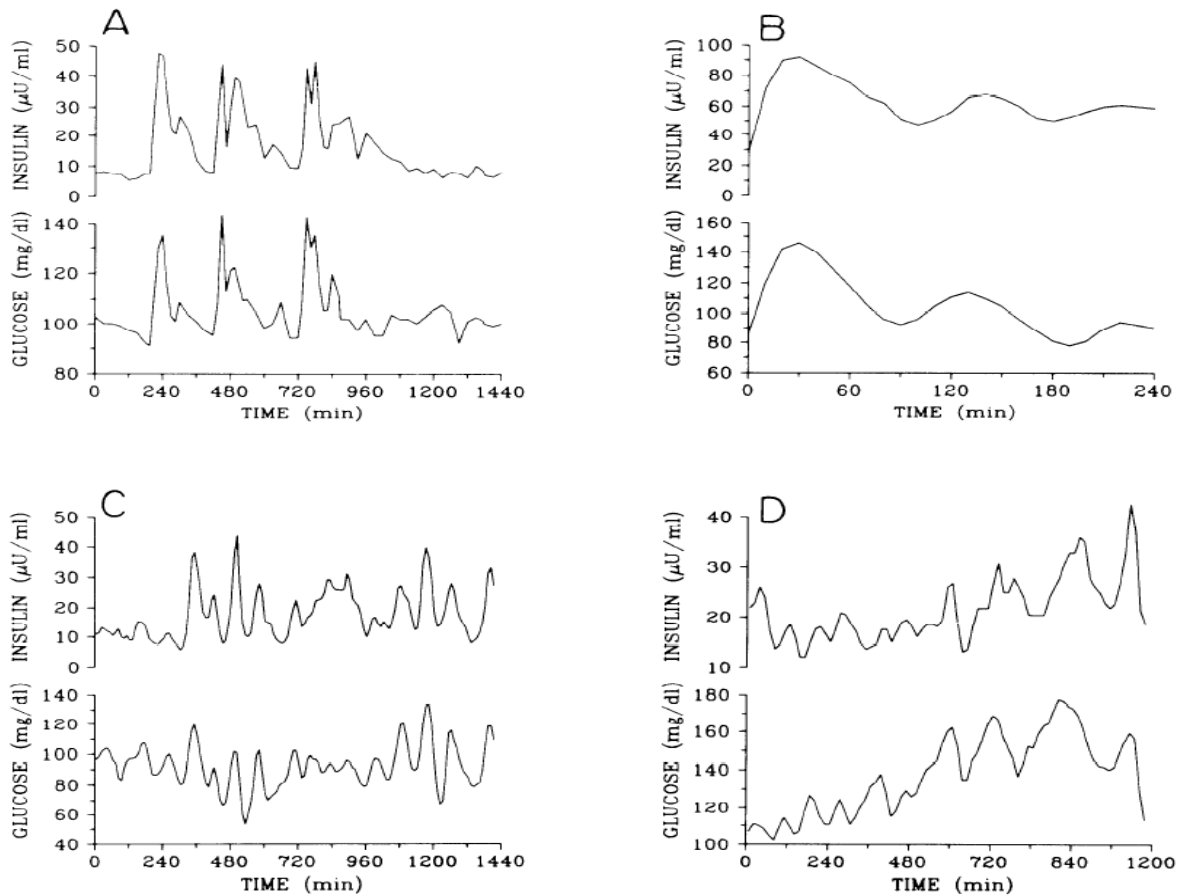
Fig. 1 Oscillation of insulin and glucose observed during: (A) ingestion of three meals; (B) during oral glucose; (C) during continuous enteral nutrition; (D) during constant glucose infusion. These profiles are from 4 different subjects. Data smoothed with 2-point moving average. Adapted from Sturis [6].

pioneering works of Bergman and his co-workers [12,13]. In 1991 Sturis [6] suggested a mathematical model consisting of six nonlinear differential equations to describe the glucose-insulin ultradian oscillation, at different glucose feeding and showed that the feedback mechanism is the underlying source of sustained oscillation however, the model includes three non-observable auxiliary variables. Topp et al. [3] incorporated the β-cell in the model in addition to the glucose and insulin concertation level, the model has two stable fixed points representing physiological and pathological steady states. Engelborghs in 2001 [14], provided a bifurcation analysis of the periodic solution of the delay differential equations system represent the glucose-insulin metabolic system, with discrete time delay. Incorporating explicitly two time delays is presented in [15] the resulting system consists of three delay differential equations with proven positiveness, stability and stability using Lyapunov function method. Jiaxu Li [16] proposed robust model for endocrine metabolic regulatory system and showed the ultradian oscillation with time delay. Two compartments model for both glucose and insulin variables and incorporating two time delays explicitly is presented in [17], their model focuses on the importance of the subcutaneous tissues glucose and insulin concertation levels. Strike in 2018 [18] provided a qualitative numerical study of

glucose dynamics in patients with stress hyperglycemia and diabetes receiving intermittent and continuous enteral feeds. Amit [2] proposed a smooth approximation of the minimal model, with linear feedback-based control algorithm.

In this paper, we proposed a time delay differential equation model to represent the metabolic endocrine glucose-insulin regulatory feedback system, two time delays have been incorporated explicitly in the model for better and more accurate representation of the biological system. The model has been analyzed through stability and Hopf bifurcation analysis. The effects of varying multiple parameters in the system model are presented and different system behaviors are captured. The paper organized as follow, section II includes the mathematical model analysis, Sec. III presents the simulation results and Sec. IV shows the final conclusions and future work.

II. THE MODEL

The main elements in the glucose-insulin metabolic regulator system are shown in the schematic diagram illustrated in Fig. (2). The delay differential equations have been used in the model to simulate the finite time response of the pancreas (to release insulin) and the liver (to secrete glucose) to changing conditions managed by the glucose insulin regulatory
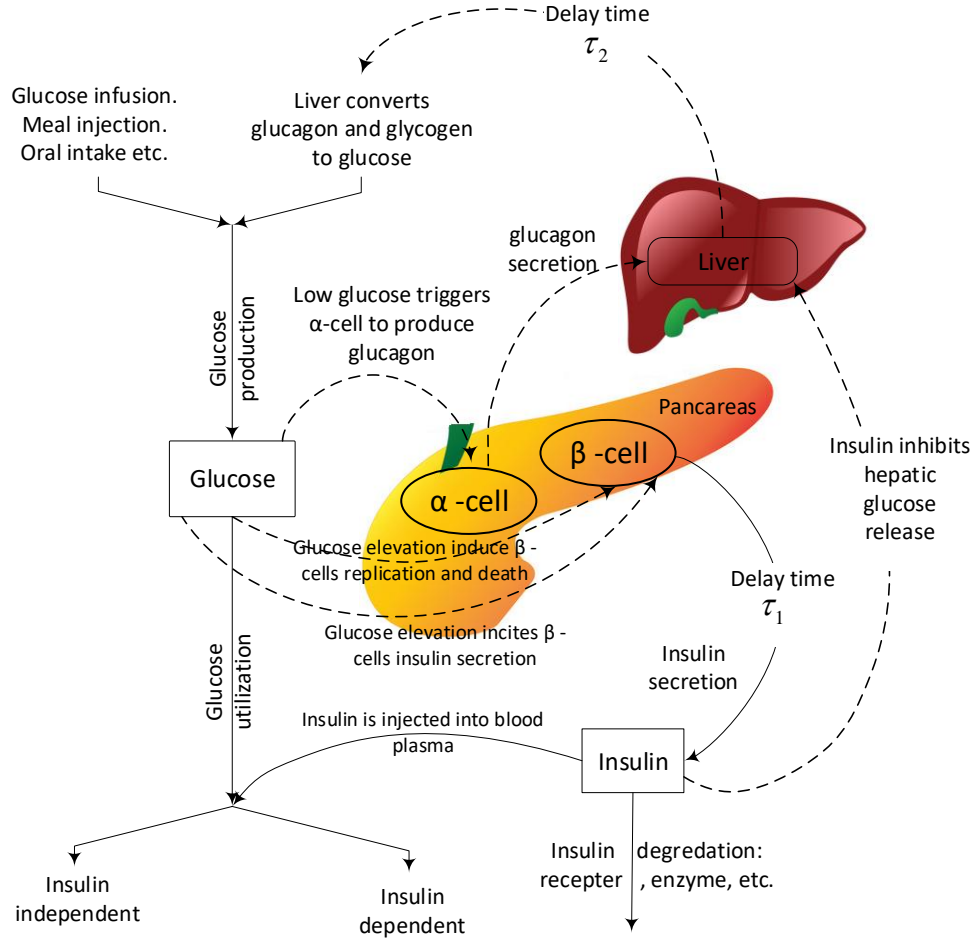
Fig. 2 A schematic diagram for glucose-insulin regulatory system.

system. The principle of mass conservation can be described as follows:

$$\dot{G}(t) = G_p(t) - G_u(t)$$
$$\dot{I}(t) = I_p(t) - I_u(t) \qquad (1)$$

where it was employed to derive the glucose insulin dynamic equations.

The equations depict the rate of change of the glucose concentration, $\dot{G}(t)$ and the rate of change of the insulin concentration, $\dot{I}(t)$, which should equal its amount produced minus the amount cleared. The glucose production, $G_p(t)$, glucose utilization, $G_u(t)$, insulin production, $I_p(t)$, and insulin clearance, $I_c(t)$, are defined by a set of highly non-linear functions (f_1 through f_6):

$$G_p(t) = G_{in}(t) + f_5\big(I(t - \tau_2)\big)$$
$$G_u(t) = f_2\big(G(t)\big) + f_3\big(G(t)\big)f_4\big(I(t)\big)$$
$$I_p(t) = I_{in}(t) + f_1\big(G(t - \tau_2)\big)$$
$$I_c(t) = -d_i I(t) - d_i f_6\big(G(t)\big)f_7\big(I(t)\big) \qquad (2)$$

$$f_1(G) = R_m/\left(1 + e^{\left((C1 - G/V_g)/a_1\right)}\right),$$
$$f_2(G) = U_b\left(1 - e^{\left(-G/(C_2 V_g)\right)}\right),$$
$$f_3(G) = G/\big(C_3 V_g\big),$$
$$f_4(I) = U_0 + (U_m - U_0)$$
$$/\left(1 + e^{-\beta ln\left(I/C_4\left(1/V_i + 1/(Et_i)\right)\right)}\right) \qquad (3)$$
$$f_5(G) = R_g/\left(1 + e^{\left(\alpha\,(I/V_p - C_5)\right)}\right),$$
$$f_6(G) = G\ /\big(C_3 V_g\big),$$
$$f_7(I) = I/\big(10\ V_p\big).$$

The functions f_i where $i = 1, 2, 3, \dots 5$, which derived directly from human physiologic data [11,16], and f_6 and f_7 are used to represent the insulin degradation which depends on glucose, they determine the various components of the glucose-insulin regulatory system; the purpose of each function is mentioned in Table 1 . Note that $G_{in}(t)$ denotes the glucose absorption from either enteral nutrition or an intravenous source. The $I_{in}(t)$ term represents insulin absorption from exogenous source, in this work, it is considered no exogenous insulin infusion. The time delay of the endogenous insulin secretion and the time delay

Table 1 Model Functions Description

Function Name	Description
$f_1(G)$	Insulin release by pancreas.
$f_2(G)$	Insulin-Independent glucose utilization.
$f_3(G)f_4(I)$	Insulin-dependent glucose utilization.
$f_5(G)$	Hepatic glucose production.
$f_6(G)f_7(I)$	Glucose-dependent insulin degradation.
$G_{in}(t)$	Nutritional source.
$I_{in}(t)$	Exogenous insulin

represented endogenous glucose release are denoted by τ_1 and τ_2 respectively. In order to investigate the effect of system parameters on the stability of the system and the possibility of periodic behavior of the system dynamics, the analysis will be as follows:

$$\dot{x}(t) = f(x(t), x(t - \tau_1), x(t - \tau_2), \theta) \tag{4}$$

where $x(t) \in \mathbb{R}^n$, $f: \mathbb{R}^{n*(m+1)} \times \mathbb{R}^k \to \mathbb{R}^n$ and $\theta \in \mathbb{R}^k$. The solution of (4) is not unique function of $x(t)$ at fixed time point due to the dependence on the past history. So, instead the initial solution should be specified over an interval of time length τ such that $\tau = max_{i=1,2,...m}\{\tau_i\}$. Then the initial function segment belongs to $= C([-\tau, 0], \mathbb{R}^n)$, the infinite dimensional space function mapping the delay interval $[-\tau, 0]$ into $\mathbb{R}^n$.

The equilibrium solution $x(t) \equiv x^* \in \mathbb{R}^n$ of (4) can be evaluated as a solution of the nonlinear system:

$$f(x_1^*, x_2^*, \theta) = 0 \tag{5}$$

It is worth noting that x^* does not depend on the time delay values, but the stability of the steady state solution x^* depends on the time delays. To find the stability, the system (4) linearized about x^* to obtain the variational equation as follows:

$$\dot{y}(t) = J_0(x^*, \theta)y(t) + \sum_{i=1}^{m} J_i(x^*, \theta)y(t - \tau_i), \tag{6}$$

where

$$J_i(x^*, \theta) = \frac{\partial f}{\partial x_i}(x^*, \theta), i = 0,1,2,...,m. \tag{7}$$

Then, the characteristic matrix can be written as follows:

$$\Lambda(\lambda) = \lambda I - J_0(x^*, \theta) + \sum_{i=1}^{m} J_i(x^*, \theta)e^{-\tau_i\lambda} \tag{8}$$

The eigenvalues of (8) can be found by solving the transcendental polynomial equation:

$$det(\Lambda(\lambda)) = 0 \tag{9}$$

where (9) has an infinite number of roots λ that give the stability of the steady state solution x^*.

Which mean that all the roots should be in the left hand side, and it is unstable otherwise. To ensure the bifurcation of the steady state solution with changing some biological parameter θ, then the eigenvalues should cross the imaginary axis not through the real axis. Therefore, a periodic solution arises at the bifurcation point. Assuming that the system (1) has a steady state $x^* = (G^*, I^*)$ then the transcendental characteristic equation (9) can be written as follows:

$$\lambda^2 + A_1\lambda + A_2 + A_3 e^{-\lambda(\tau_1+\tau_2)} + A_4 e^{-\lambda(\tau_1)}$$
$$+ A_5 e^{-\lambda(\tau_2)} = 0 \tag{10}$$

where
$A_1 = -a_1 - a_4,$
$A_2 = a_1a_4 - a_2a_3,$
$A_3 = -f_1'(G^*)f_5'(I^*),$
$A_4 = -a_2 f_1'(G^*),$
$A_5 = -a_3 f_5'(I^*),$
with
$a_1 = -f_2'(G^*) - f_3'(G^*)f_4'(I^*),$
$a_2 = -f_3'(G^*)f_4'(G^*),$
$a_3 = -d_i f_6'(G^*)f_7(I^*),$
$a_4 = -d_i - d_i f_6(G^*)f_7'(I^*).$

Then the steady state solution x^* loses its stability as the eigenvalue real part become positive. So, the stability boundary where $\lambda = j\omega$, $\omega \in \mathbb{R}^+$ can be obtained by

$$\frac{-\omega^2 + jA_1\omega + A_2 + A_5 e^{-j\omega\tau_2}}{-A_4 - A_3 e^{-j\omega\tau_2}} = e^{-j\omega\tau_1} \tag{11}$$

So, the solution of the equation (11) can be found by intersection of the two curve the first is $e^{-j\omega\tau_1}$ that is scanned repeatedly as increasing $\omega\tau_1$. The second curve is the ratio curve given by (12) as shown below:

Which scanned once as ω increase from 0 to ∞. This curve

$$\frac{A_4\,\omega^2 - A_2A_4 - A_3A_5 - (A_4A_5 + A_3(A_2 - \omega^2)\,cos\,(\omega\tau_2) + A_1A_3\,sin(\omega\tau_2)}{A_3^2 + A_4^2 + 2A_3A_4cos(\omega\tau_2)}$$
$$+ j\frac{-A_1A_4\omega + (A_4A_5 - A_3(A_2 - \omega^2))sin(\omega\tau_2) - A_1A_3\omega cos(\omega\tau_2)}{A_3^2 + A_4^2 + 2A_3A_4cos(\omega\tau_2)} \tag{12}$$

start at the point $-(A_2 + A_5)/(A_3 + A_4)$ for $\omega = 0$, then growth toward the ∞ as $\omega \to \infty$, and making a spiral around the point $-(A_2 + A_5)/(A_3 + A_4)$. The spiral form and number of intersections with the unit circle change depending on the parameter values.

Table 2 System (1) Parameters

Parameter	Value	Unit
V_g	10	l
R_m	210	mU min^{-1}
a_1	300	mgl^{-1}
C_1	2000	mgl^{-1}
U_b	72	mg min^{-1}
C_2	144	mgl^{-1}
C_3	1000	mgl^{-1}
V_p	3	l
V_i	11	l
E	0.2	l min^{-1}
U_0	40	mg min^{-1}
U_m	940	mg min^{-1}
β	1.77	
C_4	80	mU l^{-1}
R_g	180	mg min^{-1}
α	0.29	lmU^{-1}
C_5	26	mU l^{-1}
t_p	6	min
t_i	100	min
t_d	36	min

III. SIMULATION RESULTS

Extensive numerical simulation for the system (1) has been implemented for the system parameters given in Table 2 to capture the variety of system dynamics and behaviors. Fig. (3) and Fig. (4) show the time courses of the glucose and inulin variables and the corresponding steady state phase portrait, which show clearly a limit cycle, for two different sets of parameters which show clearly that the proposed model ensures sustain oscillation and robust performance for wide range of time delay. To demonstrate the system dynamics and the evolution of the solutions, four parameters will be changed consequently to reveal the Hopf bifurcation dynamics. The parameters that will be chosen are the two time delay (τ_1 and τ_2) and the exogenous glucose infusion rate G_{in} and the insulin degradation rate d_i. Fig. (5) shows the bifurcation diagram and phase portrait for range of values of $\tau_1 \in [0, 20]$. It is clear that the bifurcation point is at $\tau_{1_h} = 2.55\ min$ and the amplitude of both variable in this case in the accepted range and consistence with the biological finding [6,11,16].
Sustained oscillation can be observed in the range $\tau_1 \in [2.55, 20]$. Fig. (6) shows the period variation with respect to the time delay where oscillation period in the range $[98, 145]$ and agree with the experiments. Fig. (7) depicts the bifurcation diagram and phase portrait for range of values of $\tau_2 \in [0, 40]$. It is clear that the bifurcation point is at $\tau_{2_h} = 6\ min$ and the amplitude of both variables in this case in the accepted range and consistent with the biological finding [6,11,16]. Fig. (8) shows the period variation with respect to the time delay is in the range $[97, 163]$ is agree with the

experiments. To investigate the effect of the glucose infusion rate G_{in} on the system behavior, the rate has been changed from 0 to 1.5 mg/dl/min, as shown in Fig. (9), the dynamics bifurcate at $G_{in_h} = 1.275$ mg/dl/min, and the system is periodic for $G_{in} < G_{in_h}$ and asymptotically stable otherwise, in other word if the exogenous glucose infusion rate is greater than the initial glucose level the glucose concertation level returns to the basal level in a definite time [19]. The corresponding period is shown in Fig. (10), the period is slightly decreasing with changing the exogenous glucose infusion rate.
Finally, the effect of the insulin degradation rate is shown Fig. (11) where degradation rate has been changed in the range $d_i \in [0.01, 0.12]$ a bifurcation point is found to be $d_{i_h} = 0.026$ where the dynamic is periodic when the insulin degradation rate above d_{i_h} and the period is monotonically decreasing as shown in Fig. (12).

IV. CONCLUSION

The modeling of the biological system is an important approach to understand the complexity of the systems, and it gives an important tool to reveal the hidden dynamics of the biological processes. As shown in the results, the slight change in the system parameter can give rise for variety of dynamics and the oscillation and periodic solution can emanate at certain bifurcation point, this behavior should be considered with much attention biologically where it enriches the medical insight about the endocrine metabolic glucose-insulin regulator feedback system which have a complex behavior. More biological facts and factors can be incorporated within the mathematical model such as the stress effect, glucagon, human state and the dynamics of the β-cell and other components of the endocrine system.

CONFLICT OF INTEREST

The authors have no conflict of relevant interest to this article.

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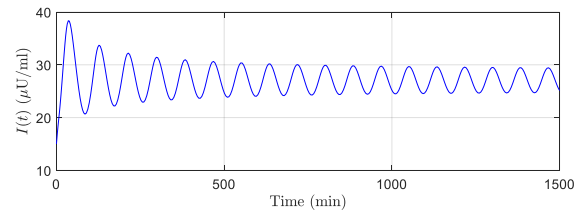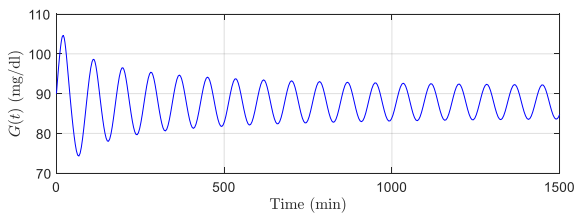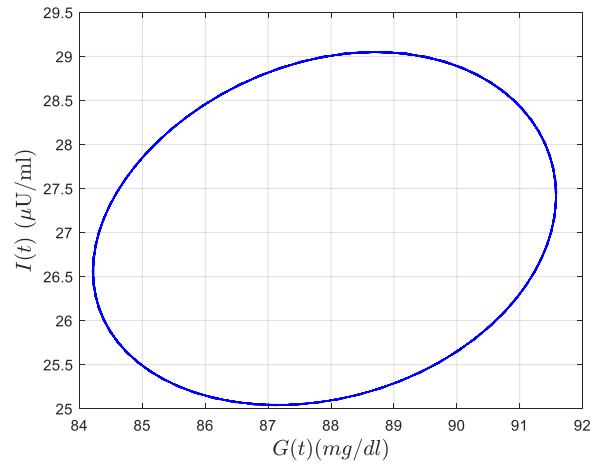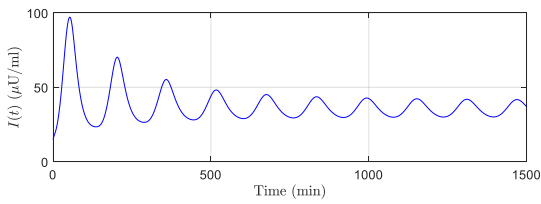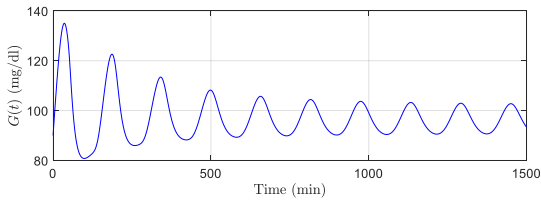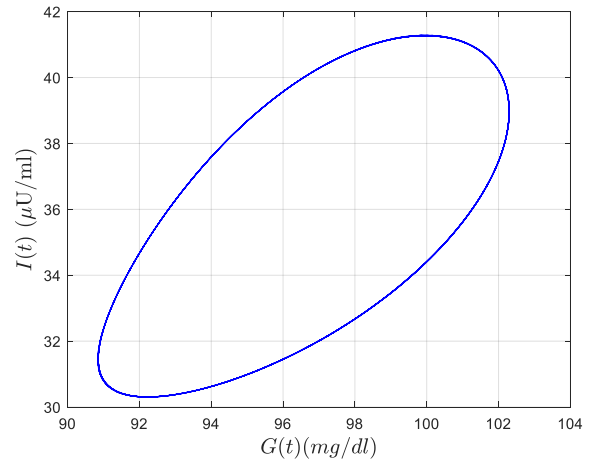
A   B

Fig. 3 System response: (A) time series at $\tau_1 = 6\ min, \tau_2 = 4.5\ min, G_{in} = 0.54\ and\ d_i = 0.06$; (B) Phase portrait.
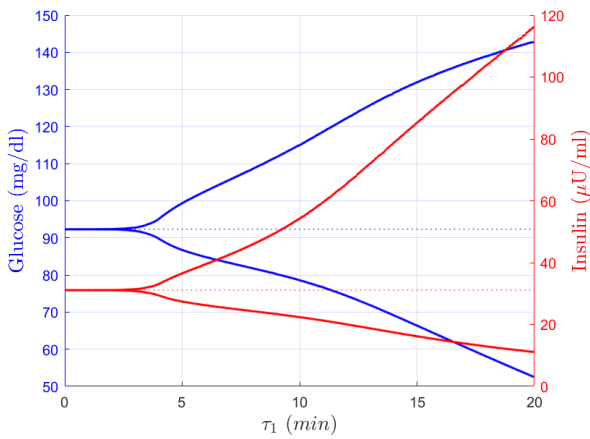

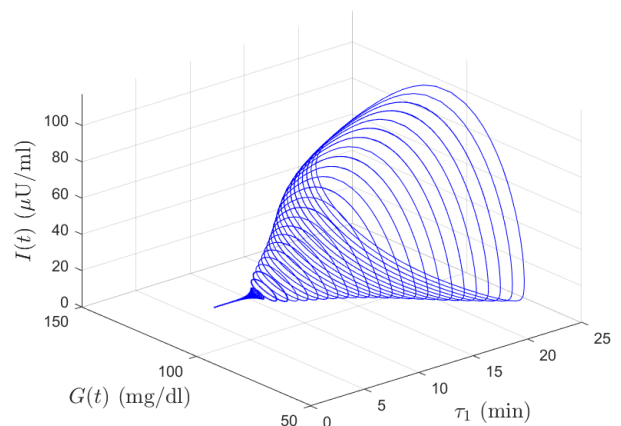A   B

Fig. 4 System response: (A) time series at $\tau_1 = 6\ min, \tau_2 = 36\ min, G_{in} = 1.35$ and $d_i = 0.06$; (B) Phase portrait.

A   B

Fig. 5 Hopf bifurcation with τ_1: (A) Bifurcation diagram; (B) Phase portrait. $\tau_2 = 12\ min, G_{in} = 1.08$ and $d_i = 0.06$.
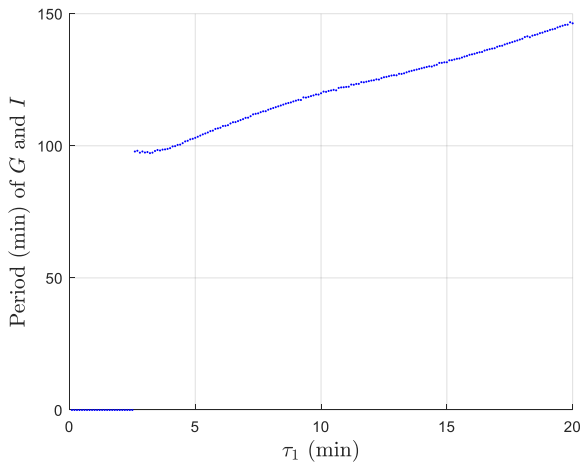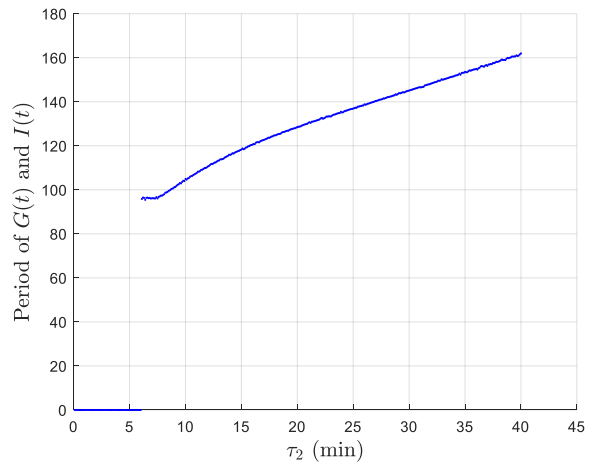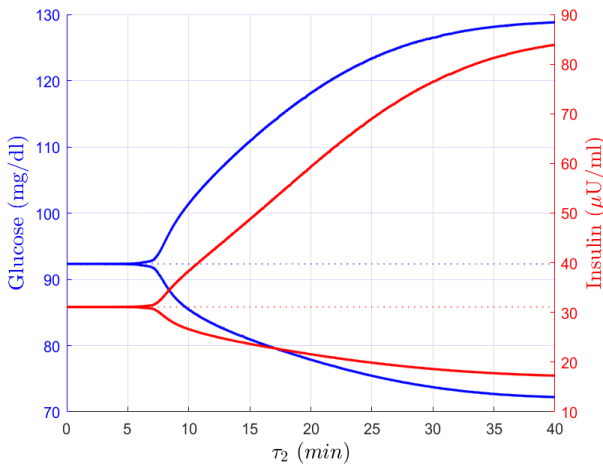
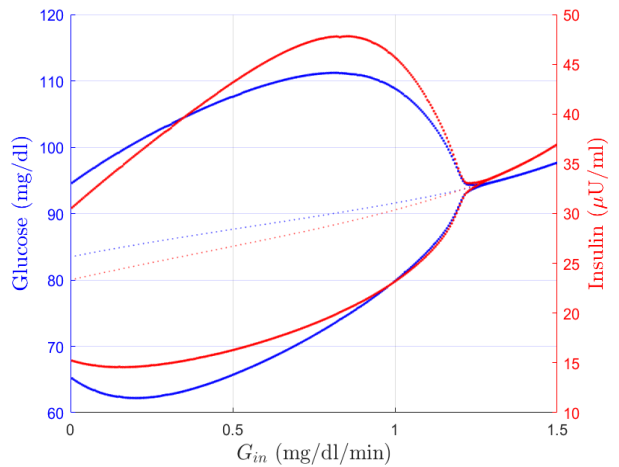Fig. 6 Period of the solution.
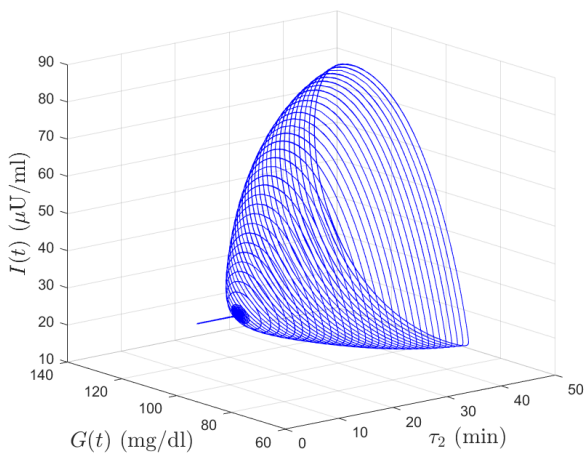

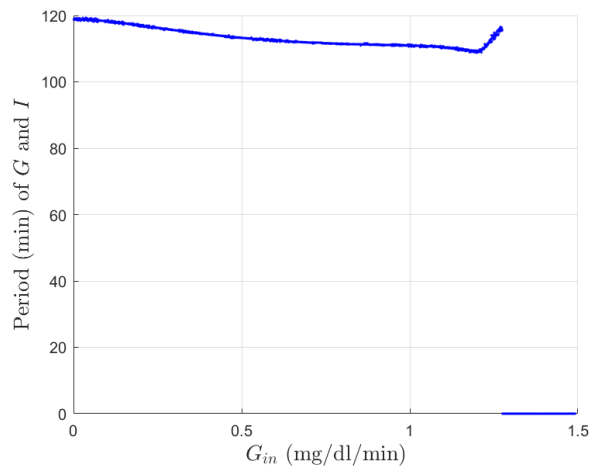Fig. 8 Period of the solution.

A

Fig. 9 Bifurcation diagram.

B

Fig. 7 Hopf bifurcation with τ_1: (A) Bifurcation diagram; (B) Phase plane portrait. $\tau_1 = 7\ min, G_{in} = 1.08$ and $d_i = 0.06\ min^{-1}$.
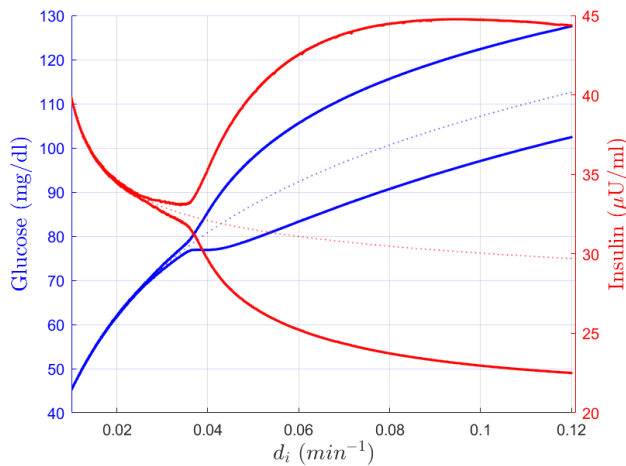

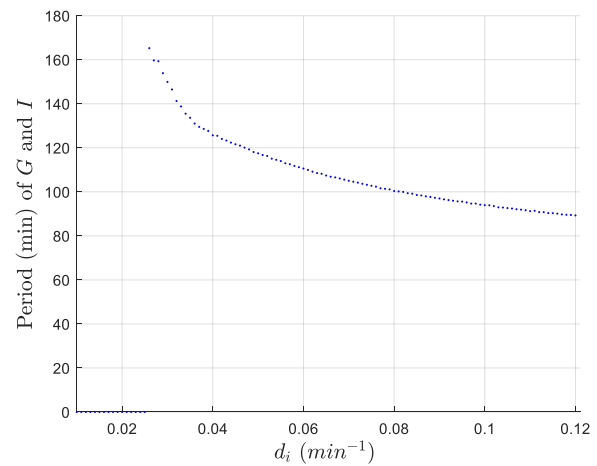Fig. 10 Period of the solution.

Fig. 11 Bifurcation diagram with d_i.

Fig. 12 Period of the solution.

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