MATHEMATICAL MODELING OF EPIDEMICS: PARAMETRIC HETEROGENEITY AND PATHOGEN COEXISTENCE

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The supervisory committee certifies that this dissertation complies with North Dakota State University's regulations and meets the accepted standards for the degree of

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ABSTRACT

No two species can indefinitely occupy the same ecological niche according to the competitive exclusion principle. When competing strains of the same pathogen invade a homogeneous population, the strain with the largest basic reproductive ratio R_0 will force the other strains to extinction. However, over 51 pathogens are documented to have multiple strains [3] coexisting, contrary to the results from homogeneous models. In reality, the world is heterogeneous with the population varying in susceptibility. As such, the study of epidemiology, and hence the problem of pathogen coexistence should entail heterogeneity. Heterogeneous models tend to capture dynamics such as resistance to infection, giving more accurate results of the epidemics. This study will focus on the behavior of multi-pathogen heterogeneous models and will try to answer the question: what are the conditions on the model parameters that lead to pathogen coexistence? The goal is to understand the mechanisms in heterogeneous populations that mediate pathogen coexistence. Using the moment closure method, Fleming et. al. [22] used a two pathogen heterogeneous model (1.9) to show that pathogen coexistence was possible between strains of the baculovirus under certain conditions. In the first part of our study, we consider the same model using the hidden keystone variable (HKV) method. We show that under some conditions, the moment closure method and the HKV method give the same results. We also show that pathogen coexistence is possible for a much wider range of parameters, and give a complete analysis of the model (1.9), and give an explanation for the observed coexistence.

The host population (gypsy moth) considered in the model (1.9) has a year life span, and hence, demography was introduced to the model using a discrete time model (1.12). In the second part of our study, we will consider a multi-pathogen compartmental heterogeneous model (3.1) with continuous time demography. We show using a Lyapunov function that pathogen coexistence is possible between multiple strains of the same pathogen. We provide analytical and numerical evidence that multiple strains of the same pathogen can coexist in a heterogeneous population.

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I would also like to give special thanks to the Department of Mathematics, NDSU and all the professors who helped me through my education.

DEDICATION

This thesis is dedicated to my mother, Theresa Sakyi, and my wife, Annalise Sarfo.

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1. INTRODUCTION

1.1. History and background

"As a matter of fact, all epidemiology concerned as it is with the variation of disease from time to time or from place to place, must be considered mathematically, however many variables as implicated, if it is to be considered scientifically at all. To say that a disease depends upon certain factors is not to say much, until we can form an estimate as to how largely each factor influences the whole result. And the mathematical method of treatment is really nothing but the application of careful reasoning to the problems at issue".

-Sir Ronald Ross 1911 [2, 25].

The mathematical study of infectious diseases began with the work of John Graunt (1620-1674), whose 1663 book *Natural and Political Observations Made upon the Bills of Mortality* was concerned with methods of public health statistics [2]. He analyzed multiple diseases and estimated the comparative risks of dying from various diseases [6]. A century later, Daniel Bernoulli (1700-1782) introduced what is considered the first model in mathematical epidemiology on the inoculation against smallpox. His publication in 1766 [5] argued that inoculation with a mild strain of the smallpox could provide a lifelong immunity. Early contributions to the study of epidemics continued through the works of Louis Pasteur (1822-1875), John Snow(1873) and William Budd (1873).

In 1906, W. H. Hamer proposed the mass action law for the rate of new infections in his studies of the recurrences of measles. He theorized that the spread of infection should depend on the number of susceptible individuals and the number of infected individuals. This idea is generally very useful in compartmental models. Sir Ronald Ross, Nobel Prize winner and the discoverer of the malaria parasite was one of the first scientists to use compartmental models in epidemic modeling. In his book *The Prevention of Malaria*, published in 1911, he developed a compartmental model to study the dynamics of the transmission of malaria between mosquitoes and humans. He was the first to introduce the concept of the basic reproductive number. Through his models, he showed that reduction in the number of mosquitoes could eradicate malaria [2, 6, 7]. Quoted in the British Medical Journal, Sir Ross pleaded that epidemics should be studied mathematically.

Mathematical epidemiology was made more popular by Kermack and McKendrick in 1927. In their three paper series [30–32], they introduced a deterministic model which categorizes the population into three distinct classes: Susceptible, Infectious, and Recovered classes.

Consider a population of size N with some initial number of infected people. People go successively through three states: the susceptible state S, the infectious state I, and the recovered state R. The model formulated by Kermack and McKendrick is mathematically detailed and generally complex, however, a simplified version of the so-called SIR model can be written as

$$\begin{aligned} \frac{dS}{dt} &= -\beta SI, \\ \frac{dI}{dt} &= \beta SI - \gamma I, \\ \frac{dR}{dt} &= \gamma I, \end{aligned} \tag{1.1}$$

where β is the transmission rate and γ is the recovery or removal rate. The reciprocal of the removal rate $1/\gamma$ is the average infectious period. In the model (1.1), $S(t) + I(t) + R(t) = N$ for any t. In their model (1.1), there are no death and birth rates, so the population size is constant. There are different versions of (1.1) depending on how the transmission term and the population size are defined, details can be found in [4].

Since the works of Kermack and McKendrick, epidemic modeling has been heavily studied among mathematicians and biologist using the SIR approach in many directions [6]. Epidemic models tend to give a snapshot of how diseases spread when there is an outbreak and help decision makers to devise strategies to tackle it.

In reality, many diseases are caused by multiple strains of the same pathogen. For instance, over 51 human pathogens including malaria, dengue fever, gonorrhea and tuberculosis can be categorized into distinct strains, each defined by its antigenic properties [3]. Phenotypic variations within a pathogen species as well as heterogeneity in pathogen virulence are key reasons why multiple-strain models are necessary. The existence of multiple strains can affect the prevention and treatment process of an infection. An accurate understanding of the spread of such diseases requires multi-strain or multi-pathogen models. The number of strains increase the number of compartments into which the population can be subdivided.

The study of multi-strains models is common and can be seen in [33]. Such models allow us to investigate the evolution of the disease, the behavior of the disease and the optimal strategy for disease control.

A possible modification of (1.1) into a two-pathogen-strain model is

$$\begin{aligned} \dot{S} &= \mu - \beta_1 S I_1 - \beta_2 S I_2 - \phi S, \\ \dot{I}_1 &= \beta_1 S I_1 - \gamma_1 I_1 - \phi I_1, \\ \dot{I}_2 &= \beta_2 S I_2 - \gamma_2 I_2 - \phi I_2, \\ \dot{R} &= \gamma_1 I_1 + \gamma_2 I_2 - \phi R. \end{aligned} \tag{1.2}$$

The four distinct compartmental classes in this model are: the susceptible to both strains S, infectious with strain 1 I_1, infectious with strain 2 I_2, and recovered and therefore immune to both, R [29]. We assume that the pathogen strains have different transmission rates β_i and different recovery rates γ_i $(i = 1, 2)$. In this model, demography is captured by μ as the birth rate and ϕ as the mortality rate.

Early multi-strain epidemic models studied the competition between two distinct strains [18, 19, 24]. The models investigated the duration of infection for each strain and analyzed the dynamics of the infection if one strain provided immunity to the other [33]. In 1989, Castillo-Chavez et al. [10] introduced a model which involved little or no cross immunity. When researchers consider multi-strain models, they are often interested in knowing the impact of each strain on the dynamics. In modeling, different strains of the same pathogen often vary in terms of their virulence or transmission rates. However, the property that is mostly of high interest is the basic reproductive number R_0.

The basic reproductive number is defined as the average number of secondary cases arising from an average primary case in an entirely susceptible population [29]. The basic reproductive number is a measure for the reproductive potential of an infectious disease. R_0 is a threshold parameter. In general, a pathogen strain i can only invade a susceptible population if and only if its strain specific basic reproductive number is greater than one, $R_{0_i} > 1$. Another useful application of R_0 is in determining the fraction of the populations that needs to be vaccinated in order to avoid a major outbreak. In (1.1), that fraction is $P_{crit} = 1 - \frac{1}{R_0}$ [29].

For multi-strain models, we have the strain-specific basic reproductive number and the overall basic reproductive number for the infection. Computation of the R_0 for compartmental models is often done by using the next generation matrix [17]. An overall discussion of basic reproductive numbers in multi-strain models can be seen in [36]. In (1.1), $R_0 = \frac{\beta N}{\gamma}$, meaning if $\gamma > \beta N$, there is no infection and the disease dies out quickly. In (1.2), the strain specific basic reproductive number is given by $R_{0_i} = \frac{\beta_i S^*}{\gamma_i + \phi}\,(i = 1, 2)$, where S^* is the density of the susceptible class at the disease free equilibrium. Studies have shown that if $R_{0_i} > R_{0_j}$, then only pathogen strain i survives in the long term [29]. In this case, we refer to pathogen strain i as the dominant strain.

We use the next generation matrix (NGM) to find R_0 of (1.2). The next generation matrix is a matrix that relates the number of newly infected individuals in the various compartmental classes in consecutive generations; it was introduced by Diekmann in 1990 [17]. The NGM can be derived from the infection subsystem (the infection subsystem describes the production of newly infected individuals and changes in the states of already existing infected). The infection subsystem of equation (1.2) is

$$\begin{aligned} \dot{I}_1 &= \beta_1 S I_1 - \gamma_1 I_1 - \phi I_1, \\ \dot{I}_2 &= \beta_2 S I_2 - \gamma_2 I_2 - \phi I_2. \end{aligned} \tag{1.3}$$

Let $x = (I_1, I_2)^{'}$, where the prime denotes the transpose. The linearized subsystem of (1.3) around the disease free equilibrium (DFE) $(S^*, 0, 0)$ is

$$\begin{aligned} \dot{x} =& (T + \Sigma)x, \\ \text{where } T =& \begin{pmatrix} \beta_1 S^* & 0 \\ 0 & \beta_2 S^* \end{pmatrix}, \text{and } \Sigma = \begin{pmatrix} -\gamma_1 - \phi & 0 \\ 0 & -\gamma_2 - \phi \end{pmatrix}. \end{aligned} \tag{1.4}$$

The matrix T corresponds to transmissions and the matrix Σ corresponds to the transitions. The basic reproductive number R_0 is computed as the spectral radius of the NGM, $K = -T\Sigma^{-1}$ [17].

$$\begin{aligned} K = -T\Sigma^{-1} &= -\begin{pmatrix} \beta_1 S^* & 0 \\ 0 & \beta_2 S^* \end{pmatrix} \begin{pmatrix} \frac{1}{-\gamma_1-\phi} & 0 \\ 0 & \frac{1}{-\gamma_2-\phi} \end{pmatrix} \\ &= \begin{pmatrix} \frac{\beta_1 S^*}{\gamma_1+\phi} & 0 \\ 0 & \frac{\beta_2 S^*}{\gamma_2+\phi} \end{pmatrix}. \end{aligned} \tag{1.5}$$

Therefore,

$$R_0 = \max\left\{\frac{\beta_1 S^*}{\gamma_1+\phi}, \frac{\beta_2 S^*}{\gamma_2+\phi}\right\} = \max\left\{R_{0_1}, R_{0_2}\right\}. \tag{1.6}$$

The system (1.2) has three equilibria when the strain-specific R_{0_i}'s are different:

$$\hat{x}_1 = (S^*, 0, 0)\,,\ \hat{x}_2 = \left(\frac{\gamma_1+\phi}{\beta_1}, I_1^*, 0\right) \text{ and } \hat{x}_3 = \left(\frac{\gamma_2+\phi}{\beta_2}, 0, I_2^*\right). \tag{1.7}$$

The case where both pathogens coexists requires $\frac{\gamma_1+\phi}{\beta_1} = \frac{\gamma_2+\phi}{\beta_2}$, which only occurs when the two pathogen strains have the same strain specific basic reproductive number. The bifurcation diagram of the homogeneous model (1.2) is given in Figure 1.1.

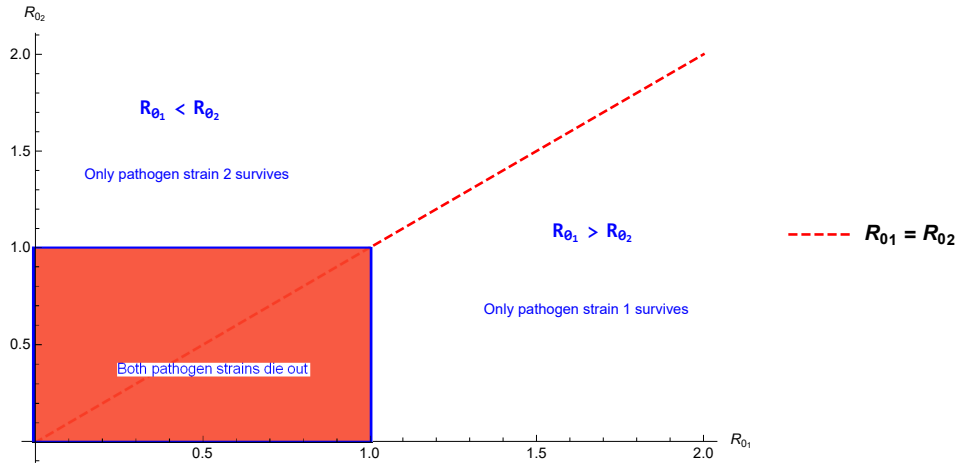

Figure 1.1. The bifurcation diagram of system (1.2). A pathogen strain is only able to invade susceptible population when its strain specific $R_{0_i} > 1$. The strain with the largest R_0 forces the other strain to extinction.

Equations (1.1) and (1.2) are considered homogeneous because they assume that the entire susceptible class has the same level of risk to infection or the same susceptibility. The real world is evidently heterogeneous with the population differing in the level of risk of infection or transmitting an infection. Almost all populations can be subdivided into different groups depending on this factor. There are multiple forms of heterogeneity. For airborne diseases, proximity to the source of infection determines the level of risk, and hence location defines the heterogeneity (spatial heterogeneity). For sexually transmitted diseases, a person with multiple sex partners is at a higher risk of getting infected than a person with one or no partners therefore heterogeneity is defined by the number of contacts (partners). Diseases like prostate cancer are only applicable to men and hence requires models which divides the population into two classes: males and females. Other diseases like arthritis, hypertension and Alzheimer's are more likely to affect old people than young people, therefore age is the heterogeneous trait. In general, genetic variations and vaccination history creates division in susceptibility levels in humans, therefore the level of risk to infection generally varies from person to person. Models that includes heterogeneity such as age, gender, behavior and risk of infection tends to give a better representation of reality.

Model (1.1) can be modified into a simple heterogeneous model with the host population varying in susceptibility. Let $s(t,\omega)$ be the density of susceptible hosts having the susceptibility that is characterized by the trait value ω. The total size of the susceptible population at time t is given by $S(t) = \int_\Omega s(t,\omega)d\omega$, where Ω is the set of trait values. Here, $s(0,\omega)$ defines the initial distribution of susceptibility before the infection starts. Let $I(t)$ be the density of the infected population and $R(t)$ be the density the recovered class at time t. A simple heterogeneous model is

$$\begin{aligned} \frac{\partial s(t,\omega)}{dt} &= -\beta(\omega)s(t,\omega)I(t), \\ \frac{dI(t)}{dt} &= \int_\Omega \beta(\omega)s(t,\omega)d\omega I(t) - \gamma I(t), \\ \frac{dR(t)}{dt} &= \gamma I(t). \end{aligned} \tag{1.8}$$

The transmission rate β is a function of this trait value ω. This particular type of heterogeneity is referred to as parametric heterogeneity.

In (1.8), we assume that difference in susceptibility with respect to the trait value ω does not lead to difference in infectiousness or difference in rate of recovery, therefore the entire infectious class can be summed up as $I(t)$ with recovery rate γ. Discussion of such types of models can be found in [28, 35].

One of the most highly discussed topics in multi-strain epidemic models is *competitive exclusion* and coexistence of pathogens. According to Gause's law or what it is commonly referred to as *competitive exclusion principle*, no two species can indefinitely occupy the same ecological niche. Studies on homogeneous multi-strain models [8] such as (1.2) shows that coexistence is not possible when the competing strains have different R_{0_i}'s. The reality, however, is that, we observe multiple strains of pathogens coexisting in the current world [3]. Our main goal for this research is to show that coexistence is possible for a wide range of parameters in heterogeneous models and identify the exact conditions that promote coexistence.

1.2. A short review of existing models

Mathematical models have been used in the study of epidemics for a long time [6], but the study of multi-strain models in heterogeneous models is a more current area of research. Such models generally have a higher number of compartmental classes making them generally more difficult to analyze. A significant part of the study on heterogeneous multi-strain models is focused on sexually transmitted diseases [13, 16, 26].

In their study of multi-strain models, Castillo-Chaves et al. showed in a series of papers [11, 14] that coexistence is not possible in a heterosexually-active homogeneous population using SIS STD models. However, they later focused their study on just the female population and divided them into two different groups based on their susceptibility to the two different pathogenic strains. They showed that heterogeneity in susceptibility to the acquisition of the infection can lead to pathogen coexistence [12]. Whilst they proved that variability in susceptibility in the female sub-population leads to pathogen coexistence, the immediate question was: how can their studies can be extended to the entire population?

In [13], Castillo-Chaves et al. extended their study in [12] to a two-sex heterosexually active population that includes a single group of males and two different groups of females. They showed that there exists a unique coexistence equilibrium if and only if the boundary equilibria both exist and have the same stability. They also presented the necessary conditions for the existence and

global stability of such equilibria. Their study shows that heterogeneity in just a subpopulation (only females) can lead to pathogen coexistence. Authors of [15] did a similar analysis and confirmed the results of [13] by increasing the number of divisions in the female population. So what happens when the entire population is heterogeneous that is when we consider different classes of the male population varying in susceptibility to infection?

Authors of [16] studied the dynamics of sexually transmitted diseases in a homosexually active population. Here, the entire population was divided into three groups based on their susceptibility to the infection (by two distinct pathogenic strains). The measure of one's susceptibility was determined by the number of contacts (partners) for the individual. Similar to [13], they presented sufficient mathematical analysis to conclude that there exists a unique coexistence equilibrium if and only if the boundary equilibra both exist and have the same stability. In the case of existence, the coexistence equilibrium is globally stable. Whilst their model addresses heterogeneity in the entire population, they do not account for heterosexually active populations.

The study of multi-strain pathogens is not only limited to sexually transmitted diseases. Many researchers have studied pathogen coexistence of the dengue virus. For instance, there are four known serotypes of the dengue arbovirus [20] each of which provides complete host immunity but not a complete cross immunity from the other serotypes. In [21], Zhilan et al. studied the interactions between two serotypes of the dengue virus in a population of variable size. With no heterogeneity in the susceptible population, they showed that there is no long term persistence of both strains in the host population. In [20] however, they showed that changes in the susceptibility to the heterologous serotype can lead to coexistence. In general, coexistence of the serotypes was favored by the increase of the susceptibility to the secondary infection and less favored by cross immunity.

There are some studies on spatial heterogeneity. The study of pathogen coexistence in such populations can be seen in [1]. Ackleh et al. considered a two-strain pathogen model described by a system of reaction-diffusion equations. They showed that spatial heterogeneity promotes coexistence. Their model assumes that individuals in the same location have the same level of susceptibility which is applicable to most airborne diseases. In addition, they assume that the total population size is a constant and demography is in the form of migration when a person move from one location to another location. Their model is applicable to short term epidemics where we can

assume that natural birth and death rates are negligible. It will be interesting to know the results for long term dynamics which incorporates natural birth and death.

1.3. The gypsy moth model

Fleming-Davies et al. [22] conducted a study on the effects of host heterogeneity on pathogen diversity and evolution. They used mathematical and statistical tools to analyze a two-pathogen competition model in which heterogeneity is modeled as a continuous variation in host susceptibilities. The two pathogens in their model were two different isolates of the baculovirus species that infected gypsy moth (*Lymantria dispar*) caterpillars. When the gypsy moth larva hatches, it gets infected by the baculovirus when it consumes contaminated egg material. The transmission happens only after the infected neonate dies. When the infected neonate dies, it contaminates the area (leaves or barks of trees) where it died. The baculovirus can only infect the gypsy moth larvae and not the adults. Therefore, infected neonates in season n only infects neonates in season $n+1$. The virus overwinters in the area where the infected neonate died, sheltered by gypsy moth egg masses. In their model, host individuals vary continuously in their susceptibility, however, the differences in their susceptibility do not lead to differences in infectiousness when they are infectious cadavers.

Let $s(t, \beta_1, \beta_2)$ be the density of the host population at time t susceptible to pathogen strain 1 with transmission rate β_1, and pathogen strain 2 with transmission rate β_2. Thus at any time t, s is a two-dimensional distribution that depends on the the infection risk with respect to pathogen 1, β_1, and pathogen 2, β_2 [22]. Here, $s(0, \beta_1, \beta_2)$ is the initial distribution of susceptibility before the outbreak, and $S(t) = \int_{\Omega_1}\int_{\Omega_2} s(t, \beta_1, \beta_2) d\beta_1 d\beta_2$ is the total population density of the host population at time t, where $\Omega_1 \times \Omega_2 = [0, \infty) \times [0, \infty)$. Let $I_i(t)$ be the density of infectious cadavers at t relative to pathogen strain i. The two-pathogen competition model that was considered in [22] is

$$\begin{aligned}
\frac{\partial s}{\partial t} &= -\beta_1 s(t, \beta_1, \beta_2) I_1 - \beta_2 s(t, \beta_1, \beta_2) I_2, \\
\frac{dI_1}{dt} &= I_1 \int_0^\infty \int_0^\infty \beta_1 s(t, \beta_1, \beta_2) d\beta_1 d\beta_2 - \gamma_1 I_1, \\
\frac{dI_2}{dt} &= I_2 \int_0^\infty \int_0^\infty \beta_2 s(t, \beta_1, \beta_2) d\beta_1 d\beta_2 - \gamma_2 I_2.
\end{aligned} \tag{1.9}$$

Model (1.9) is a generalization of (1.2) and (1.8).

Let $P(\beta_1, \beta_2)$ be a bivariate probability distribution. The initial conditions for (1.9) are

$$s(0, \beta_1, \beta_2) = S_0 P(\beta_1, \beta_2), \quad I_i(0) = I_{0_i}, \quad i = 1, 2, \tag{1.10}$$

where S_0 is the total initial density of the host population.

Fleming-Davies et al. [22] used moment closure method to simplify (1.9). The moment closure method uses properties of the joint j-k-th moment of $s(t, \beta_1, \beta_2)$, $S_{j,k} = \int_0^\infty \int_0^\infty \beta_1^j \beta_2^k s(t, \beta_1, \beta_2)$ $d\beta_1 d\beta_2$ to derive differential equations for the marginal mean transmission rates. In this case, the method worked under the assumption that the coefficients of variation $C_i, i = 1, 2$ for each pathogen is constant, and the Pearson product-moment correlation coefficient ρ is also constant. In model (1.9), the susceptibility of the host population varies continuously with time, as such the instantaneous mean transmission rate changes with time. During the epidemic, the transmission rate will drop since the highly susceptible individuals are infected first, and removed from the susceptible class. This causes a decrease in the instantaneous mean transmission rate. The measure of the changes in the instantaneous mean transmission rate is what we call variation in transmission (coefficient of variation). The coefficient of variation, $C_i = \frac{\sigma}{\bar{\beta}}$ is the ratio of the standard deviation σ to the mean $\bar{\beta}$. The correlation coefficient, $\rho = \frac{cov(\beta_1, \beta_2)}{\sigma_1 \sigma_2}$ (where $cov(\beta_1, \beta_2)$ is the covariance between the transmission rates and $\sigma_i, \imath = 1, 2$ are the standard deviations) is a measure of the relationship between the transmission rates β_i, $i = 1, 2$. A measure of $\rho = 1$ means that there is a strong relation between the transmission rates that is, the probability of being infected by pathogen strain 1 is highly dependent on the probability of being infected by pathogen strain 2. A measure of $\rho = 0$ means that there is not correlation that is, the probability of being infected by pathogen strain 1 is independent (has no relation) of the probability of being infected by pathogen strain 2. A measure of $\rho = -1$ means that there is a negative correlation that is, the higher probability of being infected by pathogen strain 1 is, the lower the probability of being infected by pathogen strain 2. Fleming-Davies et. al. assumed that the time dependent coefficients of variation and the correlation coefficient are constant, in effect, they proved in Appendix of [22] the following theorem.

Theorem 1.3.1. *Let $s(t, \beta_1, \beta_2)$ solve system (1.9). Assume that the initial distribution $P(\beta_1, \beta_2)$ of susceptibility is such that the time dependent coefficients of variations and the correlation coefficient are constant and equal to C_1, C_2, ρ. Also assume that $\bar{\beta}_1(0) = \int \int_{\Omega_1 \times \Omega_2} \beta_1 p(\beta_1, \beta_2) d\beta_2 d\beta_1$,*

$\bar{\beta}_2(0) = \int\int_{\Omega_1\times\Omega_2} \beta_2 p(\beta_1,\beta_2)d\beta_1 d\beta_2$ *in (1.9). Then given the same initial conditions* S_0, I_{0_1}, I_{0_2}, $S(t) = \int\int_{\Omega_1\times\Omega_2} s(t,\beta_1,\beta_2)d\beta_1 d\beta_2$ *solves problem (1.11).*

$$\begin{aligned}
\frac{dS}{dt} &= -(\bar{\beta}_1(t)I_1 + \bar{\beta}_2(t)I_2)S,\\
\frac{d\bar{\beta}_1(t)}{dt} &= -\bar{\beta}_1(t)^2 C_1^2 I_1 - \rho C_1 C_2 I_2 \bar{\beta}_1(t)\bar{\beta}_2(t),\\
\frac{d\bar{\beta}_2(t)}{dt} &= -\bar{\beta}_2(t)^2 C_2^2 I_2 - \rho C_1 C_2 I_1 \bar{\beta}_1(t)\bar{\beta}_2(t),\\
\frac{dI_1}{dt} &= \bar{\beta}_1(t)SI_1 - \gamma_1 I_1,\\
\frac{dI_2}{dt} &= \bar{\beta}_2(t)SI_2 - \gamma_2 I_2,
\end{aligned} \tag{1.11}$$

where $\bar{\beta}_i$ *is the instantaneous mean transmission rate of pathogen strain* i, C_i *is the coefficient of variation, and* ρ *is the correlation coefficient.*

Proof. A comprehensive proof can be seen in the Appendix of [22]. □

The life-cycle of the gypsy moth larvae is one year. Therefore the susceptible population for the current infected neonates is the next generation of larvae. The process is represented by a discrete time model. Let the entire population density at the end the nth season be denoted by N_n, the fraction of larvae infected by pathogen strain i by ι_i, and both pathogen strains reproduce at the rate ϕ. Let $Z_{i,n+i}$ denote the density of pathogen strain i at the beginning of the $(n+1)$-th season. Demography was introduced to the model (1.9) using the following discrete time model:

$$\begin{aligned}
N_{n+1} &= \lambda_n N_n(1-\iota_1-\iota_2),\\
Z_{1,n+1} &= \phi N_n \iota_1,\\
Z_{2,n+1} &= \phi N_n \iota_2.
\end{aligned} \tag{1.12}$$

At the end of the season, surviving hosts $N_n(1-\iota_1-\iota_2)$ reproduce at rate λ_N, to give the host population for the next year, N_{n+1} . A pathogen was said to be extinct if its density at the end of a season was less than 10^{-6}.

Using data from field and laboratory experiments, they found that two pathogen strains are more likely to coexist if they differ in transmission rates: a low variability, low mean transmission is able to coexist with a more variable, high mean transmission (about 10 times the low one) pathogen

[22]. They also produced evidence that pathogen coexistence was not possible in homogeneous systems. A sample of their simulation is shown in Figure 1.2.

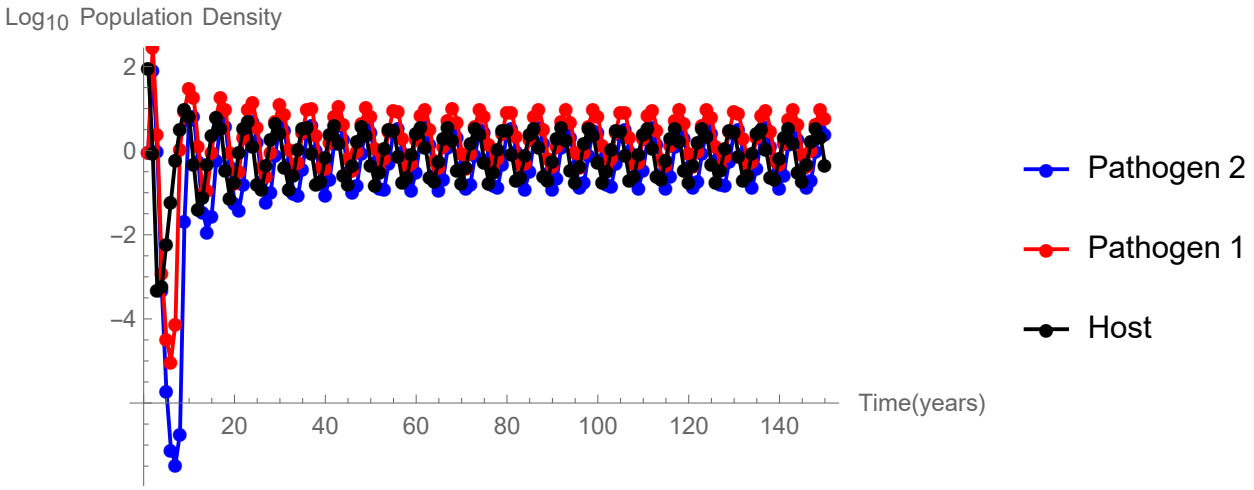

Figure 1.2. Two strains of baculovirus can survive in multiple generations of gypsy moths when one pathogen strain has a high mean transmission rate $\bar{\beta}_1 = 10.5$ and a high coefficient of variation $C_1 = 2.06$, and the other pathogen strain has a low transmission rate $\bar{\beta}_2 = 0.5$ coupled with a low coefficient of variation $C_2 = 0.68$. Other parameter values are $\rho = 0.5$, $\gamma_1 = 0.99$, $\gamma_2 = 0.32$, $\phi = 0.4$, $\lambda_N = 10$, initial densities $N_0 = 100$, $Z_{1,0} = Z_{2,0} = 1$.

The work of Fleming-Davies et al. [22] leads to a number of questions:

- What if the coefficients of variation were not constant?
- What if the correlation coefficient was not constant?
- What happens if we replace the discrete seasons with continuous time?
- What probability distribution describes the initial distribution of the susceptible population?
- Is it possible to find other conditions for pathogen coexistence?

1.4. Preview of results

In this study, we use a different approach, the hidden keystone variable (HKV) or Reduction theorem method to analyze the integro-differential system (1.9) and discuss the topic of pathogen coexistence. We show that it is possible to derive a simplification of model (1.9) without assuming that the coefficients of variation and the correlation coefficient are constant. We show that the initial

distribution of susceptibility in the moment closure model used by [22] can be approximated by the gamma distribution if the correlation coefficient is zero. We analyze our model using multiple initial distributions for the susceptible population, and show that when the assumptions on the coefficients of variation and correlation coefficient are lifted, pathogen coexistence is possible for a much wider range of parameters. Example: a pathogen strain with a high mean coupled with low variation can coexist with a strain with a low mean, high variation (contrary to the results in [22], where coexistence was only possible between a pathogen strain with a high mean, high variation and a low mean low variation pathogen strain).

It is important to understand the effect of the maintenance population and the maintenance community in our models [9]. As a next step, we extend model (1.9) to include demographics which are continuous with respect to time, thus replacing the discrete seasons. We show that even in cases where pathogens go extinct, heterogeneity can prolong coexistence compared to homogeneous models. We use bifurcation analysis to explain the reason behind the coexistence observed in the gypsy moth model. In addition, we use numerical simulations showcase some interesting behaviors of heterogeneous models. Example: a pathogen strain with the largest initial basic reproductive number can go extinct faster than the strain with the lowest initial basic reproductive number, this observation is not possible in homogeneous models.

The reduction method only works for a special types of equations (of the form $N(t)' = N(t)F(t, f(E^t[a]))$ for a population N distributed to the parameter a). Therefore for model (1.9), we can only consider demographic terms of the form $s(t, \beta_1, \beta_2)(f(S))$. To account for models which do not have this form of demography, we will also consider a multi-pathogen heterogeneous model with compartmentalized host population (3.1). Heterogeneity is going to be addressed through the transmission rates with each susceptible subclass having a different transmission rate. We show that in general, the strictly positive endemic equilibrium is globally asymptotically stable when it exists. We give some general conditions that can lead to the existence of coexistence equilibrium. As evidence of pathogen coexistence, we consider some specific cases of (3.1), and show numerically that pathogen coexistence is possible among multiple strains of the same pathogen.

2. ANALYTICAL AND NUMERICAL ANALYSIS OF HETEROGENEOUS MODELS WITH TWO PATHOGENS AND DISCRETE SEASONS

2.1. Two-pathogen competition model with no demography

We use an approach introduced by Georgiy P. Karev (On mathematical theory of selection: continuous time population dynamics) [27] to analyze (1.9). Let $s(t, \beta_1, \beta_2)$ denote the density of susceptibles varying in susceptibility with respect to the transmission rates β_1 and β_2 at time t. Therefore, the total density of the susceptible population at any time t is $S(t) = \iint_\Omega s(t, \beta_1, \beta_2) d\beta_1 d\beta_2$ (here $\Omega = [0, \infty) \times [0, \infty)$). Let $I_i(t)$ be the density of the population infected by pathogen i. The following theorem is a particular case of a more general statement proved in [27]. We state it here and provide a simplified proof to make the text self contained.

Theorem 2.1.1. *Consider model (1.9) and let $P(\beta_1, \beta_2)$ be an initial distribution of susceptibility, and $M(0, \lambda_1, \lambda_2)$ be its moment generating function. Then $S(t) = \int \int_\Omega s(t, \beta_1, \beta_2) d\beta_1 d\beta_2$ solves the system of ordinary differential equations (2.1) provided the initial conditions S_0, I_{0_1}, I_{0_2} are the same for both (1.9) and (2.1).*

$$\begin{aligned} \frac{dS(t)}{dt} &= -\bar{\beta}_1(t) S(t) I_1(t) - \bar{\beta}_2(t) S(t) I_2(t), \\ \frac{dI_1(t)}{dt} &= \bar{\beta}_1(t) S(t) I_1(t) - \gamma_1 I_1(t), \\ \frac{dI_2(t)}{dt} &= \bar{\beta}_2(t) S(t) I_2(t) - \gamma_2 I_2(t), \\ \frac{q_i(t)}{dt} &= -I_i(t), \quad q_i(0) = 0, \quad i = 1, 2, \end{aligned} \tag{2.1}$$

where $\bar{\beta}_i(t) = \frac{d}{d\lambda_i} M(t, \lambda_1, \lambda_2)|_{\lambda_i = 0}, \quad i = 1, 2, \quad$ *and*

$$M(t, \lambda_1, \lambda_2) = \frac{M(0, \lambda_1 + q_1(t), \lambda_2 + q_2(t))}{M(0, q_1(t), q_2(t))}.$$

Proof. Consider the equation

$$\frac{\partial s(t,\beta_1,\beta_2)}{dt} = -\beta_1 I_1(t)s(t,\beta_1,\beta_2) - \beta_2 I_2(t)s(t,\beta_1,\beta_2). \tag{2.2}$$

Dividing through by $s(t,\beta_1,\beta_2)$, we get

$$\frac{\dot{s}(t,\beta_1,\beta_2)}{s(t,\beta_1,\beta_2)} = -\beta_1 I_1 - \beta_2 I_2.$$

It follows that $s(t,\beta_1,\beta_2) = s(0,\beta_1,\beta_2)e^{\int -\beta_1 I_1(t) - \beta_2 I_2(t)dt}$.

Let $\dot{q_i} = -I_i(t), i = 1, 2,$

then

$$s(t,\beta_1,\beta_2) = s(0,\beta_1,\beta_2)e^{\beta_1 q_1(t) + \beta_2 q_2(t)} \tag{2.3}$$

By definition, the total susceptible class is

$$S(t) = \iint_\Omega s(t,\beta_1,\beta_2)d\beta_1 d\beta_2.$$

Hence we have

$$\begin{aligned} S(t) &= \iint_\Omega s(0,\beta_1,\beta_2)e^{\beta_1 q_1(t)+\beta_2 q_2(t)}d\beta_1 d\beta_2 \\ &= S(0)\iint_\Omega \frac{s(0,\beta_1,\beta_2)}{S(0)}e^{\beta_1 q_1(t)+\beta_2 q_2(t)}d\beta_1 d\beta_2 \\ &= S(0)\iint_\Omega P(0,\beta_1,\beta_2)e^{\beta_1 q_1(t)+\beta_2 q_2(t)}d\beta_1 d\beta_2, \end{aligned} \tag{2.4}$$

where P is a time dependent probability density function.

Using the definition of the moment generating function (MGF),

$$S(t) = S(0)M(0, q_1(t), q_2(t)).$$

By definition, the MGF is

$$M(t,\lambda_1,\lambda_2) = \iint_\Omega P(t,\beta_1,\beta_2)e^{\lambda_1\beta_1+\lambda_2\beta_2}d\beta_1 d\beta_2$$

$$= \frac{1}{S(t)} \iint_{\Omega} s(t, \beta_1, \beta_2) e^{\lambda_1 \beta_1 + \lambda_2 \beta_2} d\beta_1 d\beta_2.$$

Putting (2.3) into the last equation, we get

$$\begin{aligned} M(t, \lambda_1, \lambda_2) &= \frac{1}{S(t)} \iint_{\Omega} s(0, \beta_1, \beta_2) e^{\beta_1 q_1(t) + \beta_2 q_2(t)} e^{\lambda_1 \beta_1 + \lambda_2 \beta_2} d\beta_1 d\beta_2 \\ &= \frac{1}{S(t)} \iint_{\Omega} s(0, \beta_1, \beta_2) e^{(\lambda_1 + q_1)\beta_1 + (\lambda_2 + q_1)\beta_2} d\beta_1 d\beta_2 \\ &= \frac{S(0)}{S(t)} \iint_{\Omega} P(0, \beta_1, \beta_2) e^{(\lambda_1 + q_1)\beta_1 + (\lambda_2 + q_1)\beta_2} d\beta_1 d\beta_2. \end{aligned}$$

Putting (2.4) into the last equation,

$$M(t, \lambda_1, \lambda_2) = \frac{S(0)}{S(0) M(0, q_1, q_2)} \iint_{\Omega} P(0, \beta_1, \beta_2) e^{(\lambda_1 + q_1)\beta_1 + (\lambda_2 + q_1)\beta_2} d\beta_1 d\beta_2.$$

Simplifying by using the definition of MGF,

$$M(t, \lambda_1, \lambda_2) = \frac{M(0, \lambda_1 + q_1(t), \lambda_2 + q_2(t))}{M(0, q_1(t), q_2(t))}.$$

From the time dependent moment generating function $M(t, \lambda_1, \lambda_2)$, we can obtain an expression for the instantaneous mean transmisssion rates using properties of the moment generating functions:

$$\bar{\beta}_i(t) = \frac{d}{d\lambda_i} M(t, \lambda_1, \lambda_2)|_{\lambda_i = 0}, \quad i = 1, 2.$$

Integrating the equation (2.2) over Ω, we get the equation for the susceptible class $S(t)$ and the auxiliary terms $q_i(t)$, $i = 1, 2$. The equations for the infectious subsystem can be obtained as follows

$$\begin{aligned} I_i(t) \int_0^{\infty} \int_0^{\infty} \beta_i s(t, \beta_1, \beta_2) d\beta_1 d\beta_2 &= I_i(t) \int_0^{\infty} \int_0^{\infty} \beta_i s(t, \beta_1, \beta_2) \frac{S(t)}{S(t)} d\beta_1 d\beta_2 \\ &= S(t) I_i(t) \int_0^{\infty} \int_0^{\infty} \beta_i P(t, \beta_1, \beta_2) d\beta_1 d\beta_2 \\ &= \bar{\beta}_i(t) S(t) I_i(t), \end{aligned} \tag{2.5}$$

where $$\bar{\beta}_i(t) = \int_0^{\infty} \int_0^{\infty} \beta_i P(t, \beta_1, \beta_2) d\beta_1 d\beta_2 \quad \text{and } i = 1, 2.$$

□

Remark 1. Actually, following [22], it is possible to show that models (1.9) and (2.1) are equivalent, but we will not need this later.

Unlike the moment closure method, which requires the coefficients of variation and the correlation coefficient of the transmission rates to be constant, Theorem 2.1.1 allows us reduce (1.9) to a system of differential equations without making any additional assumptions. Moreover, we can use any bivariate probability distribution with a known MGF as the initial distribution of the transmission rates. We therefore have more information of the model as we know the properties of that probability distribution.

2.1.1. Comparison between the moment closure method and the reduction method of Theorem 2.1.1

The moment closure method, which was used to derive system (1.11), assumes that the coefficients of variation of the distribution of the parameters ($\beta_i, i = 1, 2$) are constants (does not change with time). The primary difference between homogeneous and heterogeneous models is that, the coefficient of variation for the transmission rate is zero in homogeneous models, therefore the transmission rate remains constant with time. It also assumes that the correlation between both parameters β_1 and β_2 are constant. It is shown in [28] that if the coefficient of variation of a parameter distribution does not change with time, then the initial distribution of the parameter follows the gamma distribution. The results can be extended to a joint bivariate gamma distribution when the correlation coefficient is zero. Let us illustrate this fact.

The moment generating function of a joint bivariate gamma distribution with zero correlation coefficient is

$$M(0, \lambda_1, \lambda_2) = \frac{1}{(1 - \theta_1\lambda_1)^{k_1}(1 - \theta_2\lambda_2)^{k_2}},$$

where $\theta_1, \theta_2, k_1, k_2$ are parameters.

Considering the assumptions made in (1.11), solutions of (2.1) with the transmission rates distributed to joint bivariate gamma distribution should coincide with solutions of (1.11) when the correlation coefficient $\bar{\rho}$ is 0. We demonstrate their similarity in the Figs. 2.1,2.2.

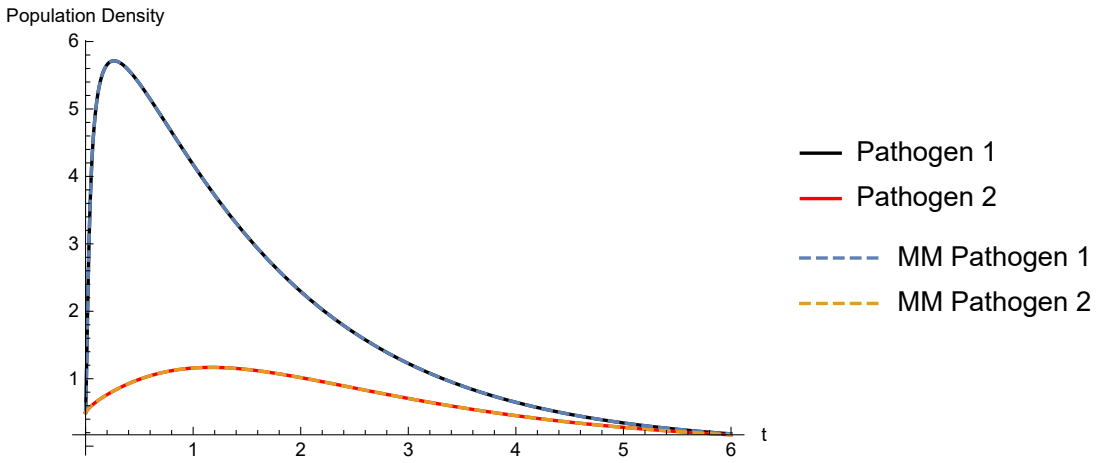

Figure 2.1. Comparison between model (2.1) and model (1.11). For model (1.11), the initial distribution of the parameters $\bar{\beta}_i, i = 1, 2$ in the host population is the bivariate gamma distribution with correlation coefficient $\bar{\rho} = 0$. Pathogen strain 1 has a high mean transmission rate $\bar{\beta}_1 = 10.5$, high coefficient of variation $C_1 = 2.06$ and pathogen strain 2 has a low mean transmission rate $\bar{\beta}_2 = 0.5$, low variation $C_2 = 0.68$. The initial conditions $S(0) = 10, I_1(0) = I_2(0) = 0.5$, parameter values $\gamma_1 = \gamma_2 = 0.65$.

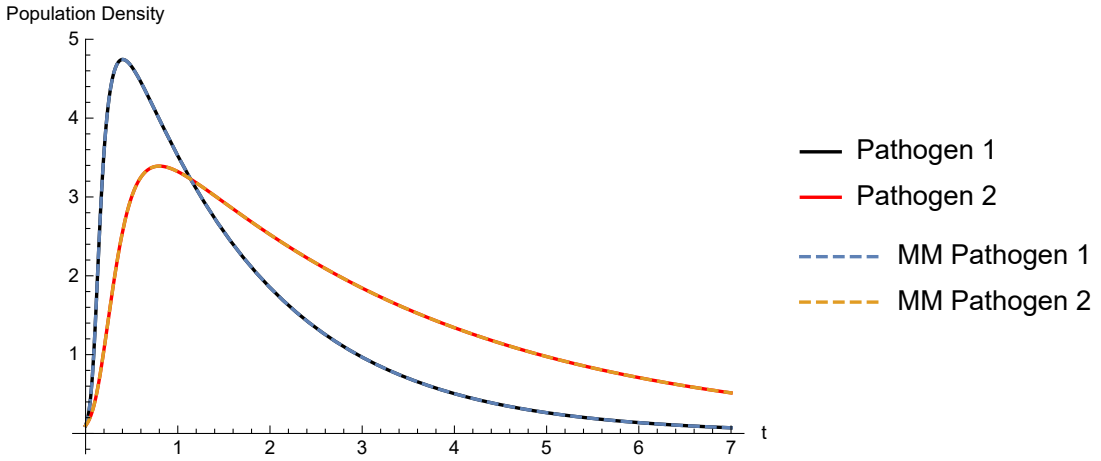

Figure 2.2. Comparison between model (2.1) and model (1.11). For model (1.11), the initial distribution of the parameters $\bar{\beta}_i, i = 1, 2$ in the host population is the bivariate gamma distribution with correlation coefficient $\bar{\rho} = 0$. The mean transmission rates are $\bar{\beta}_1 = 3, \bar{\beta}_2 = 1.5$ with the coefficients of variation $C_1 = 1.5, C_2 = 0.5$. The initial conditions $S(0) = 10, I_1(0) = I_2(0) = 0.5$, parameter values $\gamma_1 = 0.65, \gamma_2 = 0.32$.

Theorem 2.1.2. *System (2.1) follows from heterogeneous model (1.11) only if the marginal distributions of the initial distribution of susceptibility are gamma distributions (with correlation coefficient equal to zero).*

2.2. Numerical analysis of (2.1) with examples of pathogen coexistence.

Using the moment closure method and the discrete time model (1.12), the authors of [22] showed that pathogen coexistence was possible between a strain with high mean transmission, high coefficient of variation ($\bar{\beta}_1 = 10.5, C_1 = 2.06$) and a strain with low mean transmission, low coefficient of variation ($\bar{\beta}_2 = 0.5, C_2 = 0.68$). We replicate their experiment by introducing demography to model (2.1) using the discrete time model (1.12), and investigate the conditions for pathogen coexistence.

We showed in the previous section that the model (1.11) is equivalent to model (2.1) when the initial distribution is gamma, where the coefficients of variation are constant. We will confirm that the conditions for coexistence (high mean, high variation versus low mean, low variation) as a result of model (1.11) is similar in the conditions for coexistence using model 2.1.

As a next step, we will extend our results to probability distributions with non-constant coefficients of variation, and show multiple conditions of coexistence. In all our simulations, we will use the same range of parameters was used by [22].

2.2.1. Probability distribution with constant coefficient of variation

We assume that the initial distribution of the susceptible population is a gamma distribution with parameters k_1,k_2,θ_1, and θ_2 with the MGF given by

$$M(0, \beta_1, \beta_2) = (1 - \theta_1\beta_1)^{-k_1}(1 - \theta_2\beta_2)^{-k_2}. \tag{2.6}$$

It follows from Theorem 2.1.1 that, for $t > 0$,

$$M(t, \beta_1, \beta_2) = \frac{(1 - \theta_1 q_1(t))^{k_1}(1 - \theta_2 q_2(t))^{k_2}}{(1 - \theta_1\beta_1 - q_1(t)\theta_1)^{k_1}(1 - \theta_2\beta_2 - q_2(t)\theta_2)^{k_2}}. \tag{2.7}$$

Using properties of moment generating functions, the mean and the variance at any time t are given by

$$E_t[\beta_i] = \frac{k_i\theta_i^2}{(-1 + q_i(t)\theta_i)^2}, \quad Var_t[\beta_i] = \frac{k_i\theta_i}{1 - q_i(t)\theta_i}. \tag{2.8}$$

At any time moment, the coefficients of variation $C_i(t) = 1/\sqrt{k_i}$ are constant.

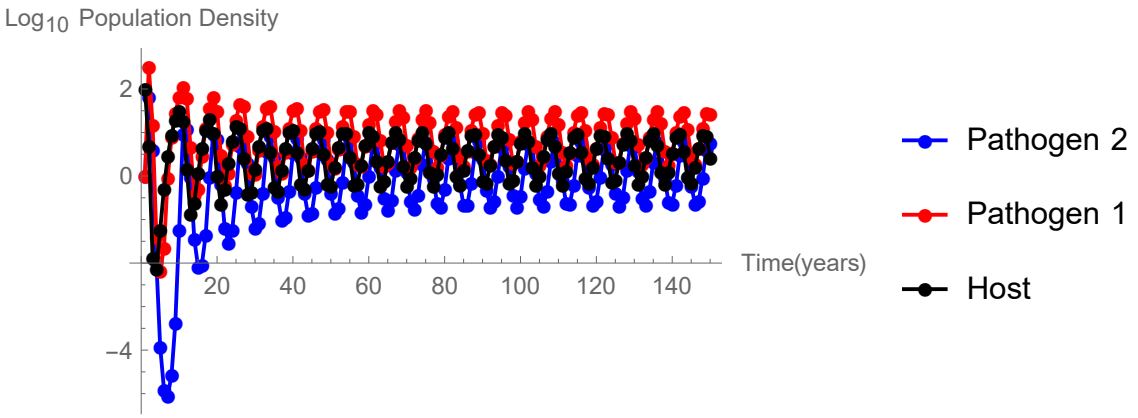

Figure 2.3. Two pathogen strains can coexist in over 150 generations (prolonged coexistence) of the gypsy moth population when pathogen 1 has a high mean transmission rate $\bar{\beta}_1 = 10.5$ and a high coefficient of variation $C_1 = 2.06$ competes against pathogen 2 with a low transmission rate $\bar{\beta}_2 = 0.15$, low coefficient of variation $C_2 = 0.68$. Other parameter values are $\mu_1 = 0.99$, $\mu_2 = 0.32$, $\phi = 0.4$, $\lambda_N = 10$, initial densities $N_0 = 100$, $Z_{1,0} = Z_{2,0} = 1$.

We know that coexistence means that the limit as $t \to \infty$ for both pathogen strains is non-zero. We do not show that the limit is non-zero in this text but for the purpose of our numerical analysis, we define pathogen coexistence as when the densities of the population infected by both strains are greater than 10^{-6} at the end of each season for 150 generations. A strain is considered extinct if at the end of the season, the density of the population infected by it is less that 10^{-6}.

As shown in Figure 2.3, coexistence is possible when a pathogen strain with high mean transmission rate, high variability in transmission compete with a strain with low mean transmission rate, low variability in transmission. This results is similar to the results in [22]. This is not surprising since we have already shown that both models are essentially the same when the initial distribution is bivariate gamma (2.6).

The coexistence parameters showcased in figure 2.3 are not unique. For a fixed pair of coefficients of variation (C_1, C_2), there are several points (β_1, β_2) for which coexistence was possible. Similarly, for a given pair of transmission rates (β_1, β_2), we can find that there were multiple points (C_1, C_2) for which coexistence is possible. When the initial distribution of the susceptible population is gamma (2.6), the simulations show in most cases that coexistence is possible when one pathogen strain possesses a high mean transmission rate paired with a high coefficient of variation and the

other pathogen strain has a relatively low transmission rate, low variability (similar results in [22]).

We show multiple cases where coexistence is possible below:

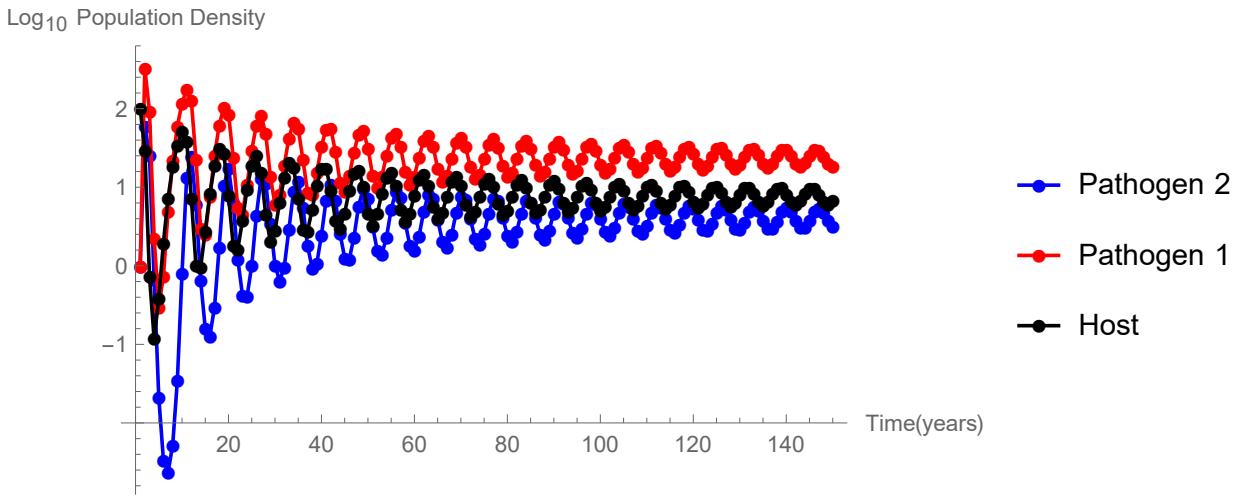

Figure 2.4. Coexistence is possible when pathogen 1 has a high mean transmission rate $\bar{\beta}_1 = 5$ and a high coefficient of variation $C_1 = 2.06$ competes against pathogen 2 with a low transmission rate $\bar{\beta}_2 = 0.1$, low coefficient of variation $C_2 = 0.68$. Other parameter values are $\mu_1 = 0.99$, $\mu_2 = 0.32$, $\phi = 0.4$, $\lambda_N = 10$, initial densities $N_0 = 100$, $Z_{1,0} = Z_{2,0} = 1$.

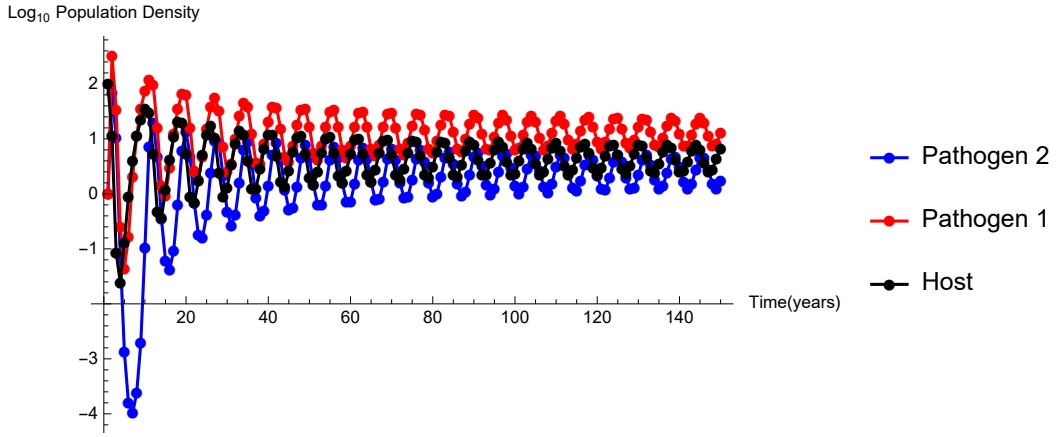

Figure 2.5. Two pathogen strains can coexist in over 150 generations of the gypsy moth population when pathogen 1 has a high mean transmission rate $\bar{\beta}_1 = 5$ and a high coefficient of variation $C_1 = 2.06$ competes against pathogen 2 with a low transmission rate $\bar{\beta}_2 = 0.1$, low coefficient of variation $C_2 = 0.68$. Other parameter values are $\mu_1 = 0.99$, $\mu_2 = 0.32$, $\phi = 0.4$, $\lambda_N = 10$, initial densities $N_0 = 100$, $Z_{1,0} = Z_{2,0} = 1$.

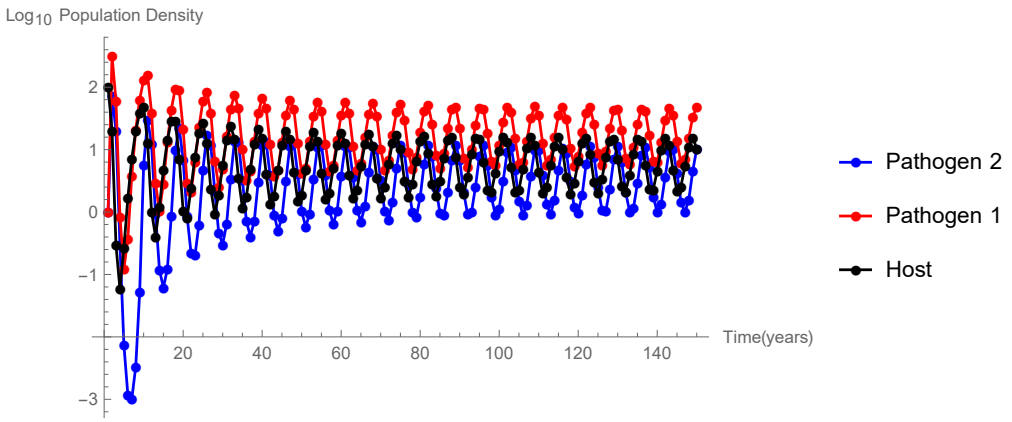

Figure 2.6. Two pathogen strains can coexist in over 150 generations of the gypsy moth population when pathogen 1 has a high mean transmission rate $\bar{\beta}_1 = 4$ and a high coefficient of variation $C_1 = 2.06$ competes against pathogen 2 with a low transmission rate $\bar{\beta}_2 = 0.12$, low coefficient of variation $C_2 = 0.68$. Other parameter values are $\mu_1 = 0.99$, $\mu_2 = 0.32$, $\phi = 0.4$, $\lambda_N = 10$, initial densities $N_0 = 100$, $Z_{1,0} = Z_{2,0} = 1$.

In Figs. 2.4, 2.5 and 2.6, we observe that coexistence is possible for different parameters and initial conditions. In all those figures, the coefficients of variation were $C_1 = 2.06$, and $C_2 = 0.68$. This shows that for a given pair of coefficients of variation, there are multiple points (transmission rates) for which pathogen coexistence is observed. On the plane of transmission rates, β_1 and β_2, we show the region for which coexistence when the coefficients of variation are $C_1 = 2.06$, and $C_2 = 0.68$ below.

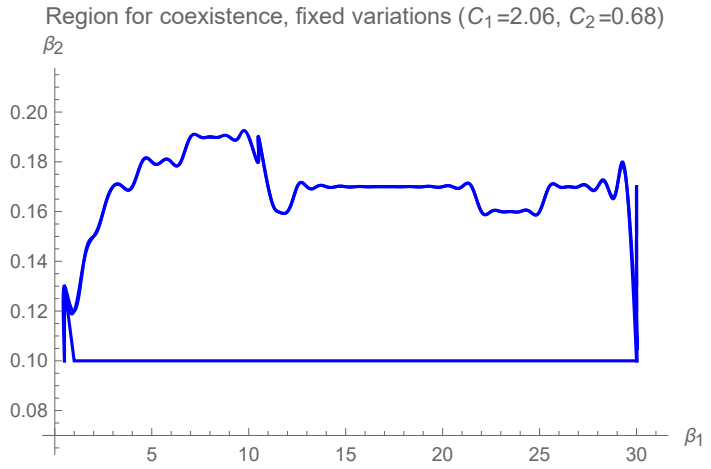

Figure 2.7. The figure shows the various points for β_1 *and* β_2 for which prolonged coexistence is possible when the coefficients of variation are fixed ($C_1 = 2.06$ and $C_2 = 0.68$). $\mu_1 = 0.65$, $\mu_2 = 0.65$, $\phi = 0.4$, $\lambda_N = 10$, initial densities $N_0 = 100$, $Z_{1,0} = Z_{2,0} = 1$. A pathogen is said to be extinct when its density is less than 10^{-6}

We observe in Figure 2.7 that, in the entire region of coexistence, coexistence occurs when the dominant pathogen strain's mean transmission is about 10 times bigger than the other strain's mean transmission rate. We conclude that when the coefficients of variation are constant, two pathogen strains can coexist in over 150 generations of the gypsy moth population between a strain with a high mean, high variation and a strain with low mean, low variation.

Intuitively, when the variation in transmission is constant, the decline in the mean transmission rate is uniform for the pathogen strain. The pathogen strain i with high mean, high variation infects a higher proportion of the susceptible population at the initial stage of the epidemic, however, its mean transmission rate decreases rapidly due to its high variation. For the pathogen strain j with low mean, low variation, it initially affects a very low proportion of the susceptible population, however, its rate of transmission decreases very slowly due to the low variation. When pathogen strain i's mean transmission rate drops rapidly, pathogen strain j gets an opportunity to fully invade the susceptible population if its mean transmission rate is still high enough. This trade-off allows both pathogen strains to coexist.

In the next section, we look at an example where the coefficient of variation is not constant for at least one pathogen i strain. This means that for that pathogen strain i, the rate of change of the mean transmission rate is different at different time t.

2.2.2. Probability distribution with a non-constant coefficient of variation

Theorem 2.1.1 allows us to use any bivariate probability distribution with a known MGF as the initial distribution for the host population. In the previous section, we showed that the conditions for prolonged pathogen coexistence (high mean high variation strain can coexist with low mean low variation strain) when the coefficient of variation is constant for both strains. In this section, we consider a probability distribution, where the coefficients of variation are not constant for both strains.

Consider the joint probability distribution with moment generating function

$$M(0,\beta_1,\beta_2)=(1-\theta\beta_1)^{-k}\exp\left(\frac{\lambda\left(1-\sqrt{1-\frac{2\beta_2\alpha^2}{\lambda}}\right)}{\alpha}\right). \tag{2.9}$$

Here, the marginal distribution of β_1 is a gamma distribution with

$$E_t[\beta_1]=\frac{k\theta^2}{(-1+q_1(t)\theta)^2},\quad Var_t[\beta_1]=\frac{k\theta}{1-q_1(t)\theta},$$

and hence $C_1(t)=1/\sqrt{k}$.

The marginal distribution of β_2 is the inverse Gaussian distribution with

$$E_t[\beta_2]=\frac{\alpha 2}{\sqrt{1-\frac{2q_2(t)\alpha^2}{\lambda}}},\quad Var_t[\beta_2]=\frac{\alpha^3}{\lambda(1-\frac{2q_2(t)\alpha^2}{\lambda})^{\frac{3}{2}}}\quad,$$

and hence $C_2(t)=\sqrt{\frac{\alpha}{\lambda(1-\frac{2q_2(t)\alpha^2}{\lambda})^{\frac{1}{2}}}}$. C_2 is therefore not a constant that is, for different time values, the coefficient of variation is different.

It must be noted that the correlation coefficient between the transmission rates in (2.9) is zero. That means the probability of a susceptible being infected by pathogen strain 1 has no effect on its probability of being infected by pathogen strain 2. Statistically, the transmission rates are independent.

Numerical simulations using (2.1) and (2.9) showed that pathogen coexistence was possible for a wider range of parameters when the coefficient of variation is not a constant. We categorize the range of parameters necessary for pathogen coexistence in the sections below.

2.2.2.1. High mean transmission, low variability versus low mean transmission, high variability

When the coefficient of variation is not constant in at least one strain, numerical simulations show that coexistence is possible between a pathogen strain with a high mean, low variation (example: β_1=10, $C_1 = 1.6$) and a strain with a low mean, high variation (example: $\beta_2 = 5$, $C_2 = 6.7$).

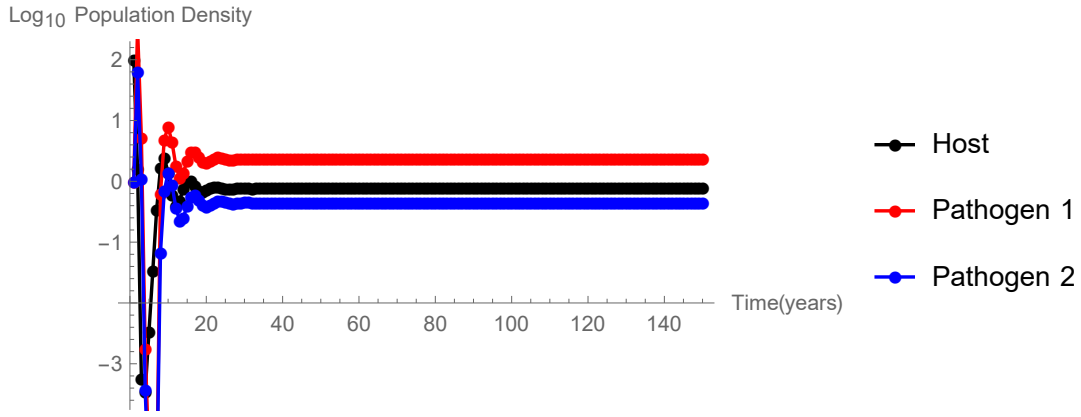

Figure 2.8. Two pathogen strains can coexist in over 150 generations of the gypsy moth population when pathogen 1 has a high mean transmission rate $\bar{\beta}_1 = 10$ and a low coefficient of variation $C_1 = 1.6$ competes against pathogen 2 with a low transmission rate $\bar{\beta}_2 = 5$, high coefficient of variation $C_2 = 6.7$. Other parameter values are $\mu_1 = 0.99$, $\mu_2 = 0.32$, $\phi = 0.4$, $\lambda_N = 10$, initial densities $N_0 = 100$, $Z_{1,0} = Z_{2,0} = 1$.

In Figure 2.8, we observe that prolonged coexistence is possible between a pathogen strain 1 with high mean, low variation ($\bar{\beta}_1 = 10, C_1 = 1.6$) and pathogen strain 2 with low mean, low variation ($\bar{\beta}_2 = 5, C_2 = 6.7$). The variation in transmission for pathogen strain 1 is not a constant, the $C_1 = 1.6$ value varies with time.

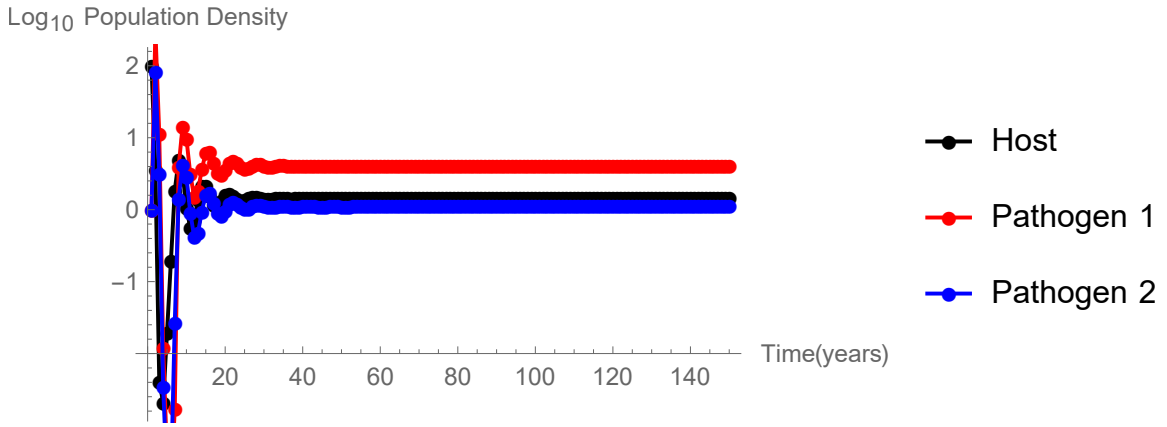

Figure 2.9. Two pathogen strains can coexist in over 150 generations of the gypsy moth population when pathogen 1 has a high mean transmission rate $\bar{\beta}_1 = 4$ and a low coefficient of variation $C_1 = 1.6$ competes against pathogen 2 with a low transmission rate $\bar{\beta}_2 = 3$, high coefficient of variation $C_2 = 6.7$. Other parameter values are $\mu_1 = 0.99$, $\mu_2 = 0.32$, $\phi = 0.4$, $\lambda_N = 10$, initial densities $N_0 = 100$, $Z_{1,0} = Z_{2,0} = 1$.

Figure 2.9 is another example where prolonged coexistence is possible between a pathogen strain 1 with high mean, low variation ($\bar{\beta}_1 = 4, C_1 = 1.6$) and pathogen strain 2 with low mean, low variation ($\bar{\beta}_2 = 3, C_2 = 6.7$).

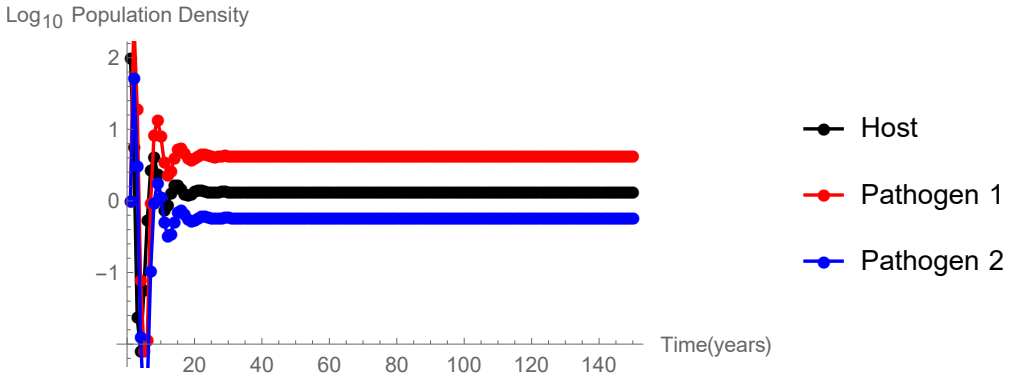

Figure 2.10. Two pathogen strains can coexist in over 150 generations of the gypsy moth population when pathogen 1 has a high mean transmission rate $\bar{\beta}_1 = 5$ and a low coefficient of variation $C_1 = 1.5$ competes against pathogen 2 with a low transmission rate $\bar{\beta}_2 = 2.5$, high coefficient of variation $C_2 = 7$. Other parameter values are $\mu_1 = 0.99$, $\mu_2 = 0.32$, $\phi = 0.4$, $\lambda_N = 10$, initial densities $N_0 = 100$, $Z_{1,0} = Z_{2,0} = 1$.

Another example where prolonged coexistence is possible between a pathogen strain 1 with high mean, low variation ($\bar{\beta}_1 = 4, C_1 = 1.6$) and pathogen strain 2 with low mean, low variation ($\bar{\beta}_2 = 3, C_2 = 6.7$) is Figure 2.10.

This case (high mean low variation versus low mean high variation) of coexistence is generally not possible when the coefficients of variation are constant. We observe such type of coexistence since the variation of transmission in pathogen strain 1 is not uniformly decreasing.

2.2.2.2. High mean transmission versus low mean transmission with same variability

It was found that two pathogen strains can coexist in over 150 generations of the gypsy moth population when a pathogen with a high mean transmission rate competed with a strain with a low mean transmission rate even though they both have the same coefficient of variation.

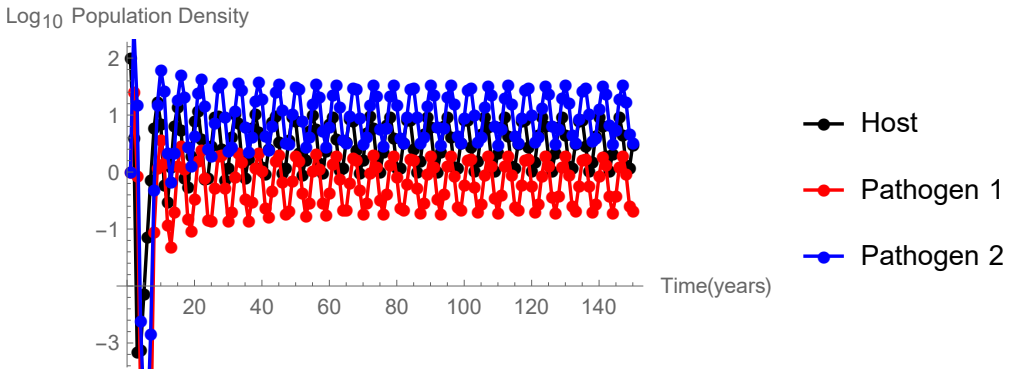

Figure 2.11. Two pathogen strains can coexist in over 150 generations of the gypsy moth population when both pathogen strains have the same variation $C_1 = C_2 = 10$ and different mean transmission rates $\bar{\beta}_1 = 10, \bar{\beta}_2 = 5$. The other parameter values are $\mu_1 = 0.99$, $\mu_2 = 0.32$, $\phi = 0.4$, $\lambda_N = 10$, initial densities $N_0 = 100$, $Z_{1,0} = Z_{2,0} = 1$.

Figure 2.11 is an example showing prolonged coexistence is possible between strains of the same variation in transmission, but differing in mean transmission rates. An interesting observation is, despite having the lower mean transmission rate, the density of the population infected by pathogen strain 2 is generally higher than the density of the population infected by pathogen strain 1. We will try and give an explanation for this observation in the subsequent sections.

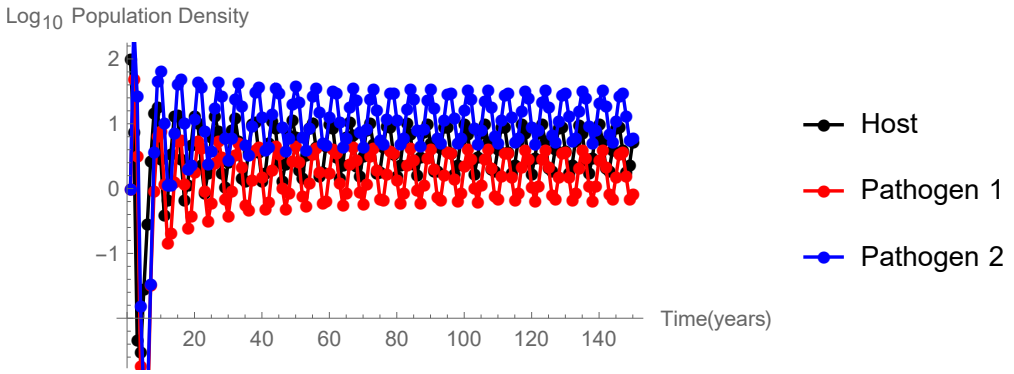

Figure 2.12. Two pathogen strains can coexist in over 150 generations of the gypsy moth population when both pathogen strains have the same variation $C_1 = C_2 = 7$ and different mean transmission rates $\bar{\beta}_1 = 8, \bar{\beta}_2 = 2$. The other parameter values are $\mu_1 = 0.99$, $\mu_2 = 0.32$, $\phi = 0.4$, $\lambda_N = 10$, initial densities $N_0 = 100$, $Z_{1,0} = Z_{2,0} = 1$.

Figure 2.12 is another example showing prolonged coexistence is possible between strains of the same variation in transmission, but differing in mean transmission rates. We show Figure (2.12) to illustrate that there are multiple parameters for which this type (high mean versus low mean with same variation) of coexistence is possible.

2.2.2.3. Same mean transmission, low variability versus high variability

Finally, we look at an example where the transmission rates are the same but they differ in variability.

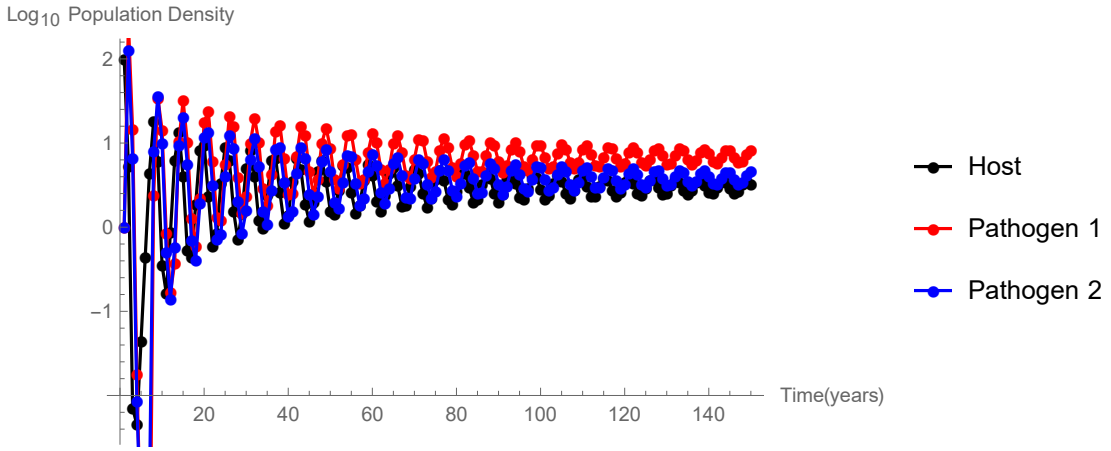

Figure 2.13. Two pathogen strains can coexist in over 150 generations of the gypsy moth population when pathogen 1 has a low mean transmission rate $\bar{\beta}_1 = 0.5$ and a low coefficient of variation $C_1 = 1.3$ competes against pathogen 2 with a low transmission rate $\bar{\beta}_2 = 0.5$, high coefficient of variation $C_2 = 3.5$. Other parameter values are $\mu_1 = 0.99$, $\mu_2 = 0.32$, $\phi = 0.4$, $\lambda_N = 10$, initial densities $N_0 = 100$, $Z_{1,0} = Z_{2,0} = 1$.

Figure 2.13 is an example where prolonged pathogen coexistence is possible between strains with the same mean transmission rate, different variations. Generally, it is possible for two pathogen strains with the same mean to coexist in homogeneous models if the resulting strain specific basic reproductive numbers are the same. However, there is no variation in transmission for homogeneous models where as there is some variation in heterogeneous models.

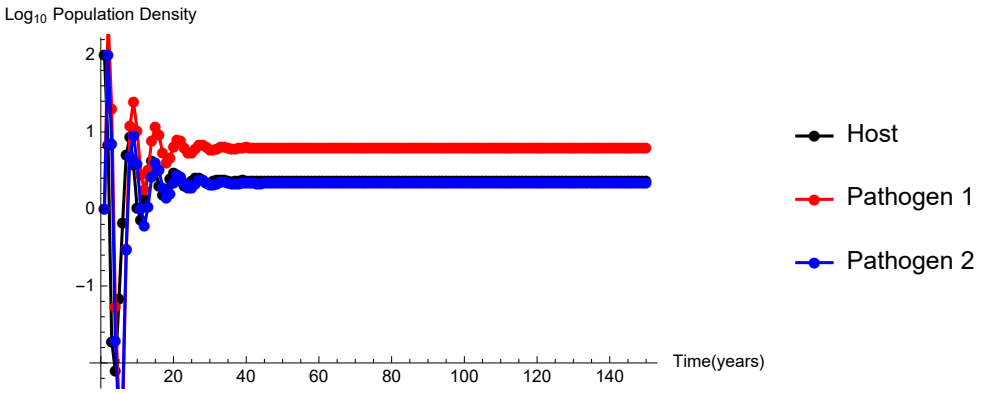

Figure 2.14. Two pathogen strains can coexist in over 150 generations of the gypsy moth population when pathogen 1 has a low mean transmission rate $\bar{\beta}_1 = 2$ and a low coefficient of variation $C_1 = 1.3$ competes against pathogen 2 with a low transmission rate $\bar{\beta}_2 = 0.5$, high coefficient of variation $C_2 = 3.5$. Other parameter values are $\mu_1 = 0.99$, $\mu_2 = 0.32$, $\phi = 0.4$, $\lambda_N = 10$, initial densities $N_0 = 100$, $Z_{1,0} = Z_{2,0} = 1$.

We show in Figure 2.14 that the parameters for prolonged coexistence in Figure 2.13 are not unique. There are multiple cases where two pathogen strains with different mean transmission rates (same variation) can coexist.

Overall, the parameters for prolonged coexistence are not unique. For a fixed pair of transmission rates (β_1, β_2), the region of coexistence in the C_1-C_2 plane may contain multiple points. Example: In Figure 2.15 below, we show the region in the C_1-C_2 plane where pathogen coexistence can be observed when the transmission rates are $\beta_1 = 10$ and $\beta_2 = 5$.

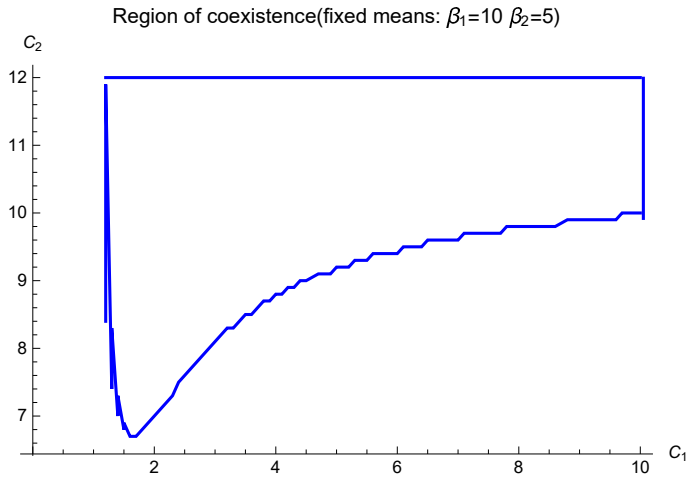

Figure 2.15. Figure shows some of the possible points (C_1 and C_2) for which prolonged coexistence was possible when the mean transmission rates are $\beta_1 = 10$ and $\beta_2 = 5$. Observe that for some of the points $C_1 \geq C_2$ and for other points $C_1 \leq C_2$. Other parameter values are $\mu_1 = 0.99$, $\mu_2 = 0.32$, $\phi = 0.4$, $\lambda_N = 10$, initial densities $N_0 = 100$, $Z_{1,0} = Z_{2,0} = 1$.

Similarly, we show in Figure 2.16 below, the region of coexistence in the β_1-β_2 plane when the variations in transmissions are $C_1 = 1.6$ and $C_2 = 6.7$.

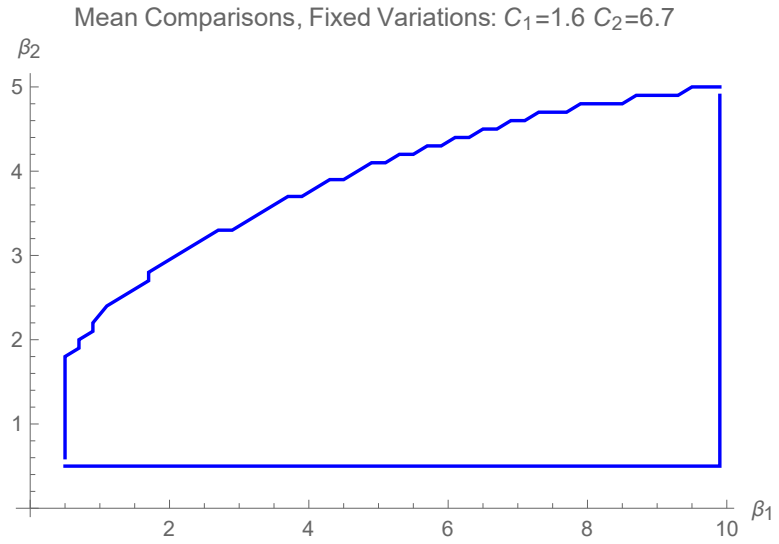

Figure 2.16. Here we see some of the other possible combinations of the mean transmission rate for which prolonged coexistence is possible when the coefficient of variation is fixed($C_1 = 1.6$ and $C_2 = 6.7$). Other parameter values are $\mu_1 = 0.99$, $\mu_2 = 0.32$, $\phi = 0.4$, $\lambda_N = 10$, initial densities $N_0 = 100$, $Z_{1,0} = Z_{2,0} = 1$. Observe that even though for most cases $\beta_1 > \beta_2$, there are some few cases where $\beta_1 < \beta_2$.

From the above Figs. 2.8-2.16, it is evident that as far as the coefficient of variation(s) is not a constant, coexistence is possible for a much wider range of parameters. The condition for coexistence is not restricted to the high mean, high variation paired with low mean, low variation as shown in [22] (where the variation is constant).

Intuitively, we can say that, the lack of uniformity in variation in transmissions allows either transmission rate to be higher at different times. When both pathogen strains have the opportunity to invade, they are able to coexist for a longer period of time.

Mathematically, we want to show the reason behind prolonged coexistence for all the cases observed. With the changes in both the mean transmission rates, and the coefficients of variation, the strain specific basic reproductive numbers also changes as a result. Ideally, we are interested in showing a bifurcation diagram for model (1.9), to see how the changes in the mean transmission rates affect the dynamics. However, since model (1.9) has no demography term, this can not be done. We therefore introduce an auxiliary birth term to (1.9), to make it possible to provide a bifurcation analysis. It is important to note that, at a fixed time t, the mean transmission rates are constant, and hence, the system can be treated as a homogeneous model. We will therefore compare our bifurcation diagram to Figure 1.1.

2.3. Heterogeneous model (1.9) with continuous demography

In the previous section, we introduced demography to heterogeneous model (1.9) using a discrete time model. In this section, we introduce demography to the heterogeneous model (1.9) as a continuous time process. The goal is show using bifurcation analysis, the reason behind the prolonged pathogen coexistence observed in the gypsy moth model.

Lemma 2.3.1. *Given a heterogeneous model (1.9) with the birth term $s(t,\beta_1,\beta_2)f(S(t))$:*

$$\begin{aligned}\frac{\partial s(t,\beta_1,\beta_2)}{\partial t} &= s(t,\beta_1,\beta_2)f(S) - \beta_1 s I_1 - \beta_2 s I_2 - \phi s,\\ \frac{dI_1}{dt} &= I_1\int_0^\infty\int_0^\infty \beta_1 s(t,\beta_1,\beta_2)d\beta_1 d\beta_2 - \gamma_1 I_1 - \phi I_1,\\ \frac{dI_2}{dt} &= I_2\int_0^\infty\int_0^\infty \beta_1 s(t,\beta_1,\beta_2)d\beta_1 d\beta_2 - \gamma_2 I_2 - \phi I_2,\end{aligned} \tag{2.10}$$

where ϕ is the mortality rate (by natural cause), and f is any population growth function of $S(t)$, pathogen coexistence is not possible.

Proof. Using theorem (2.1.1), the system can be reduced to

$$\begin{aligned}
\frac{dS(t)}{dt} &= S(f(S)) - \bar{\beta}_1(t)S(t)I_1(t) - \bar{\beta}_2(t)S(t)I_2(t) - \phi S(t),\\
\frac{dI_1(t)}{dt} &= \bar{\beta}_1(t)S(t)I_1(t) - \gamma_1 I_1(t) - \phi I_1(t),\\
\frac{dI_2(t)}{dt} &= \bar{\beta}_2(t)S(t)I_2(t) - \gamma_2 I_2(t) - \phi I_2(t),\\
\frac{dq_i(t)}{dt} &= -I_i(t), i = 1, 2.
\end{aligned} \tag{2.11}$$

where $\bar{\beta}_i(t) = \frac{d}{d\lambda_i}M(t, \lambda_1, \lambda_2), \lambda_i = 0, i = 1, 2$ and

$$M(t, \lambda_1, \lambda_2) = \frac{M(0, \lambda_1 + q_1(t), \lambda_2 + q_2(t))}{M(0, q_1(t), q_2(t))}.$$

Observe that the system has only one equilibrium $(S^*, I_1^*, I_2^*) = (S^*, 0, 0)$. Therefore, there is no endemic equilibrium pathogen, and hence coexistence is not possible. □

Even though both pathogen strains go extinct, numerical analysis of model (2.11) gives an insight on the reason behind coexistence when the demography is discrete. For the purpose of our analysis, we will let $f(S) = A(1 - \frac{S}{K})$, therefore the birth term is $f(S) = A(1 - \frac{S}{K})s(t, \beta_1, \beta_2)$ is a logistic equation. We will compare model (2.11) to the homogeneous model:

$$\begin{aligned}
\frac{dS(t)}{dt} &= AS(1 - \frac{S}{K}) - \beta_1 S(t)I_1(t) - \beta_2 S(t)I_2(t) - \phi S(t),\\
\frac{dI_1(t)}{dt} &= \beta_1 S(t)I_1(t) - \gamma_1 I_1(t) - \phi I_1(t),\\
\frac{dI_2(t)}{dt} &= \beta_2 S(t)I_2(t) - \gamma_2 I_2(t) - \phi I_2(t),
\end{aligned} \tag{2.12}$$

whose bifurcation diagram is shown in Figure 1.1.

In the example below, we will use the parameters ($A = 5$, $K = 20$) coupled with the initial conditions $S(0) = 100$, $I_1(0) = I_2(0) = 1, \gamma = 1, \mu_1 = \mu_2 = 0.99$. The initial distribution of the susceptible population is the joint gamma distribution (2.6) with no correlation.

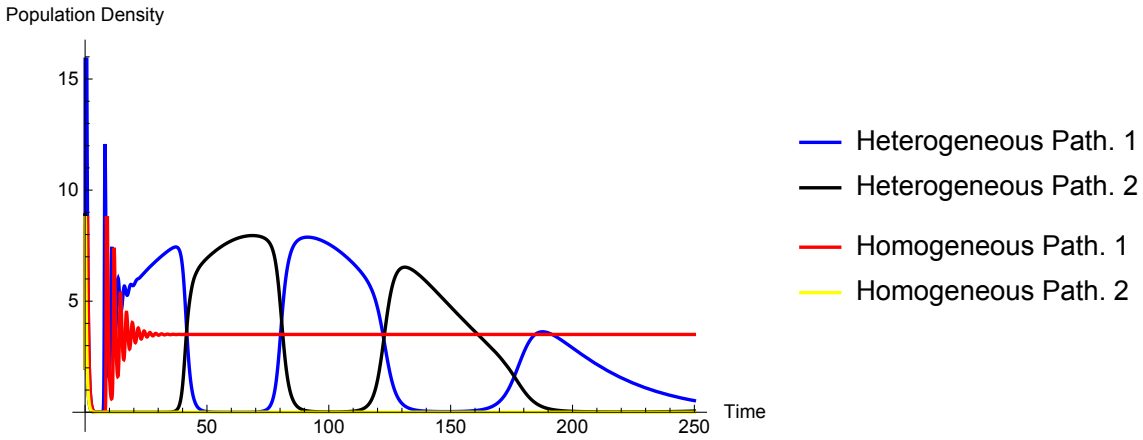

Figure 2.17. The initial strain specific basic reproductive numbers are 8 and 4 for pathogen 1 and pathogen 2 respectively ($\beta_1 = 1, C_1 = 0.1, \beta_2 = 0.5, C_2 = 0.1$)

In Figure 2.17, we observe that heterogeneity prolongs pathogen coexistence. Pathogen strain 1 has a higher initial transmission rate. As it slowly declines, it reaches a point where the transmission rate of pathogen strain 2 becomes momentarily higher in terms of mean transmission rate, it slowly declines and the process repeats. The continuous tradeoff in dominance allows both pathogen strains to coexist for a long period of time. We get more understanding by looking at the changes in the mean transmission rates below.

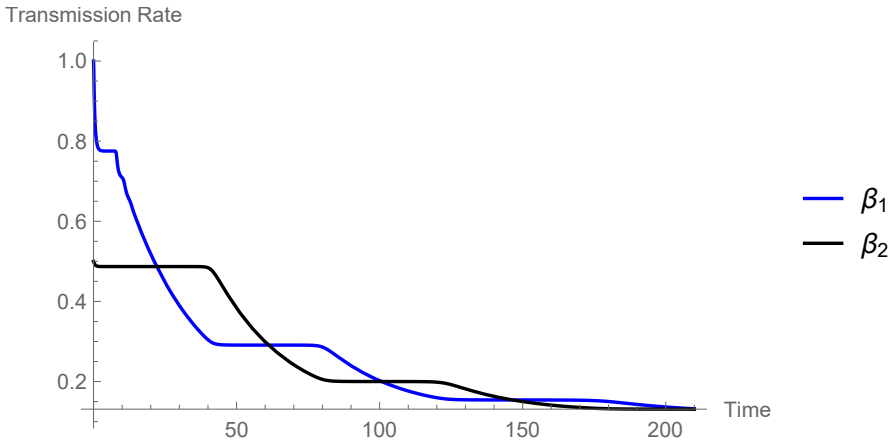

Figure 2.18. The mean transmission rate of pathogen strain 1 slowly declined with time contrast to that of pathogen strain 2 which almost reduced to zero during the entire epidemic. It explains why figure 11 hardly showed any sign of pathogen strain 1.

We observe that, at different times t, the pathogen with the highest mean transmission rate is different. The changes in the means were significant enough to affect the behavior of basic reproductive ratios at different times. The graph of the means keeps crossing the bifurcation line (equal basic reproductive ratios) showing that at any fixed time, the pathogen strain with the dominant R_0 can be either strains.

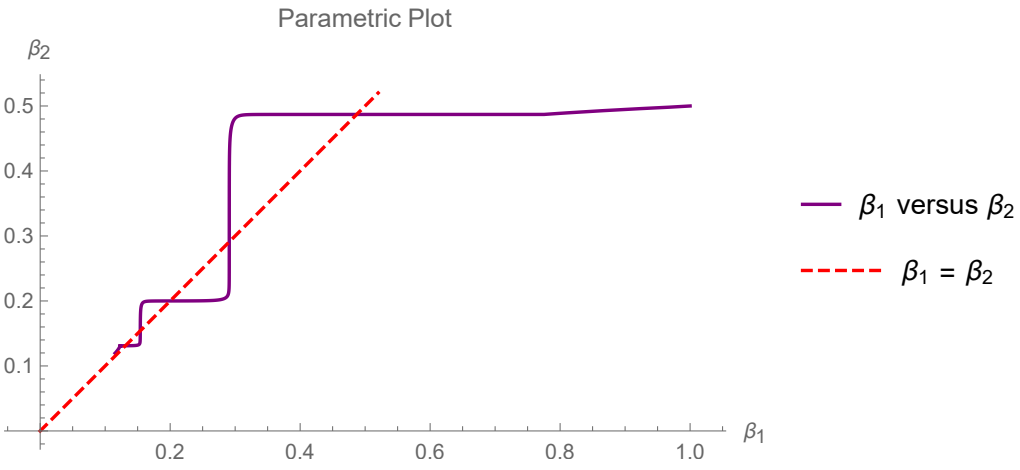

Figure 2.19. The phase portrait showing the changes in the mean, and consequently the changes in the basic reproductive ration assuming that at a fixed time, the system is homogeneous. The dotted red line is the bifurcation line $\beta_1 = \beta_2$ (consequently $R_{0,1} = R_{0,2}$) and the purple line represents the changes in the means.

The bifurcation diagram for the homogeneous model (2.12) is the same for (1.2). Recall the bifurcation diagram Figure 1.1 for the homogeneous model (1.2) is

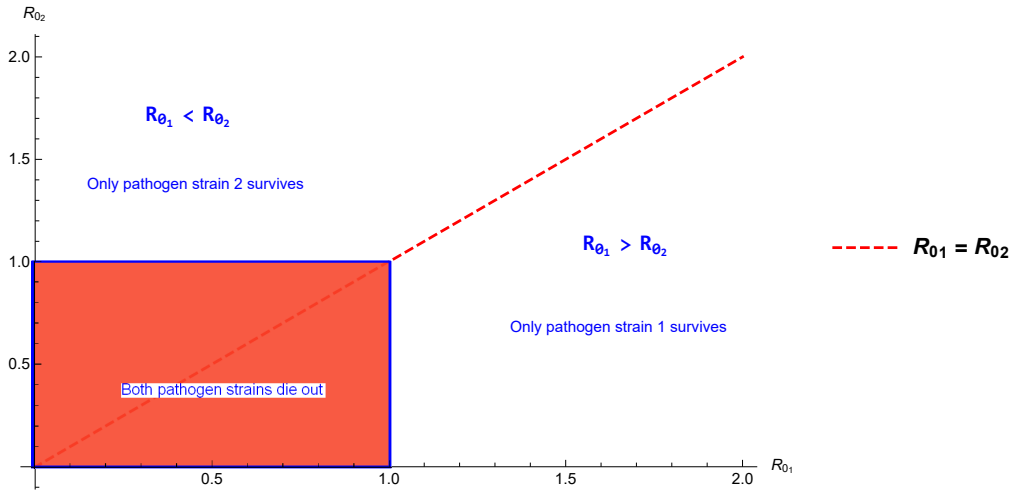

Figure 2.20. The bifurcation diagram of system (2.12). A pathogen strain is only able to invade susceptible population when its strain specific $R_{0_i} > 1$. The strain with the largest R_0 forces the other strain to extinction.

In homogeneous models, there are no changes in the transmission rates with time. Therefore, when you start at any of the 3 regions (only pathogen 1 survives, only pathogen 2 survives, both die out) in the bifurcation diagram, Figure 1.1, you stay there throughout the infection period. In Figure 2.19 however, we observe that the changes in the means allows us to travel across all 3 regions. As a result, both pathogen strains are able to survive for a long period of time.

With the discrete seasons (discrete time model), the dynamics start all over again every year (season). Within each year, if the case is similar to the example above (where coexistence is prolonged), there will be enough pathogen strains from the previous year to successfully invade the population the following season. This results in the overall prolonged coexistence observed in the gypsy moth model.

2.3.1. Some interesting observations of heterogeneous models

Even though both pathogens always go extinct in model (2.11), numerical simulations revealed some interesting cases. In homogeneous models, the pathogen strain with the highest mean transmission rate is always the dominant strain. Heterogeneous models however can be unpredictable with regards to which pathogen strain is dominant. We show some few examples in this section.

In this first example, we observe that despite both pathogens eventually dying out, the heterogeneous model has a prolonged high incidence compared to the homogeneous model.

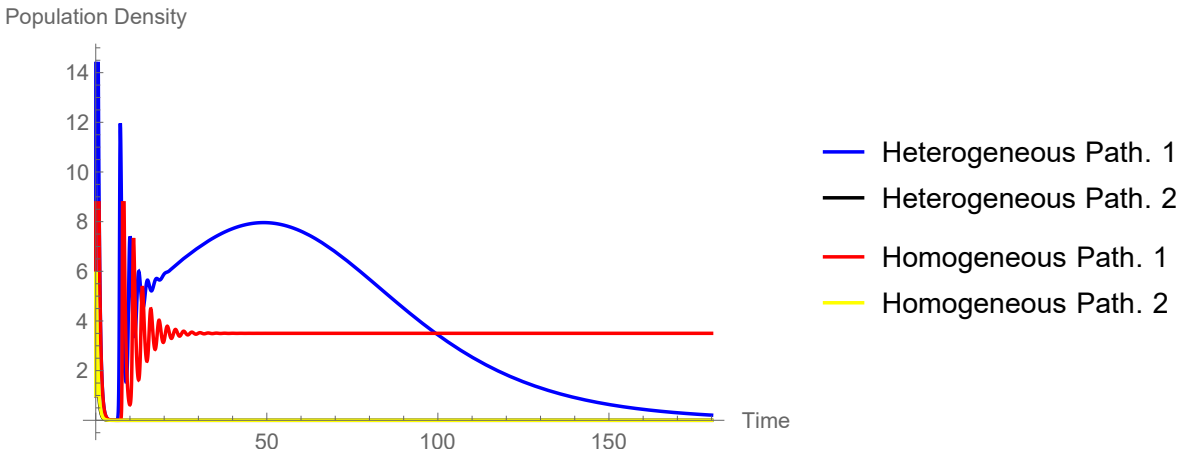

Figure 2.21. The basic reproductive rates are 8 and 4 for pathogen 1 and pathogen 2 respectively ($\beta_1 = 1, C_1 = 0.1, \beta_2 = 0.5, C_2 = 2$). In both models, pathogen 1 dies out pretty quickly. It will be interesting to find the reason behind the behavior of the heterogeneous model (pathogen 1) considering how high it relatively rises before eventually dying.

Since the coefficient of variation is not zero, the mean transmission rate changes with time in the heterogeneous model. Equation (2.11) allows us to observe the changes in transmission rates with time. We see below in Figure 2.22 that the transmission rate for pathogen strain 1 remained consistently higher than the transmission rate for pathogen strain 2. The average rate at which the transmission rate is changing is the coefficient of variation.

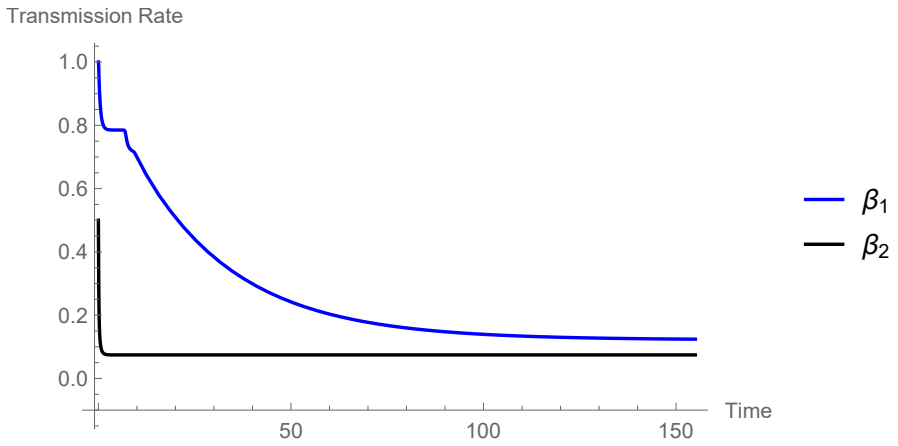

Figure 2.22. Figure showing how the strain specific infectious rates changes with time. The mean transmission rate of pathogen strain 1 slowly declined with time contrast to that of pathogen strain 2 which almost reduced to zero during the entire epidemic. It explains why Figure 2.21 hardly showed any sign of Pathogen strain 1

The phase portrait for the dynamics shows that throughout the epidemic, pathogen strain 1 has a higher basic reproductive ratio than strain 2 (that is, at any fixed time t, if the system was homogeneous, pathogen strain 1 would die out).

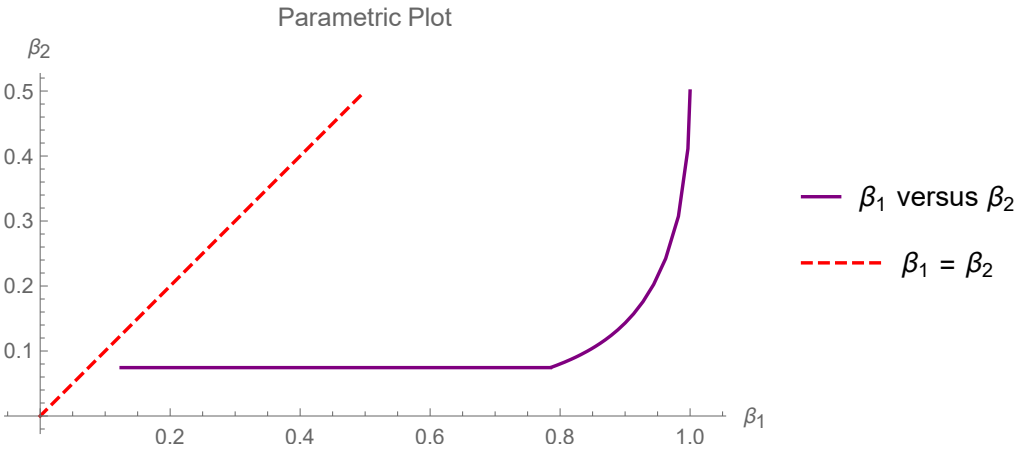

Figure 2.23. The phase portrait showing the changes in the mean, and consequently the changes in the basic reproductive ratio assuming that at a fixed time, the system is homogeneous. The dotted red line is the bifurcation line $\beta_1 = \beta_2$ (consequently $R_{0,1} = R_{0,2}$) and the purple line represents the changes in the means.

In our next example simulation, we show with an example that the pathogen with the highest initial R_0 in the heterogeneous model can go extinct at a faster rate than the other strain.

This is a consequence of the difference in the coefficient of variance. A high variation means the mean transmission rate declines faster and a low variation means the transmission rate declines slowly.

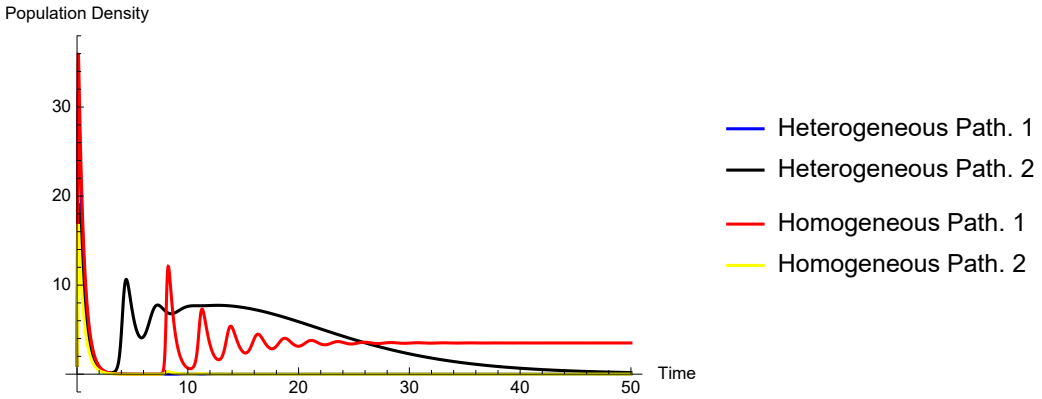

Figure 2.24. Even though pathogen strain 1 has $R_{0_1} = 8$ and pathogen strain 2 has $R_{0_2} = 6.4$, pathogen 1 is hardly seen in the epidemic process as it dies out pretty quickly. This due to its high coefficient of variation $C_1 = 1.5$ compared to $C_2 = 0.2$, the transmission rates are $\beta_1 = 1$ and $\beta_2 = 0.8$.

With its high initial transmission rate, pathogen strain 1 infects a higher proportion of the susceptible class and its infectious rate drops rapidly due to its high coefficient of variation. The transmission rate for pathogen strain 2 declines relatively slow whilst successfully invading the susceptible population before eventually dying out.

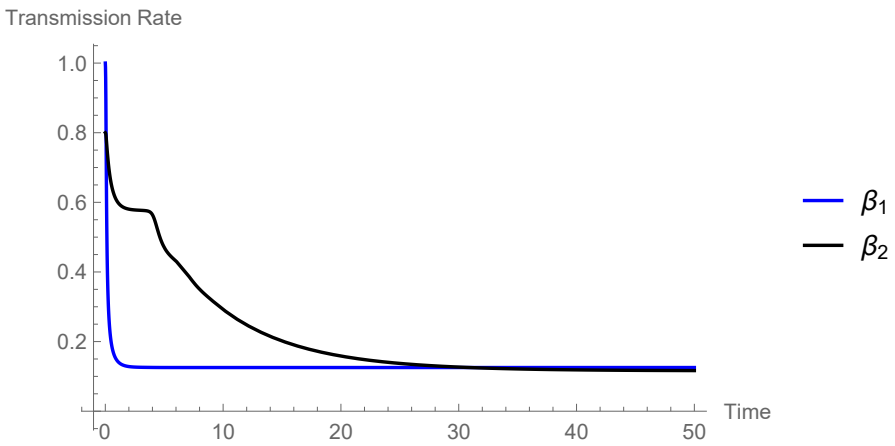

Figure 2.25. Figure showing how the marginal mean transmission rates change with time in Figure 2.24. The mean transmission rate of pathogen strain 1 rapidly declined due to its high variability. The decline was so fast that it failed to successfully invade the susceptible population.

We observe that due to its high variation in transmission, pathogen strain 1 had a steep decline in its mean transmission rate, the variation for pathogen strain 2 allows it to have a prolonged high mean transmission rate.

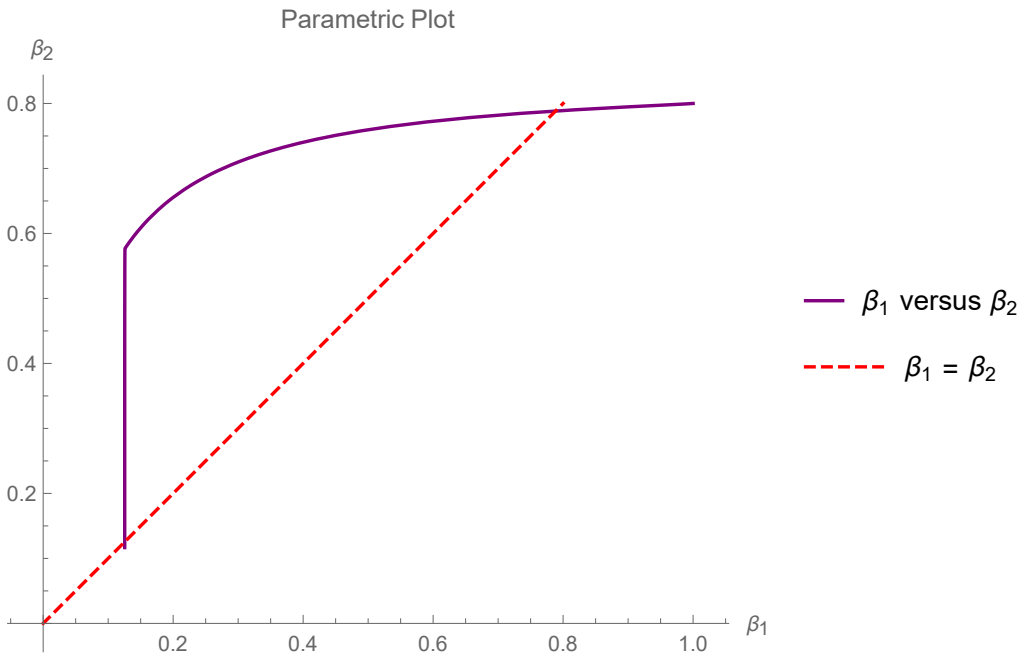

Figure 2.26. The phase portrait showing the changes in the mean, and consequently the changes in the basic reproductive ration assuming that at a fixed time, the system is homogeneous. The dotted red line is the bifurcation line $\beta_1 = \beta_2$ (consequently $R_{0,1} = R_{0,2}$) and the purple line represents the changes in the means.

We observe in Figure 2.26 that even though the initial basic reproductive number of pathogen strain 1 is higher, the rest of the infection period has pathogen strain 2 as the dominant strain. This observation is simply not possible in homogeneous models.

3. ANALYTICAL AND NUMERICAL ANALYSIS OF HETEROGENEOUS MODELS WITH MULTIPLE PATHOGENS AND CONTINUOUS TIME DEMOGRAPHY

In the previous chapter, we considered a two pathogen heterogeneous model, and gave a full analysis on why we observe pathogen coexistence in the gypsy moth problem. In general, Theorem 2.1.1 which was used in our analysis of model (1.9) only works for a special class of equations (of the form $N'(t) = N(t)F(t, E^t[a])$. Therefore, we could only consider demographic terms of the form $s(t, \beta_1, \beta_2)f(S(t))$ in model (1.9). In this section, we consider heterogeneous models which do not have this specific form, and show that pathogen coexistence is possible.

We consider a multi-pathogen heterogeneous model with compartmentalized host population. We will generalize the birth term as $f_i(S, I)$ for each susceptible compartmental class. Here, S denote the density of the susceptible population and I denote the density of the infected population. We investigate pathogen coexistence by considering infectious classes I_j as the density of the population infected by pathogen strain j.

Consider the model

$$\begin{aligned}
\dot{S}_i &= f_i(S, I) - \sum_{j=1}^{n} \beta_{ij} S_i I_j - \phi S_i, \quad i = 1, \ldots, m, \\
\dot{I}_j &= \sum_{i=1}^{m} \beta_{ij} S_i I_j - (\gamma_j + \phi) I_j, \quad j = 1, \ldots, n, \\
\dot{R} &= \sum_{j=1}^{n} \gamma_j I_j - \phi R.
\end{aligned} \tag{3.1}$$

Here S_i is the density of the susceptible population in compartment i, infected by pathogen strain j at the transmission rate β_{ij}, $f_i(S, I)$ is the birth term for each susceptible class i, and ϕ is the mortality rate for the population. For the purpose of our analysis, we assume that f_i is continuous, bounded, monotonically increasing, and at any point in time, $f_i(S, I) > \phi \geq 0$. The S, I terms in the birth term is to signify that f_i is a function of the densities of the susceptible population and the infected population. β_{ij} is the rate at which individuals in susceptible class i is infected by

pathogen strain j. Assuming there is a recovery class R, γ_j is the recovery rate, otherwise, γ_j is the removal rate due to infection by pathogen strain j.

We start by proving some basic facts about model (3.1). In the analysis, we in part follow [34].

3.1. Positiveness and boundedness

Proposition 3.1.1. *Given the non-negative initial conditions, $S_i(0) \geq 0$ and $I_j(0) \geq 0$, for all i, j, each sub-population remains non-negative.*

Proof. Let us assume $S_i(0) \geq 0$ and $I_j(0) \geq 0$ for all i and j.
Consider the equation for the susceptible compartment $S_i(t)$

$$\dot{S}_i = f_i(S, I) - \sum_{j=1}^{n} \beta_{ij} S_i I_j - \phi S_i, \quad i = 1, \ldots, m.$$

Let $\tau \geq 0$ be the time such that $S_i(\tau) = 0$. Then

$$\begin{aligned} \dot{S}_i(\tau) &= f_i(S, I) - \sum_{j=1}^{n} \beta_{ij} S_i(\tau) I_j(\tau) - \phi S_i(\tau), \quad i = 1, \ldots, m. \\ &= f_i(S, I) > 0, \end{aligned}$$

since the birth term $f_i(S, I)$ is a positive function. Therefore, $S_i(t) \geq 0$ at any time t.

Next, consider the equation corresponding to the population infected by pathogen strain j

$$\dot{I}_j(t) = \sum_{i=1}^{m} \beta_{ij} S_i(t) I_j(t) - (\gamma_j + \phi) I_j(t).$$

Let $\tau \geq 0$ be the time such that $I_j(\tau) = 0$. Then

$$\dot{I}_j(\tau) = \sum_{i=1}^{m} \beta_{ij} S_i(\tau) I_j(\tau) - (\gamma_j + \phi) I_j(\tau) = 0.$$

Therefore when $I_j(\tau) = 0$, $I_j(t)$ remains 0 for any time $t \geq \tau$. Since the initial condition is such that $I_j(0) \geq 0$, we have $I_j(t) \geq 0$ for all t.

Similarly for the recovered class, if τ is the time such that $R(\tau) = 0$. At time $t = \tau$, $\dot{R}(\tau) = \sum_j^m \gamma_j I_j(\tau) - \phi R(\tau) \geq 0$. Therefore, since $I_j(t) \geq 0$, $R(t) \geq 0$. □

Proposition 3.1.2. *Given the non-negative initial conditions:* $S_i(0) \geq 0, \quad I_j(0) \geq 0,$ *and* $R(0) = 0$ *for all* i, j*, the total population size* $N(t) = \sum_{i=1}^{m} S_i(t) + \sum_{j=1}^{n} I_j(t) + R(t)$ *is bounded, that is, there exists a scalar* $\aleph$ *such that* $0 \leq N(t) \leq \aleph$ *at any time* t*.*

Proof. Summing up all the equations in model (3.1), we get

$$\begin{aligned}\dot{N}(t) &= \sum_{i=1}^{m} f_i(S, I) - \phi \left(\sum_{i=1}^{m} S_i + \sum_{j=1}^{n} I_j + R(t) \right) - \sum_{j=1}^{n} \gamma_j I_j \\ &= \sum_{i=1}^{m} f_i(S, I) - \phi N(t) - \sum_{j=1}^{n} \gamma_j I_j.\end{aligned}$$

Since each $f_i(S, I)$ is assumed bounded, let $\kappa = \sum_{i=1}^{m} \max_i f_i(S, I),$ also we have $I_j \geq 0$, for all j. Therefore, $\dot{N}(t) \leq \kappa - \phi N(t)$. Consider also an ODE $\dot{x}(t) = k - \phi x(t)$, $x(0) = N_0$. We have $x(t) \to \frac{k}{\phi}$ as $t \to \infty$ and hence bounded for all t. By comparison theorem, $N(t) \leq x(t)$ for all t and hence also bounded by, say, constant $\aleph$. Together with Proposition 3.1.1, we have $0 \leq N(t) \leq \aleph$. □

Corollary 1. *Given positive initial conditions, every compartmental class in model (3.1) is bounded.*

Proof. Observe that at any time t, $S_i(t), I_j(t), R(t) < N(t)$ for all i and j.

Therefore, from Proposition (3.1.1) and Proposition (3.1.2), we have

$$0 \leq S_i(t), I_j(t), R(t) < N(t) \leq \aleph.$$ □

Remark 2. From Proposition 3.1.1 and Corollary 1, we conclude that, given non-negative initial conditions, the epidemic model (3.1) always have non-negative solutions. Furthermore, the solutions are bounded and defined for all $t \in (0, \infty)$

3.2. Basic reproductive number of model (3.1)

We compute the basic reproductive number R_0 using the next generation matrix. Details on this method can be found in [17].

Consider the infection subsystem of model (3.1)

$$\dot{I}_j = \sum_{i=1}^{m} \beta_{ij} S_i I_j - (\gamma_j + \phi) I_j, \quad j = 1, \ldots, n. \tag{3.2}$$

We linearize the infection subsystem (3.2) around the disease free equilibrium (dfe),

$$dfe = (S_1^*, S_2^*, \ldots, S_m^*, I_1^* = 0, I_2^* = 0, \ldots, I_n^* = 0).$$

The Jacobian matrix is

$$\begin{aligned} J_I &= \begin{pmatrix} \sum_{i=1}^m \beta_{i1} S_i^* & 0 & \ldots & 0 \\ 0 & \sum_{i=1}^m \beta_{i2} S_i^* & \ldots & 0 \\ \vdots & \vdots & \ldots & \vdots \\ 0 & 0 & \ldots & \sum_{i=1}^m \beta_{in} S_i^* \end{pmatrix} + \begin{pmatrix} -\gamma_1 - \phi & 0 & \ldots & 0 \\ 0 & -\gamma_2 - \phi & \ldots & 0 \\ \vdots & \vdots & \ldots & \vdots \\ 0 & 0 & \ldots & -\gamma_n - \phi \end{pmatrix} \\ &= T + \Sigma, \end{aligned}$$

where T corresponds to the transmissions and Σ corresponds to the transitions.
The next generation matrix K is $K = -T\Sigma^{-1}$.

$$\begin{aligned} K &= \begin{pmatrix} \frac{\sum_{i=1}^m \beta_{1n} S_i^*}{\gamma_1 + \phi} & 0 & \ldots & 0 \\ 0 & \frac{\sum_{i=1}^m \beta_{i2} S_i^*}{\gamma_2 + \phi} & \ldots & 0 \\ \vdots & \vdots & \ldots & \vdots \\ 0 & 0 & \ldots & \frac{\sum_{i=1}^m \beta_{in} S_i^*}{\gamma_n + \phi} \end{pmatrix} \\ &= \begin{pmatrix} R_{0_1} & 0 & \ldots & 0 \\ 0 & R_{0_2} & \ldots & 0 \\ \vdots & \vdots & \ldots & \vdots \\ 0 & 0 & \ldots & R_{0_n} \end{pmatrix}. \end{aligned}$$

Therefore, the basic reproductive number is

$$R_0 = \max_j R_{0_j}, \tag{3.3}$$

where the strain specific basic reproductive number is

$$R_{0_j} = \frac{\beta_{1j} S_1^* + \beta_{2j} S_2^* + \cdots + \beta_{mj} S_m^*}{\gamma_j + \phi}, \quad j = 1, \ldots, n. \tag{3.4}$$

3.3. Stability of the disease free equilibrium

The disease free equilibrium is such that $I_j = 0$ for all j.

Consider the equations for the susceptible classes in model (3.4.1):

$$\dot{S}_i = f_i(S, I) - \sum_{j=1}^{n} \beta_{ij} S_i I_j - \phi S_i, \quad i = 1, \ldots, m.$$

Since $I_j = 0$, at the dfe,

$$0 = f_i(S^*, I^*) - \phi S_i, \quad i = 1, \ldots, m.$$

Let $\mu_i = f_i(S^*, I^*)$, then $S_i^* = \frac{\mu_i}{\phi}$. It follows from equation (3.4) that the strain specific basic reproductive number is

$$R_{0_j} = \frac{\sum_{i=1}^{m} \beta_{ij} S_i^*}{\gamma_j + \phi} = \frac{\sum_{i=1}^{m} \frac{\beta_{ij}\mu_i}{\phi}}{\gamma_j + \phi} = \sum_{i=i}^{m} \frac{\beta_{ij}\mu_i}{\phi(\gamma_j + \phi)}.$$

Theorem 3.3.1. *The disease free equilibrium (dfe) of model (3.1) is asymptotically stable if the basic reproductive number is less than 1, $R_0 < 1$. Precisely, the dfe is stable if all the strain specific basic reproductive numbers are less than 1, $R_{0_i} < 1$.*

Proof. We linearize the sytem (3.1) around the dfe to study its stability.

The Jacobian for the system (3.1) is

$$J = \begin{pmatrix} A & B \\ C & D \end{pmatrix}, \tag{3.5}$$

where

$$A = \begin{pmatrix} -\sum_{j=1}^{n} \beta_{1j} I_j - \phi & 0 & \dots & 0 \\ 0 & -\sum_{j=1}^{n} \beta_{2j} I_j - \phi & \dots & 0 \\ \vdots & \vdots & \dots & \vdots \\ 0 & 0 & \dots & -\sum_{j=1}^{n} \beta_{mj} I_j - \phi \end{pmatrix},$$

$$B = \begin{pmatrix} -\beta_{11} S_1 & -\beta_{12} S_1 & \dots & -\beta_{1n} S_1 \\ -\beta_{21} S_2 & -\beta_{22} S_2 & \dots & -\beta_{2n} S_2 \\ \vdots & \vdots & \dots & \vdots \\ -\beta_{m1} S_m & -\beta_{m2} S_m & \dots & -\beta_{mn} S_m \end{pmatrix},$$

$$C = \begin{pmatrix} \beta_{11} I_1 & \beta_{21} I_1 & \dots & \beta_{m1} I_1 \\ \beta_{12} I_2 & \beta_{22} I_2 & \dots & \beta_{m2} I_2 \\ \vdots & \vdots & \dots & \vdots \\ \beta_{1n} I_n & \beta_{2n} I_n & \dots & \beta_{mn} I_n \end{pmatrix},$$

and

$$D = \begin{pmatrix} \sum_{i=1}^{m} \beta_{i1} S_i - \gamma_1 - \phi & 0 & \dots & 0 \\ 0 & \sum_{i=1}^{m} \beta_{i2} S_i - \gamma_2 - \phi & \dots & 0 \\ \vdots & \vdots & \dots & \vdots \\ 0 & 0 & \dots & \sum_{i=1}^{m} \beta_{in} S_i - \gamma_n - \phi \end{pmatrix}.$$

At the dfe, $C = 0$, therefore, the Jacobian takes the form

$$J_{dfe} = \begin{pmatrix} A & B \\ 0 & D \end{pmatrix}. \tag{3.6}$$

The eigenvalues therefore depends on the sub-matrices A and D.

At the dfe, matrix A is

$$A_{dfe} = \begin{pmatrix} -\phi & 0 & \dots & 0 \\ 0 & -\phi & \dots & 0 \\ \vdots & \vdots & \dots & \vdots \\ 0 & 0 & \dots & -\phi \end{pmatrix},$$

therefore, the eigenvalues of A are all negative.

For matrix D, we have at the dfe

$$D_{dfe} = \begin{pmatrix} \sum_{i=1}^{m} \frac{\beta_{i1}\mu_i}{\phi} - \gamma_1 - \phi & 0 & \dots & 0 \\ 0 & \sum_{i=1}^{m} \frac{\beta_{i2}\mu_i}{\phi} - \gamma_2 - \phi & \dots & 0 \\ \vdots & \vdots & \dots & \vdots \\ 0 & 0 & \dots & \sum_{i=1}^{m} \frac{\beta_{in}\mu_i}{\phi} - \gamma_n - \phi \end{pmatrix}.$$

The eigenvalues of D_{dfe} are all negative if and only if for all $j = 1, \dots, n$,

$$\begin{aligned} &\sum_{i=1}^{m} \frac{\beta_{ij}\mu_i}{\phi} - \gamma_j - \phi < 0 \iff \\ &\sum_{i=1}^{m} \frac{\beta_{ij}\mu_i}{\phi} < \gamma_j + \phi \iff \\ &\sum_{i=1}^{m} \frac{\beta_{ij}\mu_i}{\phi(\gamma_j + \phi)} < 1 \iff \\ &R_{0_j} < 1. \end{aligned} \tag{3.7}$$

Therefore, the dfe is asymptotically stable if all the strain specific R_{0_j} are less than 1. □

Corollary 2. *If the strain specific basic reproductive number R_{0_j} is greater than 1 for at least one j, the disease free equilibrium is unstable.*

Proof. It follows directly from Theorem 3.3.1. □

3.4. Stability of strictly positive endemic equilibrium

Consider the equilibrium state of model (3.1).

Let $\mu_i = f_i^* = f_i(S^*, I^*)$ at the equilibrium, then

$$\mu_i = \sum_{j=1}^{n} \beta_{ij} S_i^* I_j^* + \phi S_i^*, \quad i = 1, \dots, m, \tag{3.8}$$

$$\gamma_j I_j^* = \sum_{i=1}^{m} \beta_{ij} S_i^* I_j^* - \phi I_j^*, \quad j = 1, \dots, n. \tag{3.9}$$

The strictly positive endemic equilibrium state $Q^* = (S_1^*, S_2^*, ..., S_m^*, I_1^*, ..., I_n^*) > 0$ is such that:

$$\frac{\mu_i}{S_i^*} - \phi = \sum_{j=1}^{n} \beta_{ij} I_j^*, \tag{3.10}$$

$$\gamma_j + \phi = \sum_{i=1}^{m} \beta_{ij} S_i^*. \tag{3.11}$$

Theorem 3.4.1. *The strictly positive endemic equilibrium state $Q^* = (S_1^*, S_2^*, ..., S_m^*, I_1^*, ..., I_n^*) > 0$ is Lyapunov stable if it exists. If it is unique, it is globally asymptotically stable.*

Proof. We consider a modified version of the Goh's logarithmic Lyapunov function [23, 37].

$$V(S_1, ..., S_m, I_1, .., I_m) = \sum_{i=1}^{m} S_i^* \left(\frac{S_i}{S_i^*} - 1 - \ln \frac{S_i}{S_i^*} \right) + \sum_{j=1}^{n} I_j^* \left(\frac{I_j}{I_j^*} - 1 - \ln \frac{I_j}{I_j^*} \right).$$

V is well defined and continuous for all $S_i, I_j > 0$, $V \geq 0$, and $V(Q^*) = 0$. Its derivative along the orbits of model (3.1) is

$$\dot{V} = \sum_{i=1}^{m} \dot{S}_i \left(1 - \frac{S_i^*}{S_i} \right) + \sum_{j=1}^{n} \dot{I}_j \left(1 - \frac{I_j^*}{I_j} \right).$$

Expand and group all the I and I^* terms.

$$\begin{aligned}
\dot{V} = & \sum_{j=1}^{n} [I_j(\beta_{1j} S_1^* + \beta_{2j} S_2^* + \ldots + \beta_{mj} S_m^* - \phi) - \gamma_j I_j] \\
& + \sum_{j=1}^{n} \left[I_j^*(\phi - \beta_{1j} S_1 - \beta_{2j} S_2 - \ldots - \beta_{mj} S_m) + \gamma_j I_j^* \right] \\
& + \sum_{i=1}^{m} \left[\mu_i \left(1 - \frac{S_i^*}{S_i} \right) + \phi S_i^* - \phi(S_i) \right].
\end{aligned}$$

At the endemic equilibrium: $\gamma_j = \sum_i \beta_{ij} S_i^* - \phi$ and $\gamma_j I_j^* = \sum_i \beta_{ij} S_i^* I_j^* - \phi I_j^*$, therefore,

$$\begin{aligned}
\dot{V} = & \sum_{j=1}^{n} \left[I_j^*(\gamma_j + \phi - \beta_{1j} S_1 - \beta_{2j} S_2 - \ldots - \beta_{mj} S_m) \right] \\
& + \mu_1 \left(1 - \frac{S_1^*}{S_1} \right) + \mu_2 \left(1 - \frac{S_2^*}{S_2} \right) + \ldots + \mu_m \left(1 - \frac{S_m^*}{S_m} \right) + \phi(S_1^* + \ldots + S_m^*) \\
& - \phi(S_1 + \ldots + S_m) \\
= & \sum_{i=1}^{m} \left[(S_i^* - S_i)(\beta_{i1} I_1^* + \beta_{i2} I_2^* + \ldots + \beta_{in} I_n^* + \phi - \frac{\mu_i}{S_i}) \right].
\end{aligned}$$

From (3.10), $\frac{\mu_i}{S_i^*} = \phi + \sum_j \beta_{ij} I_j^*$, therefore,

$$\begin{aligned}
\dot{V} &= \sum_{i=1}^{m} \left[(S_i^* - S_i)(\frac{\mu_i}{S_i^*} - \frac{\mu_i}{S_i}) \right] \\
&= -\sum_{i=1}^{m} \frac{\mu_i}{S_i^* S_i} (S_i^* - S_i)^2 \\
&\leq 0.
\end{aligned}$$

Hence all the conditions for Lyapunov function are satisfied and we conclude that Q^* is Lyapunov stable. If Q^* is unique, the maximum invariant subset of the set $\{(S, I) : \dot{V}(S, I) = 0\}$ coincides with Q^* and hence by the Krasovskii-LaSalle invariance principle, Q^* will be globally stable. □

3.5. Existence of the strictly positive endemic equilibrium

In the previous section we proved that the strictly positive endemic equilibrium is always asymptotically stable if it exists. The theorem did not, however, guarantee that such equilibrium always exists. Since the dimension of the generalized model (3.1) is unknown, we cannot write an explicit formula for the strictly positive endemic equilibrium. However, we can look and the behavior of the equilibrium points and give some general conditions which may lead to the existence of endemic equilibrium. In general, each pathogen strain is only able to invade the population if and only if its strain specific basic reproductive ratio R_{0_j} is greater than one. In addition, from Corollary 2, the dfe is unstable when all the strain specific basic reproductive number are greater than 1, which makes us suspect that there might be other equilibrium points.

Theorem 3.5.1 (Necessary conditions for existence of coexistence equilibrium)**.** *Let the strain specific basic reproductive numbers be* $R_{0_j} > 1, \quad j = 1, \ldots, n.$

- *if* $m = n$*, then there exist a unique an internal strictly positive equilibrium only if* $\det(B) \neq 0$*, where* $B = [\beta_{i,j}]$ *is an* $n \times n$ *matrix of transmission coefficients.*
- *if* $m < n$*, and the vectors* $\{(\beta_{11}, \beta_{21}, \ldots, \beta_{m1}, \gamma_1), \ldots, (\beta_{1n}, \beta_{2n}, \ldots, \beta_{mn}, \gamma_n)\}$ *are not linearly dependent, then there is no coexistence equilibrium.*
- *if* $m > n$*,* $S_i^* > 0, \quad i = 1, \ldots, m$*, and the vectors* $\{(\beta_{11}, \beta_{12}, \ldots, \beta_{1n}, \frac{\mu_1}{S_1^*}), \ldots,$ $(\beta_{m1}, \beta_{m2}, \ldots, \beta_{mn}, \frac{\mu_m}{S_m^*})\}$ *are not linearly dependent, then there is no coexistence equilibrium.*

Proof. The equations for the equilibrium can be written

$$\begin{aligned} \mu_i &= \sum_{j=1}^{n} \beta_{ij} S_i^* I_j^* + \phi S_i^*, \quad i = 1, \ldots, m, \\ \gamma_j I_j^* &= \sum_{i=1}^{m} \beta_{ij} S_i^* I_j^* - \phi I_j^*, \quad j = 1, \ldots, n, \end{aligned} \tag{3.12}$$

where $\mu_i = f_i^* = f_i(S^*, I^*)$.

Consider the infectious subsystem of (3.12)

$$\begin{aligned} \beta_{11} S_1^* I_1^* + \beta_{21} S_2^* I_1^* + \ldots + \beta_{m1} S_m^* I_1^* &= (\gamma_1 + \phi) I_1^*, \\ \beta_{12} S_1^* I_2^* + \beta_{22} S_2^* I_2^* + \ldots + \beta_{m2} S_m^* I_2^* &= (\gamma_2 + \phi) I_2^*, \\ &\vdots \\ \beta_{1n} S_1^* I_n^* + \beta_{2n} S_2^* I_n^* + \ldots + \beta_{mn} S_m^* I_n^* &= (\gamma_n + \phi) I_n^*. \end{aligned} \tag{3.13}$$

Observe the system (3.13) has a trivial solution $I_j^* = 0$ for all j. Suppose $I_j^* \neq 0$ for all j, then the system (3.13) can be written as

$$\begin{aligned} \beta_{11} S_1^* + \beta_{21} S_2^* + \ldots + \beta_{m1} S_m^* &= (\gamma_1 + \phi), \\ \beta_{12} S_1^* + \beta_{22} S_2^* + \ldots + \beta_{m2} S_m^* &= (\gamma_2 + \phi), \\ &\vdots \\ \beta_{1n} S_1^* I_n^* + \beta_{2n} S_2^* + \ldots + \beta_{mn} S_m^* &= (\gamma_n + \phi). \end{aligned} \tag{3.14}$$

Let $\bar{\gamma_j} = \gamma_j + \phi$, $B = \begin{pmatrix} \beta_{11} & \beta_{21} & \ldots & \beta_{m1} \\ \beta_{12} & \beta_{22} & \ldots & \beta_{m2} \\ \vdots & \vdots & \vdots & \\ \beta_{1n} & \beta_{2n} & \ldots & \beta_{mn} \end{pmatrix}$, $\vec{S} = \begin{pmatrix} S_1^* \\ S_2^* \\ \vdots \\ S_m^* \end{pmatrix}$, and, $\vec{w} = \begin{pmatrix} \bar{\gamma_1} \\ \bar{\gamma_2} \\ \vdots \\ \bar{\gamma_n} \end{pmatrix}$, then

$$B\vec{S} = \vec{w}. \tag{3.15}$$

Similarly, we consider the subsystem for the susceptible population in (3.1). At the equilibrium, we have

$$\begin{aligned}
\beta_{11}S_1^*I_1^* + \beta_{12}S_1^*I_2^* + \cdots + \beta_{1n}S_1^*I_n^* - \phi S_1^* &= f_1(S^*, I^*),\\
\beta_{21}S_2^*I_1^* + \beta_{22}S_2^*I_2^* + \cdots + \beta_{2n}S_2^*I_n^* - \phi S_1^* &= f_2(S^*, I^*),\\
&\vdots\\
\beta_{11}S_1^*I_1^* + \beta_{12}S_1^*I_2^* + \cdots + \beta_{1n}S_1^*I_n^* - \phi S_1^* &= f_m(S^*, I^*).
\end{aligned} \tag{3.16}$$

The system (3.16) has a trivial solution if and only if $S_i^* = 0$ and $f_i(S^*, I^*) = 0$ for all i. Let $\mu_i = f_i(S^*, I^*)$ and assume $S_i^* \neq 0$ for all i, then system (3.16) becomes

$$\begin{aligned}
\beta_{11}I_1^* + \beta_{12}I_2^* + \cdots + \beta_{1n}I_n^* &= \phi + \frac{\mu_1}{S_1^*},\\
\beta_{21}I_1^* + \beta_{22}I_2^* + \cdots + \beta_{2n}I_n^* &= \phi + \frac{\mu_2}{S_2^*},\\
&\vdots\\
\beta_{m1}I_1^* + \beta_{m2}I_2^* + \cdots + \beta_{mn}I_n^* &= \phi + \frac{\mu_m}{S_m^*}.
\end{aligned} \tag{3.17}$$

Therefore,

$$B^\tau \vec{I} = \vec{\mu},$$

where τ denotes matrix transpose, $\vec{I} = \begin{pmatrix} I_1^* \\ I_2^* \\ \vdots \\ I_n^* \end{pmatrix}$ and $\vec{\mu} = \begin{pmatrix} \frac{\mu_1+\phi S_1^*}{S_1^*} \\ \frac{\mu_2+\phi S_2^*}{S_2^*} \\ \vdots \\ \frac{\mu_m+\phi S_m^*}{S_m^*} \end{pmatrix}$. We observe that the solution of the susceptible subsystem (3.17) depends on the solution of the infectious subsystem (3.15) (at the equilibrium).

From Remark 2, we know that given non-negative initial conditions, all solutions of system (3.1) are non-negative.

If $m = n$, a unique solution for the systems $B\vec{S} = \vec{w}$ and $B^\tau \vec{I} = \vec{\mu}$ will require $\det(B) = \det(B^\tau) \neq 0$.

If $m \neq n$, then the systems will only have a solution if the rows/columns of the augmented matrices $\left[\begin{array}{c|c} B & \vec{w} \end{array}\right]$ and $\left[\begin{array}{c|c} B^\tau & \vec{\mu} \end{array}\right]$ are linearly dependent. □

As evidence of pathogen coexistence resulting from model (3.1), we consider specific cases of (3.1), and give a generalized condition for the existence of a strictly positive endemic equilibrium in the next section. We will show both analytically and numerically that pathogen coexistence is possible between multiple strains of the same pathogen.

3.6. Two pathogen heterogeneous model with constant birth rate

Consider the heterogeneous multi-pathogen model

$$\begin{aligned}
\dot{S_1} &= Kp - \beta_{11} S_1 I_1 - \beta_{12} S_1 I_2, \\
\dot{S_2} &= K(1-p) - \beta_{21} S_2 I_1 - \beta_{22} S_2 I_2, \\
\dot{I_1} &= \beta_{11} S_1 I_1 + \beta_{21} S_2 I_1 - \gamma_1 I_1, \\
\dot{I_2} &= \beta_{12} S_1 I_2 + \beta_{22} S_2 I_2 - \gamma_2 I_2,
\end{aligned} \tag{3.18}$$

where S_i is the density of susceptible class i, I_i is the density of those infected by pathogen strain i, β_{ij} is the transmission rate of pathogen strain j with respect to susceptible class i, and p is the probability that a new born will be in susceptible class in susceptible class 1. Hence $0 \leq p \leq 1$.

3.6.1. Existence of strictly positive endemic equilibrium

Consider the heterogeneous system (3.18), each pathogen strain can only invade if and only if their strain specific basic reproductive ratios R_{0_i} is greater than one. In addition, if

$$\beta_{11} > \frac{\beta_{12}\gamma_1}{\gamma_2}\,,\ \beta_{22} > \frac{\beta_{21}\gamma_2}{\gamma_1},\ \text{and}\ \frac{\beta_{11}\beta_{21}\gamma_2 - \beta_{12}\beta_{21}\gamma_1}{\beta_{11}\beta_{22}\gamma_1 - \beta_{11}\beta_{21}\gamma_2} < 1 - p < \frac{\beta_{11}\beta_{22}\gamma_1 - \beta_{12}\beta_{22}\gamma_1}{\beta_{12}\beta_{22}\gamma_1 - \beta_{12}\beta_{21}\gamma_2},$$

then for any $K \in \mathbb{R}^+$, the system has a unique strictly positive endemic equilibrium.

3.6.1.1. Stability of the strictly positive endemic equilibrium

Let $\mu_1 = Kp$ and $\mu_2 = k(1-p)$, the endemic equilibrium state $Q^* = (S_1^*, S_2^*, I_1^*, I_2^*)$ is such that

$$\beta_{11} S_1^* I_1^* + \beta_{12} S_1^* I_2^* = \mu_1, \tag{3.19}$$

$$\beta_{21} S_2^* I_1^* + \beta_{22} S_2^* I_2^* = \mu_2, \tag{3.20}$$

$$\beta_{11} S_1^* I_1^* + \beta_{21} S_2^* I_1^* = \gamma_1 I_1^*, \tag{3.21}$$

$$\beta_{12} S_1^* I_2^* + \beta_{22} S_2^* I_2^* = \gamma_2 I_2^*. \tag{3.22}$$

Corollary 3. *The endemic equilibrium state Q^* of system (3.18) is Lyapunov stable if it exists.*

Proof. It follows from Theorem 3.4.1. □

Consider a specific example of model (3.18). Let $K = 5$, $p = 0.6$, $\beta_{11} = 0.7$, $\beta_{12} = 0.3$, $\beta_{21} = 0.4$, $\beta_{22} = 1$, and $\gamma_1 = \gamma_2 = 1$. The system becomes

$$\begin{aligned}
\dot{S}_1 &= 3 - 0.7S_1I_1 - 0.3S_2I_2,\\
\dot{S}_2 &= 2 - 0.4S_2I_1 - S_2I_2,\\
\dot{I}_1 &= 0.7S_1I_1 + 0.4S_2I_1 - I_1,\\
\dot{I}_2 &= 0.3S_1I_2 + S_2I_2 - I_2.
\end{aligned}$$

We look at the equilibria of the system and analyze its stability. The endemic equilibrium is $S_1^* = 1.03, S_2^* = 0.6895, I_1^* = 3.52142,\ I_2^* = 1.49208$. The Jacobian matrix of the system is

$$J = \begin{pmatrix}
-0.7I_1 - 0.3I_2 & 0 & -0.7S_1 & -0.3S_1\\
0 & -0.4I_1 - I_2 & -0.4S_2 & -S_2\\
0.7I_1 & 0.4I_1 & 0.7S_1 + 0.4S_2 - 1 & 0\\
0.3I_2 & I_2 & 0 & 0.3S_1 + S_2 - 1
\end{pmatrix}$$

At the equilibrium, the eigenvalues are $\lambda_1 = -2.7478, \lambda_2 = -0.1597, \lambda_{3,4} = -1.4553 \pm 0.888i$. Therefore, the endemic equilibrium is asymptotically stable since $Re(\lambda_i) < 0$ for all i, which implies that coexistence is possible.

3.7. More examples of coexistence equilibrium in model (3.1)

We construct examples of model (3.1) where there exist a stable positive coexistence. Since model (3.1) has arbitrary number of compartmental classes, we will consider different cases with different compartmental classes and number of pathogen strains.

3.7.1. Case 1: m=2, n=3 (2 susceptible classes, 3 pathogen strains)

We consider a specific case of model (3.1) with 2 susceptible classes and 3 pathogen strains. We assume that individuals within each susceptible class have the same risk of infection to the various strains. We will show two examples of this case where pathogen coexistence is possible.

The model is

$$\begin{aligned}
\dot{S}_1 &= Kp - \beta_{11}S_1I_1 - \beta_{12}S_1I_2 - \beta_{13}S_1I_3 - \phi S_1,\\
\dot{S}_2 &= K(1-p) - \beta_{21}S_2I_1 - \beta_{22}S_2I_2 - \beta_{23}S_2I_3 - \phi S_2,\\
\dot{I}_1 &= \beta_{11}S_1I_1 + \beta_{21}S_2I_1 - \gamma_1 I_1 - \phi I_1,\\
\dot{I}_2 &= \beta_{12}S_1I_2 + \beta_{22}S_2I_2 - \gamma_2 I_2 - \phi I_2,\\
\dot{I}_3 &= \beta_{13}S_1I_3 + \beta_{23}S_2I_3 - \gamma_3 I_3 - \phi I_3,
\end{aligned} \tag{3.23}$$

where S_i is the density of susceptible class i, I_i is the density of those infected by pathogen strain i, β_{ij} is the transmission rate of pathogen strain j with respect to susceptible class i, and p is the probability that a new born will be in susceptible class in susceptible class 1. Hence $0 \leq p \leq 1$.

Example 1. Let

$$\begin{gathered}
\beta_{11} = 5, \quad \beta_{12} = 0.4, \quad \beta_{13} = 5.4,\\
\beta_{21} = 0.3, \quad \beta_{22} = 4, \quad \beta_{23} = 4.3,\\
K = 5, \quad p = 0.6, \quad \gamma_1 = 0.1, \quad \gamma_2 = 0.2, \quad \gamma_3 = 0.3 \quad \phi = 0.
\end{gathered}$$

Then, the equilibrium point is

$$S_1 = 0.0387324, \quad S_2 = 0.0211268, \quad I_1 = 1.22313, \quad I_2 = 10.1842, \quad I_3 = 12.4565.$$

Hence from Theorem 3.4.1, the equilibrium point is globally stable. Mathematica simulations for this case is Figure 3.1.

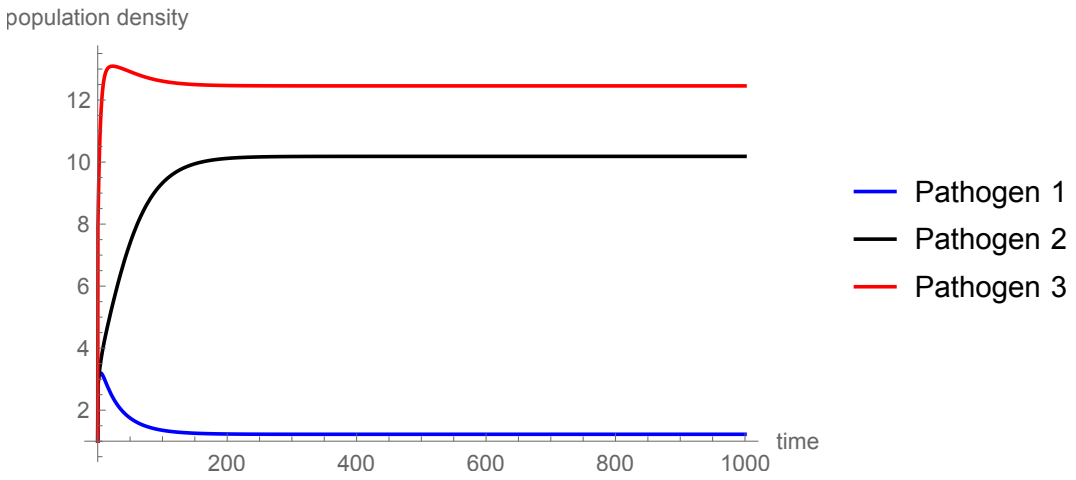

Figure 3.1. An example of pathogen coexistence in (3.1) with 2 susceptible classes and 3 pathogen strains. The parameters used are $K = 5$, $p = 0.6$, $\beta_{11} = 5$, $\beta_{12} = 0.4$, $\beta_{13} = 5.4$, $\beta_{21} = 0.3$, $\beta_{22} = 4$, $\beta_{23} = 4.3, \gamma_1 = 0.1, \gamma_2 = 0.2, \gamma_3 = 0.3$ and, $\phi = 0$. The initial conditions are $S_1(0) = S_2(0) = 5$, $I_1(0) = I_2(0) = I_3(0) = 1$.

We conclude that theoretically, 3 strains of the same pathogen can coexist in a heterogeneous population with 2 sub-populations with different risk levels of infection (consequently the transmission rates).

3.7.2. Case 2: m=3, n=2 (3 susceptible classes, 2 pathogen strains)

We consider a specific case of model (3.1) where there are 3 susceptible classes and 2 pathogen strains. The model is

$$\begin{aligned}
\dot{S}_1 &= \mu_1 - \beta_{11} S_1 I_1 - \beta_{12} S_1 I_2 - \phi S_1, \\
\dot{S}_2 &= \mu_2 - \beta_{21} S_2 I_1 - \beta_{22} S_2 I_2 - \phi S_2, \\
\dot{S}_3 &= \mu_3 - \beta_{31} S_3 I_1 - \beta_{32} S_2 I_2 - \phi S_3, \\
\dot{I}_1 &= \beta_{11} S_1 I_1 + \beta_{21} S_2 I_1 - \gamma_1 I_1 + \beta_{31} S_3 I_1 - \phi I_1, \\
\dot{I}_2 &= \beta_{12} S_1 I_2 + \beta_{22} S_2 I_2 - \gamma_2 I_2 + \beta_{32} S_3 I_2 - \phi I_2,
\end{aligned} \tag{3.24}$$

where S_i is the density of susceptible class i, I_i is the density of those infected by pathogen strain i, β_{ij} is the transmission rate of pathogen strain j with respect to susceptible class i, and μ_i is the birth rate of susceptible class i.

Example 1. Let

$$\mu_1 = \mu_2 = \mu_3 = 3.1, \quad \beta_{11} = 1, \quad \beta_{12} = 0.5,$$
$$\beta_{21} = 0.5, \quad \beta_{22} = 0.5, \quad \beta_{31} = 0.4, \quad \beta_{32} = 0.8,$$
$$\gamma_1 = 2.2, \quad \gamma_2 = 2.16, \quad \phi = 1.$$

The coexistence equilibrium point is

$$S_1^* = 1.49891, \quad S_2^* 1.90327, \quad S_3^* = 1.87364, \quad I_1^* = 0.878779, \quad I_2^* = 0.378779.$$

Therefore, by Theorem 3.4.1, the coexistence equilibrium is globally stable. Numerical simulation using Mathematica confirms the results:

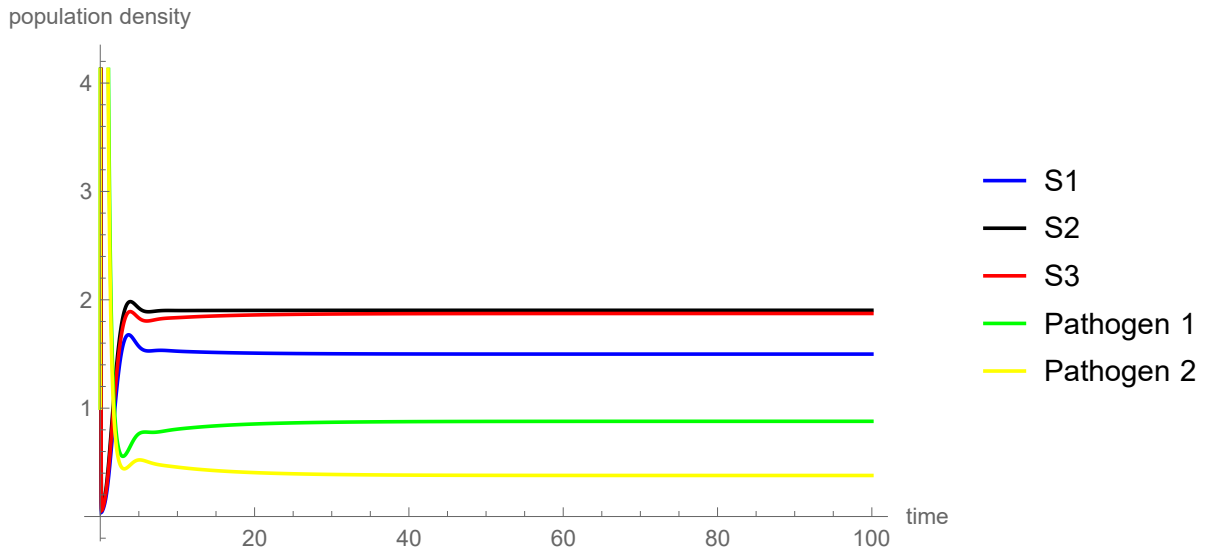

Figure 3.2. An example of pathogen coexistence in (3.1) with 3 susceptible classes and 2 pathogen strains. The parameters used are $\mu_1 = \mu_2 = \mu_3 = 3.1$, $\beta_{11} = 1$, $\beta_{12} = 0.5$, $\beta_{21} = 0.5$, $\beta_{22} = 0.5$, $\beta_{31} = 0.4$, $\beta_{32} = 0.8, \gamma_1 = 2.2, \gamma_2 = 2.16$ and, $\phi = 1$ The initial conditions are $S_1(0) = S_2(0) = S_3(0) = 5$, $I_1(0) = I_2(0) = 1$.

Other numerical simulations showing examples of pathogen coexistence are shown in Figure 3.3 and Figure 3.4.

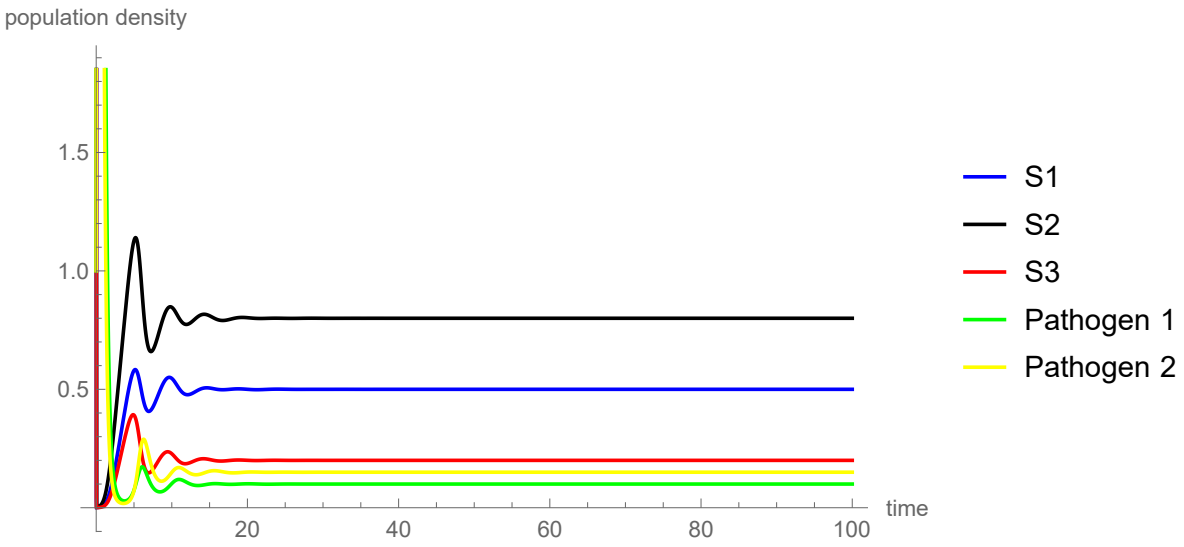

Figure 3.3. An example of pathogen coexistence in (3.1) with 3 susceptible classes and 2 pathogen strains. The parameters used are $\mu_1 = 0.2375$, $\mu_2 = 0.384$, $\mu_3 = 0.191$, $\beta_{11} = 4$, $\beta_{12} = 0.5$, $\beta_{21} = 0.3$, $\beta_{22} = 3$, $\beta_{31} = 4.3$, $\beta_{32} = 3.5, \gamma_1 = 3.1, \gamma_2 = 3.35$ and, $\phi = 0$ The initial conditions are $S_1(0) = S_2(0) = S_3(0) = 50$, $I_1(0) = I_2(0) = 1$.

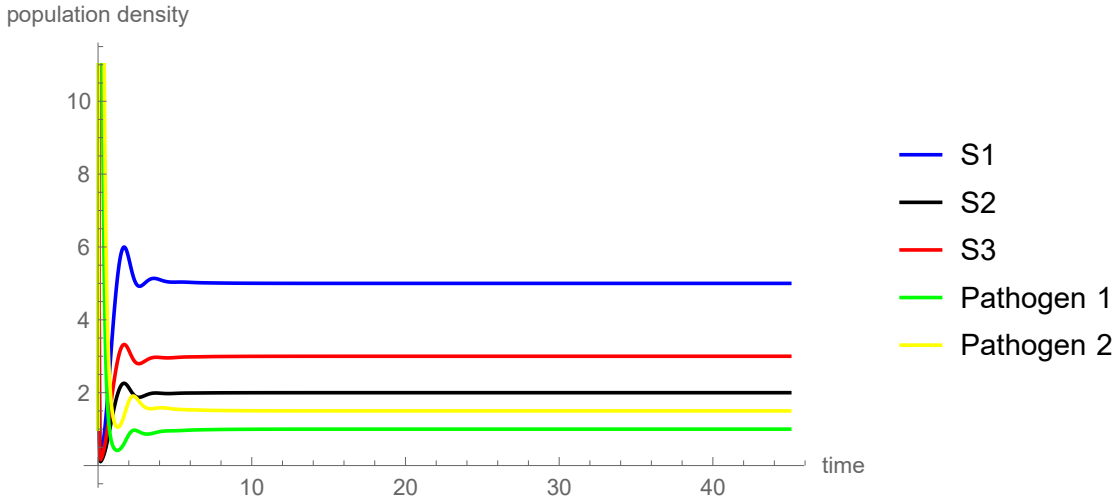

Figure 3.4. An example of pathogen coexistence in (3.1) with 3 susceptible classes and 2 pathogen strains. The parameters used are $\mu_1 = 13.75$, $\mu_2 = 5.4$, $\mu_3 = 7.8$, $\beta_{11} = 1$, $\beta_{12} = 0.5$, $\beta_{21} = 0.5$, $\beta_{22} = 0.8$, $\beta_{31} = 0.4$, $\beta_{32} = 0.8, \gamma_1 = 6.2, \gamma_2 = 5.5$ and, $\phi = 1$ The initial conditions are $S_1(0) = S_2(0) = S_3(0) = 50$, $I_1(0) = I_2(0) = 1$.

We conclude that theoretically, 2 strains of the same pathogen can coexist in a heterogeneous population with 3 sub-populations, with each having a different level of susceptibility.

Overall, multiple strains of the same pathogen can coexist in a heterogeneous population. This is the reality that we observe [3]. Model (3.1) and Theorem 3.4.1 show that mathematically, n multiple strains of the same pathogen can coexist in heterogeneous population with m distinct sub-populations of different levels of risks of infection.

4. CONCLUSION

In this text, we studied mathematical models that describe an epidemic spread in populations with parametric heterogeneity. We gave evidence that host heterogeneity promotes pathogen coexistence in both host populations with discrete life cycles (e.g., gypsy moths), and host populations with continuous life cycles (e.g., human beings). The form of heterogeneity described was parametric heterogeneity, where the host population varies in susceptibility, that is, different individuals are assumed to have different resistance to infection or different levels of risk of infection.

One of our main discussions was on the gypsy moth model (1.9) with the demographic model (1.12). With the help of the reduction theorem, we gave analytic and numerical analysis of system (1.9), and showed that two pathogen (baculovirus) strains can survive within multiple generations (over 150) of the gypsy moth population. Our analysis on (1.9) made no assumptions on neither the coefficients of variation nor the correlation coefficient. Our results can be summarized as follows.

1. When the variations in transmission for both pathogen strains are constant, the initial distribution of susceptibility follows the gamma distribution.

2. When the variations in transmission are constant, a pathogen strain with a high mean, high variation can coexist with a pathogen strain with a low mean, low variation. That was the case considered initially in [22].

3. When the time dependent coefficients of variation are not constant, it is possible for a pathogen strain with a high mean, low variation to coexist with a pathogen strain with low mean, high variation. It is also possible for two strains with the same mean or the same variation to coexist. Hence, coexistence is possible for a wide range of parameters when the variations in transmission are not constant.

4. Coexistence is only possible because the infection period starts over every season with the same initial distribution of susceptibility. Coexistence occur if both pathogen strains successfully invaded the previous season with a prolonged intra-season coexistence.

5. The behavior of heterogeneous models can be counterintuitive that is the dominant strain is not always the strain with the largest basic reproductive number. Example: a high initial basic reproductive number and initial mean transmission rate does not always guarantee a successful invasion.

In chapter 3, we gave analytical and numerical analysis of heterogeneous models with multiple pathogens and continuous time demography. The model considered was system (3.1) where the host population was divided into m sub-populations, each characterized by their level of risk of infection, and the demographic terms are continuous with respect to time. We showed using a Lyapunov function that, the coexistence equilibrium is Lyapunov stable if it exists. Using numerical simulations, we presented evidence of several special cases where pathogen coexistence is possible. Our results can be summarized as follows.

1. The basic reproductive number for model (3.1) is the maximum of all the strain specific basic reproductive numbers.

2. When the basic reproductive number is less than 1, there exists a disease free equilibrium.

3. The dfe is asymptotically stable if all the strain specific basic reproductive numbers are less than 1.

4. The strictly positive endemic equilibrium is Lyapunov stable if it exists. It is globally asymptotically stable if it is unique.

5. A necessary condition for the existence of the coexistence equilibrium is $R_0 > 1$. (This condition does not however guarantee the existence of coexistence equilibrium).

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