A Model for Disease Transmission in a Patchy Environment

by

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Abstract

A disease transmission model is formulated as a system of ordinary differential equations for a population with individuals traveling between discrete geographic patches. An expression for the basic reproduction number $\mathcal{R}_0$ is derived, and the disease free equilibrium is proved to be globally asymptotically stable for $\mathcal{R}_0 < 1$. For a disease with very short exposed and immune periods in a two patch environment with all individuals traveling, $\mathcal{R}_0$ gives a sharp threshold with the endemic equilibrium being globally asymptotically stable for $\mathcal{R}_0 > 1$. If for isolated patches the disease is endemic in only one patch, then travel of infectious individuals from the patch with endemic disease may lead to the disease becoming endemic in both patches. However, if this rate of travel is increased, then the disease may die out in both patches. Thus travel of infectious individuals in a patchy environment can have an important influence on disease spread.

Supervisor: Dr. P. van den Driessche, (Department of Mathematics and Statistics)

To:

my daughter, *Zahra*

and

my husband, *Bahram*

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Contents

List of Tables

List of Figures

Chapter 1

Introduction

1.1 An introduction to epidemic models

The basic aims of mathematical modeling of communicable disease spread are to obtain a better understanding of transmission mechanisms and the features that are most influential in the spread of diseases. Models enable predictions to be made, and can be used to suggest and evaluate control strategies.

For many deterministic disease transmission models, the population is divided into four disease-state compartments: susceptible individuals, people who can catch the disease; exposed individuals, people whose body is a host for the infectious agent but are not yet able to transmit the disease; infectious (infective) individuals, people who have the disease and can transmit the disease; recovered individuals, people who have recovered from the

disease. Susceptible individuals may become exposed (latent) after contact with an infectious individual. Exposed individuals become infectious and as the infection wanes they enter the recovered compartment. If the disease confers only temporary immunity, then recovered individuals return to the susceptible compartment as immunity fades. This general model is known as an SEIRS model. For a disease in which the exposed and recovered periods can be ignored, for example gonorrhea, an SIS model is appropriate. For a disease with a short exposed period that confers permanent immunity an SIR model can be used. Such a model is also used as an approximation for many diseases, e.g., influenza, plague [BC, Section 7.2].

Deterministic epidemic models have been formulated and discussed since the beginning of the 20th century. In 1927 Kermack and McKendrick introduced a simple SIR model and they showed that the density of susceptible individuals must exceed a threshold value in order for an epidemic outbreak to occur. An epidemic is a quick outbreak of a disease that infects many individuals in a population; it may be restricted to one area or be global (pandemic). By contrast, a disease is said to be endemic in a region if it is present at all times in that region, e.g., prior to widespread immunization, measles was endemic in many large cities; see [C, p. 330].

We now state two definitions that are used in analyzing models.

Definition 1.1. A *disease free equilibrium* (DFE) is a steady state solution of an epidemic model with all infected variables equal to zero.

Definition 1.2. [AM, p. 17]. The *basic reproduction number*, denoted by $\mathcal{R}_0$, is the average number of secondary infections produced when one infected individual is introduced into a host population where everyone is susceptible.

In many epidemic models, if $\mathcal{R}_0 < 1$ then the disease can not invade the population. On the other hand, if $\mathcal{R}_0 > 1$, then the disease can invade a susceptible population.

Consider a disease with a latent period and that confers temporary immunity; in this case an SEIRS epidemic model is appropriate. The flow between compartments is summarized in Figure 1.1.

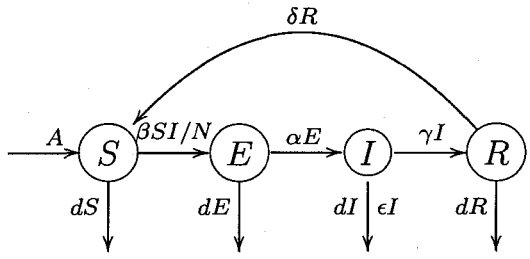

Figure 1.1: Flow diagram of an SEIRS model

The population dynamics for the SEIRS model is given by the following system of ordinary differential equations subject to non-negative initial con-

ditions.

$$\frac{dS}{dt} = A - \frac{\beta SI}{N} - dS + \delta R \tag{1.1}$$

$$\frac{dE}{dt} = \frac{\beta SI}{N} - (\alpha + d)E \tag{1.2}$$

$$\frac{dI}{dt} = \alpha E - (\epsilon + \gamma + d)I \tag{1.3}$$

$$\frac{dR}{dt} = \gamma I - (d + \delta)R \tag{1.4}$$

Here $N(t) = S(t) + E(t) + I(t) + R(t)$ is the total population number at time t and the parameters represent

A: number of individuals entering the population per unit time,

d: natural death rate,

δ: rate of loss of immunity,

α: rate that exposed individuals become infectious,

γ: recovery rate and

ϵ: rate of death due to the disease.

Thus $1/d$ is the average lifetime, $1/\delta$ is the average immune period, and $1/\alpha$ is the average exposed (latent) period. The average number of effective contacts of an infective individual per unit time is denoted by β, and called the (effective) contact rate. A fraction S/N of these is with susceptible individuals and so produces new infections. Thus the average number of new cases per unit time is $(\beta S/N)I$. This kind of incidence (proportional to SI/N) is called standard incidence and is generally regarded as more accurate for transmission of sexually transmitted diseases. For a discussion of incidence functions, see, for example, [H, Section 2.1].

The basic reproduction number for the SEIRS model is

$$\mathcal{R}_0 = \frac{\beta\alpha}{(\epsilon+\gamma+d)(\alpha+d)} \tag{1.5}$$

This number $\mathcal{R}_0$ is the average number of new infections produced by one infected individual during the infective period (see Appendix A.1 for more details). If $\mathcal{R}_0 < 1$, then the DFE is globally asymptotically stable, as can be shown by using the Lyapunov function $V = dI + \alpha(N - S - R)$. Thus methods of disease control aim to reduce $\mathcal{R}_0$ below 1.

This SEIRS model with $\epsilon = 0$ and $A = dN$ (so the total population is constant) is discussed in [LMvdD], where it is proved that the endemic equilibrium is globally asymptotically stable for sufficiently small or large values of δ. This includes the corresponding SEIR, SEIS and SIS models. The authors expect that the global asymptotic stability holds for all values of δ.

A variety of models for different infectious diseases have been formulated and mathematically analyzed; for example, an MSEIR model with age groups, in which infants with passive immunity are in compartment M, is formulated in [H]. This model is analyzed and the results are applied to measles in Niger, Africa [H, Section 7].

Hadeler and van den Driessche [HvdD] considered an SIRS model with two social groups with different susceptibility. They assumed equal birth and death rates and constant population size. They showed that if the reproduction number modified by the education rate for susceptible individuals is less

than one, then the DFE is locally asymptotically stable, and for some parameter values the model can exhibit a backward bifurcation, and a locally stable endemic equilibrium also exists. If this reproduction number is greater than one, then there is a unique endemic equilibrium.

Kribs-Zaleta and Velasco-Hernández [KV] considered an SIS model that includes vaccination that may wane over time. Their model has mass action incidence (i.e., incidence term proportional to SI), equal birth and death rates and constant population size. Since the population size is constant, they reduced the model to 2-dimensions and proved that the DFE is globally asymptotically stable if $\mathcal{R}_0 < 1$. They showed that if the vaccine is not completely effective, then there is exactly one endemic equilibrium when the vaccination reproduction number is greater than 1. However, if the vaccination reproduction number is less than 1, then for some parameter values backward bifurcation is possible, with two endemic equilibria. In this case the number of infective individuals may go to an endemic equilibrium or to zero depending on the initial conditions.

Brauer and van den Driessche [BvdD] considered simple models for disease transmission that include immigration of infective individuals and variable population size. They introduced an SIS model with general contact rate and proved that the model has a unique endemic equilibrium that is globally asymptotically stable. They showed that with immigration of infective individuals there is no disease free equilibrium, and thus no threshold associated

with a basic reproduction number. They also applied their SIS model to the screening for HIV in a prison system and showed numerically how screening and quarantining infective prisoners could considerably reduce the number of infective individuals at the endemic equilibrium.

Hethcote and Yorke [HY, Chapter 2] considered a one sex constant population SIS model for transmission of gonorrhea in a population of constant size. Since the latent period is ignored, $\mathcal{R}_0 = \beta/\gamma$ from (1.5) in the limit as $\alpha \to \infty$ and $\epsilon = d = 0$. Using fractions of infective and susceptible individuals, they showed that if $\mathcal{R}_0 \leq 1$ then the disease dies out, while if $\mathcal{R}_0 > 1$ then the disease remains endemic. They also considered a model for a heterogeneous population [HY, Chapter 3] by dividing the population into n homogeneous groups. Within each group the contact rate and mean duration of infection are constant. Let B be the $n \times n$ coefficient matrix of the linearization of the system of infective equations at the DFE. They proved that if all the groups have contact with each other (the model is irreducible), then the DFE is globally asymptotically stable if the spectral abscissa (see Definition B.2) of B is less than or equal to 0; whereas if this number is greater than 0, then the endemic equilibrium is globally asymptotically stable.

Castillo-Chávez and coauthors [CHL] considered an SIS model for the transmission of gonorrhea and other sexually transmitted diseases in a heterosexually active population. They assumed that there are two competing strains or two distinct sexually transmitted pathogens and that a host can

not be invaded by both strains at the same time. The population is divided into males and females with different contact rates. For each sex the infectious individuals are divided into two groups: those infected with strain 1 and those infected with strain 2. They computed the basic reproduction number for each strain and showed that, if these are both less than or equal to 1, then the disease free equilibrium is globally asymptotically stable; whereas if at least one reproduction number is greater than 1, then the disease spreads in the population, normally with one strain present.

1.2 Discrete patch epidemic models

The SEIRS model given in (2.1)-(2.4) assumes random mixing of the population, and takes no account of spatial variation. Since communicable diseases can be transmitted easily from one area to another, it is important to study the impact of population travel on the spread of such diseases, and to determine whether travel can increase disease persistence. To account for spatial heterogeneity in mathematical models of disease spread, geographic regions can be considered as continuous or discrete regions. If the geographic regions are assumed to be continuous, then for continuous time the mathematical model involves reaction diffusion equations, see e.g., [M, Chapter 20]. If the geographic regions are considered to be discrete, namely patches, then for continuous time the mathematical model involves a system of ordinary differential equations with population dispersal among the patches. This

formulation is appropriate for travel between cities or regions (considered as patches). Compartmental models with discrete patches have been formulated and discussed by several authors in the past ten years. The following describes some studies closely related to the model formulated in Section 2.1.

Sattenspiel and Dietz [SD] introduced an SIR model in which the population in each compartment is subdivided keeping track of both the patch (city) where an individual normally resides and the patch that an individual is visiting. They showed how their model can be applied to a population with two types of mobility, in which there are both within-group and between-group contacts. They also applied their model to the spread of measles on the West Indies island of Dominica in which transmission of measles is highly related to travel within the school system. The population is also divided into separate age classes because children in Dominica travel to different regions depending on their school age activities.

Arino and van den Driessche gave some analytical results for a similar SIS model [AvdD1, MPS, 2003], and for an SEIRS model [AvdD2, LNCIS, 2003]. For these models, an explicit expression for the basic reproduction number was given, and numerical simulation for the SIS model indicated that this number acts as a threshold between extinction and invasion of the disease. These simulations also illustrated that travel can stabilize or destabilize the disease free equilibrium.

Hyman and LaForce [HF] considered modeling the spread of influenza

among cities. For each city, they assumed an SIRP model in which P denotes partially immune individuals. They assumed standard incidence, population travel independent of disease status and symmetric, thus the population of each city remained constant. Fluctuation in infectivity between seasons (assumed the same in all cities) was incorporated, since influenza is more likely to spread in the winter. They applied their model, which accounts for non-random mixing among the cities, to influenza spread among 33 large cities in the US. They obtained their parameter values from the epidemiology literature, and they estimated migration between cities from airline flight data. By numerically integrating their equations, they calculated the disease deaths in the cities during the 1996-2000 influenza seasons and compared these calculations with actual influenza mortality data.

In the models cited above, travel was assumed independent of disease status. Wang and coauthors [WM, 2003], [W, 2004] and [WZ, 2004] have formulated and analyzed SIS models in terms of the number of susceptible and infective individuals in a given patch, but they allowed for different travel rates between individuals in these two different disease states. Mass action incidence was assumed in [WZ][W] and the disease was assumed not to cause death. Wang [W] concluded that for a 2-patch SI model with constant input, susceptible travel should also be controlled to eradicate a disease. In [WZ], numerical examples showed that population travel can both intensify and reduce the spread of disease in patches. A 2-patch SIS model for a

constant total population was analyzed in [WM] by sometimes working in terms of proportions of infective individuals and so reducing the system to 3-dimensions. It was found that if in isolation the disease is endemic in one patch but extinct in the other, then different travel rates can cause the disease to spread in both patches, or to go extinct in both patches. These studies indicate that a patchy environment and travel between patches can influence disease spread in a complicated way, and this thesis aims to give some precise results about this influence in terms of disease reproduction numbers.

The formulation of the SEIRS model on p patches and description of its parameters are introduced in Section 2.1 along with a basic theorem showing that the model is well-posed. Section 2.2 deals with the computation of the basic reproduction number $\mathcal{R}_0$. If this number is less than 1, it is proved that the unique disease free equilibrium is globally asymptotically stable. Section 2.3 describes a special case of the SEIRS model with $p = 4$ patches, along with some numerical simulations. All numerical simulations use MATLAB ode23. Chapter 3 is concerned with an SIS model for two patches. In Section 3.1 an explicit formula for the basic reproduction number for a two patch SIS model is derived. Section 3.2 describes the special case in which there is no disease death and natural death rates are the same in both patches. Equal travel rates for susceptible and infective individuals of each patch are assumed in Section 3.3. A situation in which infective individuals of one patch do not travel is considered in Section 3.4. Section 3.5 deals with a

case in which infective individuals of both patches do not travel. Stability of each equilibrium is studied for these special cases, accompanied by numerical simulations. Chapter 4 contains conclusion and suggestions for further research. Appendix A.1 deals with interpretation of $\mathcal{R}_0$ for the SEIRS model. Appendix A.2 includes the details of the Routh-Hurwitz conditions for the proof of Theorem 3.8. Basic definitions and results from matrices and ordinary differential equations that are used in the proof of some theorems are briefly described in Appendix B.1.

Chapter 2

SEIRS model with p patches

2.1 Model derivation

Consider an SEIRS epidemic model for transmission of a communicable disease with population travel between p patches. Figure 2.1 shows the flow diagram between patch i and j of an SEIRS model. The number of susceptible, exposed, infectious and recovered individuals in patch i at time t, is denoted by $S_i(t)$, $E_i(t)$, $I_i(t)$ and $R_i(t)$, respectively. We assume there is population travel between patches with different travel rates for each compartment. The population dynamics for this SEIRS model is given by the

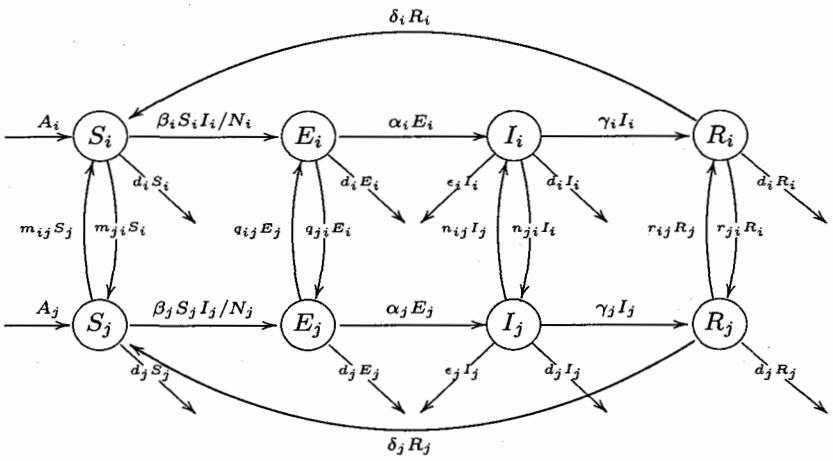

Figure 2.1: Flow diagram between patch i and j for an SEIRS model with p patches

following system of $4p$ ordinary differential equations with $i = 1, \ldots, p$.

$$\frac{dS_i}{dt} = A_i - \frac{\beta_i S_i I_i}{N_i} + \sum_{j=1}^{p} m_{ij} S_j - (\sum_{j=1}^{p} m_{ji} + d_i) S_i + \delta_i R_i \tag{2.1}$$

$$\frac{dE_i}{dt} = \frac{\beta_i S_i I_i}{N_i} + \sum_{j=1}^{p} q_{ij} E_j - (\sum_{j=1}^{p} q_{ji} + \alpha_i + d_i) E_i \tag{2.2}$$

$$\frac{dI_i}{dt} = \alpha_i E_i + \sum_{j=1}^{p} n_{ij} I_j - (\sum_{j=1}^{p} n_{ji} + \epsilon_i + \gamma_i + d_i) I_i \tag{2.3}$$

$$\frac{dR_i}{dt} = \gamma_i I_i + \sum_{j=1}^{p} r_{ij} R_j - (\sum_{j=1}^{p} r_{ji} + d_i + \delta_i) R_i \tag{2.4}$$

Here $N_i(t) = S_i(t) + E_i(t) + I_i(t) + R_i(t)$ is the total population number in patch i at time t, A_i is the number of individuals born per unit time, d_i is the natural death rate, δ_i is the rate of loss of immunity, α_i is the rate that exposed individuals become infectious, γ_i is the recovery rate and ϵ_i is the rate of death due to the disease in patch i. Thus $1/d_i$ is the average lifetime, $1/\delta_i$ is

the average immune period, and $1/\alpha_i$ is the average exposed (latent) period. The rate at which susceptible, exposed, infectious and recovered individuals travel from patch j to patch i is denoted by m_{ij}, q_{ij}, n_{ij} and r_{ij}, respectively. It is assumed that all parameters are positive constants except that ϵ_i, δ_i can be zero, and without loss of generality $m_{ii} = q_{ii} = n_{ii} = r_{ii} = 0$. The average number of effective contacts of an infectious individual per unit time in patch i is denoted by β_i, and standard incidence is assumed. Initially all variables are non-negative, $S_i(0) > 0$ for $i = 1, \ldots, p$ and $\sum_{i=1}^{p}(E_i(0) + I_i(0)) > 0$ (except that this last condition is strengthened in Sections 3.4 and 3.5); thus $N_i(0) > 0$. There are referred to as non-negative initial conditions.

The total population size in all patches is $N(t) = \sum_{i=1}^{p} N_i(t)$. Let $d = \min\{d_1, \ldots, d_p\}$ and $\mathcal{A} = \sum_{i=1}^{p} A_i$. The following result shows that the model is well posed and that each variable lies in the interval $[0, \mathcal{M}]$, where $\mathcal{M} = \max\{N(0), \mathcal{A}/d\}$.

Theorem 2.1. *Consider the system (2.1)-(2.4) with non-negative initial conditions. Then $E_i(t)$, $I_i(t)$ and $R_i(t)$ remain non-negative, $S_i(t)$ and $N_i(t)$ remain positive, and the total population $N(t)$ is bounded above for $t \geq 0$.*

Proof. Assume non-negative initial conditions. If for instance I_i becomes zero at a time t_1, before I_k, S_i, E_i, R_i $(i = 1, \ldots, p,\ k = 1, \ldots, p, k \neq i)$ become zero, then from (2.3), $dI_i/dt = \alpha_i E_i + \sum_{j=1}^{p} n_{ij} I_j \geq 0$ at t_1. Thus I_i is a non-decreasing function of t at t_1, and therefore I_i stays non-negative. Similarly it can be shown that E_i, R_i stay non-negative for non-negative initial conditions.

From (2.1) for $i = 1, \ldots, p$, $dS_i(t)/dt \geq -(\beta_i + \sum_{j=1}^{p} m_{ji} + d_i)S_i$. Thus

$$S_i(t) \geq S_i(0) \exp(-(\beta_i + \sum_{j=1}^{p} m_{ji} + d_i)t) \quad \text{for} \quad t \geq 0$$

which proves that $S_i(t) > 0$ provided that $S_i(0) > 0$. Thus $N_i(t) > 0$ provided that $S_i(0) > 0$. By summing all the equations $dN/dt = d(\sum_{i=1}^{p} N_i)/dt = \sum_{i=1}^{p}(A_i - \epsilon_i I_i - d_i N_i) \leq \mathcal{A} - dN$. If at a certain time t_2, $N(t_2) = \mathcal{A}/d$, then $dN/dt \leq 0$ at t_2, so $N(t)$ is non-increasing at t_2. Thus $N(t)$ is bounded above by $\mathcal{M}$. Since the right hand sides of (2.1)-(2.4) are continuously differentiable, basic theorems (see e.g., [P, Chapter 2]) can be used to show that there is a unique solution to the system with specified non-negative initial conditions and that this solution exists for all $t \geq 0$. □

2.2 Basic reproduction number $\mathcal{R}_0$

First it is shown that the model system has a unique disease free equilibrium, and then, using the next generation matrix method [vdDW], $\mathcal{R}_0$ is determined and used for stability results.

Theorem 2.2. *System (2.1)-(2.4) has a unique disease free equilibrium.*

Proof. According to Definition 1.1, a DFE of system (2.1)-(2.4) has all infected variables set to zero, namely $E_i = I_i = 0$ for $i = 1, \ldots, p$. Setting $E_i = I_i = 0$ for $i = 1, \ldots, p$ in (2.4) at a steady state (i.e, $dR_i/dt = 0$), for

$i = 1, \ldots, p$ gives

$$-GR = 0$$

with

$$G = \begin{bmatrix} \sum_{j=1}^{p} r_{j1} + d_1 + \delta_1 & -r_{12} & \cdots & -r_{1p} \\ -r_{21} & \sum_{j=1}^{p} r_{j2} + d_2 + \delta_2 & \cdots & -r_{2p} \\ \vdots & \vdots & \ddots & \\ -r_{p1} & -r_{p2} & \cdots & \sum_{j=1}^{p} r_{jp} + d_p + \delta_p \end{bmatrix}$$

and $R = [R_1, \ldots, R_p]^T$, where ^{T} denotes transpose. By Theorem B.6, Matrix G is a nonsingular M-matrix, because all off-diagonal entries are negative and every column sum of G is positive. Since $r_{ij} > 0$ for $i, j = 1, \ldots, p$, $i \neq j$, it follows that G is irreducible. Using Theorem B.4, G has a positive inverse, therefore it can be seen that $R_i = 0$ for $i = 1, \ldots, p$. A DFE for model (2.1)-(2.4) is thus given by

$$S_i = S_i^0 = N_i^0, E_i = I_i = R_i = 0 \text{ for } i = 1, \ldots, p$$

At equilibrium, $dS_i/dt = 0$ and from (2.1), $S^0 = [S_1^0, \ldots, S_p^0]^T$ satisfies the linear system $CS^0 = A$ with $A = [A_1, \ldots, A_p]^T$ and

$$C = \begin{bmatrix} \sum_{j=1}^{p} m_{j1} + d_1 & -m_{12} & \cdots & -m_{1p} \\ -m_{21} & \sum_{j=1}^{p} m_{j2} + d_2 & \cdots & -m_{2p} \\ \vdots & & \ddots & \\ -m_{p1} & -m_{p2} & \cdots & \sum_{j=1}^{p} m_{jp} + d_p \end{bmatrix}$$

Thus $C = -M + D$ where $M = [m_{ij}]$ and the positive diagonal matrix $D = \text{diag}(\sum_{j=1}^{p} m_{j1} + d_1, \ldots, \sum_{j=1}^{p} m_{jp} + d_p)$. By Theorem B.6, matrix C is irreducible, has positive column sums and negative off-diagonal entries. Thus C is a non-singular M-Matrix and according to Theorem B.4 has $C^{-1} > 0$, thus there is a unique solution, given by $S^0 = C^{-1}A > 0$. This gives the unique disease free equilibrium. □

Remark 2.3. In the particular case in which travel rates are independent of disease status, thus $m_{ji} = q_{ji} = n_{ji} = r_{ji}$ and the disease is not fatal (i.e., $\epsilon_i = 0$), then

$$\frac{dN_i}{dt} = A_i + \sum_{j=1}^{p} m_{ij} N_j - (\sum_{j=1}^{p} m_{ji} + d_i) N_i$$

showing that the equations for the total populations in each patch uncouple from the S_i, E_i, I_i and R_i variables. At any equilibrium (not just the DFE)

$$A_i = (\sum_{j=1}^{p} m_{ji} + d_i) N_i - \sum_{j=1}^{p} m_{ij} N_j$$

and so $[N_1, \ldots, N_p]^T = C^{-1}A$.

Theorem 2.4. *With non-negative initial conditions, the DFE of (2.1)-(2.4) is locally asymptotically stable if $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 > 1$.*

Proof. To consider linear stability of the DFE for the full system, order variables as

$$E_1, \ldots, E_p, I_1, \ldots, I_p, S_1, \ldots, S_p, R_1, \ldots, R_p$$

where $u = (E_1, \ldots, E_p, I_1, \ldots, I_p)^T$ is the vector of infected variables. The DFE, $\mathcal{E}^0$, is locally asymptotically stable if all eigenvalues of the Jacobian matrix of system (2.1)-(2.4) at $\mathcal{E}^0$ namely,

$$\mathcal{J}^0 = \begin{bmatrix} F - V & 0 \\ J_3 & J_4 \end{bmatrix}$$

have negative real parts, and unstable if $\mathcal{J}^0$ has at least one eigenvalue with positive real part. The eigenvalues of $\mathcal{J}^0$ are the eigenvalues of $F - V$ and those of J_4. To determine F and V consider the right hand sides of (2.2) and (2.3) written as $\mathcal{F} - \mathcal{V}$, where

$$\mathcal{F} = \begin{bmatrix} \frac{\beta_1 S_1 I_1}{N_1} \\ \vdots \\ \frac{\beta_p S_p I_p}{N_p} \\ 0 \\ \vdots \\ 0 \end{bmatrix} \text{ and } \mathcal{V} = \begin{bmatrix} -\sum_{j=1}^{p} q_{1j} E_j + (\sum_{j=1}^{p} q_{j1} + \alpha_1 + d_1) E_1 \\ \vdots \\ -\sum_{j=1}^{p} q_{pj} E_j + (\sum_{j=1}^{p} q_{jp} + \alpha_p + d_p) E_p \\ -\alpha_1 E_1 - \sum_{j=1}^{p} n_{1j} I_j + (\sum_{j=1}^{p} n_{j1} + \epsilon_1 + \gamma_1 + d_1) I_1 \\ \vdots \\ -\alpha_p E_p - \sum_{j=1}^{p} n_{pj} I_j + (\sum_{j=1}^{p} n_{jp} + \epsilon_p + \gamma_p + d_p) I_p \end{bmatrix}$$

Here $\mathcal{F}$ accounts for new infections and $\mathcal{V}$ accounts for other transfers into and out of infected compartments. Linearising $\mathcal{F} - \mathcal{V}$ about the DFE gives the matrix $F - V$ where $F = [\partial \mathcal{F}_i / \partial u_j]$ and $V = [\partial \mathcal{V}_i / \partial u_j]$. Block matrices F and V are given by

$$F = \left[\begin{array}{c:c} 0 & F_{12} \\ \hdashline 0 & 0 \end{array}\right] \text{ and } V = \left[\begin{array}{c:c} V_{11} & 0 \\ \hdashline V_{21} & V_{22} \end{array}\right]$$

Here $F_{12} = \text{diag}(\beta_1, \ldots, \beta_p)$

$$V_{11} = \begin{bmatrix} \sum_{j=1}^{p} q_{j1} + \alpha_1 + d_1 & -q_{12} & \cdots & -q_{1p} \\ -q_{21} & \sum_{j=1}^{p} q_{j2} + \alpha_2 + d_2 & \cdots & \vdots \\ \vdots & & \ddots & \vdots \\ -q_{p1} & \cdots & & \sum_{j=1}^{p} q_{jp} + \alpha_p + d_p \end{bmatrix}$$

$$V_{22} = \begin{bmatrix} \sum_{j=1}^{p} n_{j1} + a_1 & -n_{12} & \cdots & -n_{1p} \\ -n_{21} & \sum_{j=1}^{p} n_{j2} + a_2 & \cdots & \vdots \\ \vdots & & \ddots & \vdots \\ -n_{p1} & \cdots & & \sum_{j=1}^{p} n_{jp} + a_p \end{bmatrix}$$

$$V_{21} = \text{diag}(-\alpha_1, \ldots, -\alpha_p)$$

are $p \times p$ matrices, and $a_i = \gamma_i + d_i + \epsilon_i$ for $i = 1, \ldots, p$. By Theorem B.6, matrices V_{11} and V_{22} are irreducible non-singular M-matrices therefore, by Theorem B.4, have positive inverses. Similarly

$$J_4 = \begin{bmatrix} -C & K \\ 0 & -G \end{bmatrix}$$

where C and G are as given in Theorem 2.2 and are non-singular M-matrices. Thus by Theorem B.5, J_4 has all eigenvalues with negative real parts. Consequently the local stability of the DFE depends only on eigenvalues of $F - V$.

By Theorem B.8, all eigenvalues of $F - V$ have negative real parts if and only if $s(F - V) < 0$ if and only if $\rho\{FV^{-1}\} < 1$. Since V has a positive inverse, then FV^{-1} is a non-negative matrix. The product

$$FV^{-1} = \left[\begin{array}{c:c} 0 & F_{12} \\ \hdashline 0 & 0 \end{array}\right] \left[\begin{array}{c:c} V_{11}^{-1} & 0 \\ \hdashline X & V_{22}^{-1} \end{array}\right] = \left[\begin{array}{c:c} F_{12}X & F_{12}V_{22}^{-1} \\ \hdashline 0 & 0 \end{array}\right]$$

where $X = V_{22}^{-1}\text{diag}(\alpha_1, \ldots, \alpha_p)V_{11}^{-1}$. Using the formula for the basic reproduction number $\mathcal{R}_0$ as given in [DH][vdDW] it follows that

$$\mathcal{R}_0 = \rho\{FV^{-1}\} = \rho\{\text{diag}(\beta_1, \ldots, \beta_p)V_{22}^{-1}\text{diag}(\alpha_1, \ldots, \alpha_p)V_{11}^{-1}\} \qquad (2.5)$$

By Theorem B.8, if $\mathcal{R}_0 < 1$ then $s(F - V) < 0$; therefore all the eigenvalues lie in the left half plane and according to Definition B.9, system (2.1)-(2.4) is locally asymptotically stable. Similarly if $\mathcal{R}_0 > 1$ then $s(F - V) > 0$; therefore at least one eigenvalue lies in the right half plane and according to Definition B.9, system (2.1)-(2.4) is unstable. □

The local stability result for the DFE in the previous theorem can be strengthened to global stability.

Theorem 2.5. *With non-negative initial conditions, the DFE of (2.1)-(2.4) is globally asymptotically stable if* $\mathcal{R}_0 < 1$, *and unstable if* $\mathcal{R}_0 > 1$.

Proof. From Theorem 2.4, if $\mathcal{R}_0 > 1$, then the DFE of (2.1)-(2.4) is unstable; and if $\mathcal{R}_0 < 1$, then the DFE is locally asymptotically stable. Consider

$\mathcal{R}_0 < 1$ and a positive solution of (2.1)-(2.4). To complete the proof, it is sufficient to show that this positive solution tends to the DFE as $t \to \infty$.

Equation (2.2) with $S_i < N_i$ gives the inequality

$$\frac{dE_i}{dt} < \beta_i I_i - (\sum_{j=1}^{p} q_{ji} + \alpha_i + d_i)E_i + \sum_{j=1}^{p} q_{ij}E_j \tag{2.6}$$

Define an auxiliary linear system by (2.6) with equality and (2.3), namely

$$\begin{aligned} \frac{dE_i}{dt} &= \beta_i I_i - (\sum_{j=1}^{p} q_{ji} + \alpha_i + d_i)E_i + \sum_{j=1}^{p} q_{ij}E_j \\ \frac{dI_i}{dt} &= \alpha_i E_i + \sum_{j=1}^{p} n_{ij}I_j - (\sum_{j=1}^{p} n_{ji} + a_i)I_i \end{aligned} \tag{2.7}$$

The right side of (2.7) has coefficient matrix $F - V$. For $\mathcal{R}_0 = \rho\{FV^{-1}\} < 1$, each eigenvalue of $F - V$ lies in the left half plane (Theorem B.8), thus each positive solution of (2.7) satisfies $\lim_{t\to\infty} E_i = 0$ and $\lim_{t\to\infty} I_i = 0$. Since (2.7) is a linear system, the DFE of (2.7) is globally asymptotically stable. Using Theorem B.12 with $g(u) = (F - V)(u)$ for $u = (E_1 \ldots, E_p, I_1, \ldots, I_p)^T$ and noting that $F - V$ has all off-diagonal entries non-negative, each positive solution of (2.2) and (2.3) satisfies $\lim_{t\to\infty} E_i(t) = 0$ and $\lim_{t\to\infty} I_i(t) = 0$ for $i = 1 \ldots p$. From (2.4), since each positive solution of $I_i(t)$ tends to zero as $t \to \infty$, then $dR_i/dt = -(\sum_{j=1}^{p} r_{ji} + d_i + \delta_i)R_i + \sum_{j=1}^{p} r_{ij}R_j$ as $t \to \infty$. This linear system has coefficient matrix $-G$ with G as defined in the proof of Theorem 2.2, therefore $\lim_{t\to\infty} R_i(t) = 0$ since all eigenvalues of $-G$ lie in the left half plane. From (2.1), since $\lim_{t\to\infty} I_i = 0$ and $\lim_{t\to\infty} R_i = 0$, then $dS_i/dt = A_i +$

$\sum_{j=1}^{p} m_{ij}S_j - (\sum_{j=1}^{p} m_{ji} + d_i)S_i$. This is the system of differential equations

$$dS/dt = A - CS \tag{2.8}$$

where $dS/dt = [dS_1/dt, \ldots, dS_p/dt]^T$, $S = [S_1, \ldots, S_p]^T$ and C are as defined in the proof of Theorem 2.2. The solutions of (2.8) can be derived in two parts, namely, homogeneous and particular solutions. The homogeneous part is the solution of $dS/dt = -CS$. Since $-C$ is the negative of a non-singular M-matrix, by Theorem B.5, all its eigenvalues lie in the left half plane. Thus $\lim_{t\longrightarrow\infty} S_h(t) = 0$, with $S_h(t)$ denoting the homogeneous solution of (2.8). Matrix C is an irreducible non-singular M-matrix and therefore by Theorem B.4, has a positive inverse. Therefore $S^0 = C^{-1}A$ is a particular solution for (2.8), and $S = S_h(t) + S^0$ is the general solution for (2.8). Thus $\lim_{t\to\infty} S_i = S_i^0$, completing the proof that the DFE is globally asymptotically stable. □

The basic reproduction number in patch i when there is no travel between patch i and other patches (i.e., patch i is isolated from the other patches) is given by

$$\mathcal{R}_0^{(i)} = \frac{\beta_i \alpha_i}{a_i(\alpha_i + d_i)} \tag{2.9}$$

where β_i is the contact rate in patch i. In the special case in which the demographic and epidemiological parameters of the patches differ only in their contact rates, the following result gives bounds on $\mathcal{R}_0$ in terms of $\mathcal{R}_0^{(i)}$.

Theorem 2.6. *Suppose $a_i = a$, $\alpha_i = \alpha$ and $d_i = d$ for each $i = 1, \ldots, p$.*

Then

$$\min_i \mathcal{R}_0^{(i)} \leq \mathcal{R}_0 \leq \max_i \mathcal{R}_0^{(i)}$$

Proof. Without loss of generality take

$$\beta_1 \leq \beta_2 \leq \cdots \leq \beta_p \tag{2.10}$$

thus

$$\min_{i=1,\ldots,p} \mathcal{R}_0^{(i)} = \mathcal{R}_0^{(1)} = \frac{\beta_1 \alpha}{a(\alpha + d)} \leq \cdots \leq \frac{\beta_p \alpha}{a(\alpha + d)} = \mathcal{R}_0^{(p)} = \max_{i=1,\ldots,p} \mathcal{R}_0^{(i)} \tag{2.11}$$

Let $V_{11}^{-1} = Y = [y_{ij}]$ and $V_{22}^{-1} = W = [w_{ij}]$, and write $\text{diag}(\alpha, \ldots, \alpha)$ as $\text{diag}(\alpha)$. From (2.5)

$$\mathcal{R}_0 = \rho\{\text{diag}(\beta_1, \ldots, \beta_p) W \text{diag}(\alpha) Y\}$$

Take $Z = \text{diag}(\beta_1, \ldots, \beta_p) W \text{diag}(\alpha) Y$, that is

$$Z = \begin{bmatrix} \beta_1\alpha(w_{11}y_{11} + \cdots + w_{1p}y_{p1}) & \ldots & \beta_1\alpha(w_{11}y_{1p} + \cdots + w_{1p}y_{pp}) \\ \vdots & \ldots & \vdots \\ \beta_p\alpha(w_{p1}y_{11} + \cdots + w_{pp}y_{p1}) & \ldots & \beta_p\alpha(w_{p1}y_{1p} + \cdots + w_{pp}y_{pp}) \end{bmatrix}$$

Let $[\mathbb{1}\mathbb{1}^T Z]_1$ denote the sum of the entries in the first column of Z, with

$\mathbb{1}^T = (1, \ldots, 1)$. Then

$$\begin{aligned}
[\mathbb{1}^T Z]_1 &= \beta_1 \alpha w_{11} y_{11} + \cdots + \beta_1 \alpha w_{1p} y_{p1} \\
&\quad + \beta_2 \alpha w_{21} y_{11} + \cdots + \beta_2 \alpha w_{2p} y_{p1} \\
&\quad + \cdots \\
&\quad + \beta_p \alpha w_{p1} y_{11} + \cdots + \beta_p \alpha w_{pp} y_{p1} \\
&\leq \beta_p \alpha \sum_{i=1}^{p} y_{i1} (w_{1i} + \cdots + w_{pi}) \\
&= \frac{\beta_p \alpha}{a} \sum_{i=1}^{p} y_{i1} \qquad (2.12)
\end{aligned}$$

where the inequality comes from (2.10), and the last equality follows from the fact that V_{22} has column sum a, thus $\mathbb{1}^T V_{22} = a\mathbb{1}^T$, giving $\mathbb{1}^T W = (1/a)\mathbb{1}^T$. The column sum of V_{11} is $\alpha + d$, thus $\mathbb{1}^T Y = 1/(\alpha + d)\mathbb{1}^T$ giving from (2.11) and (2.12)

$$[\mathbb{1}^T Z]_1 \leq \frac{\beta_p \alpha}{a(\alpha + d)} = \mathcal{R}_0^{(p)} = \max_{i=1,\ldots,p} \mathcal{R}_0^{(i)}$$

Similarly

$$\min_{i=1,\ldots,p} \mathcal{R}_0^{(i)} = \mathcal{R}_0^{(1)} = \frac{\beta_1 \alpha}{a(\alpha + d)} \leq [\mathbb{1}^T Z]_1$$

The same arguments show that these inequalities remain true for every column of Z. From Theorem B.7 the spectral radius of a non-negative matrix lies between its minimum and maximum column sums, thus

$$\min_{i=1,\ldots,p} \mathcal{R}_0^{(i)} \leq \rho\{(\mathrm{diag}(\beta_1, \ldots, \beta_p) W \mathrm{diag}(\alpha) Y)\} \leq \max_{i=1,\ldots,p} \mathcal{R}_0^{(i)}$$

and the result follows. □

Remark 2.7. Suppose if in addition to the assumptions in Theorem 2.6 the contact rates are the same in all patches, i.e., $\beta_i = \beta$ for $i = 1, \ldots, p$, then $\mathcal{R}_0 = \mathcal{R}_0^{(i)}$.

Remark 2.8. If the rate of travel matrices $[m_{ij}]$, $[q_{ij}]$, $[n_{ij}]$ and $[r_{ij}]$ are irreducible (not necessarily having every off-diagonal entry positive), then the matrices G, C, V_{11}, and V_{22} are non-singular M-matrices and the above results still hold. Note that the rates of travel of susceptible individuals enter into the equilibrium values, but not into the stability criteria for the DFE. In the special case in which exposed and infectious individuals do not travel between patches, that is $q_{ij} = n_{ij} = 0$ for $i, j = 1, \ldots, p$, then $V_{11} = \text{diag}(\alpha_1 + d_1, \ldots, \alpha_p + d_p)$ and $V_{22} = \text{diag}(a_1, \ldots, a_p)$. In this case, the matrix $F_{12}V_{22}^{-1}\text{diag}(\alpha_1, \ldots, \alpha_p)V_{11}^{-1}$ is diagonal, therefore

$$\mathcal{R}_0 = \max_{i=1,\ldots,p} \mathcal{R}_0^{(i)}$$

where $\mathcal{R}_0^{(i)}$ is the basic reproduction number of patch i in isolation, as given by (2.9).

2.3 SEIRS model with $p = 4$ patches

Consider a particular case of (2.1)-(2.4) with $p = 4$. In this case the population dynamics among 4 patches is given by a system of 16 ordinary differential equations. If matrices V_{11} and V_{22} as defined in the proof of Theorem 2.4

with $p = 4$, are irreducible then using (2.5),

$$\mathcal{R}_0 = \rho\{FV^{-1}\} = \rho\{\text{diag}(\beta_1, \ldots, \beta_4)V_{22}^{-1}\text{diag}(\alpha_1, \ldots, \alpha_4)V_{11}^{-1}\} \qquad (2.13)$$

Assume now that exposed and infective individuals of patches 2, 3 and 4 can not travel to patch 1 but those of patch 1 can travel to other patches i.e., $q_{1j} = n_{1j} = 0$ for $j = 2, 3, 4$. For example, this situation could arise if patch (city) 1 implements strict border control measures. Matrices V_{11} and V_{22} are no longer irreducible.

$$V_{11} = \begin{bmatrix} b_1 + q_{21} + q_{31} + q_{41} & 0 & 0 & 0 \\ -q_{21} & b_2 + q_{32} + q_{42} & -q_{23} & -q_{24} \\ -q_{31} & -q_{32} & b_3 + q_{23} + q_{43} & -q_{34} \\ -q_{41} & -q_{42} & -q_{43} & b_4 + q_{24} + q_{34} \end{bmatrix}$$

$$V_{22} = \begin{bmatrix} a_1 + n_{21} + n_{31} + n_{41} & 0 & 0 & 0 \\ -n_{21} & a_2 + n_{32} + n_{42} & -n_{23} & -n_{24} \\ -n_{31} & -n_{32} & a_3 + n_{23} + n_{43} & -n_{34} \\ -n_{41} & -n_{42} & -n_{43} & a_4 + n_{24} + n_{34} \end{bmatrix}$$

where $b_i = \alpha_i + d_i$ for $i = 1, \ldots, 4$. Thus

$$FV^{-1} = \left[\begin{array}{c:c} \dfrac{\beta_1\alpha_1}{(a_1 + n_{21} + n_{31} + n_{41})(b_1 + q_{21} + q_{31} + q_{41})} & 0 \\ \hdashline X & Y \end{array}\right]$$

where

$$Y = \text{diag}(\beta_2, \beta_3, \beta_4)U_{22}^{-1}\text{diag}(\alpha_1, \ldots, \alpha_4)U_{11}^{-1}$$

$$U_{11} = \begin{bmatrix} b_2 + q_{32} + q_{42} & -q_{23} & -q_{24} \\ -q_{32} & b_3 + q_{23} + q_{43} & -q_{34} \\ -q_{42} & -q_{43} & b_4 + q_{24} + q_{34} \end{bmatrix}$$

$$U_{22} = \begin{bmatrix} a_2 + n_{32} + n_{42} & -n_{23} & -n_{24} \\ -n_{32} & a_3 + n_{23} + n_{43} & -n_{34} \\ -n_{42} & -n_{43} & a_4 + n_{24} + n_{34} \end{bmatrix}$$

So

$$\mathcal{R}_0 = \max\{\tilde{\mathcal{R}}_0^{(1)}, \mathcal{R}_0^{(2,3,4)}\} \tag{2.14}$$

where $\tilde{\mathcal{R}}_0^{(1)} = \frac{\beta_1 \alpha_1}{(a_1+n_{21}+n_{31}+n_{41})(b_1+q_{21}+q_{31}+q_{41})}$ and $\mathcal{R}_0^{(2,3,4)} = \rho\{Y\}$. Here $\tilde{\mathcal{R}}_0^{(1)}$ is the modified reproduction number for patch 1 taking travel of infective and exposed individuals into consideration, and $\mathcal{R}_0^{(2,3,4)}$ is the basic reproduction number on patches 2, 3 and 4. The next two examples illustrate the important role of travel of exposed individuals.

Example 2.1. Assume that parameters in system (2.1)-(2.4) with $p = 4$ are as follows, with a time scale of a day: $A_1 = 10, A_2 = 15, A_3 = 20, A_4 = 25$, $d_1 = d_2 = d_3 = d_4 = 0.365e - 4$, $\delta_1 = \delta_2 = 0.1, \delta_3 = \delta_4 = 0.2$, $\alpha_1 = 0.02, \alpha_2 = 0.01, \alpha_3 = 0.015, \alpha_4 = 0.03$, $\gamma_1 = \gamma_2 = \gamma_3 = \gamma_4 = 0.04$, $\epsilon_1 = 0.03, \epsilon_2 = \epsilon_3 =$

$0.05, \epsilon_4 = 0.04,\ \beta_1 = 0.06, \beta_2 = 0.07, \beta_3 = 0.3, \beta_4 = 0.35$

$$[m_{ij}] = \begin{bmatrix} 0 & 0.2 & 0.1 & 0.4 \\ 0.1 & 0 & 0.3 & 0.2 \\ 0.1 & 0.2 & 0 & 0.1 \\ 0.1 & 0.1 & 0.2 & 0 \end{bmatrix} \quad [q_{ij}] = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0.08 & 0 & 0.2 & 0.2 \\ 0.09 & 0.2 & 0 & 0.1 \\ 0.08 & 0.1 & 0.2 & 0 \end{bmatrix}$$

$$[n_{ij}] = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0.01 & 0 & 0.05 & 0.01 \\ 0.01 & 0.01 & 0 & 0.03 \\ 0.01 & 0.02 & 0.01 & 0 \end{bmatrix} \quad [r_{ij}] = \begin{bmatrix} 0 & 0.1 & 0.1 & 0.3 \\ 0.1 & 0 & 0.2 & 0.2 \\ 0.1 & 0.1 & 0 & 0.1 \\ 0.08 & 0.09 & 0.1 & 0 \end{bmatrix}$$

The basic reproduction numbers in each patch in isolation are as follows,

$$\mathcal{R}_0^{(1)} = 0.86, \quad \mathcal{R}_0^{(2)} = 0.77, \quad \mathcal{R}_0^{(3)} = 3.32, \quad \mathcal{R}_0^{(4)} = 4.37$$

the modified reproduction number for patch 1 is $\tilde{\mathcal{R}}_0^{(1)} = 0.04$ and the basic reproduction number for patches 2, 3 and 4 is $\mathcal{R}_0^{(2,3,4)} = 2.97$. According to (2.14), the basic reproduction number for (2.1)-(2.4) is $\mathcal{R}_0 = 2.97$.

Taking initial conditions as $E_i(0) = R_i(0) = 0$ for $i = 1, \ldots, 4$, $I_1(0) = 15, I_2(0) = 10, I_3(0) = 15, I_4(0) = 10, N_1(0) = 4800, N_2(0) = 3800, N_3(0) = 2000, N_4(0) = 2400$ and solving (2.1)-(2.4) for $p = 4$ numerically gives Figure 2.2. This shows that the disease dies out in patch 1 and becomes endemic in patches 2, 3 and 4. The numbers of infectious individuals in patches 2, 3 and 4 stay small for about 10 days and then increase to an epidemic, before decreasing to their endemic values.

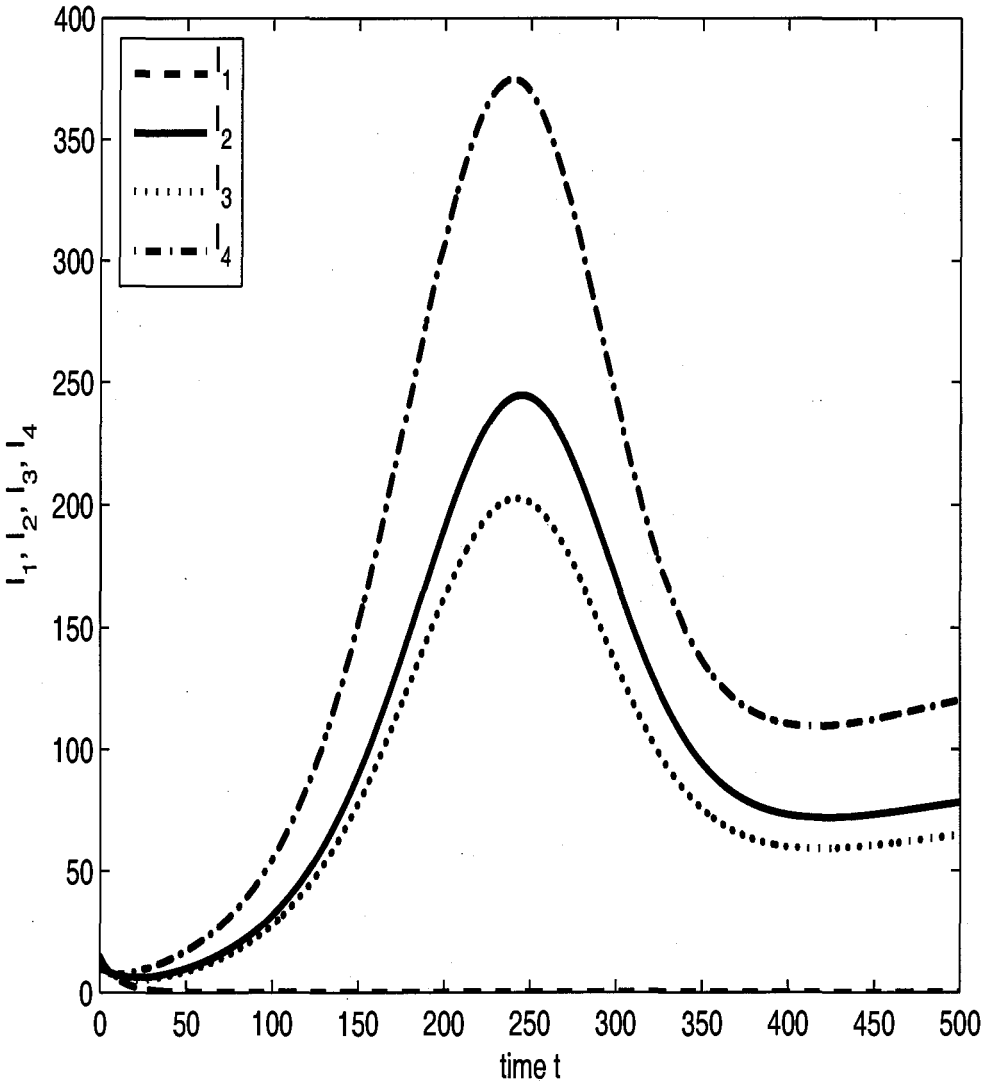

Figure 2.2: SEIRS model with four patches for $q_{1j} = n_{1j} = 0$ and $\tilde{\mathcal{R}}_0^{(1)} < 1$, $\mathcal{R}_0^{(2,3,4)} > 1$

Example 2.2. Assume that parameters in system (2.1)-(2.4) with $p = 4$ are as in Example 2.1 except that $q_{1j} = 0.1$ for $j = 2, 3, 4$. The basic reproduction numbers in each patch in isolation are as in Example 2.1. Matrix FV^{-1} is irreducible, and from (2.13), the basic reproduction number for the system is $\mathcal{R}_0 = 2.51$.

Taking the same initial conditions as Example 2.1 and solving (2.1)-(2.4) for $p = 4$ numerically gives Figure 2.3. This shows that the disease becomes endemic in all patches. In this case the numbers of infectious individuals stay small for about 50 days, then increase to an epidemic, before decreasing to their endemic values.

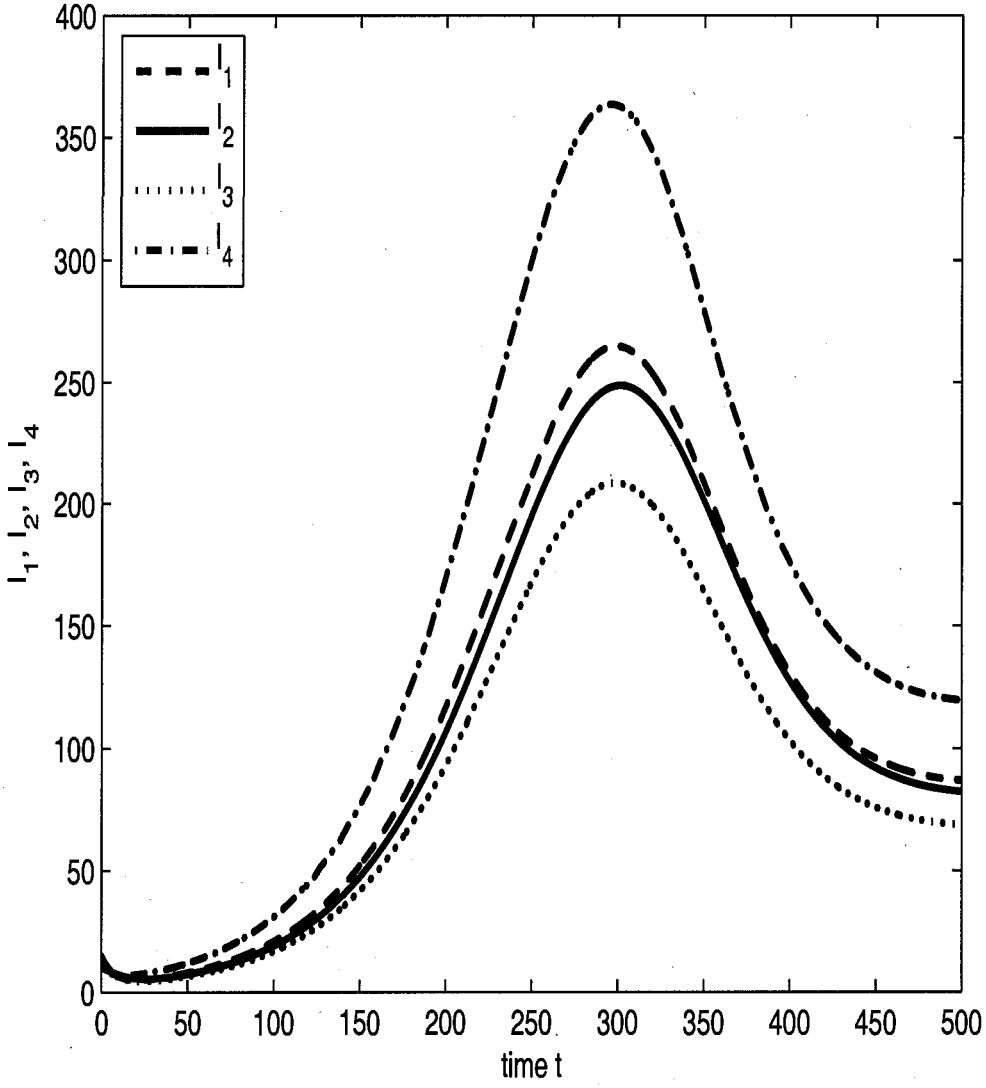

Figure 2.3: SEIRS model with four patches for $n_{1j} = 0$ and $\tilde{\mathcal{R}}_0^{(1)} < 1$, $\mathcal{R}_0^{(2,3,4)} > 1$

Chapter 3

SIS model with two patches

For a disease with very short exposed (latent) and immune (recovered) periods, then approximately $\alpha_i \to \infty$ and $\delta_i \to \infty$. This approximation can be used to model bacterial diseases, such as gonorrhea, which has the following epidemiological characteristics [HY], [C, pp. 223-227]. Firstly, gonorrhea does not confer immunity, thus infected individuals are susceptible again as soon as they recover from the infection. Secondly, the latent period for gonorrhea is very short with contacted individuals becoming infectious within a day or two. Thirdly, the seasonal oscillations in gonorrhea incidence are very small. Because of these characteristics, an SIS model is suitable for modeling the transmission of gonorrhea. For a one sex model, the population is then divided only into susceptible and infectious individuals. For such a disease with two patches ($p = 2$) system (2.1)-(2.4) can be written as the following four equations, where for simplicity we use variable $N_i = S_i + I_i$ instead of

S_i in each patch i.

$$\frac{dI_1}{dt} = \frac{\beta_1(N_1 - I_1)I_1}{N_1} + n_{12}I_2 - (n_{21} + a_1)I_1 \tag{3.1}$$

$$\frac{dI_2}{dt} = \frac{\beta_2(N_2 - I_2)I_2}{N_2} + n_{21}I_1 - (n_{12} + a_2)I_2 \tag{3.2}$$

$$\frac{dN_1}{dt} = A_1 - (d_1 + m_{21})N_1 + (m_{21} - \epsilon_1 - n_{21})I_1 + (n_{12} - m_{12})I_2 + m_{12}N_2 \tag{3.3}$$

$$\frac{dN_2}{dt} = A_2 - (d_2 + m_{12})N_2 + (m_{12} - \epsilon_2 - n_{12})I_2 + (n_{21} - m_{21})I_1 + m_{21}N_1 \tag{3.4}$$

Adding the last two equations gives

$$\frac{dN}{dt} = \frac{dN_1}{dt} + \frac{dN_2}{dt} = (A_1 + A_2) - d_1N_1 - d_2N_2 - \epsilon_1I_1 - \epsilon_2I_2$$

The population in each patch is not constant. This is in contrast to the model of [WM] in which birth and death are equal and there is no disease related death.

Assume non-negative initial conditions, i.e., $S_1(0) > 0$, $S_2(0) > 0$, $I_1(0) + I_2(0) > 0$. The DFE for the system (3.1)-(3.4) has $I_1 = I_2 = 0$, and thus is given by $\mathcal{E}^0 = (0, 0, N_1^0, N_2^0)$ where

$$N_1^0 = \frac{m_{12}A_2 + (d_2 + m_{12})A_1}{b} \quad \text{and} \quad N_2^0 = \frac{m_{21}A_1 + (d_1 + m_{21})A_2}{b} \tag{3.5}$$

with $b = d_1d_2 + d_1m_{12} + d_2m_{21} > 0$.

3.1 $\mathcal{R}_0$ for SIS model with two patches

For system (3.1)-(3.4) an explicit expression for $\mathcal{R}_0$ can be obtained. Proceeding as in Section 2.2 with infected variables I_1 and I_2,

$$F = \begin{bmatrix} \beta_1 & 0 \\ 0 & \beta_2 \end{bmatrix} \quad \text{and} \quad V = \begin{bmatrix} a_1 + n_{21} & -n_{12} \\ -n_{21} & a_2 + n_{12} \end{bmatrix}$$

Since V is an irreducible non-singular M-matrix (Theorem B.6), it has a positive inverse (Theorem B.4), namely

$$V^{-1} = \frac{1}{detV} \begin{bmatrix} a_2 + n_{12} & n_{12} \\ n_{21} & a_1 + n_{21} \end{bmatrix}$$

with $detV = a_1a_2 + a_1n_{12} + a_2n_{21} > 0$. From (2.5)

$$\mathcal{R}_0 = \rho\{FV^{-1}\} = \frac{[\beta_1u_2 + \beta_2u_1] + \sqrt{[\beta_1u_2 - \beta_2u_1]^2 + 4\beta_1\beta_2n_{12}n_{21}}}{2detV} \tag{3.6}$$

where $u_1 = a_1 + n_{21}$ and $u_2 = a_2 + n_{12}$. From Theorem 2.1, the DFE is globally asymptotically stable if $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$.

In this case $\mathcal{R}_0^{(i)} = \frac{\beta_i}{a_i}$, and bounds for $\mathcal{R}_0$ given in Theorem 2.2 hold without any additional assumption on the parameters.

Theorem 3.1. *The basic reproduction number for the SIS model with two patches satisfies the following inequality,*

$$\min_{i=1,2} \mathcal{R}_0^{(i)} \leq \mathcal{R}_0 \leq \max_{i=1,2} \mathcal{R}_0^{(i)}$$

Proof. Without loss of generality assume $\mathcal{R}_0^{(1)} \leq \mathcal{R}_0^{(2)}$, then

$$\mathcal{R}_0^{(1)} = \beta_1/a_1 \leq \beta_2/a_2 = \mathcal{R}_0^{(2)}$$

Thus,

$$\beta_1 \leq \beta_2 a_1/a_2 \tag{3.7}$$

From above,

$$FV^{-1} = \frac{1}{a_1a_2 + n_{12}a_1 + n_{21}a_2} \begin{bmatrix} \beta_1(a_2 + n_{12}) & \beta_1 n_{12} \\ \beta_2 n_{21} & \beta_2(a_1 + n_{21}) \end{bmatrix}$$

Now if $[\mathbb{1}^T FV^{-1}]_1$ denotes the first column sum of FV^{-1} then

$$\begin{aligned} [\mathbb{1}^T FV^{-1}]_1 &= \frac{\beta_1(a_2 + n_{12}) + \beta_2 n_{21}}{a_1a_2 + n_{12}a_1 + n_{21}a_2} \\ &\leq \frac{\beta_2[\frac{a_1}{a_2}(a_2 + n_{12}) + n_{21}]}{a_2(a_1 + n_{12}\frac{a_1}{a_2} + n_{21})} \\ &= \frac{\beta_2}{a_2} = \mathcal{R}_0^{(2)} = \max_{i=1,2} \mathcal{R}_0^{(i)} \end{aligned}$$

The inequality follows by (3.7). The second column sum of FV^{-1} gives the same inequality. Similarly, by inequality (3.7)

$$[\mathbb{1}^T FV^{-1}]_j \geq \frac{\beta_1}{a_1} = \mathcal{R}_0^{(1)} = \min_{i=1,2} \mathcal{R}_0^{(i)} \quad j = 1, 2$$

Using (3.6) and Theorem B.7, the result follows. □

Taking traveling between patches into account, define

$$\tilde{\mathcal{R}}_0^{(i)} = \frac{\beta_i}{a_i + n_{ji}} \quad \text{for } i, j = 1, 2,\ i \neq j \tag{3.8}$$

The term $1/(a_i + n_{ji})$ is the average time in I_i taking traveling to patch j into account; $\tilde{\mathcal{R}}_0^{(i)}$ is a modified reproduction number that includes travel of infectious individuals.

Remark 3.2. From (3.6)

$$\mathcal{R}_0 \geq \frac{(\tilde{\mathcal{R}}_0^{(1)} + \tilde{\mathcal{R}}_0^{(2)} + |\tilde{\mathcal{R}}_0^{(1)} - \tilde{\mathcal{R}}_0^{(2)}|)}{2} = \max_{i=1,2} \tilde{\mathcal{R}}_0^{(i)}$$

thus the basic reproduction number for the SIS model (3.1)-(3.4) with two patches satisfies the inequality

$$\max\{\min_{i=1,2} \mathcal{R}_0^{(i)}, \max_{i=1,2} \tilde{\mathcal{R}}_0^{(i)}\} \leq \mathcal{R}_0 \leq \max_{i=1,2} \mathcal{R}_0^{(i)}$$

According to Remark 3.2, if both patches have $\mathcal{R}_0^{(i)} < 1$ ($\mathcal{R}_0^{(i)} > 1$), then $\mathcal{R}_0 < 1$ ($\mathcal{R}_0 > 1$). An interesting case occurs when $\mathcal{R}_0^{(1)} > 1$ but $\mathcal{R}_0^{(2)} < 1$; see Examples 3.1 and 3.2 below.

To proceed further with the analysis of (3.1)-(3.4), we consider some special cases. For the first two cases (Section 3.2 and 3.3) the disease is assumed to be non-fatal and both susceptible and infectious individuals travel, for instance gonorrhea can be an example of such a disease. For the last two cases (Section 3.4 and 3.5), susceptible individuals are assumed to travel between patches but infectious individuals are restricted in travel, either by the severity of the disease or by isolation. In addition, death due to disease is included. This model may be appropriate for bacterial pneumonia [C, pp. 387-390].

3.2 Susceptible and infectious individuals travel

In this case parameters $m_{12}, m_{21}, n_{12}, n_{21}$ are positive. It is assumed that there is no disease death (i.e., $\epsilon_i = 0$) and the natural death rate is equal in each patch (i.e., $d_1 = d_2 = d$). Then system (3.1)-(3.4) becomes for $i, j = 1, 2$ and $i \neq j$

$$\frac{dI_i}{dt} = \frac{\beta_i(N_i - I_i)I_i}{N_i} + n_{ij}I_j - (n_{ji} + a_i)I_i \tag{3.9}$$

$$\frac{dN_i}{dt} = A_i - (d + m_{ji})N_i + (m_{ji} - n_{ji})I_i + (n_{ij} - m_{ij})I_j + m_{ij}N_j \tag{3.10}$$

with $a_i = \gamma_i + d$. Two non-negative equilibria are possible for system (3.9)-(3.10), namely:

(i) $\mathcal{E}^0 = (0, 0, N_1^0, N_2^0)$ the DFE with N_1^0, N_2^0 given in (3.5) and $d_i = d$

(ii) $\mathcal{E}^* = (I_1^*, I_2^*, \frac{\beta_1 I_1^{*2}}{(\beta_1 - (a_1 + n_{21}))I_1^* + n_{12}I_2^*}, \frac{\beta_2 I_2^{*2}}{(\beta_2 - (a_2 + n_{12}))I_2^* + n_{21}I_1^*})$

which is found numerically to exist if and only if $\mathcal{R}_0 > 1$. For this case $\mathcal{R}_0^{(i)} = \frac{\beta_i}{\gamma_i + d}$ and $\tilde{\mathcal{R}}_0^{(i)} = \frac{\beta_i}{\gamma_i + d + n_{ji}}$.

Using Theorem 2.5, the DFE is globally asymptotically stable if $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 > 1$. In considering the stability of $\mathcal{E}^*$, we assume $m_{ij} \geq n_{ij}$, a condition that is biologically reasonable.

Theorem 3.3. *For non-negative initial conditions and $\mathcal{R}_0 > 1$, the endemic equilibrium $\mathcal{E}^*$ of (3.9)-(3.10) with $m_{ij} \geq n_{ij}$ is locally asymptotically stable whenever it exists.*

Proof. The Jacobian of (3.9)-(3.10) at $\mathcal{E}^*$ is

$$M = \begin{bmatrix} -n_{12}\,L_{21} - \beta_1\,K_1 & n_{12} & \beta_1\,{K_1}^2 & 0 \\ n_{21} & -n_{21}\,L_{12} - \beta_2\,K_2 & 0 & \beta_2\,{K_2}^2 \\ m_{21} - n_{21} & n_{12} - m_{12} & -d - m_{21} & m_{12} \\ n_{21} - m_{21} & m_{12} - n_{12} & m_{21} & -d - m_{12} \end{bmatrix}$$

where $L_{ji} = \frac{I_j^*}{I_i^*}$ and $K_i = \frac{I_i^*}{N_i^*} < 1$ for $i, j = 1, 2$ and $i \neq j$. Notice that the $(1,1)$ and $(2,2)$ entries are obtained from taking the derivative of the right side of (3.9) with respect to I_i and evaluating at $\mathcal{E}^*$, namely

$$\begin{aligned} \frac{d(dI_i/dt)}{dI_i} &= (\beta_i - (n_{ji} + a_i)) - 2\frac{\beta_i I_i^*}{N_i^*} \\ &= -n_{ij}L_{ji} - \frac{\beta_i I_i^*}{N_i^*} \quad \text{for } i = 1, 2 \end{aligned}$$

The last equality follows from the fact that at this steady state $\frac{dI_i}{dt} = 0$ with $I_i^* \neq 0$.

Note that $[0, 0, 1, 1]M = -d[0, 0, 1, 1]$, thus $-d$ is an eigenvalue of M. The characteristic equation of M is as follows,

$$(\lambda + d)(\lambda^3 + c_1\lambda^2 + c_2\lambda + c_3) = 0$$

where

$$c_1 = d + m_{21} + m_{12} + n_{12}L_{21} + \beta_1 K_1 + n_{21}L_{12} + \beta_2 K_2$$

$$\begin{aligned} c_2 =& \beta_1\beta_2 K_1 K_2 + \beta_1 K_1(m_{12} + m_{21}(1 - K_1) + n_{21}(K_1 + L_{12}) + d) + \\ & \beta_2 K_2(m_{21} + m_{12}(1 - K_2) + n_{12}(K_2 + L_{21}) + d) + \\ & (m_{12} + m_{21} + d)(n_{21}L_{12} + n_{12}L_{21}) \end{aligned}$$

$$\begin{aligned} c_3 =& \beta_1\beta_2 K_1 K_2(d + m_{21}(1 - K_1) + m_{12}(1 - K_2) + n_{12}K_2 + n_{21}K_1) + \\ & \beta_1 n_{21} K_1(n_{21}L_{12}K_1 + K_1(m_{12} - n_{12}) + m_{12}L_{12} + m_{21}L_{12}(1 - K_1) + dL_{12}) + \\ & \beta_2 n_{12} K_2(n_{12}L_{21}K_2 + K_2(m_{21} - n_{21}) + m_{21}L_{21} + m_{12}L_{21}(1 - K_2) + dL_{21}) \end{aligned}$$

Since all the parameters are assumed to be positive, then $c_1 > 0$. Since $K_1, K_2 < 1$, and it is assumed that $m_{ij} \geq n_{ij}$, then $c_3 > 0$. Calculating

$$\begin{aligned} & c_1 c_2 - c_3 = \\ & \beta_1^2\beta_2 K_1^2 K_2 + \beta_1\beta_2^2 K_1 K_2^2 + \beta_1^2 K_1^2(K_1 n_{21} + m_{21}(1 - K_1) + n_{21}L_{12} + d + m_{12}) + \\ & \beta_2^2 K_2^2(K_2 n_{12} + m_{12}(1 - K_2) + n_{12}L_{21} + d + m_{21}) + \beta_1 K_1(m_{21}(2 - K_1)(m_{12} \\ & + n_{12}L_{21} + d) + n_{21}K_1(d + m_{21}) + m_{21}^2(1 - K_1) + K_1 n_{21} n_{12}(1 + L_{21}) \\ & + 2n_{21}L_{12}(d + m_{21}) + 2n_{12}L_{21}(m_{12} + d) + m_{12}^2 + 2dm_{12} + n_{12}n_{21} \\ & + n_{21}^2 L_{12}^2 + d^2) + \beta_2 K_2(m_{12}(2 - K_2)(m_{21} + n_{21}L_{12} + d) + n_{12}K_2(d + m_{12}) \\ & + m_{12}^2(1 - K_2) + K_2 n_{12} n_{21}(1 + L_{12}) + 2n_{12}L_{21}(d + m_{12}) + 2n_{21}L_{12}(m_{21} + d) \\ & + m_{21}^2 + 2dm_{21} + n_{21}n_{12} + n_{12}^2 L_{21}^2 + d^2) \end{aligned}$$

it is easy to see that $c_1 c_2 - c_3 > 0$. Using Theorem B.10 for $n = 3$, the

	$\tilde{\mathcal{R}}_0^{(1)} < 1$	$\tilde{\mathcal{R}}_0^{(1)} > 1$
$\tilde{\mathcal{R}}_0^{(2)} < 1$	$\mathcal{R}_0 < 1$: $\mathcal{E}^0$ GAS	$\mathcal{E}^0$U
	$\mathcal{R}_0 > 1$: $\mathcal{E}^0$ U, $\mathcal{E}^*$ LAS	$\mathcal{E}^*$ LAS
$\tilde{\mathcal{R}}_0^{(2)} > 1$	$\mathcal{E}^0$ U, $\mathcal{E}^*$ LAS	$\mathcal{E}^0$ U, $\mathcal{E}^*$ LAS

Table 3.1: Stability of equilibria for (3.9)-(3.10). Globally asymptotically stable, locally asymptotically stable, unstable are denoted by GAS, LAS, U, respectively.

Routh-Hurwitz criteria are satisfied. Thus the endemic equilibrium $\mathcal{E}^*$ is locally asymptotically stable whenever it exists. □

The stability of each equilibrium is summarized in Table 3.1 where $\tilde{\mathcal{R}}_0^{(i)}$ are included for comparison with Table 3.2. Numerical simulations indicate local asymptotic stability can be replaced by global asymptotic stability, but $\mathcal{E}^*$ is proved to be globally asymptotically stable only under additional assumptions (see Theorem 3.5).

The following numerical example illustrates one interesting result of Table 3.1 by showing that if $\tilde{\mathcal{R}}_0^{(i)} < 1$ in one patch i, then the disease can be endemic in both patches provided $\mathcal{R}_0 > 1$. Parameters are chosen to model gonorrhea with an average infectious period of 25 days [HY, p. 37] and average life expectancy of humans of 75 years.

Example 3.1. Assume that parameters in system (3.10) are as follows, with the time scale of a day: $A_1 = 20$, $A_2 = 15$, $d_1 = d_2 = 3.6e{-}5$, $\gamma_1 = \gamma_2 = 0.04$, $\epsilon_1 = \epsilon_2 = 0$, $m_{12} = m_{21} = 0.01$, $n_{12} = 0.002$, $n_{21} = 0.01$ and $\beta_1 = 0.10$, $\beta_2 = 0.03$. The reproduction numbers for both patches are

$$\mathcal{R}_0^{(1)} = 2.50,\ \mathcal{R}_0^{(2)} = 0.75,\ \tilde{\mathcal{R}}_0^{(1)} = 2.00,\ \tilde{\mathcal{R}}_0^{(2)} = 0.71$$

Using (3.6), $\mathcal{R}_0 = 2.03$. The system (3.10) has two non-negative equilibria:

$$\mathcal{E}^0 = (0, 0, 486235.9, 485986.3) \text{ and}$$

$$\mathcal{E}^* = (223805.5, 119381.0, 438569.3, 533653.0)$$

Notice that the proportion of infective individuals in patch 1 and patch 2 at endemic equilibrium is $\frac{I_1^*}{N_1^*} = 0.51$ and $\frac{I_2^*}{N_2^*} = 0.22$. Taking initial conditions as $I_1(0) = 100, I_2(0) = 150, N_1(0) = 430000, N_2(0) = 530000$ and solving (3.9)-(3.10) numerically gives Figure 3.1, which shows that the disease becomes endemic in both patches. In this case the numbers of infectious individuals stay small for about 50 days and then increase to their endemic values. In isolation, the disease would die out in patch 2, but goes to an endemic level with travel. In this way travel can increase disease spread.

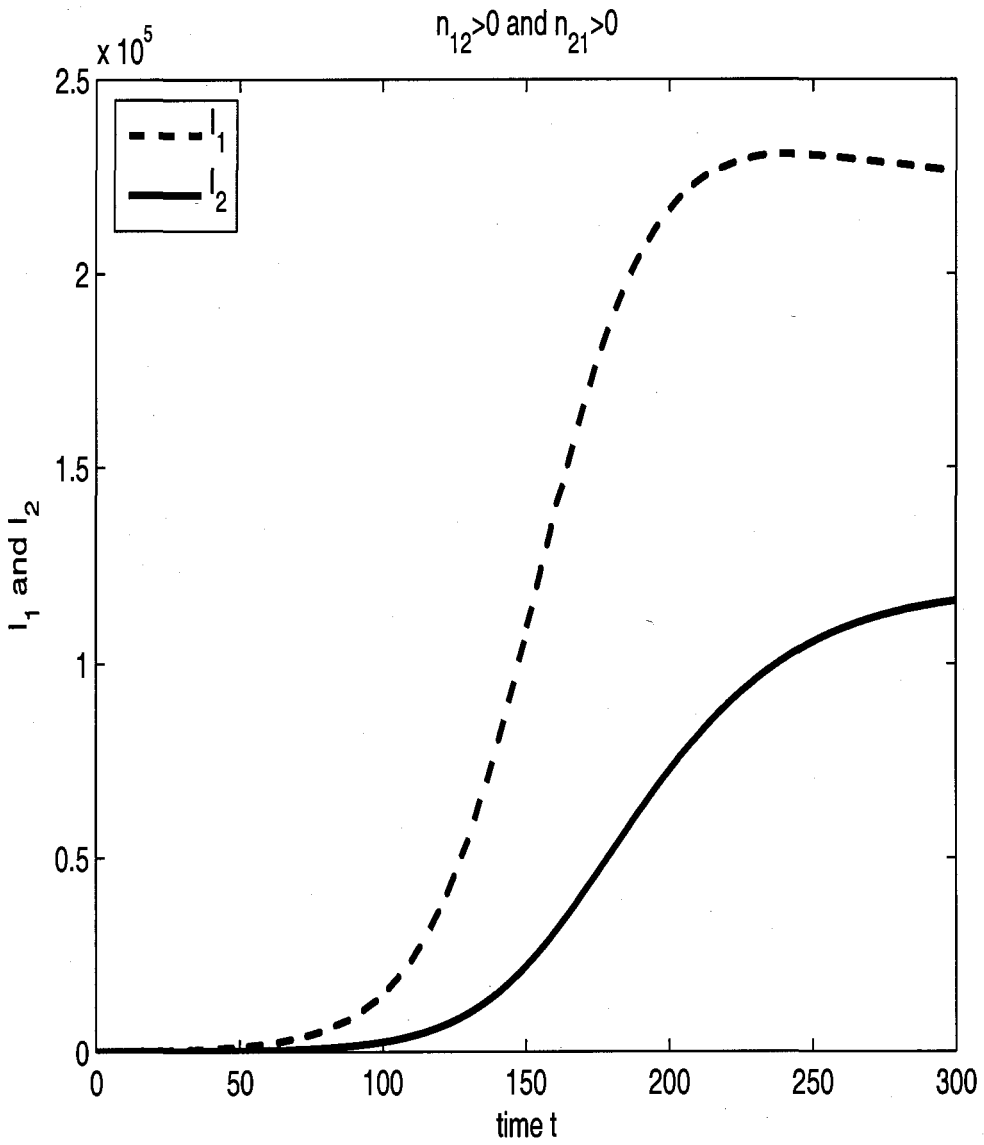

Figure 3.1: SIS model with two patches for $\tilde{\mathcal{R}}_0^{(1)} > 1$, $\tilde{\mathcal{R}}_0^{(2)} < 1$, $\mathcal{R}_0 > 1$

Example 3.2. If in Example 3.1 the contact rates in each patch are reduced to $\beta_1 = 0.042$ and $\beta_2 = 0.002$ with the other parameters unchanged, then $\mathcal{R}_0^{(1)} = 1.05$, $\mathcal{R}_0^{(2)} = 0.05$, $\tilde{\mathcal{R}}_0^{(1)} = 0.84$, $\tilde{\mathcal{R}}_0^{(2)} = 0.048$ and $\mathcal{R}_0 = 0.85$. Taking initial conditions as $I_1(0) = 10, I_2(0) = 15, N_1(0) = 430000, N_2(0) = 530000$ and solving (3.9)-(3.10) numerically gives Figure 3.2, which shows that the disease goes extinct in both patches, and travel controls the disease in patch 1. Alternatively, if the contact rates are retained at $\beta_1 = 0.1$ and $\beta_2 = 0.03$, but the travel rates increased to $m_{12} = 0.04$, $m_{21} = 0.08$, $n_{12} = 0.002$, $n_{21} = 0.075$, then $\mathcal{R}_0 = 0.98$ so that the disease first rises to an epidemic in patch 2 and then dies out in both patches in large time. In this case, travel of individuals also controls the disease.

3.3 Susceptible and infectious travel rates equal

Assume that travel is independent of disease status so that infectious individuals travel at the same rates as susceptible individuals; thus $m_{12} = n_{12}$ and $m_{21} = n_{21}$. As in the previous case, the disease is assumed to be non-fatal (i.e., $\epsilon_i = 0$), but the natural death rates in each patch may be different, thus

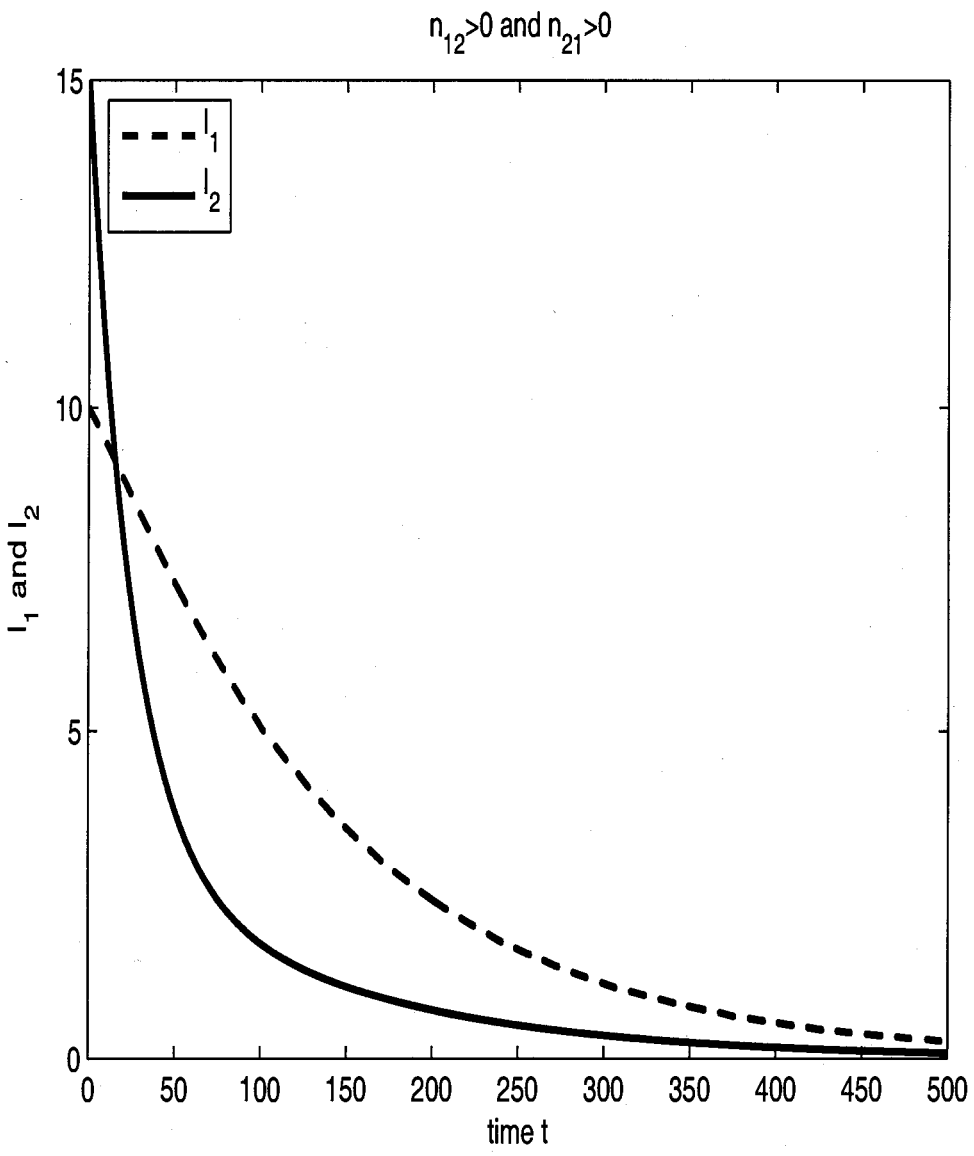

Figure 3.2: SIS model with two patches for $\tilde{\mathcal{R}}_0^{(1)} < 1$, $\tilde{\mathcal{R}}_0^{(2)} < 1$, $\mathcal{R}_0 < 1$

$a_i = \gamma_i + d_i$. Therefore system (3.1)-(3.4) for $i, j = 1, 2$ and $i \neq j$ is

$$\frac{dI_i}{dt} = \frac{\beta_i(N_i - I_i)I_i}{N_i} + n_{ij}I_j - (a_i + n_{ji})I_i \tag{3.11}$$

$$\frac{dN_i}{dt} = A_i - (d_i + n_{ji})N_i + n_{ij}N_j \tag{3.12}$$

Theorem 3.4. *The system (3.11)-(3.12) has a unique endemic equilibrium $\mathcal{E}^*$ if and only if $\mathcal{R}_0 > 1$.*

Proof. According to Remark 2.3, at any equilibrium, $N_1 = N_1^0 = N_1^*$ and $N_2 = N_2^0 = N_2^*$ are given by (3.5) with $m_{ij} = n_{ij}$, and I_1^* and I_2^* are the unique positive solutions of the equations

$$I_2 = \frac{\beta_1}{n_{12}}\left(\frac{I_1}{N_1^*} + \frac{1}{\tilde{\mathcal{R}}_0^{(1)}} - 1\right)I_1 \tag{3.13}$$

$$I_1 = \frac{\beta_2}{n_{21}}\left(\frac{I_2}{N_2^*} + \frac{1}{\tilde{\mathcal{R}}_0^{(2)}} - 1\right)I_2 \tag{3.14}$$

If at least one $\tilde{\mathcal{R}}_0^{(i)} > 1$ (implying that $\mathcal{R}_0 > 1$ from Remark 3.2), then it is easy to see by considering geometrically the two parabolas in (3.13), (3.14), that there is a unique positive equilibrium $\mathcal{E}^* = (I_1^*, I_2^*, N_1^*, N_2^*)$. Assume that both $\tilde{\mathcal{R}}_0^{(i)} < 1$, then the two parabolas intersect in the positive quadrant at a unique $\mathcal{E}^*$ if and only if

$$\frac{dI_2 \text{ from (3.13)}}{dI_1}\Big|_{I_1=0} < \frac{dI_2 \text{ from (3.14)}}{dI_1}\Big|_{I_1=0}$$

namely if and only if

$$\beta_1(a_2 + n_{12}) + \beta_2(a_1 + n_{21}) > detV + \beta_1\beta_2 \tag{3.15}$$

The characteristic equation of $F - V$ is

$$\lambda^2+(\beta_1-(a_1+n_{21})+\beta_2-(a_2+n_{12}))\lambda+(detV+\beta_1\beta_2-\beta_1(a_2+n_{12})-\beta_2(a_1+n_{21}))=0$$

Since $\tilde{\mathcal{R}}_0^{(i)} < 1$ for $i = 1, 2$, and using (3.15), it follows from the above equation that $F - V$ has a positive eigenvalue, which in turn, using Theorem B.8, is equivalent to $\rho\{FV^{-1}\} > 1$, namely $\mathcal{R}_0 > 1$. Thus $\mathcal{E}^*$ exists and is unique if and only if $\mathcal{R}_0 > 1$. □

The next theorem deals with global asymptotic stability of the unique positive equilibrium of (3.11)-(3.12).

Theorem 3.5. *With non-negative initial conditions, the positive equilibrium of (3.11)-(3.12), $\mathcal{E}^*$, is globally asymptotically stable if $\mathcal{R}_0 > 1$.*

Proof. The characteristic polynomial of (3.11)-(3.12) at $\mathcal{E}^*$ reduces to two quadratics

$$\lambda^2 + (\frac{\beta_2 I_2^*}{N_2^*} + \frac{n_{12}I_2^*}{I_1^*} + \frac{\beta_1 I_1^*}{N_1^*} + \frac{n_{21}I_1^*}{I_2^*})\lambda + \frac{\beta_1\beta_2 I_1^* I_2^*}{N_1^* N_2^*} + \frac{n_{21}\beta_1 I_1^{*2}}{N_1^* I_2^*} + \frac{n_{12}\beta_2 I_2^{*2}}{I_1^* N_2^*}$$

and

$$\lambda^2 + (d_1 + d_2 + n_{12} + n_{21})\lambda + d_1 d_2 + n_{21}d_2 + n_{12}d_1 \tag{3.16}$$

Since all coefficients are positive, then using Theorem B.10, the real parts of all the eigenvalues are negative. Using Definition B.9, system (3.11)-(3.12) is locally asymptotically stable at $\mathcal{E}^*$ whenever it exists, namely if $\mathcal{R}_0 > 1$.

Since the equations in (3.12) for N_i are linear, they can be solved with the initial conditions $N_1(0)$, $N_2(0)$, to give

$$\begin{bmatrix} N_1(t) \\ N_2(t) \end{bmatrix} = c_1 \begin{bmatrix} 1 \\ \frac{d_1+n_{21}+\lambda_1}{n_{12}} \end{bmatrix} e^{\lambda_1 t} + c_2 \begin{bmatrix} \frac{d_2+n_{12}+\lambda_2}{n_{21}} \\ 1 \end{bmatrix} e^{\lambda_2 t} + \begin{bmatrix} N_1^* \\ N_2^* \end{bmatrix}$$

where by Remark 2.5, $N_1^* = N_1^0$, $N_2^* = N_2^0$ as given in (3.5) and λ_1 and λ_2 are the distinct roots of the characteristic polynomial (3.16). Notice that the real parts of λ_1 and λ_2 are negative. Constants c_1 and c_2 depend on $N_1(0)$ and $N_2(0)$.

Substituting $N_1(t)$ and $N_2(t)$ into (3.11) gives an asymptotically autonomous planar system. Since $\lim_{t\to\infty} N_i(t) = N_i^*$, the asymptotically autonomous planar system has limit system

$$\frac{dI_i}{dt} = \frac{\beta_i(N_i^* - I_i)I_i}{N_i^*} + n_{ij}I_j - (a_i + n_{ji})I_i \text{ for } i,j = 1,2 \text{ and } i \neq j \quad (3.17)$$

having the same equilibria as (3.11), namely $(0,0)$ and (I_1^*, I_2^*).

Every forward bounded solution of the system (3.17) lies in $X = \{(I_1, I_2) : I_1, I_2 \geq 0\}$ and its ω-limit set lies in $Y = \{(I_1, I_2) : 0 \leq I_1, I_2, I_1 + I_2 \leq \mathcal{M}\}$. Let $D = \{(I_1, I_2) : 0 < I_1, I_2 < \mathcal{M}\}$. Using a Dulac function $\rho = 1/(I_1 I_2)$, which is continuously differentiable in D,

$$\frac{d(\rho\frac{dI_1}{dt})}{dI_1} + \frac{d(\rho\frac{dI_2}{dt})}{dI_2} = -\frac{\beta_1}{N_1^* I_2} - \frac{n_{12}}{I_1^2} - \frac{\beta_2}{N_2^* I_1} - \frac{n_{21}}{I_2^2}$$

is strictly negative. Thus the system (3.17) has no periodic orbits. In addition $(0,0)$ is not part of any cycle chain. Using Theorem B.14, every bounded

forward orbit of (3.17) in X and every bounded forward orbit of (3.11)-(3.12) in X converges towards an equilibrium of (3.17). If $\mathcal{R}_0 > 1$, then $(0,0)$ is unstable for (3.17) and is repelling in the positive quadrant. Therefore (I_1^*, I_2^*) is globally asymptotically stable for (3.17) and $\mathcal{E}^* = (I_1^*, I_2^*, N_1^*, N_2^*)$ is globally asymptotically stable for (3.11)-(3.12). □

Table 3.1 summarizes existence and stability of equilibria, and for this case (with $m_{12} = n_{12}$ and $m_{21} = n_{21}$) the result of Theorem 3.1 shows that LAS can be strengthened to GAS for $\mathcal{E}^*$. Thus $\mathcal{R}_0$ acts as a sharp threshold for this system, with the disease dying out if $\mathcal{R}_0 < 1$ and going to an endemic value if $\mathcal{R}_0 > 1$ (since $\mathcal{R}_0 \geq \max_{i=1,2} \tilde{\mathcal{R}}_0^{(i)}$). These results extend those for a constant population in [WM].

Example 3.3. Assume that all parameters are as in Example 3.1 (with $\beta_1 = 0.10$, $\beta_2 = 0.03$) except that $n_{12} = n_{21} = 0.01$ so that $m_{ij} = n_{ij}$. Then

$$\mathcal{R}_0^{(1)} = 2.50, \mathcal{R}_0^{(2)} = 0.75, \tilde{\mathcal{R}}_0^{(1)} = 2.00, \tilde{\mathcal{R}}_0^{(2)} = 0.60$$

Using (3.6), $\mathcal{R}_0 = 2.12$. From Remark 2.5 at any equilibrium $N_i^0 = N_i^*$. Numerical solution shows that $N_1^0 = N_1^* = 486235.9$ and $N_2^0 = N_2^* = 485986.3$, and numerical values for I_1, I_2 at equilibria are as follows. At $\mathcal{E}^0$: $(I_1, I_2) = (0,0)$, and at $\mathcal{E}^*$: $(I_1^*, I_2^*) = (261503.1, 99818.6)$ with $\frac{I_1^*}{N_1^*} = 0.54$, $\frac{I_2^*}{N_2^*} = 0.21$. Taking initial conditions as $I_1(0) = 100, I_2(0) = 150, N_1(0) = 486000, N_2(0) = 480000$ and solving (3.11)-(3.12) numerically gives Figure 3.3, which shows that the disease becomes endemic in both patches.

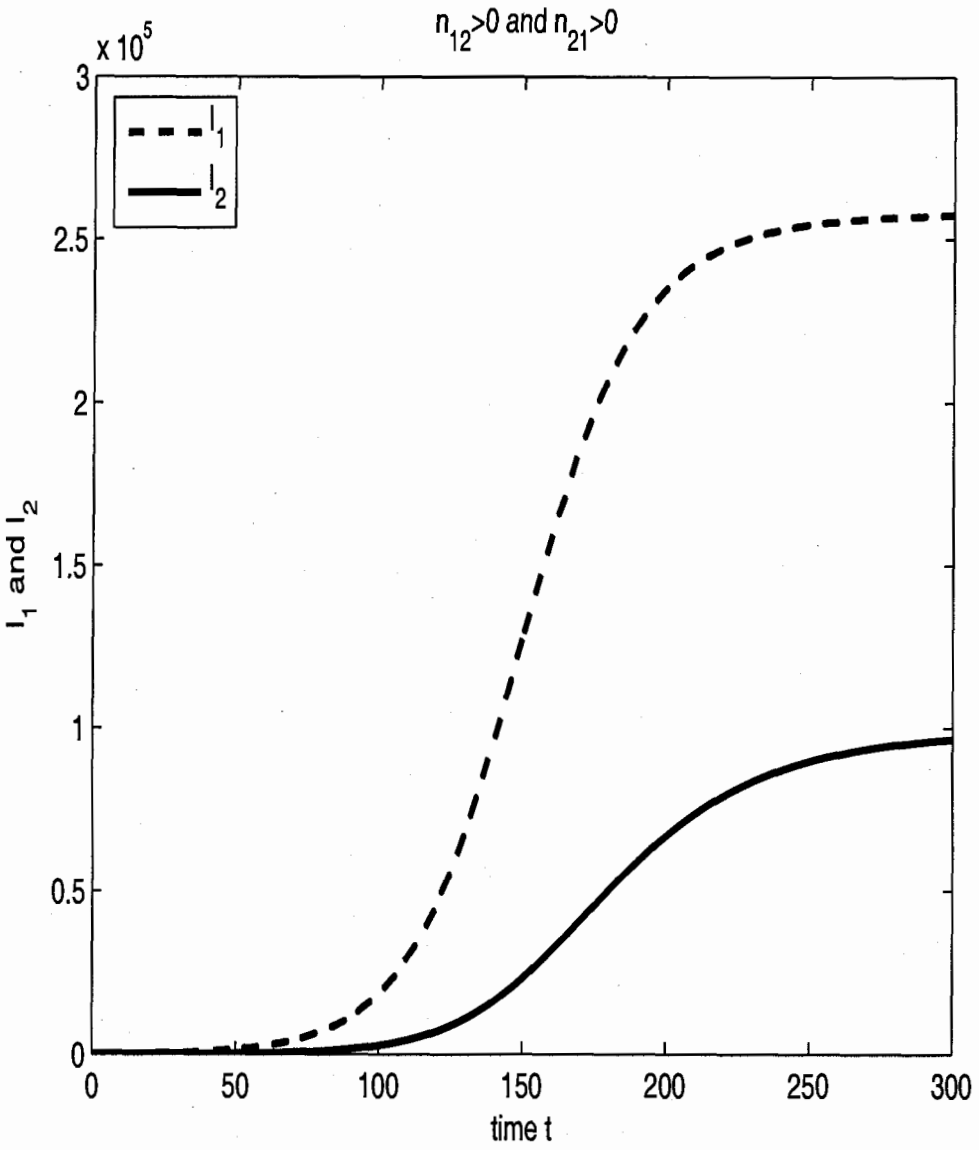

Figure 3.3: SIS model with two patches for $m_{12} = n_{12}$ and $m_{21} = n_{21}$

3.4 Infectious individuals of one patch travel

Assuming that infectious individuals of patch 2 do not travel but those of patch 1 do travel, so $n_{12} = 0$ and $n_{21} > 0$. All susceptible individuals travel, so $m_{12}, m_{21} > 0$. This case applies to a situation in which infectious individuals in patch 2 are prevented from entering patch 1. The disease may cause fatalities, so $a_i = \gamma_i + d_i + \epsilon_i$. System (3.1)-(3.4) becomes

$$\begin{aligned}
\frac{dI_1}{dt} &= \frac{\beta_1(N_1 - I_1)I_1}{N_1} - (n_{21} + a_1)I_1 \\
\frac{dI_2}{dt} &= \frac{\beta_2(N_2 - I_2)I_2}{N_2} - a_2 I_2 + n_{21} I_1 \\
\frac{dN_1}{dt} &= A_1 - (d_1 + m_{21})N_1 + (m_{21} - \epsilon_1 - n_{21})I_1 - m_{12}I_2 + m_{12}N_2 \\
\frac{dN_2}{dt} &= A_2 - (d_2 + m_{12})N_2 + (m_{12} - \epsilon_2)I_2 + (n_{21} - m_{21})I_1 + m_{21}N_1 \quad (3.18)
\end{aligned}$$

Assume that $S_1(0) > 0, S_2(0) > 0$ and $I_1(0) > 0$, $I_2(0) \geq 0$. In this case, since V is a triangular matrix, $\mathcal{R}_0 = \max\{\tilde{\mathcal{R}}_0^{(1)}, \mathcal{R}_0^{(2)}\}$. Three non-negative equilibria are possible for system (3.18), that is, $\mathcal{E}^0$, $\mathcal{E}^{(2)}$ and $\mathcal{E}^*$. In terms of N_1 and N_2 they are as follows, where $N_1^{(2)}$ and $N_2^{(2)}$ are positive and can be found from the following system:

$$\begin{aligned}
A_1 &= (d_1 + m_{21})N_1 - N_2 m_{12}/\mathcal{R}_0^{(2)} \\
A_2 &= -m_{21}N_1 + N_2(d_2 + \epsilon_2(1 - 1/\mathcal{R}_0^{(2)}) + m_{12}/\mathcal{R}_0^{(2)})
\end{aligned}$$

(i) $\mathcal{E}^0$ DFE as given in (3.5)

(ii) $\mathcal{E}^{(2)} = (0, N_2^{(2)}(1 - 1/\mathcal{R}_0^{(2)}), N_1^{(2)}, N_2^{(2)})$, $I_2^{(2)}$ is positive if $\mathcal{R}_0^{(2)} > 1$

(iii) $\mathcal{E}^* = (N_1^*(1 - 1/\tilde{\mathcal{R}}_0^{(1)}), I_2^*, N_1^*, N_2^*)$ is positive if $\tilde{\mathcal{R}}_0^{(1)} > 1$.

Here I_2^* is the positive solution of the following quadratic equation

$$\frac{\beta_2 I_2^2}{N_2^*} - (\beta_2 - a_2)I_2 - n_{21}N_1^*(1 - \frac{1}{\tilde{\mathcal{R}}_0^{(1)}}) = 0$$

Note that this quadratic has a unique positive solution if $\tilde{\mathcal{R}}_0^{(1)} > 1$.

Theorem 3.6. *For non-negative initial conditions, the endemic equilibrium of (3.18), $\mathcal{E}^{(2)}$, is locally asymptotically stable if $\mathcal{R}_0^{(2)} > 1$ and $\tilde{\mathcal{R}}_0^{(1)} < 1$.*

Proof. According to (ii)) $\mathcal{E}^{(2)}$ exisits if $\mathcal{R}_0^{(2)} > 1$. The Jacobian of (3.18) at $\mathcal{E}^{(2)}$ is as follow,

$$J_2 = \begin{bmatrix} \beta_1 - (a_1 + n_{21}) & 0 & 0 & 0 \\ n_{21} & -\beta_2 K_2 & 0 & \beta_2 K_2^2 \\ m_{21} - n_{21} - \epsilon_1 & -m_{12} & -d_1 - m_{21} & m_{12} \\ n_{21} - m_{21} & m_{12} - \epsilon_2 & m_{21} & -d_2 - m_{12} \end{bmatrix}$$

Thus the characteristic equation of J_2 is

$$p(\lambda) = (\lambda - \beta_1 + a_1 + n_{21})(\lambda^3 + c_1\lambda^2 + c_2\lambda + c_3) = 0 \qquad (3.19)$$

with

$$\begin{aligned} c_1 &= \beta_2 K_2 + m_{12} + m_{21} + d_1 + d_2 \\ c_2 &= \beta_2\{d_1 + d_2 + m_{21} + m_{12}(1 - K_2) + K_2\epsilon_2\} + d_1 m_{12} + d_2 m_{21} + d_1 d_2 \\ c_3 &= \beta_2 K_2(d_1 d_2 + d_1 m_{12}(1 - K_2) + K_2 m_{21}\epsilon_2 + d_2 m_{21} + K_2 d_1 \epsilon_2) \end{aligned} \qquad (3.20)$$

Thus one of the eigenvalues is $\lambda_1 = \beta_1 - (a_1 + n_{21})$. So λ_1 is negative if $\beta_1 < a_1 + n_{21}$, which is equivalent to $\tilde{\mathcal{R}}_0^{(1)} < 1$. Eigenvalues λ_i, $i = 1, 2, 3$ are roots of $\lambda^3 + c_1\lambda^2 + c_2\lambda + c_3 = 0$. Since $K_2 < 1$, it is clear from (3.20) that $c_1, c_3 > 0$ and

$$\begin{aligned} c_1c_2 - c_3 =& \beta_2^2K_2^2\{m_{21} + m_{12}(1 - K_2) + K_2\epsilon_2 + d_1 + d_2)\}+ \\ & K_2\beta_2\{(d_1 + d_2)^2 + m_{12}(2 - K_2)(d_2 + m_{21}) + m_{12}^2(1 - K_2)+ \\ & \epsilon_2K_2(m_{12} + d_2) + m_{12}(m_{21} + 2d_1 + 2d_2)\}+ \\ & K_2^2\{(m_{21} + m_{12}(1 - K_2) + K_2\epsilon_2 + d_1 + d_2)\} \end{aligned}$$

It is easy to see from the above expression that $c_1c_2 - c_3 > 0$. Using Theorem B.10 for $n = 3$, $\mathcal{E}^{(2)}$ exists and is locally asymptotically stable if $\tilde{\mathcal{R}}_0^{(1)} < 1$ and $\mathcal{R}_0^{(2)} > 1$. □

Existence and stability of $\mathcal{E}^*$ is shown numerically. Global stability of $\mathcal{E}^{(2)}$ and analytical results on $\mathcal{E}^*$ remain open. Stability results are summarised in Table 3.2, with the notation as in Table 3.1. For a constant total population [WM, Theorem 2.4] shows that if $\mathcal{R}_0^{(1)} > 0$, then the disease is uniformly persistent.

In this case the stability depends on $\mathcal{R}_0^{(2)}$ and $\tilde{\mathcal{R}}_0^{(1)}$, which depends on the rate of travel of the infectious individuals from patch 1 to patch 2. If $\mathcal{R}_0^{(2)} < 1$ but $\tilde{\mathcal{R}}_0^{(1)} > 1$, then disease persists in both patches, whereas if $\mathcal{R}_0^{(2)} < 1$, disease would not persist in patch 2 in isolation. A numerical example of this case is now given.

	$\tilde{\mathcal{R}}_0^{(1)} < 1$	$\tilde{\mathcal{R}}_0^{(1)} > 1$
$\mathcal{R}_0^{(2)} < 1$	$\mathcal{E}^0$ GAS	$\mathcal{E}^0$ U $\mathcal{E}^*$ LAS
$\mathcal{R}_0^{(2)} > 1$	$\mathcal{E}^0$ U $\mathcal{E}^{(2)}$ LAS	$\mathcal{E}^0$, $\mathcal{E}^{(2)}$ U $\mathcal{E}^*$ LAS

Table 3.2: Stability of equilibria for (3.18) having $n_{12} = 0$ and $n_{21} > 0$

Example 3.4. Consider Example 3.1 with the same parameters except $\epsilon_1 = 0.06$, $\epsilon_2 = 0.09$, $n_{12} = 0$, $\beta_1 = 0.22$ and $\beta_2 = 0.1$. Thus $\mathcal{R}_0^{(1)} = 2.20$, $\tilde{\mathcal{R}}_0^{(1)} = 2.0$ and $\mathcal{R}_0^{(2)} = 0.77$, giving $\mathcal{R}_0 = 2.0$. System (3.18) has two non-negative equilibria as follows:

$$\mathcal{E}^0 = (0, 0, 486235.9, 485986.3) \text{ and } \mathcal{E}^* = (416.3, 110.5, 832.8, 1444.0)$$

with $\frac{I_1^*}{N_1^*} = 0.50$ and $\frac{I_2^*}{N_2^*} = 0.08$. Taking initial conditions $I_1(0) = 10, I_2(0) = 15, N_1(0) = 2000, N_2(0) = 1500$ and solving (3.18) numerically gives Figure 3.4, which shows that the disease becomes endemic in both patches, agreeing with Table 3.2. Thus the patchy environment and travel of infectious individuals from patch 1 to patch 2 means that disease persists in patch 2, whereas it would die out in patch 2 in isolation. If n_{21} is increased to $n_{21} = 0.14$ (with other parameters unchanged), then $\tilde{\mathcal{R}}_0^{(1)} = 0.92$. Thus $\mathcal{R}_0 < 1$ and so the DFE is globally asymptotically stable. The increased travel rate of infectious individuals from patch 1 to patch 2 causes the disease to die out.

In a case in which $\mathcal{R}_0^{(2)} > 1$ and $\tilde{\mathcal{R}}_0^{(1)} < 1$, the disease becomes endemic in patch 2 and dies out in patch 1. The following example is a numerical representation of such a case.

Example 3.5. Consider Example 3.4 with $\beta_1 = 0.08$ and $\beta_2 = 0.20$ and the other parameter unchanged. The reproduction numbers for both patches are

$$\mathcal{R}_0^{(1)} = 0.80, \ \mathcal{R}_0^{(2)} = 1.54, \ \tilde{\mathcal{R}}_0^{(1)} = 0.73$$

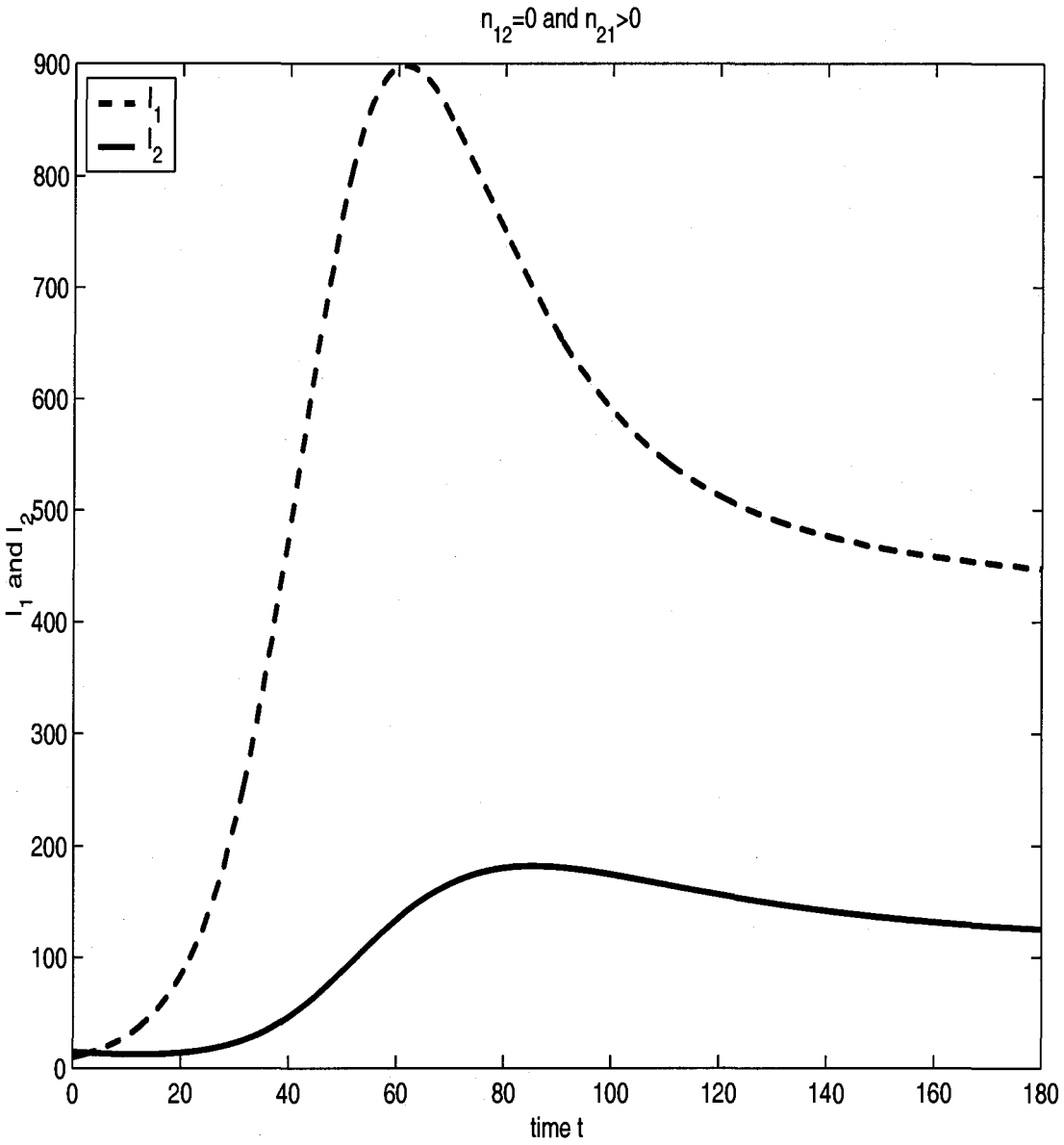

Figure 3.4: SIS model with two patches for $\tilde{\mathcal{R}}_0^{(1)} > 1$, $\mathcal{R}_0^{(2)} < 1$, $n_{12} = 0$ and $n_{21} > 0$

Using (3.6) $\mathcal{R}_0 = 1.54$. The system (3.18) has two non-negative equilibria:

$$\mathcal{E}^0 = (0, 0, 486235.9, 485986.3) \text{ and}$$

$$\mathcal{E}^{(2)} = (0, 387.4, 2710.2, 1107.3)$$

Taking the same initial conditions as in Example 3.4 and solving (3.18) numerically gives Figure 3.5, which shows that the disease becomes endemic in patch 2 and dies out in patch 1.

3.5 Infectious individuals do not travel

In this case, $m_{12}, m_{21} > 0$ and $n_{21} = n_{12} = 0$, thus (3.1)-(3.4) reduce to

$$\begin{aligned}
\frac{dI_1}{dt} &= \frac{\beta_1(N_1 - I_1)I_1}{N_1} - a_1 I_1 \\
\frac{dI_2}{dt} &= \frac{\beta_2(N_2 - I_2)I_2}{N_2} - a_2 I_2 \\
\frac{dN_1}{dt} &= A_1 - (d_1 + m_{21})N_1 + (m_{21} - \epsilon_1)I_1 - m_{12}I_2 + m_{12}N_2 \\
\frac{dN_2}{dt} &= A_2 - (d_2 + m_{12})N_2 + (m_{12} - \epsilon_2)I_2 - m_{21}I_1 + m_{21}N_1
\end{aligned} \tag{3.21}$$

As expected, if the initial number of infectious individuals in one patch is zero, then the number of infectious individuals stays at zero in that patch. Assume that $S_1(0)$, $S_2(0)$, $I_1(0)$ and $I_2(0)$ are all positive. For this case, matrix V is diagonal, and as in Remark 2.8, the basic reproduction number for (3.21) is

$$\mathcal{R}_0 = \max_{i=1,2} \mathcal{R}_0^{(i)} = \max_{i=1,2} \frac{\beta_i}{a_i} \tag{3.22}$$

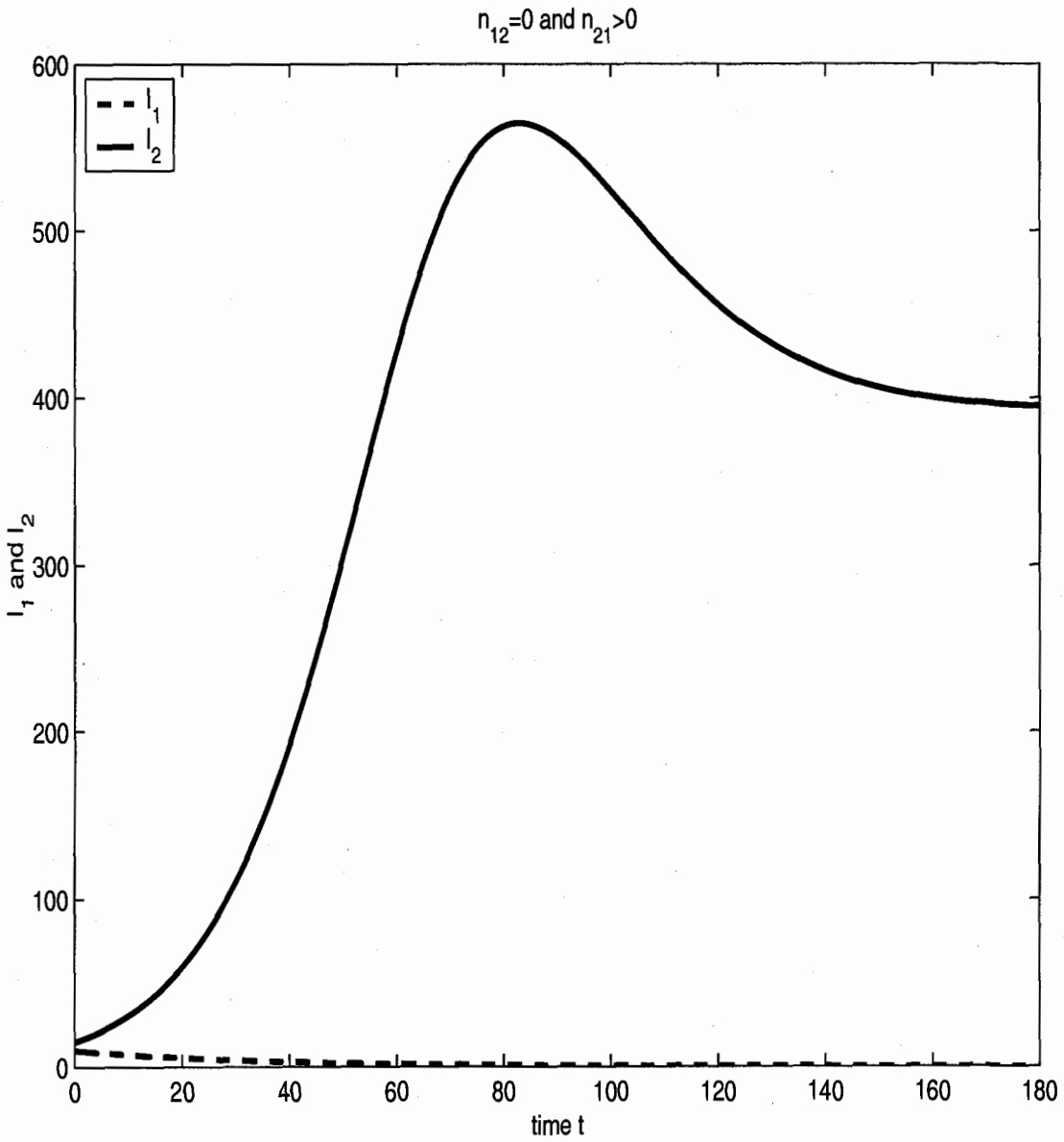

Figure 3.5: SIS model with two patches for $\tilde{\mathcal{R}}_0^{(1)} < 1$, $\mathcal{R}_0^{(2)} > 1$, $n_{12} = 0$ and $n_{21} > 0$

Solving (3.21) at a steady state gives (possibly) four non-negative equilibria as follows:

(i)

$$\mathcal{E}^0 = (0, 0, N_1^0, N_2^0), \quad \text{namely the DFE as given in (3.5)}$$

(ii),(iii)

$$\mathcal{E}^{(i)} = (I_i^{(i)}, I_j^{(i)}, N_i^{(i)}, N_j^{(i)}) \quad \text{for } i, j = 1, 2 \text{ and } i \neq j, \text{ where}$$

$$I_i^{(i)} = \frac{(\beta_i - a_i)(m_{ij}A_j + d_jA_i + m_{ij}A_i)}{\kappa_i}, \qquad I_j^{(i)} = 0$$

$$N_i^{(i)} = \frac{\beta_i(m_{ij}A_j + d_jA_i + m_{ij}A_i)}{\kappa_i}$$

$$N_j^{(i)} = \frac{\beta_i d_i A_j + \epsilon_i A_j(\beta_i - a_i) + m_{ji}a_iA_j + m_{ji}a_iA_i}{\kappa_i}$$

with $\kappa_i = \beta_i d_i m_{ij} + \epsilon_i(\beta_i - a_i)(d_j + m_{ij}) + \beta_i d_i d_j + m_{ji}a_i d_j$

Equilibrium $\mathcal{E}^{(i)}$ exists (since $I_i^{(i)}$ is positive) if $\mathcal{R}_0^{(i)} > 1$

(iv)

$$\mathcal{E}^* = (I_1^*, I_2^*, N_1^*, N_2^*), \text{where for } i = 1, 2 \text{ and } i \neq j,$$

$$I_i^* = \frac{(\beta_i - a_i)(\beta_j d_j A_i + \epsilon_j A_i(\beta_j - a_j) + m_{ij}a_jA_i + m_{ij}a_jA_j)}{\kappa_3}$$

$$N_i^* = \frac{\beta_i(\beta_j d_j A_i + \epsilon_j A_i(\beta_j - a_j) + m_{ij}a_jA_i + m_{ij}a_jA_j)}{\kappa_3}$$

with $\kappa_3 = \epsilon_2(\beta_2 - a_2)(m_{21}a_1 + \epsilon_1(\beta_1 - a_1) + d_1\beta_1) + d_1d_2\beta_1\beta_2 +$

$$\epsilon_1(\beta_1 - a_1)(d_2\beta_2 + m_{12}a_2) + m_{12}a_2d_1\beta_1 + m_{21}a_1d_2\beta_2$$

Equilibrium $\mathcal{E}^*$ is positive if both $\mathcal{R}_0^{(1)} > 1$ and $\mathcal{R}_0^{(2)} > 1$

The following theorem gives local stability criteria of $\mathcal{E}^{(i)}$ for $i = 1, 2$.

Theorem 3.7. *For $I_i(0) > 0$ and $\mathcal{R}_0^{(j)} < 1$, $i \neq j$, the equilibrium $\mathcal{E}^{(i)}$ is locally asymptotically stable when it exists.*

Proof. According to (ii) and (iii), $\mathcal{E}^{(i)}$ exists if $\mathcal{R}_0^{(i)} > 1$. Assume that $i = 2$. The Jacobian matrix of (3.21) at $\mathcal{E}^{(2)}$ is as J_2 in Theorem 3.6 with $n_{21} = 0$. Similarly, the characteristic equation of J_2 at $\mathcal{E}^{(2)}$ is the same as (3.19) with $n_{21} = 0$. Thus using Theorem 3.6, $\mathcal{E}^{(2)}$ is locally asymptotically stable if $\mathcal{R}_0^{(1)} < 1$. A similar argument shows that $\mathcal{E}^{(1)}$ exists and is locally asymptotically stable if $\mathcal{R}_0^{(1)} > 1$ and $\mathcal{R}_0^{(2)} < 1$. □

The following theorem gives local stability criteria for $\mathcal{E}^*$ via a polynomial of degree 4. For a constant total population Wang and Mulone [WM] work in proportions of infective individuals, and show LAS of $\mathcal{E}^*$ via a polynomial of degree 3.

Theorem 3.8. *With positive initial conditions, $\mathcal{E}^*$ is locally asymptotically stable when it exists.*

Proof. Using (iv), $\mathcal{E}^*$ exists if both $\mathcal{R}_0^{(1)} > 1$ and $\mathcal{R}_0^{(2)} > 1$. Linearizing (3.21) at $\mathcal{E}^*$ gives,

$$J_* = \begin{bmatrix} -\beta_1 K_1 & 0 & \beta_1 K_1^2 & 0 \\ 0 & -\beta_2 K_2 & 0 & \beta_2 K_2^2 \\ m_{21} - \epsilon_1 & -m_{12} & -(d_1 + m_{21}) & m_{12} \\ m_{12} - \epsilon_2 & -m_{21} & -(d_2 + m_{12}) & m_{21} \end{bmatrix}$$

with K_1, K_2 as in the proof of Theorem 3.3. Thus the characteristic equation of J_* is as follows,

$$p(\lambda) = \lambda^4 + c_1\lambda^3 + c_2\lambda^2 + c_3\lambda + c_4 = 0 \tag{3.23}$$

The proof of local asymptotic stability is completed by using Theorem B.10 for $n = 4$. Details of the Routh-Hurwitz conditions showing stability are given in Appendix A.2. □

The global stability result for $\mathcal{E}^0$ follows from a comparison theorem argument as used in Theorem 2.1. Analyzing the stability of the above equilibria gives Table 3.3 with the notation as in Table 3.1. Numerical simulation of (3.21) with many parameter values indicate that the locally stability results are in fact global (for positive $I_i(0)$). Disease may persist in one or two patches depending on the value of the basic reproduction number in each patch. A representative example is now given.

Example 3.6. Assume parameters are as Example 3.1 except $\epsilon_1 = 0.06$, $\epsilon_2 = 0.09$, $n_{12} = n_{21} = 0$, $\beta_1 = 0.22$, $\beta_2 = 0.30$. From (3.22) with these parameter values $\mathcal{R}_0^{(1)} = 2.20$, $\mathcal{R}_0^{(2)} = 2.30$, and thus $\mathcal{R}_0 = 2.30$. For these parameter values, there are four non-negative equilibria as follows:

$$\mathcal{E}^0 = (0, 0, 486235.9, 485986.3), \quad \mathcal{E}^{(1)} = (581.5, 0, 1066.4, 1977.8),$$

$$\mathcal{E}^{(2)} = (0, 387.7, 2288.4, 684.3), \quad \mathcal{E}^* = (312.5, 180.2, 573.1, 318.0)$$

with $\frac{I_1^*}{N_1^*} = 0.55$ and $\frac{I_2^*}{N_2^*} = 0.57$. Taking initial conditions $I_1(0) = 10$, $I_2(0) = 15$, $N_1(0) = 2000$, $N_2(0) = 1500$, and numerically solving (3.21) gives

	$\mathcal{R}_0^{(1)} < 1$	$\mathcal{R}_0^{(1)} > 1$
$\mathcal{R}_0^{(2)} < 1$	$\mathcal{E}^0$ GAS	$\mathcal{E}^0$ U $\mathcal{E}^{(1)}$ LAS
$\mathcal{R}_0^{(2)} > 1$	$\mathcal{E}^0$ U $\mathcal{E}^{(2)}$ LAS	$\mathcal{E}^0, \mathcal{E}^{(1)}, \mathcal{E}^{(2)}$ U $\mathcal{E}^*$ LAS

Table 3.3: Stability of equilibria for (3.21) having $n_{12} = n_{21} = 0$.

Figure 3.6, which shows that the disease becomes endemic in each patch, adding strength to the local stability result for $\mathcal{E}^*$ in Table 3.3. Note that for these parameters the number of infectious individuals initially rises fairly quickly to an epidemic peak in each patch and then falls to an endemic value.

The next example shows that if infectious individuals of both patches do not travel, then the disease will not spread in patch i with $\mathcal{R}_0^{(i)} < 1$, even though $\mathcal{R}_0 > 1$.

Example 3.7. Assume all parameters and initial conditions are as in Example 3.6 except that $\beta_1 = 0.005$. Then $\mathcal{R}_0^{(1)} = 0.05$, $\mathcal{R}_0^{(2)} = 2.30$ and thus $\mathcal{R}_0 = 2.30$. There are two non-negative equilibria, with $\mathcal{E}^0$ and $\mathcal{E}^{(2)}$ as in Example 3.6. Numerical solution of (3.21) gives Figure 3.7, which shows that although $\mathcal{R}_0 > 1$, the disease is endemic in patch 2 but dies out in patch 1.

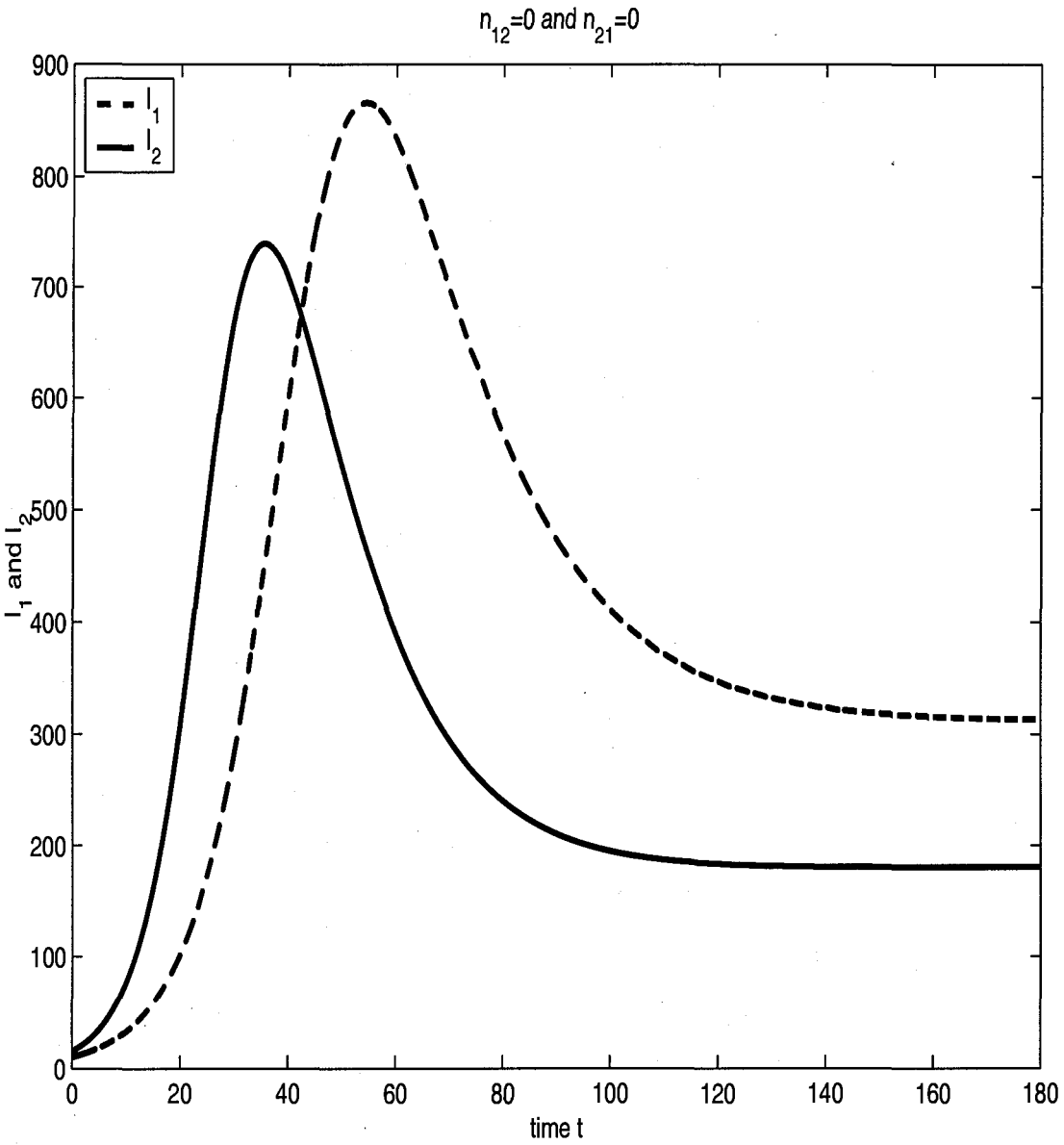

Figure 3.6: SIS model with two patches for $\mathcal{R}_0^{(1)} > 1$, $\mathcal{R}_0^{(2)} > 1$ and $n_{12} = n_{21} = 0$

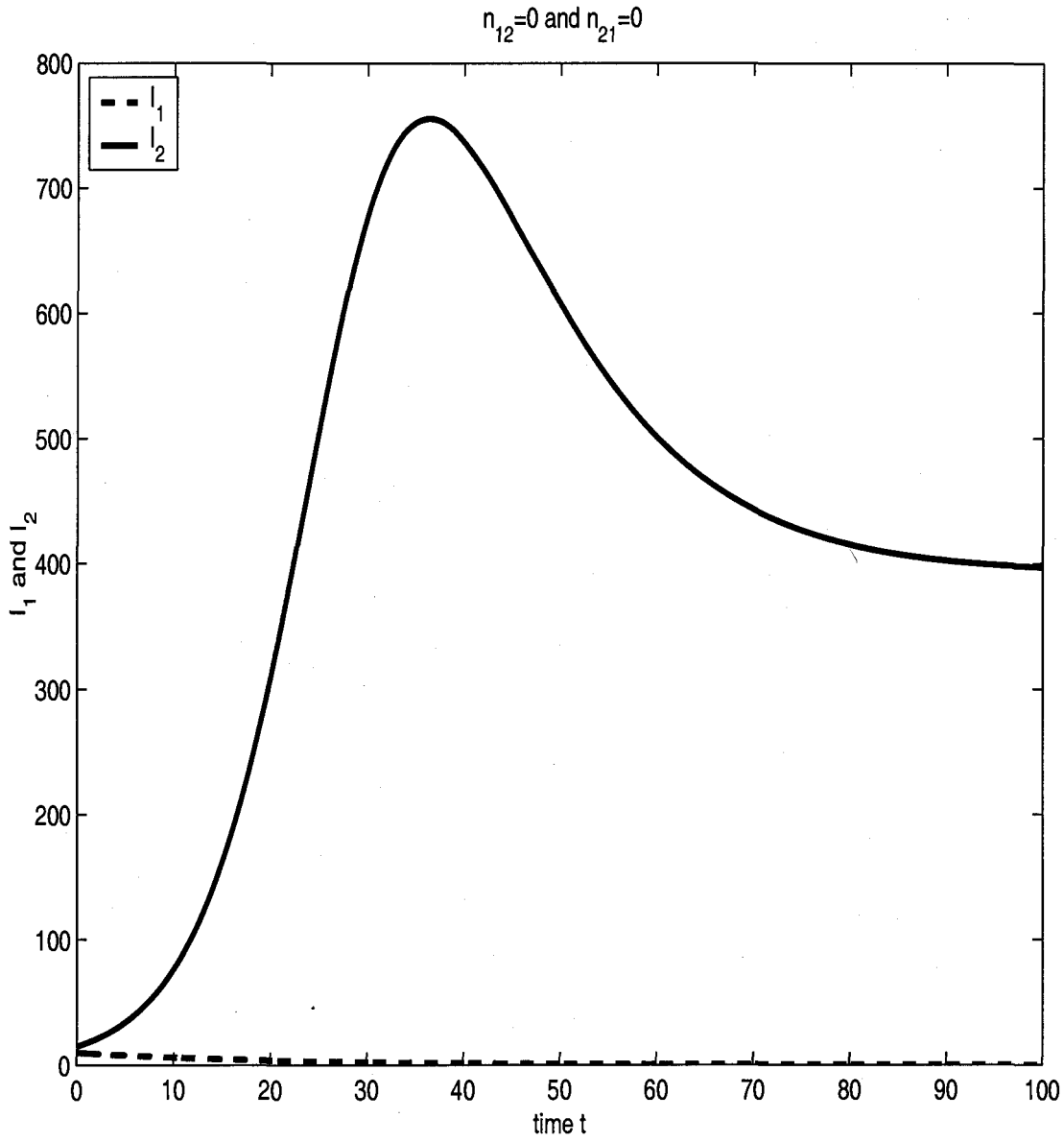

Figure 3.7: SIS model with two patches for $\mathcal{R}_0^{(1)} < 1$, $\mathcal{R}_0^{(2)} > 1$ and $n_{12} = n_{21} = 0$

Chapter 4

Conclusions

The SEIRS epidemic model for p patches formulated in (2.1)-(2.4) describes the dynamics of an infectious disease in a population in which individuals travel between patches. This is a general spatially heterogeneous model and special cases can be applied to many infectious diseases. A formula and bounds for $\mathcal{R}_0$ for this general model are determined and it is proved that the DFE is globally asymptotically stable for $\mathcal{R}_0 < 1$. This extends the result for 2 patches given by [WM, Theorem 2.1] for a constant population. In the special case when there are 4 patches, it is shown numerically that if patch 1 restricts incoming travel of exposed and infectious individuals, then the disease either dies out or becomes endemic in patch 1 depending on $\mathcal{R}_0^{(1)} < 1$ (Example 2.1) or $\mathcal{R}_0^{(1)} > 1$, respectively. If patch 1 allows exposed individuals to enter (but still restricts incoming infective individuals) then the disease either dies out or becomes endemic in all patches (Example 2.2) depending

on $\mathcal{R}_0 < 1$ or $\mathcal{R}_0 > 1$, respectively.

The SIS model with two patches formulated in (3.1)-(3.4) is applicable for diseases with short exposed and immune periods, e.g., gonorrhea. The explicit formula and bounds for $\mathcal{R}_0$ are obtained. If infectious individuals of both patches can travel between patches, it is proved that either the disease dies out or becomes endemic in both patches depending on $\mathcal{R}_0 < 1$ or $\mathcal{R}_0 > 1$, respectively. For $\mathcal{R}_0 > 1$, analytical proofs of the existence and stability of the endemic equilibrium in the case that traveling rates depend on disease status remain open. However, if the travel rates are independent of disease status, then it is proved that the unique endemic equilibrium is globally asymptotically stable. These results show that $\mathcal{R}_0$ is an important threshold parameter that depends on the disease characteristics and the travel rates of exposed and infectious individuals. This parameter determines whether travel of infectious individuals increases or controls disease persistence.

If infectious individuals of patch 1 can travel but those of patch 2 do not, then the disease can die out in both patches, become endemic in patch 2 and die out in patch 1, or become endemic in both patches depending on the values of $\tilde{\mathcal{R}}_0^{(1)}$ (the modified reproduction number for the patch from which infectious individuals can travel) and $\mathcal{R}_0^{(2)}$; see Table 3.2. If $\tilde{\mathcal{R}}_0^{(1)} > 1$, then the disease becomes endemic in both patches (global stability of the endemic equilibrium remains open). However, for increased rate of travel, $\tilde{\mathcal{R}}_0^{(1)} < 1$ and if $\mathcal{R}_0^{(2)} < 1$, then the disease dies out in both patches. Thus restriction

of travel may help control disease spread. If $\tilde{\mathcal{R}}_0^{(1)} < 1$ and $\mathcal{R}_0^{(2)} > 1$, then the disease becomes endemic in patch 2 and dies out in patch 1, provided that there are some infectious individuals initially (Example 3.5).

When infectious individuals do not travel, it is shown that the disease can become endemic, die out in both patches or die out in one patch and become endemic in the other patch depending on the values of $\mathcal{R}_0^{(1)}$ and $\mathcal{R}_0^{(2)}$ (Table 3.3). In this case the disease can not invade a patch for which the basic reproduction number in isolation is less than 1. These results quantify how the reproduction numbers predict the outcome of disease spread in a patchy environment.

It should be noted that patch models have some similarities with multi-groups models. For an SIS two group model with mass action [HvdD], backward bifurcation was shown to be possible. However, no such bifurcation has been found in these patch models.

In order to make the patch models formulated in Chapters 2 and 3 more biologically realistic, additional features should be included. Some of these are now listed. The first two deal with the contact rate, where the remainder are related to travel.

- Some diseases, such as influenza, have seasonal oscillations in infectivity. Influenza is more likely to spread in the winter than in the summer and that may be caused by increased infectiousness of the disease, increased susceptibility of individuals or increase in the contact

rates. This seasonality is included in the influenza study of Hyman and LaForce [HF].

- Since in practice the contact rate for each patch may change over time, it is useful to consider the contact rate for each patch as a function of time. In this case the models are no longer autonomous, but numerical simulations with real data for a particular disease can be made. The contact rate may also depend on the level of infection or on the number of individuals in patch i. In particular, taking mass action incidence may be more realistic for smaller populations in which the contact rate increases linearly with population size [H, Section 2.1].

- The models in Chapter 2 and 3 assume only one type of mobility for each disease status in each patch, while in real life there might be more than one type of mobility. For instance for the model introduced in [SD], it is assumed that there are different types of mobility depending on age. In some communities it may be appropriate to take travel rates depending on season. It may also be important to consider where an individual resides as well as where an individual currently is. This can introduce different contacts, namely within and between patch contacts. These are considered in the models of [SD], [AvdD1] and [AvdD2] in which the contact between residents of city i is different from the contact of a resident of city i and a visitor from city j.

- Since individuals take time to travel, time delays should be included in the return travel terms. In such a model the time scales need to be well understood, since individuals could change disease status while traveling.

The above list contains challenges for future work on patch models for disease spread.

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Appendix A

A.1 Interpretation of $\mathcal{R}_0$ for SEIRS model

To interpret $\mathcal{R}_0$ as given by (1.5) for the SEIRS model given by (1.1)-(1.4), consider the process of leaving the infective compartment. Using (1.3),

$$\frac{dI}{dt} = -aI \tag{A.1}$$

where $a = \epsilon + \gamma + d$ is the rate of leaving compartment I. Solving (A.1) with initial condition $I(0)$ gives

$$I(t) = I(0)e^{-at} \quad \text{for } t \geq 0$$

Hence e^{-at} is the proportion of individuals who were in the infective compartment at time 0 and still are there at time t. Thus

$$P(X \leq t) = F(t) = \begin{cases} 1 - e^{-at} & t \geq 0 \\ 0 & t < 0 \end{cases}$$

where $F(t)$, the cumulative distribution function, denotes the probability of leaving the infective compartment in the time interval $[0, t)$, and X denotes

the time to leaving the infective compartment. Then the probability density function, $f(t)$, is

$$f(t) = F'(t) = \begin{cases} ae^{-at} & t \geq 0 \\ 0 & t < 0 \end{cases}$$

with the following properties

(i) $f(t) \geq 0$ for all t

(ii) $\int_{-\infty}^{\infty} f(t)dt = 1$

The expected or mean value is given by

$$\mu_X = E(X) = \int_{-\infty}^{+\infty} tf(t) = \int_0^{\infty} tae^{-at}dt = \frac{1}{a}$$

Thus the length of the infective period is distributed exponentially with mean $1/a$, which is the expected time that individuals spend in the infective compartment taking natural and disease death into account (called the average infective period). Similarly the length of the exposed period is distributed exponentially with mean $1/(\alpha + d)$. Thus the proportion of those entering the exposed compartment who survive this compartment is $1 - \frac{d}{\alpha+d} = \frac{\alpha}{\alpha+d}$. Therefore

$$\mathcal{R}_0 = (\beta)(\frac{1}{a})(\frac{\alpha}{\alpha + d}) =$$

(effective contact rate) $\times$ (average infective period) $\times$

(proportion of infected individuals surviving the exposed compartment)

Here the average infective period takes account of disease death, recovery and natural death. For an SIS model, $\alpha \longrightarrow \infty$, and so $\mathcal{R}_0 = \beta/a$.

A.2 Details of proof of Theorem 3.8

The coefficients of the characteristic polynomial (3.23)

$$p(\lambda) = \lambda^4 + c_1\lambda^3 + c_2\lambda^2 + c_3\lambda + c_4 = 0$$

are as follows,

$$\begin{aligned}
c_1 =& \beta_1 K_1 + \beta_2 K_2 + m_{12} + m_{21} + d_1 + d_2 \\
c_2 =& \beta_1\beta_2 K_1 K_2 + \beta_1 K_1(m_{12} + m_{21}(1 - K_1) + K_1\epsilon_1 + d_1 + d_2) + \\
& \beta_2 K_2(m_{21} + m_{12}(1 - K_2) + K_2\epsilon_2 + d_1 + d_2) + m_{12}d_1 + m_{21}d_2 + d_1 d_2 \\
c_3 =& \beta_1\beta_1 K_1 K_2(m_{12}(1 - K_2) + m_{21}(1 - K_1) + K_1\epsilon_1 + K_2\epsilon_2 + d_1 + d_2) + \\
& \beta_1 K_1(d_1 m_{12} + m_{21}d_2(1 - K_1) + \epsilon_1 K_1(m_{12} + d_2) + d_1 d_2) + \\
& \beta_2 K_2(d_2 m_{21} + m_{12}d_1(1 - K_2) + \epsilon_2 K_2(m_{21} + d_1) + d_1 d_2) \\
c_4 =& \beta_1\beta_2 K_1 K_2(m_{12}(1 - K_2)(d_1 + \epsilon_1 K_1) + m_{21}(1 - K_1)(d_2 + \epsilon_2 K_2) + \\
& \epsilon_2 d_1 K_2 + \epsilon_1 d_2 K_1 + \epsilon_1\epsilon_2 K_1 K_2 + d_1 d_2)
\end{aligned}$$

Since $K_1, K_2 < 1$, then $c_i > 0$ for $i = 1, \ldots, 4$. Calculating the Routh-Hurwitz conditions and using MAPLE

$$\begin{aligned}
c_1 c_2 - c_3 =& \beta_1^2\beta_2 K_1^2 K_2 + \beta_1^2 K_1^2(m_{12} + m_{21}(1 - K_1) + \epsilon_1 K_1 + d_1 + d_2) + \\
& \beta_2^2 K_2^2(m_{21} + m_{12}(1 - K_2) + \epsilon_2 K_2 + d_1 + d_2) + \\
& 2\beta_1\beta_2 K_1 K_2(m_{12} + m_{21} + d_1 + d_2) + \beta_1\beta_2^2 K_1 K_2^2 + \\
& (d_1 d_2 + m_{21}d_2 + m_{12}d_1)(m_{12} + m_{21} + d1 + d_2)
\end{aligned}$$

It is easy to see that $c_1c_2 - c_3 > 0$ since $K_1, K_2 < 1$. Similarly calculating

$$\begin{aligned} c_3(c_1c_2 - c_3) - c_1^2c_4 =& \beta_1^3\beta_2^2K_1^3K_2^2\mathcal{P}_1 + \beta_1^2\beta_2^3K_1^2K_2^3\mathcal{P}_2 + \\ & \beta_1^3\beta_2K_1^3K_2\mathcal{P}_3 + \beta_1\beta_2^3K_1K_2^3\mathcal{P}_4 + \\ & \beta_1\beta_2^2K_1K_2^2\mathcal{P}_5 + \beta_1^2\beta_2K_1^2K_2\mathcal{P}_6 + \\ & \beta_1^2\beta_2^2K_1^2K_2^2\mathcal{P}_7 + \beta_1\beta_2K_1K_2\mathcal{P}_8 + \\ & \beta_1^3K_1^3\mathcal{P}_9 + \beta_2^3K_2^3\mathcal{P}_{10} + \\ & \beta_1^2K_1^2\mathcal{P}_{11} + \beta_2^2K_2^2\mathcal{P}_{12} + \\ & \beta_1K_1\mathcal{P}_{13} + \beta_2K_2\mathcal{P}_{14} \end{aligned} \tag{A.2}$$

where

$$\mathcal{P}_1 = m_{12}(1 - K_2) + m_{21}(1 - K_1) + \epsilon_1K_1 + \epsilon_2K_2 + d_1 + d_2$$

$$\mathcal{P}_2 = m_{21}(1 - K_1) + m_{12}(1 - K_2) + \epsilon_1K_1 + \epsilon_2K_2 + d_1 + d_2$$

$$\begin{aligned} \mathcal{P}_3 =& m_{21}(1 - K_1)(m_{21}(1 - K_1) + m_{12}(2 - K_2) + 2\epsilon_1K_1 + 2d_1 + 2d_2) + \\ & m_{12}(1 - K_2)(2d_2 + m_{12}) + m_{12}\epsilon_2K_2 + \epsilon_2d_2K_2 + 2\epsilon_1d_1K_1 + 2d_1d_2 + \\ & 2m_{12}d_1 + 2m_{12}\epsilon_1K_1 + 2d_2\epsilon_1K_1 + \epsilon_1^2K_1^2 + d_1^2 + d_2^2 \end{aligned}$$

$$\begin{aligned} \mathcal{P}_4 =& m_{12}(1 - K_2)(m_{12}(1 - K_2) + m_{21}(2 - K_1) + 2\epsilon_2K_2 + 2d_1 + 2d_2) + \\ & m_{21}(1 - K_1)(2d_1 + m_{21}) + m_{21}\epsilon_1K_1 + \epsilon_1d_1K_1 + 2\epsilon_2d_2K_2 + 2d_1d_2 + \\ & 2m_{21}d_2 + 2m_{21}\epsilon_2K_2 + 2d_1\epsilon_2K_2 + \epsilon_2^2K_2^2 + d_1^2 + d_2^2 \end{aligned}$$

$$\begin{aligned} \mathcal{P}_5 =& 4d_1d_2^2 + m_{21}d_2^2(4 - K_1) + 4m_{21}^2d_2(1 - K_1) + m_{12}m_{21}d_2(7 - 3K_1 - 2K_2) + \\ & 4m_{21}d_1d_2(2 - K_1) + 4d_1^2d_2 + 4m_{12}d_1^2 + m_{12}d_1d_2(8 - K_2) + 4\epsilon_1d_1d_2K_1 + \\ & m_{12}m_{21}\epsilon_1K_1(3 - K_1) + 2m_{12}\epsilon_1d_2K_1 + 4m_{21}\epsilon_1d_2K_1 + 4m_{12}\epsilon_1d_1K_1 + \end{aligned}$$

$$m_{12}^2\epsilon_1 K_1 + \epsilon_1 d_2^2 K_1 + m_{21}\epsilon_2 d_2 K_2 + m_{21}^3(K_1-1)^2 + m_{12}^2 d_1(4-K_2)+$$
$$m_{21}m_{12}\epsilon_2 K_2 + \epsilon_2 d_1 d_2 K_2 + m_{12}\epsilon_2 d_1 K_2 + m_{21}^2 d_1(K_1-1)(K_1-3)+$$
$$m_{21}^2 m_{12}(K_1-1)(K_1+K_2-3) + m_{12}^2 m_{21}(2-K_1)(2-K_2)+$$
$$m_{21}\epsilon_1^2 K_1^2 + d_1\epsilon_1^2 K_1^2 + m_{12}m_{21}d_1(2K_1K_2 - K_2 - 5K_1 + 7)+$$
$$m_{12}d_2^2(3-K_2) + 2m_{21}^2\epsilon_1 K_1(1-K_1) + m_{12}^2 d_2(3-2K_2) + 2\epsilon_1 d_1^2 K_1+$$
$$d_1^3 + m_{12}^3(1-K_2) + d_2^3 + m_{12}m_{21}\epsilon_1 K_1 K_2 + m_{21}d_1^2(3-2K_1)$$
$$2m_{21}\epsilon_1 d_1 K_1(2-K_1) + 2m_{12}^2\epsilon_1 K_1 K_2 + 2m_{12}\epsilon_2 d_2 K_2 + 2m_{12}d_2\epsilon_1 K_1 K_2+$$
$$\epsilon_2 d_2^2 K_2 + m_{12}^2\epsilon_2 K_2 + m_{12}m_{21}\epsilon_2 K_2 K_1 + 2m_{21}\epsilon_2 d_2 K_2 K_1-$$
$$2\epsilon_1\epsilon_2 d_2 K_2 K_1 - 2m_{12}\epsilon_1\epsilon_2 K_2 K_1$$

$$\mathcal{P}_6 = 4d_2 d_1^2 + m_{12}d_1^2(4-K_2) + 4m_{12}^2 d_1(1-K_2) + m_{12}m_{21}d_1(7-3K_2-2K_1)+$$
$$4m_{12}d_1 d_2(2-K_2) + 4d_2^2 d_1 + 4m_{21}d_2^2 + m_{21}d_1 d_2(8-K_1) + 4\epsilon_2 d_1 d_2 K_2+$$
$$m_{21}m_{12}\epsilon_2 K_2(3-K_2) + 2m_{21}\epsilon_2 d_1 K_2 + 4m_{12}\epsilon_2 d_1 K_2 + 4m_{21}\epsilon_2 d_2 K_2+$$
$$m_{21}^2\epsilon_2 K_2 + \epsilon_2 d_1^2 K_2 + m_{12}\epsilon_1 d_1 K_1 + m_{12}^3(K_2-1)^2 + m_{21}^2 d_2(4-K_1)+$$
$$m_{12}m_{21}\epsilon_1 K_1 + \epsilon_1 d_2 d_1 K_1 + m_{21}\epsilon_1 d_2 K_1 + m_{12}^2 d_2(K_2-1)(K_2-3)+$$
$$m_{12}^2 m_{21}(K_2-1)(K_2+K_1-3) + m_{21}^2 m_{12}(2-K_2)(2-K_1)+$$
$$m_{12}\epsilon_2^2 K_2^2 + d_2\epsilon_2^2 K_2^2 + m_{21}m_{12}d_2(2K_2K_1 - K_1 - 5K_2 + 7)+$$
$$m_{21}d_1^2(3-K_1) + 2m_{12}^2\epsilon_2 K_2(1-K_2) + m_{21}^2 d_1(3-2K_1) + 2\epsilon_2 d_2^2 K_2+$$
$$d_2^3 + m_{21}^3(1-K_1) + d_1^3 + m_{21}m_{12}\epsilon_2 K_1 K_2 + m_{12}d_2^2(3-2K_2)$$
$$2m_{12}\epsilon_2 d_2 K_2(2-K_2) + 2m_{21}^2\epsilon_2 K_1 K_2 + 2m_{21}\epsilon_1 d_1 K_1 + 2m_{21}d_1\epsilon_2 K_1 K_2+$$
$$\epsilon_1 d_1^2 K_1 + m_{21}^2\epsilon_1 K_1 + m_{21}m_{12}\epsilon_1 K_2 K_1 + 2m_{12}\epsilon_1 d_1 K_2 K_1-$$
$$2\epsilon_1\epsilon_2 d_1 K_1 K_2 - 2m_{21}\epsilon_1\epsilon_2 K_1 K_2$$

$$\begin{aligned}
\mathcal{P}_7 =& 2m_{21}\epsilon_1 K_1 + 2m_{21}d_1(2-K_1) + 2d1^2 + 2d_2^2 + 2m_{12}\epsilon_1 K_1 K_2 + \\
& 2(m_{21}(1-K_1) + m_{12}(1-K_2))(m_{12}+m_{21}) + 2\epsilon_2 d_2 K_2 + m_{21}\epsilon_2 K_2 + \\
& m_{21}d_2(4-K_1) + m_{12}d_1(4-K_2) + 2m_{12}\epsilon_2 K_2 + m_{12}\epsilon_1 K_1 + \\
& 2\epsilon_1 d_1 K_1 + 4d_1 d_2 + \epsilon_1 d_2 K_1 + \epsilon_2 d_1 K_2 + 2m_{21}\epsilon_2 K_1 K_2 + \\
& 2m_{12}d_2(2-K_2) - 2\epsilon_1\epsilon_2 K_1 K_2 \\
\mathcal{P}_8 =& 2m_{12}^3 d_1(1-K_2) + 2m_{12}^2 m_{21} d_1(2-K_1-K_2) + 2m_{12}^2 m_{21} d_2(1-K_2) + \\
& m_{12}m_{21}K_1K_2(m_{12}+m_{21})(d_1+d_2+\epsilon_1+\epsilon_2) + 2m_{12}m_{21}^2 d_2(2-K_2-K_1) + \\
& 2m_{21}^2(1-K_1)(m_{12}d_1+m_{21}d_2) + 2m_{12}^2\epsilon_1 d_1 K_2 K_1 + m_{12}^2 d_1^2(4-K_2) + \\
& m_{12}^2\epsilon_1 d_1 K_1 + 2m_{12}^2\epsilon_2 d_1 K_2 + 2m_{12}^2 d_1 d_2(3-2K_2) + \\
& m_{12}m_{21}(2d_2^2(2-K_2) + 4d_1^2(2-K_1) + 3d_1d_2(4-K_2-K_1) + \\
& K_2K_1(\epsilon_1 d_1 + \epsilon_2 d_2 + \epsilon_1 d_2 + \epsilon_2 d_1 + d_1^2 + d_2^2) + 2\epsilon_2 d_2 K_2 + \epsilon_2 d_1 K_2 + \\
& \epsilon_1 d_2 K_1 + 2d_1\epsilon_1 K_1) + m_{21}^2(2d_1d_2(3-2K_1) + 2d_2^2(2-K_1) + 2\epsilon_1 d_2 K_1 + \\
& 2\epsilon_2 d_2 K_2 K_1 + \epsilon_2 d_2 K_2) + m_{12}d_1^2\epsilon_2 K_2 + 8m_{12}d_1^2 d_2(8-K_2) + \\
& 2m_{12}d_1^2\epsilon_1 K_1 + 4m_{12}\epsilon_2 d_1 d_2 K_2 + 2m_{12}d_1^3 + 2m_{12}d_2^2 d_1(3-K_2) + \\
& 2d_1d_2(m_{12}\epsilon_1 K_1 + m_{12}\epsilon_1 K_2 K_1 + m_{21}\epsilon_2 K_2 K_1 + \epsilon_2 m_{21} K_2) + \\
& 4m_{21}\epsilon_1 d_2 d_1 K_1 + m_{21}\epsilon_1 d_2^2 K_1 + m_{21}d_1 d_2^2(8-K_1) + 2m_{21}\epsilon_2 d_2^2 K_2 + \\
& 2m_{21}d_2^3 + 2m_{21}d_1^2 d_2(3-K_1) + 4d_1^2 d_2^2 + 2d_1^2 d_2\epsilon_1 K_1 + d_1 d_2^2\epsilon_1 K_1 + \\
& 2d_1 d_2^2\epsilon_2 K_2 + d_1^2 d_2\epsilon_2 K_2 + 2d_2^3 d_1 + 2d_1^3 d_2 - 2m_{12}\epsilon_1\epsilon_2 d_1 K_2 K_1 - \\
& 2\epsilon_1\epsilon_2 d_1 d_2 K_2 K_1 - 2m_{12}m_{21}\epsilon_1\epsilon_2 K_2 K_1 - 2m_{21}\epsilon_1\epsilon_2 d_2 K_2 K_1 \\
\mathcal{P}_9 =& (m_{12}\epsilon_1 K_1 + m_{21}d_2(1-K_1) + \epsilon_1 d_2 K_1 + \\
& m_{12}d_1 + d_1 d_2)(m_{21}(1-K_1) + m_{12} + K_1\epsilon_1 + d_1 + d_2)
\end{aligned}$$

$$\begin{aligned}
\mathcal{P}_{10} =&(m_{21}\epsilon_2 K_2 + m_{12}d_1(1-K_2) + \epsilon_2 d_1 K_2 + \\
&m_{21}d_2 + d_1 d_2)(m_{12}(1-K_2) + m_{21} + K_2\epsilon_2 + d_1 + d_2)
\end{aligned}$$

$$\begin{aligned}
\mathcal{P}_{11} =&(m_{21}\epsilon_1 K_1 + m_{21}(2-K_1)(2m_{12}+d_1) + m_{21}^2(1-K_1) + d_1\epsilon_1 K_1 + \\
&2m_{21}d_2 + m_{12}^2 + 2m_{12}d_1 + 2m_{12}d_2 + (d_1+d_2)^2) \\
&(\epsilon_1 d_2 K_1 + m_{12}\epsilon_1 K_1 + m_{12}d_1 + m_{21}d_2(1-K_1) + d_1 d_2)
\end{aligned}$$

$$\begin{aligned}
\mathcal{P}_{12} =&(m_{12}\epsilon_2 K_2 + m_{12}(2-K_2)(2m_{21}+d_2) + m_{12}^2(1-K_2) + d_2\epsilon_2 K_2 + \\
&2m_{12}d_1 + m_{21}^2 + 2m_{21}d_2 + 2m_{21}d_1 + (d_1+d_2)^2) \\
&(\epsilon_2 d_1 K_2 + m_{21}\epsilon_2 K_2 + m_{21}d_2 + m_{12}d_1(1-K_2) + d_1 d_2)
\end{aligned}$$

$$\begin{aligned}
\mathcal{P}_{13} =&(m_{12}+m_{21}+d_1+d_2)(d_1 m_{12} + m_{21}d_2 + d_1 d_2) \\
&((d_2+m_{12})(\epsilon_1 K_1 + d_1) + m_{21}d_2(1-K_1))
\end{aligned}$$

$$\begin{aligned}
\mathcal{P}_{14} =&(m_{12}+m_{21}+d_1+d_2)(d_1 m_{12} + m_{21}d_2 + d_1 d_2) \\
&((d_1+m_{21})(\epsilon_2 K_2 + d_2) + m_{12}d_1(1-K_2))
\end{aligned}$$

The remaining negative terms cancel out using the existence conditions for $\mathcal{E}^*$, namely $\mathcal{R}_0^{(i)} > 1$ for $i = 1, 2$. For instance from (A.2) the term $-2\epsilon_1\epsilon_2 K_1 K_2$ in $\mathcal{P}_7$ cancels with the terms $\epsilon_2 K_2$ in $\mathcal{P}_1$ and $\epsilon_1 K_1$ in $\mathcal{P}_2$, since

$$\beta_1^2\beta_2^2 K_1^3 K_2^3(\epsilon_2(\beta_1-\epsilon_1) + \epsilon_1(\beta_2-\epsilon_2)) > 0 \text{ if } \mathcal{R}_0^{(i)} > 1,\ i = 1,2$$

From the above expressions it can be seen that if $\mathcal{R}_0^{(i)} > 1$, then $\mathcal{P}_j > 0$ for $j = 1, \ldots, 14$, thus (A.2) is positive.

Appendix B

B.1 Mathematical background

Some mathematical results used to analyze the epidemic models are now given. First some matrix results are stated.

Definition B.1. [BP, p. 27] Matrix $A \in \mathbb{R}^{n\times n}$ is *irreducible* if there does not exist a permutation matrix P and an integer r with $1 \leq r \leq n-1$ such that

$$P^T A P = \begin{bmatrix} B & C \\ 0 & D \end{bmatrix}$$

where B, D, C and 0 are $r \times r$, $n-r \times n-r$, $r \times n-r$ and $n-r \times r$ respectively.

Note that if all the off-diagonal entries of A are non-zero, then A is irreducible.

Definition B.2. Let $A \in \mathbb{R}^{n\times n}$ have eigenvalues $\lambda_1, \ldots, \lambda_n$. Then the *spectral radius* of A denoted by $\rho\{A\}$ and the *spectral abscissa* (spectral bound) of A, denoted by $s(A)$, are defined as

$$\rho\{A\} = \max_{i=1,\ldots,n} |\lambda_i| \qquad s(A) = \max_{i=1,\ldots,n} \text{Re } (\lambda_i)$$

Definition B.3. [BP, p. 133] Let A and $B = [b_{ij}] \in \mathcal{R}^{n\times n}$. If $A = kI - B$, where I is the $n \times n$ identity matrix, $k > 0$, $b_{ij} \geq 0$ with $k \geq \rho(B)$, then A is called an *M-matrix*. If $k > \rho(B)$, then A is a *non-singular M-matrix*.

Theorem B.4. [BP, p. 141] If $A = [a_{ij}]$ is an irreducible non-singular M-matrix, then A has a (entry-wise) positive inverse i.e., $A^{-1} = [k_{ij}]$ with $k_{ij} > 0$.

Theorem B.5. [BP, p. 135] If A is an M-matrix, then $s(-A) \leq 0$. If A is a non-singular M-matrix, then $s(-A) < 0$.

Theorem B.6. [BP, p. 137] Let $A = [a_{ij}] \in \mathbb{R}^{n\times n}$ have $a_{ij} \leq 0$ for $i \neq j$. If the sum of the entries in each column is positive, then A is a non-singular M-matrix.

Theorem B.7. [BP, p. 37] Let $A = [a_{ij}]$ with $a_{ij} \geq 0$ be irreducible. Then

$$\min_i s_i \leq \rho\{A\} \leq \max_i s_i$$

where s_i denotes the sum of entries of the ith column of A.

Theorem B.8. [vdDW, proof of Thoerem 2] If F is a non-negative matrix and V is a non-singular M-matrix then

$$s(F - V) < 0 \ (> 0) \iff \rho\{FV^{-1}\} < 1 \ (> 1)$$

The following definitions and theorems are results about differential equations.

Definition B.9. Consider the system

$$u' = g(u) \tag{B.1}$$

with $g \in C^1[\mathbb{R}^n, \mathbb{R}^n]$ and $g(u_0) = 0$. Let A be the Jacobian of $g(u)$ at u_0. Then the equilibrium u_0 is *locally asymptotically stable* if $s(A) < 0$ and *unstable* if $s(A) > 0$.

Theorem B.10. *Routh-Hurwitz criteria* (see for example, [E, p. 234]) Let the characteristic equation of $A \in \mathbb{R}^{n\times n}$ be

$$p(\lambda) = \lambda^n + c_1\lambda^{n-1} + \cdots + c_{n-1}\lambda + c_n = 0$$

then all roots λ of $p(\lambda) = 0$ have strictly negative real parts if and only if

- for $n = 2$: $c_1 > 0$, $c_2 > 0$
- for $n = 3$: $c_1 > 0$, $c_3 > 0$, $c_1c_2 - c_3 > 0$
- for $n = 4$: $c_1 > 0$, $c_3 > 0$, $c_4 > 0$, $c_3(c_1c_2 - c_3) - c_1^2c_4 > 0$

Definition B.11. [SW, p. 261] Consider the differential equation system (B.1) with $u(t_0) = u_0$ and $g \in C[\mathbb{R}^n, \mathbb{R}^n]$. The function g is said to be of *type K* if for each $i \in \{1, \ldots, n\}$, $g_i(x) \leq g_i(y)$ whenever $x \leq y$ and $x_i = y_i$.

Note that in [LLM] a function of type K is called a quasi-monotone non-decreasing function. If $g(u) = Au$, where $A \in \mathbb{R}^{n\times n}$ with $a_{ij} \geq 0$, $j = 1, 2, \ldots, n$, $i \neq j$, then g is of type K. Definition B.11 will be used with the following comparison theorem to prove global asymptotic stability.

Theorem B.12. *Comparison Theorem* [SW, Theorem B.1]
Let $g \in C[\mathbb{R}^n, \mathbb{R}^n]$, $g(u)$ be of type K and $u(t)$ be a solution of (B.1) defined on $[t_0, \infty)$. If $z(t)$ is a continuous function on $[t_0, \infty)$ satisfying $z' \leq g(z)$ on (t_0, ∞) with $z(t_0) \leq u(t_0)$, then $z(t) \leq u(t)$ for all $t \geq t_0$.

Definition B.13. [CT, p. 35] Any ordinary differential equation in $C[\mathbb{R}^n, \mathbb{R}^n]$,

$$\dot{x} = f(t, x) \tag{B.2}$$

is called *asymptotically autonomous*, with *limit equation*

$$\dot{y} = h(y) \tag{B.3}$$

if $f(t, x) \longrightarrow h(x)$ as $t \longrightarrow \infty$, locally uniformly in $x \in \mathbb{R}^n$, i.e., for x in any compact subset of $\mathbb{R}^n$.

The following result shows that if solutions of (B.2) are bounded and the equilibrium of the limit equation (B.3) is globally asymptotically stable, then any solution of (B.2) tends to this equilibrium for large time.

Theorem B.14. [CT, p. 36] Let X be a subset of $\mathbb{R}^2$ such that any equilibrium of (B.3) in X is the only equilibrium in a sufficiently small neighborhood. Further assume that there exist a subset Y of $\mathbb{R}^2$ and an open simply connected subset D of $\mathbb{R}^2$ with the following properties:

- Every bounded forward orbit of (B.2) in X has its ω-limit set in Y.
- All possible periodic orbits of (B.3) in Y and the closures of all possible orbits of (B.3) that chain equilibria of (B.3) cyclically in Y are contained in D.
- h is continuously differentiable on D and there is a real-valued continuously differentiable function ρ on D such that the divergence of ρh, namely

$$\nabla.(\rho h)(x_1, x_2) = \frac{\partial}{\partial x_1}(\rho h_1)(x_1, x_2) + \frac{\partial}{\partial x_2}(\rho h_2)(x_1, x_2)$$

is either strictly positive almost everywhere on D or strictly negative almost everywhere on D.

Then every bounded forward solution of (B.3) in X and every bounded forward solution of (B.2) in X converge towards an equilibrium of (B.3) as $t \longrightarrow \infty$.