A Delay Differential Equation Model of HIV Infection, with Therapy and CTL Response

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Abstract: In this work we investigate a new mathematical model that describes the interactions between CD4⁺ T cells, human immunodeficiency virus (HIV), immune response and therapy with two drugs. Also an intracellular delay is incorporated into the model to express the lag between the time the virus contacts a target cell and the time the cell becomes actively infected. The model dynamics is completely defined by the basic reproduction number R_0 . If $R_0 \leq 1$ the disease-free equilibrium is globally asymptotically stable, and if $R_0 > 1$, two endemic steady states exist, and their local stability depends on value of R_0 . We show that the intracellular delay affects on value of R_0 because a larger intracellular delay can reduce the value of R_0 to below one. Finally, numerical simulations are presented to illustrate our theoretical results.

1 Introduction

Mathematical modeling of HIV infection has provided a lot of understandings of the dynamics of HIV infection [9, 12, 11, 10, 4, 7]. In these papers, the authors considered that once a cell is infected, it immediately becomes productively infected and starts producing virus. But, as mentioned in [3, 17] there are cascade of events which occur between infection of cell with virus and production of virus at cellular level; this leads to time delay in the infection of the cell.

Culshaw et al in [3] simplify the ODE model proposed by Perelson et al. [10] by considering only three components and they 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. They concluded that, according to specific parameters, the stability for the infected steady state is independent of the delays. But, under another set of assumptions on the parameters, the stability of the steady state depends on the delay and even delay-induced oscillations could occur via instability.

Zhu et al in [17] incorporated a fixed discrete delay into the cell infection equation to model, in order to denote the lag between the time the virus contacts a target cell and the time the cell becomes actively infected (including the steps of successful attachment of virus to the cell, and penetration of virus into the cell). The model led to the conclusion that large delays can help eliminate the virus.

In [13], the authors proved that the intracellular delays can cause periodic oscillations through Hopf bifurcations. It is also known that Hopf bifurcations can occur in certain classes of HIV models without intracellular delays, in which the target-cell dynamics have a mitosis component given by a logistic term [14].

In this paper, we consider our model presented in [4] which takes account the cure of infected cells, and we incorporate a discrete time 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 [17]. In our work, we show that the delay can not cause periodic oscillations.

The paper is organized as follows. The mathematical model is described in section 2. Section

3 illustrates some properties of the model's solutions. The model analysis and simulation are given in section 4. Discussion, conclusion and future directions of this research are presented in section 5.

2 Presentation of model

We consider the model presented in [4] by the following system:

$$\begin{cases} \dot{x}(t) = \lambda - dx(t) - (1 - \eta)\beta v_I(t)x(t) + ry(t) \\ \dot{y}(t) = (1 - \eta)\beta v_I(t)x(t) - (a + r)y(t) - py(t)z(t) \\ \dot{v}_I(t) = (1 - \varepsilon)ky(t) - \mu v_I(t) \\ \dot{v}_{NI}(t) = \varepsilon ky(t) - \mu v_{NI}(t) \\ \dot{z}(t) = cy(t)z(t) - bz(t) \end{cases} \quad (1)$$

where the variables are: the concentrations of uninfected CD4+ T-cells (x), infected cells (y), infectious virus (v_I), noninfectious virus (v_{NI}) and CTLs (z).

Uninfected CD4+ T-cells (x) are produced at a rate λ , die at a rate d and become infected by virus at a rate β . Infected cells (y) die at a rate a . Free virus (v_{NI} and v_I) are produced by infected cells at a rate k and cleared at a rate μ . p is the infected cells elimination rate by the CTL response, c is the CTL reproduction rate and b is the CTL death rate. In addition, through therapy, a part of infected cells may also revert to the uninfected state by loss of all cccDNA from their nucleus at a rate r . The parameters ε and η measure the efficacy of reverse transcriptase inhibitor (RTIs) and protease inhibitor (PIs) respectively.

In the model (1), we introduce a time delay between infection of a cell and production of new virus particles, we assume that virus production lags by a delay τ behind the infection of a cell. This implies that recruitment of virus producing cells at time t is not given by the density $(1 - \eta)\beta v_I(t)x(t)$ of newly infected cells, but rather by the density of cells that were newly infected at time $t - \tau$ and are still alive at time t . We assume that the death rate a for infected but not yet virus-producing cells, Therefore, the $-a\tau$ probability of surviving from time $t - \tau$ to time t is $e^{-a\tau}$. Thus, we obtain the following model:

$$\begin{cases} \dot{x}(t) = \lambda - dx(t) - (1 - \eta)\beta v_I(t)x(t) + ry(t) \\ \dot{y}(t) = (1 - \eta)\beta e^{-a\tau} v_I(t - \tau)x(t - \tau) - (a + r)y(t) - py(t)z(t) \\ \dot{v}_I(t) = (1 - \varepsilon)ky(t) - \mu v_I(t) \\ \dot{v}_{NI}(t) = \varepsilon ky(t) - \mu v_{NI}(t) \\ \dot{z}(t) = cy(t)z(t) - bz(t) \end{cases} \quad (2)$$

We put $\theta = \varepsilon + \eta - \varepsilon\eta$, which represents the combined efficacy of the two drugs. Then $1 - \theta = (1 - \varepsilon)(1 - \eta)$ which implies that each drug acts independently.

We define the basic reproduction number R_0 of the model (2) by

$$R_0 = \frac{(1 - \theta)\beta k \lambda e^{-a\tau}}{d\mu(a + r)}$$

Recall that R_0 is defined as the average number of secondary infections produced by one infected cell over its average life time $1/a$ when all cells are uninfected.

2.1 Parameters estimation

Ciupre et al in [2], based on Monte Carlo method, estimated the death rate of infected cells, a , to be between 0.00019 day⁻¹ and 0.711 day⁻¹ and the total number of viral particles produced by an

infected cell during its lifetime, N , was estimated by [2] to be between 160.26 and 591851. Hence the production rate of virus by infected cells, k , is between 0.0304 day^{-1} and $420806.061 \text{ day}^{-1}$, because we have the relation $k = aN$.

The other parameters are given in the following table.

Table 1: Parameters, their symbols and default values used in the model (2)

Parameters	Value	References
λ	$5 - 10 \text{ day}^{-1} \text{mm}^{-3}$	[1, 3, 7, 8, 10, 13, 16, 17]
d	$0.01 - 0.03 \text{ day}^{-1}$	[1, 2, 3, 7, 8, 10, 13, 16, 17]
β	$24.10^{-6} - 48.10^{-4} \text{ mm}^3 \text{day}^{-1}$	[1, 2, 3, 7, 8, 10, 13, 16, 17]
η	$0 - 1$	[7]
ε	$0 - 1$	[7]
r	0.01 day^{-1}	[7]
a	$0.00019 - 0.711 \text{ day}^{-1}$	[1, 2, 3, 7, 8, 10, 13, 16, 17]
k	$0.0304 - 420806.061 \text{ day}^{-1}$	Calculated
μ	$1.8 - 3 \text{ day}^{-1}$	[1, 3, 7, 8, 10, 13, 16, 17]
c	$0.2 \text{ day}^{-1} \text{mm}^3$	[17]
b	$0.1 - 0.3 \text{ day}^{-1}$	[1, 13, 17]
p	$0.01 - 0.05 \text{ day}^{-1} \text{mm}^3$	[1, 13, 17]

3 Properties of solutions

3.1 Positivity and boundedness of solutions

In this section, we establish the positivity and boundedness of solutions of model (2). Since this model describes the evolution of a cell population, the cell densities must remain non-negative and bounded. These properties imply global existence of the solutions.

Let $C = C([-\tau, 0], \mathbb{R}^5)$ be the Banach space of continuous functions mapping the interval $[-\tau, 0]$ into $\mathbb{R}^5$ with the topology of uniform convergence. By the fundamental theory of functional differential equations (see J. Hale et al [6]), it is easy to show that there exists a unique solution $(x(t), y(t), v_I(t), v_{NI}(t), z(t))$ of system (2) with initial data $(x_0, y_0, v_I(0), v_{NI}(0), z_0) \in C$.

In addition, for biological reasons, we assume that the initial data for system (2) satisfy:

$$x_0(s) \geq 0, y_0(s) \geq 0, v_I(0(s)) \geq 0, v_{NI}(0(s)) \geq 0, z_0(s) \geq 0, \text{ for all } s \in [-\tau, 0] \quad (3)$$

Proposition 1

All solutions of system (2) subject to condition (3) remain bounded and non-negative for all $t \in [0, +\infty[$.

Moreover, we have

- i) $T(t) \leq T(0) + \frac{\lambda}{\delta}$
- ii) $v_I(t) \leq v_I(0) + \frac{(1-\varepsilon)k}{\mu} \|y\|_\infty$
- iii) $v_{NI}(t) \leq v_{NI}(0) + \frac{\varepsilon k}{\mu} \|y\|_\infty$

where $T(t) = x(t) + y(t) + \frac{p}{c} z(t) + (1 - \eta)\beta \int_{t-\tau}^t e^{-a(t-s)} x(s)v_I(s)ds$ and $\delta = \min(a, b, d)$

Proof.

From system (2) we have:

$$x(t) = e^{-dt} [x(0)e^{-(1-\eta)\beta \int_0^t v_I(u)du} + \int_0^t (\lambda + ry(s))e^{ds-(1-\eta)\beta \int_s^t v_I(u)du} ds] \quad (4)$$

$$y(t) = y(0)e^{-\int_0^t (a+r+pz(s))ds} + \int_0^t (1-\eta)\beta v_I(w-\tau)x(w-\tau)e^{-a\tau}e^{-\int_w^t (a+r+pz(s))ds} dw \quad (5)$$

$$v_I(t) = v_I(0)e^{-\mu t} + (1-\varepsilon)k \int_0^t y(s)e^{\mu(s-t)} ds \quad (6)$$

$$v_{NI}(t) = v_{NI}(0)e^{-\mu t} + \varepsilon k \int_0^t y(s)e^{\mu(s-t)} ds \quad (7)$$

$$z(t) = z(0)e^{-\int_0^t (b-cy(s))ds} \quad (8)$$

Let $t \in [0, \tau]$, we have $s - \tau \in [-\tau, 0]$ for all $s \in [0, \tau]$. Using (3) and (5), we deduce that $y(t) \geq 0$ for $t \in [0, \tau]$. Consequently we have that $x(t)$, $v_I(t)$, $v_{NI}(t)$, and $z(t)$ are all non negative on the interval $[0, \tau]$. This method can now be repeated to deduce non-negativity of x , y , v_I , v_{NI} , and z on the interval $[\tau, 2\tau]$ and then on successive intervals $[n\tau, (n+1)\tau]$, $n \geq 2$, to include all positive times. This proves the positivity of solutions.

As $\dot{T}(t) = \lambda - dx(t) - ay(t) - \frac{pb}{c}z(t) - a(1-\eta)\beta \int_{t-\tau}^t e^{-a(t-s)}x(s)v_I(s)ds$.

we deduce that $\dot{T}(t) \leq \lambda - \delta T(t)$. ie $T(t) \leq T(0)e^{-\delta t} + \frac{\lambda}{\delta}(1 - e^{-\delta t})$.

Since $0 \leq e^{-\delta t} \leq 1$ and $1 - e^{-\delta t} \leq 1$ thus i) Now we show ii), From relation (6) we deduce $v_I(t) \leq v_I(0)e^{-\mu t} + \frac{(1-\varepsilon)k}{\mu} \|y\|_{\infty} (1 - e^{-\mu t})$.

Since $1 - e^{-\mu t} \leq 1$, and $e^{-\mu t} \leq 1$ we deduce ii).

By the same technique that ii), we show iii).

3.2 Non-periodicity and Limiting Behavior

Proposition 2

Let $V(t) = (x(t), y(t), v_I(t), v_{NI}(t), z(t))$ be a solution of system (2) subject to condition (3), then the limit of $V(t)$ exists when $t \rightarrow +\infty$.

In particular, V is periodic if and only if V is stationary. Moreover, we have:

$$\begin{aligned} \lim_{t \rightarrow +\infty} x(t) &\leq \frac{\lambda}{d} \\ \lim_{t \rightarrow +\infty} y(t) &\leq \frac{\lambda(\lambda - d \lim_{t \rightarrow +\infty} x(t))}{a\lambda + dR_0(a+r)(e^{a\tau} - 1) \lim_{t \rightarrow +\infty} x(t)} \\ \lim_{t \rightarrow +\infty} v_I(t) &= \frac{(1-\varepsilon)k}{\mu} \lim_{t \rightarrow +\infty} y(t) \\ \lim_{t \rightarrow +\infty} v_{NI}(t) &= \frac{\varepsilon k}{\mu} \lim_{t \rightarrow +\infty} y(t) \\ \lim_{t \rightarrow +\infty} z(t) &= \frac{c}{pb} \left(\lambda - d \lim_{t \rightarrow +\infty} x(t) - a \lim_{t \rightarrow +\infty} y(t) - R_0 d(a+r)(e^{a\tau} - 1) \lim_{t \rightarrow +\infty} x(t) \lim_{t \rightarrow +\infty} y(t) \right) \end{aligned}$$

From system(2) we have

$$\dot{y} + ay = \lambda - (\dot{x} + dx) - \frac{p}{c}(\dot{z} + bz) - (\dot{l} + al) \quad (9)$$

with $l(t) = (1 - \eta)\beta \int_{t-\tau}^t e^{-a(t-s)} x(s) v_I(s) ds$. Hence

$$(ye^{at})' = \lambda e^{at} - (xe^{dt})' e^{(a-d)t} - \frac{p}{c}(ze^{bt})' e^{(a-b)t} - (le^{at})'$$

Using the integration by parts, we get

$$\begin{aligned} \int_0^t (x(s)e^{ds})' e^{(a-d)s} ds &= x(t)e^{at} - x(0) - (a-d) \int_0^t x(s)e^{as} ds \\ \int_0^t (z(s)e^{bs})' e^{(a-b)s} ds &= z(t)e^{at} - z(0) - (a-b) \int_0^t z(s)e^{as} ds \end{aligned}$$

hence

$$\begin{aligned} y(t) &= (x_0 + y_0 + \frac{p}{c}z_0 + l(0))e^{-at} + \frac{\lambda}{a}(1 - e^{-at}) - (x(t) + \frac{p}{c}z(t) + l(t)) \\ &\quad + \int_0^t [(a-d)x(s) + \frac{p}{c}(a-b)z(s)]e^{a(s-t)} ds \end{aligned} \quad (10)$$

If $\max(a, b, d) = a$, according to lemma 3.3 (see Yousfi et al [15]), we have

$$\begin{aligned} \limsup_{t \rightarrow +\infty} y(t) &\leq \frac{1}{a}[\lambda - d \limsup_{t \rightarrow +\infty} x(t) - \frac{pb}{c} \limsup_{t \rightarrow +\infty} z(t) - a \limsup_{t \rightarrow +\infty} l(t)] \\ \liminf_{t \rightarrow +\infty} y(t) &\geq \frac{1}{a}[\lambda - d \liminf_{t \rightarrow +\infty} x(t) - \frac{pb}{c} \liminf_{t \rightarrow +\infty} z(t) - a \liminf_{t \rightarrow +\infty} l(t)] \end{aligned}$$

If $\max(a, b, d) = b$, from (9), and using the same technique as in (10), we have

$$\begin{aligned} z(t) &= \frac{c}{p} \left[\left(x(0) + y(0) + \frac{p}{c}z(0) + l(0) \right) e^{-bt} + \frac{\lambda}{b}(1 - e^{-bt}) - \left(x(t) + y(t) + l(t) \right) \right. \\ &\quad \left. + \int_0^t \left((b-d)x(s) + (b-a)y(s) + (b-a)l(s) \right) e^{b(s-t)} ds \right]. \end{aligned} \quad (11)$$

According to lemma 3.3 ([15]), we have

$$\begin{aligned} \limsup_{t \rightarrow +\infty} z(t) &\leq \frac{c}{pb}[\lambda - d \limsup_{t \rightarrow +\infty} x(t) - a \limsup_{t \rightarrow +\infty} y(t) - a \limsup_{t \rightarrow +\infty} l(t)] \\ \liminf_{t \rightarrow +\infty} z(t) &\geq \frac{c}{pb}[\lambda - d \liminf_{t \rightarrow +\infty} x(t) - a \liminf_{t \rightarrow +\infty} y(t) - a \liminf_{t \rightarrow +\infty} l(t)] \end{aligned}$$

If $\max(a, b, d) = d$, from (9), and using the same technique as in (10), we have

$$\begin{aligned} x(t) &= \left(x(0) + y(0) + \frac{p}{c}z(0) + l(0) \right) e^{-dt} + \frac{\lambda}{d}(1 - e^{-dt}) - \left(y(t) + \frac{p}{c}z(t) + l(t) \right) \\ &\quad + \int_0^t \left[(d-a)y(s) + \frac{p}{c}(d-b)z(s) + (d-a)l(s) \right] e^{d(s-t)} ds \end{aligned} \quad (12)$$

According to lemma 3.3 ([15]), we have

$$\begin{aligned} \limsup_{t \rightarrow +\infty} x(t) &\leq \frac{1}{d}[\lambda - a \limsup_{t \rightarrow +\infty} y(t) - \frac{pb}{c} \limsup_{t \rightarrow +\infty} z(t) - a \limsup_{t \rightarrow +\infty} l(t)] \\ \liminf_{t \rightarrow +\infty} x(t) &\geq \frac{1}{d}[\lambda - a \liminf_{t \rightarrow +\infty} y(t) - \frac{pb}{c} \liminf_{t \rightarrow +\infty} z(t) - a \liminf_{t \rightarrow +\infty} l(t)] \end{aligned}$$

So, for every parameters value $a > 0$, $b > 0$ and $d > 0$, we have

$$\begin{aligned}\limsup_{t \rightarrow +\infty} z(t) &\leq \frac{c}{pb} [\lambda - d \limsup_{t \rightarrow +\infty} x(t) - a \limsup_{t \rightarrow +\infty} y(t) - a \limsup_{t \rightarrow +\infty} l(t)] \\ \liminf_{t \rightarrow +\infty} z(t) &\geq \frac{c}{pb} [\lambda - d \liminf_{t \rightarrow +\infty} x(t) - a \liminf_{t \rightarrow +\infty} y(t) - a \liminf_{t \rightarrow +\infty} l(t)]\end{aligned}$$

Hence,

$$\begin{aligned}\limsup_{t \rightarrow +\infty} z(t) - \liminf_{t \rightarrow +\infty} z(t) &\leq \frac{c}{pb} [d(\liminf_{t \rightarrow +\infty} x(t) - \limsup_{t \rightarrow +\infty} x(t)) + a(\liminf_{t \rightarrow +\infty} y(t) - \limsup_{t \rightarrow +\infty} y(t)) \\ &\quad + a(\liminf_{t \rightarrow +\infty} l(t) - \limsup_{t \rightarrow +\infty} l(t))]\end{aligned}$$

Thus,

$$\begin{aligned}\limsup_{t \rightarrow +\infty} x(t) &= \liminf_{t \rightarrow +\infty} x(t) \\ \limsup_{t \rightarrow +\infty} y(t) &= \liminf_{t \rightarrow +\infty} y(t) \\ \limsup_{t \rightarrow +\infty} z(t) &= \liminf_{t \rightarrow +\infty} z(t)\end{aligned}$$

Hence

$$\lim_{t \rightarrow +\infty} x(t) = \frac{1}{d} [\lambda - a \lim_{t \rightarrow +\infty} y(t) - \frac{pb}{c} \lim_{t \rightarrow +\infty} z(t) - a \lim_{t \rightarrow +\infty} l(t)] \quad (13)$$

$$\lim_{t \rightarrow +\infty} z(t) = \frac{c}{pb} \left(\lambda - d \lim_{t \rightarrow +\infty} x(t) - a \lim_{t \rightarrow +\infty} y(t) - a \lim_{t \rightarrow +\infty} l(t) \right) \quad (14)$$

As $y(t) > 0$, $z(t) > 0$, and $l(t) > 0$ for all $t > 0$, (13) implies that

$$\lim_{t \rightarrow +\infty} x(t) \leq \frac{\lambda}{d}.$$

From (6), and using lemma 3.3 ([15]) we have

$$\lim_{t \rightarrow +\infty} v_I(t) = \frac{(1 - \epsilon)k}{\mu} \lim_{t \rightarrow +\infty} y(t).$$

Also from (7), and lemma 3.3 ([15]) we have

$$\lim_{t \rightarrow +\infty} v_{NI}(t) = \frac{\epsilon k}{\mu} \lim_{t \rightarrow +\infty} y(t).$$

From system (2) we have

$$\dot{y} + ay \leq \lambda - (\dot{x} + dx) - (1 - \eta)\beta[-e^{-a\tau} v_I(t - \tau)x(t - \tau) + v_I(t)x(t)].$$

Implies that

$$\dot{y} + ay \leq \lambda - (\dot{x} + dx) - (l + al).$$

Hence

$$y(t) \leq (x(0) + y(0) + l(0))e^{-at} + \frac{\lambda}{a}(1 - e^{-at}) - (x(t) + l(t)) + \int_0^t (a - d)x(s)e^{a(s-t)} ds.$$

Then

$$\lim_{t \rightarrow +\infty} y(t) \leq \frac{\lambda}{a} - \frac{d}{a} \lim_{t \rightarrow +\infty} x(t) - \lim_{t \rightarrow +\infty} l(t). \quad (15)$$

We have

$$l(t) = (1 - \eta)\beta \left[\int_0^t e^{-a(t-s)} x(s) v_I(s) ds - \int_0^{t-\tau} e^{-a(t-s)} x(s) v_I(s) ds \right].$$

Using lemma 3.3 ([15]) and (6) we have

$$\lim_{t \rightarrow +\infty} l(t) = \frac{(1 - \eta)\beta}{a} (1 - e^{-a\tau}) \lim_{t \rightarrow +\infty} x(t) \lim_{t \rightarrow +\infty} v_I(t).$$

This implies

$$\lim_{t \rightarrow +\infty} l(t) = \frac{(1 - \eta)\beta}{a} \frac{(1 - \varepsilon)k}{\mu} (1 - e^{-a\tau}) \lim_{t \rightarrow +\infty} x(t) \lim_{t \rightarrow +\infty} y(t). \quad (16)$$

From (15) and (16) we deduce

$$\lim_{t \rightarrow +\infty} y(t) \leq \frac{\lambda(\lambda - d \lim_{t \rightarrow +\infty} x(t))}{a\lambda + dR_0(a + r)(e^{a\tau} - 1) \lim_{t \rightarrow +\infty} x(t)}.$$

From (14) and (16) we deduce

$$\lim_{t \rightarrow +\infty} z(t) = \frac{c}{pb} \left(\lambda - d \lim_{t \rightarrow +\infty} x(t) - a \lim_{t \rightarrow +\infty} y(t) - R_0 d(a + r)(e^{a\tau} - 1) \lim_{t \rightarrow +\infty} x(t) \lim_{t \rightarrow +\infty} y(t) \right)$$

4 Analysis of the model

In this section we show that there exist three equilibrium points: disease free equilibrium point, endemic equilibrium without immune response, and endemic equilibrium with immune response. We will study the stability of these equilibrium points.

4.1 Equilibrium points

The system (2) always has a disease free equilibrium $E_f = ((\lambda/d), 0, 0, 0, 0)$ level of healthy CD4⁺ T-cells, and two endemic equilibrium points:

$$E_1 = \left(\frac{\lambda}{dR_0}, \frac{\lambda(R_0 - 1)e^{-a\tau}}{a_{r\tau}R_0}, \frac{(a + r)d(R_0 - 1)}{a_{r\tau}\beta(1 - \eta)}, \frac{(a + r)\epsilon d(R_0 - 1)}{a_{r\tau}\beta(1 - \theta)}, 0 \right)$$

$$E_2 = \left(\frac{\lambda}{d} \left(\frac{rb + \lambda c}{c\lambda + R_0 b(a + r)e^{a\tau}} \right), \frac{b}{c}, \frac{(1 - \epsilon)kb}{\mu c}, \frac{\epsilon kb}{\mu c}, \frac{(a + r)}{p} \left(\frac{-c\lambda + R_0(c\lambda + rb) - R_0(a + r)be^{a\tau}}{c\lambda + R_0 b(a + r)e^{a\tau}} \right) \right)$$

where $a_{r\tau} = a_{r\tau} + r - re^{-a\tau}$

From the biological point of view, the point E_1 represents absence of CTL immune response and E_2 represents HIV chronic state of disease with CTL response.

4.2 Stability of free equilibria

Let $E = (x, y, v_I, v_{NI}, z)$ be any arbitrary equilibrium. Then the characteristic equation about E is given by :

$$\begin{vmatrix} -d - (1 - \eta)\beta v_I - \xi & r & -(1 - \eta)\beta x & 0 & 0 \\ (1 - \eta)\beta v_I e^{-(a+\xi)\tau} & -(a + r) - pz - \xi & (1 - \eta)\beta x e^{-(a+\xi)\tau} & 0 & -py \\ 0 & (1 - \epsilon)k & -\mu - \xi & 0 & 0 \\ 0 & \epsilon k & 0 & -\mu - \xi & 0 \\ 0 & cz & 0 & 0 & cy - b - \xi \end{vmatrix} = 0 \quad (17)$$

Here we study the stability of the equilibrium point $E_f = ((\lambda/d), 0, 0, 0, 0)$

Theorem 1

i) If $R_0 \leq 1$, then the disease free equilibrium, E_f , is globally asymptotically stable.

ii) If $R_0 > 1$, then E_f is unstable.

Proof.

We first show i), using proposition 2, we have $\lim_{t \rightarrow +\infty} X(t)$ is finite.

According to Barbalat's lemma, we have: $\lim_{t \rightarrow +\infty} X'(t) = (0, 0, 0, 0, 0)$. Hence $\lim_{t \rightarrow +\infty} X(t) = E_f$ or $\lim_{t \rightarrow +\infty} X(t) = E_1$ or $\lim_{t \rightarrow +\infty} X(t) = E_2$

• If $R_0 < 1$ then E_1 and E_2 do not exist Hence $\lim_{t \rightarrow +\infty} X(t) = E_f$.

• If $R_0 = 1$ then $E_1 = E_f$ and E_2 do not exist Hence $\lim_{t \rightarrow +\infty} X(t) = E_f$.

To show ii), we use the Jacobian matrix of E_f

The characteristic equation corresponding to E_f is given by:

$$\begin{vmatrix} -d - \xi & r & -(1 - \eta)\beta \frac{\lambda}{d} & 0 & 0 \\ 0 & -(a + r) - \xi & (1 - \eta)\beta \frac{\lambda}{d} e^{-(a + \xi)\tau} & 0 & 0 \\ 0 & (1 - \epsilon)k & -\mu - \xi & 0 & 0 \\ 0 & \epsilon k & 0 & -\mu - \xi & 0 \\ 0 & 0 & 0 & 0 & -b - \xi \end{vmatrix} = 0 \quad (18)$$

(18) reduces to

$$(d + \xi)(\mu + \xi)(b + \xi)[\xi^2 + (a + r + \mu)\xi + \mu(a + r)(1 - R_0 e^{-\tau \xi})] = 0$$

The roots $\xi_1 = -d$, $\xi_2 = -\mu$, $\xi_3 = -b$ are negative. On the other hand, it easy to show that the function, $f(\xi) = \xi^2 + (a + r + \mu)\xi + \mu(a + r)(1 - R_0 e^{-\tau \xi})$, has a real positive root when $R_0 > 1$. Because we have $f(0) = (a + r)\mu(1 - R_0) < 0$, if $R_0 > 1$ and $\lim_{\xi \rightarrow +\infty} f(\xi) = +\infty$, and f is increasing and continuous on $[0, +\infty[$. Consequently, f has a positive real root and the disease free equilibrium E_f is unstable if $R_0 > 1$.

Figure 1: Shows the stability of E_f . The parameters are $\varepsilon = 0.2$, $\eta = 0.1$, $\lambda = 10$, $\beta = 0.000024$, $k = 1000$, $a = 0.5$, $r = 0.01$, $d = 0.02$, $\mu = 3$, $c = 0.2$, $b = 0.1$, $p = 0.01$. $\tau = 5$ In this case, $R_0 = 0.4635$ and $E_f(500, 0, 0, 0, 0)$.

4.3 Stability of the equilibrium without immune response

Here we study the existence and stability of the endemic equilibrium point without immune response, E_1 .

In this part, we put $R_1 = \frac{R_0(c\lambda + rb)}{c\lambda + R_0b(a+r)e^{a\tau}}$

Theorem 2

- i) If $R_0 < 1$, then the point E_1 does not exist; and $E_1 = E_f$ when $R_0 = 1$.
- ii) If $R_0 > 1$, and $R_1 < 1$, then E_1 is locally asymptotically stable.
- iii) If $R_1 > 1$, then E_1 is unstable.

Proof.

It easy to verify that if $R_0 < 1$, then the point E_1 does not exists and $E_1 = E_f$ when $R_0 = 1$.

From (17), the characteristic equation corresponding to E_1 reduces to

$$\left[\frac{c\lambda + b(a+r)R_0e^{a\tau}}{a_{r\tau}R_0e^{a\tau}}(R_1 - 1) - \xi \right] \left[\mu + \xi \right] \left[\xi^3 + a_1(\tau)\xi^2 + a_2(\tau)\xi + a_3(\tau) + (b_1(\tau) + b_2(\tau)\xi)e^{-\xi\tau} \right] = 0 \quad (19)$$

where

$$\begin{aligned} a_1(\tau) &= a + r + \mu + d + \frac{(a+r)d(R_0-1)}{a_{r\tau}} \\ a_2(\tau) &= (a+r)\mu + (a+r+\mu)\left[d + \frac{(a+r)d(R_0-1)}{a_{r\tau}}\right] \\ a_3(\tau) &= (a+r)\mu\left[d + \frac{(a+r)d(R_0-1)}{a_{r\tau}}\right] \\ b_1(\tau) &= -(a+r)d\mu\left[\frac{r(R_0-1)e^{-a\tau}}{a_{r\tau}} + 1\right] \\ b_2(\tau) &= -(a+r)\left[\frac{rd(R_0-1)e^{-a\tau}}{a_{r\tau}} + \mu\right] \end{aligned}$$

We have: the eigenvalue $\xi_1 = -\mu$ of (19) is no positive, and the eigenvalue

$\xi_2 = \frac{c\lambda + b(a+r)R_0e^{a\tau}}{a_{r\tau}R_0e^{a\tau}}(R_1 - 1)$ is no positive if $R_1 < 1$. Then the stability of E_1 is determined by the distribution of the roots of equation

$$\xi^3 + a_1(\tau)\xi^2 + a_2(\tau)\xi + a_3(\tau) + (b_1(\tau) + b_2(\tau)\xi)e^{-\xi\tau} = 0 \quad (20)$$

If $\tau = 0$, equation (20) reduces to

$$\xi^3 + c_1\xi^2 + c_2\xi + c_3 = 0 \quad (21)$$

where

$$\begin{aligned} c_1 &= a + r + \mu + dR_0 + \frac{rd(R_0 - 1)}{a} \\ c_2 &= (a + r + \mu)dR_0 + \frac{\mu rd(R_0 - 1)}{a} \\ c_3 &= (a + r)d\mu(R_0 - 1) \end{aligned}$$

Using the same technique as that defined in [7] by K.Hattaf and N.Yousfi, and from the Routh-Hurwitz theorem given in [5], all the roots of equation (21) have negative real parts if $R_0 > 1$.

If $\tau > 0$, equation (20) has infinitely many roots. By Rouché's Theorem and continuity in τ , the sign of the roots of equation (20) will change if it crosses imaginary axis, i.e. if Eqs (20) has purely imaginary. Let $\xi = i\omega$ with $\omega > 0$ be a purely imaginary root of (20). Then,

$$-\omega^3 i - a_1(\tau)\omega^2 + a_2(\tau)i\omega + a_3(\tau) = -(b_1(\tau) + b_2(\tau)i\omega)e^{-i\omega\tau}$$

Taking the modulus in the above equation and grouping in terms of the powers of ω , we obtain the following equation

$$\omega^6 + [a_1^2(\tau) - 2a_2(\tau)]\omega^4 + [a_2^2(\tau) - 2a_1(\tau)a_3(\tau) - b_2^2(\tau)]\omega^2 + a_3^2(\tau) - b_1^2(\tau) = 0 \quad (22)$$

where

$$\begin{aligned} a_1^2(\tau) - 2a_2(\tau) &= (a + r)^2 + \mu^2 + d^2\left(1 + \frac{(a + r)(R_0 - 1)}{a_{r\tau}}\right)^2 > 0 \\ a_2^2(\tau) - 2a_1(\tau)a_3(\tau) - b_2^2(\tau) &= \frac{(a + r)^2 d}{a_{r\tau}^2} \left[2a_{r\tau} r d \mu (R_0 - 1) e^{-a\tau} + (a^2 + \mu^2 + 2ar) R_0^2 \right. \\ &\quad \left. + r^2 [R_0 + (R_0 - 1)e^{-a\tau}] [R_0(1 - e^{-a\tau}) + e^{-a\tau}] \right] > 0 \\ a_3^2(\tau) - b_1^2(\tau) &= (a_3(\tau) - b_1(\tau))(a + r)d\mu(R_0 - 1) > 0 \end{aligned}$$

Let $X = \omega^2$ then (22) becomes

$$F(X) = X^3 + [a_1^2(\tau) - 2a_2(\tau)]X^2 + [a_2^2(\tau) - 2a_1(\tau)a_3(\tau) - b_1^2(\tau)]X + a_3^2(\tau) - b_1^2(\tau) = 0. \quad (23)$$

The function F is increasing in $X \in [0, +\infty[$ with

$$F(0) = (a+r)^2 d^2 \mu^2 (R_0 - 1) \left[2 + \left(\frac{R_0 - 1}{a_{r\tau}} \right) (a + r + r e^{-a\tau}) \right] > 0.$$

Then (23) has no positive solutions if $R_0 > 1$. Therefore, there is no root $\xi = i\omega$, with $\omega > 0$ for (20), implying that the roots of (20) can not cross the purely imaginary axis. Thus all roots of (20) have a negative real parts provided $R_0 > 1$. Then E_1 is locally asymptotically stable. If $R_1 > 1$, the eigenvalue ξ_2 is not negative, then E_1 is unstable.

Figure 2: Shows the stability of E_1 . The parameters are $\varepsilon = 0.2$, $\eta = 0.1$, $\lambda = 10$, $\beta = 0.000024$, $k = 1000$, $a = 0.5$, $r = 0.01$, $d = 0.02$, $\mu = 3$, $c = 0.2$, $b = 0.1$, $p = 0.01$. $\tau = 3.3$ In this case, $R_0 = 1.0845$, and $R_1 = 0.9485$, and $E_1 (461.0347, 0.2946, 78.5524, 19.6381, 0)$

4.4 Stability of the equilibrium with immune response

Here we study the existence and stability of the endemic equilibrium point with immune response, E_2 . We can write E_2 by

$$E_2 = \left(\frac{\lambda}{d} \left(\frac{R_1}{R_0} \right), \frac{b}{c}, \frac{(1-\epsilon)kb}{\mu c}, \frac{\epsilon kb}{\mu c}, \frac{a+r}{p} (R_1 - 1) \right) \quad (23)$$

It's clear that if $R_1 < 1$, the point E_2 does not exist and $E_2 = E_1$ when $R_1 = 1$. We seek what will happen for the point E_2 if $R_1 > 1$.

From (17), the characteristic equation corresponding to E_2 reduces to

$$\left[\mu + \xi \right] \left[\xi^4 + \tilde{a}_1(\tau)\xi^3 + \tilde{a}_2(\tau)\xi^2 + \tilde{a}_3(\tau)\xi + \tilde{a}_4(\tau) + \xi(\tilde{b}_1(\tau)\xi + \tilde{b}_2(\tau))e^{-\xi\tau} \right] = 0 \quad (24)$$

as the eigenvalue $\xi_1 = -\mu$ of (24) is negative, then the stability of E_2 is determined by the distribution of the roots of equation

$$\left[\xi^4 + \tilde{a}_1(\tau)\xi^3 + \tilde{a}_2(\tau)\xi^2 + \tilde{a}_3(\tau)\xi + \tilde{a}_4(\tau) + \xi(\tilde{b}_1(\tau)\xi + \tilde{b}_2(\tau))e^{-\xi\tau} \right] = 0 \quad (25)$$

where

$$\begin{aligned}
 \tilde{a}_1(\tau) &= \mu + \frac{dM}{c\lambda} + (a+r)R_1 \\
 \tilde{a}_2(\tau) &= \frac{d(a+r)(R_1M)}{c\lambda} + \mu\left[\frac{dM}{c\lambda} + (a+r)R_1\right] + b(a+r)(R_1-1) \\
 \tilde{a}_3(\tau) &= \frac{d\mu(a+r)(R_1M)}{c\lambda} + b(a+r)(R_1-1)\left[\frac{dM}{c\lambda} + \mu\right] \\
 \tilde{a}_4(\tau) &= \frac{db\mu(a+r)M(R_1-1)}{c\lambda} \\
 \tilde{b}_1(\tau) &= -((a+r)\mu R_1 + \frac{dbr(a+r)R_0}{c\lambda}) \\
 \tilde{b}_2(\tau) &= -\frac{(a+r)d\mu}{c\lambda}[brR_0 + c\lambda R_1]
 \end{aligned}$$

and $M = c\lambda + R_0b(a+r)e^{ar}$.

If $\tau = 0$, equation (25) reduces to

$$\xi_4 + c\tilde{1}\xi_3 + c\tilde{2}\xi_2 + c\tilde{3}\xi + c\tilde{4} = 0 \quad (26)$$

where the coefficients $c\tilde{i}$ are obtained from the previous coefficients $\tilde{a}_i(\tau)$ and $\tilde{b}_i(\tau)$ by replacing τ by 0.

We have already shown in [4], where there is no delay ($\tau = 0$), that the roots of equation (26) have negative real parts when $R_1 > 1$. Consequently E_2 is locally asymptotically stable when $R_1 > 1$, and $\tau = 0$.

If $\tau > 0$, the equation (25) has infinitely many roots. By Rouché's Theorem and continuity in τ , the sign of the roots of equation (25) will change if it crosses imaginary axis, i.e. if Eqs (25) has purely imaginary root. Hence, we put $\xi = i\psi$ a purely imaginary root of (25), with $\psi > 0$, and separate the real and imaginary parts, we have

$$\psi^4 - \tilde{a}_2\psi^2 + \tilde{a}_4 = -\tilde{b}_1\psi^2 \cos(\tau\psi) - \tilde{b}_2\psi \sin(\tau\psi) \quad (27)$$

$$-\tilde{a}_1\psi^3 + \tilde{a}_3\psi = -\tilde{b}_2\psi \cos(\tau\psi) + \tilde{b}_1\psi^2 \sin(\tau\psi) \quad (28)$$

where the $\tilde{a}_i$ and $\tilde{b}_i$ are the previous $\tilde{a}_i(\tau)$ and $\tilde{b}_i(\tau)$.

Squaring and adding Eqs (27) and (28), we have

$$\psi^8 + e_1\psi^6 + e_2\psi^4 + e_3\psi^2 + e_4 = 0 \quad (29)$$

where

$$\begin{aligned}
 e_1 &= \tilde{a}_1^2 - 2\tilde{a}_2 \\
 e_2 &= \tilde{a}_2^2 + 2\tilde{a}_4 - 2\tilde{a}_1\tilde{a}_3 - \tilde{b}_1^2 \\
 e_3 &= \tilde{a}_3^2 - 2\tilde{a}_2\tilde{a}_4 - \tilde{b}_2^2 \\
 e_4 &= \tilde{a}_4^2
 \end{aligned}$$

Let $Y = \psi^2$ then (29) becomes

$$G(Y) = Y^4 + e_1Y^3 + e_2Y^2 + e_3Y + e_4 = 0. \quad (30)$$

The first and second derivative of function G are respectively

and $G''(Y) = 12Y^2 + 6e_1Y + 2e_2$ the minimum value of G'' is $G''(\frac{-6e_1}{24}) = 3e_1Y^2 + 2e_2Y + e_3$

$$\begin{aligned}
 G''(\frac{-6e_1}{24}) &= \frac{-3}{4}e_1^2 + 2e_2 \\
 &= \frac{-3}{4}\tilde{a}_1^4 - \tilde{a}_2^2 - 3\tilde{a}_1^2\tilde{a}_2 + 4\tilde{a}_4 - 4\tilde{a}_1\tilde{a}_3 - 2\tilde{b}_1^2 \\
 &= \frac{-3}{4}\tilde{a}_1^4 - \tilde{a}_2^2 - 3\tilde{a}_1^2\tilde{a}_2 - 4\mu\left[\frac{d\mu(a+r)(R_1M)}{c\lambda} + b(a+r)\mu(R_1-1)\right] \\
 &\quad - 4\left[\frac{dM}{c\lambda} + (a+r)R_1\right]\tilde{a}_3 - 2\tilde{b}_1^2.
 \end{aligned}$$

Then, in case where $R_1 > 1$, we have $G''(\frac{-6e_1}{24}) < 0$, because all $a_i > 0$ for $i \in \{1, 2, 3, 4\}$. Hence, since G'' is a polynomial of degree 2 and $\lim_{Y \rightarrow +\infty} G''(Y) = +\infty$ and $\lim_{Y \rightarrow -\infty} G''(Y) = +\infty$, the equation $G''(Y) = 0$ has exactly two real solutions, that are $\alpha_1 = \frac{-3e_1 - \sqrt{9e_1^2 - 24e_2}}{6}$ and $\alpha_2 = \frac{-3e_1 + \sqrt{9e_1^2 - 24e_2}}{6}$. We have $\alpha_1 < \alpha_2 < 0$, then $G''(Y) > 0$ on $\mathbb{R}^+$. Hence G' is increasing on $\mathbb{R}^+$. And $G'(0) = e_3 > 0$ because

$$\begin{aligned} e_3 = & (b(a+r)(R_1-1)[\mu - \frac{dM}{c\lambda}]^2 + 2(d\mu^2(a+r)^2)\frac{dM}{c\lambda}R_1(R_0-R_1) + 2(d\mu(a+r))^2R_1(R_0-R_1) \\ & + 2b(a+r)\mu(R_1-1)\frac{dM}{c\lambda}(\frac{1}{2} - \frac{dM}{c\lambda}\mu)^2 \\ & + \frac{1}{2}b(a+r)\mu(R_1-1)\frac{dM}{c\lambda} \end{aligned}$$

and $R_0 > R_1 > 1$.

Then $G(Y) > 0$, therefore the function G is increasing on $\mathbb{R}^+$. Since $G(0) = e_4 > 0$, the equation (30) admits no solutions in $\mathbb{R}^+$. Thus, all roots of (25) have a negative real parts provided $R_1 > 1$. Then, E_2 is locally asymptotically stable. Thus, in the case where $R_1 > 1$, we have the following theorem.

Theorem 3

If $R_1 > 1$, then E_2 is locally asymptotically stable for all $\tau > 0$.

Figure 3: Shows the stability of E_2 . The parameters are $\varepsilon = 0.1$, $\eta = 0.2$, $\lambda = 10$, $\beta = 0.000024$, $k = 1000$, $a = 0.5$, $r = 0.01$, $d = 0.02$, $\mu = 3$, $c = 0.2$, $b = 0.1$, $p = 0.01$. $\tau = 1.5$ In this case, $R_0 = 2.6675$, and $R_1 = 2.3329$, and $E_2 (437.2815, 0.5, 133.3333, 33.3333, 67.9769)$

5 Discussion and Conclusion

In this work, we gave a new mathematical model that describes HIV infection of CD4+ T-cells and immune response with intracellular delay and therapy with two drugs.

We conclude that to control the concentrations of the virus, a strategy should aim to reduce the value of R_0 to below one. By the explicit formula for $R_0 = \frac{(1-\theta)\lambda\beta k e^{-a\tau}}{(a+r)d\mu}$, we see that R_0 can be decreased by increasing the efficacy of PIs and RTIs.

Also the intracellular delay plays a positive role in preventing the virus, because with all other parameters fixed, larger τ can bring R_0 to a level lower than 1, making the infection free equilibrium point globally asymptotically stable (see figure (4)).

Figure (5) gives the following results:

R_0 decreases in τ and $R_0(\infty) = 0$.

If $\tau \in [0, 3.1942[$, then $R_0 > 1$ and $R_1 > 1$, and E_2 exist and locally asymptotically stable.

If $\tau \in]3.1942, 3.4629[$, then $R_0 > 1$ and $R_1 < 1$, and E_1 exist and locally asymptotically stable.

If $\tau \in [3.4629, +\infty[$, then $R_0 \leq 1$, and E_f exist and globally asymptotically stable.

Figure 4: HIV population cell with and without intracellular delay. The parameters are $\varepsilon = 0.3$, $\eta = 0.35$, $\lambda = 10$, $\beta = 0.000024$, $k = 1000$, $a = 0.26$, $r = 0.01$, $d = 0.02$, $\mu = 3$, $c = 0.2$, $b = 0.1$, $p = 0.01$. In this case, the value of delay is $\tau = 7.5$

Figure 5: Gives R_0 and R_1 as a function of the delay τ . The parameters are $\varepsilon = 0.1$, $\eta = 0.2$, $\lambda = 10$, $\beta = 0.000024$, $k = 1000$, $a = 0.5$, $r = 0.01$, $d = 0.02$, $\mu = 3$, $c = 0.2$, $b = 0.1$, $p = 0.01$.

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