

**MOMENT STABILITY FOR NONLINEAR STOCHASTIC
GROWTH KINETICS OF BREAST CANCER STEM CELLS
WITH TIME-DELAYS**

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(Communicated by Qing Nie)

ABSTRACT. Solid tumors are heterogeneous in composition. Cancer stem cells (CSCs) are a highly tumorigenic cell type found in developmentally diverse tumors that are believed to be resistant to standard chemotherapeutic drugs and responsible for tumor recurrence. Thus understanding the tumor growth kinetics is critical for development of novel strategies for cancer treatment. In this paper, the moment stability of nonlinear stochastic systems of breast cancer stem cells with time-delays has been investigated. First, based on the technique of the variation- of-constants formula, we obtain the second order moment equations for the nonlinear stochastic systems of breast cancer stem cells with time-delays. By the comparison principle along with the established moment equations, we can get the comparative systems of the nonlinear stochastic systems of breast cancer stem cells with time-delays. Then moment stability theorems have been established for the systems with the stability properties for the comparative systems. Based on the linear matrix inequality

2010 *Mathematics Subject Classification.* 34K50, 60H10, 93Dxx.

Key words and phrases. Stochastic systems, breast cancer stem cells, comparison principle, mean square stability, moment stability, linear matrix inequality (LMI).

[†]These authors contributed equally to this work. CJ Guo's work is partially supported by National Natural Science Foundations of China (No. 51275094), by Cultivation Plan for Outstanding Young Teachers of Guangdong University of Technology found (No. 112410004204) and by the State Scholarship Fund of China (No. 201308440327). CX Guo's work is partially supported by National Natural Science Foundations of China (No. 81301924). Liu's Work is partially supported by USA National Science Foundation (No. DMS1308948).

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(LMI) technique, we next obtain a criteria for the exponential stability in mean square of the nonlinear stochastic systems for the dynamics of breast cancer stem cells with time-delays. Finally, some numerical examples are presented to illustrate the efficiency of the results.

1. Introduction. Breast cancer is a malignant disease with a heterogeneous distribution of cell types. Despite aggressive clinical treatment including surgical resection, radiation, and chemotherapy, tumor recurrence is essentially universal. Therapeutic failure is due, in part, to tumor cell heterogeneity, derived from both genetic and non-genetic sources, which contributes to therapeutic resistance and tumor progression. Understanding this heterogeneity is the key for the development of targeted cancer-preventative and -therapeutic interventions. One of the currently prevailing models explaining intratumoral heterogeneity is the CSC hypothesis [1, 18].

Cancer stem cells (CSCs) are defined as “a small subset of cancer cells” within a cancer that can self-renew and replenish the heterogeneous lineage of cancer cells that comprise the tumor. CSCs are often resistant to chemotherapeutic drugs, sharing similar gene expression profiles and properties with normal stem cells such as formation of spheres in culture, and may be responsible for tumor relapse and metastasis [19, 17, 2]. A broad range of CSC frequency, often spanning multiple orders of magnitude, has been observed in human solid tumors of various organ types [21, 20, 5, 9, 15]. According to the CSC hypothesis [19], CSCs possess the ability to divide either symmetrically to yield two identical immortal cancer stem cells; or asymmetrically, to simultaneously self-renew and yield one mortal non-stem cancer cell with finite replicative potential [20]. The proportion of CSCs has been speculated to be maintained through alternative use of symmetric and asymmetric division. However, it is largely unknown how to control the switch between these two dividing modes. Mathematical modeling has been utilized to study underlying mechanistic principles and to help design appropriate experiments for better understanding of complex dynamics and interactions of tumor cell populations [4].

In [6], via the contraction fixed point theorem, the exponential stability has been achieved in mean square of the stochastic neutral cellular neural network. Motivated by [6], this paper will investigate the moment stability of nonlinear stochastic systems of breast cancer stem cells with time-delays based on comparison principle, variation-of-constants formula and linear matrix inequality (LMI) techniques.

The rest of the paper is organized in the following. In §2, we will generalize the population dynamics with different cell types by a system of differential equations, and introduce some notations. In §3, we will study the stability properties in mean square of the the stochastic system as developed in §2. In §4, some numerical examples are provided to further demonstrate the results. Finally, a brief conclusion is drawn.

2. Preliminaries. In [14], a mathematical model has been developed to explore the growth kinetics of CSC population both in vitro and in vivo. Here we denote $x_i(t)$ the number of cells at time t for cell types $i, i = 0, 1, \dots, n - 1$. P_i the probability that the cell type i is divided into a pair of itself, Q_i the probability that the cell type i is divided into a pair of next cell lineage (cell type $i+1$). Thus $1 - P_i - Q_i$ denotes the probability that an asymmetric cell division takes place from cell type i to cell type $i - 1$. Here v_i is the synthesis rate which quantifies the speed for cell type i to divide in unit time, d_i is the degradation rate, and $w(t) = (w_1(t), w_2(t), \dots, w_m(t))^T \in R^m$ is a m -dimensional Brownian motion defined on a complete probability space

(Ω, \mathcal{F}, P) . The stochastic disturbance term, $h_j^{k,i}(t, u_1, u_2) \in C(\mathbf{R} \times \mathbf{R}^+ \times \mathbf{R}^+)$ ($k, i = 0, 1, \dots, n-1, j = 1, 2, \dots, m$), can be viewed as stochastic perturbations on the stem cells states and delayed stem cells states. Here τ is a positive constant, $P_i > 0, Q_i > 0, \nu_i > 0$ ($i = 0, 1, 2, \dots, n-2$) are all decreasing functions of x_{n-1} , which represents the negative feedback from the terminally differentiated cell type $n-1$. Based on the model as developed in [14], a general population dynamics of different cell types can be described by a system of stochastic ordinary differential equations,

$$\begin{aligned}
 dx_0(t) &= \{[P_0(x_{n-1}(t-\tau)) - Q_0(x_{n-1}(t-\tau))]\nu_0(x_{n-1}(t-\tau))x_0(t) \\
 &\quad - d_0x_0(t)\}dt + \sum_{j=1}^m [\sum_{i=0}^{n-1} h_j^{0,i}(t, x_i(t), x_i(t-\tau))]dw_j(t), \\
 dx_1(t) &= \{[1 - P_0(x_{n-1}(t-\tau)) + Q_0(x_{n-1}(t-\tau))]\nu_0(x_{n-1}(t-\tau))x_0(t) \\
 &\quad + [P_1(x_{n-1}(t-\tau)) - Q_1(x_{n-1}(t-\tau))]\nu_1(x_{n-1}(t-\tau))x_1(t) - d_1x_1(t)\}dt \\
 &\quad + \sum_{j=1}^m [\sum_{i=0}^{n-1} h_j^{1,i}(t, x_i(t), x_i(t-\tau))]dw_j(t), \\
 &\quad \vdots \\
 dx_{n-2}(t) &= \{[1 - P_{n-3}(x_{n-1}(t-\tau)) + Q_{n-3}(x_{n-1}(t-\tau))] \\
 &\quad \times \nu_{n-3}(x_{n-1}(t-\tau))x_{n-3}(t) \\
 &\quad + [P_{n-2}(x_{n-1}(t-\tau)) - Q_{n-2}(x_{n-1}(t-\tau))]\nu_{n-2}(x_{n-1}(t-\tau))x_{n-2}(t) \\
 &\quad - d_{n-2}x_{n-2}(t)\}dt + \sum_{j=1}^m [\sum_{i=0}^{n-1} h_j^{n-2,i}(t, x_i(t), x_i(t-\tau))]dw_j(t), \\
 dx_{n-1}(t) &= \{[1 - P_{n-2}(x_{n-1}(t-\tau)) + Q_{n-2}(x_{n-1}(t-\tau))] \\
 &\quad \times \nu_{n-2}(x_{n-1}(t-\tau))x_{n-2}(t) \\
 &\quad - d_{n-1}x_{n-1}(t)\}dt + \sum_{j=1}^m [\sum_{i=0}^{n-1} h_j^{n-1,i}(t, x_i(t), x_i(t-\tau))]dw_j(t)
 \end{aligned} \tag{1.1}$$

Let (Ω, \mathcal{F}, P) be a complete probability space with a filtration $\{\mathcal{F}_t\}_{t \geq 0}$ satisfying the usual conditions, i.e. it is right continuous and \mathcal{F}_0 contains all P -null sets. Let $C_{\mathcal{F}_0}^b([-\tau, 0]; \mathbf{R})$ be the family of all bounded, \mathcal{F}_0 -measurable functions. We denote by $C([-\tau, 0]; \mathbf{R})$ the family of all continuous functions $\phi : [-\tau, 0] \rightarrow \mathbf{R}$ with

$$\|\phi\|_2 = \sup_{-\tau \leq \theta \leq 0} |\phi(\theta)|_1.$$

Since P_i, Q_i and ν_i ($i = 0, 1, 2, \dots, n-2$) are all decreasing functions of x_{n-1} , there exist some positive constants \bar{P}_i, \bar{Q}_i and $\bar{\nu}_i$ such that

$$P_i(x_{n-1}) \leq \bar{P}_i, \quad Q_i(x_{n-1}) \leq \bar{Q}_i, \quad \nu_i(x_{n-1}) \leq \bar{\nu}_i \quad \text{for } (i = 0, \dots, n-2). \tag{1.2}$$

To simplify, we can rewrite (1.1) as

$$dx = [F(t, x(t), x(t-\tau)) - D x(t)]dt + \sum_{j=1}^m H_j(t, x(t), x(t-\tau))dw_j(t) \tag{1.3}$$

with the initial condition

$$x(s) = \varphi(s) \in C([-\tau, 0]; \mathbf{R}^n), \quad -\tau \leq s \leq 0, \tag{1.4}$$

where $x(t) = (x_0(t), x_1(t), \dots, x_{n-1}(t))^T, D = \text{diag}(d_0, d_1, \dots, d_{n-1}),$

$$H_j(t, x(t), x(t - \tau)) = \begin{pmatrix} \sum_{i=0}^{n-1} h_j^{0,i}(t, x_i(t), x_i(t - \tau)) \\ \sum_{i=0}^{n-1} h_j^{1,i}(t, x_i(t), x_i(t - \tau)) \\ \vdots \\ \sum_{i=0}^{n-1} h_j^{n-2,i}(t, x_i(t), x_i(t - \tau)) \\ \sum_{i=0}^{n-1} h_j^{n-1,i}(t, x_i(t), x_i(t - \tau)) \end{pmatrix},$$

$$F(t, x(t), x(t - \tau)) = \begin{pmatrix} f_1 \\ f_2 \\ \vdots \\ f_{n-2} \\ f_{n-1} \end{pmatrix} = A(x_{n-1}(t - \tau)) \begin{pmatrix} x_0 \\ x_1 \\ \vdots \\ x_{n-2} \\ x_{n-1} \end{pmatrix}$$

$$= \begin{pmatrix} [P_0(x_{n-1}(t - \tau)) - Q_0(x_{n-1}(t - \tau))] \\ \quad \times \nu_0(x_{n-1}(t - \tau))x_0(t) \\ [1 - P_0(x_{n-1}(t - \tau)) + Q_0(x_{n-1}(t - \tau))] \\ \quad \times \nu_0(x_{n-1}(t - \tau))x_0(t) \\ + [P_1(x_{n-1}(t - \tau)) - Q_1(x_{n-1}(t - \tau))] \\ \quad \times \nu_1(x_{n-1}(t - \tau))x_1(t) \\ \vdots \\ [1 - P_{n-3}(x_{n-1}(t - \tau)) + Q_{n-3}(x_{n-1}(t - \tau))] \\ \quad \times \nu_{n-3}(x_{n-1}(t - \tau))x_{n-3}(t) \\ + [P_{n-2}(x_{n-1}(t - \tau)) - Q_{n-2}(x_{n-1}(t - \tau))] \\ \quad \times \nu_{n-2}(x_{n-1}(t - \tau))x_{n-2}(t) \\ [1 - P_{n-2}(x_{n-1}(t - \tau)) + Q_{n-2}(x_{n-1}(t - \tau))] \\ \quad \times \nu_{n-2}(x_{n-1}(t - \tau))x_{n-2}(t) \end{pmatrix},$$

$$A(x_{n-1}(t - \tau)) = \begin{pmatrix} [P_0 - Q_0]\nu_0 & 0 & \cdots & 0 & 0 \\ [1 - P_0 + Q_0]\nu_0 & [P_1 - Q_1]\nu_1 & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & \cdots & 0 & 0 \\ 0 & 0 & \cdots & 0 & 0 \\ \cdots & 0 & \cdots & 0 & 0 \\ \cdots & 0 & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ \cdots & [1 - P_{n-3} + Q_{n-3}]\nu_{n-3} & [P_{n-2} - Q_{n-2}]\nu_{n-2} & 0 & 0 \\ \cdots & 0 & [1 - P_{n-2} + Q_{n-2}]\nu_{n-2} & 0 & 0 \end{pmatrix}.$$

Let $B = [b_{ij}(t)]_{n \times n}$ with

$$|x(t)|_1 = \sum_{i=1}^n |x_i(t)|,$$

and

$$\|B(t)\|_3 = \sum_{i,j=1}^n |b_{ij}(t)|.$$

We denote the mathematical expectation by E throughout the paper.

Definition 2.1. The system (1.3) with the initial condition is said to be the first moment exponentially stable if there exist two positive constants μ and β such that

$$\|Ex(t; \varphi)\|_2 \leq \mu \|\varphi\|_2 e^{-\beta t}, \quad t \geq 0. \tag{2.1}$$

Definition 2.2. The system (1.3) with the initial condition is said to be exponentially stable in mean square if there exists a solution x of (1.3) and there exists a pair of positive constants μ and β with

$$E\|x(t; \varphi)\|_2^2 \leq \mu E\|\varphi\|_2^2 e^{-\beta t}, \quad t \geq 0. \tag{2.2}$$

Definition 2.3. The system (1.3) with the initial condition is said to be globally exponentially stable in mean square if there exists a scalar $\varsigma > 0$, such that

$$\limsup_{t \rightarrow \infty} \frac{1}{t} \log(E\|x(t; \varphi)\|_2^2) \leq -\varsigma. \tag{2.3}$$

Let $C^{1,2}(R^+ \times R^n; R^+)$ denote the family of all nonnegative functions $V(t, x)$ on $R^+ \times R^n$ which are continuously twice differentiable in x and once differentiable in t . In order to study the mean square globally exponential stability, for each $V \in C^{1,2}([-\tau, \infty) \times R^+; R^+)$, define an operator LV , associated with the uncertain stochastic neural networks with multiple mixed time-delays (1.3), from $(R^+ \times C[-\tau^*, \infty); R^n)$ to R by

$$\begin{aligned} LV(t, x) &= \frac{1}{2} \text{trace}[(\sum_{j=1}^m H_j^T(t, x(t), x(t - \tau))) V_{xx}(t, x) \\ &\quad \times (\sum_{j=1}^m H_j(t, x(t), x(t - \tau)))] \\ &\quad + V_t(t, x) + V_x(t, x)[F(t, x(t), x(t - \tau)) - Dx(t)], \end{aligned}$$

where

$$\begin{aligned} V_t(t, x) &= \left(\frac{\partial V(t, x)}{\partial t}\right), \\ V_x(t, x) &= \left(\frac{\partial V(t, x)}{\partial x_1}, \frac{\partial V(t, x)}{\partial x_2}, \dots, \frac{\partial V(t, x)}{\partial x_n}\right), \\ V_{xx}(t, x) &= \left(\frac{\partial^2 V(t, x)}{\partial x_i \partial x_j}\right)_{n \times n}. \end{aligned}$$

3. Stability of nonlinear stochastic systems of breast cancer stem cells with time-delays. In this section, we will study the stability properties in mean square of the stochastic nonlinear growth kinetics of breast cancer stem cells.

Throughout this paper, we always assume the following:

(A₁) there exist positive constants $\alpha^{(j)}$, and positive definite constant matrices $C_j^{(0)}$, $\tilde{C}_j^{(0)}$, $C_j^{(1)}$, $\tilde{C}_j^{(1)}$, $C_j^{(2)}$ and $\tilde{C}_j^{(2)}$ such that

$$\begin{aligned} &\|H_j(t, x(t), x(t - \tau(t))) - H_j(t, y(t), y(t - \tau(t)))\|_2 \\ &\leq \alpha^{(j)} [\|x - y\|_1 + \|x(t - \tau(t)) - y(t - \tau(t))\|_2] \end{aligned}$$

and

$$\begin{aligned} & \|\tilde{C}_j^{(0)}\|_3 + x^T(t)\tilde{C}_j^{(1)}x(t) + x^T(t-\tau)\tilde{C}_j^{(2)}x(t-\tau) \\ & \leq H_j^T(t, x(t), x(t-\tau)) \times H_j(t, x(t), x(t-\tau)) \\ & \leq \|C_j^{(0)}\|_3 + x^T(t)C_j^{(1)}x(t) + x^T(t-\tau)C_j^{(2)}x(t-\tau), \end{aligned}$$

where T represents the transpose, $j = 1, 2, \dots, \dots, m$, and

$$H_j(t, x(t), x(t-\tau)) = \begin{pmatrix} \sum_{i=0}^{n-1} h_j^{0,i}(t, x_i(t), x_i(t-\tau)) \\ \sum_{i=0}^{n-1} h_j^{1,i}(t, x_i(t), x_i(t-\tau)) \\ \vdots \\ \sum_{i=0}^{n-1} h_j^{n-2,i}(t, x_i(t), x_i(t-\tau)) \\ \sum_{i=0}^{n-1} h_j^{n-1,i}(t, x_i(t), x_i(t-\tau)) \end{pmatrix}.$$

Note from (1.3) and (1.4) that

$$\begin{aligned} x(t) &= \exp(-Dt)\{\varphi(0) + \int_0^t \exp(Ds)[F(s, x(s), x(s-\tau))]ds \\ &+ \sum_{j=1}^m \int_0^t H_j(s, x(s), x(s-\tau)) \exp(Ds)dw(s)\}. \end{aligned} \tag{3.1}$$

From (A_1) we have that $F(\cdot, \cdot, \cdot)$ and $H_j(\cdot, \cdot, \cdot)$ satisfy the Lipschitzian condition. Then there is a unique solution of the system (1.1) through (t, φ) .

3.1. The first moment stability.

Let $x(t)$ be the solution of (1.1) and (1.2), we have from (3.1)

$$\|Ex(t; \varphi)\|_2 = \|\exp(-Dt)\{\varphi(0) + \int_0^t \exp(Ds)[F(s, x(s), x(s-\tau))]ds\}\|_2. \tag{3.2}$$

Now, we consider the following deterministic equation

$$\begin{cases} dx = [-Dx(t) + F(t, x(t), x(t-\tau))]dt, \\ x(s) = \varphi(s) \in C([-\tau, 0]; R^n), \quad -\tau \leq s \leq 0. \end{cases} \tag{3.3}$$

Let $x_\varphi(t)$ be the solution of (3.3).

Theorem 3.1. *Suppose*

(A_2) *The solution of (3.3) is exponentially stable, i.e., there exist two positive constants κ and λ such that*

$$\|x_\varphi(t)\|_2 \leq \kappa \|\varphi\|_2 e^{-\lambda t}, \quad t \geq 0.$$

Then the system (1.1) is first moment exponentially stable, i.e.,

$$\|Ex(t; \varphi)\|_2 = \|x_\varphi(t)\|_2 \leq \kappa \|\varphi\|_2 e^{-\lambda t}, \quad t \geq 0. \tag{3.4}$$

Proof of Theorem 3.1. The result follows from (A_2) and (3.2). □

Remark 1. In fact, if the equilibrium of the system (3.3) is stable, or asymptotically stable, then the equilibrium of the system (1.1) is also stable in first moment, or asymptotically stable in first moment, respectively, i.e., the stability of the system (3.3) implies the same stability of the system (1.1) in first moment.

For convenience, in the following discussions, we always assume that the system (1.1) is first moment exponentially stable.

3.2. Mean square stability.

Now we study the stability in mean square of the system (1.1).

Since $dw_j ds = 0$, $E dw_j = 0$ and $E(dw_j(s), dw_k(s)) = \delta_{jk} ds (j, k = 1, 2, \dots, m)$, we have from the definitions of $|\cdot|_1, \|\cdot\|_2, \|\cdot\|_3$ and (3.1) that

$$\begin{aligned}
 & E|x(t)|_1^2 \\
 &= E|\exp(-Dt)\{\varphi(0) + \int_0^t \exp(Ds)[F(s, x(s), x(s - \tau))]\} ds \\
 &+ \sum_{j=1}^m \int_0^t H_j(s, x(s), x(s - \tau)) \exp(Ds) dw(s)\}_1^2 \\
 &\leq E\{2\|\varphi(0)\|_2^2 \|\exp(-Dt)\|_3^2 + 2 \int_0^t \|\exp D(s - t)F(s, x(s), x(s - \tau))\|_2^2 ds \\
 &+ \int_0^t \|\exp D(s - t)\|_3^2 [\sum_{j=1}^m H_j^T(s, x(s), x(s - \tau)) \\
 &\times H_j(s, x(s), x(s - \tau))] ds\} \\
 &\leq E\{2n^2 \|\varphi(0)\|_2^2 e^{-2\lambda_{\min}(D)t} + 2n^2 \int_0^t e^{2\lambda_{\min}(D)(s-t)} \|A(x_{n-1}(s - \tau))\|_3^2 \\
 &\times |x(s)|_1^2 ds + \int_0^t n^2 e^{2\lambda_{\min}(D)(s-t)} [\sum_{j=1}^m (\|C_j^{(0)}\|_3 + x^T(s)C_j^{(1)}x(s) \\
 &+ x^T(s - \tau)C_j^{(2)}x(s - \tau))] ds\} \\
 &\leq E\{2n^2 \|\varphi(0)\|_2^2 e^{-2\lambda_{\min}(D)t} + 2n^2 \int_0^t e^{2\lambda_{\min}(D)(s-t)} \\
 &\times [\sum_{i=0}^{n-2} \bar{\nu}_i (1 + 2\bar{P}_i + 2\bar{Q}_i)]^2 |x(s)|_1^2 ds + \int_0^t n^2 e^{2\lambda_{\min}(D)(s-t)} \\
 &\times [\sum_{j=1}^m (\|C_j^{(0)}\|_3 + x^T(s)C_j^{(1)}x(s) + x^T(s - \tau)C_j^{(2)}x(s - \tau))] ds\} \\
 &\leq E\{\Phi e^{-2\lambda_{\min}(D)t} + \int_0^t e^{2\lambda_{\min}(D)(s-t)} \\
 &\times [\bar{C}^{(0)} + \bar{C}^{(1)}|x(s)|_1^2 + \bar{C}^{(2)}\|x(s - \tau)\|_2^2] ds\} \\
 &= \Phi e^{-2\lambda_{\min}(D)t} + E \int_0^t e^{2\lambda_{\min}(D)(s-t)} \\
 &\times [\bar{C}^{(0)} + \bar{C}^{(1)}|x(s)|_1^2 + \bar{C}^{(2)}\|x(s - \tau)\|_2^2] ds,
 \end{aligned} \tag{3.5}$$

where $\lambda_{\min}(D)$ represents the minimal eigenvalue of matrix D , $\lambda_{\max}(C_j^{(0)})$, $\lambda_{\max}(C_j^{(1)})$ and $\lambda_{\max}(C_j^{(2)})$ represent the maximal eigenvalues of $C_j^{(0)}$, $C_j^{(1)}$ and $C_j^{(2)}$ ($j = 1, 2, \dots, m$),

$$\Phi = 2n^2 \|\varphi(0)\|_2^2, \quad \bar{C}^{(0)} = n^3 \sum_{j=1}^m \lambda_{\max}(C_j^{(0)}), \quad \bar{C}^{(2)} = n^3 \sum_{j=1}^m \lambda_{\max}(C_j^{(2)})$$

$$\bar{C}^{(1)} = n^3 \sum_{j=1}^m \lambda_{\max}(C_j^{(1)}) + 2n^2 [\sum_{i=0}^{n-2} \bar{\nu}_i (1 + 2\bar{P}_i + 2\bar{Q}_i)]^2,$$

$$\exp D(s - t) = \begin{pmatrix} e^{d_0(s-t)} & 0 & 0 & \dots & 0 \\ 0 & e^{d_1(s-t)} & 0 & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & \dots & e^{d_{n-1}(s-t)} \end{pmatrix}$$

and

$$\|\exp D(s - t)\|_3 = \sum_{i=0}^{n-1} e^{d_i(s-t)}.$$

Theorem 3.2. *Let (A_1) and (A_2) be satisfied. Then*

$$E|x(t)|_1^2 \leq u(t), \quad t \geq 0,$$

where $u(t)$ is the solution of the comparison equation

$$\begin{cases} \dot{u}(t) = (-2\lambda_{\min}(D) + \bar{C}^{(1)})u(t) + \bar{C}^{(2)}u(t - \tau) + \bar{C}^{(0)}, & t \geq 0, \\ u(s) \geq \Phi \geq 0, & s \in [-\tau, 0]. \end{cases} \quad (3.6)$$

Proof of Theorem 3.2. Let

$$\begin{cases} M(t) = \Phi e^{-2\lambda_{\min}(D)t} \\ + E \int_0^t e^{2\lambda_{\min}(D)(s-t)} [\bar{C}^{(0)} + \bar{C}^{(1)}|x(s)|_1^2 + \bar{C}^{(2)}\|x(s - \tau)\|_2^2] ds, \\ M(s) \geq \Phi, \quad s \in [-\tau, 0]. \end{cases} \quad (3.7)$$

We have from (3.5) and (3.7)

$$\begin{aligned} \dot{M}(t) &= -2\lambda_{\min}(D)\{\Phi e^{-2\lambda_{\min}(D)t} + E \int_0^t e^{2\lambda_{\min}(D)(s-t)} [\bar{C}^{(0)} + \bar{C}^{(1)}|x(s)|_1^2 \\ &\quad + \bar{C}^{(2)}\|x(s - \tau)\|_2^2] ds\} + \bar{C}^{(0)} + \bar{C}^{(1)}E|x(t)|_1^2 + \bar{C}^{(2)}E\|x(t - \tau)\|_2^2 \\ &\leq -2\lambda_{\min}(D)M(t) + \bar{C}^{(0)} + \bar{C}^{(1)}M(t) + \bar{C}^{(2)}M(t - \tau) \\ &= (-2\lambda_{\min}(D) + \bar{C}^{(1)})M(t) + \bar{C}^{(2)}M(t - \tau) + \bar{C}^{(0)}, \quad t \geq 0. \end{aligned}$$

From (3.7), let $u(s) = M(s)$, $s \in [-\tau, 0]$. From the comparison theorem of ordinary differential equations, we get $u(t) \geq M(t)$, $t \geq 0$, $u(s) \geq M(s)$, $s \in [-\tau, 0]$, and thus

$$E|x(t)|_1^2 \leq M(t) \leq u(t), \quad t \geq 0.$$

The proof is complete. □

Theorem 3.3. *If the assumptions of Theorem 3.2 are satisfied, and the equilibrium of system (3.6) is stable, or asymptotically stable, then the equilibrium of system (1.1) is also stable in mean square, or asymptotically stable in mean square, respectively, i.e., the stability of system (3.6) implies the same stability of system (1.1) in mean square.*

3.3. Mean square instability.

Similar reasoning as in (3.5), we have from the definition of $|\cdot|_1$ and (3.1) that

$$\begin{aligned} E|x(t)|_1^2 &= E|\exp(-Dt)\{\varphi(0) + \int_0^t \exp(Ds)[F(s, x(s), x(s - \tau))]ds \\ &\quad + \sum_{j=1}^m \int_0^t H_j(s, x(s), x(s - \tau)) \exp(Ds)dw(s)\}|_1^2 \\ &= E\{\|\exp(-Dt)\|_3^2[\varphi(0) + \int_0^t \exp(Ds)F(s, x(s), x(s - \tau))]ds\}^T \\ &\quad \times [\varphi(0) + \int_0^t \exp(Ds)F(s, x(s), x(s - \tau))]ds \\ &\quad + \int_0^t \|\exp D(s - t)\|_3^2 [\sum_{j=1}^m H_j^T(s, x(s), x(s - \tau)) \\ &\quad \times H_j(s, x(s), x(s - \tau))]ds \\ &\geq E\{\int_0^t n^2 e^{2\lambda_{\max}(D)(s-t)} [\sum_{j=1}^m (n\lambda_{\min}(\tilde{C}_j^{(0)}) + n\lambda_{\min}(\tilde{C}_j^{(1)}))|x(s)|_1^2 \end{aligned}$$

$$\begin{aligned}
 & +n\lambda_{\min}(\tilde{D}_j^{(2)})|x(s-\tau)|_1^2]ds - 2n^2 \int_0^t e^{2\lambda_{\min}(D)(s-t)} \\
 & \times \|A(x_{n-1}(s-\tau))\|_3^2 |x(s)|_1^2 ds \} \\
 & \geq E \{ \int_0^t n^3 e^{2\lambda_{\max}(D)(s-t)} [\sum_{j=1}^m (\lambda_{\min}(\tilde{C}_j^{(1)})|x(s)|_1^2 \\
 & + \lambda_{\min}(\tilde{D}_j^{(2)})|x(s-\tau)|_1^2 + \lambda_{\min}(\tilde{C}_j^{(0)}))] ds \\
 & - 2n^2 \int_0^t e^{2\lambda_{\min}(D)(s-t)} [\sum_{i=0}^{n-2} \bar{v}_i(1+2\bar{P}_i+2\bar{Q}_i)]^2 |x(s)|_1^2 ds \} \\
 & = E \int_0^t e^{2\lambda_{\max}(D)(s-t)} [\hat{C}^{(0)} + \hat{C}^{(1)}|x(s)|_1^2 + \hat{C}^{(2)}\|x(s-\tau)\|_2^2] ds,
 \end{aligned} \tag{3.8}$$

where $\lambda_{\max}(D)$ represents the maximal eigenvalue of D , $\lambda_{\min}(\tilde{C}_j^{(1)})$ and $\lambda_{\min}(\tilde{C}_j^{(2)})$ represent the minimal eigenvalues of $\tilde{C}_j^{(1)}$ and $\tilde{C}_j^{(2)}$ ($j = 1, 2, \dots, m$),

$$\begin{aligned}
 \hat{C}^{(0)} &= n^3 \sum_{j=1}^m \lambda_{\min}(\tilde{C}_j^{(0)}), \quad \hat{C}^{(2)} = n^3 \sum_{j=1}^m \lambda_{\min}(\tilde{C}_j^{(2)}), \\
 \hat{C}^{(1)} &= n^3 \sum_{j=1}^m \lambda_{\min}(\tilde{C}_j^{(1)}) - 2n^2 [\sum_{i=0}^{n-2} \bar{v}_i(1+2\bar{P}_i+2\bar{Q}_i)]^2.
 \end{aligned}$$

Theorem 3.4. *Suppose*

- 1) *The assumptions (A₁) and (A₂) are satisfied;*
- 2)

$$\hat{C}^{(1)} = n^3 \sum_{j=1}^m \lambda_{\min}(\tilde{C}_j^{(1)}) - 2n^2 [\sum_{i=0}^{n-2} \bar{v}_i(1+2\bar{P}_i+2\bar{Q}_i)]^2 > 0.$$

Then

$$E|x(t)|_1^2 \geq u(t), \quad t \geq 0,$$

where $u(t)$ is the solution of the comparison equation

$$\begin{cases} \dot{u}(t) = (-2\lambda_{\max}(D) + \hat{C}^{(1)})u(t) + \hat{C}^{(2)}u(t-\tau) + \hat{C}^{(0)}, & t \geq 0, \\ u(s) \geq 0, & s \in [-\tau, 0]. \end{cases} \tag{3.9}$$

Proof of Theorem 3.4. Let

$$\begin{cases} M(t) = E \int_0^t e^{2\lambda_{\max}(D)(s-t)} [\hat{C}^{(0)} + \hat{C}^{(1)}|x(s)|_1^2 + \hat{C}^{(2)}\|x(s-\tau)\|_2^2] ds, \\ M(s) \geq 0, & s \in [-\tau, 0]. \end{cases} \tag{3.10}$$

We have from (3.10)

$$\begin{aligned}
 \dot{M}(t) &= -2\lambda_{\max}(D)E \int_0^t e^{2\lambda_{\max}(D)(s-t)} [\hat{C}^{(0)} + \hat{C}^{(1)}|x(s)|_1^2 + \hat{C}^{(2)}\|x(s-\tau)\|_2^2] ds \\
 &+ \hat{C}^{(0)} + \hat{C}^{(1)}E|x(t)|_1^2 + \hat{C}^{(2)}E\|x(t-\tau)\|_2^2 \\
 &\geq -2\lambda_{\max}(D)M(t) + \hat{C}^{(0)} + \hat{C}^{(1)}M(t) + \hat{C}^{(2)}M(t-\tau) \\
 &= (-2\lambda_{\max}(D) + \hat{C}^{(1)})M(t) + \hat{C}^{(2)}M(t-\tau) + \hat{C}^{(0)}.
 \end{aligned}$$

From (3.10), let $u(s) = M(s), s \in [-\tau, 0]$. By the comparison theorem of ordinary differential equations, we get $u(t) \leq M(t), t \geq 0$, and thus

$$E|x(t)|_1^2 \geq M(t) \geq u(t), \quad t \geq 0.$$

The proof is complete. □

Theorem 3.5. *If the assumptions of Theorem 3.4 are satisfied, and the equilibrium of system (3.10) is unbounded, then the equilibrium of system (1.1) is also unbounded in mean square, i.e., the unboundedness of system (3.10) implies the same unboundedness of system (1.1) in mean square.*

3.4. Mean square globally exponentially stable.

Theorem 3.6. *Suppose (A₁) and (A₂) hold and assume that there exist matrices $P > 0, Q > 0, M_0 \geq 0$ and $M_i \geq 0 (j = 1, 2, \dots, m)$ such that*

$$\begin{aligned} & \text{trace}[\sum_{j=1}^m H_j^T(t, x(t), x(t - \tau))PH_j(t, x(t), x(t - \tau))] \\ & \leq x^T(t)M_0x(t) + \sum_{j=1}^m x^T(t - \tau)M_jx(t - \tau). \end{aligned} \tag{3.11}$$

Then system (1.1) is globally exponentially stable in mean square, if there exist positive scalars $\mu > 0, \rho > 0$ and positive definite matrices $\Gamma_i > 0 (i = 1, 2, \dots, m)$ such that the LMI holds:

$$\left(\begin{array}{cc} -PD - DP + \mu Q + M_0 & 0 \\ + \sum_{j=1}^m \rho \Gamma_j + 2 \sum_{i=1}^{n-2} \bar{\nu}_i (1 + 2\bar{P}_i + 2\bar{Q}_i)P & \\ 0 & \sum_{j=1}^m (M_j - \rho \Gamma_j) - \mu Q \end{array} \right) < 0.$$

Proof of Theorem 3.6. Let

$$V(t, x(t)) = x^T(t)Px(t) + \mu \int_{t-\tau}^t x^T(s)Qx(s)ds + \sum_{j=1}^m \rho \int_{t-\tau}^t x^T(s)\Gamma_jx(s)ds. \tag{3.12}$$

From Itô's differential formula (see, e.g., [12]) we have along (1.3)

$$\begin{aligned} LV(t, x(t)) & = x^T(t)[-PD - DP]x(t) \\ & + \text{trace} \sum_{j=1}^m H_j^T(t, x(t), x(t - \tau))PH_j(t, x(t), x(t - \tau)) \\ & + 2x^T(t)PF(t, x(t), x(t - \tau)) + \mu x^T(t)Qx(t) + \sum_{j=1}^m \rho x^T(t)\Gamma_jx(t) \\ & - \mu x^T(t - \tau)Qx(t - \tau) - \sum_{j=1}^m \rho x^T(t - \tau)\Gamma_jx(t - \tau). \end{aligned} \tag{3.13}$$

From (3.11) and (3.13), we have that

$$\begin{aligned} LV(t, x(t)) & \leq x^T(t)[-PD - DP + \mu Q + M_0 + \sum_{j=1}^m \rho \Gamma_j]x(t) \\ & + 2x^T(t)PA(x_{n-1}(t - \tau))x(t) \\ & + x^T(t - \tau)[\sum_{j=1}^m (M_j - \rho \Gamma_j) - \mu Q]x(t - \tau) \\ & \leq x^T(t)[-PD - DP + \mu Q + M_0 + \sum_{j=1}^m \rho \Gamma_j] \\ & + 2 \sum_{i=1}^{n-2} \bar{\nu}_i (1 + 2\bar{P}_i + 2\bar{Q}_i)P]x(t) \\ & + x^T(t - \tau)[\sum_{j=1}^m (M_j - \rho \Gamma_j) - \mu Q]x(t - \tau) \\ & = \xi \Pi \xi^T, \end{aligned} \tag{3.14}$$

where

$$\xi = (x^T(t), x^T(t - \tau))$$

and

$$\Pi = \begin{pmatrix} -PD - DP + \mu Q + M_0 + & 0 \\ \sum_{j=1}^m \rho \Gamma_j + 2 \sum_{i=1}^{n-2} \bar{v}_i (1 + 2\bar{P}_i + 2\bar{Q}_i) P & \\ 0 & \sum_{j=1}^m (M_j - \rho \Gamma_j) - \mu Q \end{pmatrix}.$$

Let $\tilde{V}(t, x(t)) = e^{kt}V(t, x(t))$, where k is to be determined. It is easy to check that

$$V(t, x(t)) \leq \lambda_{\max}(P)|x(t)|_1^2 + \mu \int_{t-\tau}^t x^T(s)Qx(s)ds + \sum_{j=1}^m \rho \int_{t-\tau}^t x^T(s)\Gamma_j x(s)ds.$$

Thus

$$\begin{aligned} L\tilde{V}(t, x(t)) &= e^{kt}[kV(t, x(t)) + LV(t, x(t))] \\ &\leq e^{kt}\{\xi^T \Pi \xi + k[\lambda_{\max}(P)|x(t)|_1^2 + \mu \int_{t-\tau}^t x^T(s)Qx(s)ds \\ &\quad + \sum_{j=1}^m \rho \int_{t-\tau}^t x^T(s)\Gamma_j x(s)ds]\}. \end{aligned} \tag{3.15}$$

Choose k sufficiently small so that

$$\begin{aligned} \xi^T \Pi \xi + k[\lambda_{\max}(P)|x(t)|_1^2 + \mu \int_{t-\tau}^t x^T(s)Qx(s)ds \\ + \sum_{j=1}^m \rho \int_{t-\tau}^t x^T(s)\Gamma_j x(s)ds] \leq 0. \end{aligned} \tag{3.16}$$

From (3.15) and (3.16), we have

$$L\tilde{V}(t, x(t)) \leq 0,$$

which implies that

$$E\tilde{V}(t, x(t)) \leq E\tilde{V}(0, x(0)). \tag{3.17}$$

Therefore, we have

$$\begin{aligned} e^{kt}EV(t, x(t)) &\leq EV(0, x(0)) \\ &\leq E\{\lambda_{\max}(P)|x(0)|_1^2 + \mu \int_{-\tau}^0 x^T(s)Qx(s)ds \\ &\quad + \sum_{j=1}^m \rho \int_{-\tau}^0 x^T(s)\Gamma_j x(s)ds\} \\ &\leq [\lambda_{\max}(P) + \mu\tau\lambda_{\max}(Q) + m\tau\rho\lambda_{\max}(\Gamma)] \max_{-\tau \leq s \leq 0} E|x(s)|_1^2, \end{aligned} \tag{3.18}$$

where $\lambda_{\max}(\Gamma) = \max\{\lambda_{\max}(\Gamma_1), \lambda_{\max}(\Gamma_2), \dots, \lambda_{\max}(\Gamma_m)\}$. Also, it is easy to see that

$$EV(t, x(t)) \geq \lambda_{\min}(P)|x(t)|_1^2. \tag{3.19}$$

From (3.18) and (3.19), it follows that

$$\begin{aligned} E|x(t)|_1^2 &\leq \lambda_{\min}^{-1}(P)[\lambda_{\max}(P) + \mu\tau\lambda_{\max}(Q) + m\tau\rho\lambda_{\max}(\Gamma)] \\ &\quad \times e^{-kt} \max_{-\tau \leq s \leq 0} E|x(s)|_1^2. \end{aligned} \tag{3.20}$$

Thus system (1.1) is globally exponentially stable in mean square. □

Remark 2. Note that [23] is a special case of system (1.1) and note that the Laplace transform technique fails for system (1.1).

Remark 3. System (1.1) can be generalized to the general form

$$\begin{aligned} dx &= [-(D + \Delta D(t))x(t) + (B + \Delta B(t))F(t, x(t), x(t - \tau_1(t)), \\ &\quad \dots, x(t - \tau_m(t))) + \sum_{p=1}^k (W_p + \Delta W_p(t)) \int_{t-\tau_p(t)}^t g_p(x(s))ds]dt \\ &\quad + \sum_{j=1}^l H_j(t, x(t), x(t - \sigma_j(t)))dw(t). \end{aligned}$$

4. Examples. We consider the following special case of (1.1) with three types of cells as in [14]

$$\left\{ \begin{aligned} dx_0 &= \left\{ \left[\frac{p_0}{1+\gamma_1^0(x_2(t-\tau))^2} - \frac{q_0}{1+\gamma_2^0(x_2(t-\tau))^2} \right] \frac{\nu_0}{1+\beta_0(x_2(t-\tau))^2} x_0(t) - d_0 x_0(t) \right\} dt \\ &\quad + h^0(x_0(t-\tau))dw_0(t), \\ dx_1 &= \left\{ \left[1 - \frac{p_0}{1+\gamma_1^0(x_2(t-\tau))^2} + \frac{q_0}{1+\gamma_2^0(x_2(t-\tau))^2} \right] \frac{\nu_0}{1+\beta_0(x_2(t-\tau))^2} x_0(t) \right. \\ &\quad \left. + \left[\frac{p_1}{1+\gamma_1^1(x_2(t-\tau))^2} + \frac{q_1}{1+\gamma_2^1(x_2(t-\tau))^2} \right] \frac{\nu_1}{1+\beta_1(x_2(t-\tau))^2} x_1(t) - d_1 x_1(t) \right\} dt \\ &\quad + h^1(x_1(t-\tau))dw_1(t), \\ dx_2 &= \left\{ \left[1 - \frac{p_1}{1+\gamma_1^1(x_2(t-\tau))^2} + \frac{q_1}{1+\gamma_2^1(x_2(t-\tau))^2} \right] \frac{\nu_1}{1+\beta_1(x_2(t-\tau))^2} x_1(t) - d_2 x_2(t) \right\} dt \\ &\quad + h^2(x_2(t-\tau))dw_2(t). \end{aligned} \right. \tag{4.1}$$

Here $x_0(t)$, $x_1(t)$, and $x_2(t)$ are the number of cancer stem cells (CSCs), progenitor cells (PCs), and terminally differentiated cells (TDCs), respectively, at time t . The time-delay τ is 0 for Figure 1 and 10 time units for Figure 2. There is only one stochastic disturbance term, $h^i(x_i(t-\tau))$, $i = 0, 1, 2$, for each cell type, and it is an explicit function of only the cell type that it affects.

The figures show the solution of (4.1) implemented in MATLAB with initial condition $x(0) = (10, 200, 800)^T$. The parameters and stochastic terms used in each figure are listed in Table 1. Figures 1 and 2 have the same parameters and stochastic terms and differ only in the time delay. Due to the presence of a stochastic term, each figure is the average of ten trials. The x -axis is time units, and the y -axis is number of cells in a log-scale. The inset shows a zoomed-in portion of the graph.

In Figure 1a, there is no noise term. The number of cells shoots up to about 10^4 and then levels off. Equilibrium is reached. In Figure 1b, the noise term is

$$H(x(t)) = \begin{pmatrix} 30 \\ 40 \\ 20 \end{pmatrix}.$$

The number of cells shoots up to about 10^4 and then levels off. Equilibrium is reached, but there is small perturbation around the equilibrium position. In Figure

1c, the noise term is

$$H(x(t)) = \begin{pmatrix} \frac{h_1 x_1^2}{1 + g_1 x_1^2} \\ \frac{h_2 x_2^2}{1 + g_2 x_2^2} \\ \frac{h_3 x_3^2}{1 + g_3 x_3^2} \end{pmatrix}.$$

The number of cells shoots up to about 10^4 and then levels off. Equilibrium is reached, but there is small perturbation around the equilibrium position. In Figure 1d, the noise term is

$$H(x(t)) = \begin{pmatrix} \frac{h_1 x_1^2}{1 + g_1 x_1} \\ \frac{h_2 x_2^2}{1 + g_2 x_2} \\ \frac{h_3 x_3^2}{1 + g_3 x_3} \end{pmatrix}.$$

The number of cells shoots up and increases by orders of magnitude more than the previous scenarios. There is large perturbation. Equilibrium is not reached, but the total number of cells is between 10^6 and 10^{12} .

In Figures 2a, b, and c, the number of cells shoots up to about 10^6 and then levels off. This is 100 times greater than in Figure 1. Equilibrium is reached, but there are oscillations in the number of PCs and TDCs around the equilibrium position. The noise term has a negligible effect in Figures 2b and c. In Figure 2d, the number of cells shoots up and increases by orders of magnitude more than the previous scenarios. There is small perturbation. Equilibrium is not reached, and the number of cells grows unboundedly.

The parameters were chosen both from biological data from our collaborator's lab [14] and from requiring that equilibrium is reached. From experiments with tumor cells we know that the degradation rate is the greatest for TDCs, then PCs, and then CSCs. We also know that the equilibrium tumor size is roughly 10^6 total cells from our collaborator's lab. Additionally, the probabilities, p_0 , q_0 , p_1 , and q_1 , and degradation rates, d_0 , d_1 , and d_2 , are between 0 and 1 by definition. With these restrictions, the parameters were then chosen through guess and check until equilibrium was reached.

5. Conclusion. Breast cancer is a malignant disease with a heterogeneous distribution of cell types. Mathematical modeling has been utilized to study underlying mechanistic principles and to help design appropriate experiments for better understanding of complex dynamics and interactions of tumor cell populations. In this paper, we have studied the moment stability of nonlinear stochastic systems of breast cancer stem cells with time-delays. Based on the technique of the variation-of-constants formula along with the comparison principle, the moment stability theorems have been established for the systems with the stability properties for the comparative systems. By applying the linear matrix inequality (LMI) technique, we also obtain a criteria for the exponential stability in mean square of the nonlinear stochastic systems. Some numerical examples are performed to further validate the results. As discussed in [14], the results developed in this paper will help to further reveal the underlying mechanisms to regulate and control the dynamics of cancer

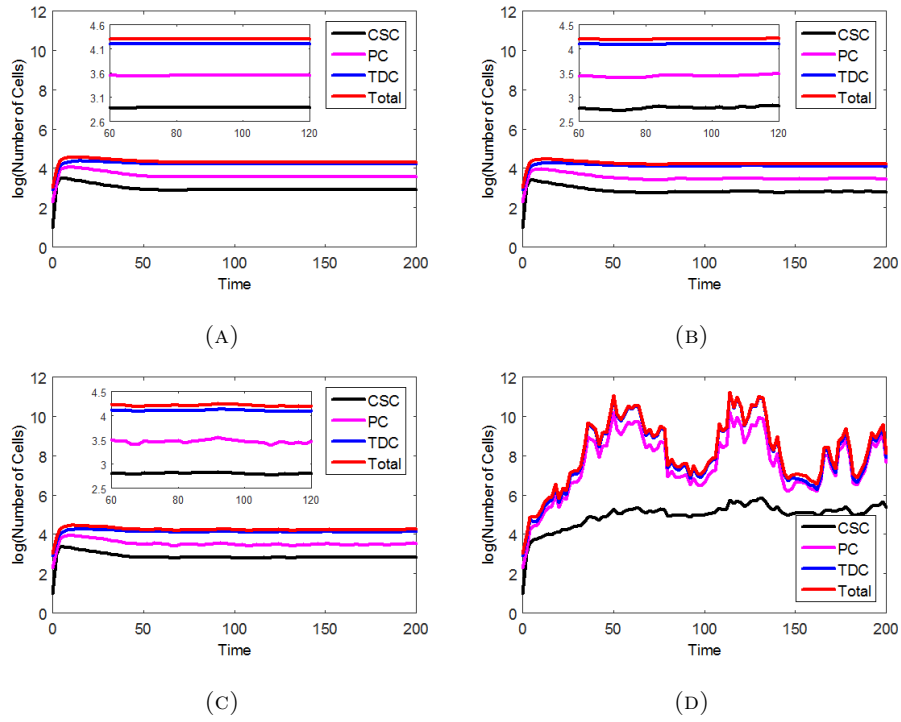


FIGURE 1. Solution of (4.1). Parameters and noise functions are listed in Table 1. Time delay is 0. All figures represent the average of ten trials. (a) There is no noise term. Equilibrium is reached. (b), (c) There is a noise term. Equilibrium is reached with small perturbation. (d) There is a noise term. The number of cells is orders of magnitude greater than the previous scenarios. Equilibrium is not reached, but the number of cells is bounded. There is large perturbation.

tumor growth. Hence the outcome of this study may potentially lead to design novel therapeutic strategies for treating cancer development. We plan next to explore the stochastic dynamics of breast cancer cells with inherent noise perturbation on the variations of different parameters.

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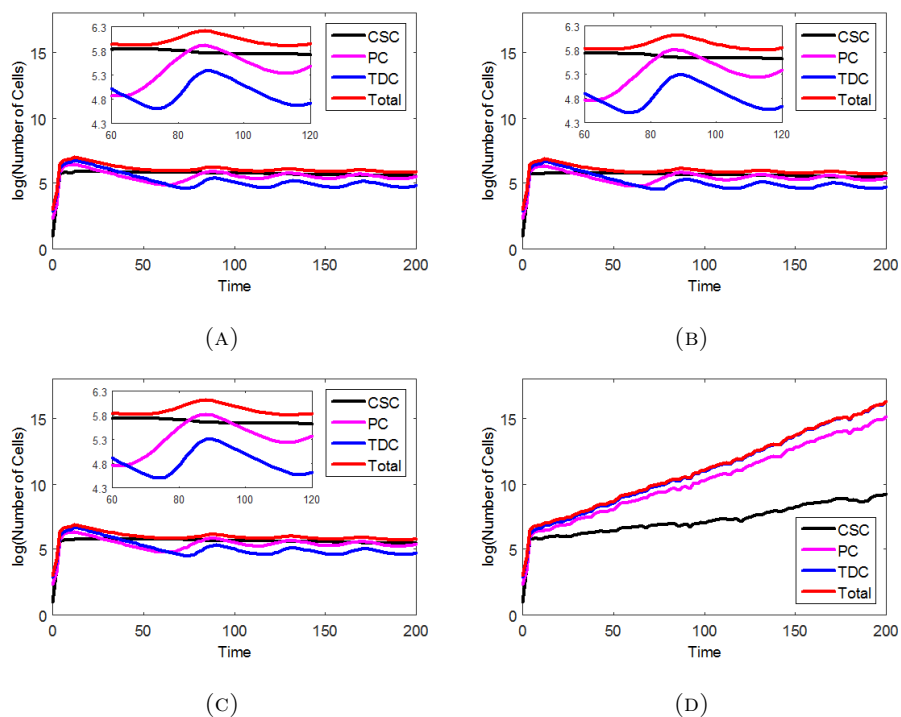


FIGURE 2. Solution of (4.1). Parameters and noise functions are listed in Table 1. Time delay is 10 time units. All figures represent the average of ten trials. (a) There is no noise term. Equilibrium is reached with oscillations in PCs and TDCs. (b), (c) There is a noise term. Equilibrium is reached with oscillations in PCs and TDCs. (d) There is a noise term. The number of cells is orders of magnitude greater than the previous scenarios. Equilibrium is not reached, and the number of cells is unbounded. There is small perturbation.

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Parameters or Function	Figure 1a, 2a	Figure 1b, 2b	Figure 1c, 2c	Figure 1d, 2d
p_0	0.5	0.5	0.5	0.5
p_1	0.001	0.001	0.001	0.001
q_0	0.2	0.2	0.2	0.2
q_1	0.9	0.9	0.9	0.9
ν_0	10	10	10	10
ν_1	10	10	10	10
γ_1^0	7×10^{-9}	7×10^{-9}	7×10^{-9}	7×10^{-9}
γ_1^1	2×10^2	2×10^2	2×10^2	2×10^2
γ_2^0	4×10^{-10}	4×10^{-10}	4×10^{-10}	4×10^{-10}
γ_2^1	8×10^{-18}	8×10^{-18}	8×10^{-18}	8×10^{-18}
β_0	3×10^{-8}	3×10^{-8}	3×10^{-8}	3×10^{-8}
β_1	2×10^{-7}	2×10^{-7}	2×10^{-7}	2×10^{-7}
d_0	0.001	0.001	0.001	0.001
d_1	0.08	0.08	0.08	0.08
d_2	0.085	0.085	0.085	0.085
$H(x(t))$	$\begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix}$	$\begin{pmatrix} 30 \\ 40 \\ 20 \end{pmatrix}$	$\begin{pmatrix} \frac{h_1 x_1^2}{1+g_1 x_1^2} \\ \frac{h_2 x_2^2}{1+g_2 x_2^2} \\ \frac{h_3 x_3^2}{1+g_3 x_3^2} \end{pmatrix}$	$\begin{pmatrix} \frac{h_1 x_1^2}{1+g_1 x_1} \\ \frac{h_2 x_2^2}{1+g_2 x_2} \\ \frac{h_3 x_3^2}{1+g_3 x_3} \end{pmatrix}$
h_0	-	-	300	3
h_1	-	-	5000	10
h_3	-	-	6000	22
g_0	-	-	10	10
g_1	-	-	10	10
g_3	-	-	20	20

TABLE 1. Parameters and noise term used in Figures 1 and 2.

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Received November 2015; revised February 2016.

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