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## **A status-based approach to multiple strain dynamics**

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**Abstract.** We present and investigate a new model for cross-immunity. Past models classify hosts according to their infection history. Here we represent hosts through their status: their current ability to respond to strains. This framework allows a different, a wider, and a more biologically interpretable range of forms of cross-immunity to be studied.

Using this new form of cross-immunity we then consider a previously studied case of four strains, each of which confers partial immunity to two of the others. In this interesting special case, with applications to the genetic maintenance of strain diversity, we can make substantial analytical progress. We present methods for exploiting the symmetries of the system to show that only a particular invariant subspace need be considered for characterizing the dynamics of the whole system. A complete bifurcation structure is given for this subspace. In contrast to systems previously studied, this system does not exhibit sustained oscillations for any set of parameter values.

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### **1. Introduction**

There are a number of infectious diseases for which it is now clear that modelling approaches based on the transmission of a single pathogen strain are inadequate. For example, Gupta *et al.* [10] found that estimates of transmission parameters for malaria may be wrong by an order of magnitude if *Plasmodium falciparum* is assumed to be functionally one strain. Meningitis [7], dengue [3] and influenza A [13] are all examples of diseases for which strain dynamics are important, and for which infection with one strain modifies the reaction of the host in subsequent encounters with other strains.

This paper is concerned with modelling partial cross-immunity, where strains interact by offering infected and recovered hosts some partial protection against other strains.

Andreasen *et al.* [1, 11] developed a model where cross-immunity acts by reducing the susceptibility to further strains (hereafter referred to as the ‘Andreasen model’), while Gupta *et al.* [8, 9] modelled cross-immunity as acting by leaving susceptibility unchanged, but reducing transmissibility by a factor (hereafter referred to as the ‘Gupta model’). In an effort to understand the relation between these

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models Ferguson and Andreasen [2] constructed a system with both of these mechanisms present, and concluded that which of these two forms of cross-immunity is used appears to have little impact on the dynamics.

There are two major technical problems in modelling strain dynamics in this manner. Firstly, there is the sheer number of variables. The number of combinations of strains that can be made grows exponentially with the number of strains, making even a modest number of strains unmanageable both analytically and numerically. For example, in the Andreasen model with four strains, there are 48 coupled differential equations. This can be simplified in a few ways, for example by not removing infecteds from the susceptible pool during illness [5], reducing the number of dimensions to 20, but the systems are still very large.

A second problem common to the modelling of any complex biological system is that the details of the choice of notation may introduce hidden assumptions. The models described above all categorize the susceptible population in terms of their history of infection: a list of strains that they have been previously infected with. Implicit in this structure is that all hosts with a given history must behave in the same way with respect to new strains, restricting the forms of cross-immunity that may be studied.

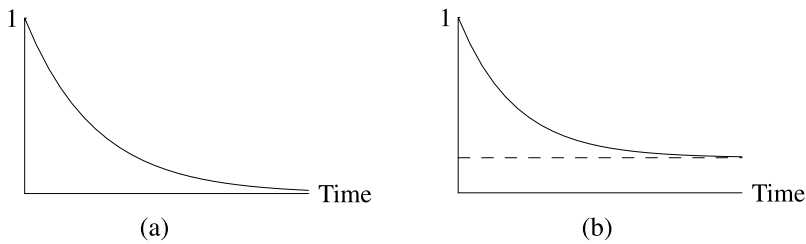
In contrast, this paper argues that the most natural formulation of multiple strain models is one that focuses on the immune state of the host, that is the host's current ability to cope with strains. We argue that this clarifies the biological interpretation of model assumptions, allows a wider range of plausible biological interactions to be modelled, and, for at least one example, allows more analytical progress than a history-based approach.

The remainder of this paper is in four sections. Section two introduces a plausible form of cross-immunity that cannot be formulated within a history-based model. Section three presents a suitable notational framework and constructs the system of differential equations. Section four looks at a particular example, employing methods that may be useful in other systems as well. Section five synthesizes these results.

## 2. Polarized immunity

We wish to study multiple disease strains with partial cross-immunity using an extension of the simple SIR model. The most obvious way to proceed is to categorize the susceptibles according to their infection history, but as discussed in the introduction, this has limitations. Instead, this paper argues for an alternative approach that focuses on the immune status of the host. We assume that each host is either entirely susceptible to a strain, or completely immune to it, and we categorize them according to this immunity. The partial aspect of the cross-immunity is brought in through heterogeneity of the destination category after recovery. This form of cross-immunity was mentioned in the discussion of the Andreasen model [1].

To illustrate how this form of cross-immunity differs from the history-based one, imagine that we have a system with two strains, and that infection by the first confers partial cross-immunity to infection by the second. Suppose that the entire population has been infected with the first strain and recovered. In a history-based model we



**Fig. 1.** One difference between history-based and status-based models. These both show the proportion of the population that has not been infected by the second strain as a function of time. The graph on the left represents the history-based models where no-one will escape infection if challenged repeatedly. The graph on the right represents total or no immunity, where some proportion is immune to infection by the second strain, no matter how often they are challenged. Note that the gradient is initially the same in both graphs.

must have that *all* hosts are now *partially* immune to the second strain. Instead, here we have that *some* hosts are *totally* immune, while others retain susceptibility. The host population has been polarized. This can be compared to ‘mixed strategy’ versus ‘polymorphic population’ in game theory [12]. In linear game theory problems, these different interpretations may lead to the same behaviour, however in a non-linear disease model these assumptions lead to different dynamics, as illustrated here.

Imagine that we repeatedly challenge this partially immune population with the second strain. In the history-based model, all hosts will eventually become infected, albeit at a slower rate than if they did not have partial immunity (Figure 1). In the all-or-nothing form of cross-immunity, permitted through status-based formulation, we have that some of the population will never be infected by the second strain.

History-based models may be interpreted in terms of this polarized immunity if we allow status to change upon unsuccessful challenges as well. The population is thought of as consisting of immunes and susceptibles in some proportions. At every exposure to subsequent strains, all those who were immune are redivided into immune and susceptible. Recalculating immunity after each exposure makes the cross-immune response to each challenge independent of other challenges. In contrast, in the model we investigate in this paper, the response is the same for all challenges: if they are protected the first time, then they are always immune. It is possible (though not presented here) to explicitly construct a status-based model with this form of immunity and to recover the history-based model equations from it.

There is good biological motivation for choosing this form of cross-immunity. There are a number of ways for a host to clear any given infection, involving both innate immunity (which would not change the host immune state) and the adaptive system (which may give long term protection). The type of response would be dependent on factors including which immune cell clones happen to be in circulation during infection, which happen to encounter the pathogen, and which undergo clonal selection. So even with two hosts being genetically identical and with the same immune histories, they could have different responses. Immune memory will depend on which combination of responses are used to clear the original infection.

A particular immune repertoire may or may not offer protection to a particular strain, and on first encounter either the host becomes infected or it does not. Suppose that a host is not infected and we attribute this to its immune memory. The assumption that this implies that it is protected for all subsequent encounters will lead to use of this polarized immunity model, as opposed to reduced susceptibility. This biological assumption of protection against subsequent infection may be based upon assuming that either the immune memory was sufficient to offer total cross-protection to that strain in the first place, or that it was not, but first exposure to the new pathogen led to it resolving into a state that gives cross-protection.

### 3. The model

#### 3.1. Notation and construction

We now construct the equations for this form of cross-immunity. Here, the immune state is denoted as the strains that a host has immunity to. The proportion of hosts that are immune to the strains in the set  $\mathbf{J}$  and susceptible to all other strains is written as  $S_{\mathbf{J}}$ . For example, if our strains are numbered from 1 to 4 then  $S_{\{1,3\}}$  is the proportion of hosts that are immune to strains 1 and 3 and susceptible to 2 and 4,  $S_{\emptyset}$  is the proportion immune to none, or susceptible to all strains. Note that all hosts are counted in a  $S_{\mathbf{J}}$  for some  $\mathbf{J}$ , even if they are currently infectious.

All hosts are born susceptible to all strains at a rate  $\mu$ . So the birth rate into class  $S_{\mathbf{J}}$  is given by  $\mu\delta_{\mathbf{J},\emptyset}$  where:

$$\delta_{\mathbf{J},\emptyset} = \begin{cases} 1 & \text{if } \mathbf{J} = \emptyset \\ 0 & \text{otherwise} \end{cases}$$

We assume that infection does not alter the death rate and that the host is at equilibrium with respect to births and deaths. So we have a constant death rate,  $\mu$ , for all classes, and:

$$\sum_{\mathbf{J}} S_{\mathbf{J}} = 1$$

The most complicated parameter is the one that encapsulates all of the information about how infection changes the immune status of the host. The proportion of hosts that recover to a state  $\mathbf{J}$ , having started in state  $\mathbf{K}$  and been infected by strain  $i$  is given by  $C(\mathbf{K}, \mathbf{J}, i)$ . We make some assumptions about  $C$ . For non-zero  $C(\mathbf{K}, \mathbf{J}, i)$ :

- $i \notin \mathbf{K}$  – hosts must be susceptible initially to the infecting strain
- $i \in \mathbf{J}$  – each strain confers total immunity to itself
- $\mathbf{K} \subset \mathbf{J}$  – immunity only gained,  $i$  makes this strict

Also, as there are no deaths due to infection, if  $i \notin \mathbf{K}$ :

$$\sum_{\mathbf{J}} C(\mathbf{K}, \mathbf{J}, i) = 1$$

Finally, we suppose that there is no removal of infecteds, i.e. on infection they move immediately to their new susceptible state. It is implicit that multiple simultaneous infections are possible within one host. This means that for the infecteds we only need to keep track of the proportion infectious with each strain and not their state. So an infected host is counted in both their immune state, and an infectious class.

- $I_i$  – The proportion of hosts infectious with strain  $i$
- $\beta_i$  – Transmission coefficient for strain  $i$
- $v_i$  – The rate of recovery from infection with strain  $i$

Hence, our full system:

$$\begin{aligned} \dot{I}_i &= \beta_i I_i \sum_{\mathbf{J}:i \notin \mathbf{J}} S_{\mathbf{J}} - v_i I_i - \mu I_i \\ \dot{S}_{\mathbf{J}} &= \sum_{i, \mathbf{K}} C(\mathbf{K}, \mathbf{J}, i) \beta_i I_i S_{\mathbf{K}} - \sum_{i \notin \mathbf{J}} \beta_i I_i S_{\mathbf{J}} - \mu S_{\mathbf{J}} + \mu \delta_{\mathbf{J}, \emptyset} \end{aligned}$$

For each strain  $i = 1, 2, \dots, n$  and  $\mathbf{J}$  = all possible subsets of  $1, 2, \dots, n$  (so  $2^n$  of these).

Note that nothing depends on the proportion of hosts that are immune to all strains, so we have no need to keep track of it. Hence we have a system of at most  $2^n + n - 1$  dimensions. It can be less than this if some states are impossible.

### 3.2. Non-dimensional system

First, we introduce the force of infection to replace the proportion infected:

$$\Lambda_i = \beta_i I_i$$

We now move to the timescale of host dynamics by rescaling time and force of infection by a factor  $\mu$  (so  $\Lambda_i = \beta_i I_i / \mu$ ):

$$e_i \dot{\Lambda}_i = (r_i \sum_{\mathbf{J}:i \notin \mathbf{J}} S_{\mathbf{J}} - 1) \Lambda_i \tag{1}$$

$$\dot{S}_{\mathbf{J}} = \sum_{i, \mathbf{K}} C(\mathbf{K}, \mathbf{J}, i) \Lambda_i S_{\mathbf{K}} - \sum_{i \notin \mathbf{J}} \Lambda_i S_{\mathbf{J}} - S_{\mathbf{J}} + \delta_{\mathbf{J}, \emptyset} \tag{2}$$

Two new parameter combinations emerge naturally. Namely, the ratio of parasite timescale to host timescale, and the basic reproduction ratio for strain  $i$ :

$$\begin{aligned} e_i &= \frac{\mu}{\mu + v_i} \\ r_i &= \frac{\beta_i}{\mu + v_i} \end{aligned}$$

For some diseases,  $e$  may be small. For example, it would be around 0.0005 for an infectious period of a couple of weeks in humans.

## 4. Four strain system

### 4.1. Cross-immunity structure

We now turn to a specific example to show this model in action, and also to compare with other approaches. We consider four strains arranged in a ring with each strain giving partial immunity to adjacent strains (Figure 2). So for example, infection by strain 1 gives immunity to 1 always, immunity to 2 with probability  $\sigma$ , immunity to 4 similarly, and never gives immunity to 3. Other parameters ( $r$ ,  $e$ ) are equal for all strains. This system is chosen as it was investigated by Andreasen *et al.* [1] with their different form of cross-immunity, and is also analogous to the Gupta model for a pathogen with two different epitopes possible at two loci.

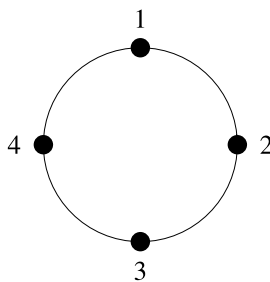
This can be represented by a cross-immunity matrix  $\mathbf{M}$  where infection by strain  $i$  confers cross immunity  $\mathbf{M}_{ij}$  to strain  $j$ :

$$\mathbf{M} = \begin{pmatrix} 1 & \sigma & 0 & \sigma \\ \sigma & 1 & \sigma & 0 \\ 0 & \sigma & 1 & \sigma \\ \sigma & 0 & \sigma & 1 \end{pmatrix}$$

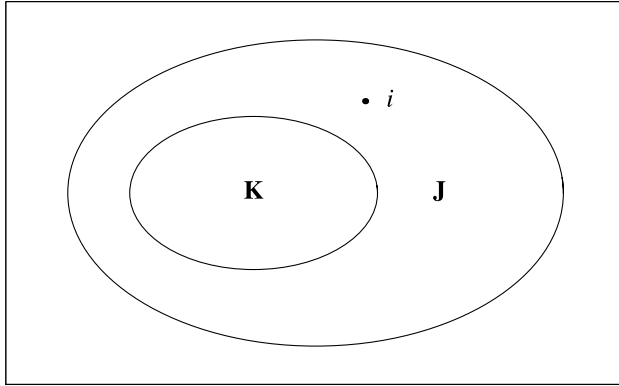
This information is used to generate values for  $C(\mathbf{K}, \mathbf{J}, i)$  as follows. Set  $C(\mathbf{K}, \mathbf{J}, i) = 0$  unless  $i \notin \mathbf{K}$  and  $\mathbf{K} \subset \mathbf{J}$ . If these conditions *are* met, then  $C(\mathbf{K}, \mathbf{J}, i)$  is interpreted as the proportion that gain immunity to strains in  $\mathbf{J} \setminus \mathbf{K}$  and do not gain immunity to strains not in  $\mathbf{J}$ . So  $C(\mathbf{K}, \mathbf{J}, i)$  will have a factor:

$$\begin{aligned} & \mathbf{M}_{ij} \text{ for each } j \in \mathbf{J} \setminus \mathbf{K} \text{ (gain immunity to } j) \\ & (1 - \mathbf{M}_{ij}) \text{ for each } j \notin \mathbf{J} \text{ (not gain immunity to } j) \end{aligned}$$

Note that as strains give immunity to themselves,  $\mathbf{M}_{ij} = 1$  for  $i = j$  and this means that if  $i \notin \mathbf{J}$  then  $C(\mathbf{K}, \mathbf{J}, i)$  has a factor  $(1 - \mathbf{M}_{ii})$  which is zero. No-one recovers to a state which does not have immunity to infecting strain. So automatically we have that  $C(\mathbf{K}, \mathbf{J}, i) = 0$  if  $i \notin \mathbf{J}$ . Figure 3 shows the arrangement of the sets for  $C(\mathbf{K}, \mathbf{J}, i)$  to be non-zero.



**Fig. 2.** Four strain arrangement. The strains are arranged in a ring, with each strain giving cross-immunity  $\sigma$  to both adjacent strains.



**Fig. 3.** The arrangement of  $\mathbf{J}, \mathbf{K}$  and  $i$ .

So, the complete expression for  $C$ :

$$C(\mathbf{K}, \mathbf{J}, i) = \begin{cases} \prod_{j \in \mathbf{J} \setminus \mathbf{K}} \mathbf{M}_{ij} \prod_{j \notin \mathbf{J}} (1 - \mathbf{M}_{ij}) & \text{if } i \notin \mathbf{K} \text{ and } \mathbf{K} \subset \mathbf{J} \\ 0 & \text{otherwise} \end{cases} \quad (3)$$

So for example:

$$C(\{1\}, \{1, 2, 3\}, 2) = \mathbf{M}_{22} \cdot \mathbf{M}_{23} \cdot (1 - \mathbf{M}_{24}) = 1 \cdot \sigma \cdot 1 = \sigma$$

#### 4.2. Symmetry arguments

This system is highly symmetric, with both rotational ( $1 \rightarrow 2, 2 \rightarrow 3, 3 \rightarrow 4, 4 \rightarrow 1$ ), and reflectional ( $1 \rightarrow 3, 3 \rightarrow 1$ ) symmetries. We can make use of these symmetries in the investigation of fixed points. At equilibrium, from (2) we have:

$$\dot{S}_{\mathbf{J}} = \sum_{i, \mathbf{K}} C(\mathbf{K}, \mathbf{J}, i) \Lambda_i S_{\mathbf{K}} - \sum_{i \notin \mathbf{J}} \Lambda_i S_{\mathbf{J}} - S_{\mathbf{J}} + \delta_{\mathbf{J}, \emptyset} = 0$$

Following Andreasen *et al.*, we may calculate equilibrium values for  $S_{\mathbf{J}}$  as functions of the forces of infection inductively on the cardinality of the immunity  $\mathbf{J}$ :

$$S_{\mathbf{J}} = \begin{cases} \frac{1}{1 + \sum_i \Lambda_i} & \text{if } \mathbf{J} = \emptyset \\ \frac{\sum_{i, \mathbf{K}} C(\mathbf{K}, \mathbf{J}, i) \Lambda_i S_{\mathbf{K}}}{1 + \sum_{i \notin \mathbf{J}} \Lambda_i} & \text{otherwise} \end{cases} \quad (4)$$

Note that  $S_{\mathbf{J}}$  can only depend on  $S_{\mathbf{K}}$  if  $\mathbf{K} \subset \mathbf{J}$ .

Next, we reduce the dimension of the space that must be investigated by extensively exploiting symmetries in the parameters and equations. Suppose for the rest of this subsection that we are at an equilibrium. Treat the  $S_{\mathbf{J}}$ 's as functions of the  $\Lambda_i$ 's (as given in 4). Forces of infection, and susceptible proportions are always positive. Now take  $\Lambda_2$  and  $\Lambda_4$  as being fixed and consider  $\Lambda_1$  and  $\Lambda_3$  as being the free variables in this series of lemmas that follow. We define:

$$\xi = \Lambda_1 - \Lambda_3 \quad (5)$$

**Lemma 1.**

$$\frac{d}{d\xi} S_{\mathbf{J} \cup \{3\}} < 0 \quad \forall \mathbf{J} \subseteq \{2, 4\} \tag{6}$$

*Proof of Lemma 1.* From (4):

$$\text{Denominator of } S_{\mathbf{J} \cup \{3\}} = 1 + \Lambda_1 (+ \text{possibly } \Lambda_2, \Lambda_4)$$

And this is positive and has positive derivative in  $\xi$ .

$$\text{Numerator of } S_{\mathbf{J} \cup \{3\}} = \sum_{i, \mathbf{K}} C(\mathbf{K}, \mathbf{J} \cup \{3\}, i) \Lambda_i S_{\mathbf{K}}$$

By using (3), we see that this involves positive multiples of terms of these forms

$$S_{\bullet} \Lambda_{\bullet}, S_{\bullet} \Lambda_3 \text{ and } S_{\mathbf{L} \cup \{3\}} \Lambda_{\bullet}$$

where the  $\bullet$ s do not involve 1 or 3, and  $\mathbf{L} \subset \mathbf{J}$ . Now differentiating with respect to  $\xi$ :

$$\begin{aligned} \frac{d}{d\xi} S_{\bullet} \Lambda_{\bullet} &= 0 \\ \frac{d}{d\xi} S_{\bullet} \Lambda_3 &= -S_{\bullet} < 0 \\ \frac{d}{d\xi} S_{\mathbf{L} \cup \{3\}} \Lambda_{\bullet} &= \Lambda_{\bullet} \frac{d}{d\xi} S_{\mathbf{L} \cup \{3\}} \end{aligned}$$

From this,

$$\frac{d}{d\xi} S_{\mathbf{J} \cup \{3\}} < 0 \quad \text{for } \mathbf{J} = \emptyset \tag{7}$$

Hence by induction on the cardinality of  $\mathbf{J}$ , we extend this to all  $\mathbf{J} \subset \{2, 4\}$ , so we have Lemma 1. □

Next, we define the effective susceptible population:

$$\theta_i = \sum_{\mathbf{J}: i \notin \mathbf{J}} S_{\mathbf{J}} \tag{8}$$

**Lemma 2.**

$$\frac{d}{d\xi} (\theta_1 - \theta_3) < 0$$

*Proof of Lemma 2.*

$$\begin{aligned}
 \theta_1 - \theta_3 &= \sum_{\mathbf{J}:1 \notin \mathbf{J}} S_{\mathbf{J}} - \sum_{\mathbf{J}:3 \notin \mathbf{J}} S_{\mathbf{J}} = \sum_{\mathbf{J} \subseteq \{2,3,4\}} S_{\mathbf{J}} - \sum_{\mathbf{J} \subseteq \{1,2,4\}} S_{\mathbf{J}} \\
 &= \left( \sum_{\mathbf{J} \subseteq \{2,4\}} S_{\mathbf{J} \cup \{3\}} + \sum_{\mathbf{J} \subseteq \{2,4\}} S_{\mathbf{J}} \right) - \left( \sum_{\mathbf{J} \subseteq \{2,4\}} S_{\mathbf{J} \cup \{1\}} + \sum_{\mathbf{J} \subseteq \{2,4\}} S_{\mathbf{J}} \right) \\
 &= \sum_{\mathbf{J} \subseteq \{2,4\}} (S_{\mathbf{J} \cup \{3\}} - S_{\mathbf{J} \cup \{1\}})
 \end{aligned}$$

From Lemma 1, we have:

$$\frac{d}{d\xi} S_{\mathbf{J} \cup \{3\}} < 0 \quad \forall \mathbf{J} \subseteq \{2, 4\}$$

And by anti-symmetry in (1, 3) of  $\xi$ :

$$\frac{d}{d\xi} S_{\mathbf{J} \cup \{1\}} > 0 \quad \forall \mathbf{J} \subseteq \{2, 4\}$$

Hence:

$$\frac{d}{d\xi} (\theta_1 - \theta_3) = \frac{d}{d\xi} \sum_{\mathbf{J} \subseteq \{2,4\}} (S_{\mathbf{J} \cup \{3\}} - S_{\mathbf{J} \cup \{1\}}) < 0 \quad \square$$

**Lemma 3.** *At equilibrium, either one of  $\Lambda_1$  and  $\Lambda_3$  is zero, or  $\Lambda_1 = \Lambda_3$ .*

*Proof of Lemma 3.* By (1), recalling that  $r_i = r \quad \forall i$  and using the definition of  $\theta$ , (8), at equilibrium we must have:

$$\begin{aligned}
 \left( r \sum_{\mathbf{J}:i \notin \mathbf{J}} S_{\mathbf{J}} - 1 \right) \Lambda_i &= 0 \quad i = 1, 3 \\
 \Rightarrow (r\theta_i - 1) \Lambda_i &= 0 \quad i = 1, 3
 \end{aligned}$$

$$\Rightarrow \text{Either } \Lambda_i = 0 \text{ for one of } i = 1, 3, \text{ or } \theta_1 = \theta_3 = r^{-1}$$

By symmetry in strains 1 and 3:

$$\Lambda_1 = \Lambda_3 \Rightarrow \theta_1 = \theta_3$$

Or equivalently:

$$\xi = 0 \Rightarrow (\theta_1 - \theta_3) = 0$$

By Lemma 2,  $(\theta_1 - \theta_3)$  is strictly monotonic in  $\xi$ , so there is at most one value of  $\xi$  for which  $(\theta_1 - \theta_3)$  is zero. Hence:

$$\xi = 0 \iff (\theta_1 - \theta_3) = 0 \quad (9)$$

Equivalently:

$$\theta_1 = \theta_3 \iff \Lambda_1 = \Lambda_3 \quad \square$$

**Lemma 4.** *Any equilibrium where  $\Lambda_1 = 0$  and  $\Lambda_3 \neq 0$  is unstable to invasion by strain 1.*

*Proof of Lemma 4.*

$$\begin{aligned}\Lambda_1 = 0, \Lambda_3 \neq 0 &\Rightarrow \xi < 0 \\ &\Rightarrow \theta_1 > \theta_3 && \text{(by Lemma 2 and (9))} \\ \text{Equilibrium} &\Rightarrow \theta_3 = r^{-1} \\ &\Rightarrow \theta_1 > r^{-1}\end{aligned}$$

Hence strain 1 has a large enough susceptible population that it may invade, so an equilibrium of this kind is unstable to the introduction of the missing strain.  $\square$

It would be both hard and unhelpful to translate these manipulations back to a biological interpretation. However, the overall result from the mathematics may be summarized as this:

- If strain 1 is not present in the system but 3 is present, then 1 may invade (and vice-versa).
- If both 1 and 3 are present but causing an unequal number of cases, then the system is not at equilibrium.

So for a fixed point analysis, we need only focus on the subspace  $\Lambda_1 = \Lambda_3$ . By symmetry in the system, this also holds for the pair of strains 2 and 4. The subspace  $(\Lambda_1 = \Lambda_3, \Lambda_2 = \Lambda_4)$  plus the corresponding symmetry constraints on the  $S_{\mathbf{J}}$  values is invariant, again by symmetries.

Numerical investigations (unpublished) suggest that all solutions starting with all strains present at any non-zero level tend to this subspace. In terms of the model, strains represented as being diametrically opposite on the circle in figure 2 tend to come into balance. Once they are there, they continue behaving identically.

#### 4.3. Fixed point location and analysis

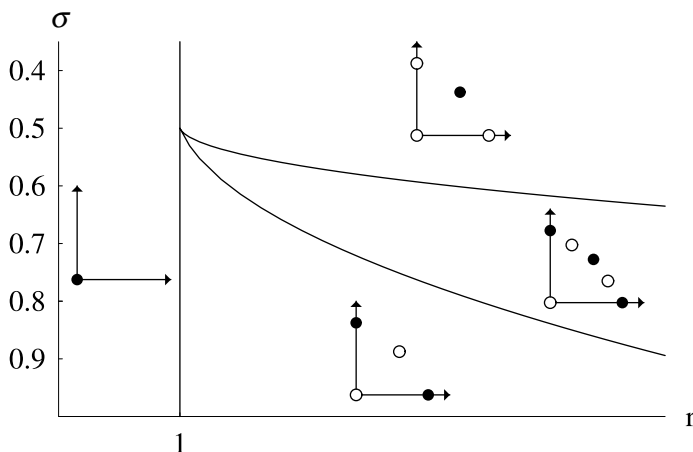
Within  $\Lambda_1 = \Lambda_3, \Lambda_2 = \Lambda_4$ , we have a few different kinds of possible fixed points of the system:

- no infection present** (origin equilibrium in  $\Lambda_1, \Lambda_2$  plane);
- one pair present** (edge equilibrium);
- both pairs present, and equally** (central equilibrium);
- both pairs present, but not equally** (asymmetric equilibrium).

A full analytic location and investigation of stability of the first three kinds of equilibria has been made. The stability analysis involved the Jacobian of the full system, and all eigenvalues transverse to the subspace in question are stable. The asymmetric equilibrium type has been more elusive, but it has been possible to find the region of parameter space for which they exist, and their location.

Some details of the analysis are given in the appendix. The results are summarized graphically in Figure 4 and described here.

Considering  $r$  increasing, we start with the edge equilibria stable and the central equilibrium unstable. We find that a pair of asymmetric equilibria emerge from the central equilibrium as it gains stability in a subcritical pitchfork bifurcation. The eigenvector involved in this bifurcation is within the  $\Lambda_1 = \Lambda_3 = -\Lambda_2 =$



**Fig. 4.** A complete schematic bifurcation diagram. The small fixed point diagrams represent the  $(\Lambda_1, \Lambda_2)$  plane. Solid circles are stable fixed points, open circles are unstable. The vertical line ( $r = 1$ ) corresponds to the change in stability of the fixed point at the origin. To the left of this, all strains will die out. The equations of the two curves are given in the appendix. They are quite close together, but have been separated in this diagram for clarity. Cross-immunity ( $\sigma$ ) increases downwards. Below the bottom curve, one pair is eliminated through competition. Above the top curve, cross-immunity is sufficiently low, or reproduction ratio ( $r$ ) is sufficiently high so that there is little competition between the strains and they co-exist equally. The middle region has two different types of stable behaviour.

$-\Lambda_4$  subspace. This pair of equilibria then move steadily apart, and eventually leave the positive quadrant (of  $\Lambda_1 = \Lambda_2$ ) by passing through the edge equilibria in a transcritical bifurcation. This leaves the edge equilibria unstable. Again, the only eigenvectors corresponding to instability of the edge equilibria are within the subspace under investigation. From all this, we deduce that the asymmetric pair of equilibria are unstable when they exist.

In contrast to the result of Andreasen *et al.* [1], the model described in this paper does not undergo any Hopf bifurcation from all strains being equal and there are apparently no oscillatory solutions: *this model does not exhibit the cycling of strains*. Also there is the region of parameter space with interesting dynamics in this model that does not appear to correspond with any region in the Andreasen model. In this region, there are two different kinds of stable behaviour, either one pair only, or all strains equally. Both types of equilibria are stable to small perturbations. Hence whether the four strains will coexist or whether one pair is eradicated through competition will depend on the initial conditions. There are also the two unstable equilibria not previously observed in other models, and they are on the edges of the basins of attraction of the stable states.

#### 4.4. Interpretation

The main distinction between the Gupta model, the Andreasen model and the model presented here is the exact mechanism for the effect of partial cross-immunity. The

Andreasen and the Gupta models both involve partial protection that affects all individuals with a given history equally and their dynamics are apparently quite similar [2]. Ours is based on heterogeneous response which allows a proportion of the population to gain total protection. This small modification leads to quite different dynamics. In particular, it does not appear to permit strain densities to oscillate in time, one of the key findings of the earlier analyses [8].

It is not intended that specific biological conclusions should be drawn from these differences between these two superficially similar systems of cross-immunity. What these differences do tell us is that the dynamics of multiple strains is sensitive to model assumptions.

Apart from the different forms of cross-immunity, there are two other aspects that may contribute to the differences between these three models. Firstly, there is the effect of cumulative cross-immunity. In the model presented in this paper, an individual who has had both adjacent strains would be less likely to be susceptible to a strain than an individual who has only had one adjacent strain. In both the Andreasen and Gupta models, having an additional adjacent strain after having the first does not change immunity or transmissibility. They take the least susceptibility given by any of the strains in their history, rather than the product (as in the model studied here).

Secondly, in the Andreasen model, infecteds are removed from susceptibility and they return upon recovery. This kind of delay is capable of generating oscillatory behaviour. However the Gupta model does allow superinfection, and yet it also displays oscillations. Therefore this difference between the models cannot on its own explain the differences in the dynamics.

In deducing which mechanisms are involved in different aspects of the dynamics in this particular four strain example, it may be useful to analyse a model of reduced susceptibility like the Andreasen model except with the susceptibility reduction factor being a product over all the history strains, rather than the minimum, and also allowing superinfection.

## 5. Conclusions

### 5.1. A status-based approach

This paper has presented a form of cross-immunity not previously studied, a framework with capacity to model it, and the analysis of a particular example. As well as permitting new forms of cross-immunity, this status-based framework helps to clarify and to interpret the effects of previous mathematical assumptions.

In extending these models, the essential idea is to categorize the susceptible population according to their current immune state. The state-space presented here, the set of strains a host is immune to, is perhaps the most basic for multiple strain dynamics. In a more advanced model, which may be tailored for a specific disease, one might have antigenic repertoire as the host-state. For example, with an allele and epitope structure used by Gupta *et al.* [8] immune status could be constructed in terms of the set of epitopes that a host has sufficient immunity to recognize, and transmission and/or susceptibility may be reduced or zero according to this state.

Another use of a status-based model would be to remove another limitation of previous models (including the example system presented here): cross immunity to each strain is independent of cross-immunity to other strains. It is not hard to imagine a situation where this is not true. For example, consider a situation where recovery from strain 1 leaves either total immunity to strain 2 or total immunity to strain 3 but never to both. This cannot be captured by previous models but is straightforward to model in a status-based framework.

Strain models have a very rich mathematical structure. In section four, symmetries were used extensively to further our analysis. It may be possible to draw upon more sophisticated theory and methodology [4] to achieve further advances using symmetry. More generally, any advance in dimensional reduction will increase greatly the range of models that may be explored in detail.

### 5.2. *The effect of different forms of cross-immunity*

This status-based approach has been used to present an alternative form of cross-immunity, and much analysis has been made possible in this model structure. Our analytic results show that even in a highly symmetric simple case, polarized immunity generates qualitatively different dynamics to previously studied models.

The immunological mechanisms of cross-immunity are being increasingly well characterized, although their implications at the epidemiological level remain unclear. Biologically, the exact mechanism of cross-immunity may be different for different pathogens and different scenarios. Currently, the appropriate model form is not clear for many situations, yet this paper has shown that the dynamics are sensitive to this form. Much further work is needed in understanding the effects of different models of cross-immunity, and in understanding the mechanisms behind the differences. Concerns with regard to the effects of the choice of cross-immunity will hold in numerical work, stochastic models and agent-based models involving cross-immunity in any form.

A still greater challenge is to develop techniques for assessing how cross-immunity works in biological practice and which epidemiological tools can be harnessed to this end [3, 6].

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## A. Appendix: Fixed point analysis

The method used to locate the fixed points in the  $\Lambda_1 = \Lambda_3 = \lambda_1, \Lambda_2 = \Lambda_4 = \lambda_2$  subspace is to substitute (4) into (8) and we can find these functions:

$$\begin{aligned}\theta_1 &= \theta_1(\lambda_1, \lambda_2, \sigma) \\ \theta_2 &= \theta_2(\lambda_1, \lambda_2, \sigma) = \theta_1(\lambda_2, \lambda_1, \sigma)\end{aligned}$$

The fixed points are described in  $(\lambda_1, \lambda_2)$  coordinates. For an equilibrium we must have:

$$\lambda_i = 0 \quad \text{or} \quad \theta_i = r^{-1} \quad \text{for } i = 1, 2 \quad (10)$$

Stability is investigated using the full 20 by 20 Jacobian. For each type of fixed point, it was possible to find a series of coordinate changes that made use of the symmetries to reduce this to block diagonal with blocks of manageable size.

### A.1. Trivial $(0, 0)$

This always exists. It is unstable exactly when  $r > 1$ .

### A.2. One pair $(\lambda, 0)$

This corresponds to an edge equilibrium in the  $(\lambda_1, \lambda_2)$  plane. It can be checked that

$$\begin{aligned} \theta_1(\lambda, 0, \sigma) &= \frac{1}{1 + \lambda} \\ \Rightarrow \lambda &= r - 1 \end{aligned}$$

so this exists for  $r > 1$ . It is stable for exactly

$$r < \frac{1}{2} + \frac{\sigma^2}{2(1 - \sigma)^2} = f_1(\sigma)$$

This bifurcation is associated with the other pair of strains being able to invade.

### A.3. All equal $(\lambda, \lambda)$

This corresponds to a central equilibrium in the  $(\lambda_1, \lambda_2)$  plane. We must have

$$\theta_1(\lambda, \lambda, \sigma) = r^{-1}$$

We can check that

$$\begin{aligned} \theta_1(0, 0, \sigma) &= 1 \\ \text{and} \quad \frac{d}{d\lambda} \theta_1(\lambda, \lambda, \sigma) &< 0 \end{aligned}$$

So there is exactly one equilibrium of this kind for each  $r > 1$ .

Investigation of the Jacobian shows that there can never be a purely imaginary eigenvalue and hence no Hopf bifurcation. There is one bifurcation, this is with a real eigenvalue passing through zero, and eigenvector which projects to  $(1, -1)$  in the  $(\lambda_1, \lambda_2)$  plane. This equilibrium is stable for exactly

$$\begin{aligned} r &> \frac{5 - 10\sigma + 12\sigma^2 - 8\sigma^3 + 4\sigma^4 + \sqrt{1 - 4\sigma - 4\sigma^2 + 48\sigma^3 - 64\sigma^4 + 32\sigma^5}}{4(1 - \sigma)^2(3 + \sigma^2)} \\ &= f_2(\sigma) \end{aligned}$$

We can check these following facts about the location of the bifurcations:

$$f_1(1/2) = f_2(1/2) = 1$$

$$\frac{d}{d\sigma} f_i(\sigma) > 0 \quad \text{for } \sigma > 1/2, i = 1, 2$$

$$f_1(\sigma) > f_2(\sigma) \quad \text{for } \sigma > 1/2$$

So there is a region of parameter space where both the central and edge equilibria are stable.

*A.4. Both pairs present, but unequally ( $\lambda_1, \lambda_2$ )*

From (10):

$$\theta_1(\lambda_1, \lambda_2, \sigma) - \theta_2(\lambda_1, \lambda_2, \sigma) = 0$$

and if we can satisfy this, then there is a unique  $r$  for which this is an equilibrium. This gives a rather cumbersome polynomial in  $\lambda_1, \lambda_2$  and  $\sigma$ . Now once again we make use of symmetries in the problem to suggest this change of variables:

$$s = \lambda_1 + \lambda_2$$

$$d = \lambda_1 - \lambda_2$$

Considering our polynomial now as an equation in  $d$ , there must be a  $d = 0$  solution corresponding to the central equilibrium. For all other solutions, if  $d$  is a solution, then so is  $-d$ . So we hope for an odd polynomial. Happily, this turns out to only be cubic:

$$\theta_1\left(\frac{s+d}{2}, \frac{s-d}{2}, \sigma\right) - \theta_2\left(\frac{s+d}{2}, \frac{s-d}{2}, \sigma\right) = 0 \iff$$

$$d \left( d^2 - (2 + 3s) \frac{2 - 4\sigma + 2s^2(1 - \sigma)^2(3 + \sigma^2) + s(7 - 14\sigma + 4\sigma^2)}{1 - 2\sigma + 4\sigma^2 - 8\sigma^3 + 4\sigma^4 + 2s(1 - \sigma)^2(1 + 3\sigma^2)} \right) = 0$$

For the second bracket to correspond to solution in positive  $\lambda_1, \lambda_2$ , we must have

$$0 < d^2 < s^2$$

First checking  $d^2 = 0$ , and combining with  $\theta_1 = r^{-1}$ , we find that this gives  $r = f_2(\sigma)$ . So, this is associated with the change of stability of the the central equilibrium. These asymmetric fixed points sprout out of a pitchfork bifurcation. At the other extreme,  $d^2 = s^2$  when the solutions move out of the positive quadrant, we find that this is at  $r = f_1(\sigma)$ . The fixed points move through the edge equilibria in a transcritical bifurcation. So this type of equilibrium exists in the region where the central and edge fixed points are stable.

The stability of these asymmetric equilibria was not directly investigated, but we can make deductions from the bifurcations with fixed points with known stability. This tells us that these asymmetric equilibria must be unstable at the edge of parameter space in which they exist. There are no other possible fixed points, and numerical investigations suggest that these stay unstable throughout.

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