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A SINGULARLY PERTURBED HIV MODEL WITH TREATMENT AND ANTIGENIC VARIATION

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Abstract. We study the long term dynamics and the multiscale aspects of a within-host HIV model that takes into account both mutation and treatment with enzyme inhibitors. This model generalizes a number of other models that have been extensively used to describe the HIV dynamics. Since the free virus dynamics occur on a much faster time-scale than cell dynamics, the model has two intrinsic time scales and should be viewed as a singularly perturbed system. Using Tikhonov's theorem we prove that the model can be approximated by a lower dimensional nonlinear model. Furthermore, we show that this reduced system is globally asymptotically stable by using Lyapunov's stability theory.

1. **Introduction.** The Acquired Immunodeficiency Syndrome (AIDS) epidemic was one of the most devastating health issues during the last decades of the XX century and remains a challenge as the XXI century ushers in [23]. The problem is even more striking in less developed areas [44]. The accumulated sequence of difficulties associated to the AIDS epidemics ranging from social and cultural to biological and modeling issues makes the topic highly relevant for research [1, 21].

As a consequence, mathematical tools have been applied to help understand the complex dynamics of the immune system and its response to viral infection [2]. Indeed, a better understanding of this dynamics seems to be an important factor in the development of effective long-term therapies or possibly preventive vaccines for deadly diseases such as the Human immunodeficiency virus (HIV) infection [21]. From the mathematical point of view, there have been several research lines and approaches [26, 27, 1, 9, 15, 20, 21, 16, 37, 25, 4, 5, 34, 42, 38]. Among those, we shall consider in the present article the within host dynamics of the HIV virus. It has received a considerable amount of attention. See for example [27, 26] and references therein.

It has been known for a while that the virus dynamics is much faster than the dynamics of the cells that host the viruses as well as of the uninfected cells [10, 17, 15, 12, 35, 28, 18]. Furthermore, it is well documented that one of the elusive characteristics of the HIV biological behavior is the regular change of its genetic signature by constant mutation [7, 11, 19, 30, 29]. Thus leading to different strains of the same viruses. Mathematical models incorporating such aspect have been studied by a number of authors. See [37] and references therein.

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In this article we consider a differential equation model for the within-host dynamics of the HIV that takes into account mutation, treatment with enzyme inhibitors and the different time scales that are relevant to a realistic analysis of the problem. To incorporate such different time scales, we make use of the multiscale analysis techniques that have been used in many other areas [24, 43, 14, 41] and in the context of biological modeling of infectious diseases in [3, 36, 32]. We prove the existence of a reduced system whose dynamics approximates in a suitable way that of the relevant variables in the full system. We also prove global stability of such system by exhibiting an appropriate Lyapunov function. Such function is inspired by the one used in [37].

1.1. **The HIV dynamics.** As the human immunodeficiency viruses are not capable of reproducing themselves, they manipulate the CD4+ T cells to generate numerous copies of themselves. The replication cycle begins with free virus connecting to the target cell and injecting HIV RNA into the cell. Once the HIV RNA is inside the cell, it makes a DNA copy of its viral RNA. The viral DNA is then inserted in the CD4+ T cells DNA.

After that, host cells will produce viral particles and assemble new HIV virions. The final step of the viral cycle is the release of these virions. The release of viral genetic material into host cells triggers a complex immune response. This process results in the activation of cytotoxic T cells (or CD8+ T cells) that will bind to infected cells and induce apoptosis.

AIDS treatments consist of antiretroviral drugs capable of inhibiting (at least partially) the enzymes required during the replication cycle. Entry inhibitors prevent entry of the virus into the cell. Integrase inhibitors block the activity of the enzyme integrase, responsible for the insertion of HIV DNA to human DNA. Reverse Transcriptase Inhibitors directly block the action of this enzyme and virus multiplication. Protease inhibitors of HIV, prevent infected cells from producing infectious virus particles. Thus, the new copies of HIV will not be able to infect new cells.

1.2. **The mathematical model.** Several models have been proposed in order to describe the HIV in-vivo dynamics [22, 21, 27, 1, 6, 9, 15, 20, 26]. The basic model of virus dynamics, proposed by Nowak and Bangham [22], considers three variables: susceptible CD4+ T cells (X), infected CD4+ T cells (Y), and virions (V). These variables denote the abundance of the corresponding quantities in a given volume of blood or tissue. The model assumes that uninfected CD4+ T cells are produced at a constant rate λ and die at rate dX. Each strain of free virus particles infects the uninfected cells at a rate proportional to the product of their concentrations, βXV. Infected cells produce free virus particles at a rate proportional to their abundance, kY, and die at a rate aY. Free viral particles die at rate uV. Considering the immune system, the model will have one more variable: cytotoxic T cells (Z). These cells have a proliferation rate given by cYZ and, in absence of stimulation, decay at rate bZ. Furthermore, infected cells are killed by cytotoxic T cells at rate pYZ. The Figure 1 summarizes the HIV replication cycle described above.

As mentioned before, one of the main characteristics of HIV is its extensive genetic variability, that is, the replication process can generate virions with slightly modified genetic content. Aiming to incorporate the interplay between immune response and virus diversity for a number of different strains, Nowak and Bangham [22] considered n different strains of virus, infected cells and cytotoxic T cells.

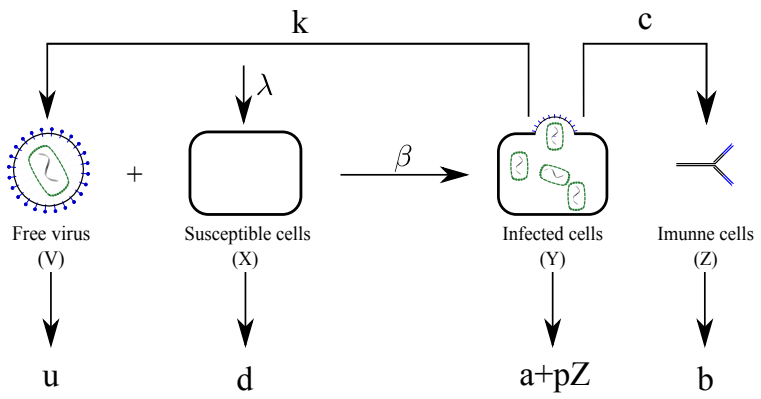


FIGURE 1. Description of the HIV model with the parameters described in Table 1.

The subindex i denotes each strains. We consider a generalized form of this model, since we consider that the parameters a, p, u, c and b can be depend of the strain.

Upon considering the enzyme inhibitors described above, defective viruses (H_i) also are part of the model with dynamic analogous to the dynamics of active virions. Furthermore, the efficiency of the inhibitors affects the process of cell infection and virion production. Thus we obtain the following first-order ODE system

$$\begin{aligned}
\dot{X} =& \lambda - dX - (1-E_E)X\sum_{i\in\mathcal{N}}\beta_i V_i \\
\dot{Y}_i =& (1-E_E)X\beta_i V_i - a_i Y_i - p_i Y_i Z_i \\
\dot{V}_i =& (1-E_T)(1-E_P)(1-E_I)k_i Y_i - u_i V_i \\
\dot{H}_i =& E_P k_i Y_i - u_i H_i \\
\dot{Z}_i =& c_i Y_i Z_i - b_i Z_i
\end{aligned} \tag{1}$$

for $i \in \mathcal{N} = \{1, \ldots, n\}$. Table 1 summarizes the biological meaning of the parameters.

Parameter	Meaning
λ	CD4+ T cells supply rate
β_i	Infection rate for the i-th strain
k_i	Free virus production rate for the i-th strain
c_i	cytotoxic T cells production rate for the i-th strain
E_T	efficiency of the reverse transcriptase inhibitor
E_E	efficiency of the entry inhibitor
E_P	efficiency of the protease inhibitor
E_I	efficiency of the integrase inhibitor
$1/d$	average life-time of uninfected CD4+ T cells
$1/a_i$	average life-time of infected CD4+ T cells for the i-th strain
$1/u_i$	average life-time of free virus for the i-th strain
$1/b_i$	average life-time of cytotoxic T cells for the i-th strain

TABLE 1. Description of parameters meaning in the compartmental model (1).

1.3. **Outline of the article.** This work is organized as follows: In Section 2 we introduce an extended version of the model previously studied by Nowak and Bangham[22, 21] and also Souza and Zubelli [37]. In practical situations such model displays different scales and in order to obtain good quantitative results it is crucial to perform a perturbation analysis. The first step consists in writing down a dimensionless version of the system. In this section we also review some of the model's key properties such as equilibria, global stability and introduce some definitions that will be used throughout the text. In Section 3, we provide the necessary background on Tikhonov's theorem. This result is then applied in Section 4 where we also present the reduced system associated to our model. Then, we describe the equilibria of the reduced system and prove global stability results using a Lyapunov function. The use of Tikhonov's theorem leads to a way of approximating the solutions of the full model by solutions of the reduced system that can be very useful in practical applications. We conclude with some numerical examples and a brief analysis of the performance of the systems involved in our result, thus substantiating the applicability of our results.

2. Model properties.

Many properties of the System (1) are already known. Indeed, Pastore [25] showed that the solutions to a similarly system are invariant on the positive orthant and identified the equilibrium points. Souza and Zubelli [37] studied the equivalent model that does not consider enzyme inhibitors. They characterized the stable equilibrium points and also showed that model is globally asymptotically stable by using appropriate Lyapunov functions. Before we review these properties in detail, we shall rewrite the system in a dimensionless form.

2.1. The dimensionless system.

Since the equation describing the evolution of H_i is uncoupled from the other ones in System (1), we can analyze the system without such equation. Moreover, we can embed $(1 - E_E)$ in the constants β_i and rename $(1 - E_T)(1 - E_P)(1 - E_I)k_i$ by the constants k_i, for $i \in \mathcal{N}$. Letting

$$(x, y_i, v_i, z_i) = \left(\frac{d}{\lambda}X, \frac{a_i}{\lambda}Y_i, \frac{\beta_i}{d}V_i, \frac{p_i}{a_i}Z_i\right)$$

and $t = d \cdot T$, we obtain the system (where the derivatives are taken w.r.t. t):

$$\begin{aligned}
\dot{x} =& 1 - x - x\sum_{i\in\mathcal{N}} v_i \\
\dot{y}_i =& \gamma_i \left(x v_i - y_i - y_i z_i\right) \\
\dot{v}_i =& \eta_i \left(R_0^i y_i - v_i\right) \\
\dot{z}_i =& \sigma_i \left(I_0^i y_i z_i - z_i\right)
\end{aligned} \tag{2}$$

for $i \in \mathcal{N}$, where $R_0^i = \beta_i \lambda k_i / d a_i u_i$ denotes the basic reproductive ratio of each strain and

$$\gamma_i = \frac{a_i}{d}, \quad \eta_i = \frac{u_i}{d}, \quad \sigma_i = \frac{b_i}{d}, \quad \text{and} \quad I_0^i = \frac{c_i \lambda}{a_i b_i}.$$

2.2. System properties: Equilibrium points and global stability.

In this section we will introduce some properties of the System (2). This result will be used in Section 4.1 to show that the equilibria of the reduced System (9) are the projections of the original System (1).

Before stating the main results, we introduce some notation. It is well known [22, 21, 37] that some quantities involving the system parameters are important in determining the global equilibria of the system. The first one is the basic reproductive ratio, defined above. Following [37], without loss of generality, we assume that the strains are indexed in a nonincreasing order of the constants R_0^i. Similarly, we define the basic reproductive ratio in the presence of the immune response

$$R_I^i = 1 + \frac{R_0^i}{I_0^i}.$$

Given a set of indices $\mathcal{I} \subseteq \mathcal{N}$, let us denote

$$R_I^{\mathcal{I}} = 1 + \sum_{i \in \mathcal{I}} \frac{R_0^i}{I_0^i}.$$

For a more concise notation, y will denote the vector $(y_1, y_2, ..., y_n)$ (similarly for v and z).

System (2) has a variety of equilibria. In order to deal with such equilibrium points, we shall follow the notation used in [37]

$$W_{j\mathcal{J}} = (x_{j\mathcal{J}}, y_{j\mathcal{J}}, v_{j\mathcal{J}}, z_{j\mathcal{J}})$$

where $\mathcal{J}$ is a subset of $\mathcal{N}$ and $j \in \{\mathcal{N} - \mathcal{J}\}$. From the biological point of view, $\mathcal{J}$ is the set of indices of the strains that remain in the organism and are fought by the immune system while j is the strain index that remains in the organism without being fought by the immune system

Theorem 2.1. [37] *If the basic reproductive ratios of the virus strains are distinct, then System (2) has $2^{n-1}(2+n)$ equilibrium points $W_{j\mathcal{J}}$ where*

1. *For $\mathcal{J} = \emptyset$ and $j = 0$, we have $x_{0\emptyset} = 1$ and $y^i_{0\emptyset} = v^i_{0\emptyset} = z^i_{0\emptyset} = 0$, $\forall i \in \mathcal{N}$.*
2. *For $\mathcal{J} = \emptyset$ and $j \in \mathcal{N}$, we have $x_{j\emptyset} = 1/R_0^j$, $y^j_{j\emptyset} = 1 - \frac{1}{R_0^j}$, $v^j_{j\emptyset} = R_0^j - 1$, $z^j_{j\emptyset} = 0$, and $y^i_{j\emptyset} = v^i_{j\emptyset} = z^i_{j\emptyset} = 0$, $\forall i \neq j$.*
3. *For $\mathcal{J} \neq \emptyset$ and $j = 0$, we have $x_{0\mathcal{J}} = 1/R_I^{\mathcal{J}}$, $y^i_{0\mathcal{J}} = \frac{1}{I_0^i}$, $v^i_{0\mathcal{J}} = \frac{R_0^i}{I_0^i}$, $z^i_{0\mathcal{J}} = \frac{R_0^i}{R_I^{\mathcal{J}}} - 1$, $\forall i \in \mathcal{J}$, and $y^i_{0\emptyset} = v^i_{0\emptyset} = z^i_{0\emptyset} = 0$, $\forall i \notin \mathcal{J}$.*
4. *For $\mathcal{J} \neq \emptyset$ and $j \in \mathcal{N} - \mathcal{J}$, we have $x_{j\mathcal{J}} = 1/R_I^{\mathcal{J}}$, $y^j_{j\mathcal{J}} = 1 - \frac{R_I^{\mathcal{J}}}{R_0^j}$, $v^j_{j\mathcal{J}} = R_0^j - R_I^{\mathcal{J}}$, $z^j_{j\mathcal{J}} = 0$. Furthermore if $i \in \mathcal{J}$, we have $y^i_{j\mathcal{J}} = \frac{1}{I_0^i}$, $v^i_{j\mathcal{J}} = \frac{R_0^i}{I_0^i}$, $z^i_{j\mathcal{J}} = \frac{R_0^i}{R_I^{\mathcal{J}}} - 1$, and $y^i_{j\mathcal{J}} = v^i_{j\mathcal{J}} = z^i_{j\mathcal{J}} = 0$ otherwise.*

To state the result of global stability we need some definitions. Following [37], let us define the set of *strong responders* as

$$\mathcal{S} = \{i \in \mathcal{N}; R_0^i > R_I^i\}.$$

We shall say that this set $\mathcal{S}$ is consistent if $j \in \mathcal{S}$ implies $i \in \mathcal{S}$ for all $i \in \mathcal{N}$ such that $i < j$. We shall say that $\mathcal{I} \subseteq \mathcal{S}$ is antigenic set if $R_0^i \geqslant R_I^{\mathcal{I}}$ for all $i \in \mathcal{I}$. In addition, if $R_0^i \leqslant R_I^{\mathcal{I}}$ for all $i \notin \mathcal{I}$ also holds, we shall say that I is a purely antigenic set. Finally, let l be the largest integer such that $\mathcal{I} = \{1, 2, ..., l\}$ is an antigenic set. If $\mathcal{I} \neq \emptyset$, then we shall say that $\mathcal{I}$ is the maximal antigenic set.

Theorem 2.2. [37] *Assume that $R_0^i > R_0^{i+1}$ for $i = 1, ..., n-1$ and that the set of strong responders is consistent. Then, System (2), defined on $\mathbb{R}^{3n+1}_{\geqslant 0}$, with initial condition in its interior, has a globally asymptotically stable equilibrium given as follows:*

1. *$W_{0\emptyset}$ if $R_0^1 \leqslant 1$;*
2. *$W_{1\emptyset}$ if $R_0^1 > 1$ and $R_0^1 \leqslant R_I^1$;*
3. *If $R_0^1 > R_I^1$, let $\mathcal{J}$ be the antigenic maximal set.*
   a. *$W_{0\mathcal{J}}$ if $\mathcal{J}$ is a purely antigenic set;*
   b. *$W_{j\mathcal{J}}$ otherwise, where j is the smallest integer outside $\mathcal{J}$.*

The proof of Theorems 2.1 and 2.2 can be found in [37]. See also [4].

Note that for the case of the system with inhibitors the basic reproductive ratio of each strain is $R_0^i(1-E_E)(1-E_T)(1-E_P)(1-E_I)$, therefore lower than in the case without inhibitors. This reduction may cause change in the type of globally stable equilibrium point. For certain values of the inhibitors efficiencies it is possible that the immune system fails to fight certain strains that would have been fought without the inhibitors. Despite of that, the presence of the inhibitor will not increase the viral load component of the new globally stable limit.

3. Tikhonov's theorem.

In practical situations, the presence of different scales in System (2) leads to a singularly perturbed system. In this context, we shall see that Tikhonov's theorem is applicable. We start with Tikhonov's theorem in its general form.

The singularly perturbed system that we are interested on possesses two characteristic time scales one of order 1 and another one of order $\varepsilon \ll 1$. The system then takes the form

$$\begin{aligned} \dot{x} &= f(t,x,y), \quad x(0) = x_0 \\ \varepsilon\dot{y} &= g(t,x,y), \quad y(0) = y_0 \end{aligned} \tag{3}$$

where f and g are sufficiently regular functions from open subsets of $\mathbb{R}\times\mathbb{R}^{m_1}\times\mathbb{R}^{m_2}$ to $\mathbb{R}^{m_1}$ and $\mathbb{R}^{m_2}$. Tikhonov's theorem gives conditions ensuring that the solution $(x(t,\varepsilon), y(t,\varepsilon))$ of Eq. (3) converges to $(\bar{x}(t), \bar{y}(t,\bar{x}))$ where $(\bar{x},\bar{y})$ is the the solutions of the degenerate system:

$$\begin{aligned} \dot{x} &= f(t,x,y), \quad x(0) = x_0 \\ 0 &= g(t,x,y) \end{aligned} \tag{4}$$

The interest in such a reduction lies on the fact that the degenerate system forms an algebraic differential system and, in many cases, the complexity of the problem is greatly reduced. Note also that, for small ε, the System (3) becomes very stiff and the solution to (4) offers a much better and more robust approximation.

To apply Tikhonov's theorem we need several assumptions as described below.

Assumption 1. *Assume that the functions*

$$f : [0,T]\times\bar{\mathcal{U}}\times\mathcal{V}\mapsto\mathbb{R}^{m_1} \text{and } g : [0,T]\times\bar{\mathcal{U}}\times\mathcal{V}\mapsto\mathbb{R}^{m_2}$$

are continuous and satisfy the Lipschitz condition w.r.t. the variables x and y in $[0,T]\times\bar{\mathcal{U}}\times\mathcal{V}$, where $\bar{\mathcal{U}}$ is a compact set in $\mathbb{R}^{m_1}$, $\mathcal{V}$ is a bounded open set in $\mathbb{R}^{m_2}$, and $T > 0$.

Assumption 2. *Assume that there exists a vector function $\phi(t,x)$ continuous in $[0,T]\times\bar{\mathcal{U}}$ such that $\phi(t,x)\in\mathcal{V}$ and*

$$g(t,x,\phi(t,x))\equiv 0.$$

This function will be referred to as a **root** *of the equation $g(t,x,y)=0$. Furthermore, the root ϕ is isolated in $[0,T]\times\bar{\mathcal{U}}$, that is, there exists $\delta>0$, independently of x, such that*

$$0<||y-\phi(t,x)||<\delta$$

implies $g(t,x,y)\neq 0$ in $[0,T]\times\bar{\mathcal{U}}$.

The system of differential equations

$$\frac{d\tilde{y}}{d\tau}=g(t,x,\tilde{y}) \tag{5}$$

for which t and x are treated as parameters, is called the **boundary layer equation** associated to the System (3).

Assumption 3. *Assume that the singular point $\phi(t,x)$ of the boundary layer Equation (5) is an asymptotically stable equilibrium, uniformly w.r.t. $(t,x)\in[0,T]\times\bar{\mathcal{U}}$, that is, for any $\eta>0$ there exists $\delta>0$ such that for all $(t,x)\in[0,T]\times\bar{\mathcal{U}}$ the inequality $||\tilde{y}(0,t,x)-\phi(t,x)||<\delta$ implies*

$$||\tilde{y}(\tau,t,x)-\phi(t,x)||<\eta \text{ and } \lim_{\tau\to\infty}\tilde{y}(\tau,t,x)=\phi(t,x),\quad\forall\tau>0$$

where the above convergence is uniform for $(t,x)\in[0,T]\times\bar{\mathcal{U}}$.

Consider now the **reduced system**, that is, the first equation of the degenerate System (4), replacing a root $\phi(t,x)$

$$\dot{\bar{x}}=f(t,\bar{x},\phi(t,\bar{x})),\quad \bar{x}(0)=x_0. \tag{6}$$

Assumption 4. *Assume that the function $(t,x)\mapsto f(t,x,\phi(t,x))$ satisfies the Lipschitz condition w.r.t. x in $[0,T]\times\bar{\mathcal{U}}$ and that the unique solution of the reduced System (6) on $[0,T]$ satisfies $\bar{x}(t)\in\mathrm{int}(\bar{\mathcal{U}})$ for all $t\in(0,T)$.*

Assumption 5. *Assume that y_0 belongs to the basin of attraction of the solution $y=\phi(0,x_0)$ of equation $g(0,x_0,y)=0$, that is, the solution $\hat{y}=\hat{y}(\tau)$ of the simplified initial layer equation*

$$\frac{d\hat{y}}{d\tau}=g(0,x_0,\hat{y}),\quad \hat{y}(0)=y_0 \tag{7}$$

satisfies $\hat{y}(\tau)\in\mathcal{V}$ for all $\tau\geqslant 0$ and

$$\lim_{\tau\to\infty}\hat{y}(\tau)=\phi(0,x_0).$$

Theorem 3.1 (Tikhonov's Theorem)**.** *Under Assumptions 1-5, there exists $\varepsilon_0>0$ such that for any $\varepsilon\in\,]0,\varepsilon_0]$ there exists a unique solution $(x(t,\varepsilon),y(t,\varepsilon))$ of the singularly perturbed System (3) on $[0,T]$ satisfying*

$$\lim_{\varepsilon\to 0}x(t,\varepsilon)=\bar{x}(t),\quad t\in[0,T]$$

and

$$\lim_{\varepsilon\to 0}y(t,\varepsilon)=\bar{y}(t),\quad t\in(0,T],$$

where $(\bar{x}(t),\bar{y}(t))$ is the solution of the degenerate System (4).

Tikhonov's theorem connects the solutions of the singularly perturbed system and the degenerate system. Note that only the first convergence in Tikhonov's theorem is uniform (w.r.t. $t \in [0,T]$). However, in the second limit, the convergence is uniform on any interval $[T_0,T]$ with $T_0 > 0$. This is the so-called initial layer effect and one can include the initial layer term to obtain the uniform convergence on $[0,T]$.

Proposition 1. *Let Assumptions 1-5 be satisfied. Then,*

$$\lim_{\varepsilon\to 0}\left[y(t,\varepsilon)-\bar{y}(t)-\hat{y}(t/\varepsilon)+\phi(0,x_0)\right]=0, \quad t\in[0,T],$$

where $\bar{y}(t)$ is the solution of the degenerate System (4), $\hat{y}(t/\varepsilon)$ is the solutions of the simplified initial layer Equation (7), and ϕ is the root of Assumption 2.

We now add one extra assumption, namely:

Assumption 6. *Suppose that $|\delta_1|<\mu$ and $|\delta_2|<\mu$ where μ is a sufficiently small but fixed number independently of ε. Assume that, for $t\in[0,T]$, $f(t,\bar{x}+\delta_1,\bar{y}+\hat{y}+\delta_2)$ and $g(t,\bar{x}+\delta_1,\bar{y}+\hat{y}+\delta_2)$ are continuous together with their derivatives w.r.t. δ_1 and δ_2 up and including the second order.*

Under this further assumption, one can prove the stronger result:

Theorem 3.2. *Let Assumptions 1-6 be satisfied and suppose that $\frac{\partial g}{\partial y}(t,x,y)\Big|_{y=\phi(t,x)}$ exists, is continuous and is negative for $t\in[0,T]$. Then, we have the following estimates*

$$\begin{aligned} x(t,\varepsilon) =& \bar{x}(t)+\mathcal{O}(\varepsilon)\\ y(t,\varepsilon) =& \bar{y}(t)+\hat{y}\,(t/\varepsilon)-\phi(0,x_0)+\mathcal{O}(\varepsilon)\end{aligned}$$

uniformly on $[0,T]$.

For the proof of the above results we refer the reader to [40, 43, 3, 41].

4. **The asymptotic expansion of the model.** As discussed in the Introduction, the dynamics of free virus occurs on a time scale much faster than the dynamics of the cells of the host organism. While the cells have a half-life of the order of days, virions have a half-life of about a few hours [35, 28, 18]. This implies that η_i is much bigger than γ_i and σ_i. Therefore, it is natural to consider the dynamics of System (2) for $\eta_i=\overline{\eta}_i/\varepsilon$ where ε is a small parameter and $\overline{\eta}_i$ has the same order of magnitude of γ_i and σ_i. On the order hand the healthy CD4 + cells have a half-life of about 35 days while the virions have a half-life of 6 hours. This leads to ε of the order of 7×10^{-3}. The System (2) takes the form

$$\begin{aligned} \dot{x} =& 1-x-x\sum_{i\in\mathcal{N}} v_i\\ \dot{y}_i =& \gamma_i\left(xv_i-y_i-y_iz_i\right)\\ \varepsilon\dot{v}_i =& \overline{\eta}_i\left(R_0^i y_i-v_i\right)\\ \dot{z}_i =& \sigma_i\left(I_0^i y_i z_i-z_i\right)\end{aligned} \tag{8}$$

subject to initial conditions x_0, y_0^i, v_0^i and z_0^i.

We now have written System (8) in the form of System (3) and we are ready to use Tikhonov's theorem to connect the solutions of (8) and the reduced system

$$\begin{aligned}\dot{x} =&1 - x - x\sum_{i\in\mathcal{N}} R_0^i y_i\\ \dot{y}_i =&\gamma_i\left(xR_0^i y_i - y_i - y_i z_i\right)\\ \dot{z}_i =&\sigma_i\left(I_0^i y_i z_i - z_i\right)\end{aligned} \tag{9}$$

with initial conditions x_0, y_0^i and z_0^i.

Note that the reduced system has the form of a food chain system [13], where the susceptible CD4+ T cells act as the environmental resources, the infected CD4+ T cells as prey and immunological response cells as predators.

4.1. **Reduced system properties.** Before we apply Tikhonov's theorem, we shall prove some properties of the reduced System (9). Note that the non-negative orthant of $\mathbb{R}^{2n+1}$ is invariant by the flow of the system. Moreover, if the initial conditions are in the interior of $\mathbb{R}^{2n+1}_{\geqslant 0}$, then all solutions will remain in this open set for all $t \geqslant 0$. We also have that the solutions are bounded, as stated in the proposition below. The proof follows the ideas of [25].

Proposition 2. *Let $\psi : [0,\infty) \to \mathbb{R}^{2n+1}$ solution of the System (9) with $\psi(t_0) \in \mathbb{R}^{2n+1}_{\geqslant 0}$. Then, $\psi \in L^\infty[t_0,\infty)$.*

Proof. As the system is positively invariant, we have

$$\dot{x}(t) = 1 - x(t) - x(t)\sum_{i\in\mathcal{N}} v_i(t) \leqslant 1 - x(t)$$

so $\frac{d}{dt}(e^t x(t)) \leqslant e^t$ and integrating from t_0 to t we have

$$x(t) \leqslant 1 - e^{t_0 - t} + e^{t_0 - t}x(t_0) \leqslant 1 + x(t_0).$$

For y_i note that

$$\begin{aligned}\dot{y}_i(t) =&\gamma_i\left(xR_0^i y_i - y_i - y_i z_i\right)\\ \leqslant&\gamma_i\left(xR_0^i - 1\right) y_i\\ \leqslant&\left(\gamma_M x R_0^i - \gamma_m\right) y_i,\end{aligned}$$

where $\gamma_M = \max_{i\in\mathcal{N}}\{\gamma_i\}$ and $\gamma_m = \min_{i\in\mathcal{N}}\{\gamma_i\}$. Denoting $\mathcal{Y}(t) = \sum_{i\in\mathcal{N}} y_i(t)$ we have

$$\dot{\mathcal{Y}}(t) + \gamma_m\mathcal{Y}(t) \leqslant \gamma_M x(t)\sum_{i\in\mathcal{N}} R_0^i y_i(t) = \gamma_M(-\dot{x} + 1 - x(t)),$$

whence

$$\begin{aligned}\mathcal{Y}(t) \leqslant&\mathcal{Y}(t_0)e^{\gamma_m(t_0-t)} + \gamma_M e^{-\gamma_m t}\int_{t_0}^{t}\left(1 - \dot{x}(s) - x(s)\right)e^{\gamma_m s}ds\\ \leqslant&\mathcal{Y}(t_0) + \frac{\gamma_M}{\gamma_m} + \gamma_M x(t_0) + \frac{\gamma_M}{\gamma_m}\left(\gamma_m - 1\right)\left(1 + x(t_0)\right)e^{-\gamma_m t_0}\end{aligned}$$

where we use $e^{\gamma_m(t_0-t)} \leqslant 1$, $x(t) \geqslant 0$ and

$$\int_{t_0}^{t} x(s)e^{\gamma_m(s-t)}ds \leqslant \frac{1 + x(t_0)}{\gamma_m}e^{-\gamma_m t_0}$$

since $x(t) \leqslant 1 + x(t_0)$. Therefore $\mathcal{Y}(t)$ is limited and, as $y_i(t) \geqslant 0$ for all $t \geqslant t_0$, it follows that $y_i(t)$ is limited.

Similarly, we can prove that

$$\mathcal{Z}(t) \leqslant \mathcal{Z}(t_0) + \frac{\sigma_M}{\sigma_m} + \sigma_M x(t_0) + \frac{\sigma_M}{\sigma_m}\left(\sigma_m - 1\right)\left(1 + x(t_0)\right) e^{-\sigma_m t_0},$$

where $\sigma_M = \max_{i\in\mathcal{N}}\{\sigma_i\}$, $\sigma_m = \min_{i\in\mathcal{N}}\{\sigma_i\}$ and $\mathcal{Z}(t) = \sum_{i\in\mathcal{N}} z_i(t)$. This and the positivity of each $z_i(t)$ implies the result. □

Using the same notation for the index for equilibrium points that was previously used, we have the following result:

Theorem 4.1. *If the basic reproductive ratios of each virus strain are distinct, then System (9) admits $2^{n-1}(2+n)$ equilibrium points $W_{j\mathcal{J}}$ that correspond to the points described in Theorem 2.1 omitting entries of v_i.*

The proof of this theorem follows the same idea of the analogous theorem presented in [37]. Finally, we prove the global stability for the System (9) using Lyapunov Theory.

Theorem 4.2. *Assume that $R_0^i > R_0^{i+1}$ for $i = 1, ..., n-1$ and that the set of strong responders is consistent. Then, System (9), defined on $\mathbb{R}^{2n+1}_{\geqslant 0}$, with initial condition in its interior, has a globally asymptotically stable equilibrium given as follows:*

1. *$W_{0\emptyset}$ if $R_0^1 \leqslant 1$;*
2. *$W_{1\emptyset}$ if $R_0^1 > 1$ and $R_0^1 \leqslant R_I^1$;*
3. *If $R_0^1 > R_I^1$, let $\mathcal{J}$ the antigenic maximal set.*
   a. *$W_{0\mathcal{J}}$ if $\mathcal{J}$ is a purely antigenic set;*
   b. *$W_{j\mathcal{J}}$ otherwise, where j is the smallest integer outside $\mathcal{J}$.*

Proof. The existence of the j mentioned in the case (3.a) is proved in [37]. For each asymptotically stable equilibrium point $W^* = (x^*, y_1^*, ..., z_n^*)$ consider the following function

$$V = x - x^* \ln\frac{x}{x^*} + \sum_{i\in\mathcal{N}}\left[\frac{1}{\gamma_i}\left(y_i - y_i^* \ln\frac{y_i}{y_i^*}\right) + \frac{1}{\sigma_i I_0^i}\left(z_i - z_i^* \ln\frac{z_i}{z_i^*}\right)\right],$$

where the term with logarithm should be omitted if the corresponding coordinate is zero. Then,

$$\dot{V} = 1 - x - \frac{x^*}{x} + x^* + \sum_{i\in\mathcal{N}}\left[x^* y_i R_0^i - y_i - R_0^i y_i^* x + y_i^* + z_i y_i^* - z_i^* y_i + \frac{z_i^*}{I_0^i} - \frac{z_i}{I_0^i}\right]. \quad (10)$$

For each case, we will replace the respective equilibrium point in the Equation (10) and we will prove that $\dot{V} \leqslant 0$, that is, V is a Lyapunov function. In addition, we have that, for each case, the set for which the equality $\dot{V} = 0$ is satisfied contains only one positively invariant subset and this subset is exactly the respective equilibrium point. This proves the theorem.

Case (1)

$$\begin{aligned}\dot{V} =& 1 - x - \frac{1}{x} + 1 + \sum_{i\in\mathcal{N}}\left[y_i R_0^i - y_i - \frac{z_i}{I_0^i}\right] \\ =& -\frac{(1-x)^2}{x} + \sum_{i\in\mathcal{N}}\left[y_i(R_0^i - 1) - \frac{z_i}{I_0^i}\right] \leqslant 0\end{aligned}$$

since $R_0^i \leqslant R_0^1 \leqslant 1$.

Case (2)

$$\begin{aligned}\dot{V} =& 1 - x - \frac{1}{R_0^1 x} + \frac{1}{R_0^1} - R_0^1 x + x + 1 - \frac{1}{R_0^1} + z_1\left(1 - \frac{1}{R_0^1}\right) - \frac{z_1}{I_0^1} - \sum_{i=2}^{n}\frac{z_i}{I_0^i} \\ =& -\frac{1}{R_0^1 x}(R_0^1 x - 1)^2 + z_1\left(1 - \frac{R_I^1}{R_0^1}\right) - \sum_{i=2}^{n}\frac{z_i}{I_0^i} \leqslant 0\end{aligned}$$

since $R_0^1 \leqslant R_I^1$.

Case (3.a)

$$\begin{aligned}\dot{V} =& 1 - x - \frac{1}{R_I^{\mathcal{J}} x} + \frac{1}{R_I^{\mathcal{J}}} + \sum_{i\in\mathcal{J}}\left[-\frac{R_0^i}{I_0^i}x + \frac{R_0^i}{R_I^{\mathcal{J}}}\frac{1}{I_0^i}\right] + \sum_{i\notin\mathcal{J}}\left[\left(\frac{R_0^i}{R_I^{\mathcal{J}}} - 1\right)y_i - \frac{z_i}{I_0^i}\right] \\ =& -\frac{1}{R_I^{\mathcal{J}} x}\left(R_I^{\mathcal{J}} x - 1\right)^2 + \sum_{i\notin\mathcal{J}}\left[\left(\frac{R_0^i}{R_I^{\mathcal{J}}} - 1\right)y_i - \frac{z_i}{I_0^i}\right] \leqslant 0\end{aligned}$$

where we use $1 + \sum_{i\in\mathcal{J}}\frac{R_0^i}{I_0^i} = R_I^{\mathcal{J}}$ and, since $\mathcal{J}$ a purely antigenic set, $\frac{R_0^i}{R_I^{\mathcal{J}}} - 1 \leqslant 0$.

Case (3.b)

$$\begin{aligned}\dot{V} =& 1 - x - \frac{1}{xR_0^j} + \frac{1}{R_0^j} + \sum_{i\in\mathcal{J}}\left[-\frac{R_0^i}{I_0^i}x + \frac{R_0^i}{R_0^j I_0^i}\right] + \sum_{i\notin\mathcal{J}\cup\{j\}}\left[\left(\frac{R_0^i}{R_0^j} - 1\right)y_i - \frac{z_i}{I_0^i}\right] \\ &+ \left[-R_0^j x\left(1 - \frac{R_I^{\mathcal{J}}}{R_0^j}\right) + \left(1 - \frac{R_I^{\mathcal{J}}}{R_0^j}\right) + z_j\left(1 - \frac{R_I^{\mathcal{J}}}{R_0^j}\right) - \frac{z_j}{I_0^j}\right] \\ &+ \sum_{i\notin\mathcal{J}\cup\{j\}}\left[\left(\frac{R_0^i}{R_0^j} - 1\right)y_i - \frac{z_i}{I_0^i}\right] \\ =& -\frac{1}{R_0^j x}\left(R_0^j x - 1\right)^2 + \frac{z_j}{R_0^j}\left(R_0^j - R_I^{\mathcal{J}} - \frac{1}{I_0^j}\right) + \sum_{i\notin\mathcal{J}\cup\{j\}}\left[\left(\frac{R_0^i}{R_0^j} - 1\right)y_i - \frac{z_i}{I_0^i}\right] \\ \leqslant& \frac{z_j}{R_0^j}\left(R_0^j - R_I^{\mathcal{J}} - \frac{R_0^j}{I_0^j}\right) + \sum_{i\notin\mathcal{J}\cup\{j\}}\left[\left(\frac{R_0^i}{R_0^j} - 1\right)y_i\right]\end{aligned}$$

where we use $\sum_{i\in\mathcal{J}}\frac{R_0^i}{I_0^i} = R_I^{\mathcal{J}} - 1$. Note that if j belongs to the set of strong responders then $R_0^j - R_I^{\mathcal{J}} - \frac{R_0^j}{I_0^j} \leqslant 0$ (since $\mathcal{J}$ is maximal). Otherwise we have $R_0^i - 1 \leqslant \frac{R_0^j}{I_0^j}$ and then $R_0^j - R_I^{\mathcal{J}} - \frac{R_0^j}{I_0^j} \leqslant -(R_I^{\mathcal{J}} - 1) \leqslant 0$. Furthermore,

$$\sum_{i\notin\mathcal{J}\cup\{j\}}\left[\left(\frac{R_0^i}{R_0^j} - 1\right)y_i\right] \leqslant 0$$

since $\forall i \notin \mathcal{J}\cup\{j\}$ we have $i > j$ and then, $R_0^i < R_0^j$. Therefore, we have $\dot{V} \leqslant 0$. □

4.2. **Main result.** We shall now apply Tikhonov's theorem in order to show that as $\varepsilon \to 0$ the solution of the System (8) approaches the solution of the degenerate system.

We know that solutions of System (8) are bounded (see [25]) and only the bounds on v_i depend on ε. However, for fixed $\varepsilon_0 > 0$, we have that for all $\varepsilon \leqslant \varepsilon_0$ the concentrations of v_i are bounded by constants independently of ε. Since the solution of the degenerate system is also bounded (independently of ε), we can choose a compact set in $\bar{\mathcal{U}} \subset \mathbb{R}^{2n+1}$ and a bounded open set $\mathcal{V} \subset \mathbb{R}^n$ such that the solutions of both systems belong to $\bar{\mathcal{U}} \times \mathcal{V}$ for all $t > 0$. Moreover, for initial conditions in the interior of $\mathbb{R}^{3n+1}_{\geqslant 0}$, we can choose $\bar{\mathcal{U}}$ such that the solutions (x, y, z) will remain in the interior of this compact set for all $t \geqslant 0$.

Theorem 4.3. *Let $\bar{\mathcal{U}}$ and $\mathcal{V}$ be the sets described above. Then, there exists $\varepsilon_0 > 0$ such that for any $\varepsilon \in]0, \varepsilon_0]$ we have a unique solution $(x(t,\varepsilon), y(t,\varepsilon), v(t,\varepsilon), z(t,\varepsilon))$ of the Problem (3) with initial conditions in the interior of the corresponding sets. Moreover,*

$$\begin{aligned}
&\lim_{\varepsilon\to 0} [x(t,\varepsilon) - \bar{x}(t)] = 0\\
&\lim_{\varepsilon\to 0} [y_i(t,\varepsilon) - \bar{y}_i(t)] = 0\\
&\lim_{\varepsilon\to 0} \left[v_i(t,\varepsilon) - R_0^i \bar{y}_i(t) - \left(v_0^i - R_0^i y_0^i\right) e^{-t/\varepsilon}\right] = 0\\
&\lim_{\varepsilon\to 0} [z_i(t,\varepsilon) - \bar{z}_i(t)] = 0
\end{aligned}$$

where $(\bar{x}, \bar{y}, \bar{z})$ is the solution of the reduced System (9).

Proof. The result follows from Tikhonov's Theorem 3.1 and the Proposition 1 since the Assumptions $1 - 5$ are valid, as we show below.

We write System (8) as

$$\begin{aligned}
\dot{x} &= f_1(t, x, y, z, v)\\
\dot{y} &= f_2(t, x, y, z, v)\\
\dot{z} &= f_3(t, x, y, z, v)\\
\varepsilon\dot{v} &= g(t, x, y, z, v)
\end{aligned}$$

where f and g are the appropriate entries of the RHS of Equation (8).

Assumption 2: Let the $\phi : [0, T] \times \bar{\mathcal{U}} \mapsto \mathbb{R}^n$ be defined by $\phi_i(t, x, y, z) = R_0^i y_i(t)$. Then ϕ is an isolated root of g since given $\delta > 0$ we have, for any $(t, x, y, z) \in [0, T] \times \bar{\mathcal{U}}$

$$\begin{aligned}
0 < ||v - \phi|| < \delta \Leftrightarrow & 0 < |v_i - R_0^i y_i| < \delta \ \forall i \in \mathcal{N}\\
\Leftrightarrow & g_i(t, x, y, z, \phi) \neq 0 \ \forall i \in \mathcal{N}.
\end{aligned}$$

Assumption 3: The boundary layer equation is given by

$$\frac{d\tilde{v}}{d\tau} = g(t, x, y, z, \tilde{v})$$

where t, x, y, and z are treated as parameters. Then, $\tilde{v}_i(\tau, t, x, y, z) = R_0^i y_i(t) + c_i e^{-\overline{\eta}_i \tau}$, with c_i constants. Given $\nu > 0$, let's choose $\delta = \nu$. So, if $|\tilde{v}_i(0, t, x, y, z) - \phi_i(t, x, y, z)| < \delta$ (that is $|c_i| < \delta$), then

$$|\tilde{v}_i(\tau, t, x, y, z) - \phi_i(t, x, y, z)| = |c_i e^{-\overline{\eta}_i \tau}| \leqslant \delta e^{-\overline{\eta}_i \tau} \leqslant \delta = \nu$$

for all $i \in \mathcal{N}$ and $(t, x, y, z) \in [0, T] \times \bar{\mathcal{U}}$.

Furthermore,

$$\lim_{\tau\to\infty} \tilde{v}_i(\tau,t,x,y,z) = R_0^i y_i(t) = \phi_i(t,x,y,z).$$

Assumption 4: As $\bar{\mathcal{U}}$ is bounded, the Lipschitz condition of f follows and the choice of $\bar{\mathcal{U}}$ yields the second part of the assumption.

Assumption 5: Note that the solution $\hat{v}$ of the simplified initial layer equation is

$$\hat{v}_i(\tau) = R_0^i y_0^i + (v_0^i - R_0^i y_0^i)e^{-\overline{\eta}_i\tau}.$$

Thus, $\hat{v}_i(\tau) \in \mathcal{V}$, due to the choice of $\mathcal{V}$, and

$$\lim_{\tau\to\infty} \hat{v}_i(\tau) = R_0^i y_0^i = \phi_i(0,x_0,y_0,z_0).$$

Therefore, v_0 belongs to the basin of attraction of the solution $v = \phi(0,x_0,y_0,z_0)$ of equation $g(0,x_0,y_0,z_0,v) = 0$.

Applying Tikhonov's Theorem, we have the limits for x, y and z. As for the limit of v, just replace

$$\begin{aligned}
\bar{v}_i &= R_0^i \bar{y}_i(t) \\
\hat{v}_i &= R_0^i y_i(t) + \left(v_0^i - R_0^i y_i(t)\right) e^{-t\overline{\eta}_i/\varepsilon} \\
\phi_i(0,x_0,y_0,z_0) &= R_0^i y_0^i
\end{aligned}$$

in the limit of Proposition 1. □

Theorem 4.4. *Let $(x(t,\varepsilon), y_i(t,\varepsilon), v_i(t,\varepsilon), z_i(t,\varepsilon))$ be the solution of the problem (3) with initial condition in the interior of $\bar{\mathcal{U}} \times \mathcal{V}$ and $(\bar{x}, \bar{y}_i, \bar{z}_i)$ be the solution of the reduced System (9). Then, we have the following estimates*

$$\begin{aligned}
x(t,\varepsilon) =& \bar{x}(t) + \mathcal{O}(\varepsilon) \\
y_i(t,\varepsilon) =& \bar{y}_i(t) + \mathcal{O}(\varepsilon) \\
v_i(t,\varepsilon) =& R_0^i \bar{y}_i(t) + \left(v_0^i - R_0^i y_0^i\right) e^{-t\overline{\eta}_i/\varepsilon} + \mathcal{O}(\varepsilon) \\
z_i(t,\varepsilon) =& \bar{z}_i(t) + \mathcal{O}(\varepsilon)
\end{aligned}$$

uniformly on $[0,T]$.

Proof. Take f and g as in the proof of the previous theorem. Since $y_0^i > 0$, we have that

$$\frac{\partial g_i}{\partial v}(t,x,y,z,v)\bigg|_{v=\phi(t,x,y,z)} = -R_0^i y_i(t) < 0\ .$$

Furthermore, it is continuous for all $t \in [0,T]$. Also, since $\bar{x}, \bar{y}, \bar{z}$ and $\hat{v}$ are continuous, is easy to see that the Assumption 6 is valid. Applying the Theorem 3.2 we obtain the above estimates. □

The estimates relatives to the System (1) can be seen in Appendix.

4.3. **Numerical examples.** In this section we present some numerical illustrations of the results presented in this paper. Note that all parameters involved are non-dimensional. It is worth pointing out that the numerical solutions of the original problem have been computed with relative tolerance of 10^{-10} to avoid any numerical instabilities. For simplicity, we consider first the case of one strain ($n = 1$) without treatment.

Figure 2 shows the attractiveness of the quasi-steady state for viral load, that is, it compares the solution of the quasi-steady state $\bar{v}(t) = R_0\bar{y}(t)$ with the approximation of $v(t, \varepsilon)$, given by Theorem 4.4, for different values of ε. Here $\bar{y}$ is the solution of the reduced System (9). This figure illustrates that the initial layer term, given by $(v_0 - R_0 y_0)\, e^{-t/\varepsilon}$, tends to disappear for ε small enough, except for the very small times due to the difference in initial conditions.

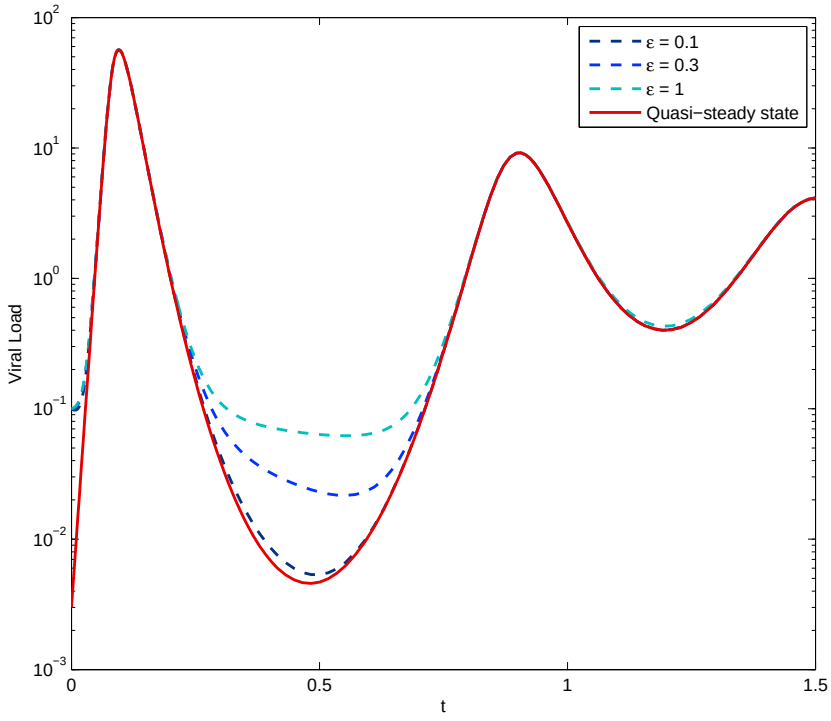
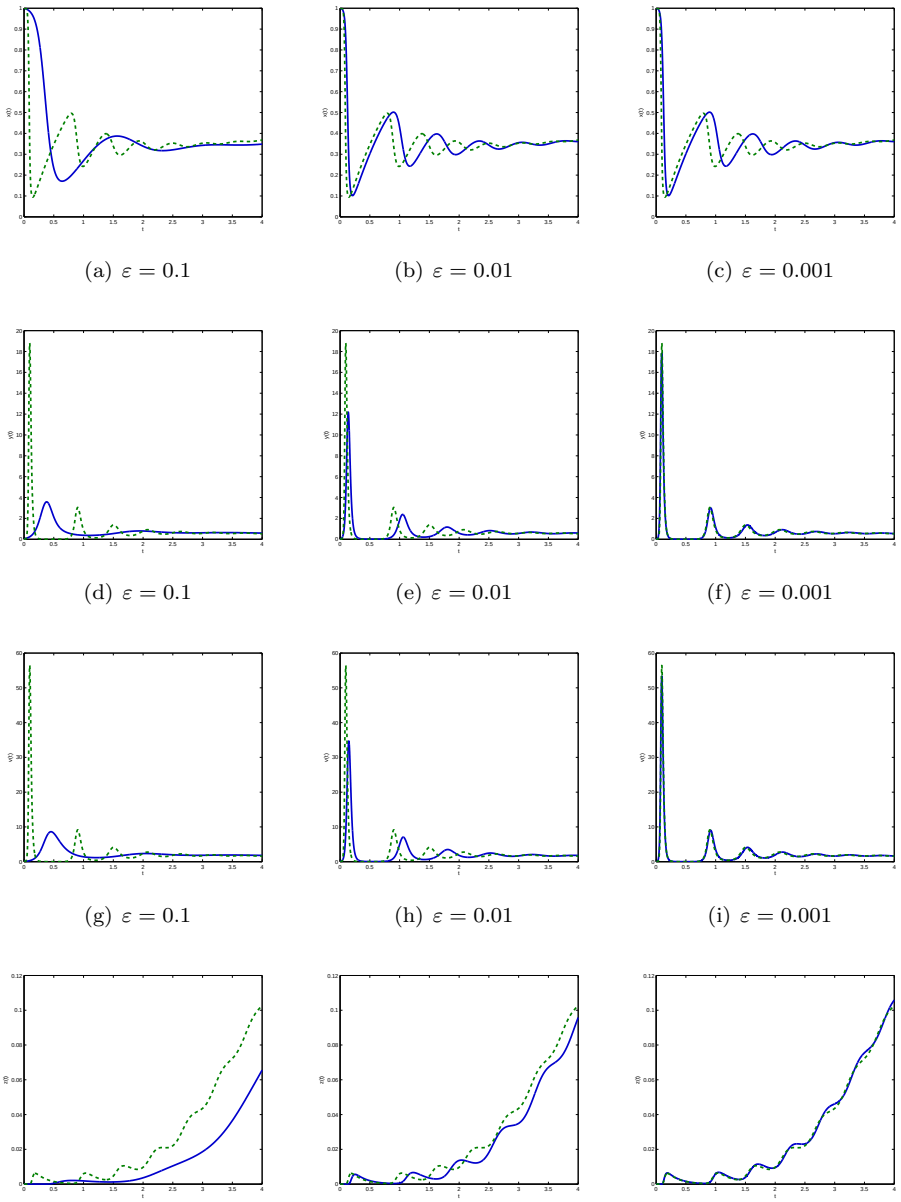


FIGURE 2. Attractiveness of the quasi-steady state for viral load: the continuous line is $\bar{v}(t) = R_0\bar{y}(t)$, where $\bar{y}$ is the solution of the reduced System (9), and the dotted lines is the approximation of $v(t, \varepsilon)$, that is, $R_0\bar{y}(t) + (v_0 - R_0 y_0)\, e^{-t/\varepsilon}$ for different values of ε. The parameters used are $\gamma = 62$, $\sigma = 5$, $x_0 = 1$, $y_0 = 10^{-3}$, $v_0 = 10^{-1}$, $z_0 = 10^{-6}$, $R_0 = 3$, $I_0 = 2$ and $\varepsilon = 1, 0.3$ and 0.1.

Figure 3 illustrates the expressions of Theorems 4.3 and 4.4 for the susceptible cells (x), infected cells (y), viral load (v) and defense cells (z), respectively. According to our results, when we decrease ε, the right hand side of the expressions approximate the solutions of Problem (8).



(a) $\varepsilon = 0.1$ (b) $\varepsilon = 0.01$ (c) $\varepsilon = 0.001$

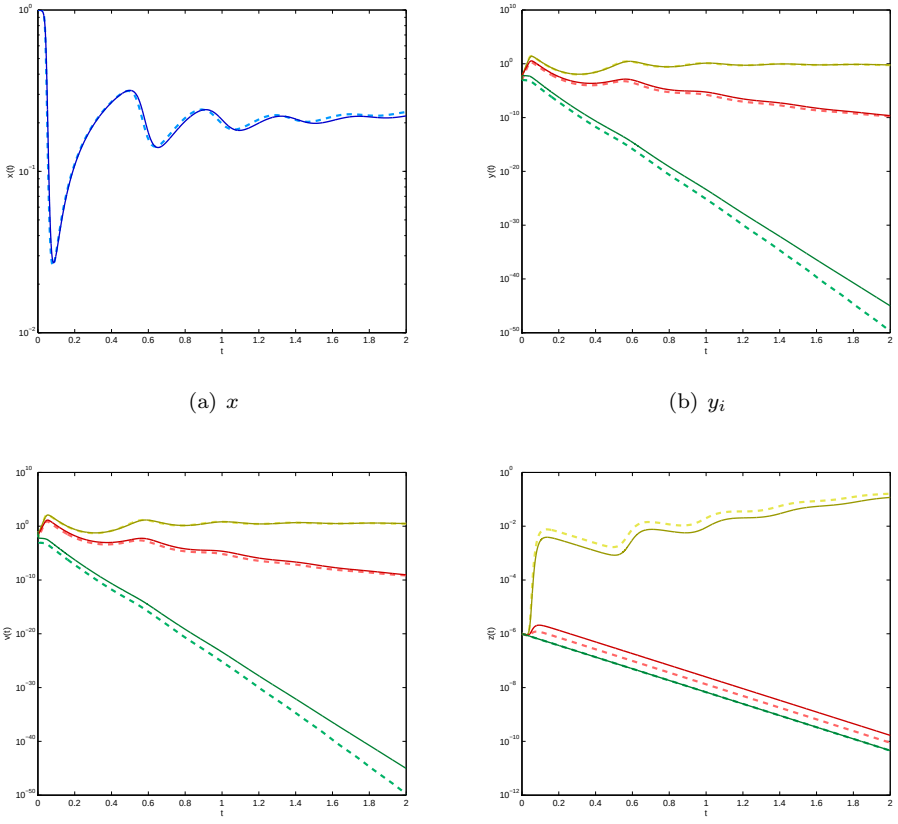
(d) $\varepsilon = 0.1$ (e) $\varepsilon = 0.01$ (f) $\varepsilon = 0.001$

(g) $\varepsilon = 0.1$ (h) $\varepsilon = 0.01$ (i) $\varepsilon = 0.001$

(j) $\varepsilon = 0.1$ (k) $\varepsilon = 0.01$ (l) $\varepsilon = 0.001$

FIGURE 3. Convergence of the asymptotic solution of Theorems 4.3 and 4.4. The continuous line represents the solution of the System (8) while the dotted lines are the respective approximations of $x(t,\varepsilon)$, $y(t,\varepsilon)$, $v(t,\varepsilon)$, and $z(t,\varepsilon)$ given by the results of Section 4.2. The parameters used are $\gamma = 62$, $\sigma = 5$, $x_0 = 1$, $y_0 = 10^{-3}$, $v_0 = 10^{-1}$, $z_0 = 10^{-6}$, $R_0 = 3$, $I_0 = 2$, $\bar{\eta} = 1$ and $\varepsilon = 0.1, 0.01$ and 0.001.

Similarly to the previous ones, Figure 4 illustrates the expressions of Theorems 4.3 and 4.4 when considering three strains. Note that the parameters were chosen to represent the case (3.b) of the Theorem 2.2, where the set of strong responders is $\mathcal{S} = \{1, 2\}$ and the antigenic maximal set is $\mathcal{J} = \{1\}$ and it is not purely antigenic. Then, the asymptotically stable equilibrium point is $W_{2\{1\}}$, that is, the virion whose index is 2 (red) remains in the organism without being fought by the immune system, the virion of index 1 (yellow) also remains in the body but being fought by the immune system, while the other virion (green) tends to disappear.



(a) x (b) y_i

(c) v_i (d) z_i

FIGURE 4. Convergence of the asymptotic solution of Theorems 4.3 and 4.4 considering three virus strains. The continuous line represents the solution of the System (8) while the dotted lines are the approximations of the solutions $x(t, \varepsilon)$, $y(t, \varepsilon)$, $v(t, \varepsilon)$ and $z(t, \varepsilon)$ given by the results of Section 4.2. The parameters used are $\gamma_i = 62$, $\sigma_i = 5$, $x(0) = 1$, $y_i(0) = 10^{-3}$, $v_i(0) = 10^{-1}$, $z_i(0) = 10^{-6}$, $I_0^i = 2$, $\bar{\eta}_i = 1$ for $i = 1, 2$ and 3, $\varepsilon = 0.001$, $R_0^1 = 5$, $R_0^2 = 4$ and $R_0^3 = 0.9$. The indices 1, 2 and 3 are represented by the colors yellow, red and green, respectively.

4.4. **Computational performance.** In this section we present a brief analysis of the performance of the systems involved in our results. We compare the numerical solution of the System (8) with the approximate solution of this system provided by our result. For simplicity, in this section we call these systems, respectively, by FS (full system) and RS (once uses the reduced system). For the analysis, we disregard the treatment with inhibitors, since that may be interpreted as a change of variables.

We compare the solutions of the FS and the RS with respect to runtime and number of one step of the ODE solver. We shall refer to that s one function evaluation.

To analyze each of these aspects we consider different numbers of strains (n), and for each fixed number of strains, we perform 1000 tests with parameters taken randomly according to the Table 2. The time interval (dimensionless) considered is $[0, 15]$.

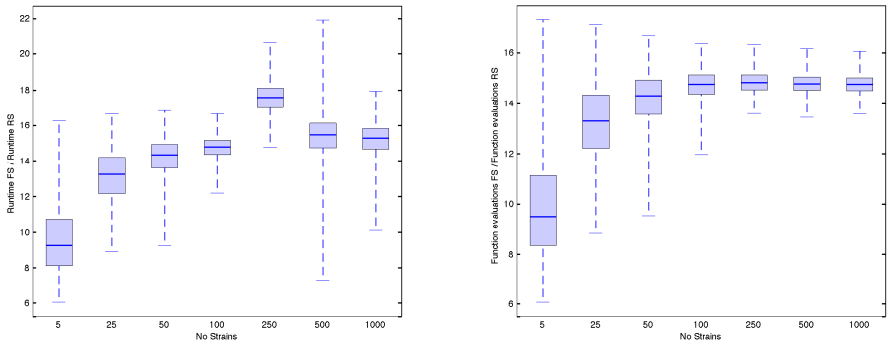
Parameter	Interval
$x(0)$	$1 \pm 20\%$
$y_i(0)$	$6 \times 10^{-9} \pm 20\%$
$v_i(0)$	$6 \times 10^{-9} \pm 20\%$
$z_i(0)$	$4 \times 10^{-6} \pm 20\%$
γ_i	$29 \pm 20\%$
η_i	$350 \pm 20\%$
σ_i	$1 \pm 20\%$
I_0^i	$7 \pm 50\%$
R_0^i	$8 \pm 50\%$

TABLE 2. Description of parameters used in the analysis of performance.

Figure 5 shows the quartiles of the quotient between the performance of the FS and the RS with regard to runtime and number of evaluations. Note that in all cases, the RS obtained a better performance than the FS. In the case of 250 strains, the RS showed a run time approximately 18 times smaller and required about 15 times fewer function evaluations. Although the running time of one system evaluation is relatively small (we obtained 1.89s for the FS and 0.01073s for the RS, both with 250 strains), many methods of parameter estimation require the use of numerical evaluations a large number of times.

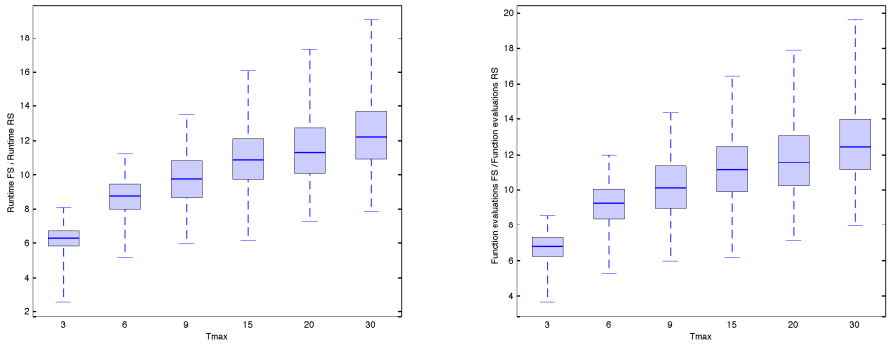
Analogously, we verified the performance by varying the size of the time interval (and setting the number of strains to 10). Again, the performance of the RS was much better than that of the FS, as shown in Figure 6.

5. **Conclusion.** The existence of an asymptotic reduced dynamics for the model that was proved in Section 4 allows a number of applications. One is the possibility of solving a simpler system for numerical simulations and predictions. Indeed, the full system leads to very stiff differential equations for realistic biological parameters because some components of the solution decay much more rapidly than others. By working with the reduced system we are avoiding this potential problem. Another application is the possibility of using it to calibrate the model in a more robust form. As presented in Subsection 4.4, we have that the time spent for the numerical solution of system using our results are at least 5 times shorter than those expended



(a) Runtime (b) Function Evaluations

FIGURE 5. Quartiles for the quotient between the performance of the FS and the RS considering different numbers of strains. For each strain, the system is evaluated 1000 times with parameters taken randomly according to the Table 2. Figure (a) depicts performance with respect to runtime while figure (b) with respect to the number of times that the ODE function was evaluated.



(a) Runtime (b) Function Evaluations

FIGURE 6. Quartiles for the quotient between the performance of the FS and the RS considering different time intervals. For each time interval, the system is evaluated 1000 times with parameters taken randomly according to the Table 2 and 10 strains. Figure (a) depicts performance with respect to runtime while figure (b) with respect to the number of times that the ODE function was evaluated.

to solve the original system. In some cases (higher number of strains) it came to be 17 times lower. The numerical solution of the system using the approach of our results still showed a better performance by analyzing the required number of function evaluations and the number of successful steps. This is very useful especially when it is necessary to solve the system many times, which is common in methods of parameter estimation. Yet another application is the possibility of inferring R_0 from the behavior and stability of the reduced dynamics in a simpler

form. In fact, when we look at our result considering the original parameters without strains or treatment (see 5) we obtain that $V(t) \sim \frac{k}{u} Y(t)$. Since the average life-time of free virus $1/u$ is a known parameter [35, 28, 18, 33], this allows us to estimate k based on the values of infected cells Y and viral load V. Despite the clinical tests for HIV used in large-scale provide the total CD4 count (infected and uninfected), a clinical test capable of estimate the infected CD4 cell count is already used in some research centers [31].

Note that, in the simplified case of only one strain, the system of ODEs discussed in this article is similar (but not the same) to the model discussed in [36]. The System (8) has one more equation (z - equation) and the second equation has one more nonlinear term, correlating the infected cells (y) and the immune system (z). Furthermore, even in the case $z(t) \equiv 0$, the two systems do not match. Indeed, the equations involving the multiscale term do not have the same format. Thus the results of the present paper are related to those of [36] but do not come as a consequence thereof.

One natural follow up of the present work would be consider more general systems than those described by the dynamics (3) and analyze then at the light of [39, 8]. We are currently pursuing such avenues.

Appendix. As mentioned in Section 4.2, we present here the main Theorem 4.4 adapted to the original variables of System (1).

Consider the reduced system below with respect to the System (1)

$$\begin{aligned}
\dot{\bar{X}} =& \lambda - d\bar{X} - (1-E_F)(1-E_T)(1-E_P)(1-E_I)\bar{X}\sum_{i\in\mathcal{N}} \beta_i \frac{k_i}{u_i}\bar{Y}_i \\
\dot{\bar{Y}}_i =& (1-E_E)(1-E_T)(1-E_P)(1-E_I)X\beta_i\frac{k_i}{u_i}\bar{Y}_i - a_i\bar{Y}_i - p_i\bar{Y}_i\bar{Z}_i \\
\dot{\bar{Z}}_i =& c_i\bar{Y}_i\bar{Z}_i - b_i\bar{Z}_i
\end{aligned}$$

for $i \in \mathcal{N} = \{1, 2, ..., n\}$.

Then the estimates of the Theorem 4.4 can be rewritten in terms of the original variables of System (1):

$$\begin{aligned}
X(T,\varepsilon) =& \bar{X}(T) + \mathcal{O}(\varepsilon) \\
Y_i(T,\varepsilon) =& \bar{Y}_i(T) + \mathcal{O}(\varepsilon) \\
V_i(T,\varepsilon) =& (1-E_T)(1-E_P)(1-E_I)\frac{k_i}{u_i}\bar{Y}_i(T) \\
&+ \left(v_0^i - (1-E_T)(1-E_P)(1-E_I)\frac{k_i}{u_i}y_0^i\right)e^{-T/\varepsilon} + \mathcal{O}(\varepsilon) \\
Z_i(T,\varepsilon) =& \bar{Z}_i(T) + \mathcal{O}(\varepsilon)
\end{aligned}$$

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