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STOCHASTIC DIFFERENTIAL DELAY EQUATION, MOMENT STABILITY, AND APPLICATION TO HEMATOPOIETIC STEM CELL REGULATION SYSTEM*

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Abstract. We study the moment stability of the trivial solution of a linear differential delay equation in the presence of additive and multiplicative white noise. The results established here are applied to examining the local stability of the hematopoietic stem cell (HSC) regulation system in the presence of noise. The stability of the first moment for the solutions of a linear differential delay equation under stochastic perturbation is identical to that of the unperturbed system. However, the stability of the second moment is altered by the perturbation. We obtain, using Laplace transform techniques, necessary and sufficient conditions for the second moment to be bounded. In applying the results to the HSC system, we find that the system stability is sensitive to perturbations in the stem cell differentiation and death rates, but insensitive to perturbations in the proliferation rate.

Key words. stochastic differential delay equation, moment stability, hematopoietic disease

AMS subject classifications. 34K50, 92C99

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1. Introduction.

Delays in feedback regulation are ubiquitous in biological control systems, where the retardation usually originates from maturing processes or finite signaling velocities [4, 15, 16, 17, 21, 30, 34, 36, 37, 39, 45, 46]. Differential delay equation model systems with retarded arguments have been extensively developed in the past several decades (see [3, 10, 11, 18, 19, 20] and the references therein). However, in applied areas, deterministic systems fail to capture the essence of the fluctuations in the real situation, and one must instead consider models with stochastic processes that take into account the perturbations present in the real world. In situations where delays are important, models with stochastic perturbations are framed by stochastic differential delay equations.

The current study is motivated by an investigation of the stability of the hematopoietic regulatory system and its connection with several hematological diseases [5, 7, 8, 9, 21, 30, 39]. All blood cells originate from the hematopoietic stem cells (HSC) in the bone marrow. These stem cells differentiate and proliferate, giving rise to the three major cell lines: the leukocytes (white blood cells), the platelets, and the erythrocytes (red blood cells). The three peripheral regulatory loops are all of a negative feedback nature, and are mediated by a variety of cytokines including erythropoietin (EPO), thrombopoietin (TPO), and granulocyte colony-stimulating factor (G-CSF) [1, 50, 53, 55, 58]. These cytokines are synthesized and released by cells of the hematopoietic system. They control the hematopoietic system by regulating the growth, differentiation, and survival of cells.

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A mathematical model of the hematopoietic regulation system that combines the delay for cell maturation and negative feedback of the differentiated cells has been studied in [7, 8]. The numbers of circulating cells in a healthy person usually fluctuate with small amplitude around their normal levels. However, there are several hematological diseases that display a highly dynamic nature characterized by statistically significant oscillations in one or more of the circulating progeny of the HSC [21]. These diseases include, but are not limited to, cyclical neutropenia [8, 21, 22, 23], periodic chronic myelogenous leukemia [7, 12, 52], cyclical thrombocytopenia [49, 54, 59], and periodic hemolytic anemia [33, 45]. For example, cyclical neutropenia is a rare genetic blood disease in which the patient's neutrophil level drops to an extremely low level for six to eight days every three weeks. Neutrophils are a type of white blood cell important in the defense of the body against infection. Since stem cell oscillations are thought to drive oscillations in several periodic hematological diseases [21], understanding the HSC dynamics is important.

The differential delay equations that model the HSC dynamics have been developed for a G_0 cell cycle model in [13, 31, 32, 33, 39, 51]. The delays in these models reflect the nonzero time that it takes the cells to complete the proliferative phase of the cell cycle. For example, the HSC takes about 2.8 days to complete one cell cycle. Previous studies suggested that the HSC population becomes unstable and develops oscillations when the steady state corresponding to the healthy state is destabilized, for example by increasing the apoptosis (death) rate or the differentiation rate in the stem cells. However, in these studies, the stochastic perturbations that occur in the real world, and which might lead to instability and oscillation, were not taken into account. In this paper, we will investigate the effects of random perturbation and answer the following two questions:

1. If the steady state of the system without noise is unstable, is it possible to stabilize the steady state by noise perturbation?

2. If the steady state of the system without noise is stable, is it possible to destabilize the steady state by noise perturbation? If the answer is "YES," such perturbation usually originates from the perturbation in the system parameters. Therefore, there are thresholds for each of the parameters such that the steady state is stable when the perturbation is smaller than this threshold and unstable otherwise. The quantitative estimation of these thresholds will also be considered in this paper.

The answers to these two questions offer insight into the stability of the hematopoietic system in the face of stochastic perturbations.

The HSC dynamics with stochastic perturbation is modeled by a nonlinear stochastic differential delay equation. To answer the questions posed above, we linearize the equation around the steady state and study the stability of the resulting equation.

Consider the process described by the differential delay equation

$$\frac{dz}{dt} = f(z, z_\tau), \tag{1.1}$$

where $z_\tau = z(t - \tau)$. It may be the case that the function $f(z, z_\tau)$ is subject to some random effect (noise), so that we have

$$\frac{dz}{dt} = f(z, z_\tau) + \sigma(t, z, z_\tau) \cdot \xi_t(\omega), \tag{1.2}$$

where $\xi_t(\omega)$ is a stochastic process that represents the noise term. In our study of the hematopoietic system, this noise is internal to the system because of random fluctuations in the system parameters, e.g., fluctuations in the differentiation rate, death rate, or proliferation rate of stem cells. However, the precise properties of the noise are not known. To gain insight into the effect of noise on the system, we assume the noise to be Gaussian distributed white noise with zero mean and a delta function autocorrelation $\langle \xi_t \xi_s \rangle = \delta(t-s)$. We assume further that the function σ does not depend on t explicitly. Using the definition of Gaussian white noise ξ_t as the derivative of the Wiener process $W(t)$, equation (1.2) can be written as

$$dz = f(z, z_\tau)dt + \sigma(z, z_\tau)dW(t). \tag{1.3}$$

From a formal point of view, we can solve (1.3) and write the stochastic process $z(t) = z(t;\omega)$ as

$$z(t) = z(0) + \int_0^t f(z(s), z_\tau(s))ds + \text{“}\int_0^t \sigma(z(s), z_\tau(s))dW(s).\text{”} \tag{1.4}$$

There are two interpretations for the stochastic integral

$$\text{“}\int_0^t \sigma(z(s), z_\tau(s))dW(s),\text{”}$$

the Itô interpretation and the Stratonovich interpretation. The Itô interpretation is usually used when the noise is white, but when the noise is colored (i.e., does not have a delta function autocorrelation), the Stratonovich interpretation is preferable. This issue has been discussed by many people (see, for example, [26, pp. 232–237], [28, pp. 346–351], [29, pp. 152–155], and [48, pp. 35–37]), and it is safe to say that the debate over the issue is far from settled. In this study we adopt the Itô interpretation for two reasons. First, the Itô approach is mathematically preferable [29], and second it is relatively straightforward to pass from results obtained using the Itô interpretation to one appropriate for the Stratonovich interpretation.

Indeed, assuming that the stochastic integral is to be interpreted as an Itô integral, (1.4) can be written as

$$z(t) = z(0) + \int_0^t f(z(s), z_\tau(s))ds + \int_0^t \sigma(z(s), z_\tau(s))dW(s). \tag{1.5}$$

There is a simple relation between the Itô interpretation and the Stratonovich interpretation [14, 48, 57]. Thus, the solution of (1.3) using the Stratonovich interpretation of the stochastic integral

$$z(t) = z(0) + \int_0^t f(z(s), z_\tau(s))ds + \int_0^t \sigma(z(s), z_\tau(s)) \circ dW(s)$$

is equivalent to the solution of the modified Itô equation

$$\begin{aligned} z(t) = z(0) &+ \int_0^t f(z(s), z_\tau(s))ds + \frac{1}{2}\int_0^t \sigma_z'(z(s), z_\tau(s))\sigma(z(s), z_\tau(s))ds \\ &+ \int_0^t \sigma(z(s), z_\tau(s))dW(s). \end{aligned}$$

Thus, the results in this paper obtained from the Itô approach are also applicable to a Stratonovich interpretation after replacing $f(z, z_\tau)$ in (1.3) by

$$f(z, z_\tau) + \frac{1}{2}\sigma_z'(z, z_\tau)\sigma(z, z_\tau). \tag{1.6}$$

We will see below that these two different interpretations can lead to significant changes in the predicted stability of the system.

Assume that $z = z_*$ is a steady state of (1.1); i.e., $f(z_*, z_*) = 0$. What we are interested to know is the effect of the noise perturbation on the steady state. In general, we do not have $\sigma(z_*, z_*) = 0$. Hence, $z(t) \equiv z_*$ is not a solution of the perturbed equation (1.3). We will address the question of under what condition the stochastic process $z(t)$ satisfying the perturbed equation (1.3) remains close to the steady state $z = z_*$, i.e., when the solution $z = z_*$ is "stable" under stochastic perturbation.

Linearizing (1.3) around the steady state yields the linear stochastic differential delay equation

$$dx = (ax + bx_\tau)dt + (\sigma_0 x + \sigma_1 x_\tau + \sigma_2)dW(t), \tag{1.7}$$

where $x(t) = z(t) - z_*$ and a, b, σ_i are constants given by

$$a = f'_z(z_*, z_*), \quad b = f'_{z_\tau}(z_*, z_*),$$

$$\sigma_0 = \sigma'_z(z_*, z_*), \quad \sigma_0 = \sigma'_{z_\tau}(z_*, z_*), \quad \sigma_2 = \sigma(z_*, z_*).$$

At this point, we will study the moment stability of (1.7) to answer the following questions:

1. Under what conditions does the ensemble mean of the solutions of (1.7) approach 0 when $t \to \infty$?
2. Under what condition is the variance of the solutions bounded (or unbounded) for all $t > 0$?
3. When the variance is bounded, then the upper limit of the variance, when $t \to \infty$, provides the estimation of its upper bound when t is large. Therefore, the estimation of the variance when $t \to \infty$ is interesting and will be studied in this paper.

Despite the apparently simple form of (1.7), the stability problem is not trivial, because of the combination of delay and stochastic terms.

Stochastic differential delay equations were introduced by Itô and Nisio in the 1960s [24]. Those authors also discussed the existence and uniqueness of the solution. However, progress in this area has been slow, and most of the results including stochastic stability, numerical approximation, etc., have been developed in the last decade [2, 27, 40, 41, 42, 43, 44, 47]; see [25] for a recent survey of these results. Despite the efforts of many researchers, this field is still in its infancy. For example, conditions for the stability of (1.7), a linear stochastic differential delay equation with constant coefficients, are not known. In the case of a stochastic ordinary differential equation ($b = \sigma_1 = 0$) and a delay differential equation ($\sigma_i = 0$), the stability conditions of the equation have been well established [20, 41]. However, when trying to extend these results to stochastic differential delay equations, one encounters serious difficulties because of the combination of delay and stochastic processes, and the explicit solution of (1.7) is not known.

The Lyapunov function method is useful for studying the stability of differential equations and has been developed for both differential delay equations and stochastic differential equations. In the 1990s, Mao extended this method to stochastic functional differential equations [41, Chapter 5]. Because of the results of Mao, we have some results for the stability of stochastic differential delay equations (see [41, section 5.6] for details). However, when applying these results to (1.7), we find that they are applicable only when $a < 0$. In our study of the hematopoietic system, the case $a > 0$

is the most interesting, and we therefore need to develop new results for the moment stability of (1.7).

In this paper, we will first develop the mathematical theory for the moment stability of the linear stochastic differential delay equation (1.7), and then apply the result to studying the stability of the hematopoietic system under stochastic perturbation. The paper is organized as follows. In section 2 we briefly present the mathematical preliminaries for linear differential delay equations needed for the rest of the paper. Section 3 examines the effect of stochastic perturbation on the behavior of the first and second moments of (1.7). This section contains the main mathematical results for the moment stability. The first moment is discussed in section 3.1. Section 3.2 considers the second moment and is divided into two parts according to the type of stochastic perturbation, namely, additive white noise and general cases. Section 4 studies the stability of the hematopoietic regulation system under stochastic perturbations. The paper concludes with a brief discussion in section 5.

In what follows, we will take $\tau = 1$ by normalizing the time through

$$(x, t, a, b, \sigma_i, \tau) \to (x, t/\tau, a/\tau, b/\tau, \sigma_i/\tau, 1).$$

Thus, we will study the equation

$$dx = (ax + bx_1)dt + (\sigma_0 x + \sigma_1 x_1 + \sigma_2)dW(t). \tag{1.8}$$

2. Mathematical preliminaries: The system without noise. When the σ_i in (1.8) are zero, we have the linear differential delay equation

$$\frac{dx}{dt} = ax + bx_1. \tag{2.1}$$

The differential delay equation (2.1) has been studied extensively, and [20] can be consulted for a detailed exposition.

The characteristic function of (2.1) is

$$h(\lambda) = \lambda - a - be^{-\lambda}. \tag{2.2}$$

The fundamental solution of (2.1), denoted by $X(t)$, has a Laplace transform given by $h^{-1}(\lambda)$ [20, Chapter 1]. This fundamental solution of (2.1) will be essential in following study.

Let $C([-1, 0], \mathbb{R})$ be the family of continuous functions ϕ from $[-1, 0]$ to $\mathbb{R}$ with the norm $\|\phi\| = \sup_{-1\leq\theta\leq 0} |\phi(\theta)|$. Using the fundamental solution, the solution of (2.1) with initial condition $x(\theta) = \phi(\theta) \in C([-1, 0], \mathbb{R})$ is given by

$$x_\phi(t) = X(t)\phi(0) + \int_{-1}^{0} X(t - 1 - s)\phi(s)ds. \tag{2.3}$$

From (2.3), the asymptotic behavior of $x_\phi(t)$ is determined by the fundamental solution $X(t)$. We have following result.

THEOREM 2.1 (see [20, Chapter 1, Theorem 5.2]). *If $\alpha_0 = \max\{\Re(\lambda) : h(\lambda) = 0\}$, then, for any $\alpha > \alpha_0$, there is a constant $K = K(\alpha)$ such that the fundamental solution X satisfies the inequality*

$$|X(t)| \leq Ke^{\alpha t} \qquad (t \geq 0). \tag{2.4}$$

From Theorem 2.1, the solutions (2.3) with any $\phi(\theta) \in C([-1,0],\mathbb{R})$ approach 0 as $t \to \infty$ if and only if $\alpha_0 < 0$. The region in the (a,b)-plane such that $\alpha_0 < 0$ is given by [20]

$$S = \{(a,b) \in \mathbb{R}^2 \mid -a\sec\xi < b < a, \text{ where } \xi = a\tan\xi,\ a < 1,\ \xi \in (0,\pi)\}. \tag{2.5}$$

Here, the values of α_0 and $K(\alpha)$ are significant for understanding the stability of the system. The estimation of α_0 and $K(\alpha)$ are given below.

The number α_0 is given by the maximum real solution of the equation

$$(\alpha_0 - a)^2 - b^2 e^{-2\alpha_0} + \left[\arccos\frac{\alpha_0 - a}{be^{-\alpha_0}}\right]^2 = 0. \tag{2.6}$$

When $b \neq 0$, for any $\alpha > \alpha_0$ define

$$K(\alpha) = 1 + \xi(\alpha) + \frac{(|a-\alpha_0|e^{\alpha} + |b|)\log 2}{|b|\pi}, \tag{2.7}$$

where

$$\xi(\alpha) = \frac{1}{2\pi}\left|\int_{-2|b|e^{-\alpha}}^{2|b|e^{-\alpha}} \frac{a + be^{-(\alpha+iz)} - \alpha_0}{(\alpha - \alpha_0 + iz)h(\alpha+iz)} dz\right|.$$

Then (2.4) is satisfied. When $b = 0$, it is obvious that (2.4) holds with $K(\alpha) = 1$ whenever $\alpha \geq a$.

When $|b| < -a$, it is not difficult to prove that

$$|X(t)| \leq e^{(a+\mu)t} \quad (\forall t > 0), \tag{2.8}$$

where $|b| < \mu < -a$ is such that $\mu e^{a+\mu} - |b| = 0$. Thus, we can specify $K(\alpha) = 1$ with $\alpha = a + \mu$ when $|b| < -a$.

These considerations provide a framework for computing α_0 and $K(\alpha)$ with $\alpha > \alpha_0$ that satisfies (2.4).

3. Moment stability: The system with noise perturbation. We now turn to a study of the system with noise; i.e., the parameters σ_i in (1.8) are not all zero.

From the fundamental solution $X(t)$ in the previous section, the solution of (1.8) with the initial function $x(\theta) = \phi(\theta) \in C([-1,0],\mathbb{R})$ is a stochastic process given by

$$x(t;\phi) = x_\phi(t) + \int_0^t X(t-s)(\sigma_0 x(s;\phi) + \sigma_1 x_1(s;\phi) + \sigma_2)dW(s), \tag{3.1}$$

where $x_1(s;\phi) = x(s-1;\phi)$ and $x_\phi(t)$, the solution of the deterministic equation (2.1), is defined by (2.3). The existence and uniqueness theorem for the stochastic differential delay equation has been established in [24] (see also [41, Chapter 5]). The solution $x(t;\phi)$ is a stochastic process with distribution at any time t determined by the initial function $\phi(\theta)$. From the Chebyshev inequality, the possible range of x at time t is "almost" determined by its mean and variance at time t. Thus, the first and second moments of the solution are important for investigating the solution behavior and will be studied in this section. We first define pth moment exponential stability and pth moment boundedness.

DEFINITION 3.1. *The solution of* (1.8) *is said to be first moment exponentially stable if there is a pair of positive constants* λ *and* C *such that*

$$|Ex(t;\phi)| \leq C\|\phi\|e^{-\lambda t} \quad (\forall t > 0)$$

for all $\phi \in C([-1,0],\mathbb{R})$. *When* $p \geq 2$, *the solution of* (1.8) *is said to be pth moment exponentially stable if there is a pair of positive constants* λ *and* C *such that*

$$E\left(|x(t;\phi) - E(x(t;\phi))|^p\right) \leq C\|\phi\|^p e^{-\lambda t} \quad (\forall t \geq 0)$$

for all $\phi \in C([-1,0],\mathbb{R})$.

DEFINITION 3.2. *For* $p \geq 2$, *the solution of* (1.8) *is said to be pth moment bounded if there is a constant* A *such that*

$$E\left(|x(t;\phi) - E(x(t;\phi))|^p\right) \leq A \quad (\forall t \geq 0)$$

for all $\phi \in C([-1,0],\mathbb{R})$. *Otherwise, the pth moment is said to be unbounded.*

We have used E to denote the mathematical expectation. In this paper, we will study the exponential stability of the first moment and the boundedness of the second moment. Hereinafter, we denote $x(t;\phi)$ simply by $x(t)$.

3.1. The first moment. Taking the mathematical expectation of both sides of (1.8), we have, with the Itô interpretation,

$$\frac{dEx(t)}{dt} = aEx(t) + bEx(t-1). \tag{3.2}$$

Thus, we obtain a differential delay equation for the first moment $Ex(t)$. From the discussion in the previous section, the first moment $Ex(t)$ approaches 0 as $t \to \infty$ if and only if the parameter α_0 defined in Theorem 2.1 is less than 0. In fact, by (3.1) and the properties of Itô integral, we have

$$Ex(t) = X(t)\phi(0) + \int_{-1}^{0} X(t-1-s)\phi(s)ds. \tag{3.3}$$

THEOREM 3.3. *If* $\alpha_0 = \max\{\Re(\lambda) : h(\lambda) = 0\}$, *then for any* $\alpha > \alpha_0$ *there is a constant* $K_1 = K_1(\alpha)$ *such that*

$$|Ex(t)| \leq K_1\|\phi\|e^{\alpha t} \qquad (t \geq 0). \tag{3.4}$$

Therefore, if $\alpha_0 < 0$, *then* (1.8) *is first moment exponentially stable.*

3.2. The second moment. We now turn to the behavior of the second moment of the solution $x(t)$. From Theorem 3.3, the stability condition of the first moment is identical to that of the unperturbed system and is determined exclusively by a and b. Thus the stability of the first moment is independent of the parameters σ_i. However, the situation of second moment is more complicated and depends on σ_i. When $\sigma_2 \neq 0$, we cannot expect the second moment to be exponentially stable. Let $M(t)$ be the second moment of the solution at a time t. Then the Chebyshev inequality yields

$$P\left[|x(t) - Ex(t)| \geq k\sqrt{M(t)}\right] \leq \frac{1}{k^2} \tag{3.5}$$

for any $k > 0$. Thus, when the second moment is bounded, the solutions of (1.8) are also bounded in some sense. We will answer in this section when the second moment is bounded for all $t > 0$.

The following notation will be used. Let $x(t)$ be a solution of (1.8), and define

$$\tilde{x}(t) = x(t) - Ex(t), \tag{3.6}$$

$$M(t) = E(\tilde{x}(t)^2), \quad M_1(t) = M(t-1), \quad N(t) = E(\tilde{x}(t)\tilde{x}(t-1)), \tag{3.7}$$

$$F(t) = \int_0^t X^2(t-s)(\sigma_0 Ex(s) + \sigma_1 Ex_1(s) + \sigma_2)^2 ds. \tag{3.8}$$

$M(t)$ is the second moment studied below. Applying the Itô isometry to $M(t)$, a simple computation yields that

$$M(t) = F(t) + \int_0^t X^2(t-s)(\sigma_0^2 M(s) + \sigma_1^2 M_1(s) + 2\sigma_0\sigma_1 N(s))ds. \tag{3.9}$$

3.2.1. Additive noise. When $\sigma_0 = \sigma_1 = 0$, we have the additive noise case, and the second moment is given explicitly by

$$M(t) = \sigma_2^2 \int_0^t X^2(t-s)ds. \tag{3.10}$$

By Theorem 2.1, we have the following result in the case of additive noise.

THEOREM 3.4. *Let $\alpha_0 = \{\Re(\lambda) : h(\lambda) = 0\}$. If $\sigma_0 = \sigma_1 = 0$, the second moment of* (1.8) *is bounded if and only if $\alpha_0 < 0$. Furthermore, for any $\alpha_0 < \alpha < 0$, there exists $K = K(\alpha)$ such that*

$$\left| M(t) - \sigma_2^2 \int_0^\infty X^2(s)ds \right| \leq -\frac{\sigma_2^2 K^2}{2\alpha} e^{2\alpha t}. \tag{3.11}$$

From Theorem 3.4, the boundedness of the second moment is characterized by α_0, which is in turn determined by a and b of the unperturbed equation. This result was presented in [38], but the proof in [38] is in error. We reprove this result here and the estimation of the second moment $M(t)$ when $t \to \infty$ is given by

$$\lim_{t\to\infty} M(t) = \sigma_2^2 \int_0^\infty X^2(s)ds \leq -\frac{\sigma_2^2 K^2}{2\alpha}. \tag{3.12}$$

3.2.2. General cases ($\boldsymbol{\sigma_0 \neq 0}$ or $\boldsymbol{\sigma_1 \neq 0}$). When $\sigma_0 \neq 0$ or $\sigma_1 \neq 0$, the noise at time t depends on x at time t or time $(t-1)$. In this general case, there is no simple form for the second moment. First, we have by (3.9) that

$$M(t) \geq F(t).$$

When $\alpha_0 \geq 0$, we have $X(t) = O(e^{\alpha_0 t})$ as $t \to \infty$. Thus, we can always take an initial function $\phi(\theta)$ such that $F(t)$ tends to infinity when $t \to \infty$, for example, the initial functions $\phi(\theta)$ such that

$$Ex(t) = \sum_i c_i e^{\lambda_i t},$$

where $h(\lambda_i) = 0$ and c_i are nonzero constants.

Therefore, we have the following necessary condition for the boundedness of the second moment.

LEMMA 3.5. *If the second moment of* (1.8) *is bounded, then* $\alpha_0 < 0$*; i.e., the unperturbed equation is exponentially stable.*

From now on, we will always assume that $\alpha_0 < 0$. In this situation, we have

$$\lim_{t\to\infty} F(t) = \sigma_2^2 \int_0^\infty X^2(s)ds. \tag{3.13}$$

We next study the second moment using the Laplace transform. We denote by $\mathcal{L}(p)(s)$ the Laplace transform of $p(t)$ when

$$p(t) < Pe^{at} \quad (t > 0)$$

for constants P and a.

Let $X_1(t) = X(t-1)$. It is easy to check that the functions $X^2(t)$, $X(t)X_1(t)$, $M(t)$, and $N(t)$ have Laplace transforms.

The following theorem establishes the condition for the second moment of the solution of (1.8) to be bounded.

THEOREM 3.6. *Let*

$$f(s) = \frac{\mathcal{L}(XX_1)(s)}{\mathcal{L}(X^2)(s)}, \qquad g(s) = \frac{\mathcal{L}(N)(s)}{\mathcal{L}(M)(s)}, \tag{3.14}$$

and

$$H(s) = s - (2a + \sigma_0^2) - (2bf(s) + 2\sigma_0\sigma_1 g(s)) - \sigma_1^2 e^{-s}. \tag{3.15}$$

The second moment of the solution of (1.8) *is bounded if and only if all solutions of the characteristic equation* $H(s) = 0$ *have negative real part. Furthermore, when the second moment is bounded, it approaches a constant exponentially when* $t \to \infty$.

Proof. We will divide the proof into several steps.

(1) By (3.9), we have

$$M(t) = F(t) + X^2 * (\sigma_0^2 M + \sigma_1^2 M_1 + 2\sigma_0\sigma_1 N),$$

where $*$ denotes convolution. Taking the Laplace transform of both sides and solving the resulting equation for $\mathcal{L}(M)(s)$, we have

$$\mathcal{L}(M)(s) = \frac{\mathcal{L}(F)(s)}{1 - \mathcal{L}(X^2)(s)(\sigma_0^2 + \sigma_1^2 e^{-s} + 2\sigma_0\sigma_1 g(s))}, \tag{3.16}$$

where $\mathcal{L}(X^2)(s)$ is given by

$$\mathcal{L}(X^2)(s) = \frac{1}{s - 2a - 2bf(s)}.$$

Thus, by (3.16), we have

$$\mathcal{L}(M)(s) = \frac{\mathcal{L}(F)(s)}{\mathcal{L}(X^2)(s)} H^{-1}(s).$$

Let

$$G(t) = \mathcal{L}^{-1}\left[\frac{\mathcal{L}(F)}{\mathcal{L}(X^2)}\right](t) = (\sigma_0 Ex(t) + \sigma_1 Ex_1(t) + \sigma_2)^2$$

and $Y(t) = \mathcal{L}^{-1}(H^{-1})(t)$. Then we have

$$M(t) = G * Y = \int_0^t G(t-s)Y(s)ds. \tag{3.17}$$

(2) Let $\beta_0 = \max\{\Re(s) : H(s) = 0\}$. We will prove that for any $\beta > \beta_0$ there is a constant $K_2 = K_2(\beta)$ such that

$$|Y(t)| \leq K_2 e^{\beta t}. \tag{3.18}$$

To start, we will show that $\beta_0 < \infty$ is well defined. To do this, noting that there exist A_1 and A_2 such that if $\Re(s)$ is large enough,

$$|f(s)| \leq A_1 e^{-\Re(s)/2} \quad \text{and} \quad |g(s)| \leq A_2 e^{-\Re(s)/2}. \tag{3.19}$$

We omit the proof of (3.19) due to space constraints. Thus, when $\Re(s)$ is large enough, $H(s) > 0$, and therefore the value $\beta_0 < \infty$ is well defined.

Now, (3.18) follows from the inverse Laplace transform

$$Y(t) = \lim_{T\to\infty} \frac{1}{2\pi} \int_{\beta - iT}^{\beta + iT} H^{-1}(s) e^{st} ds \leq K_2 e^{\beta t}$$

for any $\beta \geq \beta_0$ and a constant $K_2 = K_2(\beta)$. The details of the proof are exactly the same as for the proof given in [20, pp. 20–21], and we omit the details here.

(3) Now we have

$$M(t) = \int_0^t G(t-s)Y(s)ds,$$

with $|Y(t)| \leq K_2 e^{\beta t}$ for any $\beta > \beta_0$. Furthermore, for any $\alpha_0 < \alpha < 0$ there exists $K_3 = K_3(\alpha, \phi)$ such that

$$|G(t)| \leq \sigma_2^2 + K_3 e^{\alpha t}.$$

If $\beta_0 < 0$, we choose $\beta_0 < \beta < 0$ and K_2 as above. Then

$$|M(t)| \leq \int_0^t (\sigma_2^2 + K_3 e^{\alpha(t-s)}) K_2 e^{\beta s} ds,$$

and thus the second moment $M(t)$ is bounded for any initial function $\phi(\theta)$. In this situation, let

$$M_\infty = \sigma_2^2 \int_0^\infty Y(s) ds,$$

so that

$$|M(t) - M_\infty| \leq K_2 \sigma_2^2 e^{\beta t} + \frac{K_2 K_3}{\beta - \alpha}(e^{\beta t} - e^{\alpha t}).$$

Thus, there exists a positive constant $K_4 = K_4(\alpha, \beta, \phi)$ such that

$$|M(t) - M_\infty| \leq K_4 e^{t \max\{\alpha, \beta\}};$$

i.e., $M(t)$ approaches to M_∞ exponentially when $t \to \infty$.

If $\beta_0 \geq 0$, by the inverse Laplace transform, we have $Y(t) = O(e^{\beta_0 t})$ when t is large enough. We can choose an initial function $\phi(\theta)$ such that

$$Ex(t) = \sum_i c_i e^{\lambda_i t},$$

where $h(\lambda_i) = 0$ and c_i are nonzero constants. For this particular initial function, we have either $G(t) = O(1)$ as $t \to \infty$ when $\sigma_2 \neq 0$, or $G(t) = O(e^{2\alpha t})$ as $t \to \infty$ for some $\alpha \leq \alpha_0 < 0$ when $\sigma_2 = 0$. In either case,

$$M(t) = \int_0^t G(t-s)Y(s)ds = O(e^{\beta_0 t})$$

when $t \to \infty$, and hence the second moment is unbounded. □

Theorem 3.6 establishes a criterion for the second moment of the linear stochastic delay differential equation to be bounded. However, this criterion is not particularly useful. The function $g(s)$ in (3.15) involves the Laplace transforms of $M(t)$ and $N(t)$ that are unknown. In many applications, perturbations for system parameters affect only the right-hand side of the equation that involves either the current state or the retarded state, and thus either $\sigma_1 = 0$ or $\sigma_0 = 0$. In this situation, the function $H(s)$ reads

$$H(s) = s - (2a + \sigma_0^2) - 2bf(s) - \sigma_1^2 e^{-s}$$

and is determined by the system coefficients and by $f(s)$, which depends on the Laplace transforms of $X^2(t)$ and $X(t)X_1(t)$. Nevertheless, it is not trivial to obtain the explicit form of $f(s)$ for a given system. In the rest of this section, we will develop some estimates for $f(s)$ and $g(s)$ and present direct criteria for the second moment stability.

THEOREM 3.7. *If $b < 0$, $\sigma_0\sigma_1 \leq 0$, and either*

$$(\sigma_0 + \sigma_1)^2 \geq -2(a+b) \tag{3.20}$$

or

$$u = \begin{cases} \dfrac{-(b+\sigma_0\sigma_1) - \sqrt{(b+\sigma_0\sigma_1)^2 - 4\sigma_1^2}}{2\sigma_1^2}, & \sigma_1 \neq 0, \\ -\dfrac{1}{b}, & \sigma_1 = 0, \end{cases}$$

such that $0 < u < 1$ and

$$-2\log u - (2a + \sigma_0^2) - (2b + 2\sigma_0\sigma_1)u - \sigma_1^2 u^2 \leq 0, \tag{3.21}$$

then the second moment is unbounded.

Proof. Let

$$H_0(s) = s - (2a + \sigma_0^2) - (2b + 2\sigma_0\sigma_1)e^{-s/2} - \sigma_1^2 e^{-s}.$$

Then when $b < 0$ and $\sigma_0\sigma_1 \leq 0$, we have $H(s) \leq H_0(s)$ for all $s \in \mathbb{R}$. Therefore, either (3.20) or (3.21) implies that there exists $s_* > 0$ such that $H(s) \leq H_0(s_*) \leq 0$. However, $H(s) > 0$ when s is large enough. Therefore the equation $H(s) = 0$ has a nonnegative solution. Thus, the theorem follows from Theorem 3.6. □

Theorem 3.7 tells us when the second moment is unbounded. The following result will tell us when the second moment is bounded.

THEOREM 3.8. *If there exists $\alpha < 0$ and $K = K(\alpha) > 0$ such that*

$$|X(t)| \leq Ke^{\alpha t} \quad (t \geq 0) \tag{3.22}$$

and

$$(|\sigma_0| + |\sigma_1|)^2 < -\frac{2\alpha}{K^2}, \tag{3.23}$$

then the second moment $M(t)$ is bounded when $t > 0$.

Theorem 3.8 will be proved using the following delay-type Gronwall inequality, the proof of which (which we omit) is similar to that of the Gronwall inequality.

LEMMA 3.9. *If $y(t)$ is a nonnegative continuous function on $[-1, \infty)$ and there are positive constants p and q such that*

$$y(t) \leq p \int_0^t y(s)ds + q \int_0^t y(s-1)ds + r(t), \tag{3.24}$$

then for any $\beta > 0$ such that

$$\beta - p - qe^{-\beta} > 0$$

and

$$\sup_{t \geq 0} |r(t)e^{-\beta t}| < \infty$$

there exists $A = A(\beta)$ such that

$$y(t) \leq Ae^{\beta t} \quad (t \geq 0). \tag{3.25}$$

We can now turn to the proof of Theorem 3.8.

Proof of Theorem 3.8. Note that

$$M(t) \leq (|\sigma_0| + |\sigma_1|) \int_0^t X^2(t-s)(|\sigma_0|M(s) + |\sigma_1|M_1(s))ds + F(t). \tag{3.26}$$

For α such that (3.22) is satisfied, we have $K_5 = K_5(\alpha, \phi)$ such that

$$0 \leq F(t) \leq K_5(1 - e^{2\alpha t}).$$

Thus from (3.26) it follows that

$$M(t) \leq K^2 \, (|\sigma_0| + |\sigma_1|)e^{2\alpha t} \int_0^t (|\sigma_0|e^{-2\alpha s}M(s) + |\sigma_1|e^{-2\alpha s}M_1(s))ds + K_5(1 - e^{2\alpha t}).$$

Let

$$y(t) = e^{-2\alpha t}M(t), \qquad r(t) = K_5(e^{-2\alpha t} - 1),$$

and

$$p = K^2|\sigma_0|(|\sigma_0| + |\sigma_1|), \qquad q = K^2|\sigma_1|(|\sigma_0| + |\sigma_1|)e^{-2\alpha}.$$

Then

$$y(t) \le p \int_0^t y(s)ds + q \int_0^t y_1(s)ds + r(t).$$

The inequality (3.23) implies

$$-2\alpha - p - qe^{2\alpha} > 0.$$

Thus, by Lemma 3.9 there is a constant A such that

$$M(t)e^{-2\alpha t} = y(t) \le Ae^{-2\alpha t},$$

i.e., $M(t) \le A$ for all $t > 0$. □

From Theorem 3.6, if the second moment $M(t)$ is bounded, it exponentially approaches a constant M_∞. Let $t \to \infty$ in (3.26) and apply (3.13) so that we have

$$M_\infty \le \frac{\sigma_2^2 \int_0^\infty X^2(s)ds}{1 - (|\sigma_0| + |\sigma_1|)^2 \int_0^\infty X^2(s)ds} \le -\frac{\sigma_2^2 K^2(\alpha)}{2\alpha + (|\sigma_0| + |\sigma_1|)^2 K^2(\alpha)} \tag{3.27}$$

for any α and $K(\alpha)$ given in Theorem 3.8. It follows from (3.27) that when $\sigma_2 = 0$, boundedness of the second moment implies exponential stability.

From Theorems 3.3 and 3.8, for any parameter pair (a, b) in the region S defined in (2.5), the first moment of the solution of the stochastic differential delay equation (1.8) approaches 0 as $t \to \infty$. Furthermore, there exists $P(a, b) > 0$ such that if

$$(|\sigma_0| + |\sigma_1|)^2 < P(a, b), \tag{3.28}$$

the second moment of the solution is bounded with an upper bound, as $t \to \infty$, given by (3.27).

From the estimates of α_0 and $K(\alpha)$ given in section 2, the function $P(a, b)$ can be computed, and its graph is shown in Figure 3.1.

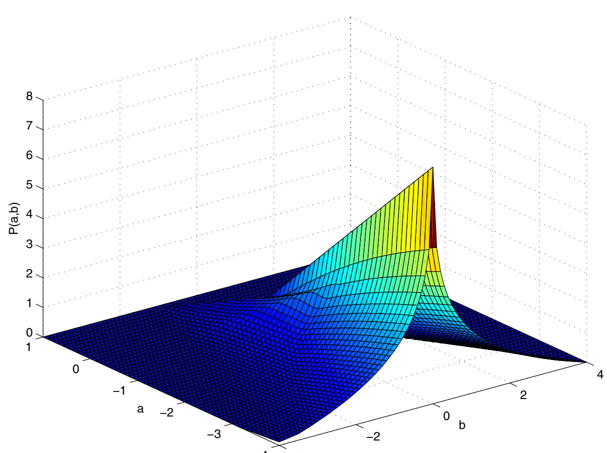

FIG. 3.1. *The function $P(a, b)$.*

4. Stability of the hematopoietic regulation system under stochastic perturbation. In this section, we will study the stability of the HSC in the face of stochastic perturbation, using the results of the previous sections. The HSC regulation system is modeled by a classical G_0 model [6, 35, 56]. Blood cells differentiate from HSC in the resting (G_0) phase. The HSC has high self-renewal capacity with the re-entry rate dependent on the number of HSC through a negative feedback loop. The proliferating phase cells include those cells in S phase (DNA synthesis), M phase (mitosis), and two segments known as the G_1 and G_2 phases (the G stands for "gap"). In addition, there is a loss of proliferating phase cells due to apoptosis (see Figure 4.1).

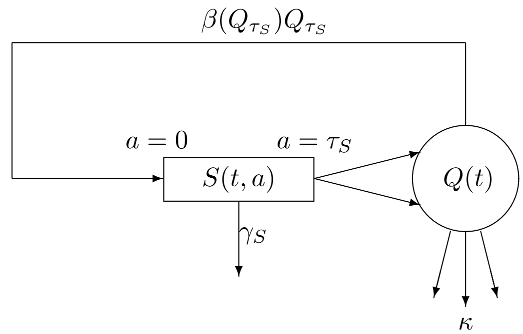

Fig. 4.1. *A cartoon representation of the HSC model.*

The HSC dynamics is modeled by a differential delay equation [7, 8, 9, 13, 51]

$$\frac{dQ}{dt} = -\beta(Q)Q - \kappa(N, R, P)Q + 2e^{-\gamma_S \tau_S}\beta(Q_{\tau_S})Q_{\tau_S}, \tag{4.1}$$

where Q, N, R, P are the quiescent stem cells, leukocytes, erythrocytes, and platelets, respectively, and $Q_{\tau_S} = Q(t - \tau_S)$. The model parameters are the apoptosis (death) rate γ_S, the maturation delay τ_S, the HSC self-renewal (proliferation) rate β, and the differentiation rate κ at which the HSC forms the three peripheral cell lines. The proliferation rate β and differentiation rate κ involve negative feedback loops that take the form of a Hill function [5, 7, 8],

$$\beta(Q) = k_0 \frac{\theta_2^s}{\theta_2^s + Q^s},$$

$$\kappa(N, P, R) = f_0 \frac{\theta_1^n}{\theta_1^n + N^n} + \frac{\bar{\kappa}_p}{1 + K_p P^p} + \frac{\bar{\kappa}_r}{1 + K_r R^r}.$$

Note that the rate κ depends on the state of three cell lines (leukocytes, erythrocytes, platelets), and thus (4.1) does not constitute a closed system. In this study, since we are interested only in the situation close to the steady state, we take the total differentiation out of the stem cell compartment to be a single constant. This decouples the model for the stem cell compartment from the full system.

Let us introduce nondimensional variables as follows:

$$q = \frac{Q}{\theta_2}, \quad \hat{t} = \frac{t}{\tau_S},$$

$$b_1 = \tau_S k_0, \quad \mu_1 = 2e^{-\gamma_S \tau_S}, \quad \delta = \tau_S \kappa.$$

We have the nondimensional form of (4.1) (see [9]),

$$\frac{dq}{dt} = -\frac{b_1}{1+q^s}q + \mu_1 \frac{b_1}{1+q_1^s}q_1 - \delta q, \tag{4.2}$$

where $q_1 = q(t-1)$ and $\hat{t}$ has been simply replaced by t. Typical values of the dimensionless parameters are $b_1 = 22.4$ and $\mu_1 = 1.64$. The parameter s, which denotes the number of cytokine molecules needed to trigger HSC proliferation in vitro, is chosen as $s = 4$ (see [9]).

When $\delta < b_1(\mu_1 - 1)$, equation (4.2) has a unique positive steady state

$$q^* = \left(\frac{b_1(\mu_1 - 1)}{\delta} - 1\right)^{1/4},$$

corresponding to the normal level of the stem cells. Linearizing (4.2) around this steady state, we obtain the variational equation

$$\frac{dx}{dt} = ax + bx_1,$$

where $x = q - q^*$,

$$a = -\frac{\delta}{b_1(\mu_1-1)^2}(-3b_1(\mu_1 - 1) + b_1(\mu_1 - 1)^2 + 4\delta),$$

and

$$b = \frac{\delta\mu_1}{b_1(\mu_1-1)^2}(-3b_1(\mu_1 - 1) + 4\delta).$$

From the discussion in section 2, there exists a critical value δ_c (≈ 0.16) such that the steady state is stable when $0 < \delta < \delta_c$.

We will now study the stability of the steady state when there are stochastic perturbations in the system parameters δ, b_1, or μ_1. We have the following equations for the perturbed system:

1. perturbation in δ:

$$dq = \left[-\frac{b_1 q}{1+q^4} - \delta q + \frac{b_1\mu_1 q_1}{1+q_1^4}\right]dt - \sigma q dW(t), \tag{4.3}$$

2. perturbation in b_1:

$$dq = \left[-\frac{b_1 q}{1+q^4} - \delta q + \frac{b_1\mu_1 q_1}{1+q_1^4}\right]dt + \sigma\left[-\frac{q}{1+q^4} + \frac{\mu_1 q_1}{1+q_1^4}\right]dW(t), \tag{4.4}$$

3. and perturbation in μ_1:

$$dq = \left[-\frac{b_1 q}{1+q^4} - \delta q + \frac{b_1\mu_1 q_1}{1+q_1^4}\right]dt + \sigma\frac{b_1 q_1}{1+q_1^4}dW(t), \tag{4.5}$$

where $W(t)$ is the standard Wiener process and σ is the noise amplitude. The linearized versions of (4.3)–(4.5) around the steady state $q = q^*$ are

$$dx = (ax + bx_1)dt - \sigma(x + q^*)dW(t), \tag{4.6}$$

$$dx = (ax + bx_1)dt + \left(\frac{\sigma}{b_1}\right)((a+\delta)x + bx_1 + \delta q^*)dW(t), \tag{4.7}$$

and

$$dx = (ax + bx_1)dt + \left(\frac{\sigma}{\mu_1}\right)\left(bx_1 + \delta q^* + \frac{b_1 q^*}{1 + q^{*4}}\right) dW(t), \tag{4.8}$$

respectively.

Applying the results from the previous section, when $0 < \delta < \delta_c$, the first moment of solutions of the perturbed system is locally stable. Furthermore, from Theorem 3.8, for any $0 < \delta < \delta_c$ (and b_1, μ_1 held at their typical values), there exists $\sigma_b(\delta)$ such that when $\sigma < \sigma_b(\delta)$ the second moment is bounded. Further, from Theorem 3.7, for any $0 < \delta < \delta_c$, there exists $\sigma_u(\delta)$ such that when $\sigma > \sigma_u(\delta)$ the second moment is unbounded. When $\sigma_b < \sigma < \sigma_u$, however, the previous results fail to delineate the stability of the second moment. A more accurate estimation for the characteristic function $H(s)$ in Theorem 3.6 is required to fill this gap. Graphs of the curves $\sigma = \sigma_b(\delta)$ and $\sigma = \sigma_u(\delta)$ are given in Figure 4.2.

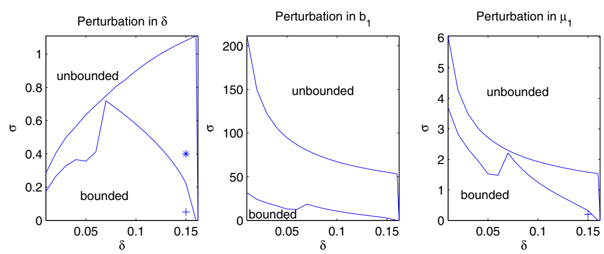

FIG. 4.2. *Parameter dependence for the second moment of the solution of the stochastic HSC system to be bounded.*

In Figure 4.2, the thresholds of the three parameter perturbations to ensure the stability of a steady state under noise perturbation are sorted from low to high as the threshold for δ, for μ_1, and for b_1. Thus, the HSC system is more easily destabilized by noise in the differentiation rate (δ) than in the death rate (μ_1), and least likely to be destabilized by perturbations in the proliferation rate (b_1).

Note that the solutions of (4.3)–(4.5) are always bounded because of the negative feedback. Thus, destabilization of the steady state may lead to fluctuating solutions characteristic of dynamic hematological disease (see Figure 4.3(b)). When the second moment is bounded, the range of the solution at time t can be estimated by the Chebyshev inequality (3.5). However, this cannot exclude the possibility of obtaining an oscillating solution (see Figure 4.3(c),(d)). In this situation, the amplitude of the oscillating solution is determined by the second moment, which is estimated by (3.27) when t is large. The graphs of M_∞ as a function of δ and σ are shown in Figure 4.4 for each of the cases. From Figure 4.4, for given values of b_1, μ_1, δ, and the perturbation amplitude σ, the second moment of the solutions of the HSC model with random perturbation in δ is larger than when there are perturbations in μ_1 and in b_1. Thus, small fluctuations in δ are able to produce large amplitude fluctuations in HSC numbers. Larger perturbations in μ_1 are required to produce a fluctuating HSC solution with the same amplitude (Figure 4.3(c),(d)). The second moment of solutions of the HSC system with perturbations in b_1 is small and not likely to produce a large amplitude fluctuation in HSC numbers.

These numerical results suggest that the dynamic hematological diseases [16] characterized by oscillations in blood cell numbers could originate from the stochastic

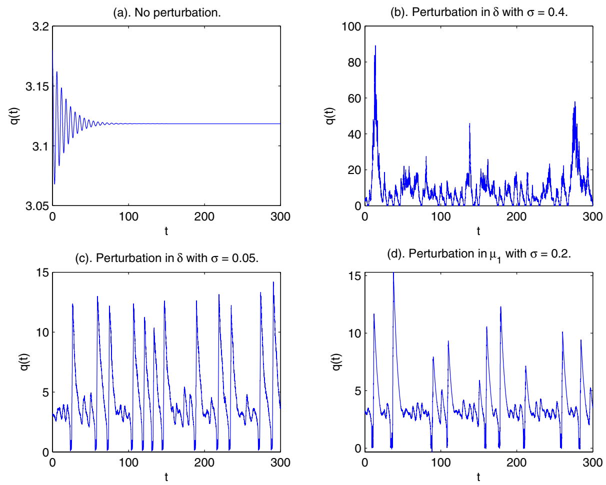

FIG. 4.3. *Sample solutions of the HSC system. In all these solutions, we choose* $b_1 = 22.4$*,* $\mu_1 = 1.64$*,* $\delta = 0.15$*. The perturbation is added to* δ *with* $\sigma = 0.4$ *and* $\sigma = 0.05$ *(cf. Figure* 4.2*, left-hand panel, marked by the "*" and "+," respectively), and to* μ_1 *with* $\sigma = 0.2$ *(cf. Figure* 4.2*, middle panel, marked with a "+"). The solution of the system without perturbation is also shown.*

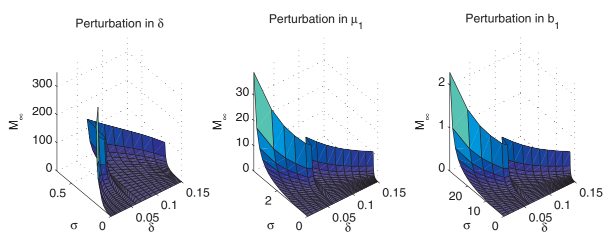

FIG. 4.4. *The function* M_∞ *as a function of* δ *and* σ*.*

perturbation of the differentiation rate and/or the death rate of HSCs. On the other hand, the system is relatively insensitive to perturbations in the proliferation rate.

5. Discussion.

We have investigated the effects of white noise on the stability of the trivial solution of a linear differential delay equation by deriving the solutions for the first and second order moments and examining the exponential estimation by the Laplace transform method.

We have shown that the stability domain of the first moment is identical to that of the unperturbed system (Theorem 3.3). This result is also true for the second moment when the perturbation is simple additive noise (Theorem 3.4). However, when there is multiplicative white noise, there are no simple results on the stability (bounded nature) of the second moment. From our study, when the trivial solution of the unperturbed equation is unstable, the second moment of solutions of the perturbed equation is unbounded. The condition for the second moment to be bounded has been shown to be related to the solutions of a characteristic equation given in Theorem 3.6. Nevertheless, the explicit expression of the characteristic equation is not available in terms of the system parameters. We have presented several direct criteria for the second moment to be bounded (Theorems 3.7 and 3.8).

Significant oscillations in one or more of the circulating progeny of the HSC are often characteristic of dynamic hematological diseases like cyclical neutropenia, cyclical thrombocytopenia, and periodic chronic myelogenous leukemia. The steady state of the HSC system can be destabilized by increasing the differentiation rate, and this has been implicated in the genesis of the hematological disorder cyclical neutropenia [21].

We have applied these results to examining the stability of HSC dynamics in the presence of stochastic perturbation. Our results indicate that stochastic perturbation cannot stabilize a large amplitude oscillation solution. When random perturbations are introduced in parameters characterizing the HSCs when the steady state is locally stable, we found that as the amplitude of the noise perturbation is increased, the system can be destabilized in the sense that the second moment becomes unbounded. In this situation, the system can display a large amplitude fluctuating solution.

When the second moment is large and bounded, however, we cannot exclude the possibility of an oscillatory solution, since the HSC system may have a large amplitude oscillatory solution in this circumstance.

We have obtained estimates of the second moment for three different types of perturbation (see Figure 4.4). These results suggest that small perturbations in the HSC differentiation or apoptosis (death) rate are able to generate large amplitude fluctuations in HSC numbers, but a much larger perturbation of the proliferation rate is needed to generate comparable fluctuations in HSC numbers. These results suggest that the HSC model system is more sensitive to random perturbations in the differentiation or death rate than in the proliferation rate.

The results in this paper were obtained under the Itô interpretation of stochastic integrals. Analogous results can be obtained for the Stratonovich interpretation. When Stratonovich interpretation is used, the solution of (1.8) can be expressed as

$$x(t) = x(0) + \int_0^t (\tilde{a}x(s) + \tilde{b}x_1(s) + \tilde{c})ds + \int_0^t (\sigma_0 x(s) + \sigma_1 x_1(s) + \sigma_2)dW(s), \tag{5.1}$$

in terms of the Itô integral, where

$$\tilde{a} = a + \frac{1}{2}\sigma_0^2, \quad \tilde{b} = b + \frac{1}{2}\sigma_0\sigma_1, \quad \tilde{c} = \frac{1}{2}\sigma_0\sigma_2. \tag{5.2}$$

Unlike the situation when the Itô interpretation is used, namely that the first moment stability is determined merely by the unperturbed system, the first moment stability is changed when we use a Stratonovich interpretation. Let

$$\tilde{h}(\lambda) = \lambda - \tilde{a} - \tilde{b}e^{-\lambda}, \qquad x_* = -\frac{\tilde{c}}{\tilde{a} + \tilde{b}},$$

so that we have the following theorem.

THEOREM 5.1. *If* $\tilde{\alpha}_0 = \max\{\Re(\lambda) : \tilde{h}(\lambda) = 0\}$*, then, for any* $\alpha > \alpha_0$*, there is a constant* $\tilde{K} = \tilde{K}(\alpha)$ *such that*

$$|Ex(t;\phi) - x_*| \le \tilde{K}\|\phi\|e^{\alpha t} \tag{5.3}$$

for any $\phi \in C([-1,0],\mathbb{R})$.

When $\tilde{\alpha}_0 < 0$, Theorem 5.1 implies that $Ex(t;\phi)$ approaches x_* exponentially when $t \to +\infty$. Thus, the expectation of the solutions drifts from zero to x_* due to the stochastic perturbation. Note that $\tilde{a} \ge a$; it is easy to show that the stochastic perturbation is able to destabilize the first moment of (1.8). On the other hand, the first moment cannot be stabilized by stochastic perturbation when the zero solution of the system without noise is unstable.

To study the second moment, let $y = x - x_*$, so that $y(t)$ satisfies

$$y(t) = y(0) + \int_0^t (\tilde{a}y(s) + \tilde{b}y_1(s))ds + \int_0^t (\sigma_0 y(s) + \sigma_1 y_1(s) + \tilde{\sigma}_2)dW(s), \tag{5.4}$$

where

$$\tilde{\sigma}_2 = \sigma_2 + (\sigma_0 + \sigma_1)x_*.$$

Applying the results in section 3 to the Itô equation (5.4), we can obtain the corresponding results for second moment stability of (1.8) in terms of the Stratonovich interpretation. The statement of these results is straightforward by replacing a, b, and σ_2 with $\tilde{a}$, $\tilde{b}$, and $\tilde{\sigma}_2$, respectively, and we omit them here.

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