Mathematical Models of Infectious Diseases: Two-Strain Infections in Metapopulations

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Abstract

Viruses and bacteria responsible for infectious diseases often mutate and are carried between geographical regions. We consider a mathematical model which begins to account for these factors. We assume two disjoint populations that only occasionally comingle, and two strains of a disease present in these populations. Of interest are the equations describing the dynamics of this system, the conditions under which epidemics will occur, and the long term behavior of the system under various initial conditions. We find general conditions under which a state of disease-free equilibrium is stable; we examine the sensitivity of our system to changes in modeling parameters; and we find evidence that two disease strains of unequal strength may coexist in a two population system.

Contents

1 Introduction

Mathematical models can provide insight into the dynamics of many important systems which impact us on a daily basis. In particular, modeling disease transmission lends itself nicely to a mathematical approach. Much work has been done on models describing the dynamics of a single population affected by one or more diseases and on the impact of a single disease on multiple, connected populations. Many situations are adequately described by these types of models; in many others, both multiple diseases *and* multiple populations must be considered. We offer some first steps into such an analysis by examining two interconnected populations affected by two strains of a single infectious disease.

We begin with a brief background discussing the SIR model in order to introduce the basics of disease modeling. We include an analysis of the system's initial and long term behavior, with special attention paid to the impact of the *basic reproductive number*. Next, we discuss our two-strain, two-population model, including our modeling assumptions and some general tools for metapopulation modeling. We use this information to construct a system of differential equations describing our model's behavior. We continue by analyzing the various equilibrium states our system may exhibit. We consider three possibilities: disease-free, competitive exclusion, and coexistence, in which zero, one, or two strains, respectively, persist in the population. We conclude with an analysis of the system's sensitivity with respect to modeling parameters.

Though the model discussed here is simplified in many ways, as compared with an actual epidemic scenario, we are able to provide insight into the general behavior of such occurrences and suggest possible directions for future research.

2 Background

Before we examine our two-strain, two-population model, we first consider the basic Susceptible-Infectious-Recovered (SIR) model. Many important concepts are identical between the two models, and will be easier to introduce in this simpler context. In particular, begining with this model will allow us to see the basic dynamics of our system, as well as the major parameters which determine those dynamics. We will consider both the initial and long term behavior of the system, as well as encounter the **basic reproductive number,** R_0, for the first time. Understanding the principles on display here will allow for greater insight as we progress to our full two-strain, two-population model.

2.1 SIR Model

In the SIR model, individuals begin their lives in the susceptible (S) class, enter the infectious (I) class as they contract the disease, and finally move to the recovered (R) class. We assume that recovery from the disease grants life-long immunity; thus individuals in the R class never leave. We assume a closed population; that is, our total population size, N, remains constant ($N = S + I + R$). We have a transmission parameter β, which incorporates factors such as

interpersonal contact rates and transmission probabilities. The per capita rate of recovery from the disease is γ. This gives an exponential distribution of recovery times, with average duration of infection $\frac{1}{\gamma}$. We assume mass action; that is, every individual is equally likely to contact every other individual in the population. Thus, infection is governed by the standard incidence term, $\frac{\beta SI}{N}$.

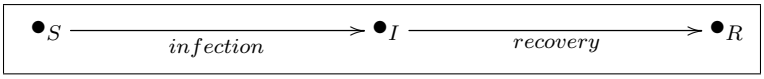

Figure 1: Flow chart describing an individual's movement through the SIR model

The closed population assumption allows us to express one of our state variables (S, I, or R — the variables describing the *state* of our system) in terms of the other two. We choose to eliminite R and focus on the dynamics of S and I. The model is described by the system of differential equations

$$\begin{aligned} \frac{dS}{dt} &= -\frac{\beta SI}{N} \\ \frac{dI}{dt} &= \frac{\beta SI}{N} - \gamma I \end{aligned} \tag{1}$$

with initial conditions $S(0) = S_0$ and $I(0) = I_0$.

2.2 Initial Behavior

Suppose we consider the early stages of an epidemic. We have a small number of infectives and no recovered individuals, while most of the population is suceptible. We can take $S_0 \approx N$ and simplify our system to

$$\begin{aligned} \frac{dS}{dt} &\approx -\beta I \\ \frac{dI}{dt} &\approx \beta I - \gamma I \end{aligned} \tag{2}$$

We see that $\frac{dI}{dt}$ is positive, and thus that I is increasing, if $\beta > \gamma$. Equivalently, we can write $\frac{dI}{dt} > 0$ if $\frac{\beta}{\gamma} > 1$. Similarly, if $\frac{\beta}{\gamma} < 1$ we have $\frac{dI}{dt} < 0$ in the outbreak's initial stage. Biologically, this means that our system will see an epidemic when $\frac{\beta}{\gamma} > 1$, while $\frac{\beta}{\gamma} < 1$ implies the disease will die out before an epidemic can take off. Let us think about the biological interpretation of this quantity: β is the rate at which new infections arise, and $\frac{1}{\gamma}$ is the average duration of infection. Multiplying these quantities, we see that $\frac{\beta}{\gamma}$ is the

average number of secondary infections that an infectious individual gives rise to over the course of his infection. This concept is of paramount importance in any disease model.

Definition 1. *We define the* **basic reproductive number** *of a disease, denoted R_0 to be the average number of secondary infections that a single infectious individual will give rise to over the duration of his infection, in an otherwise entirely susceptible population.*

As we have seen, in the simple SIR model, $R_0 = \frac{\beta}{\gamma}$ and $R_0 = 1$ provides a threshold condition on whether we will experience an epidemic. While the particular expression for R_0 will change depending on the model employed, the concept remains consistant — including the threshold value of $R_0 = 1$.

2.3 Equilibrium Analysis

We have seen what happens in the initial stages of a disease outbreak, so a natural next step is to examine the long term behavior of the system. In particular, we are interested in finding points of equilibrium — points where each of our state variables are unchanging. If our state variables are unchanging their derivatives must be 0, so we set

$$\begin{aligned} \frac{dS}{dt} &= -\frac{\beta SI}{N} = 0 \\ \frac{dI}{dt} &= \frac{\beta SI}{N} - \gamma I = 0. \end{aligned} \tag{3}$$

Let S^* and I^* be the equilibrium values of S and I, respectively. Solving $\frac{dI}{dt} = 0$ gives $I^* = 0$ or $\frac{\beta S}{N} - \gamma = 0 \Rightarrow S^* = \frac{\gamma N}{\beta}$. If $I^* = 0$ then $\frac{dS}{dt} = 0$, is satisfied by any biologically relevant value of S^*. If $S^* = \frac{\gamma N}{\beta}$, then $\frac{dS}{dt} = 0$ is satisfied by $I^* = 0$. We discover that the second point is really just a special case of the first and that our equilibrium point is $(S^*, I^*) = (S^*, 0)$. Our system is in equilibrium once the disease has died out, while some number of susceptibles remain.

3 The Two-Strain, Two-Population Model

The simple SIR model provides a broad framework for disease modeling. We, however, seek to account for the posibilities of disease mutation and of the spread of disease between geographical regions. We begin this process with the natural extension to an SIR-based model with two disease strains and two loosely connected populations.

3.1 Flow Charts

We begin with a visual depiction of our model. We consider two populations ($i = 1$ or 2) in which two strains ($\alpha = A$ or B) of a single infectious disease are present. Our model includes demography - births and deaths. In this compartmental model, for each population people

are born into the susceptible (S_i) classes, become infected by either strain of the disease and enter the infectious (I_i^α) classes, and then transition to the recovered (R_i) classes. Individuals may also leave any class through death.

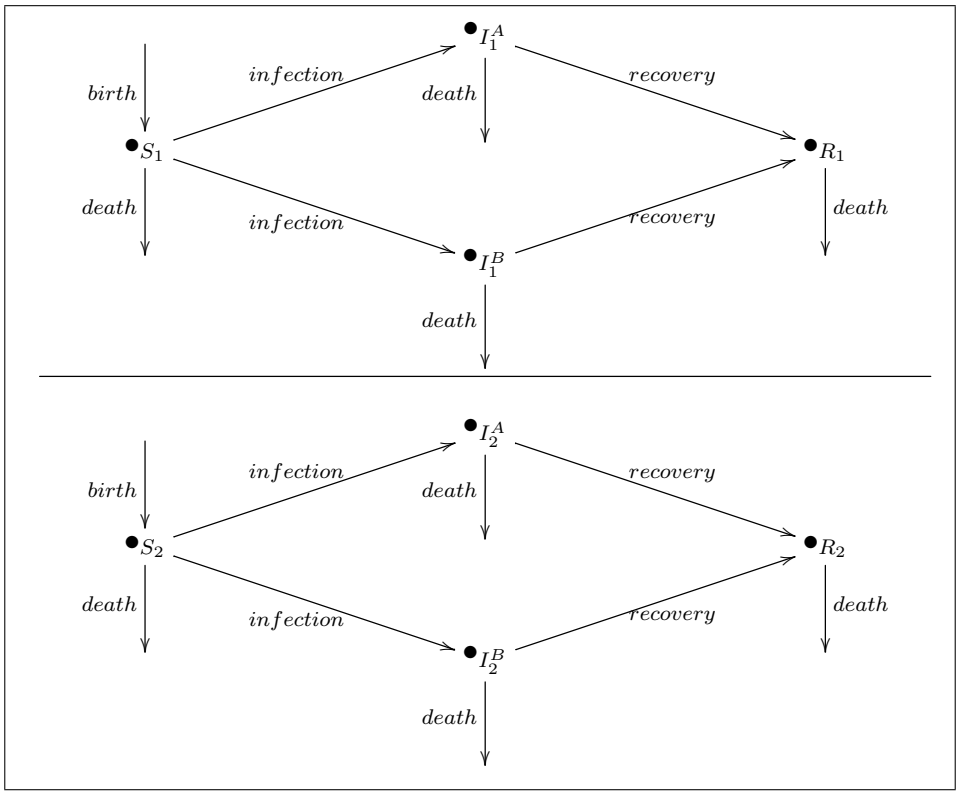

Figure 2: Flow chart describing an individual's movement through our two-strain, two-population SIR model

3.2 Assumptions

In order to simplify the model, we make a number of assumptions. To ensure that each population is closed (N_i is constant) we assume that the per capita birth and death rates are equal. We further assume that this rate is equal for each population. As in the simple SIR model, the closed population assumption allows us to reduce the dimension of our system, while the inclusion of demography ensures that we have a continually replenished supply of susceptible individuals and that our disease will not die out due simply to lack of susceptibles.

We assume that the mixing between populations is temporary (no permanent immigration) and subject to preferred mixing. In preferred mixing the majority of each individual's interpersonal contacts are with members of her own population. We assume that every individual follows the same mixing pattern and that the out-of-group mixing proportion for each population is equal.

We assume that each individual, regardless of population, has the same contact rate per unit time. We further assume that any contact between a susceptible and an infective leads to successful transmission of the disease with probability dependant only on the strain.

Finally, we assume that an infected individual's recovery rate is indepentent of his population and depends only on the strain he is infected with.

3.3 Metapopulation Modeling Basics

Recall from our discussion of the basic SIR model that finding a value of R_0 is a very important step in analyzing our system's behavior. Finding an expression for R_0 in this model is not as straightforward as it was in our simple SIR model. We require a more robust framework in which to express our model.

3.3.1 Mixing Matrix

A mixing matrix describes the manner in which our populations interact. Its entries m_{ij} denote the fraction of contacts made by individuals from group j with individuals from group $i (i, j = 1, 2)$ [2]. We assume that each population's out of group mixing proportion is equal, so for our model

$$M = \frac{1}{1+\epsilon} \begin{bmatrix} 1 & \epsilon \\ \\ \epsilon & 1 \end{bmatrix} \tag{4}$$

The entries of 1 on the diagonal indicate that most contacts are with members from an individual's home group while the ϵ entries on the off diagonal represent the small remaining proportion of each group's contacts. Since these entries represent fractional mixing rates, we must ensure that each column sums to 1. Thus we scale the entire matrix by a factor of $\frac{1}{1+\epsilon}$.

3.3.2 Next Generation Matrix

A next generation matrix describes the transmission of a disease through our various subpopulations. The entry k_{ij} is the number of secondary infections caused in populations i by a single infectious individual in population j [2]. Because we are considering two disease strains, (A and B) we will have two next generation matrices, (K^A and K^B), to describe the transmission of each strain. We now look to actually construct these matrices. Suppose we introduce a single individual infected with strain α of the disease into population j. The average duration of infection is $\frac{1}{\gamma+\mu}$. This corresponds to the amount of time our infectious individual has to spread the disease. Determining the rate at which new infections arise is similarly straightforward. We assumed a constant rate of contact for all individuals; let a denote this number. We also assumed a probability of transmission only depends on the strain involved so let p^α denote this probability for strain α. The rate at which new

infections arise is therefore $a \cdot p^\alpha$ - the total rate of contact multiplied by the probability that each contact is effective. We let $\beta^\alpha = a \cdot p^\alpha$ denote this rate. Thus the toal number of new infections caused by this individual is $\dfrac{\beta^\alpha}{\gamma^\alpha + \mu}$. Finally, the proportion of these new infections which arise in populations i is found by multiplying the total number of new cases by m_{ij}, the fractional contact rate with population i. Putting this all together, we find that $k_{ij}^\alpha = \beta^\alpha \cdot m_{ij} \cdot \dfrac{1}{\gamma^\alpha + \mu}$. This gives the next generation matrices

$$K^A = \begin{bmatrix} \dfrac{\beta^A}{(\gamma^A + \mu)(1+\epsilon)} & \dfrac{\epsilon\beta^A}{(\gamma^A + \mu)(1+\epsilon)} \\ \dfrac{\epsilon\beta^A}{(\gamma^A + \mu)(1+\epsilon)} & \dfrac{\beta^A}{(\gamma^A + \mu)(1+\epsilon)} \end{bmatrix} \tag{5}$$

$$K^B = \begin{bmatrix} \dfrac{\beta^B}{(\gamma^B + \mu)(1+\epsilon)} & \dfrac{\epsilon\beta^B}{(\gamma^B + \mu)(1+\epsilon)} \\ \dfrac{\epsilon\beta^B}{(\gamma^B + \mu)(1+\epsilon)} & \dfrac{\beta^B}{(\gamma^B + \mu)(1+\epsilon)} \end{bmatrix} \tag{6}$$

3.3.3 Finding $\mathbf{R_0}$

We can use the next generation matrix to find an R_0 value for each strain. If we let ϕ_m^α be a vector describing the number of invectives in each population after m generations of strain α, it can be shown [2] that

$$\phi_m^\alpha = \sum_{j=1}^{n} c_j \lambda_j^m \Psi_j, \tag{7}$$

where c_j is a constant and Ψ_j is an eigenvector of K with the corresponding eigenvalue, λ_j. If K has a largest eigenvalue λ_1 then for large values of m,

$$\phi_m^\alpha \approx c_1 \lambda_1^m \Psi_1 \tag{8}$$

That is, the number of incentives increases by a factor of λ_1 with each generation. This matches exactly with our definition of R_0. Thus R_0^α is the dominant eigenvalue of the next generation matrix, K^α [2].

3.4 Equations

The differential equations describing our system are similar to those of the SIR model (1), but have more complexity. Note that $\dot{X}$ is a shorthand notation for $\dfrac{dX}{dt}$.

$$
\begin{aligned}
\dot{S}_1 &= \mu N_1 - \mu S_1 - S_1(\beta_{11}^A I_1^A + \beta_{12}^A I_2^A + \beta_{11}^B I_1^B + \beta_{12}^B I_2^B) \\
\dot{S}_2 &= \mu N_2 - \mu S_2 - S_2(\beta_{21}^A I_1^A + \beta_{22}^A I_2^A + \beta_{21}^B I_1^B + \beta_{22}^B I_2^B) \\
\dot{I}_1^A &= S_1(\beta_{11}^A I_1^A + \beta_{12}^A I_2^A) - (\gamma^A + \mu) I_1^A \\
\dot{I}_2^A &= S_2(\beta_{21}^A I_1^A + \beta_{22}^A I_2^A) - (\gamma^A + \mu) I_2^A \\
\dot{I}_1^B &= S_1(\beta_{11}^B I_1^B + \beta_{12}^B I_2^B) - (\gamma^B + \mu) I_1^B \\
\dot{I}_2^B &= S_2(\beta_{21}^B I_1^B + \beta_{22}^B I_2^B) - (\gamma^B + \mu) I_2^B
\end{aligned}
\tag{9}
$$

β_{ij}^{α} is the transmission rate of strain α from population j to i. We have $\beta_{ij}^{\alpha} = \dfrac{\beta^{\alpha} m_{ij}}{N_i}$. We will write our transmission rates as β_{ij}^{α} when we value succinctness and as $\dfrac{\beta^{\alpha} m_{ij}}{N_i}$ when it is more advantageous to reduce the number of parameters in the system.

μ is our per capita birth and death rate. μN_1 is the rate at which individuals are born into the S_1 class and μS_1 is the rate at which they leave it via death. Infection is again governed by the standard incidence term; here, though, susceptible individuals from population 1 may become infected with either strain A or B of the disease, and may acquire the infection from an individual in either population 1 or 2. $\dot{S}_2$ is entirely symmetric.

In each of our $\dot{I}_i^{\alpha}$ equations, the positive term corresponds to the individuals exiting the S_i class, after having acquired strain α of the infection. $\gamma^{\alpha} + \mu$ is the rate at which individuals leave the class, through either recovery or death. As in the SIR model, this implies that the duration of infection is exponentially distributed, with mean $\dfrac{1}{\gamma^{\alpha} + \mu}$.

Finally, we supress the equations for $\dot{R}_i$, as the values of R_i can be calculated by $N_i - (S_i + I_i^A + I_i^B)$. This allows us to reduce the dimension of our system and focus solely on the most interesting population dynamics.

4 Equilibrium Analysis

4.1 Disease-Free

We begin our equilibrium analysis with the simplest type of equilibrium — disease-free. In this case, neither strain of our disease is present in either of our populations. The enitre population is susceptible.

4.1.1 Finding Equilibrium Point

By solving

$$
\dot{I}_1^A = S_1(\beta_{11}^A I_1^A + \beta_{12}^A I_2^A) - (\gamma^A + \mu) I_1^A = 0 \tag{10}
$$

for I_1^A we find

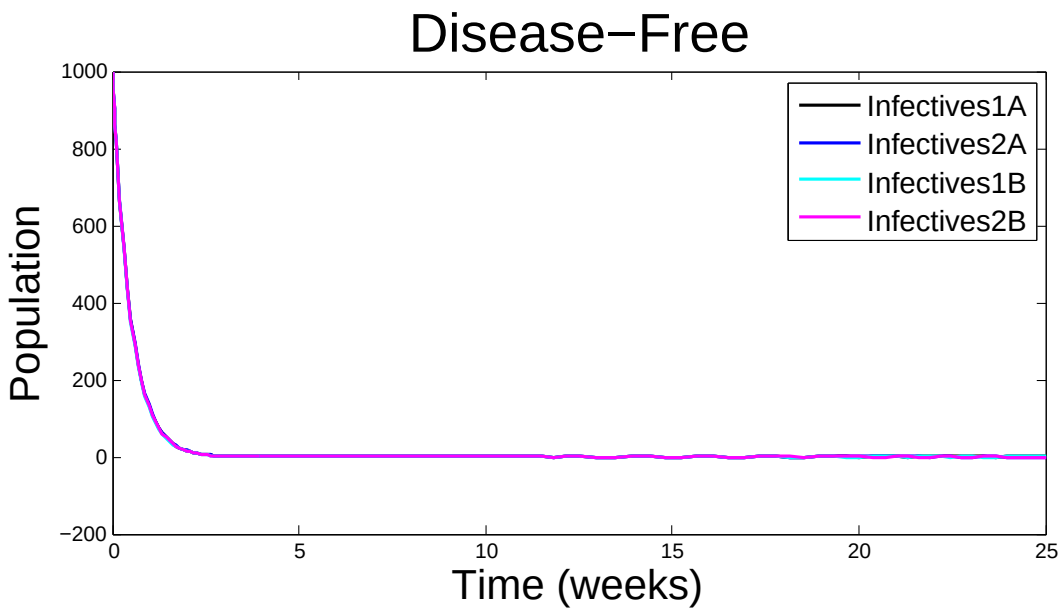

Figure 3: $R_0^A \approx 0.67, R_0^B \approx 0.81, N_1 = 100000, N_2 = 150000, \epsilon = .1, \mu = \frac{1}{70*52}$ 600 initial infectives in each infective class

$$I_1^A = \frac{-S_1(\beta_{12}^A I_2^A)}{S_1\beta_{11}^A - (\gamma^A + \mu)}. \tag{11}$$

Substituting this expression into $\dot{I}_2^A$ and then factoring gives

$$0 = I_2^A \left(\frac{-S_1 S_2 \beta_{12}^A \beta_{21}^A}{S_1\beta_{11}^A - \mu - \gamma^A} + \beta_{22}^A S_2 - \mu - \gamma^A \right). \tag{12}$$

Because we are first interested in disease-free equilibrium, we will take $I_2^A = 0$. Plugging this into our previous expression for I_1^A gives $I_1^A = 0$. Through an entirely similar process we can find that $I_1^B = I_2^B = 0$ satisfies $\dot{I}_1^B = \dot{I}_2^B = 0$.

With these four conditions, we find that $\dot{S}_1 = \dot{S}_2 = 0$ is only satisfied by $S_1 = N_1$ and $S_2 = N_2$. We now have our disease free equilibrium point (see Figure 3):

$$\begin{aligned} &(S_1, S_2, I_1^A, I_2^A, I_1^B, I_2^B) \\ =&(N_1, N_2, 0, 0, 0, 0) \end{aligned} \tag{13}$$

4.1.2 Stability Analysis

To determine the stability of disease-free equilibrium, we first evaluate the Jacobian matrix, J, at the equilibrium point:

$$J(N_1, N_2, 0, 0, 0, 0) = \begin{bmatrix} -\mu & 0 & -N_1\beta_{11}^A & -N_1\beta_{12}^A & -N_1\beta_{11}^B & -N_1\beta_{12}^B \\ 0 & -\mu & -N_2\beta_{21}^A & -N_2\beta_{22}^A & -N_2\beta_{21}^B & -N_2\beta_{22}^B \\ 0 & 0 & N_1\beta 11^A - (\mu + \gamma^A) & N_1\beta_{12}^A & 0 & 0 \\ 0 & 0 & N_2\beta 21^A & N_2\beta_{21}^A - (\mu + \gamma^A) & 0 & 0 \\ 0 & 0 & 0 & 0 & N_1\beta 11^B - (\mu + \gamma^B) & N_1\beta_{12}^B \\ 0 & 0 & 0 & 0 & N_2\beta 21^B & N_2\beta_{21}^B - (\mu + \gamma^B) \end{bmatrix}$$

Next, we find the eigenvalues of J:

$$\lambda = \begin{cases} -\mu \\ -\mu \\ \beta^A - \gamma^A - \mu \\ -\dfrac{\mu + \mu\epsilon + \gamma^A\epsilon + \gamma^A - \beta^A + \beta^A\epsilon}{1+\epsilon} \\ \beta^B - \gamma^B - \mu \\ -\dfrac{\mu + \mu\epsilon + \gamma^B\epsilon + \gamma^B - \beta^B + \beta^B\epsilon}{1+\epsilon} \end{cases} \tag{14}$$

The equilibrium is stable whenever the real component of each eigenvalue is negative. Since we assume $\mu > 0$ we have $-\mu < 0$ under all conditions. To satisfy

$$\beta^A - (\gamma^A + \mu) < 0$$

we must have

$$\beta^A < \gamma^A + \mu \Rightarrow R_0^A = \frac{\beta^A}{\gamma^A + \mu} < 1.$$

For our fourth eigenvalue, we have

$$\begin{aligned} -\frac{\mu + \mu\epsilon + \gamma^A\epsilon + \gamma^A - \beta^A + \beta^A\epsilon}{1+\epsilon} &= \\ \frac{(1-\epsilon)\beta^A}{1+\epsilon} - (\gamma^A + \mu) &< \\ \beta^A - (\gamma^A + \mu). & \end{aligned}$$

Thus, this eigenvalue is also negative whenever $R_0^A < 1$. By an entirely similar analysis, we find that our final two eigenvalues are both negative precisely when $R_0^B < 1$ and so all eigenvalues are negative if and only if R_0^A, $R_0^B < 1$. This implies that disease-free equilibrium is stable iff the R_0 value for each strain is less than 1.

4.1.3 Generalizing Disease-Free Equilibrium

Because disease-free equilibrium is relatively simple, we seek to extend our findings to metapopulation models considering any number of disease strains and any number of populations.

Theorem: In a metapopulation consisting of n sub-populations and m disease strains, whose dynamics are governed by an SIR model with identical assumptions to our 2-strain, 2-population model, the disease free equilibrium is stable if and only if $R_0^\alpha < 1$ for each strain α.

Proof: If we have n populations and m strains, then the differential equations modelling our scenario are given by:

$$\begin{aligned} \dot{S}_i &= \mu N_i - \mu S_i - S_i \left(\sum_\alpha \sum_{j=1}^{n} \beta_{ij}^\alpha I_j^\alpha \right) \\ \dot{I}_i^\alpha &= S_i \left(\sum_{j=1}^{n} \beta_{ij}^\alpha I_j^\alpha \right) - (\gamma^\alpha + \mu) I_i^\alpha \end{aligned} \tag{15}$$

The partial derivatives of our equations with respect to our state variable (S's and I's), evaluated at equilibrium, are:

$$\begin{aligned} \frac{\partial \dot{S}_i}{\partial S_j} &= \begin{cases} 0 & i \neq j \\ -\mu & i = j \end{cases} \\ \frac{\partial \dot{S}_i}{\partial I_j^\alpha} &= -S_i \beta_{ij}^\alpha \\ \frac{\partial \dot{I}_i^\alpha}{\partial S_j} &= 0 \\ \frac{\partial \dot{I}_i^\alpha}{\partial I_j^\kappa} &= \begin{cases} 0 & \kappa \neq \alpha \\ S_i \beta_{ij}^\alpha & \kappa = \alpha, i \neq j \\ S_i \beta_{ij}^\alpha - (\gamma^\alpha + \mu) & \kappa = \alpha, i = j \end{cases} \end{aligned} \tag{16}$$

By dividing our Jacobian matrix into 4 blocks, M_{ij}, we see that M_{21} is the 0-matrix and so our Jacobian, J, is block upper-triangular. The eigenvalues of J are simply the union of the eigenvalues of M_{11} and M_{22}. M_{11} is diagonal, with diagonal entries $-\mu$, so its eigenvalues are simply $-\mu$, with multiplicity n. M_{22} is more complicated, but it too is block diagonal. It consists of m nxn blocks on the diagonal, composed of the $\dfrac{\partial \dot{I}_i^\alpha}{\partial I_j^\alpha}$ entries, while every other entry is 0. The eigenvalues of M_{22} are the union of the eigenvalues of each block, A^α.

To find these eigenvalues we will compute $|A^\alpha - \lambda I|$ and find the values of λ which make this determinant equal to 0. Each of these blocks is of the form:

$$A = \begin{bmatrix} y-x & y & \dots & y \\ y & y-x & \ddots & \vdots \\ \vdots & \ddots & \ddots & y \\ y & \dots & y & y-x \end{bmatrix}$$

where

$$y = \frac{\epsilon\beta}{1+(n-1)\epsilon}$$
$$x = \frac{(\epsilon-1)\beta}{1+(n-1)\epsilon} - (\gamma+\mu+\lambda).$$

In each block, the only thing that changes is the letter on β and γ, indicating the strain of the disease; so finding the eigenvalues of this general block will allow us to find the eigenvalues of M_{22}. Our challenge, therefore, is first to compute $det(A)$. Consider the sequences a_i and b_i defined by:

$$a_i = \begin{cases} y-x & i=0 \\ (y-x)a_{i-1} - iyb_{i-1} & i \geq 1 \end{cases} \tag{17}$$

and

$$b_i = \begin{cases} y & i=0 \\ b_i = ya_{i-1} - iyb_{i-1} & i \geq 1 \end{cases} \tag{18}$$

Let A_{nxn} be an nxn matrix of the form

$$\begin{bmatrix} y-x & y & \dots & y \\ y & y-x & \ddots & \vdots \\ \vdots & \ddots & \ddots & y \\ y & \dots & y & y-x \end{bmatrix}$$

and B_{nxn} be an nxn matrix of the form

$$\begin{bmatrix} y & y & \dots & y \\ y & y-x & \ddots & \vdots \\ \vdots & \ddots & \ddots & y \\ y & \dots & y & y-x \end{bmatrix}.$$

Claim: a_{n-1} gives the determinant for A_{nxn} and b_{n-1} gives the determinant for B_{nxn}.

Proof: We prove the claim by induction on n. For $n = 1$ we have $A_{1\text{x}1} = det(A_{1\text{x}1}) = y - x = a_0$ and $B_{1\text{x}1} = det(B_{1\text{x}1}) = y = b_0$.

Now suppose the claim holds for all $n < k$. First we introduce some notation: Let $B^0_{nxn} = B_{nxn}$ and for $1 < i < n$ let $B^i_{nxn} = B^{nxni-1}$ with the $(i-1)^{st}$ and i^{th} rows interchanged. Suppose we perform cofactor expansion along the top row of A_{nxn}. Then we have

$$det(A_{nxn}) = (y-x)det(A_{(n-1)\text{x}(n-1)}) - y\sum_{i=0}^{n} det(B^i_{(n-1)\text{x}(n-1)})$$

Notice that for i even we can change $B^i_{(n-1)\text{x}(n-1)}$ to $B^0_{(n-1)\text{x}(n-1)}$ by performing an even number of row switches, and thus $det(B^i_{(n-1)\text{x}(n-1)}) = det(B^0_{(n-1)\text{x}(n-1)}) = det(B_{(n-1)\text{x}(n-1)})$. Similarly, for i odd $det(B^i_{(n-1)\text{x}(n-1)}) = -det(B_{(n-1)\text{x}(n-1)})$. Then we have

$$\begin{aligned} det(A_{nxn}) &= (y-x)det(A_{(n-1)\text{x}(n-1)}) - y\sum_{i=0}^{n} det(B_{(n-1)\text{x}(n-1)}) \\ &= (y-x)det(A_{(n-1)\text{x}(n-1)}) - (n-1)ydet(B_{(n-1)\text{x}(n-1)}). \end{aligned}$$

By the induction hypothesis, $(A_{(n-1)\text{x}(n-1)}) = a_{n-2}$ and $det(B_{(n-1)\text{x}(n-1)} = b_{n-2}$ and so

$$det(A_{nxn}) = (y-x)a_{n-2} - (n-1)ydetb_{n-2} = a_{n-1}$$

as claimed.

Performing cofactor expansion along the top row of B_{nxn} and using the same method as above, we find

$$det(B_{nxn}) = ya_{n-2} - (n-1)ydetb_{n-2} = b_{n-1}.$$

Thus the claim holds for all n. $\square$

Claim: a_i and b_i have closed forms given by

$$a_i = (-1)^i\left[(i+1)x^iy - x^{i+1}\right]$$

and

$$b_i = (-1)^i(x^iy).$$

Proof: We prove the claim by induction on i. For $i = 0$ we have

$$a_0 = (y-x) = (-1)^0\left[x^0y - x\right]$$

and

$$b_0 = y = (-1)^0 \left(x^0 y\right).$$

Now suppose that for $i = k$ the claim holds. Then for $i = k+1$ we have:

$$\begin{aligned}
&a_{k+1} && = \\
&(y-x)a_k - (k+1)yb_k && = \\
&(y-x)\left[(-1)^k\left((k+1)x^k y - x^{k+1}\right)\right] - (k+1)y\left[(-1)^k x^k y\right] && = \\
&(-1)^k(k+1)x^k y^2 - (-1)^k x^{k+1} y - (-1)^k(k+1)x^{k+1} y - (-1)^k(k+1)x^k y^2 && = \\
&-(-1)^k x^{k+1} y - (-1)^k(k+1)x^{k+1} y && = \\
&(-1)(-1)^k\left[x^{k+1} y + (k+1)x^{k+1} y - x^{k+2}\right] && = \\
&(-1)^{k+1}\left[(k+2)x^{k+1} y - x^{k+2}\right]
\end{aligned}$$

as claimed. We also have:

$$\begin{aligned}
&b_{k+1} && = \\
&ya_k - (k+1)b_k && = \\
&y\left[(-1)^k\left((k+1)x^k y - x^{k+1}\right)\right] - (k+1)y\left[(-1)^k x^k y\right] && = \\
&(-1)^k\left[(k+1)x^k y^2 - x^{k+1} y\right] - (-1)^k(k+1)x^k y^2 && = \\
&(-1)^k(-x^{k+1} y) && = \\
&(-1)^{k+1}(x^{k+1} y)
\end{aligned}$$

as claimed. Thus the claim holds for all i. □

Now that we have an expression for $det(A)$ we can compute the eigenvalues of A.

Claim: The eigenvalues of A_{nxn} are

$$\lambda = \beta - (\gamma + \mu)$$

with multiplicity 1 and

$$\lambda = \frac{(1-\epsilon)\beta}{1 + (n-1)\epsilon} - (\gamma + \mu)$$

with multiplicity $(n-1)$.

Proof: We have just shown that

$$det(A_{nxn}) = a_{n-1} = (-1)^{n-1}\left(nx^{n-1} y - x^n\right) = (-1)^{n-1} x^{n-1}(ny - x).$$

Substituting in values for x and y as defined above, we have:

$$
\begin{aligned}
a_{n-1} & = \\
(-1)^{n-1}\left[\frac{(\epsilon-1)\beta}{1+(n-1)\epsilon}+(\gamma+\mu+\lambda)\right]^{n-1}\left[n\frac{\epsilon\beta}{1+(n-1)\epsilon}-\frac{(\epsilon-1)\beta}{1+(n-1)\epsilon}+(\gamma+\mu+\lambda)\right] & = \\
(-1)^{n-1}\left[\frac{(\epsilon-1)\beta}{1+(n-1)\epsilon}+(\gamma+\mu+\lambda)\right]^{n-1}\left[\frac{n\epsilon\beta-(\epsilon-1)\beta}{1+(n-1)\epsilon}-(\gamma+\mu)-\lambda\right] & = \\
(-1)^{n-1}\left[\frac{(\epsilon-1)\beta}{1+(n-1)\epsilon}+(\gamma+\mu+\lambda)\right]^{n-1}\left[\frac{\beta\left((n-1)\epsilon+1\right)}{(n-1)\epsilon+1}-(\gamma+\mu)-\lambda\right] & = \\
(-1)^{n-1}\left[\frac{(\epsilon-1)\beta}{1+(n-1)\epsilon}+(\gamma+\mu+\lambda)\right]^{n-1}\left[\beta-(\gamma+\mu)-\lambda\right] &
\end{aligned}
$$

Setting $a_{n-1}=0$ we see that

$$\left(\frac{(\epsilon-1)\beta}{1+(n-1)\epsilon}+(\gamma+\mu+\lambda)\right)^{n-1}=0$$

or

$$(\beta-(\gamma+\mu)-\lambda)=0.$$

The first case gives

$$
\begin{aligned}
\lambda &= -\left(\frac{(\epsilon-1)\beta}{1+(n-1)\epsilon}+(\gamma+\mu)\right) \\
&= \left(\frac{(1-\epsilon)\beta}{1+(n-1)\epsilon}-(\gamma+\mu)\right)
\end{aligned}
$$

with multiplicity $(n-1)$. The second case gives

$$\lambda=\beta-(\gamma+\mu)$$

with multiplicity 1. Thus the eigenvalues of A are as claimed. □
As in the 2-strain, 2-population case of disease-free equilibrium, we have $\beta-(\gamma+\mu)<1$ when $R_0<1$. Also as before, we have

$$\left(\frac{(1-\epsilon)\beta}{1+(n-1)\epsilon}-(\gamma+\mu)\right)<\beta-(\gamma+\mu)$$

and thus each eigenvalue of A is negative iff $R_0<1$. Because A is the general form for each of our sub-blocks A^α of M_{22}, the eigenvalues of A^α are negative for each α iff $R_0^\alpha<1$ for each α.

Recall that the eigenvalues of our Jacobian, J, were the union of the eigenvalues of blocks M_{11} and $M22$. We have just found the eigenvalues of M_{22} and determined when they are negative and M_{11} had eigenvalues $-\mu$, with multiplicity n, which are always negative. So J has negative eigenvalues — and thus disease-free equilibrium is stable — iff $R_0^\alpha<1$ for each strain α. ■

4.2 Competitive Exclusion

Our second type of equilibrium is competitive exclusion. This equilibrium occurs when one strain in the populations is stronger than the other strain, causing the weaker strain to die out. Only one strain will be present in the long term of our populations.

4.2.1 Finding Equilibrium Point

Referring to equation (9), we find the equation where $\dot{I}_2^A = 0$. Using (12), we know to satisfy the expression, $I_2^A = 0$ or $\left(\frac{-S_1 S_2 \beta_{12}^A \beta_{21}^A}{S_1 \beta_{11}^A - \mu - \gamma^A} + \beta_{22}^A S_2 - \mu - \gamma^A\right) = 0$. We also know that when $I_2^A = 0$, then $I_1^A = 0$. This gives us the equilibrium point for the strain that will die out.

Knowing that strain B can be computed the same way as strain A, and that we want a strain to be present in the population, we know

$$I_1^B = \frac{-S_1(\beta_{12}^B I_2^B)}{S_1 \beta_{11}^B - (\gamma^A + \mu)}. \tag{19}$$

This gave us the equilibrium point for I_1^B. We also know that substituting I_1^B into $\dot{I}_2^B$ and then factoring gives

$$0 = I_2^B \left(\frac{-S_1 S_2 \beta_{12}^B \beta_{21}^B}{S_1 \beta_{11}^B - \mu - \gamma^B} + \beta_{22}^B S_2 - \mu - \gamma^B\right). \tag{20}$$

Since we do not want $I_2^B = 0$, we used

$$\left(\frac{-S_1 S_2 \beta_{12}^B \beta_{21}^B}{S_1 \beta_{11}^B - \mu - \gamma^A} + \beta_{22}^B S_2 - \mu - \gamma^A\right) = 0. \tag{21}$$

to satisfy the equation.

By solving (ref) for S_2 we find

$$S_2 = \frac{\gamma^B + \mu}{\left(\frac{\beta_{21}^B S_1 \beta_{12}^B}{S_1 \beta_{11}^B - (\gamma^B + \mu)} + \beta_{22}^B\right)} \tag{22}$$

By solving

$$\dot{S}_2 = \mu N_2 - \mu S_2 - S_2(\beta_{21}^A I_1^A + \beta_{22}^A I_2^A + \beta_{21}^B I_1^B + \beta_{22}^B I_2^B) = 0 \tag{23}$$

for S_1 when S_2 satisfies equation (22) $I_i^A = 0$ and when I_1^B satisfies equation (19), we find

$$S_1 = \frac{-2\mu^2\gamma^B + \mu^3 + I_2^B(\gamma^B)^2\beta_{22}^B - \mu N_2 \beta_{22}^B \gamma^B + 2I_2^B \mu \beta_{22}^B \gamma^B + I_2^B \mu^2 \beta_{22}^B + \mu(\gamma^B)^2 - \mu^2 N_2 \beta_{22}^B}{\mu^2 \beta_{11}^B - \beta_{11}^B I_2^B \mu \beta_{22}^B + \beta_{11}^B \mu N_2 \beta_{22}^B - \beta_{11}^B I_2^B \gamma^B \beta_{22}^B - \mu \beta_{11}^B \gamma^B + I_2^B \mu \beta_{12}^B \beta_{21}^B - \mu N_2 \beta_{12}^B \beta_{21}^B + I_2^B \gamma^B \beta_{12}^B \beta_{21}^B}$$

Finding our last state variable I_2^B, we use $\dot{S}_1 = 0$ and all the other solved state variables to give us an expression all in our parameters. Since I_2^B was such a large expression, we use

✠to represent the equation.

We now have our equilibrium point.

$$\begin{cases} S1 = \dfrac{-\mu^2 N_2 \beta_{22}^B - \mu N_2 \beta_{22}^B + \mu^3 + 2\mu^2 \gamma^B + I_2^B \beta_{22}^B \mu^2 + 2 I_2^B \beta_{22}^B \mu \gamma^B + I_2^B \beta_{22}^B (\gamma^B)^2}{\mu N_2 \beta_{21}^B \beta_{12}^B - \mu N_2 \beta_{22}^B \beta_{11}^B + \beta 11^B \mu^2 + \beta_{11}^B \mu \gamma^B - I_2^B \mu \beta_{21}^B \beta 12^B + I_2^B \mu \beta_{22}^B \beta_{12}^B - I_2^B \gamma^B \beta 12^B \beta_{21}^B + I_2^B \gamma^B \beta_{22}^B \beta_{11}^B} \\ S2 = \dfrac{\mu + \gamma^B}{\beta_{22}^B - \dfrac{S_1 \beta_{12}^B \beta_{21}^B}{S_1 \beta_{11}^B + (\mu + \gamma^B)}} \\ I_1^A = 0 \\ I_2^A = 0 \\ I_1^B = \dfrac{-S_1 (\beta_{12}^B I_2^B)}{S_1 \beta_{11}^B - (\gamma^B + \mu)} \\ I_2^B = ✠^B \end{cases}$$

By using an entirely similar process where the I_i^A are 0, we can find the competitive exclusion when strain B is the weak strain.

4.2.2 Stability Analysis

To determine the stability of competitive exclusion equilibrium, we find that our large explicit solution for our equilibrium point makes proving stability difficult. However, using simulations in *MATLAB*, we are able to analyze what is happening in the long term.

By changing the different initial values for the infected classes, we are able to show that the equilibrium was stable only as long as one $R_0 \geq 1$ and larger than the other R_0 value. To be more specific, when the R_0 of one strain is greater than one and larger than the other strain's R_0, the weaker strain will be excluded (Figures 4, 5).

4.3 Coexistence

Coexistence, the most complicated form of equilibrium, is even more complicated to solve explicity in terms of parameters than our previous equilibriums were. Becuase of this, we have not explicity solved our coexistence equilibrium. However, even without fully solving the system of equations for a point of equilibrium, it is possible to determine the conditions for which a coexistence equilibrium can potentially occur.

Recall from previous work with competitive exclusion that solving the system of equations $\dot{I}_1^A = \dot{I}_2^A = \dot{I}_1^B = \dot{I}_2^B = 0$ yields the following two equations:

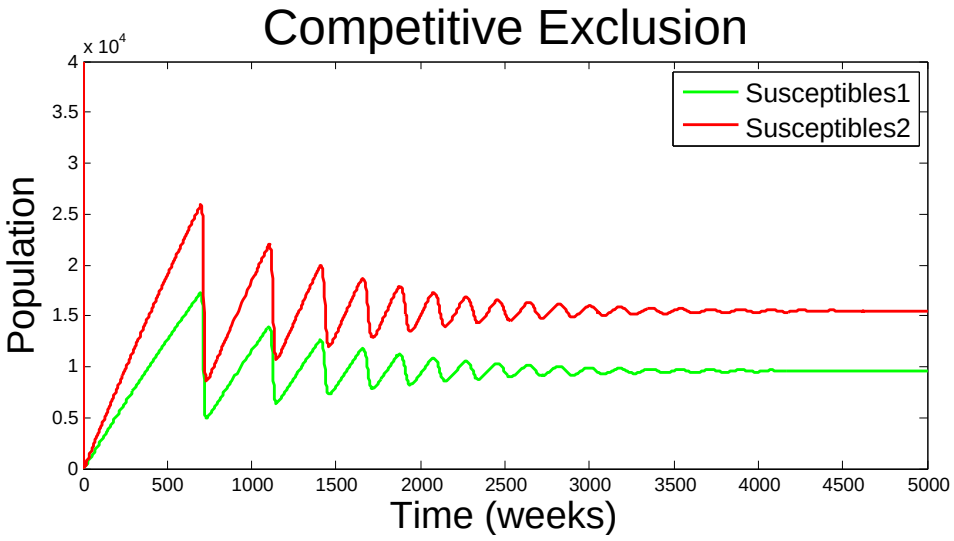

Figure 4: $R_0^A = 2.69, R_0^B = 13.46, N_1 = 100000, N_2 = 150000, \epsilon = .1, \mu = \frac{1}{70*52}$

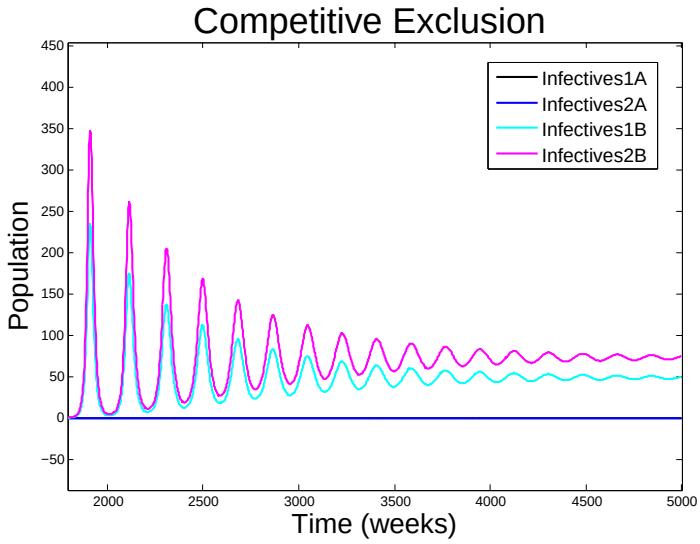

Figure 5: Infectives from Figure 4. Note that strain A is forced to extinction, while strain B persists.

$$0 = I_2^{A*}\left(\frac{-S_1^* S_2^* \beta_{12}^A \beta_{21}^A}{S_1^* \beta_{11}^A - \mu - \gamma^A} + \beta_{22}^A S_2^* - \mu - \gamma^A\right) \tag{24}$$

$$0 = I_2^{B*}\left(\frac{-S_1^* S_2^* \beta_{12}^B \beta_{21}^B}{S_1^* \beta_{11}^B - \mu - \gamma^B} + \beta_{22}^B S_2^* - \mu - \gamma^A\right) \tag{25}$$

In order to find conditions for coexistence, we assume $I_1^{A*}, I_2^{A*}, I_1^{B*}$ and $I_2^{B*} \neq 0$, so all strains are present in both populations. To satisfy the previous equations, and ensure that I_1^A, I_2^A, I_1^B and $I_2^B \neq 0$, the following must be true:

$$\frac{-S_1^* S_2^* \beta_{12}^A \beta_{21}^A}{S_1^* \beta_{11}^A - \mu - \gamma^A} + \beta_{22}^A S_2^* - \mu - \gamma^A = 0 \tag{26}$$

and

$$\frac{-S_1^* S_2^* \beta_{12}^B \beta_{21}^B}{S_1^* \beta_{11}^B - \mu - \gamma^B} + \beta_{22}^B S_2^* - \mu - \gamma^A = 0. \tag{27}$$

Solving each of these equations for S_2, and changing each β_{ij}^{α} value into the corresponding expression involving β^A or β^B, we find that

$$S_2^* = \frac{(\mu + \gamma^A)(\mu N_1 + \mu N_1 \epsilon + \gamma^A N_1 + \gamma^A N_1 \epsilon - S_1^* \beta^A) N_2}{\beta^A (S_1^* \beta^A \epsilon + \mu N_1 + \gamma^A N_1 - S_1^* \beta^A)} \tag{28}$$

and

$$S_2^* = \frac{(\mu + \gamma^B)(\mu N_1 + \mu N_1 \epsilon + \gamma^B N_1 + \gamma^B N_1 \epsilon - S_1^* \beta^B) N_2}{\beta^B (S_1^* \beta^B \epsilon + \mu N_1 + \gamma^B N_1 - S_1^* \beta^B)} \tag{29}$$

By setting the two previous equations equal and solving for β^B, we find the following conditions for coexistence to exist:

$$\beta^B = (\mu + \gamma^B)\frac{\beta^A}{\gamma^A + \mu} \tag{30}$$

or

$$\beta^B = \frac{N_1(-S_1^* \gamma^B \beta^A + \beta^A \gamma^B \epsilon^2 S_1^* + \beta^A \mu \epsilon^2 S_1 - \mu S_1^* \beta^A + \gamma^B N_1 \epsilon + \mu \gamma^B N_1 \epsilon + \mu \gamma^B N_1 \epsilon \gamma^A + \gamma^B N_1 \gamma^A + \mu \gamma^B N_1 + \mu \gamma^A N_1 \epsilon + \mu^2 N_1 + \mu^2 N_1 \epsilon + \mu \gamma^A N_1)}{S_1^*(S_1^* \beta^A \epsilon - S_1^* \beta^A - N_1 \epsilon^2 \gamma^A - \mu N_1 \epsilon^2 + \mu N_1 + \gamma^A N_1)}$$

Note that if we divide both sides of equation (30) by $(\mu + \gamma^B)$, the resulting equation defines a case of coexistence for which $R_0^A = R_0^B$. The second posibility defines a case where the R_0's are not equal. This is an interesting and unexpected result, differing from the single case of coexistence that occurs in one-population models. We will now discuss each type of coexistence equilibrium, both the simple coexistence in which R_0's are equal, and the complex coexistence in which R_0's are not equal.

4.3.1 Simple coexistence

Our simple coexistence occurs when $R_0^A = R_0^B$. At this equilibrium, both strains co-exist in each population. Based on MATLAB simulations we believe this equilibrium is stable (Figures 6, 7).

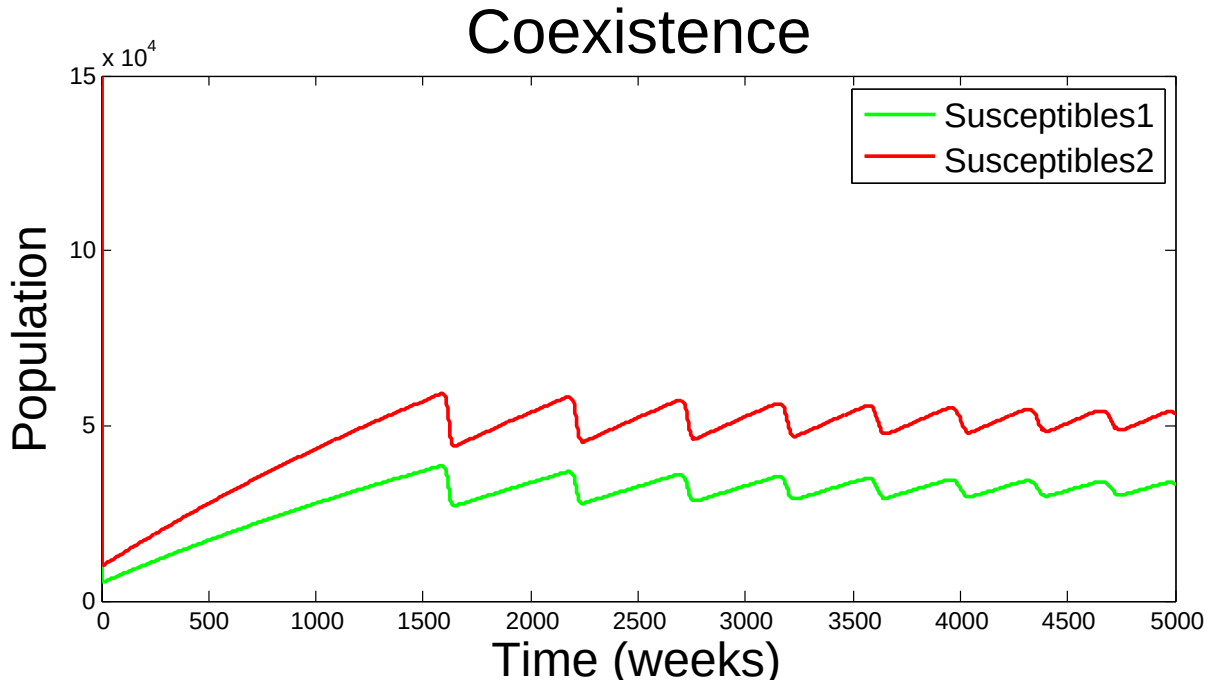

Figure 6: $R_0^A = 4.04, R_0^B = 4.04, N_1 = 100000, N_2 = 150000, \epsilon = .1, \mu = \frac{1}{70*52}$

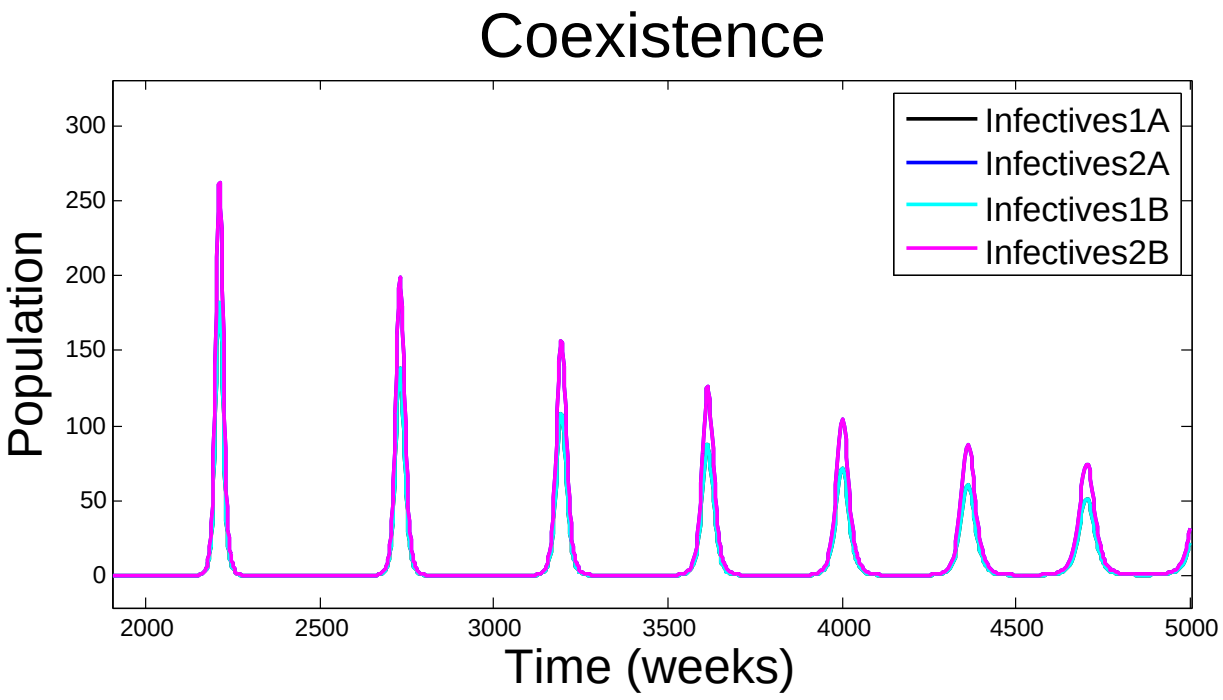

Figure 7: Infectives from Figure 6. Note that both strains remain in the population

4.3.2 Complex coexistence

Let us now return to the complex case of coexistence, in which differing R_0^α's are involved. We find that the equation for β^B with unequal R_0's must hold for this complex case of coexistence. We can change this equation for β^B to one for R_0^B by dividing each side by $(\gamma^B + \mu)$, resulting in the condition

$$R_0^B = \frac{N_1(-S_1^*\beta^A + \beta^A\epsilon^2 S_1^* + \mu N_1\epsilon + N_1\epsilon\gamma^A + \gamma^A N_1 + \mu N_1)}{S_1^*(-S_1^*\beta^A + S_1^*\beta^A\epsilon + \mu N_1 - N_1\epsilon^2\gamma^A - \mu N_1\epsilon^2 + \gamma^A N_1)} \tag{31}$$

Unfortunately, this expression for R_0^B is in terms of S_1^*, which is a state variable at equilibrium. Because of the complexity of our equations, it is difficult to solve for a point of equilibrium, and therefore anything defined in terms of a state variable at equilibrium is not easily solvable. Therefore, we rewrite our equation as follows:

$$S_1^* = N_1\left(\frac{-R_0^A(\epsilon-1) + R_0^B(1-\epsilon^2)}{2R_0^A R_0^B(1-\epsilon)}\right) \pm N_1\left(\frac{\sqrt{(\epsilon-1)(R_0^B)^2\epsilon^3 + 2R_0^A R_0^B\epsilon^2 + (R_0^B)^2\epsilon^2 + (R_0^A)^2\epsilon + 4R_0^B R_0 A\epsilon - \epsilon(R_0^B)^2 + 2R_0^A R_0 B - (R_0^A)^2 - (R_0^B)^2}}{2R_0^A R_0^B(1-\epsilon)}\right).$$

This equation for S_1^* is written entirely in terms of parameters. In order for S_1^* to be biologically significant, it must be real, positive, and less than N_1. The reasoning for this is straightforward: since S_1^* is a subpopulation of N_1, it cannot be complex or negative, and it must be less than or equal to the total population of N_1. In order for S_1^* to be real, the discriminant must be greater than or equal to 0. This is easy to solve, and we find that either

$$\frac{R_0^A}{R_0^B} \geq \frac{(\epsilon + 1 + 2\sqrt{\epsilon})(\epsilon+1)}{(1-\epsilon)} = \frac{(1+\epsilon)(1-\epsilon)}{\epsilon + 1 - 2\sqrt{\epsilon}} \tag{32}$$

or

$$\frac{R_0^A}{R_0^B} \leq \frac{(\epsilon + 1 - 2\sqrt{\epsilon})(\epsilon+1)}{(1-\epsilon)} = \frac{(1+\epsilon)(1-\epsilon)}{\epsilon + 1 + 2\sqrt{\epsilon}}. \tag{33}$$

Note: It is simple to show that $\frac{(\epsilon + 1 + 2\sqrt{\epsilon})(\epsilon+1)}{(1-\epsilon)}$ is indeed equivalent to $\frac{(1+\epsilon)(1-\epsilon)}{\epsilon + 1 - 2\sqrt{\epsilon}}$, and also that $\frac{(\epsilon + 1 - 2\sqrt{\epsilon})(\epsilon+1)}{(1-\epsilon)}$ is equal to $\frac{(1+\epsilon)(1-\epsilon)}{\epsilon + 1 + 2\sqrt{\epsilon}}$.

In order for S_1^* to be greater than 0 and less than N_1, we set the equation for S_1 at our complex coexistence equilibrium equal to 0 and N_1, respectively, and solve. We find that in order for $S_1^* > 0$, the only condition to be satisfied is

$$R_0^\alpha > 0. \tag{34}$$

In order for S_1^* to be less than or equal to N_1, we first find the boundary condition, in which S_1^* equals N_1. This is found to be

$$R_0^A = \frac{R_0^B\epsilon^2 + \epsilon + 1 - R_0^B}{-\epsilon + R_0^B\epsilon + 1 - R_0^B}. \tag{35}$$

Solving this numerically in order to find regions in which S_1^* is less than N_1, we find that using all previous restraints given by equations (31) and (32) in order for S_1^* to be real, S_1^* will always be less than the total population. Therefore, our restraints in order for S_1^* to be biologically significant can be summed as follows:

$$R_0^\alpha > 0$$

and either

$$\frac{R_0^A}{R_0^B} \leq \frac{(\epsilon + 1 - 2\sqrt{\epsilon})(\epsilon + 1)}{(1 - \epsilon)}$$

or

$$\frac{R_0^A}{R_0^B} \leq \frac{(\epsilon + 1 - 2\sqrt{\epsilon})(\epsilon + 1)}{(1 - \epsilon)}$$

We continue to narrow our range of possibility for complex coexistence by looking at conditions necessary for S_2^* to be biologically significant. S_2^*, similar to S_1^*, must be real, positive, and less than N_2. Solving

$$\frac{-S_1^* S_2^* \beta_{12}^A \beta_{21}^A}{S_1^* \beta_{11}^A - \mu - \gamma^A} + \beta_{22}^A S_2^* - \mu - \gamma^A = 0$$

and

$$\frac{-S_1^* S_2^* \beta_{12}^B \beta_{21}^B}{S_1^* \beta_{11}^B - \mu - \gamma^B} + \beta_{22}^B S_2^* - \mu - \gamma^A = 0,$$

this time for S_1^*, yields the following:

$$S_1^* = -\frac{N1(-\mu^2 N_2\epsilon - 2\mu N_2\epsilon\gamma^A - (\gamma^A)^2 N_2\epsilon + \beta^A S_2^*\mu + \beta^A S_2^*\gamma^A - \mu^2 N_2 - 2\mu N_2\gamma^A - (\gamma^A)^2 N_2)}{\beta^A(\beta^A S_2^*\epsilon + \gamma^A N_2 - \beta^A S_2^* + \mu N_2)}$$

and

$$S_1^* = -\frac{N1(-\mu^2 N_2\epsilon - 2\mu N_2\epsilon\gamma^B - (\gamma^B)^2 N_2\epsilon + \beta^B S_2^*\mu + \beta^B S_2^*\gamma^B - \mu^2 N_2 - 2\mu N_2\gamma^B - (\gamma^B)^2 N_2)}{\beta^B(\beta^B S_2^*\epsilon + \gamma^B N_2 - \beta^B S_2^* + \mu N_2)}.$$

Setting the two expressions for S_1^* equal and solving for β^B shows that either

$$\beta^B = \frac{(\gamma^B + \mu)\beta^A}{\mu + \gamma^A} \tag{36}$$

or

$$\beta^B = \frac{N_2(1+\epsilon)(\gamma^B + \mu)(\beta^A S_2^*\epsilon + \gamma^A N_2 - \beta^A S_2^* + \mu N_2)}{S_2^*(\epsilon - 1)(\beta^A S_2^* - \gamma^A N_2 - \mu N_2\epsilon - \gamma^A N_2\epsilon - \mu N_2)} \tag{37}$$

Once again, the first case gives us a case where $R_0^A = R_0^B$.

We can rewrite the second case in terms of R_0^A and R_0^B:

$$\begin{aligned}
\beta^B &= \frac{N_2(1+\epsilon)(\gamma^B + \mu)(\beta^A S_2^*\epsilon + \gamma^A N_2 - \beta^A S_2^* + \mu N_2)}{S_2^*(\epsilon - 1)(\beta^A S_2^* - \gamma^A N_2 - \mu N_2\epsilon - \gamma^A N_2\epsilon - \mu N_2)} \\
\frac{\beta^B}{\gamma^B + \mu} &= \frac{N_2(1+\epsilon)(\beta^A S_2^*\epsilon + (\gamma^A + \mu)N_2 - \beta^A S_2^*)}{S_2^*(\epsilon - 1)(\beta^A S_2^* - (\gamma^A + \mu)N_2 - (\gamma^A + \mu)N_2\epsilon)} \\
R_0^B &= \frac{N_2(1+\epsilon)(R_0^A S_2^*\epsilon + N_2 - R_0^A S_2^*)(\gamma^A + \mu)}{S_2^*(\epsilon - 1)(R_0^A S_2^* - N_2 - N_2\epsilon)(\gamma^A + \mu)} \\
&= \frac{N_2(1+\epsilon)(R_0^A S_2^*\epsilon + N_2 - R_0^A S_2^*)}{S_2^*(\epsilon - 1)(R_0^A S_2^* - N_2 - N_2\epsilon)}
\end{aligned} \tag{38}$$

Solving this equation for S_2^* gives us

$$S_2^* = \left(\frac{N_2}{2R_0^A R_0^B(\epsilon-1)}\right)\left(R_0^B\mu\epsilon^2 - R_0^B\gamma^A - R_0^B\mu - \beta^A + \beta^A\epsilon^2 + R_0^B\gamma^A\epsilon^2 \right.$$
$$\left. \pm\sqrt{(\epsilon-1)(\epsilon+1)(\beta^A + \epsilon\beta^A - R_0^B\gamma^A + \epsilon R_0^B\gamma^A - R_0^B\mu + \epsilon R_0^B\mu)(-\beta^A + \epsilon\beta^A + R_0^B\gamma^A + \epsilon R_0^B\gamma^A + R_0^B\mu + \epsilon R_0^B\mu)}\right)$$

Just as before, we want S_2^* to be biologically significant. S_2^* is real when the following conditions are satisfied:

$$\frac{R_0^A}{R_0^B} \geq \frac{1+\epsilon}{1-\epsilon} \tag{39}$$

or

$$\frac{R_0^A}{R_0^B} \leq \frac{1-\epsilon}{1+\epsilon}. \tag{40}$$

Solving for $S_2^* = 0$, we find that there is no boundary condition necessary for S_2^* to be positive; S_2^* is always positive.

Finally, the boundary condition for S_2^* to be less than N_2 is

$$R_0^B = \frac{(\epsilon+1)(\beta^A\epsilon - \beta^A + \gamma^A + \mu)}{(\epsilon-1)(-\epsilon\mu - \gamma^A\epsilon + \beta^A - \gamma^A - \mu)} \tag{41}$$

Similarly to S_1^*, the condition that S_2^* must be less than N_2 is satisfied by previous conditions.

All conditions for S_1^* and S_2^* to be biologically significant can be combined into the following regions of feasibility of coexistence when $R_0^A \neq R_0^B$:

$$R_0^\alpha > 0, \tag{42}$$

and either

$$\frac{R_0^A}{R_0^B} \leq \frac{(\epsilon+1-2\sqrt{\epsilon})(\epsilon+1)}{1-\epsilon} \tag{43}$$

or

$$\frac{R_0^A}{R_0^B} \geq \frac{(\epsilon+1+2\sqrt{\epsilon})(\epsilon+1)}{1-\epsilon} \tag{44}$$

4.3.3 Simulation

To search for the complex case of coexistence, we have used *MATLAB*. The program being used loops through a wide range of parameters in order to find parameter combinations that satisfy the above conditions. These combinations are used as input into an ode45 solver, which outputs any results in which *all* I_i^α values are greater than 0. We have run the program over a large range of values ($N_1 = 100,000, N_2 = 150,000, \gamma^A = .5, \gamma^B = .5, \epsilon$ from .01 to .99 by .01, $\frac{1}{\mu}$ from 32 years to 82 years by 1 year, β^A from 1 to 50 by .1, and β^B from 1 to 50 by .1, with initial conditions S_1, S_2 calculated based on R_0 values and $I_i^\alpha = 50$) and so far have found no complex coexistence equilibrium. From these results, we hypothesize that if the complicated coexistence does exist, it is unstable, and likely not biologically significant.

5 Sensitivity

5.1 Importance of Sensitivity

Sensitivity is a way to quantify how a small change in parameters affects state variables over time. As such, sensitivity can help us to determine how easily affected our equilibrium is by small changes in parameters. This, in turn, can help us to analyze how stable the equilibrium in question is. To minimize the number of parameters we need to deal with, we rewrite our equations in terms of β^A and , using the fact that values of β_{ij}^{α} are determined by $\beta^{\alpha} \cdot m_{ij}$. Our rewritten equations are as follows:

$$\begin{aligned}
\dot{S}_1 &= \mu N_1 - \mu S_1 - \frac{S_1}{N_1(1+\epsilon)}(\beta^A I_1^A + \epsilon\beta^A I_2^A + \beta^B I_1^B + \epsilon\beta^B I_2^B) \\
\dot{S}_2 &= \mu N_2 - \mu S_2 - \frac{S_2}{N_2(1+\epsilon)}(\epsilon\beta^A I_1^A + \beta^A I_2^A + \epsilon\beta^B I_1^B + \beta^B I_2^B) \\
\dot{I}_1^A &= \frac{S_1}{N_1(1+\epsilon)}(\beta^A I_1^A + \epsilon\beta^A I_2^A) - (\gamma^A + \mu) I_1^A \\
\dot{I}_2^A &= \frac{S_2}{N_2(1+\epsilon)}(\epsilon\beta^A I_1^A + \beta^A I_2^A) - (\gamma^A + \mu) I_2^A \\
\dot{I}_1^B &= \frac{S_1}{N_1(1+\epsilon)}(\beta^B I_1^B + \epsilon\beta^B I_2^B) - (\gamma^B + \mu) I_1^B \\
\dot{I}_2^B &= \frac{S_2}{N_2(1+\epsilon)}(\epsilon\beta^B I_1^B + \beta^B I_2^B) - (\gamma^B + \mu) I_2^B
\end{aligned} \tag{45}$$

In order to calculate results, we use previous results [1], based on chain rule, showing that if we have a system, F, defined in terms of x, the state variables of the system, θ, the parameters of the system, and time, t, then the matrix of sensitivities (denoted $\frac{\partial x}{\partial \theta}$) satisfies

$$\frac{\partial}{\partial x}\frac{\partial x}{\partial \theta} = \frac{\partial F}{\partial x}\frac{\partial x}{\partial \theta} + \frac{\partial F}{\partial \theta}, \tag{46}$$

with initial conditions

$$\frac{\partial x(0)}{\partial \theta} = 0_{m \times p}$$

.

$\frac{\partial F}{\partial x}$ is the Jacobian of the model, and can be written as shown in Figure 8.
$\frac{\partial F}{\partial \theta}$ can be written as shown in Figure 9.

$$\frac{\partial F}{\partial x} = \begin{bmatrix}
-\mu - \frac{1}{N_1(1+\epsilon)}\left(\beta^A I_1^A + \epsilon\beta^A I_2^A + \beta I_1^B + \epsilon\beta^B I_2^B\right) & 0 & -\frac{S_1\beta^A}{N_1(1+\epsilon)} & -\frac{\epsilon S_1\beta^A}{N_1(1+\epsilon)} & \dots \\
0 & -\mu - \frac{1}{N_2(1+\epsilon)}\left(\epsilon\beta^A I_1^A + \beta^A I_2^A + \epsilon\beta I_1^B + \beta^B I_2^B\right) & -\frac{\epsilon S_2\beta^A}{N_2(1+\epsilon)} & -\frac{S_2\beta^A}{N_2(1+\epsilon)} & \dots \\
\frac{1}{N_1(1+\epsilon)}\left(\beta^A I_1^A + \epsilon\beta^A I_2^A\right) & 0 & \frac{S_1\beta^A}{N_1(1+\epsilon)} - (\gamma^A + \mu) & \frac{\epsilon S_1\beta^A}{N_1(1+\epsilon)} & \dots \\
0 & \frac{1}{N_2(1+\epsilon)}\left(\epsilon\beta^A I_1^A + \beta^A I_2^A\right) & \frac{\epsilon S_2\beta^A}{N_2(1+\epsilon)} & \frac{S_2\beta^A}{N_2(1+\epsilon)} - (\gamma^A - mu) & \dots \\
\frac{1}{N_1(1+\epsilon)}\left(\beta I_1^B + \epsilon\beta^B I_2^B\right) & 0 & 0 & 0 & \dots \\
0 & \frac{1}{N_2(1+\epsilon)}\left(\epsilon\beta I_1^B + \beta^B I_2^B\right) & 0 & 0 & \dots
\end{bmatrix}$$

$$\begin{bmatrix}
\dots & -\frac{S_1\beta^B}{N_1(1+\epsilon)} & -\frac{\epsilon S_1\beta^B}{N_1(1+\epsilon)} \\
\dots & -\frac{\epsilon S_2\beta^B}{N_2(1+\epsilon)} & -\frac{S_2\beta^B}{N_2(1+\epsilon)} \\
\dots & 0 & 0 \\
\dots & 0 & 0 \\
\dots & \frac{S_1\beta^B}{N_1(1+\epsilon)} - (\gamma^B + \mu) & \frac{\epsilon S_1\beta^B}{N_1(1+\epsilon)} \\
\dots & \frac{\epsilon S_2\beta^B}{N_2(1+\epsilon)} & \frac{S_2\beta^B}{N_2(1+\epsilon)} - (\gamma^B + \mu)
\end{bmatrix}$$

Figure 8: Matrix of $\dfrac{\partial F}{\partial x}$ (This is the Jacobian of our system)

$$\frac{\partial F}{\partial \theta} = \begin{bmatrix} N - S_1 & \frac{S_1(\beta^A I_1^A + \beta^B I_1^B - \beta^A I_2^A - \beta^B I_2^B)}{N_1(1+\epsilon)^2} & -\frac{S_1}{N_1(1+\epsilon)}\left(I_1^A + \epsilon I_2^A\right) & -\frac{S_1}{N_1(1+\epsilon)}\left(I_1^B + \epsilon I_2^B\right) & 0 & 0 \\ N - S_2 & -\frac{S_2(\beta^A I_1^A + \beta^B I_1^B - \beta^A I_2^A - \beta^B I_2^B)}{N_2(1+\epsilon)^2} & -\frac{S_2}{N_2(1+\epsilon)}\left(\epsilon I_1^A + I_2^A\right) & -\frac{S_2}{N_2(1+\epsilon)}\left(\epsilon I_1^B + I_2^B\right) & 0 & 0 \\ -I_1^A & -\frac{S_1\beta^A(I_1^A - I_2^A)}{N_1(1+\epsilon)^2} & \frac{S_1}{N_1(1+\epsilon)}\left(I_1^A + \epsilon I_2^A\right) & 0 & -I_1^A & 0 \\ -I_2^A & \frac{S_2\beta^A(I_1^A - I_2^A)}{N_2(1+\epsilon)^2} & \frac{S_2}{N_2(1+\epsilon)}\left(\epsilon I_1^A + I_2^A\right) & 0 & -I_2^A & 0 \\ -I_1^B & -\frac{S_1\beta^B(I_1^B - I_2^B)}{N_1(1+\epsilon)^2} & 0 & \frac{S_1}{N_1(1+\epsilon)}\left(I_1^B + \epsilon I_2^B\right) & 0 & -I_1^B \\ -I_2^B & \frac{S_2\beta^B(I_1^B - I_2^B)}{N_2(1+\epsilon)^2} & 0 & \frac{S_2}{N_2(1+\epsilon)}\left(\epsilon I_1^B + I_2^B\right) & 0 & -I_2^B \end{bmatrix}$$

Figure 9: Matrix of $\frac{\partial F}{\partial \theta}$. In columns from left to right, the partial derivatives are with respect to μ, ϵ, β^A, β^B, γ^A, γ^B.

Using *MATLAB*'s ode45 solver, we created a program which produces graphs of sensitivity for given initial state variables and parameters. Using this program, we were able to analyze the sensitivities of state variables for each form of equilibrium. Now we will look into both our competitive exclusion and simple coexistence equilibria and analyze I_1^A sensitivities for each.

5.2 Competitive Exclusion

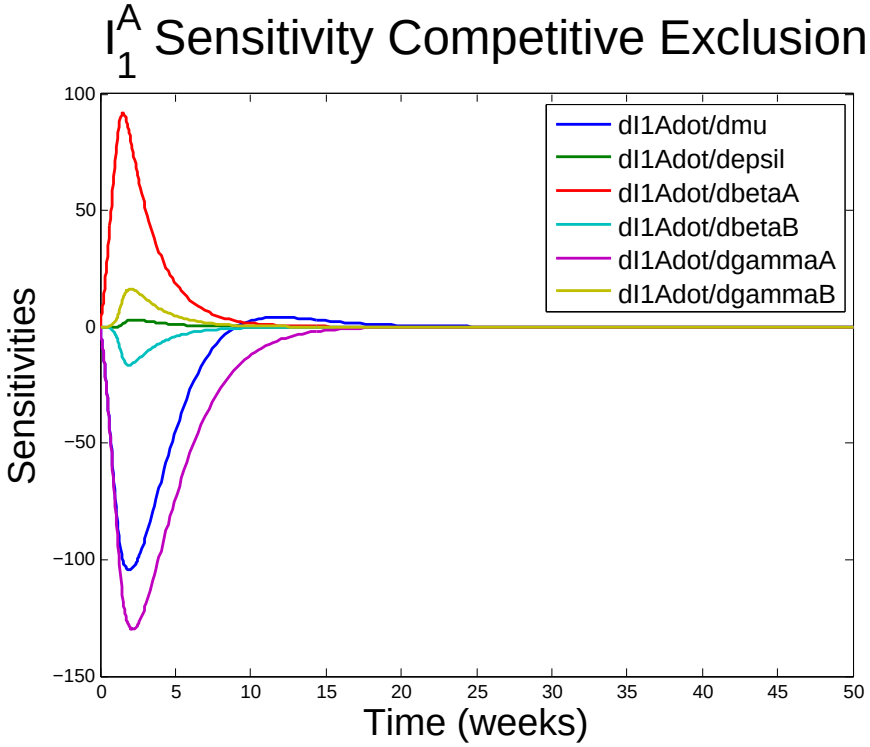

Figure 10: $R_0^A = 13.46, R_0^B = 2.69$ Sensitivity of I_1^A when B is competitively excluded

ϵ has little effect on our state variable. This is reasonable, given that ϵ is related to mixing, and as such affects when an initial outbreak occurs in a population connected to an infected population, but little else.

Small changes in β^B and γ^B initially have small effects on I_1^A because the B strain is weak compared to the A strain. After some time, the sensitivities with respect to β^B and γ^B go to 0 because the B strain dies out. μ's affect appears very large, but is easily explained. Because we have not normalized our sensitivities and μ is very small compared to all other parameters, a unit change in μ has a much larger effect on I_1^A than a unit change in any other parameter. Initially, an increase in μ causes a decrease in I_1^A, but as time continues, the effect of μ eventually becomes slightly positive. Recall that μ is the reciprocal of the average life span of a population, and is used in both birth and death rates. An increase in μ relates to an increase in the rate of replenishment in the S classes, and also to an increase in deaths from each class, including the I classes. Therefore, the effect of μ is as we would

expect.

I_1^A increases as β^A is increased and decreases as γ^A is increased. Since

$$\dot{I}_1^A = \frac{S_1}{N_1(1+\epsilon)}(\beta^A I_1^A + \epsilon\beta^A I_2^A) - (\gamma^A + \mu)I_1^A,$$

and therefore $\dot{I}_1^A$ is directly related to β^A and inversely related to γ^A, this also makes sense.

Since competitive exclusion is a stable equilibrium when the stronger strain's R_0 is larger than 1 and larger than the weaker strain's R_0, we expect to see the effects of all parameters eventually go to 0, so long as a unit change in parameters does not competely change our R_0 values. We see these results in the graph.

5.3 Coexistence

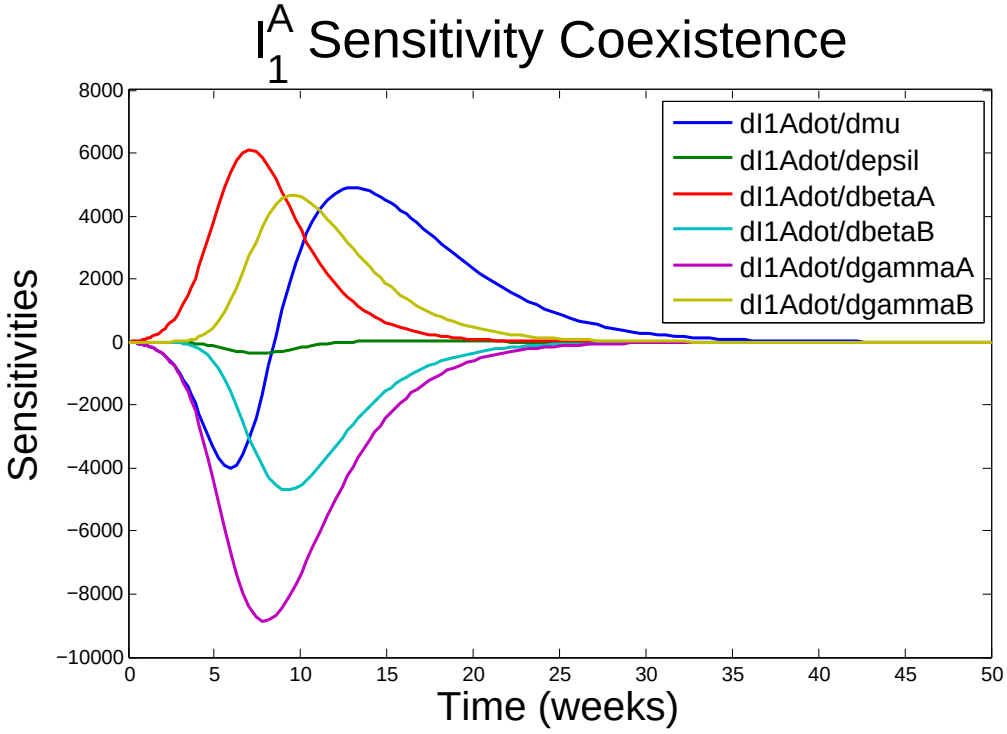

Figure 11: $R_0^A = 3.23, R_0^B = 3.23$ Sensitivity of I_1^A when R_0s are the same

The effect of ϵ on our state variable is again minimal, as we expect. The effects of β^A and γ^A on I_1^A at our coexistence equilibrium are similar to their effects of I_1^A at our competitive exclusion equilibrium. However, the effects of β^B and γ^B are much more pronounced, since neither strain is competitively excluded. μ also has a similar effect, although it has a much more pronounced positive effect on I_1^A than in the previous equilibrium. Again, this is because both strains remain in the population. We also note that the effects of all β and

γ parameters are more pronounced at the peak of infection, when the largest changes are occuring in state variables. Finally, as the model approaches a stable equilibrium, the impact of all parameters on our state variable of interest again goes to 0.

6 Conclusions and Future Directions

6.1 Concluding Remarks

We used differential equations to model a two strain two population infectious disease system . We examined the equilibria of such systems and the stability of these points. We found that in many ways, these points were qualitatively similar to the equilibria of simpler systems. We also were able to quantify the sensitivity of this model to parameter changes.

In the first section, we offer an introduction to epidemiological modeling by examining the simple SIR model. We also introduce a general methodology for analyzing such models. This included finding equilibria and their stability, as well as the importance of R_0, both biologically and as a modeling parameter.

We then consider our two-strain two-population model. We outline the assumptions on which the model is based and introduce some general tools of metapopulation modeling. Thus equipped, we construct differential equations to describe the behavior of our system.

In the following section, we conduct an analysis of the system's equilibria. We find three types: disease-free, competitive exclusion, and coexistence. We are able to prove that in systems obeying our stated assumptions the disease free equilibrium is stable regardless of the number of disease strains and number of populations, exactly when the R_0 value for each strain is less than one. We find simulated evidence that competitive exclusion equilibrium is stable exactly when R_0 of the surviving strain is greater than one and greater than R_0 of the excluded strain. The complexity of our system makes finding an explicit point for coexistence equilibrium impractical. However, we have found conditions under which coexistence can occur. In the first, the R_0 value for both strains are equal. In this case, simulations suggest that the equilibrium is stable. Analysis of the second case, with unequal R_0's proved more problematic, but we have evidence to suggest that this equilibrium, if even biologically relevant, is unstable.

We conclude by analyzing the sensitivity of our system to changes in parameter values. We find that ϵ has a minor effect on any state variable. The number of individuals infected by a given strain is positively affected by an increase in that strain's R_0 or a decrease in the competing strain's R_0. μ's greatest impact on the system is to shift the timing of disease outbreaks.

Perhaps the most striking realization of this work was the unexpected quickness with which the complexity of such models increases. The simultaneous inclusion of just two strains and two populations complicated the model considerably, when compared with models consider-

ing only one of these factors. Nonetheless, we have taken some small steps toward a more general understanding of SIR epidemiological models.

6.2 Future Directions

There remain many research directions which this work only briefly, if at all, begins to explore. Most obvious is the conclusion of the equilibrium analyses begun here, by proving the hypothesized stability of our competitive exclusion and coexistence equilibria. Additionally, resolving the biological relevance of our coexistence case with unequal R_0's would complete an understanding of this model's long-term dynamics.

This work also suggests numerous future extensions. Multistrain metapopulation models may be generalized by considering arbitrary numbers of strains and/or populations, or by shedding many of the assumptions included here. In particular, removing the assumptions on our parameters might drastically alter the system's dynamics. Introducing disease control methods, such as vaccination or quarantine, to the model may offer insight as to the preventability of epidemics. Additionally, one could consider a wider class of diseases, which may not be adequately described by an SIR model. One wonders how the system's dynamics would change if the underlying model is, for instance, SIS or SEIR, rather than SIR.

References

[1] Capaldi, Alex. *Exploring the Inverse Problem with Infectious Disease Models*. 2010.

Lloyd, Alun. *Introduction to Epidemiological Modeling: Basic Models and Their Properties*. March 23, 2011.