Mathematical Analysis of the Role of Movement in the Spread of Tuberculosis

by

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DEDICATION

To the memory of my lovely father and to my beloved mom, my husband, my sweet kids (Mohamed, Raouf, Hanin), my sisters and my brother.

ABSTRACT

Tuberculosis (TB) is an infectious respiratory disease caused by the bacterium *Mycobacterium tuberculosis*. TB is the second largest cause of mortality by infectious diseases and is a challenging disease to control. It spreads easily among people via droplets propagated by an infectious person. Treatment against TB has been available since the 1950s; however, various problems with treatment have led to the emergence of drug-resistance in TB bacteria, which further complicates disease control.

Furthermore, TB is a disease that predominantly affects poor countries or countries with high population densities. With the generalization of travel and migration in the second half of the twentieth century, individuals infected in such countries are likely to move to or spend some time in richer countries, making TB a worldwide problem.

In this thesis, we consider the role of population movement in the spread of tuberculosis by studying two different models. The first one is an extension to a spatialized context of a simple existing mathematical model for the spread of TB. We establish that, similarly to the original model, the equilibrium without disease is globally asymptotically stable when the basic reproduction number $\mathcal{R}_0$ is less than one. In the case that $\mathcal{R}_0 > 1$, we prove that the system is uniformly persistent. The second model considers the spread of drug-resistant TB in a population, then between connected populations. We establish that a backward bifurcation can occur and that the coupled system has more types of equilibria than the systems in isolation. Finally, we consider a general class of models including the previous two in isolation

and after coupling. We investigate which dynamical properties of the isolated models are preserved when coupling the models through movement. Some new results are provided in that direction.

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1. INTRODUCTION

Infectious diseases are caused by pathogenic microorganisms such as bacteria, viruses, parasites or fungi; infectious diseases can be spread, directly or indirectly, from one person to another [35]. Direct spread of disease happens when an individual is infected by contact with the reservoir; a reservoir for a disease is the place or individual where the infectious agent survives. Humans and animal are examples of living reservoirs and soil and water are nonliving reservoirs. Contact with the reservoir happens by touching an infected person, eating an infected meal or being bitten by an infected animal or insect. It could also happen by inhaling the infectious agent in droplets emitted by an infected person, or by sexual contact. Examples of diseases that are transmitted directly from person to person are tuberculosis, AIDS, influenza and malaria. Indirect contact occurs when an individual touches or uses an object in the environment where a pathogen lives for a period before it reaches an individual, e.g. an infected tissue with a cold virus, a toy that was used by a sick kid or infected water used in drinking, cooking, etc. Influenza, cholera, cryptosporidiosis and giardiasis are examples of indirectly infecting diseases [22].

1.1 Epidemiology and Mathematical Modelling

Epidemiology is the discipline that studies the spread of diseases in populations. The concern of epidemiologists is to study how to prevent, minimize or control the impact of diseases in populations. Since understanding the mechanisms of spread of infectious diseases can help in controlling them, that brings mathematical modelling into

the picture. Mathematical modelling plays a key role in developing an understanding of the mechanisms of spread of infectious diseases. Generally, obtaining information about a disease can be done by scientific experiments and collecting data, which is costly and requires a long time. A mathematical *model* is a mathematical description of the disease based on some hypothesis taken from expert and scientific knowledge of the disease (medical doctors, public health officials, epidemiologists). The solutions of the model give conclusions which are compared to the scientific experiments and collected data. Moreover, mathematical models can be the only way to decide on which of two different control strategies is to be applied when it could be hard or sometimes impossible to decide on them epidemiologically, specially with inaccurate or incomplete data. More details on mathematical modelling is given in Section 2.2 .

1.2 Transmission of Tuberculosis

Tuberculosis (TB) is a very harmful disease caused by a bacteria called *Mycobacterium tuberculosis*. It was first discovered in 1882 by a German physician named Robert Koch, who received the Nobel Prize in 1905 for this discovery. TB usually attacks lungs, but in uncommon cases, it can also infect other parts of the body such as kidneys, spine and brain. Bad cough (mixed with blood), loss of weight, fever and feeling weak are some of the main symptoms of tuberculosis. The problems about TB are the following facts [23, 29, 30, 37]:

- About one third of the world's population is infected (latently) with TB.
- It is the second (after HIV) cause of death by infectious disease. It is estimated that TB killed 1.45 million people in 2011.
- Without proper treatment, almost two thirds of the infected cases will die.
- It infects all age groups; 64,000 children died from TB in 2011.

There are several ways to diagnose TB, such as skin tests, chest X-rays, sputum analysis and PCR tests to detect the genetic material of the causative bacteria. As Mycobacterium tuberculosis is an airborne bacteria, germs can stay in the air for hours and people with active TB can spread the germs by coughing, sneezing, talking, laughing, singing, etc. Susceptible people inhale the germs into their lungs, their immune system starts fighting the germs and depending on its strength, it will either stop the germs from taking control or the germs settle inside the patient, leaving them with an inactive TB infection [36]. Fifty years back, TB was considered an incurable disease. With the discovery of different anti-TB agents in early 1940's, a cure of such deadly disease was considered to be feasible. Unfortunately, it soon emerged that the use of anti-TB agents as single agents caused a resistance toward the given agent in the bacteria. That resistance could be treated with a combination of these agents [14]. Higher resistance toward combination of agents started to appear as well. So controlling such a disease is considered to be a challenging but not impossible job. Another challenge about TB is the fact that TB is not spread homogeneously all over the world. Over 95% of infection and death caused by TB occurs in the developing countries [37]. As of 2010, the International Organization for Migration (IOM) estimated the number of migrants worldwide to be 214 million; 57% of all migrants settled in the developed countries [13]. Such flows of potentially TB infected individuals changes the dynamic of TB and complicate control strategies used in countries. It is definitely causing more burden on the developed countries to control TB. More details on the biology of TB and its challenges are given in Section 2.3.

1.3 Motivation of the Thesis

The purpose of this thesis is to investigate the influence of migration in the spread of tuberculosis. For that we started by considering a mathematical model developed for

a single population by Castillo-Chavez and Feng in 1997[9]. That model was chosen as it is simple enough to begin the investigation on the influence of migration i.e., of connecting multiple populations. Moreover as it was well studied qualitatively by the authors, we were able to compare the results before and after considering migration.

But as that model is a very simple model, it does not capture number of very important facts about TB that play a very important role in understanding the mechanism of spread of TB, such as exogenous reinfection, fast infection and resistance to antibiotics in TB. For that, we developed a new comprehensive mathematical model that presents most of the important facts on TB and qualitatively analyzed the new model.

Next, we again added migration to the new model to study its role in spreading TB. In the qualitative analysis, emphasis was given to determine the existence and stability of the solutions as well as the type of bifurcation developed by the studied dynamical systems.

Analyzing a model with migration can be quite a challenge, because the developed model will be of large dimensionality. For example if we start with a model for disease that divides the total population into n compartments, then adding migration between p countries or cities gives us a model of dimensionality np. The challenge of studying such models led us to try to develop as much as possible a theoretical framework to minimize the efforts needed in analyzing models with linear migrations; this was the second challenge of this thesis. More generally, this thesis seeks to address the following question:

> *Starting with n duplicates of a mathematical model (Π_i) for a given disease, what type of change is caused by adding linear migration to that model giving us a new meta-model (Π)?*
>
> *More precisely, suppose a property P is known/shown to hold for all*

(Π_i) *(e.g., invariance of the positive orthant under the flow, persistence, global stability of a certain type of equilibrium, etc.). Does property P still hold for the meta-model* (Π)*?*

In another words,

- Which features of model (Π_i) is inherited by model (Π)?
- Can adding linear migration in model (Π) induce properties that were not possessed originally by model (Π_i)?

This thesis attempts to answer some of these challenging and interesting questions, setting the stage for future work on the topic.

1.4 Thesis Outline

The thesis is organized as follows. Chapter 2 is devoted to some preliminaries in mathematics, mathematical epidemiology and biology of tuberculosis relevant to the thesis. In Chapter 3, the terminology, theories and construction of metapopulation models are described. Some new theoretical results about metapopulation are proved in Chapter 3. In Chapter 4, we adapt a simple model of drug-sensitive TB studied by Castillo-Chavez and Feng in [9] by adding migration to study its effect on the dynamics of TB. Chapter 5 presents a new model to study three strains of TB (drug-sensitive strain, MDR-TB, XDR-TB). The model takes the form of a deterministic system of non-linear differential equations and is qualitatively analyzed. The impact of migration on spreading the different strains of TB is studied in Chapter 6.

2. PRELIMINARIES

2.1 Mathematical Preliminaries

A summary of some of the main mathematical theories and methodologies used in this thesis is presented in this section. We start by stating some notation for matrices that are used throughout this thesis.

Definition 2.1.1 ([17]). *Let A, B be two $n \times n$-matrices, with $A = [a_{ij}]$ and $B = [b_{ij}]$. Then*

- $A \geq 0$ *is a* nonnegative *matrix if $a_{ij} \geq 0$ for all i, j and $A \geq B$ if $A - B \geq 0$.*
- $A > 0$ *is a* positive *matrix if A is a nonnegative matrix and there exists i, j such that $a_{ij} > 0$; we write $A > B$ if $A - B > 0$.*
- $A \gg 0$ *is* strongly positive *if $a_{ij} > 0$ for all i, j and $A \gg B$ if $A - B \gg 0$.*
- *The same notation are used for vectors.*
- *The set of all $\lambda \in \mathbb{C}$ that are eigenvalues of A is called the* spectrum *of A and denoted $\sigma(A)$.*
- *The* spectral radius *$\rho(A)$ of A is the nonnegative real number defined by*

$$\rho(A) = \sup \{|\lambda| : \lambda \in \sigma(A)\}.$$

- *The* spectral abscissa *$\eta(A)$ of A is*

$$\eta(A) = \sup\{\Re(\lambda) : \lambda \in \sigma(A)\},$$

where $\Re(\lambda)$ *is the real part of the eigenvalue* λ*.*

A special type of matrices that plays a very important role in this thesis called *M - matrices* is defined as follow

Definition 2.1.2 ([6])**.** *Any matrix A that can be written in the form*

$$A = s\mathbb{I} - B, \quad s > 0, \quad B \geq 0,$$

for which $s \geq \rho(B)$ *is called an* M-Matrix*.*

2.1.1 First-Order Systems of Ordinary Differential Equations

A first-order system of ordinary differential equations (ODE) is given by

$$\frac{dx}{dt} = f(t, x), \tag{2.1}$$

where $t \in \mathbb{R}$, $x \in U \subset \mathbb{R}^n$, with U is open and $f : \mathbb{R} \times \mathbb{R}^n \to \mathbb{R}^n$. System (2.1) is called *autonomous* if $f : \mathbb{R}^n \to \mathbb{R}^n$ does not depend explicitly on time t, *non-autonomous* otherwise.

Throughout this thesis, we deal with autonomous systems of ordinary differential equations and unless ambiguous, the dependence of $x(t)$ on t, will not be explicitly shown.

From now on, for $x \in U \subset \mathbb{R}^n$ and U open, $t \in \mathbb{R}$, we consider the following autonomous system:

$$\frac{dx}{dt} = f(x). \tag{2.2}$$

The following theorem gives a sufficient condition that a system should fulfill to have a unique solution.

Theorem 2.1.3 (Fundamental Existence-Uniqueness Theorem [26]). *Let U be an open subset of $\mathbb{R}^n$ containing an initial value $x(t_0) = x_0$ and assume that $f \in \mathcal{C}^1(U)$, i.e. a continuous function whose derivative is also continuous function. Then there exists a constant $a > 0$ such that the initial value problem (IVP):*

$$\begin{aligned} \frac{dx}{dt} &= f(x), \\ x(t_0) &= x_0. \end{aligned} \tag{2.3}$$

has a unique solution $x(t)$ on the interval $(t_0 - a, t_0 + a)$.

From now on, it is assumed, unless otherwise indicated, that f is such that solutions exist and are unique.

Definition 2.1.4 ([34]).

- *A constant solution of (2.2), $x(t) = x^* \in \mathbb{R}^n$, is called an* equilibrium *if and only if $f(x^*) = 0$.*

- *The equilibrium x^* is said to be* stable *if given $\epsilon > 0$, there exists $\delta = \delta(\epsilon) > 0$ such that for any solution $y(t)$ of (2.2) satisfying $\|x^* - y(t_0)\| < \delta$, then $\|x^* - y(t)\| < \epsilon$ for $t > t_0$, $t_0 \in \mathbb{R}$.*

- *The equilibrium x^* is said to be* asymptotically stable *if*

  (i) it is stable and,

  (ii) there exists a constant $c > 0$ such that for any solution $y(t)$ of (2.2) satisfying $\|x^* - y(t_0)\| < c$, there holds $\lim_{t\to\infty} \|x^* - y(t)\| = 0$.

- *A solution which is not stable is said to be* unstable.

In some cases, an equilibrium could be stable not on $\mathbb{R}^n$ but in a neighborhood of the equilibrium. The size of that neighborhood varies from an equilibrium to another depending on the dynamical system considered. So we say the equilibrium is a locally stable equilibrium. The following is a precise definition of the phenomenon.

Definition 2.1.5 ([34]). *Let x^* be an equilibrium of the initial value problem* (2.3) *and the region $\mathcal{D}$ be the set of all points $x_0 \in \mathbb{R}^n$ such that the solution of* (2.3) *is defined for all $t \geq 0$ and converges to x^* as $t \to \infty$.*

- *If $\mathcal{D} \subsetneq \mathbb{R}^n$, then x^* is called* locally asymptotically stable. *$\mathcal{D}$ is called* domain of attraction *of x^*.*

- *If $\mathcal{D} = \mathbb{R}^n$, then x^* is called* globally asymptotically stable.

To decide whether an equilibrium is stable or not the following definition is useful.

Definition 2.1.6. *The Jacobian matrix of f at the equilibrium x^*, denoted $J(x^*)$, is $J : \mathbb{R}^m \to \mathbb{R}^n$ defined by the matrix*

$$J(x^*) = Df(x^*) = \begin{pmatrix} \frac{\partial f_1}{\partial x_1}(x^*) & \cdots & \frac{\partial f_1}{\partial x_n}(x^*) \\ \vdots & \ddots & \vdots \\ \frac{\partial f_m}{\partial x_1}(x^*) & \cdots & \frac{\partial f_m}{\partial x_n}(x^*) \end{pmatrix}$$

of partial derivatives of f evaluated at x^*.

Definition 2.1.7. *Let $x(t) = x^*$ be an equilibrium solution of* (2.2). *Then, x^* is called* hyperbolic *if none of the eigenvalues of $Df(x)$ have zero real part. An equilibrium point that is not hyperbolic is called* non-hyperbolic.

2.1.2 Determining the Local Asymptotic Stability of Equilibria

To decide on the local asymptotic stability of an equilibrium x^* of the system (2.2), one can proceed as follows.

As the stability of an equilibrium x^* depends on the behaviour of the system near x^*, let

$$x(t) = x^* + \epsilon(t), \tag{2.4}$$

and substitute with (2.4) into (2.2). By Taylor expension, we get

$$\frac{dx}{dt}(t) = \frac{dx^*}{dt}(t) + \frac{d\epsilon}{dt}(t) = f(x^* + \epsilon(t)) = f(x^*) + Df(x^*)\epsilon(t) + O(\|\epsilon(t)\|^2).$$

Hence,

$$\frac{d\epsilon}{dt}(t) = Df(x^*)\epsilon(t) + O(\|\epsilon(t)\|^2),$$

which describes the evolution of orbits near x^*. So the behaviour of solutions arbitrarily close to x^* is obtained by studying the associated linear system

$$\frac{d\epsilon}{dt}(t) = Df(x^*)\epsilon(t),$$

where $Df(x^*)$ is a matrix with constant entries because it is evaluated at x^*. Therefore its associated solution with the initial value $\epsilon_0 \in \mathbb{R}^n$ is given by

$$\epsilon(t) = e^{Df(x^*)t}\epsilon_0.$$

Theorem 2.1.8. *Suppose all of the eigenvalues of $Df(x^*)$ have negative real parts. Then, the equilibrium solution x^* of the system (2.2) is locally-asymptotically stable.*

2.1.3 Comparison Theorem

Comparison theorems are sometimes used to establish the global asymptotic stability of equilibria. The idea of this method is to compare the solutions of the system of

differential equations (2.2) with the solutions of a comparable differential system. Suppose we have

$$z'(t) \leq f(z), \tag{2.5}$$

or

$$z'(t) \geq f(z), \tag{2.6}$$

on a suitable time interval and where $z \in \mathbb{R}^n$.

Consider the autonomous system (2.2), where f is continuously differentiable on an open subset $\mathcal{D} \subset \mathbb{R}^n$.

Definition 2.1.9 ([27]). *f is said to be of* Type K *in $\mathcal{D}$ if for each i, $f_i(a) \leq f_i(b)$ for any two points in $\mathcal{D}$ satisfying $a \leq b$ and $a_i = b_i$.*

Studying the sign structure of the Jacobian matrix of the system (2.2) helps in identifying functions of type K as follow:

Definition 2.1.10 ([27]). *$\mathcal{D}$ is* p-convex *if $tx+(1-t)y \in \mathcal{D}$ for all $t \in [0,1]$ whenever $x, y \in \mathcal{D}$ and $x \leq y$.*

Obviously, a convex set $\mathcal{D}$ is also p-convex. One very useful characterization of functions of Type K is the following: If $\mathcal{D}$ is a p-convex subset of $\mathbb{R}^n$ and

$$\frac{\partial f_i}{\partial x_j} \geq 0, i \neq j, x \in \mathcal{D}, \tag{2.7}$$

then f is of Type K in $\mathcal{D}$.

Theorem 2.1.11 (Comparison Theorem [28]). *Let f be continuous on $\mathbb{R} \times \mathcal{D}$ and of type K. Let $x(t)$ be a solution of (2.2) defined on $[a,b]$. If $z(t)$ is a continuous function on $[a,b]$ satisfying (2.5) on (a,b), with $z(a) \leq x(a)$, then $z(t) \leq x(t)$ for all t in $[a,b]$. If $y(t)$ is continuous on $[a,b]$ satisfying (2.6) on (a,b), with $y(a) \geq x(a)$, then $y(t) \geq x(t)$ for all t in $[a,b]$.*

2.1.4 Bifurcations

In this section, some basic results of bifurcation theory are presented. We write (2.2) as

$$\frac{dx}{dt} = f(x, \mu),$$

to indicate that f depends on a parameter $\mu \in \mathbb{R}$. Further, we assume that $f(x, \mu) \in C^1(E)$, where E is an open subset of $\mathbb{R}^n$.

Definition 2.1.12 ([26]). *Let*

$$x' = f(x, \mu), \tag{2.8}$$
$$f \in C^1(E),\ E \subset \mathbb{R}^n,$$

depend on a parameter $\mu \in \mathbb{R}$. If the qualitative behaviour of the solutions of system (2.8) *remain the same as the parameter μ changes, then system* (2.8) *is said to be* structurally stable. *System* (2.8) *is not structurally stable if its solutions change their qualitative behaviour as μ varies through a certain value μ_0. A value μ_0 of the parameter μ in which $f(x, \mu_0)$ is not structurally stable is called a bifurcation value.*

There are several types of bifurcation. We present here the most common ones in the context of mathematical epidemiology, in the lowest dimension required for their existence; for more details see [26].

1. *Saddle node bifurcation:* This type is when fixed points exist and are destroyed by changing the values of some parameters.

   Canonical Form: Consider the non-linear differential equation

$$\frac{dx}{dt} = \mu + x^2.$$

Fixed points are $x^* = \pm\sqrt{\mu}$. So, when $\mu < 0$, there are no real fixed points (which are the only ones of interest here), while when $\mu > 0$, we have two fixed points and only one fixed point is present when $\mu = 0$. In this example the bifurcation taking place at $\mu = 0$ is called a saddle node bifurcation.

2.Transcritical Bifurcation: This type corresponds to the case where the fixed points change stability with the change of the values of some parameter.

Canonical Form: Consider the non-linear differential equation

$$\frac{dx}{dt} = \mu x - x^2.$$

The fixed points are $x^* = 0$ and $x^* = \mu$. For any value of μ, these fixed points do not disappear but their stability changes with the values of μ. Here, a transcritical bifurcation happens at $\mu = 0$ since $\frac{df}{dx} = \mu - 2x$, therefore

- $\mu < 0$, the fixed point $x^* = 0$ is stable, while $x^* = \mu$ is unstable.
- $\mu > 0$, the fixed point $x = 0^*$ is unstable, while ${}^*x = \mu$ is stable.

Transcritical Bifurcation are of two types: supercritical (forward) bifurcation or subcritical (backward) bifurcation.

3. Pitchfork Bifurcation: Canonical Form:

- The non-linear differential equation

$$\frac{dx}{dt} = \mu x - x^3.$$

is the canonical form of supercritical pitchfork bifurcation.

- The non-linear differential equation

$$\frac{dx}{dt} = \mu x + x^3 = f(x, \mu)$$

is the canonical form of subcritical pitchfork bifurcation.

4. *Hopf bifurcation:* This is a bifurcation that happens when a fixed point of a dynamical system loses stability as a pair of complex conjugate eigenvalues of the linearization around the fixed point cross the imaginary axis of the complex plane. There are two types of Hopf bifurcations (supercritical / subcritical) depending on the stability of the limit cycle. If the limit cycle is orbitally stable then the bifurcation is supercritical. Otherwise it is unstable and the bifurcation is subcritical.

   Canonical Form: The complex valued non-linear differential equation

$$\frac{dz}{dt} = z\left(\mu + b|z|^2\right),\ b, z \in \mathbb{C}, \quad \mu \in \mathbb{R} \text{ parameter.}$$

2.1.5 Persistence Theory

Let $\mathcal{D}$ be a metric space with metric d, $F : \mathcal{D} \to \mathcal{D}$ be continuous and $\partial\mathcal{D}$ be closed.

Definition 2.1.13. *We say that F is* uniformly persistent *(with respect to $\partial\mathcal{D}$), if there exists $\eta > 0$ such that for all $x \in \mathcal{D}\backslash\partial\mathcal{D}$,*

$$\liminf_{n\to\infty} d(F^n(x), \partial\mathcal{D})) > \eta, \tag{2.9}$$

where $F^n(x) = (F \circ \cdots \circ F)(x)$.

Next, we present a theorem that characterizes uniform persistence. For that, assume that $F\left(\mathcal{D}\backslash\partial\mathcal{D}\right) \subset \mathcal{D}\backslash\partial\mathcal{D}$.

Definition 2.1.14. *X is a* global attractor *of $\mathcal{D}$ if*

1. *X is the maximal compact invariant subset of $\mathcal{D}$, and*
2. *$d(F^n(x), X) \to 0$ as $n \to \infty$, for all $x \in \mathcal{D}$.*

Suppose X is a global attractor of $\mathcal{X}$ and M be the maximal compact invariant set in $\partial\mathcal{D}$. Then $M \subset X$.

Theorem 2.1.15 ([16])**.** *F is uniformly persistent (with respect to $\partial\mathcal{D}$) if and only if*

1. *M is isolated in X, and*
2. *$W^s(M) \subset \partial\mathcal{D}$, where $W^s(M)$ is the stable set of M and is defined by $W^s(M) = \{x \in X : F^n(x) \to M \text{ as } n \to \infty\}$.*

2.2 Mathematical Epidemiology

Some basic notation and terminology in mathematical modeling is given. Then a simple example is presented to show how one models infectious disease spread.

2.2.1 Reproduction Number and Bifurcations

To qualitatively analyze the dynamics of an infectious disease model, one basic yet very important quantity is *the basic reproduction number*, denoted by $\mathcal{R}_0$. The basic reproduction number $\mathcal{R}_0$ represents the average number of new cases a typical infectious individual can generate in a completely susceptible population [1, 18]. If $\mathcal{R}_0 < 1$ then on average, an infected individual generates less than one new infection in the susceptible population; therefore the disease dies out eventually. If $\mathcal{R}_0 > 1$, then an infected person is infecting on average more than one person, which leads to persistence of the disease in the population. At $\mathcal{R}_0 = 1$, the disease-free equilibrium (DFE) changes its stability, becoming unstable for $\mathcal{R}_0 > 1$ and a new endemic

equilibrium (EE) is born. If the EE is locally asymptotically stable when $\mathcal{R}_0 > 1$, then this phenomena is known as *forward bifurcation*, which is observed in most epidemiological models.

In other epidemiological models, another phenomenon, *backward bifurcation*, occurs, where a stable EE co-exists with a stable DFE for $\mathcal{R}_0 < 1$; see for example [5, 15]. The existence of a backward bifurcation makes it more difficult to eliminate the disease.

2.2.2 Next Generation Operator Method

Section 2.1.2 introduced a classical method to decide on the local asymptotic stability of an equilibrium. This section presents a method specific to infectious disease models known as *the next generation operator method* [33]. This method was originally introduced by Diekmann *et al.* [11] and formulated to be used in epidemiological models by van den Driessche and Watmough [33]. This method is basically a method to compute the reproduction number. An advantage of using this method is that it allows direct calculation of $\mathcal{R}_0$ without carrying out the local stability analysis. For example, given an infectious disease model with n compartments, order those compartments such that the first m compartments stand for the infected compartments and the remaining $n - m$ are the non-infected ones. Using the classical method, to decide on the local stability of the DFE we need to study the eigenvalues of a Jacobian matrix of size $n \times n$, while using the next generation method, the local stability of the DFE is decided by studying a matrix corresponding to the infectious compartments only, i.e., of size $m \times m$. The formulation of the method in [33] is given in Appendix A and an example to show how to apply it is given in Section 2.2.3.

2.2.3 A Simple SLI Mathematical Model

Consider a disease with a latent period during which an individual is a carrier of the disease but cannot transmit it to others, after which the person becomes infectious. An example of such a disease is tuberculosis in the absence of treatment. To mathematically model the disease in a certain population, we divide the total population of N individuals into three different compartments according to the disease status: susceptible (S), latently infected (L) and infectious (I). Then the total population is $N = S + L + I$. The interactions between the compartments represent the disease transmission in the population.

The number of new infections generated per unit time in a given community is known as *disease incidence*. To model incidence in a disease model, we need to define a function which describes the rate at which new infections are generated. This rate is called *incidence rate*. Two main types of incidence functions have been used in disease modeling: *standard incidence*, using the function $\beta SI/N$ and *mass action incidence*, using βSI. The parameter β describes the probability that a contact is infecting. The choice of function to use plays an important role in the dynamics of the model.

We assume that upon infection, and individual becomes latently infected, i.e., moves from the S to the L compartment. The individual spends an average $1/k$ time units in the L compartment before progressing to the I compartment, wherein he/she becomes infectious, i.e., is actively propagating the disease. Birth occurs only in the susceptible compartment (there is no vertical transmission of the disease) at the rate λ and natural death occurs in all compartments at the rate d, i.e., the average duration of life is exponentially distributed with mean $1/d$ time units.

To model a disease such as the one described above, the following SLI model is

used

$$\frac{dS}{dt} = \lambda - dS - \frac{\beta SI}{N}, \tag{2.10a}$$
$$\frac{dL}{dt} = \frac{\beta SI}{N} - dL - kL, \tag{2.10b}$$
$$\frac{dI}{dt} = kL - dI. \tag{2.10c}$$

Note that depending on the characteristics of the disease under consideration and the purpose of the study, the model can take different forms such as $SLIR$, $SLIRS$, SIS, SIR, $SIRS$, where S, L, I and R are the susceptible, latently infected, infectious and recovered (or "treated") compartments, respectively. Many other variations (and additional compartments) are possible.

To find the disease free equilibrium (DFE) of system 2.10, we set $I = 0$ in (2.10a) and find that the DFE is unique and given by

$$\left(\frac{\lambda}{d}, 0, 0\right). \tag{2.11}$$

To decide on the linear stability of the DFE, the next generation method is used; see Appendix A. We start by ordering the infected classes as L, I. The vector representing new infections into the infected classes, $\mathcal{F}$, is given by

$$\mathcal{F} := \begin{pmatrix} \beta\dfrac{SI}{N} \\ 0 \end{pmatrix}.$$

The vector, $\mathcal{V}$, representing other flows within and out of the infected classes is given by

$$\mathcal{V} := \begin{pmatrix} dL + kL \\ -kL + dI \end{pmatrix}$$

The matrix of new infections F and the matrix of transfers between compartments

V are the Jacobian matrices obtained by differentiating $\mathcal{F}$ and $\mathcal{V}$ with respect to the infected variables, evaluated at the disease free equilibrium (DFE). They take the form

$$F = \begin{pmatrix} 0 & \beta \\ 0 & 0 \end{pmatrix},$$

$$V = \begin{pmatrix} d+k & 0 \\ -k & d \end{pmatrix}.$$

Then the next generation matrix defined in Appendix A is

$$FV^{-1} = \frac{1}{d(d+k)} \begin{pmatrix} \beta k & \beta(d+k) \\ 0 & 0 \end{pmatrix},$$

FV^{-1} has spectral radius, denoted ρ, given by

$$\rho(FV^{-1}) = \frac{\beta k}{d(d+k)}.$$

Defining $\mathcal{R}_0 = \rho(FV^{-1})$, we have by Theorem (A.2) that the DFE is locally asymptotically stable if $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 > 1$.

2.3 Biology and epidemiology of Tuberculosis

To design a model that accurately describes a given disease, a clear understanding of the way that the disease spreads is important, in order to avoid ignoring important factors or facts related to the studied disease. This section gives a brief explanation of the mechanism of TB infection.

2.3.1 Person to Person Transmission

TB can remain in an inactive state in an individual for years without causing symptoms or spreading to other people. Individuals who are latently infected with tuberculosis can only progress to active disease in two ways. Either by reactivation of the latent infection, a mechanism known as *endogenous reactivation*, which usually happens when the immune system of a latent patient is weakened due to old age or infection with another disease such as HIV or cancer. Reinfection when a latently infected person acquires a new infection from another actively infected individual, known as *exogenous reinfection*, is the other way to develop active TB.

Although TB is considered to be a curable disease, over 8 million new cases of TB occur each year worldwide and TB is the second causes of mortality, second to human immunodeficiency virus (HIV) [24]. In 2011, 8.7 million people got infected with TB and 1.4 million lost their lives because of it [37]. Therefore, getting proper treatment is very important when dealing with this disease. Latently infected individuals can be treated with an antibiotic, isoniazid (INH), to prevent the TB infection from becoming active. INH is usually very successful in treating active TB as well as in combination with a few other drugs, but the course of treatment usually takes six months to a year under supervision and support given to the patient by a doctor. Poorly managed TB care due to limited resources, inappropriate dosing or prescribing of medication, poorly formulated medications and/or an inadequate supply of medication may complicate the treatment and the germs can develop a new strain which is resistant against the drug. The new strain is known as Multi-drug resistant TB (MDR-TB). MDR-TB strains are resistant to at least two of the first line anti-TB drug. MDR-TB has been reported in every country. In the case of the MDR-TB, a second type of the anti-TB drugs should be used. However, those drugs are not always available, which leads to the need for extensive chemotherapy (up to two years of treatment). Resistance against the second line drugs can be also

developed, which is referred to as extensively drug-resistant TB, XDR-TB. XDR-TB is a type of tuberculosis that is resistant to three or more drugs, including the most effective second-line anti-TB drugs [25]. In 2011, 310 000 cases of MDR-TB were reported in the world, 9% of them are XDR-TB. India, China and Russia had 60% of those cases.

Drug-resistant TB is a serious, as yet unsolved, public-health problem, especially in Southeast Asia, the countries of the former Soviet Union, Africa, and in prison populations. Poor patient compliance, lack of detection of resistant strains and unavailable therapy are key reasons for the development of drug-resistant TB.

2.3.2 Spatial Heterogeneity

The spread of TB does not happen homogeneously over the world. That is because TB is a disease of poverty, as evidenced by the fact that about 95 percent of TB deaths occur in low- and middle-income countries [24, 37]. According to the last WHO report, the burden of TB is highest in Asia and Africa as India and China together account for 40% of the worlds TB cases. The African Region has 24% of the world's cases and the highest rates of cases and deaths per capita [37]. Table 2.1 shows the estimated burden of TB in 2011 in some developing countries, Table 2.2 shows the same information in a few developed countries.

Country	Population	Mortality	Incidence	Prevalence
Bangladesh	150 494 000	68 000	340 000	620 000
China	1 347 565 000	47 000	1 000 000	1 400 000
India	1 241 492 000	300 000	2 200 000	3 100 000
Nigeria	162 471 000	27 000	190 000	280 000
South Africa	50 460 000	25 000	500 000	390 000

Tab. 2.1: Estimated burden of disease caused by TB in 2011 in some developing countries [38].

Country	Population	Mortality	Incidence	Prevalence
Canada	34 000 000	61	1 600	1 900
France	63 000 000	290	2 700	3 500
UK	62 000 000	350	8 800	12 000
US	313 000 000	420	12 000	15 000

Tab. 2.2: Estimated burden of disease caused by TB in 2011 in some developed countries [38].

Figure 2.1 shows an estimation of TB incidence rate in the world [37].

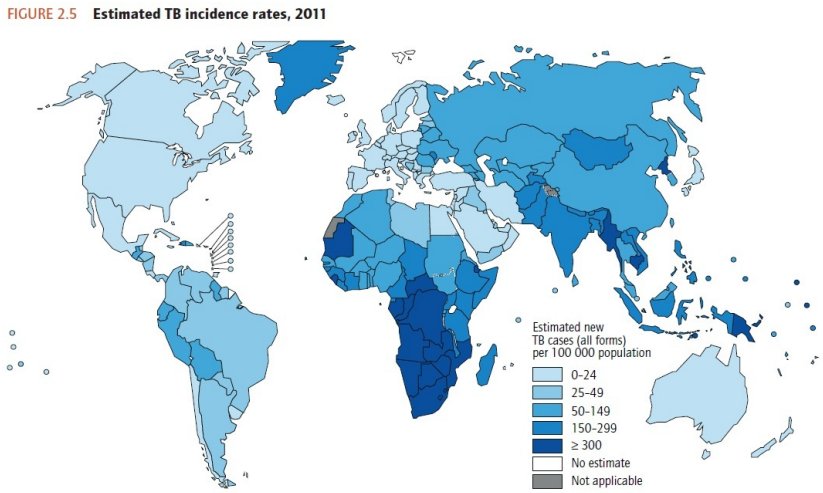

Fig. 2.1: Estimated TB incidence rate 2011. Figure from WHO [37, p. 22].

Even though TB is more prevalent in developing counties than in developed ones, in 2005, the United Nations reported that there were around 200 millions international migrants at that time, with sixty percent of these immigrants now in developed countries [32]. Recently, the International Organization for Migration (IOM) reports the increase in the number of the international migrants to 214 million international migrants around the world today [19]. This shows that TB is a worldwide problem, not only a local one. And this stresses the importance of not only studying the disease in every country but also putting some effort in studying the impact of the movement in spread of TB.

3. GENERAL METAPOPULATION MODELS

Chapter 2 presents estimated data showing that TB is not homogeneously spread worldwide and that the presence of TB depends, to a large extent, on whether the country is developed or not. It also presents some estimated numbers of international migration worldwide and the main direction of migration from the developing countries to the developed ones. These estimated numbers show that movement between countries or cities could play a very important role in the spread of TB, which is what this thesis is trying to study.

For that reason, metapopulation models are used to study the spread of TB, since metapopulation models allow us to study the dynamics of a given disease taking into account the migration or movement between countries/cities.

The term metapopulation was first used in the ecological literature by Richard Levins to describe the population of populations in 1970. Although it has been used since that time in ecology, it is relatively recent in the mathematical epidemiology field. Arino in [2] defines a *metapopulation model* as a model involving explicit movement of individuals between distinct locations. In other words, a metapopulation defines a graph with vertices called *patches* containing subpopulations with nontrivial dynamics linked by arcs representing the possibility of movement. A main question investigated in this chapter is the following

> *Starting with isolated patches each with certain dynamical properties, does a model resulting from the linear coupling of these patches inherit any of the properties of the original isolated patches?*

We begin by presenting some of the graph and dynamical theories used in metapopulation models below. The formulation follows [2].

3.1 Notation from Graph Theory

Assume that we have p distinct patches in a set $\mathcal{P}$ of patches. Each patch contains a certain number of compartments belonging to a common set $\mathcal{S}$. Each patch is a vertex in a graph $\mathcal{G}$. The arcs of $\mathcal{G}$, collected in a set $\mathcal{A}$, represent the possibility for individuals in a given compartment to move between two patches. Therefore $\mathcal{G}$ is the multi-digraph determined by $\mathcal{G} = (\mathcal{P}, \mathcal{A})$.

Definition 3.1.1. *Consider the multi-digraph $\mathcal{G} = (\mathcal{P}, \mathcal{A})$, where $\mathcal{P}$ is the set of patches and $\mathcal{A}$ is the set of arcs.*

- **Direct access** *is the binary relation R^s given by $R^s(X, Y)$ if, for compartments $s \in \mathcal{S}$, there exists an arc $A^s \in \mathcal{A}$ from X to Y, where $X, Y \in \mathcal{P}$.*

- **Indirect access** *occurs when a given compartment $s \in \mathcal{S}$ from patch X has an access to patch Y only through a different patch Z.*

- *For a given $s \in \mathcal{S}$,* **the connection matrix $\mathcal{C}_s$ associated to $\mathcal{G}$** *is given as follows*

$$(\mathcal{C}_s)_{(i,j)} = \begin{cases} 1 & \text{if } R^s(P_j, P_i), \\ 0 & \text{otherwise} \end{cases}$$

Example 3.1.1. *For a given compartment $s \in \mathcal{S}$, consider the digraph described by Figure 3.1.*

Patch 1 has direct access to 2 and indirect access to 3, while 3 does not have any access to either 1 or 2. Keeping the order as in Figure 3.1, the associated connection matrix $\mathcal{C}_s$ is given by

Fig. 3.1: An example of a multi-digraph for a given compartments s.

$$\mathcal{C}_s = \begin{pmatrix} 0 & 1 & 0 \\ 1 & 0 & 0 \\ 0 & 1 & 0 \end{pmatrix}.$$

Definition 3.1.2. *In a multi-digraph* $\mathcal{G}$

- **Movement is similar for all compartments** *if the existence of an* $s \in \mathcal{S}$ *such that* $R^s(X, Y)$*, implies that* $R^s(X, Y)$ *exists for all* $s \in \mathcal{S}$*.*
- **A strongly connected component** *for a compartment* $s \in \mathcal{S}$ *is a subset of the patches,* $\mathcal{Q} \subset \mathcal{P}$ *such that for all patches* $X, Y \in \mathcal{Q}$*, if compartment* s *in* X*, then* X *has access to* Y*.*
- **A strongly connected digraph** *for a compartment* s *is the digraph where all the patches belong to the same strongly connected component, i.e.,* $\mathcal{Q} = \mathcal{P}$*.*

Remark 1. *Strong connectedness is equivalent to irreducibility of the connection matrix* $\mathcal{C}_s$*, where an* **irreducible matrix** *is a matrix that is not similar to a block upper triangular matrix by permutation matrices.*

3.2 The Dynamics of a Metapopulation Model

The dynamics of a metapopulation model combines the dynamics within each patch (resulting from the interactions between compartments that are present in the patch) with an operator describing the movement of individuals between the patches. This operator is assumed to be linear throughout this thesis.

Let $N_{si}(t)$ be the number of individuals of compartment $s \in \mathcal{S}$ in patch $i \in \mathcal{P}$ at time t, $N_s = (N_{s1}, \cdots, N_{sp})^T$ be the vector of distribution of individuals of a given compartment s among the different patches and $N^i = (N_{1i}, \cdots, N_{ni})^T$ be the vector of composition of the population of a given patch i, where $n = |\mathcal{S}|$, and $p = |\mathcal{P}|$. To describe the evolution of the population, we start by writing the evolution of the individual components of the system as follows

$$\frac{dN_{si}}{dt} = f_{si}(N^i) + \sum_{j=1}^{p} m_{ij}^s N_{sj} - \sum_{j=1}^{p} m_{ji}^s N_{si}, \tag{3.1}$$

where for $s = 1, \ldots, n$ and $i = 1, \ldots, p$, m_{ji}^s is the rate of travel from patch i to patch j of individuals in compartment s and $f_{si} : \mathbb{R}^n \to \mathbb{R}$ is the function describing the dynamics within patch i of individuals of compartment s. Note that it is assumed here that the dynamics in a patch only depends on those individuals who are physically present in the patch.

The term $\sum_{j=1}^{p} m_{ij}^s N_{sj}$ describes the inflow of individuals of compartment s into patch i from all the other patches, while the outflow of individuals of compartment s from patch i to all other patches is described by $\sum_{i=1}^{p} m_{ji}^s N_{si}$. It is assumed here that $m_{ii}^s = 0$ for all s. Another way to write equation (3.1) uses a vector form,

$$\frac{dN_s}{dt} = f_i(N^i) + \mathcal{M}_s N_s, \tag{3.2}$$

where $f_i : \mathbb{R}^n \to \mathbb{R}^p$ and $\mathcal{M}_s$ is a $p \times p$ matrix called the *movement matrix*, as it shows the movements between the patches; this matrix is given by

$$\mathcal{M}_s = \begin{pmatrix} -\sum_{j=1}^{p} m_{j1}^s & m_{12}^s & \cdots & m_{1p}^s \\ m_{21}^s & -\sum_{j=1}^{p} m_{j2}^s & \cdots & m_{2p}^s \\ \vdots & \vdots & \ddots & \vdots \\ m_{p1}^s & m_{p2}^s & \cdots & -\sum_{j=1}^{p} m_{jp}^s \end{pmatrix}. \tag{3.3}$$

So $\mathcal{M}_s$ represents the connection matrix associated with the graph of patches combined with a description of the intensity of the connections. As the movement matrix plays a very important role in metapopulation models, the next theorem gives some of the most important properties of that matrix.

Theorem 3.2.1 ([2])**.** *Consider a compartment $s \in \mathcal{S}$. Then $(\mathcal{M}_s)$ is a singular M-matrix. All eigenvalues of $-\mathcal{M}_s$ have non-positive real parts. 0 is an eigenvalue of $\mathcal{M}_s$, and one of the eigenvectors associated to the eigenvalue 0 is the eigenvector $\mathbb{1}_p^T = (1, \cdots, 1)$. In the case that $\mathcal{M}_s$ is irreducible, then 0 is an eigenvalue with multiplicity 1, $\mathbb{1}_p^T$ is (to a multiple) the only strongly positive left eigenvector associated with $\mathcal{M}_s$, and all other eigenvalues have negative real parts.*

3.3 Compartmental Models

To describe and to study the dynamics of a disease, a system of ordinary differential equations called *compartmental system* is developed. Jacquez and Simon in [20] define a *compartment* to be "an amount of some material that is kinetically homogeneous". That means that the amount of material is always homogeneous at any time and mixes with the content of the compartment once entering it. Defining q_i to represent compartment i, I_i to represent inflows into q_i from outside the system and g_{0i} to represent outflows of q_i out of the compartmental system, g_{ji} to represent the transfers from compartment i to compartment j, then

$$q_i'(t) = I_i(t) - g_{0i}(t) + \sum_{j \neq i} g_{ij(t)} - g_{ji}(t),$$

such that the following two conditions hold

$$I_i \geq 0,\ g_{0i} \geq 0,\ g_{ji} \geq 0 \text{ for all } i, j \text{ and } t. \tag{C$_1$}$$

$$\text{If } q_i = 0, \text{ then } g_{0i} = 0 \text{ and } g_{ji} = 0 \text{ for all } j, \text{ so that } q_i \geq 0. \tag{C$_2$}$$

3.4 Studying the Dynamics of a Metapopulation Model

To study a metapopulation epidemic model, a certain number of steps should be undertaken, which typically include several or all of the following:

- Studying the well-posedness of the system.
- Studying the existence of disease-free equilibria.
- Computing a reproduction number for the system and considering the local asymptotic stability of the disease-free equilibria.
- If the disease-free equilibrium is unique, proving that it is globally asymptotically stable when $\mathcal{R}_0 < 1$.
- Studying the existence of a backward bifurcation phenomenon.
- Studying the existence of either endemic or mixed equilibria and their stabilities.

We will start by proving some results in the direction of the question presented at the beginning of the chapter, which we reformulate here.

Consider p isolated patches, where the population of each patch i is divided into n compartments and the dynamics is given, for $i = 1, \ldots, p$, *by*

$$\begin{aligned} x'_{i1} &= f_{i1}\left(x_{i1}, \cdots, x_{in}\right), \\ &\vdots \\ x'_{in} &= f_{in}\left(x_{i1}, \cdots, x_{in}\right). \end{aligned} \tag{Π_i}$$

Consider also the dynamics describing the p linearly coupled patches, given, for $i = 1, \ldots, p$, *by*

$$\begin{aligned} x'_{i1} &= f_{i1}\left(x_{i1}, \cdots, x_{in}\right) + \sum_{j=1}^{p} m_{ij}^{1} x_{j1} - \sum_{j=1}^{p} m_{ji}^{1} x_{i1}, \\ &\vdots \\ x'_{in} &= f_{in}\left(x_{i1}, \cdots, x_{in}\right) + \sum_{j=1}^{p} m_{ij}^{n} x_{jn} - \sum_{j=1}^{p} m_{ji}^{n} x_{in}. \end{aligned} \tag{Π}$$

Question: Does model (Π) *inherit any of the properties of model* (Π_i)*?*

3.5 New Results on Metapopulations

The following are some results developed as a contribution to the understanding of the role of linear movement between p patches in changing the dynamical properties of the metapopulation model compared to the models within each patch in isolation.

3.5.1 Well-posedness

Obviously, linear movement will not violate the existence and uniqueness principle of the solutions of (Π) if (Π_i) satisfies that theorem as the difference between the two models are linear terms which are infinitely many times differentiable. In the case of nonlinear movement, we need the additional condition that the movement functions are continuously differentiable in order to preserve the existence and uniqueness

property. Hence movement does not change the existence and uniqueness of solutions and the continuous dependence on parameters and initial data of (Π_i).

Theorem 3.5.1. *If the positive orthant $\mathbb{R}^n_+$ is positively invariant under the flow of (Π_i), then the positive orthant $\mathbb{R}^{np}_+$ is positively invariant under the flow of (Π).*

Proof. The positive orthant $\mathbb{R}^n_+$ being positively invariant under the flow of the isolated patches described by (Π_i) means that on each of the faces of the positive orthant the vector field points inward. In other words and using Condition C_2 in Section 3.3, in any patch i , $i \in \{1, \cdots, p\}$, if there is t_1 such that one of the compartments $x_{ij}(t_1) = 0$ becomes zero that implies

$$x'_{ij}(t_1) \geq 0 \Leftrightarrow f_{ij}\left(x_{i1}, \cdots, x_{in}\right)(t_1) \geq 0, \tag{3.4}$$

otherwise, if $x'_{ij}(t_1) < 0$, $x_{ij}(t_1+\epsilon) < 0$ which contradicts of a compartmental model, for which solutions must remain nonnegative. So, if there is a t^* such that $x_{ij}(t^*) = 0$, then $x'_{ij}(t^*) = f_{ij}\left(x_{i1}, \cdots, x_{in}\right)(t^*) \geq 0$, where $j \in \{1, \ldots, n\}$. Now assume that the initial conditions are positive for (Π) and that for some $i \in \{1, \cdots, p\}$ and $k \in \{1, \cdots, n\}$, $x_{ik}(t_1) = 0$, with t_1 the first t for which any variable becomes zero. Studying the vector field of x_{ik} at t_1 gives

$$\begin{aligned} x'_{ik}(t_1) &= f_{ik}\left(x_{i1}, \cdots, x_{in}\right)(t_1) + \sum_{j=1}^{p} m^k_{ij} x_{ji}(t_1) - \sum_{j=1}^{p} m^k_{ji} x_{ik}(t_1), \\ &= f_{ik}\left(x_{i1}, \cdots, x_{in}\right)(t_1) + \sum_{j=1}^{p} m^k_{ij} x_{ji}(t_1). \end{aligned}$$

Since $x_{ik}(t_1) = 0$, then all outflow terms in $f_{ik}\left(x_{i1}, \cdots, x_{in}\right)(t_1)$ vanish. Hence $f_{ik}\left(x_{i1}, \cdots, x_{in}\right)(t_1)$ is a sum of the inflow terms of positive variables only, therefore by (3.4), $f_{ik}\left(x_{i1}, \cdots, x_{in}\right)(t_1) \geq 0$, which implies that $x'_{ik}(t_1) > 0$. □

3.5.2 disease-free Equilibrium

Arino *et al* considered in [3] an SEIR model and proved a result establishing conditions under which the DFE is preserved under linear migration. The same method of proof can be used to prove the same type of result for a general metapopulation system (Π).

Theorem 3.5.2. *Consider p well posed systems given by (Π_i). Suppose that (Π) is at an equilibrium and that there is no disease in patch i. If Y_i is the vector of infected compartments in patch i, then $Y_j = 0$ for each patch j that has an access to patch i.*

Proof. The proof follows [3]. Suppose that there is no disease in a given patch i, fixed, i.e. $Y_i = 0$. But $Y_i = 0$ implies that $Y_i' = 0$. Using (Π),

$$Y_i' = 0 = f_i(X_i, 0) + \sum_{j=1}^{p} m_{ij}^Y Y_j = 0. \tag{3.5}$$

Since the positive orthant is invariant under the flow of (Π_i), then $f_i(X_i, 0) \geq 0$. But since $\sum_{j=1}^{p} m_{ij}^Y Y_j$ is nonnegative as well, then Equation (3.5) implies that, $f_i(X_i, 0) = 0$, and $\sum_{j=1}^{p} m_{ij}^Y Y_j = 0$. But

$$\sum_{j=1}^{p} m_{ij}^Y Y_j = 0 \Rightarrow Y_j = 0, \ \forall j,$$

which means that $Y_j = 0$ for any patch j that has direct access to patch i. Continuing this reasoning for all patches in the direct ancestry of patch i, i.e., those patches having direct access to i, the result follows. □

A straightforward corollary of Theorem 3.5.2 is given below.

Corollary 3.5.3. *Assume that system (Π) is at an equilibrium and that all migration matrices are irreducible. Then all patches are disease free if and only if one patch is disease free.*

3.5.3 Endemic Equilibrium

In this section a generalization of another result proved in [3] is presented.

Theorem 3.5.4. *Consider p well posed systems given by (Π_i). Suppose that (Π) is at an equilibrium. If the disease in patch i is at an endemic equilibrium, then the disease is also at an endemic equilibrium in all patches j to which patch i has an access.*

Proof. The proof, using ideas as in [3], will be done by contradiction. Fix patch i where the disease is endemically present, i.e., $\sum_k Y_{ik} > 0$. Now assume that patch i has an access to patch j where the disease is not present, i.e. $Y_j = 0$. Using (Π) and denoting $y_j := \sum_l Y_{jl}$ the total number of infected in compartments in patch j, we get

$$0 = y_j' = \sum_k \left(f_{jk}(X_j, Y_j) + \sum_{r=1}^{p} m_{jr}^{Y_k} Y_{rk} - \sum_{r=1}^{p} m_{rj}^{Y_k} Y_{ik} \right).$$

Since $Y_j = 0 \Rightarrow Y_{jk} = 0$ for every infected compartment in patch j, then using (Π_i) and [31, Lemma 2.1], $Y_{jk} = 0 \Rightarrow Y_{jk}' = 0 \Leftrightarrow f_{jk}(X_j, Y_j) = 0$. Hence the above equation reduces to $y_j' = \sum_{r=1}^{p} \left(\sum_k m_{jr}^{Y_k} \right) y_r = 0$ which implies that either $\left(\sum_k m_{jr}^{Y_k} \right) = 0$ or $y_r = 0$ for every patch r that has access to patch j. Since patch i has an access for patch j, then $m_{ji}^{Y_k} \neq 0$ for some infected compartment k.Therefore $y_r = 0$ for every patch r that has access to patch j, a contradiction. □

A straightforward corollary of Theorem 3.5.4 is given below.

Corollary 3.5.5. *Assume that system (Π) is at an equilibrium and that all migration matrices are irreducible. Then the disease is endemic at all patches if and only if it is endemic on one patch.*

Remark 2. *Corollaries 3.5.3 and 3.5.3 together establish the following fact: if all migration matrices are irreducible, then any equilibrium of the coupled system is*

either disease free (disease free on all patches) or endemic (endemic on all patches). This rules out the existence of mixed equilibria (disease free on some patches While endemic on others).

3.5.4 Backward Bifurcation

In this section, we investigate the following question.

Can coupling patches linearly change the type of the bifurcation they undergo provided that all isolated patches are of the same bifurcation type?

For any system such as (Π_i), two types of bifurcations could happen at $\mathcal{R}_{0i} = 1$, forward and backward. A forward bifurcation (supercritical) happens as R_0 crosses unity to the right. That time a positive asymptotically stable equilibrium appears (Endemic) and the disease-free equilibrium becomes unstable. While the backward bifurcation (subcritical) happens while R_0 is still smaller than unity. In this case, a positive unstable equilibrium and a stable positive equilibrium appear while the disease-free equilibrium is still locally asymptotically stable. The existence of the backward bifurcations means that to eliminate the disease it is not enough to just reduce $\mathcal{R}_0$ to be less than unity. Castillo-Chavez and Song in [10] gave an approach to determine the direction of the bifurcation at $\mathcal{R}_0 = 1$ depending on the sign of two constant a_i and b_i which they defined; see Appendix B for the statement of the theorem.

Conjecture 3.5.6. *Consider p patches with dynamics described by (Π_i). The new model with linear migration between the p patches, with dynamics generated by (Π) has constants a and b of Theorem B.1 given by*

$$a = C(p)\sum_{i=1}^{p} a_i, \qquad b = C(p)\sum_{i=1}^{p} b_i, \tag{3.6}$$

where a_i and b_i are the a and b in patch i for Theorem B.1 and $C(p) > 0$.

Idea of the proof. To illustrate the idea, consider 2 patches with dynamics described with (Π_i), such that the 2 patches are at the bifurcation point and with the same bifurcation type. That means that $\mathcal{R}_{0i} = 1$ for $i \in \{1, 2\}$, $\mathsf{sgn}\ a_1 = \mathsf{sgn}\ a_2$ and $\mathsf{sgn}\ b_1 = \mathsf{sgn}\ b_2$. Constants a and b of (Π) are defined by

$$a = \sum_{i,j,k=1}^{2n} v_k w_i w_j \frac{\partial^2 F_k}{\partial x_i \partial x_j}(x^*, 0), \tag{3.7}$$

$$b = \sum_{i,k=1}^{2n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(x^*, 0), \tag{3.8}$$

where w and v such that $v^T w = 1$ are a nonnegative right eigenvector and left eigenvector corresponding to the zero eigenvalue of the Jacobian of the linearization matrix of (Π) around the equilibrium x^* with the bifurcation parameter ϕ equal to 0. It is easy to see that the second derivatives of (Π) relates to the second derivatives of (Π_i) as follows

$$\frac{\partial^2 F_k}{\partial X_i \partial X_j}(x^*, 0) = \begin{cases} \frac{\partial^2 f_{1k}}{\partial x_{1i} \partial x_{1j}}(x^*, 0) & ; k, i, j \in \{1, \cdots, n\} \\ \frac{\partial^2 f_{2(k-n)}}{\partial x_{2(i-n)} \partial x_{2(j-n)}}(x^*, 0) & ; k, i, j \in \{n+1, \cdots, 2n\} \\ 0 & ; \text{ otherwise.} \end{cases} \tag{3.9}$$

To be able to prove this conjecture, we need to find a relation between the right eigenvectors of the Jacobians of (Π) and (Π_i). As proved before,

$$\mathcal{J} := \left(\frac{dF_i}{dx_j}\right)\Big|_{(x^*,0)} = \bigoplus_{i=1}^{p} \mathcal{J}_i + \mathcal{M}.$$

Define $W := (W_1, W_2)$ where W_1 and W_2 are the right eigenvectors of the Jacobian

of (Π_i). The result will follow if we can prove or find conditions under which

$$\mathcal{M}W = 0$$

does not only have the trivial solution. We have not been able to do this at present.

4. THE EFFECT OF MIGRATION IN THE SPREAD OF TUBERCULOSIS

Tuberculosis (TB) is one of the most serious public health diseases facing society. One third of the human population is infected by that bacterial disease, which is considered to be the second leading cause of death by an infectious disease in the world [7, 21]. TB progression depends on many factors such as nutritional status and/or access to decent medical care and living conditions [7]. Lack of compliance with an antibiotic treatment not only may lead to relapse, but also to the development of antibiotic resistance in TB bacteria, which is a very serious problem. The implicit good news is that latent and active TB can be treated with antibiotics.

Castillo-Chavez and Feng in [9] formulated two basic transmission models to study both simple and two-strain TB in a very simple setting. For the single strain TB model, they computed the basic reproductive number, studied its role on the dynamics and proved the stability properties of that model in a special case .

In this chapter we consider the effect of migration on a the single strain TB model of [9], in the general setting allowing the rate of movement to depend on the disease status. The basic reproduction number is calculated, its role on the dynamics is studied and we prove the global stability of the disease free equilibrium.

4.1 Metapopulation Model on p Patches

We start by formulating the general deterministic metapopulation $SLIT$ epidemic model. Assume that we have p distinct geographical locations that could be cities,

counties, countries, etc. and that we call patches. Within each patch $i = 1, \cdots, p$, the population is divided into compartments of susceptible, latent, infective and treated individuals with number in each compartment denoted by $S_i(t), L_i(t), I_i(t)$ and $T_i(t)$, respectively. The total number of individuals in each patch i is $N_i(t) = S_i(t)+L_i(t)+I_i(t)+T_i(t)$ and the total population in the system is $N(t) = N_1(t) + \cdots + N_p(t)$.

Birth in patch i is assumed to be in to the susceptible class at the rate $\Lambda_i > 0$ per unit time and natural death is assumed to be independent of disease status and occur at the constant per capita rate $d_i > 0$. $\beta_i \geq 0$ is the rate at which susceptible individuals become infected by infectious individuals per unit time and $\sigma_i\beta_i$ is the rate at which treated individuals become infected by infectious individuals per unit time, where $1 - \sigma_i \in [0, 1]$ is the efficiency of treatment in preventing infection. If $\sigma = 0$, then the treatment always prevents infection.While if $\sigma = 1$, then treatment has no benefit. Note that we assume that treatment cannot be detrimental for infection, i.e., $\sigma_i \leq 1$.

Once infected, a susceptible or treated individual moves to the latent infection compartment, then into the infective compartment as the individual becomes able to transmit the disease with constant rate k_i. Infectious individuals can recover naturally and move back to the latent compartment with a constant rate r_i. Both latently infected and infectious individuals can move to the treated compartment by getting the treatment at constant rate t_{1i} an t_{2i}, respectively. The disease induced death rate constant for infectious individuals is denoted by μ_i. It is assumed that while undergoing treatment, individuals are not subject to disease induced death. The rates of movement of individuals between patches are assumed to depend on disease status travel; travel is instantaneous and individuals do not change status during travel. Let $m_{ij}^S, m_{ij}^L, m_{ij}^I,$ and m_{ij}^T denote the rate of travel from patch j to patch i of susceptible, latent, infective and treated individuals, respectively, where for all $i = 1, \ldots, p, m_{ii}^X = 0$ and $m_{ij}^X \geq 0$ for all $X \in \{S, L, I, T\}$. This structure

defines a multi-digraph with patches as vertices and arcs given by the travel rates, which can be represented by the mobility matrices $\mathcal{M}^S$, $\mathcal{M}^L$, $\mathcal{M}^I$ and $\mathcal{M}^T$, where, for a given epidemiological status $X \in \{S, L, I, T\}$,

$$\mathcal{M}^X = \begin{pmatrix} -\sum_{j=1}^{p} m_{j1}^X & m_{12}^X & \cdots & m_{1p}^X \\ m_{21}^X & -\sum_{j=1}^{p} m_{j2}^X & \cdots & m_{2p}^X \\ \vdots & \vdots & \ddots & \vdots \\ m_{p1}^X & m_{p2}^X & \cdots & -\sum_{j=1}^{p} m_{jp}^X \end{pmatrix}. \tag{4.1}$$

It is assumed that these matrices are irreducible. The flow diagram of the model in the absence of movement is as follows:

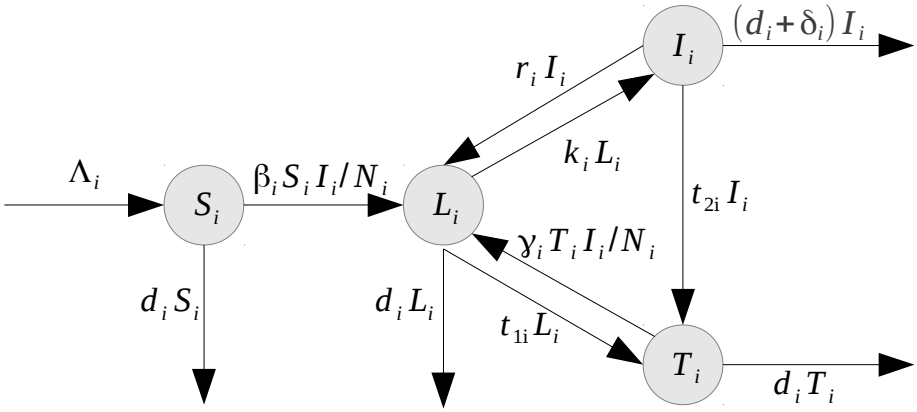

Fig. 4.1: The flow diagram of TB model in absence of movement.

Finally to write the model describing TB taking into the account the expression of the matrix $\mathcal{M}^X$ given by (4.1), we can consider for every $X \in \{S, L, I, T\}$ and $i = 1, \ldots, p$ m_{ii}^X to be

$$m_{ii}^X = -\sum_{j=1}^{p} m_{ji}^X.$$

Hence all the previously discussed assumptions lead to the following system of $4p$ ordinary differential equations, for $i = 1, \cdots, p$,

$$S_i' = \Lambda_i - d_i S_i - \beta_i \frac{S_i I_i}{N_i} + \sum_{j=1}^{p} m_{ij}^S S_j, \tag{4.2a}$$

$$L_i' = \beta_i \frac{S_i I_i}{N_i} - \{d_i + k_i + t_{1i}\} L_i + \sigma_i \beta_i \frac{T_i I_i}{N_i} + r_i I_i + \sum_{j=1}^{p} m_{ij}^L L_j, \tag{4.2b}$$

$$I_i' = k_i L_i - \{d_i + \mu_i + t_{2i} + r_i\} I_i + \sum_{j=1}^{p} m_{ij}^I I_j, \tag{4.2c}$$

$$T_i' = t_{1i} L_i + t_{2i} I_i - \sigma_i \beta_i \frac{T_i I_i}{N_i} - d_i T_i + \sum_{j=1}^{p} m_{ij}^T T_j. \tag{4.2d}$$

The model in each patch generalizes the model in [9] to include the rate of natural recovery of the infectious individuals.

4.2 Mathematical Analysis

4.2.1 Basic Properties of Solutions

Proposition 4.2.1. *Given nonnegative initial conditions, solutions to* (4.2) *exist and are unique for all* $t \geq 0$. *Furthermore, the positive orthant* $\mathbb{R}_+^{4p}$ *is invariant under the flow of* (4.2).

Proof. Since the vector field in (4.2) consists of sums of constants and rational polynomial functions in S_i, L_i, I_i, T_i and that we show later that the N_i are positive, it is differentiable. Hence solutions to (4.2) exist and are unique.

To prove the nonnegativity of solutions, first consider S_i; setting $S_i = 0$ in (4.2a), we get

$$S_i' = \Lambda_i > 0.$$

This implies that for nonnegative initial conditions $S_i(0) \geq 0$, $S_i(t)$ remains positive for all $t > 0$. Assume that the initial conditions are positive, i.e., $S_i(0) > 0, L_i(0) >$

$0, I_i(0) > 0$ and $T_i(0) > 0$. Consider L_i and assume that there exists $t_1 > 0$ such that $L_i(t_1) = 0$, and that t_1 is the first t for which any variable becomes zero. At t_1,

$$L_i'(t_1) = \frac{\beta_i S_i(t_1) I_i(t_1)}{N_i(t_1)} + \frac{\sigma_i \beta_i T_i(t_1) I_i(t_1)}{N_i(t_1)} + r_i I_i(t_1) + \sum_{j=1}^{p} m_{ij}^L L_j(t_1) > 0,$$

since the negative term m_{ii}^L vanishes as it was multiplied by $L_i(t_1)$. But, if $L_i(t_1) = 0$, then $L_i'(t_1) \leq 0$ as initial conditions are positive (and for some interval $\mathcal{I} = [t_2, t_1), L_i'(t_1) < 0$), a contradiction. Then there is no t_1 such that $L_i(t_1) = 0$. Hence L_i is positive for all t. Similarly, the variables I_i and T_i are positive. □

Proposition 4.2.2. *Given nonnegative initial conditions, solutions to* (4.2) *are bounded for all* $t \geq 0$.

Proof. To establish boundedness, note that in each patch i we have,

$$N_i' = \Lambda_i - d_i N_i - \mu_i I_i + \sum_{X \in \{S,L,I,T\}} \sum_{j=1}^{p} m_{ij}^X X_j. \tag{4.3}$$

Hence the total population satisfies

$$N' = \Lambda - \sum_{i=1}^{p} d_i N_i - \sum_{i=1}^{p} \mu_i I_i + \sum_{i=1}^{p} \sum_{X \in \{S,L,I,T\}} \sum_{j=1}^{p} m_{ij}^X X_j \tag{4.4}$$

where $\Lambda := \sum_{i=1}^{p} \Lambda_i$. Now, we can notice that the finite sum

$$\sum_{i=1}^{p} \sum_{X \in \{S,L,I,T\}} \sum_{j=1}^{p} m_{ij}^X X_j = \sum_{i=1}^{p} \sum_{X \in \{S,L,I,T\}} \left(\sum_{j=1}^{p} m_{ij}^X X_j - \sum_{j=1}^{p} m_{ji}^X X_i \right) = 0,$$

since

$$\begin{aligned}
\sum_{i=1}^{p} \sum_{X\in\{S,L,I,T\}} & \left(\sum_{j=1}^{p} m_{ij}^{X} X_j - \sum_{j=1}^{p} m_{ji}^{X} X_i \right) \\
&= \sum_{X\in\{S,L,I,T\}} \sum_{i=1}^{p} \left(\sum_{j=1}^{p} m_{ij}^{X} X_j - \left(\sum_{j=1}^{p} m_{ji}^{X} \right) X_i \right) \\
&= \sum_{X\in\{S,L,I,T\}} \sum_{i=1}^{p} \sum_{j=1}^{p} m_{ij}^{X} X_j - \sum_{i=1}^{p} \left(\sum_{j=1}^{p} m_{ji}^{X} \right) X_i \\
&= \sum_{X\in\{S,L,I,T\}} \sum_{j=1}^{p} \left(\sum_{i=1}^{p} m_{ij}^{X} \right) X_j - \sum_{i=1}^{p} \left(\sum_{j=1}^{p} m_{ji}^{X} \right) X_i \\
&= 0.
\end{aligned}$$

Defining $\underline{d} := \min_{i=1,\ldots,p} \{d_i\}$, equation (4.4) for the total population gives

$$N' \leq \Lambda - \underline{d} N. \tag{4.5}$$

As solutions to scalar first order equations are monotone, this implies that $N(t)$ is bounded above by solutions of the differential equation $\Psi' = \Lambda - \underline{d}\Psi$, i.e., $N(t) \leq \max(\Psi(0), \Lambda/\underline{d})$, with, for all sufficiently large t, $N(t) \leq \Lambda/\underline{d}$. Whence, since $N = \sum_{i=1}^{p} N_i$ and each $N_i \geq 0$, N_i is also bounded for each i, and for the same reason S_i, L_i, I_i, T_i are bounded for each i. □

4.2.2 Disease Free Equilibrium Point (DFE)

The metapopulation is at an equilibrium if the time derivatives in (4.2) are zero. Patch i is at a disease free equilibrium (DFE) if $L_i = I_i = 0, \forall i = 1, \ldots, p$. This implies that $T_i = 0, \forall i = 1, \ldots, p$, as established in the following result.

Lemma 4.2.3. *Given system (4.2), suppose that $L_i = I_i = 0$ for all $i = 1, ..., p$. Then*

$$T_i = 0, \quad \forall i = 1, ..., p.$$

Proof. See [2]. □

Thus at a DFE, (4.2) is such that $S_i = N_i,\ \forall i = 1, \ldots, p$ and satisfies

$$S_i' = \Lambda_i - d_i S_i + \sum_{j=1}^{p} m_{ij}^S S_j - \sum_{j=1}^{p} m_{ji}^S S_i, \tag{4.6}$$

which has the following matrix/vector form

$$S' = \mathcal{B} + \left(\mathcal{M}^S - diag(d_i)\right) S, \tag{4.7}$$

where $\mathcal{B} = (\Lambda_1, \Lambda_2, \ldots, \Lambda_p)^T \in \mathbb{M}_{p\times 1}$. Then the DFE is given by

$$\left(\left(\mathsf{diag}\ (d_i) - \mathcal{M}^S\right)^{-1} \mathcal{B}, 0, 0, 0\right). \tag{4.8}$$

By Gershgorin's circle theorem, [40], all eigenvalues of $\mathcal{M}^S$ have nonpositive real parts. Therefore, shifting them by $-d_i < 0$ ensures that all the eigenvalues of $\mathsf{diag}\ (d_i) - \mathcal{M}^S$ have strictly positive real parts. Hence $\left(\mathsf{diag}\ (d_i) - \mathcal{M}^S\right)$ is an invertible matrix implying that the DFE is unique. Linear stability of the DFE can be investigated using the next generation method [12, 33]. To derive a formula for $\mathcal{R}_0$ using the next generation method, we follow the method of [33] and order the infected variables as $L_1, \ldots, L_p, I_1, \ldots, I_p$. The vector representing new infections into the infected classes, $\mathcal{F}$, is given by

$$\mathcal{F} := \left(\beta_1 \frac{S_1 I_1}{N_1} + \sigma_1 \beta_1 \frac{T_1 I_1}{N_1}, \ldots, \beta_p \frac{S_p I_p}{N_p} + \sigma_p \beta_p \frac{T_p I_p}{N_p}, 0, \ldots, 0\right)^T. \tag{4.9}$$

The vector $\mathcal{V}$ representing other flows within and out of the infected classes $L_1, \ldots, L_p, I_1, \ldots, I_p$ is given by

$$\mathcal{V} := -\begin{pmatrix} -\{d_1+k_1+t_{11}\}L_1 + r_1I_1 + \sum_{j=1}^{p} m_{1j}^L L_j - \sum_{j=1}^{p} m_{j1}^L L_1 \\ \vdots \\ -\{d_p+k_p+t_{1p}\}L_p + r_pI_p + \sum_{j=1}^{p} m_{pj}^L L_j - \sum_{j=1}^{p} m_{jp}^L L_p \\ k_1L_1 - \{d_1+\mu_1+t_{21}+r_1\}I_1 + \sum_{j=1}^{p} m_{1j}^I I_j - \sum_{j=1}^{p} m_{j1}^I I_1 \\ \vdots \\ k_pL_p - \{d_p+\mu_p+t_{2p}+r_p\}I_p + \sum_{j=1}^{p} m_{pj}^I I_j - \sum_{j=1}^{p} m_{jp}^I I_p \end{pmatrix} \tag{4.10}$$

The matrix of new infections F and the matrix of transfers between compartments V are the Jacobian matrices obtained by differentiating $\mathcal{F}$ and $\mathcal{V}$ with respect to the infected variables, evaluated at the disease free equilibrium (DFE). They take the form

$$F = \begin{pmatrix} 0 & \mathsf{diag}\ (\beta_i) \\ 0 & 0 \end{pmatrix}, \tag{4.11}$$

$$V = \begin{pmatrix} V_{11} & -\mathsf{diag}\ (r_i) \\ -\mathsf{diag}\ (k_i) & V_{22} \end{pmatrix}, \tag{4.12}$$

where $V_{11} := \mathsf{diag}\ (d_i + k_i + t_{1i}) - \mathcal{M}^L$ and $V_{22} := \mathsf{diag}\ (d_i + \mu_i + r_i + t_{2i}) - \mathcal{M}^I$ are both irreducible $M-$matrices and so have positive inverses. Then the next generation matrix is

$$FV^{-1} = \begin{pmatrix} \mathsf{diag}\ (\beta_i)A_{11} & \mathsf{diag}\ (\beta_i)A_{12} \\ 0 & 0 \end{pmatrix}, \tag{4.13}$$

where

$$\begin{aligned} A_{11} &= \left(V_{11}\mathsf{diag}\ \left(\frac{1}{k_i}\right) V_{22} - \mathsf{diag}\ (r_i) \right)^{-1} \\ A_{12} &= \mathsf{diag}\ \left(\frac{1}{k_i}\right) V_{22} \left(V_{11}\mathsf{diag}\ \left(\frac{1}{k_i}\right) V_{22} - \mathsf{diag}\ (r_i) \right)^{-1}. \end{aligned} \tag{4.14}$$

FV^{-1} has spectral radius, denoted ρ, given by

$$\rho(FV^{-1}) = \rho(\mathsf{diag}\ (\beta_i)A_{11}) \cup \{0\}. \tag{4.15}$$

Since the matrix V is an $M-$matrix, it has a positive inverse [6]. Hence A_{11} is positive and therefore $\mathsf{diag}\ (\beta_i)A_{11}$ is also positive. Then using the Perron Frobenius theorem, $\rho(\mathsf{diag}\ (\beta_i)A_{11}) > 0$, whence the basic reproduction number, $\mathcal{R}_0$, is given by

$$\mathcal{R}_0 = \rho(FV^{-1}) = \rho(\mathsf{diag}\ (\beta_i)A_{11}), \tag{4.16}$$

where A_{11} is given by (4.14).

4.2.3 Global Stability of the DFE

Theorem 4.2.4. *Define the basic reproduction number for system (4.2) by* (4.16). *Then the DFE is globally asymptotically stable if* $\mathcal{R}_0 < 1$ *and unstable if* $\mathcal{R}_0 > 1$.

Proof. We prove the global stability of the DFE by showing that if $\mathcal{R}_0 < 1$, then

$$\lim_{t\to\infty} I(t) = \lim_{t\to\infty} L(t) = 0,$$

and then proving that the equilibrium (DFE) is (globally) asymptotically stable for the linear system deduced from (4.2) by setting $I = L = 0$. Equations (4.2b) and (4.2c) can be written in the form:

$$\begin{pmatrix} L'(t) \\ I'(t) \end{pmatrix} = \mathcal{A} \begin{pmatrix} L(t) \\ I(t) \end{pmatrix} + \mathcal{C}(t), \tag{4.17}$$

where

$$\mathcal{A} := \begin{pmatrix} -\mathsf{diag}\ (d_i + k_i + t_{1i}) + \mathcal{M}^L & \mathsf{diag}\ (\beta_i + r_i) \\ \\ \mathsf{diag}\ (k_i) & -\mathsf{diag}\ (d_i + \mu_i + t_{2i} + r_i) + \mathcal{M}^I \end{pmatrix}, \tag{4.18}$$

and

$$\mathcal{C}(t) := \begin{pmatrix} \left(\frac{\beta_1 S_1 + \sigma_1 \beta_1 T_1}{N_1} - \beta_1\right) I_1 \\ \vdots \\ \left(\frac{\beta_n S_n + \sigma_n \beta_n T_n}{N_n} - \beta_n\right) I_n \\ 0 \\ \vdots \\ 0 \end{pmatrix}. \tag{4.19}$$

Note that, for $i = 1, \ldots, p$,

$$\left(\frac{S_i(s) + \sigma_i T_i(s)}{N_i(s)} - 1\right) \beta_i \leq \left(\frac{S_i(s) + T_i(s)}{N_i(s)} - 1\right) \beta_i,$$

as $\sigma_i \leq 1$. So, using the fact that $\dfrac{S_i(s) + T_i(s)}{N_i(s)} \leq 1$ gives

$$\left(\frac{S_i(s) + T_i(s)}{N_i(s)} - 1\right) \beta_i \leq (1 - 1)\beta_i = 0$$

and it follows that $\mathcal{C}(t) \leq 0$ for all t. So (4.17) satisfies

$$\begin{pmatrix} L \\ I \end{pmatrix}' = \mathcal{A} \begin{pmatrix} L \\ I \end{pmatrix} + \mathcal{C}(t) \leq \mathcal{A} \begin{pmatrix} L \\ I \end{pmatrix}.$$

Let $(\Psi, \Phi) \in \mathbb{R}^{p \times p}$. Then the behaviour of (4.17) can be obtained by studying the linear system

$$\begin{pmatrix} \Psi \\ \Phi \end{pmatrix}' = \mathcal{A} \begin{pmatrix} \Psi \\ \Phi \end{pmatrix}. \tag{4.20}$$

The solution to (4.20) is clearly given by

$$\begin{pmatrix} \Psi(t) \\ \Phi(t) \end{pmatrix} = e^{\mathcal{A}t} \begin{pmatrix} \Psi(0) \\ \Phi(0) \end{pmatrix}.$$

To study properties of $e^{\mathcal{A}t}$, notice that the Jacobian of (4.2) at the DFE is given by

$$J|_{DFE} := \begin{pmatrix} \mathcal{M}^S - \mathsf{diag}\ (d_i) & \mathcal{D} & 0 \\ 0 & \mathcal{A} & 0 \\ 0 & \mathcal{E} & \mathcal{M}^T - \mathsf{diag}\ (d_i) \end{pmatrix}, \tag{4.21}$$

where $\mathcal{D} = [0 \quad -\mathsf{diag}\ (\beta_i)]$ and $\mathcal{E} = [\mathsf{diag}\ (t_{1i}) \quad \mathsf{diag}\ (t_{2i})]$.

Because the DFE is locally asymptotically stable when $\mathcal{R}_0 < 1$, all eigenvalues of (4.21) have negative real parts when $\mathcal{R}_0 < 1$. But the eigenvalues of (4.21) are the eigenvalues of $\mathcal{M}^S - \mathsf{diag}\ (d_i)$, $\mathcal{M}^T - \mathsf{diag}\ (d_i)$ and $\mathcal{A}$. The eigenvalues of $\mathcal{M}^S - \mathsf{diag}\ (d_i)$ and $\mathcal{M}^T - \mathsf{diag}\ (d_i)$ all have negative real parts, as by Gershgorin's circle theorem, all eigenvalues of $\mathcal{M}^S$ and $\mathcal{M}^T$ have nonpositive real parts and shifting them by $-d_i < 0$, $i = 1, \ldots, p$, makes all real parts negative. It follows that if $\mathcal{R}_0 < 1$, then all eigenvalues of $\mathcal{A}$ have negative real parts.

As a consequence, when $\mathcal{R}_0 < 1$,

$$\lim_{t\to\infty} \begin{pmatrix} \Psi(t) \\ \Phi(t) \end{pmatrix} = \lim_{t\to\infty} e^{\mathcal{A}t} \begin{pmatrix} \Psi(0) \\ \Phi(0) \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix}.$$

and therefore,

$$\lim_{t\to\infty} I(t) = \lim_{t\to\infty} L(t) = 0.$$

So, when $\mathcal{R}_0 < 1$ and for sufficiently large times, L and I are zero and the nonzero components in system (4.2) reduce to the following linear system:

$$\begin{pmatrix} S \\ T \end{pmatrix}' = \mathcal{G} \begin{pmatrix} S \\ T \end{pmatrix} + \begin{pmatrix} \mathcal{B} \\ 0 \end{pmatrix}, \tag{4.22}$$

where $\mathcal{B} := (\Lambda_1, \ldots, \Lambda_p)^T$ and

$$\mathcal{G} := \begin{pmatrix} \mathcal{M}^S - \mathsf{diag}\ (d_i) & 0 \\ 0 & \mathcal{M}^T - \mathsf{diag}\ (d_i) \end{pmatrix}.$$

Using the same reasoning as previously, it is clear that all eigenvalues of $\mathcal{G}$ have negative real parts. So $\mathcal{G}$ is invertible and the equilibrium of (4.22) is given by

$$\begin{pmatrix} S^* \\ T^* \end{pmatrix} = -\mathcal{G}^{-1} \begin{pmatrix} \mathcal{B} \\ 0 \end{pmatrix}.$$

By [2, Theorem 2], $-(\mathcal{M}^S - \mathsf{diag}\ (d_i))$ and $-(\mathcal{M}^T - \mathsf{diag}\ (d_i))$ are nonsingular M-

matrices with nonnegative inverses, so

$$\begin{pmatrix} S^* \\ T^* \end{pmatrix} = - \begin{pmatrix} (\mathcal{M}^S - \mathsf{diag}\ (d_i))^{-1} & 0 \\ 0 & (\mathcal{M}^T - \mathsf{diag}\ (d_i))^{-1} \end{pmatrix} \begin{pmatrix} \mathcal{B} \\ 0 \end{pmatrix}$$
$$= \begin{pmatrix} -(\mathcal{M}^S - \mathsf{diag}\ (d_i))^{-1}\mathcal{B} \\ 0 \end{pmatrix}$$

is such that $S^* > 0$. Further, as all eigenvalues have negative real parts, all solutions of (4.22) tend to this equilibrium. Thus, when $\mathcal{R}_0 < 1$, the DFE is globally asymptotically stable. The instability of the DFE when $\mathcal{R}_0 > 1$ is a direct consequence of [33, Theorem 2].

□

4.2.4 Uniform Persistence

Next we study the dynamics of model (4.2) when $\mathcal{R}_0 > 1$. So let $\mathcal{R}_0 > 1$ and define

$$\Omega := \left\{ \left(S(t)^T, L(t)^T, I(t)^T, T(t)^T\right) \in \mathbb{R}_+^{4p} : S(t), L(t), I(t), T(t) \leq \mathcal{H} \right\},$$

where $S := (S_1, \cdots, S_p)^T, L := (L_1, \cdots, L_p)^T, I := (I_1, \cdots, I_p)^T, T := (T_1, \cdots, T_p)^T, \mathcal{H} := \left(\frac{\Lambda_1}{d_1}, \cdots, \frac{\Lambda_p}{d_p}\right)^T$. In the interior of Ω, (4.2) is called to be *uniformly persistent* in $\mathring{\Omega}$ with respect to $\partial\Omega$, if there exists a constant vector $0 < \epsilon^T \in \mathbb{R}^p$ such that, any solution $\left(S(t)^T, L(t)^T, I(t)^T, T(t)^T\right)$ with initial value $\left(S(0)^T, L(0)^T, I(0)^T, T(0)^T\right) \in \mathring{\Omega}$,

$$\begin{aligned} \liminf_{t\to\infty} I(t) &\geq \epsilon & \liminf_{t\to\infty} L(t) &\geq \epsilon \\ \liminf_{t\to\infty} S(t) &\geq \epsilon & \liminf_{t\to\infty} R(t) &\geq \epsilon. \end{aligned} \tag{4.23}$$

The disease is endemic if model (4.2) is uniformly persistent as that means that both the infectious and the latent compartments persist above a certain positive level

when $\mathcal{R}_0 > 1$.

Theorem 4.2.5. *Model* (4.2) *is uniformly persistent in* $\mathring{\Omega}$ *with respect to* $\partial\Omega$ *if and only if* $\mathcal{R}_0 > 1$.

Proof. The necessity of $\mathcal{R}_0 > 1$ follows from theorem 4.2.4 because $\mathcal{R}_0 < 1$ implies that $\lim_{t\to\infty} I(t) = \lim_{t\to\infty} L(t) = \lim_{t\to\infty} T(t) = 0$. But since $\liminf_{t\to\infty} I(t) = \epsilon > 0$ implies $\lim_{t\to\infty} I(t) \neq 0$, if it exists, that implies $\mathcal{R}_0 \geq 1$. To prove sufficiency, we use theorem proved by Hofbauer and So in [16, Theorem 4.1]. For that, choose $\mathcal{X} := \mathbb{R}^{4p}_+$ to be the metric space with the normal metric d. Then $X := \Omega$ is the global attractor of $\mathcal{X}$ and define $\mathcal{Y} := \partial\Omega$. The maximal invariant set M in $\mathcal{Y}$ is the singleton set of the DFE , (4.8), which is isolated, therefore the first assumption of Theorem 4.1 in [16] holds. Finally to show that $W^s(M) \subset \mathcal{Y}$, since $\mathcal{R}_0 > 1$, then DFE is unstable and hence $W^s(M)$ is only the DFE itself, i.e. $W^s(M) \subset \mathcal{Y}$. Hence model (4.2) is uniformly persistence if and only if $\mathcal{R}_0 > 1$ [16, Theorem 4.1]. □

4.3 Numerical considerations

We consider the countries: Canada, China, India, Pakistan and the Philippines, as the latter four countries are with the highest migration rate to Canada. We mainly use data for 2010 since we also have transportation data for that year.

4.3.1 Parameter estimation

	Canada	China	India	Pakistan	Philippines
Population (milions)	34.017	1,348.932	1,224.614	173.593	93.261
Life expectancy (years)	80.8	73.3	65.1	65.2	68.5
GDP	46,212	4,433	1,375	1,017	2,140
Health expenditure	5,222	221	54	22	77

Tab. 4.1: Country-related data from [35]. Monetary amounts are given in current (as of 2013) US dollars. GDP and Health expenditure are per capita.

Estimates for 2010 of the population of Canada, China, India, Pakistan and the Philippines are given in Table 4.1. As a proxy for travel between these countries, we use IATA air travel data from the Bio.Diaspora Project (see, e.g., [4]), which details the number of trips between locations. Although the data is available for each month, to simplify the problem we use the total number of trips for 2010 between any two countries in this list and report this as a daily average in Table 4.2.

Movement rates and demography

	CA	CN	IN	PA	PH
Canada (CA)	–	1,274	985	515	209
China (CN)	1,268	–	703	893	174
India (IN)	900	678	–	144	90
Pakistan (PA)	489	859	148	–	12
Philippines (PH)	200	150	58	9	–

Tab. 4.2: Average number of trips per day in the IATA database (see, e.g., [4]) from one country (column) to another country (row). The two letter ISO 3166 code for the countries is indicated.

Converting Table 4.2 into effective movement rates requires to approximate some components, as the ODE model (4.2) is too simple to describe the complex reality of mobility pictured here. We proceed as follows:

1. Compute movement rates $\mathcal{M}^S$.

2. Set death rates d_i.

3. Using (4.8), find $\mathcal{B}$ so that $N = S^*$ at the DFE corresponds to the population of the various countries.

To compute movement rates, consider two countries in isolation from the others, say, Canada and China. We want to describe the actual number of movements between the countries. For a short time interval of, say, one day, we can neglect the

variation of population due to birth and death and thus consider those rates to be zero. Thus, after one day,

$$S_{\mathrm{CA}}(1) = e^{-m_{\mathrm{CN,CA}}} S_{\mathrm{CA}}(0),$$

where $S_{\mathrm{CA}}(1) - S_{\mathrm{CA}}(0) = -1,268$ is the loss of population in Canada from trips to China in one day. Thus,

$$m_{\mathrm{CN,CA}} = -\ln\left(1 - \frac{1,268}{S_{\mathrm{CA}}(0)}\right),$$

where $S_{\mathrm{CA}}(0)$ is the population of Canada. So, more generally, trips from X to Y occur at the rate

$$m_{\mathrm{YX}} = -\ln\left(1 - \frac{\Delta_{YX}}{S_{\mathrm{X}}(0)}\right),$$

where Δ_{YX} is the number of trips per day originating in X and terminating in Y. Using the population information, travel data in Table 4.2 and setting diagonal terms so that $\mathcal{M}^S$ has all column sums zero, we find

$$\mathcal{M}^S \simeq \begin{pmatrix} -8.4e-05 & 9.45e-07 & 7.94e-07 & 2.91e-06 & 2.2e-06 \\ 3.73e-05 & -2.20e-06 & 5.66e-07 & 5.05e-06 & 1.83e-06 \\ 2.65e-05 & 5.03e-07 & -1.53e-06 & 8.14e-07 & 9.47e-07 \\ 1.44e-05 & 6.37e-07 & 1.19e-07 & -8.82e-06 & 1.26e-07 \\ 5.88e-06 & 1.11e-07 & 4.67e-08 & 5.08e-08 & -5.11e-06 \end{pmatrix}.$$

Next, we estimate death rates by noting that $1/d_i$ is the average duration of life, with life duration exponentially distributed. Finally, we deduce from (4.8) the value $\mathcal{B} = (\mathsf{diag}\ (d_i) - \mathcal{M}^S)S^*$ such that the population in each country remains constant in the absence of disease if initial conditions are chosen equal to S^*.

Choosing parameters this way allows to focus on the effect of disease transmission irrespective of initial convergence of the underlying demographic model to the

equilibrium present in the absence of disease.

TB parameters

To identify TB related parameters, we use data from WHO [37], collected in Table 4.3 for convenience.

	CA	CN	IN	PA	PH
Population	34	1348	1241	177	95
Mortality	0.18	3.5	24	33	29
Prevalence	5.6	104	249	350	484
Incidence	4.5	75	181	231	270
Total new cases	1,332	865,059	1,211,441	255,094	192,343
Treatment success	76%	96%	88%	91%	91%

Tab. 4.3: Country-related data used in parameter identification. Data from [37] for 2011 except Treatment success, 2010. Population is in millions. Mortality, Prevalence and Incidence are per 100,000 population. Mortality excludes individuals coinfected with HIV, while Prevalence and Incidence includes them. Total new cases are TB case notifications. Treatment success is in percent of new smear-positive and/or culture-positive.

Estimation of the number of latently infected individuals is virtually impossible. Estimates vary widely even within a given country. As a consequence, we use a variation on the commonly used statement that one third of the world's population has latent TB infection (LTBI), weighting that value by the GDP and health expenditure per capita in Table 4.1 as well as incidence from Table 4.3. Canada has the highest GDP and health expenditure, and prevalence of TB skin test (TST) positivity in the general (not at specific risk) community were seen to vary from 0.9% in grade 10 students in Montréal to 33% in the personnel of a secondary school in Montérégie (Québec); see the studies referenced in [39]. We thus choose LTBI prevalence to be 15% in Canada. China is second best in per capita GDP and health expenditure and second lowest for incidence, we therefore use a prevalence of 20%. Finally, India, Pakistan and the Philippines are assumed to have a prevalence of 33%. The prevalence of LTBI is then transformed into the initial number of latently infected individuals in each country, $L_i(0)$.

Then we compute the total number of new cases in a year (including retreatment) and assume that all active TB cases undergo treatment. We further assume that the average duration of treatment is six months and that the detection of an active infection occurs equiprobably throughout the year. Thus, at the start of a new year (time 0), only individuals who developed active TB during the second half of the previous year are undergoing treatment, so we set $T_i(0)$ to be half of the total new cases. The initial condition for the number of individuals with active TB, i.e., $I_i(0)$, is taken as the difference between prevalence and incidence. Finally, $S_i(0)$ is chosen so that initial conditions match the country population.

To evaluate the rate of infection β_X in country X, we note that, from (4.2b), the number of new (primary infection) cases per unit time is $\beta_X S_X I_X / N_X$, where numbers in compartments are considered at $t = 0$. Equating this quantity to the number of new cases per day from Table 4.3 gives us a value of β_X. (By doing this, we neglect all other sources of change in the number of infections.)

Other rates are evaluated in a manner similar to that used for movement rates. If Δ_X is the number of deaths due to TB in a year in country X, then expressing this number per time unit,

$$\delta_X = -\ln\left(1 - \frac{\Delta_X}{I_X(0)}\right).$$

Note that we use here the number of individuals with active TB, not the total population. Indeed, δ_X acts on I_X, not N_X.

Suppose, again, that there were no other factors at play. Then the rate π_i of movement from L_i to I_i can be obtained by writing the variation of L_i due to new infections, $L_i' = -\pi_i L_i$ and solving for π_i. We find

$$\pi_X = -\ln\left(1 - \frac{\Delta_X}{L_X(0)}\right),$$

where Δ_X is the number of individuals having gone from LTBI to active TB in a year, which we take to be the number of new TB infections.

The rate of treatment t_{1i} of LTBI cases is very difficult to estimate. We take it to be very small, at it is the least likely method of treatment. The rate of treatment of infectious cases, on the other hand, is quite large since infectious cases are more easily detected.

4.3.2 Numerical results

In conclusion, we produce some simulations one that shows the convergence of the prevalence when $\mathcal{R}_0 < 1$ in Figure (4.3.2), another one that shows that the total population in each patch does not change too much with migration in Figure (4.3.2) and the last one is to show that asymptotic behaviour of the prevalence when $\mathcal{R}_0 > 1$ in Figure (4.3.2). In all simulations the number of the infected is per 100,000 people.

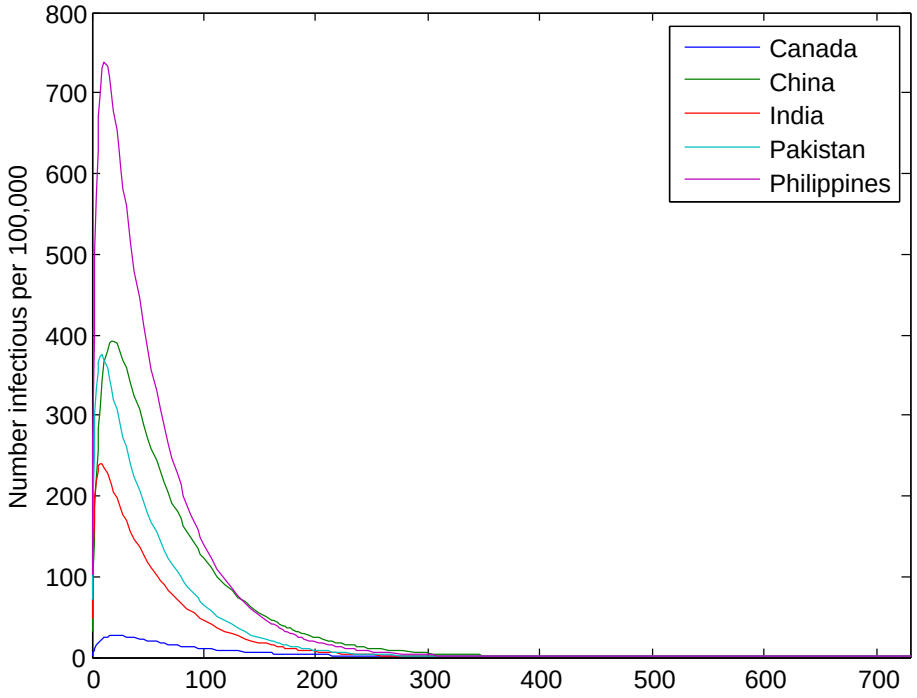

Fig. 4.2: The prevalence when $\mathcal{R}_0 < 1$.

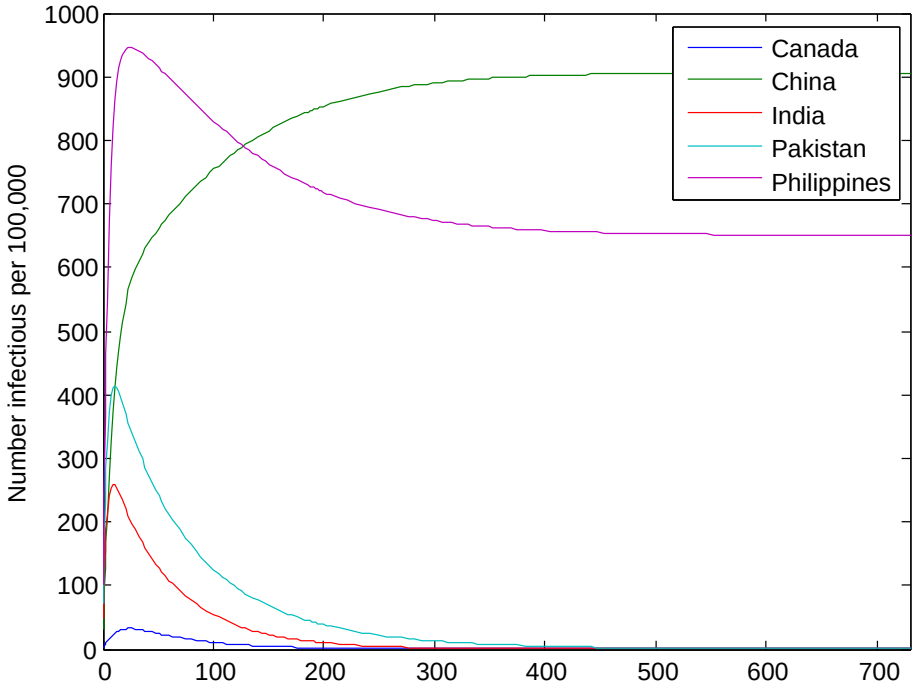

Fig. 4.3: The prevalence when $\mathcal{R}_0 > 1$.

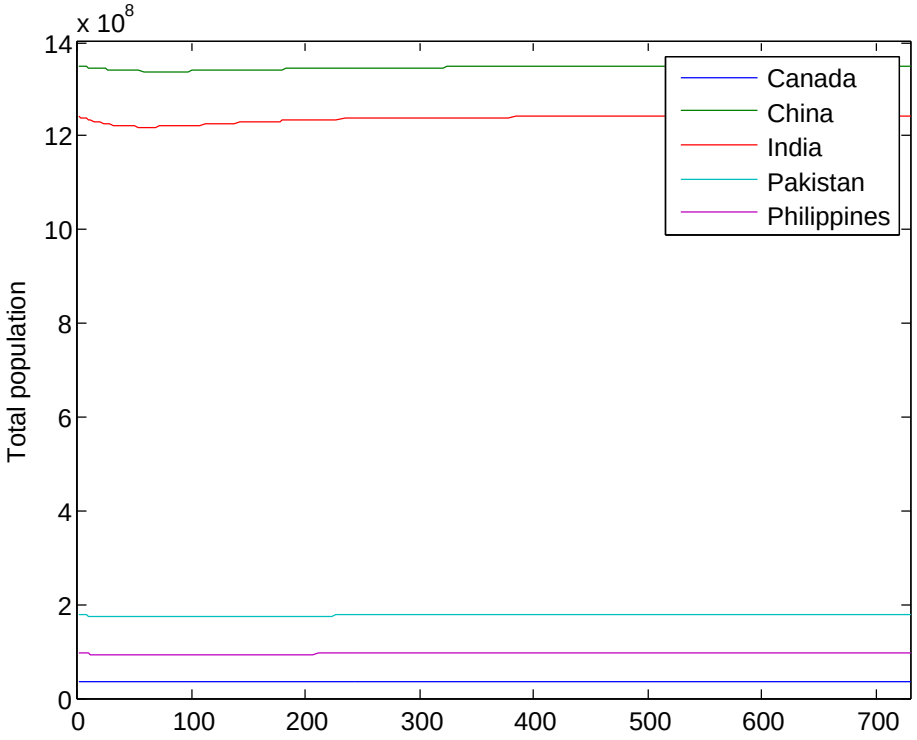

Fig. 4.4: The total population.

4.4 Summary

In this chapter, we analyzed model describing the dynamics of TB taking into account the migration. The two most important results proved in this chapter are

1. Model (4.2) has a globally asymptotically stable DFE when $\mathcal{R}_0 < 1$ (Theorem 4.2.4).

2. Model (4.2) is uniformly persistent when $\mathcal{R}_0 > 1$ (Theorem 4.2.5).

Considering the TB model given in [9] and model (4.2), the mathematical analyses done in this chapter shows that though the two models have two different DFE due to the linear migration, however the global stability of the DFE was preserved under the linear migration.

5. MODELLING MULTI-STRAIN TUBERCULOSIS

5.1 Introduction

Drug resistant tuberculosis (either MDR-TB or XDR-TB) makes it a considerable challenge to control TB, since treatment is less efficacious for a patient infected with MDR-TB or XDR-TB. In this chapter we consider modelling drug resistant tuberculosis.

5.2 The Model

We start by formulating a general deterministic mathematical model of the transmission of drug-sensitive, multidrug-resistant and extensively drug-resistant strains of TB. The population of interest is divided into eight compartments depending on their epidemiological stages, see Table 5.1.

Compartments		
Variable	Name	Interpretation
$S(t)$	Susceptible	have never encountered TB
$L_s(t)$	Latently infected with drug-sensitive TB	Infected with drug-sensitive TB but not infectious
$L_m(t)$	Latently infected with MDR TB	Infected with MDR-TB but not infectious
$L_x(t)$	Latently infected with XDR TB	Infected with XDR-TB but not infectious
$I_s(t)$	Sensitive drug TB infectious	Able to infect others with drug-sensitive strain
$I_m(t)$	MDR TB infectious	Able to infect others with MDR strain
$I_x(t)$	XDR TB infectious	Able to infect others with XDR strain
$R(t)$	Recovered	Recovered by getting a successfully treatment

Tab. 5.1: Description of the epidemiological states

The total population $N(t)$ is given by

$$N(t) = S(t) + L_s(t) + L_(t) + L_x(t) + I_s(t) + I_m(t) + I_x(t) + R(t) \tag{5.1}$$

Table 5.2 lists all parameters and their interpretation.

Parameter	Interpretation
λ	recruitment
β_s	drug-sensitive strain transmission coefficient
β_m	MDR strain transmission coefficient
β_x	XDR strain transmission coefficient
f_i	proportion of infected individuals that move to $L_i, i \in \{s, m, x\}$
$1 - f_i$	proportion of infected individuals making a fast trasition to $I_i, i \in \{s, m, x\}$
w_i	per-capita rate of endogenous reactivation of $L_i, i \in \{s, m, x\}$
α_{ij}	proportion of exogenous reinfection of L_i due to contact with $I_j, i \in \{s, m, x\}$
r_i	per-capita rate of I_i moving back to L_i without treatment $i \in \{s, m, x\}$
t_{s1}	per-capita rate of treatment for L_s
t_{s2}	per-capita rate of treatment for I_s
t_i	per-capita rate of treatment for $I_i, i \in \{m, x\}$
$1 - \sigma_i$	efficiency of treatment in preventing infection with strain $i, i \in \{s, m, x\}$
p_1	probability of treatment success for L_s
$1 - p_1$	proportion of L_s moved to L_m due to incomplete treatment or lack of strict compliance in the use of drugs
p_2	probability of treatment success for I_s
$1 - p_2$	proportion of I_s moved to L_m due to incomplete treatment or lack of strict compliance in the use of drugs
p_3	probability of treatment success for I_m
$1 - p_3$	proportion of I_m moved to L_x due to incomplete treatment or lack of strict compliance in the use of drugs
d	per-capita of natural death rate
μ_i	pre-capita rate of death due to TB of strain $i, i \in \{s, m, x\}$

Tab. 5.2: Description of model parameters

The flow diagram of the model is as in Figure 5.1.

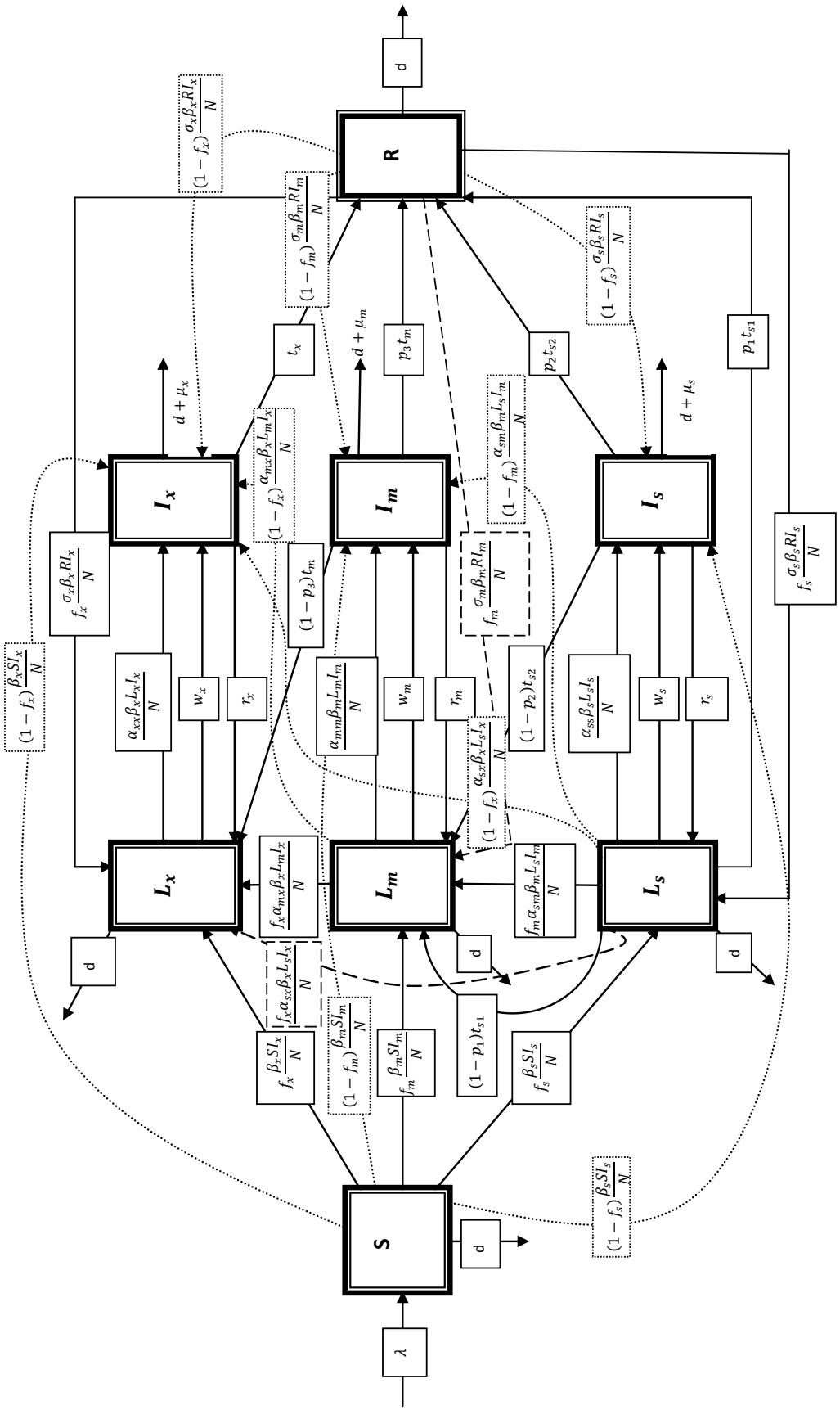

Fig. 5.1: Flow diagram of the model with drug-sensitive, MDR-TB and XDR-TB for a single population.

All these assumptions lead to a system of 8 ordinary differential equations describing the disease dynamics.

The evolution of the number of susceptible individuals in the population is governed by the following equation:

$$S' = \lambda - dS - \beta_s \frac{SI_s}{N} - \beta_m \frac{SI_m}{N} - \beta_x \frac{SI_x}{N} \tag{5.2a}$$

where λ is the rate at which new individuals join the population (birth) and the β_r, with $r \in \{s, m, x\}$ are coefficients indicating the rate at which new infections arise given contacts between susceptible and infectious individuals in the different infectious classes.

When an individual is infected with any strain of TB, that person leaves the S compartment and transitions to the latently infected compartment corresponding to the strain they were infected with, i.e., to compartment L_r, where $r \in \{s, m, x\}$. A proportion $1 - f_r$, where $r \in \{s, m, x\}$, of the infected individuals moves to infectious compartment I_r in what is called *fast infection*.

The number of latently infected individuals with drug-sensitive TB, $L_s(t)$, is increased by primary infections with the drug-sensitive strain I_s, at the rate $f_s\beta_s SI_s/N$, by reinfection of treated individuals at the rate $\sigma_s f_s \beta_s RI_s/N$ and by natural recovery of individuals in the drug-sensitive infectious compartment I_s at the per capita rate r_s. We assume that the efficiency $1 - \sigma_s$ of treatment is in $(0, 1)$, implying that treatment does indeed reduce the probability of reinfection. On the other hand, L_s decreases at the rate $\alpha_{sr}\beta_r$, where $r \in \{s, m, x\}$, due to reinfection or secondary infection with the same strain I_s, which is known as *exogenous reinfection* or a different strain I_m or I_x, following which the individual transitions from L_s to the corresponding infectious compartment. Treatment, natural death and natural progression to the infectious stage (due to a weakening immune system) also decrease the population in the L_s compartment. These facts are transcribed in the following

equation.

$$\begin{aligned} L_s' =& f_s\beta_s\frac{SI_s}{N} + \sigma_s f_s\beta_s\frac{RI_s}{N} - \alpha_{ss}\beta_s\frac{L_sI_s}{N} - \alpha_{sm}\beta_m\frac{L_sI_m}{N} \\ & - \alpha_{sx}\beta_x\frac{L_sI_x}{N} - \{d + w_s + t_{s1}\}\, L_s + r_sI_s. \end{aligned} \tag{5.2b}$$

Similarly to the drug-sensitive situation, the number L_m of individuals latently infected with MDR-TB increases when individuals in the S or R compartments are infected with MDR-TB. Reinfection in L_s by an MDR-TB strains occurs at the rate $f_m\alpha_{sm}\beta_m L_sI_m/N$ and developing resistance to the drugs offered to individuals infected with the drug-sensitive strain at rates $(1-p_1)t_{s1}$ and $(1-p_2)t_{s2}$ for latently infected and infectious individuals, respectively; both increase the population in L_m. The number of individuals in L_m decreases because of reinfection with I_x and exogenous reinfection at the rates $\alpha_{mx}\beta_x$ and $\alpha_{mm}\beta_m$, respectively. Taking into account the fact that unlike for individuals in L_s, treatment is not offered to either L_m or L_x, the rate of change of L_m is given by

$$\begin{aligned} L_m' = & f_m\beta_m\frac{SI_m}{N} + f_m\sigma_m\beta_m\frac{RI_m}{N} + f_m\alpha_{sm}\beta_m\frac{L_sI_m}{N} - \alpha_{mm}\beta_m\frac{L_mI_m}{N} \\ & - \alpha_{mx}\beta_x\frac{L_mI_x}{N} - \{d + w_m\}\, L_m + r_mI_m + (1-p_1)t_{s1}L_s \\ & + (1-p_2)t_{s2}I_s. \end{aligned} \tag{5.2c}$$

Similarly the rate of change of L_x is given by

$$\begin{aligned} L_x' = & f_x\beta_x\frac{SI_x}{N} + f_x\sigma_x\beta_x\frac{RI_x}{N} + f_x\alpha_{sx}\beta_x\frac{L_sI_x}{N} + f_x\alpha_{mx}\beta_x\frac{L_mI_x}{N} \\ & - \alpha_{xx}\beta_x\frac{L_xI_x}{N} - \{d + w_x\}\, L_x + r_xI_x + (1-p_3)t_mI_m. \end{aligned} \tag{5.2d}$$

To describe the rate of change of the numbers in infectious compartment I_s, we notice that natural recovery, natural death, death due to TB and failure of treatment

that causes resistance to drugs in I_s are the only reasons to leave I_s at rates r_s, d_s, μ_s and t_s, respectively. All other facts such as exogenous reinfection in L_s, fast infection in S or R and individuals who become infectious in L_s are feeding into I_s at rate $\alpha_{ss}\beta_s, (1-f_s)\beta_s$ and w_s respectively.

$$\begin{aligned} I_s' = \alpha_{ss}\beta_s\frac{L_sI_s}{N} + (1-f_s)\beta_s\left(\frac{SI_s}{N} + \sigma_s\frac{RI_s}{N}\right) + w_sL_s \\ - \{d+\mu_s+t_{s2}+r_s\}I_s. \end{aligned} \tag{5.2e}$$

Similarly, exogenous reinfection in L_m, fast infection in S, R or L_s and individuals who become infectious in L_m are feeding into I_m at the corresponding rates; see Table 5.2. Natural recovery, natural death, death due to TB and failure in treatment that causes resistance to drugs in I_m decrease I_m at rates given in Table 5.2.

$$\begin{aligned} I_m' = \alpha_{mm}\beta_m\frac{L_mI_m}{N} + w_mL_m - \{d+\mu_m+t_m+r_m\}I_m \\ + (1-f_m)\beta_m\left(\frac{SI_m}{N} + \sigma_m\frac{RI_m}{N} + \alpha_{sm}\frac{L_sI_m}{N}\right). \end{aligned} \tag{5.2f}$$

Similarly, the rate of change of I_x is given by

$$\begin{aligned} I_x' = \alpha_{xx}\beta_x\frac{L_xI_x}{N} + w_xL_x - \{d+\mu_x+t_x+r_x\}I_x \\ + (1-f_x)\alpha_{sx}\left(\beta_x\frac{L_sI_x}{N} + \alpha_{mx}\frac{L_mI_x}{N} + \frac{SI_x}{N} + \sigma_x\frac{RI_x}{N}\right). \end{aligned} \tag{5.2g}$$

Finally the rate of change of R depends positively on the proportion of individuals in L_s, I_s, I_m and I_x who successfully got treated and negatively on reinfection with the sensistive, MDR and XDR strains and natural death at rates given in Table 5.2.

$$\begin{aligned} R' = p_1t_{s1}L_s + p_2t_{s2}I_s + p_3t_mI_m + t_xI_x - \sigma_s\beta_s\frac{RI_s}{N} - \sigma_m\beta_m\frac{RI_m}{N} \\ - \sigma_x\beta_x\frac{RI_x}{N} - dR. \end{aligned} \tag{5.2h}$$

5.3 Mathematical Analysis

5.3.1 Basic Properties of Solutions

Proposition 5.3.1. *Given nonnegative initial conditions, solutions to* (5.2) *exist and are unique for all* $t \geq 0$. *Futhermore, the positive orthant* $\mathbb{R}^8_+$ *is positively invariant under the flow of* (5.2).

Proof. Since the vector field in (5.2) consists of sums of constants and rational polynomial functions in $S, L_s, L_m, L_x, I_s, I_m, I_x, R$ and the total population N is positive (as we will show later), it is differentiable.. Hence solutions to (5.2) exist and are unique.

To prove the nonnegativity of solutions, first consider S; setting $S = 0$ in (5.2a), we get

$$S' = \lambda > 0.$$

This implies that for nonnegative initial conditions $S(0) \geq 0$, $S(t)$ remains positive for all $t > 0$. Assume that the initial conditions are positive, i.e., $S(0) > 0, L_s(0) > 0, L_m(0) > 0, L_x(0) > 0, I_s(0) > 0, I_m(0) > 0, I_x(0) > 0$ and $R(0) > 0$. Consider L_s and assume that there exists $t_1 > 0$ such that $L_s(t_1) = 0$, and that t_1 is the first t for which any variable becomes zero. At t_1,

$$L_s'(t_1) = f_s\beta_s\frac{S(t_1)I_s(t_1)}{N(t_1)} + f_s\sigma_s\beta_s\frac{R(t_1)I_s(t_1)}{N(t_1)} + r_sI_s(t_1) > 0$$

But, if $L_s(t_1) = 0$, then $L_s'(t_1) \leq 0$ as initial conditions are positive (and for some interval $\mathcal{I} = [t_2, t_1), L_s'(t_1) < 0$), a contradiction. Then there is no t_1 such that $L_s(t_1) = 0$. Hence L_s is positive for all t. Similarly, the variables L_m, L_x, I_s, I_m, I_x and R are positive. □

Proposition 5.3.2. *Given nonnegative initial conditions, solutions to* (5.2) *are*

bounded for all $t \geq 0$. *Furthermore, the closed set*

$$\Omega := \Big\{ \big(S, L_s, L_m, L_x, I_s, I_m, I_x, R\big) \in \mathbb{R}^8_+ : \\ S + L_s + L_m + L_x + I_s + I_m + I_x + R \leq \frac{\lambda}{d} \Big\} \tag{5.3}$$

attracts the flow of (5.2) *for any initial condition in* $\mathbb{R}^8_+$.

Proof. To establish boundedness, we remark that the rate of change of the total population is given by

$$N' = \lambda - dN - \mu_s I_s - \mu_m I_m - \mu_x I_x \leq \lambda - dN. \tag{5.4}$$

This implies that $N(t)$ is bounded above by solutions of the differential equation $\Psi' = \lambda - d\Psi$, i.e., $N(t) \leq \max(\Psi(0), \lambda/d)$, with, for all sufficiently large t, $N(t) \leq \lambda/d$. Whence, since $S, L_s, L_m, L_x, I_s, I_m, I_x, R$ are nonnegative, $S, L_s, L_m, L_x, I_s, I_m, I_x, R$ are also bounded. Now consider Ω given by (5.3). We have that Ω is invariant, i.e., any solution of model (5.2) with initial condition in Ω remains in Ω for $t \geq 0$. Moreover, for any solution with initial condition outside Ω, i.e., $N \geq \frac{\lambda}{d}$, by (5.4) $N' < 0$. Thus Ω attracts all solutions of (5.2) with any initial condition in $\mathbb{R}^8_+$. □

5.3.2 Stability of Disease Free Equilibrium (DFE)

The system is at an equilibrium if the time derivatives in (5.2) are zero. An equilibrium is a disease free equilibrium (DFE) if $L_s = L_m = L_x = I_s = I_m = I_x = 0$. This implies that $R = 0$.

Thus at a DFE, (5.2) is such that $S = N = \frac{\lambda}{d}$. Then the unique DFE is given by

$$\mathcal{E}^* = \left(\frac{\lambda}{d}, 0, 0, 0, 0, 0, 0, 0\right). \tag{5.5}$$

Local Asymptotic Stability of the DFE

Linear stability of the DFE can be investigated using the next generation method [12, 33]. To derive a formula for $\mathcal{R}_0$ using the next generation method, we follow the method of [33] and order the infected variables as

$$\mathcal{I} := (L_s, L_m, L_x, I_s, I_m, I_x)^T .$$

The vector representing new infections into the infected classes $\mathcal{F}$ is given by

$$\mathcal{F} := \begin{pmatrix} f_s \left(\beta_s \frac{SI_s}{N} + \sigma_s \beta_s \frac{RI_s}{N}\right) \\ f_m \left(\beta_m \frac{SI_m}{N} + \sigma_m \beta_m \frac{RI_m}{N}\right) \\ f_x \left(\beta_x \frac{SI_x}{N} + \sigma_x \beta_x \frac{RI_x}{N}\right) \\ (1-f_s)\left(\beta_s \frac{SI_s}{N} + \beta_s \frac{RI_s}{N}\right) \\ (1-f_m)\left(\beta_m \frac{SI_m}{N} + \beta_m \frac{RI_m}{N}\right) \\ (1-f_x)\left(\beta_x \frac{SI_x}{N} + \sigma_x \beta_x \frac{RI_x}{N}\right) \end{pmatrix} . \tag{5.6}$$

The vector $\mathcal{V}$ representing other flows within and out of the infected classes $\mathcal{I}$ is given by

$$\mathcal{V} := \begin{pmatrix} \{d + w_s + t_{s1}\} L_s - r_s I_s \\ +\alpha_{ss}\beta_s \frac{L_s I_s}{N} + \alpha_{sm}\beta_m \frac{L_s I_m}{N} + \alpha_{sx}\beta_x \frac{L_s I_x}{N} \\ \\ \{d + w_m\} L_m - r_m I_m - (1-p_1) t_{s1} L_s - (1-p_2) t_{s2} I_s \\ -f_m \alpha_{sm}\beta_m \frac{L_s I_m}{N} + \alpha_{mm}\beta_m \frac{L_m I_m}{N} + \alpha_{mx}\beta_x \frac{L_m I_x}{N} \\ \\ \{d + w_x\} L_x - r_x I_x - (1-p_3) t_m I_m \\ -f_x \alpha_{sx}\beta_x \frac{L_s I_x}{N} - f_x \alpha_{mx}\beta_x \frac{L_m I_x}{N} + \alpha_{xx}\beta_x \frac{L_x I_x}{N} \\ \\ -\alpha_{ss}\beta_s \frac{L_s I_s}{N} + \{d + \mu_s + t_{s2} + r_s\} I_s - w_s L_s \\ \\ \{d + \mu_m + t_m + r_m\} I_m - w_m L_m \\ -\alpha_{mm}\beta_m \frac{L_m I_m}{N} - \alpha_{sm}\beta_m \frac{L_s I_m}{N} \\ \\ \{d + \mu_x + t_x + r_x\} I_x - w_x L_x - \alpha_{xx}\beta_x \frac{L_x I_x}{N} \\ -(1-f_x)\left(\alpha_{sx}\beta_x \frac{L_s I_x}{N} + \alpha_{mx}\beta_x \frac{L_m I_x}{N}\right) \end{pmatrix} \tag{5.7}$$

The matrix of new infections F and the matrix of transfers between compartments V are the Jacobian matrices obtained by differentiating $\mathcal{F}$ and $\mathcal{V}$ with respect to the infected variables $\mathcal{I}$ and evaluating at the disease free equilibrium (DFE). They take the form

$$F = \begin{pmatrix} 0 & A \\ 0 & B \end{pmatrix}, \qquad V = \begin{pmatrix} C & D \\ E & H \end{pmatrix}, \tag{5.8}$$

where

$$A = \begin{pmatrix} f_s\beta_s & 0 & 0 \\ 0 & f_m\beta_m & 0 \\ 0 & 0 & f_x\beta_x \end{pmatrix}, \quad B = \begin{pmatrix} (1-f_s)\beta_s & 0 & 0 \\ 0 & (1-f_m)\beta_m & 0 \\ 0 & 0 & (1-f_x)\beta_x \end{pmatrix},$$

$$C = \begin{pmatrix} d+w_s+t_{s1} & 0 & 0 \\ (-1+p_1)t_{s1} & d+w_m & 0 \\ 0 & 0 & d+w_x \end{pmatrix},$$

$$D = \begin{pmatrix} -r_s & 0 & 0 \\ (-1+p_2)t_{s2} & -r_m & 0 \\ 0 & (-1+p_3)t_m & -r_x \end{pmatrix},$$

$$H = \begin{pmatrix} d+mu_s+t_{s2}+r_s & 0 & 0 \\ 0 & d+mu_m+t_m+r_m & 0 \\ 0 & 0 & d+mu_x+t_x+r_x \end{pmatrix},$$

$$E = \begin{pmatrix} -w_s & 0 & 0 \\ 0 & -w_m & 0 \\ 0 & 0 & -w_x \end{pmatrix}.$$

Then the basic reproduction number $\mathcal{R}_0$ for system (5.2) is the spectral radius of the next generation matrix and is given by

$$\mathcal{R}_0 = \rho(FV^{-1}) = \max\left(\mathcal{R}_{0x}, \mathcal{R}_{0m}, \mathcal{R}_{0s}\right), \tag{5.9}$$

where

$$\mathcal{R}_{0x} = \frac{(w_x + (1-f_x)d)\,\beta_x}{d^2 + (t_x + \mu_x + w_x + r_x)\,d + w_x\,(t_x + \mu_x)}$$
$$\mathcal{R}_{0m} = \frac{(w_m + (1-f_m)d)\,\beta_m}{d^2 + (t_m + \mu_m + w_m + r_m)\,d + w_m\,(t_m + \mu_m)}$$
$$\mathcal{R}_{0s} = \frac{(w_s + (1-f_s)d + (1-f_s)t_{s1})\,\beta_s}{d^2 + (t_{s1} + t_{s2} + \mu_s + w_s + r_s)\,d + w_s\,(t_{s2} + \mu_s) + t_{s1}\,(t_{s2} + \mu_s + r_s)}$$

It is worth mentioning here that $\mathcal{R}_{0x}, \mathcal{R}_{0m}$ and $\mathcal{R}_{0s}$ are the basic reproduction numbers of the extensively drug resistant, multidrug resistant and drug-sensitive resistant strains respectively.

Lemma 5.3.3. *The DFE of model (5.2), given by* (5.5)*, is locally asymptotically stable if* $\mathcal{R}_0 < 1$ *and unstable if* $\mathcal{R}_0 > 1$*, where* $\mathcal{R}_0$ *is defined by* (5.9)*.*

Lemma 5.3.3 says that if the average numbers of new infections generated by a single individual infected with extensively drug resistant, multidrug resistant and drug-sensitive resistant strains are less than 1, then we can eliminate TB if the initial sizes of the subpopulations of the model are in the domain of attraction of the DFE. To ensure that the elimination is global, we should prove the global stability of the DFE. Before that, it is wise to check the possibility of existence of a backward bifurcation.

Existence of a Backward Bifurcation

Theorem 5.3.4. *In the absence of exogenous reinfection of* E_x*, i.e., if* $\alpha_{xx} = 0$*, or when the proportion of infected individuals making a fast trasition to* I_x*,* $(1 - f_x)$ *, is greater than or equal to the proportion of exogenous reinfection of* E_x *due to contact with* I_x*, i.e.*

$$\alpha_{xx} \leq (1 - f_x), \tag{5.10}$$

Model 5.2 has a forward bifurcation at $\mathcal{R}_0 = 1$. *Otherwise, the model has a backward bifurcation at* $\mathcal{R}_0 = 1$ *if*

$$(\alpha_{xx} + f_x - 1)(f_x\beta_x + r_x)d\Big(1 - \frac{w_x}{(w_x+d)^2} + \frac{w_x}{(w_x+d)}\Big) > f_x(1-\sigma_x)\left(\frac{w_x}{(w_x+d)} + t_x\right) + (1-f_x)d \tag{5.11}$$

Proof. The proof is using the Centre Manifold Theory given in [33, 10], see Appendix B. To use the Centre Manifold Theory, consider the model when $\mathcal{R}_0 = 1$ and using β_x as the bifurcation parameter, then

$$\beta_x = \frac{d^2 + (t_x + \mu_x + w_x + r_x)\,d + w_x\,(t_x + \mu_x)}{(w_x + (1-f_x)d)}. \tag{5.12}$$

Checking the eigenvalues of the Jacobian of model (5.2) evaluated at the DFE, $\mathcal{E}^*$, and β_x shows that 0 is a simple eigenvalue and all other eigenvalues have a negative real parts. Hence we can use Theorem B.1. The Jacobian of model (5.2) has a right eigenvector $\mathbf{w}$ (corresponding to the zero eigenvalue) given by

$$\mathbf{w} = \left[-\frac{w_7\beta_x}{d}, 0, 0, \frac{w_7(f_x\beta_x + r_x)}{d + w_x}, 0, 0, w_7 > 0, \frac{w_7 t_x}{d}\right]^T, \tag{5.13}$$

and a left eigenvector $\mathbf{v}$ given by

$$\mathbf{v} = \left[-\frac{w_7\beta_x}{d}, 0, 0, \frac{w_7(f_x\beta_x + r_x)}{d + w_x}, 0, 0, w_7 > 0, \frac{w_7 t_x}{d}\right]^T, \tag{5.14}$$

To use Theorem B.1, it is convenient to change the variable names as follows

$$S = x_1, L_s = x_2, L_m = x_3, L_x = x_4, I_s = x_5, I_m = x_6, I_x = x_7, R = x_8,$$

and the vector field in (5.2) as

$$(f_1, f_2, f_3, f_4, f_5, f_6, f_7, f_8) := (S', L'_s, L'_m, L'_x, I'_s, I'_m, I'_x, R').$$

Hence,

$$\begin{aligned} a :=& \sum_{i,j,k=1}^{8} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(\mathcal{E}^*, \beta_x), \\ =& \frac{2v_7 w_7^2 \beta_x d}{\lambda}\Big[-(f_x\beta_x + r_x)\frac{f_x + \alpha_{xx}}{(d+w_x)^2} - \frac{f_x}{(d+w_x)} - (f_x\beta_x + r_x)\frac{1 - f_x - \alpha_{xx}}{(d+w_x)} \\ & - t_x f_x \beta_x \frac{1-\sigma_x}{d(d+w_x)} - (1-f_x) - t_x(1-f_x)\frac{1-\sigma_x}{d}\Big], \end{aligned}$$

which is strictly negative if $\alpha_{xx} = 0$ or inequality (5.3.4) holds. Moreover, we can find that

$$b = \sum_{i,k=1}^{8} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \beta_x}(\mathcal{E}^*, \beta_x) = v_7 w_7 \frac{d(1-f_x) + w_x}{d + w_x} > 0$$

is always positive. Therefore, by Theorem B.1 Model (5.2) has a forward bifurcation at $\mathcal{R}_0 = 1$. If condition (5.3.4) is broken, then Model (5.2) goes under backward bifurcation if condition (5.11) holds.

□

Theorem 5.3.4 shows that model (5.2) develops a backward bifurcation only if the XDR strain has a backward bifurcation, regardless of whether or not the other two strains are in backward bifurcation. That is because, as can be noticed in the model, there is a vertical movement between the strains starting with the sensitive drug TB and terminating with the XDR strain. So, because of that movement, whether or not the first two strain are in backward bifurcation, the whole model will a develop backward bifurcation only if the terminal strain is in backward bifurcation.

Global Stability of the DFE

We now investigate the global stability of the DFE under the conditions that perclude a backward bifurcation.

Theorem 5.3.5. *Assume that*

$$0 \leq \alpha_{xx} \leq (1 - f_x), \tag{A$_1$}$$

$$0 \leq \alpha_{mm} \leq (1 - f_m), \tag{A$_2$}$$

$$0 \leq \alpha_{ss} \leq (1 - f_s). \tag{A$_3$}$$

Then the DFE (5.5) *of* (5.2) *is globally asymptotically stable when* $\mathcal{R}_0 < 1$.

Proof. Define $\mathcal{X} := (S, L_s, L_m L_x, I_s, I_m, I_x, R)$. We prove the global stability of the DFE by showing that if $\mathcal{R}_0 < 1$, then $\lim_{t\to\infty} \mathcal{X}(t) = \mathcal{E}^*$.

However, in this case system (5.2) is not of type K, therefore a standard comparison theorem is not applicable. Let $t_n \to \infty$ be a sequence such that $L_s(t_n) \to L_s^\infty =: \limsup L_s(t)$. Then $L_s(t_n)' \to 0$ using Lemma 2.1 in [31]. Then equation (5.2b) gives

$$\begin{aligned} 0 &= f_s\beta_s \frac{S + \sigma_s R}{N}(t_n) I_s(t_n) - \alpha_{ss}\beta_s \frac{L_s}{N}(t_n) I_s(t_n) - \alpha_{sm}\beta_m \frac{I_m}{N}(t_n) L_s(t_n) \\ &\quad - \alpha_{sx}\beta_x \frac{I_x}{N}(t_n) L_s(t_n) - \{d + w_s + t_{s1}\} L_s^\infty + r_s I_s(t_n) \\ &\leq f_s\beta_s \frac{S + \sigma_s R}{N}(t_n) I_s(t_n) - \{d + w_s + t_{s1}\} L_s^\infty + r_s I_s(t_n). \end{aligned}$$

Using the fact that $\dfrac{S(t) + \sigma_s R(t)}{N(t)} < 1$ and that $I_s(t) \leq I_s^\infty$ at any t, it follows that

$$L_s^\infty \leq \frac{f_s\beta_s + r_s}{d + w_s + t_{s1}} I_s^\infty. \tag{5.15}$$

Now let $s_n \to \infty$ be the sequence such that $I_s(s_n) \to I_s^\infty$; this again implies that $I_s(s_n)' \to 0$ [31, Lemma 2.1]. Then equation (5.2e) gives

$$\begin{aligned} 0 = \alpha_{ss}\beta_s \frac{L_s}{N}(s_n) I_s^\infty + (1-f_s)\beta_s \frac{S+\sigma_s R}{N}(s_n) I_s^\infty + w_s L_s(s_n) \\ - \left\{d + \mu_s + t_{s2} + r_s\right\} I_s^\infty. \end{aligned}$$

Using Assumption (A_3),

$$\begin{aligned} 0 \leq (1-f_s)\beta_s \frac{S+\sigma_s R + L_s}{N}(s_n) I_s^\infty + w_s L_s(s_n) \\ - \left\{d + \mu_s + t_{s2} + r_s\right\} I_s^\infty. \end{aligned}$$

For simplicity, define $a_1 := (d + \mu_s + t_{s2} + r_s)$ and $a_2 := (d + w_s + t_{s1})$. The fact that $\frac{S(t)+\sigma_s R(t)+L_s(t)}{N(t)} < 1$ and $L_s(t) \leq L_s^\infty$, together with equation (5.15) imply that

$$\begin{aligned} 0 &\leq \left[(1-f_s)\beta_s - a_1 + \frac{f_s\beta_s w_s + r_s w_s}{a_2}\right] I_s^\infty \\ &\leq \left[a_2(1-f_s)\beta_s - a_1 a_2 + f_s\beta_s w_s + r_s w_s\right] \frac{1}{a_2} I_s^\infty \\ &\leq \left[\mathcal{R}_{0s} - 1\right] \frac{1}{a_2(a_1 a_2 - w_s r_s)} I_s^\infty. \end{aligned} \tag{5.16}$$

Since $\mathcal{R}_0 = \max\{\mathcal{R}_{0s}, \mathcal{R}_{0m}, \mathcal{R}_{0x}\}$, $\mathcal{R}_0 < 1$ implies that $\mathcal{R}_{0s} < 1$. Therefore, (5.16) implies that $I_s^\infty = 0$. Hence, $\lim_{t\to\infty} I_s(t) = 0$. Similarly, using Assumptions (A_1) and (A_2), we can prove the following inequalities involving I_m and I_x

$$\begin{aligned} 0 &\leq \left[\mathcal{R}_{0m} - 1\right] \frac{1}{a_3(a_3 a_4 - w_m r_m)} I_m^\infty \\ 0 &\leq \left[\mathcal{R}_{0x} - 1\right] \frac{1}{a_5(a_5 a_6 - w_x r_x)} I_x^\infty, \end{aligned} \tag{5.17}$$

where

$$a_3 := d + w_m, \qquad a_4 := d + t_m + \mu_m + r_m, \tag{5.18}$$

$$a_5 := d + w_x, \qquad a_6 := d + t_x + \mu_x + r_x. \tag{5.19}$$

Inequalities (5.17) imply that $I_m^\infty = I_x^\infty = 0$ when $\mathcal{R}_0 < 1$, therefore $\lim_{t\to\infty} I_m(t) = \lim_{t\to\infty} I_x(t) = 0$. As a consequence, the total population $N(t)$ converges to λ/d (using (5.4)). To finish the proof, we study system (5.2) after the convergence of N, I_s, I_m and I_x, thereby reducing (5.2) to the following system

$$\begin{aligned} S' &= \lambda - dS \\ L_s' &= -\{d + w_s + t_{s1}\} L_s \\ L_m' &= -\{d + w_m\} L_m + (1-p_1) t_{s1} L_s \\ L_x' &= -\{d + w_x\} L_x \\ R' &= p_1 t_{s1} L_s - dR. \end{aligned} \tag{5.20}$$

The conclusion follows since model (5.20) is linear and clearly limits to $(\lambda/d, 0, 0, 0, 0)$.

□

Remark 3. *In the absence of the exogenous reinfection factor, Castillo-Chavez and Feng in [9] proved under certain conditions the global stability of the DFE of a drug-sensitive TB model and of two strains TB. Then considering the exogenous reinfection, Capurro, Castillo-Chavez and Feng in [8] considered a drug-sensitive TB strain only and showed the existence of the backward bifurcation phenomena because of exogenous reinfection. Theorem 5.3.5 shows that even with exogenous reinfection, there is a range for the exogenous reinfection parameter for which the model undergoes a forward bifurcation. Outside that range, the system undergoes a backward bifurcation as established in Theorem 5.3.4.*

Remark 4. *Conditions in Theorem 5.3.5 mean that although the existence of backward bifurcation of model* (5.2) *mainly depends on the existence of the backward bifurcation in the terminal group XDR strain as seen in Theorem 5.3.4, the global stability of the DFE of model* (5.2) *happens only when the DFE is globally asymptotically stable for each strain. This is shown in the following three theorems.*

Theorem 5.3.6. *Under assumption* (A_1)*, the DFE* (5.5) *of the submodel of the XDR-TB is globally a asymptotically stable.*

Proof. The submodel for XDR-TB in the absence of the other strains is as follows

$$S' = \lambda - dS - \beta_x \frac{SI_x}{N}, \tag{5.21a}$$

$$L_x' = f_x\beta_x \frac{SI_x}{N} + f_x\sigma_x\beta_x \frac{RI_x}{N} - \alpha_{xx}\beta_x \frac{L_xI_x}{N} - \{d + w_x\} L_x + r_xI_x, \tag{5.21b}$$

$$I_x' = \alpha_{xx}\beta_x \frac{L_xI_x}{N} + (1 - f_x)\beta_x \left(\frac{SI_x}{N} + \sigma_x \frac{RI_x}{N}\right) + w_xL_x - \{d + \mu_x + t_x + r_x\} I_x, \tag{5.21c}$$

$$R' = t_xI_x - \sigma_x\beta_x \frac{RI_x}{N} - dR. \tag{5.21d}$$

Similarly to the proof of Theorem 5.3.5, we prove the global stability of the DFE by showing that, if $\mathcal{R}_0 < 1$, then

$$\lim_{t\to\infty} S(t) = \frac{\lambda}{d}, \lim_{t\to\infty} I_x(t) = \lim_{t\to\infty} L_x(t) = \lim_{t\to\infty} R(t) = 0.$$

Here again, (5.21) is not of type K and a standard comparison theorem cannot be used. Again, let $t_n \to \infty$ be the sequence such that $L_x(t_n) \to L_x^\infty$. Then $L_x(t_n)' \to 0$ using Lemma 2.1 in [31]. Then equation (5.21b) gives

$$0 \leq f_x\beta_xI_x(t_n) - \{d + w_x\} L_x^\infty + r_xI_x(t_n) \tag{5.22}$$

$$L_x^\infty \leq \frac{f_x\beta_x + r_x}{d + w_x} I_x^\infty \tag{5.23}$$

Now let $s_n \to \infty$ be the sequence such that $I_x(s_n) \to I_x^\infty$, again implying that $I_x(s_n)' \to 0$ [31, Lemma 2.1]. Then equation (5.21c) gives

$$0 < \alpha_{xx}\beta_x \frac{L_x}{N}(s_n)I_x^\infty + (1-f_x)\beta_x \frac{S+\sigma_x R}{N}(s_n)I_x^\infty + w_x L_x(s_n) - \{d+\mu_x+t_x+r_x\} I_x^\infty.$$

Using Assumption (A_3), it follows from $\frac{S(t)+\sigma_s R(t)+L_s(t)}{N(t)} < 1$, $L_s(t) \leq L_s^\infty$ and equation (5.23) that

$$0 \leq [\mathcal{R}_{0x} - 1] \frac{1}{a_5(a_5a_6 - w_s r_s)} I_s^\infty. \tag{5.24}$$

where a_5 and a_6 are given by (5.19). If $\mathcal{R}_{0x} < 1$, then $I_x^\infty = 0$. Hence $\lim_{t\to\infty} I_x(t) = 0$. Moreover, the total population N converges to λ/d. To finish the proof, we study (5.21) after convergence of N and I_x, reducing it to the following model

$$\begin{aligned} S' &= \lambda - dS \\ L_x' &= -\{d+w_x\} L_x \\ R' &= -dR. \end{aligned} \tag{5.25}$$

The proof is finished by remarking that (5.25) is linear and converges to $(\lambda/d, 0, 0)$.

□

Theorem 5.3.7. *Under assumption* (A_2)*, the DFE* (5.5) *of the submodel for MDR - TB is globally asymptotically stable.*

Proof. Similar to the proof of Theorem 5.3.6 □

Theorem 5.3.8. *Under assumption* (A_3)*, the DFE* (5.5) *of the submodel for drug-sensitive TB is globally asymptotically stable.*

Proof. Similar to the proof of Theorem 5.3.6 □

In the rest of the chapter, we investigate further properties of model (5.2) under assumptions (A_1), (A_2) and (A_3).

5.3.3 Existence of Boundary Equilibria

In this section, we investigate the existence and stability of boundary equilibria where at least one of the infected variables is non-zero. It is important to notice that:

1. The TB drug-sensitive strain I_s happens only when susceptible or treated individuals acquire primary infection with the sensitive strain at the rate β_s.

2. There are three ways to generate individuals into the infected multidrug resistant TB strain class I_m,

   - when susceptible or treated individuals acquire primary infection with the resistant strain at the rate β_m;
   - when latently infected individuals with sensitives TB strain acquire secondary infection with the resistant strain at the rate $\alpha_{sm}\beta_m$;
   - when treated individuals infected (actively or latently) with the sensitive strain develop resistance to treatment with proportion $(1-p_1)$ and $(1-p_2)$.

3. Finally, to generate individuals into the infected extensively drug resistant TB strain class I_x, there are four ways:

   - when susceptible or treated individuals acquire primary infection with the XDR-TB strain at the rate β_x;
   - when latently infected individuals with sensitives TB strain acquire secondary infection with the XDR-TB strain at the rate $\alpha_{sx}\beta_x$;
   - when latently infected individuals with MDR-TB strain acquire secondary infection with the XDR-TB strain at the rate $\alpha_{mx}\beta_x$;
   - when treated individuals infected with the MDR-TB strain develop resistance to treatment with proportion $(1-p_3)$.

Taking this into account, we have in total 10 endemic and boundary equilibria.

Boundary equilibria: when one strain endemically exists only as follow

1. Drug sensitive TB only,

$$\mathcal{E}_s = (S^*, L_s^*, 0, 0, I_s^*, 0, 0, R^*)\,.$$

2. MDR-TB only,

$$\mathcal{E}_m = (S^*, 0, L_m^*, 0, 0, I_m^*, 0, R^*)\,.$$

3. XDR-TB only,

$$\mathcal{E}_x = (S^*, 0, 0, L_x^*, 0, 0, 0, I_x^*, R^*)\,.$$

Low endemicity coexistence equilibria: More than one strain exists in this type. But the existence of the resistant strain is due to treatment, not a new infection. E.g. $(S^*, L_s^*, L_m^*, 0, I_s^*, I_m^*, 0, R^*)$, in this case $\beta_m = 0$ but $L_m^* \neq 0, I_m^* \neq 0$ and $\lim_{t\to\infty} L_m^*(t) \neq 0, \lim_{t\to\infty} I_m^*(t) \neq 0$. The possible equilibria of this type are

4. $\mathcal{E}_{sm} = (S^*, L_s^*, L_m^{**}, 0, I_s^*, I_m^{**}, 0, R^*)$.
5. $\mathcal{E}_{mx} = (S^*, 0, L_m^*, L_x^{**}, 0, I_m^*, I_x^{**}, R^*)$.

Here the existence of $\mathcal{E}_{sm} = (S^*, L_s^*, 0, L_x^{**}, I_s^*, 0, I_x^{**}, R^*)$ is not possible as outflow of the drug sensitive strain goes into MDR strain, not the XDR one.

High endemicity co-existence equilibria: this type includes the new infections as well i.e., $\beta_i \neq 0,\ i \in \{s, m, x\}$. The possible equilibria of this type are

6. $\mathcal{E}_{sm}^* = (S^*, L_s^*, L_m^*, 0, I_s^*, I_m^*, 0, R^*)$.
7. $\mathcal{E}_{mx}^* = (S^*, 0, L_m^*, L_x^*, 0, I_m^*, I_x^*, R^*)$.
8. $\mathcal{E}_{smx}^* = (S^*, L_s^*, L_m^*, L_x^*, I_s^*, I_m^*, I_x^*, R^*)$.

Again, the existence of $\mathcal{E}^*_{sm} = (S^*, L^*_s, 0, L^*_x, I^*_s, 0, I^*_x, R^*)$ is not possible because even if we started with $L_m = 0$ and $I_m = 0$ but $L_s \neq 0$ and $I_s \neq 0$ then

$$L'_m = (1 - p_1)t_{s1}L_s + (1 - p_2)t_{s2}I_s > 0,$$

which implies that L_m will not remain 0, leading to

$$I'_m = w_m L_m > 0.$$

Mixed of high and low endemicity equilibira: this type occurs when one of the new infection rates is zero but the class is there due to the treatment inflow as following

9. $\mathcal{E}^{**}_{smx} = (S^*, L^*_s, L^*_m, L^{**}_x, I^*_s, I^*_m, I^{**}_x, R^*)$, when $\beta_x = 0$.
10. $\mathcal{E}^{**}_{sxm} = (S^*, L^*_s, L^{**}_m, L^*_x, I^*_s, I^{**}_m, I^*_x, R^*)$, when $\beta_m = 0$.

Drug-sensitive TB strain, $\mathcal{E}_s$, This equilibrium, $\mathcal{E}_s = (S^*, L^*_s, 0, 0, I^*_s, 0, 0, R^*)$, exists only when the drug-sensitive TB strain exists and the other two strains disappear. That would happen if $\beta_m = \beta_x = 0$ and the treatment did not induce resistance, i.e., $p_1 = p_2 = p_3 = 1$. To investigate the local stability of this equilibrium we consider the corresponding submodel of model (5.2) given by

$$S' = \lambda - dS - \beta_s \frac{SI_s}{N}, \tag{5.26a}$$

$$L_s' = f_s\beta_s \frac{SI_s}{N} + f_s\sigma_s\beta_s \frac{RI_s}{N} - \alpha_{ss}\beta_s \frac{L_sI_s}{N} - \{d + w_s + t_{s1}\} L_s + r_sI_s, \tag{5.26b}$$

$$L_m' = -\{d + w_m\} L_m + r_mI_m, \tag{5.26c}$$

$$L_x' = -\{d + w_x\} L_x + r_xI_x, \tag{5.26d}$$

$$I_s' = \alpha_{ss}\beta_s \frac{L_sI_s}{N} + (1 - f_s)\beta_s \left(\frac{SI_s}{N} + \sigma_s \frac{RI_s}{N} \right) + w_sL_s - \{d + \mu_s + t_{s2} + r_s\} I_s, \tag{5.26e}$$

$$I_m' = w_mL_m - \{d + \mu_m + t_m + r_m\} I_m, \tag{5.26f}$$

$$I_x' = w_xL_x - \{d + \mu_x + t_x + r_x\} I_x, \tag{5.26g}$$

$$R' = t_{s1}L_s + t_{s2}I_s + t_mI_m + t_xI_x - \sigma_s\beta_s \frac{RI_s}{N} - dR. \tag{5.26h}$$

Theorem 5.3.9. *Under assumption* (A_3)*, the boundary equilibrium*

$$\mathcal{E}_s = (S^*, L_s^*, 0, 0, I_s^*, 0, 0, R^*)$$

exists and is locally asymptotically stable when $\mathcal{R}_0 > 1$.

Proof. To show that we apply Theorem B.1 on model (5.26) and prove that the

constants a is always negative and b is always positive. Hence there exists a local asymptotically stable endemic equilibrium. In this case, we consider the model when $\mathcal{R}_0 = 1$ using β_s as a bifurcation parameter, then

$$\beta_s = \frac{d^2 + (t_{s1} + t_{s2} + \mu_s + w_s + r_s)\, d + w_s\,(t_{s2} + \mu_s) + t_{s1}\,(t_{s2} + \mu_s + r_s)}{(w_s + (1 - f_s)d + (1 - f_s)t_{s1})}. \quad (5.27)$$

Checking the eigenvalues of the Jacobian of model (5.26) evaluated at the DFE and β_s shows that 0 is a simple eigenvalue and all other eigenvalues have a negative real parts. Hence we can use Theorem B.1. The Jacobian of model (5.26) has a right eigenvector, $\mathbf{w}$, (corresponding to the zero eigenvector) given by

$$\mathbf{w} = \left[-\frac{w_5\beta}{d}, \frac{w_5(f_s\beta + r_s)}{d + w_s + t_{s1}}, 0, 0, w_5, 0, 0, \frac{w_5\,(t_{s1}(f_s\beta + r_s) + t_{s2}(d + w_s + t_{s1}))}{d(d + w_s + t_{s1})}\right]^T, \quad (5.28)$$

where $w_5 > 0$ and a left eigenvector ,$\mathbf{v}$, given by

$$\mathbf{v} = \left[0, \frac{w_s v_5}{(d + w_s + t_{s1})}, 0, 0, v_5 > 0, 0, 0, 0\right]^T, \quad (5.29)$$

with $v_5 > 0$. We change the variable names and the vector field in (5.26) as follows

$$S = x_1, L_s = x_2, L_m = x_3, L_x = x_4, I_s = x_5, I_m = x_6, I_x = x_7, R = x_8,$$

$$S' = f_1, L_s' = f_2, L_m' = f_3, L_x' = f_4, I_s' = f_5, I_m' = f_6, I_x' = f_7, R' = f_8.$$

Hence using assumption (A_3)

$$\begin{aligned}
a =& \sum_{i,j,k=1}^{8} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(\mathcal{E}^*, \beta_s), \\
=& \frac{2w_s v_5 w_5^2 \beta}{x_1^*} \left[-(f_s\beta + r_s)\frac{f_s + \alpha_{ss}}{(d + w_s + t_{s1})^2} - \frac{f_s}{(d + w_s + t_{s1})} - (f_s\beta + r_s)\frac{1 - f_s - \alpha_{ss}}{(d + w_s + t_{s1})} \right. \\
& - (t_{s1}(f_s\beta + r_s) + t_{s2}(d + w_s + t_{s1}))\, f_s \frac{1 - \sigma_s}{d(d + w_s + t_{s1})^2} - (1 - f_s) \\
& \left. - (t_{s1}(f_s\beta + r_s) + t_{s2}(d + w_s + t_{s1}))\,(1 - f_s)\frac{1 - \sigma_s}{d(d + w_s + t_{s1})} \right] < 0
\end{aligned}$$

and

$$\begin{aligned}
b =& \sum_{i,k=1}^{8} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \beta}(\mathcal{E}^*, \beta_s), \\
=& v_5 w_5 \frac{(d + t_{s1})(1 - f_s) + w_s}{(d + w_s + t_{s1})} > 0
\end{aligned}$$

Therefore as a is always negative and b is always positive under condition (A_3), then there exists a locally asymptotically stable equilibrium. At any equilibrium the model (5.26) implies $L_m = L_x = I_m = I_x = 0$. Hence , $\mathcal{E}_s = (S^*, L_s^*, 0, 0, I_s^*, 0, 0, R^*)$ exists and is locally asymptotically stable. □

Studying the local stability of the remaining 9 endemic and boundary equilibria is done in a manner similar to the proof of Theorem 5.3.9, by applying Theorem B.1 to the submodel corresponding to each endemic or boundary equilibrium. The following theorem summarizes this.

Theorem 5.3.10. *Under assumption* (A_1), (A_2) *and* (A_3), *the boundary and endemic equilibria*

$$
\begin{aligned}
\mathcal{E}_m &= (S^*, 0, L_m^*, 0, 0, I_m^*, 0, R^*)\,,\\
\mathcal{E}_x &= (S^*, 0, 0, L_x^*, 0, 0, 0, I_x^*, R^*)\,,\\
\mathcal{E}_{sm} &= (S^*, L_s^*, L_m^{**}, 0, I_s^*, I_m^{**}, 0, R^*)\,,\\
\mathcal{E}_{mx} &= (S^*, 0, L_m^*, L_x^{**}, 0, I_m^*, I_x^{**}, R^*)\,,\\
\mathcal{E}_{sm}^* &= (S^*, L_s^*, L_m^*, 0, I_s^*, I_m^*, 0, R^*)\,,\\
\mathcal{E}_{mx}^* &= (S^*, 0, L_m^*, L_x^*, 0, I_m^*, I_x^*, R^*)\,,\\
\mathcal{E}_{smx}^* &= (S^*, L_s^*, L_m^*, L_x^*, I_s^*, I_m^*, I_x^*, R^*)\,,\\
\mathcal{E}_{smx}^{**} &= (S^*, L_s^*, L_m^*, L_x^{**}, I_s^*, I_m^*, I_x^{**}, R^*)\,,\ \textit{when } \beta_x = 0,\\
\mathcal{E}_{sxm}^{**} &= (S^*, L_s^*, L_m^{**}, L_x^*, I_s^*, I_m^{**}, I_x^*, R^*)\,,\ \textit{when } \beta_m = 0,
\end{aligned}
$$

exist for their corresponding models and are locally asymptotically stable when $\mathcal{R}_0 > 1$.

Proof. Similar to the proof of Theorem 5.3.9 □

5.4 Summary

In this chapter, a new model to study the dynamics of drug-resistant TB is developed and comprehensively analyzed. The most important results proved in this chapter are:

1. System (5.2) has a globally asymptotically stable DFE when $\mathcal{R}_0 < 1$ (Theorem 5.3.5) under suitable conditions.

2. If condition (A_1) in Theorem 5.3.5 is broken, system (5.2) can undergo a backward bifurcation.

3. System (5.2) has 10 locally asymptotically stable endemic and boundary equilibria when $\mathcal{R}_0 > 1$ (Theorems 5.3.9 and 5.3.10).

6. THE EFFECT OF MIGRATION IN SPREADING RESISTANT TUBERCULOSIS

6.1 Introduction

One of the main objectives of this thesis is to study the role of migration in the spread of TB. In Chapter 4, we considered system (4.2), essentially a previously developed model for TB [9] in which we introduced linear migration. We qualitatively studied (4.2) and proved some results that show the effect of migration by comparing to the properties of the model without migration in [9]. Next, in Chapter 5, we developed system (5.2), which captures the most important facts about drug resistance in TB. We analyzed (5.2) and proved a number of results that helped us in understanding the mechanism of the spread of drug resistant TB. In this chapter, we proceed as in Chapter 4and introduce linear migration to system (5.2) to study the effect of migration in spreading the three strains of tuberculosis.

6.2 The Model

As in Chapter 4, we assume that we have p distinct geographical locations. Within each patch and in the absence of migration, the model describing transmission of TB is the one studied in Chapter 5, where the population of any patch i, where $i \in \{1, \cdots, p\}$, is divided into eight compartment depending on the epidemiological stage that an individual is in.

The total population of each patch is given by $N_i(t) = S_i(t) + L_{si}(t) + L_{mi}(t) +$

$L_{xi}(t) + I_{si}(t) + I_{si}(t) + I_{si}(t) + R_i(t)$ and the total population in the system is $N(t) = N_1(t) + \cdots + N_p(t)$. Table 6.1 lists parameters used in the model and their interpetation.

Parameter	Explanation
λ_i	recruitment coefficient in patch i
β_{si}	drug-sensitive strain transmission coefficient in patch i
β_{mi}	MDR strain transmission coefficient in patch i
β_{xi}	XDR strain transmission coefficient in patch i
f_{zi}	proportion of infected individuals that move to L_{zi} in patch i
$(1 - f_{zi})$	proportion of infected individuals making a fast transition to I_{zi} in patch i
w_{zi}	per-capita rate of endogenous reactivation of L_{zi} in patch i
α_{szi}	proportion of exogenous reinfection of L_{si} due to contact with $I_{zi}, s \in \{s, m, x\}$, in patch i
r_{zi}	per-capita rate of I_{zi} moving back to L_{zi} without treatment in patch i
$t_{s_1 i}$	per-capita of treatment rate for L_{si} in patch i
$t_{s_2 i}$	per-capita of treatment rate for I_{si} in patch i
t_{zi}	per-capita of treatment rate for I_z in patch i
$1 - \sigma_{zi}$	efficiency of treatment in preventing infection with strain z, in patch i
p_{1i}	probability of treatment success for L_{si} in patch i
$1 - p_{1i}$	proportion of L_{si} moved to L_{mi} in patch i due to incomplete treatment or lack of strict compliance in the use of drugs
p_{2i}	probability of treatment success for I_{si}, in patch i
$1 - p_{2i}$	proportion of I_{si} moved to L_{mi} in patch i due to incomplete treatment or lack of strict compliance in the use of drugs
p_{3i}	probability of treatment success for I_{mi}, in patch i
$1 - p_{3i}$	proportion of I_{mi} moved to L_{xi} in patch i due to incomplete treatment or lack of strict compliance in the use of drugs
d_i	per-capita of natural death rate in patch i
μ_{zi}	pre-capita rate of death due to TB of strain z, in patch i
m_{ij}^x	immigration rate from patch j to patch i of compartment $x \in \{S, L_s, L_m, L_x, I_s, I_m, I_x, R\}$

Tab. 6.1: Description of parameters in patch $i = 1, \ldots, p$. We use the index $z \in \{s, m, x\}$ when refering to a strain.

See Chapter 5 for a description of the parameters, which are the same here except that they are indexed by the patch number. In this model to study the migration between the patches we assume that the rates of movement of individuals between patches depend on disease status travel; travel is instantaneous and individuals do not change status during travel. Let $m_{ij}^S, m_{ij}^{L_s}, m_{ij}^{L_m}, m_{ij}^{L_x}, m_{ij}^{I_s}, m_{ij}^{I_m}, m_{ij}^{I_x}$, and m_{ij}^R denote the rate of travel from patch j to patch i of susceptible, latent, infective and treated individuals, respectively, where for all $i = 1, \ldots, p, m_{ii}^X = 0$ and $m_{ij}^X \geq 0$ for all $X \in \{S, L_s, L_m, L_x, I_s, I_m, I_x, R\}$. This structure defines a multi-digraph with patches

as vertices and arcs given by the travel rates, which can be represented by the mobility matrices $\mathcal{M}^S$, $\mathcal{M}^{L_s}$, $\mathcal{M}^{L_x}$, $\mathcal{M}^{L_x}$, $\mathcal{M}^I_s$, $\mathcal{M}^I_m$, $\mathcal{M}^I_x$ and $\mathcal{M}^T$, where, for a given epidemiological status $X \in \{S, L_s, L_m, L_x, I_s, I_m, I_x, R\}$,

$$\mathcal{M}^X = \begin{pmatrix} -\sum_{j=1}^{p} m^X_{j1} & m^X_{12} & \cdots & m^X_{1p} \\ m^X_{21} & -\sum_{j=1}^{p} m^X_{j2} & \cdots & m^X_{2p} \\ \vdots & \vdots & \ddots & \vdots \\ m^X_{p1} & m^X_{p2} & \cdots & -\sum_{j=1}^{p} m^X_{jp} \end{pmatrix}. \tag{6.1}$$

It is assumed that these matrices are irreducible.

Finally to write the model describing the dynamics of the three strains of TB along with the linear migration between the patches, we introduce new variables to simplify the model.

- For every $X_i \in \{S_i, L_{si}, L_{mi}, L_{xi}, I_{si}, I_{mi}, I_{xi}, R_i\}$ where $i = 1, \ldots, p$, define the vector X to be

$$X = \left(X_1, X_2, \ldots, X_p\right)^T.$$

- Define the variable $\mathcal{X}$ to be

$$\mathcal{X} := (S, L_s, L_m, L_x, I_s, I_m, I_x, R),$$

and

$$\mathcal{X}_i := (S_i, L_{si}, L_{mi}, L_{xi}, I_{si}, I_{mi}, I_{xi}, R_i).$$

- Define $\mathcal{G}_X$ to be the vector

$$\mathcal{G}_X = \begin{pmatrix} \mathcal{G}_{X_1} \\ \mathcal{G}_{X_2} \\ \vdots \\ \mathcal{G}_{X_p} \end{pmatrix} := \begin{pmatrix} X_1' \\ X_2' \\ \vdots \\ X_p' \end{pmatrix},$$

where $\mathcal{G}_{X_i}$ describes the evolution of compartment X_i in patch i for $i = 1, \ldots, p$.

Hence our model of concern describing the dynamics of TB resistant strains along with linear migration is given by $8p$ ordinary differential equations. The rate of change of S is given by

$$S' = \mathcal{G}_S(\mathcal{X}) + \mathcal{M}^S S, \tag{6.2a}$$

where using (5.2a),

$$\mathcal{G}_{S_i}(\mathcal{X}_i) := \lambda_i - d_i S_i - \beta_{si}\frac{S_i I_{si}}{N_i} - \beta_{mi}\frac{S_i I_{msi}}{N_i} - \beta_{xi}\frac{S_i I_{xi}}{N_i}.$$

The rate of change of L_s is given by

$$L_s' = \mathcal{G}_{L_s}(\mathcal{X}) + \mathcal{M}^{L_s} L_s, \tag{6.2b}$$

where using (5.2b),

$$\begin{aligned}\mathcal{G}_{L_{si}}(\mathcal{X}_i) := {} & f_{si}\beta_{si}\frac{S_i I_{si}}{N_i} + f_{si}\sigma_{si}\beta_{si}\frac{R_i I_{si}}{N_i} - \alpha_{ssi}\beta_{si}\frac{L_{si} I_{si}}{N_i} - \alpha_{smi}\beta_{mi}\frac{L_{si} I_{mi}}{N_i} \\ & - \alpha_{sxi}\beta_{xi}\frac{L_{si} I_{xi}}{N_i} - \{d_i + w_{si} + t_{s1i}\} L_{si} + r_{si} I_{si}.\end{aligned}$$

The rate of change of L_m is given by

$$L_m' = \mathcal{G}_{L_m}(\mathcal{X}) + \mathcal{M}^{L_m} L_m, \tag{6.2c}$$

where using (5.2c),

$$\begin{aligned}\mathcal{G}_{L_{mi}}(\mathcal{X}_i) := {} & f_{mi}\beta_{mi}\frac{S_i I_{mi}}{N_i} + f_{mi}\sigma_{mi}\beta_{mi}\frac{R_i I_{mi}}{N_i} + f_{mi}\alpha_{smi}\beta_{mi}\frac{L_{si}I_{mi}}{N_i} \\ & - \alpha_{mmi}\beta_{mi}\frac{L_{mi}I_{mi}}{N_i} - \alpha_{mxi}\beta_{xi}\frac{L_{mi}I_{xi}}{N_i} - \{d_i + w_{mi}\}L_{mi} + r_{mi}I_{mi} \\ & + (1-p_{1i})t_{s1i}L_{si} + (1-p_{2i})t_{s2i}I_{si}.\end{aligned}$$

The rate of change of L_x is given by

$$L'_x = \mathcal{G}_{L_x}(\mathcal{X}) + \mathcal{M}^{L_x}L_x, \tag{6.2d}$$

where using (5.2d),

$$\begin{aligned}\mathcal{G}_{L_{xi}}(\mathcal{X}_i) := {} & f_{xi}\beta_{xi}\frac{S_i I_{xi}}{N_i} + f_{xi}\sigma_{xi}\beta_{xi}\frac{R_i I_{xi}}{N_i} + f_{xi}\alpha_{sxi}\beta_{xi}\frac{L_{si}I_{xi}}{N_i} \\ & + f_{xi}\alpha_{mxi}\beta_{xi}\frac{L_{mi}I_{xi}}{N_i} - \alpha_{xxi}\beta_{xi}\frac{L_{xi}I_{xi}}{N_i} - \{d_i + w_{xi}\}L_{xi} \\ & + r_{xi}I_{xi} + (1-p_{3i})t_{mi}I_{mi}.\end{aligned}$$

The rate of change of I_s is given by

$$I'_s = \mathcal{G}_{I_s}(\mathcal{X}) + \mathcal{M}^{I_s}I_s, \tag{6.2e}$$

where using (5.2e),

$$\begin{aligned}\mathcal{G}_{I_{si}}(\mathcal{X}_i) := {} & \alpha_{ssi}\beta_{si}\frac{L_{si}I_{si}}{N_i} + (1-f_{si})\beta_{si}\frac{S_i I_{si}}{N_i} + (1-f_{si})\beta_{si}\sigma_{si}\frac{R_i I_{si}}{N_i} \\ & + w_{si}L_{si} - \{d_i + \mu_{si} + t_{s2i} + r_{si}\}I_{si}.\end{aligned}$$

The rate of change of I_m is given by

$$I'_m = \mathcal{G}_{I_m}(\mathcal{X}) + \mathcal{M}^{I_m}I_m, \tag{6.2f}$$

where using (5.2f),

$$\begin{aligned}\mathcal{G}_{I_{mi}}(\mathcal{X}_i) := {} & \alpha_{mmi}\beta_{mi}\frac{L_{mi}I_{mi}}{N_i} + (1-f_{mi})\beta_{mi}\frac{S_iI_{mi}}{N_i} + (1-f_{mi})\sigma_{mi}\beta_{mi}\frac{R_iI_{mi}}{N_i} \\ & + (1-f_{mi})\alpha_{smi}\beta_{mi}\frac{L_{si}I_{mi}}{N_i} + w_{mi}L_{mi} - \{d_i + \mu_{mi} + t_m + r_{mi}\}I_{mi}.\end{aligned}$$

The rate of change of I_x is given by

$$I_x' = \mathcal{G}_{I_x}(\mathcal{X}) + \mathcal{M}^{I_x}I_x, \tag{6.2g}$$

where using (5.2g),

$$\begin{aligned}\mathcal{G}_{I_{xi}}(\mathcal{X}_i) := {} & \alpha_{xxi}\beta_{xi}\frac{L_{xi}I_{xi}}{N_i} + (1-f_{xi})\alpha_{sxi}\beta_{xi}\frac{L_{si}I_{xi}}{N_i} + (1-f_{xi})\alpha_{mxi}\beta_{xi}\frac{L_{mi}I_{xi}}{N_i} \\ & + (1-f_{xi})\beta_{xi}\frac{S_iI_{xi}}{N_i} + (1-f_{xi})\sigma_{xi}\beta_{xi}\frac{R_iI_{xi}}{N_i} + w_{xi}L_{xi} \\ & - \{d_i + \mu_{xi} + t_{xi} + r_{xi}\}I_{xi}.\end{aligned}$$

Finally, the rate of change of R is given by

$$R' = \mathcal{G}_R(\mathcal{X}) + \mathcal{M}^R R, \tag{6.2h}$$

where using (5.2h),

$$\begin{aligned}\mathcal{G}_R(\mathcal{X}_i) := {} & p_{1i}t_{s1i}L_{si} + p_{2i}t_{s2i}I_{si} + p_{3i}t_mI_{mi} + t_xI_{xi} \\ & - \sigma_{si}\beta_{si}\frac{R_iI_{si}}{N}_i - \sigma_{mi}\beta_{mi}\frac{R_iI_{mi}}{N_i} - \sigma_{xi}\beta_{xi}\frac{R_iI_{xi}}{N_i} - d_iR_i.\end{aligned}$$

6.3 Mathematical Analysis

6.3.1 Properties of the Solutions

Proposition 6.3.1. *Given nonnegative initial conditions, solutions to* (6.2) *exist and are unique for all* $t \geq 0$. *Futhermore, the positive orthant* $\mathbb{R}^{8p}_+$ *is positively invariant under the flow of* (6.2).

Proof. By Proposition 5.3.1, the solutions of the isolated patches exist and the positive orthant $\mathbb{R}^8_+$ is positively invariant under the flow of (5.2). Thus, the result follows by Theorem 3.5.1. □

Proposition 6.3.2. *Given nonnegative initial conditions, solutions to* (6.2) *are bounded for all* $t \geq 0$. *Furthermore, the closed set*

$$\Omega := \Big\{ \Big(S, L_s, L_m, L_x, I_s, I_m, I_x, R \Big) \in \mathbb{R}^{8p}_+ : \\ S + L_s + L_m + L_x + I_s + I_m + I_x + R \leq D^{-1}\Lambda \Big\}, \quad (6.3)$$

attracts the flow of (6.2) *for any initial condition in* $\mathbb{R}^{8p}_+$, *where*

$$\Lambda = \begin{pmatrix} \lambda_1, & \ldots, & \lambda_p \end{pmatrix}^T \quad \textit{and} \quad D = \mathsf{diag}\,(d_i).$$

Proof. To establish boundedness, define $\mathcal{A} := \{S, L_s, L_m, L_x, I_s, I_m, I_x, R\}$ and note that in each patch i we have,

$$N_i' = \lambda_i - d_i N_i - \mu_{si} I_{si} - \mu_{mi} I_{mi} - \mu_{xi} I_{xi} + \sum_{X \in \mathcal{A}} \left(\sum_{j=1}^{p} m_{ij}^X X_j - \sum_{j=1}^{p} m_{ji}^X X_i \right). \quad (6.4)$$

Hence the total population satisfies

$$N' = \Lambda - \sum_{i=1}^{p} d_i N_i - \sum_{i=1}^{p} (\mu_{si} I_{si} + \mu_{mi} I_{mi} + \mu_{xi} I_{xi}) + \sum_{i=1}^{p} \sum_{X \in \mathcal{A}} \left(\sum_{j=1}^{p} m_{ij}^{X} X_j - \sum_{j=1}^{p} m_{ji}^{X} X_i \right) \tag{6.5}$$

where $\Lambda := \sum_{i=1}^{p} \lambda_i$. Now, as shown in Chapter 4,

$$\sum_{i=1}^{p} \sum_{X \in \mathcal{A}} \left(\sum_{j=1}^{p} m_{ij}^{X} X_j - \sum_{j=1}^{p} m_{ji}^{X} X_i \right) = 0,$$

then defining $\underline{d} := \min_{i=1,\ldots,p} \{d_i\}$, equation (6.5) for the total population gives

$$N' \leq \Lambda - \underline{d} N. \tag{6.6}$$

This implies that $N(t)$ is bounded above by solutions of the differential equation $\Psi' = \Lambda - \underline{d}\Psi$, i.e., $N(t) \leq \max(\Psi(0), \Lambda/\underline{d})$, with, for all sufficiently large t, $N(t) \leq \Lambda/\underline{d}$. Whence, since $N = \sum_{i=1}^{p} N_i$ and each $N_i \geq 0$, N_i is also bounded for each i, and for the same reason $S_i, L_{si}, L_{mi}, L_{xi}, I_{si}, I_{mi}, I_{xi}, R_i$ are bounded for each i. Now consider Ω defined (6.3). Any solution of model (6.2) with initial condition in Ω remains in Ω for $t \geq 0$. Moreover, for any solution outside Ω, i.e., with $N(t) \geq \frac{\Lambda}{d}$ for some t, by (6.5), $N' < 0$ until such time as $N(t) \leq \frac{\Lambda}{d}$. Thus Ω attracts all solutions of (6.2) with any initial condition in $\mathbb{R}_{+}^{8p}$.

□

6.3.2 Stability of the Disease Free Equilibrium (DFE)

The metapopulation is at an equilibrium if the time derivatives in (6.2) are zero. Patch i is at a disease free equilibrium (DFE) if

$$L_{si} = L_{mi} = L_{xi} = I_{si} = I_{mi} = I_{xi} = 0, \quad \forall i = 1, \ldots, p.$$

This implies that $R_i = 0, \forall i = 1, \ldots, p$, as established in the following result.

Lemma 6.3.3. *Given system* (6.2)*, suppose that*

$$L_{si} = L_{mi} = L_{xi} = I_{si} = I_{mi} = I_{xi} = 0,$$

for all $i = 1, ..., p$*. Then*

$$R_i = 0, \quad \forall i = 1, ..., p.$$

Proof. See [2]. □

Thus, at a DFE, (6.2) is such that $S_i = N_i$, $\forall i = 1, \ldots, p$ and satisfies

$$S_i' = \lambda_i - d_i S_i + \sum_{j=1}^{p} m_{ij}^S S_j - \sum_{j=1}^{p} m_{ji}^S S_i, \tag{6.7}$$

which has the following matrix/vector form

$$S' = \mathcal{B} + \left(\mathcal{M}^S - \mathsf{diag}\ (d_i)\right) S, \tag{6.8}$$

where $\mathcal{B} = (\lambda_1, \lambda_2, \ldots, \lambda_p)^T \in \mathbb{M}_{p\times 1}$. Then the DFE is given by

$$\left(\left(\mathsf{diag}\ (d_i) - \mathcal{M}^S\right)^{-1} \mathcal{B}, 0, 0, 0\right). \tag{6.9}$$

By Gershgorin's circle theorem, all eigenvalues of $\mathcal{M}^S$ have nonpositive real parts. Therefore, shifting them by $-d_i < 0$ ensures that all eigenvalues of $\mathsf{diag}\ (d_i) - \mathcal{M}^S$ have strictly negative real parts. Hence $\mathsf{diag}\ (d_i) - \mathcal{M}^S$ is an invertible matrix implying that the DFE is unique. Also, it is shown in [2] that a matrix of the form $\mathsf{diag}\ (d_i) - \mathcal{M}^S$ is an $M-$matrix, implying that $\left(\mathsf{diag}\ (d_i) - \mathcal{M}^S\right)^{-1} \geq 0$. So the DFE is indeed nonnegative.

Local Asymptotic Stability of the DFE

Linear stability of the DFE (6.9) can be investigated using the next generation method [12, 33]. To derive a formula for $\mathcal{R}_0$ using the next generation method, we follow the method of [33] and order the infected variables as

$$\mathcal{I} = (L_s, L_m, L_x, I_s, I_m, I_x)^T,$$

where $X = \left(X_1, X_2, \ldots, X_p\right)^T$, for every $X \in \{L_s, L_m, L_x, I_s, I_m, I_x\}$. The vector representing new infections into the infected classes $\mathcal{F}$ is given by

$$\mathcal{F} := \begin{pmatrix} A_1^T & A_2^T & A_3^T & A_4^T & A_5^T & A_6^T \end{pmatrix}^T, \tag{6.10}$$

where

$$A_1 := \begin{pmatrix} f_{s1}\beta_{s1}\left(S_1 + \sigma_{s1}R_1\right)\frac{I_{s1}}{N_1} \\ \vdots \\ f_{sp}\beta_{sp}\left(S_p + \sigma_{sp}R_p\right)\frac{I_{sp}}{N_p} \end{pmatrix},$$

$$A_2 := \begin{pmatrix} f_{m1}\beta_{m1}\left(S_1 + \sigma_{m1}R_1\right)\frac{I_{m1}}{N_1} \\ \vdots \\ f_{mp}\beta_{mp}\left(S_p + \sigma_{mp}R_p\right)\frac{I_{mp}}{N_p} \end{pmatrix},$$

$$A_3 := \begin{pmatrix} f_{x1}\beta_{x1}\left(S_1 + \sigma_{x1}R_1\right)\frac{I_{x1}}{N_1} \\ \vdots \\ f_{xp}\beta_{xp}\left(S_p + \sigma_{xp}R_p\right)\frac{I_{xp}}{N_p} \end{pmatrix},$$

$$A_4 := \begin{pmatrix} \beta_{s1}(1-f_{s1})\left(S_1 + \sigma_{s1}R_1\right)\frac{I_{s1}}{N_1} \\ \vdots \\ \beta_{sp}(1-f_{sp})\left(S_p + \sigma_{sp}R_p\right)\frac{I_{sp}}{N_p} \end{pmatrix},$$

$$A_5 := \begin{pmatrix} \beta_{m1}(1-f_{m1})\left(S_1 + \sigma_{m1}R_1\right)\frac{I_{m1}}{N_1} \\ \vdots \\ \beta_{mp}(1-f_{mp})\left(S_p + \sigma_{mp}R_p\right)\frac{I_{mp}}{N_p} \end{pmatrix},$$

$$A_6 := \begin{pmatrix} \beta_{x1}(1-f_{x1})\left(S_1 + \sigma_{x1}R_1\right)\frac{I_{x1}}{N_1} \\ \vdots \\ \beta_{xp}(1-f_{xp})\left(S_p + \sigma_{xp}R_p\right)\frac{I_{xp}}{N_p} \end{pmatrix}.$$

The vector $\mathcal{V}$ representing other flows within and out of the infected classes $\mathcal{I}$ is given by

$$\mathcal{V} := -\begin{pmatrix} B_1^T & B_2^T & B_3^T & B_4^T & B_5^T & B_6^T \end{pmatrix}^T, \tag{6.11}$$

where

$$B_1 := \begin{pmatrix} -\left(\alpha_{ss1}\beta_{s1}I_{s1} + \alpha_{sm1}\beta_{m1}I_{m1} + \alpha_{sx1}\beta_{x1}I_{x1}\right)\frac{L_{s1}}{N_1} \\ -\left\{d_1 + w_{s1} + t_{s11}\right\}L_{s1} + r_{s1}I_{s1} + \sum_{j=1}^{p} m_{1j}^{L_s} L_{sj} \\ \vdots \\ -\left(\alpha_{ssp}\beta_{sp}I_{sp} + \alpha_{smp}\beta_{mp}I_{mp} + \alpha_{sxp}\beta_{xp}I_{xp}\right)\frac{L_{sp}}{N_p} \\ -\left\{d_p + w_{sp} + t_{s1p}\right\}L_{sp} + r_{sp}I_{sp} + \sum_{j=1}^{p} m_{pj}^{L_s} L_{sj} \end{pmatrix},$$

$$B_2 := \begin{pmatrix} \alpha_{sm1}f_{m1}\beta_{m1}\frac{L_{s1}I_{m1}}{N_1} + \left(-f_{m1}\beta_{m1}\alpha_{mm1}I_{m1} - \alpha_{mx1}\beta_{x1}I_{x1}\right)\frac{L_{s1}}{N_1} \\ -\left\{d_1 + w_{m1}\right\}L_{m1} + r_{m1}I_{m1} + (1-p_{11})t_{s11}L_{s1} \\ +(1-p_{21})t_{s21}I_{s1} + \sum_{j=1}^{p} m_{1j}^{L_m} L_{mj} \\ \vdots \\ \alpha_{smp}f_{mp}\beta_{mp}\frac{L_{sp}I_{mp}}{N_p} + \left(-f_{mp}\beta_{mp}\alpha_{mmp}I_{mp} - \alpha_{mxp}\beta_{xp}I_{xp}\right)\frac{L_{sp}}{N_p} \\ -\left\{d_p + w_{mp}\right\}L_{mp} + r_{mp}I_{mp} + (1-p_{1p})t_{s1p}L_{sp} \\ +(1-p_{2p})t_{s2p}p_{sp} + \sum_{j=1}^{p} m_{pj}^{L_m} L_{mj} \end{pmatrix},$$

$$B_3 := \begin{pmatrix} f_{x1}\beta_{x1}\left(\alpha_{sx1}L_{s1} + \alpha_{mx1}L_{m1}\right)\frac{I_{x1}}{N_1} - \alpha_{xx1}\beta_{x1}\frac{L_{x1}I_{x1}}{N_1} - \left\{d_1 + w_{x1}\right\}L_{x1} \\ +r_{x1}I_{x1} + (1-p_{31})t_{m1}I_{m1} + \sum_{j=1}^{p} m_{1j}^{L_x} L_{xj} \\ \vdots \\ f_{xp}\beta_{xp}\left(\alpha_{sxp}L_{sp} + \alpha_{mxp}L_{mp}\right)\frac{L_{sp}I_{xp}}{N_p} - \alpha_{xxp}\beta_{xp}\frac{L_{xp}I_{xp}}{N_p} - \left\{d_p + w_{xp}\right\}L_{xp} \\ +r_{xp}I_{xp} + (1-p_{3p})t_{mp}I_{mp} + \sum_{j=1}^{p} m_{pj}^{L_x} L_{xj} \end{pmatrix},$$

$$B_4 := \begin{pmatrix} \alpha_{ss1}\beta_{s1}\frac{L_{s1}I_{s1}}{N_1} + w_{s1}L_{s1} - \{d_1 + \mu_{s1} + t_{s21} + r_{s1}\} I_{s1} + \sum_{j=1}^{p} m_{1j}^{I_s} I_{sj} \\ \vdots \\ \alpha_{ssp}\beta_{sp}\frac{L_{sp}I_{sp}}{N_p} + w_{sp}L_{sp} - \{d_p + \mu_{sp} + t_{s2p} + r_{sp}\} I_{sp} + \sum_{j=1}^{p} m_{pj}^{I_s} I_{sj} \end{pmatrix},$$

$$B_5 := \begin{pmatrix} (\alpha_{mm1}\beta_{m1}L_{m1} + (1-f_{m1})\alpha_{sm1}\beta_{m1}L_{s1})\frac{I_{m1}}{N_1} + w_{m1}L_{m1} \\ -\{d_1 + \mu_{m1} + t_{m1} + r_{m1}\} I_{m1} + \sum_{j=1}^{p} m_{1j}^{I_m} I_{mj} \\ \vdots \\ (\alpha_{mmp}\beta_{mp}L_{mp} + (1-f_{mp})\alpha_{smp}\beta_{mp}L_{sp})\frac{I_{mp}}{N_p} + w_{mp}L_{mp} \\ -\{d_p + \mu_{mp} + t_{mp} + r_{mp}\} I_{mp} + \sum_{j=1}^{p} m_{pj}^{I_m} I_{mj} \end{pmatrix},$$

$$B_6 := \begin{pmatrix} (\alpha_{xx1}\beta_{x1}L_{x1} + (1-f_{x1})\alpha_{sx1}\beta_{x1}L_{s1} + (1-f_{x1})\alpha_{mx1}\beta_{x1}L_{m1})\frac{I_{x1}}{N_1} \\ +w_{x1}L_{x1} - \{d_1 + \mu_{x1} + t_{x1} + r_{x1}\} I_{x1} + \sum_{j=1}^{p} m_{1j}^{I_x} I_{xj} \\ \vdots \\ (\alpha_{xxp}\beta_{xp}L_{xp} + (1-f_{xp})\alpha_{sxp}\beta_{xp}L_{sp} + (1-f_{xp})\alpha_{mxp}\beta_{xp}L_{mp})\frac{I_{xp}}{N_p} \\ +w_{xp}L_{xp} - \{d_p + \mu_{xp} + t_{xp} + r_{xp}\} I_{xp} + \sum_{j=1}^{p} m_{pj}^{I_x} I_{xj} \end{pmatrix},$$

using $m_{ii}^X = -\sum_{j=1}^{p} m_{ji}^X$ for $X \in \{S, L_s, L_m, L_m, L_x, I_s, I_m, I_x, R\}$ and $i = 1, \ldots, p$. The matrix of new infections F and the matrix of transfers between compartments V are the Jacobian matrices obtained by differentiating $\mathcal{F}$ and $\mathcal{V}$ with respect to the

infected variables $\mathcal{I}$ and evaluating at the disease free equilibrium (DFE). They take the form

$$F = \begin{pmatrix} (0)_{3p\times 3p} & F_{12} \\ (0)_{3p\times 3p} & F_{22} \end{pmatrix}, \tag{6.12}$$

$$V = \begin{pmatrix} V_{11} & V_{12} \\ V_{21} & V_{22} \end{pmatrix}, \tag{6.13}$$

where

$$F_{12} := \begin{pmatrix} \mathsf{diag}\ (f_{si}\beta_{si}) & (0)_{p\times p} & (0)_{p\times p} \\ (0)_{p\times p} & \mathsf{diag}\ (f_{mi}\beta_{mi}) & (0)_{p\times p} \\ (0)_{p\times p} & (0)_{p\times p} & \mathsf{diag}\ (f_{xi}\beta_{xi}) \end{pmatrix},$$

$$F_{22} := \begin{pmatrix} \mathsf{diag}\ (\beta_{si}(1-f_{si})) & (0)_{p\times p} & (0)_{p\times p} \\ (0)_{p\times p} & \mathsf{diag}\ (\beta_{mi}(1-f_{mi})) & (0)_{p\times p} \\ (0)_{p\times p} & (0)_{p\times p} & \mathsf{diag}\ (\beta_{xi}(1-f_{xi})) \end{pmatrix}.$$

$$V_{11} := \begin{pmatrix} C_1 - \mathcal{M}^{L_s} & (0)_{p^2} & (0)_{p^2} \\ -\mathsf{diag}\ ((1-p_{1i})t_{s1i}) & C_2 - \mathcal{M}^{L_m} & (0)_{p^2} \\ (0)_{p^2} & (0)_{p^2} & C_3 - \mathcal{M}^{L_x} \end{pmatrix},$$

$$V_{12} := \begin{pmatrix} -\mathsf{diag}\ (r_{si}) & (0)_{p^2} & (0)_{p^2} \\ -\mathsf{diag}\ ((1-p_{2i})t_{s2i}) & -\mathsf{diag}\ (r_{mi}) & (0)_{p^2} \\ (0)_{p^2} & -\mathsf{diag}\ ((1-p_{3i})t_{mi}) & -\mathsf{diag}\ (r_{xi}) \end{pmatrix},$$

$$V_{21} := \begin{pmatrix} -\mathsf{diag}\ (w_{si}) & (0)_{p^2} & (0)_{p^2} \\ (0)_{p^2} & -\mathsf{diag}\ (w_{si}) & (0)_{p^2} \\ (0)_{p^2} & (0)_{p^2} & -\mathsf{diag}\ (w_{xi}) \end{pmatrix},$$

$$V_{22} := \begin{pmatrix} C_4 - \mathcal{M}^{I_s} & (0)_{p^2} & (0)_{p^2} \\ (0)_{p^2} & C_5 - \mathcal{M}^{I_m} & (0)_{p^2} \\ (0)_{p^2} & (0)_{p^2} & C_6 - \mathcal{M}^{I_x} \end{pmatrix},$$

where

$$C_1 := \mathsf{diag}\ (d_i + w_{si} + t_{s1i}),\ C_2 := \mathsf{diag}\ (d_i + w_{mi}),\ C_3 := \mathsf{diag}\ (d_i + w_{xi}),$$

$$C_4 := \mathsf{diag}\ (d_i + \mu_{si} + t_{s2i} + r_{si}),\ C_5 := \mathsf{diag}\ (d_i + \mu_{mi} + t_{mi} + r_{mi}),$$

$$C_6 := \mathsf{diag}\ (d_i + \mu_{xi} + t_{xi} + r_{xi}).$$

Then the basic reproduction number $\mathcal{R}_0$ for system (6.2) is the spectral radius of the next generation matrix and is given by

$$\mathcal{R}_0 = \rho(FV^{-1}) = \rho \begin{pmatrix} F_{12}\tilde{V}_{21} & F_{12}\tilde{V}_{22} \\ F_{22}\tilde{V}_{21} & F_{22}\tilde{V}_{22} \end{pmatrix}, \tag{6.14}$$

where $\tilde{V}_{21}$ and $\tilde{V}_{22}$ are the entries of $V^{-1} = \begin{pmatrix} \tilde{V}_{11} & \tilde{V}_{12} \\ \tilde{V}_{21} & \tilde{V}_{22} \end{pmatrix}$, and given by

$$\tilde{V}_{21} = -(V_{22})^{-1}V_{21}\left(V_{11} - V_{12}(V_{22})^{-1}V_{21})\right)^{-1}$$
$$\tilde{V}_{22} = \left(V_{22} - V_{21}(V_{11})^{-1}V_{12}\right),$$

Since V is an $M-$matrix, it has a nonnegative inverse. Hence $\tilde{V}_{21}$ and $\tilde{V}_{22}$ are positive. Moreover, F_{12} and F_2 are nonnegative matrices therefore FV^{-1} is a positive. Then using the Perron Frobenius theorem, the spectral radius of FV^{-1} is positive, $\rho(FV^{-1}) > 0$. Then, from [33, Theorem 2]; see Appendix A

Lemma 6.3.4. *The DFE* (6.9) *of model* (6.2) *is locally asymptotically stable if* $\mathcal{R}_0 < 1$ *and unstable if* $\mathcal{R}_0 > 1$*, where* $\mathcal{R}_0$ *is defined by* (6.14)*.*

6.3.3 Existence of the Endemic Equilibria

In this section, we study the existence of endemic equilibria for model (6.2). Here we recall that the movement matrices are assumed to be irreducible.The assumption that $\mathcal{M}^X$ is irreducible for all infected classes means that considering any infected compartment, all the patches have access to each other directly or indirectly. That implies that if a TB strain is endemically present in patch i, i.e, for any $X_i \in \{L_{si}, L_{mi}, L_{xi}, I_{si}, I_{mi}, I_{xi}\}, X_i \neq 0$, while that strain does not exist in patch j, then the irreducibly of $\mathcal{M}^X$ implies that

$$X_j' = \sum_{k=1}^{p} m_{jk}^X X_k > 0 \Rightarrow X_j > 0.$$

That means that the endemic equilibrium for model (6.2) will follow the highest type of endemicity existing already within the patches in isolation. There are 10 types of endemic equilibria that could exist in each isolated patches, as studied in

Chapter 5. So to have any of the following endemic equilibria

1. Drug sensitive TB only,

$$\mathcal{E}_{si} = (S_i^*, L_{si}^*, 0, 0, I_{si}^*, 0, 0, R_i^*)\,,$$

2. MDR-TB only,

$$\mathcal{E}_{mi} = (S_i^*, 0, L_{mi}^*, 0, 0, I_{mi}^*, 0, R_i^*)\,,$$

3. XDR-TB only,

$$\mathcal{E}_{xi} = (S_i^*, 0, 0, L_{xi}^*, 0, 0, 0, I_{xi}^*, R_i^*)\,,$$

4. No XDR-TB

$$\mathcal{E}_{smi}^* = (S_i^*, L_{si}^*, L_{mi}^*, 0, I_{si}^*, I_{mi}^*, 0, R_i^*)\,,$$

5. No drug-sensitive TB

$$\mathcal{E}_{mxi}^* = (S_i^*, 0, L_{mi}^*, L_{xi}^*, 0, I_{mi}^*, I_{xi}^*, R_i^*)\,,$$

6. High endemicity in all strains

$$\mathcal{E}_{smxi}^* = (S_i^*, L_{si}^*, L_{mi}^*, L_{xi}^*, I_{si}^*, I_{mi}^*, I_{xi}^*, R_i^*)\,,$$

then all p patches must share same type of equilibria in isolation. Similarly as in Chapter 5, the existence of $\mathcal{E}_{smi}^* = (S_i^*, L_{si}^*, 0, L_{xi}^*, I_{si}^*, 0, I_{xi}^*, R_i^*)$ is not possible because even if we started with $L_{mi} = 0$ and $I_{mi} = 0$ in a fixed patch i, but $L_{si} \neq 0$ and $I_{si} \neq 0$, then

$$L'_{mi} = (1 - p_{1i})t_{s1i}L_{si} + (1 - p_{2i})t_{s2i}I_{si} > 0,$$

which implies that $L_{mi} > 0$, leading to

$$I'_{mi} = w_{mi} L_{mi} > 0.$$

Since $\mathcal{M}^{I_m}$ is irreducible by assumption, that implies that $I_{mi} > 0$ for every $i = 1, \ldots, p$.

Low endemicity coexistence equilibria: More than one strain exists in this type. But the existence of the resistant strain is due to treatment, not a new infection. E.g. $(S_i^*, L_{si}^*, L_{mi}^*, 0, I_{si}^*, I_{mi}^*, 0, R_i^*)$, in this case $\beta_{mi} = 0$ but $L_{mi}^* \neq 0, I_{mi}^* \neq 0$ and $\lim_{t\to\infty} L_{mi}^*(t) \neq 0$, $\lim_{t\to\infty} I_{mi}^*(t) \neq 0$. The possible equilibria of this type are

7. $\mathcal{E}_{smi} = (S_i^*, L_{si}^*, L_{mi}^{**}, 0, I_{si}^*, I_{mi}^{**}, 0, R_i^*)$.
8. $\mathcal{E}_{mxi} = (S_i^*, 0, L_{mi}^*, L_{xi}^{**}, 0, I_{mi}^*, I_{xi}^{**}, R_i^*)$.

Again similarly to Chapter 5, the existence of $\mathcal{E}_{smi} = (S_i^*, L_{si}^*, 0, L_{xi}^{**}, I_{si}^*, 0, I_{xi}^{**}, R_i^*)$ is not possible as outflow of the drug sensitive strain goes into MDR strain, not the XDR one.

Mixed of high and low endemicity equilibira: this type when one of the new infection rates is zero but the class is there due to the treatment inflow as following

9. $\mathcal{E}_{smx}^{**} = (S^*, L_s^*, L_m^*, L_x^{**}, I_s^*, I_m^*, I_x^{**}, R^*)$, when $\beta_x = 0$.
10. $\mathcal{E}_{sxm}^{**} = (S^*, L_s^*, L_m^{**}, L_x^*, I_s^*, I_m^{**}, I_x^*, R^*)$, when $\beta_m = 0$.

All the above endemic equilibira are due to the dynamics of TB. However, the movement between patches can introduce new endemic equilibria in the case of irreducible matrices. The following is an example of such case, consider p patches that are coupled linearly. For fixed i and j, patch i is endemic with MDR-TB and XDR-TB, while patch j is endemic with MDR-TB only. Due irreducibility of the migration matrix,

$$I'_{xj} = m_{ji}^{I_x} I_{xi} > 0 \Rightarrow I_{xj} > 0,$$

patch j develops XDR-TB by the time

That gives us three new additional equilibria that can exist due to migration and not because of the dynamics of TB. They are:

11. $\mathcal{E}_1^{**} = (S^*, L_s^*, L_m^{**}, L_x^{**}, I_s^*, I_m^{**}, I_x^{**}, R^*)$,

12. $\mathcal{E}_2^{**} = (S^*, L_s^{**}, L_m^{**}, L_x^*, I_s^{**}, I_m^{**}, I_x^*, R^*)$,

13. $\mathcal{E}_3^{**} = (S^*, L_s^*, L_m^{**}, L_x^{**}, I_s^*, I_m^{**}, I_x^{**}, R^*)$.

In short, irreducible migration matrix can keep the state of endemicity of the considered patches, or can change the type of endemic equilibria in a model comparing to the patches in isolation.

APPENDIX

A. NEXT GENERATION OPERATOR METHOD

The next generation operator method is a method to decide on the local asymptotic stability of the disease free equilibrium in a model for the spread of an infectious disease. The method was originally introduced by Diekmann *et al.* [11] and formulated for the use in ordinary differential equations compartmental epidemiological models by van den Driessche and Watmough [33]. The formulation in [33] is given below.

Given an infectious disease model with n compartments, start by ordering compartments for $i = 1, \ldots, n$: so that the first $m \leq n$ compartments stand for the infected compartments and the rest are the non-infected ones. Suppose the transmission model associated with a non-negative initial conditions can be written as follows:

$$x_i' = f_i(x) = \mathcal{F}_i(x) - \mathcal{V}_i(x), \tag{A.1}$$

where $\mathcal{F}$ is the vector representing new infections into the infected classes, and $\mathcal{V}_i = \mathcal{V}_i^- - \mathcal{V}_i^+$ is the vector representing other flows within and out of the infected classes. Assume that $X_s = \{x \geq 0 | x_i = 0, i = 1, \cdots, m\}$ is the disease-free states (non-infected state) of the model, and the functions described above satisfy the following axioms:

(A1) If $x \geq 0$, then $\mathcal{F}_i, \mathcal{V}_i^+, \mathcal{V}_i \geq 0$ for $i = 1, \cdots, n$.

(A2) If $x_i = 0$, then $\mathcal{V}_i^- = 0$. In particular, if $x \in X_s$ then $\mathcal{V}_i^- = 0$ for $i = 1, \cdots, m$.

(A3) $\mathcal{F}_i = 0$ if $i > m$.

(A4) If $x \in X_s$, then $\mathcal{F}_i(x) = 0$ and $\mathcal{V}_i^+(x) = 0$ for $i = 1, \cdots, m$.

(A5) If $\mathcal{F}(x)$ is set to zero, then all eigenvalues of $Df(x^*)$ have negative real part, where x^* is the DFE.

It is assumed that these functions are at least twice continuously differentiable in each variable.

Lemma A.1 (van den Driessche and Watmough [33]). *If x^* is a DFE of* (A.1) *and $f_i(x)$ satisfy (A1) - (A5), then the derivatives $D\mathcal{F}(x^*)$ and $D\mathcal{V}(x^*)$ are partitioned as*

$$D\mathcal{F}(x^*) = \begin{pmatrix} F & 0 \\ 0 & 0 \end{pmatrix} \quad D\mathcal{V}(x^*) = \begin{pmatrix} V & 0 \\ J_3 & J_4 \end{pmatrix}, \tag{A.2}$$

where F and V are the $m \times m$ matrices defined for $1 \leq i, j \leq m$ by,

$$F = \left[\frac{\partial \mathcal{F}_i}{\partial x_j}(x^*)\right], \quad \text{and } V = \left[\frac{\partial \mathcal{V}_i}{\partial x_j}(x^*)\right].$$

Further, F is non-negative, V is a non-singular $M-$matrix and J_3, J_4 are matrices associated with the transition terms of the model and all eigenvalues of J_4 have positive real parts.

Theorem A.2 (van den Driessche and Watmough [33]). *Consider the disease transmission model given by* (A.1) *with $f(x)$ satisfying axioms (A1)–(A5). If x^* is a DFE of the model, then x^* is locally asymptotically stable if $\mathcal{R}_0 = \rho(FV^1) < 1$ and unstable if $\mathcal{R}_0 > 1$.*

B. BIFURCATION

The next theorem is used to prove the presence of backward bifurcation in some of the models of this thesis.

consider a general system of ODEs with a parameter ϕ:

$$\frac{dx}{dt} = f(x, \phi), \quad f : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}^n \text{ and } f \in \mathbb{C}^2 \left(\mathbb{R}^n \times \mathbb{R}\right). \tag{B.1}$$

With 0 is an equilibrium point of the system for all values of the parameter ϕ, that is

$$f(0, \phi) \equiv 0 \text{ for all } \phi. \tag{B.2}$$

Theorem B.1 (Castillo-Chavez & Song [10]). *Assume*

A1 : $A = D_x f(0,0) = \left(\frac{\partial f_i}{\partial x_j}(0,0)\right)$ *is the linearization matrix of System* (B.1) *around the equilibrium* 0 *with* ϕ *evaluated at* 0. *Zero is a simple eigenvalue of* A *and all other eigenvalues of* A *have negative real parts;*

A2 : Matrix A *has a nonnegative right eigenvector* w *and a left eigenvector* v *corresponding to the zero eigenvalue such that* $v.w = 1$.

Let $_k$ *be the* k*th component of* f *and*

$$a = \sum_{i,j,k=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0), \tag{B.3}$$

$$b = \sum_{i,k=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0,0). \tag{B.4}$$

The local dynamics of (B.1) *around* 0 *are totally determined by* a *and* b.

i. $a > 0, b > 0$. *When* $\phi < 0$ *with* $|\phi| \ll 1$, 0 *is locally asymptotically stable, and there exists a positive unstable equilibrium; when* $0 < \phi \ll 1$, 0 *is unstable and there exists a negative and locally asymptotically stable equilibrium;*

ii. $a < 0, b < 0$. *When* $\phi < 0$ *with* $|\phi| \ll 1$, 0 *is unstable; when* $0 < \phi \ll 1$, 0 *is locally asymptotically stable, and there exists a positive unstable equilibrium;*

iii. $a > 0, b < 0$. *When* $\phi < 0$ *with* $|\phi| \ll 1$,0 *is unstable, and there exists a locally asymptotically stable negative equilibrium; when* $0 < \phi \ll 1$, 0 *is stable, and a positive unstable equilibrium appears;*

iv. $a < 0, b > 0$. *When* ϕ *changes from negative to positive,* 0 *changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable.*

We notice that the forward bifurcation represented in case (iv) and the backward bifurcation is in case (i).

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