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Mathematical model describing HIV infection with time-delayed CD4 T-cell activation

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Version April 26, 2020 submitted to Journal Not Specified

Abstract: A mathematical model, composed of two non-linear differential equations that describe the population dynamics of CD4 T cells in the human immune system, as well as viral HIV particles, is proposed. The invariance region is determined, classical equilibria stability analysis is performed using the basic reproduction number, and numerical simulations are carried out, in order to illustrate stability results. Later, the model is modified with a delay term, which describes the time that cells require for immunological activation. This generates a two-dimensional integro-differential system, which is transformed into a system with three ordinary differential equations, via auxiliary variable use. For the new model, equilibrium points are determined, their local stability is examined, and results are studied by way of numerical simulation.

Keywords: Mathematical model; delay differential equations; HIV; immune system

1. Introduction

Acquired Immunodeficiency Syndrome (AIDS) represents a risk for a large part of the world population because it not only affects the person with the virus, but also, indirectly, their family and friends. Historically, AIDS has been among the most significant public health problems worldwide, owing to the number people it has infected and the deaths which it has caused. It additionally constitutes a social problem, as it has inhibited poverty reduction efforts. Since its emergence in the 1980s, AIDS has generated considerable challenges for the scientific community, which include comprehension of its dynamics and the search for a definitive cure [5,12,36].

AIDS is a group of clinical symptoms which are produced as a result of the destruction of the immune system, caused by the Human Immunodeficiency Virus (HIV). This virus makes it impossible for the body to defend itself, and as such, facilitates the emergence of opportunistic illnesses. For this reason, AIDS and HIV have caused a considerable number of human deaths, primarily in regions which have inadequate prevention mechanisms [13,36]. UNAIDS reports in 2018 the estimated number of people (all ages) living with HIV in 37.9 million [32.7 - 44.0], of which 23.3 million people were receiving antiretroviral treatment by end 2018, equivalent to 62 % of people living with HIV. However, it is worrying that 1.7 million [1.4 - 2.3] new cases are reported, implying a rate of 0.24 [0.18 - 0.31] new HIV infections (per 1000 uninfected population) [29].

To date, no cure has been found for HIV infection, which lends relevance to the development of strategies which impede the virus' dispersion. Without doubt, the greatest risk of infection stems from sexual intercourse. However, other contagion factors exist, including blood transfusions, inadequate use of surgical materials (needles, scalpels, etc.) and vertical transmission (from mother to child) [30].

In order to briefly explain the dynamics of the HIV virus on a cellular level, it must be mentioned that infection begins when the virus crosses the body's physical barriers and is detected by dendritic cells (leucocytes that play an important role in the body's immunity) and macrophages, which are antigen-producing cells (antigens are substances that unchain the antibody formation and may cause an immune response). Once the virus is identified, CD4 T cells come into play. These specialize in recognizing viral proteins and are tasked with activating humoral and cellular immune responses to fight the infection. It is precisely the CD4 T cells that are the virus' main target, as those which become infected lose the ability to recognize vital proteins. This, together with the virus' high replication rate and its evasion strategies (use of reservoirs, sanctuaries, or dormant states) cause the body to gradually lose its ability to control the HIV infection [1].

A wide variety of mathematical models have been formulated to study HIV infection at the cellular level [2,3,18,20,21,23,24,26,28,31–35,37,38,40,46–48] as well as its spread in susceptible populations [7,10,22,39,44,45]. Such models approach the study of infection from different perspectives, and have made it possible to evaluate the effect that preventive measures or prophylaxis and diagnosis may have in reducing transmission [10,11,17,39,41,43], the effectiveness of antiretrovirals in controlling viral loads, in this case, optimal control models have been very important tools [20,23,31,41–44,46]. Finally, any study must begin from the knowledge of the virus and how it interacts with the host's immune system, in particular, a more relevant topic is latent infection in people who are unaware of its serological status. One of the reasons for the slow development of the infection in people carrying the virus is the state of latency in which a proportion of the infected cells is found; in deed this cell population consists of resting T cells that have not been immunologically activated, different from the activated T cells, also known as helper T-lymphocytes. The importance of this distinction is that HIV infects resting lymphocytes, but only 1 % actively replicate viruses, which indicates that, in 99 % the proviral genome is housed and dormant [1–3,26–28,31,32,35,47,48]. Considering the above, and with the objective of studying CD4 T cell interaction with viral HIV particles, two mathematical models, based on ordinary differential equations, are proposed here, and will be studied from a qualitative perspective. First, the dynamics of HIV infection at the cellular level are addressed, without considering immunological activation, which implies that it is assumed that viral replication begins immediately after infection of the cell; later, these results are compared with those of a second model, incorporating a delay time, that does consider immunological activation as a determining factor in the dynamics of cell–to–cell infection with HIV. Although the results obtained do not constitute a definitive solution to the problem, they do contribute theoretically to its comprehension.

The stability analysis of the model allows concluding conditions on the parameters that would guarantee the reduction of the viral load to undetectable levels, fundamentally reducing the value of the basic number of reproduction R_0. This reduction can be achieved with adequate antiretroviral therapy strategies. Additionally, it is illustrated that under certain parameter values the system may present Hopf bifurcation, which implies the alternation, sustained over time, of very high and very low levels of viremia in the host, significantly affecting their quality of life. These cyclical scenarios should be avoided, and in this sense, the results of this work studies one of the parameters of the model that relates cyclical behavior to the rate of cellular activation.

2. Basic model

2.1. Basic model formulation

The formulation of this model is based on predator-prey dynamics, supposing that an increase in the number of viral particles depends on the number of infected T cells that later die. This is a legitimate consideration due to the virus' high replication rate. The assumption is made that infected cells are instantly activated, and are producers of viral particles, which are simplifications that have been considered in studies including [23,34]. However, in Section 3, this assumption is weakened

Table 1. Description of state variables, initial conditions, and parameters used in the basic model simulation (1), with its respective reference.

	Description of state variables	*Initial conditions*	*Reference*
T	Uninfected CD4 T cell concentration at an initial time	1000 mm^{-3}	–
V	Infectious viral load at an initial time	1 mm^{-3}	–
	Parameter description	*Value*	*Reference*
σ	Constant CD4 T cell production	10 $mm^{-3}d^{-1}$	[9,31,37]
α	Uninfected cell proliferation rate	0.03 d^{-1}	[8,33]
μ	Uninfected CD4 T cell natural death rate	0.01d^{-1}	[9,31,37]
N	Number of viral particles produced per infected cell	1000	[9]
c	Natural virus elimination rate	2.4 d^{-1}	[31,33]
k	CD4 T cell load capacity	1500 mm^{-3}	[8,33]
γ	Infected CD4 T cell death rate	0.26 d^{-1}	[8,31]
β	Rate of effective contact between CD4 T cells and virus	6×10^{-6} and 4×10^{-5} mm^3d^{-1}	[8,23,31,33]

when delay time, which describes the time that cells require to activate (wait time which implies a delay in the onset of viral replication), is included.

Let $T = T(t)$ be the average number of CD4 T cells in t time and $V = V(t)$ be the average concentration of viral particles in t time. The constant rate of CD4 T cell liberation is indicated by σ and μ represents the rate of natural death. Additionally, the fact that that the proliferation of CD4 T cells in response to the infection follows the logistic law of growth is considered, where $\alpha > 0$ is the proliferation rate and k is the load capacity. In general, $\alpha > \mu$ [8]. With β the rate of T cell infection with the free virus is indicated, such that the βTV expression represents the average number of infected cells created in t time. Thus, the differential equation for the T cell population susceptible to infection is:

$$\dot{T} = \sigma + \alpha T\left(1 - \frac{T}{k}\right) - \beta TV - \mu T.$$

A simplification considered in studies including [20,23,24] and which consists of excluding an explicit state variable for the infected cell population, will be considered. Thus, in each t instant, an average of βTV cells become infected. The constant death rate of infected cells, owing to causes associated with viral replication, is indicated by γ and it is assumed that the number of infected cells that die in t instant is proportional to those which are created. As such, thus the average number of infected cells that die in each t instant is $\gamma(\beta TV)$. That said, if each infected cell produces N viral particles during its infectious period, the expression $N(\gamma\beta TV)$ represents the average number of viral particles produced in t instant. If $\eta = N\gamma\beta$, then ηTV determines the number of free viral particles produced in t time. This η parameter is comparable to the rate of biomass utilization (growth) seen in predator-prey models. Finally, it is assumed that viral particles are eliminated at proportionality rate c and so, the model takes the following form:

$$\begin{cases} \dot{T} = \sigma + \alpha T\left(1 - \frac{T}{k}\right) - \beta TV - \mu T \\ \dot{V} = \eta TV - cV. \end{cases} \tag{1}$$

Where parameters σ, α, k, β, μ, η and c are positive and have non-negative initial conditions $T(0) = T_0$ and $V(0) = V_0$. Table 1 contains a description of state variables and model parameters.

Now that the model has been described, a Proposition corresponding to the invariance region is enunciated and demonstrated; it corresponds to a set of biological interest, where the solutions are bounded and also preserve their positivity over time.

Proposition 1. *If initial conditions T_0 and V_0 are non-negative, then the solutions to System (1) are limited to the positively invariant region given by:*

$$\Omega = \left\{ (T,V) \in \mathbb{R}^2 \mid 0 \leq T \leq k, 0 \leq V \leq \frac{M\eta}{c\beta} \right\}$$

with $M = 2\sigma + \frac{k\alpha}{4} + ck$.

Proof. This demonstration was carried out considering procedures similar to those carried out in [4] and [33], which suggest certain restrictions on the parameters, in order to ensure that the model provides a realistic population dynamic. Thus, it is assumed that $k > \frac{\sigma}{\mu}$ such that the death rate at k is greater than the growth rate. Were this not the case, the population could grow beyond k. Considering this, the first equation in System (1) becomes:

$$\begin{aligned} \dot{T} &= \sigma - \mu T + \alpha T \left(1 - \tfrac{T}{k}\right) - \beta T V \\ &\leq \sigma - \mu T + \alpha T \left(1 - \tfrac{T}{k}\right). \end{aligned}$$

As such, in $T = k$,

$$\dot{T} \leq \sigma - \mu k < 0.$$

So, in the case of HIV infection, the T cell population is limited by k. Further, by defining function

$$\omega(t) = T(t) + \frac{\beta}{\eta} V(t),$$

and calculating the derivative of ω with respect to time along System (1), the following is obtained:

$$\begin{aligned} \dot{\omega} &= \dot{T} + \tfrac{\beta}{\eta}\dot{V} \\ &= \sigma + \alpha T \left(1 - \tfrac{T}{k}\right) - \left(\mu T + \tfrac{\beta}{\eta} c V\right) \\ &\leq V\sigma + \alpha T \left(1 - \tfrac{T}{k}\right). \end{aligned}$$

As the maximum value of the quadratic expression $\sigma + \alpha T \left(1 - \frac{T}{k}\right)$ is $\sigma + \frac{\alpha}{4}k$ when $0 < T \leq k$,

$$\begin{aligned} \dot{\omega} + c\omega &= \sigma + \alpha T \left(1 - \tfrac{T}{k}\right) - \mu T - \tfrac{\beta}{\eta} c V + c\left(T + \tfrac{\beta}{\eta} V\right) \\ &= \sigma + \alpha T \left(1 - \tfrac{T}{k}\right) + cT - \mu T \\ &\leq \sigma + \alpha T \left(1 - \tfrac{T}{k}\right) + cT \\ &\leq 2\sigma + \tfrac{k\alpha}{4} + ck = M. \end{aligned}$$

Then, $0 \leq \dot{\omega} + c\omega \leq M$ and so, $c\omega \leq M$. Thus,

$$\begin{aligned} \omega \leq \tfrac{M}{c} &\Leftrightarrow T + \tfrac{\beta}{\eta} V \leq \tfrac{M}{c} \\ &\Leftrightarrow \tfrac{\beta}{\eta} V \leq \tfrac{M}{c} \\ &\Leftrightarrow V \leq \tfrac{M\eta}{c\beta}. \end{aligned}$$

As such, $V \to \frac{M\eta}{c\beta}$, when $t \to \infty$. In other words, the solutions to System (1) are limited to the positively invariant region Ω. □

2.2. Basic model stability analysis

2.2.1. Trivial equilibrium point

It is now intended to qualitatively study the system (1) , that is, without the explicit knowledge of its solutions, determine the behavior of these solutions after a long time. To do so, it is necessary to

determine the equilibrium solutions or stationary solutions (which do not change over time), which requires solving the algebraic system (2).

$$\begin{cases} \sigma + \alpha T(1 - \frac{T}{k}) - \beta TV - \mu T = 0 \\ \eta TV - cV = 0. \end{cases} \tag{2}$$

Its trivial solutions are given by $E_0^+ = (\overline{T}_0, 0)$ and $E_0^- = (T_0^-, 0)$ which correspond to the absence of infection, in which:

$$\overline{T}_0 = \frac{k\mu}{2\alpha}\left[(\xi_0 - 1) + \sqrt{(\xi_0 - 1)^2 + \frac{4\alpha\sigma}{k\mu^2}}\right]$$

and,

$$T_0^- = \frac{k\mu}{2\alpha}\left[(\xi_0 - 1) - \sqrt{(\xi_0 - 1)^2 + \frac{4\alpha\sigma}{k\mu^2}}\right]$$

with $\xi_0 = \frac{\alpha}{\mu}$.

So far trivial equilibrium solutions have been found, later non-trivial solutions are discussed. It is now necessary to establish conditions that guarantee the biological meaning or ecological coherence of this trivial equilibrium solutions, which is done in Propositions 2 and 3, stated and demonstrated below.

Proposition 2. *Equilibrium point* $E_0^+ = (\overline{T}_0, 0)$ *makes biological sense, i.e.,* $\overline{T}_0 > 0$.

Proof. Taking into account that all considered parameters are positive, the $4k\alpha\sigma > 0$ expression is valid. Then,

$$\begin{aligned} 4k\alpha\sigma > 0 \quad &\Leftrightarrow \quad (k\alpha - k\mu)^2 + 4k\alpha\sigma > (k\alpha - k\mu)^2 \\ &\Leftrightarrow \quad \sqrt{(k\alpha - k\mu)^2 + 4k\alpha\sigma} > k\mu - k\alpha \\ &\Leftrightarrow \quad k\alpha - k\mu + \sqrt{(k\alpha - k\mu)^2 + 4k\alpha\sigma} > 0 \\ &\Leftrightarrow \quad k\mu\left[\frac{\alpha}{\mu} - 1 + \frac{\sqrt{k^2\mu^2\left(\frac{\alpha}{\mu} - 1\right)^2 + 4k\alpha\sigma}}{k\mu}\right] > 0 \\ &\Leftrightarrow \quad \frac{k\mu}{2\alpha}\left[(\xi_0 - 1) + \sqrt{(\xi_0 - 1)^2 + \frac{4\alpha\sigma}{k\mu^2}}\right] > 0. \end{aligned}$$

As such, $\overline{T}_0 > 0$. □

Proposition 3. *Equilibrium point* $E_0^- = (T_0^-, 0)$ *does not make biological sense, or* $T_0^- < 0$.

Proof. Taking into account that all considered parameters are positive, $\frac{4\alpha\sigma}{k\mu^2} > 0$ is satisfied. Then,

$$\begin{aligned} \frac{4\alpha\sigma}{k\mu^2} > 0 \quad &\Leftrightarrow \quad (\xi_0 - 1)^2 + \frac{4\alpha\sigma}{k\mu^2} > (\xi_0 - 1)^2 \\ &\Leftrightarrow \quad \sqrt{(\xi_0 - 1)^2 + \frac{4\alpha\sigma}{k\mu^2}} > (\xi_0 - 1) \\ &\Leftrightarrow \quad 0 > (\xi_0 - 1) - \sqrt{(\xi_0 - 1)^2 + \frac{4\alpha\sigma}{k\mu^2}} \\ &\Leftrightarrow \quad 0 > \frac{k\mu}{2\alpha}\left[(\xi_0 - 1) - \sqrt{(\xi_0 - 1)^2 + \frac{4\alpha\sigma}{k\mu^2}}\right]. \end{aligned}$$

As such, $T_0^- < 0$. □

It is important to investigate the conditions under which the infection enters and establishes in the individual, i.e., the conditions which promote continued infection. This information is obtained

through analysis of the *basic reproduction number* denoted by R_0. Theoretically, if $R_0 < 1$ the infection is eliminated, but if $R_0 > 1$ an epidemic outbreak occurs, which leads to a viral attack. Thus, the R_0 acts as a threshold which determines the conditions with no risk of outbreak. The R_0 is tied both to the strength of the means of viral infection transmission and the duration of epidemiological periods. As such, it is defined as the average number of secondary infections caused by a single infected CD4 T cell in a population of entirely susceptible CD4 T cells throughout its infectious period [21,38,40,46].

In order to determine the R_0, consider that an entirely susceptible population of cells is introduced to a small initial virus load ($V > 0$). The conditions under which said virus concentration increases, or equivalently $\dot{V} > 0$, must then be determined. The second equation in (1) which $\eta TV - cV > 0$ is presented, and so,

$$\begin{aligned} V(\eta T - c) > 0 \quad &\Leftrightarrow \quad \eta T - c > 0 \\ &\Leftrightarrow \quad \frac{\eta T}{c} > 1. \end{aligned}$$

Considering that,

$$\overline{T}_0 = \frac{k\mu}{2\alpha}\left[(\xi_0 - 1) + \sqrt{(\xi_0 - 1)^2 + \frac{4\alpha\sigma}{k\mu^2}}\right]$$

is the susceptible cell population in the absence of infection, and which additionally $\eta = N\beta\gamma$, R_0 is defined as

$$R_0 = \frac{N\beta\gamma}{c}\overline{T}_0. \tag{3}$$

In order to study the stability of the E_0^+ trivial equilibrium point, one begins by linearizing System (1) by determining the jacobian matrix, given by:

$$\mathbf{A}(T,V) = \begin{pmatrix} \alpha - \frac{2\alpha T}{k} - \beta V - \mu & -\beta T \\ \eta V & c\left(\frac{\eta}{c}T - 1\right) \end{pmatrix}. \tag{4}$$

Matrix (4) is evaluated at E_0^+, and the sign of the real part of its eigenvalues is analyzed, as shown in the next proposition.

Proposition 4. *The E_0^+ trivial equilibrium in System (1) is local and asymptotically stable if and only if $R_0 < 1$.*

Proof. Evaluation of Jacobian matrix (4) in the equilibrium free of infection $E_0^+ = (\overline{T}_0, 0)$ results in the following:

$$\mathbf{A_0} = \mathbf{A}(E_0^+) = \begin{pmatrix} \alpha - \mu - \frac{2\alpha\overline{T}_0}{k} & -\beta\overline{T}_0 \\ 0 & c\left(\frac{\eta}{c}\overline{T}_0 - 1\right) \end{pmatrix}.$$

As $\mathbf{A_0}$ is a superior triangular matrix, its eigenvalues are:

$$\lambda_1 = \alpha - \mu - \frac{2\alpha\overline{T}_0}{k}$$

$$\lambda_2 = c\left(\frac{\eta}{c}\overline{T}_0 - 1\right).$$

Firstly, $\lambda_1 < 0$ will be demonstrated, based on the equivalence of the following inequalities

$$\begin{aligned}
\frac{\sqrt{(k\alpha-k\mu)^2+4k\alpha\sigma}}{k\alpha} > 0 \quad &\Leftrightarrow \quad \frac{\mu}{\alpha} - \frac{k\mu}{k\alpha} + \frac{\sqrt{(k\alpha-k\mu)^2+4k\alpha\sigma}}{k\alpha} + 1 > 1 \\
&\Leftrightarrow \quad \frac{\mu}{\alpha} + \frac{k\alpha-k\mu+\sqrt{(k\alpha-k\mu)^2+4k\alpha\sigma}}{k\alpha} > 1 \\
&\Leftrightarrow \quad \frac{\mu}{\alpha} + \frac{2}{k}\left(\frac{k\alpha-k\mu+\sqrt{(k\alpha-k\mu)^2+4k\alpha\sigma}}{2\alpha}\right) > 1 \\
&\Leftrightarrow \quad \frac{\mu}{\alpha} + \frac{2\overline{T}_0}{k} > 1 \\
&\Leftrightarrow \quad \mu + \frac{2\alpha\overline{T}_0}{k} > \alpha.
\end{aligned}$$

Thus, it is revealed that $\alpha - \mu - \frac{2\alpha\overline{T}_0}{k} < 0$ and so, $\lambda_1 < 0$. On the other hand, it is evident that $\lambda_2 = c\left(\frac{\eta}{c}\overline{T}_0 - 1\right) = c\left(R_0 - 1\right) < 0$ if and only if $R_0 < 1$. As the two eigenvalues are negative, it is concluded that the trivial equilibrium E_0^+ is local and asymptotically stable. □

2.2.2. Non-trivial equilibrium point

Now, the goal is to determine the equilibrium point at which the infection is present, or $V > 0$ viral load. From System (2), T is cleared from the second equation, and the equilibrium coordinate below is obtained:

$$\overline{T}_1 = \frac{c}{\eta}.$$

A result which is replaced in the first System (2) and so

$$\sigma + \alpha\frac{c}{\eta}\left(1 - \frac{c}{\eta}\right) - \beta\frac{c}{\eta}V - \mu\frac{c}{\eta} = 0$$

where the V coordinate in the equilibrium is given by:

$$\begin{aligned}
\overline{V}_1 &= \frac{1}{\beta}\left(\frac{\eta}{c}\sigma + \alpha\left(1 - \frac{c}{k\eta}\right) - \mu\right) \\
&= \frac{1}{\beta}\left(\frac{k\eta^2\sigma + ck\alpha\eta - (c^2\alpha + ck\eta\mu)}{ck\eta}\right) \\
&= \frac{(c\alpha + k\eta\mu)(\xi_1 - 1)}{k\beta\eta}
\end{aligned}$$

with

$$\xi_1 = \frac{k\eta(c\alpha + \eta\sigma)}{c(c\alpha + k\eta\mu)}. \tag{5}$$

Then, the non-trivial $E_1 = (\overline{T}_1, \overline{V}_1)$ equilibrium point is given by:

$$E_1 = \left(\frac{c}{\eta}, \frac{(c\alpha + k\eta\mu)(\xi_1 - 1)}{k\beta\eta}\right). \tag{6}$$

Note that the E_1 equilibrium makes biological sense, when $\xi_1 > 1$, case in which $\overline{V}_1 > 0$. The intention now is to study the stability of the non-trivial equilibrium E_1, which is done in Proposition 6 from the basic reproduction number B_0, but whose demonstration requires the following Lemma.

Lemma 5. *$R_0 > 1$ if and only if $\xi_1 > 1$.*

Proof. In effect,

$$\begin{aligned} R_0 > 1 &\Leftrightarrow \tfrac{\eta}{c}\tfrac{k\mu}{2\alpha}\left[(\xi_0-1)+\sqrt{(\xi_0-1)^2+\tfrac{4\alpha\sigma}{k\mu^2}}\right] > 1 \\ &\Leftrightarrow \sqrt{(\xi_0-1)^2+\tfrac{4\alpha\sigma}{k\mu^2}} > \tfrac{2c\alpha}{k\eta\mu}-(\xi_0-1) \\ &\Leftrightarrow (\xi_0-1)^2+\tfrac{4\alpha\sigma}{k\mu^2} > \left[\tfrac{2c\alpha}{k\eta\mu}-(\xi_0-1)\right]^2 \\ &\Leftrightarrow \tfrac{4\alpha\sigma}{k\mu^2} > \tfrac{4c^2\alpha^2}{k^2\eta^2\mu^2}-\tfrac{4c\alpha}{k\eta\mu}(\xi_0-1). \end{aligned}$$

When both sides are multiplied by $\frac{k\mu^2\eta}{4\alpha}$ and considering that $\xi_0 = \frac{\alpha}{\mu}$,

$$\begin{aligned} R_0 > 1 &\Leftrightarrow \sigma\eta > \frac{\alpha c^2}{k\eta} - c\mu\left(\tfrac{\alpha}{\mu}-1\right) \\ &\Leftrightarrow \sigma\eta - \frac{\alpha c^2}{k\eta} + c\alpha - c\mu > 0 \\ &\Leftrightarrow \sigma\eta k\eta - \alpha c^2 + c\alpha k\eta - c\mu k\eta > 0 \\ &\Leftrightarrow k\eta(\sigma\eta + c\alpha) - c(c\alpha + \mu k\eta) > 0 \\ &\Leftrightarrow c(\alpha c + \mu k\eta)\left(\tfrac{k\eta(\sigma\eta+c\alpha)}{c(\alpha c+\mu k\eta)}-1\right) > 0 \\ &\Leftrightarrow \tfrac{k\eta(\sigma\eta+c\alpha)}{c(\alpha c+\mu k\eta)} > 1 \\ &\Leftrightarrow \xi_1 > 1. \end{aligned}$$

□

Proposition 6. *The non-trivial E_1 equilibrium in System (1) is local and asymptotically stable if and only if $R_0 > 1$.*

Proof. Evaluating Jacobian matrix (4) in the E_1 non-trivial equilibrium as described in (6), results in:

$$\mathbf{A_1} = \mathbf{A}(E_1) = \begin{pmatrix} \alpha - \mu - \frac{2\alpha\overline{T}_1}{k} - \beta\overline{V}_1 & -\beta\overline{T}_1 \\ \eta\overline{V}_1 & 0 \end{pmatrix}.$$

From which the line and determinant of $\mathbf{A_1}$ are respectively,

$$\operatorname{tr}(\mathbf{A_1}) = \alpha - \mu - \tfrac{2\alpha\overline{T}_1}{k} - \beta\overline{V}_1$$

$$\det(\mathbf{A_1}) = \beta\eta\overline{T}_1\overline{V}_1.$$

Firstly, $\operatorname{tr}\mathbf{A_1} < 0$, a result which is obtained by replacing $\overline{T}_1$ and $\overline{V}_1$, and simplifying as shown:

$$\operatorname{tr}(\mathbf{A_1}) = -\left(\frac{\alpha c^2 + \eta^2\sigma k}{\eta c k}\right) < 0.$$

Secondly, it is clear that $\overline{T}_1 = \frac{c}{\eta} > 0$ and according to (6) and Lemma 5, it is verified that $\overline{V}_1 > 0$ if and only if $R_0 > 1$, thus $\det(\mathbf{A_1}) > 0$. Then, by the trace-determinant criteria, the proposition is proven. □

2.3. Basic model simulation

For the model described in (1), two numerical simulations are performed with the mathematical software Matlab, in order to graphically illustrate the stability results which were obtained analytically. Two scenarios associated with the R_0 are shown, specifically $R_0 < 1$ and $R_0 > 1$. In both cases, the solution curves associated with the CD4 T cell populations (T) and viral particulates (V) are shown, in addition to the corresponding phase planes. Also, the numerical value of R_0 is determined in order to observe the incidence that it has on system behavior. The initial conditions considered

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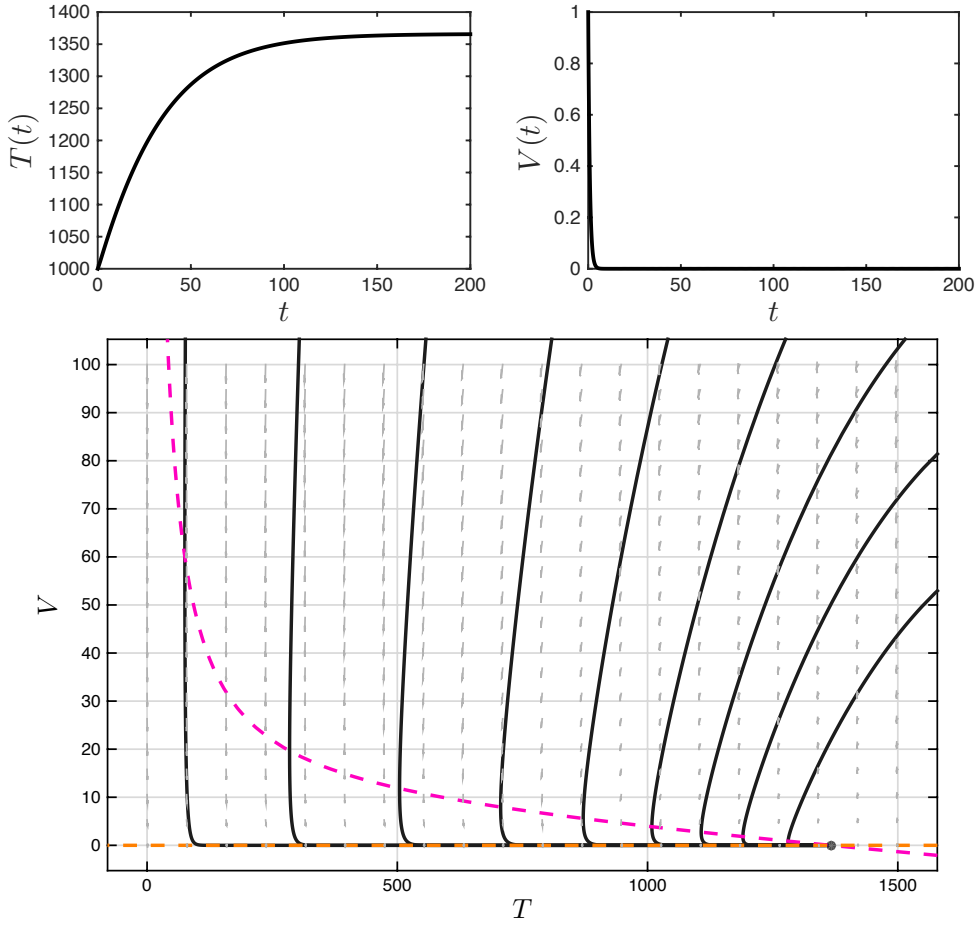

Figure 1. Solutions and the phase plane corresponding to susceptible CD4 T cells and viral particles in Model (1), with $\beta = 6 \times 10^{-6}$ and $R_0 = 0.8953$. In this equilibrium scenario, E_0 is local and asymptotically stable.

for the simulation are $T(0) = 1000$ and $V(0) = 1$ [23,33]. Parameter values are shown in Table 1, while different values for the effective contact rate between CD4 T cells and the virus are assigned for parameter β.

For the first simulation, it was considered that $\beta = 6 \times 10^{-6}$, together with those values mentioned in Table 1, cause $R_0 = 0.8953$. Since $R_0 < 1$, trivial equilibrium E_0 given by $E_0 = (1366, 0)$, is local and asymptotically stable, as shown in Figure 1. Note that CD4 T cells achieve equilibrium at approximately 120 days, while the concentration of viral particles is immediately eliminated. The phase plane in the lower part shows that the trivial equilibrium point presents stable node behavior.

For the second simulation, the values mentioned in Table 1 were considered once again, and the value of the effective contact rate between CD4 T cells and the virus was increased, specifically $\beta = 4 \times 10^{-5}$, with which $R_0 = 5.0175$ was obtained. As $R_0 > 1$, the E_1 non-trivial equilibrium, given numerically in approximate form by $E_1 = (231, 1468)$, is local and asymptotically stable, as observed in Figure 2. In both populations, oscillations were present, and were most visible in the T cell population, until achievement of the corresponding equilibriums. However, the fact that the viral particle concentration grows extremely quickly from initial condition point $(V(0) = 1)$ until achieving a maximum point of approximately 120000 viral particles mm^{-3} is underscored. In the lower part of the phase plane, the non-trivial equilibrium point presents stable spiral-type behavior.

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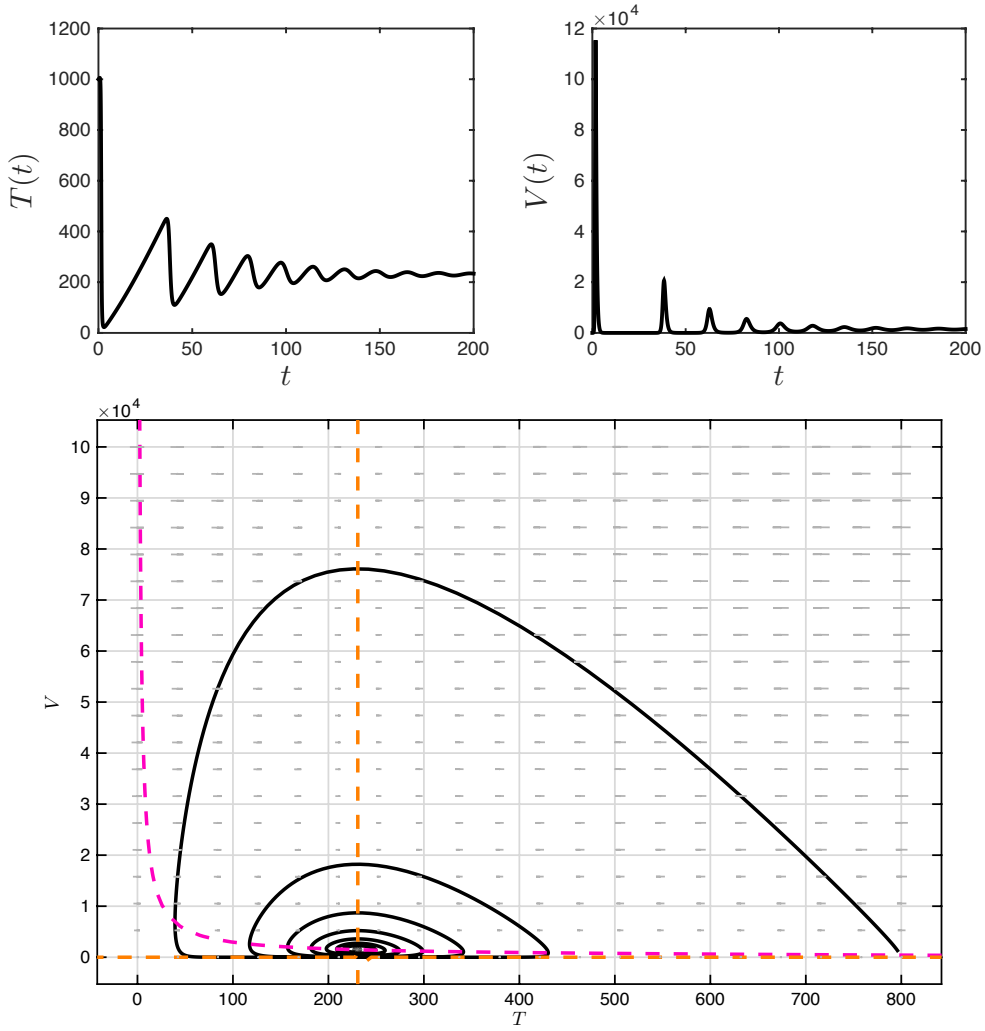

Figure 2. Solutions and the phase plane corresponding to susceptible CD4 T cells and viral particles in Model (1), with $\beta = 4 \times 10^{-5}$ and $R_0 = 5.0175$. In this scenario, equilibrium E_1 is local and asymptotically stable.

3. Model with activation time

3.1. Model formulation

The susceptible CD4 T cell population consists of resting T cells that have not been immunologically activated, and of activated T cells, also known as helper T-lymphocytes. The importance of this distinction is that HIV infects resting lymphocytes, but only 1% actively replicate, which indicates that, in 99% the proviral genome is housed and dormant [1,27,28,31,35].

Assume then, that τ is the average time that immunological activation of resting T cells requires to convert into active HIV replicators. In Model (1), it was assumed that ηTV was the average number of particles produced in t time, with $\eta = N\gamma\beta$. Consider that the number of new virions produced depends on the T cells that were previously infected, which permits consideration of those which were infected during their idle state. One way to enact this consideration in a differential equation system is through the incorporation of a *continuous delay term*, as proposed by Volterra, and given by

$$\eta V \int_{-\infty}^{t} F(t-\tau)T(\tau)d\tau,$$

where F is a factor considerating the emphasis that should be given to the T cell population size in the recent past. In accordance with this, Model (1) adopts the integro-differential form shown below:

$$\begin{cases} \dot{T} = \sigma + \alpha T\left(1 - \frac{T}{k}\right) - \beta TV - \mu T \\ \dot{V} = \eta V \int_{-\infty}^{t} F(t-\tau)T(\tau)d\tau - cV. \end{cases} \tag{7}$$

Function F in (7) is called *kernel* and has been used by authors including [6,15,16], in the context of predator-prey models, but with different forms. On the topic, [49] states that F's general form is

$$F_m(t) = \frac{a^m}{(m-1)!}t^{m-1}e^{-at}, \tag{8}$$

with $a > 0$ and $m \in \mathbb{N}$. In [25] it is warned that cases different from $m = 1$ and $m = 2$, are minimally objective from the point of view of expected results, as from $m = 3$ significant changes in function behavior are not observed. Further, when m tends toward infinity, the F_m function tends toward the δ function. In this case, $m = 1$ is considered, with which (8) takes the following form

$$F(t) = ae^{-at}; \;\; a > 0.$$

Thus, Model (7) takes the following form:

$$\begin{cases} \dot{T} = \sigma + \alpha T\left(1 - \frac{T}{k}\right) - \beta TV - \mu T \\ \dot{V} = \eta V \int_{-\infty}^{t} ae^{-a(t-\tau)}T(\tau)d\tau - cV. \end{cases} \tag{9}$$

One way to study the integro-differential System (9) is to transform it into a system of ordinary differential equations via the introduction of a new variable, suggested by [15] and given by:

$$W(t) = \int_{-\infty}^{t} ae^{-a(t-\tau)}T(\tau)d\tau; \quad t \geq 0.$$

Expressed again in equivalent form the following results:

$$W = a\left[\int_{-\infty}^{s} e^{-a(t-\tau)}T(\tau)d\tau + \int_{s}^{t} e^{-a(t-\tau)}T(\tau)d\tau\right],$$

with $s \leq t$. Deriving W with respect to t:

$$\begin{aligned} \dot{W} &= a\left[\int_{-\infty}^{s} \frac{\partial}{\partial t}\left[e^{-a(t-\tau)}T(\tau)\right]d\tau + \frac{d}{dt}\int_{s}^{t} e^{-a(t-\tau)}T(\tau)d\tau\right] \\ &= a\left[-\int_{-\infty}^{s} ae^{-a(t-\tau)}T(\tau)d\tau + T(t)\right] \\ &= a\left[T(t) - \int_{-\infty}^{s} ae^{-a(t-\tau)}T(\tau)d\tau\right] \\ &= a(T - W). \end{aligned}$$

As such:

$$\dot{W} = a(T - W).$$

Thus, the integro-differential System (9) is transformed into a system of ordinary differential equations, which will be the object of study in the following sections, and which is shown below:

$$\begin{cases} \dot{T} = \sigma + \alpha T\left(1 - \frac{T}{k}\right) - \beta TV - \mu T \\ \dot{V} = \eta VW - cV \\ \dot{W} = a(T - W). \end{cases} \tag{10}$$

The topological equivalence of systems (9) and (10) may be consulted in [15].

3.2. Model stability analysis with activation time

In order to find System (10)'s stationary solutions, the algebraic system that results from equaling the derivatives to zero is solved and two equilibrium points are obtained: trivial and non-trivial. The trivial equilibrium point is denoted by E_0, which corresponds to the absence of viral load, and is given by $E_0 = (\overline{T}_0, \overline{V}_0, \overline{W}_0)$, where:

$$\begin{aligned} \overline{T}_0 &= \frac{k\mu}{2\alpha}\left[(\xi_0 - 1) + \sqrt{(\xi_0 - 1)^2 + \frac{4\alpha\sigma}{k\mu^2}}\right] \\ \overline{V}_0 &= 0 \\ \overline{W}_0 &= \frac{k\mu}{2\alpha}\left[(\xi_0 - 1) + \sqrt{(\xi_0 - 1)^2 + \frac{4\alpha\sigma}{k\mu^2}}\right]. \end{aligned}$$

This equilibrium point makes biological sense because $\overline{T}_0 = \overline{W}_0$ and the positivity of $\overline{T}_0$ was previously studied in Proposition 2. Further, E_0 may be expressed in terms of R_0, as follows:

$$E_0 = (\overline{T}_0, \overline{V}_0, \overline{W}_0) = \left(\frac{c}{\eta}R_0, 0, \frac{c}{\eta}R_0\right).$$

On the other hand, non-trivial equilibrium point $E_1 = (\overline{T}_1, \overline{V}_1, \overline{W}_1)$, where there is a viral load, presents the following coordinates:

$$\begin{aligned} \overline{T}_1 &= \frac{c}{\eta} \\ \overline{V}_1 &= \frac{c\alpha + k\eta\mu}{k\beta\eta}\left(\frac{k\eta(c\alpha + \eta\sigma)}{c(c\alpha + k\eta\mu)} - 1\right) = \frac{c\alpha + k\eta\mu}{k\beta\eta}(\xi_1 - 1) \\ \overline{W}_1 &= \frac{c}{\eta}. \end{aligned}$$

It is observed that the first two coordinates $\overline{T}_1$ and $\overline{V}_1$, coincide with those shown in (6), which corresponds to the non-trivial equilibrium point of the basic model (1), whose biological logic was previously discussed, with the help of Lemma 5. As $\overline{W}_1 = \frac{c}{\eta} > 0$, it is concluded that $E_1 = (\overline{T}_1, \overline{V}_1, \overline{W}_1)$, also makes biological sense.

We now analyze the stability of the trivial equilibrium points E_0 and non-trivial equilibrium points E_1 in Propositions 7 and 8, respectively. In both cases the Jacobian matrix given in (11) is required

$$\mathbf{J}(T, V, W) = \begin{pmatrix} \alpha - \frac{2\alpha T}{k} - \beta V - \mu & -\beta T & 0 \\ 0 & \eta W - c & \eta V \\ a & 0 & -a \end{pmatrix}. \tag{11}$$

Proposition 7. *The trivial equilibrium E_0 in System (10) is local and asymptotically stable if and only if $R_0 < 1$.*

Proof. Evaluating the Jacobian matrix (11) in the trivial equilibrium E_0, results in

$$\mathbf{J}(E_0) = \begin{pmatrix} \alpha - \mu - \frac{2\alpha\overline{T}_0}{k} & -\beta\overline{T}_0 & 0 \\ 0 & \eta\overline{W}_0 - c & 0 \\ a & 0 & -a \end{pmatrix}$$

whose characteristic equation is given by:

$$(\lambda + a)(\lambda - \eta\overline{W}_0 + c)(k\lambda - k\alpha + k\mu + 2\alpha\overline{T}_0) = 0.$$

Then, its eigenvalues are:

$$\begin{aligned} \lambda_1 &= -a \\ \lambda_2 &= \eta\overline{W}_0 - c = \eta\overline{T}_0 - c = c\left(\frac{\eta}{c}\overline{T}_0 - 1\right) = c(R_0 - 1) \\ \lambda_3 &= \alpha - \mu - \frac{2\alpha\overline{T}_0}{k}. \end{aligned}$$

Clearly, $\lambda_1 < 0$, for λ_2 one have $\lambda_2 < 0$ if and only if $R_0 < 1$ and for $\lambda_3 < 0$ it must be ensured that $\alpha - \mu - \frac{2\alpha\overline{T}_0}{k} < 0$, which was previously verified in the proof of Proposition 4. Thus, it is concluded that trivial equilibrium E_0 is local and asymptotically stable if and only if $R_0 < 1$. □

Proposition 8. *If $R_0 > 1$ and $a > a_0 = \frac{c^2(c\alpha + k\eta\mu)(\xi_1 - 1)}{c^2\alpha + k\eta^2\sigma}$, non-trivial equilibrium E_1 in System (10) is local and asymptotically stable.*

Proof. Evaluating the Jacobian matrix (11) in non-trivial equilibrium E_1 results in

$$\mathbf{J}(E_1) = \begin{pmatrix} \alpha - \frac{2\alpha\overline{T}_1}{k} - \beta\overline{V}_1 - \mu & -\beta\overline{T}_1 & 0 \\ 0 & 0 & \eta\overline{V}_1 \\ a & 0 & -a \end{pmatrix}$$

whose characteristic equation is given by:

$$\lambda^3 + b_1\lambda^2 + b_2\lambda + b_3 = 0$$

where coefficients b_1, b_2, and b_3 correspond to:

$$\begin{aligned} b_1 &= a + \mu - \alpha + \frac{2c\alpha + (c\alpha + k\eta\mu)(\xi_1 - 1)}{k\eta} \\ b_2 &= a\left[\mu - \alpha + \frac{2c\alpha + (c\alpha + k\eta\mu)(\xi_1 - 1)}{k\eta}\right] \\ b_3 &= \frac{ac(c\alpha + k\eta\mu)(\xi_1 - 1)}{k\eta} \end{aligned}$$

and where it is observed that:

$$b_1 = a + \frac{1}{a}b_2. \tag{12}$$

If in b_1 and b_2, ξ_1 is replaced as in (5), the following is obtained

$$\begin{aligned} b_1 &= \frac{c^2\alpha + ack\eta + k\eta^2\sigma}{ck\eta} > 0 \\ b_2 &= \frac{a\left(c^2\alpha + k\eta^2\sigma\right)}{ck\eta} > 0. \end{aligned}$$

On the other hand, it is observed that $\xi_1 > 1$ implies $b_3 > 0$. As in Lemma 5 it was demonstrated that $R_0 > 1$ if and only if $\xi_1 > 1$, and so it is concluded that $R_0 > 1$ implies $b_3 > 0$. Conversely,

$$\begin{aligned} a > \tfrac{c^2(c\alpha+k\eta\mu)(\xi_1-1)}{c^2\alpha+k\eta^2\sigma} &\Leftrightarrow a(c^2\alpha + k\eta^2\sigma) > c^2(c\alpha + k\eta\mu)(\xi_1 - 1) \\ &\Leftrightarrow a\left[\tfrac{a(c^2\alpha+k\eta^2\sigma)}{ck\eta}\right] > \tfrac{ac(c\alpha+k\eta\mu)(\xi_1-1)}{k\eta} \\ &\Leftrightarrow ab_2 > b_3 \\ &\Rightarrow ab_2 + \tfrac{1}{a}b_2^2 > b_3 \\ &\Leftrightarrow \left(a + \tfrac{1}{a}b_2\right) b_2 > b_3. \end{aligned}$$

If on the left side of the last inequality, expression (12) is replaced, $b_1 b_2 > b_3$ is obtained. Then, with the Routh-Hurwitz [19] criteria, it is concluded that the equilibrium point E_1 is local and asymptotically stable whenever $R_0 > 1$ and $a > a_0 = \frac{c^2(c\alpha+k\eta\mu)(\xi_1-1)}{c^2\alpha+k\eta^2\sigma}$. □

3.3. Model simulation with CD4 T cell activation time

With the objective of graphically illustrating the stability results obtained analytically, for the model for CD4 T cell HIV infection with activation time described in (10), two numerical simulations were performed, again using the parameter values from Table 1 and assigning different values for the effective contact rate between CD4 T cells and the virus, parameter β. The W variable does not appear explicitly in the simulation, but it requires an initial condition, for which $W(0) = 0$ was considered. In this case also, two scenarios associated with the R_0 value are shown, specifically $R_0 < 1$ and $R_0 > 1$, displaying the numerical solutions associated with CD4 T cell populations and viral particles, in addition to phase depictions.

Firstly, for Figure 3, $T(0) = 500$ and $V(0) = 1$ were taken as initial conditions. Additionally, $\beta = 6 \times 10^{-6}$ was considered, with which $R_0 = 0.8953 < 1$ was obtained. At the top, the numerical solutions to Model (10) are shown, which tend towards the trivial equilibrium point E_0 coordinates, i.e., T tends toward $\overline{T}_0 = \frac{c}{\eta}R_0$ and V tends toward $\overline{V}_0 = 0$. This coincides with the stability result from Proposition 7. Just as in the Model (1) simulations, the viral particle concentration grows very quickly from initial condition $(V(0) = 1)$, to an approximate maximum average number of 50000 mm^{-3}. In the lower part, the phase plot is shown, in which the non-trivial equilibrium point presents a stable spiral behavior.

Secondly, from the values of the parameters in Table 1 a numerical value was obtained for the Proposition 8 threshold, given by

$$a = \frac{c^2(c\alpha + k\eta\mu)(\xi_1 - 1)}{c^2\alpha + k\eta^2\sigma} = 2.939037433.$$

Thus, a simulation with $a = 5$ and $\beta = 4 \times 10^{-5}$ was carried out, which generated $R_0 = 5.0175 > 1$ and the numerical results coincided with those described in Proposition 8. However, the dynamic observed in the Model (10) simulation was more interesting, considering that $a = 2 < 2.939037433$ and that shown in Figure 4, in which $\beta = 4 \times 10^{-5}$ was considered, with which $R_0 = 5.0175 > 1$ was obtained. In the upper part, the numerical solutions are shown, but no stability is observed. In fact, although the simulation is displayed for $t = 1000$ (phase plane below), numerical solution behavior

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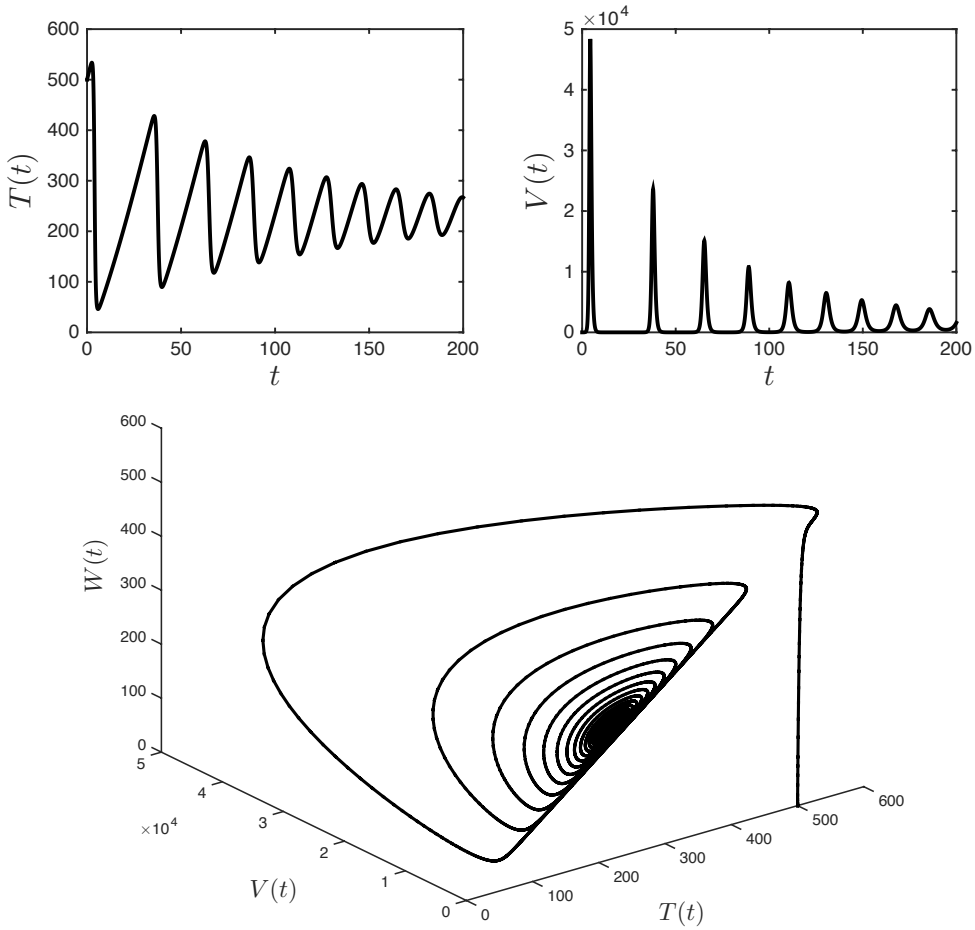

Figure 3. Numerical solutions and phase space which correspond to susceptible CD4 (T) T cells and viral particulates (V) from Model (10), with $\beta = 6 \times 10^{-6}$ and $R_0 = 0.8953$. The initial conditions are $T(0) = 500$ and $V(0) = 1$. In this scenario, the trivial equilibrium E_0 is local and asymptotically stable.

were not modified. Note additionally that the times at which the CD4 T cell concentration minimums coincide approximately with the times at which viral particle concentration maximums occur, and vice versa. Without doubt, the main characteristic observed in the numerical solutions in this simulation is a periodic behavior after a certain amount of time. In the lower part is the phase states plot for Model (10), in which two curves are shown, one black and one blue, both attracted not by an equilibrium point, but by a limit cycle. The initial conditions of the black curve were $T(0) = 500$ and $V(0) = 1$, while the initial conditions for the blue curve were $T(0) = 230$ and $V(0) = 1467$.

4. Conclusions

The study of the basic model allowed to know local stability conditions of the system depending on the value of the basic number of reproduction. Certainly, it is enough to bring that value below 1 for the viral load of the infected host to be controlled. This viral load control may be done through the use of antiretroviral therapy and it should focus on reducing the value of the model's own parameters such as the rate of effective contact between CD4 T cells and the virus, or the number of viral particles produced per infected cell.

The study of models for infection with HIV, with and without activation time, in this investigation contribute to the comprehension of the effect that this activation time has on the infected cells in the virus infection dynamic. In general, consider that activation time delays the time at which infection begins, and fewer oscillations in curve behavior are observed. However, those observed exhibit greater amplitude, which indicates a more profound effect (lack of equilibrium) on the immunological state of

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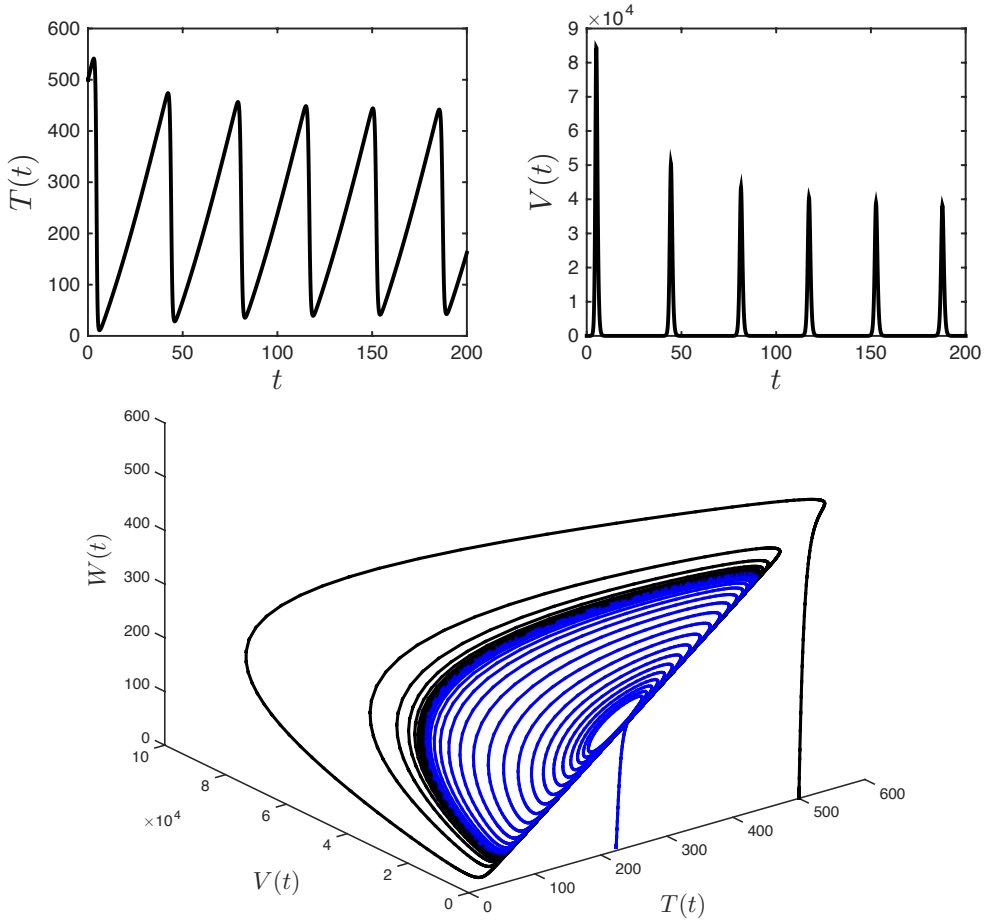

Figure 4. Numerical solutions and phase space which correspond to susceptible CD4 T cells (T) and viral particles (V) from Model (10), with $\beta = 4 \times 10^{-5}$ and $R_0 = 5.0175$. In this scenario, the trivial equilibrium E_1 is unstable. In the phase space, the initial conditions for the black curve are $T(0) = 500$ and $V(0) = 1$, and the initial conditions for the blue curve are $T(0) = 230$ and $V(0) = 1467$.

the infected individual. It is important to highlight that, the threshold value a_0 given in Proposition 8, corresponds to a bifurcation parameter, as mentioned in Section 3.3, for $R_0 > 1$ and $a > a_0$, the equilibrium the non-trivial equilibrium is local and asymptotically stable, i.e., high sustained viremia levels are reched by the host. However, in the case of $R_0 > 1$ and $a < a_0$ it is necessary to perform a more in-depth analytical study of the model; however, it was shown numerically that the equilibrium was unstable. In deed, according to [14], if the kernel in Model (7) has the form of (8), a *Hopf bifurcation* is presented. This is verified, at least numerically, with the phase plot shown in Figure 4, where a limit cycle is observed.

Mathematical models permit the implementation of different theories, which help to interpret and analyze an epidemiological problem such as HIV infection. However, it should be considered that this type of model is quite sensitive to the values of the parameters used, and as such, its use for decision takers should always be supported by clinical evidence, and the criteria of expert doctors on the topic.

Author Contributions: All authors have had a part in conceptualization, methodology, software, formal analysis, investigation, and writing–original draft preparation. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Universidad del Quindío grant number 614.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

HIV	Human immunodeficiency virus
AIDS	Acquired immune deficiency syndrome
MDPI	Multidisciplinary Digital Publishing Institute
DOAJ	Directory of open access journals

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