Received: Added at production | Revised: Added at production | Accepted: Added at production

DOI: xxx/xxxx

RESEARCH ARTICLE

Dynamic modeling of the glucose-insulin system with inhibitors impulsive control

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Abstract

Pulse injection of insulin analogues is an important strategy to control blood glucose concentrations and can be combined with α– glucosidase inhibitors to reduce adverse effects to improve glucose control. We propose a novel mathematical models with pulse injection insulin and α– glucosidase inhibitors , eating in the form of pulse blood glucose injection. The existence and uniqueness of the positive periodic solution is confirmed In type 1 diabetes, which is globally asymptotically stable. Further, the permanence of the system is given in type 2 diabetes. The numerical analysis verified the correctness of the theoretical calculation results, and show that the period and the dose of insulin injections and α– glucosidase inhibitors are crucial for insulin therapies. In addition, we systematically evaluated a reasonable strategy to treat diabetes combined with α– glucosidase inhibitors, which can provide more reasonable clinical strategies.

KEYWORDS
diabetes, LambertW function, periodic solution, globally stability, permanence.

1 | INTRODUCTION

Diabetes is a chronic disease in which the blood sugar level rises due to the lack of insulin or the impaired function of insulin secretion. With the change of age structure and lifestyle habits, the prevalence rate of diabetes has a rising trend and the characteristics of young people [1], thus it has become a chronic non-hereditary disease that seriously endangers people's health. Diabetes mellitus can be divided into *Type* 1 *Diabetes Mellitus* (T1DM) and *Type* 2 *Diabetes Mellitus* (T2DM) according to its causes. T1DM is an autoimmune disease, *T* lymphocytes mediate the activation of the autoimmune system, leading to the destruction and functional failure of islet cells, and the absolute lack of endogenous insulin; in people with T2DM, the body's cells can not absorb and metabolize glucose to produce energy [2,3]. In the existing treatment regimen, patients with diabetes need continuous injection of exogenous subcutaneous insulin analogues or use insulin pumps, but adverse reactions such as hypoglycemia, insulin resistance, increased body mass, lipodystrophy and so on lead to unsatisfactory therapeutic effect and substandard glucose. Base on medical clinical research and data statistics, on the basis of exogenous insulin injection to control blood sugar, combined with α– glucosidase inhibitors can reduce adverse reactions, so that diabetic patients can get better treatment effect.

The α – *glucosidase inhibitors* (AGIs) are a class of oral drugs that reduce the absorption of carbohydrates in the organism by inhibiting glucosidase, thus reducing the concentration of blood glucose [4]. Clinical studies have shown that the main drugs of AGIs, including Acarbose and hemoglobin, used in treatment can reduce the level of *glycated hemoglobin* (HbA1c) without increasing body mass in patients with T2DM [5,6,7]. At present, there are studies on the treatment of T1DM patients with AGIs, and found that it can significantly improve the control of blood glucose in T1DM patients [8,9].

In recent years, in order to get the right dose of insulin and the right time of injection, a class of diabetes models targeting

Abbreviations: T1DM(T2DM), Type 1(2) Diabetes Mellitus; AGIs, α-glucosidase inhibitors.

artificial pancreas has brought new hope for the control or cure of diabetes[10,11,12,13,14,15,16,17]. However, few scholars have studied the influence of AGIs on diabetes models. In order to better understand the dynamic regulation of glucose and insulin in the organism under the treatment of insulin, and the effect of AGIs on postprandial blood glucose concentration, it is necessary to study the dynamic regulation of glucose-insulin system glucose and insulin in physiology with periodic intakes of insulin injections and α– glucosidase inhibitors[18,19,20]. According to the biological mechanism of insulin-glucose biodynamics, AGIs can delay the absorption of carbohydrates to reduce postprandial hyperglycemia, and the time interval between ingestion and administration of AGIs is negligible relative to the effect of AGIs, so pulse can depict the dynamic process of AGIs. Eating is approximately pulse glucose injection, and the time interval between eating and taking medicine was approximately negligible compared with the time of drug effect, we developed a insulin-glucose interaction systems with two different control strategies. In addition, elevated blood glucose levels stimulate cells in the pancreas to secrete insulin, and the rate of insulin degradation is *Michaelis – Menten* function $\frac{dI}{k+I}$, it's more realistic than a linear rate, where d is maximum insulin clearance rate, k is the half-saturation value (see[21]). Therefore, the insulin injection and medication of diabetic patients can be regarded as pulse injection to simulate the injection of insulin before eating and the oral administration of AGIs during eating, and then the insulin-glucose feedback system of insulin combined with AGIs to control blood glucose can be described in more detail. Thus, this paper proposes a dynamic system of impulse differential equations with double fixed time:

$$\begin{cases} \left.\begin{aligned} G'(t) &= -(\sigma_2 + a(c + \tfrac{mI(t)}{k+I(t)}))G(t) + \tilde{b}, \\ I'(t) &= \tfrac{\sigma_1 G^2(t)}{\alpha^2+G^2(t)} - \tfrac{dI(t)}{k+I(t)}, \end{aligned}\right\} t \neq (n+\lambda-1)\tau, t \neq n\tau, \\ \left.\begin{aligned} G(t^+) &= G(t), \\ I(t^+) &= I(t) + \tilde{\sigma}, \end{aligned}\right\} t = (n+\lambda-1)\tau, \\ \left.\begin{aligned} G(t^+) &= qG(t) + G_{in}, \\ I(t^+) &= I(t), \end{aligned}\right\} t = n\tau, \lambda, q \in (0,1), \end{cases} \tag{1.1}$$

with initial conditions $G(0) = G_0 > 0$, $I(0) = I_0 > 0$, where $G(t)$ and $I(t)$ denote the blood glucose concentration and insulin concentration at $t > 0$ time, respectively. The parameter $\tilde{G}_{in}$ represents the continuous exogenous injection of glucose (mimicking food intake) and $\sigma_2 G(t)$ represents the independent breakdown of glucose consumption by insulin. $aG(c + \frac{mI(t)}{k+I(t)})$ denotes insulin-dependent glucose utilization, and $\tilde{b} > 0$ is the rate of hepatic glucose production. $\frac{\sigma_1 G^2(t)}{\alpha_1^2+G^2(t)}$ is amount of insulin secretion stimulated by the increase of glucose concentration indicates. $\sigma_1, \sigma_2, \alpha_1, a, c, m, k$is the normal number. Parameter $\tilde{\sigma}(\mu U/ml) > 0$ represents the dose of exogenous insulin injected, $\tau(\min) > 0$ denote the injection period, $\tilde{\sigma}(\mu U/ml)$ denote that insulin is injected into the organism at $t = n\tau (n \in Z_+)$ discrete pulse times, and the n^{th} instant after injection is denoted as $t = n\tau^+$, and $t = (n+\lambda-1)\tau$ the representative represents glucose infusion in which pulse insulin is injected at discrete times, $\tilde{\sigma}(\mu U/ml) > 0$ is the amount of each exogenous insulin injection at discrete time, G_{in} is the glucose intake at $t = n\tau$ discrete time, and $qG(t)$ is the blood glucose concentration after oral administration of AGIs at $t = n\tau$ discrete time.

2 | PRELIMINARIES

Let $R_+ = [0, \infty)$ and $R_+^2 = \{X = (x_1, x_2)^T \in R^2 : x_i \in R_+, i = 1, 2\}$. Denote by $f = (f_1, f_2)^T$ the map defined by right-hand sides of the first two equation of (1.1)[22]. Set $V : R_+ \times R^n \to R_+$ and then V is said to belong to class V_0 if
(i) V is continuous in $((n-1)\tau, (n+\lambda-1)\tau] \times R_+^2 \cup ((n+\lambda-1)\tau, n\tau] \times R_+^2$, for each $X \in R_+^2$,

$$\lim_{(t,s)\to((n+\lambda-1)\tau^+, X)} V(t,s) = V((n+\lambda-1)\tau^+, X)$$

and

$$\lim_{(t,s)\to(n\tau^+, X)} V(t,s) = V(n\tau^+, X)$$

exist;
(ii) V is locally Lipschitzian in X.

Definition 1. Let $V \in V_0$, then for $((t,X) \in ((n-1)\tau, (n+\lambda-1)\tau] \times R_+^2 \cup ((n+\lambda-1)\tau, n\tau] \times R_+^2$, the upper right derivative of $V(t,X)$ with respect to system (1.1) is defined as

$$D^+V(t,X) = \lim_{h\to 0^+} \sup \frac{1}{h}[V(t+h, X+hf(t,X)) - V(t,X)].$$

Definition 2. System is said to be permanent if there exist positive constant m and M with $M \geq m \geq 0$ such that every positive solution $G(t)$,$I(t)$ satisfying

$$m \leq G(t) \leq M \text{ and } m \leq I(t) \leq M,$$

for all t large enough. The solution of system (1.1), denoted by $X(t) = (G(t), I(t)) : R_+ \to R_+^2$, is continuously differentiable on $((n-1)\tau, (n+\lambda-1)\tau] \cup ((n+\lambda-1)\tau, n\tau],\ n \in Z_+$.

Definition 3. The *Lambert W* function is defined to be a multivalued inverse of the function $z \mapsto ze^z$ satisfying

$$Lambert\ W(z)exp(LambertW(z)) = z,$$

It follows from above definition that we have

$$Lambert\ W^{'}(z) = \frac{LambertW(z)}{z(1 + LambertW(z))},$$

and which has two real branches will play an important role in calculating the analytical solutions of one compartment with a constant input.(see Figure.1)

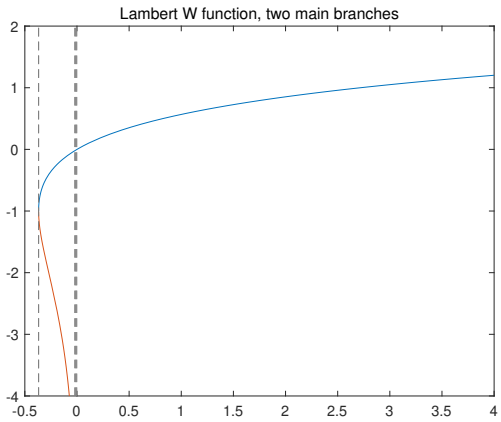


FIGURE 1 the two real branches of *Lambert Wfucntion*

Lemma 1. *Suppose that* $(G(t), I(t))$ *is a solution of system (1.1) with* $G(0^+) \geq 0,\ I(0^+) \geq 0$*, then* $G(t) > 0,\ I(t) > 0$ *for all* $t \geq 0$*. Furthermore,* $G(t) > 0, I(t) > 0$ *if* $G(0^+) > 0, I(0^+) > 0$*.*

Lemma 2. *Both systems (2.1) and (2.2)*

$$\begin{cases} u'_1(t) = a_1 - b_1 u_1(t), & t \neq (n+\lambda-1)\tau, t \neq n\tau, \\ u_1(t^+) = u_1(t) + \sigma, & t = (n+\lambda-1)\tau, \\ u_1(t^+) = u_1(t), & t = n\tau, \\ u_1(0^+) = u_{01}, \end{cases} \tag{2.1}$$

and

$$\begin{cases} u'_2(t) = a_2 - b_2 u_2(t), & t \neq (n+\lambda-1)\tau, t \neq n\tau, \\ u_2(t^+) = u_2(t), & t = (n+\lambda-1)\tau, \\ u_2(t^+) = u_2(t) + G_{in}, & t = n\tau, \\ u_2(0^+) = u_{02}, \end{cases} \tag{2.2}$$

have unique positive periodic solutions $u_1^*(t)$ and $u_2^*(t)$, respectively, and for every solutions $u_1(t)$ of (2.1) and $u_2(t)$ of (2.2), satisfying

$$|u_i(t) - u_i^*(t)| \to 0, t \to \infty, i = 1, 2,$$

where

$$u_i^*(t) = \begin{cases} \frac{a_i}{b_i} + (u_i^*(0^+) - \frac{a_i}{b_i})e^{-b_i(t-(n-1)\tau)}, & t \in ((n-1)\tau, (n+\lambda-1)\tau], \\ \frac{a_i}{b_i} + (u_i^*((n+\lambda-1)\tau^+) - \frac{a_i}{b_i})e^{-b_i(t-(n+\lambda-1)\tau)}, & t \in ((n+\lambda-1)\tau, n\tau], \end{cases}$$

$$\begin{aligned} u_1^*(0^+) = u_1^*(n\tau^+) &= \frac{a_1}{b_1} + \frac{\sigma e^{-b_1(1-\lambda)\tau}}{1-e^{-b_1\tau}}, \\ u_1^*((n+\lambda-1)\tau^+) &= \frac{a_1}{b_1} + \frac{\sigma}{1-e^{-b_1\tau}}, \\ u_2^*(0^+) = u_2^*(n\tau^+) &= \frac{a_2}{b_2} + \frac{G_{in}}{1-e^{-b_2\tau}}, \\ u_2^*((n+\lambda-1)\tau^+) &= \frac{a_2}{b_2} + \frac{G_{in}e^{-b_2\lambda\tau}}{1-e^{-b_2\tau}}. \end{aligned}$$

Especially, when $a_i = 0$, both systems (2.1) and (2.2) have unique positive periodic solutions

$$u_1^*(t) = \begin{cases} \frac{\sigma e^{-b_1(1-\lambda)\tau}}{1-e^{-b_1\tau}} e^{-b_1(t-(n-1)\tau)}, & t \in ((n-1)\tau, (n+\lambda-1)\tau], \\ \frac{\sigma}{1-e^{-b_1\tau}} e^{-b_1(t-(n+\lambda-1)\tau)}, & t \in ((n+\lambda-1)\tau, n\tau], \end{cases} \tag{2.3}$$

and

$$u_2^*(t) = \begin{cases} \frac{G_{in}}{1-e^{-b_2\tau}} e^{-b_2(t-(n-1)\tau)}, & t \in ((n-1)\tau, (n+\lambda-1)\tau], \\ \frac{G_{in}}{1-e^{-b_2\tau}} e^{-b_2(t-(n+\lambda-1)\tau)}, & t \in ((n+\lambda-1)\tau, n\tau]. \end{cases} \tag{2.4}$$

Lemma 3. *Let $V \in V_0$ and assume that*

$$\begin{cases} D^+V(t,x) \le g(t, v(t,x)), & t = (n+\lambda-1)\tau, t \ne n\tau, \\ V(t, X(t^+)) \le \phi_n(V(t,X)), & t = (n+\lambda-1)\tau, \\ V(t, X(t^+)) \le \phi_n(V(t,X)), & t = n\tau, \end{cases}$$

where $g : R_+ \times R_+ \to R$ is continues in $((n-1)\tau, (n+\lambda-1)\tau] \times R_+ \cup ((n+\lambda-1)\tau, n\tau] \times R_+$ and for each $X(t) \in R_+^2, n \in Z_+$,

$$\lim_{(t,s)\to((n+\lambda-1)\tau^+, X)} g(t,s) = g((n+\lambda-1)\tau^+, X),$$

$$\lim_{(t,s)\to(n\tau^+, X)} g(t,s) = g(n\tau^+, X),$$

exist and is finite; $\Phi_n, \Psi_n : R_+ \to R_+$ are non-decreasing. Let $R(t)$ be the maximal solution of the scalar impulsive differential equation

$$\begin{cases} u'(t) = g(t, u(t)), & t \ne (n+\lambda-1)\tau, t \ne n\tau, \\ u(t^+) = \Phi_n(u(t)), & t = (n+\lambda-1)\tau, \\ u(t^+) = \Psi_n(u(t)), & t = n\tau, \\ u(0^+) = u_0 \ge 0, \end{cases} \tag{2.5}$$

defined on $[0, \infty)$. Then $V(0^+, x(0^+)) \le u_0$ implies that

$$V(t, X(t)) \le R(t),$$

for all $t \ge 0$, where $X(t) = (G(t), I(t))$ is any solution of system (1.1).

3 | MATHEMATICAL ANALYSIS AND RESULTS

For system (1.1), when $\sigma_1 = 0$ means that the pancreas does not secrete or releases very little insulin, and it is precisely because of the impaired function of its own β islet cells in T1DM patients that the endogenous insulin pair is deficient. Thus the model degrades to:

$$\begin{cases} \left.\begin{aligned} G'(t) &= -(\sigma_2 + a(c + \tfrac{mI(t)}{k+I(t)}))G(t) + \tilde{b}, \\ I'(t) &= -\tfrac{dI(t)}{k+I(t)}, \end{aligned}\right\} t \neq (n+\lambda-1)\tau, t \neq n\tau, \\ \left.\begin{aligned} G(t^+) &= G(t), \\ I(t^+) &= I(t) + \tilde{\sigma}, \end{aligned}\right\} t = (n+\lambda-1)\tau, \\ \left.\begin{aligned} G(t^+) &= qG(t) + G_{in}, \\ I(t^+) &= I(t), \end{aligned}\right\} t = n\tau, \lambda, q \in (0,1). \end{cases} \tag{3.1}$$

Then we discuss the existence, uniqueness, persistence and global asymptotic stability of periodic solutions of model system (3.1).

3.1 | Existence and stability of periodic solutions in the model of T1DM

Theorem 1. *Model system (3.1) have unique positive periodic solution* $(G^*(t), I^*(t))$*, if* $\frac{\tilde{\sigma}}{\tau} < d$.

Proof. According to model system (3.1), this is equivalent to ignoring the stimulation of insulin secretion caused by the increase of blood glucose concentration, and only considering the degradation of insulin. Therefore, the degraded system does not appear $G(t)$ in the second equation, and the following subsystem is considered:

$$\begin{cases} I'(t) = -\dfrac{dI(t)}{k+I(t)}, & t \neq (n+\lambda-1)\tau, t \neq n\tau, \\ I(t^+) = I(t) + \tilde{\sigma}, & t = (n+\lambda-1)\tau, \\ I(t^+) = I(t^+), & t = n\tau, \\ I(0^+) = I_0 > 0, \end{cases} \tag{3.2}$$

from the first equation,

$$\frac{k+I(t)}{-dI(t)}dI = dt, \tag{3.3}$$

integrate Equ.(3.3) in $t \in ((n-1)\tau, (n+\lambda-1)\tau]$,

$$-\frac{k}{d}\ln|\frac{I((n-1)\tau^+)}{I(t)}| - \frac{1}{d}(I((n-1)\tau^+) - I(t)) = (n-1)\tau - t,$$

then we have

$$\frac{I(t)}{k}e^{\frac{I(t)}{k}} = \frac{I((n-1)\tau^+)}{k}\exp\Big\{\frac{1}{k}(-d(t-(n-1)\tau) + I((n-1)\tau^+))\Big\},$$

by Definition 3., the equation is constant positive, which can be solved by the upper branch of *Lambert W* function

$$I^*(t) = kLambert\ W(\frac{I((n-1)\tau^+)}{k}\exp\Big\{\frac{1}{k}(-d(t-(n-1)\tau) + I((n-1)\tau^+))\Big\}), \tag{3.4}$$

similarly, when $t \in ((n+\lambda-1)\tau, n\tau]$,

$$I^*(t) = kLambert\ W(\frac{I((n+\lambda-1)\tau^+)}{k}\exp\Big\{\frac{1}{k}(-d(t-(n+\lambda-1)\tau) + I((n+\lambda-1)\tau^+))\Big\}), \tag{3.5}$$

thus, if satisfied $\frac{\tilde{\sigma}}{\tau} < d$, $I^*(t)$ given by (the detailed mathematical analysis is given in Appendix A)

$$I^*(t) = \begin{cases} kLambert\ W(\frac{I^*(0^+)}{k}\exp\Big\{\frac{1}{k}(-d(t-(n-1)\tau + I^*(0^+))\Big\}), \\ \qquad\qquad t \in ((n-1)\tau, (n+\lambda-1)\tau], \\ kLambert\ W(\frac{I^*((n+\lambda-1)\tau^+)}{k}\exp\Big\{\frac{1}{k}(-d(t-(n+\lambda-1)\tau + I^*((n+\lambda-1)\tau^+))\Big\}), \\ \qquad\qquad t \in ((n+\lambda-1)\tau, n\tau], \end{cases} \tag{3.6}$$

where

$$I(0^+) = I(n\tau^+) = kLambert\ W\left(\frac{\tilde{\sigma} exp\{\frac{\tilde{\sigma} exp\{\frac{1}{k}(\tilde{\sigma}-d\tau)\}}{k(1-exp\{\frac{1}{k}(\tilde{\sigma}-d\tau)\})}\}}{k(exp\{\frac{1}{k}(d(1-\lambda)\tau-\tilde{\sigma})\}-exp\{-\frac{d\lambda\tau}{k}\})}\right),$$

$$I((n+\lambda-1)\tau^+) = \frac{\tilde{\sigma}}{1-exp\{\frac{1}{k}(\sigma-d\tau)\}}.$$

Substituting the subsystem periodic solution (3.3) into model system (3.1) gives

$$\begin{cases} G'(t) = -(\sigma_2 + a(c + \dfrac{mI^*(t)}{k+I^*(t)}))G(t) + \tilde{b}, & t \neq (n+\lambda-1)\tau, t \neq n\tau \\ G(t^+) = G(t), & t = (n+\lambda-1)\tau, \\ G(t^+) = qG(t) + G_{in}, & t = n\tau, \\ G(0^+) = G_0 > 0. \end{cases} \tag{3.7}$$

To solve this impulse equation by integration, according to the fixed time, we can obtain:
(1) $t \in ((n-1)\tau, (n+\lambda-1)\tau]$,

$$G(t) = G((n-1)\tau^+)e^{-\int_{(n-1)\tau^+}^{t} ac+\sigma_2+\frac{amI^*(s)}{k+I^*(s)}ds} + \tilde{b}\int_{(n-1)\tau^+}^{t} e^{-\int_u^t ac+\sigma_2+\frac{amI^*(s)}{k+I^*(s)}ds}du,$$

by $G(t^+) = qG(t) + G_{in}$,

$$G(t) = (qG((n-1)\tau + G_{in})e^{-\int_{(n-1)\tau^+}^{t} ac+\sigma_2+\frac{amI^*(s)}{k+I^*(s)}ds} + \tilde{b}\int_{(n-1)\tau^+}^{t} e^{-\int_u^t ac+\sigma_2+\frac{amI^*(s)}{k+I^*(s)}ds}du,$$

Further, according to system (3.1), $\exists k_1, k_2 \in [(n-1)\tau^+, (n+\lambda-1)\tau]$, and $k_1 \leq k_2$, obtain

$$\begin{aligned} e^{-am\int_{k_1}^{k_2}\frac{I^*(s)}{k+I^*(s)}ds} &= e^{\frac{am}{d}\int_{k_1}^{k_2}\frac{-dI^*(s)}{k+I^*(s)}ds} \\ &= e^{\frac{am}{d}\int_{k_1}^{k_2} I'(s)ds} \\ &= e^{\frac{am}{d}(I(k_2)-I(k_1))}, \end{aligned}$$

therefore,

$$\begin{aligned} G(t) = (qG((n-1)\tau) + G_{in})e^{(-(ac+\sigma_2)(t-(n-1)\tau))+\frac{am}{d}(I^*(t)-I^*(0^+))} \\ + \tilde{b}\int_{(n-1)\tau^+}^{t} e^{(-(ac+\sigma_2)(t-u))+\frac{am}{d}(I^*(t)-I^*(u))}du, \end{aligned}$$

when $t = (n+\lambda-1)\tau$,

$$\begin{aligned} G((n+\lambda-1)\tau) = (qG(n-1)\tau + G_{in})e^{(-(ac+\sigma_2)\lambda\tau)+\frac{am}{d}(I^*(\lambda\tau)-I^*(0^+))} \\ + \tilde{b}\int_{0^+}^{\lambda\tau} e^{(-(ac+\sigma_2)(\lambda\tau-u))+\frac{am}{d}(I^*(\lambda\tau)-I^*(u))}du, \end{aligned} \tag{3.8}$$

(2) $t \in ((n+\lambda-1)\tau, n\tau]$,

$$\begin{aligned} G(t) &= G((n+\lambda-1)\tau^+)e^{-\int_{n+\lambda-1\tau^+}^{t}(ac+\sigma_2+\frac{amI^*(s)}{k+I^*(s)})ds} + \tilde{b}\int_{n+\lambda-1\tau^+}^{t} e^{-\int_v^t(ac+\sigma_2+\frac{amI^*(s)}{k+I^*(s)})ds}dv \\ &= G((n+\lambda-1)\tau)e^{-\int_{n+\lambda-1\tau^+}^{t}(ac+\sigma_2+\frac{amI^*(s)}{k+I^*(s)})ds} + \tilde{b}\int_{n+\lambda-1\tau^+}^{t} e^{-(ac+\sigma_2)(t-v)}e^{-\int_v^t\frac{amI^*(s)}{k+I^*(s)})ds}dv, \end{aligned} \tag{3.9}$$

in the same way,

$$\begin{aligned} G(t) = G((n+\lambda-1)\tau)e^{-(ac+\sigma_2)(t-\lambda\tau)+\frac{am}{d}(I^*(t)-I^*(\lambda\tau^+))} \\ + \tilde{b}\int_{(n+\lambda-1)\tau^+}^{t} e^{-(ac+\sigma_2)(t-v)+\frac{am}{d}(I^*(t)-I^*(v))}dv, \end{aligned} \tag{3.10}$$

then

$$\begin{aligned} G(n\tau) = G((n+\lambda-1)\tau)e^{-(ac+\sigma_2)((1-\lambda)\tau)+\frac{am}{d}(I^*(\tau)-I^*(\lambda\tau^+))} \\ + \tilde{b}\int_{\lambda\tau^+}^{\tau} e^{-(ac+\sigma_2)(\tau-v)+\frac{am}{d}(I^*(\tau)-I^*(v))}dv, \end{aligned} \tag{3.11}$$

Equ.(3.8) and Equ.(3.11) can be obtained simultaneously,

$$\begin{cases} G((n+\lambda-1)\tau) = A_\lambda G((n+\lambda-2)\tau) + B_\lambda G_{in} + C_\lambda, \\ G(n\tau) = A_\lambda G((n-1)\tau) + B_\lambda \Lambda G_{in} + D_\lambda, \end{cases} \tag{3.12}$$

where

$$\begin{aligned} A_\lambda &= qe^{-(ac+\sigma_2)\tau+\frac{am}{d}(I^*(\lambda\tau)-I^*(\lambda\tau^+))}, \\ B_\lambda &= e^{-(ac+\sigma_2)\lambda\tau+\frac{am}{d}(I^*(\lambda\tau)-I^*(0^+))}, \\ C_\lambda &= \tilde{b}e^{-(ac+\sigma_2)\lambda\tau+\frac{am}{d}(I^*(\lambda\tau)-I^*(0^+))}\int_{\lambda\tau^+}^{\tau} e^{-(ac+\sigma_2)(\tau-v)+\frac{am}{d}(I^*(\tau)-I^*(v))}dv \\ &+ \tilde{b}\int_{0^+}^{\lambda\tau} e^{-(ac+\sigma_2)(\lambda\tau-u)+\frac{am}{d}(I^*(\lambda\tau)-I^*(u))}du, \\ \Lambda &= e^{-(ac+\sigma_2)(1-\lambda)\tau+\frac{am}{d}(I^*(\tau)-I^*(\lambda\tau^+))}, \\ D_\lambda &= \tilde{b}\cdot\Lambda\cdot\int_{0^+}^{\lambda\tau} e^{-(ac+\sigma_2)(\lambda\tau-u)+\frac{am}{d}(I^*(\lambda\tau)-I^*(u))}du\cdot e^{-(ac+\sigma_2)\lambda\tau+\frac{am}{d}(I^*(\lambda\tau)-I^*(0^+))} \\ &+ \tilde{b}\int_{\lambda\tau^+}^{\tau} e^{-(ac+\sigma_2)(\tau-v)+\frac{am}{d}(I^*(\tau)-I^*(v))}dv. \end{aligned}$$

Definitely, by $I(\lambda\tau^+) = I(\lambda\tau) + \tilde{\sigma}$, obtain $0 < A_\lambda < 1$ i.e. $\tau > \frac{am\tilde{\sigma}+d\ln q}{(ac+\sigma_2)d}$, thus Equ.(3.12) has a unique fixed point:

$$G^* = \begin{cases} \dfrac{B_\lambda G_{in} + C_\lambda}{1-A_\lambda}, & t \in ((n-1)\tau, (n+\lambda-1)\tau], \\ \dfrac{B_\lambda \Lambda G_{in} + D_\lambda}{1-A_\lambda}, & t \in ((n+\lambda-1)\tau, n\tau], \end{cases} \tag{3.13}$$

and Equ.(3.13) is globally asymptotically stable[23], and its periodic solution $G^*(t)$ is also globally asymptotically stable[17,24], where

$$G^*(t) = \begin{cases} \left.\begin{aligned} &(q\frac{B_\lambda G_{in}+C_\lambda}{1-A_\lambda} + G_{in})e^{(-(ac+\sigma_2)(t-(n+\lambda-1)\tau))+\frac{am}{d}(I^*(t)-I^*(0^+))} \\ &+ \tilde{b}\int_{(n-1)\tau^+}^{t} e^{(-(ac+\sigma_2)(t-u))+\frac{am}{d}(I^*(t)-I^*(u))}du, \end{aligned}\right\} t \in ((n-1)\tau, (n+\lambda-1)\tau], \\ \left.\begin{aligned} &\frac{B_\lambda \Lambda G_{in}+D_\lambda}{1-A_\lambda}e^{(-(ac+\sigma_2)(t-(n+\lambda-1)\tau))+\frac{am}{d}(I^*(t)-I^*(\lambda\tau^+))} \\ &+ \tilde{b}\int_{(n+\lambda-1)\tau^+}^{t} e^{(-(ac+\sigma_2)(t-v))+\frac{am}{d}(I^*(t)-I^*(v))}dv, \end{aligned}\right\} t \in ((n+\lambda-1)\tau, n\tau], \end{cases} \tag{3.14}$$

with

$$\begin{cases} G^*(0^+) = G^*(n\tau^+) = \dfrac{B_\lambda \Lambda G_{in} + D_\lambda}{1-A_\lambda}, \\ G^*((n+\lambda-1)\tau^+) = \dfrac{B_\lambda G_{in} + C_\lambda}{1-A_\lambda}. \end{cases}$$

Thus the unique positive periodic solution $(G^*(t), I^*(t))$ of model system (3.1) is obtained. □

3.2 | Stability of periodic solutions in the model of T1DM

Theorem 2. *The positive periodic solution $(G^*(t), I^*(t))$ of system (3.1) is globally asymptotically stable.*

Proof. Suppose $(G(t), I(t))$ is any solution of system (3.1), first of all, using the *Floquet* multiplier theory that $(G^*(t), I^*(t))$ is local stability. To this end, adding the consideration of small amplitude disturbance behavior $\omega_1(t)$ and $\omega_2(t)$, namely, it holds that:

$$\begin{aligned} G(t) &= G^*(t) + \omega_1(t), \\ I(t) &= I^*(t) + \omega_2(t). \end{aligned} \tag{3.15}$$

By using the Taylor expansion Equ.(3.15) and ignoring the higher-order terms, the linearized system can be obtained as follows.

$$\begin{pmatrix}\omega_1(t)\\ \omega_2(t)\end{pmatrix} = \Phi(t)\begin{pmatrix}\omega_1(0)\\ \omega_2(0)\end{pmatrix}, \tag{3.16}$$

and satisfied

$$\frac{d\Phi(t)}{dt} = \begin{pmatrix}-(ac+\sigma_2)-\frac{amI^*(t)}{k+I^*(t)} & -\frac{amkG^*(t)}{(k+I^*(t))^2}\\ 0 & -\frac{dk}{(k+I^*(t))^2}\end{pmatrix}, \tag{3.17}$$

where

$$\Phi(t) = \begin{pmatrix}\exp[(\int_0^t -(ac+\sigma_2)-\frac{amI^*(t)}{k+I^*(t)})dt] & *\\ 0 & \exp(\int_0^t -\frac{dk}{(k+I^*(t))^2}dt)\end{pmatrix},$$

obviously, $\Phi(0) = I$, where $*$ is not discussed because it does not affect the stability analysis, and I is the identity matrix.

Equ.(3.15) has a reset pulse condition

$$\begin{pmatrix}\omega_1((n+\lambda-1)\tau^+)\\ \omega_2((n+\lambda-1)\tau^+)\end{pmatrix} = \begin{pmatrix}1 & 0\\ 0 & 1\end{pmatrix}\begin{pmatrix}\omega_1((n+\lambda-1)\tau)\\ \omega_2((n+\lambda-1)\tau)\end{pmatrix},$$

and

$$\begin{pmatrix}\omega_1(n\tau^+)\\ \omega_2(n\tau^+)\end{pmatrix} = \begin{pmatrix}q & 0\\ 0 & 1\end{pmatrix}\begin{pmatrix}\omega_1(n\tau)\\ \omega_2(n\tau)\end{pmatrix},$$

Let

$$\begin{aligned} M &= \begin{pmatrix}1 & 0\\ 0 & 1\end{pmatrix}\begin{pmatrix}q & 0\\ 0 & 1\end{pmatrix}\Phi(\tau)\\ &= \begin{pmatrix}q\exp[(-\int_0^\tau ac+\sigma_2+\frac{amI^*(t)}{k+I^*(t)})dt] & *\\ 0 & \exp[-\int_0^\tau \frac{dk}{(q+I^*(t))^2}dt]\end{pmatrix}, \end{aligned} \tag{3.18}$$

where

$$\Phi(\tau) = \begin{pmatrix}\exp(\int_0^\tau -(ac+\sigma_2)-\frac{amI^*(t)}{k+I^*(t)})dt & *\\ 0 & \exp(\int_0^\tau -\frac{dk}{(k+I^*(t))^2})\end{pmatrix}.$$

According to *Floquet* multiplier theory, $(G^*(t), I^*(t))$, the local stability of decided by the eigenvalues of Equ.(3.18), and the eigenvalues for

$$\lambda_1 = q\exp[-(\int_0^\tau ac+\sigma_2+\frac{amI^*(t)}{k+I^*(t)}dt] < 1,$$
$$\lambda_2 = \exp[-\int_0^\tau \frac{dk}{(k+I^*(t))^2}dt] < 1,$$

thus, the positive periodic solution $(G^*(t), I^*(t))$ is locally stable.

Secondly, to obtain that $(G^*(t), I^*(t))$ is globally asymptotically stable, using Lemma2.3, since

$$\lim_{t\to\infty} I(t) = I^*(t),$$

so that for $\forall\varepsilon_1 > 0$,

$$I^*(t)-\varepsilon_1 < I^*(t) < I^*(t)+\varepsilon_1,$$

where, t is large enough to facilitate discussion as follows $t \geq 0$. The inequation is substituted into model system (3.1) to obtain

$$-(ac+\sigma_2)G(t)-\frac{am(I^*(t)+\varepsilon_1)}{k+I^*(t)+\varepsilon_1}G(t)+\tilde{b} \leq G'(t) \leq -(ac+\sigma_2)G(t)-\frac{am(I^*(t)-\varepsilon_1)}{k+I^*(t)-\varepsilon_1}G(t)+\tilde{b}. \tag{3.19}$$

Then we discuss the subsystem formed by the two subsystems:

$$\begin{cases} G'_1(t) = -(ac+\sigma_2)G(t)-\dfrac{am(I^*(t)+\varepsilon_1)}{k+I^*(t)+\varepsilon_1}G(t)+\tilde{b}, & t\neq(n+\lambda-1)\tau, t\neq n\tau,\\ G_1(t^+) = G_1(t), & t=(n+\lambda-1)\tau,\\ G_1(t^+) = qG(t)+G_{in}, & t=n\tau, \end{cases} \tag{3.20}$$

and

$$\begin{cases} G'_2(t) = -(ac+\sigma_2)G(t) - \dfrac{am(I^*(t)-\varepsilon_1)}{k+I^*(t)-\varepsilon_1}G(t) + \tilde{b}, & t \neq (n+\lambda-1)\tau, t \neq n\tau, \\ G_2(t^+) = G_2(t), & t = (n+\lambda-1)\tau, \\ G_2(t^+) = qG(t) + G_{in}, & t = n\tau. \end{cases} \tag{3.21}$$

Obviously, according to the above proof procedure, the unique globally asymptotically stable periodic solutions $G_1^*(t)$ and $G_2^*(t)$ can be obtained, then for sufficiently small $\forall \varepsilon > 0$, it follows from Theorem 1., then by Lemma 3.:

$$G_1^*(t) - \varepsilon < G_1(t) \leq G(t) \leq G_2(t) < G_2^*(t) + \varepsilon,$$

let $\varepsilon \to 0$, have $G_1^*(t) \to G^*(t)$, $G_2^*(t) \to G^*(t)$,
i.e.

$$G(t) \to G^*(t),$$

where $t \to \infty$.

This proves that $(G^*(t), I^*(t))$ is globally asymptotically stable. □

3.3 | Permanence of model system with T2DM

The diagnostics of T2DM and prediabetes are hyperglycemia and hyperinsulinmia, which are most likely caused by insulin resistance. Pancreatic β–cells still secrete insulin and might possibly secrete extra insulin to compensate the insulin resistance in this case, although the compensation is not enough for T2DM to uptake glucose. In this subsection, we study the permanence of system (1.1) with T2DM. This result means that both episodes of hyperglycemia and hypoglycemia can be avoided during the design regimes of exogenous insulin injection.

Theorem 3. *System (1.1) is permanent, if $\sigma_1 > 0$ and $\sigma_1 - d < 0$.*

Proof. The second equation of system satisfied

$$-\frac{dI(t)}{k+I(t)} \leq I'(t) \leq \sigma_1 - \frac{dI(t)}{k+I(t)} \tag{3.22}$$

thus, consider the following two impulsive differential subsystem:

$$\begin{cases} I'_1(t) = -\dfrac{dI(t)}{k+I(t)}, & t \neq (n+\lambda-1)\tau, t \neq n\tau, \\ I_1(t^+) = I(t) + \tilde{\sigma}, & t = (n+\lambda-1)\tau, \\ I_1(t^+) = I(t), & t = n\tau, \\ I_1(t_0^+) = I_0 > 0, \end{cases} \tag{3.23}$$

and

$$\begin{cases} I'_2(t) = \sigma_1 - \dfrac{dI(t)}{k+I(t)}, & t \neq (n+\lambda-1)\tau, t \neq n\tau, \\ I_2(t^+) = I(t) + \tilde{\sigma}, & t = (n+\lambda-1)\tau, \\ I_2(t^+) = I(t), & t = n\tau, \\ I_2(t_0^+) = I_0 > 0. \end{cases} \tag{3.24}$$

By above proof, system (3.23) has an unique globally asymptotically stable positive periodic solutions:

$$I_1^*(t) = \begin{cases} \dfrac{\tilde{\sigma}e^{-d(1-\lambda)\tau}}{1-e^{-d\tau}} e^{-d(t-(n-1)\tau)}, & t \in ((n-1)\tau, (n+\lambda-1)\tau], \\ \dfrac{\tilde{\sigma}}{1-e^{-d\tau}} e^{-d(t-(n+\lambda-1)\tau)}, & t \in ((n+\lambda-1)\tau, n\tau]. \end{cases} \tag{3.25}$$

Notice the first equation of model system (3.24), the explicit solution has been investigated by[25]. We present the positive completely analytical formula for any solution of the model system (3.24)(The detailed mathematical calculation is given in

Appendix B.):

$$I_2^*(t) = -\frac{\sigma_1 k}{\sigma_1 - d} - \frac{kd}{\sigma_1 - d} Lambert\ W(-(\frac{\sigma_1}{d} + \frac{kd}{\sigma_1 - d} I_0) \exp\{-(\frac{kd}{\sigma_1 - d} I_0 + \frac{(kd)^2}{\sigma_1 - d}(t_0 - t) + \frac{\sigma_1}{d}\}), \tag{3.26}$$

and the condition of positivity and boundedness is

$$\delta = \sigma_1 - d < 0. \tag{3.27}$$

By Lemma 3., for any $\epsilon_2 > 0$ is small enough, holds t large enough, then get

$$I_1^*(t) - \epsilon_2 < I_1(t) \leq I(t) \leq I_2(t) < I_2^*(t) - \epsilon_2. \tag{3.28}$$

Furthermore,

$$\begin{aligned} m_1 &\triangleq \frac{\tilde{\sigma} e^{-d\tau}}{1 - e^{-d\tau}} \\ &= \liminf_{t\to\infty} I_1^*(t) \\ &\leq \liminf_{t\to\infty} I(t) \\ &\leq \limsup_{t\to\infty} I(t) \\ &\leq \limsup_{t\to\infty} I_2^*(t) \\ &= \max I_0, -\frac{\sigma_1 k}{\sigma_1 - d} \quad \triangleq M_1. \end{aligned} \tag{3.29}$$

Therefore $I(t)$ is ultimately positively bounded. For $G(t)$ which is ultimately positively bounded, if there exists constants $m_2, M_2 > 0$ such that $m_2 \leq \liminf_{t\to\infty} G(t) \leq \limsup_{t\to\infty} G(t) \leq M_2$, holds for t large enough.

By inequation (3.29) and the first equation of system (1.1), have

$$\tilde{b} - (ac + \sigma_2)G(t) - \frac{amM_1 G(t)}{k + M_1} \leq G'(t) \leq \tilde{b} - (ac + \sigma_2)G(t) - \frac{amm_1 G(t)}{k + m_1}, \tag{3.30}$$

similar to (3.24)$\sim$(3.29), consider the two impulsive equations

$$\begin{cases} G_1'(t) = \tilde{b} - (ac + \sigma_2 + \frac{amM_1}{k + M_1})G_1(t), & t \neq (n + \lambda - 1)\tau, t \neq n\tau, \\ G_1(t^+) = G_1(t), & t = (n + \lambda - 1)\tau, \\ G_1(t^+) = qG_1(t) + G_{in}, & t = n\tau, \\ G_1(0^+) = G_0 > 0, \end{cases} \tag{3.31}$$

and

$$\begin{cases} G_2'(t) = \tilde{b} - (ac + \sigma_2 + \frac{amm_1}{k + m_1})G_2(t), & t \neq (n + \lambda - 1)\tau, t \neq n\tau, \\ G_2(t^+) = G_2(t), & t = (n + \lambda - 1)\tau, \\ G_2(t^+) = qG_2(t) + G_{in}, & t = n\tau, \\ G_2(0^+) = G_0 > 0, \end{cases} \tag{3.32}$$

By Lemma 2., system (3.31) and (3.32) have unique globally asymptotically stable positive periodic solutions:

$$G_1^*(t) = \begin{cases} \frac{\tilde{b}}{h} + (G_1^*(0^+) - \frac{\tilde{b}}{h}) e^{-h(t-(n-1)\tau)}, & t \in ((n-1)\tau, (n + \lambda - 1)\tau], \\ \frac{\tilde{b}}{h} + (G_1^*((n + \lambda - 1)\tau^+) - \frac{\tilde{b}}{h}) e^{-h(t-(n+\lambda-1)\tau)}, & t \in ((n + \lambda - 1)\tau, n\tau], \end{cases} \tag{3.33}$$

with

$$\begin{aligned} h &= ac + \sigma_2 + \frac{amM_1}{k + M_1}, \\ G_1^*(0^+) &= G_1^*(n\tau^+) = \frac{\tilde{b}(1 - e(-h\tau))}{h(q - e(-h\tau))} + \frac{G_{in}}{q - e^{-h\tau}}, \\ G_1^*((n + \lambda - 1)\tau^+) &= \frac{\tilde{b}(1 - e^{-h\lambda\tau})}{h(1 - qe^{-h\lambda\tau})} + \frac{G_{in}e^{-h\lambda\tau}}{1 - qe^{-h\lambda\tau}}, \end{aligned} \tag{3.34}$$

and

$$G_2^*(t) = \begin{cases} \frac{\tilde{b}}{H} + (G_2^*(0^+) - \frac{\tilde{b}}{H})e^{-H(t-(n-1)\tau)}, & t \in ((n-1)\tau, (n + \lambda - 1)\tau], \\ \frac{\tilde{b}}{H} + (G_2^*((n + \lambda - 1)\tau^+) - \frac{\tilde{b}}{H})e^{-H(t-(n+\lambda-1)\tau)}, & t \in ((n + \lambda - 1)\tau, n\tau], \end{cases} \tag{3.35}$$

with

$$\begin{aligned} H &= ac + \sigma_2 + \frac{amm_1}{k + m_1}, \\ G_2^*(0^+) &= G_2^*(n\tau^+) = \frac{\tilde{b}(1 - e(-H\tau))}{H(q - e(-H\tau))} + \frac{G_{in}}{q - e^{-H\tau}}, \\ G_2^*((n + \lambda - 1)\tau^+) &= \frac{\tilde{b}(1 - e^{-H\lambda\tau})}{H(1 - qe^{-H\lambda\tau})} + \frac{G_{in}e^{-H\lambda\tau}}{1 - qe^{-H\lambda\tau}}. \end{aligned} \tag{3.36}$$

By Lemma 2. and Lemma 3., for any $\epsilon_3 > 0$ is small enough, holds t large enough, then get

$$G_1^*(t) - \epsilon_3 < G_1(t) \leq G(t) \leq G_2(t) < G_2^*(t) - \epsilon_3, \tag{3.37}$$

thus,

$$\begin{aligned} m_2 \triangleq\ & \frac{\tilde{b}(1 - e^{-h\lambda\tau})}{h(1 - qe^{-h\lambda\tau})} + \frac{G_{in}e^{-h\lambda\tau}}{1 - qe^{-h\lambda\tau}} \\ =\ & \liminf_{t\to\infty} G_1^*(t) \\ \leq\ & \liminf_{t\to\infty} G(t) \\ \leq\ & \limsup_{t\to\infty} G(t) \\ \leq\ & \limsup_{t\to\infty} G_2^*(t) \\ =\ & \frac{\tilde{b}(1 - e(-H\tau))}{H(q - e(-H\tau))} + \frac{G_{in}}{q - e^{-H\tau}} \quad \triangleq M_2. \end{aligned} \tag{3.38}$$

Therefore $I(t)$ is ultimately positively bounded. By Equ.(3.29) and Equ.(3.38), the system (1.1) with T2DM is permanent. □

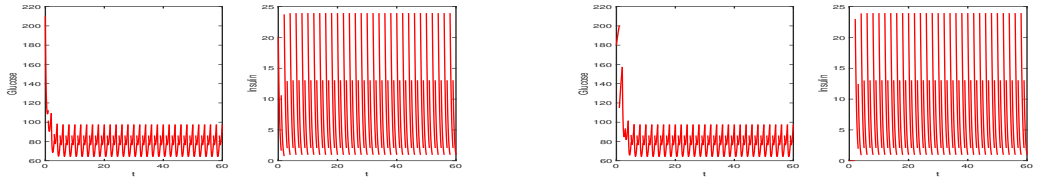
4 | NUMERICAL SIMULATION

In this section, the analytical findings will be verified numerically. It is still controversial whether the use of AGIs in addition to insulin can improve HbA1c and affect the risk of hypoglycemia in clinical insulin therapies. Therefore, this study systematically evaluated the effects of insulin combined with AGIs on blood glucose control in adult patients with T1DM, in order to provide evidence for the use of AGIs in adult patients with T1DM. The dynamics of model (3.1) is explored and give a method for combine insulin injection dose with alpha glucosidase inhibitors to control glucose levels within an ideal range with impulsive injection at different fixed times to avoid both hyperglycemia and hypoglycemia. Model variables, parameter values and their symbols are shown in Table.1.

The glucose control ability of two different clinical treatment strategies was compared, and the following results were obtained: Figure.3. Obviously, the treatment strategy of exogenous insulin injection combined with AGIs can lower the blood glucose concentration better under the same initial value, control the blood glucose concentration within the appropriate range and less insulin dose, thereby reducing the dose of exogenous insulin or the number of injections can take a more active role in treatment.

TABLE 1 T1DM numerical simulation of parameters

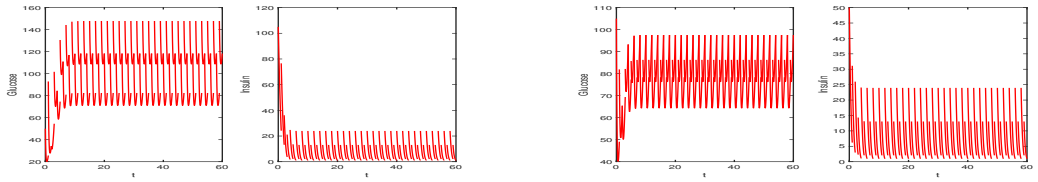
Parameter/variable definition	Symbol	Baseline value[Range]	Unit
Glucose production rate	$\tilde{b}$	100	*mg/dl min*
Glucose clearance independent of insulin	c	40	*/min*
Rates of insulin – induced glucose saturase reactions	m	900	*/min*
Michaelis – Menten constant	k/e_m	60	*/min*
Insulin saturates the maximum degradation rate	d	169	*/min*
Proportionally functional term of alpha glucosidase inhibitors	q	0.24	–
The amount of exogenous insulin injected	$\tilde{\sigma}$	23	*mIU/ml*
The amount of exogenous eating glucose injected	G_{in}	70	*mg/dl*
Insulin	I	[0 – 25]	*mIU/ml*
Glucose	G	[70 – 200]	*mg/dl*



(a) (b)

FIGURE 2 (*a*) initial values $(G, I) = (210, 20)$, (*b*) initial values $(G, I) = (180, 0)$.

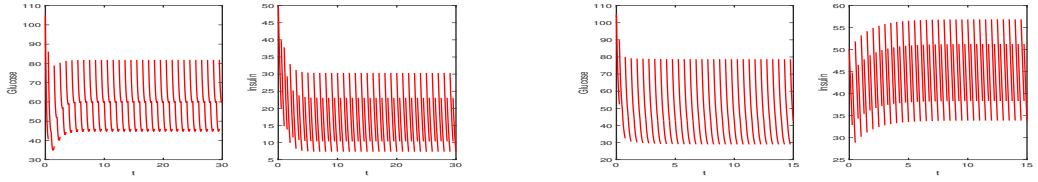
Simulations of T1DM model system have the periodic solution with two different initial conditions in Figure.2. Different initial values have little effect on the periodic solution, which means that the clinical application of this treatment strategy is feasible in theory. However, adverse symptoms such as sudden hypoglycemia still need to be paid attention.



(a) (b)

FIGURE 3 (Initial values is $(G, I) = (105, 50)$)Strategy (*a*) is only exogenous insulin treatment; Strategy (*b*) is exogenous insulin combined with AGIs.

If the duration of use of AGIs was unchanged, but the duration of exogenous insulin injection was doubled or more, numerical simulations (as given in Figure.3) showed that the drug still had a better therapeutic effect on glucose control.



(a) (b)

FIGURE 4 (Initial values is $(G, I) = (105, 50)$)Figure (*a*) is twice the injection period ; Strategy (*b*) is four times the injection period

These results suggest that compared with exogenous insulin exclusively, which combined with AGIs in the treatment of adult patients with T1DM can have better result, such as improving blood glucose levels , glycemic variability and reducing the total daily insulin dose. Moreover according to the clinical efficacy, insulin combined with AGIs in the treatment of adult patients with T1DM does not increase cardiovascular risk factors (body weight and lipid) and the hypoglycemia. However, it is still necessary to pay attention to the occurrence of adverse reactions, especially gastrointestinal adverse reactions because of their influence adherence of the patients. AGIs are mainly used in the treatment of T2DM patients, but in recent years, the role of AGIs in the treatment of T1DM patients has been explored at home and abroad[26,27]. The glucose-lowering mechanism of AGIs does not depend on the spontaneous release of insulin secreted by the organism, which lays the foundation for the feasibility of using AGIs drugs in T1DM. Based on the current medical clinical experiments and research, this paper proves the existence of the periodic solution and the global asymptotic stable periodic solution of a novel impulsive model by the theory of impulsive differential equations for T1DM. The permanence of system for T2DM means the glucose concentration level is uniformly bounded. The all conclusion means that the glucose of patients can be controlled in the ideal range under the treatment of exogenous insulin combined with AGIs. The results of numerical investigations indicate that the pulse period and the insulin dose are crucial for insulin therapies, and the results provide clinical strategies for insulin-administration practices.

FINANCIAL DISCLOSURE

This work was partially supported by the National Natural Science Foundation of China (No. 12326417); National Foreign Expert Program (No. G2023041033L); The Natural Science Basic Research Plan in Shaanxi Province of China (No. 2023JCYB258, 2023 YBGY-016, 2023WGZJZD08).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this paper.

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□

APPENDIX

A

For $t \in ((n-1)\tau, (n+\lambda-1)\tau]$, the Equ.(3.4) satisfies

$$I((n+\lambda-1)\tau^+) = kLambertW(\frac{I(n-1)\tau^+}{k}\exp\{\frac{1}{k}(-d\lambda\tau + I((n-1)\tau^+))\}) + \tilde{\sigma}, \tag{A1}$$

by *Lambert W* function definition,

$$\begin{aligned}(\frac{I((n+\lambda-1)\tau^+)}{k} - \frac{\tilde{\sigma}}{k})\exp\Big\{\frac{I((n+\lambda-1)\tau^+)}{k} - \frac{\tilde{\sigma}}{k}\Big\} &= \frac{I((n-1)\tau^+)}{k}\exp\Big\{\frac{1}{k}(-d\lambda\tau + I((n-1)\tau^+))\Big\} \\ &= \frac{I((n-1)\tau^+)}{k}\exp\{\frac{I((n-1)\tau^+)}{k}\}\exp\Big\{-\frac{d}{k}\lambda\tau\Big\},\end{aligned} \tag{A2}$$

similarly, for $t \in ((n+\lambda-1)\tau, n\tau]$, we have

$$I(n\tau^+) = kLambert\ W(\frac{I((n+\lambda-1)\tau^+)}{k}\exp\Big\{\frac{1}{k}(-d(1-\lambda)\tau + I((n+\lambda-1)\tau^+))\Big\}), \tag{A3}$$

i.e.

$$\frac{I(n\tau^+)}{k}\exp\{\frac{I(n\tau^+)}{k}\} = \frac{I((n+\lambda-1)\tau^+)}{k}\exp\Big\{\frac{1}{k}(-d(1-\lambda)\tau + I((n+\lambda-1)\tau^+))\Big\}, \tag{A4}$$

notice $I(n\tau^+) = I((n-1)\tau^+) = I(0^+)$, substitute Equ.(A4) into Equ.(A2),

$$\begin{aligned}(\frac{I(n+\lambda-1)\tau^+}{k} - \frac{\tilde{\sigma}}{k})\exp\{\frac{I((n+\lambda-1)\tau^+)}{k} - \frac{\tilde{\sigma}}{k}\} &= \frac{I((n+\lambda-2)\tau^+)}{k}\exp\Big\{\frac{1}{k}(-d(1-\lambda)\tau \\ &\quad + I((n+\lambda-2)\tau^+)) - \frac{d}{k}\lambda\tau\Big\} \\ &= \frac{I((n+\lambda-2)\tau^+)}{k}\exp\Big\{\frac{1}{k}(-d\tau + I((n+\lambda-2)\tau^+))\Big\},\end{aligned} \tag{A5}$$

If we denote $I_n = I((n+\lambda-1)\tau^+)$ then it satisfies the following difference equation

$$(\frac{I_n}{k}-\frac{\tilde{\sigma}}{k})\exp\{\frac{I_n}{k}-\frac{\tilde{\sigma}}{k}\} = \frac{I_{n-1}}{k}\exp\{\frac{1}{k}(-d\tau+I_{n-1})\}, \tag{A6}$$

the difference Equ.(A6) has a unique steady state I^* and satisfies

$$I^* = I((n+\lambda-1)\tau^+) = \frac{\tilde{\sigma}}{1-\exp\{\frac{1}{k}(\tilde{\sigma}-d\tau)\}}. \tag{A7}$$

we should observe $I(t)$ is concentration that can not be negative, which implies $I(t)$ exists only if $I((n+\lambda-1)\tau^+)$ is satisfied, that is

$$\frac{\tilde{\sigma}}{\tau} < d. \tag{A8}$$

By Equ.(A4), we can obtain

$$\frac{I((n+\lambda-1)\tau^+)}{k}\exp\{\frac{I((n+\lambda-1)\tau^+)}{k}\} = \frac{I(n\tau^+)}{k}\exp\{\frac{I(n\tau^+)}{k}\}\exp\{\frac{1}{k}d(1-\lambda)\tau\}, \tag{A9}$$

i.e.

$$\begin{aligned}(\frac{I((n+\lambda-1)\tau^+)}{k}-\frac{\tilde{\sigma}}{k})\exp\{\frac{I((n+\lambda-1)\tau^+)}{k}-\frac{\tilde{\sigma}}{k}\} &= \frac{I(n\tau^+)}{k}\exp\{\frac{I(n\tau^+)}{k}\}\exp\{\frac{d}{k}(1-\lambda)\tau-\frac{\tilde{\sigma}}{k}\}\\ &\quad -\frac{\tilde{\sigma}}{k}\exp\{-\frac{\tilde{\sigma}}{k}\}\exp\{\frac{I((n+\lambda-1)\tau^+)}{k}\},\end{aligned} \tag{A10}$$

substitute the left of Equ.(A2),

$$\begin{aligned}\frac{I((n-1)\tau^+)}{k}\exp\{\frac{I((n-1)\tau^+)}{k}\}\exp\{\frac{d\lambda\tau}{k}\} &= \frac{I(n\tau^+)}{k}\exp\{\frac{I(n\tau^+)}{k}\}\exp\{\frac{d}{k}(1-\lambda)\tau-\frac{\tilde{\sigma}}{k}\}\\ &\quad -\frac{\tilde{\sigma}}{k}\exp\{-\frac{\tilde{\sigma}}{k}\}\exp\{\frac{I((n+\lambda-1)\tau^+)}{k}\},\end{aligned} \tag{A11}$$

Let $I_n = I(n\tau^+)$, Equ.(A11) corresponding to following difference equation

$$\begin{aligned}\frac{I_{n-1}}{k}\exp\{\frac{I_{n-1}}{k}\}\exp\{\frac{d\lambda\tau}{k}\} &= \frac{I_n}{k}\exp\{\frac{I_n}{k}\}\exp\{\frac{d}{k}(1-\lambda)\tau-\frac{\tilde{\sigma}}{k}\}\\ &\quad -\frac{\tilde{\sigma}}{k}\exp\{-\frac{\tilde{\sigma}}{k}\}\exp\{\frac{I((n+\lambda-1)\tau^+)}{k}\},\end{aligned} \tag{A12}$$

which has an unique fixed point I^* and by Equ.(A7) satisfies

$$\frac{I^*}{k}\exp\{\frac{I^*}{k}\} = \frac{\tilde{\sigma}e^{\frac{\tilde{\sigma}e^{\frac{1}{k}(\tilde{\sigma}-d\tau)}}{k(1-e^{\frac{1}{k}(\tilde{\sigma}-d\tau)})}}}{k(e^{\frac{1}{k}(d(1-\lambda)\tau-\tilde{\sigma})}-e^{-\frac{d\lambda\tau}{k}})}, \tag{A13}$$

consider the signal of Equ.(A13) is positive, thus the equation can be solved by the upper branch of *Lambert W* function

$$I^* = I(n\tau^+) = I(0^+) = kLambert\ W(\frac{\tilde{\sigma}e^{\frac{\tilde{\sigma}e^{\frac{1}{k}(\tilde{\sigma}-d\tau)}}{k(1-e^{\frac{1}{k}(\tilde{\sigma}-d\tau)})}}}{k(e^{\frac{1}{k}(d(1-\lambda)\tau-\tilde{\sigma})}-e^{-\frac{d\lambda\tau}{k}})}). \tag{A14}$$

Consequently, if satisfy Equ.(A8) the initial value of subsystem (3.2) is

$$\begin{aligned}I(0^+) = I(n\tau^+) &= kLambert\ W(\frac{\tilde{\sigma}e^{\frac{\tilde{\sigma}e^{\frac{1}{k}(\tilde{\sigma}-d\tau)}}{k(1-e^{\frac{1}{k}(\tilde{\sigma}-d\tau)})}}}{k(e^{\frac{1}{k}(d(1-\lambda)\tau-\tilde{\sigma})}-e^{-\frac{d\lambda\tau}{k}})}),\\ I((n+\lambda-1)\tau^+) &= \frac{\tilde{\sigma}}{1-e^{\frac{1}{k}(\sigma-d\tau)}}.\end{aligned}$$

B

For model system (3.24), the explicit solution of the first equation had been investigated, based on this, the analytical formula depends on the relations between σ_1 and d. Fristly, for the sake of convenience, introduce the parameterization:

$$\zeta = kd,\ \delta = \sigma_1 - d,\ \gamma = \sigma_1 k,$$

so the first equation can be rewrite as

$$I_2'(t) = \frac{\sigma_1 k + \sigma_1 I_2(t) - dI_2(t)}{k + I_2(t)} = \frac{\delta(-\frac{\gamma}{\zeta} - \frac{\delta}{\zeta}I_2(t))}{1 - \frac{\gamma}{\zeta} - \frac{\delta}{\zeta}I_2(t)}. \tag{B1}$$

In $t \in (t_0, t)$, the Equ.(B1) can be integrated

$$\frac{\zeta}{\delta}\ln|\frac{\frac{\gamma}{\zeta} + \frac{\delta}{\zeta}I_2(t)}{\frac{\gamma}{\zeta} + \frac{\delta}{\zeta}I_2(t_0)}| - I_2(t) + I_2(t_0) = -\delta(t - t_0), \tag{B2}$$

we can obtain after calculation

$$-(\frac{\gamma}{\zeta} + \frac{\delta}{\zeta}I_2(t))\exp\{-(\frac{\gamma}{\zeta} + \frac{\delta}{\zeta}I_2(t))\} = -(\frac{\gamma}{\zeta} + \frac{\delta}{\zeta}I_2(t_0))\exp\{-(\frac{\delta}{\zeta}I_2(t_0) + \frac{\delta^2}{\zeta}(t - t_0) + \frac{\gamma}{\zeta})\}. \tag{B3}$$

Obviously, Equ.(B3) fits the definition of *Lambert W* function. Due to the sign positive(negative) and increase(decrease) characteristics of Equ.(B3), depends on δ that will be decided which branch of *Lambert W* function the analytical solution is, specifically in the following three cases:
(1) If $\delta > 0$, $\frac{\gamma}{\zeta} + \frac{\delta}{\zeta}I_2(t) > 0$ always holds true, the right term of Equ.(B3)

$$-(\frac{\gamma}{\zeta} + \frac{\delta}{\zeta}I_2(t_0))\exp\{-(\frac{\delta}{\zeta}I_2(t_0) + \frac{\delta^2}{\zeta}(t - t_0) + \frac{\gamma}{\zeta})\} \in [-e^{-1}, 0),$$

for all $t \geq t_0$(considering the properties of the function $f(x) = xe^{-x}$, the function has unique maximum e^{-1} when $x > 0$, so $-xe^{-x} \geq -e^{-1}$ always holds ture if $x \geq 0$). Further, the right term of Equ.(B3) satifies

$$\lim_{t\to\infty} -(\frac{\gamma}{\zeta} + \frac{\delta}{\zeta}I_2(t_0))\exp\{-(\frac{\delta}{\zeta}I_2(t_0) + \frac{\delta^2}{\zeta}(t - t_0) + \frac{\gamma}{\zeta})\} = 0,$$

that implies two posibilities:
1. $\frac{\gamma}{\zeta} + \frac{\delta}{\zeta}I_2(t) \to 0$ which is term in the left equation of Equ.(B3) as $t \to \infty$.
2. $\frac{\gamma}{\zeta} + \frac{\delta}{\zeta}I_2(t) \to \infty$ as $t \to \infty$.
but the first situation exists if $I_2(t) = -\frac{\gamma}{\delta} < 0$ and $I_2(t)$ is not negative, thus just the second situation exists and implies $I_2(t) \to \infty$. Consequently,

$$\lim_{t\in\infty} -(\frac{\gamma}{\zeta} + \frac{\delta}{\zeta}I_2(t))\exp\{-(\frac{\gamma}{\zeta} + \frac{\delta}{\zeta}I_2(t))\} = 0,$$

as

$$\frac{\gamma}{\zeta} + \frac{\delta}{\zeta}I_2(t) \to +\infty,$$

therefore, Equ.(B3) can be solved by the lower branch of *Lambert W* function(see Figure.(1)) if $\delta > 0$,

$$I_2(t) = -\frac{\gamma}{\delta} - \frac{\zeta}{\delta}Lambert\ W(-(\frac{\gamma}{\zeta} + \frac{\delta}{\zeta}I_2(t_0))\exp\{-(\frac{\delta}{\zeta}I_2(t_0) + \frac{\delta^2}{\zeta}(t - t_0) + \frac{\gamma}{\zeta})\}), \tag{B4}$$

where

$$Lambert\ W(-(\frac{\gamma}{\zeta} + \frac{\delta}{\zeta}I_2(t_0))\exp\{-(\frac{\delta}{\zeta}I_2(t_0) + \frac{\delta^2}{\zeta}(t - t_0) + \frac{\gamma}{\zeta})\}) < -1 \tag{B5}$$

for all $t \geq t_0$, and $I_2(t)$ is monotonically increasing. Obviously, but, the model system (3.24) has an unique positive state $I_2^* = -\frac{\sigma_1 k}{\sigma - d} = -\frac{\gamma}{\delta}$ if $\delta \neq 0$, which is a concentration thus it is not negative, so the model system does not have any positive state

when $\delta > 0$.
(2) If $\delta = 0$, in $t \in (t_0, t)$, the formula in Equ.(B1) can be easily obtained and it is given by

$$I_2(t) = -k + ((k + I_2(t_0)^2) + 2\gamma(t - t_0))^{\frac{1}{2}} \tag{B6}$$

and Equ.(B6) is obviously monotonically increasing with respect to t and unboundedness.
(3) If $\delta < 0$, we assume $I_2^* \neq I(t_0)$ and $Z(I_2(t)) = \frac{\gamma}{\zeta} + \frac{\delta}{\zeta} I_2(t)$, the sign of the function

$$Z(I_2(t_0)) = \frac{\gamma}{\zeta} + \frac{\delta}{\zeta} I_2(t_0) = \frac{\delta}{\zeta}(I_2^* + I_2(t_0))$$

depends on the relations between the I_2^* and $I_2(t_0)$.

$Z(I_2(t_0)) > 0$ if $I_2^* > I_2(t_0)$, therefore, $Z_1 = -\frac{\gamma+\delta I_2(t_0)}{\zeta} \exp\{-\frac{\gamma+\delta I_2(t_0)+\delta^2(t-t_0)}{\zeta}\} \in (-e^{-1}, 0)$, for all $t \geq 0$. Since

$$Z_2 = \frac{dLambert\ W(Z_1)}{dt} = \frac{\delta^2 Lambert\ W(Z_1)}{\zeta(1 + Lambert\ W(Z_1))} > 0,$$

which implies the solution is monotonically increasing. Similarly, it is the first situation of (1) in this case, which implies $I_2(t) \to I_2^*$, the solution will asymptotically tend to I_2^*. Thus, the uniqueness of solution can be solved by the real upper branch of *Lambert W* function. $Z(I_2(t_0)) < 0$ if $I_2^* < I_2(t_0)$, $Z_1 \leq -\frac{\gamma+\delta I_2(t_0)}{\zeta} \exp\{-\frac{\gamma+\delta I_2(t_0)+\delta^2(t-t_0)}{\zeta}\} \in (-e^{-1}, 0)$ and $Z_2 < 0$, thus $I_2(t)$ is monotonically decreasing and will asymptotically tend to I_2^*, the solution can be solved by the real upper branch of *Lambert W* funciton.

In general, if $\delta < 0$, the analytical solution of Equ.(B3) is given by

$$I_2(t) = -\frac{\gamma}{\delta} - \frac{\zeta}{\delta} Lambert\ W(-(\frac{\gamma}{\zeta} + \frac{\delta}{\zeta} I_2(t_0)) \exp\{-(\frac{\delta}{\zeta} I_2(t_0) + \frac{\delta^2}{\zeta}(t - t_0) + \frac{\gamma}{\zeta})\}), \tag{B7}$$

and it has two possible upper bounds, depending on the relation between I_2^* and $I_2(t_0)$,
1. if $I_2^* > I_2(t_0)$, the upper bound is I_2^*.
2. if $I_2^* < I_2(t_0)$, the upper bound is $I_2(t_0)$.