DYNAMICS OF A STOCHASTIC GLUCOSE-INSULIN MODEL WITH IMPULSIVE INJECTION OF INSULIN

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Abstract. In this paper, the dynamics of a stochastic glucose-insulin model with impulsive injection of insulin are investigated analytically and numerically. Firstly, we show that the system admits unique positive global solution starting from the positive initial value, which is a prerequisite for analyzing the long-term behavior of the stochastic model. Then, according to the theory of Khasminskii, we show that there exists at least one nontrivial positive periodic solution. Finally, numerical simulations are carried out to support our theoretical results. It is found that: (i) The presence of environmental noises is capable of supporting the irregular oscillation of blood glucose level, and the average level of the glucose always increases with the increase in noise intensity. (ii) The higher the volatility of the environmental noises, the more difficult the prediction of the peak size of blood glucose level.

Keywords: diabetes mellitus; type 1 diabetes mellitus; impulse; environmental fluctuations; positive periodic solution.

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1. INTRODUCTION

Diabetes mellitus, a metabolic disorder is one of the major problems in global public health. It is caused by the fact that the pancreas aren't able to produce enough insulin which is the only

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hormone in the body that lowers blood sugar, or the cells of the body can not respond appropriately to the insulin produced. Diabetes mellitus can generally be divided into two types: type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). T1DM is a metabolic disorder characterized by insufficient or insufficient insulin secretion, resulting in elevated plasma glucose levels and the inability of beta cells to respond appropriately to metabolic stimuli. It is an autoimmune disease that causes insulin deficiency by autoimmune destruction of islet beta cells. T2DM (also known as adult or non-insulin-dependent diabetes mellitus) is characterized by a patient's insensitivity to insulin secreted in the body resulting in elevated blood glucose levels. It can be controlled through regular exercise and healthy eating.

The blood glucose level is regulated by two negative feedback loops, where short-term hyperglycemia stimulates islet beta cells to secrete insulin and simultaneously inhibits the secretion of glucagon in islet A cells, thereby lowering blood sugar. In order to better understand the dynamics of insulin and blood glucose concentration, many scholars have established mathematical models to describe the principle of insulin and blood glucose, and given insulin injection strategies through mathematical theory and numerical simulation then to better control blood sugar levels. For instance, Li et al. [1] have reviewed multiple models of subcutaneous injection of regular insulin and insulin analogues, and found that these models provide key building blocks for some important endeavors into physiological questions of insulin secretion and action. Li and Kuang [2] proposed two systemic models to model the subcutaneous injection of rapid-acting insulin analogues and long-acting insulin analogues, respectively. Their work shows the two models will be good choices in practical applications. Particularly, Huang et al. [3] formulated a physiological and metabolic model by a semicontinuous dynamical system. They found that the glucose level of a diabetic can be controlled within a desired level by adjusting the values of two model parameters, injection period and injection dose. The model in

[3] is given by

$$(1.1) \quad \begin{cases} \left. \begin{aligned} dG(t) &= \left(G_{in} - \alpha G(t) - a(c + \tfrac{mI(t)}{n+I(t)})G(t) + b \right)dt, \\ dI(t) &= -\gamma I(t)dt \; t \neq nT, \end{aligned} \right\} t \neq nT \\ \left. \begin{aligned} \Delta S(t) &= 0, \\ \Delta I(t) &= q, \end{aligned} \right\} t = nT \end{cases}$$

where $G(t), I(t)$ are the concentration of blood glucose and blood insulin at time t, respectively. G_{in} is the estimated average constant rate of glucose input, $\alpha G(t)$ is the insulin-independent glucose uptake, $a(c + \tfrac{mI(t)}{n+I(t)})G(t)$ stands for the insulin-dependent glucose utilization, b is the hepatic glucose production, and $\gamma I(t)$ indicates the insulin degradation with γ as the constant degradation rate, T and q represent the period of the impulsive injection of insulin and the insulin input amount every time, respectively. $\Delta \rho(t) = \rho(t^+) - \rho(t)$, $n \in \{1,2,3,...\}$. All parameters above are positive. The other parameters can be seen in [3].

It is well known that meals and exercise, the age and weight of the patient also affect the insulin/glucose dynamics. Liu et al. [4] pointed out that glucose tolerance, insulin response to the glucose challenge, insulin sensitivity and β cell morphology can be affected by environmental noise. These daily and hourly fluctuations of patient parameters can create difficulties in continuous glucose control. Hence, it is necessary and important to study the impact of those uncertain factors on the insulin/glucose level in the body of the patients. In present paper, we intend to consider model (1.1) incorporating the influence of those uncertain factors, moreover, we take into account the effect of randomly factors into model (1.1) by assuming $\alpha \rightarrow \alpha + \sigma dB(t)$, then we can obtain the SDE model as follows

$$(1.2) \quad \begin{cases} \left. \begin{aligned} dG(t) &= \left(G_{in} - \alpha G(t) - a\left(c + \tfrac{mI(t)}{n+I(t)}\right)G(t) + b \right)dt - \sigma G(t)dB(t), \\ dI(t) &= -\gamma I(t)dt, \end{aligned} \right\} t \neq nT \\ \left. \begin{aligned} \Delta S(t) &= 0, \\ \Delta I(t) &= q, \end{aligned} \right\} t = nT \end{cases}$$

where $B(t)$ is a real-valued standard Brownian motion defined on the complete probability space $(\Omega, \mathscr{F}, \{\mathscr{F}_t\}_{t \geq 0}, P)$ with a filtration $\{\mathscr{F}_t\}_{t \geq 0}$ satisfying the usual conditions (i.e. it is right continuous and $\mathscr{F}_0$ contains all P-null sets); σ^2 represents the intensities of the white noise. Our main purpose is to investigate the effect of random fluctuations on the glucose dynamics based on realistic parameters obtained from previous literatures. The rest of this article is organized as follows: In Section 2, we present some preliminaries which will be used in our following analysis. In Section 3, we present the detailed proof of the theoretical results. Section 4 is devoted to illustrate our analytical results by using some numerical examples. In Section 5, we provide a brief discussion and summary of main results.

2. PRELIMINARIES

Throughout this paper, unless otherwise specified, we let $(\Omega, \mathscr{F}, \{\mathscr{F}_t\}_{t \geq 0}, P)$ be a complete probability space with a filtration $\{\mathscr{F}_t\}_{t \geq 0}$ satisfying the usual conditions (i.e. it is right continuous and $\mathscr{F}_0$ contains all P-null sets). Throughout this paper, let $R_+ = [0, \infty)$, $R_+^2 = \{x = (x_1, x_2) \in R^2 : x_i > 0, i = 1, 2\}$.

Definition 2.1. [5] *A stochastic process $\xi(t) = \xi(t, \omega)(-\infty < t < +\infty)$ is said to be T-periodic if for every finite sequence of numbers $t_1, t_2, \cdots, t_n$, the joint distribution of random variables $\xi(t_1 + h), \xi(t_2 + h), \cdots, \xi(t_n + h)$ is independent of h, where $h = kT, (k = 1, 2, \cdots)$.*

Consider the integral equation

$$(2.1) \qquad x(t) = x(t_0) + \int_{t_0}^{t} b(s, x(s)) ds + \sum_{r=1}^{k} \int_{t_0}^{t} \sigma_r(s, x(s)) d\xi_r(s).$$

where $b(s, x), \sigma_r(s, x)(r = 1, 2, \cdots, k)(s \in [t_0, T], x \in R^d)$ are continuous functions of (s, x) and for some constant B, the following conditions hold.

$$(2.2) \qquad \begin{aligned} &|b(s,x) - b(s,y)| + \sum_{r=1}^{k} |\sigma_r(s,x), \sigma_r(s,y)| \leq B|x - y|, \\ &|b(s,x)| + \sum_{r=1}^{k} |\sigma_r(s,x)| \leq B(1 + |x|). \end{aligned}$$

Let U be a given open set in the d-dimensional Euclidean space R^d. $E = R^d \times [0, \infty)$, $C^{2,1}$ is the family functions on E which are twice continuously differentiable with respect to $x \in R^d$ and continuously differentiable with respect to $t \in [0, \infty)$.

Lemma 2.1. [5] *Suppose that the coefficients of* (2.1) *are T-periodic in t and satisfy the conditions* (2.2) *in every cylinder $I \times U$, and assume further there exists a function $V(t,x) \in C^{2,1}$, which is T-periodic in t and satisfies,*

(Q_1) $\displaystyle\inf_{|x|>R} V(t,x) \to \infty$ *as* $R \to \infty$.

(Q_2) $LV(t,x) \leq -1$ *outside some compact set.*

Then system (2.1) *has at least a T-periodic Markov process.*

Next, we consider the following stochastic insulin-glucose model

$$(2.3) \quad \begin{cases} d\bar{G}(t) = \left(G'_{in} - \alpha'\bar{G}(t) - \frac{a'\bar{G}(t)\bar{I}(t)}{n+\bar{I}(t)} \right) dt - \sigma\bar{G}(t)dB(t), \\[2mm] d\bar{I}(t) = -\gamma\bar{I}(t)dt, \end{cases}$$

where $G'_{in} = G_{in} + b$, $\alpha' = \alpha + ac$, $a' = am$.

Lemma 2.2. *For any given initial value $\bar{X}(0) = \left(G(0), I(0) \right) \in R^2_+$, there exists a unique solution $\bar{X}(t) = \left(\bar{G}(t), \bar{I}(t) \right)$ of system (2.3) and the solution will remain in R^2_+ with probability 1, that is $\bar{X}(t) \in R^2_+$ for all $t \geq 0$ almost surely (a.s.).*

Proof. Since the coefficients of model (2.3) satisfy the local Lipschitz condition, then there exists a unique local solution on $t \in [0, \tau_e)$, where τ_e is the explosion time. Now, let us show that this solution is global, i.e., $\tau_e = \infty$ a.s..

Let $k_0 > 0$ be sufficiently large for $\bar{X}(0)$ lying within the interval $[\frac{1}{k_0}, k_0] \times [\frac{1}{k_0}, k_0]$. For each integer $k \geq k_0$, define the stopping time

$$\tau_k = \inf\{t \in [0, \tau_e) : \bar{G}(t) \notin (\frac{1}{k}, k); \bar{I}(t) \notin (\frac{1}{k}, k)\}.$$

Throughout this paper we set $\inf\emptyset = \infty$ (as usual $\emptyset$ denotes the empty set). Clearly, τ_k is increasing as $k \to \infty$. Set $\tau_\infty = \lim_{k\to\infty} \tau_k$, hence $\tau_\infty \leq \tau_e$ a.s.. If we can show that $\tau_\infty = \infty$ a.s., then $\tau_e = \infty$ a.s. and $\bar{X}(t) \in R^2_+$ a.s. for all $t \geq 0$. In other words, to complete the proof all we need

to show is that $\tau_\infty = \infty$ a.s.. If this statement is false, then there is a pair of constants $T' > 0$ and $\varepsilon \in (0, 1)$ such that

$$(2.4) \qquad\qquad P\{\tau_\infty \leq T'\} > \varepsilon,$$

hence, there is an integer $k_1 \geq k_0$ such that $P\{\tau_k \leq T'\} \geq \varepsilon$, for all $k \geq k_1$.

Define a function $V : R_+^2 \to R_+$ by $V(\bar{G}, \bar{I}) = \bar{G} - 1 - \ln\bar{G} + \bar{I} - 1 - \ln\bar{I}$. The nonnegativity of this function can be seen from $u - 1 - \ln u \geq 0$ on $u > 0$. Then, by Itô's formula, one can see that

$$(2.5) \qquad\qquad dV = LV\,dt - \sigma\bar{G}dB + \sigma dB$$

where

$$
\begin{aligned}
LV =\ & G'_{in} - \alpha'\bar{G} - \frac{a'\bar{G}(t)\bar{I}(t)}{n + \bar{I}(t)} - \left(\frac{G'_{in}}{\bar{G}} - \alpha' - \frac{a'\bar{I}}{n + \bar{I}} - \frac{\sigma^2}{2}\right) - \gamma\bar{I} + \gamma \\
\leq\ & G'_{in} - \alpha'\bar{G} + \alpha' + \frac{a'\bar{I}}{n + \bar{I}} + \frac{\sigma^2}{2} - \gamma\bar{I} + \gamma \\
\leq\ & M,
\end{aligned}
$$

here $M = \sup\limits_{(\bar{G},\bar{I})\in R_+^2} G'_{in} - \alpha'\bar{G} + \alpha' + \frac{a'\bar{I}}{n+\bar{I}} + \frac{\sigma^2}{2} - \gamma\bar{I} + \gamma$.

Substituting this inequality into Eq. (2.5), we see that

$$(2.6) \qquad\qquad dV \leq M\,dt - \sigma\bar{G}dB + \sigma dB,$$

which implies that

$$\int_0^{\tau_k \wedge T'} dV\left(\bar{G}, \bar{I}\right) \leq \int_0^{\tau_k \wedge T'} M\,dt - \int_0^{\tau_k \wedge T'} (\sigma\bar{G} - \sigma)dB,$$

where $\tau_k \wedge T' = \min\{\tau_k, T'\}$. Taking the expectations of the above inequality leads to

$$(2.7) \qquad\qquad EV\left(\bar{G}_{\tau_k \wedge T'}, \bar{I}_{\tau_k \wedge T'}\right) \leq V\left(\bar{G}(0), \bar{I}(0)\right) + MT'.$$

Set $\Omega_k = \{\tau_k \leq T'\}$ for $k \geq k_1$ and from (2.4), we have $P(\Omega_k) \geq \varepsilon$. Note that for every $\omega \in \Omega_k$, there is at least one of $\bar{G}_{\tau_k}(\omega)$ and $\bar{I}_{\tau_k}(\omega)$ equaling either k or $\frac{1}{k}$, hence

$$V\left(\bar{G}_{\tau_k \wedge T'}, \bar{I}_{\tau_k \wedge T'}\right) \geq (k - 1 - \ln k) \wedge \left(\frac{1}{k} - 1 + \ln k\right).$$

It then follows from (2.7) that

$$V\left(\bar{G}(0),\bar{I}(0)\right)+MT' \geq E\left[1_{\Omega_k}(\omega)V\left(\bar{G}_{\tau_k}(\omega),\bar{I}_{\tau_k}(\omega)\right)\right]$$

$$\geq \varepsilon(k-\ln k-1)\wedge(\frac{1}{k}+\ln k-1),$$

where 1_{Ω_k} is the indicator function of Ω_k. Letting $k \to \infty$ leads to the contradiction

$$\infty > V\left(\bar{G}(0),\bar{I}(0)\right)+MT' = \infty.$$

So we must have $\tau_\infty = \infty$. The conclusion is confirmed.   □

Now, we give some basic properties of the following subsystem of model (1.2), which are very important for obtaining our main results.

(2.8)
$$\begin{cases} dI(t) = -\gamma I(t)dt, \ t \neq nT \\\\ \Delta I(t) = q, \ t = nT \\\\ I(0) = I_0. \end{cases}$$

Lemma 2.3. [3, 11] *System (2.8) has a unique positive T-periodic solution $I^*(t)$ which is globally asymptotically stable, where*

(2.9)
$$I^*(t) = \frac{qe^{-\gamma(t-kT)}}{1-e^{-\gamma T}},$$

for $t \in (kT,(k+1)T]$ and $k \in \{1,2,\cdots\}$.

Remark 2.1. *Substituting $I^*(t)$ into the first equation of system (1.2) for $I(t)$, we obtain the following system*

(2.10)
$$dG(t) = \left(G'_{in} - \alpha'G(t) - \frac{a'G(t)I^*(t)}{n+I^*(t)}\right)dt - \sigma G(t)dB(t),$$

where $G'_{in} = G_{in}+b$, $\alpha' = \alpha+ac$, $a' = am$. Next, we will consider the system (2.10).

Lemma 2.4. *Let $G(t)$ be the solution of model (2.10) with initial value $G(0) > 0$, then*

$$\lim_{t\to\infty}\frac{G(t)}{t} = 0 \ a.s..$$

Proof. Define $W(G) = (1+G)^{\theta}$, where θ is a positive constant to be determined later. Then, by Itô's formula, we obtain

$$(2.11) \qquad dW = LW\,dt - \sigma\theta G(1+G)^{\theta-1}dB,$$

where

$$(2.12) \qquad \begin{aligned} LW =& \theta(1+G)^{\theta-1}\left(G'_{in} - \alpha'G - \frac{a'GI^*}{n+I^*}\right) + \frac{\theta(\theta-1)\sigma^2}{2}G^2(1+G)^{\theta-2} \\ \leq& \theta(1+G)^{\theta-2}\left(G'_{in} - (\alpha' - G'_{in})G - (\alpha' - \frac{(\theta-1)\sigma^2}{2})G^2\right), \end{aligned}$$

choose $\theta > 1$ such that

$$(2.13) \qquad \alpha' - \frac{(\theta-1)\sigma^2}{2} := \lambda > 0 \text{ and } a' + G'_{in} - (\theta-1)\sigma^2 > 0,$$

that is

$$(2.14) \qquad dW \leq \theta(1+G)^{\theta-2}\left(G'_{in} - (\alpha' - G'_{in})G - \lambda G^2\right)dt - \sigma\theta G(1+G)^{\theta-1}dB.$$

Then applying Itô's formula to $e^{kt}(1+G)^{\theta}$, where $0 < k < \theta\lambda$, we have

$$(2.15) \qquad \begin{aligned} L\left(e^{kt}(1+G)^{\theta}\right) \leq& e^{kt}\left(k(1+G)^{\theta} + \theta(1+G)^{\theta-2}[G'_{in} - (\alpha' - G'_{in})G - \lambda G^2]\right) \\ =& e^{kt}(1+G)^{\theta-2}\left(k + G'_{in}\theta - (\alpha' - G'_{in} - 2k)G - (\lambda\theta - k)G^2\right) \\ \leq& e^{kt}H, \end{aligned}$$

here $H := \sup\limits_{G \in R_+}(1+G)^{\theta-2}\left(k + G'_{in}\theta - (\alpha' - G'_{in} - 2k)G - (\lambda\theta - k)G^2\right) + 1$. Therefore

$$E\left(e^{kt}\left[1+G(t)\right]^{\theta}\right) \leq \left(1+G(0)\right)^{\theta} + \frac{H}{k}e^{kt},$$

that is

$$\limsup_{t\to\infty} E\left(\left[1+G(t)\right]^{\theta}\right) \leq \frac{H}{k} := K \text{ a.s.,}$$

which together with the continuity of $G(t)$ implies that there exists a constant $K > 0$ such that

$$(2.16) \qquad E\left(\left[1+G(t)\right]^{\theta}\right) \leq K,\ t \geq 0.$$

Note that (2.14), then for sufficiently small $\delta > 0$, $k = 1, 2, ...,$ yields

$$(2.17) \qquad E\left(\sup_{k\delta \leq t \leq (k+1)\delta}\left[1+G(t)\right]^{\theta}\right) \leq E\left(\left[1+G(k\delta)\right]^{\theta}\right) + F_1 + F_2 \leq K + F_1 + F_2,$$

where

$$F_1 = E\left\{ \sup_{k\delta \leq t \leq (k+1)\delta} \left| \int_{k\delta}^t \theta(1+G)^{\theta-2}\left(G'_{in} - (\alpha' - G'_{in})G - \lambda G^2\right)dr \right| \right\}$$

$$\leq c_1 E\left(\sup_{k\delta \leq t \leq (k+1)\delta} \left| \int_{k\delta}^t (1+G(r))^\theta dr \right| \right)$$

$$\leq c_1 \delta E\left(\sup_{k\delta \leq t \leq (k+1)\delta} (1+G(t))^\theta \right),$$

where $c_1 = \sup\limits_{G \in R_+} \left| \frac{\theta(G'_{in} - (\alpha'-G'_{in})G - \lambda G^2)}{(1+G)^2} \right|$. In fact, noting that $\varphi(G) = \frac{\theta(G'_{in} - (\alpha'-G'_{in})G - \lambda G^2)}{(1+G)^2}$ is monotone decreasing for $G > 0$, if $a' + G'_{in} > (\theta - 1)\sigma^2$ holds. That is

$$\sup_{G \in R_+} \left| \varphi(G) \right| \leq \max\left\{ \theta G'_{in}, \lambda \right\},$$

and

$$F_2 = E\left\{ \sup_{k\delta \leq t \leq (k+1)\delta} \left| \int_{k\delta}^t \sigma \theta G(1+G)^{\theta-1} dB \right| \right\}$$

$$\leq \sqrt{32} E\left(\int_{k\delta}^{(k+1)\delta} \theta^2 \sigma^2 G^2 (1+G(r))^{2(\theta-1)} dr \right)^{\frac{1}{2}}$$

$$\leq \sqrt{32} \theta \sigma \delta^{\frac{1}{2}} E\left(\sup_{k\delta \leq t \leq (k+1)\delta} (1+G(r))^\theta \right).$$

We have mainly applied the Burkholder-Davis-Gundy inequality [7] in the above calculation. Therefore

(2.18)

$$E\left(\sup_{k\delta \leq t \leq (k+1)\delta} [1+G(t)]^\theta \right) \leq E\left([1+G(k\delta)]^\theta \right) + (c_1\delta + \sqrt{32}\theta\sigma\delta^{\frac{1}{2}})E\left(\sup_{k\delta \leq t \leq (k+1)\delta} (1+G(t))^\theta \right).$$

In particular, choose $\delta > 0$ such that $c_1\delta + \sqrt{32}\theta\sigma\delta^{\frac{1}{2}} \leq \frac{1}{2}$, and according to (2.17), it is easy to obtain that

$$E\left(\sup_{k\delta \leq t \leq (k+1)\delta} [1+G(t)]^\theta \right) \leq 2E\left([1+G(k\delta)]^\theta \right) \leq 2K.$$

Let $\varepsilon_u > 0$ be arbitrary, an then by Chebyshev's inequality, we have

(2.19)

$$P\left\{ \sup_{k\delta \leq t \leq (k+1)\delta} (1+G(t))^\theta > (k\delta)^{1+\varepsilon_u} \right\} \leq \frac{E\left(\sup\limits_{k\delta \leq t \leq (k+1)\delta} [1+G(t)]^\theta \right)}{(k\delta)^{1+\varepsilon_u}} \leq \frac{2K}{(k\delta)^{1+\varepsilon_u}}, \quad k = 1, 2, \ldots$$

Applying the well-known Borel-Cantelli's Lemma (see [7]), we obtain that for almost all $\omega \in \Omega$

$$(2.20) \qquad \sup_{k\delta \leq t \leq (k+1)\delta} \left(1+G(t)\right)^{\theta} \leq (k\delta)^{1+\varepsilon_u},$$

holds for all but finitely many k. Hence, there exists a $k_0(\omega)$, for almost all $\omega \in \Omega$, for which (2.19) holds whenever $k \geq k_0$. Consequently, for almost all $\omega \in \Omega$, if $k \geq k_0$ and $k\delta \leq t \leq (k+1)\delta$,

$$\frac{\ln\left(\left[1+G(t)\right]^{\theta}\right)}{\ln t} \leq \frac{(1+\varepsilon_u)\ln(k\delta)}{\ln(k\delta)} = 1+\varepsilon_u.$$

Therefore

$$\frac{\ln\left(\left[1+G(t)\right]^{\theta}\right)}{\ln t} \leq 1+\varepsilon_u \ a.s..$$

Letting $\varepsilon_u \to 0$, yields

$$\limsup_{t\to\infty} \frac{\ln\left(\left[1+G(t)\right]^{\theta}\right)}{\ln t} \leq 1 \ a.s..$$

Noting that $1 < \theta < 1+\frac{2\alpha'}{\sigma^2}$ implies

$$\limsup_{t\to\infty} \frac{\ln G(t)}{\ln t} \leq \limsup_{t\to\infty} \frac{\ln\left(\left[1+G(t)\right]^{\theta}\right)}{\ln t} \leq \frac{1}{\theta} \ a.s..$$

That is to say, for arbitrary small $0 < \xi < 1-\frac{1}{\theta}$, there exist a constant $\tau = \tau(\omega)$ and a set Ω_ξ such that $P(\Omega_\xi) \geq 1-\xi$ and for $t \geq \tau, \omega \in \Omega_\xi$, $\ln G(t) \leq (\frac{1}{\theta}+\xi)\ln t$ and so

$$(2.21) \qquad \limsup_{t\to\infty} \frac{G(t)}{t} \leq \frac{t^{\frac{1}{\theta}+\xi}}{t} = 0 \ a.s..$$

This ends the proof. $\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\square$

Lemma 2.5. *Suppose that $\alpha' > \frac{\sigma^2}{2}$ and $G(t)$ is the solution of stochastic model (2.10) with initial value $G(0) > 0$, then the following statement is valid with probability 1:*

$$\lim_{t\to\infty} \frac{\int_0^t G(s)dB(s)}{t} = 0.$$

Proof. Let $X(t) = \int_0^t G(s)dB(s)$ and $2 < \theta < 1+\frac{2\alpha'}{\sigma^2}$. By Burkholder-Davis-Gundy inequality [7] and (2.16), we have

$$E\left[\sup_{0\leq s\leq t} |X(s)|^{\theta}\right] \leq C_\theta E\left[\int_0^t G^2(r)dr\right]^{\frac{\theta}{2}} \leq C_\theta t^{\frac{\theta}{2}} E\left[\sup_{0\leq s\leq t} G^2(r)\right]^{\frac{\theta}{2}} \leq 2KC_\theta t^{\frac{\theta}{2}}.$$

Let ε_X be an arbitrary positive constant. Then, according to Doob's martingale inequality [7], it is easy to see that

$$P\left\{\omega: \sup_{k\delta \leq t \leq (k+1)\delta} |X(t)|^\theta > (k\delta)^{1+\varepsilon_X+\frac{\theta}{2}}\right\} \leq \frac{E\left[|X((k+1)\delta)|^\theta\right]}{(k\delta)^{1+\varepsilon_X+\frac{\theta}{2}}} \leq \frac{2KC_\theta \left((k+1)\delta\right)^{\frac{\theta}{2}}}{(k\delta)^{1+\varepsilon_X+\frac{\theta}{2}}} \leq \frac{2^{1+\frac{\theta}{2}}KC_\theta}{(k\delta)^{1+\varepsilon_X}}.$$

So by the well-known Borel-Cantelli's Lemma [7], we obtain that for almost all $\omega \in \Omega$,

$$(2.22) \qquad \sup_{k\delta \leq t \leq (k+1)\delta} |X(t)|^\theta \leq (k\delta)^{1+\varepsilon_X+\frac{\theta}{2}},$$

holds for all but finitely many k. Hence, there exists a positive $k_{X_0}(\omega)$, for almost all $\omega \in \Omega$, (2.22) holds whenever $k \geq k_{X_0}$. Consequently, for almost all $\omega \in \Omega$, if $k \geq k_{X_0}$ and $k\delta \leq t \leq (k+1)\delta$,

$$\frac{\ln |X(t)|^\theta}{\ln t} \leq \frac{(1+\varepsilon_X+\frac{\theta}{2})\ln(k\delta)}{\ln(k\delta)} = 1+\varepsilon_X+\frac{\theta}{2}.$$

Therefore

$$\limsup_{t\to\infty} \frac{\ln |X(t)|}{\ln t} \leq \frac{1+\varepsilon_X+\frac{\theta}{2}}{\theta} \quad a.s..$$

Letting $\varepsilon_X \to 0$, yields

$$\limsup_{t\to\infty} \frac{\ln |X(t)|}{\ln t} \leq \frac{1}{2}+\frac{1}{\theta} \quad a.s..$$

Then, for arbitrary small $0 < \eta < \frac{1}{2}-\frac{1}{\theta}$, there exist a constant $\bar{\tau} = \bar{\tau}(\omega) > 0$ and a set Ω_η such that $P(\Omega_\eta) \geq 1-\eta$ and for $t \geq \bar{\tau}, \omega \in \Omega_\eta$

$$\ln |X(t)| \leq \left(\frac{1}{2}+\frac{1}{\theta}+\eta\right)\ln t,$$

which implies

$$\limsup_{t\to\infty} \frac{|X(t)|}{t} \leq \frac{t^{\frac{1}{2}+\frac{1}{\theta}+\eta}}{t} = 0 \ a.s..$$

Together with $\liminf_{t\to\infty} \frac{|X(t)|}{t} \geq 0$, yields

$$\limsup_{t\to\infty} \frac{|X(t)|}{t} = 0 \ a.s..$$

That is

$$\limsup_{t\to\infty} \frac{X(t)}{t} = 0 \ a.s..$$

This ends the proof. $\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad \square$

3. MAIN RESULTS

First of all, we show that there is a unique positive solution, which is a prerequisite for analyzing the long-term behavior of the stochastic model (1.2).

Theorem 3.1. *For any given initial value $X(0) = \left(G(0), I(0) \right) \in R_+^2$, there is a unique solution $X(t) = \left(G(t), I(t) \right)$ of system (1.2) and the solution will remain in R_+^2 with probability 1, that is $X(t) \in R_+^2$ for all $t \geq 0$ almost surely.*

Proof. For $t \in [0, T]$ and for any initial condition $X(0) = \left(G(0), I(0) \right) \in R_+^2$ and by Lemma 2.2, Eq. (2.3) has a unique global solution $\bar{X}\left(t; 0, X(0) \right) \in R_+^2$ that is defined and continuous on interval $[0, T]$, hence Eq. (1.2) also has a unique global solution $X\left(t; 0, X(0) \right) = \bar{X}\left(t; 0, X(0) \right) \in R_+^2$ on interval $[0, T]$. At $t = T$, there is an impulse which transfers solution $X(T) = \bar{X}\left(T; 0, X(0) \right) = \left(\bar{G}(T), \bar{I}(T) \right) \in R_+^2$ into $X(T^+) = \left(\bar{G}(T), \bar{I}(T) + q \right) \in R_+^2$. By the Lemma 2.2 and the same deduction, we get there is a unique global solution $X\left(t; T, X(T^+) \right) = \bar{X}\left(t; T, X(T^+) \right)$ that is defined on $[T^+, 2T]$ and $X(2T^+) = \left(\bar{G}(2T), \bar{I}(2T) + q \right) \in R_+^2$. It is easy to see the above deduction can go on infinitely. The proof is completed. $\square$

Theorem 3.2. *Suppose that $\alpha' > \frac{\sigma^2}{2}$ and $G(t)$ is the solution of stochastic model (2.10) with initial value $G(0) > 0$, then the following statement is valid with probability 1:*

$$\frac{G'_{in}}{\alpha' + a'} \leq \lim_{t \to \infty} \frac{1}{t} \int_0^t G(s) ds \leq \frac{G'_{in}}{\alpha'}.$$

The proof is the application of the well-known comparison theorem for stochastic differential equation, Lemmas 2.4 and 2.5. Here it is omitted.

Theorem 3.3. *System (2.10) has at least one nontrivial positive T-periodic solution.*

Proof. By Lemma 2.1, one can see that in order to verify Theorem 3.3, it suffices to find a $C^{2,1}$-function $V(x, t)$ which is T-periodic in t and a closed set $U \in R_+$ such that conditions (Q_1) and (Q_2) of Lemma 2.1 hold.

Define a $C^{2,1}$-function $V : R_+ \times R_+ \to R_+$ as follows

$$V(G, t) = \omega(t) + G - \ln G,$$

where $\omega(t)$ is positive T-periodic continuous functions. Obviously, $V(G,t)$ is T periodic in t and satisfies

$$\liminf_{k\to\infty,\ G\in R_+\backslash D_k} V(G,t) \to +\infty,$$

where $D_k = [\frac{1}{k}, k]$, which shows that (Q_1) in Lemma 2.1 holds. Making use of Itô's formula, we have

$$LV = \dot{\omega}(t) + G'_{in} - \alpha' G - \frac{a' G I^*}{n+I^*} - \left(\frac{G'_{in}}{G} - \alpha' - \frac{a' I^*}{n+I^*} - \frac{\sigma^2}{2}\right)$$

$$\leq \dot{\omega}(t) + G'_{in} - \alpha' G - \frac{G'_{in}}{G} + \alpha' + a' + \frac{\sigma^2}{2}.$$

Consider the bounded open subset

$$D_\varepsilon = \{G \in R_+ | \varepsilon \leq G \leq \frac{1}{\varepsilon}\},$$

where $0 < \varepsilon < 1$ is a sufficiently small number. In the set $D_\varepsilon^C = R_+ \backslash D_\varepsilon$, let us choose sufficiently small ε such that

$$\dot{\omega}(t) + G'_{in} - \frac{G'_{in}}{\varepsilon} + \alpha' + a' + \frac{\sigma^2}{2} \leq -1,$$

$$\dot{\omega}(t) + G'_{in} - \frac{\alpha'}{\varepsilon} + \alpha' + a' + \frac{\sigma^2}{2} \leq -1.$$

For convenience, we divide D_ε^C into two domains,

$$D_1 = \{G \in R_+ | 0 < G < \varepsilon\}, \quad D_2 = \{G \in R_+ | G > \frac{1}{\varepsilon}\},$$

clearly, $D_\varepsilon^C = D_1 \cup D_2$.

Case 1. On domain D_1, we get

$$LV \leq \dot{\omega}(t) + G'_{in} - \alpha' G - \frac{G'_{in}}{G} + \alpha' + a' + \frac{\sigma^2}{2}$$

$$\leq \dot{\omega}(t) + G'_{in} - \frac{G'_{in}}{\varepsilon} + \alpha' + a' + \frac{\sigma^2}{2}$$

$$\leq -1$$

Case 2. On domain D_2, one can see that

$$LV \leq \dot{\omega}(t) + G'_{in} - \alpha' G - \frac{G'_{in}}{G} + \alpha' + a' + \frac{\sigma^2}{2}$$

$$\leq \dot{\omega}(t) + G'_{in} - \frac{\alpha'}{\varepsilon} + \alpha' + a' + \frac{\sigma^2}{2}$$

$$\leq -1$$

Consequently

$$LV(G,t) \le -1, \quad \text{for } \forall\, G \in D_\varepsilon^C,$$

that is, the condition (Q_2) holds. Hence in view of Lemma 2.1, we obtain that system (2.10) has a nontrivial positive T-periodic solution. In addition, one can see that for any initial value $G(0) \in R_+$ system (2.10) has a unique global positive solution and so system (2.10) has at least one nontrivial positive T-periodic solution. This completes the proof. $\qquad\square$

4. NUMERICAL SIMULATIONS

In this section, we provide numerical simulation results to substantiate the analytical findings for the stochastic model (1.2) reported in the previous sections by using the Milstein method mentioned in [8].

Motivated by [6, 3, 9, 10], the parameter values are chosen as follow: $G_{in} = 1.35, b = 1.93, \alpha = 0.0221502, a = 3 \times 10^{-5}, c = 40, m = 900, n = 80, \gamma = 0.09, T = 30, q = 80$ (See Table 1 for details). In addition, we always assume that the initial value of system (1.2) is $(G(0), I(0)) = (150, 20)$. Then we use different values of σ to investigate the effect of the white noise on the transmission dynamics of the disease. We start our numerical simulation with environmental forcing intensity $\sigma = 0$ and the initial value $(150, 20)$. The results are reported in Fig.1. One can see that, for any positive initial value, the solution of the deterministic system will enter the periodic orbit after a period of time. Next we increase strength of environmental forcing to $\sigma = 0.001$ and we observe that the solution of the stochastic system (1.2) is fluctuating in a small neighborhood of the periodic orbit (See, Fig.1 and Fig.2).

For comparison, we also plot the mean evolution of blood glucose and the corresponding evolution of the stochastic model (1.2) for various values of σ, where $\sigma : 0.001, 0.005, 0.02$ (See Fig.3 and Fig.4). Here we can conclude that the presence of environmental noises is capable of supporting the irregular fluctuate of the concentration of blood glucose $G(t)$ and as the noise intensity decreases, the variability of the stochastic model decreases and approaches the deterministic model dynamics (See Figs. 1, 2 and 3(b)). It is worthy to note that the average level of the number of the concentration of blood glucose $G(t)$ always increases with

the increase of noise intensity (See Fig.3(a)). Therefore, it is important to consider the effect of noise on diabetes mellitus and try to reduce the interference of noise on diabetes mellitus.

TABLE 1. Parameter values in numerical simulations for model (1.2) .

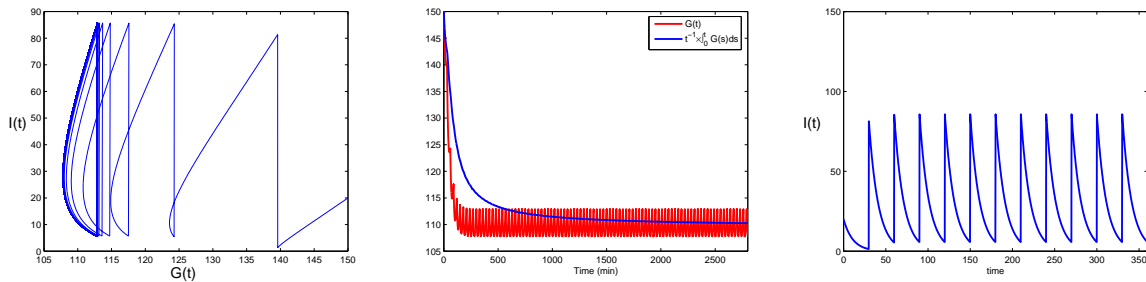| Parameters	Values	Units	References
G_{in}	1.35	$mg/dl/\min$	[6]
b	1.93	$mg/dl/\min$	[9]
α	0.0221502	$\min^{-1}$	[10]
a	3×10^{-5}	mg^{-1}	[3]
c	40	$mg/\min$	[3]
m	900	$mg/\min$	[3]
n	80	mg	[3]
γ	0.09	$\min^{-1}$	[10]
T	30	$\min$	[3]
q	0.08	mU	[3]

FIGURE 1. The left is a sample phase portrait of deterministic system (1.1); middle and right are the solutions of deterministic model (1.1) with initial value $\left(G(0), I(0)\right) = (150, 20)$. The parameters are taken as Table 1.
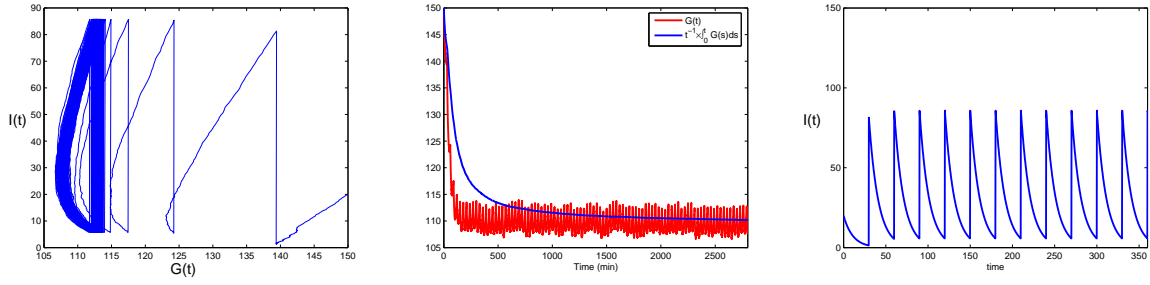
FIGURE 2. The left is a sample phase portrait of stochastic system (1.2); middle and right are the solutions of stochastic model (1.2) with initial value $\left(G(0), I(0)\right) = (150, 20)$ and $\sigma = 0.001$. The parameters are taken as Table 1.
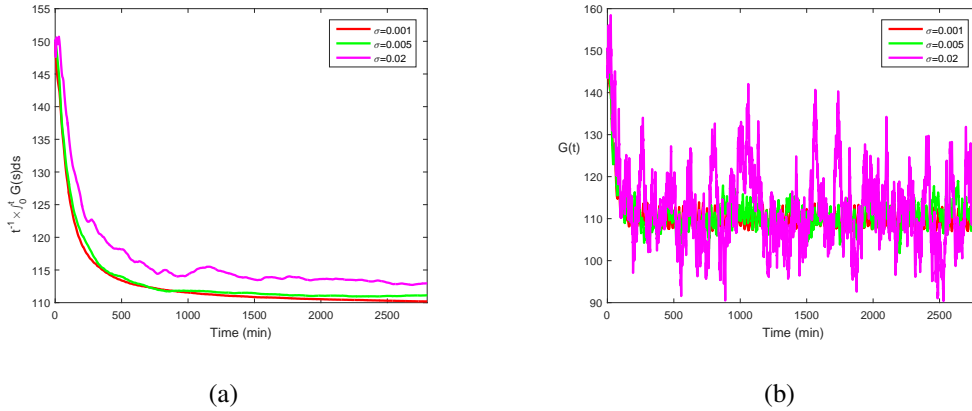

(a)   (b)

FIGURE 3. (a) The mean evolution of blood glucose of the stochastic model (1.2) is graphed for various values of σ, where $\sigma : 0.001, 0.005, 0.02$. (b) The corresponding evolution of blood glucose of the stochastic model (1.2).

5. DISCUSSION

Over the decades subcutaneous injection of insulin analogues was considered as the most widely method in treating diabetes. In the point of view of treating diabetes, the ultimate purpose of the subcutaneous injection of insulin analogues is to increase the plasma insulin concentration and thus lower blood glucose to maintain normal glycemia. In the real ecological systems, meals and exercise, the age and weight of the patient also affect the insulin/glucose dynamics. These daily and hourly fluctuations of patient parameters can create difficulties in continuous glucose control. In order to better understand the dynamics of the insulin analogues

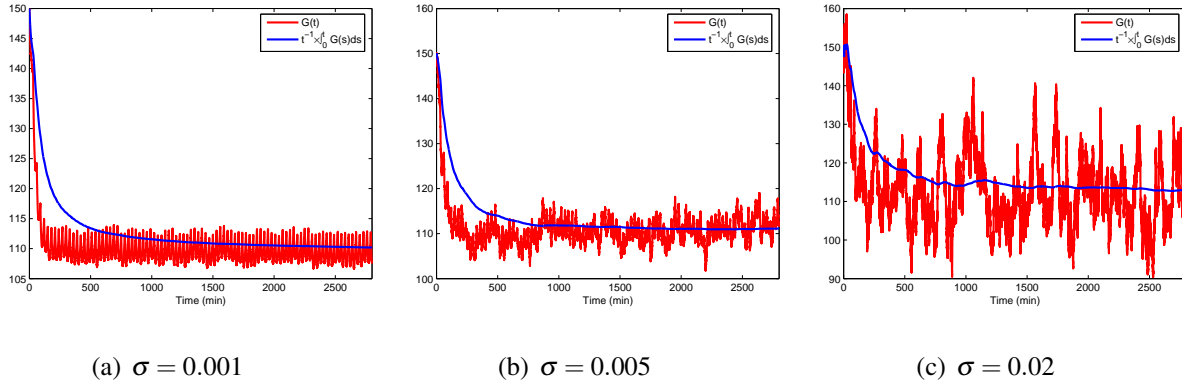(a) $\sigma = 0.001$ (b) $\sigma = 0.005$ (c) $\sigma = 0.02$

FIGURE 4. The evolution of a single path of blood glucose of the stochastic model (1.2).

from subcutaneous injection to absorption, we have considered the basic features of insulin-glucose stochastic model of subcutaneous injection of regular insulin. Our results show that there exists at least one nontrivial positive periodic solution for model (1.2), which means that the glucose and insulin will exhibit periodicity in the long run. In addiion, we found that the noise has great effects on the diabetic patient, such as, (i) the presence of environmental noises is capable of supporting the irregular oscillation of blood glucose level, and the average level of the glucose always increases with the increment in noise intensity; (ii) the higher the volatility of the environmental noises, the more difficult the prediction of the peak size of blood glucose level. Hence, diabetic patient should avoid the influence of uncertain factors on them, such as, mood and stress.

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CONFLICT OF INTERESTS

The author(s) declare that there is no conflict of interests.

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