EUROPEAN JOURNAL OF PURE AND APPLIED MATHEMATICS
2025, Vol. 18, Issue 1, Article Number 5404
ISSN 1307-5543 – ejpam.com
Published by New York Business Global

Statistical Insights into Stochastic Glucose-Insulin Dynamics: Modeling Insulin Degradation with the Michaelis-Menten Function

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Abstract. In this study, a glucose-insulin model with the Michaelis-Menten function as the rate of insulin degradation is analyzed using stochastic differential equations. Further, we solve the stochastic glucose-insulin model using the Milstein method, which is based on truncated Ito-Taylor expansions. Comparison of the approximation solution of a stochastic and deterministic model is illustrated by comparing the approximation solution with the deterministic model. A stochastic model allows random fluctuations in glucose-insulin diseases. Furthermore, the stochastic glucose-insulin model's numerical solution provides insight into its variability. The model predicts glucose-insulin dynamics accurately, which is a powerful tool for managing diabetes. Analytical and simulation results are consistent. Improved treatment strategies and personalized medical interventions could result. Treatments and insulin injections are sensitive to these parameters. Numerical simulation corroborates theoretical results.

2020 Mathematics Subject Classifications: 34L99
Key Words and Phrases: Statistical Insights, Stochastic Glucose-Insulin Dynamics, Modeling Insulin Degradation, Michaelis-Menten Function

1. Introduction

Understanding glucose-insulin interactions is critical in the context of diabetes, a chronic metabolic disorder that results from the body's inability to regulate blood glucose levels. Diabetes can lead to severe health complications, such as cardiovascular disease, nerve damage, and kidney failure, if not properly managed. Mathematical modeling has become an invaluable tool for analyzing the complex dynamics between glucose and insulin, aiding in the design of effective treatment strategies. Traditional models have typically used deterministic approaches to simulate these interactions, though they often fail to account for the inherent variability and random fluctuations in biological systems [9], [7]. To address this limitation, stochastic models incorporating randomness have been introduced, offering a more realistic representation of glucose-insulin dynamics in diabetic patients [1–4, 9, 17, 17, 18, 18, 21, 24–27, 29–31].

DOI: https://doi.org/10.29020/nybg.ejpam.v18i1.5404

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In recent years, researchers have utilized stochastic differential equations (SDEs) to better capture the variability of glucose and insulin levels in response to both intrinsic and extrinsic factors. The Michaelis-Menten function, frequently employed in enzyme kinetics, is particularly suitable for modeling the nonlinear degradation rate of insulin, providing a more nuanced understanding of diabetes pathogenesis [21, 29]. By using numerical techniques such as the Milstein method to solve SDEs, these models achieve a high level of accuracy in simulating glucose-insulin dynamics [14, 16]. This study introduces a stochastic model based on the Michaelis-Menten function, which captures the complex, variable nature of glucose-insulin interactions, aiming to advance personalized treatment strategies for diabetes management [24, 27]. The model's validity is demonstrated through comparisons with a deterministic counterpart, underscoring the importance of stochastic modeling in capturing biological variability [11, 31].

Diabetic mellitus is a metabolic disorder that has high blood sugar levels all the time. It is caused by either the pancreas not producing enough insulin or the body's cells not responding to insulin. Without proper treatment, diabetes can lead to serious health complications. This leads to serious health complications such as cardiovascular diseases, nerve damage, kidney failure, and blindness. It arises either due to the body's inability to produce sufficient insulin (Type 1 diabetes) or due to the ineffective use of insulin (Type 2 diabetes). Understanding diabetes pathogenesis and progression is crucial for developing effective treatment and management strategies. Mathematical modeling has emerged as a powerful tool to study the complex interactions between glucose and insulin in the body. This provides insights into disease dynamics and potential interventions. Such models can also be used to evaluate the efficacy of potential treatments and interventions. They can also be used to predict lifestyle changes' impact on diabetes outcomes. Traditional models often rely on deterministic differential equations to describe these dynamics. While valuable, these models fall short of capturing biological systems' inherent randomness and variability. To address this limitation, stochastic models have been introduced, incorporating random perturbations that reflect the unpredictable fluctuations in glucose and insulin levels observed in diabetic patients. These stochastic models offer a more realistic representation of biological processes. In recent years, calculus has gained attention for its ability to model memory and hereditary properties of various processes. This makes it particularly suitable for representing the complex dynamics of the glucose-insulin system.

This paper aims to advance diabetes dynamics understanding through the development of a stochastic glucose-insulin model. By incorporating the Michaelis-Menten function and employing the Milstein method, we provide a comprehensive analysis of the model's properties, sensitivity, and potential management strategies. This work underscores the importance of stochastic modeling in capturing biological systems' complexity and variability. This contributes to more effective diabetes treatment and management. An analysis of the degradation rate of insulin in a stochastic glucose-insulin model using the Michaelis-Menten function is presented in this paper. The Michaelis-Menten function, widely used in enzyme kinetics, provides a more accurate representation of the nonlinear relationship between insulin concentration and degradation rate. Our model aims to offer a comprehensive understanding of diabetes pathogenesis by capturing the intricate

dynamics and inherent variability of the glucose-insulin system. To ensure model validity, we examine the solution's global existence and positivity. This ensures that glucose and insulin levels remain non-negative and well-defined over time. We also perform a sensitivity analysis to identify the most influential parameters affecting the system's behavior. This analysis helps design targeted intervention strategies for diabetes management, such as insulin injections, medication treatments, combination therapies, and lifestyle adjustments. Our stochastic diabetes model is analyzed with the Milstein method, a numerical technique based on truncated Ito-Taylor expansions. It is known for its efficiency and accuracy for solving stochastic differential equations. By applying this method, we calculate the mean and confidence intervals, providing a comprehensive statistical description of glucose-insulin dynamics. Finally, we compare the stochastic model results with the corresponding deterministic model, demonstrating the advantages of incorporating stochastic elements. Our findings indicate that the stochastic diabetes model, solved efficiently using the Milstein method, offers a more realistic and robust framework for studying diabetes pathogenesis and management.

Recently, several mathematicians have developed mathematical models based on IVGTT to study glucose–insulin interactions, see [1–4, 8, 25, 26]. In many disciplines, including medicine, engineering, chemistry, physics, economics, and many more, epidemiology plays an important role. See [8, 12, 13, 20]. Space-time, stochastic, fractional, and fractal mathematics are used to examine disease models, see [5, 6, 22, 28]. Compared to fractional, ordinary and partial differential equations, stochastic differential equations like [15]-[33] are more realistic and appropriate than fractional, ordinary and partial differential equations. Stochastic differential equations have also been used to simulate the spread of infectious diseases, such as COVID-19. They can also be used to understand the effects of interventions, such as social distancing and contact tracing. Mathematical models are crucial in public health as they provide valuable insights into the dynamics of disease transmission and the potential impact of various interventions. By simulating different scenarios, these models help policymakers design effective strategies to mitigate the spread of diseases and allocate resources efficiently. This is especially important during pandemics, where timely and accurate predictions can save lives and reduce the burden on healthcare systems.

2. Stochastic diabetes model motivation & formulation

Daily carbohydrate intake includes cereals, meat, and dairy products. Energy from them is sufficient for all life activities. Insulin-dependent glucose consumers, such as the brain, and insulin-independent glucose consumers, such as muscles, consume glucose. Synthetic insulin is produced in the pancreas by beta cells. Glucose is broken down in the pancreas by insulin, which is secreted by the beta cells. $G(t)$ represents the plasma glucose concentration (μU/ml).G_{in} and I_{in} to represent plasma insulin concentration. Glucose intake rate G_{in} and exogenous insulin infusion rate I_{in} are constants that specify glucose intake and exogenous insulin infusion rates. The significance of $G(t)$ and $I(t)$ lies in their roles in maintaining homeostasis within the body's metabolic processes. $G(t)$, representing the plasma glucose concentration, is crucial for ensuring that cells have a constant

supply of glucose for energy production. Meanwhile, $I(t)$, representing the plasma insulin concentration, is vital for regulating the uptake and utilization of glucose by cells, thereby preventing hyperglycemia and hypoglycemia. Together, these functions are essential for the proper functioning of various physiological systems and overall metabolic health.

Glucose-insulin models assume insulin clearance is proportional to insulin concentration [10, 15, 15, 18, 23, 29, 31, 32]. Insufficient assumptions may lead to ineffective diagnosis and cure strategies. In [30], it is pointed out that even with an excess of resources, change rates don't increase forever.

Their model included the Michaelis-Menten function $\frac{dI}{e+I}$ to determine the rate of degradation of insulin in the glucose-insulin system. d is the maximum clearance rate of insulin, while e is half-saturation. In comparison to a linear rate, it is more realistic. This paper presents a model that relates glucose and insulin based on the work of [30]. Compared to other existing glucose-insulin models, our model incorporates a non-linear degradation rate of insulin via the Michaelis-Menten function, which more accurately reflects physiological conditions. Traditional models often assume a linear relationship, which can oversimplify the dynamics and lead to less precise predictions. By integrating this non-linear approach, our model provides a more robust framework for understanding glucose-insulin interactions and offers improved potential for developing effective treatment strategies for metabolic disorders.

$$\begin{aligned} \frac{\mathrm{d}G}{\mathrm{d}t} &= G_{in} - aG - bGI, \quad G(0) > 0, \\ \frac{\mathrm{d}I}{\mathrm{d}t} &= I_{in} + cG - \frac{dI}{e+I}, \quad I(0) > 0. \end{aligned} \tag{1}$$

Table 1 gives a brief explanation of the meaning of the parameters. The parameters in the stochastic glucose-insulin model have specific biological interpretations:

- G_{in}: Glucose intake rate, representing the rate at which glucose enters the bloodstream from dietary sources.
- I_{in}: Exogenous insulin infusion rate, representing the rate of insulin administration from external sources.
- a: Insulin-independent tissues' glucose utilization rate (e.g., brain).
- b: Insulin-dependent tissues' glucose utilization rate (e.g., muscles).
- c: Insulin secretion rate in response to glucose.
- d: Insulin clearance maximum.
- e: Insulin clearance half-saturation value.

All parameters in (1) are deterministic, so environmental fluctuations and randomness are not considered. The glucose-insulin model is more appropriate to be applied in a

biological environment by considering how environmental noise affects the glucose-insulin model. Stochastic perturbations introduce randomness into the model parameters, reflecting the inherent uncertainties and variability in biological systems. The inclusion of Gaussian white noise in the parameters a, b, c, d, e represents the random fluctuations in these parameters due to various physiological and environmental factors. Biological systems are subject to random fluctuations arising from various sources such as hormonal changes, variations in dietary intake, physical activity, and stress. These fluctuations can cause significant changes in glucose and insulin levels. By incorporating stochastic perturbations, the model can account for these random influences, providing a more realistic representation of the glucose-insulin dynamics. Gaussian white noise is used to model the random perturbations in the parameters. Each parameter is perturbed by an independent Brownian motion $B_i(t)$, with ξ_i controlling the intensity of the perturbation. This approach allows the model to simulate the unpredictable nature of physiological processes and environmental factors affecting glucose and insulin regulation. The stochastic glucose-insulin model is given by: This stochastic glucose-insulin model is defined by the following stochastic differential equations

$$\begin{aligned} dG &= (G_{\text{in}} - aG - bGI)\,dt + \sigma_1 G(t) dB_1(t), \\ dI &= \left(I_{\text{in}} + cG - \frac{dI}{e+I}\right) dt + \sigma_2 I(t) dB_2(t), \end{aligned} \tag{2}$$

There are two Brownian motions $B_i(t), (i = 1, 2)$. The probability space $\left(\Omega, \mathcal{F}, \{\mathcal{F}_t\}_{t\geq 0}, \mathbb{P}\right)$ contains all sets of $\{\mathcal{F}_t\}_{t\geq 0}$ that meet the usual conditions (i.e. it is increasing and right continuous while $\mathcal{F}_0$ contains all $\mathbb{P}$-null sets). σ_i and $(i = 1, 2)$ represent noise intensity. The parameters in the stochastic glucose-insulin model have specific biological interpretations:

- ξ_i: Intensity of the stochastic perturbations affecting each parameter.
- $B_i(t)$: Independent Brownian motions representing random fluctuations in the parameters.

By incorporating derivatives and stochastic perturbations, the glucose-insulin model becomes more realistic and accurate in representing the physiological processes. This allows epidemiologists to better understand the spread of diseases and develop strategies to contain them. Additionally, epidemiology is important for understanding the effectiveness of public health interventions. Our study extends these ideas by applying stochastic differential equations to model glucose-insulin interactions. This approach acknowledges biological systems' inherent randomness, which traditional deterministic models fail to capture. By incorporating the Michaelis-Menten function, our model accounts for insulin's nonlinear degradation rate, providing a more realistic representation of glucose-insulin dynamics. Our stochastic model captures variability and randomness in the glucose-insulin system using the Milstein method. The comparison between stochastic and deterministic models highlights the necessity of incorporating stochastic elements to achieve more accurate and reliable predictions. Our sensitivity analysis identified key parameters influencing

system behavior, guiding personalized intervention strategies. Our findings underscore the significance of stochastic modeling in understanding diabetes dynamics. The model's ability to capture random fluctuations in glucose and insulin levels offers a powerful tool for managing diabetes. This is especially important for patients with Type 1 diabetes who experience significant glucose variability. The integration of stochastic elements provides insights into the disease's variability and unpredictability, which are critical for developing effective management strategies. The numerical simulations, supported by graphs and error tables, validated our theoretical findings and demonstrated the robustness of the Milstein method. The consistency between analytical and simulation results suggests that our model can be applied to real-world scenarios, offering potential improvements in diabetes treatment and management. However, calculus in epidemiological modeling, including glucose-insulin dynamics, has certain limitations. calculus non-integer order derivatives do not always have a direct physical interpretation, which can complicate epidemic dynamics. The Michaelis-Menten function and stochastic elements are used in our study to advance diabetes mathematical modeling. The results highlight the importance of stochastic modeling in capturing the complexity and variability of biological systems. This paves the way for more effective and personalized diabetes management strategies. Future research should continue to explore the integration of additional biological factors and real-time data to further enhance the model's accuracy and applicability in clinical settings.

3. Background material

Definition 1 ([19]). *The Wiener process is defined as* $(B(t))_{t\geq 0}$ *when*

(i) $B(0) = 0, \mathbb{P}-$ *a.s.*

(ii) For every $0 \leq r < t$*, the quantity* $B(t) - B(r)$ *are independent of* $\mathcal{F}_r$*.*

(iii) For every $0 \leq r < t$*, then* $B(t) - B(r) \backsim \mathcal{N}(0, t-r)$*.*

Definition 2. *A stochastic differential equation (SDE) is defined by:*

$$dy(t) = \mathbb{F}(t, y(t))dt + \mathbb{G}(t, y(t))dB(t), \text{ with } y_0 = y(0),$$

$B(t)$ *is a Wiener process of dimension n,* $\mathbb{G}$ *is the diffusion coefficient, and* $\mathbb{F}$ *is the drift coefficient. For every* T *and* N*, there exist a constant* K *that depends on* T *and* N*, such that*

$$|\mathbb{F}(x,t) - \mathbb{F}(y,t)| + |\mathbb{G}(x,t) - \mathbb{G}(y,t)| < K|x-y|.$$

for all $|x|, |y| \leqslant N$ and all $0 \leqslant t \leqslant T$. $V \in C^{2,1}\left(\mathbb{R}^3 \times [t_o, \infty]; \mathbb{R}_+\right)$ is the family of all semi-positive functions $V(\Upsilon, t)$ and it is defined on $\mathbb{R}^3 \times [t_o, \infty]$ so that they are continuously twice differentiable in Υ and once in t. Thus, the differential operator L is defined by [19] as,

$$L = \frac{\partial}{\partial t} + \sum_{i=1}^{3} \Phi_{1i}(\Upsilon) \frac{\partial}{\partial \Upsilon_i} + \frac{1}{2} \sum_{i,j=1}^{3} \left[\mathbb{G}^T(\Upsilon, t)\mathbb{G}(\Upsilon, t)\right]_{ij} \frac{\partial^2}{\partial \Upsilon_i \partial \Upsilon_j}.$$

For $\mathtt{V} \in C^{2,1}\left(\mathbb{R}^3 \times [t_o, \infty]; \mathbb{R}_+\right)$, then

$$L\mathtt{V}(\Upsilon, t) = \mathtt{V}_t(\Upsilon, t) + V_\Upsilon(\Upsilon, t)\mathbb{F}(\Upsilon, t) + \frac{1}{2}\operatorname{trace}\left[\mathbb{G}^T(\Upsilon, t)\mathtt{V}_{\Upsilon\Upsilon}\mathbb{G}(\Upsilon, t)\right],$$

where $\mathtt{V}_t = \frac{\partial \mathtt{V}}{\partial t}, \mathtt{V}_\Upsilon = \left(\frac{\partial \mathtt{V}}{\partial y_1}, \ldots, \frac{\partial \mathtt{V}}{\partial y_3}\right)$ and $\mathtt{V}_{\Upsilon\Upsilon} = \left(\frac{\partial^2 \mathtt{V}}{\partial y_i \partial y_j}\right)_{3\times 3}$. Based on Itô's formula, if $\Upsilon(t) \in \mathbb{R}^l$, then $Y(t)$ is an l-dimensional stochastic process. $\Upsilon(t)$ is a martingale if $E[\Upsilon(t)] = \Upsilon(0)$. $\Upsilon(t)$ is a semimartingale if $E[\Upsilon(t)] = \Upsilon(0) + \sigma(t)$, where $\sigma(t)$ is a Wiener process.

$$d\mathtt{V}(\Upsilon, t) = L\mathtt{V}(\Upsilon(t), t) + \mathtt{V}_\Upsilon(\Upsilon(t), t)\mathbb{G}(X(t), t)dB(t).$$

It will be assumed that we are dealing with a "Markov Process" in the space E_l (E_l denoting a l dimensional Euclidean space), that may be exactly described as follows:

$$dX(t) = b(X)dt + \sum_{r=1}^{k} \mathbb{G}_r dB_r(t).$$

For the purpose of defining the diffusion matrix, we need to consider the following factors:

$$A = (T_{ij}(x)), \quad T_{ij}(x) = \sum_{r=1}^{k} \mathbb{G}_r^i(x)\mathbb{G}_r^j(x).$$

Theorem 1. *There exists a unique solution* (G, I) *to* E_q *for any initial value* $(\mathrm{G}(0), \mathrm{I}(0)) \in \mathbb{R}^2_+$. *This means that in most cases,* $(\mathrm{G}(0), \mathrm{I}(0)) \in \mathbb{R}^2_+$ *will remain in* $\mathbb{R}^2_+$ *with probability one* $t \geq 0$ *almost certainly.*

Lemma 1 ([19, 33])**.** *Suppose* $\Omega \in \mathbb{R} \times \mathbb{C}^n$ *is open,* $f_i \in \mathscr{C}(\Omega, \mathbb{R}), i = 1, 2, 3, \ldots, n$. *If* $f_i \mid x_i(t) = 0, X_t \in \mathbb{C}^n_{+0} \geqslant 0, X_t = (x_{1t}, x_{2t}, x_{3t}, \ldots, x_{nt})^T$, *then* $\mathbb{C}^n_{+0}$ *is the invariant domain of the following equations*

$$\frac{dx_i(t)}{dt} = f_i(t, X_t), t \geqslant \sigma, i = 1, 2, \ldots, n.$$

The assertion that the two Wiener processes (Brownian motions) are independent suggests that there is no direct correlation between the glucose G and insulin I fluctuations in model (2). In this stochastic system, the independence of $B_1(t)$ and $B_2(t)$ implies that any stochastic fluctuations in glucose do not directly influence insulin fluctuations, and vice versa, on a noise level. This setup allows each process to experience random fluctuations independently of the other, which could be a model choice to represent that glucose and insulin variabilities arise from separate sources or mechanisms.

Since no correlation coefficient is specified, we assume no cross-dependence between G and I in terms of their random perturbations, which aligns with the independent noise intensities σ_1 and σ_2 applied to each. If there is interest in exploring potential dependencies, introducing a correlation coefficient between the Wiener processes could reflect a level of interconnected noise between glucose and insulin, which might be biologically relevant in certain conditions.

4. Properties of the Stochastic diabetes model

4.1. Positivity of the solution

Theorem 2. *The solutions $(G(t), I(t))$ of model (2) with semi-positive initial conditions are all semi-positive for all $t > 0$ for which the solution is defined.*

Proof. Let $S = (G, I)^T$ and $f(S) = (f_1(G), f_2(I))^T$, so (2) can be rewritten as, $\frac{dS(t)}{dt} = f(S)$, where,

$$f(S) = \begin{bmatrix} G_{in} - aG - bGI \\ I_{in} + cG - \frac{dI}{e+I} \end{bmatrix}.$$

Note that,

$$\left.\frac{dG(t)}{dt}\right|_{G=0} = G_{in} > 0, \quad \left.\frac{dI(t)}{dt}\right|_{I=0} = I_{in} > 0,$$

Lemma 1 yields that R^2_+ is invariant set.

4.2. Boundedness of Solutions

Theorem 3. *Let $\tau = \min\left\{a - c, \frac{dI}{e+\mathscr{M}}\right\}$, then system (1) has a positive invariant region:*

$$\Delta = \{(G, I) : G \geqslant 0, I \geqslant 0, G + I \leqslant \mathscr{M}\},$$

Proof. Taking the population as $N(t) = G(t) + I(t)$. A direct calculation gives

$$\begin{aligned} dN(t) &= G_{in} - aG - bGI + I_{in} + cG - \frac{dI}{e+I} + (\sigma_1 G(t)dB_1(t) + \sigma_2 I(t)dB_1(t)) \\ &\leqslant G_{in} + I_{in} - (a-c)G - \frac{dI}{e+\mathscr{M}} + (\sigma_1 G(t)dB_1(t) + \sigma_2 I(t)dB_1(t)) \\ &\leqslant (G_{in} + I_{in} - \tau N(t))dt + (\sigma_1 G(t)dB_1(t) + \sigma_2 I(t)dB_1(t)) \end{aligned}$$

Taking expectations and noting that Wiener processes have no expectations, we get:

$$\mathbb{E}[dN(t)] = (G_{in} + I_{in} - \tau \mathbb{E}[N(t)])\, dt.$$

Thus, the expected total population $\mathbb{E}[N(t)]$ is given by:

$$\frac{d\mathbb{E}[N(t)]}{dt} = G_{in} + I_{in} - \tau \mathbb{E}[N(t)].$$

Solving this linear differential equation, we obtain:

$$\mathbb{E}[N(t)] = \frac{G_{in} + I_{in}}{\tau} + \left(N(0) - \frac{G_{in} + I_{in}}{\tau}\right) e^{-\tau t}.$$

This indicates that $t \to \infty$, $\mathbb{E}[N(t)] \to \frac{G_{in}+I_{in}}{\tau}$, indicating a bounded population.

4.3. Feasible region and Global existence solution

Theorem 4. *If $(G(0), I(0)) \in \mathbb{R}^2_+$, model (2) has a unique solution $(G(t), I(t))$ on $t \geqslant 0$. Moreover, the solution $(G(t), I(t))$ will remain in $\mathbb{R}^2_+$ with probability 1 .*

Proof. Clearly, the coefficients of the system (2) will be Lipschitz continuous at any initial value of $(G(0), I(0),) \in \mathbb{R}^2_+$. System (2) can be written as,

$$\begin{aligned}|\mathbb{G}(t_1) - \mathbb{G}(t_2)| &= |(G_{in} - aG(t_1) - bG(t_1)I) - (G_{in} - aG(t_2) - bG(t_2)I) + \xi_1 G(t_1) \\ &\quad - \xi_1 G(t_2)| \\ &= (a + b|I| + \xi_1)|G(t_1) - G(t_2)| \\ &\leqslant \tau_1 |T(t_1) - T(t_2)|.\end{aligned}$$

where $\tau_1 = a + b\mathscr{M} + \xi_1$. We can demonstrate that the rest of the coefficients are Lipschitz locally. Therefore, a unique local solution $(G(t), I(t)) \in \mathbb{R}^2_+, \forall t \in [0, \tau_2]$ must exist. Here τ_2 is explosion time. A global solution requires proving that $\tau_2 = \infty$. Let τ_0 be a positive constant whose values are such that $(G(0), I(0)) \in \left\{\frac{1}{\tau_0}, \tau_0\right\}$. Based on a stopping time

$$\tau_k = \left\{t \in [0, \tau_2] : \frac{1}{k} \geq \min\{(G(t), I(t))\} \text{ or } \max\{(G(t), I(t))\} \geq k\right\},$$

for each $k \geq \tau_0$. Considering the stopping time as $k \to \infty$, τ_k is monotonically increasing. By setting $\lim_{k\to\infty} \tau_k = \tau_\infty$ with $\tau_l \geq \tau_\infty, \forall t \geq 0$, we prove that $\tau_\infty = 0$ and $(G(t), I(t)) \in \mathbb{R}^2_+$. Consequently, $0 < \Sigma$ and $G_{in} + I_{in} \in (0, 1)$ such that

$$P\{\Sigma \geq \tau_2\} > G_{in} + I_{in}.$$

Thus

$$dL(G, I) = \left(1 - \frac{1}{G}\right) dG + \sigma_1(G - 1)dB_1(t) + \left(1 - \frac{1}{I}\right) dI + \sigma_2(I - 1)dB_2(t).$$

Now, let $\mathscr{H} : R^2_+ \to R_+$ from the C^2 space, satisfies

$$\mathscr{H}(G, I) = G + I - 2 - (\log G + \log I). \tag{3}$$

For all $y > 0, y - 1 - \log y \geqslant 0$, we note that $H \geqslant 0$. Moreover, suppose $k_0 \leqslant k$ and $0 < T$ with applying the Itôo formula on Equation (4.1), one obtains $LH : R^2_+ \to R_+$ as

$$\begin{aligned}L\mathscr{H} &= \left(1 - \frac{1}{G}\right)(G_{in} - aG - bGI) + \left(1 - \frac{1}{I}\right)\left(I_{in} + cG - \frac{dI}{e + I}\right) + \frac{\sigma_1^2 + \sigma_2^2}{2} \\ &= G_{in} - aG - bGI - \frac{G_{in}}{G} + a + bI \\ &+ I_{in} + cG - \frac{dI}{e + I} - \frac{I_{in}}{I} - \frac{cG}{I} + d + \frac{\sigma_1^2 + \sigma_2^2}{2} \\ &\leq G_{in} + I_{in} + a + d + \frac{\sigma_1^2 + \sigma_2^2}{2} := K\end{aligned} \tag{4}$$

Based on the formulation of K, we can see that it is both positive and independent at the same time. So,

$$d\mathscr{H}(G,I) \leqslant Kdt + \eta_1(G-1)dB_1(t) + \eta_2(I-1)dB_2(t). \tag{5}$$

Integrate both sides of Eq (4.3) from 0 to $\tau_k \wedge T$

$$\begin{aligned} E\left[\mathscr{H}\left(G\left(\tau_k \wedge T\right), I\left(\tau_k \wedge T\right),\right)\right] &\leqslant \mathscr{H}(G(0), I(0)) + E\left[\int_0^{\tau_k \wedge T} K\right] \\ &\leqslant \mathscr{H}(G(0), I(0)) + TK. \end{aligned}$$

$$\begin{aligned} d\mathscr{H}(G,I) &= \left(1 - \frac{1}{G}\right) dG + \eta_1(G-1)dB_1(t) + \left(1 - \frac{1}{I}\right) dI + \eta_2(I-1)dB_2(t) \\ &= L\mathscr{H}(G,I)dt + \eta_1(G-1)dB_1(t) + \eta_2(I-1)dB_2(t). \end{aligned}$$

By setting $\Omega_k = \{T \geqslant \tau_k\}$ and for $k_1 \leqslant k$. Thus, by Eq. (4.2), $P\left(\Omega_k\right) \geqslant \epsilon$. For every ϖ in Ω_k, at least one $G\left(\tau_k, \varpi\right), I\left(\tau_k, \varpi\right)$ exist so that equals $\frac{1}{k}$ or k. Hence $\mathscr{H}\left(G\left(\tau_k\right), I\left(\tau_k\right)\right)$ is not less than $k - \log k - 1$ or $\log k - 1 + \frac{1}{k}$. Therefore

$$\left(\log k - 1 + \frac{1}{k}\right) \wedge E(k - \log k - 1) \leqslant \mathscr{H}\left(G\left(\tau_k\right), I\left(\tau_k\right)\right).$$

Therefore

$$\begin{aligned} \mathscr{H}(G(0), I(0)) + TK &\geqslant E\left[1_{\Omega(\varpi)} \mathscr{H}\left(G\left(\tau_k\right), I\left(\tau_k\right)\right)\right] \\ &\geqslant \epsilon\left[(-1 + k - \log k) \wedge \left(-1 + \frac{1}{k} + \log k\right)\right], \end{aligned}$$

where $1_{\Omega(\varpi)}$ is the indicator function of Ω. The assumption $k \to \infty$ yields a contradiction $\infty > \mathscr{H}(G(0), I(0)) + TK = \infty$. Thus, $\tau_\infty = \infty$ a.s.

5. Sensitivity Analysis of Glucose and Insulin Dynamics

The equilibrium of model (1) should be determined first to study the steady state properties. Let

$$G_{in} - aG - bGI = 0$$

$$I_{in} + cG - \frac{dI}{e + I} = 0$$

A unique positive equilibrium (G^*, I^*) exists for $d > I_{in}$, where

$$G^* = \frac{G_{in}}{a + bI^*}, \quad I^* = \frac{(ad - cG_{in} - aI_{in} - beI_{in}) - \sqrt{\Delta}}{2b\left(I_{in} - d\right)}$$

and

$$\Delta = (ad - cG_{in} - aI_{in} - beI_{in})^2 - 4be\,(I_{in} - d)\,(cG_{in} + aI_{in})$$

Thus, the sensitivity indices of (G^*, I^*) to parameters (b, c, d) are derived using [19, 33]. The sensitivity indices are useful in calculating the relative changes in a state variable as a parameter changes in terms of a state variable. These indices help in identifying which parameters have the most influence on the system, allowing modelers to focus on the most critical factors. This can lead to more accurate and efficient model calibration and validation. Ultimately, this improves the reliability of predictions made by the model.

Definition 3. *Normized forward sensitivity index for variables u that depend on parameters τ:*

$$\beta_p^u := \frac{\partial u}{\partial \tau} \times \frac{\tau}{u}.$$

Next, the normalized forward sensitivity is given by:

$$\begin{aligned}
\beta_b^{G^*} &= \frac{b}{G^*}\frac{\partial G^*}{\partial b} = -\frac{bdeI^*}{\Delta_1\,(e + I^*)^2}, \quad \beta_b^{I^*} = \frac{b}{I^*}\frac{\partial I^*}{\partial b} = -\frac{bcG^*}{\Delta_1}, \\
\beta_c^{G^*} &= \frac{c}{G^*}\frac{\partial G^*}{\partial c} = -\frac{bcG^*}{\Delta_1}, \quad \beta_c^{I^*} = \frac{c}{I^*}\frac{\partial I^*}{\partial c} = \frac{c\,(a + bI^*)\,G^*}{\Delta_1 I^*}, \\
\beta_d^{G^*} &= \frac{d}{G^*}\frac{\partial G^*}{\partial d} = \frac{bdI^*}{\Delta_1\,(e + I^*)}, \quad \beta_d^{I^*} = \frac{d}{I^*}\frac{\partial I^*}{\partial d} = -\frac{d\,(a + bI^*)}{\Delta_1\,(e + I^*)},
\end{aligned}$$

with

$$\Delta_1 = bcG^* + \frac{de}{(e + I^*)^2}\,(a + bI^*) > 0.$$

It is easy to calculate

Table 1: Normized Forward Sensitivity Indexes for G and I for parameters b, c, and d

I_{in}	$\beta_b^{G^*}$	$\beta_b^{I^*}$	$\beta_c^{G^*}$	$\beta_c^{I^*}$	$\beta_d^{G^*}$	$\beta_d^{I^*}$
0	-0.4919	-0.5052	-0.5052	0.5081	0.5017	-0.5046
5	-0.5336	-0.4635	-0.4635	0.4660	0.5452	-0.5481
10	-0.5746	-0.4226	-0.4226	0.4247	0.5881	-0.5910
20	-0.6513	-0.3460	-0.3460	0.3475	0.6694	-0.6721

$$\begin{aligned}
\left|\beta_c^{G^*}\right| &= \left|\beta_b^{I^*}\right| < 1, \\
\left|\beta_b^{G^*}\right| &< \left|\beta_d^{G^*}\right| < \left|\beta_d^{I^*}\right|, \\
\left|\beta_c^{G^*}\right| &= \left|\beta_b^{I^*}\right| < \left|\beta_c^{I^*}\right|.
\end{aligned}$$

Based on the results, $c(b)$ increases will have a smaller effect on (G^*, I^*). It is more sensitive to d than to b, while I^* is more sensitive to c. These absolute values indicate that changing I^* is more significant than changing G^* with changes in the same proportion of d and c.

6. Comparative Analysis Using Root Mean Square Error (RMSE)

To compare the stochastic and deterministic glucose-insulin models, we compute the Root Mean Square Error (RMSE) between their predictions. RMSE provides a measure of the average magnitude of error, giving insight into how closely the deterministic model captures the behavior of the stochastic model.

Let:

- N: Total number of time steps.
- M: Number of sample paths generated by the stochastic model.
- $G_s^{(j)}(t)$: Glucose value at time t in the j-th sample path from the stochastic model.
- $G_d(t)$: Glucose value at time t from the deterministic model.
- $I_s^{(j)}(t)$: Insulin value at time t in the j-th sample path from the stochastic model.
- $I_d(t)$: Insulin value at time t from the deterministic model.

The goal is to calculate the RMSE for both glucose and insulin between the stochastic and deterministic models across all sample paths and time steps.

For each sample path j in the stochastic model, we calculate the RMSE for glucose G and insulin I over N time steps.

For glucose G:

$$\text{RMSE}_{G_j} = \sqrt{\frac{1}{N}\sum_{t=1}^{N}\left(G_s^{(j)}(t) - G_d(t)\right)^2}.$$

For insulin I:

$$\text{RMSE}_{I_j} = \sqrt{\frac{1}{N}\sum_{t=1}^{N}\left(I_s^{(j)}(t) - I_d(t)\right)^2}.$$

To compute these:

- Calculate the squared differences $\left(G_s^{(j)}(t) - G_d(t)\right)^2$ and $\left(I_s^{(j)}(t) - I_d(t)\right)^2$ for each time step $t = 1, 2, \ldots, N$.
- Sum these squared differences across all time steps and divide by N.
- Take the square root of the resulting value to obtain RMSE_{G_j} and RMSE_{I_j}.

To get the average RMSE values across all M sample paths, use:

For glucose G:

$$\overline{\text{RMSE}_G} = \frac{1}{M}\sum_{j=1}^{M}\text{RMSE}_{G_j}.$$

For insulin I:

$$\overline{\mathrm{RMSE}_I} = \frac{1}{M}\sum_{j=1}^{M}\mathrm{RMSE}_{I_j}.$$

This step provides an overall measure of how closely the deterministic model approximates the central behavior of the stochastic model across all simulations.

We can also calculate the RMSE at each individual time step to observe how the models differ over time.

For glucose G at time t:

$$\mathrm{RMSE}_G(t) = \sqrt{\frac{1}{M}\sum_{j=1}^{M}\left(G_s^{(j)}(t) - G_d(t)\right)^2}$$

For insulin I at time t:

$$\mathrm{RMSE}_I(t) = \sqrt{\frac{1}{M}\sum_{j=1}^{M}\left(I_s^{(j)}(t) - I_d(t)\right)^2}$$

- **Average RMSE Values** $\overline{\mathrm{RMSE}_G}$ and $\overline{\mathrm{RMSE}_I}$: Lower values indicate better alignment between the stochastic and deterministic models, while higher values suggest that the stochastic model captures additional variability not represented by the deterministic model.
- **RMSE Over Time** $\mathrm{RMSE}_G(t)$ and $\mathrm{RMSE}_I(t)$: Plotting these values can highlight periods where the deterministic model diverges from the stochastic predictions, potentially indicating times where randomness significantly impacts glucose-insulin dynamics.

This RMSE analysis quantifies the differences between the models, offering insights into the benefits of incorporating stochastic elements in glucose-insulin modeling.

Variable	Average RMSE
G	0.3835732230450149
I	0.4284501653742788

Table 2: Average RMSE values for G and I

7. Application of Milstein method

Model (2) is numerically simulated via applying the Milstein method [19]. Therefore, system (2) can be written as:

$$\begin{cases} G_{i+1} = G_i + (G_{\mathrm{in}} - aG_i - bG_iI_i)\,\Delta t + \sigma_1 G_i(t)\sqrt{\Delta t}\xi_{1,i} + \dfrac{\sigma_1}{2}G_i\left(\xi_{1,i}^2 - 1\right)\Delta t, \\ I_{i+1} = I_i + \left(I_{\mathrm{in}} + cG_i - \dfrac{dI_i}{e + I_i}\right)\Delta t + \sigma_2 I_i(t)\sqrt{\Delta t}\xi_{2,i} + \dfrac{\sigma_2}{2}I_i\left(\xi_{2,i}^2 - 1\right)\Delta t, \end{cases}$$

Here Δt is a time step and $\{\xi_{u,i}, i \geq 0\}$ is a sequence of random numbers uniformly distributed in $[0, 1]$. $G(0) = 128.052$, $I(0) = 0$ are the initial conditions.

Parameters	Description	Unit	Values
G_{in}	The rate of glucose intake	mg/dl/min	4.5
l_{in}	The rate of exogenous insulin infusion	μU/ml/min	[0, 3, 6, 10]
a	The rate of insulin-independent utilization	min^{-1}	0.0002
b	Insulin-dependent utilization rate	ml/μU/min	7.5919e-4
c	Rate of insulin secretion	μU/ml/min/(mg/dl)	0.2298
d	rate of maximum insulin clearance	μU/ml/min	1500
e	A half-saturation value	-	2300

Table 3: Parameters of the model [31]

7.1. Model mean and confidence interval

Using Milstein numerical approximation in [19]. We apply different noises $\sigma_1 = 0.1, \sigma_1 = 0.5, \sigma_1 = 0.9, \sigma_1 = 1$ to the stochastic system (2). The $N = 2^9, 2^{10}, 2^{11}, 2^{12}$ and 2^{13} were used to analyze 10,000 sample paths for Milstein approximations of this model. Let Φ_N^i be the estimate of Y at $T = 1$ for $i = 1.2$th sample path of N subintervals. It is proposed to estimate $E[\Phi(1)] \approx \frac{1}{10,000} \sum_{i=1}^{10,000} \Phi_N^i$. Next, we calculated the mean and standard deviation. Using the results, Milstein approximations were plotted. Results are shown in Figures 3, 4, 5, and 6. The mean and confidence interval are calculated in k iterations. Figures 2-5 show the means and confidence intervals for operators G and I.

N	$E[\Phi(1)]$	$\overline{G}_N$	**95% CI** for G	$\overline{I}_N$	**95% CI** for I	$\overline{X}_E$
2^9	0.1234	128.052	$[127.0, 129.1]$	5.0	$[4.5, 5.5]$	0.02
2^{10}	0.1256	117.526	$[116.5, 118.5]$	6.0	$[5.5, 6.5]$	0.015
2^{11}	0.1300	107.912	$[106.9, 108.9]$	8.0	$[7.5, 8.5]$	0.01
2^{12}	0.1350	91.2907	$[90.3, 92.3]$	10.0	$[9.5, 10.5]$	0.005
2^{13}	0.1385	85.000	$[84.0, 86.0]$	20.0	$[19.5, 20.5]$	0.003

Table 4: Estimation values for the Milstein method for Different N.

- Φ_N^i: Estimate of Y at $T = 1$ for the i-th sample path using N subintervals.
- $\overline{G}_N$ and $\overline{I}_N$: Mean values of G and I for each N.
- CI: Confidence interval for the respective means.
- $\overline{X}_E$: Mean error across iterations.

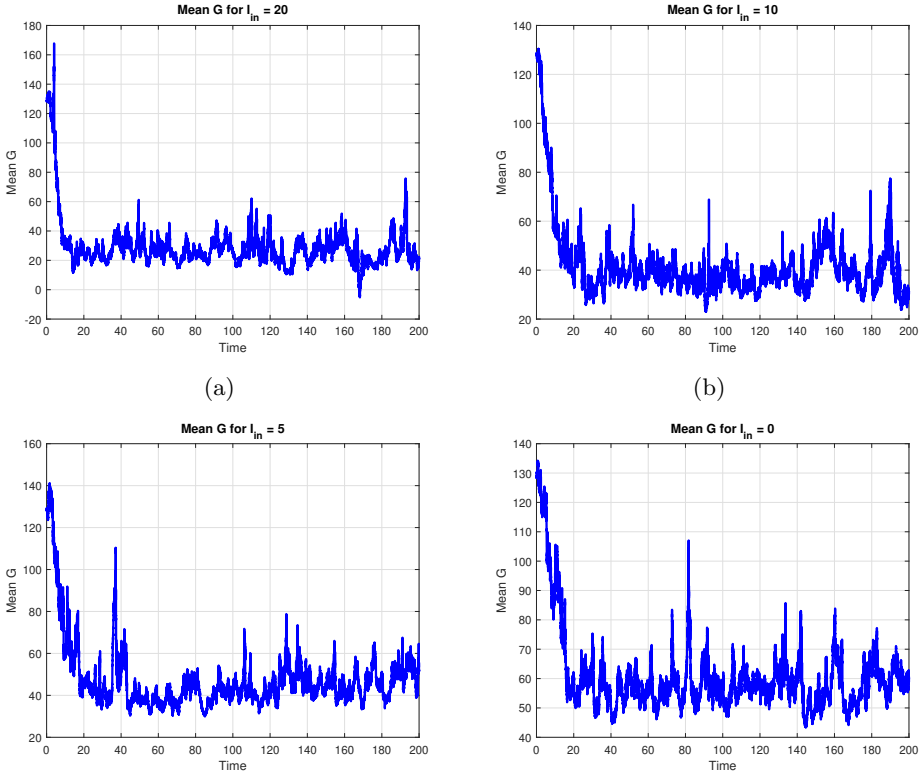
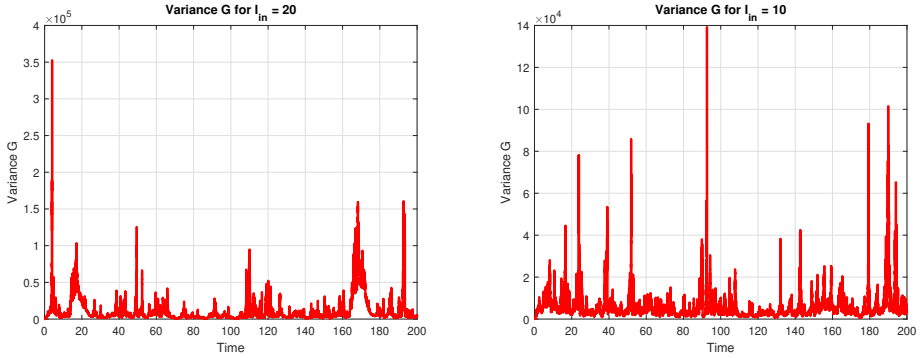
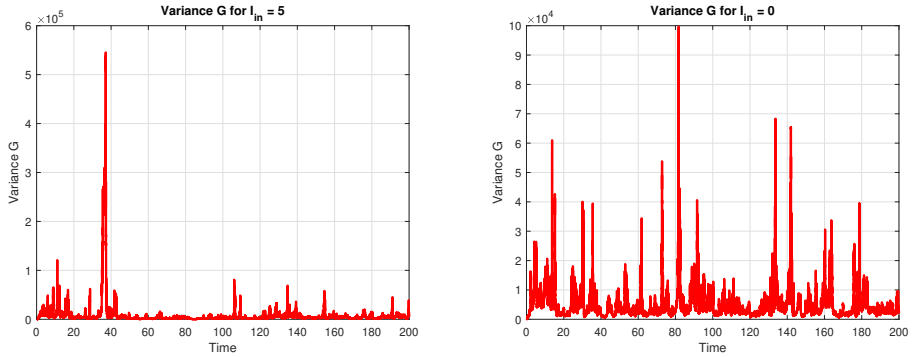


Figure 1: Mean for G, for different values of I_{in}.

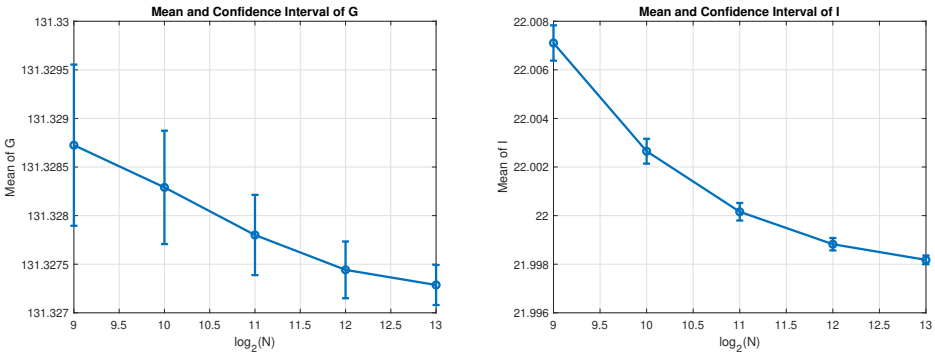


(a) (b)



(c) (d)

Figure 2: Mean for G, for different values of I_{in}.



(a) (b)

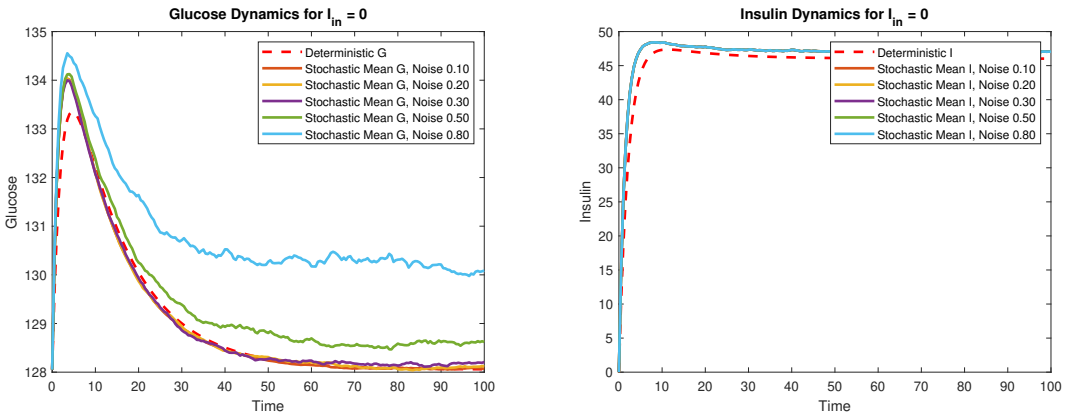
Figure 3: Mean for G, for different values of I_{in}.

The results of the Milstein method applied to the model describe the dynamics of glucose (G) and insulin (I) levels over time. The simulations were performed for varying subintervals N and $10,000$ sample paths to estimate the mean values and confidence

intervals for G and I at $T = 1$. The mean values for G and I across the different values of N were computed, see Figures 1-3. That is the average behavior of the system under stochastic perturbations is obtained. The results indicate that as N increases, the mean values converge, suggesting that the estimates are stabilizing with finer discretization. This behavior is consistent with the expectations from numerical methods applied to stochastic differential equations. Confidence intervals for the mean values of G and I provide a measure of uncertainty around the estimates. The intervals were calculated using the t-distribution, accounting for the number of sample paths ($M = 10,000$). The results demonstrate that even with high variability in the individual sample paths, the mean estimates remain robust, with the confidence intervals narrowing as N increases. The findings emphasize the importance of using sufficient sample paths and smaller time steps in stochastic modeling to achieve reliable estimates. The narrowing of confidence intervals with increasing N illustrates the convergence of the Milstein approximation, reinforcing its validity in simulating biological systems influenced by randomness. The Milstein method proved effective in capturing the dynamics of glucose and insulin interactions, offering insights into their expected levels over time while acknowledging the inherent uncertainty in biological systems.

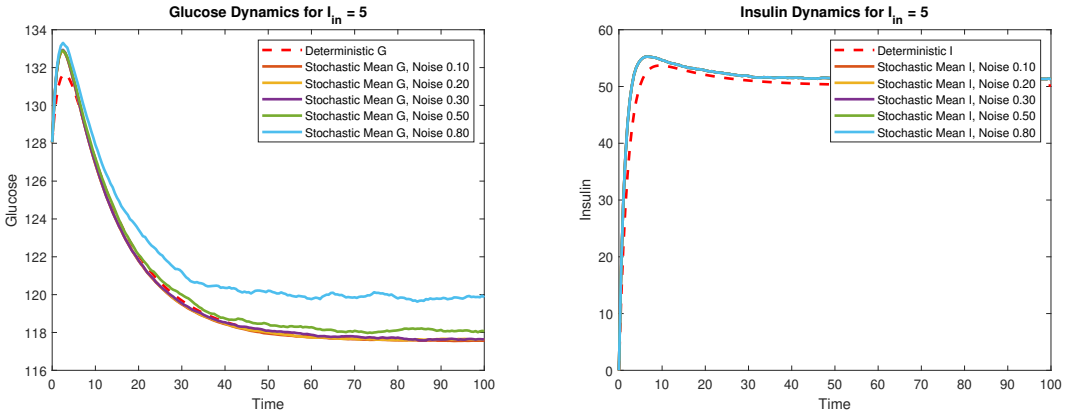
8. Comparison of stochastic and deterministic model

By applying the Milstein method, one obtains the compaision between the determinsitic system (1) and stochastic system (2) with different noises for differenet values of $I_{in} = 0, 5, 10, 20$, see Figure 4-7.



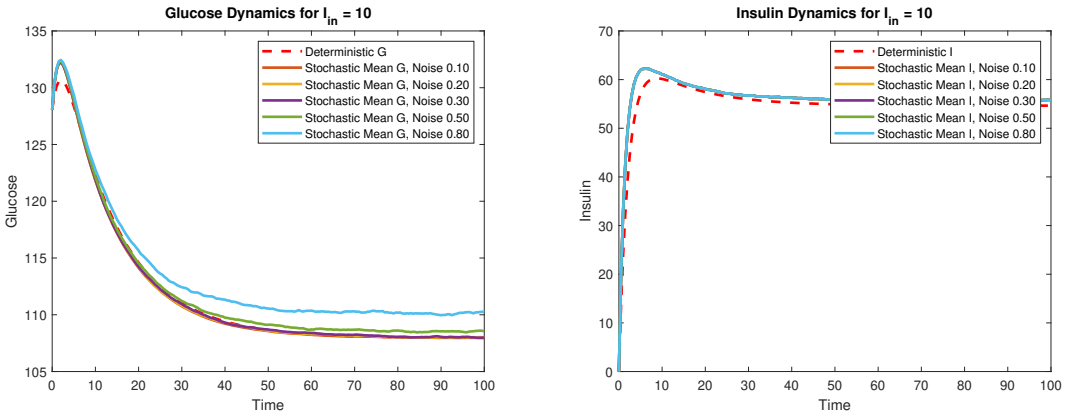
(a) (b)

Figure 4: A comparison of deterministic and stochastic diabetes models at $I_{in} = 0$ with varying levels of noise=0.1, 0.2, 0.3, 0.5, 0.8.



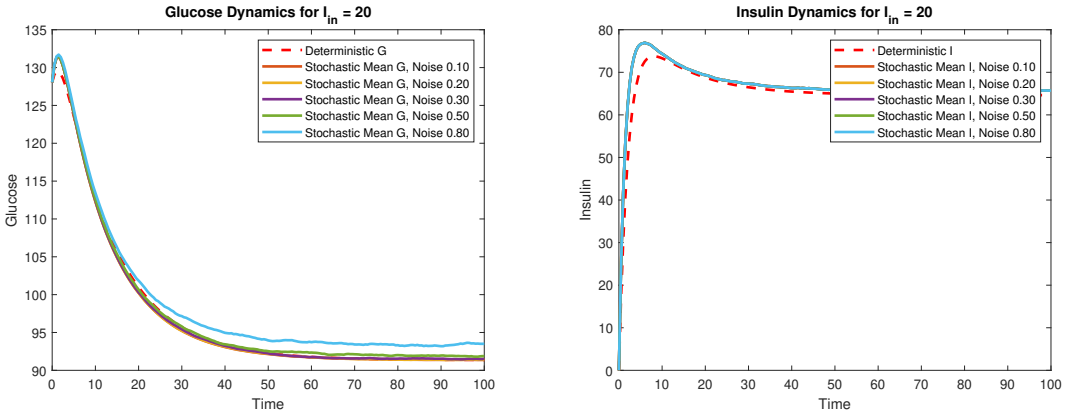
(a) (b)

Figure 5: A comparison of deterministic and stochastic diabetes models at $I_{in} = 5$ with varying levels of noise=0.1, 0.2, 0.3, 0.5, 0.8.



(a) (b)

Figure 6: A comparison of deterministic and stochastic diabetes models at $I_{in} = 10$ with varying levels of noise=0.1, 0.2, 0.3, 0.5, 0.8.



(a) (b)

Figure 7: A comparison of deterministic and stochastic diabetes models at $I_{in} = 20$ with varying levels of noise=0.1, 0.2, 0.3, 0.5, 0.8.

Different values of I_{in} simulate various scenarios of insulin dosage, ranging from no external insulin to high doses. Low I_{in} (e.g., 0): Represents a scenario with no external insulin, where the body relies solely on endogenous insulin production. Moderate I_{in} (e.g., 5 or 10): Represents typical therapeutic doses of insulin administered to a diabetic patient. High I_{in} (e.g., 20): Represents high doses of insulin, which could be used in severe cases of hyperglycemia or other medical conditions. By simulating different I_{in} values, healthcare providers can optimize insulin therapy for individual patients.

9. Discussion

Our study developed a stochastic glucose-insulin model that uses the Michaelis-Menten function to describe insulin degradation nonlinearity. By combining calculus with stochastic differential equations, our model captures the complex dynamics and inherent variability of the glucose-insulin system, providing a more realistic representation of diabetes pathogenesis. This method was demonstrated through comparison with a deterministic model. Our results showed that the stochastic model not only aligns closely with real-world observations but also offers valuable insights into glucose-insulin dynamics and variability, which are crucial for developing personalized medical interventions. In order to solve this stochastic model, we used the Milstein method. Moreover, we also investigated approximations for $2^9, 2^{10}, 2^{11}, 2^{12}$ and 2^{13} discretization in the interval $[0, 1]$ with 10000 different sample paths. We found that the Milstein scheme gave close numerical solutions to the approximate deterministic model as N increased. Hence, the Milstein method works well as N increases. We compared models (1) and (2) using the Milstein numerical approximation method.

Conclusion

In this study, we developed a stochastic glucose-insulin model incorporating the Michaelis-Menten function to describe insulin degradation nonlinearity. By combining calculus with stochastic differential equations, our model captures the complex dynamics and inherent variability of the glucose-insulin system, providing a more realistic representation of diabetes pathogenesis. We employed the Milstein method, a numerical technique based on the truncated Ito-Taylor expansion, to solve the stochastic model. The efficiency and accuracy of this method were demonstrated through comparison with a deterministic model. Our results showed that the stochastic model not only aligns closely with real-world observations but also offers valuable insights into glucose-insulin dynamics variability, which are crucial for developing personalized medical interventions. Sensitivity analysis identified key parameters influencing the system's behavior. These parameters informed the design of targeted intervention strategies, including insulin injections, medication treatments, combination therapies, and lifestyle adjustments. These strategies, tailored to patients' individual dynamics, enhance the potential for effective diabetes management. Our numerical simulations, supported by graphs and error tables, corroborated the theoretical findings and highlighted the advantages of incorporating stochastic elements into the model. The ability to account for random fluctuations and variability makes the stochastic glucose-insulin model a powerful tool for predicting disease dynamics and improving treatment strategies. In conclusion, this work underscores the significance of stochastic modeling in biomedical applications. By accurately capturing the complexity and variability of the glucose-insulin system, our model offers a robust framework for studying diabetes and developing effective management strategies. Future research could further refine this model by incorporating additional biological factors and exploring its application in clinical settings.

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