# HIV Infection Models with Delay

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# 1 Introduction

In the last decade, many mathematical models have been developed to describe the immunological response to infection with human immunodeficiency virus (HIV). See, for example, [1, 2, 4, 6, 15, 32, 31, 33, 34, 40, 41, 47, 48, 49, 50, 52, 56, 60, 62], etc. For more references and detailed mathematical analysis on some models, we refer to the survey papers by Kirschner [30] and Perelson and Nelson [51].

HIV-1 targets, among others, the $CD4^+$ T lymphocytes, which are the most abundant white blood cells of the immune system (referred to as helper T cells or $CD4^+$ T-cells). It is thought that HIV-1, although attacking many different cells, wreaks the most havoc on the $CD4^+$ T-cells by causing their destruction and decline, and decreasing the body's ability to fight infection.

Assume that peripheral blood CD4 counts (generally $1000/mm^3$) are a good indicator for CD4 densities in the body. When HIV-1 enters the body, it targets all cells with $CD4^+$ receptors, including the $CD4^+$ T-cells. The gp120 protein on the viral particle binds to the $CD4^+$ receptors on the $CD4^+$ T-cell and injects its core. After an intracellular delay associated with reverse transcription, integration, and the production of capsid proteins, the infected cell releases hundreds of virions that can infect other $CD4^+$ T-cells.

In 1989, Perelson [49] developed a simple model for the interaction between the human immune system and HIV-1. Perelson, Kirschner and De Boer [50] extended Perelson's model and proved mathematically some of the model's behavior. They observed that the model exhibits many of the symptoms of AIDS seen clinically: the long latency period, low levels of free virus in the body, and the depletion of $CD4^+$ T-cells. They defined the model by considering four compartments: cells that are uninfected, cells that are latently infected, cells that are actively infected and free virus. They described the dynamics of these populations by a system of four ordinary differential equations.

There is precedent for studying *in vitro* cell-to-cell spread of HIV-1 (as well as that of other viruses) since many features are easier to determine experimentally in tissue cultures than in, for example, a more complex medium such as the bloodstream. Also, HIV-1 is thought to be active in areas such as the lymph nodes and the brain where cell-to-cell spread would be a much more important mode of infection than cell-free viral spread. In fact, it has been reported (Dimitrov et al. [17] and Sato et al. [57]) that cell-to-cell spread of virus is favored over infections with cell-free virus inocula. The data of Gummuluru et al. [22] support the hypothesis that cell-to-cell spread of HIV-1 is the *predominat* route of viral spread since viral replication in a system with rapid cell turnover kinetics depends on cell-to-cell transfer of virus. See also Bailey et al. [4], Bajaria et al. [3], Chun [10], Finzi and Siliciano [18], Haase et al. [23, 24], Philips et al. [53], Schacker et al. [58], etc.

In [60], Spouge et al. have studied HIV-1 cell-to-cell infection kinetics in tissue cultures in terms of mathematical models and observed that the asymptotic behavior is similar to that of a model representing cell-free viral spread. That is, in ordinary differential equations models, under all realistic parameter ranges, the system tends toward an "infected equilibrium", in

which healthy cells and infected cells co-exist.

Time delays of one type or another have been incorporated into biological models by many authors, for example, Busenberg and Cooke [7], Cushing [14], MacDonald [39], Stépán [61] and the references cited therein. In general, delay differential equations exhibit much more complicated dynamics than ordinary differential equations since a time delay could cause a stable equilibrium to become unstable and cause the populations to fluctuate. Recently, in studying the viral clearance rates Perelson et al. [52] assumed that there are two types of delays that occur between the administration of drug and the observed decline in viral load: a pharmacological delay that occurs between the ingestion of drug and its appearance within cells and an intracellular delay that is between initial infection of a cell by HIV-1 and the release of new virions. Herz et al. [26] assumed that cells become productively infected $\tau$ time units after initial infection. They reported that including an intracellular delay did change the estimates of the viral clearance rate but did not change the productively infected T cell loss rate. Tam [63] investigated the delay effect in a model which describes the interaction between a replicating virus and host cells. Mittler et al. [42] assumed that the intracellular delay was continuous and varied according to a gamma distribution and observed dramatical changes in the estimates of viral clearance. Using the method of stages, Grossman [19, 20] found that including a delay model for the death of infected cells resulted in different conclusions about residual transmission of infection in the presence of drugs that effectively reduce viral load. Nelson et al. [44, 45, 46] extended the development of delay models of HIV-1 infection and treatment to more general cases of combination antiviral therapy that is less than completely efficacious. Lloyd [38] observed that the models neglecting the intracellular delay before virion production can lead to severe underestimates of the reproductive number and to overly optimistic predictions of how efficacious treatment must be in order to prevent the disease.

In this lecture, we first simplify the ODE model proposed by Perelson, Kirschner and De Boer [50] by considering only three components: the uninfected $CD4^+$ T-cells, infected $CD4^+$ T-cells, and free virus. The existence and stability of the infected steady state are considered. We then incorporate a discrete delay to the model to describe the time between infection of a $CD4^+$ T-cell and the emission of viral particles on a cellular level as proposed by Herz et al. [26]. The resulting model is a system of three delay differential equations. To determine the dynamics of the delay model, we study the transcendental characteristic equation of the linearized system at the positive infected steady state and obtain analytic conditions on the parameters under which the infected steady state is asymptotically stable for all delay.

In the second part of this lecture, we consider the cell-to-cell spread of HIV-1 in tissue cultures (in vitro) and model the intracellular eclipse phase by a gamma distribution, that is, a distributed delay representing the lag between the time a cell becomes infected and when it begins to infect other cells. The model is then described by a system of differential equations with distributed delay. When the distribution takes the form of a delta function at a positive number $\tau$, the model becomes a system of differential equations with a discrete

delay. When $\tau = 0$, the model reduces to a system of ordinary differential equations (ODE) considered by Spouge et al. [60].

Does the cellular eclipse phase affect the qualitative properties of the model? If so, how? We try to answer these questions and find that in fact the cellular eclipse phase does change the dynamics of the model: it can cause the model to lose its stability and induce fluctuations in the cell concentrations. This result indicates that we must exercise caution when extrapolating such a model's qualities to the cell-free (or the *in vivo*) case.

# 2 Cell-to-Free Virus Spread

## 2.1 The ODE Model

We first reduce the dimension of Perelson, Kirschner and De Boer's system by assuming that all infected cells are capable of producing virus. Similar reduction has been done in Kirschner and Webb [33], Perelson and Nelson [51], etc. The reduced ODE model is:

$$\begin{aligned} \frac{dT}{dt} &= s - \mu_T T + rT(1 - \frac{T+I}{T_{max}}) - k_1 VT, \\ \frac{dI}{dt} &= k_1' VT - \mu_I I, \\ \frac{dV}{dt} &= N\mu_b I - k_1 VT - \mu_V V, \end{aligned} \tag{2.1.1}$$

where $T(t)$ represents the concentration of healthy CD4$^+$ T-cells at time $t$, $I(t)$ represents the concentration of infected CD4$^+$ T-cells, and $V(t)$ the concentration of free HIV-1 at time $t$.

To explain the parameters, we note that $s$ is the source of CD4$^+$ T-cells from precursors, $\mu_T$ is the natural death rate of CD4$^+$ T-cells, $r$ is their growth rate (thus, $r > \mu_T$ in general), and $T_{max}$ is their carrying capacity. The parameter $k_1$ represents the rate of infection of T cells with free virus and so is given as a loss term for both healthy cells and virus, since they are both lost by binding to one another, and is the source term for infected cells. $k_1'$ is the rate at which infected cells become actively infected (the ratio $k_1'/k_1$ is the proportion of T cells which ever become actively infected). $\mu_I$ is a blanket death term for infected cells, to reflect the assumption that we do not initially know whether the cells die naturally or by bursting. In addition, $\mu_b$ is the lytic death rate for infected cells. Since $N$ viral particles are released by each lysing cell, this term is multiplied by the parameter $N$ to represent the source for free virus (assuming a one-time initial infection). Finally, $\mu_V$ is the loss rate of virus.

In the absence of virus, the T cells population has a steady state value

$$T_0 = \frac{r - \mu_T + [(r-\mu_T)^2 + 4rsT_{max}^{-1}]^{1/2}}{2rT_{max}^{-1}}. \tag{2.1.2}$$

Thus reasonable initial conditions for infection by free virus only are:

$$T(0) = T_0, \quad I(0) = 0, \quad V(0) = V_0. \tag{2.1.3}$$

System (2.1.1) has two steady states: the uninfected steady state $E_0 = (T_0, 0, 0)$ and the (positive) infected steady state $\overline{E} = (\overline{T}, \overline{I}, \overline{V})$, where

$$\begin{aligned} \overline{T} &= \frac{\mu_V \mu_I}{k_1' N \mu_b - k_1 \mu_I}, \\ \overline{I} &= \frac{k_1' \overline{T} V}{\mu_I}, \\ \overline{V} &= \frac{\mu_I [(s + (r - \mu_T)\overline{T}) T_{max} - r\overline{T}^2]}{\overline{T}[k_1' r \overline{T} + k_1 \mu_I T_{max}]}. \end{aligned} \tag{2.1.4}$$

**Table 1—Variables and Parameters for Viral Spread**

| | Parameters and Variables | Values |
|---|---|---|
| | *Dependent Variables* | |
| $T$ | uninfected CD4$^+$ T-cell population size | $1000/mm^3$ |
| $I$ | infected CD4$^+$ T-cell density | 0 |
| $V$ | initial density of HIV-1 RNA | $10^{-3}/mm^3$ |
| | *Parameters and Constants* | |
| $\mu_T$ | natural death rate of CD4$^+$ T-cells | $0.02/day$ |
| $\mu_I$ | blanket death rate of infected CD4$^+$ T-cells | $0.26/day$ |
| $\mu_b$ | lytic death rate for infected cells | $0.24/day$ |
| $\mu_V$ | death rate of free virus | $2.4/day$ |
| $k_1$ | rate CD4$^+$ T-cells become infected with virus | $2.4 \times 10^{-5} mm^3/day$ |
| $k_1'$ | rate infected cells becomes active | $2 \times 10^{-5} mm^3/day$ |
| $r$ | growth rate of CD4$^+$ T-cell population | $0.03/day$ |
| $N$ | number of virions produced by infected CD4$^+$ T-cells | varies |
| $T_{max}$ | maximal population level of CD4$^+$ T-cells | $1500/mm^3$ |
| $s$ | source term for uninfected CD4$^+$ T-cells | $10/(day)(mm^3)$ |
| | *Derived Quantities* | |
| $T_0$ | CD4$^+$ T-cell population for HIV-negative persons | $1000/mm^3$ |

We can see that $N$ is a bifurcation parameter. When

$$N < N_{crit} = \frac{\mu_I(\mu_V + k_1 T_0)}{k_1' \mu_b T_0}, \tag{2.1.5}$$

the uninfected steady state $E_0$ is stable and the infected steady state $\overline{E}$ does not exist (unphysical). When $N = N_{crit}$, the uninfected and infected steady states collide and there is a transcritical bifurcation. When $N > N_{crit}$, $E_0$ becomes unstable and $\overline{E}$ exists.

To discuss the local stability of the positive infected steady states $\overline{E}$ for $N > N_{crit}$, we consider the linearized system of (2.1.1) at $\overline{E}$. The Jacobian matrix at $\overline{E}$ is given by

$$A = \begin{pmatrix} -(\mu_T + \frac{r(2\overline{T}+\overline{I})}{T_{max}} + k_1\overline{V} - r) & -\frac{r\overline{T}}{T_{max}} & -k_1\overline{T} \\ k_1'\overline{V} & -\mu_I & k_1'\overline{T} \\ -k_1\overline{V} & N\mu_b & -(k_1\overline{T} + \mu_V) \end{pmatrix}.$$

Denote

$$M = \mu_T + \frac{r(2\overline{T} + \overline{I})}{T_{max}} + k_1\overline{V} - r. \tag{2.1.6}$$

Then the characteristic equation of the linearized system is

$$\lambda^3 + a_1\lambda^2 + (a_2 + a_4)\lambda + (a_3 + a_5) = 0, \tag{2.1.7}$$

where

$$\begin{aligned} a_1 &= \mu_I + \mu_V + k_1\overline{T} + M, \\ a_2 &= M(k_1\overline{T} + \mu_I + \mu_V) + \mu_I(\mu_V + k_1\overline{T}) - k_1^2\overline{TV}, \\ a_3 &= k_1'\overline{T}(k_1 N\mu_b\overline{V} + \frac{r\mu_V\overline{V}}{T_{max}} - MN\mu_b), \\ a_4 &= k_1'\overline{T}(\frac{r\overline{V}}{T_{max}} - N\mu_b), \\ a_5 &= M\mu_I(\mu_V + k_1\overline{T}) - \mu_I k_1^2\overline{TV}. \end{aligned} \tag{2.1.8}$$

We should point out that writing the coefficients in equation (2.1.7) as $a_2 + a_4$ and $a_3 + a_5$ is for the sake of convenience and comparison, since the characteristic equation of the corresponding delay equation in next section has all five $a_i'$s as coefficients.

By the Routh-Hurwitz criterion, it follows that all eigenvalues of equation (2.1.7) have negative real parts if and only if

$$a_1 > 0, \;\; a_3 + a_5 > 0, \;\; a_1(a_2 + a_4) - (a_3 + a_5) > 0. \tag{2.1.9}$$

**Proposition 2.1** *The infected steady state $\overline{E}$ is asymptotically stable if the inequalities in (2.1.9) are satisfied.*

For the parameter values given in Table 1, $N_{crit} = 131.3$. The number of infectious viruses released, $N$, varies in the literature. It has been suggested to be hundreds (see Haase et al. [24] and Cavert et al. [9]) and even thousands (see Hockett et al. [27]). We first take $N = 500$, then

$$a_1 = 2.71, \; a_2 = 0.7418, \; a_3 = -0.0003, \; a_4 = -0.6238, \; a_5 = 0.0273 \tag{2.1.10}$$

and

$$a_3 + a_5 = 0.027 > 0, \quad a_1(a_2 + a_4) - (a_3 + a_5) = 0.2928. \tag{2.1.11}$$

Thus, all conditions in (2.1.9) are satisfied and the infected steady state $\overline{E} = (260.7, 42.5, 1768.2)$ is asymptotically stable. Numerical simulations show that trajectories of system (2.1.1) approach to the steady state (Figure 2.1). Increasing the $N$ value will decrease the numbers of uninfected $CD4^+$ T-cells and virus and increases the number of infected cells substantially, but does not change the stability of the steady state. With $N = 1000$ the steady state becomes $\overline{E} = (130.2, 34.9, 3480.1)$, which is asymptotically stable.

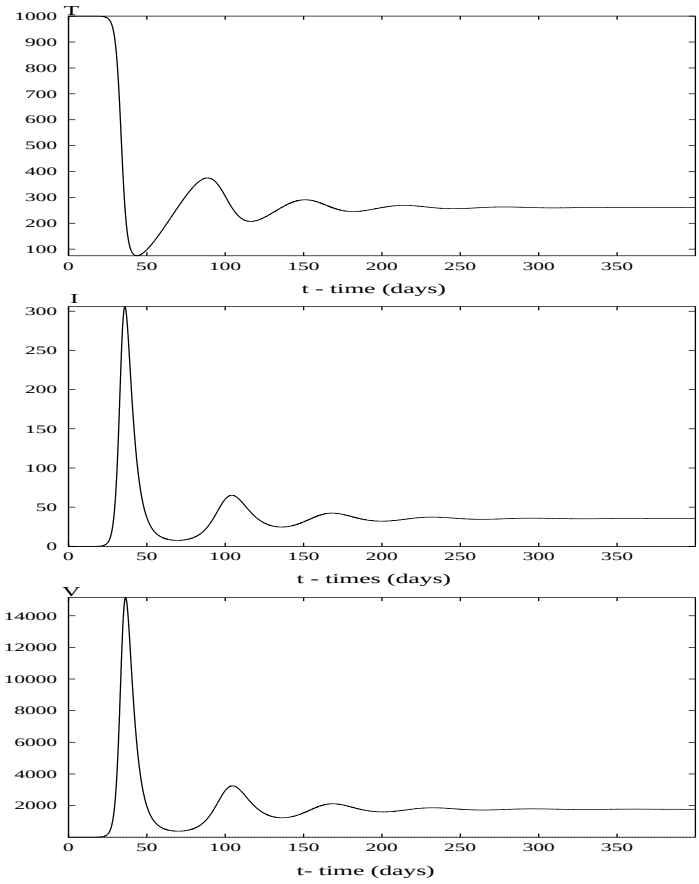


Figure 2.1: The ODE model with $N = 500$. All other parameter values are given in Table 1.

## 2.2 The DDE Model

In this section, we introduce a time delay into system (2.1.1) to represent the viral eclipse phase. The model is given as follows:

$$\begin{aligned} \frac{dT}{dt} &= s - \mu_T T(t) + rT(t)(1 - \frac{T(t)+I(t)}{T_{max}}) - k_1 T(t)V(t), \\ \frac{dI}{dt} &= k_1' T(t-\tau)V(t-\tau) - \mu_I I(t), \\ \frac{dV}{dt} &= N\mu_b I(t) - k_1 T(t)V(t) - \mu_V V(t) \end{aligned} \tag{2.2.1}$$

under the initial values

$$T(\theta) = T_0, \quad I(0) = 0, \quad V(\theta) = V_0, \quad \theta \in [-\tau, 0].$$

All parameters are the same as in system (2.1.1) except that the positive constant $\tau$ represents the length of the delay in days.

We find, again, an uninfected steady state $E_0 = (T_0, 0, 0)$ and an infected steady state $\overline{E} = (\overline{T}, \overline{I}, \overline{V})$, where $\overline{T}, \overline{I}$ and $\overline{V}$ are the same as in section 2.1, given by (2.1.4). Since the uninfected steady state $E_0$ is unstable when $\tau = 0$ and $N > N_{crit}$, incorporation of a delay will not change the instability. Thus, $E_0$ is unstable if $N > N_{crit}$, which is also the feasibility condition for the infected steady state $\overline{E}$.

To study the stability of the steady states $\overline{E}$, define

$$x(t) = T(t) - \overline{T}, \quad y(t) = I(t) - \overline{I}, \quad z(t) = V(t) - \overline{V}.$$

Then the linearized system of (2.2.1) at $\overline{E}$ is given by

$$\begin{aligned} \frac{dx}{dt} &= -(\mu_T + \frac{2r\overline{T} + r\overline{I}}{T_{max}} + k_1\overline{V} - r)x(t) - \frac{r\overline{T}}{T_{max}}y(t) - k_1\overline{T}z(t), \\ \frac{dy}{dt} &= k_1'\overline{V}x(t-\tau) - \mu_I y(t) + k_1\overline{T}z(t-\tau), \\ \frac{dz}{dt} &= -k_1\overline{V}x(t) + N\mu_b y(t) - (k_1\overline{T} + \mu_V)z(t). \end{aligned} \tag{2.2.2}$$

We then express system (2.2.2) in matrix form as follows:

$$\frac{d}{dt}\begin{pmatrix} x(t) \\ y(t) \\ z(t) \end{pmatrix} = A_1 \begin{pmatrix} x(t) \\ y(t) \\ x(t) \end{pmatrix} + A_2 \begin{pmatrix} x(t-\tau) \\ y(t-\tau) \\ z(t-\tau) \end{pmatrix},$$

where $A_1$ and $A_2$ are $3 \times 3$ matrices given by

$$A_1 = \begin{pmatrix} -M & -\frac{r\overline{T}}{T_{max}} & -k_1\overline{T} \\ 0 & -\mu_I & 0 \\ -k_1\overline{V} & N\mu_b & -(k_1\overline{T} + \mu_V) \end{pmatrix}, \quad A_2 = \begin{pmatrix} 0 & 0 & 0 \\ k_1'\overline{V} & 0 & k_1'\overline{T} \\ 0 & 0 & 0 \end{pmatrix},$$

where $M$ is defined by (2.1.6). The characteristic equation of system (2.2.2) is given by:

$$\Delta(\lambda) = |\lambda I - A_1 - e^{-\lambda\tau}A_2| = 0,$$

that is,

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3e^{-\lambda\tau} + a_4\lambda e^{-\lambda\tau} + a_5 = 0, \tag{2.2.3}$$

where $a_i (i = 1, \cdots, 5)$ are defined in (2.2.8).

It is known that $\overline{E}$ is asymptotically stable if all roots of the corresponding characteristic equation (2.2.3) have negative real parts (see Bellman and Cooke [7]). However, compared with the polynomial characteristic equation (2.1.7) for the ODE model, equation (2.2.3) is much more difficult to deal with. First, it is a transcendental equation and has infinitely many eigenvalues. Second, since it is transcendental the classical Routh-Hurwitz criterion cannot be used to discuss equation (2.2.3) anymore. Third, though there are some general tests (see Stépán [61], for example) that can be used to determine when all eigenvalues of the transcendental equations have negative real parts, applying such a general test to specific transcendental equations is very complicated and far from trivial (Culshaw [11]).

We shall study the distribution of the roots of the transcendental equation (2.2.3) analytically. Recall that for the ODE model (2.1.1) the infected steady state $\overline{E}$ is stable for the parameter values given in Table 1. Our starting point is to assume that the steady state of the ODE model (2.1.1) is stable, then we shall derive conditions on the parameters to ensure that the steady state of the delay model is still stable.

To proceed, we consider equation (2.2.3) with $\tau = 0$, that is equation (2.1.7), and assume that all roots of equation (2.1.7) have negative real parts. This is equivalent to the assumption (2.1.9). By Rouché's Theorem (Dieudonné [16], Theorem 9.17.4) and the continuity in $\tau$, the transcendental equation (2.2.3) has roots with positive real parts if and only if it has purely imaginary roots. We shall determine if (2.2.3) has purely imaginary roots, from which we then shall be able to find conditions for all eigenvalues to have negative real parts.

Denote $\lambda = \eta(\tau) + i\omega(\tau)(\omega > 0)$ the eigenvalue of the characteristic equation (2.2.3), where $\eta(\tau)$ and $\omega(\tau)$ depend on the delay $\tau$. Since the equilibrium $\overline{E}$ of the ODE model is stable, it follows that $\eta(0) < 0$ when $\tau = 0$. By continuity, if $\tau > 0$ is sufficiently small we still have $\eta(\tau) < 0$ and $\overline{E}$ is still stable. If $\eta(\tau_0) = 0$ for certain value $\tau_0 > 0$ (so that $\lambda = i\omega(\tau_0)$ is a purely imaginary root of (2.2.3)), then the steady state $\overline{E}$ loses its stability and eventually becomes unstable when $\eta(\tau)$ becomes positive. In other words, if such an $\omega(\tau_0)$ does not exist, that is, if the characteristic equation (2.2.3) does not have purely imaginary roots for all delay, then the steady state $\overline{E}$ is always stable. We shall show that this indeed is true for the characteristic equation (2.2.3).

Clearly, $i\omega(\omega > 0)$ is a root of equation (2.2.3) if and only if

$$-i\omega^3 - a_1\omega^2 + ia_2\omega + a_3(\cos\omega\tau - i\sin\omega\tau) + a_4\omega(\sin\omega\tau + i\cos\omega\tau) + a_5 = 0. \tag{2.2.4}$$

Separating the real and imaginary parts, we have

$$a_1\omega^2 - a_5 = a_3\cos\omega\tau + a_4\omega\sin\omega\tau, \tag{2.2.5}$$

$$\omega^3 - a_2\omega = -a_3\sin\omega\tau + a_4\omega\cos\omega\tau. \tag{2.2.6}$$

Adding up the squares of both equations, we obtain

$$\omega^6 + (a_1^2 - 2a_2)\omega^4 + (a_2^2 - 2a_1a_5 - a_4^2)\omega^2 + (a_5^2 - a_3^2) = 0. \tag{2.2.7}$$

Let

$$z = \omega^2, \;\; \alpha = a_1^2 - 2a_2, \;\; \beta = a_2^2 - 2a_1a_5 - a_4^2, \;\; \gamma = a_5^2 - a_3^2.$$

Then equation (2.2.7) becomes

$$h(z) = z^3 + \alpha z^2 + \beta z + \gamma = 0. \tag{2.2.8}$$

Since $\gamma = a_5^2 - a_3^2 > 0$ for the parameter values given in Table 1, we assume that $\gamma \geq 0$ and have the following claim.

**Lemma 2.2** *If*

$$\gamma \geq 0 \tag{2.2.9}$$

*and*

$$\beta > 0, \tag{2.2.10}$$

*then equation (2.2.8) has no positive real roots.*

In fact, notice that

$$\frac{dh(z)}{dz} = 3z^2 + 2\alpha z + \beta.$$

Set

$$3z^2 + 2\alpha z + \beta = 0. \tag{2.2.11}$$

Then the roots of equation (2.2.11) can be expressed as

$$z_{1,2} = \frac{-\alpha \pm \sqrt{\alpha^2 - 3\beta}}{3}. \tag{2.2.12}$$

If $\beta > 0$, then $\alpha^2 - 3\beta < \alpha^2$; that is, $\sqrt{\alpha^2 - 3\beta} < \alpha$. Hence, neither $z_1$ nor $z_2$ is positive. Thus, equation (2.2.11) does not have positive roots. Since $h(0) = \gamma \geq 0$, it follows that the equation (2.2.8) has no positive roots.

Lemma 2.2 thus implies that there is no $\omega$ such that $i\omega$ is an eigenvalue of the characteristic equation (2.2.3). Therefore, the real parts of all eigenvalues of (2.2.3) are negative for all delay $\tau \geq 0$. Summarizing the above analysis, we have the following proposition.

**Proposition 2.3** *Suppose that*

*(i)* $a_1 > 0, \;\; a_3 + a_5 > 0, \;\; a_1(a_2 + a_4) - (a_3 + a_5) > 0;$

*(ii)* $\gamma \geq 0$ *and* $\beta > 0$.

*Then the infected steady state $\overline{E}$ of the delay model (2.2.1) is absolutely stable; that is, $\overline{E}$ is asymptotically stable for all $\tau \geq 0$.*

Notice that for given parameter values in Table 1 all conditions in Proposition 2.3 are satisfied. Thus, the infected steady state $\overline{E}$ is asymptotically stable for all $\tau \geq 0$. Take $N = 500, \tau = 1$, and other parameter values given in Table 1, numerical simulations show that the infected steady state $\overline{E} = (260.7, 42.5, 1768.2)$ is asymptotically stable (Figure 2.2). Compared with Figure 2.1, we can see that though the delay causes transient oscillations in the components, the steady state $\overline{E}$ is still stable.

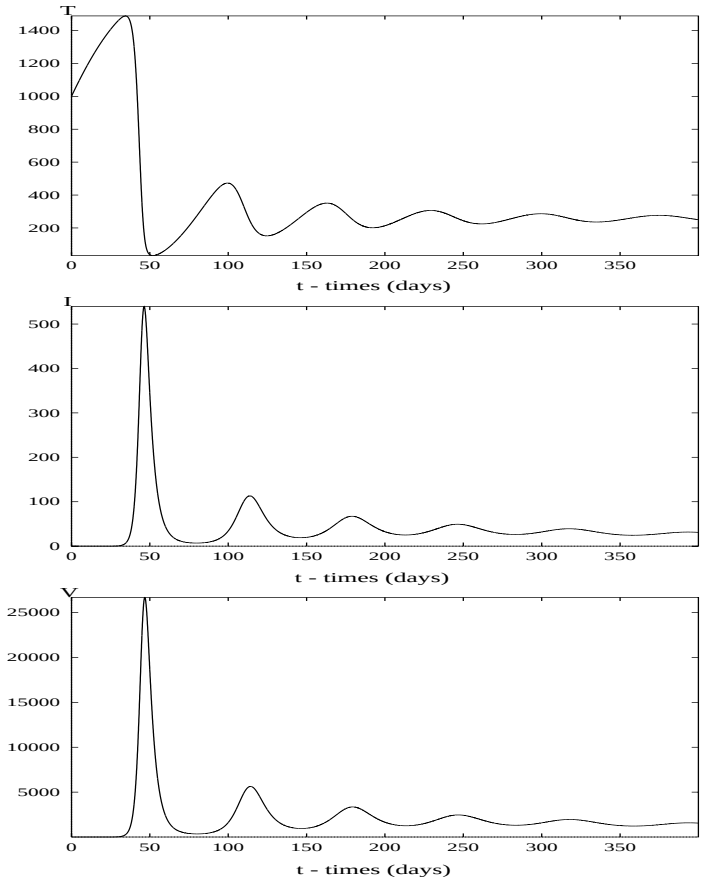


Figure 2.2: The delay model with $\tau = 1$ and $N = 500$. All other parameter values are given in Table 1.

**Remark 2.4** Proposition 2.3 indicates that if the parameters satisfy conditions (i) and (ii), then the steady state of the delay model (2.2.1) is asymptotically stable for all delay values; that is, independent of the delay. However, we should point out that if the conditions

(condition (ii)) in Proposition 2.2 are not satisfied, then the stability of the steady state depends on the delay value and the delay could even induce oscillations.

For example, if (a) $\gamma < 0$, from equation (2.2.8) we have $h(0) < 0$ and $\lim_{z\to\infty} h(z) = \infty$. Thus, equation (2.2.8) has at least one positive root, say $z_0$. Consequently, equation (2.2.7) has at least one positive root, denoted by $\omega_0$. If (b) $\beta < 0$. Then, $\sqrt{\alpha^2 - 3\beta} > \alpha$. By (2.2.12), $z_1 = \frac{1}{3}(-\alpha + \sqrt{\alpha^2 - 3\beta}) > 0$. It follows that equation (2.2.8), hence equation (2.2.7) has a positive root $\omega_0$. This implies that the characteristic equation (2.2.3) has a pair of purely imaginary roots $\pm i\omega_0$.

Let $\lambda(\tau) = \eta(\tau) + i\omega(\tau)$ be the eiganvalue of equation (2.2.3) such that $\eta(\tau_0) = 0,\ \omega(\tau_0) = \omega_0$. From (2.2.5)-(2.2.6) we have

$$\tau_j = \frac{1}{\omega_0} \arccos\left(\frac{a_4\omega_0^4 + (a_1a_3 - a_2a_4)\omega_0^2 - a_3a_5}{a_3^2 + a_4^2\omega_0^2}\right) + \frac{2j\pi}{\omega_0}, \quad j = 0, 1, 2, \ldots.$$

Also, we can verify that the following transversality condition

$$\frac{d}{d\tau}\mathrm{Re}\lambda(\tau)|_{\tau=\tau_0} = \frac{d}{d\tau}\eta(\tau)|_{\tau=\tau_0} > 0.$$

holds. By continuity, the real part of $\lambda(\tau)$ becomes positive when $\tau > \tau_0$ and the steady state becomes unstable. Moreover, a Hopf bifurcation occurs when $\tau$ passes through the critical value $\tau_0$ (see Hassard, Kazarinoff and Wan [25]).

The above analysis can be summarized into the following proposition.

**Proposition 2.5** *Suppose that*

*(i)* $a_1 > 0,\ \ a_3 + a_5 > 0,\ \ a_1(a_2 + a_4) - (a_3 + a_5) > 0.$

*If either*

*(ii)* $\gamma < 0$

*or*

*(iii)* $\gamma \geq 0$ *and* $\beta < 0$

*is sastisfied, then the infected steady state* $\overline{E}$ *of the delay model (2.2.1) is asymptotically stable when* $\tau < \tau_0$ *and unstable when* $\tau > \tau_0$, *where*

$$\tau_0 = \frac{1}{\omega_0} \arccos\left(\frac{a_4\omega_0^4 + (a_1a_3 - a_2a_4)\omega_0^2 - a_3a_5}{a_3^2 + a_4^2\omega_0^2}\right).$$

*When* $\tau = \tau_0$, *a Hopf bifurcation occurs; that is, a family of periodic solutions bifurcates from* $\overline{E}$ *as* $\tau$ *passes through the critical value* $\tau_0$.

Proposition 2.5 indicates that the delay model could exhibit Hopf bifurcation at certain value of the delay if the parameters satisfy the conditions in (ii) and (iii). However, for the parameter values given in Table 1, neither (ii) nor (iii) holds.

# 3 Cell-to-Cell Infection

## 3.1 The General Model

Let $C(t)$ represent the concentration of healthy cells and $I(t)$ be the concentration of infected cells. We consider the following system modeling the interaction of the healthy and infected cells:

$$\begin{aligned} \frac{dC}{dt} &= r_C C(t)\Big(1 - \frac{C(t)+I(t)}{C_M}\Big) - k_I C(t) I(t), \\ \frac{dI}{dt} &= k_I' \int_{-\infty}^{t} C(u) I(u) F(t-u) du - \mu_I I(t), \end{aligned} \tag{3.1.1}$$

where $r_C$ is the effective reproductive rate of healthy cells (the term is the total reproductive rate for healthy cells $r$ minus the death rate for healthy cells $\mu_C$), $C_M$ is the effective carrying capacity of the system, $k_I$ represents the infection of healthy cells by the infected cells in a *well-mixed* system, $k_I'/k_I$ is the fraction of cells surviving the incubation period, $\mu_I$ is the death rate of the infected cells. The interpretation of the variables and parameters and the values of the parameters are given in Table 2.

The initial values of system (3.1.1) are

$$C(s) = \phi(s) \geq 0, \quad I(s) = \psi(s) \geq 0, \quad s \in (-\infty, 0],$$

where $\phi$ and $\psi$ are continuous functions on $(-\infty, 0]$.

We assume that the cells, which are productively infectious at time $t$, were infected $u$ time units ago, where $u$ is distributed according to a probability distribution $F(u)$, called the *delay kernel*. Throughout this paper, we use the family of generic delay kernels of the form

$$F(u) = \frac{\alpha^{n+1} u^n}{n!} e^{-\alpha u},$$

where $\alpha > 0$ is a constant and $n \geq 0$ is an integer. According to MacDonald [39], $n$ is called the *order* of the delay kernel and the *average delay* is defined by

$$\tau = \int_0^\infty u F(u) du = \frac{n+1}{\alpha}.$$

In the literature, the kernels with $n = 0$ and $n = 1$, i.e.,

$$F(u) = \alpha e^{-\alpha u} \quad \text{and} \quad F(u) = \alpha^2 u e^{-\alpha u},$$

are called the *weak* and *strong* kernels, respectively, and are frequently used in biological modeling. Such kernels were also used in mathematical models of HIV-1 infections by Mittler et al. [42].

The system (3.1.1) has three equilibria: the trivial equilibrium $E_0 = (0, 0)$, the healthy equilibrium $E_1 = (C_M, 0)$, and the infected equilibrium $\overline{E} = (\overline{C}, \overline{I})$, where

$$\overline{C} = \frac{\mu_I}{k_I'}, \quad \overline{I} = \frac{r_C(k_I' C_m - \mu_I)}{k_I'(k_I C_m + r_C)}$$

**Table 2 – Variables and Parameters for Cell-to-Cell Spread**

| | *Parameters and Variables* | *Values* | Ref. |
|---|---|---|---|
| | Dependent Variables | | |
| $C$ | concentration of healthy cells | $5 \times 10^5/mL$ | [60] |
| $I$ | concentration of infected cells | $500/mL$ | [60] |
| | Parameters and Constants | | |
| $C_M$ | effective carrying capacity of healthy cells | $2 \times 10^6/mL$ | [35] |
| $k_I$ | rate constant for cell-to-cell spread | $2 \times 10^{-6}/mL/day$ | [60] |
| $r$ | healthy cell reproductive rate | $0.7/day$ | [17] |
| $\mu_c$ | death rate of healthy cells | $0.02/day$ | [50] |
| $\mu_I$ | death rate of infected cells | $0.3/day$ | [37] |
| | Derived Quantities | | |
| $r_C$ | $(= r - \mu_C)$ effective healthy cell reproductive rate | $0.68/day$ | [60] |
| $k_I'$ | $k_I'/k_I$ fraction of cells surviving the incubation period | varies | |

if $k_I' > \mu_I/C_M$.

Notice that system (3.1.1) has some special cases. When

$$F(u) = \delta(u),$$

the delta function, we have the following ordinary differential equations (ODE):

$$\begin{aligned} \frac{dC}{dt} &= r_C C(t)\Big(1 - \frac{C(t)+I(t)}{C_M}\Big) - k_I I(t)C(t), \\ \frac{dI}{dt} &= k_I' I(t)C(t) - \mu_I I(t). \end{aligned} \tag{3.1.2}$$

The initial conditions are

$$C(0) = C_0 \geq 0, \quad I(0) = I_0 \geq 0,$$

where $C_0$ and $I_0$ are constants.

When the kernel takes the following form

$$F(u) = \delta(u - \tau),$$

where $\tau \geq 0$ is a constant, then system (3.1.1) becomes the following delay differential equations (DDE) with a discrete delay:

$$\begin{aligned} \frac{dC}{dt} &= r_C C(t)\Big(1 - \frac{C(t)+I(t)}{C_M}\Big) - k_I I(t)C(t), \\ \frac{dI}{dt} &= k_I' I(t-\tau)C(t-\tau) - \mu_I I(t). \end{aligned} \tag{3.1.3}$$

The initial conditions are

$$C(s) = \phi(s) \geq 0, \quad I(s) = \psi(s) \geq 0, \quad s \in [-\tau, 0],$$

where $\phi$ and $\psi$ are continuous functions on $[-\tau, 0]$. Note that the ODE model (3.1.2) is also a special case of the DDE model (3.1.3) with $\tau = 0$.

In the following sections, we will consider the ODE model (3.1.2), the model (3.1.3) with a discrete delay, and the following distributed model with a weak kernel

$$\begin{aligned} \frac{dC}{dt} &= r_C C(t)\Big(1 - \frac{C(t) + I(t)}{C_M}\Big) - k_I C(t) I(t), \\ \frac{dI}{dt} &= k_I' \int_{-\infty}^{t} \alpha e^{-\alpha(t-u)} C(u) I(u) du - \mu_I I(t), \end{aligned} \tag{3.1.4}$$

for which the initial values are

$$C(s) = \phi(s) \geq 0, \quad I(s) = \psi(s) \geq 0, \quad s \in [-\infty, 0],$$

where $\phi$ and $\psi$ are continuous functions on $[-\infty, 0]$.

## 3.2 The ODE Model

In this section, we discuss the ODE model (3.1.2). Notice that the system has the same three equilibria as the general system (3.1.1) has: the trivial equilibrium $E_0 = (0, 0)$, the healthy equilibrium $E_1 = (C_M, 0)$, and the infected equilibrium $\overline{E} = (\overline{C}, \overline{I})$. Stability analysis of these three equilibria reveals two possible scenarios:

(i) When $C_M < \frac{\mu_I}{k_I}$ (which, under parameter ranges given, usually is not the case), the healthy cells predominate and infected cells die exponentially. In this case $E_0$ is unstable, $E_1$ is asymptotically stable, and $\overline{E}$ is unstable. We note that the condition for $E_1$ to be stable is that $k_I < 1.5 \times 10^{-7}$, or that *less than* 7.5% of infected cells survive the incubation period to become infectious. In this case $E_1$ is asymptotically stable. We note, however, that in reality it is unlikely that so few cells would survive latency, and that the following case is more likely.

(ii) When $\frac{\mu_I}{k_I'} < C_M < \frac{r_C}{C_M}$, healthy cells and infected cells co-exist. This would correspond to the case where, in models representing cell-free viral spread, we have an endemically infected steady state. This means that infection is present but it does not grow out of bound, and levels of healthy cells do not crash to zero. In this case $E_0$ remains unstable, $E_1$ is now also unstable and $\overline{E}$ has become asymptotically stable. A transcritical bifurcation occurs at $C_M > \mu_I/k_I'$, corresponding to $k_I' = 1.5 \times 10^{-7}$. With parameter values given in Table 2, numerical simulations show that the positive equilibrium $\overline{E}$ is asymptotically stable (see Figure 3.1).

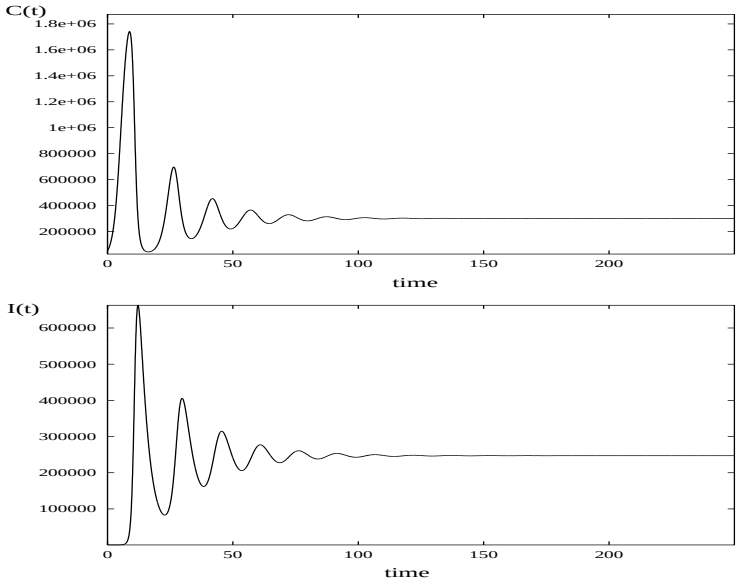


Figure 3.1: $C(t)$ and $I(t)$ converge to the steady state values.

In the $(C, I)-$plane, trajectories spiral towards the equilibrium (see Figure 3.2).

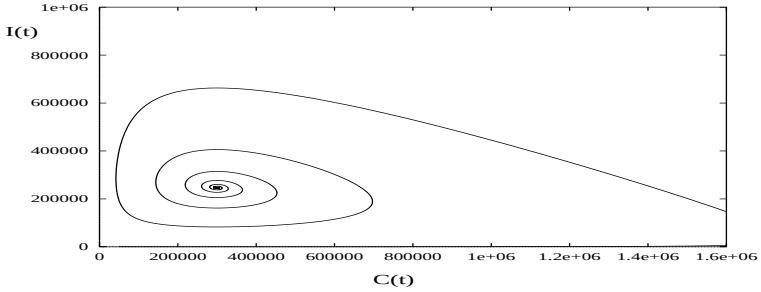


Figure 3.2: The infected equilibrium is asymptotically stable.

The equilibrium $\overline{E}$ is, in fact, globally stable for $\frac{\mu_I}{k'_I} < C_M < \frac{r_C}{C_M}$. We can see this by applying Liapunov's theorem. We choose the following Liapunov function:

$$V(C, I) = c_1\Big( - \overline{C} \log \frac{C}{\overline{C}} + C - \overline{C}\Big) + c_2\Big( - \overline{I} \log \frac{I}{\overline{I}} + I - \overline{I}\Big) \tag{3.2.1}$$

This function is clearly positive if we choose $c_1, c_2$ to be positive constants, and it equals zero for $E = \overline{E}$. We have

$$\frac{dV}{dt} \quad = \quad c_1 \frac{dC/dt}{C}(C - \overline{C}) + c_2 \frac{dI/dt}{I}(I - \overline{I})$$

$$= \quad -c_1\frac{r_C}{C_M}(C-\overline{C})^2 + \left[c_2k_I' - c_1\frac{(r_C-k_IC_M)}{C_M}\right](C-\overline{C})(I-\overline{I}).$$

Assume that $C_M < \frac{r_C}{k_I}$ and choose $c_1 = k_I',\ c_2 = \frac{(r_C-k_IC_M)}{C_M} > 0$. We have

$$\frac{dV}{dt} = -\frac{k_I'r_C}{C_M}(C-\overline{C})^2 < 0,$$

which implies that the equilibrium $\overline{E}$ is globally asymptotically stable for $\frac{\mu_I}{k_I'} < C_M < \frac{r_C}{k_I}$. We thus have proved

**Proposition 3.1** *If*

$$\frac{\mu_I}{k_I'} < C_M < \frac{r_C}{k_I}, \tag{3.2.2}$$

*then the infected equilibrium $\overline{E}$ of the ODE model (3.1.2) is globally asymptotically stable.*

## 3.3 The Discrete Delay Model

Now we consider the delay differential equation model with a discrete delay, namely, system (3.1.3). Notice that the model has the same equilibria given in section 3.2, $E_0 = (0,0)$, $E_1 = (C_M, 0)$, and $\overline{E} = (\overline{C}, \overline{I})$.

We are interested in the stability of the infected equilibrium $\overline{E}$. The characteristic equation of the linearized system is given by:

$$\Delta(\lambda) = \lambda^2 + p\lambda + r + (s\lambda + q)e^{-\lambda\tau} = 0, \tag{3.3.1}$$

where

$$p = \frac{\mu_I(k_I'C_M + r_C)}{k_I'C_M},\quad q = r_C\mu_I\frac{(k_I'C_M - 2\mu_I)}{k_I'C_M},\quad r = \frac{r_C\mu_I^2}{k_I'C_M},\quad s = -\mu_I.$$

Characteristic equations of this form have been extensively examined in [55]. Certain conditions on the coefficients $p$, $q$, $r$ and $s$ will ensure either all roots of the characteristic equation have negative real part or at least one root has positive real part. The results of interest to us are as follows:

**Lemma 3.2** *Consider a characteristic equation of the form (3.3.1).*

*(i) If $p + s > 0$ and $q + r > 0$, then all roots of the characteristic equation have negative real part in the absence of delay.*

*(ii) If $p+s > 0$, $q+r > 0$, and either ($s^2 - p^2 + 2r < 0$ and $r^2 - q^2 > 0$) or $(s^2 - p^2 + 2r)^2 < 4(r^2 - q^2)$, then all roots of the characteristic equation have negative real part for all delay values, that is, the equilibrium is absolutely stable.*

*(iii) If $p+s>0$, $q+r>0$, and either $r^2-q^2<0$ or ($s^2-p^2+2r>0$ and $(s^2-p^2+2r)^2=4(r^2-q^2)$), then there is a critical value $\tau_0$ defined by:*

$$\tau_0=\frac{1}{\omega_+}\arccos\frac{q(\omega_+^2-r)-ps\omega_+^2}{s^2\omega_+^2+q^2}, \tag{3.3.2}$$

*where $\omega_+$ satisfies*

$$2\omega_+^2=(s^2-p^2+2r)+\sqrt{(s^2-p^2+2r)^2-4(r^2-q^2)}, \tag{3.3.3}$$

*when $\tau\in[0,\tau_0)$, all roots of the characteristic equation have negative real part; when $\tau=\tau_0$, there is a pair of purely imaginary roots $\pm i\omega_+$; and when $\tau>\tau_0$, the characteristic equation has at least one root with positive real part.*

We will use the above results to analyze the stability of the infected equilibrium. Checking the first two conditions, we note that $p+s>0$ holds if

$$\mu_I\left(\frac{k_I'C_M+r_C}{k_I'C_M}-1\right)>0$$

which is obviously the case, since $r_C$ is positive. The second condition, $q+r>0$, holds whenever $k_I'>\mu_I/C_M$, which is exactly the condition for the feasibility of the interior equilibrium in the ODE model.

Consider the third condition for the characteristic equation to have only roots with negative real part. For this to be true, we require that *both* of the following conditions hold:

$$r^2-q^2>0, \tag{3.3.4}$$
$$s^2-p^2+2r<0. \tag{3.3.5}$$

The second condition holds for all values of parameters. However, the first condition is somewhat more interesting. Notice that for $r^2-q^2>0$, we require the following inequality to be satisfied:

$$C_M^2k_I'^2-4\mu_IC_Mk_I'+3\mu_I^2<0.$$

This is true when

$$\frac{\mu_I}{C_M}<k_I'<\frac{3\mu_I}{C_M}.$$

We summarize the conditions on stability as follows:

**Proposition 3.3** *The positive equilibrium $\overline{E}$ of system (4.1) is asymptotically stable for all delay $\tau$ when*

$$\frac{\mu_I}{C_M}<k_I'<\frac{3\mu_I}{C_M}. \tag{3.3.6}$$

Thus, there is a region of absolute stability for the infected equilibrium. Notice that this region corresponds to only between 7.5% and 22.5% of infected cells surviving the latent period. The obvious question to ask is, what happens when more cells survive (which, in realistic situations, is likely)?

We note that for $k_I' > 3\mu_I/C_M$, $r^2 - q^2 < 0$, and delay-induced instability may occur because the characteristic equation has a root with positive real part. Define

$$A = \sqrt{((k_I'C_M)^2 - \mu_I)((k_I'C_M)^2 - 3\mu_I)}.$$

We summarize the conditions for bifurcation as follows:

**Proposition 3.4** *Assume that*

$$k_I' > \frac{3\mu_I}{C_M}. \tag{3.3.7}$$

*Then there is a critical value $\tau_0$ given by*

$$\tau_0 = \frac{1}{\omega_+} \arccos \frac{1}{k_I'C_M}\left[\frac{(k_I'C_M(r_C + \mu_I) - r_C\mu_I)A - 2r_C\mu_I k_I'C_M(k_I'C_M - 2\mu_I)}{\mu_I A + 2r_C(k_I'C_M - 2\mu_I)^2}\right],$$

*where*

$$\omega_+ = \frac{1}{2k_I'C_M}\sqrt{2r_C\mu_I(2A - r_C\mu_I)},$$

*such that the infected equilibrium $\overline{E}$ of system (4.1) is asymptotically stable when $\tau \in [0, \tau_0)$ and unstable when $\tau > \tau_0$. A Hopf bifurcation occurs at $\overline{E}$ when $\tau = \tau_0$; that is, a family of periodic solutions bifurcates from $\overline{E}$ when $\tau$ passes through the critical value $\tau_0$.*

Notice that $\tau_0$ depends on $k_I'$. In the following, we will see that for larger values of $k_I'$, the critical value $\tau_0$ gets smaller, whereas the periods and amplitudes of the oscillatory solutions get larger.

Using values of $k_I'$ corresponding to $25\%, 50\%, 75\%$ of cells surviving incubation, we obtain the following results for the critical value of the delay.

Suppose that 25% of infected cells survive incubation. This corresponds to a value of $k_I' = 5 \times 10^{-7}$. In this case, using the formulas given above, we obtain a critical value of the delay to be $\tau_0 = 6.23$ days. Since the actual incubation period is one day, we do not expect this to be of biological significance. Numerical simulations show that both $C$ and $I$ are stable for realistic values of all other parameters, when $k_I' = 5 \times 10^{-7}$.

Now suppose that half the infected cells survive incubation. In this case, the critical value for $\tau_0$ obtained analytically is 0.82 days, which *is* of biological significance. Numerical simulations show that for $k_I' = 10^{-6}$ and $\tau = 0.4 < \tau_0$, the components $C(t)$ and $I(t)$ are converging to the steady state values as time increases (see Figure 3.3).

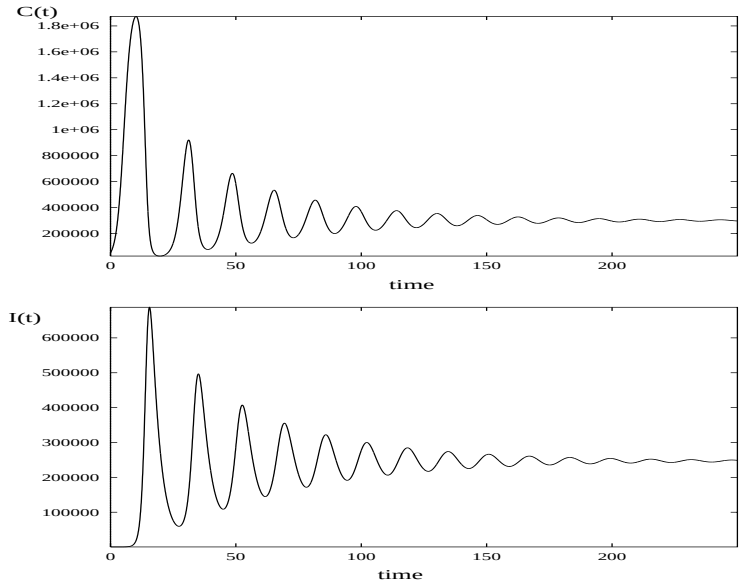


Figure 3.3: $C(t)$ and $I(t)$ converge to the steady state values when $\tau < \tau_0$, here $\tau = 0.4$.

In the $(C, I)-$plane, trajectories spiral towards the equilibrium (see Figure 3.4).

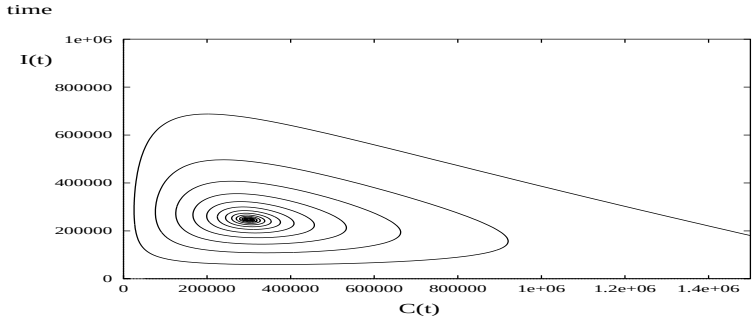


Figure 3.4: The infected equilibrium is asymptotically stable when $\tau = 0.4 < \tau_0$.

When the delay is increased to $\tau = 1 > \tau_0$, the components $C(t)$ and $I(t)$ oscillate with increasing time (see Figure 3.5).

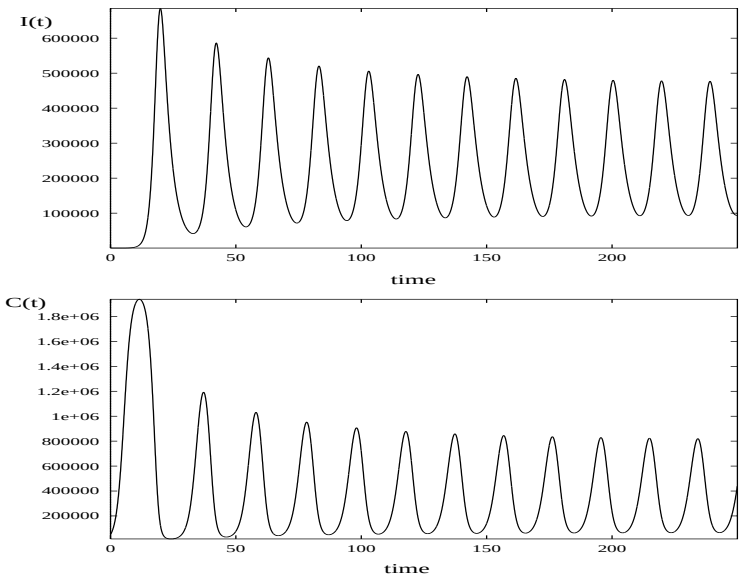


Figure 3.5: The oscillations of $C$ and $I$ vs. time, $\tau = 1$

In the $(C, I)-$plane, trajectories are approaching the periodic solution as the time increases (see Figure 3.6).

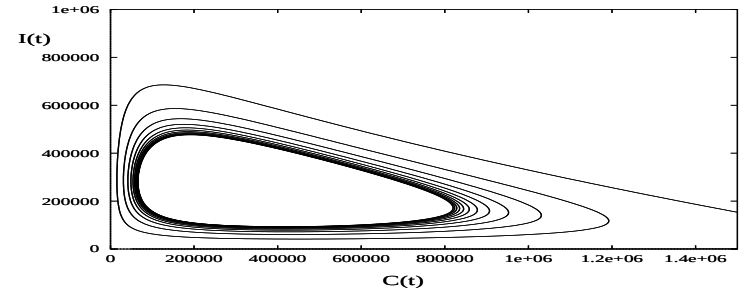


Figure 3.6: There is an orbitally asymptotically stable periodic solution when $\tau = 1 > \tau_0$.

If 75% of the infected cells survive, numerical analysis shows that when $k_I'$ is smaller the oscillations are more frequent (i.e., the periods are shorter) and the amplitudes are smaller. Thus, increasing the value of $k_I'$ will increase the periods and the amplitudes of the periodic solutions. There appears to be an interplay between the value of the delay and the fraction of infected cells surviving incubation. Specifically, the more cells survive incubation, the smaller the critical value of the delay must be to induce instability of the interior equilibrium.

## 3.4 The Distributed Delay Model

Finally we consider the distributed delay model with a weak kernel, that is, system (3.1.4). To study the stability of the infected equilibrium, let

$$X(t) = \int_{-\infty}^{t} \alpha e^{-\alpha(t-u)} C(u) I(u) du. \tag{3.4.1}$$

Then system (3.1.4) is equivalent to the following ODE system

$$\begin{aligned} \frac{dC}{dt} &= r_C C(t)\Big(1 - \frac{C(t)+I(t)}{C_M}\Big) - k_I C(t) I(t), \\ \frac{dI}{dt} &= k_I' X(t) - \mu_I I(t), \\ \frac{dX}{dt} &= \alpha C(t) I(t) - \alpha X(t). \end{aligned} \tag{3.4.2}$$

The positive steady state of system (3.4.2) is given by $\overline{E} = (\overline{C}, \overline{I}, \overline{X})$, where $\overline{X} = \frac{\mu_I}{k_I'}\overline{I}$. Linearizing the system at the steady state $\overline{E}$, we obtain the characteristic equation

$$\lambda^3 + a_1(\alpha)\lambda^2 + a_2(\alpha)\lambda + a_3(\alpha) = 0, \tag{3.4.3}$$

where

$$\begin{aligned} a_1(\alpha) &= \frac{r_C}{C_M}\overline{C} + \mu_I + \alpha, \\ a_2(\alpha) &= \alpha(\frac{r_C}{C_M}\overline{C}) + \frac{\mu_I r_C}{C_M}\overline{C}, \\ a_3(\alpha) &= \alpha(k_I' + \frac{r_C}{C_M})\mu_I \overline{I}. \end{aligned}$$

By Routh-Hurwitz criteria, the positive steady state $\overline{E}$ is asymptotically stable if and only if

$$a_1(\alpha) > 0, \quad a_3(\alpha) > 0 \quad \text{and} \quad a_1(\alpha)a_2(\alpha) - a_3(\alpha) > 0 \tag{3.4.4}$$

for all values of $\alpha$. If there is an $\alpha_0 > 0$ such that

$$a_1(\alpha_0)a_2(\alpha_0) = a_3(\alpha_0), \tag{3.4.5}$$

then the characteristic equation (3.4.3) becomes

$$[\lambda + a_1(\alpha_0)][\lambda^2 + a_2(\alpha_0)] = 0,$$

which has roots

$$\lambda_1 = -a_1(\alpha_0) < 0, \quad \lambda_{2,3} = \pm i\sqrt{a_2(\alpha_0)}.$$

If the transversality condition

$$\frac{d\mathrm{Re}\lambda_{2,3}}{d\alpha}\Big|_{\alpha=\alpha_0} \neq 0 \tag{3.4.6}$$

holds, then a Hopf bifurcation occurs at $\overline{E}$ when $\alpha$ passes through the critical value $\alpha_0$. After some calculations, we have

$$\left.\frac{d\mathrm{Re}\lambda_{2,3}}{d\alpha}\right|_{\alpha=\alpha_0} = -\frac{1}{4[a_1^2(\alpha)+a_2(\alpha)]}\,\frac{d}{d\alpha}[a_1(\alpha)a_2(\alpha)-a_3(\alpha)]|_{\alpha=\alpha_0}.$$

Summarizing the above analysis, we have the following results.

**Proposition 3.5** *If conditions in (3.4.4) are satisfied, then the positive steady state $\overline{E}$ of system (3.1.4) is asymptotically stable. If there is a critical value $\alpha_0 > 0$ such that conditions (3.4.5) and*

$$\frac{d}{d\alpha}[a_1(\alpha)a_2(\alpha)-a_3(\alpha)]|_{\alpha=\alpha_0} \neq 0$$

*are satisfied, then a Hopf bifurcation occurs at $\overline{E}$; that is, a family of periodic solutions bifurcates from $\overline{E}$ when $\alpha$ passes through the critical value $\alpha_0$.*

Notice that for the weak kernel $\alpha e^{-\alpha u}$, the average delay is defined as $\overline{\tau} = \frac{1}{\alpha}$. The above analysis demonstrates that when $\overline{\tau}$ is small (i.e. when $\alpha$ is large), the steady state is stable. When $\overline{\tau}$ is sufficiently large (i.e. as $\alpha$ becomes smaller), the steady state becomes unstable and a Hopf bifurcation occurs. That is, a periodic solution bifurcates from the steady state when $\alpha$ passes a critical value $\alpha_0$.

With parameter values given in Table 2 and a value of $k_I' = 1.5 \times 10^{-6}$, $\alpha_0 \approx 1.95$. Numerical simulations show that the steady state $\overline{E} = (\overline{C}, \overline{I})$ is asymptotically stable when $\alpha > \alpha_0$ (i.e., $\bar{\tau} < \bar{\tau}_0$)(see Figure 3.7).

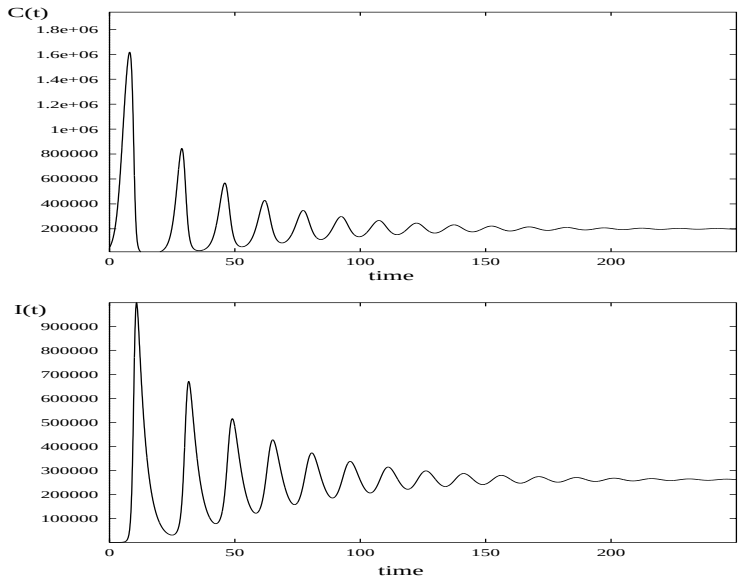


Figure 3.7: $C(t)$ and $I(t)$ converge to the steady state values when $\alpha > \alpha_0$, here $\alpha = 5$.

In the $(C, I)-$plane, trajectories spiral towards the equilibrium (see Figure 3.8).

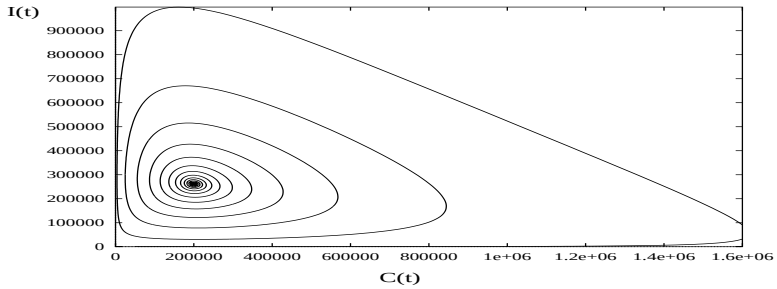


Figure 3.8: The infected equilibrium is asymptotically stable when $\alpha = 5 > \alpha_0$.

When $\alpha = \alpha_0$ (i.e., $\bar{\tau} = \bar{\tau}_0$), the steady state $\bar{E}$ loses its stability and Hopf bifurcation occurs. When $\alpha < \alpha_0$ (i.e., $\bar{\tau} > \bar{\tau}_0$), the steady state $\bar{E}$ becomes unstable and there is a periodic solution surrounding $\bar{E}$ (see Figures 3.9 and 3.10).

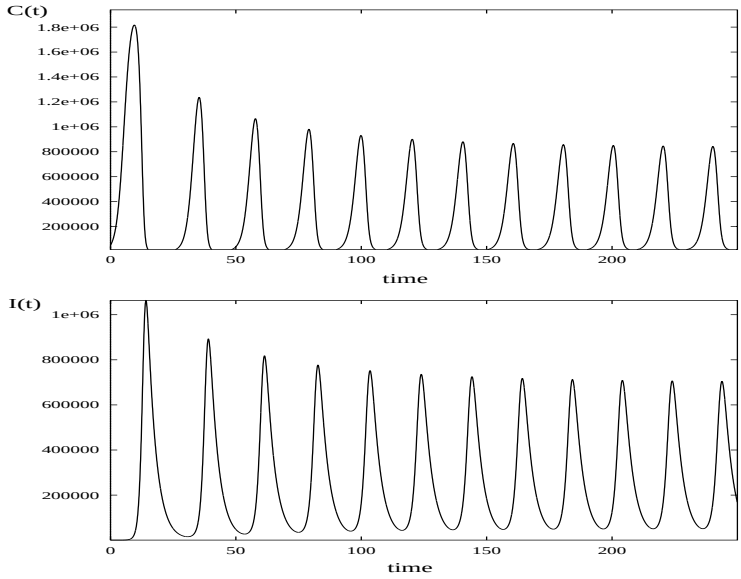


Figure 3.9: $C(t)$ and $I(t)$ oscillate about the steady state values when $\alpha < \alpha_0$, here $\alpha = 1.5$.

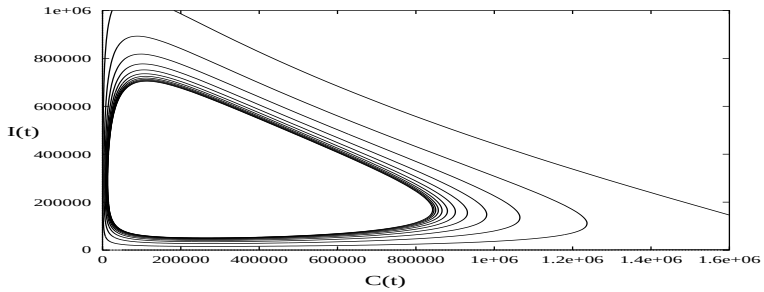


Figure 3.10: There is a periodic solution when $\alpha = 1.5 < \alpha_0$.

Similarly, we can analyze system (3.1.1) with a strong kernel $F(u) = \alpha^2 u e^{-\alpha u}$ obtain similar results on stability and bifurcation of the model.

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