Dynamics of Virus and Immune Response in Multi-Epitope Network

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Abstract

The host immune response can often efficiently suppress a virus infection, which may lead to selection for immune-resistant viral variants within the host. For example, during HIV infection, an array of CTL immune response populations recognize specific epitopes (viral proteins) presented on the surface of infected cells to effectively mediate their killing. However HIV can rapidly evolve resistance to CTL attack at different epitopes, inducing a dynamic network of interacting viral and immune response variants. We consider models for the network of virus and immune response populations, consisting of Lotka-Volterra-like systems of ordinary differential equations. Stability of feasible equilibria and corresponding uniform persistence of distinct variants are characterized via a Lyapunov function. We specialize the model to a “binary mutation” setting, where for \( n \) epitopes there can be \( 2^n \) distinct viral variants mapped on a hypercube graph. The dynamics in several cases are analyzed and sharp polychotomies are derived characterizing persistent variants. In particular, we prove that if the viral fitness costs for gaining resistance to each epitope are equal, then the system of \( 2^n \) virus strains converges to a “perfectly nested network” with less than or equal to \( n + 1 \) persistent virus strains. Overall, our results suggest that immunodominance, i.e. relative strength of immune response to an epitope, is the most important factor determining the persistent network structure.

1 Introduction

The dynamics of virus and immune response within a host can be viewed as a complex ecological system. Both predator-prey and competitive interactions are especially important during a host infection. The immune response predates on the pathogen, and distinct viral strains compete for a target cell population, while immune response populations compete for the virus since their proliferation occurs upon pathogen recognition. The immune response can cause significant mortality of the virus, which may lead to selection for immune-resistant viral variants within the host. For example during HIV infection, an extensive repertoire of CTL immune effectors recognize specific epitopes (viral proteins) presented on the surface of infected cells to effectively mediate their killing, however HIV can rapidly evolve resistance to CTL attack at different epitopes. The ensuing battle precipitates a dynamic network of interacting viral strains and immune response variants, analogous to an ecosystem of rapidly evolving prey countering attack from a diverse collection of predators.

While the virus-immune interactions may be quite complex, patterns and structure can emerge. For the cellular immune response, a consistent and reproducible hierarchy of T cell populations organize in response to multiple epitopes of a pathogen, according to their (vertical) immunodominance, i.e. relative expansion levels of the responding immune populations within the host [19]. Vertical T cell immunodominance patterns are highly variable among HIV infected individuals and change over time, largely due to sequence variability in the viral “quasispecies” [24]. Rapidly evolving pathogens, such as HIV and HCV, can evade the immune response via mutations at multiple epitopes. The pattern of epitope mutations, called the escape pathway, is of significant interest, and there is some evidence that the viral evolution is predictable [3]. The fitness of an emerging viral mutant strain, along with the strength of the CTL response, certainly affect the selection pressure for a single epitope mutation [14]. However the concurrent interaction of diverse virus and immune response populations necessitate considering the whole system together in order to understand viral escape

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of multiple epitopes [24]. In this paper, we introduce and analyze mathematical models for the dynamics of virus and immune response in a network determined by interaction at multiple epitopes.

A large amount of work on modeling within-host virus dynamics has been based on the “standard” virus model: an ordinary differential equation system describing the coupled changes in target cells, infected cells, and free virus particles through time in an infected individual [28]. The CTL immune response has been included in variations of the standard virus model by considering an immune effector population which kills and is activated by infected cells according to a mass-action (bilinear) rate, although other functional forms for the activation rate have been utilized [6, 9]. Nowak et al. [25], along with other subsequent works [5, 16, 32], have considered the dynamics of multiple virus strains which are attacked by strain-specific CTL immune response populations (“one-to-one” virus-immune network). However the assumption of strain-specific immune response does not correspond to the biological reality that CTLs are specific to epitopes and, in general, multiple epitopes will be shared among virus strains.

Multi-epitope models have been utilized with different datasets cataloging several epitope specific CTL response and viral escape mutations, in order to quantify escape rates and patterns [24, 23, 27]. Earlier work often considered escape dynamics at epitopes separately, but some recent work has emphasized the concurrent interaction of distinct CTLs with the virus at multiple epitopes. Ganusov et al. [12, 13] explicitly include multiple CTL clones specific to different epitopes in the standard virus model, and utilize statistical approaches on a linearized version of the model to estimate rates of escape. Althaus et al. and van Deutekom et al. have also considered multiple epitopes and viral strains in the standard virus model, although results were mostly based on stochastic simulations [1, 11].

Browne [8] recently analyzed the stability and uniform persistence of a multi-epitope virus-immune model with a perfectly nested interaction network. The model setup mirrors a tri-trophic chemostat ecosystem with a single resource (healthy cells), and a network of consumers (viral strains) and their predators (immune variants). The perfectly nested network constrains the viral escape pathway so that resistance to multiple epitopes is built sequentially in the order of the immunodominance hierarchy. The successive rise of more broadly resistant prey (coming with a fitness cost) and weaker but more generalist predators, in a perfectly nested fashion, is the route to persistence of nested bacteria-phage communities argued in [17, 34, 20, 22, 21]. The analysis of more complex interaction networks, which allow arbitrary viral escape pathways for building multi-epitope resistance, will be addressed in this paper.

Here we extend the previous work by analyzing a within-host virus model with a general interaction network of multiple variants of virus and immune response. We characterize the structure of feasible equilibria, along with finding a Lyapunov function for stability and corresponding uniform persistence of distinct variants. Next, we consider the “binary mutation” case where a viral strain is either completely susceptible (0) or has evolved complete resistance (1) to immune attack at a specific epitope, in which for n epitopes, there can be $2^n$ distinct viral variants distinguished by their immune resistance profile. After deriving some graph-theoretic properties of feasible equilibria, we consider several special cases where the Lyapunov function can be applied to classify dynamics. In particular, if we constrain the virus-immune response network to be “strain-specific”, “perfectly nested”, or have $n = 2$ epitopes, sharp polychotomies are derived characterizing persistent variants. Finally, we prove that if the viral fitness costs for gaining resistance to each epitope are equal, then the system of $2^n$ virus strains converges to a perfectly nested network with less than or equal to $n + 1$ persistent virus strains. Overall, our results suggest that immunodominance is the most important factor determining the viral escape pathway.

2 Mathematical model

We consider the following general virus-immune dynamics model, as in Browne [8], which includes a population of target cells ($X$), $m$ competing virus strains ($Y_i$ denotes strain $i$ infected cells), and $n$ variants of immune response ($Z_j$):

$$\frac{dX}{dt} = b - cX - X \sum_{i=1}^{m} \beta_i Y_i,$$

$$\frac{dY_i}{dt} = \beta_i Y_i X - \delta_i Y_i - Y_i \sum_{j=1}^{m} r_{ij} Z_j, \quad i = 1, \ldots, m$$

(1)
activation rates are mass-action, representative of these events occurring as immune response cells recognize virus and immune variant components. Define the population $Z$ with terms of the positive virus and immune variant components. We assume immune killing and activation rates are mass-action, representative of these events occurring as immune response cells recognize epitopes on the surface of infected cells. The parameter $r_{ij}$ describes the killing/interaction rate of immune population $Z_j$ on a strain-$i$ infected cell, whereas $q_{ij}$ describes the corresponding activation rate for $Z_j$ (proportional to interaction rate $r_{ij}$). In the present paper, we assume that virus load (the abundance of virions) is proportional to the amount of (productively) infected cells. This assumption has frequently been made for HIV since the dynamic of free virions occurs on a much faster time scale than the other variables. Another reason for not explicitly including free virus in our present work is to keep the tri-trophic chemostat model made for HIV since the dynamic of free virions occurs on a much faster time scale than the other variables. It is assumed that virus load (the abundance of virions) is proportional to the amount of (productively) infected cells. This assumption has frequently been made for HIV since the dynamic of free virions occurs on a much faster time scale than the other variables. Another reason for not explicitly including free virus in our present work is to keep the tri-trophic chemostat model made for HIV since the dynamic of free virions occurs on a much faster time scale than the other variables. Another reason for not explicitly including free virus in our present work is to keep the tri-trophic chemostat model made for HIV since the dynamic of free virions occurs on a much faster time scale than the other variables.

The model then becomes:

$$\frac{dZ_j}{dt} = q_{ij}Z_j \sum_{i=1}^{n} r_{ij} Y_i - \mu_j Z_j, \quad j = 1, \ldots, n.$$  

The function $f(X) = b - cX$ represents the net growth rate of the uninfected cell population. The parameter $\beta_i$ is the infection rate and $\delta_i$ is the decay rate for infected cells infected with virus strain $i$. The parameter $\mu_j$ denotes the decay rate of the immune response population $j$. We assume immune killing and activation rates are mass-action, representative of these events occurring as immune response cells recognize epitopes on the surface of infected cells. The parameter $r_{ij}$ describes the killing/interaction rate of immune population $Z_j$ on a strain-$i$ infected cell, whereas $q_{ij}$ describes the corresponding activation rate for $Z_j$ (proportional to interaction rate $r_{ij}$). In the present paper, we assume that virus load (the abundance of virions) is proportional to the amount of (productively) infected cells. This assumption has frequently been made for HIV since the dynamic of free virions occurs on a much faster time scale than the other variables. Another reason for not explicitly including free virus in our present work is to keep the tri-trophic chemostat model made for HIV since the dynamic of free virions occurs on a much faster time scale than the other variables. Another reason for not explicitly including free virus in our present work is to keep the tri-trophic chemostat model made for HIV since the dynamic of free virions occurs on a much faster time scale than the other variables. Another reason for not explicitly including free virus in our present work is to keep the tri-trophic chemostat model made for HIV since the dynamic of free virions occurs on a much faster time scale than the other variables. Another reason for not explicitly including free virus in our present work is to keep the tri-trophic chemostat model made for HIV since the dynamic of free virions occurs on a much faster time scale than the other variables.

The model can be rescaled by introducing the following quantities:

$$x = \frac{c}{b} Y, \quad y_i = \frac{\delta_i}{b} Y_i, \quad \tau = ct,$$

$$a_{ij} = \frac{r_{ij}}{\delta_i}, \quad \gamma_i = \frac{\delta_i}{c}, \quad \sigma_j = \frac{\mu_j}{c},$$

$$R_i = \frac{b \beta_i}{c \delta_i}, \quad \rho_j = \frac{\mu_j}{b \gamma_j},$$

The model then becomes:

$$\dot{x} = 1 - x - x \sum_{i=1}^{m} R_i y_i,$$

$$\dot{y}_i = \gamma_i y_i \left( R_i x - 1 - \sum_{j=1}^{n} a_{ij} Z_j \right), \quad i = 1, \ldots, m$$

$$\dot{Z}_j = \frac{\sigma_j}{\rho_j} Z_j \left( \sum_{i=1}^{m} a_{ij} y_i - \rho_j \right), \quad j = 1, \ldots, n.$$  

Here $R_i$ represents the basic reproduction number of virus strain $i$. Note that $\rho_j$ represents the reciprocal of the immune response fitness excluding the (rescaled) avidity to each strain $j$. The $m \times n$ nonnegative matrix $A = (a_{ij})$ describes the virus-immune interaction network, which determines each immune effector population’s avidity to the distinct viral strains. In section 4, we will introduce biologically reasonable simplifications to constrain the network size and define a reproduction number for each immune response. The following proposition from [8] establishes the non-negativity and boundedness of solutions.

**Proposition 2.1.** Consider the system (2) with initial conditions $\omega_0 = \left( x(0), y(0), Z(0) \right)$ belonging to the non-negative cone of $\mathbb{R}^{1+m+n}$ (denoted by $\mathbb{R}^{1+m+n}_+$). Solutions remain non-negative for all time $t$ and there exists a bounded set in $\mathbb{R}^{1+m+n}_+$ which attracts all solutions.

In preceding work on chemostat-type models with predator-prey networks, either a “one-to-one” network [35, 20] or perfectly nested network [8, 20] is assumed. Here we consider the model (2) with general interaction network, analyzing feasible equilibria and stability in the next section.

### 3 Equilibria and Lyapunov function

A general non-negative equilibrium point, $E^* = \left( x^*, y^*, Z^* \right) \in \mathbb{R}^{1+m+n}_+$, of system (2) will be characterized in terms of the positive virus and immune variant components. Define the “persistent variant sets” associated with $E^*$ as:

$$\Omega_y = \{ i \in [1, m] : y^*_i > 0 \} \quad \text{and} \quad \Omega_z = \{ j \in [1, n] : Z_j^* > 0 \}.$$  

3
Proof. Let \( E \) denote the equilibrium conditions for a set of \( y \)
\( i \) where \( \rho \) where \( \Omega \)
where \( \rho \) and \( \Omega \) \( \rho \) and \( \Omega \).
Following Hofbauer and Sigmund [15], we call an equilibrium \( E^\ast \) = \( x^\ast, y^\ast, Z^\ast \) of (2) saturated if the following holds when \( E^\ast \) has zero components:
\[
R_i x^\ast - 1 - \sum_{j \in \Omega_y} a_{ij} Z_j^\ast \leq 0, \quad \forall i \notin \Omega_y, \quad \sum_{i \in \Omega_y} a_{ij} y_i^\ast - \rho_j \leq 0, \quad \forall j \notin \Omega_z.
\]
Note that if \( E^\ast \) has all positive components, i.e. \( \Omega_y = [1, m] \) and \( \Omega_z = [1, n] \), the inequalities (6) trivially hold. Note also that each term in (6) is an “invasion eigenvalue” of the Jacobian matrix evaluated at \( E^\ast \) and thus a saturated equilibrium enjoys a weak stability against invasion by missing species. It immediately follows that a stable equilibrium must be saturated. As part of the main theorem later in this section, we will conversely show that every saturated equilibrium is stable. First, the following proposition states that there exists at least one saturated equilibrium, with the proof in the Appendix A.1.

**Proposition 3.1.** There exists a saturated equilibrium of system (2).

More properties of relevant equilibria can be ascertained. The following proposition states that any equilibria in the same positivity class must share the same value at \( x^\ast \).

**Proposition 3.2.** If \( E' = (x', y', Z') \) and \( E'' = (x'', y'', Z'') \) are both equilibria in the same positivity class, \( \Gamma_\Omega \), then \( x' = x'' \).

**Proof.** Let \( A' \) denote the submatrix of \( A \) which contains only the rows in \( \Omega_y \) and columns in \( \Omega_z \). Then the equilibrium conditions for \( E' \) can be rewritten as:
\[
y' A' = \rho', \quad A' \bar{Z}' = \frac{\bar{R}'}{1 + y' \bar{R}'}, \quad -\bar{I},
\]
where \( \rho' \) is the row vector with components \( \rho_j \) where \( j \in \Omega_z \), \( \bar{R}' \) is the column vector with components \( R_i \) where \( i \in \Omega_y \) and \( \bar{I} \) is the vector with all components one. Since \( E'' \) satisfies the same conditions, we obtain:
\[
(y' - y'') A' = 0, \quad A' (\bar{Z}' - \bar{Z}'') = \left( \frac{(y'' - y') \bar{R}'}{(1 + y'' \bar{R}')(1 + y' \bar{R}')} \right) \bar{R}', \quad \Rightarrow 0 = (y' - y'') A' (\bar{Z}' - \bar{Z}'') = (y' - y'') \left( \frac{(y'' - y') \bar{R}'}{(1 + y'' \bar{R}')(1 + y' \bar{R}')} \right) \bar{R}'.
\]
\[ \Rightarrow 0 = \left( (y' - y'') \hat{R}' \right)^2 \Rightarrow y' \hat{R}' = y'' \hat{R}' \]

\[ \Rightarrow x' = x'' \]

The previous proposition implies that if an equilibrium \( E^* = (x^*, y^*, Z^*) \) exists in positivity class \( \Gamma_\Omega \), then any equilibrium \( E' = (x', y', Z') \) belonging to \( \Gamma_\Omega \) will satisfy the following Lotka-Volterra equilibria conditions within \( \Gamma_\Omega \):

\[
\hat{r}' = B' \hat{v}', \quad \hat{r}' = \left( \hat{R}' x^* - \hat{\rho}' \right), \quad B' = \begin{pmatrix} 0 & A' \\ (A')^T & 0 \end{pmatrix}, \tag{7}
\]

where \( A' \) is the submatrix of \( A \) with rows in \( \Omega_y \) and columns in \( \Omega_z \), \( \rho' \) is the row vector with components \( \rho_j \) where \( j \in \Omega_z \), \( \hat{R}' \) is the column vector with components \( \hat{r}_i \) where \( i \in \Omega_y \), and \( \hat{v}' = (y', Z')^T \). Note that if the cardinality of \( \Omega_y \) and \( \Omega_z \) are equal (\( |\Omega_y| = |\Omega_z| \)) and \( A' \) is non-singular, then clearly \( E^* \) is unique in it’s positivity class \( \Gamma_\Omega \). More generally, if \( B' \) is non-singular, then \( E^* \) is unique in \( \Gamma_\Omega \). The following proposition sharpens the condition for uniqueness of an equilibrium within a positivity class, and shows that in such equilibria the number of virus strains either is equal to or exactly one more than the number of immune responses.

**Proposition 3.3.** Suppose the equilibrium \( E^* = (x^*, y^*, Z^*) \) exists in positivity class \( \Gamma_\Omega \), where \( (y^*, Z^*) \) satisfy the linear system of equations (7) and the cardinality of \( \Omega_y \) and \( \Omega_z \) are \( \mid \Omega_y \mid = m' \) and \( \mid \Omega_z \mid = n' \). Then \( E^* \) is the unique equilibrium in \( \Gamma_\Omega \), i.e. \( \hat{v} = (y^*, Z^*)^T \) is the unique solution to (7), if and only if \( \text{Ker}(A')^T \cap \hat{R}' = \{0\} \) and \( \text{Ker}(A') = \{0\} \).

Moreover, if \( E^* \) is the unique equilibrium in \( \Gamma_\Omega \), then one of the following holds:

(i) \( m' = n' \), and \( x^* = 1/\left(1 + (\hat{\rho}')^T (A')^{-1} \hat{R}' \right) \).

(ii) \( m' = n' + 1 \), and \( x^* = \hat{\Gamma} C_{(n'+1)}^{-1} \), where \( C_{(n'+1)}^{-1} \) is the last column in the \( (n'+1) \times (n'+1) \) matrix inverse of \( C = (A \hat{R}')^T \).

**Proof.** The submatrix \( A' \) is \( m' \times n' \) where \( m' = \mid \Omega_y \mid \) and \( n' = \mid \Omega_z \mid \). In the proof of Proposition 3.2, we ascertain that there are distinct equilibria in positivity class \( \Gamma_\Omega \) if and only if either \( y' \neq y'' \) or \( Z' \neq Z'' \). It is shown that

\[ y' - y'' \in \text{Ker}(A')^T \cap \hat{R}' \] and \( Z' - Z'' \in \text{Ker}A' \).

Therefore, the condition

\[ \text{Ker}(A')^T \cap \hat{R}' = \{0\} \] and \( \text{Ker}(A') = \{0\} \)

is equivalent to uniqueness of \( E^* \) in \( \Gamma_\Omega \).

Moreover \( \text{Ker}(A')^T \cap \hat{R}' = \{0\} \) if and only if the augmented \( (n'+1) \times m' \) matrix \( C' \) consisting of adding the final row \( \hat{R}' \) to \( (A')^T \) has trivial Kernel. Applying the rank-nullity theorem, we obtain that \( C \) has rank equal to \( m' \). Since rank cannot exceed the number of rows, \( m' \leq n' + 1 \). Applying to \( A' \), gives rank equal to \( n' \) and \( n' \leq m' \). Thus \( n' \leq m' \leq n' + 1 \).

In the case (i), \( m' = n' \), the matrix \( A \) is invertible and so from the equilibria equations (5), we obtain

\[ x^* = 1/\left(1 + (\hat{\rho}')^T (A')^{-1} \hat{R}' \right) \].

Finally, consider case (ii), \( m' = n' + 1 \). Since \( n' = \text{rank}(A') = \text{rank} ((A')^T) \), by the rank-nullity theorem we obtain that null \( ((A')^T) = 1 \). We claim that \( \text{Ker}(A')^T \) contains a vector \( \hat{w} \) such that \( \hat{w}^T \hat{R}' = 1 \) and \( \sum_i w_i = x^* \). Since the matrix \( C \) (defined in previous paragraph) has trivial Kernel, it is invertible. Let \( \hat{w} \) be the last column of \( C^{-1} \). Then it is not hard to see that \( (A')^T \hat{w} = 0 \) and \( (\hat{R}')^T \hat{w} = 1 \). Furthermore

\[ 0 = \hat{w}^T A' \hat{Z}' = \hat{w}^T \left( \hat{R}' x^* - \hat{\Gamma} \right) = x^* \hat{w}^T \hat{R}' - \sum_i w_i = x^* - \sum_i w_i. \]

Thus \( x^* = \sum_i w_i = \hat{\Gamma} C_{n'+1}^{-1} \).
Notice from the above proof that if an equilibrium $\mathcal{E}^*$ is not unique in it’s positivity class $\Gamma_\Omega$, then $\Gamma_\Omega$ contains an infinite number (a continuum) of equilibria. Conversely, if $\mathcal{E}^*$ is unique in a positivity class $\Gamma_\Omega$ containing $n'$ (persistent) immune responses, then there are either (i) $n'$ virus strains or (ii) $n'+1$ virus strains in $\Gamma_\Omega$.

Additionally some results on existence of saturated equilibria in Lotka-Volterra systems can be recast in our setting. For example, a sufficient condition for $\mathcal{E}^*$ to be saturated (and unique equilibrium in $\Gamma_\Omega$) is if the matrix $-B'$ in (7) is a $P$-matrix, i.e. all principal minors of $-B'$ are positive, by Theorem 15.4.5 in [15].

In what follows, we will be interested the global behavior of solutions to system (2). In doing so, we will determine which viral strains and immune responses uniformly persist [33] and which go extinct. Define the system to be $\Omega_{yz}$ permanent if

$$\exists \epsilon, M > 0 \text{ and } T(\vec{w}_0) \text{ such that } M > y_i(t), Z_j(t) > \epsilon, \ i \in \Omega_y, j \in \Omega_z, \ \forall t > T(\vec{w}_0),$$

and

$$\lim_{t \to \infty} y_i(t), Z_j(t) = 0, \ i \notin \Omega_y, j \notin \Omega_z, \ \text{ for every solution with initial condition } \vec{w}_0 \in \Omega.$$

We will sometimes use the terminology that $y_i, Z_j \ i \in \Omega_y, j \in \Omega_z$ are uniformly persistent and $y_i, Z_j \to 0 \ i \notin \Omega_y, j \notin \Omega_z$ to signify the system being $\Omega_{yz}$ permanent.

In the spirit of permanence as a sufficient condition for existence of a unique interior rest point in Lotka-Volterra systems [15], we find the following proposition.

**Proposition 3.4.** If the system is $\Omega_{yz}$ permanent, then there is a unique equilibrium $\mathcal{E}$ in the positivity class $\Gamma_\Omega$.

**Proof.** By Theorem 6.2 in [31], $\Omega_{yz}$ permanence implies that there exists an equilibrium in the positivity class $\Gamma_\Omega$. Suppose by way of contradiction that there are two equilibria, $\mathcal{E}'$ and $\mathcal{E}''$, in $\Gamma_\Omega$. By Proposition 3.2, $x' = x''$. Since the remaining equilibria equations (5) are linear, it can be shown that the line through $\mathcal{E}'$ and $\mathcal{E}''$ consist entirely of equilibria. Then, we can find equilibria arbitrarily close to the boundary of $\Gamma_\Omega$. This contradicts the fact that the system is $\Omega_{yz}$ permanent.

Now we state the main theorem of this section concerning the persistence of viral and immune variants. It builds off a result by Korytowski and Smith concerning bacteria-phage communities in a generalized Lotka-Volterra system [21].

**Theorem 3.1.** Suppose that $\mathcal{E}^* = \left( x^*, y^*, Z^* \right)$ is a non-negative equilibrium of system (2) with positivity class $\Gamma_\Omega$. Suppose further that $\mathcal{E}^*$ is saturated, i.e. the inequalities (6) hold. Then $\mathcal{E}^*$ is locally stable and $x(t) \to x^*$ as $t \to \infty$.

Furthermore, if $\mathcal{E}^*$ is the unique equilibrium in its positivity class $\Gamma_\Omega$ and the inequalities (6) are strict, then $y_i, Z_j \to 0$ for all $i \notin \Omega_y, j \notin \Omega_z$. If $i \in \Omega_y$ and $a_{ij} = 0 \ \forall j \in \Omega_z$, i.e. $\Lambda_i \cap \Omega_z = \emptyset$, then $y_i \to y_i^*$ and $x^* = 1/R_i$. In addition, omega limit sets corresponding to positive initial conditions are contained in invariant orbits satisfying

$$\sum_{i \in \Omega_y} \mathcal{R}_iy_i = \sum_{i \in \Omega_y} \mathcal{R}_iy_i^* \quad (8)$$

$$\dot{y}_i = \gamma_i y_i \left( \sum_{j \in \Omega_z} a_{ij} (Z_j^* - Z_j) \right) \quad i \in \Omega_y \quad (9)$$

$$\dot{Z}_j = \sigma_j Z_j \left( \sum_{i \in \Omega_y} a_{ij} (y_i - y_i^*) \right) \quad j \in \Omega_z,$$

and for each $i \in \Omega_y, j \in \Omega_z$, $y_i$ and $Z_j$ persist (the system is $\Omega_{yz}$ permanent) with asymptotic averages converging to equilibria values, i.e.

$$\lim_{t \to \infty} \frac{1}{t} \int_0^t y_i(s) \, ds = y_i^*, \quad \lim_{t \to \infty} \frac{1}{t} \int_0^t Z_j(s) \, ds = Z_j^*.$$
In the case that there are less than or equal to two persistent viral strains with non-empty epitope sets (restricted to \( \Omega_z \)), i.e. \( |\{i \in \Omega_y: \Lambda_i \cap \Omega_z \neq \emptyset\}| \leq 2 \), then \( E^* \) is globally asymptotically stable.

**Proof.** Consider the following Lyapunov function:

\[
W(x, \bar{x}, \bar{z}) = x - x^* \ln \frac{x}{x^*} + \sum_{i=1}^{m} \frac{1}{\gamma_i} \left( y_i - y_i^* \ln \frac{y_i}{y_i^*} \right) + \sum_{j=1}^{n} \frac{\rho_j}{\sigma_j} \left( Z_j - Z_j^* \ln \frac{Z_j}{Z_j^*} \right)
\]

\[
:= W_1 + W_2 + W_3,
\]

where the term with logarithm should be omitted if the corresponding coordinate in the particular equilibrium is zero. Then taking the time derivatives, we obtain

\[
\dot{W}_1 = 1 - x - x^* + x^* + \sum_{i=1}^{m} \mathcal{R}_i y_i (x^* - x),
\]

\[
\dot{W}_2 = \sum_{i=1}^{m} \left( \mathcal{R}_i x - 1 - \sum_{j=1}^{n} a_{ij} Z_j \right) (y_i - y_i^*),
\]

\[
\dot{W}_3 = \sum_{j=1}^{n} \left( \sum_{i=1}^{m} a_{ij} y_i - \rho_j \right) (Z_j - Z_j^*)
\]

Thus

\[
\dot{W} = 1 - x - x^* + x^* + \sum_{i=1}^{m} \left[ \mathcal{R}_i (y_i x^* - y_i^* x) - y_i + y_i^* \left( 1 + \sum_{j=1}^{n} a_{ij} Z_j \right) \right] - \sum_{j=1}^{n} \left[ Z_j \sum_{i=1}^{m} a_{ij} y_i + \rho_j (Z_j - Z_j^*) \right]
\]

\[
= 1 - x - x^* + x^* + \sum_{i=1}^{m} y_i \left( \mathcal{R}_i x^* - 1 - \sum_{j \in \Omega_z} a_{ij} Z_j^* \right) + \sum_{j=1}^{n} \sum_{i \in \Omega_y} a_{ij} y_i^* - \rho_j + \sum_{i \in \Omega_y} y_i^* \left( 1 - R_i x^* + \sum_{j \in \Omega_z} a_{ij} Z_j^* \right) + (x^* - x) \sum_{i \in \Omega_y} R_i y_i^* - \rho_j + \sum_{i \in \Omega_y} y_i^* \left( 1 - R_i x^* + \sum_{j \in \Omega_z} a_{ij} Z_j^* \right) + (x^* - x) \frac{1 - x^*}{x^*}
\]

\[
= \frac{1}{x^*} (x - x^*)^2 + \sum_{i \in \Omega_y} y_i \left( \mathcal{R}_i x^* - 1 - \sum_{j \in \Omega_z} a_{ij} Z_j^* \right) + \sum_{j \in \Omega_z} Z_j \left( \sum_{i \in \Omega_y} a_{ij} y_i^* - \rho_j \right)
\]

where we make use of equilibrium conditions (5) in the final line. By the assumed inequalities (6), we obtain that \( \dot{W} \leq 0 \), and thus \( W \) is a Lyapunov function at the equilibrium \( E^* \). Noting that \( E^* \) is the unique minimizer of \( W \), we obtain that \( E^* \) is (locally) stable. Additionally, since \( \dot{W} \leq 0 \) and \( W \to \infty \) as \( y_i, z_j \) goes to 0 or \( \infty \) for \( i \in \Omega_y, j \in \Omega_z \), we find that for any solution there exists \( p, P > 0 \) such that \( p \leq y_i, z_j \leq P \) for \( i \in \Omega_y, j \in \Omega_z \). Applying La Salle’s Invariance principle, the \( \omega \)-limit set corresponding to any solution of (2) with positive initial conditions is contained in the largest invariant set, \( \mathcal{L} \), where \( W = 0 \). Clearly \( W = 0 \Rightarrow x = x^* \), thus \( x = x^* \) in \( \mathcal{L} \). This implies that \( x(t) \to x^* \) as \( t \to \infty \) for all solutions with positive
Thus the above equation can be satisfied if \( Z \) we might assume that each strain has identical infected cell death rate \( \delta \). Recall that \( \Omega \) is still an open question when there are more than two persistent immune responses. Note that the loss of generality suppose that \( a_{ij} = 0 \) for any other strains where \( \Lambda \cap \Omega = \emptyset \). Now clearly there exists time \( t_1 \) such that \( y_i(t_1) = y_i^* \) by (10), and this implies that \( y_2(t_1) = y_2^* \) by the previous sentence. Without loss of generality assume \( t_1 = 0 \). Differentiating (8) twice and evaluating at time \( t = 0 \), we obtain:

\[
0 = R_1 y_1 + R_2 y_2 = \sum_{i=1}^{2} R_i \gamma_i \left[ \left( \sum_{j \in \Omega} (Z_j - Z_j(0)) \right)^2 - y_i(0) \left( \sum_{j \in \Omega} \frac{a_{ij}}{\rho_j} Z_j \sum_{k \in \Omega} a_{kj} (y_k(0) - y_k^*) \right) \right]
\]

\[
0 = \sum_{i=1}^{2} R_i \gamma_i \left[ \sum_{j \in \Omega} (Z_j - Z_j(0)) \right]^2,
\]

where the last equality comes from the fact that \( y_k(0) = y_k^* \) for \( k = 1, 2 \), and \( a_{kj} = 0 \) for \( k > 2 \). The only way the above equation can be satisfied is if \( Z_j(0) = Z_j^* \) for all \( j \). Then \( y_i(0) = y_i^* \), \( Z_j(0) = Z_j^* \), \( i \in \Omega_y, j \in \Omega_z \). Thus \( \mathbf{E}^* \) is globally asymptotically stable in this case.

More general results can be obtained in special cases, in particular, the inequalities (6) need not be strict for persistence results in certain cases discussed in Section 4. However, the global convergence to persistent variants is still an open question when there are more than two persistent immune responses. Note that the proof for global stability of “strictly saturated” equilibria \( \mathbf{E}^* \) with \( |\Omega_z| \leq 2 \) does not extend to \( |\Omega_z| > 2 \). Our numerical simulations that we have conducted support the global stability of \( \mathbf{E}^* \). We conjecture that an equilibrium \( \mathbf{E}^* \) of (2), which is unique in it’s positivity class \( \Gamma_\Omega \) and satisfies inequalities (5) strictly, is globally asymptotically stable for positive initial conditions regardless of the dimension of \( \Gamma_\Omega \).

4 Special Cases of Multi-epitope model

Suppose there are \( n \) epitopes each recognized by a specific CTL variant population. Recall that each virus strain \( i \) (cells infected with strain \( i \)), \( y_i \), has an epitope set defined by \( \Lambda_i := \{ j \in [1, n] : a_{ij} > 0 \} \), i.e. \( j \in \Lambda_i \), if \( y_i \) is not resistant to CTL \( z_j \). To make further progress on the analysis of model (2), it is useful to make the following assumption:

\[
\forall i \in [1, m] : \quad a_{ij} = a_j > 0 \quad \text{if} \quad j \in \Lambda_i.
\]  

(11)

Recall that \( a_{ij} = r_{ij}/\delta_i \), where \( r_{ij} \) is the killing/interaction rate and \( \delta_i \) is the infected cell death rate. Thus, we might assume that each strain has identical infected cell death rate \( \delta_i = \delta \) (so that they differ only in
Infection or viral production rate) and \( r_{ij} = r_j > 0 \) for all \( i \) such that \( j \in \Lambda_i \), i.e. the immune response \( Z_j \) either attacks strain \( i \) at rate \( r_j \) or strain \( i \) is resistant to \( Z_j \). Since a cell infected by virus strain \( i \) can be either resistant or susceptible to each of the \( n \) CTL variants, there are in principle \( 2^n \) possible viral mutant strains distinguished by their (basic) reproduction number, \( \mathcal{R}_i \), and epitope set, \( \Lambda_i \). The quantity \( I_j := \frac{a_j}{\rho_j} = \frac{b q_j r_j}{\rho_j} \) describes the reproductive potential of immune population \( j \). We say that an immune response \( Z_j \) is **immunodominant** over another immune response \( Z_k \) if \( I_j > I_k \). Sometimes we refer to the immune response \( Z_j \) with maximal \( I_j \) as immunodominant.

After rescaling the immune response variables as \( z_j = a_j Z_j \) and introducing the parameter \( s_j = 1/I_j \), we obtain the following system:

\[
\dot{x} = 1 - x - x \sum_{i=1}^{m} \mathcal{R}_i y_i, \quad \dot{y}_i = \gamma_i y_i \left( \mathcal{R}_i x - 1 - \sum_{j \in \Lambda_i} z_j \right), \quad \dot{z}_j = \frac{\sigma_j}{s_j} z_j \left( \sum_{i : j \in \Lambda_i} y_i - s_j \right),
\]

where \( i = 1, \ldots, m, j = 1, \ldots, n \). Each of the potential virus strains can be represented by a binary string of length \( n \) signifying its resistance profile (epitope set), i.e. \( y_i \equiv i_1 \cdots i_n \) where \( i_j = 0 \) if \( j \in \Lambda_i \) and \( i_j = 1 \) if \( j \notin \Lambda_i \). In the full virus mutant network, \( m = 2^n \) and no particular ordering is assumed, but we allow \( m \leq 2^n \) and choose convenient orderings for constrained networks in special cases considered in subsequent subsections.

First, notice that the \( 2^n \) potential virus strains can be viewed in a mutational pathway network, where each strain is a vertex in the **hypercube graph** according to the strain's epitope set represented as a binary sequence. The \( n \)-dimensional hypercube graph, denoted \( Q_n \), can be generated by connecting two distinct vertices (binary sequences of length \( n \)) with an edge if their Hamming distance is exactly one. In other words, for our setting, viral strains \( y_i \equiv i_1 \cdots i_n \) and \( y_j \equiv j_1 \cdots j_n \) are connected by an edge, which we denote \( y_i \sim y_j \), if the sequences \( i_1 \cdots i_n \) and \( j_1 \cdots j_n \) differ in exactly one slot, i.e. \( | \{ k \in [1, n] : i_k \neq j_k \} | = 1 \). In this way, \( y_i \) can mutate into \( y_j \) (or vice-versa) through a single epitope mutation if \( y_i \sim y_j \). We use the notation \( d(y_i, y_j) \) to denote the Hamming distance between the sequences corresponding to strains \( y_i \) and \( y_j \): \( d(y_i, y_j) = | \{ k \in [1, n] : i_k \neq j_k \} | \). Note that the wild-type virus, denoted here by \( y_w \), is represented by the sequence of all zeros since it is susceptible to attack by all immune responses. Since each mutation of an epitope comes with a fitness cost, we should assume that

\[
\text{If } y_i \sim y_j \text{ and } d(y_i, y_w) < d(y_j, y_w), \text{ then } \mathcal{R}_i > \mathcal{R}_j.
\]

We can establish some restrictions on the positivity class of feasible equilibria in model (12) based on graph-theoretic considerations of the viral strains viewed in the hypercube graph. In particular, we show that equilibria with persistent viral strains forming a cycle of order \( 2^l \) in the associated hypercube graph can only occur in degenerate cases. For \( 2 \leq j \leq n \), there are \( 2^{n-j} \) disjoint \( 2^l \)-cycles which cover the vertices of the hypercube graph \( Q_n \). In particular, it is well-known that there is a Hamiltonian cycle covering \( Q_n \). The following proposition concerns feasibility of equilibria with cycles in the viral mutational pathway network.

**Proposition 4.1.** For \( n \geq 2 \), consider model (12). Let \( 2 \leq j \leq n \) and \( l = 2^l \). Suppose there is a simple \( l \)-cycle in the representative hypercube graph, \( y_{k_1} \sim y_{k_2} \sim \cdots \sim y_{k_l} \sim y_{k_1} \), and \( \sum_{i=1}^{l} (-1)^i \mathcal{R}_{k_i} = \sum_{i=1}^{\ell} (-1)^{d(y_{i}, y_{w})} \mathcal{R}_{k_i} \neq 0 \), then there can not be an equilibrium with \( y_{k_1}^*, y_{k_2}^*, \ldots, y_{k_l}^* > 0 \).

**Proof:** Fix \( 2 \leq j \leq n \) and let \( l = 2^l \). Each simple cycle of length \( l \) can be seen as an embedded hypercube graph on \( 2^l \) vertices, \( Q_l \), corresponding to binary strings where \( n - j \) slots are fixed to be all zeros or all ones. Without loss of generality suppose that these fixed slots are indices \( [j + 1, n] \) corresponding to \( z_j+1, \ldots, z_n \). Without loss of generality, assume that the epitope sets of \( y_1, \ldots, y_{l} \) all contain \( [j + 1, n] \), more precisely \( \bigcap_{i=1}^{l} \Lambda_i = [j + 1, n] \), and there is an \( l \)-cycle between their corresponding vertices in the hypercube graph, given as \( y_1 \sim \cdots \sim y_l \sim y_1 \). Suppose that \( y_1^*, y_2^*, \ldots, y_{l}^* > 0 \). Then we find that

\[
0 = \sum_{i=1}^{l} (-1)^i \frac{\gamma_{i} y_{i}^{*}}{\mathcal{R}_{i}} = x^* \sum_{i=1}^{l} (-1)^i \mathcal{R}_{i} - \sum_{i=1}^{l} (-1)^i - (z_{j+1}^{*} + \cdots + z_{n}^{*}) \sum_{i=1}^{l} (-1)^i - (z_{1}^{*} + \cdots + z_{j}^{*}) \sum_{i=0}^{j-1} \binom{j-1}{i} (-1)^{i} = x^* \sum_{i=1}^{l} (-1)^i \mathcal{R}_{i} = x^* \sum_{i=1}^{l} (-1)^{d(y_{i}, y_{w})} \mathcal{R}_{i}.
\]

9
A couple remarks about the above proposition are in order. First, we highlight the of case \( j = 2 \) of Proposition 4.1, which implies the generic non-existence of equilibria with persistent viral strains forming a 4-cycle in the associated hypercube graph. In particular, if viral strains \( y_{k_1}, \ldots, y_{k_4} \) form a cycle, then there exists an equilibrium \( \mathcal{E}^* \) with \( y^*_k > 0 \) only if \( \sum_{i=1}^{4} (-1)^{i+1} \mathcal{R}_k = 0 \) where \( p_i = d(y_{k_i}, y_{k_{i+1}}) \). In Section 4.3, the degeneracy of “four-cycle equilibria” will be detailed further for the case of \( n = 2 \) epitopes. In general, for \( n \geq 2 \), there are \( 2^{n-2} \) disjoint 4-cycles which cover the vertices of \( Q_n \), and their unions form larger cycles with order as powers of two. Each of these cycles of order \( 2^j, j \geq 2 \), can be seen as an embedded \( j \)-dimensional hypercube. Thus the proposition establishes the degeneracy of equilibria with positive viral components forming an embedded hypercube subgraph in the associated hypercube \( Q_n \), which suggests that these combinations of viral strains generally do not persist together in model (12).

In the following subsections, we analyze a few special cases of the multi-epitope model where stable equilibria can be sharply characterized by quantities derived from the parameters. Throughout the following, we assume without loss of generality that immune responses \( z_1, \ldots, z_n \) are ordered according to an immunodominance hierarchy:

\[
s_1 \leq s_2 \leq \cdots \leq s_n, \quad \text{i.e. } \mathcal{I}_1 \geq \mathcal{I}_2 \geq \cdots \geq \mathcal{I}_n
\]  

(14)

Sections 4.1 and 4.2 mostly summarize previous analytical results when the network is constrained to be “one-to-one” and perfectly nested, respectively. These cases provide nice applications of our general Theorem 3.1, and also are important for the analysis of the full network. We consider the full network with \( m = 2^n \) virus strains in section 4.3 for \( n = 2 \) epitopes, and in section 4.4 for arbitrary \( n \) in the special case of equal fitness costs for each epitope mutation.

### 4.1 Strain-Specific network

First, consider the case where \( m = n \) and \( \Lambda_i = \{i\} \) in model (12), i.e. \( A \) is a diagonal \( n \times n \) matrix, \( A = \text{diag} (a_1, \ldots, a_n) \), in system (2). This particular assumption of a “one-to-one” interaction network, where each immune response population attacks a unique specific viral strain, has been considered in [35, 20, 22, 5]. In this case, model (12) reduces to the following \( n + 1 \)-strain and \( n \)-immune variant model:

\[
\dot{x} = 1 - x - x \sum_{i=1}^{n} \mathcal{R}_i y_i, \quad \dot{y}_i = \gamma_i y_i (\mathcal{R}_i x - 1 - z_i), \quad \dot{y}_{n+1} = \gamma_{n+1} y_{n+1} (\mathcal{R}_{n+1} x - 1), \quad \dot{z}_i = \sigma_i s_i (y_i - s_i)
\]  

(15)

where \( i = 1, \ldots, n \). We impose the additional assumption that \( \mathcal{R}_i \) are decreasing with \( i \), along with our immunodominance hierarchy (14), to avoid degeneracy,

\[
\mathcal{R}_1 > \mathcal{R}_2 > \cdots > \mathcal{R}_n.
\]  

(16)

For \( k \in [1, n] \) define:

\[
\mathcal{P}_k = \frac{\mathcal{P}_{k-1} + s_k \mathcal{R}_k}{\mathcal{P}_0 = 1, s_k = 1/\mathcal{I}_k}.
\]  

(17)

More generally we can define \( \mathcal{P}_J = 1 + \sum_{i \in J} \mathcal{R}_i s_i \) for any subset \( J \subseteq [1, n] \). For each \( k \in [0, n] \), define the following equilibria:

\[
\mathcal{E}^+_k = (x^+_k, y^+_k, z^+_k), \quad x^+_i = \frac{1}{\mathcal{R}_{k+1}}, \quad y^+_i = s_i, \quad z^+_i = \frac{\mathcal{R}_i}{\mathcal{R}_{k+1}} - 1, \quad i = 1, \ldots, k,
\]  

(18)

\[
\mathcal{E}^+_{k+1} = (x^+_k, y^+_k, z^+_{k+1}), \quad y^+_{k+1} = 1 - \frac{\mathcal{P}_k}{\mathcal{R}_{k+1}}, \quad z^+_{k+1} = 0, \quad y_i = z_i^+ = 0, \quad i > k + 1,
\]  

\[
\mathcal{E}^+_k = (x^+_k, y^+_k, z^+_k), \quad x^+_i = \frac{1}{\mathcal{P}_k}, \quad y^+_i = s_i, \quad z^+_i = \frac{\mathcal{R}_i}{\mathcal{P}_k} - 1, \quad i = 1, \ldots, k,
\]  

(19)
Let \( k \in [1, n+1] \) be maximal such that

\[
R_k > 1 + \sum_{i=1}^{k-1} R_i s_i
\]

where the sum on the right vanishes if \( k = 1 \). There are two cases depending on whether (for \( k < n+1 \))

\[
R_k > 1 + \sum_{i=1}^{k} R_i s_i
\]

or not. If the inequality holds (for \( k < n+1 \)), then there is a unique saturated equilibrium, \( \mathcal{E}^+_k \), with \( \Omega_y = [1, k] \) and if it does not or \( k = n+1 \), then there is a unique saturated equilibrium, \( \mathcal{E}^+_k \), with \( \Omega_y = [1, k-1], \Omega_y = [1, k] \). The inequalities (6) are strict in either case so the system is \( \Omega_y \) permanent and \( y_i, z_j \to 0 \) for all \( i \notin \Omega_y, j \notin \Omega_z \), by Theorem 3.1. In fact, much more can be said about the asymptotic behavior of solutions. In particular, the other conclusions of Theorem 3.1 imply that the components \( y_i, z_j \) where \( i \notin \Omega_y, j \notin \Omega_z \) converge to zero, the asymptotic means of the persistent variants converge to equilibria values, and the global attractor satisfies (9) which consists of \( k \) or \( k - 1 \) distinct planar Lotka-Volterra predator-prey differential equations for \((y_i, z_i)\) constrained by the relation \( \sum_{i} R_i y_i = \sum_{j} R_j s_j \). This fact was utilized in a chemostat model by Wolkowicz [35] to prove that a unique saturated equilibrium is globally asymptotically stable for \( k = 1, 2 \) (including when \( \Omega_z = \{1, 2\}, \Omega_y = \{1, 2, 3\} \)). These results are summarized in the following theorem.

**Theorem 4.1.** If \( R_1 > P_1 \), let \( k \) be the largest integer in \([1, n]\) such that \( R_k > P_k \), otherwise let \( k = 0 \). If \( R_{k+1} \leq P_k \), then for \( 1 \leq i \leq k, y_i, z_i \) are uniformly persistent (if \( R_{k+1} > P_k \) also persists), and the other variants globally converge to zero, \( x(t) \to 1/P_k \) (if \( R_{k+1} > P_k \), \( x(t) \to 1/P_{k+1} \) and \( y_{k+1}(t) \to 1 - \frac{P_k}{R_{k+1}} \)) as \( t \to \infty \). Additionally, the corresponding equilibria (\( \mathcal{E}^+_k \) or \( \mathcal{E}^+_{k+1} \)) are locally stable (globally asymptotically stable when \( k = 0, 1, 2 \)), asymptotic averages converge to equilibria, and the global attractor satisfies (8) and (9).

If the assumptions of decreasing and distinct reproduction numbers are relaxed, then the system can have degeneracies which allow for multiple saturated equilibria. However when the full network for \( n \) epitopes containing \( 2^n \) strains is considered (the strain-specific network is a subgraph in the representative hypercube graph), we can relax assumptions while avoiding any degeneracy of “strain-specific equilibria”. For \( i = 1, \ldots, n \), we identify the viral strain \( y_i \) with the binary sequence \( i_1 \cdots i_n \) where \( i_j = 1 \) for all \( j \neq i \) and \( i_i = 0 \), and \( y_{n+1} \equiv 1 \cdots 1 \). Note in other sections we use different orderings of the strains on the hypercube. Then denoting the wild strain as \( y_{w} \), where \( y_{w} \equiv 0 \cdots 0 \), we have \( d(y_i, y_{w}) = n - 1 \) for all \( i = 1, \ldots, n \). We assume that for any \( i, j \in [1, 2^n] \), if \( y_i \sim y_j \), then \( d(y_i, y_{w}) < d(y_j, y_{w}) \Rightarrow R_i > R_j \), as mentioned before since mutations incur fitness costs. We claim that any equilibrium \( \mathcal{E} \) with \( \Omega_z \subseteq [1, n] \) and \( \Omega_y \subseteq [1, n+1] \) is saturated only if \( \Omega_z = [1, n] \) and \( \Omega_y \equiv [1, n] \). In other words \( \mathcal{E}^+_n \) and \( \mathcal{E}^+_{n+1} \) are the only strain-specific equilibria which can be saturated in the full hypercube network. Suppose by way of contradiction that we can choose \( i, j \in [1, n] \) such that \( i \in \Omega_z \) and \( j \notin \Omega_z \). Then consider strain \( y_{\ell} \) such that \( \Lambda_\ell = \{i, j\} \), i.e. \( y_{\ell} \sim y_i \) and \( y_{\ell} \sim y_j \). At equilibrium \( \mathcal{E} \), it’s invasion rate is given by \( \frac{d_{w|y_{\ell}}}{d_{w|y_{i}}} = (R_\ell - R_i)/P_{\ell} \), where \( P = \mathcal{P}_{\ell} \) or \( R_{n+1} \) with \( \ell \in [1, n] \). Since \( R_\ell > R_i \), equilibrium \( \mathcal{E} \) cannot be saturated. The conditions for equilibria \( \mathcal{E}^+_n \) to be saturated is as follows in the general model:

\[
(|\Lambda_\ell| - 1) P_n + R_\ell \leq \sum_{i \in \Lambda_\ell} R_i \quad \forall \ell \in [n + 1, 2^n]
\]

(20)

We will further analyze the full network for special cases of \( n = 2 \) epitopes and equal viral fitness costs of mutations from each of \( n \) epitopes, in Sections 4.3 and 4.4, respectively. First, we examine key results from Browne [8] in the case of a perfectly nested network.
4.2 Nested Network

While the virus-immune epitope interaction network generally can be quite complex, patterns of viral escape and dynamic immunodominance hierarchies often emerge. In observations of HIV infection, the initial CTL response occurs at a few immunodominant epitopes and is followed by viral mutations at these epitopes conferring resistance, along with a fall in these specific CTLs and rise in subdominant CTLs [24]. This pattern continues, albeit at diminishing rates as time proceeds, resulting in viral strains with resistance at multiple epitopes and corresponding fitness costs, along with subdominant CTLs of increasing breadth. An idealized description of this process is a perfectly nested network, where resistance to multiple epitopes is built sequentially according to the immunodominance hierarchy. Nested networks have been of recent interest in explaining the biodiversity and structure of bacteria-phage communities [17, 20, 34], and there is some evidence that nestedness is a feature of HIV-CTL dynamics [18, 24, 11]. In a recent work [8], the stability of equilibria, along with uniform persistence or extinction of the populations are characterized for system (12) in the case of a perfectly nested network.

The perfectly nested network consists of n epitope specific CTLs, $z_1, \ldots, z_n$, and $m = n + 1$ virus strains $y_1, \ldots, y_{n+1}$ where the epitope set of $y_i$ is $\Lambda_i = \{i, \ldots, n\}$ (having escaped immune responses $z_1, \ldots, z_{i-1}$). The equations are

$$\dot{x} = 1 - x - x \sum_{i=1}^{n} R_i y_i, \quad \dot{y}_i = \gamma_i y_i \left( R_i x - 1 - \sum_{j \geq i} z_j \right), \quad \dot{y}_{n+1} = \gamma_{n+1} y_{n+1} (R_{n+1} x - 1),$$

$$\dot{z}_i = \frac{\sigma_i}{s_i} \left( \sum_{j \leq i} y_j - s_i \right), \quad \text{where } i = 1, \ldots, n. \quad (21)$$

As before we assume a fitness cost for each mutation, and here we also assume a strict immunodominance:

$$R_1 > R_2 > \cdots > R_{n+1} \quad \text{and} \quad I_1 > I_2 > \cdots > I_n.$$ 

Out of a multitude of non-negative equilibria ($> 2^n$), there are $2n + 2$ feasible attractors, the stability of which depend upon quantities derived from parameters. For $k \geq 1$ define:

$$Q_k = Q_{k-1} + (s_k - s_{k-1}) R_k, \quad \text{where} \quad Q_0 = 1, s_0 = 0, s_k = 1/I_k. \quad (22)$$

Then, for each $k \in [0, n]$, define the following equilibria:

$$\tilde{E}_{k+1} = (\tilde{x}, \tilde{y}, \tilde{z}), \quad \tilde{x} = \frac{1}{R_{k+1}}, \quad \tilde{y}_i = s_i - s_{i-1}, \quad \tilde{z}_i = \frac{R_i - R_{i+1}}{R_{k+1}} \quad \text{for } 1 \leq i \leq k, \quad (23)$$

$$\tilde{y}_{k+1} = 1 - \frac{Q_k}{R_{k+1}}, \quad \tilde{z}_{k+1} = 0, \quad \tilde{y}_i = \tilde{z}_i = 0 \quad \text{for } k + 1 < i \leq n$$

$$\tilde{E}_k = (\tilde{x}, \tilde{y}, \tilde{z}), \quad \tilde{x} = \frac{1}{Q_k}, \quad \tilde{y}_i = s_i - s_{i-1}, \quad \tilde{z}_i = \frac{R_i - R_{i+1}}{Q_k} \quad \text{for } 1 \leq i \leq k, \quad (24)$$

$$\tilde{y}_k = s_k - s_{k-1}, \quad \tilde{z}_k = \frac{R_k}{Q_k} - 1, \quad \tilde{y}_i = \tilde{z}_i = 0 \quad \text{for } k < i \leq n, \quad \tilde{y}_{k+1} = 0$$

Equilibrium $\tilde{E}_{k+1}$ represents the appearance of escape mutant $y_{k+1}$ from equilibrium $\tilde{E}_k$.

The main result of [8] is summarized as follows:

**Theorem 4.2** ([8]). If $R_1 > Q_1$, let $k$ be the largest integer in $[1, n]$ such that $R_k > Q_k$, otherwise let $k = 0$. If $R_{k+1} \leq Q_k$, then for $1 \leq i \leq k$, $y_i, z_i$ are uniformly persistent (if $R_{k+1} > Q_k, y_{k+1}$ persists), and the other variants globally converge to zero, $x(t) \rightarrow 1/Q_k$ (if $R_{k+1} > Q_k, x(t) \rightarrow 1/R_{k+1}$ and $y_{k+1}(t) \rightarrow 1 - \frac{Q_k}{R_{k+1}}$) as $t \rightarrow \infty$. Additionally, the corresponding equilibria ($\tilde{E}_{k+1}$ or $\tilde{E}_k$) are locally stable (globally asymptotically stable when $k = 0, 1, 2$), asymptotic averages converge to equilibria, and the global attractor satisfies (8) and (9).

**Proof.** The theorem is proved in [8], and also can be seen as a direct application of Theorem 3.1. 

Figure 1: (a) The full virus-immune network on \( n = 3 \) epitopes visualized through the viral escape pathway hypercube graph, \( Q_3 \). (b) The strain-specific (one-to-one) network, as a subgraph of the hypercube graph. (c) The perfectly nested network, as a subgraph of the hypercube graph. (d) The full network on \( n = 2 \) epitopes.

Theorem 4.2 suggests a stable diverse set of viral strains and immune response which can be built up by the nested accumulation of epitope resistance and rise of subdominant CTLs. The diversity achieved depends upon potential breadth \( n \) and “immune invasion” number at epitope \( k \leq n \), \( R_k/Q_k \), which depends upon the strengths of CTL directed at the \( k \) epitopes in immunodominance hierarchy and the viral fitness costs of \( k \) sequential mutations, along with initial fitness \( R_1 \). Observe that since \( R_k \) decreases and \( Q_k \) increases with breadth \( k \), Theorem 4.2 implies exclusion of \( y_{k+1} \) is more likely as the breadth increases. Additionally, it is shown in [8] that the rate of \( y_{k+1} \) invasion decreases as the breadth \( k \) increases, which is consistent with several studies showing rate of HIV viral escape from CTL responses slows down after acute infection, along with relatively few escapes [2, 12].

Overall, the analysis in the case of the nested network confirms some patterns of multi-epitope viral escape and reinforces the importance of strong immune responses directed at conserved epitopes (high fitness cost for resistance) in order to control HIV with CTL response. However, constraining multi-epitope resistance to be built in a nested fashion leaves out other potential mutational pathways. The question remains, with \( n \) epitopes targeted by distinct immune responses, what are the potential escape patterns and stable equilibria? We begin to answer this question in the next subsection in the simplest case of multiple epitopes, \( n = 2 \).

4.3 Dynamics for full network on \( n = 2 \) epitopes

If two epitopes are concurrently targeted by two distinct specific immune responses, which escape pathway will the virus follow and what mutant strains persist? In the nested network, we assumed that the virus escaped the most immunodominant response. However, in general, both CTL pressure and virus fitness cost determine selective advantage of a resistant mutant. For a single epitope, an escape mutant \( y_2 \) invades the wild-type \( y_1 \), if its reproductive number, \( R_2 = fR_1 \), is large enough given the CTL pressure, \( s_1R_1 \); in particular, if \( (f - s_1)R_1 > 1 \), where \( f \) is the fitness proportion of the wild-type reproductive number \( R_1 \) and \( s_1 = 1/I_1 \) is the immune response reproduction number as before. For the general case of \( n = 2 \) epitopes, although the situation is fundamentally more complex, we will sharply characterize the dynamics in this section and the results suggest that immunodominance may play a larger role than viral fitness in determining the structure of the persistent virus-immune network.
The full network for \( n = 2 \) epitopes (shown in Fig. 1(d)) consists of 2 CTL populations, \( z_1 \) and \( z_2 \), and \( m = 4 \) virus strains, \( y_i \), \( i = 1, \ldots, 4 \), each with an associated binary string describing their resistance profile; \( y_1 \equiv 00, y_2 \equiv 10, y_3 \equiv 01, y_4 \equiv 11 \). Recall that a 0 in the \( j \)th slot of the binary string signifies susceptible to \( z_j \), whereas 1 signifies resistance; for example \( y_2 \) (10) is resistant to \( z_1 \) but susceptible to \( z_2 \). We assume that \( z_1 \) is strictly immunodominant, i.e. \( I_1 > I_2 \) or \( s_1 < s_2 \). Each epitope escape comes with a fitness cost as before, therefore the viral reproduction numbers satisfy \( R_4 > \max(R_2, R_3) \geq \min(R_2, R_3) > R_4 \). We note that the fitness cost for resistance to \( z_1 \) may be greater than or equal to the fitness cost to \( z_2 \), in other words the fitness of mutant \( y_2 \) is less than or equal to \( y_3 \) \((R_2 \leq R_3)\). Conversely, it may be the case that resistance to the dominant immune response, \( z_1 \), comes at less cost than resistance to the weaker response \((R_2 > R_3)\). Our underlying assumptions are summarized below:

\[
I_1 > I_2 \quad (s_1 < s_2) , \quad R_1 > \max(R_2, R_3) \geq \min(R_2, R_3) > R_4
\]  
(25)

For clarity, we write the 7 equations in model (12) for this case \( n = 2 \) with the chosen index notation:

\[
\begin{align*}
\dot{x} &= 1 - x - x \sum_{i=1}^{4} R_i y_i, \quad \dot{y}_1 = \gamma_1 y_1 (R_1 x - 1 - (z_1 + z_2)), \quad \dot{y}_2 = \gamma_2 y_2 (R_2 x - 1 - z_2), \\
\dot{y}_3 &= \gamma_3 y_3 (R_3 x - 1 - z_1), \quad \dot{y}_4 = \gamma_4 y_4 (R_4 x - 1), \quad \dot{z}_1 = \frac{\sigma_1}{s_1} (y_1 + y_3 - s_1), \quad \dot{z}_2 = \frac{\sigma_2}{s_2} (y_1 + y_2 - s_2),
\end{align*}
\]  
(26)

The dynamics are rigorously characterized in the Theorems 4.3 and 4.4 stated below. The theorems together present a sharp polychotomy which delineates the stability of nine potential distinct equilibria, along with a degenerate case where a continuum of equilibria exists, and the corresponding uniform persistence of variants in each case. First, we list these nine potential equilibria with corresponding component values. In this way, we can capture all of the possible equilibrium forms and avoid listing equilibria that are always unstable. Note that there are five feasible equilibria (which can be strictly saturated) with both immune responses, \( z_1 \) and \( z_2 \), persistent: the nested and "strain-specific" type (with 2 or 3 virus strains), along with a new form where \( y_1, y_2, y_3 \) coexist. The distinct regimes are determined by the values of the reproductive numbers and the following quantities

\[
Q_1 = 1 + R_1 s_1, \quad Q_2 = Q_1 + R_2 (s_2 - s_1), \quad P_2 = 1 + s_1 R_3 + s_2 R_2, \quad R = R_2 + R_3 - R_1.
\]  
(27)

The following equilibria have two immune responses present:

\[
\begin{align*}
\bar{E}_2 &= \left( \frac{1}{R_4}, \tilde{y}_1, \tilde{y}_2, 0, \tilde{y}_4, \tilde{z}_1, \tilde{z}_2 \right), \quad \bar{E}_2 = \left( \frac{1}{Q_2}, \tilde{y}_1, \tilde{y}_2, 0, 0, \tilde{z}_1, \tilde{z}_2 \right), \quad \bar{E}_2 = \left( \frac{1}{R_1}, \tilde{y}_1, \tilde{y}_2, \tilde{y}_3, 0, \tilde{z}_1, \tilde{z}_2 \right),
\end{align*}
\]  
(28)

The four equilibria with one or zero immune responses are:

\[
\begin{align*}
\bar{E}_1 &= \left( \frac{1}{R_2}, s_1, 1 - \frac{Q_1}{R_2}, 0, 0, \frac{R_1 - R_2}{R_4} \right), \quad \bar{E}_1 = \left( \frac{1}{Q_2}, s_1, 0, 0, 0, \frac{R_1 - R_2}{Q_2} \right),
\end{align*}
\]  
(29)

The theorems classifying dynamics for model (26) with strict immunodominance, \( s_1 < s_2 \), are as follows (proofs are in Appendix A.2):
Consider the model with two epitopes (26) under the assumptions (25) and suppose positive initial conditions, i.e. \( x(0), y_i(0), z_j(0) > 0 \) for all \( i = 1, \ldots, 4, j = 1, 2 \). Then the following results hold:

i. If \( R_1 < 1 \), then \( \tilde{E}_0 \) is GAS (globally asymptotically stable).

ii. If \( 1 < R_1 \leq Q_1 \), then \( \tilde{E}_0 \) is GAS.

iii. If \( R_1 > Q_1 \geq R_2 \), then \( \tilde{E}_1 \) is GAS.

iv. If \( Q_2 \geq R_2 > Q_1 \), then \( \tilde{E}_1 \) is GAS.

Theorem 4.4 (Stability of equilibria with two immune responses present). Consider the model with two epitopes (26) under the assumptions (25) and suppose positive initial conditions, i.e. \( x(0), y_i(0), z_j(0) > 0 \) for all \( i = 1, \ldots, 4, j = 1, 2 \). Then the stability of equilibria (28) are characterized as follows:

1. if \( R < Q_2 \) and \( R_4 \leq Q_2 \), then \( \tilde{E}_2 \) is GAS.

2. if \( R < R_4 \), then \( \tilde{E}_2 \) is GAS.

3. if \( Q_2 < R < P_2 \) and \( R_4 < R \), then \( \tilde{E}_2 \) is (locally) stable. Additionally, \( \lim_{t \to \infty} x(t) = \bar{x} = \frac{1}{R} \), \( \lim_{t \to \infty} y_4(t) = 0 \), and

\[
\lim_{t \to \infty} \frac{1}{t} \int_0^t y_i(s) \, ds = \bar{y}_i, \quad i = 1, 2, 3, \quad \lim_{t \to \infty} \frac{1}{t} \int_0^t z_j(s) \, ds = \bar{z}_j, \quad j = 1, 2.
\]

Furthermore \( y_i, z_j, \quad i = 1, 2, 3, \quad j = 1, 2 \) are uniformly persistent.

4. if \( P_2 < R \) and \( R_4 \leq P_2 \), then \( E^1_2 \) is GAS.

5. if \( Q_2 < P_2 < R_4 < R \), then \( E^1_2 \) is GAS.

6. If \( R = R_4 \), then there is a continuum of saturated equilibria which forms a line connecting \( y_4 = 0 \) and \( y_3 = 0 \) boundaries at \( \bar{y}_3 \) and \( \bar{y}_4 \), respectively, in the \((y_3, y_4)\) plane.

We make the following observations concerning the above theorems. First, note that the inequalities in the hypotheses of Theorems 4.3 and 4.4 cover all possible parameter combinations under the conditions (25). Indeed, observe that \( P_2 \leq Q_2 \Leftrightarrow R \leq 0 \) and of course \( Q_2, P_2 > 0 \), therefore the case \( P_2 \leq Q_2 \) falls under case 1 or case 2 of the theorem. Additionally, \( R > Q_2 \Rightarrow R_2 > Q_2 \), separating this case from the cases considered in Theorem 4.3. Note also that any equilibrium, \( E^* \), with \( z_2^* > 0 \) and \( z_1^* = 0 \) or \( y_3^* > 0 \) and \( y_2^* = 0 \) will not be saturated when \( s_1 < s_2 \).

For the case \( R_4 = R \) and \( Q_2 < R < P_2 \), both equilibria \( \tilde{E}_2 \) and \( \tilde{E}_4 \) are saturated, but the inequalities (6) are not strict. In this case, there are a continuum of saturated (neutrally stable) non-negative equilibria with
Figure 3: Convergence to $\tilde{E}_1$ with (a) healthy cells and virus, (b) immune response. Despite a “single epitope advantage” of $y_3$, the mutant $y_2$ (resistant to immunodominant response $z_1$) excludes $y_3$ in the two-epitope scenario. The parameters are as follows: $R_1 = 12.5$, $R_2 = 3$, $R_3 = 10$, $R_4 = 2$, $I_1 = 6.67$, $I_2 = 5$, thus $Q_1 < R_2 < Q_2$. Also, $\gamma_i = \gamma = 70$ and $\sigma_j = 10$ for $i = 1, \ldots, 4$, $j = 1, 2$, and initial conditions are $x(0) = \frac{1}{R_1}$, $y_1(0) = 1 - \frac{1}{R_1}$, $y_2(0) = y_3(0) = 0.1$, $y_4(0) = 0.001$, $z_1(0) = z_2(0) = 0.01$. The comparison of single-epitope invasion eigenvalues yields $\lambda_2 = 0.044\gamma < \lambda_3 = 1.86\gamma$, and the single-epitope densities are $y_2 = 0.042 < y_3 = 0.65$.

Figure 4: (a) Convergence to $\tilde{E}_2$ after decreasing $R_1$ from 12.5 to 12 and increasing $R_2$ from 3 to 5 (with all other parameters the same as for Fig. 3). (b) Convergence to $\tilde{E}_2$ after decreasing $R_1$ from 12 to 11.8. (c) Convergence to $\tilde{E}_2$ after decreasing $R_1$ from 11.8 to 11.5. (d) Convergence to $\tilde{E}_2$ after increasing $R_4$ to 3.6. Note $z_1$ and $z_2$ both persist in these simulations.
Table 1: Stable equilibria values for healthy & infected cells in Theorem 4.4 where six regimes sharply characterize distinct viral strain persistence scenarios (0 components go extinct) when both immune responses \( z_1 \) & \( z_2 \) persist (when \( R_2 \leq Q_2 \)). Note that if \( R_2 \leq Q_2 \), then only \( z_1 \) and \( y_1 \), \( y_2 \) can persist and the dynamics are detailed in Theorem 4.3.

\[
x(t) \to \frac{1}{\tilde{R}} \quad \text{and} \quad y_4(t) \to 1 - \frac{\tilde{q}_1^4}{\tilde{R}} - y^*_4, \quad 0 \leq y^*_4 \leq 1 - \frac{\tilde{q}_1^4}{\tilde{R}}. \quad \text{The endpoints on the line of equilibria in the} \quad (y_3, y_4) \quad \text{plane correspond to} \quad \tilde{\xi}_2 \quad \text{and} \quad \tilde{\xi}_2, \quad \text{where} \quad \tilde{y}_3 = 0 \quad \text{and} \quad \tilde{y}_4 = 0, \quad \text{respectively. The bifurcation at} \quad R_4 = R \quad \text{is illustrated in Figure 2. When} \quad R_4 \neq R, \quad \text{it is not possible for all} \quad y_i \quad \text{to persist, as the dynamics will fall into one of the cases in Theorems 4.3 and 4.4. These results illustrate Proposition 4.1, which precludes the possibility of equilibria with all components} \quad y_i \quad \text{positive when} \quad R_4 \neq R \quad \text{since the viral strains form a 4-cycle in the associated hypercube graph.}

\text{An interesting finding is that strain} \quad y_2 \quad \text{(10)} \quad \text{is present in all equilibria (and uniformly persistent) with mutation, even if it has a much higher fitness cost than} \quad y_3 \quad \text{(01), i.e.} \quad R_3 >> R_2. \quad \text{Thus, if escape occurs in the two epitope setting, the viral quasispecies always includes the mutant} \quad y_2 \quad \text{with resistance to the immunodominant epitope,} \quad z_1. \quad \text{We can characterize the (linearized) invasion rate of an escape mutant, say} \quad y_2, \quad \text{from the single epitope,} \quad z_1, \quad \text{by calculating} \quad \frac{\tilde{y}_3}{y^*_2} \quad \text{at equilibrium} \quad \tilde{\xi}_1, \quad \text{to obtain} \quad \lambda_2 = \gamma_2 \left( \frac{y^*_2}{\tilde{R}} - 1 \right) = \frac{y_3}{1+R_1s_1} - 1. \quad \text{The mutant} \quad y_2 \quad \text{then converges to} \quad y^*_2 = 1 - \frac{1+R_1s_1}{R_2}, \quad \text{in equilibrium} \quad \tilde{\xi}_1. \quad \text{The comparable quantities for mutant} \quad y_3 \quad \text{in escaping the single epitope} \quad z_2 \quad \text{(in the absence of} \quad z_1) \quad \text{are} \quad \lambda_3 = \gamma_3 \left( 1 - \frac{R_1}{1+R_1s_2} \right) \quad \text{and} \quad y^*_3 = 1 - \frac{1+R_1s_2}{R_3}. \quad \text{Even when} \quad y_3 \quad \text{(escaping} \quad z_2) \quad \text{has larger invasion characteristics in the single epitope escape setting} \quad (y^*_3 > y^*_2 \quad \text{and} \quad \lambda_3 > \lambda_2), \quad y_2 \quad \text{will still persist and may actually exclude} \quad y_3 \quad \text{in the two epitope model. Figure 3 depicts simulations of this scenario of} \quad y_2 \quad \text{excluding} \quad y_3 \quad \text{despite the larger selective advantage of} \quad y_3 \quad \text{in the single epitope setting. Figure 4 shows further simulations of (26), which are all consistent with assertions of} \quad \text{Theorem 4.3 and} \quad \text{Theorem 4.4.}

\text{There are two special cases of model (26) where analysis further suggests the superior role of immunodominance over viral reproductive fitness. First, if we relax the assumption of strict immunodominance hierarchy, i.e. we allow that} \quad s_1 = s_2, \quad \text{then a “strictly saturated” non-negative equilibrium} \quad \tilde{\xi}^* \quad \text{has the following properties:} \quad z^*_1 > 0 \iff z^*_2 > 0 \quad \text{and} \quad y^*_2 > 0 \iff y^*_3 > 0. \quad \text{The calculations for this case are presented in the Appendix A.3. Essentially, non-trivial strictly saturated equilibria are of the form} \quad \tilde{\xi}_2, \quad \tilde{\xi}_1^\dagger \quad \text{or} \quad \tilde{\xi}_2^\dagger \quad \text{with the corresponding parameter regimes as defined in Table 1. Therefore, in the case of equal immunodominance} \quad (s_1 = s_2), \quad \text{no matter the fitness of the distinct mutant strains} \quad y_2 \quad \text{and} \quad y_3, \quad \text{both strains can only persist together. Next, consider the case where the viral fitness cost to each epitope is equal, say the cost is} \quad c = 1 - f, \quad \text{and the strict immunodominance holds,} \quad s_1 > s_2. \quad \text{Then} \quad R_2 = R_3 = fR_1 \quad \text{and} \quad R_4 = f^2R_1. \quad \text{This scenario will be analyzed in further generality for} \quad n \quad \text{epitopes in the next section. The result for this special case of model (26) is that one of the nested equilibria,} \quad \tilde{\xi}_i \quad \text{or} \quad \tilde{\xi}_j \quad (i = 0, 1, 2) \quad \text{will be globally asymptotically stable. Thus, in contrast to the previous special case} \quad (s_1 = s_2) \quad \text{where viral fitness did not determine persistence, here (in this special case of equal viral fitness costs) we find that persistence is determined by immunodominance.}

\text{The above results indicate that the immunodominance hierarchy is the most important factor in directing epitope escape, more so than viral fitness cost. In addition, the persistent variants depend upon reproductive numbers and quantities defined in (27), implying that the escape pathway depends upon the entire interacting}
system, not just the parameters associated with the single epitopes and corresponding resistant viral mutant strains. Both of these implications coincide with the findings in an in vivo study of HIV patients [24]. From a broader ecological point of view, our results suggest top-down control of food webs, where top predators have more influence than intermediate species, along with the interconnectedness of complex ecological networks.

4.4 Uniform fitness costs for escape on full \( n \)-epitope network

We consider the full network for \( n \) epitopes, in the special case where each viral mutation of an epitope incurs a uniform fitness cost, \( c = 1 - f \), where \( f \in (0, 1) \) is the ratio between reproduction number of mutant and descendent strain. In particular, indexing the wild-strain here as \( y_1 = y_w \) with fitness \( \mathcal{R}_1 \), then we make the following assumption on the \( 2^n \) viral strains in the full network:

\[
d(y_i, y_1) = p \Rightarrow \mathcal{R}_i = f^p \mathcal{R}_1, \quad \forall i \in [1, 2^n],
\]

where \( d(y_i, y_1) \) is the Hamming distance between the associated binary sequences of the viral strains as defined earlier. Note that since the wild-strain \( y_1 \) is susceptible at all epitopes \( (y_1 \cong 0 \cdots 0) \), a viral strain \( y_i \) with \( d(y_i, y_1) = p, \ p \in [0, n] \) has mutated \( p \) epitopes and thus has a (susceptible) epitope set of cardinality \( n - p \), i.e. \( |\Lambda_i| = n - p \). Then, we can write the model (12) as follows:

\[
\begin{align*}
\dot{x} &= 1 - x - x \sum_{i=1}^{2^n} \mathcal{R}_i y_i, \\
\dot{y}_i &= \gamma_i y_i \left( f^p \mathcal{R}_1 x - 1 - \sum_{j=1}^{n-p} s_j \right), \quad i = 1, \ldots, 2^n, \ d(y_i, y_1) = p, \ \Lambda_i = \{i_1, \ldots, i_{n-p}\}, \ p \in [0, n], \\
\dot{z}_j &= \frac{\sigma_j}{s_j} \sum_{i: j \in \Lambda_i} y_i - s_j, \quad j = 1, \ldots, n.
\end{align*}
\]

As before, we assume the immunodominance hierarchy (14), \( s_1 \leq \cdots \leq s_n \). We denote the viral strains associated with “nested” (sequential) escape, in addition to the wild strain \( y_1 \), as \( y_2, \ldots, y_{n+1} \). This means that for \( i = 1, \ldots, n \), the epitope set of \( y_i \) is \( \Lambda_i = \{i, \ldots, n\} \) (having escaped immune responses \( z_1, \ldots, z_{i-1} \)) and \( \Lambda_{n+1} = \emptyset \). Our main result of this section is, informally, that viral escape from \( n \) epitopes follows a “nested pattern” when the hierarchy (14) is strict. In other words, one of the nested equilibria, \( \tilde{E}_{k+1} \) or \( \tilde{E}_k \) (introduced in Section 4.2) is stable. In the Appendix A.4, we show that two other classes of equilibria, namely “strain-specific” and “one-mutation” equilibria, are unstable in this case of equal fitness costs, even when inequalities (14) are not strict. Now for the main theorem, we assume the strict immunodominance hierarchy:

\[
s_1 < s_2 < \cdots < s_n.
\]

**Theorem 4.5.** Consider model (31), the full network on \( n \) epitopes \( (n = 2^n) \) with equal fitness costs (30) and strict immunodominance hierarchy (32). Suppose \( y_1, \ i \in [1, n+1] \), is indexed so that \( \Lambda_i = \{i, \ldots, n\} \) for \( i = 1, \ldots, n \), \( \Lambda_{n+1} = \emptyset \). Then \( y_1(t) \to 0 \) as \( t \to \infty \) for all \( i \in [n+2, 2^n] \), and Theorem 4.2 holds in system (31). In particular, \( y_{1}, y_{2} \) are uniformly persistent for \( 1 \leq i \leq k \leq n \) when \( \mathcal{R}_k > \mathcal{Q}_k \) (and \( y_{k+1} \) is also persistent if \( \mathcal{R}_{k+1} > \mathcal{Q}_k \)).

**Proof.** If \( \mathcal{R}_1 > \mathcal{Q}_1 \), let \( k \) be the largest integer in \([1, n]\) such that \( f^{k-1} \mathcal{R}_1 = \mathcal{R}_k > \mathcal{Q}_k \), otherwise let \( k = 0 \). We will apply Theorem 3.1. It suffices to check the invasion rate for \( y_k \) in (6) for \( \ell \in [n+2, 2^n] \) since Theorem 4.2 establishes the result in the perfectly nested submodel consisting of \( y_1, \ldots, y_{n+1} \) and \( z_1, \ldots, z_n \). First suppose that \( f^k \mathcal{R}_1 = \mathcal{R}_{k+1} \leq \mathcal{Q}_k \). Let \( \ell \in [n+2, 2^n] \) and it suffices to consider \( \Lambda_{\ell} \cap [1, k] \) since the calculations will be considered at equilibrium \( \tilde{E}_k \) where \( z_i^* = 0 \) for \( i \geq k+1 \). Suppose that \( d(y_k, y_1) = p \) where \( p \in [1, n-1] \). Then \( \mathcal{R}_\ell = f^p \mathcal{R}_1 \). Consider the invasion rate for \( y_k \) at the equilibrium \( \tilde{E}_k \):

\[
\frac{\dot{y}_k}{\gamma/y_k} = \frac{f^p \mathcal{R}_1}{\mathcal{Q}_k} - 1 - \sum_{i \in \Lambda_{\ell} \cap [1, k]} z_i.
\]
If \( p > k \), then clearly
\[
\frac{\dot{y}_\ell}{\gamma y_\ell} \leq f^p R_1 - 1 - \frac{f^k R_1}{Q_k} - 1 \leq 0.
\]

If \( p \leq k \), \(|\Lambda_\ell| = n - p \geq n - k \) and note that \( \Lambda_\ell \neq \Lambda_{k+1} = \{k+1, \ldots, n\} \) (where \( \Lambda_{k+1} \) is the epitope set of \( y_{k+1} \)). Thus, \([1,k] \cap \Lambda_\ell \neq \emptyset\). By (24), for \( 2 \leq i \leq k - 1 \),
\[
\tau_i - \tau_{i-1} = \frac{R_i - R_{i+1} - (R_{i-1} - R_i)}{Q_k} = -\frac{f^{i-2} R_1}{Q_k} (f^2 - 2f + 1) = -\frac{f^{i-2} R_1}{Q_k} (f - 1)^2 < 0 \quad \text{for} \quad f \in (0,1).
\]

Similarly \( \tau_k - \tau_{k-1} < 0 \), and thus at equilibrium \( \mathcal{E}_k \), we find
\[
\tau_k < \tau_{k-1} < \cdots < \tau_1.
\]

If \( p = k \), then
\[
\frac{\dot{y}_\ell}{\gamma y_\ell} \leq f^p R_1 - 1 - \tau_k \leq f^k R_1 - 1 - \left( \frac{f^{k-1} R_1}{Q_k} - 1 \right) < 0 \quad \text{for} \quad f \in (0,1).
\]

If \( p \leq k - 1 \), then
\[
\frac{\dot{y}_\ell}{\gamma y_\ell} < f^p R_1 \leq \frac{f^{k-1} R_1}{Q_k} - 1 - \tau_k \leq f^{k-1} R_1 - 1 - \left( \frac{f^{k-1} R_1}{Q_k} - 1 \right) = 0 \quad \text{for} \quad f \in (0,1).
\]

Therefore, the equilibrium \( \mathcal{E}_k \) is saturated with inequalities (6) strictly holding and \( \mathcal{E}_k \) is unique in its positivity class. Thus Theorem 3.1 can be applied to obtained the conclusions of Theorem 4.2. If \( f^k R_1 = R_{k+1} > Q_k \), then a similar argument works with \( x^* = \frac{1}{R_{k+1}} \) instead of \( x^* = \frac{1}{Q_k} \), which shows that \( \mathcal{E}_{k+1} \) is stable in that case.

In Figure 5, we illustrate Theorem 4.5 by numerical solution of the model (31) in the case of \( n = 3 \) epitopes. The simulations show that after some transient dynamics, only the viral strains associated with the nested network, \( y_1, y_2, y_3, y_4 \), persist. In other words, the full network of \( n = 3 \) epitopes (displayed in Figure 1(a)) converges to the perfectly nested subgraph (displayed in Figure 1(c)).

5 Discussion

In this paper, we analyzed a virus model consisting of target cells, multiple virus strains and several immune response populations. The interaction of virus and immune response is described by a network reflecting the avidity of each distinct immune response in recognizing each particular virus strain. We find some general conditions on stability and feasibility of equilibria, along with uniformly persistent virus and immune response variants by utilizing Lyapunov function techniques.

We specialize the model to consider the scenario where the immune response populations are \( n \) different CTL lines, each specific to a particular epitope, and there are \( 2^n \) virus strains containing all possible combinations of (resistance conferring) epitope mutations. In this case, the virus-immune network can be
translated to an $n$-dimensional hypercube graph representative of the potential pathways of immune escape by the virus. The number of uniformly persistent viral strains and CTL populations can be built up in an ordered fashion dependent on derived invasion thresholds for “one-to-one” and “perfectly nested” subgraphs. For the full network of $2^n$ viral strains, we characterize the dynamics in two cases: (i) $n = 2$ epitopes and (ii) equal fitness costs for each of $n$ epitopes. Distinct parameter regimes delineate stability of multiple potential feasible equilibria for the case (i) with $n = 2$ CTL populations. The escape pathway always includes the mutant resistant to the immunodominant epitope, even when it suffers a relatively high fitness cost. In case (ii), the network of $2^n$ viral strains always converges to a perfectly nested subgraph with less than or equal to $n + 1$ strains.

The results indicate that a diverse viral “quasispecies” can be built through resistance mutations at multiple epitopes and the immunodominance hierarchy is the most important factor determining the escape pathway. These notions are supported by observations in HIV infection. Indeed, the efficacy and breadth of cognate CTL immune responses increase within-host HIV diversity, driving viral evolution so that different combinations of multiple epitope escapes become prevalent in the viral population [27]. Also, recent studies have shown that immunodominance hierarchies in HIV are major determinants of viral escape from multiple epitopes [3, 24], in particular immunodominance was found to play a substantially larger role than the viral fitness costs and other factors [24]. Understanding the main factors shaping viral escape pathways and immune dynamics is important for design of effective vaccines and immunotherapies.

Future research can build upon the results presented here in several ways. First, since rapid evolution of HIV due to CTL pressure is motivation for our model, mutation between the different viral strains can be explicitly included in the model. Preliminary simulations from stochastic versions of the model show that qualitative dynamics are preserved under mutation. Rigorous global perturbation arguments in the deterministic setting may be attempted to show the effect of small mutation rates, however for the general case, this would rely upon the conjecture of global stability for equilibria. Thus, another important theoretical question is proving global stability when uniform persistence occurs. Finally, further extensions of our work can be applicable to other dynamic ecological systems, such as the coevolving network of HIV and antibodies within a host.

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A Appendix

A.1 Existence of saturated equilibrium

Proof of Proposition 3.1. We find it somewhat easier to work with the unscaled system (1) so we introduce some new parameters into it. Let $\epsilon > 0$ be so small that $b - \epsilon(m + n) > 0$ and $0 \leq \lambda \leq 1$ be a homotopy parameter. Our perturbed system is given by:

\[
X' = b - cX - \lambda X \sum_i \beta_i Y_i - \epsilon(m + n)
\]

\[
Y'_i = \lambda Y_i \left( \beta_i X - \sum_j r_{ij} Z_j \right) - \delta_i Y_i + \epsilon, 1 \leq i \leq m,
\]

\[
Z'_j = \lambda q_j Z_j \sum_i r_{ij} Y_i - \mu_j Z_j + \epsilon q_j, 1 \leq j \leq n.
\]

We refer to the vector field on the right side as $G(W, \lambda, \epsilon)$, where $W = (X, Y, Z) \in \mathbb{R}^{m+n+1}$. Then $G(W, 1, 0)$ is the vector field given in equations (1).

Straightforward calculation establishes that

\[
(X + \sum_i Y_i + \sum_j Z_j/q_j)' &= b - cX - \sum_i \delta_i Y_i - \sum_j \frac{\mu_j}{q_j} Z_j \\
&\leq b - d(X + \sum_i Y_i + \sum_j Z_j/q_j)
\]

for $d = \min\{c, \delta_i, \mu_j\}$. Fix $p > b/d$ and let

\[
U = \{W \in \mathbb{R}_{+}^{m+n+1} : X + \sum_i Y_i + \sum_j Z_j/q_j \leq p\}
\]

We claim that there are no equilibria on the boundary of $U$. Notice that any equilibrium $E = (X, Y, Z) \in U$ satisfies $Y_i > 0$ and $Z_j > 0$. If it belongs to the boundary of $U$, then either $X = 0$ or $X + \sum_i Y_i + \sum_j Z_j/q_j = p$. Each of these is easy to rule out. Suppose, for example the latter holds. Then the left side of the differential inequality above vanishes at $E$ so we have $0 \leq b - pb$, a contradiction to $p > b/d$.

Now we can employ degree theory, as in Hofbauer and Sigmund. By Homotopy invariance of degree we have that $\deg(G(\bullet, 1, \epsilon), U) = \deg(G(\bullet, 0, \epsilon), U)$ and the latter is easy to compute since it is linear and has a unique equilibrium $\bar{E} \in U$

\[
\deg(G(\bullet, 0, \epsilon), U) = \text{sgn } \det G_W(\bar{E}, 0, \epsilon) = \text{sgn}(-1)^{m+n+1} \epsilon \prod_i \delta_i \prod_j \mu_j = (-1)^{m+n+1}
\]

As the degree is nonzero, $G(\bullet, 1, \epsilon)$ has at least one equilibrium in the interior of $U$ for each small $\epsilon$. Now, the argument for the existence of a saturated equilibrium of $G(\bullet, 1, 0)$ follows as in Hofbauer & Sigmund’s text [15] by taking limits as $\epsilon \to 0$. \hfill $\Box$

A.2 Two-epitope model: dynamics when $s_1 < s_2$

Proof of Theorems 4.3 and 4.4. We apply Theorem 3.1 for each equilibrium and case. First in Theorem 4.3:

Case i.:

\[
\dot{W} = -\frac{1}{x}(x - 1)^2 - \sum_{i=1}^4 (1 - R_i) y_i - \sum_{i=1}^2 s_i z_i
\]

Case ii.:

\[
\dot{W} = -\frac{1}{R_1 x}(R_1 x - 1)^2 - \sum_{i=2}^4 \frac{y_i}{R_0} (R_1 - R_i) - \sum_{i=1}^2 s_i z_i
\]
Case iii.: 
\[ \dot{W} = -\frac{1}{Q_1x} (Q_1x - 1)^2 - \frac{y_3}{Q_1} (R_1 - R_3) - \sum_{i=2,4} \frac{y_i}{Q_1} (Q_1 - R_i) - z_2 (s_2 - s_1) \]

Case iv.: 
\[ \dot{W} = -\frac{1}{R_2x} (R_2x - 1)^2 - \frac{y_3}{R_2} (R_1 - R_3) - \frac{y_4}{R_2} (R_2 - R_4) - \frac{z_2}{R_2} (R_2 - R_2) \]

In case iii, on the invariant set \( L \) we have \( x = 1/Q_1, \ y_3 = y_4 = 0 \) and \( z_2 = 0 \). If \( R_1 < Q_1 \), then \( \dot{W} = 0 \Rightarrow y_2 = 0 \), otherwise \( R_1 = Q_1 \Rightarrow y_2 = 0 \). Either way the equation \( \dot{x} = 0 \) implies that \( y_1 = y_1^* \) and \( y_2 = 0 \). Thus \( y_1 = 0 \), which implies \( z_1 = z_1^* \). Therefore in this case \( L \) consists solely of the equilibrium \( \mathcal{E}_1 \).

In case iv, i.e. \( Q_1 < R_2 \leq Q_2 \), then we prove \( \mathcal{E}_1 \) is GAS. Here, \( \dot{W} = 0 \) iff \( x = x^* = \frac{1}{R_1}, \ y_3 = y_4 = 0, \) and \( z_2 = 0 \). (Note if \( Q_2 > R_2, \ z_2 = 0 \) is immediate. If not, we can still reason that the asymptotic average of \( z_2 \) must converge to \( z_2^* = 0, \) hence \( z_2 = 0 \).) In addition by Theorem 3.1, we can obtain \( y_2 = y_2^* = 1 - \frac{Q_1}{R_1} \). The last relation combined with \( x = x^* \) implies that \( y_1 = y_1^* = s_1 \). Then \( y_1 = 0 \) implies \( z_1 = z_1^* \). Thus \( L \) consists solely of the equilibrium \( \mathcal{E}_1 \).

Next in Theorem 4.4: 

**Case 1:** \((x^*, y^*, z^*) = \mathcal{E}_2\):

\[ \dot{W} = -\frac{1}{Q_2x} (Q_2x - 1)^2 - \frac{y_3}{Q_2} (Q_2 - R) - \frac{y_4}{Q_2} (Q_2 - R_4) \]

Notice that \( \dot{W} \leq 0 \) when \( R \leq Q_2 \) and \( R_4 \leq Q_2 \). Also, the equilibrium \( \mathcal{E}_2 \) is non-negative when \( R_2 > Q_2 \). If \( R < Q_2 \) and \( R_4 < Q_2 \), applying Theorem 3.1, all inequalities (6) are strict and only two strains, \( y_1 \) and \( y_2 \) have non-empty epitope sets, and therefore \( \mathcal{E}_2 \) is globally asymptotically stable. If \( R_4 = Q_2 \), then the differential equations in (9) hold along with \( y_4 = 0 \) and \( \sum_{i=1,2,4} R_i y_i = Q_2 - 1 \). Taking asymptotic averages as in the proof of Theorem 3.1 in [8], we obtain that indeed \( y_4 = 0 \), and we similarly obtain that \( \mathcal{E}_2 \) is globally asymptotically stable.

**Case 2:** \((x^*, y^*, z^*) = \mathcal{E}_2^1\):

\[ \dot{W} = -\frac{1}{R_4x} (R_4x - 1)^2 - \frac{y_3}{R_4} (R_4 - R) \]

Notice that \( \dot{W} \leq 0 \) when \( R < R_4 \). Also, the equilibrium \( \mathcal{E}_2^1 \) is non-negative when \( R_4 > Q_2 \). Applying Theorem 3.1, we obtain that \( \mathcal{E}_2^1 \) is globally asymptotically stable.

**Case 3:** \((x^*, y^*, z^*) = \mathcal{E}_2^2\):

\[ \dot{W} = -\frac{1}{R_4} (R_4x - 1)^2 - \frac{y_4}{R} (R - R_4) \]

Notice that \( \dot{W} \leq 0 \) when \( R_4 \leq R \). Also, the equilibrium \( \mathcal{E}_2^2 \) is non-negative when \( Q_2 < R < P_2 \). The result is a direct consequence of Theorem 3.1.

**Case 4:** \((x^*, y^*, z^*) = \mathcal{E}_3^1\):

\[ \dot{W} = -\frac{1}{P_2x} (P_2x - 1)^2 - \frac{y_1}{P_2} (P - P_2) - \frac{y_4}{P_2} (P_2 - R_4) \]

Notice that \( \dot{W} \leq 0 \) when \( R \geq P_2 \) and \( R_4 \leq P_2 \). The equilibrium \( \mathcal{E}_3^1 \) is non-negative when \( \min(R_2, R_3) > P_2 \). Global stability follows from Theorem 3.1.

**Case 5:** \((x^*, y^*, z^*) = \mathcal{E}_3^2\):

\[ \dot{W} = -\frac{1}{R_4x} (R_4x - 1)^2 - \frac{y_4}{R_4} (R - R_4) \]

Notice that \( \dot{W} \leq 0 \) when \( R_4 \leq R \). Also, the equilibrium \( \mathcal{E}_3^2 \) is non-negative when \( R_4 > P_2 \). Global stability follows from Theorem 3.1.

\[ \square \]
\section*{A.3 Two-epitope model: dynamics when $s_1 = s_2$}

We analyze the feasible stable equilibria with immune response for the case of equal immunodominance of $z_1$ and $z_2$ ($s_1 = s_2 = s$) in model (26). First, consider equilibria with one immune response present. Since $s_1 = s_2$, without loss of generality, we can take $z_1^* > 0$. From the equilibrium equations, $y_1^*, y_2^* > 0$ if $R_4 = R_2$, which is not possible since $R_2 > R_4$. Also, an equilibrium with $y_3^* > 0$ and $z_2^* = 0$ will not be saturated since $R_2 > R_3$, therefore take $y_3^* = 0$. Similarly, we can take $y_4^* = 0$. Thus, consider equilibria $E_1$ and $E_2$. The equilibrium $E_1$ cannot be stable since $s_1 = s_2 \Rightarrow Q_2 = Q_1$, which does not permit conditions for case iv of Theorem 4.3 to be satisfied. The equilibrium $E_2$ will not be “strictly saturated” under conditions for case iii of Theorem 4.3 because there is a continuum of equilibria of the form $E_2(z_2^\ast)$ where $z_1 = \frac{R_4}{s_1} - 1 - z_2^\ast, z_2 = z_2^\ast$.

Now consider the possibility of equilibria with $z_1^*, z_2^* > 0$. Observe that at least two of the viral strain components $y_1^*, y_2^*, y_3^*$ are positive and $y_4^* = y_3^*$ from the $z_1, z_2$ equations. Therefore $y_2^*, y_3^* > 0$ and for the case $s_1 = s_2$, non-trivial strictly saturated equilibria are of the form $E_2, E_2^1$ or $E_2^2$ with the corresponding parameter regimes as defined in Table 1.

\section*{A.4 Instability of “one-mutation” and “strain-specific” equilibria for model (31)}

We assume equal viral fitness costs for mutation from each of $n$ epitopes, yielding system (31), as described in Section 4.4. Consider the set $S_1$ of $n$ viral strains which have exactly one mutation, i.e. $y_i \in S_1 \Rightarrow d(y_i, y_1) = 1$. For clarity here, we label these strains as $S_1 = \{y_i \mid i = 1, \ldots, n\}$ where $y_i$ has escaped $z_i$ but is susceptible all other immune responses. Note that $y_i$ is strain $y_2$ with our “nested” indexing introduced in Section 4.2. The subsystem only containing these viral strains looks as follows:

$$
\dot{x} = 1 - x - x \sum_{i=1}^{n} fR_1 y_i, \quad \dot{y}_i^1 = \gamma_j y_j \left(fR_1 x - 1 - \sum_{j \neq i} z_j\right), \quad z_i = \frac{\sigma_i}{s_i} z_i \left(\sum_{j \neq i} y_j - s_i\right), \quad i = 1, \ldots, n. 
$$

A positive equilibrium $E_1^\ast = (x^\ast, y_i^\ast, z_i^\ast)$ to (33) satisfies

$$
Ag^\ast = \vec{z}, \quad x^\ast = \frac{1}{1 + fR_1 \sum y_i^\ast}, \quad Az^\ast = (fR_1 x^\ast - 1)\vec{1},
$$

where $A = \vec{1}^T(1) - I_n, \quad A^{-1} = \frac{1}{n-1} \vec{1}^T(1)^T - I_n, \quad \vec{y} = (y_1^\ast, y_2^\ast, \ldots, y_n^\ast)^T$, where $I_n$ is the $n \times n$ identity matrix. Here we find that:

$$
y_1^\ast = \frac{1}{n-1} \left(-(n-2)s_i + \sum_{j \neq i} s_j\right), \quad x^\ast = \frac{n-1}{n-1 + fR_1 \sum s_i}, \quad z_i^\ast = \frac{1}{n-1} (fR_1 x^\ast - 1)
$$

Assuming our hierarchy $s_i \leq s_{i+1}$, then $y_i^\ast > 0$ if $s_1 > \sum_{i=1}^{n} (s_n - s_i)$ and $z_i^\ast > 0$ if $fR_1 (n-1 - \sum_{i=1}^{n} s_i) > n-1$. If these conditions are satisfied, then the equilibrium $E_1^\ast$ is saturated in the subsystem (33) where $y_i \in S_1$. However, if we consider a larger network of viral strains, then equilibrium $E_1^\ast$ is always unstable in this case with equal fitness costs for mutation. Indeed, consider the wild strain $y_1 \cong 0 \cdots 0$ and strain $y_3 \cong 110 \cdots 0$, which correspond to backward and forward mutations from the strain $y_1^\ast \in S_1$. We calculate their invasion rates at equilibrium $E_1^\ast$. Note that $y_1$ has reproduction number $R_1$ and $y_3$ has reproduction number $R_3 = f^2R_1$. In order for $E_1^\ast$ to be saturated (stable), we find that:

$$
\frac{\dot{y}_1}{\gamma_1 y_1} = R_1 x^\ast - 1 - \sum_{i=1}^{n} z_i^\ast \leq 0, \quad \frac{\dot{y}_3}{\gamma_3 y_3} = f^2R_1 x^\ast - 1 - \sum_{i=3}^{n} z_i^\ast \leq 0
$$

$$
R_1 x^\ast - 1 - \frac{n}{n-1} (fR_1 x^\ast - 1) \leq 0, \quad f^2R_1 x^\ast - 1 - \frac{n-2}{n-1} (fR_1 x^\ast - 1) \leq 0
$$
\[ \Leftrightarrow \mathcal{R}_1 x^\ast (fn - (n - 1)) \geq 1, \quad f \mathcal{R}_1 x^\ast (f(n - 1) - (n - 2)) \leq 1 \]
\[ \Leftrightarrow f > \frac{n - 1}{n}, \quad f((n - 1)f - (n - 2)) \leq nf - (n - 1) \]
\[ \Leftrightarrow 0 \geq (n - 1)(f - 1)^2 \]

However, \((n - 1)(f - 1)^2 > 0\) for all \(f \neq 1, n > 1\), giving a contradiction. Thus \(E_1\) can only be stable when restricted to the subsystem (33) consisting of strains in \(S_1\), and becomes unstable in the larger network in this case.

Similarly, we can show that the “strain-specific” (or “one-to-one”) equilibria, \(E_{i}^\ast\) and \(E_{i+1}^\ast\) (introduced in Section (4.1)), are always unstable in this case of uniform fitness costs. Indeed, for clarity here, denote \(y\) this case. Restricted to the subsystem (33) consisting of strains in \(S\), \(\Lambda_0 = \{i\}\), and \(y_{n+1}\) as the strain which has completely escaped all \(z_i\), i.e. \(\Lambda_{n+1} = \emptyset\). Then \(E_{i}^\ast\) (and \(E_{i+1}^\ast\)) consist of equilibria where \(y_i^\ast > 0\) (and \(y_{i+1}^\ast > 0\)). First, consider the case that \(\mathcal{R}_{n+1} = f^n\mathcal{R}_1 \leq \mathcal{P}_n^o = 1 + \sum_i s_i\mathcal{R}_i^o = 1 + f^{n-1}\mathcal{R}_1 \sum_i s_i\) and \(f^n\mathcal{R}_1 > \mathcal{P}_n^o\), so that \(E_{i}^\ast\) is positive, but \(E_{i+1}^\ast\) is not positive. Then consider the invasion rate of viral strain \(y_{n-1} \equiv 1 \cdots 100\) (with \(\Lambda_{n-1} = \{n - 1, n\}\) and reproduction number \(\mathcal{R}_{n-1} = f^{n-2}\mathcal{R}_1\)). Utilizing (20), if \(E_{i}^\ast\) is stable, then
\[ \mathcal{P}_n^o + f^{n-2}\mathcal{R}_1 \leq 2f^{n-1}\mathcal{R}_1 \]
\[ \Leftrightarrow \mathcal{R}_1 f^{n-2} (f^2 - 2f + 1) \leq 0, \quad \text{since} \quad f^n\mathcal{R}_1 \leq \mathcal{P}_n^o, \]

which is clearly a contradiction since \((f^2 - 2f + 1) = (f - 1)^2 > 0\) for \(f < 1\). A similar argument applies to \(E_{i+1}^\ast\) in the case \(f^n\mathcal{R}_1 > \mathcal{P}_n^o\). Thus the “strain-specific” equilibria are always unstable for system (31).

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