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ON DRUG THERAPY FOR AN HIV INFECTION AGE MODEL WITH CELLULAR AND IMMUNE DELAYS

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Abstract. We study the effectiveness of drug therapy for an HIV infection age mathematical model that considers both virus-to-cell and cell-to-cell infections, as well as the immune response. As expected, in the presence of perfect inhibitors, the populations of infected cells, virus, and effector cells decay exponentially to zero. When protease inhibitors are used, the production of infectious virions is diminished, as demonstrated in our drug therapy model.

We begin our model analysis by proving the positivity and boundedness of the solutions, which are necessary conditions for the model's well-posedness. Our main result shows that, under a certain condition, both the infected cell population and the infectious virus decay exponentially to zero.

1. Introduction

The human immunodeficiency virus (HIV) and the acquired immunodeficiency syndrome (AIDS) remain persistent problems for many countries around the world. According to a report by the Center for Disease Control and Prevention [4], HIV and AIDS continue to represent a serious health concern for large parts of the world. Worldwide, there were about 1.3 million new cases of HIV in 2022. About 39 million people were living with HIV around the world at the end of 2022, and 29.8 million of them were receiving medicines to treat HIV. It is well-known that HIV infects $CD4^+$ T helper cells, which are an important part of the immune system because they facilitate the body's response to many common but potentially fatal infections. Without treatment with HIV medicines, HIV infection advances in stages, getting worse over time. The phase of primary infection is characterized by a strong viral replication, which is followed by a strong immune response. In the second phase of HIV infection, infected individuals display no symptoms, but have persistent viral replications. This eventually results in the development of AIDS [9], which is the final, most severe stage of HIV infection. Individuals are diagnosed with AIDS if they have a T cells count of less than 200 $cells/mm^3$ or if they have certain opportunistic infections (see [9]). Without treatment, people with AIDS typically survive about 3 years. Over 40 million people have died from AIDS-related illnesses since the start of the epidemic (see [4] for statistics and more information).

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Over the past two decades, mathematical models have made substantial contributions to our understanding of HIV infection, immune responses, and anti-retroviral treatment (see [3, 6, 8, 17, 19, 20]). Time delays have also been incorporated into mathematical models to study virus dynamics. Introducing time delays to HIV models usually brings challenges to both mathematical analysis of the models and comparison of model predictions with patient data. Herz et al. [10] were first to characterize the time delay between the initial viral entry into a target cell and subsequent viral production. Assuming that the level of target cells is constant and that the protease inhibitor is completely effective, they obtained the expression of the viral load and explored the effect of the intracellular delay on viral load change. The delay model with imperfect drug treatment was analyzed in [16], and an analytical expression of the dominant eigenvalue that determines the rate of viral decay was provided. More recently, in [14] the authors combined density-dependent responses to formulate an immune effect and considered two delays associated with virus growth and immune response. Several other studies have investigated the effect of multiple delays on whole viral dynamics; see [1, 2, 7, 12, 15, 18, 29], among many others.

In this article, we analyze drug treatment outcomes for a HIV mathematical model introduced by the author in [23]. In this model, the virus transmission process takes into account mitosis of healthy target cells and three infection age time delays in the way of virus-to-cell and cell-to-cell infections and immune response. The delays indicate the times for processing chemical reaction in virus-to-cell infection, intracellular incubation period in cell-to-cell infection, and the time lag in immune response to active viruses. In Theorem 3.2, we show that the solution of the initial-value problem associated to the system is positive and bounded; a necessary condition for the model's well-posedness. The main result of this paper, Theorem 3.4, provides an upper bound for the combined population of infected cells and infectious virus. As an immediate consequence of this result, the exponential decay to zero of this population is proven, if a condition depending on the drug(s) effectiveness is satisfied.

This article is organized as follows. In Section 2, we present the HIV model introduced in [23] and some of its analysis. In Section 3, we investigate the effect of inhibitors and effectiveness of protease inhibitors on the evolution of the virus and infected cell populations.

2. HIV Infection Model Description

In [5], the authors consider the following viral model incorporating mitosis of the healthy target cells which is described by the logistic term and two routes of infection: virus-to-cell and cell-to-cell infections. The model also exhibits three time delays accounting, respectively, for a period of the chemical reaction in the virus-to-cell infection, an intracellular incubation period in the cell-to-cell infection, and a period of the immune lag incurred by antigenic activation and selection.

$$\frac{dT}{dt} = S - \mu_1 T(t) + rT(t)\Big(1 - \frac{T(t)}{T_{\max}}\Big) - \beta_1 T(t)V(t) - \beta_2 T(t)I(t) \tag{2.1}$$

$$\begin{aligned}\frac{dI}{dt} &= \beta_1 e^{-a_1\tau_1} T(t-\tau_1)V(t-\tau_1) + \beta_2 e^{-a_2\tau_2} T(t-\tau_2)I(t-\tau_2) \\ &\quad - \mu_2 I(t) - \delta E(t)I(t)\end{aligned} \tag{2.2}$$

$$\frac{dV}{dt} = bI(t) - \mu_3 V(t) \tag{2.3}$$

$$\frac{dE}{dt} = ce^{-a_3\tau_3} I(t-\tau_3) - \mu_4 E(t) \tag{2.4}$$

Here, the four dynamic variables are the healthy target cells $T(t)$, the infected cells $I(t)$, the virus $V(t)$, and the effector cells $E(t)$. In equation (2.1) for $T(t)$, S is the constant input rate, and β_1 and β_2 are the virus-to-cell and cell-to-cell infection rates, respectively. The mitosis of healthy target cells is described by the logistic term $rT(t)\Big(1-\frac{T(t)}{T_{\max}}\Big)$, where r is the intrinsic mitosis rate and $T_{\max}$ is the carrying capacity of the target cell population. That is, if the T cells population ever reaches $T_{\max}$ (in the uninfected case) it should decrease. Thus, the constraint $S < \mu_1 T_{\max}$ appears naturally. Furthermore, all cells have a natural lifespan; here μ_i, $i = 1, \dots, 4$, denote the death rates of populations $T(t)$, $I(t)$, $V(t)$, and $E(t)$, respectively, and δ is the death rate of infected cells due to action of the immune response. The first two terms in the $I(t)$ equation (2.2) represent the delayed sources of infection by free virus and infected cells, respectively, and b in (2.3) denotes the average production rate of virus from an infected cell. The first term of the equation (2.4) quantifies the delayed production rate of the effector cells $E(t)$. Effector cells are assumed to be generated at a rate proportional to the delayed level of productively infected cells, and die at a rate proportional with their population.

In [11], the authors propose a model that incorporates both the cell-to-cell infection mechanism and the virus-to-cell infection mode, considering infection age as well (the notations are synchronized with the notations of the model (2.1)-(2.4)).

$$\frac{dT}{dt} = S - \mu_1 T(t) - \beta_1 T(t)V(t) - \beta_2 T(t)I(t) \tag{2.5}$$

$$\frac{dI}{dt} = \int_0^\infty [\beta_1 T(t-s)V(t-s) + \beta_2 T(t-s)I(t-s)]e^{-as} f(s)\, ds - \mu_2 I(t) \tag{2.6}$$

$$\frac{dV}{dt} = bI(t) - \mu_3 V(t) \tag{2.7}$$

Here, it is assumed that the infected cells may die or be cleared at a rate a before becoming productively infected, that is, only a proportion e^{-as} survives after a time period s. As explained in [11], the time for infected cells to become productively infected may vary from case to case; this explains the distribution function $f : [0,\infty) \to [0,\infty)$, which is nonnegative, has compact support (i.e., $\operatorname{supp}(f) \subseteq [0, A]$, for some $A > 0$), and satisfies $\int_0^\infty f(s)\, ds = 1$.

Based on (2.1)-(2.4) and (2.5)-(2.7), we have proposed the following model in [23], whose dynamical variables and parameters are exactly as in (2.1)-(2.4) and (2.5)-(2.7).

$$\frac{dT}{dt} = S - \mu_1 T(t) + rT(t)\Big(1-\frac{T(t)}{T_{\max}}\Big) - \beta_1 T(t)V(t) - \beta_2 T(t)I(t) \tag{2.8}$$

$$\begin{aligned}\frac{dI}{dt} &= \int_0^\infty [\beta_1 T(t-s)V(t-s) + \beta_2 T(t-s)I(t-s)]e^{-as} f(s)\, ds \\ &\quad - \mu_2 I(t) - \delta E(t)I(t)\end{aligned} \tag{2.9}$$

$$\frac{dV}{dt} = bI(t) - \mu_3 V(t) \tag{2.10}$$

$$\frac{dE}{dt} = c\int_0^\infty I(t-s)e^{-as}f(s)\,ds - \mu_4 E(t) \tag{2.11}$$

This mathematical model for the HIV virus transmission process takes into account mitosis of healthy target cells and three infection age time delays in the way of virus-to-cell and cell-to-cell infections and immune response. The next result says that the solution of the initial-value problem associated to the system (2.8)-(2.11) is positive and bounded, a necessary condition for the model's well-posedness.

Theorem 2.1 ([23, Theorem 1]). *Let $(T(t), I(t), V(t), E(t))$ be the solution of system (2.8)-(2.11) with continuous, bounded initial conditions $T_0, I_0, V_0, E_0 : (-\infty, 0] \to [0, \infty)$. Assume that either $I_0(t_0) > 0$ or $V_0(t_0) > 0$ for some $t_0 \in (-\infty, 0]$ (i.e., infection occurs). Then $T(t)$, $I(t)$, $V(t)$, and $E(t)$ are all positive and bounded for $t > 0$.*

The equilibrium (or steady-state) solutions are obtained by solving the algebraic system that arises from seeking time-independent solutions. System (2.8)-(2.11) admits an infection-free equilibrium $E_0 = (\bar{T}, 0, 0, 0)$, with

$$\bar{T} := \frac{T_{\max}}{2r}\Big(r - \mu_1 + \sqrt{(r-\mu_1)^2 + \frac{4rS}{T_{\max}}}\Big).$$

Let $\mathcal{R}_0$ be the basic reproduction number defined by

$$\mathcal{R}_0 := \frac{b\beta_1\bar{T}\mathcal{L}_f(a)}{\mu_2\mu_3} + \frac{\beta_2\bar{T}\mathcal{L}_f(a)}{\mu_2},$$

where $\mathcal{L}_f(a) := \int_0^\infty e^{-as}f(s)\,ds$ is the Laplace transform of f at a. Observe that $\mathcal{R}_0$ depends on the delays related to infections but not on the delay related to the effector cells production. As explained in [5], the first term in the definition of $\mathcal{R}_0$, $\mathcal{R}_{01} := b\beta_1\bar{T}\mathcal{L}_f(a)\mu_2^{-1}\mu_3^{-1}$, measures the average number of secondary infected generation caused by an existing free virus, while the second term, $\mathcal{R}_{02} := \beta_2\bar{T}\mathcal{L}_f(a)\mu_2^{-1}$, measures the average number of secondary infected generation caused by an infected cell. It is shown in [23] that $\mathcal{R}_0$ is a measure of whether or not an infection caused by a small inoculation of virus can persist, that is, the infection-free equilibrium is locally asymptotically stable if and only if the basic reproduction number is strictly less than one.

System (2.8)-(2.11) also admits an infected equilibrium $E_0^* = (T^*, I^*, V^*, E^*)$, where

$$T^* = \frac{r - \mu_1 + \theta(\frac{b\beta_1}{\mu_3} + \beta_2) + \sqrt{[r - \mu_1 + \theta(\frac{b\beta_1}{\mu_3} + \beta_2)]^2 + 4S[\frac{r}{T_{\max}} + \alpha(\frac{b\beta_1}{\mu_3} + \beta_2)]}}{2[\frac{r}{T_{\max}} + \alpha(\frac{b\beta_1}{\mu_3} + \beta_2)]}$$

$$I^* = \alpha T^* - \theta, \quad V^* = \frac{b}{\mu_3}I^*, \quad E^* = \frac{c\mathcal{L}_f(a)}{\mu_4}I^*,$$

with

$$\theta = \frac{\mu_2\mu_3}{c\delta\mathcal{L}_f(a)} \quad \text{and} \quad \alpha = \frac{\theta}{\bar{T}}\mathcal{R}_0,$$

whenever $T^* > \bar{T}/\mathcal{R}_0$. The necessary and sufficient condition for the existence of the infected equilibrium E_0^* is that $\mathcal{R}_0 > 1$ (see [23]). In the next section we address models of drug therapy derived from (2.8)-(2.11).

3. Drug Therapy Models

Many drug therapies involve inhibiting either the enzyme reverse transcriptase or HIV protease. While in the former case, HIV can enter a cell without successfully infecting it, in the latter case defective or deactivated viral particles are made. There have been a variety of modifications of HIV mathematical models that have resulted from incorporating drug therapies. It is known that there is no perfect treatment for HIV infection, but HIV medicines can prevent HIV from advancing to AIDS. HIV medicines help people with HIV live longer, healthier lives. HIV medicines also reduce the risk of HIV transmission to other people. For examples of how mathematical models predict HIV treatment outcomes, see [21, 22, 24, 25, 26, 27, 28], and references therein.

3.1. **Perfect inhibitors.** Let us assume that perfect inhibitors are administered at time $t = 0$. That is, both virus-to-cell and cell-to-cell infections are completely stopped; in mathematical terms, $\beta_1 = \beta_2 = 0$, if $t \geq 0$. Nonetheless, the infections started before $t = 0$ will continue, which explains the integral in the equation (3.2) for $I(t)$ in the resulting system

$$\frac{dT}{dt} = S - \mu_1 T(t) + rT(t)\Big(1 - \frac{T(t)}{T_{\max}}\Big) \tag{3.1}$$

$$\begin{aligned}\frac{dI}{dt} &= \int_t^\infty [\beta_1 T(t-s)V(t-s) + \beta_2 T(t-s)I(t-s)]e^{-as} f(s)\,ds \\ &\quad - \mu_2 I(t) - \delta E(t)I(t)\end{aligned} \tag{3.2}$$

$$\frac{dV}{dt} = bI(t) - \mu_3 V(t) \tag{3.3}$$

$$\frac{dE}{dt} = c\int_0^\infty I(t-s)e^{-as} f(s)\,ds - \mu_4 E(t) \tag{3.4}$$

Observe that the T cell equation becomes decoupled from the other equations. Thus, the T cell population should recover to the preinfection steady state level. Furthermore, productively infected cells I will still be generated for a period of time (see (3.2)).

One of the tools for the next results is the classical Gronwall inequality, which states that if $y : [0, T] \to \mathbb{R}$ is differentiable and $y(t)$ satisfies the differential inequality

$$y'(t) \leq h(t) + g(t)y(t),$$

with g continuous and h locally integrable, then

$$y(t) \leq y(0)e^{G(t)} + \int_0^t e^{G(t)-G(s)} h(s)\,ds,$$

for $G(t) := \int_0^t g(r)dr$.

The next result states that although the infected cells $I(t)$, virus $V(t)$, and effector cells $E(t)$ can still be generated, their numbers decay exponentially to zero with time.

Proposition 3.1. *If $\beta_1 = \beta_2 = 0$ for $t \geq 0$, then*

$$\lim_{t\to\infty} I(t) = \lim_{t\to\infty} V(t) = \lim_{t\to\infty} E(t) = 0$$

exponentially.

Proof. We know that the solution is positive and bounded for $t \leq 0$, before the inhibitors are administered. Let M_I and M_V be the least upper bounds for the initial data $I_0(t)$ and $V_0(t)$, respectively, for $t \leq 0$. From (3.2), we obtain

$$\frac{dI}{dt} \leq (\beta_1 T_{\max} M_V + \beta_2 T_{\max} M_I) e^{-at} - \mu_2 I(t), \quad \text{for } t \geq 0,$$

and so, by Gronwall's inequality,

$$I(t) \leq I(0)e^{-\mu_2 t} + \mu_2^{-1}(\beta_1 T_{\max} M_V + \beta_2 T_{\max} M_I)e^{-at} \leq Ce^{-\min\{a,\mu_2\}t}, \tag{3.5}$$

where C, hereafter, represents a generic positive constant, which may vary from calculation to calculation. The last inequality implies that $I(t)$ decays exponentially to zero as t goes to infinity.

Similarly, from equation (3.3), it follows that

$$\frac{dV}{dt} \leq Ce^{-\min\{a,\mu_2\}t} - \mu_3 V(t),$$

and so, as a consequence of Gronwall's inequality,

$$V(t) \leq Ce^{-\min\{a,\mu_2,\mu_3\}t},$$

which implies the exponential decay of $V(t)$ to zero in time.

Finally, from (3.4), (3.5), and the properties of the distribution function f, we obtain

$$\frac{dE}{dt} \leq Ce^{-\min\{a,\mu_2\}t} - \mu_4 E(t).$$

Then, Gronwall's inequality implies that

$$E(t) \leq Ce^{-\min\{a,\mu_2,\mu_4\}t},$$

which completes the proof. □

Of course, it is not realistic to assume that perfect inhibitors exist. Henceforth, we will assume that β_1 and β_2 are nonnegative constants.

3.2. **Protease inhibitors.** Because of protease inhibitors the infected cells produce only non-infectious virions. The virions that were produced prior to drug treatment remain infectious. Therefore, we consider two types of virions in the presence of protease inhibitors: infectious virions V_I and noninfectious virions V_{NI}. More precisely, V_I represents the virus particles unaffected by the protease inhibitor, whereas V_{NI} denotes the virus particles deactivated by the protease inhibitor. Denote by $0 \leq \eta \leq 1$ the effectiveness of a protease inhibitor or combination of protease inhibitors in suppressing the production of infectious virions. If $\eta = 1$, the inhibition is completely effective, whereas if $\eta = 0$, there is no inhibition.

The following model only deals with dynamics occurring after drug treatment. It is not designed to examine the progression from time of infection until drug initiation (see [23]).

$$\frac{dT}{dt} = S - \mu_1 T(t) + rT(t)\Big(1 - \frac{T(t)}{T_{\max}}\Big) - \beta_1 T(t) V_I(t) - \beta_2 T(t) I(t) \tag{3.6}$$

$$\begin{aligned}\frac{dI}{dt} &= \int_0^\infty [\beta_1 T(t-s) V_I(t-s) + \beta_2 T(t-s) I(t-s)] e^{-as} f(s)\, ds \\ &\quad - \mu_2 I(t) - \delta E(t) I(t)\end{aligned} \tag{3.7}$$

$$\frac{dV_I}{dt} = (1-\eta) b I(t) - \mu_3 V_I(t) \tag{3.8}$$

$$\frac{dV_{NI}}{dt} = \eta b I(t) - \mu_3 V_{NI}(t) \tag{3.9}$$

$$\frac{dE}{dt} = c\int_0^\infty I(t-s)e^{-as}f(s)\,ds - \mu_4 E(t) \tag{3.10}$$

The next result addresses positiveness and boundedness of solutions for system (3.6)-(3.10). Although it is not realistic to assume that protease inhibitors are perfect drugs (i.e., $\eta = 1$), our following result covers this case too.

Theorem 3.2. *Let $0 < \eta \leq 1$. Then, the solution to the initial value problem associated with system* (3.6)-(3.10) *is positive and bounded from above.*

Proof. First, let us prove that the solution of (2.8)-(2.11) is positive for all $t > 0$ if $0 < \eta < 1$. From Theorem 2.1, solution continuity, and $V'_{NI}(0) > 0$, observe that $T(t)$, $I(t)$, $V_I(t)$, $V_{NI}(t)$, and $E(t)$ must be positive in a right-side neighborhood of $t = 0$. Arguing by contradiction, assume that there exists $t_1 > 0$ such that

$$\min\{T(t_1), I(t_1), V_I(t_1), V_{NI}(t_1), E(t_1)\} = 0$$

for the first time.

First, assume $T(t_1) = 0$. Then, from (3.6) it follows that $T'(t_1) = S > 0$, which is in contradiction with the positivity of $T(t)$ in a left-side neighborhood of t_1. In fact, exactly the same argument proves that $T(t)$ must be positive on the entire interval $[0, \infty)$, independently of the behavior of the other variables of the system. Similar arguments show that neither $V_I(t_1)$ nor $V_{NI}(t_1)$ can be zero. Next, we prove the positivity of $I(t)$. If $I(t_1) = 0$, then, from (3.7), we obtain

$$I'(t_1) = \int_0^\infty [\beta_1 T(t_1 - s)V_I(t_1 - s) + \beta_2 T(t_1 - s)I(t_1 - s)]e^{-as}f(s)\,ds > 0,$$

which contradicts the positivity of $I(t)$ in a left-side neighborhood of t_1. Similarly,

$$E'(t_1) = c\int_0^\infty I(t_1 - s)e^{-as}f(s)\,ds > 0,$$

and so $E(t_1) \neq 0$. In conclusion, the solution to (2.8)-(2.11) is positive for all $t > 0$.

Let us now prove that the solution is bounded from above. To prove the boundedness of $T(t)$, observe that

$$\frac{dT}{dt} \leq S - \mu_1 T(t) + rT(t)\Big(1 - \frac{T(t)}{T_{\max}}\Big),$$

which when coupled with the constraint $S < \mu_1 T_{\max}$ shows that $T \leq T_{\max}$ for all time $t > 0$, because $T'(t) < 0$ wherever $T(t) = T_{\max}$.

Let m be the maximum value of the function $g(y) := S + ry(1 - y/T_{\max})$, that is $m := S + rT_{\max}/4$. Consider the function

$$H(t) := \int_0^\infty T(t-s)e^{-as}f(s)\,ds + I(t),$$

and observe that

$$\begin{aligned}\frac{dH}{dt} &= \int_0^\infty g(T(t-s))e^{-as}f(s)\,ds - \mu_1\int_0^\infty T(t-s)e^{-as}f(s)\,ds - \mu_2 I(t) - \delta E(t)I(t)\\ &\leq m - \mu H(t),\end{aligned}$$

where $\mu := \min\{\mu_1, \mu_2\}$. From Gronwall's inequality, it follows that

$$H(t) \le H(0)e^{-\mu t} + \int_0^t e^{-\mu t+\mu s} m\, ds \le H(0)e^{-\mu t} + \frac{m}{\mu} \le T_{\max} + I(0) + \frac{m}{\mu} \quad \text{for } t \ge 0.$$

Hence, $H(t)$ is bounded from above by $M := T_{\max} + I(0) + m/\mu$, which in turn implies the upper boundedness of $I(t)$.

From equations (3.8), (3.9), and (3.10), and Gronwall's inequality, one can obtain the following upper bounds for $V_I(t)$, $V_{NI}(t)$, and $E(t)$, respectively, for $t \ge 0$

$$V_I(t) \le V_I(0)e^{-\mu_3 t} + \frac{(1-\eta)bM}{\mu_3}(1 - e^{-\mu_3 t}) \le V_I(0) + \frac{(1-\eta)bM}{\mu_3},$$
$$V_{NI} \le \frac{\eta bM}{\mu_3}(1 - e^{-\mu_3 t}) \le \frac{\eta bM}{\mu_3},$$
$$E(t) \le E(0)e^{-\mu_4 t} + \frac{cM_I}{\mu_4}(1 - e^{-\mu_4 t}) \le E(0) + \frac{cM_I}{\mu_4},$$

where M_I is an upper bound of $I(t)$ on $(-\infty, \infty)$ (possibly greater than M).

For $\eta = 1$, equation (3.8) yields $V_I(t) = V(0)e^{-\mu_3 t}$, which implies V_I is positive and bounded. The positivity and boundedness of the other quantities follow exactly as in the $0 < \eta < 1$ case. □

The notation in the following Gronwall-type lemma are unrelated to the rest of the paper. This result will be used in what follows, but it could be of independent interest.

Lemma 3.3. *Let $y,\ h \in C([a,T), \mathbb{R}_+)$, $g \in C([a,T)\times\mathbb{R}, \mathbb{R}_+)$, and $\alpha,\ \beta \in C([a,T), \mathbb{R})$, where $a \le T \le \infty$. Assume that f is nondecreasing and $\alpha(u) \le \beta(u) \le u$, for all $u \in [a,T)$. Then, the inequality*

$$y(t) \le h(t) + \int_a^t \int_{\alpha(u)}^{\beta(u)} g(u,s)y(s)\, ds\, du, \quad a \le t < T,$$

implies that

$$y(t) \le h(t)e^{\int_a^t \int_{\alpha(u)}^{\beta(u)} g(u,s)\, ds\, du}, \quad a \le t < T.$$

Proof. Define

$$b(t) = h(t) + \int_a^t \int_{\alpha(u)}^{\beta(u)} g(u,s)y(s)\, ds\, du, \quad a \le t < T.$$

Then

$$\frac{b'(t)}{b(t)} \le \frac{h'(t)}{b(t)} + \int_{\alpha(t)}^{\beta(t)} g(t,s)\frac{y(s)}{b(t)}\, ds \le \frac{h'(t)}{h(t)} + \int_{\alpha(t)}^{\beta(t)} g(t,s)\, ds, \quad \forall t \in [a,T),$$

where the last inequality holds because $y(s) \le b(t)$ if $s \le t$. The conclusion of this lemma follows from integration. That is,

$$\int_a^t \frac{b'(u)}{b(u)}\, du \le \int_a^t \frac{h'(u)}{h(u)}\, du + \int_a^t \int_{\alpha(u)}^{\beta(u)} g(u,s)\, ds\, du, \quad \forall t \in [a,T),$$

or

$$\ln b(t) \le \ln h(t) + \int_a^t \int_{\alpha(u)}^{\beta(u)} g(u,s)\, ds\, du, \quad \forall t \in [a,T),$$

which implies

$$y(t) \le b(t) \le h(t)e^{\int_a^t \int_{\alpha(u)}^{\beta(u)} g(u,s)\,ds\,du}, \quad a \le t < T.$$

□

Theorem 3.4. *Let $L(t) := I(t) + V_I(t)$ be the combined population of infected cells $I(t)$ and infectious virus $V_I(t)$. Then,*

$$L(t) \le L(0)e^{(k\int_0^\infty e^{(\nu-a)s}f(s)\,ds-\nu)t}, \quad \text{for all } t \ge 0,$$

where $k := T_{\max}\max\{\beta_1, \beta_2\}$ and $\nu := \min\{\mu_3, \mu_2 - (1-\eta)b\}$.

Proof. Define $L(t) := I(t) + V_I(t)$. Then, from (3.7), (3.8), and $\operatorname{supp}(f) \subseteq [0, A]$ it follows that

$$\frac{dL}{dt} \le k\int_0^A L(t-s)e^{-as}f(s)\,ds - \nu L(t),$$

where $k := T_{\max}\max\{\beta_1, \beta_2\}$ and $\nu := \min\{\mu_3, \mu_2 - (1-\eta)b\}$. Thus,

$$\frac{d}{dt}(e^{\nu t}L) \le ke^{\nu t}\int_0^A L(t-s)e^{-as}f(s)\,ds,$$

and so

$$\begin{aligned} e^{\nu t}L(t) &\le L(0) + \int_0^t ke^{\nu u}\int_0^A L(u-s)e^{-as}f(s)\,ds\,du \\ &= L(0) + \int_0^t \int_{u-A}^u ke^{(\nu-a)(u-s)}f(u-s)e^{\nu s}L(s)\,ds\,du. \end{aligned}$$

From Lemma 3.3 with $y(t) := e^{\nu t}L(t)$, $h(t) := L(0)$, and $g(u,s) := ke^{(\nu-a)(u-s)}f(u-s)$, it follows that

$$e^{\nu t}L(t) \le L(0)e^{\int_0^t \int_{u-A}^u ke^{(\nu-a)(u-s)}f(u-s)\,ds\,du},$$

and so

$$\begin{aligned} L(t) &\le L(0)e^{k\int_0^t \int_{u-A}^u e^{(\nu-a)(u-s)}f(u-s)\,ds\,du - \nu t} \\ &= L(0)e^{k\int_0^t \int_0^\infty e^{(\nu-a)s}f(s)\,ds\,du - \nu t} \\ &= L(0)e^{(k\int_0^\infty e^{(\nu-a)s}f(s)\,ds-\nu)t}, \quad \text{for all } t \ge 0. \end{aligned}$$

□

The following result is an immediate consequence of Theorem 3.4. Essentially, it says that under a certain restriction that involves drug(s) effectiveness η the cumulative population of infected cells $I(t)$ and infectious virus $V_I(t)$ decays to zero exponentially in time. The notations are the same as in Theorem 3.4.

Corollary 3.5. *If $k < \nu \le a$, then $L(t)$ decays exponentially to zero in time.*

Proof. By Theorem 3.4, observe that

$$L(t) \le L(0)e^{(k\int_0^\infty e^{(\nu-a)s}f(s)\,ds-\nu)t} \le L(0)e^{(k\int_0^\infty f(s)\,ds-\nu)t} = L(0)e^{(k-\nu)t},$$

for all $t \ge 0$, where the second inequality above follows from $\nu \le a$. Finally, from $k < \nu$, $L(t)$ converges to 0 exponentially as $t \to \infty$. □

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