

**A Metapopulation Model for Mass
Gatherings
Application: Global Travel, Hajj and the
Spread of Measles**

by

Liliana Menjivar

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Department of Mathematics
University of Manitoba
Winnipeg

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Abstract

Mass gatherings stress local and global health care systems as they bring together individuals from all over the world that have very different health conditions. We firstly provide an overview of the concepts and results of mathematical epidemiology and public health. Secondly, we present an introduction to the mathematical modelling of measles using deterministic and stochastic approaches for both single and multiple populations. Lastly, we develop a model for mass gatherings and present an application to measles during the Hajj by studying an SIR deterministic metapopulation model with residency and its stochastic analogue. The models incorporate real world country data and time dependent movement and transmission rates, accounting for realistic volume of international travel and seasonality of measles activity. Numerical results for the deterministic system are presented. We conclude with a discussion on further work.

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Dedication

I dedicate this work to my Savior Jesus Christ. Everything I do is for you, without you I would not be able to accomplish anything. My faith in Him and his Word has provided me with hope, inspiration and strength to continue this work! His words, “For I am the Lord, your God, who takes hold of your right hand and says to you, Do not fear; I will help you,” has been the motivation of my ambitions. It is also dedicated to my hard-working parents who sacrificed their lives by moving to a new country for my brother and I to have better opportunities to pursue our academic careers. Thank you Mom and Dad, I owe you the greatest debt of all.

Los amo mucho.

Introduction

As a matter of fact all epidemiology, concerned as it is with variation of disease from time to time or from place to place, must be considered mathematically (...), if it is to be considered scientifically at all. (...) And the mathematical method of treatment is really nothing but the application of careful reasoning to the problems at hand.

Sir Ronald Ross [91]

Sir Ronald Ross is arguably the founding father of modern epidemiology theory [43], who 116 years ago made a ground breaking conclusion; he identified mosquitoes as vectors in the propagation of malaria [98]. He was a physician by training who used his extensive knowledge of mathematics to study the spread of malaria. Of his contributions to mathematical epidemiology, the most notable was on mosquito-control; he was the first to discover that in order to eliminate malaria, one did not need to wipe out the entire mosquito population [90]. He laid the foundation for global control campaigns that successfully reduced the transmission of malaria in endemic

areas by targeting the mosquito vectors of malaria [98].

Mathematical models used to understand local disease dynamics are ideal for single population studies; an example is the malaria model formulated by Ross. However, the study of single populations and local disease dynamics is not sufficient as our world is becoming more and more connected by transportation networks.

International travel is identified as one of the major factors associated with the global spread of infectious diseases [84, 118]. Due to massive improvements of international transportation networks, potential global disease spread is becoming easier and easier and therefore is of prominent concern. It is obvious that the spatial distribution of an infectious diseases depends on how fast and how far people can travel, i.e., spatial propagation of disease depends on the transportation services of society.

To study the present phenomenon of global connectivity and the risk of global disease spread that arises from it, mathematical models must incorporate local disease dynamics and the spatio-temporal spread of infectious diseases due to dispersion of multiple populations by transportation networks.

In 1985, Leonid Rvachev and Ira Longini formulated an susceptible-latent-infectious-recovered-susceptible (*SLIRS*) system of difference equations for N cities and applied it to forecast the 1968-1969 Hong Kong influenza A pandemic among 52 major world cities [93]. The model successfully forecasts the actual spatio-temporal spread of the Hong Kong influenza pandemic as documented by the World Health Organization (WHO). Their study in 1985

paved the way for the successful use of mathematical models that incorporate spatial heterogeneities, in predicting the global spread of disease.

The malaria single population model formulated by Ross, and the influenza A multi-population model formulated by Rvachev and Longini are only a couple of examples of how inter-disciplinary work between the two disciplines of epidemiology and mathematics provides a unique collaboration that is incredibly vital in the local and global understanding of the spread of infectious disease.

Mathematical techniques applied to epidemiology provide time and cost effective methods that are paving a way for real-time intelligence of local and global disease spread. One can see that *mathematical epidemiology* has the potential to significantly influence the decision making process of public health officials. The manuscript and ideas therein are inspired by the following quote, taken from [63]:

mathematical models applied to real-time public and world health problems can serve as a sort of ‘epidemic intelligence’ for understanding local disease dynamics with single populations and spatial propagation of a disease via international travel of multiple populations.

The manuscript consists of three parts.

In Part I, public health terms are defined, a general framework and introduction to mathematical modelling is presented, historical contributions of mathematical epidemiology are outlined and analytical defi-

nitions, methods and results used throughout the manuscript are presented.

In Part II, a mathematical study of measles at the local and global levels is presented. We study a measles epidemic model and a measles endemic model for single populations. Deterministic and corresponding stochastic processes for the two models are formulated, analyzed and numerically studied. The importance of using stochastic processes and the benefits that arise from such models is discussed. Then a mathematical study of measles transmission at a global level is presented using *metapopulation* theory. A deterministic *metapopulation model with residency* is presented and analyzed along with its stochastic analogue to study the world wide connectivity of N patches tracking individuals by their patch of residence. The subpopulations of each patch are described by an SLIR model of the type studied in the single population case.

In Part III, a model for mass gatherings is presented using essentially the deterministic metapopulation model with residency under certain assumptions and conditions. The deterministic and stochastic analogues of the mass gathering residency model is studied numerically as analytical results are limited. Next, we apply the mass gathering model to a real time public health problem, could measles be spread globally due to the Hajj, one of the largest most diverse mass gatherings in history. The mass gathering model will aid in understanding, describing

and predicting how measles can be propagated spatially due to international travel of pilgrims attending the Hajj. Subpopulations of each patch are described by a susceptible-infectious-recovered (*SIR*) model. In the ‘mass gathering patch’ (the patch that hosts the mass gathering), there is transmission of the disease between the host population and attending populations.

Following the conclusions of the Hajj application we present a general discussion of future work and refinements of the mass gathering model and its application the Hajj.

The stochastic processes used in the manuscript are continuous time Markov chains. The local and global mathematical models developed in the manuscript will aid in the understanding of how local populations interact with the measles virus and how the local dynamic is affected as populations no longer remain in their local environment but spatially disperse from one geographical location to another.

Our approach will be *qualitative*, so rather than finding explicit solutions to the system of differential equations, we will be concerned with the systems asymptotic behaviour, that is, the behaviour of the solutions as $t \rightarrow \infty$. All mathematical and statistical analyses were performed using Matlab version 7.7.0. All illustrations were created using Adobe Illustrator CS5.

Part I

Preliminaries

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Chapter 1

Mathematical preliminaries

This chapter is dedicated to an overview of deterministic and stochastic systems and matrix analysis.

Ordinary differential equations. The independent variable in compartmental models is time t and the rates of transfer between compartments are expressed mathematically by derivatives of the compartments with respect to time; thus, our models take the form of *ordinary differential equations*. An underlying assumption is that the number of individuals in a compartment is a differentiable function with respect to time. The formulation of models as ordinary differential equations (ODE) makes the assumption that population sizes are predicted with absolute certainty and so the solution of an ODE follows a prescribed path or solution trajectory in solution space. In other words, the behaviour of a population is completely determined (or known) by its history and the rules which describe the model [43].

Stochastic process. The independent variable in the compartmental models, time t , is an exponentially distributed random variable. The formation of *stochastic* models use probabilistic concepts to study population sizes and so the behaviour of the population is not known with certainty. A solution trajectory of a stochastic process represents only a single realization of the process; each realization is different.

1.1 Ordinary differential equations

1.1.1 Useful definitions, notations and results

The following is based on material in [10, 11, 121].

A system of first order autonomous ordinary differential equations can be written in the following form,

$$\begin{aligned}
 \frac{d}{dt}x_1(t) &= f_1(x_1, x_2, \dots, x_n) \\
 \frac{d}{dt}x_2(t) &= f_2(x_1, x_2, \dots, x_n) \\
 &\vdots \quad \quad \quad \vdots \\
 \frac{d}{dt}x_n(t) &= f_n(x_1, x_2, \dots, x_n)
 \end{aligned}
 \tag{1.1}$$

System (1.1) is called *autonomous* since the independent variable t does not appear explicitly on the right hand side of each differential equation. System (1.1) can be written in compact (column) vector form,

$$x' = f(x)$$

with

$$x(t) = \begin{pmatrix} x_1(t) \\ x_2(t) \\ \vdots \\ x_n(t) \end{pmatrix}, \quad f(x) = \begin{pmatrix} f_1(x_1, x_2, \dots, x_n) \\ f_2(x_1, x_2, \dots, x_n) \\ \vdots \\ f_n(x_1, x_2, \dots, x_n) \end{pmatrix}$$

Definition 1.1.1 (Ordinary differential equation). *An autonomous ODE is an equation involving one independent variable (often called time), t , and a dependent variable, $x(t)$, with $x \in \mathbb{R}^n$, $n \geq 1$, and taking the form*

$$x' = f(x) \tag{1.2}$$

where $f : \mathbb{R}^n \times \mathbb{R}^n \rightarrow \mathbb{R}^n$ is called the vector field.

System (1.2) is an example of a *dynamical system* and a solution $\mathbf{x}(t)$ is the *state* of the system at time t .

Definition 1.1.2 (Initial value problem). *An autonomous IVP consists of an ODE and an initial condition,*

$$\begin{aligned} x' &= f(x) \\ x(t_0) &= x_0 \end{aligned} \tag{1.3}$$

where $t_0 \in \mathbb{R}$ and $x_0 \in \mathbb{R}^n$ is the initial condition.

The initial condition $x(t_0)$ represents the position of the objects at some initial time t_0 . Here we look for solutions of the system of ODEs on an interval \mathcal{I} that contains t_0 so that the solution curves passes through the point $(t_0, f(t_0))$.

Definition 1.1.3 (Well-posedness). *System (1.2) is well-posed if solutions exist, are unique, and for systems describing populations, solutions remain bounded and are non-negative for all non-negative initial conditions.*

Theorem 1.1.4 (Cauchy-Lipschitz). *Consider the differential equation (1.2) with $x \in \mathbb{R}^n$, and suppose that $f \in C^1$. Then there exists a unique solution of (1.2) such that $x(t_0) = x_0$, where $t_0 \in \mathbb{R}$ and $x_0 \in \mathbb{R}^n$, defined on the largest interval $t_0 \in \mathcal{I}$ on which $f \in C^1$.*

Definition 1.1.5 (Flow). *Consider System (1.3). The flow $\phi(t, x_0)$ of (1.3) gives the spatial solution of (1.3) over time given an initial condition provided that the solutions to the differential equation exist and are unique.*

Changing initial conditions in phase space will change flows in a continuous fashion because we have a continuous vector field f in \mathbb{R}^n .

Definition 1.1.6 (Equilibrium point). *Consider (1.2) with $x \in \mathbb{R}^n$ and $f : \mathbb{R}^n \rightarrow \mathbb{R}^n$. Then x^* is an equilibrium solution of (1.2) if $f(x^*) = 0$.*

In words, equilibrium points are found by setting the time derivatives (i.e the left hand sides) of the differential equation (1.2) equal to zero.

Definition 1.1.7 (Hyperbolic fixed point). *A hyperbolic equilibrium point for System (1.2) is a point at which the eigenvalues of $Df|_{x^*}$ (i.e., the Jacobian matrix for the system evaluated at the equilibrium x^*) all have nonzero real part.*

Definition 1.1.8 (Locally stable equilibrium point). *Let $\phi(t)$ be the flow of (1.2), assumed to be defined for all $t \in \mathbb{R}$. An equilibrium x^* of (1.2) is*

locally stable if for all $\epsilon > 0$, there exists $\delta > 0$ such that for all $x \in \mathcal{N}_\delta(x^*)$ and $t \geq 0$, there holds

$$\phi(t, x) \in \mathcal{N}_\epsilon(x^*),$$

where $\mathcal{N}_\delta(x^*)$ is a δ -neighbourhood of x^* , for instance an open ball centred at x^* with radius δ .

In crude wording, an equilibrium point is locally stable if all solutions which start near x^* (meaning that the initial conditions are in a neighbourhood of x^*) remain near x^* for all time. The equilibrium point is unstable if it is not stable.

Definition 1.1.9 (Locally asymptotically stable equilibrium point). *Let $\phi(t)$ be the flow of (1.2). An equilibrium x^* of (1.2) is locally asymptotically stable if there exists $\delta > 0$ such that for all $x \in \mathcal{N}_\delta(x^*)$ and $t \geq 0$, there holds*

$$\lim_{t \rightarrow \infty} \phi(t, x) = x^*.$$

It is clear that asymptotically stable implies stable.

Definition 1.1.10 (Globally asymptotically stable equilibrium point). *We say an equilibrium point x^* is globally asymptotically stable if it is locally asymptotically stable for all initial conditions $x_0 \in \mathbb{R}^n$.*

Definition 1.1.11 (Invariant set). *A set $A \subset \mathbb{R}^n$ is invariant if for every $x_0 \in A$, $\phi(t, x_0) \in A$, $\forall t \in \mathbb{R}$.*

Definition 1.1.12 (Positive invariant set). *A set $A \subset \mathbb{R}^n$ is positive invariant if for every $x_0 \in A$, $\phi(t, x_0) \in A$, $\forall t \geq 0$. We also say that A is positively invariant under the flow $\phi(t, x_0)$.*

1.1.2 Linearization

The Hartman-Grobman theorem [11, 121] allows us to approximate the flow of the nonlinear ODE about equilibria by a corresponding (simpler) linear system that we can find by computing the system's Jacobian matrix at the equilibrium point.

The following result is adapted from [11, 121]. The behaviour of System (1.2) near a hyperbolic equilibrium point x^* is linked to the behaviour of its corresponding linearized system,

$$x' = Df|_{x^*}(x - x^*), \quad (1.4)$$

where

$$Df|_{x^*} = \begin{bmatrix} \frac{\partial f_1}{\partial x_1} & \frac{\partial f_1}{\partial x_2} & \frac{\partial f_1}{\partial x_n} \\ \frac{\partial f_2}{\partial x_1} & \frac{\partial f_2}{\partial x_2} & \frac{\partial f_2}{\partial x_n} \\ \vdots & \vdots & \vdots \\ \frac{\partial f_n}{\partial x_1} & \frac{\partial f_n}{\partial x_2} & \frac{\partial f_n}{\partial x_n} \end{bmatrix} \Big|_{(x_1^*, x_2^*, \dots, x_n^*)}$$

Matrix $Df|_{x^*}$ is called the *Jacobian matrix* of (1.2) evaluated at the equilibrium point x^* .

Definition 1.1.13 (Homeomorphism). *Let W be a space. A map $h : W \rightarrow$*

W is a homeomorphism if h is a continuous bijection whose inverse is continuous.

Definition 1.1.14 (Topologically conjugate). *Let $\phi(t, x)$ and $\psi(t, x)$ be two flows on a space W . ϕ and ψ are topologically conjugate if there exists an homeomorphism $h : W \rightarrow W$ such that*

$$h(\phi(t, x)) = \psi(t, x)(h(x))$$

for all $x \in W$ and all $t \in \mathbb{R}$.

Theorem 1.1.15 (Hartman-Grobman Theorem). *Let $f \in C^1(E)$, E an open subset of \mathbb{R}^n containing x^* where $f(x^*) = 0$, and let $\phi(t, x)$ be the flow of the nonlinear System (1.2). Suppose x^* is a hyperbolic equilibrium point. Then there exists a homeomorphism $h : U \rightarrow V$ with open set $U \subset \mathbb{R}^n$ onto an open set $V \subset \mathbb{R}^n$ each containing the origin such that for each $x_0 \in U$, there is an open interval $\mathcal{I}_0 \subset \mathbb{R}$ containing x^* such that $\forall x_0 \in U$ and $t \in \mathcal{I}_0$,*

$$h\phi(t, x_0) = \psi(t, x_0)h(x_0) = e^{Df|_{x^*}t}h(x_0)$$

Thus, the flow of the nonlinear system $\phi(t, x)$ is topologically conjugate to the flow $\psi(t, x)$ of the linear system.

Roughly speaking, two topologically conjugate flows have the same dynamics. In particular, the flow of the nonlinear system has the same dynamics as the flow of its corresponding linear system.

The Hartman-Grobman theorem tells us that, in a neighbourhood of the equilibrium point, if the system's Jacobian matrix has all eigenvalues with nonzero real part (i.e. hyperbolic equilibrium point), then we can get a qualitative idea of the behaviour of solutions of the nonlinear system by studying its corresponding linear system. So we can determine whether solution trajectories approach or move away from the equilibrium point over time, that is, we can determine the stability of equilibria in System (1.2) without finding explicit solutions.

1.1.3 Stability

Theorem 1.1.16. ([42]) *Let x^* be a equilibrium point of the autonomous System (1.2), where f_1, f_2, \dots, f_n have continuous first partial derivatives in a neighborhood of x^* .*

1. *If all the eigenvalues of $J = Df|_{x^*}$ have negative real part, then x^* is an locally asymptotically stable equilibrium point.*
2. *If $J = Df|_{x^*}$ has an eigenvalue with positive real part, then x^* is an unstable equilibrium point.*

Local stability of equilibrium points can be determined using the *Routh-Hurwitz Criteria*. The *Routh-Hurwitz theorem* for $N = 4$ is stated below,

Theorem 1.1.17 (Routh-hurwitz criterion for polynomial of degree 4 [67]). *Given the polynomial, $P(\lambda) = \lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4$, where the coefficients*

$a_i, i = 1, 2, 3, 4$ are real constants, define the 4 Hurwitz matrices using the coefficients a_i of the characteristic polynomial:

$$H_1 = (a_1), H_2 = \begin{bmatrix} a_1 & 1 \\ a_3 & a_2 \end{bmatrix}, H_3 = \begin{bmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ 0 & a_4 & a_3 \end{bmatrix}$$

$$H_4 = \begin{bmatrix} a_1 & 1 & 0 & 0 \\ a_3 & a_2 & a_1 & 1 \\ 0 & a_4 & a_3 & a_2 \\ 0 & 0 & 0 & a_4 \end{bmatrix}$$

All the roots of $P(\lambda)$ are negative or have negative real part if and only if the determinants of all Hurwitz matrices are positive:

$$\det H_i > 0, \quad i \in \{1, 2, 3, 4\}$$

So the Routh-Hurwitz criteria for $n = 4$ can be summarized as:

$$a_1 > 0, a_3 > 0, a_4 > 0 \text{ and } a_1 a_2 a_3 > a_3^2 + a_1^2 a_4.$$

1.2 Stochastic processes

1.2.1 Definitions

The following results are adapted from [6, 21].

Let Ω be a set, a collection of elements that correspond to the possible outcomes of a random experiment, referred to as *sample or outcome space*. The elements of Ω are called *sample points*. The subsets of Ω are called *events* and are assigned a probability. The class of events are to be closed under complement, finite or countable union and intersection, and the sample space itself should be an event.

Definition 1.2.1. Let $\Omega \neq \emptyset$ be a set. Let \mathcal{F} be a collection of subsets of Ω . That is, $\mathcal{F} \subset 2^\Omega$. \mathcal{F} is called a σ -algebra if

1. $\Omega \in \mathcal{F}$
2. If $A \in \mathcal{F}$, then $A^c \in \mathcal{F}$
3. If $A_1, A_2, \dots \in \mathcal{F}$, then $\bigcup_{i=1}^{\infty} A_i \in \mathcal{F}$

Definition 1.2.2. A measure on a σ -algebra \mathcal{F} , is a nonnegative, extended real-valued function μ defined on \mathcal{F} , $\mu : \mathcal{F} \rightarrow \mathbb{R}$, such that

1. $\mu(A) \geq 0, \forall A \in \mathcal{F}$
2. If $A_i \cap A_j = \emptyset$ for $i, j \in \{1, 2, \dots\}$, $i \neq j$ (pairwise disjoint), $\forall A_i \in \mathcal{F}$, then

$$\mu \left(\bigcup_{i=1}^{\infty} A_i \right) = \sum_{i=1}^{\infty} \mu(A_i)$$

μ is determined on the collection of *Borel sets* of \mathbb{R} , denoted by $\mathcal{B}(\mathbb{R})$ and is defined as the smallest σ -field of subsets of \mathbb{R} containing all intervals

$(a, b]$, $a, b \in \mathbb{R}$. If $B \in \mathcal{B}(\mathbb{R})$,

$$\mathcal{B}(B) = \{A \in \mathcal{B}(\mathbb{R}) : A \subset B\}.$$

μ is a *probability measure* on \mathcal{F} if in addition to properties (1) and (2) in Definition 1.2.2, $\mu(\Omega) = 1$. In this case, μ will be replaced by \mathcal{P} to denote the probability measure. $\mathcal{P} : \Omega \rightarrow [0, 1]$. A *probability space* is a triple $(\Omega, \mathcal{F}, \mathcal{P})$ where Ω is an outcome set, \mathcal{F} is the σ -algebra of subsets of Ω , and \mathcal{P} is a probability measure on \mathcal{F} .

If $(\Omega, \mathcal{F}, \mathcal{P})$ is the probability space and the outcome of an experiment corresponds to $\omega \in \Omega$, a measuring process is carried out to obtain a quantity for $X(\omega)$. This implies that X is a function from the sample space Ω to the reals.

Definition 1.2.3. A random variable X on a probability space $(\Omega, \mathcal{F}, \mathcal{P})$ is a real-valued function defined from Ω to \mathbb{R} . That is, $X : \Omega \rightarrow \mathbb{R} = (-\infty, \infty)$. Let Y be the range of X , $Y = \{y | X(\omega) = y, \omega \in \Omega\}$. The range Y is known as the state space of X .

If the range of X is finite or countably finite, the X is called a *discrete random variable*. If the range of X is an interval, which could be finite or infinite in length, then X is called a *continuous random variable*.

Events are subsets of the outcome space Ω but can also be expressed as subsets of \mathbb{R} . For $y \in \mathbb{R}$ let the event $\{\omega | X(\omega) = y, \omega \in \Omega\}$ be represented in shorthand notation by $\{X = y\}$. Likewise, the event $\{\omega | X(\omega) \leq y, \omega \in \Omega\}$ is denoted by $\{X \leq y\} = (-\infty, y]$. It follows that the probability measure \mathcal{P}

associated with the random variable X can be defined on \mathbb{R} . This measure will be denoted by $\mathcal{P}_X : \mathbb{R} \rightarrow [0, 1]$ and is known as the *induced probability measure*.

$$\mathcal{P}_X(B) = \mathcal{P}\{\omega | X(\omega) \in B\}, B \in \mathcal{B}(\mathbb{R})$$

A stochastic process is a collection of random variables.

Definition 1.2.4. A stochastic process is a collection of random variables $\{X(t, \omega) : t \in T, \omega \in \Omega\}$, where T is some index set and Ω is the outcome space of the random variables. For each fixed t , $X(t, \omega)$ denotes a single random variable defined on Ω . For each fixed $\omega \in \Omega$, $X(t, \omega)$ corresponds to a function defined on T that is called a *sample path* or *stochastic realization of the process*.

When speaking of stochastic processes, random variables can be simply denoted by $X(t)$. Random variables and index sets can be discrete or continuous. There are three common types of stochastic models; their distinction depends on how the index set and random variables are classified. Let $t \in T$ denote *time* in our stochastic model. *Discrete time Markov chains* (DTMC) are those that have both the index set and random variables discrete ($T = \mathbb{N}$ and $X(t) \in \mathbb{N}$). *Continuous time Markov chains* (CTMC) are those that have a continuous index set but discrete random variables ($T = \mathbb{R}_+$ and $X(t) \in \mathbb{N}$). *Stochastic differential equations* (SDE) have both continuous index set and random variables ($T = \mathbb{R}_+$ and $X(t) \in \mathbb{R}_+$). In this study, we focus on the *CTMC* analogue of deterministic systems of the form (1.2).

Let $\{X(t)\}$, $t \in [0, \infty)$ be a collection of discrete random variables with

values in a finite or infinite set, i.e.,

$$X(t) \in \{1, 2, \dots, N\} \text{ or } X(t) \in \{0, 1, 2, \dots\}$$

Definition 1.2.5. A stochastic process $\{X(t)\}$, $t \in [0, \infty)$, is called a continuous time Markov chain (CTMC) if it satisfies the following condition: For any sequence of real numbers satisfying $0 \leq t_0 < t_1 < \dots < t_n < t_{n+1}$,

$$\begin{aligned} \text{Prob}\{X(t_{n+1}) = i_{n+1} | X(t_0) = i_0, X(t_1) = i_1, \dots, X(t_n) = i_n\} \\ = \text{Prob}\{X(t_{n+1}) = i_{n+1} | X(t_n) = i_n\} \end{aligned}$$

The *Markov Property* is shown in the latter part of the definition. It is also known as the *memoryless property* since the new state of the stochastic process does not depend on its history. In words, the transition to the next state, i_{n+1} , at time t_{n+1} depends only on the value of the present state, i_n , at the present time t_n .

The state of the system at time t is denoted by $X(t)$. Let τ_t represent the amount of time spent in the present state before transitioning into a new state. The state of the system after transition is denoted by $X(t + \tau_t)$.

Each random variable $X(t)$ has an associated probability distribution $\{p_i(t)\}_{i=1}^{\infty}$, where

$$p_i(t) = \text{Prob} \{X(t) = i\}.$$

The *transition probabilities* are defined by

$$p_{(j,i)}(t + \tau_t, t) = \text{Prob}\{X(t + \tau_t) = j | X(t) = i\}$$

for $i, j \in \{1, 2, \dots\}$.

1.2.2 Gillespie's algorithm

In 1977, Gillespie [54] provided a stochastic simulation algorithm to numerically study fluctuations in a given spatially homogeneous system of coupled chemical reactions. In our study instead of reactions, we look at populations but the same idea follows. The algorithm correctly accounts for the inherent ideas of randomness that are otherwise ignored by deterministic formulations. The algorithm is as follows,

1. Initial values.
 - N discrete random (state) variables $X_i(t)$ for $i \in \{1, \dots, N\}$ such that $X_i(t) \in \{1, 2, \dots\}$, parameters, the weights of M events, initial time $t = t_0$ and final time $t = t_f$.
2. Calculate the weights of each event, denoted by $w_k(t)$ for $k = \{1, \dots, M\}$.
3. Calculate the sum of the weights of the events, which is denoted by $f(t)$.

$$f(t) = \sum_{k=1}^M w_k(t)$$

4. Calculate the time to the next event, denoted by $\tau(t)$.

- Draw $\zeta(t)$ from $\mathcal{U}([0, 1])$.
- (Derivation of $\tau(t)$ is shown below).

$$\tau(t) = -\frac{\ln(1 - \zeta(t))}{f(t)}$$

5. Find the index of the next event that occurs, denoted by r .

- Draw $\zeta'(t)$ from $\mathcal{U}([0, 1])$.
- (Detailed explanation of this step below). Return the index r such that,

$$\sum_{k=1}^{r-1} w_k(t) < \zeta'(t)f(t) \leq \sum_{k=1}^r w_k(t) \quad (1.5)$$

6. Adjust values of $X_i(t)$ according to the event of index r that occurs.

7. Put $t = t + \tau(t)$

8. Go to step 2 and repeat until $t \leq t_f$

Deriving $\tau(t)$. Take T an exponentially distributed random variable with mean $f(t)$, i.e., $T \sim \mathcal{E}(f(t))$. T has probability density or distribution function,

$$g(t, f(t)) = f(t)e^{-f(t)t}, \quad t \geq 0$$

Let $G : \mathbb{R}_+ \rightarrow [0, 1]$ be the cumulative distribution function,

$$G(t, f(t)) = \int_0^t g(s, f(t)) ds, \quad t \geq 0$$

Next, we draw ζ from $\mathcal{U}([0, 1])$. Then preimage of G , $G^{-1}(\zeta)$ gives $\tau(t) \in \mathbb{R}_+$. That is,

$$\begin{aligned} \zeta = G(\tau(t), f(t)) &= \int_0^{\tau(t)} f(t)e^{-f(t)s} ds \quad \Leftrightarrow \zeta = 1 - e^{-f(t)\tau(t)} \\ &\Leftrightarrow \tau(t) = -\frac{\ln(1 - \zeta)}{f(t)} \end{aligned}$$

Therefore, the time to the next event is then given by,

$$\tau(t) = -\frac{\ln(1 - \zeta)}{f(t)}, \quad \zeta \text{ is } \mathcal{U}([0, 1]).$$

Detailing step 5 above. If the size of the events are very small, then computer precision might miss the next event so the multiplication of $\zeta'(t)$ (the uniformly distributed parameter on $[0, 1]$) with $f(t)$ correctly captures the next event, as illustrated above in (1.5). On the contrary, if the size of the weights exceed computer precision, then we would modify step 5 to capture the correct index of the next event. We create a vector v denoted by $v = [v_i]$ with entries $v_i = \sum_{k=1}^i w_k(t)$. The vector v is the vector of successive cumulative event weights. We would then need to divide v by $f(t)$ which is called ‘normalization of v ’ in order for the size of the weights to be within computer precision. So index r returned in step 5 is the first occurrence such that,

$$\frac{v_{r-1}}{f(t)} < \zeta'(t) \leq \frac{v_r}{f(t)}.$$

A detailed formulation of Gillespie's algorithm is provided below in Section 1.3.

1.3 Two compartment model: Theoretical example

In this section, we derive the differential equations associated to a two-compartment model and detail the derivation of its stochastic analogue using a continuous time markov chain (CTMC).

1.3.1 Deterministic system

The flow diagram of a compartmental process can be used to derive the differential equations that describe the compartmental process. To illustrate, lets consider a simple two compartment model, the compartments will be denoted by X and Y . The rate into the X compartment will be denoted by a , the per capita rate out of the X compartment will be denoted by b and the per capita rate out of the Y compartment will be denoted by c . The flow diagram of such a model is given below in Figure 1.1

Next, in Figure 1.2 we isolate each compartment and the flows that correspond to it.

The flows into each compartment are a '+' sign entry in the differential

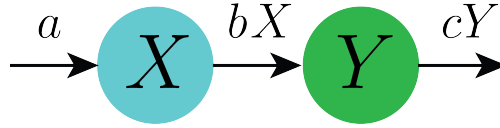


Figure 1.1: Flow diagram

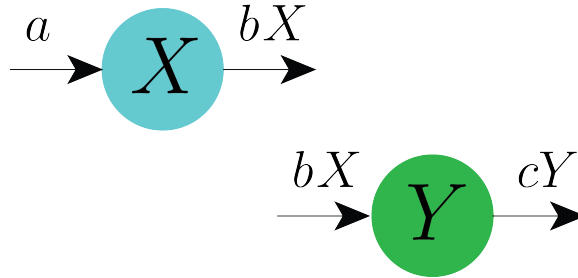


Figure 1.2: Flows of each compartment

equation and the flows out of each compartment are a ‘-’ sign entry in the differential equation. Thus, the differential equations that describes the two compartment model in Figure 1.1 are as follows,

$$\begin{aligned} \frac{d}{dt}X(t) &= a - bX(t) \\ \frac{d}{dt}Y(t) &= bX(t) - cY(t) \end{aligned} \tag{1.6}$$

1.3.2 Stochastic analogue

A stochastic version of the two compartment model is derived using a continuous time Markov chain (CTMC). To derive the stochastic analogue of System (1.6), we look back at Figure 1.2, the flow diagram. Rather than focusing on each compartment and its corresponding in and out flows, as we did to derive the deterministic system, we instead focus on the *arrows*, which represent the transitions between the compartments. The arrows represent

all possible *events*.

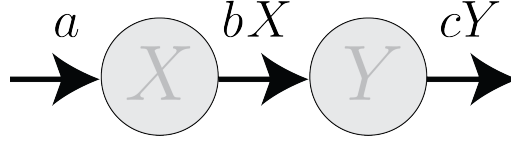


Figure 1.3: The two compartment model, with emphasis on the events (transitions between the compartments).

Let $X(t)$ and $Y(t)$ be discrete random variables, i.e.,

$$X(t), Y(t) \in \{1, 2, \dots, N\}$$

The two compartment model has 3 events. The *CTMC* makes transitions from state to state, independent of the past. The present state at time t is denoted by $Z(t) = (X(t), Y(t))$. The process then jumps to a new state at time $t + \tau(t)$, which is denoted by $Z(t + \tau(t)) = (X(t + \tau(t)), Y(t + \tau(t)))$. Let $\tau(t)$ represent the amount of time that the process remains in the state before transitioning into a new state; it is an exponentially distributed random variable. The time to the next event is then given by,

$$\tau(t) = -\frac{\ln(1 - \zeta(t))}{f(t)}, \quad \zeta(t) \text{ is } \mathcal{U}([0, 1])$$

Let $f(t)$ denote the weights of all possible events,

$$f(t) = a + bX(t) + cY(t)$$

The *transition probabilities* (or probability of events) of the two compart-

ment model are given below,

$$\begin{aligned}
 P_{((X'(t), Y'(t)), (X(t), Y(t)))}(t + \tau(t), t) &= \\
 \text{Prob} \left\{ (X(t + \tau(t)), Y(t + \tau(t))) = (X', Y') \mid (X(t), Y(t)) = (X, Y) \right\} \\
 &= \frac{1}{f_t} \begin{cases} a & \text{if } (X', Y') = (X + 1, Y) \\ bX & \text{if } (X', Y') = (X - 1, Y + 1) \\ cY & \text{if } (X', Y') = (X, Y - 1) \end{cases}
 \end{aligned}$$

We can use Gillespie's Algorithm in Section 1.2.2 to study the stochastically of System 1.6.

1. Set $t \leftarrow t_0$, $X(t) \leftarrow X(t_0)$ and $Y(t) \leftarrow Y(t_0)$, rate a , per capita rate b and per capita rate c .

while $t \leq t_f$ **do**

2. Event weights.

$$w_1 = a$$

$$w_1 = bX(t)$$

$$w_2 = cY(t)$$

3. Sum of event weights.

$$f(t) \leftarrow w_1(t) + w_2(t) + w_3(t) = a + bX(t) + cY(t)$$

4. Time to next event.

- Draw $\zeta(t)$ from $\mathcal{U}([0, 1])$.
- Draw $\tau(t)$ from $T \sim \mathcal{E}(f(t))$,

$$\tau(t) = - \frac{\ln(1 - \zeta(t))}{a(t) + bX(t) + cY(t)}$$

5. Index of next event.

- Create vector of cumulative event weights, denoted by v .

$$v \leftarrow [a, a + bX(t), a + bX(t) + cY(t)]$$

- Normalize v .

$$\frac{v}{f(t)} \leftarrow \left[\frac{a}{f(t)}, \frac{a + bX(t)}{f(t)}, \frac{a + bX(t) + cY(t)}{f(t)} \right]$$

- Draw $\zeta'(t)$ from $\mathcal{U}([0, 1])$.
- Find pos such that

$$\zeta' \leq \frac{v}{f(t)}(pos)$$

6. **switch (pos)**

Case 1: Into X , $X(t + \tau(t)) = X(t) + 1$

Case 1: Out of X , $X(t + \tau(t)) = X(t) - 1$ and $Y(t + \tau(t)) = Y(t) + 1$

Case 2: Out of Y , $Y(t + \tau(t)) = Y(t) - 1$

end switch

7. $t \leftarrow t + \tau(t)$

end while

1.4 Matrix Analysis

The following definitions and results on matrices that are used throughout the manuscript are adapted from [29, 49, 107].

Definition 1.4.1. *Let A be an $N \times N$ matrix. Then the spectrum of A , denoted by $\sigma(A)$ is the set of all eigenvalues of A :*

$$\sigma(A) = \{\lambda \in \mathbb{C} : \det(A - \lambda I_n) = 0\}.$$

Definition 1.4.2. *Let A be an $N \times N$ matrix with real entries. Then the spectral radius of A , denoted by $\rho(A)$, is the maximum of the modulus of the eigenvalues of A :*

$$\rho(A) = \max \{|\lambda|, \lambda \in \sigma(A)\}.$$

Definition 1.4.3. *Let A be an $N \times N$ matrix with real entries. Then the spectral bound or spectral abscissa of A , denoted by $s(A)$, is the maximum real part of the eigenvalues of A .*

$$s(A) = \max \{\Re(\lambda), \lambda \in \sigma(A)\}.$$

Definition 1.4.4. *A nonnegative matrix is one in which all entries are non-negative, i.e. $A = [a_{ij}] \geq 0$. It is denoted by $A \geq 0$.*

Definition 1.4.5. The direct sum, denoted by \bigoplus , of n matrices of size $n \times n$ constructs a block diagonal matrix, i.e.,

$$\bigoplus_{i=1}^n A_i = \text{diag} (A_1, \dots, A_n) = \begin{bmatrix} A_1 & \mathbf{0} & \cdots & \mathbf{0} \\ \mathbf{0} & A_2 & \cdots & \mathbf{0} \\ \vdots & \vdots & \cdots & \vdots \\ \mathbf{0} & \mathbf{0} & \cdots & A_n \end{bmatrix}$$

where $\mathbf{0}$ are $n \times n$ zero matrices.

Definition 1.4.6. A square matrix A has a Z-sign pattern if it is of the form $A = sI - B$ where I is the identity matrix and $B \geq 0$, $s > 0$.

In words, A has off-diagonal entries that are negative or zero.

Definition 1.4.7. A square matrix A is called an M-matrix if it has a Z-sign pattern and $s \geq \rho(B)$.

Definition 1.4.8. A square matrix A is called a nonsingular M-matrix if it has a Z-sign pattern and $s > \rho(B)$. If $s = \rho(B)$ then A is a singular M-matrix.

Theorem 1.4.9. A is a nonsingular M-matrix iff A is positive stable, that is, the real part of each eigenvalue of A is positive.

Lemma 1.4.10. If A has the Z-sign pattern, then $A^{-1} \geq 0$ if and only if A is a nonsingular M-matrix.

Theorem 1.4.11. *If A has the Z sign pattern, and if there exists a positive vector v such that $Av \geq 0$, then $A \in \mathcal{K}$, where \mathcal{K} denotes the set of all (possibly singular) M -matrices.*

Definition 1.4.12. *A matrix $M = [m_{ij}] \in \mathbb{R}^n \times \mathbb{R}^n$ is irreducible if there does not exist a permutation matrix P such that*

$$P^{-1}MP$$

is a block triangular matrix. Equivalently, M is irreducible if for all $i, j \in \{1, \dots, n\}$, there exists k such that

$$m_{ij}^k \neq 0$$

where m_{ij}^k is the (i, j) entry in M^k .

Definition 1.4.13. *Suppose $A = [a_{ij}] \in \mathbb{R}^{n \times n}$. Let $r_i(A)$ denote the sum of row i of A , that is,*

$$r_i(A) = \sum_{j \neq i} |a_{ij}| \text{ for } i = \{1, \dots, n\} \quad (1.7)$$

and let $\mathcal{D}_i(A)$ be a Geršgorin disk of radius $r_i(A)$ with center a_{ii} ,

$$\mathcal{D}_i(A) = \{z \in \mathbb{C} : |z - a_{ii}| \leq r_i(A)\} \quad (1.8)$$

Definition 1.4.14. *Suppose $A = [a_{ij}] \in \mathbb{R}^{n \times n}$. A matrix A is an irreducibly*

diagonally dominant matrix if A is irreducible, diagonally dominant, i.e.,

$$|a_{ij}| \geq r_i(A) \text{ for } i = \{1, \dots, n\} \quad (1.9)$$

and if strict inequality holds in (1.9) for at least one i .

Theorem 1.4.15. For any matrix $A = [a_{ij}] \in \mathbb{R}^{n \times n}$ which is irreducibly diagonally dominant, then A is nonsingular.

Theorem 1.4.16 (Geršgorin's Theorem). Suppose $A = [a_{ij}] \in \mathbb{R}^{n \times n}$. Let $r_i(A)$ and $\mathcal{D}_i(A)$ be defined as (1.7) and (1.8), respectively.

Then for any A ,

$$\sigma(A) \subset \bigcup_{i=1}^n \mathcal{D}_i(A)$$

Chapter 2

Public health terms and definitions

In this chapter, public health terms that are relevant to our study of communicable diseases at a population level are defined. Basic definitions of terms such as health, epidemic and population are presented. The differences between population health and public health are explained. We end the chapter by defining the scientific discipline of epidemiology.

2.1 Epidemiological background

Health. The World Health Organizations (WHO) defines *health* as

a state of complete physical, mental and social well being, and not merely the absence of disease or infirmity [117].

Population. *Population* refers to the number of people in a given region [66]. When individuals are counted, they are often placed in *membership* groups so that they are not counted twice. There are two criteria for counting individuals; they are known as *de jure* and *de facto* [120]. *De jure* is an example of how individuals are counted in our mass gathering application: individuals are categorized by their place of residence irrespective of where they temporarily travel to; they are always counted as *members* of their place of residence. *De facto* counts individuals based on where they are at the time of counting. If we were to use the *de facto* criteria for counting individuals after travel, they would be members of the region they traveled to, regardless of where they reside.

Epidemic, endemic and pandemic. The words *epidemic*, *endemic* and *pandemic* have Greek origins. The Greek ‘epi’ means ‘upon’, ‘en’ means ‘in’, ‘pan’ means ‘all’ and ‘demos’ means people. WHO defines an *epidemic* as [117]

the occurrence in a community or region of cases of an illness, [...] in excess of normal expectancy. The community or region and the period in which the cases occur are specified precisely. The number of cases indicating the presence of an epidemic varies according to the agent, size, and type of population exposed, previous experience or lack of exposure to the disease, and time and place of occurrence.

Simply put, an epidemic occurs when the number of infected people rises beyond the expected level within a specific country or region. When the same infection starts to take place in several countries at the same time the epidemic turns into a *pandemic*. WHO characterizes a *pandemic* (or widespread human infection) as [110]

human-to-human spread of the virus into at least two countries in one WHO region.

and a *global pandemic* as [110]

community level outbreaks in at least one other country in a different WHO region.

Thus, a pandemic covers wide geographical regions, often worldwide (crossing international boundaries), affects large numbers of people and causes greater social disruptions than an epidemic. Note that like an epidemic, pandemics also carries the underlying idea of an ‘unexpected’ or ‘sudden’ event. However, some diseases are constantly present within a region as they can always be found in a certain population; these are known as *endemic* diseases. Formally, an endemic is defined as a disease that is constantly present in a area or population- it is a baseline level for a locality [120]. To highlight the differences, an epidemic has a short time span and is an unexpected event, whereas an endemic occurs for long periods of time and is more predictable.

Incidence and prevalence. Incidence is defined as the rate at which *new* events occur in a population in a defined period of time [20]. Incidence is concerned with the *change* in status, for example, from healthy to sick [20]. Prevalence is defined as the proportion of people who possess a certain attribute either at a certain point in time or within a specific time period [120]. Prevalence is concerned with *existing* status, for example, how many people *have* a certain disease [20].

Public health and population health. *Population health* is defined as the health status of a group of people and its distribution within the group and as a field of study that focuses on both health outcomes and health determinants, as well as the policies and interventions that link them [65]. In simplified terms, population health is a conceptual framework for thinking about why some people are healthier than others and the policy development, research agenda, and resource allocation that flow from this [120]. *Public health* is the science and art of preventing disease, prolonging life and promoting health through the organized efforts of society [75]. From these definitions, one can conclude that population health provides theories and seeks to describe health issues and implement programs that protect, promote and restore the health of citizens [75], whereas Public health focuses more on the development of such programs. When studying population health, there are four main objectives: *to describe*, *to explain*, *to predict* and *to control*. The first step is to describe the state of health of populations in order to identify which health problems are most prevalent [76]. The second step is

to provide an explanation as to why the health of the population is in its current state and why that population suffers with certain health problems [76]. The third step involves the use of population health studies; such studies provide information on disease patterns and identify factors that affect the outcome of disease; the results are then used to make predictions on the state of health of a population [76]. Lastly, the results from step three must be turned into public health policy to plan and implement control strategies to effectively respond to health problems and detect outcomes of disease [120].

Epidemiology. Many of the social sciences, such as geography, sociology and anthropology are concerned with population dynamics. Within these disciplines, there are specific fields of study that focus on health related issues. A few examples of this include a medical anthropologist that studies a culture and its traditions on healing and sickness [120] and a medical geographer. *Epidemiology* is another scientific discipline that is concerned with studying health at a population level; it is a core branch of population health. Being a branch of population health, epidemiology seeks to describe, explain, prevent and control. Epidemiology is defined as the study of the distribution and determinants of health related states or events in human populations and the application of this study to control health problems [20, 68]. From the definition, one can see the three types of epidemiology that exist: descriptive, analytical and experimental or interventional [120]. *Descriptive epidemiology* describes how disease is distributed and the health conditions of a population. *Analytical epidemiology* identifies the causative agents or determinants

of disease. *Experimental* or *interventional epidemiology* provides prevention and control programs and strategies to respond to health problems. Another discipline worth noting is *Medical geography*, which uses analytical techniques to identify the relationship between geographic processes and the health status of different regions [70]. Medical geography can be used to study changes in geography in space over time and its effect on the spread of disease [70].

Chapter 3

Measles

In this chapter we present the epidemiology of measles in single and multiple populations worldwide. The epidemiological process of measles in a single population is broken down and illustrated. We end the chapter by analyzing monthly measles incidence data worldwide and detail the seasonality property that the measles virus carries.

3.1 Single population

Measles is a highly contagious infectious disease that has been claiming the lives of people for many years and is currently still one of the leading causes of death among young children [116]. It is a respiratory disease caused by a virus that is a member of the genus *morbillivirus* of the family *paramyxovirus* [101]. In the 1980's, before the widespread use of measles vaccination, measles claimed about 2.6 million lives each year [39]. In 2002, WHO reported that

there was an estimated 614,000 measles deaths worldwide and 35 million cases of the disease [57]. In 2008, there was remarkable reduction in death due to measles; there was an estimated 164,000 deaths attributed to measles [77]. Despite worldwide efforts to vastly improve routine measles vaccination coverage, measles still claimed an estimated 139,300 lives in 2010 and 158,000 lives in 2011 [116]. So, in 2011, a person died of measles every 3.3 minutes!

Measles is common in many developing countries and is predominant among malnourished children [77, 116]. Countries that have low per capita income and inadequate health care systems account for more than 95% of measles deaths [39, 116]. Developing countries in Africa and Asia are being affected by the measles virus [116]. Young children with vitamin A deficiency and already weakened immune systems due to other diseases such as HIV/AIDS, malaria and tuberculosis are at risk of contracting measles [116]. Areas with (reported) high measles containing vaccine (MCV) coverage had higher numbers of susceptible people among adolescents and adults which has grown over the years [39].

Measles is a disease that solely affects humans; there has been no confirmed case of measles among animals. Young children are not the only ones that are vulnerable to measles. Anyone who has not had measles, has not received a vaccination, or has received vaccination but has not developed immunity, is susceptible to the measles virus [101, 116].

Transmission of measles is most likely to occur if a susceptible person is in close or direct contact with an infected person or surface [116]. When an infected person coughs or sneezes, tiny droplets containing the measles virus

become air borne and can be breathed in by a susceptible person. Likewise, if the droplets have settled on a surface, a susceptible person can touch the surface and then in turn touch their nose or mouth and introduce the virus into their body [116]. The virus can remain active and contagious in the air or surfaces for up to two hours [37].

Due to the fact that measles is highly contagious, overcrowding or densely populated environments provide optimal conditions for the spread of measles. Of a pool of susceptible persons, 90% contracted the disease once they came into contact with a person infected with measles [37].

3.2 Epidemiological process of measles

The following results come from [101, 102, 116].

Upon exposure individuals can enter a incubation period which ranges from 5 to 12 days with an average of 10 days. Symptoms typically appear 10 days after being exposed to the measles virus but can range from 7 to 21 days. The first symptoms of measles is usually a high fever, followed by a cough, runny nose, red eyes and sore throat. Shortly after, tiny white spots may appear inside the mouth. Approximately 14 days after initial exposure to the measles virus a rash appears within a range of 7 to 18 days. The rash typically starts on the face and in about 3 days, spreads throughout the entire body and can last for approximately 5 to 6 days. An infected person can transmit measles from 4 days before the onset of the rash to 4 days after the rash has spread throughout the entire body, the duration of this period

is assumed to be the infectious period. It takes approximately 10 to 21 days to fully recover from measles. Once recovered, the person's body has built an immunity that lasts for their entire lifetime [57]. Figure 3.1 illustrates the epidemiological process of measles.

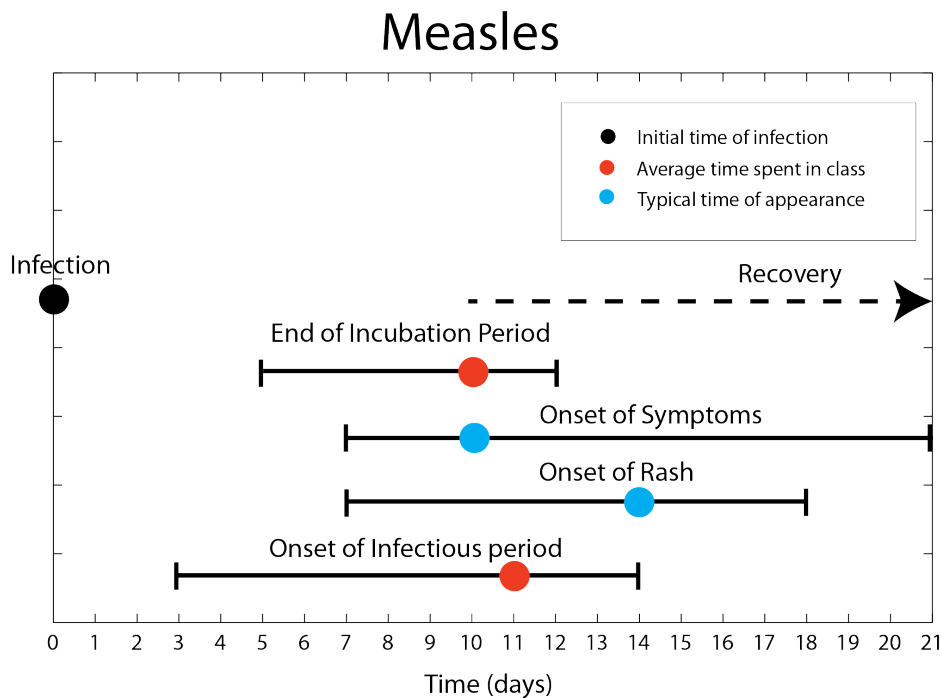


Figure 3.1: Epidemiological process of measles [101, 102, 116]. Solid lines indicate the range of the (end of) the incubation period, onset of symptoms, onset of rash, onset of infectious period and the recovery period. Red and blue dots illustrate average and typical times in each class respectively. The dotted recovery line illustrates the dependence of the recovery period on the time spent in the latent class and infectious class which varies per individual.

When looking at Figure 3.1, one should keep in mind that different people have different reactions to the measles virus and this is only an average or typical illustration of measles infection. We assume that the infectious

period lasts on average 11 days and that the latency period last on average 10 days. The arrow head on the recovery line or immunity line to measles illustrates that once a person acquires immunity after illness they are immune permanently.

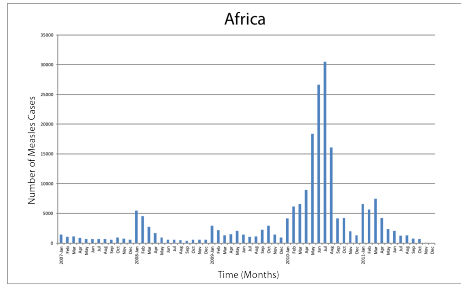
3.3 Multiple populations

During 2009 to 2010 a number of countries (including Bulgaria, France, Iraq, Malawi, Nigeria and Vietnam) experienced large measles outbreaks; most of the measles outbreaks in the countries were attributed to low measles containing vaccine coverage [39].

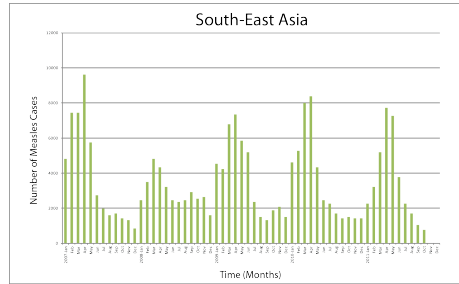
The member states of WHO are grouped into six geographical regions: the African Region (AFR), South-East Asia Region (SEAR), Eastern Mediterranean Region (EMR), European Region (EUR), Western Pacific Region (WPR) and Region of the Americas (AMR).

Figure 3.2 illustrates the incidence of measles for five WHO regions from January 2007 to December 2011 [50] (we note here that this data is used in Part III of the manuscript for the application). In 2010, AFR, WPR and EUR experienced large outbreaks of measles cases. For EUR, the outbreak continued into 2011. SEAR and EMR experience measles epidemics each year.

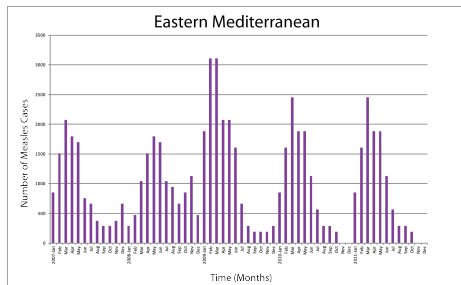
Seasonality of Measles Worldwide Upon comparing measles incidence for the five WHO regions each year, we can see that there is a seasonal aspect



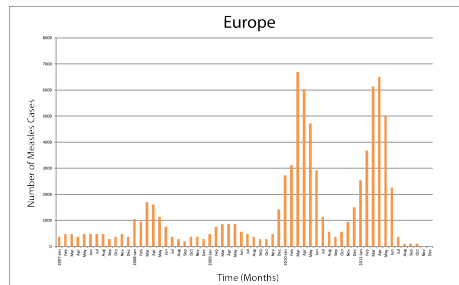
(a) AFR



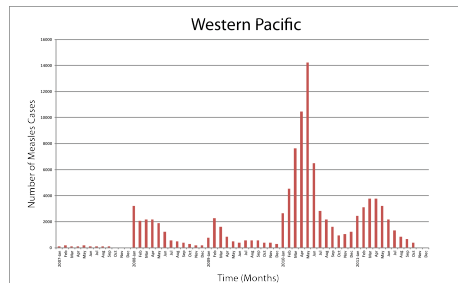
(b) SEAR



(c) EMR



(d) EUR



(e) WPR

Figure 3.2: Measles incidence data per month per WHO region from January 2007 to December 2011. Data was extracted by the Bio.Diaspora project team from monthly measles incidence data provided by WHO [50]. AMR is neglected in our study due to the relatively low number of measles cases from 2007 to 2010 compared to other WHO regions. India is not included in SEAR.

to measles incidence. The seasonality of measles is in March, April and May. That is, worldwide, the incidence of measles cases peaks during the spring. In 2010, the number of measles cases peaked in March for EMR and EUR, in April for SEAR, May for WPR and July for AFR. In 2011, all WHO regions had measles cases that peaked in March and/or April. See illustration in Figure 3.3.

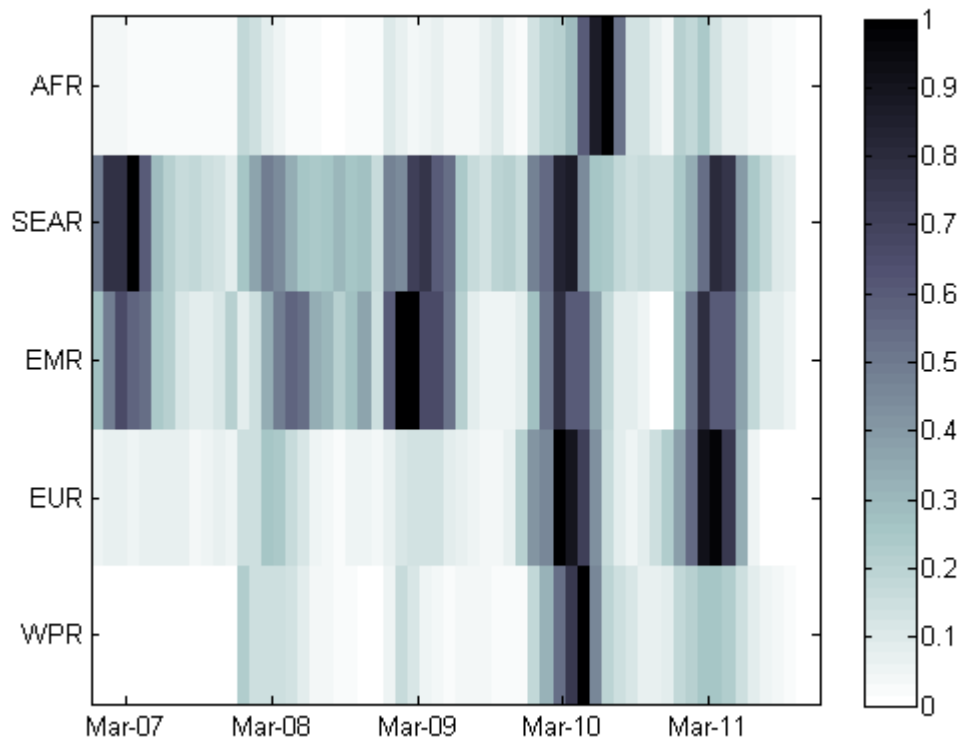


Figure 3.3: Using the data provided by [50] (see Figure 3.2) we illustrate the seasonality of measles for 5 WHO regions. The data is normalized in each region, with 1 representing the maximum value of the incidence for that region (AFR: 30,504 in July 2010, SEAR: 9,608 in April 2007, EMR: 3,107 in February and March 2009, EUR: 6,689 in March 2010 and WPR: 14,215 in May 2010).

Chapter 4

Mathematical epidemiology

The contents of this chapter include the definition of *mathematical epidemiology*, the mathematical *break down* of an epidemiological process as a chain of fixed events and we introduce compartmental models. We present the basic framework of how mathematics is used to aid in answering questions of public health concern. We then introduce and explain key concepts of mathematical modelling such as *the basic reproductive number* and the transmission function. Two methods for finding the basic reproductive number are detailed. We conclude the chapter with historical and current mathematical contributions to public health.

4.1 Mathematical modelling

In Figure 4.1, the process of mathematical modelling of biological problems is illustrated. First, a biological problem (or question) is posed, which is

then translated into a mathematical description. Second, we formulate a mathematical model after making certain assumptions, i.e., focusing on key factors and ignoring irrelevant ones. Third, we analyze the model and make theoretic conclusions. The theoretical understanding of the model is used to formulate an application using real life data. Fourth, numerical simulations give rise to predictions. Lastly, we translate the mathematical prediction into a biological conclusion.

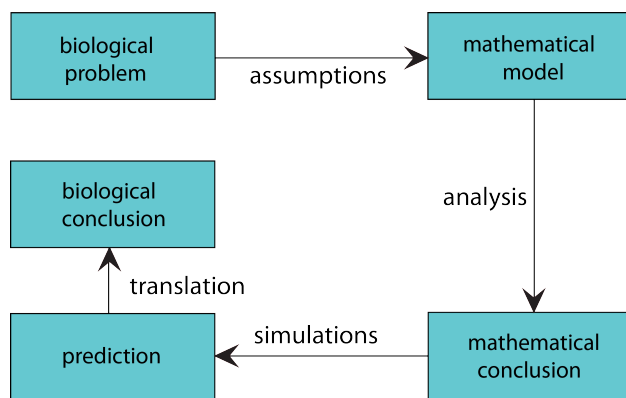


Figure 4.1: Relationship between biological problems and mathematical modelling [32].

4.2 The mathematics of an epidemiological process

Mathematical epidemiology is defined as [12]

the use of mathematical techniques to understand mechanisms leading to the spread of diseases in populations.

It is a branch of mathematics that has its roots as early as the eighteenth century (see Section 4.4).

Mathematicians break down the epidemiological process of disease transmission into a chain of *fixed* events. One of the simplest such chain of events is as follows: a *susceptible* person is initially exposed to the disease, they become *infected* with the disease, an active form of the disease develops and the person becomes *infectious*; if the person recovers, they become *recovered* or *immune*; immunity can be either be temporary or permanent. Populations such as these, i.e., the susceptible, latent, infectious or recovered individuals are divided *into* compartments. It is worth clearly defining what these terms mean, as they will be used repeatedly throughout the manuscript.

Susceptible. A *susceptible* person is a person who is vulnerable or lacking protection or defense to contracting a particular disease. Susceptible individuals are part of the susceptible compartment which is denote by S .

Latent. Once the disease enters the body, individuals can harbour the pathogen in an inactive or dormant form; during this phase, they do not show symptoms and they cannot transmit the pathogen to other people. That is, they are not yet infectious. This period in which the pathogen remains dormant is known as the *incubation* or *latency* period. Latent individuals are part of the latent compartment which is denote by L .

Infectious: asymptomatic or symptomatic. After the *latent* period, infected individuals move into a *infectious* period in which individuals can

transmit the disease to other people. Infectious people can be classified as symptomatic or asymptomatic. *Symptomatic* people are people that have developed symptoms of the disease and can transmit the disease to others. *Asymptomatic* people are people that show no symptoms of disease but can transmit the disease to others. Individuals are removed from the infectious class by isolation from the rest of the population, recovery from the disease or death (due to the disease or not). Infectious individuals are part of the symptomatic or asymptomatic compartments, denoted by I and A respectively.

Infected. In the two above stages (latent and infectious), we say that the individuals are *infected* with the disease, i.e., they harbour the pathogen whether in an inactive or active form. Infected individuals may or may not be able to transmit the disease to other people. Infected compartments play a very specific role in mathematical epidemiology, as will be seen later. Infected individuals are part of the $L + I$ compartment.

Recovered. Once the infection is cleared, whether induced or natural, the person moves into the recovered compartment. *Recovered* individuals are defined as people that are free from the disease or have developed temporary or permanent immunity to the disease. Individuals can also progress directly from the susceptible class to the recovered class by vaccination. Another term used for recovered individuals is *removed* individuals, in which case the focus is on their leaving the infectious compartments (and thus their ceasing

to infect others), even through death. Recovered individuals are part of the recovery compartment which is denoted by R .

After the recovery period the individual can become infected again (e.g. influenza) or gain permanent immunity (e.g. chicken pox). In the case that an individual gained only temporary immunity, the individual would become susceptible to the disease again. However, if the individual gained permanent immunity they would never be susceptible again.

The models used in this manuscript divide individuals composing a population into the compartments previously mentioned, which are based on their disease status. Classifying populations this way and making assumptions about the nature and rate of transfer from one compartment to another gives rise to *compartmental models* [34, 60]. Depending on the disease of interest, a mathematical model has a certain compartmental structure. A general model usable as a first approximation to measles can be the so-called *SLIR* model.

The *SLIR* model has four compartments; the notation indicates the passage of individuals from the susceptible compartment S to the latent compartment L to the infectious compartments I and then to the removed (or immune) R compartment. The *SLIR* model describes the following disease dynamics:

- Upon exposure and infection of measles, individuals enter a latency period.
- Latent individuals proceed to the symptomatic (infectious) compart-

ment.

- Symptomatic individuals proceed to the immune compartment and acquire permanent immunity (i.e. life time immunity against re-infection).

For the majority of the manuscript we formulate, analyze and study the *SLIR* model for single and multiple populations. Then for the application in Chapter 9 of Part III we use the *SIR* sub-model of *SLIR* (the use of *SIR* is detailed there).

4.3 Mathematical modelling of infectious diseases

4.3.1 Mathematical expression of the incidence rate

The following concepts are adapted from [33, 34].

$\phi(\beta, S, I)$ is called the *transmission function* or incidence rate which denotes the number of new infections per unit time. $\phi(\beta, 0, I) = \phi(\beta, S, 0) = \phi(0, S, I) = 0$ since no susceptibles, no infectious individuals, or zero transmission rate, produces no new cases of infection. The transmission rate $\beta(c, q, k)$ has three parameters that are all assumed to be constant. Let c denote the average number of people a individual contacts, q denote the frequency of contacts between them and $0 \leq k \leq 1$ denote the fraction of the contacts that develop into new cases of infection per unit time. The transmission rate is defined by $\beta = cqk$.

Let $S(t)$ and $I(t)$ denote the number of susceptible and infective individuals at time t and $N(t)$ the total number of individuals at time t . The total number of contacts of all susceptible individuals at time t is given by $cqS(t)$. If individuals mix at random, known as *homogeneous mixing*, then the number of contacts between susceptibles per unit time is $cqS(t)\frac{S(t)}{N(t)}$ and the number of contacts between susceptibles and infectious individuals per unit time is given by $cqS(t)\frac{I(t)}{N(t)}$. With $\beta = cqk$ we have an expression for the incidence function in a randomly mixing population called *standard incidence*,

$$\phi(\beta, S, I) = \beta S(t) \frac{I(t)}{N(t)}. \quad (4.1)$$

If susceptibles and infectives make contacts sufficient to transmit infection with N other individuals per unit time, we have another expression for the incidence function in a randomly mixing population called *mass action incidence*,

$$\phi(\beta, S, I) = \beta N(t) S(t) \frac{I(t)}{N(t)} = \beta S(t) I(t). \quad (4.2)$$

Mass action incidence is more suitable for small populations as it assumes that every susceptible comes into contact with every infectious individual. Standard incidence is more suitable for large populations since it assumes that every susceptible interacts with a proportion of the infectious population (denoted by the term $\frac{I}{N}$); for large populations it is highly unlikely that every susceptible would interact with every infectious individual.

In Chapter 5 of Part II in the manuscript the transmission function is assumed to take the form of mass action incidence (4.2) since the size of the population is assumed to be small. In Chapter 6 of Part II and in Part III we use the the form of standard incidence (4.1) since we are interested in studying populations of large size. We can combine this fact with a well known hypothesis for human diseases which states that the use of standard incidence is more accurate than the use of mass action [18].

Explicit values for c , q , k are not derived as they are incorporated in the β value. The incidence rate, β , is estimated by different methods since it is a parameter that is not easily measured. In Chapter 5 of Part II, β takes on the value of a function dependent on \mathcal{R}_0 , that is, we assume that the basic reproductive number is known. In Chapter 9 of Part III, $\beta(t)$ takes the form of a sinusoidal time dependent function and is estimated using *parameter identification*.

4.3.2 The basic reproductive number

A crucial concept in mathematical epidemiology is the *basic reproductive number*. To illustrate it, let us assume that *transmission of infection* refers to transmission of an active form of the disease; in other words, the susceptible individuals become infectious with no latency.

Now visualize a completely susceptible population and then introduce one infectious individual into that population. Once the infectious individual makes contact with the susceptible population, there is a certain probability

that the contact leads to transmission of the infection. Assume that two of the susceptible individuals become infectious and in turn each infect on average two more susceptible people. A scenario like this would result in a basic reproductive number of 2. The number of infectious individuals would then initially be growing exponentially (with base 2); this is called a *disease outbreak*. On the other hand, following the same example but now assuming that on average, less than one susceptible individual becomes infectious; the basic reproductive number would be less than one; this is known as *disease extinction*. Thus, the reproductive number represents a threshold value.

In epidemiological terms, the basic reproductive number is defined as the expected number of secondary infectious cases produced, in a completely susceptible population, by a typical infectious individual [43]. Mathematically, we denote the basic reproductive number by \mathcal{R}_0 , pronounced *R-zero* or *R-naught*. If $\mathcal{R}_0 < 1$, then an infectious individual, during his/her infectious period, produces on average less than one newly infectious individual; in this case, the disease will die out. If $\mathcal{R}_0 > 1$, then an infectious individual, during his/her infectious period, produces on average more than one newly infectious individual; in this case, the disease prevails. In epidemiology terms, the *prevalence of infection* increases if $\mathcal{R}_0 > 1$ and decreases if $\mathcal{R}_0 < 1$. Methods for calculating \mathcal{R}_0 are presented below in Section 4.3.3.

4.3.3 Next generation method for calculating \mathcal{R}_0

The following results are reproduced from [105].

Order the compartments first by the m infected compartments then by the non-infected compartments. Let $X(t) = (X_1(t), X_2(t), \dots, X_n(t))^T$ be the number of individuals in each compartment with each $X_i \geq 0, i \in \{1, \dots, n\}$. Let $F_i(X)$ be the rate of appearance of new infections in compartment i . Let $V_i^+(X)$ be the rate of transfer of individuals into compartment i by all other means and let $V_i^-(X)$ be the rate of transfer of individuals out of compartment i . We assume that F_i, V_i^-, V_i^+ are continuously differentiable at least twice in each variable X_i . The disease transmission model with nonnegative initial conditions, $X_i(0) \geq 0$, takes the following form,

$$\frac{d}{dt}X_i(t) = f_i(X(t)) = F_i(X(t)) - V_i(X(t)), \quad i \in \{1, \dots, n\}. \quad (4.3)$$

where $V_i = V_i^- - V_i^+$ and the function f_i satisfies conditions (C1) to (C5) below. Let X_{DF} denote the set of all disease free states. That is,

$$X_{DF} = \{X \geq 0 | X_i = 0, i \in \{1, \dots, m\}\} = \{X_{m+1}, \dots, X_n\}$$

- (C1) If $X \geq 0$ then $F_i, V_i^-, V_i^+ \geq 0$ for $i \in \{1, \dots, n\}$. In words, since the components of each vector represents a direct transfer of individuals, they are all nonnegative.
- (C2) If $X_i = 0$ then $V_i^- = 0$ for $i \in \{1, \dots, n\}$. In words, if a compartment is empty, then there can be no transfer of individuals out of the

compartment by death, infection or by any other means.

- (C3) $F_i = 0$ if $i > m$. That is, $F_{m+1} = \dots = F_n = 0$. In words, the incidence of infection for uninfected compartments is zero.
- (C4) If $\bar{X} \in X_{DF}$ then $F_i(\bar{X}) = 0$ and $V_i^+(\bar{X}) = 0$ for $i \in \{1, \dots, m\}$. We will denote this by $F_i|_{\bar{X}} = 0$ and $V_i|_{\bar{X}} = 0$ with $|_{\bar{X}}$ denoting *evaluated at the disease free equilibrium*.

We define a disease free equilibrium (DFE) of System (4.3) to be a locally asymptotically stable equilibrium solution of the disease free model, i.e. System (4.3) restricted to X_{DF} . Let \bar{X} denote the DFE. Consider a population near \bar{X} . If our initial condition remains near \bar{X} , that is, the introduction of a few number of infectives does not result in an epidemic, then the evolution of the population can be approximated by the the linearized system

$$\frac{d}{dt}X = Df|_{\bar{X}}(X - \bar{X}), \quad (4.4)$$

where $Df(\bar{X})$ is the derivative $\partial f_i / \partial X_j$ for $i, j \in \{1, \dots, n\}$ (i.e., the Jacobian matrix) evaluated at the DFE, \bar{X} .

- (C5) If $F(X)$ is set to zero, then all eigenvalues of $Df|_{DFE}$ have negative real parts. That is, the disease free model has a locally asymptotically

stable disease free equilibrium.

To determine the local asymptotic stability of the *DFE* of System (4.3), it is sufficient to look at a subsystem of System (4.3) composed of only the infected compartments, given by

$$\frac{d}{dt}\mathcal{X} = \mathcal{F} - \mathcal{V}, \quad (4.5)$$

with $\mathcal{X} = \{X_1, \dots, X_m\}$. The vector \mathcal{F} represents the new infections into the infected classes and \mathcal{V} represents the in and out flows of individuals in the infected classes other than new infections. The linear stability of System (4.3) is determined by the linear stability of (4.5) (shown in the Lemma below).

Lemma 4.3.1. *If \bar{X} is a DFE of System (4.3) and $f_i(X)$ satisfies (C1) to (C5) above, then the Jacobian matrices $D\mathcal{F}|_{\bar{X}}$ and $D\mathcal{V}|_{\bar{X}}$ are given by,*

$$D\mathcal{F}|_{\bar{X}} = \mathbb{F}, \quad D\mathcal{V}|_{\bar{X}} = \mathbb{V}$$

where \mathbb{F} and \mathbb{V} are $m \times m$ matrices defined by,

$$\mathbb{F} = \left[\frac{\partial \mathcal{F}}{\partial \mathcal{X}} \right] |_{\bar{X}}, \quad \mathbb{V} = \left[\frac{\partial \mathcal{V}}{\partial \mathcal{X}} \right] |_{\bar{X}} \text{ with } \mathcal{X} = \{X_1, \dots, X_m\}.$$

Further, \mathbb{F} is nonnegative and \mathbb{V} is a nonsingular *M*-matrix.

Theorem 4.3.2 (Next generation method). *Consider model (4.3) with f*

satisfying conditions (C1) to (C5) and let

$$\mathcal{R}_0 = \rho(\mathbb{F}\mathbb{V}^{-1})$$

where \mathbb{F} and \mathbb{V} are Jacobian matrices of \mathcal{F} and \mathcal{V} in (4.5) obtained by differentiating with respect to the infected classes and then evaluating at a disease free equilibrium \bar{X} . Then \bar{X} is locally asymptotically stable if $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 > 1$.

4.3.4 An alternate method for calculating \mathcal{R}_0 for epidemic models.

The following results are reproduced from [14]. The derivation of the basic reproductive number in [14] uses the same definition of \mathcal{R}_0 in the next generation method, refer to Section 4.3.3, with different definitions for the matrices \mathbb{F} and \mathbb{V} .

For epidemic models we ignore demographic effects since epidemics are short lived in comparison to the life of an individual (explanation is further detailed in the section on modelling epidemic measles). And so birth and death does not take place. Consider a general epidemic disease transmission model in which $\mathcal{I} \in \mathbb{R}^n$ represents the $n \times 1$ column vector of infected compartments, $\mathcal{S} \in \mathbb{R}^m$ represents the $m \times 1$ column vector of susceptible compartments and $\mathcal{R} \in \mathbb{R}^k$ represents the $k \times 1$ column vector of recovered or immune compartments. Let D be a $m \times m$ diagonal matrix whose entries

$\sigma_i > 0$ are the relative susceptibilities of the corresponding susceptible class. It is assumed that $\sigma_1 = 1$. Let Π be an $n \times m$ matrix whose entries $\Pi(i, j)$ represent the fraction of the j^{th} susceptible compartment that goes into the i^{th} infective compartment on becoming infected. Let b be a $1 \times n$ row vector of relative horizontal transmissions. The general incidence function, $\beta(\mathcal{I}, \mathcal{S}, \mathcal{R})$ depends on the population in the infective population compartment and the total population size. It is assumed that mass action incidence is used with $\beta(\mathcal{I}, \mathcal{S}, \mathcal{R}) = \beta$, a constant. Let V be a $n \times n$ matrix that describes the transmissions between the infected compartments including removals (i.e. death, recovery etc.). Let W be $k \times n$ matrix with entries $W(i, j)$ represent the rate at which members of the j^{th} disease compartment go into the i^{th} removed compartment upon recovery.

The epidemic model takes on the following form,

$$\mathcal{I}' = \Pi D \mathcal{S} \beta b \mathcal{I} - V \mathcal{I} \tag{4.6a}$$

$$\mathcal{S}' = - D \mathcal{S} \beta b \mathcal{I} \tag{4.6b}$$

$$\mathcal{R}' = W \mathcal{I} \tag{4.6c}$$

With nonnegative initial conditions, that is, $\mathcal{I}_0 \geq 0$, $\mathcal{S}_0 \geq 0$, $\mathcal{R}_0 \geq 0$ such that at least one component of \mathcal{I}_0 is positive.

\mathcal{S} contributes to disease transmission whereas \mathcal{R} does not so the equations are considered separately. Since we assume the use of mass action incidence Equation (4.6c) can be decoupled from System (4.6) which reduces the di-

mension of the system. The point $(0, \mathcal{S}^*, \mathcal{R}^*)$ is a disease free equilibrium of System (4.6). Define the $n \times n$ matrix F to be,

$$F = \Pi D \mathcal{S}^* \beta b.$$

The basic reproductive number is

$$\mathcal{R}_0 = \rho(FV^{-1}) = \rho(\Pi D \mathcal{S}^* \beta b V^{-1}) = \text{Tr}(\Pi D \mathcal{S}^* \beta b V^{-1}) = \beta b V^{-1} \Pi D \mathcal{S}^*.$$

Theorem 4.3.3 (The basic reproductive number for epidemic model). \mathcal{R}_0 for System (4.6) at the disease free equilibrium $DFE = (0, \mathcal{S}^*, \mathcal{R}^*)$ is given by,

$$\mathcal{R}_0 = \beta b V^{-1} \Pi D \mathcal{S}^*$$

The DFE is locally asymptotically stable if $\mathcal{R}_0 < 1$ and is unstable if $\mathcal{R}_0 > 1$.

4.4 Brief history of mathematical epidemiology

There are numerous historical contributions of mathematics and statistics to the study of epidemiology; only some are listed here.

4.4.1 Single population dynamics

In 1760, Daniel Bernoulli, a physician and mathematician, formulated a model for smallpox to answer the question, “can variolation against smallpox eliminate the risk of death due to smallpox so that life expectancy can be increased?” [44]. Farr and Ransome were both physicians who promoted the use of statistical instruments. In 1866, Farr used curve fitting techniques to describe cattle-plague epidemic curves [44]. Shortly after, in 1868, Ransome studied underlying mechanisms of epidemics, specifically explaining how the density of the susceptible population affects the spread of an epidemic [44]. In 1889, En’ko, a physician, presented a chain binomial (discrete-time) model for the spread of childhood diseases [44, 99]. In 1906, Hamer, a physician, studied and analyzed epidemic diseases in England, among them where influenza, dengue and measles [55]. Hamer formulated a discrete-time model to understand periodic epidemics of measles [51]. In 1907, Brownlee, a physician and statistician provided results on how to measure the *infectivity* of an epidemic [51]; he was one of the pioneers who formulated the mass action law [44]. The other pioneer was a physician, Sir Ronald Ross, who we quoted in our introduction. In 1902, Ross was awarded the *Nobel Prize for Medicine* for his work on malaria [35, 72]. From 1908 to 1921, Ross formulated mathematical models to study transmission dynamics of malaria, treatment methods and concepts of ‘control’ which were applied to mosquito borne diseases [99]. In 1927, Kermack, a physician and McKendrick, a physician and epidemiologist, formulated the well-known simple *SIR* compartmental model to

describe how epidemics behave and how the density of a population exhibits threshold behavior [62]. In 1971, statisticians Gani and Jerwood provided stochastic analogues for chain binomial models using Markov chain methods [61]. In 1978, May, a physicist, and Anderson, an epidemiologist, used simple mathematical models to study the dynamical behavior of host and parasite populations [7]. Following their work in 1978, in 1982 and 1985, Anderson and May studied *SLIR* and *MSLIR* systems of partial differential equations, as parameters depended on both age and time, where M represented the population of infants that were protected by maternally acquired antibodies [8, 9]. The purpose of their age-dependent model was to study the concept of *herd immunity* in relation to the age of an individual and they applied their study to a variety of diseases, among them where measles and whooping cough in Britain.

4.4.2 Spatial dynamics

Permanent movement (migration)

The models in this section are referred to as *migration* models, i.e. permanent travel models. When an individual travels, they become part of the population in the location to which they traveled. A model with N cities and p different epidemiological classes results in a system of pN differential equations. In 1956, Bartlett, a statistician, studied the spatio-temporal disease spread process of a two-patch *SI* deterministic model. In his two-patch model individuals migrate from one patch to the other and transmission of

disease is defined by *cross patch infection* in addition to local transmission [27]. In 1967, Baroyan and Rvachev studied the spatial spread of influenza type diseases within a large territory [25] that they partitioned into smaller sub-regions; sub-regions were interconnected by an explicit transportation network. They studied variations of the *SIRS* discrete time deterministic system with rapid and slow methods of transportation. It was assumed that movement was independent of disease status since influenza like diseases do not hinder travel ability. They further assumed that during movement individuals interact with one another but not with people who use different transportation networks or those that do not use any form of travel at all. In 1971, Baroyan, Rvachev and collaborators formulated a model to study and provide predictions for the spatial spread of influenza between 43 of the largest cities in USSR using real country passenger traffic data [26]. Their model contained the daily incidence of influenza as unknown functions of time in order to approximate the real daily registered morbidity for each city. In 1985, as mentioned in the introduction, Rvachev and Longini formulated an *SLIRS* system of difference equations to forecast the 1968-1969 Hong Kong influenza A pandemic from its origins in Hong Kong to 51 other major world cities [93]. In 1986, Faddy presented a *SI* deterministic system of N spatially connected locations that incorporated both cross patch infection and migration [47]. He found that the epidemic in each location experiences a *conservation law*, one that is similar to a law found in the case of a single location with no spatial dispersion of populations. He derived an expression for the final size relation of the epidemic in terms of

the final number of susceptible remaining uninfected in location i . In 1996, an *SIR* N -group deterministic epidemic model and its stochastic analogue (Markov) was formulated by Clancy [41]. His study made certain assumptions which included that all individuals move between groups except for removed individuals and upon contact with infected individuals susceptible are immediately removed. In 2001, Rodriguez and Torres-Sorando formulated an N -patch vector-host malaria model where they consider the effect of different migration patterns and environmental heterogeneities of the patches and their influence on disease propagation [89]. In 2003, Hyman and LaForce studied a *SIRPS* multi-city (or N patch) deterministic model for Influenza where P denotes individuals that are partially immune; both susceptible and partially immune individuals can become infected [58]. The infection rate is a periodic function since influenza is more likely to spread in the winter than in the summer. Their model used 1996-2001 influenza H3N2 data, 2000 census data for the population of the 33 largest cities in the United States and migration between the cities was approximated using daily airline flight data. All the models discussed so far are referred to as single-species models with the exception of [89] which is of 2-species type (the vector and the host). In 2005, Arino et al., studied a multi-species metapopulation model [15]. They formulated a *SEIR* N -patch S -species model to describe the spatial propagation of disease that can be transmitted between more than one species. Analytical results included the computation of \mathcal{R}_0 , the global stability of the Disease Free Equilibrium and a proof that all patches are at an endemic equilibrium in species i provided that a fixed patch is at an endemic equilib-

rium in species i and irreducibility of the movement matrix holds. In 2011, Arino, Ducrot and Zongo formulated a metapopulation malaria model using an SI -model for the vector population and $SIRS$ -model for the host population with human movement and no movement of mosquitoes [16]. Their model accounts for *transmission blocking immunity*. That is, they consider semi-immune individuals who are defined to be asymptomatic human carriers of malaria who are less infectious to mosquitoes than symptomatic carriers and have less susceptibility than non-immune individuals. Analytical results include the following: uniqueness of DFE , expression for \mathcal{R}_0 which establishes the local asymptotically stability of DFE , (if disease induced death is assumed zero for all patches) the use of certain incidence functions establishes the global stability of DFE when $\mathcal{R}_0 < 1$ with an extra restriction that backward bifurcation cannot occur. Type reproductive numbers were used to identify the *spatial infection reservoirs* which are subpopulations to which control strategies are applied to in order to eradicate the disease in the whole system. The malaria model was applied to different disease and environmental characteristics, movement between an endemic patch and non-endemic patch was studied and due to increased urbanization movement between rural patches and an urban patch was also studied.

Temporary movement (travel)

The models in this section are referred to as *movement* models, i.e. travel models. Here individuals are assigned to a particular region (usually their country of residence) and travel does not change that assignment. That is, re-

ardless of where individuals travel to, they are always part of the population they are resident of. A model with N cities and p different epidemiological classes results in a system of pN^2 differential equations.

In 1995, Sattenspiel and Dietz formulated a *SIR* multi-patch epidemic model that described travel between N discrete geographic regions where individuals are tracked by the patch in which they are born and where they are at a given time [95]. Here individuals are assumed to return home before travelling to another patch. The transmission of infection takes movement and non-random mixing into account, that is, the transmission term is adjusted to reflect individuals of all patches actually present in a location. As an application, they developed an age-structured 7-patch residency model to numerically study the 1984 measles outbreak on the West Indian Island of Dominica. Mobility patterns differed depending on age: school activity mobility, general children's mobility and adult mobility. In 1998, Sattenspiel and Herring used the framework of [95] to numerically study the spread of the 1918-1919 influenza epidemic in three isolated communities in the Central Canadian Subarctic [96]. Results showed that the timing of epidemics within and among the communities is affected by mobility patterns and contact rates within communities. In 2003, Arino and van den Driessche provided analytical results for *SIS* and *SEIRS* N -patch epidemic residency models [17, 18]. An explicit formula for the basic reproductive number was derived giving the first examples that applied the next generation method of [105] to such high dimensional models. Uniqueness and stability of the DFE is proved for both models. Numerical results in [18] show that a change in mobility

can lead to a bifurcation at $\mathcal{R}_0 = 1$ which tell us that travel can stabilize or destabilize the DFE. In 2006, Arino and van den Driessche extended the residency model of Sattenspiel and Dietz in [95] and allowed individuals to travel between two patches with neither patch being their residency patch [19]. In 2006, Ruan, Wang and Levin proposed a *SEQIR* N-patch model to study the global spread of SARS; E refers to the exposed or latent individuals and Q refers to the individuals that are in quarantine [92]. It was assumed that those in quarantine do not travel. They determined the existence of the DFE, derived the basic reproductive number by method [105] thereby deducing the local stability of the DFE. They presented an example of a 2-patch model with Hong Kong and Toronto being the two regions. Results showed that the return rate of residence of Toronto in Hong Kong and residence of Hong Kong in Toronto did not affect the basic reproductive number, i.e. \mathcal{R}_0 is invariant, if infectious individuals are barred at borders and if both Hong Kong and Toronto residence do not travel outside their native cities. In 2012, Iggidr, Sallet and Tsanou analytically proved a conjecture of Arino and van den Driessche in [18] on the global asymptotic stability of the endemic equilibrium of the *SIS*-model [59].

Part II

Modelling the dynamics of measles

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Chapter 5 is dedicated to mathematical modelling of *disease dynamics within a single population* using two types of models for measles. Both epidemic and endemic models for measles are studied using deterministic and stochastic approaches. We derive a deterministic *epidemic* model, analyze the model and provide numerical results. We then derive the stochastic analogue of the deterministic epidemic model and provide simulations for the stochastic process. The results of the deterministic epidemic model and its corresponding stochastic analogue are compared. We motivate the use of stochastic processes, discuss their importance in modelling disease dynamics and highlight vital results that would of have been missed had a stochastic process not been studied and analyzed. Similar techniques are used to derive and analyze the deterministic endemic model for measles. The stochastic analogue of the deterministic endemic model is derived. Numerical solutions for both the deterministic system and stochastic process are provided. The results of the deterministic endemic model and its corresponding stochastic analogue are compared.

The comparison study of the epidemic model versus the endemic model will allow us to make an informed decision on the model most suitable for describing measles. These two models represent different hypothesis but do

share some similarities in light of their evident contrasting characteristics.

Measles is an endemic disease; it has persisted for centuries, so including demography is vital. Thus, when modelling measles the endemic measles model is used. We will see later in the manuscript that populations around the world have large immune populations because the large infected population eventually acquired natural immunity to the virus.

In Chapter 6 we model the spatial dynamics of measles using metapopulation theory. Metapopulation modelling incorporates a transportation network that connects diverse populations from around the world. An endemic metapopulation model with residency is studied; the formulation of the deterministic system and its stochastic analogue is detailed and analytical results for the deterministic system are provided. The implementation of Gillespie's algorithm for the metapopulation model with residency is detailed.

Chapter 5

Mathematical modelling of measles transmission in a single population

5.1 Deterministic model of *epidemic* measles

An epidemic is an outbreak of disease that in a short duration of time, *kicks off*, spreads rapidly and infects a large portion of a population before it dies out. Epidemics initially start off with small numbers of infectious individuals. The time scale of an epidemic is much shorter than the time scale for demographic effects such as birth and death, therefore, demography can be ignored when studying epidemics. An epidemic model for measles is formulated using a system of ordinary differential equations. To derive the differential equations, we first *compartmentalize* the epidemiological process,

i.e., identify the mathematical compartments.

Adopting the same terminology as in Section 4.2, the epidemiological process of transmission of measles is broken down into four fixed events. Once a susceptible individual has come into contact with the measles virus, they may become infected with the disease. In the case of *inactive* infection with the measles virus, susceptible individuals enter an *incubation or latency* period, wherein individuals are infected but not yet infectious. After the *latency* period, the infected individuals move into the *infectious* period, that is, they can transmit the disease to other people. As the infection dies out, the person moves into the *recovery* period; the individual no longer spreads the disease to others. Upon recovery, the individual gains lifelong immunity to the measles virus and therefore remains in the recovery or immune class until their death.

Thus, we assume there are four mathematical compartments: *susceptible*, *latent*, *infectious* and *recovered*; see Figure 5.1. We denote

- S the compartment of susceptible individuals,
- L the compartment of latent individuals,
- I the compartment of infectious individuals,
- R the compartment of recovered or immune individuals.

ϕ denotes the rate at which new infections are generated, the *force of infection*. Using mass action incidence, $\phi = \beta SI$, where β is the transmission parameter. Let ϵ be the per capita rate of incubation and α be the per

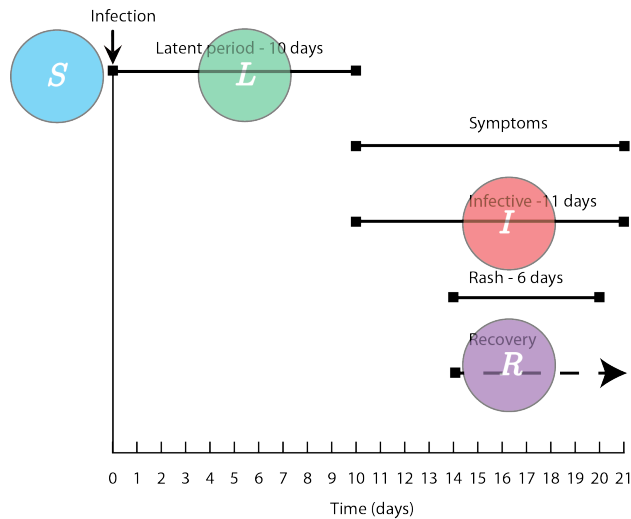


Figure 5.1: Compartments for measles

capita recovery rate. The time spent in the L and I compartments are exponentially distributed with a mean of $1/\epsilon$ and $1/\alpha$, respectively. Parameters β, ϵ, α are assumed to be nonnegative. Initial conditions are all nonnegative, $S(0), L(0), I(0), R(0) \geq 0$.

The flows between the epidemiological classes, are shown in Figure 5.2.

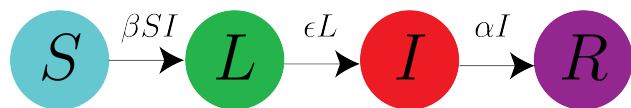


Figure 5.2: The compartmental model for the $SLIR$ deterministic system without demography.

Following the same methods and techniques in Section 1.3, the differential equations that describe the $SLIR$ system can be derived from its corresponding flow diagram. Thus, the four differential equations that represent the $SLIR$ deterministic system without demography are expressed as,

$$\frac{d}{dt}S(t) = -\beta SI \quad (5.1a)$$

$$\frac{d}{dt}L(t) = \beta SI - \epsilon L \quad (5.1b)$$

$$\frac{d}{dt}I(t) = \epsilon L - \alpha I \quad (5.1c)$$

$$\frac{d}{dt}R(t) = \alpha I \quad (5.1d)$$

We consider System (5.1) with nonnegative initial conditions, $S(0) \geq 0$, $L(0) \geq 0$, $I(0) \geq 0$, $R(0) \geq 0$. Furthermore, $S(0) + L(0) + I(0) + R(0) = N(0) > 0$ to avoid a trivial case.

5.1.1 Existence and uniqueness

Proposition 5.1.1 (Existence and uniqueness). *Consider System (5.1) with nonnegative initial conditions. Then solutions to System (5.1) exist and are unique for all $t \geq 0$.*

Proof. Let $x(t) = (S(t), L(t), I(t), R(t))^T \in \mathbb{R}^4$. System (5.1) is written in form (1.2), that is, $\frac{d}{dt}x = f(x)$. The components of f are denoted by f_i for $i = \{1, 2, 3, 4\}$.

$$f_1 = -\beta SI$$

$$f_2 = \beta SI - \epsilon L$$

$$f_3 = \epsilon L - \alpha I$$

$$f_4 = \alpha I$$

The vector field f consists of sums of linear terms written in terms of S , L , I and R . Thus, f_i are continuous functions on \mathbb{R}^4 . $\frac{df_i}{dS}$, $\frac{df_i}{dL}$, $\frac{df_i}{dI}$ and $\frac{df_i}{dR}$ exist, which implies that f_i are differentiable functions. Hence, by Theorem 1.1.4, a unique solution exists to the initial value problem $\frac{d}{dt}x = f(x)$ for any initial condition $(S(0), L(0), I(0), R(0)) \in \mathbb{R}^4$. \square

5.1.2 Nonnegativity

Proposition 5.1.2 (Nonnegativity of solutions). *Given nonnegative initial conditions to System (5.1), the solutions of (5.1), $S(t)$, $L(t)$, $I(t)$, $R(t)$ are all nonnegative $\forall t \geq 0$.*

Proof. Assume that the initial conditions are nonnegative, that is, $S(0)$, $I(0)$, $L(0)$ and $R(0) \geq 0$. Setting $S = 0$ in (5.1a) gives

$$S' = 0$$

Since we started with a nonnegative initial condition and $S' = 0$ at $S = 0$, S cannot cross into the negative region; therefore, S is nonnegative for all $t \geq 0$. Now let $I = 0$ in (5.1c), giving

$$I' = \epsilon L \tag{5.2}$$

and so the sign of I' depends on the sign of L . Now set $I = 0$ also in (5.1b),

$$L' = -\epsilon L \tag{5.3}$$

From (5.3) we see that $L' \leq 0$ which implies that L is a decreasing function that eventually hits zero (i.e. the velocity will be zero) so it will never cross into the negative region. Thus, L is nonnegative for all $t \geq 0$. From (5.2), since L is nonnegative $I(t)$ is an increasing function which implies that I is nonnegative for all $t \geq 0$. Consider R' in (5.1d) and let $R = 0$,

$$R' = \alpha I$$

Since I is nonnegative, $R' \geq 0$ and so $R(t)$ is an increasing function which implies that $R(t)$ is nonnegative for all $t \geq 0$. \square

5.1.3 Boundedness

Summing all the equations of (5.1) gives the evolution of the total population, $N(t)$

$$N'(t) = 0.$$

Integrating with respect to t , $N(t)$ is a constant:

$$N(t) = N, \quad N \text{ constant}$$

Therefore, the total population is constant. And so, for any t ,

$$N = N(0) = S(t) + L(t) + I(t) + R(t).$$

System (5.1) is said to *conserve the total population*. Conservation of the total population number is reasonable biologically since the course of an epidemic is short compared to the life of an individual. So during an epidemic, birth and death can be ignored and hence the population being considered essentially remains constant.

System (5.1) is well-posed since solutions to (5.1) exist and are unique, remain nonnegative for nonnegative initial conditions for all $t \geq 0$ and the total population size is constant.

5.1.4 Definition of outbreak

For (5.1), an outbreak of disease is defined by certain conditions on the infected classes. Recall that the infected classes are the latent and infectious individuals, L and I .

Definition 5.1.3. *An outbreak of measles occurs if the number of individuals in the infected classes is an increasing function for some period of time,*

$$(L + I)' > 0 \Leftrightarrow (L + I) \uparrow \text{ for some } t \in [0, t^*)$$

where t^* is the first instant at which $L + I$ starts to decrease.

No outbreak occurs if the number of individuals in the infected classes is a decreasing function for all time, i.e.,

$$(L + I)' < 0 \Leftrightarrow (L + I) \downarrow 0 \quad \forall t \geq 0$$

Summing the infected classes,

$$\frac{d}{dt}(L + I) = \beta SI - \alpha I = (\beta S - \alpha)I,$$

from which it follows that,

$$\begin{aligned} \frac{d}{dt}(L + I) < 0 &\Leftrightarrow (\beta S - \alpha)I < 0 \Leftrightarrow \frac{\beta S}{\alpha} < 1 \\ \frac{d}{dt}(L + I) > 0 &\Leftrightarrow (\beta S - \alpha)I > 0 \Leftrightarrow \frac{\beta S}{\alpha} > 1. \end{aligned}$$

5.1.5 Existence of the Disease Free Equilibrium (DFE)

The first step is to calculate the equilibrium point or points. The equilibrium points are found when the time derivatives of each state in (5.1) are set to zero, giving

$$0 = -\beta SI \tag{5.4a}$$

$$0 = \beta SI - \epsilon L \tag{5.4b}$$

$$0 = \epsilon L - \alpha I \tag{5.4c}$$

$$0 = \alpha I \tag{5.4d}$$

Equation (5.4d) gives that $I^* = 0$. Since $I^* = 0$, Equation (5.4c) gives that $L^* = 0$. Equation (5.4a) gives that S^* is arbitrary, $0 \leq S^* \leq S_0$. The restriction on S^* as $0 \leq S^* \leq S_0$ is due to the fact that S is a monotone decreasing function and so $S(0) = S_0$ is its maximum. Since $N = S(t) +$

$L(t) + I(t) + R(t)$ (see Section 5.1.3) $\forall t \in \mathbb{R}_+$ where N is a constant, it follows that at equilibrium, $R^* = N - S^*$.

From above, we have shown that the *SLIR* model without demography has a unique equilibrium which is called the *disease free equilibrium*:

$$DFE = (S^*, 0, 0, N - S^*), \text{ with } 0 \leq S^* \leq S_0 \text{ where } R^* = N - S^*.$$

Due to the conservation of the total population or the fact that no other equation depends on R , (5.1d) can be omitted in the analysis. This reduces our system to three equations instead of four. In \mathbb{R}^3 , the *DFE*,

$$DFE = (S^*, 0, 0) \text{ with } 0 \leq S^* \leq S_0.$$

We remark here that if System (5.1) is at equilibrium, $S = S^*$, then $\mathcal{R}_0 = \frac{\beta S^*}{\alpha}$ (shown below in the following section). And so, at equilibrium, an outbreak of measles is defined by

$$\begin{aligned} \frac{d}{dt}(L + I) < 0 &\Leftrightarrow \mathcal{R}_0 < 1 \\ \frac{d}{dt}(L + I) > 0 &\Leftrightarrow \mathcal{R}_0 > 1 \quad t \in [0, t^*) \end{aligned}$$

5.1.6 The reproductive number

The method in Section 4.3.4 is used to derive the basic reproductive number of System (5.1). System (5.1) has two infected compartments $n = 2$, one susceptible compartment $m = 1$ and one immune compartment $k = 1$.

The method in Section 4.3.4 re-orders the compartments with the infected compartments first, followed by the susceptible and immune compartments. Thus, the DFE takes on the form, $(0, 0, S^*, N - S^*)$.

Theorem 5.1.4. \mathcal{R}_0 for System (5.1) at DFE $= (0, 0, S^*, N - S^*)$ is given by

$$\mathcal{R}_0 = \frac{\beta S^*}{\alpha}.$$

The computation of \mathcal{R}_0 using Theorem 4.3.3 in Section 4.3.4 is as follows,

$$\mathcal{R}_0 = \beta b V^{-1} \Pi D S^*$$

with,

$$\beta(L, I, S, R) = \beta \text{ a constant}$$

$$b_{1 \times 2} = [0, 1]$$

$$V_{2 \times 2} = \begin{bmatrix} \epsilon & 0 \\ -\epsilon & \alpha \end{bmatrix}$$

$$V_{2 \times 2}^{-1} = \begin{bmatrix} \frac{1}{\epsilon} & 0 \\ \frac{1}{\alpha} & \frac{1}{\alpha} \end{bmatrix}$$

$$\Pi_{2 \times 1} = \begin{bmatrix} 1 \\ 0 \end{bmatrix}$$

$$D_{1 \times 1} = \sigma_1 = 1$$

$$D_{1 \times 1}^{-1} = 1$$

and so,

$$\mathcal{R}_0 = \beta \begin{bmatrix} 0 & 1 \end{bmatrix} \begin{bmatrix} \frac{1}{\epsilon} & 0 \\ \frac{1}{\alpha} & \frac{1}{\alpha} \end{bmatrix} \begin{bmatrix} 1 \\ 0 \end{bmatrix} S^* = \begin{bmatrix} \frac{\beta}{\alpha} & \frac{\beta}{\alpha} \end{bmatrix} \begin{bmatrix} S^* \\ 0 \end{bmatrix} = \frac{\beta S^*}{\alpha}.$$

In order for \mathcal{R}_0 to exist, positivity of α is required. So from now on, $\alpha > 0$.

5.1.7 Attractivity of the disease free equilibrium

All solution trajectories of (5.1) limit to the *DFE* independent of the values of \mathcal{R}_0 which can be shown using similar methods detailed in [31, 69]. In particular, if $\mathcal{R}_0 \leq 1$ the *DFE* is GAS. We proceed to study the epidemic model numerically.

5.1.8 Numerical results

Assume that the average time spent in the latent class is 10 days and in the infectious class is 11 days, that is, $1/\epsilon = 10$ and $1/\alpha = 11$. Let the total population size be $N = N(0) = 100$. We assume that $S^* = S_0$ and the value of \mathcal{R}_0 is known and thus take

$$\beta = \frac{\alpha \mathcal{R}_0}{S_0}.$$

Let $L(0) = 0$, $I(0) = 1$ and $R(0) = 0$ so $S(0) + L(0) + I(0) + R(0) = N = 100$. Which implies that $S(0) = N - (L(0) + I(0) + R(0)) = 99$.

For $\mathcal{R}_0 = 0.5$, there is no outbreak of disease. The *DFE* is globally asymptotically stable, that is, the latent and infectious individuals approach

zero as $t \rightarrow \infty$, see Figure 5.3.

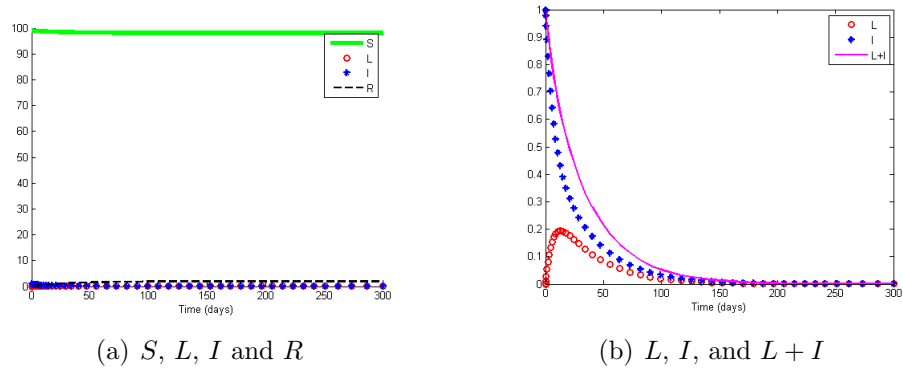


Figure 5.3: The evolution of the populations for $\mathcal{R}_0 < 1$.

For $\mathcal{R}_0 = 1.5$, there is an outbreak of disease. There exists a time interval in which the sum of latent and infectious individuals increase and then after some time t^* they eventually decrease. As $t \rightarrow \infty$ the infected individuals go to zero; see Figure 5.4.

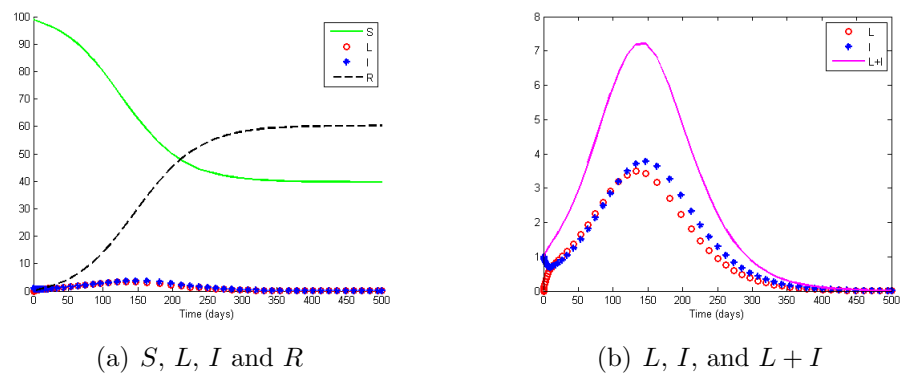


Figure 5.4: The evolution of the populations for $\mathcal{R}_0 > 1$.

5.2 Stochastic model for epidemic measles

A stochastic version of the SLIR system without demography is vital when studying epidemics as it is more suitable for infectious populations of small size, an important characteristic of epidemics. The stochastic process used is a Continuous Time Markov Chain (CTMC).

The derivation of the the stochastic analogue of System (5.1) follows the same methods and techniques in Section 1.3. From Figure 5.2 we see that System 5.1 has three arrows that represent the transitions between the compartments. And so, the *SLIR* model with no demography has 3 events.

Let $S(t)$, $L(t)$, $I(t)$, $R(t)$ be discrete random (state) variables, i.e.,

$$S(t), L(t), I(t), R(t) \in \{1, 2, \dots, N\}$$

- $S(t)$: the number of susceptible individuals at time t .
- $L(t)$: the number of latent individuals at time t .
- $I(t)$: the number of infected individuals at time t .
- $R(t)$: the number of recovered individuals at time t .

Since $S(t) = N - L(t) - I(t) - R(t)$, we omit the S -dynamics.

Like we mentioned in Section 1.2, the *CTMC* makes transitions from state to state, independent of the past. The present state at time t is denoted by $X(t) = (S(t), L(t), I(t), R(t))$. The process then jumps to a new state at time $t + \tau$, which is denoted by $X(t + \tau) = X' = (S', L', I', R')$. The weights

of all possible events for the epidemic measles model, denoted by $f(t)$, is given by

$$f(t) = \beta SI + \epsilon L + \alpha I$$

The *transition probabilities* (or probability of events) of the *SLIR - CTMC* with no demography are given below,

$$\begin{aligned} P_{(L',I',R'),(L,I,R)}(t + \tau, t) &= \\ & \text{Prob} \left\{ X(t + \tau) = (L', I', R') | X(t) = (L, I, R) \right\} \\ &= \frac{1}{f_t} \begin{cases} \beta SI & \text{if } (L', I', R') = (L + 1, I, R) \\ \epsilon L & \text{if } (L', I', R') = (L - 1, I + 1, R) \\ \alpha I & \text{if } (L', I', R') = (L, I - 1, R + 1) \end{cases} \end{aligned}$$

where $S = N - L - I - R$.

Using *Gillespie's Algorithm* in Section 1.2.2 with

- $N = 4$ discrete random (state) variables: S, L, I and R .
- 3 parameters β, ϵ, α .
- Weights of 3 events : $w_1 = \beta SI, w_2 = \epsilon L$ and $w_3 = \alpha I$,

we run numerous simulations of the *CTMC* to study the stochasticity of the *SLIR* epidemic measles model.

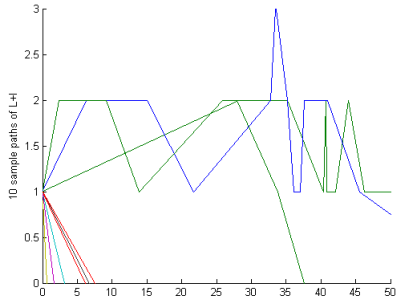
5.2.1 Numerical results

Numerically, it can be illustrated that the stochastic process captures features that would have been *missed* by the deterministic system. The parameter values are the same as those used in the numeric example of the deterministic *SLIR* epidemic model. Thus, $\epsilon = 1/10$, $\alpha = 1/11$ and $N = 100$. Let $L(0) = 0$, $I(0) = 1$, $R(0) = 0$. As before, we assume values of \mathcal{R}_0 are known and thus take

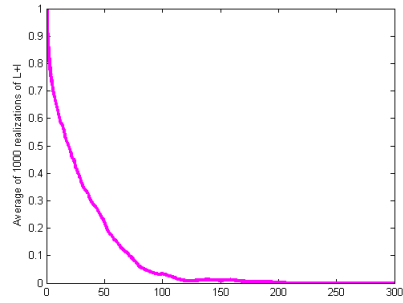
$$\beta = \frac{\alpha \mathcal{R}_0}{S_0}$$

For $\mathcal{R}_0 = 0.5$, 10 sample paths of the number of individuals in the infected classes (L+I) of the *CTMC – SLIR* epidemic model are graphed in Figure 5.5(a). It can be seen that some sample paths have disease outbreaks. These realizations would have been missed by the $L+I$ solution of the deterministic system. The average of the 1000 sample paths of $L + I$ is computed and illustrated in Figure 5.5(b). Numerically we see that, on average, as $t \rightarrow \infty$ the number of infected individuals dies out.

For $\mathcal{R}_0 = 1.5$, 10 sample paths of the number of individuals in the infected classes (L+I) of the *CTMC – SLIR* epidemic model are graphed in Figure 5.6(a). It can be seen that some sample paths have disease extinction. These realizations would have been missed by the $L+I$ solution of the deterministic system. The average of 1000 sample paths of $L + I$ is illustrated in Figure 5.6(b). Numerically we see that, on average, infected individuals increase for some time interval and then as $t \rightarrow \infty$, they die out.

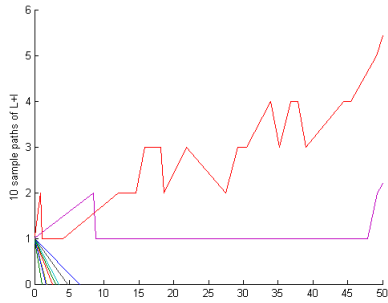


(a) 10 sample paths of $L + I$

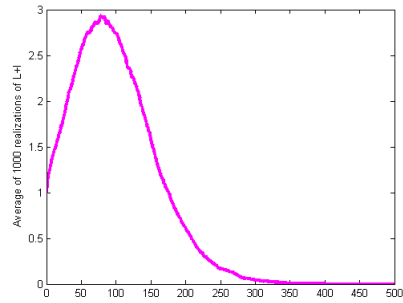


(b) Average sample path of 1000 realizations of $L + I$

Figure 5.5: Stochastic solutions for epidemic model, $\mathcal{R}_0 < 1$.



(a) 10 sample paths of $L + I$



(b) Average sample path of 1000 realizations of $L + I$

Figure 5.6: Stochastic solutions for epidemic model, $\mathcal{R}_0 > 1$.

We note here that in order to compute the average of numerous simulations, a linear interpolant is used due to the variable time steps of each realization of the stochastic process. Next, we compare the average solution of the stochastic process with the deterministic solution.

5.3 Comparison of deterministic and stochastic epidemic measles models

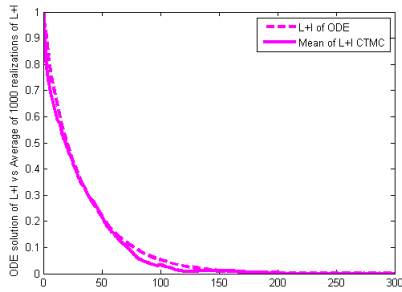
Numerical simulations for the stochastic analogue of the deterministic system illustrates the similarities between the deterministic and the stochastic systems. For $\mathcal{R}_0 < 1$ and $\mathcal{R}_0 > 1$, the average of 1000 realizations of $L + I$ is compared to the solution of $L + I$ for the deterministic system in Figure 5.7(a) and Figure 5.7(b), respectively. We see that the deterministic solution for $L + I$ and the average of the realizations of $L + I$ of the stochastic process exhibit the same behavior. One can note that the maximum of the CTMC is lower than that of the deterministic solution for $L + I$; this is due to the fact that the SLIR-CTMC is nonlinear. Also, as we increase the number of realizations, the average of numerous stochastic realizations becomes more smooth.

In summary,

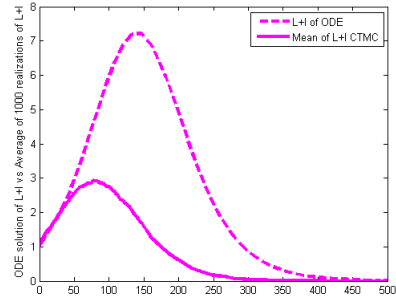
Deterministic System:

- \mathcal{R}_0 is the threshold

– $\mathcal{R}_0 < 1 \Rightarrow L(t) + I(t) \rightarrow 0$. $L(t) + I(t)$ monotonically decreases



(a) $\mathcal{R}_0 < 1$



(b) $\mathcal{R}_0 > 1$

Figure 5.7: Average of 1000 realizations of $L + I$ for the CTMC model, compared to the deterministic solution of $L + I$.

to 0.

- $\mathcal{R}_0 > 1 \Rightarrow L(t) + I(t) \rightarrow 0$. $L(t) + I(t)$ decreases to 0 after an outbreak occurs.

Stochastic System:

- \mathcal{R}_0 is the threshold for the mean of the total number of realizations
 - $\mathcal{R}_0 < 1 \Rightarrow L(t) + I(t) \rightarrow 0$. $L(t) + I(t)$ decreases monotonically to 0 on average but some realizations have outbreaks.
 - $\mathcal{R}_0 > 1 \Rightarrow L(t) + I(t) \rightarrow 0$. $L(t) + I(t)$ decreases monotonically to 0 on average after an outbreak occurs but some realizations have no outbreaks at all.

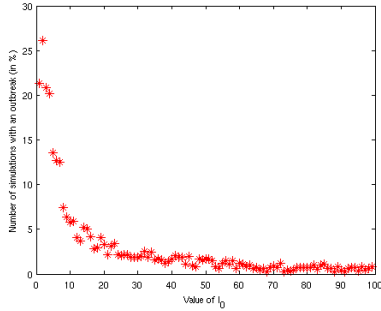
5.4 Simulations that produce an outbreak for

$\mathcal{R}_0 < 1$ and no outbreak for $\mathcal{R}_0 > 1$

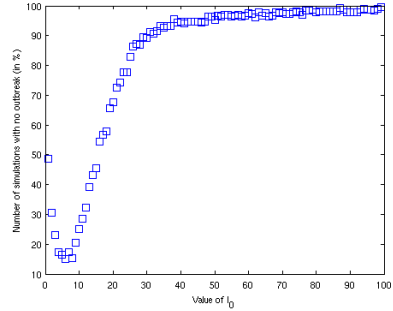
An illustration of the number of simulations that produce an outbreak for $\mathcal{R}_0 < 1$ and $\mathcal{R}_0 > 1$ are given in Figures 5.8(a) and 5.8(b). We consider the same *SLIR* system without demography. We let the initial number of *infectious* individuals vary from 1 to 99 and the rest of the compartments are fixed at an initial value of 0. At each variation of I_0 we run 1000 realizations of the stochastic process and then record the number of simulations that do produce an outbreak. An outbreak will be defined somewhat naively as,

$$\exists t \text{ s.t } I(t) > I(0).$$

For $\mathcal{R}_0 < 1$ the deterministic system concludes that there is no outbreak of disease, whereas the stochastic system produces some realizations that represent disease outbreak even when $\mathcal{R}_0 < 1$. For small values of $I_0 < 7$, the percentage of realization with an outbreak ranges from 10% to 30%. 26.1% of the sample paths show disease outbreak when $I_0 = 2$, this may seem like a relatively small number, however, it is relevant to public health officials. For $\mathcal{R}_0 > 1$, the deterministic system concludes that a disease outbreak occurs and then eventually dies out, whereas the stochastic system produces some realizations that have no outbreak of disease at all. For $I_0 < 15$, the percentage of realizations that do not show disease outbreak ranges from 10% to 50%.



(a) $\mathcal{R}_0 < 1$



(b) $\mathcal{R}_0 > 1$

Figure 5.8: Percentage of realizations (out of a total of 1000) that (a) produce an outbreak, defined as a realization such that $\exists t, I(t) > I(0)$ when $\mathcal{R}_0 < 1$ and (b) produce no outbreak when $\mathcal{R}_0 > 1$.

For both graphs, notice that as the number of initial infectious individuals increases, the number of simulations that have an outbreak is greatly reduced. Recall that we have a constant population. If most of the population is in the infectious class then the probability of a new infection (i.e. making the number of infectious individuals greater than the initial number of infectious individuals) is very small. Therefore, an outbreak, as we defined it, is less likely to occur.

Since life is a random process, the stochastic sample paths that provide different conclusions than that of the deterministic system are vital in understand the behavior of the infectious populations; the sample paths that conclude outbreak for $\mathcal{R}_0 < 1$ (or the sample paths that conclude no outbreak for $\mathcal{R}_0 > 1$) would have been missed if we solely based our conclusions on the results of the deterministic system.

5.5 Deterministic model of endemic measles

An endemic disease is defined as a disease that is present in a population for a long period of time. Due to the long time scale of endemics, demographic effects such as birth and death must be included when studying its dynamics. The deterministic system is represented by differential equations that are derived from the flow diagram of the *SLIR* system, given below by Figure 5.9.

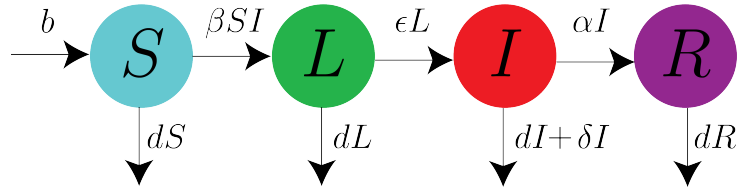


Figure 5.9: The compartmental model for the *SLIR* deterministic system with demography.

The in flows of each compartment will be denoted by ‘+’ and the outflow’s will be denoted by ‘-’. Thus, the four differential equations that represent the *SLIR* deterministic system with demography are expressed below,

$$\frac{d}{dt}S(t) = b - dS - \beta SI \quad (5.5a)$$

$$\frac{d}{dt}L(t) = \beta SI - dL - \epsilon L \quad (5.5b)$$

$$\frac{d}{dt}I(t) = \epsilon L - dI - \delta I - \alpha I \quad (5.5c)$$

$$\frac{d}{dt}R(t) = \alpha I - dR \quad (5.5d)$$

We assume that the disease is not transmitted vertically, that is, all individuals are born susceptible. In measles, there is a transmission of temporary immunity from the mother to the child [57] which would be represented here by an additional epidemiological class; however, I choose to ignore this mechanism for simplicity.

Birth is assumed constant with birth rate denoted by b . All epidemiological classes experience natural death at the per capita rate d . The infectious class experiences additional death due to measles at the per capita rate δ .

ϕ denotes the rate at which new infections are generated, the *force of infection*. Using mass action incidence, $\phi = \beta SI$, where β is the transmission parameter. Let ϵ be the per capita rate of incubation and α be the per capita recovery rate. The time spent in the L and I compartments is exponentially distributed with a mean of $1/\epsilon$ and $1/\alpha$ time units, respectively. The parameters $b, \beta, d, \delta, \epsilon$ and α are assumed to be nonnegative. The initial conditions are all nonnegative, $S(0), L(0), I(0), R(0) \geq 0$. Furthermore, $S(0) + L(0) + I(0) + R(0) > 0$ to avoid a trivial case.

5.5.1 Existence and uniqueness

Proposition 5.5.1 (Existence and uniqueness). *Consider System (5.5) with nonnegative initial conditions. Then solutions to System (5.5) exist and are unique for all $t \geq 0$.*

The proof is similar to the proof of Proposition 5.1.1.

5.5.2 Nonnegativity

Proposition 5.5.2 (Nonnegativity of solutions). *Given nonnegative initial conditions to System (5.5), $S(t)$, $L(t)$, $I(t)$, $R(t)$ are all nonnegative $\forall t \geq 0$.*

Proof. Assume that the initial conditions are nonnegative, that is, $S(0), I(0), L(0), R(0) \geq 0$. Consider S' . Let $S = 0$ in (5.5a),

$$S' = b > 0$$

Therefore, S is an increasing function and so $S(t)$ is nonnegative for all $t \geq 0$. Consider I' and let $I = 0$ in (5.5c),

$$I' = \epsilon L \tag{5.6}$$

The sign of I' depends on the sign of L . Consider L' in (5.5b),

$$L' = -(d + \epsilon)L \tag{5.7}$$

Recall $L(0) \geq 0$. From (5.7) we see that $L' \leq 0$ which implies that L is a decreasing function that eventually hits zero (i.e. the velocity will be zero) so it will never cross into the negative region. Thus, L is nonnegative for all $t \geq 0$. From (5.6), since L is nonnegative, $I(t)$ is an increasing function which implies that I is nonnegative for all $t \geq 0$. Consider R' in (5.5d) and let $R = 0$,

$$R' = \alpha I$$

Since I is nonnegative, $R' \geq 0$ and so $R(t)$ is an increasing function which implies that $R(t)$ is nonnegative for all $t \geq 0$.

□

5.5.3 Boundedness

The evolution of the total population is given

$$N'(t) = b - dN(t) - \delta I(t),$$

so with the simple use of the integrating factor method, the solution is given by

$$N(t) = \frac{b}{d} - \frac{\delta}{d}I(t) + e^{-dt}k$$

It is trivial that e^{-dt} is a decreasing function; it is also a decaying function since it decays to zero as $t \rightarrow \infty$. Thus, the function reaches its maximum when $t = 0$. That is, the maximum of e^{-dt} is 1. And so,

$$N(t) = \frac{b}{d} - \frac{\delta}{d}I(t) + e^{-dt}k \leq \frac{b}{d} + e^{-dt}k \leq \frac{b}{d} + k$$

The total population is bounded above by $\frac{b}{d} + k$. Since solutions to (5.5) exist and are unique, remain nonnegative and bounded System (5.5) is well-posed.

5.5.4 Disease Free Equilibria (DFE)

System (5.5) is at a *DFE* if it is at an equilibrium and $L = I = 0$. We find:

$$0 = b - dS - \beta SI \quad (5.8a)$$

$$0 = \beta SI - dL - \epsilon L \quad (5.8b)$$

$$0 = \epsilon L - dI - \delta I - \alpha I \quad (5.8c)$$

$$0 = \alpha I - dR \quad (5.8d)$$

Let $(\bar{S}, \bar{L}, \bar{I}, \bar{R})$ denote the populations at equilibrium. Equation (5.8d) gives that $\bar{R} = 0$. Setting $I = 0$ in Equation (5.8a),

$$\bar{S} = \frac{b}{d}$$

Thus, the *DFE* of System (5.5) is given by,

$$DFE = \left(\frac{b}{d}, 0, 0, 0\right)$$

For existence of \bar{S} , positivity of d is required. And so from now on $d > 0$. We use the *next generation method* from Section 4.3.3 to find the stability of the *DFE*.

Local stability

Using the *next generation matrix method* in Section 4.3.3 we derive \mathcal{R}_0 . The measles model has four compartments. The infected compartments are L and I . And the non-infected compartments are S and R . The endemic measles model, System (5.5), can be written in form 4.3,

$$\frac{d}{dt} \underbrace{\begin{bmatrix} L \\ I \\ S \\ R \end{bmatrix}}_X = f(X) = \underbrace{\begin{bmatrix} \beta SI \\ 0 \\ 0 \\ 0 \end{bmatrix}}_F - \left(\underbrace{\begin{bmatrix} dL + \epsilon L \\ dI + \delta I + \alpha I \\ dS + \beta SI \\ dR \end{bmatrix}}_{V^-} - \underbrace{\begin{bmatrix} 0 \\ \epsilon L \\ b \\ \alpha I \end{bmatrix}}_{V^+} \right) \quad (5.9)$$

The function f satisfies conditions (C1) to (C5) given in Section 4.3.3.

- (C1) If $S, L, I, R \geq 0$, then $F \geq 0$, $V^- \geq 0$, $V^+ \geq 0$.
- (C2) If $S = L = I = R = 0$ then $V^- = 0$.
- (C3) $F_3 = 0$ and $F_4 = 0$.
- (C4) If $DFE = (\frac{b}{d}, 0, 0, 0)$ then $F_1|_{DFE} = 0$, $F_2|_{DFE} = 0$, $V_1|_{DFE}^+ = 0$ and $V_2|_{DFE}^+ = 0$.
- (C5) If $F = 0$, we have the resulting disease-free model of System (5.5):

$$\frac{d}{dt} \begin{bmatrix} S \\ R \end{bmatrix} = \begin{bmatrix} b - dS \\ -dR \end{bmatrix}$$

With Jacobian matrix,

$$J = \begin{bmatrix} -d & 0 \\ 0 & -d \end{bmatrix}$$

then $\lambda_1 = -d < 0, \lambda_2 = -d < 0$. Thus, DFE is locally asymptotically stable LAS .

Using Theorem 4.3.2, we compute \mathcal{R}_0 and determine the stability condition of the DFE of (5.5).

1. **Write the subsystem of only infected compartments of system (5.5).** Let the vector \mathcal{F} represents the new infections into the infected classes, \mathcal{V} represents the in-and-out flows of individuals in the infected classes other than new infection. We have, $\frac{d}{dt}\mathcal{X} = \mathcal{F} - \mathcal{V}$ with $\mathcal{X}(t) = (L(t), I(t))^T$:

$$\frac{d}{dt} \begin{bmatrix} L \\ I \end{bmatrix} = \underbrace{\begin{bmatrix} \beta SI \\ 0 \end{bmatrix}}_{\mathcal{F}} - \underbrace{\begin{bmatrix} dL + \epsilon L \\ -\epsilon L + dI + \delta I + \alpha I \end{bmatrix}}_{\mathcal{V}}$$

The 0 entry in \mathcal{F} corresponds to the fact that the I class does not have new infections.

2. **Differentiate \mathcal{F} and \mathcal{V} with respect to the infected classes $(L(t), I(t))$.** \mathbb{F} and \mathbb{V} are the Jacobian matrices obtained by differentiating \mathcal{F} and \mathcal{V} with respect to the infected classes L and I and then evaluating at the DFE :

$$\mathbb{F} = \begin{bmatrix} 0 & \beta \frac{b}{d} \\ 0 & 0 \end{bmatrix}, \quad \mathbb{V} = \begin{bmatrix} d + \epsilon & 0 \\ -\epsilon & d + \alpha + \delta \end{bmatrix}$$

\mathbb{F} is non-negative. \mathbb{V} has negative or zero off diagonal entries so \mathbb{V} has the Z sign pattern. All eigenvalues of \mathbb{V} have positive real parts, $\lambda_1 = d + \epsilon > 0$ and $\lambda_2 = d + \alpha + \delta > 0$ so by Theorem (1.4.9) in Chapter 1.4 \mathbb{V} is a non-singular M-matrix. By Lemma (1.4.10) in Chapter 1.4, $\mathbb{V}^{-1} \geq 0$.

Without the complicating result above, due to the low dimension of our system it is obvious from direct computation to see that the inverse of \mathbb{V} is a nonnegative matrix (recall that $d > 0$),

$$\mathbb{V}^{-1} = \begin{bmatrix} \frac{1}{d+\epsilon} & 0 \\ \frac{\epsilon}{(d+\epsilon)(d+\alpha+\delta)} & \frac{1}{d+\alpha+\delta} \end{bmatrix}$$

The *next generation matrix* is then given by

$$\mathbb{F}\mathbb{V}^{-1} = \begin{bmatrix} \frac{\beta b \epsilon}{d(d+\epsilon)(d+\alpha+\delta)} & \frac{\beta b}{d(d+\alpha+\delta)} \\ 0 & 0 \end{bmatrix}$$

3. Find \mathcal{R}_0 .

The basic reproductive number for System (5.5) is given by,

$$\mathcal{R}_0 = \rho(\mathbb{F}\mathbb{V}^{-1}) = \frac{\beta b \epsilon}{d(d+\epsilon)(d+\alpha+\delta)}$$

By Theorem (4.3.2) in Section 4.3.3 we proved the following result.

Theorem 5.5.3. *Consider System (5.5) with $DFE = (\frac{b}{d}, 0, 0, 0)$, f satisfies (C1) to (C5) in Section 4.3.3 and $\mathcal{R}_0 = \frac{\beta b \epsilon}{d(d+\epsilon)(d+\alpha+\delta)}$. The*

DFE is locally asymptotically stable if $\mathcal{R}_0 < 1$ and is unstable if $\mathcal{R}_0 > 1$.

5.5.5 The Endemic Equilibrium Point (EEP)

At the *EEP*, the infectious class is not zero, $I \neq 0$. Equation (5.8d) gives that $\bar{R} = \frac{\alpha}{d}\bar{I}$. Equation (5.8c) gives that $\bar{I} = \frac{\epsilon}{d+\alpha+\delta}\bar{L}$. Substituting the value of \bar{I} into Equation (5.8b) results in the following,

$$\begin{aligned} 0 &= \beta S \left(\frac{\epsilon}{d+\alpha+\delta}\bar{L} \right) - dL - \epsilon L \Leftrightarrow \\ 0 &= L \left(\frac{\beta\epsilon}{d+\alpha+\delta}S - d - \epsilon \right) \text{ with } L \neq 0 \Leftrightarrow \\ \bar{S} &= \frac{(d+\epsilon)(d+\alpha+\delta)}{\beta\epsilon} \end{aligned}$$

For existence of \bar{S} , $\beta\epsilon > 0$. This implies that $\beta > 0$ and $\epsilon > 0$ from now on. Referring back to the $N'(t)$ equation in Section 5.5.3 it is easily seen that at equilibrium, $\bar{N} = \frac{b}{d} - \frac{\delta}{d}\bar{I}$. We use this result to find the explicit value of \bar{I} .

$$\begin{aligned} \frac{b}{d} - \frac{\delta}{d}\bar{I} &= \frac{(d+\epsilon)(d+\alpha+\delta)}{\beta\epsilon} + \frac{(d+\alpha+\delta)}{\epsilon}\bar{I} + \bar{I} + \frac{\alpha}{d}\bar{I} \\ \Leftrightarrow \frac{b\beta\epsilon - d(d+\epsilon)(d+\alpha+\delta)}{d\beta\epsilon} &= \left(\frac{d^2(d+\alpha+\delta) + \epsilon d^2 + \alpha\epsilon d + \delta\epsilon d}{\epsilon d^2} \right) \bar{I} \\ \Leftrightarrow \bar{I} &= \frac{b\beta\epsilon - d(d+\epsilon)(d+\alpha+\delta)}{\beta(d+\epsilon)(d+\epsilon+\delta)} \end{aligned}$$

The EEP of system (5.5) is given by,

$$\begin{aligned}
EEP &= (\bar{S}, \bar{L}, \bar{I}, \bar{R}) \\
&= \left(\frac{(d + \epsilon)(d + \alpha + \delta)}{\beta\epsilon}, \frac{b\beta\epsilon - d(d + \epsilon)(d + \alpha + \delta)}{\beta\epsilon(d + \epsilon)}, \right. \\
&\quad \left. \frac{b\beta\epsilon - d(d + \epsilon)(d + \alpha + \delta)}{\beta(d + \epsilon)(d + \alpha + \delta)}, \frac{\alpha b\beta\epsilon - d\alpha(d + \epsilon)(d + \alpha + \delta)}{d\beta(d + \epsilon)(d + \alpha + \delta)} \right) \\
&= \left(\frac{b}{d\mathcal{R}_0}, \frac{b}{d + \epsilon} \left(1 - \frac{1}{\mathcal{R}_0}\right), \frac{d}{\beta} (\mathcal{R}_0 - 1), \frac{\alpha}{\beta} (\mathcal{R}_0 - 1) \right)
\end{aligned}$$

Writing \bar{S} and \bar{L} in terms of \mathcal{R}_0 requires that $\mathcal{R}_0 > 0$. Therefore, in addition to $\beta > 0$ and $\epsilon > 0$ we have that $b > 0$.

Condition of existence of EEP. The \bar{L} , \bar{I} and \bar{R} endemic equilibrium solutions do not make sense when they are negative,

$$1 - \frac{1}{\mathcal{R}_0} < 0 \Leftrightarrow \mathcal{R}_0 < 1 \quad \text{and} \quad \mathcal{R}_0 - 1 < 0 \Leftrightarrow \mathcal{R}_0 < 1$$

That is, the *EEP* exists (or is biologically relevant) only when $\mathcal{R}_0 > 1$.

Local stability

Both Linearization and the *Routh-Hurwitz Criteria* are used to prove the local asymptotic stability of the *EEP*. First, we find the characteristic polynomial of the Jacobian matrix evaluated at the *EEP*.

The Jacobian matrix, denoted by \mathcal{J} , is obtained by differentiating the right hand equations of (5.5) with respect to each state variable (S, L, I, R),

giving

$$\mathcal{J} = \begin{bmatrix} -d - \beta I & 0 & -\beta S & 0 \\ \beta I & -d - \epsilon & \beta S & 0 \\ 0 & \epsilon & -d - \alpha - \delta & 0 \\ 0 & 0 & \alpha & -d \end{bmatrix} \quad (5.10)$$

We use the *EEP* in expanded form as it helps with simplification of the coefficients of the characteristic polynomial.

1. **Evaluate (5.10) at the *EEP*, $\mathcal{J}|_{EEP}$**

$$\mathcal{J}|_{EEP} = \begin{bmatrix} -d - \left(\frac{b\beta\epsilon - d(d+\epsilon)(d+\alpha+\delta)}{(d+\epsilon)(d+\alpha+\delta)} \right) & 0 & -\frac{(d+\epsilon)(d+\alpha+\delta)}{\epsilon} & 0 \\ \left(\frac{b\beta\epsilon - d(d+\epsilon)(d+\alpha+\delta)}{(d+\epsilon)(d+\alpha+\delta)} \right) & -d - \epsilon & \frac{(d+\epsilon)(d+\alpha+\delta)}{\epsilon} & 0 \\ 0 & \epsilon & -d - \alpha - \delta & 0 \\ 0 & 0 & \alpha & -d \end{bmatrix}$$

2. **Find the eigenvalues of (1).**

To find the eigenvalues of the $\mathcal{J}|_{EEP}$, solve the characteristic equation for λ :

$$P(\lambda) = \det (\mathcal{J}|_{EEP} - \lambda \mathbb{I}) = 0$$

where \mathbb{I} is the identity matrix. That is,

$$\det \begin{bmatrix} -d - \left(\frac{b\beta\epsilon - d(d+\epsilon)(d+\alpha+\delta)}{(d+\epsilon)(d+\alpha+\delta)} \right) - \lambda & 0 & -\frac{(d+\epsilon)(d+\alpha+\delta)}{\epsilon} & 0 \\ \left(\frac{b\beta\epsilon - d(d+\epsilon)(d+\alpha+\delta)}{(d+\epsilon)(d+\alpha+\delta)} \right) & -d - \epsilon - \lambda & \frac{(d+\epsilon)(d+\alpha+\delta)}{\epsilon} & 0 \\ 0 & \epsilon & -d - \alpha - \delta - \lambda & 0 \\ 0 & 0 & \alpha & -d - \lambda \end{bmatrix}$$

Using cofactor expansion along the fourth column then the first column we find the *characteristic equation*.

$$P(\lambda) = \lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4$$

where a_1 , a_2 , a_3 and a_4 take the following form:

$$\begin{aligned}
a_1 &= \frac{(d + \epsilon)(d + \alpha + \delta)(3d + \alpha + \delta + \epsilon) + b\beta\epsilon}{(d + \epsilon)(d + \alpha + \delta)} \\
&= 3d + \alpha + \delta + \epsilon + d\mathcal{R}_0 \\
a_2 &= \frac{d(d + \epsilon)(d + \alpha + \delta)(2d + \alpha + \delta + \epsilon) + b\beta\epsilon(3d + \epsilon + \alpha + \delta)}{(d + \epsilon)(d + \alpha + \delta)} \\
&= d(2d + \alpha + \delta + \epsilon) + d\mathcal{R}_0(3d + \epsilon + \delta + \alpha) \\
a_3 &= \frac{-d(d + \epsilon)^2(d + \alpha + \delta)^2 + b\beta\epsilon(2\epsilon d + \epsilon\alpha + 3d^2 + 2d\alpha + 2d\delta + \epsilon\delta)}{(d + \epsilon)(d + \alpha + \delta)} \\
&= -d(d + \epsilon)(d + \alpha + \delta) + d\mathcal{R}_0(2\epsilon d + \epsilon\alpha + 3d^2 + 2d\alpha + 2d\delta + \epsilon\delta) \\
a_4 &= d(b\beta\epsilon - d(d + \epsilon)(d + \alpha + \delta)) \\
&= d^2(d + \epsilon)(d + \alpha + \delta)(\mathcal{R}_0 - 1)
\end{aligned} \tag{5.11}$$

The eigenvalues are given by solving for the roots of a polynomial of degree four. That is, solve the below equation for λ

$$\lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4 = 0 \tag{5.12}$$

Since the characteristic equation is a fourth order polynomial, there are four eigenvalues including multiplicities. Determining the roots of (5.12) is difficult. Instead, we use the Routh-Hurwitz Criteria (refer back to Theorem 1.1.17) to study the sign of the real parts of the eigenvalues of $\mathcal{J}|_{EEP}$.

3. Local asymptotic stability of EEP and threshold parameter

using **Routh-Hurwitz Criteria**.

The polynomial (5.12) with coefficients (5.11) is written in the form of the polynomial in the Theorem 1.1.17. Next, we seek conditions for which the determinants of the Hurwitz matrices in Theorem 1.1.17 remain positive. We have:

(a) $a_1 > 0$.

$$a_1 > 0 \Leftrightarrow 3d + \alpha + \delta + \epsilon + d\mathcal{R}_0 > 0$$

Condition 3a is always true since $d > 0$, $\epsilon > 0$ and $\mathcal{R}_0 > 0$.

(b) $a_3 > 0$

$$\begin{aligned} a_3 > 0 &\Leftrightarrow -d(d + \epsilon)(d + \alpha + \delta) + d\mathcal{R}_0(2\epsilon d + \epsilon\alpha + 3d^2 + 2d\alpha + 2d\delta + \epsilon\delta) > 0 \Leftrightarrow \\ \mathcal{R}_0 &> \frac{(d + \epsilon)(d + \alpha + \delta)}{(2\epsilon d + \epsilon\alpha + 3d^2 + 2d\alpha + 2d\delta + \epsilon\delta)} \end{aligned} \tag{5.13}$$

For EEP to exist $\mathcal{R}_0 > 1$ and so we need to show that the last quantity above is less than 1.

$$\begin{aligned} 2\epsilon d + \epsilon\alpha + 3d^2 + 2d\alpha + 2d\delta + \epsilon\delta &> (d + \epsilon)(d + \alpha + \delta) \Leftrightarrow \\ d(2d + \alpha + \delta + \epsilon) &> 0 \end{aligned}$$

which is always true since $d > 0$ and $\epsilon > 0$. Thus,

$$\frac{(d + \epsilon)(d + \alpha + \delta)}{(2\epsilon d + \epsilon\alpha + 3d^2 + 2d\alpha + 2d\delta + \epsilon\delta)} < 1 < \mathcal{R}_0$$

Condition 3b is always true.

(c) $a_4 > 0$

$$a_4 > 0 \Leftrightarrow$$

$$d^2(d + \epsilon)(d + \alpha + \delta)(\mathcal{R}_0 - 1) > 0 \Leftrightarrow$$

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

Condition 3c is true iff $\mathcal{R}_0 > 1$.

(d) Show that $a_1 a_2 a_3 > a_3^2 + a_1^2 a_4$ holds.

$$a_1 a_2 a_3 - a_3^2 - a_1^2 a_4 > 0 \Leftrightarrow$$

$$\begin{aligned} & d^2 \left(\overbrace{\epsilon\alpha\mathcal{R}_0 - \epsilon\alpha + 2d\mathcal{R}_0\epsilon + 2d^2 + 4d^2\mathcal{R}_0 + 2d\mathcal{R}_0\alpha + 2d\mathcal{R}_0\delta + \epsilon\delta\mathcal{R}_0 - \epsilon\delta}^{Eq(1)} \right) \\ & \left(\underbrace{2d^2\mathcal{R}_0^2 + d\mathcal{R}_0^2\delta + d\mathcal{R}_0^2\alpha + d\mathcal{R}_0^2\epsilon + 3d^2\mathcal{R}_0 + 3d\mathcal{R}_0\epsilon + 3d\mathcal{R}_0\alpha + 3d\mathcal{R}_0\delta}_{Eq(2)} \right. \\ & \left. + \underbrace{\epsilon^2\mathcal{R}_0 + \alpha^2\mathcal{R}_0 + \epsilon\alpha\mathcal{R}_0 + \delta^2\mathcal{R}_0 + \epsilon\delta\mathcal{R}_0 + 2\alpha\delta\mathcal{R}_0 + (d + \epsilon)(d + \alpha + \delta)}_{Eq(2)} \right) > 0 \end{aligned}$$

For $\alpha \geq 0$ and $\delta \geq 0$, since $d > 0$, $\epsilon > 0$ and $\mathcal{R}_0 > 0$, $Eq(2) > 0$.

Next, we show the positivity of $Eq(1)$. For $\alpha > 0$ and $\delta = 0$ or $\delta > 0$ and $\alpha = 0$ or $\alpha > 0$ and $\delta > 0$,

$$Eq(1) > 0 \Leftrightarrow \epsilon\alpha(\mathcal{R}_0-1)+\epsilon\delta(\mathcal{R}_0-1) > 0 \Leftrightarrow (\epsilon\alpha+\epsilon\delta)(\mathcal{R}_0-1) > 0 \Leftrightarrow \mathcal{R}_0 > 1$$

(recalling the fact that $\epsilon > 0$). For $\alpha = \delta = 0$ it is easily seen that $Eq(1) > 0$. Thus, for $\alpha > 0$ and $\delta = 0$ or $\delta > 0$ and $\alpha = 0$ or $\alpha > 0$ and $\delta > 0$ condition 3d holds iff $\mathcal{R}_0 > 1$. And for $\alpha = \delta = 0$ condition 3d always holds.

Theorem 5.5.4. *The EEP is locally asymptotically stable iff $\mathcal{R}_0 > 1$. Otherwise, the EEP is not biologically relevant.*

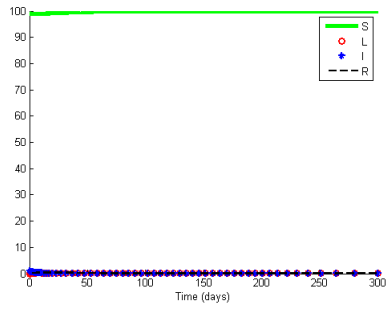
5.5.6 Numerical results

To model measles, assume that the average time spent in the latent class is 10 days and in the infectious class is 11 days, that is, $1/\epsilon = 10$, $1/\alpha = 11$ which implies that $\epsilon = 1/10$ and $\alpha = 1/11$. Let $N(0) = 100$, $L(0) = 0$, $I(0) = 1$ and $R(0) = 0$, then $S(0) = N(0) - L(0) - I(0) - R(0) = 99$. Given the parameter values and assuming values of \mathcal{R}_0 are known we thus take

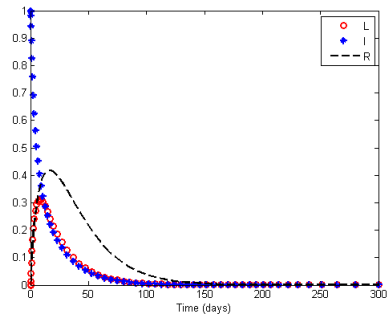
$$\beta = \frac{d(d+\epsilon)(d+\alpha+\delta)}{b\epsilon}\mathcal{R}_0$$

For $\mathcal{R}_0 = 0.5$, we observe that solutions tend to the *DFE*, indicating that it may be globally asymptotically stable when $\mathcal{R}_0 < 1$ see Figure 5.5.6.

For $\mathcal{R}_0 = 1.5$, we observe that solutions tend to the *EEP*, indicating that it may be globally asymptotically stable when $\mathcal{R}_0 > 1$ see Figure 5.5.6.

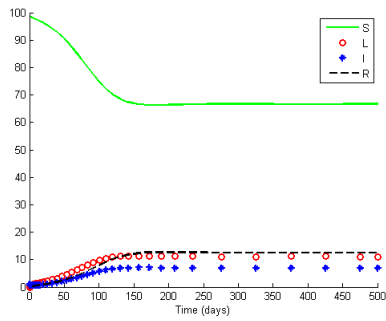


(a) The evolution of the populations

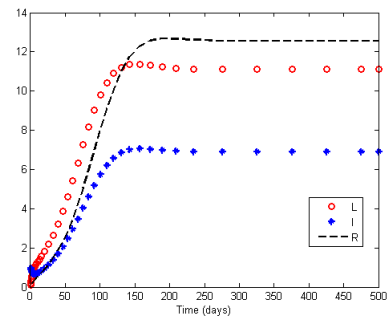


(b) L , I and R

Figure 5.10: The evolution of the populations for $\mathcal{R}_0 < 1$.



(a) The evolution of the populations



(b) L and I

Figure 5.11: The evolution of the populations for $\mathcal{R}_0 > 1$

The behaviour of the *SLIR* deterministic model with demography has been discussed and now the deterministic results will be compared to the results of its corresponding stochastic model.

5.6 Stochastic model for endemic measles

The derivation of the the stochastic analogue of System (5.5) follows the same methods and techniques in Section 1.3. From Figure 5.9 we see that System 5.5 has eight arrows that represent the transitions between the compartments. And so, the *SLIR* model with demography has 8 events. Let $S(t)$, $L(t)$, $I(t)$, $R(t)$ be discrete random (state) variables with the same definitions as in Section 5.2.

The present state at time t is denoted by $X(t) = (S(t), L(t), I(t), R(t))$. The process then jumps to a new state at time $t + \tau$, which is denoted by $X(t + \tau) = X' = (S', L', I', R')$. The weights of all possible events for the endemic measles model, denoted by $f(t)$, are given by

$$f_t = b + dS + \beta SI + \epsilon L + \alpha I + dL + (d + \delta)I + dR$$

The *transition probabilities* (or probability of events) of the *SLIR-CTMC* are given below,

$$\begin{aligned}
P_{(S',L',I',R'),(S,L,I,R)}(t + \tau, t) = \\
\text{Prob} \left\{ X(t + \tau) = (S', L', I', R') | X(t) = (S, L, I, R) \right\} \\
= \frac{1}{f_t} \left\{ \begin{array}{ll}
b & \text{if } (S', L', I', R') = (S + 1, L, I, R) \\
\beta SI & \text{if } (S', L', I', R') = (S - 1, L + 1, I, R) \\
\epsilon L & \text{if } (S', L', I', R') = (S, L - 1, I + 1, R) \\
\alpha I & \text{if } (S', L', I', R') = (S, L, I - 1, R + 1) \\
dS & \text{if } (S', L', I', R') = (S - 1, L, I, R) \\
dL & \text{if } (S', L', I', R') = (S, L - 1, I, R) \\
(d + \delta)I & \text{if } (S', L', I', R') = (S, L, I - 1, R) \\
dR & \text{if } (S', L', I', R') = (S, L, I, R - 1)
\end{array} \right.
\end{aligned}$$

Using *Gillespie's Algorithm* in Section 1.2.2 with

- $N = 4$ discrete random (state) variables: S , L , I and R .
- 6 parameters b , β , ϵ , α , d and δ .
- Weights of 8 events : $w_1 = b$, $w_2 = \beta SI$, $w_3 = \epsilon L$, $w_4 = \alpha I$, $w_5 = dS$,
 $w_6 = dL$, $w_7 = (d + \delta)I$ and $w_8 = dR$,

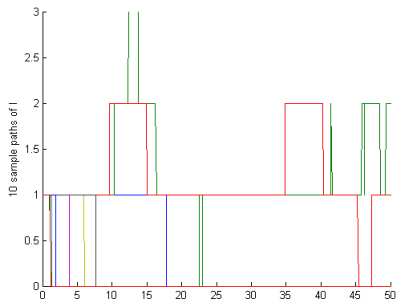
we run numerous simulations of the *CTMC* to study the stochasticity of the *SLIR* endemic measles model.

5.6.1 Numerical results

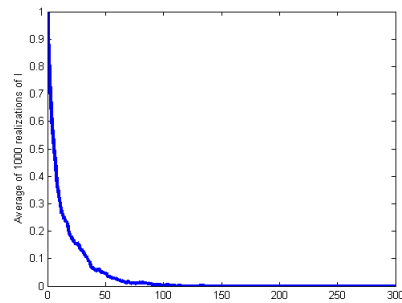
The parameter values are the same as those used in the numeric example of the deterministic *SLIR* endemic model, in Section 5.5.6. As before in the deterministic case, given the parameter values and assuming values of \mathcal{R}_0 are known we take

$$\beta = \frac{d(d + \epsilon)(d + \alpha + \delta)}{b\epsilon} \mathcal{R}_0$$

For $\mathcal{R}_0 = 0.5$, 10 sample paths of the number of individuals in the infectious class (I) of the *CTMC – SLIR* endemic model are graphed in Figure 5.12(a). Observe that some realizations produce an outbreak. From Figure 5.12(b) it can be seen that, on average, as $t \rightarrow \infty$ the infectious population dies out.



(a) 10 sample paths of I



(b) Average sample path of 1000 realizations of I

Figure 5.12: Stochastic solutions for endemic model, $\mathcal{R}_0 < 1$.

For $\mathcal{R}_0 = 1.5$, 10 sample paths of the number of individuals in the infectious class (I) of the *CTMC – SLIR* endemic model are graphed in Figure

5.13(a). Observe that some realizations produce no outbreak. From Figure 5.13(b) it can be seen that, on average, as $t \rightarrow \infty$ the number of infectious individuals stabilize close to the endemic equilibrium value of I of the deterministic system.

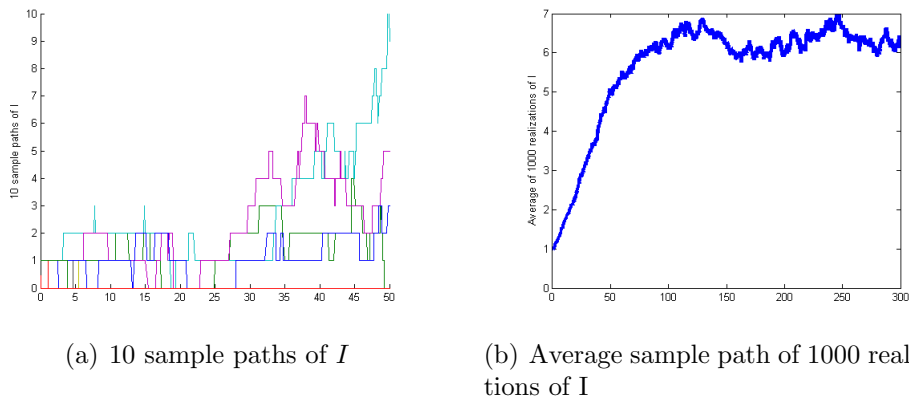
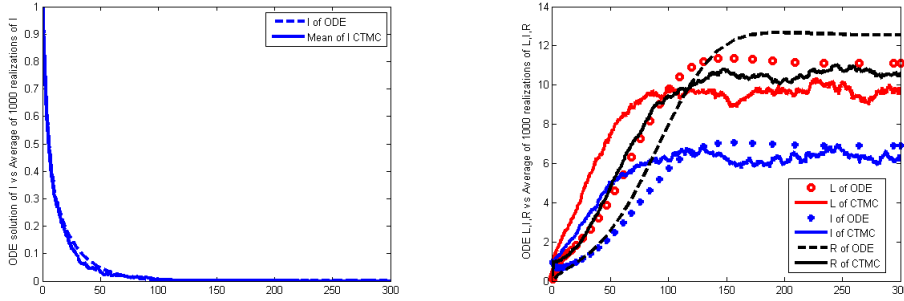


Figure 5.13: Stochastic solutions for endemic model, $\mathcal{R}_0 > 1$.

5.7 Comparison of deterministic and stochastic endemic measles models

For $\mathcal{R}_0 < 1$, the average of the 1000 realization of I is compared to the solution of I for the deterministic system; refer to Figure 5.14(a). From Figure 5.14(a), it can be seen that, on average, as $t \rightarrow \infty$ the infectious population dies out which is the same behaviour as the I population for the deterministic system. For $\mathcal{R}_0 > 1$, the average of the 1000 realization of L , I and R is compared to the solution of L , I and R for the deterministic system, refer to Figure 5.14(b). From Figure 5.14(b) it can be seen that, on average,

as $t \rightarrow \infty$ the number of latent, infectious and recovered individuals stabilize close to the endemic equilibrium value of L, I, R of the deterministic system. The discrepancy or gaps between the stochastic average and the deterministic solution are due to the fact that the $SLIR$ CTMC is nonlinear.



(a) Average of I in 1000 realizations of the CTMC model compared to the deterministic solution of I for $R_0 < 1$.

(b) Average of L, I, R in 1000 realizations of the CTMC model compared to the deterministic solution of L, I, R for $R_0 > 1$.

Figure 5.14: Deterministic solutions versus stochastic solutions of the endemic model.

In summary,

Deterministic System

- \mathcal{R}_0 is the threshold. Numerically we see that,
 - $\mathcal{R}_0 < 1 \Rightarrow (S(t), L(t), I(t), R(t)) \rightarrow DFE$ as $t \rightarrow \infty$.
 - $\mathcal{R}_0 > 1 \Rightarrow (S(t), L(t), I(t), R(t)) \rightarrow EEP$ as $t \rightarrow \infty$.

Stochastic System

- \mathcal{R}_0 is the threshold for the mean of the total number of realizations. Numerically we see that,

- $\mathcal{R}_0 < 1 \Rightarrow (S(t), L(t), I(t), R(t)) \rightarrow \approx DFE$ on average as $t \rightarrow \infty$.
- $\mathcal{R}_0 > 1 \Rightarrow (S(t), L(t), I(t), R(t)) \rightarrow \approx EEP$ on average as $t \rightarrow \infty$.

5.8 Epidemic versus endemic models

So far, we have defined an *epidemic* as an outbreak of disease that in a short period of time ‘kicks off’, spreads rapidly and infects a large portion of a population before it dies out. Due to the short time scale, demography is ignored while modelling the spread of epidemic measles. On the other hand, an *endemic* was defined as a disease that is present in a population for a long period of time. Endemics are diseases that are continuously present in the population and so the number of infectious individuals remains detectable year after year. Due to the large time scale of endemics, demographic effects such as birth and death are included when modelling the spread of endemic measles. Some interesting differences arise when comparing the results of the epidemic model with the results of the endemic model.

The derivation of the reproductive number of the epidemic model from the equation of the reproductive number of the endemic model is not possible. For example, removing the demographic effects by setting $d = 0$ or $b = 0$ in \mathcal{R}_0 for the endemic model would result in a value of zero which is not correct. In fact, \mathcal{R}_0 for the endemic measles model is only defined for $d > 0$.

For the epidemic model, the definition of measles outbreak depend on the L and I classes. As t goes to infinity, L and I always tend to zero whether they decrease instantly or go through a bump before they decrease and the

DFE is the only equilibrium point. All solution trajectories of the epidemic model limit to the *DFE* irrespective of the value of \mathcal{R}_0 .

When demography is added, an equilibrium point different from the *DFE* appears, the *EEP*. For the endemic model, when $\mathcal{R}_0 > 1$, measles persists, i.e., L and I classes limit to a positive quantity. This is unlike the epidemic model, since as we mentioned above, L and I tend to zero as t goes to infinity. When $\mathcal{R}_0 < 1$ the *DFE* is *LAS* and the *EEP* is not biologically relevant so the *DFE* is the only equilibrium point that exists. When $\mathcal{R}_0 > 1$ the *EEP* exists and is *LAS* and the *DFE* is unstable. Numerical solutions of the endemic model indicated the possible globally asymptotically stable of the *DFE* and *END*.

By numerical observation when $\mathcal{R}_0 < 1$ the *DFE* is *GAS* for both models. Also, by numerical observation, when $\mathcal{R}_0 > 1$ the solutions of the epidemic model limit to the only equilibrium in the system, the *DFE*, whereas for the endemic model solutions tend to the *EEP* and the *DFE* does not exist.

Chapter 6

A Metapopulation model with residency

For the vast majority of history, populations from different geographical regions have been relatively isolated from each other. Ancient transportation services included horseback riding, wheelbarrows, river boats and walking; such methods were often time consuming, exhausting and limited in the spatial distance they allowed to travel. Today's transportation network is anything but mundane! The volume, speed and distance traveled of today's transportation networks is unprecedented [118]. Presently, more than any other point in history, people from around the world have ample opportunity to be in extensive contact with one another due to the innovative and affordable methods of travel. Motorcycles, cars, submarines, boats, trains, helicopters and airplanes are just some examples of innovative modes of travel that have made the world accessible to a vast majority of individuals.

Metapopulation models that describe the spatial dispersion of populations have been around since the 1960s. The model presented in this chapter is based on the model of Sattenspiel and Dietz in [95] and the refinements of Arino and van den Driessche in [13] and [19].

6.1 Overview – Metapopulations

Metapopulations are populations of populations that are linked together by a transportation network. In this study, we assume that the populations move via air transportation only. Each *patch* corresponds to a different geographical location and contains a certain number of subpopulations. The subpopulations can move (shown by *arcs* in the graph) to other geographical locations (patches).

The resulting deterministic system incorporates the spatial dynamics of disease by allowing movement between patches, tracks the residency of the individuals and describes the dynamics of interaction of individuals within and between each patch.

The Graph. We consider a graph \mathcal{G} whose vertices are the *patches*. As mentioned above, each *patch* contains a certain number of subpopulations. The edges of \mathcal{G} represents the possibility of movement for individuals in a given compartment to the same compartment in another patch. The edges are given an orientation and are called *arcs*, to show directionality of movement. $\mathcal{G} = (\mathcal{P}, \mathcal{A})$ is a multi-digraph where \mathcal{A} is the set of arcs. \mathcal{A} is an

ordered set of pairs of elements of \mathcal{P} . The term *multiple* is used since two or more migration arcs join the same two patches. The term *directed* is used since the graph has orientation on its edges. \mathcal{P} denotes the set of patches and \mathcal{X} denotes the set of compartments. Let there be N patches and \tilde{N} compartments in the system. That is, $|\mathcal{P}| = N$ and $|\mathcal{X}| = \tilde{N}$. Each patch $p \in \mathcal{P}$ contains a certain number of compartments s that belong to \mathcal{X} . In this context, two compartments represent two different epidemiological states. In mathematical terms, any two vertices $C_1, C_2 \in \mathcal{P}$ are connected by at most \tilde{N} edges from C_1 to C_2 and at most \tilde{N} edges from C_2 to C_1 .

Heterogeneity of health conditions The metapopulation model with residency incorporates a key realistic component that describes the differences between individuals from different countries around the world. This is vital as different countries have different health care infrastructures and policies. In particular, individuals from different countries have different *health histories*. For example, individuals from different countries experience different vaccination routines, health care, nutritional practices, treatment methods, economic status, life expectancy, rate of disease transmission and immunity, to name a few.

6.2 A deterministic metapopulation model with residency

The general metapopulation model with residency holds for any number of epidemiological classes and this model is presented first. Next, we detail the *SLIR* metapopulation model with residency. The deterministic system is autonomous with respect to time, i.e., the function that describes population dynamics does not explicitly contain the independent variable time t .

6.2.1 General model

Let $\mathcal{N}_{rj}^{\mathcal{X}}(t)$ denote the number of individuals in epidemiological state \mathcal{X} resident of patch r that are currently in patch j at time t . Recall that it is assumed that there are N patches in the system. The metapopulation model with residency is written as a system of $|\mathcal{X}|N^2$ differential equations. For all $r, j \in \{1, \dots, N\}$ and all epidemiological states in \mathcal{X} , the evolution of \mathcal{N}_{rj} is governed by:

$$\frac{d}{dt} \mathcal{N}_{rj}^{\mathcal{X}} = f_{rj}(\mathcal{N}_{rj}) + \sum_{\substack{k=1 \\ k \neq j}}^N m_{rjk}^{\mathcal{X}} \mathcal{N}_{rk}^{\mathcal{X}} - \sum_{\substack{k=1 \\ k \neq j}}^N m_{rkj}^{\mathcal{X}} \mathcal{N}_{rj}^{\mathcal{X}}. \quad (6.1)$$

Here, $\mathcal{N}_{rj} = \{\mathcal{N}_{rj}^{\mathcal{X}}, \text{ for all } \mathcal{X}\}$.

f_{rj} describes the population dynamics within patch j of individuals resident of patch r currently in patch j . Suppose individuals of epidemiological class \mathcal{X} are currently in patch j . The term $\sum_{\substack{k=1 \\ k \neq j}}^N m_{rjk}^{\mathcal{X}}$ describes the inflow of

individuals in epidemiological state \mathcal{X} resident of patch r into patch j from all other patches k . The term $-\sum_{\substack{k=1 \\ k \neq j}}^N m_{rkj}^{\mathcal{X}}$ describes the outflow of individuals of epidemiological state \mathcal{X} resident of patch r out of patch j into all other patches k . We assume that there is no travel within the same patch; that is, if $j = k$, $\forall r$, $m_{rkk}^{\mathcal{X}} = 0$.

Alternatively, let us suppose that if $j = k$,

$$m_{rkk}^{\mathcal{X}} = -\sum_{\substack{k=1 \\ k \neq j}}^N m_{rkj}^{\mathcal{X}}. \quad (6.2)$$

Then we can write (6.1) as

$$\frac{d}{dt} \mathcal{N}_{rj}^{\mathcal{X}} = f_{rj}(\mathcal{N}_{rj}) + \sum_{k=1}^N m_{rjk}^{\mathcal{X}} \mathcal{N}_{rk}^{\mathcal{X}}. \quad (6.3)$$

For a fixed r , the number of individuals born in patch r , called the residents of patch r , is given by

$$N_r^{res} = \sum_{j=1}^N \mathcal{N}_{rj}$$

For a fixed j , the number of individuals currently in patch j is given by

$$N_j^{in} = \sum_{r=1}^N \mathcal{N}_{rj}$$

The movement operators are assumed to be linear and movement of individuals between patches depends on disease status. Travel is instantaneous so individuals do not change disease status during travel, nor is there any

death during travel. It is assumed that the movement rates m_{rjk} are non-negative. In general form, the nonnegative matrix $\mathbf{M}_r^\mathcal{X} = [m_{rjk}^\mathcal{X}]$ gives the movement rates of individuals in epidemiological state \mathcal{X} who are resident of patch r and travel from patch k to patch j . These nonnegative matrices are used to derive the movement matrices $\mathcal{M}_r^\mathcal{X}$ for residents of patch r in state \mathcal{X} .

Let $\mathbf{1}_N$ be a $N \times 1$ column vector of ones. Then the movement matrix takes the form

$$\mathcal{M}_r^\mathcal{X} = \mathbf{M}_r^\mathcal{X} - \text{diag}(\mathbf{1}_N^T \mathbf{M}_r^\mathcal{X}),$$

i.e.,

$$\mathcal{M}_r^\mathcal{X} = \begin{bmatrix} -\sum_{\substack{j=1 \\ j \neq 1}}^N m_{rj1}^\mathcal{X} & m_{r12}^\mathcal{X} & \cdots & m_{r1N}^\mathcal{X} \\ m_{r21}^\mathcal{X} & -\sum_{\substack{j=1 \\ j \neq 2}}^N m_{rj2}^\mathcal{X} & \cdots & m_{r2N}^\mathcal{X} \\ \vdots & \vdots & \ddots & \vdots \\ m_{r,N-1,1}^\mathcal{X} & m_{r,N-1,2}^\mathcal{X} & \cdots & m_{r,N-1,N}^\mathcal{X} \\ m_{rN1}^\mathcal{X} & m_{rN2}^\mathcal{X} & \cdots & -\sum_{\substack{j=1 \\ j \neq N}}^N m_{rjN}^\mathcal{X} \end{bmatrix} \quad (6.4)$$

We assume that $\mathcal{M}_r^\mathcal{X}$ is irreducible for all r and \mathcal{X} , that is, individual residents of r can access all patches.

6.2.2 *SLIR* model

The model used here carries the same general ideas as the single population endemic measles model (5.5) of Section 5.5 with the modifications that follow. The metapopulation model with residency takes into account temporary travel and is thus ideal in describing mass gatherings as people leave their country of residence only for a short period of time and then return home after the event has finished. The deterministic system considered in this manuscript is an *SLIR* metapopulation model with residency. Suppose j, k and r are all different, let the index r correspond to the patch individuals are resident of, index j corresponds to the patch individuals are in and index k corresponds to the patch individuals travel to. The model has N patches (or countries) so $r, j, k \in \{1, 2, \dots, N\}$. $\mathcal{X} = \{S_{rj}, L_{rj}, I_{rj}, R_{rj}\} \forall r, j$, where for $r \neq j$ index rj denotes residence away from home and for $r = j$ index rr denotes residence at home. Thus, $|\mathcal{X}| = 4N^2$. In summary,

- $\mathcal{X} = \{S_{rj}, L_{rj}, I_{rj}, R_{rj}\}$, where $|\mathcal{X}| = 4N^2$.
- Fix r . Each $p \in \mathcal{P}$ contains 1 resident subpopulation denoted by $N_{rr} = S_{rr} + L_{rr} + I_{rr} + R_{rr}$ and $N - 1$ visiting subpopulations denoted by $N_{rj} = S_{rj} + L_{rj} + I_{rj} + R_{rj}$ for $r \neq j$. Thus, each patch contains N subpopulations.
- The system is described with $4N^2$ ordinary differential equations.

The subpopulations of the patches are described by a large system of differential equations that are coupled together. In the model with residency

these subpopulations can move between patches and will always be identified by the patch they are resident of.

The $N \times N$ matrix $\mathbf{M}_r^S = [m_{rjk}^S]$ gives the movement rates for susceptible individuals resident of patch r . Similarly, $\mathbf{M}_r^L = [m_{rjk}^L]$, $\mathbf{M}_r^I = [m_{rjk}^I]$, $\mathbf{M}_r^R = [m_{rjk}^R]$ give the movement rates for the latent, symptomatic and recovered individuals residents of patch r .

The transmission parameter, β_{jrk} denotes the contact between a susceptible resident of patch r and an infectious resident of patch k who are both currently in patch j that results in the successful transmission of disease. It is assumed throughout that the β_{jrk} are nonnegative parameters. If individuals mix at random, then the force of infection is expressed by standard incidence or mass action incidence.

Using standard incidence, the force of infection is

$$\sum_{k=1}^N \beta_{jrk} \frac{S_{rj} I_{kj}}{N_j^{in}} \quad (6.5)$$

Using mass action incidence, we have

$$\sum_{k=1}^N \beta_{jrk} S_{rj} I_{kj} \quad (6.6)$$

Fix an r and j , the summation over k accounts for all *successful* contacts (those that result in transmission of infection) between susceptibles resident of patch r currently in patch j with infectious individuals resident of all other patches k that are also currently in patch j . Throughout the rest of

the manuscript, it is assumed that the force of infection function takes on the form of standard incidence (6.5).

The birth rate of susceptible individuals resident of country r currently in patch j takes on a constant rate denoted by Λ_{rj} . Since we are looking at temporary travel it is reasonable to assume that birth only occurs at home, i.e., $\Lambda_{rr} > 0$ with $\Lambda_{rj} = 0$ for $r \neq j$. Natural death occurs for individuals resident of patch r currently in patch j at the per capita rate d_{rj} and is assumed to be the same for all disease classes. Infectious individuals resident of patch r currently in patch j are subject to additional death due to infection denoted by the per capita rate δ_{rj} . The time in the latent class is exponentially distributed with a mean of $1/\epsilon_{rj}$; ϵ_{rj} denotes the per capita rate at which latent individuals resident of patch r currently in patch j become infectious. The time in the infectious class is exponentially distributed with a mean of $1/\alpha_{rj}$, where α_{rj} denotes the recovery rate of infectious individuals resident of patch r currently in patch j . In the R class, individuals have acquired permanent immunity to measles. The parameters Λ_{rj} , d_{rj} , ϵ_{rj} , δ_{rj} and α_{rj} are assumed to be nonnegative. To alleviate notation burden, we use the form (6.2), i.e., consider that

$$m_{rkk}^{\mathcal{X}} = - \sum_{\substack{k=1 \\ k \neq j}}^N m_{rjk}^{\mathcal{X}}$$

For N patches, $N \in \mathbb{N} \setminus \{0\}$, the model for $r, j = \{1, 2, \dots, N\}$ is a system of $4N^2$ differential equations which is given below.

$$\frac{d}{dt}S_{rj}(t) = \Lambda_{rj} - d_{rj}S_{rj} - \sum_{k=1}^N \beta_{jrk} \frac{S_{rj}I_{kj}}{N_j^{in}} + \sum_{k=1}^N m_{rjk}^S S_{rk} \quad (6.7a)$$

$$\frac{d}{dt}L_{rj}(t) = \sum_{k=1}^N \beta_{jrk} \frac{S_{rj}I_{kj}}{N_j^{in}} - (d_{rj} + \epsilon_{rj})L_{rj} + \sum_{k=1}^N m_{rjk}^L L_{rk} \quad (6.7b)$$

$$\frac{d}{dt}I_{rj}(t) = \epsilon_{rj}L_{rj} - (d_{rj} + \delta_{rj} + \alpha_{rj})I_{rj} + \sum_{k=1}^N m_{rjk}^I I_{rk} \quad (6.7c)$$

$$\frac{d}{dt}R_{rj}(t) = \alpha_{rj}I_{rj} - d_{rj}R_{rj} + \sum_{k=1}^N m_{rjk}^R R_{rk} \quad (6.7d)$$

Here, $\Lambda_{rr} > 0$ and $\Lambda_{rj} = 0$ if $r \neq j$.

The biological meaning of each epidemiological state of System (6.7) is given in Table 6.1.

Variable	Epidemiological interpretation
S_{rj}	number of susceptible individuals resident of patch r currently in patch j
L_{rj}	number of latent individuals resident of patch r currently in patch j
I_{rj}	number of symptomatic individuals resident of patch r currently in patch j
R_{rj}	number of immune individuals resident of patch r currently in patch j
N_{rj}	total number of individuals resident of patch r currently in patch j
N_r^{res}	total number of individuals resident of patch r
N_j^{in}	total number of individuals currently in patch j

Table 6.1: Epidemiological interpretation of the state variables.

All parameters and their biological meanings are given in Table 6.2.

Parameter	Biological meaning
Λ_{rj}	constant birth rate for individuals resident of patch r currently in patch j
$m_{rjk}^{\mathcal{X}}$	movement rate of individuals in epidemiological state \mathcal{X} resident of patch r travelling from patch k to patch j
β_{jrk}	rate of transmission of measles between a susceptible from patch r and an infective from patch k who are both currently in patch j
d_{rj}	natural death rate of individuals resident of patch r currently in patch j
ϵ_{rj}	rate at which latent individuals resident of patch r currently in patch j become infectious with the measles virus
δ_{rj}	additional death due to measles of infectious individuals resident of patch r currently in patch j
α_{rj}	recovery rate of infectious individuals resident of patch r currently in patch j

Table 6.2: Biological meaning of the parameters.

Vector and matrix form In order to simplify notation, System (6.7) can be written in terms of vectors and matrices. Let $N^2 \times 1$ column vectors represent the populations and parameters; they will be denoted by S, L, I, R , and $\Lambda, \epsilon, \delta$, and α respectively. Each state is ordered by residency patch in increasing order:

$$\begin{aligned} S &= (S_{11}, \dots, S_{1N}, S_{21}, \dots, S_{2N}, \dots, S_{NN})^T \\ L &= (L_{11}, \dots, L_{1N}, L_{21}, \dots, L_{2N}, \dots, L_{NN})^T \\ I &= (I_{11}, \dots, I_{1N}, I_{21}, \dots, I_{2N}, \dots, I_{NN})^T \\ R &= (R_{11}, \dots, R_{1N}, R_{21}, \dots, R_{2N}, \dots, R_{NN})^T \end{aligned}$$

Parameters are ordered similarly. The total population currently in patch j and the total population resident of patch r will be represented by $N^2 \times 1$ column vectors N^{in}, N^{res} respectively. Recall that birth takes place solely in the patch of residency. Λ, N^{in} , and N^{res} take on the following vector forms,

$$\Lambda = (\Lambda_{11}, \dots, 0, \dots, 0, \dots, \Lambda_{NN})^T$$

$$N^{in} = (N_1^{in}, \dots, N_N^{in}, \dots, N_1^{in}, \dots, N_N^{in})^T$$

$$N^{res} = \left(\overbrace{N_1^{res}, \dots, N_1^{res}}^{\text{residence of patch 1}}, \dots, \overbrace{N_N^{res}, \dots, N_N^{res}}^{\text{residence of patch N}} \right)^T$$

Let \mathcal{D} denote the $N^2 \times N^2$ block diagonal death matrix:

$$\mathcal{D} = \bigoplus_{r=1}^N \mathcal{D}_r$$

where \mathcal{D}_r denotes the $N \times N$ block matrix of \mathcal{D} :

$$\mathcal{D}_r = \text{diag} (d_{r1}, d_{r2}, \dots, d_{rN})$$

Let $\mathcal{M}^{\mathcal{X}}$ denote the $N^2 \times N^2$ block diagonal movement matrix of individuals of epidemiology state \mathcal{X} :

$$\mathcal{M}^{\mathcal{X}} = \bigoplus_{r=1}^N \mathcal{M}_r^{\mathcal{X}}$$

As before, $\mathcal{M}_r^{\mathcal{X}}$ is expressed by (6.4) and will now denote the $N \times N$ block matrices of $\mathcal{M}^{\mathcal{X}}$.

Let \mathcal{T} denote the $N^2 \times N^2$ block matrix of transmission of infection between susceptible and symptomatic individuals.:

$$\mathcal{T} = \begin{bmatrix} T_{11} & T_{12} & \cdots & T_{1N} \\ T_{21} & T_{22} & \cdots & T_{2N} \\ \vdots & & & \vdots \\ T_{N1} & T_{N2} & \cdots & T_{NN} \end{bmatrix}$$

where T_{rk} denote the $N \times N$ block matrices of \mathcal{T} with position in block row r and block column k . Fix r and k , for $j \in \{1, 2, \dots, N\}$,

$$T_{rk} = \text{diag}(\beta_{1rk}, \beta_{2rk}, \dots, \beta_{Nrk})$$

System (6.7) written in terms of vectors and matrices is as follows,

$$\frac{d}{dt}S = \Lambda - (\mathcal{T}I \odot S) \odot \frac{1}{N^{in}} - \mathcal{D}S + \mathcal{M}^S S \quad (6.8a)$$

$$\frac{d}{dt}L = -\epsilon \odot L + (\mathcal{T}I \odot S) \odot \frac{1}{N^{in}} - \mathcal{D}L + \mathcal{M}^L L \quad (6.8b)$$

$$\frac{d}{dt}I = \epsilon \odot L - (\delta + \alpha) \odot I - \mathcal{D}I + \mathcal{M}^I I \quad (6.8c)$$

$$\frac{d}{dt}R = \alpha \odot I - \mathcal{D}R + \mathcal{M}^R R \quad (6.8d)$$

where \odot denotes the Hadamard product. For clarity, $\frac{1}{N^{in}}$ is a $N^2 \times 1$ vector with entries given by $\frac{1}{N_j^{in}}$.

6.2.3 Existence and Uniqueness

Proposition 6.2.1. *Consider System (6.7) with nonnegative initial conditions. Then solutions to System (6.7) exist and are unique for all $t \geq 0$.*

Proof. The vector field in System (6.7) consists of sums of linear terms and rational functions that are written in terms of $S_{rj}, L_{rj}, I_{rj}, R_{rj}$ and N_j^{in} , with N_j^{in} non-zero (shown below in Section 6.2.4). Thus, the vector field of System (6.7) is continuous and differentiable. Hence, solutions to System (6.7) exist and are unique. \square

6.2.4 Non-Negativity

Proposition 6.2.2 (Positivity of solutions). *Given positive initial conditions, solutions of (6.7) $S_{rj}(t)$, $L_{rj}(t)$, $I_{rj}(t)$ and $R_{rj}(t)$ are all positive $\forall t \geq 0$.*

Proof. To show positivity of solutions, let us assume first that initial conditions are positive, that is, $S_{rj}(0) > 0$, $L_{rj}(0) > 0$, $I_{rj}(0) > 0$ and $R_{rj}(0) > 0$. Recall that parameters are assumed to be non-negative. First let us consider the state variable S_{rj} and assume that $\exists t^* > 0$ such that $S_{rj}(t^*) = 0$ and t^* is the first value t for which the state variable hits zero. At t^* ,

$$\begin{aligned} \frac{d}{dt}S_{rj}(t^*) &= \Lambda_{rj} - d_{rj}S_{rj}(t^*) - \sum_{k=1}^N \beta_{jrk} \frac{S_{rj}(t^*)I_{kj}(t^*)}{N_j^{in}(t^*)} \\ &\quad + \sum_{k=1}^N m_{rjk}^S S_{rk}(t^*) - \sum_{k=1}^N m_{rkj}^S S_{rj}(t^*) \end{aligned}$$

Since $S_{rj}(t^*) = 0$,

$$\frac{d}{dt}S_{rj}(t^*) = \Lambda_{rj} + \sum_{k=1}^N m_{rjk}^S S_{rk}(t^*) > 0$$

However, since initial conditions are positive and $S_{rj}(t^*) = 0$, it follows that $S'_{rj}(t^*) \leq 0$ since the solution must be decreasing there. This is a contradiction. Therefore, there does not exist a t^* such that $S_{rj}(t^*) = 0$. This implies that $S_{rj}(t) > 0 \forall t$. Next, let us consider the state variable L_{rj} and assume that $\exists t^* > 0$ such that $L_{rj}(t^*) = 0$ with t^* defined as above. At

t^* ,

$$\begin{aligned} \frac{d}{dt}L_{rj}(t^*) &= \sum_{k=1}^N \beta_{jrk} \frac{S_{rj}(t^*)I_{kj}(t^*)}{N_j^{in}(t^*)} - (d_{rj} + \epsilon_{rj})L_{rj}(t^*) \\ &\quad + \sum_{k=1}^N m_{rjk}^L L_{rk}(t^*) - \sum_{k=1}^N m_{rkj}^L L_{rj}(t^*) \end{aligned}$$

Setting $L_{rj}(t^*) = 0$,

$$\frac{d}{dt}L_{rj}(t^*) = \sum_{k=1}^N \beta_{jrk} \frac{S_{rj}(t^*)I_{kj}(t^*)}{N_j^{in}(t^*)} + \sum_{k=1}^N m_{rjk}^L L_{rk}(t^*) > 0$$

Since the sum of linear terms and rational functions that are positive is positive. Using the same logic as before this leads to a contradiction. Therefore, $L_{rj}(t) > 0 \forall t$. The positivity of I_{rj} and R_{rj} are trivial. Thus, $N_j^{in}(t) > 0$ for all t . \square

Using the same type of argument as in Proposition 6.2.2, with nonnegative initial conditions, it can be shown that solutions to (6.7) remain nonnegative.

Demographic component The total population \mathcal{N}_{rj} resident of patch r currently in patch j is represented by the following equation, obtained by summing the equations of System (6.7)

$$\frac{d}{dt}\mathcal{N}_{rj} = \Lambda_{rj} - d_{rj}\mathcal{N}_{rj} - \delta_{rj}I_{rj} + \sum_{\mathcal{X} \in \{S,L,I,R\}} \left(\sum_{k=1}^N m_{rjk}^{\mathcal{X}} \mathcal{X}_{rk} - \sum_{k=1}^N m_{rkj}^{\mathcal{X}} \mathcal{X}_{rj} \right)$$

with $\Lambda_{rr} > 0$ and $\Lambda_{rj} = 0$ $r \neq j$.

6.2.5 Boundedness of solutions

The proof presented here is a variation of the boundedness proof in [13].

Theorem 6.2.3 (Boundedness). *Solutions to System (6.7) are bounded.*

Proof. First, we fix r . The evolution of the total number of people resident of patch r , N_r^{res} , is given below.

$$\begin{aligned}
\frac{d}{dt} N_r^{res} &= \frac{d}{dt} (\mathcal{N}_{r1} + \dots + \mathcal{N}_{rN}) \\
&= \Lambda_{rr} - \sum_{j=1}^N (d_{rj} \mathcal{N}_{rj} + \delta_{rj} I_{rj}) \\
&\quad + \underbrace{\left(\sum_{k=1}^N m_{r1k}^S S_{rk} - \sum_{k=1}^N m_{rk1}^S S_{r1} \right)}_{\text{In and out of state } S_{r1}} + \dots + \underbrace{\left(\sum_{k=1}^N m_{r1k}^R R_{rk} - \sum_{k=1}^N m_{rk1}^R R_{r1} \right)}_{\text{In and out of state } R_{r1}} + \dots + \dots \\
&\quad + \underbrace{\left(\sum_{k=1}^N m_{rNk}^S S_{rk} - \sum_{k=1}^N m_{rkN}^S S_{rN} \right)}_{\text{In and out of state } S_{rN}} + \dots + \underbrace{\left(\sum_{k=1}^N m_{rNk}^R R_{rk} - \sum_{k=1}^N m_{rkN}^R R_{rN} \right)}_{\text{In and out of state } R_{rN}} \\
&= \Lambda_{rr} - \sum_{j=1}^N (d_{rj} \mathcal{N}_{rj} + \delta_{rj} I_{rj}) \\
&\quad + \sum_{j=1}^N \left(\sum_{k=1}^N m_{rjk}^S S_{rk} - \sum_{k=1}^N m_{rkj}^S S_{rj} \right) + \dots + \sum_{j=1}^N \left(\sum_{k=1}^N m_{rjk}^R R_{rk} - \sum_{k=1}^N m_{rkj}^R R_{rj} \right) \\
&= \Lambda_{rr} - \sum_{j=1}^N (d_{rj} \mathcal{N}_{rj} + \delta_{rj} I_{rj}) \\
&\quad + \sum_{\mathcal{X} \in \{S, L, I, R\}} \left(\sum_{j=1}^N \left(\sum_{k=1}^N m_{rjk}^{\mathcal{X}} \mathcal{X}_{rk} - \sum_{k=1}^N m_{rkj}^{\mathcal{X}} \mathcal{X}_{rj} \right) \right)
\end{aligned}$$

with $\mathcal{X} \in \{S, L, I, R\}$.

Now, let us consider the evolution of the total global population of the metapopulation residency patch model, $\mathbf{N} = \sum_{r=1}^N N_r^{res}$, below. That is, we now sum on r .

$$\begin{aligned}
\frac{d}{dt} \mathbf{N} &= \frac{d}{dt} \sum_{r=1}^N N_r^{res} = \frac{d}{dt} (N_1^{res} + \dots + N_N^{res}) \\
&= \sum_{r=1}^N \left(\Lambda_{rr} - \sum_{j=1}^N (d_{rj} \mathcal{N}_{rj} + \delta_{rj} I_{rj}) \right) \\
&\quad + \sum_{r=1}^N \left(\sum_{\mathcal{X} \in \{S, L, I, R\}} \left(\sum_{j=1}^N \left(\sum_{k=1}^N m_{rjk}^{\mathcal{X}} \mathcal{X}_{rk} - \sum_{k=1}^N m_{rkj}^{\mathcal{X}} \mathcal{X}_{rj} \right) \right) \right) \\
&= \sum_{r=1}^N \Lambda_{rr} - \sum_{r=1}^N \sum_{j=1}^N (d_{rj} \mathcal{N}_{rj} + \delta_{rj} I_{rj}) \\
&\quad + \sum_{\mathcal{X} \in \{S, L, I, R\}} \left(\sum_{r=1}^N \left(\sum_{j=1}^N \left(\sum_{k=1}^N m_{rjk}^{\mathcal{X}} \mathcal{X}_{rk} - \sum_{k=1}^N m_{rkj}^{\mathcal{X}} \mathcal{X}_{rj} \right) \right) \right) \\
&= \sum_{r=1}^N \Lambda_{rr} - \sum_{r=1}^N \sum_{j=1}^N (d_{rj} \mathcal{N}_{rj} + \delta_{rj} I_{rj})
\end{aligned} \tag{6.9}$$

The last equality holds since for each state $\mathcal{X} \in \{S, L, I, R\}$ the sums

$$\sum_{r=1}^N \sum_{j=1}^N \sum_{k=1}^N m_{rjk}^{\mathcal{X}} \mathcal{X}_{rk} = \sum_{r=1}^N \sum_{j=1}^N \sum_{k=1}^N m_{rkj}^{\mathcal{X}} \mathcal{X}_{rj}$$

To see this, notice that for these sums each term appears exactly once with a positive sign and once with a negative sign.

$$\begin{aligned}
\frac{d}{dt}\mathbf{N} &= \sum_{r=1}^N \sum_{j=1}^N \Lambda_{rj} - \sum_{r=1}^N \sum_{j=1}^N d_{rj} \mathcal{N}_{rj} - \sum_{r=1}^N \sum_{j=1}^N \delta_{rj} I_{rj} \\
&= \Lambda - \sum_{r=1}^N \sum_{j=1}^N d_{rj} \mathcal{N}_{rj} - \sum_{r=1}^N \sum_{j=1}^N \delta_{rj} I_{rj} \text{ with } \Lambda = \sum_{r=1}^N \sum_{j=1}^N \Lambda_{rj} \\
&\leq \Lambda - \sum_{r=1}^N \sum_{j=1}^N d_{rj} \mathcal{N}_{rj} \\
&\leq \Lambda - \sum_{r=1}^N \sum_{j=1}^N \hat{d} \mathcal{N}_{rj} \text{ with } \hat{d} = \min_{r,j} \{d_{rj}, d_{rj} > 0\} \\
&= \Lambda - \hat{d} \sum_{r=1}^N \sum_{j=1}^N \mathcal{N}_{rj} \\
&= \Lambda - \hat{d} \mathbf{N}
\end{aligned}$$

Consider the system,

$$\frac{d}{dt}\Psi = \Lambda - \hat{d}\Psi \tag{6.10}$$

using the integrating factor method, the solution to System (6.10) is

$$\Psi(t) = \frac{\Lambda}{\hat{d}} + e^{-\hat{d}t} k, \text{ with } k \text{ constant.}$$

Taking $t \rightarrow \infty$,

$$\lim_{t \rightarrow \infty} \Psi(t) = \frac{\Lambda}{\hat{d}}$$

and since any convergent function is bounded, the total population \mathbf{N} of System (6.7) is bounded. \square

6.2.6 Existence of the DFE

The metapopulation model is at equilibrium when there is no evolution of the states with respect to time, i.e., all time derivatives are zero. The System (6.7) is at a DFE if there are no infected individuals, $L_{rj} = I_{rj} = 0, \forall r, j \in \{1, 2, \dots, N\}$. When using vector and matrix form (6.8), let $S|_{DFE} = \bar{S}$, $L|_{DFE} = \bar{L}$, $I|_{DFE} = \bar{I}$ and $R|_{DFE} = \bar{R}$ be $N^2 \times 1$ vectors that denote the equilibrium solutions.

Theorem 6.2.4. *The DFE to System (6.7) is,*

$$DFE = ((\mathcal{D} - \mathcal{M}^S)^{-1} \Lambda, 0, 0, 0).$$

Proof. Suppose in System (6.8) $L = I = 0$ and substitute this into equation (6.8d) to find the DFE value of R :

$$(\mathcal{D} - \mathcal{M}^R)\bar{R} = 0_{N^2}$$

with 0_{N^2} denoting the $N^2 \times 1$ vector of zeros. Recall that $\mathcal{M}^R = \bigoplus_{r=1}^N \mathcal{M}_r^R$, $\mathcal{D} = \bigoplus_{r=1}^N \mathcal{D}_r$. Assume that \mathcal{D} has at least one entry that is strictly positive. Then because $-\mathcal{M}^R$ is irreducible and diagonally dominant, $\mathcal{D} - \mathcal{M}^R$ is irreducibly diagonally dominant. So by Theorem 1.4.15, $\mathcal{D} - \mathcal{M}^R$ is nonsingular. So

$$\bar{R} = 0_{N^2}.$$

At the DFE, System (6.7) is such that for all $r, j \in \{1, \dots, N\}$, $\bar{N}_{rj} = \bar{S}_{rj}$ and satisfies

$$\Lambda_{rj} - d_{rj}\bar{S}_{rj} + \sum_{k=1}^N m_{rjk}^S \bar{S}_{rk} - \sum_{k=1}^N m_{rkj}^S \bar{S}_{rj} = 0 \quad (6.11)$$

Using vector and matrix notation, at the DFE, System (6.8) takes the following form,

$$\Lambda - \mathcal{D}\bar{S} + \mathcal{M}^S \bar{S} = 0 \quad (6.12)$$

If $\Lambda \neq \mathcal{D}^S \bar{S}$, then (6.12) can be written as the following,

$$\bar{S} = (\mathcal{D} - \mathcal{M}^S)^{-1} \Lambda$$

similarly to $\mathcal{D} - \mathcal{M}^R$, the matrix $\mathcal{D} - \mathcal{M}^S$ is irreducibly diagonally dominant and thus invertible. Hence, the DFE is unique and is given by $DFE = ((\mathcal{D} - \mathcal{M}^S)^{-1} \Lambda, 0, 0, 0)$. \square

6.2.7 Local asymptotic stability of the DFE

Local asymptotic stability of the DFE is studied using the next generation method. The *infected compartments* are those with latent (L) and infectious (I) individuals. The uninfected compartments are those with Susceptible (S) and Recovered (R) individuals. We order the infected compartments as below, first by epidemiological state, then by residency patch:

$$L_{11}, \dots, L_{1N}, \dots, \dots, L_{N1}, \dots, L_{NN},$$

$$I_{11}, \dots, I_{1N}, \dots, \dots, I_{N1}, \dots, I_{NN}.$$

The $N^2 \times 1$ column vector Φ represent the force of infection:

$$\Phi = (\phi_{11}, \dots, \phi_{1N}, \phi_{21}, \dots, \phi_{2N}, \dots, \phi_{NN}),$$

where ϕ_{rj} is the rate at which new infections are generated for residents of patch r currently in patch j . The vector \mathcal{F} represents the new infections into the infected classes.

Let $\mathbf{X}(t) = (L(t), I(t))$; the evolution of the infected states of (6.7) can we written as $\frac{d}{dt}\mathbf{X} = \mathcal{F} - \mathcal{V}$, where \mathcal{F} and \mathcal{V} are given below in vector form. First,

$$\mathcal{F} = \begin{pmatrix} \Phi \\ 0 \end{pmatrix} = \begin{pmatrix} (\mathcal{T}I \odot S) \odot \frac{1}{N^{in}} \\ 0 \end{pmatrix}$$

The $N^2 \times 1$ zero vector corresponds to the fact that the I classes do not have new infections. The vector \mathcal{V} represents the in and out flows of individuals in the infected classes other than new infection. \mathcal{V} is a $2N^2 \times 1$ vector.

$$\mathcal{V} = - \begin{pmatrix} -\epsilon \odot L - \mathcal{D}L + \mathcal{M}^L L \\ \epsilon \odot L - (\delta + \alpha) \odot I - \mathcal{D}I + \mathcal{M}^I I \end{pmatrix}$$

Recall that \mathbb{F} and \mathbb{V} are the Jacobian matrices obtained by differentiating \mathcal{F} and \mathcal{V} with respect to the infected classes L, I and then evaluating at the DFE . Let \bar{S}_{rj} denote S_{rj} evaluated at the DFE , i.e $S_{rj}|_{DFE} = \bar{S}_{rj}$. Since

contacts between a susceptible and infected individual occurs only when they are present in the same patch, $\frac{\partial \phi_{rj}}{\partial L_{pq}} = 0$ and $\frac{\partial \phi_{rj}}{\partial I_{pq}} = 0$ if $j \neq q$ for all $r, j, p, q \in \{1, \dots, N\}$.

The result is a block matrix \mathbb{F} ,

$$\mathbb{F} = \begin{bmatrix} 0 & G \\ 0 & 0 \end{bmatrix}$$

G is a $N^2 \times N^2$ matrix with N^2 blocks. Each block is denoted by G_{rk} ; they are $N \times N$ diagonal matrices for all $r, k \in \{1, 2, \dots, N\}$. For a given r and k , the blocks of G take the following form,

$$G_{rk} = \text{diag} \left(\frac{\beta_{1rk} \bar{S}_{r1}}{\bar{S}_1^{\text{in}}}, \dots, \frac{\beta_{Nrk} \bar{S}_{rN}}{\bar{S}_N^{\text{in}}} \right)$$

For $r \in \{1, 2, \dots, N\}$, let A_r , B_r and C_r be the $N \times N$ diagonal sub-blocks of the blocks of \mathbb{V} . The blocks of \mathbb{V} are given below; fix r , for $j \in \{1, 2, \dots, N\}$,

$$A_r = \text{diag} (d_{r1} + \epsilon_{r1}, \dots, d_{rN} + \epsilon_{rN}) - \mathcal{M}_r^L$$

$$B_r = \text{diag} (d_{r1} + \delta_{r1} + \alpha_{r1}, \dots, d_{rN} + \delta_{rN} + \alpha_{rN}) - \mathcal{M}_r^I$$

$$C_r = \text{diag} (\epsilon_{r1}, \dots, \epsilon_{rN}).$$

\mathbb{V} is a block lower triangular matrix,

$$\mathbb{V} = \begin{bmatrix} \bigoplus_{r=1}^N A_r & 0 \\ -\bigoplus_{r=1}^N C_r & \bigoplus_{r=1}^N B_r \end{bmatrix}$$

Next we show that the inverses of A_r and B_r are nonnegative. First, we show that A_r and B_r are M-matrices. The matrices $-\mathcal{M}_r^L$ and $-\mathcal{M}_r^I$ have zero column sums (e.g., $-1_N^T \mathcal{M}_r^I = 0 \cdot 1_N^T$) and so by Theorem 1.4.11, $-\mathcal{M}_r^L, -\mathcal{M}_r^I \in \mathcal{K}$. That is, they are M-matrices. This implies that A_r and B_r are M-matrices. By Lemma 4.3.1, the matrix \mathbb{V} is invertible and therefore the blocks A_r and B_r are invertible. Therefore, A_r and B_r are nonsingular M-matrices. By Lemma 1.4.10 this implies that A_r^{-1} and B_r^{-1} are nonnegative. The nonnegativity of A_r^{-1} and B_r^{-1} is necessary for a biologically relevant \mathcal{R}_0 . We could further assume that C_r is invertible, i.e., $\epsilon_{rj} > 0 \forall r, j$ which would imply that $C_r > 0$ and $C_r^{-1} > 0$. Note that,

$$\left(\bigoplus_{r=1}^N B_r^{-1} \right) \left(\bigoplus_{r=1}^N C_r \right) \left(\bigoplus_{r=1}^N A_r^{-1} \right) = \bigoplus_{r=1}^N (A_r C_r^{-1} B_r)^{-1}.$$

From the results gathered above, the inverse of \mathbb{V} is a nonnegative matrix,

$$\mathbb{V}^{-1} = \begin{bmatrix} \bigoplus_{r=1}^N A_r^{-1} & 0 \\ \bigoplus_{r=1}^N (A_r C_r^{-1} B_r)^{-1} & \bigoplus_{r=1}^N B_r^{-1} \end{bmatrix}$$

\mathbb{V}^{-1} is a block lower triangular matrix and \mathbb{F} is a block upper triangular matrix. Multiplying two block matrices, $\mathbb{F}\mathbb{V}^{-1}$, results in a block matrix. By Theorem 4.3.2, the basic reproductive number for (6.7) is

$$R_0 = \rho \left(G \left(\bigoplus_{r=1}^N A_r C_r^{-1} B_r \right)^{-1} \right) \quad (6.13)$$

This allows us to state the following result,

Theorem 6.2.5 (Local asymptotic stability). *Let \mathcal{R}_0 be defined as in (6.13). If $\mathcal{R}_0 < 1$, then the DFE of System (6.7) is locally asymptotically stable. If $\mathcal{R}_0 > 1$, then the DFE of System (6.7) is unstable.*

6.3 Stochastic model

Let $S_{rj}(t)$, $L_{rj}(t)$, $I_{rj}(t)$, $R_{rj}(t) \forall r, j \in \{1, 2, \dots, N\}$ be discrete random variables,

$$S_{rj}(t), L_{rj}(t), I_{rj}(t), R_{rj}(t) \in \{1, 2, \dots, N\}.$$

The present state at time t is denoted by $X(t) = (S(t), L(t), I(t), R(t))$.

Where,

$$\begin{aligned} S &= (S_{11}, \dots, S_{1N}, S_{21}, \dots, S_{2N}, \dots, S_{NN}) \\ L &= (L_{11}, \dots, L_{1N}, L_{21}, \dots, L_{2N}, \dots, L_{NN}) \\ I &= (I_{11}, \dots, I_{1N}, I_{21}, \dots, I_{2N}, \dots, I_{NN}) \\ R &= (R_{11}, \dots, R_{1N}, R_{21}, \dots, R_{2N}, \dots, R_{NN}) \end{aligned}$$

The present state then jumps to a new state at time $t + \tau$ which is denoted by $X(t + \tau) = (S', L', I', R')$.

Recall that the birth *event* takes place only in a person's patch of resi-

dence. Also, recall that it is assumed that there is no movement within the same patch, that is, $m_{rkj} > 0$ when $k \neq j$.

The probability of events of the N -patch *SLIR CTMC* with residency are given below, $\forall r, k, j \in \{1, 2, \dots, N\}$.

$$P\left(X(t + \tau) = (S', L', I', R') | X(t) = (S, L, I, R)\right) = \frac{1}{f_t} \left\{ \begin{array}{ll} \Lambda_{rr} & \text{if } X' = (\dots, S_{rr} + 1, \dots) \\ d_{rj} S_{rj} & \text{if } X' = (\dots, S_{rj} - 1, \dots) \\ d_{rj} L_{rj} & \text{if } X' = (\dots, L_{rj} - 1, \dots) \\ (d_{rj} + \delta_{rj}) I_{rj} & \text{if } X' = (\dots, I_{rj} - 1, \dots) \\ d_{rj} R_{rj} & \text{if } X' = (\dots, R_{rj} - 1, \dots) \\ \sum_{k=1}^N \frac{\beta_{jrk} S_{rj} I_{kj}}{N_j^{in}} & \text{if } X' = (\dots, S_{rj} - 1, L_{rj} + 1, \dots) \\ \epsilon_{rj} L_{rj} & \text{if } X' = (\dots, L_{rj} - 1, I_{rj} + 1, \dots) \\ \alpha_{rj} I_{rj} & \text{if } X' = (\dots, I_{rj} - 1, R_{rj} + 1, \dots) \\ m_{rkj}^S S_{rj} & \text{if } X' = (\dots, S_{rk} + 1, S_{rj} - 1, \dots) \\ m_{rkj}^L L_{rj} & \text{if } X' = (\dots, L_{rk} + 1, L_{rj} - 1, \dots) \\ m_{rkj}^I I_{rj} & \text{if } X' = (\dots, I_{rk} + 1, I_{rj} - 1, \dots) \\ m_{rkj}^R R_{rj} & \text{if } X' = (\dots, R_{rk} + 1, R_{rj} - 1, \dots) \end{array} \right. \quad (6.14)$$

Total number of events The total number of events of System (6.7) are given below in Table 6.3.

Using *Gillespie's Algorithm* in Section 1.2.2 with

- $4N^2$ discrete random (state) variables.

Possible events	Number of events
Birth	N
Death	$4N^2$
Transmission of infection	N^2
Out of L class	N^2
Recovery	N^2
Movement	$4N^2(N - 1)$
Total	$4N^2(N + 1)$

Table 6.3: Number of events of System (6.7)

- $5N^3 + N$ parameters.
- Weights of $4N^2(N + 1)$ events,

we can run numerical simulations of the *CTMC* to study the stochasticity of *SLIR* N -patch metapopulation model with residency.

Part III

Application – Mass gatherings and the Hajj

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The research work presented in Part III began with an idea and suggestion from Dr. Arino to formulate a model for mass gatherings using metapopulation theory. We began working on a metapopulation model with residency for influenza and the Hajj. For seasonal influenza, the role of asymptomatic individuals (those who do not show symptoms) is determinant. When performing parameterization for the influenza model, it became very difficult. Thus, realistic numerical results were not achieved. The completed work of the influenza model is not included in my manuscript for reasons of space but this type of model will be returned to in the future.

During the summer of 2012, I had the opportunity to work as an academic intern with the Bio.Diaspora project team, a Saint Micheal’s Hospital (Toronto) based project devoted to the study of the global spread of infectious pathogens. The project was founded by Dr. Kamran Khan, a specialist in mass gatherings and infectious respiratory diseases. Dr. Arino, Dr. Khan and the team members on the Bio.Diaspora project allowed the mass gath-

ering model presented for the remaining of this manuscript to come to life. I had hands on access to real country data which included International Air Transport Association (IATA) data, visas data and prevalence of immunity data, just to name a few. During my internship, Dr. Arino and Dr. Khan presented me with an idea to re-formulate the mass gathering influenza model to instead describe measles as the resurgence of measles in recent years sparked attention towards a potential global pandemic. In Part III we detail our study of measles in the context of mass gatherings.

The metapopulation models of Arino and van den Driessche in [17, 18, 13] incorporated constant movement rates and transmission rates. We used their metapopulation models and adapt them to include time dependent movement rates and time dependent transmission rates. We did this in order to account for air travel during the year, movement volumes for a mass gathering event, inherent properties of a mass gathering and the seasonal characteristic of measles. The transmission rates were found from fitting actual measles incidence data per country. Also, to account for small numbers of infectious individuals that could potentially lead to an outbreak of measles we derived and studied a stochastic analogue of the deterministic metapopulation model with residency.

In Chapter 7, we provide an overview of mass gatherings. We explore the unique inherent properties of mass gatherings. Next, a mass gathering model is formulated. We break up the mass gathering event into five phases and detail why each phases is important. The stochastic analogue of the mass gathering model is formulated.

Chapter 8 is dedicated to the introduction of the part of the Arab world that hosts the Hajj and its corresponding religious practices and provides a detailed explanation of the Hajj and the health risks that rise from hosting such an event.

Chapter 9 is dedicated to an application of the metapopulation model with residency for the 2008 Hajj and measles. A deterministic model for the Hajj and measles is formulated and studied along with its corresponding stochastic analogue. We studied the 2008 Hajj because accurate movement data, namely, Hajj visa data, was made available by the Bio.Diaspora project team for 2008. In Chapter 9 we reduced the *SLIR* measles model to an *SIR* model. The omission of the *L* class was recommended by Dr. Khan. He noted that in order to aim for more realistic results mathematical models should incorporate classes that we know a lot about. In particular, the number of latent individuals or the time spent in latency is not easy to measure and accurate data for such a measurement is not easy to come by (for example, latent people would not show symptoms such as fever so it would be nearly impossible for doctors, screening methods or thermal cameras to detect these individuals). Likewise, mathematicians can impose their expertise in problems of public health concern that can also positively influence the decision making process of public health officials. In Chapter 9 we also detail methods of collecting data and the computation and derivation of parameters in the model. We conclude with some numerical solutions for the deterministic system.

Chapter 7

Specialization to mass gatherings

7.1 Introduction

Mass gathering are a stress test for public health. Crowds, and the infrastructures that support them can be an ideal setting for outbreaks of disease.

Dr. Margaret Chan, Director-General of WHO [40]

Mass gatherings (MGs) are defined as *any occasion, spontaneous or planned, that attracts sufficient number of people to strain the planning and response resources of the community, city, or nation hosting the event* [113]. MGs are held for events such as religious or political occasions, music concerts, festivals and sporting tournaments. MGs can have few people or millions of

people. They take place within a confined time span and location. They can be planned or spontaneous. They can be one-time events, such as a royal wedding, repeat regularly at different locations, such as the Olympics, or they can be repeated regularly at the same location, such as the Hajj [113]. In February 2013, the largest mass gathering took place in Allahabad, India where an estimated 100 million (up from 70 million in 2007) Hindu pilgrims gathered in a 55 day span for the Ardh Kumbh Mela, the world's largest religious festival [30]. MGs have a unique property in that they attract diverse populations from different nations and cultures. International transport by means of air, road or sea or a combination of these has made it increasingly easy for diverse populations to travel across international borders to attend mass gatherings.

The following overview on mass gatherings is adapted from [63].

At a local level, an MG puts a strain on the local health care system. The combination of high crowd density, restricted points of entry, and minimum crowd control, to name a few, pose dangers for the host country. International travel further strains local health services with the sudden influx of a large number of people from around the world. In addition to these problems, the host and visiting populations can carry infectious diseases that are endemic to their home countries. In an MG, contagious diseases can spread rapidly since the highly dense environment is optimal for human-to-human transmission. Due to the ease of global transportation, an MG can potentially threaten global health security.

MGs can be thought of as global-local-global events. The infectious dis-

ease can be endemic to an attendee's country or endemic to the host country. If the infectious disease originates from an attendee's country, those traveling to the MG can transport the disease into the MG environment. In turn, the host population and other visiting populations can become infected with the disease. This is known as a global to local event. If the infectious disease originates from the host country, international travellers can acquire the disease at the MG and when they travel back home, they can transport the disease they acquired at the MG to their home country. This is known as a local to global event. The result: taking part of a MG puts the hosting nation of the MG and the attending countries in a vulnerable position in potentially acquiring a foreign-born or locally-born disease.

By hosting a MG, a potential infectious case that was endemic to a local environment can now get introduced into a global network. And so a major concern arises: *will there be an international spread of an infectious disease?* Ideally, real-time integration of information on travel and infectious disease outbreaks from both local and global surveillance systems will improve the ability to detect and respond to infectious disease threats arising from a MG event. Metapopulation epidemic mathematical modelling can aid in strengthening awareness of global infectious disease threats before, during and after mass gatherings. The deterministic and stochastic metapopulation mass gathering model will aid in predicting the spread of the infectious diseases between the host and attendees countries to, in, and from the MG event and predict the global effect, if any, that arises from hosting a mass gathering event. The MG model incorporates real-time data on a monthly

basis.

We break up the study of a particular mass gathering into five phases.

1. In the first phase, referred to as the *pre-event* stage, is the stage prior to travel to the mass gathering site. Mathematical modelling will aid in understanding the local dynamics of measles in the host country and all attending countries, thus identifying the level of threat (or no threat) of that country. Countries of threat can be tagged ‘a risk’ prior to the event. This will give insight into which countries are more likely to transport measles to the MG or if the host country is likely to transmit measles to attendees.
2. The second phase, referred to as the *movement to the event* stage, occurs when attendees travel to the mass gathering site. The host country will experience a sudden influx of travellers. Existing health services will be tested in their ability to manage millions of new international travellers, properly detect a threat and carry out an effective response. By following the evolution of the populations going to the mass gathering we will be able to approximate the number of attendees from each country that go to the mass gathering site whether susceptible, latent, infectious or immune.
3. The third phase, referred to as the *the event* stage with *movement cut off* occurs when all international attendees have now made their way into the mass gathering site. Here attendees interact with each other in the mass gathering location in addition to interacting with the host

population. By following the evolution of the host and visiting populations in the mass gathering site we will be able to detect those populations that are contracting (vulnerable) or resisting (healthy) measles. Here we neglect movement to focus on the disease dynamics between all populations that take part in the event. Our goal is to identify *high risk* populations before returning home so we can pin point the countries that might need to prepare for possible importation of measles.

4. The fourth phase, referred to as *movement back home with outbound air travel*, occurs when pilgrims travel back to their home countries after the mass gathering event has ended. Studying the evolution of attendees returning home we will be able to detect the outflow traffic of pilgrims. These travellers returning to homes increase the risk in global health security.
5. And finally the fifth phase, referred to as *post-event*, is when all attendees are back in their countries of residence after the mass gathering event has taken place and interaction with their local population begins.

Upon comparing the first and fifth phase one will can study the effects of the mass gathering event on the host or ‘at home’ populations.

Theoretically, the spread of the infectious agent at a global level largely depends on the size of the infectious population, their rate of transmissibility and the number of infected people travelling to and from the MG.

7.2 The metapopulation model with residency for mass gatherings

We propose a metapopulation model with residency for mass gatherings and its stochastic derivation using *SLIR* and *SIR* classifications for the epidemiological states of the populations attending the MG and the host population of the MG. Movement between patches is assumed to be via the airline transportation network.

7.2.1 Deterministic model

In order to formulate the metapopulation model with residency for mass gatherings, we make certain assumption on the general metapopulation model with residency in Chapter 6 and break up the model into three phases of movement.

Assumptions For the mass gathering application we restrict the populations we consider; we are solely interested in the host population resident of the MG site in the MG site, attendees of the MG in the MG site and attendees of the MG at home. This restriction reduces our populations to $4(2N - 1)$ compared to the $4N^2$ populations of the general metapopulation model with residency. Let the index $j = 1$ correspond to the MG site. $\mathcal{X}_{11}(t)$ denotes the number of individuals in epidemiological state \mathcal{X} resident of the mass gathering site in the MG site at time t . $\mathcal{X}_{r1}(t)$ denotes the number of attendees in epidemiological state \mathcal{X} resident of country r that are presently

in the mass gathering site at time t where $r \in \{2, \dots, N\}$. $\mathcal{X}_{rr}(t)$ denotes the attendees in epidemiological state \mathcal{X} resident of patch r that are in their home country r at time t where $r \in \{2, \dots, N\}$. Consequently, S_{rj} , L_{rj} , I_{rj} , R_{rj} are considered for the following index values: (a) $r = j = 1$ which corresponds to the host population in the MG site, (b) $\forall r \neq 1$ and $j = 1$ which corresponds to attendee populations in the MG site and (c) $\forall r = j \neq 1$ which corresponds to the attendee populations in their country of residence. And so, the populations we study are given below for $r, j \in \{2, \dots, N\}$.

$$\begin{aligned}
N_{11} &= S_{11} + L_{11} + I_{11} + R_{11} \\
N_1^{res} &= N_{11} \\
N_1^{in} &= \sum_{r=1}^N N_{r1} \\
N_{r1} &= S_{r1} + L_{r1} + I_{r1} + R_{r1} \\
N_{rr} &= S_{rr} + L_{rr} + I_{rr} + R_{rr} \\
N_{r \neq 1}^{res} &= N_{r1} + N_{rr} \\
N_{j \neq 1}^{in} &= N_{rr}
\end{aligned}$$

The epidemiological interpretation for each epidemiological state is given in Table 7.1 for $r \in \{2, \dots, N\}$.

In addition to restricting the populations of interest, another assumption on System (6.7) is that only direct movement to MG site from home and from the MG site to home is allowed. To elaborate, the attendees that take part in the MG travel to the MG site directly from their country of residence and

State	Epidemiological interpretation
$S_{11}, L_{11}, I_{11}, R_{11}$	number of susceptible, latent, symptomatic and immune individuals resident of MG site in MG site
N_{11}	total number of individuals resident of MG site in MG site
$N_1^{res} = N_{11}$	total number of individuals resident of MG site in the MG site
N_1^{in}	total number of attendees in MG site (N_{r1}) and total number of individuals resident of MG site in the MG site (N_{11})
$S_{r1}, L_{r1}, I_{r1}, R_{r1}$	number of susceptible, latent, symptomatic and recovered and recovered attendees resident of country r in MG site
N_{r1}	total number of attendees resident of country r in MG site
N_r^{res}	total number of attendees resident of country r at home (N_{rr}) and total number of attendees resident of country r in MG site (N_{r1})
$S_{rr}, L_{rr}, I_{rr}, R_{rr}$	number of susceptible, latent, symptomatic and recovered attendees resident of country r at home
N_{rr}	total number of attendees resident of country r at home
$N_j^{in} = N_{rr}$	total number of attendees resident of country r at home

Table 7.1: Epidemiological interpretation of the state variables.

after the event has finished, they travel back to their country of residence directly from the MG site. It is also assumed that there is no in or out movement of the host population. Since there is only direct travel to the mass gathering site from home, m_{rjk}^x is non-zero only when $j = 1$ and $k = r$ where $r, k \in \{2, \dots, N\}$. And since there is only direct travel back home from the mass gathering site, m_{rkj}^x is non-zero only when $j = 1$ and $k = r$ where $r, k \in \{2, \dots, N\}$.

Since the birth process only occurs at home, $\Lambda_{rr} > 0$ for $r \in \{1, 2, \dots, N\}$. The rates of transmission between susceptible residents of the MG location, $r = 1$, with attending infectious populations resident of country $k > 1$ and infectious residence of the MG location $k = 1$, all currently in the MG site $j = 1$ are non-zero. And so, β_{jrk} is non-zero for $j = r = 1$ where $k \in \{1, 2, \dots, N\}$. The rates of transmission between susceptible attendees resident of country $r > 1$ with all other attending infectious populations resident of country $k > 1$ and infectious residence of the MG location $k = 1$ all currently in the MG site $j = 1$ are non-zero. And so, β_{jrk} is non-zero for $j = 1$ where $k \in \{1, 2, \dots, N\}$ and $r \in \{2, \dots, N\}$. The rates of transmission between susceptible and infectious attendees resident of country $r > 1$ at home are non-zero. And so, β_{jrk} non-zero for $\forall r = j = k$ where $j, r, k \in \{2, \dots, N\}$. The remaining parameters, d_{rj} , ϵ_{rj} , δ_{rj} and α_{rj} are non-zero for the host population in the MG site $r = j = 1$, attendees of the MG in the MG site $r > 1$ and $j = 1$, and attendees of the MG at home $r = j > 1$. All other parameters are zero. And so, the parameters of interest are given below for $r \in \{2, \dots, N\}$ and $k \in \{1, 2, \dots, N\}$.

$$\Lambda_{11}, \Lambda_{rr}, \beta_{11k}, \beta_{1rk}, \beta_{rrr}, m_{r1r}^{\mathcal{X}}, m_{rr1}^{\mathcal{X}}, d_{11}, d_{r1}, d_{rr}$$

$$\epsilon_{11}, \epsilon_{r1}, \epsilon_{rr}, \delta_{11}, \delta_{r1}, \delta_{rr}, \alpha_{11}, \alpha_{r1}, \alpha_{rr}$$

All parameters and their biological meanings are given in Table 7.2 and Table 7.3.

State	Biological Meaning
Λ_{11}	birth function of individuals resident of MG site in MG site
Λ_{rr}	birth function of attendees resident of country r at home
β_{11k}	The rates of transmission between susceptible residence of the MG location with attending infectious populations and infectious residence of the MG location, all currently in the MG site.
β_{1rk}	The rates of transmission between susceptible attendees with all other attending infectious populations and infectious residence of the MG location, all currently in the MG site.
β_{rrr}	rates of transmission between susceptible and infectious attendees at home.
$m_{r1r}^{\mathcal{X}}$	movement rate of attendees in state \mathcal{X} resident of country r travelling from their home to MG site
$m_{rr1}^{\mathcal{X}}$	movement rate of attendees in state \mathcal{X} resident of country r travelling back home from the MG site

Table 7.2: Biological meaning of the parameters.

State	Biological Meaning
d_{11}	natural death rate of residents of the MG site in the MG site
d_{r1}	natural death rate of attendees resident of country r in the MG site
d_{rr}	natural death rate of attendees resident of country r at home
ϵ_{11}	rate at which latent individuals resident of the MG site become infectious in the MG site
ϵ_{r1}	rate at which latent attendees resident of country r become infectious in the MG site
ϵ_{rr}	rate at which latent attendees resident of country r become infectious at home
δ_{11}	additional death due to measles of symptomatic individuals resident of the MG site in the MG site
δ_{r1}	additional death due to measles of symptomatic attendees resident of country r in the MG site
δ_{rr}	additional death due to measles of symptomatic attendees resident of country r at home
α_{11}	recovery rate of symptomatic individuals resident of the MG site in the MG site
α_{r1}	recovery rate of symptomatic attendees resident of country r in the MG site
α_{rr}	recovery rate of symptomatic attendees resident of country r at home

Table 7.3: Biological meaning of the parameters (continued).

The metapopulation model with residency applied to mass gatherings for $r, j \in \{1, 2, \dots, N\}$ results in a system of $4(N + (N - 1)) = 4(2N - 1)$ differential equations.

For the mass gathering site $r = j = 1$,

$$\frac{d}{dt}S_{11}(t) = \Lambda_{11} - d_{11}S_{11} - \sum_{k=1}^N \beta_{11k} \frac{S_{11}I_{k1}}{N_1^{in}} \quad (7.1a)$$

$$\frac{d}{dt}L_{11}(t) = \sum_{k=1}^N \beta_{11k} \frac{S_{11}I_{k1}}{N_1^{in}} - (d_{11} + \epsilon_{11})L_{11} \quad (7.1b)$$

$$\frac{d}{dt}I_{11}(t) = \epsilon_{11}L_{11} - (d_{11} + \delta_{11} + \alpha_{11})I_{11} \quad (7.1c)$$

$$\frac{d}{dt}R_{11}(t) = -d_{11}R_{11} + \alpha_{11}I_{11} \quad (7.1d)$$

For all visiting populations in the MG site, that is, for $r = \{2, \dots, N\}$ and $j = 1$,

$$\frac{d}{dt}S_{r1}(t) = -d_{r1}S_{r1} - \sum_{k=1}^N \beta_{1rk} \frac{S_{r1}I_{k1}}{N_1^{in}} + m_{r1r}^S S_{rr} - m_{rr1}^S S_{r1} \quad (7.1e)$$

$$\frac{d}{dt}L_{r1}(t) = \sum_{k=1}^N \beta_{1rk} \frac{S_{r1}I_{k1}}{N_1^{in}} - (d_{r1} + \epsilon_{r1})L_{r1} + m_{r1r}^L L_{rr} - m_{rr1}^L L_{r1} \quad (7.1f)$$

$$\frac{d}{dt}I_{r1}(t) = \epsilon_{r1}L_{r1} - (d_{r1} + \delta_{r1} + \alpha_{r1})I_{r1} + m_{r1r}^I I_{rr} - m_{rr1}^I I_{r1} \quad (7.1g)$$

$$\frac{d}{dt}R_{r1}(t) = -d_{r1}R_{r1} + \alpha_{r1}I_{r1} + m_{r1r}^R R_{rr} - m_{rr1}^R R_{r1} \quad (7.1h)$$

For all populations in their country of residence, that is, for $r = \{2, \dots, N\}$,

$$\frac{d}{dt}S_{rr}(t) = \Lambda_{rr} - d_{rr}S_{rr} - \beta_{rrr}\frac{S_{rr}I_{rr}}{N_r^{in}} + m_{rr1}^S S_{r1} - m_{r1r}^S S_{rr} \quad (7.1i)$$

$$\frac{d}{dt}L_{rr}(t) = \beta_{rrr}\frac{S_{rr}I_{rr}}{N_r^{in}} - (d_{rr} + \epsilon_{rr})L_{rr} + m_{rr1}^L L_{r1} - m_{r1r}^L L_{rr} \quad (7.1j)$$

$$\frac{d}{dt}I_{rr}(t) = \epsilon_{rr}L_{rr} - (d_{rr} + \delta_{rr} + \alpha_{rr})I_{rr} + m_{rr1}^I I_{r1} - m_{r1r}^I I_{rr} \quad (7.1k)$$

$$\frac{d}{dt}R_{rr}(t) = -d_{rr}R_{rr} + \alpha_{rr}I_{rr} + m_{rr1}^R R_{r1} - m_{r1r}^R R_{rr} \quad (7.1l)$$

The mass gathering system above will be referred to as System (7.1). Recall that the mass gathering processes can be further broken down into three movement phases; refer to Table 7.4.

Phase	Type of movement	Existence of movement term
2	In flow: to the MG site	$m_{r1r}^{\mathcal{X}}$ non-zero, $m_{rr1}^{\mathcal{X}} = 0$
3	No movement: during MG event	$m_{r1r}^{\mathcal{X}} = m_{rr1}^{\mathcal{X}} = 0$
4	Out flow: return back home	$m_{rr1}^{\mathcal{X}}$ non-zero, $m_{r1r}^{\mathcal{X}} = 0$

Table 7.4: Phases of movement, with $\mathcal{X} \in \{S, L, I, R\}$. In Phase 1 (pre-MG) and 5 (post-MG) individuals are in their countries of residence interacting with their local populations so we assume there is no movement.

I mention the phases because we can break down the mass gathering model to focus on the phase we are most interested in. For example, to test screening methods and their efficacy we could focus on Phase 1 and screen passengers at the airport of the mass gathering site and try to impose certain restrictions so that we can contain any potential outbreak.

7.3 Stochastic model for mass gatherings

The Continuous Time Markov Chain for the *SLIR* metapopulation model with residency for mass gathering is developed.

Let \mathcal{X}_{11} , \mathcal{X}_{r1} and \mathcal{X}_{r1} for $\mathcal{X} \in \{S, L, I, R\}$ be discrete random variables,

$$\mathcal{X}_{11}, \mathcal{X}_{r1} \text{ and } \mathcal{X}_{rr} \in \{1, 2, \dots, N\}.$$

The present state at time t is denoted by $X(t) = (\mathcal{X}_{11}, \mathcal{X}_{r1}, \mathcal{X}_{rr})$ for $r \in \{2, \dots, N\}$. Where,

$$\mathcal{X}_{11} = (S_{11}, L_{11}, I_{11}, R_{11})$$

$$\mathcal{X}_{r1} = (S_{21}, \dots, S_{N1}, L_{21}, \dots, L_{N1}, I_{21}, \dots, I_{N1}, R_{21}, \dots, R_{N1})$$

$$\mathcal{X}_{rr} = (S_{22}, \dots, S_{NN}, L_{22}, \dots, L_{NN}, I_{22}, \dots, I_{NN}, R_{22}, \dots, R_{NN})$$

The present state then jumps to a new state at time $t + \tau$ which is denoted by $X(t + \tau) = (\mathcal{X}'_{11}, \mathcal{X}'_{r1}, \mathcal{X}'_{rr})$.

Like we mentioned in Section 1.2, the *CTMC* makes transitions from state to state, independent of the past. Once again, let τ represent the amount of time that the process remains in the state before transitioning into a new state; it is an exponentially distributed random variable, it takes on the same value as in Section 1.2.

The probability of events of the N -patch *SLIR CTMC* model with res-

identity for mass gatherings are given below, $\forall r \in \{2, \dots, N\}$.

$$P\left(X(t + \tau) = (\mathcal{X}'_{11}, \mathcal{X}'_{r1}, \mathcal{X}'_{rr}) | X(t) = (\mathcal{X}_{11}, \mathcal{X}_{r1}, \mathcal{X}_{rr})\right) =$$

$$\frac{1}{f_t} \left\{ \begin{array}{ll}
\Lambda_{11} & \text{if } X' = (S_{11} + 1, \dots) \\
\Lambda_{rr} & \text{if } X' = (\dots, S_{rr} + 1, \dots) \\
d_{11}S_{11} & \text{if } X' = (\dots, S_{11} - 1, \dots) \\
d_{r1}S_{r1} & \text{if } X' = (\dots, S_{r1} - 1, \dots) \\
d_{rr}S_{rr} & \text{if } X' = (\dots, S_{rr} - 1, \dots) \\
d_{11}L_{11} & \text{if } X' = (\dots, L_{11} - 1, \dots) \\
d_{r1}L_{r1} & \text{if } X' = (\dots, L_{r1} - 1, \dots) \\
d_{rr}L_{rr} & \text{if } X' = (\dots, L_{rr} - 1, \dots) \\
(d_{11} + \delta_{11})I_{11} & \text{if } X' = (\dots, I_{11} - 1, \dots) \\
(d_{r1} + \delta_{r1})I_{r1} & \text{if } X' = (\dots, I_{r1} - 1, \dots) \\
(d_{rr} + \delta_{rr})I_{rr} & \text{if } X' = (\dots, I_{rr} - 1, \dots) \\
d_{11}R_{11} & \text{if } X' = (\dots, R_{11} - 1, \dots) \\
d_{r1}R_{r1} & \text{if } X' = (\dots, R_{r1} - 1, \dots) \\
d_{rr}R_{rr} & \text{if } X' = (\dots, R_{rr} - 1, \dots) \\
\sum_{k=1}^N \frac{\beta_{11k}S_{11}I_{k1}}{N_1^{in}} & \text{if } X' = (\dots, S_{11} - 1, L_{11} + 1, \dots) \\
\sum_{k=1}^N \frac{\beta_{1rk}S_{r1}I_{k1}}{N_1^{in}} & \text{if } X' = (\dots, S_{r1} - 1, L_{r1} + 1, \dots) \\
\beta_{rrr} \frac{S_{rr}I_{rr}}{N_r^{in}} & \text{if } X' = (\dots, S_{rr} - 1, L_{rr} + 1, \dots) \\
\epsilon_{11}L_{11} & \text{if } X' = (\dots, L_{11} - 1, I_{11} + 1, \dots) \\
\epsilon_{r1}L_{r1} & \text{if } X' = (\dots, L_{r1} - 1, I_{r1} + 1, \dots) \\
\epsilon_{rr}L_{rr} & \text{if } X' = (\dots, L_{rr} - 1, I_{rr} + 1, \dots) \\
\alpha_{11}I_{11} & \text{if } X' = (\dots, I_{11} - 1, R_{11} + 1, \dots) \\
\alpha_{r1}I_{r1} & \text{if } X' = (\dots, I_{r1} - 1, R_{r1} + 1, \dots) \\
\alpha_{rr}I_{rr} & \text{if } X' = (\dots, I_{rr} - 1, R_{rr} + 1, \dots) \\
m_{r1r}^S S_{rr} & \text{if } X' = (\dots, S_{rr} - 1, S_{r1} + 1, \dots) \\
m_{r1r}^I L_{rr} & \text{if } X' = (\dots, L_{rr} - 1, L_{r1} + 1, \dots) \\
m_{r1r}^L I_{rr} & \text{if } X' = (\dots, I_{rr} - 1, I_{r1} + 1, \dots) \\
m_{r1r}^R R_{rr} & \text{if } X' = (\dots, R_{rr} - 1, R_{r1} + 1, \dots) \\
m_{rr1}^S S_{r1} & \text{if } X' = (\dots, S_{rr} + 1, S_{r1} - 1, \dots) \\
m_{rr1}^I L_{r1} & \text{if } X' = (\dots, L_{rr} + 1, L_{r1} - 1, \dots) \\
m_{rr1}^L I_{r1} & \text{if } X' = (\dots, I_{rr} + 1, I_{r1} - 1, \dots) \\
m_{rr1}^R R_{r1} & \text{if } X' = (\dots, R_{rr} + 1, R_{r1} - 1, \dots)
\end{array} \right. \quad (7.2)$$

Total number of events The total number of events of System (7.1) are given below in Table 7.5.

Using *Gillespie's Algorithm* in Section 1.2.2 with

Possible events	Number of events
Birth	N
Death	$4(2N - 1)$
Transmission of infection	$2N - 1$
Out of L class	$2N - 1$
Recovery	$2N - 1$
Movement	$8(N - 1)$
Total	$23N - 15$

Table 7.5: Number of events of System (7.1).

- $4(2N - 1)$ discrete random (state) variables.
- $N^2 + 19N - 13$ parameters.
- Weights of $23N - 15$ events,

we can run numerical simulations of the *CTMC* to study the stochasticity of *SLIR* metapopulation model with residency for mass gatherings.

Chapter 8

The Arab world and the Hajj

In this Chapter we begin with explaining the differences between the Islamic Calendar and the Western Calendar. The provinces, relevant cities and pillars of the Islamic faith are presented. We explain what the Hajj is, Hajj visas and present some data on the age of pilgrims that attend. The dates in which the Hajj was held and predicted dates of future Hajj dates are given. Modes of transportation, their popularity and leading points of entry used by pilgrims to arrive to Mecca are presented. The number of pilgrims that attended the Hajj are given for 2005-2012. The factors of the Hajj that contribute to the spread of infectious disease are presented. Historical accounts of disease outbreaks due to the Hajj are given and emerging infectious disease threats are introduced. Finally, we conclude by motivating the importance of studying the Hajj, as its unique characteristics pose global threats of disease spread.

8.1 The Islamic calendar

The Islamic calendar is a lunar calendar that has 12 lunar (29.5 days) months: Muharram, Safar, Rabi al-awwal, Rabi al-thani, Jumada al-awwal, Jumada al-thani, Rajab, Sha'ban, Ramadan, Shawwal, Dhu al-Qi'dah and Dhu al-Hijjah [103]. The Islamic calendar is shorter than the Gregorian calendar, it has 354 days per year [103, 104]. The thin crescent moon is the most widely recognized symbol in Islam [36]. The first of each month occurs on the day of the first sighting of the crescent moon after conjunction, that is, the phase after the new moon [36, 109].

Depending on the region, different methods are used to determine the first of each month, the methods are real time observance or predictive. The traditional method of Muslim communities is visual observation where the months are determined by the naked-eye sighting of the crescent moon in their geographic location [109]. Thus, the actual sighting can only be documented once it has occurred. The traditional method is not definitive or conclusive as the visibility of the crescent moon depends on good sky conditions (clouds, pollution, city light etc.), geographical location and experience and preparation of the observer [97, 104]. Despite the difficulties that arise, many Muslim regions including Bangladesh, India, Morocco, Oman and Pakistan, still currently rely on the traditional method [22]. However, in order for planning committees and response teams to effectively prepare for a variety of potential outcomes at Islamic religious events, they need to know dates of events ahead of time. Being advised last minute or after the moon

sighting has already occurred of the timing of such events is not practical and so countries are replacing traditional methods with methods of prediction. Predictive methods use astronomical calculations to meet criteria on characteristics such as the moons altitude, the geometry of the sun, moon and natural horizon, the width of the crescent, the brightness of the moon's surface or age of the moon (the time counted from new moon) to name a few [71, 97, 109]. Therefore, calendars used in each region vary and are not reliable in the sense that they are not consistent with the actual sighting of the crescent moon. A general consensus by all regions on the use of one method has not been reached and has resulted in a historical debate [36, 94]. As a result, Muslim regions worldwide celebrate religious holidays at different times with a discrepancy of one or two days [36].

8.2 Saudi Arabia, host country of the Hajj

Saudi Arabia is the largest Arab state in western Asia in terms of land area. Saudi Arabia occupies 80% of the Arabian Peninsula and is the largest and most populated state of the six member states of the Gulf Cooperation Council (GCC) [74]. All states of the GCC border the Persian Gulf, Gulf of Oman and the Arabian Sea. To the east of Saudi Arabia is the Persian Gulf and to the west is the Red Sea. The World Health Organization (WHO) ranked Saudi Arabia 26th overall based on performance of its health system out of 176 nations [74]. The official religion of Saudi Arabia is Islam [83]. Saudi Arabia is home to the two of the holiest cities in Islam which are the

cities of Medina and Mecca [74].

8.2.1 Provinces of Saudi Arabia

Saudi Arabia is partitioned into 13 administrative areas or provinces [80]; the relevant cities in our study are in the provinces of Makkah and Medina. Makkah province is the most populated province and is the home to the second and third most populated cities in Saudi Arabia (after Riyadh, the capital), the cities of Jeddah and Mecca (the capital city of Makkah province) respectively [87, 80]. Jeddah has a large population, twice the size of Mecca's population and is the commercial capital of Saudi Arabia [82, 87]. All pilgrims travel to and from Mecca to perform the Hajj; it is the focal point or location of our MG study. Mecca will be known as the *MG or host patch* as it is the location in which the Hajj pilgrimage takes place [1]. Mecca's population will be referred to as the *host* population. Another province of Saudi Arabia is the Madinah province which is home to the city of Medina [80]. Medina is where Mohammed emigrated to from Mecca and lived and is the location of his grave [82, 86]. Jeddah, Mecca and Medina are highlighted here as they are cities used or mentioned in our MG study.

8.2.2 Pillars of faith.

There are five pillars of the Islamic faith: *shahaada* (the profession of faith), *salat* (praying five times a day), *zakat* (alms giving), *sawm* (fasting during Ramadan) and undertaking of the Hajj pilgrimage [5, 86, 80]. These pillars

define the basic identity of Muslims which incorporate their faith, beliefs and practices [80].

8.3 What is the Hajj?

The Hajj is a mass gathering event in Mecca that has been occurring annually for more than 14 centuries [64]. It is a pilgrimage or spiritual journey undertaken annually by many people of the Muslim faith. It is the largest, most diverse, re-occurring MG in existence today [2, 52]. All Muslims who are physically and financially able to are obligated to undertake the Hajj pilgrimage at least once in their lifetime [1, 53, 86]; as mentioned above, it is one of the five pillars of the Muslim faith.

8.4 Hajj visas

To attend the Hajj, international pilgrims are required entry visas. To obtain entry visas, pilgrims must meet certain requirements and recommendations and have a valid passport [79, 115]. A passport guarantees that the pilgrim has resided in that country for at least three to five years (rules vary depending on the country). The issued visas to pilgrims is a policy implemented by Saudi Arabia to restrict the number of travelers to Mecca [73].

8.5 Age of pilgrims that attend the Hajj

Men, women and children of different ages are attending the Hajj in increasing numbers. A 2002 study on the Hajj found that the mean age of Hajjis was 33.5 years [3]. Depending on the culture, the age of pilgrims varies; in Indonesia and Malaysia for example, those that take part to Hajj are of a uniformly young age whereas other nations wait until the later phases in life to attend, in hopes of death at the Hajj as this is thought to carry beneficial outcomes in the afterlife [73]. From 2006 to 2008, the overwhelming majority of pilgrims were 60 or more years old [46].

8.6 Hajj dates

The Hajj occurs earlier each year that passes. The dates of the Hajj are given by methods used in Saudi Arabia. The Hajj is a five day event that starts on the 8th day and continues to the 12th day of Dhu al-Hijjah, the last month of the Islamic lunar calendar [28]. As previously mentioned, the lunar calendar is 11 days shorter than the Gregorian calendar, thus, each Hajj occurs approximately 11 days (sometimes 10 or 12 days) before the start date of the previous year's Hajj. Since the Hajj takes place in Mecca, it is only suitable to use dates announced by the Supreme Judicial Council of Saudi Arabia to study past Hajj events and predict future dates from the calendar most widely used in Saudi Arabia.

Past Hajj dates. The dates for past Hajj events are announced by the Supreme Judicial Council of Saudi Arabia and are available from 2005-2012.

Future (predicted) Hajj dates. The *Umm al-Qura* calendar is used by the government of Saudi Arabia, The Islamic Society of North America, the Fiqh Council of North America and the European Council for Fatwa and Research [106]. The months are determined based on astronomical criteria [4, 106]. The pre-determined dates from the Umm al-Qura calendar can be one or two days off from the actual first sighting of the crescent moon [106]. As a result, the dates for future Hajj events can be off from the actual first sighting of the crescent moon by one or two days. The Umm al-Qura calendar converter in [106] was used to calculate the dates of the Hajj for 2013-2035.

The dates of the Hajj for 2007 to 2035 are given in Figure 8.1.

8.7 Transportation systems

The modes of transportation to Mecca to perform the Hajj consists of air, land and sea travel [3, 64, 73]. Pilgrims travelled in the past mostly by sea; and nowadays pilgrims are travelling mostly by air [73, 108]. Air travel consists of commercial flights and unscheduled chartered flights [64]. Land travel is by bus or car [3]. As mentioned before, ongoing globalization has lead to an improved global transportation network that is increasingly connecting very large and diverse populations from around the world. Since commercial air travel has become readily accessible, it is replacing maritime and land

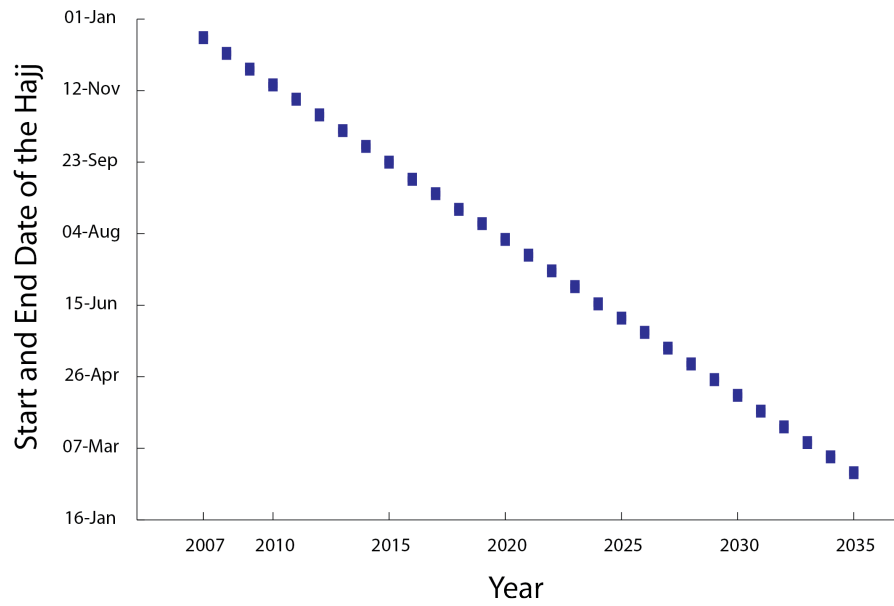


Figure 8.1: Dates of the Hajj, 2007 - 2035.

travel. In March of 2001, roughly 1.3 million pilgrims of international origin performed the Hajj and the majority of them, 88.6%, arrived by air, 9.7% travelled by land and 1.7% arrived by sea [74]. In December 2008, roughly 1.7 million pilgrims of international origin from 140 countries performed the Hajj; the vast majority of the international pilgrims, 91.0%, arrived by air, 7.7% travelled by land and 1.3% arrived by sea [64]. Since the vast majority of pilgrims of international origin travelled to Mecca by air, movement data used in our study will come from popular *commercial airports* used by pilgrims travelling to and from Mecca.

Commercial airports. The two main commercial airports used by pilgrims are the King Abdulaziz International Airport in Jeddah, IATA code JED and the Prince Mohammed Bin Abdulaziz International Airport in Medina, IATA code MED [64]. JED IAP has a separate terminal that was constructed specifically for pilgrims performing the Hajj [64, 73]. The terminal is only two thirds of the way completed and has 18 hubs to receive inbound and outbound pilgrims with a capacity of 80,000 travellers at any time [73]. Once the terminal is fully completed, more than 30 million travellers will be accommodated each year [73]! JED is the leading port of entry for pilgrims travelling by air; falling right behind in popularity is MED, which is the second port of entry for pilgrims [64]. In fact, most pilgrims who used maritime travel disembarked in Jeddah which for centuries has been the leading port of entry for pilgrims [73].

It is worth noting that it is not clear as to the number of pilgrims that

go to MED first then to Mecca to perform the Hajj. Travellers who enter and leave MED cannot be guaranteed participants of the Hajj as it is a non-essential part of the Hajj pilgrimage to visit Mohammed's burial place or to perform other rites outside of Mecca. Also, some of the pilgrims that perform religious rituals in Medina may decide to travel to Mecca by car, bus or train to perform the Hajj but capturing the number of passengers that do so is challenging. Regardless of this fact, in our study, we consider the aggregate total of international passengers flying into MED and JED as an approximation of the passenger volume going into Mecca.

8.8 Number of pilgrims from 2005-2012

Non-domestic vs domestic pilgrims. Pilgrims of international origin are known as non-domestic, foreign, visitors or attendees. Pilgrims that are resident of Saudi Arabia are known as domestic. These terms will be used interchangeably.

Due to affordable and timely air transportation, international travelers are taking part in the Hajj in increasing numbers. The number of international pilgrims attending the Hajj since 2005 has increased from 1.5 million to nearly 2 million pilgrims in 2012, with 2009 as an exception. Refer to Table 8.1.

Year	Month	Pilgrims		
		Foreign	Domestic	Total
2005	January	1,557,447	700,603	2,258,050
2006	December	1,654,407	724,229	2,378,636
2007	December	1,707,814	746,511	2,454,325
2008 ¹	December	1,732,246	800,000	2,535,246
2009 ²	November	1,613,965	699,313	2,313,278
2010	November	1,799,601	989,798	2,789,399
2011 ³	November	1,828,195	1,099,522	2,927,717
2012 ³	October	1,752,932	1,408,641	3,161,573

Table 8.1: Number of pilgrims attending the Hajj for 2005 to 2012 [83].
¹2008 Hajj study by Khan and collaborators [64]. Domestic pilgrims given in [83] numbered 679,008 versus 800,000 in [64]. ²Another data source [81] reported a total of 2,520,000 pilgrims that participated in the 2009 Hajj which included 154,000 domestic pilgrims, 1,613,000 foreign pilgrims and 753,000 illegal pilgrims (those without valid Hajj permits). ³Reported by the Royal Embassy of Saudi Arabia in Washington DC [81].

8.9 Hajj factors that contribute to the spread of disease

Each year, the Hajj poses global health security threats due to increased air travel, diversity of attendees, size of event, crowd behaviors associated with the religious rites and the seasonality of the event.

Air travel and the spread of disease. Increased globalization and affordable air travel makes air transportation a vital factor in facilitating the spread of infectious diseases. An infected pilgrim can transmit the disease to other travellers on the airplane or travellers they contact at international

airports that he or she passes through; this is known as *transmission during travel*. In my research study, it is assumed that transmission of disease *during* travel is not possible. If the infected pilgrim successfully lands in Mecca without being detected, the disease could be potentially imported into Mecca; this is known as *imported cases of disease*. Once the disease is introduced into Mecca, the domestic and non-domestic pilgrims in Mecca are exposed to the disease and can acquire the disease; this is known as *disease acquired upon attendance of the Hajj*. Lastly, upon returning home, infected pilgrims may introduce the disease into their home countries, burdening the health care systems of various countries worldwide; this is known as *exported cases of disease*.

Diversity. The Hajj brings people from different nations, cultures and societies together and their diverse interaction increases susceptibility to foreign diseases. Hajj pilgrims vary in age, gender, country of origin, access to health care and health literacy [2]. Due to the different geographical locations that pilgrims come from, they are accustomed to different climates and have different social, cultural and health backgrounds. Pilgrims that come from countries that have endemic diseases unfamiliar to the MG location and vice versa pose a threat to global outbreaks of disease.

Country of residence. The health of pilgrims and their ability to protect themselves against disease depends on their country of residence. Pilgrims from developing countries may not be able to afford or have timely access

to H1N1 vaccine in order to develop immunity before attending the Hajj [64]. In the case of measles, people born in low-income countries had seven times higher immunity than people born in high-income countries [88]. In a 2002 study, non-Saudi Hajjis were 1.25 times more likely to contract acute respiratory infections than Saudi (or domestic) Hajjis [64].

Crowdedness. The densely populated Hajj, the nature of the rituals and shoulder-to-shoulder contact during prayer create a perfect atmosphere for transmission of disease [1, 46]. In 2010, the population of Mecca more than doubled during the Hajj season. The large influx of pilgrims places an additional burden on the health infrastructures of Mecca. Pilgrims stay in tents overnight at Mina and Arafat and there can be 50-100 people in one tent [52]. During the 1993 Hajj, it was found that crowdedness was one of the factors that contributed to carrier rates for meningococcal meningitis as high as 80% [74]. In a 2002 study, one of the factors that caused increased risks of Acute Respiratory Infections (ARI) among Hajjis was crowdedness while performing rites at the Hajj. They found that pilgrims who prayed at the Namera mosque in Arafat suffered a 3.17 times higher risk of ARI compared to Hajjis who did not pray there [3]. In the same study, it was found that the time spent at the Hajj site had a linear association with increased risk of acquiring an ARI. A pilgrim who stayed in the Hajj site for eight or more days was 1.75 times more likely to acquire an ARI than those who stayed four to five days [3]. Disease transmission upon touching of surfaces becomes a real threat as floors, carpets and objects that carry religious significance are

routinely touched by pilgrims [46].

Seasonal Variability. The Hajj experiences variation in climate and seasons due to its unique shift in time each year [2] which aids in the spread of seasonal infectious diseases. Depending on the year, since the Hajj falls in the same (*shifting*) lunar month it will occur in the spring, summer, fall or winter. The changes in climate and season that the Hajj experiences throughout the years is known as *seasonal variability* of the MG event [2]. Such variation imposes diverse epidemiological conditions in Mecca which, depending on the season, brings about the emergence of infectious diseases that have seasonal characteristics. In the northern hemisphere, seasonal influenza peaks predominantly in the winter months, that is, in December, January and February [38]. From 2005-2009 the Hajj coincided with the peak of seasonal influenza. So when the Hajj is held in the winter months, pilgrims become susceptible to seasonal influenza. Worldwide, the seasonality of measles falls predominantly in the spring months, that is, in March, April and May; see Section 3.3. So when the Hajj is held in the spring months, pilgrims become susceptible to measles.

8.10 Historical disease outbreaks due to the Hajj

Historical infectious disease outbreaks due to the Hajj include cholera, meningococcal meningitis, respiratory tract infections, diarrheal diseases and zoonotic

diseases. In 1984-86 Hajj season, there were several outbreaks of cholera [1]. The last epidemic of cholera occurred in 1989, which affected 102 pilgrims. In 1987 a large outbreak of serogroup A meningococcal disease occurred in pilgrims [1, 53]. During the 2000 Hajj season, the largest outbreak in the world of *Neisseria meningitis* serogroup W135 [1] occurred, which is a uncommon cause of a meningococcal epidemic [74]. During the 2001 Hajj season, 109 cases of meningococcal meningitis were reported (more than 50% of the cases were due to *N. meningitis* serogroup W135), which included 35 deaths; the majority of cases were from outside the Kingdom of Saudi Arabia (KSA) [74]. In a 2003 study, respiratory system and gastrointestinal disease were ranked the second and third reasons for hospital admissions (the first was cardiovascular disease) [1]. Acute respiratory infections (ARI) are common when the Hajj occurs in the winter months (December, January and February) [3, 74]. The 2002 Hajj was held in February. Out of the cohort of 1027 pilgrims that attended the 2002 Hajj, 40% of pilgrims developed ARI during and immediately after the Hajj [3]. The main viruses that cause upper respiratory tract infections (URTI) at the Hajj are the respiratory syncytial virus, parainfluenzae, influenzae and adenovirus [1, 74]. The Hajj season in 2003 experienced an estimated 400,000 pilgrims with respiratory symptoms and 24,000 possible cases of influenza [1]. The annual risk of tuberculosis (TB) infection and the prevalence of resistant TB to anti-TB drugs are 3 times higher in Mecca when compared to the Saudi national average [1, 74]. Such a result is attributed to the annual influx of pilgrims from countries where tuberculosis is highly endemic [1]. Diarrheal diseases are one of the

most common health problems associated with the Hajj [74]. Improper food habits like buying unhygienic street food from vendors, lack of refrigeration, the use of ice cubes or unclean water are some probable causes [74]. Food poisoning has been found to be an important cause of diarrhea and vomiting with cases ranging from 44-132 from the 1994-2005 Hajj season [1]. Orf, a viral disease of sheep and goats, can be transmitted to humans from direct contact with infected animals which manifests itself as skin lesions [1, 74]. There was 8 cases of hand orf infection attributed to slaughtering in the Hajj month [56].

8.11 Emerging infectious diseases

Viral haemorrhagic fevers (VHF) such as Rift Valley fever (RVF), Alkumra virus and Ebola virus, blood born diseases, brucellosis, severe acute respiratory syndrome (SARS), Avian influenza A (H5N1), pandemic influenza A (H1N1) and measles are emerging infectious disease concerns for the Hajj.

RVF and Alkumra virus affects livestock as well as humans. In 2000, reports stated that RVF cases were found in Saudi Arabia and Yemen [1]. In 2000-2001 a RVF outbreak in Saudi Arabia resulted in more than 100 Saudi fatalities [74]. In 1995, Alkumra virus was found in 6 patients south of Jeddah and in 2001, four cases were confirmed in Mecca [1]. Ebola virus, which likely comes from fruit bats, has caused several outbreaks in Africa, is endemic to Uganda and is a lethal virus that has a mortality rate of 92% [1, 45, 48, 74]. Upon completion of the Hajj men shave their heads which increases the risk

of the transmission of blood-borne diseases such as hepatitis B, hepatitis C and HIV [1, 53, 74]. At the end of the Hajj, thousands of cattle are slaughtered, which could endanger pilgrims of contracting zoonotic diseases such as brucellosis [74]. Saudi Arabia imports animals for slaughter during the Hajj from brucellosis-endemic countries and Saudi Arabia itself is highly endemic for brucellosis; despite this, there have been no documented cases of brucellosis outbreak during the Hajj [74]. Avian influenza A (H5N1) is a major global concern [1]. As of 2006, WHO reported 175 confirmed human cases of Avian influenza A (H5N1); among them were 95 deaths [1]. Despite such a low number of cases, the mutating characteristics of the virus can make it easily transmissible between humans, thus posing a threat to pilgrims [1].

Air transportation can facilitate the spread of and increase the risk of exposure to infectious diseases such as SARS, influenza and measles [1, 46, 114]. These diseases pose a major threat to the host and attending pilgrims and can then be further spread into susceptible populations. The conditions of the Hajj, combined with international air travel could turn a single case of these highly communicable diseases into an pandemic of unprecedented scale.

In the 2003 season of the Hajj, SARS posed a major threat to pilgrims [1, 2]. The first SARS case in Vietnam was reported on February 23, 2003 just a couple weeks after the start date of the 2003 Hajj [100, 112]. Within weeks, SARS spread from the Guangdong province of China to 37 countries around the world [100]. By May 2003, 7,919 probable cases with 662 deaths were reported by 28 countries [112]. No cases of SARS were reported in Saudi

Arabia [1].

The 2009 H1N1 influenza pandemic posed a threat to the 2009 and 2010 Hajj [46, 64]. In March of 2009, H1N1 emerged in Mexico and in the United States [119]. From April 2009 to August 2010, more than 214 countries reported confirmed cases of 2009 H1N1 pandemic which included over 18,449 deaths [111].

The resurgence of measles cases has sparked attention towards widespread outbreaks of measles during the Hajj [115]. In April 2011, 33 countries in Europe reported 6,500 measles cases with confirmed transmission across borders to other countries in the region and the Americas [114].

8.12 Policies and regulations in place

Saudi Arabia has put regulations and policies in place to mitigate the risk of infectious diseases outbreaks such as cholera, diarrheal diseases, meningococcal meningitis, influenza, blood-borne diseases, SARS, H5N1 and RVF.

To prevent cholera and diarrheal diseases, Saudi Arabia improved their water supply and sewage systems [1]. Saudi Arabia also accommodates for proper food handling and makes clean drinking water readily available at the MG site [74]. Authorities in Saudi Arabia do not allow pilgrims to carry food unless it is canned food sufficient for a 24 hour period [1]. The Saudi Arabia ministry of health (SAMH) requires the surveillance of pilgrims arriving from cholera affected countries [1].

Hajj workers, seasonal workers, all citizens and residents of Medina and

Mecca, in addition to foreign pilgrims, are obligated to provide proof of quadrivalent meningococcal vaccination; without it Hajj passports will not be issued [1, 74, 115].

SAMH recommends influenza vaccination to pilgrims with co-morbidities (such as diabetes and cardiovascular disease) and vaccine is mandatory for all health workers in Mecca and Medina [1, 74]. Jeddah recommends that pilgrims at high risk for suffering complications due to influenza (pregnant mothers, people with chronic disease and those under 12 and over 65) voluntarily refrain from attending the Hajj [46].

SAMH recommends the use of face masks to reduce airborne transmission but compliance has been poor [1, 3, 46, 74].

To prevent the spread of blood borne disease, regulations require the testing of barbers for hepatitis B, hepatitis C and HIV and they must all be licensed barbers [1, 74]. The use of single disposable blades is also mandatory [1].

To identify communicable diseases such as SARS and influenza, thermal cameras in Saudi Arabia international airports detect pilgrims with fever [1, 46]. Some strategies to prevent the entry of SARS included delayed entry for pilgrims from countries reporting local SARS transmission and the implementation of educational programs for health-care personnel who might encounter SARS patients [1]. In response to the number of H5N1 cases in 2006, Saudi Arabia restricted bird importation [1].

In 2001, to mitigate the risk of an RVF outbreak in Saudi Arabia, SAMH banned the importation of sheep from RVF endemic countries or RVF en-

demic regions south of Saudi Arabia, set up educational campaigns for abattoir workers in Mecca and implemented strict surveillance and supervision efforts [74].

8.13 Motivation for study

The policies and regulations implemented by Saudi Arabia have made a significant impact in mitigating the spread of certain diseases; however, they do have limitations. First, if a preventative measure such as a face mask or vaccine is not mandatory or if the disease is thought to be eradicated or of relatively low threat or mortality, most people do not place an extra burden on themselves. Second, the resources of countries and their ability to receive vaccines in a timely fashion become vital factors in acquiring immunity against vaccine preventable diseases prior to the Hajj. Third, thermal screening methods are limited in catching all ill pilgrims.

High risk pilgrims remain un-immunized against influenza [52]. Only 4.7% of pilgrims over 65 and 5.9% of health workers in the 2003 Hajj followed the recommendations for seasonal influenza vaccine. Another study stated that pilgrims are not likely to comply with recommendations of voluntarily abstaining from the Hajj since H1N1 has low mortality [46]. Measles is widely thought to be eradicated and is known as a childhood disease so uninformed pilgrims may not know its evolving danger.

Resource limited countries are at risk of disease outbreaks since they may not have the economic means to afford vaccines or may not have the recourse

needed to deploy public health systems that effectively detect and respond to potential imported cases of diseases carried by returning pilgrims [64]. There are also limitations and delays in the production and distribution of vaccines [46, 64]. During the 2009 Hajj, there was a delay in the production of H1N1 vaccines and only a handful of economically prosperous countries had the ability to vaccinate their pilgrims with sufficient time to develop immunity before the start of the Hajj [64]. Another preventable measure for reducing transmission of communicable diseases is the use of face masks but covering one's face during Hajj is considered prohibited by many Muslims [46, 52].

Thermal screening misses those that at entry have not developed symptoms, those that are asymptomatic and those that use medicine to prevent fever [46]. In addition to not capturing febrile pilgrims, multiple points of entry to perform the Hajj make screening difficult [46].

In addition to better policies, equipment, educational programs and preparation, the rise of global air travel and the many factors associated with the Hajj that contributes to the spread of disease further provokes global outbreaks. Worldwide outbreaks of highly communicable diseases such as influenza or SARS are thought to be long overdue and preparation to minimize such risks has been inadequate [1, 2, 52, 73]. The global effect of outbreaks of influenza, SARS or measles during Hajj season remains unknown. Based on these conclusions, my mathematical study on the global spread of measles due to the Hajj is of critical importance. My manuscript is the beginning of an ongoing study of the Hajj and infectious diseases; future work will be on the spread of Influenza A H1N1 and the Hajj.

Chapter 9

The 2008 Hajj and measles

9.1 Overview

In this chapter, the application of an *SIR* metapopulation model with residency to the 2008 Hajj and measles is detailed. First, some general assumptions made in our study are presented. Second, we detail the countries or patches that we are interested in, present country data and classify each country into its respective WHO region. Thirdly, the theoretical phases of the Hajj are explained and illustrations are presented for each of these phases. Forth, we detail the derivation and computation of the birth, death, recovery, movement and transmission rates and present the country data used in the computation of these parameters. Fifth, we present the deterministic metapopulation model for the Hajj and measles and formulate its stochastic analogue. Some numerical results are presented for the deterministic system.

9.2 Assumptions

We detail the results of [64] since their findings contributed to key assumptions made in my study of the 2008 Hajj and measles.

The 2008 data in [64] of the number of international and domestic pilgrims in attendance was provided by the Saudi Ministry of Health. The analysis of international pilgrim data identified the pilgrims country of origin, mode of travel and point of entry into Saudi Arabia. The visas data measures the number of Hajj visas issued to pilgrims which provides the most accurate data on the number of pilgrims attending the Hajj and their country of origin. The Hajj visas data includes all pilgrims exclusive of their mode of travel, that is, all pilgrims travelling via commercial and chartered flights, sea and land. It was found that a total of 2,532,246 pilgrims attended the 2008 Hajj. Of the 2.5 million pilgrims, 1,732,256 were of non-Saudi origin and 800,000 were of Saudi origin. The majority of pilgrims, 91% travelled to the Hajj by air, 7% travelled by land and 1.3% travelled by sea. Non-Saudi or international pilgrims came from 140 countries around the world, with 20 of the 140 countries accounting for 82.6% of all non-Saudi pilgrims. In the same study, it was also found that the main point of entry used by pilgrims travelling by air was the Jeddah IAP (JED) and the second point of entry was the Medina IAP (MED). The purpose of their study was to pinpoint vulnerable pilgrim populations to the 2009 H1N1 seasonal influenza virus due to the potential importation of H1N1 into Mecca and how the limited supplies of H1N1 vaccines could be best distributed among visiting

countries (in particular, wealthier countries to donate vaccine to limited-resource countries).

Due to findings in [64] we were able to make some general assumptions in our study of the 2008 Hajj and measles. First, only countries with the largest number of pilgrims in attendance are studied. Since 20 countries accounted for the majority of non-Saudi pilgrims, rather than studying 140 international countries or patches, we simplify our analysis to 20 international patches. Second, movement data for the month in which that Hajj was held uses the Hajj visas data provided by [64] which, like we mentioned before, is the most accurate measure of the number of pilgrims in attendance per country. Third, since MED and JED are the two main points of entry used by pilgrims, movement data on months other than the Hajj month uses data of international passengers flying into Medina IAP or Jeddah IAP.

9.3 The 22 patches of interest

Since our study is on MGs, we first need to isolate the MG location. The Hajj journey takes place solely in Mecca. That is, it is assumed that pilgrims do not go to other cities to perform Hajj rituals. Therefore, Mecca is considered a separate patch from Saudi Arabia (SAU); once isolated, it is the patch that represents the MG location and is called the MG patch or site. To isolate the MG patch we subtract the population of Mecca from the population of Saudi Arabia ($\text{population}(\text{SAU}) = \text{population}(\text{SAU}) - \text{population}(\text{Mecca})$) which results in two patches, one for SAU and one for Mecca. So from now

on, it is assumed that Saudi Arabia’s population will exclude the population of Mecca.

Domestic and foreign pilgrims are included in our study to accurately depict all pilgrims performing the Hajj. Domestic pilgrims come from SAU and foreign or non-domestic pilgrims come from all other countries. The host location of Mecca, the country of Saudi Arabia and the 20 countries that accounted for the majority of international pilgrims, are the patches considered in the metapopulation MG model. Thus, in total, we have $N = 22$ patches. The MG site and the 21 countries of interest are listed in Table 9.1 and illustrated in Figure 9.1.

No.	Countries	No.	Countries
1	Mecca (MG patch)	12	Lebanon
2	Saudi Arabia	13	Malaysia
3	Afghanistan	14	Morocco
4	Algeria	15	Nigeria
5	Bangladesh	16	Oman
6	Egypt	17	Pakistan
7	India	18	Russia
8	Indonesia	19	Sudan
9	Iran	20	Syria
10	Iraq	21	Turkey
11	Jordan	22	Yemen

Table 9.1: The MG site and the 21 countries with the largest number of pilgrims that attended the 2008 Hajj.



Figure 9.1: The MG site and the 21 countries with the largest number of pilgrims that attended the 2008 Hajj.

9.3.1 Country data

The susceptible and immune populations per country were computed using prevalence of measles immunity data (in percentage) which was based on a countries income status; the data was provided by the Bio.Diaspora team in [88]. The total population, gross national income per capita in US dollars, income status, percentage of immune people per country and the total number of individuals that are susceptible and immune for the 21 countries and the MG site are listed in Table 9.2. The income status of the countries will determine the percentage of the population that is immune to measles [88]. Therefore, the population that is immune to measles is calculated by multiplying the total population of a country by the proportion of immune peoples in that population. The susceptible population of each country is

calculated by subtracting the immune population from the total population of that country.

No. = r	Countries	Total ¹ population N_{rr}	GNI ¹	Income status ¹	Prevalence(%) of immunity to measles ²	Susceptible population S_{rr}	Immune population R_{rr}
1	Mecca (MG patch)	1,294,168 ³	16,790	High income	95.9	53,061	1,241,107
2	Saudi Arabia	24,872,471	16,790	High income	95.9	1,019,771	23,852,700
3	Afghanistan	32,517,656	300	Low income	99.4	195,106	32,322,550
4	Algeria	34,428,028	4,260	Upper middle income	95.1	1,686,973	32,741,055
5	Bangladesh	145,478,300	570	Low income	99.4	872,870	144,605,430
6	Egypt	78,323,298	1,880	Low middle income	95.1	3,837,842	74,485,456
7	India	1,190,863,679	1,030	Lower middle income	95.1	58,352,320	1,132,511,359
8	Indonesia	234,951,154	1,950	Lower middle income	95.1	11,512,607	223,438,547
9	Iran	72,289,291	4,100	Upper middle income	95.1	3,542,175	68,747,116
10	Iraq	30,178,292	2,100	Lower middle income	95.1	1,478,736	28,699,556
11	Jordan	5,787,000	3,530	Lower middle income	95.1	283,563	5,503,437
12	Lebanon	4,166,915	7,040	Upper middle income	95.1	204,179	3,962,736
13	Malaysia	27,502,008	7,440	Upper middle income	95.1	1,347,598	26,154,410
14	Morocco	31,321,453	2,540	Lower middle income	95.1	1,534,751	29,786,702
15	Nigeria	150,665,730	1,150	Lower middle income	95.1	7,382,621	143,283,109
16	Oman	2,636,963	18,750	High income	95.9	108,115	2,528,848
17	Pakistan	167,442,258	940	Lower middle income	95.1	8,204,671	159,237,587
18	Russia	141,950,000	9,710	Upper middle income	95.1	6,955,550	134,994,450
19	Sudan	32,438,306	1,080	Lower middle income	95.1	1,589,477	30,848,829
20	Syria	19,637,776	2,230	Lower middle income	95.1	962,251	18,675,525
21	Turkey	70,923,730	9,260	Upper middle income	95.1	3,475,263	67,448,467
22	Yemen	22,626,595	980	Lower middle income	95.1	1,108,703	215,178,912

Table 9.2: Total Population, GNI per capita (in US \$), classification of income status per country, percentage of population that has immunity to measles, total number of susceptible and immune individuals of 21 countries and the MG site for 2008. ¹2008 Data from World Bank: total population, GNI per capita (in US \$) and income status [24]. Income classification of a country is defined by the World Bank for all economies with populations greater than 30,000 according to 2008 GNI per capita calculated using the World Bank Atlas method. For 2008, groups are classified as: low income, <=\$935; lower middle income, \$936-\$3,705; upper middle income, \$3,706-\$11,455; and high income, > \$11,455 [24]. ²Measles prevalence data is given by [88] where lower middle and upper middle income countries are both considered middle income countries. ³Population of Mecca city based on 2004 census data [87]

9.3.2 Classification into a WHO region

Figure 3.2 in Section 3.3 illustrates monthly measles incidence for the WHO regions (except AMR) for 2007-2011. Although the data is not provided per country we classify each country into its respective WHO region, see Table 9.3.

AFR	SEAR	EMR	EUR	WPR
Algeria Nigeria	Bangladesh India ¹ Indonesia	Afghanistan Egypt Iran Iraq Jordan Lebanon Mecca Morocco Oman Pakistan Saudi Arabia Sudan Syria Yemen	Turkey Russian Federation	Malaysia

Table 9.3: The 22 patches are classified into their respective WHO region.
¹India is not included in WHO data. However, it is assumed that India experiences the same measles cases as SEAR.

We assume that the 21 countries, due to their large volumes of pilgrims that attend the Hajj each year, are the countries most at risk to potentially export (or import) measles cases to (or from) Mecca.

We assume that there is no risk of exportation (or importation) of measles to (or from) the MG site from countries in AMR for two reasons: measles incidence is low (mentioned in Section 3.3) and the number of pilgrims from

AMR countries that attend the Hajj is relatively low when compared to the volume of pilgrims from countries in the other WHO regions. Therefore, AMR is neglected in our study.

9.4 Phases of the Hajj event

Like the general mass gathering model, the Hajj event is broken down into five phases which includes three phases of movement, see Figure 9.2.

1. The first phase, referred to as *the pre-Hajj* phase, is when all pilgrims are in their country of origin, interacting with their local population, before the MG event. The study of the local dynamics of measles in Mecca and all attending countries will enable us to pin point the countries of ‘high risk’ prior to the Hajj. This will give insight into which countries are more likely to transport measles to Mecca or if the pilgrims resident of Mecca are likely to transmit measles to attendees.
2. The second phase, referred to as *movement to the Hajj*, occurs when all pilgrims travel from their home countries to Mecca. By following the evolution of pilgrims going to the Hajj can approximate the number of foreign pilgrims from each country that go to the Hajj whether susceptible, infectious or immune.
 - In the second phase, the first phase of movement occurs, *inbound air travel*.

3. The third phase, referred to as *the Hajj phase*, occurs when all pilgrims from the 21 patches of interest are in the MG location. Here foreign pilgrims interact with other international and domestic pilgrims that are also in the MG location. By following the evolution of the host and visiting pilgrims in Mecca we will be able to detect the resident country of pilgrims that are contracting or resisting measles. Here we neglect movement to focus on the disease dynamics between all pilgrims that take part in the Hajj. We can then identify ‘high risk’ populations before returning home, for example, those attending populations that have large infectious individuals. This would pinpoint the countries that would need to prepare for possible importation of measles. The duration of the third phase is equivalent to the duration of the MG event.
 - In the third phase, the second phase of movement occurs which is referred to as *no air travel*. In this phase all air travel is cut off.
4. The fourth phase, referred to as *movement back home*, occurs when pilgrims travel back to their home countries after the MG event has ended. Here pilgrims returning to their homes can potentially increase the risks of a global pandemic.
 - In the fourth phase, the third and last phase of movement occurs, *outbound air travel*.
5. Finally the fifth phase, referred to as *post-Hajj*, is when all pilgrims are

back in their countries of residence after the Hajj has taken place and interaction with their local population begins.

Comparing the results of the fifth stage with those of the first stage can provide some understanding as to the effect of the Hajj on the local population.

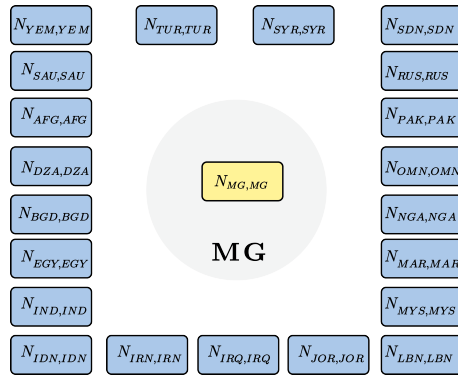
In Figures 9.2(a) to 9.2(e), we illustrate total populations at home, i.e., $N_{r,r} = S_{r,r} + I_{r,r} + R_{r,r}$ and away, i.e., $N_{r,1} = S_{r,1} + I_{r,1} + R_{r,1}$ (illustration of the differential equations is not given because it would crowd the figure). Here, the mass gathering patch contains $3 \times 22 = 66$ differential equations and *each* home patch contains 3 differential equations. So a total of $3 \times 21 = 63$ differential equations describe *all* the home patches.

9.5 Movement

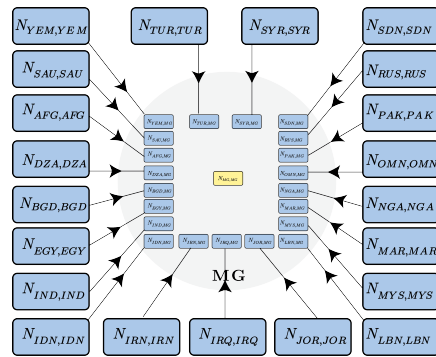
International Air Transport Association (IATA) data, provided by the Bio-Diaspora Project Team, is used to analyze air travel (movement) world wide.

9.5.1 International Air Transport Association (IATA)

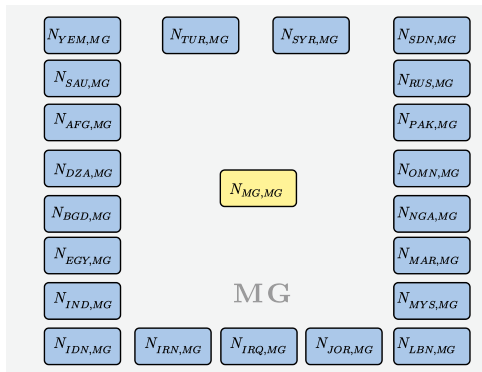
IATA captures flight itineraries of passengers on commercial flights worldwide, it does not provide information of passengers travelling by unscheduled chartered flights, sea or land and does not distinguish between passengers attending the Hajj and other international passengers. Itineraries say nothing about a passenger's country of residence, they only indicate the locations



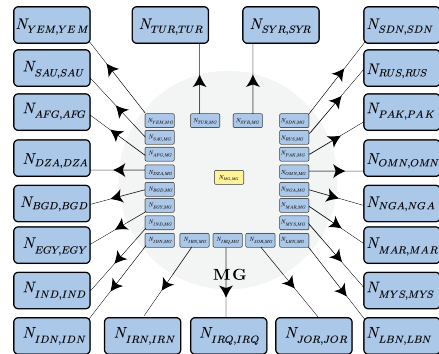
(a) Phase 1– pre-Hajj, pilgrims are in their country of residence, interacting with the local population, before the MG event.



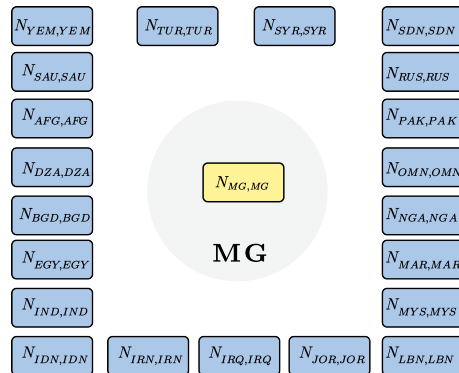
(b) Phase 2– pilgrims travel to Mecca from their countries of residence. In-bound air travel.



(c) Phase 3– the Hajj, all pilgrims are in Mecca, all pilgrims are interacting with each other. Terminate air travel.



(d) Phase 4– pilgrims return home to their countries of residence from Mecca. Outbound air travel.



(e) Phase 5– post-Hajj, all pilgrims have returned home and interaction with their local population begins.

Figure 9.2: The Hajj event is broken down into five phases which include three phases of movement.

from which passengers depart and what their destinations are.

Connections IATA data accounts for all trips that have up to five connections. A trip is broken into two if a person spends more than 17 hours on the ground between two destinations [85].

Country to Country. IATA data can be classified as passenger itineraries departing from origin country r with destination country SAU. Trips into destination country SAU (or from origin country SAU) accounts for passenger arrivals (or departures out of SAU) into (or out of) all international airports in Saudi Arabia.

City to City. IATA data can be classified as passenger itineraries departing from origin city r with destination city JED or MED. Trips into destination city JED (or from origin city JED) account for passenger arrivals (or departures out of JED) into (or out of) the international airport associated to Jeddah.

Country to City. Itineraries with passengers departing from origin country r with destination city JED or MED.

All countries into Saudi Arabia for 2005 to 2010. IATA data is used to study trends of international air traffic into SAU for 2005-2010 using country to country classification. So we study monthly flows of passengers travelling to all airports in SAU from all countries. We then observe where the

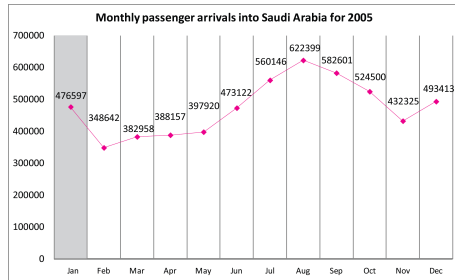
volume of international air traffic into SAU coincides with the timing of the Hajj.

IATA data does not differentiate between Saudi Arabian residents returning home from visiting other countries and international passengers arriving in Saudi Arabia. So we assume that passengers travelling into Saudi Arabia are non-domestic or international; they do not account for residence returning home.

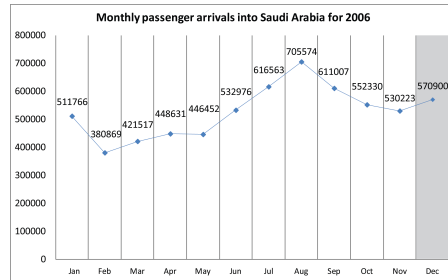
Figure 9.3 illustrates how the timing of the Hajj coincides with peaks of international passenger volume into SAU for 2005-2010. The peaks of passenger volumes in the summer months can be attributed to a summer tourist festival located in JED [64]. Other peaks of passenger volumes can be attributed to other Muslim holidays such as Umrah, which is another pilgrimage that can be undertaken throughout the year (unlike the Hajj which is held at a specific time each year). Upon comparing the data for 2005-2010 we observe that air travel into Saudi Arabia has become increasingly popular. Each year, the maximum number of passengers into Saudi Arabia occurs in August. The number of passenger arrivals in August 2010 increased by 60% compared to the number of passenger arrivals in August 2005.

All countries into Saudi Arabia versus top contributing countries

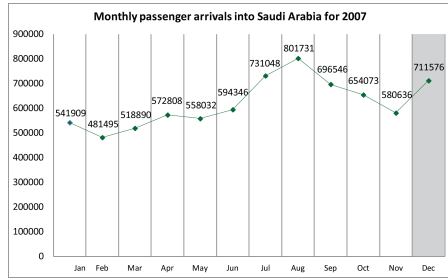
The 20 international countries in Table 9.1 account for the majority of international passenger traffic into Saudi Arabia. More specifically, in 2008, they account for 67% to 74% of the total inflow air traffic into Saudi Arabia, refer to Figure 9.4. This strengthens the conclusions made in [64] as the same top



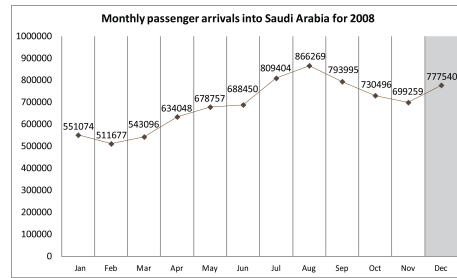
(a) 2005



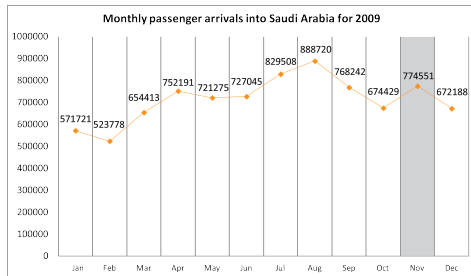
(b) 2006



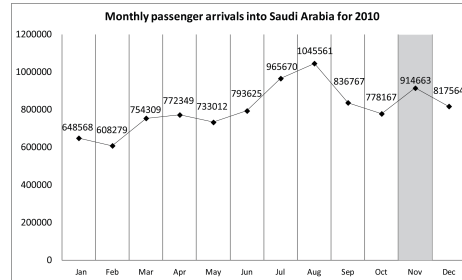
(c) 2007



(d) 2008



(e) 2009



(f) 2010

Figure 9.3: Monthly international passenger arrivals into all airports in Saudi Arabia for 2005 to 2010. Shaded region illustrates the month in which the Hajj was held.

20 contributing countries of pilgrims to the hajj account for the majority of air traffic into SAU.

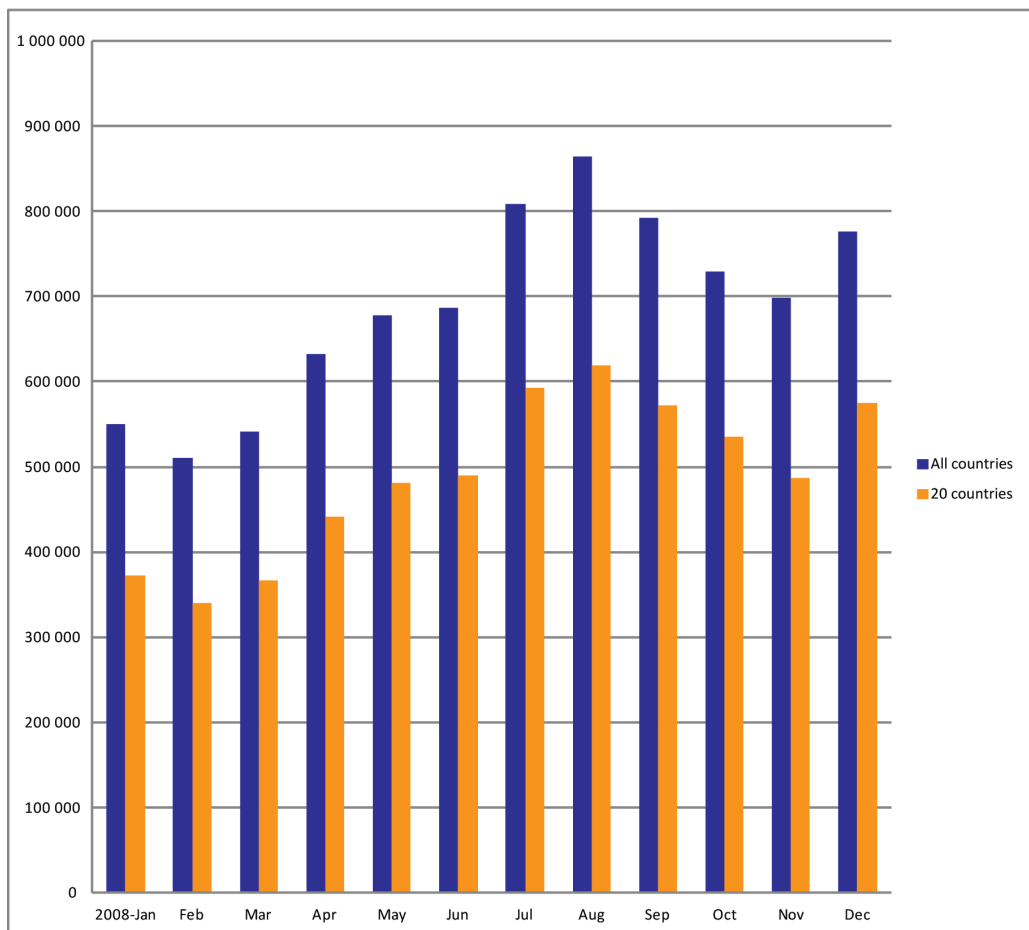


Figure 9.4: 2008 IATA data, international passenger arrivals into Saudi Arabia: all countries versus top 20 contributing international countries.

IATA data (used for months other than the Hajj month). To estimate the movement of international passengers travelling directly to the

MG site in Mecca from their country of residence and directly back to their country of residence from MG site throughout the year, we use the IATA database with country to city classification with a few assumptions. It is assumed that JED and MED will be the two airports considered in analyzing air traffic data since, as we mentioned before, they are the two leading points of entry for pilgrims. More specifically, JED has a terminal dedicated specifically for pilgrims performing the Hajj and is the closest airport to Mecca. Some pilgrims may travel to MED first, for example, to visit prophet Mohammed's burial site and then travel to Mecca. It is unclear whether pilgrims travelling to all other airports in Saudi Arabia would then use land travel to travel to Mecca to perform the Hajj, thus it is a reasonable assumption to exclude the remaining airports. It is also assumed that the number of international passengers travelling to Mecca is equivalent to the number of pilgrims with an itinerary of origin country r and destination city JED or MED. We further assume that origin country r on the itinerary is the resident country of pilgrims. Lastly, we assume that all trips, up to five connections, will be considered non-stop or direct flights. That is, whether a person makes five connections or none, it is assumed that their trip is direct.

9.5.2 Hajj visas

Movement rates in the Hajj month were computed using visa data provided in [64].

Approved visas data (used for the Hajj month). The most accurate data on the number of international pilgrims performing the Hajj for a given year is the number of approved visas per country. The database on the number of visas issued to international pilgrims is only provided for Hajj 2008 in [64]. With such a dataset, the country of residence of pilgrims is known and all modes of travel are accounted for. Since the 2008 Hajj took place in December, we classify the visas data as *December 2008 visa data*. The number of pilgrims that attended the 2008 Hajj measured by the number of issued visas for the 20 international countries of interest and the number of pilgrims resident of SAU in attendance are given in Table 9.4; domestic pilgrims are listed first, then non-domestic pilgrims follow.

9.5.3 Movement data

The movement data that we use in our application is summarized here. We use the IATA database to estimate the number of international pilgrims going to Mecca throughout the year (which can be thought of as baseline travel to the MG site on months other than the Hajj). The only month IATA data will not be used is in the month of the Hajj since an accurate visa data set is available for 2008. Specifically, for all months except December, IATA data provides the number of international pilgrims arriving into JED or MED which is assumed to be equivalent to the number of pilgrims travelling into Mecca. For December, approved visas data provides the number of international pilgrims attending the Hajj. We illustrate the movement data

No. =r	Countries	Country Code	No. Pilgrims N_{r1}
1	Mecca (MG patch)	MG	–
2	Saudi Arabia	SAU	800,000
3	Afghanistan	AFG	32,621
4	Algeria	DZA	44,484
5	Bangladesh	BGD	50,419
6	Egypt	EGY	94,015
7	India	IND	173,265
8	Indonesia	IDN	214,159
9	Iran	IRN	111,511
10	Iraq	IRQ	35,326
11	Jordan	JOR	22,373
12	Lebanon	LBN	19,945
13	Malaysia	MYS	36,877
14	Morocco	MAR	48,483
15	Nigeria	NGA	97,396
16	Oman	OMN	21,587
17	Pakistan	PAK	170,573
18	Russia	RUS	25,749
19	Sudan	SDN	38,562
20	Syria	SYR	30,556
21	Turkey	TUR	134,693
22	Yemen	YEM	28,018
	Total		2,230,612

Table 9.4: 2008 approved visas data, top 21 countries with the largest number of pilgrims that attended the 2008 Hajj [64]. Residence of Mecca in attendance is unknown.

used in our study for 6 countries in Figure 9.5 (the remaining countries are left out for reasons of space).

9.5.4 Movement rate derivation

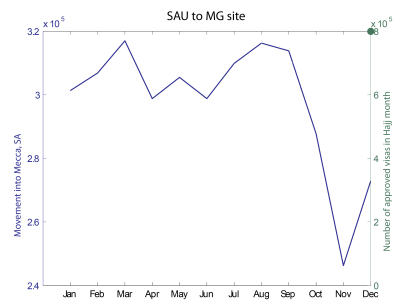
Recall that it is assumed that movement of pilgrims is direct (or non-stop) to and from the MG site. The movement rate $m_{r1r}^{\mathcal{X}}(t)$ represents the volume of international passengers resident of country r of epidemiological state \mathcal{X} travelling to the Hajj site from their country of residence r at time t . The movement rate $m_{rr1}^{\mathcal{X}}(t)$ represents the volume of international passengers resident of country r travelling back to their home country from the Hajj site at time t . It is assumed the the movement rates of the different epidemiological classes are equivalent except for the infectious class, i.e., $\forall t$, $m_{r1r}^S(t) = m_{r1r}^R(t) = m_{r1r}(t)$, $m_{r1r}^I(t) < m_{r1r}(t)$. We assume that the infectious movement rate is half the movement rate of the susceptible individuals, i.e., $m_{r1r}^I(t) = .5 \times m_{r1r}^S$.

Let $N(t)$ be the number of people in a given population at time t , $N(t_0+1)$ be the total population at time $t_0 + 1$ and $N(t_0)$ be the number of people at some initial time t_0 .

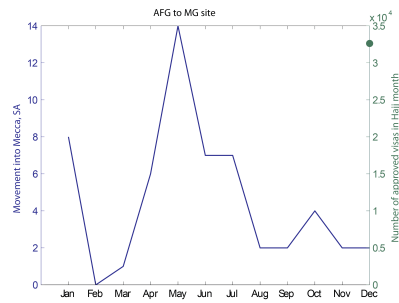
The movement rate for any t can be derived by considering the following system,

$$\frac{d}{dt}N(t) = -mN(t) \tag{9.1}$$

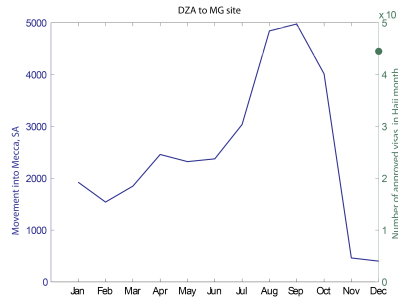
The solution to (9.1) with initial condition $N(t_0)$ is given by,



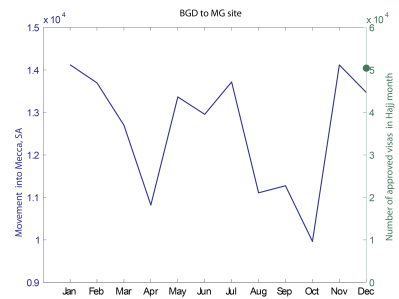
(a) SAU



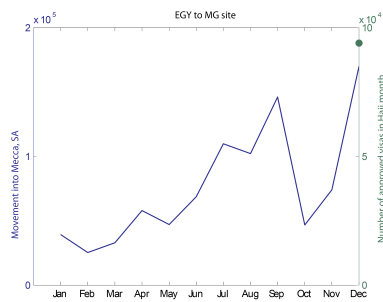
(b) AFG



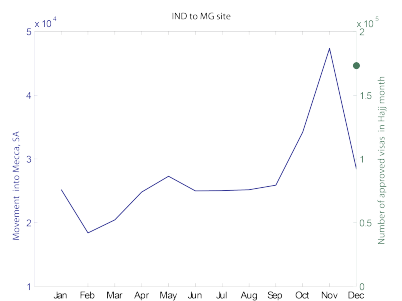
(c) DZA



(d) BGD



(e) EGY



(f) IND

Figure 9.5: Movement of international and domestic pilgrims into Mecca (JED + MED) for 2008. The right axis shows the number of approved Hajj visas for December 2008 for the country 9.5(a) Saudi Arabia, 9.5(b) Afghanistan, 9.5(c) Algeria, 9.5(d) Bangladesh, 9.5(e) Egypt and 9.5(f) India.

$$N(t) = e^{-m(t-t_0)}N(t_0)$$

The number of people that left due to travel, denoted by $N^{\text{travelled}}$, can be represented mathematically by $N(t_0 + 1) - N(t_0)$. This relation is used to derive the movement rate,

$$\begin{aligned} N(t_0 + 1) - N(t_0) &= e^{-m(t_0+1-t_0)}N(t_0) - N(t_0) \\ \frac{N(t_0 + 1)}{N(t_0)} &= e^{-m} \\ m &= -\ln\left(\frac{N(t_0 + 1)}{N(t_0)}\right) \\ m &= -\ln\left(\frac{N(t_0) - N^{\text{travelled}}}{N(t_0)}\right) \\ m &= -\ln\left(1 - \frac{N^{\text{travelled}}}{N(t_0)}\right) \end{aligned}$$

$N(t_0 + 1) - N(t_0) = N^{\text{travelled}}$ but the term $N^{\text{travelled}}$ is negative since we are looking at movement the population decreases after one unit time. Thus, $N(t_0 + 1) - N(t_0) = -N^{\text{travelled}}$.

Let $N_{rr}(t_0 + 1)$ be the total pilgrim population resident of country r at time $t_0 + 1$. Let $N_{rr}(t_0)$ be the total pilgrim population resident of country r at time t_0 . Let $N_{rr}^{\text{travelled}}(t)$ be the total pilgrim population resident of country r that travelled to the Hajj at time t . So, $N_{rr}(t_0 + 1) = N_{rr}(t_0) - N_{rr}^{\text{travelled}}(t)$. And so, the movement rates (per month) for the pilgrims travelling to the Hajj are given by,

$$m_{r1r} = -\ln \left(1 - \frac{N_{rr}^{\text{travelled}}(t)}{N_{rr}(0)} \right).$$

9.6 Measles cases per WHO region

WHO provides a graph of the number of measles cases per country on a monthly basis. It would be optimal for us to have access to the actual data tables of the number of new measles cases per country per month. Since we did not have access to the tables, an approximation was made possible by the Bio.Diaspora team by computationally extracting the monthly measles data from the WHO graph [50]. The approximation produced the incidence of measles curves shown in Figure 3.2 in Section 3.3. The data on measles incidence per WHO region in Figure 3.2 is the measles data used in our application for the Hajj. We assume that countries in the same WHO region experience the same measles incidence curve.

9.7 Movement and measles cases

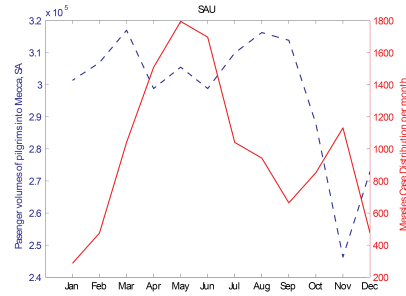
If the number of measles cases in a country peaks around the same time that large influxes of pilgrims travel to the Hajj from that country, there is a considerable possibility the measles can be imported into Mecca and an outbreak can occur. Figure 9.6 illustrates the relationship between the seasonality of measles and international air traffic into Mecca for domestic pilgrims (SAU) and foreign pilgrims from 5 countries each in different WHO

regions. We remark that the remaining countries are not shown here for reasons of space.

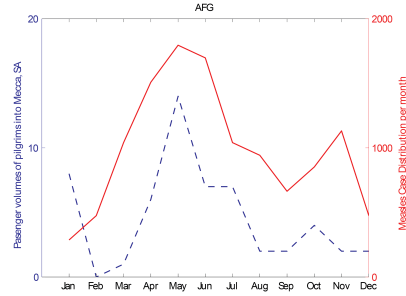
Notice that in the figures, we used IATA data for December, this was more for illustrative purposes so that the relative size of movement and measles cases could be compared (visas data would blow up the movement result and we would not see what happens for the rest of the year because of the high value point in December).

For SAU, from April to June 2008, the number of measles cases ranges from approximately 1,500 to 1,800 and the number of domestic pilgrims from SAU travelling to Mecca exceeds 290,000 passengers. In these months there is a potential risk of measles importation as measles cases and domestic travel to Mecca are both high during the same time period. As we approach the Hajj month the potential risk of importation is reduced substantially. Notice that in November measles cases peaks to over 1000 but the number of domestic pilgrims from SAU travelling to Mecca drops to its lowest point throughout the year. In December, the number of measles cases is approximately 500 but movement picks up to 800,000 pilgrims (remember we take the approved visas and not IATA data) so the risk of importation from SAU is not high during 2008 Hajj. The remaining figures can be analyzed the similarly.

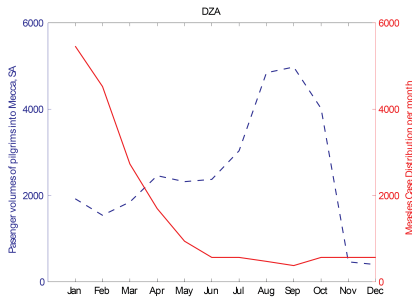
In the following section we present all other parameter data used in the application; derivation and computation of the birth rates, death rates, recovery rates, transmission rates and the size of the infectious populations are detailed. In passing, our study is performed on a monthly basis. The monthly time period was chosen because we did not have access to daily travel data or



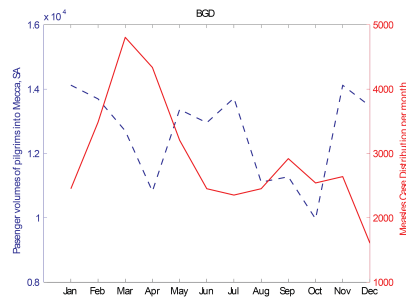
(a) SAU: EMR



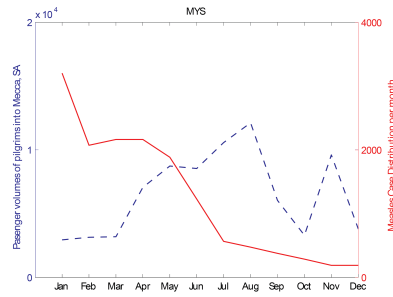
(b) AFG: EMR



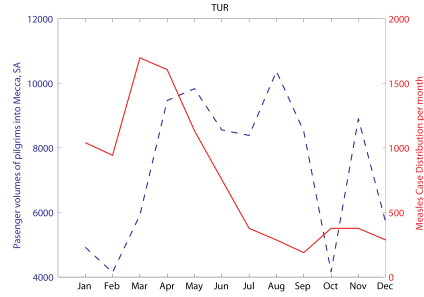
(c) DZA: AFR



(d) BGD: SEAR



(e) MYS: WPR



(f) TUR: EUR

Figure 9.6: Seasonality of measles activity (solid line) and international air traffic (dashed line) into Mecca from the country 9.6(a) Saudi Arabia, 9.6(b) Afghanistan, 9.6(c) Algeria, 9.6(d) Bangladesh, 9.6(e) Malaysia and 9.6(f) Turkey.

daily biological parameter data which would have been optimal considering the Hajj is a five day event.

9.8 Parameter data

The crude birth, crude death and total population per country was provided by the World Bank [23].

All countries experience additional death due to infection. The number of individuals who died due to measles is estimated using WHO data in [78] which is provided per WHO region for 2008. It is estimated since it remains unclear as to the number of individuals whose death was induced by secondary illnesses or solely by the measles virus. Measles deaths can be attributed to weakened immune systems due to other disease like HIV or tuberculosis so they can be an inaccurate measure of death due to the measles virus. Nevertheless, we use the data in [78] as a rough initial estimate. And so, the number of measles death per country is approximated by dividing the total number of measles deaths per WHO region by the number of countries in that WHO region.

Since the number of individuals that recover per country is unknown the recovery rate was approximated using the average time spent in the infectious class; for measles we assumed that the average was 11 days which we deduced from WHO data [116]. Due to the heterogeneity of the countries it is further assumed that the income status of a country is an indicator of the individuals recovery time. More specifically we assume that high

income countries recover much faster than low income countries. We assume a average recovery time of one week for high income countries, average of two weeks for low income countries and average of 11 days for middle income countries.

The birth, death and recovery rates discussed so far are the ones used for the resident populations at home. The actual number of infectious individuals per month was approximated using monthly measles incidence data which we presented in Section 9.6. In Section 9.6 we mentioned that the data was provided per WHO region. So measles incidence *per country* was approximated by dividing the measles incidence data given per WHO region by the number of countries in that region, in turn, this gives an approximation to the infectious populations per country. The susceptible and recovered individuals (given in Table 9.2) and the infectious populations provides the initial ‘at home’ population data. Also, the number of infectious individuals is used in the computation of the transmission rate (explained in detail in Section 9.12.1).

For away populations, there is no birth. We assume that the death and recovery rates for the away populations is equivalent to the death and recovery rates of their corresponding home populations. The susceptible, infectious and recovered individuals for the initial ‘away’ populations are assumed to be zero.

9.9 Parameter derivation

In this section we derive the birth, death and recovery rates.

Birth rate b . Let $N(t)$ be the number of people in a given population at time t , $N(0)$ be the number of people at time $t = 0$ and $N(1)$ be the number of people after 1 time unit. The evolution of the population can be described by the following ordinary differential equation,

$$N' = \Lambda \tag{9.2}$$

The solution of (9.2), using integration, with initial condition $N(0)$ is given by,

$$N(t) = \Lambda t + N(0)$$

The number of births in the population per unit time can be represented mathematically by $N(1) - N(0)$. This relation is used to derive the birth rate,

$$N(1) - N(0) = \Lambda + N(0) - N(0) = \Lambda$$

Notice, that $N(1) - N(0)$ is a positive quantity because when we are looking at births the population increases over one unit time. The crude birth rate of country r at home is given per 1000 people per year, it is denoted by CBR_{rr} . Let $N_{rr}(0)$ denote the total population of country r at

home at time $t = 0$. Thus,

$$\Lambda = \left(\frac{CBR_{rr}}{12} \right) \times \left(\frac{N_{rr}(0)}{1000} \right)$$

Division by 12 is for an approximation of monthly birth rates.

Death rate d . Let $N(t)$ be the number of people in a given population at time t , $N(0)$ be the number of people at time $t = 0$ and $N(1)$ be the number of people after 1 time unit. The evolution of the population can be described by the following ordinary differential equation,

$$N'(t) = -dN(t) \tag{9.3}$$

The solution of Equation 9.3, using separation of variables, with initial condition $N(0)$ is given by,

$$N(t) = e^{-dt}N(0)$$

The number of deaths in the population per unit time, denoted by D^* , can be represented mathematically by $N(1) - N(0)$. This relation is used to derive the death rate,

$$N(1) - N(0) = e^{-d}N(0) - N(0) = (e^{-d} - 1)N(0) \Leftrightarrow -\ln \left(\frac{N(1) - N(0)}{N(0)} + 1 \right) = d$$

Notice, that $N(1) - N(0)$ is a negative quantity since we are looking at

deaths the population decreases after one unit time.

So,

$$d = -\ln\left(\frac{-D^*}{N(0)} + 1\right)$$

where,

$$D^* = \left(\frac{CDR_{rr}}{12}\right) \times \left(\frac{N_{rr}(0)}{1000}\right)$$

and the crude death rate, given per 1000 people, of country r at home per year is denoted by CDR_{rr} . Division of 12 is for an approximation of monthly death rates.

The addition death due to infection rate, δ , is derived the exact same way as the derivation of the death rate. Except, we would instead use the number of individuals who died due to measles per country. Like we mentioned in Section 9.8 we approximate the number of measles deaths per country by using estimated WHO data provided per WHO region. Therefore,

$$\delta = -\ln\left(\frac{-A^*}{N(0)} + 1\right)$$

where,

$$A^* \approx \left(\frac{\# \text{ measles deaths in WHO region} / \# \text{ countries in WHO region}}{12}\right).$$

The recovery rate, α , is also derived the exact same way except N is replaced with I . I would then denote the number of infectious individuals, $I(1)$ the number of infectious individuals after one unit of time and $I(0)$ is

the number of infectious individuals at $t = 0$. The number of individuals that recovered per month is denoted by R^* . As we mentioned in Section 9.8, R^* is unknown so the average time spent in the infectious classes per country is used for the computation of the recovery rate.

9.10 Transmission coefficient function

In our application we use a time dependent transmission coefficient function, $\beta(t)$. Looking back to the shape of the incidence of measles curves given in Section 3.3 one can see that the sine curve is a good approximation to the curves. Therefore, it is a reasonable assumption to use a sinusoidal continuous function to describe the shape of the transmission coefficient function.

In order to find a suitable transmission coefficient function, we use the deterministic metapopulation model with residency for mass gatherings and performed an optimization routine solely for the ‘at home’ populations without considering movement. The transmission coefficient function is estimated using a method known as *parameter identification* which is a method of *data fitting*. Parameter identification produces locally optimal parameter values of \hat{m}_r , \hat{a}_r , \hat{p}_r and $\hat{d}_r \forall r$ that minimizes the error between the computed number of measles cases provided by the numerical ODE solver and the actual number of new measles cases provided by the data. In turn, these optimal parameter values produce sine curves that best fits the measles curves in Section 3.3. The resulting sine curve is the transmission coefficient function.

The transmission coefficient function between susceptibles and infectives

resident of country r at home for $r \in \{1, 2, \dots, 22\}$ is denoted by $\beta_{rrr}(t)$ and is given by,

$$\beta_{rrr}(t) = \hat{m}_r + \hat{a}_r \left(1 + \sin(\hat{p}_r + \frac{2\pi}{\hat{d}_r}t) \right)$$

where \hat{m}_r is the minimum, \hat{a}_r is the amplitude, \hat{p}_r is the time peak and \hat{d}_r is the period. These parameters produce an optimal coefficient transmission function for all countries r at home. It is further assumed that the transmission coefficient function for the away populations is the same as their corresponding home transmission coefficient function.

Since each country is classified into its respective WHO region, and each WHO region experiences a different measles curve, the countries that are classified in the same WHO region share the same transmission coefficient function.

We summarize the parameter values used in the numerical analysis of the 2008 Hajj and measles in Table 9.5 and Table 9.6 for $r \in \{2, \dots, 22\}$.

9.11 The Model

9.11.1 ODE

The metapopulation MG model applied to measles and the 2008 Hajj will aid in understanding the relationship between the seasonality of measles, measles transmission and the movement of international pilgrims to and from the

Biological Meaning	Parameter	Formula
Birth rate of host population in the MG site	Λ_{11}	$\left(\frac{CBR_{11}}{12}\right) \times \left(\frac{N_{11}(0)}{1000}\right)$
Birth rate of international pilgrims at home	Λ_{rr}	$\left(\frac{CBR_{rr}}{12}\right) \times \left(\frac{N_{rr}(0)}{1000}\right)$
Death rate of host population in the MG site	d_{11}	$-\ln\left(-\frac{D^*}{N_{11}(0)} + 1\right)$
Death rate of international pilgrims at home	d_{rr}	$-\ln\left(-\frac{D^*}{N_{rr}(0)} + 1\right)$
Death rate of international pilgrims in MG	d_{r1}	d_{rr}
Additional death rate due to measles of host population in the MG site	δ_{11}	$-\ln\left(-\frac{A^*}{N_{11}(0)} + 1\right)$
Additional death rate due to measles of international pilgrims at home	δ_{rr}	$-\ln\left(-\frac{A^*}{N_{rr}(0)} + 1\right)$
Additional death rate due to measles of international pilgrims in MG	δ_{r1}	δ_{rr}
Recovery rate of host population in MG	α_{11}	$-\ln\left(-\frac{R^*}{N_{11}(0)} + 1\right)$ $\approx \frac{1}{\text{average time in I (in months)}}$
Recovery rate of international pilgrims at home	α_{rr}	$-\ln\left(-\frac{R^*}{N_{rr}(0)} + 1\right)$ $\approx \frac{1}{\text{average time in I (in months)}}$
Recovery rate of international pilgrims in MG	α_{r1}	α_{rr}

Table 9.5: Formulas used for birth rates, death rates, additional death rates due to measles and recovery rates.

Biological Meaning	Parameter	Formula
Movement rate of international pilgrims travelling to MG	$m_{r1r}(t)$	$-\ln\left(1 - \frac{N_{rr}^{\text{travelled}}(t)}{N_{rr}(0)}\right)$
Movement rate of pilgrims travelling back home from MG	$m_{rr1}(t)$	$m_{r1r}(t)$
Movement rate of infectious international pilgrims travelling to MG	$m_{r1r}^I(t)$	$.5 \times m_{r1r}(t)$
Movement rate of infectious pilgrims travelling back home from MG	$m_{rr1}^I(t)$	$.5 \times m_{rr1}(t)$
Transmission rate for international pilgrims at home	$\beta_{rrr}(t)$	$\hat{m}_r + \hat{a}_r \left(1 + \sin(\hat{p}_r + \frac{2\pi}{d_r}t)\right)$
Transmission rate for host population in MG	$\beta_{111}(t)$	$\hat{m}_1 + \hat{a}_1 \left(1 + \sin(\hat{p}_1 + \frac{2\pi}{d_1}t)\right)$
Transmission rate for host population interacting with all other pilgrims in MG	$\beta_{11k}(t)$	$\beta_{111}(t)$ as above. Vector form: $\begin{bmatrix} \beta_{112}(t) & \beta_{113}(t) & \cdots & \beta_{1,1,22}(t) \\ \beta_{222}(t) & \beta_{333}(t) & \cdots & \beta_{22,22,22}(t) \end{bmatrix} =$
Transmission rate for international pilgrims interacting with all other pilgrims in MG	$\beta_{1rk}(t)$	$\beta_{111}(t)$ as above. Vector form: $\begin{bmatrix} \beta_{1r2}(t) & \beta_{1r3}(t) & \cdots & \beta_{1,r,22}(t) \\ \beta_{222}(t) & \beta_{333}(t) & \cdots & \beta_{22,22,22}(t) \end{bmatrix} =$

Table 9.6: Formulas used for movement rates and transmission rates.

Hajj.

For the Hajj application, we use the *SLIR* metapopulation residency model for mass gatherings presented in Chapter 7 with $N = 22$ and the removal of the *L* class. Justification of the refinement of the *SLIR* model to an *SIR* measles model was explained in the introduction of Part III.

The populations considered are $S_{11}, S_{r1}, S_{rr}, I_{11}, I_{r1}, I_{rr}, R_{11}, R_{r1}$ and R_{rr} for $r \in \{2, \dots, 22\}$. Thus, we reduce the most general model of $3N^2 = 1452$ populations to $3(2 \times 22 - 1) = 129$ populations. The metapopulation model with residency for the Hajj with $N = 22$ patches is as follows

For the mass gathering site $r = j = 1$,

$$\frac{d}{dt}S_{11}(t) = \Lambda_{11} - d_{11}S_{11} - \sum_{k=1}^{22} \beta_{11k}(t) \frac{S_{11}I_{k1}}{N_1^{in}} \quad (9.4a)$$

$$\frac{d}{dt}I_{11}(t) = \sum_{k=1}^{22} \beta_{11k}(t) \frac{S_{11}I_{k1}}{N_1^{in}} - (d_{11} + \alpha_{11} + \delta_{11})I_{11} \quad (9.4b)$$

$$\frac{d}{dt}R_{11}(t) = -d_{11}R_{11} + \alpha_{11}I_{11} \quad (9.4c)$$

For all visiting populations in the MG site, that is, for $r = \{2, \dots, 22\}$ and $j = 1$,

$$\frac{d}{dt}S_{r1}(t) = -d_{r1}S_{r1} - \sum_{k=1}^{22} \beta_{1rk}(t) \frac{S_{r1}I_{k1}}{N_1^{in}} + m_{r1r}(t)S_{rr} - m_{rr1}(t)S_{r1} \quad (9.4d)$$

$$\frac{d}{dt}I_{r1}(t) = \sum_{k=1}^{22} \beta_{1rk}(t) \frac{S_{r1}I_{k1}}{N_1^{in}} - (d_{r1} + \alpha_{r1} + \delta_{r1})I_{r1} + m_{r1r}^I(t)I_{rr} - m_{rr1}^I(t)I_{r1} \quad (9.4e)$$

$$\frac{d}{dt}R_{r1}(t) = -d_{r1}R_{r1} + \alpha_{r1}I_{r1} + m_{r1r}(t)R_{rr} - m_{rr1}(t)R_{r1} \quad (9.4f)$$

For all populations in their country of residence, that is, for $r = \{2, \dots, 22\}$,

$$\frac{d}{dt}S_{rr}(t) = \Lambda_{rr} - d_{rr}S_{rr} - \beta_{rrr}(t) \frac{S_{rr}I_{rr}}{N_r^{in}} + m_{rr1}(t)S_{r1} - m_{r1r}(t)S_{rr} \quad (9.4g)$$

$$\frac{d}{dt}I_{rr}(t) = \beta_{rrr}(t) \frac{S_{rr}I_{rr}}{N_r^{in}} - (d_{rr} + \alpha_{rr} + \delta_{rr})I_{rr} + m_{rr1}^I(t)I_{r1} - m_{r1r}^I(t)I_{rr} \quad (9.4h)$$

$$\frac{d}{dt}R_{rr}(t) = -d_{rr}R_{rr} + \alpha_{rr}I_{rr} + m_{rr1}(t)R_{r1} - m_{r1r}(t)R_{rr} \quad (9.4i)$$

The *SIR* model is a particular case/extension of the *SLIR* metapopulation model with residency studied in Chapter 6 of Part II in the manuscript. We added time dependency to both migration and the transmission function. Due to the time dependency terms in the *SIR* model, analytical results previously obtained do not hold. The model is used only for numerical analysis.

9.11.2 Stochastic model

The use of *SIR* instead of *SLIR* reduces the number of events from $23N - 15$ in Section 7.3 to $17N - 11$. The present state at time t is denoted by $X(t) = (S_{11}, S_{r1}, S_{rr}, I_{11}, I_{r1}, I_{rr}, R_{11}, R_{r1}, R_{rr})$ for $r \in \{2, \dots, 22\}$. The present state then jumps to a new state at time $t + \tau$ which is denoted by $X(t + \tau) = (S'_{11}, S'_{r1}, S'_{rr}, I'_{11}, I'_{r1}, I'_{rr}, R'_{11}, R'_{r1}, R'_{rr})$.

Possible events	Number of events
Birth	N
Death	$3(2N - 1)$
Transmission of infection	$2N - 1$
Out of L class	$2N - 1$
Recovery	$2N - 1$
Movement	$6(N - 1)$
Total	$17N - 11$

Table 9.7: Number of events of System (9.4). In our application with $N = 22$, there are 363 events.

The probability of events of the CTMC for the 22-patch SIR metapopulation model with residency for the Hajj and measles are given below $\forall r \in \{2, \dots, N\}$,

$$\begin{aligned}
P\left(X(t + \tau) = (S'_{11}, S'_{r1}, S'_{rr}, I'_{11}, I'_{r1}, I'_{rr}, R'_{11}, R'_{r1}, R'_{rr}) \mid \right. \\
\left. X(t) = (S_{11}, S_{r1}, S_{rr}, I_{11}, I_{r1}, I_{rr}, R_{11}, R_{r1}, R_{rr})\right) = \\
\frac{1}{f t} \left\{ \begin{array}{ll}
\Lambda_{11} & \text{if } X' = (S_{11} + 1, \dots) \\
\Lambda_{rr} & \text{if } X' = (\dots, S_{rr} + 1, \dots) \\
d_{11} S_{11} & \text{if } X' = (\dots, S_{11} - 1, \dots) \\
d_{r1} S_{r1} & \text{if } X' = (\dots, S_{r1} - 1, \dots) \\
d_{rr} S_{rr} & \text{if } X' = (\dots, S_{rr} - 1, \dots) \\
d_{11} I_{11} & \text{if } X' = (\dots, I_{11} - 1, \dots) \\
(d_{r1} + \delta_{r1}) I_{r1} & \text{if } X' = (\dots, I_{r1} - 1, \dots) \\
(d_{rr} + \delta_{rr}) I_{rr} & \text{if } X' = (\dots, I_{rr} - 1, \dots) \\
d_{11} R_{11} & \text{if } X' = (\dots, R_{11} - 1, \dots) \\
d_{r1} R_{r1} & \text{if } X' = (\dots, R_{r1} - 1, \dots) \\
d_{rr} R_{rr} & \text{if } X' = (\dots, R_{rr} - 1, \dots) \\
\sum_{k=1}^{22} \frac{\beta_{11k} S_{11} I_{k1}}{N_1^{in}} & \text{if } X' = (\dots, S_{11} - 1, I_{11} + 1, \dots) \\
\sum_{k=1}^{22} \frac{\beta_{1rk} S_{r1} I_{k1}}{N_1^{in}} & \text{if } X' = (\dots, S_{r1} - 1, I_{r1} + 1, \dots) \\
\beta_{rrr} \frac{S_{rr} I_{rr}}{N_r^{in}} & \text{if } X' = (\dots, S_{rr} - 1, I_{rr} + 1, \dots) \\
\alpha_{11} I_{11} & \text{if } X' = (\dots, I_{11} - 1, R_{11} + 1, \dots) \\
\alpha_{r1} I_{r1} & \text{if } X' = (\dots, I_{r1} - 1, R_{r1} + 1, \dots) \\
\alpha_{rr} I_{rr} & \text{if } X' = (\dots, I_{rr} - 1, R_{rr} + 1, \dots) \\
m_{r1r} S_{rr} & \text{if } X' = (\dots, S_{rr} - 1, S_{r1} + 1, \dots) \\
m_{r1r}^I I_{rr} & \text{if } X' = (\dots, I_{rr} - 1, I_{r1} + 1, \dots) \\
m_{r1r} R_{rr} & \text{if } X' = (\dots, R_{rr} - 1, R_{r1} + 1, \dots) \\
m_{rr1} S_{r1} & \text{if } X' = (\dots, S_{rr} + 1, S_{r1} - 1, \dots) \\
m_{rr1}^I I_{r1} & \text{if } X' = (\dots, I_{rr} + 1, I_{r1} - 1, \dots) \\
m_{rr1} R_{r1} & \text{if } X' = (\dots, R_{rr} + 1, R_{r1} - 1, \dots)
\end{array} \right. \quad (9.5)
\end{aligned}$$

Using *Gillespie's Algorithm* in Section 1.2.2 with

- 129 discrete random (state) variables.
- $N^2 + 17N - 11 = 847$ parameters.
- Weights of 363 events,

we can run numerical simulations of the *CTMC* to study the stochasticity of 22-patch *SIR* metapopulation model with residency applied to the Hajj and measles.

9.12 Some numerical solutions

9.12.1 Transmission coefficient function $\beta_{rrr}(t)$

For 2008, the $\beta_{rrr}(t) \forall r \in \{1, 2, \dots, 22\}$ function will be approximated by minimizing the error between the computed infectious populations of country r at home provided by the ODE45 solver in Matlab and the actual number of infectious individuals of country r at home provided by the measles incidence data mentioned in Section 9.8.

When we performed parameter identification for the transmission coefficient function we kept the total population size constant and neglected movement. We did this to focus on the transmission of infection between the populations and not get results distorted by events like birth or death. In order to maintain a constant population we redefined the birth function in the following way,

$$\Lambda_{rr} = d_{rr} \odot N_{rr}(0) + \delta_{rr} I_{rr}(0)$$

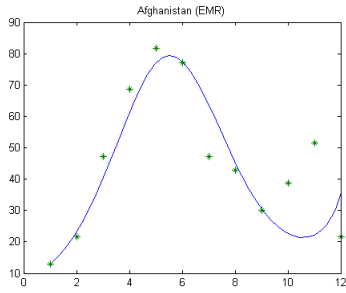
I stress here that a constant population size and termination of movement was *only* implemented in the parameter identification of the transmission coefficient functions. We illustrate the minimal error solution that resulted in the proper transmission function for five countries each from different WHO regions as results are similar for countries classified under the same WHO region, see Figure 9.7.

9.12.2 Deterministic

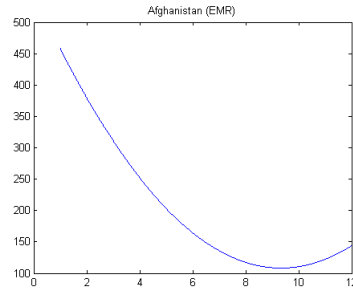
We perform numerical simulations using the ODE45 solver in Matlab from January 2008 to December 2008; we use Hajj movement in December, regular IATA movement for all other months, time dependent transmission coefficient functions and parameter data already detailed and presented.

The *total number of infection months* is approximated using the TRAPZ numerical integration method in Matlab which computes an approximation of the integral of the infectious populations using the trapezoidal method. Figure 9.8 and Figure 9.9 illustrate the total number of infection months for the 5 countries mentioned in Section 9.12.1.

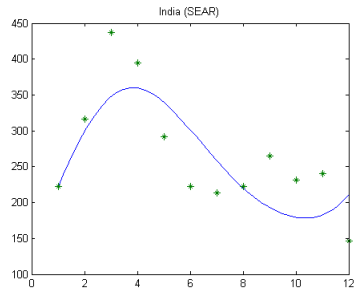
Numerically, from Figure 9.8 we see that the total number of infection months of the five countries in the MG site ranges between 40 to over 2000 infection months; the away population could be infectious home populations that travelled or susceptible away populations that acquired measles during



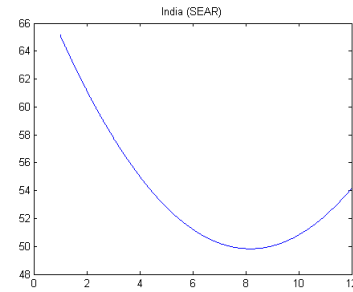
(a) AFG



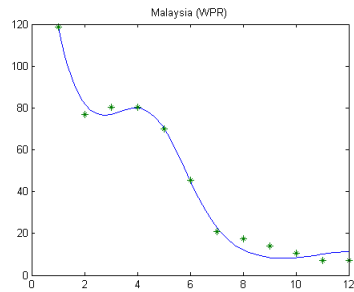
(b) $AFG-\beta_{AFG,AFG}(t)$



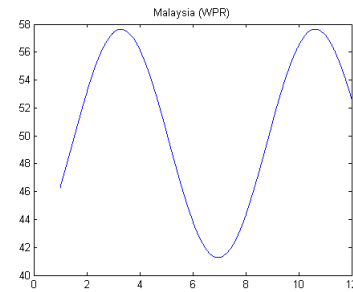
(c) IND



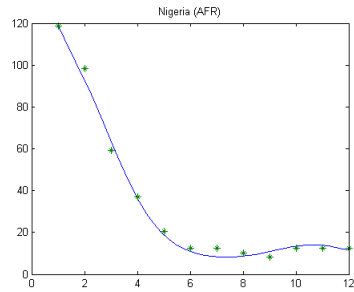
(d) $IND-\beta_{IND,IND}(t)$



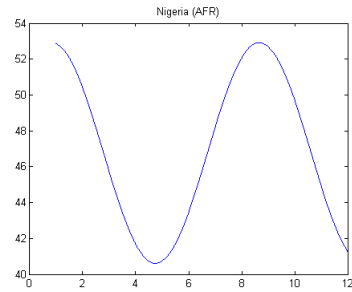
(e) MYS



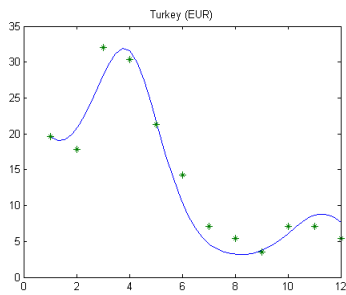
(f) $MYS-\beta_{MYS,MYS}(t)$



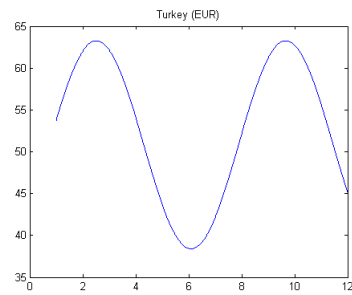
(g) NGA



(h) $NGA-\beta_{NGA,NGA}(t)$



(i) TUR



(j) $TUR-\beta_{TUR,TUR}(t)$

Figure 9.7: The figures to the left illustrate the numerical results of the optimization routine that minimizes the error between actual measles cases per month as reported by WHO (green asterisks) [50] with computed measles cases from numerical solver (blue curve). The figures to the right illustrate the transmission coefficient function for 9.7(b) Afghanistan, 9.7(d) India, 9.7(f) Malaysia, 9.7(h) Nigeria and 9.7(j) Turkey.

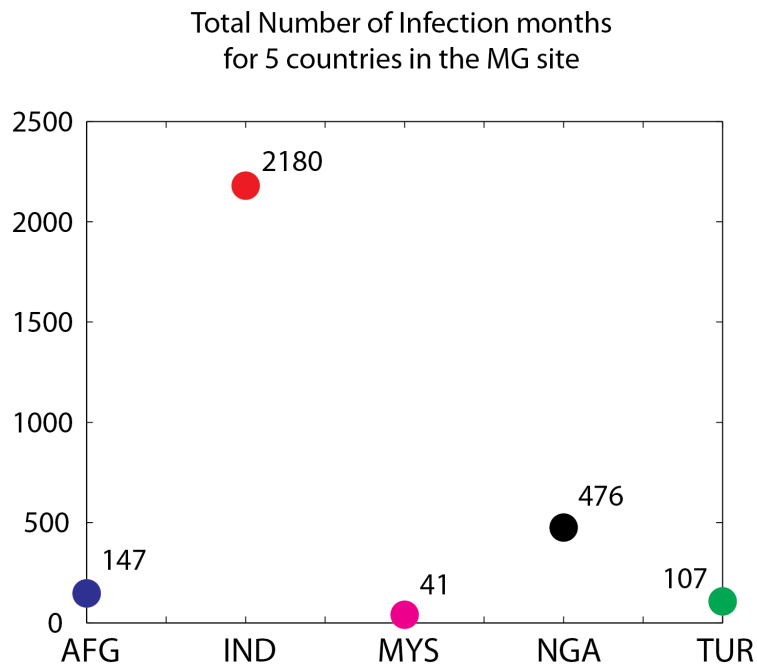


Figure 9.8: The total number of infection months for the away infectious populations ($I_{AFG,MG}$, $I_{IND,MG}$, $I_{MYS,MG}$, $I_{NGA,MG}$, $I_{TUR,MG}$). We list the ‘away’ countries from most vulnerable to least vulnerable to measles: IND, NGA, AFG, TUR then MYS.

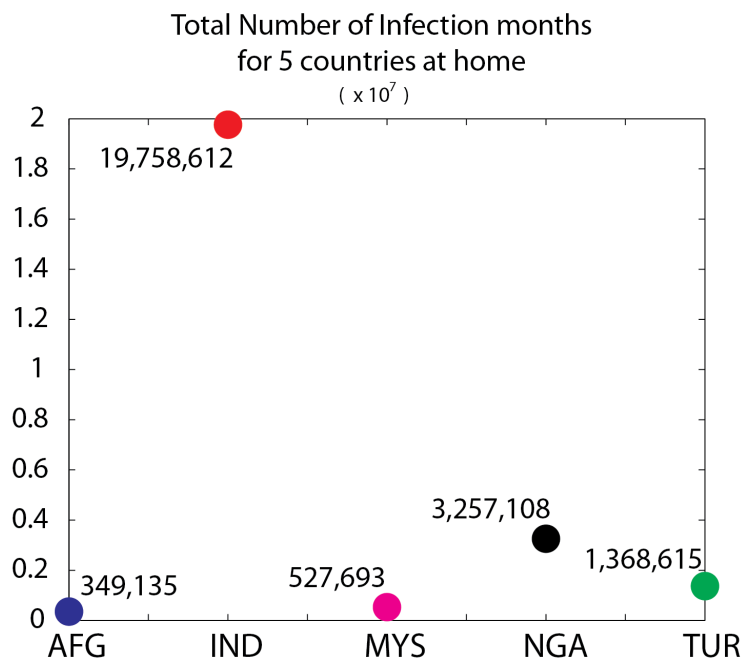


Figure 9.9: The total number of infection months for the home populations ($I_{AFG,AFG}$, $I_{IND,IND}$, $I_{MYS,MYS}$, $I_{NGA,NG}$, $I_{TUR,TUR}$). We list the ‘home’ countries from most vulnerable to least vulnerable to measles: IND, NGA, TUR, MYS then AFG.

the Hajj (recall infectious away populations were initially set to zero).

From Figure 9.9 we see very large numbers of infection months for the infectious populations at home; the home populations may have experienced measles outbreaks before the Hajj and exported the cases to Mecca or they may have received imported cases of measles upon the return of their away populations.

The large number of infection months can be attributed to the large transmission coefficient functions obtained from parameter identification (see Figure 9.7). At this point, we can not conclude whether regular travel, travel to Hajj or the transmission coefficient function are the parameters contributing to the large number of infection months. Some indicators will have to be derived in order to better understand the effect of the Hajj on the spread of measles. In the future we would like to map the total number of infection months as a function of the start date of the Hajj. More numerical work needs to be done on the sensitivity of the parameters. For example, for each country, finding which parameters (e.g. movement or transmission) are contributing the most to disease outbreak.

9.12.3 Stochastic process

When we ran stochastic simulations, using Gillespie's algorithm in Section 9.11.2, we found that the between-event times were extremely small. This resulted from the large event weights of our stochastic model. To detail, after running the stochastic simulations for two days the time between the events

increased from 10^{-15} to only 10^{-14} . And so, results on the stochasticity of the metapopulation model with residency for the Hajj and measles were inconclusive. In an effort to speed up the simulations we began to formulate a *mixed* model where we used the deterministic S and R and a stochastic I ; the mixed model will be studied in the future.

Conclusion and perspectives

In this manuscript, we have studied both single and multiple population models of measles. The models considered were of *SLIR* and *SIR* type. Both deterministic and stochastic versions of the models were studied. Mathematical analysis and numerical simulations were performed. In Chapter 9 our study incorporated real-time world data that was provided to us by the World Health Organization, World Bank and the Bio.Diaspora Team in Toronto. The movement, transmission, recovery, birth and death rates were derived using the following 2008 data sets per country: International air transport association airline ticket sales, approved visas, measles incidence, average time spent infectious, birth, death, number of deaths due to measles and total population. The number of susceptible and recovered individuals per country was obtained by data on the prevalence of immunity to measles based on a countries income status. The number of infectious individuals was approximated using measles incidence. Chapter 9 was an introduction to my ongoing study of the spatial dispersion of measles in the context of the Hajj, the yearly pilgrimage to Mecca.

Further work will involve:

1. Measure of indicators. Some indicators will have to be derived in order to better understand the numerical simulations for the deterministic system. Indeed, at present it is difficult to evaluate the results. For example, the total number of infection months as a function of the start date of the Hajj will be mapped.
2. Finding better methods to speed up simulations. When simulating the continuous time Markov chain for the Hajj application, we run into the problem of very small inter-event times because of the large total weight of events. We have started investigating the use of a mixed model where we use the deterministic solutions for S and R and a stochastic model for I. Further work will consider such methods as tau-leaping which takes time steps that leap over many events.
3. Sensitivity analysis on the parameters. Future work will include numerically testing parameters to study which ones are altering disease dynamics.
4. Model formulation. The model for measles describes the main features of measles. However, it fails to describe temporary immunity at birth as well as the precise effect of vaccination since it lumps together individuals who acquired disease induced immunity and vaccinated individuals. Further work will considerate more elaborate models of measles.
5. Biology of the disease. A better understanding of latency and infectious periods can improve the model to be even more realistic.

6. Data. Monthly or daily measles data per country (for example, incidence of measles and number of deaths due to measles, to name a few), approved visas data for years other than 2008.
7. The mass gathering model was originally formulated for seasonal and pandemic influenza which included asymptomatic infections. The analysis of this particular metapopulation model was conducted but is not included for reasons of space and because parametrization was difficult. We will return to this type of model in the future.

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