

SUFFICIENT CONDITIONS FOR STABILITY OF LINEAR DIFFERENTIAL EQUATIONS WITH DISTRIBUTED DELAY

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ABSTRACT. We develop conditions for the stability of the constant (steady state) solutions of linear delay differential equations with distributed delay when only information about the moments of the density of delays is available. We use Laplace transforms to investigate the properties of different distributions of delay. We give a method to parametrically determine the boundary of the region of stability, and sufficient conditions for stability based on the expectation of the distribution of the delay. We also obtain a result based on the skewness of the distribution. These results are illustrated on a recent model of peripheral neutrophil regulatory system which include a distribution of delays. The goal of this paper is to give a simple criterion for the stability when little is known about the distribution of the delay.

1. Introduction. Delay differential equations (DDE) have been studied extensively for the past 50 years. They have applications in domains as diverse as engineering, biology and medicine where information transmission and/or response in control systems is not instantaneous. For a good introduction to the subject,

1991 *Mathematics Subject Classification.* 34K20, 34K06, 92C37.

Key words and phrases. Differential Equations, Distributed Delay, Stability, Cyclical Neutropenia.

see [4]. Much of the work that has been done treats DDEs with one or a few discrete delays.

A number of realistic physiological models however include distributed delays and a problem of particular interest is to determine the stability of the steady state solutions. For applications in physiological systems see [5, 6, 10, 14, 15]. Although results concerning DDEs with particular distributed delays (for extensive results about the *gamma* distribution see [3]) have been published, there has been no systematic study of this problem when little is known about the density of the delay distribution: most notably, results on sufficient conditions for stability of solutions of equations such as those considered in the present paper are given in [7, 16].

The problem of stability is very important in physiology and medicine. One class of diseases is characterized by a dramatic change in the dynamics of a physiological variable or a set of variables and there is sometime good clinical evidence that these changes are a consequence of a bifurcation in the underlying dynamics of the physiological control system. In [6] it was proposed that these diseases be called *dynamical diseases*. In many cases, one variable starts (or stops) to oscillate. In order to treat these diseases, it is useful to know the parameter which causes the oscillation (or the suppression thereof). An example of a dynamical disease is cyclical neutropenia which is the subject of Section 6.

In Section 2 we briefly set the stage for the type of problem that we are considering. In Section 3, we define our notion of stability and discuss how to parametrically determine the region of stability of a simple DDE for three particular distributions of delay: when the delay is a single discrete delay, a uniformly distributed delay and a distribution with the gamma density. In Section 4 we introduce a sufficient condition to have stability based on the expected delay and the symmetry of the distribution of delays. In Section 5 we give some examples again turning to the single delay, and the uniformly and gamma distributed cases. In Section 6 we apply our results to a recently published model for the peripheral regulation of neutrophil production.

2. Preliminaries. In this paper we study the stability of the linear differential Equation

$$\dot{x}(t) = -\alpha x(t) - \beta \int_0^\infty x(t-\tau) f(\tau) d\tau \quad (1)$$

where α and β are constants. We show that the symmetry of the distribution f plays an important role in the stability of the trivial solution, and our first result considers the characteristic equation of the DDE (1) if the density f is symmetric. If f is skewed to the left (meaning that there is more weight to the left of the expectation) then stability is stronger (*i.e.* holds for a wider range of parameter values) than for a single delay.

We restrict the values of α and β to $\beta \geq |\alpha|$ because we are interested in the influence of the distribution f on the stability properties of (1). It is straightforward to show that if $\beta \leq -\alpha$ then the trivial solution of Equation (1) is not stable. Moreover if $\alpha > |\beta|$, Equation (1) is stable for all values of τ . The interesting parameter values are therefore located in the cone $\beta \geq |\alpha|$.

Consider the general differential delay equation

$$\frac{dx(t)}{dt} = \mathcal{F}(x(t), \tilde{x}(t)), \tag{2}$$

where $\tilde{x}(t)$ is $x(t - \tau)$ weighted by a distribution of maturation delays. $\tilde{x}(t)$ is given explicitly by

$$\tilde{x}(t) = \int_{\tau_m}^{\infty} x(t - \tau)f(\tau)d\tau \equiv \int_{-\infty}^{t-\tau_m} x(\tau)f(t - \tau)d\tau. \tag{3}$$

τ_m is a minimal delay and $f(\tau)$ is the density of the distribution of maturation delays. Since $f(\tau)$ is a density, $f \geq 0$ and

$$\int_0^{\infty} f(\tau)d\tau = 1. \tag{4}$$

To completely specify the semi-dynamical system described by Equations (2) and (3) we must additionally have an initial function

$$x(t') \equiv \varphi(t') \quad \text{for} \quad t' \in (-\infty, 0). \tag{5}$$

Steady states x_* of Equation (2) are defined implicitly by the relation

$$\frac{dx_*}{dt} \equiv 0 \equiv \mathcal{F}(x_*, x_*). \tag{6}$$

Definition 2.0.1. *If there is a unique steady state x_* of Equation (2) it is globally asymptotically stable if, for all initial functions φ ,*

$$\lim_{t \rightarrow \infty} x(t) = x_*. \tag{7}$$

The primary consideration of this paper is the stability of the steady state(s), defined implicitly by Equation (6), and how that stability may be lost. Though we would like to be able to examine the global stability of x_* to perturbations, one must often be content with an examination of the *local* stability of x_* .

Definition 2.0.2. *A steady state x_* of Equation (2) is locally asymptotically stable if, for all initial functions φ satisfying $|\varphi(t') - x_*| \leq \epsilon$, $0 < \epsilon \ll 1$,*

$$\lim_{t \rightarrow \infty} x(t) = x_*. \tag{8}$$

3. Local Stability. To examine its local stability, we linearize Equation (2) in the neighborhood of any one of the steady states defined by (6), and define $z(t) = x(t) - x_*$ as the deviation of $x(t)$ from that steady state. The resulting linear equation is

$$\frac{dz(t)}{dt} = -\alpha z(t) - \beta \tilde{z}(t), \tag{9}$$

where

$$\tilde{z}(t) = \int_{\tau_m}^{\infty} z(t - \tau)f(\tau)d\tau \equiv \int_{-\infty}^{t-\tau_m} z(\tau)f(t - \tau)d\tau, \tag{10}$$

and α and β are defined by

$$\alpha \equiv -\frac{\partial \mathcal{F}(x, \tilde{x})}{\partial x} \Big|_{x=x_*} \quad \beta \equiv -\frac{\partial \mathcal{F}(x, \tilde{x})}{\partial \tilde{x}} \Big|_{\tilde{x}=x_*}. \tag{11}$$

If we make the *ansatz* that $z(t) \simeq e^{st}$ in Equation (9), the resulting eigenvalue equation is

$$s + \alpha + \beta e^{-s\tau_m} \hat{f}(s) = 0, \tag{12}$$

where

$$\hat{f}(s) = \int_0^\infty e^{-s\tau} f(\tau) d\tau \tag{13}$$

is the Laplace transform of f .

3.1. The single delay case. The “usual” situation considered by many authors is that in which there is a single discrete delay. The density f is then given as a Dirac delta function, $f(\tau) = \delta(\tau - \bar{\tau})$. In this case the eigenvalue Equation (12) takes the form

$$s + \alpha + \beta e^{-s\bar{\tau}} = 0. \tag{14}$$

If $s = \mu + i\omega$, then the boundary between locally stable behaviour ($\mu < 0$) and unstable behaviour ($\mu > 0$) is given by the values of α , β , and $\bar{\tau}$ satisfying

$$i\omega + \alpha + \beta e^{-i\omega\bar{\tau}} = 0, \tag{15}$$

which has been studied by Hayes [12]. Isolating the real

$$\alpha + \beta \cos(\omega\bar{\tau}) = 0, \tag{16}$$

and imaginary

$$\omega - \beta \sin(\omega\bar{\tau}) = 0 \tag{17}$$

parts of (15) it is straightforward to show that $\mu < 0$ whenever

1. $\alpha > |\beta|$, or if
2. $\beta \geq |\alpha|$ and

$$\bar{\tau} < \tau_{crit} \equiv \frac{\arccos\left(-\frac{\alpha}{\beta}\right)}{\sqrt{\beta^2 - \alpha^2}}. \tag{18}$$

The stability boundary defined by Equation (18) is shown in Figure 2 in Section 5 where we have parametrically plotted

$$\beta(\omega) = \frac{\omega}{\sin(\omega\bar{\tau})} \tag{19}$$

versus

$$\alpha(\omega) = -\omega \cot(\omega\bar{\tau}). \tag{20}$$

When $\bar{\tau} = \tau_{crit}$ there is a Hopf bifurcation [8] to a periodic solution of (9) with *Hopf period*

$$T_{Hopf} = \frac{2\pi}{\sqrt{\beta^2 - \alpha^2}}. \tag{21}$$

3.2. The uniform (rectangular) density. Suppose we have the simple situation wherein there is distribution of delays with a uniform rectangular density given by

$$f(\tau) = \begin{cases} 0 & 0 \leq \tau < \tau_m \\ \frac{1}{\delta} & \tau_m \leq \tau \leq \tau_m + \delta \\ 0 & \tau_m + \delta < \tau. \end{cases} \quad (22)$$

The expected value E of the delay is

$$E = \int_0^{\infty} \tau f(\tau) d\tau = \frac{\delta}{2}, \quad (23)$$

so the average delay is

$$\langle \tau \rangle = \tau_m + E = \tau_m + \frac{\delta}{2} \quad (24)$$

and the variance (denoted by V) is

$$V = \frac{\delta^2}{12} = \frac{E^2}{3}. \quad (25)$$

The Laplace transform of f as given by (22) is easily computed to be

$$\hat{f}(s) = \frac{e^{\delta s} - 1}{\delta s}, \quad (26)$$

so the eigenvalue Equation (12) takes the form

$$\delta s(s + \alpha) + \beta e^{-s\tau_m} [e^{\delta s} - 1] = 0. \quad (27)$$

This may be rewritten in terms of the expectation E as

$$2Es(s + \alpha) + \beta e^{-s\tau_m} [e^{2Es} - 1] = 0. \quad (28)$$

Taking $s = i\omega$ and proceeding as before we obtain parametric equations for $\alpha(\omega)$ and $\beta(\omega)$ as follows:

$$\alpha(\omega) = -\omega \frac{\sin[(\delta - \tau_m)\omega] + \sin(\omega\tau_m)}{\cos[(\delta - \tau_m)\omega] - \cos(\omega\tau_m)}, \quad (29)$$

and

$$\beta(\omega) = \frac{\delta\omega^2}{\cos[(\delta - \tau_m)\omega] - \cos(\omega\tau_m)}. \quad (30)$$

Refer to Figure 3 to see a graphical representation of the region of stability.

3.3. The gamma density. The density of the gamma distribution with parameters (a, m)

$$f(\tau) = \begin{cases} 0 & 0 \leq \tau < \tau_m \\ \frac{a^m}{\Gamma(m)} (\tau - \tau_m)^{m-1} e^{-a(\tau - \tau_m)} & \tau_m \leq \tau \end{cases} \quad (31)$$

with $a, m \geq 0$, is often encountered [10] in applications. The parameters m , a , and τ_m in the density of the gamma distribution can be related to certain easily determined statistical quantities. Thus, the average of the *unshifted* density is given by

$$E = \int_0^{\infty} \tau f(\tau) d\tau = \frac{m}{a}, \quad (32)$$

so the average delay is

$$\langle \tau \rangle = \tau_m + E = \tau_m + \frac{m}{a} \quad (33)$$

and the variance is

$$V = \frac{m}{a^2}. \quad (34)$$

Using (32) and (34) the parameters m and a can be expressed as

$$a = \frac{E}{V} \quad (35)$$

and

$$m = \frac{E^2}{V}. \quad (36)$$

Using the Laplace transform of (31) the eigenvalue Equation (12) becomes

$$(s + \alpha) \left[1 + \frac{s}{a} \right]^m + \beta e^{-s\tau_m} = 0. \quad (37)$$

Equation (37) can be used to give a pair of parametric equations in α and β defining the local stability boundary ($\mu \equiv \text{Re } s \equiv 0$). We start by setting $s = i\omega$ and

$$\tan \theta = \frac{\omega}{a}. \quad (38)$$

Using de Moivre's formula in Equation (37) with $s = i\omega$ gives

$$(\alpha + i\omega)(\cos[m\theta] + i \sin[m\theta]) = -\beta \cos^m \theta (\cos \omega\tau_m - i \sin \omega\tau_m) \quad (39)$$

Equating the real and imaginary parts of Equation (39) gives the coupled equations

$$\alpha + \beta r \cos \omega\tau_m = \omega \tan[m\theta], \quad (40)$$

and

$$\alpha \tan[m\theta] - \beta r \sin \omega\tau_m = -\omega, \quad (41)$$

where

$$r = \frac{\cos^m \theta}{\cos[m\theta]}. \quad (42)$$

Equations (40) and (41) are easily solved for α and β as parametric functions of ω to give

$$\alpha(\omega) = -\frac{\omega}{\tan[\omega\tau_m + m \tan^{-1}(\omega/a)]} \quad (43)$$

and

$$\beta(\omega) = \frac{\omega}{\cos^m[\tan^{-1}(\omega/a)] \sin[\omega\tau_m + m \tan^{-1}(\omega/a)]} \quad (44)$$

respectively. Refer to Figure 4 to see the region of stability.

3.4. General density case. The method employed above can be generalized for any density. Consider Equation (12) and let $s = i\underline{\omega}$. Separating the real and imaginary parts leads to

$$\alpha + \beta \int_0^\infty \cos(\underline{\omega}\tau) f(\tau) d\tau = 0 \quad (45)$$

$$\underline{\omega} - \beta \int_0^\infty \sin(\underline{\omega}\tau) f(\tau) d\tau = 0. \quad (46)$$

Define

$$C(\underline{\omega}) \equiv \int_0^{\infty} \cos(\underline{\omega}\tau) f(\tau) d\tau \quad (47)$$

and

$$S(\underline{\omega}) \equiv \int_0^{\infty} \sin(\underline{\omega}\tau) f(\tau) d\tau. \quad (48)$$

Then we can solve for α and β to obtain them as parametric functions of $\underline{\omega}$:

$$\alpha(\underline{\omega}) = -\underline{\omega} \frac{C(\underline{\omega})}{S(\underline{\omega})} \quad (49)$$

and

$$\beta(\underline{\omega}) = \frac{\underline{\omega}}{S(\underline{\omega})}. \quad (50)$$

4. Stability Conditions. One method to study the stability is to find conditions for which the eigenvalue equation (or *characteristic equation*) has no roots with positive real part. The difficulty with Equation (1) is that the characteristic equation often involves a transcendental term. A noticeable exception is the unshifted gamma distribution for which the characteristic equation [Equation (37) with $\tau_m = 0$] is a polynomial. This term, the Laplace transform of the density of the distribution of delays, can be expressed as $C(\underline{\omega}) + iS(\underline{\omega})$ [Equations (47) and (48)] on the imaginary axis. The first Lemma gives a bound on the term $C(\underline{\omega}) = \int_0^{\infty} \cos(\underline{\omega}\tau) f(\tau) d\tau$ when the density f is symmetric.

Lemma 4.0.1. *Let f be a probability density such that:*

1. $f : R \rightarrow R^+$
2. $E = \int_{-\infty}^{\infty} \tau f(\tau) d\tau,$
3. $f(E - \tau) = f(E + \tau)$

(The third property implies that f is symmetric about its expectation). Then

1. *for all $\omega,$*

$$\left| \int_{-\infty}^{\infty} \cos(\omega\tau) f(\tau) d\tau \right| \leq |\cos(\omega E)| ; \quad (51)$$

2. *if $\underline{\omega} < \pi/2E,$*

$$\int_{-\infty}^{\infty} \cos(\omega\tau) f(\tau) d\tau > 0. \quad (52)$$

Proof. For the first part of the Lemma, assume that f is piecewise constant and given by

$$f(\tau) = \sum_{i=1}^N C_i \chi_{[A_i, B_i]}(\tau)$$

where $\chi_{[A_i, B_i]}$ denotes the indicator function on the interval $[A_i, B_i]$:

$$\chi_{[A, B]}(\tau) = \begin{cases} 0 & \tau \notin [A, B] \\ 1 & \tau \in [A, B] \end{cases}. \quad (53)$$

Then

$$\begin{aligned} \left| \int_{-\infty}^{\infty} \cos(\omega\tau) f(\tau) d\tau \right| &= \left| \int_{-\infty}^{\infty} \cos(\omega\tau) \sum_{i=1}^N C_i \chi_{[A_i, B_i]}(\tau) d\tau \right| \\ &= \left| \sum_{i=1}^N C_i \int_{A_i}^{B_i} \cos(\omega\tau) d\tau \right| \\ &= \left| \sum_{i=1}^N \frac{C_i}{\omega} (\sin(\omega B_i) - \sin(\omega A_i)) \right|, \end{aligned}$$

which must be less than $|\cos(\omega E)|$ as we now show.

Using the trigonometric identity

$$\sin(x+y) - \sin(x-y) = 2 \cos(x) \sin(y),$$

we have

$$\left| \sum_{i=1}^N \frac{C_i}{\omega} (\sin(\omega B_i) - \sin(\omega A_i)) \right| = \left| \sum_{i=1}^N \frac{C_i}{\omega} 2 \cos\left(\omega \frac{B_i + A_i}{2}\right) \sin\left(\omega \frac{B_i - A_i}{2}\right) \right|.$$

By the symmetry of f , we know that $C_i = C_{N-i+1}$, and the distance between the expectation E and the middle of the i th interval is equal to the one between E and the middle of the $(N-i+1)$ th interval. That is,

$$\left| E - \frac{A_i + B_i}{2} \right| = \left| E - \frac{A_{N-i+1} + B_{N-i+1}}{2} \right|.$$

Set $E_i = \left| E - \frac{1}{2}(A_i + B_i) \right|$. For $1 \leq i \leq N/2$, we have $\frac{1}{2}(A_i + B_i) = E - E_i$, $\frac{1}{2}(A_{N-i+1} + B_{N-i+1}) = E + E_{N-i+1}$ and $E_i = E_{N-i+1}$. Substitute these values in the summation:

$$\begin{aligned} &\left| \sum_{i=1}^N \frac{C_i}{\omega} 2 \cos\left(\omega \frac{B_i + A_i}{2}\right) \sin\left(\omega \frac{B_i - A_i}{2}\right) \right| = \\ &\left| \sum_{i=1}^{N/2} 2 \frac{C_i}{\omega} \sin\left(\omega \frac{B_i - A_i}{2}\right) (\cos(\omega(E - E_i)) + \cos(\omega(E + E_i))) \right| = \\ &\left| \sum_{i=1}^{N/2} 2 \frac{C_i}{\omega} \sin\left(\omega \frac{B_i - A_i}{2}\right) (2 \cos(\omega E) \cos(\omega E_i)) \right| \end{aligned}$$

The last equality is obtained by the trigonometric identity

$$\cos(x+y) + \cos(x-y) = 2 \cos(x) \cos(y).$$

Apply the triangle inequality and bound $|\cos(\underline{\omega}E_i)|$ by 1 and the sine by its argument to obtain

$$\begin{aligned} \left| \sum_{i=1}^{N/2} 2 \frac{C_i}{\underline{\omega}} \sin(\underline{\omega} \frac{B_i - A_i}{2}) (2 \cos(\underline{\omega}E) \cos(\underline{\omega}E_i)) \right| &\leq \\ \sum_{i=1}^{N/2} \left| 4 \frac{C_i}{\underline{\omega}} \sin(\underline{\omega} \frac{B_i - A_i}{2}) \right| |\cos(\underline{\omega}E)| |\cos(\underline{\omega}E_i)| &\leq \\ \sum_{i=1}^{N/2} \left| 4 \frac{C_i}{\underline{\omega}} \sin(\underline{\omega} \frac{B_i - A_i}{2}) \right| |\cos(\underline{\omega}E)| &\leq \\ \sum_{i=1}^{N/2} \left| 4 C_i \frac{B_i - A_i}{2} \right| |\cos(\underline{\omega}E)| &= \sum_{i=1}^N |C_i(B_i - A_i)| |\cos(\underline{\omega}E)| \end{aligned}$$

Since f is a probability density,

$$\int_{-\infty}^{\infty} f(\tau) d\tau = \sum_{i=1}^N \int_{A_i}^{B_i} C_i d\tau = \sum_{i=1}^N C_i(B_i - A_i) = 1.$$

So

$$\sum_{i=1}^N |C_i(B_i - A_i)| |\cos(\underline{\omega}E)| = |\cos(\underline{\omega}E)|.$$

Then

$$\left| \sum_{i=1}^N \frac{C_i}{\underline{\omega}} (\sin(\underline{\omega}B_i) - \sin(\underline{\omega}A_i)) \right| \leq |\cos(\underline{\omega}E)|.$$

We thus have (51) when f is piecewise constant. If f is any symmetric probability density, we can approximate it by a sequence of functions $\{f_n\}_{n=1}^{\infty}$, when f_n is a piecewise constant symmetric probability density, with $f_n \rightarrow f$ as $n \rightarrow \infty$ and $\int_{-\infty}^{\infty} \tau f_n(\tau) d\tau = \int_{-\infty}^{\infty} \tau f(\tau) d\tau = E$. Note that

$$\left| \int_{-\infty}^{\infty} \cos(\omega\tau) f_n(\tau) d\tau \right| \leq |\cos(\omega E)|$$

for every n , so

$$\begin{aligned} \lim_{n \rightarrow \infty} \left| \int_{-\infty}^{\infty} \cos(\omega\tau) f_n(\tau) d\tau \right| &= \left| \int_{-\infty}^{\infty} \cos(\omega\tau) \lim_{n \rightarrow \infty} f_n(\tau) d\tau \right| \\ &= \left| \int_{-\infty}^{\infty} \cos(\omega\tau) f(\tau) d\tau \right| \leq |\cos(\underline{\omega}E)|. \end{aligned}$$

To prove the second part of the Lemma, observe that

$$|\cos(\underline{\omega}(E - \tau))f(E - \tau)| \geq |\cos(\underline{\omega}(E + \tau))f(E + \tau)|,$$

so the integral over the positive part is greater than the one over the negative part. \square

Remark 4.0.2. We can also prove, under the same hypothesis of Lemma 4.0.1, that

$$\left| \int_{-\infty}^{\infty} \sin(\omega\tau) f(\tau) d\tau \right| \leq |\sin(\omega E)|. \quad (54)$$

The stability of Equation (1) depends on all moments of f about its mean. The expectation obviously plays an important role in stability; Anderson [1, 2] also showed the importance of the variance (second moment about the mean) in these stability considerations.

We now study the location of the first root of $C(\underline{\omega})$. Lemma 4.0.1 states that the first root of $C(\underline{\omega})$ is at $\underline{\omega} = \pi/2E$ whenever the density f is symmetric. It is of primary interest to see how this root changes when the distribution is not symmetric. Around $\underline{\omega}\tau = \pi/2$, the cosine in $C(\underline{\omega}) = \int_0^\infty \cos(\omega\tau)f(\tau)d\tau$ can be expanded in Taylor series,

$$C(\underline{\omega}) = \int_{-\infty}^\infty \sum_{n=0}^\infty \frac{(-1)^{n+1} (\underline{\omega}\tau - \pi/2)^{2n+1}}{(2n+1)!} f(\tau)d\tau, \tag{55}$$

leading to the integral of a sum of terms with odd power (odd because we expand around a root). The higher moments about the mean do not necessarily converge and for this reason we can not usually switch the sum and the integral. The first term of this expansion is

$$-\frac{\pi}{2E} \int_0^\infty (\tau - E)f(\tau)d\tau = 0 \tag{56}$$

since the mean E is precisely the value for which this relation hold. The second term is the third moment about the mean (up to a multiplicative factor).

$$\frac{\pi^3}{(2E)^3 3!} \int_0^\infty (\tau - E)^3 f(\tau)d\tau. \tag{57}$$

The third moment is in general the first nonzero term of the Taylor expansion and so the sign of this term has a great importance in determining the position of the root of $C(\underline{\omega})$. The *skewness* of a distribution is usually defined as the third moment about the mean divided by the third power of the standard deviation. If the density f is symmetric, all moment about the mean are zero. So a symmetric density has a skewness equal to zero, which is coherent with intuition. But a third moment equal to zero does not imply that the density is symmetric. We require a definition in which a skewness equal to zero means that the density is symmetric. For the purpose of the paper, we will use the following definition of skewness.

Definition 4.0.3. *Let f be a probability density with expectation E . The skewness of f , $B(f)$, is defined as*

$$B(f) = (-1)^{k+1} \int_0^\infty (\tau - E)^{2k+1} f(t + E)d\tau \tag{58}$$

where

$$k = \min \left\{ n \left| \int_0^\infty (\tau - E)^{2n+1} f(t + E)d\tau \neq 0 \right. \right\}. \tag{59}$$

The density f is said to be skewed to the left if $B(f) > 0$ and skewed to the right if $B(f) < 0$. In the case where $k = \infty$ we define $B(f) = 0$.

Remark 4.0.4. *It is clear that f is symmetric if and only if all the moments about its mean are zero, i.e. f is symmetric if and only if $B(f) = 0$. In general, for a non-symmetric density, the third moment about the mean is nonzero, so the definition of $B(f)$ reduces to the standard case (up to a positive multiplicative factor).*

We can now look for sufficient conditions for stability of Equation (1).

Theorem 4.0.5 (Sufficient Conditions). *Let f be a probability density defined on $[0, +\infty)$ with expectation $\int_0^\infty \tau f(\tau) d\tau = E$. Suppose $\beta > |\alpha|$. Then in Equation (1)*

1. *The solution $x_* = 0$ is asymptotically stable (a.s.) if*

$$E < \frac{\pi \left(1 + \frac{\alpha}{\beta}\right)}{c\sqrt{\beta^2 - \alpha^2}} \tag{60}$$

where $c = \sup \{c | \cos(x) = 1 - cx/\pi, x > 0\} \approx 2.2764$.

2. *If the skewness $B(f) = 0$ we have the stronger sufficient condition for asymptotic stability:*

$$E < \frac{\arccos\left(\frac{-\alpha}{\beta}\right)}{\sqrt{\beta^2 - \alpha^2}}. \tag{61}$$

3. *If the skewness is positive ($B(f) > 0$), then there is a $\delta > 0$ such that condition (61) holds for $|\alpha| < \delta$.*

Proof. The characteristic equation of (1) is

$$s + \alpha + \beta \int_0^\infty e^{-s\tau} f(\tau) d\tau = 0. \tag{62}$$

If $E = 0$, (62) reduces to $s + \alpha + \beta = 0$ which trivially has no root with positive real part so $x_* = 0$ is asymptotically stable. If an increase in E leads to instability of $x_* = 0$, then a root s of (62) must intersect the imaginary axis, i.e. there exists E such that (62) has pure imaginary roots. We seek roots of the form $s = i\underline{\omega}$, and because the roots come in conjugate pairs, we can restrict our search to $\underline{\omega} > 0$. In this case Equation (62) splits into a real part

$$\alpha + \beta \int_0^\infty \cos(\underline{\omega}\tau) f(\tau) d\tau = 0, \tag{63}$$

and an imaginary part

$$\underline{\omega} - \beta \int_0^\infty \sin(\underline{\omega}\tau) f(\tau) d\tau = 0. \tag{64}$$

First note that $\underline{\omega} \leq \sqrt{\beta^2 - \alpha^2}$ since:

$$\begin{aligned} \left[\int_0^\infty \cos(\underline{\omega}\tau) f(\tau) d\tau \right]^2 + \left[\int_0^\infty \sin(\underline{\omega}\tau) f(\tau) d\tau \right]^2 &\leq \\ \int_0^\infty \cos^2(\underline{\omega}\tau) f(\tau) d\tau + \int_0^\infty \sin^2(\underline{\omega}\tau) f(\tau) d\tau &= \\ \int_0^\infty f(\tau) d\tau &= 1. \end{aligned}$$

and thus, by Equations (63) and (64), $\alpha^2 + \underline{\omega}^2 \leq \beta^2$.

To show condition (60), notice that

$$\begin{aligned} \int_0^\infty \cos(\underline{\omega}\tau) f(\tau) d\tau &\geq \int_0^\infty 1 - \frac{c\underline{\omega}\tau}{\pi} f(\tau) d\tau \\ = \int_0^\infty f(\tau) d\tau - \frac{c\underline{\omega}}{\pi} \int_0^\infty \tau f(\tau) d\tau &= 1 - \frac{c\underline{\omega}}{\pi} E. \end{aligned}$$

If $1 - c\underline{\omega}E/\pi > -\alpha/\beta$, Equation (63) thus has no root. However, $\underline{\omega} \leq \sqrt{\beta^2 - \alpha^2}$ so a sufficient condition for (63) to have no root is

$$E < \frac{\pi \left(1 + \frac{\alpha}{\beta}\right)}{c\sqrt{\beta^2 - \alpha^2}}.$$

For the proof of the second part of Theorem 4.0.5. suppose that f is symmetric about its mean and $\alpha \geq 0$. We want $\int_0^\infty \cos(\underline{\omega}\tau)f(\tau)d\tau > -\alpha/\beta$ for $0 < \underline{\omega} \leq \sqrt{\beta^2 - \alpha^2}$. By Lemma 4.0.1, we know that $\int_0^\infty \cos(\underline{\omega}\tau)f(\tau)d\tau > 0$ for $\underline{\omega} < \pi/2E$. For $\underline{\omega} \geq \pi/2E$,

$$\left| \int_0^\infty \cos(\omega\tau) f(\tau) d\tau \right| \leq |\cos(\omega E)|.$$

This implies that

$$\int_0^\infty \cos(\underline{\omega}\tau)f(\tau)d\tau \geq \cos(\omega E)$$

whenever $\int_0^\infty \cos(\underline{\omega}\tau)f(\tau)d\tau < 0$. If $\cos(\underline{\omega}E) > -\alpha/\beta$ then $E < \underline{\omega}^{-1} \arccos(-\alpha/\beta)$ and

$$\int_0^\infty \cos(\underline{\omega}\tau)f(\tau)d\tau > -\alpha/\beta.$$

A sufficient condition for (62) with $\alpha \geq 0$ to have no root with positive real part is therefore:

$$E < \frac{\arccos\left(\frac{-\alpha}{\beta}\right)}{\sqrt{\beta^2 - \alpha^2}}.$$

If $\alpha < 0$, compare the boundary of region of stability $(\alpha(\underline{\omega}), \beta(\underline{\omega}))$ defined by Equations (49) and (50) and the curve $(\alpha_E(\underline{\omega}), \beta_E(\underline{\omega}))$ defined by the boundary of region of stability of the single delay at E . These two curves intersect for $\underline{\omega} = 0$ at the point $(-1/E, 1/E)$:

$$\lim_{\underline{\omega} \rightarrow 0} \alpha(\underline{\omega}) = \lim_{\underline{\omega} \rightarrow 0} \frac{-\underline{\omega}C(\underline{\omega})}{S(\underline{\omega})} = \lim_{\underline{\omega} \rightarrow 0} \frac{-\underline{\omega}}{S(\underline{\omega})} = - \lim_{\underline{\omega} \rightarrow 0} \beta(\underline{\omega})$$

This limit is 1 over the slope of $S(\underline{\omega})$ at 0, which is E . This is true for all distributions with expectation E and this is their only intersection point. To have intersection we must get

$$\frac{-\underline{\omega}C(\underline{\omega})}{S(\underline{\omega})} = \frac{-\underline{\omega} \cos(\underline{\omega}E)}{\sin(\underline{\omega}E)}$$

and

$$\frac{\underline{\omega}}{S(\underline{\omega})} = \frac{\underline{\omega}}{\sin(\underline{\omega}E)}$$

which imply, for $\underline{\omega} \neq 0$, that $C(\underline{\omega}) = \cos(\underline{\omega}E)$ and $S(\underline{\omega}) = \sin(\underline{\omega}E)$. These equalities can not occur until $\underline{\omega} = \pi/2E$. Moreover, when $\underline{\omega} = \pi/2E$, both curves cross the β -axis and at this point $\beta(\underline{\omega}) > \beta_E(\underline{\omega}) = \pi/2E$. These facts imply that the curve $(\alpha(\underline{\omega}), \beta(\underline{\omega}))$ lies always above the ‘‘sufficient’’ curve $(\alpha_E(\underline{\omega}), \beta_E(\underline{\omega}))$ and condition (61) holds for $\alpha < 0$.

Now we have to show that if $B(f) \geq 0$, no root crosses the imaginary axis when α is sufficiently small. Consider any density f with positive skewness. Let $p \in [0, 1]$, and define

$$f_p = pf(\tau) + (1 - p)f(2E - \tau).$$

The function $f_{1/2}$ is a symmetric density and we have shown that:

$$\left| \int_{-\infty}^{\infty} \cos(\underline{\omega}\tau) f_{1/2}(\tau) d\tau \right| \leq |\cos(\underline{\omega}E)|.$$

Moreover we have that

$$\int_{-\infty}^{\infty} \cos(\underline{\omega}\tau) f_p(\tau) d\tau = \int_{-\infty}^{\infty} \sum_{n=0}^{\infty} \frac{(-1)^{n+1} (\underline{\omega}\tau - \pi/2)^{2n+1}}{(2n + 1)!} f_p(\tau) d\tau.$$

By Definition 4.0.3 the first nonzero term of the series evaluated at $\underline{\omega} = \pi/2E$ is

$$\begin{aligned} & \int_{-\infty}^{\infty} \frac{(-1)^{k+1} (\underline{\omega}\tau - \pi/2)^{2k+1}}{(2k + 1)!} f_p(\tau) d\tau = \\ & \left(\frac{\pi}{2E}\right)^{2k+1} \frac{1}{(2k + 1)!} \int_{-\infty}^{\infty} (-1)^{k+1} (\tau - E)^{2k+1} f_p(\tau) d\tau. \end{aligned}$$

For $p > 1/2$, it is clear that $B(f_p) > 0$ so

$$\left(\frac{\pi}{2E}\right)^{2k+1} \frac{1}{(2k + 1)!} \int_{-\infty}^{\infty} (\tau - E)^{2k+1} f_p(\tau) d\tau = \left(\frac{\pi}{2E}\right)^{2k+1} \frac{1}{(2k + 1)!} B(f_p) > 0.$$

This means that for $p = 1/2 + \varepsilon$, with small $\varepsilon > 0$,

$$\int_{-\infty}^{\infty} \cos(\underline{\omega}\tau) f_p(\tau) d\tau > 0$$

for $\underline{\omega}$ in a neighborhood of $\pi/2E$. This implies that

$$\int_0^{\infty} \cos(\underline{\omega}\tau) f(\tau) d\tau > 0.$$

Thus, we have shown that

$$B(f) \equiv \int_0^{\infty} (\tau - E)^{2k+1} f(\tau) d\tau > 0$$

implies

$$\int_0^{\infty} \cos(\underline{\omega}\tau) f(\tau) d\tau > 0$$

around $\underline{\omega} = \pi/2E$.

The first root of $C(\underline{\omega})$ is thus to the right of $\underline{\omega} = \pi/2E$ (If this is were not true, there would be a (continuous) family of densities f_μ , $\mu \in [0, 1]$, with $B(f_0) = 0$, $B(f_\mu) > 0$ for $\mu > 0$ and $f_1 = f$. There would then exist $\mu = \mu_0 > 0$ where a root of $C_{f_{\mu_0}}(\underline{\omega})$ appears before $\pi/2E$. This would mean that at $\mu = \mu_0$, a root of the characteristic equation could suddenly appear in the right half complex plane, which is impossible (see Lemma 1.1 in [17])).

Thus, an increase in p increases

$$\int_{-\infty}^{\infty} \cos(\underline{\omega}\tau) f_p(\tau) d\tau,$$

and

$$\int_0^{\infty} \cos(\underline{\omega}\tau) f(\tau) d\tau > \int_{-\infty}^{\infty} \cos(\underline{\omega}\tau) f_{1/2}(\tau) d\tau.$$

This means that a positive skewness increases the stability of Equation (1) when $|\alpha|$ is small. \square

Remark 4.0.6. *We can apply condition (61) to any density with a (small) positive skewness. By the last part of the proof, a small perturbation which increases the skewness of a symmetric density will not cause roots of characteristic equation to cross the imaginary axis.*

Conditions (60) and (61) differ only when α is small or negative. If α is of the same order of magnitude as β , the conditions are equivalent. When $\alpha = 0$ we get for conditions (60) and (61) respectively:

$$E < \frac{\pi}{c\beta}$$

and

$$E < \frac{\pi}{2\beta}.$$

The difference is a factor of $2/c \approx 0.88$, and the difference decreases when α increases. These two bounds are asymptotic to the line $\beta = \alpha$ so the difference vanishes asymptotically.

5. Specific Examples. When we know the distribution of the delay in (1), we can find the region \mathcal{S} of stability in the plane of the parameters α and β . Theorem 4.0.5 gives sufficient conditions to have stability in a region \mathcal{R} , which must therefore be included in \mathcal{S} . A crucial question is: how does \mathcal{R} approach \mathcal{S} ? In case of a symmetric density, the approximation of the real bound is good if α in Equation (1) is small. In any case the stability of (1) tends to increase when the variance of f increases or the expectation decreases as discussed by Anderson in [1]. If we consider the relative variance R defined [1, 2] by

$$R = \frac{V}{R^2},$$

we can see that (in general) $\mathcal{R} \rightarrow \mathcal{S}$ as $R \rightarrow 0$. For an example in which this is not the case see Boese [3]. When $R = 0$, the distribution is a Dirac delta $f = \delta_E(\tau)$, and it is well known [4] that for a discrete delay, Equation (1) is stable if and only if

$$E < \frac{\arccos\left(\frac{-\alpha}{\beta}\right)}{\sqrt{\beta^2 - \alpha^2}}$$

when $|\alpha| < \beta$. Moreover, suppose that the distribution has a minimal delay τ_m ($f(\tau) = 0$ for $\tau < \tau_m$). This distribution has an expectation greater than τ_m . Then one could suppose that this distribution is strictly less stable than the single delay at $\tau = \tau_m$ because all information comes after this time. Generally, increasing the expectation of the delay decreases the stability. But other factors also influence the stability. If the variance and skewness are large enough, the stability is improved.

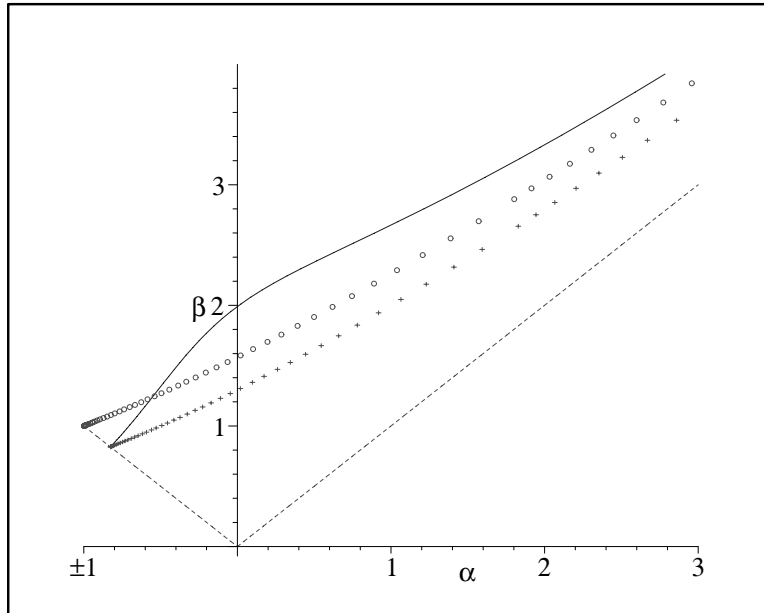


FIGURE 1. Comparison of stability boundaries for different distributions of delays. In all cases, the stability region is bounded above by the curve displayed. The solid curve is the boundary of the region of stability with the two discrete delay distribution defined by (65). The curve with crosses is the sufficient condition computed using condition (61) of Theorem 4.0.5 and the middle one (circle) defines the stability region of the single delay with $\tau = 1$. The dotted line is the cone $\beta = |\alpha|$.

Consider for instance the single delay distribution $\delta_{\bar{\tau}}$ with delay $\bar{\tau} = 1$ and the distribution with two delays at $\tau = 1$ and 3.1 :

$$f(\tau) = \frac{9}{10}\delta_1(\tau) + \frac{1}{10}\delta_{3.1}(\tau). \tag{65}$$

Then the density f is more stable than the single delay at 1! This shows the sometimes non-intuitive nature of the necessary conditions for stability of (1) [See Figure 1 for details].

Let us now compare the stability regions \mathcal{S} and \mathcal{R} for some common distributions: a single delay, a uniform delay and a gamma distribution.

5.1. The single delay. The single delay density takes the form $\delta_{\bar{\tau}} = \delta(\tau - \bar{\tau})$ which is the Dirac delta function at the fixed time $\bar{\tau}$. With $f(\tau) = \delta_{\bar{\tau}}(\tau)$, Equation (1) take the simple form

$$\dot{x}(t) = -\alpha x(t) - \beta x(t - \bar{\tau}), \tag{66}$$

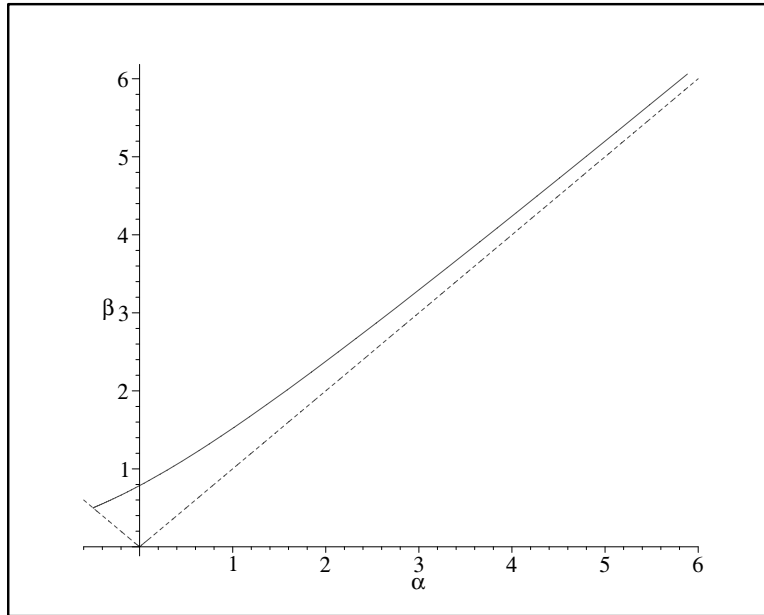


FIGURE 2. Upper bound (solid line) of the region of stability for Equation (66). Here $\mathcal{S} = \mathcal{R}$ and the delay $\bar{\tau} = 2$. Note that the boundary is asymptotic to the line $\beta = \alpha$ (dashed line).

and the characteristic equation is

$$s + \alpha + \beta e^{-s\bar{\tau}} = 0. \quad (67)$$

This density is symmetric and by Theorem (4.0.5), we know that Equation (66) is stable if

$$\bar{\tau} < \frac{\arccos\left(\frac{-\alpha}{\beta}\right)}{\sqrt{\beta^2 - \alpha^2}}.$$

In this case, this condition is also necessary. Figure 2 shows the region of stability, plotted with the method outlined in Section 3.1.

5.2. Uniform density. When the delay is uniformly distributed, the density can be written

$$f(\tau) = \begin{cases} 0 & 0 \leq \tau < \tau_m \\ 1/\delta & \tau_m \leq \tau \leq \tau_m + \delta \\ 0 & \tau_m + \delta < \tau \end{cases} \quad (68)$$

The expectation is $E = \tau_m + \delta/2$. We can apply Theorem 4.0.5, since f is symmetric, to obtain Figure 3 when $\tau_m = 2$ and $\delta = 2$.

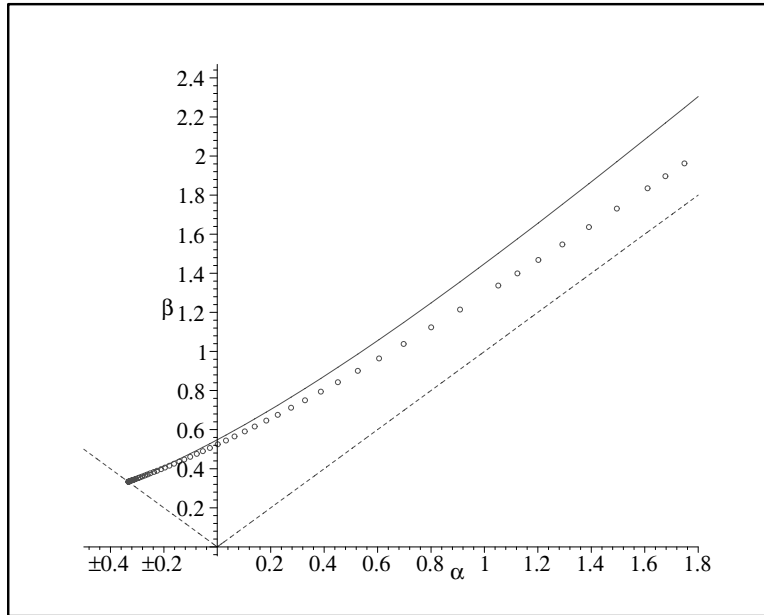


FIGURE 3. Stability region for a density uniform on the interval [2,4]. The solid line is the boundary of \mathcal{S} , the one with circles is the sufficient condition [Equation (61)] for stability and the dotted line is the cone $\beta = |\alpha|$.

5.3. **Gamma density.** The shifted gamma distribution with parameters (m, a) is

$$f(\tau) = \begin{cases} 0 & 0 \leq \tau < \tau_m \\ \frac{a^m}{\Gamma(m)} (\tau - \tau_m)^{m-1} e^{-a(\tau - \tau_m)} & \tau_m < \tau. \end{cases} \quad (69)$$

This distribution has expectation $E = \tau_m + m/a$. The third moment about the mean is

$$\int_0^\infty \frac{a^m}{\Gamma(m)} \tau^{m-1} e^{-a\tau} (\tau - m/a)^3 d\tau = \frac{2m}{a^3} > 0. \quad (70)$$

Note that the skewness is independent of τ_m because the third moment is taken about the mean which varies with τ_m . The skewness $B(f)$ is positive, so we can apply Theorem 4.0.5. Figure 4 shows the difference between the real boundary of \mathcal{S} and the boundary of \mathcal{R} . The characteristic equation is

$$s + \alpha + \beta \hat{f}(s) = 0. \quad (71)$$

where \hat{f} denotes the Laplace transform of f . For the unshifted distribution ($\tau_m = 0$),

$$\hat{f}(s) = \left(1 + \frac{s}{a}\right)^{-m}, \quad (72)$$

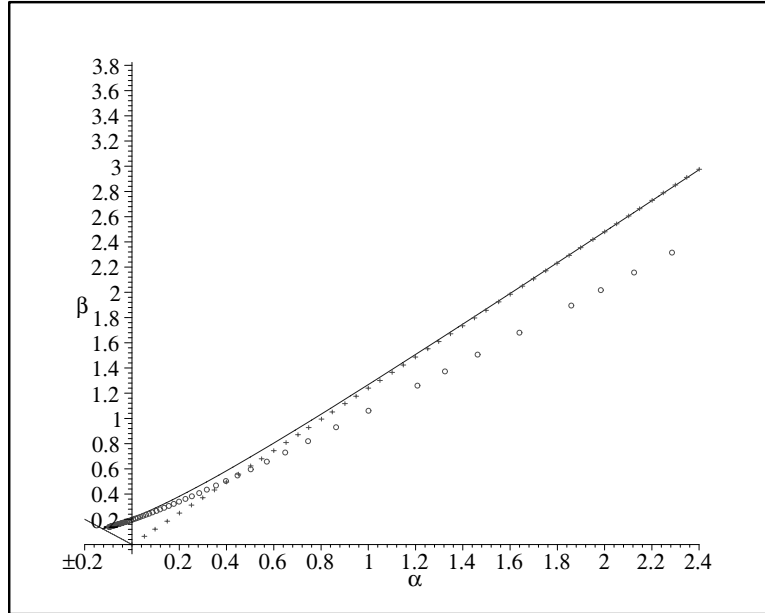


FIGURE 4. Region of stability (solid line) for a gamma distribution with parameters $m = 3$, $a = 1$ and $\tau_m = 5$. The curve with circles is the sufficient condition(61) of Theorem 4.0.5. The upper curve was computed with Equations (43) and (44). The asymptote (crosses) comes from Equation (79).

so that we can write Equation (71) as

$$(s + \alpha) \left(1 + \frac{s}{a}\right)^m + \beta = 0. \quad (73)$$

For large β , there should exist K such that the boundary of the region of stability is asymptotic to $\beta = K\alpha$. This boundary is implicitly expressed by Equation (71) when $s = i\underline{\omega}$. Moreover, when β is large, $\underline{\omega}$ should be near π/E . The reason for this is that the imaginary part of $\hat{f}(i\underline{\omega})$, $S(\underline{\omega})$, takes its first zero near this point, so $S(\pi/E) \approx \underline{\omega}/\beta \approx 0$. Remember that in the parametric representation of the boundary of \mathcal{S} , $\beta(\underline{\omega}) = \underline{\omega}/S(\underline{\omega})$. If β is very large, since $\underline{\omega}$ is bounded, $S(\underline{\omega})$ must be very small. Substituting $s = i\pi/E = i\pi a/m$ in Equation (71), we obtain

$$\left(\frac{i\pi a}{m} + \alpha\right) \left(1 + \frac{i\pi}{m}\right)^m + \beta \approx 0. \quad (74)$$

Thus

$$\beta \approx -\alpha \left(1 + \frac{i\pi}{m}\right)^m - \frac{i\pi a}{m} \left(1 + \frac{i\pi}{m}\right)^m. \quad (75)$$

When α is large enough, the second term in Equation (75) is negligible and β is asymptotic to

$$\alpha \left| 1 + \frac{i\pi}{m} \right|^m. \quad (76)$$

This term only depends on m . If m increases to infinity, for fixed E , f converges weakly to a Dirac delta function. In this case the asymptote is $\beta = \alpha$ and we see that

$$\left(1 + \frac{i\pi}{m} \right)^m \rightarrow e^{i\pi} = -1 \quad (77)$$

as $m \rightarrow \infty$, which is consistent with the case of the single delay with density given by the Dirac delta function. Thus, for large β and large m , we obtain an informal condition for the stability for the unshifted gamma density:

$$\beta \leq K\alpha = \left| 1 + \frac{i\pi}{m} \right|^m \alpha. \quad (78)$$

For the shifted gamma density, we must evaluate $S(\underline{\omega})$ at $\pi/E = \pi/(\tau_m + m/a)$. This leads to the condition

$$\beta \leq K\alpha = \left| 1 + \frac{i\pi}{a\tau_m + m} \right|^m \alpha. \quad (79)$$

In our example (Figure 4), $m = 3$, $a = 1$ and $\tau_m = 5$ so $K = 1.24$.

6. Neutrophil Dynamics. As mentioned in the Introduction, in some diseases a normally approximately constant physiological variable changes its qualitative dynamics and displays an oscillatory nature. This is the case of cyclical neutropenia (CN) in which there is a periodic fall in the neutrophil count from approximately normal to virtually zero and then back up again [9, 10, 11]. Haurie *et al.* [10] developed a model for the peripheral regulation of neutrophil production. Their results and other evidence strongly suggest that the origin of the oscillatory behavior in CN is not due to an instability in the peripheral neutrophil regulatory system. Rather, the oscillations are probably due to a pathological low level oscillatory stem cell input to the neutrophil regulatory system, caused by a destabilization of the hematopoietic stem cell compartment [18, 19]. Haurie *et al.* analyzed the data from nine grey collies and found different dynamics between dogs. When the amplitude of the oscillation of the neutrophil is low, the oscillation is approximately sinusoidal. However, when the amplitude increases, a small “bump” appears on the falling phase of the oscillation which increases the neutrophil count before the count falls to zero. Many models of neutrophil production incorporate a negative feedback with delay. However, in a recent modeling study Hearn *et al.* [13] have shown that this feedback alone cannot lead to the oscillations seen in CN. The principal source of oscillation of the neutrophil count comes from the oscillation of the stem cell input which is exterior to the neutrophil regulatory system.

A regulatory model for neutrophil dynamics with *delayed negative feedback* can be written as

$$\dot{x}(t) = -\alpha x(t) + \mathcal{M}_o(\tilde{x}(t)) \quad (80)$$

where

$$\tilde{x}(t) = \int_{\tau_m}^{\infty} x(t - \tau) f(\tau) d\tau. \quad (81)$$

The function $\mathcal{M}_o(\tilde{x}(t))$ is the feedback control and is a decreasing function. The constant α is the rate of elimination of neutrophil and f is the distribution of maturation delay. This model, proposed by Haurie *et al* in [10], can be expressed in linearized form as

$$\dot{z}(t) = -\alpha z(t) + \varepsilon I(\underline{\omega}) e^{i\underline{\omega}t} \mathcal{M}_{o*} + \mathcal{M}'_{o*} [1 + \varepsilon I(\underline{\omega}) e^{i\underline{\omega}t}] \tilde{z}(t). \quad (82)$$

The distribution f is taken to be the shifted gamma defined in Equation (31) since it offers an excellent fit to the data [13]. The term $\varepsilon I(\underline{\omega}) e^{i\underline{\omega}t}$ accounts for the oscillation of the stem cell input. The constant \mathcal{M}_{o*} is the granulocyte turnover rate defined by

$$\alpha x_* = \mathcal{M}_o(x_*) \equiv \mathcal{M}_{o*}. \quad (83)$$

where x_* is the unique stable steady state of Equation (80). The other parameters are the period of oscillation of the stem cell input $2\pi/\underline{\omega}$, ε which is assumed to be 1 and \mathcal{M}'_{o*} , the slope of the feedback function at the steady state x_* . The term $I(\underline{\omega})$ depends on a and m :

$$I(\underline{\omega}) = \left(\frac{a}{i\underline{\omega} + a} \right)^{m+1} e^{-i\underline{\omega}\tau m}. \quad (84)$$

The value of a is 14.52, m is 8.86 and $\underline{\omega}$ is around 0.45. The maximum value of the oscillation factor $\varepsilon \Re I(\underline{\omega})$ is nearly one, so

$$\max |\mathcal{M}'_{o*} [1 + \varepsilon I(\underline{\omega}) e^{i\underline{\omega}t}]| \approx 2 |\mathcal{M}'_{o*}|. \quad (85)$$

Now if we look at the autonomous part of Equation (82), we get

$$\dot{z}(t) = -\alpha z(t) + \mathcal{M}'_{o*} [1 + \varepsilon I(\underline{\omega}) e^{i\underline{\omega}t}] \tilde{z}(t). \quad (86)$$

When the amplitude of the stem cell input reaches its maximum, we can approximate Equation (86) using Equation (85) by

$$\dot{z}(t) = -\alpha z(t) + 2\mathcal{M}'_{o*} \tilde{z}(t). \quad (87)$$

Since we suppose that $\mathcal{M}_o(\tilde{z}(t))$ is a decreasing function, we know that \mathcal{M}'_{o*} is non-positive. We can therefore apply Theorem 4.0.5 to study the stability of Equation (87). If $2\mathcal{M}'_{o*} \leq \alpha$, Equation (87) is always stable. In this case, oscillation in the neutrophil count is due only to the oscillation of the stem cell input in the neutrophil regulatory system and the behavior of the neutrophil count is sinusoidal.

However, in some cases, even if $\mathcal{M}'_{o*} \leq \alpha$, we may have that $2\mathcal{M}'_{o*} \geq \alpha$. Then to study the stability, we can use condition (61) which gives

$$E < \frac{\arccos(\alpha(2\mathcal{M}'_{o*})^{-1})}{\sqrt{(2\mathcal{M}'_{o*})^2 - \alpha^2}}. \quad (88)$$

The decay rate α is between 2.18 and 2.48 (days^{-1}), and the expected delay E is between 3.21 and 3.42 days. From data fitting [10], we obtain \mathcal{M}'_{o*} ranging from -0.05 to -2.20. Taking $\alpha = 2.4$, we see that $|\mathcal{M}'_{o*}| \geq 1.20$ can destabilize Equation (87). From Table 4 of Haurie *et al.* (reproduced in Table 1) the smallest slope $|\mathcal{M}'_{o*}|$ greater than 1.20 is 1.50. With $\mathcal{M}'_{o*} = -1.50$, a sufficient condition to have stability is

$$E < \frac{\arccos(-0.80)}{\sqrt{3.24}} = 1.39.$$

However, since E is far greater than 1.39 (at least 3.21), we expect that Equation (87) will not be stable for values of $|\mathcal{M}'_{o*}| \geq 1.50$. This implies that Equation (82)

Dog	\mathcal{M}'_{o*}	\mathcal{M}'_{o*} fit	$\bar{\omega}$	T_{ins}
127	-0.20	-0.10	0.465	0
113	-0.91	-0.05	0.470	0
128	-1.09	-2.00	0.464	5.39
118	-0.48	-0.50	0.500	0
126	-1.00	-1.80	0.463	4.70
101	-1.24	-1.50	0.426	3.27
125	-1.15	-2.20	0.421	6.55
117	-1.05	-1.70	0.438	4.49
100	-1.20	-1.80	0.418	5.20

TABLE 1. Data for nine grey collies. The computations for T_{ins} were made using \mathcal{M}'_{o*} fit. Note that with \mathcal{M}'_{o*} , only Dog 101 has a slope high enough to destabilize the peripheral regulatory system. This suggests that the fitted values are close to the real ones. The units of \mathcal{M}'_{o*} , \mathcal{M}'_{o*} fit and $\bar{\omega}$ are days⁻¹ and T_{ins} is in days. From Haurie *et al.* [10].

will be destabilized when the amplitude of the stem cell input reaches a threshold which depend on \mathcal{M}'_{o*} . From Table 1, we can estimate the interval of time during which Equation (87) will be destabilized. The expected delay E must satisfy

$$E \gg \frac{\arccos[\alpha\{\mathcal{M}'_{o*}(1 + \Re(\varepsilon I(\bar{\omega})))\}^{-1}]}{[1 + \varepsilon\Re(I(\bar{\omega}))]^2 \mathcal{M}'_{o*}{}^2 - \alpha^2}^{1/2}. \tag{89}$$

At worst this condition becomes

$$E \gg \pi[\{1 + \varepsilon\Re(I(\bar{\omega}))\}^2 \mathcal{M}'_{o*}{}^2 - \alpha^2]^{-1/2}. \tag{90}$$

We can approximate $\Re(I(\bar{\omega}))$ with Equation (84) by

$$\Re(I(\bar{\omega})) \simeq 0.96 \cos[\bar{\omega}(t - \tau_m)]. \tag{91}$$

Equation (90) becomes, with $\alpha = 2.4$,

$$\cos[\bar{\omega}(t - \tau_m)] \gg \frac{2.71}{|\mathcal{M}'_{o*}|} - 1.04. \tag{92}$$

Given that the density of the maturation delays is concentrated around its expectation (the variance is 0.042), we can replace in our approximation the symbol \gg by the usual $>$. Solving for t gives that t must lie in an interval of length

$$T_{ins} \equiv \frac{2}{\bar{\omega}} \arccos\left(\frac{2.71}{|\mathcal{M}'_{o*}|} - 1.04\right) \tag{93}$$

The value of T_{ins} for each dog is given in Table 1. We find that the peripheral neutrophil regulatory system is destabilized during an average of 4.93 days each period of stem cell input which is of length between 12.6 and 15 days. The effect of this is the small bump seen after the spikes of the neutrophil count.

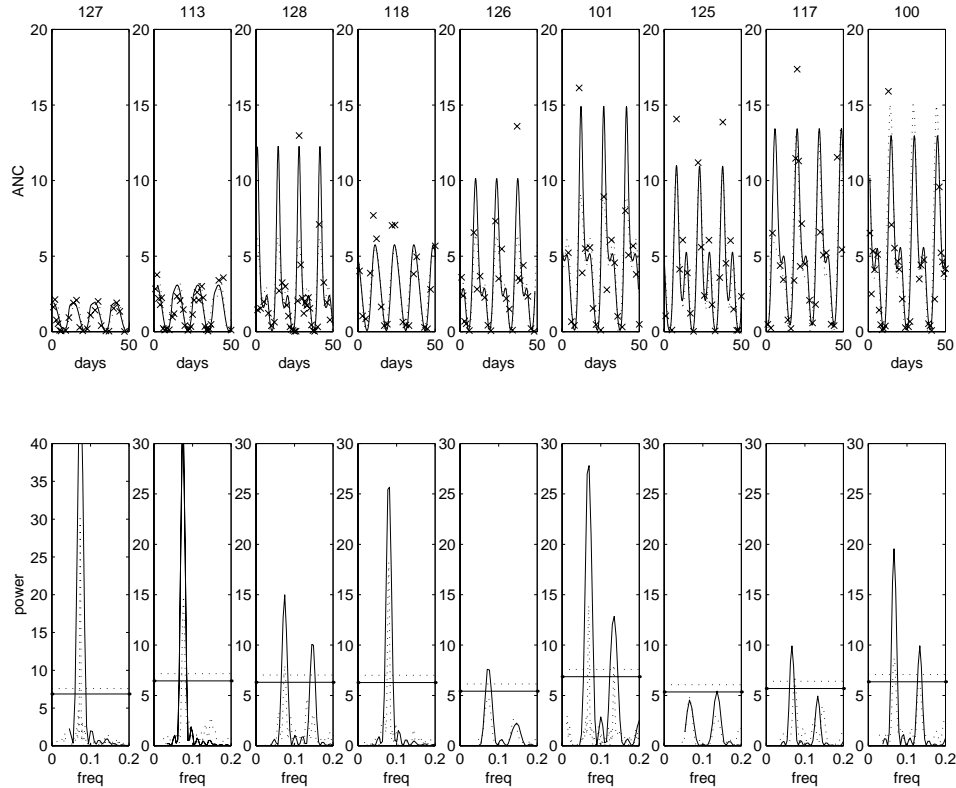


FIGURE 5. Simulation results of the model to the absolute neutrophil count (ANC,top) and the Lomb periodogram (bottom). The units for ANC are $\text{cells} \times 10^{-3} \text{mm}^{-3}$. The x's are the data points and the solid lines are the simulation results of Equation (80). Note the existence of a second harmonic in the Lomb periodogram for all but three dogs (127,113 and 118), which is consistent with the theoretical computation done in Table 1.

7. Conclusion. We have analysed the influence of the distribution of delays on the stability properties of the null solution of Equation (1). In general, distributed delays seem to increase the stability of the steady state of a DDE when compared to a discrete delay. With a gamma distribution of the delay, if α and β are sufficiently large, then the steady state will be stable for more values of the parameters than with any equation with a discrete delay.

Theorem 4.0.5 shows that even limited properties of the distribution of delay provide a good indication for the stability when α is relatively small. In many cases, the study of the stability of a differential equation with distributed delays can be reduced to the problem of stability with a discrete delay. When the distribution of delays is known, results of Section 3 gives a way to find the boundary of the stability region even if it is not always possible to find an explicit bound in term of intrinsic parameters of the distribution.

In a modeling context, it is often difficult to precisely determine the distribution of delays in the description of a delayed regulated process. Results such as

those presented here thus have great interest since they provide *general* bounds on stability regions, irrespective of the particulars of these distributions.

We end this paper with a conjecture which we have found to hold in all cases of distributions of delays that we have studied. Proving it would be very useful and would make the results of Section 4 obsolete. In words, it amounts to stating that the most destabilizing distribution of delays is a single Dirac δ function. If true, it could provide, by consideration of simplified models containing single discrete delays, uniform upper bounds on regions of stability in parameter space.

Conjecture 7.0.1. *In the notation of Section 4, let f be a probability density defined on R^+ with expectation E . Suppose that $\underline{\omega}^*$ is the first root of $C(\underline{\omega})$, then*

$$\beta(\underline{\omega}^*) \equiv \frac{\underline{\omega}^*}{S(\underline{\omega}^*)} \geq \frac{\pi}{2E}. \quad (94)$$

Acknowledgments. Support for this work has been provided by grants from the Natural Sciences and Engineering Research Council (Canada) [OGP-0008806 to JB and OGP-0036920 to MCM], MITACS (Canada) [JB,MCM], the Alexander von Humboldt Stiftung [MCM] and Le Fonds pour la Formation de Chercheurs et l'Aide à la Recherche (Québec) [98ER1057 to MCM,JB]. SB is supported by a studentship from MITACS.

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Received November 2000; in revised January 2001.

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