MATHEMATICAL BIOSCIENCES
AND ENGINEERING
Volume **15**, Number **5**, October **2018**

doi:10.3934/mbe.2018048

pp. **1077–1098**

STOCHASTIC DYNAMICS AND SURVIVAL ANALYSIS OF A CELL POPULATION MODEL WITH RANDOM PERTURBATIONS

Cristina Anton* and Alan Yong

Department of Mathematics and Statistics
Grant MacEwan University, Edmonton, AB T5J 4S2, Canada

(Communicated by Jianhong Wu)

Abstract. We consider a model based on the logistic equation and linear kinetics to study the effect of toxicants with various initial concentrations on a cell population. To account for parameter uncertainties, in our model the coefficients of the linear and the quadratic terms of the logistic equation are affected by noise. We show that the stochastic model has a unique positive solution and we find conditions for extinction and persistence of the cell population. In case of persistence we find the stationary distribution. The analytical results are confirmed by Monte Carlo simulations.

1. **Introduction.** Cell-based in vitro assays [27] are efficient methods to study the effect of industrial chemicals on environment or human health. Our work is based on the cytotoxicity profiling project carried by Alberta Centre for Toxicology in which initially 63 chemicals were investigated using the xCELLigence Real-Time Cell Analysis High Troughput (RTCA HT) Assay [26]. We consider a mathematical model represented by stochastic differential equations to study cytotoxicity, i.e. the effect of toxicants on human cells, such as the killing of cells or cellular pathological changes.

The cells were seeded into wells of micro-electronic plates (E-Plates), and the test substances with 11 concentrations (1:3 serial dilution from the stock solution) were dissolved in the cell culture medium [20]. The microelectrode electronic impedance value was converted by a software to Cell Index (n), which closely reflects not only cell growth and cell death, but also cell morphology. The time-dependent concentration response curves (TCRCs) for each test substance in each cell line were generated [26] and based on these curves the toxicants in the present study were divided in 10 groups [30]. In Fig. 1 we display the TCRCs for the toxicant monastrol.

The success of clustering and classification methods depends on providing TCRCs that illustrates the cell population evolution from persistence to extinction. In [1] we consider a model represented by a system of ordinary differential equations to determine an appropriate range for the initial concentration of the toxicant. The model's parameters were estimated based on the data included in the TCRCs [1].

2010 *Mathematics Subject Classification.* Primary: 37H10, 60J70; Secondary: 60H10.

Key words and phrases. Stochastic logistic equation, stationary distribution, ergodic property, extinction, stochastic permanence.

The first author is supported by NSRC grant DDG-2015-00041.

* Corresponding author: Cristina Anton.

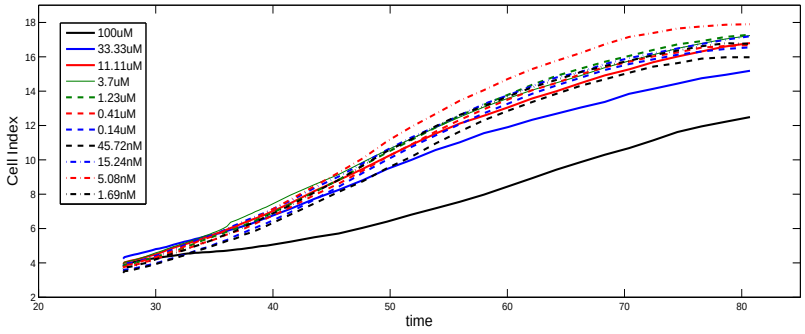


FIGURE 1. TCRCs for monastrol

Let $n(t)$ be the cell index, which closely reflects the cell population, $C_o(t)$ be the concentration of internal toxicants per cell, and $C_e(t)$ be the concentration of toxicants outside the cells at time t. We suppose that the toxicants do not exist in the cells before experiments, so $C_o(0) = 0$, and that $C_e(0)$ is equal to the concentration of toxicant used in the experiments. We assume that the death rate of cells is linearly dependent on the concentration C_o of internal toxicants and we consider linear kinetic, so we get the following deterministic model [1]:

$$\frac{dn(t)}{dt} = \beta n(t) - \gamma n^2(t) - \alpha C_o(t) n(t), \tag{1}$$

$$\frac{dC_o(t)}{dt} = \lambda_1^2 C_e(t) - \eta_1^2 C_o(t), \tag{2}$$

$$\frac{dC_e(t)}{dt} = \lambda_2^2 C_o(t) n(t) - \eta_2^2 C_e(t) n(t) \tag{3}$$

Here $\beta > 0$ denotes the cell growth rate, $\gamma = \frac{\beta}{K}$, where $K > 0$ is the capacity volume, $\alpha > 0$ is the cell death rate, λ_1^2 represents the uptake rate of the toxicant from environment, η_1^2 is the toxicant input rate to the environment, λ_2^2 is the toxicant uptake rate from cells, and η_2^2 represents the losses rate of toxicants absorbed by cells.

The deterministic model (1)-(3) is a special case of the class of models proposed in [5], and it is related to the models considered in [7, 11, 15]. However, since we consider an acute dose of toxicant instead of a chronic one, the analysis of the survival/death of the cell population is different from the one done in the previously mentioned papers.

We have noticed that, for the toxicants considered here, the estimated values of the parameters η_1, η_2, λ_1, and λ_2 verify $\eta_1^2\eta_2^2 - \lambda_1^2\lambda_2^2 > 0$ [1]. In this case we have $0 < C_e(t) \le C_e(0)$, $0 \le C_o(t) \le \frac{\lambda_1^2 C_e(0)}{\eta_1^2}$, and $n(t) > 0$, for all $t \ge 0$. (see Lemma 3.1 in [1]). Moreover from Theorem 3.2 in [1] we know that $\lim_{t\to\infty} C_e(t)$ exists and its value determines the asymptotic behavior of the system:

1. If $\lim_{t\to\infty} C_e(t) < \frac{\beta\eta_1^2}{\alpha\lambda_1^2}$ then the population is uniformly persistent:

$$\lim_{t\to\infty} n(t) = K, \quad \lim_{t\to\infty} C_o(t) = \lim_{t\to\infty} C_e(t) = 0.$$

2. If $\lim_{t\to\infty} C_e(t) > \frac{\beta\eta_1^2}{\alpha\lambda_1^2}$ then $|n|_1 = \int_0^\infty n(t)dt < \infty$ and the population goes to local extinction:

$$\lim_{t\to\infty} n(t) = 0, \quad \lim_{t\to\infty} C_o(t) = C_e^* \frac{\lambda_1^2}{\eta_1^2}, \quad \lim_{t\to\infty} C_e(t) = C_e^* > \frac{\beta\eta_1^2}{\alpha\lambda_1^2},$$

In practice we usually estimate a parameter by an average value plus an error term. To keep the stochastic model as simple as possible, we ignore the relationship between the parameters β and γ, and we replace them by the random variables

$$\tilde{\beta} = \beta + \text{error}_1 \quad , \tilde{\gamma} = \gamma + \text{error}_2 \tag{4}$$

By the central limit theorem, the error terms may be approximated by a normal distribution with zero mean. Thus we replace equation (1) by a stochastic differential equation and, together with equations (2) and (3), we get the stochastic model

$$dn(t) = n(t)\left(\beta - \gamma n(t) - \alpha C_o(t)\right)dt + \sigma_1 n(t)dB_1(t) - \sigma_2 n^2(t)dB_2(t), \tag{5}$$

$$dC_o(t) = (\lambda_1^2 C_e(t) - \eta_1^2 C_o(t))dt, \tag{6}$$

$$dC_e(t) = (\lambda_2^2 C_o(t)n(t) - \eta_2^2 C_e(t)n(t))dt, \tag{7}$$

Here $\sigma_i \geq 0$, $i = 1, 2$ are the noise intensities. $(\Omega, \mathcal{F}, \{\mathcal{F}_t\}_{t\geq 0}, \mathbb{P})$ is a complete probability space with an increasing, right continuous filtration $\{\mathcal{F}_t\}_{t\geq 0}$ such that $\mathcal{F}_0$ contains all $\mathbb{P}$-null sets, and B_i, $i = 1, 2$ are independent standard Brownian motions defined on the above probability space.

Several versions of a stochastic logistic equation similar with (5) were considered in [18], [19], [8], [9], [10] and [21]. The system of stochastic differential equations (5)-(7) is closely related with the stochastic models in a polluted environment considered in [15], [16], and [24]. However, for the models considered in these papers, instead of the equations (6) and (7), $C_o(t)$ and $C_e(t)$ obey two linear equations without any terms involving $n(t)$. Moreover, instead of a combination of linear and quadratic terms as in (5), in [15] only a linear stochastic term is considered, and in [16] two stochastic competitive models are considered including exclusively either linear stochastic terms or quadratic stochastic terms.

In this paper we extend the methods applied in [15] and [16] to find conditions for extinction, weakly persistence, and weakly stochastically permanence for the model (5)-(7). In addition to this we focus on the ergodic properties when the cell population is strongly persistent. The main contribution of this paper is the proof that $n(t)$ converges weakly to the unique stationary distribution. If only one of the noise variances σ_1^2, σ_2^2 is non-zero, we also determine the density of the stationary distribution. For the study of the ergodic properties we apply techniques used for stochastic epidemic models in [4], [28], [29] and [23], and for a stochastic population model with partial pollution tolerance in a polluted environment in [25].

In the next section we prove that there is a unique non-negative solution of system (5)-(7) for any non-negative initial value. In section 3 we investigate the asymptotic behavior, and in section 4 we study the weak convergence of $n(t)$ to the unique stationary distribution using Lyapunov functions. Numerical simulations that illustrate our results are presented in section 5. The last section of the paper contains a short summary and conclusions.

2. Existence and uniqueness of a positive solution.

We have to show that system (5)-(7) has a unique global positive solution in order for the stochastic model to be appropriate. Let $\mathbb{R}_+ = \{x \in \mathbb{R} : x \geq 0\}$, and $\mathbb{R}_+^* = \{x \in \mathbb{R} : x > 0\}$.

Since equations (6) and (7) are linear in C_o and C_e we have

$$C_o(t) = C_o(0)e^{-\eta_1^2 t} + \lambda_1^2 e^{-\eta_1^2 t}\int_0^t C_e(s)e^{\eta_1^2 s}ds \tag{8}$$

$$C_e(t) = C_e(0)\exp\left(-\eta_2^2\int_0^t n(s)ds\right) + \lambda_2^2\exp\left(-\eta_2^2\int_0^t n(s)ds\right)$$
$$\int_0^t C_o(s)n(s)\exp\left(\eta_2^2\int_0^s n(l)dl\right)ds, \quad t \geq 0. \tag{9}$$

Let's define the differential operator L associated with the system (5)-(7) by

$$L = \frac{\partial}{\partial t} + \left(\beta n - \gamma n^2 - \alpha C_o n\right)\frac{\partial}{\partial n} + (\lambda_1^2 C_e - \eta_1^2 C_o)\frac{\partial}{\partial C_o} + (\lambda_2^2 C_o n$$
$$- \eta_2^2 C_e n)\frac{\partial}{\partial C_e} + \frac{1}{2}\left((\sigma_1^2 n^2 + \sigma_2^2 n^4)\frac{\partial^2}{\partial^2 n}\right)$$

For any function $V \in C^{2,1}\left(\mathbb{R}^3 \times (0,\infty);\mathbb{R}\right)$, by Itô's formula ([17]) we have

$$dV(x(t),t) = LV(x(t),t)dt + \frac{\partial V(x(t),t)}{\partial n}\left(\sigma_1 n(t)dB_1(t) - \sigma_2 n^2(t)dB_2(t)\right), \tag{10}$$

where $x(t) = (n(t), C_o(t), C_e(t))'$, $t \geq 0$.

Theorem 2.1. *Let $D = \mathbb{R}_+^* \times \mathbb{R}_+ \times \mathbb{R}_+^*$. For any given initial value $x(0) \in D$ the system (5)-(7) has a unique global positive solution almost sure (a.s.), i.e. $\mathbb{P}\{x(t) \in D, t \geq 0\} = 1$.*

Proof. The proof is similar with the proof of theorem 3.1 in [29]. Since the coefficients are locally Lipschitz continuous functions, there exists a unique solution on $[0,\tau_e)$, where τ_e is the explosion time ([3]). To prove that the solution is in D and $\tau_e = \infty$ we define the stopping time

$$\tau_m = \inf\{t \in [0,\tau_e) : \min\{n(t), C_e(t)\} \leq m^{-1} \text{ or } \max\{n(t), C_o(t),$$
$$C_e(t)\} \geq m\}, \tag{11}$$

where $m > m_0$ and $m_0 > 0$ is a positive integer sufficiently large such that $n(0) \in [1/m_0, m_0]$, $0 \leq C_o(0) \leq m_0$, and $C_e(0) \in [1/m_0, m_0]$. Here we set $\inf\emptyset = \infty$. Obviously $\{\tau_m\}$ is increasing and let $\tau_\infty = \lim_{n\to\infty}\tau_m$, where $0 \leq \tau_\infty \leq \tau_e$ a.s.. From formula (8) it is easy to see that $C_o(t) \geq 0$ for any $t < \tau_\infty$.

We show that $\tau_\infty = \infty$ a.s., so $\tau_e = \infty$ a.s. and the solution is in D for any $t \geq 0$ a.s. Assume that there exists $T > 0$, and $\epsilon > 0$ such that $P(\tau_\infty \leq T) > \epsilon$. Thus there exists an integer $m_1 \geq m_0$ such that $P(\Theta_m) \geq \epsilon$ for any $m \geq m_1$, where $\Theta_m = \{\tau_m \leq T\}$.

We define the C^3- function $V : D \to R_+^*$ as follows

$$V(x) = C_o + \frac{\alpha}{4\lambda_2^2}(C_e - \log C_e - 1) + \frac{\alpha C_e}{4\lambda_2^2} + \left(\sqrt{n} - \log\sqrt{n} - 1\right) + n.$$

We get

$$LV(x) = (\lambda_1^2 C_e - \eta_1^2 C_o) + \frac{\alpha}{4\lambda_2^2}\left(1 - \frac{1}{C_e}\right)(\lambda_2^2 C_o n - \eta_2^2 C_e n)$$
$$+ \frac{\alpha}{4\lambda_2^2}(\lambda_2^2 C_o n - \eta_2^2 C_e n) + \left(\beta n - \gamma n^2 - \alpha C_o n\right)\left(\frac{1}{2\sqrt{n}} - \frac{1}{2n}\right) + \frac{1}{2}(\sigma_1^2 n^2$$

$$+\sigma_2^2 n^4)\left(-\frac{1}{4n\sqrt{n}}+\frac{1}{2n^2}\right)+\left(\beta n-\gamma n^2-\alpha C_o n\right)$$

Omitting some of the negative terms, for any $x \in D$ we have

$$\begin{aligned} LV(x) &\le \lambda_1^2 C_e + \frac{\alpha C_o n}{4} + \frac{\alpha C_o n}{4} + \frac{\alpha C_o}{2} - \alpha C_o n + f(n), \\ &\le \lambda_1^2 C_e + \frac{\alpha C_o}{2} + f(n), \end{aligned}$$

where

$$f(n) = -\frac{\sigma_2^2 n^2\sqrt{n}}{8} + \frac{\alpha}{4\lambda_1^2}\eta_2^2 n + \frac{\beta\sqrt{n}}{2} + \frac{\gamma n}{2} + \frac{\sigma_1^2}{4} + \frac{\sigma_2^2 n^2}{4} + \beta n$$

Since f is continuous on $(0,\infty)$ and $\lim_{n\to\infty} f(n) = -\infty$ it can easily be shown that $LV(x) \le CV(x) + C$, where the constant $C > 0$ and $x \in D$.

Let's define $\tilde{V}(t,x) = e^{-Ct}(1+V(x))$. We have

$$L\tilde{V}(x,t) = -Ce^{-Ct}(1+V(x)) + e^{-Ct}LV(x) \le 0.$$

Using Itô's formula (10) for $\tilde{V}$ and taking expectation we have for any $m \ge m_1$:

$$\begin{aligned} E\left[\tilde{V}(x(t\wedge\tau_m), t\wedge\tau_m)\right] &= \tilde{V}(x(0),0) + E\left[\int_0^{t\wedge\tau_m} L\tilde{V}(x(u\wedge\tau_m), u\wedge\tau_m)du\right] \\ &\le \tilde{V}(x(0),0). \end{aligned}$$

Notice that for any $\omega \in \Theta_m$, $m \ge m_1$ we have $V(x(\tau_m,\omega)) \ge b_m = \min\{V(y) | y = (y_1,y_2,y_3)'$ has the components y_1 or y_3 equal with m^{-1} or m, or $y_2 = m\}$. Hence

$$E\left[V(x(\tau_m,\omega))I_{\Theta_m}(\omega)\right] \ge P(\Theta_m)b_m \ge \epsilon b_m \to \infty$$

as $m \to \infty$. But $E\left[V(x(\tau_m,\omega))I_{\Theta_m}(\omega)\right] \le e^{CT}\tilde{V}(x(0),0)) < \infty$, for any $m \ge m_1$. Thus we have proved by contradiction that $\tau_\infty = \infty$. □

Here we focus on the case when $n(0) > 0$, we have only an acute dose of toxicant $C_e(0) > 0$, $C_o(0) = 0$, and the external concentration of toxicant $C_e(t)$ is never larger than $C_e(0)$. For this we have to impose some conditions on the parameters. Similarly with the deterministic case we obtain the following results (for completion the proofs are included in Appendix A and Appendix B).

Lemma 2.2. *If $\eta_1^2\eta_2^2 - \lambda_1^2\lambda_2^2 > 0$, $n(0) > 0$, $C_e(0) > 0$, and $C_o(0) = 0$ then almost surely we have $0 < C_e(t) \le C_e(0)$, $0 \le C_o(t) \le \frac{\lambda_1^2 C_e(0)}{\eta_1^2}$ for all $t \ge 0$.*

Theorem 2.3. *If $\eta_1^2\eta_2^2 - \lambda_1^2\lambda_2^2 > 0$, $n(0) > 0$, $C_e(0) > 0$, and $C_o(0) = 0$, then almost surely $\lim_{t\to\infty} C_o(t)$ and $\lim_{t\to\infty} C_e(t)$ exist and*

$$\lim_{t\to\infty} C_o(t) = \frac{\lambda_1^2}{\eta_1^2}\lim_{t\to\infty} C_e(t).$$

3. **Survival analysis.** In this section we assume that $n(0) > 0, C_o(0) = 0, C_e(0) > 0$. We have the following definitions ([16]).

Definition 3.1. The population $n(t)$ is said to go to extinction a.s. if $\lim_{t\to\infty} n(t) = 0$ a.s..

Definition 3.2. The population $n(t)$ is weakly persistent a.s. if $\limsup_{t\to\infty} n(t) > 0$ a.s..

Definition 3.3. The population $n(t)$ is said to be strongly persistent a.s. if $\liminf_{t\to\infty} n(t) > 0$ a.s..

Definition 3.4. The population $n(t)$ is said to be stochastically permanent if for any $\epsilon > 0$ there exist the positive constants $c_1(\epsilon)$ and $c_2(\epsilon)$ such that $\liminf_{t\to\infty} P\Big(n(t) \leq c_1(\epsilon)\Big) \geq 1-\epsilon$ and $\liminf_{t\to\infty} P\left(n(t) \geq c_2(\epsilon)\right) \geq 1-\epsilon$.

Theorem 3.5. *a. If* $\beta - \frac{\sigma_1^2}{2} - \alpha \liminf_{t\to\infty} \frac{\int_0^t C_o(s)ds}{t} < 0$ *a.s. then the population* $n(t)$ *goes exponentially to extinction a.s..*
b. If $\beta - \frac{\sigma_1^2}{2} - \alpha \liminf_{t\to\infty} \frac{\int_0^t C_o(s)ds}{t} > 0$ *a.s. then the population* $n(t)$ *is weakly persistent a.s.*

Proof. The proof is similar with the proof of Theorem 6 in [16]. We start with some preliminary results. By Itô's formula in (5) we have

$$d\ln n(t) = \left(\beta - \gamma n(t) - \alpha C_o(t) - \frac{\sigma_1^2 + \sigma_2^2 n^2(t)}{2}\right) dt + \sigma_1 dB_1(t) - \sigma_2 n(t) dB_2(t).$$

This means that we have

$$\begin{aligned} \ln n(t) - \ln n(0) = &\left(\beta - \frac{\sigma_1^2}{2}\right) t - \gamma \int_0^t n(s)ds - \alpha \int_0^t C_o(s)ds \\ &- \frac{\sigma_2^2}{2} \int_0^t n^2(s)ds + \sigma_1 B_1(t) - \sigma_2 \int_0^t n(s) dB_2(s), \end{aligned} \tag{12}$$

Notice that the quadratic variation [17] of $M(t) = -\sigma_2 \int_0^t n(s) dB_2(s)$ is

$$\langle M(t), M(t)\rangle = \sigma_2^2 \int_0^t n^2(s)ds.$$

Now we do the proof for part a. Using the exponential martingale inequality (Theorem 7.4 [17]) and Borel-Cantelli lemma ([22], pp. 102), and proceeding as in the proof of Theorem 6 in [16] we can show that for almost all ω there exists a random integer $n_0 = n_0(\omega)$ such that for all $n \geq n_0$ we have

$$\sup_{0\leq t\leq n} \left(M(t) - \frac{1}{2}\langle M(t), M(t)\rangle\right) \leq 2\ln n.$$

Hence, for all $n \geq n_0$ and all $0 \leq t \leq n$ we have

$$-\frac{\sigma_2^2}{2} \int_0^t n^2(s)ds - \sigma_2 \int_0^t n(s) dB_2(s) \leq 2\ln n \text{ a.s..}$$

Substituting the above inequality in (12) we get

$$\frac{\ln n(t) - \ln n(0)}{t} \leq \beta - \frac{\sigma_1^2}{2} - \alpha \frac{\int_0^t C_o(s)ds}{t} + \sigma_1 \frac{B_1(t)}{t} + 2\frac{\ln n}{n-1} \text{ a.s.},$$

for all $n \geq n_0$, and any $0 < n-1 \leq t \leq n$. Since $\lim_{t\to\infty} \frac{B(t)}{t} = 0$ a.s. (see Theorem 3.4 in [17]) we get

$$\limsup_{t\to\infty} \frac{\ln n(t)}{t} \leq \beta - \frac{\sigma_1^2}{2} - \alpha \liminf_{t\to\infty} \frac{\int_0^t C_o(s)ds}{t} < 0 \text{ a.s..}$$

Next we prove part b. Suppose that $P(\Omega) > 0$ where $\Omega = \{\limsup_{t\to\infty} n(t) \le 0\}$. From Theorem 2.1 we know that $n(t) > 0$, $t \ge 0$ a.s., so $P(\Omega_1) > 0$ where $\Omega_1 = \{\lim_{t\to\infty} n(t) = 0\}$, and $\Omega_1 \subseteq \Omega$. Thus, for any $\omega \in \Omega_1$ we have

$$\limsup_{t\to\infty} \frac{\ln n(t,\omega)}{t} \le 0 \tag{13}$$

Moreover, from the law of large numbers for local martingales (Theorem 3.4 in [17]) there exists a set $\Omega_2 \subseteq \Omega_1$ with $P(\Omega_2) > 0$ such that for any $\omega \in \Omega_2$ we have

$$\lim_{t\to\infty} \frac{M(t,\omega)}{t} = \lim_{t\to\infty} \frac{B_1(t,\omega)}{t} = 0.$$

From (12) we get:

$$\frac{\ln(n(t))}{t} = \frac{\ln(n(0))}{t} + \left(\beta - \frac{\sigma_1^2}{2}\right) - \alpha\frac{\int_0^t C_o(s)ds}{t} - \frac{\int_0^t \left(\gamma n(s) + \frac{\sigma_2^2}{2} n^2(s)\right) ds}{t} + \sigma_1 \frac{B_1(t)}{t} + \frac{M(t,\omega)}{t}$$

Hence, for any $\omega \in \Omega_2$ we have

$$\limsup_{t\to\infty} \frac{\ln n(t,\omega)}{t} = \left(\beta - \frac{\sigma_1^2}{2}\right) - \alpha \liminf_{t\to\infty} \frac{\int_0^t C_o(s,\omega)ds}{t}$$

Since we know that $\beta - \frac{\sigma_1^2}{2} - \alpha \liminf_{t\to\infty} \frac{\int_0^t C_o(s,\omega)ds}{t} > 0$ a.s., we have a contradiction with (13), so $\limsup_{t\to\infty} n(t) > 0$ a.s. □

We have the following result regarding the expectation of $n(t)$.

Lemma 3.6. *There exists a constant $K_1 > 0$ such that $\sup_{t\ge 0} E[n(t)] \le K_1$.*

Proof. Using Itô's formula in (5) we get:

$$\begin{aligned} d(e^t n(t)) &= n(t)e^t\Big(1 + \beta - \alpha C_o(t) - \gamma n(t)\Big)dt + \sigma_1 n(t)e^t dB_1(t) - \sigma_2 n^2(t) \\ e^t dB_2(t) &\le n(t)e^t\left(1 + \beta - \gamma n(t)\right)dt + \sigma_1 n(t)e^t dB_1(t) - \sigma_2 n^2(t)e^t dB_2(t) \\ &\le e^t \frac{(1+\beta)^2}{4\gamma} dt + \sigma_1 n(t)e^t dB_1(t) - \sigma_2 n^2(t)e^t dB_2(t) \end{aligned} \tag{14}$$

Let

$$\eta_m = \inf\{t \ge 0 : n(t) \notin (1/m, m)\}, \tag{15}$$

for any $m > m_0$, where $m_0 > 0$ was defined in the proof of Theorem 2.1. Obviously $\eta_m \ge \tau_m$, $m > m_0$, where τ_m is given in (11). In Theorem 2.1 we have proved that $\lim_{m\to\infty} \tau_m = \infty$ a.s., so we also have $\lim_{m\to\infty} \eta_m = \infty$ a.s.. Taking expectation in (14) we get:

$$E\left[e^{t\wedge\tau_m} n(t\wedge\tau_m)\right] \le n(0) + E\left[\int_0^{t\wedge\tau_m} e^s \frac{(1+\beta)^2}{4\gamma} ds\right] \le n(0) + \frac{(1+\beta)^2}{4\gamma}(e^t - 1).$$

Letting $m \to \infty$ we get

$$E\left[n(t)\right] \le \frac{n(0)}{e^t} + \frac{(1+\beta)^2}{4\gamma}(1 - e^{-t}).$$

Thus, there exists a constant $K_1 > 0$ such that $\sup_{t\ge 0} E[n(t)] \le K_1$. □

Corollary 1. *For any $\epsilon > 0$ there exists $c_1(\epsilon)$ such that* $\liminf_{t\to\infty} \mathbb{P}(n(t) \leq c_1(\epsilon)) \geq 1-\epsilon$.

Proof. For any $\epsilon > 0$, set $c_1(\epsilon) = K_1/\epsilon$, where the constant $K_1 > 0$ is given in the previous lemma. From the Markov's inequality [22] we obtain

$$P\left(n(t) > c_1(\epsilon)\right) \leq \frac{E[n(t)]}{c_1(\epsilon)}.$$

Hence, from Lemma 3.6 we get

$$\limsup_{t\to\infty} P\left(n(t) > c_1(\epsilon)\right) \leq \limsup_{t\to\infty} \frac{E[n(t)]}{c_1(\epsilon)} \leq \epsilon.$$

□

Theorem 3.7. *If $\eta_1^2\eta_2^2 - \lambda_1^2\lambda_2^2 > 0$ and $\beta - \sigma_1^2 - \alpha\frac{\lambda_1^2 C_e(0)}{\eta_1^2} > 0$, then the cell population is stochastically permanent.*

Proof. First we show that $\limsup_{t\to\infty} E[1/n(t)] \leq M_2$, where M_2 is a positive constant.

By Itô's formula in (5) we get for any real constant c:

$$d\left(\frac{e^{ct}}{n(t)}\right) = e^{ct}\left(\frac{1}{n(t)}\left(c - \beta + \sigma_1^2 + \alpha C_o(t)\right) + \gamma + \sigma_2^2 n(t)\right)dt$$
$$- \frac{\sigma_1 e^{ct}}{n(t)}dB_1(t) + \sigma_2 e^{ct}dB_2(t)$$

Since $\eta_1^2\eta_2^2 - \lambda_1^2\lambda_2^2 > 0$, from Lemma 2.2 we know that $0 \leq C_o(t) \leq \frac{\lambda_1^2 C_e(0)}{\eta_1^2}$ for all $t \geq 0$ a.s..We choose any $0 < c < \beta - \sigma_1^2 - \alpha\frac{\lambda_1^2 C_e(0)}{\eta_1^2}$, and we get:

$$d\left(\frac{e^{ct}}{n(t)}\right) \leq e^{ct}\left(\gamma + \sigma_2^2 n(t)\right)dt - \frac{\sigma_1 e^{ct}}{n(t)}dB_1(t) + \sigma_2 e^{ct}dB_2(t) \tag{16}$$

Taking expectation in (16) and using Lemma 3.6 we get:

$$E\left[\frac{e^{c(t\wedge\eta_m)}}{n(t\wedge\eta_m)}\right] \leq \frac{1}{n(0)} + E\left[\int_0^{t\wedge\eta_m} e^{cs}\left(\gamma + \sigma_2^2 n(s)\right)ds\right]$$
$$\leq \frac{1}{n(0)} + \left(\gamma + \sigma_2^2 K_1\right)\frac{(e^{ct}-1)}{c},$$

where η_m was defined in (15). Letting $m \to \infty$ we get

$$E\left[\frac{1}{n(t)}\right] \leq \frac{1}{n(0)e^{ct}} + \frac{\left(\gamma + \sigma_2^2 K_1\right)}{c}(1 - e^{-ct}),$$

so $\limsup_{t\to\infty} E[1/n(t)] \leq M_2$, where $0 < M_2 = (\gamma + \sigma_2^2 K_1)/c$.

Next we show that for any $\epsilon > 0$ there exists $c_2(\epsilon)$ such that $\liminf_{t\to\infty} \mathbb{P}(n(t) \geq c_2(\epsilon)) \geq 1-\epsilon$.

For any $\epsilon > 0$ set $c_2(\epsilon) = \epsilon/M_2$. From Markov's inequality we have

$$\mathbb{P}(n(t) < c_2(\epsilon)) = \mathbb{P}\left(\frac{1}{n(t)} > \frac{1}{c_2(\epsilon)}\right) \leq c_2(\epsilon)E\left[\frac{1}{n(t)}\right]$$

Hence

$$\limsup_{t\to\infty} \mathbb{P}\left(n(t) < c_2(\epsilon)\right) \leq \epsilon \limsup_{n\to\infty} E[1/n(t)]/M_2 \leq \epsilon.$$

Thus $\liminf_{t\to\infty} \mathbb{P}(n(t) \geq c_2(\epsilon)) \geq 1-\epsilon$, and this inequality and Corollary 1 implies that $n(t)$ is stochastically permanent. □

4. **Stationary distributions.** The deterministic system (1)-(3) has a maximum capacity equilibrium point $(K,0,0)'$, where K is the capacity volume ([1]). For the stochastic system (5)-(7), $(K,0,0)'$ is not a fixed point, and, when the cell population is persistent, we no longer have $\lim_{t\to\infty} n(t) = K$. In this section we study the asymptotic behavior of $n(t)$ when $\lim_{t\to\infty} C_o(t) = 0$ a.s..

For stochastic differential equations, invariant and stationary distributions play the same role as fixed points for deterministic differential equations. In general, let $X(t)$ be the temporally homogeneous Markov process in $E \subseteq \mathbb{R}^l$ representing the solution of the stochastic differential equation

$$dX(t) = b(X(t))dt + \sum_{r=1}^{d} \sigma_r(X(t))dB_r(t), \tag{17}$$

where $B_r(t)$, $r = 1,\ldots,d$ are standard Brownian motions. We define the operator L associated with equation (17):

$$L = \sum_{i=1}^{l} b_i(x)\frac{\partial}{\partial x_i} + \frac{1}{2}\sum_{i,j=1}^{l} A_{i,j}(x)\frac{\partial^2}{\partial x_i \partial x_j}, \quad A_{i,j}(x) = \sum_{r=1}^{d} \sigma_{r,i}(x)\sigma_{r,j}(x).$$

Let $P(t,x,\cdot)$ denote the probability measure induced by $X(t)$ with initial value $X(0) = x \in E$: $P(t,x,A) = P(X(t) \in A | X(0) = x)$, $A \in \mathcal{B}(E)$, where $\mathcal{B}(E)$ is the $\sigma-$algebra of all the Borel sets $A \subseteq E$.

Definition 4.1. A stationary distribution [6] for $X(t)$ is a probability measure μ for which we have

$$\int_E P(t,x,A)\mu(dx) = \mu(A), \text{ for any } t \geq 0, \text{ and any } A \in \mathcal{B}(E).$$

Definition 4.2. The Markov process $X(t)$ is stable in distribution if the transition distribution $P(t,x,\cdot)$ converges weakly to some probability measure $\mu(\cdot)$ for any $x \in E$.

It is clear that the stability in distribution implies the existence of a unique stationary measure, but the converse is not always true [2]. We have the following result (see lemma 2.2 in [29] and the references therein).

Lemma 4.3. *Suppose that there exists a bounded domain $U \subseteq E$ with regular boundary, and a non-negative C^2-function V such that $A(x) = (A_{i,j}(x))_{1\leq i,j\leq l}$ is uniformly elliptical in U and for any $x \in E \setminus U$ we have $LV(x) \leq -C$, for some $C > 0$. Then the Markov process $X(t)$ has a unique stationary distribution $\mu(\cdot)$ with density in E such that for any Borel set $B \subseteq E$*

$$\lim_{t\to\infty} P(t,x,B) = \mu(B)$$
$$P_x\left\{\lim_{T\to\infty}\frac{1}{T}\int_0^T f(X(t))dt = \int_E f(x)\mu(dx)\right\} = 1,$$

for all $x \in E$ and f being a function integrable with respect to the probability measure μ.

We now study the stochastic system (5)-(7) when $\lim_{t\to\infty} C_o(t) = 0$ a.s.. We introduce two new stochastic process $X(t)$ and $X_\epsilon(t)$ which are defined by the initial conditions $X(0) = X_\epsilon(0) = n(0) \in \mathbb{R}_+^*$ and the stochastic differential equations

$$dX(t) = \left(\beta X(t) - \gamma X^2(t)\right) dt + \sigma_1 X(t) dB_1(t) - \sigma_2 X^2(t) dB_2(t), \tag{18}$$

$$dX_\epsilon(t) = \left(\beta X_\epsilon(t) - \gamma X_\epsilon^2(t) - \alpha\epsilon X_\epsilon(t)\right) dt + \sigma_1 X_\epsilon(t) dB_1(t) - \sigma_2 X_\epsilon^2(t) dB_2(t), \tag{19}$$

Lemma 4.4. *a. For any given initial value $X(0) > 0$, the equation (18) has a unique global solution $X(t)$ such that $\mathbb{P}\{X(t) > 0, t \geq 0\} = 1$.*
b. For any $\epsilon > 0$ and any given initial value $X_\epsilon(0) > 0$, the equation (19) has a unique global solution $X_\epsilon(t)$ such that $\mathbb{P}\{X_\epsilon(t) > 0, t \geq 0\} = 1$.
c. There exists a constant $C_1 > 0$ such that $\sup_{t\geq 0} E[X(t)] \leq C_1$ and, for any $\epsilon > 0$, $\sup_{t\geq 0} E[X_\epsilon(t)] \leq C_1$.

Proof. The proofs for a. and b. can be done similarly with the proof of Theorem 2.1, using the C^2-function $V : \mathbb{R}_+^* \to \mathbb{R}_+$, $V(x) = \sqrt{x} - \log\sqrt{x} - 1$. The proof of c. is analogous with the proof of Lemma 3.6. □

Let $P_X(t, x, \cdot)$ denote the probability measure induced by $X(t)$ with initial value $X(0) = x \in \mathbb{R}_+^*$, $t \geq 0$. In the following theorem, using Lemma 4.3, we show that the Markov process $X(t)$ is stable in distribution.

Theorem 4.5. *If $\sigma_1^2 < 2\beta$ then the Markov process $X(t)$ has a unique stationary distribution $\mu_1(\cdot)$ with density in $\mathbb{R}_+^*$ such that for any Borel set $B \subseteq \mathbb{R}_+^*$*

$$\lim_{t\to\infty} P_X(t, x, B) = \mu_1(B)$$

$$P_x\left\{\lim_{T\to\infty} \frac{1}{T}\int_0^T f(X(t))dt = \int_E f(x)\mu_1(dx)\right\} = 1,$$

for all $x \in \mathbb{R}_+^*$ and f being a function integrable with respect to the probability measure μ_1.

Proof. We consider the C^2-function $V : \mathbb{R}_+^* \to \mathbb{R}_+$, $V(x) = \sqrt{x} - \log\sqrt{x} - 1$. Simple calculations show that

$$LV(x) = -\frac{\sigma_2^2}{8}x^{5/2} + \frac{\sigma_2^2}{4}x^2 - \frac{\gamma}{2}x^{3/2} + \frac{\gamma}{2}x + \left(\frac{\beta}{2} - \frac{\sigma_1^2}{8}\right)x^{1/2} + \left(\frac{\sigma_1^2}{4} - \frac{\beta}{2}\right).$$

Since $LV(\cdot)$ is a continuous function on $\mathbb{R}_+^*$ and $LV(0) = \frac{\sigma_1^2}{4} - \frac{\beta}{2} < 0$, there exists a constant $A_1 > 0$ such that $LV(x) < -C_1$ for any $x \in (0, A_1]$, for some $C_1 > 0$. We also have $\lim_{x\to\infty} LV(x) = -\infty$. Thus, there exists a constant $A_2 > A_1 > 0$ such that $LV(x) < -C_2$ for any $x \in [A_2, \infty)$, for some $C_2 > 0$.

Let $U = (A_1, A_2) \subset \mathbb{R}_+^*$. Then U is a bounded domain, and $LV(x) < -C$ for any $x \in \mathbb{R}_+^* \setminus U$, where $C > 0$ is the minimum between C_1 and C_2. Notice that $A(x) = \sigma_1^2 x^2 + \sigma_2^2 x^4$ is uniformly elliptical on U, so the assumptions of Lemma 4.3 are met. Therefore, the Markov process $X(t)$ has a unique stationary distribution $\mu_1(\cdot)$ and it is ergodic. □

Let define the processes $N(t) = 1/n(t)$ a.s., $Y(t) = 1/X(t)$ a.s., $Y_\epsilon(t) = 1/X_\epsilon(t)$ a.s., $t \geq 0$, with $N(0) = Y(0) = Y_\epsilon(0) = 1/n(0) > 0$. Then from Lemma 4.4 and

Theorem 2.1 we have $\mathbb{P}\{N(t) > 0, Y(t) > 0, Y_\epsilon(t) > 0, t \geq 0\} = 1$. Applying Itô's formula in equations (5), (18) and (19) we get

$$dN(t) = \left(N(t)(\sigma_1^2 - \beta) + \alpha N(t)C_o(t) + \gamma + \frac{\sigma_2^2}{N(t)}\right)dt - \sigma_1 N(t)dB_1(t) + \sigma_2 dB_2(t) \text{ a.s.}, \tag{20}$$

$$dY(t) = \left(Y(t)(\sigma_1^2 - \beta) + \gamma + \frac{\sigma_2^2}{Y(t)}\right)dt - \sigma_1 Y(t)dB_1(t) + \sigma_2 dB_2(t) \text{ a.s.}, \tag{21}$$

$$dY_\epsilon(t) = \left(Y_\epsilon(t)(\sigma_1^2 - \beta + \alpha\epsilon) + \gamma + \frac{\sigma_2^2}{Y_\epsilon(t)}\right)dt - \sigma_1 Y_\epsilon(t)dB_1(t) + \sigma_2 dB_2(t) \text{ a.s..} \tag{22}$$

From the proof of Theorem 3.7 we know that if $\eta_1^2\eta_2^2 - \lambda_1^2\lambda_2^2 > 0$ and $\beta - \sigma_1^2 - \alpha\frac{\lambda_1^2 C_e(0)}{\eta_1^2} > 0$ then there exist a constant $K_2 > 0$ such that $\sup_{t\geq 0} E[N(t)] \leq K_2$. We have similar results for the processes $Y(t)$ and $Y_\epsilon(t)$.

Lemma 4.6. *If $\sigma_1^2 < \beta$ then $\sup_{t\geq 0} E[Y(t)] < \infty$ and $\sup_{t\geq 0} E[Y_\epsilon(t)] < \infty$, for any $0 < \epsilon < \frac{\beta - \sigma_1^2}{\alpha}$.*

Proof. The proof is based on the results in Lemma 4.4 and it is similar with the first part of the proof of Theorem 3.7. For completeness we have included it in Appendix C. □

We use the processes $N(t)$, $Y(t)$, $Y_\epsilon(t)$ to prove the main result of this section.

Theorem 4.7. *Let $(n(t), C_o(t), C_e(t))$ be the solution of the system (5)-(7) with any initial value $(n(0), C_o(0), C_e(0))' \in D = \mathbb{R}_+^* \times \mathbb{R}_+ \times \mathbb{R}_+^*$. If $\lim_{t\to\infty} C_o(t) = 0$ a.s. and $\beta - \sigma_1^2 > 0$ then $n(t) \underset{t\to\infty}{\overset{w}{\to}} \mu_1$, where $\overset{w}{\to}$ means convergence in distribution (weak convergence [22]) and μ_1 is the probability measure on $\mathbb{R}_+^*$ given in Theorem 4.5.*

Proof. We follow the same idea as in the proof of Theorem 2.4 in [28]. From theorem 4.5 we know that $X(t) \underset{t\to\infty}{\overset{w}{\to}} \mu_1$, where μ_1 is a probability measure on $\mathbb{R}_+^*$. By the Continuous Mapping Theorem [22], $Y(t) = 1/X(t)$ also converges weakly to a probability measure ν_1 on $\mathbb{R}_+^*$, the reciprocal of μ_1. We will show that $N(t) = 1/n(t) \underset{t\to\infty}{\overset{w}{\to}} \nu_1$.

Firstly, let's notice that

$$Y(t) \leq N(t) \text{ and } Y(t) \leq Y_\epsilon(t) \text{ for any } t \geq 0 \text{ a.s..} \tag{23}$$

Indeed, if we denote $\xi(t) = N(t) - Y(t)$, then $\xi(0) = 0$ and from equations (20) and (21) we get

$$d\xi(t) = \left(\xi(t)\left(\sigma_1^2 - \beta - \frac{\sigma_2^2}{N(t)Y(t)}\right) + \alpha N(t)C_o(t)\right)dt - \sigma_1\xi(t)dB_1(t) \text{ a.s..}$$

The solution of the previous linear equation is given by (see chapter 3, [17])

$$\xi(t) = \Phi(t)\int_0^t \frac{\alpha N(s)C_o(s)}{\Phi(s)}ds \text{ a.s.},$$

where

$$\Phi(t) = \exp\left\{-t\left(\beta - \frac{\sigma_1^2}{2}\right) - \int_0^t \frac{\sigma_2^2}{N(s)Y(s)}ds - \sigma_1 B_1(t)\right\} > 0$$

Obviously $\xi(t) \geq 0$, $t \geq 0$, a.s., and this means that we have $Y(t) \leq N(t)$ for any $t \geq 0$ a.s. Similarly, using equations (21) and (22), we can show that $Y(t) \leq Y_\epsilon(t)$ for any $t \geq 0$ a.s..

Secondly we show that for any $0 < \epsilon < \frac{2\beta - \sigma_1^2}{2\alpha}$

$$\liminf_{t\to\infty}(Y_\epsilon(t) - N(t)) \geq 0 \text{ a.s..} \tag{24}$$

From equations (20) and (22) we get

$$d(Y_\epsilon(t) - N(t)) = \left((Y_\epsilon(t) - N(t))\left(\sigma_1^2 + \alpha\epsilon - \beta - \frac{\sigma_2^2}{N(t)Y_\epsilon(t)}\right)\right.$$
$$\left. + \alpha N(t)(\epsilon - C_o(t))\right)dt - \sigma_1(Y_\epsilon(t) - N(t))dB_1(t) \text{ a.s..}$$

The solution of the linear equation is given by

$$Y_\epsilon(t) - N(t) = \Phi_1(t)\int_0^t \frac{\alpha N(s)\,(\epsilon - C_o(s))}{\Phi_1(s)}ds \text{ a.s.,}$$

where

$$0 < \Phi_1(t) = \exp\left\{-t\left(\beta - \alpha\epsilon - \frac{\sigma_1^2}{2}\right) - \int_0^t \frac{\sigma_2^2}{N(s)Y_\epsilon(s)}ds - \sigma_1 B_1(t)\right\}$$
$$\leq \exp\left\{-t\left(\beta - \alpha\epsilon - \frac{\sigma_1^2}{2} + \sigma_1\frac{B_1(t)}{t}\right)\right\}$$

Since $\lim_{t\to\infty} B_1(t)/t = 0$ a.s., for any $0 < \epsilon < \frac{2\beta - \sigma_1^2}{2\alpha}$ we get $\lim_{t\to\infty}\Phi_1(t) = 0$ a.s.. Moreover, because $\lim_{t\to\infty} C_o(t) = 0$ a.s., for almost any ω there exist $0 < T = T(\omega)$ such that $\epsilon - C_o(t,\omega) > 0$ for any $t > T(\omega)$. Thus for almost any ω and any $t > T$,

$$Y_\epsilon(t) - N(t) = \Phi_1(t)\left(\int_0^T \frac{\alpha N(s)\,(\epsilon - C_o(s))}{\Phi_1(s)}ds + \int_T^t \frac{\alpha N(s)\,(\epsilon - C_o(s))}{\Phi_1(s)}ds\right)$$
$$\geq \Phi_1(t)\int_0^T \frac{\alpha N(s)\,(\epsilon - C_o(s))}{\Phi_1(s)}ds$$

Therefore for any $0 < \epsilon < \frac{2\beta - \sigma_1^2}{2\alpha}$ we have

$$\liminf_{t\to\infty}(Y_\epsilon(t) - N(t)) \geq \lim_{t\to\infty}\Phi_1(t)\int_0^T \frac{\alpha N(s)\,(\epsilon - C_o(s))}{\Phi_1(s)}ds = 0 \quad a.s..$$

Thirdly we prove that

$$\lim_{\epsilon\to 0}\lim_{t\to\infty} E[Y_\epsilon(t) - Y(t)] = 0. \tag{25}$$

We know from (23) that $Y_\epsilon(t) - Y(t) \geq 0$, $t \geq 0$ a.s. Using equations (21) and (22) we get

$$d(Y_\epsilon(t) - Y(t)) = \left((Y_\epsilon(t) - Y(t))\left(\sigma_1^2 + \alpha\epsilon - \beta - \frac{\sigma_2^2}{Y(t)Y_\epsilon(t)}\right)\right.$$

$$+\alpha\epsilon Y(t)\Big)dt-\sigma_1(Y_\epsilon(t)-Y(t))dB_1(t)$$
$$\leq\Big((Y_\epsilon(t)-Y(t))\left(\sigma_1^2+\alpha\epsilon-\beta\right)+\alpha\epsilon Y(t)\Big)dt-\sigma_1(Y_\epsilon(t)-Y(t))dB_1(t)\text{ a.s..}$$

From Lemma 4.6 we know that $\sup_{t\geq 0}E[Y(t)]<\infty$, so taking expectations in the previous inequality we have

$$E[Y_\epsilon(t)-Y(t)]\leq\int_0^t E[Y_\epsilon(s)-Y(s)]\left(\sigma_1^2+\alpha\epsilon-\beta\right)+\alpha\epsilon E[Y(s)]ds$$
$$\leq\int_0^t E[Y_\epsilon(s)-Y(s)]\left(\sigma_1^2+\alpha\epsilon-\beta\right)ds+t\alpha\epsilon\sup_{t\geq 0}E[Y(t)]\text{ a.s..}$$

For any $0<\epsilon<(\beta-\sigma_1^2)/\alpha$, by the comparison theorem (see theorem 1.4.1 in [14]) we get

$$0\leq E[Y_\epsilon(t)-Y(t)]\leq\frac{\alpha\epsilon\sup_{t\geq 0}E[Y(t)]}{\beta-\sigma_1^2-\alpha\epsilon}\left(1-\exp(-t(\beta-\sigma_1^2-\alpha\epsilon))\right)$$

Taking limits in the previous inequality we get equation (25).

Finally, using (23), (24), and (25) we obtain that $\lim_{t\to\infty}(N(t)-Y(t))=0$, in probability. But it has been shown that $Y(t)\xrightarrow[t\to\infty]{w}\nu_1$, where ν_1 is a probability measure on $\mathbb{R}_+^*$. Thus, from Slutsky's theorem [22], $N(t)\xrightarrow[t\to\infty]{w}\nu_1$, and, by the Continuous Mapping Theorem, $n(t)=1/N(t)\xrightarrow[t\to\infty]{w}\mu_1$. □

Corollary 2. *Let $(n(t),C_o(t),C_e(t))$ be the solution of the system (5)-(7) with any initial value $(n(0),C_o(0),C_e(0))'\in D$, and such that $\lim_{t\to\infty}C_o(t)=0$ a.s..*

a. If $\sigma_1=0$ then $n(t)\xrightarrow[t\to\infty]{w}\mu_1$ where μ_1 is the probability measure on $\mathbb{R}_+^*$ with density

$$p(x)=\frac{1}{G_1x^4}\exp\left(-\frac{\beta}{\sigma_2^2}\left(\frac{1}{x}-\frac{\gamma}{\beta}\right)^2\right),\quad x>0 \tag{26}$$

$$G_1=\frac{\sigma_2}{2\beta^{5/2}}\left(\Psi\left(\frac{\gamma\sqrt{2\beta}}{\beta\sigma_2}\right)\sqrt{\pi}(\sigma_2^2\beta+2\gamma^2)+\gamma\sigma_2\beta^{1/2}\exp\left(-\frac{\gamma^2}{\sigma_2^2\beta}\right)\right) \tag{27}$$

where $\Psi(x)=\mathbb{P}(Z\leq x)$ is the distribution function for the standard normal distribution $Z\sim N(0,1)$.

b. If $\sigma_1^2<\beta$ and $\sigma_2=0$ then $n(t)\xrightarrow[t\to\infty]{w}\mu_1$ where μ_1 is a gamma distribution with shape parameter $\frac{2(\beta-\sigma_1^2)}{\sigma_1^2}+1$ and scale parameter $\frac{\sigma_1^2}{2\gamma}$.

Proof. We know that $Y(t)\xrightarrow[t\to\infty]{w}\nu_1$, where ν_1 is a probability measure on $\mathbb{R}_+^*$. When $\sigma_1=0$ or $\sigma_2=0$ we can prove the ergodicity of $Y(t)$ directly using Theorem 1.16 in [13].

a. If $\sigma_1=0$ the equation (21) become

$$dY(t)=\left(-Y(t)\beta+\gamma+\frac{\sigma_2^2}{Y(t)}\right)dt+\sigma_2dB_2(t)\text{ a.s.,} \tag{28}$$

Let define

$$q(y) = \exp\left(-\frac{2}{\sigma_2^2}\int_1^y \left(-\beta u + \frac{\sigma_2^2}{u} + \gamma\right) du\right) = \frac{1}{y^2}\exp\left(-\frac{\beta}{\sigma_2^2}\left(1-\frac{\gamma}{\beta}\right)^2\right)$$
$$\exp\left(\frac{\beta}{\sigma_2^2}\left(y-\frac{\gamma}{\beta}\right)^2\right)$$

It can be easily shown that

$$\int_0^1 q(y)dy = \infty, \quad \int_1^\infty q(y)dy = \infty, \quad \int_0^\infty \frac{1}{\sigma_2^2 q(y)}dy = \frac{G_1}{\sigma_2^2}\exp\left(\frac{\beta}{\sigma_2^2}\left(1-\frac{\gamma}{\beta}\right)^2\right),$$

where G_1 is given in (27). So, by Theorem 1.16 in [13], $Y(t)$ is ergodic and with respect to the Lebesgue measure its stationary measure ν_1 has density

$$p_1(x) = \frac{1}{\sigma_2^2 q(x)\int_0^\infty \frac{1}{\sigma_2^2 q(y)}dy} = \frac{x^2\exp\left(-\frac{\beta}{\sigma_2^2}\left(x-\frac{\gamma}{\beta}\right)^2\right)}{G_1}$$

Thus, by Theorem 4.5, $X(t) = 1/Y(t)$ is ergodic and its stationary measure μ_1 is the reciprocal of the measure ν_1, so with respect to the Lebesgue measure has density $p(x) = p_1(1/x)/x^2$ given in equation (26). Notice that we also have

$$\lim_{t\to\infty}\frac{1}{t}\int_0^t X(u)du = \int_0^\infty xp(x)dx = \frac{\sigma_2}{2\beta^{3/2}G_1}\left(\sigma_2\sqrt{\beta}\exp\left(-\frac{\gamma^2}{\sigma_2^2\beta}\right)\right.$$
$$\left. + 2\gamma\sqrt{\pi}\Psi\left(\frac{\gamma\sqrt{2\beta}}{\beta\sigma_2}\right)\right) \text{ a.s..}$$

b. If $\sigma_2 = 0$, then the equation (21) becomes

$$dY(t) = \left(\gamma - Y(t)(\beta-\sigma_1^2)\right)dt - \sigma_1 Y(t)dB_1(t) \text{ a.s..}$$

Proceeding similarly as for a. we can show that ν_1 is the reciprocal gamma distribution with shape parameter $\frac{2(\beta-\sigma_1^2)}{\sigma_1^2}+1$ and scale parameter $\frac{\sigma_1^2}{2\gamma}$ (see also the proof of Theorem 4.5 in [29]). Thus, by Theorem 4.5, $X(t) = 1/Y(t)$ is ergodic and its stationary measure μ_1 is the gamma distribution with shape parameter $\frac{2(\beta-\sigma_1^2)}{\sigma_1^2}+1$ and scale parameter $\frac{\sigma_1^2}{2\gamma}$. Since the mean for this gamma distribution is $\left(\frac{2(\beta-\sigma_1^2)}{\sigma_1^2}+1\right)\frac{\sigma_1^2}{2\gamma}$, we also have

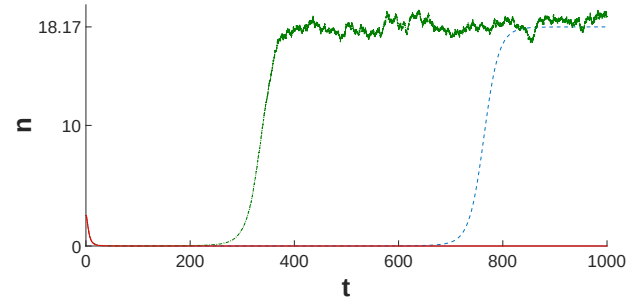
$$\lim_{t\to\infty}\frac{1}{t}\int_0^t X(u)du = \left(\frac{2(\beta-\sigma_1^2)}{\sigma_1^2}+1\right)\frac{\sigma_1^2}{2\gamma} \text{ a.s..}$$

□

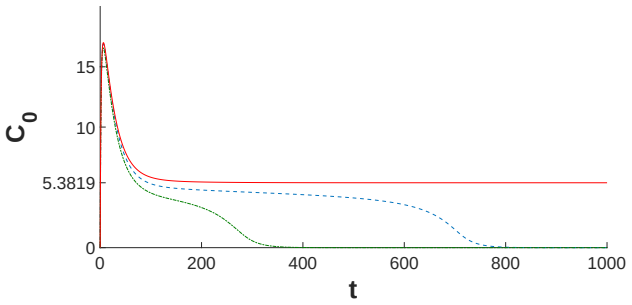
Notice that if $\sigma_1^2 > 2\beta - 2\alpha\liminf_{t\to\infty}\frac{\int_0^t C_o(s)ds}{t}$ a.s. then, according to Theorem 3.5, $\lim_{t\to\infty} n(t) = 0$, so $n(t) \underset{t\to\infty}{\overset{w}{\to}} \delta_0$, where δ_0 is the Dirac distribution centered in 0.

On the other hand, if $\sigma_1^2 < \beta$, $\eta_1^2\eta_2^2 - \lambda_1^2\lambda_2^2 > 0$, and $\liminf_{t\to\infty} n(t) > 0$ a.s., then according to Theorem 4.7 $n(t) \underset{t\to\infty}{\overset{w}{\to}} \mu_1$. Indeed, since $\liminf_{t\to\infty} n(t) > 0$ a.s., then $\int_0^\infty n(t)dt = \infty$ a.s., and from the proof of Theorem 2.3 we know that $\lim_{t\to\infty} C_o(t) = \lim_{t\to\infty} C_e(t) = 0$, so the assumptions of Theorem 4.7 are satisfied.

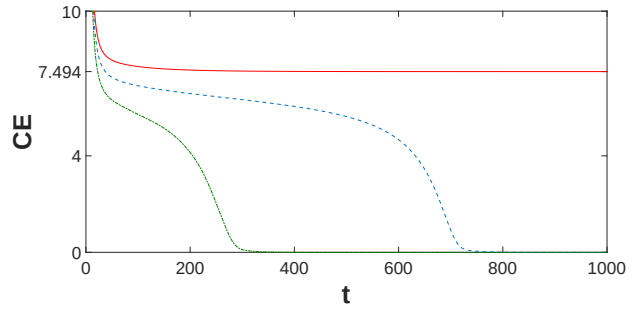
5. **Numerical simulations.** First we illustrate numerically the results obtained in section 3 regarding survival analysis. We consider a cell population exposed to the toxicant monastrol as in the experiments described in [1] . The parameters' values for this toxicant are estimated in [1]: $\beta = 0.074$, $K = 18.17$, $\eta_1 = 0.209$, $\lambda_1 = 0.177$, $\lambda_2 = 0.204$, $\eta_2 = 0.5$, and $\alpha = 0.016$. Notice that for this toxicant we have $\eta_1^2\eta_2^2 - \lambda_1^2\lambda_2^2 > 0$. We solve numerically the system (5)-(7) using an order 2 strong Taylor numerical scheme [12].



(a) Cell index n



(b) Concentration of internal toxicant C_o

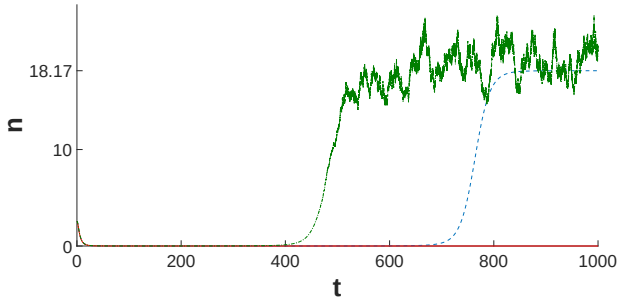


(c) Concentration of toxicant outside the cells C_e

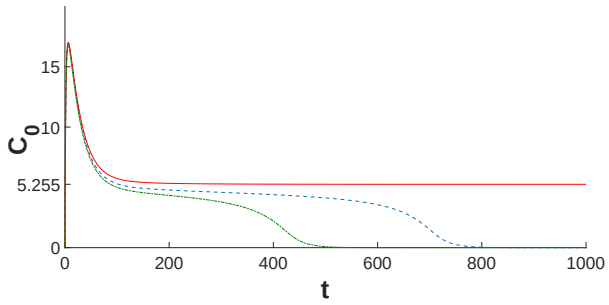
FIGURE 2. Trajectories corresponding to initial values $n(0) = 2.5$, $C_o(0) = 0$, $\sigma_1 = 0.01$, $\sigma_2 = 0$: blue "- -" line deterministic model, $C_e(0) = 380$; red "-" line stochastic model, $C_e(0) = 380$; green "-.-" line stochastic model, $C_e(0) = 375$.

One of the applications of the mathematical model is for finding the threshold value for $C_e(0)$ at which the population becomes extinct. This value depends on the initial value $n(0)$ and for the deterministic model (1)-(3) can be found numerically (see also Fig. 3 in [1]). From Theorem 3.5 we can see that large values of the noise variance σ_1^2 result in population extinction, so we expect that the presence of noise will lower the values of the threshold.

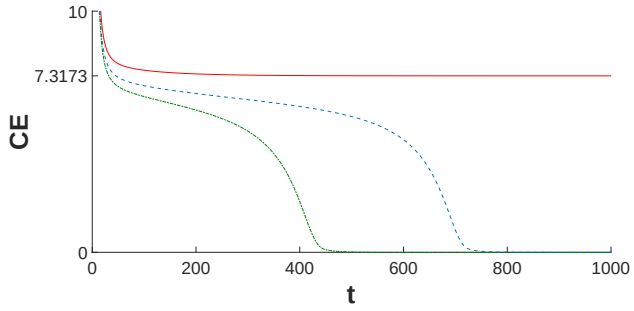
We illustrate this for the model with initial values $n(0) = 2.5$ and $C_o(0) = 0$. In the deterministic case the threshold value where the population goes extinct can be



(a) Cell index n



(b) Concentration of internal toxicant C_o



(c) Concentration of toxicant outside the cells C_e

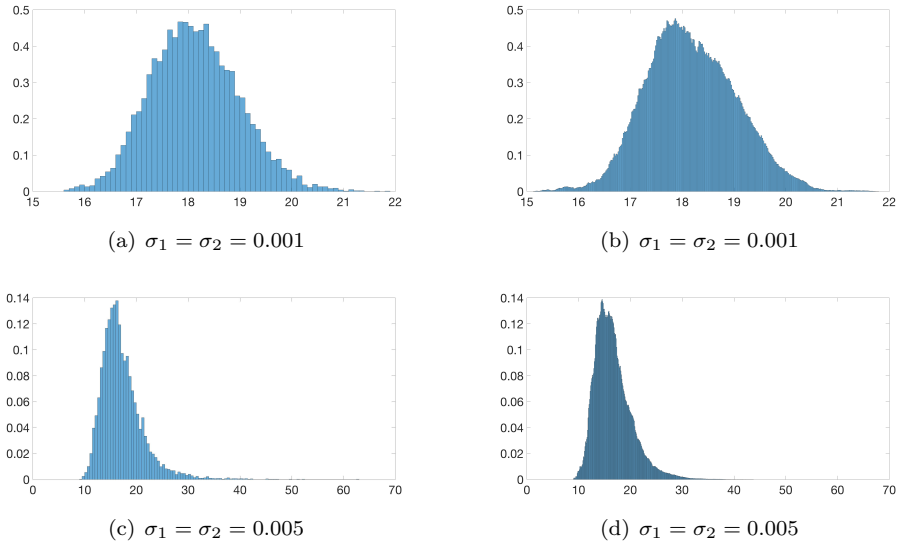
FIGURE 3. Trajectories corresponding to initial values $n(0) = 2.5$, $C_o(0) = 0$, $\sigma_1 = 0$, $\sigma_2 = 0.002$: blue "- -" line deterministic model, $C_e(0) = 380$; red "-" line stochastic model, $C_e(0) = 380$; green "-.-" line stochastic model, $C_e(0) = 379$.

found numerically, and it is approximately $C_e^{det}(0) = 382.2$. We can see in Fig. 2 (a) that for the stochastic model with $\sigma_1 = 0.01$, $\sigma_2 = 0$ and initial value $C_e(0) = 380$ the population goes to extinction, while in the deterministic case ($\sigma_1 = \sigma_2 = 0$) the population is persistent for these initial values. According to Fig. 2 (a), in the stochastic case the threshold value for this simulation is $C_e^{stoch}(0) \in (375, 380)$. Similar results are obtained for the stochastic model with $\sigma_1 = 0$, $\sigma_2 = 0.001$ and are presented in Fig. 3 (a). For this simulation the threshold value in the stochastic case is $C_e^{stoch}(0) \in (379, 380)$.

Notice also that the results displayed in Figs. 2 and 3 agree with the conclusion of Theorem 2.3. For the stochastic model with $C_e(0) = 380$, for the simulations presented in Figs. 2 and 3 we have $\lim_{t\to\infty} n(t,\omega) = 0$ (the trajectories plotted with red plain lines). For $\sigma_1 = 0.01$ and $\sigma_2 = 0$ we can see that $\lim_{t\to\infty} C_o(t,\omega) = 5.3819$ and $\lim_{t\to\infty} C_e(t,\omega) = 7.494$ (the trajectories plotted with red plain lines in Fig. 2 (b), (c)). For $\sigma_1 = 0$ and $\sigma_2 = 0.002$ from Fig. 3 (b), (c) we can notice that $\lim_{t\to\infty} C_o(t,\omega) = 5.255$ and $\lim_{t\to\infty} C_e(t,\omega) = 7.3173$. For both simulation we have $\lim_{t\to\infty} C_o(t) = \frac{\lambda_1^2}{\eta_1^2} \lim_{t\to\infty} C_e(t)$, as given in Theorem 2.3. Moreover, for the stochastic model with $C_e(0) = 375$, $\sigma_1 = 0.01$ and $\sigma_2 = 0$ (the green dot -dashed lines in Fig. 2) and the model with $C_e(0) = 379$, $\sigma_1 = 0$ and $\sigma_2 = 0.002$ (the green dot -dashed lines in Fig. 3), we have

$$\liminf_{t\to\infty} n(t,\omega) > 0, \lim_{t\to\infty} C_o(t,\omega) = \lim_{t\to\infty} C_e(t,\omega) = 0$$

Next we use the same parameters values as stated at the beginning of this section and the initial values $n(0) = 2.5$, $C_o(0) = 0$, $C_e(0) = 1.8$ to illustrate the stability in distribution of the process $n(t)$. For both $\sigma_1 = \sigma_2 = 0.001$ and $\sigma_1 = \sigma_2 = 0.005$ the assumptions of Theorem 4.7 are met. In Figs. 4 (a) and (c) we show



(a) $\sigma_1 = \sigma_2 = 0.001$ (b) $\sigma_1 = \sigma_2 = 0.001$

(c) $\sigma_1 = \sigma_2 = 0.005$ (d) $\sigma_1 = \sigma_2 = 0.005$

FIGURE 4. Histograms of the values of n(t) for the last iteration from 10 000 runs (a) and (c) and for the last 4 000 000 samples out of 5 000 000 sample of a single run (b) and (d).

the histograms of the result of running 10 000 simulations of the path $n(t)$ for a long run of 5 000 0000 iterations, but storing only the last of these $n(t)$ values. For comparison Figs. 4 (b) and (d) show the histograms of the last 4 000 000 samples from a single run of 5 000 000 iterations. For both sets of values for σ_1 and σ_2 the corresponding histograms are similar. Because of this similarity and of the huge number of iterations considered, we may assume that the probability distribution of $n(t)$ has more or less reached the distribution μ_1 given in Theorem 4.7. When $\sigma_2 = 0$ or $\sigma_1 = 0$, the density of the probability distribution μ_1 is

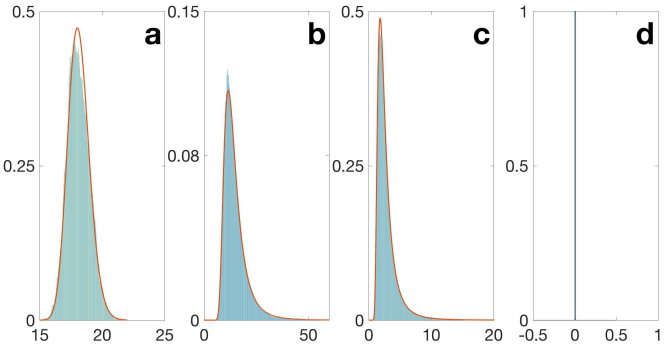


FIGURE 5. Histograms for the last 4 000 000 samples of a single run of 5 000 000 iterations and corresponding density functions a. $\sigma_2 = 0.001$ b. $\sigma_2 = 0.01$ c. $\sigma_2 = 0.1$ d. $\sigma_2 = 0.15$

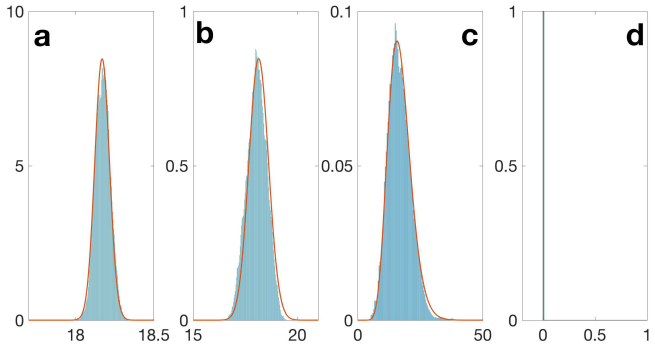


FIGURE 6. Histograms for the last 4 000 000 samples of a single run of 5 000 000 iterations and corresponding Gamma density functions a. $\sigma_1 = 0.001$ b. $\sigma_1 = 0.01$ c. $\sigma_1 = 0.1$ d. $\sigma_1 = 0.5$

given in Corollary 2 (a) and (b), respectively. To illustrate these results we use the same parameter values as stated at the beginning of this section and the initial values $n(0) = 2.5$, $C_o(0) = 0$, $C_e(0) = 180$. For $\sigma_1 = 0$ and several values of σ_2 we display the histograms for the last 4 000 000 samples of a single run of 5 000 000 iterations (shaded areas in Fig. 5) and the graph of the corresponding density given in Corollary 2 (a). In Fig. 6 we do similar plots for $\sigma_2 = 0$, several values of σ_1, and

the density of the corresponding Gamma distribution in Corollary 2 (b). We can notice that the histograms give very accurate approximations for the densities in Corollary 2. Also, in both Fig. 5 and Fig. 6, when the values of σ_1 or σ_2 increase, the histograms become right skewed. Moreover, for large values of σ_1 or σ_2 the population becomes extinct and $\mu_1 = \delta_0$ (see also Theorem 3.5).

6. **Conclusions.** We present a stochastic model to study the effect of toxicants on human cells. To account for parameter uncertainties, the model is expressed as a system of coupled ordinary stochastic differential equations. The variables are the cell index $n(t)$, which closely reflects the cell population, the concentration $C_o(t)$ of internal toxicants per cell, and the concentration $C_e(t)$ of toxicants outside the cells at time t. There are a few papers that consider similar stochastic models for population dynamics, but they mainly study conditions for extinction and persistence. Here we focus on the ergodic properties when the population is persistent.

We first prove the positivity of the solutions. Then we investigate the influence of noise on the cell population survival. When the noise variances σ_1^2 or σ_2^2 are sufficiently large, the population goes to extinction. Numerical simulations show that, for the stochastic model, the population goes to extinction at threshold values $C_e^{stoch}(0)$ below the deterministic threshold value $C_e^{det}(0)$. Furthermore, increasing the noise variances σ_1^2 or σ_2^2 results in a lower value $C_e^{stoch}(0)$ at which the population becomes extinct.

Moreover, we prove that when the noise variance σ_1^2 is sufficiently small and the population is strongly persistent, then the cell index converges weakly to the unique stationary probability distribution. Increasing the noise intensity causes a right skewness of the stationary distribution.

Here we illustrate our results for the toxicant monastrol. We have also considered other toxicants from the experiments described in [1] classified in various clusters [30]. We have noticed that the cluster type does not change the type of stationary distribution, nor has an effect on the behavior of the distributions in response to increased noise variances.

Appendix A. Proof of Lemma 2.2.

Proof. The proof is similar with the proof of Lemma 3.1 in [1]. We define the stopping time $\tau = \inf\{t \geq 0 : C_e(t) > C_e(0)\}$. We show that $\tau = \infty$ a.s.. Assume that there exists $T > 0$, and $\epsilon > 0$ such that $P(\tau \leq T) > \epsilon$ and let Ω be the set where the solution $(n(t), C_o(t), C_e(t))'$ of the system (5)-(7) is continuous. Hence $P(\Omega) = 1$ ([3]), and $P(\Omega_1) > 0$, where $\Omega_1 = \Omega \cap \{\tau \leq T\}$.

From (8) with $C_o(0) = 0$ we get for any $\omega \in \Omega_1$ and any $0 < t < \tau(\omega)$

$$0 \leq C_o(t,\omega) = \lambda_1^2 e^{-\eta_2^2 t} \int_0^t C_e(s,\omega) e^{\eta_1^2 s} ds \leq \lambda_1^2 e^{-\eta_2^2 t} C_e(0) \int_0^t e^{\eta_1^2 s} ds$$
$$= \frac{\lambda_1^2 C_e(0)}{\eta_1^2} \left(1 - e^{-\eta_1^2 t}\right) \leq \frac{\lambda_1^2 C_e(0)}{\eta_1^2}$$

Moreover, on Ω_1 we have $C_e(\tau) = C_e(0)$, and then from equation (7) we obtain

$$\left.\frac{dC_e}{dt}\right|_{t=\tau} = \lambda_2^2 C_o(\tau) n(\tau) - \eta_2^2 C_e(\tau) n(\tau)$$
$$\leq C_e(0) n(\tau) \left(\frac{\lambda_1^2 \lambda_2^2}{\eta_1^2} - \eta_2^2\right) < 0$$

Thus we have a contradiction with the definition of τ. □

Appendix B. Proof of Theorem 2.3.

Proof. The proof is similar with the proof of Theorem 3.2 in [1]. Let Ω be the set where the solution $(n(t), C_o(t), C_e(t))'$ of the system (5)-(7) is continuous and $n(t) > 0$, $0 < C_e(t) \leq C_e(0)$, $0 \leq C_o(t) \leq \lambda_1^2 C_e(0)/\eta_1^2$ for any $t \geq 0$. From Theorem 2.1 and Lemma 2.2 we know that $P(\Omega) = 1$. Let $\Omega_1 = \{\omega \in \Omega : |n|_1(\omega) < \infty\}$ and $\Omega_2 = \{\omega \in \Omega : |n|_1(\omega) = \infty\}$, where $|n|_1(\omega) = \int_0^\infty n(t,\omega)dt$.

If $P(\Omega_1) > 0$, then for any $\omega \in \Omega_1$ and any $t \geq 0$, we have

$$\int_0^t C_o(s,\omega)n(s,\omega)\exp\left(\eta_2^2\int_0^s n(l,\omega)dl\right)ds \leq \frac{\lambda_1^2 C_e(0)}{\eta_1^2}\exp\left(\eta_2^2|n|_1(\omega)\right)|n|_1(\omega).$$

Thus $0 \leq M(\omega) := \int_0^\infty C_o(s,\omega)n(s,\omega)\exp\left(\eta_2^2\int_0^s n(l,\omega)dl\right)ds < \infty$, and from (9) we get

$$\lim_{t\to\infty} C_e(t,\omega) = C_e(0)\exp(-\eta_2^2|n|_1(\omega)) + \lambda_2^2 M(\omega)\exp(-\eta_2^2|n|_1(\omega)) < \infty.$$

Consequently, there exists $T_1(\omega) > 0$ such that for any $t > T_1(\omega)$ we have $C_e(t,\omega) > C_e(0)\exp(-\eta_2^2|n|_1(\omega))/2$. This implies that $\int_0^\infty C_e(s,\omega)e^{\eta_1^2 s}ds = \infty$ because for any $t > T_1(\omega)$ we have

$$\begin{aligned}\int_0^t C_e(s,\omega)e^{\eta_1^2 s}ds &\geq \int_{T_1(\omega)}^t C_e(s,\omega)e^{\eta_1^2 s}ds\\ &\geq C_e(0)\exp(-\eta_2^2|n|_1(\omega))/2\int_{T_1(\omega)}^t e^{\eta_1^2 s}ds.\end{aligned}$$

So we can apply L'Hospital's rule in (8), and we get

$$\lim_{t\to\infty} C_o(t,\omega) = \frac{\lambda_1^2}{\eta_1^2}\lim_{t\to\infty} C_e(t,\omega) > 0.$$

Thus, on Ω_1, $\lim_{t\to\infty} C_e(t)$ and $\lim_{t\to\infty} C_o(t)$ exist and they are related by the previous equation.

Next, if $P(\Omega_2) > 0$ we consider any $\omega \in \Omega_2$. If $0 \leq \int_0^\infty C_o(s,\omega)n(s,\omega)\exp\left(\eta_2^2\int_0^s n(l,\omega)dl\right)ds < \infty$, from (9) we get $\lim_{t\to\infty} C_e(t,\omega) = 0$. On the other hand, if $\int_0^\infty C_o(s,\omega)n(s,\omega)\exp\left(\eta_2^2\int_0^s n(l,\omega)dl\right)ds = \infty$, from L'Hospital's rule in (9) we have

$$0 \leq \frac{\lambda_2^2}{\eta_2^2}\liminf_{t\to\infty} C_o(t,\omega) \leq \liminf_{t\to\infty} C_e(t,\omega) \leq \limsup_{t\to\infty} C_e(t,\omega) \leq \frac{\lambda_2^2}{\eta_2^2}\limsup_{t\to\infty} C_o(t,\omega)$$

Similarly, from (8) we either get that $\lim_{t\to\infty} C_o(t,\omega) = 0$ (if $\int_0^\infty C_e(s,\omega)e^{\eta_1^2 s}ds < \infty$), or we have

$$0 \leq \frac{\lambda_1^2}{\eta_1^2}\liminf_{t\to\infty} C_e(t,\omega) \leq \liminf_{t\to\infty} C_o(t,\omega) \leq \limsup_{t\to\infty} C_o(t,\omega) \leq \frac{\lambda_1^2}{\eta_1^2}\limsup_{t\to\infty} C_e(t,\omega),$$

(if $\int_0^\infty C_e(s,\omega)e^{\eta_1^2 s}ds = \infty$). All these possible cases give

$$\lim_{t\to\infty} C_o(t,\omega) = \lim_{t\to\infty} C_e(t,\omega) = 0,$$

because $\eta_1^2\eta_2^2 - \lambda_1^2\lambda_2^2 > 0$. Thus, on Ω_2, $\lim_{t\to\infty} C_e(t)$ and $\lim_{t\to\infty} C_o(t)$ exist and they are equal with zero.

In conclusion, on $\Omega = \Omega_1 \cup \Omega_2$ we have shown that $\lim_{t\to\infty} C_e(t)$ and $\lim_{t\to\infty} C_o(t)$ exist, and we have $\lim_{t\to\infty} C_o(t) = \frac{\lambda_1^2}{\eta_1^2} \lim_{t\to\infty} C_e(t)$. □

Appendix C. Proof of Lemma 4.6.

Proof. We choose any $0 < c < \beta - \sigma_1^2$. Using Itô's formula in (21) we get:

$$d(e^{ct}Y(t)) = e^{ct}\Big(Y(t)(c+\sigma_1^2-\beta)+\gamma+\sigma_2^2X(t)\Big)dt - \sigma_1 e^{ct}Y(t)dB_1(t)$$
$$+\sigma_2 e^{ct}dB_2(t) \le e^{ct}\Big(\gamma+\sigma_2^2X(t)\Big)dt - \sigma_1 e^{ct}Y(t)dB_1(t)+\sigma_2 e^{ct}dB_2(t) \qquad (29)$$

Let $\tau_m = \inf\{t \ge 0 : Y(t) \notin (1/m, m)\}$, for any $m > m_0$, where $m_0 > 0$ is sufficiently large such that $n(0) \in (1/m_0, m_0)$. Obviously $\lim_{m\to\infty} \tau_m = \infty$ a.s.. Taking expectation in (29) and using Lemma 4.4 we get:

$$E\left[e^{c(t\wedge\tau_m)}Y(t\wedge\tau_m)\right] \le \frac{1}{n(0)} + E\left[\int_0^{t\wedge\tau_m} e^{cs}\left(\gamma+\sigma_2^2X(s)\right)ds\right]$$
$$\le \frac{1}{n(0)} + \left(\gamma+\sigma_2^2C_1\right)\frac{(e^{ct}-1)}{c}.$$

Letting $m \to \infty$ we get

$$E\left[Y(t)\right] \le \frac{1}{n(0)e^{ct}} + \frac{\left(\gamma+\sigma_2^2C_1\right)}{c}(1-e^{-ct}).$$

Thus, there exists a constant $C_2 > 0$ such that $\sup_{t\ge0} E[Y(t)] \le C_2$. The proof that $\sup_{t\ge0} E[Y_\epsilon(t)] < \infty$, for any $0 < \epsilon < \frac{\beta-\sigma_1^2}{\alpha}$, is similar. □

REFERENCES

[1] C. Anton, J. Deng, Y. Wong, Y. Zhang, W. Zhang, S. Gabos, D. Huang and C. Jin, Modeling and simulation for toxicity assessment, *Math. BioSci. Eng.*, **14** (2017), 581–606.

[2] G. K. Basak and R. Bhattcharya, Stability in distribution for a class of singular diffusions, *Ann. Prob.*, **20** (1992), 312–321.

[3] A. Friedman, *Stochastic Differential Equations and Applications*, Dover, New York, 2006.

[4] A. Grey, D. Greenhalgh, L. Hu, X. Mao and J. Pan, A stochastic differential equation SIS epidemic model, *SIAM. J. Appl. Math.*, **71** (2011), 876–902.

[5] T. Hallam, C. Clark and G. Jordan, Effects of toxicants on populations: A qualitative approach II. First order kinetics, *J. Math. Biology*, **18** (1983), 25–37.

[6] R. Z. Hasminskii, *Stochastic Stability of Differential Equations*, Springer, Berlin, 2012, 2nd ed.

[7] J. He and K. Wang, The survival analysis for a population in a polluted environment, *Nonlinear Analysis: Real World Applications*, **10** (2009), 1555–1571.

[8] C. Ji, D. Jiang, N. Shi and D. O'Regan, Existence, uniqueness, stochastic persistence and global stability of positive solutions of the logistic equation with random perturbation, *Math. Methods in the Appl. Sciences*, **30** (2007), 77–89.

[9] D. Jiang and N. Shi, A note on non-autonomous logistic equation with random perturbation, *J. Math. Anal. Appl.*, **303** (2005), 164–172.

[10] D. Jiang, N. Shi and X. Li, Global stability and stochastic permanence of a non-autonomous logistic equation with random perturbation, *J. Math. Anal. Appl.*, **340** (2008), 588–597.

[11] J. Jiao, W. Long and L. Chen, A single stage-structured population model with mature individuals in a polluted environment and pulse input of environmental toxin, *Nonlinear Analysis: Real World Applications*, **10** (2009), 3073–3081.

[12] P. Kloeden and E. Platen, *Numerical Solutions of Stochastic Differential Equations*, Springer–Verlag, Berlin, 1992.

[13] Y. A. Kutoyants, *Statistical Inference for Ergodic Diffusion Processes*, Springer, London, 2004.

[14] V. Lakshmikantham and S. Leela, *Differential and Integral Inequalities, Vol. I*, Academic Press, New York, 1969.
[15] M. Liu and K. Wang, Survival analysis of stochastic single-species population models in polluted environments, *Ecological Modelling*, **220** (2009), 1347–1357.
[16] M. Liu, K. Wang and Q. Wu, Survival analysis of stochastic competitive models in a polluted environment and stochastic competitive exclusion principle, *Bull. Math. Biol.*, **73** (2011), 1969–2012.
[17] X. Mao, *Stochastic Differential Equations and Applications*, Woodhead Pubilshing, Philadelphia, 2011, 2nd ed.
[18] X. Mao, G. Marion and E. Renshaw, Environmental brownian noise suppresses explosions in population dynamics, *Markov Proc. and Their Appl.*, **97** (2002), 95–110.
[19] X. Mao, S. Sabanis and E. Renshaw, Asymptotic behaviour of the stochastic Lotka-Volterra model, *J. Math. Anal. Appl.*, **287** (2003), 141–156.
[20] T. Pan, B. Huang, W. Zhang, S. Gabos, D. Huang and V. Devendran, Cytotoxicity assessment based on the AUC_50 using multi-concentration time-dependent cellular response curves, *Anal. Chim. Acta*, **764** (2013), 44–52.
[21] S. Pinheiro, On a logistic growth model with predation and power-type diffusion coefficient: I. Existence of solutions and extinction criteria, *Math. Meth. Appl. Sci.*, **38** (2015), 4912–4930.
[22] S. Resnik, *A Probability Path*, Birkhauser, Boston, 1999.
[23] Z. Teng and L. Wang, Persistence and extinction for a class of stochastic SIS epidemic models with nonlinear incidence rate, *Physica A*, **451** (2016), 507–518.
[24] F. Wei and L. Chen, Psychological effect on single-species population models in a polluted environment, *Math. Biosci.*, **290** (2017), 22–30.
[25] F. Wei, S. Geritz and J. Cai, A stochastic single-species population model with partial pollution tolerance in a polluted environment, *Appl. Math. Letters*, **63** (2017), 130–136.
[26] Z. Xi, S. Khare, A. Cheung, B. Huang, T. Pan, W. Zhang, F. Ibrahim, C. Jin and S. Gabos, Mode of action classification of chemicals using multi-concentration time-dependent cellular response profiles, *Comp. Biol. Chem.*, **49** (2014), 23–35.
[27] J. Xing, L. Zhu, S. Gabos and L. Xie, Microelectronic cell sensor assay for detection of cytotoxicity and prediction of acute toxicity, *Toxicology in Vitro*, **20** (2006), 995–1004.
[28] Q. Yang, D. Jiang, N. Shi and C. Ji, The ergodicity and extinction of stochastically perturbed SIR and SEIR epidemic models with saturated incidence, *J. Math. Anal. Appl.*, **388** (2012), 248–271.
[29] Q. Yang and X. Mao, Stochastic dynamics of SIRS epidemic models with random perturbation, *Math. BioSci. Eng.*, **11** (2014), 1003–1025.
[30] Y. Zhang, Y. Wong, J. Deng, C. Anton, J. Deng, S. Gabos, W. Zhang, D. Huang and C. Jin, Machine learning algorithms for mode-of-action classification in toxicity assessment, *BioData Mining*, **9** (2016), p19.

Received March 22, 2017; Accepted April 06, 2018.

E-mail address: popescuc@macewan.ca
E-mail address: yong@ualberta.ca