

GLOBAL STABILITY FOR A CLASS OF VIRUS MODELS WITH CTL IMMUNE RESPONSE AND ANTIGENIC VARIATION

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ABSTRACT. We study the global stability of a class of models for in-vivo virus dynamics, that take into account the CTL immune response and display antigenic variation. This class includes a number of models that have been extensively used to model HIV dynamics. We show that models in this class are globally asymptotically stable, under mild hypothesis, by using appropriate Lyapunov functions. We also characterise the stable equilibrium points for the entire biologically relevant parameter range. As a byproduct, we are able to determine what is the diversity of the persistent strains.

1. INTRODUCTION

1.1. Models for in-vivo virus dynamics. A number of population dynamics models have been proposed in order to describe the HIV in-vivo dynamics (Perelson & Nelson 1999, Nowak & May 2000). Although these models have distinct features, since they attempt to incorporate different aspects of the interaction between the virus and the immune system, many of them share a common long-term behaviour, evolving towards an isolated equilibrium state (Nowak & May 2000).

The basic model for the HIV in-vivo dynamics is given by a three-by-three, first-order system of ordinary differential equations (ODEs)—(Nowak & Bangham 1996, Bonhoeffer, et al. 1997, Nowak & May 2000):

$$(1) \quad \begin{cases} \dot{x} &= \lambda - dx - \beta xv, \\ \dot{y} &= \beta xv - ay, \\ \dot{v} &= ky - uv. \end{cases}$$

In this model, x denotes the uninfected cells, y the infected cells and v the free virus particles. The average lifetime of an infected cell is $1/a$, while the average lifetime of a virus particle is $1/u$. The total number of virus particles produced by an infected cell is k/a . Healthy cells

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are infected at a rate βxv . New CD4+ T cells are produced, in the thymus, at a rate λ , and die at a rate dx .

System (1) has two equilibrium points:

- (1) The disease free equilibrium: $x^* = \lambda/d$, $y^* = v^* = 0$;
- (2) The endemic equilibrium: $x^* = au/\beta k$, $y^* = (\beta\lambda k - dau)/\beta ak$, $v^* = (\beta\lambda k - dau)/\beta au$.

The long term dynamics of System (1) can be entirely described in terms of the dimensionless parameter

$$(2) \quad R_0 = \frac{\beta\lambda k}{dau},$$

also known as the *basic reproductive ratio*.

If $R_0 \leq 1$, the disease free equilibrium is a global attractor, and the infection cannot persist. If $R_0 > 1$, the endemic equilibrium becomes a global attractor, and the infection persists indefinitely. This has been first observed numerically (Nowak & Bangham 1996, Bonhoeffer et al. 1997, Nowak & May 2000). Mathematical proofs of these global stability characteristics were given by Li & Muldowney (1995), using Hirsch's theory of competitive differential systems—see Smith (1995)—and, more recently by de Leenheer & Smith (2003) and Korobeinikov (2004a) using a Lyapunov function approach.

Given the notable ability of the HIV to escape from immune response, there is interest in studying models that account for a more detailed immune response as, for instance, the role of cytotoxic T lymphocytes (CTLs). An example is the following four-by-four system of ODEs (Nowak & Bangham 1996):

$$(3) \quad \begin{cases} \dot{x} &= \lambda - dx - \beta xv, \\ \dot{y} &= \beta xv - ay - pyz, \\ \dot{v} &= ky - uv, \\ \dot{z} &= cyz - bz. \end{cases}$$

System (3) extends (1) by introducing the z variable, that denotes the CTL response. Infected cells are killed at a rate pyz , while antigen stimulation produces CTL cells at a rate cyz . In the absence of such a stimulation, CTL cells decay at a rate bz .

In the same vein, the high mutation rate of HIV naturally leads to the study of the interplay between immune response and virus diversity for a number of different strains. The immune response produces a selection pressure on these different strains of the virus, as discussed in Nowak & Bangham (1996), when studying and numerically analysing a $(3n + 1)$ -by- $(3n + 1)$ first-order ODE system of the form:

$$(4) \quad \begin{cases} \dot{x} &= \lambda - dx - x \sum_{i=1}^n \beta_i v_i, \\ \dot{y}_i &= \beta_i xv_i - a_i y_i - p_i y_i z_i, & i = 1, \dots, n, \\ \dot{v}_i &= k_i y_i - u_i v_i, & i = 1, \dots, n, \\ \dot{z}_i &= c_i y_i z_i - b_i z_i, & i = 1, \dots, n. \end{cases}$$

System (4) is a slightly generalised form of the system studied by Nowak & Bangham (1996), where the more restricted case $a_i = a$, $p_i = p$, $u_i = u$, $c_i = c$, and $b_i = b$ was addressed.

In all these models, there is the question as whether the long term dynamics approaches an equilibrium or, more generally, an attractor, and how this might depend on the initial condition. There is compelling numerical evidence—cf. (Nowak & Bangham 1996, Bonhoeffer et al. 1997, Nowak & May 2000)—that Systems (3) and (4) are globally asymptotically stable. However, no mathematical proof of this fact seems to be available. In System (4) there is also the question of determining the antigenic diversity at the equilibrium.

In this work, we study the stability characteristics of the models given by (4) following a Lyapunov approach. The Lyapunov functional used here has been used before by Korobeinikov & Wake (1999), in the global analysis of three-dimensional predator-prey systems, and by Korobeinikov (2004a) and Korobeinikov (2004b) in the global analysis of various virus models. More precisely, by using an appropriate linear combination of this Lyapunov functional, we are able to show global asymptotic stability results for System (4), and hence to (3).

The plan for this article goes as follows: We close this introductory section with further biological background and motivations. In Section 2 we address some preliminary issues such as choice of dimensionless variables and parameter reductions. We study the global stability characteristics of model (3). In Section 3, we study the equilibria and global stability of model (4) under the assumption of unique fitnesses of the strains. In this case, we determine the possible equilibria of (4), and show that there are $2^{n-1}(n+2)$ equilibrium points. We also show that system is globally asymptotic stable, and we determine what is the global attractor in the nonnegative orthant of \mathbb{R}^{3n+1} . As a byproduct, we characterise the attained diversity and show that it is monotonically increasing with the strength of the immune response. Some additional results for the case of nonunique fitnesses are also presented. We conclude in Section 4 with a discussion of some of the implications of our results.

1.2. Biological Background and Motivation. The models studied by equation 4 have many potential biological applications. Most notably, to within-host infections connected to cytotoxic T lymphocytes with antigenic variation including, but not restricted to, HIV infection. A better understanding of how the within-host HIV, interacts with immune cells seems to be a key factor in the development of effective long-term therapies or possibly preventive vaccines for deadly diseases such as the acquired immunodeficiency syndrome (Nowak & May 2000). Mathematical modeling of the underlying biological mechanisms and a good understanding of the theoretical implications of such models is crucial in this process. Indeed, it helps clarifying and testing assumptions, finding the smallest number of determining factors to explain the biological phenomena, and analysing the experimental results (Asquith & Bangham 2003). Furthermore, modeling has already impacted on research at molecular level (Nowak & May 2000) and important results have been obtained in modeling the

virus dynamics for several infections, such as the HIV (Nowak & Bangham 1996, Perelson, et al. 1993, Perelson, et al. 1996), hepatitis B (Marchuk, et al. 1991), hepatitis C (Neumann, et al. 1998), and influenza (Bocharov & Romanyukha 1994).

In the particular case of the HIV infection, the dynamics of the within-host infection goes as follows: First, the HIV enters a T cell. Being a retrovirus, once the HIV is inside the T cell, it makes a DNA copy of its viral RNA. For this process it requires the reverse transcriptase (RT) enzyme. The DNA of the virus is then inserted in the T-cell's DNA. The latter in turn will produce viral particles that can bud off the T cell to infect other ones. Before one such viral particle leaves the infected cell, it must be equipped with *protease*, which is an enzyme used to cleave a long protein chain. Without protease the virus particle is incapable of infecting other T cells.

One of the key characteristics of HIV is its extensive genetic variability. In fact, the HIV seems to be changing continuously in the course of each infection and typically the virus strain that initiates the patient's infection differs from the one found a year or more after the infection. In this respect, the introduction of the different strains in the model is crucial for it to be realistic.

In general terms, one can also say that Model (4) is similar in spirit to other models such as food-chain models. The latter have attracted substantial interest by a number of authors. See for example (Roy & Solimano 1986, Kooi & Hanegraaf 2001, Kooi, et al. 1998) and references therein. However, the presence of more general quadratic terms or of logistic terms on the right hand side of the different "strains" leads to a potentially richer dynamics than the globally stable present in Model 4. See for example (Kooi & Hanegraaf 2001) for a bifurcation analysis of certain food chain models.

2. PRELIMINARIES

2.1. Parameter reduction. As already noticed in the introduction, a more restricted form of (4) with a number of parameters being strain-independent has been studied by Nowak & Bangham (1996). It turns out that some parameters in (4) can indeed be taken to be strain-independent, as we now show.

We start by noting that if $k_i = 0$, then v_i decays exponentially with rate u_i . Also, if $p_i = 0$, then the dynamics of z_i does not impinge on the rest of the system. Thus, without loss of generality, we can assume that $k_i, p_i \neq 0$, $i = 1, \dots, n$. In this case, following Pastore (2005), we rescale the v_i s and β_i s. In addition, we also rescale the z_i s. More precisely, the change of variables

$$(5) \quad v_i \mapsto \frac{k_i}{k} v_i, \quad z_i \mapsto \frac{p}{p_i} z_i \quad \text{and} \quad \beta_i \mapsto \frac{k}{k_i} \beta_i$$

takes (4) into

$$(6) \quad \begin{cases} \dot{x} &= \lambda - dx - x \sum_{i=1}^n \beta_i v_i, \\ \dot{y}_i &= \beta_i x v_i - a_i y_i - p y_i z_i, & i = 1, \dots, n, \\ \dot{v}_i &= k y_i - u_i v_i, & i = 1, \dots, n, \\ \dot{z}_i &= c_i y_i z_i - b_i z_i, & i = 1, \dots, n. \end{cases}$$

Intuitively, the change of variables (5) reflects that only the ratio β_i/k_i turns out to be important, and that this can be already taken into account in the β_i s, provided we rescale the v_i s. Moreover, it also shows that the precise value p_i does not matter, as long as it is nonzero.

2.2. Dimensionless constants. In Nowak & Bangham (1996), it was already observed that, in addition to R_0 , the quantity cy^*/b is also important in determining the global equilibria. In a more precise fashion, Nowak & May (2000) define

$$R_I = 1 + \frac{\beta b k}{c d u},$$

which they term the basic reproductive ratio in the presence of immune response. However, we follow Pastore (2005), and find more convenient to write

$$R_I = 1 + \frac{R_0}{I_0},$$

where

$$I_0 = \frac{c\lambda}{ab}.$$

An alternative dimensionless constant is the CTL reproduction number given by

$$P_0 = \frac{I_0(R_0 - 1)}{R_0}.$$

Although only two constants among R_0 , I_0 and P_0 are independent, and are sufficient to describe the regimes of (6), we have chosen to use both, three constants, as some conditions are better characterised by P_0 , while much of the algebra in the Lyapunov functional derivatives is better handled by expressing them in terms of R_0 and I_0 . Thus, we shall use the strain dependent constants:

$$(7) \quad R_0^i = \frac{\beta_i \lambda k}{d a_i u_i}, \quad I_0^i = \frac{c_i \lambda}{a_i b_i} \quad \text{and} \quad P_0^i = \frac{I_0^i (R_0^i - 1)}{R_0^i}.$$

2.3. Strain sets. In order to deal with plethora of equilibria that arises in System (6), we shall now define some notation for some special set of strain indices. This will allow us to deal conveniently with the combinatorial structure of the equilibria.

Without loss of generality, we shall assume that the strains are indexed by increasing order of R_0^i .

Let $\mathcal{N} = \{1, 2, \dots, n\}$. Then, we define the set of the strong responders as

$$\mathcal{S} = \{i \in \mathcal{N} \mid P_0^i > 1\}.$$

Definition 1. We shall say that the set \mathcal{S} of strong responders is consistent, if

$$\mathcal{S} = \{1, \dots, m\}, \quad 1 \leq m \leq n.$$

This is certainly the cases, if the I_0^i satisfy $I_0^i \geq I_0^{i+1}$. In particular, this holds if $I_0^i = I_0$ as in the model studied by Nowak & Bangham (1996).

Given a set of indices \mathcal{I} , we define

$$\rho_0^{\mathcal{I}} = \sum_{i \in \mathcal{I}} \frac{R_0^i}{I_0^i}.$$

Two important definitions are given below:

Definition 2. We shall say that $\mathcal{I} \subset \mathcal{S}$ is an antigenic set, if

$$(8) \quad R_0^i \geq 1 + \rho_0^{\mathcal{I}}, \quad i \in \mathcal{I}$$

holds. In addition, if

$$(9) \quad R_0^i \leq 1 + \rho_0^{\mathcal{I}}, \quad i \notin \mathcal{I}.$$

also holds, we shall say that \mathcal{I} is a stable antigenic set.

Notice that, if $\mathcal{S} \neq \emptyset$, we have that $\mathcal{I} = \{1\}$ is an antigenic set. Let l be the largest integer for which the set $\mathcal{J} = \{1, \dots, l\}$ is an antigenic set. Then we shall say that \mathcal{J} is the maximal antigenic set.

Two important facts about the maximal and stable antigenic sets are collected below:

Lemma 1. Assume that $\mathcal{S} \neq \emptyset$, and that the strain basic reproductive numbers are distinct.

- (1) If a stable antigenic set exists, then it is also the maximal antigenic set. In particular, stable antigenic sets are unique.
- (2) If \mathcal{N} is the maximal antigenic set, then it is a stable antigenic set.

Proof. (1) Assume that \mathcal{I} is a stable antigenic set and let $i_l = \max \mathcal{I}$. If $1 \leq k < l$, then $i_k \in \mathcal{I}$. Indeed, by the increasing ordering and (8), we have that

$$R_0^{i_k} > R_0^{i_l} \geq 1 + \rho_0^{\mathcal{I}}.$$

But this contradicts (9), thus we must have $i_k \in \mathcal{I}$. Now assume that $\mathcal{I}' = \{i_1, \dots, i_{l+1}\}$ is also an antigenic set. Then we must have

$$R_0^{l+1} \geq 1 + \rho_0^{\mathcal{I}'} = 1 + \rho_0^{\mathcal{I}} + \frac{R_0^{l+1}}{I_0^{l+1}} \geq 1 + \rho_0^{\mathcal{I}}.$$

But this again contradicts (9) and, hence, that \mathcal{I} is stable antigenic. Therefore, it is maximal.

- (2) This follows since, in this case, (9) cannot be violated. □

3. THE MODEL WITH ANTIGENIC VARIATION

In this section we shall study the stability of (6) in the non-negative orthant of \mathbb{R}^{3n+1} which we shall denote by \mathbb{O} . The positive orthant will be denoted by \mathbb{O}^+ .

We observe that the planes $z_i = 0$ and that \mathbb{O} are positive invariant sets for (4), since the field points inwards.

The equilibria and stability characteristics of (6) depend significantly whether the R_0^i s are distinct or not. In §3.1 and §3.2, we describe the equilibria and study their stability in the case of unique fitnesses, i.e., we assume that if $R_0^i = R_0^j$, then $i = j$. In this case, with the adopted order, we have that

$$R_0^i > R_0^{i+1}, \quad i = 1, \dots, n-1.$$

Additional remarks when the fitnesses are not unique can be found in Section 3.3.

3.1. Equilibria. Let $\mathcal{N} = \{1, 2, \dots, n\}$. It turns out that the equilibria of (4) can be conveniently indexed by (j, \mathcal{J}) , where $\mathcal{J} \subseteq \mathcal{N}$, and either $j = 0$ or $j \notin \mathcal{J}$. The corresponding equilibrium point will be denoted by $X_{j, \mathcal{J}}$.

Using this notation, we have

Lemma 2. *System (6) has $2^{n-1}(2+n)$ equilibrium points which can be written as*

$$X_{j, \mathcal{J}} = \left(\frac{\lambda}{d} Q_{j, \mathcal{J}}^x, \frac{\lambda}{a_1} Q_{j, \mathcal{J}}^{y_1}, \dots, \frac{\lambda}{a_n} Q_{j, \mathcal{J}}^{y_n}, \frac{d}{\beta_1} Q_{j, \mathcal{J}}^{v_1}, \dots, \frac{d}{\beta_n} Q_{j, \mathcal{J}}^{v_n}, \frac{a_1}{p} Q_{j, \mathcal{J}}^{z_1}, \dots, \frac{a_n}{p} Q_{j, \mathcal{J}}^{z_n} \right),$$

where

(1)

$$Q_{0, \emptyset}^x = 1, \quad \text{and} \quad Q_{0, \emptyset}^{y_i} = Q_{0, \emptyset}^{v_i} = Q_{0, \emptyset}^{z_i} = 0.$$

(2) *If j is such that $1 \leq j \leq n$, then we have*

$$Q_{j, \emptyset}^x = \frac{1}{R_0^j}, \quad Q_{j, \emptyset}^{y_j} = 1 - \frac{1}{R_0^j}, \quad Q_{j, \emptyset}^{v_j} = R_0^j - 1 \quad \text{and} \quad Q_{j, \emptyset}^{z_j} = 0.$$

and

$$Q_{j, \emptyset}^{y_i} = Q_{j, \emptyset}^{v_i} = Q_{j, \emptyset}^{z_i} = 0, \quad i = 1, \dots, n, \quad i \neq j.$$

(3) *Given $\mathcal{J} \subseteq \mathcal{N}$, we have*

$$Q_{0, \mathcal{J}}^x = \frac{1}{1 + \rho_0^{\mathcal{J}}}$$

and

$$Q_{0, \mathcal{J}}^{y_i} = \frac{1}{I_0^i}, \quad Q_{0, \mathcal{J}}^{v_i} = \frac{R_0^i}{I_0^i}, \quad Q_{0, \mathcal{J}}^{z_i} = \frac{R_0^i}{1 + \rho_0^{\mathcal{J}}} - 1, \quad i \in \mathcal{J};$$

also

$$Q_{0, \mathcal{J}}^{y_i} = Q_{0, \mathcal{J}}^{v_i} = Q_{0, \mathcal{J}}^{z_i} = 0, \quad i \notin \mathcal{J}.$$

(4) Given a proper subset $\mathcal{J} \subset \mathcal{N}$, and $1 \leq j' \leq n, j' \notin \mathcal{J}$, we have that

$$Q_{j',\mathcal{J}}^x = \frac{1}{R_0^{j'}}, \quad Q_{j',\mathcal{J}}^{y_{j'}} = 1 - \frac{1}{R_0^{j'}} - \frac{\rho_0^{\mathcal{J}}}{R_0^{j'}}, \quad Q_{j',\mathcal{J}}^{v_{j'}} = R_0^{j'} - 1 - \rho_0^{\mathcal{J}}, \quad Q_{j',\mathcal{J}}^{z_{j'}} = 0;$$

for $i \in \mathcal{J}$, we have

$$Q_{j',\mathcal{J}}^{y_i} = \frac{1}{I_0^i}, \quad Q_{j',\mathcal{J}}^{v_i} = \frac{R_0^i}{I_0^i}, \quad Q_{j',\mathcal{J}}^{z_i} = \frac{R_0^i}{R_0^{j'}} - 1.$$

For $i \notin \mathcal{J}$, and $i \neq j'$, we have

$$Q_{j',\mathcal{J}}^{y_i} = Q_{j',\mathcal{J}}^{v_i} = Q_{j',\mathcal{J}}^{z_i} = 0.$$

Proof. The first equilibrium is trivial. The second type of equilibria is obtained by choosing an index j such that $z_j = 0$, but $y_j \neq 0$. We can choose only one such j , since this determines x . For the other indices i , we set $y_i = v_i = z_i = 0$. The first equation then determines v_j . The third type is obtained by choosing a set \mathcal{J} of indices, such that, for $i \in \mathcal{J}$, we have $z_i \neq 0$. This readily determines y_i and v_i . For $i \notin \mathcal{J}$, we have $y_i = v_i = z_i = 0$. The first equation, then, determines x . Finally, the last equilibria is found by having a set of indices \mathcal{J} , as in the equilibrium of the third type, and then choosing an index $j' \notin \mathcal{J}$ as in the second equilibrium. Again, only one such j' can be chosen. \square

3.2. Stability analysis. We are now ready to study the global stability of the equilibria of System 6. Surprisingly, although there is a large number of equilibria, only four of them will be globally stable. In what follows, unless otherwise is said, we shall assume that that $R_0^i > R_0^{i+1}$, for $i = 1, \dots, n-1$, and that the set of strong responders is consistent.

Theorem 1. *For system (6), defined on \mathbb{O} , and with initial condition at its interior, there is always a globally asymptotically stable equilibrium given as follows:*

- (1) $X_{0,\emptyset}$, if $R_0^n \leq 1$;
- (2) $X_{1,\emptyset}$, if $1 < R_0^1$, and $P_0^1 \leq 1$.
- (3) If $P_0^1 > 1$, let \mathcal{J} be the maximal antigenic set. Then
 - (a) If \mathcal{J} is a stable antigenic set, then the equilibrium $X_{0,\mathcal{J}}$ is globally asymptotically stable.
 - (b) Otherwise, let j' be the smallest integer such that $j' \notin \mathcal{J}$, which exists by virtue of Lemma 1. Then the equilibrium $X_{j',\mathcal{J}}$ is globally asymptotically stable.

Proof of Theorem 1. Following Korobeinikov (2004a), we shall use the following Lyapunov function:

$$\begin{aligned} V(x, \mathbf{y}, \mathbf{v}, \mathbf{z}) = & x - x^* \ln(x/x^*) + \sum_{i=1}^n (y_i - y_i^* \ln(y_i/y_i^*)) + \\ & + \sum_{i=1}^n C_i (v_i - v_i^* \ln(v_i/v_i^*)) + p \sum_{i=1}^n \frac{1}{c_i} (z_i - z_i^* \ln(z_i/z_i^*)), \end{aligned}$$

where C_i will be a constant to be specified later on.

Then, using the uniform notation of the the equilibria of (6), that is set in Lemma 2, see §3.1, we have that

$$\begin{aligned}
\dot{V} &= \frac{d}{dt} V(x(t), \mathbf{y}(t), \mathbf{v}(t), \mathbf{z}(t)) \\
&\lambda \left[+Q_{j,\mathcal{J}}^x + \sum_{i=1}^n Q_{j,\mathcal{J}}^{y_i} + \frac{d}{\lambda} \sum_{i=1}^n C_i \frac{u_i}{\beta_i} Q_{j,\mathcal{J}}^{v_i} + \sum_{i=1}^n \frac{Q_{j,\mathcal{J}}^{z_i}}{I_0^i} \right] - \left[dx + \frac{\lambda^2 Q_{j,\mathcal{J}}^x}{dx} \right] - \\
(10) \quad &- \lambda \sum_{i=1}^n \frac{\beta_i}{a_i} Q_{j,\mathcal{J}}^{y_i} \frac{xv_i}{y_i} - dk \sum_{i=1}^n \frac{C_i}{\beta_i} Q_{j,\mathcal{J}}^{v_i} \frac{y_i}{v_i} + \sum_{i=1}^n y_i \left[kC_i - a_i - a_i Q_{j,\mathcal{J}}^{z_i} \right] + \\
&\frac{\lambda}{d} Q_{j,\mathcal{J}}^x \sum_{i=1}^n v_i \beta_i - \sum_{i=1}^n C_i u_i v_i + p\lambda \sum_{i=1}^n a_i z_i \left[Q_{j,\mathcal{J}}^{y_i} - \frac{1}{I_0^i} \right].
\end{aligned}$$

For the first two equilibria, we consider the Lyapunov function (10), with $C_i = a_i/k$. Then, on using the structure of equilibria of (6), we may write \dot{V} as follows:

$$\begin{aligned}
\dot{V} &= \lambda \left[1 + Q_{j,\mathcal{J}}^x + \sum_{i=1}^n Q_{j,\mathcal{J}}^{y_i} + \sum_{i=1}^n \frac{Q_{j,\mathcal{J}}^{v_i}}{R_0^i} + \sum_{i=1}^n \frac{Q_{j,\mathcal{J}}^{z_i}}{I_0^i} \right] - \left[dx + \frac{\lambda^2 Q_{j,\mathcal{J}}^x}{dx} \right] - \\
&- \lambda \sum_{i=1}^n \frac{\beta_i}{a_i} Q_{j,\mathcal{J}}^{y_i} \frac{xv_i}{y_i} - d \sum_{i=1}^n \frac{a_i}{\beta_i} Q_{j,\mathcal{J}}^{v_i} \frac{y_i}{v_i} - \sum_{i=1}^n a_i Q_{j,\mathcal{J}}^{z_i} y_i + \\
&+ \frac{\lambda}{d} \sum_{i=1}^n \beta_i v_i \left[Q_{j,\mathcal{J}}^x - \frac{1}{R_0^i} \right] + p\lambda \sum_{i=1}^n \frac{z_i}{a_i} \left[Q_{j,\mathcal{J}}^{y_i} - \frac{1}{I_0^i} \right].
\end{aligned}$$

For $X_{0,\emptyset}$, we find, using Lemma 2, that

$$\dot{V} = 2\lambda - \left[dx + \frac{\lambda^2}{dx} \right] + \frac{\lambda}{d} \sum_{i=1}^n \beta_i v_i \left[1 - \frac{1}{R_0^i} \right] - p\lambda \sum_{i=1}^n \frac{z_i}{a_i I_0^i}.$$

Since $R_0^i \leq 1$, for $i = 1, \dots, n$, and

$$dx + \frac{\lambda^2}{dx} \geq 2\lambda,$$

we have that $\dot{V} < 0$ in \mathbb{O}^+ . Hence, that $X_{0,\emptyset}$ is globally asymptotically stable in this case.

Now, suppose that $1 < R_0^1$, and that $P_0^1 \leq 1$. In this case, Lemma 2 yields that

$$\begin{aligned}
\dot{V} &= \lambda \left[3 \left(-\frac{1}{R_0^1} \right) + \frac{2}{R_0^1} \right] - \left[dx + \frac{\lambda^2}{R_0^1 dx} \right] - \frac{\lambda}{a_1} \beta_1 \left(1 - \frac{1}{R_0^1} \right) \frac{xv_1}{y_1} - \frac{a_1 d}{\beta_1} (R_0^1 - 1) \frac{y_1}{v_1} + \\
&+ \frac{\lambda}{d} \sum_{i=1}^n \beta_i v_i \left[\frac{1}{R_0^1} - \frac{1}{R_0^i} \right] + p\lambda \frac{z_1}{a_1} \left[1 - \frac{1}{R_0^1} - \frac{1}{I_0^1} \right] - p\lambda \sum_{i=2}^n \frac{z_i}{a_i I_0^i}.
\end{aligned}$$

The last term in \dot{V} is clearly negative. We also observe that, since $R_0^i < R_0^1$, for $1 < i \leq n$, we have that

$$\sum_{i=1}^n \beta_i v_i \left[\frac{1}{R_0^1} - \frac{1}{R_0^i} \right] < 0.$$

Also, since $P_0^1 \leq 1$, then we have that $R_0^1 \leq 1 + R_0^1/I_0^1$. Therefore, the last three terms in the expression for \dot{V} are negative.

For the remaining terms, let us write

$$\frac{\lambda^2}{R_0^1} = \left(\frac{\lambda}{R_0^1}\right)^2 + \left(1 - \frac{1}{R_0^1}\right) \frac{\lambda^2}{R_0^1}.$$

Then we have that

$$dx + \left(\frac{\lambda^2}{R_0^1 dx}\right)^2 \geq 2 \frac{\lambda}{R_0^1},$$

and that

$$\frac{\lambda^2}{R_0^1 dx} \left(1 - \frac{1}{R_0^1}\right) + \lambda \frac{\beta_1}{a_1} \left(1 - \frac{1}{R_0^1}\right) \frac{xv_1}{y_1} + \frac{da_1}{\beta_1} (R_0^1 - 1) \frac{y_1}{v_1} \geq 3\lambda \left(1 - \frac{1}{R_0^1}\right).$$

Thus $\dot{V} < 0$ in \mathbb{O}^+ , and hence we have that $X_{1,\emptyset}$ is a globally asymptotically stable equilibrium.

Finally, if $P_0^1 > 1$, then let \mathcal{J} be the maximal antigenic set. First, we assume that \mathcal{J} is stable antigenic and show that $X_{0,\mathcal{J}}$ is globally asymptotically stable. In this case, we use the Lyapunov function (10), with $C_i = x^* \beta_i / u_i$.

Using Lemma 2, this can be further recast as $\dot{V} = \dot{V}_1 + \dot{V}_2$, where

$$\begin{aligned} \dot{V}_1 &= \lambda \left[3 - \frac{1}{1 + \rho_0^{\mathcal{J}}} \right] - \left[dx + \frac{\lambda^2}{dx(1 + \rho_0^{\mathcal{J}})} \right] - \lambda \sum_{i \in \mathcal{J}} \frac{\beta_i}{I_0^i a_i} \frac{xv_i}{y_i} - \frac{\lambda k}{1 + \rho_0^{\mathcal{J}}} \sum_{i \in \mathcal{J}} \frac{R_0^i}{u_i I_0^i} \frac{y_i}{v_i}; \\ \dot{V}_2 &= \sum_{i \notin \mathcal{J}} a_i y_i \left[\frac{R_0^i}{1 + \rho_0^{\mathcal{J}}} - 1 \right] - p\lambda \sum_{i \notin \mathcal{J}} \frac{z_i}{a_i I_0^i}. \end{aligned}$$

We treat \dot{V}_2 first. The last term is clearly negative. Also, since for $i \notin \mathcal{J}$, we have that

$$\frac{R_0^i}{1 + \rho_0^{\mathcal{J}}} < 1 \quad \text{and thus that} \quad \sum_{i \notin \mathcal{J}} y_i \left[\frac{R_0^i}{1 + \rho_0^{\mathcal{J}}} - 1 \right] < 0.$$

Therefore, $\dot{V}_2 < 0$, when $\mathcal{J} \neq \mathcal{N}$.

Let

$$\eta = \frac{\rho_0^{\mathcal{J}}}{1 + \rho_0^{\mathcal{J}}} \quad \text{and} \quad \eta_i = \frac{\frac{R_0^i}{I_0^i}}{1 + \rho_0^{\mathcal{J}}}, \quad i \in \mathcal{J}.$$

Then, we may write \dot{V}_1 as

$$\begin{aligned} \dot{V}_1 &= \lambda \left[3 - \frac{1}{1 + \frac{\rho_0^{\mathcal{J}}}{I_0}} \right] - \left[dx + \frac{\lambda^2}{dx(1 + \rho_0^{\mathcal{J}})^2} \right] - \\ &\quad - \sum_{i \in \mathcal{J}} \frac{\lambda^2 \eta_i}{dx(1 + \rho_0^{\mathcal{J}})} - \lambda \sum_{i \in \mathcal{J}} \frac{\beta_i}{I_0^i a_i} \frac{xv_i}{y_i} - \frac{\lambda k}{1 + \rho_0^{\mathcal{J}}} \sum_{i \in \mathcal{J}} \frac{R_0^i}{u_i I_0^i} \frac{y_i}{v_i} \end{aligned}$$

For each $i \in \mathcal{J}$, we have

$$-\frac{\lambda^2 \frac{R_0^i}{I_0^i}}{dx (1 + \rho_0^{\mathcal{J}})^2} - \lambda \frac{\beta_i}{I_0^i a_i} \frac{xv_i}{y_i} - \frac{\lambda k}{1 + \rho_0^{\mathcal{J}}} \frac{R_0^i}{u_i I_0^i} \frac{y_i}{v_i} \leq -3\lambda \left(\frac{\frac{R_0^i}{I_0^i}}{1 + \rho_0^{\mathcal{J}}} \right),$$

and that

$$dx + \frac{\lambda^2}{dx (1 + \rho_0^{\mathcal{J}})^2} > 2\lambda \frac{1}{1 + \rho_0^{\mathcal{J}}}.$$

After combining these estimates and summing for $i \in \mathcal{J}$, we get that $\dot{V}_1 \leq 0$ and thus we have the result, If \mathcal{J} is a proper subset of \mathcal{N} . In the case that $\mathcal{J} = \mathcal{N}$, we have $\dot{V} \leq 0$, with equality occurring only when

$$x = \frac{\lambda}{d} Q_{0,\mathcal{J}}^x \quad \text{and} \quad \frac{v_i}{y_i} = \frac{k_i}{u_i}.$$

Inasmuch this plane is not invariant by the corresponding flow—other than the point $X_{0,\mathcal{J}}$ —we have global stability as a consequence of LaSalle's theorem (LaSalle 1964). For the fourth point, we use a mix of the two Lyapunov functions above, namely:

$$\begin{aligned} V(x, \mathbf{y}, \mathbf{v}, \mathbf{z}) = & x - x^* \ln(x/x^*) + \sum_{i=1}^n (y_i - y_i^* \ln(y_i/y_i^*)) + \\ & + x^* \sum_{\substack{i=1 \\ i \neq j'}}^n \frac{\beta_i}{u_i} (v_i - v_i^* \ln(v_i/v_i^*)) + p \sum_{i=1}^n \frac{1}{c_i} (z_i - z_i^* \ln(z_i/z_i^*)) + \\ & + \frac{a_{j'}}{k} (v_{j'} - v_{j'}^* \ln(v_{j'}/v_{j'}^*)). \end{aligned}$$

Computing \dot{V} and using the uniform notation, we find that

$$\begin{aligned} \dot{V} = & \lambda \left[1 + Q_{j',\mathcal{J}}^x + \sum_{i=1}^n Q_{j',\mathcal{J}}^{y_i} + Q_{j',\mathcal{J}}^x \sum_{\substack{i=1 \\ i \neq j'}}^n Q_{j',\mathcal{J}}^{v_i} + \sum_{i=1}^n \frac{Q_{j',\mathcal{J}}^{z_i}}{I_0^i} + \frac{Q_{j',\mathcal{J}}^{v_{j'}}}{R_0^{j'}} \right] - \left[dx + \frac{\lambda^2 Q_{j',\mathcal{J}}^x}{dx} \right] - \\ & - \lambda \sum_{i=1}^n \frac{\beta_i Q_{j',\mathcal{J}}^{y_i}}{a_i} \frac{xv_i}{y_i} - \lambda k Q_{j',\mathcal{J}}^x \sum_{\substack{i=1 \\ i \neq j'}}^n \frac{Q_{j',\mathcal{J}}^{v_i}}{u_i} \frac{y_i}{v_i} + \sum_{\substack{i=1 \\ i \neq j'}}^n y_i \left[\frac{\beta_i \lambda k}{du_i} Q_{j',\mathcal{J}}^x - a_i - a_i Q_{j',\mathcal{J}}^{z_i} \right] + \\ & + p \lambda \sum_{i=1}^n \frac{z_i}{a_i} \left[Q_{j',\mathcal{J}}^{y_i} - \frac{1}{I_0^i} \right] - \frac{da_{j'}}{\beta_{j'}} Q_{j',\mathcal{J}}^{v_{j'}} \frac{y_{j'}}{v_{j'}} - a_{j'} Q_{j',\mathcal{J}}^{z_{j'}} y_{j'} + \frac{\lambda \beta_{j'}}{d} v_{j'} \left[Q_{j',\mathcal{J}}^x - \frac{1}{R_0^{j'}} \right] \end{aligned}$$

On using Lemma 2, and that

$$1 = \left(1 - \frac{1}{R_0^{j'}} - \frac{\rho_0^{\mathcal{J}}}{R_0^{j'}} \right) + \frac{1}{R_0^{j'}} + \frac{\rho_0^{\mathcal{J}}}{R_0^{j'}},$$

where each term in the sum is positive, but smaller than one, we rewrite it as $\dot{V} = \dot{V}_1 + \dot{V}_2 + \dot{V}_3 + \dot{V}_4$, where

$$\begin{aligned}\dot{V}_1 &= \left(1 - \frac{1}{R_0^{j'}} - \frac{\rho_0^{\mathcal{J}}}{R_0^{j'}}\right) \left[3\lambda - \frac{\lambda^2}{dx R_0^{j'}} - \frac{\lambda \beta_{j'} x v_{j'}}{a_{j'} y_{j'}} - \frac{da_{j'} R_0^{j'} y_{j'}}{\beta_{j'} v_{j'}}\right], \\ \dot{V}_2 &= \frac{2\lambda}{R_0^{j'}} - \left[dx + \frac{\lambda^2}{dx (R_0^{j'})^2}\right], \\ \dot{V}_3 &= 3\lambda \frac{\rho_0^{\mathcal{J}}}{R_0^{j'}} - \frac{\lambda^2 \rho_0^{\mathcal{J}}}{dx (R_0^{j'})^2} - \lambda \sum_{i \in \mathcal{J}} \frac{\beta_i x v_i}{a_i I_0^i y_i} - \frac{\lambda k}{R_0^{j'}} \sum_{i \in \mathcal{J}} \frac{R_0^i y_i}{u_i I_0^i v_i}, \\ \dot{V}_4 &= \frac{p \lambda z_{j'}}{a_{j'}} \left(1 - \frac{1}{R_0^{j'}} - \frac{\rho_0^{\mathcal{J}}}{R_0^{j'}} - \frac{1}{I_0^{j'}}\right).\end{aligned}$$

The terms \dot{V}_1 , \dot{V}_2 and \dot{V}_3 can be treated similarly as in the previous equilibria and are all nonpositive in the interior.

As for \dot{V}_4 , first we observe that

$$1 - \frac{1}{R_0^{j'}} - \frac{\rho_0^{\mathcal{J}}}{R_0^{j'}} - \frac{1}{I_0^{j'}} = \frac{1}{R_0^{j'}} \left(R_0^{j'} - 1 - \rho_0^{\mathcal{J}} - \frac{R_0^{j'}}{I_0^{j'}}\right)$$

if $j' \notin \mathcal{S}$, then we that

$$R_0^{j'} - 1 - \rho_0^{\mathcal{J}} - \frac{R_0^{j'}}{I_0^{j'}} < R_0^{j'} - 1 - \frac{R_0^{j'}}{I_0^{j'}} \leq 0.$$

If $j' \in \mathcal{S}$, then let $\mathcal{J}' = \mathcal{J} \cup \{j'\}$. Then we have that

$$1 - \frac{1}{R_0^{j'}} - \frac{\rho_0^{\mathcal{J}}}{R_0^{j'}} - \frac{1}{I_0^{j'}} = \frac{1}{R_0^{j'}} \left(R_0^{j'} - 1 - \rho_0^{\mathcal{J}'}\right).$$

Since \mathcal{J} is the maximal antigenic set, we must have that

$$R_0^{j'} - 1 - \rho_0^{\mathcal{J}'} \leq 0.$$

□

3.3. Nonunique Fitness. Given the non-generic nature of this case, we shall only briefly discuss the stability when some of the strains have the same fitness, i.e., there exists at least one index set Γ , such that $R_0^i = R_0^j$, for $i, j \in \Gamma$. Notice that, in this case, we have non-isolated equilibria.

We start by observing that the computation with the Lyapunov function for the equilibrium $X_{0,\emptyset}$ does not depend on the uniqueness of fitness. Hence we have

Corollary 1. *If $R_0^i \leq 1$, for $i = 1, \dots, n$, then $X_{0,\emptyset}$ is a globally asymptotically stable equilibrium.*

The case $I_0^i = I_0$, $1 < R_0^1$ and $P_0^1 < 1$ can also be partially treated:

Proposition 1. *Let Γ be the set of indices $i \in \mathcal{N}$ such that $R_0^i = R_0^n$. Let E_Γ be the set satisfying*

$$x^* = \frac{\lambda}{dR_0^n}, \quad y_j = v_j = 0, \quad j \notin \Gamma, \quad \sum_{j \in \Gamma} \beta_j v_j = \frac{dx^* - \lambda}{x^*}, \quad v_j \geq 0,$$

$$v_i = \frac{k}{u} y_i, \quad \text{and} \quad z_i = 0, \quad i \in \mathcal{N}.$$

If $\mathbf{x}(t, \mathbf{x}_0)$ is a solution of (4), with initial condition \mathbf{x}_0 , then

$$\mathbf{x}(t) \rightarrow E_\Gamma, \quad \text{as} \quad t \rightarrow \infty.$$

Proof. Let us denote the omega set of $\mathbf{x}(t, \mathbf{x}_0)$ by $\Omega(\mathbf{x}_0)$. As shown in (Pastore 2005), the solutions to (4) are bounded in \mathbb{R}_+^{3n+1} . Hence, $\Omega(\mathbf{x}_0)$ is compact.

Using the same Lyapunov function for $X_{1, \emptyset}$ as in Section 3.2, we find that

$$\begin{aligned} \dot{V} = & \lambda \left[3 - \frac{1}{R_0^1} \right] - \left[dx + \frac{\lambda^2}{R_0^1 dx} \right] - \frac{\lambda}{a} \beta_1 \left(1 - \frac{1}{R_0^1} \right) \frac{xv_1}{y_1} - \frac{ad}{\beta_1} (R_0^1 - 1) \frac{y_1}{v_1} + \\ & + \frac{\lambda}{d} \sum_{i \notin \Gamma} \beta_i v_i \left[\frac{1}{R_0^1} - \frac{1}{R_0^i} \right] + \frac{p\lambda}{a} \sum_{i=1}^n z_i \left[1 - \frac{1}{R_0^i} - \frac{1}{I_0} \right]. \end{aligned}$$

The same calculations in section 3.2 shows that $\dot{V} \leq 0$. However, notice that $\dot{V} = 0$ in E_Γ . If $s \in \mathbb{R}^N$ and $S \subset \mathbb{R}^N$ is closed, then let

$$d(s, S) = \min_{s' \in S} \|s - s'\|.$$

LaSalle's invariant principle then yields that,

$$\lim_{t \rightarrow \infty} d(\mathbf{x}(t), E_\Gamma) = 0.$$

□

Corollary 2. *If $R_0^1 > R_0^i$ for $i = 2, \dots, n$, then $X_{1, \emptyset}$ is a globally asymptotically stable equilibrium, when $1 < R_0^1 \leq 1 + R_0^1/I_0$.*

We have performed numerical calculations of (4), using a high order Runge-Kutta method, which suggest that in the case treated by proposition 1, a solution of System (4) will converge to a unique equilibrium point in E_Γ , that depends only on the initial condition.

Finally, when the viable set of strains is not the full antigenic variation, we have

Proposition 2. *If $I_0^i = I_0$, $P_0^1 > 1$. Assume that $\mathcal{J} \neq \mathcal{I}$ is a stable antigenic set, then we have that $X_{0, \mathcal{J}}$ is a globally asymptotic stable equilibrium.*

Proof. In this case, the estimate $\dot{V}_1 \leq 0$ remains valid. Moreover, if $\mathcal{J} \neq \mathcal{I}$, then we must have $\dot{V}_2 < 0$, which yields the result. □

4. CONCLUSIONS

In this work, we have performed a thorough study of System (4). As a preliminary result, we have shown that, when the both the virus production rate and the CTL interaction rate are nonzero for all strains, then System (4) is dynamically equivalent to System (6), which has strain-independent virus production and CTL interaction rates. In particular, the precise nonzero values of the CTL interaction rates are completely irrelevant to the dynamical behaviour of the system. This seems to suggest that a more refined model which is able to capture this difference is needed.

We have also identified all the $2^{n-1}(2+n)$ equilibria of (6) in Lemma 2. When n is large this can be quite a large number. Nevertheless, under the hypothesis of unique fitness, we were able to show that only four of them are dynamically relevant. More precisely, we assume that the virus basic reproduction rates, R_0^i are distinct and that the CTL reproduction numbers, P_0^i have the same ordering as the R_0^i . This last condition is automatically satisfied if $I_0^i = I_0$ for all i . In this case, Theorem 1 shows that, if the largest reproduction number, R_0^1 , is smaller than one, the the disease-free equilibrium— $X_{0,\emptyset}$ in the notation of Lemma 2—is globally asymptotic stable. In this case, no strain is viable and the infection dies out. On the other hand, if $R_0^1 > 1$, but $P_0^1 < 1$, then only the first strain survives, and the infection persists. If $P_0^1 > 1$, then we have that the two outcomes are possible: either a (unique) stable antigenic set exists and then $X_{0,\mathcal{J}}$ is globally asymptotic stable. In this case, the set \mathcal{J} determines the antigenic diversity. In other words, a strong immune response generates a larger antigenic variation. Alternatively, there exists a pair (j', \mathcal{J}) such that the point $X_{j',\mathcal{J}}$ is globally asymptotic stable. In this case, the strain with the weakest fitness will not actually trigger the CTL response at all in the long run. In the case of absence of antigenic variation, i.e. System (3), then only the first outcome is possible. We were unable to interpret in a biological sense the combinatorial conditions of existence of a stable antigenic set, and we believe that this should be addressed in the future. The results presented in Theorem 1 show rigorously some of the inferences that have already been made in Nowak & Bangham (1996) based on extensive simulations of System (4).

We have also shown some results for very special cases in which the R_0^i s are not distinct. In these cases, the equilibria is not isolated and this complicates the matters further. Also, we have not addressed that case when the set of strong responders is not consistent, and this might also merit further study in the future.

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