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 occurs 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.

Keywords Global stability · Multi-scale analysis · HIV · Immune response · Mutation · Lyapunov functions

Contents

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 [20]. The problem is even more striking in less developed areas [37]. 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, 18].

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 a 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 [18]. From the mathematical point of view, there has been several research lines and approaches [1,4,5,8,13,14,17,18,22–24,27,30,31,35]. Among those, we shall consider in the present article the within host dynamics of the HIV virus. It has received a substantial amount of attention. See for example [23, 24] 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 [9, 10, 13, 15, 16, 25, 28]. 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. Thus leading to different strains of the same viruses. Mathematical models incorporating such aspect have been studied by a number of authors. See [30] and references therein.

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 (see for example [12, 21, 34, 36]) and in the context of biological modeling of infectious diseases in [3, 26, 29]. 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 [30].

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.

As mentioned before, one of the main characteristics of HIV is its extensive genetic variability, that is, the replication process can generate new virions with slightly modified genetic content. From the point of view of the model, this will result in a different class of infected cells and immune cells. This leads to the study of the interplay between immune response and virus diversity for a number of different strains, as discussed in [19].

The Mathematical Model

Several models have been proposed in order to describe the HIV in-vivo dynamics [1, 6, 8, 13, 17–19, 23, 24]. We consider a slightly generalized form of the model studied by Nowak and Bangham [19]. Let n be the number of strains and i denote the index indicating each different strains. The model that we consider has $(4n + 1)$ variables: susceptible CD4+ T cells (X), infected CD4+ T cells (Y_i), virions (V_i), defective viruses (H_i) and cytotoxic T cells (Z_i). These

quantities 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, $\beta_i X V_i$. Infected cells produce free virus particles at a rate proportional to their abundance, $k_i Y_i$, die at a rate $a_i Y_i$ and are killed by cytotoxic T cells at rate $p_i Y_i Z_i$. Free viral particles die at rate $u_i V_i$. Finally, the rate of proliferation of defense cells is given by $b_i Z_i$. The Figure 1 summarizes the HIV replication cycle described above in the case of a single strain.

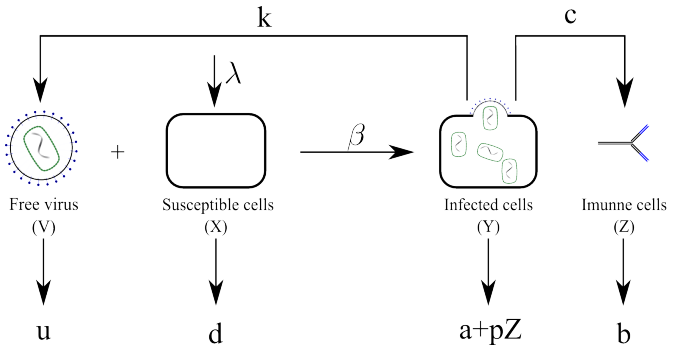


Figure 1: Description of the HIV model with the parameters described in Table 1.

Upon considering the enzyme inhibitors described above and combining the dynamics of HIV, host cells and defense cells we obtain the following first-order ODE system

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

for $i \in \mathcal{N} = \{1, 2, ..., n\}$. Table 1 summarizes the biological meaning of each parameter.

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 [18, 19] and also [30]. 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

Parameter	Meaning
λ	CD4+ T cells supply rate
β_i	Infection rate
k_i	Free virus production rate
c_i	cytotoxic T cells production rate
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
$1/u_i$	average life-time of free virus
$1/b_i$	average life-time of cytotoxic T cells

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

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 theorem 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 illustration of our results.

2 Model Properties

Many properties of the System (1) are already known. Indeed, Pastore [22] showed that the solutions to a similarly system are invariant on the positive orthant and identified the equilibrium points. Souza & Zubelli [30] 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):

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

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 Properties of the System: 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 (10) are the projections of the original System (1).

Before stating the main results, we introduce some notation. It is well known (see for example [18, 19, 30]) 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 [30], 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 [30]

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

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 indice of the strain that remains in the organism without been fought by the immune system

Theorem 1. [30] *If the basic reproductive ratios of the virus strains are distinct, then System* (2) *has* $2^{n-1}(2+n)$ *equilibrium points* $W_{j\mathcal{J}}$ *are described by*

1. *For* $\mathcal{J} = \emptyset$ *and* $j = 0$, *then* $x_{0\emptyset} = 1$ *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* $j \in \mathcal{N}$, *then* $x_{j\emptyset} = 1/R^j_0$,

$$y^j_{j\emptyset} = 1 - \frac{1}{R^j_0}, \quad v^j_{j\emptyset} = R^j_0 - 1, \quad z^j_{j\emptyset} = 0, \quad \textit{and} \quad y^i_{j\emptyset} = v^i_{j\emptyset} = z^i_{j\emptyset} = 0, \quad \forall i \neq j \ .$$

3. *For* $\mathcal{J} \neq \emptyset$ *and* $j = 0$, *then* $x_{0\mathcal{J}} = 1/R^{\mathcal{J}}_I$,

$$y^i_{0\mathcal{J}} = \frac{1}{I^i_0}, \quad v^i_{0\mathcal{J}} = \frac{R^i_0}{I^i_0},, \quad z^i_{0\mathcal{J}} = \frac{R^i_0}{R^{\mathcal{J}}_I} - 1, \quad \forall i \in \mathcal{J}$$

and

$$y^i_{j\emptyset} = v^i_{j\emptyset} = z^i_{j\emptyset} = 0, \quad \forall i \notin \mathcal{J} \ .$$

4. *For* $\mathcal{J} \neq \emptyset$ *and* $j \in \mathcal{N} - \mathcal{J}$, *then* $x_{j\mathcal{J}} = 1/R^{\mathcal{J}}_I$,

$$y^j_{j\mathcal{J}} = 1 - \frac{R^{\mathcal{J}}_I}{R^j_0}, \quad v^j_{j\mathcal{J}} = R^j_0 - R^{\mathcal{J}}_I, \quad z^j_{j\mathcal{J}} = 0,$$

$$y^i_{j\mathcal{J}} = \frac{1}{I^i_0}, \quad v^i_{j\mathcal{J}} = \frac{R^i_0}{I^i_0}, \quad z^i_{j\mathcal{J}} = \frac{R^i_0}{R^j_0} - 1, \quad \forall i \in \mathcal{J},$$

and

$$y^i_{j\mathcal{J}} = v^i_{j\mathcal{J}} = z^i_{j\mathcal{J}} = 0 \quad \textit{otherwise.}$$

To state the result of global stability we need some definitions. Following [30], let us define the set of *strong responders* as

$$\mathcal{S} = \{i \in \mathcal{N}; R^i_0 > R^i_I\} \ .$$

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 $\mathcal{J} \neq \emptyset$, then we shall say that $\mathcal{J}$ is the maximal antigenic set.

Theorem 2. [30] *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:*

(i) *$W_{0\emptyset}$ if $R_0^1 \leqslant 1$;*

(ii) *$W_{1\emptyset}$ if $R_0^1 > 1$ and $R_0^1 \leqslant R_I^1$;*

(iii) *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 1 and 2 can be found in [30]. 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 (2). 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) converge 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 a 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 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*

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

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 $\phi(t,x)$

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

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 $\bar{x}(t) \in \text{int}(\bar{\mathcal{U}})$ 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 (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*

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

and

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

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 $[T_0, T], T_0 > 0$. 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 4. *Let Assumptions 1-5 be satisfied. Then,*

$$\lim_{\varepsilon \to 0} [y(t,\varepsilon) - \bar{y}(t) - \hat{y}(t/\varepsilon) + \phi(0, x_0)] = 0, \quad t \in [0,T] \tag{8}$$

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 5. *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 [3, 33, 34, 36].

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 [16, 25, 28]. 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) will be in the form

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

subject to initial conditions x_0, y_0^i, v_0^i and z_0^i. We now have System (9) in the form of System (3) and we are ready to use Tikhonov's theorem to connect the solutions of (9) and the following reduced system

$$\begin{aligned} \dot{x} &= 1 - x - x \textstyle\sum_{i \in \mathcal{N}} R_0^i y_i \\ \dot{y}_i &= \gamma_i \left(x R_0^i y_i - y_i - y_i z_i \right) \\ \dot{z}_i &= \sigma_i \left(I_0^i y_i z_i - z_i \right) \end{aligned} \tag{10}$$

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 [11], 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 Properties of the Reduced System

Before we apply Tikhonov's theorem, we shall prove some properties of the reduced System (10). 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 solution will be 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 [22].

Proposition 6. *Let $\psi : [0, \infty) \to \mathbb{R}^{2n+1}$ solution of the System (10) 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

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

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 7. *If the basic reproductive ratios of each virus strain are distinct, then System* (10) *admits* $2^{n-1}(2+n)$ *equilibrium points* $W_{j\mathcal{J}}$ *that correspond to the points described in Theorem 1 omitting entries of* v_i*.*

The proof of this theorem follows the same idea of the analogous theorem presented in [30]. Finally, we prove the global stability for the System (10) using Lyapunov Theory.

Theorem 8. *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* (10)*, defined on* $\mathbb{R}^{2n+1}_{\geqslant 0}$*, with initial condition in its interior, has a globally asymptotically stable equilibrium given as follows:*

(i) $W_{0\emptyset}$ *if* $R_0^1 \leqslant 1$*;*

(ii) $W_{1\emptyset}$ *if* $R_0^1 > 1$ *and* $R_0^1 \leqslant R_I^1$*;*

(iii) *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 $(iii)(b)$ is proved in [30]. 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,

$$\dot{V} = 1 - x - \frac{x^*}{x} + x^* + \sum_{i \in \mathcal{N}} \left[x^* y_i R_0^i - y_i - R_0^i y_i^* x + y_i^* + z_i y_i^* - z_i^* y_i + \frac{z_i^*}{I_0^i} - \frac{z_i}{I_0^i} \right]. \tag{11}$$

For each case, we will replace the respective equilibrium point in the Equation (11) 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 (i)

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

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

Case (ii)

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

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

Case (iii)(a)

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

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 (iii)(b)

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

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 The Main Result

We shall now apply the Tikhonov's theorem to System (9) in order to show that the limit equation satisfied by the solutions as $\varepsilon \to 0$ is the solutions of an algebraic differential system.

We known that solutions of System (9) are bounded (see [22]) and only the bounds on v_i depend on ε. However, fixed $\varepsilon_0 > 0$, we have that for all $\varepsilon \leqslant \varepsilon_0$ the concentrations of v_i is bounded by constants independently of ε. Because of this and as the degenerate system also is bounded (independently of ε), we can choose a compact set in $\bar{\mathcal{U}} \subset R^{2n+1}$ and a bounded open set $\mathcal{V} \subset R^n$ such that $(x, y, z, v) \in \bar{\mathcal{U}} \times \mathcal{V}$ for all $t > 0$, where (x, y, z, v) are the solutions of the degenerate system or of System (9). 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 be remain in the interior of this compact set for all $t \geqslant 0$.

Theorem 9. *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 (10).

Proof: The result follows from Tikhonov's Theorem 3 and the Proposition 4 since the Assumptions $1 - 5$ are valid, as we shown below.

We write System (9) 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 (9).

(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

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

in the limit of Proposition 4. ∎

Theorem 10. *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 (10). Then, we have the following estimates*

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

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 5 we obtain the above estimates. ∎

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

4.3 Numerical Illustration

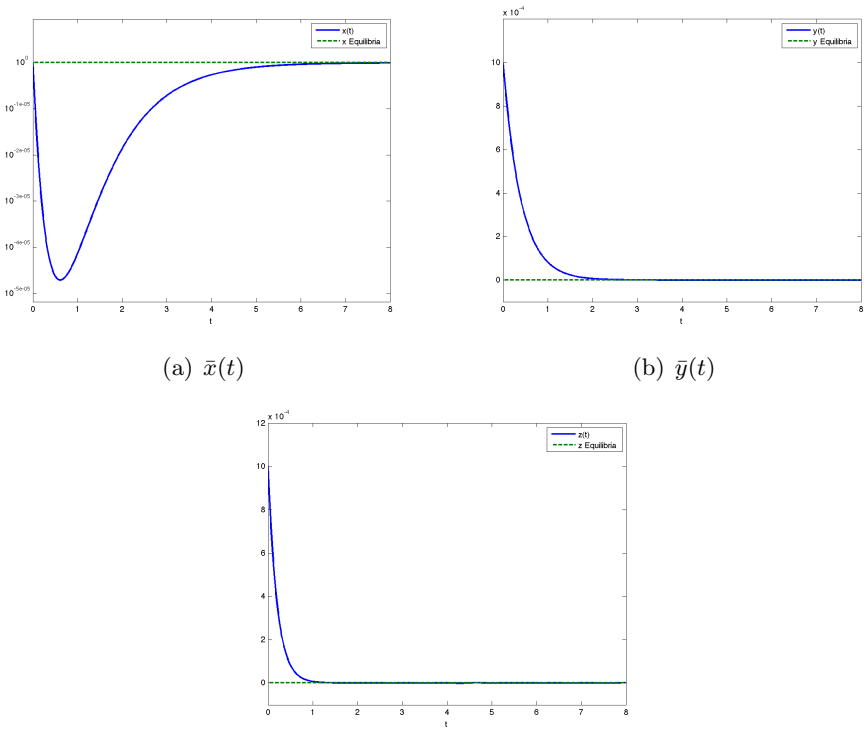
In this section we present some numerical illustrations of the results presented in this paper. Note that all parameters involved are non-dimensional. For simplicity we consider the case of one strain ($n = 1$).

Figures (2), (3) and (4) illustrate the three cases of the Theorem 8, that is, show the conver-

gence of the solutions of the reduced System (10) to one of the globally asymptotically stable equilibrium points.

Figure (5) shows the attractiveness of the quasi-steady state for viral load, that is, compare the solution of the quasi-steady state of the viral load $\bar{v}(t) = R_0\bar{y}(t)$ with the approximation of $v(t,\varepsilon)$, given by Theorem 10, for different values of ε. Here $\bar{y}$ is the solution of the reduced System (10). 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.

Figures (6), (7), (8) and (9) illustrate the expressions of Theorems 9 and 10 for the susceptible cells (x), infected cells (y), viral load (v) and defense cells (z), respectively. According to the theorems, when we decrease ε the right side of the expressions approximate the solutions of the Problem (9).



(a) $\bar{x}(t)$ (b) $\bar{y}(t)$

(c) $\bar{z}(t)$

Figure 2: Convergence of solutions of the (reduced) System (10) the equilibrium points, according to the case (i) of the Theorem 8. The parameters used were $I_0 = R_0 = 0.5 < 1$, $\gamma = \sigma = 5$, $x_0 = 1$, $y_0 = 10^{-3}$ and $z_0 = 10^{-3}$.

5 Conclusion

The existence of an asymptotic reduced dynamics for the model that was proved in Section 4 allows a number of applications. A first one is the possibility of solving a simpler system for numerical simulations and predictions. Indeed, the full system leads to very stiff differential equations if we use the constants associated to the realistic biological parameters. Another application is the possibility of using it to predict in a more robust form the short term dynamics and to calibrate the model. Yet another application is the possibility of inferring R_0 from the behavior and stability of the reduced dynamics in a simpler form.

Note that, in the simplified case of only one strain, the system of ODE's discussed in this article is similar (but not the same) to the model discussed in [29]. The System (9) 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 [29] 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 [7, 32]. We are currently pursuing such avenue.

Appendix

As mentioned in Section 4.2, we present here the main Theorem 10 adapted to the original variables of System (1).

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

$$\begin{cases} \dot{\bar{X}} &= \lambda - d\bar{X} - (1-E_F)(1-E_T)(1-E_P)(1-E_I)\bar{X}\sum_{i\in\mathcal{N}}\beta_i\frac{k_i}{u_i}\bar{Y}_i \\ \dot{\bar{Y}}_i &= (1-E_E)(1-E_T)(1-E_P)(1-E_I)X\beta_i\frac{k_i}{u_i}\bar{Y}_i - a_i\bar{Y}_i - p_i\bar{Y}_i\bar{Z}_i \\ \dot{\bar{Z}}_i &= c_i\bar{Y}_i\bar{Z}_i - b_i\bar{Z}_i \end{cases} \tag{12}$$

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

Then the estimates of the Theorem 10 can be rewritten in terms of the original variables of System (1):

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

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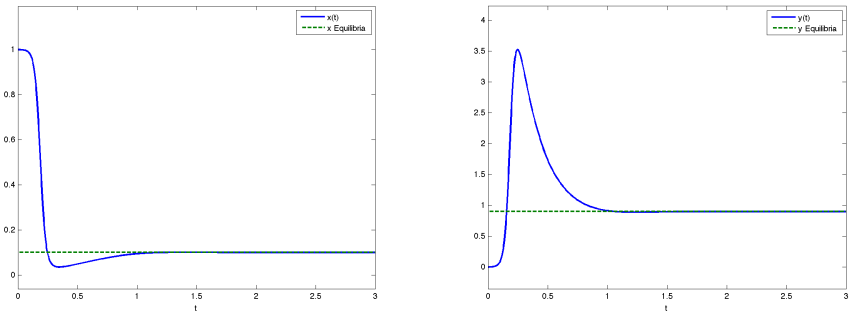
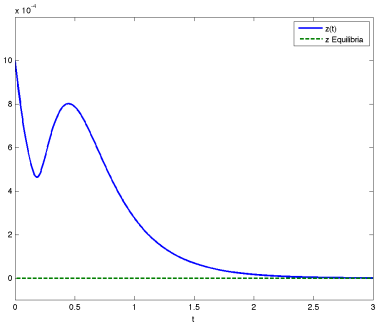
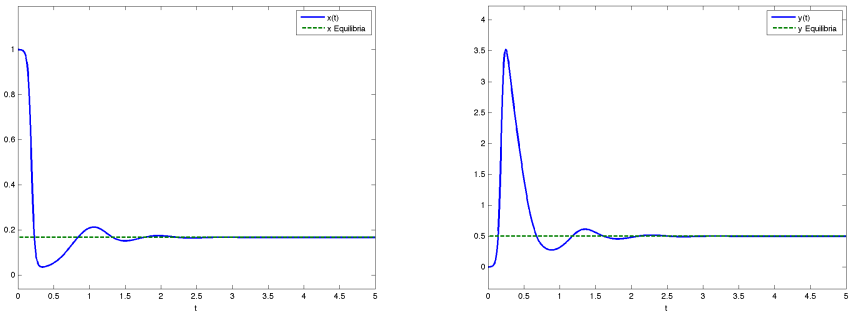


(a) $\bar{x}(t)$ (b) $\bar{y}(t)$

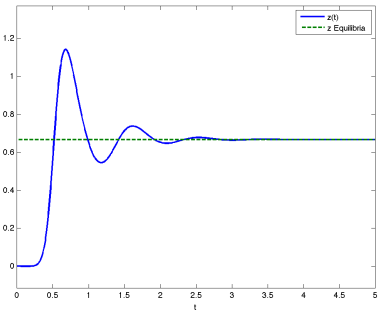


(c) $\bar{z}(t)$

Figure 3: Convergence of solutions of the reduced System (10) to the equilibrium points, according to the case (ii) of the Theorem 8. The parameters used were $R_0 = 10 > 1$ and $I_0 = 0.5$, getting $R_I = 21 > R_0$, $\gamma = \sigma = 5$, $x_0 = 1$, $y_0 = 10^{-3}$ and $z_0 = 10^{-3}$.



(a) $\bar{x}(t)$ (b) $\bar{y}(t)$



(c) $\bar{z}(t)$

Figure 4: Convergence of solutions of the reduced System (10) to the equilibrium points, according to the case (iii) of the Theorem 8. The parameters used were $I_0 = 2$ and $R_0 = 10$, getting $R_I = 6 < R_0$, $\gamma = \sigma = 5$, $x_0 = 1$, $y_0 = 10^{-3}$ and $z_0 = 10^{-3}$.

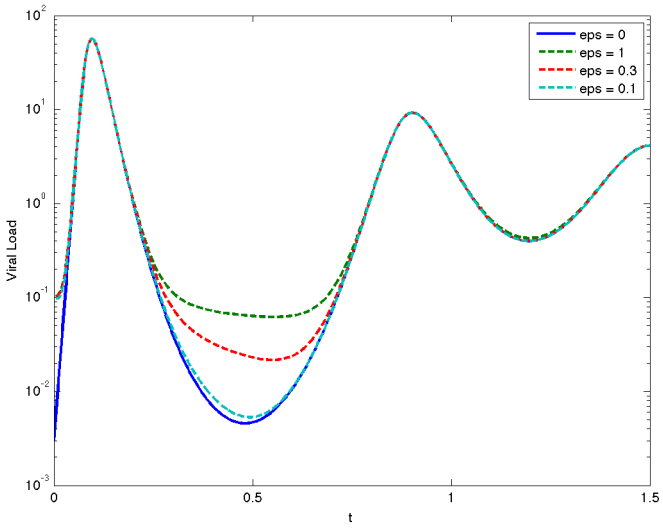
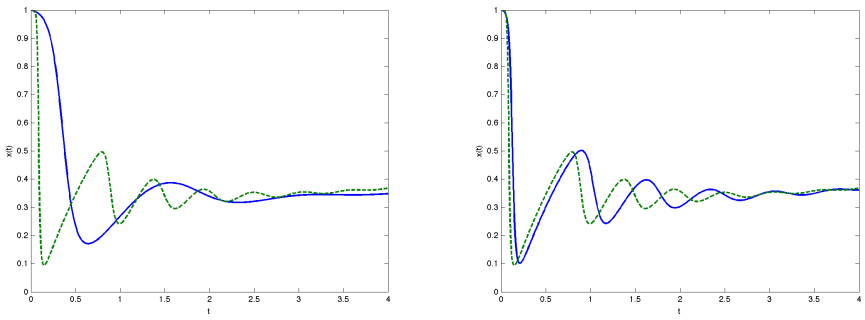
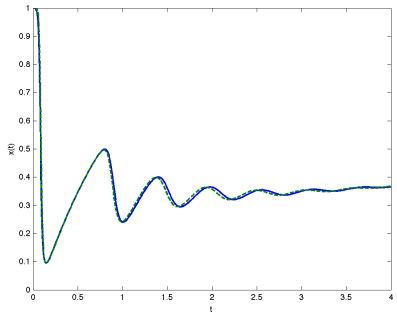


Figure 5: Attractiveness of the quasi-steady state for viral load: the continuous line is $\bar{v}(t) = R_0\bar{y}(t)$, where $\bar{y}$ is the solution of the reduced System (10), and the dotted lines is the approximation of $v(t,\varepsilon)$, that is, $R_0\bar{y}(t) + (v_0 - R_0y_0)\,e^{-t/\varepsilon}$ for different values of ε. The parameters used were $\gamma = 62$, $\sigma = 5$, $x_0 = 1$, $y_0 = 10^{-3}$, $v_0 = 10^{-1}$, $z_0 = 10^{-6}$, $R_0 = 3$, $I_0 = 2$ and $\varepsilon = 1, 0.3$ and 0.1.



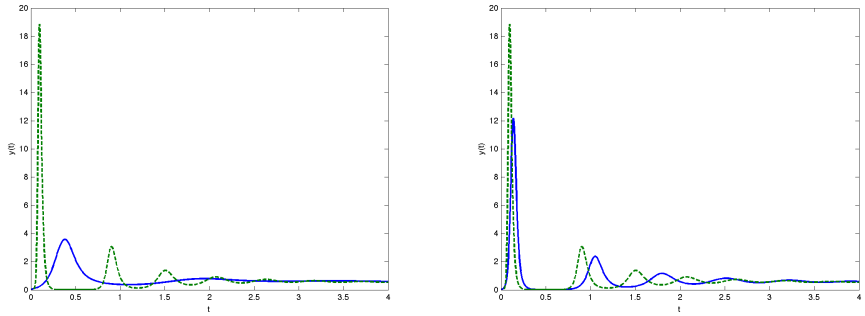
(a) $\varepsilon = 0.1$

(b) $\varepsilon = 0.01$

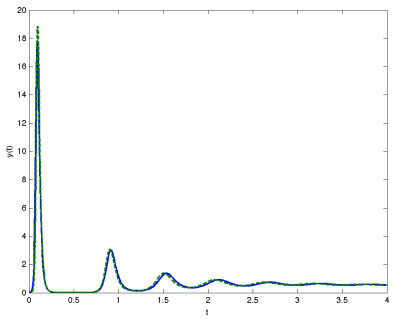


(c) $\varepsilon = 0.001$

Figure 6: Convergence of the asymptotic solution of Theorems 9 and 10 for the susceptible cells (x). The continuous line represents the solution of the System (9) while the dotted line are the approximation of $x(t,\varepsilon)$ given by the results of Section 4.2. The parameters used were $\gamma = 62$, $\sigma = 5$, $x_0 = 1$, $y_0 = 10^{-3}$, $v_0 = 10^{-1}$, $z_0 = 10^{-6}$, $R_0 = 3$, $I_0 = 2$, $\bar{\eta} = 1$ and $\varepsilon = 0.1, 0.01$ and 0.001.

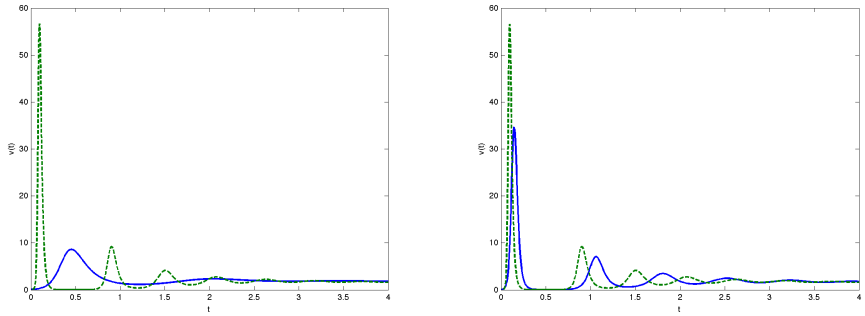


(a) $\varepsilon = 0.1$ (b) $\varepsilon = 0.01$

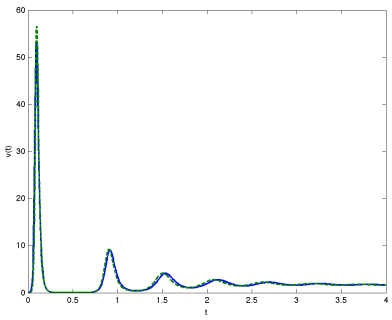


(c) $\varepsilon = 0.001$

Figure 7: Convergence of the asymptotic solution of Theorems 9 and 10 for the infected cells (y). The continuous line represents the solution of the System (9) while the dotted line are the approximation of $y(t, \varepsilon)$ given by the results of Section 4.2. The parameters used were $\gamma = 62$, $\sigma = 5$, $x_0 = 1$, $y_0 = 10^{-3}$, $v_0 = 10^{-1}$, $z_0 = 10^{-6}$, $R_0 = 3$, $I_0 = 2$, $\bar{\eta} = 1$ and $\varepsilon = 0.1, 0.01$ and 0.001.

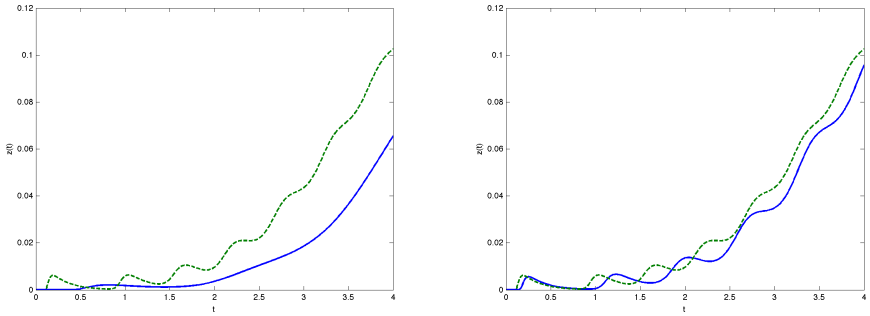


(a) $\varepsilon = 0.1$ (b) $\varepsilon = 0.01$



(c) $\varepsilon = 0.001$

Figure 8: Convergence of the asymptotic solution of Theorems 9 and 10 for the viral load (v). The continuous line represents the solution of the System (9) while the dotted line are the approximation of $v(t, \varepsilon)$ given by the results of Section 4.2. The parameters used were $\gamma = 62$, $\sigma = 5$, $x_0 = 1$, $y_0 = 10^{-3}$, $v_0 = 10^{-1}$, $z_0 = 10^{-6}$, $R_0 = 3$, $I_0 = 2$, $\bar{\eta} = 1$ and $\varepsilon = 0.1, 0.01$ and 0.001.



(a) $\varepsilon = 0.1$

(b) $\varepsilon = 0.01$

(c) $\varepsilon = 0.001$

Figure 9: Convergence of the asymptotic solution of Theorems 9 and 10 for the defense cells (z). The continuous line represents the solution of the System (9) while the dotted line are the approximation of $z(t, \varepsilon)$ given by the results of Section 4.2. The parameters used were $\gamma = 62$, $\sigma = 5$, $x_0 = 1$, $y_0 = 10^{-3}$, $v_0 = 10^{-1}$, $z_0 = 10^{-6}$, $R_0 = 3$, $I_0 = 2$, $\bar{\eta} = 1$ and $\varepsilon = 0.1, 0.01$ and 0.001.