Mathematical Analysis of a Multiple Strain, Multi-locus-allele System for Antigenically Variable Infectious Diseases Revisited

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Abstract

Many important pathogens such as HIV/AIDS, influenza, malaria, dengue and meningitis generally exist in phenotypically distinct serotypes that compete for hosts. Models used to study these diseases appear as meta-population systems. Herein, we revisit one of the multiple strain models that have been used to investigate the dynamics of infectious diseases with co-circulating serotypes or strains, and provide analytical results underlying the numerical investigations. In particular, we establish the necessary conditions for the local asymptotic stability of the steady states and for the existence of oscillatory behaviours via Hopf bifurcation. In addition, we show that the existence of discrete antigenic forms among pathogens can either fully or partially self-organize, where (i) strains exhibit no strain structures and coexist or (ii) antigenic variants sort into non-overlapping or minimally overlapping clusters that either undergo the principle of competitive exclusion exhibiting discrete strain structures, or co-exist cyclically.

Keywords: Multiple strain epidemic model, Stability analysis, Periodic Solutions, Hopf bifurcation, Antigenically diverse diseases, Strain structures

1. Introduction

One of the major challenges in the study and modelling of infectious diseases is understanding the interactive interplay between epidemiological, immunological and evolutionary dynamics for antigenically variable pathogens. Many important pathogens responsible for significantly high morbidity and mortality in the modern era have been infectious diseases with antigenically diverse pathogens (Andreasen et al., 1997; Lin et al., 1999; Plotkin et al., 2002; Gog and Grenfell, 2002; Cliff et al., 1986; Gupta et al., 1996; Gupta and Anderson, 1999; Gupta et al., 1994). Many of these pathogens are known to achieve immune escape by antigenic variation, a process by which a pathogen continuously keeps altering its surface proteins thereby preventing antibodies from recognizing and destroying it, which allows the viruses to present themselves with many antigenically different pathogenic forms. Diseases such as influenza (Earn et al., 2002; Ferguson et al., 2003; Smith et al., 1999, 2004; Buckee et al., 2011; Recker et al., 2007), dengue (Gog and Grenfell, 2002; Recker et al., 2009), AIDS (Nowak et al., 1995), malaria (Gupta et al., 1994; Recker et al., 2004) and meningitis (Gupta and Anderson, 1999; Gupta et al., 1996) are caused by pathogens that use antigenic variation as an immuno-evasion strategy.

To understand and explain the mechanisms underlying antigenic variation and diversity maintenance on co-evolution of pathogens, several researchers have formulated mathematical models incorporating the diversifying selection mediated by host immunity. All of these mathematical models use the standard compartmentalized structure of the SIR model in a meta-population framework (Andreasen et al., 1997; Gupta et al., 1998; Gog and Swinton, 2002). These theoretical models link infectious disease dynamics

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to antigenic diversity using different modelling assumptions in order to show how immunological cross-reactive strains invade a partially protected susceptible. The pioneering work of Elveback et al. (1964) provided one of the first Monte Carlo simulations of multiple strain dynamics; Dietz (1979) provided the mathematical description of Elveback et al. (1964) which was later modified by Castillo-Chavez et al. (1989) to include cross-immunity in both discrete and continuous age-structured models. Similar extensions and generalizations of these models have appeared in the literature (Andreasen et al., 1997; Lin et al., 1999; Plotkin et al., 2002; Gog and Grenfell, 2002; Cliff et al., 1986; Gupta et al., 1996, 1994; Gupta and Anderson, 1999; Gupta and Galvani, 1999; Buckee et al., 2004; Buckee and Gupta, 2010; Recker and Gupta, 2005; Calvez et al., 2005; Ferguson and Andreasen, 2001; Ferguson et al., 2003; Sasaki and Haraguchi, 2000; Nuno et al., 2009) and are characterized by one of the two dichotomies based on the way in which competition between strains is incorporated or how the properties of cross-immunity are mediated within the host and the ecology of the pathogens.

The first dichotomy is related to the bookkeeping of the phenotypic structure of the pathogen of interest. In particular, there have been two commonly used approaches to keep track of either the immunological history or status of the hosts. The history-based framework characterizes hosts by their immunological histories, whereby the the hosts are grouped into classes by their disease histories defined in terms of all the phenotypes to which an individual has ever been exposed (Castillo-Chavez et al., 1989; Elveback et al., 1964; Dietz, 1979; Andreasen et al., 1997; Gomes et al., 2002; Gupta et al., 1998, 1996; Lin et al., 1999; Recker et al., 2007). In contrast, the status-based framework highlights the importance of the current immune state and is immunologically path-independent (Gog and Swinton, 2002; Kryazhimsky et al., 2007). That is, the status-based approach is only concerned with the current, but not previous, immunological memories defined in terms of all strains against which an individual has gained immunity.

The second dichotomy is based on how the properties of cross-immunity are mediated within the hosts. That is, whether a secondary infection reduces the chance of an immune individual becoming re-infected, or the infectivity of an immune individual. These are known as either reduced susceptibility (Kryazhimsky et al., 2007) or reduced infectivity (Gupta et al., 1998; Recker et al., 2007), respectively. Mathematically, models constructed under both susceptibility and infectivity reduction assumptions within the history-based framework have been shown to exhibit similar qualitative behaviours (see Ferguson and Andreasen, 2001; Dawes and Gog, 2002). On the other hand, status-based models require one to impose assumptions on the nature of susceptibility and infectivity reductions. In addition, the reduced susceptibility models may yield qualitative and quantitative behaviours that are different from reduced infectivity models.

Whilst there have been some mathematical studies establishing generic stability results for multiple strain systems, generalization of the results usually becomes intractable, for the number of possible equilibria increases exponentially. Given the difficulty in fully analyzing these models, there have been various approaches designed for studying both their steady state solutions and dynamic features. For instance, Andreasen et al. (1997) and Lin et al. (1999) considered, respectively, four-strain and three-strain epidemic models with partial cross-immunity between strains. For both models, the authors studied the stability of two of the boundary equilibria (equilibria representing discordant or unrelated strains for the former model) and the coexistence equilibrium. Dawes and Gog (2002) also considered a four-strain system and, using an unfolding approach to study the bifurcation structure of the system, found similar behaviours to those in the aforementioned papers of Andreasen et al. (1997) and Lin et al. (1999). Recker and Gupta (2005) have also considered a variant model of Gupta et al. (1998) and studied the stability of the partially synchronous and fully synchronous steady states via an ε -fluctuation method and numerically showed the existence of cyclic dynamics. More recently, Chan and Yu (2013) and Blyuss (2014) used the groupoid formalism of Golubitsky et al. (2005) and centre-manifold reduction, and an equivariant dynamical system approach to study synchronous clustering and symmetric dynamics, respectively.

Herein, we present a different approach to perform a detailed study of the multi-locus-allele system of Gupta et al. (1996, 1998) with particular emphases on stability analysis of the equilibria and the existence of a Hopf bifurcation, which have not been out until recently by Chan and Yu (2013) and Blyuss (2014). The study presented generalizes the results of Chan and Yu (2013) and Blyuss (2014), for our approach introduces additional constants that capture the topology of the strain spaces and are applicable to multiple strain systems beyond four strains. In the proceeding sections, we first describe the model including boundedness

and positivity of solutions in Sections 2 and 3, respectively. This is followed by both local and global stability analyses of the disease-free steady-state, and the conditions for the existence of multiple endemic equilibria of the model. The asymptotic stability conditions are provided for these different notions of endemicity in Section 4. Section 4 is concluded by establishing the existence of cyclic and/or chaotic dynamics. Throughout the paper, we provide some numerical simulations of different dynamics and discuss their behaviours. In Section 5, we discuss how different allelic architectures give rise to different clustering patterns. We summarize these results and provide further research directions in Section 6.

2. Model Description: Multi-locus-allele Systems

In the standard classical compartmental epidemic theory, the population is generally divided into different epidemiological groups: susceptible, infected, and removed. To incorporate multiple groups into this standard compartmentalization, strain structures are typically imposed, based on assumptions on both immunological and genetic processes (Gog and Grenfell, 2002; Dawes and Gog, 2002; Gog and Swinton, 2002). In order to circumvent the imposition of strain structures and to simplify the descriptions of various epidemiological groupings, Gupta et al. (1996, 1998) introduced the multi-locus-allele system, where pathogenic strains are defined by multiple loci, each occupied by one allele from a specified set. In this framework, the combination of alleles at different loci constitute a strain where each strain can incorporate either asymmetric (differential) or symmetric (uniform) allelic combinations. In general, there are $N := \prod_{i=1}^n m_i$ strains, where n denotes the number of loci and m_i denotes the number of alleles at the i th locus. We denote the case when $m_i \neq m_j$, $i \neq j$ as differential allelic variations, and $m_i = m_j$, $i \neq j$ as a uniform allelic combination.

Here we focus on the 2-locus-2-allele system for the sake of simplicity, and use two indices i, j to indicate each locus, where i is one locus and j the other locus, $i, j = 1, 2$. Using the multi-locus-allele framework, Gupta et al. (1996, 1998) and Recker et al. (2007) characterized individuals based on their immunological history and divided the host population into three partially overlapping epidemiological compartments for each strain ij : the proportion of the population that has been exposed to pathogenic type ij and/or is now immune to strain ij , z_{ij} ; the proportion of the individuals who have been exposed and are immune to any antigenic type sharing alleles with strain ij , w_{ij} and the proportion of the population infectious with strain ij , y_{ij} . The model is given by the following set of differential equations:

$$\frac{dz_{ij}(t)}{dt} = \beta(1 - z_{ij})y_{ij} - \mu z_{ij} \quad (1)$$

$$\frac{dw_{ij}(t)}{dt} = \beta \left(\sum_l y_{lj} + \sum_k y_{ik} - y_{ij} \right) (1 - w_{ij}) - \mu w_{ij} \quad (2)$$

$$\frac{dy_{ij}(t)}{dt} = \beta [(1 - w_{ij}) + (1 - \gamma)(w_{ij} - z_{ij})] y_{ij} - (\mu + \sigma) y_{ij}, \quad (3)$$

where the force of infection is given by $\lambda_{ij} = \beta y_{ij}$, and β is the transmission rate. In addition, the model assumes that individuals leave the population at a constant rate μ due to natural death (i.e., $\frac{1}{\mu}$ is the average life-expectancy of the host), and recover from the infectious class at the rate of σ (where $\frac{1}{\sigma}$ is the average period or séjour of infectiousness).

Furthermore, the model assumes that immunity to an infecting strain is obtained immediately upon infection and is lifelong; in addition, multiple concurrent infections with allelomorphically different strains are possible. However, individuals who have never been infected with strain type ij , or any strain that shares alleles with ij , have no protection against the strain. Those that have previously been exposed to strains sharing alleles with strains ij excluding ij itself, have probability $(1 - \gamma)$ of becoming infected due to cross-immunity, where the strength of cross-immunity $\gamma \in [0, 1]$. In other words, strains that are *allelomorphically* different do not affect each others' transmissibility, while infection with *allelomorphically* similar strains provides some cross-protection. Here, it is assumed that, for all non-identity strains, sharing one allele has the same protective outcome as sharing more than one.

3. Positivity and Invariant Feasible Region

The model (1)-(3) describes the population dynamics, and the variables are all non-negative. Therefore, one can easily show that there is a feasible region for which the model is epidemiologically relevant and the solutions to Eqs. (1)-(3) with non-negative initial conditions will remain non-negative for all time $t \in [0, \infty)$, i.e., $1 \geq z_{ij}(t) \geq 0$, $1 \geq w_{ij}(t) \geq 0$, and $1 \geq y_{ij}(t) \geq 0$ for all strains ij , and are uniformly bounded. In particular, we have the following biologically-feasible region

$$\Omega := \{z_{ij}, w_{ij}, y_{ij} \in \mathbb{R}_+^{3M} : 0 \leq z_{ij}, w_{ij}, y_{ij} \leq 1; i, j = 1, \dots, m\},$$

where M is the number of strains. In addition, the model is dissipative and positively invariant. Thus it is sufficient to consider the flow generated by the system (1)-(3) in $\Omega \subset \mathbb{R}_+^{3M}$, where the model is both biologically relevant and mathematically well-posed. We state the following theorem:

Theorem 3.1. *Suppose the initial data $z_{ij}(0) \geq 0, w_{ij}(0) \geq 0, y_{ij}(0) \geq 0$ and are inside the invariant biologically feasible simplex Ω . Then the solutions $z_{ij}(t), w_{ij}(t), y_{ij}(t)$ of the model are non-negative for all time $t \in \mathbb{R}_+$. In addition, the following hold:*

1. *If $y_{ij}(0) = 0$ for all i, j , then all solutions $y_{ij}(t)$ remain zero,*
2. *If $y_{ij}(0) > 0$ for all i, j , then all solutions remain inside the feasible region Ω .*

Moreover, $\limsup_{t \rightarrow \infty} w_{ij} \leq 1$, $\limsup_{t \rightarrow \infty} z_{ij} \leq 1$ and $\limsup_{t \rightarrow \infty} y_{ij} \leq 1$.

Proof. The proof is provided in Cherif (2011). See Appendix A.1. □

4. Steady State and Stability Analysis

In this section, we establish the conditions for the stability of equilibria in the model given by Eqs. (1)-(3).

4.1. Disease-Free Equilibrium

We observe that the system of Eqs. (1)-(3) admits a trivial steady state (disease-free) solution where $y_{ij} = 0$ for all $i, j = 1, 2$, and it is denoted by $\mathcal{E}_0 := \{z_{11}, \dots, z_{22}; w_{11}, \dots, w_{22}; y_{11}, \dots, y_{22}\} = \{0, \dots, 0; 0, \dots, 0; 0, \dots, 0\}$. The linear stability of the disease-free steady state $\mathcal{E}_0$ can easily be investigated and depends on the basic reproductive number $\mathcal{R}_0 = \frac{\beta}{\sigma + \mu}$, which can be calculated by the next generation method (see, for example, Diekmann and Heesterbeek, 2000; Castillo-Chavez et al., 2002). Here, $\mathcal{R}_0$ denotes the average number of secondary cases caused by each infected individual at the beginning of infection in the population with no pre-existing immunity, and measures the initial growth rate of the epidemic. The following condition determines the stability of the disease-free equilibrium, $\mathcal{E}_0$.

Lemma 4.1. *The disease-free equilibrium $\mathcal{E}_0 := (z_{ij}, w_{ij}, y_{ij})_{i,j=1,2} = (0, 0, 0)$ exists for all $\mathcal{R}_0$. Moreover, it is asymptotically stable if and only if $\mathcal{R}_0 < 1$. It is unstable when $\mathcal{R}_0 > 1$.*

The proof of Lemma 4.1 relies on the eigenvalues of the Jacobian matrix generated by Eqs. (1)-(3) and evaluated at the disease-free equilibrium point $\mathcal{E}_0$. It is trivial and has been ignored herein (see Appendix A.2). If the disease-free equilibrium point is the only steady state in Ω , then we obtain the following statement.

Theorem 4.2. *Suppose $z_{ij}(0) \geq 0, w_{ij}(0) \geq 0$ and $y_{ij}(0) \geq 0$ and are inside the biologically invariant feasible simplex Ω . Then there is only one steady state $\mathcal{E}_0$, and is globally asymptotically stable provided $\mathcal{R}_0 < 1$.*

Proof. See Appendix A.3 □

Figure 1: **Multi-locus System (Possible Equilibria for Four Strain System on a Square Lattice with $\mathbb{D}_4$ -Symmetry)**: The sketch shows different configurations of the equilibrium clusters, where black circles (●) denote the persistent strains while white circles (○) represent extinct strains. For labelling purposes, the columns are denoted by *a-d*, and the row 1-4. Note for the multiple loci-alleles system, the steady state structures correspond to the power set of the strain set. See the text.

4.2. Endemic Equilibria

To determine the existence of non-trivial equilibrium points or endemic steady states, we use Fig. 1 to help us simplify the search for endemic equilibria and stability analysis. Suppose we have a 2-strain system, then there are three possible endemic configurations when the reproductive number $\mathcal{R}_0 > 1$: either strain 1 persists while strain 2 goes to extinction, or strain 2 persists while strain 1 goes to extinction, or both strains 1 and 2 coexist. Hence, we denote the persistent set as follows: $\{1\}$, $\{2\}$ and $\{1, 2\}$. These correspond to the power set of the strain set, where the empty set represents the disease-free steady state (see Cherif (2011) for more details). For 4-strain system, Fig. 1 illustrates all the possible endemic configurations of different clustering type in a 2-locus-2-allele configuration, where black circles (●) denote the persistent strains while white circles (○) represent extinct strains. From the insight garnered from previous numerical studies (see Gupta et al., 1996, 1998; Recker et al., 2007; Wikramaratna et al., 2010; Gomes et al., 2002; Andreasen et al., 1997; Gog and Swinton, 2002, and references therein) and using the representation summarized in Fig. 1, we propose the following mathematical notion to provide an easy framework for analyzing the model. Using the above notion, we define the following notion of endemic solutions (Thieme, 2003):

Definition 4.1. 1. A non-trivial and non-negative steady state is called weakly endemic if $y_{ij} = y_{ij}^* \neq 0$ for some pair ij .

2. A non-trivial steady state solution is called strongly endemic if $y_{ij} = y_{ij}^* \neq 0$ for all ij .

In the definition above, a weakly endemic equilibrium is equivalent to having a principle of competitive exclusion and a strongly endemic equilibrium represents full coexistence. Throughout the proceeding sections, we will use the multi-locus-allele notation for ease of illustration and will focus on the 2-locus-2-allele system. However, the results are valid for any multi-locus system without the need of re-analyzing the model with higher strain numbers.

4.2.1. Weak Endemicity: Principle of Competitive Exclusion and Discrete Strain Structure

In principle, one could calculate all the endemic equilibria. However, this could be very difficult as the dimensionality of the system is increased. Instead, we simplify our study and break up the steady state analysis according to equilibrium clusters (see Figs. 1 and B.10-B.12). Suppose we are interested in studying one of the equilibrium cluster types shown in Fig. 1 (say, any of the structures in Fig. 1 except d-3 and d-4), then using the definition of weak endemicity, we can place strains into two disjoint sets based on whether they persist or not. We denote the two disjoint sets of equilibrium clusters as $\mathcal{D}_p$ and $\mathcal{D}_\emptyset$, where $\mathcal{D}_p$ contains all the strains that are persistent while $\mathcal{D}_\emptyset$ contains all the strains that go extinct. Observe that the set $\mathcal{D}_p \cup \mathcal{D}_\emptyset$ contains all the strains and $\mathcal{D}_p \cap \mathcal{D}_\emptyset = \emptyset$. Using this, we separate the coordinates of the steady state subspace for weak endemicity into sub-coordinates that are persistent and those that go to extinction. Let $\rho_p \in \mathbb{Z}_+$ be the number of discordant strains in $\mathcal{D}_p$, and $\rho_\emptyset \in \mathbb{Z}_+$ denote the number of discordant strains in $\mathcal{D}_\emptyset$. We begin by first considering the simple balanced case where $\rho = \rho_p = \rho_\emptyset$. We rewrite Eqs. (1)-(3) according to whether strains belong to $\mathcal{D}_p$ or not. For strains belonging to $\mathcal{D}_p$, $\sum_l y_{lj} + \sum_k y_{ik} - y_{ij}$ reduces to y_{ij} . For those strains which do not belong to $\mathcal{D}_p$ but are members of $\mathcal{D}_\emptyset$, $\sum_i y_{ik} + \sum_m y_{km} + y_{kl}$ reduces to ρy_{ij} . Solving for the weak endemic steady states, we find that, for $ij \in \mathcal{D}_p$, $z_{ij}^* = w_{ij}^* = 1 - \frac{1}{\mathcal{R}_0}$, $y_{ij}^* = \frac{\mu}{\beta} (\mathcal{R}_0 - 1)$, and for $kl \in \mathcal{D}_\emptyset$, $z_{kl}^* = y_{kl}^* = 0$ and $w_{kl}^* = \frac{\rho (\mathcal{R}_0 - 1)}{\rho (\mathcal{R}_0 - 1) + 1}$, where we recall $\mathcal{R}_0 = \frac{\beta}{\mu + \sigma}$. Note that these points only exist in biologically relevant regimes if $\mathcal{R}_0 > 1$; and when $\mathcal{R}_0 = 1$, we recover the disease-free equilibrium $\mathcal{E}_0$. In addition, by symmetry, interchanging the role of ij and kl , we can obtain the other weakly endemic equilibrium. Whenever the equilibrium clustering type in d -1 exists in Fig. 1, equilibrium clustering type d -2 in Fig. 1 also exists. Similarly, if the equilibrium clustering type in b -1 exists in Fig. 1, then equilibrium clustering types b -2, b -3, and b -4 in Fig. 1 also exist. Moreover, by the equivariance of the system, all weakly endemic steady states in the same clustering type gave the same stability outcome. That is, if clustering type in b -1 is (un)stable, then equilibrium clustering types b -2, b -3, and b -4 in Fig. 1 are also (un)stable.

Evaluating the Jacobian matrix generated by the model at the above equilibrium point, we obtain the following theorem which establishes the stability of the discrete strain structure endemic steady state:

Theorem 4.3. Suppose $\mathcal{R}_0 > 1$ and $\rho \neq 0$. Let $\mathcal{E}_1$ and $\mathcal{E}_2$ be defined as:

$$\mathcal{E}_1 = \left(1 - \frac{1}{\mathcal{R}_0}, 1 - \frac{1}{\mathcal{R}_0}, \frac{\mu}{\beta} (\mathcal{R}_0 - 1), 0, \frac{\rho (\mathcal{R}_0 - 1)}{\rho (\mathcal{R}_0 - 1) + 1}, 0 \right), \quad (4)$$

$$\mathcal{E}_2 = \left(0, \frac{\rho (\mathcal{R}_0 - 1)}{\rho (\mathcal{R}_0 - 1) + 1}, 0, 1 - \frac{1}{\mathcal{R}_0}, 1 - \frac{1}{\mathcal{R}_0}, \frac{\mu}{\beta} (\mathcal{R}_0 - 1) \right), \quad (5)$$

be the steady states corresponding to weakly endemic equilibria of discordant type, where ρ is the number of discordant sets (non-overlapping set or minimally overlapping set), and $\mathcal{E}_i$, $i = 1, 2$ condenses the steady state expression according to clusters (i.e., we use the above notation rather than using $\mathcal{E} = \{z_{11}, w_{11}, y_{11}, \dots, z_{22}, w_{22}, y_{22}\}$) when strains are in the same cluster. The weak endemic equilibria exist provided that $\mathcal{R}_0 > 1$. In addition, the following hold:

1. The weakly endemic equilibria $\mathcal{E}_1$ and $\mathcal{E}_2$ are locally asymptotically stable provided

$$\gamma > \bar{\gamma}(\mathcal{R}_0) =: \frac{1 + \rho (\mathcal{R}_0 - 1)}{\rho \mathcal{R}_0}. \quad (6)$$

2. If $\gamma < \bar{\gamma}(\mathcal{R}_0)$, then the weakly endemic equilibria $\mathcal{E}_1$ and $\mathcal{E}_2$ are unstable.

Proof. See Appendix A.4. □

Corollary 4.4. Suppose $\mathcal{R}_0 > 1$, $\rho_p = \rho_\emptyset$ and let $\rho_p \in \mathbb{Z}_+$ and $\rho_\emptyset \in \mathbb{Z}_+$ be the number of discordant strains in $\mathcal{D}_p$ and in $\mathcal{D}_\emptyset$, respectively, where $\mathcal{D}_p$ is the set containing persistent strains while $\mathcal{D}_\emptyset$ is the set containing non-persistent (extinct) strains. If $\rho = \min\{\rho_p, \rho_\emptyset\} \neq 0$, then all weakly endemic equilibria with the steady states having such discrete strain structures are locally asymptotically stable provided that $\gamma > \bar{\gamma}(\mathcal{R}_0)$.

The proof of Corollary 4.4 follows directly from Theorem 4.3. The expression above in Theorem 4.3 determines the necessary condition for the existence and stability of weakly endemic equilibria. In addition, it should also be noted that $\bar{\gamma}(\mathcal{R}_0) \rightarrow 1$ as $\mathcal{R}_0 \rightarrow +\infty$. We note that weakly endemic equilibria consist of strain clusters that are structured discretely (i.e., not all strains are present due to the principle of competitive exclusion), hence the name discrete strain structures (DSS) in Gupta et al. (1998). These persistent strains are discordant (i.e., consist of non-overlapping alleles). Note that the condition for a DSS endemic equilibrium is a generalization of the condition discussed in Gupta et al. (1996, 1998), Ferguson and Andreasen (2001) and Recker et al. (2007). That is, in the particular 2-locus-2-allele case where the number of discordant strains is $\rho = 2$, the threshold condition for the local stability of DSS is given by $\gamma > 1 - 1/2\mathcal{R}_0$ which is equivalent to the condition given by Gupta et al. (1996, 1998). When $\mathcal{R}_0 = 1$, Chan and Yu (2013) showed, using quotient network and central manifold reduction, that discrete strain structures consisting of discordant sets are stable provided $\gamma\rho > 1$, where ρ was given in terms of the quotient network parameters (i.e., difference between the number of each strain in $\mathcal{D}_p$ sharing alleles with strains in $\mathcal{D}_\emptyset$ and number of strains sharing alleles in the same set $\mathcal{D}_p$). This is not surprising since there is a natural pairing of strains. If we denote the four strains by **ax**, **ay**, **bx** and **by**. Then, strains **ax** and **by**, for example, are non-overlapping and therefore induce no cross-immunity between each other. Hence, strains **ax** and **by** (and similarly for strains **ay** and **bx**) form a discordant set. Biologically, if the immune response of pathogen antigens is high and the immunity to a specific variant antigen within the host is able to reduce the transmissibility fitness of subsequent infections by allelomorphous serotypes, then the strain population will self-organize into discrete strain structures containing discordant sets with either non-overlapping or minimally overlapping structures (see Gupta et al., 1996, 1998). Because the competition between different discordant sets is high, one discordant set will persist at higher frequency than the others. This phenomenon yields specific discrete strain structures with high degree of discordance and low diversity in the population.

Figure 2 summarizes the temporal evolution of the prevalence z_i where the pathogen population is structured into discrete discordant sets with one discordant pair of strains, strain **ay** and strain **bx**, dominates in equal abundance into perpetuity while the other discordant pair of strains, strain **ax** and **by**, is suppressed.

The behaviours for DSS are observed when $\gamma > \frac{1 + \rho(\mathcal{R}_0 - 1)}{\rho\mathcal{R}_0}$ and $\mathcal{R}_0 > 1$ in the region of weak endemicity.

When this condition is satisfied, introducing a new strain related to either or both strains will not be able to invade unless it is allelomorphically distinct from the endemic strains. Figure 2 reproduces the result illustrated in Gupta et al. (1998). Figures B.10-B.12 show that the DSS behaviours are preserved for higher strain systems (see Appendix B for more details). Moreover, Buckee et al. (2011) have recently shown that discrete strain structure consisting mainly of discordant sets in a uniform multi-locus-multi-allele system is replaced with minimally overlapping structure in a system with variable allelic combinations, in which the discrete strain structures consist of persistent strains containing strains with maximal possible antigenic (allelic) distances. We summarize the above discussion in the following statement:

Conjecture 4.5. *Suppose $\mathcal{R}_0 > 1$ and let $\rho_p \in \mathbb{Z}_+$ and $\rho_\emptyset \in \mathbb{Z}_+$ be the number of discordant strains in $\mathcal{D}_p$ and in $\mathcal{D}_\emptyset$, respectively, where $\mathcal{D}_p$ is the set containing persistent strains while $\mathcal{D}_\emptyset$ is the set containing non-persistent (extinct) strains. Then the following holds:*

1. *Suppose $\rho_p = \rho_\emptyset$. If $\rho = \min\{\rho_p, \rho_\emptyset\} = 0$, then all weakly endemic equilibria with the steady states having such discrete strain structures are unstable.*
2. *Suppose $\rho_p \neq \rho_\emptyset$. If $\rho = \min\{\rho_p, \rho_\emptyset\} = 0$, then all weakly endemic equilibria with the steady states having such discrete strain structures are always unstable.*

The proof of Conjecture 4.5 follows from the symmetry structure of the equilibrium clusters (see Cherif (2011) for illustrative examples for 4-strain system and Appendix B graphical illustrations for general multi-locus-allele systems). In particular, we observe that equilibrium cluster types of the form shown in Fig. 1 associated with panels ranging a-1 to a-4 and b-1 to b-4, where $\rho_p \neq \rho_\emptyset$ (i.e., $\rho_p = 2$ and $\rho_\emptyset = 0$, and $\rho = \rho_p = 0$ and $\rho = \rho_\emptyset = 2$, respectively), cannot be stable. That is, when $\rho = \rho_p = 2$, the condition in Theorem 4.3 can be satisfied but when $\rho = \rho_\emptyset = 0$ the condition in Theorem 4.3 is violated. However, from the symmetry of the antigenic space, these two discrete strain structures are conjugate structures where the

Figure 2: **DSS Time Evolution (Eqs. (1)-(3))**: Dynamics of a stable DSS for a 2-locus-2-allele system where two strains coexist in equal abundance, and the other two strains are suppressed and go to extinction. Here z_i denotes the prevalence of strain i , where $i = \{\mathbf{ax}, \mathbf{ay}, \mathbf{bx}, \mathbf{by}\}$ and $\mathcal{R}_0 = 4$, $\sigma = 9.98$, $\mu = 0.02$, $\rho = 2$, and $\gamma = 0.95$ are used to reproduce the dynamics in Gupta et al. (1998). The dynamics in both panels have the same parameters but with different initial conditions. Equations (1)-(3) were solved using the Runge-Kutta fourth- and fifth-order method solver ODE45 in MATLAB (The Mathworks Inc., Natick, MA, USA) with the following initial conditions: (a) $z(0) = [0.5 \ 0.51 \ 0.55 \ 0.6]$, $w(0) = [0.4 \ 0.3 \ 0.3 \ 0.30]$ and $y(0) = [0.5 \ 0.4 \ 0.3 \ 0.2]$ and (b) $z(0) = [0.3 \ 0.51 \ 0.55 \ 0.6]$, $w(0) = [0.4 \ 0.3 \ 0.3 \ 0.30]$ and $y(0) = [0.5 \ 0.4 \ 0.3 \ 0.2]$; and relative and absolute error tolerance of 10^{-5} and 10^{-6} , respectively.

structures are related by either $\mathbb{Z}_4$ -rotations or reflections along the horizontal/vertical axes. Hence, this gives rise a contradiction. Moreover, if we let $\rho = \min\{\rho_p, \rho_\emptyset\}$, then we can clearly see that the stability condition in Theorem 4.3 is automatically violated when $\rho = \min\{\rho_p, \rho_\emptyset\} = 0$, for $\bar{\gamma} \rightarrow \infty$ as $\rho \rightarrow 0$. But $\gamma \in [0, 1]$ and $\gamma > \bar{\gamma} = \infty$ implies instability. Similarly, equilibrium cluster types in Fig. 1 in the panels ranging c-1 to c-4 cannot exist because $\rho = 0$, i.e. $\rho_p = 0$ and $\rho_\emptyset = 0$ because they violate the necessary stability condition in Theorem 4.3. These observations are consistent with numerical simulations presented herein and in Gupta et al. (1996, 1998), Andreasen et al. (1997), Ferguson and Andreasen (2001), Dawes and Gog (2002), Recker et al. (2004), Recker and Gupta (2005), Calvez et al. (2005), Recker et al. (2007) and Chan and Yu (2013).

4.2.2. Strong Endemicity: No Strain Structure

In order to find the unique strongly endemic equilibrium, we use the second part of Def. 4.1, for strong endemicity, that is, $y_{ij} = y_{ij}^* > 0$ for all $i, j = 1, 2$, where the abundance of y_{ij}^* is commensurable with the transmissibility fitness of strain ij . Since we have assumed that all strains have the same transmissibility success and $\mathcal{R}_0$ is the same for all strains, the abundance of y_{ij}^* becomes $y_{ij}^* = y^*$, and similarly for $z_{ij}^* = z^*$ and $w_{ij}^* = w^*$. Hence, the steady state is fully symmetric and all strains coexist in equal abundance (see Figs. 3 and B.8). In Gupta et al. (1998), this symmetric steady state is called no strain structure (NSS) because there is no distinction between the strains in the pathogen population structure. Using this, we note that $y_{ij} = y_{kl}$ for $ij \neq kl$, and $\sum_l y_{lj} + \sum_k y_{ik} - y_{ij}$ in Eqs. (1)-(3) reduces to αy_{ij} where $\alpha = m^n - (m-1)^n$, $\alpha \in \mathbb{Z}_+$ is the number of strains sharing alleles with strain ij (including ij itself). Then at the steady state, we have

$$z^* = \frac{\beta y^*}{\mu + \beta y^*} \quad (7)$$

$$w^* = \frac{\alpha\beta y^*}{\mu + \alpha\beta y^*} \quad (8)$$

$$y^* = \frac{\mu}{2\alpha\beta} \left(-\Gamma + \sqrt{4\alpha(\mathcal{R}_0 - 1) + \Gamma^2} \right) \quad (9)$$

$$\Gamma = 1 - \gamma\mathcal{R}_0 + \alpha(1 - \mathcal{R}_0(1 - \gamma)). \quad (10)$$

It should be noted that when $\alpha = 1$, the steady state for system (1)-(3) reduces to a single strain system. Henceforth, we assume $\alpha > 1$.

We calculate the Jacobian matrix at the NSS endemic steady state. The Jacobian matrix $\mathcal{J}$ is given by:

$$\mathcal{J} := \begin{bmatrix} -(\beta y^* + \mu)1_{m^2 \times m^2} & 0_{m^2 \times m^2} & \beta(1 - z^*)1_{m^2 \times m^2} \\ 0_{m^2 \times m^2} & -(\beta\alpha y^* + \mu)1_{m^2 \times m^2} & \beta(1 - w^*)\Omega_{m^2 \times m^2} \\ -\beta(1 - \gamma)y^*1_{m^2 \times m^2} & -\gamma\beta y^*1_{m^2 \times m^2} & 0_{m^2 \times m^2} \end{bmatrix}, \quad (11)$$

where $\Omega_{m^2 \times m^2} = \mathbb{I}_{m^2 \times m^2} + \mathbb{A}_{m^2 \times m^2}$, $\mathbb{I}_{m^2 \times m^2}$ is the identity matrix and $\mathbb{A}_{m^2 \times m^2}$ is the adjacency (strain similarity) matrix for strains sharing alleles in common. Note that the characteristic equation of this Jacobian is an 12^{th} order polynomial and its characterization is difficult. However, because of the sparseness of the Jacobian matrix, we were able to obtain the characteristic polynomial function of the form of $P(\zeta) = \prod_{k=1}^4 P_k(\zeta)$, where $P_k(\zeta)$ is a cubic polynomial function of the form $P_k(\zeta) = \sum_{l=0}^3 \mathcal{A}_{k,3-l}\zeta^l$ and where $\mathcal{A}_{k,0} = 1$ for all $k = 1, 2, 3, 4$; and the coefficients and Hurwitz determinants $\mathcal{A}_k$, $k = 1, 2, 3, 4$ are given in Appendix A.5. It should be noted that, using the symmetry property of the 2-locus-2-allele system and isotopic decomposition of the phase space to diagonalize the Jacobian, Blyuss (2014) also obtained similar expressions for the fully symmetric steady state. We observe that the characteristic polynomials $P_k(\zeta)$ have positive coefficient $\mathcal{A}_{k,l}$, $k = 1, 2, 3, l = 0, 1, \dots, 3$ and their Hurwitz determinants are all positive. That is, $\mathcal{A}_k > 0$ for $k = 1, 2, 3$. Hence, from the Routh-Hurwitz stability criterion, the characteristic polynomials $P_k(\zeta)$, $k = 1, 2, 3$ have all their eigenvalues with negative real parts. For the characteristic polynomial $P_4(\zeta)$, we observe that $\mathcal{A}_{4,0} > 0$ and $\mathcal{A}_{4,1} > 0$. It suffices to show that the coefficients $\mathcal{A}_{4,2}$ and $\mathcal{A}_{4,3}$, and Hurwitz determinant $\mathcal{A}_4$ are positive. In order to determine the condition for the stability of the strongly endemic or co-existence equilibrium, we must solve a fixed problem $\gamma^* = \bar{\gamma}_r(\gamma^*, \mathcal{R}_0)$ for any fixed $\mathcal{R}_0 > 1$, where $\bar{\gamma}_r(\gamma, \mathcal{R}_0)$ $r = 1, 2, 3$ are given below (see Appendix A.5). For the strongly endemic equilibrium to be locally asymptotically stable, we state the following results:

Theorem 4.6. Suppose $\mathcal{R}_0 > 1$ and $\gamma \in [0, 1]$. Let $\bar{\gamma}_r(\gamma, \mathcal{R}_0)$, $r = 1, 2, 3$ be defined as follows:

$$\begin{aligned} \bar{\gamma}_1(\gamma, \mathcal{R}_0) &= \frac{(\beta y^* + \mu)(\beta\alpha y^* + \mu) + \beta^2 y^* (1 - z^*)}{\beta^2 y^* (1 - w^*) + \beta^2 y^* (1 - z^*)}, \\ \bar{\gamma}_2(\gamma, \mathcal{R}_0) &= \frac{(1 - z^*)(\beta\alpha y^* + \mu)}{(1 - w^*)(\beta y^* + \mu) + (1 - z^*)(\beta\alpha y^* + \mu)}, \\ \bar{\gamma}_3(\gamma, \mathcal{R}_0) &= \frac{[\beta(1 + \alpha)y^* + 2\mu][(\beta y^* + \mu)(\beta\alpha y^* + \mu)] + \beta^2 y^* (1 - z^*)[\beta(2\alpha + 1)y^* + 3\mu]}{\beta^2 y^* (1 - w^*)[\beta(\alpha + 2)y^* + 3\mu] + (\beta^2 y^* (1 - z^*))[\beta(2\alpha + 1)y^* + 3\mu]}. \end{aligned}$$

Then the strongly endemic (no strain structure (NSS)) equilibrium is locally asymptotically stable provided that $\gamma < \bar{\gamma}_1(\gamma, \mathcal{R}_0)$, $\gamma > \bar{\gamma}_2(\gamma, \mathcal{R}_0)$ and $\gamma < \bar{\gamma}_3(\gamma, \mathcal{R}_0)$. The strongly endemic equilibrium is unstable if any one of the above conditions is false. That is, if $\gamma \geq \bar{\gamma}_1(\gamma, \mathcal{R}_0)$, $\gamma \leq \bar{\gamma}_2(\gamma, \mathcal{R}_0)$, and/or $\gamma \geq \bar{\gamma}_3(\gamma, \mathcal{R}_0)$, then the strongly endemic steady state is unstable.

Proof. See Appendix A.6 □

4.2.3. Strong Endemicity: Cyclical Strain Structures and Existence of Oscillatory Behaviours

To consider the existence of cyclical behaviours, we look for the necessary condition for a Hopf bifurcation in the system. Because of the forms of $P(\zeta)$ and $P_k(\zeta)$, $k = 1, 2, 3$, we note that $P(\zeta)$ and $P_k(\zeta)$, $k = 1, 2, 3$ always have eigenvalues with negative real part. As a result, we focus on $P_4(\zeta)$. If $\mathcal{A}_{4,0} > 0$, $\mathcal{A}_{4,1} > 0$,

Figure 3: **Time Evolution of No Strain Structure (NSS) (Eqs. (1)-(3))**: Dynamics of a stable NSS for the 2-locus-2-allele system where all strains coexist in equal abundance. Here z_i denotes the prevalence of strain i and $\mathcal{R}_0 = 4$, $\sigma = 9.98$, $\mu = 0.02$ and $\gamma = 0.46$ are used to reproduce the dynamics in Gupta et al. (1998). Equations (1)-(3) were solved using the Runge-Kutta fourth- and fifth-order method solver ODE45 in MATLAB (The Mathworks Inc., Natick, MA, USA) with the following initial conditions $z(0) = [0.50 \ 0.51 \ 0.55 \ 0.6]$, $w(0) = [0.40 \ 0.30 \ 0.3 \ 0.30]$ and $y(0) = [0.50 \ 0.40 \ 0.30 \ 0.20]$, and relative and absolute error tolerance of 10^{-5} and 10^{-6} , respectively.

$\mathcal{A}_{4,2} > 0$ and $\mathcal{A}_{4,3} > 0$, then a Hopf bifurcation can take place at the transit through the surface defined by the Hurwitz determinant $\mathcal{A}_4 = 0$. The strongly endemic equilibrium is unstable if there is pair of complex conjugate roots for $P_4(\zeta)$. Let $\zeta_{1,2} = \pm i\omega$, then $\zeta_1 + \zeta_2 + \zeta_3 = -\mathcal{A}_{4,1}$. Hence $\zeta_3 = -\mathcal{A}_{4,1}$ and $\omega^2 = \mathcal{A}_{4,2}$. Then $P_4(\zeta_3) = -\mathcal{A}_{4,1}\mathcal{A}_{4,2} + \mathcal{A}_{4,3}\mathcal{A}_{4,0} = 0$ and $\gamma = \gamma_3^*$, where $\gamma_3^* \in [0, 1]$ is the unique solution for the fixed point problem $\gamma = \bar{\gamma}_3(\gamma, \mathcal{R}_0)$. Thus, a Hopf bifurcation may occur at the strongly endemic equilibrium. We state the following results:

Lemma 4.7. Suppose $\mathcal{R}_0 > 1$, and let $\mathcal{H}_0$ or $\mathcal{H}_1$ be defined as:

$$\mathcal{H}_0 = \{(\beta, \mu, \sigma, \gamma) \in \mathbb{R}_+^4 : \mathcal{A}_4 = 0\}, \text{ or equivalently} \quad (12)$$

$$\mathcal{H}_1 = \{(\mathcal{R}_0, \gamma) \in \mathbb{R}_+^2 : \mathcal{A}_4 = 0\}. \quad (13)$$

Then the characteristic polynomial $P_4(\zeta)$ has one real negative and two purely imaginary solutions if and only if $(\beta, \mu, \sigma, \gamma) \in \mathcal{H}_0$ (or $(\mathcal{R}_0, \gamma) \in \mathcal{H}_1$). In addition, the roots are given by $\zeta_1 = -\mathcal{A}_{4,1}$ and $\zeta_{2,3} = \pm i\omega$, where $\omega^2 = \mathcal{A}_{4,2}$.

Corollary 4.8. Suppose $\mathcal{R}_0 > 1$. Let $\bar{\gamma}_r(\gamma, \mathcal{R}_0)$, $r = 1, 2, 3$ be defined as above for $\gamma \in [0, 1]$ and suppose that they are differentiable and monotone on $\gamma \in (0, 1)$. Let

1. $1 > \bar{\gamma}_r(0, \mathcal{R}_0) > \bar{\gamma}_r(1, \mathcal{R}_0) > 0$, or
2. $0 < \bar{\gamma}_r(0, \mathcal{R}_0) < \bar{\gamma}_r(1, \mathcal{R}_0) < 1$.

Then there exist γ_r^* , $r = 1, 2, 3$ such that $\gamma_r^* = \bar{\gamma}_r(\gamma_r^*, \mathcal{R}_0)$ and $\gamma_r^* \in (\bar{\gamma}_r(0, \mathcal{R}_0), \bar{\gamma}_r(1, \mathcal{R}_0))$. In addition, the following hold:

1. The strongly endemic equilibrium undergoes a steady state bifurcation when $\gamma = \gamma_1^*$ and/or $\gamma = \gamma_2^*$.

Figure 4: **Parameter Space $\mathcal{R}_0$ - γ for 2-locus-2-allele system:** Different dynamic behaviours are possible depending on the combination of $\mathcal{R}_0$ and γ . The solid curve is given by inequality (6). In the yellow region (i.e., $\mathcal{R}_0 < 1$), the disease-free equilibrium is the only biologically relevant steady state and is globally asymptotically stable. In the white region with black squares, the weakly endemic equilibrium exhibiting discrete strain structures (DSS) are locally asymptotically stable, and they are unstable outside this region. In the region of stability, the maintenance of invading strains related to the discordant persisting set is impossible. In the cyan region with black dots, the unique strongly endemic equilibrium is locally asymptotically stable and exhibits no strain structures (NSS); it is unstable outside this region. In the white region between the black line and cyan boundary, the unique strongly endemic equilibrium is unstable and exhibits cyclical behaviours (hence cyclical strain structures, CSS, see Theorem 4.6). The black lines are steady state bifurcation curves (see inequality (6)), and the cyan boundary is a Hopf bifurcation curve. The parameter values $\sigma = 9.98$, $\mu = 0.02$, $\rho = 2$ and $\alpha = 3$ are used.

2. The strongly endemic equilibrium undergoes a Hopf bifurcation when $\gamma = \gamma_3^*$.

Theorem 4.9. Assume $\mathcal{R}_0 > 1$ and $\mathcal{A}_{4,2} > 0$ (or equivalently $\gamma < \gamma_1(\gamma, \mathcal{R}_0)$) and $\mathcal{A}_{4,3} > 0$ (or equivalently $\gamma > \gamma_2(\gamma, \mathcal{R}_0)$). When γ passes through a critical value γ_3^* , where γ_3^* is the solution of $\gamma = \bar{\gamma}_3(\gamma, \mathcal{R}_0)$, the system undergoes a Hopf bifurcation.

Due to the complicated form of $\gamma = \bar{\gamma}_3(\gamma, \mathcal{R}_0)$, we will not address the properties of the Hopf bifurcation (i.e., direction of bifurcation, orbital stability of periodic solutions). In particular, we will not discuss the direction, stability of the periodic orbits, uniqueness of the orbit and period of solutions. We leave these for future investigations. Instead, we use numerical simulations to show that the system indeed undergoes a Hopf bifurcation at some critical value of γ .

Figures 4-5 summarize these results. The region bounded by the discrete strain structure (DSS) and no strain structure (NSS) in Figs. 4-5 exhibit complex dynamics where a set of strains oscillate. In Gupta et al. (1998), these oscillatory behaviours are dubbed cyclical strain structures (CSS) due to their cyclical dynamic natures. These results are further illustrated in the temporal evolution of the state variables for a fixed value of the basic reproductive number $\mathcal{R}_0 = 4$. Figure 6 shows the dynamics as the values of cross-immunity change. As we vary the level of cross-immunity γ from near a subcritical threshold (e.g., threshold value of cross-immunity separating CSS and NSS), the symmetry and/or synchronicity of NSS where all strains are at equal abundance is broken, and the temporal dynamics of the strain population denoted by the strongly endemic equilibrium becomes oscillatory via a Hopf bifurcation. In addition, we observe that, in the CSS region, the strains start to self-organize into sets of discordant strains alternating in strain abundance, where

Figure 5: **Steady-State Bifurcation Diagram:** For the 2-locus-2-allele system, the stability of the original system (see Eqs. (1)-(3)) varies with respect to cross-immunity level γ , for $\mathcal{R}_0 = 4$, $\sigma = 9.98$, $\mu = 0.02$. Note the three distinct regions emerging, namely no strain structure, cyclic strain structure, and discrete strain structure (see text for details). Here, we are showing only z_1 (i.e., z_{ax}) and stable solutions. Equations (1)-(3) were solved using the Runge-Kutta fourth- and fifth-order method solver ODE45 in MATLAB (The Mathworks Inc., Natwick, MA, USA) with the following initial conditions $z(0) = [0.50 \ 0.51 \ 0.55 \ 0.6]$, $w(0) = [0.40 \ 0.30 \ 0.3 \ 0.30]$ and $y(0) = [0.50 \ 0.40 \ 0.30 \ 0.20]$, and relative and absolute error tolerance of 10^{-5} and 10^{-6} , respectively.

each discordant set is half a period out of phase. Furthermore, as we increase the cross-immunity level γ close to the supercritical value (curve separating CSS and DSS), the frequency of oscillation decreases and the strains exhibit period-doubling dynamics. In fact, numerical studies of 3-locus-2-allele and other higher multiple locus-allele systems have shown the existence of chaotic behaviour via period-doubling bifurcation (Gupta et al., 1998; Recker et al., 2007, see Fig. B.9), where the periodicity degenerates into chaotic behaviours with the possibility of myriad of exotic dynamical patterns (see Appendix B for numerical illustrations). However, in the 2-locus-2-allele system, we do not observe any chaotic dynamics. Various works have observed similar behaviours. In particular, Andreasen et al. (1997); Lin et al. (1999) and Dawes and Gog (2002) have considered multi-strain epidemic models with cross-immunity between strains and showed that their systems (particularly the coexistence steady state) can undergo Hopf bifurcation and homoclinic bifurcation where a periodic orbit appears and then disappears. A further increase in the cross-immunity level γ eventually leads to the emergence of the discrete strain structure (see Figs. 2, and B.10-B.12), where weakly endemic equilibria are locally asymptotically stable. The existence of these three distinct dynamic regions presents an epidemiological conundrum. That is, if we increase the level of cross-immunity either through natural infections or prophylactic means such as vaccination, the observation of CSS behaviours becomes more frequent in high strain space or in high multi-locus-allele systems where there are possibility of chaotic patterns and the predictability of the dynamics is reduced substantially.

5. Discussion

Using the multi-locus-allele framework, we have shown the exact conditions under which the linear (local asymptotic) stability of disease-free and endemic equilibria holds. We established that the disease-free equilibrium is globally asymptotically stable whenever the basic reproductive number is less than unity (e.g., $\mathcal{R}_0 < 1$), and is unstable when this threshold condition is violated. When $\mathcal{R}_0 > 1$, at least one endemic

Figure 6: **Time Evolution of Cyclic Strain Structure (Eqs. (1)-(3)).** The plot illustrates the dependency of the dynamics of γ , where (a) $\gamma = 0.58$, (b) $\gamma = 0.62$, (c) $\gamma = 0.72$, and (d) $\gamma = 0.85$. Here, $\mathcal{R}_0 = 4$, $\sigma = 9.98$, $\mu = 0.02$. Equations (1)-(3) were solved using the Runge-Kutta fourth- and fifth-order method solver ODE45 in MATLAB (The Mathworks Inc., Natick, MA, USA) with the following initial conditions $z(0) = [0.50 \ 0.51 \ 0.55 \ 0.6]$, $w(0) = [0.40 \ 0.30 \ 0.3 \ 0.30]$ and $y(0) = [0.50 \ 0.40 \ 0.30 \ 0.20]$, and relative and absolute error tolerance of 10^{-5} and 10^{-6} , respectively.

equilibrium exists. However, this condition alone is not sufficient for the stability of the endemic equilibria. We found additional conditions which depend on the value of cross-immunity level in the population.

We observed that at one extreme, when the immunological responses to the strains are very low, the diversity of the strains is high and all possible allelomorph combinations of strains are maintained at abundances commensurable with their transmissibility successes. However, because the strains are assumed to have the same transmissibility success, they have equal abundance and are fully synchronized. At the other extreme, when the immune response is high and the transmissibility fitness of subsequent infections by allelomorphically similar serotypes is reduced, the pathogen population self-organizes into a discrete strain structure with persistence of one of the discordant sets. We established the conditions for these behaviours to be locally asymptotically stable. In addition, we showed the existence of a region where pathogens elicit high immune responses which, however, are not strong enough to suppress the transmissibility successes of subsequent infections by similar serotypes. In this region, the strains exhibit cyclical temporal dynamics with sequential domination of different self-organized discordant strains, where the fully synchronized steady state or strongly endemic equilibrium is unstable and undergoes a Hopf bifurcation. These observations are consistent with both our results of the system presented herein and the numerical results of Gupta

et al. (1996, 1998), Recker et al. (2007) and others (see Chan and Yu, 2013; Blyuss, 2014). Therefore, knowing the number of discordant strains in the equilibrium clusters can provide valuable information in determining whether a steady state is always unstable or can change stability based on the model parameters. Recently, Chan and Yu (2013) have found, using the groupoid formalism of Golubitsky et al. (2005) and centre-manifold reduction, the condition for the stability of partial synchrony exhibited by weakly endemic equilibria. However, the results presented herein for weakly endemic equilibria (e.g., DSS) are more general than those obtained by Chan and Yu (2013). The results of Chan and Yu (2013) is a special case of Eq. (6) in Theorem 4.3, and correspond to the case where DSS exists when $\gamma\rho > 1$ for $\mathcal{R}_0 = 1$, where ρ was given in terms of the quotient network parameters (i.e., difference between the number of each strain in $\mathcal{D}_p$ sharing alleles with strains in $\mathcal{D}_\emptyset$ and number of strains sharing alleles in the same set $\mathcal{D}_p$). The stability of the unique strongly endemic equilibrium and the nature of its bifurcation structure were not addressed in Chan and Yu (2013). Blyuss (2014) has recently extended the work of Chan and Yu (2013) and has provided, using equivariant bifurcation tools techniques used in Blyuss (2013), more detailed results of the model which are again consistent with our results when $\alpha = 3$ and $\rho = 2$ for the case of 2-loci-2-alleles model. Again our results are consistent to those obtained in Blyuss (2014). Hence, our results can be seen as a generalization of the conditions obtained in Chan and Yu (2013) and Blyuss (2014) without the need of re-analyzing the model for higher strain numbers, and can be applied to models discussed in Blyuss (2013) and Mitchell and Carr (2012) to obtain more general results. Figures B.8-B.12 show that the analyses represented herein hold for higher strain spaces without the need of calculating the values and stability conditions for each equilibrium cluster, provided the correct values of α and ρ for strongly and weakly endemic equilibria are calculated, respectively. For instance, in Fig. B.8, we show that, by calculating α for each strain space, the values of the steady state in Eqs. (7)-(10) are consistent with those obtained from the numerical simulations of Eqs. (1)-(3) (see Fig. B.8a for a 3-locus-2-allele system and Fig B.10 for a 4-locus-2-allele system, where $\alpha = 7$ and $\alpha = 15$, respectively). For the stability of the discrete strain structure for certain clustering types, we observe (as illustrated in Figs. 2 and B.10-B.12) that the existence of clustering type may not necessarily be delineated by parametric regions. Instead, there are cluster-specific sub-regions of attraction within the state space where selected individual clustering type depends on the initial conditions.

Different aspects of the observations outlined above have been discussed elsewhere (see Buckee et al., 2004; Calvez et al., 2005, see Appendix B for illustrative examples; and Cherif (2011)). In particular, for a 3-locus-2-allele system, Buckee et al. (2004) illustrated the formation of these clusters and their relationship with maintenance of diverse strain populations. Using a modified version of the model studied herein, Calvez et al. (2005) made similar observations on the type and structure of clusters possible as the number of loci is increased beyond two and provided a detailed discussion on the behaviour of force of infection (specifically relative force of infection) of individual clusters, mainly the regularity of force of infection of individual clusters and chaotic dynamics of individual strains. The exposition in Calvez et al. (2005) focused primarily on the dynamics in CSS regions and did not investigate the behaviour of cluster types and structures in DSS and NSS regions. However, our analytical results suggest that, because these clusterings are inherent properties of the Mendelian combinatorial structure of the strain space, the clustering behaviours are not restricted to the CSS region. In addition, one can also observe simple cluster transition with complex and/or exotic strain dynamics, as illustrated in Calvez et al. (2005), Gupta et al. (1996, 1998), Recker et al. (2007), Minayev and Ferguson (2009a,b), Recker et al. (2009), Chan and Yu (2013) and Blyuss (2014). These arrays of complex behaviours are especially observed in the CSS region where no stable equilibria exist. That is, the CSS regions only contain behaviours that include limit cycles, quasi-periodicity, and intermittency and chaos. Recently, Blyuss (2014) has provided some detailed discussion of the type of cyclical behaviours possible based on equivariant bifurcation theory and the H/K Theorem to explain some of these oscillatory behaviours. Moreover, from the insight gained from the symmetric structure of the strain space, we observe that the general multi-locus-allele system of m^n strains with $(m!)^{n-1}$ discordant sets of m members can exhibit symmetry-breaking phenomena not captured by the bifurcation diagram in Fig. 5. For instance, in Fig. 6, these symmetry-breaking phenomena are seen in the temporal evolution of strains. We observe that as we increase the level of cross-immunity in the CSS region, coherence among discordant strains is lost with symmetry-breaking where decoherence is observed in the limit cycles. As we approach the discrete strain structure region, coherence between strains is regained in high amplitude cyclical dynamics. The

coherence between members of discordant sets is enhanced in allele configurations higher than $m \geq 2$. To fully understand the parameter regions where these different clustering types and structures, and their respective dynamics, are observed, we must go to a co-dimensional parameter space higher than two or develop a relative cross-immunity measure capable of capturing the diversifying cluster selective properties of multiple cross-immunity levels in order to obtain a parameter space diagram similar to Fig. 4.

6. Conclusion

Herein, we have studied one of the models often used to investigate the interplay between epidemiological, immunological and evolutionary dynamics. In particular, we have provided a detailed analysis of a multi-locus-allele model proposed previously by Gupta et al. (1996, 1998), and focused our attention on the basic model of 2-locus-2-allele system. Using both biological insights and some mathematical definitions of endemicity and persistent sets, we split the steady state analysis into two parts based on the nature of endemicity, namely weakly endemicity and strongly endemicity where in the former some strains are persistent while others go extinct and in the latter all strains coexist. Reducing the system according to the steady state types allows us to simplify our analysis. Analyzing these steady state types, we found that weakly endemic equilibria can only undergo steady-state bifurcation while the unique strong endemic equilibrium can undergo bifurcation either to a steady-state or to an oscillatory solution (Hopf).

Although the results presented herein have focused on local properties of the equilibria, the assumptions of life-long immunity, uniformity of model parameters, and that a strain sharing one allele has the same cross-reactivity effect as having more than one allele in common, one could pursue further research in a variety of directions. The easiest extensions of the model are to relax the uniformity assumption of the epidemiological parameters and of allelic variation in the general multi-locus-allele system with cross-immunity based on differential allelic distance which will introduce a weighted serotypic cross-immunity network. Furthermore, one can consider the effect of general graph or network topology (e.g., small network topology, random network, real-world strain network motivated by biological evidence) on the dynamical behaviours of the multi-locus-allele systems where the symmetry structure of the network is not easily observable. In addition, the assumption on a life-long immunity can be relaxed to include exponential, discrete and/or distributed strain-transcending immunity which can be accomplished by the use of delay and/or functional differential equations. This extension provides a deterministic generalization of the multi-locus-allele framework of Gupta et al. (1996, 1998). Another possibility is incorporating the strain-transcending time-since-infection or the time-since-recovery with or without varying rates of loss of immunity assumption and/or age-specificity into the model. Another mathematical direction one could explore is the effect of intrinsic stochasticity on the transitions between different cluster types and structures. Recently, Buckee et al. (2011) and Minayev and Ferguson (2009b) have considered the effect of stochasticity on the dynamical patterns of the model proposed in Gupta et al. (1998) and its variation, whereas in Buckee et al. (2011) the authors show that although the self-organization of strains into discordant/non-overlapping or minimally overlapping sets will break down under differential allelic combination assumption, self-organization is recovered in the stochastic system. It will be noteworthy to investigate mathematically the underlying mechanism of this process.

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Appendix A. Proof of Lemmas and Theorems

Appendix A.1. Proof of Theorem 3.1

The model (1)-(3) describes population dynamics, and therefore it is important to show the feasible region for which the model is epidemiologically relevant. We need to show that the solutions to Eqs. (1)-(3) with

non-negative initial conditions will remain non-negative for all time $t \in [0, \infty)$, i.e., $1 \geq z_{ij}(t) \geq 0$, $1 \geq w_{ij}(t) \geq 0$, and $1 \geq y_{ij}(t) \geq 0$ for all strains ij . First, we provide the positivity condition for y_{ij} and then argue that w_{ij} and z_{ij} are both positive. This can be done in the standard way. We prove the positivity of y_{ij} by contradiction. Let $y_{ij}(0) \geq 0$ be the initial condition of $y_{ij}(t)$ and $T_0 := \inf\{t \in [0, \infty) \mid y_{ij}(t) = 0\}$ be the first time when $y_{ij}(T_0) = 0$. Noting that $y_{ij}(T_0) = 0$ implies $y_{ij}(t) \geq 0$ for all $t \in [0, T_0]$, we let

$$\psi := \min_{0 \leq t \leq T_0} \{\beta [(1 - w_{ij}) + (1 - \gamma)(w_{ij} - z_{ij})] - (\sigma + \mu)\}$$

then for $t \in [0, T_0]$ the expression for y_{ij} becomes:

$$\frac{dy_{ij}}{dt} = \beta [(1 - w_{ij}) + (1 - \gamma)(w_{ij} - z_{ij})] y_{ij} - (\sigma + \mu) y_{ij} \geq \psi y_{ij}.$$

Therefore, $y_{ij}(T_0) \geq y_{ij}(0)e^{\psi T_0}$. Clearly, if $y_{ij}(0) = 0$, then $y_{ij}(t) = 0$ for all $t \geq 0$. However, if $y_{ij}(0) > 0$, then $y_{ij}(T_0) \geq y_{ij}(0)e^{\psi T_0} > 0$, which implies that $y_{ij}(t) > 0$ for all $t \in [0, T_0]$.

For $z_{ij}(t)$ and $w_{ij}(t)$, we let T_1 and T_2 be defined similarly to T_0 and assume that there exist first times T_1 and T_2 such that $z_{ij}(t)$ and $w_{ij}(t)$ become zero. Let $z_{ij}(0) \geq 0$ and $w_{ij}(0) \geq 0$. This implies that $z_{ij}(t) \geq 0$ and $w_{ij}(t) \geq 0$ for all time $t \in [0, T_1]$ and $t \in [0, T_2]$, respectively; in addition,

$$\frac{dz_{ij}(T_1)}{dt} = \beta y_{ij} > 0,$$

and

$$\frac{dw_{ij}(T_2)}{dt} = \beta \left(\sum_l y_{lj} + \sum_k y_{ik} - y_{ij} \right) = \beta \left(\sum_{l \neq i} y_{lj} + \sum_{k \neq j} y_{ik} + y_{ij} \right) > 0,$$

because $y_{ij}(t) > 0$ for time $t \geq 0$ and for all ij . These contradict our assumptions, for they imply that $z_{ij}(t)$ and $w_{ij}(t)$ must be negative for t right before T_1 and T_2 , which violate the choices of T_1 and T_2 . We have therefore shown the positivity of our solutions for all times. To show the solutions of Eqs. (1)-(3) are bounded, we unfold the overlap of immuno-epidemiological classes (e.g., $w_{ij}(t) = \bigcup_{\langle i, j \rangle} z_{ij}(t)$ where $\langle i, j \rangle$ means strains sharing alleles with ij). That is, we extract the SIR-type dynamics in Eqs. (1)-(3). For convenience, we let $s_{ij}(t) = 1 - w_{ij}(t)$, $v_{ij}(t) = w_{ij}(t) - z_{ij}(t)$ and $z_{ij}(t) = 1 - s_{ij}(t) - v_{ij}(t)$. Using these variables and substituting them in (1)-(3), we transform the equations into the following system:

$$\frac{dz_{ij}(t)}{dt} = \beta (s_{ij}(t) + v_{ij}(t)) y_{ij}(t) - \mu z_{ij}(t), \quad (\text{A.1})$$

$$\frac{ds_{ij}(t)}{dt} = \mu - \beta s_{ij}(t) \left(\sum_l y_{lj}(t) + \sum_k y_{ik}(t) - y_{ij}(t) \right) - \mu s_{ij}(t), \quad (\text{A.2})$$

$$\frac{dv_{ij}(t)}{dt} = \beta s_{ij}(t) \left(\sum_{l \neq i} y_{lj}(t) + \sum_{k \neq j} y_{ik}(t) \right) - \beta v_{ij}(t) y_{ij}(t) - \mu v_{ij}(t), \quad (\text{A.3})$$

where $y_{ij}(t)$ is the same as in Eq. (3) with $1 - w_{ij}(t)$ and $w_{ij}(t) - z_{ij}(t)$ replaced by $s_{ij}(t)$ and $v_{ij}(t)$, respectively. It suffices to show the positivity of Eqs (A.1)-(A.3) in order to determine the boundedness of Eqs. (1)-(3). From Eq. (A.2), it follows that

$$\begin{aligned} s_{ij}(t) &= s_{ij}(0) \exp \left(-\beta \int_0^t \Xi_{\langle l, k \rangle}^{ij}(\tau) d\tau - \mu t \right) + \exp \left(-\beta \int_0^t \Xi_{\langle l, k \rangle}^{ij}(\tau) d\tau - \mu t \right) \\ &\quad \times \int_0^t \mu \exp \left(\beta \int_0^\tau \Xi_{\langle l, k \rangle}^{ij}(\nu) d\nu - \mu \tau \right) d\tau \geq 0, \end{aligned}$$

where $\Xi_{<l,k>}^{ij}(\nu) := \sum_l y_{lj}(\nu) + \sum_k y_{ik}(\nu) - y_{ij}(\nu) \geq 0$. This indicates that $s_{ij}(t) \geq 0$ for $t \in [0, \infty)$. Similarly, using the same method, it can be shown that $v_{ij} \geq 0$ and $z_{ij} \geq 0$ for all $t \in [0, \infty)$. Since $s_{ij} \geq 0$, $v_{ij} \geq 0$, $z_{ij} \geq 0$ and $w_{ij} \geq 0$, it follows, from $w_{ij} = 1 - s_{ij}$ and $z_{ij} = 1 - s_{ij} - v_{ij}$, that $z_{ij} \leq 1$ and $w_{ij} \leq 1$. Furthermore, we observe, from Eqs. (1)-(3), that $\frac{dz_{ij}}{dt}|_{z_{ij}=w_{ij}=y_{ij}=1} = -\mu < 0$, $\frac{dw_{ij}}{dt}|_{z_{ij}=w_{ij}=y_{ij}=1} = -\mu < 0$, and $\frac{dy_{ij}}{dt}|_{z_{ij}=w_{ij}=y_{ij}=1} = -(\sigma + \mu) < 0$. Clearly, w_{ij} , z_{ij} and y_{ij} are bounded by 1. We have thus shown that the model described by Eqs. (1)-(3) is dissipative and all feasible solutions are uniformly bounded and remain positive for all time $t > 0$, for any given positive initial data in a proper subset, say $\Omega \subset \mathbb{R}_+^{3M}$, where M is the number of strains. Therefore, the bounded region:

$$\Omega := \{z_{ij}, w_{ij}, y_{ij} \in \mathbb{R}_+^{3M} : 0 \leq z_{ij}, w_{ij}, y_{ij} \leq 1; i, j = 1, \dots, m\}$$

is positively invariant. Thus it is sufficient to consider the flow generated by the system (1)-(3) in Ω , where the model is both biologically relevant and mathematically well-posed. This completes the proof.

Appendix A.2. Proof of Lemma 4.1

Proof of Lemma 4.1. To determine the stability of the disease-free equilibrium $\mathcal{E}_0$, we calculate the Jacobian matrix evaluated at the disease-free equilibrium point. Here the Jacobian matrix is given as:

$$\mathcal{J} := \begin{bmatrix} -\mu \mathbb{I}_{m^2 \times m^2} & \mathbf{0}_{m^2 \times m^2} & \beta \mathbb{I}_{m^2 \times m^2} \\ \mathbf{0}_{m^2 \times m^2} & -\mu \mathbb{I}_{m^2 \times m^2} & \beta \mathbb{I}_{m^2 \times m^2} \\ \mathbf{0}_{m^2 \times m^2} & \mathbf{0}_{m^2 \times m^2} & (\beta - \sigma - \mu) \mathbb{I}_{m^2 \times m^2} \end{bmatrix}.$$

where $m = 2$. We note the upper right triangular structure of the matrix. It suffices to show that the Jacobian matrix above has all its eigenvalues with negative real part, which in this case are determined by its diagonal entries. The eigenvalues for the first $2m^2$ entries are given by $\zeta_{1,2,\dots,2m^2} = -\mu < 0$, while the remaining eigenvalues are $\zeta_{2m^2+1,2m^2+2,\dots,3m^2} = \beta - \sigma - \mu$. Therefore, $\mathcal{E}_0$ is locally asymptotically stable if $\zeta_{2m^2+1,2m^2+2,\dots,3m^2} < 0$. That is, $\mathcal{E}_0$ is stable provided $\mathcal{R}_0 = \frac{\beta}{\sigma + \mu} < 1$. This completes the proof. $\square$

Appendix A.3. Proof of Theorem 4.2

Proof. To show $\mathcal{E}_0$ is globally stable, we employ a differential inequality approach. It suffices to show that $y_{ij}(t) \rightarrow 0$ as $t \rightarrow \infty$ provided $\mathcal{R}_0 < 1$. Note that,

$$\begin{aligned} \frac{dy_{ij}}{dt} &= \beta [(1 - w_{ij}) + (1 - \gamma)(w_{ij} - z_{ij})] y_{ij} - (\sigma + \mu) y_{ij} \\ &= \beta [(1 - z_{ij}) - \gamma(w_{ij} - z_{ij})] y_{ij} - (\sigma + \mu) y_{ij} \\ &\leq \beta (1 - z_{ij}) y_{ij} - (\sigma + \mu) y_{ij} \leq (\beta - \sigma - \mu) y_{ij}, \end{aligned}$$

Hence, $y_{ij}(t) \leq y_{ij}(0)e^{(\beta - \sigma - \mu)t}$. Noting that $\beta - \sigma - \mu < 0$ implies that $\mathcal{R}_0 < 1$ and $y_{ij}(t)$ is decreasing exponentially. However, from Theorem 3.1, $y_{ij} \in [0, 1]$. Therefore $\lim_{t \rightarrow \infty} y_{ij}(t) \rightarrow 0$ for all i, j . In Eqs. (1)-(3), the limiting system under $\mathcal{R}_0 < 1$ is $\frac{dz_{ij}}{dt} \leq -\mu z_{ij}$ and $\frac{dw_{ij}}{dt} \leq -\mu w_{ij}$, which imply that $z_{ij}(t) \leq z_{ij}(0)e^{-\mu t}$ and $w_{ij}(t) \leq w_{ij}(0)e^{-\mu t}$. Hence, as $t \rightarrow \infty$, we have $\lim_{t \rightarrow \infty} z_{ij} \rightarrow 0$, and $\lim_{t \rightarrow \infty} w_{ij} \rightarrow 0$. This completes the proof. $\square$

Appendix A.4. Proof of Theorem 4.3

Proof of Theorem 4.3. We calculate the Jacobian matrix and observe the following triangular structure

$\mathcal{J} := \begin{bmatrix} \mathcal{J}_u & * \\ 0 & \mathcal{J}_l \end{bmatrix}$, where the entries are given by the following matrices:

$$\mathcal{J}_u = \begin{bmatrix} -\mu\mathcal{R}_0 & 0 & \beta\mathcal{R}_0^{-1} \\ 0 & -\mu\mathcal{R}_0 & \beta\mathcal{R}_0^{-1} \\ -(1-\gamma)(\mathcal{R}_0-1) & -\gamma\mu(\mathcal{R}_0-1) & 0 \end{bmatrix},$$

$$\mathcal{J}_l = \begin{bmatrix} -\mu & 0 & \beta \\ 0 & -\rho\mu(\mathcal{R}_0-1)-\mu & \frac{\rho\beta}{\rho(\mathcal{R}_0-1)+1} \\ 0 & 0 & \beta\left(1-\gamma\left[\frac{\rho(\mathcal{R}_0-1)}{\rho(\mathcal{R}_0-1)+1}\right]\right) - \sigma - \mu \end{bmatrix}.$$

Since $\mathcal{J}$ is a triangular block matrix of six dimensions, it suffices to consider each block matrix individually. We calculate the characteristic polynomial $P(\zeta) = \zeta^3 + \mathcal{A}_1\zeta^2 + \mathcal{A}_2\zeta + \mathcal{A}_3$ for the upper block matrix $\mathcal{J}_u$, where $\mathcal{A}_1 = 2\mu\mathcal{R}_0 \geq 0$, $\mathcal{A}_2 = (\mu\mathcal{R}_0)^2 + (\mu\mathcal{R}_0)^{-1}\mathcal{A}_3 \geq 0$ and $\mathcal{A}_3 = \mu\beta(\mathcal{R}_0-1)[\mu\gamma + (1-\gamma)] \geq 0$. All the coefficients $\mathcal{A}_j$, $j = 1, 2, 3$, are non-negative. By the Routh-Hurwitz criterion, it suffices to show that $\mathcal{A}_1\mathcal{A}_2 - \mathcal{A}_3 > 0$. That is,

$$\begin{aligned} \mathcal{A}_1\mathcal{A}_2 - \mathcal{A}_3 &= \mathcal{A}_1[\mu\mathcal{A}_0]^2 + \mathcal{A}_1\mathcal{A}_3[\mu\mathcal{R}_0]^{-1} - \mathcal{A}_3 = \mathcal{A}_1[\mu\mathcal{A}_0]^2 + \mathcal{A}_3 \\ &= 2(\mu\mathcal{R}_0)^3 + \beta\mu(\mathcal{R}_0-1)[\mu\gamma + (1-\gamma)] > 0. \end{aligned}$$

Hence, $\mathcal{J}_u$ has all its eigenvalues with negative real part for $\gamma \in [0, 1]$ and $\mathcal{R}_0 > 1$. Therefore, it suffices to show that the DSS weak endemic equilibrium is stable if the lower block matrix $\mathcal{J}_l$ has all its eigenvalues with negative real part. To show this, we observe that $\mathcal{J}_l$ is a triangular matrix with its eigenvalues determined by its diagonal entries. For the lower left block, notice that the eigenvalues are $\zeta_1 = -\mu < 0$, $\zeta_2 = -\rho\mu(\mathcal{R}_0-1) - \mu < 0$ and $\zeta_3 = \beta\left(1-\gamma\left[\frac{\rho(\mathcal{R}_0-1)}{\rho(\mathcal{R}_0-1)+1}\right]\right) - \sigma - \mu$. It suffices to show that $\mathcal{E}_1$ is locally asymptotically stability if $\zeta_3 < 0$. That is, $\mathcal{E}_1$ is stable provided $\gamma > \bar{\gamma} := \frac{1+\rho(\mathcal{R}_0-1)}{\rho\mathcal{R}_0}$. This completes the proof. $\square$

Appendix A.5. No Strain Structure Characteristic Polynomial $P_k(\zeta)$

The characteristic polynomial function for strongly endemic or coexistence equilibrium is of the form of $P(\zeta) = \prod_{k=1}^4 P_k(\zeta)$, where $P_k(\zeta)$ is a cubic polynomial function of the form $P_k(\zeta) = \sum_{l=0}^3 \mathcal{A}_{k,3-l}\zeta^l$ and $\mathcal{A}_{k,0} = 1$ for all $k = 1, 2, 3, 4$. Moreover, the coefficients are given as follows:

$$\mathcal{A}_{1,0} = \mathcal{A}_{2,0} = \mathcal{A}_{3,0} = \mathcal{A}_{4,0} = 1 > 0, \quad (\text{A.4})$$

$$\mathcal{A}_{1,1} = \mathcal{A}_{2,1} = \mathcal{A}_{3,1} = \mathcal{A}_{4,1} = \beta(1+\alpha)y^* + 2\mu > 0, \quad (\text{A.5})$$

$$\begin{aligned} \mathcal{A}_{1,2} &= \mathcal{A}_{2,2} = (\beta y^* + \mu)(\beta\alpha y^* + \mu) + \beta^2\gamma y^*(1-w^*) \\ &\quad + \beta^2 y^*(1-\gamma)(1-z^*) > 0, \end{aligned} \quad (\text{A.6})$$

$$\begin{aligned} \mathcal{A}_{1,3} &= \mathcal{A}_{2,3} = \beta^2\gamma y^*(1-w^*)(\beta y^* + \mu) \\ &\quad + \beta^2(1-\gamma)y^*(1-z^*)(\beta\alpha y^* + \mu) > 0, \end{aligned} \quad (\text{A.7})$$

$$\begin{aligned} \mathcal{A}_{3,2} &= (\beta y^* + \mu)(\beta\alpha y^* + \mu) + \beta^2\gamma\alpha y^*(1-w^*) \\ &\quad + \beta^2 y^*(1-\gamma)(1-z^*) > 0, \end{aligned} \quad (\text{A.8})$$

$$\begin{aligned} \mathcal{A}_{3,3} &= \beta^2\gamma\alpha y^*(1-w^*)(\beta y^* + \mu) \\ &\quad + \beta^2(1-\gamma)y^*(1-z^*)(\beta\alpha y^* + \mu) > 0 \end{aligned} \quad (\text{A.9})$$

$$\begin{aligned} \mathcal{A}_{4,2} &= (\beta y^* + \mu)(\beta\alpha y^* + \mu) - \beta^2\gamma y^*(1-w^*) \\ &\quad + \beta^2 y^*(1-\gamma)(1-z^*) \end{aligned} \quad (\text{A.10})$$

$$\mathcal{A}_{4,3} = \beta^2\gamma y^*(1-w^*)(\beta y^* + \mu)$$

$$-\beta^2 (1 - \gamma) y^* (1 - z^*) (\beta \alpha y^* + \mu). \quad (\text{A.11})$$

In addition, the Hurwitz determinants $\mathcal{A}_k$, $k = 1, 2, 3, 4$ for a cubic characteristic polynomial are given by

$$\begin{aligned} \mathcal{A}_1 &= \mathcal{A}_{1,1}\mathcal{A}_{1,2} - \mathcal{A}_{1,0}\mathcal{A}_{1,3} = (\beta(1 + \alpha)y^* + 2\mu)[(\beta y^* + \mu) \\ &\quad \times (\beta \alpha y^* + \mu)] + \beta^2 \gamma y^* (1 - w^*) (\beta \alpha y^* + \mu) \\ &\quad + (\beta^2 y^* (1 - \gamma) (1 - z^*)) (\beta y^* + \mu) > 0, \end{aligned} \quad (\text{A.12})$$

$$\begin{aligned} \mathcal{A}_2 &= \mathcal{A}_{2,1}\mathcal{A}_{2,2} - \mathcal{A}_{2,0}\mathcal{A}_{2,3} = (\beta(1 + \alpha)y^* + 2\mu)[(\beta y^* + \mu) \\ &\quad \times (\beta \alpha y^* + \mu)] + \beta^2 \gamma y^* (1 - w^*) (\beta \alpha y^* + \mu) \\ &\quad + (\beta^2 y^* (1 - \gamma) (1 - z^*)) (\beta y^* + \mu) > 0, \end{aligned} \quad (\text{A.13})$$

$$\begin{aligned} \mathcal{A}_3 &= \mathcal{A}_{3,1}\mathcal{A}_{3,2} - \mathcal{A}_{3,0}\mathcal{A}_{3,3} = (\beta(1 + \alpha)y^* + 2\mu)[(\beta y^* + \mu) \\ &\quad \times (\beta \alpha y^* + \mu)] + \beta^2 \alpha \gamma y^* (1 - w^*) (\beta \alpha y^* + \mu) \\ &\quad + (\beta^2 y^* (1 - \gamma) (1 - z^*)) (\beta y^* + \mu) > 0, \end{aligned} \quad (\text{A.14})$$

$$\begin{aligned} \mathcal{A}_4 &= \mathcal{A}_{4,1}\mathcal{A}_{4,2} - \mathcal{A}_{4,0}\mathcal{A}_{4,3} = (\beta(1 + \alpha)y^* + 2\mu)[(\beta y^* + \mu) \\ &\quad \times (\beta \alpha y^* + \mu)] - \beta^2 \gamma y^* (1 - w^*) [\beta(\alpha + 1)y^* + 2\mu + \beta y^* + \mu] \\ &\quad + (\beta^2 y^* (1 - \gamma) (1 - z^*)) [\beta(\alpha + 1)y^* + 2\mu + \beta \alpha y^* + \mu]. \end{aligned} \quad (\text{A.15})$$

It should be noted that w^* , z^* and y^* are functions of both γ and $\mathcal{R}_0$. In order to find the critical γ^* satisfying conditions for $\bar{\gamma}_r(\gamma, \mathcal{R}_0)$ $r = 1, 2, 3$, where

$$\begin{aligned} \bar{\gamma}_1(\gamma, \mathcal{R}_0) &= \frac{(\beta y^* + \mu)(\beta \alpha y^* + \mu) + \beta^2 y^* (1 - z^*)}{\beta^2 y^* (1 - w^*) + \beta^2 y^* (1 - z^*)}, \\ \bar{\gamma}_2(\gamma, \mathcal{R}_0) &= \frac{(1 - z^*)(\beta \alpha y^* + \mu)}{(1 - w^*)(\beta y^* + \mu) + (1 - z^*)(\beta \alpha y^* + \mu)}, \\ \bar{\gamma}_3(\gamma, \mathcal{R}_0) &= \frac{[\beta(1 + \alpha)y^* + 2\mu][(\beta y^* + \mu)(\beta \alpha y^* + \mu)] + \beta^2 y^* (1 - z^*)[\beta(2\alpha + 1)y^* + 3\mu]}{\beta^2 y^* (1 - w^*)[\beta(\alpha + 2)y^* + 3\mu] + (\beta^2 y^* (1 - z^*))[\beta(2\alpha + 1)y^* + 3\mu]}, \end{aligned}$$

we must solve the fixed-point problem $\gamma^* = \bar{\gamma}_r(\gamma^*, \mathcal{R}_0)$ for any fixed $\mathcal{R}_0 > 1$. The conditions for the stability of the strongly endemic or co-existence equilibrium is stated in Theorem 4.6, and the proof is provided below.

Appendix A.6. Proof of Theorem 4.6

Proof. The proof follows directly from the previous calculations. That is, we note that the characteristic polynomials $P_k(\zeta)$ have positive coefficient $\mathcal{A}_{k,l}$, $k = 1, 2, 3, l = 0, 1, \dots, 3$ and their Hurwitz determinants $\mathcal{A}_k$ are positive for $k = 1, 2, 3$. Therefore, the characteristic polynomials $P_k(\zeta)$, $k = 1, 2, 3$ have all their eigenvalues with negative real parts. It suffices to show that the coefficients $\mathcal{A}_{4,2}$ and $\mathcal{A}_{4,3}$, and Hurwitz determinant $\mathcal{A}_4$ are positive for $P_4(\zeta)$. We observe that $\mathcal{A}_{4,0} > 0$ and $\mathcal{A}_{4,1} > 0$. Hence, the coefficients $\mathcal{A}_{4,2}$, $\mathcal{A}_{4,3}$, and the Hurwitz determinant $\mathcal{A}_4$ are each positive provided that $\gamma < \bar{\gamma}_1(\gamma, \mathcal{R}_0)$, $\gamma > \bar{\gamma}_2(\gamma, \mathcal{R}_0)$ and $\gamma < \bar{\gamma}_3(\gamma, \mathcal{R}_0)$, respectively. The instability follows when the conditions do not hold. This completes the proof. $\square$

Appendix B. From 2-locus-2-allele System to m-locus-n-allele System: Three Illustrative Example

From the results of the analysis presented for the basic 2-locus-2-allele system, we can extend our results to more general cases of multi-locus-allele model, and use the structure (see Fig. B.7) envisioned by the pathogen population to postulate the nature of the immune responses against the various serotypes. As we increase the number of loci, we observe that the number of cluster types and structures increase, and their dynamics become highly complex. However, the general characterization of the behaviours is conserved. That is, the general properties (e.g., NSS, CSS and DSS) of parameter space shown in Fig. 4 remain

Figure B.7: **Strain Space Structures.** See text for details.

consistent. To illustrate this concretely, we look at three examples where the number of loci is two, three, and four, respectively, with two alleles each, which are summarized in Fig. B.7. For NSS, Figures 3 and B.8 show that all strains coexist when the conditions in Theorem 4.6 are satisfied in the case of 2-locus-2-allele, 3-locus-2-allele and 4-locus-2-allele systems, where $\alpha = 3$ in Fig. 3, and in Fig. B.8 $\alpha = 7$ and $\alpha = 15$. The value of the strongly endemic steady state remains the consistent when the values of the steady states from Eqs. (7)-(10) are compared with the values obtained from the numerical simulation of Eqs. (1)-(3). It should be noted, however, that if the conditions in Theorem 4.6 are violated then the strongly endemic equilibrium becomes unstable and undergoes Hopf bifurcation, exhibiting CSS. In the CSS region, there are oscillatory behaviours with a varying degree of exotic cluster-specific sequential domination. In particular, for a general multi-locus system, the model can exhibit various complex forms of synchronization and dynamic patterns. For example, the model is capable of exhibiting cyclical behaviours, where dominant types are cyclically replaced, and we can detect sharp epidemics dominated by, among a number of other behaviours, (1) a single strain with erratic multi-year abundance similar to the dynamic feature of influenza epidemics with irregular emergence and re-emergence of certain pathogenic forms, (2) ordered alternating appearance of a single antigenic type in periodic or quasi-periodic form similar to periodic travelling waves in strain space, (3) erratic appearance and disappearance of synchrony between discordant antigenic types with minimally overlapping or non-overlapping structures, and (4) phase-synchronization with (periodic or chaotic) uncorrelated amplitudes. These cyclical behaviours are summarized in Fig. B.9 for 3-locus-2-allele and 4-locus-2-allele systems, see the main text for the 2-locus-2-allele system. The characterization of the clustering behaviours of the oscillatory dynamics for higher strain structures are not discussed herein. Here, we focus on the weakly endemic equilibria with DSS and show that our results are indeed general for all multi-locus-allele strain space with uniform allelic combination.

In the case of the 2-locus-2-allele system $\mathcal{G}_2(2, 2)$, we observe a natural pairing of discordant sets resulting in two clusters where strains marked by blue belong to one cluster (e.g., $C_1 = \{00; 11\}$ or **ax** and **by** of the motivating notation) and by black belong to the other (e.g., $C_2 = \{10; 01\}$ or **ay** and **bx**) as shown in Fig. B.7(a). The dynamics corresponding to this system is illustrated in Figs. 2, 3 and 6. In this system only DSS of discordant types, CSS with discordant sets exhibiting anti-phase periodic solution and fully synchronized steady state exhibiting NSS are possible.

For the 3-locus-2-allele system, there are numerous weakly endemic equilibria, but most of them are unstable. Discrete strain structures containing a balanced numbers of persistent strains are locally asymptotically stable provided $\rho \neq 0$. For example, in the 3-locus-2-allele system, one clustering structure consists of discordant strains, where there are four clusters with two discordant strains corresponding to the main diagonal of the 3-hypercube in Fig. B.7(b) (e.g., $C_1 = \{000, 111\}$, $C_2 = \{001, 110\}$, $C_3 = \{011, 100\}$ and $C_4 = \{010, 101\}$). Any one of these clusters can persist provided the initial condition is in the appropriate stability region (i.e., cluster-specific region of attraction, see Figs. B.10). In addition, we also observe that the clustering $C_1 = \{000, 100, 011, 111\}$ and $C_2 = \{010, 110, 001, 101\}$ can also persist since $\rho \neq 0$ (see Figs. B.11). Furthermore, the cluster type of two tetrahedral structure with four strains each (strains marked by a

Figure B.8: **Time Evolution of NSS.** The plot illustrates the steady-state behaviours of the strongly endemic equilibrium with (a) 3-locus-2-allele and (b) 4-locus-2-allele in NSS region, where $\gamma = 0.45$, $\mathcal{R}_0 = 4$, $\sigma = 9.98$, $\mu = 0.02$. The steady state values calculated (black square-dotted horizontal line) from Eqs. (7)-(10) are consistent with the numerical values obtained from the simulation of Eqs. (1)-(3) with $\alpha = 7$ for (a) and $\alpha = 15$ for (b), where all other parameters remain the same. Equations (1)-(3) were solved using the Runge-Kutta fourth- and fifth-order method solver ODE45 in MATLAB (The Mathworks Inc., Natwick, MA, USA) with randomly generated initial conditions, and relative and absolute error tolerance of 10^{-5} and 10^{-6} , respectively.

blue colour form one cluster, and those marked by a black colour form another), where members of each cluster share one allele at the same locus location (e.g., $\mathcal{C}_1 = \{000, 011, 101, 110\}$ and $\mathcal{C}_2 = \{111, 100, 010, 001\}$) cannot persist since $\rho = 0$. These observations are consistent with the groupoid approach of Chan and Yu (2013).

For the third example, the system formed by the 4-locus-2-allele results in a 4-hypercube, the number of weakly endemic equilibria increases substantially. As in the previous case, all clusters containing an unbalanced number of persistent strains are unstable. For simplicity, we focus on three cluster types. The first structure as in all the above cases consists of eight clusters with two discordant strains that correspond to the main diagonal of the 4-hypercube in Fig. B.7(c) (e.g., $\mathcal{C}_1 = \{0000, 1111\}$, $\mathcal{C}_2 = \{0001, 1110\}$, $\mathcal{C}_3 = \{0101, 1010\}$, $\mathcal{C}_4 = \{0100, 1011\}$, $\mathcal{C}_5 = \{0010, 1101\}$, $\mathcal{C}_6 = \{0110, 1001\}$, $\mathcal{C}_7 = \{0111, 1000\}$ and $\mathcal{C}_8 = \{0011, 1100\}$, see Fig. B.12). The second case has eight clusters with two strains where members of each cluster share one allele that is at the same locus. This has the same structure of the second cluster type in the 3-hypercube, whereas strains in this case belong to the diagonal of the 3-hypercube face of the 4-hypercube (e.g., $\mathcal{C}_1 = \{0000, 0111\}$, $\mathcal{C}_2 = \{0001, 0110\}$, $\mathcal{C}_3 = \{0011, 0100\}$, $\mathcal{C}_4 = \{0010, 0101\}$, $\mathcal{C}_5 = \{1000, 1111\}$, $\mathcal{C}_6 = \{1001, 1110\}$, $\mathcal{C}_7 = \{1011, 1100\}$ and $\mathcal{C}_8 = \{1010, 1101\}$). The third type is the formation of two clusters (marked by black colour and blue colour) of eight strains where members of each cluster share either no allele or two alleles as illustrated in Fig. B.7(c) (e.g., the first cluster is marked by a blue colour: $\mathcal{C}_1 = \{0000, 0101, 0011, 0110, 1010, 1100, 1001, 1111\}$ and the second cluster is marked by a black colour: $\mathcal{C}_2 = \{0001, 0100, 0010, 0111, 1000, 1101, 1011, 1110\}$). Under the results of Corollary 4.4, the first and the third cases are possible since $\rho \neq 0$, and can be selected by an appropriate initial conditions.

From these examples, one observes that as we increase the number of loci, the clusters formed consist of clusters in the lower dimensional $(n - 1)$ -hypercubes and additional clusters that account for the inherited structure of the n -hypercube. Using the Mendelian combinatorial property of strain space and the type of cluster structures possible, we can predict the type of weakly endemic equilibria that are stable (hence the

Figure B.9: **Time Evolution of Cyclic Strain Structure** (Eqs. (1)-(3)). The plot illustrates the dependency of the dynamics of γ for (a)-(c) 3-locus-2-allele system and (d)-(f) 4-locus-2-allele system with a discrete periodic travelling wave solutions for (a) $\gamma = 0.56$ and (d) $\gamma = 0.62$, chaotic dynamics for (b) $\gamma = 0.76$ and (e) $\gamma = 0.76$, and discrete large-amplitude travelling wave cyclical solutions in (c) $\gamma = 0.86$ and (f) $\gamma = 0.86$. Here, $\mathcal{R}_0 = 4$, $\sigma = 9.98$, $\mu = 0.02$. Equations (1)-(3) were solved using the Runge-Kutta fourth- and fifth-order method solver ODE45 in MATLAB (The Mathworks Inc., Natick, MA, USA) with randomly generated initial conditions, and relative and absolute error tolerance of 10^{-5} and 10^{-6} , respectively.

dynamics of partial synchrony). This is due to the fact the structure of higher dimensional strain space are built from the building block of the lower dimensional strain space (see the results of Recker et al. (2007) and of cluster behaviours discussed in Calvez et al. (2005) and above). In addition, we also observe that within the same parametric regime, multiple cluster types co-existence and are not necessarily delineated by the parameter values. In another words, different clustering types can be observe depending on the initial condition. But the majority of the stability region within the DSS regime exhibits discrete structures with discordant pairs. This suggests that the stability region of the strongly endemic steady states exhibiting discrete structure with discordant pairs are transverse with other stability regions with other clustering types.

References

- V. Andreasen, et al. (1997). The dynamics of cocirculating influenza strains conferring partial cross-immunity. *J. Math. Biol.*, 35:825-842.
- D. Bandaranayake, et al. (2010). Risk factors and immunity in a nationally representative population following the 2009 influenza A(H1N1) pandemic. *PLoS One* 5:e13211
- A. Barragan, et al. (1998). Age-related buildup of humoral immunity against epitopes for rosette formation and agglutination in African areas of malaria endemicity. *Infection & Immunity* 66:4783-4787.
- K.B. Blyuss. (2013). The effects of symmetry on the dynamics of antigenic variation. *J. Math. Biol.*, 66: 115-137.
- K.B. Blyuss. (2014). Analysis of symmetries in models of multi-strain infections. *J. Math Biol.*, 69: 1431-1459.
- C.O. Buckee, et al. (2004). The effects of host contact structure on pathogen diversity and strain structure. *PNAS*, 101(29):10839-10844.
- C.O. Buckee, et al. (2008). Role of selection in the emergence of lineages and the evolution of virulence in *Neisseria meningitidis*. *Proc. Natl. Acad. Sci.*, 105:15082-15087.
- C.O. Buckee and S. Gupta. (2010). A Network Approach to Understanding Pathogen Population Structure, in V. Sintchenko (Ed.), *Infectious disease informatics*. Springer Verlag, New York
- C.O. Buckee, et al. (2011). Role of stochastic processes in maintaining discrete strain structure in antigenically diverse pathogen populations. *Proc. Natl Acad. Sci.* 108:15504-15509.
- V. Calvez, et al. (2005). Cluster formation for multi-strain infections with cross-immunity. *J. Theor. Biol.*, 233:75-83.
- C. Castillo-Chavez, et al. (1989). Epidemiological models with age structure, proportionate mixing and cross-immunity. *J. Math. Biol.*, 27:233-258.
- C. Castillo-Chavez, et al. (2002). On the computation of R_0 and its role on global stability. In: C. Castillo-Chavez, S. Blower, P. van den Driessche and D. Kirschner, Editors, *Mathematical Approaches for Emerging and Reemerging Infectious Diseases Part I: An Introduction to Models, Methods and Theory*. Springer-Verlag, Berlin.
- B.S. Chan and P. Yu. (2013). Bifurcation, stability, and cluster formation of multi-strain infection models. *J Math Biol.* 67(6-7):1507-32.
- A. Cherif. (2011). Evolutionary Epidemiology: Limited Epitopes and Age-Specificity. Transfer Thesis. University of Oxford.
- P. Chossat and R. Lauterbach (2000) *Methods in Equivariant Bifurcations and Dynamical Systems*. World Scientific, Singapore.
- A.D. Cliff, P. Haggett and J.K. Ord. (1986). *Spatial Aspects of Influenza Epidemics*. Pion, London.
- J.H.P. Dawes and J.R. Gog. (2002). The onset of oscillatory dynamics in models of multiple disease strains. *J. Math. Biol.*, 45:471-510.
- O. Diekmann and J.A.P. Heesterbeek. (2000). *Mathematical Epidemiology of Infectious Diseases: Model Building, Analysis and Interpretation*. Wiley, NY.
- K. Dietz. (1979). Epidemiological interference of virus populations. *J. Math. Biol.* 8:291-300.
- D.J.D. Earn, J. Dushoff, and S.A. Levin. (2002). Ecology and evolution of the flu. *Trends in Ecology & Evolution*, 17(7):334-340.
- L.R. Elveback, J.P. Fox and A. Varma. (1964). An extension of the Reed-Frost epidemic model for the study of competition between viral agents in the presence of interference. *Am. J. Hyg.* 80:356-364
- N.M. Ferguson and V. Andreasen. (2001). The influence of different forms of cross-protective immunity on the population dynamics of antigenically diverse pathogens. In: S. Blower, C. Castillo-Chavez, K.L. Cooke, D. Kirschner, P. van der Driessche (eds). *Mathematical Approaches for Emerging and Re-emerging Infections*, IMA Volumes in Mathematics and its Applications. Springer, New York.
- N.M. Ferguson, A.P. Galvani and R.M. Bush. (2003). Ecological and immunological determinants of influenza evolution. *Nature*, 422:428-433.
- G.L. Gilbert, et al. (2010). Influenza A (H1N1) 2009 antibodies in residents of New South Wales, Australia, after the first pandemic wave in the 2009 southern hemisphere winter. *PLoS One* 5: e12562.
- J.R. Gog and B.T. Grenfell. (2002). Dynamics and selection of many-strain pathogens. *Proc. Natl. Acad. Sci.*, 99:17209-17214.
- J.R. Gog and J. Swinton. (2002). A status-based approach to multiple strain dynamics. *J. Math. Biol.*, 44:169-184.
- M. Golubitsky, I. Stewart and A. Torok. (2005). Patterns of synchrony in coupled cell networks with multiple arrows. *SIAM J. Appl. Dynam. Sys.* 4(1):78-100.
- M.G.M. Gomes, G. Medley, and D.J. Nokes. (2002). On the determinants of population structure in antigenically diverse pathogens. *Proc. R. Soc. Lond. B*, 269:227233.
- S. Gupta, et al. (1994). Antigenic diversity and the transmission dynamics of *Plasmodium falciparum*. *Science*, 263:961-963.

- 1 S. Gupta, et al. (1996). The maintenance of strain structure in populations of recombining infectious agents. *Nat. Med.*,
2 2:437-442.
- 3 S. Gupta, N.M. Ferguson and R.M. Anderson. (1998). Chaos, persistence, and evolution of strain structure in antigenically
4 diverse infectious agents. *Science*, 280: 912-915
- 5 S. Gupta and R.M. Anderson. (1999). Population structure of pathogens: the role of immune selection. *Parasitol. Today*,
6 15:497-501.
- 7 S. Gupta and A. Galvani. (1999). The effects of host heterogeneity on pathogen population structure. *Proc Roy. Soc. B* 354:
8 711-719
- 9 M. Nowak, et al. (1995). Antigenic oscillations and shifting immunodominance in HIV-1 infections. *Nature* 375(6532):606611
- 10 H.R. Thieme. (2003). *Mathematics in Population Biology*. Princeton University Press, New Jersey.
- 11 S. Kryazhinsky, U. Dieckmann, S.A. Levin and J. Dushoff. (2007). On state-space reduction in multi-strain pathogen models,
12 with an application to antigenic drift in influenza A. *PLoS Comput. Biol.*, 3:e159.
- 13 J. Lin, V. Andreasen and S.A. Levin. (1999). Dynamics of influenza A drift: the linear three-strain model. *Math. Biosci.* 162,
14 3351.
- 15 P. Minayev and N.M. Ferguson. (2009a). Improving the realism of deterministic multistrain models: implications for modelling
16 influenza A. *J. Royal Soc. Interface*, 6(35):509-518
- 17 P. Minayev and N.M. Ferguson. (2009b). Incorporating demographic stochasticity into multi-strain epidemic models: application
18 to influenza A. *J. Royal Soc. Interface*, 6(40): 989-96
- 19 J.L. Mitchell and T.W. Carr. (2012). Synchronous versus asynchronous oscillations for antigenically varying *Plasmodium*
20 *falciparum* with host immune response. *J. Biol. Dyn.*, 6: 333-357.
- 21 M. Nuno, M. Martcheva and C. Castillo-Chavez. (2009). Immune level approach For multiple strain pathogens. *J. Biol. Sys.*
22 17(4): 713-737.
- 23 J.B. Plotkin, J. Dushoff and S.A. Levin. (2002). Hemagglutinin sequence clusters and the antigenic evolution of influenza A
24 virus. *Proc. Natl. Acad. Sci.*, 99:6263-6268.
- 25 M. Recker, et al. (2004). Transient cross-reactive immune responses can orchestrate antigenic variation in malaria. *Nature*
26 429:555-558
- 27 M. Recker and S. Gupta. (2005). A model for pathogen population structure with cross-protection depending on the extent of
28 overlap in antigenic variant repertoires. *J Theor Bio.* 232:363-373
- 29 M. Recker, et al. (2007). The generation of influenza outbreaks by a network of host immune responses against a limited set of
30 antigenic types. *Proc. Natl. Acad. Sci.*, 104:7711-7716.
- 31 M. Recker, et al. (2009). Immunological serotype interactions and their effect on the epidemiological pattern of dengue. *Proc*
32 *Roy. Soc. London B* 276: 2541-2548
- 33 A. Sasaki and Y. Haraguchi. (2000). Antigenic drift of viruses within a host: a finite site model with demographic stochasticity.
34 *J Mol. Evol.* 51: 245-255
- 35 D.J. Smith, et al. (1999). Variable efficacy of repeated annual influenza vaccination. *Proc Natl Acad Sci. USA* 96: 14001-14006
- 36 D.J. Smith, et al. (2004). Mapping the antigenic and genetic evolution of influenza virus. *Science*, 305(5682):371-376.
- 37 P.S. Wikramaratna, et al. (2010). The effects of tertiary and quaternary infections on the epidemiology of dengue. *PLoS One*,
38 5(8):e12347.