

**A FOUR DIMENSIONAL FUNCTIONAL  
DIFFERENTIAL EQUATION FOR  
THE DYNAMICS OF CD4+ T-CELLS AND HIV-1**

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**Abstract:** A four compartment delay model for HIV-1 and T-cell concentrations is given so that the time delay  $\tau \geq 0$  corresponds directly (both by definition and location in the equations) with the fact that conversion processes require positive time. Hence, at  $\tau = 0$ , the system reduces to the model in [11]. Since the characteristic equation is transcendental, the classical Routh-Hurwitz criteria, of course, cannot

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be used directly. The approach in the present paper uses the *derived polynomial*  $h_\tau(r)$ . Part of what is new includes applying the Routh-Hurwitz criteria to  $h_\tau(r)$ . Results do not depend on obtaining roots as such, and so can be used in the stability analysis of delay systems of any order. We obtain new explicit sufficient criteria for sustained stability of steady states across real intervals of delay  $\tau$ . Critical delays are calculated that produce bifurcation in the steady states. For the non-infected steady states, a delay dependent upper bound function  $N_{crit}(\tau)$  for the lysing rate is explicitly calculated. This upper bound is connected with the PDK stability parameter  $N_{crit}^{PDK}$  by the equality  $N_{crit}^{PDK} = N_{crit}(\tau = 0)$ . As would be required on medical grounds, the function  $N_{crit}(\tau)$  increases in  $\tau$ . Throughout the paper, qualitative results are illustrated with numerical simulations.

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**Key Words:** functional differential equation, delay equation, T-Cells, HIV-1, stability analysis, derived polynomial, delay dependent bifurcation

## 1. Introduction

There is an established body of work in the literature that pertains to the use of differential equations in modeling HIV infection of CD4+ T-cells in the human bloodstream. For comprehensive bibliographies and more complete background, one may consult the articles cited in the references section below (see, for example, [11], [2], [9]).

One of the first papers on such HIV modeling was [10]. The following system of ordinary differential equations was introduced:

$$\begin{aligned} \frac{\partial T}{\partial t} &= s - \mu_T T(t) + rT(t) \left(1 - \frac{T(t)}{T_{\max}}\right) - kV(t)T(t), \\ \frac{\partial T^*}{\partial t} &= kV(t)T(t) - \mu_{T^*} T^*(t), \\ \frac{\partial V}{\partial t} &= N\mu_b T^*(t) - \mu_V V(t). \end{aligned} \tag{1.1}$$

Here  $T(t)$ ,  $T^*(t)$  and  $V(t)$  are the densities of the healthy CD4+ T-cells, infected CD4+ T-cells and free virus at time  $t$ , respectively. The pa-

parameter  $s$  represents the production of CD4+ T-cells due to precursors;  $\mu_T$  is the natural death rate of healthy CD4+ T-cells;  $r$  is the growth rate of healthy CD4+ T-cells;  $\mu_{T^*}$  is the death rate of latently T-cells – usually taken to be approximately equal to  $\mu_T$ ;  $\mu_b$  is the death rate of infected T-cells; and  $\mu_V$  is the death rate of infectious virus.

Later it became known that there can be considerable latency periods between HIV infection and the actual onset of AIDS, extending months or even eight to ten years (see [11], p. 86). Perelson, Kirschner, and De Boer then considered a model that might better account for a typical latency period [11]. Their model divided the CD4+ T-cell population into two groups, namely, those CD4+ T-cells that are latently infected and those that are actively infected. Below is the system of equations for their model:

$$\begin{aligned}\frac{\partial T}{\partial t} &= s - \mu_T T(t) + rT(t) \left(1 - \frac{T(t)}{T_{\max}}\right) - k_1 V(t)T(t), \\ \frac{\partial T^*}{\partial t} &= k_1 V(t)T(t) - \mu_T T^*(t) - k_2 T^*(t), \\ \frac{\partial T^{**}}{\partial t} &= k_2 T^*(t) - \mu_b T^{**}(t), \\ \frac{\partial V}{\partial t} &= N\mu_b T^{**}(t) - k_1 V(t)T(t) - \mu_V V(t).\end{aligned}\tag{1.2}$$

Here  $T^*(t)$  represents the density of latently infected cells and  $T^{**}(t)$  denotes the density of actively infected cells. Parameters and clinical values are given in Table 1 (taken from [11]), reproduced at the end of Section 2 below.

As discussed in [6], there also can be a time delay between the infection of CD4+ T-cells and the emission of viral particles. Culshaw and Ruan [2] introduced a delay differential equation to describe this feature of the HIV-1 infection. For HIV, this was one of the first stability analyses using a system of delay-differential equations. Their approach was to reduce the PDK model to a three component model, by re-combining the latently infected cells  $T^*(t)$  and the actively infected cells  $T^{**}(t)$  into one group of infected cells  $I(t)$ . Introducing delay into the second equation, the model in [2] is as follows:

$$\begin{aligned}
\frac{\partial T}{\partial t} &= s - \mu_T T(t) + rT(t) \left( 1 - \frac{T(t) + I(t)}{T_{\max}} \right) - k_1 V(t)T(t), \\
\frac{\partial I}{\partial t} &= k'_1 V(t - \tau)T(t - \tau) - \mu_I I(t), \\
\frac{\partial V^*}{\partial t} &= N\mu_b I(t) - k_1 V(t)T(t) - \mu_V V(t).
\end{aligned} \tag{1.3}$$

Note that in these models, the cell and virus terms  $T$ ,  $V$ , etc. are ideal population densities. That  $\tau$  is called “the delay” means that in the model it is a fixed quantity. The fixed delay, however, does not refer to individual cells as such, but is implicitly defined by the differential equations and so regards the production of ideal population densities.

Individual delay at the cellular level can of course vary, and by all accounts, is a statistical process. Consequently, this points to the possibility of statistical analysis that takes into account the full range of possible random delays. In [8], [9] and [3], distributed delay is built into the models through integration kernels. In [8], Section 2.3 and Appendix A, together establish that the distributed-delay model of their paper is equivalent to an ordinary differential equation. In [3], conversion to an equivalent ODE is at their equation (5.2).

The following contextual remarks regard the prevalence of this type of conversion to a system of ODE's. In fact (as we now show), equivalence to an ODE is a property of several classes of distributed-delay models.

In the papers just mentioned, the distributed terms introduced are of the form

$$X(t) = \int_{-\infty}^a K(t, \tau) d\tau,$$

where  $a = t < \infty$  or  $a = \infty$ .

In both cases, since the kernel has been integrated across the parameter range for  $\tau$ , this quantity is a function of  $t$  alone, and not a function of  $\tau$ . Assume that quantities are suitably integrable and finite.

If  $a = \infty$ , then

$$\frac{dX}{dt} = \int_{-\infty}^{\infty} \frac{\partial K(t, \tau)}{\partial t} d\tau. \tag{1.4}$$

If  $a = t < \infty$ , then by the product rule,

$$\frac{dX}{dt} = K(t, t) + \int_{-\infty}^t \frac{\partial K(t, \tau)}{\partial t} d\tau. \quad (1.5)$$

In either case, if  $\int_{-\infty}^a \frac{\partial K(t, \tau)}{\partial t} d\tau$  can be expressed as  $\Phi(X, V_1, \dots, V_r)$  ( $\Phi$  a function of  $X$  and the variables  $V_1, \dots, V_r$  of the original ODE), then we obtain an extended system. Evidently, if the original system is an ODE, so is the extended system.

In [8], the kernel is given in terms of the gamma distribution and is both polynomial and exponential in the variable  $t$ . The function  $\Phi(X, V_1, \dots, V_r)$  is therefore a first-order recursive relation with variables of the original system.

In [3], equivalence to an ODE follows from the fact that the kernel  $K(t, \tau)$  is exponential in  $t$  and satisfies its own partial differential equation of the form  $\frac{\partial K}{\partial t} = g(t)K(t, \tau)$ . Hence

$$\begin{aligned} \frac{\partial X}{\partial t} &= K(t, t) + \int_{-\infty}^t \frac{\partial K(t, \tau)}{\partial t} d\tau = K(t, t) + g(t) \int_{-\infty}^t K(t, \tau) d\tau \\ &= K(t, t) + g(t)X(t). \end{aligned} \quad (1.6)$$

In general, a distributed-delay model introduces a global quantity determined by the overall effect of a weighted range of possible individual delays. From the above calculations, the type of model that results from a typical kernel frequently will be equivalent to a system of ordinary differential equations.

In addition to models that distribute delay terms through an integration kernel, there also have been delay-differential equation models with two sources of delay (see [4], [1], [13]).

What would be desirable, eventually, is a general theory that would account for and correlate these various types of model. For fixed delay, equations for population densities also are intrinsically statistical, for they regard ideal densities. Within a general context, therefore, such an equation could be taken as a  $\tau$  – cross section of a distributed delay model. So, structure theorems will be needed. The general multi-delay

equation determined by a system of  $n$  equations and  $k$  discrete delays is studied in [12], where a practical algorithm is obtained for determining information regarding root location for the general multi-delay transcendental characteristic equation. In the present work, preliminary and particular results focus on certain models pertaining to HIV.

As discussed in [11], clinically, there are at least four main populations present during HIV infection, namely,  $T$ ,  $T^*$ ,  $T^{**}$ ,  $V$ . Also, it is known that there are real delays involved in cellular conversion processes. A purpose of the present paper therefore is to adhere to known distinctions between these four groups  $T$ ,  $T^*$ ,  $T^{**}$ ,  $V$ , but also to build in a natural delay term. Specifically, for model (1.7), the discrete time delay  $\tau$  represents the time required for latently infected cells (densities) to become actively infected. This builds on the discussion in [11] (both by definition and location of terms in the equations); and at  $\tau = 0$ , the system reduces to the model in [11].

Our model (1.7), therefore, is as follows:

$$\begin{aligned} \frac{\partial T}{\partial t} &= s - \mu_T T(t) + rT(t) \left( 1 - \frac{T(t) + T^*(t) + T^{**}(t)}{T_{\max}} \right) \\ &\quad - k_1 V(t) T(t), \\ \frac{\partial T^*}{\partial t} &= k_1 V(t) T(t) - \mu_T T^*(t) - k_2 e^{-\mu_T \tau} T^*(t - \tau), \\ \frac{\partial T^{**}}{\partial t} &= k_2 e^{-\mu_T \tau} T^*(t - \tau) - \mu_b T^{**}(t), \\ \frac{\partial V}{\partial t} &= N \mu_b T^{**}(t) - k_1 V(t) T(t) - \mu_V V(t). \end{aligned} \tag{1.7}$$

See Table 1 (below) for clinical values of the various constants, as given in [11].

The transcendental characteristic equation of (1.7) is of the form  $\Delta_\tau(\lambda) = P_\tau(\lambda) + e^{-\lambda\tau} Q_\tau(\lambda)$ . The functions  $P_\tau(\lambda)$  and  $Q_\tau(\lambda)$  are polynomials in  $\lambda$ , of degree four and three respectively. Some of the coefficients depend explicitly on the delay  $\tau$ .

We note that the third degree characteristic equation (26) of [9] also has a delay quantity in its coefficients. As is customary, their stability analysis investigates possible purely imaginary roots. In their equation

(28), however, the effect of setting the real part of the possible root to zero removes the delay term from the coefficients. For stability analysis of (1.7), the delay remains in the calculation and plays a key role in the results. Also, as in [2], (1.7) is not reducible to an ordinary differential equation.

Model (1.7) is a four dimensional system of delay differential equations, with one real discrete delay  $\tau \geq 0$ . Since the characteristic equation is transcendental, the classical Routh-Hurwitz criteria of course cannot be used directly, and so special techniques are needed for a local stability analysis. The standard approach to stability analysis of delay equations is based on a technique that goes back to [5], and normally is limited to models where the degree of the polynomial parts of the transcendental equation are not greater than three, that is, where roots of related equations can be explicitly calculated. The approach in the present paper uses the *derived polynomial*  $h_\tau(r)$ . Part of what is new, therefore, is applying the Routh-Hurwitz criteria to  $h_\tau(r)$ . Results do not depend on obtaining roots as such, and so can be used in the stability analysis of delay systems of any order. The derived polynomial has the property that if  $i\omega$  is a purely imaginary root of the (transcendental) characteristic equation, then  $r = \omega^2$  is a non-negative root of the derived polynomial  $h_\tau(r)$ . From the contra-positive, we obtain new explicit sufficient criteria for sustained stability of steady states across real intervals of delay  $\tau$ .

Using clinical data from [11], steady states of the delay model in [2] were found to be mathematically stable for all  $\tau \geq 0$ . But real steady states can be unstable, for virus population densities are known to change in their growth patterns. Indeed, in some cases, accelerations can lead to terminal results. In model (1.7), coefficients of the (transcendental) characteristic equation depend explicitly on  $\tau$ ; and the approach allows explicit analysis of the effect of these delay dependent coefficients on stability of steady states (both non-infected and infected). In particular, new bifurcation results are obtained that qualitatively correspond to what can occur in patients (more precise results would be obtained with further clinical data). In other words, analysis of the Routh-Hurwitz criteria for  $h_\tau(r)$  allows critical delays to be calculated that produce bifurcation in the steady states. For the non-infected steady states, a delay dependent upper bound function  $N_{crit}(\tau)$  for the lysing rate is explicitly calculated. This upper bound is connected with the PDK stability

parameter  $N_{crit}^{DDK}$  by the equality  $N_{crit}^{DDK} = N_{crit}(\tau = 0)$ . As would be expected on medical grounds, the function  $N_{crit}(\tau)$  is increasing (as it turns out, it is monotone) with respect to  $\tau$ . Throughout the paper, qualitative results are illustrated with numerical simulations.

Finally, some details on the ordering of the sections below: In Section 2, we give the linearization of the delay equation (1.7). In Section 3, we calculate the derived polynomial  $h_\tau(r)$  and develop some general results. Section 4 includes the stability analysis of steady states (non-infected and infected), as well as a result on Hopf bifurcation. In Section 5, we discuss numerical results. In Section 6 we give concluding remarks and indicate possible further lines of enquiry.

## 2. Steady States and Linearization

Standard calculations show that there are two classes of steady state:

(i) Non-infected:  $\bar{T} = T_0$ ,  $\bar{T}^* = \bar{T}^{**} = \bar{V} = 0$ ; and

(ii) For the infected steady state, the values  $\bar{T}$ ,  $\bar{T}^*$ ,  $\bar{T}^{**}$ ,  $\bar{V}$  are related as follows

$$\begin{aligned}\bar{T} &= \frac{\mu_v}{\frac{Nk_1k_2}{k_2 + \mu_T e^{\mu_T \tau}} - k_1}, \\ \bar{T}^* &= \frac{k_1 \bar{V} \bar{T}}{\mu_T + k_2 e^{-\mu_T \tau}} = \frac{\mu_v e^{\mu_T \tau} \bar{V}}{Nk_2 - k_2 - \mu_T e^{\mu_T \tau}}, \\ \bar{T}^{**} &= \frac{k_2 e^{-\mu_T \tau}}{\mu_b} \bar{T}^* = \frac{k_1 k_2 \bar{V} \bar{T}}{\mu_b (k_2 + \mu_T e^{\mu_T \tau})}, \\ \bar{V} &= \frac{(s + (r - \mu_T) \bar{T}) (k_2 + \mu_T e^{\mu_T \tau}) \mu_b T_{\max}}{k_1 \bar{T} ((k_2 + \mu_T e^{\mu_T \tau}) \mu_b T_{\max} + r (k_2 + \mu_T e^{\mu_T \tau}) \bar{T})}.\end{aligned}\tag{2.1}$$

Observe that for  $\tau = 0$ , these steady state values are same as those obtained in [11].

The linearization of the model at a steady state gives an equation of the form

$$\frac{dx}{dt}(t) = A_1(t) + A_2 x(t - \tau),\tag{2.2}$$



where

$$x = \begin{pmatrix} x_1 \\ \vdots \\ x_n \end{pmatrix},$$

and  $A_1, A_2$  are  $n \times n$  matrices of constants.

Since the steady states depend explicitly on the delay  $\tau$ , so do the Jacobian matrices  $A_1, A_2$ . As will be seen below this delay dependence can induce bifurcations (see Remark 3.5, Proposition 3.6 and the numerical results of Section 5). Note that, for simplicity of notation, we sometimes suppress the notation for this dependence on the delay term.

The Jacobian matrices  $A_1$  and  $A_2$  for the model is:

$$A_1 = \begin{bmatrix} \rho - \alpha\beta - k_1\bar{V} & -\alpha\bar{T} & -\alpha\bar{T} & -k_1\bar{T} \\ k_1\bar{V} & -\mu_T & 0 & k_1\bar{T} \\ 0 & 0 & -\mu_b & 0 \\ -k_1\bar{V} & 0 & N\mu_b & -k_1\bar{T} - \mu_v \end{bmatrix}, \quad (2.3)$$

$$A_2 = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & -k_2e^{-\mu_T\tau} & 0 & 0 \\ 0 & k_2e^{-\mu_T\tau} & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix},$$

where for convenience we have set

$$\rho = r - \mu_T, \quad \alpha = \frac{r}{T_{\max}}, \quad \beta = 2\bar{T} + \bar{T}^* + \bar{T}^{**}.$$

Note that for the non-infected steady state,  $A_1$  becomes

$$A_1 = \begin{bmatrix} \rho - 2\alpha T_0 & -\alpha T_0 & -\alpha T_0 & -k_1 T_0 \\ 0 & -\mu_T & 0 & k_1 T_0 \\ 0 & 0 & -\mu_b & 0 \\ 0 & 0 & N\mu_b & -k_1 T_0 - \mu_v \end{bmatrix}. \quad (2.4)$$

To obtain the characteristic equation, recall the general technique. Suppose that for some constant  $\lambda$  there is a solution of (2.2) of the form

$$x(t) = e^{\lambda t} \begin{pmatrix} a_1 \\ \vdots \\ a_n \end{pmatrix},$$

where  $a_1, \dots, a_n$  are constants. Calculation then shows  $x(t)$  is in the kernel of the combined Jacobian, and so the determinant

$$\Delta(\lambda) = \left| \lambda \mathbf{I} - A_1 - e^{-\lambda \tau} A_2 \right| = 0.$$

It follows that the general form of the (transcendental) characteristic function is  $\Delta_\tau(\lambda) = P_\tau(\lambda) + e^{-\lambda \tau} Q_\tau(\lambda)$ .

For model (1.7) we obtain

$$\begin{aligned} \Delta_\tau(\lambda) &= (\lambda^4 + A\lambda^3 + B\lambda^2 + C\lambda + D) + (a\lambda^3 + b\lambda^2 + c\lambda + d) e^{-\lambda \tau}. \end{aligned} \quad (2.5)$$

A routine, but lengthy, calculation shows that the coefficients of the equation are given by:

$$\begin{aligned} A &= \mu_T + \mu_b + k_1 \bar{T} + \mu_V - \rho + \alpha\beta + k_1 \bar{V}, \\ B &= -\rho\mu_T + \alpha\beta\mu_T + k_1\mu_T \bar{V} + \mu_T\mu_b + \mu_T\mu_V + \mu_b k_1 \bar{T} \\ &\quad + \mu_b\mu_V - \rho\mu_b - \rho k_1 \bar{T} - \rho\mu_V + \alpha\beta\mu_b + \alpha\beta k_1 \bar{T} \\ &\quad + \alpha\beta\mu_V + 2k_1\mu_V \bar{V} + \alpha k_1 \bar{V} \bar{T} - \alpha k_1^2 \bar{V} \bar{T}^2, \end{aligned} \quad (2.6)$$

$$\begin{aligned}
C &= -\rho\mu_T\mu_b - \rho\mu_Tk_1\bar{T} - \rho\mu_T\mu_V + \alpha\beta\mu_T\mu_b \\
&+ \alpha\beta\mu_Tk_1\bar{T} + \alpha\beta\mu_T\mu_V + k_1\mu_T\mu_b\bar{V} + \mu_T\mu_bk_1\bar{V} \\
&+ \mu_T\mu_bk_1\bar{T} + \mu_T\mu_b\mu_V - \rho\mu_bk_1\bar{T} - \rho\mu_b\mu_V \\
&+ \alpha\beta k_1\mu_b\bar{T} + \alpha\beta\mu_b\mu_V + k_1\mu_b\mu_V\bar{V} + \alpha\mu_bk_1\bar{V}\bar{T} \\
&+ \alpha k_1^2\bar{V}\bar{T}^2 + \alpha\mu_Vk_1\bar{V}\bar{T}, \\
D &= -\rho\mu_T\mu_bk_1\bar{T} - \rho\mu_T\mu_b\mu_V + \alpha\beta\mu_T\mu_bk_1\bar{T} \\
&+ \alpha\beta\mu_T\mu_b\mu_V + \mu_T\mu_b\mu_Vk_1\bar{V} + \mu_b\mu_V\alpha k_1\bar{V}\bar{T}, \\
a &= k_2e^{-\mu_T\tau}, \\
b &= (-\rho k_2 + \alpha\beta k_2 + k_1k_2\bar{V} + \mu_bk_2 + k_1k_2\bar{T} + \mu_Vk_2)e^{-\mu_T\tau}, \\
c &= (-\rho\mu_bk_2 - \rho k_1k_2\bar{T} - \rho\mu_Vk_2 + \alpha\beta\mu_bk_2 + \alpha\beta k_1k_2\bar{T} \\
&+ \alpha\beta\mu_Vk_2 + \mu_bk_1k_2\bar{V} + \mu_Vk_1k_2\bar{V} + \mu_bk_1k_2\bar{T} - k_1k_2\mu_bN\bar{T} \\
&+ \mu_b\mu_Vk_2 + \alpha k_1k_2\bar{V}\bar{T})e^{-\mu_T\tau}, \\
d &= (-\rho\mu_bk_1k_2\bar{T} - \rho\mu_b\mu_Vk_2 + \rho\mu_bk_1k_2N\bar{T} + \alpha\beta\mu_bk_1k_2\bar{T} \\
&+ \alpha\beta\mu_b\mu_Vk_2 - \alpha\beta\mu_bk_1k_2N\bar{T} + \mu_b\mu_Vk_1k_2\bar{V} \\
&- k_1^2k_2\mu_bN\bar{V}\bar{T} + \alpha k_1^2k_2\bar{V}\bar{T}^2 + \alpha k_1k_2\mu_V\bar{V}\bar{T} \\
&+ k_1^2k_2\mu_bN\bar{V}\bar{T} - \alpha k_1^2k_2\bar{V}\bar{T}^2)e^{-\mu_T\tau}.
\end{aligned}$$

		Initial or default values
<b>Dependent variables</b>		
$T$	Uninfected CD4+ cell population size	1000 mm <sup>-3</sup>
$T^*$	Latently infected CD4+ helper cell population size	0
$T^{**}$	Actively infected CD4+ helper cell population size	0
$V$	HIV population size	10 <sup>-3</sup> mm <sup>-3</sup>
<b>Parameters and constants</b>		
$s$	Rate of supply of CD4+ T-cells from precursors	10 day <sup>-1</sup> mm <sup>-3</sup>
$r$	Rate of growth for the CD4+ cell population	0.03 day <sup>-1</sup>
$T_{\max}$	Maximum CD4+ cell population level	1500 mm <sup>-3</sup>
$\mu_T$	Death rate of uninfected and latently infected CD4+ cells	0.02 day <sup>-1</sup>
$\mu_b$	Death rate of actively infected CD4+ cell population	0.24 day <sup>-1</sup>
$\mu_V$	Death rate of free virus	2.4 day <sup>-1</sup>
$k_1$	Rate constant for CD4+ cells becoming infected by virus	(2.4)(10 <sup>-5</sup> ) mm <sup>3</sup> day <sup>-1</sup>
$k_2$	Rate latently infected cells convert to actively infected	(3.0)(10 <sup>-3</sup> ) day <sup>-1</sup>
$N$	Number of free virus produced by lysing CD4+ cell	Varies
<b>Derived quantities</b>		
$T_0$	Steady-state level of CD4+ cells in uninfected individuals	1000 mm <sup>-3</sup>
$N_{crit}$	Critical number of viral progeny needed for endemic infection	774
$k_3$	= $k_2 + \mu_T$	0.023day <sup>-1</sup>
$k_4$	= $k_1 T_0 + \mu_V$	2.424day <sup>-1</sup>

Table 1: Variables and parameters (quantities in Table 1 are taken from Table 1 of [11])

### 3. Some General Results and the Derived Polynomial

As is well known, asymptotic stability of steady states can depend on the real parts of eigenvalues of the corresponding Jacobian matrix (see, however, Remark 3.1 below). If the real parts of all eigenvalues are negative, then all solutions are asymptotically stable; and if there is an eigenvalue whose real part is strictly positive, then not all solutions are asymptotically stable.

Consider a system of delay-equations whose terms depend smoothly on the delay parameter  $\tau$ . Suppose also that for  $\tau = 0$ , all eigenvalues have negative real parts. By a standard application of Rouché's Theorem, if there is a positive delay for which at least one of the eigenvalues becomes strictly positive (and so for which there is loss of asymptotic stability) then there is a positive delay  $\tau$  for which the characteristic function has a purely imaginary root of the form  $\lambda = i\omega$ . If, on the other hand, the real parts of the spectra remain strictly negative for all positive  $\tau$ , then (as follows from the first paragraph) the steady states correspondingly remain asymptotically stable (for all positive  $\tau$ ).

**Remark 3.1.** Stability analysis therefore typically involves investigating the possible existence of purely imaginary roots of the characteristic function. However, if at  $\tau = 0$ , the eigenvalues are strictly negative; and if there is a positive delay for which there is a purely imaginary root  $\lambda = i\omega$ , it need not follow that there is loss of asymptotic stability. Rather, a key issue is whether or not the real part of the spectrum becomes strictly positive. Hence, one of the hypotheses in Hopf Bifurcation Theorem is that the derivative with respect to  $\tau$  be non-zero, thus ensuring a change of sign of the real parts of a selected path of eigenvalues.

If  $\Delta = 0$  has a purely imaginary root  $\lambda = i\omega$ , we obtain  $\Delta(i\omega) = P(i\omega) + Q(i\omega)e^{-i\omega\tau} = 0$ . The term  $e^{-i\omega\tau}$  is a rotation in the complex plane of modulus one. It follows that  $|P|^2 = |Q|^2$ . In other words, if the (transcendental) characteristic equation has a purely imaginary root  $i\omega$  then the real function  $F(\omega) = |P|^2 - |Q|^2$  has a real root  $\omega$  (see also Theorem 4.1(v) recorded in [7], p. 83).

For an alternative derivation of this result, one explicitly calculates real and imaginary parts of the transcendental characteristic equation. Regarding the function  $F(\omega)$ , the result is the same. Special cases may

be found throughout the literature. For convenience, we give the general calculation:

Separating  $P(i\omega)$  and  $Q(i\omega)$  into real and imaginary parts, we obtain

$$[\operatorname{Re} P + i\operatorname{Im} P] + [\operatorname{Re} Q + i\operatorname{Im} Q] [\cos(\omega\tau) + i\sin(\omega\tau)] = 0. \quad (3.1)$$

Equating each of the real and imaginary parts of (3.1) to zero, and putting the trigonometric terms to the right hand side, we obtain

$$\operatorname{Re} P = -\operatorname{Re} Q \cos(\omega\tau) - \operatorname{Im} Q \sin(\omega\tau), \quad (3.2)$$

$$\operatorname{Im} P = -\operatorname{Im} Q \cos(\omega\tau) + \operatorname{Re} Q \sin(\omega\tau).$$

Squaring both sides of each equation, adding the left sides and the right sides respectively, the cross-terms of the right-hand sides cancel, and we are left with

$$(\operatorname{Re} P)^2 + (\operatorname{Im} P)^2 = (\operatorname{Re} Q)^2 + (\operatorname{Im} Q)^2. \quad (3.3)$$

Note that this real equation depends on two real variables  $(\omega, \tau)$ , is polynomial in  $\omega$ , and we again obtain the real equation  $F(\omega) = 0$ . In special cases where the coefficients of  $F(\omega)$  do not depend explicitly on  $\tau$ , this reduces to a polynomial in one real variable  $\omega$  (see [2], [1] and examples from [7]).

If one traces through the derivation of the polynomial  $F(\omega)$ , it turns out that  $F(\omega)$  has only even powers of  $\omega$ . So, making the substitution  $r = \omega^2$ , we obtain the *derived polynomial*  $h_\tau(r) = h(r)$ . As polynomials in  $\omega$  and  $r$ , respectively,  $\deg F(\omega) = 2 \deg h(r)$ .

**Remark 3.2.** Summary of how the zeros of the functions  $\Delta_\tau(\lambda)$ ,  $F_\tau(\lambda)$ ,  $h_\tau(\lambda)$  are related: If the (transcendental) characteristic function  $\Delta_\tau = P_\tau + e^{-\lambda\tau}Q_\tau$  has a purely imaginary root  $\lambda = i\omega$  then  $F_\tau = |P_\tau|^2 - |Q_\tau|^2$  has a real root  $\omega$ . Since  $h_\tau$  is defined by  $h_\tau(\omega^2) = F_\tau(\omega)$ , it follows that  $F_\tau$  has a real root  $\omega$ , then  $h_\tau$  has a non-negative root  $r = \omega^2$ .

Observe that since the polynomial  $h(r)$  is real, using calculus, analysis of zeros may be reduced by one more degree. No doubt, this is part of mathematical folklore. For reference, we record the result as Lemma 3.3.

**Lemma 3.3.** *Let  $h(r)$  be a real polynomial of degree  $n$ , whose leading coefficient is strictly positive. Suppose that on the interval  $x \geq a$ , the critical values for the derivative  $h'(r) = 0$  are the elements  $\{x_1, \dots, x_k\}$  (this set could be empty). Then  $h(r)$  is strictly positive on the interval  $x \geq a$  if and only if  $h(a) > 0$  and  $h(x_i) > 0$  for all  $i = 1, \dots, k$ .*

*Proof.* Suppose that  $h(r)$  is strictly positive on the interval  $x \geq a$ . Then, in particular,  $h(x_i) > 0$  for all  $x_i$ , where  $i = 1, \dots, k$ . We prove the converse by contradiction. Suppose that  $h(y) > 0$ , for some  $y \geq a$ . Since  $h(a) > 0$ , it follows that  $y > a$ . Since the leading term of the polynomial is strictly positive, for large positive  $x$ , the positive values of the function eventually become positive and unbounded. By continuity, there is at least one absolute minimum  $x_{\min} \geq y > a$ . That is, for all  $x \in [a, \infty)$ ,  $h(x) \geq h(x_{\min})$ . Since  $h(y) = 0$ , it follows that  $h(x_{\min}) \leq 0$ . By the Mean Value Theorem,  $h'(x_{\min}) = 0$ . This contradicts the hypothesis on the critical points  $x_1, \dots, x_k$ .  $\square$

Next, we indicate how these results can be used in the stability analysis of the model (1.7).

Applying the decomposition from equation (3.2) to the characteristic equation of (1.7), we obtain

$$\begin{aligned} \omega^4 - B\omega^2 + D &= (b\omega^2 - d) \cos(\omega\tau) + (a\omega^3 - x\omega) \sin(\omega\tau), \\ A\omega^3 - C\omega &= (-a\omega^3 + c\omega) \cos(\omega\tau) + (b\omega^2 - d) \sin(\omega\tau). \end{aligned} \quad (3.4)$$

The polynomial  $F(\omega)$  is of degree eight. Making the substitution  $r = \omega^2$ , we obtain

$$\begin{aligned} h(r) &= r^4 + (-2B + a^2 - a^2)r^3 + (B^2 - b^2 + 2D - 2AC + 2ac)r^2 \\ &\quad + (-2BD + 2bd + C^2 - c^2)r + (D^2 - d^2) = 0, \end{aligned} \quad (3.5)$$

and

$$\begin{aligned} h'(r) &= 4r^3 + 3(-2B + a^2 - a^2)r^2 + 2(B^2 - b^2 + 2D - 2AC + 2ac)r \\ &\quad + (-2BD + 2bd + C^2 - c^2). \end{aligned} \quad (3.6)$$

From Lemma 3.3, one could investigate the initial value  $h(0)$ , and the values for  $h(r)$  at any of the at most three positive critical values for

$h'(r) = 0$ . Indeed, since  $h'(r)$  is a third degree polynomial, critical values for  $r$  could be obtained using radicals. Then, by requiring  $h(r) > 0$  both at these critical values and at  $r = 0$ , one would obtain bounds on the delay that would constitute sufficient conditions for asymptotic stability.

Examples in the literature where  $h(r)$  is linear, quadratic or cubic, and where coefficients of  $h(r)$  do not depend on  $\tau$ , include the references mentioned above ([2], [1] and [7]). The approach just described can be applied to the case where coefficients do depend on the delay term. As is well known, however, there are no general formulas for roots of polynomials that are of degree greater than four. So, for larger systems, an alternative approach would be useful. For this, we appeal to the Routh-Hurwitz criteria, applied to the polynomial  $h(r)$ .

**Theorem 3.4.** *Let  $\tau \geq 0$  be a fixed delay. If the Routh-Hurwitz criteria are satisfied for the real polynomial  $h(r)$ , then all (possibly complex) zeros of  $h(r) = 0$  have real parts that are strictly negative. In particular, any “purely real” root must be strictly negative.*

**Remark 3.5.** If the Routh-Hurwitz criteria are not satisfied by the coefficients of  $h(r)$ , then at least one of the roots has a non-negative ( $\geq 0$ ) real part. It would require further analysis to determine whether or not one of those non-negative roots was purely real.

Recall that for  $h(r) = r^4 + b_1r^3 + b_2r^2 + b_3r + b_4$ , the Routh-Hurwitz criteria are as follows:

$$b_1 > 0, \quad b_3 > 0, \quad b_4 > 0, \quad b_1b_2b_3 > b_3^2 + b_1^2b_4.$$

From equation (3.5) we obtain, therefore, the following result.

**Proposition 3.6.** *Suppose that, for  $\tau = \tau_0$ ,  $h(r)$  is strictly positive for all  $r \geq 0$ . Let*

$$R = \{ \tau \geq \tau_0 : \text{coefficients of } h(r) \}$$

*do not satisfy the Routh-Hurwitz inequalities below} ,*

*and let  $\tau_R$  be the infimum of the set  $R$ . Then solutions of (1.7) are asymptotically stable for all  $\tau$  satisfying  $\tau_0 \leq \tau < \tau_R$ .*

$$(-2B + A^2 - a^2) > 0,$$



$$\begin{aligned}(-2BD + 2bd + C^2 - c^2) &> 0, \\(D^2 - d^2) &> 0,\end{aligned}$$

$$\begin{aligned}(-2B + A^2 - a^2)(B^2 - b^2 + 2D - 2AC + 2ac)(-2BC + 2bd + C^2 - c^2) \\> (-2BD + 2bd + C^2 - c^2)^2 + (-2B + A^2 - a^2)^2(D^2 - d^2).\end{aligned}$$

*Proof.* This follows from Theorem 3.5 and the converse of Remark 3.2.  $\square$

**Remark 3.7** The stability interval for the delay was determined using the indirect infimum of the set where the Routh-Hurwitz criteria are not satisfied. This is because, in general, the derived polynomial can reveal a family of intervals where the Routh-Hurwitz criteria are satisfied. Proposition 3.6 produces the first such interval, namely, the one containing  $\tau_0$ . The boundary points of these intervals reveal candidates for changes in stability profiles.

## 4. Stability Analysis of Steady States

### 4.1.1. Non-Infected Steady States

Using the Jacobian matrices  $A_1$  and  $A_2$  from (2.4), the characteristic equation for the non-infected steady state is given by

$$\begin{aligned}\Delta(\lambda) &= (\lambda - (\rho - \alpha\beta_0)) \Pi(\lambda), \\ \Pi(\lambda) &= (\lambda^3 + A\lambda^2 + B\lambda + C) \\ &\quad + e^{-\lambda\tau} (a(\tau)\lambda^2 + b(\tau)\lambda + c(\tau)).\end{aligned}\tag{4.1}$$

The coefficients of the polynomials are:

$$\begin{aligned}
A &= (k_1\bar{T} + \mu_V) + (\mu_b + \mu_T) , \\
B &= (k_1\bar{T} + \mu_V) (\mu_b + \mu_T) + \mu_b\mu_T , \\
C &= \mu_b\mu_T (k_1\bar{T} + \mu_V) , \\
a(\tau) &= -k_2e^{-\mu_T\tau} , \\
b(\tau) &= -k_2e^{-\mu_T\tau} (k_1\bar{T} + \mu_V) , \\
c(\tau) &= -k_2\mu_b e^{-\mu_T\tau} ((k_1\bar{T} + \mu_V) + k_1N\bar{T}) .
\end{aligned} \tag{4.2}$$

From (2.3),  $\rho - \alpha\beta_0 = r \left(1 - \frac{2\bar{T}_0}{T_{\max}}\right) - \mu_T$ . In general, therefore, for this root to be strictly negative, it is necessary and sufficient that

$$\left(1 - \frac{2\bar{T}_0}{T_{\max}}\right) < \frac{\mu_T}{r} . \tag{4.3}$$

**Using the clinical values from Table 1 for  $\tau = 0$ :**

$$\rho - \alpha\beta_0 = r \left(1 - \frac{2\bar{T}^*}{T_{\max}}\right) - \mu_T = -.03 .$$

**Parameterization of non-infected steady states by  $\tau \geq 0$ :**

By the factorization given in (4.1), in addition to inequality (4.3), it remains to add an analysis of possible purely imaginary roots of  $\Pi(\lambda) = P_\tau(\lambda) + e^{-\lambda\tau}Q_\tau(\lambda) = 0$ . As in Section 3, if  $\Pi(\lambda)$  has a purely imaginary root  $\lambda = i\omega$ , then the real function  $F(\omega) = |P_\tau(\omega)|^2 - |Q_\tau(\omega)|^2 = 0$ .

Collecting terms, we obtain

$$\begin{aligned}
F(\omega) &= \omega^6 + \omega^4 (A^2 - 2B - a^2(\tau)) \\
&\quad + \omega^2 (-2AC + 2a(\tau)c(\tau) + B^2 - b^2(\tau)) + (C^2 - c^2(\tau)) .
\end{aligned} \tag{4.4}$$

Making the substitution  $r = \omega^2$  we get

$$\begin{aligned}
h(r) &= r^3 + r^2 (A^2 - 2B - a^2(\tau)) \\
&\quad + r (-2AC + 2a(\tau)c(\tau) + B^2 - b^2(\tau)) + (C^2 - c^2(\tau)) .
\end{aligned} \tag{4.5}$$

The function  $h(r)$  is of the form  $h_\tau(r) = r^3 + \alpha r^2 + \beta r + \gamma$ ; and the derivative  $h'(r)$  is of the form

$$h'(r) = 3r^2 + 2\alpha r + \beta. \quad (4.6)$$

The coefficients are given by

$$\begin{aligned} \alpha(\tau) &= A^2 - a^2(\tau) - 2B, \\ \beta(\tau) &= -2AC + 2a(\tau)c(\tau) + B^2 - b^2(\tau), \\ \gamma(\tau) &= C^2 - c^2(\tau). \end{aligned} \quad (4.7)$$

See Figure 1 for plots of these functions when  $N$  is 500, 774, and 1000, respectively.

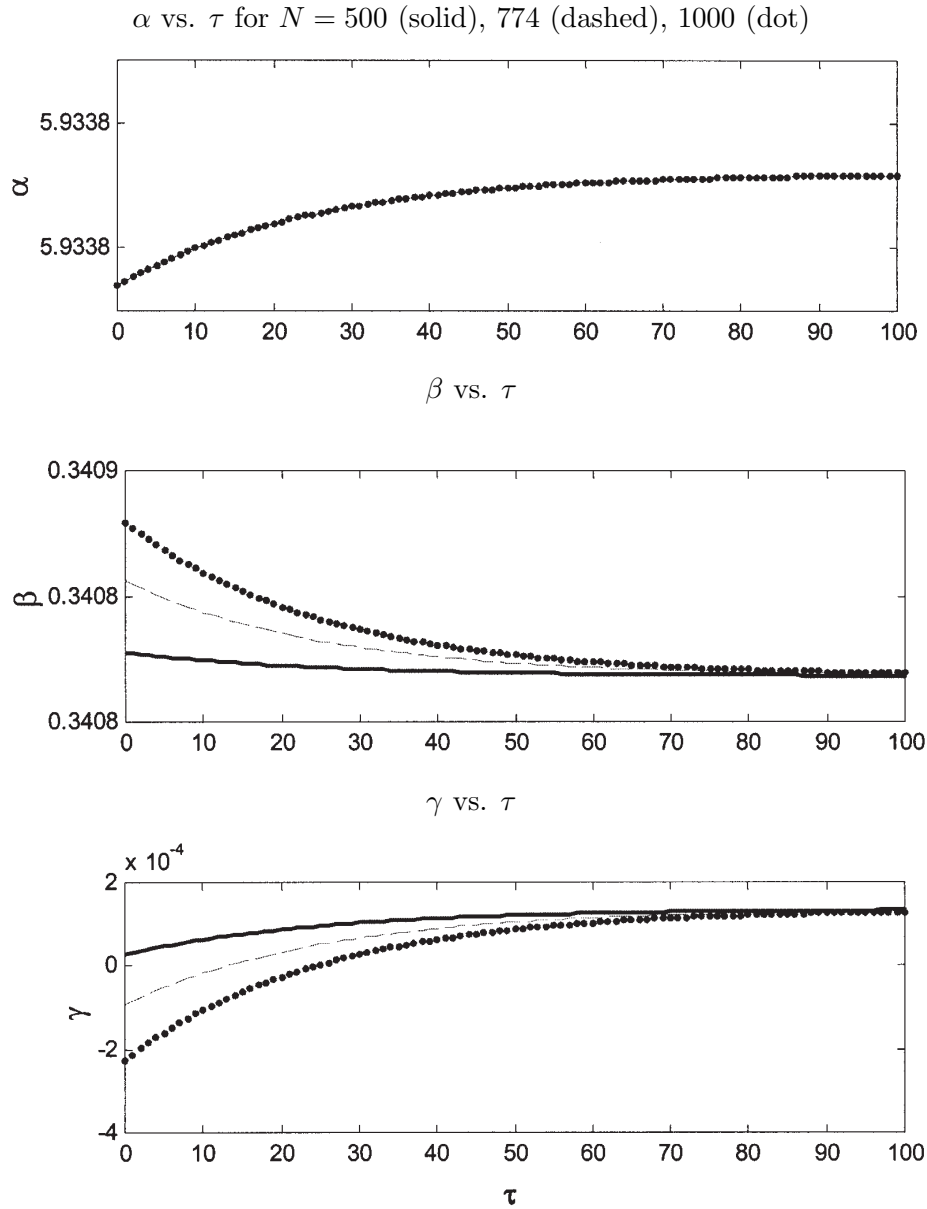


Figure 1:  $\alpha, \beta, \gamma$  of equation (4.7) as a functions of  $\tau$  and  $N$

**Corollary 4.1.** (a) For each  $N$ , when  $\tau$  is sufficiently large  $h(0) > 0$ ;

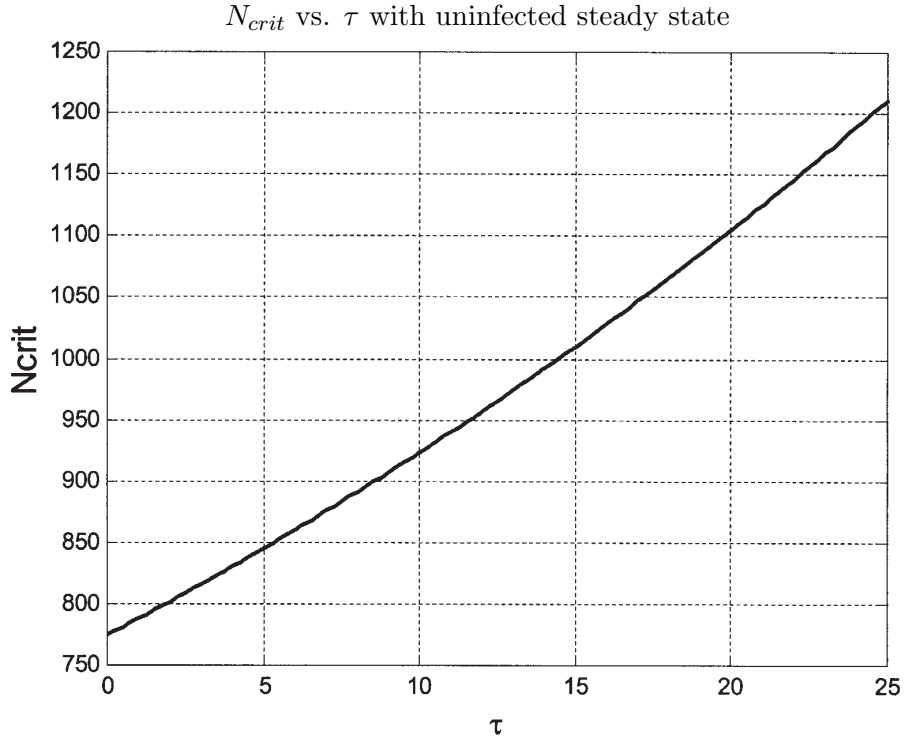


Figure 2:  $N_{crit}(\tau)$  as a function of  $\tau$  for uninfected steady state

and

(b) For each  $\tau \geq 0$ ,  $h(0) > 0$  if and only if

$$N < N_{crit}(\tau) = \frac{(k_1 \bar{T} + \mu_V)(k_2 + \mu_T e^{\mu_T \tau})}{k_1 k_2 \bar{T}}.$$

*Proof.* (a) The quantity  $h(0) = C^2 - x^2(\tau) > 0$  if and only if  $C^2 > c^2(\tau)$ . Explicitly, this inequality becomes

$$\begin{aligned} & [\mu_T \mu_b (k_1 \bar{T} + \mu_V)]^2 \\ & > [- (k_2 e^{-\mu_T \tau} \mu_b) ((k_1 \bar{T} + \mu_v) + k_1 N \bar{T})]^2. \quad (4.8) \end{aligned}$$

Since  $\mu_T > 0$ , for  $\tau > 0$  the exponent  $-\mu_T \tau$  is negative and the result follows.

(b) We solve  $h(0) = C^2 - c^2(\tau) > 0$  for  $N$ . Since  $C \geq 0$ , this is equivalent to  $-C < -c(\tau) < C$ . The right-hand side gives  $N > 0$ ; and the left-hand side gives

$$N < \frac{(k_1 \bar{T} + \mu_V)(k_2 + \mu_T e^{\mu_T \tau})}{k_1 k_2 \bar{T}} = N_{crit}(\tau). \quad (4.9)$$

□

The result from Corollary 4.1(b) means that for a given delay  $\tau$ , bounds on the lysing rate  $N$  may be calculated that ensure  $h(0) > 0$  for the uninfected steady state  $V = 0$ . In Section 3.1 of [11], a stability parameter  $N_{crit}^{PDK}$  is calculated, with the property that for  $N < N_{crit}^{PDK}$ , the steady state  $V = 0$  is asymptotically stable and for  $N > N_{crit}^{PDK}$ , the steady state is unstable. Observe that when  $\tau = 0$ , the PDK value  $N_{crit}^{PDK} = N_{crit}(\tau = 0)$ . As can be seen in equation (4.9),  $N_{crit}(\tau)$  is a monotone and increasing function of  $\tau$ . Hence, where in [11] ( $\tau = 0$ ) a single parameter is obtained, in the present delay model, for each delay  $\tau$ , an  $N_{crit}$  is obtained as shown in Figure 2.

Corollary 4.1 regards only the initial value  $h(0)$ , and so determination of a complete set of necessary stability criteria from application of Lemma 3.3 requires a fuller analysis of the polynomial  $h(r)$ .

To that end, let  $\wp = \{r \geq 0 \mid h'_\tau(r) = 0\}$ . Then, since the derivative  $\frac{dh_\tau(r)}{dr} = h'_\tau(r)$  is quadratic in  $r$ , there are in general three mutually exclusive cases:

Case 1.  $\wp = \emptyset$ .

Case 2.  $|\wp| = 1$ .

Case 3.  $|\wp| = 2$ .

Using the quadratic formula (applied to  $h'_\tau(r)$ ), these three cases translate into three sets of inequalities:

Case 1.

$$\alpha^2 < 3\beta \quad \text{or} \quad -\alpha + \sqrt{\alpha^2 - 3\beta} < 0.$$

Case 2.

$$\begin{aligned}\alpha^2 &\geq 3\beta, \\ -\alpha - \sqrt{\alpha^2 - 3\beta} &\leq 0, \\ -\alpha + \sqrt{\alpha^2 - 3\beta} &> 0, \\ h\left(\frac{-\alpha + \sqrt{\alpha^2 - 3\beta}}{3}\right) &> 0.\end{aligned}$$

Case 3.

$$\begin{aligned}\alpha^2 &\geq 3\beta, \\ -\alpha - \sqrt{\alpha^2 - 3\beta} &> 0, \\ h\left(\frac{-\alpha - \sqrt{\alpha^2 - 3\beta}}{3}\right) &> 0, \\ h\left(\frac{-\alpha + \sqrt{\alpha^2 - 3\beta}}{3}\right) &> 0.\end{aligned}$$

**Example 4.2.** Using clinical values from Table 1 and  $N = 1000$ , we obtain  $\alpha^2 > 3\beta$  and  $-\alpha + \sqrt{\alpha^2 - 3\beta} < 0$  (Case 1) for  $0 \leq \tau \leq 100$ , as can be seen in Figure 3.

#### 4.1.2. Infected Steady States

Using the clinical values from Table 1 for  $\tau = 0$ , parameterization of infected steady states by  $\tau \geq 0$ .

For the infected steady states, we refer the reader to the discussion and numerical results of Section 5, below.

#### 4.2. Hopf Bifurcation

For the final topic of this Section 4, there is the issue of possible Hopf bifurcation at a purely imaginary root  $\lambda = i\omega$  of the (transcendental)

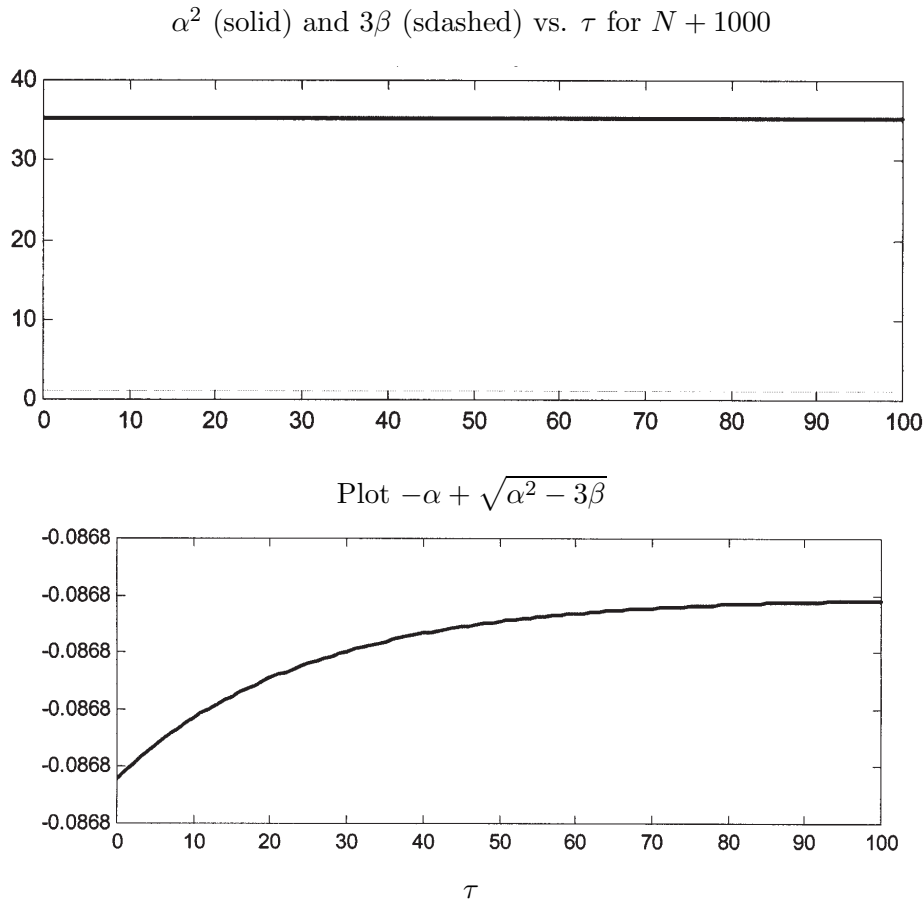


Figure 3: Plot for Example 4.2, Case 1

characteristic equation  $\Delta_\tau(\lambda) = P_\tau(\lambda) + e^{-\lambda\tau}Q_\tau(\lambda) = 0$ . Before proceeding, however, we add a few contextual remarks.

In Hopf Bifurcation Theorem, it is assumed that there is a smooth selection of roots  $\lambda(\tau)$  (when terms of a delay-equation depend smoothly on the delay parameter  $\tau$ , classical selection theorems provide the existence of such smooth selections). As briefly mentioned in Remark 3.1, change of stability profile (stability to instability or vice versa) can be partially understood in terms of the real parts of a path of eigenvalues. So, Hopf Bifurcation Theorem applied at  $\tau = \tau_c$  requires (among other things) (a) the existence of an isolated pair of purely imaginary conju-



gate roots  $\lambda = \pm i\omega$ ; and (b) that for  $\lambda(\tau_c) = i\omega$ , the real part of the derivative  $\operatorname{Re} \left( \frac{d\lambda}{d\tau} \right) \Big|_{\tau=\tau_c} \neq 0$ .

Following the standard approach, implicit differentiation of  $\Delta_\tau(\lambda) = P_\tau(\lambda) + e^{-\lambda\tau} Q_\tau(\lambda) = 0$  can be used to calculate the derivative  $\frac{d\lambda}{d\tau}$ . Then, at a root  $\lambda = i\omega$ , the sign of  $\frac{d\lambda}{d\tau}$  can be expressed in terms of the real and imaginary parts of  $P(\lambda)$ ,  $Q(\lambda)$ . Results along these lines are given in [7], p. 85.

As in [7], write

$$\begin{aligned} P(\lambda) &= P_R(\lambda) + iP_I(\lambda), \\ Q(\lambda) &= Q_R(\lambda) + iQ_I(\lambda). \end{aligned} \tag{4.10}$$

Define the terms  $P'_R$ ,  $P'_I$ ,  $Q'_R$ ,  $Q'_I$  by

$$\begin{aligned} P'_R(\lambda) &= \operatorname{Re} \left( \frac{dP}{d\lambda} \right), & P'_I(\lambda) &= \operatorname{Im} \left( \frac{dP}{d\lambda} \right), \\ Q'_R(\lambda) &= \operatorname{Re} \left( \frac{dQ}{d\lambda} \right), & Q'_I(\lambda) &= \operatorname{Im} \left( \frac{dQ}{d\lambda} \right). \end{aligned} \tag{4.11}$$

Supposing that  $\lambda = \lambda(\tau)$  is not a double root, and that appropriate quantities are not zero to allow for division, implicit differentiation yields

$$\frac{d\lambda}{d\tau} = \frac{\lambda P(\lambda)}{P'(\lambda)e^{\lambda\tau} + Q'(\lambda) - \tau Q(\lambda)}. \tag{4.12}$$

Now, for any non-zero complex number  $z = a + ib$ , we have

$$\frac{1}{a + ib} = \frac{a - ib}{a^2 + b^2}.$$

Hence,  $\operatorname{sign} \operatorname{Re} z = \operatorname{sign} \operatorname{Re} z^{-1}$ . Using this, together with  $Q(\lambda) = -e^{\lambda\tau} P(\lambda)$ , one may show (as in [7], p. 85) that

$$S = -\operatorname{sign} \operatorname{Im} [P'(i\omega)\bar{P}(i\omega) - Q'(i\omega)\bar{Q}(i\omega)],$$

where  $P'$  and  $Q'$  are derivatives with respect to  $\lambda$ .

Calculating the bracketed quantity, the sign is given by

$$\begin{aligned}
S &= \text{sign} \left[ \text{Re} \frac{d\lambda}{d\tau} \right] \\
&= -\text{sign} [P_R P'_I - P_I P'_R + Q_R Q'_I - Q_I Q'_R] . \quad (4.13)
\end{aligned}$$

The sign  $S$  is of course determined by the angular rate of change as the root path crosses the imaginary axis at  $\lambda = i\omega$ . To make this explicit, we also give the following alternative derivation of equation (4.13). Write  $\lambda(\tau) = r(\tau)e^{i\theta(\tau)}$  and take the derivative with respect to  $\tau$  at  $\tau = \tau_c$ .

Since for the purely imaginary root  $\lambda = i\omega_c$ ,  $\theta(\tau_c) = \frac{\pi}{2}$ , we get that

$$\text{Re} \frac{d\lambda}{d\tau}(\tau_c) = -r(\tau_c) \frac{d\theta}{d\tau}(\tau_c) = -|\omega| \frac{d\theta}{d\tau}(\tau_c). \quad (4.14)$$

On the other hand, since  $P(i\omega) + Q(i\omega)e^{-i\omega\tau} = 0$  it follows that  $|P| = |Q|$ . This can be taken, therefore, as a mechanical system in  $\tau$ , with two lever arms

$$\begin{bmatrix} P_R(\tau) \\ P_I(\tau) \end{bmatrix}$$

and

$$\begin{bmatrix} Q_R(\tau) \\ Q_I(\tau) \end{bmatrix}$$

of uniform mass density and equal radii rotating in the same plane about a common axis. The total angular rate at  $\lambda = i\omega$  (corresponding to the total angular momentum relative to the common axis) is proportional to the sum of oriented area derivatives determined by the lever arms. From classical geometry, the area derivatives are given by

$$\det \begin{bmatrix} P_R & \frac{dP_R}{d\tau} \\ P_I & \frac{dP_I}{d\tau} \end{bmatrix} \quad \text{and} \quad \det \begin{bmatrix} Q_R & \frac{dQ_R}{d\tau} \\ Q_I & \frac{dQ_I}{d\tau} \end{bmatrix},$$

and so (4.13) follows from (4.14).

Now, let  $\Re = P_R P'_I - P_I P'_R + Q_R Q'_I - Q_I Q'_R$ . From (2.5) we get  $P'_R, P'_I, Q'_R, Q'_I$ . Suppose that  $\lambda = i\omega$  is a purely imaginary root of the transcendental equation for model (1.7). Evaluating, we obtain a polynomial in  $\omega$  (coefficients depend on  $\tau$ )

$$\begin{aligned} \Re(\omega) = & -4\omega^7 + (6B - 3A^2 - 3a^2)\omega^5 \\ & + (-2B^2 - 2b^2 - 4D - 4d + 4AC + 4ac)\omega^3 \\ & + (2BD + 2bd - C^2 - c^2)\omega. \end{aligned} \quad (4.15)$$

Direct application of Hopf Bifurcation Theorem then requires that  $\Re(\omega) \neq 0$ . In our application, for  $\tau = 0$ , clinical values give steady states that are asymptotically stable at  $\tau = 0$ . Hence, starting from  $\tau = 0$ , a change in sign of the real parts of a path of eigenvalues of (1.7) at  $\tau_R$  would be equivalent to  $\Re\tau_R(\omega) > 0$  (for the definition of  $\tau_R$ , see Proposition 3.6).

## 5. Numerical Results

A direct calculation shows that for the sampling  $0.3 \leq \tau \leq 10$  and  $1000 \leq N \leq 1200$ , the criteria of Proposition 3.6 are satisfied. These steady states therefore must be asymptotically stable.

In Figure 4, the delay is set to  $\tau = 0$ , in order to cross-check our results with the original PDK model. The trajectories are the same. Note that in [11], simulations for  $T^*$ ,  $T^{**}$  and  $V$  use logarithmic scales for the vertical axis, with time in years on the horizontal axis.

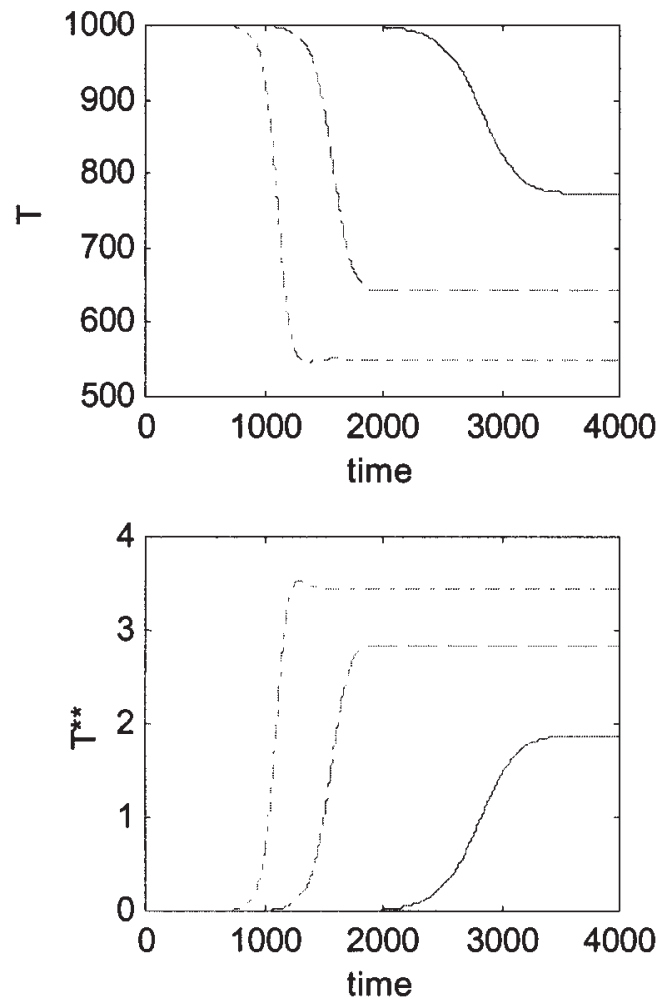


Figure 4: Repeat of PDK simulation. Parameter values from Table 1. Solid  $N=1000$ , dashed  $N=1200$ , dash-dot  $N=1400$ . Time is in days

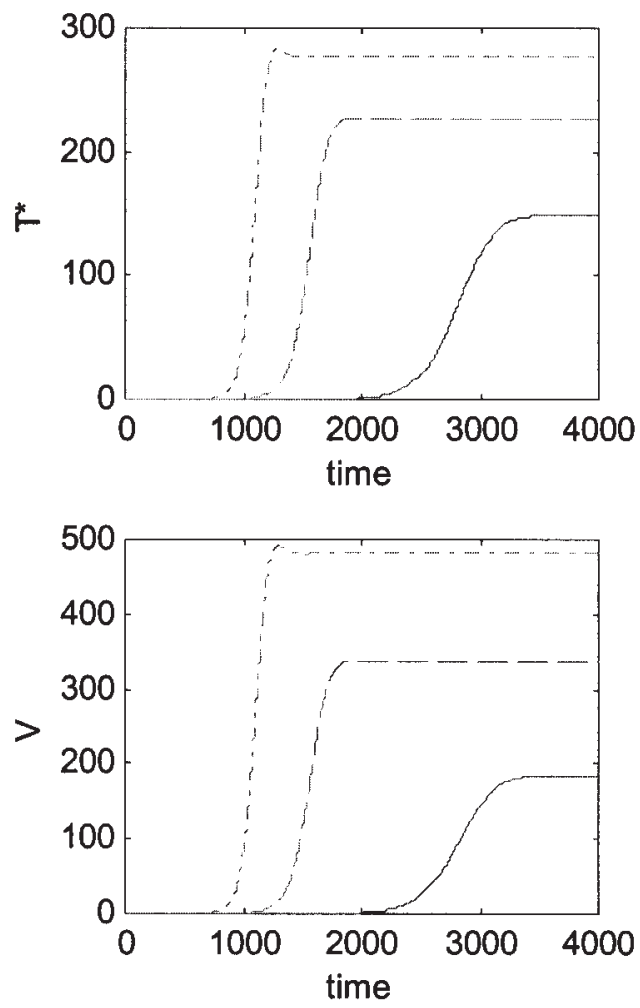


Figure 4: Continuation

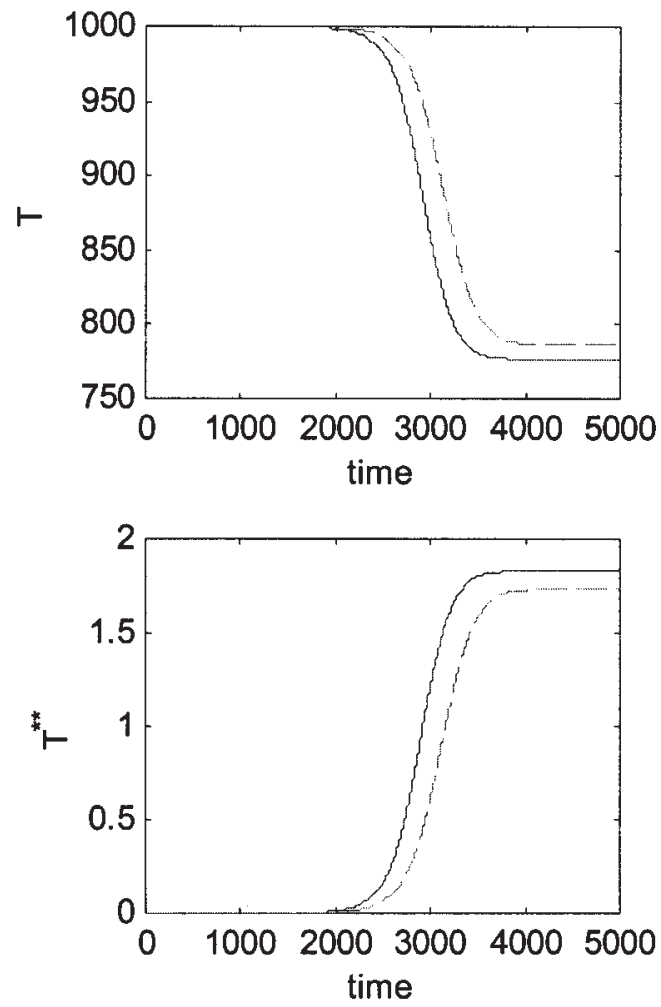


Figure 5:  $N = 1000$ , solid line  $\tau = 0.3$ , dashed line  $\tau = 1$

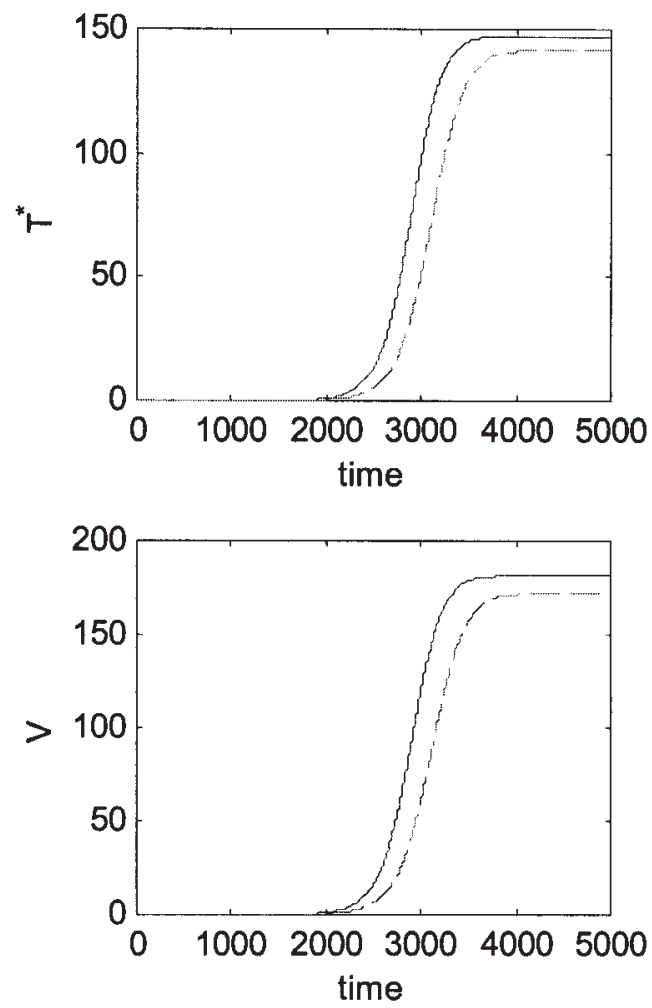


Figure 5: Continuation

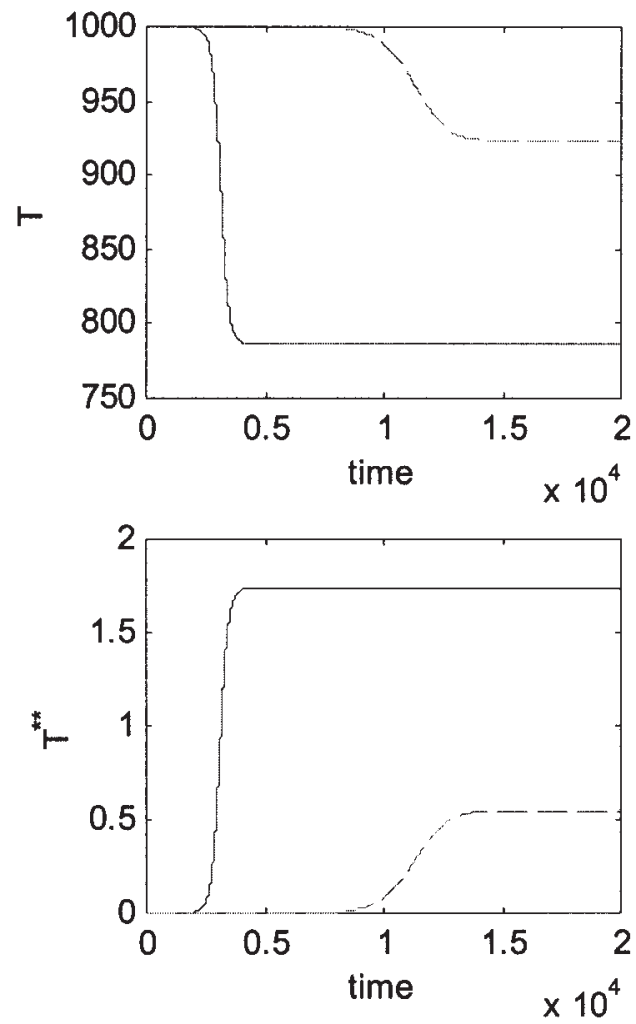


Figure 6:  $N = 1000$ , solid line  $\tau = 1$ , dashed line  $\tau = 10$



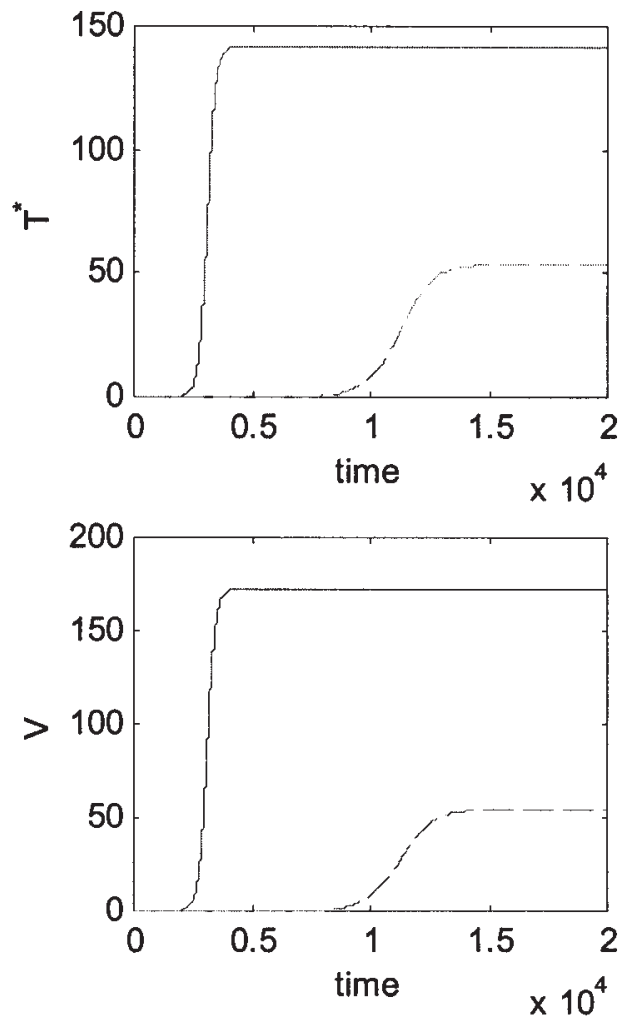


Figure 6: Continuation

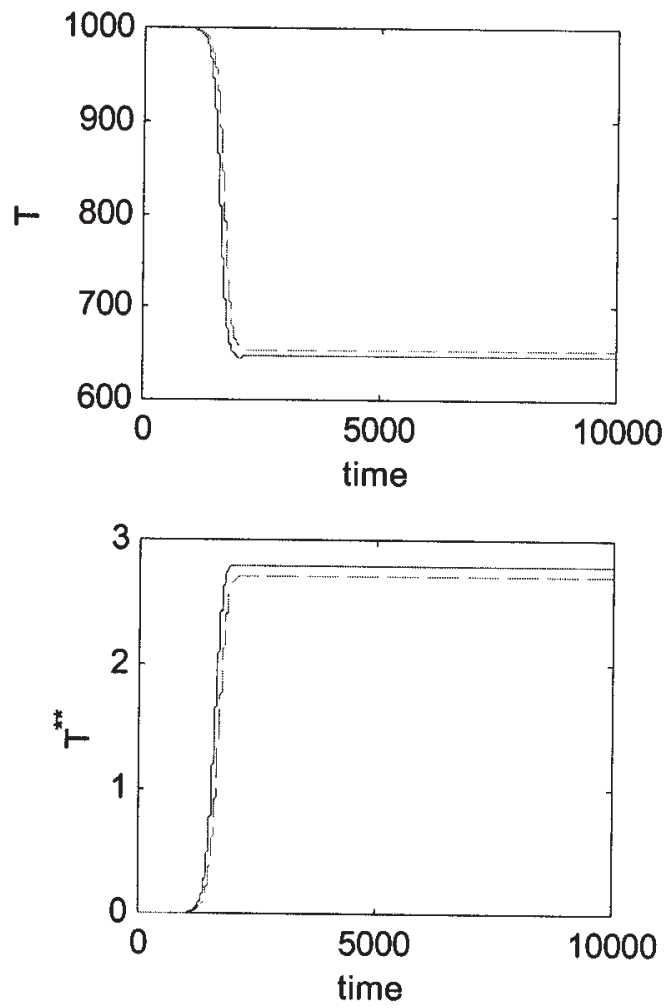


Figure 7:  $N = 1200$ , solid line  $\tau = 0.3$ , dashed line  $\tau = 1$

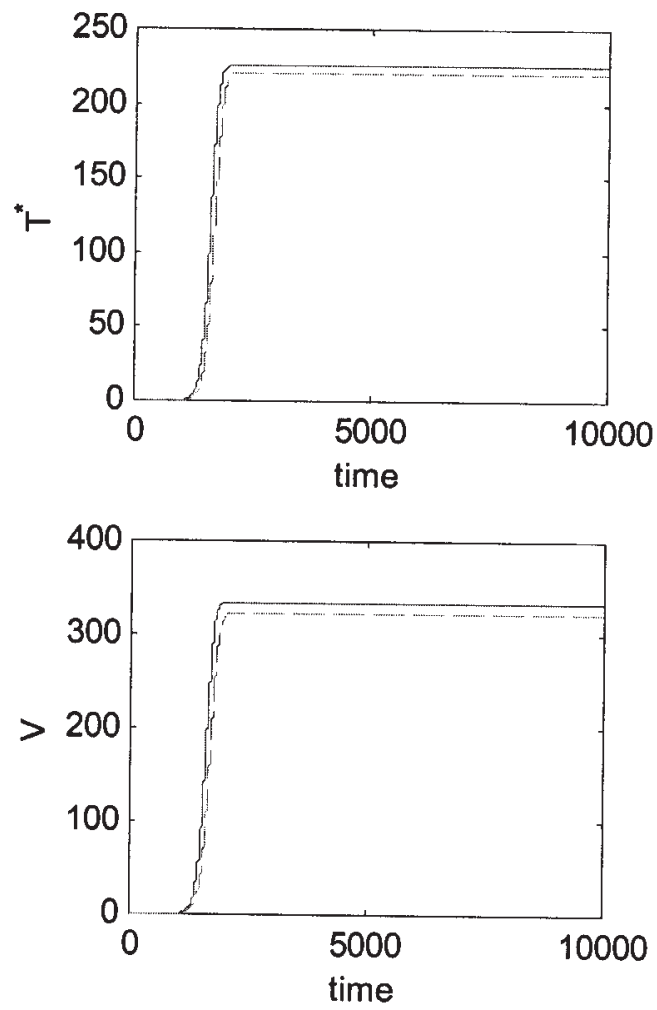
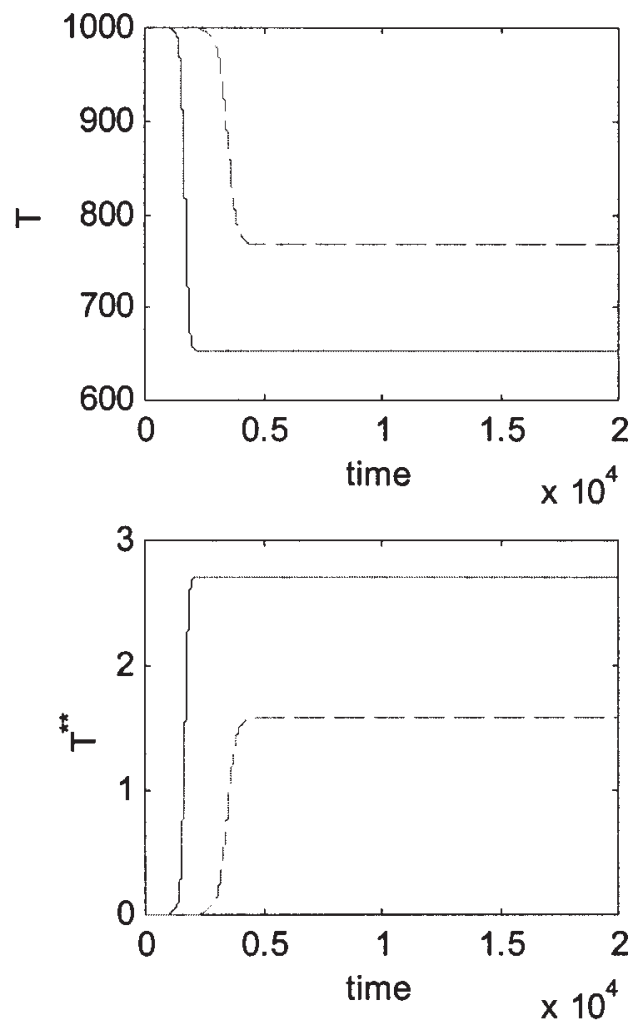


Figure 7: Continuation

Figure 8:  $N = 1200$ , solid line  $\tau = 1$ , dashed line  $\tau = 10$

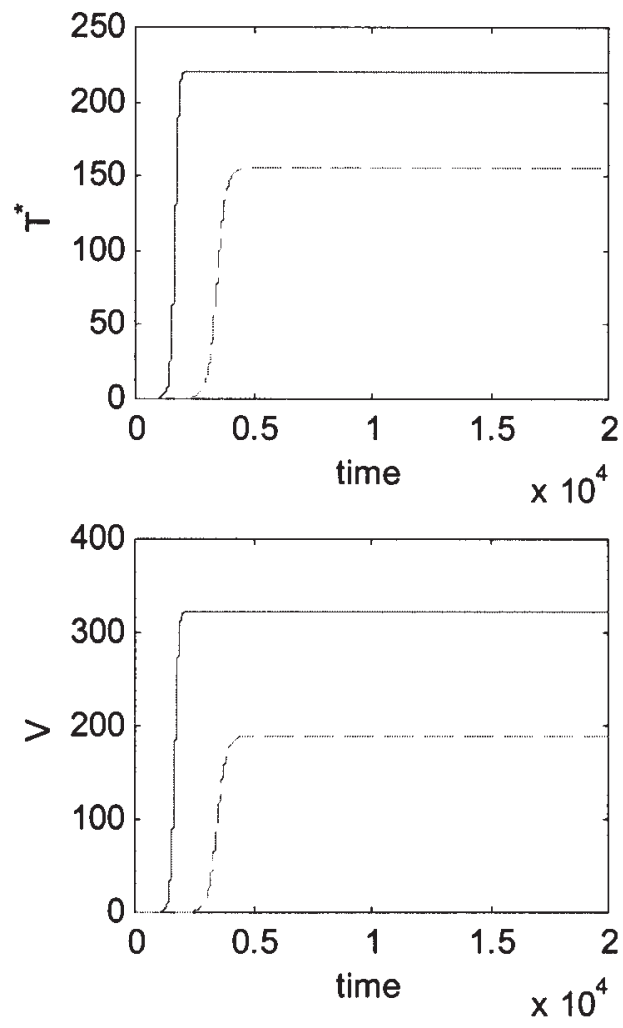


Figure 8: Continuation

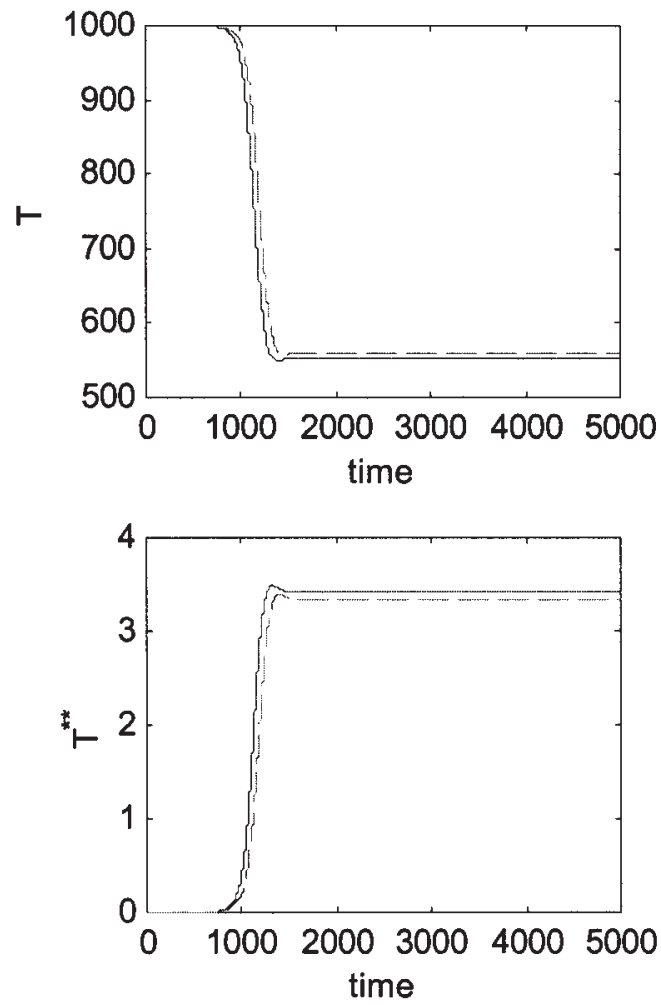


Figure 9:  $N = 1400$ , solid line  $\tau = 0.3$ , dashed line  $\tau = 1$

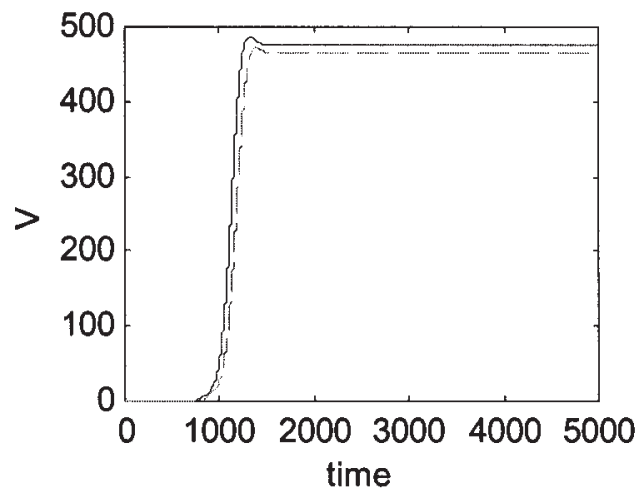
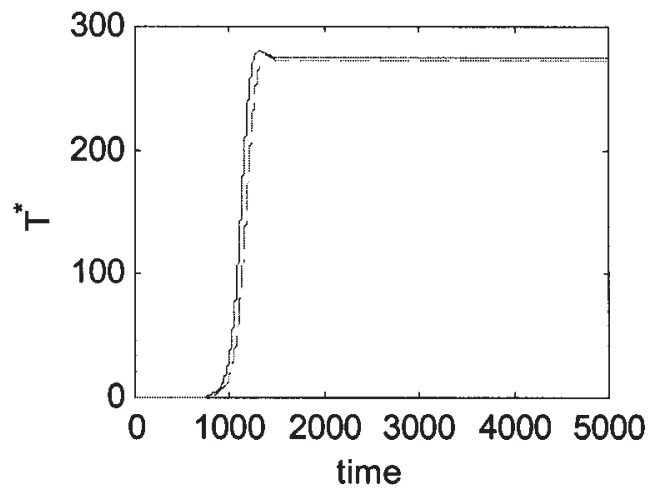


Figure 9: Continuation

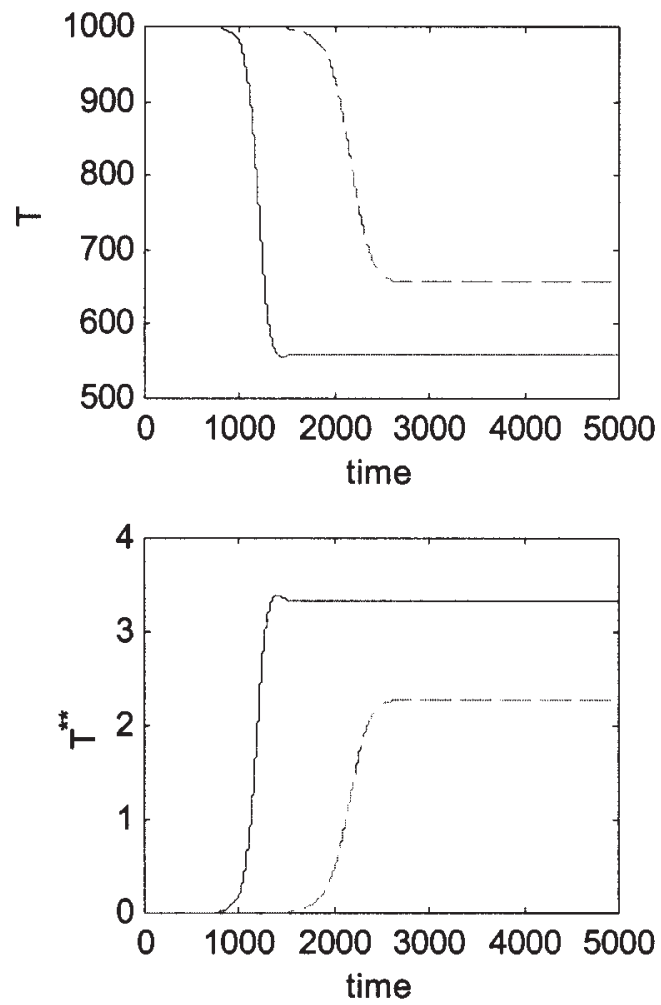


Figure 10:  $N = 1400$ , solid line  $\tau = 1$ , dashed line  $\tau = 10$



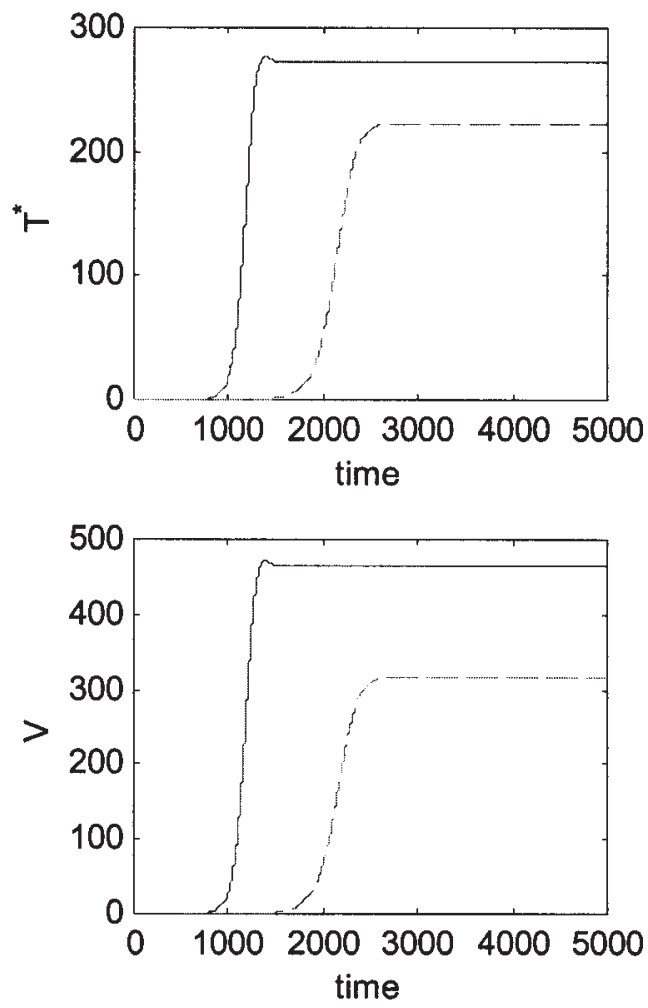


Figure 10: Continuation

In Figures 5-10 we show simulations for the following combinations:

- Figure 5:  $N = 1000$ ;  $\tau = .3$  versus  $\tau = 1$ ,  
 Figure 6:  $N = 1000$ ;  $\tau = 1$  versus  $\tau = 10$ ,  
 Figure 7:  $N = 1200$ ;  $\tau = .3$  versus  $\tau = 1$ ,  
 Figure 8:  $N = 1200$ ;  $\tau = 1$  versus  $\tau = 10$ ,  
 Figure 9:  $N = 1400$ ;  $\tau = .3$  versus  $\tau = 1$ ,  
 Figure 10:  $N = 1400$ ;  $\tau = 1$  versus  $\tau = 10$ .

Recall that  $\tau$  is an average population density delay for the turnover of healthy  $T$ -cells into actively infected  $T^*$ -cells. So, as might be expected, the simulations further illustrate that larger values of  $\tau$  produce somewhat higher steady state values for the healthy  $T$ -cells, and correspondingly lower values for  $V$ .

What is of special interest, however, is obtained from Proposition 3.6. That is, for given values of  $N$ , we obtain values for  $\tau$  where the Routh-Hurwitz criteria break down. We expect therefore that the nature of the solutions of model (1.7) will also change. For  $N = 1000$ , Figure 11 shows that  $b_4$  of the Routh-Hurwitz criteria (see Remark 3.5) becomes negative for  $\tau$  between 14.4 and 14.5. Similarly, for  $N = 850$ , Figure 12 shows that  $b_4$  becomes negative for  $\tau$  between 5 and 5.5.

The corresponding solution trajectories of (1.7) are given in Figure 13-16.

## 6. Concluding Remarks

We conclude the paper by indicating further lines of inquiry that promise to be practical and/or mathematically significant.

1. Using the new tools being developed that apply to systems of arbitrary order, investigate delay models where treatments are included (such as reverse transcriptase and protease inhibitors), see also 5, below). Work in progress.

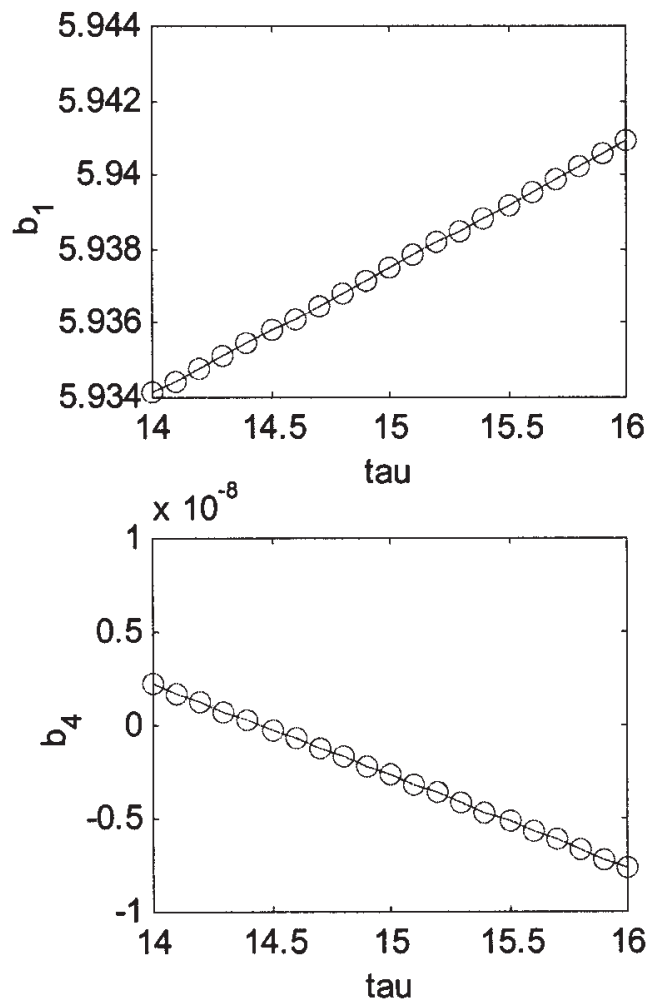


Figure 11:  $N = 1000$ . Plot for variation in Routh-Hurwitz parameters, with  $\tau$  in the interval (14-16). The parameter  $b_4$  becomes negative between 14.4 and 14.5

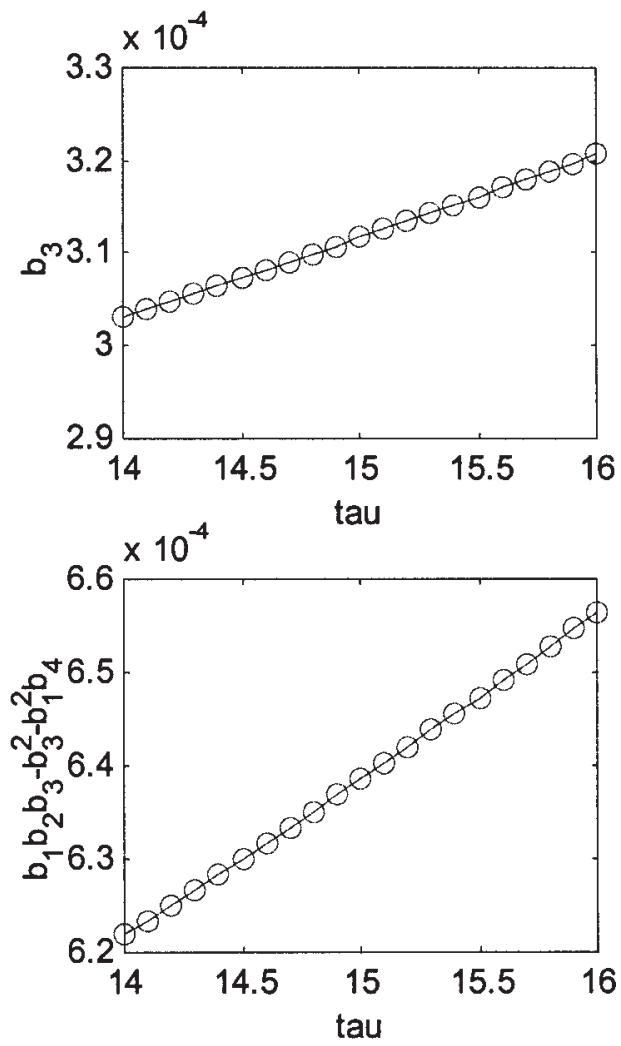


Figure 11: Continuation

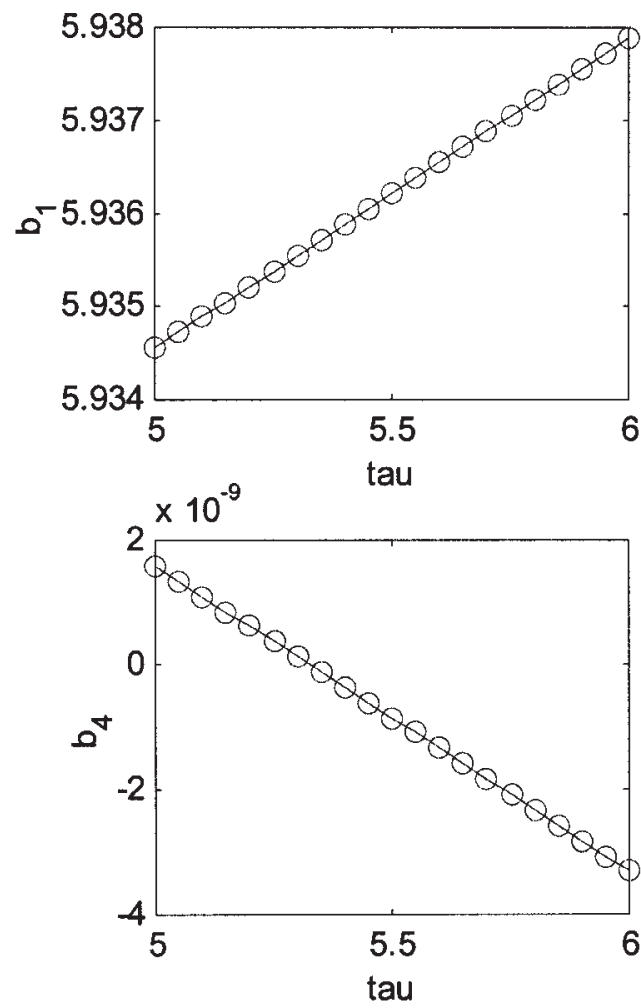


Figure 12:  $N = 850$ . Plot for variation in Routh-Hurwitz parameters with  $\tau$  in the interval (5,6). The parameter  $b_4$  becomes negative between 5 and 5.5

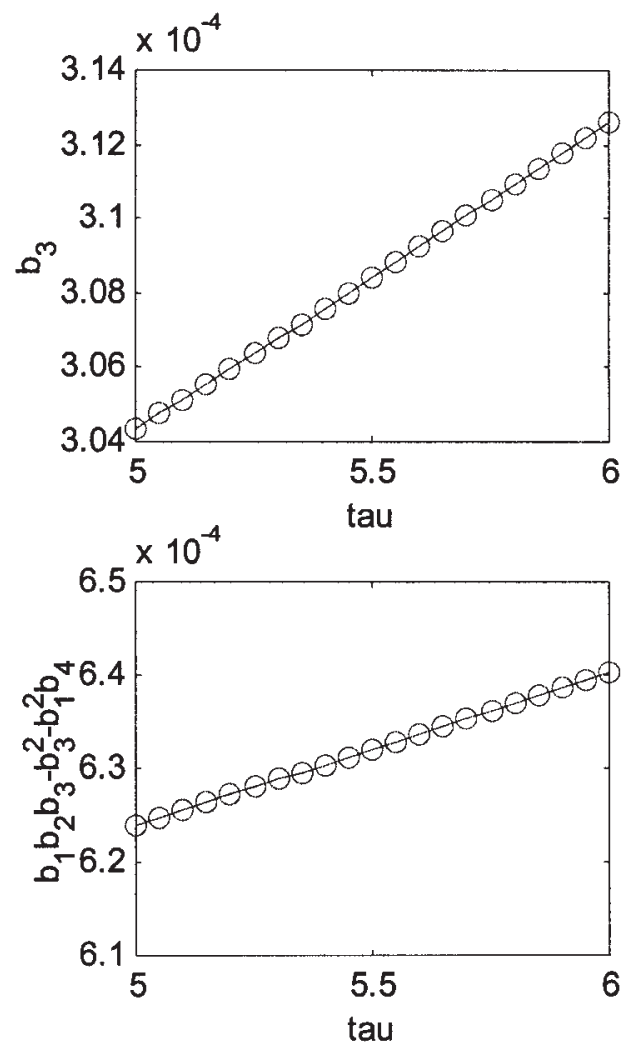


Figure 12: Continuation

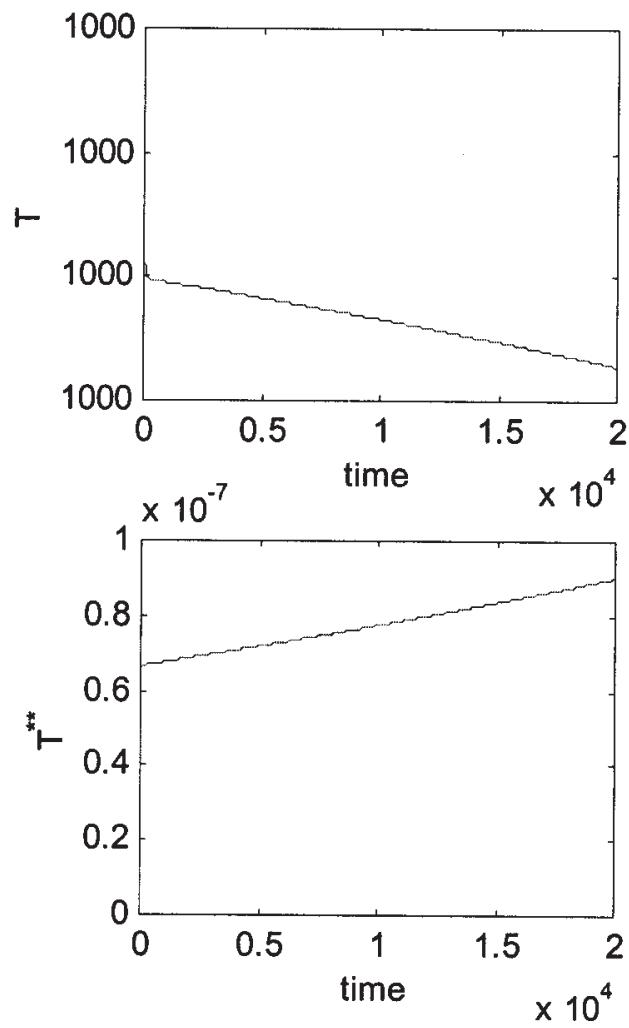


Figure 13: Plots for  $\tau = 14.4$  and  $N=1000$ .  $T$  is seen to decrease with time

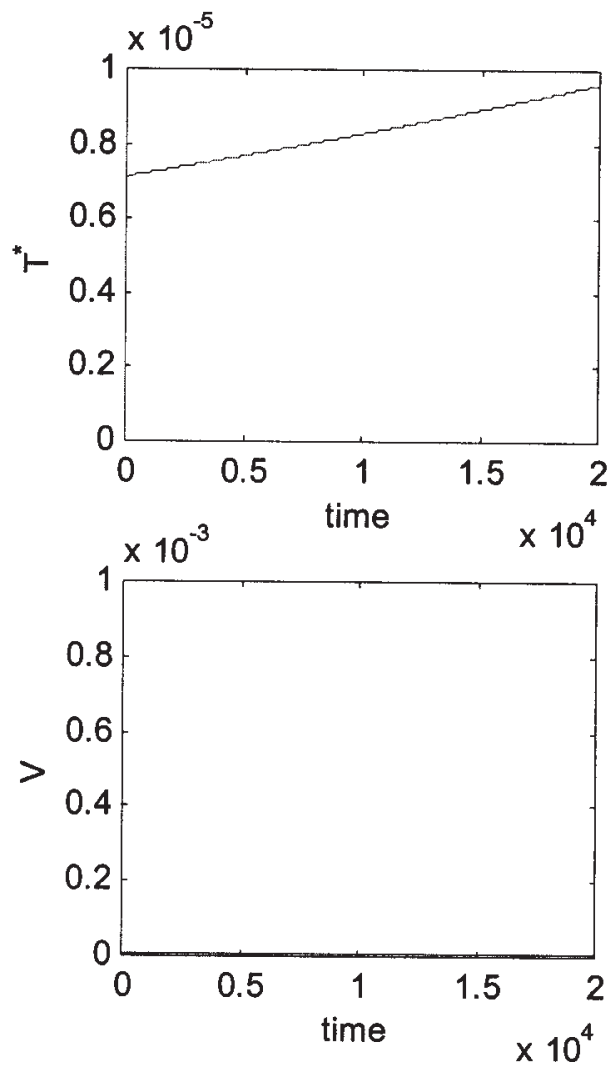


Figure 13: Continuation



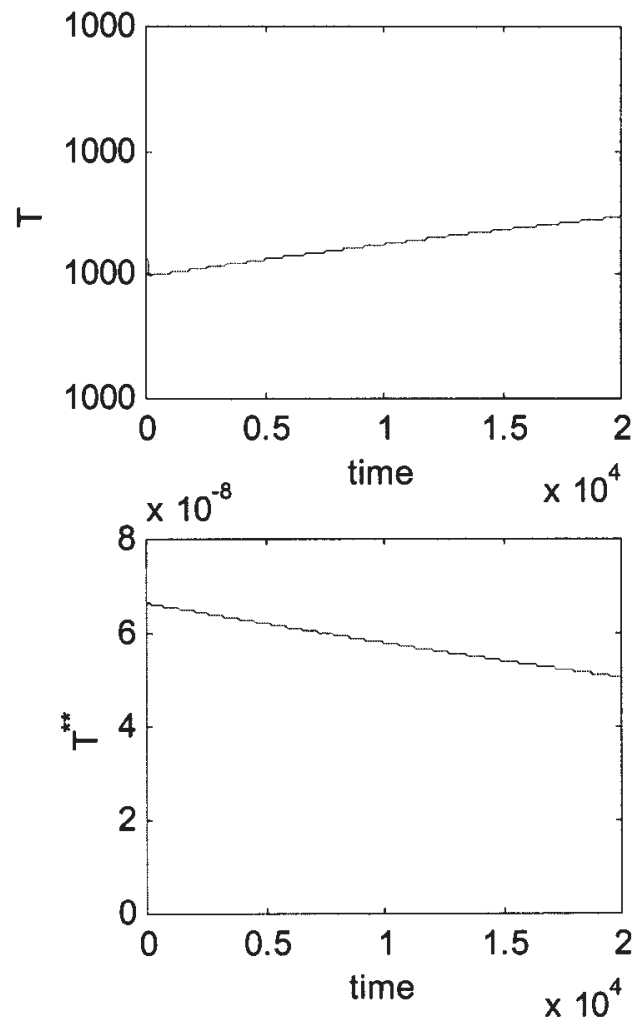


Figure 14: Plots for  $\tau = 14.5$  and  $N = 1000$ .  $T$  is seen to increase with time

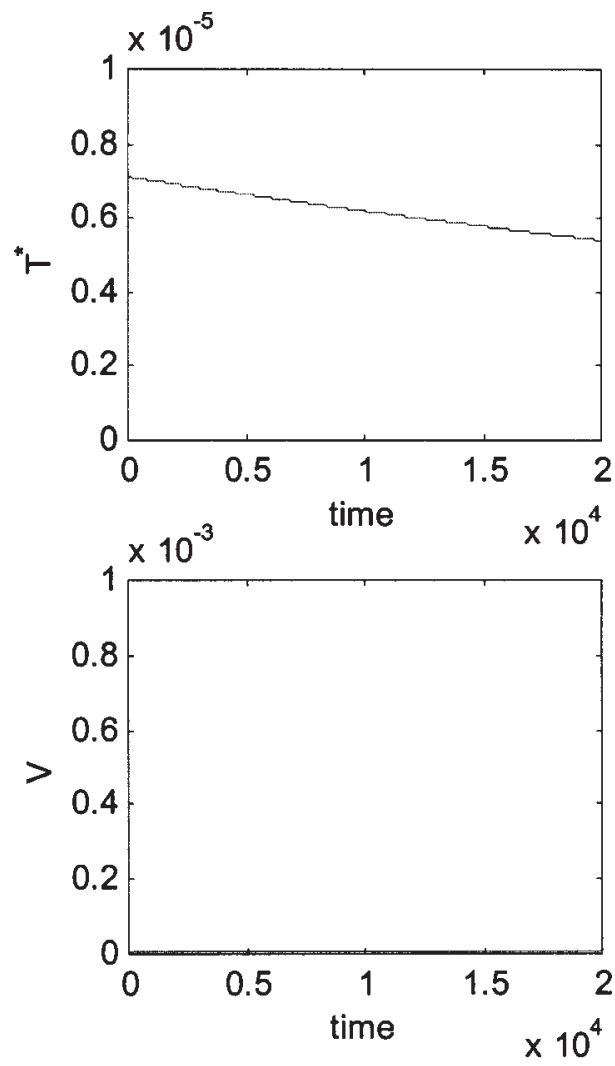


Figure 14: Continuation

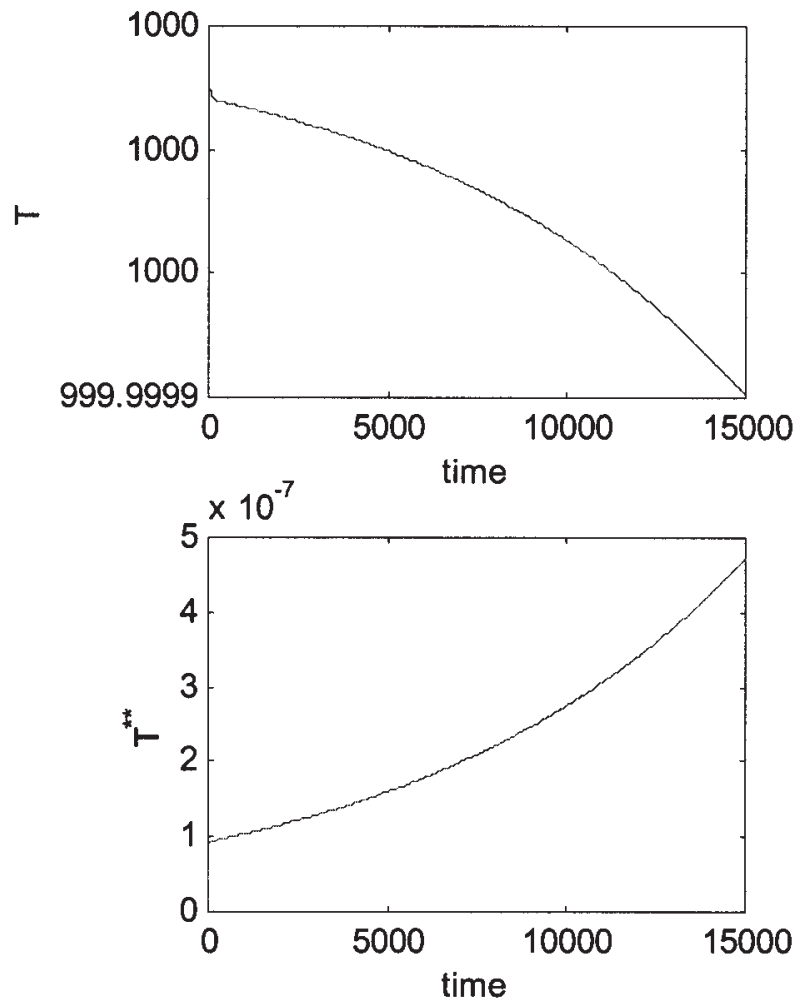


Figure 15: Plots for  $\tau = 5$  and  $N = 850$ .  $T$  is seen to decrease with time

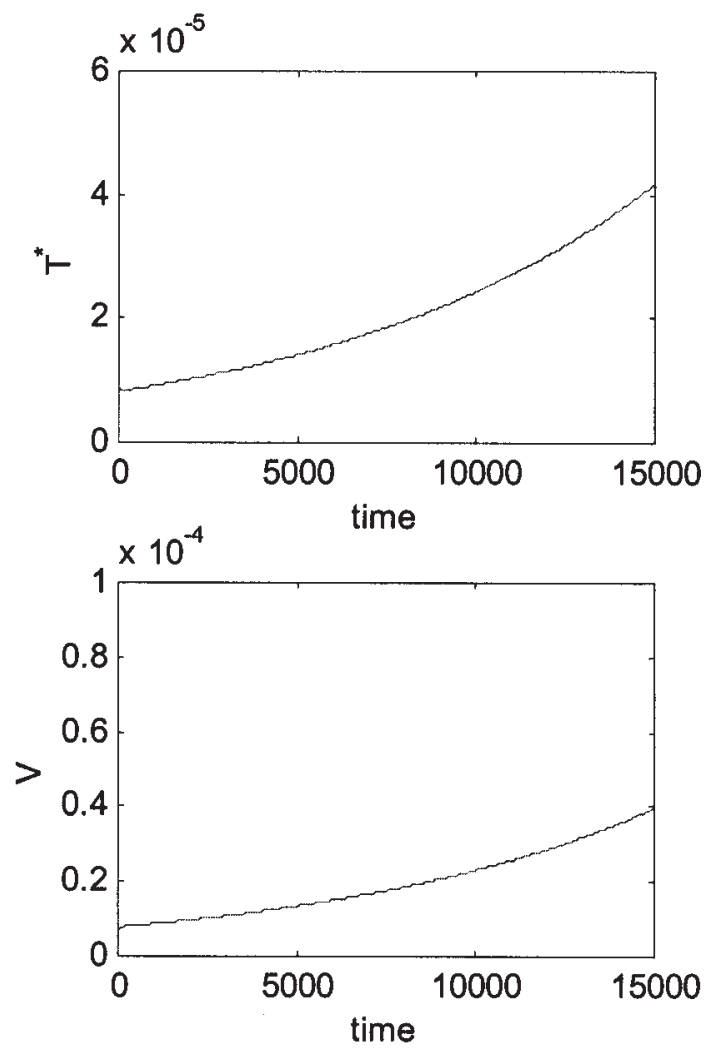


Figure 15: Continuation

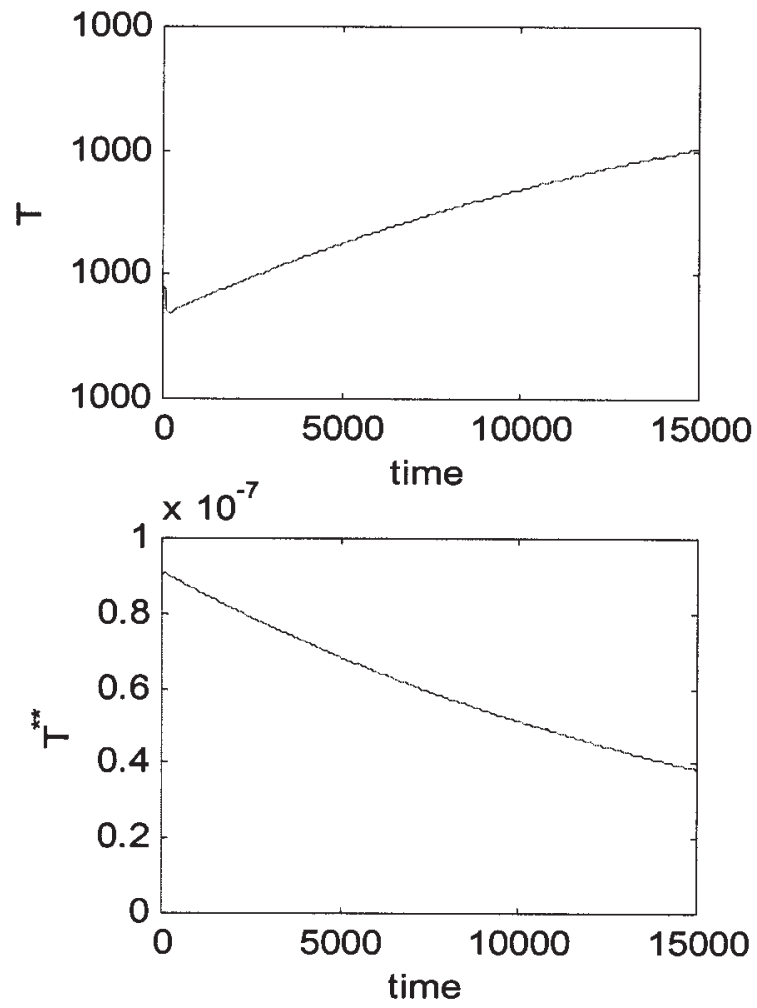


Figure 16: Plots for  $\tau = 5.5$  and  $N = 850$ .  $T$  is seen to increase with time

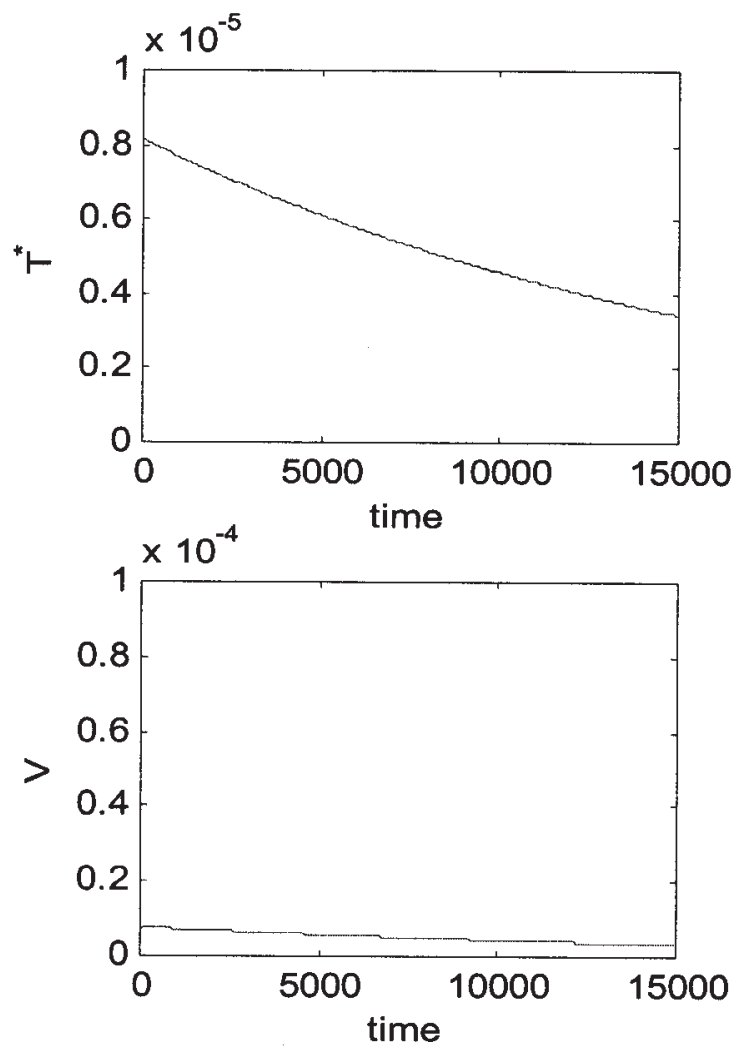


Figure 16: Continuation

2. Investigate systems of equations where delay quantities are state dependent. Work in progress.

3. In the present paper, analysis of the Routh-Hurwitz criteria for  $h_\tau(r)$  revealed that  $b_4(\tau)$  was the key parameter that was sensitive to variation in  $\tau$ , in a way that could affect the stability profile of the corresponding system and its trajectories (see Remark 3.5, Proposition 3.6 and Section 5). Evidently, in general one may calculate “critical boundary directions” for the Routh-Hurwitz criteria. In fact, it is possible to give a coordinate-free formulation that allows for the delay analysis of “critical directions” of the boundary regions determined by the delay-dependent Routh-Hurwitz criteria. It also would be interesting and useful to obtain a coordinate-free formulation for the dependence of eigenvalues of a delay system as functions on neighborhoods of these delay dependent Routh-Hurwitz boundary regions. Work in Progress.

4. As was discussed briefly in the Introduction, real biological processes involve statistical ranges of delay quantities. One approach to modeling has been to integrate these distributed delays and so obtain ordinary differential equations. It could be worthwhile to investigate general structures that would accommodate both integrated distributed delay and discrete delay systems. So, there would be a total bundle system, with some quantities obtained by integrating across the probability space (trace, etc); and there would be point-wise discrete delay equations. In that way, a system with a discrete delay  $\tau$  would appear as a *weighted  $\tau$ - cross section* of the “total probability bundle”. General structures that could be useful here are direct integrals and actions (internal and external) defined on direct integrals.

5. Techniques of the present paper that are based on the analysis of the derived polynomial can be applied to systems of any order. However, in addition to multiple equations, a system also may have multiple delays. This invites work that would pertain to general multi-delay systems, that is, systems of equations that would involve  $k$  delays  $\tau_1, \tau_2, \dots, \tau_k$ . In [12], we make some progress in this direction. We generalize Hale’s technique [5] to the  $k$ -delay system and obtain results specific to the class of  $k$ -delay transcendental equations. In particular, we obtain practical necessary and sufficient conditions (given in terms of the coefficients of the equations) that locate the roots of the tran-

scendental characteristic equation. These issues, and related questions, promise to be a rich focus of further inquiry.

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