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# Modeling the glucose–insulin regulatory system and ultradian insulin secretory oscillations with two explicit time delays

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**Abstract**

In the glucose–insulin regulatory system, ultradian insulin secretory oscillations are observed to have a period of 50–150 min. After pioneering work traced back to the 1960s, several mathematical models have been proposed during the last decade to model these ultradian oscillations as well as the metabolic system producing them. These currently existing models still lack some of the key physiological aspects of the glucose–insulin system. Applying the mass conservation law, we introduce two explicit time delays and propose a more robust alternative model for better understanding the glucose–insulin endocrine metabolic regulatory system and the ultradian insulin secretory oscillations for the cases of continuous enteral nutrition and constant glucose infusion. We compare the simulation profiles obtained from this two time delay model with those from the other existing models. As a result, we notice many unique features of this two delay model. Based on our intensive simulations, we suspect that one of the possibly many causes of ultradian insulin secretion oscillations is the time delay of the insulin secretion stimulated by the elevated glucose concentration.


*Keywords:* Glucose–insulin regulatory system; Insulin secretion; Ultradian oscillation; Time delay; Delay differential equation model

## 1. Introduction

It is well known that the human body needs to maintain its glucose concentration level within a narrow range following an overnight fast (70–109 mg/dl). In the glucose–insulin regulatory system, elevated glucose concentration level incites the $\beta$-cells in the pancreas to secrete insulin, helping to return the glucose concentration to normal levels. As the glucose concentration level decreases, the secretion stops gradually. For a normal subject, after an overnight fast, the basal plasma insulin is in the range of 5–10 μU/ml (Ahren and Taborsky, 2002). It can be as wide as 10–40 μU/ml during continuous enteral nutrition (Simon and Brandenberger, 2002, Fig. 2) and as large as 30–150 μU/ml during meal consumption while the glucose concentration level is high (Ahren and Taborsky, 2002). If the human pancreas does not release sufficient insulin or the insulin does not trigger cells to utilize the glucose in the plasma and inhibit hepatic glucose production, diabetes mellitus is likely to develop (Bergman et al., 2002).

Diabetes mellitus is a disease with considerable complications which include retinopathy, nephropathy, peripheral neuropathy and blindness (Derouich and Boutayeb, 2002). Also noteworthy is the growing size of the affected population, with extreme incidence rates occurring among Native Americans (http://diabetes.niddk.nih.gov/dm/pubs/americanindian). Ever increasing high health-related expenses also highlight the seriousness of the condition (http://www.diabetes.org). Due to these factors, many researchers have been motivated to study the glucose–insulin endocrine metabolic regulatory system with hopes to better understand the mechanistic functions and causes of metabolic system dysfunctions, improvement of early detection of the onset of either type of diabetes including the newly classified pre-diabetic condition, and eventually provide more reasonable, effective, efficient and economic

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treatments to diabetic patients (Bergman et al., 2002; Bergman, 2002; Mari, 2002; Makroglou et al., 2006 and the references therein).

The secretion of insulin in the glucose–insulin endocrine metabolic system occurs in an oscillatory manner over a range of 50–150 min and is usually referred to as ultradian oscillations (Simon and Brandenberger, 2002). Two noticeable time delays exist in this system. One is due to the electric action inside of $\beta$-cells upon glucose stimulation to release insulin, and physiological action that the glucose utilization correlates the so-called "*remote insulin*" which requires certain time for the newly synthesized insulin to cross the endothelial barrier (Ahren and Taborsky, 2002; Sturis et al., 1991; Tolic et al., 2000; Cherrington et al., 2002). The other represents the delayed effect of insulin on hepatic glucose production (Sturis et al., 1991; Tolic et al., 2000). Although "insulin regulates the liver in a direct fashion", however, "its effect occurs within several minutes" (Cherrington et al., 2002). Pioneering work on modeling the glucose–insulin regulatory system and the ultradian insulin secretory oscillations can be traced back to Bolie (1961), in which the linearized system of the glucose–insulin regulation in terms of the differential equations of feedback was analysed with the so-called critical damping criteria of servomechanism theory. In the past few decades, several mathematical models have been proposed to model this system (Sturis et al., 1991; Tolic et al., 2000; Engelborghs et al., 2001; Bennett and Gourley, 2004).

In this paper, we propose a DDE (delay differential equation) model by introducing two explicit time delays and model the glucose–insulin endocrine metabolic regulatory system. With the same set of experimental data used in the existing models such as those in Sturis et al. (1991), and Tolic et al. (2000), the two time delay model not only confirms most of existing observations of experiments and models, but also demonstrates robustness, and produces simulation profiles in better agreement with physiological data. As a result, we suspect that one of the possibly many causes of ultradian insulin secretion oscillations is the time delay of the insulin secretion stimulated by the elevated glucose concentration.

To detect the onset of diabetes or the potential to develop diabetes, a series of glucose tolerance tests have been developed over the years and applied in clinics and experiments (Bergman et al., 1985), for examples, Oral Glucose Tolerance Test (OGTT), Fasting Glucose Tolerance Test (FGTT), Intra Venous Glucose Tolerance Test (IVGTT) and frequently sampled Intra Venous Glucose Tolerance Test (fsIVGTT). The subjects are given a large bolus of glucose and the glucose concentration is sampled in those glucose tolerance tests. Due to the initial large amount of glucose is infused, the kinetics of the glucose–insulin system does not, and should not, behave the same way as the dynamics of glucose–insulin system in normal situation. The model proposed in this paper does not target the situation of glucose tolerance tests.

We organize this paper as follows. In Section 2, we describe the glucose–insulin endocrine metabolic regulatory system and present the two time delay model. In Section 3, we discuss the simulation profiles obtained from the two time delay model as well as those obtained from these previously existing models. In Section 4, we present numerical simulations of the two time delay model using the same experimental data used by the previous models in their simulations. In Section 5, we discuss observations from the two time delay model.

## 2. Modeling the glucose–insulin regulatory system and ultradian insulin secretory oscillations

In the glucose–insulin endocrine metabolic regulatory system, the two pancreatic endocrine hormones, insulin and glucagon, are the primary regulatory factors. Numerous in vivo and in vitro experiments have revealed that insulin secretion consists of two oscillations occurring with different time scales: rapid oscillations having a period of 5–15 min (Pørksen et al., 2002) and ultradian oscillations occurring in the period of every 50–150 min (Sturis et al., 1991; Tolic et al., 2000; Simon and Brandenberger, 2002). The mechanisms underlying both types of oscillations are still not fully understood. The rapid oscillations may arise from an intra-pancreatic pacemaker mechanism causing a coordination of periodic secretory bursting of insulin from pancreatic $\beta$-cells contained in the millions of Langerhans islets (Sturis et al., 1991; Tolic et al., 2000). These bursts are the dominant mechanism of insulin release at the basal level (Pørksen et al., 2002). This rapid oscillation is usually superimposed on the slow (ultradian) oscillation (Sturis et al., 1991).

The ultradian oscillations of insulin secretion are assumed to result from an instability in the glucose–insulin endocrine metabolic regulatory system (Sturis et al., 1991; Tolic et al., 2000; Simon and Brandenberger, 2002; Mari, 2002), although the precise mechanisms are still not fully understood (Simon and Brandenberger, 2002). These ultradian oscillations are best seen after meal ingestion, oral glucose intake, continuous enteral nutrition or intravenous glucose infusion (Fig. 1). In addition, muscles, the brain, nerves and other tissues continuously utilize the plasma glucose completing the regulatory system feedback loop (Sturis et al., 1991 and its Fig. 2, Tolic et al., 2000).

The hypothesis that the ultradian insulin secretion is an instability in the glucose–insulin endocrine metabolic regulatory system has been the subject of a number of studies, including some which have developed a mathematical model of the insulin–glucose feedback system (Sturis et al., 1991; Keener and Sneyd, 1998; Tolic et al., 2000; Engelborghs et al., 2001; Bennett and Gourley, 2004). Glucose–insulin feedback loop was the major consideration when the six-equation ODE model was proposed by Sturis et al. (1991) and simplified by Tolic et al. (2000). However, the feedback system has not been rigorously

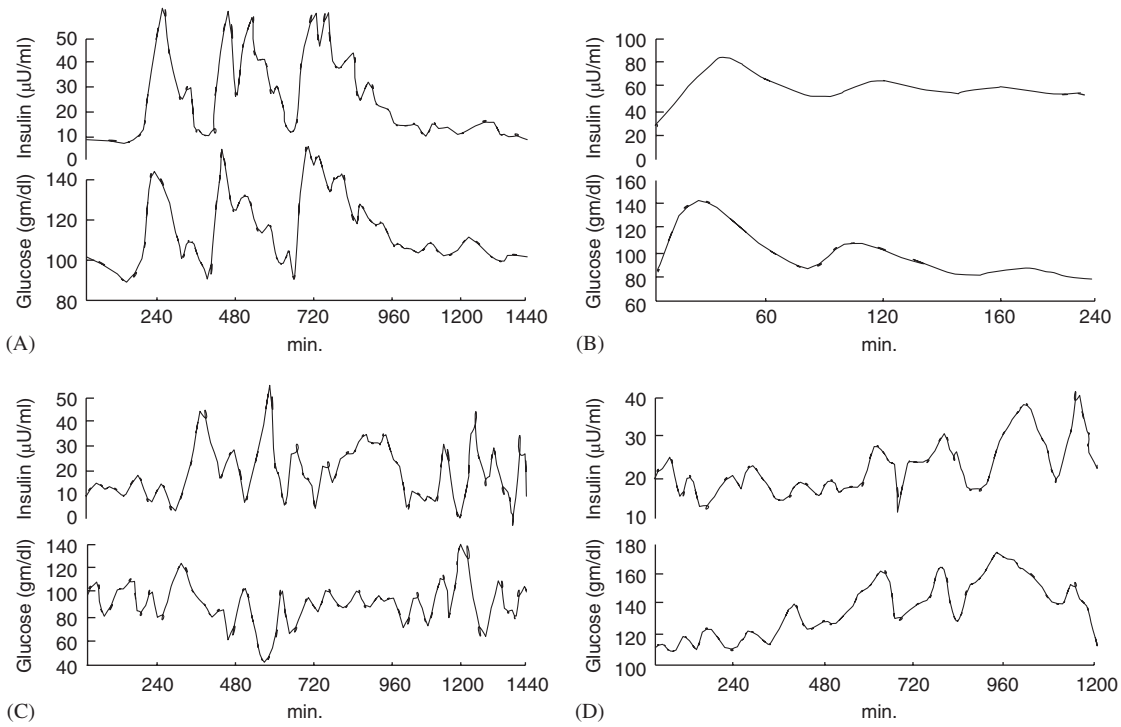


Fig. 1. Ultradian insulin secretory oscillations. Profiles for glucose and insulin for various glucose infusion rates: (A) meal ingestion; (B) oral glucose intake; (C) continuous enteral nutrition; (D) constant glucose infusion. These figures are adapted from Sturis et al. (1991).

proven to be the mechanism of the ultradian oscillations of insulin secretion.

Applying the mass conservation law, similar to the approach of Topp et al. (2000), we attempt to model the glucose–insulin endocrine metabolic regulatory system illustrated in Fig. 2. The two major factors in the regulatory system model are glucose and insulin. Let $G(t)$ and $I(t)$ be the glucose and insulin concentration at time $t \geqslant 0$, respectively, we obtain

$$\mathrm{d}G(t)/\mathrm{d}t = \textit{glucose production} - \textit{glucose utilization},$$
$$\mathrm{d}I(t)/\mathrm{d}t = \textit{insulin production} - \textit{insulin clearance}.$$

*Insulin production*: Insulin can only be produced from $\beta$-cell secretion, mainly in response to the elevated glucose concentration. Although there are other secretagogues, e.g. free fatty acid and most amino acids, glucose is the most critical stimulus for insulin release (Ahren and Taborsky, 2002). A series of complex electric processes occur inside of each islet. This process includes: the entering of glucose molecules into the islets through a glucose transporter GLUT2, the elevation of ATP:ADP, the subsequent closing of the $K^+$ channels, the opening of the $Ca^{2+}$ channels and eventually the insulin exocytosis from $\beta$-cell granules caused by the influx of $Ca^{2+}$ ions (Gilon et al., 2002). We use $f_1(G)$ to stand for the insulin production stimulated by glucose concentration $G$. We assume $f_1(G)$ is bounded, of sigmoidal shape, $f_1(0) > 0$, $f_1(x) > 0$, and $f_1'(x) > 0$ for $x > 0$ (refer to Fig. 3 for the shape of function $f_1$).

*Insulin degradation and clearance*: Insulin is cleared by all insulin sensitive tissues. Insulin degradation is mediated primarily by the insulin receptor with a smaller contribution from non-specific processes. The liver and kidney are the primary sites of portal insulin degradation and peripheral insulin clearance, respectively. Insulin not cleared by liver and kidney is ultimately removed by other tissues, for examples, muscle and adipose cells. The insulin degradation is a regulated process involving insulin binding to its receptor, internalization, and degradation as in other tissues. The function of insulin clearance and degradation is to remove and inactivate circulating insulin in order to control insulin action (refer to Duckworth et al., 1998). Experiments have shown that the relationship of insulin degradation is proportional to insulin concentration (Topp et al., 2000). Thus, as in Topp et al. (2000), we assume the clearance rate is a positive constant $d_i > 0$.

*Glucose production*: There are two sources for glucose production. Glucose is liberated from dietary carbohydrates such as starch or sucrose by hydrolysis within the small intestine, subsequently being absorbed into the blood. The most common ways of glucose infusion are through meal ingestion, oral glucose intake, continuous enteral nutrition, and constant glucose infusion (Sturis et al., 1991; Tolic et al., 2000) (refer to Fig. 1). We assume the infusion rate is a constant, denoted by $G_{in} \geqslant 0$. The other source of glucose production is the liver. When the plasma glucose concentration level drops, the $\beta$-cells stop releasing insulin, but $\alpha$-cells, also located in the Langerhans islets in the pancreas, start to release another hormone, glucagon.

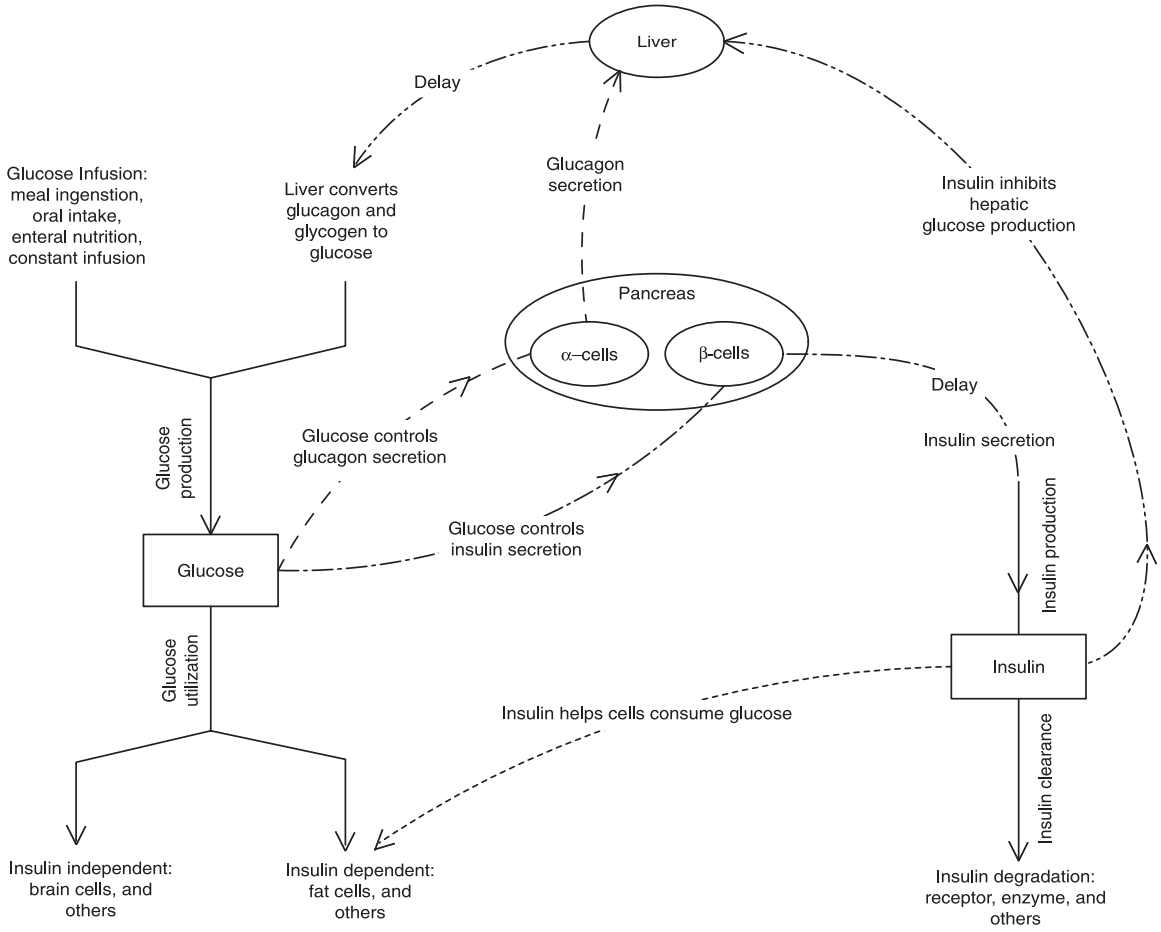


Fig. 2. Two time delay glucose–insulin regulatory system model. The dash-dot-dot lines indicate that insulin inhibits hepatic glucose production with time delay; the dash-dot lines indicate insulin secretion from the $\beta$-cells stimulated by elevated glucose concentration level and the short dashed line indicates the insulin caused acceleration of glucose utilization in cells with time delay; the dashed lines indicate low glucose concentration level triggering $\alpha$-cells in the pancreas to release glucagon.

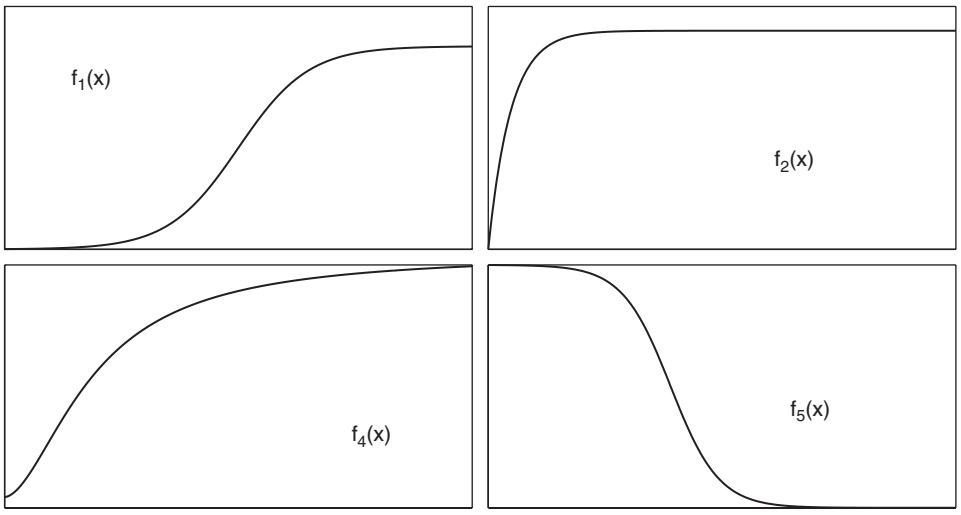


Fig. 3. Shapes of functions $f_1$ (upper left), $f_2$ (upper right), $f_4$ (lower left) and $f_5$ (lower right). The shapes of the functions, instead of their forms, are more important (Keener and Sneyd, 1998).

Glucagon exerts control over pivotal metabolic pathways in the liver and leads the liver to dispense glucose. We denote glucose production as $f_5(I)$ controlled by insulin concentration $I$. It is assumed to satisfy that $f_5(0)>0$ and $f_5'(x)<0$ for $x>0$. Under euglycemic conditions, the insulin-induced increase in glucose utilization almost

exclusively reflects the action of the hormone on muscle (Cherrington et al., 2002) instead of storing glucose as glycogen. Hence, we assume that $f_5(x)>0$ for $x>0$. When the insulin concentration level is three-fold above its basal level, glucose production by the liver can quickly be halted (Cherrington et al., 2002, Fig. 1(B)). Therefore, we assume that the functions $f_5(x)$ and $|f_5'(x)|$ are bounded above for $x>0$, and $f_5(x)$ rapidly decreases to zero as $x$ increases (refer to Fig. 3 for the shape of function $f_5$).

*Glucose utilization*: Glucose utilization also consists of two parts, namely, insulin-independent utilization and insulin-dependent utilization. The insulin-independent glucose consumers are mainly the brain and nerve cells. We denote this type of utilization by $f_2(G)$ indicating its dependency on the glucose concentration level alone. Further, we assume that $f_2(x)>0$ is in sigmoidal shape with $f_2(0)=0$, and $f_2'(x)>0$ is bounded for $x>0$. The insulin-dependent glucose uptake is mostly due to muscle, fat cells and other tissues. Insulin receptors activate the signaling cascade for GLUT4 translocation. GLUT4 transporters lead glucose molecules into muscle. The cells then consume the glucose and convert it into energy. We denote the insulin-dependent glucose uptake by $f_3(G)f_4(I)$. This insulin-dependent glucose utilization is accomplished by the so-called "*remote insulin*". We may reasonably assume that $f_3(0)=0$, $0<f_3(x)\leqslant k_3x$ and $f_3'(x)>0$ for $x>0$, where $k_3>0$ is a constant. Also, $f_4(0)>0$, $f_4(x)>0$ and $f_4'(x)>0$ are bounded above for $x>0$. We again require that $f_4(x)$ has a sigmoidal shape as in Sturis et al. (1991) (refer to Fig. 3 for the shape of function $f_2$, and $f_4$).

*Time delays in the system*: Insulin secretion from $\beta$-cells involve a series of complex electric processes occurring inside of each islet. These processes primarily include following steps: the entering of glucose molecules into the islets through a glucose transporter GLUT2, the elevation of ATP:ADP, the subsequent closing of the $K^+$ channels, the opening of the $Ca^{2+}$ channels and eventually the insulin exocytosis from $\beta$-cell granules caused by the influx of $Ca^{2+}$ ions (Gilon et al., 2002). Due to this chain of events, a time delay in responding to the stimulation of elevated glucose concentration exists. Insulin release has effects on both hepatic glucose production and insulin-dependent glucose utilization (Cherrington et al., 2002). It takes certain time for the newly synthesized insulin to cross the endothelial barrier and eventually become the so-called "*remote insulin*", then help to uptake glucose. This total delay time is approximately over the range of 5–15 min (Sturis et al., 1991; Tolic et al., 2000; Cherrington et al., 2002). We use $\tau_1$ to denote this total time delay from the time that the glucose concentration level is elevated to the moment that the insulin has been transported to interstitial space and becomes "remote insulin". Thus, insulin secretion can be approximated by $f_1(G(t-\tau_1))$ with time delay $\tau_1>0$.

Another time lag in the system is the delay of the effect of hepatic glucose production. In healthy people, the pancreas continually measures blood glucose levels and responds by secreting just the right amount of insulin to adjust blood glucose levels. Insulin has both inhibitory effect on hepatic glucose production via insulin secretion, and recovery effect of hepatic glucose production from insulin suppression. Although "insulin regulates the liver in a direct fashion", however, its effect takes several minutes to occur (Cherrington et al., 2002). This suggests a time lag for insulin effect on liver exists. However, both length of the delay and its pathway remain unknown. According to the in vivo experiments performed by Prager et al. (1986), under different insulin infusion rate, the time to reach the half-maximal suppression is between 11 and 22 min, while the time to reach the half-maximal recovery is in the range from 54 to 119 min (Prager et al., 1986, p. 477, Table III). It was also observed that it took 15 min for glucose production rate to peak after the portal insulin was made deficient in an in vivo experiment using overnight fasted conscious dogs (Cherrington et al., 2002). Based on the data in Prager et al. (1986), we can state that the length of this delay varies significantly in different subjects, from just a few minutes to a much longer time. So, most likely, the length of this delay is longer than the delay that $\tau_1$ represents. We use $\tau_2$ to represent the time taken for noticeable insulin effect on liver to occur. This is measured from the time that insulin has become "*remote insulin*" to the moment that a significant (e.g. half-maximal) change of hepatic glucose production takes place. Thus, function $f_5(I(t-\tau_2))$ represents the delayed hepatic glucose production, indicating that the production is controlled by insulin with time delay $\tau_2>0$.

*Two time delay model*: By introducing two explicit time delays $\tau_1$ and $\tau_2$ in the system, with the above notations, the model we propose here takes the form of

$$\begin{cases} G'(t) = G_{in} - f_2(G(t)) - f_3(G(t))f_4(I(t)) + f_5(I(t-\tau_2)), \\ I'(t) = f_1(G(t-\tau_1)) - d_iI(t), \end{cases} \tag{1}$$

with the initial conditions $I(0)=I_0>0$, $G(0)=G_0>0, G(t)\equiv G_0$ for $t\in[-\tau_1,0]$ and $I(t)\equiv I_0$ for $t\in[-\tau_2,0]$, $\tau_1,\tau_2>0$.

We take the functions, $f_i$, $i=1,2,3,4,5$, used in Sturis et al. (1991), Tolic et al. (2000) and Bennett and Gourley (2004) for numerical analysis. These functions take the following forms with experimentally determined parameters given in Table 1 (Sturis et al., 1991; Tolic et al., 2000). The shapes of the functions, instead of their forms, are more important (Keener and Sneyd, 1998)

$$f_1(G) = R_m/(1+\exp((C_1 - G/V_g)/a_1)), \tag{2}$$

$$f_2(G) = U_b(1-\exp(-G/(C_2V_g))), \tag{3}$$

$$f_3(G) = G/(C_3V_g), \tag{4}$$

$$f_4(I) = U_0 + (U_m - U_0)/ (1+\exp(-\beta\ln(I/C_4(1/V_i + 1/(Et_i))))), \tag{5}$$

$$f_5(I) = R_g/(1+\exp(\alpha(I/V_p - C_5))). \tag{6}$$

Table 1
Parameters of the functions in (2)–(6)

| Parameters | Units | Values |
|---|---|---|
| $V_g$ | l | 10 |
| $R_m$ | mU min$^{-1}$ | 210 |
| $a_1$ | mg l$^{-1}$ | 300 |
| $C_1$ | mg l$^{-1}$ | 2000 |
| $U_b$ | mg min$^{-1}$ | 72 |
| $C_2$ | mg l$^{-1}$ | 144 |
| $C_3$ | mg l$^{-1}$ | 1000 |
| $V_p$ | l | 3 |
| $V_i$ | l | 11 |
| $E$ | l min$^{-1}$ | 0.2 |
| $U_0$ | mg min$^{-1}$ | 40 |
| $U_m$ | mg min$^{-1}$ | 940 |
| $\beta$ | | 1.77 |
| $C_4$ | mU l$^{-1}$ | 80 |
| $R_g$ | mg min$^{-1}$ | 180 |
| $\alpha$ | l mU$^{-1}$ | 0.29 |
| $C_5$ | mU l$^{-1}$ | 26 |
| $t_p$ | min | 6 |
| $t_i$ | min | 100 |
| $t_d$ | min | 36 |

Notice that the units of $G$ and $I$ are mg and mU, respectively, in the functions (2)–(6). These are converted to mg/dl and μU/ml when plotting the figures in all simulations excluding those which include plots of the periods.

Fig. 4 exhibits the profiles obtained from the two time delay model (1) with different parameter values. The simulations in Fig. 4 exhibit that the oscillations of the glucose–insulin regulatory system model (1) are self-sustained. It also exhibits that the two time delay model is robust as the wide range selections of the parameters, for example, $\tau_2$ can be as small as 4.5 min and it can be as large as 36 min. While Sturis et al. (1991) and Tolic et al. (2000) chose to estimate this delay by the amount of 36 min, it is likely (as seen by data in Prager et al., 1986) that there could be a great deal of variation from this level, both between various individuals and differing insulin infusion rates. However, for the model in Sturis et al. (1991), self-sustained oscillations occurred only if the hepatic glucose production delay is within 25–50 min. Hence, a model that is robust to a wide range of values for $\tau_2$ is highly desirable.

Fig. 5 demonstrates the time course of glucose concentration, insulin concentration, insulin secretion rate (ISR), insulin-dependent glucose clearance rate, and hepatic glucose production rate as simulated by the two delay model when $\tau_1 = 7$ min, $\tau_2 = 12$ min, $G_{in} = 1.08$ mg/dl min and $d_i = 0.06\,\text{min}^{-1}$. The self-sustained oscillation is clearly shown with period $\approx 110$ min. Since our goal of this paper is to model the self-sustained oscillatory behavior of the system and ultradian insulin secretion, the time course shown in Fig. 5 starts from the second cycle so that the noise caused by the artifact initial conditions of (1) can be filtered out. The simulation demonstrates that increasing glucose concentration causes IRS to increase (A is precedent of B) and the increase is slightly ahead of insulin concentration increases (B is in front of D). When IRS increases, the liver is signaled and stops its glucose production quickly (area pointed by E). Insulin-dependent glucose clearance is almost in synch with ISR and insulin concentration (C is between B and D).

As compared with the models in Sturis et al. (1991), Tolic et al. (2000), Engelborghs et al. (2001) and Bennett and Gourley (2004), we have removed the insulin compartment split effort in which Sturis et al. (1991), Tolic et al. (2000) and Bennett and Gourley (2004) mimic the delayed insulin-dependent glucose uptake by applying so-called first-order kinetics. Also, we have kept the time delay $\tau_2$ of insulin effect on liver in Bennett and Gourley (2004) and Engelborghs et al. (2001) which replaces the third-order kinetics (represented by a chain of three intermediate variables linking plasma insulin to glucose production) used in Sturis et al. (1991) and Tolic et al. (2000). Slightly differently, we measure $\tau_2$ from the time that insulin has become "remote insulin" to the moment that hepatic glucose production takes significant effect.

The two delay model (1) is suitable to simulate the case of continuous enteral nutrition and constant glucose infusion. The infusion rate in such cases can be considered as a constant.

When testing for insulin sensitivity during an IVGTT, a subject is infused with a large bolus of glucose (0.3 g/kg) following an overnight fast (Bergman et al., 1985). A large bolus of glucose stimulus initiates a biphasic release of insulin. The first phase consists of a rapid (within 2 min) but short-lasting secretion of insulin, followed (after 5–10 min) by a larger and up to 4 h secretion of insulin (Bergman et al., 1985; Cherrington et al., 2002; Ahren and Taborsky, 2002). While it is physiologically important in testing insulin sensitivity, the two distinct phases of insulin secretion are less apparent under non-abrupt glucose changes. For situations where the glucose enters the bloodstream more slowly, such as during the consumption of a carbohydrate meal, continuous glucose infusion and enteral nutrition uptake, the absorption of glucose into the circulation is not fast enough to distinguish the initial phase of insulin secretion (Ahren and Taborsky, 2002). As in the other aforementioned models, we do not include this biphasic insulin release in our two time delay model as we are attempting to model the glucose–insulin metabolic system under conditions of continuous enteral nutrition and constant glucose infusion. The most widely used mathematical model for the biphasic kinetics is the so-called "*Minimal Model*" (Bergman et al., 1985; Bergman, 2002). Several other models were proposed recently (DeGaetano and Arino, 2000; Li et al., 2001; Mukhopadhyay et al., 2004).

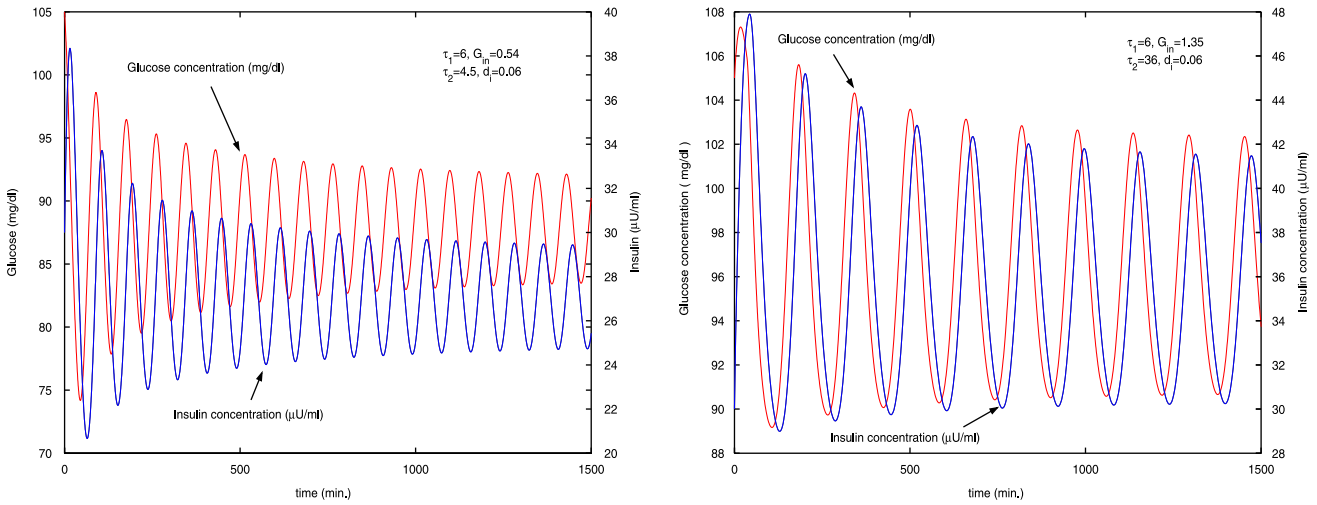


Fig. 4. Profiles of two delay model (1) with different parameters. Self-sustained oscillations by model (1) when $\tau_1 = 5, \tau_2 = 4.5, G_{in} = 0.54, d_i = 0.06$ (left) and $\tau_1 = 6, \tau_2 = 36, G_{in} = 1.35, d_i = 0.06$ (right).

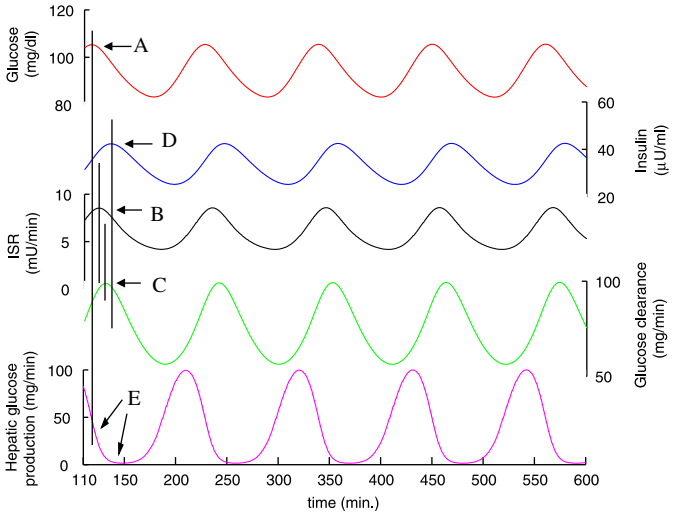


Fig. 5. Time course of glucose concentration, insulin concentration, insulin secretion rate (ISR), hepatic glucose production and insulin-dependent glucose clearance when $\tau_1 = 7$ min, $\tau_2 = 12$ min, $G_{in} = 1.08$ mg/dl min and $d_i = 0.06\,\text{min}^{-1}$.

## 3. Comparison of the two time delay model with existing models

This section discusses the currently existing models: an ODE (ordinary differential equation) model proposed by Sturis et al. (1991) and simplified by Tolic et al. (2000), a single explicit time delay DDE model proposed by Engelborghs et al. (2001) without an insulin compartment split, another single explicit time delay DDE model proposed by Bennett and Gourley (2004) containing an insulin compartment split, and two alternative DDE models with explicit time delay(s). We then compare the simulation profiles obtained from all these models with that from the two time delay model (1) proposed in Section 2.

### 3.1. Negative feedback ODE models

To determine whether the ultradian oscillations could result from the interaction between insulin and glucose, an ODE model consisting of six equations including the major mechanisms involved in glucose regulation was developed by Sturis et al. (1991) and recently simplified by Tolic et al. (2000). The purpose of these two models was to investigate a possible mechanism for the origin of the ultradian insulin secretion sustained oscillations. Included in this model is the feedback loop (refer to Fig. 2 in Sturis et al., 1991): glucose stimulates pancreatic insulin secretion, insulin stimulates glucose uptake and inhibits hepatic glucose production, and glucose enhances its own uptake. The model takes the following form:

$$\begin{cases} G'(t) = G_{in} - f_2(G(t)) - f_3(G(t))f_4(I_i(t)) + f_5(x_3), \\ I_p'(t) = f_1(G(t)) - E(I_p(t)/V_p - I_i(t)/V_i) - I_p(t)/t_p, \\ I_i'(t) = E(I_p(t)/V_p - I_i(t)/V_i) - I_i(t)/t_i, \\ x_1'(t) = 3(I_p - x_1)/t_d, \\ x_2'(t) = 3(x_1 - x_2)/t_d, \\ x_3'(t) = 3(x_2 - x_3)/t_d, \end{cases} \tag{7}$$

where $G(t)$ is the amount of glucose, $I_p(t)$ and $I_i(t)$ are the amount of insulin in the plasma and the intercellular space, respectively, $V_p$ is the plasma insulin distribution volume, $V_i$ is the effective volume of the intercellular space, $E$ is the diffusion transfer rate, $t_p$ and $t_i$ are the insulin degradation time constants in the plasma and intercellular space, respectively, $G_{in}$ indicates the (exogenous) glucose supply rate to the plasma, and $x_1(t)$, $x_2(t)$ and $x_3(t)$ are three auxiliary variables associated with certain delays of the insulin effect on the hepatic glucose production having total time $t_d$.

Description of the functional aspects are as follows. $f_1(G)$ is a function modeling the pancreatic insulin production as controlled by the glucose concentration, $f_2(G)$ and $f_3(G)f_4(I_i)$ are functions representing insulin-independent and insulin-dependent glucose utilization, respectively, by various body parts (for example, brain and nerves ($f_2$), and muscle and fat cells ($f_3f_4$)), and $f_5(x_3)$ is a function modeling hepatic glucose production with time delay $t_d$ associated with auxiliary variables $x_1$, $x_2$ and $x_3$.

Based on experimental results (Sturis et al., 1991; Tolic et al., 2000), all the parameters in the model are given in Table 1. The functions $f_i$, $i=1,2,3,4,5$, are the same functions as in model (1) given in (2)–(6) with the same parameters.

This model which consists of two major negative feedback loops, describes the effects of insulin on glucose utilization and glucose production, respectively. Both loops include the stimulatory effect of glucose on insulin secretion. The model mimics the delayed insulin-dependent glucose uptake by splitting the insulin into two separate compartments, plasma and interstitial space. The hepatic glucose production time delay is simulated by introducing three auxiliary variables $x_1$, $x_2$ and $x_3$, which is called the third-order delay. We demonstrate how the auxiliary variables simulate the time delay as follows. For simplicity, assume the delay is of first order, that is, $x_1'(t)=(I_p(t)-x_1(t))/t_d$, where $t_d>0$ is the time delay. Then

$$I_p(t-t_d)=x_1(t-t_d)+x_1'(t-t_d)t_d.$$

Observing that the Taylor's expansion of $x_1(t)$ at $t-t_d$ is given as

$$x_1(t)=x_1(t-t_d)+x_1'(t-t_d)t_d+o(t_d^2).$$

Thus, $x_1(t)\approx I_p(t-t_d)$. However, our calculations showed that the expression of $x_3(t)$ in terms of $x_3(t-t_d)$ is not a third-order Taylor polynomial for the so-called third-order delay in Sturis et al. (1991) and Tolic et al. (2000).

Tolic et al. (2000) simplified this model by using the linear or up to second-order terms in the Taylor expansions of the functions $f_i$, $i=1,2,4,5$, in the model (7) and showed that the numerical results are similar. Numerical analysis of the model (7) suggested that the ultradian oscillations of insulin secretion could arise from a Hopf bifurcation in the insulin–glucose feedback mechanism and gives the following major observations:

(ST1) The ultradian insulin secretion oscillation is critically dependent on hepatic glucose production, that is, if there is no hepatic glucose production, then there is no insulin secretion oscillation.

(ST2) When and only when the hepatic glucose production time delay is in the range of 25–50 min, self-sustained oscillations occur and the period of the periodic solutions of both insulin and glucose is in between 95 and 140 min.

(ST3) To obtain the ultradian oscillation (periodic solutions), it is necessary to break the insulin into two separate compartments, the plasma and interstitial tissues.

(ST4) The ultradian oscillation is sensitive to both the speed of insulin reaction to the increased plasma glucose concentration level and the speed of the hepatic glucose production triggered by insulin. Specifically, if the slope at the reflexive points of function $f_1$ and $f_5$ is reduced by 10–20%, the oscillation becomes damped.

### 3.2. Single explicit time delay DDE models

Engelborghs et al. (2001) replaced the auxiliary variables $x_i$, $i=1,2,3$, and introduced a single time delay in the Negative Feedback Loop Model and proposed the following DDE model:

$$\begin{cases} G'(t)=E_g-f_2(G(t))-f_3(G(t))f_4(I(t))+f_5(I(t-\tau)),\\ I'(t)=f_1(G(t))-I(t)/t_1, \end{cases} \tag{8}$$

where the functions, $f_i$, $i=1,2,3,4,5$, and their parameters are assumed to be the same as those in model (7). In their model, $E_g$ stands for the glucose infusion rate and the term $1/t_1$ represents the insulin degradation rate. The positive constant delay $\tau$ mimics the hepatic glucose production delay.

Unfortunately, this model overlooked the time delay from glucose stimulated insulin release to the delayed insulin-dependent glucose uptake. Due to the complex chemical reactions of the $\beta$-cells, it takes a few minutes (5–15 min) for the insulin being ready to help cells utilizing glucose after the plasma glucose concentration is elevated. This significant time delay is not negligible physiologically, which is confirmed by Sturis et al. (1991), Tolic et al. (2000) and this paper (refer to Section 4).

Bennett and Gourley (2004) modified the ODE model (7) by removing the three auxiliary linear chain equations and their associated artificial parameters by introducing a time delay into the model explicitly. This time delay $\tau$ mimics the hepatic glucose production, which is the same as proposed in Engelborghs et al. (2001). Unlike Engelborghs et al. (2001), Bennett and Gourley (2004) kept the idea in Sturis et al. (1991) and Tolic et al. (2000) of breaking the insulin into two compartments to simulate the delayed insulin-dependent glucose uptake. The DDE model takes the following form (all parameters and functions are the same as that in model (7) given in (2)–(6), Table 1):

$$\begin{cases} G'(t)=G_{in}-f_2(G(t))-f_3(G(t))f_4(I_i(t))+f_5(I_p(t-\tau)),\\ I_p'(t)=f_1(G(t))-E(I_p(t)/V_p-I_i(t)/V_i)-I_p(t)/t_p,\\ I_i'(t)=E(I_p(t)/V_p-I_i(t)/V_i)-I_i(t)/t_i. \end{cases} \tag{9}$$

The major analytical results of this model were a sufficient condition for global asymptotical stability induced by a Liapunov function for the case that the hepatic glucose production time delay satisfied $\tau = 0$ and for the case of $\tau > 0$. This analytical result shows that:

(BG1) If the hepatic glucose production time delay $\tau$ and the insulin transfer time between the plasma and interstitial compartments $t_i$ and $t_p$ are sufficiently small, then solutions converge globally to the steady state or the basal levels of glucose and insulin. In other words, there are no sustained oscillations. For larger delay, whose range is not given, sustained oscillatory solutions become possible and under these circumstances it seems that likely candidates for having sustainable oscillatory insulin and glucose levels are those subjects with slower transfer rates of the two insulin compartments.

(BG2) The oscillation could not be sustained if the hepatic glucose production rate $R_g$ is too small.

### 3.3. Alternative explicit time delay DDE models

We also discuss in this paper two alternative approaches in modeling the glucose–insulin regulatory system. In first alternative approach, we keep one explicit time delay $\tau_1$ as that in the two time delay model (1), but mimic the hepatic glucose production time delay by variable chain as in model (7) (Sturis et al., 1991; Tolic et al., 2000). The alternative model with single explicit delay is given as

$$\begin{cases} G'(t) = G_{in} - f_2(G(t)) - f_3(G(t))f_4(I(t)) + f_5(x_3), \\ I'(t) = f_1(G(t-\tau_1)) - d_i I(t), \\ x_1'(t) = 3(I - x_1)/t_d, \\ x_2'(t) = 3(x_1 - x_2)/t_d, \\ x_3'(t) = 3(x_2 - x_3)/t_d. \end{cases} \tag{10}$$

In another alternative approach, we model the effect of time delay $\tau_1$ in glucose utilization by $f_3(G(t))f_4(I(t-\tau_1))$. This results in the following alternative model with two explicit delays:

$$\begin{cases} G'(t) = G_{in} - f_2(G(t)) - f_3(G(t))f_4(I(t-\tau_1)) \\ \qquad\quad + f_5(I(t-\tau_2)), \\ I'(t) = f_1(G(t)) - d_i I(t). \end{cases} \tag{11}$$

The notations in the model (10) and (11) have the same meanings as those in the models discussed in previous sections. The simulations in the next subsection will show that the profiles produced from these models are not as well fit to experiment observations as the profile created by the two time delay model (1).

### 3.4. Comparison

In this subsection, we compare the temporal profiles of the two time delay model (1) with the profiles produced by the ODE model (7) as well as models (9)–(11). Glucose concentration level can range from 40 to 180 mg/dl in normal individuals following meal consumption while the normal insulin concentration level can vary from 5 to 50 μU/ml. However, normal values of plasma glucose concentration levels for a normal subject are between 70 and 109 mg/dl before a meal, or below 120 mg/dl 2 h after eating a meal.

Using the same experimental data from Table 1 used in Sturis et al. (1991) and Tolic et al. (2000), we performed simulations on the above models with Matlab 6.5 (excluding model (8) due to its lack of physiological applicability). With two different sets of parameters, Figs. 6 and 7 show the simulation profiles of glucose and insulin concentration produced by the two time delay model (1) (thick solid curve), ODE model (7) (dotted-dashed curve), single explicit time delay model (9) (dotted curve), the two alternative model (10) (dashed curve) and (11) (thin solid curve).

It is clearly shown in Fig. 6 that the profile from two time delay model (1) shows self-sustained oscillation. The profile produced by the alternative model (10) with single explicit delay is almost as good as the profile produced by two time delay model (1). All other models apparently do not produce self-sustained oscillations. Notice that the explicit delay $\tau_1$ in model (10) presents the same time lag as that in model (1), while $\tau_1$ in model (11) represents glucose utilization delay only. This suggests that the time delay from insulin secretion stimulated by glucose to the insulin becoming "*remote insulin*" is not negligible, especially, the delay of insulin secretion triggered by elevated glucose plays a key role. Therefore, we suspect that one of the possibly many causes of ultradian insulin secretion oscillations is the time delay of the insulin secretion stimulated by the elevated glucose concentration.

In Fig. 7, the profiles from all models demonstrate self-sustained oscillations. However, normally, the glucose concentration of normal subjects is within the range from 70 to 109 mg/dl except some abundant glucose infusion, e.g. meal ingestion. At such constant infusion, the profile obtained from two time delay model (1) is within physiological reasonable range. The profiles produced by the ODE model (7) and single delay model (9) are slightly out of physiological reasonable range. Apparently, these two figures indicate that the two time delay model is more robust and possibly more accurate.

## 4. Numerical simulations of two time delay model

We used DDE23 in Matlab 6.5 (Shampine and Thompson , 2001) to perform the simulations for the two time delay model (1). The results of our intensive simulations reveal profiles in good agreement with physiological findings, confirm most of the observations by Sturis et al. (1991), Tolic et al. (2000) and Bennett and Gourley (2004) and provide additional observable insights. The simulations focus on detecting bifurcation points on a

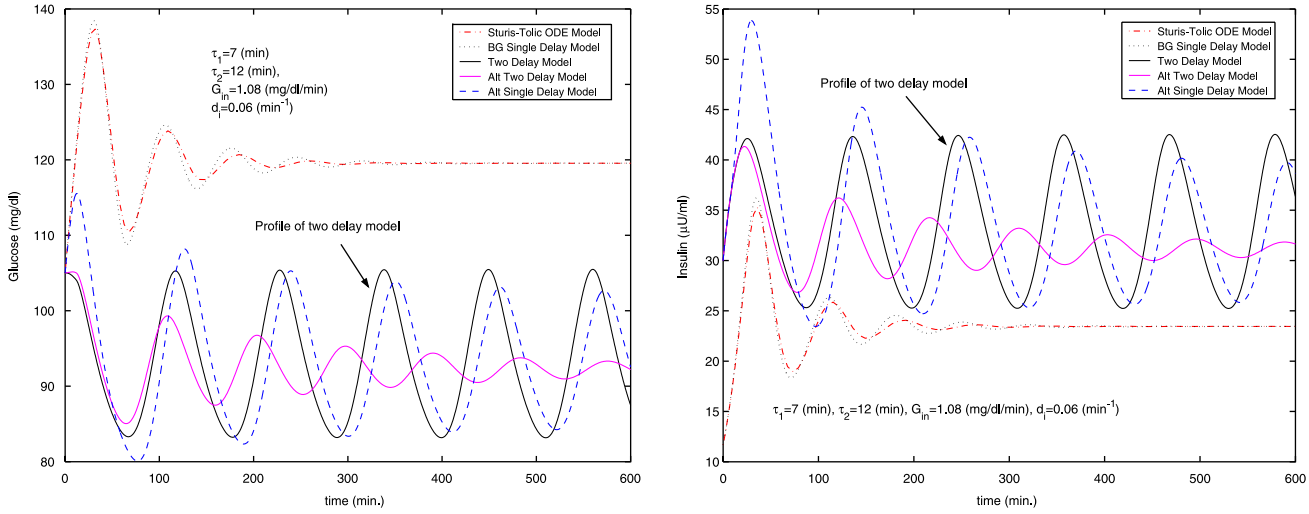


Fig. 6. Glucose (left) and insulin (right) concentration solution curves produced by the five models when $\tau_1 = 7$ min, $\tau_2 = 12$ min, $G_{in} = 1.08\,\mathrm{mg/(dl\ min)}$ and $d_i = 0.06\,\mathrm{min}^{-1}$. In model (7), $t_d = \tau_2 = 12$. In model (9), $\tau = \tau_2 = 12$.

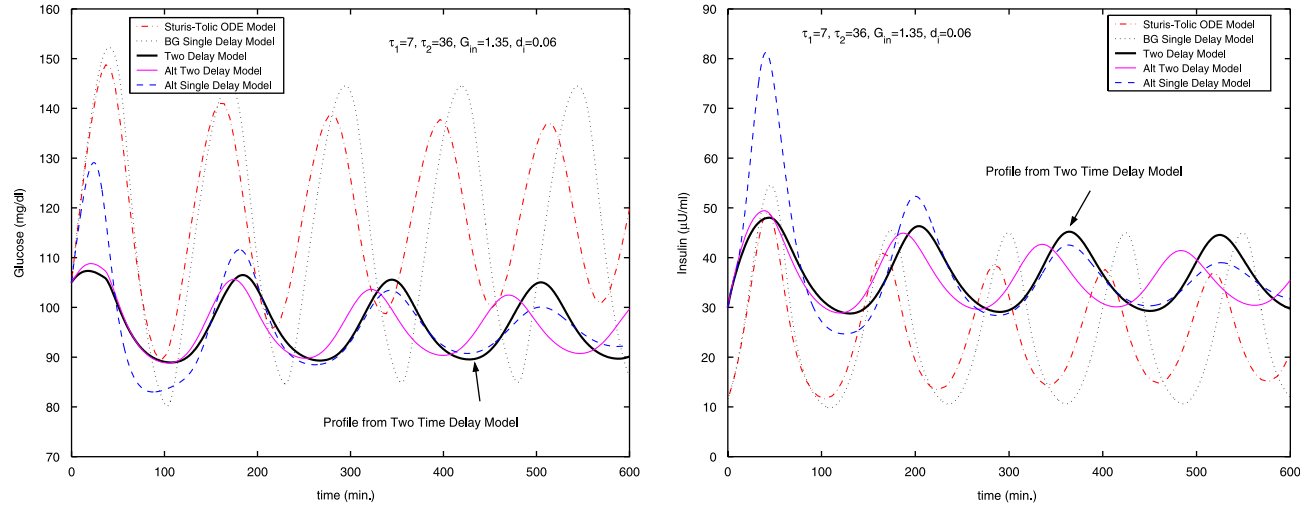


Fig. 7. Glucose (left) and insulin (right) concentration solution curves produced by the five models when $\tau_1 = 7$ min, $\tau_2 = 36$ min, $G_{in} = 1.35\,\mathrm{mg/(dl\ min)}$ and $d_i = 0.06\,\mathrm{min}^{-1}$. In model (7), $t_d = \tau_2 = 12$. In model (9), $\tau = \tau_2 = 12$.

single parameter of the four parameters: delay parameter $\tau_2$ (min), $\tau_1$ (min), constant glucose infusion rate $G_{in}$ (mg/dl/min) and insulin degradation rate $d_i$ ($\mathrm{min}^{-1}$). Unless a parameter is taken as the bifurcation parameter, the parameter values are assumed as $\tau_2 = 12$ min, $\tau_1 = 7$ min, $G_{in} = 1.08\,\mathrm{mg/dl}$ min and $d_i = 0.06\,\mathrm{min}^{-1}$.

### 4.1. Delay parameter $\tau_2$

We first take the delay $\tau_2$ as the bifurcation parameter. The simulation results are shown in Figs. 8 and 9 (left). According to Fig. 8, while $\tau_2$ changes from 0 to 40, a bifurcation point is detected at $\tau_2 \approx 6.75$. It is clearly demonstrated that the oscillation is sustained when $\tau_2 \in (6.75, 40]$. Furthermore, the amplitudes of glucose concentration are within the range of euglycemia. Fig. 9 (left) shows that in each cycle of the oscillation, the glucose concentration peaks before the insulin concentration approximately 17–20 min. All of the above simulated findings are in good agreement with the experimental data (Sturis et al., 1991; Tolic et al., 2000; Simon and Brandenberger, 2002). In the same figure, the periods of the periodic solutions generated from the bifurcation are in the interval of [95, 155] when $\tau_2 \in (6.75, 40)$ and the period increases when $\tau_2$ increases. This confirms observation (ST2) in Sturis et al. (1991) and Tolic et al. (2000).

### 4.2. Insulin secretion and glucose utilization time delay $\tau_1$

We take delay parameter $\tau_1$ as a bifurcation parameter. We let $\tau_1$ change in [0, 20]. The right panel of Fig. 9 is the bifurcation diagram of $\tau_1$ and Fig. 10 demonstrates the

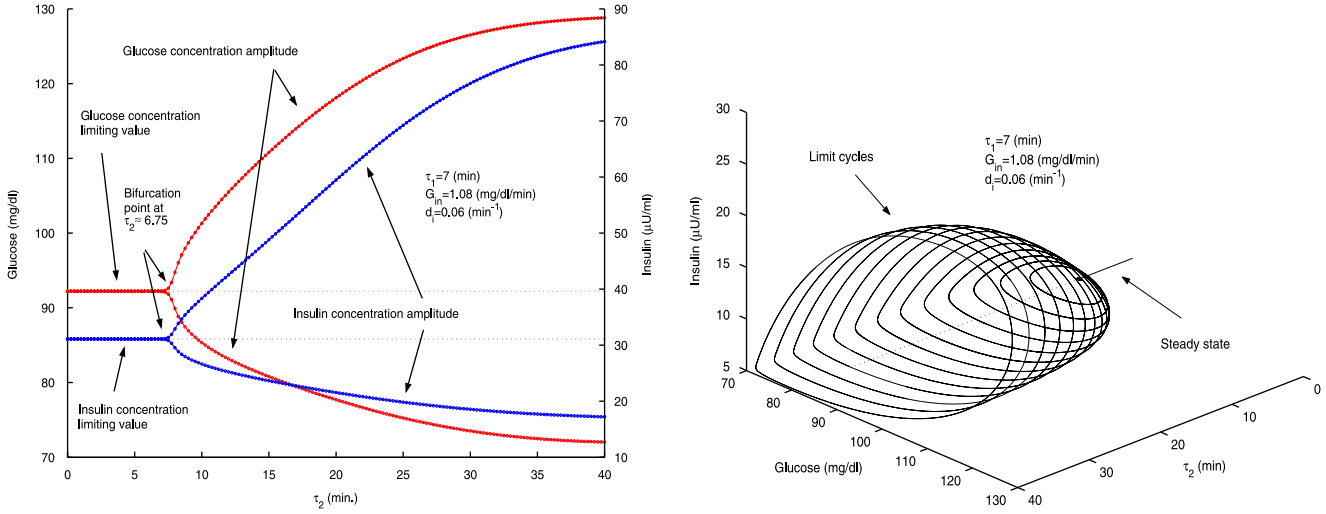


Fig. 8. Left: Bifurcation diagram of $\tau_2 \in [0, 40]$. The bifurcation point is at $\tau_2 \approx 6.75$. Right: Periodic solutions.

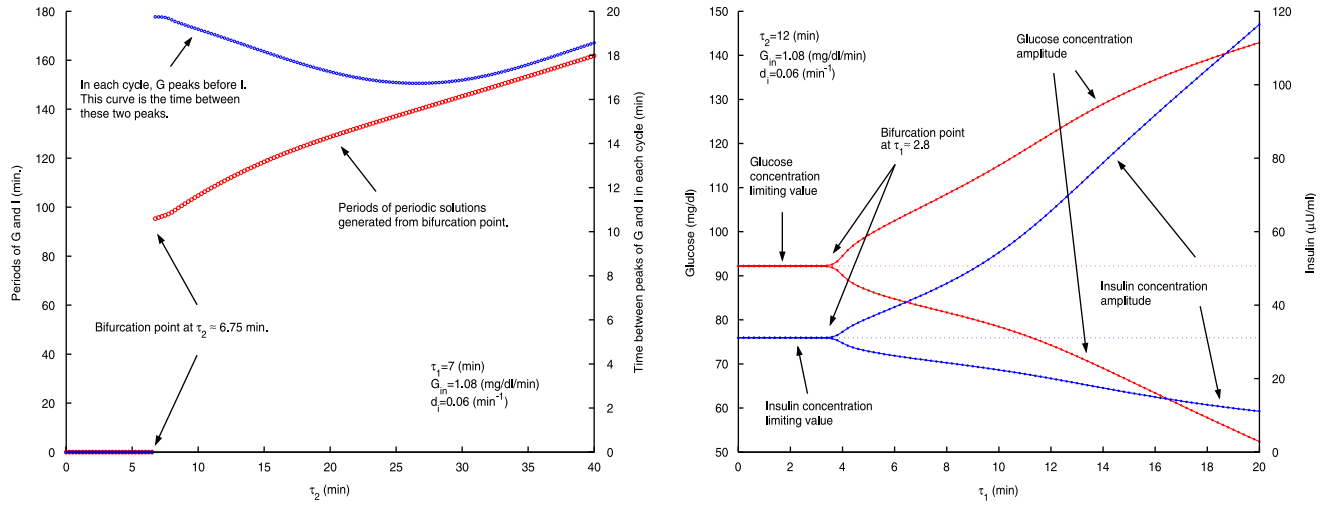


Fig. 9. Left: Periods of periodic solutions when $\tau_2 \in [0, 40]$. Right: Bifurcation diagram of $\tau_1 \in [0, 20]$.

limit cycles generated from the bifurcation and the periods of periodic solutions. Clearly, there exists a bifurcation point $\tau_{10} \approx 2.8$ such that the insulin secretion oscillations are sustained when $\tau_1 > \tau_{10}$. The left panel of Fig. 10 confirms the bifurcation diagram given in the right panel of Fig. 9 by exhibiting the limit cycles. The right panel of Fig. 10 indicates that the periods of periodic solutions fall within the range of 95–150 min in an increasing manner. In each cycle, the glucose concentration reaches its peak about 15–28 min before the insulin concentration peaks. The time difference between the peaks increases when $\tau_1$ increases.

### 4.3. Glucose infusion rate $G_{in}$

Next, we let the glucose infusion rate $G_{in}$ vary from 0 to 1.50 mg/dl min as a bifurcation parameter and investigate how the changes of the glucose infusion rate affect the sustained oscillations. Fig. 11 demonstrates the bifurcation diagrams of $G_{in} \in [0, 1.50]$. The computation results indicate that there exists a bifurcation point at $G_{in}^0 \approx 1.25$. When $G_{in} < G_{in}^0$, the oscillations of the insulin concentrations are sustained. When the exogenous glucose infusion rate is large ($G_{in} > G_{in}^0$), no oscillation will be sustained. This can possibly be explained by the following well accepted observations. That is, during the IVGTT, when the initial exogenous glucose infusion is large, the plasma glucose concentration level returns to the basal level in about 30 min (Bergman et al., 1985; DeGaetano and Arino, 2000; Li et al., 2001; Bergman, 2002).

### 4.4. Insulin degradation rate $d_i$

Finally, we take the insulin degradation rate $d_i$ as a bifurcation parameter and let $d_i$ vary from 0.001 to 0.07 min$^{-1}$. Bifurcation diagram plotted in Fig. 12 (left)

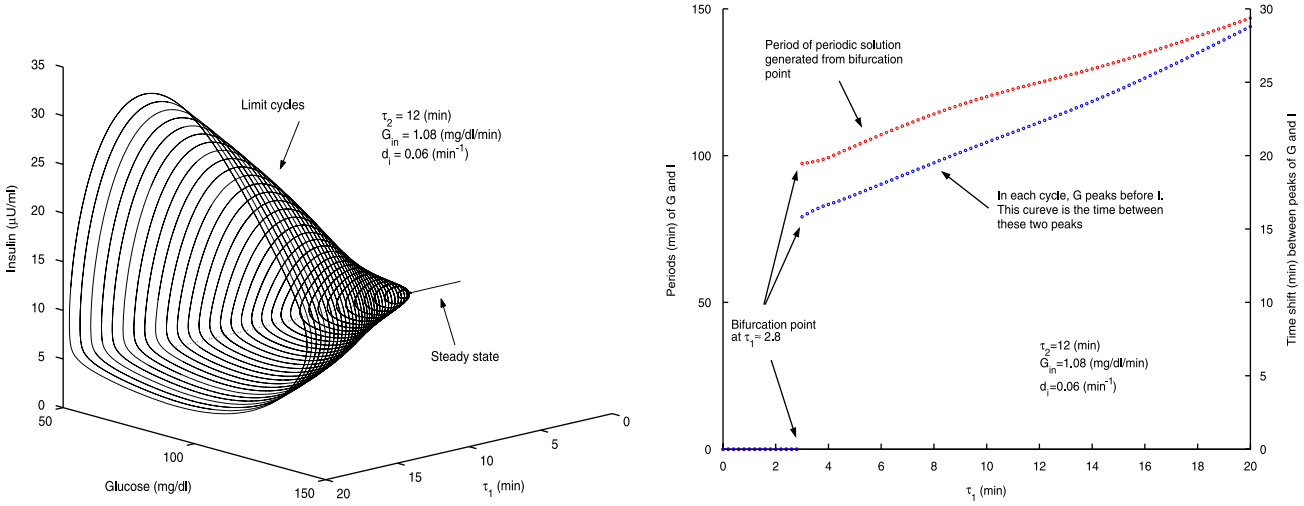


Fig. 10. Left: Periods of periodic solutions when $\tau_1 \in [0, 20]$. Right: Periods of periodic solutions and time between peaks of glucose and insulin concentrations.

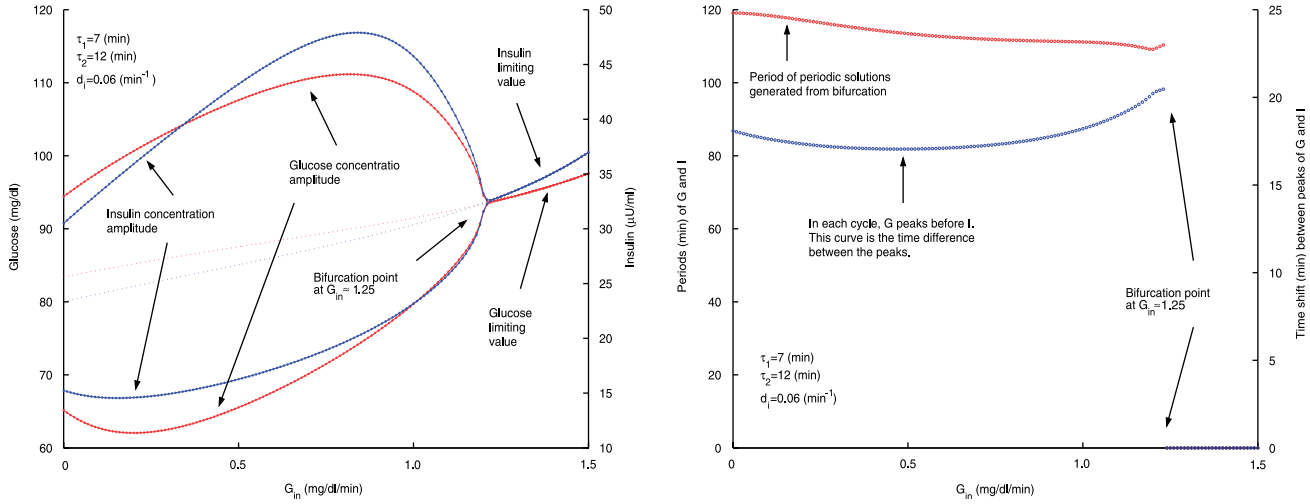


Fig. 11. Left: Bifurcation diagram of $G_{in} \in [0, 1.50]$ mg/dl min. Right: Periods of the periodic solutions and the time differences between the peaks of glucose and insulin concentrations in each cycle.

shows that there exists a bifurcation point at $d_{i0} \approx 0.0325$. When $d_i > d_{i0}$, the oscillations are sustained. Fig. 12 (right) shows the periods of the periodic solutions as $d_i$ changes in [0.01, 0.12]. It indicates that the periods of the periodic solutions decrease monotonically from approximately 138 to 95. The other curve in Fig. 12 (right) shows that in each cycle, it takes about 13.5–28 min for the insulin concentration to peak after the glucose concentration peaks. The time differences decrease correspondingly as $d_i$ increases.

## 5. Discussions

The numerical analysis results of the two time delay model (1) have confirmed most of the existing research observations as well as provided additional insights and quantitative information. We summarize and discuss these observations as follows:

(A1) The profiles of glucose concentration and insulin concentration in Figs. 4 and 5 satisfy normal pre-prandial physiological ranges in non-diabetics (refer to, for example, Simon and Brandenberger, 2002). The profiles of glucose utilization and production in Fig. 5 are in agreement with the experimental data in Cherrington et al. (2002) and Luzi and DeFrenzo (1989), if assume a person's weight is 60–75 kg and divide the data by 65–70 kg to produce the data in the units used in Cherrington et al. (2002) and Luzi and DeFrenzo (1989).

(A2) The simulation results in Section 4.1 demonstrate that the delay $\tau_2$ plays a key role for the sustained glucose–insulin regulatory oscillations and insulin secretory oscillations. The range ($>6.75$ min) of $\tau_2$ for sustained

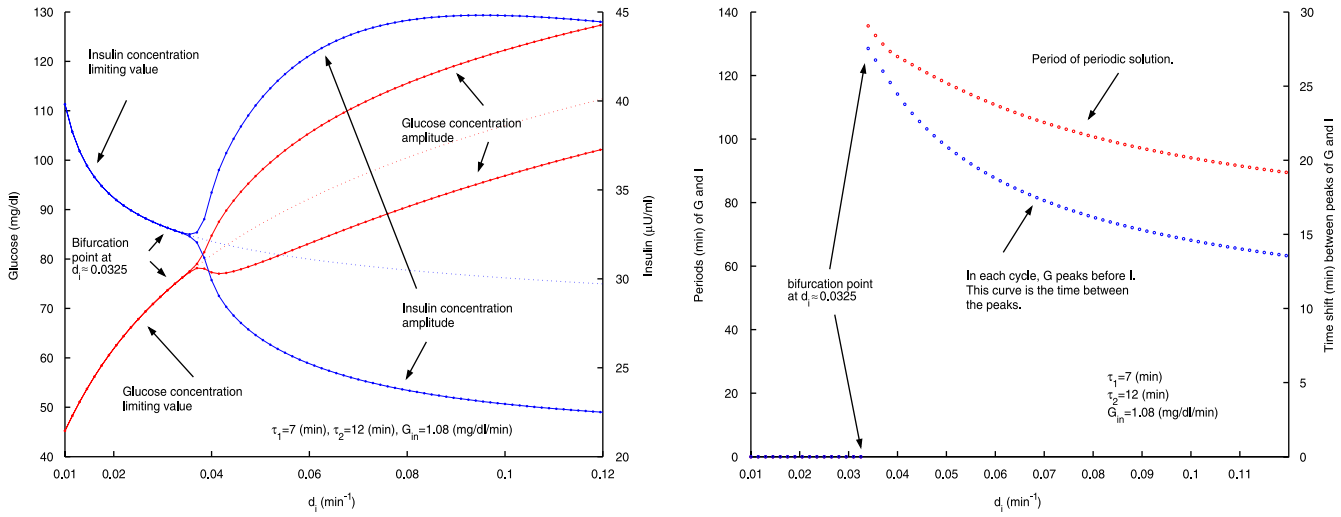


Fig. 12. Left: Bifurcation diagram of $d_i \in [0.01, 0.12]\,\text{min}^{-1}$. Right: Periods of the periodic solutions and the time differences between the peaks of glucose and insulin concentrations in each cycle.

oscillation and the periods (95–155 min) of periodic solutions are in agreement with observed experimental data (Sturis et al., 1991; Tolic et al., 2000). Simulations also show that in each cycle the time between the glucose concentration peak and insulin concentration peak is in the range of 17–20 min. This quantifies the statement "slight advance of the glucose oscillation compared with the insulin oscillation" in Sturis et al. (1991).

(A3) The simulations in Section 4.2 indicate that the time delay $\tau_1$, as well as the time delay $\tau_2$, play a key role in the oscillatory regulation of the glucose–insulin metabolic system. When $\tau_1$ is between 5 and 15 min, the amplitude is between 65 and 125 mg/dl. These simulations are in agreement with previous experiments (Sturis et al., 1991; Simon and Brandenberger, 2002 and references therein).

(A4) According to the numerical simulations using the constant glucose infusion rate $G_{in}$ as a parameter in Section 4.3, for low infusion rates, the amplitude of glucose concentration can be as low as that of the hypoglycemic range. When the infusion rate is larger, the steady state becomes stable.

(A5) The simulations of Section 4.4 (right) show that large insulin degradation rates correspond to quicker insulin concentration peaks following the peaks of glucose concentration. Fig. 12 (left) shows that glucose concentration is at higher levels when the insulin degradation rate becomes larger.

(A6) It is clear that during one cycle of the insulin and glucose concentration oscillations, the insulin concentration level peaks subsequent to the glucose concentration level. This reflects the physiological fact that glucose stimulates insulin secretion. On the other hand, the glucose concentration level decays before the insulin concentration level does. This reflects the phenomena that higher insulin concentration increases glucose uptake by the cells. Our simulations quantify the time of the two peaks in each cycle as approximately 20 min.

(A7) The statement "$t_i$ and $t_p$ are small" in (BG1) implies that the insulin degradation rate $d_i$ in the two time delay model (1) is large. Our simulation (Fig. 12) reveals that, if $d_i > d_{i0} \approx 0.0325$, then the model (1) can have a sustained periodic solution. This observation is in agreement with (BG1).

(A8) When we let $\tau_1 = 0$ or $\tau_2 = 0$, our simulations show that the system does not have sustained oscillations when the other delay parameter is not large ($\tau_2 > 46$ or $\tau_1 > 18$). This confirms observations (ST1) and (ST3) in Sturis et al. (1991) and Tolic et al. (2000). Hence, the extra effort of splitting insulin into two compartments is reduced by introducing the time delay explicitly.

(A9) According to the profiles in Figs. 6 and 7, and our intensive simulations, the ODE model (7) and the single delay model (9) behave very similarly. The alternative two delay model (11) is somewhat more robust. The alternative single delay model (10) is even more robust and is almost as good as the two delay model (1). With wide delay parameter ranges, the two delay model (1) produces best dynamics in more reasonable physiological range that are in agreement with experimental data. Notice that the position of the delay parameter $\tau_1$ in these models, if there is any, it suggests that the time delay from insulin secretion stimulated by glucose to the insulin becoming "*remote insulin*" plays a key role for self-sustained oscillation in the glucose–insulin regulatory system. Thus it is not only significant, but also has to be in the term reflecting the insulin secretion triggered by glucose concentration. Thus, we suspect that one of the possibly many causes of ultradian insulin secretion oscillations is due to the time delay of the insulin secretion stimulated by the elevated glucose concentration.

Observable delay effects are often gradual (distributed) and smooth in most physiological systems, it is thus natural to utilize distributed delay parameters rather than discrete delays when modeling these systems. In other words,

discrete delay is often a simplification of the complicated physiology process that is almost always best represented by smooth (continuous and distributed) delay. However, mathematically, a single discrete delay alone can often generate rich dynamics that enable and facilitate non-trivial and interesting biological observations as evidenced by this work. Nevertheless, we plan to pursue additional studies on the glucose–insulin regulatory system and the ultradian insulin secretory oscillations through models with distributed time delays.

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