Journal of Biological Systems, Vol. 17, No. 4 (2009) 713–737

World Scientific
www.worldscientific.com

IMMUNE LEVEL APPROACH FOR MULTIPLE STRAIN PATHOGENS

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Received 18 July 2008
Accepted 18 August 2009

We introduce a general framework to study the dynamics of multiple strain pathogens that can impart cross–immunity through a variety of structures. We propose two types of immunity and apply them to assess the dynamics of two competing strains. We illustrate this framework using two "visions": the *next–to–kin protection* (*NTKP*) approach which assumes that strains confer cross–immunity to next in order (neighboring) strains, while providing no protection against all other strains; and the *differential protection* (*DP*) approach assumes that individuals randomly gain partial (may be reinfected) and full cross-immunity following an infection with respective probabilities. We show that the risk of infection with a particular strain is significantly higher in the DP model that the NKTP. Moreover, we demonstrate that weaker cross-immunity structures in these models are more likely to lead to instability (sustained oscillations) in the strain coexistence mode. That is, periodic oscillations are sustained in the two-strain DP model for intermediate to weak levels of cross-immunity, while the NTKP model requires at least three strains to support these unstable dynamics.

Keywords: Multiple Strains; Cross–Immunity; Reinfection; Coexistence; Sustained Oscillations; Oscillatory Coexistence; *Next–to–Kin Protection*; *Differential Protection*.

1. Introduction

Studying the dynamics of infectious diseases often involves the interaction of multiple strain pathogens. Some commonly studied pathogens include dengue and influenza (flu) viruses. These viruses differ significantly in their cross-reactive immunological response induced by between-strain competition. The cross-reactive antibody response for influenza follows the more common immunological response in which a previous virus exposure yields partial protection against prospective

strains, as long as virus strains are antigenically similar. Unlike flu viruses, cross-reactive antibodies following a dengue infection act to enhance (rather than to restrict) the severity of subsequent infections by other dengue strains.[1] In view of the complexities that arise when multiple pathogens interact and affect a host's susceptibility to infection or transmissibility of future infections, many studies have been proposed to study the dynamics of co-circulating pathogens and the immunological structures by which they interact/compete.

In particular, flu viruses have been studied extensively, yet their ability (virulence) to continuously evade a host's immune system through genetic mutations allows them to persist, primarily during winter in temperate zones. The coupled interaction of a host's immunity and a pathogen's ability to invade a host are at the forefront of mechanisms that seem to promote the emergence and re–emergence of flu outbreaks. The virus gradual evolutionary changes that occur through minor mutations (antigenic drift) are responsible for annual epidemics that affect 20 to 50% of the US population each winter season. Other more dramatic and less common mutations (antigenic shift) involve abrupt major changes in the virus surface proteins (Hemagglutinin, Neuraminidase), resulting in a new virus subtype. While cross-immunity is conferred among antigenically similar strains (antigenic drift), this is not the case between strains that belong to distinct subtypes (e.g. H1N1 and H3N2).

Mathematical models have been used to assess the impact of age–structure, quarantine, and isolation (among a few) in supporting the seasonality of flu, but clearly, evolution plays the critical role. Studies that assess the impact of cross–immunity on influenza dynamics within a population that incorporates multiple strains with diverse forms of immune responses typically involve complex and frequently untractable frameworks, but an effort must be made to carry out such analysis.

In fact, recent modeling efforts include high dimensional strain interactions and "detailed" immunological structures that capture virus–host interactions effectively. The work of Andreasen, Lin and Levin[2] noted as the "ALL" scheme in Gomes and Medley,[3] used a "History Based Approach" (*HBA*) to classify a population's susceptibility according to prior infections. This history of previous infections was used to determine future susceptibility through a cross–immunity structure that reduced the probability of transmission or susceptibility among antigenically similar strains.[4–9] The *HBA* approach assumed that individuals with a similar history of infections were equally susceptible to new infections. Ferguson and Andreasen[10] evaluated two "expressions" of cross–immunity: reduction in susceptibility or in infectiousness. They showed that the choice of immunity–based interactions made little difference in the dynamics of these models. More recently, Gog's *et al.* "Status Based Approach" (*SBA*)[11,12] assessed the impact of cross–immunity from a "pathogen's perspective". Their approach was used to capture the dynamics of a host's ability to escape infection from circulating strains. These researchers studied

the case where partial induced cross–immunity via heterogeneous immunological host response ("polar immunity") followed recovery.[13–15] Alternative methods that incorporate multiple strain interaction have been proposed, however, they are not discussed herein.[16–19]

The choice of cross–immunity structure, not surprisingly, naturally plays a critical role in determining the dynamics of co-circulating pathogens. At some level we observe dual outcomes. Some models are capable of supporting periodic solutions[2,3,10,20] while others lead to slowly dampening oscillations.[11,12] This study presents a modeling framework that incorporates the effects of interference competition when *multiple* strains try to invade the same population. The impact of alternative cross–immunity structures is explored with detail in two specific scenarios. The paper is organized as follows: Sec. 2 introduces the modeling framework; Sec. 3 computes the epidemic threshold and identifies stability conditions for the general model in the absence of the pathogen; Sec. 4 identifies strain invasion conditions; Sec. 5 investigates the usefulness of this framework by exploring the dynamics of two cross–immunity structures: the *next–to–kin* and *differential protection*; Sec. 6 assesses model outcomes numerically; and, Sec. 7 collects results and conclusions.

2. The Model

Our model assumes a Susceptible–Infected–Recovered (SIR) framework for a population facing multiple strains (antigenic variants) of a single virus subtype. The population is further divided into sub–classes based on the current immunological status of the host, a function of the circulating strains. S_J denotes the susceptible individuals with immunity index set denoted by $J \in \mathcal{P}$. Similarly, I_M^i designates strain i infected individuals with immunity index set $M \in \mathcal{P}$. The population of Recovered individuals are implicitly absorbed in S_J. Immunity index sets J and M give a multi–level description of a host's current immunity (and susceptibility) with respect to all strains in circulation. Past infections are assumed to confer partial protection against future infections with antigenically similar strains, therefore, we assume that immunity is enhanced with previous infections; these are $\mathbf{m}$ levels of increasing protection with respect to each strain, $\mathcal{L}_\mathbf{1} < \cdots < \mathcal{L}_\mathbf{k} < \cdots < \mathcal{L}_\mathbf{m}$. Consequently, the immunity index J is an ordered n–tuple (n strains) whose entries take values from $\mathcal{L}_\mathbf{1}$ to $\mathcal{L}_\mathbf{m}$. We let $\mathcal{P}$ denote the set of all immunity indices, that is, of all n–tuples with entries in the set $\mathcal{L}_\mathbf{1}, \ldots, \mathcal{L}_\mathbf{k}, \ldots \mathcal{L}_\mathbf{m}$. In particular, the index of individuals who are in immune level 1 ($\mathcal{L}_\mathbf{1}$) with respect to all n strains would be denoted by a n–tuple $(\mathcal{L}_\mathbf{1}, \ldots, \mathcal{L}_\mathbf{1}, \ldots, \mathcal{L}_\mathbf{1})$. In order to simplify the notation, we dropped the $\mathcal{L}$'s and denote them by an n–tuple of $\mathbf{1}'s$, namely, $J \equiv \mathbf{1} = (1, \ldots, 1)$.

Since natural protection against future infections is acquired primarily through previous exposures, we assume that hosts are born fully susceptible to all strains, that is, they are born into the epidemiological class $S_{\{\mathbf{1},\ldots,\mathbf{1}\}}$ at the per–capita rate μ.

We neglect disease related mortality, however, we assume a natural mortality rate of μ. The birth rate into S_J is thereby denoted by $\mu\ \delta_{J,\mathbf{1}}$, where

$$\delta_{J,\mathbf{1}} = \begin{cases} 1, & \text{if } J = (1,\ldots,1) \\ 0, & \text{otherwise, } J \in \mathcal{P}. \end{cases}$$

The set of all possible state indexes $\mathcal{P}$ has $\mathbf{m}^n$ elements, however, not all index n–tuples $J \in \mathcal{P}$ yield viable ordered infections sets. The routes of infection (infectious classes) that are not feasible under some cross–immunity schemes are called *unattainable* states. Accessible (e.g. *attainable*) states are denoted by $\mathcal{A}$ and $\mathcal{A} \subset \mathcal{P}$. $J = (1,\ldots,1)$ represents a naturally *attainable* state (e.g. $(1,\ldots,1) \in \mathcal{A}$). The subset of *attainable* states through infection with strain i is denoted by $\mathcal{A}_i$, and hence, $\mathcal{A}_i \subset \mathcal{A}$ and

$$\mathcal{A} = \bigcup_i \mathcal{A}_i \bigcup (1,\ldots,1).$$

Consider a hypothetical population facing three strains ($n = 3$) and capable of generating three immunity response levels ($\mathcal{L}_\mathbf{1}$, $\mathcal{L}_\mathbf{2}$, $\mathcal{L}_\mathbf{3}$). $S_{\{1,2,3\}}$ describes the susceptible population with immune response level $\mathcal{L}_\mathbf{1}$ against strain 1, immune response $\mathcal{L}_\mathbf{2}$ against strain 2 and immune response $\mathcal{L}_\mathbf{3}$ against strain 3. Similarly, $I^2_{\{1,3,3\}}$ denotes the strain–2 infected individuals with immune response level 1 against strain 1, and immune response level 3 to strains 2 and 3. Infectious class $I^2_{\{1,3,3\}}$ may be attained from susceptible class $S_{\{1,2,3\}}$ following an infection with strain 2. Strain–2 infected individuals in class $I^2_{\{1,3,3\}}$ that go on to recover are implicitly accounted for in $S_{\{1,3,3\}}$ (e.g. we do not explicitly include a recovered class). A change in a host's immune status occurs upon infection, that is, susceptibles $S_{\{1,2,3\}}$ get infected by strain 2 and move to $I^2_{\{1,3,3\}}$ ($J = \{1,2,3\} \to M = \{1,3,3\}$). We evaluate the userfulness of the *next–to–kin* ($NTKP$) and *differential protection* (DP) models. We illustrate these two models by assuming a population with two co–circulating strains and three levels of cross–immunity.

2.1. *Next–to–kin model*

This cross–immunity structure assumes that each strain provides full immunity to those infected who recover, partial immunity to the "*next–to–kin*" strain, and no immunity to the remaining strains. This approach differs from[1] in that we do not allow for infection of opposite strains. Strains are numbered so that infection with strain 1 confers partial protection to strain 2, strain–2 infection protects partially against strain 3, and strain–3 infection protects partially against strain 1. All states (with the exception of $\{1,1,1\}$) for which there is no immune level three in one entry are *unattainable* (e.g. $\{1,1,2\}$ and $\{2,2,2\}$). States with complete immunity ($\mathcal{L}_3$) to one strain but naive to the other two are also *unattainable* (e.g. $\{3,1,1\}$). The set of all *attainable* states is therefore given by

$$\mathcal{A} = \{\{1,1,1\},\{3,2,1\},\{1,3,2\},\{2,1,3\},\{3,2,3\},\{3,3,2\},\{2,3,3\},\{3,3,3\}\},$$

while

$$\mathcal{A}_1 = \{\{3,2,1\},\{3,2,3\},\{3,3,2\},\{3,3,3\}\}$$

describes the set of attainable states via infection with strain 1 (all states with immunity level 3 in the first position).

2.2. *Differential protection model*

This model assumes that each strain provides partial protection against itself with probability p and complete protection with probability q (hence $p+q=1$), while providing no protection against the remaining strains. This framework allows for reinfection with the same strain. In this three strain example, the set of attainable states coincides with the set of all possible states, that is, $\mathcal{P} = \mathcal{A}$ (27 possible states). In general,

$$\mathcal{A} = \{(i,j,k) : \text{where } i,j,k \in \{1,2,3\}\}.$$

For instance, the set of attainable states via infection with strain 1 is given by the states without immunity level 1 in the first position:

$$\begin{aligned}\mathcal{A}_1 = \{&\{2,2,1\},\{2,3,1\},\{2,2,2\},\{2,3,2\},\{2,2,3\},\{2,3,3\},\{3,2,1\},\\ &\{3,3,1\},\{3,2,2\},\{3,2,3\},\{3,3,3\}\}.\end{aligned}$$

Individuals in S_J can be infected by any strain as long as $J \neq \mathbf{3} = \{3,3,3\}$, and by strain i as long as the ith component of J is not $\mathbf{m}$ ($J_i \neq \mathbf{m}$). More generally, S_J may be infected by all strain i–infected hosts who are in any infectious class within the *attainable* states associated with strain i (the set $\mathcal{A}_i$).

The force of infection for strain i takes the form

$$\Lambda_i = \beta_i \sum_{K \in \mathcal{A}_i} I_K^i,$$

where β_i denotes the transmissibility of strain i. This model assumes that all i–strain infected individuals have the same probability of transmitting the disease and contact rate. It can be noted that while the force of infection for strain 1 under the DP model involves 18 attainable states, the $NTKP$ model yields only four attainable states. Hence, it is evident that the risk of new infections (per unit time) is more likely under the DP modeling framework. A significant parameter in our model denoted by $p(J,M,i)$ keeps track of changes and updates of the population's immune status. It captures the immunological changes of S_J (with immune status J) to I_M^i (with immune status M) following an infection with strain i. The rate at which individuals in S_J move into I_M^i ($J \subset M$) after an infection with strain i is

reduced by $p(J, M, i)$. Therefore, we have that

$$\sum_{M \in \mathcal{A}_i} p(J, M, i) \leq 1 \tag{1}$$

and

$$\sum_{M \in \mathcal{A}_i} p(\mathbf{1}, M, i) = 1 \quad \forall i. \tag{2}$$

2.3. *Model equations*

Susceptible individuals S_J become infected with strain i at rate β_i, recover from strain i with rate γ_i or succumb to natural mortality at a rate μ. Recovered individuals are absorbed in S_J. Based on these assumptions, we model susceptibles by

$$\frac{d}{dt}S_J = \sum_{i:J\subset\mathcal{A}_i} \gamma_i I_J^i - \sum_{\substack{i\,:\,J_i \neq m,\\ M\,:\,J\subset M,\ M\in\mathcal{A}_i.}} \Lambda_i p(J, M, i) S_J - \mu S_J \quad J \neq 1. \tag{3}$$

The inflow rate of S_J is given by the sum of recoveries from infections with different strains i for which J belongs to $(\mathcal{A}_i)$. The loss terms are due to deaths μS_J and infections of susceptibles not completely immune ($J_i \neq m$). The inflow to the I_M^i class comes from all those immune states from which one moves to immune state M after infection with strain i. Individuals in I_M^i can have immune status in the set of states attainable through infection with strain i, that is, if M is the immune state of an infectious individual, we necessarily have that $M \in \mathcal{A}_i$. The incidence terms in all inflow terms include the force of infection Λ_i. The outflow of (4) includes recovery and deaths of strain–i infected individuals. Thus, the dynamics of I_M^i are modeled by

$$\frac{d}{dt}I_M^i = \sum_{J:J\subset M} \Lambda_i p(J, M, i) S_J - (\mu + \gamma_i) I_M^i. \tag{4}$$

For a description of the completely susceptible class $S_{\mathbf{1}}$, we consider that no previous infections have occurred and therefore no recoveries are accounted for in the equation for susceptibles. Since $\sum_{M\in\mathcal{A}_i} p(J, M, i) = 1$ for every i and $\delta_{J,\mathbf{1}} = 1$, we obtain

$$\frac{d}{dt}S_{\mathbf{1}} = \mu - \sum_{i=1}^{n} \Lambda_i S_{\mathbf{1}} - \mu S_{\mathbf{1}}. \tag{5}$$

We assume that as soon as hosts become infected with strain i, they acquire immediate immunity, therefore no strain–i infectives with immune status level $\mathcal{L}_1$ with index position i are included. The population is structured into non–intersecting sub–classes and the total population (N) is given by the sum of all classes

$$N = \sum_J S_J + \sum_{i,M} I_M^i,$$

which has been normalized so that $N = 1$ ($\frac{dN}{dt} = 0$).

3. Stability and Threshold Conditions

We simplify and reduce the number of parameters in the original model (3)–(4) by re–scaling time to μ^{-1} units

$$\begin{aligned}\frac{d}{dt}S_J &= \delta_{J,1} - S_J + \sum_{i:J\subset\mathcal{A}_i}(e_i-1)I^i_J - \sum_{\substack{i\,:\,J_i\neq m\\ M\,:\,J\subset M,\ M\subset\mathcal{A}_i}}\Lambda_i p(J,M,i)S_J\\ \frac{d}{dt}I^i_M &= \sum_{J:J\subset M}\Lambda_i p(J,M,i)S_J - e_i I^i_M,\end{aligned} \tag{6}$$

where

$$e_i = \frac{\mu+\gamma_i}{\mu}.$$

Re–scaling β_i replaces it by $\frac{\beta_i}{\mu}$, however, we will continue to denote this re–scaled force of infection term by Λ_i. The equation for $S_{\mathbf{1}}$ is given by

$$\frac{d}{dt}S_{\mathbf{1}} = \mathbf{1} - \sum_{i=1}^{n}\Lambda_i S_{\mathbf{1}} - S_{\mathbf{1}}. \tag{7}$$

We study the equilibria of the original linearized system. The existence of non–trivial equilibria and their stability is derived from the reproduction number of strain i given by

$$\mathcal{R}_i = \frac{\beta_i}{\gamma_i+\mu}. \tag{8}$$

The basic reproduction number of strain i ($\mathcal{R}_i$) describes the average number of secondary infections generated by a strain–i infected individual in a fully susceptible population. It can be noted that $\mathcal{R}_i$ does not depend on the cross–immunity function $p(J,M,i)$. However, the explicit formulation of the reproduction numbers is described by

$$\mathcal{R}_i = \frac{\beta_i}{\gamma_i+\mu}\times\mathbf{1}\times\sum_{M\in\mathcal{A}_i}p(\mathbf{1},M,i),$$

where the last sum is equal to one (see Eq. (2)). Using Eq. (7), we calculate $S_{\mathbf{1}}$–equilibrium

$$S_{\mathbf{1}}(\underline{\Lambda}) = \frac{\mathbf{1}}{1+\sum_{i=1}^{n}\Lambda_i},$$

where $\underline{\Lambda}$ denotes the force of infection at equilibrium, $\underline{\Lambda} = (\Lambda_1,\ldots,\Lambda_n)$. The rest of the S_J-equilibria terms are obtained by solving (6) inductively and using ordering of the index set J. First, we solve for immunity state levels M which can be obtained directly from the completely immunity–naive level $\mathbf{1}$ through infection with one of

the strains. We obtain I_M^i and the corresponding S_J. We continue with the next levels of immunity levels by applying

$$S_J(\underline{\Lambda}) = \frac{\sum_{i:J\subset\mathcal{A}_i}(e_i-1)I_J^i}{\sum\limits_{\substack{i\,:\,J_i\neq m\\ M\,:\,J\subset M,\ M\in\mathcal{A}_i}} \Lambda_i p(J,M,i)+1} \quad J\neq\mathbf{1} \tag{9}$$

and

$$I_M^i(\underline{\Lambda}) = \sum_{J\,:\,J\subset M} \frac{\Lambda_i p(J,M,i)S_J}{e_i}. \tag{10}$$

It can be shown that if all coordinates of Λ_i are non–negative, then all values of S_J and I_M^i are non–negative and sum to $\mathbf{1}$. These values correspond to an attainable equilibrium provided that $\underline{\Lambda}$ satisfies

$$\Lambda_i = \mathcal{R}_i e_i \sum_{M\in\mathcal{A}_i} I_M^i(\Lambda) = \mathcal{R}_i \sum_{M\in\mathcal{A}_i}\sum_{J:J\subset M} \Lambda_i p(J,M,i)S_J(\underline{\Lambda}).$$

The ith force coordinate of infection Λ_i at a given equilibrium ($\underline{\Lambda}$) can be determined provided that it satisfies $\Lambda_i = 0$, or

$$1 = \mathcal{R}_i \sum_{M\in\mathcal{A}_i}\sum_{J:J\subset M} p(J,M,i)S_J(\underline{\Lambda}), \quad \text{for those } i \text{ for which } \Lambda_i\neq 0.$$

The disease–free equilibrium $\mathcal{E}_0$ is calculated by setting $\Lambda_i = 0$ for all i. In the $\mathcal{E}_0$ state, the entire population is completely susceptible ($S_{\mathbf{1}} = \mathbf{1}$) and all other classes equate to zero

$$\begin{aligned} &S_J = 0 \quad \forall J\neq\mathbf{1}\\ &I_M^i = 0 \quad i=1,\dots,n, \quad M\in\mathcal{A}_i. \end{aligned} \tag{11}$$

Note that the disease–free equilibrium always exists. Besides $\mathcal{E}_0$, there are n *simple boundary equilibria* where only strain i strain is established. We denote such equilibria by $\mathcal{E}_i$, $i\in\{1,\dots,n\}$.

Proposition 3.1. *If $\mathcal{R}_i > 1$ then there exists the ith edge (simple boundary) equilibrium $\mathcal{E}_i$.*

Proof. To see this let $\Lambda_j = 0$ for $j\neq i$. Let

$$\mathcal{F}_i(\Lambda_i) = \mathcal{R}_i \sum_{M\in\mathcal{A}_i}\sum_{J:J\subset M} p(J,M,i)S_J(\Lambda_i).$$

First we notice $\mathcal{F}_i(0) = \mathcal{R}_i$. Hence $\mathcal{F}_i(0) > 1$ for $\mathcal{R}_i > 1$. Next we notice that $\mathcal{F}_i(\Lambda_i)$ satisfies

$$\lim_{\Lambda_i\to\infty} \mathcal{F}_i(\Lambda_i) = 0.$$

To see this we notice that from (9) we have

$$S_{\mathbf{1}}(\Lambda_i) = \frac{\mathbf{1}}{1+\Lambda_i}.$$

Thus, $S_{\mathbf{1}}(\Lambda_i)$ is decreasing and going to zero as $\Lambda_i \to \infty$. We continue following the order provided by the set M. For all index sets M which can be obtained from $\mathbf{1}$ by infection with the strain i we have that terms like $p(\mathbf{1}, M, i)S_{\mathbf{1}}$ are going to zero as $\Lambda_i \to \infty$. Thus, $\frac{I^i_M}{\Lambda_i}$ are going to zero (see Eq. (10)). For S_J with J like M and $J_i \neq m$, we have

$$S_J(\Lambda_i) = \frac{(e_i - 1)I^i_J}{\Lambda_i \sum_{M:J\subset M, M\in\mathcal{A}_i} p(J, M, i) + 1} \leq \frac{(e_i - 1)I^i_J}{\Lambda_i \sum_{M:J\subset M, M\in\mathcal{A}_i} p(J, M, i)}$$

and consequently, it is going to zero as Λ_i goes to infinity. We notice that I^i_M for $M \in \mathcal{A}_i$ depends on S_J for $J \subset M$ and hence J does not have its ith component equal to m. Hence,

$$\lim_{\Lambda_i\to\infty} S_J(\Lambda_i) = 0$$

and the same is true for $\mathcal{F}(\Lambda_i)$. Consequently, there exists $\Lambda^*_i > 0$ such that

$$\mathcal{F}_i(\Lambda^*_i) = 1. \qquad \square$$

In order to determine the stability of the general system, we approximate the solution near a steady state (S^*_J, I^*_M) by its linearization as follows:

$$\frac{\partial \dot{S}_J}{\partial S_{\mathcal{M}}} = \begin{cases} -1 - \displaystyle\sum_{\substack{i\,:\,J_i\neq m \\ M\,:\,J\subset M,\ M\in\mathcal{A}_i}} \Lambda_i p(J, M, i), & \text{if } J = \mathcal{M}, \\ 0, & \text{if } J \neq \mathcal{M}. \end{cases} \tag{12}$$

$$\frac{\partial \dot{S}_J}{\partial I^i_{\mathcal{M}}} = \begin{cases} (e_i - 1), \\ \qquad \text{if } J = \mathcal{M}, \mathcal{M} \in \mathcal{A}_i \quad \text{and} \quad J_i = m, \\ (e_i - 1)\mathcal{R}_i e_i \displaystyle\sum_{M:J\subset M, M\in\mathcal{A}_i} p(J, M, i)S_J, \\ \qquad J = \mathcal{M}, \mathcal{M} \in \mathcal{A}_i \quad \text{and} \quad J_i \neq m, \\ -\mathcal{R}_i e_i \displaystyle\sum_{M:J\subset M, M\in\mathcal{A}_i} p(J, M, i)S_J, \\ \qquad \text{if } \mathcal{M} \neq J, \mathcal{M} \in \mathcal{A}_i, J_i \neq M \\ 0, \quad \text{else.} \end{cases} \tag{13}$$

$$\frac{\partial \dot{I}^i_M}{\partial S_{\mathcal{M}}} = \begin{cases} \Lambda_i p(\mathcal{M}, M, i), & \text{if } \mathcal{M} \subset M, \\ 0, & \text{else.} \end{cases} \tag{14}$$

$$\frac{\partial \dot{I}^i_M}{\partial I^j_{\mathcal{M}}} = \begin{cases} R_i e_i \displaystyle\sum_{J:J\subset M} p(J, M, i)S_J - e_i, & \text{if } i = j, \quad M = \mathcal{M}, \mathcal{M} \in \mathcal{A}_i \\ R_i e_i \displaystyle\sum_{J:J\subset M} p(J, M, i)S_J, & \text{if } i = j, \quad M \neq \mathcal{M},\ \mathcal{M} \in \mathcal{A}_i \\ 0, & \text{else.} \end{cases} \tag{15}$$

We use the linearization above to establish the local stability of the disease–free equilibrium.

Proposition 3.2. *If $\mathcal{R}_i < 1$ for all i then the disease–free equilibrium $\mathcal{E}_0$ is locally stable. If $\mathcal{R}_i > 1$ for some i, the disease–free equilibrium $\mathcal{E}_0$ is unstable.*

Proof. The partial derivatives in the expressions above simplify significantly when computed at the disease–free equilibrium. We have that

$$\frac{\partial \dot{S}_J}{\partial S_{\mathcal{M}}} = \begin{cases} -1, & \text{if } J = \mathcal{M}, \\ 0, & \text{if } J \neq \mathcal{M}. \end{cases}$$

The derivatives of the right hand sides of S_J with respect with $I^i_{\mathcal{M}}$ are complicated but are not relevant for $\mathcal{E}_0$. The derivatives of I^i_M with respect to $S_{\mathcal{M}}$ equate to zero

$$\frac{\partial \dot{I}^i_M}{\partial S_{\mathcal{M}}} = 0$$

for all M, $\mathcal{M}$ and i.

$$\frac{\partial \dot{I}^i_M}{\partial I^j_{\mathcal{M}}} = \begin{cases} \mathcal{R}_i e_i p(\mathbf{1}, M, i) - e_i, & \text{if } i = j,\ M = \mathcal{M}, \mathcal{M} \in \mathcal{A}_i \\ \mathcal{R}_i e_i p(\mathbf{1}, M, i), & \text{if } i = j,\ M \neq \mathcal{M}, \mathcal{M} \in \mathcal{A}_i \\ 0, & \text{else.} \end{cases}$$

Thus, the Jacobian $\mathcal{J}$ consists of -1's along the diagonal and block matrices $\mathcal{B}_i$ and additional simplifying structure discussed below.

$$\mathcal{J} = \begin{pmatrix} -1 & * & \cdots & * & \cdots & * \\ 0 & -1 & \cdots & * & \cdots & * \\ 0 & 0 & \cdots & & \cdots & * \\ 0 & 0 & \cdots & \mathcal{B}_1 & \cdots & * \\ 0 & 0 & \cdots & 0 & \cdots & * \\ 0 & 0 & \cdots & 0 & \cdots & \mathcal{B}_n \end{pmatrix}.$$

Thus, the eigenvalues of the Jacobian at the disease–free equilibrium consist of -1 while the eigenvalues of the matrices $\mathcal{B}_i$ (for $i = 1, \ldots, n$) are described further. The ith block has the form $\mathcal{B}_i = e_i \hat{\mathcal{B}}_i$ where

$$\hat{\mathcal{B}}_i = \begin{pmatrix} \mathcal{R}_i p(\star) - 1 & \mathcal{R}_i p(\diamond) & \cdots & \mathcal{R}_i p(\circ) \\ \mathcal{R}_i p(\star) & \mathcal{R}_i p(\diamond) - 1 & \cdots & \mathcal{R}_i p(\circ) \\ & & \cdots & \\ \mathcal{R}_i p(\star) & \mathcal{R}_i p(\diamond) & \cdots & \mathcal{R}_i p(\circ) - 1 \end{pmatrix}$$

and M_j are indices in $\mathcal{A}_i$, $p(\mathbf{1}, M_1, i) = p(\star)$, $p(\mathbf{1}, M_2, i) = p(\diamond)$ and $p(\mathbf{1}, M_2, i) = p(\circ)$. We find the eigenvalues by computing the determinant

$$|\hat{\mathcal{B}}_i - \lambda I|.$$

The determinant is calculated by multiplying the first row by -1 and adding it to the remaining rows. The resulting determinant will have $1+\lambda$ in the first column except the first entry, $-1-\lambda$ in the diagonal entry for rows $2,\ldots,k$ and zeroes elsewhere. The first row is as before. We proceed to add each column from the second to the last, and to the first column. The first entry becomes

$$\mathcal{R}_i \sum_{M\in\mathcal{A}_i} p(\mathbf{1}, M, i) - 1 - \lambda = \mathcal{R}_i - 1 - \lambda.$$

The remaining entries along the diagonal are given by $-1-\lambda$ and those entries below–the–diagonal equal to zero. Thus, the eigenvalues of $\hat{\mathcal{B}}_i$ are -1 and $\mathcal{R}_i - 1$. Consequently, if all $\mathcal{R}_i < 1$ then all eigenvalues of the Jacobian are negative and the disease–free equilibrium is locally stable. However, if there is a single $\mathcal{R}_j > 1$ then the $\mathcal{B}_j$th block has a positive eigenvalue and the disease–free equilibrium becomes unstable. This completes the proof. □

Notice that the eigenvalues of $\mathcal{B}_i$ are e_i times the eigenvalues of $\hat{\mathcal{B}}_i$, hence, the eigenvalues of $\mathcal{B}_i$ and $\hat{\mathcal{B}}_i$ have the same sign. Next, we show that the disease–free equilibrium is not only locally stable but globally stable whenever all the reproduction numbers are less than unity. Thus, keeping all reproduction numbers below one prevents an outbreak from becoming established.

Proposition 3.3. *If $\mathcal{R}_i < 1$ for all i, then the disease–free equilibrium $\mathcal{E}_0$ is globally stable.*

Proof. We consider the original equations rather than the non–dimensional equations. Let

$$\mathcal{I}_i = \sum_{M\in\mathcal{A}_i} I^i_M,$$

where

$$\beta_i \mathcal{I}_i = \Lambda_i.$$

Adding the equations in (4) for all $M \in \mathcal{A}_i$ while assuming a fixed i gives

$$\frac{d}{dt}\mathcal{I}_i = \sum_{M\in\mathcal{A}_i} \sum_{J:J\subset M} \beta_i \mathcal{I}_i p(J, M, i) S_J - (\gamma_i + \mu)\mathcal{I}_i.$$

The value of the sum increases if we include all J rather than only those which are subsets of M. Hence, we can exchange the two sums. Hence, using Eq. (1) gives

$$\frac{d}{dt}\mathcal{I}_i \le \beta_i \mathcal{I}_i \sum_J S_J - (\gamma_i + \mu)\mathcal{I}_i.$$

Integrating these equations yields

$$\mathcal{I}_i(t) = e^{-(\gamma_i+\mu)t} I_i(0) + \beta_i \int_0^t e^{-(\gamma_i+\mu)(t-\tau)} I_i(\tau) \sum_J S_J(\tau)\, d\tau. \tag{16}$$

Notice that

$$\sum_J S_J < \mathbf{1} \quad \text{and} \quad \limsup_t \sum_J S_J \leq \mathbf{1}.$$

Hence, taking the lim sup as $t \to \infty$ in inequality (16) we obtain,

$$\limsup_t \mathcal{I}_i \leq \mathcal{R}_i \limsup_t \mathcal{I}_i.$$

Since $\mathcal{R}_i < 1$, this inequality can only be true if

$$\limsup_t \mathcal{I}_i = 0.$$

The same argument applies for every i. Hence, the number of individuals in all infectious classes goes to zero. From Eq. (3), for $J \neq \mathbf{1}$, we have that

$$\limsup_t S_J = 0,$$

and we know that,

$$\lim_t S_{\mathbf{1}} = \mathbf{1}.$$

This completes the proof. □

4. Strain Invasion

A pathogen's ability to invade a population seems to depend on a combined set of factors that include the host's immune system and the population's susceptibility. At the host level, a pathogen is most likely to generate an infection (invade) if a host has little–to–none acquired cross–immunity, that is, prior exposure to a similar (antigenically) strain. At the population level, a pathogen (strain) may be capable of becoming established if sufficient levels of susceptibility are present.

We study the scenario for which a single strain may invade a population at equilibrium, that is, a population supporting co–circulating strains. The conditions that support the successful invasion of strain i are computed by evaluating the Jacobian at the equilibrium $\mathcal{E}$. That is, we start with a system at equilibrium (S_J^*, I_M^*), where it is assumed that strain i (and possibly other strains) are absent. The invasion reproduction number of strain i is given by

$$\hat{\mathcal{R}}_i = \mathcal{R}_i \sum_{M \in \mathcal{A}_i} \sum_{J : J \subset M} p(J, M, i) S_J^*. \tag{17}$$

Strain i becomes established if $\hat{\mathcal{R}}_i > 1$ (unstable equilibrium (S_J^*, I_M^*)) while $\hat{\mathcal{R}}_i < 1$ implies that strain i is unable to invade, rendering a *possibly* stable equilibrium

(S_J^*, I_M^*). In general, if $\mathcal{R}_i < 1$ we do not know whether the equilibrium is stable or not, we do not expect strain i to persist.

Proposition 4.1. *Let $\mathcal{E} = (S_J^*, I_M^*)$ be an equilibrium in which strain i is not present, that is $I_M^i = 0$ for all $M \in \mathcal{A}_i$. If $\hat{\mathcal{R}}_i > 1$ then the equilibrium $\mathcal{E}$ is unstable, that is, strain i can invade.*

Proof. The partial derivatives of the right-hand sides of the system (6) are computed in the expressions (12)–(15). The variables are arranged so that leading entries are all the susceptible classes followed by all I_M^1 classes, then all I_M^2 classes and so on until we include all I_M^n classes. With this arrangement we let $\mathcal{S}$ be the matrix $\mathcal{S} = (\frac{\partial \dot{S}_J}{\partial S_{\mathcal{M}}})$, where the different entries are obtained by varying J and $\mathcal{M}$. The diagonal entries of this matrix are nonzero and the rest are zero. We denote by $\mathcal{X}_j$ the matrix $\mathcal{X}_j = (\frac{\partial \dot{I}_M^j}{\partial S_{\mathcal{M}}})$ where the different entries are obtained by varying M and $\mathcal{M}$. The matrix $\mathcal{X}_j$ is identically zero if and only if the strain j is not present in the equilibrium $\mathcal{E}$. In particular $\mathcal{X}_i = 0$. Furthermore, we denote by $\mathcal{B}_i = (\frac{\partial \dot{I}_M^i}{\partial I_{\mathcal{M}}^i})$ where

$$\frac{\partial \dot{I}_M^i}{\partial I_{\mathcal{M}}^j} = \begin{cases} \mathcal{R}_i e_i \displaystyle\sum_{J:J\subset M} p(J,M,i) S_J - e_i, & \text{if } i=j,\ M=\mathcal{M}, \mathcal{M}\in\mathcal{A}_i \\ \mathcal{R}_i e_i \displaystyle\sum_{J:J\subset M} p(J,M,i) S_J, & \text{if } i=j,\ M\neq\mathcal{M}, \mathcal{M}\in\mathcal{A}_i \\ 0, & \text{else.} \end{cases}$$

With this notation the Jacobian at the equilibrium $\mathcal{E}$ consists of the matrix $\mathcal{S}$, the matrices $\mathcal{X}_j$ and block matrices $\mathcal{B}_i$ which are full without zero entries:

$$\mathcal{J} = \begin{pmatrix} \mathcal{S} & * & \cdots & * & \cdots & * \\ \mathcal{X}_1 & \mathcal{B}_1 & \cdots & 0 & 0 & 0 \\ \cdots & \cdots & \cdots & & \cdots & \cdots \\ 0 & 0 & \cdots & \mathcal{B}_i & \cdots & 0 \\ \cdots & \cdots & \cdots & \cdots & \cdots & \cdots \\ \mathcal{X}_n & 0 & \cdots & 0 & \cdots & \mathcal{B}_n \end{pmatrix}.$$

Thus, the eigenvalues of the Jacobian at the equilibrium $\mathcal{E}$ includes the eigenvalues of the matrix $\mathcal{B}_i$ which has the form $\mathcal{B}_i = e_i \hat{\mathcal{B}}_i$ where

$$\hat{\mathcal{B}}_i = \begin{pmatrix} \mathcal{R}_i \displaystyle\sum_{J\subset M_1} p(\star) S_J - 1 & \mathcal{R}_i \displaystyle\sum_{J\subset M_2} p(\diamond) S_J & \cdots & \mathcal{R}_i \displaystyle\sum_{J\subset M_k} p(\circ) S_J \\ \mathcal{R}_i \displaystyle\sum_{J\subset M_1} p(\star) S_J & \mathcal{R}_i \displaystyle\sum_{J\subset M_2} p(\diamond) S_J - 1 & \cdots & \mathcal{R}_i \displaystyle\sum_{J\subset M_k} p(\circ) S_J \\ & & \cdots & \\ \mathcal{R}_i \displaystyle\sum_{J\subset M_1} p(\star) S_J & \mathcal{R}_i \displaystyle\sum_{J\subset M_2} p(\diamond) S_J & \cdots & \mathcal{R}_i \displaystyle\sum_{J\subset M_3} p(\circ) S_J - 1 \end{pmatrix}.$$

S_J is the corresponding value in the equilibrium $\mathcal{E}$, M_j are indices in $\mathcal{A}_i$, $p(J, M_1, i) = p(\star)$, $p(J, M_2, i) = p(\diamond)$ and $p(J, M_2, i) = p(\circ)$. To find the eigenvalues of $\hat{\mathcal{B}}_i$ we compute the determinant

$$|\hat{\mathcal{B}}_i - \lambda I|.$$

We multiply the first row by -1 and add it to the remaining rows. We obtain a determinant which has $1 + \lambda$ in the first column, except the first entry $-1 - \lambda$ in the diagonal entry for rows $2, \ldots, k$ and zeroes elsewhere. The first row is as before. Then we add each column from the second, to the last, to the first column. The first entry becomes

$$\mathcal{R}_i \sum_{M \in \mathcal{A}_i} \sum_{J: J \subset M} p(J, M, i) S_J - 1 - \lambda.$$

The remaining entries along the diagonal are $-1 - \lambda$ and the entries below the diagonal are zero. Thus, the eigenvalues of $\mathcal{B}_i$ are -1 and $\hat{\mathcal{R}}_i - 1$. Consequently, if $\hat{\mathcal{R}}_i > 1$ then the Jacobian $\mathcal{J}$ has a positive eigenvalue and the corresponding equilibrium $\mathcal{E}$ is unstable. This completes the proof. □

5. Two–Strain Models

We apply the *next–to–kin protection* and *differential protection* models to study the dynamics of a population supporting two co–circulating strains under specific assumptions on $p(J, M, i)$. We simulate the dynamics supported by these models and provide details on the equations and assumptions on $p(J, M, i)$ in the Appendix.

5.1. *Next–to–kin protection model*

We assume a population of two antigenically similar (i.e. strains of a common flu subtype) strains that interact via the *next–to–kin protection* (see Fig. 1). Probabilities p_1 and p_2 denote reduced susceptibility of fully naive individuals ($S_{\{1,1\}}$) to infection with strains 1 and 2, respectively. Following a prior infection, p_3 and p_4 denote the acquired protection against future infections for the susceptible classes $S_{\{3,2\}}$ and $S_{\{2,3\}}$ (respectively). For simplicity, we assume that fully naive individuals become infected with strain 1, and strain 2 with probabilities

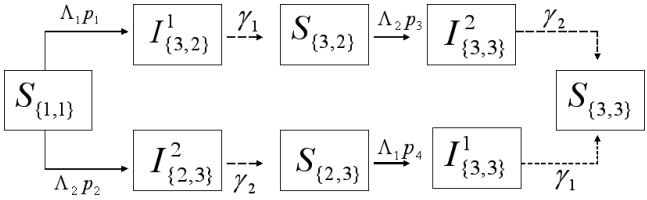


Fig. 1. Schematic diagram of a two–strain model assuming the *next–to–kin protection* framework.

equal to one, respectively (e.g. $p_1 = 1$, $p_2 = 1$). Secondary infections occur with probability p (e.g. $p_3 = p_4 = p$). For a two–strain model, flu may prevail in three possible states. That is, either strain 1 or 2 persist independently, or they coexist. We study the stability of strain 1 ($\mathcal{E}_1^*$) and strain 2 ($\mathcal{E}_2^*$) by letting $\mathcal{W} = (S_{\{1,1\}}, S_{\{2,3\}}, S_{\{3,2\}}, S_{\{3,3\}}, I^1_{\{3,2\}}, I^1_{\{3,3\}}, I^2_{\{2,3\}}, I^2_{\{3,3\}})$ denote the state variables in system (A1) described in the Appendix. Assessment of the equilibrium of a single strain yields $S_{\{2,3\}} = S_{\{3,3\}} = I^1_{\{3,3\}} = I^2_{\{2,3\}} = I^2_{\{3,3\}} = 0$ in (A1) and the boundary equilibria for strains 1 and 2 are given by

$$\mathcal{E}_1^* = (S^*_{\{1,1\}}, 0, S^*_{\{3,2\}}, 0, I^{1*}_{\{3,2\}}, 0, 0, 0)$$

$$\mathcal{E}_2^* = (S^*_{\{1,1\}}, S^*_{\{2,3\}}, 0, 0, 0, 0, I^{2*}_{\{2,3\}}, 0),$$

respectively, where $S^*_{\{1,1\}}$, $S^*_{\{3,2\}}$, $S^*_{\{2,3\}}$, $I^{1*}_{\{3,2\}}$ and $I^{2*}_{\{2,3\}}$ are described in the Appendix.

We evaluate the ability of a particular strain to invade in terms of the invasion reproduction numbers denoted by $\hat{\mathcal{R}}_1$ and $\hat{\mathcal{R}}_2$. We let $\hat{\mathcal{R}}_1$ (also denoted by $\mathcal{R}_1^2$) describes the number of secondary infections generated by a "typical" strain–1 infected individual in a population where strain 2 is endemic ($\mathcal{E}_2^*$). We show that $\mathcal{R}_1^2 < 1$ and $\mathcal{R}_2^1 > 1$ support the stability of $\mathcal{E}_2^*$, while $\mathcal{R}_2^1 < 1$ and $\mathcal{R}_1^2 > 1$ guarantee the stability of $\mathcal{E}_1^*$. Stable coexistence is possible when $\mathcal{R}_2^1 > 1$ or $\mathcal{R}_1^2 > 1$, however, neither strain becomes established when $\mathcal{R}_2^1 < 1$ and $\mathcal{R}_1^2 < 1$. The invasion reproduction number in Eq. (17) takes the form:

$$\hat{\mathcal{R}}_1 \equiv \mathcal{R}_1^2 = \frac{\mathcal{R}_1}{\mathcal{R}_2} + p\frac{\mathcal{R}_1}{\mathcal{R}_2}\frac{\gamma_2(\mathcal{R}_2 - 1)}{(\mu + \gamma_2)}. \tag{18}$$

Similarly, the invasion reproduction number of strain 2 given that strain 1 is at equilibrium ($\mathcal{E}_1^*$) may be obtained by replacing indices 1's by 2's and vice–versa in Eq. (18).

5.2. *Differential protection model*

We apply the *differential* protection approach to evaluate a two–strain scenario among strains in which cross-immunity may or may not conferred (see Fig. 2). This scenario corresponds to a situation in which the strains confer partial or full protection to an antigenically similar strain (of similar subtype). However, this cross-immunity structure may also apply in a situation in which the strains interacting provide some protection against each other and no protection against other strains as it is observed among strains belonging to distinct influenza subtypes (H1N1 and H3N2). In the case when strains are antigenically similar, we assume that immunity is enhanced uniformly with increasing viral exposures (captured by p). However, if strains belong to different subtypes, no cross–immunity is assumed. For instance, assuming an initial probability of 0.6, implies a reduction probability of 0.36 (p^2) against a secondary infection, a reduction of 0.22 against a third infection (p^3), and so on. We make specific assumptions on the probabilities of infection

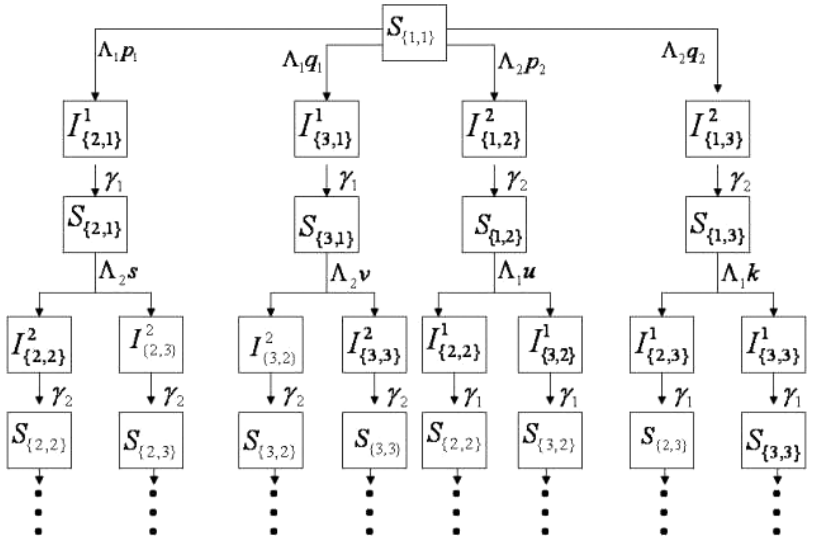


Fig. 2. Schematic diagram of a two–strain model assuming the *differential* protection framework. Susceptible individuals $S_{\{2,2\}}$ (bottom-left box) may get reinfected with strain 1 and progress to infectious class $I^1_{\{3,2\}}$ or progress to infectious class $I^2_{\{2,3\}}$ following reinfection with strain 2.

as shown below in order to simplify our simulations and compare the dynamics of the two–strain models supported by the *NTKP* and *DP*. However, the generality of this framework allows for the simulation of these models without the specific assumptions on p as shown below.

$$\begin{array}{llllll} p_1 = p & \text{and} & q_1 = (1-p) & p_2 = p & \text{and} & q_2 = (1-p) \\ z_1 = p^2 & \text{and} & z_2 = p(1-p) & u_1 = p^2 & \text{and} & u_2 = p(1-p) \\ v_1 = p^2 & \text{and} & v_2 = p(1-p) & k_1 = p^2 & \text{and} & k_2 = p(1-p) \\ x_1 = p^2 & \text{and} & x_2 = p(1-p) & s_1 = p^2 & \text{and} & s_2 = p(1-p) \\ w = p & \text{and} & r = p. & & & \end{array}$$

The boundary equilibria for this model are given by:

$$\mathcal{E}_1^* = (S^*_{\{1,1\}}, S^*_{\{2,1\}}, S^*_{\{3,1\}}, 0,0,0,0,0,0, I^{1*}_{\{2,1\}}, I^{1*}_{\{3,1\}}, 0,0,0,0,0,0,0,0,0,0)$$
$$\mathcal{E}_2^* = (S^*_{\{1,1\}}, 0, 0, S^*_{\{1,2\}}, S^*_{\{1,3\}}, 0,0,0,0,0,0, I^{2*}_{\{1,2\}}, I^{2*}_{\{1,3\}}, 0,0,0,0,0,0,0,0),$$

where

$$I^{1*}_{\{2,2\}} = I^{2*}_{\{2,2\}} = I^{1*}_{\{2,3\}} = I^{2*}_{\{2,3\}} = I^{1*}_{\{3,2\}} = I^{2*}_{\{3,2\}} = I^{1*}_{\{3,3\}} = I^{2*}_{\{3,3\}} = 0,$$

and

$$S^*_{\{2,2\}} = S^*_{\{2,3\}} = S^*_{\{3,2\}} = S^*_{\{3,3\}} = 0.$$

The steady states $S^*_{\{1,1\}}$, $S^*_{\{2,1\}}$, $S^*_{\{3,1\}}$, $S^*_{\{1,2\}}$, $S^*_{\{1,3\}}$, $I^{1*}_{\{3,1\}}$, $I^{1*}_{\{2,1\}}$, $I^{2*}_{\{1,2\}}$, $I^{2*}_{\{1,3\}}$ are provided in the Appendix. We derive the invasion reproduction number of strain 1 while assuming that strain 2 is established as follows:

$$\hat{\mathcal{R}}_1 \equiv \mathcal{R}_1^2 = \frac{\mathcal{R}_1\mu}{\Lambda_2+\mu} + p\xi_1^2[p\mu(\mu+\gamma_2) + (1-p)(\Lambda_2 p+\mu)(\mu+\gamma_2) + p^2\gamma_2\Lambda_2], \quad (19)$$

where

$$\xi_1^2 = \frac{\mathcal{R}_1\Lambda_2\gamma_2}{(\mu+\gamma_2)^2(\mu+\Lambda_2)(\mu+p\Lambda_2)}.$$

The force of infection for strain 2 is given by the unique positive solution of the quadratic in Λ_2, namely

$$\Lambda_2^2\mathcal{A} + \Lambda_2\mathcal{B} + \mathcal{C} = 0, \quad (20)$$

where

$$\mathcal{A} = p(\mu+\gamma_2),$$
$$\mathcal{B} = \mu(\mu+\gamma_2) + p[\mu^2(1-\mathcal{R}_2) + \mu\gamma_2(1-\mathcal{R}_2(1+p))],$$
$$\mathcal{C} = (\mu^2+\mu^2\gamma_2)(1-\mathcal{R}_2).$$

The invasion reproductive number in (19) is evaluated through incorporating 'feasible' solutions in (20). A similar calculation yields $\hat{\mathcal{R}}_2$ (replacing indices 1's by 2's and vice–versa in (19) and finding the corresponding feasible solutions with respect to Λ_1).

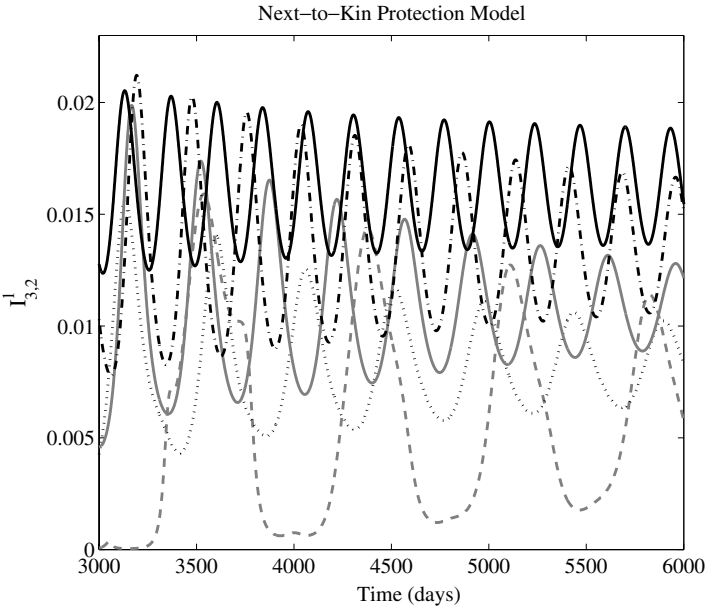
6. Numerical Simulations

We simulate the *next–to–kin* and *differential* protection models for a range of parameter values that describe a disease with mild basic reproduction numbers and ranging cross-immunity levels (see Table 1). Figure 3 illustrates the results for two strain models assuming p values between 0.3 and 0.8. Assuming the $NTKP$

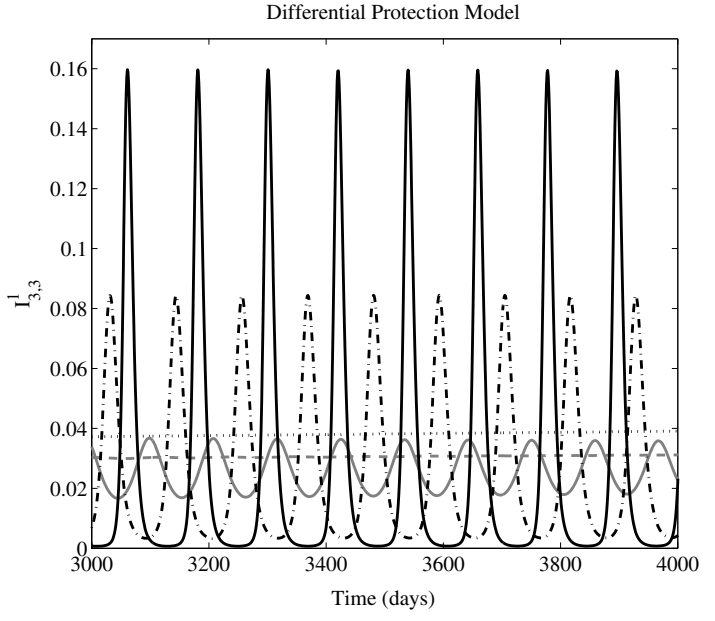
Table 1. Parameter values and initial conditions assumed for simulations. Assumed values represent a hypothetical disease (strains) with a rate of spread as denoted by $\mathcal{R}_i$.

Next–to–kin Model	p	$\beta_i^\dagger$	$\mathcal{R}_i^\dagger$	$\gamma_i^\dagger$ (days^{-1})	μ (days^{-1})	$S_J^\dagger$	$I_M^{i\,\S}$
Fig. 3(a)	(0.3–0.8)	0.25; 0.28	1.2; 1.4	0.2	4×10^{-4}	100	1
Fig. 4	(0.3–0.8)	0.25; 0.28	1.2; 1.4; 1.6	0.2	4×10^{-4}	100	1
Differential Protection Model							
Fig. 3(b)	(0.3–0.8)	0.25; 0.28	1.2; 1.4	0.2	4×10^{-4}	100	1

Note: $^\dagger i = 1, 2$ for strains 1 and 2; $^\ddagger J = \{1, 1\}$ is the immunity index set of the fully susceptible population; $^\S M$ is the immunity index set describing the infectious classes.



(a)



(b)

Fig. 3. Numerical integration of the *next–to–kin* protection model. (a) illustrates $I^1_{\{3,2\}}$ and (b) $I^1_{\{3,3\}}$ for various cross–immunity levels. Incidence levels decrease with increasing cross–immunity. That is, highest levels occurs for $p = 0.8$ (dark–solid) and smallest for $p = 0.3$ (gray–dashed).

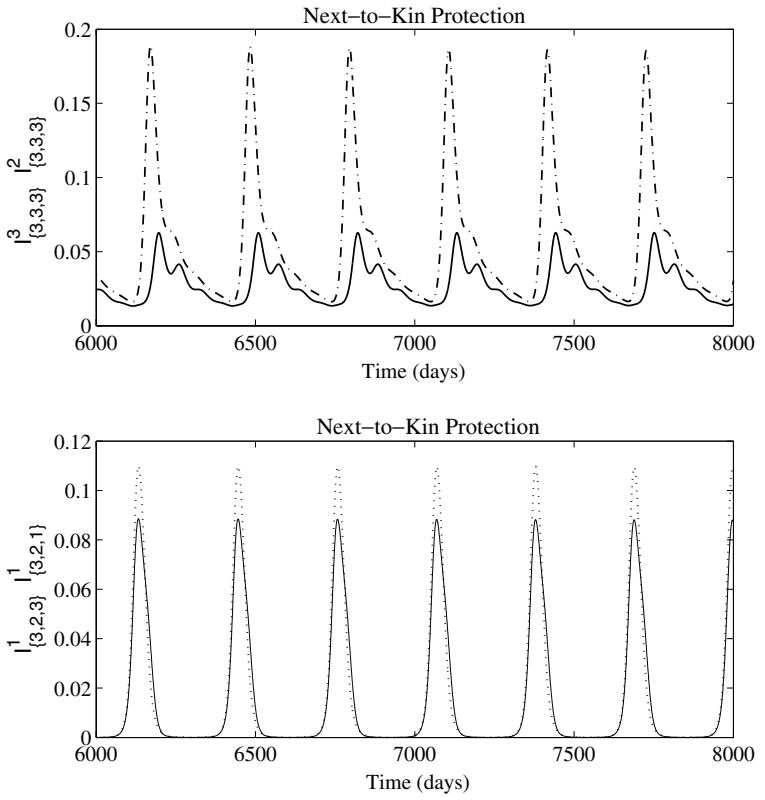


Fig. 4. Numerical integration of the *next–to–kin* protection model for three strains. Top panel illustrates the dynamics of $I^3_{\{3,3,3\}}$ and $I^2_{\{3,3,3\}}$ and bottom panel of $I^1_{\{3,2,3\}}$ and describes the dynamics of $I^1_{\{3,2,1\}}$.

approach, we show that regardless of the levels of cross–immunity, oscillations dampen over time as previously noted.[13,14] However, under the DP model, two strains are sufficient to drive sustained oscillations. To further explore the possibility of oscillatory dynamics in the $NTKP$ approach, we extended the model to include three strains. Our simulations illustrate that three strains are sufficient to support sustained oscillations for a wide range of cross-immunity levels (Fig. 4).

7. Discussion

Multiple strain models have been applied to study the dynamics of co-circulating pathogens and suggest that competition mediated by cross–immunity plays a critical role in determining not only the fate but also the specific qualitative dynamics of disease spread in a population. The early work of Castillo–Chavez *et al.,*[13,14] established that age–dependent survival and cross–immunity among two competing flu strains were significant in supporting sustainable periodic solutions. Nowak and

May[21] show that assuming a framework that allows super–infection in a two–strain model supports high levels of disease virulence which lead to coexistence.

We propose a general framework that can be used to explore specific cross–immunity structures for multiple strain pathogens. We explore the $NTKP$ approach for two and three strain while assuming that strains are arbitrarily close in terms of the host immune response (point mutations). Furthermore, we explore the DP framework among two strains in which cross–immunity is conferred strictly against the currently infecting strain and not the remaining strain.

We provide conditions that guarantee the local and global stability of the equilibrium in the absence of disease ($\mathcal{E}_0$). The global stability ($\mathcal{E}_0$) results suggest that sub–threshold coexistence as discussed in earlier work when applied to influenza[22] cannot occur within this framework. That is, this demonstrates that an invading strain may only become established in a population if its basic reproduction number ($\mathcal{R}_i$) exceeds 1. Assuming that strains invade endemic (coexistence) states, we determine conditions for the invasion of a "new" incoming strain in a population that may be partially protected. In order to illustrate the flexibility of this framework, we evaluate the role of two types of cross-immunity structures. We show that the *next–to–kin* protection (NTKP) model seems unable to support the persistence of periodic solutions, while the *differential* protection model, whose immunity structure is weaker than the $NTKP$ model, is capable of generating sustained oscillations for intermediate to weak the cross–immunity parameters.

The generality of this framework makes it useful for the assessment of the dynamics of various diseases (strains) and their interactions. Here, we illustrate the proposed cross-immunity structures via a limited set of examples, however, the general framework may be applied to include more strains and possibly other cross–immunity structures not discussed herein. As shown in previous studies, our model confirms with two particular examples ($NTKP$ and DP) that cross-immunity plays a significant role in determining the dynamics in a model of competing pathogens. Not surprisingly, we show that reinfection supports the persistence of sustained oscillations and that reducing the pool of susceptible hosts in a population is critical in curtailing disease burden. Under the two-strain $NTKP$ model, the depletion of susceptibles leads to the eventual extinction of both strains. However, including a third strain supports a more dynamic rising and replacement of strains, yielding a new susceptible population that continuously supports the persistence of these strains.

This study differs from other approaches in that we do not assume simultaneous infections; we considered cross–immunity structures not previously explored and applicable to a range of pathogens. However, one of the strengths on this study is that it provides a flexible framework that may be used to explore the role of various cross–immunity structures among multiple strains without restricting the interactions among the competing strains. Although the aim of this study was not to compare the dynamics supported by each of the models discussed, further

assessment of these models are required in order to compare these findings with other multiple strain studies.[3]

Acknowledgments

M. Nuño was partially funded by the Yerby Postdoctoral Fellowship and National Institutes of Health grants T32AI07358 and R01EB006195 during her affiliation with Harvard School of Public Health; most recently, UCLA has supported M. Nuño under National Institutes of Health grant AI28697. M. Martcheva was supported by the NSF grants "DMS-0137687", "DMS-0406119". This research was also partially supported through the visit of M. Nuño and C. Castillo–Chavez to the Statistical and Applied Mathematical Sciences Institute (SAMSI), Research Triangle Park, NC, which is funded by NSF under the grant DMS-0112069. C. Castillo-Chavez is also supported through NSF Grant (DMS-0441114), NSA Grant H98230-05-1-0097 and The Alfred P. Sloan Foundation Grant (016935-001).

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Appendix

Next–to–kin model

The next–of–kin protection model assumes that infection with strain 1 confers partial protection p_3 against a future infection while infection with strain 2 protects against strain 1 with probability p_4. Fully susceptible individuals $S_{\{1,1\}}$ become infected with strains 1 and 2 with probabilities p_1 and p_2, respectively. Infected individuals with strain i recovered at a rate γ_i. Based on the flow diagram illustrated in Fig. 1, we derive the following system of equations.

$$\frac{dS_{\{1,1\}}}{dt} = b - (\Lambda_1 p_1 + \Lambda_2 p_2) S_{\{1,1\}} - \mu S_{\{1,1\}},$$

$$\frac{dS_{\{2,3\}}}{dt} = \gamma_2 I^2_{\{2,3\}} - \Lambda_1 p_4 S_{\{2,3\}} - \mu S_{\{2,3\}},$$

$$\frac{dS_{\{3,2\}}}{dt} = \gamma_1 I^1_{\{3,2\}} - \Lambda_2 p_3 S_{\{3,2\}} - \mu S_{\{3,2\}},$$

$$\frac{dS_{\{3,3\}}}{dt} = \gamma_1 I^1_{\{3,3\}} + \gamma_2 I^2_{\{3,3\}} - \mu S_{\{3,3\}},$$

$$\frac{dI^1_{\{3,2\}}}{dt} = \Lambda_1 p_1 S_{\{1,1\}} - (\mu + \gamma_1) I^1_{\{3,2\}},$$

$$\frac{dI^1_{\{3,3\}}}{dt} = \Lambda_1 p_4 S_{\{2,3\}} - (\mu + \gamma_1) I^1_{\{3,3\}},$$

$$\frac{dI^2_{\{2,3\}}}{dt} = \Lambda_2 p_2 S_{\{1,1\}} - (\mu + \gamma_2) I^2_{\{2,3\}},$$

$$\frac{dI^2_{\{3,3\}}}{dt} = \Lambda_2 p_3 S_{\{3,2\}} - (\mu + \gamma_2) I^2_{\{3,3\}}. \tag{A1}$$

Probabilities of disease reduction can be explicitly given by:

$$p_1 = p(\{1,1\},\{3,2\},1) \quad p_2 = p(\{1,1\},\{2,3\},2)$$
$$p_3 = p(\{3,2\},\{3,3\},2) \quad p_4 = p(\{2,3\},\{3,3\},1).$$

In order to compare the dynamics of the *NTKP* and *DP* models, we assume that $p_1 = p_2 = 1$ and $p_3 = p_4 = p$. Letting p_1 and p_2 equal to 1 means that naive individuals are fully susceptible (noted by $S_{\{1,1\}}$). Similarly, replacing p_3 and p_4 with p implies that individuals previously infected with either strain 1 or 2 conferred partial protection. Here, we assume that this partial protection is the same regardless of whether the former infection was with strain 1 or 2. The steady state of the various epidemiological sub–classes for the *NTKP* model are given by:

$$S^*_{\{1,1\}} = \frac{b}{\Lambda_1 p_1 + \Lambda_2 p_2 + \mu}$$

$$S^*_{\{3,2\}} = \frac{\gamma_1}{(\Lambda_2 p_3 + \mu)} \frac{\Lambda_1 p_1}{(\mu + \gamma_1)} \frac{b}{\Lambda_1 p_1 + \Lambda_2 p_2 + \mu}$$

$$S^*_{\{2,3\}} = \frac{\gamma_2}{(\Lambda_1 p_4 + \mu)} \frac{\Lambda_2 p_2}{(\mu + \gamma_2)} \frac{b}{\Lambda_1 p_1 + \Lambda_2 p_2 + \mu}$$

$$I^{1*}_{\{3,2\}} = \frac{\Lambda_1 p_1}{(\mu + \gamma_1)} \frac{b}{\Lambda_1 p_1 + \Lambda_2 p_2 + \mu}$$

$$I^{2*}_{\{2,3\}} = \frac{\Lambda_2 p_2}{(\mu + \gamma_2)} \frac{b}{\Lambda_1 p_1 + \Lambda_2 p_2 + \mu}.$$

Differential protection model

This model assumes that each strain provides partial protection against itself with probability p and full protection with $1 - p$ (post infection), thereby, providing a

"uniform" enhancement of cross–immunity with increasing infections. We derive the system of equations for the *DP* according to Fig. 2. Note that for simplicity and to facilitate the comparison of simulations for the *NTKP* and *DP* model, we assumed specific choices of protective cross-immunity.

$$\frac{dS_{\{1,1\}}}{dt} = b - \Lambda_1(p_1+q_1)S_{\{1,1\}} - \Lambda_2(p_2+q_2)S_{\{1,1\}} - \mu S_{\{1,1\}},$$

$$\frac{dI^1_{\{2,1\}}}{dt} = \Lambda_1 p_1 S_{\{1,1\}} - (\mu+\gamma_1)I^1_{\{2,1\}},$$

$$\frac{dI^1_{\{3,1\}}}{dt} = \Lambda_1 q_1 S_{\{1,1\}} + \Lambda_1 r S_{\{2,1\}} - (\mu+\gamma_1)I^1_{\{3,1\}},$$

$$\frac{dS_{\{2,1\}}}{dt} = \gamma_1 I^1_{\{2,1\}} - \Lambda_1 r S_{\{2,1\}} - \Lambda_2 s S_{\{2,1\}} - \mu S_{\{2,1\}},$$

$$\frac{dS_{\{3,1\}}}{dt} = \gamma_1 I^1_{\{3,1\}} - \Lambda_2 v S_{\{3,1\}} - \mu S_{\{3,1\}},$$

$$\frac{dI^2_{\{1,2\}}}{dt} = \Lambda_2 p_2 S_{\{1,1\}} - (\mu+\gamma_2)I^2_{\{1,2\}},$$

$$\frac{dI^2_{\{1,3\}}}{dt} = \Lambda_2 q_2 S_{\{1,1\}} + \Lambda_2 w S_{\{1,2\}} - (\mu+\gamma_2)I^2_{\{1,3\}},$$

$$\frac{dS_{\{1,2\}}}{dt} = \gamma_2 I^2_{\{1,2\}} - \Lambda_1 u S_{\{1,2\}} - \Lambda_2 w S_{\{1,2\}} - \mu S_{\{1,2\}},$$

$$\frac{dS_{\{1,3\}}}{dt} = \gamma_2 I^2_{\{1,3\}} - \Lambda_1 k S_{\{1,3\}} - \mu S_{\{1,3\}},$$

$$\frac{dI^1_{\{2,2\}}}{dt} = \Lambda_1 u_1 S_{\{1,2\}} - (\mu+\gamma_1)I^1_{\{2,2\}},$$

$$\frac{dI^1_{\{2,3\}}}{dt} = \Lambda_1 k_1 S_{\{1,3\}} - (\mu+\gamma_1)I^1_{\{2,3\}},$$

$$\frac{dI^1_{\{3,2\}}}{dt} = \Lambda_1 u_2 S_{\{1,2\}} + \Lambda_1 z_1 S_{\{2,2\}} - (\mu+\gamma_1)I^1_{\{3,2\}},$$

$$\frac{dI^2_{\{2,3\}}}{dt} = \Lambda_2 s_2 S_{\{2,1\}} + \Lambda_2 z_2 S_{\{2,2\}} - (\mu+\gamma_2)I^2_{\{2,3\}},$$

$$\frac{dI^2_{\{2,2\}}}{dt} = \Lambda_2 s_1 S_{\{2,1\}} - (\mu+\gamma_2)I^2_{\{2,2\}},$$

$$\frac{dI^2_{\{3,2\}}}{dt} = \Lambda_2 v_1 S_{\{3,1\}} - (\mu+\gamma_2)I^2_{\{3,2\}},$$

$$\frac{dI^1_{\{3,3\}}}{dt} = \Lambda_1 k_2 S_{\{1,3\}} + \Lambda_1 x_1 S_{\{2,3\}} - (\mu+\gamma_1)I^1_{\{3,3\}},$$

$$\frac{dI^2_{\{3,3\}}}{dt} = \Lambda_2 v_2 S_{\{3,1\}} + \Lambda_2 x_2 S_{\{3,2\}} - (\mu + \gamma_2) I^2_{\{3,3\}},$$
$$\frac{dS_{\{2,2\}}}{dt} = \gamma_1 I^1_{\{2,2\}} + \gamma_2 I^2_{\{2,2\}} - \Lambda_1 z_1 S_{\{2,2\}} - \Lambda_2 z_2 S_{\{2,2\}} - \mu S_{\{2,2\}},$$
$$\frac{dS_{\{2,3\}}}{dt} = \gamma_1 I^1_{\{2,3\}} + \gamma_2 I^2_{\{2,3\}} - \Lambda_1 x_1 S_{\{2,3\}} - \mu S_{\{2,3\}},$$
$$\frac{dS_{\{3,2\}}}{dt} = \gamma_1 I^1_{\{3,2\}} + \gamma_2 I^2_{\{3,2\}} - \Lambda_2 x_2 S_{\{3,2\}} - \mu S_{\{3,2\}},$$
$$\frac{dS_{\{3,3\}}}{dt} = \gamma_1 I^1_{\{3,3\}} + \gamma_2 I^2_{\{3,3\}} - \mu S_{\{3,3\}}, \tag{A2}$$

We compare this model with the *NTKP* by assuming the following properties, however, these assumptions may be relaxed as needed:

$$\begin{aligned} p_1 + q_1 &= 1 & p_2 + q_2 &= 1 \\ z_1 + z_2 &= z & u_1 + u_2 &= u \\ v_1 + v_2 &= v & k_1 + k_2 &= k \\ x_1 + x_2 &= x & s_1 + s_2 &= s \end{aligned}$$

We assessed the stability of this model at the following steady states:

$$S^*_{\{1,1\}} = \frac{b}{(\Lambda_1 + \Lambda_2 + \mu)}$$
$$S^*_{\{2,1\}} = \frac{\gamma_1}{(\Lambda_1 r + \Lambda_2 s + \mu)} \frac{\Lambda_1 p_1}{(\mu + \gamma_1)} \frac{b}{(\Lambda_1 + \Lambda_2 + \mu)}$$
$$S^*_{\{3,1\}} = \frac{\gamma_1}{\Lambda_1 v + \mu} \left[\frac{\Lambda_1 q_1}{(\mu + \gamma_1)} + \frac{\Lambda_1 r}{(\mu + \gamma_1)} \frac{\Lambda_1 p_1}{(\mu + \gamma_1)} \frac{\gamma_1}{(\Lambda_1 r + \Lambda_2 s + \mu)} \right] \frac{b}{(\Lambda_1 + \Lambda_2 + \mu)}$$
$$S^*_{\{1,2\}} = \frac{\gamma_2}{(\Lambda_1 u + \Lambda_2 w + \mu)} \frac{\Lambda_2 p_2}{(\mu + \gamma_2)} \frac{b}{(\Lambda_1 + \Lambda_2 + \mu)}$$
$$S^*_{\{1,3\}} = \frac{\gamma_2}{\Lambda_1 k + \mu} \left[\frac{\Lambda_2 q_2}{(\mu + \gamma_2)} + \frac{\Lambda_2 w}{(\mu + \gamma_2)} \frac{\Lambda_2 p_2}{(\mu + \gamma_2)} \frac{\gamma_2}{(\Lambda_1 u + \Lambda_2 w + \mu)} \right] \frac{b}{(\Lambda_1 + \Lambda_2 + \mu)}$$
$$I^{1*}_{\{3,1\}} = \frac{\Lambda_1 q_1}{(\mu + \gamma_1)} \frac{b}{(\Lambda_1 + \Lambda_2 + \mu)} + \frac{\Lambda_1 r}{\mu + \gamma_1} \frac{\gamma_1}{(\Lambda_1 r + \Lambda_2 s + \mu)} \frac{\Lambda_1 p_1}{(\mu + \gamma_1)} \frac{b}{(\Lambda_1 + \Lambda_2 + \mu)}$$
$$I^{1*}_{\{2,1\}} = \frac{\Lambda_1 p1}{(\mu + \gamma_1)} \frac{b}{(\Lambda_1 + \Lambda_2 + \mu)}$$
$$I^{2*}_{\{1,2\}} = \frac{\Lambda_2 p_2}{(\mu + \gamma_2)} \frac{b}{(\Lambda_1 + \Lambda_2 + \mu)}$$
$$I^{2*}_{\{1,3\}} = \frac{\Lambda_2 q_2}{(\mu + \gamma_2)} \frac{b}{(\Lambda_1 + \Lambda_2 + \mu)} + \frac{\Lambda_2 w}{\mu + \gamma_2} \frac{\gamma_2}{(\Lambda_1 u + \Lambda_2 w + \mu)} \frac{\Lambda_2 p_2}{(\mu + \gamma_2)} \frac{b}{(\Lambda_1 + \Lambda_2 + \mu)} \tag{A3}$$