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ANALYSIS OF A NEW STOCHASTIC GOMPERTZ DIFFUSION MODEL FOR UNTREATED HUMAN GLIOBLASTOMAS

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In this paper, we analyze a new Ito stochastic differential equation model for untreated human glioblastomas. The model was the best fit of the average growth and variance of 94 pairs of a data set. We show the existence and uniqueness of solutions in the positive spatial domain. When the model is restricted in the finite domain $(0, b)$, we show that the boundary point 0 is unattainable while the point b is reflecting attainable. We prove there is a unique ergodic stationary distribution for any non-zero noise intensity, and obtain the explicit probability density function for the stationary distribution. By using Brownian bridge, we give a representation of the probability density function of the first passage time when the diffusion process defined by a solution passes the point b firstly. We carry out numerical studies to illustrate our analysis. Our mathematical and numerical analysis confirm the soundness of our randomization of the deterministic model in that the stochastic model will set down to the deterministic model when the noise intensity approaches zero. We also give physical interpretation of our stochastic model and analysis.

Keywords: Stochastic Gompertz model; glioblastoma; boundary classification; ergodic

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stationary distribution; first passage time.

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1. Introduction

Mathematical modeling of solid tumor growth has a long history. Gompertz proposed a mathematical model to express his law of human mortality [1], which was purely phenomenologically fitted to his data. The Gompertz curve was originally applied to actuaries. It then was used by various authors as a growth curve, both for biological and for economic phenomena [2]. It was until 1960s the Gompertz curve was verified for some solid tumor growth in a study by Laird [3]. After Laird's work, there have been many studies about applications of the Gompertz curve in tumor growth [4, 5]. A recent review tried to unify all Gompertz type models [6]. A recent work [7] still showed the Gompertz model was a good fit for their experimental data. However, there always exist discrepancies between predicted curves and data when we study all fitted Gompertz models and corresponding experimental or clinical data. It is clear that there are errors in measurements which may contribute data variations. But, there are intrinsic noises or fluctuations in tumor growth due to interactions between tumor cells and their microenvironment including nutrition and oxygen supplies. To count these uncertainties, there are several generalized Gompertz types of mathematical models in terms of stochastic processes and stochastic differential equations [8, 9, 10, 11]. These models have some applications or provide some theoretical understanding of tumor growth with white noise perturbations.

We recently proposed a new stochastic Gompertzian model for untreated human glioblastoma growth [12]. Based on the data set of 94 untreated glioblastoma patients [13], we found the best fit of deterministic Gompertz curve, and then found the best fit of white noise term for data variance. We combined these two best fits, and the resulted model is a Ito stochastic differential equation. The model has the following form

$$dX = f(X)dt + g(X)dW, \tag{1.1}$$

where $f(x) = ax \log \frac{b}{x}$ and $g(x) = \epsilon\sigma(x)$ with $\sigma(x) = \frac{x}{h+\sqrt{x}}$. Here $X = X(t)$ (or X_t) stands for the tumor volume at time t; a represents the intrinsic tumor growth rate; b is the carrying capacity of the tumor; ϵ is a positive parameter which is related to the noise intensity; and $W = W(t)$ (or W_t) is the one-dimensional standard Wiener process.

In [12], we showed how the stochastic model was established, and then carried out extensive computations to simulate the distribution of patient survival time with and without treatments, and obtained empirical formulas to calculate the average survival time and its variance. The study provided physicians with optimal times for operating surgery on glioblastoma patients. In current study, our goal is to rigorously analyze behaviors of the stochastic model (1.1) and to obtain a complete understanding of our new model. We show that the model has a unique globally positive solution for any nonnegative initial condition. We classify the boundary properties of the stochastic model when it is restricted to a finite spatial interval. Interestingly, the stochastic model possesses a unique ergodic stationary distribution to which transition probabilities of all solutions would approach no matter how large the noise intensity is. We also derive a representation for the first passage time when the solution crosses a certain level by using the three-dimensional Brownian bridge. We carry out some numerical simulations to show how solutions of stochastic and deterministic model behave, how the probability density function of the stationary distribution changes as the noise intensity value changes, and we approximate the probability density function of the first passage time by using Monte Carlo estimation.

The rest of the article is organized as follows. In Section 2, the analysis is carried out in 4 subsections. In Section 3, we carry out numerical studies. In Section 4, we briefly discuss why our stochastic differential equation model is reasonable and sound mathematically, also discuss how to interpret our model physically.

2. Analysis of the model

In this section, we analyze our stochastic model. We first prove the existence and uniqueness of the solution for the stochastic differential equation (1.1) in the whole positive spatial domain. If we restrict to the invariant domain of the deterministic part of the model $(0, b)$ which has two boundary points, we carry out a detailed analysis for boundary classification. We then prove there exists a unique ergodic invariant measure in the whole positive domain. Lastly, we study the first passage time and its density representation.

2.1. *Existence and uniqueness of the solution*

First of all, for the sake of completion, we mention the deterministic part of our model (1.1), namely, the Gompertz model,

$$\frac{dX}{dt} = aX \log \frac{b}{X}. \tag{2.1}$$

It is clear that $X(t) > 0$ for all t and we assume that $0 < X(0) < b$. It is easy to obtain it's solution as follows,

$$X(t) = b \left(\frac{X(0)}{b} \right)^{e^{-at}}.$$

Note that $\lim_{t\to\infty} X(t) = b$. Since $0 < e^{-at} < 1$, $0 < X(t) < b$. This shows that $(0, b)$ is the positive invariant domain of the deterministic equation (2.1).

Now we consider the stochastic differential equation (1.1). First, we need to specify an appropriate filtered probability space for (1.1). Let $\Omega = \{\omega \in C(\mathbb{R}^+, \mathbb{R}) : \omega(0) = 0\}$, $\mathcal{F}$ be the Borel σ-algebra on Ω, and $\mathbb{P}$ be the measure induced by

$\{W_t\}_{t\in\mathbb{R}^+}$, the one-dimensional Wiener process in (1.1). Without loss of generality, we can assume that $\mathcal{F}$ is completed by $\mathbb{P}$. Then the filtration $\mathcal{F}_t$ is given by the canonical filtration generated by $\{W_t\}_{t\in\mathbb{R}}$ completed by all $\mathbb{P}$-null sets of $\mathcal{F}$. Then a completed filtered probability space $(\Omega, \mathcal{F}, \{\mathcal{F}_t\}_{t\in\mathbb{R}^+}, \mathbb{P})$ for our stochastic differential equation model is obtained.

For our model (1.1), we define the differential operator

$$\mathcal{L}h(x) = f(x)\frac{dh(x)}{dx} + \frac{1}{2}g^2(x)\frac{d^2h(x)}{dx^2}$$

and its adjoint as

$$\mathcal{L}^*h(x) = -\frac{d}{dx}(f(x)h(x)) + \frac{d^2}{dx^2}\left(\frac{1}{2}g^2(x)h(x)\right)$$

where $h(x)$ is a smooth enough function.

It is natural to expect that $(0, b)$ would also be the positive invariant domain of (1.1). It is useful to know whether or not the sample path of the solution of (1.1) exit from the domain $(0, b)$ in a finite time. For our model, the exit of the solution path through the boundary b within a finite time might happen. In the next subsection, we will study the exit probability of the solution path through the boundaries to classify the boundary points for (1.1) when we restrict our model to a finite spatial interval. Now, we show that $(0,\infty)$ is the almost sure invariant domain of the equation (1.1). In fact, we cannot use the standard theorems that provide the existence of a solution because f and g do not satisfy the Lipschitz condition and the linear growth condition on the domain $(0,\infty)$. Instead, our method is based on Corollary 3.1 in [14].

Let $D = (0,\infty)$ and $D_n = (\frac{1}{n}, n)$ for each $n \geq 1$, then $D_n \subset D_{n+1}$, $\overline{D}_n \subset D$, for each $n \geq 1$, and $\bigcup_{n=1}^{\infty} D_n = D$. Note that f and g satisfy the Lipschitz condition and the linear growth condition on each D_n. Consider the function $V(x) = x + 1 - b - b\log\frac{x}{b}$ for $x \in D$, which is positive and twice continuously differentiable on D. Furthermore, it is easy to check that for all $x \in D$, we have

$$\mathcal{L}V = -a(\log x - \log b)(x - b) + \frac{1}{2}\frac{b\epsilon^2}{(h+\sqrt{x})^2}.$$

Since $\log x$ is increasing on $(0,\infty)$ and $\frac{1}{2}\frac{b\epsilon^2}{(h+\sqrt{x})^2} \leq \frac{1}{2}b(\frac{\epsilon}{h})^2$, $\mathcal{L}V \leq \frac{1}{2}b(\frac{\epsilon}{h})^2$. As $V \geq 1$ for all $x \in D$, so $\mathcal{L}V \leq \bar{c}V$ with $\bar{c} = \frac{1}{2}b(\frac{\epsilon}{h})^2$. Notice that $V(x) \to \infty$ as either $x \to 0$ or $x \to \infty$. If $x \in D\backslash D_n$, then, as $n \to \infty$, either $x \to 0$ or $x \to \infty$. Therefore

$$\inf_{D\backslash D_n} V(x) \to \infty \text{ as } n \to \infty.$$

According to Corollary 3.1 in [14], these two conditions guarantee that, with $X(0) > 0$, the equation (1.1) possesses a pathwise unique continuous solution $X(t) > 0$ with probability 1.

Theorem 2.1. *The stochastic model* (1.1) *has a pathwise unique continuous strong positive solution $X(t)$ almost surely with any positive initial value $X(0)$. This solution defines a scalar homogeneous diffusion process on $(0,\infty)$.*

2.2. *Boundary classification*

For the deterministic model (2.1), the domain is $(0,b)$. For the stochastic model (1.1) with the drift term $f(x) = ax\log\frac{b}{x}$ and the diffusion coefficient $g^2(x) = \epsilon^2\sigma^2(x)$, where $\sigma(x) = \frac{x}{h+\sqrt{x}}$, the domain is $(0,\infty)$. If we restrict the stochastic differential equation (1.1) in the finite domain $D = (0,b)$, it is important to know the properties of two boundary points or how the solutions behave around two boundary points [17, 18]. In this subsection, we study the boundary classification. We use methods developed by Gihman and Skorohod [19].

Note that $g(x) > 0$ for all $x \in (0,b)$. Set

$$\varphi(x) = \exp\left\{-\frac{2}{\epsilon^2}\int_{x_0}^{x}\frac{f(y)}{\sigma^2(y)}dy\right\} \text{ and } \psi(x) = \int_{y_0}^{x}\varphi(y)dy$$

where x_0 and y_0 are arbitrary and fixed in $(0,b)$. By computation,

$$\begin{aligned}\int_{x_0}^{x}\frac{f(y)}{\sigma^2(y)}\,dy &= ah^2\log b\log x - \frac{1}{2}ah^2(\log x)^2 + 4ah\sqrt{x}\log b\\ &\quad - 4ah\sqrt{x}\log x + 8ah\sqrt{x} + ax\log b - ax\log x + ax + C,\end{aligned}$$

where

$$\begin{aligned}C := &-ah^2\log b\log x_0 + \frac{1}{2}ah^2(\log x_0)^2 - 4ah\sqrt{x_0}\log b\\ &+ 4ah\sqrt{x_0}\log x_0 - 8ah\sqrt{x_0} - ax_0\log b + ax_0\log x_0 - ax_0.\end{aligned}$$

Then we get

$$\varphi(x) = \frac{\exp\{\frac{1}{\epsilon^2}\log x(ah^2\log x + 8ah\sqrt{x} + 2ax - ah^2\log b)\}}{b^{(8ah\sqrt{x}+2ax)/\epsilon^2}\exp\{2(8ah\sqrt{x} + ax + C)/\epsilon^2\}}.$$

Let $X_x(t)$ be the solution to

$$dX_x(t) = f(X_x(t))\,dt + g(X_x(t))\,dW(t)$$

until first exit from $(0,b)$ with $X_x(0) = x \in (0,b)$ and $\tau_x[\alpha,\beta]$ the first time $X_x(t)$ attains the boundary of $(\alpha,\beta) \subset (0,b)$ where $x \in (\alpha,\beta)$. By Theorem 4 in Chapter 3 [19],

$$\mathbb{P}\left(X_x(\tau_x[\alpha,\beta]) = \alpha\right) = \frac{\psi(\beta) - \psi(x)}{\psi(\beta) - \psi(\alpha)}, \tag{2.2}$$

and

$$\mathbb{P}(X_x(\tau_x[\alpha,\beta]) = \beta) = \frac{\psi(x) - \psi(\alpha)}{\psi(\beta) - \psi(\alpha)}. \tag{2.3}$$

First of all, we show that the boundary point 0 of (1.1) in the domain D is unattainable. In fact, the property of the boundary point of 0 depends only on the following constant

$$L_1^0 := \int_0^{\beta}\varphi(y)\,dy, \text{ for some fixed } \beta \in (0,b).$$

Now, since $\log(x^2 \exp[\frac{ah^2}{\epsilon^2}(\log x)^2]) = 2\log x + \frac{ah^2}{\epsilon^2}(\log x)^2$ approaches ∞ as $x \downarrow 0$,

$$\lim_{x\downarrow 0} x^2 \exp\left[\frac{ah^2}{\epsilon^2}(\log x)^2\right] = \infty.$$

On the other hand, as x is getting close to 0, the denominator of $\varphi(x)$ tends to a finite number while its numerator blows up to ∞ exponentially fast because of the term $\exp\left[\frac{ah^2}{\epsilon^2}(\log x)^2\right]$. This implies that $\lim_{x\downarrow 0} x^2\varphi(x) = \infty$, so there exists a $0 < \delta < \beta$ such that for $0 < x < \delta$ we get $\varphi(x) > x^{-2}$. Thus, for any $0 < \alpha < \delta$,

$$\begin{aligned}\psi(\alpha) &= -\int_\alpha^\delta \varphi(y)\,dy - \int_\delta^{y_0} \varphi(y)\,dy \\ &\le -\int_\alpha^\delta \frac{dy}{y^2} - \int_\delta^{y_0} \varphi(y)\,dy = \frac{1}{\delta} - \frac{1}{\alpha} - \int_\delta^{y_0} \varphi(y)\,dy,\end{aligned}$$

which follows that $L_1^0 = \psi(\beta) - \lim_{\alpha\downarrow 0}\psi(\alpha) = \psi(\beta) - \psi(0+0) = \infty$. Hence, from (2.2), letting $\alpha \downarrow 0$ gives

$$\mathbb{P}\left(X_x(\tau_x[0,\beta]) = 0\right) = \frac{\psi(\beta) - \psi(x)}{\psi(\beta) - \psi(0+0)} = 0.$$

In other words, $\mathbb{P}\left(X_x(\tau_x[\epsilon,\beta]) = \epsilon\right)$ can be made arbitrarily small by suitable choice of $\epsilon > 0$ for any initial value $x \in (0,b)$. Therefore, the boundary point 0 cannot be attained in finite time before the boundary point b. Moreover, the solution $X_x(t)$ cannot reach 0 with positive probability as $t \to \infty$ since then $X_x(t)$ would, with the same probability, reach ϵ before b for each $\epsilon > 0$, which is impossible. Hence 0 is an unattainable boundary point of (1.1).

Secondly, we claim that b is a reflecting attainable boundary point of (1.1). Indeed, the property of the boundary point b depends on the following constants

$$L_1^b := \int_\alpha^b \varphi(y)\,dy,\ L_2^b := \int_\alpha^b \frac{\psi(b) - \psi(y)}{\epsilon\sigma^2(y)\varphi(y)}dy, \text{ and } L_3^b := \int_\alpha^b \frac{dy}{\epsilon\sigma^2(y)\varphi(y)},$$

for some fixed $\alpha \in (0,b)$. Since $\varphi(x)$ is continuous at b,

$$L_1^b = \psi(b-0) = \lim_{x\uparrow b}\int_\alpha^x \varphi(y)\,dy < \infty.$$

Then, from (2.3), letting $\beta \uparrow b$ gives

$$\mathbb{P}(X_x(\tau_x[\alpha,b]) = b) = \frac{\psi(x) - \psi(\alpha)}{\psi(b-0) - \psi(\alpha)} > 0. \tag{2.4}$$

Next, set $Y(t) = \psi(X(t))$, where $\psi(x) = \int_{y_0}^x \varphi(y)\,dy$. By Ito's formula,

$$\begin{aligned}dY(t) &= \psi'(X(t))dX(t) + \frac{1}{2}\psi''(X(t))(dX(t))^2 \\ &= \varphi(X(t))[f(X(t))dt + g(X(t))dW(t)] + \frac{\epsilon^2}{2}\varphi'(X(t))\,\sigma^2(X(t))dt \\ &= \left[\varphi(X(t))f(X(t)) + \frac{\epsilon^2}{2}\varphi'(X(t))\,\sigma^2(X(t))\right]dt + \epsilon\varphi(X(t))\sigma(X(t))dW(t).\end{aligned}$$

Since $\varphi(x) = \exp\left\{-\frac{2}{\epsilon^2}\int_{x_0}^{x}\frac{f(y)}{\sigma^2(y)}dy\right\}$, differentiating both sides with respect to x gives

$$\frac{\epsilon^2}{2}\varphi'(x)\sigma^2(x) + f(x)\varphi(x) = 0.$$

Hence

$$dY(t) = \epsilon\sigma(X(t))\,\varphi(X(t))\,dW(t).$$

As $\psi(x)$ is increasing and differentiable over $(0, b)$ with $\psi'(x) = \varphi(x) > 0$ for all $x \in (0, b)$, so ψ has a unique differentiable inverse function $\xi = \psi^{-1}$. Then $X(t) = \xi(Y(t))$ and so

$$dY(t) = \bar{\sigma}(Y(t))\,dW(t), \tag{2.5}$$

where $\bar{\sigma}(x) = \epsilon\,\sigma(\xi(x))\,\varphi(\xi(x))$. The process $Y(t)$ will be defined up to the first exit from (r_1, r_2) in which $r_1 = \psi(0) = \int_{y_0}^{0}\varphi(y)\,dy$ and $r_2 = \psi(b) = \int_{y_0}^{b}\varphi(y)\,dy$. Let $Y_y(t)$ satisfy $dY_y(t) = \bar{\sigma}(Y_y(t))\,dW(t)$ up to the first exit from (r_1, r_2) with initial condition $Y_y(0) = y \in (r_1, r_2)$. Let $\bar{\tau}_y[s_1, s_2]$ be the first time $Y_y(t)$ reaches the boundary of (s_1, s_2), where $r_1 < s_1 < s_2 < r_2$. Set $V(y) = \mathbb{E}\,\bar{\tau}_y[s_1, s_2]$, $s_1 \le y \le s_2$. By Theorem 2 in Section 15 in [19], since $\bar{\sigma}(y) > 0$ for all $y \in [s_1, s_2]$, $\bar{\tau}_y[s_1, s_2] < \infty$ w.p.1 and $V(y)$ solves

$$\frac{1}{2}\bar{\sigma}^2(y)\,V''(y) = -1,\;\; V(s_1) = V(s_2) = 0.$$

By computation, we obtain

$$V(y) := \mathbb{E}\,\bar{\tau}_y[s_1, s_2] = 2\int_{s_1}^{y}\frac{(s_2 - y)(t - s_1)}{(s_2 - s_1)\bar{\sigma}^2(t)}dt + 2\int_{y}^{s_2}\frac{(s_2 - t)(y - s_1)}{(s_2 - s_1)\bar{\sigma}^2(t)}dt. \tag{2.6}$$

It follows from (2.6) that a necessary and sufficient condition that

$$\mathbb{E}\,\bar{\tau}_y[s_1, r_2] = \lim_{s_2\uparrow r_2}\mathbb{E}\,\bar{\tau}_y[s_1, s_2] < \infty$$

is, for some $z_0 \in (r_1, r_2)$, $\lim\limits_{s_2\uparrow r_2}\int_{z_0}^{s_2}\frac{(s_2-t)(y-s_1)}{(s_2-s_1)\bar{\sigma}^2(t)}dt < \infty$. This is equivalent to

$$\int_{z_0}^{r_2}\frac{r_2 - t}{\bar{\sigma}^2(t)}dt < \infty.$$

Since $\bar{\sigma}(t) = \epsilon\,\sigma(\xi(t))\varphi(\xi(t))$, by making the substitution $\xi(t) = y$ and $t = \psi(y)$ we obtain

$$\int_{z_0}^{r_2}\frac{r_2 - t}{\bar{\sigma}^2(t)}dt = \int_{z_1}^{b}\frac{[\psi(b) - \psi(y)]\varphi(y)}{\epsilon^2\,\sigma^2(y)\varphi^2(y)}dy = \int_{z_1}^{b}\frac{\psi(b) - \psi(y)}{\epsilon^2\,\sigma^2(y)\varphi(y)}dy < \infty, \tag{2.7}$$

where $z_1 := \xi(z_0)$. We can assume that z_0 is chosen such that $\alpha = \xi(z_0)$. Then the above condition (2.7) is equivalent to $L_2^b < \infty$. Hence a necessary and sufficient condition that $\mathbb{E}\,\tau_x[\alpha, b] < \infty$ is $L_2^b < \infty$. It is clear that $\frac{\psi(b)-\psi(y)}{\epsilon\sigma^2(y)\varphi(y)}$ is continuous on $[\alpha, b]$ and $L_1^b = \psi(b-0) < \infty$. Therefore $L_2^b < \infty$. Then, by Theorem 1 chapter 5 in [19], for all $x \in (\alpha, b)$ we have $\mathbb{E}\,\tau_x[\alpha, b] < \infty$, which means that $\tau_x[\alpha, b] < \infty$ a.s.

and $\mathbb{P}\{X_x(\tau_x[\alpha, b]) = b\} > 0$. In other words, b is an attainable boundary point of (1.1).

For the moment, we study properties ensuring a continuous passage from the boundary b into the interior of the interval $(0, b)$. Let $\delta > 0$ be arbitrary and let $X_\delta(t)$ be a process on (α, b) constructed as follows: $X_\delta(0) = b-\delta$, $X_\delta(t)$ satisfy (1.1) in (α, b), if τ is the first exit time of $X_\delta(t)$ from (α, b), then take $X_\delta(\tau) = b - \delta$ and let the further behavior of $X_\delta(t)$ for $t > \tau$ be governed by (1.1) until it again reaches the boundary of (α, b) etc. Then $X_\delta(t)$ is defined for all $t > 0$ in this way. Denote by τ_k the k-th time $X_\delta(t)$ reaches the boundary of (α, b). The variables $\tau_{k+1} - \tau_k$ are identically distributed and are independent (see Corollary 1 section 15 in [19]). Also, the events $U_k = \{X_\delta(\tau_k) = \alpha\}$ are independent. Using the above notation, we can write for all $k \geq 1$

$$V(b-\delta) := \mathbb{E}(\tau_{k+1} - \tau_k) = \mathbb{E}\,\tau_1 \text{ and } \mathbb{P}(U_k) = \frac{\psi(b) - \psi(b-\delta)}{\psi(b) - \psi(\alpha)}.$$

Then the probability that $X_\delta(t)$ hits α for the first time after $(n-1)$ times it hits b is

$$\mathbb{P}\left\{\inf_{t\leq\tau_n} X_\delta(t) = \alpha\right\} = 1 - \left(1 - \frac{\psi(b) - \psi(b-\delta)}{\psi(b) - \psi(\alpha)}\right)^n.$$

Let n_δ be the integral part of $1/\mathbb{E}\tau_1$ and $t > 1$ arbitrary. Consider

$$\mathbb{P}\{\tau_{n_\delta} < t\} = \mathbb{P}\left\{\sum_{k=1}^{n_\delta}(\tau_k - \tau_{k-1}) < t\right\} = 1 - \mathbb{P}\left\{\sum_{k=1}^{n_\delta}(\tau_k - \tau_{k-1}) \geq t\right\}.$$

If $\sum_{k=1}^{n_\delta}(\tau_k - \tau_{k-1}) \geq t$ then $\sum_{k=1}^{n_\delta}[\tau_k - \tau_{k-1} - \mathbb{E}(\tau_k - \tau_{k-1})] \geq t - n_\delta\mathbb{E}\tau_1$. Note that $n_\delta\mathbb{E}\tau_1 \leq 1$ and so $t - n_\delta\mathbb{E}\tau_1 \geq 0$. Then, using the fact that the $\tau_k - \tau_{k-1}$ are identically distributed and independent,

$$\begin{aligned}\mathbb{P}\{\tau_{n_\delta} < t\} &\geq 1 - \mathbb{P}\left\{\left|\sum_{k=1}^{n_\delta}[\tau_k - \tau_{k-1} - \mathbb{E}(\tau_k - \tau_{k-1})]\right| \geq t - n_\delta\mathbb{E}\tau_1\right\} \\ &\geq 1 - \frac{\mathrm{Var}(\sum_{k=1}^{n_\delta}(\tau_k - \tau_{k-1}))}{(t - n_\delta\mathbb{E}\tau_1)^2} \\ &= 1 - \frac{n_\delta\mathrm{Var}\tau_1}{(t - n_\delta\mathbb{E}\tau_1)^2} \geq 1 - \frac{\mathrm{Var}\tau_1}{\mathbb{E}\tau_1}\frac{1}{(t-1)^2}.\end{aligned}$$

By the proof of Corollary 1 chapter 5 in [19], we can obtain

$$\limsup_{\delta\downarrow 0}\frac{\mathrm{Var}\tau_1}{\mathbb{E}\tau_1} = 0.$$

Let $\tau = \lim_{\delta\downarrow 0}\tau_{n_\delta}$, then for $t > 1$ arbitrary we get $\mathbb{P}\{\tau \leq t\} = 1$. Hence $\mathbb{P}\{\tau < \infty\} = 1$. Thus, in order that $\mathbb{P}\{\inf_{t\leq\tau} X_\delta(t) = \alpha\} > 0$, it is necessary and sufficient that

$$\limsup_{\delta\downarrow 0}\left(1 - \frac{\psi(b) - \psi(b-\delta)}{\psi(b) - \psi(\alpha)}\right)^{n_\delta} < 1, \text{ i.e., } \limsup_{\delta\downarrow 0} n_\delta[\psi(b) - \psi(b-\delta)] > 0.$$

This is equivalent to

$$\limsup_{\delta\downarrow 0} \frac{V(b-\delta)}{\psi(b)-\psi(b-\delta)} < \infty.$$

Note that $\lim_{\delta\downarrow 0} \dfrac{V(b-\delta)}{\psi(b)-\psi(b-\delta)}$ exists (it might assume the value ∞). Set $z(x) := \dfrac{V'(x)}{\psi'(x)}$, then it is easy to check that $z'(x) = \dfrac{-2}{\epsilon^2\,\varphi(x)\sigma^2(x)} < 0$ for $x \in [\alpha, b]$, that is, $z(x)$ is monotone and so $\lim_{x\uparrow b} z(x) = \lim_{x\uparrow b} \frac{V'(x)}{\psi'(x)} = \frac{V'(b)}{\psi'(b)}$. On the other hand,

$$\lim_{\delta\downarrow 0} \frac{V(b-\delta)}{\psi(b)-\psi(b-\delta)} = -\lim_{\delta\downarrow 0} \frac{(V(b)-V(b-\delta))/\delta}{(\psi(b)-\psi(b-\delta))/\delta} = -\frac{V'(b)}{\psi'(b)}.$$

Thus, in order that $\lim_{\delta\downarrow 0} \dfrac{V(b-\delta)}{\psi(b)-\psi(b-\delta)}$ is finite, it is necessary and sufficient that

$$L_3^b := \int_\alpha^b \frac{dx}{\epsilon^2\,\sigma^2(x)\varphi(x)} < \infty. \tag{2.8}$$

From the formula of φ, it is easy to see that the condition (2.8) is verified. Thus, we have proved that the probability that $X(t)$ moves back to the interior of the interval $(0, b)$ after hitting the boundary b in finite time is positive. This means that b is a reflecting attainable boundary point of (1.1).

Lastly, we study the probability of first exit through the boundary point b, that is, the probability that the solution firstly reaches the boundary point b in finite time, which is $p(\epsilon) := \mathbb{P}\left(X_x(\tau_x^\epsilon[\alpha, b]) = b\right)$ where $\tau_x^\epsilon[\alpha, b]$ is the first time that the solution $X_x(t)$ reaches the boundary of $[\alpha, b]$. We claim that $\lim_{\epsilon\downarrow 0} p(\epsilon) = 0$. To emphasize the dependence of all the quantities and functions involving $p(\epsilon)$ on ϵ, we denote

$$\varphi^\epsilon(x) := \exp\left\{-\frac{2}{\epsilon^2}\int_{x_0}^x \frac{f(z)}{\sigma^2(z)}dz\right\},\ \psi^\epsilon(x) := \int_{y_0}^x \varphi^\epsilon(z)dz,$$
$$L_1^b(\epsilon) := \int_\alpha^b \varphi^\epsilon(y)dy,\ \text{and}\ L_2^b(\epsilon) := \int_\alpha^b \frac{\psi^\epsilon(b)-\psi^\epsilon(y)}{\epsilon\sigma^2(y)\varphi^\epsilon(y)}.$$

Indeed, we look at the behavior of two constants L_1^b and L_2^b as ϵ is getting close to 0. For convenience, we treat these two constants as a function of ϵ and so we can write them as $L_1^b(\epsilon)$ and $L_2^b(\epsilon)$. If $L_1^b(\epsilon+0) := \lim_{\epsilon\downarrow 0} L_1^b(\epsilon) = \infty$ then, of course, $p(\epsilon) \to 0$ as $\epsilon \to 0$ due to (2.4). If $L_1^b(\epsilon+0) < \infty$ then $\psi^\epsilon(b) - \psi^\epsilon(y) < \infty$ as $\epsilon \to 0$ for any $y \in (\alpha, b)$. Since $\epsilon\varphi^\epsilon(y) = \epsilon \exp\left\{-\frac{2}{\epsilon^2}\int_{x_0}^y \frac{f(z)}{\sigma^2(z)}dz\right\} \to 0$ as $\epsilon \to 0$ for any $y \in (x_0, b)$. Thus $L_2^b(\epsilon+0) := \lim_{\epsilon\downarrow 0} L_2^b(\epsilon) = \infty$. By (2.6), a necessary and sufficient condition that $\mathbb{E}\,\tau_x^{\epsilon+0}[\alpha, b] = \infty$ is $L_2^b(\epsilon+0) = \infty$, where $\tau_x^{\epsilon+0}[\alpha, b] := \lim_{\epsilon\downarrow 0} \tau_x^\epsilon[\alpha, b]$. This implies that $\mathbb{E}\,\tau_x^{\epsilon+0}[\alpha, b] = \infty$ for all $x \in (\alpha, b)$. By Corollary 2 Chapter 5 in [19],

$$\mathbb{P}\left\{X_x(\tau_x^{\epsilon+0}[\alpha, \beta]) = b,\ \tau_x^{\epsilon+0}[\alpha, b] < \infty\right\} = 0.$$

In other words, either $\tau_x^{\epsilon+0}[\alpha, b] < \infty$ a.s. and $X_x(\tau_x^{\epsilon+0}[\alpha, \beta]) = \alpha$ a.s. for any $\alpha \in (0, b)$, or $\tau_x^{\epsilon+0}[\alpha, b] = \infty$ a.s. The first case cannot happen since 0 is unattainable boundary point. Therefore $\tau_x^{\epsilon+0}[\alpha, b] = \infty$ a.s. and hence the first time the solution $X_x^\epsilon(t)$ reaches the boundary of $[\alpha, b]$ is infinity as ϵ approaches 0. This means that $p(\epsilon) \to 0$ as $\epsilon \to 0$.

We summarize our results in this section as the following theorem.

Theorem 2.2. *If the stochastic model* (1.1) *is restricted to the interval* $(0, b)$*, then* 0 *is an unattainable boundary point while* b *is reflecting attainable. When the noise intensity parameter is small enough, the exit probability of the solution of* (1.1) *from this interval becomes arbitrarily small.*

Remark 2.1. From the derivation above, the exit probability at b from $(0, b)$ is zero if the noise intensity parameter ϵ is zero. This matches the deterministic case. When ϵ is zero, the stochastic model is reduced to the deterministic model. Since $x = b$ is a stable equilibrium point for the deterministic model, starting from any initial point in $(0, b)$, the solution of the deterministic model can never pass through the point b.

2.3. *Ergodic stationary distributions*

We know that $x = b$ is a stable equilibrium point of the deterministic model $dX = f(X)dt$. For the stochastic differential equation (1.1) in the domain $E = (0, \infty)$, $x = b$ is no longer an equilibrium point (or a stationary solution). However, we obtain a unique invariant distribution that can be considered as the stochastic analogue of the deterministic stationary solution. In this subsection, we construct the invariant measure by using the Fokker-Planck equation and show it is ergodic.

Theorem 2.3. *The stochastic differential equation* (1.1) *has a unique invariant measure* μ *that is ergodic. The probability density function of this invariant measure is of the form*

$$p^\epsilon(x) = \overline{K}^\epsilon \, \frac{2(h+\sqrt{x})^2}{\epsilon^2 x^2} \exp\left\{\frac{1}{\epsilon^2} H(x)\right\}, \ x > 0,$$

where

$$H(x) = -ah^2\left(\log\frac{b}{x}\right)^2 + 8ah\left(\sqrt{x}\log\frac{b}{x} + 2\sqrt{x} - 2\sqrt{b}\right) + 2a\left(x\log\frac{b}{x} + x - b\right)$$

and

$$(\overline{K}^\epsilon)^{-1} = \int_0^\infty \frac{2(h+\sqrt{y})^2}{\epsilon^2 y^2} \exp\left\{\frac{1}{\epsilon^2} H(y)\right\} dy$$

is the normalizing constant.

Proof. By Zhu in [22], since $g(x) > 0$ for all $x \in (0, \infty)$, it suffices to find a C^2 function $V : \mathbb{R}^+ \to \mathbb{R}^+$ and a neighborhood U of b such that $\mathcal{L}V(x) < 0$ for all

$x \in E\backslash U$. Now consider $V(x) = x - b - b\log\frac{x}{b}$. Then

$$\begin{aligned}\mathcal{L}V &= ax\log\frac{b}{x}\left(1-\frac{b}{x}\right)+\frac{1}{2}\frac{b}{x^2}\frac{\epsilon^2x^2}{(h+\sqrt{x})^2}\\ &= -a(\log x-\log b)(x-b)+\frac{1}{2}\frac{b\epsilon^2}{(h+\sqrt{x})^2}\\ &\le -a(\log x-\log b)(x-b)+\frac{1}{2}b\left(\frac{\epsilon}{h}\right)^2.\end{aligned}$$

Let $q(x) = a(\log x - \log b)(x-b) - \frac{1}{2}b\left(\frac{\epsilon}{h}\right)^2$, where $x \in E = (0,\infty)$. Then

$$q'(x) = a - \frac{ab}{x} + a\log x - a\log b, \text{ and } q''(x) = \frac{ab}{x^2}+\frac{a}{x} > 0.$$

It implies that $q'(x)$ is strictly increasing on $(0,\infty)$. Since $q'(b) = 0$, $q'(x)$ has a unique solution $(0,\infty)$. Note that $q(b) < 0$, $\lim_{x\downarrow 0} q(x) = \infty$, and $\lim_{x\to\infty} q(x) = \infty$. Then there exist $x_1 \in (0,b)$ and $x_2 \in (b,\infty)$ so that $q(x_1) = q(x_2) = 0$. As $q'(x)$ has a unique solution, so q has exactly two solutions x_1 and x_2. Choose $U = (x_1, x_2)$. If $x \notin U$ then $q(x) < 0$. Thus $\mathcal{L}V(x) < 0$ for $x \in E\backslash U$. Hence we can conclude that there exists a unique ergodic invariant measure μ for the solution $X(t)$ of the stochastic equation (1.1) no matter how large the noise strength ϵ is.

Next, we compute the density of this invariant measure μ using the Fokker-Planck equation associated with the stochastic equation (1.1). Let $p^\epsilon = p^\epsilon(x)$, $x \in (0,\infty)$, be the invariant probability density function of μ. Then $\mathcal{L}^*p^\epsilon = 0$ where

$$\mathcal{L}^*p^\epsilon = -\frac{d}{dx}(f(x)p^\epsilon) + \frac{d^2}{dx^2}\left(\frac{1}{2}g^2(x)p^\epsilon\right).$$

The equation $\mathcal{L}^*p^\epsilon = 0$ is equivalent to

$$\frac{d}{dx}\left[\frac{d}{dx}\left(\frac{1}{2}g^2(x)p^\epsilon(x)\right) - \frac{2f(x)}{g^2(x)}\left(\frac{1}{2}g^2(x)p^\epsilon(x)\right)\right] = 0. \tag{2.9}$$

Set $y_\epsilon(x) := \frac{1}{2}g^2(x)p^\epsilon(x) = \frac{1}{2}\frac{\epsilon^2x^2}{(h+\sqrt{x})^2}p^\epsilon(x)$ and $\alpha_\epsilon(x) := \frac{2f(x)}{g^2(x)} = \frac{2a}{\epsilon^2}\frac{(h+\sqrt{x})^2}{x}\log\frac{b}{x}$. Then the equation (2.9) is equivalent to

$$y'_\epsilon(x) - \alpha_\epsilon(x)\,y_\epsilon(x) = -c \tag{2.10}$$

for some constant c. The solution of (2.10) has the form of

$$y_\epsilon(x) = A^\epsilon(x)\left(K - c\int_b^x \frac{dt}{A^\epsilon(t)}\right)$$

where $A^\epsilon(t) = \exp\{\int_b^t \alpha_\epsilon(u)\,du\}$ and K is a positive constant. By computation, we get

$$\begin{aligned}\int_b^x \alpha_\epsilon(u)\,du &= \frac{2ah^2}{\epsilon^2}\left(\log b\log x - \frac{1}{2}(\log x)^2 - \frac{1}{2}(\log b)^2\right)\\ &\quad + \frac{8ah}{\epsilon^2}\left(\sqrt{x}\log\frac{b}{x} + 2\sqrt{x} - 2\sqrt{b}\right) + \frac{2a}{\epsilon^2}\left(x\log\frac{b}{x} + x - b\right).\end{aligned}$$

Denote

$$H(x) := -ah^2\left(\log\frac{b}{x}\right)^2 + 8ah\left(\sqrt{x}\log\frac{b}{x} + 2\sqrt{x} - 2\sqrt{b}\right) + 2a\left(x\log\frac{b}{x} + x - b\right).$$

Therefore the density $p^\epsilon(x)$ has the form of

$$p^\epsilon(x) = \frac{2(h+\sqrt{x})^2}{\epsilon^2 x^2}A^\epsilon(x)\left[K + c\int_x^b \frac{dt}{A^\epsilon(t)}\right]$$

in which

$$A^\epsilon(x) = \exp\left\{\frac{1}{\epsilon^2}H(x)\right\}.$$

Note that

$$\lim_{x\downarrow 0}\frac{2(h+\sqrt{x})^2}{\epsilon^2 x^2}A^\epsilon(x) = 0 \text{ and } \lim_{x\uparrow\infty}\frac{2(h+\sqrt{x})^2}{\epsilon^2 x^2}A^\epsilon(x) = 0.$$

Now we claim that $p^\epsilon(x)$ is a density function if and only if $c = 0$. We show that, in some neighborhood of 0, $p^\epsilon(x)$ has bounded integral only when $c = 0$. Here we take $K > 0$ and $c \geq 0$ because p^ϵ is a density. Suppose that $c > 0$. Write $H(x) = -\epsilon^2\gamma(\log\frac{b}{x})^2 + H_1(x)$ where $\gamma := \frac{ah^2}{\epsilon^2}$ and

$$H_1(x) = 8ah\left(\sqrt{x}\log\frac{b}{x} + 2\sqrt{x} - 2\sqrt{b}\right) + 2a\left(x\log\frac{b}{x} + x - b\right).$$

Then

$$A^\epsilon(x) = \exp\left\{-\gamma\left(\log\frac{b}{x}\right)^2\right\}\exp\left\{\frac{1}{\epsilon^2}H_1(x)\right\}.$$

Since

$$\lim_{x\downarrow 0}\exp\left\{\frac{1}{\epsilon^2}H_1(x)\right\} = \exp\left\{\frac{1}{\epsilon^2}(-16ah\sqrt{b} - 2ab)\right\} > 0,$$

there are positive constants K_1^ϵ and K_2^ϵ such that in some neighborhood of 0

$$K_1^\epsilon\exp\left\{-\gamma\left(\log\frac{b}{x}\right)^2\right\} \leq A^\epsilon(x) \leq K_2^\epsilon\exp\left\{-\gamma\left(\log\frac{b}{x}\right)^2\right\}.$$

Then

$$\begin{aligned} p^\epsilon(x) &\geq 2cK_1^\epsilon\left(\frac{h}{\epsilon}\right)^2 x^{-2}\exp\left\{-\gamma\left(\log\frac{b}{x}\right)^2\right\}\int_x^b K_2^\epsilon\exp\left\{\gamma\left(\log\frac{b}{t}\right)^2\right\}dt \\ &= K_3^\epsilon x^{-2}\exp\left\{-\gamma\left(\log\frac{b}{x}\right)^2\right\}\int_x^b \exp\left\{\gamma\left(\log\frac{b}{t}\right)^2\right\}dt \end{aligned}$$

where $K_3^\epsilon > 0$ is a constant. Denote

$$L := \lim_{x\downarrow 0}(H_2(x))^{-1}\int_x^b \exp\{\gamma(\log(b/t))^2\}dt,$$

where $H_2(x) = x^2 \exp\{\gamma(\log(b/x))^2\}$. We will prove that $L = \infty$. Indeed, since $\lim_{t\downarrow 0} t^2 \exp\{\gamma(\log(b/t))^2\} = \infty$, there is a $0 < \delta_1 < b$ such that $0 < t < \delta_1$ implies $\exp\{\gamma(\log(b/t))^2\} > t^{-2}$. Then

$$\int_x^b \exp\{\gamma(\log(b/t))^2\}dt \geq \int_x^{\delta_1} t^{-2}dt = \frac{1}{x} - \frac{1}{\delta_1} \to \infty \text{ as } x \downarrow 0.$$

On the other hand, $H_2(x) \to \infty$ as $x \downarrow 0$. So applying L'Hospital's Rule gives

$$\begin{aligned} L &= \lim_{x\downarrow 0} \frac{\int_x^b \exp\{\gamma(\log(b/t))^2\}dt}{H_2(x)} \\ &= \lim_{x\downarrow 0} \frac{-\exp\{\gamma(\log(b/x))^2\}}{2x\exp\{\gamma(\log(b/x))^2\}[1-\gamma\log(b/x)]} \\ &= \lim_{x\downarrow 0} \frac{1}{2x(\gamma\log b - \gamma\log x - 1)} = \infty. \end{aligned}$$

Given $N > 0$ there is $0 < \delta_2 < 1$ such that $0 < x < \delta_2$ implies

$$K_3^\epsilon x^{-2} \exp\left\{-\gamma\left(\log\frac{b}{x}\right)^2\right\} \int_x^b \exp\left\{\gamma\left(\log\frac{b}{t}\right)^2\right\} dt > \frac{N}{\delta_2}.$$

Hence

$$\int_0^1 p^\epsilon(x)dx \geq \int_0^{\delta_2} \frac{N}{\delta_2}dx = N.$$

Since N is arbitrary, $\int_0^1 p^\epsilon(x)dx = \infty$. This completes the proof. □

Remark 2.2. We have two observations. First, the ergodic stationary distribution exists for any non-zero noise intensity ϵ. Second, when the noise intensity ϵ approaches 0, the probability density function $p^\epsilon(x)$ tends to the Dirac delta function with mass concentrated in b. In fact, let $\delta(x) = \lim_{\epsilon\downarrow 0} p^\epsilon(x)$. Taking natural log of $p^\epsilon(x)$, we get

$$\log p^\epsilon(x) = \log\left(\frac{2(h+\sqrt{x})^2}{x^2}\right) + \frac{1}{\epsilon^2}(H(x) - \epsilon^2 \log I(\epsilon)),$$

where

$$I(\epsilon) := \int_0^\infty \frac{2(h+\sqrt{y})^2}{y^2} \exp\left\{\frac{1}{\epsilon^2}H(y)\right\} dy.$$

Notice that the function $H(x)$ is increasing on $(0, b)$, decreasing on (b, ∞), and attains its maximum 0 at $x = b$. This implies that $H(x) < 0$ for $x \neq b$ and $H(x) = 0$ when $x = b$. Furthermore, using standard calculus, we can prove that $I(\epsilon) \to 0$ as $\epsilon \downarrow 0$ which follows that $\epsilon^2 \log I(\epsilon) \to 0$ as $\epsilon \downarrow 0$. So, for $x \neq b$, as $\epsilon \downarrow 0$ we have $\log p^\epsilon(x) \to -\infty$ which implies that $p^\epsilon(x) \to 0$. When $x = b$, $\log p^\epsilon(b) = \log\left(\frac{2(h+\sqrt{b})^2}{b^2}\right) - \log I(\epsilon) \to \infty$ as $\epsilon \downarrow 0$ and hence $p^\epsilon(x) \to \infty$ as $\epsilon \downarrow 0$. Therefore $\delta(x) = 0$ for all $0 < x \neq b$ and $\delta(b) = \infty$.

We will simulate the probability density function of the stationary distribution and make some numerical observations in Section 3.

2.4. *The first passage time density*

We have shown that, in the section 2.1, with $X_0 = x > 0$ w.p.1, the stochastic differential equation (1.1) has a pathwise unique strong solution $X_t > 0$ w.p.1. Then $\mathbb{P}_x[S = \infty] = 1$, where

$$S = \inf\{t > 0;\ X_t \notin (0, \infty)\}$$

is the explosion time of the diffusion process X_t. We have also proved that 0 is an unattainable boundary point of the diffusion process X_t starting at any point $X_0 = x \in (0, \infty)$. If we restrict our attention to the interval $(0, b_1)$ (with $b_1 < b$) then, by the same argument as the previous section, b_1 is a reflecting attainable boundary point. Now we are interested in the distribution of the first passage time of the diffusion process X_t at level b_1

$$\tau_{b_1} = \inf\{t > 0;\ X_t = b_1\}.$$

For simplicity, we can reduce X_t to a diffusion process with unit diffusion coefficient by using the transformation

$$Y = \int_{b_1}^{X} \frac{dz}{g(z)} =: \phi(X).$$

Note that $g(x) = \frac{\epsilon x}{h+\sqrt{x}} > 0$ on $(0, \infty)$ and $\frac{1}{g(x)}$ is locally integrable over $(0, \infty)$. Then this transformation defines a new 1-dimensional diffusion process Y_t with dynamics

$$dY_t = \phi'(X_t)dX_t + \frac{1}{2}\phi''(X_t)(dX_t)^2,$$

which is equivalent to

$$dY_t = \left(\frac{f(X_t)}{g(X_t)} - \frac{1}{2}g'(X_t)\right) dt + dW_t.$$

Since

$$\phi(X) = \int_{b_1}^{X} \frac{dz}{g(z)} = \frac{h}{\epsilon}\log\frac{X}{b_1} + \frac{2}{\epsilon}\left(\sqrt{X} - \sqrt{b_1}\right)$$

is continuously differentiable and increasing on $(0, b_1)$ and $\phi'(X) = \frac{1}{g(X)} > 0$ for all $X \in (0, b_1)$, there is a unique inverse function $\psi = \phi^{-1}$ defined on $(\phi(0), \phi(b_1)) = (-\infty, 0)$ such that $\psi'(Y) = \frac{1}{\phi'(X)} = g(X) > 0$ for all $Y = \phi(X) \in (-\infty, 0)$. With $y := \phi(x)$, the first passage time of X_t with $X_0 = x \in (0, b_1)$ at level b_1 is equal to the first passage time of Y_t with $Y_0 = y \in (-\infty, 0)$ at level 0. Let

$$\tau_0 = \inf\{t > 0;\ Y_t = 0\},$$

and $\mathbb{P}_y$ denote the probability law on the canonical path space $C(\mathbb{R}^+, \mathbb{R})$ of continuous functions from $\mathbb{R}^+$ to $\mathbb{R}$ that makes the process Y_t behave according to

$$dY_t = c(Y_t)\, dt + dW_t, \tag{2.11}$$

where

$$c(Y_t) = \frac{f(\psi(Y_t))}{g(\psi(Y_t))} - \frac{1}{2}g'(\psi(Y_t)) = \frac{a}{\epsilon}\log\frac{b}{\psi(Y_t)}\left(h+\sqrt{\psi(Y_t)}\right) - \frac{\epsilon}{2}\frac{2h+\sqrt{\psi(Y_t)}}{\left(h+\sqrt{\psi(Y_t)}\right)^2}.$$

Since ψ is continuously differentiable over $(-\infty,0)$ and takes values on $(0,b_1)$, c is also continuously differentiable over $(-\infty,0)$. Note that the function $\gamma := \frac{1}{2}(c^2+c')$ is continuous and locally integrable on $(-\infty,0)$. By the transformation, the equation (2.11) admits a unique strong solution $Y_t < 0$ w.p.1 with initial value $Y_0 = y \in (-\infty,0)$ w.p.1. Thus, Y_{τ_0} does not explode to ∞.

Now we will consider the problem of finding a convenient representation of the quantity

$$p_y(t) := \frac{\partial}{\partial t}\mathbb{P}_y[\tau_0 \le t], \quad y \in (-\infty,0),\ t \in \mathbb{R}^+,$$

i.e. the density of the first passage time of the diffusion Y_t at level 0. The representation of this density function is described in the following theorem.

Theorem 2.4. *Consider a standard 3-dimensional Brownian bridge β on the probability space $\left(C[0,1],\mathbb{R}^3,P_{BB^3}\right)$. Then*

$$p_y(t) = \frac{|y|e^{-y^2/2t}}{\sqrt{2\pi t^3}}\exp\left(\int_y^0 c(v)dv\right)\mathbb{E}_{BB^3}\left[\exp\left(-t\int_0^1 \gamma\left(-\left|u|y|e_1+\sqrt{t}\beta_u\right|\right)du\right)\right]$$

holds for all $t \in \mathbb{R}^+$, where $e_1 = (1,0,0)^T$ and $|\cdot|$ denotes the usual Euclidean norm in $\mathbb{R}^3$.

Proof. Consider the non-negative $\mathbb{P}_y$-supermartingale

$$Z_t := \exp\left(-\int_0^{t\wedge\tau_0} c(Y_u)\,dW_u - \frac{1}{2}\int_0^{t\wedge\tau_0} c^2(Y_u)\,du\right).$$

Since $\mathbb{P}_y\left[\bar{S}=\infty\right]=1$ where $\bar{S} = \inf\{t>0;\, Y_t \notin (-\infty,0)\}$, by Exercise 5.5.38(iii) in [16] Z_t is a martingale. Let $\mathbb{Q}_y$ be the probability law on $C(\mathbb{R}^+,\mathbb{R})$ that makes the process Y_t behave like a Brownian motion starting from y and stopping when it reaches level 0. Then Girsanov's theorem follows that

$$\left.\frac{d\mathbb{Q}_y}{d\mathbb{P}_y}\right|_{\mathcal{F}_t} = Z_t$$

for all $t \in \mathbb{R}^+$. Now applying Ito's formula under $\mathbb{Q}_y$ gives

$$d\left(\int_0^{Y_t} c(v)\,dv\right) = c(Y_t)\,dY_t + \frac{1}{2}c'(Y_t)(dY_t)^2$$

on the set $\{\tau_0 < \infty\}$. Integrating the above from 0 to τ_0 and using the fact that $Y_{\tau_0} = 0$ yield

$$\int_0^{Y_{\tau_0}} c(v)\,dv - \int_0^{Y_0} c(v)\,dv = \int_0^{\tau_0} c(Y_u)\,dY_u + \frac{1}{2}\int_0^{\tau_0} c'(Y_u)\,du$$

and so

$$\int_y^0 c(v)\,dv = \int_0^{\tau_0} c(Y_u)\,dY_u + \frac{1}{2}\int_0^{\tau_0} c'(Y_u)\,du.$$

Hence on $\{\tau_0 < \infty\}$ we have

$$\begin{aligned}\frac{1}{Z_{\tau_0}} &= \exp\left(\int_0^{\tau_0} c(Y_u)\,dW_u + \frac{1}{2}\int_0^{\tau_0} c^2(Y_u)\,du\right)\\ &= \exp\left(\int_0^{\tau_0} c(Y_u)[dY_u - c(Y_u)du] + \frac{1}{2}\int_0^{\tau_0} c^2(Y_u)\,du\right)\\ &= \exp\left(\int_0^{\tau_0} c(Y_u)\,dY_u - \frac{1}{2}\int_0^{\tau_0} c^2(Y_u)\,du\right)\\ &= \exp\left(\int_y^0 c(v)\,dv - \int_0^{\tau_0} \gamma(Y_u)\,du\right).\end{aligned}$$

Note that $d\mathbb{P}_y = \frac{1}{Z_{t\wedge\tau_0}} d\mathbb{Q}_y$ and this implies that

$$\begin{aligned}\mathbb{P}_y[\tau_0 \le t] &= \mathbb{E}_{\mathbb{Q}_y}\left[\frac{1}{Z_{t\wedge\tau_0}}\mathbb{1}_{\{\tau_0\le t\}}\right]\\ &= \mathbb{E}_{\mathbb{Q}_y}\left[\exp\left(\int_y^0 c(v)\,dv - \int_0^{\tau_0}\gamma(Y_u)\,du\right)\mathbb{1}_{\{\tau_0\le t\}}\right]\\ &= \mathbb{E}_{\mathbb{Q}_y}\left[\exp\left(\int_y^0 c(v)\,dv - \int_0^{\tau_0}\gamma(Y_u)\,du\right)\Big|\tau_0\le t\right]\mathbb{Q}_y[\tau_0\le t]\\ &= \exp\left(\int_y^0 c(v)\,dv\right)\mathbb{E}_{\mathbb{Q}_y}\left[\exp\left(-\int_0^{\tau_0}\gamma(Y_u)\,du\right)\Big|\tau_0\le t\right]\mathbb{Q}_y[\tau_0\le t].\end{aligned}$$

Then we get

$$\begin{aligned}p_y(t) &= \lim_{h\to 0}\frac{1}{h}\mathbb{P}_y[t\le\tau_0\le t+h]\\ &= \exp\left(\int_y^0 c(v)\,dv\right)\lim_{h\to 0}\mathbb{E}_{\mathbb{Q}_y}\left[\exp\left(-\int_0^{\tau_0}\gamma(Y_u)\,du\right)\Big|t\le\tau_0\le t+h\right]\times\\ &\quad\lim_{h\to 0}\frac{1}{h}\,\mathbb{Q}_y[t\le\tau_0\le t+h]\\ &= \exp\left(\int_y^0 c(v)\,dv\right)\mathbb{E}_{\mathbb{Q}_y}\left[\exp\left(-\int_0^{\tau_0}\gamma(Y_u)\,du\right)\Big|\tau_0 = t\right]q_y(t)\end{aligned}$$

where $q_y(t) \equiv \frac{|y|}{\sqrt{2\pi t^3}}\exp(-\frac{y^2}{2t})$ is the first exit time density at level 0 of a standard Brownian motion starting from y. Thus

$$p_y(t) = \frac{|y|e^{-y^2/2t}}{\sqrt{2\pi t^3}}\exp\left(\int_y^0 c(v)\,dv\right)\mathbb{E}_{\mathbb{Q}_y}\left[\exp\left(-\int_0^{\tau_0}\gamma(Y_u)\,du\right)\Big|\tau_0 = t\right].$$

Given $\tau_0 = t$, the regular conditional $\mathbb{Q}_y$-distribution of the process $-Y_{t-s}$, $0\le s\le t$, is that of a 3-dimensional Bessel bridge from 0 to $|y|$ over $[0,t]$ (see the proof of Proposition 2.1 in [21]). On the canonical space $(C[0,1],\mathbb{R}^3,P_{BB^3})$ with the stardand 3-dim Brownian bridge β, the process $\left|(s/t)|y|e_1 + \sqrt{t}\,\beta_{s/t}\right|$, $0 \le s \le t$, has the exact law of the above Bessel bridge. Thus

$$\begin{aligned}\mathbb{E}_{\mathbb{Q}_y}\left[\exp\left(-\int_0^{\tau_0}\gamma(Y_u)du\right)\right] &= \mathbb{E}_{BB^3}\left[\exp\left(-\int_0^t \gamma\left(-\left|(s/t)|y|e_1+\sqrt{t}\beta_{s/t}\right|\right)ds\right)\right]\\ &= \mathbb{E}_{BB^3}\left[\exp\left(-t\int_0^1 \gamma(-|u|y|e_1+\sqrt{t}\,\beta_u|)du\right)\right],\end{aligned}$$

and therefore the result follows. □

This theorem is a representation of the probability density function of the first passage time which is very useful to simulate the first passage time. We will numerically compute it in the next section.

3. Numerical studies

In this section, we carry out some numerical studies to demonstrate how solutions to stochastic model and corresponding deterministic model behave differently, how the stationary distribution of the stochastic model changes as noise intensity parameter value changes, and how the first passage time behave as the tumor volume changes. In Figure 1, we illustrate solutions of stochastic and deterministic model for 4 different values of the noise intensity parameter ϵ. In each plot, the initial values for both stochastic and deterministic model are the same. From these plots, we can see that the fluctuation of the solution to stochastic model becomes large as the noise intensity parameter value becomes large. The solution of the stochastic model will merge into the solution of the deterministic model as the noise intensity parameter ϵ approaches zero.

In Subsection 2.3, using the Fokker-Plank equation we obtain an explicit expression of the density function of the stationary distribution for the stochastic model. To visualize it, we plot the density against the tumor volume for 4 different values of the noise intensity parameter ϵ in Figure 2. From these plots, we see that the stationary distribution always exists even for large noise perturbation. When the noise intensity parameter ϵ becomes small, the density function becomes more concentrated, and approaches the Dirac delta function at $x = b$. This verifies that $x = b$ is a stationary point (equilibrium point) of the model when $\epsilon = 0$, which is the equilibrium solution of the deterministic model.

In Subsection 2.4, we obtain a representation of the probability density function of the first passage time. It is still difficult to understand how the the first passage time behaves. We now use the Monte Carlo simulation technique (see [21]) to simulate the density function of the first passage time. In order to estimate the density $p_y(t)$ at a given time $t \in \mathbb{R}^+$, we simulate N independent paths of the 3-dimensional Brownian bridge, β^1, β^2,..., β^N, then define the estimator $p_y^N(t)$ for

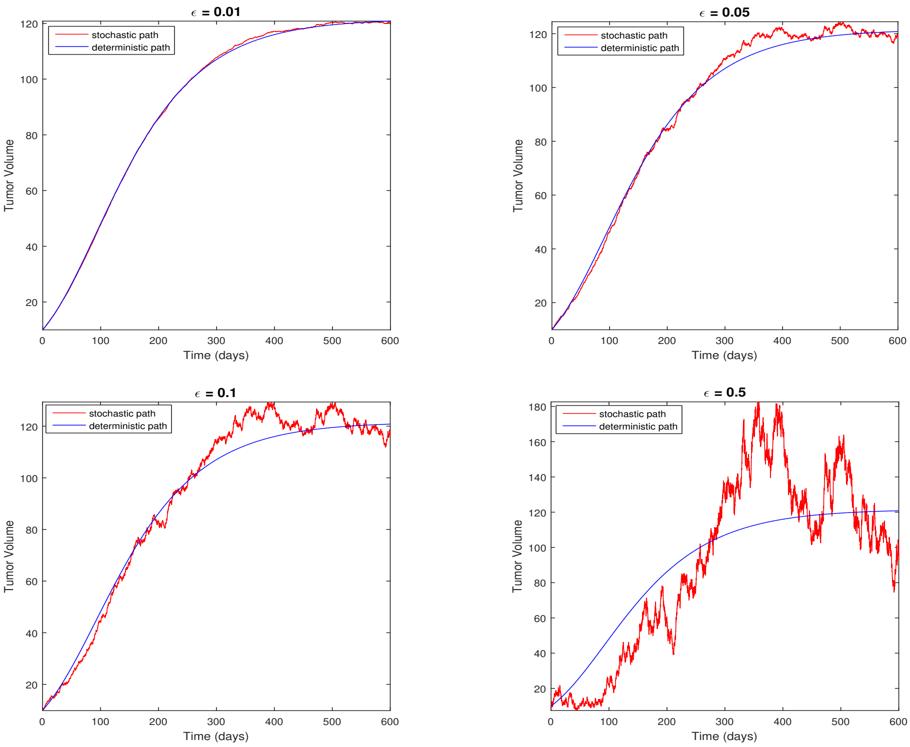

Fig. 1. Comparison: solutions of stochastic and deterministic model for different ϵ values.

$p_y(t)$ via

$$p_y^N(t) := \frac{|y|e^{-\frac{y^2}{2t}}}{\sqrt{2\pi t^3}} \exp\left(\int_y^0 c(v)dv\right) \frac{1}{N}\sum_{i=1}^{N} \exp\left(-t\int_0^1 \gamma\left(-\left|u|y|e_1 + \sqrt{t}\beta_u^i\right|\right)du\right).$$

By strong law of large numbers, the estimator $p_y^N(t)$ converges almost surely to the true density $p_y(t)$ as N goes to ∞ for each fixed $t \in \mathbb{R}^+$. Furthermore, based on Propositions 3.1 and 3.2 in [21], we can show that $\{p_y^N(t)\}_{t\in\mathbb{R}^+}$ converges uniformly to $p_y(t)$ with rate $1/\sqrt{N}$ over compact time intervals. We generate a standard 3-dimensional Brownian bridge β from 0 to 1 over the time interval $[0, 1]$ using the pathwise unique solution of the system of SDEs

$$d\beta = \frac{-\beta}{1-t}dt + dw(t),\ \ 0 \le t < 1,\ \beta(0) = \beta(1) = 0,$$

where $w(t) = (w^1(t), w^2(t), w^3(t))$ is a 3-dimensional standard Brownian motion (see [23]). All data of parameter values for the stochastic model (1.1) are taken from [12], in which $a = 0.009916$, $b = 121.6$, $\epsilon = 0.0769$, and $h = 0.2241$. Since we are interested in the survival time for each patient and this survival time can be expressed as the first passage time that the volume of the tumor, X, reaches a

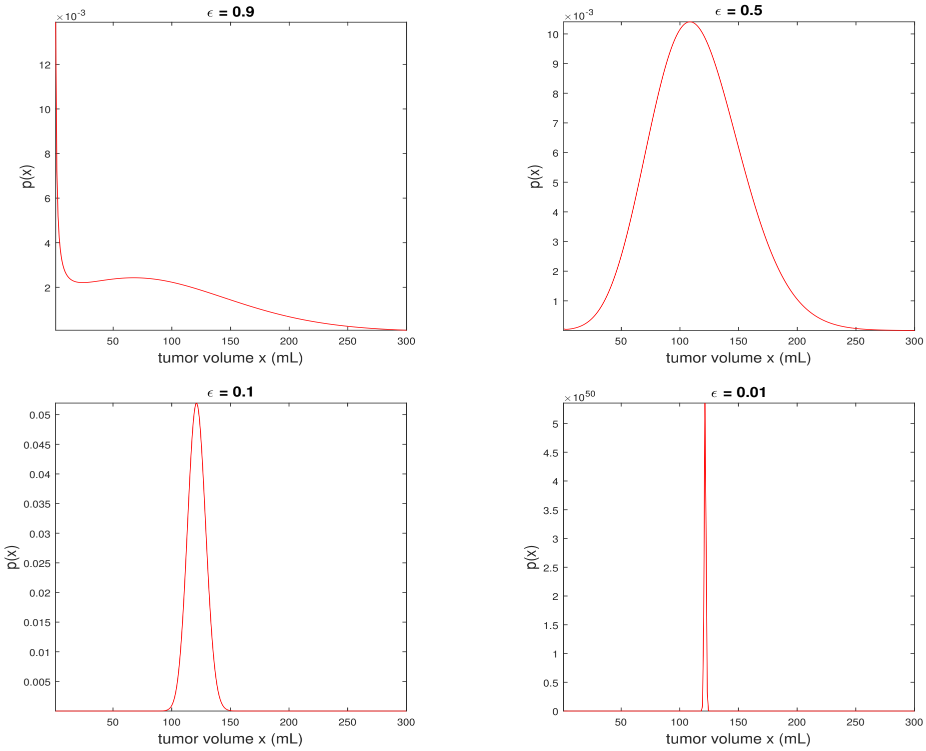

Fig. 2. The density functions $p^{\epsilon}(x)$ for different values of ϵ.

specific value, we do simulations for the densities of the first passage time random variable

$$\tau(X_0, X_c) = \inf\{t > 0;\ X_t = X_c\}$$

where $X_0 < X_c$, X_0 is the tumor size at time we start to observe and X_c is the tumor size when we stop to observe. As in [12], we choose $X_0 = 20$ and $X_c \in \{60, 70, 80, 90\}$. The density curves are presented in Picture 3. From these numerical simulations, we can see some reasonable features of the first passage time. For example, for a given tumor size, there is a critical time around which the probability density is concentrated; that means, the probability to grow to the given size of the tumor is almost zero if the time is too early, and the probability is large if the time is close to the critical time. We can compute the probability and the time interval when the tumor size is given. For example, if we want to know the probability that the tumor will grow to the size of 60 ML after 100 days if the initial observed size is 20 ML, we then compute (integrate) the probability density function of the first passage time until 100 days; if we want to know when the tumor size is 60 ML with probability 80% if the initial observed size is 20 ML, we need to find the critical

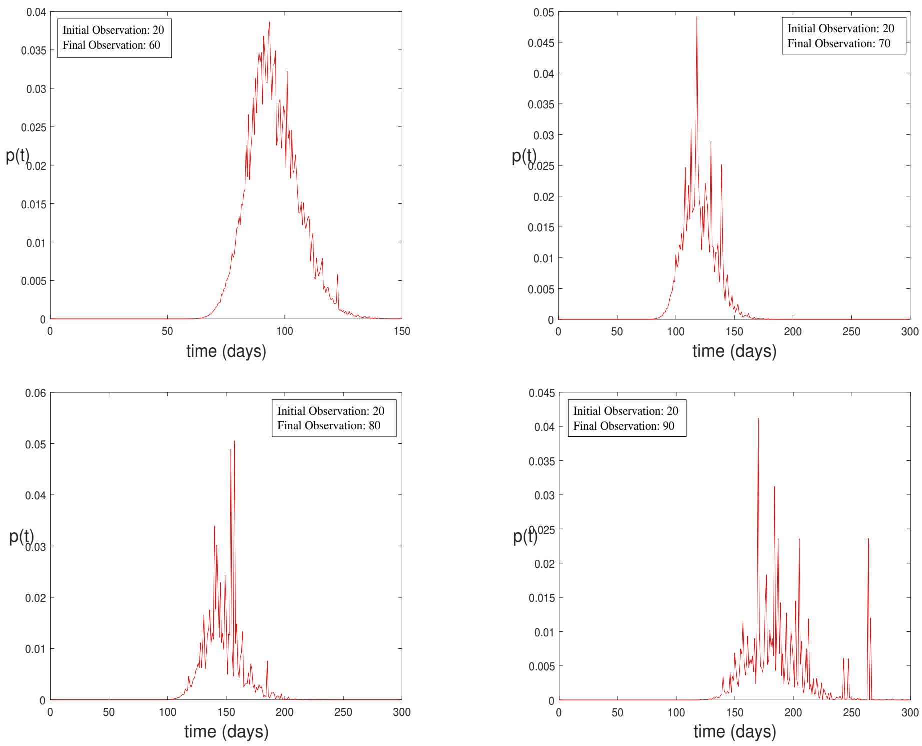

Fig. 3. The first passage time densities of the solution X (the volume of the tumor), starting at $X_0 = 20$ (initial observation), at level $X_c = 60$, 70, 80, 90 (final observation).

time, then local a lower bound and upper bound of time centered at the critical time using 80%.

4. Conclusion and discussion

In this study, we analyze a new Ito stochastic differential equation model for untreated human gliomas. The model is based deterministic Gompertz model for solid tumor growth. We show the existence and uniqueness of solutions in positive spatial domain. When the model is restricted in finite domain $(0, b)$, we show that the boundary point 0 is unattainable while the point b is reflecting attainable. The stochastic model does not have non-trivial equilibrium points. But, we show there is a unique ergodic stationary distribution for any non-zero noise intensity parameter value, and obtain the explicit probability density function for the stationary distribution. We also obtain a representation of the density function of the first passage time. In addition, our mathematical and numerical analysis confirms that the stochastic model will set down to the deterministic model when the noise intensity parameter approaches zero [24]. Therefore, our randomization of the deterministic Gompertz model is mathematically sound and reasonable.

We know the solution of an Ito stochastic differential equation is a diffusion process when it exists and is unique. We may consider tumor growth as follows [20]. The velocity of the macroscopic motion of the tumor cells at the point x and the instant t is equal to $a(t,x)$. We assume that fluctuational component of the displacement is random variable $\xi_{t,x_t,\Delta t}$ whose distribution depends on the position x of the tumor cell and the instant t at which the displacement is observed, and the quantity Δt which is the length of time interval during which the displacement is observed. Then, we have the change of tumor volume $X_{t+\Delta t} - X_t = a(t,x_t)\Delta t + \xi_{t,x_t,\Delta t}$. We also assume that $\xi_{t,x_t,\Delta t} = b(t,x)\xi_{t,\Delta t}$, where $b(t,x)$ characterizes the properties of the tumor microenvironment at the point x and instant t; $\xi_{t,\Delta t}$ is the increment that is obtained in the local homogeneous environment under the condition that $b(t,x) = 1$. We may also consider $b(t,x)$ is a standard deviation of the displacement. We simply take $\xi_{t,\Delta t}$ is distributed as Brownian motion $w(t+\Delta t) - w(t)$. Consequently, $X_{t+\Delta t} - X_t \approx a(t,x_t)\Delta t + b(t,x_t)[w(t+\Delta t) - w(t)]$. A reasonable approximation of this growth process is Ito stochastic differential equations. For our case, we take the fitted average growth rate $ax \log \frac{b}{x}$ as the growth velocity $a(t,x)$, and the fitted standard deviation $\frac{x}{h+\sqrt{x}}$ with a multiplicative parameter ϵ as $b(t,x)$. This parameter can somehow measure randomness of fluctuational terms. Therefore, each term in our stochastic model has certain physical significance, and our stochastic model is physically sound.

If we consider the stochastic model only in the spatial domain $(0,b)$, we might need some extra conditions for the boundary b. From our analysis of boundary classification, the boundary point 0 is unattainable and b is reflecting attainable. In this case, the diffusion process cannot be uniquely determined [17, 19]. In order to have a unique diffusion process which can be applied to tumor growth, we have to specify some condition at the boundary point b, while there is no need of boundary conditions at point 0. There are several ways to impose boundary conditions. However, this will be a completely different study which is beyond this study. We plan to conduct this study in the future.

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