Local Immunodeficiency: Minimal Networks and Stability

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Abstract

Some basic aspects of the recently discovered phenomenon of local immunodeficiency [1] generated by antigenic cooperation in cross-immunoreactivity networks are investigated. We prove that stable under perturbations local immunodeficiency already occurs in very small networks and under general conditions on their parameters. A major necessary feature of such networks is non-homogeneity of their topology. It is also shown that one can construct larger cross-immunoreactivity networks with stable local immunodeficiency by using small networks with stable local immunodeficiency as their building blocks. Our results imply that stable local immunodeficiency occurs in networks with quite general topology. In particular the scale-free property of a cross-immunoreactivity network, assumed in [1], is not required.

Keywords: cross-immunoreactivity network, local immunodeficiency, minimal stable network

1. Introduction

Cross-immunoreactivity (CR) is a well known phenomenon which was observed in the studies of AIDS, influenza, Hepatitis C, dengue and other diseases (see e.g. [2, 3, 4, 5, 6, 7, 8, 9]). In a nutshell CR means that the generation of antibodies to some antigen (virus) can be stimulated by other antigens (viruses). Therefore CR generates (indirect, i.e. via the corresponding antibodies) interactions between the antigens (viruses). For a long time CR was recognized as an important phenomenon in the in-host dynamics of various diseases and was used in building their mathematical models [7, 8, 6, 4].

However, in all these models CR was incorporated as a mean-field process where all interactions between different antigens (viruses) are assumed to have the same strength. Recent experiments with Hepatitis C viruses demonstrated that this assumption is incorrect, and instead the CR network has a very complicated structure (topology) which resembles the topology of the scale-free networks [3, 2].

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A new Hepatitis C (HC) dynamics model [1] is conceptually simpler than the previous ones (see e.g. [2]). In fact the new model involves only two (necessary) types of variables in immunological models, which are the sizes of the populations of various types of viruses (antigens) and the sizes of the populations of corresponding antibodies. For instance, the Hepatitis C model in [6] contains three more types of variables, namely the sizes of populations of infected and of non-infected hepatocytes as well as a total (mean field) cross-immunoreactivity response.

This fact naturally causes some doubts and suspicion. Indeed, how can a simpler model have richer dynamics? The reason is that our model is just conceptually simpler, it actually contains more parameters (although fewer types of variables). Different pairs of viruses generally have different strengths of interaction in the cross-immunoreactivity network, but in the old model they were all equal to each other.

Traditionally a mathematical model is made more complicated by adding more variables and/or more equations in order to describe new experimental findings which old models failed to reproduce. The model introduced in [1] is instead based on new specially conducted experiments [3, 2] which proved essential heterogeneity of the CR network. Although the model in [1] was dealing with dynamics of the Hepatitis C, in fact it provides a model of evolution of any disease which has cross-immunoreactivity. In the paper [1] dynamics of this new model was analyzed numerically. Scale-free CR networks of sizes 500-1000 were generated and then numerical simulations were performed.

The main result was the discovery of a new phenomenon called [1] a Local Immunodeficiency (LI), which showed up in all of the performed several hundred simulations there. Namely, in all these simulations the pool of HC viruses got partitioned into three types (subsets). The first type consists of persistent viruses which have large population sizes but there is virtually zero immune response against them. Therefore persistent viruses remain undetected by the human immune system and thus a clear immunodeficiency (with respect to persistent viruses) is present. However we call it a local immunodeficiency because it is completely determined by the (localized) positions of the persistent viruses in the CR network.

Persistent viruses enjoy such a relaxing life because the second type, altruistic viruses sacrifice themselves in order to protect persistent viruses from the immune response. Concentrations of altruistic viruses are very small but they carry almost the entire immune response against all of the in-host population of viruses. The rest (third type) of viruses plays a much smaller role in the HC evolution [1]. In what follows we call these viruses neutral.

In the present paper we demonstrate rigorously that local immunodeficiency is a much more general phenomenon than one may conclude from the results of [1].

First, we prove that stable local immunodeficiency appears already in certain networks with just three viruses under general conditions. These conditions are expressed as realistic inequalities between parameters of the model. We also prove stability of the phenomenon of LI with respect to perturbations of the parameters of the model, i.e. robustness of this phenomenon.

It is proved that local immunodeficiency is a stable state of evolution of the model
only in one (out of many possible topologies) of the three element (viruses) networks, while in all two element networks LI is unstable. This three element network with stable LI is characterized by the maximal asymmetry of its structure (topology) among all three element networks. In this network there is one persistent virus and one altruistic virus while the third virus is neutral.

We also prove that there are no two element CR networks with stable LI. It should be mentioned that the two virus network with stable LI found in [1] assumes very restrictive relations between parameters of the model which have the form of exact equalities. Clearly such strict constraints cannot be maintained in real life situations. Indeed, only inequalities remain true under small changes of parameters which always occur because of fluctuations of real environments. In the present paper we demonstrate that the regions in the phase space where stable local immunodeficiency exists have the same (full) dimension as the dimension of the phase space of the system (model). However, it happens only in certain networks with at least three elements. Once again, these networks must also be sufficiently non-homogeneous.

We then demonstrate how one can build larger CR networks with stable local immunodeficiency by attaching to each other the three element (three viruses) minimal network with stable local immunodeficiency. For instance, we proved that by combining two such networks one gets a network with five viruses where two viruses are persistent and two are altruistic. And the dynamics of HC with such a CR network is stable and robust. Our results were mostly obtained by direct computations. Therefore for large networks one would require numerical simulations although our rigorous results about smaller CR networks basically give a proof of concept that stable and robust LI is present in all larger networks with sufficiently non-homogeneous topology.

To justify it even more we proved presence of stable and robust local immunodeficiency also in one network with seemingly mild non-homogeneity of its topology. It is important to mention that among CR networks with four viruses there are quite a few with more non-homogeneous topology than in the one we studied. Therefore our results essentially provide no doubts that in those CR networks stable and robust LI must be also present. It is for this purpose we studied a less non-homogeneous network. The proof of stable and robust LI (essentially by long direct computations) in this CR network is given in the Appendix.

It is important to mention that in this paper we are dealing with strong local immunodeficiency which is a stronger property than the one found in [1]. Namely, we say that a certain virus causes strong local immunodeficiency if the immune response against this virus is identically zero, so just completely absent. Analogously, we say that some virus is altruistic if it is not present at all (i.e. its concentration is zero) but immune response against this non-existing virus is present (strictly positive).

In [1], instead of these identical zeroes, some (sufficiently) small quantities were considered. We call this case a weak local immunodeficiency. Clearly a weak LI is a more general phenomenon than strong LI. Indeed, if the strong LI takes place then the weak LI is automatically present. Thus our results on the existence and stability of strong LI imply that weak LI does exist and is stable, under even weaker conditions than our conditions on
the existence and stability of strong LI. Therefore it is present in an even larger variety of CR networks.

These (rigorously proven) results demonstrate that stable local immunodeficiency does not require a special (scale-free) structure (topology) of the CR network. In fact, it is enough that CR network be sufficiently non-homogeneous. It is natural to expect that this condition is satisfied in real life situations because there is no reason for CR networks to be homogeneous (unless some new biological law of symmetry will be discovered, which is very doubtful). Non-homogeneity of CR networks is a mild and very general condition, and thus the phenomenon of local immunodeficiency should be ubiquitous for diseases with cross-immunoreactivity.

We also show that local immunodeficiency is a robust phenomenon. Recall that a state (an orbit or solution) of a system is stable if small variations of initial conditions result in small variations of this state, i.e. a new (perturbed) orbit stays close to the initial (unperturbed) state. On the other hand, a state of a system is robust if small variations of the system parameters (i.e. transitions to formally different systems) result in a stable state which is close to the state of the initial (unperturbed) system.

Our results demonstrate once again [1] that a key role in LI is played by the altruistic viruses which have very small concentrations but occupy central positions in the CR networks by having the largest in-degrees among all other elements (viruses). Therefore these altruistic local hubs of CR networks must be primary targets of prevention and elimination of the corresponding disease.

The structure of the paper is the following. In section 2 we introduce the model. Section 3 is devoted to a general analysis of stability of dynamics of this model. Section 4 deals with analysis of two virus networks. Three virus networks are studied in section 5. The building of larger networks with stable local immunodeficiency is considered in section 6. Lastly section 7 contains some concluding remarks. Some long technical computations are placed into the Appendix. We also put some long computations with a larger four element CR network with stable and robust LI to demonstrate that local immunodeficiency appears in networks with a relatively mild non-homogeneity of network’s topology in the appendix.

2. Model of evolution of a disease with heterogeneous cross-immunoreactivity network

In this section we define the model of the HC evolution introduced in [1]. It is very important though to stress again that this model is applicable to any disease with cross-immunoreactivity. In fact, this model involves only two necessary types of variables for any immunological model, a population of $n$ viral antigenic variants $x_i$ inducing $n$ immune responses $r_j$ in the form of antibodies (Abs). Viral variants exhibit cross-immunoreactivity (CR) which results in a CR network (CRN). The latter is a directed weighted 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, there are two weight functions that correspond to 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 $0 \leq u_{ij}, v_{ij} \leq 1$; $u_{ij}$ is a coefficient representing the binding affinity of Ab to $j$ ($r_j$) with the $i$-th variant; and $v_{ij}$ is a coefficient reflecting 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 evolution of the antigen (virus) and antibody populations is given by the following system of ordinary differential equations (ODEs):

$$
\dot{x}_i = f_i x_i - p x_i \sum_{j=1}^n u_{ji} r_j, \quad i = 1, \ldots, n,
\dot{r}_i = c \sum_{j=1}^n x_j \frac{v_{ji} r_i}{\sum_{k=1}^n v_{jk} r_k} - b r_i, \quad i = 1, \ldots, n.
$$

The viral variant $x_i$ replicates at the rate $f_i$ and is eliminated by the immune responses $r_j$ at the rates $p u_{ji} r_j$. The immune responses $r_i$ are stimulated by the $j$-th variant at the rates $g_{ij} x_j$, where $g_{ij} = \frac{v_{ji} r_i}{x_j \sum_{k=1}^n v_{jk} r_k}$ represents the probability of stimulation of the immune response $r_i$ by the variant $x_j$. This model (as in [1]) allows us to incorporate the phenomenon of the original antigenic sin [10, 11, 12, 13, 14, 15], 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.

Here 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 CRN, i.e.,

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

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 [4] for heterogeneous viral population. Because neutralization of an antigen (virus) may require more than one antibodies, we assume ([1]) that $0 < \beta = \alpha^k < \alpha < 1$. It is important to mention that we analyze a more general model here than the one studied in [1], where it was assumed that all viruses (antigens) replicate with the same rate.

3. Stationary states of the Model

Fixed (stationary) points of the system (1) are determined by the relations

$$
\begin{align*}
    f_i x_i &= p x_i \sum_{j=1}^n u_{ji} r_j, \quad i = 1, \ldots, n, \\
    c r_i \sum_{j=1}^n \frac{v_{ji} x_j}{\sum_{k=1}^n v_{jk} r_k} &= b r_i, \quad i = 1, \ldots, n.
\end{align*}
$$

(2)
Clearly we are interested only in such fixed points where all variables assume non-negative values, and the populations of all viruses and antibodies can not be simultaneously equal to zero.

Consider the following two sets
\[
N = \{ i \in \mathbb{N}, 1 \leq i \leq n \}, I = \{ i \in N : x_i > 0 \}, J = \{ i \in N : r_i > 0 \}.
\]

**Definition 1.** We say that strong local immunodeficiency occurs when there exists \( i \) such that \( x_i > 0, r_i = 0 \), or when \( P := I \setminus J \neq \emptyset \).

In what follows we will call neutral nodes with \( x_i = r_i = 0 \) the neutral idle nodes since they don’t contribute to the dynamics of the network. We also will call neutral nodes with \( x_i > 0, r_i > 0 \) the neutral active nodes. In the paper [1] a weaker local immunodeficiency condition was considered. Namely a new phenomenon of antigenic cooperation was discovered when some (altruistic) viral variants sacrifice themselves, being strongly exposed to an immune response, for the benefit of other (persistent) viral variants which become practically hidden from the immune system. Therefore in [1] local immunodeficiency was considered to be present when persistent viruses increase their population but the immune response against them was relatively small. Although these conditions are more practical for computer simulations, because it could take a very long time to completely eliminate some virus, they are not very precise. Here we consider a stronger but well defined case, strong local immunodeficiency (SLI). By showing that SLI is ubiquitous for non-homogeneous CR networks we automatically demonstrate that LI is even more common for such networks. Indeed a strong LI automatically implies weak LI. By making use of the notations introduced above we get a simpler formula for the fixed points:

\[
\sum_{j \in N} u_{ji} r_j = r_i + \beta \sum_{j \in E} r_j = f_i / p, \forall i \in I,
\]
\[
\sum_{j \in N} w_{ji} x_j = \delta_i x_i + \alpha \sum_{j \in E} \delta_j x_j = b / c, \forall i \in J,
\]
\[
\delta_i = \frac{1}{r_i + \alpha \sum_{j \in E} r_j}.
\]

In our parameter space \( \{ f_1, f_2, \ldots, f_n > 0, p, c, b > 0, \alpha, \beta > 0 \} \), any relation having a form of equality (e.g. \( f_1 = \beta f_2 \)) defines a subset of co-dimension 1, (i.e. a non-typical subset), in the phase space of all systems described by the differential equations (1). Therefore with respect to a natural phase volume such subsets have volume (measure) zero. It is practically impossible that these very restrictive conditions will be met in a real system evolving according to model (1). Because of that we are only interested in stationary points which exist without extra conditions or under conditions expressed as inequalities between the parameters of the model. (See the examples in the following sections). This should be contrasted with [1] where local immunodeficiency was shown to exist under much more restrictive conditions, when there are some exact equalities between the system’s parameters.
Suppose that the matrices $V = (\text{Id} + \alpha A)$ and $U = (\text{Id} + \beta A^T)$ are invertible. Denote $F = (f_1, \ldots, f_n)^T$. Then one stationary point is defined by the following relation

$$R^* = \frac{1}{p} (U^T)^{-1} F, X^* = \frac{b}{c} (V^T)^{-1} (VR^*) =: Xr(R^*).$$

More generally, we have a stationary space defined by the following relations

$$R = R^* + \ker(U^T I), X = Xr(R) + \ker(V^T J),$$

where

$$\ker(U^T I) = \{ w \in \mathbb{R}^n : (U^T w)_i = 0, \forall i \in I \}, \quad \ker(V^T J) = \{ w \in \mathbb{R}^n : (V^T w)_j = 0, \forall j \in J \}.$$

To verify the stability of a stationary point, we need to consider the Jacobian matrix of the right hand side of (1). It can be written in block form as

$$J = \begin{pmatrix} A_J & B \\ C & D \end{pmatrix},$$

where

$$A_J = \text{diag}(f_i - p \sum_{j=1}^n u_{ji} r_j), \quad B_{i,j} = -px_i u_{ji},$$

$$C_{i,j} = c \frac{v_{ji} r_i}{\sum_{k=1}^n v_{jk} r_k}, \quad D_{i,i} = -cr_i \sum_{j=1}^n \frac{v_{ji} x_j r_i}{(\sum_{k=1}^n v_{jk} r_k)^2}, \quad D_{i,j} = c \frac{v_{ji} x_j}{\sum_{k=1}^n v_{jk} r_k} - b - cr_i \sum_{j=1}^n \frac{v_{ji} x_j}{(\sum_{k=1}^n v_{jk} r_k)^2}.$$

4. Analysis of size 2 CRN

Clearly there is only one network of size 2 where one may expect local immunodeficiency. Indeed the only two elements of this network must be connected asymmetrically. Otherwise one of these elements cannot be altruistic while the other is persistent. For a local immunodeficiency it is necessary to have elements of both these types in a network.

Thus let us consider the following size 2 CR network.

![Figure 1: size 2 CRN](image)

The equations describing the evolution of these two viruses and two antibodies are

$$\begin{cases}
\dot{x}_1 = f_1 x_1 - px_1 (r_1 + \beta r_2), \\
\dot{x}_2 = f_2 x_2 - px_2 r_2, \\
\dot{r}_1 = cx_1 \frac{r_1}{r_1 + r_2} - br_1, \\
\dot{r}_2 = c(x_1 \frac{r_2}{r_1 + r_2} + x_2) - br_2.
\end{cases}$$
Here there is only one fixed point of interest, the one where the values of the variables are non-negative and the strong local immunodeficiency is present without exact equality conditions on the parameters. This fixed point is given by the relations

\[ x_1 = \frac{bf_1}{c p b}, x_2 = 0, r_1 = 0, r_2 = \frac{f_1}{p b}. \]

The Jacobian of the system is

\[
J = \begin{pmatrix}
0 & 0 & -p x_1 & -p b x_1 \\
\frac{c r_1}{r_1 + ar_2} & \frac{f_2 - pr_2}{c r_2} & -b & -\frac{c x_2}{c r_2} \\
0 & c & \frac{c x_1}{c r_2} & \frac{c x_1}{c r_2} - b \\
0 & 0 & \frac{b x_1}{c} & -\frac{b x_1}{c}
\end{pmatrix}.
\]

At the fixed point the Jacobian equals

\[
J = \begin{pmatrix}
0 & 0 & -\frac{b x_1}{c} & -\frac{b x_1}{c} \\
0 & 0 & \frac{b x_1}{c} & 0 \\
0 & 0 & \frac{b x_1}{a - b} & 0 \\
0 & 0 & -\frac{b x_1}{a} & -b
\end{pmatrix}.
\]

It has the eigenvalue \( \lambda = \frac{b}{a} - b > 0 \), and therefore this fixed point is unstable.

It is important to mention that a stable fixed point for this two virus network was found in [1]. However, as we already mentioned before it has been done under unrealistic (i.e. much too restrictive) condition. One can also check that the symmetric network of two viruses doesn’t have a stable local immunodeficiency (we will list the detailed computations in the appendix). Our analysis proves that no two virus network can have a stable and robust state of Local Immunodeficiency.

5. Analysis of size 3 CRNs

In this section we study the stability of dynamics of CRN with three viruses (elements). In some of such networks there is no stable local immunodeficiency because of their symmetry or not enough non-homogeneity. Actually only one topology of a CRN with three elements demonstrates a stable strong local immunodeficiency. We present here analysis of this size 3 CRN as well as of another one. Some other CRN are analyzed in the appendix.

Consider at first the chain-branch CRN (Fig. 2). Such a network was briefly mentioned in [1] to demonstrate that long distance action in networks may lead to local immunodeficiency. No studies of stability were conducted in that paper though. Also recall here that we are after robust conditions of stable local immunodeficiency which would not be violated under variations of parameters. The latter always occurs because of permanently changing environments. Besides, any mathematical model (including [1] of course) is
just an approximation to reality. Therefore robustness is a necessary condition for any predictive model of a real system or phenomenon.

Now the system (1) becomes

$$\begin{cases}
\dot{x}_1 = f_1 x_1 - px_1 (r_1 + \beta r_2), \\
\dot{x}_2 = f_2 x_2 - px_2 (r_2 + \beta r_3), \\
\dot{x}_3 = f_3 x_3 - px_3 r_3, \\
\dot{r}_1 = c x_1 - r_1^\alpha - b r_1, \\
\dot{r}_2 = c (x_1 (r_2 + r_3) + x_2 (r_2 + r_3)) - b r_2, \\
\dot{r}_3 = c (x_2 + r_3) - b r_3.
\end{cases}$$

The fixed points with local immunodeficiency are:

$$x_1 = \frac{b f_1}{c p \beta}, x_2 = 0, x_3 = 0, r_1 = 0, r_2 = \frac{f_1}{p \beta}, r_3 = 0;$$

$$x_1 = \frac{b f_1}{c p \beta}, x_2 = 0, x_3 = \frac{b f_2}{c p}, r_1 = 0, r_2 = \frac{f_1}{p \beta}, r_3 = \frac{f_2}{p};$$

$$x_1 = \frac{b f_1}{c p}, x_2 = \frac{b f_2}{c p \beta}, x_3 = 0, r_1 = \frac{f_1}{p}, r_2 = 0, r_3 = \frac{f_2}{p \beta}.$$
There are eigenvalues $\lambda = f_1, \frac{b}{a} - b > 0$. Therefore this fixed point is unstable.

At another fixed point $x_1 = \frac{b_f}{c_p}, x_3 = \frac{b_f}{c_p}, x_2 = 0, r_2 = \frac{f_1}{g}, r_3 = \frac{f_3}{g}, r_1 = 0$, we have

$$J = \begin{pmatrix}
0 & 0 & 0 & -\frac{b_f}{c_p} & -\frac{b}{a}f_1 & 0 \\
0 & f_2 - \frac{f_1}{g} & -\beta f_3 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & -\frac{b}{a}f_3 \\
0 & 0 & 0 & \frac{b}{a} - b & 0 & 0 \\
c & \frac{c f_1}{f_1 + g f_3} & 0 & -\frac{b}{a} & -b & 0 \\
0 & \frac{c f_3}{f_1 + g f_3} & c & 0 & 0 & -b
\end{pmatrix},$$

Hence $\lambda = \frac{b}{a} - b > 0$ is an eigenvalue, and this fixed point is also unstable.

At the fixed point $x_1 = \frac{b_f}{c_p}, x_2 = \frac{b_f}{c_p}, x_3 = 0, r_1 = \frac{f_1}{g}, r_3 = \frac{f_3}{g}, r_2 = 0$, the Jacobian takes the form

$$J = \begin{pmatrix}
0 & 0 & 0 & -\frac{b}{a} f_1 & -\frac{b}{a} \beta f_1 & 0 \\
0 & 0 & 0 & 0 & -\frac{c f_1}{c_p} f_2 & -\frac{b}{a} f_2 \\
0 & 0 & f_3 - \frac{f_1}{g} & 0 & 0 & 0 \\
c & 0 & 0 & -b & -\alpha b & 0 \\
0 & 0 & 0 & \frac{b}{a} + \alpha b & -b & 0 \\
0 & c & c & 0 & -\frac{b}{a} & -b
\end{pmatrix},$$

Thus one eigenvalue equals $\lambda = \frac{b}{a} + ab - b > 0$, and hence this critical point is unstable as well.

Next we consider a CRN with three elements (viruses) which has maximal asymmetry among all thirteen topologically different networks of three elements. In view of its essential asymmetry this network would most likely maintain LI out of all thirteen. It happened to be the case. This network is depicted in Fig. 3 and we call it a branch-cycle network.

![Figure 3: branch-cycle CRN](image)

Clearly one gets a network with similar properties by relabeling the vertex 3 as 1 and vice versa. The equations for population evolution in this case are

$$\begin{align*}
\dot{x}_1 &= f_1 x_1 - p x_1 (r_1 + \beta r_2), \\
\dot{x}_2 &= f_2 x_2 - p x_2 (r_2 + \beta r_3), \\
\dot{x}_3 &= f_3 x_3 - p x_3 (\beta r_2 + r_3), \\
\dot{r}_1 &= c x_1 \frac{r_1}{r_1 + r_2} - br_1, \\
\dot{r}_2 &= c (x_1 \frac{r_2}{r_1 + r_2} + x_2 \frac{r_2}{r_2 + r_3} + x_3 \frac{r_2}{r_3 + r_2}) - br_2, \\
\dot{r}_3 &= c (x_2 \frac{r_3}{r_2 + r_1} + x_3 \frac{r_3}{r_3 + r_1}) - br_3.
\end{align*}$$
The fixed points of interest (i.e. all population values are non-negative, there is a local immunodeficiency, and the relations between system parameters are inequalities rather than equalities) are in this case

\[
x_1 = 0, x_2 = 0, x_3 = \frac{b f_1}{c p \beta}, r_1 = 0, r_2 = \frac{f_1}{p \beta}, r_3 = 0;
\]

\[
x_1 = \frac{b f_1}{c p \beta}, x_2 = 0, x_3 = 0, r_1 = 0, r_2 = \frac{f_1}{p \beta}, r_3 = 0;
\]

\[
f_3 > f_1, x_1 = \frac{b f_1}{c p \beta}(1 - \alpha), x_2 = 0, x_3 = \frac{b}{c p}(f_3 - f_1 + \frac{\alpha}{\beta} f_1), r_1 = 0, r_2 = \frac{f_1}{p \beta}, r_3 = \frac{f_3 - f_1}{p};
\]

\[
f_3 < f_1, x_1 = \frac{b}{c p}(f_1 - f_3 + \frac{\alpha}{\beta} f_3), x_2 = 0, x_3 = \frac{b f_3}{c p \beta}(1 - \alpha), r_1 = \frac{f_1 - f_3}{p}, r_2 = \frac{f_3}{p \beta}, r_3 = 0;
\]

\[
x_1 = \frac{b f_1}{c p}, x_2 = \frac{b f_2}{c p \beta}, x_3 = 0, r_1 = \frac{f_1}{p}, r_2 = 0, r_3 = \frac{f_2}{p \beta}.
\]

The Jacobian of the system is

\[
J = \begin{pmatrix}
  f_1 - p(r_1 + \beta r_2) & 0 & 0 & -p x_1 & -p \beta x_1 & 0 \\
  0 & f_2 - p(r_2 + \beta r_3) & 0 & 0 & -p x_2 & -p \beta x_2 \\
  \frac{c x_1 r_1}{r_1 + ar_2} & \frac{c x_2 r_2}{r_2 + ar_2} & \frac{c x_3 r_3}{r_3 + ar_2} & 0 & 0 & 0 \\
  0 & \frac{c x_2 r_2}{r_2 + ar_2} & \frac{c x_3 r_3}{r_3 + ar_2} & -\frac{c x_1 r_1}{(r_1 + ar_2)^2} & -\frac{c x_2 r_2}{(r_2 + ar_2)^2} & 0 \\
  0 & 0 & 0 & \frac{c x_3 r_3}{(r_3 + ar_2)^2} & A - b & -B \\
  A = \frac{c x_1 ar_1}{(r_1 + ar_2)^2} + \frac{c x_2 ar_2}{(r_2 + ar_2)^2} + \frac{c x_3 ar_3}{(ar_2 + r_3)^2} & B = \frac{c x_2 ar_2}{(r_2 + ar_2)^2} + \frac{c x_3 ar_3}{(ar_2 + r_3)^2} & 0 & 0 & 0 & 0
\end{pmatrix}
\]

At the fixed point \( x_3 = \frac{b f_3}{c p \beta}, x_1 = x_2 = 0, r_2 = \frac{f_1}{p \beta}, r_1 = r_3 = 0, \) we have

\[
A = 0, B = \frac{b}{\alpha}, J = \begin{pmatrix}
  f_1 - f_3 & 0 & 0 & 0 & 0 & 0 \\
  0 & f_2 - \frac{f_1}{\beta} & 0 & 0 & 0 & 0 \\
  0 & 0 & 0 & -\frac{b}{c} f_3 & -\frac{b}{c} f_3 & 0 \\
  0 & 0 & 0 & -b & 0 & 0 \\
  c & c & c & 0 & -b & \frac{b}{\alpha} \\
  0 & 0 & 0 & 0 & \frac{b}{\alpha} - b & 0
\end{pmatrix}
\]

Because \( \lambda = \frac{b}{\alpha} - b > 0 \) is an eigenvalue, this fixed point is unstable.

At the next fixed point \( x_1 = \frac{b f_1}{c p \beta}, x_2 = x_3 = 0, r_2 = \frac{f_1}{p \beta}, r_1 = r_3 = 0, \) we get

\[
A = B = 0, J = \begin{pmatrix}
  0 & 0 & 0 & \frac{b f_1}{c \beta} & -\frac{b}{c} f_1 & 0 \\
  0 & f_2 - \frac{f_1}{p} & 0 & 0 & 0 & 0 \\
  0 & 0 & f_3 - f_1 & 0 & 0 & 0 \\
  0 & 0 & 0 & \frac{b}{\alpha} - b & 0 & 0 \\
  c & c & c & -\frac{b}{\alpha} & -b & 0 \\
  0 & 0 & 0 & 0 & -b & 0
\end{pmatrix}
\]
Hence \( \lambda = \frac{b}{c} - b > 0 \) is an eigenvalue, and this fixed point is unstable.

At the fixed point \( x_1 = \frac{b f_1}{c p}, x_2 = \frac{b f_2}{c p g}, x_3 = 0, r_1 = \frac{f_1}{p}, r_3 = \frac{f_3}{p g}, r_2 = 0 \), we obtain

\[
A = ab + \frac{b}{\alpha}, B = 0, J = \begin{pmatrix}
0 & 0 & 0 & -\frac{b}{c} f_1 & -\frac{b}{c} \beta f_1 & 0 \\
0 & 0 & 0 & 0 & -\frac{b}{c} f_2 & -\frac{b}{c} f_2 \\
0 & 0 & f_3 - \frac{f_2}{p} & 0 & 0 & 0 \\
c & 0 & 0 & -b & -ab & 0 \\
0 & 0 & 0 & ab + \frac{b}{\alpha} - b & 0 & 0 \\
c & c & 0 & -\frac{b}{\alpha} & -b & 0
\end{pmatrix}.
\]

Then \( \lambda = ab + \frac{b}{\alpha} - b > 0 \) is an eigenvalue. Hence this fixed point is also unstable.

For the fixed point \( f_3 > f_1, x_1 = \frac{b f_1}{c p}(1 - \alpha), x_3 = \frac{b f_3}{c p}(f_3 - f_1 + \frac{b}{\alpha} f_1), x_2 = 0, r_2 = \frac{f_2}{p g}, r_3 = \frac{f_3}{p g}, r_1 = 0 \), we have

\[
A = ab \frac{f_3 - f_1}{f_3 - f_1 + \alpha/\beta f_1}, B = b \frac{\alpha/\beta f_1}{f_3 - f_1 + \alpha/\beta f_1},
\]

\[
J = \begin{pmatrix}
0 & 0 & 0 & -\frac{b}{c} f_1(1 - \alpha) & -\frac{b}{c} f_1(1 - \alpha) & 0 \\
0 & f_2 - \frac{f_1}{p} - \beta(f_3 - f_1) & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & -\frac{b}{c} f_3(1 - \alpha) & -\frac{b}{c} f_3(1 - \alpha) \\
c & c & \frac{f_1}{f_1 + \alpha/\beta f_1} & \frac{f_1}{f_1 + \alpha/\beta f_1} & \frac{f_1}{f_1 + \alpha/\beta f_1} & \frac{f_1}{f_1 + \alpha/\beta f_1} \\
c & c & \frac{f_1}{f_1 + \alpha/\beta f_1} & \frac{f_1}{f_1 + \alpha/\beta f_1} & \frac{f_1}{f_1 + \alpha/\beta f_1} & \frac{f_1}{f_1 + \alpha/\beta f_1} \\
0 & 0 & 0 & 0 & 0 & -A - B
\end{pmatrix}.
\]

Let \( D = f_3 - f_1 + \alpha/\beta f_1, \lambda_1 = f_2 - f_1/\beta - \beta(f_3 - f_1), \lambda_2 = b/\alpha - 2b \). Then

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

\[
P(\lambda) = b f_1(1 - \alpha)[\lambda^2 + (b - B)\lambda + \frac{AD}{\alpha}],
\]

\[
\lambda(b \beta D(\lambda + b - B) - AbD + (\lambda + b)[\lambda^2 + (b - B - A)\lambda + \frac{AD}{\alpha}(1 - \beta)]
\]

\[
= \lambda^4 + b(1 + \frac{1 - \alpha(f_3 - f_1)}{f_3 - f_1 + \alpha/\beta f_1})\lambda^3 + (b f_3 + b^2(1 - \alpha(f_3 - f_1))\frac{1}{f_3 - f_1 + \alpha/\beta f_1})\lambda^2 + b^2(1 - \alpha)(f_3 - f_1)(1 + \frac{f_1}{f_3 - f_1 + \alpha/\beta f_1})\lambda + b^2(1 - \alpha)f_3(f_3 - f_1).
\]

One can check that all coefficients of \( P(\lambda) \) are positive. It implies that \( P(\lambda) \) does not have real positive roots. So in this case a stable LI is possible. We list below a few exact values of the system parameters where stable local immunodeficiency is present.

1. \( f_1 = 1, f_2 = 3, f_3 = 4, b = 1, \alpha = 2/3, \beta = 4/9 \), we have \( \lambda_1 = -7/12 < 0, \lambda_2 = -1/2 < 0, P(\lambda) \) has 2 pairs of conjugate complex roots, both with negative real part.
2. \( f_1 = 1/4, f_2 = 1/2, f_3 = 1/2, b = 2, \alpha = 3/4, \beta = 9/16 \), we have \( \lambda_1 = -49/576 < 0, \lambda_2 = -4/3 < 0, P(\lambda) \) has 1 pair of conjugate complex roots with negative real part and 2 distinct negative real roots.

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It is easy to see that the roots of \( P(\lambda) \) depend continuously on the parameters. Moreover, the set of parameters for which the roots are real negative, or complex with negative real parts have strictly positive volume in the parameter space of the system. Therefore local immunodeficiency in this system remains a stable type of behavior under variation of the system’s parameters.

At the fixed point \( f_3 < f_1, x_1 = \frac{b}{e_p}(f_1 - f_3 + \frac{a}{p}f_3), x_3 = \frac{b_f}{e_p\beta}(1 - \alpha), x_2 = 0, r_1 = \frac{f_1 - f_3}{p}, r_2 = \frac{f_1}{p}, r_3 = 0 \), we have

\[
A = ab\frac{f_1 - f_3}{f_1 - f_3 + \alpha/\beta f_3}, B = \frac{b}{\alpha} - b,
\]

\[
J = \begin{pmatrix}
0 & 0 & 0 & -\frac{b}{e}\left(f_1 - f_3 + \frac{a}{p}f_3\right) & -\frac{b p}{e}\left(f_1 - f_3 + \frac{a}{p}f_3\right) & 0 \\
0 & f_2 - \frac{c f_1}{p} & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & -\frac{b}{e}\left(f_1 - f_3\right) \left(1 - \alpha\right) & -\frac{b}{e}\left(f_1 - f_3\right) \left(1 - \alpha\right) \\
\frac{c(f_1 - f_3)}{f_1 - f_3 + \alpha/\beta f_3} & 0 & 0 & \frac{b a/\beta f_3}{f_1 - f_3 + \alpha/\beta f_3} & -\frac{b}{e}\left(f_1 - f_3\right) \left(1 - \alpha\right) & 0 \\
\frac{f_1 - f_3 + \alpha/\beta f_3}{f_1 - f_3 + \alpha/\beta f_3} & c & c & -\frac{f_1 - f_3 + \alpha/\beta f_3}{f_1 - f_3 + \alpha/\beta f_3} & A - b & -B \\
0 & 0 & 0 & 0 & 0 & B - b
\end{pmatrix}.
\]

Let \( D = f_1 - f_3 + \alpha/\beta f_3, \lambda_1 = f_2 - f_3/\beta, \lambda_2 = b/\alpha - 2b \). Then

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

\[
P(\lambda) = bf_3\left(1 - \alpha\right)(\lambda^2 + \frac{A}{\alpha} \lambda + \frac{AD}{\alpha} + \lambda b)D
\]

\[
= \lambda^4 + b(1 + \frac{(1 - \alpha)(f_1 - f_3)}{f_1 - f_3 + \alpha/\beta f_3})\lambda^3 + (bf_1 + b^2(1 - \alpha)(f_1 - f_3)^2)\lambda^2
\]

\[
+ b^2(1 - \alpha)(f_1 - f_3)(1 + \frac{f_1}{f_1 - f_3 + \alpha/\beta f_3})\lambda + b^2(1 - \alpha)f_3(f_1 - f_3).
\]

At this point we also have that all coefficients of the polynomial \( P(\lambda) \) are positive.

Again we list below several numerical values for parameters of the model where stable local immunodeficiency occurs.

1. \( f_1 = 4, f_2 = 2, f_3 = 1, b = 1, \alpha = 2/3, \beta = 4/9 \), we get \( \lambda_1 = -1/4 < 0, \lambda_2 = -1/2 < 0 \). \( P(\lambda) \) here has 2 pairs of complex conjugate roots, both with negative real part.

2. \( f_1 = 1/2, f_2 = 1/4, f_3 = 1/4, b = 2, \alpha = 3/4, \beta = 9/16 \), then \( \lambda_1 = -7/36 < 0, \lambda_2 = -4/3 < 0 \). \( P(\lambda) \) has 1 pair of complex conjugate roots with negative real part, and 2 distinct negative real roots.

It follows by continuity that there are positive volume sets in the parameter space of the model where there is a stable (i.e. practically observable) fixed point with strong local immunodeficiency.

The last size 3 CRN we consider is a 3-cycle with no stable LI. The corresponding computations are given in the Appendix.
6. Coexistence: Building larger networks with stable & robust LI

In this section we demonstrate how one can construct CR networks with multiple strong local immunodeficiencies. We construct a CRN with several persistent viruses which remain hidden from the host’s immune system because they are protected by the altruistic viruses. To do this we put together two identical size 3 CR networks with stable LI found in the previous section. We prove that the corresponding size 5 CR network has two persistent viruses and two altruistic viruses. We also demonstrate the stability of strong local immunodeficiency for both persistent viruses. Consider the following network.

![Figure 4: size 5 CRN](image)

The model (I) equations for this network are

\[
\begin{align*}
\dot{x}_1 &= f_1 x_1 - p x_1 (r_1 + \beta r_2 + \beta r_4), \\
\dot{x}_2 &= f_2 x_2 - p x_2 (r_2 + \beta r_3), \\
\dot{x}_3 &= f_3 x_3 - p x_3 (\beta r_2 + r_3), \\
\dot{x}_4 &= f_4 x_4 - p x_4 (r_4 + \beta r_5), \\
\dot{x}_5 &= f_5 x_5 - p x_5 (\beta r_4 + r_5), \\
\dot{r}_1 &= c x_1 \frac{x_1}{r_1+ar_2+ar_4} - br_1, \\
\dot{r}_2 &= c x_2 \frac{x_2}{r_2+ar_3+ar_4} + x_3 \frac{x_3}{r_3+ar_2+ar_5} - br_2, \\
\dot{r}_3 &= c x_2 \frac{x_2}{r_2+ar_3+ar_4} + x_3 \frac{x_3}{r_3+ar_2+ar_5} - br_3, \\
\dot{r}_4 &= c x_2 \frac{x_2}{r_2+ar_3+ar_4} + x_3 \frac{x_3}{r_3+ar_2+ar_5} - br_4, \\
\dot{r}_5 &= c x_2 \frac{x_2}{r_2+ar_3+ar_4} + x_3 \frac{x_3}{r_3+ar_2+ar_5} - br_5.
\end{align*}
\]

Here we mirrored the chain-branch network about node 1. We want local immunodeficiencies at both ends of this network, in the form of \(x_5 > 0, r_5 = 0, x_4 = 0, r_4 > 0, x_1 > 0, r_1 > 0, x_2 = 0, r_2 > 0, x_3 > 0, r_3 = 0\). The corresponding fixed point is

\[
\begin{align*}
f_1 - f_3 - f_5 > 0, x_1 &= \frac{b}{cp}(f_1 - f_3 - f_5 + \frac{\alpha}{\beta} f_3 + \frac{\alpha}{\beta} f_5), r_1 = \frac{f_1 - f_3 - f_5}{p}, \\
x_2 = 0, r_2 &= \frac{f_3}{p\beta}, x_3 = \frac{b f_3}{cp\beta}(1 - \alpha), r_3 = 0, x_4 = 0, r_4 = \frac{f_5}{p\beta}, x_5 = \frac{b f_5}{cp\beta}(1 - \alpha), r_5 = 0.
\end{align*}
\]

The Jacobian is

\[
J = \begin{pmatrix}
A & B \\
C & D
\end{pmatrix},
\]

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$A = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & f_2 - pr_2 & 0 & 0 & 0 \\ 0 & 0 & 0 & f_4 - pr_4 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}, B = \begin{pmatrix} -px_1 & -p\beta x_1 & 0 & -p\beta x_1 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & -p\beta x_3 & -px_3 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -p\beta x_5 & -px_5 \end{pmatrix},$

$C = \begin{pmatrix} \frac{c_1}{r_1 + ar_2 + ar_4} & 0 & 0 & 0 & 0 \\ \frac{c_2}{r_1 + ar_2 + ar_4} & \frac{c_3}{r_1 + ar_2 + ar_4} & 0 & 0 & 0 \\ \frac{c_4}{r_1 + ar_2 + ar_4} & \frac{c_5}{r_1 + ar_2 + ar_4} & 0 & 0 & 0 \\ \frac{c_6}{r_1 + ar_2 + ar_4} & \frac{c_7}{r_1 + ar_2 + ar_4} & \frac{c_8}{r_1 + ar_2 + ar_4} & \frac{c_9}{r_1 + ar_2 + ar_4} & 0 \\ 0 & 0 & 0 & 0 & 0 \\ \end{pmatrix}, D = \begin{pmatrix} D_1 \\ D_2 \end{pmatrix},$

$D_1 = \begin{pmatrix} \frac{c_1 a (r_2 + r_1)}{(r_1 + ar_2 + ar_4)^2} - b \\ \frac{c_1 a}{(r_1 + ar_2 + ar_4)^2} - \frac{c_3 a}{(r_2 + ar_4)^2} - \frac{c_3 a}{(r_2 + ar_4)^2} - b \\ \frac{c_3 a}{(r_2 + ar_4)^2} - \frac{c_3 a}{(r_2 + ar_4)^2} - b \\ \frac{c_3 a}{(r_2 + ar_4)^2} - \frac{c_3 a}{(r_2 + ar_4)^2} - b \\ 0 \end{pmatrix}, D_2 = \begin{pmatrix} 0 \\ -\frac{c_3 a}{(r_1 + ar_2 + ar_4)^2} - \frac{c_3 a}{(r_1 + ar_2 + ar_4)^2} - b \\ \frac{c_3 a}{(r_1 + ar_2 + ar_4)^2} - \frac{c_3 a}{(r_1 + ar_2 + ar_4)^2} - b \\ \frac{c_3 a}{(r_1 + ar_2 + ar_4)^2} - \frac{c_3 a}{(r_1 + ar_2 + ar_4)^2} - b \\ 0 \end{pmatrix}.$

Let $\lambda_1 = f_2 - pr_2 = f_2 - f_3/\beta, \lambda_2 = f_4 - pr_4 = f_4 - f_5/\beta, \lambda_3 = b/\alpha - 2b$, then

$$\det(J - \lambda I) = (\lambda_1 - \lambda)(\lambda_2 - \lambda)(\lambda_3 - \lambda)^2 T(\lambda),$$
where
\[
T(\lambda) = \left(\frac{b^2 r_1}{c x_1} + pbr_1\right)[\lambda^2 + b(1 - \alpha)\lambda + cp\beta x_1][\lambda^2 + b(1 - \alpha)\lambda + cp\beta x_1]
\]
\[
+ \lambda^3[\lambda + b(1 - \alpha)][\lambda^2 + b(1 - \alpha)\lambda + \left(\frac{ba}{c}\lambda + p\beta x_1\right)\frac{b\alpha(r_2 + r_4)}{x_1}]
\]
\[
+ cp\beta x_3[\lambda^2 + b(1 - \alpha)\lambda + \frac{b\alpha r_2}{c}\frac{b\alpha r_4}{c}\lambda + p\beta x_1 + cp\beta x_3]
\]
\[
= \lambda^6 + \left[\frac{b^2 r_1}{c x_1}(1 - \alpha) + b(2 - \alpha)\right] \lambda^5 + b\left[f_1 + (1 - \alpha)\left[\frac{b^2 r_1}{c x_1}(2 - \alpha) + b\right]\right] \lambda^4
\]
\[
+ b^2(1 - \alpha)[2f_1 - f_3 - f_5 + \frac{b}{c x_1}[r_1(b(1 - \alpha) + f_3 + f_5) + 2\alpha^2 f_3 r_4]] \lambda^3
\]
\[
+ b^2(1 - \alpha)\left[\frac{b^2 r_1}{c x_1}(1 - \alpha)\left(f_3 + f_5\right) + pr_1[f_3 + f_5 + b(1 - \alpha)] + f_3 f_5(1 + \alpha)\right] \lambda^2
\]
\[
+ b^3(1 - \alpha)^2\left[\frac{br_1}{c x_1}f_3 f_5 + pr_1(f_3 + f_5)\right] \lambda + p b^3 r_1 f_3 f_5 (1 - \alpha)^3.
\]

Detailed computation of $T(\lambda)$ can be found in the Appendix. One can see that all the coefficients are positive, thus $T(\lambda)$ does not have real positive roots. Indeed we can easily find various groups of parameters for which our two LIs stably coexist. For instance, among them are the following two groups.

1. $f_1 = 3, f_2 = 2, f_3 = 1, f_4 = 2, f_5 = 1, b = 1, \alpha = 2/3, \beta = 4/9; \lambda_1 = -1/4 = \lambda_2 < 0, \lambda_3 = -1/2 < 0, T(\lambda)$ has 3 pairs of complex roots, all with negative real parts.

2. $f_1 = 4, f_2 = 1, f_3 = 2, f_4 = 1, f_5 = 1, b = 2, \alpha = 3/4, \beta = 9/16; \lambda_1 = -23/9 < 0, \lambda_2 = -7/9 < 0, \lambda_3 = -4/3 < 0, T(\lambda)$ has 3 pairs of complex roots, all with negative real parts.

By continuity there are positive measure sets in the parameter space where the LIs coexist stably.

7. Discussion

In this paper we proved that local immunodeficiency discovered in [1] is a stable and robust phenomenon which may appear already in cross-immunoreactivity networks with just three viruses (antigens). Moreover we rigorously demonstrated that it is easy to build larger networks with several elements (persistent viruses) which remain invisible to the host’s immune system because of their positions in the CR network. We also demonstrate that local immunodeficiency is a much more general phenomenon than it was assumed in [1]. Indeed a CR network need not to be scale-free as in [1] to produce local immunodeficiency; it should just have a non-homogeneous topology. Although our
results are built on exact computations for small networks, they leave actually no doubts about presence of stable and robust local immunodeficiency in large CR networks with heterogeneous topology of a general type.

Therefore local immunodeficiency is an ubiquitous phenomenon which likely will be present in all diseases demonstrating cross-immunoreactivity. Hence a public health strategy to fight such diseases should be focused on detecting and destroying altruistic viruses. It is a challenging task because these viruses have low in-host concentrations.

**Appendix A. Computation for symmetric size 2 CRN**

Consider the symmetric size 2 CRN below.

![Figure A.5: size 2 CRN (symmetric)]

The dynamics of this CRN is described by

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

Consider the fixed point with local immunodeficiency \( x_1 > 0, r_1 = 0, x_2 = 0, r_2 > 0 \). One can solve it to be

\[
x_1 = \frac{b f_1}{c \beta}, r_1 = 0, x_2 = 0, r_2 = \frac{f_1}{\beta}.
\]

The Jacobian of the system is

\[
J = \begin{pmatrix}
\frac{f_1 - p(r_1 + \beta r_2)}{r_1 + r_2} & 0 & -p x_1 & -p \beta x_1 \\
0 & \frac{f_2 - p(\beta r_1 + r_2)}{r_1 + r_2} & -p x_2 & -p x_2 \\
\frac{c x_1}{(r_1 + r_2)^2} & \frac{c x_2}{(r_1 + r_2)^2} & -\frac{c x_1}{(r_1 + r_2)^2} - \frac{c x_2}{(r_1 + r_2)^2} - b & -\frac{c x_1}{(r_1 + r_2)^2} - \frac{c x_2}{(r_1 + r_2)^2} - b
\end{pmatrix}
\]

\[
= \begin{pmatrix}
0 & 0 & -p x_1 & -p \beta x_1 \\
0 & f_2 - pr_2 & 0 & 0 \\
0 & 0 & \frac{b}{a} - b & 0 \\
c & c & -\frac{b}{a} - b & -b
\end{pmatrix}.
\]

\( \lambda = \frac{b}{a} - b > 0 \) is an eigenvalue, so the fixed point is unstable.
Appendix B. Computation for 3-cycle CRN

The last size three CRN we consider here for illustration is the 3-cycle network in Fig B.6.

The governing equations in this case are

\[
\begin{align*}
\dot{x}_1 &= f_1 x_1 - px_1 (r_1 + \beta r_2), \\
\dot{x}_2 &= f_2 x_2 - px_2 (r_2 + \beta r_3), \\
\dot{x}_3 &= f_3 x_3 - px_3 (r_3 + \beta r_1), \\
\dot{r}_1 &= c \left( x_1 \frac{r_1}{r_1+ar_2} + x_3 \frac{ar_1}{ar_1+ar_3} \right) - br_1, \\
\dot{r}_2 &= c \left( x_1 \frac{ar_2}{ar_1+ar_2} + x_2 \frac{r_2}{r_2+ar_3} \right) - br_2, \\
\dot{r}_3 &= c \left( x_2 \frac{r_2}{r_2+ar_3} + x_3 \frac{ar_3}{ar_1+ar_3} \right) - br_3.
\end{align*}
\]

The fixed points of interest are

\[
\begin{align*}
x_1 &= 0, x_2 = \frac{bf_2}{cp}, x_3 = \frac{bf_3}{cp\beta}, r_1 = \frac{f_3}{p\beta}, r_2 = \frac{f_2}{p}, r_3 = 0; \\
x_1 = \frac{bf_1}{cp\beta}, x_2 = 0, x_3 = \frac{bf_3}{cp}, r_1 = 0, r_2 = \frac{f_1}{p\beta}, r_3 = \frac{f_3}{p}; \\
x_1 = \frac{bf_1}{cp}, x_2 = \frac{bf_2}{cp\beta}, x_3 = 0, r_1 = \frac{f_1}{p}, r_2 = 0, r_3 = \frac{f_2}{p\beta}.
\end{align*}
\]

The Jacobian of the system equals

\[
J = \begin{pmatrix}
f_1 - p(r_1 + \beta r_2) & 0 & 0 & -px_1 & -p\beta x_1 & 0 \\
0 & f_2 - p(r_2 + \beta r_3) & 0 & 0 & -px_2 & -p\beta x_2 \\
\frac{c_1 r_1}{r_1+ar_2} & 0 & f_3 - p(r_3 + \beta r_1) & -p\beta x_3 & 0 & 0 \\
\frac{c_2 r_2}{r_2+ar_3} & \frac{c_3 r_3}{ar_1+ar_3} & A - b & \frac{-c_1 a r_1}{(r_1+ar_2)^3} & C - b \\
0 & \frac{c_2 r_2}{r_2+ar_3} & \frac{c_3 r_3}{ar_1+ar_3} & \frac{-c_1 a r_1}{(r_1+ar_2)^3} & B - b & \frac{-c_3 a r_3}{(r_2+ar_3)^3}
\end{pmatrix},
\]

where

\[
A = \frac{cx_1 a r_2}{(r_1 + ar_2)^2} + \frac{cx_3 a r_3}{(ar_1 + r_3)^2}, B = \frac{cx_1 a r_1}{(r_1 + ar_2)^2} + \frac{cx_2 a r_3}{(r_2 + ar_3)^2}, C = \frac{cx_2 a r_2}{(r_2 + ar_3)^2} + \frac{cx_3 a r_1}{(ar_1 + r_3)^2}.
\]
At the fixed point $x_1 = 0, x_2 = \frac{b f_1}{c p}, x_3 = \frac{b f_1}{c p^2}, r_1 = \frac{f_1}{p^2}, r_2 = \frac{f_1}{p}, r_3 = 0$, we have

$$A = B = 0, C = ab + \frac{b}{\alpha},$$

$$J = \begin{pmatrix} f_1 - \beta f_2 - \frac{b}{p} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -\frac{b}{c} f_2 & -\frac{b}{f_2} \\ 0 & 0 & 0 & -\frac{b}{c} f_3 & 0 & -\frac{b}{f_3} \\ \frac{c f_1}{f_3 + \alpha b f_3} & 0 & c & -b & 0 & -\alpha b \\ \frac{c f_2}{f_3 + \alpha b f_3} & 0 & c & 0 & -b & -\alpha b \\ 0 & 0 & 0 & 0 & \frac{b}{c} + \alpha b - b & \end{pmatrix}.$$  

Because $\lambda = ab + \frac{b}{\alpha} - b > 0$ is an eigenvalue, this point is unstable.

At the fixed point $x_1 = \frac{b f_1}{c p}, x_2 = 0, x_3 = \frac{b f_1}{c p^2}, r_1 = 0, r_2 = \frac{f_1}{p^2}, r_3 = \frac{f_1}{p}$, we obtain

$$A = \frac{b}{\alpha} + ab, B = C = 0,$$

$$J = \begin{pmatrix} 0 & 0 & 0 & -\frac{b f_1}{c p} & -\frac{b}{c} f_1 & 0 \\ 0 & f_2 - \frac{b}{p} - \beta f_3 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -\frac{b}{c} f_3 & 0 & -\frac{b}{f_3} \\ c & \frac{c f_1}{f_3 + \alpha b f_3} & 0 & -\frac{b}{c} & -b & 0 \\ 0 & \frac{c f_2}{f_3 + \alpha b f_3} & c & -\alpha b & 0 & -b \\ 0 & 0 & 0 & 0 & \frac{b}{c} + \alpha b - b & \end{pmatrix}.$$  

Again $\lambda = \frac{b}{\alpha} + ab - b > 0$ is an eigenvalue, and this fixed point is unstable.

At the fixed point $x_1 = \frac{b f_1}{c p}, x_2 = \frac{b f_1}{c p^2}, x_3 = 0, r_1 = \frac{f_1}{p}, r_2 = 0, r_3 = \frac{f_1}{p^2}$, we get analogously

$$A = 0, B = ab + \frac{b}{\alpha}, C = 0,$$

$$J = \begin{pmatrix} 0 & 0 & 0 & -\frac{b}{c} f_1 & -\frac{b}{c} f_1 & 0 \\ 0 & 0 & 0 & -\frac{b}{c} f_2 & -\frac{b}{c} f_2 & 0 \\ 0 & 0 & f_3 - \beta f_1 - \frac{b}{p} & 0 & 0 & 0 \\ c & \frac{c f_1}{f_3 + \alpha b f_3} & 0 & -b & -ab & 0 \\ 0 & \frac{c f_2}{f_3 + \alpha b f_3} & 0 & ab + \frac{b}{\alpha} - b & 0 & -b \\ 0 & c & \frac{c f_1}{f_3 + \alpha b f_3} & 0 & -\frac{b}{c} & -b \\ \end{pmatrix}.$$  

This fixed point is also unstable because $\lambda = ab + \frac{b}{\alpha} - b > 0$ is an eigenvalue.

It is not surprising that for a cyclic network there is no stable local immunodeficiency because this network is invariant with respect to rotations. Therefore it is a homogeneous network while the networks with local immunodeficiency are characterized by a strong non-homogeneity [$\text{[1]}$].
Appendix C. Size 4 mildly asymmetric networks: existence & stability of LI

The CR network we consider here is the following "T-shaped" network with four viruses.

![T-shaped network diagram]

Figure C.7: size 4 CRN

For this specific size 4 CR network, we want node 1 to be altruistic, i.e. \( x_1 = 0, r_1 > 0 \). Observe that the nodes 2, 3 and 4 are situated symmetrically. Without loss of generality we may assume that the node 2 is persistent while the nodes 3, 4 are neutral active, i.e. \( x_2 > 0, r_2 = 0, x_3 > 0, r_3 > 0, x_4 > 0, x_4 > 0 \).

The dynamical equations (1) assume the form

\[
\begin{align*}
\dot{x}_1 &= f_1 x_1 - p x_1 r_1, \\
\dot{x}_2 &= f_2 x_2 - p x_2 (\beta r_1 + r_2), \\
\dot{x}_3 &= f_3 x_3 - p x_3 (\beta r_1 + r_3), \\
\dot{x}_4 &= f_4 x_4 - p x_4 (\beta r_1 + r_4), \\
\dot{r}_1 &= c (x_1 + x_2 \frac{r_1}{ar_1+r_2} + x_3 \frac{r_1}{ar_1+r_3} + x_4 \frac{r_1}{ar_1+r_4}) - br_1, \\
\dot{r}_2 &= c x_2 \frac{r_2}{ar_1+r_2} - br_2, \\
\dot{r}_3 &= c x_3 \frac{r_3}{ar_1+r_3} - br_3, \\
\dot{r}_4 &= c x_4 \frac{r_4}{ar_1+r_4} - br_4.
\end{align*}
\]

Under assumptions \( f_2 < f_3, f_2 < f_4, \alpha < 1/2 \) (so that the population values are positive), we get the fixed point with local immunodeficiency:

\[
\begin{align*}
x_1 &= 0, r_1 = \frac{f_2}{p\beta}, x_2 = \frac{b f_2 (1 - 2\alpha)}{c p \beta}, r_2 = 0, \\
x_3 &= \frac{b}{c p} \left( \frac{\alpha}{\beta} f_2 + f_3 - f_2 \right), r_3 = \frac{f_3 - f_2}{p}, x_4 = \frac{b}{c p} \left( \frac{\alpha}{\beta} f_2 + f_4 - f_2 \right), r_4 = \frac{f_4 - f_2}{p}.
\end{align*}
\]

The corresponding Jacobian is,

\[
J = \begin{pmatrix} A & B \\ C & D \end{pmatrix},
\]

\[
A = \begin{pmatrix} f_1 - p r_1 & 0 & 0 & 0 \\ 0 & f_2 - p (\beta r_1 + r_2) & 0 & 0 \\ 0 & 0 & f_3 - p (\beta r_1 + r_3) & 0 \\ 0 & 0 & 0 & f_4 - p (\beta r_1 + r_4) \end{pmatrix} = \begin{pmatrix} f_1 - p r_1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix},
\]

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system's parameters assuming the following values

\[ B = \begin{pmatrix}
-px_1 & 0 & 0 & 0 \\
-p\beta x_2 & -px_2 & 0 & 0 \\
-p\beta x_3 & 0 & -px_3 & 0 \\
-p\beta x_4 & 0 & 0 & -px_4 \\
\end{pmatrix} = \begin{pmatrix}
0 & 0 & 0 & 0 \\
-p\beta x_2 & -px_2 & 0 & 0 \\
-p\beta x_3 & 0 & -px_3 & 0 \\
-p\beta x_4 & 0 & 0 & -px_4 \\
\end{pmatrix}, \]

\[ C = \begin{pmatrix}
c & \frac{c}{x_1} & \frac{c}{x_2} & \frac{c}{x_3} & \frac{c}{x_4} \\
0 & \frac{a}{x_1} & \frac{a}{x_2} & \frac{a}{x_3} & \frac{a}{x_4} \\
0 & 0 & \frac{a}{x_3} & \frac{a}{x_4} & \frac{a}{x_4} \\
0 & 0 & 0 & \frac{a}{x_4} & \frac{a}{x_4} \\
\end{pmatrix}, \]

\[ D = \begin{pmatrix}
\frac{a}{x_1} & \frac{a}{x_1} & \frac{a}{x_1} & \frac{a}{x_1} & \frac{a}{x_1} \\
\frac{b}{x_1} & \frac{b}{x_1} & \frac{b}{x_1} & \frac{b}{x_1} & \frac{b}{x_1} \\
\frac{c}{x_1} & \frac{c}{x_1} & \frac{c}{x_1} & \frac{c}{x_1} & \frac{c}{x_1} \\
\frac{d}{x_1} & \frac{d}{x_1} & \frac{d}{x_1} & \frac{d}{x_1} & \frac{d}{x_1} \\
\end{pmatrix}, \]

As an exact numerical example with a stable local immunodeficiency consider the system’s parameters assuming the following values \( b = c = p = 1, \alpha = 2/5, \beta = 4/25, f_1 = f_2 = 1, f_3 = f_4 = 2 \). One can compute the Jacobian numerically and see all the eigenvalues are either real negative or complex with negative real parts. It follows by continuity that there exists a positive measure set in the parameter space where this local immunodeficiency is stable.

**Appendix D. Detailed computation of \( T(\lambda) \)**

After column reduction, we get

\[
T(\lambda) = \begin{pmatrix}
-\lambda & 0 & 0 & -px_1 - \frac{b}{c} \lambda & -p\beta x_1 - \frac{ab}{c} \lambda & -p\beta x_1 - \frac{ab}{c} \lambda \\
0 & -\lambda & 0 & 0 & -p\beta x_3 & 0 \\
0 & 0 & -\lambda & 0 & 0 & -p\beta x_3 \\
0 & 0 & 0 & -\lambda & 0 & 0 \\
0 & 0 & 0 & 0 & -\lambda & 0 \\
0 & 0 & 0 & 0 & 0 & -\lambda \\
\end{pmatrix}.
\]

There are many zeros among these entries. Expanding along the rows or columns with the most number of 0s is the simplest way to compute the determinant. The following computation uses the expansion along the row that has the lowest index number among
all rows and columns with the most number of 0s.

\[
T(\lambda) = -\lambda
\]

\[
\begin{array}{cccccc}
-\lambda & 0 & -px_1 - \frac{b}{c} \lambda & -p\beta x_1 - \frac{ab}{c} \lambda & -p\beta x_1 - \frac{ab}{c} \lambda \\
0 & -\lambda & 0 & 0 & -p\beta x_1 \\
0 & 0 & -\lambda & 0 & 0 \\
c & 0 & 0 & 0 & \alpha b - b - \lambda \\
\end{array}
\]

\[
+ p\beta x_3
\]

\[
\begin{array}{cccccc}
-\lambda & 0 & -px_1 - \frac{b}{c} \lambda & -p\beta x_1 - \frac{ab}{c} \lambda \\
0 & 0 & -\lambda & 0 & -p\beta x_1 \\
c & 0 & 0 & 0 & 0 \\
\end{array}
\]

\[
= \lambda^2
\]

\[
-\lambda & 0 & -px_1 - \frac{b}{c} \lambda & -p\beta x_1 - \frac{ab}{c} \lambda \\
0 & -\lambda & 0 & 0 & -p\beta x_1 \\
c & 0 & 0 & 0 & \alpha b - b - \lambda
\]

\[
\]

\[
= \lambda^2
\]

\[
-\lambda & 0 & -px_1 - \frac{b}{c} \lambda & -p\beta x_1 - \frac{ab}{c} \lambda \\
0 & 0 & -\lambda & 0 & -p\beta x_1 \\
c & 0 & 0 & 0 & \alpha b - b - \lambda
\]

\[
-\lambda & -px_1 - \frac{b}{c} \lambda & -p\beta x_1 - \frac{ab}{c} \lambda \\
0 & \alpha b - b - \lambda & 0 & 0 & -p\beta x_1 \\
c & 0 & \alpha b - b - \lambda & 0 & \alpha b - b - \lambda
\]

\[
-\lambda & -px_1 - \frac{b}{c} \lambda & -p\beta x_1 - \frac{ab}{c} \lambda \\
0 & \alpha b - b - \lambda & 0 & 0 & -p\beta x_1 \\
c & 0 & \alpha b - b - \lambda & 0 & \alpha b - b - \lambda
\]

\[
-\lambda & -px_1 - \frac{b}{c} \lambda & -p\beta x_1 - \frac{ab}{c} \lambda \\
0 & \alpha b - b - \lambda & 0 & 0 & -p\beta x_1 \\
c & 0 & \alpha b - b - \lambda & 0 & \alpha b - b - \lambda
\]

\[
-\lambda & -px_1 - \frac{b}{c} \lambda \\
0 & \alpha b - b - \lambda & 0 & 0 & -p\beta x_1 \\
c & 0 & \alpha b - b - \lambda & 0 & \alpha b - b - \lambda
\]

\[
-\lambda & 0 & -px_1 - \frac{b}{c} \lambda \\
0 & \alpha b - b - \lambda & 0 & 0 & -p\beta x_1 \\
c & 0 & \alpha b - b - \lambda & 0 & \alpha b - b - \lambda
\]

\[
-\lambda & 0 & -px_1 - \frac{b}{c} \lambda \\
0 & \alpha b - b - \lambda & 0 & 0 & -p\beta x_1 \\
c & 0 & \alpha b - b - \lambda & 0 & \alpha b - b - \lambda
\]

\[
-\lambda & 0 & -px_1 - \frac{b}{c} \lambda \\
0 & \alpha b - b - \lambda & 0 & 0 & -p\beta x_1 \\
c & 0 & \alpha b - b - \lambda & 0 & \alpha b - b - \lambda
\]
= \lambda^2 \frac{br_1}{x_1} (p x_1 + \frac{b}{c}) (\lambda + b - ab)^2 \\
+ \lambda \left[ \frac{bar_2}{x_1} (p \beta x_1 + \frac{b \alpha}{c}) (\lambda + b - ab) + (\lambda + b - ab) (\lambda^2 + (b - ab) \lambda + (p \beta x_1 + \frac{b \alpha}{c}) \frac{bar_2}{x_1}) \right] \\
+ c p \beta x_3 \lambda \left[ \frac{br_1}{x_1} (p x_1 + \frac{b}{c}) (\lambda + b - ab) + \lambda [ \lambda^2 + (b - ab) \lambda + (p \beta x_1 + \frac{b \alpha}{c}) \frac{bar_1}{x_1}) \right] \\
+ c p \beta x_3 \lambda \left[ \frac{br_1}{x_1} (p x_1 + \frac{b}{c}) (\lambda + b - ab) + \lambda [ \lambda^2 + (b - ab) \lambda + (p \beta x_1 + \frac{b \alpha}{c}) \frac{bar_1}{x_1}) \right] \\
+ c^2 p^2 \beta^2 x_3 x_5 (\lambda^2 + \frac{b^2 r_1}{c x_1} \lambda + p b r_1) \\
= \lambda^2 \frac{br_1}{x_1} (p x_1 + \frac{b}{c}) (\lambda + b - ab)^2 \\
+ \lambda \left[ \frac{bar_2}{x_1} (p \beta x_1 + \frac{b \alpha}{c}) (\lambda + b - ab) + (\lambda + b - ab) (\lambda^2 + (b - ab) \lambda + (p \beta x_1 + \frac{b \alpha}{c}) \frac{bar_2}{x_1}) \right] \\
+ c p \beta x_3 \lambda \left[ \frac{br_1}{x_1} (p x_1 + \frac{b}{c}) (\lambda + b - ab) + \lambda [ \lambda^2 + (b - ab) \lambda + (p \beta x_1 + \frac{b \alpha}{c}) \frac{bar_1}{x_1}) \right] \\
+ c^2 p^2 \beta^2 x_3 x_5 (\lambda^2 + \frac{b^2 r_1}{c x_1} \lambda + p b r_1) \\
= \lambda^2 \frac{br_1}{x_1} (p x_1 + \frac{b}{c}) (\lambda + b - ab)^2 \\
+ \lambda \left[ \frac{bar_2}{x_1} (p \beta x_1 + \frac{b \alpha}{c}) (\lambda + b - ab) + (\lambda + b - ab) (\lambda^2 + (b - ab) \lambda + (p \beta x_1 + \frac{b \alpha}{c}) \frac{bar_2}{x_1}) \right] \\
+ c p \beta x_3 \lambda \left[ \frac{br_1}{x_1} (p x_1 + \frac{b}{c}) (\lambda + b - ab) + \lambda [ \lambda^2 + (b - ab) \lambda + (p \beta x_1 + \frac{b \alpha}{c}) \frac{bar_1}{x_1}) \right] \\
+ c^2 p^2 \beta^2 x_3 x_5 (\lambda^2 + \frac{b^2 r_1}{c x_1} \lambda + p b r_1) \\
= \lambda^2 \frac{br_1}{x_1} (p x_1 + \frac{b}{c}) (\lambda + b - ab)^2 \\
+ \lambda \left[ \frac{bar_2}{x_1} (p \beta x_1 + \frac{b \alpha}{c}) (\lambda + b - ab) + (\lambda + b - ab) (\lambda^2 + (b - ab) \lambda + (p \beta x_1 + \frac{b \alpha}{c}) \frac{bar_2}{x_1}) \right] \\
+ c p \beta x_3 \lambda \left[ \frac{br_1}{x_1} (p x_1 + \frac{b}{c}) (\lambda + b - ab) + \lambda [ \lambda^2 + (b - ab) \lambda + (p \beta x_1 + \frac{b \alpha}{c}) \frac{bar_1}{x_1}) \right] \\
+ c^2 p^2 \beta^2 x_3 x_5 (\lambda^2 + \frac{b^2 r_1}{c x_1} \lambda + p b r_1).

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References

[1] P. Skums, L. Bunimovich, Y. Khudyakov, Antigenic cooperation among intrahost HCV variants organized into a complex network of cross-immunoreactivity, Proceedings of the National Academy of Sciences of the United States of America 112 (21) (2015) 6653-6658.
[2] M. Hattori, K. Yashioka, T. Aiyama, K. Iwata, Y. Terazawa, M. Ishigami, M. Yano, S. Kakumu, 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) (1998) 1703-1710.

[3] D. S. Campo, Z. Dimitrova, L. Yamasaki, P. Skums, D. T. Lau, G. Vaughan, J. C. Forbi, C.-G. Teo, Y. Khudyakov, Next-generation sequencing reveals large connected networks of intra-host HCV variants, BMC Genomics 15 (Suppl 5) (2014) S4.

[4] M. A. Nowak, R. M. May, Virus Dynamics: Mathematical Principles of Immunology and Virology, Oxford University Press, 2000.

[5] K. Yoshioka, T. Aiyama, A. Okumura, M. Takayanagi, K. Iwata, T. Ishikawa, Y. Nagai, S. Kakumu, Humoral Immune Response to the Hypervariable Region of Hepatitis C Virus Differs between Genotypes 1b and 2a, The Journal of Infectious Diseases 175 (3) (1997) 505-510.

[6] D. Wodarz, Hepatitis C virus dynamics and pathology: the role of CTL and antibody responses, Journal of General Virology 84 (Pt 7) (2013) 1743-1750.

[7] M. A. Nowak, R. M. May, R. M. Anderson, The evolutionary dynamics of HIV-1 quasispecies and the development of immunodeficiency disease, AIDS 4 (11) (1990) 1095-1103.

[8] M. A. Nowak, R. M. May, Mathematical biology of HIV infections: antigenic variation and diversity threshold, Mathematical Biosciences, 106 (1) (1991) 1-21.

[9] M. A. Nowak, R. M. Anderson, A. R. Mclean, R. M. May, Antigenic Diversity Thresholds and the Development of AIDS, Science 254 (5034) (1991) 963-969.

[10] T. Francis, Jr., On the Doctrine of Original Antigenic Sin, Proceedings of the American Philosophical Society 104 (6) (1960) 572-578.

[11] K. Pan, Understanding Original Antigenic Sin in Influenza with a Dynamical System, PLoS ONE 6 (8) (2011) e23910.

[12] B. Rehermann, E.-C. Shin, Private aspects of heterologous immunity, Journal of Experimental Medicine 201 (5) (2005) 667-670.

[13] M. S. Parsons, S. Muller, H. Kholer, M. D. Grant, N. F. Bernard, On the benefits of sin:Can greater understanding of the 1F7-idiotypic repertoire freeze enhance HIV vaccine development?, Human Vaccines and Immunotherapeutics 9 (7) (2013) 1532-1538.

[14] J. H. Kim, I. Skountzou, R. Compan, J. Jacob, Original Antigenic Sin Responses to Influenza Viruses, J Immunol 183 (5) (2009) 3294-3301.

[15] C. M. Midgley, M. Bajwa-Joseph, S. Vasanawathana, W. Limpitikul, B. Wills, A. Flanagan, E. Waiyiya, H. B. Tran, A. E. Cowper, P. Chotiyarnwon, J. M. Grimes, S. Yoksan, P. Malasit, C. P. Simmons, J. Mongkolsapaya, G. R. Screaton, An In-Depth Analysis of Original Antigenic Sin in Dengue Virus Infection, Journal of Virology 85 (1) (2011) 410-421.