Local Immunodeficiency: Role of Neutral Viruses

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Abstract
This paper analyzes the role of neutral viruses in the phenomenon of local immunodeficiency. We show that, even in the absence of altruistic viruses, neutral viruses can support the existence of persistent viruses and thus local immunodeficiency. However, in all such cases neutral viruses can maintain only bounded (relatively small) concentration of persistent viruses. Moreover, in all such cases the state of local immunodeficiency could only be marginally stable, while it is known that altruistic viruses can maintain stable local immunodeficiency. We also present an absolutely minimal cross-immunoreactivity network where a stable and robust state of local immunodeficiency can be maintained. It is now a challenge to synthetic biology to build such small networks with stable local immunodeficiency. Another important challenge for biology is to understand which types of viruses can play a role of persistent, altruistic and neutral ones and whether a role which a given virus plays depends on the structure (topology) of a given cross-immunoreactivity network.

Keywords Cross-immunoreactivity network · Local immunodeficiency · Neutral · Altruistic and persistent viruses

1 Introduction

Local immunodeficiency (LI) is a recently discovered phenomenon (Skums et al. 2015) that appears in diseases characterized by cross-immunoreactivity of the corresponding pathogens (viruses). Examples of such diseases include hepatitis C, HIV, dengue, influenza, etc. (Hattori et al. 1998; Campo et al. 2014; Nowak and May 2000).
The phenomenon of local immunodeficiency means that some persistent antigens (viruses) manage to escape immune response because they are protected by altruistic viruses that take virtually all the response of the host’s immune system on themselves. This discovery was made through the (numerical) analysis of a new model of hepatitis C dynamics (evolution) that explained clinical and experimental observations that previous evolution models (and theory) of hepatitis C failed to explain. Remarkably, this new mathematical model has fewer (types of) variables than the previous ones (Wodarz 2003). Yet this new model makes much more delicate exploration of the well-known phenomenon of cross-immunoreactivity than all previous evolution models of infectious diseases, including the fundamental dynamics model of HIV (Nowak et al. 1990, 1991; Nowak and May 1991). Namely, the new model does not assume that all cross-immunoreactivity interactions between different antigens (viruses) have the same (equal) strength. This was experimentally verified for Hepatitis C in the Center for Disease Control and Prevention (CDC) (Campo et al. 2014; Hattori et al. 1998) before a final structure of a new model was created (Skums et al. 2015). It is important to emphasize that all previous models of various diseases with cross-immunoreactivity always used the so-called mean-field approximation where the strengths of interactions between all antigens (viruses) were assumed to be equal to one and the same constant.

A striking discovery made in analyzing the dynamics of the new model was that in equilibrium state, all intrahost viruses fall into one of three classes. The first class consists of persistent viruses that have the highest concentrations but the immune response against them is virtually zero. Therefore, the host’s immune system “does not see” persistent viruses and thus demonstrates immunodeficiency against them. The second class of so-called altruistic viruses is characterized by extremely low (virtually zero) concentrations. However, almost all strength of the host’s immune response goes against these altruistic viruses. This situation becomes possible because of special locations and structure of connections between persistent and altruistic viruses in the intrahost cross-immunoreactivity (CR) network of viruses (antigens) (Skums et al. 2015). Each of these two types of viruses comprises a very small (a few percent) part of all intrahost viruses. The rest of viruses (which comprise about 90% of all) are called neutral. It is important to mention that such structure of cross-immunoreactivity networks appeared in all several hundred numerical experiments with our model (Skums et al. 2015). Therefore, it seems to be an extremely stable and robust phenomenon.

The host’s immune system demonstrates immunodeficiency against persistent viruses because of their special positions (locations) within the intrahost CR network (CRN) and because of the structure of their connections to altruistic viruses (Skums et al. 2015). This is where the term “local immunodeficiency” comes from. A central biological question in this area is to determine which types of viruses can play a role of persistent and/or altruistic viruses. Indeed, it is very interesting biologically and important for public health policies on how to handle the diseases with cross-immunoreactivity.

Paper (Bunimovich and Shu 2019) shows that the phenomenon of local immunodeficiency is typically stable and robust under various realistic conditions. Moreover,
it was proved in this paper that stable and robust local immunodeficiency can already occur in very small CR networks consisting of just three nodes. We already know diseases like hepatitis C have large CR networks; now we have shown small CR networks can also have stable local immunodeficiency. These results are very interesting in general and have attracted experimentalists. For example, the recent paper (Domingo-Calap et al. 2019) studied a social structure of population of viruses in an experimental framework. Interestingly, their results showed a different type of altruism. Indeed, true altruists should sacrifice themselves for others [as Skums et al. (2015) demonstrated] but the viruses called altruistic in Domingo-Calap et al. (2019) help themselves and also some other viruses. It is not quite altruism as it is usually understood.

In the present paper, we analyze the role of neutral viruses in CR networks and their ability to maintain persistent viruses, i.e., to generate local immunodeficiency. The question whether and why neutral viruses are needed to create and maintain local immunodeficiency remained unanswered in previous studies. We show that an answer to this natural question is nontrivial and unexpected (as is essentially everything in the studies of the phenomenon of local immunodeficiency so far). Namely, we show that neutral viruses (without the presence of altruistic viruses) could maintain only marginally stable state of a local immunodeficiency. Moreover, without altruistic viruses the population of persistent viruses can not be large and is bounded from above by exact computed values. This contrasts with the results of Bunimovich and Shu (2019) that in the presence of altruistic viruses, there is no upper bound on the population size of persistent viruses.

Another fundamental question is whether some viruses may play different roles becoming persistent, altruistic or neutral depending on the structure of a smaller subnetwork that belongs to a (large) cross-immunoreactivity network. Also altruistic viruses should be a primary target of public health policies.

We also present here a new minimal (three-node) CRN with a stable and robust state of a local immunodeficiency. This new one and the one found in Bunimovich and Shu (2019) are the only two CRNs with just three types of viruses which maintain a stable and robust local immunodeficiency. However, the three-virus network presented here is in fact the absolutely minimal because it contains just two edges, the minimal number of edges in any network with three nodes. It would be very interesting to create small cross-immunoreactivity networks which demonstrate stable and robust phenomenon of local immunodeficiency. This seems to be a natural challenge to synthetic biology, and the absolutely minimal network presented in this paper is the first candidate to be considered in such studies because it has the minimal number of elements (nodes) and the simplest possible structure (topology) of a network.

2 Model of Evolution of a Disease with Heterogeneous CR Network

In this section, we define the model of the hepatitis C (HC) evolution introduced in Skums et al. (2015). It is important to note that this model is applicable to any disease with cross-immunoreactivity.

Consider a system which contains a population of $n$ viral antigenic variants $x_i$ inducing $n$ immune responses $r_i$ in the form of antibodies (Abs). The viral variants
exhibit cross-immunoreactivity, which results in a CR network. The latter can be represented as a directed graph $G_{CRN} = (V, E)$, with vertices corresponding to viral variants and directed edges connecting CR variants. Because not all interactions with Ab lead to neutralization, we consider two sets of weight functions for the CRN. These functions are defined by immune neutralization and immune stimulation matrices $U = (u_{ij})_{i, j=1}^n$ and $V = (v_{ij})_{i, j=1}^n$, where $0 \leq u_{ij}, v_{ij} \leq 1$; $u_{ij}$ represents the binding affinity of Ab to $j$ ($r_j$) with the $i$th variant; and $v_{ij}$ reflects the strength of stimulation of Ab to $j$ ($r_j$) by the $i$th variant. The immune response $r_i$ against variant $x_i$ is neutralizing, i.e., $u_{ii} = v_{ii} = 1$. The resulting evolution of the antigens (viruses) and antibodies populations is given by the following system of ordinary differential equations (Skums et al. 2015; Bunimovich and Shu 2019).

$$\dot{x}_i = f_i x_i - px_i \sum_{j=1}^n u_{ji} r_j, \quad i = 1, \ldots, n,$$

$$\dot{r}_i = c \sum_{j=1}^n x_j \frac{v_{ji} r_i}{\sum_{k=1}^n v_{jk} r_k} - b r_i, \quad i = 1, \ldots, n.$$ (1)

In this model, the viral variant $x_i$ replicates at the rate $f_i$ and is eliminated by the immune responses $r_j$ at the rates $pu_{ji} r_j$, where $p$ is a constant. The immune responses $r_i$ are stimulated by the $j$th variant at the rates $c g_{ji} x_j$, where $g_{ji} = \frac{u_{ji} r_i}{\sum_{k=1}^n v_{jk} r_k}$ represents the probability of stimulation of the immune response $r_i$ by the variant $x_j$ and $c$ is a constant. This model (Skums et al. 2015) allows us to incorporate the phenomenon of the original antigenic sin (Francis 1960; Pan 2011; Rehermann and Shin 2005; Parsons et al. 2013; Kim et al. 2009; Midgley et al. 2011), which states that $x_i$ preferentially stimulates preexisting immune responses capable of binding to $x_i$. The immune response $r_i$ decays at rate $b$ in the absence of stimulation.

As in Skums et al. (2015) and Bunimovich and Shu (2019), we consider the situation where the immune stimulation and neutralization coefficients are equal to constants $\alpha$ and $\beta$, respectively. To be more specific, both the immune neutralization and stimulation matrices are completely defined by the structure of the CR network, i.e.,

$$U = \text{Id} + \beta A^T, \quad V = \text{Id} + \alpha A,$$

where $A$ is the adjacency matrix of $G_{CRN}$. In the absence of CR, among viral variants the system reduces to the model developed in Nowak and May (2000) for a heterogeneous viral population. Because the neutralization of an antigen may require more than one antibodies, we assume that $0 < \beta = \alpha^k < \alpha < 1$ (Skums et al. 2015). It is important to mention that we analyze a more general model here than the one studied in Skums et al. (2015), where it was assumed that all viruses replicate at the same rate, i.e., all the $f_i$’s are equal to each other. Here, as in Bunimovich and Shu (2019) we allow the $f_i$’s to be different and consider all possible values of them as long as they make sense, i.e., are positive.
3 An Absolutely Minimal Network with Stable Local Immunodeficiency

In this section, we present a minimal cross-immunoreactivity network with stable and robust state of local immunodeficiency.

Recall that an equilibrium solution to a system of differential equations is called stable if the solution to the system under any perturbation of the initial condition converges with time to this solution. A solution is robust if there is a solution to the system under small perturbations of its parameters (coefficients) with dynamics analogous to the solution of the unperturbed system.

As in Bunimovich and Shu (2019) we will consider “extreme” stable fixed points (equilibrium solutions) with local immunodeficiency. This means that we assume the immune response against a persistent virus is zero and the concentration of an altruistic virus is also identically zero. Of course, these may sound like unrealistic assumptions. Observe, however, that the right-hand side of system (1) depends on parameters continuously (and even smoothly); under small perturbations of parameters, there will be a stable fixed point close to the extreme one with stable local immunodeficiency (LI) in the unperturbed system of ODEs (see, e.g., Chicone 2006).

Certainly, these stable solutions should make (biological) sense, i.e., both the concentrations of altruistic viruses and the immune response against persistent viruses have to be positive. Both these values will be close to zero under small perturbations of parameters of system (1). Fixed points that make sense do exist because a neighborhood of zero (here the fixed points depend continuously on parameters of the system) always contains a subset with only positive values for all coordinates.

Observe also that in reality, a system is never exactly at a fixed point but close to it because of ever-present small perturbations/fluctuations. The dynamics always pushes the state of the system closer to the steady state. Therefore, a real system will evolve toward a fixed point. This evolution takes infinite time, and the steady state will never be achieved although (in the absence of random perturbations) the current state of the system will become closer and closer to this stable fixed point with time.

It is worthwhile to mention here that in numerical simulations, one must set a (positive) threshold such that if the population size of some virus becomes less than this threshold, then this virus is considered to be eliminated. For instance, simulations of system (1) in Skums et al. (2015) assumed that a virus gets eliminated by the immune system if its concentration becomes lower than the initial concentration of this virus.

Consider the following network with three types of viruses (Fig. 1).

Although this network looks rather similar to the three-virus network with stable and robust local immunodeficiency found in Bunimovich and Shu (2019), it actually has fewer edges. We will show that this smaller cross-immunoreactivity network is also able to support stable and robust local immunodeficiency.

Fig. 1 Symmetric CRN
The adjacency matrix and the corresponding neutralization and stimulation matrices of this network are

\[
A = \begin{pmatrix} 0 & 1 & 0 \\ 0 & 0 & 0 \\ 0 & 1 & 0 \end{pmatrix}, \quad
U = \begin{pmatrix} 1 & 0 & 0 \\ \beta & 1 & \beta \\ 0 & 0 & 1 \end{pmatrix}, \quad
V = \begin{pmatrix} 1 & \alpha & 0 \\ 0 & 1 & 0 \\ 0 & \alpha & 1 \end{pmatrix}.
\]

All our networks are finite simple graphs; therefore, the adjacency matrix has 0–1 entries indicating whether there is an edge going from node \(i\) to node \(j\).

The model of population evolution for this network is given by the following differential equations:

\[
\begin{align*}
\dot{x}_1 &= f_1 x_1 - p x_1 (r_1 + \beta r_2), \\
\dot{x}_2 &= f_2 x_2 - p x_2 r_2, \\
\dot{x}_3 &= f_3 x_3 - p x_3 (\beta r_2 + r_3), \\
\dot{r}_1 &= c \frac{x_1 r_1}{r_1 + ar_2} - br_1, \\
\dot{r}_2 &= c \left( \frac{\alpha x_1 r_2}{r_1 + ar_2} + \frac{\alpha x_2 r_2}{r_2} + \frac{\alpha x_3 r_2}{ar_2 + r_3} \right) - br_2, \\
\dot{r}_3 &= c \frac{x_3 r_3}{ar_2 + r_3} - br_3.
\end{align*}
\]

The Jacobian of this model is

\[
J = \begin{pmatrix} A_J & B \\ C & D \end{pmatrix}, \quad
A_J = \begin{pmatrix} f_1 - p(r_1 + \beta r_2) & 0 & 0 \\ 0 & f_2 - pr_2 & 0 \\ 0 & 0 & f_3 - p(\beta r_2 + r_3) \end{pmatrix},
\]

\[
B = \begin{pmatrix} -p x_1 & -p \beta x_1 & 0 \\ 0 & -p x_2 & 0 \\ 0 & -p \beta x_3 & -p x_3 \end{pmatrix}, \quad
C = \begin{pmatrix} c \frac{x_1 r_1}{r_1 + ar_2} & 0 & 0 \\ c \frac{ar_2}{r_1 + ar_2} & c & \frac{ar_2}{ar_2 + r_3} \\ 0 & 0 & c \frac{r_3}{ar_2 + r_3} \end{pmatrix},
\]

\[
D = \begin{pmatrix} -c \frac{x_1 r_2}{(r_1 + ar_2)^2} - b & -c \frac{ax_1 r_1}{(r_1 + ar_2)^2} & 0 \\ -c \frac{ax_1 r_1}{(r_1 + ar_2)^2} & -c \frac{ax_1 r_1}{(r_1 + ar_2)^2} + c \frac{ax_3 r_3}{(ar_2 + r_3)^2} - b & -c \frac{ax_1 r_2}{(ar_2 + r_3)^2} \\ -c \frac{ax_2 r_2}{(r_1 + ar_2)^2} & -c \frac{ax_2 r_2}{(r_1 + ar_2)^2} & c \frac{ax_3 r_2}{(ar_2 + r_3)^2} - b \end{pmatrix}.
\]

Based on the observation that altruistic nodes should have the highest in-degree (Skums et al. 2015; Bunimovich and Shu 2019), we will be looking for a fixed point with local immunodeficiency where node 2 is altruistic (no virus concentration but high immune response, i.e., \(x_1 = 0, r_i > 0\)). Since nodes 1 and 3 are symmetric, without loss of generality we pick either one of them to be persistent (high virus concentration but no immune response, i.e., \(x_i > 0, r_i = 0\)) and the other one to be neutral (positive virus concentration and immune response, i.e., \(x_i > 0, r_i > 0\)), i.e.,

\[
x_2 = 0, \quad r_2 > 0, \quad x_1 > 0, \quad r_1 = 0, \quad x_3 > 0, \quad r_3 > 0.
\]
The virus populations and corresponding antibody populations at such a fixed point (steady state) with local immunodeficiency are

\[ r_1 = 0, \quad r_2 = \frac{f_1}{p\beta}, \quad r_3 = \frac{f_3 - f_1}{p} > 0, \quad f_3 > f_1. \]

\[ x_1 = \left( br_2 - \frac{c\alpha x_3 r_2}{ar_2 + r_3} \right) r_1 + \alpha r_2 = \frac{b}{c} r_2 (1 - \alpha), \quad x_2 = 0, \quad x_3 = \frac{b}{c} (\alpha r_2 + r_3). \]

To see whether this fixed point with local immunodeficiency we just found is stable, we consider the Jacobian of the system at this point.

\[
A_J = \begin{pmatrix}
0 & 0 & 0 \\
0 & f_2 - pr_2 & 0 \\
0 & 0 & 0
\end{pmatrix}, \quad B = \begin{pmatrix}
-p x_1 & -p\beta x_1 & 0 \\
0 & 0 & 0 \\
0 & -p\beta x_3 & -p x_3
\end{pmatrix},
\]

\[
C = \begin{pmatrix}
c & 0 & 0 \\
c & c & \frac{car_2}{ar_2 + r_3} \\
0 & 0 & \frac{br_2}{ar_2 + r_3}
\end{pmatrix}, \quad D = \begin{pmatrix}
\frac{c x_1}{ar_2} - b & 0 & 0 \\
\frac{c x_1}{ar_2} & \frac{c x_1}{ar_2} b & 0 \\
\frac{c x_1}{ar_2} & \frac{c x_1}{ar_2} b & \frac{c x_1}{ar_2}
\end{pmatrix},
\]

\[
J = \begin{pmatrix}
0 & 0 & 0 & -p x_1 & -p\beta x_1 & 0 \\
0 & f_2 - pr_2 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & -p\beta x_3 & -p x_3 \\
c & c & \frac{br_2}{ar_2 + r_3} & b - \frac{c}{c} & \frac{br_2}{ar_2 + r_3} - b & \frac{br_2}{ar_2 + r_3} \\
0 & 0 & \frac{br_2}{ar_2 + r_3} & 0 & \frac{br_2}{ar_2 + r_3} - b & \frac{br_2}{ar_2 + r_3}
\end{pmatrix}.
\]

If all the eigenvalues of the Jacobian are negative, or complex with negative real parts, then the fixed point has stable local immunodeficiency. Since the eigenvalues are the roots of the characteristic polynomial, we need to compute the characteristic polynomial of the Jacobian matrix.

Let \( \lambda_1 = f_2 - pr_2 = f_2 - f_1/\beta, \lambda_2 = \frac{b}{\alpha} - 2b. \)

\[
\det(J - \lambda I) = (\lambda - \lambda_1)(\lambda - \lambda_2) = (\lambda - \lambda_1)(\lambda - \lambda_2) \quad P(\lambda).
\]

The detailed computation of \( P(\lambda) \) is shown in Appendix. The result is

\[
P(\lambda) = abf_1\lambda^2 + bf_1(1 - \alpha) \left( \lambda^2 + \frac{br_3}{ar_2 + r_3} - \lambda + bpr_3 \right) + \lambda^2(\lambda + b) \left( \lambda + \frac{br_3(1 - \alpha)}{ar_2 + r_3} + px_3\lambda \right) \left[ \frac{cr_3}{ar_2 + r_3} - \lambda \right].
\]
Observe that all coefficients of the polynomial $P(\lambda)$ are positive. Therefore, it cannot have positive real roots. Combining all conditions on the parameters $f_3 > f_1$, $\lambda_1 = f_2 - f_1/\beta < 0$, $\lambda_2 = b/\alpha - 2b < 0$, one gets $\beta f_2 < f_1 < f_3$, $\alpha > 1/2$.

We present now some numerical examples where the LI is stable. These numerical values are consistent with the ranges of the corresponding parameters considered in the literature (Nowak and May 2000; Rong et al. 2010; Dahari et al. 2009; Skums et al. 2015; Bunimovich and Shu 2019).

1. $f_1 = 2$, $f_2 = 3$, $f_3 = 3$, $p = 2$, $c = 1$, $b = 3$, $\alpha = 2/3$, $\beta = 4/9$. With these parameters, $\lambda_1 = \lambda_2 = -1.5$, the polynomial $P(\lambda)$ has two pairs of complex roots, both with negative real parts.

2. $f_1 = 2$, $f_2 = 2$, $f_3 = 3$, $p = 2$, $c = 1$, $b = 1$, $\alpha = 3/4$, $\beta = 9/16$. Under such parameters, $\lambda_1 = -14/9 < 0$, $\lambda_2 = -2/3 < 0$, $P(\lambda)$ has two pairs of complex roots, both with negative real parts.

By continuity, this fixed point is stable on a positive measure set in the parameter space. This means that this fixed point is physically observable, i.e., there is a positive probability (real-life chance) to generate (e.g., numerically) a system with the CRN in Fig. 1 which has a stable and robust steady state of local immunodeficiency. It (positive measure in parameter space) also means that there is a real chance to generate a biological CR viral network with stable local immunodeficiency.

Observe that we only computed one fixed point. Certainly, there are other stable fixed points with local immunodeficiency that are stable and robust under perturbation of initial conditions and parameters. For example, there is at least one other fixed point where we switch the roles of nodes 1 and 3. Also small variations of parameters result in a “shift” of a fixed point. Such fixed points will remain stable in view of continuity of the coefficients of the system of differential equations under study.

Compare this network in Fig. 1 to the network with stable and robust local immunodeficiency found in Bunimovich and Shu (2019) (Fig. 2).

It is easy to see that the new network in Fig. 1 is really simpler than the branch-cycle CRN. Indeed, both networks contain three types of viruses, but the symmetric CRN contains fewer edges. This shows that the removal of an edge going out of an altruistic node (virus) may not destroy the state of stable local immunodeficiency.

### 4 A Role of Neutral Viruses in CR Networks

In this section, we will analyze the role of neutral viruses in local immunodeficiency, i.e., whether neutral viruses alone, without altruistic viruses, can sustain stable local immunodeficiency. Recall that persistent nodes represent types of viruses whose concentration is high but immune response against them is zero, and neutral nodes are the ones where both the virus and the antibody population are positive. From now on, we
will use the light pink color to represent persistent nodes and the dark green color for neutral nodes in CR networks.

Consider first the simplest CR network consisting of just one persistent and one neutral node. It is an asymmetric network, where the persistent node is connected to the neutral one. Dynamics equations for evolution of this system are (Fig. 3)

\[
\begin{align*}
\dot{x}_1 &= f_1 x_1 - p x_1 (r_1 + \beta r_2) \\
\dot{x}_2 &= f_2 x_2 - p x_2 r_2 \\
\dot{r}_1 &= c x_1 \frac{r_1}{r_1 + ar_2} - b r_1 \\
\dot{r}_2 &= c \left( x_1 \frac{r_2}{r_1 + ar_2} + x_2 \right) - b r_2.
\end{align*}
\]

A family of fixed points where node 1 is persistent and node 2 is neutral is given by the following relations:

\[
\begin{align*}
f_1 &= \beta f_2, \quad 0 < x_1 < \frac{bf_2}{cp}, \quad x_2 = \frac{bf_2}{cp} - x_1, \quad r_1 = 0, \quad r_2 = \frac{f_2}{p}.
\end{align*}
\]

Notice that this represents infinitely many numbers of fixed points (equilibrium states) that vary continuously on a line segment. To study the stability of these fixed points, we need to find the eigenvalues of the Jacobian. The Jacobian of the system is

\[
J = \begin{pmatrix}
0 & -p x_1 & -p \beta x_1 \\
\frac{cr_1}{r_1 + ar_2} & f_2 - pr_2 & 0 & -px_2 \\
\frac{cr_1}{r_1 + ar_2} & 0 & c & -\frac{cx_1 ar_2}{(r_1 + ar_2)^2} - b
\end{pmatrix},
\]

At those fixed points, the Jacobian becomes

\[
J = \begin{pmatrix}
0 & -p x_1 & -p \beta x_1 \\
0 & 0 & -px_2 \\
0 & c & -\frac{cx_1}{ar_2} - b
\end{pmatrix}.
\]

Let \( \lambda_1 = \frac{cx_1}{ar_2} - b \). The detailed computation of the characteristic polynomial of the Jacobian is shown in Appendix, and the result is

\[
\det(J - \lambda I) = \lambda (\lambda - \lambda_1)[\lambda^2 + b\lambda + cp(x_2 + \beta x_1)] = \lambda (\lambda - \lambda_1) P(\lambda),
\]
where
\[
\lambda_1 = \frac{cx_1}{ar_2} - b = \frac{cp}{\alpha f_2} x_1 - b < \frac{b}{\alpha} - b.
\]
All coefficients of the quadratic polynomial \(P(\lambda)\) are positive. Therefore, its roots are either real, negative or complex with negative real parts. Depending on the value of \(x_1\), the eigenvalue \(\lambda_1\) could be positive or negative. And for every fixed point in the family, the Jacobian has a 0 eigenvalue. This means that the corresponding state (fixed point with local immunodeficiency) is never stable but it could be marginally stable (because of the zero eigenvalue). However, in this case the concentration of persistent viruses cannot exceed some fixed value.

Indeed, for this family of fixed points, when \(x_1\) is small \((x_1 < \alpha b f_2/cp)\), the fixed points are stable on the subspace \(f_1 = \beta f_2\), and when \(x_1\) is big \((\alpha b f_2/cp < x_1 < b f_2/cp)\), the fixed points are unstable. It should be contrasted with the results of Bunimovich and Shu (2019) where, in the presence of an altruistic node, the state of local immunodeficiency can be stable (rather than marginally stable) and there is no bound on the concentration of persistent viruses.

Consider now a larger network with one persistent and two neutral nodes (Fig. 4). The adjacency matrix, neutralization and stimulation matrices for this CR network are
\[
A = \begin{pmatrix} 0 & 1 & 1 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \quad U = \begin{pmatrix} 1 & 0 & 0 \\ \beta & 1 & 0 \\ \beta & 0 & 1 \end{pmatrix}, \quad V = \begin{pmatrix} 1 & \alpha & \alpha \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix}.
\]

The population growth equations for this system are
\[
\begin{align*}
\dot{x}_1 &= f_1 x_1 - px_1 (r_1 + \beta r_2 + \beta r_3) \\
\dot{x}_2 &= f_2 x_2 - px_2 r_2 \\
\dot{x}_3 &= f_3 x_3 - px_3 r_3 \\
\dot{r}_1 &= cx_1 \frac{r_1}{r_1 + \alpha r_2 + \alpha r_3} - br_1 \\
\dot{r}_2 &= cx_1 \frac{\alpha r_2}{r_1 + \alpha r_2 + \alpha r_3} + cx_2 - br_2 \\
\dot{r}_3 &= cx_1 \frac{\alpha r_3}{r_1 + \alpha r_2 + \alpha r_3} + cx_3 - br_3.
\end{align*}
\]
A family of fixed points for this network is given via the following relations
\[
f_1 = \beta (f_2 + f_3), \quad 0 < x_1 < \frac{b}{c} (r_2 + r_3), \quad x_2 = \frac{b}{c} r_2 - x_1 \frac{r_2}{r_2 + r_3}, \quad x_3 = \frac{b}{c} r_3 - x_1 \frac{r_3}{r_2 + r_3}, \quad r_1 = 0, \quad r_2 = \frac{f_2}{p}, \quad r_3 = \frac{f_3}{p}.
\]
Again this is a group of steady states with local immunodeficiency (node 1 is persistent with positive virus population but 0 antibody population) that vary continuously on a line segment. The Jacobian of the system is

\[
J = \begin{pmatrix}
f_1 - p(r_1 + r_2 + r_3) & 0 & 0 & -px_1 & -p\beta x_1 & -p\beta x_1 \\
0 & f_2 - pr_2 & 0 & 0 & -px_2 & 0 \\
0 & 0 & f_3 - pr_3 & 0 & 0 & 0 \\
\frac{cr_1}{r_1 + r_2 + r_3} & 0 & 0 & -\frac{cx_1 a(r_2 + r_3)}{r_2 + r_3} & -\frac{cx_1 a(r_2 + r_3)^2}{r_2 + r_3} & -\frac{cx_1 a(r_2 + r_3)^3}{r_2 + r_3} \\
\frac{cr_2}{r_1 + r_2 + r_3} & c & 0 & -\frac{cx_1 a r_2 (r_2 + r_3)}{r_2 + r_3} & -\frac{cx_1 a r_2 (r_2 + r_3)^2}{r_2 + r_3} & -\frac{cx_1 a r_2 (r_2 + r_3)^3}{r_2 + r_3} \\
\frac{cr_3}{r_1 + r_2 + r_3} & 0 & c & -\frac{cx_1 a r_3 (r_2 + r_3)}{r_2 + r_3} & -\frac{cx_1 a r_3 (r_2 + r_3)^2}{r_2 + r_3} & -\frac{cx_1 a r_3 (r_2 + r_3)^3}{r_2 + r_3}
\end{pmatrix}.
\]

At the fixed points, under analysis we have

\[
J = \begin{pmatrix}
0 & 0 & 0 & -px_1 & -p\beta x_1 & -p\beta x_1 \\
0 & 0 & 0 & 0 & -px_2 & 0 \\
0 & 0 & 0 & 0 & 0 & -px_3 \\
\frac{cr_1}{r_1 + r_2 + r_3} & 0 & 0 & -\frac{cx_1 a(r_2 + r_3)}{r_2 + r_3} & -\frac{cx_1 a(r_2 + r_3)^2}{r_2 + r_3} & -\frac{cx_1 a(r_2 + r_3)^3}{r_2 + r_3} \\
\frac{cr_2}{r_1 + r_2 + r_3} & c & 0 & -\frac{cx_1 a r_2 (r_2 + r_3)}{r_2 + r_3} & -\frac{cx_1 a r_2 (r_2 + r_3)^2}{r_2 + r_3} & -\frac{cx_1 a r_2 (r_2 + r_3)^3}{r_2 + r_3} \\
\frac{cr_3}{r_1 + r_2 + r_3} & 0 & c & -\frac{cx_1 a r_3 (r_2 + r_3)}{r_2 + r_3} & -\frac{cx_1 a r_3 (r_2 + r_3)^2}{r_2 + r_3} & -\frac{cx_1 a r_3 (r_2 + r_3)^3}{r_2 + r_3}
\end{pmatrix}.
\]

We compute the characteristic polynomial of the Jacobian for stability analysis of the fixed points. Let \(\lambda_1 = \frac{cx_1}{a(r_2 + r_3)} - b < \frac{b}{a} - b\), the detailed computation is shown in Appendix, and the characteristic polynomial is

\[
|J - \lambda I| = (\lambda - \lambda_1)[\lambda D_1(\lambda) + px_2 D_2(\lambda)],
\]

where

\[
D_1(\lambda) = \lambda \left( \lambda + b - \frac{cx_1}{r_2 + r_3} \right) \left[ \lambda^2 + b\lambda + cp\beta x_1 \right]
+ cp x_3 \left[ \lambda^2 + \left( b - \frac{cx_1 r_3}{(r_2 + r_3)^2} \right) \lambda + cp\beta x_1 \frac{r_2}{r_2 + r_3} \right],
\]

\[
D_2(\lambda) = c\lambda \left[ \lambda^2 + \left( b - \frac{cx_1 r_2}{(r_2 + r_3)^2} \right) \lambda + cp x_3 \right] + cp\beta x_1 \lambda \frac{cr_3}{r_2 + r_3}.
\]

So, in this case again 0 is an eigenvalue. Another eigenvalue \(\lambda_1\) can be positive or negative depending on the value of \(x_1\). The rest of the eigenvalues are the roots of a degree four polynomial whose coefficients are all positive.

Therefore, for small values of \(x_1\), namely if \(x_1 < \frac{b}{c} r_2 r_3\), the fixed points are stable on positive measure subsets of the subspace \(f_1 = \beta (f_2 + f_3)\). If \(x_1\) has larger values \(\frac{b}{c} r_2 r_3 < x_1 < \frac{b}{c} (r_2 + r_3)\), then the fixed points are unstable.

In general, for any size network to have fixed points with only persistent and neutral nodes (viruses), the parameters \(f_i\)'s have to satisfy some condition that forms a positive codimension subspace (Bunimovich and Shu 2019). And based on the previous two examples, it is natural to assume that there is a family of fixed points, where the
Jacobian has a 0 eigenvalue, and an eigenvalue whose sign depends on the size of the viral population of the persistent node. The rest of the eigenvalues are the roots of a polynomial with positive coefficients.

Consider now a CR network with one persistent node and any (finite) number of neutral nodes to support it. Without loss of generality, we assume that the persistent node is node 1, and nodes 2 through $n$ are neutral (Fig. 5). There is an edge going from the persistent node to each of the neutral nodes.

The adjacency matrix of such a network is

$$
A = \begin{pmatrix}
0 & 1 & \cdots & 1 \\
0 & 0 & \cdots & 0 \\
\vdots & \vdots & \ddots & \vdots \\
0 & 0 & \cdots & 0
\end{pmatrix}.
$$

Then,

$$
U = \text{Id} + \beta A^T = \begin{pmatrix}
1 & 0 & \cdots & 0 \\
\beta & 1 & \cdots & 0 \\
\vdots & \vdots & \ddots & \vdots \\
\beta & 0 & \cdots & 1
\end{pmatrix}, \quad V = \text{Id} + \alpha A = \begin{pmatrix}
1 & \alpha & \cdots & \alpha \\
0 & 1 & \cdots & 0 \\
\vdots & \vdots & \ddots & \vdots \\
0 & 0 & \cdots & 1
\end{pmatrix}.
$$

The evolution equations for this system are

$$
\begin{cases}
\dot{x}_1 = f_1 x_1 - p x_1 \left( r_1 + \beta \sum_{j=2}^n r_j \right), \\
\dot{x}_i = f_i x_i - p x_i r_i, \quad 2 \leq i \leq n; \\
\dot{r}_1 = c \frac{x_1 r_1}{r_1 + \alpha \sum_{j=2}^n r_j} - b r_1, \\
\dot{r}_i = c \frac{x_1 r_i}{r_1 + \alpha \sum_{j=2}^n r_j} + c x_i - b r_i, \quad 2 \leq i \leq n.
\end{cases}
$$
Let $N_r = \sum_{j=2}^{n} r_j$. Consider the Jacobian of this system.

\[
J = \begin{pmatrix} A_J & B \\ C & D \end{pmatrix}, \quad A_J = \begin{pmatrix} f_1 - p(r_1 + \beta N_r) & 0 & \cdots & 0 \\ 0 & f_2 - pr_2 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & f_n - pr_n \end{pmatrix},
\]

\[
B = \begin{pmatrix} -px_1 & -p\beta x_1 & \cdots & -p\beta x_1 \\ 0 & -px_2 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & -px_n \end{pmatrix}, \quad C = \begin{pmatrix} c_{\frac{r_1}{r_1 + \alpha N_r}} & 0 & \cdots & 0 \\ c_{\frac{r_2}{r_1 + \alpha N_r}} & c & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ c_{\frac{r_n}{r_1 + \alpha N_r}} & 0 & \cdots & c \end{pmatrix},
\]

\[
D = \begin{pmatrix} \frac{c_{x_1}(r_1 + \alpha N_r - r_1)}{(r_1 + \alpha N_r)^2} - b & -\frac{c_{x_1}r_1}{(r_1 + \alpha N_r)^2} & \cdots & -\frac{c_{x_1}r_1}{(r_1 + \alpha N_r)^2} \\ -\frac{c_{x_1}r_2}{(r_1 + \alpha N_r)^2} & \frac{c_{x_1}(r_1 + \alpha N_r - \alpha r_2)}{(r_1 + \alpha N_r)^2} - b & \cdots & -\frac{c_{x_1}r_2}{(r_1 + \alpha N_r)^2} \\ \vdots & \vdots & \ddots & \vdots \\ -\frac{c_{x_1}r_n}{(r_1 + \alpha N_r)^2} & -\frac{c_{x_1}r_n}{(r_1 + \alpha N_r)^2} & \cdots & \frac{c_{x_1}(r_1 + \alpha N_r - \alpha r_n)}{(r_1 + \alpha N_r)^2} - b \end{pmatrix}.
\]

The fixed points, where node 1 is persistent and all other nodes are neutral, are

\[x_i > 0, \quad 1 \leq i \leq n, \quad r_1 = 0, \quad r_i > 0, \quad 2 \leq i \leq n.\]

From these conditions, we get

\[f_1 = p\beta N_r = \beta \sum_{j=2}^{n} f_j, \quad f_i = pr_i, \quad 0 < x_1 < \frac{b}{c} N_r, \quad x_i = \frac{b}{c} r_i - \frac{r_i}{N_r} x_1, \quad 2 \leq i \leq n.\]

So these fixed points belong to the subspace $f_1 = \beta \sum_{j=2}^{n} f_j$. At each fixed point,

\[
A_J = 0, \quad C = \begin{pmatrix} 0 & 0 & \cdots & 0 \\ \frac{c_{r_2}}{N_r} & c & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ \frac{c_{r_n}}{N_r} & 0 & \cdots & c \end{pmatrix}, \quad D = \begin{pmatrix} \frac{c_{x_1}}{N_r} - b & \frac{c_{x_1}r_1}{N_r} & \cdots & 0 \\ \frac{c_{x_1}r_2}{N_r} & \frac{c_{x_1}(N_r - r_2)}{N_r^2} - b & \cdots & \frac{c_{x_1}r_2}{N_r} \\ \vdots & \vdots & \ddots & \vdots \\ \frac{c_{x_1}r_n}{N_r} & \frac{c_{x_1}r_n}{N_r} & \cdots & \frac{c_{x_1}(N_r - r_n)}{N_r^2} - b \end{pmatrix}.
\]

The matrix $B$ is an upper triangular matrix with negative diagonal entries. Assume now that the Jacobian is invertible. Then, we get

\[
\begin{pmatrix} A_J & B \\ C & D \end{pmatrix} \begin{pmatrix} E & F \\ G & H \end{pmatrix} = \begin{pmatrix} 0 & B \\ C & D \end{pmatrix} \begin{pmatrix} E & F \\ G & H \end{pmatrix} = \begin{pmatrix} BG & BH \\ CE + DG & CF + DH \end{pmatrix} = \begin{pmatrix} I & 0 \\ 0 & I \end{pmatrix}.
\]

Then,

\[BG = I, \quad G = B^{-1}; \quad BH = 0, H = 0; \quad CE + DG = 0; \quad CF + DH = CF = I.\]
Observe that $C$ is a lower triangular matrix with diagonal entries $0, c, c, \ldots, c$. This matrix is not invertible because there is no $F$ such that $CF = I$. Therefore, we have shown that the Jacobian is not invertible. Hence, it has a zero eigenvalue at any fixed point of the considered family.

Now we compute the eigenvector which corresponds to the eigenvalue 0.

\[
\begin{pmatrix}
0 & B \\
C & D
\end{pmatrix}
\begin{pmatrix}
u \\
v
\end{pmatrix}
= \begin{pmatrix}
Bv \\
Cu + Dv
\end{pmatrix}
= \begin{pmatrix}
0 \\
0
\end{pmatrix}.
\]

$Bv = 0 \Rightarrow v = 0$; $Cu + Dv = Cu = 0$, $u = (N_r - r_2 - r_3 \cdots - r_n)^T$.

Therefore, the eigenspace corresponding to eigenvalue 0 is such that all $r_i$’s are fixed (since $v = 0$), but all the $x_i$’s can move along the $u$ direction. The $x_i$ values at the fixed points are $0 < x_1 < \frac{b}{c} N_r$, $x_i = \frac{b}{c} r_i - \frac{x_1}{N_r} r_i$, $2 \leq i \leq n$, and the $r_i$ values are $r_1 = 0, r_i = f_i / p, 2 \leq i \leq n$. So all the fixed points lie on the eigenspace of eigenvalue zero.

Clearly, there is only one nonzero entry in the $(n + 1)$th row of the Jacobian at the fixed points. It is the $(n + 1)$th element $\frac{cx_1}{aN_r} - b$, and it is an eigenvalue of the Jacobian. Thus, this eigenvalue $\lambda_1 = \frac{cx_1}{aN_r} - b$ is negative when $x_1 < \alpha \frac{b}{c} N_r$ and it is positive when $\alpha \frac{b}{c} N_r < x_1 < \frac{b}{c} N_r$.

Therefore, as we have shown, neutral viruses can support the existence of persistent viruses. However, in contrast to altruistic viruses, neutral viruses can only support the existence of bounded concentrations of persistent viruses, while altruistic viruses can support any concentrations of persistent viruses (Bunimovich and Shu 2019). Moreover, without the presence of altruistic viruses the states with persistent viruses could only be marginally stable, while in the presence of altruistic viruses the state of local immunodeficiency can be stable (Bunimovich and Shu 2019).

5 Attaching Minimal Networks to Large CR Networks with Random Structure (Topology)

We have found two minimal CR networks with three types of viruses (nodes) each. In this section, we analyze whether these networks can maintain the state of local immunodeficiency in their persistent viruses if we attach them to a large random CR network.

This question is important for understanding what may happen when CR networks are growing, particularly when some interactions between two hosts result in transmission of some CR subnetwork from one host to the other. In this section, we discuss results of our numerical experiments attempting to address this question.

Shown in Fig. 6 is a 100-node network that looks like a dandelion or a ball with a tail. The ball consists of nodes 0 through 97 and edges between them. The edges are generated by a $98 \times 98$ random matrix with 0–1 entries. The $(i, j)$ entry of the matrix being 1 means there is an edge from node $i - 1$ to node $j - 1$ and 0 means no edge. The tail is built by identifying nodes 97, 98 and 99 with nodes 1, 2 and 3 from the branch-cycle CRN (Fig. 2), i.e., there is an edge from node 97 to 98, an edge
from node 98 to 99 and an edge from node 99 back to node 98. Node 97 is where our minimal network, the tail, attaches to a large network, the ball. Since the edges inside of the ball are randomly generated, all nodes are equally important, attaching the minimal network to node 97 is as good as attaching it to any other node in the ball.

After building a randomly generated ball and attaching a minimal network to it as a tail, we build the evolution model (1) on this 100-node network. Then, we solve it numerically by the forward Euler method. In each numerical experiment, we randomly generate a set of parameters. The parameters $f_i$’s are allowed to be different, and they are generated as a random vector with entry values between 0 and 1. The ranges for all parameters are listed below (2). Initial conditions for virus and antibody populations are also randomly generated.

$$f_i \sim U(0, 1), f_{98} \sim U(1, 2), p \sim U(0, 1), b, c \sim U(0, 5),$$

$$\alpha \sim U(0.5, 1), \beta = \alpha^2, x_i(0), r_i(0) \sim U(0, 0.1).$$

(2)

Here, $f_i \sim U(0, 1)$ means that $f_i$ is a uniformly distributed random number in the interval (0, 1). The ranges of these parameters are consistent with the ones accepted in the literature (Nowak and May 2000; Rong et al. 2010; Dahari et al. 2009; Skums et al. 2015; Bunimovich and Shu 2019).

We repeated this numerical experiment multiple times. The results were consistent in all simulations, even though the structure of the large network (the ball) changes.
every time (since it is randomly generated), and the parameters are different and randomly generated each time as well. We always observed local immunodeficiency at equilibrium on the tail (i.e., the attached minimal network).

We also repeated the same numerical experiments for the new minimal symmetric CRN (Fig. 1). Again, we consistently observed local immunodeficiency at equilibrium on the tail. In conclusion, both minimal networks [one from Bunimovich and Shu (2019) and the new one from the present paper] maintain local immunodeficiency after being attached to a large CR network.

6 Discussion

Bunimovich and Shu (2019) proved that local immunodeficiency discovered in Skums et al. (2015) is a stable and robust phenomenon which may already appear in CRNs with just three viruses. Therefore, LI should likely be present in all diseases that demonstrate cross-immunoreactivity. Indeed, it is not necessary for CRNs to be large, which is typical for hepatitis C (Skums et al. 2015), to have local immunodeficiency. We also rigorously demonstrated in Bunimovich and Shu (2019) that there are easy ways to build larger networks with several persistent nodes (viruses) which remain invisible to the host’s immune system because of their positions in the CRN.

In the present paper, we prove that the simplest cross-immunoreactivity network with three nodes (viruses) and just two edges can have a state of stable and robust local immunodeficiency. It is truly the smallest network of this type because no network with three nodes can have fewer than two edges. (It is worthwhile to mention that Bunimovich and Shu (2019) showed no CRN with two nodes can maintain stable local immunodeficiency). These results raise a natural question whether it is possible to experimentally build such small cross-immunoreactivity networks with stable and robust local immunodeficiency.

We also analyze here the role of neutral viruses in the creation of local immunodeficiency. It turns out that in the absence of altruistic viruses, neutral viruses (even when any number of them is present to help a persistent node) can maintain local immunodeficiency only as a marginally stable state. Moreover, if only neutral and persistent viruses are present, then the population of persistent viruses cannot exceed a relatively small value in a sharp contrast to the situation when altruistic viruses are also present and then population of persistent viruses becomes virtually unbounded (Skums et al. 2015; Bunimovich and Shu 2019).

Lastly, we also showed numerically that small networks with stable LI can be attached to large CR networks and keep the state of stable local immunodeficiency.

Overall, it is shown that local immunodeficiency will likely be present in all diseases with cross-immunoreactivity. Indeed, we proved that very small CR networks may have a stable state with local immunodeficiency. Moreover, if such a small network is attached to another CR network, this small subnetwork may retain its stable LI state. All these results call for future numerical, analytic and, first of all, biological studies. The most important and pressing question is which types of viruses can play a role of persistent and/or altruistic ones (Domingo-Calap et al. 2019). Another question is whether one and the same virus may become persistent, altruistic or, perhaps, neutral.
Appendix A. Computation of \( P(\lambda) \) from the Characteristic Polynomial of the Jacobian for Fig. 1

\[
P(\lambda) = -\lambda \left| \begin{array}{ccc}
-\lambda & -p_\beta x_3 & -p x_3 \\
-c_{ar_2} & b_{ar_2} & b_{ar_2} \\
c_{ar_2} & b_{ar_2} & b_{ar_2}
\end{array} \right| - \lambda \left| \begin{array}{ccc}
-p_\beta x_3 & -p x_3 & 0 \\
-b_{ar_2} & b_{ar_2} & b_{ar_2} \\
0 & b_{ar_2} & b_{ar_2}
\end{array} \right| - \lambda \left| \begin{array}{ccc}
p x_3 & 0 & -p x_3 \\
c_{ar_2} & b_{ar_2} & b_{ar_2} \\
c_{ar_2} & b_{ar_2} & b_{ar_2}
\end{array} \right|
\]

\[
= -\lambda \left[ \frac{c_{ar_2}}{ar_2 + r_3} (\lambda + b) \right] + \lambda^2 \left( \frac{b_{ar_2}}{ar_2 + r_3} - \lambda \right)
\]

\[
= b_{f_1}(1 - \alpha) \left( \lambda^2 + \frac{b_{r_3}}{ar_2 + r_3} \lambda + b_{pr_3} \right) + \lambda^2 (\lambda + b) \left( \lambda + b \right) \left( \lambda - \frac{b_{ar_2}}{ar_2 + r_3} \right)
\]

\[
+ \lambda \left( \frac{c_{ar_2}}{ar_2 + r_3} \lambda + b_{cr_3} \right)
\]

\[
= b_{f_1}(1 - \alpha) \left( \lambda^2 + \frac{b_{r_3}}{ar_2 + r_3} \lambda + b_{pr_3} \right) + \lambda^2 (\lambda + b) \left( \lambda + b \right) \left( \lambda - \frac{b_{ar_2}}{ar_2 + r_3} \right)
\]

\[
+ \lambda \left( \frac{c_{ar_2}}{ar_2 + r_3} \lambda + b_{cr_3} \right)
\]

\[
= b_{f_1}(1 - \alpha) \left( \lambda^2 + \frac{b_{r_3}}{ar_2 + r_3} \lambda + b_{pr_3} \right) + \lambda^2 (\lambda + b) \left( \lambda + b \right) \left( \lambda - \frac{b_{ar_2}}{ar_2 + r_3} \right)
\]

\[
+ \lambda \left( \frac{c_{ar_2}}{ar_2 + r_3} \lambda + b_{cr_3} \right)
\]
Appendix B. Computation of the Characteristic Polynomial of the Jacobian for Fig. 3

Let $\lambda_1 = \frac{c_1}{ar_2} - b$,

$$\det(J - \lambda I) = \det \begin{pmatrix} -\lambda & 0 & 0 & -px_1 & -p\beta x_1 \\ 0 & -\lambda & 0 & 0 & -px_2 \\ 0 & 0 & \lambda_1 - \lambda & 0 & 0 \\ c & c & -\frac{c_1}{ar_2} & -b - \lambda & 0 \\ c & c & c & c & c \end{pmatrix} = (\lambda_1 - \lambda) \det \begin{pmatrix} -\lambda & 0 & 0 & -p\beta x_1 \\ 0 & -\lambda & 0 & -px_2 \\ 0 & 0 & \lambda_1 - \lambda & 0 \\ c & c & -\frac{c_1}{ar_2} & -b - \lambda \end{pmatrix} = (\lambda - \lambda_1) \left[ \lambda(\lambda^2 + b\lambda + cpx_2) + p\beta x_1 \alpha \right] = \lambda(\lambda - \lambda_1) \left[ \lambda^2 + b\lambda + cpx_2 \right].$$

Appendix C. Computation of the Characteristic Polynomial of the Jacobian for Fig. 4

Let $\lambda_1 = \frac{c_1}{ar_2(r_2 + r_3)} - b < \frac{b}{a} - b$, then

$$|J - \lambda I| = \begin{vmatrix} -\lambda & 0 & 0 & -px_1 & -p\beta x_1 & -p\beta x_1 \\ 0 & -\lambda & 0 & 0 & -px_2 & 0 \\ 0 & 0 & -\lambda & 0 & 0 & -px_3 \\ \frac{c_1}{ar_2} & c & 0 & \frac{c_1 r_3}{ar_2 (r_2 + r_3)^2} & -b - \lambda & -\frac{c_1 r_3}{ar_2 (r_2 + r_3)^2} \\ \frac{c_2}{r_2 + r_3} & 0 & c & \frac{c_1 r_3}{ar_2 (r_2 + r_3)^2} & -b - \lambda & -\frac{c_1 r_3}{ar_2 (r_2 + r_3)^2} \\ \frac{c_3}{r_2 + r_3} & 0 & 0 & \frac{c_1 r_3}{ar_2 (r_2 + r_3)^2} & -b - \lambda & -\frac{c_1 r_3}{ar_2 (r_2 + r_3)^2} \end{vmatrix}.$$

By expanding along the fourth row, we get

$$|J - \lambda I| = (\lambda_1 - \lambda) \begin{vmatrix} -\lambda & 0 & 0 & -p\beta x_1 & -p\beta x_1 \\ 0 & -\lambda & 0 & -px_2 & 0 \\ 0 & 0 & -\lambda & 0 & -px_3 \\ \frac{c_1}{ar_2} & c & 0 & \frac{c_1 r_3}{ar_2 (r_2 + r_3)^2} & -b - \lambda \\ \frac{c_2}{r_2 + r_3} & 0 & c & \frac{c_1 r_3}{ar_2 (r_2 + r_3)^2} & -b - \lambda \end{vmatrix}.$$

Expanding now along the second row, we obtain

$$|J - \lambda I| = (\lambda - \lambda_1) \left[ \lambda D_1(\lambda) + px_2 D_2(\lambda) \right],$$
where

\[
D_1(\lambda) = \begin{vmatrix}
-\lambda & 0 & -p\beta x_1 & -p\beta x_1 \\
0 & -\lambda & 0 & -px_3 \\
\frac{cr_2}{r_2+r_3} & 0 & \frac{cx_1 r_3}{r_2+r_3} & -b - \lambda \\
0 & c & c & -b - \lambda
\end{vmatrix}
\]

\[
= -\lambda \begin{vmatrix}
\frac{cr_2}{r_2+r_3} & 0 & -p\beta x_1 & -p\beta x_1 \\
0 & -\lambda & 0 & -px_3 \\
\frac{cx_1 r_3}{r_2+r_3} & 0 & \frac{cx_1 r_2}{r_2+r_3} & -b - \lambda \\
0 & c & c & -b - \lambda
\end{vmatrix} + cp_3 \beta \left( \frac{cr_2}{r_2+r_3} \right) \beta + cp_3 \beta + cp_3 \beta x_1 \frac{r_2}{r_2+r_3}
\]

\[
D_2(\lambda) = \begin{vmatrix}
-\lambda & 0 & 0 & -p\beta x_1 \\
0 & -\lambda & 0 & -px_3 \\
\frac{cr_3}{r_2+r_3} & 0 & \frac{cx_1 r_2}{r_2+r_3} & -b - \lambda \\
0 & c & c & -b - \lambda
\end{vmatrix} = c\lambda \beta \left( \frac{cr_3}{r_2+r_3} \right) \beta + cp_3 \beta x_1 \frac{r_2}{r_2+r_3}
\]

References

Bunimovich L, Shu L (2019) Local immunodeficiency: minimal networks and stability. Math Biosci 310:31–49

Campo DS, Dimitrova Z, Yamasaki L, Skums P, Lau DT, Vaughan G, Forbi JC, Teo C-G, Khudyakov Y (2014) Next-generation sequencing reveals large connected networks of intra-host HCV variants. BMC Genom 15(Suppl 5):S4

Chicone C (2006) Ordinary differential equations with applications. Springer, New York

Dahari H, Layden-Almer JE, Kallwitz E, Rebeiro RM, Cotler SJ, Layden TJ, Perelson AS (2009) A mathematical model of hepatitis C virus dynamics in patients with high baseline viral loads or advanced liver disease. Gastroenterology 136(4):1402–1409

Domingo-Calap P, Segredo-Otero E, Duran-Moreno M, Sanjuan R (2019) Social evolution of innate immunity evasion in a virus. Nat Microbiol 4:1006–1013

Francis T Jr (1960) On the doctrine of original antigenic sin. Proc Am Philos Soc 104(6):572–578

Hattori M, Yashioka K, Aiyama T, Iwata K, Terazawa Y, Ishigami M, Yano M, Kakumu S (1998) Broadly reactive antibodies to hypervariable region 1 in hepatitis C virus-infected patient sera: relation to viral loads and response to interferon. Hepatology 27(6):1703–1710

Kim JH, Skountzou I, Compans R, Jacob J (2009) Original antigenic sin responses to influenza viruses. J Immunol 183(5):3294–3301

Midgley CM, Bajwa-Joseph M, Vasanawathana S, Limpitikul W, Wills B, Flanagan A, Waiyaiya E, Tran HB, Cowper AE, Chotiyarnwong P, Grimes JM, Yoksan S, Malasit P, Simmons CP, Mongkolsapaya J, Screaton GR (2011) An in-depth analysis of original antigenic sin in dengue virus infection. J Virol 85(1):410–421

Nowak MA, May RM (1991) Mathematical biology of HIV infections: antigenic variation and diversity threshold. Math Biosci 106(1):1–21

Nowak MA, May RM (2000) Virus dynamics: mathematical principles of immunology and virology. Oxford University Press, Oxford
Nowak MA, May RM, Anderson RM (1990) The evolutionary dynamics of HIV-1 quasispecies and the development of immunodeficiency disease. AIDS 4(11):1095–1103

Nowak MA, Anderson RM, Mclean AR, May RM (1991) Antigenic diversity thresholds and the development of aids. Science 254(5034):963–969

Pan K (2011) Understanding original antigenic sin in influenza with a dynamical system. PLoS ONE 6(8):e23910

Parsons MS, Muller S, Kholer H, Grant MD, Bernard NF (2013) On the benefits of sin: can greater understanding of the 1f7-idiotypic repertoire freeze enhance HIV vaccine development? Hum Vaccines Immunother 9(7):1532–1538

Rehermann B, Shin E-C (2005) Private aspects of heterologous immunity. J Exp Med 201(5):667–670

Rong L, Dahari H, Ribeiro RM, Perelson AS (2010) Rapid emergence of protease inhibitor resistance in hepatitis C virus. Sci Transl Med 2(30):30ra32

Skums P, Bunimovich L, Khudyakov Y (2015) Antigenic cooperation among intrahost HCV variants organized into a complex network of cross-immunoreactivity. Proc Natl Acad Sci USA 112(21):6653–6658

Wodarz D (2003) Hepatitis C virus dynamics and pathology: the role of CTL and antibody responses. J Gener Virol 84(Pt 7):1743–1750

Yoshioka K, Aiyama T, Okumura A, Takayanagi M, Iwata K, Ishikawa T, Nagai Y, Kakumu S (1997) Humoral immune response to the hypervariable region of hepatitis C virus differs between genotypes 1b and 2a. J Infect Dis 175(3):505–510

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