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A Model for the Spread of an SIS Epidemic in a Human Population

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Abstract

The aim of this work is to understand how infectious diseases spread through human populations. Attention is given to those diseases which follow the Susceptible–Infective–Susceptible (SIS) pattern.

When modelling diseases spread in a human population, it is important to consider the social and spatial structure of the population. Humans usually live in groups such as work places, households, towns and cities. However, an individual's membership of a particular group is not fixed. Rather, it changes over time. This structure determines two paths for a disease to spread through the population. Disease is spread between individuals in the same group by contact between infected and susceptible individuals, and is spread from one group to another by the migration of infected individuals. This type of population structure can be modelled by a metapopulation network. I develop a continuous–time Markov chain (CTMC) model that describes the spread of an SIS epidemic in a metapopulation network.

I establish an ordinary differential equations (ODE) and a Gaussian diffusion analogue of the stochastic process by applying, respectively, the theory of differential equation approximations for Markov chains, and the theory of density dependent Markov chains. I use the ODE model to derive analytic expressions for various epidemiological quantities of interest. In particular, I obtain expressions for two threshold quantities; the basic reproduction number, and a quantity called $\mathscr{T}_0$ which is greater than the basic reproduction number. If the basic reproduction number is above 1, then the disease persists and if the basic reproduction number is below 1, then the disease–free equilibrium (DFE) is locally attractive. However, if $\mathscr{T}_0$ is less than or equal to 1, then the DFE is globally attractive. Using the theory of cooperative differential equations and the theory of asymptotically autonomous differential equations, I show the existence and global stability of a unique endemic equilibrium (EE) and the global stability of the DFE in terms of the basic reproduction number, provided that the migration rates of susceptible and infected individuals are equal. Numerical examples indicate that a unique stable EE exists when the condition on the migration rates is relaxed. The approximating Gaussian diffusion shows that the distribution of the population at the endemic level has an approximate multivariate normal distribution whose mean is centered at the endemic equilibrium of the ODE model.

The results of this study can serve as a basic framework on how to formulate and analyse a more realistic stochastic model for the spread of an SIS epidemic in a metapopulation which accounts for births, deaths, age, risk, and level of infectivities.

Assuming that the model presented here accurately describes the spread of an SIS epidemic in a metapopulation, another question which I address is how to control the spread of the disease. Since most control strategies such as vaccination, treatment and public awareness require a high cost for their implementation, I aim to provide a strategy whose cost is minimal and which only requires control of the migration pattern. Using convex optimisation theory, I obtain an exact analytic expression for the optimal migration pattern for susceptible individuals which minimises the basic reproduction number and the initial growth rate of the epidemic, provided that the migration rate of infected individuals follow a specific pattern. It turns out that the optimal migration pattern for susceptible individuals can be satisfied if the migration rates between any two patches (or groups) are symmetric. The control strategy obtained here can be applied to reduce the early growth rate of a disease in conjunction with or in the absence of another prevention measure.

Declaration by author

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There has been no contribution by others to the writing of the thesis, however P. K. Pollett and R. McVinish have proof–read all of the thesis and provided suggestions and guidance of the work as it progressed.

Statement of parts of the thesis submitted to qualify for the award of another degree

None.

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Metapopulation, SIS epidemic, continuous–time Markov chain, density–dependent Markov process, deterministic approximation, diffusion approximation, mobility, convex optimisation, optimal migration.

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List of Abbreviations

CTMC	continuous–time Markov chain.
DFE	disease–free equilibrium.
EE	endemic equilibrium.
ODEs	ordinary differential equations.
OU	Ornstein–Uhlenbeck.
SEIR	Susceptible–Exposed–Infective–Recovered.
SEIRS	Susceptible–Exposed–Infective–Recovered–Susceptible.
SIR	Susceptible–Infective–Recovered.
SIS	Susceptible–Infective–Susceptible.

List of Symbols

$B^{'}$	transpose of matrix B.
R_0	the basic reproduction number.
Ω^c	complement of the set Ω.
$\bar{\Omega}$	closure of the set Ω.
$\mathbb{E}$	expectation.
$\mathbb{P}$	probability.
$\mathbb{R}$	the set of real numbers.
$\mathbb{R}_+$	the set of nonnegative real numbers.
$\mathbb{R}_+^J \setminus \{\mathbf{0}\}$	the set of J dimensional nonnegative real numbers excluding the zero vector.
$\mathbb{Z}$	the set of integers.
$\rho(A)$	the spectral radius of matrix A.
$\mathbf{Re}\lambda_i$	the real part of the i–th eigenvalue of a matrix.
$\mathbf{diag}(\mathbf{v})$	the diagonal matrix whose diagonal entries are given by the vector $\mathbf{v}$.
$\mathbf{a}^{'}$	transpose of vector $\mathbf{a}$.
$s(A)$	the spectral abscissa of matrix A.
$sp(A)$	the spectrum of matrix A.

Chapter 1

Introduction

A continuous–time Markov chain is used to describe the spread of a Susceptible–Infective–Susceptible type epidemic in a metapopulation network. This chapter begins with the motivation for studying infectious diseases spread in human populations. It then reviews some of the common disease characteristics in epidemic modelling. Following this, some of the basic mathematical concepts used in epidemic modelling are reviewed and motivates the use of continuous–time Markov chains to formulate epidemic models. The chapter closes by outlining the materials presented in the thesis.

1.1 Motivation

The spatial spread of infectious diseases, following their introduction at distinct locations, has always been a major concern for human populations. This is because infectious diseases remain one of the main cause of morbidity and mortality in both developed and developing countries. One notable example is the spread of bubonic plague or the Black Death in Europe in the fourteenth century, which caused the deaths of around 25 per cent of the population in that region [15, page 3], [99]. The plague was brought to Italy by ships from the East in about December 1347. During the following few years it spread up through Europe at approximately 200-400 miles per year [146, page 655]. It continued to strike parts of Europe throughout the fourteenth, fifteenth and sixteenth centuries with different degrees of intensity and mortality. In 1665, the plague reappeared in London and is thought to have killed more than 68,000 people in that city [5, page 1].

Another significant example is the spread of smallpox in America between 1507 and 1900. Smallpox is a viral infection which spreads from person to person mainly by droplets shed by the infected

person through coughing or sneezing, and by direct contact [78, page 186]. The disease was introduced to America by the Spanish explorers and the African slaves. The first case was identified in 1507 in the island of Hispaniola [78, page 236]. An outbreak of the disease began in 1517 and killed about one-third of the indigenous population in Hispaniola. In 1520, the disease reached the Valley of Mexico and it is believed that half the population of Mexico died due to it [5, page 1], [78, page 237]. By the time a vaccine for smallpox was developed by Edward Jenner in 1798, the disease had spread to the North and devastated thousands of people.

At present, the spread of human immunodeficiency virus (HIV), which causes the acquired immunodeficiency syndrome (AIDS), is beginning to have a remarkable impact on patterns of mortality in both developed and developing countries [160], [201, pages 1–2]. The most affected region of the world is the sub–Saharan Africa, where, by the end of 2004, there were around 23.6 million people infected with HIV [201, page 2]. Studies indicate that migration of individuals between rural and urban areas is a key factor in the spread of HIV in West Africa [130, 166, 188]. Furthermore, individuals migrating from West Africa to Europe, America and Asia have contributed to the global spread of HIV [166].

Similarly, the worldwide spread of severe acute respiratory syndrome (SARS) in 2003 created a major public health concern in many countries. SARS was first reported in November 2002 in the Guangdong province of China [155]. It was carried out of China in February 2003 by an infected physician who had spent a single night in a Hong Kong hotel. By the end of February 2003, the disease had spread to other parts of the world through international air travel as guests at the hotel returned to their home cities. By the time SARS came under control in August 2003, it had spread to 30 countries and caused 623 deaths [155]. International air travel was identified as the key factor in the global spread of SARS [175, 196, 198]. For this reason, possible control strategies such as screening for infection at borders and travel bans for residents in highly infected areas were proposed [180].

Lastly, the outbreak of influenza caused by the H1N1 virus in 2009 is a further example which elucidates the impact of human mobility on the spatial spread of infectious diseases. The disease was first identified in March and early April 2009 in Mexico and the United States [49]. As of May 2009, it had spread to 30 countries with a total of 1,882 confirmed cases [49, 193]. Mobility was known to be the main reason for the large scale spread of influenza [46, 120, 34].

The examples above highlight the significant role that human mobility plays in the spatial spread of diseases. Therefore, when modelling the spread of diseases in human populations, it is essential to consider the structure of the populations. Before discussing mathematical models for disease spread, I will first describe some commonly studied disease patterns in epidemiology and the basic

mathematical concepts used in the formulation of such models.

1.2 Characterisation of Diseases

As a disease progresses through a given population, individuals in that population can be classified according to their ability to transmit it to others. *Susceptible* individuals are those people who do not have the disease but who can become infected. *Exposed* (or *latent*) individuals are those people who act as hosts for the infectious pathogen but are not yet able to transmit the disease. *Infectious* (or *infective*) individuals are those people who have the disease and can transmit it to susceptible individuals. *Recovered* individuals are those people who have recovered from the disease.

For a disease in which infected individuals do not have an exposed period and recover with no immunity, the disease is said to follow the Susceptible–Infective–Susceptible (SIS) pattern. Thus, in the SIS disease dynamic, a susceptible individual who becomes infected after a successful contact with an infectious individual is immediately infectious and remains in this state for a period of time. This period is called the individual's infectious period. At the end of the infectious period, the individual returns to the susceptible class, as he or she does not develop immunity to the disease. The flow diagram in Figure 1.1 describes the dynamics of the SIS epidemic model without demography. Diseases such as tuberculosis, meningitis and gonorrhea follow the SIS pattern [2], [38, pages 345–346], [101], [113, page 4].

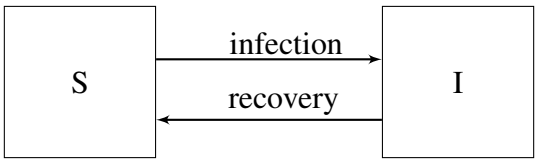


Figure 1.1: Flow diagram showing the dynamics of SIS epidemic model.

A disease for which infected individuals do not have an exposed period and from which they recover with permanent immunity, is said to follow the Susceptible–Infective–Recovered (SIR) pattern. However, if the disease has an exposed period, it is said to have the Susceptible–Exposed–Infective–Recovered (SEIR) dynamic. Recovered individuals in both SIR and SEIR patterns are also known as *removed* individuals, as they play no further role in the epidemic. Influenza, rubella, chicken pox and mumps are examples of diseases which have the SIR dynamic [2, 4, 60]. On the other hand, diseases such as measles and AIDS are known to have exposed periods [146, page 618].

1.3 Epidemic Modelling

Mathematical models provide an important tool for understanding the spread of infectious diseases. Models can be used to capture features that are most influential in the spread of diseases. They allow us to make predictions of the disease progression and to suggest possible control strategies. It is the aim of this section to provide some of the basic concepts used in the formulation epidemic models.

For any infectious disease to make progress through a given population, there has to be disease transmission between susceptible and infective individuals. This transmission depends on three factors: the rate of contacts which are of an appropriate type for transmission to be possible if one of the individual is infectious, the probability that a contact is made with an infectious individual, and the probability that contact between an infectious and a susceptible individual leads to a successful transmission [33]. The probability of successful transmission is usually assumed to be constant for any given disease. The probability that the contact is with an infectious individual is usually assumed to be equal to the prevalence of infection within the population. The product of these three factors is called the *force of infection*, λ. The force of infection gives the per capita rate at which susceptible individuals contract the infection [113, page 17]. Therefore, the rate at which new infectives are produced is λS, where S is the number of susceptible individuals in the population. The term λS is known as the *transmission term* [33] or the *incidence* [99] of the disease. There are two common forms for the force of infection according to the way the contact rate is defined. If the contact rate depends on the population size, N, then $\lambda = \beta I$, where I is the number of infectious individuals and β is called the disease transmission rate, which is equal to the product of the contact rate and the probability of successful transmission. This type of transmission is known as *density–dependent transmission*. If the contact rate is independent of the population size, then $\lambda = \beta I/N$. This type of transmission is known as *frequency–dependent* transmission. The SIS model developed in this thesis is density–dependent according to the above definition.

The concept that the rate of transmission depends on the numbers of susceptibles and infectives was first formulated by Hamer in 1906 [92]. He referred to $\lambda = \beta I$ as the *mass–action transmission* rate. However, it was Kermack and Mckendrick [116, 117, 118] (see also [4, 60]) who first applied Hamer's idea to epidemic modelling and introduced the simple deterministic SIR model whose variants are widely being studied and applied in studying specific diseases. The term simple used in this context means that the models do not include any demographic factors such as births, deaths or migration of individuals. Hence, the population is unstructured and has a fixed size. Kermack and Mckendrick used a system of ordinary differential equations (ODE) to describe the SIR disease dynamic. By studying the simple SIR model, they proved their celebrated threshold result, which states

that the initial number of susceptibles must exceed a critical value in order for an epidemic to occur. An epidemic is a sudden outbreak of a disease which infects a significantly large proportion of the population. It may be restricted to one area or be global, in which case it is called pandemic. For example, the outbreak of influenza caused by H1N1 in 2009 is considered pandemic [80]. In contrast, if a disease is always present in a region, then it is called endemic. It is observed that tuberculosis (TB) is endemic in some African countries [75]. The simple SIR model is not suitable for modelling endemic diseases as it cannot display endemic behaviour. One way of accounting for endemicity is to use an SIS model.

The simple deterministic SIS model is a generalisation of the Susceptible–Infective (SI) model studied by Bailey [14, page 20] and [15, page 33]. If N is the population size and $I(t)$ is the number of infected individuals at time $t \geq 0$, then, the simple deterministic SIS model is given by

$$\frac{dI}{dt} = \beta I(N-I) - \gamma I, \tag{1.1}$$

where β is the infection rate and γ is the recovery rate. Since the population size is fixed, the number of susceptible individuals at time t is given by $S(t) = N - I(t)$. To ecologists, (1.1) is the classic model considered by Levins [134, 135] (see also [94, Chapter 4]) for modelling the number of occupied patches in a *metapopulation* – a collection of interacting subpopulations of the same species, each of which occupies a distinct habitat patch. In this context, β is the colonisation rate, γ is the local population extinction rate, and N is the number of patches in the metapopulation. Levins' metapopulation model has a very similar structure to the *island model* studied in population genetics [44, 47, 64, 85, 157, 158, 96]. In the island model, each individual in the population is considered as a habitat patch for pathogens. The metapopulation consists of a finite number, N, of identical patches, each containing a finite number of individuals (pathogens) which reproduce according to the Wright–Fisher model [79, 213]. This means that all individuals in the population during the current generation are equally likely to be the parents of the next generation. The island model was originally introduced by Wright in 1930s [213, 214] to study the variations of gene frequency in a given population. Recently, the SIS model (1.1) has been applied in population genetics to understand the patterns of genetic variations in infectious agents [44, 64, 85]. In these models, the population structure was modelled as the island model. Similar to the Levins' model, an occupied patch is equivalent to an infected individual, an extinct patch is equivalent to a susceptible individual, γ is the local population extinction rate. An extinct patch can become recolonised by the migrants it receives from the occupied patches. Therefore, β is proportional to the migration rate. In this thesis, I will restrict discussion of model (1.1) to the epidemiology context and direct the interested reader to the books of Hanski and co–authors [94, 93] for further details regarding the connection between Levins type metapopulation

and genetics.

The solution of equation (1.1) is derived in [211] and it is shown that if $N\beta/\gamma$ is less than or equal to 1, then $I(t)$ converges to 0 as t goes to infinity and for all initial values. Hence, the disease dies out in the long run. On the other hand, if $N\beta/\gamma$ is greater than 1, then $I(t)$ converges to a positive equilibrium as t goes to infinity whenever the initial number of infectives is positive. This implies that the disease will remain endemic in the population. Thus, $N\beta/\gamma$ is a threshold quantity in this model which determines whether the disease will invade the population and remain endemic or will die out. This threshold quantity is called the *basic reproduction ratio* (*or number*) of the model, and is denoted by R_0. It gives the expected number of secondary infections produced by a single infected individual in a completely susceptible population [5, page 17], [65, page 4], [66], [97]. For the model developed here, one aim of its analysis is to determine if such a threshold condition exists or not.

The vast majority of epidemic models in the literature are formulated using differential equations, mainly because of their simpler analysis, in particular regarding the long term behaviour of the population. However, a key limitation of these models is that they predict the same dynamic and equilibrium for each realisation of the process; given the same initial condition, we always observe exactly the same trajectory. Such a static scenario does not apply to real world diseases. If it were possible for us to re–run a real world epidemic, we would not expect to observe exactly the same people becoming infected at exactly the same time. Thus, the element of chance is an important factor to consider when modelling diseases. This chance or probabilistic element can only be captured in a stochastic setting. Furthermore, there are events which are genuinely stochastic and cannot be explained by differential equations. For example, in a large population, an outbreak initiated by few initial infectives may lead either to a minor outbreak infecting only a small proportion of the population, or else to a major outbreak infecting a more or less deterministic proportion of the population [20, 21, 24, 28, 42]. The probability of the occurrence of these two events can only be determined by using a stochastic model. Additionally, when considering extinction of endemic diseases, the probability of disease extinction and the expected time to extinction can only be analysed using stochastic models [149, 150, 151, 152]. Finally, using a stochastic model allows for uncertainty in parameter estimations, which may be used to create possible control strategies [4, Chapters 9 to 12].

One of the earliest stochastic treatments of epidemic modelling dates back to 1926 and is due to McKendrick [142]. However, it is the chain binomial model studied by Reed and Frost in 1928 which gained much attention [1, 212] (see also [60, page 12]). It is an SIR model and was formulated using a discrete–time Markov chain (see Chapter 2 for a definition and also [154, Chapter 1]). The Markovian character (the future predictions depend only on the current observation) of the model is due to the assumption that the probabilities of new infection occurring have a binomial distribution

depending on the number of susceptible and infectious individuals present at the previous stage. After the introduction of the chain binomial model, most significant developments of stochastic epidemic models seem to have started in the late 1940s when Bartlett [32] formulated the stochastic version of the simple SIR model of Kermack and McKendrick. A continuous–time Markov chain (or a Markov process) was used to describe the model [87, 154].

Since the development of Bartlett's model, the prevalence of stochastic models for epidemic processes in the literature has increased rapidly. Most were constructed using either a discrete or a continuous time Markov chain. In comparison with the differential equations, the main advantage of Markov chains lies in their ability to incorporate individual variation arising from chance elements, which is an important character in population processes. Moreover, they have a discrete state space and therefore treat individuals as discrete units which is more appropriate for population modelling. For example, the stochastic analogue of (1.1) is a continuous–time Markov chain with state space $\{0,\ldots,N\}$ where the number of infectives at time t, $I(t)$, is defined to increase by one at rate $\beta I(N-I)$ and decrease by one at rate γI, where the parameters β and γ are defined as earlier. Although these transition rates are related to (1.1), the long term behaviour of the stochastic model is very different from what is predicted above for the deterministic model. The stochastic model predicts absorption at state 0 with probability 1, implying that the disease will ultimately die out. However, if we consider a typical sample path of the stochastic process given in Figure 1.2, we can see that the stochastic process appears to track the deterministic trajectory and fluctuates around the positive equilibrium of the deterministic trajectory. Therefore, it seems that, despite the fact that the stochastic process predicts ultimate absorption at state 0, it may attain an equilibrium before absorption. This equilibrium is known as a *quasi–equilibrium* [63, 106, 123, 147, 148, 164, 205] and describes the behaviour of the population at an endemic level. For the continuous–time Markov chain model constructed in this work, one aim of the analysis is to describe the behaviour of the population at an endemic level.

Despite their usefulness in epidemic modelling, Markov processes have some limitations which must be addressed. One of the main disadvantages is that as a result of the Markov property, the time between events is exponentially distributed. This means that the infectious period and the exposed periods are exponentially distributed, which may not be applicable in some disease modelling scenarios. An alternative approach would be to consider Semi–Markov processes which allow for different holding time distributions [129, 186]. Another limitation of Markov processes is that they are usually difficult to analyse. A common approach to analysing Markov processes is to derive forward (or backward) Kolmogorov equations, which describe the dynamics of the transition probability functions (see Chapter 2), and solve the system of ODE to determine the quantities of interest such as mean, variance and higher order moments. However, the system can be difficult to solve for these

quantities when the state space of the Markov chain is large as in our case. In such situations, the method frequently applied is to simulate the process of interest and use statistical methods to analyse the result. However, large numbers of repeated simulations are required in order to ensure that the simulated dynamics are representative of average behaviour of the process rather than a chance outlier due to a rare event. This is also true in the case when the aim is to look for rare events such as extinctions or unusually large epidemics, despite the fact that methods such as importance sampling and cross–entropy have been developed to improve efficiency [181]. In order to overcome these limitations, analytical approximation methods are often sought. In Chapter 2, I will present work of Kurtz [125, 126], Pollett [163], and Darling and Norris [62], which will be employed to obtain explicit analytical approximations for the Markov process developed here. Before addressing such mathematical details, I will highlight in the following section the research to date on those types of epidemic models to which I contribute; that is, models which account for mobility.

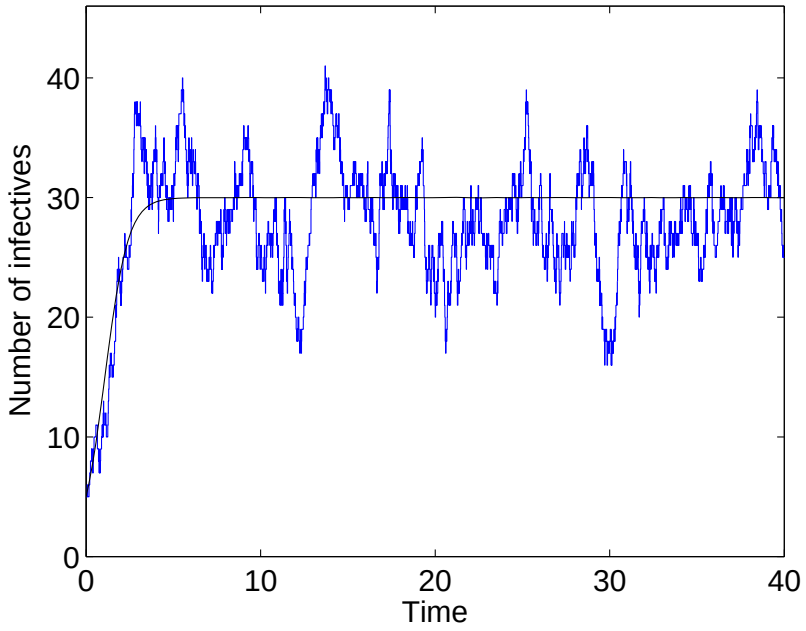


Figure 1.2: A sample path of the simple stochastic SIS model (blue) and the trajectory of (1.1) (black)

1.4 Accounting for Mobility

Early epidemic models were formulated assuming that individuals in the population mix homogeneously (mass–action principle) [5, 15, 116, 211]. That is, all pairs of individuals in the population have the same probability of coming into contact with each other. Although this is a reasonable assumption for modelling diseases spread in small groups such as households, workplaces and schools,

there are doubts as to its applicability for larger groups. In a large population, there can be several group formations due to heterogeneity arising, for example, from social and economic factors. Some people may live in cities while others may live in rural areas. Consequently, demographic and disease parameters may vary for each group. Furthermore, people may travel between the groups, either by foot or by using various transportation networks, which leads to the spread of diseases between groups. These considerations have lead to the development of epidemic models that take into account the structure of the population.

One way of accounting for the heterogeneity arising from the social and spatial structure is to model the epidemic on a lattice. In these models, individuals are positioned on a regular grid of points, usually in just one or two dimensions, and adjacent individuals (nearest neighbours) are connected. Therefore, contacts are localised in space which is appropriate for modelling the close connection that an individual has with some members of the population. The best known examples for disease transmission through lattices are the *contact process* [74, 109, 133] and *the forest–fire* [70, 86, 108, 167, 168, 169, 170, 171, 172, 173] model. The *contact process* is closely related to the spread of an SIS type infection. In its traditional form, the contact process, as introduced by Harris in 1974 [95], is a Markov process on $\{0,1\}^S$, where S is the number of vertices in the lattice. Translated into disease metaphor, states 0 and 1, respectively, correspond to the site being susceptible or infected. Infected individuals recover at a given rate independent of the status of their neighbours and become susceptible to the disease once more, while susceptible individuals become infected at a rate that is proportional to the number of infected neighbours. The contact process is an example of a stochastic interacting particle systems whose general theory can be found in the book of Liggett [138] and in the work done by Durrett [71, 72, 73].

On the other hand, the *forest–fire* model is closely associated with the spread of SIRS–type infection and is generally studied on a two–dimensional lattice. In the original formulation, lattice sites can be empty, occupied by a healthy tree, or occupied by a burning tree. The rules which govern the model are as follows: burning trees die to leave empty spaces, fire can spread between neighbouring trees, healthy trees can colonise empty spaces, and occasional random lightning strikes can cause spontaneous fires. In epidemiological terms, healthy trees are susceptibles, burning trees are infectious, empty sites are recovered (and immune), colonisation by trees resembles either the birth of new susceptibles or wanning immunity, and lightning represents the import of new infection. Again, the dynamics of this process can be given in terms of rates of change of lattice sites. This model was originally developed in 1990 by Per Bak and coworkers [16] and has been applied to study diseases spread in small geographically isolated island populations [169, 171, 173]. In both the contact process and the forest–fire models, disease is spread between nearest neighbours. However, there are various

other lattice models with a different choice of neighbourhood. The most common form is to choose neighbours according to a contact distribution. This approach was first introduced by Mollison in 1977 [144] and has been applied by others [20, 26, 23, 58, 127, 128] since then. Lattice models are applicable in situations where the spatial location of individuals are important, such as diseases spread in plants and animals. Furthermore, since individuals are assumed to interact with a small number of other members (neighbours) in the population, lattice models do not capture the complex and heterogeneous contacts through which human infections pass, which limits their applicability in studying diseases spread in human populations.

An alternative approach of modelling the population structure seen in human populations is to divide the population into distinct groups, assuming that each group mixes homogeneously within itself as well as there being cross–group infection. For deterministic models, this assumption leads the force of infection at a given group to be the product of the number of susceptibles in that group and the sum of the transmission coefficients for all groups. Furthermore, individuals belonging to the same group are assumed to have equal recovery rate [38, 88, 89, 98, 132, 192]. For stochastic models, within group and between group transmissions are obtained by assuming that individuals mix at two levels: *local* and *global*. At the global level, a given infective makes contacts at a given rate with individuals chosen independently and uniformly from the whole population. At the local level, the infected individual makes contacts at a much higher rate with individuals chosen independently and uniformly from a set of neighbours of that individual. These stochastic models are known as *household* models [12, 20, 23, 26, 27, 28, 41]. The major drawback of these models is the absence of mobility, in both deterministic and stochastic settings.

This is overcome for deterministic models in the studies made by Bailey [15, Section 7.33], Hethcote [98], Sattenspeil and Dietz [187], Allen et al. [3], McCormack and Allen [141], van den Driessche [202], Salmani and van den Driessche [183], Arino and van den Driessche [9, 10, 11], Arino et al. [7, 8], Wang and Zhao [210], Wang and Mulone [209], Jin and Wang [107], Kuniya and Muroya [124], and Muroya et al. [145]. The authors who have contributed on the stochastic side include Ball [22], Ball and Clancy [24, 25], Clancy [50, 52], Keeling et al. [112, 114], Sani et al. [185], Lahodny Jr and Allen [131] and Neal [152]. In all these models the population structure is modelled by a metapopulation network [93, 134, 135]. More precisely, the population is divided into distinct groups where each group lives in a discrete location (or patch) and individuals are assumed to travel between the patches. Some authors refer to these stochastic models as multi–group models. For deterministic models, the patch dynamics are usually modelled by a system of ODE. One of the most important differences between the deterministic and stochastic epidemic models is their asymptotic dynamics. Although for most stochastic epidemic models, disease extinction in finite time occurs

with probability one, such behaviour is not possible for the corresponding deterministic models as they predict either disease extinction or persistence in the long–run. Therefore, the type of questions often investigated using deterministic models include the asymptotic dynamic of disease–free or endemic equilibria. Stochastic models are normally described by a continuous–time Markov chain with mobility modelled by transition rates between groups. Often, these stochastic processes are analysed by using an approximating branching process or an approximating system of ODE. The type of questions addressed, when such an approximation is possible, include the probability of disease outbreak or extinction, the final size of the epidemic, the equilibrium behaviour of the population at an endemic level, and the effect of the speed of movement of individuals on the final size of the epidemic. In the rest of this section I will provide a brief overview of these studies, summarising only those findings which are related to my work. I will begin with deterministic models.

Bailey [15, Section 7.33] considered a two patch deterministic SIR model, assuming equal travel rates between patches for susceptibles and similarly for infectives. Disease transmissions within, as well as between, patches were allowed. Equilibrium points were derived and their stability analysed. Hethcote [98] also studied a two patch deterministic model but for a disease having the SIS dynamic. Travel rates were assumed to be the same as in [15]. However, cross patch infections were ignored. It was shown that if the transmission rate of one patch is slightly bigger than 1 and that of the other patch is less than 1, then travel can eventually cause disease extinction in both patches. In contrast, if the transmission rate of one patch is significantly greater than 1 and that of the other patch is less than 1, then travel can cause the disease to remain endemic in both patches.

Sattenspeil and Dietz [187] introduced a deterministic SIR model in which the population in each disease class is subdivided and which keeps track of the patch where an individual is visiting and the patch in which an individual normally resides. They showed how their model can be applied to a population with two types of mobility and in which there are both within group and between group transmissions. They also applied their model to the spread of measles on the West Indies island of Dominica. Although their model allows for the simultaneous considerations of both epidemic and behavioural processes, there are some limitations to the model. Firstly, they have assumed that travel rates are independent of disease status, which is somewhat questionable. Secondly, it was assumed that individuals who travel to a given patch must return directly to the patch they originated from before visiting another patch, which may not be the case for long distance trips. These limitations have been successfully dealt with in [11] by Arino and van den Driessche.

Arino and van den Driessche have also studied an SIS [10, 202] and an Susceptible–Exposed–Infective–Recovered–Susceptible (SEIRS) [9] deterministic models using a similar approach to [187]. They obtained an analytic expression for the basic reproduction ratio of these models. Using numer-

ical simulations, they showed that the basic reproduction ratio acts as a sharp threshold between disease extinction and invasion. Simulations of the SIS model also indicated that mobility can stabilise or destabilise the disease–free equilibrium. Arino et al. introduced a multi–species SEIR [7] model in which disease transmissions between species were allowed in each patch. This model was extended in [8] to allow for temporary immunity, giving a SEIRS model. In contrast to the models given in [187, 10, 9], these models did not keep track of where an individual usually resides, but only tracks where an individual is at a given time. However, similar to [9, 10, 187], the travel rates were assumed independent of the disease status. Numerical simulations for the SEIR model with two patches and for a single species suggested that increased travel rates reduce the basic reproduction number to a value less than 1 and the disease dies out in all patches, while small travel rates help the disease to persist. For the SEIRS model, the role of quarantine in the form of travel restriction was investigated for the special case when patches are arranged in a ring, and assuming that travel can only take place between neighbouring patches. Using numerical examples, they showed that perfect travel restriction is required for disease extinction for both one way and two way migrations. The models studied in [7, 8] have been generalised by Arino and van den Driessche by allowing disease dependent travel rates [11].

Wang and Mulone [209], Wang and Zhao [210] and Jin and Wang [107] studied SIS deterministic models in which travel rates depended on disease status. For a two patch frequency–dependent model, Wang and Mulone [209] concluded that travel rates of susceptibles do not have any influence on disease persistence and extinction. Wang and Zhao [210], and Jin and Wang [107] considered a density–dependent model, and have provided analytical results for stability of disease–free and endemic equilibrium considering equal travel rates for susceptibles and infectives. Using numerical simulations, Wang and Zhao [210] showed that population travel can both intensify and reduce the spread of disease in patches. This was further explored in [107], again by using simulations, to show that travel between patches may result in multiple endemic equilibria and even multi stable equilibria, and also may result in disease extinction, even though the disease cannot be eradicated in each isolated patch, provided that the basic reproduction numbers of isolated patches are not very large.

Salmani and van den Driessche [183] considered an SEIRS deterministic model in which travel rates were assumed to depend on disease status. They showed that, while the population is at an endemic level, increased travel rates of infectives can cause disease extinction in all patches. In a similar setting, Allen et al. [3] showed for a frequency–dependent SIS deterministic model that, while the population is at an endemic level and if infectious individuals travel between the patches but the rate of travel for susceptible individuals approaches 0, then, contrary to what is expected, the endemic equilibrium approaches a disease–free equilibrium. McCormack and Allen [141] studied an SIR and

an SIS model in both deterministic and stochastic settings, assuming disease independent travel rates. Their analysis of the deterministic models showed that if the disease persists in some patches and is extinct in others when in isolation, then travel between patches can lead to either disease persistence or extinction in all patches. They also showed that increased travel rates can cause disease extinction in all patches. Their numerical examples suggest that the mean of stochastic models is close to the solution of the deterministic models. For these models, existence and uniqueness of disease–free and endemic equilibrium were not established. However, for similar models which allow for cross patch infections, existence uniqueness and global stability for endemic and disease–free equilibrium were established by Kuniya and Muroya [124] and Muroya et al. [145].

Considering stochastic models, Ball [22] proposed an SIR model in which only infectives were allowed to move between groups and could infect only those susceptibles in their current group. Mobility of infectives was modelled by a Markov transition matrix and contacts were modelled by homogeneous Poisson processes. The recovery period of infectives was assumed to have an exponential distribution, which implies that the process as a whole has the Markov property. Transmission rates and recovery rates were assumed independent of the group. Approximating branching processes were used to determine the conditions under which a major epidemic occurs and to calculate the probability of this event. A deterministic analogue of this model was also investigated. It was shown that the final size of the epidemic (that is the total number of initial susceptibles ultimately infected in each group) has an asymptotically Gaussian distribution with mean equal to the final size of the corresponding deterministic model. Numerical examples were used to show that, for the deterministic model, the final size of the epidemic increases as the speed at which infectives move around the groups increases. The author of [22] has conjectured that this observation will be true for all parameter values and a similar result will hold for the stochastic model. These conjectures were proven by Clancy [50], but for the stochastic model, the result was shown for a population consisting of two groups with equal travel rates between the groups.

The complex relationship between migration of individuals and the spread of diseases can be seen in the models studied by Clancy [51] and [52]. The model studied in [52] was a generalisation of the SIR model presented in [22] in which movement of both susceptibles and infectives was allowed and between group infections were considered. An approximating multi–type birth–and–death process was used to analyse the model. The analysis showed that movement of infectives decreases the spread of the disease. However, the model in [51] describes the spread of a carrier–borne disease, and movement of both susceptibles and infectives was allowed while between group infection was not considered, it was shown that increasing the speed of movement of either infectives or susceptibles tends to increase the spread of infection.

For the above stochastic models in which only movement of infective individuals was considered [22, 50], the general assumptions have been that there were no between group infections and infectious periods were exponentially distributed and movement processes were Markovian. These assumptions were relaxed in the model studied by Ball and Clancy [24]. In their model, they allowed disease transmission rate between a given infective and a given susceptible to depend upon the infectives' group of origin, its current group and the group of the susceptible. Infectious period and movement process were assumed to have an arbitrary distribution and could depend on each other.

Sani et al. [185] studied a multi–group SIR model for the spread of AIDS. A Markov process was used to describe their model. By using an approximating system of ODE, they analysed equilibrium behaviour of their stochastic process. Furthermore, a central limit theorem was used to model the fluctuations in the stochastic process around an endemic equilibrium of the deterministic model. Neal [152] also studied an SIR model, but he allowed for an arbitrarily distributed infectious period. For a population consisting of only two groups, he showed that the basic reproduction number of the model is maximised by a constant length infectious period and is decreased when the speed of movement between the two populations is increased.

All of the above cited stochastic models were concerned with diseases following the SIR pattern. However, Lahodny Jr and Allen [131] considered frequency–dependent SIS models which allowed for disease induced deaths. The stochastic models applied in their investigations were formulated using Markov processes and stochastic differential equations. An approximating branching process for the Markov process was used to determine the probability of disease extinction. In their analysis, they classified a given patch as being high–risk if the basic reproduction number for that patch was greater than 1; otherwise it was called a low–risk patch. Using these classifications, they showed that, in the early stage of the epidemic, directing movement of infectious individuals into low–risk patches is an effective control strategy, while movement of susceptible individuals does not impact the probability of disease extinction.

Various other stochastic metapopulation models exist and some were developed to study specific diseases [18, 34, 55, 56, 61, 91, 104, 112, 114, 120]. However, due to the size and complexity of the populations involved, these models needed to be analysed numerically.

The above studies indicate that mobility of individuals between patches and patch dependent disease transmission and recovery rates can influence disease spread in various ways. This work aims to give some precise results about this influence in terms of optimal travel patterns.

1.5 Outline of the Thesis

This thesis concerns an epidemic model that account for mobility. Chapter 1 has provided the motivation behind incorporating mobility in epidemic models and reviewed mathematical models that account for such behaviour. The Markov chain approach is particularly popular with the applied metapopulation community, however these studies mainly focused on understanding the spread of diseases following the SIR pattern. The model presented in Chapter 3 adapts the continuous–time Markov chain approach to describe the spread of a disease following the SIS dynamics in a metapopulation network. However, first, Chapter 2 collects the basic materials on continuous–time Markov chains which are required to understand the materials presented in the latter chapters. Additionally, it provides two approximation methods (an ODE approximation and a diffusion approximation) for those continuous–time Markov chains whose transition rates satisfy the density–dependent property. Furthermore, the background materials required to analyse equilibrium points of an ODE arising from an epidemic model is provided along with the necessary properties of Metzler, Positive and M–matrices. Chapter 2 also collects some properties of convex optimisation and closed migration process which are applied to derive results in the latter chapters.

Chapter 3 introduces the SIS epidemic model studied in this thesis. A number of explicit expressions for quantities of interest are presented, including the basic reproduction number, the disease–free and endemic equilibria, and the distribution of the population at the disease–free and an endemic level. The stability of the disease–free and endemic equilibria is also investigated. These analyses are based on an ODE approximation and a diffusion approximation to the Markov chain model.

Chapter 4 provides optimal migration (or travel) strategies for susceptible individuals which minimise the basic reproduction number of the SIS model and the spectral abscissa of the Jacobian matrix of the ODE derived in Chapter 3, evaluated at the disease–free equilibrium. Both Chapter 3 and Chapter 4 provide concluding comments about the analysis made in them.

Chapter 2

Background Theory

This chapter begins with the definition of a stochastic process and then defines those properties of a stochastic process required for it to be classified as a continuous–time Markov chain. It then summarises some of the basic properties of continuous–time Markov chains which are required to interpret the terminologies and results discussed in this thesis. Following this, an ODE approximation and a diffusion approximation method for continuous–time Markov chains, which are applied to analyse the Markov chain studied in the thesis, are discussed. The background materials needed to establish stability of fixed points of the ODE model is then discussed. Afterwards, some results on Metzler and positive matrices are collected which are used to prove some of the results in the following chapters. Following this the properties of convex optimisation and M–matrices are discussed. The chapter closes by a description of the closed migration process, which describes the population when it is disease–free.

2.1 Introduction

A stochastic process $(X(t);t \in T)$ is a collection of random variables which take values in a set S and are indexed by a set T. The set S is called the *state space* of the process and may be discrete or continuous. The variable t usually represents time and may once again be discrete or continuous. If t is discrete, then $(X(t);t \in T)$ is referred to as a *discrete–time process*. If t is continuous, then $(X(t);t \in T)$ is referred to as a *continuous–time process*. In this thesis, I will consider a continuous–time stochastic process whose state space is discrete and finite. So, the time variable t shall hereafter takes values in $[0,\infty)$.

I am particularly interested in stochastic processes which satisfy the Markov property.

Definition 2.1. A continuous–time stochastic process $(X(t);t \geq 0)$ satisfies the *Markov property* if for any $n \geq 1$ and any finite sequence of times $0 \leq t_1 < \cdots < t_n < t_{n+1}$

$$\begin{aligned}&\mathbb{P}(X(t_{n+1}) = j \mid X(t_n) = i, X(t_{n-1}) = i_{n-1}, \ldots, X(t_1) = i_1)\\ &= \mathbb{P}(X(t_{n+1}) = j \mid X(t_n) = i),\end{aligned}$$

for all states $i_1, i_2 \ldots, i_{n-1}, i, j \in S$.

Thus, the Markov property states that, provided that the present and past states are known, the future state of the process is independent of the past states. Due to this property, Markov processes are sometimes referred to as "memoryless" processes. Among Markov processes, I am particularly interested in those processes which are time–homogeneous.

Definition 2.2. A Markov process $(X(t);t \geq 0)$ is said to be *time–homogeneous* if for any $s,t > 0$ and $i, j \in S$,

$$p_{ij}(t) := \mathbb{P}(X(s+t) = j \mid X(s) = i) = \mathbb{P}(X(t) = j \mid X(0) = i). \tag{2.1}$$

That is, given that the process is in state i at time s, the probability of the process is in state j after an additional t time units pass is independent of s. The probabilities $p_{ij}(t)$ are called the *transition probabilities* of the Markov process and gives the probability that the process moves from state i to state j in time t. The corresponding matrices $P(t) = (p_{ij}(t); i, j \in S), t \geq 0$ are called the *transition probability matrices*.

Time–homogeneous Markov processes have been applied in many areas as they have a high degree of analytical tractability. The model developed and methods applied in this thesis are concerned with time–homogeneous Markov processes.

2.2 Continuous–Time Markov Chains

A continuous–time Markov chain (CTMC) is a Markov process which takes values in a discrete set S. Such processes are often referred to as simply Markov Processes. The sample paths of a continuous–time Markov chain consist of a sequence of states such that the process remains in each state for some exponentially distributed random time, after which it jumps to another state. The time that the process spends in a given state is called the *holding time* of that state. Below I summarise features of continuous–time Markov chains needed to understand the materials presented in this thesis. For further details regarding this subject, I refer the reader to Anderson [6, Chapters 1 and 2] and Norris [154, Chapters 2 and 3].

2.2.1 Transition Rates and Probabilities

The evolution of a CTMC as described above is determined by its transition rates $Q = (q_{ij}, i, j \in S)$, where q_{ij} represents the rate of transition from state i to state j, for $i \neq j$, and $q_{ii} = -q_i$, where $q_i \geq \sum_{j \neq i} q_{ij}$, is the total rate out of state i. Q is called the *Q–matrix*, or transition rate matrix of the Markov chain and a model is generally defined in terms of Q. A Q–matrix satisfies the following conditions:

(a) $-\infty \leq q_{ii} \leq 0, \quad i \in S,$

(b) $0 \leq q_{ij} < +\infty, \quad i \neq j \in S,$

(c) $\sum_{j \in S} q_{ij} \leq 0, \quad i \in S.$

Thus, the diagonal elements of Q are nonpositive, the off–diagonal elements are nonnegative and the row sums are nonpositive. If all row sums are equal to 0 (that is, $q_i = \sum_{j \neq i} q_{ij}$ for all $i \in S$), then Q is called *conservative*. If $q_i < +\infty$, then state i is called a *stable* state, otherwise it is said to be an *instantaneous* state. Q is called stable if *all* of its states are stable. The Q–matrix of the CTMC considered in this thesis is stable and conservative. Hence, any Q–matrix mentioned hereafter is assumed stable and conservative.

Although the Q–matrix provides us with information about the transition rates of a CTMC, it does not give us any information about the transition probabilities of the process, because if we know these probabilities then we know the probability of the process going from any state i to any state j in any period of time t, and we can therefore, at least in principle, answer any question about the behaviour of the process. These transition probabilities are given by the transition probability matrix, $P(t)$, of the Markov chain. The fundamental relationships between a transition probability matrix and its Q–matrix are given by the (Kolmogorov) forward and backward equations.

Definition 2.3. For a given Q–matrix $Q = (q_{ij}, i, j \in S)$, the system of differential equations

$$\frac{dp_{ij}(t)}{dt} = \sum_{k \in S} p_{ik}(t) q_{kj}, \quad p_{ij}(0) = \delta_{ij}, \quad i, j \in S,\ t \geq 0,$$

is called the (Kolmogorov) *forward equations*. Similarly, the system of differential equations

$$\frac{dp_{ij}(t)}{dt} = \sum_{k \in S} q_{ik} p_{kj}(t), \quad p_{ij}(0) = \delta_{ij}, \quad i, j \in S,\ t \geq 0,$$

is called the (Kolmogorov) *backward equations*. Here, δ_{ij} is the Kronecker delta which is equal to 1 when $i = j$ and 0 otherwise. The forward and backward equations can easily be written in matrix form: $dP(t)/dt = P(t)Q$ and $dP(t)/dt = QP(t)$ with initial condition $P(0) = I$, where I is the identity

matrix. If the state space S is a finite set, as in our case, then both the forward and backward equations have the unique solution, $P(t) = exp(tQ)$, where exp is the matrix exponential. Specifically,

$$P(t) = exp(tQ) = \sum_{n=0}^{\infty} \frac{t^n}{n!} Q^n.$$

In most situations it is not possible to evaluate the transition probability matrix explicitly. An alternative approach often sought in order to study the behaviour of the process in such situations is to apply numerical computation procedures. However, for process with a large state space, such as the metapopulation network considered in this thesis, the numerical tasks which need to undertake may be so large as to make them impracticable due to computer memory constraints and/or time. Hence, there is a desire for analytic approximations in these situations. In Section 2.3, I will introduce two such approximation methods– an ODE approximation and a diffusion approximation– which are valid for large system sizes and which provide a means to study the equilibrium behaviour of the CTMC considered in this thesis. But, first, I will briefly review the classification of the states of CTMCs which is useful in understanding the long–term behaviour of the Markov chain studied in this thesis.

2.2.2 Classification of States

As mentioned previously, a CTMC is mostly defined by specifying Q, the transition rates. Therefore, it is Q which is readily available and not the transition probability matrix, $P(t)$. Of course, if the state space is finite, then $P(t) = exp(tQ)$, but in practice, this may be difficult to evaluate explicitly. Hence, it is convenient to classify the states of such processes in terms of Q.

State j is said to be *accessible* from state i if $q_{i_0 i_1} q_{i_1 i_2} \dots q_{i_{n-1} i_n} > 0$ for some finite sequence of states $i_0, i_1, \dots, i_n$, with $i_0 = i$, $i_n = j$ and $n \geq 1$. If i is accessible from j and j is accessible from i, then i and j *communicate* with each other. A *communicating class* is a non–empty set of states consisting of all states that communicate with each other. If the entire state space is a single communicating class, then the state space (also the Q–matrix and transition probability matrix) is said to be *irreducible*. In this case we simply say that the Markov chain is irreducible. If the state space contains more than one communicating class, then we may break the state space into disjoint sets, each representing one communicating class, in which case the Markov chain is said to be *reducible*. Furthermore, a communicating class, say $A \subseteq S$, is called *closed* if $i \in A$ and j is accessible from i implies $j \in A$. Thus a closed class is one from which there is no escape and such a set is called an *absorbing* set. If $A = \{i\}$, then state i is called an absorbing state and in this case $q_i = 0$.

I note that if $P(t)$ is known, then the above classification can also be determined in terms of the transition probabilities of the Markov chain. In that case we say state j is accessible from state i if

$p_{ij}(t) > 0$ for some (and then for all) positive time t. Communicating classes can then be determined based upon this definition. Once we have determined the communicating classes of a CTMC we can further classify the states in each class as recurrent or transient. In what follows T_i is the random variable representing the time at which the Markov chain first visits state i after the first jump has occurred, which is said to be the *first passage time* of the process to state i.

Theorem 2.1. *State i is called recurrent if $q_i = 0$ or $\mathbb{P}(T_i < +\infty \mid X(0) = i) = 1$, and it is called transient if $q_i > 0$ and $\mathbb{P}(T_i < +\infty \mid X(0) = i) < 1$. A recurrent state i is called positive if $q_i = 0$ or $\mathbb{E}(T_i \mid X(0) = i) < +\infty$, otherwise it is called null.*

When $q_i = 0$, state i is absorbing, so this theorem ensures that an absorbing state must be positive recurrent. Conversely, if state i is nonabsorbing, then it is said to be recurrent if, upon leaving it, the process is certain to return to state i and such a state will be visited infinitely often. Positivity and nullity then recognise, respectively, the cases where the expected return time is finite or infinite. On the other hand, a nonabsorbing state i is said to be transient if, upon leaving it, the process is not certain to return to state i and such a state will be visited at most a finite number of time (see for example, Norris [154, pages 115 and 118]). Positivity, nullity and transience are all solidarity properties, in that all states in a communicating class have the same classification of positivity, nullity or transience. The state space of the CTMC studied in this thesis can be decomposed as $S = A \cup C$, where S is finite, A is an absorbing set and C is an irreducible transient set.

2.2.3 Equilibrium and Quasi–Equilibrium Behaviour

When studying any epidemic model, we are often interested in the long–term behaviour of the population. For a CTMC whose state space S is finite and irreducible, the long–term behaviour of the process is determined by the unique solution $\pi = (\pi_j; j \in S)$, with $\pi_j \geq 0$, to

$$\pi Q = \mathbf{0},$$

and $\sum_{j \in S} \pi_j = 1$. In such a case π is called the *equilibrium distribution* of the process and, for all states $i, j \in S$, we have

$$\lim_{t \to \infty} \mathbb{P}(X(t) = j \mid X(t) = i) = \pi_j,$$

which implies that π is also the *limiting distribution* of the process. However, if the state space has the form $S = A \cup C$, where S is finite, A is an absorbing set and C is an irreducible transient set, the absorbing set A is accessible from any state in C. Hence, whichever the initial state is, the process will eventually escape from C into the absorbing set A with probability 1. For such

processes, the equilibrium distribution is not necessarily unique and is degenerate, with probability mass concentrated in the absorbing states. But, such processes often exhibit equilibrium behaviour prior to absorption over any reasonable time scale. This behaviour, as mentioned previously, is known as *quasi–equilibrium* [31, 63, 106, 123, 147, 148, 164, 205]. When $A = \{0\}$ and $C = \{1,2,\ldots,N\}$, where N is finite, the *quasi–equilibrium distribution* is the unique solution π^* to

$$\pi^* Q_C = -x\pi^*,$$

and $\sum_{i\in C} \pi_i^* = 1$, where Q_C is the Q–matrix restricted to the irreducible transient class C, and $-x$ is the eigenvalue of Q_C with smallest magnitude. In this case, the quasi–equilibrium distribution is also the *limiting conditional distribution* of the process for all initial distributions concentrated on the transient class C (see, Darroch and Seneta [63, Section 3], and also van Doorn and Pollett [205, Theorem 3]). The term limiting conditional is used to denote that the distribution is derived from considering the long–term behaviour of the process conditioned upon it still being in the transient class. More precisely,

$$\lim_{t\to\infty} \mathbb{P}(X(t) = j \mid X(0) = i, X(t) \in C) = \pi_j^*, \quad i, j \in C.$$

When the absorbing set A contains more than one state, they can be amalgamated into one single absorbing state and we can set $q_A = 0$ and $q_{Aj} = 0$ for $j \in C$. Consequently, the above procedure can be applied to derive a quasi–equilibrium distribution of the Markov chain (see for example [40, 13] and [121, Section 4.7]). If the state space is multi–dimensional, then we can use an appropriate bijection, as discussed in the following paragraph, which makes Q_C a square matrix.

It is often difficult to obtain an explicit formula for the quasi–equilibrium distribution, even for a process with a small state space, but it can be found relatively simply using any numerical eigenproblem solver when the state space is small [205]. In order to numerically evaluate the quasi–equilibrium distribution, one requires first to construct the N by N matrix Q_C and then compute all eigenvalues of Q_C and the corresponding left eigenvectors. It is then easy to select the required eigenvalue and the corresponding eigenvector, which can be normalised. For example, in MATLAB, the function *eig* can be used to compute the eigenvalues and the eigenvectors of a square matrix. However, in this case we need to use the transpose of Q_C instead of Q_C to compute the left eigenvectors, since MATLAB evaluates the right eigenvectors. Alternatively, the *Eigenvectors* function in Maple can be used to compute the eigenvalues and the right eigenvectors of a square matrix. If the state space is multi–dimensional we may use a bijection $f : C \mapsto C'$, where $C' = \{1,2,...,|C|\}$, which is easily invertible, to make Q_C as a square matrix over C'. In this case, the Q–matrix over C' can be constructed using the transition rates $q_{f(i),f(j)}$, for all states i and j in C. We then compute the eigenvalues and the left eigenvectors

of $Q_{C'}$ and obtain the quasi–equilibrium distribution. Once this has been done, we can use the inverse transformation so that the distribution is indexed according to the original state space. If the state space is large but sparse, in which case most of its elements are zero, then we can use sparse matrix technology to compute eigenvalues and eigenvectors of Q_C. For example, the *eigs* command in MATLAB can be used to evaluate a selection of eigenvalues and eigenvectors of a sparse matrix. The *eigs* command implements Arnoldi's algorithm which is iterative. More details regarding the Arnoldi's algorithm and how it is implemented in MATLAB can be found in the web appendix accompanying the paper [205] (see also [165]). The web appendix accompanying [205] also provides MATLAB codes which can be used to compute the eigenvalues and the corresponding left eigenvectors of a square matrix using the *eig* and *eigs* functions. If the state space is infinite, then we can approximate a quasi–equilibrium distribution of the Markov process by employing a truncation method. The idea behind this approach is that the quasi–equilibrium distribution of an infinite–state process with restricted Q–matrix Q_C might be approximated by the quasi–equilibrium distribution of the process with Q-matrix $Q_{C^*} = (q_{ij}, i, j \in C^*)$, where C^* is a large but finite subset of C. Note that since C^* is finite, a quasi–equilibrium distribution for the process defined by Q_{C^*} always exists as long as C^* is irreducible. Such truncation techniques are known to work well for birth–death processes [40, 122].

Despite their convenience, the above stated numerical methods may not be applicable for processes with a large state space due to computer memory constraint and/or time. Therefore, explicit analytical approximations to these distributions are of great importance. The following section introduces two approximation methods–an ODE approximation and a diffusion approximation–for CTMCs whose transition rates follow the *density–dependent* property according to Kurtz [125]. It will be shown in Chapter 3 that, once the approximating ODE is identified for the Markov chain considered in this thesis, fixed points of the ODE provide a means to approximate a quasi–equilibrium of the Markov chain. A Diffusion approximation is then used to describe the distribution of the Markov chain around a fixed point of the ODE.

2.3 An ODE and A Diffusion Approximation Method

As mentioned above, the dynamic behaviour of the Markov chain considered here is studied by using an approximating ODE model. This approximation is achieved by applying Theorem 4.1 of Darling and Norris [62]. However, I note that the Markov chain studied in this work has the *density–dependent* property, according to the definition of Kurtz [125]. Therefore, I will first provide the definition of density–dependent Markov chains as stated in [125]

In his analysis of deterministic approximations to pure jump Markov chains, Kurtz [125] intro-

duced the notion of density–dependence as follows.

Definition 2.4. A one–parameter family of continuous–time Markov chains $(X^N(t);N>0)$ with state space $S^N \subset \mathbb{Z}^J$ (J–row vectors with integer components) and Q–matrix $Q^N = (q^N_{ij}; i,j \in S^N)$ is called *density–dependent* if there exists a continuous function $f(x,l) : \mathbb{R}^J \times \mathbb{Z}^J \to \mathbb{R}$, such that

$$q^N_{i,i+l} = Nf\left(\frac{i}{N},l\right), \quad l \neq \mathbf{0}. \tag{2.2}$$

Thus, the family of Markov chains is density dependent if the transition rates of the corresponding *scaled (or density) process* $(\bar{X}^N(t);N>0)$, defined by

$$\bar{X}^N(t) := \frac{X^N(t)}{N}, \quad t \geq 0,$$

depends on the present state i only through the density i/N. The index parameter N need not be discrete and it is chosen for a particular process by recognising that the approximation is achieved by letting N becomes large. For the Markov chain considered in this thesis, the index parameter N is chosen as the population size. I now proceed to summarise a method which applies Theorem 4.1 of [62] to *density–dependent* Markov chains. This method provides an explicit bound on the probability that the largest deviation between the scaled process $(\bar{X}^N(t);N>0)$ and the solution of an ODE exceeds a given amount, over a finite time interval. For further details regarding such bounds, I refer the reader to Section 4 of [62].

When the transition rates of the family of Markov chains $(X^N(t);N>0)$ has the density–dependent property, as described above, the *drift vector* $\beta(i)$ defined in Section 4 of [62] is given by

$$\beta(i) = \sum_{l \neq \mathbf{0}} l f\left(\frac{i}{N},l\right), \tag{2.3}$$

for each $i \in S^N$. The corresponding variance of a jump is given by

$$\alpha(i) = \sum_{l \neq \mathbf{0}} \frac{|l|^2}{N} f\left(\frac{i}{N},l\right), \tag{2.4}$$

for each $i \in S^N$. Now, let E be a subset of $\mathbb{R}^J$ and let the function $b : E \mapsto \mathbb{R}^J$ be a Lipschitz vector field. Also, let K be the Lipschitz constant of b on E with respect to the Euclidean norm $|\cdot|$. Let $x(t,x_0)$ be the unique solution to the differential equation $dx(t)/dt = b(x(t))$, starting with $x(0) = x_0 \in E$, which remains in E for for all $t \leq T$, where $T>0$ fixed and finite. Set $\delta = (\varepsilon e^{-KT})/3$, where $\varepsilon > 0$, and fix $A > 0$. Now, consider the following events.

$$\Omega_0 = \{|\bar{X}^N(0) - x(0)| \leq \delta\}, \qquad \Omega_1 = \left\{\int_0^T |\beta(X^N(t)) - b(\bar{X}^N(t))|dt \leq \delta\right\}, \tag{2.5}$$

$$\Omega_2 = \left\{\int_0^T \alpha(X^N(t))dt \leq AT\right\}. \tag{2.6}$$

The following result provides a probabilistic bound on the largest deviation between the scaled process, $\bar{X}^N(t)$, and the solution, $x(t)$, of the differential equation by a given amount, over finite time intervals. The symbol Ω^c represents the complement of the set Ω.

Theorem 2.2. (*Theorem 4.1 of [62]*) *Under the conditions stated in the previous paragraph,*

$$\mathbb{P}\left(\sup_{t\leq T}|\bar{X}^N(t)-x(t,x_0)|>\varepsilon\right)\leq\frac{4AT}{\delta^2}+\mathbb{P}(\Omega_0^c\cup\Omega_1^c\cup\Omega_2^c).$$

Since the transition rates of the Markov chain concerned in this thesis satisfy Kurtz's density–dependent property, we shall have the limiting drift $b(x)$ equal to the drift vector $\beta(Nx)$ when Nx is in S^N, which implies that the probability of Ω_1^c equals zero. This simplifies the application of Theorem 2.2 to our model. Then, to determine the bound on the probability given in Theorem 2.2, we can choose the initial value of the ODE, $x(0)$, to be the same as the initial value of the scaled process, $\bar{X}^N(0)$, so that the probability of Ω_0^c is zero. It remains to determine the constants A in Ω_2 and the Lipschitz constant, K, of $b(\cdot)$ to give the bound.

At this point, I note that Theorem 3.1 of Kurtz [125] provides some sufficient conditions for weak convergence of density–dependent Markov processes, which are appropriately scaled, to a solution of an ODE. That is convergence in probability to zero of the largest deviation of the scaled process from its limiting deterministic path over any finite time interval on which the deterministic trajectory is defined. However, the deterministic path in this case must be defined on an open subset O of $\mathbb{R}^J$. This limits the application of Kurtz's result to the Markov chain concerned in this thesis in its original form, so I use Theorem 2.2 instead. But, Kurtz's result can easily be applied to our Markov chain after eliminating one variable from its state vector and this is made possible since the population is assumed closed. Theorem 3.1 of Kurtz [125] can then be used to approximate the scaled process $(\tilde{X}^N(t);N>0)$ of the reduced Markov chain by the unique solution of the ODE satisfying

$$x(0,x_0)=x_0\in O, \tag{2.7}$$

$$x(t,x_0)\in O,\quad 0\leq t\leq T,$$

$$\tfrac{\partial}{\partial t}x(t,x_0)=F(x(t,x_0)), \tag{2.8}$$

where

$$F(x)=\sum_{l\neq\mathbf{0}}l f(x,l),$$

with $f(\cdot)$ as given in (2.2). We can then apply results of Kurtz [126] and Pollett [163] to the reduced ODE to obtain a central limit theorem which accounts for the random fluctuations about the deterministic path. In particular, the central limit theorem shows that the random fluctuations about the

deterministic path follow a Gaussian diffusion. Before presenting the central limit result, I will first review some necessary background material about diffusion processes.

A diffusion process $(\mathbf{Z}(t);t \geq 0)$, where $\mathbf{Z}(t) = (Z_1(t),\ldots,Z_J(t))$, is a continuous time Markov chain with almost sure continuous sample paths. The type of diffusion processes that are considered in this thesis satisfy the following properties (see for example [111, Chapter 15]).

$$\mathbb{E}[Z_i(t+h) - Z_i(t) \mid \mathbf{Z}(t) = \mathbf{z} = (z_1,\ldots,z_J)] = a_i(t,\mathbf{z})h + o(h), \quad i = 1,\ldots,J,$$
$$\mathbb{E}[(Z_i(t+h) - Z_i(t))(Z_j(t+h) - Z_j(t)) \mid \mathbf{Z}(t) = \mathbf{z}] = c_{ij}(t,\mathbf{z})h + o(h), \quad i,j = 1,\ldots,J,$$

where $(c_{ij}(t,\mathbf{z}))$, $i,j = 1,\ldots,J$, is a positive definite matrix. That is

$$\sum_{i,j=1}^{J} c_{ij}(t,\mathbf{z})a_i a_j > 0$$

for all nontrivial real J–tuples $(a_1,\ldots,a_J)$ and $\mathbf{z} \in \mathbb{R}^J$. The functions $\mathbf{a}(\cdot)$ and $\mathbf{c}(\cdot)$, respectively, are called the *local (or instantaneous) drift* and *local (or instantaneous) covariance*. The diffusion process that this thesis is specifically concerned with is the *Ornstein–Uhlenbeck (OU) process*, which experiences a drift towards the origin of magnitude proportional to its displacement. That is, $\mathbf{a}(t,\mathbf{z}) = -B\mathbf{z}$ and $\mathbf{c}(t,\mathbf{z}) = G$, for some constant matrices B and G. The matrix B is known as the the local drift of the process.

Now, I present the central limit result which models the random fluctuations between the density process $(\tilde{X}^N(t);N > 0)$ and the deterministic path, $x(t,x_0)$, defined in (2.7)–(2.8). In the following, transpose of a vector $\mathbf{a}$ is denote by $\mathbf{a}'$ and transpose of a matrix is denoted similarly, and these notations are used throughout the thesis.

Theorem 2.3. (*Theorem 3.5 of [126]*) *Suppose that $F(\cdot)$ is bounded, Lipschitz continuous and has uniformly continuous first partial derivatives on O. Suppose also that $G(x)$, a $J \times J$ matrix with elements*

$$g_{ij}(x) = \sum_{l \neq \mathbf{0}} l_i l_j f(x,l), \qquad x \in O, \quad l = (l_1,\ldots,l_J) \in \mathbb{Z}^J,$$

is bounded and uniformly continuous on O. If, in addition,

$$\sup_{x \in O} \sum_{l} |l|^2 f(x,l) < +\infty, \tag{2.9}$$
$$\lim_{\delta \to +\infty} \sup_{x \in O} \sum_{l:|l|>\delta} |l|^2 f(x,l) = 0, \tag{2.10}$$

then, provided

$$\lim_{N \to \infty} \sqrt{N}(\tilde{X}^N(0) - x_0) = z, \tag{2.11}$$

the family of processes $(Z_N(\cdot))$*, defined by*

$$Z_N(t) = \sqrt{N}(\tilde{X}^N(t) - x(t,x_0)), \quad 0 \le t \le T,$$

converges weakly in $D[0,T]$ *(the space of right-continuous, left-hand limits functions on* $[0,T]$*), as* $N \to \infty$*, to a Gaussian diffusion,* $Z(\cdot)$*, with initial value* $Z(0) = z$ *and with characteristic function* $\psi = \psi(t,\theta) = \mathbb{E}e^{i\theta Z(t)}$ *that satisfies*

$$\frac{\partial \psi}{\partial t}(t,\theta) = -\frac{1}{2}\sum_{j,k}\theta_j g_{jk}(x(t,x_0))\theta_k \psi(t,\theta) + \sum_{j,k}\theta_j \frac{\partial F_j}{\partial x_k}(x(t,x_0))\frac{\partial \psi}{\partial \theta_k}(t,\theta).$$

The mean of $Z(t)$ is given by

$$\mu(t) := \mathbb{E}Z(t) = M(t)z,$$

where $M(t)$ is the unique solution to $dM(t)/dt = B(t)M(t)$ with $M(0) = I$, where $B(t) = \nabla F(x(t,x_0))$ with $\nabla F = \left(\frac{\partial F_i}{\partial x_j}\right)$ as the matrix of the first partial derivatives (the Jacobian matrix) of $F(\cdot)$. That is

$$M(t) = e^{\left(\int_0^t B(u)du\right)}.$$

The covariance matrix, $\sum(t)$, of $Z(t)$ is the unique solution to

$$\frac{d\sum(t)}{dt} = B(t)\sum(t) + \sum(t)B(t)' + G(x(t,x_0))$$

with $\sum(0) = 0$. That is

$$\sum(t) := \mathrm{Cov}(Z(t)) = M(t)\left(\int_0^t M(u)^{-1}G(x(u,x_0))(M(u)^{-1})'du\right)M(t)'.$$

Although Theorem 2.3 gives us an explicit expression for the asymptotic distribution of the time–dependent fluctuations about the deterministic path, the required integration often leads to formulas that are too complicated to be of practical use. However, if x_0 is chosen to be equal to an equilibrium point, x^*, of the limiting deterministic model, then the diffusion approximation can be simplified by identifying an appropriate Ornstein–Uhlenbeck (OU) process. To be specific, if we now consider fluctuations about an equilibrium point of the deterministic model, we can derive simple explicit formulas for the mean and covariance of our density process. This is obtained as follows.

Corollary 2.4. *(Ornstein–Uhlenbeck (OU) approximation)*
If x^* *satisfies* $F(x^*) = 0$ *and if* $\lim_{N\to\infty}\sqrt{N}(\tilde{X}^N(0) - x^*) = z$*, , then under conditions of Theorem 2.3, the family* $(Z_N(\cdot))$ *defined by*

$$Z_N(t) = \sqrt{N}(\tilde{X}^N(t) - x^*), \quad 0 \le t \le T,$$

converges weakly in $D[0,T]$, as $N \to \infty$, to an OU process $Z(\cdot)$, with initial value $Z(0) = z$, and with local drift matrix $B = \nabla F(x^*)$ and local covariance matrix $G(x^*)$, where ∇F and $G(\cdot)$ as defined in Theorem 2.3. In particular, $Z(t)$ has a normal distribution with mean

$$\mu(t) = \mathbb{E}Z(t) = e^{Bt}z \tag{2.12}$$

and covariance matrix

$$\sum(t) := e^{Bt}\left(\int_0^t e^{(-Bu)}G(x^*)e^{-B'u}du\right)e^{B't}. \tag{2.13}$$

It follows that, for large N, $(\tilde{X}^N(t); N > 0)$ has an approximate normal distribution with

$$\mathrm{Cov}(\tilde{X}^N(t)) \simeq \frac{1}{N}\sum(t), \tag{2.14}$$

and a "working approximation" for the mean (i.e., for a fixed value of N), obtained by setting $z = \sqrt{N}(\tilde{X}^N(0) - x^*)$, is given by

$$\mathbb{E}\tilde{X}^N(t) \simeq x^* + e^{(Bt)}(\tilde{X}^N(0) - x^*). \tag{2.15}$$

I note that, as mentioned by Pollett [163] and Barbour [30], in order to use Corollary 2.4 the equilibrium point x^* need not be asymptotically stable. In fact the OU approximation is often very accurate in describing the fluctuations about unstable equilibrium points. This is specifically useful in systems that have quasi-equilibrium behaviour (see for example, [159]).

When the real part of the eigenvalues of matrix B in equation (2.12) are all negative (in which case the equilibrium point x^* is asymptotically stable), the process $Z(t)$ is stable [30]. The stationary distribution of $Z(t)$ is multivariate normal distribution with mean $\mathbf{0}$ and covariance matrix $\sum$ satisfying

$$B\sum + \sum B' = -G. \tag{2.16}$$

In this case the density process $(\tilde{X}^N(t); N > 0)$ has an approximate normal distribution with mean as x^* and $\mathrm{Cov}(\tilde{X}^N(t)) \simeq N^{-1}\sum$, where $\sum$ satisfies equation (2.16).

Equation (2.16) is a Lyapunov matrix equation. It admits a unique, real symmetric positive definite solution $\sum$ (that is $\mathbf{a}'\sum\mathbf{a} > 0$, for any J dimensional real vector $\mathbf{a}$) for any real, symmetric, positive definite matrix G if and only if the real part of all of the eigenvalues B are negative (see for example [59] for a statement of this result).

2.4 Disease–Free and Endemic Equilibria and Their Stability

In analysing any epidemic model, one of the most important questions to address is when a disease will spread through a population. This is often examined by studying the early stage of the epidemic,

when the population initially contains few infected individuals. As the CTMC concerned here can be approximated by a system of ODE, the stability of a disease–free equilibrium (DFE) of the ODE provides a means to study the early stage of the epidemic. A DFE is an equilibrium of the ODE at which there are no infected individuals in the population. If the disease can invade the population, the next question to address is whether it can persist in the population. This is mostly examined by analysing the stability of an endemic equilibrium (EE) of the ODE at which there are some infected individuals in the population. Determining the existence and stability of an EE to the ODE is important for this analysis as it provides an approximation to a quasi–equilibrium of the Markov chain. This section provides some methods which can be used to establish the existence and stability of a DFE and an EE of the ODE. Before, proceeding to state these theories, I will firstly give the definition of local and global stability of equilibrium points of an ODE arising from an epidemiological model.

Suppose the evolution of susceptibles and infectives in a population is described by the ODE system

$$\frac{d\mathbf{x}}{dt} = f(\mathbf{x}), \quad \mathbf{x}(0) = \mathbf{x}_0, \tag{2.17}$$

where $f : \mathbb{R}^J_+ \mapsto \mathbb{R}^J$ is a continuously differentiable function, and $x_i \geq 0$ represents the number (or density) of individuals in state i. An equilibrium point of (2.17) is a point $\mathbf{x}^* \in \mathbb{R}^J_+$ such that $f(\mathbf{x}^*) = \mathbf{0}$.

Definition 2.5. The equilibrium point $\mathbf{x}^*$ of (2.17) is called

(a) *stable* if, for each $\varepsilon > 0$, there is a $\delta = \delta(\varepsilon) > 0$ such that if $|\mathbf{x}_0 - \mathbf{x}^*| < \delta$ then $|\mathbf{x}(t) - \mathbf{x}^*|$, for all $t \geq 0$.

(b) *unstable* if it is not stable.

(c) *locally asymptotically stable*, if it is stable and δ can be chosen such that, if $|\mathbf{x}_0 - \mathbf{x}^*| < \delta$, then $\mathbf{x}(t) \to \mathbf{x}^*$ as $t \to +\infty$.

(b) *globally asymptotically stable*, if it is stable and $\mathbf{x}(t) \to \mathbf{x}^*$ as $t \to +\infty$ for all $\mathbf{x}_0 \in \mathbb{R}^J_+$.

From this definition we see that an equilibrium point of (2.17) is stable if all solutions starting at nearby points stay nearby, otherwise it is unstable. Furthermore, it is locally asymptotically stable, if all solutions starting at nearby points not only stay nearby, but also tend to the equilibrium point as time approaches infinity. If the latter situation occurs for all initial points in $\mathbb{R}^J_+$ then the equilibrium point is globally asymptotically stable (see for example [69, page 151] and [82, pages 27–30]). Thus, if the population initially contains few infected individuals and the DFE is locally asymptotically stable, then the disease cannot spread through the population, but if it is unstable then the disease can

invade the population. However, if the DFE is globally asymptotically stable then the disease cannot remain endemic in the population.

Local stability of a DFE or an EE equilibrium of (2.17) can be established by linearising the ODE in a neighbourhood $\Omega \subset \mathbb{R}_+^J$ of the equilibrium point. More precisely, the following result can be used to determine local stability of a DFE or an EE of the ODE.

Theorem 2.5. (*Theorem 4.7 of* [119]) *Consider system* (2.17) *and let* $\mathbf{x}^*$ *be an equilibrium point of system* (2.17)*, where* $f : \Omega \to \mathbb{R}^J$ *is continuously differentiable and* Ω *is a neighborhood of* $\mathbf{x}^*$*. Let A be the Jacobian matrix of* $f(\cdot)$*, evaluated at the equilibrium point* $\mathbf{x}^*$*. That is*

$$A = \left(\frac{\partial f_i(\mathbf{x}^*)}{\partial x_j} \right), \quad i, j = 1, \ldots, J.$$

Let λ_i*,* $i = 1, \ldots, J$ *be the eigenvalues of A. Then,*

1. *the equilibrium point* $\mathbf{x}^*$ *is locally asymptotically stable if* $Re\lambda_i < 0$ *for all eigenvalues of A.*

2. *the equilibrium point* $\mathbf{x}^*$ *is unstable if* $Re\lambda_i > 0$ *for one or more of the eigenvalues of A.*

The results of Theorem 2.5 are used to establish local stability of an EE of the ODE concerned in this thesis (see Appendix section of Chapter 3). However, note that Theorem 2.5 does not say anything about the case for which the real part of at least one eigenvalue of A is zero. In this case linearisation fails to determine the stability of the equilibrium point and we may use alternative approaches such as the center manifold and bifurcation theories (see for example Chapter 8 of [82]) to investigate the stability and bifurcations at these equilibrium points. But, instead of applying these methods, I use the results on Metzler matrices (see Theorem 2.7) and cooperative systems (see Theorem 2.10) to establish global stability of a DFE and an EE of the ODE studied in this thesis.

It can be inferred from Theorem 2.5 that if the maximum real part of the eigenvalues of the Jacobian matrix A, evaluated at the DFE is less than 0, then the disease cannot invade the population as the DFE is stable in this case. However, if this real part is positive, then the disease can invade the population as the DFE is unstable in this case. Therefore, the maximum real part of the eigenvalue of A, evaluated at the DFE, equals to 1 is a threshold condition for the model [137]. In some cases, it may be possible to rearrange this threshold condition to produce a threshold in terms of the *basic reproduction number* R_0. However, this is not a unique process and may not produce the desired threshold condition in terms of R_0 [137]. Furthermore, as the number of equations in the system gets large, it becomes difficult to compute the eigenvalues of A. Therefore, in my analysis, I apply the *next generation matrix* approach [65, 97] (see also Section 6.3 of [204]) to compute R_0 and use Theorem 1 of [204] to establish local stability of the DFE of the ODE studied in this thesis. R_0 is defined as

the expected number of secondary infections produced by an index case in a completely susceptible population [5, page 17], [65, page 4], [66], [97]. This number is a measure of the potential for disease spread within a population. If $R_0 < 1$, then a few infected individuals introduced into a completely susceptible population will, on average, fail to replace themselves, and the disease will not spread. On the contrary, if $R_0 > 1$, then the number of infected individuals will increase with each generation and the disease will spread [204]. Before presenting the next generation method and Theorem 1 of [204], I will first establish some definitions and notations which will be used in the rest of the thesis.

Definition 2.6. Let $\mathbf{x} \in \mathbb{R}^n$ be an n–dimensional real vector and $A = (a_{ij}) \in \mathbb{R}^{n\times n}$ be a real square matrix. Then,

(a) $\mathbf{x}$ is said to be *positive* (*nonnegative*) if $x_i > 0$ ($x_i \geq 0$) for all $i = 1, \ldots, n$, and this is denoted by $\mathbf{x} > \mathbf{0}$ ($\mathbf{x} \geq \mathbf{0}$).

(b) A is said to be *positive* (*nonnegative*) if $a_{ij} > 0$ ($a_{ij} \geq 0$) for all $i, j = 1, \ldots, n$, and this is denoted by $A > \mathbf{0}$ ($A \geq \mathbf{0}$).

(c) A is said to be *Metzler* if $a_{ij} \geq 0$ for all $i \neq j$, $i, j = 1, \ldots, n$.

(d) the *spectral radius* of A is the maximum absolute value of all the eigenvalues of A, and this is denoted by $\rho(A)$.

(e) the *spectral abscissa* of A is the maximum real part of all the eigenvalues of A, and this is denoted by $s(A)$.

(f) if $B = (b_{ij}) \in \mathbb{R}^{n\times n}$, and $A > B$ ($A \geq B$) means $a_{ij} > b_{ij}$ ($a_{ij} \geq b_{ij}$) for all pairs (i, j) of row and column indices.

(g) the matrix A is said to be *reducible* if there exists a nontrivial partition of the index set $\{1, \ldots, n\} = M \cup N$ such that $(i, j) \in M \times N$ implies $a_{ij} = 0$. The matrix A is said to be *irreducible* if it is not reducible (see for example [191, Section 3.11]).

Under this definition, all elements of a positive vector or a positive matrix are positive, and all elements of a nonnegative vector or a nonnegative matrix are greater than or equal to zero. Furthermore, a Metzler matrix has all its off diagonal elements greater than or equal to zero. Thus, any Q–matrix as defined in Section 2.2.1 is a Metzler matrix.

Now, returning to the computation of R_0 and the local stability of a DFE of the ODE (2.17),

suppose equation (2.17) can be written in the form

$$\begin{aligned}\frac{d\mathbf{y}_i}{dt} &= \mathscr{F}_i(\mathbf{y},\mathbf{z}) - \mathscr{V}_i(\mathbf{y},\mathbf{z}), \quad i = 1,\ldots,J_1,\\ \frac{d\mathbf{z}_i}{dt} &= g_i(\mathbf{y},\mathbf{z}), \quad i = 1,\ldots,J_2,\end{aligned} \tag{2.18}$$

where $J = J_1 + J_2$, $\mathbf{y} \in \mathbb{R}_+^{J_1}$ represents all infected states and $\mathbf{z} \in \mathbb{R}_+^{J_2}$ represents all susceptible states and $\mathbf{x} = (\mathbf{y},\mathbf{z})$ is the state of the system. The function $\mathscr{F}_i(\cdot)$ denotes the rate at which new infectives are generated in the i–th infected state and $\mathscr{V}_i(\cdot)$ stands for all other rates (for example recovery and death) in the the i–th infected state. The following assumptions are made to ensure the model is well posed and to make certain the existence of a DFE.

(A1) $\mathscr{F}_i(\mathbf{0},\mathbf{z}) = 0$ and $\mathscr{V}_i(\mathbf{0},\mathbf{z}) = 0$ for all $\mathbf{z} \geq \mathbf{0}$ and $i = 1,\ldots,J_1$.

(A2) $\mathscr{F}_i(\mathbf{y},\mathbf{z}) \geq 0$ for all $\mathbf{y} \geq \mathbf{0}$ and $\mathbf{z} \geq \mathbf{0}$ and $i = 1,\ldots,J_1$.

(A3) $\mathscr{V}_i(\mathbf{y},\mathbf{z}) \leq 0$ whenever $y_i = 0$, $i = 1,\ldots,J_1$.

(A4) $\sum_{i=1}^{J_1} \mathscr{V}_i(\mathbf{y},\mathbf{z}) \geq 0$ for all $\mathbf{y} \geq \mathbf{0}$ and $\mathbf{z} \geq \mathbf{0}$.

(A5) The *disease–free system* $d\mathbf{z}/dt = g(\mathbf{0},\mathbf{z})$ has a unique equilibrium that is asymptotically stable.

Assumption (A1) implies that all new infections are secondary infections arising from infected individuals, and there is no immigration of individuals into the infected states. Since the function $\mathscr{F}(\cdot)$ represents new infections, Assumption (A2) ensures that it cannot be negative. Similarly, since each $\mathscr{V}_i(\cdot)$ represents a net *outflow* from state i, Assumption (A3) implies that it must be negative whenever the state is empty. Assumption (A4) ensures that the total outflow from all infected states must be nonnegative. Assumption (A5) states that all solutions with initial conditions of the form $(\mathbf{0},\mathbf{z})$ approach a point $\mathbf{x}^* = (\mathbf{0},\mathbf{z}^*)$ as t approaches positive infinity. The point $\mathbf{x}^*$ is called the DFE of system (2.18). The Jacobian matrix for the linearisation of system (2.18) about the DFE, $\mathbf{x}^*$, has the block structure

$$\mathscr{J} = \begin{bmatrix} F - V & 0 \\ \mathscr{J}_{21} & \mathscr{J}_{22} \end{bmatrix}, \tag{2.19}$$

where F and V given by

$$F = \left(\frac{\partial \mathscr{F}_i}{dy_j}(\mathbf{x}^*)\right) \quad V = \left(\frac{\partial \mathscr{V}_i}{dy_j}(\mathbf{x}^*)\right), \quad i,j = 1,\ldots,J_1.$$

Since $\mathscr{J}$ is block triangular, the eigenvalues of $\mathscr{J}$ are those of $F - V$ and $\mathscr{J}_{22}$. By Assumption (A5), all eigenvalues of $\mathscr{J}_{22}$ have negative real part. Therefore, the local stability of the DFE is

determined by the eigenvalues of $F-V$. The (i,j)–th entry of matrix V^{-1} can be interpreted as the expected time an individual initially introduced into state j spends in state i, with i and j being infected states. The (i,j)–th entry of F is the rate secondary infections are produced in state i by an index case in state j. With these interpretations for F and V^{-1}, and following Diekmann and Heesterbeek [66, 65, 97], the matrix FV^{-1} is referred to as the *next generation matrix* for system (2.18) at the DFE. The (i,j)–th entry of FV^{-1} is the expected number of secondary infections in state i produced by an infected individual initially in state j, assuming that the environment seen by the individual remains homogeneous for the duration of its infection. The basic reproduction number R_0 is then defined as the spectral radius of FV^{-1}. More specifically,

$$R_0 = \rho(FV^{-1}). \tag{2.20}$$

The following result of van den Driessche and Watmaough [204] shows that R_0 can be used to determine the local asymptotic stability of the DFE.

Theorem 2.6. (*Theorem 1 of* [*204*]) *Consider the disease transmission model given by* (2.18) *with* $\mathscr{F}(\cdot)$, $\mathscr{V}(\cdot)$ *and* $g(\cdot)$ *satisfying conditions (A1)–(A5). The DFE* $\mathbf{x}^*$ *of* (2.18) *is locally asymptotically stable if* $R_0 < 1$, *but unstable if* $R_0 > 1$, *where* R_0 *as defined in* (2.20).

It can be inferred from Theorem 2.6 that $R_0 = 1$ is a threshold condition for disease invasion or persistence. As the DFE is locally asymptotically stable when $R_0 < 1$, and if the trajectory of the ODE starts close to the DFE, then it will tend to the DFE. Thus if $R_0 < 1$ and the population initially contains few infected individuals, the disease will not spread. However, since the DFE is unstable when $R_0 > 1$, then any trajectory of the ODE which starts close to the DFE will be repelled by the DFE. Hence, if $R_0 > 1$, the disease will spread. Although we can determine local stability of the DFE using Theorem 2.6 for the cases when $R_0 < 1$ and $R_0 > 1$, it does not inform anything about stability of the DFE when $R_0 = 1$. Thus, the local stability result given by Theorem 2.6 does not completely determine the stability of the DFE. A stronger result can be obtained if we can determine the global stability of the DFE. I use the novel procedure given by Kamgang and Sallet [110] to investigate the global stability of the DFE. Before stating this result, I will first establish the setting required for its statement.

Suppose equation (2.17) can be written in the form

$$\begin{aligned} \frac{d\mathbf{y}}{dt} &= A_2(\mathbf{y},\mathbf{z})\mathbf{y}, \\ \frac{d\mathbf{z}}{dt} &= A_1(\mathbf{y},\mathbf{z})(\mathbf{z}-\mathbf{z}^*) + A_{12}(\mathbf{y},\mathbf{z})\mathbf{y} \end{aligned} \tag{2.21}$$

where, as previously defined, $\mathbf{y} \in \mathbb{R}_+^{J_1}$ represents all infected states and $\mathbf{z} \in \mathbb{R}_+^{J_2}$ represents all susceptible states and $\mathbf{x} = (\mathbf{y},\mathbf{z})$ is the state of the system. $A_1(\mathbf{x})$ and $A_2(\mathbf{x})$ are square matrices with

dimensions $J_2 \times J_2$ and $J_1 \times J_1$, respectively. A_{12} is a $J_2 \times J_1$ matrix and $\mathbf{x}^* = (\mathbf{0}, \mathbf{z}^*) \in \mathbb{R}_+^{J_1} \times \mathbb{R}_+^{J_2}$ is a DFE of (2.21). For the model (2.21) to be well posed, we assume that it is defined on a *positively invariant* subset Ω of $\mathbb{R}_+^{J_1+J_2}$, which means that any solution of system (2.21) which starts in Ω must remain in Ω for all positive time. The following theorem of Kamgang and Sallet [110] provides a method to determine global asymptotic stability of the DFE, $\mathbf{x}^* = (\mathbf{0}, \mathbf{z}^*)$.

Theorem 2.7. (*Theorem 4.3 of [110]*) *Consider the system* (2.21) *on a positively invariant set* $\Omega \subset \mathbb{R}_+^{J_1+J_2}$. *Assume that*

(H1) the system is dissipative on Ω (*that is, there exists a bounded set B in* Ω *that attracts each point of* Ω *under the flow of system* (2.21) *[90, Section 3.4]*).

(H2) the equilibrium z^* *of the disease–free system*

$$\frac{dz}{dt} = A_1(\boldsymbol{y}, \mathbf{z})(z - z^*)$$

is globally asymptotically stable on the canonical projection of Ω *on* $\mathbb{R}_+^{J_1}$.

(H3) the matrix $A_2(\boldsymbol{y}, \mathbf{z})$ *is Metzler and irreducible for any given* $(\boldsymbol{y}, \mathbf{z}) \in \Omega$,

(H4) there exists an (elementwise) upper bound matrix $\bar{A}_2$ *for the set* $\mathscr{M} = \{A_2(\boldsymbol{y}, \mathbf{z}) : (\boldsymbol{y}, \mathbf{z}) \in \Omega\}$ *with the property that either* $\bar{A}_2 \notin \mathscr{M}$ *or if* $\bar{A}_2 \in \mathscr{M}$ (*that is,* $\bar{A}_2 = \max_\Omega \mathscr{M}$), *then for any* $\bar{\boldsymbol{x}} \in \Omega$ *such that* $\bar{A}_2 = A_2(\bar{\boldsymbol{y}}, \bar{\mathbf{z}})$, $(\bar{\boldsymbol{y}}, \bar{\mathbf{z}}) \in \mathbb{R}_+^{J_1} \times \{\boldsymbol{0}\}$ (*that is, the points where the maximum is realised are contained in the disease–free sub–manifold*).

(H5) $s(\bar{A}_2) \leq 0$.

Then, the DFE is globally asymptotically stable for system (2.21) *in* $\bar{\Omega}$, *where* $\bar{\Omega}$ *is the closure of* Ω.

Assumption (H1) implies that, for any trajectory which starts in Ω, there exists a time $\bar{t} > 0$ depending on the initial point, such that the trajectory is in B for any time $t \geq \bar{t}$. Assumption (H2) ensures that when there are no infected individuals, the population will stabilise at the DFE. Assumption (H3) supposes that there is no block of states which does not interact with others. Assumption (H4) looks for the (elementwise) least upper–bound matrix to obtain the best conditions for the threshold given by (H5).

Now, from Theorem 2.6 it is clear that if $R_0 > 1$, then the disease will spread. In this case, it is important to investigate the existence and then stability of any endemic equilibria, since it is these equilibria which can approximate a quasi–equilibrium of the Markov chain. In Chapter 3, I have shown the existence of an EE, when $R_0 > 1$, for the ODE concerned in this thesis, under a

specific assumption on the migration rates. Specifically, it is assumed that, for each patch, the rate that a susceptible individual travels from the patch to all other patches is equal to the rate that a susceptible individual enters into that patch from all other patches. The same assumption is imposed on the migration rates of infected individuals. The stability of this EE is proved using Theorem 2.5. However, these assumptions on the migration rates are relaxed for the EE derived in Section 3.2.1. More precisely, it is assumed, that susceptible and infected individuals have the same migration rates. In the latter case, we need to deal with a nonautonomous ODE of the form

$$\frac{d\mathbf{x}}{dt} = f(t,\mathbf{x}),, \tag{2.22}$$

which has the following autonomous ODE in the limit as $t \to +\infty$

$$\frac{d\mathbf{y}}{dt} = g(\mathbf{y}). \tag{2.23}$$

The asymptotic behaviour of solutions of system (2.22) can be related to equilibrium points of system (2.23) using the results of Markus [139] on *asymptotically autonomous* differential equations. Therefore, I will review these results here.

Definition 2.7. Consider systems (2.22) and (2.23) in $\mathbb{R}^J$ and assume that $f(\cdot)$ and $g(\cdot)$ are continuous functions and locally Lipschitz in $\mathbf{x} \in \mathbb{R}^J$. Further all solutions are supposed to exist for all positive times. Then, equation (2.22) is called *asymptotically autonomous* with limit equation (2.23) if

$$f(t,\mathbf{x}) \to g(\mathbf{x}) \qquad \text{as} \quad t \to \infty,$$

locally uniformly in $\mathbf{x} \in \mathbb{R}^J$. That is, for all $\mathbf{x}$ in any compact subset Ω of $\mathbb{R}^J$ and for all $\varepsilon > 0$, there exists a $T = T(\Omega,\varepsilon) > 0$ such that $|f(t,\mathbf{x}) - g(\mathbf{x})| < \varepsilon$ for all $t > T$.

Note that $g(\mathbf{x})$ is said to be *locally Lipschitz* in $\mathbf{x}$, if each point $\mathbf{x} \in \mathbb{R}^J$ has a neighbourhood Ω_0 such that $|g(\mathbf{x}) - g(\mathbf{y})| \leq L_0|\mathbf{x} - \mathbf{y}|$, for all points in Ω_0 with some Lipschitz constant L_0. A similar interpretation holds for the function $f(\cdot)$ to be locally Lipschitz. Now, define the ω–limit set $\omega(t,\mathbf{x}_0)$ of a forward bounded solution $\mathbf{x}(t)$ to (2.22), satisfying $\mathbf{x}(t_0) = \mathbf{x}_0$, as:

$$\mathbf{y} \in \omega(t,\mathbf{x}_0) \Longleftrightarrow y = \lim_{j \to +\infty} \mathbf{x}(t_j),$$

for some sequence $t_j \to +\infty$ as $j \to +\infty$. The following result of Markus, which can be found in Thieme [199] (see also [45, 100, 136, 216]), relates asymptotic behaviour of solutions of system (2.22) to equilibrium points of system (2.23).

Theorem 2.8. (*Theorem 1.2 of [199]*) *Let $\mathbf{y}^*$ be a locally asymptotically stable equilibrium of* (2.23) *and ω be the ω–limit set of a forward bounded solution $\mathbf{x}(t)$ of* (2.22)*. If ω contains a point $\mathbf{y}_0$ such that the solution of* (2.23)*, with initial condition $\mathbf{y}_0$ converges to $\mathbf{y}^*$ as $t \to +\infty$, then, $\omega = \{\mathbf{y}^*\}$; that is $\mathbf{x}(t) \to \mathbf{y}^*$ as $t \to +\infty$.*

When the equilibrium of (2.23) is globally asymptotically stable, the following result is observed in [100, 136, 216] from Theorem 2.8.

Corollary 2.9. *If solutions of system* (2.22) *are bounded and the equilibrium* $\boldsymbol{y}^*$ *of the limit system* (2.23) *is globally asymptotically stable, then, any solution* $\boldsymbol{x}(t)$ *of system* (2.23) *satisfies* $\boldsymbol{x}(t) \to \boldsymbol{y}^*$ *as* $t \to +\infty$.

Corollary 2.9 implies that if the limiting system (2.23) has an equilibrium point which is globally asymptotically stable, then the equilibrium is globally asymptotically stable also for the nonautonomous ODE (2.22), provided that the solutions of (2.22) are bounded. This result is used to prove global stability of the EE concerned in Section 3.2.1 of the thesis. Of course, in order to apply Corollary 2.9 it is first necessary to show the existence and global asymptotic stability of the equilibrium of system (2.23). This is achieved by applying the following result of Zhao and Jing [218] concerning cooperative systems.

Corollary 2.10. (*Corollary 3.2 of* [218]) *Consider system* (2.23) *and let* $g : \mathbb{R}^J_+ \to \mathbb{R}^J$ *be a continuously differentiable function. Assume that*

(1) g *is cooperative on* $\mathbb{R}^J_+$*; that is for any* $\boldsymbol{y} \in \mathbb{R}^J_+$, $\partial g_i/\partial y_j \geq 0$, $i \neq j$, $i, j = 1, \ldots, J$;

(2) $Dg(\boldsymbol{y}) = (\partial g_i/\partial y_j)$, $i, j = 1, \ldots, J$ *is irreducible for every* $\boldsymbol{y} \in \mathbb{R}^J_+$;

(3) $g(\boldsymbol{0}) = \boldsymbol{0}$ *and* $g_i(\boldsymbol{y}) \geq 0$ *for all* $\boldsymbol{y} \in \mathbb{R}^J_+$ *with* $y_i = 0$, $i = 1, \ldots, J$;

(4) g *is strictly sublinear on* $\mathbb{R}^J_+$*; that is for any* $\alpha \in (0,1)$ *and any* $\boldsymbol{y} \geq \boldsymbol{0}$, $g(\alpha \boldsymbol{y}) > \alpha g(\boldsymbol{y})$.

Then

(a) If $s(Dg(\boldsymbol{0})) \leq 0$, *then* $\boldsymbol{y} = \boldsymbol{0}$ *is globally asymptotically stable with respect to* $\mathbb{R}^J_+$;

(b) If $s(Dg(\boldsymbol{0})) > 0$, *then either*

(i) for any $\mathbf{y}_0 \in \mathbb{R}^J_+ \setminus \{\boldsymbol{0}\}$, $\lim_{t \to +\infty} |\mathbf{y}(t, \mathbf{y}_0)| = +\infty$, *where* $\mathbf{y}(t, \mathbf{y}_0)$ *is the unique solution of* (2.23) *starting at* $\mathbf{y}_0$, *or alternatively,*

(ii) (2.23) *admits a unique positive equilibrium point* $\boldsymbol{y}^* \geq \boldsymbol{0}$ *and* $\boldsymbol{y}^*$ *is globally asymptotically stable with respect to* $\mathbb{R}^J_+ \setminus \{\boldsymbol{0}\}$.

Note that assumptions (1) and (2) imply that the Jacobian matrix of $g(\cdot)$ is an irreducible Metzler matrix. Assumption (3) ensures that $\boldsymbol{0}$ is an equilibrium point of system (2.23) and that the domain $\mathbb{R}^J_+$ is positively invariant set for $g(\cdot)$.

In addition to all the theories reviewed in this section, the proofs of most results obtained in Chapter 3 and Chapter 4 applies properties of matrices, particularly those properties on positive and Metzler matrices. Therefore, I gather these results in the following section.

2.5 Metzler and Positive Matrices

The population structure of the SIS epidemic model considered in this thesis is modelled by a metapopulation network in which individuals migrate or travel between patches. In the model, the matrices describing the migration rates of susceptible and infected individuals are Metzler matrices. Therefore, the proofs of most results derived in Chapter 3 and Chapter 4 heavily rely on properties of Metzler matrices. Furthermore, some results in Chapter 4 require theories on positive matrices. Therefore, I collect the required results of Metzler and positive matrices in this section.

Recall from Definition 2.6 that a positive matrix has all its elements greater than 0 and a Metzler matrix has all its off diagonal elements greater than or equal to 0. Recall also from Definition 2.6 that a matrix $A = (a_{ij})$ is irreducible if its index set cannot be partitioned into two disjoint subset such that $a_{ij} = 0$ for i in one subset and j in the other subset. The following result on positive matrices can be found for example in [68, pages 21–23].

Theorem 2.11. *Let $A \in \mathbb{R}^{J\times J}$ and assume that A is positive. Then,*

(a) the spectral radius $\rho(A)$ of A is a positive eigenvalue of A.

(b) with $\rho(A)$ can be associated strictly positive left and right eigenvectors;

(c) $\rho(A) > |\lambda|$ for any eigenvalue λ of A such that $\lambda \neq \rho(A)$;

(d) the eigenvectors associated with $\rho(A)$ are unique to constant multiples;

(e) $\rho(A)$ is a simple root of the characteristic equation of A.

The results of Theorem 2.11 are used in Chapter 4 to prove Theorem 4.1. Now I provide some definitions and results regarding Metzler matrices.

Definition 2.8. (Definition 3.2 of [110]) For a real Metzler matrix M, $M = A+N$ is a *regular splitting* if A is a Metzler stable matrix (that is every eigenvalue of A has strictly negative real part) and N is a nonnegative matrix.

The following result of Bermann and Plemmons [35] and Varga [206], which relates stability of a Metzler matrix with the spectral radius of a matrix, can be found in Kamgang and Sallet [110].

Proposition 2.12. (*Proposition 3.3 of [110]*) *Let $M = A + N$ be a regular splitting of a real Metzler matrix M. Then M is Metzler stable if and only if $\rho(-NA^{-1}) < 1$.*

Furthermore, the following observations are made in [110] (see also proof of Theorem 1 of [204]) from Proposition 2.12 for any regular splitting of a Metzler matrix M.

Lemma 2.13.

$$s(M) < 0 \Longleftrightarrow \rho(-NA^{-1}) < 1,$$
$$s(M) = 0 \Longleftrightarrow \rho(-NA^{-1}) = 1.$$

It can be inferred from Lemma 2.13 that M has at least one eigenvalue with positive real part if and only if $\rho(-NA^{-1}) > 1$ [203, 204]. Proposition 2.12 and Lemma 2.13 can be used to show the local stability result of the DFE in Theorem 2.6 and to relate R_0 in (2.20) with the matrix $F - V$ in the Jacobian matrix (2.19). These connections can be made as follows. By the proof of Theorem 2.6 in [204], the matrix $F - V$ in the Jacobian matrix (2.19) is a Metzler matrix having a regular splitting, with F being a nonnegative matrix and $-V$ being a stable Metzler matrix. Thus, if $R_0 = \rho(FV^{-1}) < 1$, then, by Lemma 2.13 and Proposition 2.12, we know that $s(F - V)$ is negative. Then, by applying part 1 of Theorem 2.5, we have that the DFE is locally asymptotically stable. On the other hand, if $R_0 = \rho(FV^{-1}) > 1$, then by Lemma 2.13, $F - V$ has at least one eigenvalue with positive real part, and, by part 2 of Theorem 2.5, the DFE is unstable. As noted previously, the weakness of Theorem 2.6 is that it does not state the stability of the DFE for the case $R_0 = 1$. The reason for this is now apparent from Lemma 2.13, as $s(F - V) = 0$ in this case, and thus linear stability cannot determining the stability of the DFE.

When M is an irreducible Metzler matrix, further results are given by Seneta [189].

Theorem 2.14. (*Theorem 2.6 of [189]*) *Let $M \in \mathbb{R}^{J \times J}$ and assume that M is irreducible and Metzler. Then there exists an eigenvalue τ such that:*

(a) τ is real;

(b) with τ are associated strictly positive left and right eigenvectors, which are unique to constant multiples;

*(c) $\tau >$ **Re** λ for any eigenvalue λ, $\lambda \neq \tau$, of M (i.e τ is larger than the real part of any eigenvalue λ of M, $\lambda \neq \tau$);*

(d) τ is a simple root of the characteristic equation of M;

(e) $\tau \leq 0$ if and only if there exists $\mathbf{y} \geq \mathbf{0}, \neq \mathbf{0}$ such that $M\mathbf{y} \leq \mathbf{0}$, in which case $\mathbf{y} > \mathbf{0}$; and $\tau < 0$ if and only if there is inequality in at least one position in $M\mathbf{y} \leq \mathbf{0}$;

(g) $\tau < 0$ if and only if $-M^{-1} > 0$.

The eigenvalue τ in Theorem 2.14 is called the *dominant* eigenvalue of M. The migration rate matrices of the model studied in this thesis are irreducible Metzler matrices. Thus, part (a) of Theorem 2.14 ensures that the dominant eigenvalue of these matrices are real. A Metzler matrix M can be related with the matrix $exp(Mt), t > 0$, when the matrix $exp(Mt)$ is defined, as shown below.

Theorem 2.15. (*Theorem 2.7 of [189]*) *A Metzler matrix M is irreducible if and only if* $exp(Mt) > \mathbf{0}$ *for all* $t > 0$. *In this case*

$$exp(Mt) = exp(\tau t)\mathbf{w}\mathbf{v}' + O(e^{\bar{\tau}t}),$$

elementwise as $t \to +\infty$, *where* $\mathbf{w}$ *and* $\mathbf{v}'$ *are the positive right and left eigenvectors of M corresponding to the dominant eigenvalue* τ *of M, normed so that* $\mathbf{v}'\mathbf{w} = 1$ *and* $\bar{\tau} < \tau$.

One of the applications of Theorem 2.15 is to show that the system $d\mathbf{z}/dt = M\mathbf{z}$, where M is an irreducible Metzler matrix with 0 as the dominant eigenvalue, has a unique equilibrium which is globally asymptotically stable. This is because the solution of $d\mathbf{z}/dt = M\mathbf{z}$ with initial condition $\mathbf{z}(0)$ is given by $\mathbf{z}(t) = exp(Mt)\mathbf{z}(0)$ and Theorem 2.15 ensures that, asymptotically, the solution converges to the constant solution $\mathbf{w}\mathbf{v}'\mathbf{z}(0)$. System $d\mathbf{z}/dt = M\mathbf{z}$ corresponds to the disease–free system of the ODE model studied in this thesis. Another application of Theorem 2.15 is that it can be used to approximate the initial growth or decay of the disease, since linearisation of system 2.18 at the DFE decouples the equations corresponding to the diseased states of the ODE. The system for the diseased states is given by $d\mathbf{y}/dt = (F - V)\mathbf{y}$, where $F - V$, as given in (2.19), is a Metzler matrix. Thus, if $F - V$ is irreducible, then Theorem 2.15 states that the solution $\mathbf{y}(t) = exp((F - v)t)\mathbf{y}(0)$ is positive for $\mathbf{y}(0) > \mathbf{0}$ and if $s(F - V) < 0$, then the disease decays, but if $s(F - V) > 0$, then there will be growth in at least one component of the solution $\mathbf{y}(t)$.

Another useful property of Metzler matrices is the following result which states that the dominant eigenvalue of an irreducible Metzler matrix is bounded.

Corollary 2.16. (*Corollary 1 of Theorem 2.8 of [189]*) *Suppose* $M \in \mathbb{R}^{J\times J}$ *is an irreducible Metzler matrix with dominant eigenvalue* τ. *Then*

$$\min_i \sum_{j=1}^{J} m_{ij} \leq \tau \leq \max_i \sum_{j=1}^{J} m_{ij},$$

with a similar result for the columns.

The result of Corollary 2.16 can be used to show that an irreducible Metzler matrix, M, is stable. Since, if either the maximum of the column sums or the maximum of the row sums of M is negative, then the dominant eigenvalue is negative, and M is stable.

In addition to the above stated results on positive and Metzler matrices, I collect one more result concerning the comparison of the spectral radius of two nonnegative matrices.

Corollary 2.17. (*Corollary 2.7 of [191]*) *Let $A \in \mathbb{R}^{J\times J}$ and let A be an irreducible. If $A \geq B \geq \mathbf{0}$ and $A \neq B$, then $\rho(A) > \rho(B)$.*

Corollary 2.17 is used in Chapter 3, to compare the basic reproduction number R_0 and the parameter $\mathscr{T}_0$ which is used in the global stability result of the DFE.

2.6 Convex Optimisation and M–Matrices

Chapter 4 of this thesis deals with two convex optimisation problems to determine the optimal migration patterns for susceptible individuals. This section provides the necessary background materials for the setting of these two problems and to aid with the proofs of the results presented in the chapter. I will begin with the definition of a convex function and then a convex optimisation problem.

Definition 2.9. (Definition 3.1.1 of [37]) Let X be a subset of $\mathbb{R}^J$. A function $f : X \to \mathbb{R}$ is called *convex* if the domain X of f is a convex set and if for all $\mathbf{x}$, $\mathbf{y}$ in X, and θ with $0 \leq \theta \leq 1$, we have

$$f(\theta\mathbf{x}+(1-\theta)\mathbf{y}) \leq \theta f(\mathbf{x})+(1-\theta)f(\mathbf{y}).$$

Geometrically, this inequality means that the line segment between $(\mathbf{x}, f(\mathbf{x}))$ and $(\mathbf{y}, f(\mathbf{y}))$, which is the chord from $\mathbf{x}$ to $\mathbf{y}$, lies above the graph of f. With this definition for a convex function, a convex optimisation function is defined as follows (see for example Section 4.2.1 of Boyd and Vandenberghe [37]).

Definition 2.10. A *convex optimisation problem* is one of the form

$$\begin{aligned} &\text{minimise } f_0(\mathbf{x}) \\ &\text{subject to } f_i(\mathbf{x}) \leq 0, \quad i = 1,\ldots,J, \\ &\qquad \mathbf{a}_i'\mathbf{x} = b_i, \quad i = 1,\ldots,p, \end{aligned} \tag{2.24}$$

where $\mathbf{x} \in \mathbb{R}^J$, $\mathbf{a}_i \in \mathbb{R}^J$, $b_i \in \mathbb{R}, i = 1,\ldots,p$ and the functions $f_i(\mathbf{x}) : \mathbb{R}^J \to \mathbb{R}, i = 0,\ldots,J$ are convex.

The function $f_0(\cdot)$ is called the *objective function*, the functions $f_i(\cdot)$ are called the *inequality constraint functions*, and the functions $h_i(\mathbf{x}) = \mathbf{a}_i'\mathbf{x} - b_i$ are called the *equality constraint functions*. Let D be the set which contains all points for which the objective and all constraint functions are defined. Then D is called the *domain* of the optimisation problem (2.24). A point $\mathbf{x} \in D$ is *feasible* if it satisfies the constraints $f_i(\mathbf{x}) \leq 0, i = 1,\ldots,J$, and $h_i(\mathbf{x}) = 0, i = 1,\ldots,p$. The problem (2.24) is said to be feasible if there exists at least one feasible point, and *infeasible* otherwise. The set of all feasible points is called the *feasible set* or the *constraint set*. The feasible set is convex, since it is the

intersection of the domain of the problem, which is a convex set. The *optimal value* p^* of the problem (2.24) is defined as

$$\mathbf{x}^* = \inf\{f_0(\mathbf{x}) \mid f_i(\mathbf{x}) \leq 0, i = 1\ldots, J,\ h_i(\mathbf{x}) = 0, i = 1, \ldots, p\}$$

A point $\mathbf{x}^*$ is called an *optimal point* or a *solution* of the problem (2.24) if $\mathbf{x}^*$ is feasible and $f_0(\mathbf{x}^*) = p^*$. A feasible point $\mathbf{x}$ is said to be *locally optimal* if there is an $R > 0$ such that

$$f_0(\mathbf{x}) = \inf\{f_0(\mathbf{z}) \mid \mathbf{z} \text{ is feasible},\ |\mathbf{z} - \mathbf{x}| \leq R\}.$$

Roughly speaking, this means $\mathbf{x}$ minimises $f_0(\cdot)$ over nearby points in the feasible set. In this thesis, optimal will mean globally optimal. A fundamental property of convex optimisation is that any locally optimal point is also (globally) optimal. Therefore, if the objective function $f_0(\cdot)$ of problem (2.24) is differentiable, then we can use the first order Taylor approximation of $f_0(\cdot)$ near a point in the domain of $f_0(\cdot)$ to determine an optimal criterion for $f_0(\cdot)$. More precisely, the following result, given in Section 4.2.3 of [37]), can be used to determine an optimal condition for problem (2.24).

Lemma 2.18. (*Section 3.1 of* [37]) *Consider the optimisation problem* (2.24) *and assume that the objective function* $f_0(\mathbf{x})$ *is differentiable, so that for all* $\mathbf{x}, \mathbf{y}$ *in* $\mathbb{R}^J$*, we have*

$$f_0(\mathbf{y}) \geq f_0(\mathbf{x}) + \sum_{i=1}^{J} (y_i - x_i) \frac{\partial f_0(\mathbf{x})}{\partial y_i}.$$

Let X denote the feasible set. That is

$$X = \{\mathbf{x} \mid f_i(\mathbf{x}) \leq 0, i = 1\ldots, J, h_i(\mathbf{x}) = 0, i = 1, \ldots, p\}.$$

Then $\mathbf{x}$ *is optimal if and only if* $\mathbf{x} \in X$ *and*

$$\sum_{i=1}^{J} (y_i - x_i) \frac{\partial f_0(\mathbf{x})}{\partial y_i} \geq 0 \tag{2.25}$$

for all $\mathbf{y}$ *in X.*

Theorem 2.18 is applied to find an optimal solution for the two optimisation problems studied in Chapter 4. However, the domain of the objective function of these two problems is a set of matrices. Specifically the objective function of the first problem is in the form $\rho(DA)$, where the inverse of A is an M–matrix (definition provided below) and D is a diagonal matrix. In the second problem the objective function is in the form $s(A + D)$, where A is a Metzler matrix and D is a diagonal matrix. Therefore, in order to apply Theorem 2.18 it requires that these two objective functions be convex. The following two theorems, which concern with spectral functions, are used to show that the two objective functions are convex. But, firstly, I will give the definition of an M–matrix.

An M–matrix is closely related to a Metzler matrix as defined below.

Definition 2.11. (Definition 1.9 of [68]) Let $A \in \mathbb{R}^{J\times J}$ be such that $a_{ij} \leq 0$ for all $i, j = 1,\ldots,J$, $i \neq j$. Then A is called an *M–matrix* if A is invertible and A^{-1} is nonnegative.

Thus, if $A = -M$ where M is Metzler, then A is an M–matrix if it is nonsingular and if its inverse is nonnegative. Now, denote by D_J^+ the set of $J \times J$ nonnegative diagonal matrices. The following theorem provides the condition required for the spectral radius of DA to be a convex function on D_J^+.

Theorem 2.19. (*Theorem 4.3 of [81]*) *Let A^{-1} be an M–matrix. Then $\rho(DA)$ is a convex functional on D_J^+.*

Similarly, the result below states the conditions required for the spectral abscissa of $A+D$ to be a convex function of diagonal matrices.

Theorem 2.20. (*[54]*) *Let D be a diagonal real $J \times J$ matrix and let A be a Metzler matrix. Then, $\rho(A+D)$ is a convex function of D.*

If a matrix has a simple eigenvalue, then the derivative of the eigenvalue with respect to the elements of the matrix can be related to the corresponding left and right eigenvectors as shown below.

Corollary 2.21. (*Corollary 2.4 of* [*195*]) *Let $A \in \mathbb{R}^{J\times J}$ and let λ be a simple eigenvalue of A. Let* $\mathbf{x}$ *and* $\mathbf{y}$*,respectively, be the right and left eigenvectors of A corresponding to λ normalised, so that* $\mathbf{y}'\mathbf{x} = 1$. *Then*

$$\frac{\partial \lambda}{\partial a_{ij}} = y_i x_j,$$

for all $i, j = 1,\ldots,J$.

This result is used to derive the optimal condition for the second optimisation problem studied in Chapter 4.

2.7 Closed Migration Process

As mentioned in Section 2.5, the population structure of the epidemic model concerned in this thesis is modelled by a metapopulation, where individuals migrate between patches. Since the population is assumed finite, the population will eventually be disease free. When this happens, the CTMC behaves as a closed migration process and the equilibrium distribution of the population can be determined by applying Theorem 2.22 below. For completeness, I describe the closed migration process and its equilibrium distribution in this section.

Consider a population consisting of N individuals where each individual is located at one of J geographically distinct patches. For $j = 1,2,\ldots,J$, let $n_j(t)$ denote the number of individuals at group j at time t. Let $\mathbf{n}(t)$ denote $(n_1(t),\ldots,n_J(t))$, and let $(\mathbf{n}(t);t \geq 0)$ be a continuous–time Markov chain with state space $S = \{\mathbf{n} \mid n_j \geq 0, j = 1,2,\ldots,J; \sum_{j=1}^{J} n_j = N\}$ and transition rates

$$q(\mathbf{n}, \mathbf{n} - \mathbf{e}_j + \mathbf{e}_k) = \lambda_{jk}\phi_j(n_j), \tag{2.26}$$

where $\phi_j(0) = 0$ and $\lambda_{jj} = 0$. The vector $\mathbf{e}_j$ is the J dimensional unit row vector whose j–th entry is 1 and 0 elsewhere. The function $\phi_j(n)$ represents the exit rate at patch j when there are n individuals present at patch j. The parameter λ_{jk} is the migration rate from patch j to k. It is assumed that the parameters λ_{jk} allow an individual to pass between any two groups, either directly or indirectly via a chain of other groups. This implies that the Markov chain $(\mathbf{n}(t);t \geq 0)$ is irreducible.

If $N = 1$ then the single individual in the system performs a random walk on the set of groups. If $\alpha_1, \alpha_2, \ldots, \alpha_j$ is the unique collection of positive numbers summing to unity which satisfy

$$\alpha_j \sum_{k=1}^{J} \lambda_{jk} = \sum_{k=1}^{J} \alpha_k \lambda_{kj} \quad j = 1,\ldots,J, \tag{2.27}$$

then α_j is the equilibrium probability that the individual is in node j. For the model concerned in this thesis, α_j is given by the proportion of susceptibles at patch j at the DFE of the approximating ODE model.

The following theorem which can be found for example in [115, page 41] and [190, 14] gives the equilibrium distribution of the Markov chain $(\mathbf{n}(t);t \geq 0)$.

Theorem 2.22. *The equilibrium distribution of* $(\boldsymbol{n}(t);t \geq 0)$ *is given by*

$$\pi(\boldsymbol{m}) = B_N \prod_{j=1}^{J} \frac{\alpha_j^{n_j}}{\prod_{r=1}^{n_j} \phi_j(r)}, \quad \boldsymbol{n} \in S, \tag{2.28}$$

where B_N is a normalizing constant, chosen so that the distribution sums to unity.

Note that if the solution $\alpha_1, \alpha_2, \ldots, \alpha_J$ of equations (2.27) is not normalized to sum to unity the expression (2.28) remains valid. In this case the normalizing constant B_N will change accordingly. Theorem 2.22 is used to derive the equilibrium distribution of the Markov chain studied in this thesis when the population is disease free.

Chapter 3

Spread of an SIS Epidemic in a Metapopulation

This chapter introduces the SIS epidemic model studied in this thesis. A continuous–time Markov chain is used to describe the model. The population structure is modelled by a metapopulation network. Under certain assumptions on the migration rates of individuals, conditions under which the disease becomes endemic are determined. An approximation of the distribution of the population at the endemic level is also determined. The analysis is based on a deterministic and a diffusion approximation to the Markov chain model.

3.1 Introduction

An important factor in modelling the spread of infectious diseases in human populations is the social and spatial structure of the populations. Humans spend much of their time in groups such as workplaces, shopping centres, cities and rural areas. However, an individual's membership of a particular group is not fixed, rather it changes over time. This structure determines two paths for disease to spread through the population. Disease is spread between individuals in the same group by contact between infected and susceptible individuals, and is spread from one group to another by the migration of infected individuals.

This type of population structure can be modelled by a metapopulation network [93, 134, 135] where the groups (or patches) of the network represent the groups and links represent the path that migrating individuals follow. There have been a number of attempts to model the spread of disease

in real populations using metapopulation networks. Some were developed considering the type of mobility that individuals make between the subgroups, either long distance travel [104, 56, 55], commuter movements [34, 61, 91, 112] or mixture of both [18]. Often these models rely on transportation data to estimate mobility. Due to the size and complexity of the populations involved, these models needed to be analysed numerically.

Other researchers have focused on simpler models incorporating similar population structure with the aim of gaining a deeper understanding of the factors affecting an epidemic's progress [22, 24, 25, 52, 50, 52, 131, 152, 185]. These models generally take the form of a continuous–time Markov chain with mobility of individuals modelled by transition rates between groups. A similar approach is used to construct the model studied here.

Much of the above–cited research concerns disease following the Susceptible–Infective–Recovered (SIR) pattern. That is, if a susceptible individual becomes infected, then, after a certain period of time, they will either recover with immunity to the disease or be removed from the population. The SIR pattern has been used to model diseases such as SARS [104] and HIV [185]. In this work I study the spread of diseases following the Susceptible–Infective–Susceptible (SIS) pattern. The SIS pattern differs from the SIR pattern in that infected individuals recover with no immunity and become immediately susceptible to reinfection. Certain human diseases such as gonorrhea [101], common cold and tuberculosis [4, 60] follow the SIS pattern.

I model the spread of an SIS type epidemic in a metapopulation network using a continuous–time Markov chain. It is assumed that the network consists of a finite number of groups and the total population size is fixed. Individuals move around the network so that population size of each group varies. In this model, the rate at which individuals migrate (or travel) between groups depends on the origin, destination and the disease status of the individual. A susceptible individual in a given group becomes infected at a rate proportional to the number of infected individuals in that group. This amounts to assuming density–dependent transmission [33]. The model formulated in this study is closely related to the frequency–dependent SIS models studied in [131, 3]; I will say more about the connection as I build the model.

For the SIS network model described, I am primarily interested in determining the conditions under which the disease becomes endemic and the distribution of the population at an endemic level. Previous analyses of the SIS epidemic model for an unstructured population have used the equilibrium distribution of an approximating stochastic model to approximate the distribution of the population at the endemic level [123, 147, 53]. Here I use an approximating ODE model and an approximating diffusion model, which are valid for large population sizes, to analyse the endemic level of infection.

Section 3.2 provides a formal mathematical description of the SIS network model and derive its

approximating ODE model. Equilibrium points of the ODE are analysed and conditions under which the disease becomes endemic is established in this section. In Section 3.3, an Ornstein-Uhlenbeck (OU) process approximation is derived which describes the distribution of the population around an endemic point of the ODE. Finally, in Section 3.4 I make some concluding comments regarding the analysis made in this chapter.

3.2 The Markov Chain and its ODE Limit

Here I present a complete mathematical description of the SIS epidemic model studied in this work and its ODE limit. I consider a population of size N where each individual is located at one of J geographically distinct locations (patches). Each individual may be either susceptible or infected. Let $m_j(t)$ and $n_j(t)$ denote the number of infected and susceptible individuals, respectively, at time t and patch j, $j = 1,\ldots,J$. Let $(\mathbf{m}(t),\mathbf{n}(t))$ denote $(m_1(t),\ldots,m_J(t),n_1(t),\ldots,n_J(t))$. Then the dynamics of the population is modelled using the continuous–time Markov chain $((\mathbf{m}(t),\mathbf{n}(t));$
$t \geq 0)$ with state space

$$S_N = \left\{ (\mathbf{m},\mathbf{n}) \mid m_j \geq 0; n_j \geq 0; j = 1,\ldots,J; \sum_{j=1}^{J} (m_j + n_j) = N \right\}.$$

Individuals within each patch are assumed to mix homogeneously and the disease is spread within a patch through contact between susceptible and infected individuals. In this model, a contact refers to the actual event of a transmission opportunity, but for some models a contact may indicate the pairing of two individuals during which several transmission opportunities can arise (see for example Chapter 10 of [65]). The latter type of contacts are usually modelled using a network in which each node represents an individual and each edge represents a contact (or connection) between two individuals. Translating homogeneous mixing assumption to such a network implies that the network is complete in which each node is connected to every other node in the network. If a complete network is used to model the contacts within each patch, the per contact rate per unit of time within a patch is equal to $m_j + n_j - 1$ (see for example [29]). However, without using such a network to model the contacts within a patch, homogeneous mixing implies that the contact rate per susceptible per unit time is proportional to $m_j + n_j$ [65, Chapter 1][15, Chapter 6] and [179]. The constant, κ_j, of this proportionality is scaled by the area occupied by the total population at patch j, which is assumed proportional to N. This leads to density–dependent transmission [33]. The probability that the contact is with an infected individual is $m_j/(m_j + n_j)$. The probability, p, that this contact in fact leads to disease transmission is assumed constant. Thus, the force of infection per susceptible individual in patch j is $(\kappa_j p m_j)/N$. Consequently, the infection rate of a susceptible individual at patch j and time t

is $\beta_j m_j/N$, where $\beta_j = \kappa_j p > 0$ is the disease transmission rate. In contrast to the above assumption on the contact rate, the SIS model studied in [131, 3] has a constant contact rate, which leads their model to have frequency–dependent transmission rates.

Infected individuals at patch j recover at rate $\gamma_j > 0$ so that the average infectious period is $1/\gamma_j$. Once an infective individual recovers, it immediately becomes susceptible to further infection. The disease is spread between patches by the migration of individuals. The migration rates from patch j to patch k for infected and susceptible individuals are η_{jk} and λ_{jk}, respectively. To summarize, the nonzero transition rates of the Markov chain are

$$q_{(\mathbf{m},\mathbf{n}),(\mathbf{m},\mathbf{n})-\mathbf{e}_j+\mathbf{e}_k} = \eta_{jk} m_j, \quad j \neq k, \tag{3.1}$$

$$q_{(\mathbf{m},\mathbf{n}),(\mathbf{m},\mathbf{n})-\mathbf{e}_{J+j}+\mathbf{e}_{J+k}} = \lambda_{jk} n_j, \quad j \neq k, \tag{3.2}$$

$$q_{(\mathbf{m},\mathbf{n}),(\mathbf{m},\mathbf{n})+\mathbf{e}_j-\mathbf{e}_{J+j}} = \frac{\beta_j m_j n_j}{N}, \tag{3.3}$$

$$q_{(\mathbf{m},\mathbf{n}),(\mathbf{m},\mathbf{n})-\mathbf{e}_j+\mathbf{e}_{J+j}} = \gamma_j m_j, \tag{3.4}$$

where $\mathbf{e}_i$ is the $2J$–dimensional unit row vector with a 1 at its i–th entry and 0 elsewhere. The Markov chain $((\mathbf{m}(t),\mathbf{n}(t)); t \geq 0)$ has an absorbing set

$$\bar{S}_N = \left\{ (\mathbf{0},\mathbf{n}) \mid n_j \geq 0; j = 1,\ldots,J; \sum_{j=1}^{J} n_j = N \right\}.$$

Any state in the absorbing set is called a disease–free state because it consists only of susceptible individuals. As the population size is fixed, the population will eventually enter a disease–free state with probability 1. However, the time taken to reach a disease–free state may be very long, so that the number of infected individuals may tend to a quasi–equilibrium prior to the population entering a disease–free state. I am interested in determining a quasi–equilibrium of the Markov chain as it describes the behaviour of the population at an endemic level. This is achieved by approximating the Markov chain by a deterministic model, assuming a large population, and using its fixed points to approximate an endemic level of the disease. More precisely, I approximate the scaled process defined by

$$((\mathbf{u}_N(t),\mathbf{v}_N(t)); N > 0) := \left(\frac{1}{N}(\mathbf{m}(t),\mathbf{n}(t)); t \geq 0 \right)$$

when N is large. Note that the scaled process takes values in $E_N := S_N/N \subset E := \{u_j \in [0,1], v_j \in$

$[0,1]; j = 1,\ldots,J; \sum_{j=1}^{J}(u_j+v_j) = 1\}$. Define the continuous function $f : E \times \mathbb{Z}^{2J} \mapsto [0,\infty)$ by

$$f((\mathbf{u},\mathbf{v}),l) = \begin{cases} \eta_{jk}u_j, & \text{if } l = -\mathbf{e}_j + \mathbf{e}_k, \qquad j \neq k, \\ \lambda_{jk}v_j, & \text{if } l = -\mathbf{e}_{J+j} + \mathbf{e}_{J+k}, \quad j \neq k, \\ \beta_j u_j v_j, & \text{if } l = \mathbf{e}_j - \mathbf{e}_{J+j}, \\ \gamma_j u_j, & \text{if } l = -\mathbf{e}_j + \mathbf{e}_{J+j}, \\ 0, & \text{otherwise.} \end{cases}$$

The transition rates (3.1) – (3.4) can now be expressed as

$$q((\mathbf{m},\mathbf{n}),(\mathbf{m},\mathbf{n})+l) = Nf\left(\frac{1}{N}(\mathbf{m},\mathbf{n}),l\right), \quad l \in \mathbb{Z}^{2J}, \quad l \neq \mathbf{0}.$$

Therefore, the Markov chain $((\mathbf{m}(t),\mathbf{n}(t)); t \geq 0)$ satisfies Kurtz's definition (see Definition 2.4) of density–dependence. Theorem 2.2 can then be applied to show that the scaled process $((\mathbf{u}_N(t),\mathbf{v}_N(t)); N > 0)$ is approximated over any finite–time interval by a deterministic path which is defined on that time interval, for large N. Before stating this result, I will first establish the settings required for the statement of this result.

Let $b : E \mapsto \mathbb{R}^{2J}$ be defined as

$$b(\mathbf{u},\mathbf{v}) := \sum_{l \neq \mathbf{0}} l f((\mathbf{u},\mathbf{v}),l).$$

Then, $b(\mathbf{u},\mathbf{v})$ is given by

$$b(\mathbf{u},\mathbf{v}) = \begin{pmatrix} -\sum_{k\neq 1}^{J}\eta_{1k}u_1 + \beta_1 u_1 v_1 - \gamma_1 u_1 + \sum_{k\neq 1}^{J}\eta_{k1}u_k, \\ \vdots \qquad\qquad \vdots \qquad\qquad \vdots \qquad\qquad \vdots \\ -\sum_{k\neq J}^{J}\eta_{Jk}u_J + \beta_J u_J v_J - \gamma_J u_J + \sum_{k\neq J}^{J}\eta_{kJ}u_k, \\ -\sum_{k\neq 1}^{J}\lambda_{1k}v_1 - \beta_1 u_1 v_1 + \gamma_1 u_1 + \sum_{k\neq 1}^{J}\lambda_{k1}v_k, \\ \vdots \qquad\qquad \vdots \qquad\qquad \vdots \qquad\qquad \vdots \\ -\sum_{k\neq J}^{J}\lambda_{Jk}v_J - \beta_J u_J v_J + \gamma_J u_J + \sum_{k\neq J}^{J}\lambda_{kJ}v_k \end{pmatrix}. \tag{3.5}$$

Note that for each $l \neq \mathbf{0}$, $f((\mathbf{u},\mathbf{v}),l)$ is a polynomial in $(\mathbf{u},\mathbf{v})$. As E is a bounded set, $b(\cdot)$ is a Lipschitz vector field. Let K be the Lipschitz constant associated with $b(\cdot)$. Let $(\mathbf{u}(t),\mathbf{v}(t))$ be the unique solution of

$$\frac{du_j}{dt} = -\sum_{k\neq j}^{J}\eta_{jk}u_j + \beta_j u_j v_j - \gamma_j u_j + \sum_{k\neq j}^{J}\eta_{kj}u_k, \tag{3.6}$$

$$\frac{dv_j}{dt} = -\sum_{k\neq j}^{J}\lambda_{jk}v_j - \beta_j u_j v_j + \gamma_j u_j + \sum_{k\neq j}^{J}\lambda_{kj}v_k, \tag{3.7}$$

for $j = 1,\ldots,J$, subject to $(\mathbf{u}(0),\mathbf{v}(0)) = (\mathbf{u}^0,\mathbf{v}^0)$. Then, the following theorem provides the required approximation for the scaled process $((\mathbf{u}_N(t),\mathbf{v}_N(t)); N > 0)$ by the solution of the ODE (3.6)–(3.7).

Theorem 3.1. *Let $(\boldsymbol{u}(t),\boldsymbol{v}(t))$ be the unique solution of the ODE* (3.6)–(3.7) *starting at $(\boldsymbol{u}(0),\boldsymbol{v}(0)) = (\boldsymbol{u}^0,\boldsymbol{v}^0) \in E$. Let T be positive and finite such that for all $0 \le t \le T$, $(\boldsymbol{u}(t),\boldsymbol{v}(t)) \in E$. Then, for all $\varepsilon > 0$,*

$$\mathbb{P}\left(\sup_{t\le T}|(\boldsymbol{u}_N(t),\boldsymbol{v}_N(t)) - (\boldsymbol{u}(t),\boldsymbol{v}(t))| > \varepsilon\right) \le \frac{36CTe^{2KT}}{N\varepsilon^2} + \mathbb{P}(\Omega_0^c), \tag{3.8}$$

where

$$\Omega_0 := \left\{|(\boldsymbol{u}_N(0),\boldsymbol{v}_N(0)) - (\boldsymbol{u}^0,\boldsymbol{v}^0)| \le \frac{\varepsilon e^{-KT}}{3}\right\} \tag{3.9}$$

and

$$C := 2\left[\sum_{j=1}^{J}(\sum_{k\ne j}^{J}(\eta_{jk}+\lambda_{jk}) + \beta_j + \gamma_j)\right].$$

Proof. The result is proved using Theorem 2.2. Set $\delta = \varepsilon e^{-KT}/3$, where $\varepsilon > 0$ and K is the Lipschitz constant associated with $b(\mathbf{u},\mathbf{v})$ in equation (3.5). Therefore, the event Ω_0 defined in (2.5) is given by

$$\Omega_0 := \left\{|(\mathbf{u}_N(0),\mathbf{v}_N(0)) - (\mathbf{u}^0,\mathbf{v}^0)| \le \frac{\varepsilon e^{-KT}}{3}\right\}.$$

As the Markov chain is density–dependent, the drift vector $\beta(\cdot)$ defined in equation (2.3) is given by $b(\cdot)$. Hence, the probability of the event Ω_1^c defined in (2.5) is 0. For each $(\mathbf{m},\mathbf{n}) \in S_N$, the corresponding variance is given by

$$\alpha(\mathbf{m},\mathbf{n}) = \sum_{l\ne\mathbf{0}} \frac{|l|^2}{N} f\left(\frac{1}{N}(\mathbf{m},\mathbf{n}),l\right),$$

and the event Ω_2 defined in equation (2.6) is given by

$$\Omega_2 = \left\{\int_0^T \sum_{l\ne\mathbf{0}} \frac{|l|^2}{N} f\left(\frac{1}{N}(\mathbf{m},\mathbf{n}),l\right)dt \le AT\right\}.$$

Now, for each $(\mathbf{m},\mathbf{n}) \in S_N$, we have $\alpha(\mathbf{m},\mathbf{n}) \le C/N$, where C as given in the theorem. Choosing $A = C/N$ in Ω_2 we have $\mathbb{P}(\Omega_2^c) = 0$. Then, by applying Theorem 2.2 the result follows. □

Condition (3.9) specifies that the distance between the initial value of the scaled process and the initial value of the deterministic path must be less than or equal to a given value. In practice, we can choose the initial value of the deterministic path, $(\mathbf{u}^0,\mathbf{v}^0)$, to be equal to the initial value of the scaled process, $(\mathbf{u}_N(0),\mathbf{v}_N(0))$, for all N, so that the probability of Ω_0^c is zero. The constant C/N appearing in (3.8) provides an upper bound for $\alpha(\cdot)$, which is the variance of the jump of the Markov chain when it makes a transition from a given state to another state. Consequently, $(CT)/N$ provides an upper bound for the integral in Ω_2. It remains to determine the Lipschitz constant, K, of the vector field $b(\cdot)$, to give an explicit expression for the bound in (3.8).

To find the Lipschitz constant, K, let $|\mathbf{x}|$ be the Euclidean norm of an n–dimensional vector $\mathbf{x}$. More precisely, $|\mathbf{x}| = (x_1^2 + \cdots + x_n^2)^{1/2}$. Let $\mathbf{z} = (\mathbf{u}, \mathbf{v})$ and $\tilde{\mathbf{z}} = (\tilde{\mathbf{u}}, \tilde{\mathbf{v}})$ be two points in E. Then, for each of the first J components of $b(\cdot)$ we have,

$$\begin{aligned}|b_j(\mathbf{z}) - b_j(\tilde{\mathbf{z}})| &= \left| \sum_{k\neq j}^{J} \eta_{jk}(\tilde{u}_j - u_j) + \sum_{k\neq j}^{J} \eta_{kj}(u_k - \tilde{u}_k) + \gamma_j(\tilde{u}_j - u_j) + \beta_j v_j(u_j - \tilde{u}_j) + \beta_j \tilde{u}_j(v_j - \tilde{v}_j) \right| \\ &\leq |\tilde{u}_j - u_j| \sum_{k\neq j}^{J} \eta_{jk} + \sum_{k\neq j}^{J} \eta_{kj}|u_k - \tilde{u}_k| + \gamma_j|\tilde{u}_j - u_j| + \beta_j v_j|u_j - \tilde{u}_j| + \beta_j \tilde{u}_j|v_j - \tilde{v}_j|\end{aligned}$$

Since $\tilde{u}_j \in [0,1]$ and $v_j \in [0,1]$ and the inequality $|z_j - \tilde{z}_j| \leq |\mathbf{z} - \tilde{\mathbf{z}}|$ holds for all $j = 1, \ldots, 2J$, we have

$$\begin{aligned}|b_j(\mathbf{z}) - b_j(\tilde{\mathbf{z}})| &\leq |\mathbf{z} - \tilde{\mathbf{z}}| \sum_{k\neq j}^{J} \eta_{jk} + |\mathbf{z} - \tilde{\mathbf{z}}| \sum_{k\neq j}^{J} \eta_{kj} + \gamma_j|\mathbf{z} - \tilde{\mathbf{z}}| + 2\beta_j|\mathbf{z} - \tilde{\mathbf{z}}| \\ &= \left(\sum_{k\neq j}^{J} \eta_{jk} + \sum_{k\neq j}^{J} \eta_{kj} + \gamma_j + 2\beta_j \right) |\mathbf{z} - \tilde{\mathbf{z}}|, \quad j = 1, \ldots, J.\end{aligned}$$

Similarly for the last J components of $b(\cdot)$, we have

$$|b_l(\mathbf{z}) - b_l(\tilde{\mathbf{z}})| \leq \left(\sum_{k\neq l}^{J} \lambda_{lk} + \sum_{k\neq l}^{J} \lambda_{kl} + \gamma_l + 2\beta_l \right) |\mathbf{z} - \tilde{\mathbf{z}}|, \quad l = 1, \ldots, J.$$

Let

$$U_j = \sum_{k\neq j}^{J} \eta_{jk} + \sum_{k\neq j}^{J} \eta_{kj} + \gamma_j + 2\beta_j, \quad j = 1, \ldots, J,$$

and

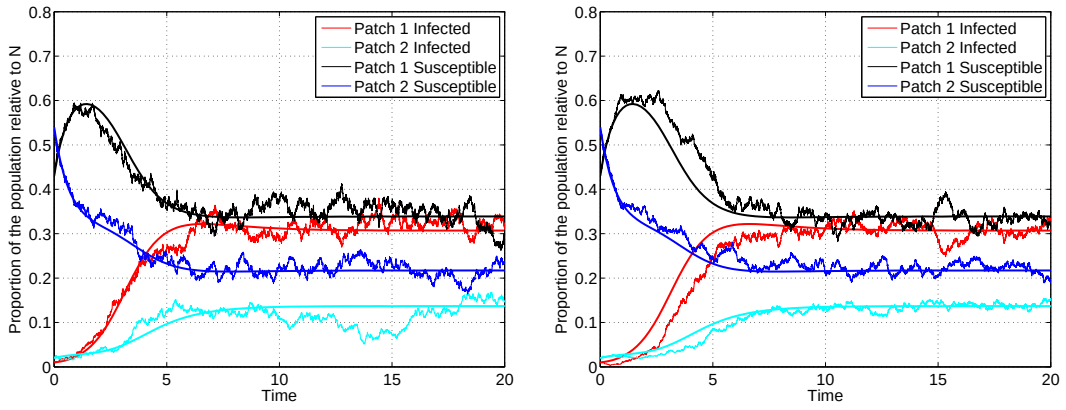
$$V_l = \sum_{k\neq l}^{J} \lambda_{lk} + \sum_{k\neq l}^{J} \lambda_{kl} + \gamma_l + 2\beta_l, \quad l = 1, \ldots, J.$$

Then, the Lipschitz constant of $b(\cdot)$ is given by $K = [\sum_{j=1}^{J} (U_j)^2 + \sum_{l=1}^{J} (V_l)^2]^{1/2}$. Using this expression for the Lipschitz constant and by choosing the initial value of the ODE to be the same as that of the scaled process for all N, the error bound on the probability in (3.8) is given by $36CTe^{2KT}/(N\varepsilon^2)$. Thus, the error approaches to zero as N increases. However, the computed errors can be too large for any practical application. As an example, consider a two patch model with parameter values $\beta_1 = \beta_2 = 1.5$, $\gamma_1 = \gamma_2 = 1$, $\lambda_{12} = \lambda_{21} = 0.5$, $\eta_{12} = 0.2$, $\eta_{21} = 0.1$ and set $T = 1$, $\varepsilon = 0.1$ and $N = 10^9$. For these values, the error is 572.0056, which is too large even for a population size as large as 10^9. On the other hand, increasing T from 1 to 2, the error increases to 1.44×10^{11}. This huge increase in the error is due to the fact that the error bound depends exponentially as well as linearly on the time horizon T.

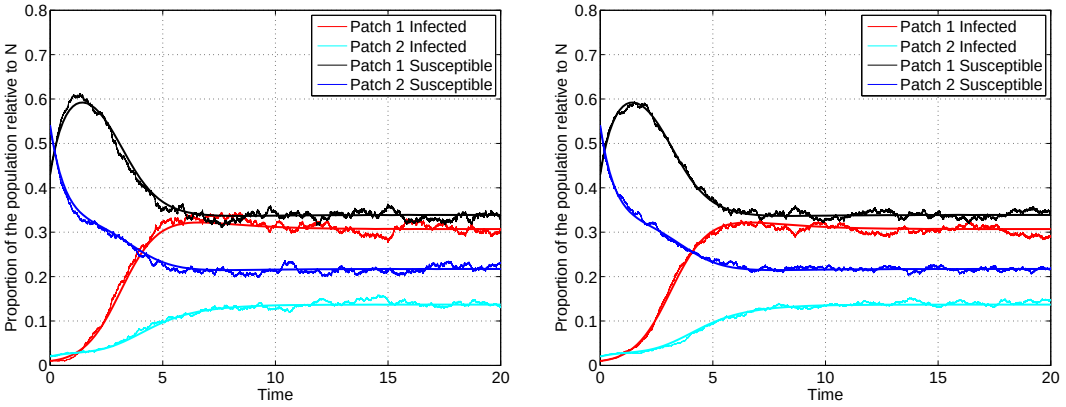
Despite the fact that the error bound is of little direct use, Theorem 3.1 ensures that, as the population size, N, becomes large, the proportion of susceptible and infected individuals at each patch relative to the population size is well approximated by the solution to the ODE given by (3.6) – (3.7),

provided that the scaled process starts close to the initial value of the ODE solution. A similar approach was used to study the stochastic SIR model proposed in [185]. However, they used Theorem 3.1 of Kurtz [125] to establish an ODE approximation for their Markov chain model. Here, I applied Theorem 4.1 of Darling and Norris [62] to derive the ODE approximation in Theorem 3.1, which provides an explicit expression for the error associated with the approximation, which is not possible from Kurtz's result. Nevertheless, obtaining the additional detail of the error bound in Theorem 3.1 is not particularly advantageous over Kurtz's result since the computed error bounds are of little practical use. However, the advantage of the method in [62] is that, unlike Kurtz's result which requires that the limiting deterministic trajectory be defined in an open set, such a restriction on the limiting deterministic path is not imposed in it, and this is the main reason behind choosing [62] over Kurtz [125]. Kurtz's result can easily be applied to the Markov chain $((\mathbf{m}(t),\mathbf{n}(t));t\geq 0)$ after eliminating one state variable from it. In this case, the approximating ODE has one dimension less than the ODE given in (3.6)–(3.7). Details of the derivation of the latter ODE is given in Section 3.3.

Figure 3.1 compares the sample paths of the scaled process with the corresponding trajectory of the limiting ODE for a two patch model as the population size, N, increases. The parameters used for the simulation are $\beta_1 = 4$, $\beta_2 = 3$, $\gamma_1 = 1.2$, $\gamma_2 = 1$, $\lambda_{12} = 0.5$, $\lambda_{21} = 1$, $\eta_{12} = 0.2$ and $\eta_{21} = 0.1$. It can be seen from the plots in Figure 3.1 that the stochastic process is well approximated by the deterministic trajectory as the population size gets large, thus confirming the result established in Theorem 3.1. However, as seen from the figure, there are some random fluctuations between the stochastic process and the deterministic trajectory. These fluctuations are not addressed in Theorem 3.1. In Section 3.3, I will show that these fluctuations can be modelled by a Gaussian diffusion in the large population limit. Before progressing to model these fluctuations, I will first analyse the equilibrium points of the ODE given by (3.6)–(3.7).



(a) $N = 500$ (b) $N = 1000$



(c) $N = 3000$ (d) $N = 5000$

Figure 3.1: Comparision of the sample paths of the scaled process of a two patch model with the corresponding deterministic trajectory as the population size, N, increases. The plots indicate that the scaled process is well approximated by the deterministic trajectory as N gets large.

3.2.1 Equilibrium Points and their Stability

As previously mentioned, the population will enter a disease–free state in the long run with probability 1. Once the Markov chain enters the disease–free set, the population can be described by a closed migration process (see Section 2.7). However, before reaching a disease–free state, the population may spend a very long time at a quasi–equilibrium. As the Markov chain model can be approximated by the solution to an ODE, the equilibrium points of the ODE provide a means of approximating this quasi–equilibrium. It is the purpose of this section to investigate equilibrium points of the ODE (3.6)–(3.7) and their stability.

Define matrices Λ and H as

$$\Lambda_{jk} = \begin{cases} \lambda_{kj}, & j \neq k, \\ -\sum_{l \neq j}^{J} \lambda_{jl}, & j = k, \end{cases} \quad \text{and} \quad H_{jk} = \begin{cases} \eta_{kj}, & j \neq k, \\ -\sum_{l \neq j}^{J} \eta_{jl}, & j = k. \end{cases}$$

The matrices Λ' and H' are Q–matrices (or transition rate matrices) of the Markov processes that describe the migration of a single individual in the network when the population consists of one susceptible and infected individual, respectively. Throughout this thesis, Λ and H are assumed irreducible. This implies that the J patches of the network cannot be separated into two distinct populations such that there is no immigration of susceptible or infected individuals from one population to the other. Note that the off diagonal elements of Λ and H are nonnegative so they are Metzler matrices. Then, under the assumption of irreducibility, and applying parts (c) and (d) of Theorem 2.14 it is known, for both Λ and H, that 0 is a simple eigenvalue with maximum real part. This fact will often be used when analysing equilibrium points of the ODE.

An equilibrium point of system (3.6)–(3.7) is a solution to the equations

$$-\sum_{k\neq j}^{J}\eta_{jk}u_j+\beta_j u_j v_j-\gamma_j u_j+\sum_{k\neq j}^{J}\eta_{kj}u_k=0, \tag{3.10}$$

$$-\sum_{k\neq j}^{J}\lambda_{jk}v_j-\beta_j u_j v_j+\gamma_j u_j+\sum_{k\neq j}^{J}\lambda_{kj}v_k=0, \tag{3.11}$$

for $(\mathbf{u},\mathbf{v})\in E$. Let $(\mathbf{u}^*,\mathbf{v}^*)$ denote an equilibrium point of the system. An equilibrium point is called a disease–free equilibrium (DFE) if $\mathbf{u}^*=\mathbf{0}$. Otherwise, it is called an endemic equilibrium (EE). The following theorem shows that system (3.6) – (3.7) always has a unique DFE.

Theorem 3.2. *System* (3.6) – (3.7) *has a unique DFE given by* $(\boldsymbol{0},\boldsymbol{v}^*)$ *where* $\Lambda\boldsymbol{v}^*=\boldsymbol{0}$ *and* $\boldsymbol{1}'\boldsymbol{v}^*=1$.

Proof. With $u_j=0$ for all $j=1,\ldots,J$, the system of equations (3.11) can be expressed as $\Lambda\mathbf{v}=\mathbf{0}$. As 0 is an eigenvalue of Λ, we can apply part (b) of Theorem 2.14 to conclude that the corresponding eigenvector is unique up to constant multiples and positive. The condition $\mathbf{1}'\mathbf{v}^*=1$ ensures that $(\mathbf{0},\mathbf{v}^*)\in E$. □

As previously noted, in the absence of infected individuals, the process (3.1)–(3.4) is a closed migration process. Therefore, it is not surprising that v_j^* is, in fact, the probability that an individual in the closed migration process is located at patch j when the process is in equilibrium (see equation (2.27)). Then, by applying Theorem 2.22 it is straightforward that this equilibrium distribution is

$$\pi(\mathbf{n})=\begin{cases}\binom{N}{n_1,n_2\ldots,n_J}v_1^*v_2^*\ldots v_J^*, & \sum_j^N n_j=N,\\ 0, & \text{otherwise.}\end{cases}$$

Thus, the equilibrium distribution is multinomial with parameters N and $\mathbf{v}^*$.

Note that if Λ satisfies $\Lambda\mathbf{1}=\mathbf{0}$ in Theorem 3.2, then, the equilibrium vector $\mathbf{v}^*$ is $\mathbf{v}^*=J^{-1}\mathbf{1}$. The assumption $\Lambda\mathbf{1}=\mathbf{0}$ implies that for each patch, the rate that a susceptible individual travels from the patch to all other patches is equal to the rate that a susceptible individual enters into that patch from

all other patches. This assumption can be satisfied if, for any given two patches, the migration rate of susceptible individuals between the two patches are equal, in which case Λ is symmetric.

As the DFE always exists for system (3.6) – (3.7), an important question is whether an outbreak of the disease can occur when the population initially contains a small number of infected individuals. This question may be addressed using stability analysis of the DFE. If the DFE is unstable, then a trajectory of the ODE which starts close to the DFE will be repelled by the DFE and so an outbreak can occur. On the other hand, if the DFE is locally asymptotically stable, the trajectory of the ODE which starts close to the DFE will be attracted towards the DFE. In this case, if the population initially contains few infected individuals, then the disease cannot spread. I will now proceed to analyse the local stability of the DFE. The analysis employs Theorem 1 of van den Driessche and Watmaough [204], which is stated in Theorem 2.6. Following the notations of equation (2.18), system (3.6)–(3.7) can be written as

$$\begin{aligned}\frac{du_j}{dt} &= \mathscr{F}_j(\mathbf{u},\mathbf{v}) - \mathscr{V}_j(\mathbf{u},\mathbf{v})\\ \frac{dv_j}{dt} &= -\sum_{k\neq j}^{J}\lambda_{jk}v_j - \beta_j u_j v_j + \gamma_j u_j + \sum_{k\neq j}^{J}\lambda_{kj}v_k,\end{aligned}$$

where $\mathscr{F}_j(\mathbf{u},\mathbf{v}) = \beta_j u_j v_j$ and $\mathscr{V}_j(\mathbf{u},\mathbf{v}) = \sum_{k\neq j}^{J}\eta_{jk}u_j + \gamma_j u_j - \sum_{k\neq j}^{J}\eta_{kj}u_k$ for $j = 1,\ldots,J$. Now I show that system (3.6)–(3.7) satisfies the following properties which are Assumptions $(A1)$–$(A5)$ of Theorem 2.6.

Proposition 3.3. *System* (3.6)–(3.7) *has the following properties.*

(i) $\mathscr{F}_j(\boldsymbol{0},\boldsymbol{v}) = 0$ *and* $\mathscr{V}_j(\boldsymbol{0},\boldsymbol{v}) = 0$ *for all nonnegative* $\boldsymbol{v}$ *and* $j = 1,\ldots,J$*;*

(ii) $\mathscr{F}_j(\boldsymbol{0},\boldsymbol{v}) \geq 0$ *for all nonnegative* $\boldsymbol{u}$ *and* $\boldsymbol{v}$ *and* $j = 1,\ldots,J$*;*

(iii) $\mathscr{V}_j(\boldsymbol{u},\boldsymbol{v}) \leq 0$ *whenever* $u_j = 0,\ j = 1,\ldots,J$*;*

(iv) $\sum_{j=1}^{J}\mathscr{V}_j(\boldsymbol{u},\boldsymbol{v}) \geq 0$ *for all nonnegative* $\boldsymbol{u}$ *and* $\boldsymbol{v}$*;*

(v) *The disease–free system has a unique equilibrium that is asymptotically stable. That is, all solutions of system* (3.6)–(3.7) *with initial condition of the form* $(\boldsymbol{0},\boldsymbol{v}_0) \in E$ *approach the DFE as* $t \to \infty$*.*

Proof. Properties (i) to (iv) can be verified for system (3.6)–(3.7) by direct substitution. To check property (v), consider the disease–free system

$$\frac{d\mathbf{v}}{dt} = \Lambda\mathbf{v}, \quad \mathbf{v}(0) = \mathbf{v}_0. \tag{3.12}$$

By Theorem 3.2, this system has a unique positive equilibrium $\mathbf{v}^*$ such that $\Lambda\mathbf{v}^* = \mathbf{0}$ and $\mathbf{1}'\mathbf{v}^* = 1$. The solution of (3.12) is given by $\mathbf{v}(t,\mathbf{v}_0) = e^{\Lambda t}\mathbf{v}_0$. Since Λ is an irreducible Metzler matrix whose maximum eigenvalue is 0, by Theorem 2.15 we have $e^{\Lambda t} = \mathbf{v}^*\mathbf{1}' + O(e^{\tau t})$, elementwise, as $t \to +\infty$, where $\tau < 0$ and $\mathbf{1}'$ is the left eigenvector of Λ associated with the eigenvalue 0. Since $\mathbf{v}_0 \in E$ we have $\mathbf{1}'\mathbf{v}_0 = 1$. This implies, $\mathbf{v}(t,\mathbf{v}_0) = \mathbf{v}^*$ as $t \to +\infty$. Therefore, any solution of (3.6)–(3.7) with initial condition of the form $(\mathbf{0},\mathbf{v}_0) \in E$ approach the DFE, $(\mathbf{0},\mathbf{v}^*)$, as $t \to +\infty$. □

Now, using equation (2.20), the basic reproduction number R_0 of system (3.6)–(3.7) is given by the spectral radius of

$$[\text{diag}(\boldsymbol{\beta})\text{diag}(\mathbf{v}^*)][\text{diag}(\boldsymbol{\gamma}) - H]^{-1}, \tag{3.13}$$

where $\boldsymbol{\beta} = (\beta_1,\ldots,\beta_J)$, $\boldsymbol{\gamma} = (\gamma_1,\ldots,\gamma_J)$ and $\mathbf{v}^*$ is the proportion of susceptible individuals at the DFE. In other words, R_0 is the maximum modulus of the eigenvalues of matrix (3.13). Matrix (3.13) is called the next generation matrix [65, 66, 67, 97, 203, 204]. Its (j,k)–th entry describes the expected number of new infections in patch j produced by an infected individual originally introduced into patch k when the population is disease–free. The following result follows from Theorem 2.6.

Theorem 3.4. *The DFE of system* (3.6)–(3.7) *is locally asymptotically stable if* $R_0 < 1$*, but unstable if* $R_0 > 1$.

It can be inferred from Theorem 3.4 that the disease will not spread if $R_0 < 1$ since the DFE is locally asymptotically stable in this case. On the other hand, it will spread if $R_0 > 1$, as the DFE is unstable in this case. This implies that $R_0 = 1$ is a threshold which determines disease invasion or extinction. However, Theorem 3.4 does not mention the stability of the DFE for the case when $R_0 = 1$. Therefore, a complete understanding of the stability of the DFE cannot be determined from the local stability results given in Theorem 3.4. Global stability of the DFE ensures that the disease cannot persist in the population. To prove global stability of the DFE, I employ the novel approach in Kamgang and Sallet [110, Theorem 4.3] which is given in Theorem 2.7. Before progressing to show global stability of the DFE, I will first show that the set E in which the ODE is defined is positively invariant. That is, any solution of (3.6)–(3.7) which starts in E must remain in E for all positive time.

Lemma 3.5. *E is a positively invariant set with respect to* (3.6)–(3.7).

Proof. Note that E is a closed and convex set. Then by Nagumo (see [36, Theorem 3.1]), E is positively invariant if the direction field of the differential equation is tangent or pointing into E at every boundary point of E. Observe that if $u_j = 0$, then, $du_j/dt = \sum_{k\neq j}^{J} \eta_{kj}u_k \geq 0$. Similarly, if $v_j = 0$, then, $dv_j/dt = \gamma_j u_j + \sum_{k\neq j}^{J} \lambda_{kj}v_k \geq 0$. Furthermore, $d\sum_{j=1}^{J}(u_j + v_j)/dt = 0$. Therefore, any solution of the ODE (3.6)–(3.7) which starts in E stays inside E for all positive time. □

The result of Lemma 3.5 is used to prove global stability of the DFE. Define $\mathscr{T}_0$ as the spectral radius of

$$\text{diag}(\boldsymbol{\beta})[\text{diag}(\boldsymbol{\gamma}) - H]^{-1}, \tag{3.14}$$

where $\boldsymbol{\beta}$ and $\boldsymbol{\gamma}$ as defined in (3.13). The following result shows that $\mathscr{T}_0 \leq 1$ is a sufficient condition which determines the global stability of the DFE.

Theorem 3.6. *The DFE of system* (3.6)–(3.7) *is globally asymptotically stable if* $\mathscr{T}_0 \leq 1$.

Proof. The theorem will hold if assumptions (H1) to (H5) of Theorem 2.7 are satisfied. Assumption (H1) holds as E is bounded and positively invariant by Lemma 3.5. From part (v) of Proposition 3.3 we know that $\mathbf{v}^*$ is globally asymptotically stable for the disease–free system (3.12) which is defined on

$$\left\{ v_j \in [0,1]; j = 1,\ldots,J; \sum_{j=1}^{J} v_j = 1 \right\}.$$

Therefore, assumption (H2) is satisfied. Matrix $A_2(\mathbf{u},\mathbf{v})$ in assumption (H3) is given by $[H - \text{diag}(\boldsymbol{\gamma}) + \text{diag}(\boldsymbol{\beta})\text{diag}(\mathbf{v})]$, which is an irreducible Metzler matrix for any $(\mathbf{u},\mathbf{v}) \in E$. So, Assumption (H3) is also satisfied. Now, to check Assumption (H4), we consider the set

$$\mathscr{M} = \{[H - \text{diag}(\boldsymbol{\gamma}) + \text{diag}(\boldsymbol{\beta})\text{diag}(\mathbf{v})] \mid (\mathbf{u},\mathbf{v}) \in E\}.$$

The smallest upper bound for $\mathscr{M}$ is given by

$$\bar{A}_2 = H - \text{diag}(\boldsymbol{\gamma}) + \text{diag}(\boldsymbol{\beta}),$$

which is not attained in E. To show that Assumption (H5) holds, we want to apply Lemma 2.13 to $\bar{A}_2$. In order to apply Lemma 2.13, we need to first show that $\bar{A}_2$ is a regular splitting (see Definition 2.8). Note that $H - \text{diag}(\boldsymbol{\gamma})$ is an irreducible Metzler matrix. Then by Corollary 2.16, the maximum real part of the eigenvalues of $H - \text{diag}(\boldsymbol{\gamma})$ is bounded above by $\max_{1\leq k\leq J}\{-\gamma_k\}$ which is negative. Therefore, $H - \text{diag}(\boldsymbol{\gamma})$ is a stable Metzler matrix. Since $\text{diag}(\boldsymbol{\beta})$ is a nonnegative matrix, $\bar{A}_2$ is a regular splitting. If $\mathscr{T}_0 \leq 1$, then, by Lemma 2.13 the maximum real part of the eigenvalues of $\bar{A}_2$ is less than or equal to 0 and Assumption (H5) holds. □

The implication of Theorem 3.6 is that the disease elimination from the population is possible if the value of $\mathscr{T}_0$ is less than or equal to 1. Although there is no biological interpretation of $\mathscr{T}_0$, comparing matrix (3.14) with the next generation matrix (3.13), it is clear that $\mathscr{T}_0$ measures the spectral radius of (3.13) when $\mathbf{v}^* = \mathbf{1}$. Furthermore, $\mathscr{T}_0$ has an association with R_0 as can be seen from the following lemma.

Lemma 3.7. $R_0 < \mathscr{T}_0$.

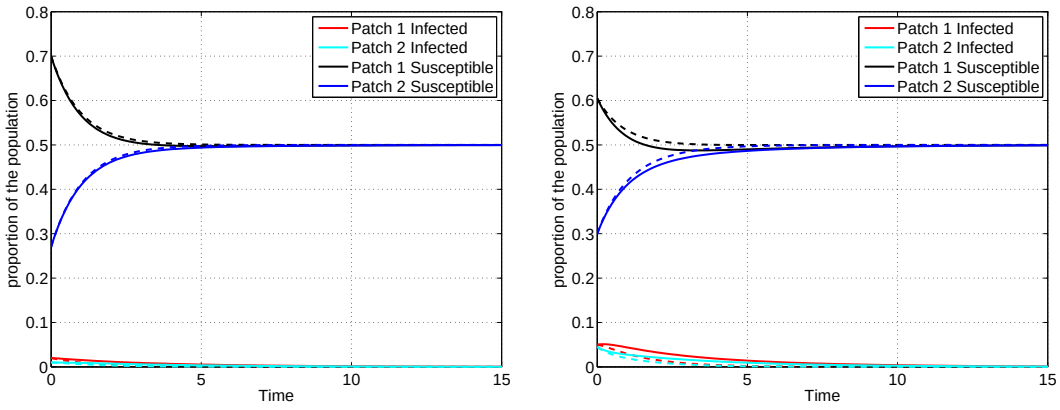
Proof. From the proof of Theorem 3.6 we know that the maximum real part of the eigenvalues of $H - \text{diag}(\boldsymbol{\gamma})$ is negative. It follows from part (g) of Theorem 2.14 that $[\text{diag}(\boldsymbol{\gamma}) - H]^{-1}$ is positive. Therefore, the matrices $[\text{diag}(\boldsymbol{\beta})\text{diag}(\mathbf{v}^*)][\text{diag}(\boldsymbol{\gamma}) - H]^{-1}$ and $\text{diag}(\boldsymbol{\beta})[\text{diag}(\boldsymbol{\gamma}) - H]^{-1}$ are also positive. Furthermore, these two matrices satisfy the relation

$$[\text{diag}(\boldsymbol{\beta})\text{diag}(\mathbf{v}^*)][\text{diag}(\boldsymbol{\gamma}) - H]^{-1} < \text{diag}(\boldsymbol{\beta})[\text{diag}(\boldsymbol{\gamma}) - H]^{-1}. \tag{3.15}$$

Then, by noting that both matrices in (3.15) are irreducible, we can apply Corollary 2.17 to conclude that $R_0 < \mathscr{T}_0$. □

From Lemma 3.7 we know that $\mathscr{T}_0$ is always greater than R_0 but it is not clear how large it is in comparison with R_0. In order to determine how large $\mathscr{T}_0$ is, in comparision with R_0, we consider a simple model in which the disease transmission rates and recovery rates are patch independent (that is $\beta_j = \beta$, $\gamma_j = \gamma$ for all j) and the migration rates of susceptible individuals satisfy $\Lambda\mathbf{1} = \mathbf{0}$. In this case the vector $\mathbf{v}^*$ in (3.13) is given by $\mathbf{v}^* = J^{-1}\mathbf{1}$ and so $R_0 = \beta/(J\gamma)$ and $\mathscr{T}_0 = \beta/\gamma$. This shows that $\mathscr{T}_0 = J \times R_0$. Furthermore, for this simple model, if we have $\beta \leq \gamma$, then by Theorem 3.6 the DFE is globally asymptotically stable. However, if $\beta < J\gamma$ but $\beta > \gamma$, then $R_0 < 1$ but $\mathscr{T}_0 > 1$.

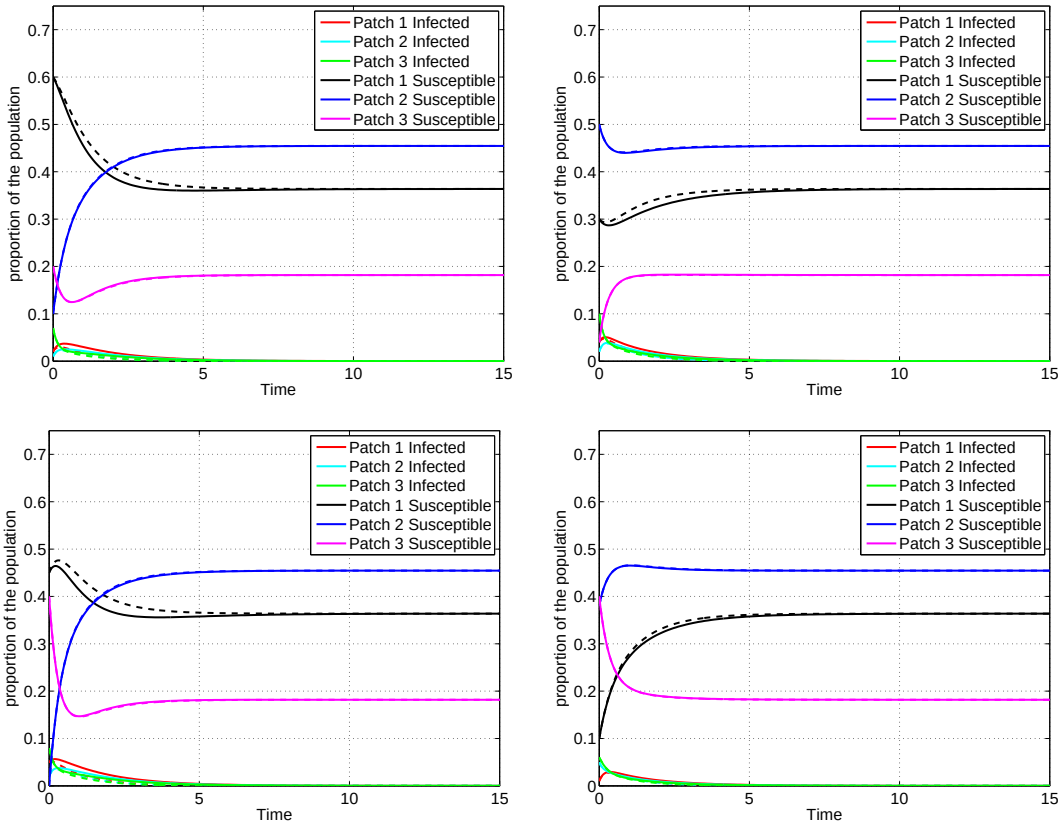
Figure 3.2 shows plots comparing the trajectory of the ODE for the cases $R_0 < 1 < \mathscr{T}_0$ (solid lines) and $R_0 < \mathscr{T}_0 < 1$ (dashed lines). The plots in part (a) correspond to trajectories of the simple model as described above for a network consisting of two patches. The plots in part (b) correspond to trajectories of a general three patch model. The numerical solutions to the ODE were computed using MATLAB's *ode45()* function. In part (a), the disease transmission rate for the case $R_0 < 1 < \mathscr{T}_0$ was assumed as $\beta = 1.5$ and the disease transmission rate for the case $R_0 < \mathscr{T}_0 < 1$ was assumed as $\beta = 0.7$. The remaining parameters used to produce the plots in part (a) are as follow: $\gamma = 1$, $\lambda_{12} = \lambda_{21} = 0.5$, $\eta_{12} = 1$ and $\eta_{21} = 1.5$. In part (b), the disease transmission rate for patch 1 for the case $R_0 < 1 < \mathscr{T}_0$ was assumed as $\beta_1 = 3.5$ and the disease transmission rate for patch 1 for the case $R_0 < \mathscr{T}_0 < 1$ was assumed as $\beta_1 = 1.5$. The remaining parameters used to produce the plots in part (b) are as follow: $\gamma_1 = 1.2$, $\gamma_2 = 1.5$, $\gamma_3 = 1$, $\lambda_{12} = 0.5$, $\lambda_{21} = 0$, $\lambda_{23} = 1$, $\lambda_{32} = 1.5$, $\lambda_{13} = 0$, $\lambda_{31} = 1$,$\eta_{12} = 3$, $\eta_{21} = 1$, $\eta_{23} = 4$, $\eta_{32} = 2$, $\eta_{13} = 1$, and $\eta_{31} = 2.5$. It can be seen from the plots in Figure 3.2 that all trajectories converge to the DFE, furthermore, there appears no significant difference between the trajectories for the cases $R_0 < \mathscr{T}_0 < 1$ and $R_0 < 1 < \mathscr{T}_0$. This suggests that the local stability result established in Theorem 3.4 for the case $R_0 < 1$ can be used as a disease control measure in its early stage even if $\mathscr{T}_0 > 1$. This is because if the population initially contains few infected individuals and if the control strategy imposed reduces R_0 to less than 1, then the disease is eliminated from the population. The problem of minimising R_0 is fully investigated in Chapter 4.



(a) Deterministic trajectories of a two patch model.

Trajectories with solid lines correspond to $R_0 = 0.75$ and $\mathscr{T}_0 = 1.5$.

Trajectories with dashed lines corresponds to $R_0 = 0.35$ and $\mathscr{T}_0 = 0.7$.



(b) Deterministic trajectories of a three patch model.

Trajectories with solid lines corresponds to $R_0 = 0.53$ and $\mathscr{T}_0 = 1.47$.

Trajectories with dashed lines corresponds to $R_0 = 0.30$ and $\mathscr{T}_0 = 0.82$.

Figure 3.2: Comparision of the trajectory of the ODE for the cases $R_0 < \mathscr{T}_0 < 1$ (dashed lines) and $R_0 < 1 < \mathscr{T}_0$ (solid lines) for a two patch (a) and a three patch (b) model. Each plot corresponds to a specific initial condition. In each plot, all trajectories converge to the DFE, and there seem to be no significant difference between the trajectories for the case $R_0 < \mathscr{T}_0 < 1$ and $R_0 < 1 < \mathscr{T}_0$.

Although I have completely determined the existence and stability of the DFE, except for the case $R_0 = 1$, I have not examined the possibility of the existence of any endemic equilibrium. The instability of the DFE given in Theorem 3.4, for the case $R_0 > 1$ implies that any solution of the ODE which starts near the DFE moves away from the DFE. This suggests that the disease may persist when $R_0 > 1$. That is, the disease may become endemic, in which case our aim is to determine the existence of any endemic equilibrium as it is an endemic equilibrium which approximates a quasi–equilibrium of the Markov chain model. In the case when susceptible and infected individuals have the same migration rates, the following result shows that a unique endemic equilibrium exists for system (3.6)–(3.7). It also determines the stability of the DFE when $R_0 = 1$, which could not be determined in Theorem 2.6. The term componentwise positive used in the statement means that the proportion of susceptible and infected individuals in each patch at equilibrium is positive.

Theorem 3.8. *Assume that $\Lambda = H$. If $R_0 \leq 1$, then, the DFE is globally asymptotically stable. If $R_0 > 1$, then system* (3.6)–(3.7) *admits a unique (componentwise) positive endemic equilibrium $(\bar{\boldsymbol{u}}, \bar{\boldsymbol{v}})$, which is globally asymptotically stable for $(\boldsymbol{u}(0), \boldsymbol{v}(0)) \in E \setminus \{(\mathbf{u}, \mathbf{v}) \,|\, \mathbf{u} = \mathbf{0}\}$.*

Proof. If $\Lambda = H$, then, by (3.6)–(3.7) we have

$$\frac{du_j}{dt} = -\sum_{k\neq j}^{J} \eta_{jk} u_j + \beta_j u_j v_j - \gamma_j u_j + \sum_{k\neq j}^{J} \eta_{kj} u_k, \tag{3.16}$$

$$\frac{dv_j}{dt} = -\sum_{k\neq j}^{J} \eta_{jk} v_j - \beta_j u_j v_j + \gamma_j u_j + \sum_{k\neq j}^{J} \eta_{kj} v_k, \tag{3.17}$$

for $j = 1, \ldots, J$. Let $y_j = u_j + v_j$, for $j = 1, \ldots, J$. Then from (3.16)–(3.17) we obtain

$$\frac{dy_j}{dt} = -\sum_{k\neq j}^{J} \eta_{jk} y_j + \sum_{k\neq j}^{J} \eta_{kj} y_k, \quad j = 1, \ldots, J. \tag{3.18}$$

By the result of DFE obtained in Theorem 3.2, system (3.18) admits a unique positive equilibrium $\mathbf{y}^* = \mathbf{v}^*$. Moreover, by using the same argument as in the proof of part (v) of Proposition 3.3, we conclude that $\mathbf{y}^*$ is globally asymptotically stable in E. Then system (3.16)–(3.17) is equivalent to the following system.

$$\frac{dy_j}{dt} = -\sum_{k\neq j}^{J} \eta_{jk} y_j + \sum_{k\neq j}^{J} \eta_{kj} y_k, \tag{3.19}$$

$$\frac{du_j}{dt} = -\sum_{k\neq j}^{J} \eta_{jk} u_j + \beta_j u_j (y_j - u_j) - \gamma_j u_j + \sum_{k\neq j}^{J} \eta_{kj} u_k, \tag{3.20}$$

for $j = 1, \ldots, J$. Note that equation (3.19) is independent of equation (3.20) and hence, $\mathbf{y}(t)$ can be obtained from equation (3.19). Then system (3.19)–(3.20) is transformed into the following nonautonomous system.

$$\frac{du_j}{dt} = -\sum_{k\neq j}^{J} \eta_{jk} u_j + \beta_j u_j (y_j(t) - u_j) - \gamma_j u_j + \sum_{k\neq j}^{J} \eta_{kj} u_k, \quad j = 1, \ldots, J. \tag{3.21}$$

Since $y_j(t) \to y_j^* = v_j^*$, $j = 1,\dots,J$, as $t \to +\infty$, system (3.21) has the following limiting system.

$$\frac{du_j}{dt} = -\sum_{k\neq j}^{J} \eta_{jk}u_j + \beta_j u_j(v_j^* - u_j) - \gamma_j u_j + \sum_{k\neq j}^{J} \eta_{kj}u_k, \quad j = 1,\dots,J. \tag{3.22}$$

Now we define the set E^u as

$$E^u := \left\{ u_j \in [0,1]; j = 1,\dots,J; \sum_{j=1}^{J} u_j = 1 \right\}$$

and let $\mathbf{f} : E^u \mapsto \mathbb{R}^J$, where $\mathbf{f} = (f_1,\dots,f_J)$, be defined by the right hand side of equation (3.22). We want to apply Corollary 2.10 to $\mathbf{f}$. Note that $\mathbf{f}$ is continuously differentiable and for all $\mathbf{u} \in E^u$, the Jacobian matrix of $\mathbf{f}$ is given by $H - \text{diag}(\boldsymbol{\gamma}) + \text{diag}(\boldsymbol{\beta})\text{diag}(\mathbf{v}^* - 2\mathbf{u})$. Since off diagonal elements of the Jacobian matrix is nonnegative, $\mathbf{f}$ is cooperative on E^u. Since H is irreducible, the Jacobian matrix is irreducible for every $\mathbf{u} \in E^u$. Furthermore, $\mathbf{f}(\mathbf{0}) = \mathbf{0}$ and if $u_j = 0$, then, $f_j(\mathbf{u}) = \sum_{k\neq j}^{J} \eta_{kj}u_k \geq 0$. For any $\alpha \in (0,1)$ and any $\mathbf{u} > \mathbf{0}$, we have

$$\begin{aligned} &\alpha[-\sum_{k\neq j}^{J} \eta_{jk}u_j + \beta_j u_j v_j^* - \gamma_j u_j + \sum_{k\neq j}^{J} \eta_{kj}u_k] - \beta_j \alpha^2 u_j^2 \\ &> \alpha[-\sum_{k\neq j}^{J} \eta_{jk}u_j + \beta_j u_j v_j^* - \gamma_j u_j + \sum_{k\neq j}^{J} \eta_{kj}u_k] - \beta_j \alpha u_j^2, \quad j = 1,\dots,J. \end{aligned}$$

That is $\mathbf{f}(\alpha\mathbf{u}) > \alpha\mathbf{f}(\mathbf{u})$, which implies that $\mathbf{f}$ is strictly sublinear on E^u. As E^u is a bounded and positively invariant set, we have for any solution $\mathbf{u}(t)$ of (3.22), with initial condition $\mathbf{u}(0) > \mathbf{0}$, that $\mathbf{u}(t)$ is bounded for all $t \geq 0$. Now, the Jacobian matrix of $\mathbf{f}$ at $\mathbf{u} = \mathbf{0}$ is given by $H - \text{diag}(\boldsymbol{\gamma}) + \text{diag}(\boldsymbol{\beta})\text{diag}(\mathbf{v}^*)$ which is an irreducible Metzler matrix. Then we can use the same argument as in the proof Theorem 3.6 to show that $H - \text{diag}(\boldsymbol{\gamma}) + \text{diag}(\boldsymbol{\beta})\text{diag}(\mathbf{v}^*)$ is a regular splitting.

If $R_0 \leq 1$, then, by Lemma 2.13 or by using the same argument as in the proof of Theorem 2 of [203] we conclude that the maximum real part of the eigenvalues of the Jacobian matrix of $\mathbf{f}$ at $\mathbf{u} = \mathbf{0}$ is less than or equal to 0. Hence, by part (a) of Corollary 2.10, $\mathbf{u} = \mathbf{0}$ is globally asymptotically stable in E^u. Now, by Definition 2.7, system (3.21) is asymptotically autonomous with limit system (3.22). Since solution $\mathbf{u}(t)$ of (3.21) is bounded for any initial condition $\mathbf{u}(0) \in E$, and $\mathbf{u} = \mathbf{0}$ is globally asymptotically stable, then by Corollary 2.9 we have $\mathbf{u}(t) \to \mathbf{0}$ as $t \to +\infty$ for solution $\mathbf{u}(t)$ of (3.21). Consequently, the DFE is globally asymptotically stable in E.

If $R_0 > 1$, then using a similar argument as above and applying part (b) (ii) of Corollary 2.10, we see that equation (3.22) admits a unique positive equilibrium $\bar{\mathbf{u}}$ in $E^u \setminus \{\mathbf{0}\}$, which is globally asymptotically stable. Let $\bar{\mathbf{v}} = \mathbf{y}^* - \bar{\mathbf{u}}$, then system (3.16)–(3.17) admits a unique positive equilibrium $(\bar{\mathbf{u}}, \bar{\mathbf{v}})$ in E. Furthermore, by Corollary 2.9, $\mathbf{u}(t) \to \bar{\mathbf{u}}$ as $t \to +\infty$ for solution $\mathbf{u}(t)$ of (3.21) with $\mathbf{u}(0) \in E^u \setminus \{\mathbf{0}\}$. Hence, the equilibrium $(\bar{\mathbf{u}}, \bar{\mathbf{v}})$ is globally asymptotically stable for any initial condition $(\mathbf{u}(0), \mathbf{v}(0)) \in E \setminus \{(\mathbf{u}, \mathbf{v}) \,|\, \mathbf{u} = \mathbf{0}\}$..

□

The condition imposed on the migration rates in Theorem 3.8 implies that travel rates of individuals do not depend on their disease status. This may be a reasonable assumption for modelling certain mild diseases such as gonorrhea [101, 102, 132] and head lice infections [197]. In contrast to the results derived in Theorem 3.8, global asymptotic stability of the DFE for frequency–dependent SIS models studied in [131, 3] was shown only for the case when $R_0 < 1$. Moreover, the result in [3] was obtained assuming that $\Lambda \propto H$ with Λ and H being symmetric. In their analysis of the SIS model in [3], the authors were not able to prove stability of the EE, but conjectured that the EE attracts all solutions whose initial conditions have a nonzero proportion of infectives. Thus, the global asymptotic stability results obtained in Theorem 3.8 for the DFE and EE are a significant step towards establishing a more general result for the density–dependent SIS model.

As the endemic equilibrium obtained in Theorem 3.8 is for a special case of the migration rates (that is for the case when $\Lambda = H$), it remains to show if the result still holds or not when this assumption is violated. The following section provides numerical examples investigating the case when $\Lambda \neq H$.

3.2.2 Numerical Examples

In order to investigate the equilibrium of the system (3.6)–(3.7) when $\Lambda \neq H$, I solved numerically the equilibrium equations given by (3.10)–(3.11). These numerical experiments were performed for the cases $J = 2$ and $J = 3$ using Maple^{TM}15 software by applying *Isolate* command in the *RootFinding* package. The *RootFinding[Isolate]* command numerically computes all real roots of polynomials and polynomial systems with a finite number of solutions. As noted in Maple's help page concerning the *RootFinding[Isolate]* command, all digits returned by the command are correct and no roots are ever lost. If the system has an infinite number of solutions the *RootFinding[Isolate]* command will return an error. In all numerical experiments computed in this section, the *RootFinding[Isolate]* command never returned an error. This confirms that Maple had found all solutions to the system (3.10)–(3.11). For more details regarding the *Isolate* command I refer the reader to Maple's help page concerned with the *RootFinding* package.

I looked at many cases for $J = 2$ and $J = 3$ and they all had similar behaviour. Figure 3.3 shows plots for the case $J = 2$ and Figure 3.4 shows plots for $J = 3$. The parameter values used to produce the plots in Figure 3.3 and Figure 3.4, respectively, are given in Table 3.1 and Table 3.2. In all examples reported I varied the infection parameter for patch 1, β_1, from 1 to 4 while fixing all other parameters. In all cases examined, when $R_0 \leq 1$, no EE point was found. However, when $R_0 > 1$, a unique EE

point was found. It was determined to be stable by computing eigenvalues of the Jacobian matrix of system (3.6)–(3.7) evaluated at the EE point.

In other examples considered for $J = 2$, I varied β_2 from 1 to 4. The specific parameters used in these examples are given in Table 3.3. Additional examples considered for $J = 3$ include varying either β_2 or β_3 from 1 to 4. The specific parameters used for plots of $J = 3$ in which β_2 was varied are given in Table 3.4 and the parameters for those examples in which β_3 was varied are given in Table 3.5. The numerical examples indicate that if the basic reproduction number is greater than 1, a unique stable endemic equilibrium exists regardless of whether $\Lambda = H$ holds. Therefore, it may be possible to drop this assumption from Theorem 3.8.

Parameters	(a)	(b)	(c)	(d)	(e)	(f)
λ_{12}	0.1	0.5	2	0.01	0.5	0.2
λ_{21}	0.5	1	1	1	3	3
η_{12}	2	0.2	0.5	2	0.5	0.3
η_{21}	1	0.1	1	0.5	1.5	1.5
γ_1	1	1.2	0.5	0.1	1.5	2
γ_2	1.2	1	1	0.6	1.8	1.5
β_1	$[1,4]$	$[1,4]$	$[1,4]$	$[1,4]$	$[1,4]$	$[1,4]$
β_2	4	2	1	3	2	2

Table 3.1: Parameter values used to produce the plots in Figure 3.3.

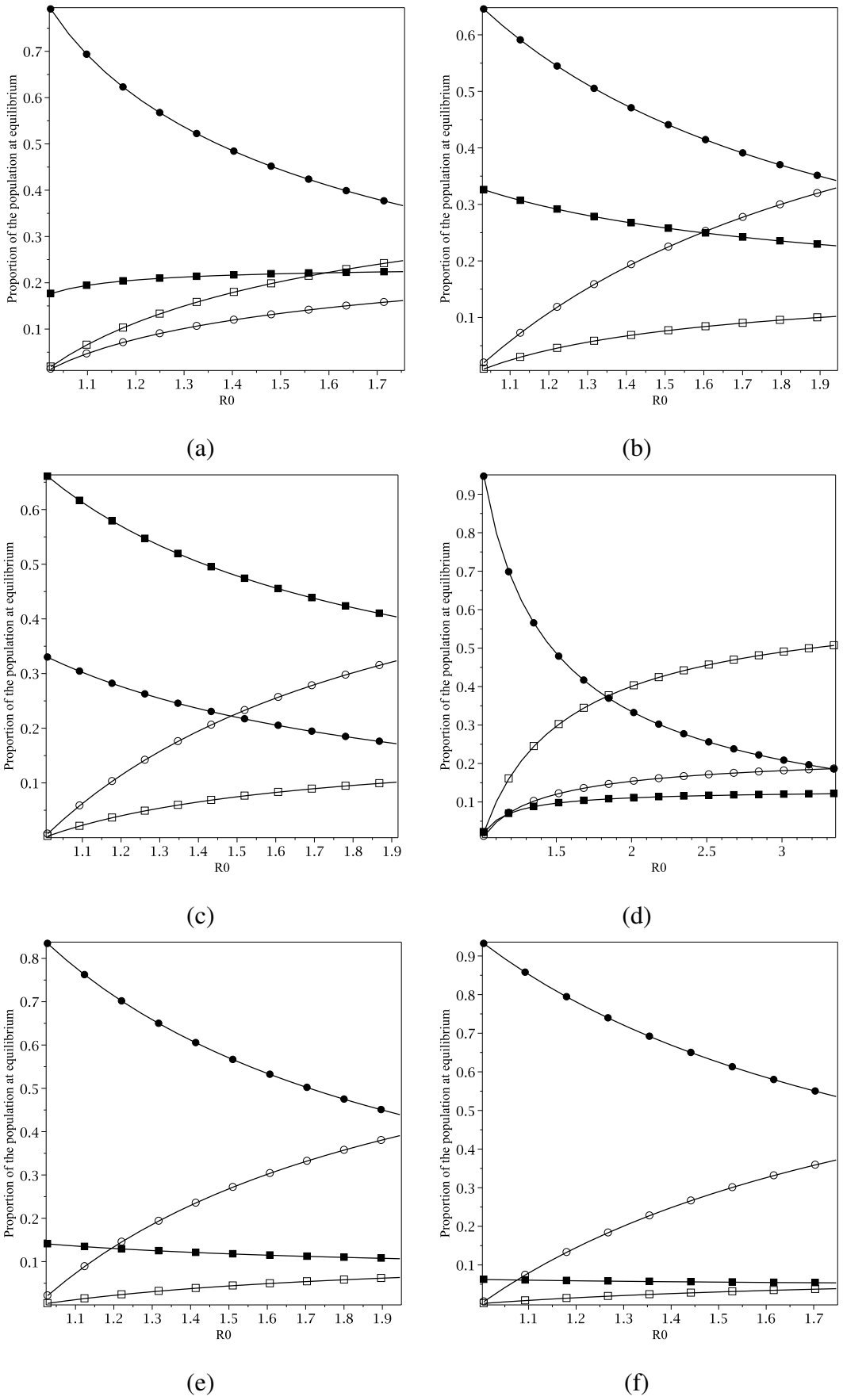


Figure 3.3: Plots for the case $J = 2$. The curves with symbols indicate the following: ○ = Patch 1 infectives, □ = Patch 2 infectives, ● = Patch 1 susceptibles, ■ =Patch 2 susceptibles. Each plot shows a unique stable EE point when R_0 is greater than 1.

Parameters	(a)	(b)	(c)	(d)	(e)	(f)
λ_{12}	0.02	1	1	0.5	0	1.5
λ_{21}	0	1.5	1.5	0	0.6	2
λ_{23}	0.03	0.03	0.3	1	0	0.3
λ_{32}	0	0	0	0	1.5	1
λ_{13}	0	2	1	0	2	2
λ_{31}	0.01	1.5	1	1	0	1.5
η_{12}	1	0.5	0.5	3	2	0.5
η_{21}	3	1	1.2	1	0	1
η_{23}	4	0.6	1	4	3	0.6
η_{32}	1	2	2	2	0	2
η_{13}	3	1	1	1	0	2
η_{31}	2	2	2.5	2.5	2.5	2
γ_1	1	0.1	0.1	1	0.1	0.7
γ_2	1.2	1.2	1	0.2	0.5	0.2
γ_3	0.2	1	1.3	1	1	2
β_1	$[1,4]$	$[1,4]$	$[1,4]$	$[1,4]$	$[1,4]$	$[1,4]$
β_2	1	2	1	3	1	2
β_3	1.5	1.5	2	2	2	3

Table 3.2: Parameter values used to produce the plots in Figure 3.4.

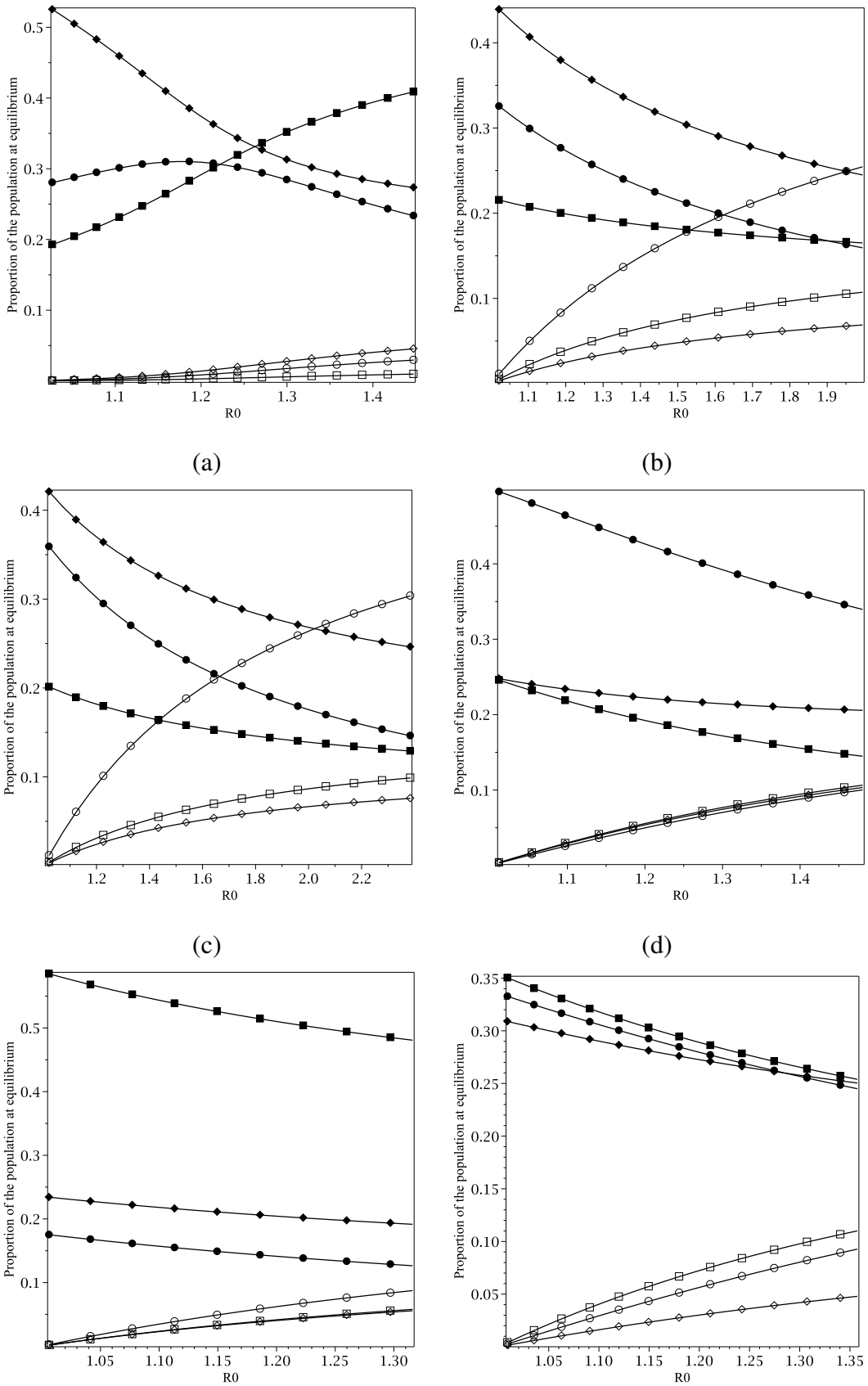


Figure 3.4: Plots for the case $J = 3$. The curves with symbols indicate the following: ○ = Patch 1 infectives, □ = Patch 2 infectives, ◊ = Patch 3 infectives, ● = Patch 1 susceptibles, ■ = Patch 2 susceptibles, ♦ = Patch 3 susceptibles. Each plot shows a unique stable EE point when R_0 is greater than 1.

Parameters	(a)	(b)	(c)	(d)	(e)	(f)
λ_{12}	0.6	2	1.5	0.3	3	1
λ_{21}	0.2	1.5	0.5	0.2	2	2
η_{12}	0.2	1	2.2	3	0.01	1.5
η_{21}	0.1	1.2	1.2	1	1.5	2.2
γ_1	1	0.3	2	0.8	1.5	0.1
γ_2	0.7	1.4	1.5	0.5	0.5	0.6
β_1	2.2	0.5	3	1	3	0.2
β_2	$[1,4]$	$[1,4]$	$[1,4]$	$[1,4]$	$[1,4]$	$[1,4]$

Table 3.3: Parameter values used in plots of $J = 2$ which are not reported.

Parameters	(a)	(b)	(c)	(d)	(e)	(f)
λ_{12}	0	1.2	1.5	0	1.5	2
λ_{21}	1	0.2	0	0.3	0	1.5
λ_{23}	0	0	1	2	0.4	1
λ_{32}	3	2	0	0.1	0	0.5
λ_{13}	2	0.5	0.5	0.7	0	0.6
λ_{31}	0	0	1.2	0	2	1.6
η_{12}	0.2	0.5	1.5	1	0	0.2
η_{21}	0	0	0.2	0	0.6	1
η_{23}	0.3	1.2	0	0.5	0	1.6
η_{32}	0	1.5	0.3	0	1	0.6
η_{13}	0	0	2	0.3	0.3	1.2
η_{31}	0.1	1	0	1.2	0	0.5
γ_1	0.2	1.2	2	0.7	0.5	0.2
γ_2	1.5	0.3	1	0.1	1	2
γ_3	1	1.7	1.3	0.5	0.8	0.7
β_1	1.4	1.5	4	1.7	1.2	1.8
β_2	$[1,4]$	$[1,4]$	$[1,4]$	$[1,4]$	$[1,4]$	$[1,4]$
β_3	2	2.2	1.5	1	3	2

Table 3.4: Parameter values used in plots of $J = 3$ which are not reported.

Parameters	(a)	(b)	(c)	(d)	(e)	(f)
λ_{12}	0.2	0.1	0.6	0	2	0
λ_{21}	1.2	1.5	0	1.5	0	1
λ_{23}	1.5	0.3	0.5	0.5	0.4	0
λ_{32}	0.5	0	0	1.5	0	1.5
λ_{13}	1.8	0	0	1	1.6	1.3
λ_{31}	0.8	0.6	0.2	0	0.6	0
η_{12}	1.6	1.6	1	0	1	0
η_{21}	0.6	0.6	0	1	0	1.4
η_{23}	1	0.4	1.2	0.2	1.3	0
η_{32}	1.2	0	0	1.2	0	1.6
η_{13}	1.3	0	0	1.5	0.6	1.2
η_{31}	0.3	1	0.8	0	0.3	0
γ_1	1	0.4	1	0.3	2	0.5
γ_2	0.7	0.1	0.5	0.7	1.5	1
γ_3	1.2	0.8	1.2	1	1	0.7
β_1	1	0.81	1.5	0.5	3	1.3
β_2	1.5	0.77	2	2.1	2	1.4
β_3	$[1,4]$	$[1,4]$	$[1,4]$	$[1,4]$	$[1,4]$	$[1,4]$

Table 3.5: Parameter values used in plots of $J = 3$ which are not reported.

3.3 Diffusion Approximation

So far, I have analysed equilibrium points of the ODE given by (3.6)–(3.7), which is an approximation to the scaled process, $((\mathbf{u}_N(t), \mathbf{v}_N(t)); t \geq 0)$. As mentioned earlier, there are some random fluctuations between the scaled process and the trajectory of the ODE. It is the aim of this section to describe these random fluctuations. I will apply Corollary 2.4 to approximate the distribution of the fluctuations of the density process about the unique endemic equilibrium of the ODE. Since Corollary 2.4 follows from Theorem 2.3, we need to check the conditions of this theorem are satisfied.

The first step is to determine the open set, O, stated in the theorem and the appropriate deterministic model defined in this open set. As the population size is fixed we can eliminate n_J from the vector

$(\mathbf{m}(t),\mathbf{n}(t))$. Then the Markov chain $((\mathbf{m}(t),\mathbf{n}(t));t\geq 0)$ has state space

$$\bar{S}_N=\left\{(\mathbf{m},\mathbf{n})\mid m_j\geq 0;j=1,\ldots,J;n_j\geq 0;j=1,\ldots,J-1;\sum_{j=1}^{J}m_j+\sum_{j=1}^{J-1}n_j\leq N\right\}.$$

Consequently, the scaled process, $((\mathbf{u}_N(t),\mathbf{v}_N(t));t\geq 0)$, takes values in $\bar{E}_N:=\bar{S}_N/N\subset\bar{E}$, where

$$\bar{E}:=\left\{u_j\in[0,1];j=1,\ldots,J;v_j\in[0,1];j=1,\ldots,J-1;\sum_{j=1}^{J}u_j+\sum_{j=1}^{J-1}v_j\leq 1\right\}.$$

The open set can be given by $O=\bar{E}\setminus\partial\bar{E}$ and the vector $F(\cdot)$ stated in Theorem 2.3 is given by

$$F(\mathbf{u},\mathbf{v})=\begin{pmatrix}
-\sum_{k\neq 1}^{J}\eta_{1k}u_1+\beta_1u_1v_1-\gamma_1u_1+\sum_{k\neq 1}^{J}\eta_{k1}u_k,\\
\quad\vdots\qquad\quad\vdots\qquad\quad\vdots\qquad\quad\vdots\\
-\sum_{k\neq J}^{J}\eta_{Jk}u_J+\beta_Ju_J[1-\sum_{j=1}^{J}u_j-\sum_{j=1}^{J-1}v_j]-\gamma_Ju_J+\sum_{k\neq J}^{J}\eta_{kJ}u_k,\\
-\sum_{k\neq 1}^{J}\lambda_{1k}v_1-\beta_1u_1v_1+\gamma_1u_1+\sum_{k\neq 1}^{J-1}\lambda_{k1}v_k+\lambda_{J1}[1-\sum_{j=1}^{J}u_j-\sum_{j=1}^{J-1}v_j],\\
\quad\vdots\qquad\quad\vdots\qquad\quad\vdots\qquad\quad\vdots\qquad\quad\vdots\\
-\sum_{k\neq J-1}^{J}\lambda_{(J-1)k}v_{J-1}-\beta_{J-1}u_{J-1}v_{J-1}+\gamma_{J-1}u_{J-1}+\sum_{k\neq J-1}^{J-1}\lambda_{k(J-1)}v_k\\
\qquad\qquad+\lambda_{J(J-1)}[1-\sum_{j=1}^{J}u_j-\sum_{j=1}^{J-1}v_j]
\end{pmatrix}.$$

Then we can use Theorem 3.1 of Kurtz to derive the following limiting system of ODE for the scaled process when N is large and for $t\in[0,T]$, where T is finite.

$$\begin{aligned}
\frac{du_j}{dt}&=-\sum_{k\neq j}^{J}\eta_{jk}u_j+\beta_ju_jv_j-\gamma_ju_j+\sum_{k\neq j}^{J}\eta_{kj}u_k,\qquad(3.23)\\
\frac{du_J}{dt}&=-\sum_{k\neq J}^{J}\eta_{Jk}u_J+\beta_Ju_J[1-\sum_{l=1}^{J}u_l-\sum_{l=1}^{J-1}v_l]-\gamma_Ju_J+\sum_{k\neq J}^{J}\eta_{kJ}u_k,\\
\frac{dv_j}{dt}&=-\sum_{k\neq j}^{J}\lambda_{jk}v_j-\beta_ju_jv_j+\gamma_ju_j+\sum_{k\neq j}^{J-1}\lambda_{kj}v_k+\lambda_{Jj}[1-\sum_{l=1}^{J}u_l-\sum_{l=1}^{J-1}v_l],\qquad(3.24)
\end{aligned}$$

for $j=1,\ldots,J-1$, subject to $(\mathbf{u}(0),\mathbf{v}(0))=(\mathbf{u}^0,\mathbf{v}^0)\in O$. Note that by substituting $v_J=1-\sum_{l=1}^{J}u_j-\sum_{l=1}^{J-1}v_l$ in (3.23)–(3.24), we get system (3.6)–(3.7). Therefore, system (3.23)–(3.24) has the same EE as that of system (3.6)–(3.7).

Now we need to check if conditions of Theorem 2.3 are satisfied for $F(\cdot)$ given above and for system (3.23)–(3.24). Note that each term in $F(\mathbf{u},\mathbf{v})$ is continuous in O and since O is a bounded set, $F(\cdot)$ is Lipschitz continuous. Next, we need to show that $F(\cdot)$ has uniformly continuous first partial derivatives. For this, we compute the Jacobian of $F(\cdot)$ as follows.

Let $\mathbf{e}$ denote the column vector of length J with a 1 in the final position and 0 elsewhere, and let $\mathbf{1}$ be the column vector with 1 in all entries and whose dimension can be implied from the context it is

used. To simplify notations, matrix Λ is partitioned as

$$\Lambda = \begin{bmatrix} \tilde{\Lambda} & \lambda_{J\cdot} \\ \lambda'_{\cdot J} & -\sum_{k=1}^{J-1} \lambda_{Jk} \end{bmatrix}. \tag{3.25}$$

Then the Jacobian of $F(\cdot)$ is given by

$$\mathscr{J}(\mathbf{u},\mathbf{v}) = \begin{bmatrix} \mathscr{J}^1 & \mathscr{J}^2 \\ \mathscr{J}^3 & \mathscr{J}^4 \end{bmatrix}, \tag{3.26}$$

where $\mathscr{J}^1$, $\mathscr{J}^2$, $\mathscr{J}^3$ and $\mathscr{J}^4$ are block matrices with dimensions, respectively, $J \times J$, $J \times (J-1)$, $(J-1) \times J$ and $(J-1) \times (J-1)$. The matrices $\mathscr{J}^1$ and $\mathscr{J}^4$ are given by

$$\mathscr{J}^1 = H + \text{diag}(\beta)\text{diag}(\mathbf{v}) - \text{diag}(\gamma) - \beta_J u_J \mathbf{e}\mathbf{1}',$$
$$\mathscr{J}^4 = \tilde{\Lambda} - \lambda_{J\cdot}\mathbf{1}' - \text{diag}(\beta)\text{diag}(\mathbf{u}),$$

and $\mathscr{J}^2$ and $\mathscr{J}^3$ are in the form

$$\mathscr{J}^2_{jk} = \begin{cases} -\beta_J u_J, & j = J, \\ \beta_j u_j, & j = k, j,k = 1,\ldots,(J-1), \\ 0, & \text{otherwise}, \end{cases}$$

$$\mathscr{J}^3_{jk} = \begin{cases} -\beta_j v_j + \gamma_j - \lambda_{Jk}, & j = k, j,k = 1,\ldots,(J-1), \\ -\lambda_{Jj}, & \text{otherwise}. \end{cases}$$

It can be seen that the Jacobian is uniformly continuous on O. The matrix $G(\cdot)$ defined in Theorem 2.3 is given by

$$G(\mathbf{u},\mathbf{v}) = \begin{bmatrix} G^1 & G^2 \\ G^3 & G^4 \end{bmatrix}, \tag{3.27}$$

where G^1, G^2, G^3 and G^4 are block matrices with dimension, respectively, $(J \times J)$, $J \times (J-1)$, $(J-1) \times J$ and $(J-1) \times (J-1)$. These matrices are given by

$$G^1_{jk} = \begin{cases} \sum_{l \neq j}^{J} \eta_{jl} u_j + \beta_j u_j v_j + \gamma_j u_j + \sum_{l \neq j}^{J} \eta_{lj} u_l, & j = k, j,k = 1,\ldots,J, \\ -\eta_{jk} u_j - \eta_{kj} u_k, & \text{otherwise}, \end{cases}$$

$$G^4_{jk} = \begin{cases} \sum_{l \neq j}^{J} \lambda_{jl} v_j + \beta_j u_j v_j + \gamma_j u_j + \sum_{l \neq j}^{J} \lambda_{lj} u_l, & j = k, j,k = 1,\ldots,(J-1), \\ -\lambda_{jk} v_j - \lambda_{kj} v_k, & \text{otherwise}, \end{cases}$$

$$G^2_{jk} = \begin{cases} -\beta_j u_j v_j - \gamma_j u_j, & j = k, j, k = 1, \ldots, (J-1), \\ 0, & \text{otherwise}, \end{cases}$$

and $G^3 = (G^2)'$. Since the elements of $G(\cdot)$ are continuous and noting that O is bounded, we see that all conditions of Theorem 2.3 are satisfied.

Let $(\mathbf{u}^*, \mathbf{v}^*)$ be the EE of system (3.23)–(3.24). Let

$$B = \mathscr{J}(\mathbf{u}^*, \mathbf{v}^*), \qquad G^* = G(\mathbf{u}^*, \mathbf{v}^*), \tag{3.28}$$

and

$$Z_N(t) = \sqrt{N}((\mathbf{u}_N(t), \mathbf{v}_N(t)) - (\mathbf{u}^*, \mathbf{v}^*)), \qquad 0 \le t \le T.$$

Thus, $(Z_N(\cdot))$ is the process of scaled difference between the density process and the EE point. The following result follows from Corollary 2.4.

Theorem 3.9. *Suppose* $\lim_{N\to\infty} \sqrt{N}((\boldsymbol{u}_N(0), \boldsymbol{v}_N(0)) - (\boldsymbol{u}^*, \boldsymbol{v}^*)) = z$. *Then the family of processes* $(Z_N(\cdot))$, *converges weakly in* $D[0,T]$ *(the space of right–continuous, left–hand limit functions on* $[0,T]$*), as* $N \to \infty$, *to an OU process* $Z(\cdot)$ *with initial value* $Z(0) = z$, *and with local drift matrix* B *and local covariance matrix* G^*, *where* B *and* G^* *as given in* (3.28). *In particular,* $Z(t)$ *has a normal distribution with mean*

$$\mu(t) = \mathbb{E}Z(t) = e^{Bt} z \tag{3.29}$$

and covariance matrix

$$\sum(t) := e^{Bt} \left(\int_0^t e^{(-Bu)} G^* e^{-B'u} du \right) e^{B't}. \tag{3.30}$$

It follows that, for large N, the scaled process $((\mathbf{u}_N(t), \mathbf{v}_N(t)); N > 0)$ has an approximate normal distribution with

$$\mathrm{Cov}(\mathbf{u}_N(t), \mathbf{v}_N(t)) \simeq \frac{1}{N} \sum(t), \tag{3.31}$$

and a "working approximation" for the mean given by

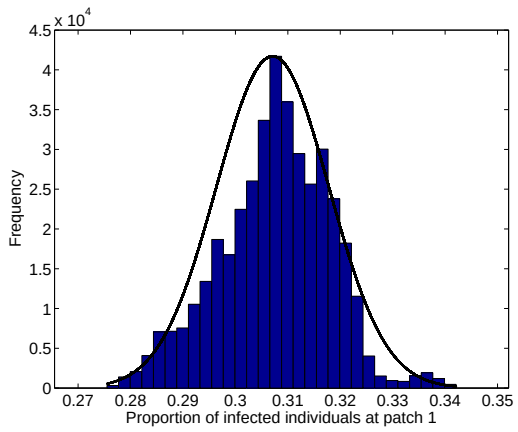
$$\mathbb{E}(\mathbf{u}_N(t), \mathbf{v}_N(t)) \simeq (\mathbf{u}^*, \mathbf{v}^*) + e^{(Bt)}((\mathbf{u}_N(0), \mathbf{v}_N(0)) - (\mathbf{u}^*, \mathbf{v}^*)). \tag{3.32}$$

Now, from the numerical examples shown in Section 3.2.2 we have that the EE is locally asymptotically stable. Therefore, the OU process $Z(\cdot)$ is stationary. Its stationary distribution is multivariate normal distribution with mean $\mathbf{0}$ and covariance matrix satisfying

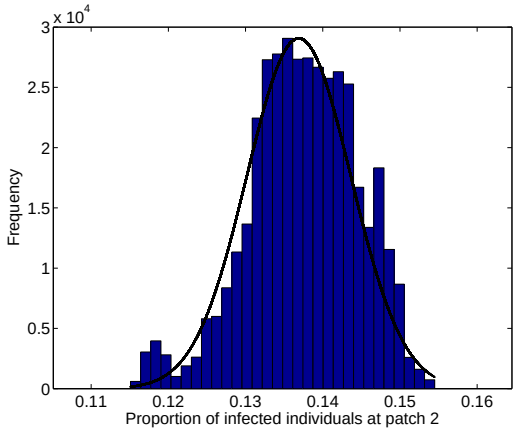
$$B \sum + \sum B' = -G^*. \tag{3.33}$$

In this case the quasi–equilibrium distribution of the original Markov chain $((\mathbf{m}(t), \mathbf{n}(t)); t \ge 0)$ has an approximate multivariate normal distribution with mean vector given by $N(\mathbf{u}^*, \mathbf{v}^*)$ and covariance matrix $N \sum$.

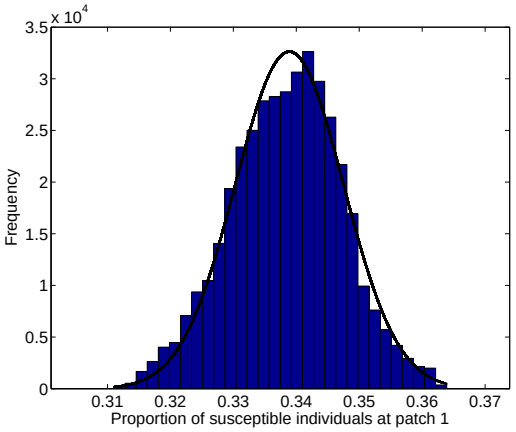
Figure 3.5 shows a numerical example illustrating the application of Theorem 3.9 to a network consisting of two patches, with a population size of 5000. The parameters used in the simulation are given in the figure. The initial point of the scaled process and that of the ODE were taken as $(u_1,u_2,v_1,v_2) = (0.417,0.58,0.002,0.003)$. The histograms show the distribution of the proportion of the population at each patch around the endemic level $(u_1,u_2,v_1,v_2) = (0.31,0.14,0.34,0.22)$. It can be seen from the plots in Figure 3.5 that the distribution of the proportion of the population at the endemic level can be approximated by a normal distribution.



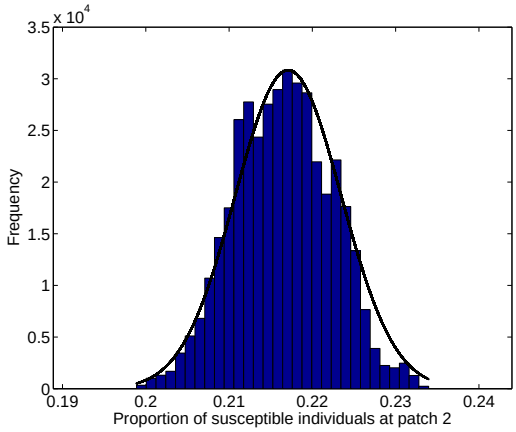
(a) Distribution of the proportion of individuals who are infected and at patch 1.



(b) Distribution of the proportion of individuals who are infected and at patch 2.



(c) Distribution of the proportion of individuals who are susceptible and at patch 1.



(d) Distribution of the proportion of individuals who are susceptible and at patch 2.

Figure 3.5: Distribution of the proportion of the population of a two patch model around the endemic equilibrium of the ODE. The parameters used are $\beta_1 = 4$, $\beta_2 = 3$, $\gamma_1 = 1.2$, $\gamma_2 = 1$, $\lambda_{12} = 0.5$, $\lambda_{21} = 1$, $\eta_{12} = 0.2$ and $\eta_{21} = 0.1$.

3.4 Conclusions

This chapter provides an analysis of the spread of a disease following the SIS pattern through a metapopulation network. I have shown that the DFE is globally asymptotically stable if the threshold quantity $\mathscr{T}_0$ is less than or equal to 1 (Theorem 3.6). Unlike the basic reproduction number, R_0, $\mathscr{T}_0$ has no biological interpretation, but it can be related to R_0 by $R_0 < \mathscr{T}_0$. In contrast to the result in Theorem 3.6, global asymptotic stability of the DFE for the frequency–dependent SIS models studied in [131, 3] was shown only for the case when $R_0 < 1$. Furthermore, the result in [3] was obtained under a specific condition on the migration rates. More precisely, for $\Lambda \propto H$ with Λ and H being symmetric. Thus, the global asymptotic stability result obtained in this work is a significant step towards establishing a more general result for the density–dependent SIS model. Additionally, the DFE obtained in [3] was spatially homogeneous in the sense that the number of susceptible individuals in all patches at the DFE is equal. A similar result can be obtained for the SIS model studied here by assuming that the migration rates of susceptible individuals satisfy $\Lambda\mathbf{1} = \mathbf{0}$. Under this condition the proportion of susceptible individuals at the DFE is given by $\mathbf{v}^* = J^{-1}\mathbf{1}$. The assumption $\Lambda\mathbf{1} = \mathbf{0}$ implies that, for each patch, the rate that a susceptible individual travels from the patch to all the other patches is equal to the rate that a susceptible individual enters that patch from all other patches. Note that if Λ is symmetric, as assumed in [3], then $\Lambda\mathbf{1} = \mathbf{0}$ is satisfied. Thus, the assumption $\Lambda\mathbf{1} = \mathbf{0}$ is more general than the symmetric condition for Λ imposed in [3].

I have also shown that under the assumption that susceptible and infected individuals have the same migration rates ($\Lambda = H$) and if $R_0 \leq 1$, then, the DFE is globally asymptotically stable, but if $R_0 > 1$, then, a unique EE exists which is globally asymptotically stable (Theorem 3.8). I note that in their analysis of the frequency–dependent SIS model, [3] were not able to prove stability of the EE, but conjectured that the EE attracts all solutions whose initial conditions have a nonzero proportion of infectives. Theorem 3.8 is an important step towards establishing a similar result for the density–dependent SIS model.

For a special case of the model, in which the disease transmission and recovery rates are independent of patches (that is $\beta_j = \beta$ and $\gamma_j = \gamma$), and assuming that migration rates of susceptible and infected individuals, respectively, satisfy $\Lambda\mathbf{1} = \mathbf{0}$ and $H\mathbf{1} = \mathbf{0}$, I have obtained an explicit form of the EE and analysed its local stability. These results are given in the Appendix of this chapter. The conditions $\beta_j = \beta$ and $\gamma_j = \gamma$ can be applied for a disease in which environmental conditions of patches do not affect much on the disease; example common cold. Conditions $\Lambda\mathbf{1} = \mathbf{0}$ and $H\mathbf{1} = \mathbf{0}$ are certainly satisfied if, for any two patches, the migration rates of susceptible individuals between the two patches are equal and the migration rates of infected individuals between the two patches are equal,

in which case Λ and H are symmetric. Furthermore, under the assumption of patch independent disease transmission and recovery rates and assuming that the migration rates of susceptible individuals satisfy $\Lambda\mathbf{1} = \mathbf{0}$, an explicit expression for R_0 and $\mathscr{T}_0$ can be computed. Specifically, $R_0 = \beta/(J\gamma)$ and $\mathscr{T}_0 = \beta/\gamma$ which implies that $\mathscr{T}_0 = J \times R_0$.

Theorem 3.4 implies that it may be possible to decrease the likelihood of a disease reaching the endemic level by reducing R_0 since, if a small number of infected individuals are introduced into a population with $R_0 < 1$, then, the disease will die out quickly. As R_0 is given by the spectral radius of the next generation matrix (3.13), it may be possible to reduce R_0 by altering the migration rates in Λ and H. As an example, suppose that $H = c\tilde{H}$ for some $\tilde{H}$ and $c > 0$, so that R_0 is now a function of c. Increasing c can be interpreted as increasing the speed at which infected individuals move around the network. Numerical results suggest that by increasing c we decrease R_0 (see Figure 3.6 for an example). Therefore, in some instances, it is possible to alter migration rates so that $R_0 < 1$. The same possibilities were observed in the two patch multi–city frequency–dependent SIS model studied in [10] and in the two patch density–dependent SIS model studied in [210], where births and death are accounted for in both models. The problem of finding an optimal strategy for migration rates will be studied in Chapter 4.

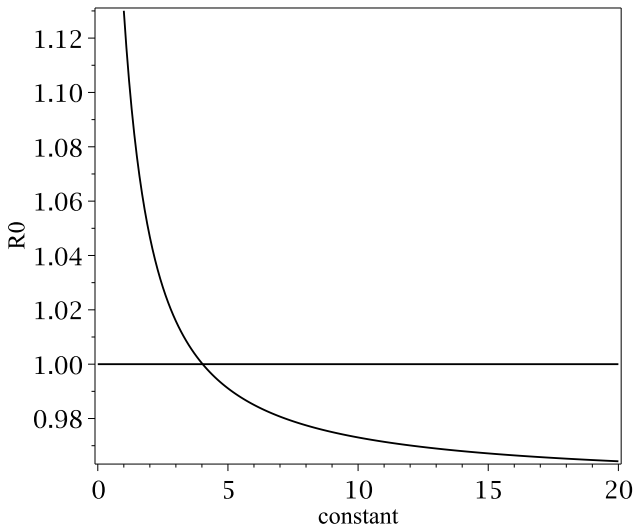


Figure 3.6: The effect of increasing the constant c on R_0 for a two patch system. The parameter values used are $\beta_1 = \beta_2 = 2.23$, $\gamma_1 = \gamma_2 = 1$, $\lambda_{12} = 0.5$, $\lambda_{21} = 1$, $\eta_{12} = c \times 0.5$, $\eta_{21} = c \times 0.2$. This example suggests that it may be possible to reduce R_0 to less than 1 by altering the migration rates of infected individuals.

Theorem 3.9 implies that the distribution of the population at the endemic level can be approximated by a multivariate normal distribution for large population size. The result of this theorem may

be used for estimating parameters of the model by applying the methods given in [177, 178]. However, as noted in [177, 178], in order to justify their method a local limit theorem will be required. I leave this problem for future studies.

As with all theoretical models, I have imposed a number of simplifications which may not always provide a good approximation to reality. For example, I have assumed that infected individuals are infectious for a period of time having an exponential distribution. However, for certain diseases such as gonorrhea and chlamydia, a gamma distribution may be a more realistic model of the infectious period [48]. The model studied in this work could incorporate gamma distributed infectious periods using a similar construction to that employed in [177]. Alternatively, the model could be generalised by incorporating a general infectious period along the lines of [153]. Another limitation is that I have ignored population dynamics such as births or deaths within the patches. This can be justified on the ground that epidemic dynamics often occur on a time scale which is much faster than population demography. I note that for the density–dependent SIS model studied in [210, 107] which incorporated births and deaths, a result similar to Theorem 3.8 was shown. Moreover, they proved global stability of the DFE for the case when $R_0 < 1$ and assuming that $\Lambda = H$. Based on this observation, I expect that the results obtained in Theorem 3.6 and Theorem 3.8 to hold even if births and deaths are included in the model. I also expect that by incorporating births and deaths in the model, existence of an endemic equilibrium may be shown by dropping the assumption $\Lambda = H$ and applying uniform persistence results given for example in [200, 217]. A similar approach was used in [210, 107] to show the existence of an endemic equilibrium for their model. A further limitation of the model is the assumption that the travel pattern of susceptible and infected individuals between patches follow Markov processes. This assumption implies that the rate of migration is unrelated to factors such as the duration of stay in a patch and the patch in which an individual initially resides. However, several studies have shown that such factors are of important consideration to accurately model human mobility patterns [19, 17, 34, 43, 57, 61, 77, 84, 91, 112, 143, 161, 162, 176, 194, 207, 208]. The model studied in this thesis could be generalised by incorporating arbitrarily distributed infectious periods and allowing infectives and susceptibles to follow specified movement processes, which are not necessarily Markovian, by following a similar construction as described by Clancy [52]. For this general model, it may be possible to apply a similar approach as in [52] to obtain a branching process approximation for the early stages of the epidemic. Of course, all these are intuitions which need to be fully investigated.

The assumptions of exponentially distributed infectious periods and Markovian travel rates imply that the SIS stochastic model studied in this thesis is a Markov process. These two assumptions are essential in deriving the ODE and the OU approximations given, respectively, by Theorem 3.1

and Theorem 3.9. An ODE and a diffusion approximations are usually hard to obtain when the stochastic process is not Markovian [4]. In such cases the process is often analysed by using an approximating branching process for the early stage of the epidemic [4, Chapter 3]. Despite the fact that the Markovian assumption may be a limitation of the model, the results of this analysis provide a useful insight into the spread of diseases following the SIS pattern. More realistic stochastic models are highly complex and their analyses mostly depend on numerical techniques. Therefore, despite their limitations, the analyses of simpler models can provide useful insights into the behaviour of more complex models and this fact is true as well for the SIS model studied in this thesis.

3.5 Appendix

Here I show the existence of a unique EE for the ODE (3.6)–(3.7) and determine its local stability for the special case when all patches have equal transmission rates and equal recovery rates. More precisely, I assume $\beta_j = \beta$ and $\gamma_j = \gamma$ for all j.

For this analysis, I use the following assumptions.

(A1) $\Lambda \mathbf{1} = \mathbf{0}$.

(A2) $H\mathbf{1} = \mathbf{0}$.

(A3) Λ is diagonalizable.

(A4) H is diagonalizable.

(A5) If $\varphi^H \neq 0$ is an eigenvalue of H then $\varphi^H \neq \rho^\Lambda - (\beta - J\gamma)/J$, where ρ^Λ is an eigenvalue of Λ.

Assumption $(\mathbf{A1})$ implies that, for each patch, the rate that a susceptible individual travels from the patch to all other patches is equal to the rate that a susceptible individual enters into that patch from all other patches. Assumption $(\mathbf{A2})$ has a similar interpretation for the migration rates of infected individuals. As previously noted these assumptions are more general than the assumptions imposed on the migration rates in [3]. Their assumptions amount to assuming that Λ and H are symmetric matrices satisfying $\Lambda \propto H$. Assumptions $(\mathbf{A3})$ – $(\mathbf{A5})$ are milder technical conditions which will be used to show the local stability of an EE. Recall from the definition of Λ and H in Section 3.2.1that the transpose of these matrices are Q–matrices, which implies that the column sums of Λ and H equal to 0. Then, Assumptions $(\mathbf{A1})$ and $(\mathbf{A2})$ ensure that the row sums of these matrices are also equal to 0.

Under Assumption $(\mathbf{A1})$, the expression for R_0 given in (3.13) simplifies to $R_0 = \beta/(J\gamma)$. The following theorem shows that, in this case, a unique EE exists for system (3.6) – (3.7).

Theorem 3.10. *Assume that* $(\boldsymbol{A1})$ *holds. If* $\beta \leq J\gamma$*, then system* (3.6) – (3.7) *has no EE. If* $\beta > J\gamma$*, then system* (3.6) – (3.7) *has a unique EE* $(\boldsymbol{u}^*, \boldsymbol{v}^*)$*, where* $v_j^* = \gamma/\beta$ *for* $j = 1, \ldots, J$*, and* $\boldsymbol{u}^*$ *satisfies* $H\boldsymbol{u}^* = \boldsymbol{0}$ *and* $\boldsymbol{1}'\boldsymbol{u}^* = (1 - J\gamma/\beta)$.

Proof. If $(\mathbf{u}^*, \mathbf{v}^*)$ is an EE, then $u_j^* > 0$ for at least one $j \in \{1, \ldots, J\}$. For $j = 1, \ldots, J$, define $\delta_j := \beta v_j^* - \gamma$. Substituting $v_j^* = (\delta_j + \gamma)/\beta$ into (3.11) and applying Assumption $(\mathbf{A1})$, we obtain

$$-\left(\sum_{j \neq k}^{J} \lambda_{jk} + \beta u_j^*\right)\delta_j + \sum_{j \neq k}^{J} \lambda_{kj}\delta_k = 0, \quad j = 1, \ldots, J,$$

which can be expressed as $A\boldsymbol{\delta} = \mathbf{0}$, where $A = \Lambda - \text{diag}(\beta \mathbf{u}^*)$ and $\boldsymbol{\delta} = (\delta_1, \ldots, \delta_J)'$. Note that A is an irreducible Metzler matrix and $A\mathbf{1} = -\beta \mathbf{u}^*$. Then we can apply part (e) of Theorem 2.14 to see that 0 is not an eigenvalue of A. Hence, $A\boldsymbol{\delta} = \mathbf{0}$ implies $\boldsymbol{\delta} = \mathbf{0}$ and $v_j^* = \gamma/\beta$ for $j = 1, \ldots, J$.

If $\beta \leq J\gamma$, then $\sum_{j=1}^{J} v_j^* = J\gamma/\beta \geq 1$. Therefore, there is no $(\mathbf{u}, \mathbf{v}) \in E$ satisfying (3.11) with $u_j > 0$ for at least one $j \in \{1, \ldots, J\}$.

If $\beta > J\gamma$, then substituting $v_j^* = \gamma/\beta$ into (3.10) we obtain

$$-\sum_{k \neq j}^{J} \eta_{jk} u_j^* + \sum_{k \neq j}^{J} \eta_{kj} u_k^* = 0, \quad j = 1, \ldots, J,$$

that is, $H\mathbf{u}^* = \mathbf{0}$. As previously noted, 0 is an eigenvalue of H. Then, by applying part (b) of Theorem 2.14, we see that the corresponding eigenvector is unique up to constant multiples and positive. The condition $\mathbf{1}'\mathbf{u}^* = (1 - J\gamma/\beta)$ ensures that $(\mathbf{u}^*, \mathbf{v}^*) \in E$. □

From Theorem 3.10 we see that the rate of infection at each patch is equal to the rate of recovery when the system is in the EE. This implies that the EE $(\mathbf{u}^*, \mathbf{v}^*)$ satisfies $H\mathbf{u}^* = \mathbf{0}$ and $\Lambda \mathbf{v}^* = \mathbf{0}$. These two equations are closely related to the equilibrium equations [190, equation 3.1] for a two–type closed migration process in which individuals do not change their type. These equations then determine how susceptible and infected individuals are distributed throughout the network.

The stability of the EE can be studied by examining the eigenvalues of the Jacobian of system (3.6)–(3.7) evaluated at the EE point. If all eigenvalues of the Jacobian have negative real part, then by part 1 of Theorem 2.5, the equilibrium point is locally asymptotically stable. However, as system (3.6) – (3.7) must satisfy $\sum_{j=1}^{J}(u_j + v_j) = 1$, the variable v_J can be eliminated, giving the reduced system (3.23)–(3.24). I use the Jacobian of this reduced system, evaluated at the EE, to investigate the stability of the EE point. Note that the Jacobian matrix of (3.23)–(3.24) is given in (3.26).

Let $\mathscr{J}_{EE}$ denote the Jacobian matrix of the system (3.23)–(3.24) evaluated at the EE given in Theorem 3.10. Recall from Section 3.3 that $\mathbf{e}$ is the column vector of length J with a 1 in the final position and 0 elsewhere, and $\mathbf{1}$ is the column vector with 1 in all entries. These two vectors are used here again to define the block matrices of $\mathscr{J}_{EE}$. Furthermore, define matrix C as

$$C = \tilde{\Lambda} - \lambda_J \mathbf{1}', \tag{3.34}$$

where $\tilde{\Lambda}$ as given by equation (3.25). The Jacobian matrix $\mathscr{J}_{EE}$ is given by

$$\mathscr{J}_{EE} = \begin{bmatrix} \overline{A} & \overline{B} \\ \overline{C} & \overline{D} \end{bmatrix}, \tag{3.35}$$

where,

$$\overline{A} = H - \frac{\beta - J\gamma}{J}\mathbf{e}\mathbf{1}^{'},$$
$$\overline{C} = -\lambda_{J.}\mathbf{1}^{'},$$
$$\overline{D} = C - \frac{(\beta - J\gamma)}{J}I,$$

and

$$\overline{B}_{jk} = \begin{cases} -\frac{(\beta - J\gamma)}{J}, & j = J, \\ \frac{(\beta - J\gamma)}{J}, & j = k, j, k = 1, \ldots, (J-1), \\ 0, & \text{otherwise.} \end{cases}$$

Let $sp(A)$ denote the spectrum (the set of eigenvalues) of matrix A. Then, the following lemma provides the relationship between eigenvalues of C and the nonzero eigenvalues of Λ .

Lemma 3.11. *Assume* (***A3***) *holds. Then,* $sp(C) = sp(\Lambda)\backslash\{0\}$.

Proof. Let φ be a nonzero eigenvalue of Λ and let $\mathbf{g}$ denote the corresponding eigenvector. Denote the first $J-1$ elements of $\mathbf{g}$ by $\mathbf{g}_{-J}$ and the last element by g_J. As $\Lambda\mathbf{g} = \varphi\mathbf{g}$,

$$\tilde{\Lambda}\mathbf{g}_{-J} + \lambda_{J.}g_J = \varphi\mathbf{g}_{-J},$$

which can be expressed as

$$\left(\tilde{\Lambda} - \lambda_{J.}\mathbf{1}^{'}\right)\mathbf{g}_{-J} + \lambda_{J.}\mathbf{1}^{'}\mathbf{g}_{-J} + \lambda_{J.}g_J = \varphi\mathbf{g}_{-J}.$$

Noted that $\mathbf{1}^{'}\Lambda = \mathbf{0}$, so $\mathbf{1}^{'}\mathbf{g} = 0$ and $g_J = -\mathbf{1}^{'}\mathbf{g}_{-J}$. Therefore,

$$\left(\tilde{\Lambda} - \lambda_{J.}\mathbf{1}^{'}\right)\mathbf{g}_{-J} = \varphi\mathbf{g}_{-J}$$

and φ is an eigenvalue of C. If all eigenvalues of Λ were distinct, the proof would be complete. I now show that all nonzero eigenvalues are repeated the same number of times in both Λ and C by showing that the identified eigenvectors are linearly independent.

From Assumption (**A3**), Λ has J linearly independent eigenvectors which we denote by $\mathbf{g}^{(i)}$, $i = 1, \ldots, J$. Assume that $\mathbf{g}^{(J)}$ denotes the eigenvector corresponding to the zero eigenvalue. We denote the first $J-1$ elements of $\mathbf{g}^{(i)}$ by $\mathbf{g}_{-J}^{(i)}$ and the last element by $g_J^{(i)}$. I want to show that the vectors $\mathbf{g}_{-J}^{(1)}, \ldots, \mathbf{g}_{-J}^{(J-1)}$ are linearly independent. Suppose the contrary holds, then there exists scalars $a_1, \ldots, a_{J-1}$ which are not all 0, such that

$$a_1\mathbf{g}_{-J}^{(1)} + \cdots + a_{J-1}\mathbf{g}_{-J}^{(J-1)} = \mathbf{0}. \tag{3.36}$$

Premultiplying equation (3.36) by $\mathbf{1}'$ gives

$$a_1 g_J^{(1)} + \cdots + a_{J-1} g_J^{(J-1)} = 0, \tag{3.37}$$

where I have used the fact that $\mathbf{1}'\mathbf{g}_{-J}^{(i)} = -g_J^{(i)}$. Together equations (3.36) and (3.37) imply that the vectors $\mathbf{g}^{(i)},\ i = 1,\ldots,J-1$ are linearly dependent, which is a contradiction. Therefore, the vectors $\mathbf{g}_{-J}^{(1)},\ldots,\mathbf{g}_{-J}^{(J-1)}$ are linearly independent. Noting that an eigenvalue's geometric multiplicity is less than or equal to its algebraic multiplicity, we see that $sp(C) = sp(\Lambda)\backslash\{0\}$. □

Lemma 3.11 shows that the eigenvalues of C are the nonzero eigenvalues of Λ. This result is used in the following theorem to investigate local stability of the EE.

Theorem 3.12. *Assume that (A1) – (A5) hold. If $\beta > J\gamma$, then the EE is locally asymptotically stable.*

Proof. Let φ be an eigenvalue of $\mathscr{J}_{EE}$ with the corresponding eigenvector $(\mathbf{h}', \mathbf{g}')'$, where $\mathbf{h}$ and $\mathbf{g}$ are column vectors whose dimensions, respectively, are J and $(J-1)$. The eigenvalue problem of $\mathscr{J}_{EE}$ is given by

$$\overline{A}\mathbf{h} + \overline{B}\mathbf{g} = \varphi\mathbf{h}, \tag{3.38}$$

$$\overline{C}\mathbf{h} + \overline{D}\mathbf{g} = \varphi\mathbf{g}. \tag{3.39}$$

Equations (3.38) and (3.39) can be expressed as

$$\overline{A}\mathbf{h} + \overline{B}\mathbf{g} = H\mathbf{h} - \frac{(\beta - J\gamma)}{J}\mathbf{e}\mathbf{1}'\mathbf{h} + \frac{(\beta - J\gamma)}{J}\begin{bmatrix}\mathbf{g}\\ -\mathbf{1}'\mathbf{g}\end{bmatrix}, \tag{3.40}$$

$$\overline{C}\mathbf{h} + \overline{D}\mathbf{g} = -\lambda_J \mathbf{1}'\mathbf{h} + \tilde{\Lambda}\mathbf{g} - \lambda_J \mathbf{1}'\mathbf{g} - \frac{(\beta - J\gamma)}{J}\mathbf{g}. \tag{3.41}$$

From Assumption (**A4**), H has J linearly independent eigenvectors, which we denote by $\mathbf{h}^{(1)},\ldots,\mathbf{h}^{(J)}$. Let $\mathbf{h}^{(J)}$ denote the eigenvector corresponding to the zero eigenvalue of H. As $\mathbf{1}'H = \mathbf{0}$, it follows $\mathbf{1}'\mathbf{h}^{(i)} = 0$ for $i = 1,\ldots,J-1$. It is easily verified that $(\mathbf{h}^{(i)'}, \mathbf{0}')'$, $i = 1,\ldots,J-1$, are eigenvectors of $\mathscr{J}_{EE}$. The corresponding eigenvalues of $\mathscr{J}_{EE}$ are the nonzero eigenvalues of H, which we know all have negative real parts from (c) and (e) of Theorem 2.14.

Next, using Assumption (**A2**), we see that $(\mathbf{1}', -\mathbf{1}')'$ is an eigenvector of $\mathscr{J}_{EE}$ with corresponding eigenvalue $\varphi = -(\beta - J\gamma)/J$, which is negative if $\beta > J\gamma$.

Let $\varphi_i^{\Lambda},\ i = 1,\ldots,J-1$ be the nonzero eigenvalues of Λ and $\mathbf{g}^{(i)}$ the corresponding eigenvectors. Applying Lemma 3.11, we see that the eigenvalues of $\overline{D}$ are $\omega_i = \varphi_i^{\Lambda} - (\beta - J\gamma)/J,\ i = 1,\ldots,J-1$. From the proof of Lemma 3.11, the corresponding eigenvectors of $\overline{D}$ are $\mathbf{g}_{-J}^{(i)}$. If Assumption (**A5**) holds, then $(H - \omega_i I)$ is invertible and we may define the vectors

$$\tilde{\mathbf{h}}^{(i)} := -\frac{(\beta - J\gamma)}{J}(H - \omega_i I)^{-1}\mathbf{g}^{(i)}, \tag{3.42}$$

for $i = 1,\ldots,J-1$. This vector satisfies $\mathbf{1}'\widetilde{\mathbf{h}}^{(i)} = 0$ since

$$\mathbf{1}'\widetilde{\mathbf{h}}^{(i)} = -\frac{(\beta - J\gamma)}{J}\mathbf{1}'(H-\omega_i I)^{-1}\mathbf{g}^{(i)} = \frac{(\beta - J\gamma)}{J\omega_i}\mathbf{1}'\mathbf{g}^{(i)}$$

and we know $\mathbf{1}'\mathbf{g}^{(i)} = 0$ as $\mathbf{1}'\Lambda = \mathbf{0}$. From equations (3.40) and (3.41), we see that $(\widetilde{\mathbf{h}}^{(i)'}, \mathbf{g}^{(i)'})'$ are eigenvectors of $\mathscr{J}_{EE}$ with corresponding eigenvalues ω_i.

If the set $\{-(\beta - J\gamma)/J\} \cup \left(\bigcup_{i=1}^{J-1} \omega_i\right) \cup sp(H)\backslash\{0\}$ contained distinct elements, then this set would be the complete set of $2J-1$ eigenvalues of $\mathscr{J}_{EE}$. Furthermore, as all these eigenvalues have negative real parts when $\beta > J\gamma$, the proof would be complete. To deal with any potential multiplicity in the eigenvalues, we show that the $2J-1$ eigenvectors $(\mathbf{h}^{(i)'}, \mathbf{0}')'$, $(\mathbf{1}', -\mathbf{1}')'$, $(\widetilde{\mathbf{h}}^{(i)'}, \mathbf{g}^{(i)'})'$, where $i = 1,\ldots,J-1$, are linearly independent. This is achieved in two parts. We first show that the vectors $(\mathbf{h}^{(i)'}, \mathbf{0}')'$, $(\widetilde{\mathbf{h}}^{(i)'}, \mathbf{g}^{(i)'})'$, where $i = 1,\ldots,J-1$, are linearly independent. We then show that $(\mathbf{1}', -\mathbf{1}')'$ is linearly independent of the rest.

Suppose $(\mathbf{h}^{(i)'}, \mathbf{0}')'$, $(\widetilde{\mathbf{h}}^{(i)'}, \mathbf{g}^{(i)'})'$, $i = 1,\ldots,J-1$, are linearly dependent. Then there exists scalars $a_i, b_i,\ i = 1,\ldots,J-1$, not all 0, such that

$$\sum_{i=1}^{J-1} a_i(\mathbf{h}^{(i)'}, \mathbf{0}')' + \sum_{i=1}^{J-1} b_i(\widetilde{\mathbf{h}}^{(i)'}, \mathbf{g}^{(i)'})' = \mathbf{0}. \tag{3.43}$$

Therefore,

$$\sum_{i=1}^{J-1} b_i\mathbf{g}^{(i)} = \mathbf{0}.$$

However, we know from Assumption (**A3**) that the vectors $\mathbf{g}^{(i)},\ i = 1,\ldots,J-1$, are linearly independent. Therefore, $b_i = 0$ for all $i = 1,\ldots,J-1$. Equation (3.43) now reduces to

$$\sum_{i=1}^{J-1} a_i\mathbf{h}^{(i)} = \mathbf{0}.$$

From Assumption (**A5**), the vectors $\mathbf{h}_{(i)}$, $i = 1,\ldots,J-1$, are linearly independent, so $a_i = 0$ for all $i = 1,\ldots,J-1$. As $a_i = 0$ and $b_i = 0$ for all $i = 1,\ldots,J-1$, we arrive at a contradiction. Therefore, the vectors $(\mathbf{h}^{(i)'}, \mathbf{0}')'$, $(\widetilde{\mathbf{h}}^{(i)'}, \mathbf{g}^{(i)'})'$, $i = 1,\ldots,J-1$, are linearly independent.

Now from Assumption (**A5**), $-(\beta - J\gamma)/J$ is not in the set $\left(\bigcup_{i=1}^{J-1} \omega_i\right) \cup sp(H)\backslash\{0\}$. As eigenvectors with distinct eigenvalues are linearly independent, the eigenvectors $(\mathbf{h}^{(i)'}, \mathbf{0}')'$, $(\widetilde{\mathbf{h}}^{(i)'}, \mathbf{g}^{(i)'})'$, $i = 1,\ldots,J-1$, and $(\mathbf{1}', -\mathbf{1}')'$ are linearly independent. Therefore, $sp(\mathscr{J}_{EE}) = \{-(\beta - J\gamma)/J\} \cup \left(\bigcup_{i=1}^{J-1} \omega_i\right) \cup sp(H)\backslash\{0\}$ and all the eigenvalues of $\mathscr{J}_{EE}$ have negative real parts. This completes the proof. □

Chapter 4

Optimal Migration Patterns

This chapter provides results for optimal migration patterns for susceptible individuals which minimise the basic reproduction number and the spectral abscissa of the Jacobian matrix of the ODE, derived in Chapter 3, evaluated at the DFE. It is shown that if the migration rates of infected individuals satisfy $H\mathbf{1} = \mathbf{0}$*, then setting the migration rates of susceptible individuals to satisfy* $\Lambda\mathbf{1} = \mathbf{0}$ *simultaneously minimises both measures.*

4.1 Introduction

One of the purposes of modelling epidemics is to provide a useful guide to decision makers about strategies which can be used to control the spread of a disease. Most control strategies aim either to decrease the number of susceptibles in the population, and, where possible, to below a threshold level, or to increase the rate of removal of infectives to reduce their mixing with the population of susceptibles (that is, increase the recovery rate), or to decrease the pairwise rate of infectious contact between infectives and susceptibles (that is, decrease the disease transmission rate), or to achieve a combination of these measures. For example, immunising some or all of the population reduces the initial number of susceptibles; operating a screening program or raising public awareness of higher disease prevalence may increase the recovery rate or reduce the disease transmission rate (or both); discouraging the assembly of large crowds or quarantining infected individuals reduces the disease transmission rate [60, Chapter 7].

Immunisation and patient isolation were shown as effective strategies in the global eradication of smallpox [39, 78, 140, 174]. On the other hand, early case detection, treatment and public awareness

were successful methods in reducing the spread of AIDS in highly endemic regions [201, 215, 156]. In the case of influenza, travel restrictions in conjunction with vaccination and discouragement of public gatherings were proposed as possible control measures [46, 76, 83, 103, 193]. Similarly, travel restrictions together with patient isolation were proposed as possible control measures in reducing the spread of SARS in its early stage [104, 175, 180]. While immunisation, treatment, patient isolation and public awareness are effective control strategies, their implementation can be more costly in comparison with travel restrictions [76]. Moreover, for an emerging disease for which a vaccine is not available and a treatment is unknown, the most sensible method of reducing its spread to distant areas is to control travel patterns. This work aims to provide an optimal migration pattern for susceptible individuals which reduces the spread of a disease in its initial stage.

Most studies concerning movement of individuals between groups have shown that movement can influence the spread of a disease in a complicated way, depending on the heterogeneity of groups with regard to the demographic and the disease parameters. While some results have shown that movement of either susceptible or infected individuals can enhance both disease extinction and persistence [10, 98, 107, 141, 202, 209, 210], others have demonstrated that increased travel rate of either susceptible or infected individuals can cause disease extinction [7, 152]. However, some results have suggested that increased movement of infected individuals can decrease the spread of a disease [3, 52, 183] or increase the final size of an epidemic [22, 50]. Most of these results were found by analysing the effect of travel rates on the stability of either the disease–free or the endemic equilibria or on the basic reproduction number.

In contrast to the above studies, the approach used here is to formulate and solve convex optimisation problems. The results provide an optimal migration strategy for susceptible individuals which minimises the basic reproduction number and the spectral abscissa of the Jacobian matrix of the ODE, which was derived in Chapter 3, evaluated at the disease–free equilibrium. Optimisation of network movement and resource allocation for minimising the total number of infected individuals for the frequency–dependent SIS model proposed in [3] was studied in [184]. They used a genetic algorithm to obtain numerical solutions for their optimisation problems. Unlike the results in [184], the analysis performed here provides exact analytic results for the optimisation problems.

The rest of this chapter is organised as follows. In Section 4.2, I review the necessary materials from Chapter 3 which are required for the analysis in this chapter. Section 4.3 provides the result on minimising the basic reproduction number. In Section 4.4, I determine an optimal migration pattern for susceptible individuals which minimises the spectral abscissa of the Jacobian matrix of the ODE, evaluated at the disease–free equilibrium. Finally, in Section 4.6, I make some concluding comments about the results obtained in this section.

4.2 The ODE Model and Relevant Results

The ODE model derived in Chapter 3 is described using the variables u_j and v_j, $j = 1,\ldots,J$, where J is the number of patches in the network. These variables, respectively, define the proportion of infected and susceptible individuals at patch j, relative to total population. Model parameters which appear in the ODE are the disease transmission rates, β_j, the recovery rates, γ_j, and the migration rates. The migration rate of susceptible and infected individuals from patch j to k, respectively, are given by λ_{jk} and η_{jk}. The ODE model is given by

$$\frac{du_j}{dt} = -\sum_{k\neq j}^{J} \eta_{jk}u_j + \beta_j u_j v_j - \gamma_j u_j + \sum_{k\neq j}^{J} \eta_{kj}u_k, \tag{4.1}$$

$$\frac{dv_j}{dt} = -\sum_{k\neq j}^{J} \lambda_{jk}v_j - \beta_j u_j v_j + \gamma_j u_j + \sum_{k\neq j}^{J} \lambda_{kj}v_k, \tag{4.2}$$

for $j = 1,\ldots,J$.

From the analysis of the ODE made in Chapter 3, the results required for this chapter are those obtained for the disease–free equilibrium (DFE). To review these results, some definitions are required. Recall that the matrices for the migration rates are defined as

$$\Lambda_{jk} = \begin{cases} \lambda_{kj}, & j \neq k, \\ -\sum_{l\neq j}^{J} \lambda_{jl}, & j = k, \end{cases} \quad \text{and} \quad H_{jk} = \begin{cases} \eta_{kj}, & j \neq k, \\ -\sum_{l\neq j}^{J} \eta_{jl}, & j = k. \end{cases} \tag{4.3}$$

These matrices are assumed irreducible.

It is shown that a unique DFE of the ODE always exists and is given by $(\mathbf{0}, \mathbf{v}^*)$ where $\Lambda\mathbf{v}^* = \mathbf{0}$ and $\mathbf{1}'\mathbf{v}^* = 1$. The DFE is locally asymptotically stable if $R_0 < 1$, but unstable if $R_0 > 1$, where R_0 is the spectral radius of the next generation matrix

$$[\mathrm{diag}(\boldsymbol{\beta})\mathrm{diag}(\mathbf{v}^*)][\mathrm{diag}(\boldsymbol{\gamma}) - H]^{-1}, \tag{4.4}$$

where $\boldsymbol{\beta} = (\beta_1,\ldots,\beta_J)$, $\boldsymbol{\gamma} = (\gamma_1,\ldots,\gamma_J)$ and $\mathbf{v}^*$ is the proportion of susceptible individuals at the DFE. For a formal statements of these results, I refer the reader to Theorems 3.2 and 3.4 of Chapter 3.

From now on I assume that all patches have the same disease transmission rate and the same recovery rate. More precisely, $\beta_j = \beta$ and $\gamma_j = \gamma$ for all $j = 1,\ldots,J$. Under these assumptions the next generation matrix is given by

$$\mathrm{diag}(\beta\mathbf{v}^*)\,(\gamma I - H)^{-1}. \tag{4.5}$$

The following assumption on the migration rates of infected individuals will be employed in the analyses made in this chapter.

(A2) $H\mathbf{1} = \mathbf{0}$.

Recall that Assumption **(A2)** implies that, for each patch, the rate that an infected individual travels from the patch to all the other patches is equal to the rate that an infected individual enters that patch from all other patches.

As discussed in Chapter 3, the local stability result for the DFE obtained in Theorem 3.4 suggests that it may be possible to stop the disease invading the population by reducing R_0 since, if a small number of infected individuals are introduced into a disease–free population with R_0 less than 1, the disease will die out. As R_0 depends on the migration rates, it may be reduced by altering the migration rates. This is explored in the following section.

4.3 Minimising R_0

It can be seen from equation (4.5) that the next generation matrix depends on the migration rates of both susceptible and infected individuals. It depends on the migration rates of susceptible individuals through $\mathbf{v}^*$, where $\mathbf{v}^*$ is the proportion of susceptible individuals at the DFE. Thus, it may be possible to reduce R_0 by altering the migration rates of infected or susceptible individuals. It can be seen from Figure 3.6 that, R_0 may be reduced by increasing the speed at which the infected individuals move around the network. However, the speed of movement of susceptible individuals has no effect on R_0. This is because if we consider the migration rates of susceptibles as given by $c\Lambda$, with $c > 0$ interpreted as the speed of movement. Then, from basic linear algebra theory, we know that $c\Lambda\mathbf{v}^* = \mathbf{0}$. This implies that the DFE remains the same, no matter the value of c we choose. Consequently, R_0 is the same for all c. This observation implies that it is only the migration pattern and not the speed of susceptibles which influences R_0. Thus, in this section I investigate the problem of finding the optimal migration pattern for susceptible individuals which minimises the basic reproduction number R_0. In order to proceed with this analysis, I firstly define some notations.

Define the matrices D and A as

$$D := \text{diag}(\beta\mathbf{v}) \quad \text{and} \quad A := (\gamma I - H)^{-1}, \tag{4.6}$$

where $v_j \geq 0$ for $j = 1, \ldots, J$ and $\mathbf{1}'\mathbf{v} = 1$. Let $\rho(DA)$ be the spectral radius of DA and define

$$\mathscr{L} := \{\Lambda \mid \Lambda_{jk} \text{ as defined in equation (4.3)}\}, \tag{4.7}$$

$$X = \left\{ D \text{ is a } J \times J \text{ diagonal matrix} \mid D_{jj} \geq 0, j = 1, \ldots, J; \sum_{j=1}^{J} D_{jj} = \beta \right\}.$$

Note that X consists of the diagonal matrices given in (4.6). Furthermore, for any D in X there is a corresponding Λ in $\mathscr{L}$ satisfying the equation $\Lambda\mathbf{v} = \mathbf{0}$. This is achieved by taking $\lambda_{jk} = D_{kk}$ for all $j,k = 1,\ldots,J$. Thus, minimising R_0 over $\mathscr{L}$ is equivalent to minimising R_0 over X. Therefore, minimising R_0 is equivalent to the following optimisation problem.

$$\begin{aligned} &\text{minimise} \quad \rho(DA), && (4.8)\\ &\text{subject to} \quad D_{jj} \geq 0, \quad \text{for} \quad j = 1,\ldots,J, \\ &\qquad \sum_{j=1}^{J} D_{jj} = \beta. && (4.9) \end{aligned}$$

This optimisation problem will be shown to be convex. Under the assumption on the migration rates of infected individuals **(A2)**, an explicit solution to the problem can be found.

Theorem 4.1. *Suppose (A2) holds. Then R_0 is minimised over $\mathscr{L}$ if Λ satisfies $\Lambda\boldsymbol{I} = \boldsymbol{0}$.*

Proof. The first step of the proof is to show that the optimisation problem given in (4.8)–(4.9) is a convex optimisation problem. Since X is a convex set, then according to Definition 2.10, problem (4.8)–(4.9) is a convex optimisation problem if $\rho(DA)$ is a convex function on X. We show that $\rho(DA)$ is a convex function on X as follows.

Note that $-A^{-1} = (H - \gamma I)$ is an irreducible Metzler matrix and $s(-A^{-1}) = -\gamma < 0$. By applying part (g) of Theorem 2.14, we see that $A = (\gamma I - H)^{-1}$ is a positive matrix. Since the off diagonal elements of $A^{-1} = (\gamma I - H)$ are nonpositive, by Definition 2.11, A^{-1} is a nonsingular M–matrix. Then, by applying Theorem 2.19, we conclude that $\rho(DA)$ is a convex function on the set X.

The next step is to find an optimal condition for the optimisation problem (4.8)–(4.9). By Lemma 2.18, D^* is optimal if and only if $D^* \in X$ and

$$\sum_{j=1}^{J} \frac{\partial \rho(DA)}{\partial D_{jj}}\bigg|_{D^*} (D_{jj} - D^*_{jj}) \geq 0 \tag{4.10}$$

for all $D \in X$. Now, suppose the diagonal elements of D^* are positive. Then, D^*A is an irreducible positive matrix. So we can apply parts (a) and (e) of Theorem 2.11 to conclude that $\rho(D^*A)$ is positive and a simple eigenvalue of D^*A. Furthermore, parts (b) and (d) of Theorem 2.11 ensure that D^*A has strictly positive left and right eigenvectors corresponding to the eigenvalue $\rho(D^*A)$, which are unique to constant multiples. Let η and ξ, respectively, be the left and right eigenvectors of D^*A corresponding to the eigenvalue $\rho(D^*A)$, such that $\eta' \xi = 1$. Then, it can be shown that (see [81, equation (4.22)])

$$\frac{\partial \rho(DA)}{\partial D_{jj}}\bigg|_{D^*} = \eta' \frac{\partial D}{\partial D_{jj}} A\xi = \rho(D^*A)\frac{\eta_j \xi_j}{D^*_{jj}}, \quad j = 1,\ldots,J. \tag{4.11}$$

Therefore, D^* minimises $\rho(DA)$ if

$$\sum_{j=1}^{J} \frac{\eta_j \xi_j}{D^*_{jj}} D_{jj} \geq 1, \tag{4.12}$$

for all $D \in X$.

I claim that $D^* = \frac{\beta}{J} I$ satisfies (4.12). Note that $D^* = \frac{\beta}{J} I$ is in the set X. The left and right eigenvectors of D^*A, corresponding to eigenvalue $\rho(D^*A)$, satisfy the following systems of equations:

$$\eta' (\gamma I - H)^{-1} = \frac{1}{\gamma} \eta' \qquad (\gamma I - H)^{-1} \xi = \frac{1}{\gamma} \xi. \tag{4.13}$$

The eigenvectors η' and ξ, respectively, are the left and right eigenvectors of H corresponding to the zero eigenvalue. Therefore, $\eta' = \mathbf{1}'$. Imposing Assumption **(A2)** implies $\xi = J^{-1}\mathbf{1}$ so that $\eta'\xi = 1$. Furthermore, the optimal D^* corresponds to $\mathbf{v}^* = J^{-1}\mathbf{1}$. To complete the proof I note that if $\mathbf{v}^* = J^{-1}\mathbf{1}$, then $\Lambda \mathbf{1} = \mathbf{0}$. □

Theorem 4.1 implies that if the infected individuals in the population move between patches under the assumption given by **(A2)**, then the susceptible individuals can take their migration pattern satisfying $\Lambda \mathbf{1} = \mathbf{0}$ to minimise R_0. Now, $R_0 = \beta/(J\gamma)$ when $\Lambda \mathbf{1} = \mathbf{0}$. Therefore, if $\beta/(J\gamma) < 1$ and the population initially contains a small number of infected individuals, then the disease will become extinct quickly since then the DFE is stable. If $\beta/(J\gamma) > 1$, then the disease will spread through the population. However, it may be possible to slow down the initial spreading rate of the disease by minimising the initial growth rate of the disease.

4.4 Minimising the Spectral Abscissa

The type of growth of a spatial epidemic in its early phase depends on how individuals are located in space. For certain diseases spread in wildlife or plants, there may not be a natural partitioning of the population into groups. Instead, it is usually assumed that individuals are either uniformly or randomly distributed, with their density reflecting landscape and environmental factors [113, Section 7.4]. In such cases, the space is treated as continuous and movement is assumed completely random. For these models, the early phase of a disease outbreak is known to have uniform growth [65, Chapter 8]. However, for the metapopulation model considered in this thesis, the initial phase of the epidemic exhibits exponential growth [67]. The rate of this exponential growth is given by the maximum real part (spectral abscissa) of the eigenvalues of the Jacobian matrix of system (4.1)–(4.1), evaluated at the DFE. If the spectral abscissa is positive but small, then the number of infectives in the population in the initial stage will be reduced. It is the aim of this section to find an optimal migration pattern for

susceptible individuals that minimises the spectral abscissa of the Jacobian matrix of the ODE (4.1)–(4.1), evaluated at the DFE. I note that minimising the spectral abscissa is not the same as minimising R_0. This is because, in general, there is no explicit relation between the value of the spectral abscissa and the value of R_0, in the sense that infection with a high R_0 does not automatically lead to fast exponential increase of infected individuals [67]. However, the value of R_0 does determine the sign of the spectral abscissa since R_0 is greater than or equal to 1 if and only if the spectral abscissa is greater than or equal to 0. Equivalently, R_0 is less than 1 if and only if the spectral abscissa is less than 0 [67].

Using the same argument as in the Appendix of Chapter 3, we can use the Jacobian of the reduced system (3.23)–(3.24) to investigate the analysis in this section. The Jacobian matrix of system (3.23)–(3.24) evaluated at the DFE is given by

$$\mathscr{J}_{DFE} = \begin{bmatrix} A & 0 \\ B & C \end{bmatrix}, \tag{4.14}$$

where

$$A = H - \gamma I + \operatorname{diag}(\beta \mathbf{v}^*),$$

$$B_{jk} = \begin{cases} -\lambda_{Jj}, & j \neq k, \\ \gamma - \beta v_j^* - \lambda_{Jj}, & j = k, \end{cases}$$

and

$$C = \tilde{\Lambda} - \lambda_{J\cdot}\mathbf{1}',$$

with $\tilde{\Lambda}$ as given in equation (3.25). The spectrum of $\mathscr{J}_{DFE}$ is given by union of the spectrum of A and the spectrum of C. Note that, by Lemma 3.11, the eigenvalues of C are the nonzero eigenvalues of Λ. Let $V = H - \gamma I$ and $A = V + D$, where D as given in (4.6). Let $s(\mathscr{J}_{DFE})$ be the spectral abscissa of $\mathscr{J}_{DFE}$. Minimising $s(\mathscr{J}_{DFE})$ over $\mathscr{L}$ is equivalent to the following optimisation problem.

$$\text{minimise} \quad s(\mathscr{J}_{DFE}), \tag{4.15}$$

$$\text{subject to} \quad D_{jj} \geq 0, \quad \text{for} \quad j = 1, \ldots, J,$$

$$\sum_{j=1}^{J} D_{jj} = \beta. \tag{4.16}$$

This optimisation problem will be shown to be convex. The following result gives an explicit solution to this optimisation problem under the assumption on the migration rates of infected individuals **(A2)**.

Theorem 4.2. *Suppose **(A2)** holds. Then $s(\mathscr{J}_{DFE})$ is minimised over $\mathscr{L}$ if Λ satisfies $\Lambda \mathbf{1} = \mathbf{0}$.*

Proof. For any D in X there is a corresponding Λ in $\mathscr{L}$ satisfying $\Lambda \mathbf{v} = \mathbf{0}$ and $s(C) \leq s(A)$. This is achieved by choosing $\lambda_{jk} = c \times s(A)\frac{D_{kk}}{\beta}$ for all $j,k = 1, \cdots, J$, where c is a constant chosen depending

on the sign of $s(A)$. With this choice of Λ, $s(C) = -c \times s(A)$. If $s(A) > 0$, we can choose c to be any positive constant so that $s(C) < s(A)$. If $s(A) < 0$, we can choose $c = -a$ with $a \geq 1$ so that $s(C) \leq s(A)$. In either case, we have $s(\mathscr{J}_{DFE}) = s(A)$. Therefore, minimising $s(\mathscr{J}_{DFE})$ reduces to minimising $s(A)$ subject to the constraints given in (4.15)–(4.16).

Since $A = V + D$, where V is an irreducible Metzler matrix and D is a diagonal matrix, then, by Theorem 2.20, $s(V + D)$ is a convex function on the set X. As X is a convex set, it follows that the problem (4.15)–(4.16) is a convex optimisation problem.

Now, by Lemma 2.18, $D^* \in X$ is optimal if and only if

$$\sum_{j=1}^{J} \frac{\partial s(V+D)}{\partial D_{jj}}\bigg|_{D^*} (D_{jj} - D^*_{jj}) \geq 0 \tag{4.17}$$

for all $D \in X$. Note that $(V + D^*)$ is an irreducible Metzler matrix. It follows from parts (b) and (d)] of Theorem 2.14, that $s(V + D^*)$ is a simple eigenvalue of $V + D^*$ and $s(V + D^*)$ has positive left and right eigenvectors, which are unique to constant multiples. Let $\mathbf{x}$ and $\mathbf{y}$ be, respectively, the left and right eigenvectors of $V + D^*$ corresponding to the eigenvalue $s(V + D^*)$, such that $\mathbf{x}'\mathbf{y} = 1$. Then by using the chain rule and applying Corollary 2.21 we have

$$\frac{\partial s(V+D)}{\partial D_{jj}}\bigg|_{D^*} = x_j y_j, \quad j = 1, \ldots, J. \tag{4.18}$$

Therefore, D^* minimises $s(V + D)$ if

$$\sum_{j=1}^{J} x_j y_j (D_{jj} - D^*_{jj}) \geq 0, \tag{4.19}$$

for all $D \in X$.

I claim that $D^* = \frac{\beta}{J} I$ satisfies (4.19). Note that the left and right eigenvectors of $V + D^*$, corresponding to the eigenvalue $s(V + D^*)$, satisfy the following systems of equations:

$$\mathbf{x}' \left(H + (\tfrac{\beta}{J} - \gamma) I \right) = (\tfrac{\beta}{J} - \gamma) \mathbf{x}', \tag{4.20}$$

$$\left(H + (\tfrac{\beta}{J} - \gamma) I \right) \mathbf{y} = (\tfrac{\beta}{J} - \gamma) \mathbf{y}. \tag{4.21}$$

By applying Assumption **(A2)** and using the same arguments as in the proof of Theorem 4.1, we have $\mathbf{x}' = \mathbf{1}'$ and $\mathbf{y} = J^{-1}\mathbf{1}$ which satisfies condition (4.19). The optimal D^* corresponds to $\mathbf{v}^* = J^{-1}\mathbf{1}$ and the proof is completed by noting that if $\mathbf{v}^* = J^{-1}\mathbf{1}$, then, $\Lambda\mathbf{1} = \mathbf{0}$. □

4.5 Numerical Examples

In this section, I provide some numerical examples which confirm the results obtained in Theorem 4.1 and Theorem 4.2, and some examples in which the assumption of the two theorems do not hold. I also

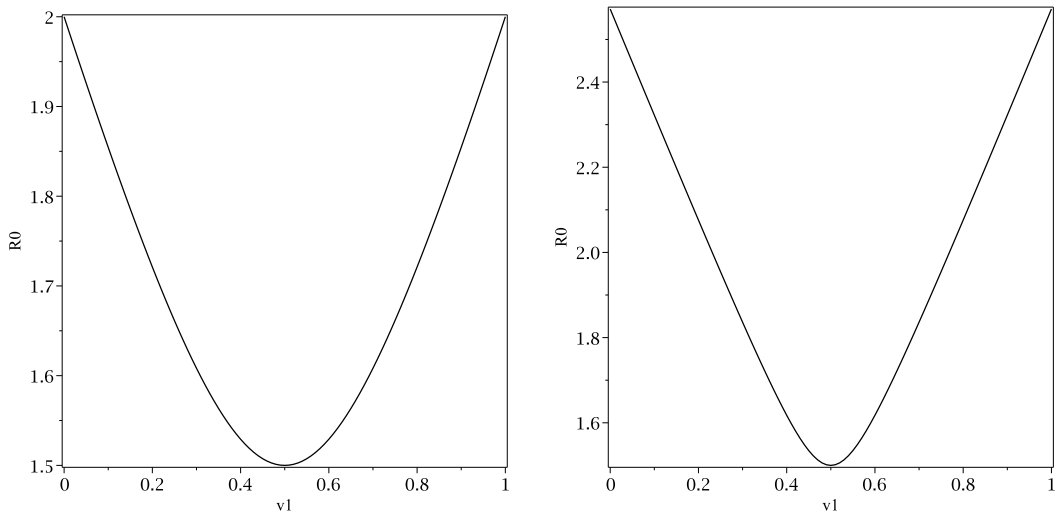
provide numerical examples in which patch dependent transmission and recovery rates are considered for the two optimisation problems studied in this chapter. One of the purposes of computing these numerical examples is to see if Assumption **(A2)** is relaxed in Theorem 4.1 and Theorem 4.2, whether the migration pattern of susceptible individuals satisfy $\Lambda\mathbf{1} = \mathbf{0}$ or not. Another aim is to see if patch dependent infection and recovery rates are assumed, whether the conclusion of Theorem 4.1 and Theorem 4.2 still holds or not. All numerical experiments were performed for the case $J = 2$ using Maple$^{\text{TM}}$15 software.

In order to compute the numerical examples, I note that the diagonal matrix D in the optimisation problems (4.8)–(4.9) and (4.15)–(4.16) depends on $\mathbf{v}$, with $v_j \in [0,1]$ and $\sum_{j=1}^{J} v_j = 1$. Therefore, to find the optimal D which minimises the basic reproduction number R_0 or the spectral abscissa of A in the Jacobian matrix (4.14) is equivalent to finding an optimal $\mathbf{v}$ such that $v_j \in [0,1]$ and $\sum_{j=1}^{J} v_j = 1$. With this observation I computed R_0 and $s(A)$ by varying v_1 from 0 to 1. The corresponding value for v_2 is determined so that $v_1 + v_2 = 1$ holds. The approximate value for the optimal $\mathbf{v}^*$ is then used to compute λ_{jk}, the migration rates for susceptible individuals.

Figures 4.1, 4.2 and 4.3 show plots for patch independent disease transmission and recovery rates. For these plots, the disease transmission and recovery rates were chosen, respectively, as $\beta_j = \beta = 3$ and $\gamma_j = \gamma = 1$ in both patches. Figures 4.4, 4.5 and 4.6 show plots for patch dependent disease transmission and recovery rates. The transmission and recovery rates for these plots were chosen as $\beta_1 = 2$, $\beta_2 = 3$, $\gamma_1 = 1$ and $\gamma_2 = 1.2$.

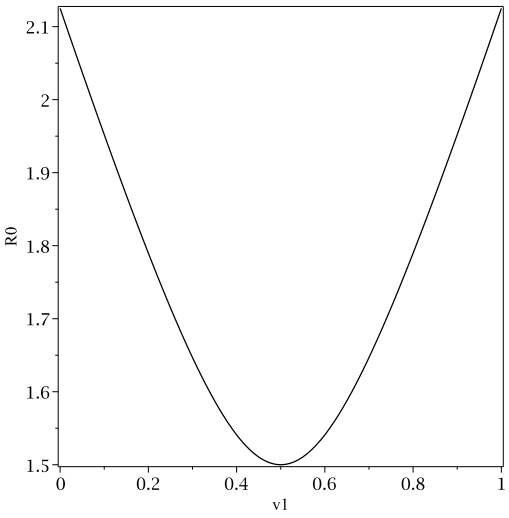
Figure 4.1 represents plots of R_0 when the migration rates of infected individuals satisfy Assumption **(A2)**, that is $H\mathbf{1} = \mathbf{0}$. The specific values for the migration rates of infected individuals are given in the figure. It can be seen from Figure 4.1 that for each plot the minimum value of R_0 is attained when $v_1^* = v_2^* = 0.5$. The corresponding optimal D is $D^* = \text{diag}(3 \times \mathbf{v}^*) = \text{diag}(1.5, 1.5)$. Choosing $\lambda_{jk} = D_{kk}^*$, for $j,k = 1,2$, implies that $\Lambda\mathbf{1} = \mathbf{0}$, confirming the result of Theorem 4.1.

Figure 4.2 show plots of R_0 when the migration rate of infected individuals do not satisfy Assumption **(A2)**. The specific parameters used for the migration rates of infected individuals are given in Table 4.1 along with the optimal $\mathbf{v}^*$, the corresponding minimum values of R_0 and the optimal migration rates of susceptible individuals. These plots show that when Assumption **(A2)** is not satisfied the optimal migration pattern for susceptible individuals do not satisfy $\Lambda\mathbf{1} = \mathbf{0}$. This suggests that for the conclusion of Theorem 4.1 to hold, Assumption **(A2)** must be satisfied.

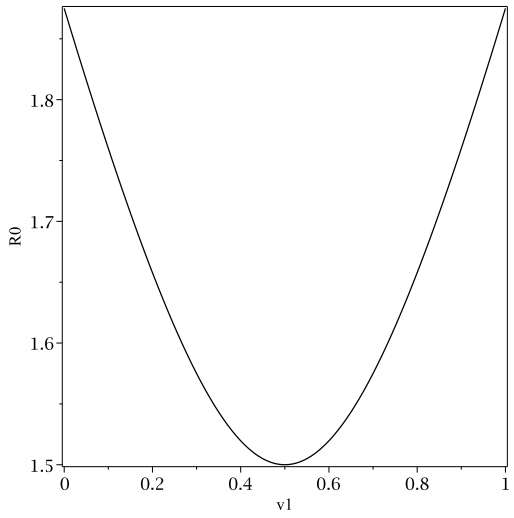


(a) $\eta_{12} = \eta_{21} = 1$

(b) $\eta_{12} = \eta_{21} = 0.2$



(c) $\eta_{12} = \eta_{21} = 0.7$

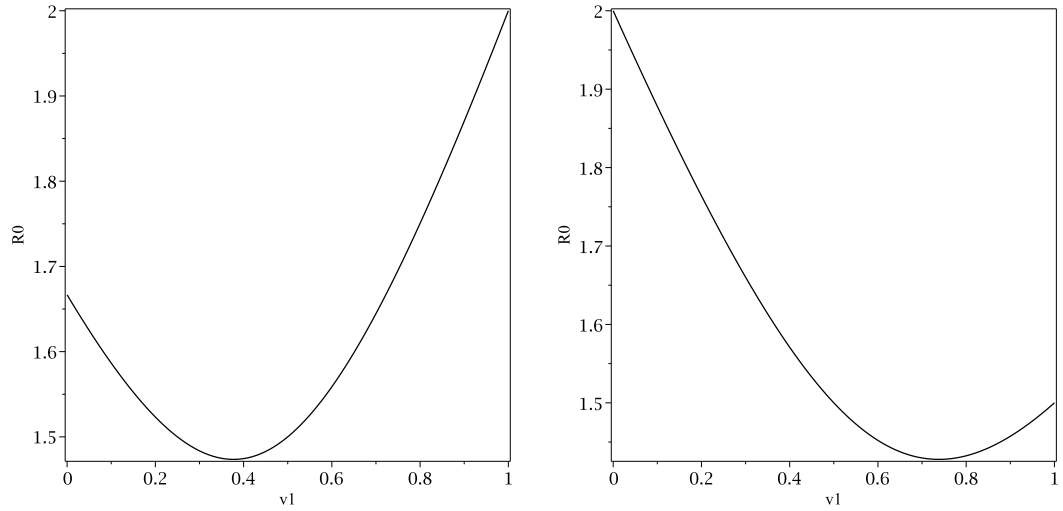


(d) $\eta_{12} = \eta_{21} = 1.5$

Figure 4.1: Plots of R_0 for the case $H\mathbf{1} = \mathbf{0}$, and for patch independent transmission and recovery rates. Each plot shows that R_0 is minimum when $v_1 = v_2 = 0.5$, which implies that $\Lambda\mathbf{1} = \mathbf{0}$.

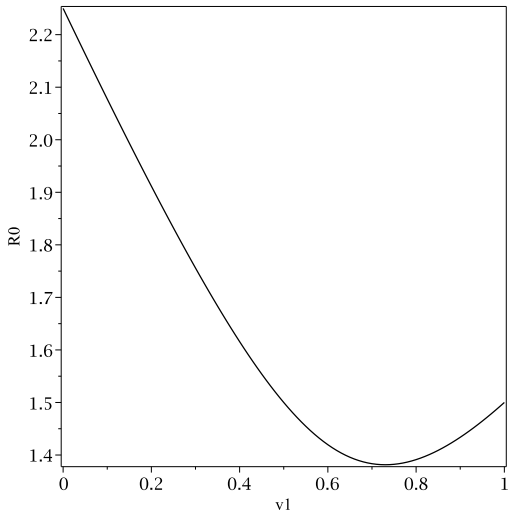
Parameters	(a)	(b)	(c)	(d)	(e)	(f)
η_{12}	1.5	3	2	0.2	0.5	2
η_{21}	2	2	1	0.5	1.5	0.5
v_1^*	0.38	0.74	0.73	0.43	0.28	0.80
v_2^*	0.62	0.26	0.27	0.57	0.72	0.20
R_0^*	1.47	1.428	1.382	1.451	1.322	1.200
λ_{12}	1.86	0.78	0.81	1.71	2.16	0.60
λ_{21}	1.14	2.22	2.19	1.29	0.84	2.40

Table 4.1: Parameter values used to produce the plots in Figure 4.2

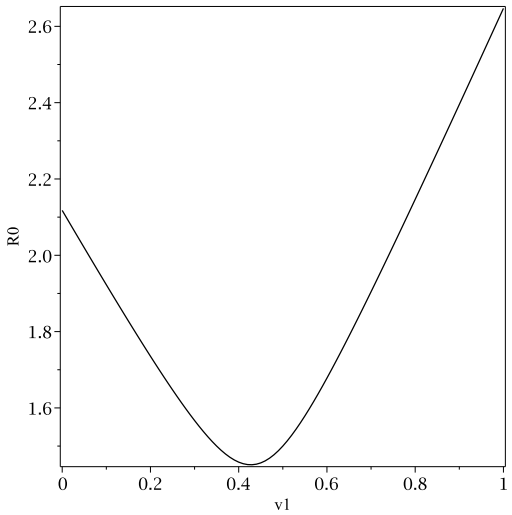


(a)

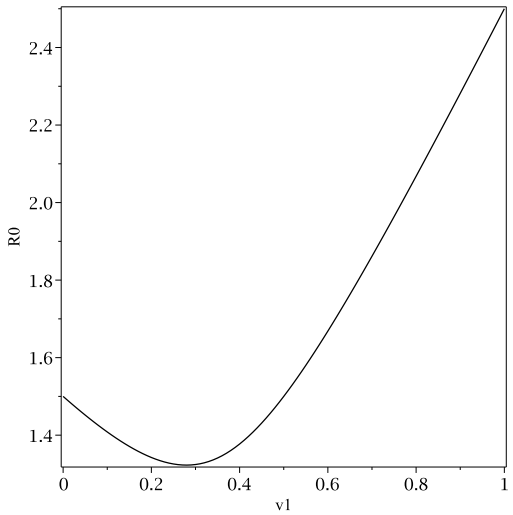
(b)



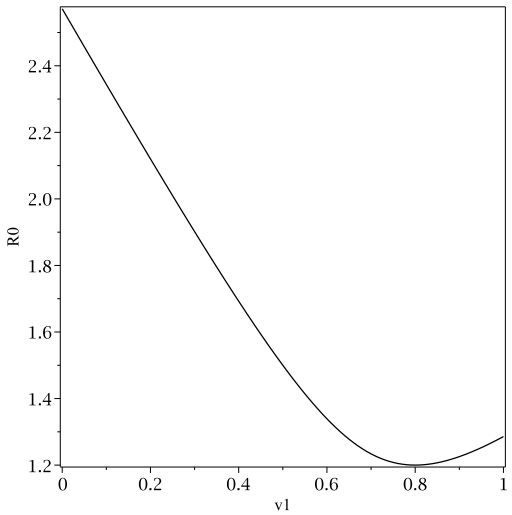
(c)



(d)



(e)



(f)

Figure 4.2: Plots of R_0 for the case $H\mathbf{1} \neq \mathbf{0}$, and for patch independent transmission and recovery rates. Each plot shows that R_0 is minimum when $v_1 \neq v_2$, which implies that $\Lambda\mathbf{1} \neq \mathbf{0}$.

Figure 4.3 (a) and (b) show plots of $s(A)$ for the case when the migration rate of infected individuals satisfy Assumption **(A2)**. Plots (c) to (f) show the case when Assumption **(A2)** is not satisfied. The specific parameters used for the migration rates of infected individuals are given in Table 4.2 along with the optimal $\mathbf{v}^*$, the corresponding optimal value of $s(A)$ and values for the migration rate of susceptible individuals. The migration rates for susceptible individuals are chosen as $\lambda_{jk} = c \times s(A)\frac{D_{kk}}{\beta} = s(A)v_k$, for $j,k = 1,2$, with $c = 1$. It can be inferred from plots (a) and (b) that when Assumption **(A2)** is satisfied, the optimal migration pattern for susceptible individuals follow $\Lambda\mathbf{1} = \mathbf{0}$, which confirms the result obtained in Theorem 4.2. However, when Assumption **(A2)** is not satisfied, plots (c) to (f), show that the optimal migration pattern for susceptible individuals cannot be chosen to follow $\Lambda\mathbf{1} = \mathbf{0}$. This suggests that Assumption **(A2)** is required for the conclusion of Theorem 4.2 to hold.

Figure 4.4 and Figure 4.5 show plots of R_0 with patch dependent transmission and recovery rates, respectively, for the case when Assumption **(A2)** holds and when it does not hold. As previously stated, the disease transmission and recovery rates for the plots in Figure 4.4 and Figure 4.5 were taken as $\beta_1 = 2$, $\beta_2 = 3$, $\gamma_1 = 1$ and $\gamma_2 = 1.2$. The remaining parameters used in these plots are given in Figure 4.4 and Figure 4.5 along with the optimal $\mathbf{v}^*$ and the corresponding optimal migration rates for susceptible individuals. In both Figure 4.4 and Figure 4.5, the migration rates for susceptible individuals are chosen as $\lambda_{jk} = D_{kk} = \beta_k v_k$. These plots suggest that when patch dependent transmission and recovery rates are considered, the conclusion of Theorem 4.1 may not hold even if Assumption **(A2)** is satisfied.

Parameters	(a)	(b)	(c)	(d)	(e)	(f)
η_{12}	1	0.2	1	0.2	0.5	2
η_{21}	1	0.2	2	0.5	1.5	0.5
v_1^*	0.50	0.50	0.33	0.45	0.33	0.75
v_2^*	0.50	0.50	0.67	0.55	0.67	0.25
$s(A)^*$	0.5	0.5	0.414	0.466	0.366	0.25
λ_{12}	0.25	0.25	0.28	0.26	0.25	0.06
λ_{21}	0.25	0.25	0.14	0.21	0.12	0.19

Table 4.2: Parameter values used to produce the plots in Figure 4.3

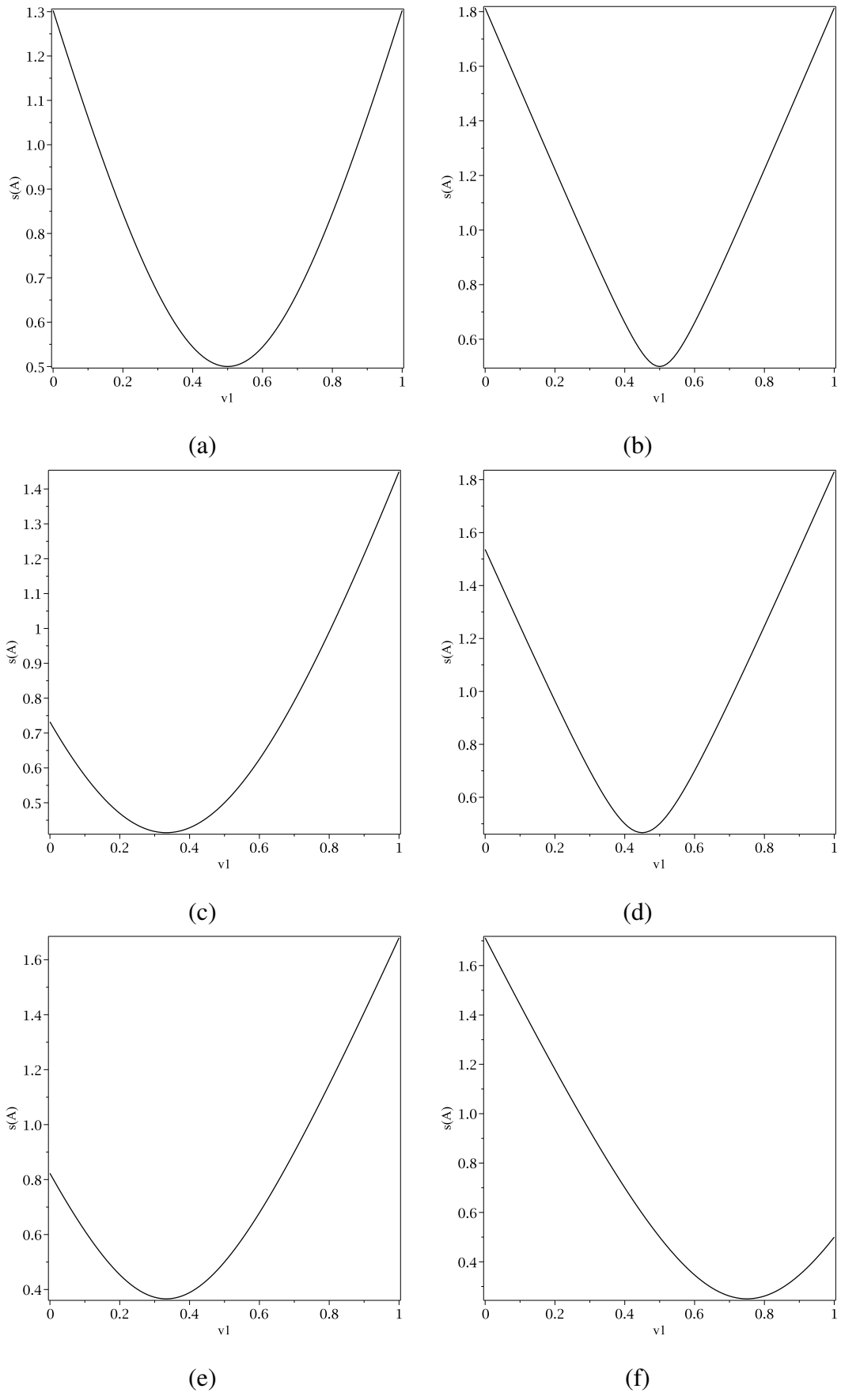
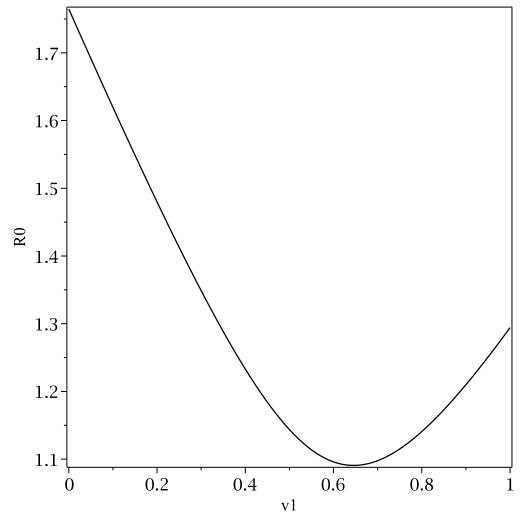
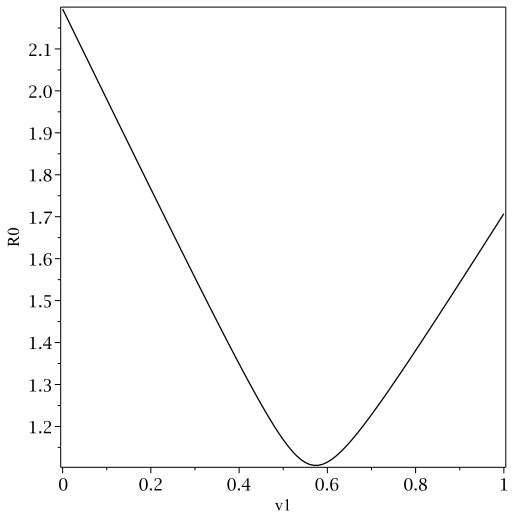


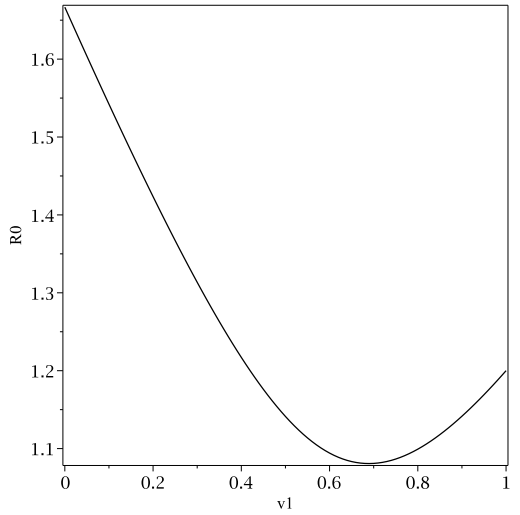
Figure 4.3: Plots of $s(A)$ for patch independent transmission and recovery rates. Plots (a) and (b) are for the case $H\mathbf{1} = \mathbf{0}$ and plots (c) to (f) are for the case $H\mathbf{1} \neq \mathbf{0}$. The minimum value of $s(A)$ and the corresponding values of v_1 and v_2 determines that, $\Lambda\mathbf{1} = \mathbf{0}$ for the plots in (a) and (b) and $\Lambda\mathbf{1} \neq \mathbf{0}$ for plots in (c) to (f).



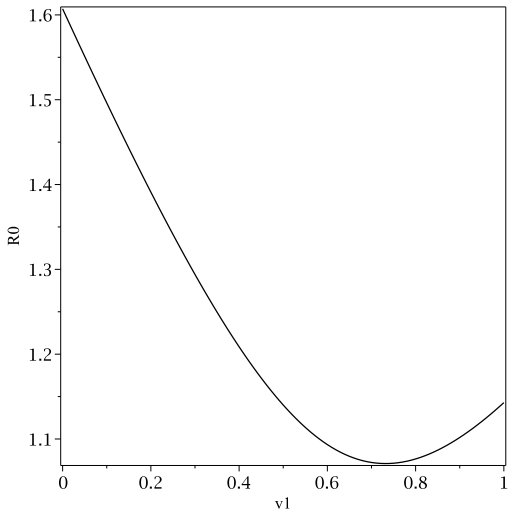
(a) $\eta_{12} = \eta_{21} = 1$, $v_1^* = 0.65$, $v_2^* = 0.35$
$\lambda_{12} = 1.05$, $\lambda_{12} = 1.30$



(b) $\eta_{12} = \eta_{21} = 0.2$, $v_1^* = 0.57$, $v_2^* = 0.43$
$\lambda_{12} = 1.29$, $\lambda_{12} = 1.14$

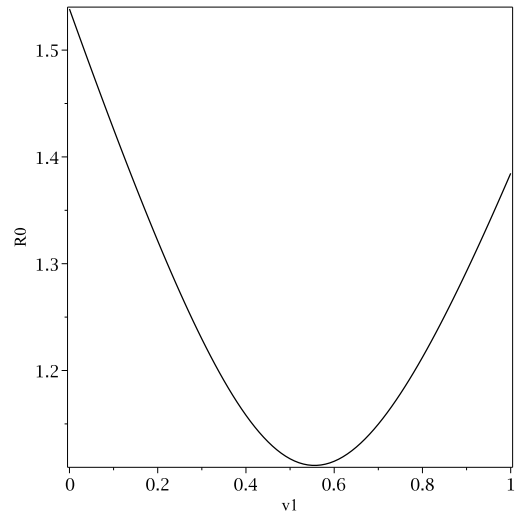


(c) $\eta_{12} = \eta_{21} = 1.5$, $v_1^* = 0.69$, $v_2^* = 0.31$
$\lambda_{12} = 0.93$, $\lambda_{12} = 1.38$

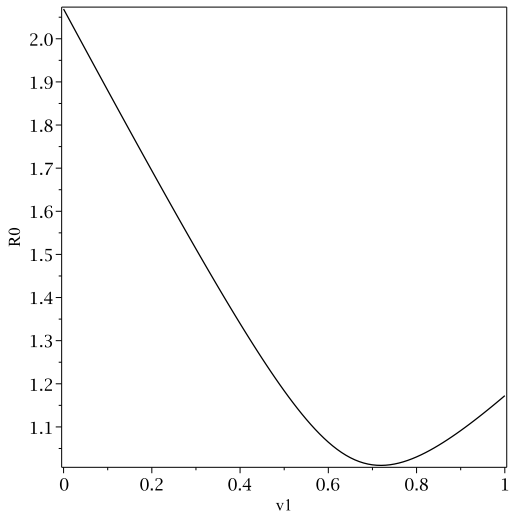


(d) $\eta_{12} = \eta_{21} = 2$, $v_1^* = 0.73$, $v_2^* = 0.27$
$\lambda_{12} = 2.19$, $\lambda_{12} = 0.54$

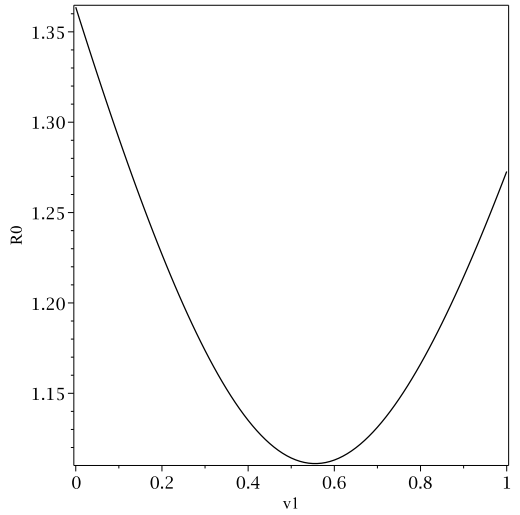
Figure 4.4: Plots of R_0 for the case when $H\mathbf{1} = \mathbf{0}$, and for patch dependent transmission and recovery rates. The values of v_1 and v_2 at which R_0 is minimum determine that $\Lambda\mathbf{1} \neq \mathbf{0}$.



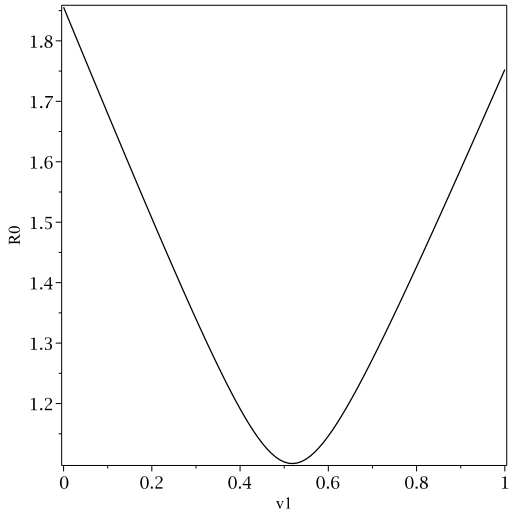
(a)$\eta_{12} = 1$, $\eta_{21} = 1.5$, $v_1^* = 0.56$, $v_2^* = 0.44$
$\lambda_{12} = 0.1.32$, $\lambda_{12} = 1.12$



(b)$\eta_{12} = 1$, $\eta_{21} = 0.5$, $v_1^* = 0.72$, $v_2^* = 0.28$
$\lambda_{12} = 0.84$, $\lambda_{12} = 1.44$



(c) $\eta_{12} = 2$, $\eta_{21} = 3$, $v_1^* = 0.56$, $v_2^* = 0.44$
$\lambda_{12} = 1.32$, $\lambda_{12} = 1.12$



(d)$\eta_{12} = 0.2$, $\eta_{21} = 0.5$, $v_1^* = 0.52$, $v_2^* = 0.48$
$\lambda_{12} = 1.44$, $\lambda_{12} = 1.04$

Figure 4.5: Plots of R_0 for the case when $H\mathbf{1} \neq \mathbf{0}$, and for patch dependent transmission and recovery rates. The values of v_1 and v_2 at which R_0 is minimum determine that $\Lambda\mathbf{1} \neq \mathbf{0}$.

Figure 4.6 show plots of $s(A)$ with patch dependent transmission and recovery rates. Parts (a) and (b) show plots for the case when Assumption **(A2)** holds and parts (c) to (f) are plots for the case when Assumption **(A2)** is not satisfied. The specific parameters used to produce the plots in Figure 4.6 are given in Table 4.3. The migration rates of susceptible individuals are chosen as $\lambda_{jk} = c \times s(A)\frac{D_{kk}}{\beta_k} = s(A)v_k$, for $j,k = 1,2$, with $c = 1$. These plots suggest that when patch dependent transmission and recovery rates are considered, the conclusion of Theorem 4.2 may not hold even if Assumption **(A2)** is satisfied.

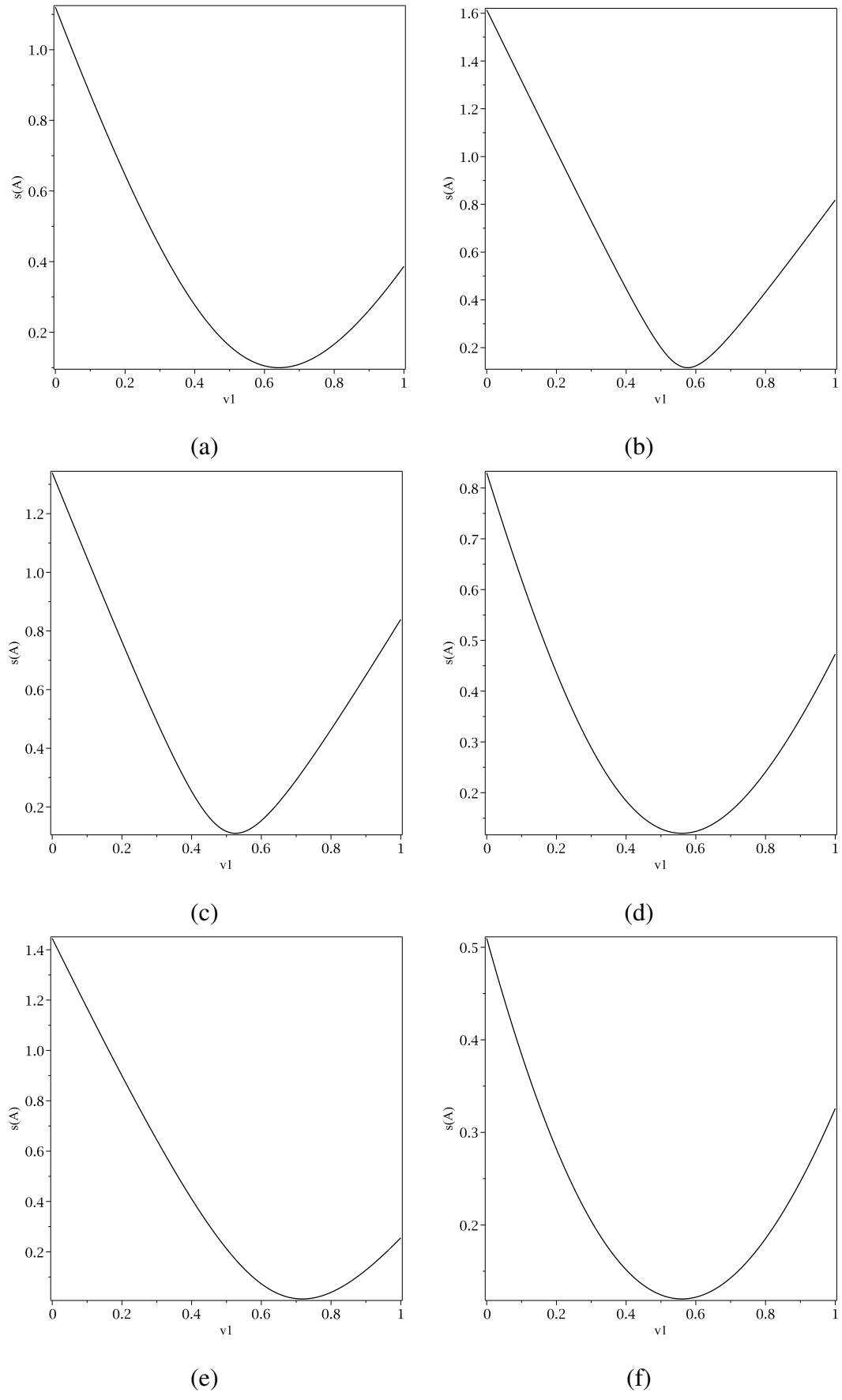


Figure 4.6: Plots of $s(A)$ for patch dependent transmission and recovery rates. Plots (a) and (b) are for the case when $H\mathbf{1} = \mathbf{0}$ and plots (c) to (f) are for the case when $H\mathbf{1} \neq \mathbf{0}$. The minimum value of $s(A)$ and the corresponding values of v_1 and v_2 determine that $\Lambda\mathbf{1} \neq \mathbf{0}$ for all cases.

Parameters	(a)	(b)	(c)	(d)	(e)	(f)
η_{12}	1	0.2	0.2	1	1	2
η_{21}	1	0.2	0.5	1.5	0.5	3
v_1^*	0.64	0.58	0.53	0.56	0.72	0.56
v_2^*	0.36	0.42	0.47	0.44	0.28	0.44
$s(A)^*$	0.10	0.116	0.11	0.12	0.013	0.12
λ_{12}	0.036	0.05	0.05	0.53	0.004	0.53
λ_{21}	0.064	0.07	10.06	0.07	0.009	0.07

Table 4.3: Parameter values used to produce the plots in Figure 4.6

It can be seen from the plots given in all figures that, whether the migration rates of infected individuals satisfy $H\mathbf{1} = \mathbf{0}$ or not, the maximum of R_0 and $s(A)$ occurs when v_1 is either 0 or 1. If $v_1 = 0$ then $\lambda_{21} = 0$, and if $v_1 = 1$, then $\lambda_{12} = 0$, as $v_2 = 0$ in this case. In either case, this implies that the migration of susceptible individuals is in one direction, either from patch 1 to patch 2 or from patch 2 to patch 1. Therefore, it appears that, for the two patch case, the worst case migration for susceptible individuals is when there is only one way migration between the two patches.

4.6 Conclusions

The aim of the analyses in this chapter is to provide optimal migration strategies which can be applied to minimise the basic reproduction number and the initial growth rate of a disease. The results show that if the migration rates of infected individuals follow $H\mathbf{1} = \mathbf{0}$, then setting the migration rates of susceptible individuals to satisfy $\Lambda\mathbf{1} = \mathbf{0}$ simultaneously minimises both measures. Instead, if we consider minimising these two measures over possible H when Λ is given, the optimisations become trivial when Λ satisfies $\Lambda\mathbf{1} = \mathbf{0}$. In this case the solution to the problem (4.8)–(4.9) is $\beta/(J\gamma)$ and that to problem (4.15)–(4.16) is $\beta/(J) - \gamma$. If $\beta/(J\gamma) < 1$, then $\beta/(J) - \gamma < 0$ and the DFE is locally asymptotically stable. Consequently, the disease will not spread. If $\beta/(J\gamma) > 1$, then the DFE is unstable and the disease will spread. The rate of the spread of the disease in its initial stage is given by $\beta/(J) - \gamma$.

As mentioned in Chapter 3, the migration patterns $H\mathbf{1} = \mathbf{0}$ and $\Lambda\mathbf{1} = \mathbf{0}$ can be satisfied when H and Λ are symmetric, in which case the migration rates of susceptible individuals between any given two patches are equal and the same implication applies to the migration rates of infected individuals. Such an assumption was used in [105, 182, 207] to model the spread of influenza between cities,

based on air travel data. Therefore, the assumption imposed on the migration rates in Theorem 4.1 and Theorem 4.2 can be applied in some practical situations. As noted above, when $\Lambda\mathbf{1} = \mathbf{0}$, the basic reproduction number is given by $\beta/J\gamma$. Therefore, complete eradication of a disease is only possible when $\beta/(J\gamma)$ is less than 1. On the other hand, if $\beta/(J\gamma)$ is greater than 1, then Theorem 4.2 provides a means to minimise the initial growth rate of the disease. This is a useful control strategy in conjunction with or in the absence of any other preventive measure.

Numerical examples suggest that the conclusion of Theorem 4.1 and Theorem 4.2 may not hold if the assumption on the migration rates of infected individuals (Assumption **(A2)**) is relaxed or when patch dependent transmission and recovery rates are considered. It is unclear if the same method of proof can be applied to provide an analytic result after relaxing Assumption **(A2)** in both theorems, since it is not easy to choose the right eigenvector to satisfy the optimal conditions given in (4.12) and (4.19) in this case. In the case of patch dependent transmission and recovery rates, the choice of both the left and right eigenvectors is difficult to determine. For an equivalent SIR model, the parameters R_0 and $s(A)$ defined in this chapter remains the same, so the results determined in Theorem 4.1 and Theorem 4.2 are applicable for the SIR model too. Further direction of exploration is to consider demographic factors such as births and deaths. In this case I expect similar techniques as in this chapter to be applicable for minimising the basic reproduction number and the spectral abscissa of the Jacobian matrix of the approximating ODE.

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