TOPICS IN DYNAMICAL SYSTEMS

A Dissertation
Presented to
The Academic Faculty

By

Longmei Shu

In Partial Fulfillment
of the Requirements for the Degree
Doctor of Philosophy in the
School of Mathematics

Georgia Institute of Technology

August 2019

TOPICS IN DYNAMICAL SYSTEMS

Approved by:

Dr. Bunimovich, Advisor
School of Mathematics
Georgia Institute of Technology

Dr. Rafael De La Llave
School of Mathematics
Georgia Institute of Technology

Dr. Christine Heitsch
School of Mathematics
Georgia Institute of Technology

Dr. Plamen Iliev
School of Mathematics
Georgia Institute of Technology

Dr. Alexander Alexeev
School of Mechanical Engineering
Georgia Institute of Technology

Date Approved: June 5, 2019

Mathematics is the queen of the sciences.

Carl Friedrich Gauss

To Georgia Tech.

ACKNOWLEDGEMENTS

I would like to thank my supervisor Professor Bunimovich and coadvisor Professor Webb for their guidance in research. I would also like to thank Professor De La Llave for his help throughout my PhD studies. I am grateful to my classmates and friends who have made my time at Georgia Tech enjoyable. I am also grateful to the professors who have taught me and inspired me.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

SUMMARY

The thesis consists of two parts. the first one is dealing with isosspectral transformations and the second one with the phenomenon of local immunodeficiency.

Isospectral transformations (IT) of matrices and networks allow for compression of either object while keeping all the information about their eigenvalues and eigenvectors. Chapter 1 [1] analyzes what happens to generalized eigenvectors under isospectral transformations and to what extent the initial network can be reconstructed from its compressed image under IT. We also generalize and essentially simplify the proof that eigenvectors are invariant under isospectral transformations and generalize and clarify the notion of spectral equivalence of networks.

In the recently developed theory of isospectral transformations of networks isospectral compressions are performed with respect to some chosen characteristics (attributes) of the network's nodes (edges). Each isospectral compression (when a certain characteristic is fixed) defines a dynamical system on the space of all networks. Chapter 2 [2] shows that any orbit of this dynamical system which starts at any finite network (as the initial point of this orbit) converges to an attractor. This attractor is a smaller network where the chosen characteristic has the same value for all nodes (or edges). We demonstrate that isospectral compressions of one and the same network defined by different characteristics of nodes (or edges) may converge to the same as well as to different attractors. It is also shown that a collection of networks may be spectrally equivalent with respect to some network characteristic but nonequivalent with respect to another. These results suggest a new constructive approach which allows to analyze and compare the topologies of different networks.

Some basic aspects of the recently discovered phenomenon of local immunodeficiency [3] generated by antigenic cooperation in cross-immunoreactivity (CR)

networks are investigated in chapter 3 [4]. We prove that stable with respect to perturbations local immunodeficiency (LI) already occurs in very small networks and under general conditions on their parameters. Therefore our results are applicable not only to Hepatitis C where CR networks are known to be large [3], but also to other diseases with CR. A major necessary feature of such networks is the non-homogeneity of their topology. It is also shown that one can construct larger CR networks with stable LI by using small networks with stable LI as their building blocks. Our results imply that stable LI occurs in networks with quite general topologies. In particular, the scale-free property of a CR network, assumed in [3], is not required.

CHAPTER 1

GENERALIZED EIGENVECTORS OF ISOSPECTRAL TRANSFORMATIONS, SPECTRAL EQUIVALENCE AND RECONSTRUCTION OF ORIGINAL NETWORKS

1.1 Introduction

The recently developed theory of Isospectral Transformations (IT) of matrices and networks allowed for advances in various areas and led to several surprising results [5]. The effectiveness of these applications raises a natural question regarding the possible limits of this approach. Although the theory of isospectral transformations was initially aimed at reduction (i.e. simplification) of networks while keeping all the information about the spectrum of their weighted adjacency, Laplace, or other matrices generated by a network, it turned out [6] that all the information about the eigenvectors of these matrices also gets preserved under ITs.

Therefore it is natural to ask what network information may not be preserved after isospectral compression. The main goal of the present paper is to answer this question. It is shown that generalized eigenvectors typically are not preserved under ITs. We also establish some sufficient conditions under which the information about generalized eigenvectors is preserved under ITs. Some new properties of ITs are found, regarding classes of spectrally equivalent matrices and networks. Particularly it is demonstrated that there are essential differences between the standard notion of isospectral matrices and spectral equivalence of networks. A new proof of the preservation of eigenvectors under ITs is given which is shorter and applicable to a more general situation than the one in [6].

1.2 Isospectral Graph Reductions

In this section we recall definitions of the isospectral transformations of graphs and networks.

Let $\mathbb{W}$ be the set of rational functions of the form $w(\lambda) = p(\lambda)/q(\lambda)$, where $p(\lambda), q(\lambda) \in \mathbb{C}[\lambda]$ are polynomials having no common linear factors, i.e., no common roots, and where $q(\lambda)$ is not identically zero. $\mathbb{W}$ is a field under addition and multiplication [5].

Let $\mathbb{G}$ be the class of all weighted directed graphs with edge weights in $\mathbb{W}$. More precisely, a graph $G \in \mathbb{G}$ is an ordered triple $G = (V, E, w)$ where $V = \{1, 2, \ldots, n\}$ is the *vertex set*, $E \subset V \times V$ is the set of *directed edges*, and $w : E \to \mathbb{W}$ is the *weight function*. Denote by $M_G = (w(i, j))_{i,j \in V}$ the *weighted adjacency matrix* of G, with the convention that $w(i, j) = 0$ whenever $(i, j) \notin E$. We will alternatively refer to graphs as networks because weighted adjacency matrices define all static (i.e. non evolving) real world networks.

Observe that the entries of M_G are rational functions. Let's write $M_G(\lambda)$ instead of M_G here to emphasize the role of λ as a variable. For $M_G(\lambda) \in \mathbb{W}^{n \times n}$, we define the spectrum, or multiset of eigenvalues to be

$$\sigma(M_G(\lambda)) = \{\lambda \in \mathbb{C} : \det(M_G(\lambda) - \lambda I) = 0\}.$$

Notice that $\sigma(M_G(\lambda))$ can have more than n elements, some of which can be the same.

Throughout the rest of the paper, the spectrum is understood to be a set that includes multiplicities. The element α of the multiset A has multiplicity m if there are m elements of A equal to α. If $\alpha \in A$ with multiplicity m and $\alpha \in B$ with multiplicity n, then

(i) the union $A \cup B$ is a multiset in which α has multiplicity $m + n$; and

(ii) the difference $A - B$ is a multiset in which α has multiplicity $m-n$ if $m-n > 0$ and where $\alpha \notin A - B$ otherwise.

Similarly, the multiset $A \subset B$ means for any $\alpha \in A$, we have $\alpha \in B$, and the multiplicity of α in A, is less than or equal to the mutliplicity of α in B.

An eigenvector for eigenvalue $\lambda_0 \in \sigma(M_G(\lambda))$ is defined to be $u \in \mathbb{C}^n, u \neq 0$ such that

$$M_G(\lambda_0)u = \lambda_0 u.$$

One can see the eigenvectors of $M_G(\lambda) \in \mathbb{W}^{n\times n}$ for λ_0 are the same as the eigenvectors of $M_G(\lambda_0) \in \mathbb{C}^{n\times n}$ for λ_0. Similarly the generalized eigenvectors of $M_G(\lambda)$ for λ_0 are the generalized eigenvectors of $M_G(\lambda_0)$ for λ_0.

A path $\gamma = (i_0, \ldots, i_p)$ in the graph $G = (V, E, w)$ is an ordered sequence of distinct vertices $i_0, \ldots, i_p \in V$ such that $(i_l, i_{l+1}) \in E$ for $0 \leq l \leq p-1$. The vertices $i_1, \ldots, i_{p-1} \in V$ of γ are called *interior vertices*. If $i_0 = i_p$ then γ is a *cycle*. A cycle is called a *loop* if $p = 1$ and $i_0 = i_1$. The length of a path $\gamma = (i_0, \ldots, i_p)$ is the integer p. Note that there are no paths of length 0 and that every edge $(i, j) \in E$ is a path of length 1.

If $S \subset V$ is a subset of all the vertices, we will write $\overline{S} = V \setminus S$ and denote by $|S|$ the cardinality of the set S.

Definition 1. *(structural set).* Let $G = (V, E, w) \in \mathbb{G}$. A nonempty vertex set $S \subset V$ is a structural set of G if

- each cycle of G, that is not a loop, contains a vertex in S;
- $w(i, i) \neq \lambda$ for each $i \in \overline{S}$.

S is called a λ_0–structural set if a structural set S also satisfies $w(i, i) \neq \lambda_0, \forall i \in \overline{S}$ for some $\lambda_0 \in \mathbb{C}$.

Definition 2. Given a structural set S, a *branch* of (G, S) is a path $\beta = (i_0, i_1, \ldots, i_{p-1}, i_p)$ such that $i_0, i_p \in V$ and all $i_1, \ldots, i_{p-1} \in \overline{S}$.

We denote by $\mathcal{B} = \mathcal{B}_{G,S}$ the set of all branches of (G, S). Given vertices $i, j \in V$, we denote by $\mathcal{B}_{i,j}$ the set of all branches in $\mathcal{B}$ that start in i and end in j. For each branch $\beta = (i_0, i_1, \ldots, i_{p-1}, i_p)$ we define the *weight* of β as follows:

$$w(\beta, \lambda) := w(i_0, i_1) \prod_{l=1}^{p-1} \frac{w(i_l, i_{l+1})}{\lambda - w(i_l, i_l)}. \tag{1.1}$$

Given $i, j \in V$ set

$$R_{i,j}(G, S, \lambda) := \sum_{\beta \in \mathcal{B}_{i,j}} w(\beta, \lambda). \tag{1.2}$$

Definition 3. *(Isospectral reduction).* Given $G \in \mathbb{G}$ and a structural set S, the reduced adjacency matrix $R_S(G, \lambda)$ is the $|S| \times |S|$−matrix with the entries $R_{i,j}(G, S, \lambda), i, j \in S$. This adjacency matrix $R_S(G, \lambda)$ on S defines the reduced graph which is the isospectral reduction of the original graph G.

1.3 Generalized eigenvectors of isospectral graph reductions

Let λ_0 be an eigenvalue of $M_G(\lambda)$ with multiplicity at least 2, and let $u = (u_1, u_2, \ldots, u_n) \in \mathbb{C}^n$ be the corresponding eigenvector, i.e. $M_G(\lambda_0)u = \lambda_0 u$. Let $v = (v_1, v_2, \ldots, v_n) \in \mathbb{C}^n$ be the corresponding rank 2 generalized eigenvector, i.e. $M_G(\lambda_0)v - \lambda_0 v = u$. Without any loss of generality we may assume that $S = \{m + 1, \ldots, n\}$ is a λ_0−structural set . It is known that λ_0 is also an eigenvalue of $R_S(G, \lambda)$, i.e. $R_S(G, \lambda_0)u_S = \lambda_0 u_S$, where $u_S = (u_{m+1}, \ldots, u_n)$ is the restriction of u to S. We will refer to this property from now on as the preservation of eigenvectors. Our goal in this section is to see what happens to generalized eigenvectors under isospectral transformations.

Theorem 1. Let S be a λ_0−structural set of a graph $G = (V, E, w)$. $M_G(\lambda)$ is the adjacency matrix of G. $u, v \in \mathbb{C}^n$ are the eigenvector and generalized eigenvector for $M_G(\lambda)$ such that $M_G(\lambda_0)u = \lambda_0 u, M_G(\lambda_0)v - \lambda_0 v = u$. Then if there is a $c \in \mathbb{C}$ such that $c \neq -1$ and

$$\sum_{l \in \overline{S}} \frac{R_{il}(\lambda_0)}{\lambda_0 - \omega(l,l)} u_l = c u_i, \forall i \in S, \tag{1.3}$$

then $R_S(G, \lambda_0) v_S - \lambda_0 v_S = (1 + c) u_S$.

We first introduce some useful notations before proceeding to the proof of theorem 1.

Given vertices $i, j \in V$, we denote by $\mathcal{B}_{i,j}^{(p)}$ the set of all branches in $\mathcal{B}$ of length p that start at i and end at j. For any $i, j \in V$ set

$$R_{i,j}^{(p)}(G, S, \lambda) := \sum_{\beta \in \mathcal{B}_{i,j}^{(p)}} w(\beta, \lambda).$$

Therefore the reduced weights $R_{i,j}(G, S, \lambda)$ for $S = \{m+1, \ldots, n\}$ satisfy

$$R_{i,j}(G, S, \lambda) = \sum_{p=1}^{m+1} R_{i,j}^{(p)}(G, S, \lambda), \forall i, j \in S.$$

$$R_{i,j}(G, S, \lambda) = \sum_{p=1}^{m-1} R_{i,j}^{(p)}(G, S, \lambda), \forall i, j \in \overline{S}, i \neq j.$$

$$R_{i,i}(G, S, \lambda) = w(i, i), \forall i \in \overline{S}.$$

$$R_{i,j}(G, S, \lambda) = \sum_{p=1}^{m} R_{i,j}^{(p)}(G, S, \lambda), \forall i \in S, j \in \overline{S} \text{ or } i \in \overline{S}, j \in S.$$

To simplify notations we will write $R_{i,j}$ and $R_{i,j}^{(p)}$ instead of $R_{i,j}(G, S, \lambda_0)$ and $R_{i,j}^{(p)}(G, S, \lambda_0)$, respectively.

Proof. Write $v = (v_{\overline{S}}, v_S)$, where $v_{\overline{S}} = (v_l)_{l \in \overline{S}}$ and $v_S = (v_i)_{i \in S}$. Since $M_G(\lambda_0) v = \lambda_0 v + u$, we have for all $l \in \overline{S}$, (for convenience, all $w(i, j)$ mean $w(i, j)(\lambda_0)$ in the proof)

$$\sum_{k \in S} \omega(l, k) v_k + \omega(l, l) v_l + \sum_{l_1 \in \overline{S}, l_1 \neq l} \omega(l, l_1) v_{l_1} = \lambda_0 v_l + u_l.$$

Therefore,

$$v_l = \sum_{k\in S} \frac{\omega(l,k)}{\lambda_0 - \omega(l,l)} v_k + \sum_{l_1\in \overline{S}, l_1\neq l} \frac{\omega(l,l_1)}{\lambda_0 - \omega(l,l)} v_{l_1} - \frac{u_l}{\lambda_0 - \omega(l,l)}. \tag{1.4}$$

Analogously for all $i \in S$,

$$v_i = \sum_{k\in S, k\neq i} \frac{\omega(i,k)}{\lambda_0 - \omega(i,i)} v_k + \sum_{l\in \overline{S}} \frac{\omega(i,l)}{\lambda_0 - \omega(i,i)} v_l - \frac{u_i}{\lambda_0 - \omega(i,i)}.$$

Substituting v_l's above by (1.4) gives,

$$\begin{aligned}
v_i &= \sum_{k\in S, k\neq i} \frac{R^{(1)}_{ik}}{\lambda_0 - \omega(i,i)} v_k + \sum_{k\in S, l\in \overline{S}} \frac{\omega(i,l)\omega(l,k)}{[\lambda_0 - \omega(i,i)][\lambda_0 - \omega(l,l)]} v_k \\
&+ \sum_{l_1, l\in \overline{S}, l_1\neq l} \frac{\omega(i,l)\omega(l,l_1)}{[\lambda_0 - \omega(i,i)][\lambda_0 - \omega(l,l)]} v_{l_1} - \sum_{l\in \overline{S}} \frac{\omega(i,l)}{[\lambda_0 - \omega(i,i)][\lambda_0 - \omega(l,l)]} u_l \\
&- \frac{u_i}{\lambda_0 - \omega(i,i)} \\
&= \sum_{k\in S, k\neq i} \frac{R^{(1)}_{ik}}{\lambda_0 - \omega(i,i)} v_k + \sum_{k\in S} \frac{R^{(2)}_{ik}}{\lambda_0 - \omega(i,i)} v_k + \sum_{l_1, l\in \overline{S}} \frac{\omega(i,l)\omega(l,l_1)}{[\lambda_0 - \omega(i,i)][\lambda_0 - \omega(l,l)]} v_{l_1} \\
&- \sum_{l\in \overline{S}} \frac{\omega(i,l)}{[\lambda_0 - \omega(i,i)][\lambda_0 - \omega(l,l)]} u_l - \frac{u_i}{\lambda_0 - \omega(i,i)}.
\end{aligned}$$

Proceeding inductively, we get

$$\begin{aligned}
v_i &= \sum_{k\in S, k\neq i} \frac{R^{(1)}_{ik}}{\lambda_0 - \omega(i,i)} v_k + \sum_{k\in S} \frac{R^{(2)}_{ik}}{\lambda_0 - \omega(i,i)} v_k + \cdots + \sum_{k\in S} \frac{R^{(p)}_{ik}}{\lambda_0 - \omega(i,i)} v_k \\
&+ \sum_{l_1,\ldots,l_{p-1}, l\in \overline{S}, l_r\neq l_s, l_s\neq l} \frac{\omega(i,l)\omega(l,l_1)\omega(l_1,l_2)\ldots\omega(l_{p-2},l_{p-1})}{[\lambda_0 - \omega(i,i)][\lambda_0 - \omega(l,l)][\lambda_0 - \omega(l_1,l_1)]\ldots[\lambda_0 - \omega(l_{p-2},l_{p-2})]} v_{l_{p-1}} \\
&- \sum_{l_{p-2}\in \overline{S}} \frac{R^{(p-1)}_{il_{p-2}}}{[\lambda_0 - \omega(i,i)][\lambda_0 - \omega(l_{p-2},l_{p-2})]} u_{l_{p-2}} - \sum_{l_{p-3}\in \overline{S}} \frac{R^{(p-2)}_{il_{p-3}}}{[\lambda_0 - \omega(i,i)][\lambda_0 - \omega(l_{p-3},l_{p-3})]} u_{l_{p-3}} - \ldots \\
&- \sum_{l\in \overline{S}} \frac{R^{(1)}_{il}}{[\lambda_0 - \omega(i,i)][\lambda_0 - \omega(l,l)]} u_l - \frac{u_i}{\lambda_0 - \omega(i,i)}.
\end{aligned}$$

The indices in the sums above which are in $\overline{S}$ are all distinct; because there are no non-loop cycles in $\overline{S}$. Since $\overline{S}$ has m elements, after $m+1$ steps we obtain the relation

$$v_i = \sum_{k\in S, k\neq i} \frac{R_{ik}^{(1)}}{\lambda_0 - \omega(i,i)} v_k + \sum_{k\in S} \frac{R_{ik}^{(2)}}{\lambda_0 - \omega(i,i)} v_k + \cdots + \sum_{k\in S} \frac{R_{ik}^{(m+1)}}{\lambda_0 - \omega(i,i)} v_k$$
$$- \sum_{l_{m-1}\in\overline{S}} \frac{R_{il_{m-1}}^{(m)}}{[\lambda_0 - \omega(i,i)][\lambda_0 - \omega(l_{m-1}, l_{m-1})]} u_{l_{m-1}} - \sum_{l_{m-2}\in\overline{S}} \frac{R_{il_{m-2}}^{(m-1)}}{[\lambda_0 - \omega(i,i)][\lambda_0 - \omega(l_{m-2}, l_{m-2})]} u_{l_{m-2}}$$
$$- \cdots - \sum_{l\in\overline{S}} \frac{R_{il}^{(1)}}{[\lambda_0 - \omega(i,i)][\lambda_0 - \omega(l,l)]} u_l - \frac{u_i}{\lambda_0 - \omega(i,i)}.$$

Therefore,

$$[\lambda_0 - \omega(i,i)]v_i + \sum_{l\in\overline{S}} \frac{R_{il}}{\lambda_0 - \omega(l,l)} u_l + u_i = \sum_{k\in S, k\neq i} R_{ik} v_k + \sum_{p=2}^{m+1} R_{ii}^{(p)} v_i,$$

$$\lambda_0 v_i + u_i + \sum_{l\in\overline{S}} \frac{R_{il}}{\lambda_0 - \omega(l,l)} u_l = \sum_{k\in S} R_{ik} v_k.$$

And finally,

$$\sum_{k\in S} R_{ik} v_k - \lambda_0 v_i = (1+c) u_i, \forall i \in S,$$

which implies

$$R_S(G, \lambda_0) v_S = \lambda_0 v_S + (1+c) u_S.$$

□

We say that the generalized eigenvector v is preserved if relation (1.3) holds. Indeed it is easy to see in this case that the projection of the generalized eigenvector to S is a generalized eigenvector for the reduced adjacency matrix.

Remark 1. Observe that we didn't use anywhere in this proof the fact that u is an eigenvector. Therefore the same proof is readily applicable to generalized eigenvectors of higher ranks. One just needs to use the rank k generalized eigenvector in place of u and the rank $k+1$ generalized eigenvector in place of v.

Remark 2. The proof is very similar to the one given in [6]. However, we allow the weights of the original graph to take rational functions. One can check the requirement in [6] for the weights to be complex numbers before reduction is not necessary for the proof to work. Also the weights of the reduced graph are rational functions instead of complex numbers only. The result in [6] would only apply to the 1st reduction, even though the preservation of eigenvectors carries through a sequence of reductions (this will be further discussed in the next section).

Clearly the complement to a single vertex is a structural set of a network (graph). The following statement demonstrates that by isospectrally removing a single element (vertex) of a network (graph) one gets a much simpler condition than in Theorem 1.

Theorem 2. Let $G = (V, E, w) \in \mathbb{G}$ be a graph with n nodes and with adjacency matrix $M_G(\lambda)$. Let $\lambda_0 \in \sigma(M_G(\lambda))$ be a repeated eigenvalue and let $S \subset V$ be a λ_0−structural set which has $n-1$ nodes. Suppose $\overline{S} = V \setminus S = \{j\}$. Then the generalized eigenvector is preserved iff $\omega(i, j) = cu_i, \forall i \in S$ for some $c \in \mathbb{C}$ where u is an eigenvector of $M_G(\lambda)$ for eigenvalue λ_0.

Proof. We have in this case

$$\sum_{l\in\overline{S}} \frac{R_{il}}{\lambda_0 - \omega(l,l)} u_l = \frac{R_{ij}}{\lambda_0 - \omega(j,j)} u_j = c_1 u_i \tag{1.5}$$

Since $\overline{S} = \{j\}$, $R_{ij} = \omega(i, j)$, the relation (1.5) is equivalent to $\omega(i, j) = cu_i, \forall i \in S$. □

Corollary 1. Let $\overline{S} = \{1, \ldots, m\}$ be such that the weighted graph induced by G on $\overline{S}$ is totally disconnected, i.e. there are no edges between vertexes in $\overline{S}$. Then

$R_{il} = \omega(i, l), \forall i \in S, l \in \overline{S}$ and condition (1.3) becomes

$$\sum_{l \in \overline{S}} \frac{\omega(i, l)}{\lambda_0 - \omega(l, l)} u_l = c u_i, \forall i \in S. \tag{1.6}$$

Hence in this case the generalized eigenvector is preserved iff (1.6) is true.

1.4 Block Matrix Approach

The proof of Theorem 1 is an entry by entry computation based on the isospectral graph reduction. Here we will use block matrices and look at the problem from the perspective of the isospectral matrix reduction, which is more general than the isospectral graph reduction because it has fewer requirements [5].

For any matrix $M \in \mathbb{W}^{n \times n}$, and any partition $S \cup \overline{S} = \{1, 2, \ldots, n\}, S \cap \overline{S} = \emptyset$, by permutation or renaming the nodes, we can always write the matrix as $M = \begin{pmatrix} M_{\overline{S}\,\overline{S}} & M_{\overline{S}S} \\ M_{S\overline{S}} & M_{SS} \end{pmatrix}$. The isospectral matrix reduction of M onto S is defined as

$$R_S = M_{SS} - M_{S\overline{S}}(M_{\overline{S}\,\overline{S}} - \lambda I)^{-1} M_{\overline{S}S}.$$

The only requirement for S here is that the inverse matrix $(M_{\overline{S}\,\overline{S}} - \lambda I)^{-1}$ exists. This is a more general condition than that of the isospectral graph reduction. Indeed for the isospectral graph reduction, there must be no non-loop cycles in $\overline{S}$, which means that under permutation $M_{\overline{S}\,\overline{S}}$ is a triangular matrix. Also, the weights of loops in $\overline{S}$ are not equal to λ. This ensures $M_{\overline{S}\,\overline{S}} - \lambda I$ is invertible, but it's a stronger condition.

However, when both of these conditions hold the isospectral matrix reduction gives the same reduced matrix as the isospectral graph reduction (theorem 2.1 [5]).

We will show now that the preservation of eigenvectors directly follows from the definition of isospectral matrix reduction.

Suppose u is an eigenvector such that $M(\lambda_0)u = \lambda_0 u, \lambda_0 \in \sigma(M(\lambda))$. Write $u = \begin{pmatrix} u_{\overline{S}} \\ u_S \end{pmatrix}$. Then we have

$$M(\lambda_0)u = \begin{pmatrix} M_{\overline{S}\overline{S}}(\lambda_0) & M_{\overline{S}S}(\lambda_0) \\ M_{S\overline{S}}(\lambda_0) & M_{SS}(\lambda_0) \end{pmatrix} \begin{pmatrix} u_{\overline{S}} \\ u_S \end{pmatrix} = \lambda_0 \begin{pmatrix} u_{\overline{S}} \\ u_S \end{pmatrix}.$$

An easy computation shows that

$$(M_{\overline{S}\overline{S}}(\lambda_0) - \lambda_0 I)u_{\overline{S}} + M_{\overline{S}S}(\lambda_0)u_S = 0,$$

$$M_{S\overline{S}}(\lambda_0)u_{\overline{S}} + (M_{SS}(\lambda_0) - \lambda_0 I)u_S = 0.$$

Assume that the matrix $(M_{\overline{S}\overline{S}}(\lambda_0) - \lambda_0 I)$ is invertible. Then the first row gives

$$u_{\overline{S}} = -(M_{\overline{S}\overline{S}}(\lambda_0) - \lambda_0 I)^{-1} M_{\overline{S}S}(\lambda_0)u_S. \tag{1.7}$$

By plugging this relation into the second row, we get

$$-M_{S\overline{S}}(\lambda_0)(M_{\overline{S}\overline{S}}(\lambda_0) - \lambda_0 I)^{-1} M_{\overline{S}S}(\lambda_0)u_S + M_{SS}(\lambda_0)u_S = \lambda_0 u_S.$$

Observe that the left side of this equation is $R_S(\lambda_0)u_S$, where $R_S(\lambda_0)$ is the isospectral matrix reduction evaluated at λ_0. Therefore $R(\lambda_0)u_S = \lambda_0 u_S$, i.e. projections of eigenvectors of the original (adjacency) matrix (of a network) are indeed eigenvectors with the same eigenvalues of the isospectrally reduced (adjacency) matrix. Thus, the property of eigenvector preservation for isospectral reductions is proved.

This is a much shorter proof than the one in [6]. Moreover, it clarifies a general structure of the isospectral reduction procedure .

Now let us turn to generalized eigenvectors. In addition to $M(\lambda_0)u = \lambda_0 u$, we have $(M(\lambda_0) - \lambda_0 I)v = u$, i.e.

$$\begin{pmatrix} M_{\overline{S}\overline{S}}(\lambda_0) - \lambda_0 I & M_{\overline{S}S}(\lambda_0) \\ M_{S\overline{S}}(\lambda_0) & M_{SS}(\lambda_0) - \lambda_0 I \end{pmatrix} \begin{pmatrix} v_{\overline{S}} \\ v_S \end{pmatrix} = \begin{pmatrix} u_{\overline{S}} \\ u_S \end{pmatrix}.$$

A simple computation gives

$$(M_{\overline{S}\overline{S}}(\lambda_0) - \lambda_0 I)v_{\overline{S}} + M_{\overline{S}S}(\lambda_0)v_S = u_{\overline{S}},$$

$$M_{S\overline{S}}(\lambda_0)v_{\overline{S}} + (M_{SS}(\lambda_0) - \lambda_0 I)v_S = u_S.$$

Assume that the matrix $(M_{\overline{S}\overline{S}}(\lambda_0) - \lambda_0 I)$ is invertible. Then we get from the first row

$$v_{\overline{S}} = (M_{\overline{S}\overline{S}}(\lambda_0) - \lambda_0 I)^{-1}u_{\overline{S}} - (M_{\overline{S}\overline{S}}(\lambda_0) - \lambda_0 I)^{-1}M_{\overline{S}S}(\lambda_0)v_S.$$

Plugging this into the second row gives

$$M_{S\overline{S}}(\lambda_0)\{[M_{\overline{S}\overline{S}}(\lambda_0) - \lambda_0 I]^{-1}u_{\overline{S}} - [M_{\overline{S}\overline{S}}(\lambda_0) - \lambda_0 I]^{-1}M_{\overline{S}S}(\lambda_0)v_S\} + (M_{SS}(\lambda_0) - \lambda_0 I)v_S = u_S,$$

$$[R_S(\lambda_0) - \lambda_0 I]v_S + M_{S\overline{S}}(\lambda_0)[M_{\overline{S}\overline{S}}(\lambda_0) - \lambda_0 I]^{-1}u_{\overline{S}} = u_S.$$

It is easy to see that v_S is a generalized eigenvector for $R_S(\lambda_0)$ iff

$$M_{S\overline{S}}(\lambda_0)(M_{\overline{S}\overline{S}}(\lambda_0) - \lambda_0 I)^{-1}u_{\overline{S}} = cu_S. \tag{1.8}$$

One necessary condition is that u_S is in the column space of $M_{S\overline{S}}(\lambda_0)$. In the case when $\overline{S}$ has only one single node, equation (1.8) agrees with Theorem 2, and the necessary condition that u_S is in the column space of $M_{S\overline{S}}(\lambda_0)$ is also sufficient.

Observe that we have not used the relation between $u_{\overline{S}}$ and u_S. Therefore generalized eigenvectors of higher ranks are preserved iff they also satisfy (1.8), with u being a generalized eigenvector instead of the eigenvector.

On the other hand, by plugging in (1.7), the relation between u_S and $u_{\overline{S}}$, we get

$$M_{S\overline{S}}(\lambda_0)(M_{\overline{S}\overline{S}}(\lambda_0) - \lambda_0 I)^{-2} M_{\overline{S}S}(\lambda_0) u_S = -c u_S \,.$$

Therefore the generalized eigenvector v is preserved iff u_S is an eigenvector of $M_{S\overline{S}}(\lambda_0)(M_{\overline{S}\overline{S}}(\lambda_0) - \lambda_0 I)^{-2} M_{\overline{S}S}(\lambda_0)$.

Theorem 3. All eigenvectors of the reduced matrix $R_S(\lambda)$ are restrictions of the eigenvectors of the original matrix M. The projection of eigenvectors of M onto the eigenvectors of $R_S(\lambda)$ corresponding to the same eigenvalue is a bijection.

Proof. Suppose $R(\lambda_0)u = \lambda_0 u$. Then

$$\{M_{SS}(\lambda_0) - M_{S\overline{S}}(\lambda_0)[M_{\overline{S}\overline{S}}(\lambda_0) - \lambda_0 I]^{-1} M_{\overline{S}S}(\lambda_0)\} u = \lambda_0 u.$$

Let $v = -[M_{\overline{S}\overline{S}}(\lambda_0) - \lambda_0 I]^{-1} M_{\overline{S}S}(\lambda_0) u$. Then we have

$$M(\lambda_0)\begin{pmatrix} v \\ u \end{pmatrix} = \begin{pmatrix} M_{\overline{S}\overline{S}}(\lambda_0) & M_{\overline{S}S}(\lambda_0) \\ M_{S\overline{S}}(\lambda_0) & M_{SS}(\lambda_0) \end{pmatrix}\begin{pmatrix} v \\ u \end{pmatrix} = \lambda_0 \begin{pmatrix} v \\ u \end{pmatrix}.$$

which proves that the projection is surjective.

Suppose now that $(v, u)^T$ and $(u_{\overline{S}}, u)^T$ are both eigenvectors of M for eigenvalue λ_0. Then by (1.7) we have $v = u_{\overline{S}} = -(M_{\overline{S}\overline{S}} - \lambda_0 I)^{-1} M_{\overline{S}S} u$. So the projection is also injective. □

Proof of the following statement can be found in [5] (corollary 1.1).

Lemma 1. For a matrix $M \in \mathbb{C}^{n\times n}$, let R be the isospectral reduction of M with respect to a structural set $S \subset \{1, \ldots, n\}$. Then $\sigma(R) = \sigma(M) - \sigma(M_{\overline{S}\overline{S}})$.

Hence for a given eigenvalue $\lambda_0 \in \sigma(M)$, if $\lambda_0 \notin \sigma(M_{\overline{S}\overline{S}})$, then the algebraic multiplicity of λ_0 as an eigenvalue won't change after isospectral reduction of M to S. Therefore if we reduce over a λ_0-structural set, then the algebraic multiplicity of λ_0 will be preserved.

Theorem 4. For a matrix $M \in \mathbb{C}^{n\times n}$, isospectral reductions preserve both the algebraic and the geometric multiplicities of any eigenvalue.

Proof. Let λ_0 be an eigenvalue of the reduced matrix $R(\lambda)$. Lemma 1 ensures that if we pick a λ_0-structural set the algebraic multiplicity of λ_0 will be preserved. In fact, lemma 1 is true as long as the reduction exists at λ_0 [5], i.e. the matrix $M_{\overline{S}\,\overline{S}} - \lambda_0 I$ is invertible.

Because of the bijection between the eigenvectors before and after isospectral reduction, the geometric multiplicity of an engenvalue is also preserved. □

Note though that Theorem 4 gives no information about the generalized eigenvectors. Unlike the bijective projection we have for eigenvectors, there are situations when the reduced matrix doesn't have a generalized eigenvector for the eigenvalue λ_0 although the original (nonreduced) matrix does.

The projection of the generalized eigenvector of the original matrix to its components corresponding to vertices contained in the structural set S is a generalized eigenvector for the reduced matrix if and only if (1.8) holds.

Remark 3. Observe that the proof of the existence of bijection between the eigenvectors, i.e. Theorem 3, doesn't require M to have complex entries. In particular, it means that M could be a matrix with entries which are rational functions of λ, which are used in isospectral reductions of networks [5]. Consequently, the geometric multiplicity of a specific eigenvalue is preserved throughout the entire sequence of isospectral reductions.

Moreover, if the original matrix has entries which are complex numbers, then the algebraic multiplicity of a specific eigenvalue is also preserved throughout the entire sequence of isospectral reductions. By the uniqueness of sequential reductions [5] the isospectral reduction to a specific structural set is the same as the one which results in reduction to the same set S via several consecutive isospectral reductions. The algebraic multiplicity of eigenvalue λ_0 at each step is equal to the algebraic multiplicity of λ_0 for the original matrix.

1.5 An Example of Isospectral Reductions over Different Structural sets

The results obtained in the previous sections demonstrate that a generalized eigenvector may or may not be preserved under isospectral reductions of matrices and networks. In this section we consider isospectral reduction of the simple small network depicted in figure 1.1. This will illustrates the different possibilities which arise after picking different structural sets. The details of the corresponding computations are presented in the Appendix.

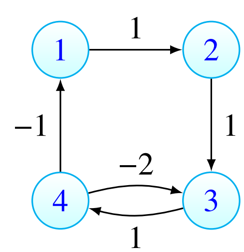


Figure 1.1: Original network

The adjacency matrix of this network is $A = \begin{pmatrix} 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \\ -1 & 0 & -2 & 0 \end{pmatrix}$. It has eigenvalues $\{i, i, -i, -i\}$. The generalized eigenvector chain for the eigenvalue i is $v^i = \begin{pmatrix} -3 \\ -2i \\ 1 \\ 0 \end{pmatrix} \rightarrow$

$u^i = \begin{pmatrix} i \\ -1 \\ -i \\ 1 \end{pmatrix}$; for the eigenvalue $-i$ the corresponding chain is $v^{-i} = \begin{pmatrix} 2i \\ 1 \\ 0 \\ 1 \end{pmatrix} \to u^{-i} = \begin{pmatrix} -1 \\ i \\ 1 \\ -i \end{pmatrix}$.

This network contains two cycles (1234) and (34). All the structural sets of size two for this network are $S = \{1,4\}, \{2,4\}, \{3,4\}, \{1,3\}, \{2,3\}$. The list of all size 3 structural sets is $S = \{1,2,4\}, \{1,3,4\}, \{2,3,4\}, \{1,2,3\}$.

For the size 3 structural sets, since $\overline{S}$ has only a single node, Theorem 2 is applicable.

If $S = \{1,2,4\}, \overline{S} = \{3\}$, then $A_{S\overline{S}} = \begin{pmatrix} 0 \\ 1 \\ -2 \end{pmatrix}, u_S^i = \begin{pmatrix} i \\ -1 \\ 1 \end{pmatrix}, u_S^{-i} = \begin{pmatrix} -1 \\ i \\ -i \end{pmatrix}$.Thus $A_{S\overline{S}} \nparallel u_S^i$, and $A_{S\overline{S}} \nparallel u_S^{-i}$. v_S^i, v_S^{-i} are not generalized eigenvectors for $R_S(\lambda)$.

To be more precise,

$$R_S(\lambda) = \begin{pmatrix} 0 & 1 & 0 \\ 0 & 0 & 1/\lambda \\ -1 & 0 & -2/\lambda \end{pmatrix}, \det(R_S(\lambda) - \lambda I) = -\frac{(\lambda^2+1)^2}{\lambda}, \sigma(R_S(\lambda)) = \{i, i, -i, -i\}.$$

$$R_S(i) = \begin{pmatrix} 0 & 1 & 0 \\ 0 & 0 & -i \\ -1 & 0 & 2i \end{pmatrix}, \det(R_S(i) - \lambda I) = -(\lambda - i)(\lambda^2 - i\lambda + 1), \sigma(R_S(i)) = \{i, \frac{1+\sqrt{5}}{2}i, \frac{1-\sqrt{5}}{2}i\}.$$

The complex number i is an eigenvalue for both $R_S(\lambda)$ and $R_S(i)$; the algebraic multiplicity of i for $R_S(\lambda)$ is 2; for $R_S(i)$ it is 1. $R_S(i)$ doesn't have a generalized eigenvector for i. It has just one eigenvector corresponding to this eigenvalue. Therefore the generalized eigenvector is lost after isospectral reduction of the matrix.

One can check that isospectral reduction to any other size 3 structural set does not preserve the generalized eigenvectors either.

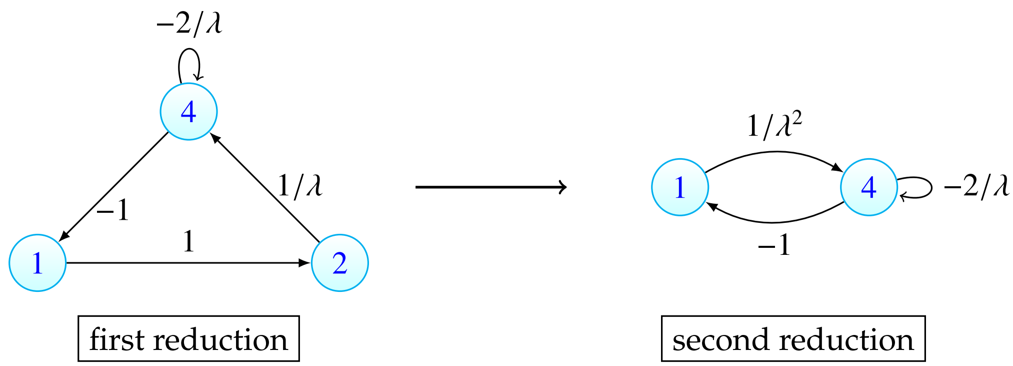


Figure 1.2: Isospectral reductions of the original network

Now let us further reduce the network to $S' = \{1, 4\} \subset S = \{1, 2, 4\}$. We have

$$R_{S'}(\lambda) = \begin{pmatrix} 0 & 1/\lambda^2 \\ -1 & -2/\lambda \end{pmatrix}, \det(R_{S'}(\lambda) - \lambda I) = \frac{(\lambda^2+1)^2}{\lambda^2}, \sigma(R_{S'}(\lambda)) = \{i, i, -i, -i\};$$

$$R_{S'}(i) = \begin{pmatrix} 0 & -1 \\ -1 & 2i \end{pmatrix}, \det(R_{S'}(i) - \lambda I) = (\lambda - i)^2, \sigma(R_{S'}(i)) = \{i, i\};$$

Here the algebraic multiplicity of i as an eigenvalue is the same for $R_{S'}(\lambda)$ and $R_{S'}(i)$. We know that the eigenvectors are always preserved because of the bijective projection. Therefore after the second reduction we gained the generalized eigenvector back. This is a quite unexpected result which raises a question about the conditions on a structural set which allow for preservation of generalized eigenvectors.

Of course we can directly reduce the original network to $S' = \{1, 4\}$ too. One can check the reduction satisfies both the entry-wise formula (1.3) and the block-wise formula (1.8). Furthermore, for all the size 2 structural sets, the reduction preserves both generalized eigenvectors (v^i, v^{-i}) except for the structural set $\{3, 4\}$. Observe that it is the only structural set of size two which contains a complete cycle of our network.

Remark 4. Let a matrix $M \in \mathbb{W}^{n\times n}$, $\lambda_0 \in \sigma(M)$. Define $a(\lambda_0, M)$ and $g(\lambda_0, M)$ to be the algebraic and geometric multiplicities of λ_0. Then for $M \in \mathbb{C}^{n\times n}$, the number of linearly independent generalized eigenvectors corresponding to λ_0 for M is $d(\lambda_0, M) = a(\lambda_0, M) - g(\lambda_0, M)$.

Consider now $R(\lambda) \in \mathbb{W}^{n\times n}$. By definition the eigenvectors satisfy $R(\lambda_0)u = \lambda_0 u$; and the generalized eigenvectors satisfy $(R(\lambda_0) - \lambda_0 I)^k v = 0$. Thus $g(\lambda_0, R(\lambda)) = g(\lambda_0, R(\lambda_0))$, $d(\lambda_0, R(\lambda)) = d(\lambda_0, R(\lambda_0))$. Observe now that $R(\lambda_0) \in \mathbb{C}^{n\times n}$. $d(\lambda_0, R(\lambda_0)) = a(\lambda_0, R(\lambda_0)) - g(\lambda_0, R(\lambda_0))$. As seen in the previous example, $a(\lambda_0, R(\lambda_0)) \neq a(\lambda_0, R(\lambda))$. Hence

$$d(\lambda_0, R(\lambda)) = a(\lambda_0, R(\lambda_0)) - g(\lambda_0, R(\lambda_0)) \neq a(\lambda_0, R(\lambda)) - g(\lambda_0, R(\lambda)).$$

Therefore the number of linearly independent generalized eigenvectors is not equal to the difference between the algebraic and geometric multiplicities of the eigenvalue. In other words, the notion of generalized eigenvectors does not make much sense for matrices with rational functions as entries.

Remark 5. Another fact worth noticing is that the reductions shown in this example form a sequence of isospectral reductions, i.e. $R_{S'}$ is an isospectral reduction of R_S. With the uniqueness of sequential reductions [5], one is tempted to believe that a property that's true for the final step of a sequence of reductions should be true in each and every step through the sequence of reductions. In our case, for the preservation of generalized eigenvectors there is no sequential property. Indeed although the generalized eigenvectors are lost in R_S, they managed to "come back" in $R_{S'}$. One might ask then under which conditions the generalized eigenvectors can be recovered.

Consider the sequence of reductions that starts from R_S, instead of A. After one reduction to $R_{S'}$, instead of "recovering" generalized eigenvectors, the reduction generated generalized eigenvectors that R_S doesn't have. This again, is caused by the fact that the concept of generalized eigenvectors does not actually apply to matrices whose entries are rational functions. Through a sequence of reductions, the generalized eigenvectors can be lost or ”recovered”, or even generated, at each step. We can not say what is going to happen in the next step in a sequence of isospectral reductions even with a knowledge of all the previous steps. Instead, one must directly analyze each new step in the sequence of reductions.

1.6 Some Sufficient conditions for preservation of generalized eigenvectors

Theorem 5. The generalized eigenvectors are preserved if either of the following conditions hold : (i) $M_{S\overline{S}}(\lambda_0) = 0$; (ii) $M_{\overline{S}S}(\lambda_0) = 0$.

Proof. If $M_{S\overline{S}}(\lambda_0) = 0$, plugging in (1.8) we have $M_{S\overline{S}}(\lambda_0)(M_{\overline{S}\overline{S}}(\lambda_0) - \lambda_0 I)^{-1}u_{\overline{S}} = 0 = 0u_S$.

If $M_{\overline{S}S}(\lambda_0) = 0$, then by (1.7) we have $u_{\overline{S}} = -(M_{\overline{S}\overline{S}}(\lambda_0) - \lambda_0 I)^{-1}M_{\overline{S}S}(\lambda_0)u_S = 0$. If $u_{\overline{S}} = 0$, then (1.8) is true. □

For a network, the relation $M_{S\overline{S}}(\lambda_0) = 0$ means that no edges go from S to $\overline{S}$; while $M_{\overline{S}S}(\lambda_0) = 0$ means there is no edge from $\overline{S}$ to S. In either case, we have $R(\lambda_0) = M_{SS}(\lambda_0)$.

1.7 Reconstruction of the original network

In this section we address the problem of reconstructing the original network or matrix from its isospectral reduction.

The eigenvectors for eigenvalue λ_0 can be reconstructed, as shown in [6]. And we can reconstruct the generalized eigenvectors for λ_0 similarly.

Definition 4. (Depth of a vertex) The depth of a vertex $i \in V$ is defined recursively as follows.

(1) A vertex $i \in S$ has depth 0.

(2) A vertex $i \in \overline{S}$ has depth k iff i has no depth less than k, and $(i, j) \in E$ implies j has depth $< k$, for all $j \in V$.

We denote by S_k the set of all vertices of depth $\leq k$. Because S is a structural set, every vertex i has a finite depth. We set the depth of (G, S) to be the maximum depth of a vertex.

Proposition 1. If $u_S = (u_i^S)_{i \in S}, v_S = (v_i^S)$ are the eigenvector and rank 2 generalized eigenvector of $R_S(G, \lambda_0)$, and $R_S(G, \lambda_0)v_S - \lambda_0 v_S = (1+c)u_S$, where $c \neq -1$ is a complex number, then the recursive relations

$$\begin{cases} v_i = v_i^S & \text{for } i \in S_0 = S \\ v_l + \dfrac{u_l}{\lambda_0 - \omega(l,l)} = \dfrac{1}{\lambda_0 - \omega(l,l)} \displaystyle\sum_{j \in S_{k-1}} \omega(l, j) v_j & \text{for all } l \in S_k \setminus S_{k-1} \end{cases} \tag{1.9}$$

determine the rank 2 generalized eigenvector v for M_G associated to λ_0.

Remark 6. The relation (1.9) comes from equation (1.4). And this reconstruction formula can reconstruct higher ranking generalized eigenvectors as well. We just need to replace u with the rank $k-1$ generalized eigenvector and v with the rank k generalized eigenvector.

Remark 7. Proposition 1 is true for any $M_G \in \mathbb{W}^{n \times n}$. For a matrix $M \in \mathbb{C}^{n \times n}$, if all its eigenvalues, eigenvectors and chains of generalized eigenvectors are preserved in an isospectral reduction, then the Jordan form of M is known, and its corresponding eigenvectors and chains of generalized eigenvectors can be reconstructed. We can reconstruct the original matrix M. This reconstruction is unique up to permutation of the nodes by $M = BJB^{-1}$, where J is the Jordan form and $B = [u_1, u_2, v_2, \dots]$ are the corresponding eigenvectors and generalized eigenvectors.

1.8 Spectral equivalence of networks and of complex matrices

In this section we introduce a more general than in [5] notion of spectral equivalence of networks and compare it with standard spectral equivalence of matrices with complex entries.

Recall that the spectrum, σ, of a matrix is the union of all eigenvalues together with their multiplicities.

Let $\mathbb{W}_\pi \subset \mathbb{W}$ be the set of rational functions $p(\lambda)/q(\lambda)$ such that $\deg(p) \leq \deg(q)$, where $\deg(p)$ is the degree of the polynomial $p(\lambda)$. And let $\mathbb{G}_\pi \subset \mathbb{G}$ be the set of graphs $G = (V, E, w)$ such that $w : E \to \mathbb{W}_\pi$. Every graph in $\mathbb{G}_\pi$ can be isospectrally reduced [5].

Two weighted directed graphs $G_1 = (V_1, E_1, w_1)$ and $G_2 = (V_2, E_2, w_2)$ are *isomorphic* if there is a bijection $b : V_1 \to V_2$ such that there is an edge e_{ij} in G_1 from v_i to v_j if and only if there is an edge $\tilde{e}_{ij}$ between $b(v_i)$ and $b(v_2)$ in G_2 with $w_2(\tilde{e}_{ij}) = w_1(e_{ij})$. If the map b exists, it is called an *isomorphism*, and we write $G_1 \simeq G_2$.

An isomorphism is essentially a relabeling of the vertices of a graph. Therefore, if two graphs are isomorphic, then their spectra are identical. The relation of being isomorphic is reflexive, symmetric, and transitive; in other words, it's an equivalence relation.

Definition 5 (Generalized Spectral Equivalence of Graphs)**.** Suppose that for each graph $G = (V, E, w)$ in $\mathbb{G}_\pi$, τ is a rule that selects a unique nonempty subset $\tau(G) \subset V$. Let R_τ be the isospectral reduction of G onto $\tau(G)$. Then R_τ induces an equivalence relation $\sim$ on the set $\mathbb{G}_\pi$, where $G \sim H$ if $R_\tau^m(G) \simeq R_\tau^k(H)$ for some $m, k \in \mathbb{N}$.

Remark 8. Observe that we do not require $\tau(G)$ to be a structural subset of G. However there is a unique isospectral reduction [5] (possibly via a sequence of isospectral reductions to structural sets if $\tau(G)$ is not a structural subset of G) of G onto $\tau(G)$.

Our definition of spectral equivalence of networks (graphs) is more general than the one in [5], where it was required that $m = k = 1$. Therefore our classes of spectrally equivalent networks are larger than the ones considered in [5]. Namely each class of equivalence in our sense consists of a countable number of equivalence classes in the sense of [5]. Our approach/definition could be of use for analysis of real world networks many of which have a hierarchical structure [7], [8].

Clearly any nonzero number is an eigenvector of any dimension 1 matrix. For this reason we do not consider reductions to one node since at that point all the geometric properties are lost.

Proof. It is easy to see that the relation defined is reflexive and symmetric.

Suppose that $G \sim H$, with $R_\tau^m(G) \simeq R_\tau^s(H)$; $H \sim K$, with $R_\tau^r(H) \simeq R_\tau^t(K)$. Without any loss of generality, we assume $r > s$. Then

$$R_\tau^{m+r-s}(G) \simeq R_\tau^r(H) \simeq R_\tau^t(K), G \sim K.$$

□

We call matrices that can be isospectrally reduced to the same matrix (up to permutation) spectrally equivalent. By lemma 1, we have $\sigma(M) = \sigma(R) \cup [\sigma(M) \cap \sigma(M_{\overline{S}\overline{S}})]$ for $M \in \mathbb{C}^{n\times n}$. If

$$\sigma(M) \cap \sigma(M_{\overline{S}\overline{S}}) = \emptyset, \tag{1.10}$$

we have $\sigma(M) = \sigma(R)$.

Proposition 2. Let $M_1, M_2 \in \mathbb{C}^{n\times n}$, both can be reduced to the same matrix $R(\lambda) \in \mathbb{W}^{m\times m}$. Let them both satisfy (1.10). Then M_1 and M_2 have the same eigenvalues, with the same algebraic and geometric multiplicities for each eigenvalue. They also have the same eigenvectors for each eigenvalue. However, they can still have different Jordan forms, since the generalized eigenvectors are generally not preserved by isospectral reductions.

Proof. Since M_1 and M_2 both satisfy (1.10), we have $\sigma(M_1) = \sigma(R) = \sigma(M_2)$, i.e. M_1 and M_2 have the same eigenvalues and the same algebraic multiplicity for each eigenvalue.

Theorem 3 implies that the eigenvectors of $R(\lambda)$ are bijective projections of eigenvectors of M_1, as well as M_2. By the reconstruction of eigenvectors in [6], we know M_1 and M_2 have the same eigenvectors for each eigenvalue, thus the same geometric multiplicity for each eigenvalue.

However, two matrices with the same eigenvalues, with the same algebraic and geometric multiplicities for each eigenvalue, and the same eigenvectors for each eigenvalue can still have different Jordan form. For example,

$$A_1 = \begin{pmatrix} 5 & 1 & 0 & 0 \\ 0 & 5 & 0 & 0 \\ 0 & 0 & 5 & 1 \\ 0 & 0 & 0 & 5 \end{pmatrix} = \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} 5 & 1 & 0 & 0 \\ 0 & 5 & 0 & 0 \\ 0 & 0 & 5 & 1 \\ 0 & 0 & 0 & 5 \end{pmatrix} \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix},$$

$$A_2 = \begin{pmatrix} 5 & 0 & 0 & 0 \\ 0 & 5 & 0 & 1 \\ 0 & 1 & 5 & 0 \\ 0 & 0 & 0 & 5 \end{pmatrix} = \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} 5 & 0 & 0 & 0 \\ 0 & 5 & 1 & 0 \\ 0 & 0 & 5 & 1 \\ 0 & 0 & 0 & 5 \end{pmatrix} \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix},$$

A_1 and A_2 both have eigenvalue 5 with algebraic multiplicity 4 and geometric multiplicity 2. They also have the same eigenvectors for eigenvalue 5, i.e. $u_1 = (1, 0, 0, 0)^T, u_2 = (0, 0, 1, 0)^T$. But A_1's Jordan form consists of 2 size 2 Jordan blocks and A_2's Jordan form consists of 1 simple eigenvalue and a size 3 Jordan block, they have different Jordan forms. □

If M_1 satisfies (1.10) but M_2 does not, it is known that M_2 loses some eigenvalues (those in the intersection in (1.10)) when reduced to R while M_1 does not. Therefore, $\sigma(M_2) \supsetneq \sigma(M_1)$ and the matrix M_2 has a higher dimension than M_1.

Not all similar matrices are spectrally equivalent. For example, a matrix that is already in Jordan form always has eigenvalues in $\overline{S}$. It will lose eigenvalues in $\overline{S}$ after reduction. For similar matrices that satisfy (1.10), their isospectral reductions will have the same eigenvalues, with the same algebraic and geometric multiplicities. However, reductions of these matrices may not be the same.

For example, matrices A and B down below have the same eigenvalues.

$$A = \begin{pmatrix} 1 & 5 & 2 \\ 3 & 6 & 8 \\ 4 & 7 & 9 \end{pmatrix}^{-1} \begin{pmatrix} 1 & 0 & 0 \\ 0 & 2 & 0 \\ 0 & 0 & 3 \end{pmatrix} \begin{pmatrix} 1 & 5 & 2 \\ 3 & 6 & 8 \\ 4 & 7 & 9 \end{pmatrix} = \frac{1}{17} \begin{pmatrix} 148 & 206 & 256 \\ -13 & -5 & -28 \\ -33 & -48 & -41 \end{pmatrix},$$

$$B = \begin{pmatrix} 2 & 1 & 0 \\ 7 & 3 & 5 \\ 8 & 9 & 4 \end{pmatrix}^{-1} \begin{pmatrix} 1 & 0 & 0 \\ 0 & 2 & 0 \\ 0 & 0 & 3 \end{pmatrix} \begin{pmatrix} 2 & 1 & 0 \\ 7 & 3 & 5 \\ 8 & 9 & 4 \end{pmatrix} = \frac{1}{27} \begin{pmatrix} 1 & -39 & -10 \\ 52 & 105 & 20 \\ 43 & 24 & 56 \end{pmatrix}.$$

The matrix A has 3 listed below dimension-2 isospectral reductions.

$$R_{12}(A) = \frac{1}{17\lambda + 41} \begin{pmatrix} 148\lambda - 140 & 206\lambda - 226 \\ 23 - 13\lambda & 67 - 5\lambda \end{pmatrix},$$

$$R_{13}(A) = \frac{1}{17\lambda + 5} \begin{pmatrix} 148\lambda - 114 & 256\lambda - 264 \\ 27 - 33\lambda & 67 - 41\lambda \end{pmatrix},$$

$$R_{23}(A) = \frac{1}{17\lambda - 148} \begin{pmatrix} -5\lambda - 114 & 48 - 28\lambda \\ 18 - 48\lambda & -41\lambda - 140 \end{pmatrix}.$$

The matrix B also has 3 dimension-2 isospectral reductions.

$$R_{12}(B) = \frac{1}{27\lambda - 56}\begin{pmatrix} \lambda - 18 & 72 - 39\lambda \\ 52\lambda - 76 & 105\lambda - 200 \end{pmatrix},$$

$$R_{13}(B) = \frac{1}{27\lambda - 105}\begin{pmatrix} \lambda - 79 & 10 - 10\lambda \\ 43\lambda - 121 & 56\lambda - 200 \end{pmatrix},$$

$$R_{23}(B) = \frac{1}{27\lambda - 1}\begin{pmatrix} 105\lambda - 79 & 20\lambda - 20 \\ 24\lambda - 63 & 56\lambda - 18 \end{pmatrix}.$$

It is easy to see that there is no pair of reductions, one for A and one for B, which are the same, meaning that one is a permutation of the other. Even though A and B are similar matrices that both satisfy (1.10), they are not spectrally equivalent.

When (1.10) does not hold, the eigenvalues which belong to both $\sigma(M)$ and $\sigma(M_{\overline{S}\overline{S}})$ will be lost after reduction or their multiplicities will decrease. Theorems 1, 2, 3, 4 and 5 require $(M_{\overline{S}\overline{S}}(\lambda_0) - \lambda_0 I)$ to be invertible, which implies $\lambda_0 \notin \sigma(M_{\overline{S}\overline{S}})$. Therefore in this case λ_0 doesn't belong to the intersection in (1.10).

CHAPTER 2

ON ATTRACTORS OF ISOSPECTRAL COMPRESSIONS OF NETWORKS

2.1 Introduction

Arguably the major scientific buzzword of our time is a "Big Data". When talking about Big Data people usually refer to (huge) natural networks in communications, bioinformatics, social sciences, etc, etc, etc. In all cases the first idea and hope is to somehow reduce these enormously large networks to some smaller objects while keeping, as much as possible, information about the original huge network.

In practice almost all the information about real-world networks is contained in their adjacency matrices [9, 10]. An adjacency matrix of a network with N elements is the $N \times N$ matrix with zero or one elements. The (i, j) element equals one if there is direct interaction between the elements number i and number j of a network. In the graph representation of a network this corresponds to the existence of an edge (arrow) connecting node i to node j. Otherwise an (i, j) element of the adjacency matrix of a network equals zero. It is very rare [9, 10] that the strength of interaction of the element (node) i with the element (node) j is also known. In such cases a network is represented by a weighted adjacency matrix where the (i, j) entry corresponds to the strength of this interaction instead of to 1.

Therefore the problem of compressing a network is essentially a problem of compressing its weighted adjacency matrix. It is a basic fact of linear algebra that all the information about a matrix is contained in its spectrum (collection of all eigenvalues of a matrix) and in its eigenvectors and generalized eigenvectors.

Recently a constructive rigorous mathematical theory was developed which allows us to compress (reduce) matrices and networks while keeping ALL the information regarding their spectrum and eigenvalues. This approach was successfully applied to various theoretical and applied problems [5]. The corresponding transformations of networks were called Isospectral Transformations. This approach is not only limited to the compression of networks. It also allows one to grow (enlarge) networks while keeping stability of their evolution (dynamics), etc (see [5, 11]).

In the present paper we further develop this approach by demonstrating that isospectral compressions generate a dynamical system on the space of all networks. We prove that such a dynamical system converges to an attractor which is a smaller network than the network which was an initial point (network) of this orbit. To create this dynamical system we need to first select some characteristic of the network's nodes (or edges). Then we pick a subset of nodes (edges) based on this characteristc. We then reduce the network onto the subset we just picked. We repeat this procedure and get a dynamical system. It is important to mention that the current graph theory is lacking classification of all graphs which have the same characteristic of the all nodes even for such basic and simplest characteristics as inner and outer degrees. Clearly any complete graph where any two nodes are connected by an edge (in case of undirected graphs) or by two opposite edges (in case of directed graphs) has the same value of any characteristic at any node. Therefore all complete graphs are attractors of any isospectral contraction. However, there are other attractors as well for any characteristic and there is no general classification or description of these attractors. However one can find such attractors when dealing with a concrete network. Therefore, this procedure is a natural tool for analysis of real-world networks. We demonstrate that by choosing different characteristics of either nodes or edges of a network one typically gets different attractors. The structure of such networks gives us new important information about a given network.

We also discuss the notions of weak and strong spectral equivalences of networks and show that classes of equivalence with respect to a weak spectral equivalence consists of a countable number of classes of strongly spectrally equivalent networks. Our results could be readily applicable to analysis of any (directed or undirected, weighted or unweighted) networks.

2.2 Isospectral Graph Reductions and Spectral Equivalence

In this section we recall definitions of the isospectral transformations of graphs and networks.

Let $\mathbb{W}$ be the set of rational functions of the form $w(\lambda) = p(\lambda)/q(\lambda)$, where $p(\lambda), q(\lambda) \in \mathbb{C}[\lambda]$ are polynomials having no common linear factors, i.e., no common roots, and where $q(\lambda)$ is not identically zero. $\mathbb{W}$ is a field under addition and multiplication [5].

Let $\mathbb{G}$ be the class of all weighted directed graphs with edge weights in $\mathbb{W}$. More precisely, a graph $G \in \mathbb{G}$ is an ordered triple $G = (V, E, w)$ where $V = \{1, 2, \ldots, n\}$ is the *vertex set*, $E \subset V \times V$ is the set of *directed edges*, and $w : E \to \mathbb{W}$ is the *weight function*. Denote by $M_G = (w(i, j))_{i,j\in V}$ the *weighted adjacency matrix* of G, with the convention that $w(i, j) = 0$ whenever $(i, j) \notin E$. We will alternatively refer to graphs as networks because weighted adjacency matrices define all static (i.e. non evolving) real-world networks. Also we will be using "vertex" and "node" interchangeably.

Observe that the entries of M_G are rational functions. Let's write $M_G(\lambda)$ instead of M_G here to emphasize the role of λ as a variable. For $M_G(\lambda) \in \mathbb{W}^{n\times n}$, we define the spectrum, or multiset of eigenvalues to be

$$\sigma(M_G(\lambda)) = \{\lambda \in \mathbb{C} : \det(M_G(\lambda) - \lambda I) = 0\}.$$

Notice that we count the multiplicities of the eigenvalues, i.e. the set $\sigma(M_G(\lambda))$

can have more than n elements, some of which can be equal to each other.

A path $\gamma = (i_0, \ldots, i_p)$ in the graph $G = (V, E, w)$ is an ordered sequence of distinct vertices $i_0, \ldots, i_p \in V$ such that $(i_l, i_{l+1}) \in E$ for $0 \le l \le p-1$. The vertices $i_1, \ldots, i_{p-1} \in V$ of γ are called *interior vertices*. If $i_0 = i_p$ then γ is a *cycle*. A cycle is called a *loop* if $p = 1$ and $i_0 = i_1$. The length of a path $\gamma = (i_0, \ldots, i_p)$ is the integer p. Note that there are no paths of length 0 and that every edge $(i, j) \in E$ is a path of length 1.

If $S \subset V$ is a subset of all the vertices, we will write $\overline{S} = V \setminus S$ and denote by $|S|$ the cardinality of the set S.

Definition 6. *(structural set).* Let $G = (V, E, w) \in \mathbb{G}$. A nonempty vertex set $S \subset V$ is a structural set of G if

- each cycle of G, that is not a loop, contains a vertex in S;
- $w(i, i) \neq \lambda$ for each $i \in \overline{S}$.

In particular, if a structural set S also satisfies $w(i, i) \neq \lambda_0, \forall i \in \overline{S}$ for some $\lambda_0 \in \mathbb{C}$, then S is called a λ_0–structural set.

Definition 7. Given a structural set S, a *branch* of (G, S) is a path $\beta = (i_0, i_1, \ldots, i_{p-1}, i_p)$ such that $i_0, i_p \in V$ and all $i_1, \ldots, i_{p-1} \in \overline{S}$.

We denote by $\mathcal{B} = \mathcal{B}_{G,S}$ the set of all branches of (G, S). Given vertices $i, j \in V$, we denote by $\mathcal{B}_{i,j}$ the set of all branches in $\mathcal{B}$ that start in i and end in j. For each branch $\beta = (i_0, i_1, \ldots, i_{p-1}, i_p)$ we define the *weight* of β as follows:

$$w(\beta, \lambda) := w(i_0, i_1) \prod_{l=1}^{p-1} \frac{w(i_l, i_{l+1})}{\lambda - w(i_l, i_l)}. \tag{2.1}$$

Given $i, j \in V$ set

$$R_{i,j}(G, S, \lambda) := \sum_{\beta \in \mathcal{B}_{i,j}} w(\beta, \lambda). \tag{2.2}$$

Definition 8. *(Isospectral Reduction(Compression)).* Given $G \in \mathbb{G}$ and a structural set S, the reduced adjacency matrix $R_S(G, \lambda)$ is the $|S| \times |S|$−matrix with the entries $R_{i,j}(G, S, \lambda), i, j \in S$. This adjacency matrix $R_S(G, \lambda)$ on S defines the reduced graph which is the isospectral reduction of the original graph G.

Remark 9. We will use the terms "reduction" and "compression" interchangeably. One can check that for a graph with complex number weights, the complement of any single node is a structural set. For any subset A of nodes of this network G, it is always possible to isospectrally compress the network G to a network whose nodes belong to A by removing the nodes in the complement of A one after another.

Now we recall the notion of spectral equivalence of networks (graphs).

Let $\mathbb{W}_\pi \subset \mathbb{W}$ be the set of rational functions $p(\lambda)/q(\lambda)$ such that $\deg(p) \leq \deg(q)$, where $\deg(p)$ is the degree of the polynomial $p(\lambda)$. And let $\mathbb{G}_\pi \subset \mathbb{G}$ be the set of graphs $G = (V, E, w)$ such that $w : E \to \mathbb{W}_\pi$. Every graph in $\mathbb{G}_\pi$ can be isospectrally reduced over any nonempty subset of its vertex set[5].

Two weighted directed graphs $G_1 = (V_1, E_1, w_1)$ and $G_2 = (V_2, E_2, w_2)$ are *isomorphic* if there is a bijection $b : V_1 \to V_2$ such that there is an edge e_{ij} in G_1 from v_i to v_j if and only if there is an edge $\tilde{e}_{ij}$ between $b(v_i)$ and $b(v_j)$ in G_2 with $w_2(\tilde{e}_{ij}) = w_1(e_{ij})$. If the map b exists, it is called an *isomorphism*, and we write $G_1 \simeq G_2$.

An isomorphism is essentially a relabeling of the vertices of a graph. Therefore, if two graphs are isomorphic, then their spectra are identical. The relation of being isomorphic is reflexive, symmetric, and transitive; in other words, it's an equivalence relation.

The notion of spectral equivalence of graphs was introduced in [5]. This is the idea that two networks G and H are spectrally equivalent if they reduce to isomorphic graphs in one step, over subsets of vertices selected by a rule τ (e.g. nodes whose inner degrees are less than 2). Then in [1] a less restrictive notion of generalized spectral equivalence of graphs (networks) was introduced. Namely, two networks are weakly spectrally equivalent if they reduce to isomorphic graphs in a finite number of steps (not necessarily the same number of steps) under the same rule for subset selection.

A proof of the following theorem can be found in [1].

Theorem 6 (Generalized Spectral Equivalence of Graphs)**.** Suppose that for each graph $G = (V, E, w)$ in $\mathbb{G}_\pi$, τ is a rule that selects a unique nonempty subset $\tau(G) \subset V$. Let R_τ be the isospectral reduction of G onto $\tau(G)$. Then R_τ induces an equivalence relation $\sim$ on the set $\mathbb{G}_\pi$, where $G \sim H$ if $R_\tau^m(G) \simeq R_\tau^k(H)$ for some $m, k \in \mathbb{N}$.

Remark 10. Observe that we do not require $\tau(G)$ to be a structural subset of G. However there is a unique isospectral reduction [5] (possibly via a sequence of isospectral reductions to structural sets if $\tau(G)$ is not a structural subset of G) of G onto $\tau(G)$.

The notion of generalized spectral equivalence of networks (graphs) is weaker than the one considered in [5], where it was required that $m = k = 1$. Therefore the classes of weakly spectrally equivalent networks are larger than the classes of spectrally equivalent networks considered in [5]. Namely each class of equivalence in the weak sense consists of a countable number of equivalence classes in the (strong) sense of [5]. In what follows we will refer to the spectral equivalence in the form introduced in [5] as strong spectral equivalence, and the notion of spectral equivalence introduced in [1] as weak spectral equivalence. Both of the strong and weak notions of spectral equivalence could be of use for analysis of real-world networks many of which have a hierarchical structure [7], [8].

2.3 Attractors of Isospectral Reductions

Isospectral reductions of networks (graphs) define a dynamical system on the space of all networks. This dynamical system arises by picking any node (edge) of a network and isospectrally reducing this network to a network where the set of nodes is a complement to a chosen node. The fact that such isospectral reductions form a dynamical system follows from the Commutativity theorem proved in [5] which states that a sequence of isospectral compressions over a set of nodes A and then over the set of nodes B gives the same result as isospectral reduction over B followed by the one over A. Therefore to one and the same network (graph) G correspond different orbits depending on the order in which we pick nodes of G for reductions.

By repeatedly compressing a graph in this manner it is possible to isospectrally reduce any network to a trivial network which has just one node, which can be any node of G. It is clearly a senseless operation. However we can choose a reasonable rule which will help us to understand some intrinsic feature(s) of the structure (topology) of the network G. Generally a network can have many different structural sets. To make the isospectral contraction focused on specific properties of networks, we can add some specific rules to the selection of structural sets.

Before we do that, let us recall a few characteristics of nodes in a graph. (There are about ten-fifteen such characteristics of nodes and edges of networks which are all borrowed from the graph theory).

For a graph $G = (V, E, w)$, the indegree for a node $v \in V$, $d^-(v)$, is the number of edges that end in v. The outdegree $d^+(v)$ is the number of edges that start at v. Let's define $d(v) = d^-(v) + d^+(v)$ to be the sum of the indegree and outdegree for any node.

Let σ_{st} be the total number of shortest paths from node s to node t, and let $\sigma_{st}(v)$ be the number of those paths that pass through v. Note that $\sigma_{st}(v) = 0$ if $v \in \{s, t\}$ or if v does not lie on any shortest path from s to t. We call

$$g(v) = \sum_{s \neq v} \sum_{t \neq v, s} \sigma_{st}(v)$$

the centrality/betweenness of node v.

Theorem 7. For any network G and a subset selecting rule τ based on some characteristic of its nodes (edges) ($\tau(G) \neq \emptyset$), the orbit of the dynamical system generated by isospectral reductions with respect to τ converges to an attractor which is a network in which τ selects all the nodes (edges).

Proof. If the network is already an attractor, then the reduction doesn't change this network and the orbit is a fixed point.

Otherwise, each reduction removes at least one vertex (edge). Thus an orbit of a network under consecutive isospectral reductions becomes an attractor in no more than N steps, where $N := |V|$ (or $N := |E|$). Therefore an orbit of a finite network G approaches an attractor in a finite number of steps which does not exceed the number of nodes (edges) in G. Such attractor always exists because any network can be isospectrally reduced to a graph with just one node. A process of consecutive isospectral reductions (i.e. an orbit of the corresponding dynamical system) will terminate at one node, if no one of the networks along this orbit was an attractor for τ. Clearly in case of a "network" with only one node (edge) the values of all characteristics of all nodes (edges) are the same because there is only one node (edge). If G is an infinite network then the corresponding orbit could be finite or infinite. □

Theorem 8. The attractors of isospectral reductions with respect to different characteristics of one and the same network are generally different.

Proof. (i) In the example shown in the figure 2.1, all nodes have degree 4. This graph cannot be further reduced based on the degree of its nodes. However, the centrality of the nodes are different. If we count the number of shortest paths through each node, we can see $c(1) = c(2) = c(3) = c(8) = c(9) = c(10) = 1, c(4) = c(6) = c(7) = c(11) = 27, c(5) = 66$. This graph can be further reduced based on

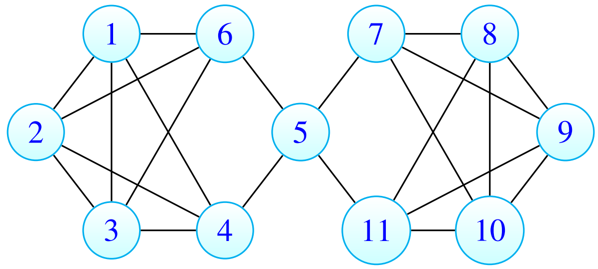


Figure 2.1: A network which is an attractor with respect to degree but not with respect to centrality

centrality. Therefore for this network (graph) attractors with respect to degree and to centrality are different.

(ii) The complete graph, where each and every node and edge have the same properties, can not be further reduced based on degree or other characteristics of a network. It is always an attractor. If we consider isospectral expansion (see [11]) of a complete graph with respect to two different characteristics, then we get two different graphs (networks) with the same attractor with respect to these two characteristics. Clearly this attractor will be the initial complete graph. □

The result of theorem 3 is not surprising because different characteristics of nodes (or edges) define different dynamical systems on the space of all networks, and orbits of these different dynamical systems are also different.

The following statement establishes that weakly as well as strongly spectrally equivalent networks have the same attractor if isospectral contractions are generated by the very same characteristic with respect to which these networks are spectrally equivalent.

Theorem 9. Strongly as well as weakly spectrally equivalent graphs with respect to some characteristic have the same attractor under the dynamical system generated by isospectral compressions according to this characteristic.

Proof. Suppose the graph G is strongly spectrally equivalent to H with respect to rule τ, i.e. $R_\tau(G) \simeq R_\tau(H) = R$, and G is weakly spectrally equivalent to K w.r.t τ, i.e.

$R_\tau^l(G) \simeq R_\tau^m(K) = S$.

If R is an attractor under τ, then the attractor for G as well as for H is R. So G and H have the same attractor R. Otherwise G and H have the same attractor, the attractor for R. Similarly G and K have the same attractor. Therefore the attractors for all three graphs, G, H, K are the same under rule τ. So all three networks (graphs) have the same attractor with respect to the rule τ. □

A very important fact is that networks can be spectrally equivalent with respect to one characteristic of nodes (edges) but not spectrally equivalent with respect to another characteristic. Therefore spectral equivalences built on different characteristics of nodes and edges allow us to uncover various intrinsic (hidden) features of networks' topology.

We now present an example where networks are isomorphic for one characteristic but not for another.

Consider the graphs G and H in figure 2.2.

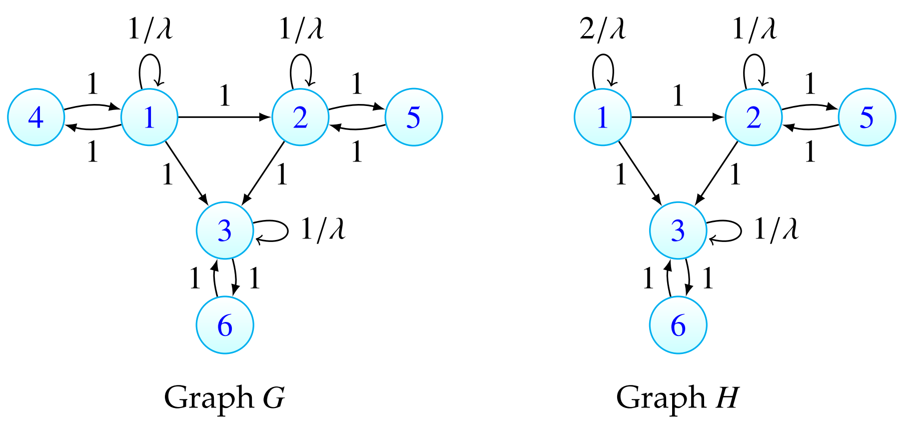


Figure 2.2: Original networks: spectrally equivalent or not?

Their adjacency matrices are

$$M_G = \begin{pmatrix} 1/\lambda & 1 & 1 & 1 & 0 & 0 \\ 0 & 1/\lambda & 1 & 0 & 1 & 0 \\ 0 & 0 & 1/\lambda & 0 & 0 & 1 \\ 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 \end{pmatrix}, \quad M_H = \begin{pmatrix} 2/\lambda & 1 & 1 & 0 & 0 \\ 0 & 1/\lambda & 1 & 1 & 0 \\ 0 & 0 & 1/\lambda & 0 & 1 \\ 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \end{pmatrix}.$$

We can always remove one node in an isospectral reduction. Let us remove node 4 from graph G. The weights of the edges after reduction become

$$R(i,j) = w(i,j) + w(i,4)\frac{w(4,j)}{\lambda}, \quad i,j = 1,2,3,5,6.$$

But $w(i,4) = 0$ for all $i = 2,3,5,6$, and $w(4,j) = 0$ for $j = 2,3,5,6$. The only weight that actually changes after the reduction is $R(1,1) = w(1,1) + w(1,4)w(4,1)/\lambda = 2/\lambda$. All the other weights satisfy $R(i,j) = w(i,j)$, $i \neq 1$ or $j \neq 1$. The reduced graph after removing node 4 is identical to graph H. Therefore H is an isospectral reduction of G. The networks H and G will have the same reduction as long as we pick the same subset of vertices to reduce on.

We introduce now a few useful notations. For any graph $G = (V, E, w)$, denote the maximum indegree by $m^- = \max\{d^-(v) : v \in V\}$, the maximum outdegree by $m^+ = \max\{d^+(v) : v \in V\}$, and the maximum sum of indegree and outdegree as $m = \max\{d(v) : v \in V\}$. We define a few different rules for picking a subset of the vertices of a graph.

$$\tau_1(G) = \{v \in V : d(v) > m/2\};$$

$$\tau_2(G) = \{v \in V : d^-(v) \geq m^-/2\};$$

$$\tau_3(G) = \{v \in V : d^-(v) > m^-/4\}.$$

The rule τ_1 picks the nodes whose sum of indegree and outdegree is greater than half of the maximum. The rule τ_2 picks the nodes whose indegree is greater than or equal to half of the maximum. And τ_3 picks the nodes whose indegree is greater than a quarter of the maximum.

Now we apply these rules to G and H and see what happens. Consider the degrees of all the nodes in the two graphs. We list them in the following table 2.1.

Table 2.1: The degrees of each node in G and H

graph	G						H				
node	1	2	3	4	5	6	1	2	3	5	6
indegree	2	3	4	1	1	1	1	3	4	1	1
outdegree	4	3	2	1	1	1	3	3	2	1	1
sum of indegree and outdegree	6	6	6	2	2	2	4	6	6	2	2

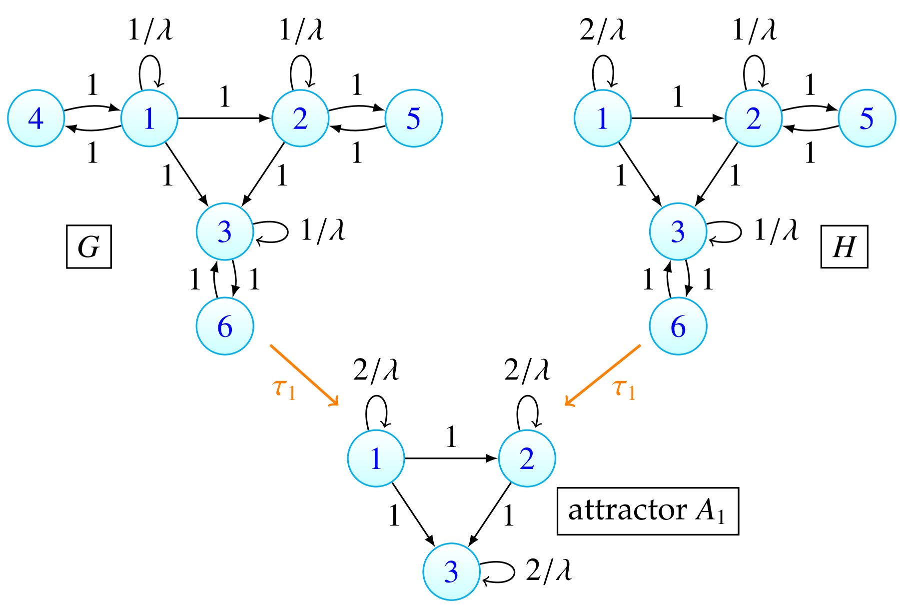


Figure 2.3: Isospectral reductions using the rule τ_1

Let us consider τ_1 first. Both G and H have a maximum sum of indegree and outdegree of 6. $\tau_1(G) = \tau_1(H) = \{1, 2, 3\}$. G and H reduce to the same graph in one step under rule τ_1, as shown in figure 2.3. So G and H are spectrally equivalent under the rule τ_1 with respect to both the 1-step definition in [5] and the multi-step definition we have here. Also the reduced graph A_1 is an attractor for the rule τ_1 since the 3 nodes have the same sum of indegree and outdegree, which is 4. To be more precise, if we write down the indegree, outdegree and the sum of the two, (d^-, d^+, d) as an ordered triple for each node, all the triples for the nodes in A_1 are node 1 with $(1, 3, 4)$, node 2 with $(2, 2, 4)$ and node 3 with $(3, 1, 4)$, so $d(1) = d(2) = d(3) = m(A_1)$.

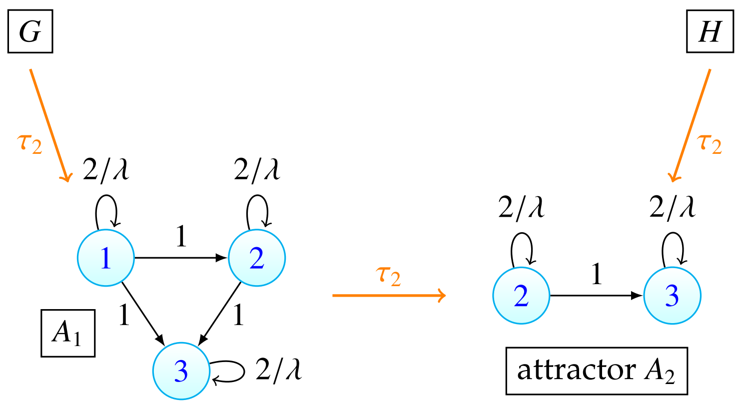


Figure 2.4: Isospectral reductions under the rule τ_2

Similarly, for the rule τ_2, we have $\tau_2(G) = \{1, 2, 3\} \neq \tau_2(H) = \{2, 3\}$. Howeve, $\tau_2(\tau_2(G)) = \{2, 3\} = \tau(H)$. Under the rule τ_2, the graph G takes 2 reductions to reach the attractor A_2 while the graph H takes only one step (see figure 2.4). So G and H are spectrally equivalent with our generalized definition but not with respect to the strong definition of spectral equivalence found in [5]. In the graph A_2, the degree triplets for each node are node 2 with $(1, 2, 3)$ and node 3 with $(2, 1, 3)$. Here $d^-(2) = 1 = 1/2m^-(A_2) = 1/2d^-(3)$. One can see A_1 is an attractor of the rule τ_1 but not of the rule τ_2 since $d^-(1) = 1 < 1/2d^-(3) = 3/2$.

Lastly, for τ_3, $\tau_3(G) = \{1, 2, 3\} = \tau_3(\tau_3(G)), \tau_3(H) = \{2, 3\} = \tau_3(\tau_3(H))$. Here G and H both reach an attractor in one step. But the attractors they reach are different. Under the rule τ_3 the graphs G and H are not isospectrally equivalent by either definition (see figure 2.5).

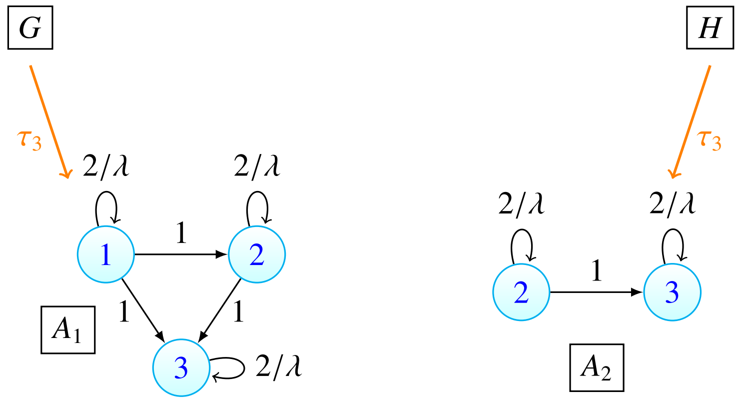


Figure 2.5: Isospectral reductions under the rule τ_3

Here A_1 and A_2 are both attractors for the rule τ_3. For A_1, $d^-(1) = 1, d^-(2) = 2, d^-(3) = 3$. For A_2 we have $d^-(2) = 1, d^-(3) = 2$. So A_1 is an attractor under the rules τ_1 and τ_3 but not under τ_2. A_2 is an attractor for all 3 rules we used in this sequence of examples.

Theorem 10. Let $G = (V, E, w)$ with $w : E \to \mathbb{C}$. If S is a structural and $S \subseteq S' \subseteq V$, then S is a structural set of the isospectral reduction $R_{S'}(G)$.

Proof. Suppose $S \subsetneq S' \subsetneq V$. Now we will show that S is also a structural set for the reduced graph $R_{S'}(G)$.

(i) Any cycle (not a loop) in $R_{S'}(G)$ comes from a cycle in G. It has to contain a vertex in S.

(ii) For any $i \in S' \setminus S$, the new weight in $R_{S'}(G)$ is given by

$$\tilde{w}(i,i) = w(i,i) + \sum_{j \in V/S'} w(i,j)\frac{w(j,i)}{\lambda - w(j,j)} + \sum_{j \neq k, j,k \in V/S'} w(i,j)\frac{w(j,k)}{\lambda - w(j,j)}\frac{w(k,i)}{\lambda - w(k,k)} + \ldots.$$

Since $w(i,i), w(j,j), w(k,k) \in \mathbb{C}$, the expression above shows that $\tilde{w}(i,i) \neq \lambda$. This implies that S is a structural set of $R_{S'}(G)$. □

Remark 11. If we allow the original graph to take weights in $\mathbb{W}$, the above proof still holds as long as $\tilde{w}(i,i) \neq \lambda, \forall i \in S' \setminus S$. Since it's a zero measure set among all the possible values $\tilde{w}(i,i)$'s can take, we can say generally, the theorem is true for any graph with weights in $\mathbb{W}$ except for unusual cases.

By the uniqueness of sequential graph reductions, we can see isospectral reduction is a dynamical system.

CHAPTER 3

LOCAL IMMUNODEFICIENCY: MINIMAL NETWORKS AND STABILITY

3.1 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. [12, 13, 14, 15, 16, 17, 18, 19]). In a nutshell, CR means that the generation of antibodies to some antigen (virus) can be stimulated by other antigens. Therefore CR generates (indirectly, i.e. via the corresponding antibodies) interactions between the antigens. 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 [17, 18, 16, 14].

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 (CRN) has a very complicated structure (topology) which resembles the topology of scale-free networks [13, 12].

A new model for the dynamics of Hepatitis C (HC) [3] is conceptually simpler than the previous ones (see e.g. [16]). In fact the new model involves only two (necessary) types of variables, the population sizes of various types of viruses and the population sizes of their corresponding antibodies, in immunological models. For instance, the HC model in [16] contains three more types of variables, namely the population sizes of infected and of non-infected hepatocytes as well as a total (mean field) CR 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. Different pairs of viruses generally have different strengths of interaction in the CRN, but in the old model they were all equal to each other.

Traditionally, to describe new experimental findings which old models fail to reproduce, one makes a more complicated mathematical model by adding more variables or more equations. The model introduced in [3] is based on new specially conducted experiments [13, 12] which proved essential heterogeneity of the CRN. Although the model in [3] was dealing with dynamics of HC, it provides a model of evolution for any disease which has cross-immunoreactivity. The paper [3] analyzed the dynamics of this new model numerically. Scale-free CRNs of sizes 500-1000 were generated and numerical simulations were performed on them.

The main result was the discovery of a new phenomenon [3], Local Immunodeficiency (LI), which showed up in all of the several hundred simulations. Namely, in all these simulations, the pool of HC viruses got partitioned into three types. The first type consists of *persistent* viruses that have large population sizes but virtually zero immune response against them. In other words, *persistent* viruses remain undetected by the human immune system. Thus a clear immunodeficiency (with respect to persistent viruses) is present. It is called [3] *local immunodeficiency* because it is completely determined by the localized positions of the *persistent* viruses in the CRN. Observe, however, that generally it may happen that only specific types of antigens are ”qualified” to be persistent viruses. Only special biological experiments may clarify this issue.

Persistent viruses enjoy such a relaxing life because the second type, *altruistic* viruses, sacrifice themselves to protect the *persistent* viruses from the immune system. Concentrations of *altruistic* viruses are very small but they carry almost the entire immune response against all of the in-host population of viruses. Again, we need further experimental biological studies to determine which antigens can and which can not play a role of altruistic viruses. The rest (third type) of viruses plays a much smaller role in the HC evolution [3]. 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 [3].

First, we prove that stable LI already appears in a specific CRN with only three nodes under general conditions. These conditions are expressed as realistic inequalities between parameters of the model. Therefore LI is likely to appear in all diseases with cross-immunoreactivity. Indeed, because of a very high mutation rate of HC viruses in host, the corresponding CRNs are very large [3]. Since both small and large CRNs can generate LI, one is tempted to believe that this phenomenon should be universal for all diseases with cross-immunoreactivity.

It is proved that LI is a stable state of evolution of the model in only one (out of many possible topologies) of the networks with three types of viruses, while in all two-node CRNs LI is unstable. This three-node network with stable LI is characterized by the maximal asymmetry of its structure among all networks of size three. Here by "maximal asymmetry" we mean that all the nodes have different indegrees. In this network there is one persistent node and one altruistic node while the third node is neutral.

We also prove that there are no two-node CRNs with stable LI. It should be mentioned that the two-node network with stable LI found in [3] 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 parameter space where stable LI exists have the same dimension as the the parameter space of the model. However, it happens only in certain networks with at least three elements (types of viruses). Once again, these networks must also be sufficiently non-homogeneous, which is (qualitatively) consistent with numerical results in [3] for large CRNs.

We then demonstrate how one can build larger CRNs with stable LI by attaching the three-node minimal network with stable LI. For instance, we proved that by combining two such networks one gets a network with five nodes where two types of viruses are persistent and two are altruistic. And the dynamics of HC with such a CRN is stable and robust. Our results were mostly obtained by direct computations. For large networks one would need numerical simulations although our rigorous results about smaller CRNs 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 also prove the presence of stable and robust LI in a network with seemingly mild non-homogeneity of its topology. It is important to mention that among CRNs with four nodes there are quite a few with more non-homogeneous topology than the one we studied. Therefore our results essentially prove that stable and robust LI must also be present in those CRNs. It is for this purpose that we studied a less non-homogeneous network. The proof of stable and robust LI (essentially by long direct computations) in this CRN is given in the Appendix.

It is important to mention that in this paper we are dealing with *strong* LI, which is a stronger property than the one found in [3]. Namely, we say that a certain type of virus causes strong local immunodeficiency if the immune response against it is identically zero, so completely absent. Analogously, we say that some kind of 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 [3], instead of these identical zeroes, some (sufficiently) small quantities were considered. We call this case a *weak* LI. 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 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 CRNs.

These rigorously proven results demonstrate that stable LI does not require a special scale-free structure of the CRN. In fact, it is enough that the CRN is sufficiently non-homogeneous. It is natural to expect that this condition is satisfied in real life situations because there is no reason for CRNs to be homogeneous. Non-homogeneity of CRNs 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 LI is a robust phenomenon. Recall that a state 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 that altruistic viruses, which have very small concentration but occupy central positions in the CRNs with the largest in-degrees [3], play a key role in LI. Namely the altruistic viruses were present in all CRNs where we found stable and robust LI. All CRNs with fixed points with LI but without altruistic viruses turned out to be non-robust, i.e. the LI could be destroyed by arbitrarily small variations of parameters. This means that such cases are non-typical, i.e. they have a positive codimension (or zero volume) in the space of all systems we study. Therefore they cannot be seen in real life situations. (In other words, it is a zero probability event to encounter an LI without altruistic viruses.) This observation also explains why altruistic viruses were always present in the several hundred numerical experiments conducted in [3]. Therefore these altruistic local hubs of CRNs must be the primary targets of prevention and elimination of the corresponding diseases. This is yet another question for the future studies, both biological and computational. From a general biomedical point of view a main challenge is to understand which types of viruses could play a role of altruistic and which persistent ones.

The structure of the paper is as follows. Section 3.2 introduces the model. Section 3.3 is devoted to a general analysis of the stability of dynamics of this model. Section 3.4 analyzes two-node networks. Three-node networks are studied in section 3.5. Section 3.6 proves the necessity of altruistic viruses. The building of larger networks with stable LI is considered in section 3.7. Lastly section 3.8 contains some concluding remarks. Some long technical computations are placed in the Appendix. We also put some long computations with a four-node CRN in the Appendix to demonstrate that LI appears in networks with a relatively mild non-homogeneity of their topology.

3.2 Model of evolution of a disease with heterogeneous CRN

In this section we define the model of the HC evolution introduced in [3]. It is important to stress again that this model is applicable to any disease with cross-immunoreactivity.

Consider any immunological model, 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 CR which results in a CR network. 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, 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 evolution of the antigen (virus) and antibody populations is given by the following system of ordinary differential equations (ODEs):

$$\begin{aligned} \dot{x}_i &= f_i x_i - p x_i \sum_{j=1}^{n} u_{ji} r_j, \quad i = 1, \ldots, n, \\ \dot{r}_i &= c \sum_{j=1}^{n} x_j \frac{v_{ji} r_i}{\sum_{k=1}^{n} v_{jk} r_k} - b r_i, \quad i = 1, \ldots, n. \end{aligned} \tag{3.1}$$

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 $c g_{ji} x_j$, where $g_{ji} = \frac{v_{ji} r_i}{\sum_{k=1}^{n} v_{jk} r_k}$ represents the probability of stimulation of the immune response r_i by the variant x_j. This model (as in [3]) allows us to incorporate the phenomenon of the original antigenic sin [20, 21, 22, 23, 24, 25], 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 α and β, respectively. To be more specific, both the immune neutralization and stimulation matrices are completely defined by the structure of the CRN, i.e.,

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

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 [14] for heterogeneous viral population. Because the neutralization of an antigen may require more than one antibodies, we assume that $0 < \beta = \alpha^k < \alpha < 1$ [3]. It is important to mention that we analyze a more general model here than the one studied in [3], where it was assumed that all viruses replicate with the same rate.

3.3 Stationary states of the model

Fixed points of system (3.1) are determined by the relations

$$\begin{aligned} f_i x_i &= p x_i \sum_{j=1}^{n} u_{ji} r_j, \quad i = 1, \dots, n, \\ c r_i \sum_{j=1}^{n} \frac{v_{ji} x_j}{\sum_{k=1}^{n} v_{jk} r_k} &= b r_i, \quad i = 1, \dots, n. \end{aligned} \tag{3.2}$$

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 sets

$$N = \{i \in \mathbb{N}, 1 \le i \le n\}, I = \{i \in N : x_i > 0\}, J = \{i \in N : r_i > 0\}.$$

Definition 9. 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 [3] a weaker LI 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. In [3] LI was considered to be present when persistent viruses increase their population but the immune response against them was relatively small. These conditions are more practical for computer simulations, since it could take a very long time to completely eliminate some virus, but they are not very precise. Here we consider a stronger but well defined case, *strong* LI. Since a strong LI automatically implies weak LI, showing that strong LI is ubiquitous for non-homogeneous CRNs demonstrates that weak LI is even more common for such networks.

By making use of the notations introduced above we get a simpler formula for the fixed points:

$$\begin{aligned}
\sum_{j \in N} u_{ji} r_j = r_i + \beta \sum_{ij \in E} r_j = f_i/p, \forall i \in I, \\
\sum_{j \in N} \frac{v_{ji} x_j}{\sum_{k \in J} v_{jk} r_k} = \delta_i x_i + \alpha \sum_{ji \in E} \delta_j x_j = b/c, \forall i \in J, \\
\delta_i = \frac{1}{r_i + \alpha \sum_{ik \in E} r_k}.
\end{aligned}$$

In our parameter space $\{f_1, f_2, \ldots, f_n > 0, p, c, b > 0, 1 > \alpha, \beta > 0\}$, 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 ODE (3.1). 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 (3.1). Because of this we are only interested in stationary points which exist without extra conditions or under conditions expressed as inequalities between the parameters of the model. This should be contrasted with [3] where LI was shown to exist under much more restrictive conditions with some exact equalities between the system's parameters.

Suppose that the matrices $V = (\mathrm{Id}+\alpha A)$ and $U = (\mathrm{Id}+\beta A^T)$ are invertible. Denote $F = (f_1, \ldots, f_n)^T$. Then one stationary point is defined by the following relation

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

Notice that U, V are constant matrices determined by the CRN and parameters, and F is a constant vector of parameters. Because of that, R^* here is a constant vector, which represents the population of the antibodies. For this R^*, we also have a corresponding constant vector for the population of the viruses X^*, given as a function of R^*, which is denoted as Xr here for convenience.

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

$$R = R^* + \ker(U_I^T), X = Xr(R) + \ker(V_J^T),$$

where

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

To verify the stability of a stationary point, we need to consider the Jacobian matrix of the right hand side of (3.1). It can be written in block form as

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

where

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

$$C_{i,j} = c\frac{v_{ji}r_i}{\sum_{k=1}^{n} v_{jk}r_k}, D_{i,l} = -cr_i\sum_{j=1}^{n}\frac{v_{ji}x_jv_{jl}}{(\sum_{k=1}^{n} v_{jk}r_k)^2}, l \neq i,$$

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

3.4 Analysis of size 2 CRN

We analyze the asymmetric network of size 2 (Fig. 3.1) in this section. We consider the only asymmetric network in hope of finding LI, based on the understanding that LI requires some level of non-homogeneity of the network.

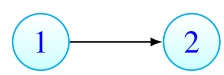


Figure 3.1: size 2 CRN

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

$$\begin{cases} \dot{x}_1 = f_1x_1 - px_1(r_1 + \beta r_2), \\ \dot{x}_2 = f_2x_2 - px_2r_2, \\ \dot{r}_1 = cx_1\frac{r_1}{r_1+\alpha r_2} - br_1, \\ \dot{r}_2 = c(x_1\frac{\alpha r_2}{r_1+\alpha r_2} + x_2) - br_2. \end{cases}$$

Here there is only one fixed point of interest, the one where the values of the variables are non-negative and the strong LI is present without exact equality conditions on the parameters. This fixed point is given by the relations

$$x_1 = \frac{bf_1}{cp\beta}, x_2 = 0, r_1 = 0, r_2 = \frac{f_1}{p\beta}.$$

The Jacobian of the system is

$$J = \begin{pmatrix} f_1 - p(r_1 + \beta r_2) & 0 & -px_1 & -p\beta x_1 \\ 0 & f_2 - pr_2 & 0 & -px_2 \\ \frac{cr_1}{r_1+\alpha r_2} & 0 & \frac{cx_1\alpha r_2}{(r_1+\alpha r_2)^2} - b & -\frac{cx_1\alpha r_1}{(r_1+\alpha r_2)^2} \\ \frac{c\alpha r_2}{r_1+\alpha r_2} & c & -\frac{cx_1\alpha r_2}{(r_1+\alpha r_2)^2} & \frac{cx_1\alpha r_1}{(r_1+\alpha r_2)^2} - b \end{pmatrix}.$$

At the fixed point the Jacobian equals

$$J = \begin{pmatrix} 0 & 0 & -\frac{bf_1}{c\beta} & -\frac{b}{c}f_1 \\ 0 & f_2 - \frac{f_1}{\beta} & 0 & 0 \\ 0 & 0 & \frac{b}{\alpha} - b & 0 \\ c & c & -\frac{b}{\alpha} & -b \end{pmatrix}.$$

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

It is important to mention that a stable LI for this two node network was found in [3]. However, as we already mentioned before it has been done under unrealistic conditions. One can also check that the symmetric network of size 2 doesn't have a stable LI. Detailed computations for it is listed in B.1. Our analysis proves that no two-node network can have a stable and robust state of LI.

3.5 Analysis of size 3 CRNs

In this section we study the stability of dynamics of CRNs with three elements. In some of these networks there is no stable LI because of their symmetry or not enough non-homogeneity. Actually only one topology of a CRN with three elements demonstrates a stable strong LI. We present here the analysis of this size 3 CRN as well as of another one. Some other CRN is analyzed in B.2.

Consider at first the chain-branch CRN (Fig. 3.2). Such a network was briefly mentioned in [3] to demonstrate that long distance action in networks may lead to LI. No studies of stability were conducted in that paper though. Also recall that here we are after *robust* conditions of stable LI which would not be violated under variations of parameters. The latter always occurs because of permanently changing environments. Besides, any mathematical model (including (3.1) of course) is just an approximation to reality. Therefore robustness is a necessary condition for any predictive model of a real system or phenomenon.

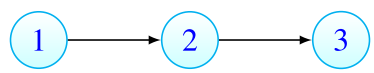


Figure 3.2: chain-branch CRN

Here system (3.1) becomes

$$\begin{cases} \dot{x}_1 = f_1 x_{(}1 - p x_1(r_1 + \beta r_2), \\ \dot{x}_2 = f_2 x_2 - p x_2(r_2 + \beta r_3), \\ \dot{x}_3 = f_3 x_3 - p x_3 r_3, \\ \dot{r}_1 = c x_1 \frac{r_1}{r_1 + \alpha r_2} - b r_1, \\ \dot{r}_2 = c(x_1 \frac{\alpha r_2}{r_1 + \alpha r_2} + x_2 \frac{r_2}{r_2 + \alpha r_3}) - b r_2, \\ \dot{r}_3 = c(x_2 \frac{\alpha r_3}{r_2 + \alpha r_3} + x_3) - b r_3. \end{cases}$$

The fixed points with local immunodeficiency are:

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

$$x_1 = \frac{b f_1}{c p \beta}, x_2 = 0, x_3 = \frac{b f_3}{c p}, r_1 = 0, r_2 = \frac{f_1}{p \beta}, r_3 = \frac{f_3}{p};$$

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

The Jacobian of the system becomes

$$J = \begin{pmatrix} f_1 - p(r_1+\beta r_2) & 0 & 0 & -px_1 & -p\beta x_1 & 0 \\ 0 & f_2 - p(r_2+\beta r_3) & 0 & 0 & -px_2 & -p\beta x_2 \\ 0 & 0 & f_3 - pr_3 & 0 & 0 & -px_3 \\ \frac{cr_1}{r_1+\alpha r_2} & 0 & 0 & \frac{c\alpha x_1 r_2}{(r_1+\alpha r_2)^2} - b & -\frac{c\alpha x_1 r_1}{(r_1+\alpha r_2)^2} & 0 \\ \frac{c\alpha r_2}{r_1+\alpha r_2} & \frac{cr_2}{r_2+\alpha r_3} & 0 & -\frac{c\alpha x_1 r_2}{(r_1+\alpha r_2)^2} & \frac{c\alpha x_1 r_1}{(r_1+\alpha r_2)^2} + \frac{c\alpha x_2 r_3}{(r_2+\alpha r_3)^2} - b & -\frac{c\alpha x_2 r_2}{(r_2+\alpha r_3)^2} \\ 0 & \frac{c\alpha r_3}{r_2+\alpha r_3} & c & 0 & -\frac{c\alpha x_2 r_3}{(r_2+\alpha r_3)^2} & \frac{c\alpha x_2 r_2}{(r_2+\alpha r_3)^2} - b \end{pmatrix}.$$

At the fixed point $x_1 = \frac{bf_1}{cp\beta}, x_2 = x_3 = 0, r_2 = \frac{f_1}{p\beta}, r_1 = r_3 = 0$, the Jacobian is

$$J = \begin{pmatrix} 0 & 0 & 0 & -\frac{bf_1}{c\beta} & -\frac{b}{c}f_1 & 0 \\ 0 & f_2 - \frac{f_1}{\beta} & 0 & 0 & 0 & 0 \\ 0 & 0 & f_3 & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{b}{\alpha} - b & 0 & 0 \\ c & c & 0 & -\frac{b}{\alpha} & -b & 0 \\ 0 & 0 & c & 0 & 0 & -b \end{pmatrix}.$$

There are eigenvalues $\lambda = f_3, \frac{b}{\alpha} - b > 0$. Therefore this fixed point is unstable.

At the second fixed point $x_1 = \frac{bf_1}{cp\beta}, x_3 = \frac{bf_3}{cp}, x_2 = 0, r_2 = \frac{f_1}{p\beta}, r_3 = \frac{f_3}{p}, r_1 = 0$, we have

$$J = \begin{pmatrix} 0 & 0 & 0 & -\frac{bf_1}{c\beta} & -\frac{b}{c}f_1 & 0 \\ 0 & f_2 - \frac{f_1}{\beta} - \beta f_3 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -\frac{b}{c}f_3 \\ 0 & 0 & 0 & \frac{b}{\alpha} - b & 0 & 0 \\ c & \frac{cf_1}{f_1+\alpha\beta f_3} & 0 & -\frac{b}{\alpha} & -b & 0 \\ 0 & \frac{c\alpha\beta f_3}{f_1+\alpha\beta f_3} & c & 0 & 0 & -b \end{pmatrix},$$

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

At the fixed point $x_1 = \frac{bf_1}{cp}, x_2 = \frac{bf_2}{cp\beta}, x_3 = 0, r_1 = \frac{f_1}{p}, r_3 = \frac{f_2}{p\beta}, r_2 = 0$, the Jacobian takes the form

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

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

Next we consider a CRN with three elements which has maximal asymmetry among all thirteen topologically different networks of three elements. Indeed only in this network indegrees of all three nodes are different and equal 0,2 and 1 respectively. 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. 3.3 and we call it a branch-cycle network.

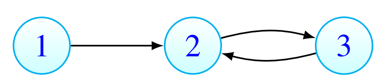


Figure 3.3: branch-cycle CRN

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

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

The fixed points of interest (i.e. all population sizes are non-negative, there is a strong LI, and the relations between system parameters are inequalities rather than equalities) in this case are

$$x_1 = 0, x_2 = 0, x_3 = \frac{b f_3}{c p \beta}, r_1 = 0, r_2 = \frac{f_3}{p \beta}, r_3 = 0;$$

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

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

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

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

The Jacobian of the system is

$$J = \begin{pmatrix} f_1 - p(r_1 + \beta r_2) & 0 & 0 & -px_1 & -p\beta x_1 & 0 \\ 0 & f_2 - p(r_2 + \beta r_3) & 0 & 0 & -px_2 & -p\beta x_2 \\ 0 & 0 & f_3 - p(\beta r_2 + r_3) & 0 & -p\beta x_3 & -px_3 \\ \frac{cr_1}{r_1+\alpha r_2} & 0 & 0 & \frac{cx_1\alpha r_2}{(r_1+\alpha r_2)^2} - b & -\frac{cx_1\alpha r_1}{(r_1+\alpha r_2)^2} & 0 \\ \frac{c\alpha r_2}{r_1+\alpha r_2} & \frac{cr_2}{r_2+\alpha r_3} & \frac{c\alpha r_2}{\alpha r_2+r_3} & -\frac{cx_1\alpha r_2}{(r_1+\alpha r_2)^2} & A - b & -B \\ 0 & \frac{c\alpha r_3}{r_2+\alpha r_3} & \frac{cr_3}{\alpha r_2+r_3} & 0 & -\frac{cx_2\alpha r_3}{(r_2+\alpha r_3)^2} - \frac{cx_3\alpha r_3}{(\alpha r_2+r_3)^2} & B - b \end{pmatrix},$$

$$\text{where } A = \frac{cx_1\alpha r_1}{(r_1 + \alpha r_2)^2} + \frac{cx_2\alpha r_3}{(r_2 + \alpha r_3)^2} + \frac{cx_3\alpha r_3}{(\alpha r_2 + r_3)^2}, B = \frac{cx_2\alpha r_2}{(r_2 + \alpha r_3)^2} + \frac{cx_3\alpha r_2}{(\alpha r_2 + r_3)^2}.$$

At the fixed point $x_3 = \frac{bf_3}{cp\beta}, x_1 = x_2 = 0, r_2 = \frac{f_3}{p\beta}, r_1 = r_3 = 0$, we have

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

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

At the next fixed point $x_1 = \frac{bf_1}{cp\beta}, x_2 = x_3 = 0, r_2 = \frac{f_1}{p\beta}, r_1 = r_3 = 0$, we get

$$A = B = 0, J = \begin{pmatrix} 0 & 0 & 0 & -\frac{bf_1}{c\beta} & -\frac{b}{c}f_1 & 0 \\ 0 & f_2 - \frac{f_1}{\beta} & 0 & 0 & 0 & 0 \\ 0 & 0 & f_3 - f_1 & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{b}{\alpha} - b & 0 & 0 \\ c & c & c & -\frac{b}{\alpha} & -b & 0 \\ 0 & 0 & 0 & 0 & 0 & -b \end{pmatrix}.$$

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

At the fixed point $x_1 = \frac{bf_1}{cp}, x_2 = \frac{bf_2}{cp\beta}, x_3 = 0, r_1 = \frac{f_1}{p}, r_3 = \frac{f_2}{p\beta}, r_2 = 0$, we obtain

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

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

For the fixed point $f_3 > f_1, x_1 = \frac{bf_1}{cp\beta}(1-\alpha), x_3 = \frac{b}{cp}(f_3 - f_1 + \frac{\alpha}{\beta}f_1), x_2 = 0, r_2 = \frac{f_1}{p\beta}, r_3 = \frac{f_3-f_1}{p}, r_1 = 0$, we have

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

$$J = \begin{pmatrix} 0 & 0 & 0 & -\frac{b}{c\beta}f_1(1-\alpha) & -\frac{b}{c}f_1(1-\alpha) & 0 \\ 0 & f_2 - \frac{f_1}{\beta} - \beta(f_3 - f_1) & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -\frac{b\beta}{c}(f_3 - f_1 + \frac{\alpha}{\beta}f_1) & -\frac{b}{c}(f_3 - f_1 + \frac{\alpha}{\beta}f_1) \\ 0 & 0 & 0 & \frac{b}{\alpha} - 2b & 0 & 0 \\ c & c\frac{f_1}{f_1+\alpha\beta(f_3-f_1)} & c\frac{\alpha/\beta f_1}{f_3-f_1+\alpha/\beta f_1} & b - \frac{b}{\alpha} & A - b & -B \\ 0 & c\frac{\alpha\beta(f_3-f_1)}{f_1+\alpha\beta(f_3-f_1)} & c\frac{f_3-f_1}{f_3-f_1+\alpha/\beta f_1} & 0 & -A & B - b \end{pmatrix}.$$

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

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

$$P(\lambda) = bf_1(1-\alpha)[\lambda^2 + (b - B)\lambda + \frac{AD}{\alpha}] +$$

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

$$= \lambda^4 + b(1 + \frac{(1-\alpha)(f_3 - f_1)}{f_3 - f_1 + \alpha/\beta f_1})\lambda^3 + (bf_3 + b^2\frac{(1-\alpha)(f_3 - f_1)}{f_3 - f_1 + \alpha/\beta f_1})\lambda^2$$

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

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 LI is present. In each such numerical example we pick the values of the parameters to satisfy the conditions (inequalities) of existence and stability of the corresponding fixed point, and close to the literature ranges (e.g. [14], [3] and references therein). This hand pick approach seems to be reasonable for demonstration as well as for applications. In fact in biomedical studies some parameters could be measured while the others are picked from some reasonable (accepted) ranges.

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.

It is easy to see that the roots of $P(\lambda)$ depend continuously on the parameters. Therefore 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. Thus LI in this system remains a stable type of behavior under variations of the system's parameters.

At the fixed point $f_3 < f_1, x_1 = \frac{b}{cp}(f_1 - f_3 + \frac{\alpha}{\beta} f_3), x_3 = \frac{bf_3}{cp\beta}(1-\alpha), x_2 = 0, r_1 = \frac{f_1 - f_3}{p}, r_2 = \frac{f_3}{p\beta}, r_3 = 0$, we have

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

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

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

$$\begin{aligned} \det(\lambda I - J) &= (\lambda - \lambda_1)(\lambda - \lambda_2)P(\lambda), \\ P(\lambda) &= bf_3(1-\alpha)(\lambda^2 + \frac{A}{\alpha}\lambda + \frac{AD}{\alpha}) + \\ &\lambda\{b\beta D(\lambda + \frac{A}{\alpha}) - bAD + (\lambda + b)[\lambda^2 + (\frac{A}{\alpha} - A)\lambda + \frac{AD}{\alpha}(1-\beta)]\} \\ &= \lambda^4 + b(1 + \frac{(1-\alpha)(f_1 - f_3)}{f_1 - f_3 + \alpha/\beta f_3})\lambda^3 + (bf_1 + b^2 \frac{(1-\alpha)(f_1 - f_3)}{f_1 - f_3 + \alpha/\beta f_3})\lambda^2 \\ &+ b^2(1-\alpha)(f_1 - f_3)(1 + \frac{f_3}{f_1 - f_3 + \alpha/\beta f_3})\lambda + b^2(1-\alpha) f_3 (f_1 - f_3). \end{aligned}$$

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 B.2.

3.6 Necessity of altruistic nodes

We will now address a problem, whether altruistic nodes must be present in all cases of LI.

We considered all the fixed points for CRNs of sizes two and three (see B.3). They can be separated into four groups.

- A: fixed points with LI and with no extra condition on the parameters.
- B: fixed points with LI with conditions on the parameters in the form of inequalities.
- C: fixed points with LI with conditions on the parameters that involve at least one equality.
- D: fixed points with no LI.

One can check that fixed points in groups A and B all have altruistic nodes, while fixed points with no altruistic nodes all belong to groups C and D. So altruistic viruses are not necessary for the existence of fixed points with LI in the group C. However conditions on parameters in the form of equalities single out a subset of zero volume in the space of all systems we consider (when parameters in (3.1) assume any reasonable/permissible values). By reasonable/permissible we mean such values of parameters that make sense. For instance, negative growth rates are not permissible.

Next we consider the existence of altruistic viruses in CRNs of arbitrary (finite) size n. We exclude neutral idle nodes with $x_i = r_i = 0$ since they don't contribute to the dynamics. For any fixed point, assume that there are no altruistic nodes. Then $x_i > 0, \forall i = 1, \ldots, n$. This results in the following relation

$$U^T R = F/p \tag{3.3}$$

where $R = (r_1, \ldots, r_n)^T, F = (f_1, \ldots, f_n)^T$. It is easy to see that for (3.3) to have a solution, F must be in the column space of $U^T = (I + \beta A^T)^T = I + \beta A$.

Consider now two cases.

i. If U^T is invertible, then the column space of U^T is $\mathbb{R}^n$. F is always in the column space of U^T;

ii. If U^T is not invertible, then its column space is a subspace of $\mathbb{R}^n$ with a positive codimension. In other words, the condition on the parameters f_i's in this case is a zero volume subset of the parameter space.

For a fixed point to have LI, we need the vector R to have at least one zero component. These vectors are on the axes and axes planes in $\mathbb{R}^n$, or the complement of the set where every component is nonzero. Hence, this is a zero volume set. Consider again two cases.

i. If U^T is invertible, then $F = pU^T R$ is also on a zero volume set.

ii. If U^T is not invertible, then (3.3) has either none or infinitely many solutions. Therefore if R has a solution, it has one solution where some component is zero. However in the previous step we already showed that if U^T is not invertible, F must belong to a zero measure subspace.

In conclusion, formally altruistic viruses are not necessary for the existence of LI. But the conditions on the parameters for fixed points to have persistent nodes without altruistic nodes are only satisfied on a zero measure subset of the parameter space. Therefore, practically speaking, altruistic viruses form a necessary component of local immunodeficiency.

3.7 Building larger networks with stable & robust LI

In this section we demonstrate how one can construct CRNs with multiple nodes with LI. In other words, we construct a CRN with several persistent nodes 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 CRNs with stable LI found in section 3.5. We prove that the corresponding size 5 CRN has a fixed point with two persistent nodes and two altruistic nodes. We also demonstrate the stability of strong LI for this specific state. Consider the following network in Fig. 3.4.

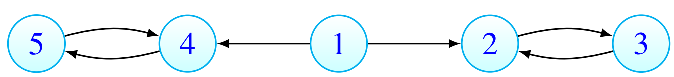


Figure 3.4: size 5 CRN

The model (3.1) equations for this network are

$$
\begin{cases}
\dot{x}_1 = f_1 x_1 - p x_1 (r_1 + \beta r_2 + \beta r_4), \\
\dot{x}_2 = f_2 x_2 - p x_2 (r_2 + \beta r_3), \\
\dot{x}_3 = f_3 x_3 - p x_3 (\beta r_2 + r_3), \\
\dot{x}_4 = f_4 x_4 - p x_4 (r_4 + \beta r_5), \\
\dot{x}_5 = f_5 x_5 - p x_5 (\beta r_4 + r_5), \\
\dot{r}_1 = c x_1 \frac{r_1}{r_1 + \alpha r_2 + \alpha r_4} - b r_1, \\
\dot{r}_2 = c(x_1 \frac{\alpha r_2}{r_1 + \alpha r_2 + \alpha r_4} + x_2 \frac{r_2}{r_2 + \alpha r_3} + x_3 \frac{\alpha r_2}{\alpha r_2 + r_3}) - b r_2, \\
\dot{r}_3 = c(x_2 \frac{\alpha r_3}{r_2 + \alpha r_3} + x_3 \frac{r_3}{\alpha r_2 + r_3}) - b r_3, \\
\dot{r}_4 = c(x_1 \frac{\alpha r_4}{r_1 + \alpha r_2 + \alpha r_4} + x_4 \frac{r_4}{r_4 + \alpha r_5} + x_5 \frac{\alpha r_4}{\alpha r_4 + r_5}) - b r_4, \\
\dot{r}_5 = c(x_4 \frac{\alpha r_5}{r_4 + \alpha r_5} + x_5 \frac{r_5}{\alpha r_4 + r_5}) - b r_5.
\end{cases}
$$

Here we mirrored the chain-branch network about node 1. We are not going to try to compute all possible fixed points with LI this time. In general, based on a vague rule (there is always an arrow going from the persistent node to the altruistic node, and the altruistic node typically has a high indegree), one can make a guess and pick a node to be altruistic and another to be persistent. Then a specific fixed node with LI can be computed based on the guess through a relatively straightforward process. However, finding all possible fixed points with LI is more complicated. In the current 5-node CRN, we want LIs 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

$$
f_1 - f_3 - f_5 > 0, x_1 = \frac{b}{cp}(f_1 - f_3 - f_5 + \frac{\alpha}{\beta} f_3 + \frac{\alpha}{\beta} f_5), r_1 = \frac{f_1 - f_3 - f_5}{p},
$$

$$
x_2 = 0, r_2 = \frac{f_3}{p\beta}, x_3 = \frac{b f_3}{c p \beta}(1 - \alpha), r_3 = 0, x_4 = 0, r_4 = \frac{f_5}{p\beta}, x_5 = \frac{b f_5}{c p \beta}(1 - \alpha), r_5 = 0.
$$

The Jacobian is

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

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

$$C = \begin{pmatrix} \frac{cr_1}{r_1+\alpha r_2+\alpha r_4} & 0 & 0 & 0 & 0 \\ \frac{c\alpha r_2}{r_1+\alpha r_2+\alpha r_4} & \frac{cr_2}{r_2+\alpha r_3} & \frac{c\alpha r_2}{\alpha r_2+r_3} & 0 & 0 \\ 0 & \frac{c\alpha r_3}{r_2+\alpha r_3} & \frac{cr_3}{\alpha r_2+r_3} & 0 & 0 \\ \frac{c\alpha r_4}{r_1+\alpha r_2+\alpha r_4} & 0 & 0 & \frac{cr_4}{r_4+\alpha r_5} & \frac{c\alpha r_4}{\alpha r_4+r_5} \\ 0 & 0 & 0 & \frac{c\alpha r_5}{r_4+\alpha r_5} & \frac{cr_5}{\alpha r_4+r_5} \end{pmatrix} = \begin{pmatrix} \frac{br_1}{x_1} & 0 & 0 & 0 & 0 \\ \frac{b\alpha r_2}{x_1} & c & c & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ \frac{b\alpha r_4}{x_1} & 0 & 0 & c & c \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

$$D = \begin{pmatrix} D_1 \\ D_2 \end{pmatrix},$$

$$D_1 = \begin{pmatrix} \frac{cx_1\alpha(r_2+r_4)}{(r_1+\alpha r_2+\alpha r_4)^2} - b & -\frac{cx_1r_1\alpha}{(r_1+\alpha r_2+\alpha r_4)^2} & 0 & -\frac{cx_1r_1\alpha}{(r_1+\alpha r_2+\alpha r_4)^2} & 0 \\ -\frac{cx_1\alpha r_2}{(r_1+\alpha r_2+\alpha r_4)^2} & \frac{cx_1\alpha(r_1+\alpha r_4)}{(r_1+\alpha r_2+\alpha r_4)^2} + \frac{cx_2\alpha r_3}{(r_2+\alpha r_3)^2} + \frac{cx_3\alpha r_3}{(\alpha r_2+r_3)^2} - b & -\frac{cx_2r_2\alpha}{(r_2+\alpha r_3)^2} - \frac{cx_3\alpha r_2}{(\alpha r_2+r_3)^2} & -\frac{cx_1\alpha^2 r_2}{(r_1+\alpha r_2+\alpha r_4)^2} & 0 \\ 0 & -\frac{cx_2\alpha r_3}{(r_2+\alpha r_3)^2} - \frac{cx_3r_3\alpha}{(\alpha r_2+r_3)^2} & \frac{cx_2\alpha r_2}{(r_2+\alpha r_3)^2} + \frac{cx_3\alpha r_2}{(\alpha r_2+r_3)^2} - b & 0 & 0 \end{pmatrix}$$

$$= \begin{pmatrix} -\frac{b^2r_1}{cx_1} & -\frac{b^2\alpha r_1}{cx_1} & 0 & -\frac{b^2\alpha r_1}{cx_1} & 0 \\ -\frac{b^2\alpha r_2}{cx_1} & \frac{b^2\alpha(r_1+\alpha r_4)}{cx_1} - b & b - \frac{b}{\alpha} & -\frac{b^2\alpha^2 r_2}{cx_1} & 0 \\ 0 & 0 & \frac{b}{\alpha} - 2b & 0 & 0 \end{pmatrix},$$

$$D_2 = \begin{pmatrix} -\frac{c\alpha x_1 r_4}{(r_1+\alpha r_2+\alpha r_4)^2} & -\frac{c\alpha^2 x_1 r_4}{(r_1+\alpha r_2+\alpha r_4)^2} & 0 & \frac{cx_1\alpha(r_1+\alpha r_2)}{(r_1+\alpha r_2+\alpha r_4)^2} + \frac{cx_4\alpha r_5}{(r_4+\alpha r_5)^2} + \frac{cx_5\alpha r_5}{(\alpha r_4+r_5)^2} - b & -\frac{cx_4\alpha r_4}{(r_4+\alpha r_5)^2} - \frac{cx_5\alpha r_4}{(\alpha r_4+r_5)^2} \\ 0 & 0 & 0 & -\frac{cx_4\alpha r_5}{(r_4+\alpha r_5)^2} - \frac{cx_5\alpha r_5}{(\alpha r_4+r_5)^2} & \frac{cx_4\alpha r_4}{(r_4+\alpha r_5)^2} + \frac{cx_5\alpha r_4}{(\alpha r_4+r_5)^2} - b \end{pmatrix}$$

$$= \begin{pmatrix} -\frac{b^2\alpha r_4}{cx_1} & -\frac{b^2\alpha^2 r_4}{cx_1} & 0 & \frac{b^2\alpha(r_1+\alpha r_2)}{cx_1} - b & b - \frac{b}{\alpha} \\ 0 & 0 & 0 & 0 & \frac{b}{\alpha} - 2b \end{pmatrix}.$$

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

$$\begin{aligned} T(\lambda) = (&\frac{b^2 r_1}{cx_1}\lambda + pbr_1)[\lambda^2 + b(1-\alpha)\lambda + cp\beta x_5][\lambda^2 + b(1-\alpha)\lambda + cp\beta x_3] \\ &+\lambda^3[\lambda + b(1-\alpha)][\lambda^2 + b(1-\alpha)\lambda + (\frac{b\alpha}{c}\lambda + p\beta x_1)\frac{b\alpha(r_2+r_4)}{x_1}] \\ &+cp\beta x_5\lambda^2[\lambda^2 + b(1-\alpha)\lambda + \frac{b\alpha r_2}{x_1}(\frac{b\alpha}{c}\lambda + p\beta x_1)] \\ &+cp\beta x_3\lambda^2[\lambda^2 + b(1-\alpha)\lambda + \frac{b\alpha r_4}{x_1}(\frac{b\alpha}{c}\lambda + p\beta x_1) + cp\beta x_5] \end{aligned}$$

$$\begin{aligned} &= \lambda^6 + [\frac{b^2 r_1}{cx_1}(1-\alpha) + b(2-\alpha)]\lambda^5 + b\{f_1 + (1-\alpha)[\frac{b^2 r_1}{cx_1}(2-\alpha) + b]\}\lambda^4 \\ &+b^2(1-\alpha)\{2f_1 - f_3 - f_5 + \frac{b}{cx_1}[r_1(b(1-\alpha) + f_3 + f_5) + 2\alpha^2 f_3 r_4]\}\lambda^3 \\ &+b^2(1-\alpha)\{\frac{b^2 r_1}{cx_1}(1-\alpha)(f_3+f_5) + pr_1[f_3 + f_5 + b(1-\alpha)] + f_3 f_5(1+\alpha)\}\lambda^2 \end{aligned}$$

$$+b^3(1-\alpha)^2[\frac{br_1}{cx_1}f_3 f_5 + pr_1(f_3+f_5)]\lambda + pb^3 r_1 f_3 f_5 (1-\alpha)^2.$$

Detailed computation of $T(\lambda)$ can be found in B.5. One can see that all the coefficients are positve, 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.

i. $f_1 = 3, f_2 = 2, f_3 = 1, f_4 = 2, f_5 = 1, b = 1, \alpha = 2/3, \beta = 4/9$; $\lambda_1 = -1/4 =$

$\lambda_2 < 0, \lambda_3 = -1/2 < 0$, $T(\lambda)$ has 3 pairs of complex roots, all with negative real parts.

ii. $f_1 = 4, f_2 = 1, f_3 = 2, f_4 = 1, f_5 = 1, b = 2, \alpha = 3/4, \beta = 9/16; \lambda_1 = -23/9 < 0, \lambda_2 = -7/9 < 0, \lambda_3 = -4/3 < 0$, $T(\lambda)$ 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.

3.8 Discussion

In this paper we proved that local immunodeficiency discovered in [3] is a stable and robust phenomenon which may appear already in CRNs with just three types of viruses. Therefore LI should be likely present in all diseases which demonstrate cross-immunodeficiency. It is not necessary to have large CRNs which are typical for Hepatisis C [3]. We also rigorously demonstrated that it is easy to build larger networks with several elements (persistent nodes) which remain invisible to the host's immune system because of their positions in the CRN.

We also demonstrate that LI is a much more general phenomenon than assumed in [3]. Indeed a CRN doesn't need to be scale-free [3] to produce LI; it just needs a sufficiently non-homogeneous topology. Since our results are built on exact computations for small networks, they leave a little doubt about the presence of stable and robust LI in large CRNs with heterogeneous topology of a general type.

Observe that the phenomenon of local immunodeficiency formally requires the presence of only persistent antigens which manage to escape immune response. However, in all cases with stable and robust LI, altruistic nodes were always present. It is consistent with extensive numerical simulations with large CRNs in [3]. Therefore it seems that altruistic antigens are necessary for LI to be a stable and robust phenomenon.

Overall local immunodeficiency seems to be an ubiquitous phenomenon which likely will be present in all diseases demonstrating cross-immunoreactivity. It calls for future numerical, analytic and, first of all, biological studies. The most important and interesting question is which types of viruses can play a role of persistent and/or altruistic ones.

Appendices

APPENDIX A

DETAILED COMPUTATIONS FOR THE NETWORK IN FIGURE 1.1

We provide here the exact analytic computations for the network depicted in Fig.1.1. For each structural set of this network the entry-wise condition (1.3) for example 1 is verified.

- $S = \{1,4\}$

  For eigenvalue i,

$$\frac{R_{12}}{i-\omega(2,2)}u_2 + \frac{R_{13}}{i-\omega(3,3)}u_3 = -i(R_{12}(-1) - iR_{13}) = iR_{12} - R_{13} = i + i = 2i = 2u_1;$$
$$\frac{R_{42}}{i-\omega(2,2)}u_2 + \frac{R_{43}}{i-\omega(3,3)}u_3 = iR_{42} - R_{43} = 0 - (-2) = 2 = 2u_4.$$

  For eigenvalue $-i$,

$$\frac{R_{12}}{-i-\omega(2,2)}u_2 + \frac{R_{13}}{-i-\omega(3,3)}u_3 = i(R_{12}i + R_{13}) = -R_{12} + iR_{13} = -1 - 1 = -2 = 2u_1;$$
$$\frac{R_{42}}{-i-\omega(2,2)}u_2 + \frac{R_{43}}{-i-\omega(3,3)}u_3 = -R_{42} + iR_{43} = 0 - 2i = -2i = 2u_4.$$

  One can check that the reduction preserves the generalized eigenvectors in this case.

- $S = \{2,4\}$

  For eigenvalue i,

$$\frac{R_{21}}{i-\omega(1,1)}u_1 + \frac{R_{23}}{i-\omega(3,3)}u_3 = -i(iR_{21} - iR_{23}) = R_{21} - R_{23} = -1 = u_2;$$
$$\frac{R_{41}}{i-\omega(1,1)}u_1 + \frac{R_{43}}{i-\omega(3,3)}u_3 = R_{41} - R_{43} = -1 - (-2) = 1 = u_4.$$

For eigenvalue $-i$,

$$\frac{R_{21}}{-i-\omega(1,1)}u_1 + \frac{R_{23}}{-i-\omega(3,3)}u_3 = i(-R_{21}+R_{23}) = -iR_{21} + iR_{23} = 0 + i = i = u_2;$$
$$\frac{R_{41}}{-i-\omega(1,1)}u_1 + \frac{R_{43}}{-i-\omega(3,3)}u_3 = -iR_{41} + iR_{43} = i - 2i = -i = u_4.$$

One can check that the reduction preserves the generalized eigenvectors here.

- $S = \{3,4\}$

  For eigenvalue i,

$$\frac{R_{31}}{i-\omega(1,1)}u_1 + \frac{R_{32}}{i-\omega(2,2)}u_2 = -i(iR_{31} - R_{32}) = R_{31} + iR_{32} = 0;$$
$$\frac{R_{41}}{i-\omega(1,1)}u_1 + \frac{R_{42}}{i-\omega(2,2)}u_2 = R_{41} + iR_{42} = -1 - 1 = -2 = -2u_4.$$

  For eigenvalue $-i$,

$$\frac{R_{31}}{-i-\omega(1,1)}u_1 + \frac{R_{32}}{-i-\omega(2,2)}u_2 = i(-R_{31} + iR_{32}) = -iR_{31} - R_{32} = 0;$$
$$\frac{R_{41}}{-i-\omega(1,1)}u_1 + \frac{R_{42}}{-i-\omega(2,2)}u_2 = -iR_{41} - R_{42} = i + i = 2i = -2u_4.$$

  Here the generalized eigenvectors are not preserved. Observe that the structural set in this case contains a complete cycle.

- $S = \{1,3\}$

  For eigenvalue i,

$$\frac{R_{12}}{i-\omega(2,2)}u_2 + \frac{R_{14}}{i-\omega(4,4)}u_4 = -i(-R_{12} + R_{14}) = iR_{12} - iR_{14} = i = u_1;$$
$$\frac{R_{32}}{i-\omega(2,2)}u_2 + \frac{R_{34}}{i-\omega(4,4)}u_4 = iR_{32} - iR_{34} = -i = u_3.$$

For eigenvalue $-i$,

$$\frac{R_{12}}{-i-\omega(2,2)}u_2 + \frac{R_{14}}{-i-\omega(4,4)}u_4 = i(iR_{12} - iR_{14}) = -R_{12} + R_{14} = -1 = u_1;$$
$$\frac{R_{32}}{-i-\omega(2,2)}u_2 + \frac{R_{34}}{-i-\omega(4,4)}u_4 = -R_{32} + R_{34} = 1 = u_3.$$

One can check that the reduction preserves the generalized eigenvectors here.

- $S = \{2, 3\}$

  For eigenvalue i,

$$\frac{R_{21}}{i-\omega(1,1)}u_1 + \frac{R_{24}}{i-\omega(4,4)}u_4 = -i(iR_{21} + R_{24}) = R_{21} - iR_{24} = 0;$$
$$\frac{R_{31}}{i-\omega(1,1)}u_1 + \frac{R_{34}}{i-\omega(4,4)}u_4 = R_{31} - iR_{34} = 0.$$

  For eigenvalue $-i$,

$$\frac{R_{21}}{-i-\omega(1,1)}u_1 + \frac{R_{24}}{-i-\omega(4,4)}u_4 = i(-R_{12} - iR_{14}) = -iR_{21} + R_{24} = 0;$$
$$\frac{R_{31}}{-i-\omega(1,1)}u_1 + \frac{R_{34}}{-i-\omega(4,4)}u_4 = -iR_{31} + R_{34} = -1 + 1 = 0.$$

  One can check that the reduction preserves the generalized eigenvectors here.

- $S = \{1, 2, 4\}$

  For eigenvalue i,

$$\frac{R_{13}}{i-\omega(3,3)}u_3 = -R_{13} = 0; \quad \frac{R_{23}}{i-\omega(3,3)}u_3 = -R_{23} = -1 = u_2; \quad \frac{R_{43}}{i-\omega(3,3)}u_3 = 2u_4.$$

  For eigenvalue $-i$,

$$\frac{R_{13}}{-i-\omega(3,3)}u_3 = iR_{13} = 0; \quad \frac{R_{23}}{-i-\omega(3,3)}u_3 = iR_{23} = i = u_2; \quad \frac{R_{43}}{-i-\omega(3,3)}u_3 = 2u_4.$$

This does not satisfy the condition. One can check that the reduction only preserves the eigenvector here.

- $S = \{1, 3, 4\}$

For eigenvalue i,

$$\frac{R_{12}}{i - \omega(2,2)} u_2 = iR_{12} = i = u_1; \quad \frac{R_{32}}{i - \omega(2,2)} u_2 = iR_{32} = 0; \quad \frac{R_{42}}{i - \omega(2,2)} u_2 = 0.$$

For eigenvalue $-i$,

$$\frac{R_{12}}{-i - \omega(2,2)} u_2 = -R_{12} = -1 = u_1; \quad \frac{R_{32}}{-i - \omega(2,2)} u_2 = -R_{32} = 0; \quad \frac{R_{42}}{-i - \omega(2,2)} u_2 = 0.$$

This does not satisfy the condition. One can check that the reduction only preserves the eigenvector here.

- $S = \{2, 3, 4\}$

For eigenvalue i,

$$\frac{R_{21}}{i - \omega(1,1)} u_1 = R_{21} = 0; \quad \frac{R_{31}}{i - \omega(1,1)} u_1 = R_{31} = 0; \quad \frac{R_{41}}{i - \omega(1,1)} u_1 = -1 = -u_4.$$

For eigenvalue $-i$,

$$\frac{R_{21}}{-i - \omega(1,1)} u_1 = -iR_{21} = 0; \quad \frac{R_{31}}{-i - \omega(1,1)} u_1 = 0; \quad \frac{R_{41}}{-i - \omega(1,1)} u_1 = i = -u_4.$$

This does not satisfy the condition. One can check that the reduction only preserves the eigenvector here.

- $S = \{1, 2, 3\}$

For eigenvalue i,

$$\frac{R_{14}}{i-\omega(4,4)}u_4 = -iR_{14} = 0; \quad \frac{R_{24}}{i-\omega(4,4)}u_4 = 0; \quad \frac{R_{34}}{i-\omega(4,4)}u_4 = -i = u_3.$$

For eigenvalue $-i$,

$$\frac{R_{14}}{-i-\omega(4,4)}u_4 = R_{14} = 0; \quad \frac{R_{24}}{-i-\omega(4,4)}u_4 = 0; \quad \frac{R_{34}}{-i-\omega(4,4)}u_4 = 1 = u_3.$$

This does not satisfy the condition. One can check that the reduction only preserves the eigenvector here.

APPENDIX B

FIXED POINTS AND STABILITY FOR DIFFERENT CRNS

B.1 Computation for symmetric size 2 CRN

Consider the symmetric size 2 CRN in Fig. B.1.

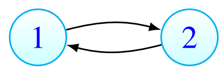


Figure B.1: size 2 CRN (symmetric)

The dynamics of this CRN is described by

$$\begin{cases} \dot{x}_1 = f_1 x_1 - p x_1 (r_1 + \beta r_2), \\ \dot{x}_2 = f_2 x_2 - p x_2 (\beta r_1 + r_2), \\ \dot{r}_1 = c(x_1 \frac{r_1}{r_1 + \alpha r_2} + x_2 \frac{\alpha r_1}{\alpha r_1 + r_2}) - b r_1, \\ \dot{r}_2 = c(x_1 \frac{\alpha r_2}{r_1 + \alpha r_2} + x_2 \frac{r_2}{\alpha r_1 + r_2}) - b r_2. \end{cases}$$

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

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

$$= \begin{pmatrix} 0 & 0 & -px_1 & -p\beta x_1 \\ 0 & f_2 - pr_2 & 0 & 0 \\ 0 & 0 & \frac{b}{\alpha} - b & 0 \\ c & c & -\frac{b}{\alpha} & -b \end{pmatrix}.$$

$\lambda = \frac{b}{\alpha} - b > 0$ is an eigenvalue, so the fixed point is unstable.

B.2 Computation for 3-cycle CRN

The last size three CRN we consider here for illustration is the 3-cycle network in Fig. B.2.

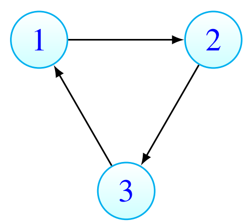


Figure B.2: 3-cycle CRN

The governing equations in this case are

$$\begin{cases} \dot{x}_1 = f_1 x_1 - px_1(r_1 + \beta r_2), \\ \dot{x}_2 = f_2 x_2 - px_2(r_2 + \beta r_3), \\ \dot{x}_3 = f_3 x_3 - px_3(r_3 + \beta r_1), \\ \dot{r}_1 = c(x_1 \frac{r_1}{r_1 + \alpha r_2} + x_3 \frac{\alpha r_1}{\alpha r_1 + r_3}) - br_1, \\ \dot{r}_2 = c(x_1 \frac{\alpha r_2}{r_1 + \alpha r_2} + x_2 \frac{r_2}{r_2 + \alpha r_3}) - br_2, \\ \dot{r}_3 = c(x_2 \frac{\alpha r_3}{r_2 + \alpha r_3} + x_3 \frac{r_3}{\alpha r_1 + r_3}) - br_3. \end{cases}$$

The fixed points of interest are

$$x_1 = 0, x_2 = \frac{bf_2}{cp}, x_3 = \frac{bf_3}{cp\beta}, r_1 = \frac{f_3}{p\beta}, r_2 = \frac{f_2}{p}, r_3 = 0;$$

$$x_1 = \frac{bf_1}{cp\beta}, x_2 = 0, x_3 = \frac{bf_3}{cp}, r_1 = 0, r_2 = \frac{f_1}{p\beta}, r_3 = \frac{f_3}{p};$$

$$x_1 = \frac{bf_1}{cp}, x_2 = \frac{bf_2}{cp\beta}, x_3 = 0, r_1 = \frac{f_1}{p}, r_2 = 0, r_3 = \frac{f_2}{p\beta}.$$

The Jacobian of the system equals

$$J = \begin{pmatrix} f_1 - p(r_1 + \beta r_2) & 0 & 0 & -px_1 & -p\beta x_1 & 0 \\ 0 & f_2 - p(r_2 + \beta r_3) & 0 & 0 & -px_2 & -p\beta x_2 \\ 0 & 0 & f_3 - p(r_3 + \beta r_1) & -p\beta x_3 & 0 & -px_3 \\ \frac{cr_1}{r_1+\alpha r_2} & 0 & \frac{c\alpha r_1}{\alpha r_1 + r_3} & A - b & -\frac{cx_1\alpha r_1}{(r_1+\alpha r_2)^2} & -\frac{cx_3\alpha r_1}{(\alpha r_1 + r_3)^2} \\ \frac{c\alpha r_2}{r_1+\alpha r_2} & \frac{cr_2}{r_2+\alpha r_3} & 0 & -\frac{cx_1\alpha r_2}{(r_1+\alpha r_2)^2} & B - b & -\frac{cx_2\alpha r_2}{(r_2+\alpha r_3)^2} \\ 0 & \frac{c\alpha r_3}{r_2+\alpha r_3} & \frac{cr_3}{\alpha r_1 + r_3} & -\frac{cx_3\alpha r_3}{(\alpha r_1+r_3)^2} & -\frac{cx_2\alpha r_3}{(r_2+\alpha r_3)^2} & C - b \end{pmatrix},$$

where $A = \frac{cx_1\alpha r_2}{(r_1 + \alpha r_2)^2} + \frac{cx_3\alpha r_3}{(\alpha r_1 + r_3)^2}, B = \frac{cx_1\alpha r_1}{(r_1 + \alpha r_2)^2} + \frac{cx_2\alpha r_3}{(r_2 + \alpha r_3)^2}, C = \frac{cx_2\alpha r_2}{(r_2 + \alpha r_3)^2} + \frac{cx_3\alpha r_1}{(\alpha r_1 + r_3)^2}.$

At the fixed point $x_1 = 0, x_2 = \frac{bf_2}{cp}, x_3 = \frac{bf_3}{cp\beta}, r_1 = \frac{f_3}{p\beta}, r_2 = \frac{f_2}{p}, r_3 = 0$, we have

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

$$J = \begin{pmatrix} f_1 - \beta f_2 - \frac{f_3}{\beta} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -\frac{b}{c} f_2 & -\frac{b\beta}{c} f_2 \\ 0 & 0 & 0 & -\frac{b}{c} f_3 & 0 & -\frac{b}{c\beta} f_3 \\ \frac{cf_3}{f_3 + \alpha\beta f_2} & 0 & c & -b & 0 & -\frac{b}{\alpha} \\ \frac{c\alpha\beta f_2}{f_3 + \alpha\beta f_2} & c & 0 & 0 & -b & -\alpha b \\ 0 & 0 & 0 & 0 & 0 & \frac{b}{\alpha} + \alpha b - b \end{pmatrix}.$$

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

At the fixed point $x_1 = \frac{bf_1}{cp\beta}, x_2 = 0, x_3 = \frac{bf_3}{cp}, r_1 = 0, r_2 = \frac{f_1}{p\beta}, r_3 = \frac{f_3}{p}$ we obtain

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

$$J = \begin{pmatrix} 0 & 0 & 0 & -\frac{bf_1}{c\beta} & -\frac{b}{c}f_1 & 0 \\ 0 & f_2 - \frac{f_1}{\beta} - \beta f_3 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -\frac{b\beta}{c}f_3 & 0 & -\frac{b}{c}f_3 \\ 0 & 0 & 0 & \frac{b}{\alpha} + \alpha b - b & 0 & 0 \\ c & \frac{cf_1}{f_1+\alpha\beta f_3} & 0 & -\frac{b}{\alpha} & -b & 0 \\ 0 & \frac{c\alpha\beta f_3}{f_1+\alpha\beta f_3} & c & -\alpha b & 0 & -b \end{pmatrix}.$$

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

At the fixed point $x_1 = \frac{bf_1}{cp}, x_2 = \frac{bf_2}{cp\beta}, x_3 = 0, r_1 = \frac{f_1}{p}, r_2 = 0, r_3 = \frac{f_2}{p\beta}$ we get analogously

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

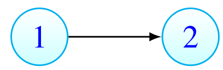
$$J = \begin{pmatrix} 0 & 0 & 0 & -\frac{b}{c}f_1 & -\frac{b\beta}{c}f_1 & 0 \\ 0 & 0 & 0 & 0 & -\frac{bf_2}{c\beta} & -\frac{b}{c}f_2 \\ 0 & 0 & f_3 - \beta f_1 - \frac{f_2}{\beta} & 0 & 0 & 0 \\ c & 0 & \frac{c\alpha\beta f_1}{\alpha\beta f_1+f_2} & -b & -\alpha b & 0 \\ 0 & 0 & 0 & 0 & \alpha b + \frac{b}{\alpha} - b & 0 \\ 0 & c & \frac{cf_2}{\alpha\beta f_1+f_2} & 0 & -\frac{b}{\alpha} & -b \end{pmatrix}.$$

This fixed point is also unstable because $\lambda = \alpha b + \frac{b}{\alpha} - b > 0$ 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 [3].

B.3 A complete list of fixed points for size 2 and 3 CRNs

- size 2 CRN



Fixed points:

i.
$$x_1 = 0, x_2 = \frac{bf_2}{cp}, r_1 = 0, r_2 = \frac{f_2}{p}$$

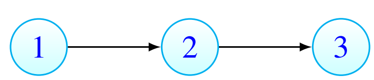
ii.
$$x_1 = \frac{bf_1}{cp\beta}, x_2 = 0, r_1 = 0, r_2 = \frac{f_1}{p\beta}$$

iii.
$$x_1 = \frac{bf_1}{cp}, x_2 = 0, r_1 = \frac{f_1}{p}, r_2 = 0$$

iv.
$$f_1 = \beta f_2, 0 < x_1 < \frac{bf_2}{cp}, x_2 = \frac{bf_2}{cp} - x_1, r_1 = 0, r_2 = \frac{f_2}{p}$$

v.
$$f_1 > \beta f_2, x_1 = \frac{b}{cp}(f_1 + (\alpha - \beta)f_2), x_2 = \frac{bf_2}{cp}(1 - \alpha), r_1 = \frac{f_1 - \beta f_2}{p}, r_2 = \frac{f_2}{p}$$

- size 3 CRN



Fixed points:

i.
$$x_1 = 0, x_2 = \frac{bf_2}{cp}, x_3 = 0, r_1 = 0, r_2 = \frac{f_2}{p}, r_3 = 0$$

ii.

$$f_2 > \beta f_3, x_1 = 0, x_2 = \frac{b}{cp}(f_2+(\alpha-\beta)f_3), x_3 = \frac{bf_3}{cp}(1-\alpha), r_1 = 0, r_2 = \frac{f_2 - \beta f_3}{p}, r_3 = \frac{f_3}{p}$$

iii.

$$x_1 = \frac{bf_1}{cp\beta}, x_2 = 0, x_3 = 0, r_1 = 0, r_2 = \frac{f_1}{p\beta}, r_3 = 0$$

iv.

$$x_1 = \frac{bf_1}{cp}, x_2 = 0, x_3 = \frac{bf_3}{cp}, r_1 = \frac{f_1}{p}, r_2 = 0, r_3 = \frac{f_3}{p}$$

v.

$$x_1 = \frac{bf_1}{cp\beta}, x_2 = 0, x_3 = \frac{bf_3}{cp}, r_1 = 0, r_2 = \frac{f_1}{p\beta}, r_3 = \frac{f_3}{p}$$

vi.

$$f_1 = \beta f_2, 0 < x_1 < \frac{bf_1}{cp\beta}, x_2 = \frac{bf_1}{cp\beta} - x_1, x_3 = 0, r_1 = 0, r_2 = \frac{f_1}{p\beta}, r_3 = 0$$

vii.

$$x_1 = \frac{bf_1}{cp}, x_2 = \frac{bf_2}{cp\beta}, x_3 = 0, r_1 = \frac{f_1}{p}, r_2 = 0, r_3 = \frac{f_2}{p\beta}$$

viii.

$$f_1 > \beta f_2, x_1 = \frac{b}{cp}(f_1+(\alpha-\beta)f_2), x_2 = \frac{bf_2}{cp}(1-\alpha), x_3 = 0, r_1 = \frac{f_1 - \beta f_2}{p}, r_2 = \frac{f_2}{p}, r_3 = 0$$

ix.

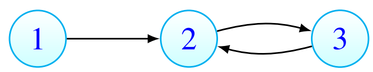
$$f_1 = \beta(f_2 - \beta f_3) > 0, 0 < x_1 < \frac{b(f_2 - \beta f_3)}{cp}, x_2 = (1 + \frac{\alpha f_3}{f_2 - \beta f_3})(\frac{b(f_2 - \beta f_3)}{cp} - x_1),$$
$$x_3 = \frac{bf_3}{cp}(1 - \alpha) + \alpha\frac{f_3}{f_2 - \beta f_3}x_1, r_1 = 0, r_2 = \frac{f_2 - \beta f_3}{p}, r_3 = \frac{f_3}{p}$$

x.

$$f_2 = \beta f_3, x_1 = \frac{bf_1}{cp}, 0 < x_2 < \frac{bf_3}{cp}, x_3 = \frac{bf_3}{cp} - x_2, r_1 = \frac{f_1}{p}, r_2 = 0, r_3 = \frac{f_3}{p}$$

xi.

$$f_1 > \beta(f_2 - \beta f_3) > 0, x_1 = \frac{b}{cp}(f_1 + (\alpha - \beta)(f_2 - \beta f_3)), x_2 = \frac{b}{cp}(1-\alpha)(f_2 + (\alpha - \beta) f_3),$$
$$x_3 = \frac{bf_3}{cp}(1 - \alpha(1-\alpha)), r_1 = \frac{f_1 - \beta f_2 + \beta^2 f_3}{p}, r_2 = \frac{f_2 - \beta f_3}{p}, r_3 = \frac{f_3}{p}$$



Fixed points:

i.

$$x_1 = 0, x_2 = 0, x_3 = \frac{bf_3}{cp\beta}, r_1 = 0, r_2 = \frac{f_3}{p\beta}, r_3 = 0$$

ii.

$$x_1 = 0, x_2 = \frac{bf_2}{cp}, x_3 = 0, r_1 = 0, r_2 = \frac{f_2}{p}, r_3 = 0$$

iii.

$$f_3 > \beta f_2 > \beta^2 f_3, x_1 = 0, x_2 = \frac{b[(1-\alpha\beta) f_2 + (\alpha - \beta) f_3]}{cp(1+\alpha)(1-\beta^2)}, x_3 = \frac{b[(1-\alpha\beta) f_3 + (\alpha - \beta) f_2]}{cp(1+\alpha)(1-\beta^2)},$$
$$r_1 = 0, r_2 = \frac{f_2 - \beta f_3}{p(1-\beta^2)}, r_3 = \frac{f_3 - \beta f_2}{p(1-\beta^2)}$$

iv.

$$f_3 = \beta f_2, x_1 = 0, 0 < x_2 < \frac{bf_2}{cp}, x_3 = \frac{bf_2}{cp} - x_2, r_1 = 0, r_2 = \frac{f_2}{p}, r_3 = 0$$

v.

$$x_1 = \frac{bf_1}{cp\beta}, x_2 = 0, x_3 = 0, r_1 = 0, r_2 = \frac{f_1}{p\beta}, r_3 = 0$$

vi.

$$f_3 = f_1, 0 < x_1 < \frac{bf_1}{cp\beta}, x_2 = 0, x_3 = \frac{bf_1}{cp\beta} - x_1, r_1 = 0, r_2 = \frac{f_1}{p\beta}, r_3 = 0$$

vii.

$$f_3 > f_1, x_1 = \frac{bf_1}{cp\beta}(1-\alpha), x_2 = 0, x_3 = \frac{b}{cp}(f_3 - f_1 + \frac{\alpha}{\beta}f_1), r_1 = 0, r_2 = \frac{f_1}{p\beta}, r_3 = \frac{f_3 - f_1}{p}$$

viii.

$$f_3 < f_1, x_1 = \frac{b}{cp}(f_1 - f_3 + \frac{\alpha}{\beta}f_3), x_2 = 0, x_3 = \frac{bf_3}{cp\beta}(1-\alpha), r_1 = \frac{f_1 - f_3}{p}, r_2 = \frac{f_3}{p\beta}, r_3 = 0$$

ix.

$$x_1 = \frac{bf_1}{cp}, x_2 = 0, x_3 = \frac{bf_3}{cp}, r_1 = \frac{f_1}{p}, r_2 = 0, r_3 = \frac{f_3}{p}$$

x.

$$f_1 = \beta f_2, 0 < x_1 < \frac{bf_2}{cp}, x_2 = \frac{bf_2}{cp} - x_1, x_3 = 0, r_1 = 0, r_2 = \frac{f_2}{p}, r_3 = 0$$

xi.

$$f_1 > \beta f_2, x_1 = \frac{b}{cp}(f_1 + (\alpha - \beta)f_2), x_2 = \frac{bf_2}{cp}(1-\alpha), x_3 = 0, r_1 = \frac{f_1 - \beta f_2}{p}, r_2 = \frac{f_2}{p}, r_3 = 0$$

xii.

$$x_1 = \frac{bf_1}{cp}, x_2 = \frac{bf_2}{cp\beta}, x_3 = 0, r_1 = \frac{f_1}{p}, r_2 = 0, r_3 = \frac{f_2}{p\beta}$$

xiii.

$$f_1 = f_3 = \beta f_2, 0 < x_1 < \frac{bf_2}{cp}, 0 < x_2 < \frac{bf_2}{cp} - x_1, x_3 = \frac{bf_2}{cp} - x_1 - x_2, r_1 = 0, r_2 = \frac{f_2}{p}, r_3 = 0$$

xiv.

$$(1-\beta^2)f_1 = \beta(f_2-\beta f_3) > 0, f_3 > \beta f_2, 0 < x_1 < b\min\{1-\alpha, \frac{f_2+f_3}{cp(1+\beta)}\},$$
$$x_2 = \frac{(1-\alpha\beta)f_2+(\alpha-\beta)f_3}{cp(1+\alpha)(1-\beta^2)}(b-\frac{x_1}{1-\alpha}), x_3 = \frac{(1-\alpha\beta)f_3+(\alpha-\beta)f_2}{cp(1+\alpha)(1-\beta^2)}(b-\frac{\alpha x_1}{1-\alpha}),$$
$$r_1 = 0, r_2 = \frac{f_2-\beta f_3}{p(1-\beta^2)}, r_3 = \frac{f_3-\beta f_2}{p(1-\beta^2)}$$

xv.

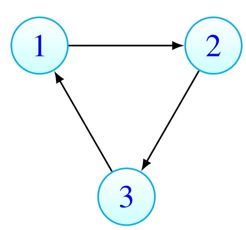
$$f_2 = \beta f_3, x_1 = \frac{bf_1}{cp}, 0 < x_2 < \frac{bf_3}{cp}, x_3 = \frac{bf_3}{cp} - x_2, r_1 = \frac{f_1}{p}, r_2 = 0, r_3 = \frac{f_3}{p}$$

xvi.

$$f_1 > \beta f_2 = f_3, x_1 = \frac{b}{cp}(f_1+(\alpha-\beta)f_2), 0 < x_2 < \frac{bf_2}{cp}(1-\alpha), x_3 = \frac{bf_2}{cp}-x_2, r_1 = \frac{f_1-\beta f_2}{p}, r_2 = \frac{f_2}{p}, r_3 = 0$$

xvii.

$$(1-\beta^2)f_1 > \beta(f_2-\beta f_3) > 0, f_3 > \beta f_2, x_1 = \frac{bf_1}{cp} + \frac{b(\alpha-\beta)}{cp(1-\beta^2)}(f_2-\beta f_3),$$
$$x_2 = \frac{b(1-2\alpha)}{cp(1-\alpha^2)(1-\beta^2)}((1-\alpha\beta)f_2+(\alpha-\beta)f_3),$$
$$x_3 = \frac{b(1-\alpha+\alpha^2)}{cp(1-\alpha^2)(1-\beta^2)}((1-\alpha\beta)f_3+(\alpha-\beta)f_2), r_1 = \frac{f_1}{p} - \beta\frac{f_2-\beta f_3}{p(1-\beta^2)},$$
$$r_2 = \frac{f_2-\beta f_3}{p(1-\beta^2)}, r_3 = \frac{f_3-\beta f_2}{p(1-\beta^2)}$$



Fixed points:

i.

$$f_2 > \beta f_3, x_1 = 0, x_2 = \frac{b}{cp}(f_2+(\alpha-\beta)f_3), x_3 = \frac{bf_3}{cp}(1-\alpha), r_1 = 0, r_2 = \frac{f_2 - \beta f_3}{p}, r_3 = \frac{f_3}{p}$$

ii.

$$x_1 = 0, x_2 = \frac{bf_2}{cp}, x_3 = \frac{bf_3}{cp\beta}, r_1 = \frac{f_3}{p\beta}, r_2 = \frac{f_2}{p}, r_3 = 0$$

iii.

$$x_1 = \frac{bf_1}{cp\beta}, x_2 = 0, x_3 = \frac{bf_3}{cp}, r_1 = 0, r_2 = \frac{f_1}{p\beta}, r_3 = \frac{f_3}{p}$$

iv.

$$f_3 > \beta f_1, x_1 = \frac{bf_1}{cp}(1-\alpha), x_2 = 0, x_3 = \frac{b}{cp}(f_3+(\alpha-\beta)f_1), r_1 = \frac{f_1}{p}, r_2 = 0, r_3 = \frac{f_3 - \beta f_1}{p}$$

v.

$$x_1 = \frac{bf_1}{cp}, x_2 = \frac{bf_2}{cp\beta}, x_3 = 0, r_1 = \frac{f_1}{p}, r_2 = 0, r_3 = \frac{f_2}{p\beta}$$

vi.

$$f_1 > \beta f_2, x_1 = \frac{b}{cp}(f_1+(\alpha-\beta)f_2), x_2 = \frac{bf_2}{cp}(1-\alpha), x_3 = 0, r_1 = \frac{f_1 - \beta f_2}{p}, r_2 = \frac{f_2}{p}, r_3 = 0$$

vii.

$$f_2 = \frac{f_1}{\beta}+\beta f_3, 0 < x_1 < \frac{bf_1}{cp\beta}, x_2 = (\frac{b}{c}-\frac{x_1 p\beta}{f_1})\frac{f_1 + \alpha\beta f_3}{p\beta}, x_3 = (\frac{b}{c}(1-\alpha)+\frac{\alpha x_1 p\beta}{f_1})\frac{f_3}{p}, r_1 = 0, r_2 = \frac{f_1}{p\beta}, r_3 = \frac{f_3}{p}$$

viii.

$$f_3 = \beta f_1+\frac{f_2}{\beta}, (1-\alpha)\frac{bf_1}{cp} < x_1 < \frac{bf_1}{cp}, x_2 = \frac{f_2}{p\alpha\beta}(\frac{x_1 p}{f_1}-(1-\alpha)\frac{b}{c}), x_3 = (\frac{f_1}{p}+\frac{f_2}{p\alpha\beta})(\frac{b}{c}-\frac{x_1 p}{f_1}), r_1 = \frac{f_1}{p}, r_2 = 0, r_3 = \frac{f_2}{p\beta}$$

ix.

$$f_1 = \beta f_2 + \frac{f_3}{\beta}, 0 < x_1 < \frac{b}{c}(r_1 + \alpha r_2), x_2 = (\frac{b}{c} - \alpha \frac{x_1}{r_1 + \alpha r_2}) r_2, x_3 = r_1(\frac{b}{c} - \frac{x_1}{r_1 + \alpha r_2}), r_1 = \frac{f_3}{p\beta}, r_2 = \frac{f_2}{p}, r_3 = 0$$

x.

$$\begin{aligned} f_1 - \beta f_2 + \beta^2 f_3 > 0, f_2 - \beta f_3 + \beta^2 f_1 > 0, f_3 - \beta f_1 + \beta^2 f_2 > 0, \\ x_1 = \frac{b}{c(1+\alpha)}(r_1 + \alpha r_2), x_2 = \frac{b}{c(1+\alpha)}(r_2 + \alpha r_3), x_3 = \frac{b}{c(1+\alpha)}(r_3 + \alpha r_1), \\ r_1 = \frac{f_1 - \beta f_2 + \beta^2 f_3}{p(1+\beta^3)}, r_2 = \frac{f_2 - \beta f_3 + \beta^2 f_1}{p(1+\beta^3)}, r_3 = \frac{f_3 - \beta f_1 + \beta^2 f_2}{p(1+\beta^3)} \end{aligned}$$

B.4 Size 4 mildly asymmetric networks: existence & stability of LI

The CRN we consider here is the "T-shaped" network with four nodes in Fig. B.3.

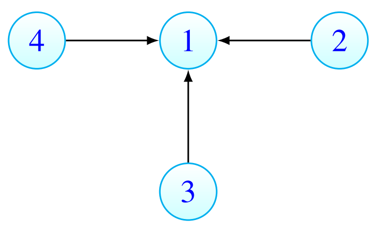


Figure B.3: size 4 CRN

For this specific size 4 CRN, 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 (3.1) assume the form

$$\begin{cases} \dot{x}_1 = f_1 x_1 - p x_1 r_1, \\ \dot{x}_2 = f_2 x_2 - p x_2(\beta r_1 + r_2), \\ \dot{x}_3 = f_3 x_3 - p x_3(\beta r_1 + r_3), \\ \dot{x}_4 = f_4 x_4 - p x_4(\beta r_1 + r_4), \\ \dot{r}_1 = c(x_1 + x_2 \frac{\alpha r_1}{\alpha r_1 + r_2} + x_3 \frac{\alpha r_1}{\alpha r_1 + r_3} + x_4 \frac{\alpha r_1}{\alpha r_1 + r_4}) - b r_1, \\ \dot{r}_2 = c x_2 \frac{r_2}{\alpha r_1 + r_2} - b r_2, \\ \dot{r}_3 = c x_3 \frac{r_3}{\alpha r_1 + r_3} - b r_3, \\ \dot{r}_4 = c x_4 \frac{r_4}{\alpha r_1 + r_4} - b r_4. \end{cases}$$

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:

$$x_1 = 0, r_1 = \frac{f_2}{p\beta}, x_2 = \frac{b f_2(1-2\alpha)}{c p \beta}, r_2 = 0,$$

$$x_3 = \frac{b}{cp}(\frac{\alpha}{\beta} f_2 + f_3 - f_2), r_3 = \frac{f_3 - f_2}{p}, x_4 = \frac{b}{cp}(\frac{\alpha}{\beta} f_2 + f_4 - f_2), r_4 = \frac{f_4 - f_2}{p}.$$

The corresponding Jacobian is,

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

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

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

$$C=\begin{pmatrix}c & \frac{c\alpha r_1}{\alpha r_1+r_2} & \frac{c\alpha r_1}{\alpha r_1+r_3} & \frac{c\alpha r_1}{\alpha r_1+r_4}\\ 0 & \frac{cr_2}{\alpha r_1+r_2} & 0 & 0\\ 0 & 0 & \frac{cr_3}{\alpha r_1+r_3} & 0\\ 0 & 0 & 0 & \frac{cr_4}{\alpha r_1+r_4}\end{pmatrix}=\begin{pmatrix}c & c & \frac{b\alpha r_1}{x_3} & \frac{b\alpha r_1}{x_4}\\ 0 & 0 & 0 & 0\\ 0 & 0 & \frac{br_3}{x_3} & 0\\ 0 & 0 & 0 & \frac{br_4}{x_4}\end{pmatrix},$$

$$D=\begin{pmatrix}\frac{c\alpha x_2r_2}{(\alpha r_1+r_2)^2}+\frac{c\alpha x_3r_3}{(\alpha r_1+r_3)^2}+\frac{c\alpha x_4r_4}{(\alpha r_1+r_4)^2}-b & -\frac{c\alpha x_2r_1}{(\alpha r_1+r_2)^2} & -\frac{c\alpha x_3r_1}{(\alpha r_1+r_3)^2} & -\frac{c\alpha x_4r_1}{(\alpha r_1+r_4)^2}\\ -\frac{c\alpha x_2r_2}{(\alpha r_1+r_2)^2} & \frac{c\alpha x_2r_1}{(\alpha r_1+r_2)^2}-b & 0 & 0\\ -\frac{c\alpha x_3r_3}{(\alpha r_1+r_3)^2} & 0 & \frac{c\alpha x_3r_1}{(\alpha r_1+r_3)^2}-b & 0\\ -\frac{c\alpha x_4r_4}{(\alpha r_1+r_4)^2} & 0 & 0 & \frac{c\alpha x_4r_1}{(\alpha r_1+r_4)^2}-b\end{pmatrix}$$

$$=\begin{pmatrix}\frac{\alpha b^2r_3}{cx_3}+\frac{\alpha b^2r_4}{cx_4}-b & 2b-\frac{b}{\alpha} & -\frac{\alpha b^2r_1}{cx_3} & -\frac{\alpha b^2r_1}{cx_4}\\ 0 & \frac{b}{\alpha}-3b & 0 & 0\\ -\frac{\alpha b^2r_3}{cx_3} & 0 & \frac{\alpha b^2r_1}{cx_3}-b & 0\\ -\frac{\alpha b^2r_4}{cx_4} & 0 & 0 & \frac{\alpha b^2r_1}{cx_4}-b\end{pmatrix}.$$

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.

B.5 Detailed computation of $T(\lambda)$

After column reduction, we get

$$T(\lambda) = \begin{vmatrix} -\lambda & 0 & 0 & -px_1 - \frac{b}{c}\lambda & -p\beta x_1 - \frac{\alpha b}{c}\lambda & -p\beta x_1 - \frac{\alpha b}{c}\lambda \\ 0 & -\lambda & 0 & 0 & -p\beta x_3 & 0 \\ 0 & 0 & -\lambda & 0 & 0 & -p\beta x_5 \\ \frac{br_1}{x_1} & 0 & 0 & -\lambda & 0 & 0 \\ \frac{b\alpha r_2}{x_1} & c & 0 & 0 & \alpha b - b - \lambda & 0 \\ \frac{b\alpha x_4}{x_1} & 0 & c & 0 & 0 & \alpha b - b - \lambda \end{vmatrix}.$$

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.

$$T(\lambda) = -\lambda \begin{vmatrix} -\lambda & 0 & -px_1 - \frac{b}{c}\lambda & -p\beta x_1 - \frac{\alpha b}{c}\lambda & -p\beta x_1 - \frac{\alpha b}{c}\lambda \\ 0 & -\lambda & 0 & 0 & -p\beta x_5 \\ \frac{br_1}{x_1} & 0 & -\lambda & 0 & 0 \\ \frac{b\alpha r_2}{x_1} & 0 & 0 & \alpha b - b - \lambda & 0 \\ \frac{b\alpha r_4}{x_4} & c & 0 & 0 & \alpha b - b - \lambda \end{vmatrix}$$

$$+p\beta x_3 \begin{vmatrix} -\lambda & 0 & 0 & -px_1 - \frac{b}{c}\lambda & -p\beta x_1 - \frac{\alpha b}{c}\lambda \\ 0 & 0 & -\lambda & 0 & -p\beta x_5 \\ \frac{br_1}{x_1} & 0 & 0 & -\lambda & 0 \\ \frac{b\alpha r_2}{x_1} & c & 0 & 0 & 0 \\ \frac{b\alpha r_4}{x_1} & 0 & c & 0 & \alpha b - b - \lambda \end{vmatrix}$$

$$
= \lambda^2 \begin{vmatrix} -\lambda & -px_1 - \frac{b}{c}\lambda & -p\beta x_1 - \frac{\alpha b}{c}\lambda & -p\beta x_1 - \frac{b\alpha}{c}\lambda \\ \frac{br_1}{x_1} & -\lambda & 0 & 0 \\ \frac{b\alpha r_2}{x_1} & 0 & \alpha b - b - \lambda & 0 \\ \frac{b\alpha r_4}{x_1} & 0 & 0 & \alpha b - b - \lambda \end{vmatrix}
$$

$$
-p\beta x_5\lambda \begin{vmatrix} -\lambda & 0 & -px_1 - \frac{b}{c}\lambda & p\beta_1 - \frac{b\alpha}{c}\lambda \\ \frac{br_1}{x_1} & 0 & -\lambda & 0 \\ \frac{b\alpha r_2}{x_1} & 0 & 0 & \alpha b - b - \lambda \\ \frac{b\alpha r_4}{x_1} & c & 0 & 0 \end{vmatrix} + cp\beta x_3 \begin{vmatrix} -\lambda & 0 & -px_1 - \frac{b}{c}\lambda & -p\beta x_1 - \frac{b\alpha}{c}\lambda \\ 0 & -\lambda & 0 & -p\beta x_5 \\ \frac{br_1}{x_1} & 0 & -\lambda & 0 \\ \frac{b\alpha r_4}{x_1} & c & 0 & \alpha b - b - \lambda \end{vmatrix}
$$

$$
= \lambda^2[-\frac{br_1}{x_1} \begin{vmatrix} -px_1 - \frac{b}{c}\lambda & -p\beta x_1 - \frac{b\alpha}{c}\lambda & -p\beta x_1 - \frac{b\alpha}{c}\lambda \\ 0 & \alpha b - b - \lambda & 0 \\ 0 & 0 & \alpha b - b - \lambda \end{vmatrix} - \lambda \begin{vmatrix} -\lambda & -p\beta x_1 - \frac{b\alpha}{c}\lambda & -p\beta x_1 - \frac{b\alpha}{c}\lambda \\ \frac{b\alpha r_2}{x_1} & \alpha b - b - \lambda & 0 \\ \frac{b\alpha r_4}{x_1} & 0 & \alpha b - b - \lambda \end{vmatrix}]
$$

$$
-cp\beta x_5\lambda \begin{vmatrix} -\lambda & -px_1 - \frac{b}{c}\lambda & -p\beta x_1 - \frac{b\alpha}{c}\lambda \\ \frac{br_1}{x_1} & -\lambda & 0 \\ \frac{b\alpha r_2}{x_1} & 0 & \alpha b - b - \lambda \end{vmatrix} - cp\beta x_3\lambda \begin{vmatrix} -\lambda & -px_1 - \frac{b}{c}\lambda & -p\beta x_1 - \frac{b\alpha}{c}\lambda \\ \frac{br_1}{x_1} & -\lambda & 0 \\ \frac{b\alpha r_4}{x_1} & 0 & \alpha b - b - \lambda \end{vmatrix}
$$

$$
-cp^2\beta^2 x_3 x_5 \begin{vmatrix} -\lambda & 0 & -px_1 - \frac{b}{c}\lambda \\ \frac{br_1}{x_1} & 0 & -\lambda \\ \frac{b\alpha r_4}{x_1} & c & 0 \end{vmatrix}
$$

$$= \lambda^2\{\frac{br_1}{x_1}(px_1 + \frac{b}{c}\lambda)(\lambda + b - \alpha b)^2$$

$$+\lambda[\frac{b\alpha r_2}{x_1}(p\beta x_1 + \frac{b\alpha}{c}\lambda)(\lambda + b - \alpha b) + (\lambda + b - \alpha b)(\lambda^2 + (b - \alpha b)\lambda + (p\beta x_1 + \frac{b\alpha}{c}\lambda)\frac{b\alpha r_4}{x_1})]\}$$

$$+cp\beta x_5\lambda\{\frac{br_1}{x_1}(px_1 + \frac{b}{c}\lambda)(\lambda + b - \alpha b) + \lambda[\lambda^2 + (b - \alpha b)\lambda + (p\beta x_1 + \frac{b\alpha}{c}\lambda)\frac{b\alpha r_2}{x_1}]\}$$

$$+cp\beta x_3\lambda\{\frac{br_1}{x_1}(px_1 + \frac{b}{c}\lambda)(\lambda + b - \alpha b) + \lambda[\lambda^2 + (b - \alpha b)\lambda + (p\beta x_1 + \frac{b\alpha}{c}\lambda)\frac{b\alpha r_4}{x_1}]\}$$

$$+c^2p^2\beta^2x_3x_5(\lambda^2 + \frac{b^2r_1}{cx_1}\lambda + pbr_1)$$

$$= \frac{br_1}{x_1}(px_1 + \frac{b}{c}\lambda)(\lambda + b - \alpha b)[\lambda^2(\lambda + b - \alpha b) + cp\beta x_5\lambda + cp\beta x_3\lambda]$$

$$+(p\beta x_1 + \frac{b\alpha}{c}\lambda)[\frac{b\alpha r_2}{x_1}\lambda^3(\lambda + b - \alpha b) + \frac{b\alpha r_4}{x_1}\lambda^3(\lambda + b - \alpha b) + \frac{b\alpha r_2}{x_1}cp\beta x_5\lambda^2 + \frac{b\alpha r_4}{x_1}cp\beta x_3\lambda^2]$$

$$+\lambda^4(\lambda + b - \alpha b)^2 + cp\beta(x_5 + x_3)\lambda^3(\lambda + b - \alpha b) + c^2p^2\beta^2x_3x_5[\lambda^2 + \frac{b^2r_1}{cx_1}\lambda + pbr_1]$$

$$= \frac{br_1}{x_1}\lambda(\frac{b}{c}\lambda + px_1)(\lambda + b - \alpha b)[\lambda^2 + (b - \alpha b)\lambda + cp\beta(x_3 + x_5)]$$

$$+\lambda^2(\frac{b\alpha}{c}\lambda + p\beta x_1)[(\frac{b\alpha r_2}{x_1} + \frac{b\alpha r_4}{x_1})\lambda(\lambda + b - \alpha b) + \frac{b\alpha}{x_1}cp\beta(r_2x_5 + r_4x_3)]$$

$$+\lambda^3(\lambda + b - \alpha b)[\lambda^2 + (b - \alpha b)\lambda + cp\beta(x_3 + x_5)]$$

$$+c^2p^2\beta^2x_3x_5(\lambda^2 + \frac{b^2r_1}{cx_1}\lambda + pbr_1)$$

$$= \lambda[\lambda + b(1 - \alpha)][\lambda^2 + b(1 - \alpha)\lambda + b(1 - \alpha)(f_3 + f_5)][\lambda^2 + \frac{b^2r_1}{cx_1}\lambda + pbr_1]$$

$$+\lambda^2(\frac{b\alpha}{c}\lambda + p\beta x_1)[(c - \frac{br_1}{x_1})\lambda(\lambda + b - \alpha b) + 2\frac{b^2\alpha(1 - \alpha)}{x_1}r_4f_3]$$

$$+b^2(1 - \alpha)^2f_3f_5(\lambda^2 + \frac{b^2r_1}{cx_1}\lambda + pbr_1).$$

REFERENCES

[1] L. Bunimovich and L. Shu, "Generalized eigenvectors of isospectral transformations, spectral equivalence and reconstruction of original networks," *Linear Algebra and its Applications*, vol. 551, no. 15, pp. 104–124, 2018.

[2] L. Bunimovich and L. Shu, "On attractors of isospectral compressions of networks," *Differential Equations and Dynamical Systems, Springer*, pp. 63–73, 2018.

[3] P. Skums, L. Bunimovich, and 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*, vol. 112, no. 21, pp. 6653–6658, 2015.

[4] L. Bunimovich and L. Shu, "Local immunodeficiency: Minimal networks and stability," *Mathematical Biosciences*, vol. 310, pp. 31–49, 2019.

[5] L. Bunimovich and B. Webb, *Isospectral Transformations*. Springer, 2014.

[6] P. Duarte and M. J. Torres, "Eigenvectors of isospectral graph transformations," *Linear Algebra and its Applications*, vol. 474, pp. 110–123, 2015.

[7] A. Clauset, C. Moore, and M. Newman, "Hierarchical structure and the prediction of missing links in networks," *Nature*, vol. 453, pp. 98–101, 2008.

[8] J. Leskovec, K. Lang, A. Dasgupta, and M. Mahoney, "Statistical properties of community structure in large social and information networks," *Proceedings of the 17th International Conference on World Wide Web*, pp. 695–704, 2008.

[9] M. Newman, A. L. Barabasi, and D. J. Watts, *The Structure and Dynamics of Networks*. Princeton University Press, 2006.

[10] M. Newman, *Networks: An Introduction*. Oxford University Press, 2010.

[11] L. Bunimovich, D. Smith, and B. Webb, "Specialization models of network growth," *arXiv 1712.01788*, 2017.

[12] M. Hattori, K. Yashioka, T. Aiyama, K. Iwata, Y. Terazawa, M. Ishigami, M. Yano, and 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*, vol. 27, no. 6, pp. 1703–1710, 1998.

[13] D. S. Campo, Z. Dimitrova, L. Yamasaki, P. Skums, D. T. Lau, G. Vaughan, J. C. Forbi, C.-G. Teo, and Y. Khudyakov, "Next-generation sequencing reveals large connected networks of intra-host hcv variants," *BMC Genomics*, vol. 15, no. Suppl 5, S4, 2014.

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

[15] K. Yoshioka, T. Aiyama, A. Okumura, M. Takayanagi, K. Iwata, T. Ishikawa, Y. Nagai, and S. Kakumu, "Humoral immune response to the hypervariable region of hepatitis c virus differs between genotypes 1b and 2a," *The Journal of Infectious Diseases*, vol. 175, no. 3, pp. 505–510, 1997.

[16] D. Wodarz, "Hepatitis c virus dynamics and pathology: The role of ctl and antibody responses," *Journal of General Virology*, vol. 84, no. Pt 7, pp. 1743–1750, 2003.

[17] M. A. Nowak, R. M. May, and R. M. Anderson, "The evolutionary dynamics of hiv-1 quasispecies and the development of immunodeficiency disease," *AIDS*, vol. 4, no. 11, pp. 1095–1103, 1990.

[18] M. A. Nowak and R. M. May, "Mathematical biology of hiv infections: Antigenic variation and diversity threshold," *Mathematical Biosciences*, vol. 106, no. 1, pp. 1–21, 1991.

[19] M. A. Nowak, R. M. Anderson, A. R. Mclean, and R. M. May, "Antigenic diversity thresholds and the development of aids," *Science*, vol. 254, no. 5034, pp. 963–969, 1991.

[20] T. Francis and Jr., "On the doctrine of original antigenic sin," *Proceedings of the American Philosophical Society*, vol. 104, no. 6, pp. 572–578, 1960.

[21] K. Pan, "Understanding original antigenic sin in influenza with a dynamical system," *PLoS ONE*, vol. 6, no. 8, e23910, 2011.

[22] B. Rehermann and E.-C. Shin, "Private aspects of heterologous immunity," *Journal of Experimental Medicine*, vol. 201, no. 5, pp. 667–670, 2005.

[23] M. S. Parsons, S. Muller, H. Kholer, M. D. Grant, and 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*, vol. 9, no. 7, pp. 1532–1538, 2013.

[24] J. H. Kim, I. Skountzou, R. Compans, and J. Jacob, “Original antigenic sin responses to influenza viruses,” *J Immunol*, vol. 183, no. 5, pp. 3294–3301, 2009.

[25] C. M. Midgley, M. Bajwa-Joseph, S. Vasanawathana, W. Limpitikul, B. Wills, A. Flanagan, E. Waiyaiya, H. B. Tran, A. E. Cowper, P. Chotiyarnwon, J. M. Grimes, S. Yoksan, P. Malasit, C. P. Simmons, J. Mongkolsapaya, and G. R. Screaton, “An in-depth analysis of original antigenic sin in dengue virus infection,” *Journal of Virology*, vol. 85, no. 1, pp. 410–421, 2011.

VITA

Longmei Shu was born in Hubei, China. She got her bachelor's in engineering and master's in applied mathematics from Tsinghua University before starting her PhD studies at Georgia Tech.