Research Article

Modeling Impulsive Intake of Glucose: The Significance of Diet to Glucose-Insulin System

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It is important to get good dietary advice such as a daily value of exogenous glucose intake to keep blood glucose within reasonable range for everyone, especially for those with diabetes mellitus or with borderline diabetes mellitus. In this paper, two novel glucose-insulin models with impulsive glucose intake are considered to investigate the significance of diet to the glucose-insulin system. For the first model, we prove the positiveness, boundedness, and permanence of the solutions and then the existence and stability of the periodic solutions are demonstrated. For the second model, we consider the insulin secretion delay based on the first model. The sufficient delay-dependent conditions which determine the stability of the periodic solution are also obtained. In addition, the theoretical results are verified by numerical simulation. The results can give people some dietary advice on how to prevent diabetes, and also, the intake amount and frequency of the exogenous glucose from diet are recommended for diabetic patients to assist in the treatment of diabetes.

1. Introduction

During recent decades, diabetes mellitus has become an epidemic disease in the sense of life style [1]. At present, diabetes is the third category of noncommunicable diseases which harms human health after malignant tumors and cardiovascular diseases, and has developed into a worldwide public health problem. In the glucose-insulin regulatory system, elevated glucose levels trigger pancreatic β-cells to secrete insulin, which helps glucose levels return to normal levels. When the concentration of glucose decreases, the secretion of insulin stops gradually [2]. Studying the dynamics between glucose and its control hormone insulin is conducive to the prevention and treatment of diabetes.

Many mathematical models have been developed to better understand the mechanisms of the glucose-insulin regulatory system ([3–12]). The most well-known clinical model is the Minimal Model, which was proposed by Bergman et al. in 1979 [6] and 1980 [7]. The Minimal Model is widely used in the intravenous glucose tolerance test (IVGTT). It was found that there is a time delay for insulin to release in responding to the elevated glucose concentration. And professionals point out that the ultradian oscillations of insulin secretion may be caused by the time delay. Therefore, a number of delayed models have been proposed to study the effect of time delay on the dynamics of the system. In 2000, De Gaetano and Arino [8] proposed a new aggregated delay differential equation model with a distributed time delay, and pointed that this model was more easier to analyze than the previous model mathematically. Later, Li et al. [9] in 2001 generalized the model to a general form. In 2007, De Gaetano et al. in their application work focused on a discrete delay model and claimed that such a model is good enough to test the insulin sensitivity [3]. In 2017, Shi et al. [5] proposed a novel approach to model the insulin secretion time delay, which uses two parameters to simulate both discrete time delay and distributed time delay. All these above models incorporate the insulin secretion delay implicitly in the ordinary differential equation (ODE) model by using compartment-split technique or explicitly in delay differential equation (DDE) models. Accounting for the effect of white noise, Shi et al. [12] discussed a stochastic IVGTT glucose-insulin model with discrete time delay.
In recent years, impulsive differential equation models have been established to provide effective therapies for diabetic patients. The treatment of diabetes is mainly insulin injection or insulin intake of hypoglycemic drugs. Continuous subcutaneous injection of insulin (CSII) therapy is achieved by the use of an insulin pump, a medical device for administering insulin or its analogues. There are many mathematical models modeling the insulin pump control of glucose level by impulsive insulin injections ([13–17]), and also, a number of impulsive differential equation models have been developed for the artificial pancreas ([18, 19]). In addition, because the constant glucose exogenous infusion is usually a discrete process, in order to investigate how to prevent hyperinsulinemia and hyperglycaemia, Yang et al. [20] developed a model involving periodic intakes of glucose with insulin injections applied only when the blood glucose level reached a given critical glucose threshold. Their results can provide clinical strategies for insulin-administration practices.

To the best of our knowledge, both diabetes and borderline diabetics need to control their glucose intake through diet control, and it is necessary to discuss the significance of diet to the glucose-insulin system. In many mathematical models of the glucose-insulin system, glucose exogenous infusion is always simulated by a constant which does not reflect the cyclical reality of eating. Therefore, in this paper, we propose novel impulsive differential equation model (1) to simulate the glucose intake from the daily diet with periodic impulses. Furthermore, to consider the effect of insulin secretion delay on the glucose and insulin regulation system in the process of glucose exogenous infusion, we add the time delay to the impulsive glucose-insulin model to study the effect of time delay on the stability of system (7).

The paper is organized as follows. In Section 2, we formulate two impulsive differential equation models to simulate the impulsive glucose intake. In Section 3, the qualitative analysis of the model is presented. The persistence, existence, and globally asymptotic stability of periodic solution of the system are discussed. In Section 4, the model with impulsive glucose intake and insulin secretion time delay is studied. We mainly prove the globally asymptotic stability of the periodic solution of the system under delay-dependent conditions. In Section 5, the numerical simulations are carried out, which not only verify the theoretical results but also are complementary to those theoretical results with specific features. A brief discussion is presented in the last section.

2. Model Formulation

In order to obtain the value of exogenous glucose intake which can keep the blood glucose in a certain range and give some reasonable dietary advice to borderline diabetic patients or diabetic patients, we propose a novel mathematical model for the periodic impulse glucose intake. The model is given by

\[
\begin{align*}
\frac{dG(t)}{dt} &= -\sigma_2 G(t) - a\left(c + \frac{kl(t)}{m + I(t)}\right)G(t) + \rho X(t) + b, \\
\frac{dI(t)}{dt} &= -d_1 I(t) + \frac{\sigma_1 G^2(t)}{a_1 + G(t)}, \\
\frac{dX(t)}{dt} &= -\mu X(t), \\
\Delta X(t) &= G_{in},
\end{align*}
\]

with the initial condition \(G(0) = G_0 > 0, I(0) = I_0 > 0,\) and \(X(0) = X_0 > 0,\) where \(G(t)\) and \(I(t)\) represent the glucose concentration and insulin concentration in the human body at time \(t \geq 0,\) respectively. \(X(t)\) represents the exogenous glucose concentration at the moment \(t\) after a meal. \(\sigma_2 G(t)\) and \(a\left(c + \frac{kl(t)}{m + I(t)}\right)G(t)\) are the insulin-independent and insulin-dependent glucose consumption, respectively. \(b\) is the hepatic glucose production rate. \(\sigma_1 G^2(t)/a_1 + G^2(t)\) represents the insulin secretion stimulated by elevated glucose concentration. \(d_1 I(t)\) is the insulin degradation with \(d_1 > 0\) as a constant degradation rate. \(\mu X(t)\) represents the ingested glucose conversion. Here, \(\sigma_1, \sigma_2, a_1, a, c, m, b, d_1, k, \mu, \) and \(\rho\) are positive constants. Since the loss of glucose absorption, we assume that \(\rho < \mu.\) \(\Delta X(t)\) represents the amount of glucose per exogenous intake. \(G_{in} (mU) > 0\) is the intake value, and \(\tau (\text{min}) > 0\) is the intake period. \(\Delta X(t) = X(nt^+) - X(nt),\) that is, intake \(G_{in} (mU)\) of glucose through the diet when \(t = nt, n \in \mathbb{Z}^+ = \{1, 2, 3, \ldots\}\). The moment immediately after the \(n\)th intake is denoted as \(t = nt^+\) here.

First, we consider the third and the forth equations of system (1); that is,

\[
\begin{align*}
\frac{dX(t)}{dt} &= -\mu X(t), & t \neq nt, \\
\Delta X(t) &= G_{in}, & t = nt.
\end{align*}
\]
From the theoretical knowledge to impulsive differential systems, the readers may refer to [20–22]. It can be easily obtained that system (2) has a globally asymptotically stable positive periodic solution:

\[
\begin{align*}
\bar{X}(t) &= G_m e^{-\mu t} \frac{1}{1 - e^{-\mu t}}, \quad t \in (nr, (n + 1)r], n \in \mathbb{Z}^+, \\
\bar{X}(0^+) &= \frac{G_m}{1 - e^{-\mu t}}.
\end{align*}
\]

The proof process is similar to the proof in Appendix A in reference [20], and we omit it here. And the solution of system (2) takes the form \( X(t) = (X(0) - \bar{X}(0^+)) e^{-\mu t} + \bar{X}(t) \), which satisfies

\[
\lim_{t \to \infty} X(t) = \bar{X}(t).
\]

Now, we consider the following system:

\[
\begin{align*}
\frac{dG(t)}{dt} &= -\sigma_2 G(t) - a \left( c + \frac{kl(t)}{m + I(t)} \right) G(t) + \rho \bar{X}(t) + b, \\
\frac{dI(t)}{dt} &= -d_I I(t) + \frac{\sigma_1 G(t)}{\alpha_1 + G(t)}, \\
\frac{dX(t)}{dt} &= -\mu X(t),
\end{align*}
\]

with initial condition \( G(0) = G_0 > 0, \quad I(0) = I_0 > 0, \quad X(0) = X_0 > 0, \) and \( t \in [-\tau_1, 0] \), and \( \tau_1 \) represents the insulin secretion delay. Each parameter in system (7) has the same meaning as system (1). Similar to system (5), the limit system of system (7) is as follows:

\[
\begin{align*}
\frac{dG(t)}{dt} &= -\sigma_2 G(t) - a \left( c + \frac{kl(t)}{m + I(t)} \right) G(t) + \rho \bar{X}(t) + b, \\
\frac{dI(t)}{dt} &= -d_I I(t) + \frac{\sigma_1 G(t)}{\alpha_1 + G(t)}, \\
\frac{dX(t)}{dt} &= -\mu X(t).
\end{align*}
\]

System (5) is the limiting system of system (1); that is, if \((\bar{G}(t), \bar{I}(t), \bar{X}(t))\) is a solution of system (5) and \((G(t), I(t))\) is a solution of system (1), then

\[
\begin{align*}
\lim_{t \to \infty} G(t) &= \bar{G}(t), \\
\lim_{t \to \infty} I(t) &= \bar{I}(t).
\end{align*}
\]

It is well known that the secretion of insulin has an impact on the production of liver glucose and the utilization of insulin-dependent glucose. When the plasma glucose concentration level is elevated, the \( \beta \)-cells secrete insulin after a complex series of cascading physiological processes, and such a process can delay the release of insulin. The total delay time is about 5–15 minutes [23]. In order to further understand the mechanism of the glucose-insulin system, we consider the effect of insulin secretion delay on system (1) and propose a model with the discrete insulin secretion delay. The model is given by

\[
\begin{align*}
\frac{dG(t)}{dt} &= -\sigma_2 G(t) - a \left( c + \frac{kl(t)}{m + I(t)} \right) G(t) + \rho \bar{X}(t) + b, \\
\frac{dI(t)}{dt} &= -d_I I(t) + \frac{\sigma_1 G(t)}{\alpha_1 + G(t)}, \\
\frac{dX(t)}{dt} &= -\mu X(t),
\end{align*}
\]

with initial condition \( G(0) = G_0 > 0, \quad I(0) = I_0 > 0, \quad X(0) = X_0 > 0, \) and \( t \in [-\tau_1, 0] \), and \( \tau_1 \) represents the insulin secretion delay. Each parameter in system (7) has the same meaning as system (1). Similar to system (5), the limit system of system (7) is as follows:

\[
\begin{align*}
\frac{dG(t)}{dt} &= -\sigma_2 G(t) - a \left( c + \frac{kl(t)}{m + I(t)} \right) G(t) + \rho \bar{X}(t) + b, \\
\frac{dI(t)}{dt} &= -d_I I(t) + \frac{\sigma_1 G(t)}{\alpha_1 + G(t)}, \\
\frac{dX(t)}{dt} &= -\mu X(t).
\end{align*}
\]

In the following, for the sake of analyzing the impulsive differential systems, we will investigate the dynamical behavior of system (1) and system (7) by studying their limit systems (5) and (8).

3. Qualitative Analyses of System (5)

3.1. Permanence. In reality, the concentrations of glucose \( G(t) \) and insulin \( I(t) \) cannot be negative at any time \( t \) and are always maintained within a certain range. Now, we will show the positiveness and boundedness of system (5).
Proposition 1. Positiveness. Suppose that \((G(t), I(t))\) is a solution of system (5) with the initial value \(G(0) = G_0 > 0\) and \(I(0) = I_0 > 0\), and then \(G(t) > 0\) and \(I(t) > 0\) for all \(t > 0\).

Proof. For system (5), except that \(X(t)\) is a periodic function, and all the other parameters are positive constants. Since \(X(t)\) is continuous, and it is easy to verify that the each function on the right side of system (5) satisfies the Lipschitz condition with respect to the variable \(G\) or \(I\); thus, for any initial value \(G(0) = G_0 > 0\), \(I(0) = I_0 > 0\), there exists a unique solution for system (5). Let \((G(t), I(t))\) be a solution of system (5) with \(G_0 > 0\), \(I_0 > 0\). Now, we show that it is nonnegative. If \(G(t)\) is not nonnegative, then there exists \(t > 0\) such that \(G(t) < 0\). Let \(t^* = \inf\{t: G(t) \leq 0\}\), then \(G(t^*) = 0\) and \(dG(t^*)/dt \leq 0\). From the first equation of system (5), we have \(dG(t^*)/dt = \rho \hat{X}(t^*) + b > 0\), which is a contradiction.

If there exists \(t > 0\) such that \(I(t) < 0\), let \(t_0 = \inf\{t: I(t) \leq 0\}\), then \(I(t_0) = 0\), and \(\lim_{t \to t^*^-} dI(t)/dt < 0\). From the second equation of system (5), we have \(\lim_{t \to t^*^-} dI(t)/dt > 0\), which is also a contradiction.

From above, we know \(G(t) \geq 0\) for all \(t \geq 0\), and it is clear that \(dG(t)/dt > 0\) when \(G(t) > 0\). Therefore, we have \(G(t) \geq 0\) for all \(t > 0\) if \(G(0) = G_0 > 0\). Besides, we know \(I(t) \geq 0\) for all \(t \geq 0\), and \(dI(t)/dt > 0\) when \(I(t) = 0\), \(G(t) > 0\). Therefore, we have \(I(t) > 0\) for all \(t > 0\) if \(G(0) = G_0 > 0\) and \(I(0) = I_0 > 0\).

Next, we show that the solution of system (5) is bounded. Let us start with a useful lemma which will be used to prove Proposition 2 and Theorem 1.

Lemma 1 (see [1]). If \(dh(t)/dt \leq p - qh(t)\) or \(dh(t)/dt \geq p - qh(t)\) all \(t \geq 0\), where \(p, q \geq 0\), then

\[
h(t) \leq \frac{p}{q} \left( h(0) - \frac{p}{q} \right) e^{-qt},
\]

\[
h(t) \geq \frac{p}{q} + \left( h(0) - \frac{p}{q} \right) e^{-qt}.
\]

Proposition 2. Boundedness. For a solution \((G(t), I(t))\) of system (5) with positive initial values, there exist positive constants \(M_1\) and \(t_0\) such that \(G(t) \leq M_1\) and \(I(t) \leq M_1\) for all \(t > t_0\).

Proof. From the first equation of system (5), we have

\[
\frac{dG(t)}{dt} \leq \sup_{t \in [0,t]} \rho \hat{X}(t) - acG(t) + b,
\]

\[
= \rho G_{in} + b \left( 1 - e^{-\mu t} \right) - acG(t).
\]

From Lemma 1, we can get

\[
G(t) \leq \frac{\rho G_{in} + b \left( 1 - e^{-\mu t} \right)}{1 - e^{-\mu t}} + \left( G_0 - \frac{\rho G_{in} + b \left( 1 - e^{-\mu t} \right)}{1 - e^{-\mu t}} \right) e^{-\alpha t}.
\]

Thus, for sufficient small constant \(\varepsilon > 0\), there exists \(N_1 > 0\) such that

\[
G(t) \leq \frac{\rho G_{in} + b \left( 1 - e^{-\mu t} \right)}{1 - e^{-\mu t}} + \varepsilon_1, \quad t > N_1.
\]

Denote

\[
M_G = \max \left\{ \frac{\rho G_{in} + b \left( 1 - e^{-\mu t} \right)}{1 - e^{-\mu t}} + \varepsilon_1, G_0 \right\}.
\]

Then,

\[
G(t) \leq M_G, \quad t > N_1.
\]

From the second equation of system (5), we have

\[
\frac{dI(t)}{dt} \leq \frac{\sigma I^2}{\alpha_1 + M_G^2} - dI(t).
\]

From Lemma 1, we can get

\[
I(t) \leq \frac{\sigma I^2}{\alpha_1 + M_G^2} + \left( I_0 - \frac{\sigma I^2}{\alpha_1 + M_G^2} \right) e^{-dt}.
\]

Thus, for sufficient small constant \(\varepsilon > 0\), there exists \(N_2 > 0\) such that

\[
I(t) \leq \frac{\sigma I^2}{\alpha_1 + M_G^2} + \varepsilon_2, \quad t > N_2.
\]

Denote

\[
M_I = \max \left\{ \frac{\sigma I^2}{\alpha_1 + M_G^2} + \varepsilon_2, I_0 \right\}.
\]

Then,

\[
I(t) \leq M_I, \quad t > N_2.
\]

Let

\[
M_1 = \max \{ M_G, M_I \},
\]

\[
t_0 = \max \{ N_1, N_2 \}.
\]

We can get \(G(t) \leq M_1\) and \(I(t) \leq M_1\) for all \(t > t_0\).

Theorem 1. System (5) is permanent; that is, for the solution \((G(t), I(t))\) of system (5) with positive initial values, there exist positive constants \(M_1\), \(M_2(0 < M_2 < M_1)\), and \(T_0\) such that \(M_2 \leq G(t), I(t) \leq M_1\), and \(t > T_0\).

Proof. From Lemma 1 and Proposition 2, we only need to prove that there exist positive constants \(M_2\) and \(T_0\), such that \(G(t) \geq M_2\) and \(I(t) \geq M_2\) for \(t > T_0\).

From the first equation of system (5), we have
\[
\frac{dG(t)}{dt} \geq \inf_{t \in [a, b]} \rho \sigma_1 G(t) + b(1 - e^{-\mu t}) \right) \sigma_2 + ac + ak) G(t),
\]
and then
\[
G(t) = \frac{\rho G_0 e^{-\mu t} + b(1 - e^{-\mu t})}{1 - e^{-\mu t}} (\sigma_2 + ac + ak) + \left( G_0 - \frac{\rho G_0 e^{-\mu t} + b(1 - e^{-\mu t})}{1 - e^{-\mu t}} (\sigma_2 + ac + ak) \right) e^{-(\sigma_2 + ac + ak)t}.
\]
(22)

So, for sufficient small constant \( \varepsilon > 0 \), there exists \( N_3 > 0 \) such that
\[
G(t) \geq \frac{\rho G_0 e^{-\mu t} + b(1 - e^{-\mu t})}{1 - e^{-\mu t}} (\sigma_2 + ac + ak) - \varepsilon_3, \quad t > N_3.
\]
(23)

Denote
\[
m_{G} = \min \left\{ \frac{\rho G_0 e^{-\mu t} + b(1 - e^{-\mu t})}{1 - e^{-\mu t}} (\sigma_2 + ac + ak) - \varepsilon_3, G_0 \right\}.
\]
(24)

We have
\[
G(t) \geq m_{G}, \quad t > N_3.
\]
(25)

From the second equation of system (5), we have
\[
\frac{dI(t)}{dt} \geq \frac{\sigma_1 m_{G}^2}{\mu \sigma_1^2 + m_{G}^2} - d_i I(t),
\]
(26)

and hence,
\[
I(t) \geq \frac{\sigma_1 m_{G}^2}{\mu \sigma_1^2 + m_{G}^2} + \left( I_0 - \frac{\sigma_1 m_{G}^2}{\mu \sigma_1^2 + m_{G}^2} \right) e^{-d_i t}.
\]
(27)

Thus, for sufficient small constant \( \varepsilon_4 > 0 \), there exists \( N_4 > 0 \) such that
\[
I(t) \geq \frac{\sigma_1 m_{G}^2}{\mu \sigma_1^2 + m_{G}^2} - \varepsilon_4, \quad t > N_4.
\]
(28)

Denote
\[
m_I = \min \left\{ \frac{\sigma_1 m_{G}^2}{\mu \sigma_1^2 + m_{G}^2} - \varepsilon_4, I_0 \right\},
\]
(29)

and then
\[
I(t) \geq m_I, \quad t > N_4.
\]
(30)

Let
\[
M_4 = \min \{m_{G}, m_I\},
\]
\[
t_I = \max \{N_3, N_4\}.
\]
(31)

We can get \( G(t) \geq M_2 \) and \( I(t) \geq M_2, \quad t > t_1 \). Let \( T_0 = \max \{t_0, t_1\} \), then \( M_2 \leq G(t), I(t) \leq M_1, \quad t > T_0 \). Therefore, system (5) is permanent.

3.2. Existence and Stability of the Periodic Solution. In this section, we will prove that system (5) exists a positive periodic solution by Arzela–Ascoli theorem and Krasnoselskii’s fixed point theorem.

Lemma 2 (Arzela–Ascoli theorem, see [24]). Let sequence \( \{f_n\}_n \) be a uniformly bounded and equicontinuous sequence of functions on the closed interval \([a, b]\). There exists a subsequence of \( \{f_n\}_n \) which converges uniformly on \([a, b]\).

Lemma 3 (Krasnoselskii’s fixed point theorem, see [25]). Let \( B \) be a Banach space and \( K \subset B \) be a cone in \( B \). Assume that \( \Omega_1 \) and \( \Omega_2 \) are open subsets of \( B \) with \( 0 \in \Omega_1 \), \( \Omega_1 \subset \Omega_2 \). And let \( T: K \cap (\overline{\Omega}_1 \setminus \Omega_1) \rightarrow K \).

be a completely continuous operator, such that either

(1) \( \|Tx\| \leq \|x\|, \quad x \in K \cap \partial \Omega_1 \) and \( \|Tx\| \geq \|x\|, \quad x \in K \cap \partial \Omega_2 \)

or

(2) \( \|Tx\| \geq \|x\|, \quad x \in K \cap \partial \Omega_1 \) and \( \|Tx\| \leq \|x\|, \quad x \in K \cap \partial \Omega_2 \)

is true.

Then, \( T \) has a fixed point in \( K \cap (\overline{\Omega}_2 \setminus \Omega_1) \).

Theorem 2. If
\[
G_{in} \geq \frac{\sigma_1 \exp(d_i \tau)(\exp(\sigma_2 \tau) - 1)(1 - \exp(-\mu \tau))}{\rho \exp(\sigma_2 \tau)(\exp(d_i \tau) - 1)} - \frac{b}{\rho} (1 - \exp(-\mu \tau)),
\]
(33)

then system (5) has a positive periodic solution \( (G^*(t), I^*(t)) \) with period \( \tau \).

Proof. To prove the theorem, we consider the Banach space
\[
B = \{(u(t), v(t)) \mid u \in C[R, R], v \in C[R, R], u(t + \tau) = u(t), v(t + \tau) = v(t)\},
\]
(34)

with
\[
\|(u, v)\| = \max \left\{ \sup_{t \in [0, \tau]} |u(t)|, \sup_{t \in [0, \tau]} |v(t)| \right\}.
\]
(35)

Define a cone \( K \) in \( B \) by
\[
K = \left\{ (u, v) \in B \mid u(t) \geq \frac{A}{B} \sup_{t \in [0, \tau]} |u(t)|, v(t) \geq \frac{C}{D} \sup_{t \in [0, \tau]} |v(t)| \right\}.
\]
(36)

where \( A, B, C, \) and \( D \) are defined by
\[
A = \frac{1}{\exp(\sigma_2 t) - 1} > 0, \\
B = \frac{\exp(\sigma_2 t)}{\exp(\sigma_2 t) - 1} > 0, \\
C = \frac{1}{\exp(d_t) - 1} > 0, \\
D = \frac{\exp(d_t)}{\exp(d_t) - 1} > 0.
\]

We have \(A < B\) and \(C < D\). Let

\[
\begin{align*}
\rho_1 &= A\left(\inf_{t \in [a,b]} \rho X(t) - a(c + kM_G + b)\right) \\
\rho_2 &= B\left(\sup_{t \in [a,b]} \rho X(t) + b\right) \\
\end{align*}
\]

Then, define two open sets \(\Omega_{\rho_1}\) and \(\Omega_{\rho_2}\) by

\[
\begin{align*}
\Omega_{\rho_1} &= \{(u, v) \in \Omega : \|u, v\| < \rho_1\}, \\
\Omega_{\rho_2} &= \{(u, v) \in \Omega : \|u, v\| < \rho_2\}, \\
\end{align*}
\]

and thus, \(\partial \Omega_i = \{(u, v) \in \Omega : \|u, v\| = \rho_i\}, i = 1, 2\), and \(K \cap (\Omega_{\rho_1} \setminus \Omega_{\rho_2}) = \{(u, v) \in \Omega : \rho_1 \leq \|u, v\| \leq \rho_2\}\). Define the map \(T(u, v) = (T_1(u, v), T_2(u, v)): K \cap (\Omega_{\rho_1} \setminus \Omega_{\rho_2}) \rightarrow K\) by

\[
T_1(u, v)(t, s) = \int_t^s U_u(t, s) \rho X(s) - a\left(c + \frac{k\lambda(s)}{m + \lambda(s)}\right) u(s) + b ds,
\]

\[
T_2(u, v)(t, s) = \int_t^s U_v(t, s) \frac{\sigma_1 u^2(s)}{\sigma_1^2 + u^2(s)} ds,
\]

where

\[
\begin{align*}
U_u(t, s) &= \frac{\exp(\sigma_2 (s - t))}{\exp(\sigma_2 t) - 1} \\
U_v(t, s) &= \frac{\exp(d_t (s - t))}{\exp(d_t t) - 1}
\end{align*}
\]

Obviously, we have \(A \leq U_u(t, s) \leq B, t \leq t \leq t + \tau, \) \(C \leq U_v(t, s) \leq D, t \leq t \leq t + \tau\).

In order to use Krasnoselskii’s fixed point theorem, we need to prove the mapping \(T\) is completely continuous. Firstly, we prove that the mapping \(T\) is continuous.

In view of the definition of \(K\), if \((u, v) \in K\), then

\[
T_1(u, v)(t + \tau) = \int_{t+\tau}^{t+2\tau} U_u(t + \tau, s) \rho X(s) - a\left(c + \frac{k\lambda(s)}{m + \lambda(s)}\right) u(s) + b ds,
\]

\[
\begin{align*}
&= \int_t^{t+\tau} U_u(t + \tau, \theta + \tau) \rho X(\theta + \tau) - a(c + \frac{k\lambda(\theta + \tau)}{m + \lambda(\theta + \tau)}) u(\theta + \tau) + b d\theta \\
&= \int_t^{t+\tau} \frac{\sigma_1 u^2(s)}{\sigma_1^2 + u^2(s)} ds,
\end{align*}
\]

Thus, \((K \cap (\Omega_{\rho_1} \setminus \Omega_{\rho_2})) \subset K\). It is easy to know that \(T\) is continuous. Next, we show \(T\) is compact by proving that it is uniformly bounded and equicontinuous.
Let $S \subseteq (K \cap (\Omega_2 \backslash \Omega_1))$ be a bounded set. For any $(u(t), v(t)) \in S$ and $t < n t < t + \tau$, we know

$$\|T(u(t), v(t))\| = \max \left\{ \sup_{t \in [0, \tau]} |T_1(u(t), v(t))|, \sup_{t \in [0, \tau]} |T_2(u(t), v(t))| \right\}.$$  

Besides,

$$T_1(u, v)(t) \leq B \int_{0}^{\tau} \left( \rho \bar{X}(s) - a \left( c + \frac{kv(s)}{m + v(s)} \right) u(s) + b \right) ds$$

$$= B \int_{0}^{\tau} \left( \rho \bar{X}(s) - a \left( c + \frac{kv(s)}{m + v(s)} \right) u(s) + b \right) ds$$

$$\leq B \left( \sup_{t \in [0, \tau]} \rho \bar{X}(s) + b \right)$$

$$= B \left( \frac{\rho \bar{G}_m}{1 - \exp(-\mu \tau)} + Brb \right),$$

$$T_2(u, v)(t) \leq D \int_{t}^{\tau} \frac{\sigma_1 G_2(s)}{\alpha_1 + G_2(s)} ds$$

$$\leq Dr \sigma_1.$$  

Therefore,

$$\|T(u(t), v(t))\| \leq \max \left\{ B \left( \frac{\rho \bar{G}_m}{1 - \exp(-\mu \tau)} + Brb \right), Dr \sigma_1 \right\}$$

(46)

which means $T(S)$ is uniformly bounded.

For every $(u(t), v(t)) \in S$, it is easy to know that the derivative functions of $T_i(u(t), v(t))$, $i = 1, 2$, are uniformly bounded, so all functions in $T(S)$ are equicontinuous.

From Arzela–Ascoli theorem, we know $T$ is compact. Thus, the compact continuous operator $T$ is a completely continuous operator.

Now, we prove that $(u, v)$ is the fixed point of $T$.

If $(u, v) \in \partial \Omega_r$, then $\|(u, v)\| = r_1$, and

$$T_1(u, v)(t) \geq A \int_{t}^{\tau} \left( \rho \bar{X}(s) - a \left( c + \frac{kv(s)}{m + v(s)} \right) u(s) + b \right) ds$$

$$\geq A \left( \inf_{t \in [0, \tau]} \rho \bar{X}(s) - a(c + k)M_G + b \right)$$

$$= r_1.$$  

(47)

So,

$$\|T(u, v)\| \geq \|(u, v)\|.$$  

(48)

If $(u, v) \in \partial \Omega_r$, then $\|(u, v)\| = r_2$, and

$$T_1(u, v)(t) \leq B \int_{t}^{\tau} \left( \rho \bar{X}(s) - a \left( c + \frac{kv(s)}{m + v(s)} \right) u(s) + b \right) ds$$

$$\leq B \left( \sup_{t \in [0, \tau]} \rho \bar{X}(s) + b \right)$$

$$= r_2.$$  

$$T_2(u, v)(t) \leq D \int_{t}^{\tau} \frac{\sigma_1 u^2(s)}{\alpha_1 + u^2(s)} ds$$

$$\leq Dr \sigma_1,$$  

(49)

From condition (33), we know $Dr \sigma_1 = \exp(d_1 \tau) \sigma_1 / \exp(d_1 \tau) - 1 \leq r_2$; thus, $\|T(u, v)\| \leq \|(u, v)\|$, where $(u, v) \in \partial \Omega_2$. Therefore, $T$ has a fixed point $(u, v)$ in $K \cap (\Omega_2 \backslash \Omega_1)$ by Kransoselskii’s fixed point theorem. Next, we will prove $(u, v)$ is the positive periodic solution of system (5).

Since $(u, v) \in K \cap (\Omega_2 \backslash \Omega_1)$ and $T_1(u, v) = u$, $T_2(u, v) = v$, 

\[
\frac{du(t)}{dt} = \frac{d}{dt} \int_{t}^{\tau} U_u(t, s) \left( \rho \bar{X}(s) - a \left( c + \frac{kv(s)}{m + v(s)} \right) u(s) + b \right) ds
\]

\[
= U_u(t, t + \tau) \left( \rho \bar{X}(t + \tau) - a \left( c + \frac{kv(t + \tau)}{m + v(t + \tau)} \right) u(t + \tau) + b \right)
\]

\[
- U_u(t, t) \left( \rho \bar{X}(t) - a \left( c + \frac{kv(t)}{m + v(t)} \right) u(t) + b \right)
\]

\[
+ \int_{t}^{\tau} \frac{du}{dt} \left( \rho \bar{X}(s) - a \left( c + \frac{kv(s)}{m + v(s)} \right) u(s) + b \right) ds
\]

\[
= (U_u(t, t + \tau) - U_u(t, t)) \left( \rho \bar{X}(t) - a \left( c + \frac{kv(t)}{m + v(t)} \right) u(t) + b \right) - \sigma_2 u(t)
\]
\[ \dot{v}(t) = \frac{d}{dt} \int_{t}^{t+\tau} U_v(t,s) \frac{\sigma_1 u^2(s)}{a_1^2 + u^2(s)} \, ds \]

Thus, \((u,v)\) is a positive periodic solution of system (5), which means system (5) has a positive periodic solution \((G^*(t), I^*(t))\) with period \(T\). This completes the proof of Theorem 2.

Then, we will prove the globally asymptotic stability of the positive periodic solution of system (5).

**Theorem 3.** If there exist \(\varepsilon_1 > 0\) and \(\varepsilon_2 > 0\) such that

\[ \sigma_2 + ac + \frac{akm_I}{m + m_I} - \frac{mkaM_G}{2(m + m_I)^2} \varepsilon_1 - \frac{3\sqrt{3}\sigma_1}{16a_1} \geq 0, \]

\[ \frac{d}{dt} \frac{1}{m + m_I} - \frac{\sigma_1 u^2(t)}{a_1^2 + u^2(t)} \geq 0, \]

then the positive periodic solution \((G^*(t), I^*(t))\) of system (5) is globally asymptotically stable.

**Proof.** Suppose \((G(t), I(t))\) is the solution of system (5). We define

\[ p(t) = G(t) - G^*(t), \]

\[ q(t) = I(t) - I^*(t). \]

Let \(f_2(G) = aG, f_3(I) = c + (kI/m + I), f_2'(G) = df_2(G)/dG, \) and \(f_3'(I) = df_3(I)/dI, \) and we can get

\[ \frac{dp}{dt} = \frac{dG(t)}{dt} - \frac{dG^*(t)}{dt} \]

\[ = -\sigma_2(G(t) - G^*(t)) - \left[ a \left( c + \frac{kl(t)}{m + I(t)} \right) G(t) \right. \]

\[ - a \left( c + \frac{kl^*(t)}{m + I^*(t)} \right) G^*(t) \]

\[ = -\sigma_2 p(t) - \left[ f_2(G) f_3(I) - f_2(G^*) f_3(I^*) \right] \]

\[ = -\sigma_2 p(t) - \left[ (G(t) - G^*(t)) f_3'(I) f_3(I) \right. \]

\[ - \left( I(t) - I^*(t) \right) f_3'(I) f_3(G^*) \]

\[ = -\sigma_2 p(t) - \left[ p(t) a \left( c + \frac{kl(t)}{m + I(t)} \right) \right. \]

\[ + \frac{km}{(m + \xi)^2} aG^*(t)q(t), \]

\[ \frac{dq}{dt} = \frac{dI(t)}{dt} - \frac{dI^*(t)}{dt} \]

\[ = -d_3 (I(t) - I^*(t)) + \left( \frac{\sigma_1 G(t)^2}{a_1^2 + G(t)^2} - \frac{\sigma_1 G^*(t)^2}{a_1^2 + G^*(t)^2} \right) \]

\[ = -d_3 q(t) + \left( f_1(G) - f_1(G^*) \right) \]

\[ = -(I(t) - I^*(t)) f_3'(I) f_3(G^*) \]

\[ = p(t) \frac{2a_1^2 \sigma_1 \xi_1}{(a_1^2 + \xi_1^2)^2} - d_3 q(t), \]

where \(\xi_1\) and \(\xi_2\) are between \(G(t)\) and \(G^*(t)\), and \(\xi_3\) is between \(I(t)\) and \(I^*(t)\).

Let \(V(t) = 1/2p^2(t) + 1/2q^2(t)\), and we use the inequality \(2ab \leq \varepsilon a^2 + b^2/\varepsilon\) in the following derivation; we have
\[
\frac{dV(t)}{dt} = p(t) \frac{dp(t)}{dt} + q(t) \frac{dq(t)}{dt} \\
= -\left( \sigma_2 + ac + \frac{akI(t)}{m + I(t)} \right) p^2(t) - \frac{mkaG^2(t)}{(m + \xi_3)^2} \rho \left( \frac{\epsilon_1}{\alpha_1^2 + \xi_3^2} \right) p(t)q(t) - d_1q^2(t) \\
< -\left( \sigma_2 + ac + \frac{akI(t)}{m + I(t)} \right) p^2(t) + \frac{mkaG^2(t)}{(m + \xi_3)^2} \rho \left( \frac{\epsilon_1}{\alpha_1^2 + \xi_3^2} \right) p(t)q(t) - d_1q^2(t) \\
< -\left( \sigma_2 + ac + \frac{akm_I}{m + m_I} \right) p^2(t) + \frac{mkaM_G}{(m + m_I)^2} \left( \frac{\epsilon_1}{2} p^2(t) + \frac{1}{2\epsilon_2} q^2(t) \right) \\
+ 3\frac{\sqrt{3}\sigma_1}{16\alpha_1} \epsilon_2 q^2(t) + \frac{3\sqrt{3}\sigma_1}{16\alpha_1} \frac{1}{\epsilon_2} q^2(t) - d_1q^2(t) \\
= -\left( \sigma_2 + ac + \frac{akm_I}{m + m_I} - \frac{mkaM_G}{2(m + m_I)^2} \frac{1}{\epsilon_1} - 3\frac{\sqrt{3}\sigma_1}{16\alpha_1} \frac{1}{\epsilon_2} \right) p^2(t) \\
- \left( d_1 - \frac{mkaM_G}{2(m + m_I)^2} \frac{1}{\epsilon_1} - 3\frac{\sqrt{3}\sigma_1}{16\alpha_1} \frac{1}{\epsilon_2} \right) q^2(t).
\]

If we choose \( \epsilon_1 > 0 \) and \( \epsilon_2 > 0 \) such that
\[
\sigma_2 + ac + \frac{akm_I}{m + m_I} - \frac{mkaM_G}{2(m + m_I)^2} \frac{1}{\epsilon_1} - 3\frac{3\sigma_1}{16\alpha_1} \frac{1}{\epsilon_2} \geq 0,
\]
\[
d_1 - \frac{mkaM_G}{2(m + m_I)^2} \frac{1}{\epsilon_1} - 3\frac{3\sigma_1}{16\alpha_1} \frac{1}{\epsilon_2} \geq 0.
\]

Then, \( \frac{dV(t)}{dt} \leq 0 \), and \( \{(p, q) \mid \frac{dV(t)}{dt} = 0\} \) contains no other trajectories other than \( (p, q) = (0, 0) \); that is, the positive periodic solution of system (5) is globally asymptotically stable.

**Remark 1.** The existence and globally asymptotic stability of the periodic solution of system (5) indicate that the glucose-insulin system can be regulated in the form of continuous oscillations by controlling the amount and period of glucose intake.

**4. Qualitative Analyses of System (8)**

4.1. **Existence and Stability of the Periodic Solution.**

System (8) satisfies positiveness, boundedness, and permanence, which can be proved in the same way as in system (5). And system (8) also has a positive periodic solution with period \( \tau \).

**Theorem 4.** If
\[
G_{in} \geq \frac{\sigma_1 \exp(d_1\tau)(\exp(\sigma_2\tau) - 1)(1 - \exp(-\mu\tau))}{\rho \exp(\sigma_2\tau)(\exp(d_1\tau) - 1)} - \frac{b}{\rho} (1 - \exp(-\mu\tau)),
\]
then system (8) has a positive periodic solution \( (G^*(t), I^*(t)) \) with period \( \tau \).

The proof of Theorem 4 is similar to Theorem 2; here, we omit it.

**Remark 2.** Let
\[
\tilde{G}(\tau) = \frac{\sigma_1 \exp(d_1\tau)(\exp(\sigma_2\tau) - 1)(1 - \exp(-\mu\tau))}{\rho \exp(\sigma_2\tau)(\exp(d_1\tau) - 1)} - \frac{b}{\rho} (1 - \exp(-\mu\tau)).
\]

Theorems 1 and 2 show that if \( G_{in} > \tilde{G}(\tau) \), then system (5) and system (8) exist periodic solutions when the intake period is constant.

Next, we prove that the positive periodic solution \( (G^*(t), I^*(t)) \) of system (8) is globally asymptotically stable.
Theorem 5. If there exist $\varepsilon_1 > 0$, $\varepsilon_2 > 0$, and $\varepsilon_3 > 0$ such that

$$
\sigma_2 + ac + \frac{akm_I}{m + m_I} - \frac{mkaM_G}{2(m + m_I)^2} \geq 3\sqrt{3}\sigma_1 \varepsilon_1 \geq 0, \quad \frac{3\sqrt{3}\sigma_1 r_s}{16a_1} \geq 0, \quad \frac{3\sqrt{3}\sigma_1 r_s}{16a_1} \geq 0,
$$

then the positive periodic solution $(G^*(t), I^*(t))$ of system (8) is globally asymptotically stable.

Proof. Suppose $(G(t), I(t))$ is a solution of system (8) with $G(t) = G_0 > 0$ and $I(t) = I_0 > 0$ for all $t \in [-\tau, 0]$. We define

$$
\bar{p}(t) = G(t) - G^*(t), \quad \bar{q}(t) = I(t) - I^*(t).
$$

Let $f_2(G) = aG$, $f_1(I) = c + kl/m + 1$, $f_2'(G) = df_2(G)/dG$, and $f_3'(I) = df_3(I)/dI$, and we get

$$
\frac{d\bar{p}}{dt} = \frac{dG(t)}{dt} - \frac{dG^*(t)}{dt} = -\sigma_2 \bar{p}(t) - [f_2(G)f_3(I) - f_2'(G^*)f_3'(I^*)]
$$

$$
= -\sigma_2 \bar{p}(t) - [(G(t) - G^*(t))f_2'(\xi_2)f_3(I(t)) - (I(t) - I^*(t))f_3'(\xi_3)f_2(G^*(t))]
$$

$$
= -\sigma_2 \bar{p}(t) - \left[ \bar{p}(t) a \left( \sigma_1 \rho I(t) + b \right) \right]
$$

$$
= \left( -d_m I(t) + \frac{\frac{\sigma_1 G(t - r_s)^2}{a_1^2} + G(t - r_s)^2}{a_1^2 + G(t - r_s)^2} \right) - \left( -d_m I^*(t) + \frac{\frac{\sigma_1 G^*(t - r_s)^2}{a_1^2} + G^*(t - r_s)^2}{a_1^2 + G^*(t - r_s)^2} \right)
$$

$$
= -d_m \bar{q}(t) + (f_1(G(t - r_s) - f_1(G^*(t - r_s)))
$$

$$
= -d_m \bar{q}(t) + G(t - r_s) - G^*(t - r_s))f_1'((\xi_1)
$$

$$
= -d_m \bar{q}(t) + (G(t - r_s) - G^*(t - r_s)) \frac{2a_1^2 \sigma_1 G_{\xi_1}}{(a_1^2 + G_{\xi_1})^2}
$$

$$
= \bar{p}(t - r_s) \frac{2a_1^2 \sigma_1 G_{\xi_1}}{(a_1^2 + G_{\xi_1})^2} - d_m \bar{q}(t),
$$

Complexity
where $\xi_1$ and $\xi_2$ are between $G(t)$ and $G^*(t)$, and $\xi_3$ is between $I(t)$ and $I^*(t)$.

Let $V_1(t) = 1/2\bar{p}^2(t) + 1/2q^2(t)$, and we make use of the inequality $2ab \leq \varepsilon a^2 + b^2/\varepsilon$ in the following derivation; then, we can have

$$
\frac{dV_1(t)}{dt} = \bar{p}(t) \frac{d\bar{p}(t)}{dt} + \bar{q}(t) \frac{d\bar{q}(t)}{dt}
$$

where

$$
= -\left(\sigma_2 + ac + \frac{a kl(t)}{m + I(t)}\right) \bar{p}^2(t) - \frac{kmG^*(t)}{(m + \xi_3)^2} \bar{p}(t)\bar{q}(t) - d_1\bar{q}^2(t)
$$

$$
+ \frac{2\alpha_1^2\sigma_1\xi_1}{(\alpha_1^2 + \xi_1^2)} \bar{p}(t - \tau_s)\bar{q}(t)
$$

$$
< -\left(\sigma_2 + ac + \frac{a kl(t)}{m + I(t)}\right) \bar{p}^2(t) + \frac{kmG^*(t)}{(m + \xi_3)^2} |\bar{p}(t)\bar{q}(t)| - d_1\bar{q}^2(t)
$$

$$
+ \frac{3\sqrt{3}\sigma_1}{8\alpha_1} |\bar{p}(t - \tau_s)\bar{q}(t)|
$$

$$
= -\left(\sigma_2 + ac + \frac{akm_1}{m + m_1}\right) \bar{p}^2(t) + \frac{kmG_M}{(m + m_1)^2} |\bar{p}(t)\bar{q}(t)| - d_1\bar{q}^2(t)
$$

$$
+ \frac{3\sqrt{3}\sigma_1}{8\alpha_1} \bar{q}(t) \left(\bar{p}(t) - \int_{t-\tau_s}^{t} \frac{d\bar{p}(s)}{ds} ds\right)
$$

$$
< -\left(\sigma_2 + ac + \frac{akm_1}{m + m_1}\right) \bar{p}^2(t) + \frac{kmG_M}{(m + m_1)^2} \left(\frac{\epsilon_1}{2}\bar{p}^2(t) + \frac{1}{2\epsilon_1} \bar{q}^2(t)\right)
$$

$$
+ \frac{3\sqrt{3}\sigma_1}{16\alpha_1} \bar{p}^2(t) + \frac{3\sqrt{3}\sigma_1}{16\alpha_1}\bar{q}^2(t) - d_1\bar{q}^2(t) - \frac{3\sqrt{3}\sigma_1}{8\alpha_1} \bar{q}(t) \int_{t-\tau_s}^{t} \frac{d\bar{p}(s)}{ds} ds
$$

$$
= -\left(\sigma_2 + ac + \frac{akm_1}{m + m_1} - \frac{kmG_M}{2(m + m_1)^2} \epsilon_1 - \frac{3\sqrt{3}\sigma_1}{16\alpha_1} \epsilon_2\right) \bar{p}^2(t)
$$

$$
- \left(d_1 - \frac{kmG_M}{2(m + m_1)^2} \epsilon_1 - \frac{3\sqrt{3}\sigma_1}{16\alpha_1} \epsilon_2\right) \bar{q}^2(t) - \frac{3\sqrt{3}\sigma_1}{8\alpha_1} \bar{q}(t) \int_{t-\tau_s}^{t} \frac{d\bar{p}(s)}{ds} ds
$$

$$
- \frac{3\sqrt{3}\sigma_1}{8\alpha_1} \bar{q}(t) \int_{t-\tau_s}^{t} \left(-\sigma_2 + ac + \frac{akl(t)}{m + I(t)}\right) \bar{p}(s) - \frac{km}{(m + \xi_3)^2} aG^* \bar{q}(s) ds
$$

$$
= -\frac{3\sqrt{3}\sigma_1}{8\alpha_1} \bar{q}(t) \int_{t-\tau_s}^{t} \left(-\sigma_2 + ac + \frac{akl(t)}{m + I(t)}\right) \bar{p}(s) - \frac{km}{(m + \xi_3)^2} aG^* \bar{q}(s) ds
$$
\[ \frac{dV_1}{dt}(t) \leq - \left( \sigma_2 + ac + \frac{akM_I}{m + M_I} \right)^2 \frac{kmaM_G}{(m + M_I)} \epsilon_1 - \frac{3\sqrt{3} \sigma_1}{16a_1\epsilon_2} \right) \bar{p}(t) \]

\[ + \left( d, - \frac{kmaM_G}{2(m + M_I)} \frac{1}{\epsilon_1} - \frac{3\sqrt{3} \sigma_1}{16a_1\epsilon_2} \right) \bar{q}(t) \]

\[ + \frac{3\sqrt{3} \sigma_1}{16a_1\epsilon_3} \left( \sigma_2 + ac + \frac{akM_I}{m + M_I} \right)^2 \frac{kmaM_G}{(m + M_I)} \epsilon_3 + \frac{kmaM_G}{(m + M_I)} \epsilon_3 \right) \bar{q}(t) \]

\[ + \frac{3\sqrt{3} \sigma_1}{16a_1\epsilon_3} \left( \sigma_2 + ac + \frac{akM_I}{m + M_I} \right)^2 \frac{kmaM_G}{(m + M_I)} \epsilon_3 + \frac{kmaM_G}{(m + M_I)} \epsilon_3 \right) \bar{q}(t) \]

Let

\[ V_2(t) = \frac{3\sqrt{3} \sigma_1}{16a_1\epsilon_3} \left( \sigma_2 + ac + \frac{akM_I}{m + M_I} \right)^2 \int_{t-\tau}^{\tau} \bar{p}(s)^2 ds dy, \]

\[ V_3(t) = \frac{3\sqrt{3} \sigma_1}{16a_1\epsilon_3} \left( \sigma_2 + ac + \frac{akM_I}{m + M_I} \right)^2 \int_{t-\tau}^{\tau} \bar{q}(s)^2 ds dy. \]

We can get

\[ \frac{dV_2}{dt}(t) = \frac{3\sqrt{3} \sigma_1}{16a_1\epsilon_3} \left( \sigma_2 + ac + \frac{akM_I}{m + M_I} \right)^2 \int_{t-\tau}^{\tau} \bar{p}(s)^2 ds dy, \]

\[ \frac{dV_3}{dt}(t) = \frac{3\sqrt{3} \sigma_1}{16a_1\epsilon_3} \left( \sigma_2 + ac + \frac{akM_I}{m + M_I} \right)^2 \int_{t-\tau}^{\tau} \bar{q}(s)^2 ds dy. \]
We define

\[ V(t) = V_1(t) + V_2(t) + V_3(t). \] (66)

Then,

\[
\frac{dV(t)}{dt} \leq -\left( \frac{\sigma_2 + ac + \frac{akm_i}{m + m_i} - \frac{mkaM_G}{2(m + m_i)^2} \epsilon_1}{16a_1 \epsilon_1} - \frac{3\sqrt{3} \sigma_1 \tau_s}{16a_1 \epsilon_1} \left( \sigma_2 + ac + \frac{akM_i}{m + M_i} \right) \epsilon_2 \right) \left( \frac{\epsilon_1}{16a_1} \left( \sigma_2 + ac + \frac{akM_i}{m + M_i} \right) \epsilon_3 \right)
\]

\[
- \left( d_i - \frac{mkaM_G}{2(m + m_i)^2} \frac{1}{\epsilon_1} - \frac{3\sqrt{3} \sigma_1 \tau_s}{16a_1 \epsilon_1} \left( \sigma_2 + ac + \frac{akM_i}{m + M_i} \right) \epsilon_3 \right) - \frac{3\sqrt{3} \sigma_1 \tau_s \frac{kmaM_G}{8a_1 (m + m_i)^2}}{(m + m_i)^2} \epsilon_2. \] (67)

If we choose \( \epsilon_1 > 0, \epsilon_2 > 0, \) and \( \epsilon_3 > 0 \) such that

\[
\frac{dV(t)}{dt} \leq 0, \quad \text{and} \quad \{ (p, q) \mid \frac{dV(t)}{dt} = 0 \} \text{ contains no other trajectories other than } (p, q) = (0, 0); \text{ that is, the}
\]

positive periodic solution \((G^* (t), I^* (t))\) of system (8) is globally asymptotically stable. This completes the proof.

From (58), we know

\[
\tau_s \leq \frac{16 \sqrt{3} \alpha_1}{9 \alpha_1} \frac{(m + M_i)(m + m_i)(\sigma_2 + ac) + (m + M_i)akm_i}{(m + M_i)(m + m_i)(\sigma_2 + ac) + (m + m_i)akM_i} \epsilon_3,
\]

\[
- \frac{8 \sqrt{3} \alpha_1}{9 \sigma_1} \frac{mkaM_G(m + M_i)}{(m + m_i)^2 ((m + M_i)(\sigma_2 + ac) + akM_i)} \epsilon_1 \epsilon_3
\]

\[
- \frac{m + M_i}{(m + M_i)(\sigma_2 + ac) + akM_i} \epsilon_3 \epsilon_2 \equiv \bar{a}.
\] (69)

Let \( \tilde{s} = (\sigma_2 + ac + akM_i/m + M_i) \epsilon_3 + 2kmaM_G/(m + m_i)^2 \), and from (59), we get

\[
\tau_s \leq \frac{16 \sqrt{3} \alpha_1 d_i}{9 \alpha_1 \tilde{s}} - \frac{8 \sqrt{3} \alpha_1 mkaM_G}{9 \sigma_1 (m + m_i)^2} \frac{1}{\tilde{s}} \epsilon_1 - \frac{1}{\tilde{s}} \epsilon_2 \equiv \bar{b}. \] (70)

**Remark 3.** From Theorem 5, we know that the globally asymptotic stability of the periodic solution of system (8) is related to the time delay. And the periodic solution is globally asymptotically stable if the insulin secretion delay \( \tau_s < \min[\bar{a}, \bar{b}] \).

### 5. Numerical Analysis

In this section, the theoretical results of Section 3 and Section 4 will be verified by numerical simulations, and the effects of glucose intake period and glucose intake amount on the glucose-insulin system are discussed based on the following assumptions:

1. By applying model (5) and model (8), once the range of glucose level is set, we can make appropriate dietary recommendations. In our simulations, we assume that the normal fasting glucose concentration is set at 70 - 110 mg/dl and the postprandial glucose concentration is no more than 140 mg/dl.

2. We assume that the volume of the plasma compartment in humans is 10 liter. The units for \( X(t) \) and \( G_m \) are usually in mg/dl and mg, respectively. So,
if we ingest $Y$ mg glucose every 180 minutes, then the concentration $dX = Y/10 \times 10$ mg/dl.

The parameter values $a_1, a, c, k, m$, and $b$ are referred from the references [18, 26]. The initial values are set at $G_0 = 100$ mg/dl, $I_0 = 70\mu$U/ml, and $X_0 = 150$ mg/dl. The parameters $\mu$ and $\rho$ represent the amount of glucose consumption and glucose conversion after the intake of glucose, respectively. Because of the individual differences, here we only consider the case of $\mu = 0.06$ and $\rho = 0.035$. The parameters are as shown in Table 1.

The exogenous glucose concentration $X(t)$ after meals is first simulated numerically. Let $G_{in} = 20000$ mg, $\tau = 180$ min, namely, glucose intake for 20000 mg every three hours. Through the numerical simulation, it is found that $X(t)$ oscillates with the periodic $\tau$ and is globally asymptotically stable (refer to Figure 1).

Next, the existence and globally asymptotic stability of the positive periodic solutions of system (5) and system (8) are verified (see Figures 2–5). Let $G_{in} = 20000$ mg, $\tau = 180$ min, and $\tau_s = 15$ min, and other parameters for details are as shown in Table 1. According to the simulations, the dynamic relationship between glucose and insulin in system (5) and system (8) can be seen; that is, when the glucose concentration increases, the secretion of insulin will be stimulated, and when the insulin concentration increases, the glucose concentration will be reduced, which is consistent with the regulation system of glucose and insulin in the human body.

In addition, substituting the above parameter values into the conditions of Theorem 2, obviously, the conditions are satisfied. For Theorem 3, if we select $\epsilon_1 = 0.2$ and $\epsilon_2 = 0.5$, the calculation is shown as follows:

$$
\sigma_2 + ac + \frac{akm_I}{m + m_I} \frac{mkaM_G}{2(m + m_I)} \frac{3\sqrt{3}\sigma_1}{16\alpha_1} = \epsilon_1 - \frac{3\sqrt{3}\sigma_1}{16\alpha_1} \frac{1}{\epsilon_2} \approx 0.0029 > 0,
$$

$$
d_i = \frac{mkaM_G}{2(m + m_I)} \frac{1}{\epsilon_1} - \frac{3\sqrt{3}\sigma_1}{16\alpha_1} \frac{1}{\epsilon_2} \approx 0.0365 > 0.
$$

(71)

The conditions of Theorem 3 are also satisfied. In order to verify Theorem 5, we choose $\epsilon_1 = 0.2$, $\epsilon_2 = 0.5$, and $\epsilon_3 = 1$

$$
\sigma_2 + ac + \frac{akm_I}{m + m_I} \frac{mkaM_G}{2(m + m_I)} \frac{3\sqrt{3}\sigma_1}{16\alpha_1} \frac{3\sqrt{3}\sigma_1}{16\alpha_1} \frac{1}{\epsilon_2} \left( \sigma_2 + ac + \frac{akM_I}{m + M_I} \right) \approx 0.0025 > 0,
$$

$$
d_i = \frac{mkaM_G}{2(m + m_I)} \frac{1}{\epsilon_1} - \frac{3\sqrt{3}\sigma_1}{16\alpha_1} - \frac{3\sqrt{3}\sigma_1}{16\alpha_1} \frac{1}{\epsilon_2} - \frac{3\sqrt{3}\sigma_1}{16\alpha_1} \frac{1}{\epsilon_3} \left( \sigma_2 + ac + \frac{akM_I}{m + M_I} \right) \approx 0.0342 > 0.
$$

(72)

The conditions of the theorem are met. Therefore, based above discussion, the theoretical results of both system (5) and (8) are verified.

Furthermore, the range of glucose intake amount to maintain normal glucose levels at different intake periods (refer to Figures 6–8) is discussed. The glucose intake periods are set and substitute the parameter values into the conditions of Theorem 5, and we get

at 120, 180, and 240 min, respectively. It is clear that the glucose concentration is successfully controlled under the threshold value 140 mg/dl and above the fasting glucose concentration range, which avoid hyperglycemia and hypoglycemia.

We assume that the time quantum of glucose intake is from 8:00 to 20:00. By calculating, when $\tau = 120$ min, one

| Parameters | Values | Units |
|-----------|--------|-------|
| $\sigma_2$ | $5 \times 10^{-6}$ | min$^{-1}$ |
| $a$ | $2 \times 10^{-5}$ | min$^{-1}$ |
| $c$ | 40 | mg/min |
| $k$ | 900 | mg/min |
| $m$ | 80 | |
| $b$ | 100 | mg/min |
| $\sigma_1$ | 90 | mU/min |
| $\sigma_3$ | 125 | |
| $I_0$ | 70 | $\mu$U/ml |
| $G_0$ | 100 | mg/dl |
| $X_0$ | 150 | mg/dl |

### Table 1: Model parameter values.
can ingest seven times and the maximum total glucose intake is $7 \times 17600 = 123200$ mg. If $\tau = 180$ min, one can ingest five times and the maximum total glucose intake is $5 \times 19500 = 98000$ mg. If $\tau = 240$ min, one can ingest 4 times and the maximum total glucose intake is $4 \times 20200 = 80800$ mg. We notice that the smaller the intake period, the greater the amount of glucose available. Therefore, if one needs a sufficient amount of glucose, he had better eat multiple times.

Lastly, we consider the effects of different insulin secretion delays on the glucose-insulin system (see Figure 9). The delay of insulin secretion is set at 5, 10, and 15 minutes, respectively. The blue solid lines in the figures represent the solution curves of system (5), in which the delay of insulin secretion is set at $\tau = 0$ min. Letting $G_{in} = 15000$ mg, $\tau = 180$ min, other parameter values are shown in Table 1. Figure 9(a) shows that insulin secretion delay has little influence on the glucose level. Figure 9(b) shows that there is a certain time lag from the rise of glucose level to the secretion of insulin.

6. Discussion

In this paper, two glucose-insulin models with impulsive intake of glucose are proposed and studied. The impulsive models that we presented can intuitively show the intake amount and intake period of exogenous glucose, which is convenient to implement numerical simulation and discuss. Different from the study in the literature [20] on pulse glucose injection in the course of diabetes physiotherapy in patients with type 1 and type 2 diabetes, we model daily dietary glucose intake on periodic pulses for general population, or those with diabetes mellitus or borderline diabetes mellitus. When the existence and stability of periodic solutions are analyzed theoretically, we do not use the usual theory of impulsive differential system but transform the
impulsive systems into nonautonomous limit systems with periodic coefficients. Thus, we obtain the theoretical results which are not easy to obtain directly with impulse differential system theory.

Firstly, qualitative analysis of the first impulsive differential equation of model (5) is given. It is proved that system (5) is persistence and has globally asymptotically stable positive periodic solution, which indicates that the glucose-insulin system (5) in the human body reaches a certain stable state after meals. And then, based on model (1), the second model with insulin secretion delay is analyzed. The delay system is more consistent with the biological background. Studies have shown that the system with delay has globally asymptotically stable positive periodic solution. From the conditions of Theorem 5, we find that the stability of periodic solution of delayed glucose-insulin system (7) is

Figure 6: Range of glucose intake amount for maintaining normal glucose level when $\tau = 180$ min: (a) range of glucose intake amount of system (5) and (b) range of glucose intake amount of system (8).

Figure 7: Range of glucose intake amount for maintaining normal glucose level when $\tau = 120$ min: (a) range of glucose intake amount of system (5) and (b) range of glucose intake amount of system (8).
affected not only by the amount and period of glucose intake, but also by the time delay.

Our numerical simulations verify these theorems of system (5) and (8) and discuss the effect of glucose intake amount and intake period on system (5) and system (8) when $\mu = 0.06$ and $\rho = 0.035$. The recommended ranges of glucose intake when $\tau = 120, 180, 240$ min are given, respectively, which keep the glucose and insulin values of system (5) and system (8) at normal ranges. And we recommend that in order to avoid hypoglycemia, adequate glucose intake can be divided into several times.

Daily diet is essential for everyone, so it is of great practical significance to use the impulsive differential system to simulate glucose intake through diet. The results obtained from the models can provide people some dietary advice how to prevent diabetes. In addition, it can also control the amount and frequency of diet of diabetic patients to assist in the treatment of diabetes.
Data Availability
The “simulation” data used to support the findings of this study are included within the article. These data are not obtained by experiments; just to satisfy the conditions of the theorem, we design them artificially and from the references [18, 26].

Conflicts of Interest
The authors declare that they have no conflicts of interest.

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