Mathematical Analysis of an $SEIRS$ Model with Multiple Latent and Infectious Stages in Periodic and Non-Periodic Environments

by

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Abstract

The thesis focuses on the qualitative analysis of a general class of $SEIRS$ models in periodic and non-periodic environments. The classical $SEIRS$ model, with standard incidence function, is, first of all, extended to incorporate multiple infectious stages. Using Lyapunov function theory and LaSalle's Invariance Principle, the disease-free equilibrium (DFE) of the resulting SEI^nRS model is shown to be globally-asymptotically stable whenever the associated reproduction number is less than unity. Furthermore, this model has a unique endemic equilibrium point (EEP), which is shown (using a non-linear Lyapunov function of Goh-Volterra type) to be globally-asymptotically stable for a special case. The SEI^nRS model is further extended to incorporate arbitrary number of latent stages. A notable feature of the resulting SE^mI^nRS model is that it uses gamma distribution assumptions for the average waiting times in the latent (m) and infectious (n) stages. Like in the case of the SEI^nRS model, the SE^mI^nRS model also has a globally-asymptotically stable DFE when its associated reproduction threshold is less than unity, and it has a unique EEP (which is globally-stable for a special case) when the threshold exceeds unity. The SE^mI^nRS model is further extended to incorporate the effect of periodicity on the disease transmission dynamics. The resulting non-autonomous SE^mI^nRS model is shown to have a globally-stable disease-free solution when the associated reproduction ratio is less than unity. Furthermore, the non-autonomous model has at least one positive (non-trivial) periodic solution when the reproduction ratio exceeds unity. It is shown (using persistence theory) that, for the non-autonomous model, the disease will always persist in the population whenever the reproduction ratio is greater than unity. One of the main mathematical contributions of this thesis is that it shows that adding multiple latent and infectious stages, gamma distribution assumptions (for the average waiting times in these stages) and periodicity to the classical $SEIRS$ model (with standard incidence) does not alter the main qualitative dynamics (pertaining to the persistence or elimination of the disease from the population) of the $SEIRS$ model.

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Dedication

This work is dedicated to my late father, Yizengaw Melesse.

May his soul rest in Peace.

Glossary

Abbreviation	Meaning
DFE	Disease-free equilibrium
EEP	Endemic equilibrium point
GAS	Globally-asymptotically stable
ILI	Influenza-like illness
IVP	Initial-value Problem
LAS	Locally-asymptotically stable
ODE	Ordinary differential equation

Table of Contents

List of Tables

List of Figures

Chapter 1

Introduction

1.1 Burden of Infectious Diseases

Since the beginning of recorded human history, infectious diseases have been inflicting severe public health and socio-economic burden around the globe. For instance, while the bubonic plague resulted in the death of about one-third of the population of Europe between 1346 to 1350 [14], smallpox killed over 300 million people in the 19th century alone (a smallpox epidemic in Quebec City in 1702-1703 killed nearly a quarter of the inhabitants [42]; furthermore, in the late 18^{th} century, about 400,000 people died annually of smallpox in Europe [11], and one-third of the survivors became blind [11, 47, 48]). The influenza pandemic of 1918 (also known as Spanish flu) affected about 500 million people (one-third of the world's population at that time) and caused between 20 to 100 million fatalities [17].

In recent decades, in addition to the devastating impact of the human immunodeficiency virus (HIV), which has so far caused over 25 million fatalities around the world [80], outbreaks of respiratory diseases such as the severe acute respiratory syndrome (SARS) [34, 35, 68] and the 2009 swine influenza pandemic [27, 74, 75] were also recorded. Malaria remains a serious public health menace, causing about 2 million

deaths [66] and about 300 to 660 million clinical cases in tropical and subtropical areas of the world each year [86] (more than 90% of the lethal cases of malaria occur in children under five years of age [31]). Diseases such as plague, cholera, hemorrhagic fevers continue to erupt occasionally [43], and some diseases (such as malaria, HIV/AIDS, mycobacterium tuberculosis, typhus, cholera and schistosomiasis) are endemic (i.e., always present) in some regions. Although significant advances have been recorded in the fields of medical and public health sciences, infectious diseases continue to cause significant morbidity, mortality and socio-economic burden in human and animal populations worldwide [25, 65, 66, 73, 81].

1.2 History of Modelling of Infectious Diseases

The use of mathematical modelling (and analysis) has, historically, played a major (and unique) role in epidemiology. Although Daniel Bernoulli [13] was, arguably, the first to use modelling to study human diseases (in his work on assessing the efficacy of inoculation against smallpox in 1760), the mathematical foundation of the entire approach to epidemiology, based on using compartmental models, was laid by a number of public health physicians, notably Sir Ronald A. Ross, W.H. Hamer, A.G. McKendrick and W.O. Kermack, between 1900 and 1935 [3, 4, 43, 51, 52, 70, 79]. Sir Ronald Ross received the Nobel prize in medicine in 1902 for his work on the control of malaria (his modelling work shows that malaria outbreaks could be avoided if the mosquito population is be reduced below a critical threshold level. This conclusion was later corroborated by field trials, and led to the success in malaria control in some regions of the world).

Kermack and McKendrick designed a simple compartmental model for studying the Great Plague of London, by spliting the total population at time t, denoted by $N(t)$, into three mutually-exclusive compartments of susceptible ($S(t)$), infected ($I(t)$) and

recovered or removed ($R(t)$) individuals (so that, $N(t) = S(t) + I(t) + R(t)$). Most of the compartmental models used in the literature (which, typically, take the forms of SIR, SIS, $SIRS$, $SEIR$, $SEIRS$ compartmental models, where E represents the class of newly-infected individuals with no clinical symptoms of the disease) are built based on the modelling framework of Kermack and McKendrick (see [43] for a detailed review, and also [16, 59, 60, 61, 77, 97, 98]). Some of these models extend the Kermack-McKendrick model by adding relevant epidemiological or biological features, such as passive immunity, gradual loss of vaccine and infection-acquired immunity, stages of infection, vertical transmission, disease vectors, age structure, social and sexual mixing groups, spatial spread, vaccination, quarantine, isolation, antiviral treatment, periodicity (or seasonality) considerations; emergence and transmission of resistant strains, zoonotic diseases, co-infection etc.

1.3 Basic Reproduction Number

A central concept in the analysis of infectious disease dynamics is the *basic reproduction number*, typically denoted by $\mathcal{R}_0$ [2, 3, 4, 43]. It is defined as the expected number of new infections generated by a typical infectious individual in a completely-susceptible population. It is a threshold parameter that determines whether a disease, starting from a typical infectious individual, can cause an epidemic. If $\mathcal{R}_0 < 1$, then, on average, an infectious individual will transmit the disease to less than one susceptible individual. Consequently (in general), the disease will not be able to spread and cause a major epidemic in the population.

On the other hand, if $\mathcal{R}_0 > 1$, then a typical infectious individual will spread the disease to more than one susceptible individual on average. Hence, in this case, the disease can take off and cause an epidemic (although it should be stated that having $\mathcal{R}_0 > 1$ does not always guarantee that an epidemic will occur, due to stochastic

effects [81]. Stochastic effects are not considered in this thesis). Figure 1.1 depicts a schematic description of the reproduction number for the case with $\mathcal{R}_0 = 2$ (for a population where some individuals are partially-protected against infection either by previous exposure to the disease or by vaccination). In this figure, a typical infected individual infects two susceptible individuals, and the vaccine (or previous exposure) induces some partial protection against infection.

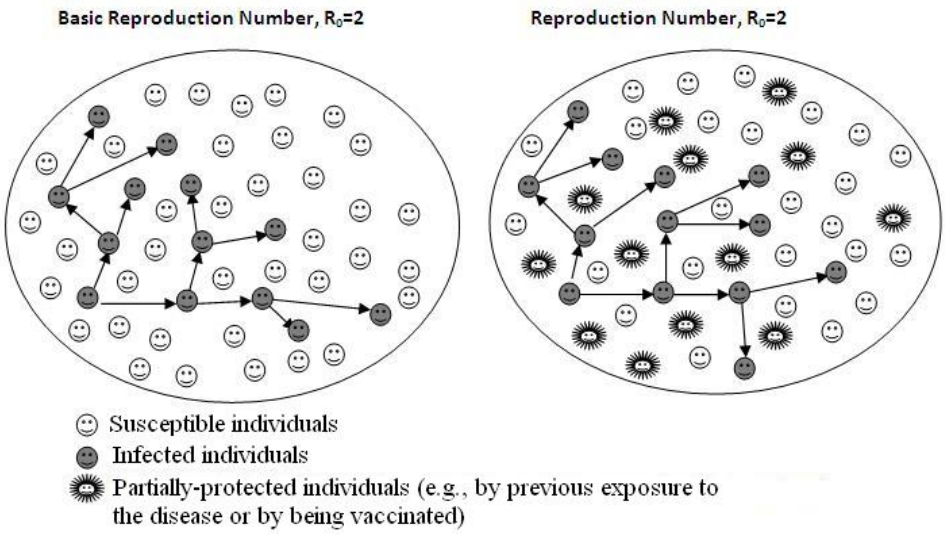

Figure 1.1: A schematic diagram illustrating the reproduction numbers.

Furthermore, if an epidemic does occur, the actual numerical value of the threshold quantity ($\mathcal{R}_0$) can be used to obtain some important information, such as the initial growth rate of the epidemic, the prevalence at the peak of an epidemic, and the proportion of the population that is ultimately infected. For simple models, the classical epidemiological requirement of having $\mathcal{R}_0 < 1$ is necessary and sufficient for effective disease control (or elimination) in the population. In such a case, the model exhibits a *forward bifurcation* at $\mathcal{R}_0 = 1$, as depicted in Figure 1.2. Bifurcation is defined as a change in the qualitative behavior of the model as a parameter ("bifurcation parameter") is varied. The reproduction numbers of the models in this thesis are computed

using the next generation operator method discussed in Section 2.4 [19, 89].

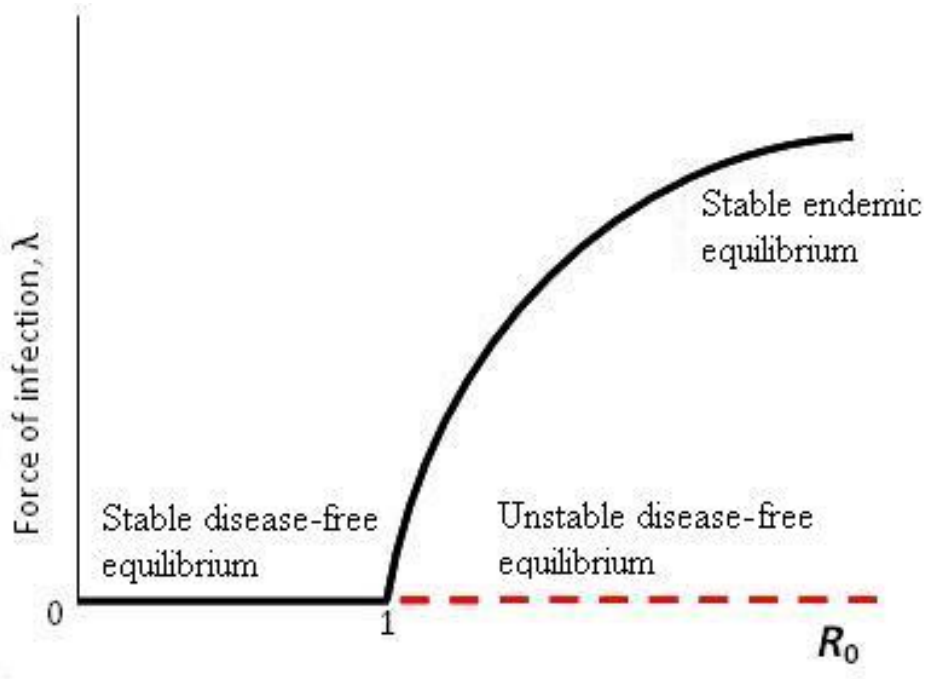

Figure 1.2: Forward bifurcation diagram.

1.4 Objectives of the Thesis

The main motivation of the thesis is to address important mathematical questions associated with the use of $SEIRS$ class of models to study the transmission dynamics of a given disease. These questions include:

(i) Does the use of multiple infectious classes and allowing for the loss of infection-acquired immunity alter the qualitative dynamics (in terms of persistence or elimination of the disease being studied) of the classical $SEIR$ model?

(ii) Does the use of multiple latent and infectious stages, coupled with gamma distribution assumptions for the average waiting times in these stages, affect the qualitative dynamics of the $SEIRS$ model?

(iii) Does periodicity effect the qualitative dynamics of the extended $SEIRS$ model with multiple latent and infectious stages (and gamma distribution assumptions) described in Item (ii) above?

Each of these questions is addressed in a separate chapter of the thesis.

1.5 Outline of the Thesis

The thesis is organized as follows. Some of the main mathematical concepts and theories relevant to the thesis are discussed (or defined) in Chapter 2. The classical $SEIRS$ model (with standard incidence) is extended in Chapter 3 to incorporate multiple infectious stages. A detailed discussion on the existence and stability of the associated equilibria of the resulting SEI^nRS model is given. In Chapter 4, the SEI^nRS model considered in Chapter 3 is further extended to include multiple exposed stages and gamma distributed average waiting times in the exposed and infectious stages. To address the issue of periodicity (or seasonality) in the transmission dynamics of the disease, the $SEIRS$ model with multiple exposed and infectious stages (considered in Chapter 4) is studied for the case where some of the associated epidemiological parameters are periodic, in Chapter 5.

It should be mentioned that the numerical simulations in this thesis are carried out using ODE45 (a MATLAB routine).

Chapter 2

Mathematical and Epidemiological Preliminaries

In this chapter, some of the the main mathematical concepts and theories relevant to the thesis are briefly discussed (most of these materials are available in standard dynamical systems texts and references).

2.1 Linear and Non-linear Systems

Many mathematical models arising in the natural and engineering sciences are expressed in terms of differential equations. A differential equation is an equation involving a function and its derivatives.

Consider, in general, the following system of n first-order ODE (where the dot represents differentiation with respect to time, t):

$$\dot{x} = f(x, t; \mu), \quad x \in U \subset \mathbb{R}^n, \quad t \in \mathbb{R}^1, \quad \text{and} \quad \mu \in V \subset \mathbb{R}^p, \tag{2.1}$$

where, U and V are open sets in $\mathbb{R}^n$ and $\mathbb{R}^p$, respectively, and μ is a parameter. The equation in (2.1) is an *ordinary differential equation* (ODE) and the right-hand side

function, $f(x,t;\mu)$, of the ODE (2.1) is called a *vector field*.

Definition 2.1. *A system of the form (2.1) is said to be autonomous if the function f does not explicitly depend on t (i.e., $f = f(x)$). If f in (2.1) explicitly depends on t, then the system (2.1) is non-autonomous.*

In this thesis, both autonomous and non-autonomous systems of non-linear differential equations are considered. However, from now on, unless otherwise stated, the system (2.1) is considered to be autonomous.

Consider the following general autonomous system of differential equations

$$\dot{x} = f(x), \quad x \in \mathbb{R}^n, \tag{2.2}$$

where the function f does not depend on the independent variable t. If the function f in equation (2.2) is a sum of terms which are either independent of x or linear in t, then the resulting equation (or system) is *linear*, otherwise it is *non-linear*. Furthermore, the trajectory of a solution, $x(t)$, of (2.2) is the set of all points reached by $x(t)$ for some value of t. The phase diagram of the system (2.2) defined to be the phase space $\mathbb{R}^n$, with trajectories of $x(t)$ drawn through each point. Thus, the phase diagram shows all possible trajectories of an autonomous differential equation. In practice, we only sketch a few trajectories.

Points where the vector field f vanishes play an important role in understanding the qualitative behavior of solutions, and are called *equilibrium points*. An equilibrium solution of the system (2.2) is given by $x = x^* \in \mathbb{R}^n$, where $f(x^*) = 0$. It should be stated that the elementary autonomous system

$$\dot{x} = f(x), \quad x \in \mathbb{R},$$

has a solution (if $f(x)$ is integrable) given by

$$x(t) = x(0) + \int_0^t f(s)ds, \quad x \in \mathbb{R}.$$

In general, solution for (2.2) exist if the right-hand side function f is continuous. But such continuity condition may not guarantee the uniqueness of solutions for the non-linear autonomous system (2.2), as shown in the example below.

Example 2.1. *Consider the following initial-value problem (IVP)[76]*

$$\dot{x} = 3x^{\frac{2}{3}}, \ x(0) = 0.$$

The IVP has two solutions through the point $(0, 0)$*, given by* $x_1(t) = t^3$ *and* $x_2(t) = 0$ $\forall t \in \mathbb{R}$*. Notice that* $f(x) = 3x^{\frac{2}{3}}$ *is continuous at* $x = 0$ *but not differentiable there.*

Definition 2.2. *The Jacobian of* f*, at the equilibrium* x^**, denoted by* $Df(x^*)$*, is given by the matrix*

$$\left[\frac{\partial f_i}{\partial x_j}\right]_{x=x^*} = \begin{pmatrix} \frac{\partial f_1}{\partial x_1}(x^*) & \cdots & \frac{\partial f_1}{\partial x_n}(x^*) \\ \vdots & \vdots & \vdots \\ \frac{\partial f_n}{\partial x_1}(x^*) & \cdots & \frac{\partial f_n}{\partial x_n}(x^*) \end{pmatrix},$$

of partial derivatives of f *evaluated at* x^**.*

Theorem 2.1 ([76])**.** *If* $f : \mathbb{R}^n \to \mathbb{R}^n$ *is differentiable at* x_0*, then all the partial derivatives* $\frac{\partial f_i}{\partial x_j}$ $(i, j, = 1, ..., n)$ *exist at* x_0 *and for all* $x \in \mathbb{R}^n$*,*

$$Df(x_0)x = \sum_{j=1}^{n} \frac{\partial f_i}{\partial x_j}(x_0)x_j.$$

Thus, if f *is a differentiable function, the derivative* Df *is given by the* $n \times n$ *Jacobian matrix*

$$Df = \left[\frac{\partial f_i}{\partial x_j}\right].$$

Definition 2.3 ([76]). *Let E be an open subset of $\mathbb{R}^n$. A function $f : E \to \mathbb{R}^n$ is said to satisfy a Liptchitz condition on E if there is a constant $K > 0$ such that $\forall x, y \in E$*

$$|f(x) - f(y)| \leq K|x - y|.$$

Lemma 2.1 ([76]). *Let E be an open subset of $\mathbb{R}^n$ and let $f : E \to \mathbb{R}^n$. Then if $f \in C^1(E)$, f is locally Liptschitz on E.*

Proof. The proof is given in [76] and is reproduced below for completeness. Since E is an open subset of $\mathbb{R}^n$, given $x_0 \in E$, there exists an $\epsilon > 0$ such that $N_\epsilon(x_0) \subset E$. Define a positive constant K by

$$K = \max_{|x| \leq \frac{\epsilon}{2}} ||Df(x)||,$$

(i.e., K is the maximum of the continuous function $Df(x)$ on the compact set $|x| \leq \frac{\epsilon}{2}$). Let N_0 be the $\frac{\epsilon}{2}-$neighbourhood of x_0, $N_{\frac{\epsilon}{2}}(x_0)$. Let $u = y - x$ for $x,\ y \in N_0$. Since N_0 is a convex set, it follows that $u + sx = y$ for $s \in [0, 1]$. Further, define the function $F : [0, 1] \to \mathbb{R}^n$ by

$$F(s) = f(x + su).$$

It follows, by using the chain rule, that

$$F'(s) = Df(x + su)u.$$

Integrating both sides of the above equation gives

$$\int_0^1 F'(s)ds = \int_0^1 Df(x + su)u,$$

so that,

$$\begin{aligned} f(y) - f(x) &= F(1) - F(0), \\ &= \int_0^1 F'(s)ds = \int_0^1 Df(x+su)uds. \end{aligned}$$

Hence,

$$\begin{aligned} \mid f(y) - f(x) \mid &\leq \int_0^1 \parallel Df(x+su) \parallel \mid u \mid ds, \\ &\leq K \mid u \mid, \\ &= K \mid y - x \mid . \end{aligned}$$

□

Theorem 2.2 (Fundamental Existence-Uniqueness Theorem [76])**.** *Let E be an open subset of $\mathbb{R}^n$ containing x_0 and assume that $f \in C^1(E)$. Then there exists $a > 0$ such that the IVP*

$$\dot{x} = f(x); \;\; x(0) = x_0,$$

has a unique solution $x(t)$ on the interval $[-a, a]$.

Definition 2.4. *Let $x = x^*$ be an equilibrium solution of (2.2). Then, x^* is called hyperbolic if none of the eigenvalues of $Df(x^*)$ has zero real part. An equilibrium point that is not hyperbolic is called non-hyperbolic.*

Consider the system

$$\begin{aligned} \dot{x} &= f(x), \quad x \in \mathbb{R}^n, \\ \dot{y} &= g(y), \quad y \in \mathbb{R}^n, \end{aligned} \tag{2.3}$$

where f and g are two C^r $(r \geq 1)$ ODEs defined on $\mathbb{R}^n$.

Definition 2.5 ([93]). *The dynamics generated by the vector fields f and g of (2.3) are said to be locally C^k conjugate ($k \leq r$) if there exist a C^k diffeomorphism h which takes the orbits of the flow generated by f, $\phi(t,x)$, to the orbits of the flow generated by g, $\psi(t,y)$, preserving orientation and parametrization by time.*

Theorem 2.3 ([93, Hartman and Grobman]). *Consider a $C^r(r \geq 1)$ vector field f and the system*

$$\dot{x} = f(x), \quad x \in \mathbb{R}^n, \tag{2.4}$$

with domain of f an open subset of $\mathbb{R}^n$. Suppose also that (2.4) has equilibrium solutions which are hyperbolic. Consider the associated linear ODE system

$$\dot{\xi} = Df(x^*)\xi, \quad \xi \in \mathbb{R}^n. \tag{2.5}$$

Then, the flow generated by (2.4) is C^0 conjugate to the flow generated by the linearized system (2.5) in a neighborhood of the equilibrium point.

It follows from the Hartman-Grobman Theorem that an orbit structure near a hyperbolic equilibrium solution is qualitatively equivalent to the orbit structure of the associated linearized (around the equilibrium point) dynamical system.

Definition 2.6 ([76, Fundamental Matrix]). *A fundamental matrix solution of*

$$\dot{x} = Ax, \tag{2.6}$$

where A is an $n \times n$ matrix, is any nonsingular $n \times n$ matrix function $\Phi(t)$ that satisfies

$$\dot{\Phi}(t) = A\Phi(t), \ \forall t \in \mathbb{R}.$$

It should be stated that $\Phi(t) = e^{At}$ is a fundamental matrix solution which satisfies $\Phi(0) = I$ (where I is an $n \times n$ identity matrix). Hence, the solution for the fundamental matrix solution $\Phi(t)$ of (2.6) is given by $\Phi(t) = Ce^{At}$, where C is a nonsingular matrix.

2.2 Stability of Solutions

Let $x^*(t)$ be any solution of system (2.2).

Definition 2.7 ([93]). *The solution $x^*(t)$ is said to be stable if for every $\epsilon > 0$, there exists a $\delta = \delta(\epsilon) > 0$ such that,*

$$|x^*(t_0) - x_0| < \delta \Rightarrow |x^*(t) - x(t)| < \epsilon, \quad t > t_0, \quad t_0 \in \mathbb{R},$$

for every solution $x(t)$ of (2.2) with $x(t_0) = x_0$.

Definition 2.8. *A solution which is not stable is said to be unstable.*

Definition 2.9. *An equilibrium point x^* is attracting if there is a $\delta > 0$ such that*

$$|x_0 - x^*| < \delta \quad \Rightarrow x(t) \to x^* \text{ as } t \to \infty,$$

for every solution $x(t)$ of (2.2) with $x(0) = x_0$.

Definition 2.10. *An equilibrium point x^* is asymptotically-stable if it is stable and attracting.*

In other words, the solution x^* is said to be asymptotically-stable if:

(i) it is stable, and

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

Theorem 2.4 ([93]). *Suppose all the eigenvalues of $Df(x^*)$ have negative real parts. Then, the equilibrium solution $x = x^*$ of the system (2.2) is locally-asymptotically-stable. The equilibrium is unstable if at least one of the eigenvalues has positive real part.*

2.3 Competitive and Cooperative Systems

Consider the autonomous system

$$\dot{x} = f(x), \tag{2.7}$$

with $f \in \mathcal{C}^1(E)$, where E is a open set of $\mathbb{R}^n$. The set E is $p-$convex if $tx + (1-t)y \in E,\ \forall t \in [0,1]$ whenever $x, y \in E$ and $x \leq y$. If E is a convex set, then it is $p-$convex. If E is a $p-$convex subset of $\mathbb{R}^n$ and the inequality

$$\frac{\partial f_i}{\partial x_j}(x) \geq 0,\ i \neq j,\ x \in E, \tag{2.8}$$

holds, then f is of "Type K" in E [83].

Remark 2.1. *Consider the linear system*

$$y' = D(x(t))y,$$

where $x(t)$ is the solution of (2.7) defined on $\mathbb{R}_+$ and $Df(x(t))y$ is the jacobian matrix of f at x provided that (2.8) holds, then $g(t,y) = D(x(t))y$ satisfies the same argument for the corresponding non-autonomous system

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

Thus, if $y(t)$ is the solution of the linear system satisfying $0 \leq y(0)$, it follows that $0 \leq y(t)$ for all $t > 0$ (see [83] for further details).

Definition 2.11. *The system (2.7) is said to be cooperative if (2.8) holds on the $p-$convex domain E. It is called competitive on E if E is $p-$convex and the inequality in (2.8) is reversed to:*

$$\frac{\partial f_i}{\partial x_j}(x) \leq 0,\ i \neq j,\ x \in E. \tag{2.9}$$

For instance, if (2.7) is a competitive system with flow ϕ_t, then $\dot{x} = -f(x)$ is a cooperative system with flow $\xi_t = \phi_{-t}$ (and the converse holds as well). It follows from the above definition that a system with a coefficient matrix $A = (a_{ij})$ is cooperative if all its off-diagonal elements are non-negative (that is, if $a_{ij} \geq 0$ for all $i \neq j$).

Theorem 2.5 ([83, Theorem 3.4]). *The flow on a compact limit set of a competitive or cooperative system in $\mathbb{R}^n$ is topologically equivalent to a flow on a compact invariant set of a Lipschitz system of differential equations in $\mathbb{R}^{n-1}$.*

Definition 2.12. *Consider a matrix A of order $n \times n$. The matrix A is called reducible either if A is the 1×1 zero matrix or if $n \geq 2$ and there exists a permutation matrix P such that*

$$PAP^T = \begin{bmatrix} B & \boldsymbol{0} \\ C & D \end{bmatrix},$$

where B and D are square matrices and $\boldsymbol{0}$ is the zero matrix. The matrix A is irreducible if it is not reducible (see [10, 28] for further discussions).

Theorem 2.6 ([83, Theorem 4.1.1]). *Let the system (2.7) be cooperative and irreducible in E. Then,*

$$\frac{\partial \phi(t,x)}{\partial x} \gg 0, \ t > 0.$$

Furthermore, if $x_0,\ y_0 \in E$ satisfy $x_0 < y_0,\ t > 0$ and $\phi_t(x_0), \phi_t(y_0)$ are defined, then

$$\phi_t(x_0) \ll \phi_t(y_0), \ t > 0.$$

Definition 2.13 ([83]). *The semiflow ϕ is said to be* monotone *provided that*

$$\phi_t(x) \leq \phi_t(y) \ \ \textit{whenever}\ x \leq y \ \ \textit{and}\ t \geq 0.$$

It is strongly monotone *if ϕ is monotone,*

$$\phi_t(x) \ll \phi_t(y),$$

and whenever $x < y$ and $t > 0$.

Let $A(t)$ be a continuous, cooperative, irreducible, and $\omega-$periodic $n \times n$ matrix function, $\Phi_{A(.)}(t)$ be the fundamental solution matrix of the linear ordinary differential system $\dot{x} = A(t)x$. Furthermore, let $\rho(\Phi_{A(.)}(\omega))$ be the spectral radius of $\Phi_{A(.)}(\omega)$. It then follows (from [5, Lemma 2]) that $\Phi_{A(.)}(t)$ is a matrix with all entries positive for each $t > 0$. Hence, by Perron-Frobenius theorem [90], $\rho(\Phi_{A(.)}(\omega))$ is the principal eigenvalue of $\Phi_{A(.)}(t)$ in the sense that it is simple and has an eigenvector $v \gg 0$.

Lemma 2.2 ([96, Lemma 2.1])**.** *Let $\mu = \frac{1}{\omega} \ln \rho(\Phi_{A(.)}(\omega))$. Then, there exists a positive, $\omega-$periodic function, $v(t)$, such that $e^{\mu t}v(t)$ is a solution of $\dot{x} = A(t)x$.*

The irreducibility hypothesis plays an important role in the stability of reducible and cooperative systems. The sufficient condition for a cooperative system of differential equations to generate a strong monotone flow is that the jacobian matrix of the vector field of the system must be irreducible at each point [83].

2.4 Next Generation Operator Method for Autonomous Systems

The *next generation operator method* (for an autonomous system) [18, 89] is typically used to establish the local asymptotic stability of the disease-free equilibrium (or a boundary equilibrium) of epidemiological models. The formulation (for the method) in [89] is described below.

Consider a given disease transmission model, with non-negative initial conditions defined by the system:

$$\dot{x}_i = f(x_i) = \mathrm{F}_i(x) - \mathrm{V}_i(x), \quad i = 1, \cdots, n, \tag{2.10}$$

where $\mathrm{V}_i = \mathrm{V}_i^- - \mathrm{V}_i^+$ with V_i^- representing the rate of transfer of individuals out of compartment i, V_i^+ representing the rate of transfer of individuals into compartment i by all other means, and $\mathrm{F}_i(x)$ representing the rate of appearance of new infections in compartment i. It is assumed that the functions (F_i and V_i; $i = 1, ..., n$) satisfy the axioms $(A1) - (A5)$ below. Furthermore, it is assumed that these functions are at least twice continuously-differentiable in each variable [89].

Let X_s be the set of all disease-free states (non-infected state variables) of the model (2.10), such that

$$X_s = \{x \geq 0 | x_i = 0,\ i = 1, \cdots, m\},$$

where, $x = (x_1, \cdots, x_n)^T, x_i \geq 0$ represents the number of individuals in each compartment of the model (2.10).

(A1) if $x \geq 0$, then $\mathrm{F}_i, \mathrm{V}_i^+, \mathrm{V}_i^- \geq 0$ for $i = 1, \cdots, m$.

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

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

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

(A5) If $\mathrm{F}(x)$ is set to zero, then all eigenvalues of $Df(x_0)$ have negative real part.

Definition 2.14 ([90, M-Matrix]). *An $n \times n$ matrix $A = [a_{i,j}]$ with $a_{i,j} \leq 0$ for all $i \neq j$ is an $M-$matrix if A is non-singular and A^{-1} is non-negative.*

Definition 2.14 implies that an $n \times n$ matrix A is an $M-$matrix if and only if every off-diagonal entry of A is non-positive and the diagonal entries are all positive.

Lemma 2.3 ([89, van den Driessche and Watmough]). *If x^* is a DFE of (2.10) satisfying the axioms $(A1)-(A5)$, then the derivatives $D\mathrm{F}(x^*)$ and $D\mathrm{V}(x^*)$ are partitioned as*

$$D\mathrm{F}(x^*) = \begin{pmatrix} F & 0 \\ 0 & 0 \end{pmatrix} \quad \textit{and} \quad D\mathrm{V}(x^*) = \begin{pmatrix} V & 0 \\ J_3 & J_4 \end{pmatrix}$$

where F and V are the $m \times m$ matrices defined by,

$$F = \left[\frac{\partial \mathrm{F}_i}{\partial x_j}(x^*)\right] \quad \textit{and} \quad V = \left[\frac{\partial \mathrm{V}_i}{\partial x_j}(x^*)\right] \quad \textit{with } 1 \leq i,\ j \leq m.$$

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

Theorem 2.7 ([89, van den Driessche and Watmough]). *Consider the disease transmission model given by (2.10) with $f(x)$ satisfying axioms $(A1)-(A5)$. If x^* is a DFE of the model, then x^* is locally-asymptotically-stable (LAS) if $\mathcal{R}_0 = \rho(FV^{-1}) < 1$ (where ρ is the spectral radius), but unstable if $\mathcal{R}_0 > 1$.*

Example 2.2. *Consider the following nonlinear ODE system (the classical SIR model for a population):*

$$\begin{aligned} \dot{S} \equiv f_1(S,I,R) &= \pi - \beta SI - \mu S, \\ \dot{I} \equiv f_2(S,I,R) &= \beta SI - \gamma I - \mu I, \\ \dot{R} \equiv f_3(S,I,R) &= \gamma I - \mu R. \end{aligned} \tag{2.11}$$

The total population at time t, denoted by $N(t)$, is sub-divided into three mutually-exclusive sub-populations of susceptible ($S(t)$), infected ($I(t)$) and recovered (or removed individuals) ($R(t)$), so that $N(t) = S(t) + I(t) + R(t)$. Furthermore, the recruitment

rate (π), natural death rate (μ) and the recovery rate of infected individuals (γ) are non-negative constants.

The system (2.11) has a DFE, given by $x^* = (S^*, I^*, R^*) = (\frac{\pi}{\mu}, 0, 0)$. Using the notation described above, the right-hand side of the system (2.11) can be written as

$$f(S, I, R) = F(S, I, R) - V(S, I, R) = \begin{pmatrix} 0 \\ \beta SI \\ 0 \end{pmatrix} - \begin{pmatrix} -\pi - \beta SI + \mu S \\ (\gamma + \mu)I \\ -\gamma I + \mu R \end{pmatrix}.$$

It follows that the matrix F (obtained from the rate of appearance of new infections in compartment I) and the $M-$Matrix, $V = V^- - V^+$ are given, by respectively,

$$F = \Big(\beta S^*\Big) \quad \textit{and} \quad V = \Big(\gamma + \mu\Big).$$

Hence, using Lemma 2.3, the basic reproduction number, $\mathcal{R}_0 = \rho(FV^{-1})$, of the model (2.11) is given by

$$\mathcal{R}_0 = \rho(FV^{-1}) = \frac{\beta S^*}{\gamma + \mu} = \frac{\beta\pi}{\mu(\gamma + \mu)}.$$

Thus, it follows from Theorem 2.7,that the DFE, $(S^*, I^*, R^*) = (\frac{\pi}{\mu}, 0, 0)$, of the model (2.11) is LAS if $\mathcal{R}_0 < 1$, and unstable whenever $\mathcal{R}_0 > 1$. The epidemiological implication of the local stability result is that if $\mathcal{R}_0 < 1$, then a small influx of infectious individuals will not generate a large outbreak of the disease in the population.

The next generation operator method described above has been extended to non-autonomous dynamical systems arising in disease transmission [91].

2.5 Global Asymptotic Stability of Equilibria

An equilibrium, x^*, is locally-asymptotically stable if it attracts solutions within a neighborhood (in a feasible region) containing x^*. It is globally-asymptotically stable (GAS) if it attracts all solutions in the feasible region (i.e., the region in space where the model is being studied). There are numerous methods for establishing the GAS property of an equilibrium point (such as using Lyapunov Function theory and LaSalle's Invariance Principle; Comparison Theorem; Fluctuation Method; etc.). The first two of the aforementioned methods are used in this thesis, and are briefly described below.

Limit Sets and Invariance

In order to understand the long-term behavior of trajectories, it is crucial that the nature of the trajectories at infinity be investigated. In this section, the concept of $\omega-$ and $\alpha-$limit sets, and their properties are introduced. Before giving a formal definition, the following example should be considered first of all.

Example 2.3. *Consider the following system of equations [76]:*

$$\begin{aligned} \dot{x} &= y + x(1 - x^2 - y^2), \\ \dot{y} &= -x + y(1 - x^2 - y^2). \end{aligned} \tag{2.12}$$

Using $r^2 = x^2 + y^2$ of the polar coordinate, and differentiating with respect to t we have

$$\begin{aligned} r\dot{r} &= x\dot{x} + y\dot{y}, \\ &= xy + x^2(1 - r^2) - xy + y^2(1 - r^2), \\ &= r^2(1 - r^2), \\ \dot{r} &= r(1 - r^2). \end{aligned}$$

Further, the angular variable, θ, satisfies $tan(\theta) = \frac{y}{x}$. Differentiating both sides of the

equation with respect to t gives

$$\begin{aligned} sec^2(\theta)\dot{\theta} &= x^{-2}\Big[-x^2+xy(1-r^2)-y^2-xy(1-r^2)\Big] = -\frac{r^2}{x^2}; \\ \dot{\theta} &= -1. \end{aligned}$$

The system in Example 2.3 has an attracting periodic orbit of radius one, and the origin is a repeller. A trajectory $\phi(t,x)$ starting outside the unit circle tends inward toward the unit circle. It does not converge to any one point in the circle, but given a point z in the circle, $\phi(t,x)$ keeps coming back near to z every 2π units of time. This implies that there exists a sequence of times, $\{t_i\}_0^\infty$, such that $\phi(t_i,x)$ converges to z. Here, clearly, if we take a different z we get a different t_i. Hence, for $t\to\infty$, the set of these points is called $\omega-$limit set. Similarly, if we consider $t\to-\infty$ (i.e., trace the trajectory backward in time), the set is called $\alpha-$limit set.

Definition 2.15. *A point $z\in\mathbb{R}^n$ is called an $\omega-$limit point of a trajectory $\phi(t,x)$, where $x\in\mathbb{R}^n$, provided there exists a sequence $\{t_i\}$ such that*

$$\phi(t_i,x)\to z \ \ as \ \ t_i\to\infty.$$

Definition 2.16. *A point $z\in\mathbb{R}^n$ is called an $\alpha-$limit point of a trajectory $\phi(t,x)$, where $x\in\mathbb{R}^n$, provided there exists a sequence $\{t_i\}$ such that*

$$\phi(t_i,x)\to z \ \ as \ \ t_i\to-\infty.$$

Definition 2.17 ([93])**.** *The set of all $\omega-$limit points of x is called the $\omega-$limit set, denoted by $\omega(x)$. Similarly, the set of all $\alpha-$limit points of x is called the $\alpha-$limit set, denoted by $\alpha(x)$.*

Definition 2.18 ([78, Invariant Set])**.** *Let f be a function such that $f:X\to X$. A subset $A\subset X$ is called invariant, provided that*

(i) if $x \in A$, then $f(x)$ is in A, and

(ii) for every point $y \in A$, there is some $x \in A$ with $y = f(x)$ (i.e., $f(A) = A$).

A subset $A \subset X$ is positively-invariant provided that if $x \in A$, then $f(x) \in A$ (i.e., $f(A) \subset A$).

Definition 2.19 ([93]). *Let $S \subset \mathbb{R}^n$ be a set. Then, S is said to be invariant under the flow generated by $\dot{x} = f(x)$ if for any $x_0 \in S$ we have $x(t, 0, x_0) \in S$ for all $t \in \mathbb{R}$.*

If the region S is restricted to positive times (i.e., $t \geq 0$), then S is said to be a *positively-invariant set*. In other words, solutions in a positively-invariant set remain there for all time. The set is negatively-invariant if we go backward in time.

2.5.1 Lyapunov Functions and LaSalle's Invariance Principle

Lyapunov functions, first introduced by Aleksandr Mikhailovich Lyapunov (1857-1908), are energy-like functions that decrease along trajectories. Furthermore, the existence of a Lyapunov function in a given neighborhood precludes the existence of closed orbits in the neighborhood [87].

Consider the following system

$$\dot{x} = f(x), \quad x \in \mathbb{R}^n. \tag{2.13}$$

Definition 2.20. *A function $V : \mathbb{R}^n \to \mathbb{R}$ is positive-definite if*

- *$V(x) > 0$ for all $x \neq 0$,*
- *$V(x) = 0$ if and only if $x = 0$.*

Definition 2.21. *Let $f(x^*) = 0$ (i.e., x^* is an equilibrium solution of (2.13)) and let $V : U \to \mathbb{R}$ be a C^1 function defined on some neighborhood U of x^* such that*

(i) *V is positive-definite,*

(ii) *$\dot{V}(x) \leq 0$ in $U \backslash \{x^*\}$.*

Any function, V, that satisfies the Conditions (i) and (ii) in Definition 2.21 is a *Lyapunov Function* [46, 76, 93].

Theorem 2.8 (LaSalle's Invariance Principle [38])**.** *Consider the system (2.13). Let,*

$$S = \{x \in \bar{U} : \quad \dot{V}(x) = 0\}, \tag{2.14}$$

and M be the largest invariant set of (2.13) in S. If V is a Lyapunov function on U and $\gamma^+(x_0)$ is a bounded orbit of (2.13) which lies in S, then the $\omega-$limit set of $\gamma^+(x_0)$ belongs to M (that is, $x(t, x_0) \to M$ as $t \to \infty$.)

Corollary 2.1. *If $V(x) \to \infty$ as $|x| \to \infty$ and $\dot{V} \leq 0$ on $\mathbb{R}^n$, then every solution of (2.13) is bounded and approaches the largest invariant set M of (2.13) in the set where $\dot{V} = 0$. In particular, if $M = \{0\}$, then the solution $x = 0$ is globally-asymptotically stable (GAS).*

An alternative definition of the LaSalle's Principle is given below [38, 58].

Theorem 2.9 ([38, 58])**.** *Suppose there is a continuously differentiable, positive definite, and radially unbounded function $V : \mathbb{R}^n \to \mathbb{R}$, such that*

$$\frac{\partial V}{\partial x}(x - x^*).f(x) = \nabla V(x - x^*).f(x) \leq W(x) \leq 0, \quad \forall\, x \in \mathbb{R}^n,$$

where $W(x)$ is any continuous function on U. Then, x^* is a globally-stable equilibrium. The solution $x(t)$ converges to the largest invariant set S contained in $E = \{x \in \mathbb{R}^n : W(x) = 0\}$.

Example 2.4. *Consider the following system,*

$$\begin{aligned} \dot{x} &= -y - x^3, \\ \dot{y} &= x - y^3. \end{aligned}$$

The system has a non-hyperbolic equilibrium solution, given by $(x^*, y^*) = (0, 0)$. *Let* $V(x, y) = \frac{1}{2}(x^2 + y^2)$. *Clearly,* $V(0, 0) = 0$, *and* $V(x, y) > 0$ *in a neighborhood of* $(x^*, y^*) = (0, 0)$. *Further,*

$$\dot{V}(x, y) = x\dot{x} + y\dot{y} = -(x^4 + y^4) < 0.$$

Hence, $\dot{V} < 0$ *except at* $(x, y) = (0, 0)$. *Thus, by Corollary 2.1, the equilibrium* $(x^*, y^*) = (0, 0)$ *is globally-asymptotically stable, and the basin of attraction of the equilibrium* $(x^*, y^*) = (0, 0)$ *is the whole plane.*

Remark 2.2. *One setback associated with the use of Lyapunov functions is that there is no general way of finding such functions (constructing a suitable Lyapunov function for a non-linear dynamical system takes a great deal of craft, and some "luck" sometimes). One of the main contributions of this thesis is the numerous Lyapunov functions (both linear and non-linear) that have been constructed for the relatively large non-linear dynamical systems considered in the thesis.*

2.5.2 Comparison Theorem

Comparison theorem can be used to establish the global stability of equilibria of a system of differential equation

$$\dot{x} = f(t, x), \tag{2.15}$$

by comparing the solution of the system (2.15) with the solution of the system of differential inequalities

$$\dot{z} \leq f(t,z),$$

or,

$$\dot{z} \geq f(t,z),$$

on an interval. It should be mentioned that solutions of the system (2.15) are assumed to be unique.

Theorem 2.10 (Comparison Theorem [84, Theorem B.1]). *A function f be a continuous function on $\mathbb{R} \times E$ and of type K, where E is an open subset of $\mathbb{R}^n$. Let $x(t)$ be a solution of $\dot{x} = f(t,x)$ defined on $[a,b]$. If $z(t)$ is a continuous function on $[a,b]$ satisfying $\dot{z} \leq f(t,z)$ on (a,b) with $z(a) \leq x(a)$, then $z(t) \leq x(t)$ for all $t \in [a,b]$. If $y(t)$ is continuous on $[a,b]$ satisfying $\dot{y} \geq f(t,y)$ on (a,b) with $y(a) \geq x(a)$, then $y(t) \geq x(t)$ for all $t \in [a,b]$.*

2.6 Periodic Solutions and Poincaré Map

Consider a non-autonomous system

$$\dot{x} = f(t,x), \qquad (x,t) \in \mathbb{R}^n \times \mathbb{R} \qquad (n \geq 2). \tag{2.16}$$

where $f \in \mathcal{C}^1(E)$, where E is an open set of $\mathbb{R}^n$.

Definition 2.22 (Periodic Solution). *A non-constant solution to the system (2.16), $x(t)$, is said to be periodic if there exists a constant ω such that*

$$x(t+\omega) = x(t)$$

for all t and for some $\omega > 0$. The period of this solution is the minimum of such ω.

Assume that $\phi(t,x)$ represents the flow of the system (2.16). Then, $\phi(.,x)$ defines a closed solution of (2.16) if and only if for all $t \in \mathbb{R}$, $\phi(t+\omega, x_0) = \phi(t, x_0)$ for some

$\omega > 0$. The minimal time where this equality holds is called the period of the periodic orbit $\phi(t, x)$. The stability of closed orbits, or periodic solutions, can be analysed in terms of the characteristic of Floquet multiplier (or using a more geometrical approach, based on the Poincaré map of the system) [32].

Definition 2.23. *Suppose that $A(t)$, a continuous matrix of $\mathbb{R}^{n\times n}$, is periodic in t of period ω. Consider the first order differential system*

$$\dot{\boldsymbol{X}} = A(t)\boldsymbol{X}. \tag{2.17}$$

*If $\boldsymbol{X}(t)$, with $\boldsymbol{X}(0) = \boldsymbol{I}$, is an $n \times n$ matrix solution of system (2.17), then the **monodromy matrix** is defined to be $\boldsymbol{X}(\omega)$. The eigenvalues of this matrix are the Floquet multipliers of system (2.17) [76].*

Definition 2.24. *A Poincaré map of the local section S is the map $P : S \to S$ defined by $P(x) = \phi(\tau, x)$ for x in the open subset of S and $\tau(x)$ is the first return of the flow to S.*

Let $x^*(t)$ be a periodic solution (a closed orbit γ) through the point x_0 in system (2.16), and S is a hyperplane perpendicular to γ at x_0 (i.e., x_0 is the point where γ intersects S). Then, for any point $x \in S$ sufficiently close to x_0, the solution of (2.16) through x at $t = 0$, given by $\phi(t, x)$, will cross S again at a point $P(x)$ near x_0 (as depicted in Figure 2.1). The first return map (or the Poincaré map) $P : S \to S$ is given by $P(x) = \phi(\tau, x)$.

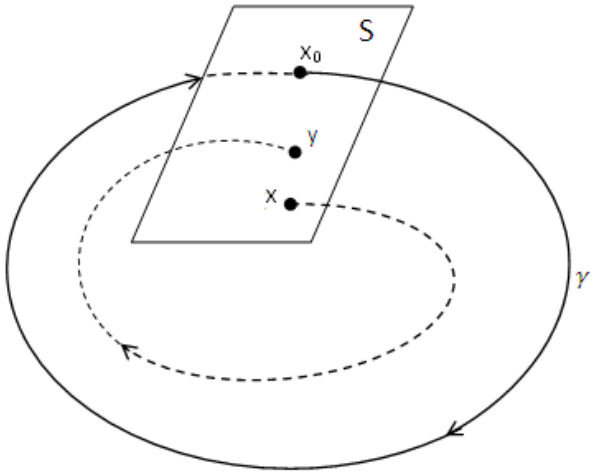

Figure 2.1: Geometry of the Poincaré map P with $x_0 \in \gamma$, a closed orbit, where $x \in S$, $y = P(t, x)$ (i.e., in Poincaré section S, the Poincaré map P projects point x onto point $y = P(t, x)$) [76] .

The Poincaré map is constructed by considering a discrete dynamical system arising from the flow $\phi(t, x) \equiv \phi_t(x)$ of the time-dependent vector field of (2.16) (see [32] for further details).

Consider a periodic point of period $n > 1$ ($P^j(x_0) = x_0$, but $P^n(x_0) \neq x_0$ for $1 \leq j \leq n-1$) corresponding to a subharmonic of period $n\omega$ [32]. Here, P^n represents the composition of P with itself n times (i.e., P^n means P iterates n times). For instance, $P^2(y) = P(P(y))$. The smallest positive value of n for which this equality holds is the period of the orbit. Such periodic points must always come in sets of $n : x_0, x_1, ..., x_{n-1}$, such that

$$x_{i+1} = P(x_i), 0 \leq i \leq n-2, \quad \text{and} \quad x_0 = P(x_{n-1}).$$

Since P is $\omega-$periodic, it follows that $\phi(x, n\omega) \equiv \phi^n(x, \omega)$, where, $P = \phi(x, \omega)$.

It should be noted that x_0 is the fixed-point of the map P, and corresponds to a periodic orbit of period ω for the flow. The map P reduces the study of the stability

of the periodic orbit ($\gamma(t)$) to that of the stability of a fixed-point, x_0.

2.6.1 Stability of Periodic Solutions and the Poincaré Map

Definition 2.25 (Stability of Periodic Solutions)**.** *The periodic solution, γ, is stable if for each $\epsilon > 0$, there exists a δ such that*

$$||x - x_0|| < \delta \implies ||P^n(x) - x_0|| < \epsilon, \ \forall n \geq 0.$$

Thus, the periodic solution, γ, of a continuous dynamical system is stable if and only if the fixed-point, x_0, of the discrete dynamical system is stable.

Definition 2.26. *The periodic solution γ is asymptotically-stable if it is stable and if there exists a $\delta > 0$ such that*

$$||x - x_0|| < \delta \implies \lim_{n\to\infty} P^n(x) = x_0.$$

It follows from the above definition that the periodic orbit γ of the continuous dynamical system is asymptotically-stable if and only if the fixed-point, x_0, of the dynamical system is asymptotically-stable. Furthermore,

- let the linearization of the map P at the fixed-point x_0 be $\frac{\partial P}{\partial x}(x_0)$. This linearized Poincaré map can be used to study the stability of the fixed-point as well as its corresponding periodic orbit
$$P(x) - x_0 = \frac{\partial P}{\partial x}(x_0)(x - x_0) + \mathcal{O}(2).$$
- let $\lambda_1, \cdots, \lambda_{n-1}$ be the eigenvalues of this linearized map. If the moduli of all eigenvalues are less than one, then x_0 is stable. If the modulus of at least one of the eigenvalues is greater than one, then x_0 is unstable.

Theorem 2.11 ([76])**.** *Let γ be a stable closed orbit. Then, no eigenvalue of $DP(x_0)$ has magnitude larger than one, where x_0 is any point on γ.*

Example 2.5 ([76]). *Consider the system given in Example 2.3, which has a limit cycle γ given by $\gamma(t) = (cos(t), sin(t))^T$. The Poincaré map for γ can be found by solving the equivalent system (2.12) (in polar coordinates)*

$$\begin{aligned} \dot{r} &= r(1-r^2), \\ \dot{\theta} &= -1, \end{aligned} \tag{2.18}$$

with $r(0) = r_0 > 0$ and $\theta(0) = \theta_0$. It follows that the solution for the system (2.18) is

$$r(t, r_0) = \left[1 + (\frac{1}{r_0^2} - 1)e^{-2t}\right]^{-\frac{1}{2}},$$

and,

$$\theta(t, \theta_0) = -t + \theta_0.$$

If S is the ray $\theta = \theta_0$ through the origin, then S is perpendicular to γ and the trajectories through the point $(r_0, \theta_0) \in S \bigcap \gamma$ at $t = 0$ intersects the ray θ_0 again at $t = 2\pi$. It follows that the Poincaré map is given by

$$P(r_0) = \left[1 + \left(\frac{1}{r_0^2} - 1\right) e^{-4\pi}\right]^{-\frac{1}{2}}.$$

Clearly, $P(1) = 1$ (which corresponds to the cycle γ). Furthermore,

$$P'(r_0) = e^{-4\pi} r_0^{-3} \left[1 + \left(\frac{1}{r_0^2} - 1\right) e^{-4\pi}\right]^{-\frac{3}{2}}.$$

Hence, $DP(1) = P'(1) = e^{-4\pi} < 1$, so that (by Theorem 2.11) the limit cycle γ is asymptotically-stable.

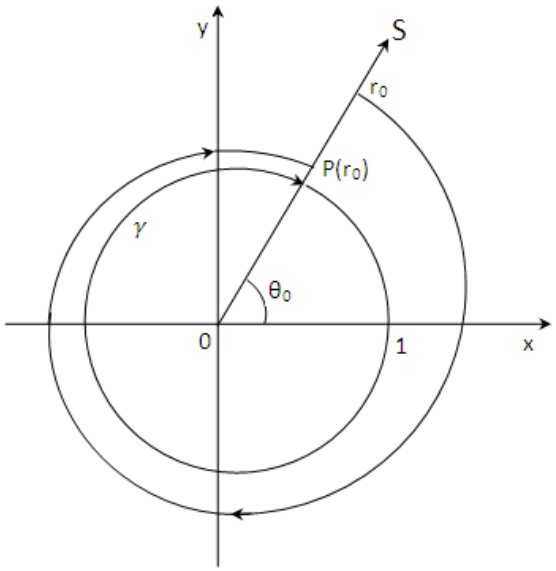

Figure 2.2: The Poincaré map for the system in Example 2.5 [76].

2.7 Uniform-Persistence Theory

Uniform-persistence is an important concept in population dynamics because it characterizes the long-term survival of some or all interacting species in an ecosystem. Before giving the theory, the following definitions and results are necessary.

Definition 2.27. *Let X be a complete metric space with metric d, and let $\omega > 0$. A family of mapping $T(t) : X \to X, \quad t \geq 0$, is called an $\omega-$periodic semiflow on X if it satisfies the following:*

(1) $T(0) = I$, where I is the identity map on X;

(2) $T(t + \omega) = T(t) \circ T(\omega), \ \forall t \geq 0$;

(3) $T(t)x$ is continuous in $(t, x) \in [0, \infty) \times X$.

Definition 2.28. *A point x_0 is periodic, corresponding to an $\omega-$periodic orbit, if $T(t+\omega)x_0 = T(t)x_0,\ \forall t \geq 0$. For an $\omega-$periodic semiflow, the point x_0 coincides with the fixed-point of its associated Poincaré map $T(\omega)$.*

Definition 2.29 ([39, 99])**.** *A continuous mapping f on a complete metric space X is said to be point-dissipative (compact-dissipative) (locally-dissipative)(bounded-dissipative) on X if there is a bounded set B in X such that B attracts each point of X (each compact set of X) (a neighborhood of each compact set of X) (each bounded set of X) under f.*

Let X be a metric space with a metric d. Let $f : X \to X$ be a continuous map and $X_0 \subset X$ be an open set. Define,

$$\begin{aligned} \partial X_0 &:= X \backslash X_0 \text{ and} \\ M_\partial &:= \left\{ x \in \partial X_0 : f^n(x) \in \partial X_0, \forall n \geq 0 \right\}, \text{ which may be empty.} \end{aligned}$$

Definition 2.30. *A bounded set A is said to attract a bounded set B in X if*

$$\lim_{n\to\infty} \sup_{x\in B} \{d(f^n(x), A)\} = 0.$$

- *A subset $A \subset X$ is said to be an attractor for f if A is non-empty, compact and invariant ($f(A) = A$), and A attracts some open neighborhood of itself.*

- *A global attractor for $f : X \to X$ is an attractor that attracts every point in X.*

- *For a non-empty invariant set M, the set $W^s(M) := \left\{ x \in X : \lim_{n\to\infty} d(f^n(x), M) = 0 \right\}$ is called the stable set of M.*

Theorem 2.12 ([99, Global Attractors, Theorem 1.1.3]). *If $f : X \to X$ is compact and point-dissipative, then there is a connected global attractor A that attracts each bounded set in X.*

Theorem 2.13 ([99, Theorem 1.3.1]). *Assume that:*

(C1) $f(X_0) \subset X_0$ and f has a global attractor A;

(C2) The maximal compact invariant set $A_\partial = A \cap M_\partial$ of f in ∂X_0, admits a Morse decomposition $\{M_1, \cdots, M_k\}$ with the following properties

(a) M_i is isolated in X;

(b) $W^s(M_i) \cap X_0 = \emptyset$ for each $1 \leq i \leq k$.

Then, there exists δ such that for any compact internally chain transitive set L with $L \not\subseteq M_i$ for all $1 \leq i \leq k$, we have $\inf_{x \in L} d(x, \partial X_0) > \delta$.

Definition 2.31 ([99, Definition 1.3.2]). *A function $f : X \to X$ is said to be*

- *uniformly-persistent with respect to $(X_0, \partial X_0)$ if there exists $\epsilon > 0$ such that*

$$\liminf_{n \to \infty} d(f^n(x), \partial X_0) \geq \epsilon, \ \forall x \in X_0,$$

and,

- *weakly uniformly-persistent with respect to $(X_0, \partial X_0)$ if there exists $\epsilon > 0$ such that*

$$\limsup_{n \to \infty} d(f^n(x), \partial X_0) \geq \epsilon, \ \forall x \in X_0.$$

Theorem 2.14 ([99, Theorem 1.3.3]). *Let a function $f : X \to X$ be a continuous map with $f(X_0) \subset X_0$. Assume that f has a global attractor A. Then weak uniform persistence implies uniform persistence.*

Theorem 2.15 ([99, Theorem 1.3.6]). *Let $S : X \to X$ be a continuous map with $S(X_0) \subset X_0$. Assume that*

(1) $S : X \to X$ is point-dissipative;

(2) S is compact;

(3) S is uniformly-persistent with respect to $(X_0, \partial X_0)$.

Then there exists a global attractor A for S in X_0 that attracts strongly bounded sets in X_0 and S has a co-existence state $x_0 \in A$.

Theorem 2.16 ([99, Theorem 1.3.7]). *Let $T(t) : X \to X$ be an $\omega-$periodic semiflow on X with $T(t)(X_0) \subset X_0$ $\forall t \geq 0$. Assume that $S = T(\omega)$ satisfies the following:*

(1) $S : X \to X$ is point-dissipative;

(2) S is compact.

Then, uniform persistence of S with respect to $(X_0, \partial X_0)$ implies that of $T(t)$.

2.8 Properties of Gamma Distribution

Gamma distribution is a two-parameter family of continuous probability distributions [45]. It has a scale parameter θ and a shape parameter k. If k is an integer, then the distribution represents the sum of k independent exponentially distributed random variables, each of which has a mean of θ. The probability density function of the gamma distribution can be expressed in terms of the gamma function parameterized in terms of a shape parameter k and scale parameter θ. Both k and θ are positive. The equation defining the probability density function of a gamma-distributed random variable x is given by

$$f(x;k,\theta) = x^{k-1}\frac{\theta^k e^{-x\theta}}{\Gamma(k)} \quad \text{for} \quad x > 0 \text{ and } k, \theta > 0.$$

A random variable X that is gamma-distributed with scale θ and shape k is denoted by

$$X \sim \Gamma(k,\theta) \text{ or } X \sim \text{Gamma}(k,\theta).$$

The gamma distribution has the following properties [45]:

(i) **Summation:**
if X_i has a $\Gamma(k_i,\theta)$ distribution for $i = 1,2,...,n$, then $\sum_{i=1}^{n} X_i \sim \Gamma\left(\sum_{i=1}^{n} k_i, \theta\right)$ provided all X_i are independent;

(ii) **Scaling:**
If $X \sim \Gamma(k,\theta)$ then for any $\alpha > 0$, $\alpha X \sim \Gamma(k, \frac{\theta}{\alpha})$.

Relationships

1. Exponential/gamma: A gamma distribution with shape parameter $k = 1$ and scale parameter θ is an exponential (θ) distribution. That is,

$$X \sim \Gamma(1,\theta) \equiv X \sim Exp(\theta).$$

2. Gamma/exponential: The sum of m exponential (θ) random variables is a gamma (m,θ) random variable. That is,

$$X_i \sim Exp(\theta); \text{ for } i = 1,...,m \equiv \sum_{i=1}^{m} X_i \sim \Gamma(m,\theta).$$

Example 2.6. *If* $E_i \sim \Gamma(1, a_i\alpha)$ *for* $i = 1, 2, \cdots, m$. *It follows, from Item (ii), that* $a_iE_i \sim \Gamma(1, \alpha)$. *Similarly,* $\dfrac{a_iE_i}{m} \sim \Gamma(1, m\alpha)$. *Finally, it follows from Item (i) that*

$$\sum_{i=1}^{m} \frac{a_iE_i}{m} \sim \Gamma\left(\sum_{i=1}^{m} 1, m\alpha\right) \Rightarrow \sum_{i=1}^{m} \frac{a_iE_i}{m} \sim \Gamma(m, m\alpha).$$

Chapter 3

Autonomous SEI^nRS Model

3.1 Introduction

Numerous Kermack-Mckendrick type models (see [51, 52]) have been designed and used, over the decades, to study the transmission dynamics of emerging and re-emerging human and animal diseases of public health interest (see, for instance, [43] for a detailed review, and also [16, 59, 60, 61, 77, 97, 98]). These models typically take the form of a deterministic system of non-linear ODEs, which split the total population at time t, denoted by $N(t)$, into mutually-exclusive compartments of susceptible ($S(t)$), exposed ($E(t)$), infectious ($I(t)$) and recovered ($R(t)$) individuals. This class of models are referred to $SEIR$ models (or $SEIRS$ models, if the infection-acquired immunity is not permanent) [16, 59, 60, 61, 77, 97, 98].

An important feature of the transmission dynamics of some human diseases is the staged-progression property of the diseases, where infected individuals progress through a long period of infectiousness involving distinct stages of infectivity. This is typically the case with HIV [22, 36, 49, 50], for instance, where an infected individual passes through several distinct stages (with different $CD4^+$ T-cell counts and viral load levels). It is, therefore, important that disease transmission models designed for such

settings capture such biological property. Guo and Li [36] studied an SIR model with n distinct infectious stages, showing global asymptotic dynamics for the associated equilibria. Korobeinikov [55] established global asymptotic dynamics of $SEIR$ and SIR models with several parallel infectious stages. Bame *et al.* [9] provided global stability analysis for $SEIS$ models with n latent classes. It should be stated, however, that the aforementioned three studies [9, 36, 55] considered bilinear (mass action) incidence to model the infection rates.

This Chapter focuses on the mathematical modeling of the transmission dynamics of an arbitrary disease with n distinct infectious stages. A deterministic model of the form SEI^nRS will be used. The model in this chapter has three important differences from those reported in [9, 36, 55] (particularly the study in [36], which also considers n infectious stages). The first is that standard incidence will be used for the disease transmission process (data suggests that standard incidence may be more suitable for modelling the transmission dynamics of human diseases [4, 43]). The second is that a class of exposed (latent) individuals (E) is incorporated (exposed individuals are individuals who are infected but have yet to show clinical symptoms of the disease). Finally, in this chapter, it is assumed that recovered individuals eventually lose their infection-acquired immunity and become fully susceptible again. In addition to the above extensions, rigorous qualitative analysis will be provided for the resulting autonomous SEI^nRS model. The main objective here is to determine whether adding multiple infectious stages to the classical $SEIRS$ model (with standard incidence) will alter the transmission dynamics of the $SEIRS$ model (particularly in regards to the persistence or elimination of the disease from the population).

The chapter is organized as follows. The model is formulated in Section 3.2. The global asymptotic stability of the disease-free equilibrium is established in Section 3.3. The existence and local asymptotic stability of the associated endemic equilibrium is considered in Section 3.5 (a sub-linearity trick [23, 24, 44] is used to establish the local

asymptotic stability property, and a Lyapunov function, of Goh-Volterra type, is used to prove its global asymptotic stability for a special case). Some of the theoretical results obtained are illustrated numerically by simulating the model using parameter values relevant to a typical influenza-like illness (ILI).

3.2 Formulation of the Model

The total human population at time t, denoted by $N(t)$, is sub-divided into four disjoint classes of susceptible ($S(t)$), exposed ($E(t)$), infectious ($I(t)$; with n infectious stages) and recovered ($R(t)$) humans, so that

$$N(t) = S(t) + E(t) + \sum_{i=1}^{n} I_i(t) + R(t).$$

The population of susceptible individuals is increased by the recruitment of individuals (assumed susceptible) into the population at a rate of π and by the loss of infection-acquired immunity among recovered individuals (at a rate θ). It is decreased by infection, following effective contact with infectious individuals (in any of the n infectious stages) at a rate of λ, where

$$\lambda = \sum_{j=1}^{n} \frac{\beta_j I_j}{N}. \tag{3.1}$$

In (3.1), β_j is the effective contact rate (i.e., contact capable of leading to infection). This population is further decreased by natural death (at a rate μ_S). Thus, the rate of change of the susceptible population is given by

$$\frac{dS}{dt} = \pi + \theta R - \lambda S - \mu_S S.$$

Exposed individuals are generated following the infection of susceptible individuals (at the rate λ). The population of exposed individuals is decreased by progression to

symptoms development (at a rate σ_E) and natural death (at a rate μ_E). Thus,

$$\frac{dE}{dt} = \lambda S - \sigma_E E - \mu_E E.$$

The population of infectious individuals in Stage 1 (I_1) is generated when exposed individuals develop symptoms (at the rate σ_E). It is decreased by progression to the next infectious stage (I_2; at a rate σ_1), natural death (at a rate μ_1) and disease-induced death (at a rate δ_1). Hence,

$$\frac{dI_1}{dt} = \sigma_E E - \sigma_1 I_1 - \mu_1 I_1 - \delta_1 I_1.$$

Similarly, the population of infectious individuals in Stage j (with $2 \leq j \leq n$) is generated by the progression of individuals in Stage I_{j-1} to Stage I_j (at the rate σ_{j-1}). It is decreased by progression to the next (I_{j+1}) infectious stage (at a rate σ_j), natural death (at a rate μ_j) and disease-induced death (at a rate δ_j). Individuals in the final (n) stage of infectiousness recover (at a rate σ_n). Thus,

$$\frac{dI_j}{dt} = \sigma_{j-1} I_{j-1} - \sigma_j I_j - \mu_j I_j - \delta_j I_j;\ j = 2, ..., n-1,$$

and,

$$\frac{dI_n}{dt} = \sigma_{n-1} I_{n-1} - \sigma_n I_n - \mu_n I_n - \delta_n I_n.$$

The population of recovered individuals is generated following the recovery of individuals in the final stage of infectiousness (at the rate σ_n). It is decreased by the loss of infection-acquired immunity (at the rate θ) and natural death (at a rate μ_R). In other words, this study assumes that infection does not confer lifelong immunity against re-infection (i.e., $\theta \neq 0$). Thus,

$$\frac{dR}{dt} = \sigma_n I_n - \theta R - \mu_R R.$$

Hence, using the above formulation and assumptions, the model for the transmission dynamics of an infectious disease with n infectious stages is given by the following system of non-linear differential equations [69] (a flow diagram of the model is depicted in Figure 3.1; and the associated variables and parameters, together with the estimated values of the parameters, are tabulated in Tables 3.2 and 3.3, respectively):

$$\begin{aligned}
\frac{dS}{dt} &= \pi + \theta R - \sum_{j=1}^{n} \frac{\beta_j I_j}{N} S - \mu_S S, \\
\frac{dE}{dt} &= \sum_{j=1}^{n} \frac{\beta_j I_j}{N} S - \sigma_E E - \mu_E E, \\
\frac{dI_1}{dt} &= \sigma_E E - \sigma_1 I_1 - \mu_1 I_1 - \delta_1 I_1, \\
\frac{dI_j}{dt} &= \sigma_{j-1} I_{j-1} - \sigma_j I_j - \mu_j I_j - \delta_j I_j; \ j = 2, ..., n-1, \\
\frac{dI_n}{dt} &= \sigma_{n-1} I_{n-1} - \sigma_n I_n - \mu_n I_n - \delta_n I_n, \\
\frac{dR}{dt} &= \sigma_n I_n - \theta R - \mu_R R.
\end{aligned} \tag{3.2}$$

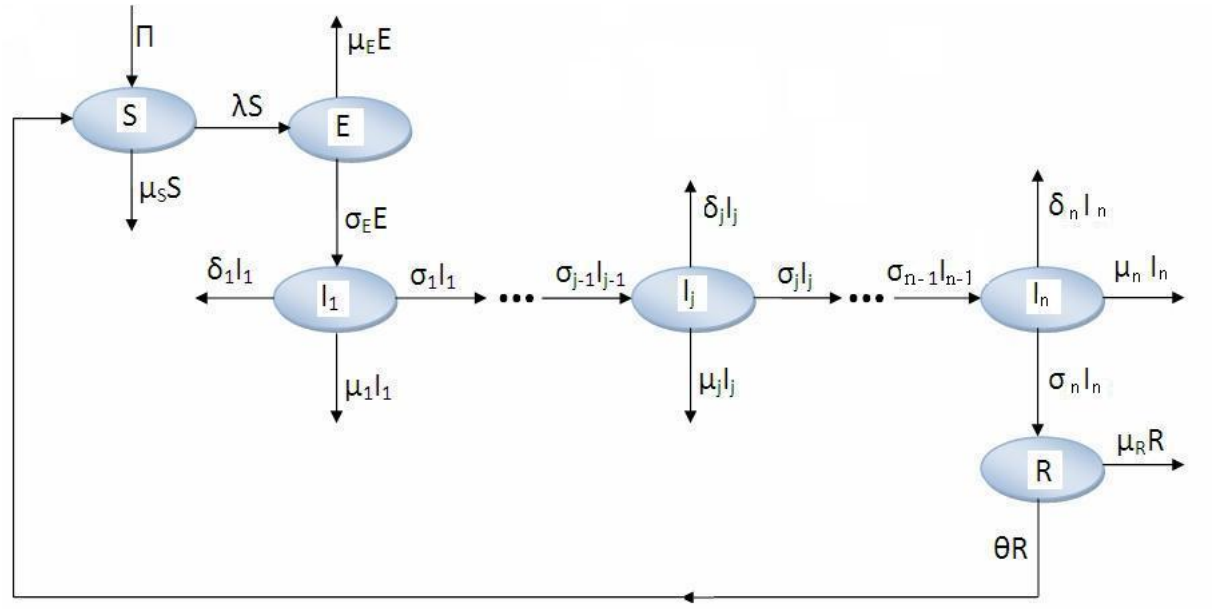

Figure 3.1: Schematic diagram of the SEI^nRS model (3.2)

The model (3.2) extends some of the earlier models in the literature, including the classical SIR Kermarck-Mckendrick model [51, 52] and the models in [16, 59, 60, 61, 77, 97, 98], by

(i) using standard incidence to model the infection rate;

(ii) adding a compartment for exposed individuals;

(ii) adding (n) arbitrary number of infectious stages;

(iv) allowing for the loss of infection-acquired immunity.

Table 3.1: Descriptions of the variables of the SEI^nRS model (3.2)

Variables	Description
S(t)	Susceptible individuals
E(t)	Exposed individuals
$I_i(t)$	Infectious individuals at i^{th} infectious stage $(i = 1, ..., n)$
R(t)	Recovered individuals

Table 3.2: Descriptions of the parameters of the SEI^nRS model (3.2)

Parameter	Description
π	Recruitment rate
μ_S	Natural death rate for susceptible individuals
η_j	Natural death rate for individuals in exposed Stage j (for $j = 1, ..., n$)
μ_i	Natural death rate for individuals in infectious Stage i (for $i = 1, ..., n$)
μ_R	Natural death rate for recovered individuals
γ_j	Progression rate from exposed Stage j to Stage $j+1$ (for $j = 1, ..., n-1$)
γ_n	Progression rate of exposed individuals in Stage n to first infectious stage
σ_i	Progression rate from infectious Stage i to Stage $i+1$ (for $i = 1, ..., n-1$)
σ_n	Recovery rate for infectious individuals in Stage n
δ_i	Disease-induced death rate for infectious individuals in Stage i (for $i = 1, ..., n$)
θ	Rate of loss of infection-acquired immunity

3.2.1 Basic Properties of the Model

Invariant region

Consider the biologically-feasible region

$$\mathcal{D} = \left\{(S, E, I_1, ..., I_n, R) \in \mathbb{R}_+^{n+3} : \ S + E + \sum_{j=1}^{n} I_j + R \leq \frac{\pi}{\mu}\right\},$$

where, $\mu = min\{\mu_S, \ \mu_E, \ \mu_R, \ \mu_j \ (j = 1, ..., n)\}$. Adding the expressions in the right-hand sides of the equations of the model (3.2) gives

$$\begin{aligned}\frac{dN}{dt} &= \pi - \mu_S S - \mu_E E - \sum_{j=1}^{n}(\delta_j + \mu_j)I_j - \mu_R R,\\ &\leq \pi - \mu\left(S + E + \sum_{j=1}^{n} I_j + R\right),\\ &= \pi - \mu N.\end{aligned}$$

Thus, $\frac{dN}{dt} < 0$ if $N > \frac{\pi}{\mu}$. Since $\frac{dN}{dt} \leq \pi - \mu N$, it can also be shown, using a standard comparison theorem [57], that

$$N(t) \leq N(0)e^{-\mu t} + \frac{\pi}{\mu}(1 - e^{-\mu t}).$$

If $N(0) \leq \frac{\pi}{\mu}$, then $N(t) \leq \frac{\pi}{\mu}$. Hence, the set $\mathcal{D}$ is positively-invariant (i.e., all initial solutions in $\mathcal{D}$ remain in $\mathcal{D}$ for all $t > 0$). This result is summarized below.

Lemma 3.1. *The region $\mathcal{D}$ is positively-invariant for the model (3.2) with initial conditions in $\mathbb{R}_+^{n+3}$.*

It is convenient to define the region (the stable manifold of the DFE, $\mathcal{E}_0$)

$$\mathcal{D}_0 = \{(S, E, I_1, ..., I_n, R) \in \mathcal{D} : E = I_1 = \cdots = I_n = R = 0\}.$$

Positivity of solutions

For the basic model (3.2), it is important to prove that all the state variables remain non-negative for all $t > 0$. In other words, the solutions of the model (3.2) with positive initial data will remain positive for all $t > 0$.

Lemma 3.2. *Let the initial data $S(0) \geq 0, E(0) \geq 0, I_1(0) \geq 0, ..., I_i(0) \geq 0, ..., R(0) \geq 0$, for $i = 2, ..., n$. Then, the solutions $(S(t), E(t), I_1(t), ..., I_i(t), ..., I_n(t), R(t))$ ($i = 2, ..., n-1$), of the model (3.2), are non-negative for all $t > 0$.*

Proof. Assume that $t_1 = sup\{t > 0 : S \geq 0, E \geq 0, I_i \geq 0, R \geq 0, i = 1, ..., n\}$. Thus, $t_1 > 0$. It follows, from the first equation of the system (3.2), that

$$\frac{dS}{dt} = \pi + \theta R - [\lambda(t) + \mu_S]S \geq \pi - [\lambda(t) + \mu_S]S(t),$$

which can be re-written as,

$$\frac{d}{dt}\left\{ S(t)exp\left[\mu_S t + \int_0^t \lambda(u)du\right] \right\} \geq \pi exp\left[\mu_S t + \int_0^t \lambda(u)du\right].$$

Hence,

$$S(t_1)exp\left[\mu_S t_1 + \int_0^{t_1} \lambda(u)du\right] - S(0) \geq \int_0^{t_1} \pi exp\left[\mu_S x + \int_0^x \lambda(\xi)d\xi\right] dx,$$

so that,

$$\begin{aligned} S(t_1) &\geq S(0)exp\left\{ -\left[\mu_S t_1 + \int_0^{t_1} \lambda(u)du\right] \right\} \\ &+ exp\left\{ -\left[\mu_S t_1 + \int_0^{t_1} \lambda(u)du\right] \right\} \times \int_0^{t_1} \pi exp\left[\mu_S x + \int_0^x \lambda(\xi)d\xi\right] dx, \\ &> 0. \end{aligned}$$

Similarly, it can be shown that $E(t) > 0, I_i(t) > 0, R(t) > 0$, (with $i = 1, ..., n$) for all $t > 0$. □

The consequence of the above result is that it is sufficient to consider the dynamics of the flow generated by the system (3.2) in the region $\mathcal{D}$, where the model can be considered to be epidemiologically and mathematically well-posed [22, 43].

3.3 Disease-Free Equilibrium

The model (3.2) has a DFE given by

$$\mathcal{E}_0 = (S^*, E^*, I_1^*, ..., I_n^*, R^*) = \left(\frac{\pi}{\mu_S}, 0, 0, ..., 0, 0\right). \tag{3.3}$$

The stability of the DFE, $\mathcal{E}_0$, is studied using the next generation operator method [19, 89]. The associated matrix F (of the new infection terms) and the M-matrix V (of the remaining transfer terms) are given, respectively, by

$$F = \begin{pmatrix} 0 & \beta_1 & \beta_2 & \beta_3 & \beta_4 & \cdots & \beta_n \\ 0 & 0 & 0 & 0 & 0 & \cdots & 0 \\ 0 & 0 & 0 & 0 & 0 & \cdots & 0 \\ 0 & 0 & 0 & 0 & 0 & \cdots & 0 \\ 0 & 0 & 0 & 0 & 0 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 & 0 & \cdots & 0 \end{pmatrix}, V = \begin{pmatrix} k_0 & 0 & 0 & 0 & 0 & \cdots & 0 \\ -\sigma_E & k_1 & 0 & 0 & 0 & \cdots & 0 \\ 0 & -\sigma_1 & k_2 & 0 & 0 & \cdots & 0 \\ 0 & 0 & -\sigma_2 & k_3 & 0 & \cdots & 0 \\ 0 & 0 & 0 & -\sigma_3 & k_4 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \cdots & 0 & -\sigma_{n-1} & k_n \end{pmatrix},$$

where, $k_0 = \sigma_E + \mu_E$, $k_j = \sigma_j + \mu_j + \delta_j$ (for $j = 1, ..., n$) and $k_\theta = \mu_R + \theta$. The associated *basic reproduction number*, denoted by $\mathcal{R}_0^s$, is then given by $\mathcal{R}_0^s = \rho(FV^{-1})$, where ρ is the spectral radius of FV^{-1}. It follows that

$$\mathcal{R}_0^s = \sum_{i=1}^{n} \beta_i \frac{\sigma_E}{k_0} \prod_{j=1}^{i} \frac{\sigma_{j-1}}{k_j}, \ \sigma_0 = 1. \tag{3.4}$$

The result below follows from Theorem 2 of [89] (or Theorem 2.7).

Lemma 3.3. *The DFE, $\mathcal{E}_0$, of the model (3.2), given by (3.3), is locally-asymptotically stable if $\mathcal{R}_0^s < 1$, and unstable if $\mathcal{R}_0^s > 1$.*

The threshold quantity $\mathcal{R}_0^s$ refers to the average number of secondary cases generated by a single infectious individual in a completely susceptible population [4, 43]. Lemma 3.3 shows that if $\mathcal{R}_0^s < 1$, a small influx of infectious individuals into the population will not generate large outbreaks of the disease. For disease elimination to be independent of the initial number of infectious individuals, a global asymptotic

stability property has to be established for the DFE (for the case when $\mathcal{R}_0^s < 1$). This is done below.

3.4 Global Stability of Disease-Free Equilibrium

Theorem 3.1. *The DFE, $\mathcal{E}_0$, of the model (3.2), is globally-asymptotically stable in $\mathcal{D}$ if $\mathcal{R}_0^s \leq 1$.*

Proof. Consider the linear Lyapunov function

$$V = B_0 E + B_1 I_1 + \sum_{j=2}^{n} B_j I_j, \tag{3.5}$$

where,

$$\begin{aligned} B_0 &= \frac{\mathcal{R}_0^s k_n}{\beta_n}, \\ B_1 &= \frac{k_0 B_0}{\sigma_E}, \\ B_j &= \frac{k_n}{\beta_n}\left(\sum_{i=j}^{n} \beta_i \prod_{l=j}^{i} \frac{\sigma_{l-1}}{k_l}\right); \quad \sigma_{p-1} = 1 \text{ for } p = j. \end{aligned} \tag{3.6}$$

It follows from (3.6) that $B_n = 1$. The Lyapunov derivative is given by

$$\dot{V} = B_0 \dot{E} + B_1 \dot{I}_1 + \sum_{j=2}^{n} B_j \dot{I}_j. \tag{3.7}$$

Substituting the expressions for $\dot{E}$ and $\dot{I}_j$ from (3.2) into (3.7) gives

$$\dot{V} = B_0\left(\sum_{j=1}^{n} \frac{\beta_j I_j}{N} S - k_0 E\right) + B_1(\sigma_E E - k_1 I_1) + \sum_{j=2}^{n} B_j(\sigma_{j-1} I_{j-1} - k_j I_j). \tag{3.8}$$

To simplify the algebraic manipulations needed to determine the sign of $\dot{V}$ from (3.7) and (3.8), it is convenient to consider the last two terms of the summation in (3.7)

(using the definitions for B_j; $j = 0, 1, ..., n$ in (3.6), and noting that $B_n = 1$) as follows.

$$\begin{aligned} B_{n-1}\dot{I}_{n-1} + B_n\dot{I}_n &= \underbrace{\frac{k_n}{\beta_n}\left(\frac{\beta_{n-1}}{k_{n-1}} + \frac{\beta_n\sigma_{n-1}}{k_{n-1}k_n}\right)}_{B_{n-1}} \underbrace{(\sigma_{n-2}I_{n-2} - k_{n-1}I_{n-1})}_{\dot{I}_{n-1}} + \underbrace{\sigma_{n-1}I_{n-1} - k_nI_n}_{B_n\dot{I}_n}, \\ &= B_{n-1}\sigma_{n-2}I_{n-2} - \frac{\beta_{n-1}k_n}{\beta_n}I_{n-1} - k_nI_n. \end{aligned}$$

Similarly, combining the result obtained in (3.9) with the third-to-the-last term of the summation in (3.7), and simplifying, gives

$$\begin{aligned} \sum_{j=n-2}^{n} B_j\dot{I}_j &= B_{n-2}\dot{I}_{n-2} + B_{n-1}\dot{I}_{n-1} + B_n\dot{I}_n, \\ &= B_{n-2}\dot{I}_{n-2} + B_{n-1}\sigma_{n-2}I_{n-2} - \frac{\beta_{n-1}k_n}{\beta_n}I_{n-1} - k_nI_n, \\ &= \underbrace{\frac{k_n}{\beta_n}\left(\frac{\beta_{n-2}}{k_{n-2}} + \frac{\beta_{n-1}\sigma_{n-2}}{k_{n-2}k_{n-1}} + \frac{\beta_n\sigma_{n-2}\sigma_{n-1}}{k_{n-2}k_{n-1}k_n}\right)}_{B_{n-2}} \underbrace{(\sigma_{n-3}I_{n-3} - k_{n-2}I_{n-2})}_{\dot{I}_{n-2}}, \\ &+ \underbrace{\frac{k_n}{\beta_n}\left(\frac{\beta_{n-1}}{k_{n-1}} + \frac{\beta_n\sigma_{n-1}}{k_{n-1}k_n}\right)}_{B_{n-1}}\sigma_{n-2}I_{n-2} - \frac{\beta_{n-1}k_n}{\beta_n}I_{n-1} - k_nI_n, \\ &= B_{n-2}\sigma_{n-3}I_{n-3} - \frac{\beta_{n-2}k_n}{\beta_n}I_{n-2} - \frac{\beta_{n-1}k_n}{\beta_n}I_{n-1} - k_nI_n. \end{aligned}$$

Following the same procedure, for $j = 1, ..., n$ (noting that $\dot{I}_1 = \sigma_E E - k_1 I_1$), it can be shown that

$$\sum_{j=1}^{n} B_j\dot{I}_j = B_1\sigma_E E - \sum_{j=1}^{n}\frac{k_n}{\beta_n}\beta_j I_j. \tag{3.9}$$

Using (3.9) in (3.7) gives,

$$\dot{V} = B_0\dot{E} + B_1\sigma_E E - \sum_{j=1}^{n}\frac{k_n}{\beta_n}\beta_j I_j. \tag{3.10}$$

The first two terms in (3.10) can be further simplified to give

$$\begin{aligned} B_0\dot{E} + B_1\sigma_E E &= B_0\left(\sum_{j=1}^{n}\frac{\beta_j I_j}{N}S - k_0 E\right) + B_1\sigma_E E, \\ &= B_0\sum_{j=1}^{n}\frac{\beta_j I_j}{N}S, \text{ since } B_0 = \frac{\sigma_E B_1}{k_0}. \end{aligned} \tag{3.11}$$

Using (3.11) in (3.10) gives

$$\begin{aligned} \dot{V} &= B_0\sum_{j=1}^{n}\frac{\beta_j I_j}{N}S - \sum_{j=1}^{n}\frac{k_n}{\beta_n}\beta_j I_j, \\ &\leq B_0\sum_{j=1}^{n}\beta_j I_j - \sum_{j=1}^{n}\frac{k_n}{\beta_n}\beta_j I_j; \text{ since } S \leq N \text{ in } \mathcal{D}, \\ &= \sum_{j=1}^{n}\frac{k_n}{\beta_n}\beta_j I_j\left(\mathcal{R}_0^s - 1\right); \text{ since } B_0 = \frac{k_n\mathcal{R}_0^s}{\beta_n}, \\ &\leq 0 \quad \text{if } \mathcal{R}_0^s \leq 1. \end{aligned}$$

Therefore, $\dot{V} \leq 0$ if $\mathcal{R}_0^s \leq 1$ and $\dot{V} = 0$ if and only if $E = I_1 = ... = I_n = 0$. Further, substituting $\sum_{i=1}^{n} I_i = 0$ and $I_n = 0$ into the equations for $\dot{S}$ and $\dot{R}$ in (3.2), respectively, shows that $S \to \frac{\pi}{\mu_S}$ and $R(t) \to 0$ as $t \to \infty$. Hence, V is the Lyapunov function in $\mathcal{D}$. It follows, by the Lyapunov function theory and the LaSalle's Invariance Principle [38, 58], that every solution to the equations of the model (3.2), with initial conditions in $\mathcal{D}$, approaches $\mathcal{E}_0$ as $t \to \infty$. Thus, since the region $\mathcal{D}$ is positively-invariant, the DFE ($\mathcal{E}_0$) is GAS in $\mathcal{D}$ if $\mathcal{R}_0^s \leq 1$. □

The epidemiological implication of the above result is that the disease can be eliminated from the community if the threshold quantity, $\mathcal{R}_0^s$, can be brought to (and maintained at) a value less than (or equal to) unity. The result of Theorem 3.1 is illustrated numerically by simulating the model (3.2), with 3 infectious stages (i.e., $n = 3$), using parameter values such that $\mathcal{R}_0^s < 1$ and various initial conditions (Figure 3.2). It should be stated that the parameter values used in the numerical simulations are relevant to the transmission dynamics of a disease that follows the $SEIR$ modeling

structure, such as influenza, and are (mostly) obtained from the literature (see Section 3.8).

3.5 Existence of Endemic Equilibrium Point

Let,

$$\mathcal{E}_1^s = (S^{***}, E^{***}, I_1^{***}, ..., I_n^{***}, R^{***}), \tag{3.12}$$

represents any arbitrary endemic (positive) equilibrium of the model (3.2) (i.e., an equilibrium where one of the infected components of the model are non-zero). Further, let

$$\lambda^{***} = \sum_{i=1}^{n} \frac{\beta_i I_i^{***}}{N^{***}}, \tag{3.13}$$

be the associated force of infection at endemic steady-state. Solving the right-hand sides of the equations in (3.2) at steady-state gives

$$\begin{aligned} \pi - \mu_S S^{***} + \theta R^{***} &= \lambda^{***} S^{***}, \\ E^{***} &= \frac{1}{k_0}\lambda^{***} S^{***} = c_0 \lambda^{***} S^{***}, \\ I_i^{***} &= c_i \lambda^{***} S^{***};\ i = 1, ..., n, \\ R^{***} &= c_{n+1} \lambda^{***} S^{***}, \end{aligned} \tag{3.14}$$

where,

$$c_i = \frac{\sigma_E}{k_0} \prod_{j=1}^{i} \frac{\sigma_{j-1}}{k_j},\ i = 1, ..., n+1,\ \sigma_0 = 1,\ k_{n+1} = k_\theta. \tag{3.15}$$

Using the expressions in (3.14) into (3.13), and simplifying (noting that $N^{***} = S^{***} + E^{***} + \sum_{i=1}^{n} I_i^{***} + R^{***}$), gives

$$1 + \lambda^{***} \sum_{i=0}^{n+1} c_i \;\; = \;\; \sum_{i=1}^{n} \beta_i c_i, \tag{3.16}$$

so that,

$$\lambda^{***} = \frac{\mathcal{R}_0^s - 1}{\sum_{i=0}^{n+1} c_i}. \tag{3.17}$$

It should be stated that the following relation (obtained by substituting the expression for c_i from (3.15) into (3.16))

$$\sum_{i=1}^{n} \beta_i c_i = \sum_{i=1}^{n} \beta_i \frac{\sigma_E}{k_0} \prod_{j=1}^{i} \frac{\sigma_{j-1}}{k_j} = \mathcal{R}_0^s, \text{ with } \sigma_0 = 1,$$

has been used in (3.17). It follows from (3.17) that $\lambda^{***} > 0$ if $\mathcal{R}_0^s > 1$. Thus, the model (3.2) has a unique endemic equilibrium if $\mathcal{R}_0^s > 1$ (the components of this equilibrium are obtained by substituting the value of λ^{***}, obtained from equation (3.17), into the expressions in (3.14)). The model has no positive equilibrium if $\mathcal{R}_0^s < 1$ (since, in this case, $\lambda^{***} < 0$ in (3.17), which is epidemiologically meaningless). Furthermore, if $\mathcal{R}_0^s = 1$, then $\lambda^{***} = 0$ in (3.17) (which corresponds to the DFE, $\mathcal{E}_0$; in other words, the epidemic equilibrium collapses to the DFE when $\mathcal{R}_0^s = 1$). This result is summarized below.

Theorem 3.2. *The model (3.2) has a unique endemic equilibrium, given by $\mathcal{E}_1^s$, whenever $\mathcal{R}_0^s > 1$, and no endemic equilibrium otherwise.*

3.6 Stability of Endemic Equilibrium: Special Case

The local asymptotic stability of the EEP, $\mathcal{E}_1^s$, is explored for a special case, where the disease-induced mortality rates ($\delta_i;\ i = 1, ..., n$) are assumed to be negligible, and are set to zero, and the natural mortality rates are assumed to be equal for all epidemiological classes (i.e., $\mu_S = \mu_E = \mu_R = \mu_i\ (i = 1, ..., n) = \mu$). Thus, under this setting (with $\delta_i = 0;\ i = 1, ..., n$ and $\mu_S = \mu_E = \mu_R = \mu_i\ (i = 1, ..., n) = \mu$), the rate of change of the total population of the model (3.2) becomes $\frac{dN}{dt} = \pi - \mu N$. Hence, $N(t) \to \frac{\pi}{\mu} = N^{**}$ as $t \to \infty$. Substituting $N = N^{**}$ in (3.1) gives

$$\hat{\lambda} = \lambda \mid_{N=N^{**}} = \sum_{i=1}^{n} \frac{\beta_i I_i}{N^{**}}. \tag{3.18}$$

Furthermore, it can be shown that the model (3.2) with $\delta_i = 0\ (i = 1, ..., n)$, $\mu_S = \mu_E = \mu_R = \mu_i\ (i = 1, ..., n) = \mu$ and $\hat{\lambda}$ as given in (3.18), has the associated reproduction number (noting that $S^* = N^{**} = \frac{\pi}{\mu}$), given by

$$\mathcal{R}_0^m = \sum_{i=1}^{n} \beta_i \frac{\sigma_E}{k_0} \prod_{j=1}^{i} \frac{\sigma_{j-1}}{kj},\ \sigma_0 = 1, \tag{3.19}$$

where, now, $k_0 = \sigma_E + \mu$ and $k_j = \sigma_j + \mu\ (j = 1, ..., n)$. Additionally, it can be shown that the model (3.2), under the above setting, has a unique endemic equilibrium, denoted by $\mathcal{E}_1^m$, where

$$\mathcal{E}_1^m = (S^{**}, E^{**}, I_1^{**}, ..., I_n^{**}, R^{**}),$$

whenever $\mathcal{R}_0^m > 1$. It follows from the expression $N = N^{**}$ that

$$S = N^{**} - E - \sum_{i=1}^{n} I_i - R. \tag{3.20}$$

Substituting (3.20) with (3.18) into the system (3.2) gives the following reduced system

$$\begin{aligned}
\dot{E} &= \hat{\lambda}(N^{**} - E - \sum_{i=1}^{n} I_i - R) - k_0 E, \\
\dot{I}_1 &= \sigma_E E - k_1 I_1, \\
\dot{I}_2 &= \sigma_1 I_1 - k_2 I_2, \\
\dot{I}_j &= \sigma_{j-1} I_{j-1} - k_j I_j;\ j = 3, ..., n-1, \\
\dot{I}_n &= \sigma_{n-1} I_{n-1} - k_n I_n, \\
\dot{R} &= \sigma_n I_n - k_\theta R,
\end{aligned} \tag{3.21}$$

where, now, $k_\theta = \mu + \theta$.

Theorem 3.3. *The unique endemic equilibrium of the reduced model (3.21), given by* $\mathcal{E}_1^m = (E^{**}, I_1^{**}, ..., I_n^{**}, R^{**})$, *is LAS whenever* $\mathcal{R}_0^m > 1$.

The proof of Theorem 3.3, based on using a Krasnoselskii sub-linearity trick [44] (see also [23, 24]), is given in Appendix A.

3.7 Global Stability of Endemic Equilibrium: Special Case

As in the case of the local stability proof, the global stability property of the endemic equilibrium, $\mathcal{E}_1^m$, is explored for the special case with $\delta_i = 0$ $(i = 1, ..., n)$, $\mu_S = \mu_E = \mu_R = \mu_i$ $(i = 1, ..., n) = \mu$ and $\hat{\lambda}$ as defined in (3.18). Let, for convenience, $\beta_i' = \frac{\beta_i}{N^{**}} = \frac{\beta_i \mu}{\pi}$ $(i = 1, ..., n)$. Hence, the equation (3.18) now becomes

$$\hat{\lambda} = \sum_{i=1}^{n} \beta_i' I_i. \tag{3.22}$$

Theorem 3.4. *The unique EEP,* $\mathcal{E}_1^m$, *of the reduced model (3.2) with* $\hat{\lambda}$ *defined by (3.22), is GAS in* $\mathcal{D} \backslash \mathcal{D}_0$ *whenever* $\mathcal{R}_0^m > 1$ *and* $2 - \frac{E}{E^{**}} - \frac{E^{**}R}{ER^{**}} - \frac{S^{**}}{S} + \frac{S^{**}R}{SR^{**}} \geq 0$.

Proof. Let $\mathcal{R}_0^m > 1$ (so that the EEP, $\mathcal{E}_1^m$, exists). Further, let $2-\frac{E}{E^{**}}-\frac{E^{**}R}{ER^{**}}-\frac{S^{**}}{S}+\frac{S^{**}R}{SR^{**}} \geq 0$. Consider the following Lyapunov function, of Goh-Volterra type (functions of this type have been used in the mathematical ecology/epidemiology literature, such as in [12, 29, 33, 36, 54, 55, 56]),

$$\begin{aligned} V &= S - S^{**} - S^{**}ln\frac{S}{S^{**}} + E - E^{**} - E^{**}ln\frac{E}{E^{**}} \\ &+ \sum_{i=1}^{n} a_i \left(I_i - I_i^{**} - I_i^{**}ln\frac{I_i}{I_i^{**}} \right) + b\left(R - R^{**} - R^{**}ln\frac{R}{R^{**}} \right), \end{aligned}$$

where the coefficients a_i $(i = 1, ..., n)$ and b are positive constants to be determined. Thus,

$$\dot{V} = \left(1 - \frac{S^{**}}{S}\right)\dot{S} + \left(1 - \frac{E^{**}}{E}\right)\dot{E} + \sum_{i=1}^{n} a_i \left(1 - \frac{I_i^{**}}{I_i}\right)\dot{I}_i + b\left(1 - \frac{R^{**}}{R}\right)\dot{R}. \quad (3.23)$$

Substituting the expressions of the derivatives from system (3.2), using (3.22), gives (it should be noted that the relation $\pi = \mu S^{**} + S^{**}\sum_{i=1}^{n}\beta_i' I_i^{**} - \theta R^{**}$, at endemic steady-state, has been used)

$$\begin{aligned} \dot{V} &= \left(1 - \frac{S^{**}}{S}\right)\left(\mu S^{**} + S^{**}\sum_{i=1}^{n}\beta_i' I_i^{**} - \theta R^{**} - S\sum_{i=1}^{n}\beta_i' I_i - \mu S + \theta R\right) \\ &+ a_1\left(\sigma_E E - k_1 I_1 - \sigma_E \frac{I_1^{**}}{I_1}E + k_1 I_1^{**}\right) \\ &+ \sum_{i=2}^{n} a_i\left(\sigma_{i-1} I_{i-1} - k_i I_i - \sigma_{i-1}\frac{I_i^{**}}{I_i}I_{i-1} + k_i I_i^{**}\right) \\ &+ b\left(\sigma_n I_n - k_\theta R - \sigma_n I_n \frac{R^{**}}{R} + k_\theta R^{**}\right) \\ &+ \sum_{i=1}^{n}\beta_i' I_i S - k_0 E - \frac{E^{**}}{E}S\sum_{i=1}^{n}\beta_i' I_i + k_0 E^{**}, \end{aligned} \quad (3.24)$$

which can be simplified to:

$$\begin{aligned}\dot{V} &= \mu S^{**}\left(2-\frac{S}{S^{**}}-\frac{S^{**}}{S}\right)+\left[S^{**}\sum_{i=1}^{n}\beta_i' I_i^{**}-\frac{(S^{**})^2}{S}\sum_{i=1}^{n}\beta_i' I_i^{**}+S^{**}\sum_{i=1}^{n}\beta_i' I_i\right]\\ &- \theta R^{**}\left(1-\frac{R}{R^{**}}-\frac{S^{**}}{S}+\frac{S^{**}R}{SR^{**}}\right)+a_1\left(\sigma_E E-k_1 I_1-\sigma_E\frac{I_1^{**}}{I_1}E+k_1 I_1^{**}\right) \qquad (3.25)\\ &+ \sum_{i=2}^{n}a_i\left(\sigma_{i-1}I_{i-1}-k_i I_i-\sigma_{i-1}\frac{I_i^{**}}{I_i}I_{i-1}+k_i I_i^{**}\right)+b\left(\sigma_n I_n-k_\theta R-\sigma_n I_n\frac{R^{**}}{R}+k_\theta R^{**}\right)\\ &- k_0 E-\frac{E^{**}}{E}S\sum_{i=1}^{n}\beta_i' I_i+k_0 E^{**}.\end{aligned}$$

Using the coefficients,

$$\begin{aligned} b &= \frac{\theta}{k_\theta},\\ a_i &= \sum_{j=i}^{n}S^{**}\frac{\beta_j' I_j^{**}}{k_i I_i^{**}}+\frac{\theta R^{**}}{k_i I_i^{**}},\ i=1,...,n, \qquad (3.26)\end{aligned}$$

in (3.25), and simplifying, gives

$$\begin{aligned}\dot{V} &= \mu S^{**}\left(2-\frac{S}{S^{**}}-\frac{S^{**}}{S}\right)-\theta R^{**}\left(1-\frac{E}{E^{**}}-\frac{S^{**}}{S}+\frac{S^{**}R}{SR^{**}}\right)\\ &+ S^{**}\beta_1' I_1^{**}\left(3-\frac{S^{**}}{S}-\frac{E^{**}SI_1}{ES^{**}I_1^{**}}-\frac{I_1^{**}E}{E^{**}I_1}\right)\\ &+ \sum_{i=2}^{n}S^{**}\beta_i' I_i^{**}\left(i+2-\frac{S^{**}}{S}-\frac{E^{**}SI_i}{ES^{**}I_i^{**}}-\frac{I_1^{**}E}{E^{**}I_1}-\sum_{j=2}^{i}\frac{I_j^{**}I_{j-1}}{I_jI_{j-1}^{**}}\right)\\ &+ \theta R^{**}\left(n+1-\frac{I_1^{**}E}{I_1E^{**}}-\frac{I_nR^{**}}{I_n^{**}R}-\sum_{j=2}^{n}\frac{I_j^{**}I_{j-1}}{I_jI_{j-1}^{**}}\right),\end{aligned}$$

so that,

$$\begin{aligned}
\dot{V} &= \mu S^{**}\left(2-\frac{S}{S^{**}}-\frac{S^{**}}{S}\right)-\theta R^{**}\left(2-\frac{E}{E^{**}}-\frac{E^{**}R}{ER^{**}}-\frac{S^{**}}{S}+\frac{S^{**}R}{SR^{**}}\right)\\
&+ S^{**}\beta_1' I_1^{**}\left(3-\frac{S^{**}}{S}-\frac{E^{**}SI_1}{ES^{**}I_1^{**}}-\frac{I_1^{**}E}{E^{**}I_1}\right)\\
&+ \sum_{i=2}^{n} S^{**}\beta_i' I_i^{**}\left(i+2-\frac{S^{**}}{S}-\frac{E^{**}SI_i}{ES^{**}I_i^{**}}-\frac{I_1^{**}E}{E^{**}I_1}-\sum_{j=2}^{i}\frac{I_j^{**}I_{j-1}}{I_jI_{j-1}^{**}}\right)\\
&+ \theta R^{**}\left(n+2-\frac{E^{**}R}{ER^{**}}-\frac{I_1^{**}E}{I_1E^{**}}-\frac{I_nR^{**}}{I_n^{**}R}-\sum_{j=2}^{n}\frac{I_j^{**}I_{j-1}}{I_jI_{j-1}^{**}}\right).
\end{aligned} \tag{3.27}$$

Since the arithmetic mean exceeds the geometric mean, the following inequalities hold:

$$\begin{aligned}
2-\frac{S}{S^{**}}-\frac{S^{**}}{S} &\leq 0,\\
3-\frac{S^{**}}{S}-\frac{E^{**}SI_1}{ES^{**}I_1^{**}}-\frac{I_1^{**}E}{E^{**}I_1} &\leq 0,\\
i+2-\frac{S^{**}}{S}-\frac{E^{**}SI_i}{ES^{**}I_i^{**}}-\frac{I_1^{**}E}{E^{**}I_1}-\sum_{j=2}^{i}\frac{I_j^{**}I_{j-1}}{I_jI_{j-1}^{**}} &\leq 0,\\
n+2-\frac{E^{**}R}{ER^{**}}-\frac{I_1^{**}E}{I_1E^{**}}-\frac{I_nR^{**}}{I_n^{**}R}-\sum_{j=2}^{n}\frac{I_j^{**}I_{j-1}}{I_jI_{j-1}^{**}} &\leq 0.
\end{aligned} \tag{3.28}$$

Hence, using (3.28) and noting that $2-\frac{E}{E^{**}}-\frac{E^{**}R}{ER^{**}}-\frac{S^{**}}{S}+\frac{S^{**}R}{SR^{**}}\geq 0$ (from the hypothesis of Theorem 3.4), it follows from (3.27) that $\dot{V}\leq 0$. Thus, by the Lyapunov function theory and the LaSalle's Invariance Principle [38, 58], every solution to the equation in the model (3.2), with (3.22), approaches the unique endemic equilibrium, $\mathcal{E}_1^m$, as $t\longrightarrow\infty$ for $\mathcal{R}_0^m>1$ and $2-\frac{E}{E^{**}}-\frac{E^{**}R}{ER^{**}}-\frac{S^{**}}{S}+\frac{S^{**}R}{SR^{**}}\geq 0$.

□

It is worth noting that the additional condition $(2-\frac{E}{E^{**}}-\frac{E^{**}R}{ER^{**}}-\frac{S^{**}}{S}+\frac{S^{**}R}{SR^{**}})\geq 0$ is not necessary (or needed) if the disease confers permanent immunity against re-infection (since, in this case, $\theta=0$, and the second term of (3.27) vanishes).

3.8 Numerical Simulations and Conclusions

The average incubation period of influenza is 1.9 days, so that $\frac{1}{\sigma_E} = 1.9$ days [17, 21, 40, 64, 67, 72]. Similarly, the average infectious period is 5 days [67, 72]. Since the numerical simulations in this chapter are based on the model (3.2) with 3 infectious stages (i.e., $n = 3$), the infectious period ($\frac{1}{\sigma_i}$; $i = 1, ..., 3$) is distributed such that the sum $\frac{1}{\sigma_1} + \frac{1}{\sigma_2} + \frac{1}{\sigma_3}$ equals the mean duration of 5 days. Consequently, the following values are used (arbitrarily): $\frac{1}{\sigma_1} = 2.25$ days, $\frac{1}{\sigma_2} = 1.5$ days and $\frac{1}{\sigma_3} = 1.25$ days.

Furthermore, since the infectiousness of influenza is highest after the onset of symptoms and declines thereafter geometrically [21], it is plausible to distribute the transmission rates (β_i; $i = 1, 2, 3$) such that $\beta_1 > \beta_2 > \beta_3$ [21]. The values $\beta_1 = 0.48, \beta_2 = 0.33$ and $\beta_3 = 0.24$ *per* day are chosen arbitrarily. However, in order to achieve convergence to the DFE ($\mathcal{E}_0$), the aforementioned values for β_i have to be reduced (for instance, to $\beta_1 = 0.24, \beta_1 = 0.15$ and $\beta_1 = 0.02$ *per* day, as in Figure 3.2). The average mortality rates (δ_i; $i = 1, 2, 3$) range between 0.0062 to 0.035 *per* day [72]. Since the average mortality rate of any typical disease is expected to decrease with decreasing infectiousness [21], we choose $\delta_1 = 0.035$, $\delta_2 = 0.015$ and $\delta_3 = 0.0062$ per day. The natural death rate in all classes ($\mu_S = \mu_E = \mu_R = \mu_i$; $i = 1, 2, 3$) is estimated as $\frac{1}{60\times365}$ *per* day (corresponding to an average lifespan of 60 years) [17].

The rate of loss of the infection-acquired immunity (θ) is assumed to be 0.012 *per* day, and the recruitment rate, π, is set at $\pi = 7.976$ *per* day [17] (obtained from the product of the total population considered and assumed natural death rate). Simulations are carried out for a time period of 100 days, and the results obtained, together with the corresponding $\mathcal{R}_0^s$ value, is depicted in Figure 3.2. Table 3.3 summarizes the parameter values used in the numerical simulations.

Further, numerical simulations of the model (3.2) for the case $m = 3$, using the parameter values in Table 3.3 (but with $\delta_i = 0$; $i = 1, 2, 3$ and $\beta_1 = 0.48$, $\beta_2 = 0.33$

and $\beta_3 = 0.24$; so that, $\mathcal{R}_0^m = 1.87$) and various initial conditions are carried out. The results obtained, depicted in Figure 3.3, show convergence to the unique EEP, $\mathcal{E}_1^m$ (in line with Theorem 3.4). Additional (extensive) numerical simulations (for the case $\mathcal{R}_0^s > 1$) suggest the following conjecture.

Conjecture 3.1. *The endemic equilibrium of the model (3.2), given by $\mathcal{E}_1^s$, is GAS in $\mathcal{D}\backslash\mathcal{D}_0$ whenever $\mathcal{R}_0^s > 1$.*

Conclusions

An $SEIRS$ deterministic model, for the transmission dynamics of an arbitrary disease with multiple infectious stages, is designed and rigourously analysed in this chapter. The new model uses a standard incidence function for the infection rate and allows for the loss of infection-acquired immunity. Some of the main findings of this chapter are summarized below:

(i) The model has a globally-asymptotically stable disease-free equilibrium whenever the associated reproduction number $\mathcal{R}_0^s$ is less than unity (Theorem 3.1);

(ii) The model has a unique endemic equilibrium, which is locally-asymptotically stable, for a special case, whenever the associated reproduction number ($\mathcal{R}_0^m$) exceeds unity (Theorems 3.2 and 3.3). The endemic equilibrium is shown to be locally- and globally-asymptotically stable for special cases (Theorems 3.3 and 3.4).

The analyses in this chapter show that the disease being considered can be eliminated from the population whenever the associated reproduction number ($\mathcal{R}_0^s$) is brought to (and maintained at) a value less than unity and the disease will persist in the community whenever the reproduction number exceeds unity. Furthermore, it is shown that adding multiple infectious stages, standard incidence and the loss of

infection-acquired immunity to the classical $SEIR$ model (with mass action incidence) does not alter the main qualitative (equilibrium) dynamics of the classical $SEIR$ model (with respect to the persistence or elimination of the disease).

Table 3.3: Parameter values for the SEI^nRS model (3.2)

Parameter	Description	Value	References
π	Recruitment rate	7.976 *per* day	[17]
$\frac{1}{\sigma_E}$	Average latency period	1.9 days	[17, 21, 40, 64, 67, 72]
$\frac{1}{\sigma_i}$ $(i = 1, 2, 3)$	Average duration of infectiousness (This is split as follows: $\frac{1}{\sigma_1} = 2.25$, $\frac{1}{\sigma_2} = 1.5$, $\frac{1}{\sigma_3} = 1.25$)	5 days	[21, 67, 72]
δ_i $(i = 1, 2, 3)$	Disease-induced death rate of infectious individuals (δ_i is split as follows: $\delta_1 = 0.35$, $\delta_2 = 0.015$, and $\delta_3 = 0.0062$)	0.0062-0.035 *per* day	[72]
$\mu_S, \mu_E, \mu_R, \mu_i$ $(i = 1, 2, 3)$	Natural death rate	$\frac{1}{60\times365}$ *per* day	[17]
θ	Rate of loss of infection-acquired immunity	0.012 *per* day	Assumed
β_i $(i = 1, 2, 3)$	Transmission rates	$[0.02 - 0.48]$ *per* day	Assumed

* The number of infectious stages is chosen to be 3 (i.e., $n = 3$) for the simulations.

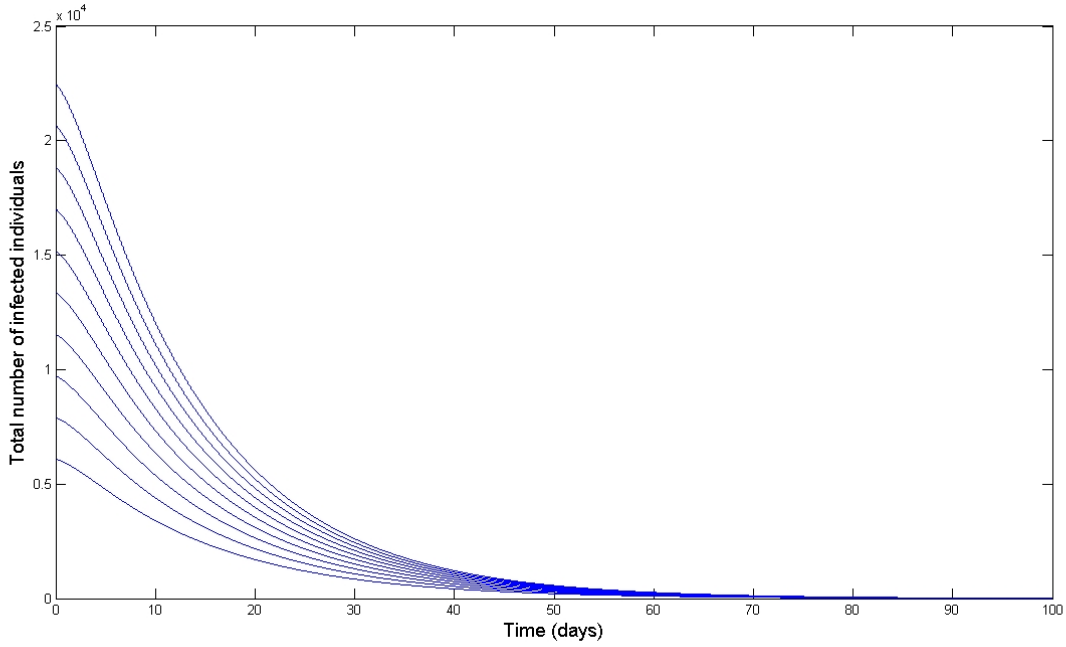

Figure 3.2: Simulations of the model (3.2) with $n = 3$, using the parameter values given in Table 3.3, with $\beta_1 = 0.24$, $\beta_2 = 0.15$ and $\beta_3 = 0.02$ *per* day (so that, $\mathcal{R}_0^s = 0.73$), and various initial conditions.

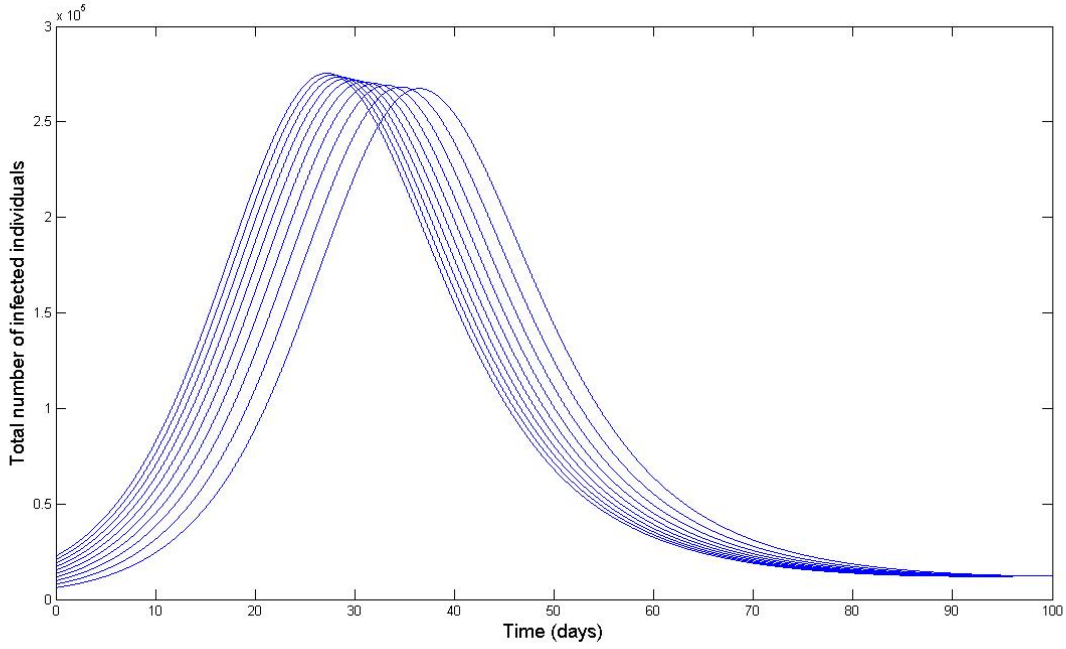

Figure 3.3: Simulations of the model (3.2)) with $n = 3$, using the parameter values given in Table 3.3, with $\delta_i = 0\,(i = 1, 2, 3)$ and $\beta_1 = 0.48$, $\beta_2 = 0.33$, $\beta_3 = 0.24$ *per* day (so that, $\mathcal{R}_0^m = 1.87$), and various initial conditions.

Chapter 4

Autonomous SE^mI^nRS Model

4.1 Introduction

In this chapter, the model developed in Chapter 3 is extended to incorporate m latent classes (in addition to the n infectious stages). The resulting SE^mI^nRS class of models, to be constructed in this chapter, may be applicable to the transmission dynamics of some diseases, such as influenza [21]. Another important feature of the new (autonomous) SE^mI^nRS model to be developed in this chapter is that it uses gamma distribution, rather than exponential distribution, to model the mean waiting times in the latent and infectious classes. Gamma distributions are shown to be more realistic, than exponential distributions, for modelling diseases with multiple infection stages [26, 92]. Eichner *et al.* [21] developed a numerical simulation software, for monitoring the transmission dynamics of pandemic influenza, using an SE^mI^nR model with mass action incidence (but no rigorous mathematical analysis is presented in [21]). In summary, the purpose of this chapter is to:

(i) extend the autonomous SEI^nRS model developed in Chapter 3 by including m compartments for latently-infected individuals, and use gamma distribution assumptions for the average waiting times in the latent and infectious classes;

(ii) carry out rigorous qualitative analyses of the resulting autonomous SE^mI^nRS model.

The main objective is to determine whether or not adding multiple latent stages (and gamma distribution assumption) alters the qualitative dynamics of the SEI^nRS model considered in Chapter 3.

4.2 Formulation of the Model

The SEI^nRS model to be considered is the same as that in Chapter 3, except for the addition of m exposed classes as described below. The total human population at time t, denoted by $N(t)$, is sub-divided into four disjoint classes of susceptible ($S(t)$), exposed ($E_j(t)$; with m latent stages), infectious ($I(t)$; with n infectious stages) and recovered ($R(t)$) humans, so that

$$N(t) = S(t) + \sum_{j=1}^{m} E_j(t) + \sum_{i=1}^{n} I_i(t) + R(t).$$

Furthermore, the effective contact with infectious individuals (in any of the n infectious stages) at a rate of λ, is given by

$$\lambda = \sum_{i=1}^{n} \frac{\beta_i I_i}{N}. \tag{4.1}$$

In (4.1), β_i ($i = 1, ..., n$) is the effective contact rate. It is assumed, for mathematical convenience, that exposed individuals (in the E_j class; with $j = 1, ..., m$) do not transmit infection. Hence, the population of exposed individuals in Stage 1 (of exposure status) is generated following the infection of susceptible individuals (at the rate λ). It is decreased by progression (at a rate of γ_1) into the second exposed exposed class (E_2) and natural death (at a rate η_1). Thus,

$$\frac{dE_1}{dt} = \lambda S - \gamma_1 E_1 - \eta_1 E_1. \tag{4.2}$$

In a similar way, the population of exposed individuals in Stage j of exposure (with $2 \leq j \leq m-1$) is generated by the progression of individuals in exposed Stage $j-1$ (at a rate γ_{j-1}) and is decreased by progression into the $(j+1)^{th}$ exposed stage (E_{j+1}; at a rate γ_j) and natural death (at a rate η_j). Hence,

$$\frac{dE_j}{dt} = \gamma_{j-1}E_{j-1} - \gamma_j E_j - \eta_j E_j;\ j = 2, 3, ..., m-1. \tag{4.3}$$

The population of individuals in the last exposed class (E_m) is generated by the progression of exposed individuals in Stage $m-1$ (in the E_{m-1} classes; at the rate γ_{m-1}) and is decreased by the progression to infectious class (I_1) (at a rate γ_m) and natural death (at a rate of η_m). Hence,

$$\frac{dE_m}{dt} = \gamma_{m-1}E_{m-1} - \gamma_m E_m - \eta_m E_m. \tag{4.4}$$

The population of infectious individuals in Stage 1 (I_1) is generated when individuals in Stage m of exposure (those in the E_m class) develop symptoms (at the rate γ_m). It is decreased by progression to the next infectious stage (I_2; at a rate σ_1), natural death (at a rate μ_1) and disease-induced death (at a rate δ_1). Hence,

$$\frac{dI_1}{dt} = \gamma_m E_m - \sigma_1 I_1 - \mu_1 I_1 - \delta_1 I_1. \tag{4.5}$$

Similarly, the population of infectious individuals in Stage i (with $2 \leq i \leq n-1$) is generated by the progression of infectious individuals in Stage I_{i-1} to Stage I_i (at a rate σ_{i-1}). It is decreased by progression to the next infectious stage (I_{i+1}; at a rate σ_i), natural death (at a rate μ_i) and disease-induced death (at a rate δ_i). Individuals in the final (n) stage of infectiousness recover (at a rate σ_n) and also decreased by natural

death (at a rate μ_n) and disease-induced death (at a rate δ_n). Thus,

$$\frac{dI_i}{dt} = \sigma_{i-1}I_{i-1} - \sigma_i I_i - \mu_i I_i - \delta_i I_i;\ i = 2, ..., n. \tag{4.6}$$

4.2.1 Gamma Distribution

Some studies (such as those in [26, 92, 95]) have emphasized the suitability of using gamma distribution assumptions, over exponential distribution assumptions, in modelling the average waiting time in the latent and infectious classes (for some epidemiological settings). In line with the studies reported in [26, 92, 95], gamma distribution assumptions will be made for the average waiting time in the latent and infectious stages. To achieve this objective, it is assumed, first of all, that the distribution of the exposed and infectious periods are exponential, and are given, respectively, by (see also [26]),

$$\begin{aligned} p_{E_j} &= a_j \alpha e^{-a_j \alpha s},\ \text{for } j = 1, ..., m, \\ p_{I_i} &= b_i \kappa e^{-b_i \kappa s},\ \text{for } i = 1, ..., n, \end{aligned} \tag{4.7}$$

where,

$$\gamma_j = a_j \alpha,\ \text{for } j = 1, ..., m,$$

and,

$$\sigma_i = b_i \kappa,\ \text{for } i = 1, ..., n.$$

Hence, the mean exposed and infectious periods in (4.7) are given by $T_{E_j} = \frac{1}{a_j\alpha}$ and $T_{I_i} = \frac{1}{b_i\kappa}$, respectively (for $j = 1, ..., m$ and $i = 1, ..., n$). In other words, the mean time for all exposed stages is given by

$$\sum_{j=1}^{m} \frac{1}{a_j\alpha} = \frac{1}{\alpha}.$$

Similarly, the mean time for all infectious stages is given by

$$\sum_{i=1}^{n} \frac{1}{b_i\kappa} = \frac{1}{\kappa}.$$

This implies that the mean time spent in a respective exposed and infectious compartment is $\frac{1}{\alpha}$ and $\frac{1}{\kappa}$, respectively; and these times ($\frac{1}{\alpha}$ and $\frac{1}{\kappa}$) are shared among the j^{th} and i^{th} stages of the exposed and infectious compartments, respectively.

Let,

$$E = \sum_{j=1}^{m} \frac{a_j E_j}{m}, \tag{4.8}$$

and,

$$I = \sum_{i=1}^{n} \frac{b_i I_i}{n}. \tag{4.9}$$

It follows from (4.8) and (4.9) (and using the property of gamma distribution [45]), that the quantities E and I indeed have gamma distributions, given by

$$P_E(s) = \frac{(m\alpha)^m e^{-m\alpha s} s^{m-1}}{\Gamma(m)},\ m \geq 1,\ s > 0;$$

$$P_I(s) = \frac{(n\alpha)^n e^{-n\kappa s} s^{n-1}}{\Gamma(n)},\ n \geq 1,\ s > 0,$$

where the exposed and infectious periods are given, respectively, by $T_E = \frac{1}{\alpha}$ and $T_I = \frac{1}{\kappa}$

(see also [26, 95]). Hence, in this chapter, it is assumed that the mean time in the m exposed (E) and n infectious (I) stages is given by $\frac{1}{\alpha}$ and $\frac{1}{\kappa}$, respectively (and these mean periods are distributed, either equally or unequally, among the various respective stages). It should be mentioned that these mean periods are equally distributed among the latent and infectious stages in [26].

In summary, by combining the model (3.2) with the new definitions for $\dot{E}_j$ ($j = 1, ..., m$) in (4.2), (4.3), (4.4) and (4.6), it follows that the autonomous SE^mI^nRS model (which uses gamma distribution assumptions to model the average waiting times in the exposed and infectious stages) for the transmission dynamics of a disease in a population is given by the following system of non-linear differential equations (a flow diagram of the model is depicted in Figure 4.1; and the associated variables and parameters are tabulated in Tables 4.1 and 4.2).

$$\begin{aligned}
\frac{dS}{dt} &= \pi + \theta R - \sum_{i=1}^{n} \frac{\beta_i I_i}{N} S - \mu_S S, \\
\frac{dE_1}{dt} &= \sum_{i=1}^{n} \frac{\beta_i I_i}{N} S - \gamma_1 E_1 - \eta_1 E_1, \\
\frac{dE_j}{dt} &= \gamma_{j-1} E_{j-1} - \gamma_j E_j - \eta_j E_j; \ j = 2, ..., m, \\
\frac{dI_1}{dt} &= \gamma_m E_m - \sigma_1 I_1 - \mu_1 I_1 - \delta_1 I_1, \\
\frac{dI_i}{dt} &= \sigma_{i-1} I_{i-1} - \sigma_i I_i - \mu_i I_i - \delta_i I_i; \ i = 2, ..., n, \\
\frac{dR}{dt} &= \sigma_n I_n - \theta R - \mu_R R.
\end{aligned} \tag{4.10}$$

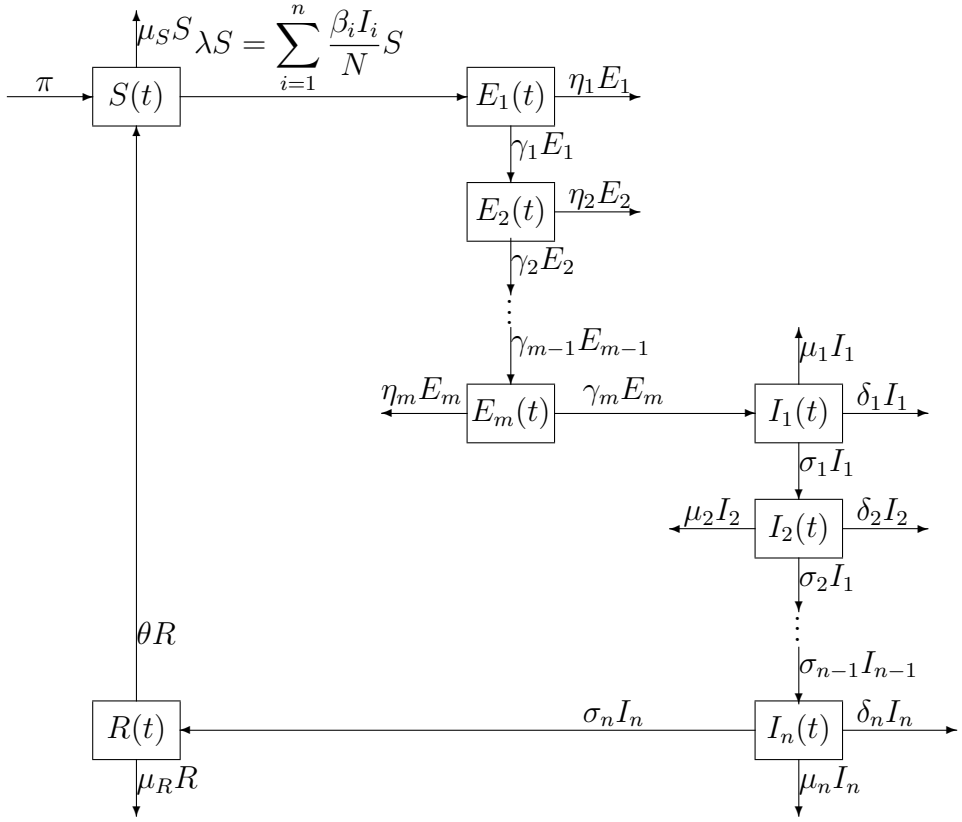

Figure 4.1: Schematic diagram of the SE^mI^nRS model (4.10).

Table 4.1: Descriptions of the variables of the SE^mI^nRS model (4.10)

Variables	Description
$S(t)$	Susceptible individuals
$E_j(t)$	Exposed individuals at j^{th} exposed stage $(j = 1, ..., m)$
$I_i(t)$	Infectious individuals at i^{th} infectious stage $(i = 1, ..., n)$
$R(t)$	Recovered individuals

Table 4.2: Descriptions of the parameters of the SE^mI^nRS model (4.10)

Parameter	Description
π	Recruitment rate
μ_S	Natural death rate for susceptible individuals
η_j	Natural death rate for individuals in exposed Stage j (for $j = 1, ..., m$)
μ_i	Natural death rate for individuals in infectious Stage i (for $i = 1, ..., n$)
μ_R	Natural death rate for recovered individuals
γ_j	Progression rate from exposed Stage j to Stage $j+1$ (for $j = 1, ..., m-1$)
γ_m	Progression rate of exposed individuals in Stage m to first infectious stage
σ_i	Progression rate from infectious Stage i to Stage $i+1$ (for $i = 1, ..., n-1$)
σ_n	Recovery rate for infectious individuals in Stage n
δ_i	Disease-induced death rate for infectious individuals in Stage i (for $i = 1, ..., n$)
θ	Rate of loss of infection-acquired immunity

As stated earlier, the SE^mI^nRS model (4.10) is as an extension of the model (3.2), by including m exposed classes $(E_j; j = 1, ..., m)$ and gamma-distributed waiting times in the exposed and infectious stages. The main objective of this chapter is to determine whether or not such inclusions (of m exposed classes and gamma distribution assumptions for the waiting times in the exposed and infectious stages) will alter the qualitative features (equilibrium dynamics) of the classical $SEIRS$ model (or the SEI^nRS model presented in Chapter 3). The model (4.10) will now be rigorously analyzed to gain insight into its dynamical features.

4.2.2 Basic Properties of the Model

Consider the biologically-feasible regions

$$\mathcal{D} = \left\{(S, E_1, ..., E_m, I_1, ..., I_n, R) \in \mathbb{R}_+^{m+n+2} : S + \sum_{j=1}^{m} E_j + \sum_{i=1}^{n} I_i + R \leq \frac{\pi}{\mu}\right\},$$

$$\mathcal{D}_0 = \left\{(S, E_1, ..., E_m, I_1, ..., I_n, R) \in \mathcal{D} : E_1 = \cdots = E_m = I_1 = \cdots = I_n = R = 0\right\},$$

where, $\mu = \min\{\mu_S, \eta_j, \mu_i, \mu_R\}$ for $j = 1, ..., m$ and $i = 1, ..., n$.

The following results can be shown using the approach in Section 3.2.

Theorem 4.1. *The region $\mathcal{D}$ is positively-invariant and attracting for the model (4.10) with initial conditions in $\mathbb{R}_+^{m+n+2}$.*

Theorem 4.2. *Let the initial data $S(0) \geq 0, E_j(0) \geq 0, I_i(0) \geq 0, R(0) \geq 0$, for $j = 1, ..., m$ and $i = 1, ..., n$. Then, the solutions*

$$(S(t), E_1(t), ..., E_j(t), ..., E_m(t), I_1(t), ..., I_i(t), ..., I_n(t), R(t))$$

($j = 2, ..., m-1$ and $i = 2, ..., n-1$), of the model (4.10), are non-negative for all $t > 0$.

4.3 Stability of Disease-Free Equilibrium

The model (4.10) has a DFE given by

$$\mathcal{E}_0^s = (S^*, E_1^*, ..., E_m, I_1^*, ..., I_n^*, R^*) = \left(\frac{\pi}{\mu_S}, 0, 0, ..., 0, 0\right). \tag{4.11}$$

The asymptotic stability property of $\mathcal{E}_0^s$ is studied using the next generation operator method [19, 89], by defining the matrix F (of the new infection terms) and the M-matrix V (of the remaining transfer terms) associated with the system (4.10), given, respectively, by

$$F = \begin{pmatrix} F_1 & F_2 \\ F_3 & F_4 \end{pmatrix}, \quad V = \begin{pmatrix} M_1 & M_2 \\ M_3 & M_4 \end{pmatrix},$$

where F_1, F_3, F_4 and M_2 are all zero matrices with dimensions $m \times m, n \times m, n \times n$ and $m \times n$, respectively, and

$$F_2 = \begin{pmatrix} \beta_1 & \beta_2 & \beta_3 & \beta_4 & \cdots & \beta_n \\ 0 & 0 & 0 & 0 & \cdots & 0 \\ 0 & 0 & 0 & 0 & \cdots & 0 \\ 0 & 0 & 0 & 0 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 & \cdots & 0 \end{pmatrix}, \; M_1 = \begin{pmatrix} h_1 & 0 & 0 & 0 & \cdots & 0 \\ -\gamma_1 & h_2 & 0 & 0 & \cdots & 0 \\ 0 & -\gamma_2 & h_3 & 0 & \cdots & 0 \\ 0 & 0 & -\gamma_3 & h_4 & \cdots & 0 \\ \vdots & \vdots & \ddots & \ddots & \ddots & \vdots \\ 0 & 0 & \cdots & 0 & -\gamma_{m-1} & h_m \end{pmatrix},$$

$$M_3 = \begin{pmatrix} 0 & 0 & 0 & 0 & \cdots & 0 & -\gamma_m \\ 0 & 0 & 0 & 0 & \cdots & 0 & 0 \\ 0 & 0 & 0 & 0 & \cdots & 0 & 0 \\ 0 & 0 & 0 & 0 & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & 0 & \cdots & 0 & 0 \end{pmatrix}, \; M_4 = \begin{pmatrix} k_1 & 0 & 0 & 0 & \cdots & 0 \\ -\sigma_1 & k_2 & 0 & 0 & \cdots & 0 \\ 0 & -\sigma_2 & k_3 & 0 & \cdots & 0 \\ 0 & 0 & -\sigma_3 & k_4 & \cdots & 0 \\ \vdots & \vdots & \ddots & \ddots & \ddots & \vdots \\ 0 & 0 & \cdots & 0 & -\sigma_{n-1} & k_n \end{pmatrix},$$

with dimensions $m \times n, m \times m, n \times m$ and $n \times n$, respectively. Furthermore, $h_j = \gamma_j + \eta_j$, $(j = 1, ..., m)$, $k_i = \sigma_i + \mu_i + \delta_i$ $(i = 1, ..., n)$ and $k_\theta = \mu_R + \theta$. Hence, the associated *basic reproduction number*, denoted by $\mathcal{R}_0^s$, is given by $\mathcal{R}_0^s = \rho(FV^{-1})$, where ρ is the spectral radius of FV^{-1}. It follows that:

$$\mathcal{R}_0^s = \prod_{j=1}^{m} \frac{\gamma_j}{h_j} \sum_{i=1}^{n} \beta_i \prod_{p=1}^{i} \frac{\sigma_{p-1}}{k_p}, \; \sigma_0 = 1. \tag{4.12}$$

Thus, using Theorem 2 of [89], the following result is established.

Theorem 4.3. *The DFE, $\mathcal{E}_0^s$, of the model (4.10), given by (4.11), is locally-asymptotically stable if $\mathcal{R}_0^s < 1$, and unstable if $\mathcal{R}_0^s > 1$.*

The *basic reproduction number*, $\mathcal{R}_0^s$, measures to the average number of secondary cases generated by a single infectious individual in a completely susceptible population [4, 43]. The epidemiological implication of Theorem 4.3 is that if $\mathcal{R}_0^s < 1$, then a small

influx of infectious individuals will not generate large outbreaks of the disease in the population.

4.3.1 Global Stability of Disease-Free Equilibrium

Theorem 4.4. *The DFE, $\mathcal{E}_0^s$, of the model (4.10), is globally-asymptotically stable in $\mathcal{D}$ if $\mathcal{R}_0^s \leq 1$.*

Proof. Consider the Lyapunov function

$$V = \sum_{j=1}^{m} A_j E_j + \sum_{i=1}^{n} B_i I_i, \tag{4.13}$$

where,

$$\begin{aligned} B_i &= \frac{k_n}{\beta_n}\left(\sum_{q=i}^{n}\beta_q \prod_{l=i}^{q}\frac{\sigma_{l-1}}{k_l}\right); \quad \sigma_{p-1}=1 \text{ for } p=i, \\ A_j &= \prod_{q=j}^{m}\frac{\gamma_q}{h_q}B_1; \ j=1,...,m. \end{aligned} \tag{4.14}$$

Some of the coefficients in (4.13) can be expressed in terms of $\mathcal{R}_0^s$, using (4.12), as follows:

$$\begin{aligned} A_1 &= \frac{k_n}{\beta_n}\mathcal{R}_0^s = \prod_{j=1}^{m}\frac{\gamma_j}{h_j}B_1, \\ A_j &= \prod_{p=1}^{j}\frac{h_p}{\gamma_p}A_{j-1}; \ j=2,...,m, \\ B_1 &= A_m\mathcal{R}_0^s. \end{aligned} \tag{4.15}$$

Furthermore, it can be shown that $B_n = 1$.

The Lyapunov derivative of (4.13) is given by

$$\dot{V} = \sum_{i=1}^{m} A_i \dot{E}_i + \sum_{j=1}^{n} B_j \dot{I}_j. \tag{4.16}$$

The last two terms of the summation $\sum_{j=1}^{n} B_j \dot{I}_j$ in (4.16) can be simplified as follows:

$$\begin{aligned} B_{n-1}\dot{I}_{n-1} + B_n \dot{I}_n &= \frac{k_n}{\beta_n}\left(\frac{\beta_{n-1}}{k_{n-1}} + \frac{\beta_n \sigma_{n-1}}{k_n k_{n-1}}\right)(\sigma_{n-2} I_{n-2} - k_{n-1} I_{n-1}) + \sigma_{n-1} I_{n-1} - k_n I_n, \\ &= \underbrace{\frac{k_n}{\beta_n}\left(\frac{\beta_{n-1}}{k_{n-1}} + \frac{\beta_n \sigma_{n-1}}{k_n k_{n-1}}\right)\sigma_{n-2} I_{n-2}}_{B_{n-1}\sigma_{n-2} I_{n-2}} - \frac{k_n}{\beta_n}\beta_{n-1} I_{n-1} - k_n I_n, \\ &= B_{n-1}\sigma_{n-2} I_{n-2} - \frac{k_n}{\beta_n}\beta_{n-1} I_{n-1} - k_n I_n. \end{aligned}$$

Similarly, the last three terms of the summation $\sum_{j=1}^{n} B_j \dot{I}_j$ in (4.16) can be simplified as follows:

$$\begin{aligned} \sum_{i=n-2}^{n} B_i \dot{I}_i &= B_{n-2}\dot{I}_{n-2} + B_{n-1}\dot{I}_{n-1} + B_n \dot{I}_n, \\ &= B_{n-2}\sigma_{n-3} I_{n-3} - \frac{k_n}{\beta_n}\beta_{n-2} I_{n-2} - \frac{k_n}{\beta_n}\beta_{n-1} I_{n-1} - k_n I_n. \end{aligned}$$

Substituting the expressions for $\dot{I}_i$ (for $i = 2, ..., n$) from (4.10) into (4.16), in the same way as done above, gives

$$\sum_{i=2}^{n} B_i \dot{I}_i = B_2 \sigma_1 I_1 - \sum_{i=2}^{n} \frac{k_n}{\beta_n}\beta_i I_i.$$

Applying the same procedure for $i = 1, ..., n$ gives

$$\sum_{i=1}^{n} B_i \dot{I}_i = B_1 \gamma_m E_m - \sum_{i=1}^{n} \frac{k_n}{\beta_n}\beta_i I_i. \tag{4.17}$$

Thus, using (4.14) and (4.17), it follows that

$$A_m\dot{E}_m + \sum_{i=1}^{n} B_i\dot{I}_i = \frac{\gamma_m}{h_m}B_1\dot{E}_m + B_1\gamma_m E_m - \sum_{i=1}^{n}\frac{k_n}{\beta_n}\beta_i I_i,$$

$$= \frac{\gamma_m\gamma_{m-1}}{h_m}B_1E_{m-1} - \sum_{i=1}^{n}\frac{k_n}{\beta_n}\beta_i I_i.$$

Similarly, for $j = m-1, ..., m$ and $i = 1, ..., n$,

$$\sum_{j=m-1}^{m} A_j\dot{E}_j + \sum_{i=1}^{n} B_i\dot{I}_i = \frac{\gamma_{m-1}\gamma_m}{h_{m-1}h_m}B_1\dot{E}_{m-1} + \frac{\gamma_m\gamma_{m-1}}{h_m}B_1E_{m-1} - \sum_{i=1}^{n}\frac{k_n}{\beta_n}\beta_i I_i,$$

$$= \frac{\gamma_{m-2}\gamma_{m-1}\gamma_m}{h_{m-1}h_m}B_1E_{m-2} - \sum_{i=1}^{n}\frac{k_n}{\beta_n}\beta_i I_i.$$

Hence, for $j = 2, ..., m$ and $i = 1, ..., n$,

$$\sum_{j=2}^{m} A_j\dot{E}_j + \sum_{i=1}^{n} B_i\dot{I}_i = \prod_{j=2}^{m}\frac{\gamma_1\gamma_j}{h_j}B_1E_1 - \sum_{i=1}^{n}\frac{k_n}{\beta_n}\beta_i I_i.$$

Finally, the expression for $\dot{V}$ can be simplified in a similar manner (using (4.15)) as follows:

$$
\begin{aligned}
\dot{V} &= \sum_{j=1}^{m} A_j \dot{E}_j + \sum_{i=1}^{n} B_i \dot{I}_i, \\
&= A_1 \dot{E}_1 + \sum_{j=2}^{m} A_j \dot{E}_j + \sum_{i=1}^{n} B_i \dot{I}_i, \\
&= \prod_{j=1}^{m} \frac{\gamma_j}{h_j} B_1 \dot{E}_1 + \prod_{j=2}^{m} \frac{\gamma_1 \gamma_j}{h_j} B_1 E_1 - \sum_{i=1}^{n} \frac{k_n}{\beta_n} \beta_i I_i, \\
&= \prod_{j=1}^{m} \frac{\gamma_j}{h_j} B_1 \left(\sum_{i=1}^{n} \frac{\beta_i I_i}{N} S - h_1 E_1 \right) + \prod_{j=2}^{m} \frac{\gamma_1 \gamma_j}{h_j} B_1 E_1 - \sum_{i=1}^{n} \frac{k_n}{\beta_n} \beta_i I_i, \\
&= \prod_{j=1}^{m} \frac{\gamma_j}{h_j} B_1 \sum_{i=1}^{n} \frac{\beta_i I_i}{N} S - \sum_{i=1}^{n} \frac{k_n}{\beta_n} \beta_i I_i, \\
&\leq \prod_{j=1}^{m} \frac{\gamma_j}{h_j} B_1 \sum_{i=1}^{n} \beta_i I_i - \sum_{i=1}^{n} \frac{k_n}{\beta_n} \beta_i I_i; \text{ since } S \leq N \text{ in } \mathcal{D}; \\
&= \prod_{j=1}^{m} \frac{\gamma_j}{h_j} \left(\frac{k_n}{\beta_n} \prod_{j=1}^{m} \frac{h_j}{\gamma_j} \mathcal{R}_0^s \right) \sum_{i=1}^{n} \beta_i I_i - \sum_{i=1}^{n} \frac{k_n}{\beta_n} \beta_i I_i; \text{ since } B_1 = \frac{k_n}{\beta_n} \prod_{j=1}^{m} \frac{h_j}{\gamma_j} \mathcal{R}_0^s, \\
&= \frac{k_n}{\beta_n} \sum_{i=1}^{n} \beta_i I_i \left(\mathcal{R}_0^s - 1 \right), \\
&\leq 0 \text{ if } \mathcal{R}_0^s \leq 1.
\end{aligned}
$$

Therefore, $\dot{V} \leq 0$ if $\mathcal{R}_0^s \leq 1$ and $\dot{V} = 0$ if and only if $E_1 = E_j = E_m = I_1 = I_i = I_n = 0$ (for $j = 1, ...m$ and $i = 1, ..., n$). Furthermore, substituting $I_n = 0$ into the equation for $\dot{R}$ in the model (4.10) shows that $R(t) \to 0$ as $t \to \infty$. Similarly, setting $E_j = 0$ $(j = 1, ..., m)$, $I_i = 0$ $(i = 1, ..., n)$ and $R = 0$ in the equation for $\dot{S}$ in (4.10) shows that $S \to \frac{\pi}{\mu_S}$ as $t \to \infty$. Hence, by the Lyapunov function theory and the LaSalle's Invariance Principle [38, 58], every solution to the equations of the model (4.10), with initial conditions in $\mathcal{D}$, approaches the DFE $(\mathcal{E}_0^s)$ as $t \to \infty$. Finally, since

the region $\mathcal{D}$ is positively-invariant, the DFE ($\mathcal{E}_0^s$) of the model (4.10) is GAS in $\mathcal{D}$ if $\mathcal{R}_0^s \leq 1$. □

Theorem 4.4 shows that the disease will be eliminated from the community if the threshold quantity, $\mathcal{R}_0^s$, is brought to (and maintained at) a value less than (or equal to) unity.

4.4 Existence of Endemic Equilibrium Point

As in Section 3.5, let

$$\mathcal{E}_1^s = (S^{***}, E_1^{***}, E_2^{***}, ..., E_m^{***}, I_1^{***}, I_2^{***}, ..., I_n^{***}, R^{***}), \tag{4.18}$$

represents any arbitrary endemic (positive) equilibrium of the model (4.10) Furthermore, let

$$\lambda^{***} = \sum_{i=1}^{n} \frac{\beta_i I_i^{***}}{N^{***}}, \tag{4.19}$$

be the associated force of infection at endemic steady-state. Solving the right-hand sides of the equations in (4.10) at steady-state gives

$$\begin{aligned}
\pi - \mu_S S^{***} + \theta R^{***} &= \lambda^{***} S^{***}, \\
E_1^{***} &= \frac{1}{h_1}\lambda^{***} S^{***} = c_1 \lambda^{***} S^{***}, \\
E_i^{***} &= c_i \lambda^{***} S^{***};\ i = 2, ..., m, \\
I_j^{***} &= d_j \lambda^{***} S^{***};\ j = 1, ..., n, \\
R^{***} &= e_1 \lambda^{***} S^{***},
\end{aligned} \tag{4.20}$$

where,

$$\begin{aligned}
c_i &= \prod_{j=1}^{i} \frac{\gamma_{j-1}}{h_j};\ i = 2, ..., m,\ \text{where } \gamma_0 = 1, \\
d_j &= \prod_{p=1}^{j} \frac{\sigma_{p-1}}{k_p} \prod_{i=1}^{m} \frac{\gamma_i}{h_i};\ j = 1, ..., n,\ \text{where } \sigma_0 = 1, \\
e_1 &= \prod_{p=1}^{n} \frac{\sigma_p}{k_{p+1}} \prod_{j=1}^{m} \frac{\gamma_j}{h_j},\ \text{with } k_{n+1} = k_\theta.
\end{aligned} \tag{4.21}$$

Using the expressions in (4.20), with (4.21), into (4.19), and simplifying (noting that $N^{***} = S^{***} + \sum_{j=1}^{m} E_j^{***} + \sum_{i=1}^{n} I_i^{***} + R^{***}$), gives

$$1 + \lambda^{***}\left(\sum_{j=1}^{m} \prod_{i=1}^{j} c_i + \prod_{p=1}^{m} \frac{\gamma_p}{h_p} \sum_{j=1}^{n} \prod_{i=1}^{j} \frac{\sigma_{i-1}}{k_i} + \prod_{i=1}^{n} \frac{\sigma_i}{k_{i+1}} \prod_{j=1}^{m} \frac{\gamma_j}{h_j} \right) = \prod_{j=1}^{m} \frac{\gamma_j}{h_j} \left(\sum_{i=1}^{n} \beta_i \prod_{p=1}^{i} \frac{\sigma_{p-1}}{k_p} \right).$$

Hence,

$$\lambda^{***} = \frac{\displaystyle\prod_{j=1}^{m}\frac{\gamma_j}{h_j}\sum_{i=1}^{n}\beta_i\prod_{p=1}^{i}\frac{\sigma_{p-1}}{k_p}-1}{\displaystyle\sum_{j=1}^{m}\prod_{i=1}^{j}c_i+\prod_{p=1}^{m}\frac{\gamma_p}{h_p}\sum_{j=1}^{n}\prod_{i=1}^{j}\frac{\sigma_{i-1}}{k_i}+\prod_{i=1}^{n}\prod_{j=1}^{m}\frac{\sigma_i}{k_{i+1}}\frac{\gamma_j}{h_j}}; \text{ with } \sigma_0=1, \quad (4.22)$$

from which it follows that (noting that $\sigma_0 = 1$),

$$\lambda^{***} = \frac{\mathcal{R}_0^s-1}{\displaystyle\sum_{j=1}^{m}\prod_{i=1}^{j}c_i+\prod_{p=1}^{m}\frac{\gamma_p}{h_p}\sum_{j=1}^{n}\prod_{i=1}^{j}\frac{\sigma_{i-1}}{k_i}+\prod_{i=1}^{n}\frac{\sigma_i}{k_{i+1}}\prod_{j=1}^{m}\frac{\gamma_j}{h_j}}. \quad (4.23)$$

It should be stated that the relation

$$\prod_{j=1}^{m}\frac{\gamma_j}{h_j}\sum_{i=1}^{n}\beta_i\prod_{p=1}^{i}\frac{\sigma_{p-1}}{k_p}=\mathcal{R}_0^s, \text{ with } \sigma_0=1,$$

has been used in (4.23).

It follows from (4.23) that $\lambda^{***} > 0$ if and only if $\mathcal{R}_0^s > 1$. Thus, the SE^mI^nRS model (4.10) has a unique endemic equilibrium if $\mathcal{R}_0^s > 1$ (the components of this equilibrium point can be obtained by substituting the value of λ^{***}, obtained from (4.23), into the expressions in (4.20)). It should be stated that the model has no positive equilibrium if $\mathcal{R}_0^s < 1$ (since, in this case, $\lambda^{***} < 0$ in (4.23), which is biologically meaningless). Furthermore, if $\mathcal{R}_0^s = 1$, then $\lambda^{***} = 0$ in (4.23) (which corresponds to the DFE, $\mathcal{E}_0^s$). This result is summarized below.

Theorem 4.5. *The model (4.10) has a unique endemic equilibrium, given by $\mathcal{E}_1^s$, whenever $\mathcal{R}_0^s > 1$, and no endemic equilibrium otherwise.*

4.5 Stability of Endemic Equilibrium: Special Case

As in Section 3.6, the asymptotic stability of the EEP ($\mathcal{E}_1^m$) of the model (4.10) is explored for the special case where the disease-induced mortality rates are set to zero

($\delta_i = 0;\ i = 1, ..., n$) and the natural death rates are assumed to be equal for all epidemiological classes (i.e., $\mu_S = \mu_R = \eta_j\ (j = 1, ..., m) = \mu_i\ (i = 1, ..., n) = \mu$). Thus, for this setting, $N = N^{**} = \frac{\pi}{\mu}$. Substituting $N = N^{**}$ in (4.1) gives

$$\hat{\lambda} = \lambda|_{N=N^{**}} = \sum_{i=1}^{n} \frac{\beta_i I_i}{N^{**}}. \tag{4.24}$$

It can be shown that the model (4.10), with $\delta_i = 0\ (i = 1, ..., n)$, $\mu_S = \mu_R = \eta_j\ (j = 1, .., m) = \mu_i\ (i = 1, ..., n) = \mu$ and $\hat{\lambda}$ as given in (4.24), has the associated reproduction number (noting that $S^* = N^{**} = \frac{\pi}{\mu}$), given by

$$\mathcal{R}_0^m = \prod_{j=1}^{m} \frac{\gamma_j}{\hat{h}_j} \sum_{i=1}^{n} \beta_i \prod_{p=1}^{i} \frac{\sigma_{p-1}}{\hat{k}_p}, \text{ with } \sigma_0 = 1, \tag{4.25}$$

where, $\hat{h}_j = \gamma_j + \mu$ (for $j = 1, ..., m$) and $\hat{k}_i = \sigma_i + \mu$ (for $i = 1, ..., n$). Additionally, it can be shown (using the approach in Section 4.4) that the model (4.10), under the above setting, has a unique endemic equilibrium, $\mathcal{E}_1^m$, of the form

$$\mathcal{E}_1^m = (S^{**}, E_1^{**}, ..., E_m^{**}, I_1^{**}, ..., I_n^{**}, R^{**}),$$

whenever $\mathcal{R}_0^m > 1$.

It follows from the expression $N = N^{**}$ that

$$S = N^{**} - \sum_{j=1}^{m} E_j - \sum_{i=1}^{n} I_i - R. \tag{4.26}$$

Substituting (4.26), together with the assumptions $\delta_i = 0\ (i = 1, ..., n)$ and $\mu_S = \mu_R = \eta_j\ (j = 1, .., m) = \mu_i\ (i = 1, ..., n) = \mu$, into the system (4.10) gives the following reduced (mass action) model

$$\begin{aligned}
\dot{E}_1 &= \hat{\lambda}\left(N^{**} - \sum_{j=1}^{m} E_j - \sum_{i=1}^{n} I_i - R\right) - \hat{h}_1 E_1, \\
\dot{E}_j &= \gamma_{j-1} E_{j-1} - \hat{h}_j E_j;\ j = 2, ..., m-1, \\
\dot{E}_m &= \gamma_{m-1} E_{m-1} - \hat{h}_m E_m, \\
\dot{I}_1 &= \gamma_m E_m - \hat{k}_1 I_1, \\
\dot{I}_j &= \sigma_{j-1} I_{j-1} - \hat{k}_j I_j;\ j = 2, ..., n, \\
\dot{R} &= \sigma_n I_n - \hat{k}_\theta R,
\end{aligned} \tag{4.27}$$

where, now, $\hat{\lambda}$ is as defined in (4.24) and $\hat{k}_\theta = \theta + \mu$ (with $\hat{h}_j$ $(j = 1, ..., m)$ and $\hat{k}_i$ $(i = 1, ..., n)$ as defined in Section 4.5). The following result (Theorem 4.6) can be established.

Theorem 4.6. *The unique endemic equilibrium of the model (4.10), with $\hat{\lambda}$ defined by (4.24), given by*

$$\mathcal{E}_1^m = (S^{**}, E_1^{**}, ..., E_m^{**}, I_1^{**}, ..., I_n^{**}, R^{**}),$$

is LAS whenever $\mathcal{R}_0^m > 1$.

The proof of Theorem 4.6, based on using the Krasnoselskii sub-linearity trick employed in Chapter 3, is given in Appendix B.

4.6 Global Stability of Endemic Equilibrium: Special Case

The global asymptotic stability property of the endemic equilibrium, $\mathcal{E}_1^m$, of the model (4.10), is explored for the special case with $\hat{\lambda}$ given in (4.24), $\hat{k}_\theta = \theta + \mu$, $\hat{h}_j$ $(j = 1, ..., m)$ and $\hat{k}_i$ $(i = 1, ..., n)$ are as defined in Section 4.5. Here, too, $\hat{\lambda}$ is re-defined (for convenience) as

$$\hat{\lambda} = \sum_{i=1}^{n} \beta_i' I_i, \tag{4.28}$$

where $\beta_i' = \frac{\beta_i}{N^{**}} = \frac{\beta_i \mu}{\pi}$ $(i = 1, ..., n)$.

Theorem 4.7. *The unique EEP, $\mathcal{E}_1^m$, of model (4.10) with (4.28) is GAS in $\mathcal{D}\backslash\mathcal{D}_0$ whenever $\mathcal{R}_0^m > 1$ and $2 - \frac{E_1}{E_1^{**}} - \frac{S^{**}}{S} + \frac{S^{**}R}{SR^{**}} - \frac{E_1^{**}R}{E_1R^{**}} \geq 0$.*

Proof. Let $2 - \frac{E_1}{E_1^{**}} - \frac{S^{**}}{S} + \frac{S^{**}R}{SR^{**}} - \frac{E_1^{**}R}{E_1R^{**}} \geq 0$. Further, let $\mathcal{R}_0^m > 1$, so that the unique endemic equilibrium, $\mathcal{E}_1^m$, of model (4.10) exists. Consider the following Lyapunov function

$$\begin{aligned} V &= S - S^{**} - S^{**} ln \frac{S}{S^{**}} + \sum_{j=1}^{m} a_j \left(E_j - E_j^{**} - E_j^{**} ln \frac{E_j}{E_j^{**}} \right) \\ &+ \sum_{i=1}^{n} b_i \left(I_i - I_i^{**} - I_i^{**} ln \frac{I_i}{I_i^{**}} \right) + c \left(R - R^{**} - R^{**} ln \frac{R}{R^{**}} \right), \end{aligned}$$

where, $a_1 = 1$ and the coefficients a_j $(j = 2, ..., m)$, b_i $(i = 1, ..., n)$ and c are positive constants to be determined. Thus,

$$\begin{aligned} \dot{V} &= \left(1 - \frac{S^{**}}{S}\right) \dot{S} + \left(1 - \frac{E_1^{**}}{E_1}\right) \dot{E}_1 + \sum_{j=2}^{m} a_j \left(1 - \frac{E_j^{**}}{E_j}\right) \dot{E}_j \\ &+ \sum_{i=1}^{n} b_i \left(1 - \frac{I_i^{**}}{I_i}\right) \dot{I}_i + c \left(1 - \frac{R^{**}}{R}\right) \dot{R}. \end{aligned} \tag{4.29}$$

Substituting the expressions of the derivatives from the system (4.10), with (4.28), gives (it should be stated that the relation $\pi = \mu S^{**} \sum_{i=1}^{n} \beta_i' I_i^{**} S^{**} - \theta R^{**}$, at the endemic steady-state, $\mathcal{E}_1^m$, has been used):

$$\begin{aligned}
\dot{V} &= \left(1-\frac{S^{**}}{S}\right)\left(\mu S^{**}+S^{**}\sum_{i=1}^{n}\beta_i' I_i^{**}-\theta R^{**}-S\sum_{i=1}^{n}\beta_i' I_i-\mu S+\theta R\right)\\
&+ \sum_{j=2}^{m} a_j\left(\gamma_{j-1}E_{j-1}-\hat{h}_j E_j-\gamma_{j-1}\frac{E_j^{**}}{E_j}E_{j-1}+\hat{h}_j E_j^{**}\right)\\
&+ b_1\left(\gamma_m E_m-\hat{k}_1 I_1-\gamma_m\frac{I_1^{**}}{I_1}E_m+\hat{k}_1 I_1^{**}\right) \qquad (4.30)\\
&+ \sum_{i=2}^{n} b_i\left(\sigma_{i-1}I_{i-1}-\hat{k}_i I_i-\sigma_{i-1}\frac{I_i^{**}}{I_i}I_{i-1}+\hat{k}_i I_i^{**}\right)\\
&+ c\left(\sigma_n I_n-\hat{k}_\theta R-\sigma_n\frac{R^{**}}{R}I_n+\hat{k}_\theta R^{**}\right)\\
&+ \sum_{i=1}^{n}\beta_i' I_i S-\hat{h}_1 E_1-\frac{E_1^{**}}{E_1}S\sum_{i=1}^{n}\beta_i' I_i+\hat{h}_1 E_1^{**},
\end{aligned}$$

which can be simplified to:

$$\begin{aligned}
\dot{V} &= \mu S^{**}\left(2-\frac{S}{S^{**}}-\frac{S^{**}}{S}\right)+\left[S^{**}\sum_{i=1}^{n}\beta_i' I_i^{**}-\frac{(S^{**})^2}{S}\sum_{i=1}^{n}\beta_i' I_i^{**}+S^{**}\sum_{i=1}^{n}\beta_i' I_i\right]\\
&- \theta R^{**}\left(1-\frac{R}{R^{**}}-\frac{S^{**}}{S}+\frac{S^{**}R}{SR^{**}}\right)+\left(-\hat{h}_1 E_1-\frac{E_1^{**}}{E_1}S\sum_{i=1}^{n}\beta_i' I_i+\hat{h}_1 E_1^{**}\right)\\
&+ \sum_{j=2}^{m} a_j\left(\gamma_{j-1}E_{j-1}-\hat{h}_j E_j-\gamma_{j-1}\frac{E_j^{**}}{E_j}E_{j-1}+\hat{h}_j E_j^{**}\right) \qquad (4.31)\\
&+ b_1\left(\gamma_m E_m-\hat{k}_1 I_1-\gamma_m\frac{I_1^{**}}{I_1}E_m+\hat{k}_1 E_1^{**}\right)\\
&+ \sum_{i=2}^{n} b_i\left(\sigma_{i-1}I_{i-1}-\hat{k}_i I_i-\sigma_{i-1}\frac{I_i^{**}}{I_i}I_{i-1}+\hat{k}_i I_i^{**}\right)\\
&+ c\left(\sigma_n I_n-\hat{k}_\theta R-\sigma_n\frac{R^{**}}{R}I_n+\hat{k}_\theta R^{**}\right).
\end{aligned}$$

Using the coefficients:

$$
\begin{aligned}
c &= \frac{\theta}{\hat{k}_\theta}, \\
a_j &= \sum_{i=1}^{n} S^{**}\frac{\beta_i' I_i^{**}}{\hat{h}_j E_j^{**}} + \frac{\theta R^{**}}{\hat{h}_j E_j^{**}},\ j = 2, ..., m, \\
b_i &= \sum_{j=i}^{n} S^{**}\frac{\beta_j' I_j^{**}}{\hat{k}_i I_i^{**}} + \frac{\theta R^{**}}{\hat{k}_i I_i^{**}},\ i = 1, ..., n,
\end{aligned} \tag{4.32}
$$

in (4.31), and simplifying, gives

$$
\begin{aligned}
\dot{V} &= \mu S^{**}\left(2 - \frac{S}{S^{**}} - \frac{S^{**}}{S}\right) - \theta R^{**}\left(1 - \frac{S^{**}}{S} + \frac{S^{**}R}{SR^{**}}\right) \\
&+ \underbrace{\left[\left(\sum_{i=1}^{n}\frac{S^{**}\beta_i' I_i^{**}}{\hat{h}_2 E_2^{**}}\right)\gamma_1 E_1 - \hat{h}_1 E_1\right]}_{=0} + \left(\frac{\theta R^{**}}{\hat{h}_2 E_2^{**}}\right)\gamma_1 E_1 \\
&+ \left(\sum_{i=1}^{n} S^{**}\beta_i' I_i^{**} + \theta R^{**}\right)\left[(m-1) - \sum_{j=2}^{m}\frac{E_j^{**}E_{j-1}}{E_{j-1}^{**}E_j}\right] \\
&+ \left(\sum_{i=1}^{n} S^{**}\beta_i' I_i^{**} + \theta R^{**}\right)\left(1 - \frac{I_1^{**}E_m}{E_m^{**}I_1}\right) \\
&\vdots \\
&+ \left(\sum_{i=j}^{n} S^{**}\beta_i' I_i^{**} + \theta R^{**}\right)\left(1 - \frac{I_i^{**}I_{i-1}}{I_{i-1}^{**}I_i}\right) \\
&\vdots \\
&+ \left(S^{**}\beta_n' I_n^{**} + \theta R^{**}\right)\left(1 - \frac{I_n^{**}I_{n-1}}{I_{n-1}^{**}I_n}\right) \\
&+ \theta R^{**}\left(1 - \frac{I_n R^{**}}{I_n^{**}R}\right),
\end{aligned}
$$

so that,

$$\begin{aligned}
\dot{V} &= \mu S^{**}\left(2-\frac{S}{S^{**}}-\frac{S^{**}}{S}\right)-\theta R^{**}\left(2-\frac{E_1}{E_1^{**}}-\frac{S^{**}}{S}+\frac{S^{**}R}{SR^{**}}-\frac{RE_1^{**}}{R^{**}E_1}\right)\\
&+ \beta_1' S^{**}I_1^{**}\left[(m+2)-\frac{S^{**}}{S}-\frac{E_1^{**}SI_1}{E_1S^{**}I_1^{**}}-\sum_{j=2}^{m}\frac{E_j^{**}E_{j-1}}{E_{j-1}^{**}E_j}-\frac{I_1^{**}E_m}{I_1E_m^{**}}\right] \qquad (4.33)\\
&+ \sum_{i=2}^{n}\beta_i' S^{**}I_i^{**}\left[(m+i+1)-\frac{S^{**}}{S}-\frac{E_1^{**}SI_i}{E_1S^{**}I_i^{**}}-\sum_{j=2}^{m}\frac{E_j^{**}E_{j-1}}{E_{j-1}^{**}E_j}-\frac{I_1^{**}E_m}{I_1E_m^{**}}-\sum_{j=2}^{i}\frac{I_j^{**}I_{j-1}}{I_jI_{j-1}^{**}}\right]\\
&+ \theta R^{**}\left[(m+n+1)-\frac{RE_1^{**}}{R^{**}E_1}-\sum_{j=2}^{m}\frac{E_j^{**}E_{j-1}}{E_{j-1}^{**}E_j}-\frac{I_1^{**}E_m}{E_m^{**}I_1}-\sum_{i=2}^{n}\frac{I_i^{**}I_{i-1}}{I_{i-1}^{**}I_i}-\frac{R^{**}I_n}{I_n^{**}R}\right].
\end{aligned}$$

Since the arithmetic mean exceeds the geometric mean, the following inequalities hold:

$$\begin{aligned}
2-\frac{S}{S^{**}}-\frac{S^{**}}{S} &\leq 0,\\
m+2-\frac{S^{**}}{S}-\frac{E_1^{**}SI_1}{E_1S^{**}I_1^{**}}-\sum_{j=2}^{m}\frac{E_j^{**}E_{j-1}}{E_{j-1}^{**}E_j}-\frac{I_1^{**}E_m}{I_1E_m^{**}} &\leq 0, \qquad (4.34)\\
(m+i+1)-\frac{S^{**}}{S}-\frac{E_1^{**}SI_i}{E_1S^{**}I_i^{**}}-\sum_{j=2}^{m}\frac{E_j^{**}E_{j-1}}{E_{j-1}^{**}E_j}-\frac{I_1^{**}E_m}{I_1E_m^{**}}-\sum_{j=2}^{i}\frac{I_j^{**}I_{j-1}}{I_jI_{j-1}^{**}} &\leq 0;\ i=1,...,n,\\
(m+n+1)-\frac{RE_1^{**}}{R^{**}E_1}-\sum_{j=2}^{m}\frac{E_j^{**}E_{j-1}}{E_{j-1}^{**}E_j}-\frac{I_1^{**}E_m}{E_m^{**}I_1}-\sum_{i=2}^{n}\frac{I_i^{**}I_{i-1}}{I_{i-1}^{**}I_i}-\frac{R^{**}I_n}{I_n^{**}R} &\leq 0.
\end{aligned}$$

Hence, using (4.34), and noting the assumption $2-\frac{E_1}{E_1^{**}}-\frac{S^{**}}{S}+\frac{S^{**}R}{SR^{**}}-\frac{RE_1^{**}}{R^{**}E_1}\geq 0$ (from the hypothesis of Theorem 4.7), it follows that $\dot{V}\leq 0$. Thus, by the Lyapunov function theory and the LaSalle's Invariance Principle [38, 58]), every solution to the equation of the model (4.10), with (4.28), approaches the endemic equilibrium, $\mathcal{E}_1^m$, as $t\longrightarrow\infty$ for $\mathcal{R}_0^m>1$ and $2-\frac{E_1}{E_1^{**}}-\frac{S^{**}}{S}+\frac{S^{**}R}{SR^{**}}-\frac{RE_1^{**}}{R^{**}E_1}\geq 0$.

□

It is worth noting that the additional condition, $2-\frac{E_1}{E_1^{**}}-\frac{S^{**}}{S}+\frac{S^{**}R}{SR^{**}}-\frac{RE_1^{**}}{R^{**}E_1}\geq 0$, is not necessary (or needed) if the disease confers permanent immunity against re-infection (since, in this case, $\theta=0$, and the second term of (4.33) vanishes).

In summary, the SE^mI^nRS model (4.10) has essentially the same qualitative (equilibrium) dynamics (with respect to the persistence or elimination of the disease) as the SEI^nRS model (3.2) considered in Chapter 3. In particular,

(i) both models ((4.10) and (3.2)) have GAS DFE whenever the associated reproduction threshold is less than unity; each model has a unique EEP whenever the threshold exceeds unity;

(ii) the unique endemic equilibrium, in each model, is GAS for a special case (where the disease-induced mortality rate is zero) when the associated threshold exceeds unity and an additional condition holds (this condition turns out to be exactly the same for both the SEI^nRS model (3.2) and the SE^mI^nRS model (4.10)).

In other words, adding multiple latent stages and gamma distribution assumptions (for the mean duration in the exposed and infectious stages) to the classical $SEIRS$ model (or even the SEI^nRS model considered in Chapter 3) does not alter its qualitative (equilibrium) dynamics.

4.7 Numerical Simulations and Conclusions

Numerical simulations of the model (4.10) are carried out to illustrate some of the theoretical results established in this chapter. In these simulations, three latent ($m = 3$) and six infectious ($n = 6$) stages will be used. Further, the parameter values in Table 4.3 are used (unless otherwise stated). It should be mentioned that Eichner *et al.* [21] considered 9 latent and 19 infectious stages. As in Chapter 3, the parameter values used in the numerical simulations in this chapter are relevant to the transmission dynamics of a typical disease that follows the $SEIRS$ modelling structure, such as influenza, and are (mostly) obtained from the literature as described in Table 4.3.

As in Chapter 3, the average incubation period of influenza is 1.9 days, so that $\frac{1}{\sigma_E} = 1.9$ days [17, 21, 40, 64, 67, 72]. Consequently, the latency period ($\frac{1}{\gamma_j}$; $j = 1, 2, 3$) is distributed such that (in line with the gamma distribution assumption)

$$\frac{1}{\gamma_1} + \frac{1}{\gamma_2} + \frac{1}{\gamma_3} = 1.9 \text{ days}.$$

Similarly, the following are (arbitrarily) chosen: $\frac{1}{\gamma_1} = 1.1$ days, $\frac{1}{\gamma_2} = 0.6$ days and $\frac{1}{\gamma_3} = 0.2$ days. Similarly, since the average infectious period ($\frac{1}{\sigma_i}$; $i = 1, ..., 6$) for influenza is 5 days [67, 72], it follows that

$$\frac{1}{\sigma_1} + \frac{1}{\sigma_2} + \frac{1}{\sigma_3} + \frac{1}{\sigma_4} + \frac{1}{\sigma_5} + \frac{1}{\sigma_6} = 5 \text{ days}.$$

Consequently, it is assumed that $\frac{1}{\sigma_1} = 1.5$ days, $\frac{1}{\sigma_2} = 1.25$ days, $\frac{1}{\sigma_3} = 1.00$ days, $\frac{1}{\sigma_4} = 0.75$ days, $\frac{1}{\sigma_5} = 0.50$ days and $\frac{1}{\sigma_6} = 0.25$ days. Furthermore, since the infectiousness of influenza is highest after the onset of symptoms and declines thereafter geometrically [21], it is plausible to distribute the transmission rates (β_i; $i = 1, ..., 6$) such that $\beta_1 > \beta_2 > \beta_3 > \beta_4 > \beta_5 > \beta_6$ [21]. The values $\beta_1 = 0.48$, $\beta_2 = 0.39$, $\beta_3 = 0.32, \beta_4 = 0.25$, $\beta_5 = 0.18$ and $\beta_6 = 0.14$ *per* day are chosen arbitrarily. However, in order to ensure convergence of the solutions to the DFE ($\mathcal{E}_0^s$), the aforementioned values for β_i ($i = 1, ..., 6$) have to be reduced (for instance, to $\beta_1 = 0.22$, $\beta_2 = 0.18$, $\beta_3 = 0.15, \beta_4 = 0.08$, $\beta_5 = 0.04$ and $\beta_6 = 0.02$ *per* day, so that $\mathcal{R}_0^s < 1$).

The average mortality rates for influenza (δ_i; $i = 1, ..., 6$) range between 0.0062 to 0.035 *per* day [72]. Since the average disease-induced mortality rate of a typical disease is expected to decrease with decreasing infectiousness [21], we set $\delta_1 = 0.035$, $\delta_2 = 0.025$, $\delta_3 = 0.015, \delta_4 = 0.008$, $\delta_5 = 0.0062$ and $\delta_6 = 0.0062$ *per* day. For simulation purposes, the natural death rates (i.e., $\mu_S = \mu_R = \eta_j = \mu_i$; for $j = 1, 2, 3$ and $i = 1, ..., 6$) are assumed to be the same in all classes. We set $\mu_S = \mu_R = \eta_j = \mu_i = \frac{1}{60 \times 365}$ *per* day (corresponding to an average lifespan of 60 years) [17]. The rate of loss of the

infection-acquired immunity (θ) is assumed to be 0.012 *per* day, and the recruitment rate, π, is set at $\pi = 7.976$ *per* day [17] (obtained from the product of the total population considered and the assumed natural death rate). These parameter values are tabulated in Table 4.3.

Using the aforementioned parameter values (and the parameter values in Table 4.3) with $\beta_1 = 0.22,\ \beta_2 = 0.18,\ \beta_3 = 0.150,\ \beta_4 = 0.08,\ \beta_5 = 0.04$ and $\beta_6 = 0.02$ *per* day (so that, $\mathcal{R}_0^s = 0.73$) and various initial conditions, the model gives solution profiles that converge to the DFE, $\mathcal{E}_0^s$ (Figure 4.2), Similarly, using the aforementioned parameter values with $\delta_i = 0$ $(i = 1, ..., 6)$, $\beta_1 = 0.48,\ \beta_2 = 0.39,\ \beta_3 = 0.32, \beta_4 = 0.25,\ \beta_5 = 0.18$ and $\beta_6 = 0.14$ (so that, $\mathcal{R}_0^m = 1.84$), the numerical simulation results obtained show convergence to an endemic equilibrium (Figure 4.3), in line with Theorem 4.7. Further extensive numerical simulations of the model (4.10) suggest the following conjecture.

Conjecture 4.1. *The endemic equilibrium of the model (4.10), given by $\mathcal{E}_1^s$, is GAS in $\mathcal{D}\backslash\mathcal{D}_0$ whenever $\mathcal{R}_0^s > 1$.*

Conclusions

An $SEIRS$ deterministic model, for the transmission dynamics of an arbitrary disease with multiple latent and infectious stages and gamma-distributed average waiting times in the exposed and infectious stages, is designed. The model, which uses a standard incidence function for the transmission rate, was rigorously analyzed to gain insight into its qualitative dynamical features. Some of the main findings of this chapter are:

(i) The model (4.10) has a globally-asymptotically stable disease-free equilibrium whenever the associated reproduction number is less than unity (Theorem 4.4);

(ii) The model has a unique endemic equilibrium whenever the threshold exceeds

unity. It is is locally- and globally-asymptotically stable for special cases (Theorems 4.6 and 4.7).

These qualitative results are essentially the same as those obtained for the SEI^nRS model (3.2) in Chapter 3. Thus, this study shows that the addition of multiple exposed stages and gamma distribution assumptions (for the mean duration in the exposed and infectious stages) does not change the qualitative (equilibrium) dynamics of the original $SEIRS$ model (or the SEI^nRS model considered in Chapter 3).

Table 4.3: Parameter values for the SE^mI^nRS model (4.10)

Parameter	Description	Value	References
π	Recruitment rate	7.976 *per* day	[17]
$\frac{1}{\gamma_i}$ $(i = 1, 2, 3)$	Average latency period (the rates are split as follows: $\frac{1}{\gamma_1} = \frac{1}{1.1}$, $\frac{1}{\gamma_2} = \frac{1}{0.6}$ and $\frac{1}{\gamma_3} = \frac{1}{0.2}$)	1.9 days	[17, 21, 40, 64, 67, 72]
$\frac{1}{\sigma_i}$ $(i = 1, ..., 6)$	Average duration of infectiousness (the rates are split as follows: $\frac{1}{\sigma_1} = 1.50$, $\frac{1}{\sigma_2} = 1.25$, $\frac{1}{\sigma_3} = 1.0$ $\frac{1}{\sigma_4} = 0.75$, $\frac{1}{\sigma_5} = 0.50$ and $\frac{1}{\sigma_6} = 0.25$)	5 days	[21, 67, 72]
δ_i $(i = 1, ..., 6)$	Disease-induced death rate of infectious individuals (the rates are split as follows: $\delta_1 = 0.35$, $\delta_2 = 0.025$, $\delta_3 = 0.015$ $\delta_4 = 0.008$, $\delta_5 = 0.0062$ and $\delta_6 = 0.0062$)	0.0062-0.035 *per* day	[72]
μ_S, μ_R, η_j; $j = 1, 2, 3$, μ_i; $i = 1, ..., 6$	Natural death rate	$\frac{1}{60\times365}$ *per* day	[17]
θ	Rate of loss of infection-acquired immunity	0.012 *per* day	Assumed
β_i $(i = 1, ..., 6)$	Transmission rates a) **for DFE**: $\beta_1 = 0.22$, $\beta_2 = 0.18$, $\beta_3 = 0.15$, $\beta_4 = 0.08$, $\beta_5 = 0.04$ and $\beta_6 = 0.02$ b) **for EEP**: $\beta_1 = 0.48$, $\beta_2 = 0.39$, $\beta_3 = 0.32$, $\beta_4 = 0.25$, $\beta_5 = 0.18$ and $\beta_6 = 0.14$	$[0.02 - 0.48]$ *per* day	Assumed

* For simulation purposes, the number of stages for the latent and infectious compartments are chosen to be 3 and 6 (i.e., $m = 3$ and $n = 6$), respectively [21].

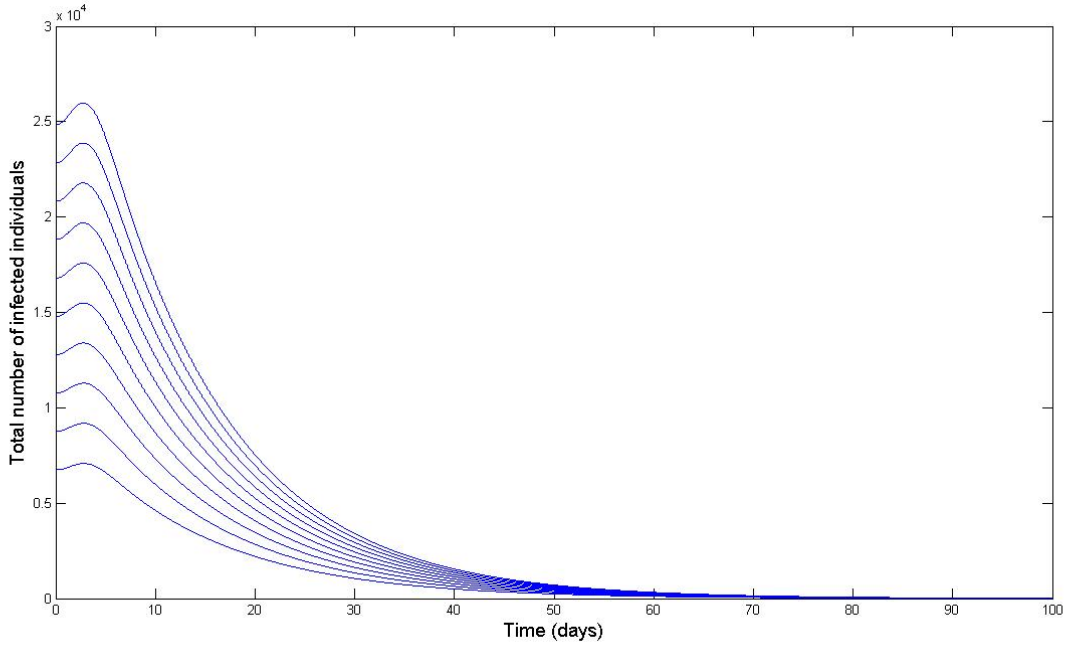

Figure 4.2: Simulations of the model (4.10) with $m = 3$ and $n = 6$, using the parameter values in Table 4.3 with $\beta_1 = 0.22$, $\beta_2 = 0.18$, $\beta_3 = 0.150$, $\beta_4 = 0.08$, $\beta_5 = 0.04$ and $\beta_6 = 0.02$ *per* day (so that, $\mathcal{R}_0^s = 0.73$), and various initial conditions.

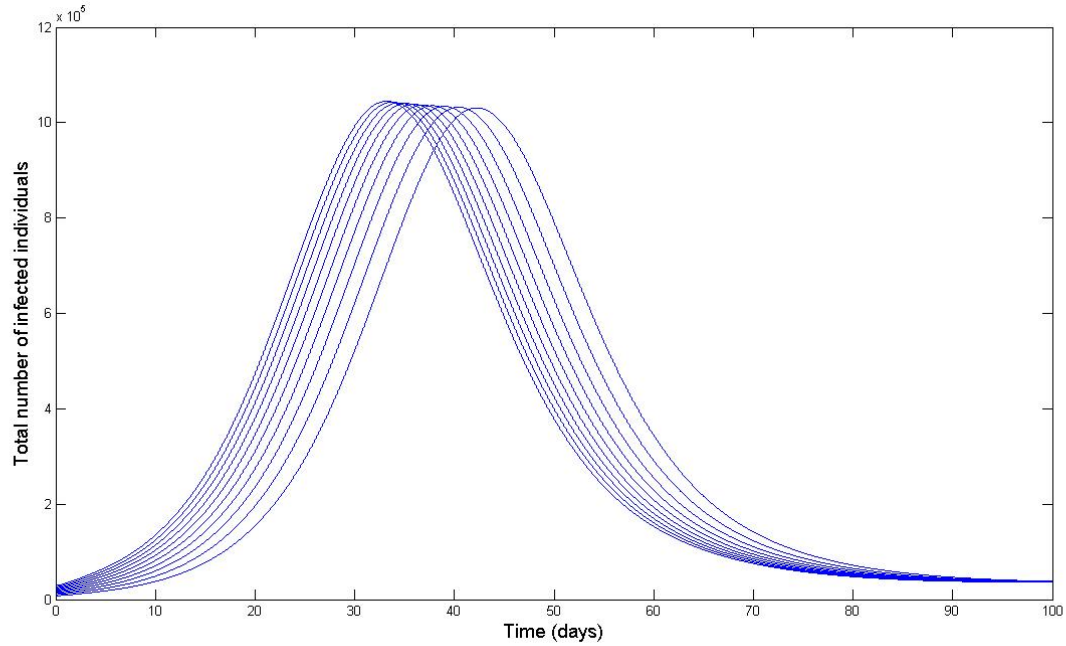

Figure 4.3: Simulations of the model (4.10) with $m = 3$ and $n = 6$, using the parameter values in Table 4.3 with $\delta_i = 0$ $(i = 1, ..., 6)$, $\beta_1 = 0.48$, $\beta_2 = 0.39$, $\beta_3 = 0.32$, $\beta_4 = 0.25$, $\beta_5 = 0.18$ and $\beta_6 = 0.14$ *per* day (so that, $\mathcal{R}_0^m = 1.84$), and various initial conditions.

Chapter 5

Non-autonomous SE^mI^nRS Model

5.1 Introduction

The motivation of this chapter stems from the fact that certain diseases exhibit seasonal/periodic behavior in their transmission dynamics. Such seasonal fluctuations are often the primary factors responsible for recurrent epidemic cycles. In the context of disease dynamics, seasonality (a periodic surge in disease incidence corresponding to seasons or other calendar periods) arise due to many factors, such as environmental and climatic changes (see, for instance, [1, 18, 30, 41, 63]). Periodic changes in social interactions can alter the contact rate for some directly-transmitted contagious infections. For example, in the case of childhood infectious diseases, the contact rates vary seasonally according to the school schedule [18, 20, 41].

In this chapter, the model developed in Chapter 4 will be extended to incorporate the effect of periodicity on the transmission dynamics of the disease being modelled. In other words, the main objective of this chapter is to determine whether or not incorporating periodicity into the SE^mI^nRS model (4.10), considered in Chapter 4, alters its qualitative dynamics (*vis-a-vis* the persistence or elimination of the disease).

5.2 Model Formulation

In this Chapter, the effective contact rate (β_i; $i = 1, ..., n$) is assumed to be periodic. Thus, the associated force of infection, λ, becomes

$$\lambda = \sum_{i=1}^{n} \frac{\beta_i(t) I_i(t)}{N(t)}. \tag{5.1}$$

Furthermore, some of the other parameters of the model (4.10) (namely: γ_j, σ_i and δ_i, with $j = 1, ..., m$ and $i = 1, ..., n$) are re-defined as time-dependent (periodic) parameters. Applying these refinements to the model (4.10) results in the following non-autonomous system of differential equations (in a periodic environment).

$$\begin{aligned}
\frac{dS}{dt} &= \pi + \theta R(t) - \sum_{i=1}^{n} \frac{\beta_i(t) I_i(t)}{N(t)} S(t) - \mu_S S(t), \\
\frac{dE_1}{dt} &= \sum_{i=1}^{n} \frac{\beta_i(t) I_i(t)}{N(t)} S(t) - \gamma_1(t) E_1(t) - \eta_1 E_1(t), \\
\frac{dE_j}{dt} &= \gamma_{j-1}(t) E_{j-1}(t) - \gamma_j(t) E_j(t) - \eta_j E_j(t); \ j = 2, ..., m, \\
\frac{dI_1}{dt} &= \gamma_m(t) E_m(t) - \sigma_1(t) I_1(t) - \mu_1 I_1(t) - \delta_1(t) I_1(t), \\
\frac{dI_i}{dt} &= \sigma_{i-1}(t) I_{i-1}(t) - \sigma_i(t) I_i(t) - \mu_i I_i(t) - \delta_i(t) I_i(t); \ i = 2, ..., n, \\
\frac{dR}{dt} &= \sigma_n(t) I_n(t) - \theta R(t) - \mu_R R(t),
\end{aligned} \tag{5.2}$$

where, as in Chapter 4,

$$N(t) = S(t) + \sum_{j=1}^{m} E_j(t) + \sum_{i=1}^{n} I_i(t) + R(t). \tag{5.3}$$

A flow diagram of the model is depicted in Figure 5.1; and the associated parameters are tabulated in Table 5.1).

Table 5.1: Descriptions of the parameters of the SE^mI^nRS model (5.2)

Parameter	Description
π	Recruitment rate
μ_S	Natural death rate for susceptible individuals
η_j	Natural death rate for individuals in exposed Stage j (for $j = 1, ..., m$)
μ_i	Natural death rate for individuals in infectious Stage i (for $i = 1, ..., n$)
μ_R	Natural death rate for recovered individuals
$\gamma_j(t)$	Progression rate from exposed Stage j to Stage $j+1$ (for $j = 1, ..., m-1$)
$\gamma_m(t)$	Progression rate of exposed individuals in Stage m to first infectious stage
σ_i(t)	Progression rate from infectious Stage i to Stage $i+1$ (for $i = 1, ..., n-1$)
$\sigma_n(t)$	Recovery rate for infectious individuals in Stage n
$\delta_i(t)$	Disease-induced death rate for infectious individuals in Stage i (for $i = 1, ..., n$)
θ	Rate of loss of infection-acquired immunity

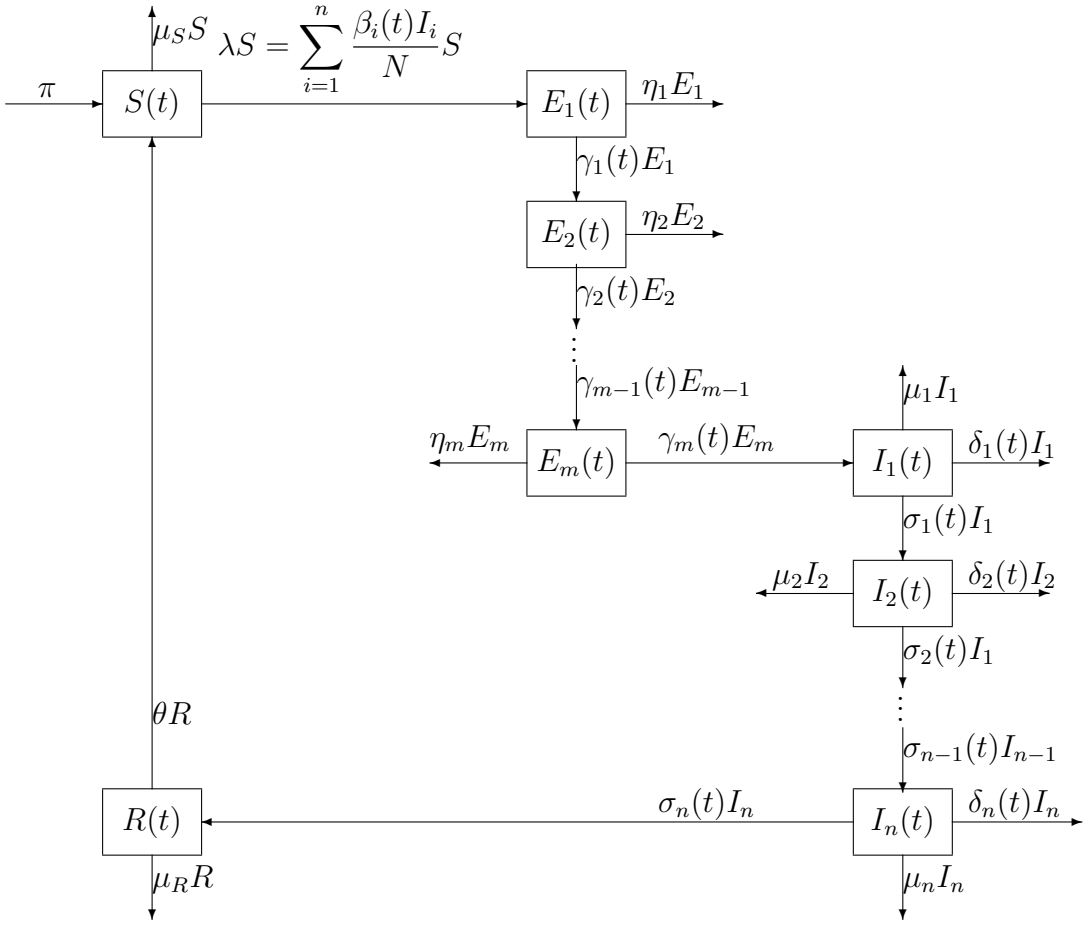

Figure 5.1: Schematic diagram of the SE^mI^nRS model (5.2).

It should be mentioned that, in the model (5.2), the demographic parameters

(π, μ_S, μ_R, η_j ($j = 1, ..., m$) and μ_i ($i = 1, ..., n$)) and the rate of loss of infection-acquired immunity (θ) are assumed to be constant (since they are not directly affected by the periodic environment). Furthermore, for mathematical convenience, all the natural death rates are assumed to be equal (i.e., $\mu = \mu_S = \mu_R = \eta_j = \mu_i$; for $j = 1, ..., m$ and $i = 1, ..., n$).

Adding the equations of the model (5.2), and using the assumption $\mu = \mu_S = \eta_j = \mu_i = \mu_R$ (for $j = 1, ..., m$ and $i = 1, ..., n$), gives

$$\frac{dN(t)}{dt} = \pi - \mu N - \sum_{i=1}^{n} \delta_i(t) I_i(t). \tag{5.4}$$

It follows from the relation (5.3) that

$$R(t) = N(t) - \Big[S(t) + \sum_{j=1}^{m} E_j(t) + \sum_{i=1}^{n} I_i(t)\Big]. \tag{5.5}$$

Hence, the model (5.2), together with (5.4) and (5.5), can further be simplified to:

$$\begin{aligned}
\frac{dS}{dt} &= \pi + \theta\left\{N(t) - \Big[S(t) + \sum_{j=1}^{m} E_j(t) + \sum_{i=1}^{n} I_i(t)\Big]\right\} - \sum_{i=1}^{n} \frac{\beta_i(t) I_i(t)}{N(t)} S(t) - \mu S(t),\\
\frac{dE_1}{dt} &= \sum_{i=1}^{n} \frac{\beta_i(t) I_i(t)}{N(t)} S(t) - \gamma_1(t) E_1(t) - \mu E_1(t),\\
\frac{dE_j}{dt} &= \gamma_{j-1}(t) E_{j-1}(t) - \gamma_j(t) E_j(t) - \mu E_j(t);\ j = 2, ..., m,\\
\frac{dI_1}{dt} &= \gamma_m(t) E_m(t) - \sigma_1(t) I_1(t) - \mu I_1(t) - \delta_1(t) I_1(t),\\
\frac{dI_i}{dt} &= \sigma_{i-1}(t) I_{i-1}(t) - \sigma_i(t) I_i(t) - \mu I_i(t) - \delta_i(t) I_i(t);\ i = 2, ..., n,\\
\frac{dN}{dt} &= \pi - \mu N(t) - \sum_{i=1}^{n} \delta_i(t) I_i(t),
\end{aligned} \tag{5.6}$$

where, $\mu = \mu_S = \mu_R = \eta_j = \mu_i$ (for $j = 1, ..., m$ and $i = 1, ..., n$).

5.2.1 Invariant Region

Theorem 5.1. *The non-autonomous system (5.6) has a unique and bounded solution in*

$$X = \left\{ (S, E_1, ..., E_m, I_1, ..., I_n, N) \in \mathbb{R}_+^{m+n+2} : \ S + \sum_{j=1}^{m} E_j + \sum_{i=1}^{n} I_i \leq N \right\}$$

with initial value $(S^0, E_1^0, ..., E_m^0, I_1^0, ..., I_n^0, N^0) \in X$. *Further, the compact set*

$$\mathcal{D}^* = \left\{ (S, E_1, ..., E_m, I_1, ..., I_n, N) \in X : \ N \leq \frac{\pi}{\mu} \right\}$$

is positively-invariant and attracts all positive orbits in X.

Proof. Following [62], let $g \in (\mathbb{R}_+^{m+n+2}, \mathbb{R})$ be defined by

$$g(\mathbf{x}) = \begin{cases} 0, & \mathbf{x} = \mathbf{0}; \\ \dfrac{\sum_{i=1}^{n} I_i S}{S + \sum_{j=1}^{m} E_j + \sum_{i=1}^{n} I_i + R}, & \mathbf{x} \in \mathbb{R}_+^{m+n+2} \backslash \{\mathbf{0}\}, \end{cases}$$

where $\mathbf{x} = (S, E_1, ..., E_m, I_1, ..., I_n, R)^T$ and $\mathbf{0} = (0, 0, ..., 0, 0..., 0, 0)^T$. The function g is continuous and globally-Lipschitz on $\mathbb{R}_+^{m+n+2}$ (where $L = m + n + 2 > 0$ is the associated Lipschitz constant). Hence, using Theorem 5.2.1 in [83], it follows that, for any initial data

$$[S(0), E_1(0), ..., E_m(0), I_1(0), ..., I_n(0), N(0)] = (S^0, E_1^0, ..., E_m^0, I_1^0, ..., I_n^0, N^0) \in \mathbb{R}_+^{m+n+2},$$

the system (5.6) has a unique local non-negative solution

$$(S(t), E_1(t), ..., E_m(t), I_1(t), ..., I_n(t), N(t)).$$

Furthermore, it follows from the last equation (5.6) that

$$\frac{dN}{dt} = \pi - \mu N(t) - \sum_{i=1}^{n} \delta_i(t) I_i(t) \leq \pi - \mu N(t),$$

from which it is clear that the associated linear differential equation,

$$\frac{dN}{dt} = \pi - \mu N,$$

has a unique equilibrium solution $N^* = \frac{\pi}{\mu}$, which is GAS. Finally, it can be shown, using comparison theorem [84], that $N(t)$ is bounded. Thus, the solution of the non-autonomous system (5.6) exists on the interval $[0, \infty)$. □

5.3 Computation of Basic Reproduction Ratio

5.3.1 Local Stability

The concept of *basic reproduction ratio* associated with disease transmission models in a periodic environment has been addressed in a number of studies (see, for instance, [6, 7, 8, 91, 99]). The methodology in [91] will be used to compute the reproduction ratio for the non-autonomous model (5.6).

The model (5.6) has a disease-free solution, given by

$$\mathcal{E}_0 = (S_0, E_{1_0}, \cdots, E_{m_0}, I_{1_0}, \cdots, I_{n_0}, \cdots, N_0) = \left(\frac{\pi}{\mu}, 0, ..., 0, \frac{\pi}{\mu}\right). \tag{5.7}$$

The equations for the rate of change of the infected components $(E_1, \cdots, E_m, I_1, \cdots, I_n)$ of the linearized version of the system (5.6), at the disease-free solution $(\mathcal{E}_0)$, are given by

$$\begin{aligned}
\frac{dE_1}{dt} &= \sum_{i=1}^{n} \beta_i(t) I_i(t) - [\gamma_1(t) + \eta_1]\, E_1(t), \\
\frac{dE_j}{dt} &= \gamma_{j-1}(t) E_{j-1}(t) - [\gamma_j(t) + \eta_j]\, E_j(t);\ j = 2, ..., m, \\
\frac{dI_1}{dt} &= \gamma_m(t) E_m(t) - [\sigma_1(t) + \mu_1 + \delta_1(t)]\, I_1(t), \\
\frac{dI_i}{dt} &= \sigma_{i-1}(t) I_{i-1}(t) - [\sigma_i(t) + \mu_i + \delta_i(t)]\, I_i(t);\ i = 2, ..., n.
\end{aligned} \tag{5.8}$$

Using the notation in [91], the next generation matrix $F(t)$ (of the new infection terms) and the M-matrix $V(t)$ (of the remaining transition terms), associated with the non-autonomous model (5.6) are given, respectively, by

$$F(t) = \begin{pmatrix} F_1(t) & F_2(t) \\ F_3(t) & F_4(t) \end{pmatrix}, \quad V(t) = \begin{pmatrix} M_1(t) & M_2(t) \\ M_3(t) & M_4(t) \end{pmatrix},$$

where, $F_1(t), F_3(t), F_4(t)$ and $M_2(t)$ are zero matrices with dimensions $m \times m, n \times m, n \times n$ and $m \times n$, respectively, and

$$F_2(t) = \begin{pmatrix} \beta_1(t) & \beta_2(t) & \beta_3(t) & \beta_4(t) & \cdots & \beta_n(t) \\ 0 & 0 & 0 & 0 & \cdots & 0 \\ 0 & 0 & 0 & 0 & \cdots & 0 \\ 0 & 0 & 0 & 0 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 & \cdots & 0 \end{pmatrix},$$

$$M_1(t) = \begin{pmatrix} \hat{h}_1(t) & 0 & 0 & 0 & \cdots & 0 \\ -\gamma_1(t) & \hat{h}_2(t) & 0 & 0 & \cdots & 0 \\ 0 & -\gamma_2(t) & \hat{h}_3(t) & 0 & \cdots & 0 \\ 0 & 0 & -\gamma_3(t) & \hat{h}_4(t) & \cdots & 0 \\ \vdots & \vdots & \ddots & \ddots & \ddots & \vdots \\ 0 & 0 & \cdots & 0 & -\gamma_{m-1}(t) & \hat{h}_m(t) \end{pmatrix},$$

$$M_3(t) = \begin{pmatrix} 0 & 0 & 0 & 0 & \cdots & 0 & -\gamma_m(t) \\ 0 & 0 & 0 & 0 & \cdots & 0 & 0 \\ 0 & 0 & 0 & 0 & \cdots & 0 & 0 \\ 0 & 0 & 0 & 0 & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & 0 & \cdots & 0 & 0 \end{pmatrix},$$

$$M_4(t) = \begin{pmatrix} \hat{k}_1(t) & 0 & 0 & 0 & \cdots & 0 \\ -\sigma_1(t) & \hat{k}_2(t) & 0 & 0 & \cdots & 0 \\ 0 & -\sigma_2(t) & \hat{k}_3(t) & 0 & \cdots & 0 \\ 0 & 0 & -\sigma_3(t) & \hat{k}_4(t) & \cdots & 0 \\ \vdots & \vdots & \ddots & \ddots & \ddots & \vdots \\ 0 & 0 & \cdots & 0 & -\sigma_{n-1}(t) & \hat{k}_n(t) \end{pmatrix},$$

with dimensions $m \times n, m \times m, n \times m$ and $n \times n$, respectively. Furthermore, $\hat{h}_j = \gamma_j + \mu$, $(j = 1, ..., m)$, $\hat{k}_i = \sigma_i + \mu + \delta_i$ $(i = 1, ..., n)$ and $k_\theta = \mu + \theta$.

In line with [91], let Φ_M be the monodromy matrix for the linear $\omega-$periodic system:

$$\frac{dZ}{dt} = M(t)Z, \tag{5.9}$$

with $\rho(\Phi_M(\omega))$ representing the spectral radius of $\Phi_M(\omega)$. Furthermore, let

$$Y(t, s), t \geq s,$$

be the evolution operator of the linear $\omega-$periodic system

$$\frac{dy}{dt} = -V(t)y.$$

Hence, for each $s \in \mathbb{R}$, the associated $(m + n) \times (m + n)$ matrix $Y(t, s)$ satisfies [91]

$$\frac{dY(t,s)}{dt} = -V(t)Y(t,s),\ \forall t \geq s,\ \text{where } Y(s,s) = I.$$

Let $\phi(s)$ ($\omega-$periodic in s) be the initial distribution of infectious individuals. Thus, it follows that $F(s)\phi(s)$ is the rate at which new infections are produced by infected individuals who were introduced into the population at time s [91]. Furthermore, $Y(t,s)F(s)\phi(s)$ represents the number of infected individuals who were newly infected at time s and remain infected at time t for $t \geq s$.

It follows from the above definition that the cumulative distribution of new infections at time t, produced by all infectious individuals, $\phi(s)$, introduced into the population at prior time $t = s$, is given by [91]

$$\Psi(t) = \int_{-\infty}^{t} Y(t,s)F(s)\phi(s)ds = \int_{0}^{\infty} Y(t,s)F(t-a)\phi(t-a)da.$$

Let $\mathbb{C}_\omega$ be the Banach space of all $\omega-$periodic functions from $\mathbb{R}$ to $\mathbb{R}^{m+n}$ equipped with the maximum norm ($\|.\|$) and positive cone [91]

$$\mathbb{C}_\omega^+ = \big\{\phi \in \mathbb{C}_\omega : \phi(t) \geq 0, \forall t \in \mathbb{R}\big\}.$$

Define a linear operator by

$$L : \mathbb{C}_\omega \to \mathbb{C}_\omega,$$

such that,

$$(L\phi)(t) = \int_{0}^{\infty} Y(t,t-a)F(t-a)\phi(t-a)da,\ \forall t \in \mathbb{R}, \phi \in \mathbb{C}_\omega.$$

The associated *reproduction ratio* (denoted by $\mathcal{R}_0$) is then given by the spectral radius of the operator L (that is, $\mathcal{R}_0 = \rho(L)$) [91]. It can be verified that the non-autonomous system (5.6) satisfy Assumptions $(A1) - (A7)$ in [91] (see Appendix C).

Hence, using Theorem 2.2 in [91] (see also Theorem C.1 in Appendix C), the following result holds.

Lemma 5.1. *The disease-free solution ($\mathcal{E}_0$) of the model (5.6), given by (5.7), is LAS whenever $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$.*

It is worth mentioning that the expression for the reproduction ratio ($\mathcal{R}_0$) (for the non-autonomous model (5.6)) reduces to that of $\mathcal{R}_0^m$ in Section 4.5 (if $\mu = \mu_S = \eta_j = \mu_i = \mu_R$ and all the time-dependent parameters ($\beta_i(t)$, $\gamma_j(t)$, $\sigma_i(t)$, $\delta_i(t)$; $j = 1, ..., m$ and $i = 1, ..., n$) are constants in (5.6)). This is because, in this case, the corresponding next generation matrix $F(t)$ (of the new infection terms) and $M-$matrix $V(t)$ (of the remaining transition terms), respectively, become $F(t) = F$ and $V(t) = V$ (so that, in this case, $\mathcal{R}_0 = \rho(L) = \rho(FV^{-1})$). This ($\mathcal{R}_0$) is exactly the same expression obtained for the reproduction number $\mathcal{R}_0^m$ in (4.25), for the corresponding autonomous model (4.10) under the setting given in Section 4.5.

The reproduction ratio, $\mathcal{R}_0$, associated with the non-autonomous model (5.6), can be computed using Theorem C.2 (given in Appendix C). This entails carrying out the following computations [91]:

(a) First of all, for a given value of λ, the matrix $W(\omega, \lambda)$ is computed numerically using a standard numerical integrator (for instance, the forward-Euler or the Runge-Kutta finite-difference method [53]).

(b) Then, the spectral radius $\rho(W(\lambda))$ is calculated.

(c) Let $f(\lambda) = \rho(W(\lambda)) - 1$. A root-finding method (such as the bisection method [53]) is used to find the zero of f. Thje zero of f is $\mathcal{R}_0$.

(d) Let $[\mathcal{R}_0]$ be the reproduction number of the corresponding non-autonomous system, obtained by averaging the time-dependent parameters of the system (5.6). That is,

$$[\mathcal{R}_0] = \prod_{j=1}^{m} \frac{\bar{\gamma}_j}{\bar{h}_j} \sum_{i=1}^{n} \bar{\beta}_i \prod_{p=1}^{i} \frac{\bar{\sigma}_{p-1}}{\bar{k}_p}, \text{ with } \bar{\sigma}_0 = 1, \tag{5.10}$$

where,

$$\begin{aligned} \bar{\gamma}_j &= \frac{1}{\omega}\int_0^\omega \gamma_j(t)dt;\ (j=1,...,m),\ \bar{\beta}_i = \frac{1}{\omega}\int_0^\omega \beta_i(t)dt;\ (i=1,...,n), \\ \bar{\sigma}_i &= \frac{1}{\omega}\int_0^\omega \sigma_i(t)dt,\ \bar{\delta}_i = \frac{1}{\omega}\int_0^\omega \delta_i(t)dt;\ (i=1,...,n). \end{aligned}$$

Hence, $\bar{h}_j = \mu + \bar{\gamma}_j$ $(j = 1, ..., m)$ and $\bar{k}_i = \bar{\sigma}_i + \mu + \bar{\delta}_i$ $(i = 1, ..., n)$.

(e) Let $\beta_i(t)$ be defined by $\beta_i(t) = \beta_0\left[1.1 + sin(\frac{\pi(t+1)}{6})\right]$ (for $i = 1, ..., n$) [62]. Other parameter values, which are largely relevant to the transmission dynamics of influenza [17], are chosen and tabulated in Table 5.2.

Figure 5.2 depicts the profiles of the average reproduction ratio $[\mathcal{R}_0]$ and the reproduction ratio, $\mathcal{R}_0$, as function of $\beta_0 \in [0.02, 0.48]$ (it should be recalled that this range for β_0 was also used for simulating the autonomous system (4.10) in Chapter 4). It is clear from Figure 5.2 that the average reproduction ratio $[\mathcal{R}_0]$, for the different values of β_0 considered, is always greater than the reproduction ratio $\mathcal{R}_0$ for the various values of β_0 used in the simulations. The epidemiological implication of Theorem 5.1 is that the disease can be eliminated from the community (when $\mathcal{R}_0 < 1$) if the initial sizes of the sub-populations of the model are in the basin attraction of the disease-free solution $(\mathcal{E}_0)$.

5.3.2 Global Stability of the Disease-Free Solution

Theorem 5.2. *The disease-free solution of the model (5.6), given by $\mathcal{E}_0$, is globally-asymptotically stable in $\mathcal{D}^*$ whenever $\mathcal{R}_0 < 1$.*

Proof. Noting, first of all, that $S(t) < N(t)$ for all $t > 0$ in $\mathcal{D}^*$, the equation for $\frac{dE_1}{dt}$ in (5.6) can be written as

$$\frac{dE_1}{dt} = \sum_{i=1}^{n} \frac{\beta_i I_i(t)}{N(t)} - \hat{h}_1 E_1(t) \leq \sum_{i=1}^{n} \beta_i I_i(t) - \hat{h}_1 E_1(t), \tag{5.11}$$

where $\hat{h}_1(t) = \gamma_1(t) + \mu$. Hence, noting (5.11), the equations for the infected classes in (5.6) can be re-written as

$$\begin{aligned}
\frac{dE_1}{dt} &\leq \sum_{i=1}^{n} \beta_i(t) I_i(t) - \gamma_1(t) E_1(t) - \mu E_1(t), \\
\frac{dE_j}{dt} &= \gamma_{j-1}(t) E_{j-1}(t) - \gamma_j(t) E_j(t) - \mu E_j(t); \ j = 2, ..., m, \\
\frac{dI_1}{dt} &= \gamma_m(t) E_m(t) - \sigma_1(t) I_1(t) - \mu I_1(t) - \delta_1(t) I_1(t), \\
\frac{dI_i}{dt} &= \sigma_{i-1}(t) I_{i-1}(t) - \sigma_i(t) I_i(t) - \mu I_i(t) - \delta_i(t) I_i(t); \ i = 2, ..., n-1, \\
\frac{dI_n}{dt} &= \sigma_{n-1}(t) I_{n-1}(t) - \sigma_n(t) I_n(t) - \mu I_n(t) - \delta_n(t) I_n(t).
\end{aligned} \tag{5.12}$$

The auxiliary equation of (5.12) (with equality) can be written in terms of the next generation matrices, $F(t)$ and $V(t)$ as below:

$$\frac{dW}{dt} = [F(t) - V(t)]W(t), \tag{5.13}$$

where $W = (E_1, \cdots, E_j, \cdots, E_m, I_1, \cdots, I_n)^T$. It follows from Lemma 2.2 that there exists a positive $\omega-$periodic function, $w(t)$, such that

$$W(t) = e^{\alpha t} w(t), \text{ where } \alpha = \frac{1}{\omega} \ln \rho(\phi_{F-V}(\omega)),$$

is the solution of (5.13). Further, $\mathcal{R}_0 < 1$ implies that $\rho(\phi_{F-V}(\omega)) < 1$ (by Theorem C.1 given in Appendix C). Hence, α is a negative constant. Consequently, $W(t) \to 0$ as $t \to \infty$.

It follows, by the Lipschitz continuity for any non-negative initial solution

$$(E_1(0), ..., E_m(0), I_1(0), ..., I_n(0))^T$$

of the system (5.13) (and noting that the matrices $F(t)$ and $V(t)$ have non-negative entries only; that, they are Type-K) that there exists a sufficiently large $M^* > 0$ such that

$$(E_1(0), ..., E_m(0), I_1(0), ..., I_n(0))^T \leq M^* w(0).$$

Thus, it follows (by comparison theorem, Theorem 2.10), that

$$(E_1(t), ..., E_m(t), I_1(t), ..., I_n(t)) \leq M^* W(t), \ \forall t > 0,$$

where, $M^*W(t)$ is also a solution of (5.13). Furthermore, by considering the auxiliary system in (5.12), it follows (by the comparison theorem mentioned above and Theorem 1.2 in [88]) that there exists an $\omega-$periodic function such that $\lim_{t\to\infty} E_j(t) = 0$ and $\lim_{t\to\infty} I_i(t) = 0$, for $j = 1, ..., m, \ i = 1, ..., n$. Finally, it follows from Theorem 1.2 in [88] that $N(t) \to \frac{\pi}{\mu}$ and $S(t) \to \frac{\pi}{\mu}$ whenever $\mathcal{R}_0 < 1$. Thus,

$$\lim_{t\to\infty} (S(t), E_1(t), ..., E_m(t), I_1(t), ..., I_n(t), N(t)) \to \mathcal{E}_0, \text{ whenever } \mathcal{R}_0 < 1 \text{ in } \mathcal{D}^*.$$

□

The epidemiological implication of Theorem 5.2 is that the disease will be eliminated from the community if $\mathcal{R}_0 < 1$. It is worth recalling that the DFE, $\mathcal{E}_0^s$, of the corresponding autonomous model (4.10) is also GAS whenever $\mathcal{R}_0^s < 1$ (Theorem 4.4). Thus, Theorem 5.2 shows that adding periodicity to the autonomous SE^mI^nRS model (4.10) does not alter the global asymptotic dynamics of the DFE of the autonomous model (4.10), for the special case where $\mu = \mu_S = \mu_R = \eta_j = \mu_i$ (for $j = 1, ..., m$ and $i = 1, ..., n$) in (4.10).

5.4 Uniform-Persistence of Periodic Solutions

Persistence addresses the long-term survival of some, or all, components of a given (epidemiological) system. In this section, the conditions needed for disease persistence in the population will be explored.

Theorem 5.3. *If the reproduction ratio $\mathcal{R}_0 > 1$, then there exists an $\epsilon > 0$ such that for any solution $(S(t), E_1(t), ..., E_m(t), I_1(t), ..., I_n(t), N(t))$ of the system (5.6) with initial value, $x^0 = (S^0, E_1^0, ..., E_m^0, I_1^0, ..., I_n^0, N^0)$, such that*

$$x^0 \in \Big\{(S(t), E_1(t), ..., E_m(t), I_1(t), ..., I_n(t), N(t)) \in X : E_j > 0,\ I_i > 0,\ (j = 1, ..., m; i = 1, ..., n)\Big\}$$

satisfies

$$\liminf_{t\to\infty} E_j(t) \geq \epsilon \quad \textit{and} \quad \liminf_{t\to\infty} I_i(t) \geq \epsilon,\ \ j = 1, ..., m;\ \ i = 1, ..., n.$$

The proof of Theorem 5.3 is based on using persistence theory (see, for instance, [71, 96, 99]). It entails defining a Poincaré map for the system (5.6), and then showing that the map is bounded, positively-invariant and uniformly-persistent (as shown below; see also [15, 37, 71, 82, 83, 85, 96, 99]).

Proof. The proof is based on the methodology given in [71, 96, 99]. The following three steps are taken.

Step 1: Construction of Poincaré map

Define, first of all, a region

$$\begin{aligned} X_0 &= \Big\{(S(t), E_1(t), ..., E_m, I_1(t), ..., I_n(t), N(t)) \in X : E_j(t) > 0,\ I_i(t) > 0\Big\}, \\ \partial X_0 &= X \backslash X_0,\ j = 1, ..., m;\ i = 1, ..., n. \end{aligned}$$

Furthermore, let $P : X \to X$ be the Poincaré map associated with the system (5.6), satisfying

$$P(x^0) \quad = \quad u(\omega, x^0), \ \forall \ x^0 \in X,$$

and,

$$u(0, x^0) \quad = \quad x^0,$$

where $u(t, x^0)$ is the unique solution of the system (5.6). Then, the map for the discrete-time system (for details see Section 2.6) is:

$$P^q(x^0) = u(q\omega, x^0), \ \forall q \geq 0.$$

The next task is to show that the map P is uniformly-persistent with respect to $(X, \partial X_0)$. It can be shown that the regions X and X_0 are positively-invariant (see Appendix D). Furthermore, it can be shown that the set ∂X_0 is relatively closed in X [99]. Then, it follows from Theorem 5.1 that the solutions of (5.6) are uniformly- and ultimately-bounded. Thus, the semi-flow P is point-dissipative on X, and the mapping P is compact. Hence, it follows from Theorem 5.1 that the discrete-time system, P^q, admits a global attractor in X, which attracts every bounded set in X (see [39, 94]).

To prove that the map P is uniformly-persistent, it is necessary to show that it is weakly uniformly-persistent (since X and X_0 are positively-invariant). Following [71], let

$$M_\partial = \Big\{ x^0 \in \partial X_0 : \ P^q(x^0) \in \partial X_0, \ \forall q \geq 0 \Big\}.$$

Next, we claim that $M_\partial = \Big\{ (S, 0, 0, ..., 0, N) \in X : S, N \geq 0 \Big\}$.

We then show that for any $x^0 \in M_\partial$, $E_j(q\omega) = I_i(q\omega) = 0$ $(j = 1, ..., m; \ i = 1, ..., n)$ $\forall q \geq 0$. This is shown by contradiction (in line with [96, 99]). Assume that

there exists a $q_1 \geq 0$ such that $(E_1(q_1\omega), ..., E_m(q_1\omega), I_1(q_1\omega), ..., I_n(q_1\omega))^T > \mathbf{0}$. Since $S(t) > 0 \ \forall t > 0$ (see Appendix D), it follows that $N(t) \geq S(t) > 0 \ \forall t \geq q_1\omega$ (where the initial time 0 is now replaced with $q_1\omega$). Hence, it follows from Theorem 2.6 (as generalized to non-autonomous systems) that

$$(E_1(q_1\omega), ..., E_m(q_1\omega), I_1(q_1\omega), ..., I_n(q_1\omega))^T \gg \mathbf{0}, \ \forall t > q_1\omega,$$

which contradicts the fact that $M_\partial \subset \partial X_0$. Thus, there is no $q_1 \geq 0$ such that

$$(E_1(q_1\omega), ..., E_m(q_1\omega), I_1(q_1\omega), ..., I_n(q_1\omega))^T > \mathbf{0}.$$

Thus, there is exactly one fixed-point, namely the disease-free solution $(\mathcal{E}_0)$, of P in M_∂.

Step 2: Weakly uniformly-persistence

It is claimed, first of all, that the Poincarè map, P, is weakly uniformly-persistent with respect to $(X_0, \partial X_0)$. That is (by Definition 2.31) there exists $\epsilon^* > 0$ such that

$$\lim_{q\to\infty} \sup d(P^q(x^0), \mathcal{E}_0) \geq \epsilon^*, \ \forall x^0 \in X_0. \tag{5.14}$$

The proof of this claim is by contradiction. Following [71], suppose for all $\epsilon^* > 0$,

$$\lim_{q\to\infty} \sup d(P^q(x^0), \mathcal{E}_0) < \epsilon^*, \text{ for some } x^0 \in X_0.$$

Thus, it is assumed that $d(P^q(x^0), \mathcal{E}_0) < \epsilon^*$ for all $q \geq 0$. It follows, by the continuity of solutions with respect to the initial values, that $\forall \epsilon > 0$, there exists $\epsilon^* > 0$ such that, for all $x^0 \in X_0$ with $|x^0 - \mathcal{E}_0| \leq \epsilon^*$,

$$||u(t, x^0) - u(t, \mathcal{E}_0)|| \leq \epsilon \ \forall t \in [0, \omega].$$

To show that inequality (5.14) holds (using the contradiction set up above), it is assumed, without loss of generality, that

$$d(P^q(x^0), \mathcal{E}_0) < \epsilon^*, \ \forall q \geq 0.$$

Hence,

$$||u(t, P^q(x^0)) - u(t, \mathcal{E}_0)|| < \epsilon, \ \forall t \in [0, \omega], \ \forall q \geq 0.$$

It follows that (from the properties of the Poincaré map (see Section 2.6) for any $t \geq 0$ such that $t = q\omega + t'$ (where $t' \in [0, \omega)$ and $q = [\frac{t}{\omega}]$ is the greatest positive integer less than or equal to $\frac{t}{\omega}$)

$$||u(t, P^q(x^0)) - u(t, \mathcal{E}_0)|| \ = \ ||u(t', P^q(x^0)) - u(t', \mathcal{E}_0)|| < \epsilon, \ \forall t \geq 0.$$

Setting $(S(t), E_1(t), ..., E_m(t), I_1(t), ..., I_n(t), N(t)) = u(t, x^0)$, it follows that

$$E_j(t) < \epsilon, \ I_i(t) < \epsilon, \text{ for } j = 1, ..., m; \ i = 1, ..., n \ \forall t \geq 0. \tag{5.15}$$

Thus, noting the inequalities in (5.15), the equation for $\frac{dS}{dt}$ in (5.6) becomes

$$\begin{aligned}
\frac{dS}{dt} &\geq \pi + \theta \left[N(t) - S(t) - \left(\sum_{j=1}^{m} \epsilon + \sum_{i=1}^{n} \epsilon \right) \right] - \sum_{i=1}^{n} \frac{\beta_i(t)\epsilon}{N(t)} S(t) - \mu S(t), \\
&= \pi + \theta \Big[N(t) - S(t) - (m+n)\epsilon \Big] - \sum_{i=1}^{n} \frac{\beta_i(t)\epsilon}{N(t)} S(t) - \mu S(t), \qquad (5.16) \\
&\geq \pi + \theta \Big[-(m+n)\epsilon \Big] - \epsilon \sum_{i=1}^{n} \beta_i(t) - \mu S(t), \text{ since } S \leq N, \\
&= \pi - (m+n)\epsilon\theta - \epsilon \sum_{i=1}^{n} \beta_i(t) - \mu S(t).
\end{aligned}$$

Consider, next, the auxiliary equation of (5.16), given by

$$\frac{d\hat{S}}{dt} = \pi - (m+n)\epsilon\theta - \epsilon\sum_{i=1}^{n}\beta_i(t) - \mu\hat{S}(t). \tag{5.17}$$

Thus, for any $\epsilon > 0$, equation (5.17) admits a globally-asymptotically stable periodic solution, denoted by $\hat{S}^*(t,\epsilon)$ (see Appendix E). It can be seen from the form of $\hat{S}^*(0,\epsilon)$, given in (E.3) of Appendix E, that $\hat{S}^*(0,\epsilon)$ is continuous in ϵ. Thus, small enough fixed values of ϵ and ν can be chosen such that

$$\hat{S}^*(t,\epsilon) > \tilde{S}^* - \nu, \ \forall t \in [0,\omega],$$

where, $\tilde{S}^* = \frac{\pi}{\mu}$ is the unique steady solution of the equation $\frac{d\tilde{S}}{dt} = \pi - \mu\tilde{S}$, which is globally-attractive in $\mathbb{R}_+$. By the periodicity property of $\hat{S}^*(t,\epsilon)$, and noting that $\tilde{S}^* - \nu$ is a constant, it follows that the inequality $\hat{S}^*(t,\epsilon) > \tilde{S}^* - \nu$ holds for sufficiently small ϵ, ν and $t \geq 0$.

Since the periodic solution $\hat{S}^*(t,\epsilon)$, of equation (5.17), is globally attractive on $\mathbb{R}_+$, and $\hat{S}^*(t,\epsilon) > \tilde{S}^* - \nu$, it follows that $S(t) > \tilde{S}^* - \nu$ for large $t > 0$. Furthermore, it follows from the last equation in (5.6) that

$$N(t) \leq \frac{\pi}{\mu} + \nu, \quad \text{for sufficiently large } t.$$

Similarly, it follows from the equations for the latent and infectious classes of the system (5.6) that, for sufficiently large t,

$$\begin{aligned}
\frac{dE_1}{dt} &\geq \sum_{i=1}^{n}\beta_i(t)I_i(t)\,(1-\Delta) - \Big[\gamma_1(t)+\mu\Big]E_1(t), \\
\frac{dE_j}{dt} &= \gamma_{j-1}(t)E_{j-1}(t) - \Big[\gamma_j(t)+\mu\Big]E_j(t), \ j = 2,...,m \\
\frac{dI_1}{dt} &= \gamma_m(t)E_m(t) - \Big[\sigma_1(t)+\mu+\delta_1(t)\Big]I_1(t), \\
\frac{dI_i}{dt} &= \sigma_{i-1}(t)I_{i-1}(t) - \Big[\sigma_i(t)+\mu+\delta_i(t)\Big]I_i(t); \ i = 2,...,n,
\end{aligned} \tag{5.18}$$

where, $\Delta = \frac{2\nu}{\frac{\pi}{\mu}+\nu}$.

Consider, next, the auxiliary (with equality) case of the first inequality in (5.18), given by

$$\frac{d\hat{E}_1}{dt} = \sum_{i=1}^{n} \beta_i(t) I_i(t) (1-\Delta) - [\gamma_1(t) + \mu] \hat{E}_1(t). \tag{5.19}$$

It follows from Lemma 2.2, applied to (5.18) with (5.19), that there exists a positive $\omega-$periodic function $(\bar{E}_1(t), ..., \bar{E}_m(t), \bar{I}_1(t), ..., \bar{I}_n(t))^T$ such that

$$(\hat{E}_1(t), ..., \hat{E}_m(t), \hat{I}_1(t), ..., \hat{I}_n(t))^T = e^{\xi t}(\bar{E}_1(t), ..., \bar{E}_m(t), \bar{I}_1(t), ..., \bar{I}_n(t))^T,$$

is the solution of the linear system (5.19) with

$$\xi = \frac{1}{\omega} \ln \rho(\Phi_{F-V-M_\Delta}(\omega)),$$

where M_Δ is an $(m+n) \times (m+n)$ matrix, given by

$$M_\Delta = \begin{pmatrix} 0 & \cdots & 0 & \beta_1\Delta & \beta_2\Delta & \cdots & \beta_n\Delta \\ 0 & \cdots & 0 & 0 & 0 & \cdots & 0 \\ 0 & \cdots & 0 & 0 & 0 & \cdots & 0 \\ \vdots & \ddots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & \cdots & 0 & 0 & 0 & \cdots & 0 \end{pmatrix}.$$

Since $\mathcal{R}_0 > 1$ implies that $\Phi_{F-V}(\omega) > 1$ (Theorem C.1 in Appendix C), it follows that ξ is a positive constant. Thus, a small enough value of ν can be chosen so that the monodromy matrix $\Phi_{F-V-M_\Delta}(\omega) > 1$.

Let $t = q\omega$, where q is a non-negative integer. Since $\xi\omega > 0$, $\bar{E}_j(t) > 0$ and $\bar{I}_i(t) > 0$ (for $j = 1, ..., m; i = 1, ..., n$), it follows from

$$(\hat{E}_1(q\omega),...,\hat{E}_m(q\omega),\hat{I}_1(q\omega),...,\hat{I}_n(q\omega))^T = e^{\xi q\omega}(\bar{E}_1(q\omega),...,\bar{E}_m(q\omega),\bar{I}_1(q\omega),...,\bar{I}_n(q\omega))^T,$$

that

$$\bar{E}_j(q\omega)\to\infty \text{ and } \bar{I}_i(q\omega)\to\infty \ (j=1,...,m;\ i=1,...,n) \text{ as } q\to\infty.$$

Thus, for any non-negative initial value of the system (5.18),

$$(E_1(0),...,E_m(0),I_1(0),...,I_n(0))^T \geq K^*(\bar{E}_1(0),...,\bar{E}_m(0),\bar{I}_1(0),...,\bar{I}_n(0))^T.$$

It follows, using comparison theorem (Theorem 2.10), that

$$(E_1(t),...,E_m(t),I_1(t),...,I_n(t))^T \geq K^*(\bar{E}_1(t),...,\bar{E}_m(t),\bar{I}_1(t),...,\bar{I}_n(t))^T,\ \forall t>0.$$

Hence,

$$E_j(q\omega)\to\infty, \text{ and } I_i(q\omega)\to\infty, \text{ (for } j=1,...,m;\ i=1,...,n) \text{ as } q\to\infty,$$

which contradicts the inequalities in (5.15). Hence, the map P is weakly uniformly-persistent with respect to $(X_0,\partial X_0)$.

Step 3: Uniform Persistence of Solutions

It follows from Theorem 2.13 and Theorem 2.14 that P is uniformly-persistent with respect to $(X_0,\partial X_0)$. Furthermore, Theorem 2.31 guarantees that the solutions of (5.6) are uniformly-persistent with respect to $(X_0,\partial X_0)$. Hence, there exists $\epsilon>0$ such that the solution, $(S(t),E_1(t),...,E_m(t),I_1(t),...,I_n(t),N(t))$, to the system (5.6) with initial value $x^0\in X_0$, satisfies

$$\liminf_{t\to\infty} E_j(t) \geq \epsilon, \liminf_{t\to\infty} I_i(t) \geq \epsilon \ (j = 1, ..., m;\ i = 1, ..., n).$$

Thus, the disease will persist in the population if $\mathcal{R}_0 > 1$.

□

5.5 Existence and Stability of Periodic Solutions

In this section, the existence and stability of non-trivial periodic solutions of the non-autonomous system (5.6) are explored. Theorem 2.15 will be used to show the existence part. First of all, it follows from Theorem 5.1 that the solutions of the system (5.6) are uniformly- and ultimately-bounded. Hence, P is point-dissipative on $\mathbb{R}_+^{m+n+2}$ and

$$P : \mathbb{R}_+^{m+n+2} \to \mathbb{R}_+^{m+n+2}.$$

Furthermore, P is uniformly-persistent with respect to $(X_0, \partial X_0)$ if $\mathcal{R}_0 > 1$ (Theorem 5.3). Thus, it follows from Theorem 2.15 that P has a fixed-point,

$$(S^\star, E_1^\star, ..., E_m^\star, I_1^\star, ..., I_n^\star, N^\star) \in Int(\mathbb{R}_+^{m+n+2}).$$

Hence, $(S^\star(t), E_1^\star(t), ..., E_m^\star(t), I_1^\star(t), ..., I_n^\star(t), N^\star(t))$ is a positive $\omega-$periodic solution of system (5.6). Since the non-autonomous system (5.6) is equivalent to (5.2), it is convenient to carry out the analysis on the latter. Consequently, let the positive $\omega-$periodic solution of the system (5.2) be $\mathcal{E}_1$, where

$$\mathcal{E}_1 = (S^\star(t), E_1^\star(t), ..., E_m^\star(t), I_1^\star(t), ..., I_n^\star(t), R^\star(t)).$$

Define a region

$$\mathcal{D}_0 = \left\{(S, E_1, ..., E_m, I_1, ..., I_n, R) \in \mathcal{D} : E_1 = \cdots = E_m = I_1 = \cdots = I_n = R = 0\right\}.$$

Theorem 5.4. *The system (5.6), or equivalently (5.2), has a positive $\omega-$periodic positive solution in X_0 given by $\mathcal{E}_1$. The solution $\mathcal{E}_1$ is GAS in $\mathcal{D}^*\backslash\mathcal{D}_0$ whenever $\mathcal{R}_0 > 1$ and $sign(S - S^\star) = sign(E_j - E_j^\star) = sign(I_i - I_i^\star) = sign(R - R^\star)$ for $j = 1, ..., m;\ i = 1, ..., n$.*

Proof. Let $\mathcal{R}_0 > 1$, so that the positive $\omega-$periodic solution of the system (5.2), given by $\mathcal{E}_1$, exists. Consider the following Lyapunov function for the system (5.2).

$$V = |S(t) - S^\star(t)| + \sum_{j=1}^{m} |E_j(t) - E_j^\star(t)| + \sum_{i=1}^{n} |I_i(t) - I_i^\star(t)| + |R(t) - R^\star(t)|. \quad (5.20)$$

It follows that the right derivative, D^+V, of V, is given by

$$\begin{aligned}
\dot{V} &= sign\Big[S(t) - S^\star(t)\Big]\Big\{[\pi + \theta R(t) - \lambda(t)S(t) - \mu S(t)] - [\pi + \theta R^\star(t) - \lambda^\star(t)S^\star(t) - \mu S^\star(t)]\Big\} \\
&+ sign\Big[E_1(t) - E_1^\star(t)\Big]\Big\{\Big[\lambda(t)S(t) - \hat{h}_1(t)E_1(t)\Big] - \Big[\lambda^\star(t)S^\star(t) - \hat{h}_1(t)E_1^\star(t)\Big]\Big\} \\
&+ \sum_{j=2}^{m} sign\Big[E_j(t) - E_j^\star(t)\Big]\Big\{\Big[\gamma_{j-1}(t)E_{j-1}(t) - \hat{h}_j(t)E_j(t)\Big] - \Big[\gamma_{j-1}(t)E_{j-1}^\star(t) - \hat{h}_j(t)E_j^\star(t)\Big]\Big\} \\
&+ sign\Big[I_1(t) - I_1^\star(t)\Big]\Big\{\Big[\gamma_m(t)E_m(t) - \hat{k}_1(t)I_1(t)\Big] - \Big[\gamma_m(t)E_m^\star(t) - \hat{k}_1(t)I_1^\star(t)\Big]\Big\} \\
&+ \sum_{i=2}^{n} sign\Big[I_i(t) - I_i^\star(t)\Big]\Big\{\Big[\sigma_{i-1}(t)I_{i-1}(t) - \hat{k}_i(t)I_i(t)\Big] - \Big[\sigma_{i-1}(t)I_{i-1}^\star(t) - \hat{k}_i(t)I_i^\star(t)\Big]\Big\} \\
&+ sign\Big[R(t) - R^\star(t)\Big]\Big\{\Big[\sigma_n(t)I_n(t) - \hat{k}_\theta R(t)\Big] - \Big[\sigma_n(t)I_n^\star(t) - \hat{k}_\theta R^\star(t)\Big]\Big\},
\end{aligned}$$

where, $\hat{h}_j(t) = \gamma_j(t) + \mu$, $\hat{k}_i(t) = \sigma_i(t) + \mu + \delta_i(t)$ $(j = 1, ..., m;\ i = 1, ..., n)$ and $\hat{k}_\theta = \theta + \mu$.

Simplifying the equation for $\dot{V}$ gives

$$\begin{aligned}
\dot{V} &= sign(S-S^\star)\Big[\theta(R-R^\star)-\lambda S+\lambda^\star S^\star-\mu(S-S^\star)\Big] \\
&+ sign(E_1-E_1^\star)\Big[-\hat{h}_1(E_1-E_1^\star)-\lambda^\star S^\star+\lambda S\Big] \\
&+ \sum_{j=2}^{m} sign(E_j-E_j^\star)\Big[\gamma_{j-1}(E_{j-1}-E_{j-1}^\star)-\hat{h}_j(E_j-E_j^\star)\Big] \\
&+ sign(I_1-I_1^\star)\Big[\gamma_m(E_m-E_m^\star)-\hat{k}_1(I_1-I_1^\star)\Big] \\
&+ \sum_{i=2}^{n} sign(I_i-I_i^\star)\Big[\sigma_{i-1}(I_{i-1}-I_{i-1}^\star)-\hat{k}_i(I_i-I_i^\star)\Big] \\
&+ sign(R-R^\star)\Big[\sigma_n(I_n-I_n^\star)-\hat{k}_\theta(R-R^\star)\Big].
\end{aligned} \tag{5.21}$$

Using the assumption $sign(S-S^\star)=sign(E_j-E_j^\star)=sign(R-R^\star)=sign(I_i-I_i^\star)$ (for $j=1,...,m$ and $i=1,...,n$) in (5.21) (and noting that, for a non-zero x, $sign\ x=\frac{x}{|x|}$), gives

$$\begin{aligned}
\dot{V} &= -\mu|S-S^\star|-\sum_{j=1}^{m}\mu|E_j-E_j^\star|-\sum_{i=1}^{n}(\mu+\delta_i)|I_i-I_i^\star|-\mu|R-R^\star|, \\
&\leq -\mu|S-S^\star|-\sum_{j=1}^{m}\mu|E_j-E_j^\star|-\sum_{i=1}^{n}\mu|I_i-I_i^\star|-\mu|R-R^\star|, \\
&= -\mu\left[|S-S^\star|+\sum_{j=1}^{m}|E_j-E_j^\star|+\sum_{i=1}^{n}|I_i-I_i^\star|+|R-R^\star|\right], \\
&= -\mu V.
\end{aligned}$$

Hence, $\lim_{t\to\infty} V(t)=0$. Thus (using the Lyapunov function above and the LaSalle's Principle), the non-trivial positive $\omega-$periodic solution of the model (5.2), $\mathcal{E}_1$, is GAS in $D^*\backslash D_0$ whenever $\mathcal{R}_0>1$ and $sign(S-S^\star)=sign(E_j-E_j^\star)=sign(I_i-I_i^\star)=sign(R-R^\star)$ for $j=1,...,m;\ i=1,...,n$. □

Theorem 5.4 shows that the disease will persist in the population whenever $\mathcal{R}_0>1$ and $sign(S-S^\star)=sign(E_j-E_j^\star)=sign(R-R^\star)=sign(I_i-I_i^\star)$ (for $j=1,...,m;\ i=1,...,n$). It should be stated that the condition $sign(S-S^\star)=sign(E_j-E_j^\star)=sign(R-R^\star)=sign(I_i-I_i^\star)$ (for $j=1,...,m;\ i=1,...,n$) is rather restrictive (and

may not be realistic epidemiologically. However, it is necessary for the proof to hold).

5.6 Numerical Simulations and Conclusions

Figure 5.3 depicts the numerical simulation results of the SE^mI^nRS model (5.6) for the case when $\mathcal{R}_0 < 1$, from which it is clear that all solutions converge to the disease-free solution, $\mathcal{E}_0$ (in line with Theorem 5.2). It is also worth mentioning that the corresponding autonomous SE^mI^nRS model (4.10) was also shown to be globally-asymptotically stable when the associated reproduction number is less than unity (Theorem 4.7).

Furthermore, Figure 5.4 shows a time series of the total number of infected individuals for the case when $\mathcal{R}_0 > 1$. Although this figure appears to show convergence to the disease-free solution ($\mathcal{E}_0$), the solutions actually converged to a non-zero periodic solution (see the blow up version of Figure 5.4, depicted in Figure 5.5).

Table 5.2: Parameter values for the SE^mI^nRS model (5.2)

Parameter	Description	Value	References
π	Recruitment rate	7.976 *per* day	[17]
$\frac{1}{\bar{\gamma}_i}$ $(i = 1, 2, 3)$	Average latency period (the rates are split as follows: $\frac{1}{\bar{\gamma}_1} = \frac{1}{1.1}$, $\frac{1}{\bar{\gamma}_2} = \frac{1}{0.6}$ and $\frac{1}{\bar{\gamma}_3} = \frac{1}{0.2}$)	1.9 days	[17, 21, 40, 64, 67, 72]
$\frac{1}{\bar{\sigma}_i}$ $(i = 1, ..., 6)$	Average duration of infectiousness (the rates are split as follows: $\frac{1}{\bar{\sigma}_1} = 1.50$, $\frac{1}{\bar{\sigma}_2} = 1.25$, $\frac{1}{\bar{\sigma}_3} = 1.0$ $\frac{1}{\bar{\sigma}_4} = 0.75$, $\frac{1}{\bar{\sigma}_5} = 0.50$ and $\frac{1}{\bar{\sigma}_6} = 0.25$)	5 days	[21, 67, 72]
$\bar{\delta}_i$ $(i = 1, ..., 6)$	Disease-induced death rate of infectious individuals (the rates are split as follows: $\bar{\delta}_1 = 0.35$, $\bar{\delta}_2 = 0.025$, $\bar{\delta}_3 = 0.015$, $\bar{\delta}_4 = 0.008$, $\bar{\delta}_5 = 0.0062$ and $\bar{\delta}_6 = 0.0062$)	0.0062-0.035 *per* day	[72]
$\mu_S, \mu_R,$ $\eta_j;\ j = 1, 2, 3,$ $\mu_i;\ i = 1, ..., 6$	Natural death rate	$\frac{1}{60\times365}$ *per* day	[17]
θ	Rate of loss of infection-acquired immunity	0.012 *per* day	Assumed
$\beta_i(t) =$ $\beta_0\left[1.1 + sin\left(\frac{\pi(t+1)}{6}\right)\right]$ $(i = 1, ..., 6)$	Transmission rates **for disease-free solution**: $\beta_0 \in [0.02 - 0.22]$ **for persistence of the disease**: $\beta_0 \in [0.14 - 0.48]$	$\beta_0 \in [0.02 - 0.48]$ *per* day *per* day	Assumed

* For simulation purposes, the number of stages for the latent and infectious compartments are chosen to be 3 and 6 (i.e., $m = 3$ and $n = 6$), respectively [21].

In summary, the non-autonomous SE^mI^nRS model (5.2) has a globally-asymptotically stable disease-free solution whenever $\mathcal{R}_0 < 1$. It has a positive periodic solution (and the disease persists in the population) whenever $\mathcal{R}_0 > 1$. The positive periodic solution is shown to be globally-asymptotically stable under ceratin conditions. These results (for system (5.6) with $\mu = \mu_S = \mu_R = \eta_j = \mu_i$ (for $j = 1, ..., m$ and $i = 1, ..., n$)) are consistent with those obtained for the corresponding autonomous SE^mI^nRS model

with gamma distributed average waiting times in the latent and infectious classes, given by (4.10) (and also the autonomous SEI^nRS model (3.2)). Thus, it can be concluded (based on the mathematical analyses in this chapter) that adding periodicity to the autonomous SE^mI^nRS model (4.10) does not alter its qualitative dynamics (with respect to the elimination or persistence of the disease in the population) for the special case model (4.10) with $\mu = \mu_S = \mu_R = \eta_j = \mu_i$ (for $j = 1, ..., m$ and $i = 1, ..., n$).

Conclusions

In this chapter, the autonomous SE^mI^nRS model presented in Chapter 4 is extended to incorporate the effect of periodicity. The resulting non-autonomous SE^mI^nRS model is rigorously analysed. Some of the the main findings of this chapter are:

(i) The non-autonomous model (5.2) has a globally-asymptotically stable disease-free solution whenever the associated reproduction ratio ($\mathcal{R}_0$) is less than unity (Theorem 5.2);

(iv) For the non-autonomous model (5.2), the disease will persist in the community whenever the associated threshold quantity exceeds unity (Theorem 5.3). It is is globally-asymptotically stable under certain conditions (Theorem 5.4).

Overall, the analyses in this chapter show that adding periodicity to the SE^mI^nRS model considered in Chapter 4 does not alter its main qualitative dynamics (with respect to the elimination or persistence of the disease in the population) if $\mu = \mu_S = \mu_R = \eta_j = \mu_i$ (for $j = 1, ..., m$ and $i = 1, ..., n$).

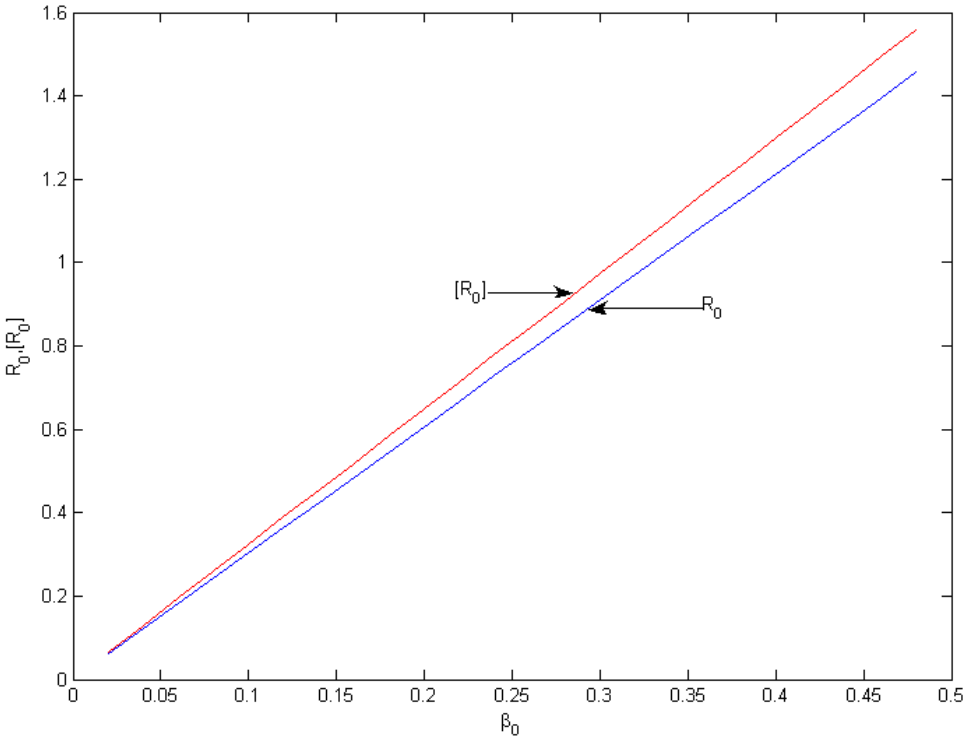

Figure 5.2: Simulations of the model (5.6) with $m = 3$ and $n = 6$, using the parameter values given in Table 5.2, showing the average reproduction ratio $[\mathcal{R}_0]$ and the reproduction ratio $\mathcal{R}_0$ for $\beta_0 \in [0.02, 0.48]$.

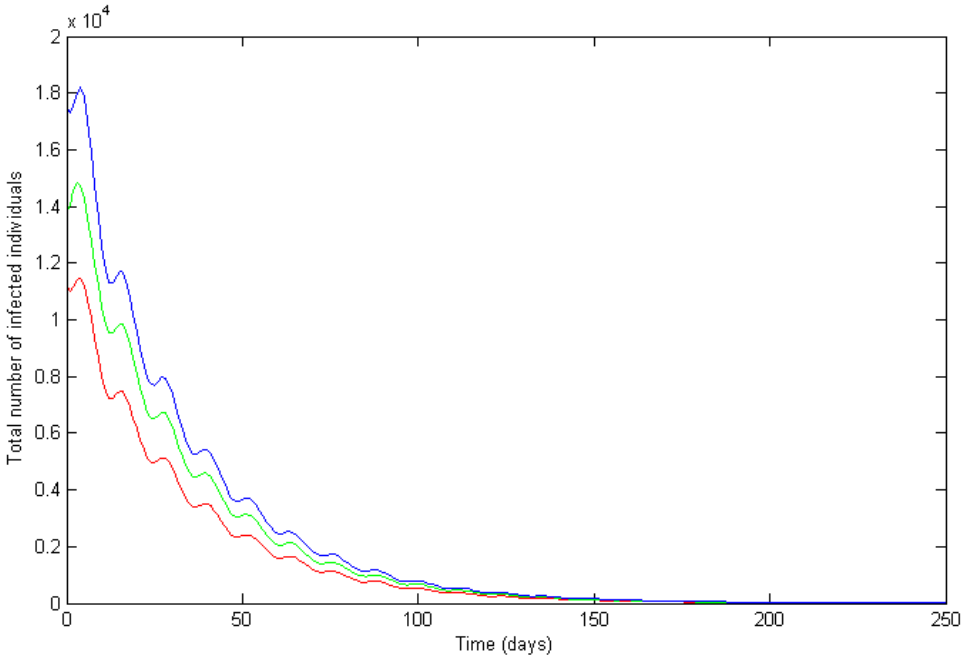

Figure 5.3: Simulations of the model (5.6) with $m = 3$ and $n = 6$ and various initial conditions, using the parameter values given in Table 5.2, with $\beta_0 \in [0.02, 0.48]$ (so that, $\mathcal{R}_0 = 0.73$) and various initial conditions.

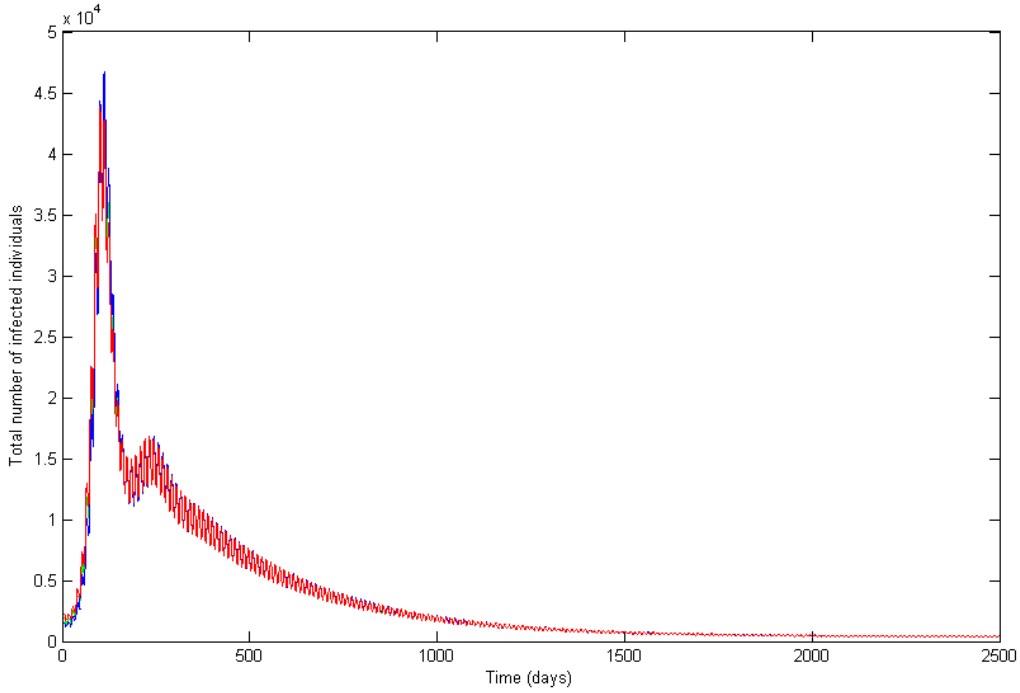

Figure 5.4: Simulations of the model (5.6) with $m = 3$ and $n = 6$ and various initial conditions, using the parameter values given in Table 5.2, with $\beta_0 \in [0.02, 0.48]$ *per* day (so that, $\mathcal{R}_0 = 1.84$), showing the total number of infected individuals as a function of time.

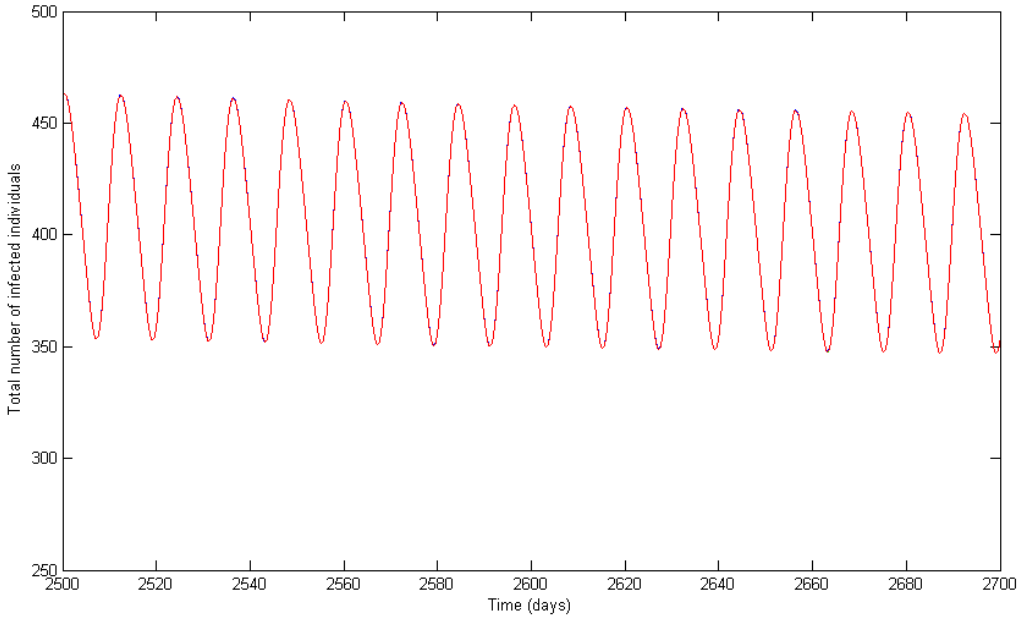

Figure 5.5: Blow up of the tail end of Figure 5.4.

Chapter 6

Summary of Contributions of the Thesis and Future Work

Contributions of the Thesis

The main contributions of the thesis can be summarized under two main catagories, namely model formulation and mathematical analysis. These categories are described below.

Model Formulation

The thesis contributes by developing three new models (which extend the classical $SEIR$ Kermack-McKendrick model) for gaining insight into the transmission dynamics of an influenza-like illness. In particular:

(i) A new deterministic mathematical model, which extends the classical $SEIR$ model (with mass action incidence) by incorporating arbitrary number of multiple infectious classes, standard incidence and the loss of infection-acquired immunity, is designed in Chapter 3;

(ii) The new model in (i) is further extended to include multiple exposed classes and

gamma-distributed waiting times in these classes in Chapter 4;

(iii) The model in (ii) is extended to include the effect of periodicity on the transmission dynamics of the disease in Chapter 5.

Mathematical Analysis

The thesis contributes by using numerous dynamical systems theories and techniques to rigorously analyse the qualitative features of the solutions of all the models presented in the thesis. These contributions are summarized below.

(i) **Chapter** 3: Lyapunov function theory, together with the LaSalle's Invariance Principle, is used to show that the disease-free equilibrium of the $SEIRS$ model (with multiple infectious and standard incidence function) is globally-asymptotically stable whenever the associated reproduction threshold is less than unity. Furthermore, the model has a unique endemic equilibrium when the threshold exceeds unity. The endemic equilibrium is shown to be locally-asymptotically stable, for a special case, using a Krasnoselskii sub-linearity trick. Furthermore, a non-linear Lyapunov function, of Goh-Voltrra type, is used to show that the unique endemic equilibrium of the model is globally-asymptotically stable for a special case.

(ii) **Chapter** 4: As in Chapter 3, the SE^mI^nRS model developed in Chapter 4 is shown (using Lyapunov function theory and LaSalle's Invariance Principle) to have a globally-asymptotically stable disease-free equilibrium whenever the associated reproduction number is less than unity. Furthermore, the model has a unique endemic equilibrium whenever the reproduction number exceeds unity. The unique endemic equilibrium is shown to be locally- and globally-asymptotically stable under certain conditions.

(iii) **Chapter** 5: The non-autonomous model in Chapter 5 is shown, using comparison theorem, to have globally-asymptotically stable disease-free periodic solution whenever the associated reproduction ratio is less than unity. Furthermore, using the theory of uniform-persistence of dynamical systems, it is shown that the disease will persist in the population under certain condistions.

In summary, a key novelty of this thesis is that it shows that extending the classical autonomous $SEIRS$ model (with standard incidence) to incorporate multiple latent and infectious stages (and gamma distribution assumptions for the average waiting times in these stages) in a periodic, or non-periodic, environment does not alter its main asymptotic dynamics (pertaining to the persistence or elimination of the disease from the population) for the case where the associated natural death rates in all epidemiological classes are assumed to be equal.

Future Work

The following is a list of extensions (to the modelling and mathematical analyses presented in the thesis) that I intend to consider in the future:

(i) Include the effect of control strategies (such as a vaccine, antiviral, quarantine, etc.) in the models;

(ii) Carry out sensitivity and uncertainty analysis on the model to investigate the effect of uncertainties in the estimate of the parameter values on the numerical simulation results obtained;

(iii) Explore the global-asymptotic stability of the endemic equilibria of the full models (and not just for special cases of the models);

(iv) Investigate the uniqueness, stability and bifurcations of the periodic solutions of the non-autonomous model presented in Chapter 5.

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Appendix A

Proof of Theorem 3.3

Proof. The proof of Theorem 3.3 is based on using the Krasnoselskii sub-linearity trick, as given in [44] (see also [23, 24]). The method entails showing that the linearized system of the system (where a prime denotes the differentiation with respect to t),

$$x' = f(x), \tag{A.1}$$

given by (where $\bar{x}$ is an equilibrium point),

$$\mathbf{Z}'(t) \;=\; Df(\bar{x})\mathbf{Z},$$

has no solution of the form,

$$\mathbf{Z}(t) = \mathbf{Z}_0 e^{\omega t}, \tag{A.2}$$

with $\mathbf{Z}_0 \in \mathbb{C}^{n+2}\backslash\{\mathbf{0}\}$, $\mathbf{Z}_0 = (Z_0, Z_1, ..., Z_n, Z_{n+1})$, $Z_i \in \mathbb{C}$, $\omega \in \mathbb{C}$ and $Re(\omega) \geq 0$, where $\mathbb{C}$ denotes the complex numbers (i.e., the eigenvalues of the characteristic polynomial associated with the linearized equations will have negative real parts, which will then confirm that the endemic equilibrium is LAS).

Linearizing the system (3.21) at the endemic equilibrium point, $\mathcal{E}_1^m$, gives

$$\begin{aligned}
\dot{E} &= (-\hat{\lambda}^{**} - k_0)E + \sum_{i=1}^{n}\left(\frac{\beta_i S^{**}}{N^{**}} - \hat{\lambda}^{**}\right) I_i - \hat{\lambda}^{**} R, \\
\dot{I}_1 &= \sigma_E E - k_1 I_1, \\
\dot{I}_2 &= \sigma_1 I_1 - k_2 I_2, \\
\dot{I}_j &= \sigma_{j-1} I_{j-1} - k_j I_j;\ j = 3, ..., n-1, \\
\dot{I}_n &= \sigma_{n-1} I_{n-1} - k_n I_n, \\
\dot{R} &= \sigma_n I_n - k_\theta R.
\end{aligned} \tag{A.3}$$

Hence, the EEP, $\mathcal{E}_1^m = (E^{**}, I_1^{**}, ..., I_n^{**}, R^{**})$, of the system (A.3) at steady-state, is given by

$$\begin{aligned}
E^{**} &= \frac{S^{**}}{k_0 N^{**}} \sum_{i=1}^{n} \beta_i I_i^{**}, \\
I_1^{**} &= \frac{\sigma_E}{k_1} E^{**}, \\
I_i^{**} &= \frac{\sigma_{i-1}}{k_i} I_{i-1}^{**};\ i = 2, .., n, \\
R^{**} &= \frac{\sigma_n}{k_\theta} I_n^{**},
\end{aligned}$$

which satisfies,

$$\mathcal{E}_1^m = H\mathcal{E}_1^m, \tag{A.4}$$

where,

$$H = \begin{pmatrix}
0 & \frac{\beta_1 S^{**}}{k_0 N^{**}} & \frac{\beta_2 S^{**}}{k_0 N^{**}} & \frac{\beta_3 S^{**}}{k_0 N^{**}} & \cdots & \frac{\beta_n S^{**}}{k_0 N^{**}} & 0 \\
\frac{\sigma_E}{k_1} & 0 & 0 & 0 & \cdots & 0 & 0 \\
0 & \frac{\sigma_1}{k_2} & 0 & 0 & \cdots & 0 & 0 \\
0 & 0 & \frac{\sigma_2}{k_3} & 0 & \cdots & 0 & 0 \\
\vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\
0 & 0 & 0 & 0 & \cdots & \frac{\sigma_n}{k_\theta} & 0
\end{pmatrix}.$$

Furthermore, substituting a solution of the form (A.2) into the linearized system (A.3) at equilibrium gives

$$\begin{aligned}
\omega Z_0 &= (-\hat{\lambda}^{**} - k_0)Z_0 + \sum_{i=1}^{n}\left(\frac{\beta_i S^{**}}{N^{**}} - \hat{\lambda}^{**}\right)Z_i - \hat{\lambda}^{**}Z_{n+1},\\
\omega Z_1 &= \sigma_E Z_0 - k_1 Z_1,\\
\omega Z_2 &= \sigma_1 Z_1 - k_2 Z_2,\\
\omega Z_j &= \sigma_{j-1} Z_{j-1} - k_j Z_j;\ j = 3, ..., n-1,\\
\omega Z_n &= \sigma_{n-1} Z_{n-1} - k_n Z_n,\\
\omega Z_{n+1} &= \sigma_n Z_n - k_\theta Z_{n+1}.
\end{aligned} \tag{A.5}$$

The system (A.5) can be simplified to give

$$\begin{aligned}
\left(1 + \frac{\hat{\lambda}^{**} + \omega}{k_0}\right)Z_0 &= \frac{S^{**}}{k_0 N^{**}}\sum_{i=1}^{n}\beta_i Z_i - \frac{\hat{\lambda}^{**}}{k_0}\sum_{i=1}^{n+1} Z_i,\\
\left(1 + \frac{\omega}{k_1}\right)Z_1 &= \frac{\sigma_E}{k_1} Z_0,\\
\left(1 + \frac{\omega}{k_2}\right)Z_2 &= \frac{\sigma_1}{k_2} Z_1,\\
\left(1 + \frac{\omega}{k_j}\right)Z_j &= \frac{\sigma_{j-1}}{k_j} Z_{j-1};\ j = 1, ..., n-1,\\
\left(1 + \frac{\omega}{k_n}\right)Z_n &= \frac{\sigma_{n-1}}{k_n} Z_{n-1},\\
\left(1 + \frac{\omega}{k_\theta}\right)Z_{n+1} &= \frac{\sigma_n}{k_\theta} Z_n.
\end{aligned} \tag{A.6}$$

Solving for Z_1 from the second equation of (A.6) and then solving for Z_i $(i = 2, ..., n+1)$ from the third to the last equations, in terms of Z_0, gives

$$Z_i = \sigma_E \prod_{j=1}^{i}\frac{\sigma_{j-1}}{\omega + k_j} Z_0;\ i = 1, ..., n+1,\ \sigma_0 = 1 \text{ and } k_{n+1} = k_\theta. \tag{A.7}$$

Substituting (A.7) into the first equation in (A.6), and simplifying, gives

$$\begin{aligned}
[1+F_1(\omega)]\,Z_0 &= \frac{S^{**}}{k_0 N^{**}}\sum_{i=1}^{n}\beta_i Z_i = (H\mathbf{Z})_1,\\
[1+F_2(\omega)]\,Z_1 &= \frac{\sigma_E}{k_1}Z_0 = (H\mathbf{Z})_2,\\
[1+F_3(\omega)]\,Z_2 &= \frac{\sigma_1}{k_2}Z_1 = (H\mathbf{Z})_3,\\
[1+F_i(\omega)]\,Z_{i-1} &= \frac{\delta_{i-2}}{k_{i-1}}Z_{i-2} = (H\mathbf{Z})_i,\ i=4,...,n-1,\\
[1+F_n(\omega)]\,Z_{n-1} &= \frac{\sigma_{n-2}}{k_{n-1}}Z_{n-2} = (H\mathbf{Z})_n,\\
[1+F_{n+1}(\omega)]\,Z_n &= \frac{\sigma_{n-1}}{k_n}Z_{n-1} = (H\mathbf{Z})_{n+1},\\
[1+F_{n+2}(\omega)]\,Z_{n+1} &= \frac{\sigma_n}{k_\theta}Z_n = (H\mathbf{Z})_{n+2}.
\end{aligned} \tag{A.8}$$

The system (A.8) has the general form

$$[1+F_i(\omega)]\,Z_{i-1} = (H\mathbf{Z})_i,\ i=1,....,n+2, \tag{A.9}$$

where,

$$F_1(\omega) = \frac{\hat{\lambda}^{**}+\omega}{k_0} + \frac{\hat{\lambda}^{**}\sigma_E}{k_0}\sum_{i=1}^{n+1}\prod_{j=1}^{i}\frac{\sigma_{j-1}}{(\omega+k_j)}, \tag{A.10}$$

$$F_i(\omega) = \frac{\omega}{k_{i-1}},\ i=2,...,n+2, \tag{A.11}$$

with $k_{n+1}=k_\theta$ and $\sigma_0=1$. The notation $(H\mathbf{Z})_i$ $(i=1,....,n+2)$ denotes the i^{th} coordinate of the vector $H\mathbf{Z}$, and Z_i $(i=1,...,n+1)$ is as given in (A.7).

It should be mentioned that all entries of the matrix H are non-negative, satisfying $\mathcal{E}_1^m = H\mathcal{E}_1^m$, with all coordinates of $\mathcal{E}_1^m$ positive. Hence, if $\mathbf{Z}$ is any solution of (A.9), then it is possible to find a minimal positive real number s, depending on $\mathbf{Z}$, such that (see [23, 24])

$$|\mathbf{Z}| \le s\mathcal{E}_1^m, \tag{A.12}$$

where, $|\mathbf{Z}| = (|Z_0|, |Z_1|, ..., |Z_{n+1}|)$ and $|.|$ is a norm in $\mathbb{C}$. The aim here is to show that if $Re(\omega) < 0$, then the linearized system (A.5) has a solution of the form (A.2).

The next task is to show that $Re(\omega) \geq 0$ is not satisfied, which will then be sufficient to conclude that $Re(\omega) < 0$. Assume that $Re(\omega) \geq 0$, and consider the following cases.

Case (i): $\omega = 0$.

For $\omega = 0$, the system given in (A.5) becomes a homogenous linear system of the form

$$\bar{\mathbf{0}} = G\mathbf{Z}_i, \ i = 0, 1, ..., n+1;$$

where,

$$G = \begin{pmatrix} -\hat{\lambda}^{**} - k_0 & \frac{\beta_1 S^{**}}{N^{**}} - \hat{\lambda}^{**} & \frac{\beta_2 S^{**}}{N^{**}} - \hat{\lambda}^{**} & \frac{\beta_3 S^{**}}{N^{**}} - \hat{\lambda}^{**} & \cdots & \frac{\beta_n S^{**}}{N^{**}} - \hat{\lambda}^{**} & -\hat{\lambda}^{**} \\ \sigma_E & -k_1 & 0 & 0 & \cdots & 0 & 0 \\ 0 & \sigma_1 & -k_2 & 0 & \cdots & 0 & 0 \\ 0 & 0 & \sigma_2 & -k_3 & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & 0 & \cdots & \sigma_n & -k_\theta \end{pmatrix}.$$

The determinant of the matrix G corresponds to the determinant of the matrix of the linearized system (A.3) (i.e., the determinant of the Jacobian of the system (3.21) at $\mathcal{E}_1^m$), and is given by

$$\begin{aligned} det(G) &= (-1)^n \prod_{i=0}^{n+1} k_i + (-1)^n \prod_{i=1}^{n+1} k_i \hat{\lambda}^{**} \left(1 + \sigma_E \sum_{i=1}^{n+1} c_i\right) + (-1)^{n+1} \prod_{i=0}^{n+1} k_i \frac{S^{**}\mathcal{R}_0^m}{N^{**}} \\ &= (-1)^n \prod_{i=1}^{n+1} k_i \hat{\lambda}^{**} \left(1 + \sigma_E \sum_{i=1}^{n+1} c_i\right) \qquad \text{(A.13)} \\ &\begin{cases} < 0, & \text{if } n \text{ is odd;} \\ > 0, & \text{if } n \text{ is even,} \end{cases} \end{aligned}$$

where,

$$c_i = \prod_{j=1}^{i} \frac{\sigma_{j-1}}{k_j}, \text{ with } \sigma_0 = 1, \ k_{n+1} = k_\theta, \ i = 1, .., n+1.$$

Solving the equations in (3.21), at the endemic steady-state, gives

$$\begin{aligned} k_0 E^{**} &= \hat{\lambda}^{**} S^{**}, \\ I_i^{**} &= c_i \hat{\lambda}^{**} S^{**}; \ i = 1, ..., n, \end{aligned} \tag{A.14}$$

with,

$$c_i = \frac{\sigma_E}{k_0} \prod_{j=1}^{i} \frac{\sigma_{j-1}}{k_j}, \ i = 1, ..., n, \ \sigma_0 = 1, \tag{A.15}$$

and $\hat{\lambda}$ is as given in (3.18). It should be mentioned that the first and last terms of (A.13) cancel out. This is described below. Simplifying (A.14) with (3.18) leads to

$$\sum_{i=1}^{n} \beta_i c_i \frac{S^{**}}{N^{**}} = 1. \tag{A.16}$$

It follows from (A.15) and (3.19) that

$$\sum_{i=1}^{n} \beta_i c_i = \mathcal{R}_0^m. \tag{A.17}$$

Using (A.17) in (A.16) shows that $\frac{S^{**}\mathcal{R}_0^m}{N^{**}} = 1$ as required.

Since the determinant of G is non-zero, it follows that the system (A.5), which has the form of the system given in (A.9), can only have a unique solution $\mathbf{Z} = \bar{\mathbf{0}}$ (which corresponds to the DFE, $\mathcal{E}_0$, of the model (3.21)).

Case (ii): $Re(\omega) > 0$**.**

Since $Re(\omega) \neq 0$ (by assumption), we have that $F_i(\omega) > 0$, which implies that $|F_i(\omega) + 1| > 1$ for all $i = 1, ..., n+2$

Define,

$$F(\omega) = \min\{(|F_i(\omega) + 1|),\ i = 1, ..., n+2\}.$$

Then, $1 < F(\omega)$. Hence, $\frac{s}{F(\omega)} < s$. This implies that $|\mathbf{Z}| > \frac{s}{F(\omega)}\mathcal{E}_1^m$, since s is the minimal positive number defined in (A.12). Since H has non-negative entries only, it follows that

$$[1 + F_i(\omega)]\mathbf{Z} \quad = \quad H\mathbf{Z},\ i = 1, ..., n+2.$$

Furthermore, since $F(\omega) \leq [1 + F_i(\omega)]$, it follows that

$$F(\omega)\mathbf{Z} \quad \leq \quad H\mathbf{Z},$$

which implies that (by taking norms on both sides),

$$F(\omega)|\mathbf{Z}| \quad \leq \quad H|\mathbf{Z}|. \tag{A.18}$$

Using (A.12), and then (A.4), in (A.18) gives

$$F(\omega)|\mathbf{Z}| \leq H|\mathbf{Z}| \leq sH\mathcal{E}_1^m \leq s\mathcal{E}_1^m,$$

so that,

$$|\mathbf{Z}| \leq \frac{s}{F(\omega)}\mathcal{E}_1^m < s\mathcal{E}_1^m.$$

It then follows, from the second equation of (A.8), that

$$|Z_1| \leq \frac{s}{F(\omega)} I_1^{**} < sI_1^{**},$$

which contradicts the fact that s is minimal. Hence, $Re(\omega) < 0$. Thus, the endemic equilibrium, $\mathcal{E}_1^m$, of the model (3.21) is LAS whenever $\mathcal{R}_0^m > 1$. □

Appendix B

Proof of Theorem 4.6

Proof. Consider the model (4.10), with $\hat{\lambda}$ defined by (4.24). Further, let $\mathcal{R}_0^m > 1$, so that the EEP ($\mathcal{E}_1^m$) exists (see Section 4.5). The proof is based on using the Krasnoselskii sub-linearity trick (as in Appendix A). System (4.27) is reproduced below for convenience.

$$\begin{aligned}
\dot{E}_1 &= \hat{\lambda}\left(N^{**} - \sum_{j=1}^{m} E_j - \sum_{i=1}^{n} I_i - R\right) - \hat{h}_1 E_1, \\
\dot{E}_j &= \gamma_{j-1} E_{j-1} - \hat{h}_j E_j;\ j = 2, ..., m-1, \\
\dot{E}_m &= \gamma_{m-1} E_{m-1} - \hat{h}_m E_m, \\
\dot{I}_1 &= \gamma_m E_m - \hat{k}_1 I_1, \\
\dot{I}_j &= \sigma_{j-1} I_{j-1} - \hat{k}_j I_j;\ j = 2, ..., n, \\
\dot{R} &= \sigma_n I_n - \hat{k}_\theta R,
\end{aligned} \tag{B.1}$$

Linearizing the reduced system (B.1), at the endemic steady-state ($\mathcal{E}_1^m$), gives

$$\begin{aligned}
\dot{E}_1 &= (-\hat{\lambda}^{**} - h_1)E_1 - \hat{\lambda}^{**}\sum_{j=2}^{m} E_j + \sum_{i=1}^{n}\left(\frac{\beta_i S^{**}}{N^{**}} - \hat{\lambda}^{**}\right) I_i - \hat{\lambda}^{**} R, \\
\dot{E}_2 &= \gamma_1 E_1 - h_2 E_2, \\
\dot{E}_j &= \gamma_{j-1} E_{j-1} - h_j E_j;\ j = 3, ..., m \\
\dot{I}_1 &= \gamma_m E_m - k_1 I_1, \\
\dot{I}_i &= \sigma_{i-1} I_{i-1} - k_i I_i;\ i = 2, ..., n, \\
\dot{R} &= \sigma_n I_n - k_\theta R.
\end{aligned} \tag{B.2}$$

Solving for the EEP, $\mathcal{E}_1^m = (E_1^{**}, \cdots, E_m^{**}, I_1^{**}, \cdots, I_n^{**}, R^{**})$, of the system (B.1), gives

$$\begin{aligned}
E_1^{**} &= \frac{S^{**}}{h_1 N^{**}} \sum_{i=1}^{n} \beta_i I_i^{**}, \\
E_2^{**} &= \frac{\gamma_1}{h_2} E_1^{**}, \\
E_j^{**} &= \frac{\gamma_{j-1}}{h_j} E_{j-1}^{**};\ j = 3, ..., m \\
I_1^{**} &= \frac{\gamma_m}{k_1} E_m^{**}, \\
I_i^{**} &= \frac{\sigma_{i-1}}{k_i} I_{i-1}^{**};\ i = 2, .., n, \\
R^{**} &= \frac{\sigma_n}{k_\theta} I_n^{**},
\end{aligned} \tag{B.3}$$

which satisfies,

$$\mathcal{E}_1^m = H\mathcal{E}_1^m, \tag{B.4}$$

where,

$$H = \begin{pmatrix} H_1 & H_2 \\ H_3 & H_4 \end{pmatrix}.$$

Here, the entries of the block matrix H are given by

$$H_1 = \begin{pmatrix} 0 & 0 & 0 & 0 & \cdots & 0 \\ \frac{\gamma_1}{h_2} & 0 & 0 & 0 & \cdots & 0 \\ 0 & \frac{\gamma_2}{h_3} & 0 & 0 & \cdots & 0 \\ 0 & 0 & \frac{\gamma_3}{h_4} & 0 & \cdots & 0 \\ \vdots & \vdots & \ddots & \ddots & \ddots & \vdots \\ 0 & 0 & \cdots & 0 & \frac{\gamma_{m-1}}{h_m} & 0 \end{pmatrix}, \; H_2 = \begin{pmatrix} \frac{\beta_1 S^{**}}{h_1 N^{**}} & \frac{\beta_2 S^{**}}{h_1 N^{**}} & \cdots & \frac{\beta_n S^{**}}{h_1 N^{**}} & 0 \\ 0 & 0 & \cdots & 0 & 0 \\ 0 & 0 & \cdots & 0 & 0 \\ 0 & 0 & \cdots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \cdots & 0 & 0 \end{pmatrix},$$

$$H_3 = \begin{pmatrix} 0 & 0 & 0 & 0 & \cdots & \frac{\gamma_m}{k_1} \\ 0 & 0 & 0 & 0 & \cdots & 0 \\ 0 & 0 & 0 & 0 & \cdots & 0 \\ 0 & 0 & 0 & 0 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 & \cdots & 0 \end{pmatrix}, \; H_4 = \begin{pmatrix} 0 & 0 & 0 & 0 & \cdots & 0 \\ \frac{\sigma_1}{k_2} & 0 & 0 & 0 & \cdots & 0 \\ 0 & \frac{\sigma_2}{k_3} & 0 & 0 & \cdots & 0 \\ 0 & 0 & \frac{\sigma_3}{k_4} & 0 & \cdots & 0 \\ \vdots & \vdots & \ddots & \ddots & \ddots & \vdots \\ 0 & 0 & \cdots & 0 & \frac{\sigma_n}{k_\theta} & 0 \end{pmatrix},$$

where, H_1, H_2, H_3 and H_4 are with dimensions of $m \times m, m \times (n+1), (n+1) \times m$ and $(n+1) \times (n+1)$, respectively.

Furthermore, substituting a solution of the form (A.2) into the linearized system (B.2) at equilibrium gives:

$$
\begin{aligned}
\omega Z_1 &= (-\hat{\lambda}^{**} - h_1)Z_1 - \hat{\lambda}^{**}\sum_{j=2}^{m} Z_j + \sum_{i=1}^{n}\left(\frac{\beta_i S^{**}}{N^{**}} - \hat{\lambda}^{**}\right) Z_{m+i} - \hat{\lambda}^{**} Z_{m+n+1},\\
\omega Z_2 &= \gamma_1 Z_1 - h_2 Z_2,\\
\omega Z_j &= \gamma_{j-1} Z_{j-1} - h_j Z_j,\ j = 3, ..., m-1\\
\omega Z_m &= \gamma_{m-1} Z_{m-1} - h_m Z_m,\\
\omega Z_{m+1} &= \gamma_m Z_m - k_1 Z_{m+1},\\
\omega Z_{m+2} &= \sigma_1 Z_{m+1} - k_2 Z_{m+2},\\
\omega Z_{m+i} &= \sigma_{i-1} Z_{m+i-1} - k_i Z_{m+i};\ i = 3, ..., n-1,\\
\omega Z_{m+n} &= \sigma_{n-1} Z_{m+n-1} - k_n Z_{m+n},\\
\omega Z_{m+n+1} &= \sigma_n Z_{m+n} - k_\theta Z_{m+n+1}.
\end{aligned} \tag{B.5}
$$

The system (B.5) can be simplified as:

$$
\begin{aligned}
\left(1 + \frac{\hat{\lambda}^{**} + \omega}{h_1}\right) Z_1 &= \frac{S^{**}}{h_1 N^{**}} \sum_{i=1}^{n} \beta_i Z_{m+i} - \frac{\hat{\lambda}^{**}}{h_1} \sum_{j=2}^{m+n+1} Z_j,\\
\left(1 + \frac{\omega}{h_2}\right) Z_2 &= \frac{\gamma_1}{h_2} Z_1,\\
\left(1 + \frac{\omega}{h_j}\right) Z_j &= \frac{\gamma_{j-1}}{h_j} Z_{j-1},\ j = 3, ..., m-1\\
\left(1 + \frac{\omega}{h_m}\right) Z_m &= \frac{\gamma_{m-1}}{h_m} Z_{m-1},\\
\left(1 + \frac{\omega}{k_1}\right) Z_{m+1} &= \frac{\gamma_m}{k_1} Z_m,\\
\left(1 + \frac{\omega}{k_2}\right) Z_{m+2} &= \frac{\sigma_1}{k_2} Z_{m+1},\\
\left(1 + \frac{\omega}{k_i}\right) Z_{m+i} &= \frac{\sigma_{i-1}}{k_i} Z_{m+i-1};\ i = 3, ..., n-1,\\
\left(1 + \frac{\omega}{k_n}\right) Z_{m+n} &= \frac{\sigma_{n-1}}{k_n} Z_{m+n-1},\\
\left(1 + \frac{\omega}{k_\theta}\right) Z_{m+n+1} &= \frac{\sigma_n}{k_\theta} Z_{m+n}.
\end{aligned} \tag{B.6}
$$

Solving for Z_2 from the second equation of (B.6) and then solving for Z_i $(i = 3, ..., m+n+1)$ from the third to the last equation, in terms of Z_1, gives

$$Z_j = \prod_{p=2}^{j} \frac{\gamma_{p-1}}{(\omega + h_p)} Z_1; \ j = 2, ..., m, \tag{B.7}$$

and,

$$Z_{m+i} = \left[\prod_{q=1}^{i} \frac{\sigma_{q-1}}{(\omega + k_q)} \prod_{p=2}^{m+1} \frac{\gamma_{p-1}}{(\omega + h_p)} \right] Z_1, ; \ i = 1, ..., n+1, \tag{B.8}$$

where,

$$\sigma_0 = 1, \ (\omega + h_{m+1}) = 1 \text{ and } k_{n+1} = k_\theta.$$

Substituting (B.7) and (B.8) into the first equation in (B.6), and simplifying, gives

$$\begin{aligned}
[1 + F_1(\omega)] Z_1 &= \frac{S^{**}}{h_1 N^{**}} \sum_{i=1}^{n} \beta_i Z_{m+i} = (H\mathbf{Z})_1, \\
[1 + F_2(\omega)] Z_2 &= \frac{\gamma_1}{h_2} Z_1 = (H\mathbf{Z})_2, \\
[1 + F_j(\omega)] Z_j &= \frac{\gamma_{j-1}}{h_j} Z_{j-1} = (H\mathbf{Z})_j; \ j = 3, ..., m, \\
[1 + F_{m+1}(\omega)] Z_{m+1} &= \frac{\gamma_m}{k_1} Z_m = (H\mathbf{Z})_{m+1}, \\
[1 + F_{m+2}(\omega)] Z_{m+2} &= \frac{\sigma_1}{k_2} Z_{m+1} = (H\mathbf{Z})_{m+2}, \\
[1 + F_{m+i}(\omega)] Z_{m+i} &= \frac{\sigma_{i-1}}{k_i} Z_{m+i-1} = (H\mathbf{Z})_{m+i}, \ i = 3, ..., n-1, \\
[1 + F_{m+n}(\omega)] Z_{m+n} &= \frac{\sigma_{n-1}}{k_n} Z_{m+n-1} = (H\mathbf{Z})_{m+n}, \\
[1 + F_{m+n+1}(\omega)] Z_{m+n+1} &= \frac{\sigma_n}{k_n} Z_{m+n} = (H\mathbf{Z})_{m+n+1}.
\end{aligned} \tag{B.9}$$

System (B.9) has the general form

$$[1 + F_i(\omega)] Z_i = (H\mathbf{Z})_i; \ i = 1, ..., m+n+1, \tag{B.10}$$

where,

$$\begin{aligned} F_1(\omega) &= \frac{\hat{\lambda}^{**}+\omega}{h_1} + \frac{\hat{\lambda}^{**}}{h_1}\sum_{j=2}^{m+n+1} Q_j, \\ F_j(\omega) &= \frac{\omega}{h_j},\ j=2,...,m, \\ F_{m+i}(\omega) &= \frac{\omega}{k_i},\ i=1,...,n+1, \end{aligned} \tag{B.11}$$

and,

$$Q_j = \begin{cases} \prod_{p=2}^{j} \frac{\gamma_{p-1}}{(\omega+h_p)}; & j=2,...,m; \\ \prod_{q=1}^{j} \frac{\sigma_{q-1}}{(\omega+k_q)} \prod_{p=2}^{m+1} \frac{\gamma_{p-1}}{(\omega+h_p)}; & j=m+1,...,m+n+1, \end{cases}$$

with, $k_{n+1} = k_\theta, (\omega + h_{m+1}) = 1$ and $\sigma_0 = 1$. The variables Z_j $(j = 2, ..., m+n+1)$ in (B.10) are defined in (B.7) and (B.8). The notation $(H\mathbf{Z})_i$ $(i = 1, ..., m+n+1)$ denotes the i^{th} coordinate of the vector $H\mathbf{Z}$.

As in Appendix A, it follows that all entries of the matrix H are non-negative, satisfying $\mathcal{E}_1^m = H\mathcal{E}_1^m$ (with all coordinates of $\mathcal{E}_1^m$ positive). Hence, if $\mathbf{Z}$ is any solution of (B.10), then it is possible to find a minimal positive real number s, depending on $\mathbf{Z}$, such that (see [23, 24])

$$||\mathbf{Z}|| \leq s\mathcal{E}_1^m, \tag{B.12}$$

where, $||\mathbf{Z}|| = (||Z_1||, ||Z_2||, ..., ||Z_{m+n+1}||)$ and $||.||$ is a norm in $\mathbb{C}$. Then, the aim is to show that if $Re(\omega) < 0$, so that the linearized system (B.5) has a solution of the form (A.2). Assume that $Re(\omega) \geq 0$, and consider the following cases.

Case (i): $Re(\omega) = 0$**.**

For $\omega = 0$, the system (B.5) becomes a homogenous linear system of the form

$$\mathbf{0} = G\mathbf{Z}_i, \ i = 1, ..., m + n + 1,$$

where,

$$G = \begin{pmatrix} G_1 & G_2 \\ G_3 & G_4 \end{pmatrix},$$

with,

$$G_1 = \begin{pmatrix} -\hat{\lambda}^{**} - h_1 & -\hat{\lambda}^{**} & -\hat{\lambda}^{**} & -\hat{\lambda}^{**} & \cdots & -\hat{\lambda}^{**} \\ \gamma_1 & -h_2 & 0 & 0 & \cdots & 0 \\ 0 & \gamma_2 & -h_3 & 0 & \cdots & 0 \\ 0 & 0 & \gamma_3 & -h_4 & \cdots & 0 \\ \vdots & \vdots & \ddots & \ddots & \ddots & \vdots \\ 0 & 0 & \cdots & 0 & \gamma_{m-1} & -h_m \end{pmatrix},$$

$$G_2 = \begin{pmatrix} \frac{\beta_1 S^{**}}{N^{**}} - \hat{\lambda}^{**} & \frac{\beta_2 S^{**}}{N^{**}} - \hat{\lambda}^{**} & \cdots & \frac{\beta_n S^{**}}{N^{**}} - \hat{\lambda}^{**} & -\hat{\lambda}^{**} \\ 0 & 0 & \cdots & 0 & 0 \\ 0 & 0 & \cdots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \cdots & 0 & 0 \end{pmatrix},$$

$$G_3 = \begin{pmatrix} 0 & 0 & \cdots & 0 & -\gamma_m \\ 0 & 0 & \cdots & 0 & 0 \\ 0 & 0 & \cdots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \cdots & 0 & 0 \end{pmatrix}, \; G_4 = \begin{pmatrix} -k_1 & 0 & 0 & 0 & \cdots & 0 & 0 \\ \sigma_1 & -k_2 & 0 & 0 & \cdots & 0 & 0 \\ 0 & \sigma_2 & -k_3 & 0 & \cdots & 0 & 0 \\ 0 & 0 & \sigma_3 & -h_4 & \cdots & 0 & 0 \\ \vdots & \vdots & \ddots & \ddots & \ddots & \vdots & \vdots \\ 0 & 0 & \cdots & 0 & \sigma_{n-1} & -k_n & 0 \\ 0 & 0 & 0 & \cdots & 0 & \sigma_n & -k_\theta \end{pmatrix}.$$

The matrices $G_1,\ G_2,\ G_3$ and G_4 have dimensions $m \times m,\ m \times (n+1),\ (n+1) \times m$ and $(n+1) \times (n+1)$, respectively.

The determinant of G corresponds to the determinant of the matrix of the linearized system (B.5) (i.e., the determinant of the Jacobian of the system (B.1) at $\mathcal{E}_1^m$), and is given by

$$\begin{aligned} det(G) &= (-1)^{m+n+1}\hat{\lambda}^{**}\prod_{i=1}^{n+1}k_i\left[\prod_{j=1}^{m}h_j\left(\sum_{j=1}^{m}d_j\right)+\prod_{j=1}^{m}\gamma_j\left(\sum_{i=1}^{n+1}c_i\right)\right] \\ &+ (-1)^{m+n+1}\prod_{i=1}^{n+1}k_i\prod_{j=1}^{m}h_j + (-1)^{m+n}\prod_{i=1}^{n+1}k_i\prod_{j=1}^{m}h_j\left[\underbrace{\prod_{j=1}^{m}\frac{\gamma_j}{h_j}\left(\sum_{i=1}^{n}\beta_i c_i\right)}_{\mathcal{R}_0^m}\frac{S^{**}}{N^{**}}\right], \end{aligned} \tag{B.13}$$

$$\begin{cases} > 0, & \text{if } m+n \text{ is odd;} \\ \\ < 0, & \text{if } m+n \text{ is even,} \end{cases}$$

where,

$$c_i = \prod_{p=1}^{i} \frac{\sigma_{p-1}}{k_p}, \text{ with } i = 1, .., n, \ \sigma_0 = 1,$$

$$d_j = \prod_{q=1}^{j} \frac{\gamma_{q-1}}{h_q}, \text{ with } j = 1, ..., m, \ \gamma_0 = 1,$$

and, $k_{n+1} = k_\theta$. Since

$$\prod_{j=1}^{m} \frac{\gamma_j}{h_j} \sum_{i=1}^{n} \beta_i c_i = \mathcal{R}_0^m,$$

it follows from (4.25) that, at endemic steady-state,

$$\frac{S^{**}\mathcal{R}_0^m}{N^{**}} = 1. \tag{B.14}$$

Using (B.14) in (B.13) shows that the determinant of G is non-zero. Hence, the linearized system (B.5), which has the form of the system given in (B.10), can only have the trivial solution $\mathbf{Z} = \mathbf{0}$ (which corresponds to the DFE, $\mathcal{E}_0$). In other words, the case with $\omega = 0$ does not correspond to the endemic equilibrium, $\mathcal{E}_1^m$.

Case (ii): $\omega > 0$**.**

Since $Re(\omega) > 0$ (by assumption), it follows that $F_i(\omega) > 0$, which implies that $|F_i(\omega) + 1| > 1 \ \forall i = 1, ..., m + n + 1$. Define

$$F(\omega) = \min\{(|F_i(\omega) + 1|), \ i = 1, ..., m + n + 1\}.$$

Thus, $F(\omega) > 1$, and $\frac{s}{F(\omega)} < s$. Since s is the minimal positive real number defined in (B.12), then

$$||\mathbf{Z}|| > \frac{s}{F(\omega)} \mathcal{E}_1^m. \tag{B.15}$$

On the other hand, by taking the norm of both sides of the second equation in (B.10), and noting that the matrix H has all entries non-negative, we have

$$F(\omega)||Z_2|| \leq |1 + F_2| \; ||Z_2|| = ||(H\mathbf{Z})_2|| \leq (H||\mathbf{Z}||)_2 \leq s(H\mathcal{E}_1^m)_2 = s(\mathcal{E}_1^m)_2 = sE_2^{**}. \tag{B.16}$$

It follows from (B.16) that

$$||Z_2|| \leq \frac{s}{F(\omega)} E_2^{**},$$

which contradicts (B.15). Hence, $Re(\omega) < 0$. Thus, all eigenvalues of the characteristics equation associated with the linearized system (B.5) will have negative real parts. Therefore, the unique endemic equilibrium of (B.2), denoted by $\mathcal{E}_1^m$, is LAS whenever $\mathcal{R}_0^m > 1$. This completes the proof. □

Appendix C

Verification of Assumptions A1-A7 in [91]

The Assumptions $A1 - A7$ given in [91] are verified for the non-autonomous system (5.2). The system (5.2) can be re-written as

$$\frac{dx(t)}{dt} = \mathcal{F}(t, x(t)) - \mathcal{V}(t, x(t)) \triangleq f(t, x(t)),$$

where $x = (S, E_1, ..., E_m, I_1, ..., I_n, R)^T$, and

$$\mathcal{F} = \begin{pmatrix} 0 \\ \sum_{i=1}^{n} \frac{\beta_i(t) I_i(t)}{N(t)} S(t) \\ \gamma_1(t) E_1(t) \\ \vdots \\ \gamma_{m-1}(t) E_{m-1}(t) \\ \gamma_m(t) E_m(t) \\ \sigma_1(t) I_1(t) \\ \vdots \\ \sigma_{n-1}(t) I_{n-1}(t) \\ 0 \end{pmatrix}, \; \mathcal{V} = \begin{pmatrix} -\pi - \theta R(t) + \sum_{i=1}^{n} \frac{\beta_i(t) I_i(t)}{N(t)} S(t) + \mu S(t) \\ \big[\gamma_1(t) + \mu\big] E_1(t) \\ \big[\gamma_2(t) + \mu\big] E_2(t) \\ \vdots \\ \big[\gamma_m(t) + \mu\big] E_m(t) \\ \big[\sigma_1(t) + \mu + \delta_1(t)\big] I_1(t) \\ \big[\sigma_2(t) + \mu + \delta_2(t)\big] I_2(t) \\ \vdots \\ \big[\sigma_n(t) + \mu + \delta_n(t)\big] I_n(t)) \\ -\sigma_n(t) I_n(t) + \big(\mu + \theta\big) R(t) \end{pmatrix}.$$

Let,

$$\mathcal{V}^+ = \begin{pmatrix} \pi + \theta R(t) \\ 0 \\ 0 \\ \vdots \\ 0 \\ 0 \\ \vdots \\ 0 \\ \sigma_n(t) I_n(t) \end{pmatrix}, \quad \mathcal{V}^- = \begin{pmatrix} \sum_{i=1}^{n} \frac{\beta_i(t) I_i}{N(t)}(t) S(t) + \mu S(t) \\ \big[\gamma_1(t) + \mu\big] E_1(t) \\ \big[\gamma_2(t) + \mu\big] E_2(t) \\ \vdots \\ \big[\gamma_m(t) + \mu\big] E_m(t) \\ \big[\sigma_1(t) + \mu + \delta_1(t)\big] I_1(t) \\ \vdots \\ \big[\sigma_n(t) + \mu + \delta_n(t)\big] I_n(t)) \\ \big[\mu + \theta\big] R(t) \end{pmatrix}.$$

It follows then that $\mathcal{V} = \mathcal{V}^- - \mathcal{V}^+$. Furthermore,

(A1) For each $1 \leq i \leq m + n + 2$, the functions $\mathcal{F}, \mathcal{V}^+$ and $\mathcal{V}^-$ are non-negative, continuous on $R \times R_+^{m+n+2}$ and continuously-differentiable with respect to x, (since each function denotes a direct non-negative transfer of individuals);

(A2) There exists a real number $\omega > 0$ such that for each $1 \leq i \leq m + n + 2$, the

functions $\mathcal{F}, \mathcal{V}^+$ and $\mathcal{V}^-$ are $\omega-$periodic in t. This follows due to the fact that some of the model parameters are assumed to be $\omega-$periodic;

(A3) If $x_i = 0$, then $\mathcal{V}^- = 0$ for $i = 2, ..., m+n+1$. In particular, we define the disease-free states by

$$X_s = \Big\{ x \geq 0 : x_i = 0, \forall i = 2, ..., m+n+1 \Big\}.$$

The epidemiological compartments are then sub-divide into:

- infected compartments: $E_1, ..., E_m, I_1, ..., I_n$ (i.e., x_i, with $i = 2, ..., m+n+1$),

- uninfected compartments: S and R (i.e., x_i, with $i = 1, m+n+2$).

Hence, if $x \in X_s$, then $\mathcal{V}^- = 0$ for $i = 2, ..., m+n+1$.

(A4) $\mathcal{F}_i = 0$ for $i = 1, m+n+2$.

(A5) Define X_s as above. If $x \in X_s$, then

$$\mathcal{F}_i = \mathcal{V}^+ = 0 \text{ for } i = 2, ..., m+n+1.$$

Assumption (A5) verifies that the population remains free of disease if it is free of disease at the beginning. We assume that the system (5.2) has a disease-free periodic solution $\mathcal{E}_0 = (\frac{\pi}{\mu}, 0, 0..., 0, 0)$. To verify this, let $F = (\mathcal{F}_1, \mathcal{F}_2, ..., \mathcal{F}_{m+n+2})^T$ and define an $((m+n+2)-(m+n+1)) \times ((m+n+2)-(m+n)) = 2 \times 2$ matrix

$$M(t) = \left(\frac{\partial \mathcal{F}_i(t, \mathcal{E}_0)}{\partial x_j} \right)_{i,j=1,m+n+2}.$$

Let $\Phi_M(t)$ be the monodromy matrix of the linear $\omega-$periodic system of the form (5.9) and $\mathcal{E}_0$ is linearly asymptotically stable in the disease-free subspace X_s. Then, it follows, by definition of $F(t)$ and $V(t)$ that

$$M(t) = \begin{pmatrix} -\mu & \theta \\ 0 & -(\theta+\mu) \end{pmatrix}.$$

(A6) Since, now, $M(t)$ is a diagonalizable matrix with negative eigenvalues, then

$$\rho(\Phi_M(\omega)) < 1;$$

(A7) Similarly, since $V(t)$ is given by

$$V(t) = \left(\frac{\partial \mathcal{V}_i(t,\mathcal{E}_0)}{\partial x_j}\right)_{i,j=2,\ldots,m+n+1} \text{ (an } (m+n)\times(m+n) \text{ matrix)},$$

it follows that

$$V(t) = \begin{pmatrix} \hat{h}_1(t) & 0 & 0 & \cdots & 0 & 0 & \cdots & 0 \\ 0 & \hat{h}_2(t) & 0 & \cdots & 0 & 0 & \cdots & 0 \\ \vdots & \ddots & \ddots & \ddots & \vdots & \vdots & \cdots & 0 \\ 0 & \cdots & 0 & \hat{h}_m(t) & 0 & 0 & \cdots & 0 \\ 0 & \cdots & 0 & 0 & \hat{k}_1(t) & 0 & \cdots & 0 \\ 0 & \cdots & 0 & 0 & 0 & \hat{k}_2(t) & \cdots & 0 \\ \vdots & \ddots & \vdots & \vdots & \vdots & \ddots & \ddots & \vdots \\ 0 & \cdots & 0 & 0 & 0 & \cdots & 0 & \hat{k}_n(t) \end{pmatrix},$$

where $\hat{h}_j(t) = \gamma_j(t) + \mu$ $(j = 1, ..., m)$ and $\hat{k}_i(t) = \sigma_i(t) + \mu + \delta_i(t)$ for $i = 1, ..., n$. Hence, $-V(t)$ is a diagonalizable matrix with negative eigenvalues. Thus,

$$\rho(\Phi_{-V}(\omega)) < 1.$$

Hence, the system (5.2) satisfy Assumptions (A1)-(A7) of [91]. □

The following results are relevant to the analysis of the non-autonomous system considered in Chapter 5.

Theorem C.1 ([91, Theorem 2.2]). *Suppose Assumptions (A1)-(A7) hold. Then, the following statements are valid.*

(1) $\mathcal{R}_0 = 1$ *if and only if* $\rho(\Phi_{F-V}(\omega)) = 1$*;*

(2) $\mathcal{R}_0 > 1$ *if and only if* $\rho(\Phi_{F-V}(\omega)) > 1$*;*

(3) $\mathcal{R}_0 < 1$ *if and only if* $\rho(\Phi_{F-V}(\omega)) < 1$.

Thus, $x^0(t)$ *is asymptotically-stable if* $\mathcal{R}_0 < 1$*, and unstable if* $\mathcal{R}_0 > 1$.

Hence, the reproduction ratio, $\mathcal{R}_0$, associated with the non-autonomous model can be computed using the following theorem.

Theorem C.2 ([91, Theorem 2.1]). *Let* $W(t, \lambda)$*,* $t \geq 0$ *be the standard fundamental matrix of*

$$\frac{dw}{dt} = \Big[- V(t) + \frac{1}{\lambda} F(t) \Big] w, \ w \in \mathbb{R}^n, \ \lambda \in (0, \infty),$$

with $W(0, \lambda) = I$*. Then, the following statements are valid:*

(i) If $\rho(W(\omega, 0, \lambda)) = 1$ *has a positive solution* λ_0*, then* λ_0 *is an eigenvalue of* L*, and hence* $\mathcal{R}_0$*;*

(ii) If $\mathcal{R}_0 > 1$*, then* $\lambda = \mathcal{R}_0$ *is the unique solution of* $\rho(W(\omega, \lambda) = 1$*;*

(iii) $\mathcal{R}_0 = 0$ *if and only if* $\rho(W(\omega, \lambda)) < 1, \ \forall \lambda > 0$.

For a continuous periodic function $g(t)$, with period ω, its average is defined as

$$[g] := \frac{1}{\omega}\int_0^{\omega} g(t)dt.$$

Theorem C.3 ([91, Theorem 2.2])**.** *Let the Assumptions (A1)-(A7) hold. Then the following statements are valid.*

(i) If $V(t) = diag(V_1(t), \cdots, V_m(t)$ *and* $F(t) = diag(V_1(t), \cdots, V_m(t)$*, then*

$$\mathcal{R}_0 = \max_{1\leq i\leq m}\left\{\frac{[F_i]}{[V_i]}\right\}.$$

(ii) If $V(t) = V$ *and* $F(t) = F$ *are two constant matrices, then* $\mathcal{R}_0 = \rho(FV^{-1})$.

Appendix D

Proof of the Positive Invariance of X and X_0

Proof. Consider the model (5.2). Assume that $t_1 = sup\Big\{t > 0 : S > 0, E_j \geq 0, I_i \geq 0, R \geq 0, \in [0,t]\Big\}$ for $j = 1, ..., m$ and $i = 1, ..., n$. Further, let $t_1 > 0$ and $z^0 = (S^0, E_1^0, ..., E_m^0, I_1^0, ..., I_m^0, N^0) \in X_0$. Using $R(t) = N(t) - \big[S(t) + \sum_{j=1}^{m} E_j(t) + \sum_{i=1}^{n} I_i(t)$ in the equation of $\frac{dS}{dt}$ in the system (5.2) gives

$$\frac{dS}{dt} = \pi + \theta\Big\{N(t) - \big[S(t) + \sum_{j=1}^{m} E_j(t) + \sum_{i=1}^{n} I_i(t)\big]\Big\} - \underbrace{\sum_{i=1}^{n} \frac{\beta_i(t) I_i(t)}{N(t)}}_{\lambda(t, I_i(t), N(t))} S(t) - \mu S(t),$$

so that,

$$\frac{dS}{dt} = \pi - \Big\{\theta + \mu + \lambda\big(t, I_i(t), N(t)\big)\Big\} S(t) + \theta \left[N(t) - \sum_{j=1}^{m} E_j(t) - \sum_{i=1}^{n} I_i(t)\right]. \quad \text{(D.1)}$$

It follows from (D.1) that

$$\frac{dS}{dt} + \left[\underbrace{\theta + \mu + \lambda(t, I_i(t), N(t))}_{=a(t)}\right] S(t) = \pi + \theta \left[\underbrace{N(t) - \sum_{j=1}^{m} E_j(t) - \sum_{i=1}^{n} I_i(t)}_{=b(t)}\right],$$

so that,

$$\frac{dS}{dt} + a(t)S(t) = \pi + \theta b(t), \tag{D.2}$$

where,

$$a(t) = \theta + \mu + \lambda(t, I_i(t), N(t)) \text{ and } b(t) = N(t) - \sum_{j=1}^{m} E_j(t) - \sum_{i=1}^{n} I_i(t).$$

The solution of (D.2) is given by

$$\int_0^{t_1} \left\{ \frac{d}{dt} \left[e^{\int_0^t a(u)du} S(t) \right] \right\} dt = \int_0^{t_1} \left\{ e^{\int_0^x a(s)ds} \left[\pi + \theta b(x) \right] \right\} dx,$$

which can be simplified as,

$$e^{\int_0^{t_1} a(u)du} S(t_1) - S^0 = \int_0^{t_1} \left\{ e^{\int_0^x a(s)ds} \left[\pi + \theta b(x) \right] \right\} dx. \tag{D.3}$$

Hence, it follows from (D.3) that

$$\begin{aligned} S(t_1) &= S^0 e^{-\int_0^{t_1} a(u)du} + e^{-\int_0^{t_1} a(u)du} \left\{ \int_0^{t_1} \left[e^{\int_0^x a(s)ds} (\pi + \theta b(x)) \right] dx \right\}, \\ &\geq e^{-\int_0^{t_1} a(u)du} \left\{ \int_0^{t_1} \left[e^{\int_0^x a(s)ds} (\pi + \theta b(x)) \right] dx \right\}, \\ &> 0. \end{aligned}$$

Similarly, it can be shown that $E_j(t) \geq 0, I_i(t) \geq 0, R(t) \geq 0$ (with $j = 1, ..., m$ and $i = 1, ..., n$) for all $t > 0$. It should be noted that $N(t) \geq S(t), \ \forall t > 0$. Furthermore, the linearized matrix for the infected variables in (5.2) is given by:

$$J = \begin{pmatrix} M_1 & M_2 \\ M_3 & M_4 \end{pmatrix},$$

where the matrix M_2 is has all zero entries with dimension $m \times n$, respectively, and

$$M_1 = \begin{pmatrix} -\hat{h}_1(t) & 0 & 0 & \cdots & 0 \\ \gamma_1(t) & -\hat{h}_2(t) & 0 & \cdots & 0 \\ 0 & \gamma_2(t) & -\hat{h}_3(t) & \cdots & 0 \\ \vdots & \ddots & \ddots & \ddots & \vdots \\ 0 & \cdots & 0 & \gamma_{m-1}(t) & -\hat{h}_m(t) \end{pmatrix}, \; M_2 = \begin{pmatrix} \beta_1(t) & \beta_2(t) & \cdots & \beta_n(t) \\ 0 & 0 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & 0 \end{pmatrix},$$

$$M_3 = \begin{pmatrix} 0 & 0 & \cdots & 0 & \gamma_m(t) \\ 0 & 0 & \cdots & 0 & 0 \\ 0 & 0 & \cdots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \cdots & 0 & 0 \end{pmatrix}, \; M_4 = \begin{pmatrix} -\hat{k}_1(t) & 0 & 0 & \cdots & 0 \\ \sigma_1(t) & -\hat{k}_2(t) & 0 & \cdots & 0 \\ 0 & \sigma_2(t) & -\hat{k}_3(t) & \cdots & 0 \\ \vdots & \ddots & \ddots & \ddots & \vdots \\ 0 & \cdots & 0 & \sigma_{n-1}(t) & -\hat{k}_n(t) \end{pmatrix},$$

with dimensions $m \times m, m \times n, n \times m$ and $n \times n$, respectively, and $\hat{h}_j(t) = \gamma_j(t) + \mu$, $\hat{k}_i(t) = \sigma_i(t) + \mu + \delta_i(t)$ (with $j = 1, ..., m$) and $i = 1, ..., n$) and $\hat{k}_\theta = \mu + \theta$. Since the matrix J is irreducible and cooperative (see Section 2.3), it follows that $(E_1(t), ..., E_m(t), I_1(t), ..., I_n(t))^T \gg \mathbf{0}$ $\forall t > 0$ (see Theorem 2.6). Thus, the regions X and X_0 are positively-invariant. □

Appendix E

Proof of Global Attractivity of $\hat{S}^*(t, \epsilon)$

Equation (5.17) can be re-written as:

$$\frac{d\hat{S}}{dt} + \mu\hat{S} = \pi - \epsilon\sum_{i=1}^{n}\beta_i(t) - (m+n)\epsilon\theta. \tag{E.1}$$

Thus,

$$e^{\mu t}\hat{S}(t,\epsilon) - \hat{S}(0,\epsilon) = \int_0^t e^{\mu x}\left[\pi - \epsilon\sum_{i=1}^{n}\beta_i(x) - (m+n)\epsilon\theta\right]dx,$$

so that,

$$\hat{S}^*(t,\epsilon) = e^{-\mu t}\left\{\hat{S}^*(0,\epsilon) + \int_0^t e^{\mu x}\Big[\pi - \epsilon\sum_{i=1}^{n}\beta_i(x) - (m+n)\epsilon\theta\Big]dx\right\}, \tag{E.2}$$

where $\hat{S}^*(0,\epsilon)$ is given by (obtained by substituting $t = \omega$ in (E.2)):

$$\hat{S}^*(0,\epsilon) = \frac{e^{-\mu\omega}\left\{\int_0^\omega e^{\mu x}\Big[\pi - \epsilon\sum_{i=1}^{n}\beta_i(x) - (m+n)\epsilon\theta\Big]dx\right\}}{e^{\mu\omega} - 1}. \tag{E.3}$$

It should be mentioned that, in (E.2), $\hat{S}^*(t,\epsilon) = \hat{S}^*(0,\epsilon)$ at $t = \omega$. Hence, it follows from the solutions of (E.1) and (E.2) that

$$|\hat{S}(t,\epsilon) - \hat{S}^*(t,\epsilon)| \to 0 \text{ as } t \to \infty.$$

Thus, $\hat{S}^*(t,\epsilon)$ is globally-attractive on $\mathbb{R}_+$. □