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Cover Page Footnote
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Multistrain 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 co-mingle 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. Additionally, we find existence of a biologically relevant equilibrium where two disease strains of unequal strength coexist in a two-population system, and we demonstrate that this equilibrium point is likely to be unstable.

Keywords: SIR model, infectious diseases, epidemiology, mathematical modeling, differential equations, metapopulation, multistrain infection, equilibrium analysis

1 Introduction

Numerous studies on the theory of the dynamics of infectious diseases have been conducted using variations on the Susceptible-Infectious-Removed (SIR) model (see, for example, [18, 2, 15, 6]). Two common extensions of the SIR model are to incorporate (1) multiple strains of a disease that offer cross-immunity and thus compete for susceptible hosts or (2) spatial heterogeneity of populations through the use of patches, commonly referred to as a metapopulation. While these two extensions of the SIR model appear frequently in the literature, they are scarcely employed together (such as in [24]). In this paper, we seek to build and analyze a deterministic multistrain, metapopulation version of the SIR model.

Multistrain models describe when multiple strains of a single pathogen type, through the process of mutation, arise within a population. Multistrain deterministic SIR models have similar dynamics to ecological competition models [26]. In these simple models, since the multiple strains each offer cross-immunity, the strongest strain is selected and will exclude its competitors. Many studies have been done with multistrain SIR models, such as examining pathogen diversity in stochastic scenarios [1], some studies even giving evidence of strain coexistence [20]. Other studies have looked at control measures such as optimizing finite vaccine allocation between multiple strains [10]. Yet, because of the Competitive Exclusion Principle, no deterministic models have been found that allows for two competing strains to coexist in a single population. Thus, we consider a metapopulation.

Similarly to multristrain models, a bevy of work has been done on metapopulation SIR models (see, for example, [3, 13, 25, 21, 12, 11, 7]). Specifically, the metapopulation is composed of n populations, or patches, and the system allows for infectious individuals to visit other patches and transmit the disease between them. The equilibrium behavior of these models is well known [19, 14, 25, 16, 17, 2]. Yet, just as stochasticity has been shown to allow for the coexistence of multiple strains in a population [26], we seek to resolve if adding spatial heterogeneity by constructing a metapopulation would allow for coexistence to occur.

This paper is organized as follows: In Section 2 we present the two-strain, two-population SIR differential equation model. We perform equilibrium and stability analyses of the model in Section 3, while also providing stability conditions for the disease-free equilibrium for the general m-strain, n-population SIR model. We conclude with a discussion in Section 4.

2 The 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 popu-

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lation i people are born into the susceptible (S_i) class, become infected by either strain of the disease and enter the infectious (I_i^α) class, then transition to the removed (R_i) class. Individuals may also leave any class through death. Note that we make a distinction between removal (R class) and death. A visual depiction of our model is given in Figure 1.

Our model is given by the following ordinary differential equation system:

$$\dot{S}_1 = \mu N_1 - \mu S_1 - S_1(\beta_{11}^A I_1^A + \beta_{12}^A I_2^A + \beta_{11}^B I_1^B + \beta_{12}^B I_2^B) \quad (1a)$$

$$\dot{S}_2 = \mu N_2 - \mu S_2 - S_2(\beta_{21}^A I_1^A + \beta_{22}^A I_2^A + \beta_{21}^B I_1^B + \beta_{22}^B I_2^B) \quad (1b)$$

$$\dot{I}_1^A = S_1(\beta_{11}^A I_1^A + \beta_{12}^A I_2^A) - (\gamma^A + \mu) I_1^A \quad (1c)$$

$$\dot{I}_2^A = S_2(\beta_{21}^A I_1^A + \beta_{22}^A I_2^A) - (\gamma^A + \mu) I_2^A \quad (1d)$$

$$\dot{I}_1^B = S_1(\beta_{11}^B I_1^B + \beta_{12}^B I_2^B) - (\gamma^B + \mu) I_1^B \quad (1e)$$

$$\dot{I}_2^B = S_2(\beta_{21}^B I_1^B + \beta_{22}^B I_2^B) - (\gamma^B + \mu) I_2^B \quad (1f)$$

where μ is the per capita birth and death rate and γ^α is the relative recovery rate for strain α. The average life expectancy is $1/\mu$ and the average time to recovery for each strain is $1/\gamma^\alpha$. The total population size for population i is N_i, which is constant. This is guaranteed because the per capita birth and death rates are equal for each population. Also, it is assumed that the mixing between populations is temporary (no permanent immigration) and subject to preferred mixing (theory developed and discussed primarily in [8]), i.e. the majority of each individual's interpersonal contacts are with members of his or 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.

A mixing matrix M describes the manner in which the populations interact. Its entries m_{ij} denote the fraction of contacts made by individuals from group j with individuals from group i [5]. We assume that each population's out of group mixing proportion is equal, so for this model

$$M = \frac{1}{1+\epsilon}\begin{bmatrix} 1 & \epsilon \\ \epsilon & 1 \end{bmatrix}. \quad (2)$$

The entries of 1 on the diagonal indicate that most contacts are with members from an individual's home population while the ϵ entries off the main diagonal represent the small remaining proportion of each group's contacts. Since these entries represent fractional mixing rates, each column must sum to 1 and thus the matrix is properly scaled.

It is assumed that each individual, regardless of population, has the same contact rate per unit time. Furthermore, any contact between a susceptible and an infectious leads to successful transmission of the disease with probability dependent only on the strain. The product of these two values gives the (strain dependent) transmission parameter, β^α. Then, β_{ij}^α is the relative transmission rate of strain α from population j to i. This rate is given by

$$\beta_{ij}^\alpha = \frac{\beta^\alpha m_{ij}}{N_i}. \quad (3)$$

Infection is governed by the standard incidence term; susceptible individuals from population i 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.

Finally, we suppress the $\dot{R}_i$ equations, as the values of R_i can be calculated by $N_i - (S_i + I_i^A + I_i^B)$. This allows for a reduction in model dimension.

2.1 The Basic Reproductive Number

A number of particular interest in epidemiology is the basic reproductive number, R_0. The basic reproductive number gives the average number of secondary infections that result from a single infectious individual over the course of their infection in an otherwise entirely susceptible population (see, for example, [2, 9]). It is often a threshold value that will determine whether or not a major outbreak will occur. Thus, we seek to construct a formulation of R_0 for each strain of the disease in our model.

A next generation matrix describes the transmission of a disease through multiple patches. The entry k_{ij} is the number of secondary infections caused in population i by a single infectious individual in population j [8]. Because we are considering two disease strains, we will have two next generation matrices, K^A and K^B, to describe the transmission of each strain, given as

$$K^\alpha = \begin{bmatrix} \frac{\beta^\alpha}{(\gamma^\alpha+\mu)(1+\epsilon)} & \frac{\epsilon\beta^\alpha}{(\gamma^\alpha+\mu)(1+\epsilon)} \\ \frac{\epsilon\beta^\alpha}{(\gamma^\alpha+\mu)(1+\epsilon)} & \frac{\beta^\alpha}{(\gamma^\alpha+\mu)(1+\epsilon)} \end{bmatrix} \quad (4)$$

where $\alpha \in \{A, B\}$.

It has been shown that the next generation matrix can be used to compute R_0. The number of infectious individuals increases by a factor of λ, the dominant eigenvalue of K^α, with each generation, which matches the definition of R_0 [8, 27]. Thus, R_0^α is the dominant eigenvalue of the next generation matrix K^α so we calculate R_0^α to be

$$R_0^\alpha = \frac{\beta^\alpha}{\gamma^\alpha + \mu}. \quad (5)$$

3 Equilibrium Analysis

We are interested in the stability of the model's equilibria, which gives insight into the long term behavior of

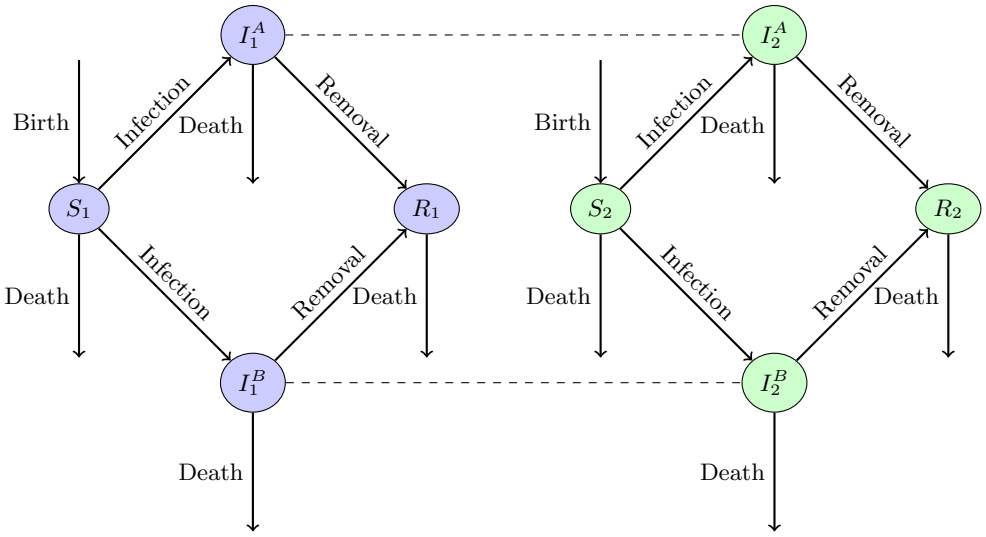

Figure 1: A flow chart illustrating an individual's movement through the two-strain, two-population SIR model. For population i, S_i represents the susceptible subpopulation, I_i^A and I_i^B represent the subpopulations that are infected with strain A or B respectively, and R_i represents the removed subpopulation. The dashed lines between the I_1^α and I_2^α subpopulations are indicating that the two populations temporarily mix, and thus infections can spread from one population to the other. However, there is no permanent immigration between populations 1 and 2.

the system. The model has three types of equilibrium solutions: a disease-free equilibrium, competitive exclusion equilibria, and coexistence equilibria.

3.1 Disease-Free

The disease-free equilibrium is so named because neither strain of the disease is present in either population. The entire metapopulation is susceptible. The point of equilibrium is

$$\left(S_1, S_2, I_1^A, I_2^A, I_1^B, I_2^B\right) = \left(N_1, N_2, 0, 0, 0, 0\right). \tag{6}$$

Figure 2 displays a model solution when the disease-free equilibrium is stable and, thus, the solution trajectory approaches the equilibrium.

An equilibrium point is stable whenever the real component of each eigenvalue of the Jacobian matrix of the system linearized around that equilibrium is negative [4]. Thus, we compute the eigenvalues of the Jacobian matrix, $J(N_1, N_2, 0, 0, 0, 0)$, and obtain

$$\lambda_1 = -\mu, \tag{7a}$$
$$\lambda_2 = -\mu, \tag{7b}$$
$$\lambda_3 = \beta^A - \gamma^A - \mu, \tag{7c}$$
$$\lambda_4 = \frac{(1-\epsilon)\beta^A}{1+\epsilon} - (\gamma^A + \mu), \tag{7d}$$
$$\lambda_5 = \beta^B - \gamma^B - \mu, \tag{7e}$$
$$\lambda_6 = \frac{(1-\epsilon)\beta^B}{1+\epsilon} - (\gamma^B + \mu). \tag{7f}$$

Since it is assumed $\mu > 0$ we have $\lambda_1, \lambda_2 < 0$. When $R_0^A = \frac{\beta^A}{\gamma^A + \mu} < 1$, we have $\lambda_3, \lambda_4 < 0$. Similarly, when $R_0^B < 1$ we have $\lambda_5, \lambda_6 < 0$. This implies that the disease-free equilibrium is stable if and only if R_0^α is less than 1 for both strains $\alpha \in \{A, B\}$.

3.1.1 Generalizing Disease-Free Equilibrium

We seek to extend this stability condition to metapopulation models considering any number of disease strains and any number of populations.

Theorem 1. *In a metapopulation consisting of n populations and m disease strains whose dynamics are governed by an SIR model with analogous assumptions as the two-strain, two-population model given in Section 2 the disease-free equilibrium is stable if and only if $R_0^\alpha < 1$ for each strain α.*

Proof. Given n populations and m strains, the ordinary differential equation system of $n(1+m)$ equations for the model is

$$\dot{S}_i = \mu N_i - \mu S_i - S_i \left(\sum_\alpha \sum_{j=1}^{n} \beta_{ij}^\alpha I_j^\alpha \right) \tag{8a}$$

$$\dot{I}_i^\alpha = S_i \left(\sum_{j=1}^{n} \beta_{ij}^\alpha I_j^\alpha \right) - (\gamma^\alpha + \mu) I_i^\alpha \tag{8b}$$

for all $i \in \{1, \ldots, n\}$ and $\alpha \in \{1, \ldots, m\}$.

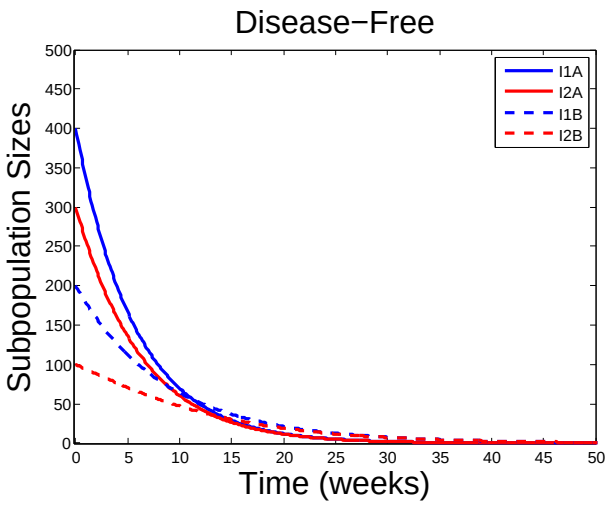

Figure 2: The four infectious subpopulations against time when the solution approaches the stable, disease-free equilibrium. Each of the four infectious subpopulations approaches zero. The solid curves are strain A, the dashed curves are strain B, the blue curves are population 1, and the red curves are population 2. The parameter values used were $R_0^A \approx 0.67$, $R_0^B \approx 0.81$, $N_1 = 100000$, $N_2 = 150000$, $\epsilon = .1$, $\mu = \frac{1}{3640}$ (this value of μ gives a 70-year average lifespan) with initial conditions of $I_1^A(0) = 400$, $I_2^A(0) = 300$, $I_1^B(0) = 200$, $I_2^B(0) = 100$, and with the remaining individuals initially susceptible.

The disease-free equilibrium is the point

$$(S_1, \ldots, S_n, I_1^1, \ldots, I_n^m) = (N_1, \ldots, N_n, 0, \ldots, 0). \quad (9)$$

The partial derivatives of the system with respect to the state variables evaluated at the disease-free equilibrium are

$$\frac{\partial \dot{S}_i}{\partial S_j} = \begin{cases} 0 & i \neq j \\ -\mu & i = j \end{cases} \quad (10a)$$

$$\frac{\partial \dot{S}_i}{\partial I_j^\alpha} = -S_i \beta_{ij}^\alpha \quad (10b)$$

$$\frac{\partial \dot{I}_i^\alpha}{\partial S_j} = 0 \quad (10c)$$

$$\frac{\partial \dot{I}_i^\alpha}{\partial I_j^\kappa} = \begin{cases} 0 & \kappa \neq \alpha \\ S_i \beta_{ij}^\alpha & \kappa = \alpha, i \neq j \\ S_i \beta_{ij}^\alpha - (\gamma^\alpha + \mu) & \kappa = \alpha, i = j \end{cases} \quad (10d)$$

Equations (10) make up the entries of the Jacobian matrix evaluated at the disease-free equilibrium, $J \in \mathbb{R}^{n(1+m)\times n(1+m)}$. By partitioning J into four blocks such that

$$J = \begin{bmatrix} J_{11} & J_{12} \\ J_{21} & J_{22} \end{bmatrix} = \begin{bmatrix} \frac{\partial \dot{S}_i}{\partial S_j} & \frac{\partial \dot{S}_i}{\partial I_j^\alpha} \\ \frac{\partial \dot{I}_i^\alpha}{\partial S_j} & \frac{\partial \dot{I}_i^\alpha}{\partial I_j^\kappa} \end{bmatrix}, \quad (11)$$

we see that J_{21} is the $nm \times n$ zero matrix and so J is block upper-triangular. Thus, the eigenvalues of J are the union of the eigenvalues of J_{11} and J_{22} [23]. The block $J_{11} \in \mathbb{R}^{n\times n}$ is diagonal, so its eigenvalues are simply $-\mu$ (with algebraic multiplicity n). The matrix J_{22} is also block diagonal; it consists of m $n \times n$ sub-blocks on the diagonal which we label A^α, while each other sub-block is an $n \times n$ zero matrix. The diagonal sub-blocks are

$$A^\alpha = \frac{\partial \dot{I}_i^\alpha}{\partial I_j^\alpha}. \quad (12)$$

Thus, the eigenvalues of J_{22} are the union of the eigenvalues of each sub-block A^α. The eigenvalues of each sub-block A^α can be obtained using a lemma proven in the appendix of this article. The eigenvalues of A^α are

$$\lambda = \beta^\alpha - (\gamma^\alpha + \mu) \quad (13a)$$

with algebraic multiplicity 1 and

$$\lambda = \frac{(1-\epsilon)\beta^\alpha}{1 + (n-1)\epsilon} - (\gamma^\alpha + \mu) \quad (13b)$$

with algebraic multiplicity $(n-1)$.

To guarantee $\beta^\alpha - (\gamma^\alpha + \mu) < 0$, we have $R_0^\alpha < 1$. Also, we have

$$\frac{(1-\epsilon)\beta^\alpha}{1 + (n-1)\epsilon} - (\gamma^\alpha + \mu) < \beta^\alpha - (\gamma^\alpha + \mu), \quad (14)$$

and thus each eigenvalue of A^α is negative if and only if $R_0^\alpha < 1$ for each α.

Recall that the set of eigenvalues of J was the union of the sets of eigenvalues of blocks J_{11} and J_{22}. We have just

found the eigenvalues of J_{22} and determined when they are negative, and that J_{11} has eigenvalues $-\mu$, with algebraic multiplicity n, which are always negative. Thus, all of the eigenvalues of J are negative so the disease-free equilibrium is stable if and only if $R_0^\alpha < 1$ for each strain α. ■

3.2 Competitive Exclusion

The second class of equilibria for the model is competitive exclusion. This type occurs when one strain in the populations is stronger than the other strain, forcing the weaker strain to extinction while the stronger strain remains endemic in the metapopulation. An explicit formula for the point of equilibrium is unruly, and so we chose to test the stability of the equilibrium via quantitative analysis. This will be outlined in subsection 3.4. Figure 3 illustrates a model solution where a competitive exclusion equilibrium is stable and is the resultant long-term behavior.

3.3 Coexistence

The third class of equilibria for the model is coexistence. This type of equilibrium arises when both strains of the disease remain in the metapopulation. By setting Equations (1) to zero and examining the case when each of $I_i^\alpha > 0$, we obtain the conditions for the coexistence equilibria. There are two different conditions, either of which can be met to obtain a coexistence equilibrium. Either

$$R_0^A = R_0^B \tag{15}$$

or

$$R_0^B = \frac{N_i(\epsilon+1)(R_0^A S_i^*(\epsilon-1)+N_i)}{S_i^*(\epsilon-1)(R_0^A S_i^* - N_i(\epsilon+1))} \tag{16}$$

for both $i = 1$ and 2, and where S_i^* is the constant value of S_i at the coexistence equilibrium. Equation (15) represents the situation when both strains are of equivalent strength, effectively treating the system as only having one strain. We call this equilibrium simple coexistence. Equation (16) defines a coexistence case when the R_0's are not equal. This situation differs from the single case of coexistence that occurs in one-population models. We will refer to this equilibrium as complex coexistence.

The case of simple coexistence occurs when $R_0^A = R_0^B$. At this equilibrium, both strains coexist in each population. Based on quantitative analysis (see subsection 3.4) this equilibrium is stable when the R_0 values are equal and greater than one. Figure 4 illustrates a model solution where the simple coexistence scenario is present; both strains are endemic in the metapopulation.

The case of complex coexistence, in which the strains have differing R_0 values, may occur when Equation (16) is met. As solving for an explicit formula for the complex coexistence equilibrium is untenable, and because, if it does exist, it is likely unstable (see subsection 3.4), quantitative methods are also unable locate it. Thus, we searched for conditions under which a biologically relevant complex coexistence equilibrium could not be ruled out.

Equation (16) is an expression for R_0^B in terms of S_i^*, which is a state variable at equilibrium. Equation (16), which is quadratic in S_i^*, can be expressed as

$$(\epsilon-1)R_0^A R_0^B S_i^{*2} - N_i(\epsilon^2-1)(R_0^B - R_0^A)S_i^* - N_i^2(\epsilon+1) = 0 \tag{17}$$

and then solved for S_i^* in terms of only parameters. Conditions can be constructed for S_i^* to be biologically relevant by examining the discriminant. All conditions for S_1^* and S_2^* to be biologically relevant, i.e.

$$0 \le S_1^* \le N_1 \quad \text{and} \quad 0 \le S_2^* \le N_2, \tag{18}$$

can be combined into the following regions of feasibility of coexistence when $R_0^A \neq R_0^B$:

$$R_0^\alpha > 0, \tag{19}$$

and either

$$\frac{R_0^A}{R_0^B} \le \frac{(\epsilon+1-2\sqrt{\epsilon})(\epsilon+1)}{1-\epsilon} \tag{20a}$$

or

$$\frac{R_0^A}{R_0^B} \ge \frac{(\epsilon+1+2\sqrt{\epsilon})(\epsilon+1)}{1-\epsilon}. \tag{20b}$$

Notice that when there is no mixing between the populations, $\epsilon = 0$, any values for $R_0^A > 1$ and $R_0^B > 1$ could potentially result in a coexistence equilibrium. This is sensible, as when there is no mixing, if one strain exists independently in each population, there is no way for them to competitively exclude each other. However, as ϵ increases, the set of feasible R_0 pairs decreases. This also makes sense, as the amount of mixing increases, the two populations approach the behavior of a single population, which has no complex coexistence equilibrium. This phenomenon can be seen in Figure 5.

The feasible region of existence of the complex coexistence equilibrium shrinks as ϵ increases. Thus, we conjecture that if a complex coexistence equilibrium does exist, the behavior of the system at such an equilibrium would be that one strain persists in one population while the other strain persists in the other population, behaving similarly to two disjoint populations.

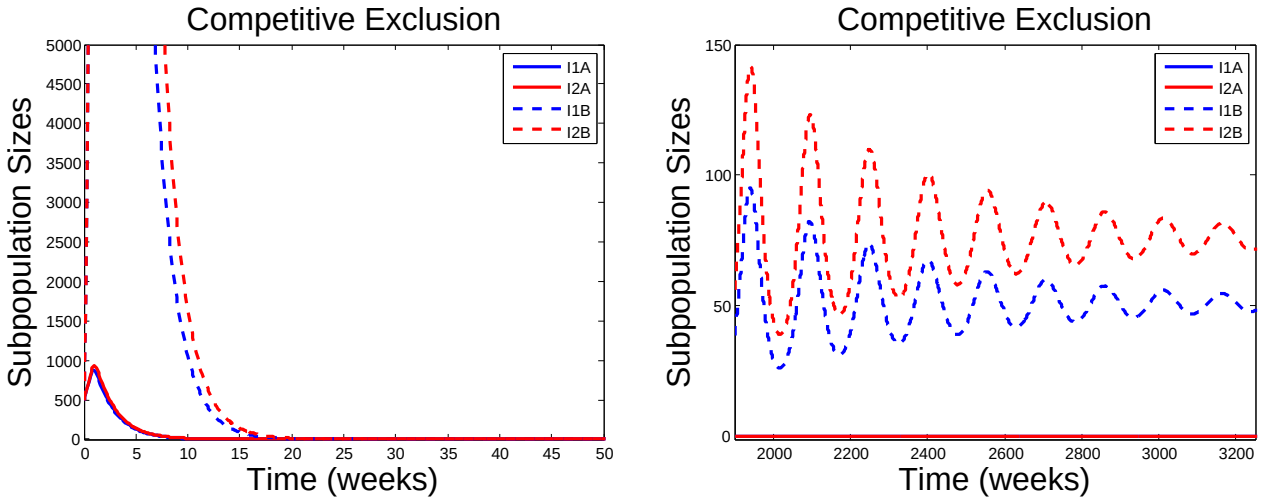

Figure 3: The four infectious subpopulations against time when strain A is competitively excluded while strain B persists. The left plot displays the initial outbreak of both strains, while the right plot displays periodic endemic outbreaks of only strain B. The solid curves are strain A, the dashed curves are strain B, the blue curves are population 1, and the red curves are population 2. The parameter values used were $R_0^A = 2.70$, $R_0^B = 13.49$, $N_1 = 100000$, $N_2 = 150000$, $\epsilon = .1$, $\mu = \frac{1}{3640}$ with initial conditions of 500 initial individuals in each infectious class with the remaining individuals initially susceptible.

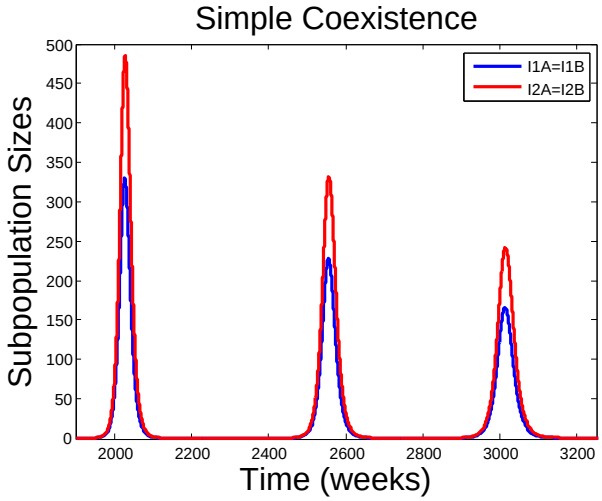

Figure 4: The four infectious subpopulations against time in a simple coexistence scenario; both strains remain endemic in the population and cause periodic outbreaks. Note that only two curves are shown, as $I_1^A = I_1^B$ and $I_2^A = I_2^B$. The blue curves are population 1, and the red curves are population 2. The parameter values used were $R_0^A = 4.04$, $R_0^B = 4.04$, $N_1 = 100000$, $N_2 = 150000$, $\epsilon = .1$, $\mu = \frac{1}{3640}$ with initial conditions of 500 initial individuals in each infectious class with the remaining individuals initially susceptible.

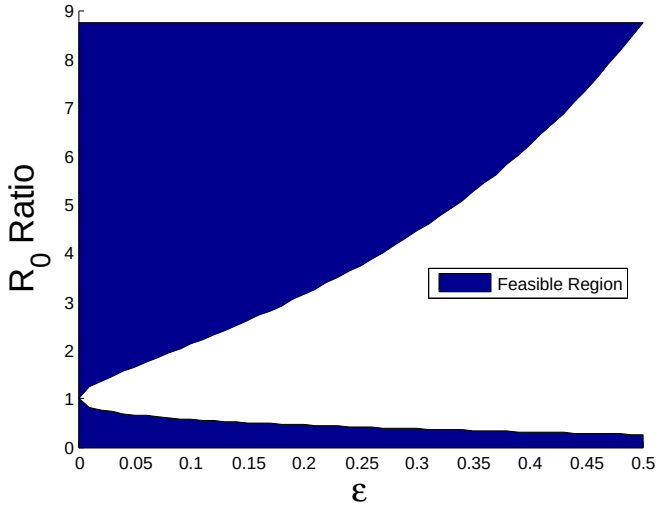

Figure 5: The feasible values for the ratio R_0^A/R_0^B against ϵ to potentially yield a complex coexistence scenario as given in Equations (20).

Parameter	**Units**	**Value**	**Varied?**
N_1	individuals	100000	N
N_2	individuals	150000	N
γ^A	weeks^{-1}	0.5	N
γ^B	weeks^{-1}	0.5	N
ϵ	1	[0.01, 0.99]	Y
$1/\mu$	years	[32, 82]	Y
β^A	weeks^{-1}	[1, 50]	Y
β^B	weeks^{-1}	[1, 50]	Y
$I_1^A(0)$	individuals	[1,1000]	Y
$I_1^B(0)$	individuals	[1,1000]	Y
$I_2^A(0)$	individuals	[1,1000]	Y
$I_2^B(0)$	individuals	[1,1000]	Y
$S_1(0)$	individuals	$N_1 - I_1^A(0) - I_1^B(0)$	N
$S_2(0)$	individuals	$N_2 - I_2^A(0) - I_2^B(0)$	N

Table 1: A list of parameters and initial conditions used for quantitative analysis. Each of the entries in the "Value" column given in brackets is a range of reasonable values. The "Varied?" column lists a "Y" if the value was included in the Latin Hypercube Sample.

3.4 Quantitative Analysis

We used a quantitative approach to determine the stability conditions for the non-disease-free equilibria. We chose to perform a Latin Hypercube Parameter Space Sampling [22] (LHS) to sample 10^8 combinations of parameters and initial conditions. The parameter values and ranges used for the sampling (from uniform distributions) are given in Table 1.

The model was then solved numerically for each set of values from the LHS in `MATLAB` over a timespan of 5000 simulated weeks. Each simulation output the values of $I_i^\alpha(5000)$ to determine which equilibrium was being approached. For simulations where $R_0^A = R_0^B$, both strains persisted, as predicted. For simulations where the R_0 values varied between strains, the dominant strain competitively excluded the weaker strain. From these results, we assert that if the complex coexistence equilibrium does exist, it is unstable.

4 Discussion

The analysis of the previous section indicates a pattern in the long-term behavior of a two-strain, two-population infectious disease system. In summary, when the basic reproductive number for both strains is below one, the disease-free equilibrium is stable and approached by all (biologically relevant) trajectories. Importantly, we have generalized that result to an n-population, m-strain situation in the theorem given in subsection 3.1. When the basic reproductive number for one strain is stronger than the other, and is greater than one, that strain competitively excludes the other. Finally, when both strains have equal basic reproductive numbers, and are greater than one, the strains exist simultaneously in the population (simple coexistence).

However, our work leaves many remaining research questions. The most obvious extension is the conclusion of the equilibrium analyses begun here, by proving the hypothesized stability of the competitive exclusion equilibria and the simple coexistence equilibrium while also proving the instability of the complex coexistence equilibrium. More generalizations could be made, such as varying the mixing rates and the birth/death rates by population, i.e. $\epsilon_1 \neq \epsilon_2$ and $\mu_1 \neq \mu_2$. This would yield different formulations for R_0 and could allow for more possibilities for complex coexistence.

Additionally, our results are specific to this deterministic model. Stochastic processes have previously been shown to have significant effects in multistrain and metapopulation models (see, for example, [26, 21, 11]). A stochastic analogue of this model may demonstrate long-term behavior where two strains of differing strengths could coexist in a metapopulation.

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Appendix

In this appendix, we provide the lemma referred to in subsection 3.1 and its proof.

Lemma 1. *Given the matrix* $\tilde{A} \in \mathbb{R}^{n\times n}$ *such that*

$$\tilde{A} = \begin{bmatrix} y-\tilde{x} & y & \dots & y \\ y & y-\tilde{x} & \ddots & \vdots \\ \vdots & \ddots & \ddots & y \\ y & \dots & y & y-\tilde{x} \end{bmatrix} \tag{21}$$

where

$$\tilde{x} = \frac{(\epsilon-1)\beta}{1+(n-1)\epsilon} - (\gamma+\mu) \tag{22a}$$

$$y = \frac{\epsilon\beta}{1+(n-1)\epsilon}, \tag{22b}$$

the eigenvalues of $\tilde{A}$ *are*

$$\lambda = \beta - (\gamma+\mu) \tag{23a}$$

with algebraic multiplicity 1 and

$$\lambda = \frac{(1-\epsilon)\beta}{1+(n-1)\epsilon} - (\gamma+\mu) \tag{23b}$$

with algebraic multiplicity $(n-1)$.

Proof. To find the eigenvalues of $\tilde{A}$, the equation $\det(\tilde{A} - \lambda I) = 0$ must be solved. Notice that $A_{n\times n} = \tilde{A} - \lambda I$ is of the form

$$A_{n\times n} = \begin{bmatrix} y-x & y & \dots & y \\ y & y-x & \ddots & \vdots \\ \vdots & \ddots & \ddots & y \\ y & \dots & y & y-x \end{bmatrix} \tag{24}$$

where

$$x = \frac{(\epsilon-1)\beta}{1+(n-1)\epsilon} - (\gamma+\mu+\lambda) \tag{25a}$$

$$y = \frac{\epsilon\beta}{1+(n-1)\epsilon}. \tag{25b}$$

Consider the sequences a_i and b_i defined by

$$a_i = \begin{cases} y-x & i=0 \\ (y-x)a_{i-1} - iyb_{i-1} & i \geq 1 \end{cases} \tag{26a}$$

and

$$b_i = \begin{cases} y & i=0 \\ ya_{i-1} - iyb_{i-1} & i \geq 1. \end{cases} \tag{26b}$$

Let $B_{n\times n}$ be an $n \times n$ matrix of the form

$$B_{n\times n} = \begin{bmatrix} y & y & \dots & y \\ y & y-x & \ddots & \vdots \\ \vdots & \ddots & \ddots & y \\ y & \dots & y & y-x \end{bmatrix}. \tag{27}$$

We claim that the value a_{n-1} gives the determinant for $A_{n\times n}$ and b_{n-1} gives the determinant for $B_{n\times n}$. We prove this claim by induction on n. For $n=1$ we have $A_{1\times 1} = \det(A_{1\times 1}) = y-x = a_0$ and $B_{1\times 1} = \det(B_{1\times 1}) = y = b_0$.

Now suppose the claim holds for all $n < k$. First we introduce some notation: Let $B^0_{n\times n} = B_{n\times n}$ and for $1 < i < n$ let $B^i_{n\times n} = B^{i-1}_{n\times n}$ with rows $i-1$ and i interchanged.

Perform cofactor expansion along the top row of $A_{n\times n}$. Then we have

$$\det(A_{n\times n}) = (y-x)\det(A_{(n-1)\times(n-1)}) - y\sum_{i=0}^{n}\det(B^i_{(n-1)\times(n-1)}). \tag{28}$$

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

$$\det(A_{n\times n}) = (y-x)\det(A_{(n-1)\times(n-1)}) - y\sum_{i=0}^{n}\det(B_{(n-1)\times(n-1)}) \tag{29a}$$

$$= (y-x)\det(A_{(n-1)\times(n-1)}) - (n-1)y\det(B_{(n-1)\times(n-1)}). \tag{29b}$$

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

$$\det(A_{n\times n}) = (y-x)a_{n-2} - (n-1)yb_{n-2} = a_{n-1} \tag{30}$$

as claimed.

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

$$\det(B_{n\times n}) = ya_{n-2} - (n-1)y(b_{n-2}) = b_{n-1}. \tag{31}$$

Thus, the claim holds for all n.

Now, we claim that the sequences a_i and b_i have closed forms given by

$$a_i = (-1)^i\left[(i+1)x^iy - x^{i+1}\right] \tag{32a}$$

$$b_i = (-1)^i(x^iy). \tag{32b}$$

Again, we prove this claim by induction on i. For $i=0$ we have

$$a_0 = (y-x) = (-1)^0\left(x^0y - x\right) \tag{33a}$$

$$b_0 = y = (-1)^0\left(x^0y\right). \tag{33b}$$

Suppose that for $i=k$ the claim holds. Then for $i = k+1$ we have

$$a_{k+1} = (y-x)a_k - (k+1)yb_k \tag{34a}$$

$$= (y-x)\left[(-1)^k\left((k+1)x^ky - x^{k+1}\right)\right] - (k+1)y\left[(-1)^kx^ky\right] \tag{34b}$$

$$= (-1)^k(k+1)x^ky^2 - (-1)^kx^{k+1}y - (-1)^k(k+1)x^{k+1}y - (-1)^k(k+1)x^ky^2 \tag{34c}$$

$$= -(-1)^kx^{k+1}y - (-1)^k(k+1)x^{k+1}y \tag{34d}$$

$$= (-1)^{k+1}\left[(k+2)x^{k+1}y - x^{k+2}\right] \tag{34e}$$

as claimed. We also have

$$b_{k+1} = ya_k - (k+1)b_k \tag{35a}$$

$$= y\left[(-1)^k\left((k+1)x^ky - x^{k+1}\right)\right] - (k+1)y\left[(-1)^kx^ky\right] \tag{35b}$$

$$= (-1)^k\left[(k+1)x^ky^2 - x^{k+1}y\right] - (-1)^k(k+1)x^ky^2 \tag{35c}$$

$$= (-1)^k(-x^{k+1}y) \tag{35d}$$

$$= (-1)^{k+1}(x^{k+1}y) \tag{35e}$$

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.

We have just shown that

$$\det(A_{n\times n}) = a_{n-1} \tag{36a}$$

$$= (-1)^{n-1}\left(nx^{n-1}y - x^n\right) \tag{36b}$$

$$= (-1)^{n-1}x^{n-1}(ny-x). \tag{36c}$$

Substituting in values for x and y found in Equation (25), we have

$$a_{n-1} = (-1)^{n-1} \cdot \left(\frac{(\epsilon - 1)\beta}{1 + (n-1)\epsilon} + \gamma + \mu + \lambda \right)^{n-1} \cdot (\beta - (\gamma + \mu) - \lambda). \quad (37)$$

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

$$\left(\frac{(\epsilon - 1)\beta}{1 + (n-1)\epsilon} + \gamma + \mu + \lambda \right)^{n-1} = 0 \quad (38)$$

or

$$(\beta - (\gamma + \mu) - \lambda) = 0. \quad (39)$$

The first case gives

$$\lambda = \frac{(1 - \epsilon)\beta}{1 + (n-1)\epsilon} - (\gamma + \mu) \quad (40)$$

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

$$\lambda = \beta - (\gamma + \mu) \quad (41)$$

with algebraic multiplicity 1. Thus, the eigenvalues of $\tilde{A}$ are as claimed. ■