Epidemic Models with Pulse Vaccination and Time Delay

by

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I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

In this thesis we discuss deterministic compartmental epidemic models. We study the asymptotic stability of the disease-free solution of models with pulse vaccination campaigns.

The main contributions of this thesis are to extend the literature of pulse vaccination models with delay. We take results for ordinary differential equation models and extend them to models with delay differential equations. Model generalizations include the use of a general incidence term as an upper bound for the actual incidence, and the use of switch parameters to approximate time-varying parameters.

In particular, we look at contact rate parameters which are piecewise constant or time-varying. We extend literature results for non-delay general incidence models to find *uniform* asymptotic stability of the disease-free solution which helps us to add delay. We find an upper bound for the susceptible population under pulse vaccination and use this bound to tighten results for eradication thresholds: that is, we use this upper bound to find sufficient conditions for the uniform asymptotic stability of the disease-free solution of delayed pulse vaccination models. We extend literature results for constant contact rate bilinear incidence delay models to models with periodic time-varying contact rate, and determine conditions under which the disease-free solution is uniformly asymptotically stable for small delay. We also find conditions for disease permanence in the corresponding non-delay, time-varying-parameter pulse vaccination model. For piecewise-constant contact rate bilinear incidence models we again find thresholds which guarantee uniform asymptotic stability under small delay.

We additionally discuss the effects of time-varying total population on our results, through a change of variables to population fractions. The total population is commonly held constant in the literature, for analytical simplicity, so we survey the methods for time-varying total population and the effects of such variation on the pulse vaccination schemes. We retain thresholds for eradication by considering the compartment populations as fractions of the total, instead of population numbers. The result is also applied to constant-population delay systems. When changing from standard incidence to bilinear incidence in delay systems, we discuss a way to estimate the effect of time-varying N.

We support our theory with simulation results.

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And finally, thank you to my family (regular and new!): Mom, Dad, Eri and Mike for being there, and Gord and Jeanette for all the help and advice. Thank you especially to my fiancé Greg, for everything.

Dedication

To Greg. You got me through this thesis, and you mean the world to me.

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Chapter 1

Introduction

This thesis focuses on dynamical systems used to model epidemics. We use deterministic compartmental models, in which a given population is divided into compartments based on disease status (susceptible, infective, *etc.*).

The transfer between compartments, as well as the entrance to the population of new individuals and the exit of others, are modelled as terms in a differential equation governing the time-evolution of each compartment value. Figure 1.1 gives examples of ways this movement between compartments could occur.

The ultimate goal of an epidemic model is to be able to closely follow and predict real-life disease outbreaks, with the aim of informing public policy. To that end we are interested in looking at control methods, that is, ways to keep the infective population low or to eradicate the infection altogether. One control method is vaccination. Some vaccination campaigns are run continuously, for example with people of a certain age receiving their vaccine. Another way is to organize large campaigns in which a large proportion of the population is vaccinated over a short time; this technique is known as pulse vaccination, which we consider in this thesis.

There are many different ways to construct a compartmental model, and, depending on the relevant disease, some models may agree with reality more closely than others. Many models assume an exponential distribution of the time to move between compartments, but another way is to use delay differential equations. A constant delay may be used if the movement time (*e.g.* time until recovery or time until development of contagiousness) is known with reasonable certainty. Model parameters are frequently assumed to be constants, but in a physical situation this assumption is unreasonable. Time-varying parameters may be used, or approximated by a piecewise constant.

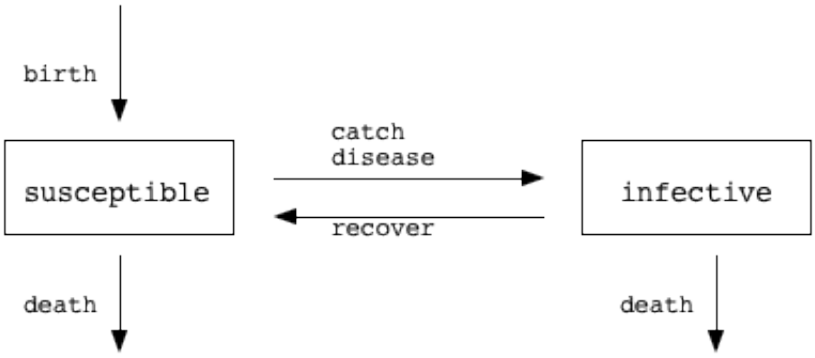

Fig. 1.1: Population movement in a basic compartmental model

1.1 Contributions

The main contributions of this thesis are to extend the literature of pulse vaccination models with delay. We particularly look at contact rate parameters which are piecewise constant or time-varying. We extend literature results from [17] for non-delay general incidence models to find *uniform* asymptotic stability of the disease-free solution, which will be helpful when we add delay. We look at uniform asymptotic stability of the disease-free solution of delayed pulse vaccination models: we combine literature results from [27] for constant contact rate bilinear incidence delay models with those general incidence results from [17] to get eradication thresholds for models with periodic time-varying contact rate, and to determine conditions under which the disease-free solution is uniformly asymptotically stable for small delay. In [17] eradication conditions are found; we also extend the results for this non-delay, time-varying-parameter pulse vaccination model to find conditions for disease permanence. For piecewise-constant contact rate bilinear incidence models we use methods from [27] to tighten thresholds obtained in [53], and extend [53] to find thresholds which guarantee uniform asymptotic stability under small delay.

The total population is commonly held constant in the literature. We survey the methods for time-varying total population and the effects of such variation on the pulse vaccination schemes. We retain thresholds for eradication by considering the compartment populations as fractions of the total, instead of population numbers, as in [12, 47], and extend the results to pulse vaccination models. The fraction technique is also applied to constant-population delay systems. When changing from standard incidence to bilinear incidence in delay systems, we discuss a way to estimate the effect of time-varying N.

We support our theory with simulation results. Additionally we look at switched contact rate models with delay in other compartments than $E(t)$.

1.2 Guide to the Thesis

The thesis is structured as follows.

Chapter 2 This chapter gives a general background to epidemic modelling theory, introducing terms, important concepts, and types of models.

Chapter 3 This chapter discusses differential equation theory relevant to the epidemic models used later. In particular we discuss stability concepts and stability theorems, comparison theorems, and especially theorems for the existence and uniqueness of solutions to ODEs, DDEs, and IDDEs.

Chapter 4 This chapter is the related research chapter. We discuss epidemic modelling literature related to general incidence terms, delay differential equations, and time-varying total populations, with a particular focus on pulse vaccination.

Chapter 5 This chapter is our first results chapter. We first extend some results from the literature to prove, for parameters below a certain threshold, the uniform asymptotic stability of the disease-free solution of a general incidence pulse vaccination model, then use this result to introduce delay. We additionally prove the permanence of the infection without delay if the parameters are above the eradication threshold.

Chapter 6 In this results chapter we survey methods for the inclusion of a time-varying total population, and their impact on pulse vaccination techniques used earlier. We consider delay models as well.

Chapter 7 In our final results chapter we look at switched system epidemic models, where the contact rate is modelled by a piecewise-constant parameter. We find results for eradication of a delayed switched pulse vaccination model with delay in the exposed class, apply similar methods to models with delay in other compartments, and support our results with simulations.

Chapter 8 This chapter gives our conclusions and ideas for future work.

Chapter 2

Epidemic Modelling Background

In epidemic modelling there are different ways to approach the problem of how to model a situation. One way is to use *probabilistic* models, involving for example Markov chains and stochastic processes, while *deterministic* models use differential equations that dictate the time-evolution of the system. In a probabilistic model we can only determine the probability of an outcome; a differential equation-based model in contrast will produce one particular outcome for any given set of parameters and initial conditions. Earn [21] discusses the advantages and disadvantages of each type of model. In particular, deterministic models can be fitted very well to a particular outbreak and, while they represent a simplified version of the events, can provide us with valuable information. In this thesis we focus on deterministic models.

In the event of an epidemic, that is, a marked rise in the incidence of some disease or contagious phenomenon, we may be interested in estimating answers to many questions, such as:

- will the infected population increase?
- how many individuals will be infected?
- what proportion of individuals will be infected? Will everyone be?
- will the infection die out over time? If not, at what level may we expect it to be endemic?
- how do we find practical ways to predict the answers to these questions?

2.1 Basic Compartmental Model

The general idea for most deterministic models is to look at a so-called *compartmental model*, in which the population is divided into *compartments* based on infection status. Individuals already

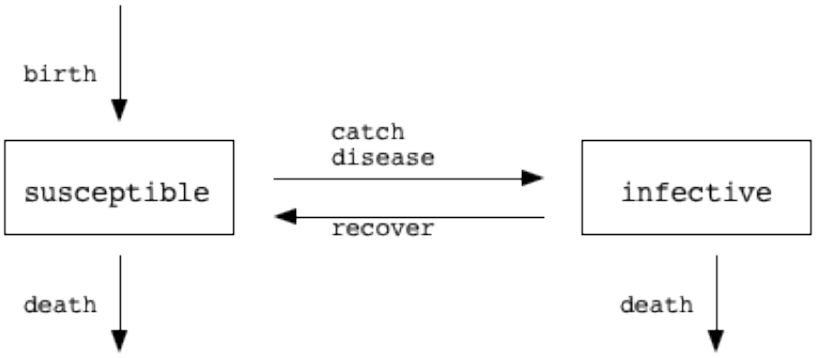

Fig. 2.1: Population movement in a basic compartmental model

in the population may either transfer to another compartment (for example by recovering from the disease) or may leave the population altogether (*e.g.* by disease death). Individuals may enter a population through processes such as immigration or births.

Some basic entrance, exit and transfer mechanisms are shown in Figure 2.1. In this example individuals are born with no defence against the infection, that is, they enter into the total population *susceptible* to the disease. They transfer to the *infected* compartment if they contract the disease, and may transfer back to the susceptible compartment by recovering from the disease without gaining immunity. Individuals in either compartment may die of "natural" causes (*i.e.* not related to the specific disease).

A differential equation-based model of the above example is as follows. The coefficients are parameters will be explained in Section 2.2.2.

$$\begin{cases} S' &= b(S+I) - \beta\frac{SI}{S+I} - dS \\ I' &= \beta\frac{SI}{S+I} - dI \end{cases} \tag{2.1}$$

Here the term $b(S+I)$ accounts for individuals entering the total population (through births), the $\pm\beta\frac{SI}{S+I}$ terms are transfer terms due to infection, and the terms $-dS$, $-dI$ represent individuals exiting the population (though natural deaths).

Compartmental models may become very complex; they may use many compartments, or assume complicated disease distribution or incidence, or have parameters which are time- or even state-dependent. These three concepts, however, of *entering* the population, *transferring* between compartments, and *leaving* the population, always underlie the assumptions.

2.1.1 Kermack and McKendrick

The modelling of epidemics with differential equations can be traced back to Kermack and McKendrick [44]. In their seminal paper they use a model without demographic effects ($b = d = 0$):

$$\begin{cases} S' = -\beta SI \\ I' = \beta SI - \gamma I \end{cases} \tag{2.2}$$

The γI term moves individuals to a removed class that has no direct effect on the dynamics of S and I and so is not analyzed.

Brauer and Castillo-Chavez [7] explain that the above system, though very simplified, can still be very instructive. For example, we note that

$$\frac{I'}{S'} = \frac{dI}{dS} = \frac{\gamma}{\beta S} - 1 \quad \Rightarrow \quad I = \frac{\gamma}{\beta} \ln S - S + c.$$

We see that the solutions of (2.2) are the level sets of the function $V(S, I) = I + S - \frac{\gamma}{\beta} \ln S$ [7]. In particular, denoting $S_\infty = \lim_{t\to\infty} S(t)$ and $I_\infty = \lim_{t\to\infty} I(t) = 0$, $V(S_0, I_0) = c = V(S_\infty, I_\infty)$. If in a population of size N we perturb the infection from 0 ($I_0 \approx 0$ and $S_0 \approx N$),

$$\begin{aligned} N - \frac{\gamma}{\beta} \ln S_0 &= S_\infty - \frac{\gamma}{\beta} \ln S_\infty \\ \Rightarrow \frac{\beta}{\gamma} &= \frac{\ln N - \ln S_\infty}{N - S_\infty}. \end{aligned}$$

Brauer and Castillo-Chavez point out that we can estimate the right-hand side of the above by using population data and incidence records from medical centres, which gives us an idea of the ratio β/γ. That is, we have found a way to estimate the so-called "basic reproduction number" (see Section 2.3) in a population of size 1. They also find from Kermack and McKendrick's model that as $t \to \infty$ the total susceptible population approaches a positive limit, implying there will always be some leftover susceptibles in a population, however virulent the disease.

Alternatively, we may estimate the maximum number of infectives: $I(t)$ reaches its maximum when $I'(t) = 0$, *i.e.* $S(t) = \frac{\gamma}{\beta}$. So [7]

$$\begin{aligned} V(\frac{\gamma}{\beta}, I_{max}) &= V(S_0, I_0) \\ I_{max} &= -\frac{\gamma}{\beta} + \frac{\gamma}{\beta} \ln \frac{\gamma}{\beta} + \left(S_0 + I_0 - \frac{\gamma}{\beta} \ln S_0 \right). \end{aligned}$$

We may not know $\frac{\gamma}{\beta}$ until we approach S_∞ in order to use the estimate above, but once this ratio has been estimated we may use it (cautiously) in future similar outbreaks.

This model gives some good estimates, but has clear limitations. For example, we see that in System (2.2) we always have $\lim_{t\to\infty} I(t) = 0$, while in real-life situations diseases may remain endemic to a population, at least over a large area. We discuss endemic situations in later sections.

2.2 Terminology and Legend

2.2.1 Compartments

The most common compartments are the susceptible and infective (contagious) populations introduced in Section 2.1; in fact, some models (such as as Kermack and McKendrick's in Section 2.1.1) use only these groups.

If recovery from a disease yields immunity then individuals transfer to the *recovered* class. It may also be the case that a model does not incorporate natural births and deaths; if the disease is potentially fatal then the recovered class may represent the population that has died of the disease. In the event of control measures, a *vaccinated* class may be used, either instead of the recovered class or in conjunction with it if the immunities conferred are of different strengths.

It is rare for a person who has just contracted a disease to become infective (contagious) immediately, so an *exposed* class is often used to model the individuals in their latent period. A susceptible individual who contacts an infective individual will transfer immediately to the exposed compartment, then transfer from the exposed to the infective compartments at the end of the latent period. The "latent period" and "incubation period" may be confused: here and in the literature, their technical definitions are such that the latent period is the time until infectiousness, while the incubation period is the time until symptoms appear [61].

Additional compartments may include a *quarantined* class. Some models structure by population age ([23]), neighbourhood ([66]), or infection progression ([19, 55]). The conventions vary for naming the compartment, but in this thesis additional but related compartments will be distinguished by a subscript as necessary.

Table 2.1 records some common compartment variable names.

Populations	
S	susceptible
E	exposed
I	infective
R	removed
V	vaccinated
Q	quarantined

Table 2.1: Common population compartments.

2.2.2 Parameters

The easiest models assume exponential distribution of births, deaths, recovery, immunity waning, vaccination, etc., *e.g.* $\frac{dI}{dt} = ... - \gamma I$.

That is, suppose we have a population $N(t)$ governed by the mortality rate μ, so

$$\frac{dN}{dt} = -\mu N. \tag{2.3}$$

As Brauer and Castillo-Chavez say in [7], this equation yields

$$\frac{N(t)}{N_0} = e^{-\mu t},\ t \geq 0,$$

so $e^{-\mu t}$ of the individuals alive at time $t = 0$ are still alive at time $t = t$. If we assume a homogeneous population, $e^{-\mu t}$ "denotes the probability of a person being alive at time $t \geq 0$ given he was alive at time $t = 0$" [7]. Then, using the convention $P(x) =$ probability of event x, we have

$$\begin{aligned} P\left(\text{dying in interval } [0,t)\right) &= 1 - P\left(\text{alive until time } t\right) \\ &= \begin{cases} 1 - e^{-\mu t} & \text{if } t \geq 0 \\ 0 & \text{if } t < 0 \end{cases} \\ &=: F(t) \end{aligned}$$

$F(t)$ is the exponential cumulative probability distribution, hence in equation (2.3) we have modelled an exponential distribution of deaths. Still following Brauer and Castillo-Chavez we find the associated probability density function $f(t) = \frac{dF(t)}{dt}$ and, modelling the time until death of an individual (alive at $t = 0$) by the random variable X, we have that the expected value of X is

$$\begin{aligned} E[X] &= \int_{-\infty}^{\infty} t f(t) dt \\ &= \int_{-\infty}^{0} t \cdot 0 dt + \int_{0}^{\infty} t(\mu e^{-\mu t}) dt \\ &= 0 + \left[-te^{-\mu t}\right]_0^{\infty} - \int_0^{\infty} (-e^{-\mu t}) dt \ \ \text{(integrating by parts)} \\ &= [0 - 0] + \left(\frac{-1}{\mu}\right) e^{-\mu t}|_0^{\infty} \ \ = \left(\frac{-1}{\mu}\right)(0 - 1) \\ &= \frac{1}{\mu}. \end{aligned}$$

Hence the average life expectancy given a mortality rate μ is $\frac{1}{\mu}$. In general, given some rate parameter η, the average length of time spent in that compartment is $\frac{1}{\eta}$; for example if the recovery rate is r then it takes an individual on average $\frac{1}{r}$ units of time to recover.

Given this result, we will consistently use the following parameters, listed in Table 2.2, for compartment entrance, transfer, and exit rates. Additionally we list some parameters that will be used later for delay and pulse vaccination (see Sections 2.5.2 and 2.4).

Parameters	
b	birth rate
d	natural death rate
μ	birth/death rate if equal
β	contact rate
κ	rate leaving latent compartment (becoming infectious)
r	latent period *i.e.* time until infectious (in delay models)
α	disease death rate
γ	recovery rate
ω	time until recovered (in delay models)
θ	vaccination rate (constant)
p	pulse vaccination fraction
τ	interpulse time
δ	immunity waning rate

Table 2.2: Common model parameters.

Models may assume unequal birth (b) and death (d) rates, although frequently the assumption $b = d = \mu$ is assumed, which can allow for constant population size: more in Sections 2.2.3 and 6.

2.2.3 Incidence and the Law of Mass Action

In a compartmental model such as System (2.1) above, the terms which transfer susceptible individuals to the infected compartment are called *incidence* terms. These terms represent the occurrence of the disease.

If we take N to be the total population, then a very common form of incidence term is the *standard incidence* ("$\beta\frac{SI}{N}$") term seen in System (2.1). A related incidence term is "βSI", which we will refer to as the *bilinear* or *mass-action* incidence.

The difference between the terms listed above comes from the following reasoning. Suppose the total population is $N(t)$ (in System 2.1 we have $N = S + I$, but there may be additional

compartments). Suppose each infective individual contacts others (with sufficient length/amount of contact for transmission) at a rate of β contacts per unit time. Then there is a $\frac{S}{N}$ chance that the contact is with a susceptible. Altogether we have an incidence term of:

$$\begin{pmatrix}\text{contacts per time}\\ \text{per infective}\end{pmatrix} \times \begin{pmatrix}\text{chance contact is}\\ \text{with susceptible}\end{pmatrix} \times \begin{pmatrix}\text{number of}\\ \text{infectives}\end{pmatrix} = \beta\frac{S}{N}I = \begin{pmatrix}\text{transmissions}\\ \text{per unit time}\end{pmatrix}$$

This reasoning is used in multiple sources (for example see [7, 12, 22, 36, 40, 47, 81]). However, an alternate reasoning is that instead of β contacts per unit time, an infective could contact a total of βN people/unit time, resulting in the βSI incidence [7]. The difference between the two incidence terms depends on the definition of β (whether or not it includes N) and on the size of N.

The $\beta\frac{SI}{N}$ and βSI incidence terms reconcile so long as N is constant. In the above, we were assuming time-varying N and dropping the "(t)" for brevity; now suppose we do have a constant $N(t) \equiv N$. We can set $N = 1$ by considering each population as a fraction of the total population: make the change of variables $s = \frac{S}{N}, i = \frac{I}{N}, r = \frac{R}{N}$. Then System 2.1 with the population variables (numbers of individuals, represented by capital letters) and the $\beta\frac{SI}{N}$ standard incidence term is equivalent to the below system (2.4) with lowercase population fraction variables and the βSI mass action incidence term:

$$\begin{aligned}
&\begin{cases} Ns' &= b(Ns + Ni) - \beta\frac{(Ns)(Ni)}{N} - dNs \\ Ni' &= \beta s(Ni) - dNi \end{cases} \\
\Rightarrow &\begin{cases} s' &= b(s+i) - \beta si - ds \\ i' &= \beta si - di \end{cases} \\
\Rightarrow &\begin{cases} s' &= b - \beta si - ds \\ i' &= \beta si - di \end{cases}
\end{aligned} \tag{2.4}$$

since $N = S + I$ in System 2.1 so $s + i = 1$. If N is constant we can transform the system through this change of variables; for brevity we can accomplish the same transformation by just assuming $N = 1$.

In the event of a total constant population, then, we can use either of the above methods; however, if the population is growing, it seems that the mass action incidence term, the βSI, must have an extra factor of N hidden within the definition of β. Hethcote [36] explains that in general we build the incidence term by defining $\tilde{\beta}$ to be the "average number of adequate contacts per person per unit time" [36], and then for a given infective individual the chance that such a contact is with a susceptible individual is $\frac{S}{N}$. Multiply by the number of infective individuals to get the standard incidence $\tilde{\beta}\frac{SI}{N}$. Comparing to the bilinear incidence βSI we see that we must have $\beta = \tilde{\beta}N$, that is, a mass-action model implicitly predicts that the average number of contacts per person will be larger in a larger population.

In some ways this N-dependent contact rate result seems reasonable, for example in a large city where populations are more dense and more people ride public transit. Hethcote quotes studies, however, that assumed an incidence $\beta \frac{SI}{N} N^\nu$ and found it likely that $\nu \in (0.03, 0.07)$ [36]; that is, the standard incidence with $\nu = 0$ is a more reasonable assumption than the bilinear with $\nu = 1$. Therefore, if the population can vary we will use the standard incidence, $\beta \frac{SI}{N}$, at least as a starting point. In Section 6 we discuss the effects of time-varying $N(t)$ on disease thresholds.

Other forms of incidence term are possible, however, and may be commonly used. The dependence on I may be nonlinear, for example, or the incidence may be time-dependent or incorporate density effects. See Section 4.2 for more review of the literature.

2.3 Reproduction Number

When we consider a very simple epidemic model we can often readily see threshold values below which an epidemic will not occur. For example, returning to Kermack and McKendrick's simple bilinear incidence model (2.2) we see that $S' < 0$ unless $I = 0$ or $S = 0$, and that $I' = I(\beta S - \gamma) < 0$ if $S < \frac{\gamma}{\beta}$. Since S will always decrease in a non-trivial case, $S < \frac{\gamma}{\beta}$ eventually so I will decrease eventually. The issue then becomes if there will be an increase in infectives at all. We see that if $\beta S(0) > \gamma$ then $I' > 0$ initially and there will be an epidemic (although we are assured it will die out later).

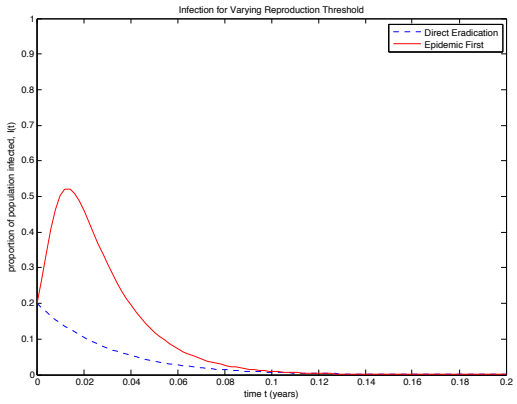

Fig. 2.2: $I(t)$ in System 2.2 for $\frac{\beta}{\gamma} < 1$ (blue dashes) and $\frac{\beta}{\gamma} > 1$ (red)

More rigorously, we have defined a threshold value

$$\mathcal{R}_0 := \frac{\beta S_0}{\gamma}, \tag{2.5}$$

where $S(0) = S_0$, and we consider whether $\mathcal{R}_0 < 1$. $\mathcal{R}_0$ is known as the *basic reproduction number*.

Heffernan *et. al.* in an overview paper define the reproduction number biologically as follows [33]:

Definition 1. The *basic reproduction number* is the number of secondary infections caused by a single infective in a wholly susceptible population.

Intuitively in a biological sense, if $\mathcal{R}_0 < 1$ then an infective is not producing enough new infectives to replace itself, and the disease will die out.

The reproduction number may not always be so easily recognizable as in System (2.2). In order to calculate it, Heffernan *et. al.* define the *survival probability* $P(a)$ to be "the probability that a newly infected individual remains infectious for at least time a." Then if $b(a)$ is the average number of secondary infections per unit time, averaged over a time a of infectiousness, that this first individual produces, the basic reproduction number is given by [33]:

$$\mathcal{R}_0 = \int_0^\infty P(a)b(a)da. \tag{2.6}$$

So the reproduction number is the integral for all future time of the number of infections multiplied by the probability the infective is still contagious (or still alive).

For Kermack and McKendrick's model (2.2), if there were no infectives ($I \equiv 0$) then $S' = 0$ so $S(t) \equiv S_0$, that is, the disease-free equilibrium has a wholly susceptible population S_0. Suppose we introduce an infective individual into the wholly susceptible population. The susceptible population will still be approximately S_0 until a large number of new secondary infections are caused. From the $\beta S \cdot I$ bilinear incidence term of (2.2), over a time interval of length a this newly-introduced infective will introduce $\beta S_0 \cdot 1$ new infections per unit time. The $-\gamma I$ term in I' tells us that the proportion of infectives who were infected at time $t = 0$ and are still infective at $t = a$ is $I(a) = I(0)e^{-\gamma a}$, that is, $P(a) = \frac{I(a)}{I(0)} = e^{-\gamma a}$. Therefore we get that $\mathcal{R}_0 = \int_0^\infty \beta S_0 e^{-\gamma a} da = \beta S_0 (\frac{-1}{\gamma}) e^{-\gamma a}|_0^\infty = \frac{\beta}{\gamma} S_0$. So the threshold value we found by analyzing the differential equation for $I'(t)$ matches the biological definition of the basic reproduction number; however we will see in later analyses that such is not always the case for complicated models.

More complicated models may have multiple infected stages (as opposed to the sole infectious compartment $I(t)$ in System (2.2). We could have, for example, an exposed compartment $E(t)$ as listed in Table 2.1. (The wording gets tricky here, but in the context of the reproduction number we are interested in all compartments in which the individuals are infect*ed*. They could be incubating the disease and not yet showing symptoms, or they could be in the latent period and are not yet infect*ive*, or they could be in one of many contagious stages or compartments

(depending on the model). $I(t)$ refers only to the infective (contagious) compartment but we are looking at all infected populations.)

If there are multiple infected stages, following Heffernan *et. al.* we need to consider all of these compartments. Suppose there are n compartments and denote the state of the epidemic model system by $x(t) \in \mathbb{R}^n$. Suppose that $m \leq n$ of these compartments are for individuals with the infection (in the Kermack and McKendrick model (2.2), $n = 2$ and $m = 1$). For $i = 1 \dots m$ we define $F_i(x)$ to be the "rate of appearance of *new* infections" in compartment i. We define $V_i^+(x)$ to be the rate of entrance of individuals into compartment i by any method except new infection and $V_i^-(x)$ to be the rate of exit. This entrance could include transfer from another infected compartment, infected births, or immigration of infected individuals, for example. The exit could be through recovery, death (natural or disease-induced), or transfer to a different infected stage. As an example, Heffernan et. al. [33] consider the SEIR model

$$\begin{cases} E' &= \beta SI - (\mu + \kappa)E \\ I' &= \kappa E - (\mu + \gamma)I \end{cases} \tag{2.7}$$

where the S and R compartments are suppressed since they are disease-free, and the parameters correspond to those in Table 2.2. They further define $V_i(x) = V_i^-(x) - V_i^+(x)$ which gives the total rate of change of infected individuals *out* of compartment i (could be negative if more are entering than exiting) except for the new infections. For model (2.7) the $\pm\kappa E$ term represents transferred infectives, not new ones. We have $x = [S, E, I, R]^T$ and

$$\begin{aligned} F_1(x) &= \beta SI \\ F_2(x) &= 0 \\ V_1(x) &= (\mu + \kappa)E - 0 \\ V_2(x) &= (\mu + \gamma)I - \kappa E \end{aligned}$$

The authors then define the $m \times m$ matrices

$$F = \left[\frac{\partial F_i(x_0)}{\partial x_j}\right], \qquad V = \left[\frac{\partial V_i(x_0)}{\partial x_j}\right], \qquad i, j = 1 \dots m \tag{2.8}$$

where the x_j are the infected populations and x_0 is the disease-free equilibrium where $E \equiv 0 \equiv I$ [33]. Heffernan *et. al.* summarize earlier work: if we define $\mathcal{R}_0$ to be the spectral radius of FV^{-1} as did Diekmann *et. al* [14], van den Driessche and Watmough prove that a disease-free equilibrium is locally asymptotically stable if $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 > 1$ [72].

In Equation (2.7) we have

$$F = \begin{bmatrix} 0 & \beta S_0 \\ 0 & 0 \end{bmatrix} \qquad V = \begin{bmatrix} \mu + \kappa & 0 \\ -\kappa & \mu + \gamma \end{bmatrix}.$$

Given the additional differential equation $S' = b - \mu S - \beta SI$ we get that $S_0 = b/\mu$ and so the biologically-defined reproduction number is $\mathcal{R}_0 = \frac{\kappa\beta b}{(\mu+\kappa)(\mu+\gamma)(\mu)}$ [33].

In the Kermack-McKendrick model (2.2), $m = 1$ and $F_1 = \beta SI$, $V_1 = \gamma I - 0$, so $F = [\beta S_0], V = [\gamma] \Rightarrow \mathcal{R}_0 = FV^{-1} = \beta S_0/\gamma$ as expected.

In this thesis we will always use the term "reproduction number" and the notation $\mathcal{R}_0$ to refer solely to those thresholds that agree with the biological definition; the other threshold values we find (that signify a change in the stability of the disease-free equilibrium) will be referred to as "threshold numbers" or similar. The notation for these threshold values ($\mathcal{R}^*, \bar{\mathcal{R}}$, *etc.*) will still be similar to that of the reproduction number to evoke the relation that they are important values to the system.

2.4 Control Methods

Modelling epidemics can be used in theory to determine how severe an epidemic or outbreak may be; however, the goal in public policy and in epidemiology is to try to influence the outcome of such problems. We want to use control methods to limit the severity of outbreaks or, ideally, to prevent them altogether.

There are different control methods available, such as quarantine, travel restrictions, or most commonly vaccination. The point of vaccination in real life is to confer immunity to an individual so they can fight off the disease if they are exposed to it; looking at the population as a whole, vaccination decreases the size of the susceptible compartment, ideally below the threshold above which there can be an outbreak.

Vaccination may be applied in different ways; two common types are *continuous vaccination* and *pulse vaccination*, explained below.

Continuous Vaccination

Continuous vaccination involves consistently immunizing individuals at some rate; for example, suppose we aim to vaccinate a population for measles, we could vaccinate each newborn a certain number of months after their birth.

Mathematically, we choose a simple compartmental model with susceptible population S, infective population I, and vaccinated population V (alternatively we could use R for "removed from disease circulation"). We assume the vaccination is continuous with rate θ (that is, the average individual is vaccinated after $1/\theta$ units of time). Ignoring demographic effects such as

births and deaths, we get the following:

$$\begin{cases} S' &= -\beta SI - \theta S \\ I' &= \beta SI - \gamma I \\ R' &= \gamma I + \theta S \end{cases}$$

Notice that S is nonincreasing since $S' \leq 0$, so $S(t) \leq S(0) =: S_0$. Consider the equation for I': We have $I' = [\beta S - \gamma]I \leq [\beta S_0 - \gamma]I$. If $S_0 < \frac{\gamma}{\beta}$ then $I' < 0 \ \forall t$ and the infective population will never rise above its initial level. If $S_0 \geq \frac{\gamma}{\beta}$, we may hope to use the vaccination to help quickly decrease $S(t)$ below this threshold level. In the absence of disease, $S' = -\theta S (S(t) = S_0 e^{-\theta t})$ so we can apply the continuous vaccination in order to drive $S(t)$ below γ/β in preparation for the possibility of disease introduction. That is, if an infective individual enters the population (for example through immigration) at $t = t_1$, we have been vaccinating since $t = 0$ to ensure $S(t_1) < \gamma/\beta$.

Brauer and Castillo-Chavez consider a model with birth rate b = death rate μ and with constant births proportional to a carrying capacity K [7]:

$$\begin{cases} S' &= \mu K - \beta SI - \mu S \\ I' &= \beta SI - (\mu + \gamma + \alpha)I \\ R' &= \gamma I - \mu R \end{cases}$$

The disease-free equilibrium is $(S, I, R) = (K, 0, 0)$. Linearizing about this equilibrium we get that the linearized system is stable when all eigenvalues of the Jacobian matrix are negative; in particular we need $\beta K - (\mu + \gamma + \alpha) < 0$. (This result corresponds to finding the reproduction number using the method in [33] with $m = 1, F_1 = \beta SI, V_1 = (\mu+\gamma+\alpha)I \Rightarrow \mathcal{R}_0 = \beta K/(\mu+\gamma+\alpha)$ and requiring $\mathcal{R}_0 < 1$.)

Looking for a non-disease-free equilibrium we see from the I' equation that such an equilibrium will satisfy $S_\infty = (\mu + \gamma + \alpha)/\beta$ and so we can rewrite the reproduction number as $\mathcal{R}_0 = K/S_\infty$. After an epidemic without vaccination we can thus use the estimated size of the susceptible population to approximate the reproduction number of the disease. If we wish to force $\mathcal{R}_0 < 1$, we can add vaccination: suppose we continuously vaccinate a fraction θ of newborns, then we will have $S' = \mu K(1 - \theta) - \ldots$ and so we will find the new effective reproduction number $\mathcal{R}_0(1 - \theta)$. Then if we want $\mathcal{R}_0(1-\theta) < 1, \Rightarrow \theta > 1 - \frac{1}{\mathcal{R}_0}$ and we have an estimate of how high our continuous vaccination rate needs to be to eradicate the disease [7].

Pulse Vaccination

Pulse vaccination involves a campaign to vaccinate a given proportion of the susceptible population after certain time intervals, with a campaign length short enough to be assumed instantaneous. With the measles example, we could organize a campaign every four years, say, to

vaccinate a given fraction (ideally all) children under the age of four. If this campaign takes place over only a few days or weeks then it is basically negligible compared to the interval (four years) between vaccination "pulses."

The main idea of pulse vaccination is to reduce the susceptible population as much as possible. Nokes and Swinton explain that repeated pulse vaccination campaigns "achieve their effect by rapidly starving the infectious disease of its supply of susceptible individuals," so incidence is reduced "drastically" [63].

Earn explains, for example, that measles incidence tends to go through periodic cycles, and conjectures that a global pulse vaccination campaign could force the incidence levels to be synchronized between different areas, so when the infective population falls in the troughs between epidemics (as the susceptibles are used up) there is a higher chance that stochastic effects will eradicate the disease [21]. If the campaign is merely local there is more chance of the disease being re-imported from other areas. In our analysis and, indeed, in much of the literature, we tend to assume a population is isolated and deterministic. If we intend to model real-life situations we would do well to keep in mind that physical situations constantly evolve.

Shulgin *et. al.* discuss cases of practical application of pulse vaccination to polio and measles in South America and the United Kingdom, respectively [68]. de Quadros *et. al.* explain that in Cuba, "annual [polio] campaigns began in 1962, and shortly thereafter paralytic poliomyelitis disappeared;" each course of the vaccine was distributed annually "only during two one-week periods each year" [13] during which all children below a certain age received the vaccine.

See [63, 62], for example, for a more thorough introduction, [1, 68] for simulations analysis, and [21, 4] for comparison to real-life data. We discuss mathematical models of pulse vaccination beginning with Section 3.3 and further in the literature review Chapter 4 and in the results Chapters 5 - 7.

2.5 Model Generalization

We have so far listed a few specific epidemic models, while in reality there are many different ways to set up a compartmental deterministic system. Generally a model may be adapted to a specific disease by:

- DE form: the inclusion or exclusion of terms or compartments; changing dependence of terms on the state; or varying the parameters
- The type of DE: add delay (finite or infinite), add discrete control methods like pulse vaccination

2.5.1 Changes to DE Form: Parameters, Terms, and Compartments

Here we discuss extra terms (often resulting in extra parameters), extra compartments, changing the form of the terms in a DE from the common incidences or exponential distributions, and varying the parameters over time.

Extra Terms

An example of extra terms would be a vaccine waning term δR transferring individuals from R to S:

$$\begin{cases} S' &= \ldots + \delta R(t) \\ &\vdots \\ R' &= \ldots - \delta R(t) \end{cases}$$

The extra $\pm\delta R$ terms are simply transferring the population between compartments. In transfer cases there will be matching terms of opposite sign in two different compartments. We could instead have something like a disease death term $I' = \ldots - \alpha I$ or an immigration term $S' = \ldots + \text{Im}$, modelling exit from and entrance to the total population. The point of extra terms in the DEs are to more accurately model the real-life dynamics by including details which may be important to disease propagation.

Extra Compartments

Adding or excluding compartments changes the dimension of the state vector $x(t)$.

A compartment may be left out, for example, if it is irrelevant to the model for a specific disease. For example, in a typical SIR model we use a removed class, representing those who have immunity, whether by recovering from the disease or by vaccination. However, for a disease which confers no immunity, the R compartment would be unnecessary and the model would become an SI model (which has no recovery, $\gamma = 0$), or an SIS model (in which individuals recovering from the disease become susceptible again):

$$\begin{cases} S' &= bN - \mu S - \beta\frac{SI}{N} + \gamma I \\ I' &= \beta\frac{SI}{N} - (\mu + \gamma + \alpha)I \end{cases}$$

Or, in an SIR model without demographic effects such as births and deaths, the compartment R could represent individuals removed from the population due to disease deaths. In both of the above cases we would have $N = S + I$, and N would still remain positive. Thus the removal of compartments doesn't affect the physicality of the population.

Some epidemic models simply do not explore every compartment. They may repress analysis of certain compartments (such as R) of which the other compartments are independent:

$$\begin{cases} S' &= bN - (\mu+\theta)S - \frac{\beta SI}{N} \\ I' &= \frac{\beta SI}{N} - (\mu+\gamma)I \end{cases}$$

Here we have ignored the differential equation $\frac{dR}{dt} = \theta S + \gamma I - \mu R$ because R has no effect on S or I. Or a model may consider only the infected population, such as in [46]:

$$h'(t) = \beta g m(t) \frac{N - h(t)}{N} - \alpha h(t) - \gamma h(t)$$

This model considers the size of the infected human population $h(t)$, where $m(t)$ is the infected mosquito population. Only a fixed fraction g of the infected mosquito population is assumed to be infective (contagious). It appears that some infection terms do not have corresponding terms of opposite sign for another section of the population, the way we have seen so far and as we claimed earlier. However, we note that by letting $s(t) := N(t) - h(t)$ be the susceptible population we get the more comprehensive human system (though without demographic effects)

$$\begin{cases} s'(t) &= -\beta g m(t) \frac{s(t)}{N} + \gamma h(t) \\ h'(t) &= \beta g m(t) \frac{s(t)}{N} - \alpha h(t) - \gamma h(t), \end{cases}$$

with corresponding total population size governed by $N'(t) = -\alpha h(t)$ ($\geq -\alpha N(t)$).

The repressed or ignored compartments may be irrelevant to the dynamics of the compartment of interest, but taking all of the (physically necessary) classes together we get a total population of size N upon which we can find bounds, which let us prove existence and uniqueness of solutions as will be discussed in Section 3.4.

Likewise the addition of compartments, which really involves the partitioning of the total population into more specific classes, doesn't affect the physical reasonableness of the total population dynamics. Another compartment may be added, as we have seen, for example if there is an exposed class E. The latent period may be modelled by an exponential distribution with mean $1/\kappa$, leading to

$$\begin{cases} S' &= bN - (\mu+\theta)S - \frac{\beta SI}{N} \\ E' &= \frac{\beta SI}{N} - (\mu+\kappa)E \\ I' &= \kappa E - (\mu+\gamma)I \\ R' &= \theta S + \gamma I - \mu R \end{cases} \tag{2.9}$$

Or, even more additional classes may be added to represent different disease states:

$$\begin{cases} S' &= b - (\mu + \theta)S - \frac{\beta_s SI}{N} + \delta R \\ V' &= \theta S - \frac{\beta_v VI}{N} - \nu V - \mu V \\ I' &= \beta_s \frac{SI}{N} + \beta_v \frac{VI}{N} - (\mu + \gamma)I \\ R' &= \nu V + \gamma I - (\mu + \delta)R \end{cases}$$

Here we have a partially-effective vaccine which causes a lower rate of successful transmission to vaccinated individuals than to those fully susceptible ($\beta_V < \beta_S$). We want to consider vaccinated individuals as a separate class because the compartment dynamics may be different from that of S, but we still see each term in V' cancels with a term in another differential equation of the system.

In both of the above cases we still have $N'(t) = (b - \mu)N(t)$ (where N is the sum of the compartments), and the new compartments didn't have any inherent discontinuities in their governing differential equations. In general, we can easily "add" extra compartments to the model (by dividing existing ones) to more accurately model the disease progression. The tradeoff is that with a larger-degree system the model may become more complicated to analyze.

Form of Differential Equation Terms

It is definitely possible to have different forms of the terms in the system than just the common incidence and exponential terms described above.

We could use a different form for the incidence terms: those so far have been of a bilinear incidence form βSI or a standard incidence $\beta \frac{SI}{N}$. Bilinear incidence comes from the law of mass action, that is, the number of transmissions is assumed to be proportional to the product of the susceptible and infective populations [32]. We could find, however, that we have a saturated contact rate [49]:

$$\dot{S}(t) = \ldots - \beta \frac{SI}{1 + aS}$$
$$\dot{I}(t) = \beta \frac{SI}{1 + aS} + \ldots$$

The saturation here occurs as S grows, but could just as easily be in terms of I, with $1 + aI$ in the denominator.

Another way to change the underlying assumptions of the associations within the system would be to allow for logistic growth. We have been continually returning to the fact that

$\dot{N} = (b - \mu)N$ (or similar), reflecting simple exponential growth or decay in the total population N. In population biology models, logistic growth may also be considered:

$$\dot{N} = \rho N(1 - \frac{N}{K})$$

where $\rho > 0$ and K is the carrying capacity of the environment.

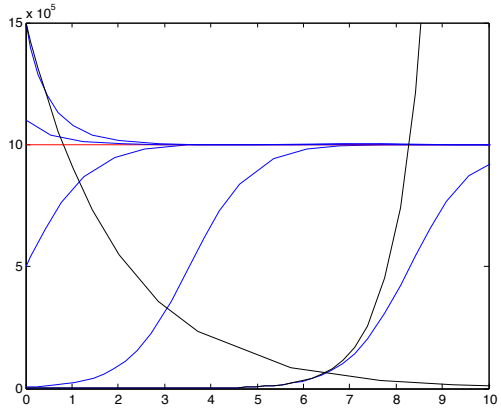

Fig. 2.3: Logistic (blue) vs. exponential (black) long-term population change.

Over the time period of an epidemic the assumption of pure growth or decay may be likely, as typical growth rates are not explosive in human populations so a population doesn't reach carrying capacity very quickly. As shown in Figure 2.3, exponential decay may not long remain close to a logistic decay with the same initial conditions, but may still be similar for the time scale of a short epidemic. Exponential growth may roughly model logistic growth for a relatively longer time.

Time-Varying Parameters

The parameters in all of the above models were assumed to be constants, but this assumption is clearly unrealistic. Although we do not consider spatially-varying parameters or systems in this chapter, it is clear that the assumption of a homogeneously-mixed population, especially if the population is meant to be human, is a very strong one. For now we merely consider time-varying parameters, which Earn explains can in themselves explain a great deal of observed epidemic effects such as seasonality [21].

The rate of successful contacts in a population, for example, is not constant over time. On the time scale of a day, a person is likely to spend some times around more people, or in closer contact to them, than other times. Over the course of weeks, children spend time in the classroom

and out of it, and Grassly and Fraser note that transmission rates increase during the school season [31]. On the time scale of a year, the weeks of schooling and the weeks of vacation may display very different transmission rates. Regarding the whole population (not just school-age children), seasonality can be observed, for example with the annual flu season. In addition to human behaviour, Grassly and Fraser discuss that causes of seasonality may include varying environmental factors (such as temperature and humidity) which may affect the survival of a pathogen, or which may affect the availability of vectors such as mosquitoes.

2.5.2 Changes to the Type of Differential Equation

So far we have only considered ordinary differential equation (ODE) models. We may use other types of differential equation to suit the model circumstances as explained below.

Spatial Variation

All models so far have assumed a homogeneously-mixed population, which is unlikely both in terms of peoples' habits and in terms of their spatial distribution. Rather than the ODE models we have been looking at so far, we can use partial differential equations to model spatial variation in the population. This thesis does not consider such models in detail.

Discrete Behaviour

The previous models assumed continuous dynamics in the system, but hybrid dynamical systems may be used to idealize physical systems or to approximate real-life behaviour.

We may introduce discrete behaviour into our systems in the form of pulse vaccination as described in Section 2.4, where we are analyzing the mathematics based on an idealized vaccination campaign. We could use switched systems, where at certain times the model switches between subsystems. These subsystems may have completely different forms, or they may simply have different parameters values from each other. In order to simplify the analysis, for example, a seasonally-varying contact rate $\beta(t)$ may be approximated by a switching parameter $\beta_{\sigma(t)}$, where $\sigma(t) \in \{1, \ldots, m\}$ (m is the number of subsystems) [52].

Switched systems may not always be simply to make the math easier; Grassly and Fraser explain that among populations of children, transmission of measles is lower over the holidays [31], and we can extrapolate roughly to assume that transmission of many diseases follows a similar pattern. When students return to school they are suddenly in close contact with other individuals, and so approximating the change with a near-instantaneous switch seems reasonable.

Earn discusses a model which uses the contact rate [21]

$$\beta(t) = \begin{cases} \beta_H & schooldays \\ \beta_L & non-schooldays. \end{cases} \tag{2.10}$$

Delay Differential Equations

In all of the previous epidemic model examples in this thesis, we have looked at ODE systems in which the time-dependence was purely based on the current time level t. That is, the incidence was dependent on the populations at time t, as were the other transfer terms and the entrance and exit terms to the populations.

Physical processes take time, however. A vaccination might need time to take effect as the recipient builds immunity, or the time until infectiousness develops may be consistent across a population so the exponential distribution is unreasonable. In such cases we use a delay differential equation, in which the arguments may be reduced ("delayed"): $x(t-r)$ instead of $x(t)$. As an example, suppose it takes a time r for individuals who have been exposed to the disease to become infectious. Instead of (2.9), which used an exposed compartment with exponential recovery rate κ, we could have the model

$$\begin{cases} S' &= bN - (\mu+\theta)S - \frac{\beta SI}{N} \\ E' &= \beta\frac{SI}{N} - \beta\frac{S(t-r)I(t-r)}{N(t-r)} - \mu E \\ I' &= \beta\frac{S(t-r)I(t-r)}{N(t-r)} - (\mu+\gamma)I \\ R' &= \theta S + \gamma I - \mu R \end{cases} \tag{2.11}$$

Delay equations can have richer dynamics than ODEs and can be a better fit to the real-world situation we intend to model. They can be complicated, however, for instance because a delay differential equation is infinite-dimensional and so chaos may occur even in low-order systems.

Previously we had individuals moving sequentially through the population compartments (*e.g.* $S \to E$, after delay $\to I \to R$), so that if any factor of a term transferring between populations is delayed, all factors are (such as in the second term in the E' equation in (2.11)). The delay in a DDE model does not have to be introduced as a consequence of this movement: we could for example have mixed delays, where different factors of a term have different delay arguments.

Vector-borne disease models can use mixed delays due to the interaction between two species populations. All previous epidemic model examples in this thesis involved the transmission of a disease through one population (*e.g.* humans). Some diseases, however, are borne by animals or by other vectors such as mosquitoes.

Meng *et.al.* discuss an equation with delay in the I factor of the incidence, but not S; that is, the incidence term is $-\beta S(t)I(t-r)$ [59]. The current rate of new infective people depends on the

current number of susceptible people and upon the current number of infective mosquitoes. With an incubation period of r, the current number of infective mosquitoes depends on the number of infective people r time units ago, so with bilinear incidence we therefore we have the product $S(t)I(t-r)$. Mixed delays are not necessary, though; an example of a vector-borne disease model without mixed delay was studied by A.J. Lotka and disussed by Kuang in [46]:

$$\begin{cases} h'(t) &= \beta_H g m(t-u)\frac{N-h(t-u)}{N} - \alpha_H h(t) - \gamma_H h(t) \\ m'(t) &= \beta_M f h(t-v)\frac{M-m(t-v)}{M} - \alpha_M m(t) - \gamma_M m(t) \end{cases}$$

u and v are the incubation delays in the human population and mosquito population respectively. N is the total human population while h is the infected human compartment, of which a fraction g are contagious (infective). M is the total mosquito population with m the infective mosquitoes and f the contagious fraction.

Delay in the previous examples has been assumed constant, but in a more general model we could have time-dependent or even state-dependent delay. For example, suppose we use a delay to model the time to recover from the disease. A sample model to start with, obtained by adding delay to System (2.2), could be

$$\begin{cases} S' &= -\beta SI \\ I' &= \beta SI - \beta S(t-\omega)I(t-\omega) \\ R' &= \beta S(t-\omega)I(t-\omega) \end{cases}$$

The time individuals take to recover, in addition to being quite likely dependent on the individuals themselves, may also depend for example on the time of year. We might recover better in the summer when the weather is warm, or during holidays when we relax, for example. It is reasonable then to include a time-dependent delay $\omega(t)$. An example of a state-dependent delay may be if there is a quarantined class Q where recovery is faster for small Q (since there may be more resources available than in a crowded situation), so $\omega = \omega(Q(t))$.

Even with time- or state-dependent delay, the delay discussed so far has been single-valued for all individuals at a particular point in time. Whereas the exponential terms (such as $\pm\gamma I$) assumed an exponentially-distributed transfer time, a single delay is equivalent to assuming a precisely-known transfer time that is the same for every individual in the population. According to Anderson the measles virus has an infectious period of 5-7 days [3]; this variation may be due to periodic environmental factors, but it is also entirely possible that healthy individuals recover faster. Assuming an exact value for a delay (whether it be the latent or recovery period or otherwise) is not very realistic. We may wish to make our model more general by using a distributed delay.

Cooke and Kaplan for example use the equation [11]

$$I'(t) = f(t, I(t)) + \int_{t-\omega}^{t} f(s, I(s))P'(t-s)ds$$

where $\omega < \infty$ is the maximum recovery time, $P(a)$ is the probability that an infective is still contagious a time units after infection. The tradeoff with a distributed delay is that the mathematical analysis becomes even more difficult. See Kuang's book [46] for a good introduction. In this thesis we focus on constant delays.

Chapter 3

Differential Equation Theory

In this chapter we present some theorems on existence, uniqueness, and stability for differential equations (DEs) relevant to the epidemic modelling literature. In Section 3.1 we discuss ordinary differential equations and in Section 3.2 we extend the results to delay DEs. In Section 3.3 we discuss hybrid systems and in particular the effects of discrete impulses on the preceding theorems.

As discussed in Section 2.5 there are many different compartmental epidemic models. After presenting theorems applicable to very general systems of differential equations, we will apply them to the following sample systems for illustration purposes:

Non-delay SIR model:

$$\begin{cases} S' &= b(N-S) - \beta \frac{I}{N} S \\ I' &= \beta \frac{I}{N} S - (\mu + \gamma) I \\ R' &= \gamma I - \mu R \end{cases} \tag{3.1}$$

Delay SEIR model:

$$\begin{cases} S' &= b(N-S) - \beta \frac{I}{N} S \\ E' &= \beta \frac{I}{N} S - \beta e^{-\mu r} \frac{I(t-r)}{N(t-r)} S(t-r) - \mu E \\ I' &= \beta e^{-\mu r} \frac{I(t-r)}{N(t-r)} S(t-r) - (\mu + \gamma) I \\ R' &= \gamma I - \mu R \end{cases} \tag{3.2}$$

The parameters were explained in Table 2.2 of Section 2.2.2.

Notice we again define the total population (sum of the compartments) to be $N(t)$; and as usual, for brevity we suppress the notation "(t)" for variables at the current time.

The generalization of our following results to other models should be clear, but in Section 3.4 we will explicitly explain why we are able to extend our results.

3.1 Ordinary Differential Equations

In this section we discuss theorems for a general ordinary differential equation (ODE)

$$x'(t) = f(t, x) \tag{3.3}$$

which will be relevant to later analyses. This equation is *nonautonomous* since it depends explicitly on the time varable t in addition to the state variable $x(t)$. We assume the ODE is subject to the initial condition (IC)

$$x(t_0) = x_0. \tag{3.4}$$

We analyze these models using results from the Fall 2009 UW Amath 751 course notes by Prof. Xinzhi Liu [50] (the theorems are commonly known but will be referenced to [50] from which they were transcribed). We then apply our results to the sample model system (3.1).

3.1.1 Existence and Uniqueness

Local Existence

Peano's existence theorem gives us conditions for when a solution to Equation (3.3) exists:

Theorem 1. *[50] Peano's Existence Theorem: Let $f \in C(F, \mathbb{R}^n)$, that is, f is a continuous function from F to $\mathbb{R}^n$ where*

$$F = \{(t, x) \in \mathbb{R} \times \mathbb{R}^n : |t - t_0| \leq a, \|x - x_0\| \leq c,\ a, c > 0\}, \tag{3.5}$$

and let $\|f(t, x)\| \leq M$ on F for some $M > 0$. Then the IVP (3.3-3.4) has at least one solution $x(t)$ defined on $[t_0 - \alpha, t_0 + \alpha]$ where $\alpha = \min\left(a, \frac{c}{M}\right)$.

Equal Birth and Death Rates

If $\mu = b$ and the population is normalized to $N = S + I + R \equiv 1$, (3.1) becomes:

$$\begin{cases} S' &= \mu(1 - S) - \beta IS \\ I' &= \beta IS - (\mu + \gamma)I \\ R' &= \gamma I - \mu R \end{cases}$$

Define $x := [S, I, R]^T$ and $f(t, x) := [x_1', x_2', x_3']^T$. Then (3.1) is equivalent to $x'(t) = f(t, x)$.

In this normalized case, the physical region is $x \in \Omega_1 := \{(S, I, R) \in [0, 1]^3 : S + I + R = 1\}$ since S, I, and R are fractions of the population. This region is positively invariant.

Using the L_1-norm,

$$\begin{aligned}\|f(t,x)\| &= |\mu(1-S) - \beta SI| + |\beta SI - (\gamma+\mu)I| + |\gamma I - \mu R| \\ &\leq |\mu(1-S)| + |\beta SI| + |\beta SI| + |(\gamma+\mu)I| + |\gamma I| + |\mu R| \\ &\leq \mu + 2\beta SI + 2\gamma I + \mu(|S| + |I| + |R|) \\ &\leq 2\mu + 2(\beta+\gamma) \quad =: M_1,\end{aligned}$$

since $S, I, R \geq 0$ and $S + I + R = 1$. Thus $\|f(t,x)\| \leq M_1$ for all $x \in \Omega_1$. If we choose any compact region $F = \{(t,x) \in \mathbb{R}_+ \times \Omega_1 : |t - t_0| \leq a, \|x - x_0\| \leq c\}$, then we have $f \in C(F, \Omega_1)$ and $\|f(t,x)\| \leq M_1$ on F. Therefore by Peano's Existence Theorem, Equation 3.3 has at least one solution on $[t_0 - \alpha, t_0 + \alpha]$, where $\alpha := \min(a, \frac{c}{M_1})$. Notice that if we choose $c \geq 3$ then $\{x : \|x - x_0\| \leq c\} \supseteq \Omega_1$.

Allowance for Population Growth

If the birth and death rates are unequal, $b \neq \mu$, then the boundedness of f is slightly more difficult to prove, since the population sizes may grow. The physical region of interest is now (potentially) unbounded; thus we define $\Omega_N := \mathbb{R}^3_+$ (where $\mathbb{R}_+ = [0, \infty)$). The region Ω_N is positively invariant with respect to the DE 3.3:

$$\begin{aligned} S = 0 &\Rightarrow S' = \mu > 0 \\ I = 0 &\Rightarrow I' = 0 \\ R = 0 &\Rightarrow R' = \gamma I \geq 0, \end{aligned}$$

so with initial conditions in Ω_N, the trajectory of the solution will never leave Ω_N.

Now suppose we again take a compact region $F = \{(t,x) \in \mathbb{R}_+ \times \Omega_N : |t - t_0| \leq a, \|x - x_0\| \leq b\}$. Consider $N = S + I + R$. Notice from system (3.1) that

$$\begin{aligned} N' &= S' + I' + R' \\ &= [b(S+I+R) - \beta\frac{S}{N}I - \mu S] + [\beta\frac{S}{N}I - (\gamma+\mu)I] + [\gamma I - \mu R] \\ &= b(S+I+R) - \mu(S+I+R) \\ \Rightarrow N' &= (b-\mu)N \qquad \Rightarrow N(t) = N_0 e^{(b-\mu)(t-t_0)}. \end{aligned} \tag{3.6}$$

So for now we find that $N(t)$ varies exponentially with time, which means $N(t)$ is bounded on the compact region F because $N(t) \leq N_0 e^{|b-\mu|a} =: N^M$. Since all of S, I, and R are non-negative and $N = S + I + R$ we must have $S(t), I(t), R(t) \leq N(t) \leq N^M$ as well. Now we can show that $\|f(t,x)\|$ is also bounded on F as follows, noting that all parameters and variables are positive

and that $N = S + I + R \Rightarrow \frac{S}{N} \leq 1$ and $I \leq N$:

$$\begin{aligned}
\|f(t,x)\| &= |b(S+I+R) - \beta\frac{S}{N}I - \mu S| + |\beta\frac{S}{N}I - (\gamma+\mu)I| + |\gamma I - \mu R| \\
&\leq \left(|bN| + |\beta\frac{S}{N}I| + |\mu S|\right) + \left(|\beta\frac{S}{N}I| + |\gamma I| + |\mu I|\right) + (|\gamma I| + |\mu R|) \\
&\leq bN + 2\beta I + 2\gamma I + \mu(|S| + |I| + |R|) \\
&= (b+\mu)N + 2(\beta+\gamma)I \\
&\leq (b+\mu+2\beta+2\gamma)N(t) \leq (b+\mu+2\beta+2\gamma)N^M \quad =: M.
\end{aligned}$$

Thus we find on an arbitrary compact $F \subset \mathbb{R}_+ \times \Omega_N$ that $f \in C(F, \Omega_N)$ and $\|f(t,x)\| \leq M$ for all $(t,x) \in F$. Hence we find that the system (3.1) has, by Peano's Existence Theorem, at least one solution on $[t_0 - \alpha, t_0 + \alpha]$, where $\alpha := \min(a, \frac{b}{M})$.

Remark. The above analysis assumes the total population will undergo exponential growth or decay depending on the relative values of b and μ. Clearly these birth rate assumptions are very simplistic; however, given any physically reasonable model we must have that $N(t)$ is bounded on any compact set and that $\frac{S}{N} \leq 1$, so the above result can be generalized.

Global Existence

We now look to see whether we can continue the local solutions of 3.3. We use the following theorem:

Theorem 2. *[50] Continuation of Solutions: Let $Q \subset \mathbb{R}^{n+1}$ be an open set and let $f \in C(Q, \mathbb{R}^n)$. If $x(t)$ is a solution of the IVP (3.3-3.4) on some interval, then it can be extended over a maximal interval of existence.*

Moreover, if (α_1, α_2) is a maximal interval of existence, then $(t, x(t))$ tends to the boundary of Q as $t \to \alpha_1^+$ and as $t \to \alpha_2^-$.

The following corollary makes Theorem 2's use explicit for our epidemic models:

Corollary 1. *[50] Let $f \in C(\mathbb{R}_+ \times \mathbb{R}^n, \mathbb{R}^n)$, $\mathbb{R}_+ = [0, \infty)$, and let $x(t)$ be a solution of IVP (3.3-3.4) on a right-maximal interval $J = [t_0, \alpha_2)$. Then $\alpha_2 = \infty$ if, for any $c > t_0$, $x(t)$ is bounded on $J \cap [t_0, c)$.*

Since in (3.1) we have $f \in C(\mathbb{R}_+ \times \mathbb{R}^3, \mathbb{R}^3)$, then a solution $x(t)$ to System 3.1 can be extended over a maximal interval of existence $[t_0, \alpha_2)$. As shown in the previous section, $N(t) = S(t) + I(t) + R(t)$ is bounded on any finite interval $[t_0, c]$ (*e.g.* in the exponential case, $N(t) \leq N(t_0)e^{|b-\mu|(c-t_0)}$), hence $\|x(t)\| \leq 3|N(t)|$ is bounded as well. Thus by the corollary to the Continuation Theorem 2 we have that $\alpha_2 = \infty$. The significance of this result is to show that an epidemic model system such as (3.1) will always have a solution continuing indefinitely.

Uniqueness

The uniqueness of a solution to system 3.3 depends on whether $f(t,x)$ is Lipschtizian in x:

Definition 2. [50] **Lipschitzian:** Say $f \in C(Q, \mathbb{R}^n)$ where $Q \subset \mathbb{R}^{n+1}$ is an open set. $f(t,x)$ is said to be *locally Lipschitzian* in x on Q if for each $(t_0, x_0) \in Q$ there exists a neighbourhood U of (t_0, x_0) and positive constant $L = L(U)$ such that for $(t,x), (t,y) \in U$

$$\|f(t,x) - f(t,y)\| \leq L\|x - y\|.$$

If L is independent of U then f is said to be Lipschitzian in x on Q.

Theorem 3. *[50] Uniqueness: Let $f \in C(F, \mathbb{R}^n)$, where F is the compact set defined in Theorem 1, and let f satisfy a Lipschitz condition on F with Lipschitzian constant L. Then the IVP (3.3-3.4) has at most one solution on an interval $[t_0 - \alpha, t_0 + \alpha]$.*

Claim 1. *If f has continuous partial derivative in x then f is locally Lipschitzian in x on Q and Lipschitzian on any compact and convex subset of Q [50].*

Fortunately in for these epidemic models the Lipschitzian property is easy to show: since $N(t) \geq N_0 e^{-|b-\mu|(t-t_0)}$, $N(t) \neq 0$ unless $N_0 = 0$, which is physically unreasonable (how can we study epidemic patterns without a population?). In fact for any time-varying population where $N(t)$ does not go to 0 in finite time, the fractions $(S+I+R)^{-1}$ are always defined, and the Jacobian,

$$\mathrm{D}f(x) = \begin{bmatrix} b - \mu - \beta\left(\frac{I+R}{(S+I+R)^2}\right) I & b - \beta\left(\frac{S+R}{(S+I+R)^2}\right) S & b + \beta\left(\frac{1}{(S+I+R)^2}\right) SI \\ \beta\left(\frac{I+R}{(S+I+R)^2}\right) I & \beta\left(\frac{S+R}{(S+I+R)^2}\right) S - (\gamma + \mu) & \beta\left(\frac{1}{(S+I+R)^2} SI\right) \\ 0 & \gamma & -\mu \end{bmatrix}$$

is defined and continuous for all $x \in \Omega_N$.

Since f has continuous partial derivatives in x it is locally Lipschitzian in x on any compact subset of $\mathbb{R}_+ \times \Omega_N$ and so there is a unique solution which may be extended to a maximal interval.

This maximal interval was shown in the previous section to be $[t_0, \infty)$. Therefore we have found that, for the SIR epidemic model without delay, there is a unique solution on $[t_0, \infty)$ without pulses.

3.1.2 Stability Theorems

We first state some stability definitions given in the AMATH 851 course at the University of Waterloo [51]. We assume that $f(t,0) \equiv 0$ in (3.3) and call $x(t) \equiv 0$ the *trivial solution.*

Definition 3. [51] **Stability:** The trivial solution of (3.3)-(3.4) is called

(i) *Stable* if for all $\epsilon > 0$ and $t_0 \in \mathbb{R}_+$, there exists $\delta = \delta(t_0, \epsilon) > 0$ such that

$$\|x_0\| < \delta \Rightarrow \|x(t)\| < \epsilon, \quad t \geq t_0.$$

(ii) *Uniformly Stable* (US) if *(i)* holds and $\delta = \delta(\epsilon)$ is independent of t_0.

(iii) *Asymptotically Stable* (AS) if *(i)* holds and there exists $\sigma = \sigma(t_0) > 0$ such that

$$\|x_0\| < \sigma \Rightarrow \lim_{t\to\infty} x(t) = 0.$$

(iv) *Globally Asymptotically Stable* (GAS) if $\sigma = \sigma(t_0)$ is arbitrary in *(iii)*.

(v) *Uniformly Asymptotically Stable* (UAS) if *(ii)* holds and if for all $\eta > 0$, there exists $\sigma > 0$ (independent of t_0) and there exists $T = T(\eta) > 0$ such that for all $t_0 \in \mathbb{R}_+$,

$$\|x_0\| < \sigma \Rightarrow \|x(t)\| < \eta, \quad t \geq t_0 + T.$$

(vi) *Globally Uniformly Asymptotically Stable* (GUAS) if σ is arbitrary in *(v)*.

(vii) *Unstable* if *(i)* fails.

Uniform stability and asymptotic stability do not combine to automatically give uniform asymptotic stability; the additional $T(\eta)$ requirement is to ensure the rate of decrease for a UAS solution. In the context of the epidemic models we discuss, we are interested in uniform asymptotic stability: it is not enough in practice to know that the disease will die out. We want some sort of assurance of how quickly it will happen.

The next definitions are necessary for the theorems on Lyapunov stability to follow.

Definition 4. [51] **Positive Definite:** A function $w(x)$ is called *positive definite* if $w(0) = 0$ and $w(x) > 0$ for $x \neq 0$.

We are interested in general nonautonomous systems for now, so we extend the definition to functions that are also function of t:

Definition 5. [51] **Positive Definite, Decrescent:** A function $V(t, x)$ is called *positive definite* if

$$V(t, x) \geq w(x) \tag{3.7}$$

where $w(x)$ is positive definite. $V(t, x)$ is called *decrescent* if

$$V(t, x) \leq W(x) \tag{3.8}$$

where $W(x)$ is positive definite.

Definition 6. Class-$\mathcal{K}$ Function: A function $a(y)$, $y \in \mathbb{R}$ is said to be in the class $\mathcal{K}$ if a is continuous, $a(0) = 0$, and $a(y)$ is strictly increasing.

According to [51],

- $V(t,x)$ is positive definite $\iff$ $V(t,x) \geq a(\|x\|)$; and
- $V(t,x)$ is decrescent $\iff$ $V(t,x) \leq b(\|x\|)$ where $a, b \in \mathcal{K}$.

We now restate commonly-known theorems on the use of Lyapunov functions for stability. These theorems were introduced to the author in the AMATH 851 course [51] at the University of Waterloo.

Theorem 4. ***Lyapunov function method for US:*** *Let $V \in C^1(\mathbb{R}_+ \times \mathbb{R}^n, \mathbb{R})$. Assume that*

(i) $V(t,x)$ is positive definite;

(ii) $V(t,x)$ is decrescent; and

(iii) $V'(t,x) = \frac{\partial V}{\partial t} + \frac{\partial V}{\partial x} \cdot f(t,x) \leq 0$ for $(t,x) \in \mathbb{R}_+ \times B_\rho(0)$, where $B_\rho(0) := \{x \in \mathbb{R}^n : \|x\| < \rho,\ \rho > 0\}$.

Then the trivial solution of (3.3) is uniformly stable. (Without condition (ii) it is stable.)

Theorem 5. ***Lyapunov function method for UAS:*** *If in Theorem 4 we strengthen condition (iii) to $V'(t,x) \leq -c(\|x\|), c \in \mathcal{K}, (t,x) \in \mathbb{R}_+ \times B_\rho(0)$, then we get uniform asymptotic stability.*

Proof. See AMATH 851 course notes [51].

3.1.3 Additional Theorems

In this section we state additional theorems which will be useful later. We first state Gronwall's Inequality, which will be used in Section 5.1, then we discuss comparison theorems for ordinary differential equations.

Theorem 6. *[50]* ***Gronwall's Inequality:*** *Let $m, v \in C(J, \mathbb{R})$ where $J = [a, b)$. For $t \in J$, let $v(t) \geq 0$ and*

$$m(t) \leq c + \int_a^t v(s)m(s)ds$$

where c is a constant. Then for $t \in J$,

$$m(t) \leq ce^{\int_a^t v(s)ds}.$$

We state some definitions relevant to the comparison theorems.

Definition 7. [50] **Dini Derivative:** Given $m \in C(J, \mathbb{R})$ where $J = [a, b]$, the upper right Dini derivative is defined by

$$D^+m(t) = \lim_{h \to 0^+} \sup \frac{1}{h}[m(t+h) - m(t)].$$

The lower-right Dini derivative is similarly

$$D_+m(t) = \lim_{h \to 0^+} \inf \frac{1}{h}[m(t+h) - m(t)].$$

When $m(t)$ is differentiable, the expression reduces to $D^+m(t) = m'(t) = D_+m(t)$.

Definition 8. [50] **Extremal Solutions:** A solutions $\gamma(t) = \gamma(t; t_0, x_0)$ of (3.3)-(3.4), defined on its maximal interval J_γ, is called a *maximal solution* if for any other solution $x(t) = x(t; t_0, x_0)$ of (3.3)-(3.4) on its maximal interval J_x we have

$$\gamma(t) \geq x(t)$$

for $t \in J_\gamma \cap J_x$. A *minimal solution* $\rho(t)$ is defined similarly, where $\rho(t) \leq x(t)$ on $J_\rho \cap J_x$.

The following comparison theorem will be used frequently Chapter 5 when we have an ODE with an upperbound or lowerbound on the derivative.

Let $m \in C(J, \mathbb{R})$ where $J = (\alpha_1, \alpha_2)$ and consider also the IVP

$$u' = g(t, u), \qquad u(t_0) = u_0 \tag{3.9}$$

where $g \in C(J \times \mathbb{R}, \mathbb{R})$.

Theorem 7. *[50]* ***ODE Comparison Theorem (≤):*** *Suppose*

$$D^+m(t) \leq g(t, m(t))$$

for $t \in J$. If $t_0 \in J$, $m(t_0) \leq u_0$, and $\gamma(t) = \gamma(t, t_0, u_0)$ is the maximal solution of (3.9), then

$$m(t) \leq \gamma(t)$$

for $t \in J$.

Corollary 2. *In the above theorem we can set $m(t) := \|x(t)\|$, where $x' = f(t, x)$ as in (3.3), then if $\|f(t, x)\| \leq g(t, \|x\|)$ and $x(t_0) = x_0$ with $\|x_0\| \leq u_0$, then $\|x(t)\| \leq \gamma(t)$.*

The inequality works in the other direction:

Theorem 8. ***ODE Comparison Theorem (≥):*** *Suppose*

$$D_+m(t) \geq g(t, m(t))$$

for $t \in J$. If $t_0 \in J$, $m(t_0) \geq u_0$, and $\rho(t) = \rho(t, t_0, u_0)$ is the minimal solution of (3.9), then

$$m(t) \geq \rho(t)$$

for $t \in J$.

Proof. We follow the same method as the proof in [50] of Theorem 7. From Equation (3.9) we extend to the IVP

$$u' = g(t, u) - \epsilon, \qquad u(t_0) = u_0 - \epsilon \tag{3.10}$$

leading to the family of solution functions $u(t, -\epsilon) = u(t, t_0, u_0 - \epsilon)$ defined on their maximum intervals J_ϵ.

The proof is nearly identical to that in [50] for $u(t, +\epsilon)$. As in [50] we get the results

1. If $\epsilon_1 < \epsilon_2$ then $u(t, -\epsilon_1) > u(t, -\epsilon_2)$.

   Proof. For any $\epsilon_1, \epsilon_2 \in \mathbb{R}$, $\epsilon_1 < \epsilon_2 \Rightarrow u(t_0, -\epsilon_1) = u_0 - \epsilon_1 > u_0 - \epsilon_2 = u(t_0, -\epsilon_2)$. Assume $\exists\ t_1 > t_0$ such that $u(t_1, -\epsilon_1) = u(t_1, -\epsilon_2)$ and $u(t, -\epsilon_1) > u(t, -\epsilon_2)$ for $t \in [t_0, t_1)$. We must have $u(t, -\epsilon_2)$ crossing above or at least being tangent to $u(t, -\epsilon_1)$ at $t = t_1$; but $u'(t_1, -\epsilon_2) = g(t_1, u(t_1, -\epsilon_2)) - \epsilon_2 = g(t_1, u(t_1, -\epsilon_1)) - \epsilon_2 < g(t_1, u(t_1, -\epsilon_1)) - \epsilon_1 = u'(t_1, -\epsilon_1)$. This contradiction shows $u(t, -\epsilon_1) > u(t, -\epsilon_2)$ for all $t > t_0$, $t \in J_{\epsilon_1} \cap J_{\epsilon_2}$ (the intersection of the maximal intervals of the two solutions). □

2. There exists a $\rho(t)$ defined on a right-maximal interval $[t_0, \alpha)$ such that $\lim_{\epsilon \to 0^+} u(t, -\epsilon) = \rho(t)$ uniformly on any compact subset of $[t_0, \alpha)$.

   Proof. Choose a sequence $\{\epsilon_k\}$ where $\epsilon_1 > \epsilon_2 > \ldots$ and $\lim_{k\to\infty} \epsilon_k = 0$. Let $u_k(t, -\epsilon_k)$ be a solution of

   $$u' = g(t, u) - \epsilon_k, \qquad u(t_0) = u_0 - \epsilon_k \tag{3.11}$$

   where the u_k are defined on right-maximal intervals $[t_0, \alpha_k)$. Let $\alpha = \lim_{k\to\infty} \inf \alpha_k$. Let $u(t)$ be any solution of (3.9) defined on its maximal interval J_u, then $u(t) = u(t, 0)$, a solution of (3.11). For all $b \in (t_0, \alpha)$, on $[t_0, b]$ we have

   $$u_1(t, -\epsilon_1) < u_k(t, -\epsilon_k) < u(t)$$

   by (1.) for all $m \in \mathbb{Z}$, and so $\{u_k\}$ is uniformly bounded on $[t_0, b]$. Since g is continuous then on this closed set g is bounded above and below, so $\{u_k'\} = \{g_k\} = \{g(t, u_k) - \epsilon_k\}$ is

uniformly bounded on $[t_0, b]$, therefore $\{u_k\}$ is equicontinous. By the Ascoli-Arzela lemma there is a subsequence which converges uniformly on $[t_0, b]$ to a solution $\rho(t)$ of (3.9). $\{u_k\}$ is monotone increasing by (1.) so $\lim_{k\to\infty} u_k(t, -\epsilon_k) = \rho(t)$ uniformly on $[t_0, b]$ for arbitrary b, that is, $\rho(t)$ is defined on $[t_0, \alpha)$ which is right-maximal by choice of α. □

3. $\rho(t)$ is the minimal solution of (3.9):

Proof. Let $u(t)$ be any solution of (3.9) defined on J_u. Then $u(t) = u(t, 0)$, a solution of (3.11), so by (1.), for any $\epsilon > 0$, $u(t) > u(t, -\epsilon)$, $t \geq t_0$ for $t \in J_u \cap J_\epsilon$. Take the limit as $\epsilon \to 0^+$ and we get $u(t) \geq \rho(t)$ for $t \in J_u \cap (t_0, \alpha)$. □

The main point to take away from the preceding proofs of (1.)-(3.) is that $\{u_m\} \to \rho$ (the minimal solution of (3.9)) uniformly on a closed interval $[a, b] \subset J_\rho$.

Now suppose $m \in C(J \times \mathbb{R}, \mathbb{R})$ and $D_+m(t) \geq g(t, m(t))$ with $m(t_0) \geq \rho(t_0)$. We choose a sequence $\{\epsilon_k\}$ where $\epsilon_1 > \epsilon_2 > \ldots$ and $\lim_{k\to\infty} \epsilon_k = 0$. We get a sequence $\{u_k(t, -\epsilon_k)\} \to \rho(t)$ uniformly as $k \to \infty$: then for all $m \in \mathbb{Z}$,

$$m(t) \geq u_k(t, -\epsilon_k). \tag{3.12}$$

If not, there exists $t_1 > t_0$ such that $m(t_1) = u_k(t_1, -\epsilon_k)$ and $m(t) < u_k(t, -\epsilon_k)$ on $(t_1, t_1 + \delta)$ for some $\delta > 0$. For $h \in (0, \delta)$,

$$\frac{m(t_1 + h) - m(t_1)}{h} < \frac{u_k(t_1 + h, -\epsilon_k) - u_k(t_1, -\epsilon_k)}{h}.$$

Taking the lim inf,

$$\begin{array}{lll} D_+m(t) & = lim_{h\to 0^+} \inf \frac{m(t_1+h)-m(t_1)}{h} & < lim_{h\to 0^+} \inf \frac{u_k(t_1+h,-\epsilon_k)-u_k(t_1,-\epsilon_k)}{h} \\ & = lim_{h\to 0^+} \frac{u_k(t_1+h,-\epsilon_k)-u_k(t_1,-\epsilon_k)}{h} & = u_k'(t_1, -\epsilon_k) \text{ since } u_k \text{ is differentiable} \\ & = g(t_1, u_k(t_1, -\epsilon_k)) - \epsilon_k & < g(t_1, u_k(t_1, -\epsilon_k)) \quad = g(t_1, m(t_1)). \end{array}$$

This result contradicts our assumption $D_+m(t) \geq g(t, m(t))$. Taking limits in (3.12) we get $m(t) \geq \rho(t)$, thus concluding the proof. □

A similar corollary applies to Theorem 8 as applied to Theorem 7. In many of our epidemic model analyses, however, we look at a comparison DE for the infected population $I(t)$; this population is scalar so the above results apply directly (without needing the corollary) with $m(t) = I(t)$.

In the case of pulse vaccination, our populations are continuous from the right and so we understand our derivatives in the dynamical systems models to be from the right as well; so we have $D^+m(t) = m'(t)$ (from the right) and $D_+m(t) = m'(t)$ as well. Therefore in the cases we are considering we may use this comparison theorem.

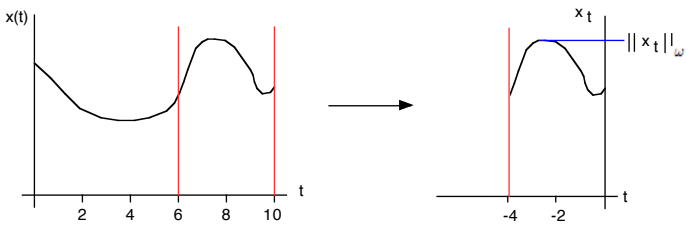

Fig. 3.1: x_t as a translation of a segment of the trajectory $x(t)$.

3.2 Delay Differential Equations

In this section we discuss theorems for a delay differential equation

$$x'(t) = f(t, x_t) \tag{3.13}$$

with initial condition

$$x_{t_0} = \phi. \tag{3.14}$$

First we discuss the notation involved in delay differential equations, then we state the existence, uniqueness, stability, and comparison theorems corresponding to those discussed in Section 3.1.

3.2.1 Notation and Definitions

Given a function $x(t) : J \mapsto \mathbb{R}^n$, we define the function $x_t : [-r, 0] \mapsto \mathbb{R}^n$ by

$$x_t(s) := x(t + s), \quad s \in [-r, 0]. \tag{3.15}$$

x_t basically translates the segment of $x(t)$ from the interval of length r to $t = 0$ (see Figure 3.1).

We use the notation $\mathcal{C} := C([-r, 0], \mathbb{R}^n)$ as shorthand for the set of continuous functions from $[-r, 0]$ to $\mathbb{R}^n$. Given a set D we further define $\mathcal{C}_D := C([-r, 0], D)$. For $a, b \in \mathbb{R}$ with $a < b$ and $D \subset \mathbb{R}^n$, following [6] we define the set of piecewise-continuous functions from $[a, b]$ to D by

$$PC([a, b], D) := \{\psi : [a, b] \to D \text{ such that}$$
$$\begin{cases} \psi(t^+) = \psi(t) \ \forall t \in [a, b), \\ \psi(t^-) \in D \ \ \forall t \in (a, b] \text{ and} \\ \psi(t^-) = \psi(t) \text{ for all but at most a finite number of points } t \in (a, b] \ \}. \end{cases}$$

Analogous to $\mathcal{C}$ and $\mathcal{C}_\mathcal{D}$, when $a = -r$ and $b = 0$ we define the shorthand notation

$$\mathcal{PC} := PC([-r, 0], \mathbb{R}^n); \quad \mathcal{PC}_D := PC([-r, 0], D).$$

Definition 9. For a function $\psi \in \mathcal{PC}$, $\|\psi\|_r := \sup_{-r \le s \le 0} \|\psi(s)\|$. (See Figure 3.1 for an illustration.)

$\| \cdot \|_r$ is a norm on $\mathcal{PC}$ but may not be on the restricted set $\mathcal{PC}_D$ if $\mathcal{PC}_D$ is not a linear space; however, we can think of $\mathcal{PC}_D$ as a subset of $\mathcal{PC}$, so $\|\cdot\|_r$ on $\mathcal{PC}_D$ is just a norm on $\mathcal{PC}$, restricted to $\mathcal{PC}_D$ [18].

3.2.2 Existence and Uniqueness

In this section we discuss existence, continuation and uniqueness theorems for delay DEs, following the explanation by Driver [18].

For an ordinary differential equation $x' = f(t, x)$ we saw that continuity of f was enough for the existence of a local solution; boundedness of f gave a continuation of the solution; and a Lipschitz condition guaranteed uniqueness. Here we extend those definitions and results.

Definition 10. [18] **Continuity Condition:** We define the *continuity condition* to be that $f(t, x_t)$, considered as a composite function of t, is continuous with respect to t in $[t_0, \alpha_1)$ for each given continuous function $x : [t_0 - r, \alpha_1) \to D$.

Claim 2. *If $f(t, x_t) \in C([-r, 0] \times \mathcal{C}_D, \mathbb{R}^n)$ then f satisfies the continuity condition.*

Proof. $f(t, x_t)$ is continuous so for any $\epsilon < 0$, there exists $\delta > 0$ such that $|t - \tilde{t}| < \delta$ and $\|\psi - \tilde{\psi}\|_r < \delta \Rightarrow \|f(t, \psi) - f(\tilde{t}, \tilde{\psi})\| < \epsilon$.

In particular, for a continuous function $x : [t_0 - r, \alpha_1) \mapsto D$ we have for $t \in [t_0 - r, \alpha_1)$ that for any $\delta > 0$, there exists $\delta_1 > 0$ such that $|t - \tilde{t}| < \delta_1 \Rightarrow \|x(t) - x(\tilde{t})\| < \delta$. Then we have for any $t \in [t_0, \alpha_1)$ and $\tilde{t} \in [t - \delta_1, t + \delta_1] \cap [t_0, \alpha_1)$:

$$\begin{aligned} \|x_t - x_{\tilde{t}}\|_r &= \max_{s \in [-r, 0]} \|x_t(s) - x_{\tilde{t}}(s)\| \\ &= \max_{s \in [-r, 0]} \|x(t + s) - x(\tilde{t} + s)\| \\ &< \max_{s \in [-r, 0]} \delta = \delta \end{aligned}$$

That is, for $t \in [t_0, \alpha_1)$, if $\delta_1 < \delta$ then if $|t - \tilde{t}| < \delta_1$ we have $|t - \tilde{t}| < \delta$ and $\|x_t - x_{\tilde{t}}\| < \delta$ and so $\|f(t, x_t) - f(\tilde{t}, x_{\tilde{t}})\| < \epsilon$. If $\delta_1 \ge \delta$ then we simply restrict $|t - \tilde{t}| < \delta$. Then we have $|t - \tilde{t}| < \delta \le \delta_1$, so $\|x_t - x_{\tilde{t}}\| < \delta$ and so $\|f(t, x_t) - f(\tilde{t}, x_{\tilde{t}})\| < \epsilon$. So $\exists\ \delta_1 > 0$ such that $|t - \tilde{t}| < \delta_1 \Rightarrow \|f(t, x_t) - f(\tilde{t}, x_{\tilde{t}})\| < \epsilon$; therefore $f(t, x_t)$ is a continuous function of t for any $t \in [t_0, \alpha_1)$.

□

Definition 11. [18] **Lipschitzian:** Given $f : J \times \mathcal{C}_D \mapsto \mathbb{R}^n$, and a subset $\mathcal{U} \subset J \times \mathcal{C}_D$, if there exists $L \geq 0$ such that

$$\|f(t,\psi) - f(t,\tilde{\psi})\| \leq L\|\psi - \tilde{\psi}\|_r$$

for any (t,ψ) and $(t,\tilde{\psi}) \in \mathcal{U}$, then we say f satisfies a Lipschitz condition on $\mathcal{U}$ with Lipschitz constant L. f is *locally Lipschitzian* in $\mathcal{U}$ if, given any $(t,\psi) \in J \times \mathcal{C}_D$, there exists a neighbourhood of (t,ψ) in which f is Lipschitzian.

We work through the theorems in a slightly different order than in Section 3.1. For ODEs, we first stated that continuity of f gave the existence of a solution on a small interval; boundedness of f or x gave continuation of that solution; and then adding a Lipschitz condition gave uniqueness. For DDEs, we follow the order given in [18]: continuity condition together with a Lipschitzian condition gives at most one solution on the time interval of definition of f, and in particular gives exactly one solution on some small interval. Then quasi-boundedness (to be defined) gives continuation of this unique solution. (The proofs in [18] are easier to follow in this sequence.)

Theorem 9. *[18]* ***Uniqueness:*** *Let $f : [t_0, \alpha_1) \times \mathcal{C}_D \mapsto \mathbb{R}^n$ satisfy the continuity condition and let it be locally Lipschitzian. Then, given any $\phi \in \mathcal{C}_D$, the system (3.13-3.14) has a most one solution on $[t_0 - r, \alpha)$ for any $\alpha \in (t_0, \alpha_1]$.*

Theorem 10. *[18]* ***Local Existence:*** *Let $f : [t_0, \alpha_1) \times \mathcal{C}_D \mapsto \mathbb{R}^n$ satisfy the continuity condition and be locally Lipschitzian. Then, for each $\phi \in \mathcal{C}_D$, the system (3.13-3.14) has a unique solution on $[t_0 - r, t_0 + \Delta)$ for some $\Delta > 0$.*

Definition 12. [18] **Quasi-bounded:** $f : [t_0, \alpha_1) \times \mathcal{C}_D \mapsto \mathbb{R}^n$ is said to be *quasi-bounded* if f is bounded on every set of the form $[t_0, \alpha_0] \times \mathcal{C}_F$ where $t_0 < \alpha_0 < \alpha_1$ and F is a closed and bounded subset of D.

That is, quasi-bounded means f is bounded on every compact subset of $[t_0, \alpha_1) \times \mathcal{C}_D$.

Theorem 11. *[18]* ***Continuation:*** *Let $f : [t_0, \alpha_1) \times \mathcal{C}_D \mapsto \mathbb{R}^n$ satisfy the continuity condition and let it be locally Lipschitzian and quasi-bounded. Then for each $\phi \in \mathcal{C}_D$, the system (3.13-3.14) has a unique noncontinuable solution on $[t_0 - r, \alpha)$; and if $\alpha < \alpha_1$ then for every closed bounded set $F \subset D$ we must have $x(t) \notin F$ for some t in (t_0, α).*

The last condition is the same as for Theorem 2 in that (t, x) must approach the boundary of $[t_0, \alpha_1) \times D$; if t does not approach α_1 then x must be approaching the boundary of the open set D, that is, leaving any closed and bounded set F.

Now that we have listed the relevant theorems, we show that they apply to the delay epidemic models. In particular we consider the model (3.2). Similarly to Section 3.1 we let $x = [x_1, x_2, x_3, x_4]^T := [S, E, I, R]^T$, then $f(t, x_t)$ is equal to the right-hand side of (3.2).

1. Continuity condition: we in fact have $f(t, x_t) = F(t, x(t), x(t-r)$, and F (looking at (3.2) is continuous in t, $x(t)$, and $x(t-r)$. So for any continuous $x : [t_0 - r, \alpha_1) \mapsto D$, f is a composition of functions which are continuous with respect to t, and therefore f itself satisfies the continuity condition. (This result is trivial in the case of a finite number of constant bounded delays.)

2. As in Section 3.1 the partial derivatives of $f(t, x_t) = F(t, x(t), x(t-r))$ with respect to $x(t)$ and $x(t-r)$ are continuous, so long as we are not in the trivial case $N = \sum_{i=1}^{n} |x_i| = 0$. So F is Lipschitzian in $x(t)$ and $x(t-r)$ by Claim 1. From Claim 3 in Section 3.3 we obtain that f is Lipschitzian in its second variable.

3. Quasi-bounded: On any closed bounded subset of $[t_0, \alpha_1) \times \mathcal{C}_D$, f is clearly bounded. That is, for any $(t, y_t) \in [t_0, \alpha_0] \times \mathcal{C}_F$ (where $F \subset D \subset \mathbb{R}^4$ is closed and bounded) we have $\|y_t\|_r \leq M$ for some $M > 0$, then if $x_t \in \mathcal{C}_F$, noticing $I/N \leq 1$ we have

$$\begin{aligned}\|f\| &\leq |x_1'| + |x_2'| + |x_3'| + |x_4'| \\ &\leq (\mu(x_2 + x_3 + x_4) + \beta x_1) + (\beta x_1 + \beta x_1(t-r) + \mu x_2) + (\beta x_1(t-r) + (\mu + \gamma)x_3) + (\gamma x_3 + \mu x_4) \\ &\leq (6\mu + 4\beta + 2\gamma)\, M,\end{aligned}$$

   and so $\|f\|$ is bounded.

The continuity condition applies for any model with a finite number of bounded delays. The quasi-boundedness of f can be generalized to different models simply by following the process above; even in a model with different incidence we will not have $\|f\| \to \infty$ in finite time or for finite x. The local Lipschitzian condition is likewise satisfied for all of the models discussed so far this chapter. Therefore we get that there exists a unique continuable solution to (3.2) (with a physically valid initial function). For any model in which f is defined for $t \in [t_0, \infty)$ and satisfies the appropriate conditions, since $\|f\|$ does not go to infinity in finite time then $\|x(t)\|$ does not and we must have that this solution is continuable for all future time.

3.2.3 Stability Theorems

The definitions of stability of the trivial solution in Section 3.1 apply for delay differential equations, with the generalization that we consider the initial condition $x_{t_0} = \phi$ instead of simply $x(t_0)$ $(= x_{t_0}(0)) = x_0$. We require that the initial conditions are "small enough" under the $\|\cdot\|_r$-norm.

For example, the trivial solution is stable if for every $\epsilon > 0$, there exists $\delta > 0$ such that $\|x(t; t_0, \phi)\| < \epsilon$ for all $t \geq t_0 - r$ so long as $\|\phi\|_r < \delta$ [18].

The next theorem comes from Driver's book and extends Theorem 4 to delay systems.

Theorem 12. *(Driver [18] 31-A) Let w and W be continuous nondecreasing functions on $[0, H)$ which are zero at 0 and positive on $(0, H)$. If there exists a nonnegative functional V on $(\alpha, \infty) \times \mathcal{C}_D$ such that*

(i) $V(t, \psi) \geq w(\|\psi(0)\|)$ (V is positive definite);

(ii) $V(t, \psi) \leq W(\|\psi\|_r)$ (V is decrescent); and

(iii) Whenever $x = x(t, t_0, \phi)$ on $[t_0 - r, \alpha_1)$ is the noncontinuable solution of equation (3.13) through some $(t_0, \phi) \in (\alpha, \infty) \times \mathcal{C}_D$, $V(t, x_t)$ defines a nonincreasing function of t on $[t_0, \alpha_1)$;

then the trivial solution of (3.13) is uniformly stable [18] .

Remark. In Theorem 4, V is continuously differentiable and in particular continuous; hence since $V' \leq 0$ we must (by Mean Value Theorem) have that V is nonincreasing. In this sense we note that condition (iii) of Theorem 4 is equivalent to condition (iii) of Theorem 12.

Remark. Note w and W could be defined as class-$\mathcal{K}$ functions on $[0, H)$, but the nondecreasing condition is slightly relaxed from the class-$\mathcal{K}$ condition of strict increase.

In [18] the proof of Theorem 12 does not use contradiction to prove the impossibility of $\|x(t)\|$ growing greater than a given ϵ. Here we prove it more rigorously, using the method from AMATH 851.

Proof. Choose any $\epsilon > 0$ small enough that $\|x(t)\| \leq \epsilon \Rightarrow x(t) \in D$ (we note that ϵ could in fact be very large if D is). Choose $\delta = \delta(\epsilon) > 0$ such that $W(\delta) < w(\epsilon)$; this choice is possible since $w(0) = 0 = W(0)$ and w and W are continuous. Then for any $\phi \in \mathcal{C}_D$ with $\|\phi\|_r < \delta$,

$$\begin{aligned} w(\|x(t_0)\|) &\leq V(t_0, x_{t_0}) = V(t_0, \phi) \text{ by } (i) \\ &\leq W(\|\phi\|_r) \text{ by } (ii) \\ &< W(\delta) \\ &< w(\epsilon), \\ \Rightarrow &\|x(t_0)\| < \epsilon. \end{aligned}$$

We claim that $\|x(t)\| < \epsilon$ for all $t \in [t_0, \alpha_1)$ (where recall α_1 is as far as $x(t)$ is continuable).

If not, then there exists some $t_1 > t_0$ such that $\|x(t_1)\| = \epsilon$ and $\|x(t)\| < \epsilon$ for $t \in [t_0, t_1)$. Since $\|x(t)\| \leq \epsilon$ then $x(t) \in D$ for $t \in [t_0, t_1]$ and by *(iii)* V is nonincreasing on $[t_0, t_1]$. Hence

$$V(t_1, x_{t_1}) \leq V(t_0, x_{t_0}) = V(t_0, \phi) < w(\epsilon), \tag{3.16}$$

but by condition *(i)*,

$$V(t_1, x_{t_1}) \geq w(\|x(t_1)\|) = w(\epsilon). \tag{3.17}$$

Combining (3.16) and (3.17) we get that

$$w(\epsilon) \leq V(t_1, x_{t_1}) < w(\epsilon)$$

which is a contradiction. Hence no such t_1 exists and the trivial solution of 3.13 is stable on $[t_0, \alpha_1)$. Since δ was independent of t_0 the stability is uniform.

Finally since $x(t)$ remains small it does not approach the boundary of D as $t \to \alpha_1$; hence we must have $\alpha_1 = \infty$, that is, the solution $x(t)$ is continuable for all future time. Therefore, the trivial solution of (3.13) is uniformly stable for all $t \geq t_0$.

□

Theorem 13. *(Driver [18] 32-C) If in Theorem 12 we strengthen condition (iii) to*

(iii') Whenever $(t_0, \phi) \in (\alpha, \infty) \times \mathcal{C}_D$ *and* $x = x(t, t_0, \phi)$ *on* $[t_0 - r, \alpha_1)$ *one has*

$$\frac{d}{dt} V(t, x_t) \leq -w_1(\|x(t)\|) \text{ for } t \in [t_0, \alpha_1)$$

and if we additionally require $\|f(t, \psi)\| \leq M$ *for some constant* $M > 0$ *for all* $(t, \psi) \in (\alpha, \infty) \times \mathcal{C}_D$*, then we get uniform asymptotic stability.*

Proof. See Driver [18], theorem 32-C.

Effects of Small Delay

We consider the linear DDE

$$x'(t) = \sum_{j=1}^{m} A_j(t) x(t - r_j) \tag{3.18}$$

with initial condition (3.14). The system for $x(t)$ is a linear system, where each of the $A_j(t)$ are continuous. Many of the results and supporting theorems in [18] hold only for a system like (3.18) with a finite number m of bounded constant delays $0 \leq r_j \leq r, j = 1, \ldots, m$. For our epidemic models to be discussed here this condition is easily met, as we have $m = 2$ with $r_1 = 0$ and $r_2 = r$.

If we define $h(t,\psi) = f(t,\psi) - \sum_{j=1}^{m} A_j(t)\psi(-r_j)$ then we can rewrite (3.13) as

$$x'(t) = \sum_{j=1}^{m} A_j(t)x(t-r_j) + h(t,x_t). \tag{3.19}$$

We are thus rewriting our general nonlinear equation as a combination of a linear part and a nonlinear perturbation [18]. If the perturbation $h(t,x_t)$ is "small enough" (a concept we will quantify in the following) then we would expect it will not affect stability of the System (3.18). First we state a theorem on uniform asymptotic stability:

Theorem 14. *(Driver [18] 34-B) The trivial solution of equation (3.18) is uniformly asymptotically stable if and only if there exist constants $M \geq 1$ and $\eta > 0$ such that for every $(t_0,\phi) \in (\alpha,\infty)\times\mathcal{C}$,*

$$\|x(t;t_0,\phi)\| \leq M\|\phi\|_r e^{-\eta(t-t_0)} \text{ for all } t \geq t_0 \tag{3.20}$$

We now state the theorem that allows us to use the smallness of r:

Theorem 15. *(Driver [18] 34-G) Let the trivial solution of (3.18) be uniformly asymptotically stable and let M and η be as in (3.20). Let constants $K > 0$ and $N \in (0,\eta/M)$ exist such that*

(i) $\|f(t,\psi) - f(t,\tilde{\psi})\| \leq K\|\psi - \tilde{\psi}\|_r$ when $(t,\psi),(t,\tilde{\psi}) \in (\alpha,\infty)\times\mathcal{C}_D$ (a global Lipschitz condition)

(ii) $\|h(t,\psi)\| \leq N\max\{\|\psi\|_r, \frac{\|\psi'\|_r}{K}\}$ just for $(t,\psi) \in (\alpha,\infty)\times\mathcal{C}_D$ with ψ continuously differentiable.

Then the trivial solution of (3.13) is uniformly asymptotically stable.

Following [18], as a simple example, suppose we consider a scalar system of the form

$$x'(t) = f(t,x_t)$$

where

$$f(t,\psi) = a\cdot\psi(0) + b\cdot\psi(-r).$$

We can rewrite f as

$$f(t,\psi) = (a+b)\cdot\psi(0) + b\cdot(\psi(-r) - \psi(0)).$$

$(a+b)\psi(0)$ is the linear part while we set $h(t,\psi) = b(\psi(-r) - \psi(0))$. Then $h(t,\psi) \leq b\cdot r\|\psi'\|_r$ and so we have $N = b\cdot r$. For small enough r we will have $N \in (0,\eta/M)$ regardless of the values of η and M, satisfying the conditions of the theorem.

3.2.4 Comparison Theorems

There is a delay analogue to the ODE comparison theorem, Theorem 7, used by Smith [69]. We use Smith's notation: for $\phi, \psi \in \mathcal{C}$, $\phi \leq \psi \iff \phi(s) \leq \psi(s)$ for all $s \in [-r, 0]$.

Definition 13. Given $\phi, \psi \in \mathcal{C} := C([-r, 0], \mathbb{R}^n)$, a function f is said to satisfy the *quasimonotone condition* if whenever $\phi \leq \psi$ and $\phi_i(0) = \psi_i(0)$ for some $i \in \{1, 2, \ldots, n\}$, we have that $f_i(\phi) \leq f_i(\psi)$.

In particular we look at the equation (3.13), that is, $x'(t) = f(t, x_t)$. Following [69] we denote by $x(t; t_0, \phi, f)$ the solution to the equations (3.13)-(3.14).

From the quasimonotone condition we get a comparison theorem for delay differential equations, proved in [69]:

Theorem 16. *[69] Let $J \in \mathbb{R}$ be open. Let $f, g : J \times \mathcal{C} \mapsto \mathbb{R}^n$ be continuous, Lipschitz on each compact subset of $J \times \mathcal{C}$, and assume either f or g satisfies the quasimonotone condition. Assume also that $f(t, \phi) \leq g(t, \phi)$ for all $(t, \phi) \in J \times \mathcal{C}$.*

If $(t, \phi), (t, \psi) \in J \times \mathcal{C}$ satisfy $\phi \leq \psi$, then

$$x(t; t_0, \phi, f) \leq x(t; t_0, \psi, g)$$

holds for all $t \geq t_0$ for which both are defined.

3.3 Impulsive Differential Equations

Delay differential equations have similar conditions to ODEs for existence and uniqueness, just slightly more complicated. The same is true for impulsive delay differential equations (IDDEs). We follow the work by Ballinger and Liu [6] in order to find more general existence and uniqueness results for IDDEs, then apply them to the delayed epidemic model (3.2) with pulse vaccination added. We deal with delay IDEs in this section but impulsive ODEs are the special case when $r = 0$.

3.3.1 Restrictions on Impulsive Behaviour

We look at the model (where $x'(t)$ is the right-hand derivative)

$$\begin{array}{rll} x'(t) & = f(t, x_t), & t \neq \tau_k, \quad t \geq t_0 \\ \Delta x(t) & = \mathcal{I}(t, x_{t^-}), & t = \tau_k, \quad t > t_0 \end{array} \tag{3.21}$$

with initial condition (3.14), where $f, \mathcal{I} : J \times \mathcal{PC}_D \to \mathbb{R}^n$, the initial time is $t_0 \in J$, and $\Delta x(t) = x(t^+) - x(t^-)$. Assumptions on impulses:

- pulse times τ_k are fixed and head off to ∞,
- impulses do not send solutions outside of the domain of f.

Otherwise, we are fortunate that $\mathcal{I}(t, x_{t^-})$ does not affect the existence and uniqueness proofs [6].

Ultimately epidemic models are meant to be used to make predictions about the course of an outbreak, or to inform better choices for control measures such as vaccination campaigns. Pulse vaccination leads to the following impulsive model, building on (3.2):

$$\begin{cases} S' &= bN - \mu S - \beta \frac{I}{N} S \\ E' &= \beta \frac{I}{N} S - \beta e^{-\mu r} \frac{I(t-r)}{N(t-r)} S(t-r) - \mu E \\ I' &= \beta e^{-\mu r} \frac{I(t-r)}{N(t-r)} S(t-r) - (\mu + \gamma) I \\ R' &= \gamma I - \mu R \end{cases} \quad t \neq k\tau$$
$$\begin{cases} S(t) &= (1-p) S(t^-) \\ E(t) &= E(t^-) \\ I(t) &= I(t^-) \\ R(t) &= R(t^-) + pS(t^-) \end{cases} \quad t = k\tau \tag{3.22}$$

We want to know, does the impulsive behaviour affect the existence and uniqueness of a solution to the system? In such a model,

- τ_k are fixed and $\lim_{k\to\infty} \tau_k = \infty$.
- The impulses do not affect the population size: at a pulse $t\tau_k = k\tau$,

$$\begin{aligned} N(t) &= S(t) + E(t) + I(t) + R(t) \\ &= [(1-\theta)S(t^-)] + [E(t^-)] + [I(t^-)] + [R(t^-) + \theta S(t^-)] \\ &= S(t^-) + E(t^-) + I(t^-) + R(t^-) \\ &= N(t^-) \end{aligned}$$

  $E(t)$ and $I(t)$ are unchanged by the pulses, $S(t)$ decreases (but not below zero), and $R(t)$ grows by an amount less than or equal to $\theta(N - R)$. Thus we find that the pulses do not drive the solution out of the range of interest, namely Ω_1 or Ω_N.

Thus the pulse vaccination meets the requirements on $\mathcal{I}(t, x_{t^-})$ needed in order to apply the existence and uniqueness theorems of Ballinger and Liu in [6]. We now discuss these theorems; the main difference between DDE existence theory and IDDE existence theory is the presence of discontinuities in the second argument of f.

3.3.2 Discontinuities in x_t

Although the total population is unchanged, pulse vaccination necessarily introduces some discontinuity into the compartment populations. Even if there is no discontinuity in the initial condition function ϕ, after the first pulse time $t = 1 \cdot \tau$ there will be discontinuity introduced that propagates through the derivatives (if, say, $S(\tau) = (1-p)S(\tau^-)$ then $I'(t)$ has a jump discontinuity at $t = \tau + r$). $\|\cdot\|_r$ is infinite-dimensional and so we find problems with drawing analogies to non-delay systems: in particular just because $x(t)$ is piecewise continuous, it does not immediately follow that $x_t : [-r, 0] \to \mathbb{R}^n$ defined by $x_t(s) = x(t+s)$ is piecewise continuous under the norm $\|\cdot\|_r$, as shown in the following example.

Example 1. Let

$$x(t) = \begin{cases} 0, & t \in [-r, 0) \\ 1, & t \in [0, r]. \end{cases}$$

$x(t)$ is clearly piecewise continuous. We wish to show continuity of x_t with respect to $\|.\|_r$ with an $\epsilon-\delta$ proof: that is, to see if for any $\epsilon > 0$, we can find $\delta > 0$ such that $t_1 - t_2 < \delta \Rightarrow \|x_{t_1} - x_{t_2}\|_r < \epsilon$. However, for any δ suppose we choose $t_1, t_2 \in [0, r]$ such that $0 < t_1 - t_2 < \delta$. Then take $s = -t_1 \in [-r, 0]$:

$$\begin{aligned} x_{t_1}(s) - x_{t_2}(s) &= x(t_1 + s) - x(t_2 + s) \\ &= x(t_1 - t_1) - x(t_2 - t_1) \\ &= x(0) - x(-(t_1 - t_2)), \text{ where } t_1 - t_2 > 0 \\ &= 1 - 0 \\ \Rightarrow \|x_{t_1} - x_{t_2}\|_r \ &\geq \ \|x_{t_1}(s) - x_{t_2}(s)\| = 1. \end{aligned}$$

Thus x_t is discontinuous with respect to $\|.\|_r$ for *any* $t \in [0, r]$.

So we find that even with a piecewise continuous initial condition for $x(t)$, x_t may not be piecewise continuous and so theorems about existence and uniqueness must use a different definition of continuity. In Section 3.2 we defined the "continuity condition," requiring f to be continuous in t for a continuous x; here we look to generalize to piecewise continuous functions.

Definition 14. [6] **Composite-PC:** A functional $f : J \times PC([-r, 0], D) \to \mathbb{R}^n$ is said to be *composite-PC* if for each $t_0 \in J$ and $\alpha_1 > t_0$ with $[t_0, \alpha_1] \subset J$, if $x \in PC([t_0 - r, \alpha_1], D)$ and x is continuous at each $t \neq \tau_k$ in $(t_0, \alpha_1]$ then the composite function g defined by $g(t) = f(t, x_t)$ is piecewise continuous ($g \in PC([t_0, \alpha_1], \mathbb{R}^n)$).

With many functionals it will easily be the case that f is composite-PC; for example, if $f(t, \psi) = \psi(e^{at})$ then $f(t, x_t) = x(t + e^{at})$ which is piecewise continuous for piecewise continuous x. Difficulties may arise if, for example, f involves an infinite series, or any other form that causes an infinite number of discontinuities.

Remark. We note that we could technically redefine the continuity condition from Section 3.2 as "composite-C:" that is, f considered as a composite function of t is continuous in t if x_t is. We chose at the time to use notation consistent with [18].

There is a need for the composite-PC definition for impulsive DEs because, as explained in Example 1 above, we may have x_t is not piecewise continuous although $x(t)$ is. Ballinger and Liu [6] say "the discontinuities inherent in solutions of impulsive delay differential equations cause sufficient complications to prevent the application of already existing theorems [such as in Driver's book [18]] for continuous delay differential equations."

In order to present a theorem from Ballinger and Liu [6] on local existence, we define another property:

Definition 15. [6] A functional $f : J \times \mathcal{PC}_D \mapsto \mathbb{R}^n$ is said to be *continuous in its second variable* if for each fixed $t \in J$, $f(t, \psi)$ is a continuous function of ψ on $\mathcal{PC}_D$.

Remark. Notice that in order for $f(t, \psi)$ to satisfy the "composite-C" continuity condition from Section 3.2, we would need f to be continuous explicitly in its first variable t. We assume this condition is true, otherwise at a point $t = t_1$ at which $f(t_1, \psi)$ is discontinuous we would have impulsive behaviour regardless of the system state, and so the time t_1 should be governed by $\mathcal{I}(t, \psi)$.

The condition of continuity in the second variable, then, is sufficient but not necessary to satisfy the composite-C continuity condition from the previous section; for composite-C we only need the composition to be continuous in t, so continuity in the second variable is a different condition than composite-C.

Theorem 17. *[6]* ***Local Existence:*** *Assume f is composite-PC, quasi-bounded, and continuous in its second variable. Then for each $(t_0, \phi) \in J \times \mathcal{PC}_D$ there exists a solution $x(t) = x(t; t_0, \phi)$ of (3.21)-(3.14) on $[t_0 - r, t_0 + \beta_1]$ for some $\beta_1 > 0$.*

In Section 3.2 the existence theorem also included the Lipschitz condition and therefore uniqueness; this current existence theorem allows for multiple solutions, but we will see later that adding the Lipschitz condition still confers uniqueness.

Based on System 3.22, we define $x = [x_1, x_2, x_3, x_4]^T = [S, E, I, R]^T$ and $g(t, x(t), x(t-r))$ by

$$g(t, x(t), x(t-r)) = \begin{bmatrix} b(x_1 + x_2 + x_3 + x_4) - \beta \frac{x_1 x_3}{x_1 + x_2 + x_3 + x_4} - \mu x_1 \\ \beta \frac{x_1 x_3}{x_1 + x_2 + x_3 + x_4} - \beta e^{-\mu r} \frac{x_1(t-r) x_3(t-r)}{(x_1 + x_2 + x_3 + x_4)|_{t-r}} - \mu x_2 \\ \beta e^{-\mu r} \frac{x_1(t-r) x_3(t-r)}{(x_1 + x_2 + x_3 + x_4)|_{t-r}} - (\mu + \gamma) x_3 \\ \gamma x_3 - \mu x_4 \end{bmatrix} \tag{3.23}$$

Since $x_1 + x_2 + x_3 + x_4 = N > 0 \ \forall t$, g is continuous in $x(t)$ and in $x(t-r)$. We will now show that System 3.22, that is, $x' = f(t, x_t) = g(t, x(t), x(t-r))$ with g as defined in (3.23), satisfies the three conditions of the theorem:

- Composite-PC: Suppose $x \in PC([t_0 - r, t_0 + \alpha], \mathbb{R}^4_+)$ is continuous at each $t \neq \tau_k$ in $(t_0, t_0 + \alpha]$. Then $x(t-r) \in PC([t_0, t_0 + \alpha], \mathbb{R}^4_+)$, and so the composite function $g(t, x(t), x(t-r)) \in PC([t_0, t_0 + \alpha], \mathbb{R}^4_+)$ (where g is a composition of piecewise-continuous functions of t, and is thus considered as a function only of t).

- Quasi-boundedness: If $t_0 \in \mathbb{R}_+, \alpha > 0$, and $F \subset \mathbb{R}^4_+$ is compact, then $[t_0, t_0 + \alpha] \times F^2$ is compact. Then g continuous in each $x_i \Rightarrow$ there exists $M \geq 0$ such that $\|g(t, y, \tilde{y})\| \leq M \ \forall t \in [t_0, t_0 + \alpha]$ and $y, \tilde{y} \in F$.

  For any $\psi \in \mathcal{PC}_F$, $\psi(0) \in F$ and $\psi(-r) \in F$ so in the above we can choose $y = \psi(0)$ and $\tilde{y} = \psi(-r)$. Hence $\|f(t, \psi)\| = \|g(t, \psi(0), \psi(-r))\| \leq M$, therefore f is quasi-bounded.

- f continuous in its 2nd variable (x_t): Let $t \in \mathbb{R}_+$ be fixed. Let $\psi \in PC([-r, 0], \mathbb{R}^4_+)$ and choose $\epsilon > 0$. $g(t, y, \tilde{y})$ as defined in (3.23) is continuous in y and $\tilde{y} \Rightarrow$ there exists $\delta_0 > 0$ such that $\|g(t, y, \tilde{y}) - g(t, \psi(0), \tilde{y})\| < \epsilon/2$ if $\|y - \psi(0)\| < \delta_0$ and there exists $\delta_1 > 0$ such that $\|g(t, y, \tilde{y}) - g(t, y, \psi(-r))\| < \epsilon/2$ if $\|\tilde{y} - \psi(-r)\| < \delta_1$. (We can use $\psi(0)$ and $\psi(-r)$ since they are both in F as stated above.) Take $\delta = \min(\delta_0, \delta_1)$ and we have that

  $$\begin{aligned} \|g(t, y, \tilde{y}) - g(t, \psi(0), \psi(-r))\| &= \|g(t, y, \tilde{y}) - g(t, \psi(0), \tilde{y}) + g(t, \psi(0), \tilde{y}) - g(t, \psi(0), \psi(-r))\| \\ &\leq \|g(t, y, \tilde{y}) - g(t, \psi(0), \tilde{y})\| + \|g(t, \psi(0), \tilde{y}) - g(t, \psi(0), \psi(-r))\| \\ &< \epsilon/2 + \epsilon/2 = \epsilon \end{aligned}$$

  So we find for our arbitrary $\epsilon > 0$ that if we choose δ as above, then

  $$\begin{aligned} \|\psi - \tilde{\psi}\|_r < \delta &\Rightarrow \|\psi(0) - \tilde{\psi}(0)\|, \quad \|\psi(-r) - \tilde{\psi}(-r)\| < \delta \\ &\Rightarrow \|f(t, \psi) - f(t, \tilde{\psi})\| = \|g(t, \psi(0), \psi(-r)) - g(t, \tilde{\psi}(0), \tilde{\psi}(-r))\| < \epsilon. \end{aligned}$$

  Hence f is continuous in its second variable.

So for the delay epidemic model with pulse vaccination, there is at least a local solution. In order to look for global existence, we use the following theorem from [Ballinger and Liu]:

Theorem 18. ***Continuation:*** *Assume f is composite-PC, quasi-bounded, and continuous in its second variable. Let $(t_0, \phi) \in J \times \mathcal{PC}_D$ and let $x = x(t_0, \phi)$ be any solution of (3.22)-(3.14).*

- *If x is defined on a closed interval of the form $[t_0 - r, t_0 + \beta_1]$, where $\beta_1 > 0$ and $[t_0, t_0 + \beta_1] \subset J$, then x is continuable.*

- *If x is defined on an interval of the form $[t_0-r, t_0+\beta_1)$ where $0 < \beta_1 < \infty$ and $[t_0, t_0+\beta_1] \subset J$, then either x is continuable or else for every compact set $F \subset D$ there exists a sequence of numbers $\{t_k\}$ with $t_0 < t_k < t_{k+1} < t_0 + \beta_1$ for $k = 1, 2, ...$ and $\lim_{k\to\infty} t_k = t_0 + \beta_1$ such that $x(t_k) \notin F$.*

We apply this theorem to our impulsive delay epidemic model by noting that, as shown earlier, $\frac{dN}{dt} = (b-\mu)N$ so $N(t)$ is bounded on any compact set, and since all of the compartment populations are non-negative and bounded above by N we have that $x(t)$ is bounded.

In particular for t on $[t_0, t_0+\beta_1)$ where $\beta_1 < \infty$, $N(t) \leq N(t_0)e^{|b-\mu|\beta_1} < \infty$. If we define F as the closure of the range of $x(t)$ over $[t_0, t_0+\beta_1]$ then $F \subset D$ $(= \mathbb{R}^4_+ \setminus \{0\})$ is closed and bounded, and therefore any sequence $x(t_k)$ must have its limit points in F, so $x(t_k) \in F$ $\forall k$. Hence we may continue our solution to the end of the interval J (where $f(t, x_t)$ is defined for $t \in J$). Since the continuous part, System (3.2), of our pulse vaccination epidemic model is defined for all t we have that solutions to (3.22)-(3.14) are defined for $t \in \mathbb{R}_+$; that is, we have global existence of solutions.

The preceding theorems merely guarantee the existence of a solution to our system, but to determine if there is a unique solution we turn to one more definition and theorem from [Ballinger and Liu]. The theorem is analogous to the ODE and non-impulsive delay case in which Lipschitz-continuity of f in its second variable guarantees uniqueness.

Definition 16. A functional $f : J \times \mathcal{PC}_D \to \mathbb{R}^n$ is said to be *locally Lipschitz in its second variable* if for each $t_0 \in J$ and $\beta_1 > 0$ with $[t_0, t_0+\beta_1] \subset J$, and for each compact set $F \subset D$ there exists some $L > 0$ such that $\|f(t,\psi) - f(t,\tilde{\psi})\| \leq L\|\psi_1 - \tilde{\psi}\|_r$ for all $t \in [t_0, t_0+\beta_1]$ and $\psi, \tilde{\psi} \in \mathcal{PC}_F$.

Theorem 19. ***Uniqueness:*** *Assume that $f : J \times \mathcal{PC}_D \to \mathbb{R}^n$ is composite-PC and locally Lipschitz in its second variable. Then there exists at most one solution of (3.22)-(3.14) on $[t_0 - r, t_0+\beta_2)$ where $0 < \beta_2 \leq \infty$ and $[t_0, t_0+\beta_2) \subset J$.*

Claim 3. *In particular, with a functional of the form $f(t, x_t) = g(t, x(t), x(t-r))$ we have that f is locally Lipschitz in its second variable as long as $g(t, y, \tilde{y})$ is locally Lipschitz in y and $\tilde{y}$.*

Proof. We want to show $f(t,\psi)$ is Lipschitzian in ψ on a compact set $F \subset D$ where $\psi \in \mathcal{PC}_F$. Suppose $g(t, y, \tilde{y})$ is locally Lipschitzian in y on F and in $\tilde{y}$ on F; this implies

$$\|g(t, y, \tilde{y}) - g(t, y', \tilde{y})\| \leq L_0\|y - y'\|$$
$$\|g(t, y, \tilde{y}) - g(t, y, \tilde{y}')\| \leq L_1\|\tilde{y} - \tilde{y}'\|$$

where $y, y', \tilde{y}, \tilde{y}' \in F$. Take $L = 2\max(L_0, L_1)$. Since $\psi(0)$, $\psi(-r) \in F$ for $\psi \in \mathcal{PC}_F$ we can replace y with $\psi(0)$ and $\tilde{y}$ with $\psi(-r)$. Then

$$\begin{aligned}
\|f(t,\psi) - f(t,\tilde{\psi}\| &= \|g(t,\psi(0),\psi(-r)) - g(t,\tilde{\psi}(0),\tilde{\psi}(-r))\| \\
&= \|g(t,\psi(0),\psi(-r)) - g(t,\tilde{\psi}(0),\psi(-r)) + g(t,\tilde{\psi}(0),\psi(-r)) - g(t,\tilde{\psi}(0),\tilde{\psi}(-r))\| \\
&\leq \|g(t,\psi(0),\psi(-r)) - g(t,\tilde{\psi}(0),\psi(-r))\| + \|g(t,\tilde{\psi}(0),\psi(-r)) - g(t,\tilde{\psi}(0),\tilde{\psi}(-r))\| \\
&\leq \frac{1}{2}L\|\psi(0) - \tilde{\psi}(0)\| + \frac{1}{2}L\|\psi(-r) - \tilde{\psi}(-r)\| \\
&\leq L\|\psi - \tilde{\psi}\|_r.
\end{aligned}$$

□

With g as defined in (3.23), the Jacobian with respect to $x(t) = [S(t), E(t), I(t), R(t)]^T$ is

$$\begin{aligned}
Dg(x(t)) &= \begin{bmatrix} \partial g_1/\partial S & \partial g_1/\partial E & \partial g_1/\partial I & \partial g_1/\partial R \\ \partial g_2/\partial S & \partial g_2/\partial E & \partial g_2/\partial I & \partial g_2/\partial R \\ \partial g_3/\partial S & \partial g_3/\partial E & \partial g_3/\partial I & \partial g_3/\partial R \\ \partial g_4/\partial S & \partial g_4/\partial E & \partial g_4/\partial I & \partial g_4/\partial R \end{bmatrix} \\
&= \begin{bmatrix} b - \mu - \beta\left(\frac{E+I+R}{N^2}\right) I & b + \beta\left(\frac{1}{N^2}\right) SI & b - \beta\left(\frac{S+E+R}{N^2}\right) S & b + \beta\left(\frac{1}{N^2}\right) SI \\ \beta\left(\frac{E+I+R}{N^2}\right) I & -\beta\left(\frac{1}{N^2}\right) SI - \mu & \beta\left(\frac{S+E+R}{N^2}\right) S & -\beta\left(\frac{1}{N^2} SI\right) \\ 0 & 0 & -(\mu + r) & 0 \\ 0 & 0 & r & -\mu \end{bmatrix}
\end{aligned}$$

Treating $x(t-r)$ as a separate variable, the Jacobian with respect to $x(t-r) = [S(t-r), E(t-r), I(t-r), R(t-r)]^T$ is

$$\begin{aligned}
Dg(x(t-r)) &= \begin{bmatrix} \frac{\partial g_1(t)}{\partial S(t-r)} & \frac{\partial g_1(t)}{\partial E(t-r)} & \cdots & \frac{\partial g_1(t)}{\partial R(t-r)} \\ \frac{\partial g_2(t)}{\partial S(t-r)} & \ddots & & \vdots \\ \vdots & & \ddots & \vdots \\ \frac{\partial g_4(t)}{\partial S(t-r)} & \cdots & \cdots & \frac{\partial g_4(t)}{\partial R(t-r)} \end{bmatrix} \\
&= \begin{bmatrix} 0 & 0 & 0 & 0 \\ -\beta\frac{N(t-r)-S(t-r)}{N(t-r)^2} I(t-r) & \beta\frac{S(t-r)I(t-r)}{N(t-r)^2} & -\beta\frac{N(t-r)-I(t-r)}{N(t-r)^2} S(t-r) & \beta\frac{S(t-r)I(t-r)}{N(t-r)^2} \\ \beta\frac{N(t-r)-S(t-r)}{N(t-r)^2} I(t-r) & -\beta\frac{S(t-r)I(t-r)}{N(t-r)^2} & \beta\frac{N(t-r)-I(t-r)}{N(t-r)^2} S(t-r) & -\beta\frac{S(t-r)I(t-r)}{N(t-r)^2} \\ 0 & 0 & 0 & 0 \end{bmatrix}
\end{aligned}$$

Since $N > 0$ for all $t \geq t_0 - r$, all partial derivatives of g with respect to $x(t)$ and $x(t-r)$ exist for $(t, x(t), x(t-r)) \in [t_0, \infty) \times \mathbb{R}^4_+ \times \mathbb{R}^4_+$ and are continuous from $[t_0, \infty) \times \mathbb{R}^4_+ \times \mathbb{R}^4_+ \mapsto \mathbb{R}^4_+$, so g is

locally Lipschitzian on F in $x(t)$ and in $x(t-r)$ where $F \subset \mathbb{R}^4_+$ is any compact subset. Therefore we can use the above claim to apply Theorem 19 and the solution to System 3.22 is unique.

Theorem 19 also says that there is at most one solution to System (3.22)-(3.14) on a general interval $[t_0, t_0 + \beta_1)$ where $0 < \beta_1 \leq \infty$ and $[t_0, t_0 + \beta_1) \subset J$, which means in particular we can use $[t_0, \infty)$, the right-maximal interval for our epidemic model system. Therefore there exists a unique solution to the delayed SEIR epidemic model with pulse vaccination, System (3.22), for all $t \in \mathbb{R}_+$, that is, for all future time.

Remark. Suppose $r = 0$ (there is no delay), and we have

$$\begin{array}{rll} x'(t) & = f(t,x), & t \neq \tau_k, \quad t \geq t_0 \\ \Delta x(t) & = \mathcal{I}(t, x(t^-)), & t = \tau_k, \quad t > t_0, \end{array}$$

where f by itself satisfies the existence and uniqueness requirements in Section 3.1. Then the composite-PC property follows because f is continuous; quasi-boundedness follows from the requirement $f(t,x) \leq M$ on F in Peano's existence theorem, Theorem 1; and Lipschitz continuity in the second variable is the same as before. Therefore pulse vaccination in an ODE system still satisfies the existence and uniqueness requirements of the IDDE theory.

3.4 Model Generalization

3.4.1 Changes to DE Form

In the preceding sections we showed existence and uniqueness for two specific epidemic models, (3.1) and (3.2) (including with pulse vaccination, (3.22)), while in reality there are many different ways to set up a compartmental deterministic system. Generally a model may be adapted to a specific disease by changes such as those discussed in Section 2.5. In all cases, however, we follow the same main idea of showing that the total population $N(t)$ is (i) strictly positive, and (ii) bounded over any finite time.

Regardless of the number of transfer terms or compartments, (i) means the right-hand side of

$$x'(t) = f(t,x) \tag{3.24}$$

is continuous wrt x and its partial derivatives in x exist and are continuous. In the delay case, for

$$x'(t) = f(t, x_t) = g(t, x(t), x(t-r_1), \ldots, x(t-r_j)), \tag{3.25}$$

$f(t, x_t)$ is continuous in its second variable and the partial derivatives in $x(t), x(t-r_1), \ldots, x(t-r_j)$ exist and are continuous.

(ii) means that $\|f(t,x)\|$ is also bounded and $f(t,x_t)$ is quasi-bounded. Thus we can keep our existence results. We can continue any solution because (ii) implies $\|x(t)\|$ $(\leq \dim(x)N(t))$ is also bounded on any finite interval. Finally uniqueness follows with or without delay because the continuous partial derivatives cause f to be locally Lipschitz in its second variable.

Extra Terms

In most cases additional terms serve simply to transfer populations from one compartment to another; hence the total population N is unchanged and the above results on boundedness hold.

One problem may arise, for example, with the inclusion of a term that models exit or entrance to the population. For example, we could account for deaths due to the disease with an exponential distribution with mean $1/\alpha$. Such an event would cause the population, in the absence of everything else, to shrink over time:

$$\begin{aligned} \frac{dI}{dt} &= \ldots - \alpha I(t) \\ \Rightarrow \frac{dN}{dt} &= (b-\mu)N(t) - \alpha I(t). \end{aligned}$$

In this case we have

$$\begin{array}{rrcccl} & (b-\mu-\alpha)N(t) & \leq & \frac{dN}{dt} & \leq & (b-\mu)N(t) \\ \Rightarrow & N(0)e^{(b-\mu-\alpha)t} & \leq & N(t) & \leq & N(0)e^{(b-\mu)t} \\ \Rightarrow & N(0)e^{-|b-\mu-\alpha|t} & \leq & N(t) & \leq & N(0)e^{|b-\mu|t} \\ & \Rightarrow \quad 0 & < & N(t) & \leq & N(0)e^{|b-\mu|t} \end{array}$$

In the above we use the Comparison Theorem 8 for (non-delay) differential equations, with the result that $N(t)$ is still always positive (and still bounded for any finite time). We note that the differential equation governing the evolution of $N(t)$ involves no delay and so for both a non-delay and a delay compartmental epidemic model we find that $f(t,x)$ and $g(t,x(t),x(t-r))$ respectively are still continuous with respect to their second (and third) variables, and their partial derivatives exist and are continuous so they satisfy a Lipschitz condition. Thus we still retain the existence and uniqueness results even when disease deaths, which do not have a corresponding increase in another compartment, are accounted for.

Extra Compartments

Adding or excluding compartments changes the dimension of the vector $x(t)$, but the general existence and uniquness results still hold as well.

Some epidemic models simply do not explore every compartment. They may repress analysis of certain compartments (such as R) of which the other compartments are independent in order to simplify the analysis of the dynamics of the compartments of interest. In such cases, for existence/uniqueness purposes we may consider the model as extended to included the repressed or ignored compartments. They may be irrelevant to the dynamics of the compartment of interest, but taking all of the (physically necessary) classes together we get a total population of size N upon which we can find bounds which let us prove existence and uniqueness of solutions.

Likewise the addition of compartments, which really involves the partitioning of the total population into more specific classes, doesn't affect the existence or uniqueness of a solution. Another compartment may be added, as we have seen, for example if there is an exposed class E, but the dimension of $x(t)$ does not affect the continuity or Lipschitz condition of f. If the extra compartment just serves to transfer populations around we still have $N'(t) = (b - \mu)N(t)$; even if the new compartments cause exit/entrance to the population, we will still have N is bounded and positive, and our results hold so long as the new compartments didn't have any inherent discontinuities in their governing differential equations.

Form of Differential Equation Terms

Such discontinuities should not be introduced with any realistic DE term form, though. We may have different forms of the terms in the system than just the mass action and exponential terms in the examples above, such as a different type of contact rate as discussed in Sections 2.2.3 and 2.5; so long as the denominator is never zero (which, for example, in the case of the saturated contact rate, it cannot be since $S \geq 0$), the derivative function f is still continuous, as are its partial derivatives, and the existence and uniqueness results hold.

As explained in Section 2.5, another way to change the underlying assumptions of the associations within the system would be to allow for logistic growth such as $N' = \rho N(1 - \frac{N}{K})$. We need to ensure, however, that the solution would still be well-defined.

For $\rho > 0$ then we will easily keep the result that $N(t)$ is bounded; in fact, $N(t) \leq \max K, N(t_0)$ for all future time. The logistic growth also doesn't affect the continuity of the function in the right-hand side of the differential equations, or the existence or continuity of the partial derivatives with respect to x.

Time-Varying Parameters

We will not describe in detail the effects of time-varying parameters; suffice it to say that, if the parameters are continuous functions of t, they will not affect the existence or uniqueness of a

solution. For example, if $\beta = \beta(t)$, then using System 4.7 for example we get

$$\begin{cases} S(t)' &= \ldots - \beta(t)S(t)I(t) \\ E(t)' &= \beta(t)S(t)I(t) - \beta(t-r)e^{-\mu r}S(t-r)I(t-r) + \ldots \\ I'(t) &= \beta(t-r)e^{-\mu r}S(t-r)I(t-r) + \ldots \\ R'(t) &= \ldots \end{cases}$$

Terms in the differential equations still have corresponding terms of opposite sign in other DEs, so again these epidemic effects (with time-varying coefficients or not) cancel in the DE for $\dot{N}(t)$. Our boundedness results still hold, and so long as the time-dependent parameters are continuous f will still be continuous (composite-C in the delay case, composite-PC with pulse vaccination) and we get the existence of a solution continuable for future time, or at least until an impulse interrupts it. These parameters do not affect the partial derivatives with respect to $x = [S, E, I, R]^T$ so again if the parameters are continuous the partial derivatives of f in x (x_t in the delay case) will be.

If the parameters are discontinuous then so long as they are single-valued and keep x in the domain of f, we can analyze the solutions on the opposite sides of a parameter discontinuity separately.

3.4.2 Changes to Type of DE

We consider the changes mentioned in Section 2.5.2:

- Spatially-varying PDEs are beyond the scope of this thesis.
- The theory in [6] deals with very general impulsive delay systems, so we may extend our results from Section 3.3. The delay existence and uniqueness pulse vaccination results depend on $f(t, x_t)$ being composite-PC, but for any f of the form

  $$f(t, x_t) = g(t, x(t), x(t - h_1(t)), \ldots, x(t - h_j(t))) \tag{3.26}$$

  we have f is composite-PC, quasi-bounded, and continuous in its second variable so long as $g \in C(\mathbb{R}_+ \times \mathbb{R}^{n(j+1)}, \mathbb{R}^n)$, j is finite, the $h_i(t)$ are continuous and bounded, and the $t - h_i(t), i = 1..j$ are strictly increasing [6]. Thus we can handle more than one delay, and many cases of time-varying delay. The results also apply for unequally-spaced impulses.
- In the case of distributed delays we may not retain such a property but for most other epidemic models there will be a finite number of delays.

Chapter 4

Literature Review

4.1 Introduction

The epidemic modelling literature is extensive, beginning formally in the early part of the 20th century. Heesterbeek [32] discusses the contributions of W. H. Hamer, R. Ross, and A. G. McKendrick in compartmental modelling and particularly discusses the use of the law of mass action for the bilinear incidence term. A seminal paper by W. O. Kermack and McKendrick [44], which introduced model (2.2) in Section 2.1.1, is credited by many ([7, 9, 15]) as a foundation in the qualitative study of epidemics through compartmental models.

The epidemic modelling literature took off in more recent decades, starting in about the 1970s due to authors such as H.W. Hethcote ([35], [34]), K.L. Cooke ([8], [11]), and J.A. Yorke ([80]). Since then there has been an abundance of publications ranging from empirical studies to purely theoretical treatments. Kermack and McKendrick's ODE model dealt nominally with two compartments (a removed class is implied) in a homogeneously mixed population, with permanent removal and no control measures [44]. The literature which followed branched into such areas as

- vaccination control measures
- heterogeneous populations (age-structured, infectious stages)
- spatial heterogeneity (PDEs)
- constant latent/infectious/immune periods (DDEs)
- distributed delay
- stochastic effects

and many, many other areas. In the following sections we discuss the literature on general forms of incidence, pulse vaccination campaigns, and delay differential equations.

4.2 Changes to Incidence Term

In Section 2.2.3 we introduced the mass-action bilinear incidence term and the standard incidence $\beta\frac{SI}{N}$ which takes into account varying population size. While these incidences are very common, more general terms are ubiquitous as well.

The dependence on I may be nonlinear, for example a saturation incidence term such as $\beta S\frac{I}{1+kI}$ where $k > 0$ [49, 78]. The contact rate still increases as I increases, but the growth is largest when I is very close to 0 and approaches a positive limit from below for large I.

Psychological effects may cause contact rates to not just level off but to decline with respect to I for high levels of infectives, for example as individuals become wary of contact. Capasso and Serio model such effects in the incidence term [9]. A sample incidence term could be something like $f(I)S = kI^p(1-I)^{q-1}S$ with $k > 0, p > 1, q \geq 1$.

More generally we can have an incidence term of the form $G(S, I, t)$. Physicality conditions are:

- $G(0, I, t) \equiv 0 \equiv G(S, 0, t)$
- $G(S, I, t) \geq 0$ for all $S \geq 0, I \geq 0, t \geq 0$

These assumptions are to keep the model physically reasonable: without infection, there can be no transmission, and there can be no "negative" transmission (a susceptible contacting an infective cannot take away the disease).

A more complicated incidence term is not just inserted to make the analysis look "fancy;" there can be very important implications to stability. Alexander and Moghadas, for example, use an incidence term $\beta[1+f(I;\nu)]IS$ where $f(I,0) = 0$ and so ν is a measure of the "departure from mass action" [2]. They find that under reasonable assumptions on f, multiple endemic equilibria can be possible even when the reproduction number is less than one! Thus we find that, for one thing, having a good empirical basis for the model structure chosen is very important, and also that while simplifications can be very instructive, merely choosing a simple model may not explain phenomena that could be observed in real-life outbreaks.

Like Alexander and Moghadas, van den Driessche and Watmough also look at bifurcations, in their case with an SIS model with incidence term $\lambda(I)SI$ where $S = 1 - I$ [71]. Korobeinikov uses the incidence term $G(S, I, t) = f(S, I)$ where f satisfies the above physicality conditions and is concave down with respect to I [45].

d'Onofrio dispenses with the parameter ν but generalizes [2] to nonautonomous systems using $G(S,I,t) = g(I,t)S^q$ for $q > 0$ [17]. Adding the t-dependence complicates the results. d'Onofrio also considers pulse vaccination control measures, as discussed in the next subsection (4.2.1).

4.2.1 Pulse Vaccination and General Incidence

Pulse vaccination has become more prevalent in the literature starting in the early 1990s; see, for example, [63] and [62] for a more thorough introduction, [1] and [68] for simulations analysis, and [4] for comparison to real-life data.

There are many recent publications in the epidemic modelling literature dealing specifically with pulse vaccination and non-bilinear incidence. Gakkhar and Negi [24] study bifurcations in a SIRS model with non-monotonic incidence in I of the form $\kappa SI/(1+\beta I+\alpha I^2)$. Wang *et. al.* [74], Xu and Ma [78], and Gao *et. al.* [25] use a saturation incidence in SIRVS, SEIRS, and SEIR models, respectively. Zhang and Teng ([82], [81]) and Meng *et. al.* [57] analyze SEIRS models with saturation in S, that is, with incidence term $\beta\frac{S}{1+\alpha S}I$; Song *et. al.* [70] use an SVEIR model with saturation in S and V. Zhang *et. al.* more recently use saturation in S in an SIR model [85]. Wang *et. al.* [75] and Luo *et. al.* [54] study a βIS^q incidence in an SEIR model and SIR model respectively, while Hui and Chen [39] study $\beta I^p S^q$.

While more complicated incidence terms may lead to richer dynamics, accurate parameter estimation and the necessity of confidence in the model choice can raise issues. Looking at a more general form of the incidence function, for example $G(S,I,t)$ discussed in the last section, may be more complicated but can lead to more widely applicable results. As stated in the previous section, d'Onofrio in [17] considers a general force of infection which is polynomial in S but a general function of I and t. The model is as follows, using pulse vaccination but with no delay [17]:

$$\begin{cases} S' &= \mu\left([1-\theta]-S\right) - g(I,t)S^q \\ I' &= g(I,t)S^q - (\mu+\gamma)I \\ R' &= \gamma I - \mu R \\ V' &= \mu\theta - \mu V \end{cases} \qquad t \neq k\tau, \quad k \in \mathbb{Z}$$
$$\begin{cases} S(k\tau^+) &= (1-p)S(k\tau) \\ I(k\tau^+) &= I(k\tau) \\ R(k\tau^+) &= R(k\tau) \\ V(k\tau^+) &= V(k\tau) + pS(k\tau) \end{cases} \qquad t = k\tau \tag{4.1}$$

V is the vaccinated compartment while R is for those who have recovered from the disease. The compartments R and V do not directly affect the dynamics of S and I, so by assuming that recovery from the disease leads to the same strength of immunity as vaccination, and by setting

$\theta = 0$ (that is, no continuous at-birth vaccination) we can combine compartments R and V in System (4.1):

$$\begin{cases} S' &= \mu(1-S) - g(I,t)S^q \\ I' &= g(I,t)S^q - (\mu+\gamma)I \qquad t \neq k\tau, \quad k \in \mathbb{Z} \\ R' &= \gamma I - \mu R \end{cases}$$
$$\begin{cases} S(k\tau) &= (1-p)S(k\tau^-) \\ I(k\tau) &= I(k\tau^-) \qquad t = k\tau \\ R(k\tau) &= R(k\tau^-) + pS(k\tau^-) \end{cases} \tag{4.2}$$

d'Onofrio in (4.1) assumes that the populations are continuous from the left, as opposed to from the right as given in background Section 3.3. This assumption does not affect the existence/uniqueness or form of solutions, so in (4.2) and later we will use right-continuous DEs in order to pick a method and be consistent.

The general incidence $g(I,t)$ is subject, as in [17], to the assumptions:

- $g(0,t) = 0$
- $g(I,t) \geq 0$ for $I \geq 0$
- $g(I,t) \leq \lambda(t)I$

As before, the first two assumptions are for physicality of the incidence. In the third assumption, we get $\lambda(t)$ from the restriction

$$\lambda(t) \quad \begin{cases} = \frac{\partial g(0,t)}{\partial I} \text{ if } \frac{\partial g(0,t)}{\partial I} > 0 \\ > \frac{\partial g(0,t)}{\partial I} \text{ if } \frac{\partial g(0,t)}{\partial I} \geq 0. \end{cases}$$

(We are not defining λ pointwise in t, that is we are not letting $\lambda(t_1) = \frac{\partial g(0,t_1)}{\partial I} > 0$ while $\lambda(t_2) > \frac{\partial g(0,t_2)}{\partial I} = 0$; rather, we are simply choosing an upperbound to $\frac{\partial g(0,t)}{\partial I}$ that is always nonzero. If $\frac{\partial g(0,t)}{\partial I}$ itself is always nonzero then we define $\lambda(t)$ equal to it, otherwise we choose a different function.) We also note that, for the purposes of the proofs in [17], $\lambda(t)$ must be periodic with period T which divides into the pulse vaccination interval τ (*i.e.* $\tau = nT$ for some $n \in \mathbb{Z}$). This restriction decreases the generality of the model, but can make physical sense in the sense that $\lambda(t)$ could model seasonal variations with a period of one year, while the pulse vaccination campaign is led every few years.

Thus we are restricting our $g(I,t)$ incidence to one that grows at most linearly in I. This $g(I,t)$, however, does allow far more general incidence rates than the usual bilinear term, as

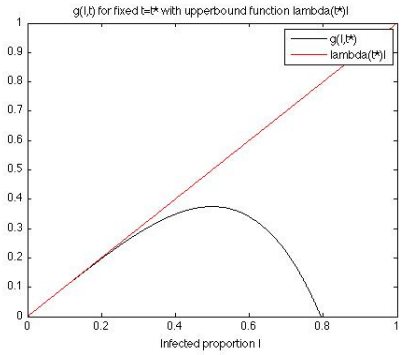

Fig. 4.1: $g(I, t^*) = I(1 - 2I^3)$ (a psychological incidence)

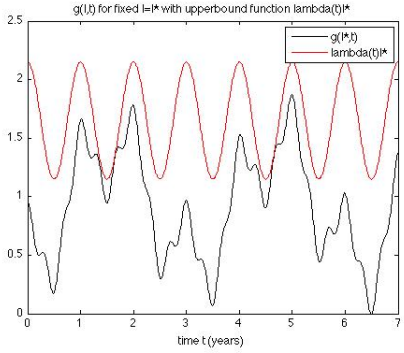

Fig. 4.2: $g(I^*, t)$ with periodic bound $\lambda(t) = \frac{1}{2}cos(2\pi t) + 1.65$

shown in Figures 4.1, 4.2, and 4.3. The bilinear incidence is the special case $g(I, t) \equiv \beta I$ and $\lambda(t) \equiv \beta$.

In [17] it is shown that the disease will die out in System (4.1) if

$$\frac{1}{\tau}\int_0^\tau \lambda(t)\tilde{S}^q(t)dt \quad \leq \quad \mu + \gamma, \tag{4.3}$$

where

$$\tilde{S}(t) = (1-\theta)\left[1 - \frac{p}{1-(1-p)e^{-\mu\tau}}e^{-\mu(t-k\tau)}\right], \quad t \in (k\tau, (k+1)\tau] \tag{4.4}$$

is the disease-free periodic solution of System (4.1). We will return to $\tilde{S}(t)$ in more detail in Lemma 1 of Section 4.3.1. The form $(\cdot, \cdot]$ of the t interval in (4.4) comes from the left-continuity of (4.1); if we have pulse vaccination such that the compartment populations are continuous from the right, it would be $[\cdot, \cdot)$.

As in [17] we may also generalize System (4.1) to a system with an exposed class E:

$$\begin{cases} S' &= \mu\left([1-\theta] - S\right) - g(I,t)S \\ E' &= g(I,t)S - (\mu+\kappa)E \\ I' &= \kappa E - (\mu+\gamma)I \qquad\qquad t \neq k\tau, \quad k \in \mathbb{Z} \\ R' &= \gamma I - \mu R \\ V' &= \mu\theta - \mu V \end{cases} \tag{4.5}$$

where the pulse behaviour is as before with $E(k\tau^+) = E(k\tau)$. This model does not use delay, and instead has an exponential distribution of the latent period: see Section 5.2 for a discussion and results involving delay.

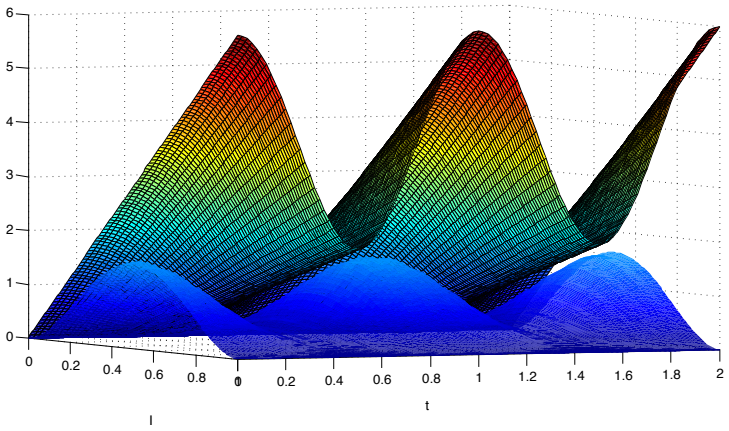

Fig. 4.3: $g(I,t) = \left(cos(2\pi t) + \frac{1}{10}sin^2(40t) + \frac{3}{2}\right)\cdot\left(10I^2(1-I)^2\right)$ *(bottom)* $\leq (cos(2\pi t)+2)\,I =: \lambda(t)I$ *(top)*; $g(I,t^*)$ models psychological effects.

In [17] it is found that a sufficient condition for eradication of the disease is

$$\frac{1}{\tau}\int_0^\tau \lambda(t)\tilde{S}^q(t)dt \quad \leq \quad \frac{\kappa-\gamma}{\kappa}(\mu+\gamma), \tag{4.6}$$

so long as $\kappa > \gamma$, that is, the average latent period $\frac{1}{\kappa}$ is shorter than the average recovery period $\frac{1}{\gamma}$. (This result can be proven with the Lyapunov function $L := \frac{\kappa}{\kappa-\gamma}E + I$.) Note that in the limit $\kappa \to \infty$ (that is, $\frac{1}{\kappa} \to 0$ so the time spent in the compartment E vanishes), we recover the result for the SIRV model (4.1).

4.3 Delay in Epidemic Models

The delay differential equation literature is also extensive. For textbooks, see Driver [18] for a solid introduction to DDEs. Kuang [46] discusses delay and distributed delay differential equations in the context of population models, including predator-prey systems but also with logistic-type equations that are applicable to epidemic models. Brauer and Castillo-Chavez have an excellent introduction to epidemic models in [7] with extensions to delay systems.

In Chapter 1 we discussed the use of exponential distributions in an epidemic model, that is, terms of the form σx_i (*i.e.* $x_i' = \ldots \sigma x_i$) for constant σ and where x_i is one of the compartment populations. Instead of an exponential distribution we might want to model a different distribution; for example d'Onofrio uses a gamma distribution for the infectious period, arguing that an exponential distribution is independent of the starting time, and concludes from [5] that "from

medical literature the latent and infectious time are known to have a well defined mean and a quite small standard deviation" [16].

More generally we can use a distributed delay term of the form $\int_{-r}^{0} g(x_t(s))ds$ for some function g. This distribution in fact includes infinite delays since the integral term (or terms) of the differential equation depends on $x(t+s)$ for all $s \in [-r, 0]$. See, for example, Cooke and Kaplan [11] or Gao *et. al.* [28].

For simplicity we will be considering discrete delays for now; that is, rather than following an exponential or other distribution, the time of latency or infectiveness or immunity is considered to be a constant. d'Onofrio's above comment helps to justify this assumption [16]. Even among just delay-related publications, the epidemic modelling literature is extensive. We list sample papers from each area but warn that the list is not comprehensive.

Delay may be incorporated through a fixed latent period (time until infectious, while the disease develops in an exposed individual), resulting in an exposed class. For example,

$$E'(t) = G(\ S(t), I(t), t\ ) - G(\ S(t-r), I(t-r), t-r\ )e^{-\mu r} - \mu E(t)$$

(assuming exponentially-distributed death rate with mean life expectancy $1/\mu$). Gao *et. al.* use such a model with bilinear incidence in [26] and [27], with the former involving time-varying population. Jiang *et. al.* in [41] and Wei *et. al.* in [77] use a delay for latent period in an SVEIR model in which the vaccinated class may still become infected, albeit at a reduced rate. Pei *et. al.* [65] consider a quarantined class. Publications with latent delay and nonlinear incidence include those by Meng *et. al.* [58] (which uses a specific case of the incidence in Alexander and Moghadas [2]), Wei and Chun [76] (saturation incidence in S), Xu and Ma [78] (saturation incidence in I), and Zhao *et. al.* [86] (polynomial incidence in S).

We could alternately have delay in the infectious class, so the infective period (time to recovery) is fixed; for example,

$$I'(t) = G(\ S(t), I(t), t\ ) - G(\ S(t-r), I(t-r), t-r\ )e^{-\mu r} - \mu I(t) - \alpha I(t)$$

where we have included disease deaths at rate α as an example. Publications using related models include those by Gao *et. al.* [30], Meng and Chen [56], and Pang and Chen [64]. Zhang *et. al.* [84, 85] use a fixed infectious period, with a saturation incidence and in a structured model with different levels of susceptibility respectively. Luo *et. al.* [54] include the delay in a model with two susceptible categories.

We could also use delay to model a fixed immune period. Suppose the infectives recover at a rate γ, then such a model would look something like

$$R'(t) = \gamma I(t) - \gamma I(t-r)e^{-\mu r} - \mu R(t).$$

Li *et. al.* consider the spatial analog of an SIRS model with temporary immunity [48] and Hethcote [37] separately considers delay during infectiousness and in the recovered (immune) period.

Clearly we could also analyze models with combinations of these delays. Cooke and Kaplan [11] use their distributed delays to model the incidence over the infectious period taking into account the distribution of time until recovery. Cooke and van den Driessche [12] and Wang [73] use fixed latent and immune periods; [12] is also notable for using the standard incidence $\beta\frac{SI}{N}$ as opposed to the usual bilinear incidence. Gao *et. al.* extend this model to include pulse vaccination and use saturation incidence [25]. Song *et. al.* and Meng *et. al.* similarly use fixed latent and immune periods, with a saturation incidence in [57, 70] and with vertical (newborn) transmission in [60]. Jiao *et. al.* [42], Gao *et. al.* [29], and Wang *et. al.* [75] use a fixed latent period followed by a fixed period of infectiousness; Wang *et. al.* additionally use an incidence that is polynomial in S.

Delay is also incorporated to model vector transmission without explicitly modelling the vector population, such as in Meng *et. al.* [59], through the presence of an incidence of the form $\beta S(t)I(t-r)$. The number of new infections at the *current* time level depends on the contact between current susceptibles $S(t)$ and vectors (*e.g.* mosquitoes) which contacted infected individuals r time units ago (where r is the incubation time in the vector), so indirectly, $I(t-r)$.

4.3.1 Pulse Vaccination and Delay

The combination of pulse vaccination in an epidemic model with delay has also been well studied. Because this thesis is focussing on pulse vaccination, a large proportion of the papers referenced in the previous section in fact use pulse vaccination as well: [41, 42, 54, 64, 65, 70, 75, 76, 77, 78, 83, 84, 85, 86] and all the papers with first author S. Gao ([25]-[30]) or X. Meng ([56]-[60]).

Gao et. al. [27] study the following pulse vaccination model with delay:

$$\begin{cases} \begin{aligned} S' &= \mu(1-S) - \beta SI \\ E' &= \beta SI - \beta e^{-\mu r} S(t-r)I(t-r) - \mu E \\ I' &= \beta e^{-\mu r} S(t-r)I(t-r) - (\mu+\gamma+\alpha)I \\ R' &= \gamma I - \mu R. \end{aligned} & t \neq k\tau, \quad k \in \mathbb{Z} \\ \begin{aligned} S(k\tau) &= (1-p)S(k\tau^-) \\ E(k\tau) &= E(k\tau^-) \\ I(k\tau) &= I(k\tau^-) \\ R(k\tau) &= R(k\tau) + pS(k\tau^-) \end{aligned} & t = k\tau \end{cases} \tag{4.7}$$

Pulse vaccination is applied to move individuals from the susceptible to the recovered compartment at $t = k\tau$. In [27] the pulse vaccination is in fact applied so the populations are continuous

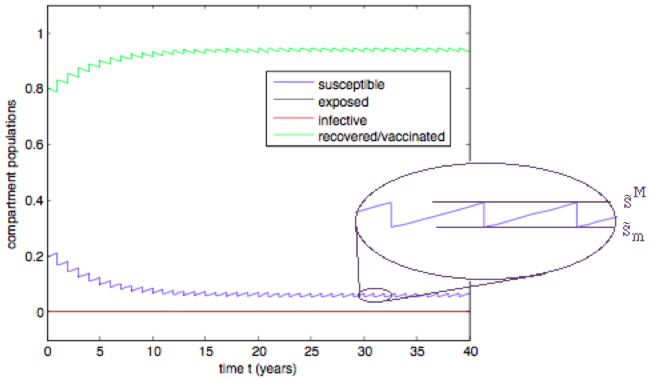

Fig. 4.4: Susceptible population converging to disease-free periodic solution $\tilde{S}(t)$.

from the left (*e.g.* $S(k\tau^+) = (1-p)S(k\tau)$). As discussed in Section 4.2.1, we change it to right-continuity for consistency with our theorems and previous models.

In this model bilinear (mass-action) incidence is used. The $e^{-\mu r}$ factor in the delayed terms arises from natural deaths over the course of the latent period, that is, integrating E' we have that

$$E(t) = \int_{t-r}^{t} \beta e^{-\mu(t-s)} S(s) I(s) ds. \tag{4.8}$$

The average life expectancy is $1/\mu$, which is on the order of decades for human populations, so μ itself is small. If the latent period is not an appreciable fraction of the year then we will get $e^{-\mu r} \approx 1$; that is, the factor may help us slightly near endemic thresholds, but is not likely to make a large difference.

In [27] the authors defined threshold numbers

$$\mathcal{R}^* = \frac{\beta e^{-\mu\omega}}{\mu+\gamma}\tilde{S}^M, \qquad \mathcal{R}_* = \frac{\beta e^{-\mu\omega}}{\mu+\gamma}\tilde{S}_m = (1-p)\mathcal{R}^*$$

where $\tilde{S}^M := \max_{t\in[0,\tau]} \tilde{S}(t) = \tilde{S}(\tau^-)$ and $\tilde{S}_m := \min_{t\in[0,\tau]} \tilde{S}(t) = \tilde{S}(\tau)$, as shown in Figure 4.4. It is found that in (4.7) the disease is eradicated if $\mathcal{R}^* < 1$ and permanent if $\mathcal{R}_* > 1$, that is, $\mathcal{R}^* > \frac{1}{1-p}$ [27].

While the incidence term βSI is very commonly used in the literature for its simplicity and accuracy, the bilinear incidence assumes that the population is homogeneously mixed and that there are no effects such as psychological issues (discussed in Section 4.2) which may change population behaviour at high or low disease incidence levels. If we want to take into account such (more physically realistic) effects then we should use a more general incidence term as described in Section 4.2.

Our coming results, in addition to the proofs in [27] for eradication and permanence, rely heavily on the knowledge of the disease-free periodic solution $\tilde{S}(t)$ given in Equation (4.4). Many papers in the literature ([17, 24, 25, 26, 27, 28, 29, 30, 41, 42, 54, 56, 57, 58, 59, 60, 64, 65, 68, 70, 74, 75, 76, 77, 81, 82, 83, 84, 85, 86]) use similar methods to find sufficient conditions for disease eradication. These methods use the following lemma, explicitly or implicitly:

Lemma 1. *[27] Consider the following impulsive differential equations:*

$$\begin{array}{rcll} x'(t) & = & a - bx(t), & t \neq k\tau \\ x(t) & = & (1-p)x(t^-), & t = k\tau \end{array} \tag{4.9}$$

where $a > 0$, $b > 0$, $0 < p < 1$. There exists a unique positive periodic solution

$$\tilde{x}(t) = \frac{a}{b} + \left(x^* - \frac{a}{b}\right) e^{-b(t-k\tau)}, k\tau \leq t < (k+1)\tau \tag{4.10}$$

to this system, which is globally asymptotically stable, where $x^* = \frac{a(1-p)(1-e^{-b\tau})}{b(1-(1-p)e^{-b\tau})}$.

If the impulsive behaviour is $x(t^+) = (1-p)x(t)$, the time interval becomes $k\tau < t \leq (k+1)\tau$.

The lemma may be proven (see [27]) by integrating between pulses (from $k\tau$ to t), then requiring $(1-p)\tilde{x}((k+1)\tau^-) = \tilde{x}(k\tau)$ for the periodic solution. Define $f(x) := (1-p)\left[\frac{a}{b} + \left(x - \frac{a}{b}\right)e^{-b\tau}\right]$, then the periodic solution is found to be globally asymptotically stable because f is a contraction mapping.

Remark. Rearranging the above, we get

$$\begin{aligned} \tilde{x}(t) &= \frac{a}{b} + \left(\frac{a(1-p)(1-e^{-b\tau})}{b(1-(1-p)e^{-b\tau})} - \frac{a}{b}\right) e^{-b(t-k\tau)} \\ &= \frac{a}{b} + \left(\frac{a(1-p)(1-e^{-b\tau})}{b(1-(1-p)e^{-b\tau})} - \frac{a(1-(1-p)e^{-b\tau})}{b(1-(1-p)e^{-b\tau})}\right) e^{-b(t-k\tau)} \\ &= \frac{a}{b} + \left(\frac{a[1-p-(1-p)e^{-b\tau}] - [1-(1-p)e^{-b\tau}]}{b(1-(1-p)e^{-b\tau})}\right) e^{-b(t-k\tau)} \\ \Rightarrow\ \tilde{x}(t) &= \frac{a}{b}\left[1 - \frac{p}{(1-(1-p)e^{-b\tau})} e^{-b(t-k\tau)}\right], \quad k\tau \leq t < (k+1)\tau. \end{aligned} \tag{4.11}$$

General procedure to determine eradication threshold with pulse vaccination:

Lemma 1 may be applied, explicitly or implicitly, to find parameter thresholds below which the infection will be eradicated. A common procedure is as follows. (We assume the births are proportional to a constant A; we could for example have $A = N$ if N is constant, or $A = K$ for a carrying capacity K.)

(i) Consider the maximum value of S' for physically valid compartment populations:

$$\begin{aligned} S' &= \mu(A-S) - G(S,I,t) \\ \Rightarrow S' &\leq \mu(A-S) \end{aligned}$$

(ii) Use a comparison system (with equality where the inequality for S' is),

$$x' = \mu(A-x) \tag{4.12}$$

and look for a solution $x(t)$. Ignoring the other compartments and considering the above as a scalar system, we let $f^1(t,\phi) = \mu(A-\phi(0)) - \beta\phi(0)I(t)$ and $f^2(t,\phi) = \mu(A-\phi(0))$. Then both f^1 and f^2 satisfy the quasimonotone condition since they only involve the current time. By Theorem 16, since $f^1(t,\phi) \leq f^2(t,\phi)$ we have that $x(t;t_0,\phi,f^1) \leq x(t;t_0,\phi,f^2)$; that is, $S(t) \leq x(t)$ for all $t \geq t_0$ [69].

(iii) Use Lemma (1) to find the periodic solution to the comparison equation (4.12) with PV and to determine that this periodic solution is GAS.

(iv) Find the resulting upperbound for $S(t)$: $S(t)$ is bounded above by $x(t)$ which is approaching the periodic solution $\tilde{x}(t)$. $\tilde{x}(t)$ has a time-independent maximum value $\tilde{S}^M$ which $S(t)$ must either be less than or become arbitrarily close to from above, *i.e.* for any $\epsilon > 0$, $S(t) < \tilde{S}^M + \epsilon$ eventually.

(v) Then, in either the delay or non-delay case, we can use the upperbound for $S(t)$ to find parameter values which ensure eradication of the infection over the long term, that is, $I(t) \to 0$.

For example, given a model with

$$\begin{aligned} I' &= \beta e^{-\mu r} S(t-r) I(t-r) - (\mu+\gamma) I \\ \Rightarrow I' &\leq \beta e^{-\mu r} \tilde{S}^M I(t-r) - (\mu+\gamma) I, \end{aligned} \tag{4.13}$$

let $f^1(t,\phi) = \beta e^{-\mu r} S(t-r)\phi(-r) - (\mu+\gamma)\phi(0)$ and $f^2(t,\phi) = \beta e^{-\mu r}\tilde{S}^M\phi(-r) - (\mu+\gamma)\phi(0)$, then f^2 satisfies the quasimonotone condition. (For a general incidence $G(S,I,t)$ if G does not satisfy the quasimonotone condition in I, then so long as it is bounded above by a function which does, such as $G(S,I,t) \leq \lambda(t)SI$ in [17], we can still use the comparison theorem.)

Suppose $y'(t) = f^2(t,y_t)$, then by Theorem 16 we have that $I(t) \leq y(t)$ for all $t \geq t_0$. If we can find conditions for $y(t) \to 0$ then since $I(t) \geq 0$ we have asymptotic stability of the trivial solution $I \equiv 0$ of 4.13 as well.

(vi) If possible, use $I \to 0$ to find a minimum value of S' (using the same idea, that of an exact solution to a comparison system) and show by squeeze theorem that $S(t)$ approaches the infection-free periodic solution as $t \to \infty$. If there is no delay term in S' we may compare the systems using ODE theory. If there is a delay term (for example, through a fixed immunity period after which individuals return to S) we cannot necessarily compare the resulting DDEs.

If we combine the above models in Systems (4.7) and (4.2) then we get a pulse vaccination delay model with general incidence:

$$\begin{cases} S' &= \mu\,(1-S) - g(I,t)S \\ E' &= g(I,t)S - g(I(t-r),t-r)e^{-\mu r}S(t-r) - \mu E \\ I' &= g(I(t-r),t-r)e^{-\mu r}S(t-r) - (\mu+\gamma+\alpha)I \\ R' &= \gamma I - \mu R \\ S(k\tau) &= (1-p)S(k\tau^-) \\ E(k\tau) &= E(k\tau^-) \\ I(k\tau) &= I(k\tau^-) \\ R(k\tau) &= R(k\tau) + pS(k\tau^-) \end{cases} \begin{array}{l} t \neq k\tau, \quad k \in \mathbb{Z} \\ \\ \\ \\ \\ \\ \\ t = k\tau \end{array} \tag{4.14}$$

It is the intent of part of this thesis to study the long-term dynamics of this system; that is, we want to combine results from Gao et. al. [27] for a SEIR delay epidemic model with the results by d'Onofrio [17] for a non-delay model with general force of infection.

4.4 Total Population, $N(t)$

In many of the models described so far, if we let $N(t)$ be the total population then we see that $N'(t) \equiv 0$, that is, $N(t) \equiv N$ a constant. This result arises from the possibly unrealistic assumptions that the birth rate and death rate are equal, that there are no disease deaths, and that the birth rate is proportional to N (as opposed to, say, logistic growth) over the time frame we are interested in. These assumptions will be discussed in more detail in Chapter 6.

While the assumption $N(t) \equiv N\ (= 1)$ is extremely common in the literature, there are also many publications dealing with time-varying total population.

Some publications which consider time-varying population $N(t)$ include those by Cooke and van den Driessche [12] and Gao *et. al.* [26] (as mentioned in Section 4.3.1); Cooke and van den Driessche model births proportional to $N(t)$ and use the standard incidence $\beta\frac{SI}{N}$. Gao *et. al.* use a constant birth rate and include disease-induced deaths, as do Wei and Chen in [76]. Hethcote [38] and Luo *et. al.* [54] analyze models with delay during infectiousness, and Zhang and Teng

add delays for the latent and immune periods [83]. Of the aforementioned papers, [26, 54, 76, 83] consider pulse vaccination.

Chapter 5

SEIR Model with Fixed Population Size, Bilinear and General Incidence

In the following three chapters we present our results.

In this chapter we look for new results for models with pulse vaccination and time delay. We apply the theorems from AMATH 851, with extensions to delay systems based on Driver [18]. We consider an epidemic model with general incidence rate as stated by d'Onofrio in [17], with help from Gao et. al. [27] for the delay aspects.

In Chapter 6 we survey ways for the total population $N(t)$ to vary over time, and their effects on the applicability of Lemma 1 and the pulse vaccination procedure listed in Section 4.3.1.

In Chapter 7 we consider a piecewise-constant contact rate. We do so using switched systems, following the lead of Liu and Stechlinski in [52], with the overall epidemic model switching between subsystems in which the contact rate is constant at a particular value.

We want to find conditions for disease eradication and permanence in the delay model System (4.14) with general incidence. First we look to strengthen the conditions that were found in [27] on System (4.7), that is, (4.14) with the common incidence term $g(I,t) = \beta I$.

In this section we will continue with the constant population assumption; many of the results carry over to a growing population, depending on the type of growth, but for simplicity we will assume N is constant for now. In particular, we must assume that $\alpha = 0$ in (4.14). If so then without loss of generality we may assume $N = 1$, that is, that the compartments are modelling fractions of the population. This assumption is the reason for the "$\mu \cdot 1$" term in the DE for $S(t)$ in models such as (4.14): the births are assumed proportional to the total population $N = 1$. We note that since the compartments are fractions of N then we must have each compartment

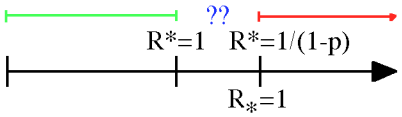

Fig. 5.1: Motivation for time-average threshold value $\bar{\mathcal{R}}$.

population in the interval $[0,1]$; that is, in Systems (4.7) and (4.14) we need

$$(S,E,I,R) \in \Omega_4 := \{(S,E,I,R) \in [0,1]^4 : S+E+I+R=1\}, \tag{5.1}$$

in System (5.4) to follow we need $(S,I,R) \in \Omega_3 := \{(S,I,R) \in [0,1]^3 : S+I+R=1\}$, and so on. These sets Ω_3, Ω_4 are invariant for their respective models: the total population is constant and equal to 1, so for each DE we can set the compartment population to 0 and see that its derivative must be ≥ 0. This result is difficult to see for $E'(t)$ in the delay model but from the definition of $E(t)$ in (4.8) we are assured that $E(t) \geq 0$ always. Then the populations are all nonnegative and sum to 1 so they must remain in their respective sets Ω_n. The vaccination pulses merely transfer populations without affecting the total population. They either do not affect the compartment populations (as for E and I), shrink them by a factor between 0 and 1 (as for S), or, in the case of R or V, they increase the population but not to a value greater than 1 since the other compartments are still nonnegative.

In [27] Gao *et.al.* defined threshold numbers $\mathcal{R}^*$ and $\mathcal{R}_* = (1-p)\mathcal{R}^*$. They found that the disease is eradicated if $\mathcal{R}^* < 1$ and permanent if $\mathcal{R}_* > 1$, that is, $\mathcal{R}^* > \frac{1}{1-p}$ [27]. In this section, we want to fill the "gap" for $1 < \mathcal{R}^* < \frac{1}{1-p}$ (see Figure 5.1).

To do so we will again look, as in condition (4.3) (with $q \equiv 1$), at the time-average of $\tilde{S}(t)$ over one period, rather than its maximum or minimum. That is, we define

$$\bar{\mathcal{R}} = \frac{1}{\tau}\int_0^\tau \frac{\beta e^{-\mu r}}{\mu+\gamma}\tilde{S}(t)dt \tag{5.2}$$

where

$$\tilde{S}(t) = 1 - \frac{p}{1-(1-p)e^{-\mu\tau}}e^{-\mu(t-k\tau)}, \quad t \in (k\tau,(k+1)\tau] \tag{5.3}$$

is the solution to

$$\begin{aligned} S' &= \mu(1-S), \quad t \neq k\tau \\ S(k\tau) &= (1-p)S(k\tau^-) \end{aligned}$$

as obtained from Lemma 1 in Section 4.3.1. We look to show that the disease will be endemic for $\bar{\mathcal{R}} > 1$ and eradicated for $\bar{\mathcal{R}} < 1$.

Let $\Omega_2 := \{(S,I) \in \mathbb{R}^2 : S,I \geq 0, S+I \leq 1\}$, i.e. Ω_2 is Ω_4 with E and R suppressed (valid but ignored). We define *disease permanence* rigorously:

Definition 17. [27]. An epidemic model system is said to be permanent if there exists a compact region $\Omega \in \text{int}(\Omega_2)$ such that every solution of the system with physically valid initial data will eventually enter and remain in the region Ω.

In Section 5.1.1 we look at the eradication conditions of the disease, and in Section 5.1.2 we look at permanence.

5.1 Eradication and Permanence without Delay

We consider the SIR model without delay:

$$\begin{cases} S' &= \mu\,(1-S) - g(I,t)S \\ I' &= g(I,t)S - (\mu+\gamma)I \qquad t \neq k\tau, \quad k \in \mathbb{Z} \\ R' &= \gamma I - \mu R \end{cases}$$
$$\begin{cases} S(k\tau) &= (1-p)S(k\tau^-) \\ I(k\tau) &= I(k\tau^-) \qquad\qquad t = k\tau \\ R(k\tau) &= R(k\tau) + pS(k\tau^-) \end{cases} \tag{5.4}$$

This model is equal to System (4.2) if $q = 1$.

5.1.1 Eradication without Delay: UAS of Disease-Free Solution

Our background theorems in Chapter 3 deal mostly with uniform asymptotic stability (UAS). We know from d'Onofrio [17] that the trivial (disease-free) solution for $I(t)$ in (5.4) is globally asymptotically stable (GAS) so long as condition (4.3) is satisfied; this section strengthens the result to uniform asymptotic stability, so we can later use it in Section 5.2 to apply the theorems that extend results to delay systems.

Define $\bar{\mathcal{R}}$ to be the period-average of the ratio of the coefficients of the upper bound for $I'(t)$, that is, if $I'(t) \leq a(t)I(t-r) - b(t)I(t)$ for positive-valued functions $a(t), b(t)$ (where r may be 0), define

$$\bar{\mathcal{R}} := \frac{1}{\tau}\int_0^\tau \frac{a(t)}{b(t)}dt.$$

For (4.7) with delay and bilinear incidence, $\bar{\mathcal{R}} = \frac{1}{\tau}\int_0^\tau \frac{\beta e^{-\mu r}\tilde{S}(t)}{\mu+\gamma}dt$. For the general incidence model such as (5.4) or (4.14) we use the bound $g(I,t) \leq \lambda(t)I(t)$ to get $\bar{\mathcal{R}} = \frac{1}{\tau}\int_0^\tau \frac{\lambda(t)e^{-\mu r}\tilde{S}(t)}{\mu+\gamma}dt$ (where again $r = 0$ for the non-delay model, and where as in [17] we are assuming $\lambda(t)$ to be τ-periodic).

Theorem 20. *In the non-delay general incidence model, the disease is eradicated if* $\bar{\mathcal{R}} < 1$.

Proof. We consider the general incidence model because the bilinear incidence is just the special case $g(I,t) \equiv \beta I$.

As explained in the "General Procedure" given after Lemma 1 in Section 4.3.1, since $S' \leq \mu(1-S)$ we have $S(t) \leq x(t)$ where x is the solution to the ODE with equality. Including pulse vaccination we get, by the global attractiveness of $\tilde{S}(t)$ explained in Lemma 1, that $x(t) < \tilde{S}(t)+\epsilon$ eventually for any $\epsilon > 0$, and so $S(t) < \tilde{S}(t) + \epsilon$ as well.

Then the GAS result comes from comparing the eventual DE for $I'(t)$,

$$\begin{aligned} I' &= g(I,t)S - (\mu+\gamma)I \\ &\leq \Big(\lambda(t)(\tilde{S}(t)+\epsilon) - (\mu+\gamma)\Big) I \end{aligned}$$

to a similar system with equality

$$\begin{aligned} x' &= \Big(\lambda(t)(\tilde{S}(t)+\epsilon) - (\mu+\gamma)\Big) x \\ &=: a(t)x, \end{aligned} \tag{5.5}$$

where $x(t_0) = I(t_0) =: x_0$. Thus we have that there exists a δ independent of t_0 such that $\|x_0\| < \delta \Rightarrow \lim_{t\to\infty} x(t) = 0$ (in fact, global asymptotic stability gives that δ is arbitrary). We then need to confirm that the other condition of uniform asymptotic stability is met; namely, for any $\sigma > 0$, there exists a $T = T(\sigma)$ independent of t_0 such that $\|x(t)\| < \sigma$ for all $t \geq t_0 + T$.

From Equation (5.5) we get

$$\begin{aligned} x'(t) - a(t)x(t) &= 0 \\ x'(t) - \frac{d}{dt}\left(\int_{t_0}^{t} a(s)ds\right) x(t) &= 0 \\ \frac{d}{dt}\left(e^{-\int_{t_0}^{t} a(s)ds} x(t)\right) &= 0 \\ \Rightarrow e^{-\int_{t_0}^{t} a(s)ds} x(t) - x(t_0) = 0 \quad &\Rightarrow \quad x(t) = x_0 e^{\int_{t_0}^{t} a(s)ds}. \end{aligned}$$

If we choose ϵ small enough then from $\bar{\mathcal{R}} < 1$ we know that

$$\frac{1}{\tau}\int_{t_0}^{t_0+\tau} [\lambda(t)\tilde{S}(t) - (\mu+\gamma)]dt \quad < 0 \quad \Rightarrow \quad \frac{1}{\tau}\int_{t_0}^{t_0+\tau} [\lambda(t)\tilde{S}(t) - (\mu+\gamma)]dt \quad < -2\epsilon\alpha$$

where $\alpha := \frac{1}{\tau}\int_{t_0}^{t_0+\tau} \lambda(t)dt > 0$, and so

$$\frac{1}{\tau}\int_{t_0}^{t_0+\tau} a(t)dt \quad = \frac{1}{\tau}\int_{t_0}^{t_0+\tau} [\lambda(t)(\tilde{S}(t)+\epsilon) - (\mu+\gamma)]dt \quad < -\epsilon\alpha.$$

Thus

$$\begin{aligned} x(t_0+\tau) &< x_0 e^{-\epsilon\alpha\tau} \\ x(t_0+2\tau) &= x(t_0+\tau)e^{\int_{t_0+\tau}^{t_0+2\tau} a(t)dt} < \left(x_0 e^{-\epsilon\alpha\tau}\right) e^{-\epsilon\alpha\tau} \\ &\cdots \\ x(t_0+k\tau) &< x_0 e^{-k\epsilon\alpha\tau} \end{aligned} \tag{5.6}$$

for any integer k.

So we get that $x(t)$ is following a negative exponential pattern at the pulse times $k\tau$. We need to show that between these times $x(t)$ is still bounded above by an appropriate exponential. We note that for any $t \in [k\tau, (k+1)\tau)$,

$$\begin{aligned} x(t) = x(k\tau) + \int_{k\tau}^{t} x'(s)ds \quad &= x(k\tau) + \int_{k\tau}^{t} a(s)x(s)ds \\ \leq x(k\tau) + \int_{k\tau}^{t} |a(s)|x(s)ds \end{aligned}$$

which implies $x(t) \leq x(k\tau)e^{\int_{k\tau}^{t}|a(s)|ds}$ by Gronwall's inequality. Define $a^M = \max_{0\leq t\leq\tau}|a(t)|$, then again for $t \in [k\tau, (k+1)\tau)$ we have

$$x(t) \leq x(k\tau)e^{\int_{k\tau}^{(k+1)\tau} a^M ds} = x(k\tau)e^{a^M\tau}$$

Thus

$$x(t) \leq x_0 e^{-k\epsilon\alpha\tau}e^{a^M\tau} = x_0 e^{-\tau(k\epsilon\alpha - a^M)} \tag{5.7}$$

As $k \to \infty$ the exponent becomes negative. So if we want $x(t) < \sigma$, we simply need

$$\begin{aligned} & x_0 e^{-\tau(k\epsilon\alpha - a^M)} && < \sigma \\ \Rightarrow \quad & -\tau(k\epsilon\alpha - a^M) && < \ln\left(\tfrac{\sigma}{x_0}\right) \\ \Rightarrow \quad & k && > \tfrac{1}{\tau\epsilon\alpha}\ln\left(\tfrac{x_0}{\sigma}\right) + \tfrac{a^M}{\epsilon\alpha}. \end{aligned}$$

(Note we assume $x_0 > \sigma$ else the condition is trivially satisfied.) Since $k \in \mathbb{Z}$ we take the largest integer greater than this value; then we define

$$T = \tau\left\lceil \frac{1}{\tau\epsilon\alpha}\ln\left(\frac{x_0}{\sigma}\right) + \frac{a^M}{\epsilon\alpha}\right\rceil$$

and get that $x(t) < \sigma$ for $t \geq t_0 + T$. Therefore the trivial solution of the linear comparison equation $x'(t) = a(t)x(t)$ is uniformly asymptotically stable. Since $0 \leq I(t) \leq x(t)$ we get that $I(t) \equiv 0$ in (5.4) is UAS as well, so the disease can be eradicated.

□

Remark. We followed through with the calculation for $T(\sigma)$ in order to be explicit, however, upon reaching (5.7) we can directly apply Theorem 14 to obtain that the trivial solution is uniformly asymptotically stable. Since $x(t) \leq x_0 e^{-k\epsilon\alpha\tau} e^{a^M\tau} \leq x_0 e^{-\epsilon\alpha(t-\tau)} e^{a^M\tau}$ for $t \in [k\tau, (k+1)\tau)$ (since $t - \tau < k\tau$), then the theorem is satisfied with $M := e^{(a^M+\epsilon\alpha)\tau}$ and $\eta := \epsilon\alpha = \epsilon\frac{1}{\tau}\int_{t_0}^{t_0+\tau} \lambda(t)dt$.

5.1.2 Permanence without Delay

Bilinear Incidence

In the previous section we were able to show that if $\bar{\mathcal{R}} < 1$ the disease-free equilibrium is UAS, that is, the disease is eradicated in the general incidence non-delay model; in this subsection we consider permanence of the disease in the bilinear incidence SIR (non-delay) model. That is, we consider system (4.7) in the limit as $r \to 0$:

$$\begin{cases} S' &= \mu(1-S) - \beta IS \\ I' &= \beta IS - (\mu+\gamma+\alpha)I \qquad t \neq k\tau, \quad k \in \mathbb{Z} \\ R' &= \gamma I - \mu R. \end{cases}$$
$$\begin{cases} S(k\tau) &= (1-p)S(k\tau^-) \\ I(k\tau) &= I(k\tau^-) \qquad\qquad t = k\tau \\ R(k\tau) &= R(k\tau) + pS(k\tau^-) \end{cases} \tag{5.8}$$

Similar to the method used by Gao et. al. [27], first we define a special value $\bar{I}$ based on $\bar{\mathcal{R}}$:

$$\bar{I} := \frac{\mu}{\beta}\left(\bar{\mathcal{R}} - 1\right) \tag{5.9}$$

and notice that if $\bar{\mathcal{R}} > 1$ then $\bar{I} > 0$, and also

$$\begin{aligned} \bar{I} &= \tfrac{\mu}{\beta}\left(\bar{\mathcal{R}} - 1\right) &&= \tfrac{\mu}{\beta}\left(\tfrac{\beta}{\mu+\gamma}\tfrac{1}{\tau}\int_0^\tau \tilde{S}(t)dt - 1\right) \\ &< \tfrac{\mu}{\beta}\left(\tfrac{\beta}{\mu+\gamma}\tfrac{1}{\tau}\int_0^\tau \tilde{S}(t)dt\right) &&\leq \tfrac{\mu}{\beta}\left(\tfrac{\beta}{\mu+\gamma}\tfrac{1}{\tau}\int_0^\tau \tilde{S}(t)dt\right) \\ &= \tfrac{\mu}{\mu+\gamma} &&< 1. \end{aligned}$$

(recall $\tilde{S} < 1$). So we have defined this value $\frac{\mu}{\beta}\left(\bar{\mathcal{R}} - 1\right)$ and named it after the compartment I for reasons evident soon; however this naming is reasonable because we can see that $0 < \bar{I} < 1$ so it is a valid compartment population.

In [27] the authors used a condition on the minimum value of $\tilde{S}(t)$ to determine conditions for permanence. Here we cannot exactly follow their method (which looks for a contradiction at a local minimum) because we are only using a time-average over one pulse period. Instead we need to define a second threshold number $\bar{\mathcal{R}}^*$:

Claim 4. *Define $\bar{S}$ as the periodic solution to the system*

$$\begin{aligned} S'(t) &= \mu - (\mu + \beta\bar{I})S, \quad t \neq k\tau \\ S(k\tau) &= (1-p)S(k\tau^-) \end{aligned} \tag{5.10}$$

Then if $\bar{\mathcal{R}} > 1$, we have

$$\bar{\mathcal{R}}^* := \frac{1}{\tau}\int_0^\tau \frac{\beta}{\mu+\gamma}\bar{S}(t)dt \quad > 1. \tag{5.11}$$

Proof. By integrating between pulses we can see that $\bar{S}$ is defined similarly to $\tilde{S}$, and we get the following values for the thresholds $\bar{\mathcal{R}}$ and $\bar{\mathcal{R}}^*$:

$$\begin{aligned} \bar{\mathcal{R}} &= \frac{\beta}{\mu+\gamma}\cdot\frac{1}{\tau}\int_0^\tau \tilde{S}(t)dt \\ &= \frac{\beta}{\mu+\gamma}\cdot\frac{1}{\tau}\int_0^\tau \left[1 - \frac{p}{1-(1-p)e^{-\mu\tau}}e^{-\mu(t-k\tau)}\right]dt \\ &= \frac{\beta}{\mu+\gamma}\cdot\left[1 - \frac{p}{1-(1-p)e^{-\mu\tau}}\cdot\frac{1-e^{-\mu\tau}}{\mu\tau}\right] \\ \bar{\mathcal{R}}^* &= \frac{\beta}{\mu+\gamma}\cdot\frac{1}{\tau}\int_0^\tau \bar{S}(t)dt \\ &= \frac{\beta}{\mu+\gamma}\cdot\frac{1}{\tau}\int_0^\tau \frac{1}{\bar{\mathcal{R}}}\left[1 - \frac{p}{1-(1-p)e^{-\mu\bar{\mathcal{R}}\tau}}e^{-\mu\bar{\mathcal{R}}(t-k\tau)}\right]dt \\ &= \frac{\beta}{\mu+\gamma}\cdot\frac{1}{\bar{\mathcal{R}}}\left[1 - \frac{p}{1-(1-p)e^{-\mu\bar{\mathcal{R}}\tau}}\cdot\frac{1-e^{-\mu\bar{\mathcal{R}}\tau}}{\mu\bar{\mathcal{R}}\tau}\right] \end{aligned}$$

So we have

$$\begin{aligned} \bar{\mathcal{R}}^* &= \frac{1}{\bar{\mathcal{R}}}\left[\bar{\mathcal{R}} + \frac{\beta}{\mu+\gamma}\left(\frac{p}{1-(1-p)e^{-\mu\tau}}\cdot\frac{1-e^{-\mu\tau}}{\mu\tau} \quad - \quad \frac{p}{1-(1-p)e^{-\mu\bar{\mathcal{R}}\tau}}\cdot\frac{1-e^{-\mu\bar{\mathcal{R}}\tau}}{\mu\bar{\mathcal{R}}\tau}\right)\right] \\ &= 1 + \frac{\beta}{\mu+\gamma}\cdot\frac{1}{\bar{\mathcal{R}}}\left(\frac{p}{1-(1-p)e^{-\mu\tau}}\cdot\frac{1-e^{-\mu\tau}}{\mu\tau} \quad - \quad \frac{p}{1-(1-p)e^{-\mu\bar{\mathcal{R}}\tau}}\cdot\frac{1-e^{-\mu\bar{\mathcal{R}}\tau}}{\mu\bar{\mathcal{R}}\tau}\right) \\ &> 1 + \frac{\beta}{\mu+\gamma}\cdot\frac{1}{\bar{\mathcal{R}}}\cdot\frac{p}{1-(1-p)e^{-\mu\tau}}\cdot\frac{1}{\mu\tau}\left(1 - e^{-\mu\tau} - \frac{1-e^{-\mu\bar{\mathcal{R}}\tau}}{\bar{\mathcal{R}}}\right) \end{aligned}$$

$\bar{\mathcal{R}}^* > 1$ if the quantity in brackets is positive. Define

$$f(\bar{\mathcal{R}}) = \bar{\mathcal{R}}(1-e^{-\mu\tau}), \qquad g(\bar{\mathcal{R}}) = 1 - e^{-\mu\bar{\mathcal{R}}\tau}.$$

Then $f(1) = g(1)$ and

$$\frac{df}{d\bar{\mathcal{R}}} = 1 - e^{-\mu\tau} > \mu\tau e^{-\mu\tau} > \mu\tau e^{-\mu\bar{\mathcal{R}}\tau} = \frac{dg}{d\bar{\mathcal{R}}}$$

for $\bar{\mathcal{R}} > 1$ and for all $\mu\tau > 0$. So $\bar{\mathcal{R}}(1 - e^{-\mu\tau}) = f(\bar{\mathcal{R}}) > g(\bar{\mathcal{R}}) = 1 - e^{-\mu\bar{\mathcal{R}}\tau}$ for $\bar{\mathcal{R}} > 1$ and so the quantity in brackets above is strictly positive, and therefore $\bar{\mathcal{R}} > 1 \Rightarrow \bar{\mathcal{R}}^* > 1$. □

Theorem 21. *If $\bar{\mathcal{R}} > 1$ in System (5.8) then the disease is permanent.*

Proof. Given $\bar{\mathcal{R}} > 1$, we assume that $I(t)$ stays "small" for all large t and look for a contradiction. Specifically, following [27], assume there exists $t_1 > 0$ such that $I(t) < \bar{I}$ for all $t > t_1$ (this assumption includes the case of eradication, where $\lim_{t\to\infty} I(t) = 0$). Then we have $S' > \mu - (\mu + \beta\bar{I})S$ for $t > t_1$. Comparing to the system (5.10) we see that for any $\epsilon > 0$, there exists $t_2 > t_1$ such that $S(t) > \bar{S}(t) - \epsilon$ for all $t > t_2$. (So far this procedure is similar to the "General procedure" given in Section 4.3.1 but with a lower bound for S rather than an upper bound.) Choose ϵ small enough so that $\bar{\mathcal{R}}^* > 1 + \epsilon\frac{\beta}{\mu+\gamma}$.Then in this non-delay case,

$$\begin{aligned} I'(t) &= (\mu+\gamma)\left[\tfrac{\beta}{\mu+\gamma}S(t) - 1\right] I(t) \\ &> (\mu+\gamma)\left[\tfrac{\beta}{\mu+\gamma}\left(\bar{S}(t) - \epsilon\right) - 1\right] I(t) \text{ for } t > t_2 \\ \Rightarrow \quad &\tfrac{d}{dt}\left(I(t)e^{-(\mu+\gamma)\int_0^t \frac{\beta}{\mu+\gamma}\left(\bar{S}(s)-\epsilon\right)-1ds}\right) \quad > 0 \end{aligned}$$

Integrating from any $t^* > t_2$ to $t^* + \tau$,

$$\begin{aligned} I(t^*+\tau)e^{-(\mu+\gamma)\int_0^{t^*+\tau}\frac{\beta}{\mu+\gamma}\left(\bar{S}(s)-\epsilon\right)-1ds} - I(t^*)e^{-(\mu+\gamma)\int_0^{t^*}\frac{\beta}{\mu+\gamma}\left(\bar{S}(s)-\epsilon\right)-1ds} &> 0 \\ I(t^*+\tau)e^{-(\mu+\gamma)\int_0^{t^*+\tau}\frac{\beta}{\mu+\gamma}\left(\bar{S}(s)-\epsilon\right)-1ds} &> I(t^*)e^{-(\mu+\gamma)\int_0^{t^*}\frac{\beta}{\mu+\gamma}\left(\bar{S}(s)-\epsilon\right)-1ds} \\ I(t^*+\tau) &> I(t^*)e^{(\mu+\gamma)\int_{t^*}^{t^*+\tau}\frac{\beta}{\mu+\gamma}\left(\bar{S}(s)-\epsilon\right)-1ds} \\ &= I(t^*)e^{(\mu+\gamma)\left(\bar{\mathcal{R}}^*-(1+\epsilon\frac{\beta}{\mu+\gamma})\right)\tau} \end{aligned}$$

Since the exponent is a strictly positive constant (for small enough ϵ, that is, for t large enough), we get $I(t^* + \tau) > I(t^*)$ for any $t^* > t_2$. In particular, define $c := (\mu + \gamma)\left(\bar{\mathcal{R}}^* - (1 + \epsilon\frac{\beta}{\mu+\gamma})\right)\tau$ and we get $I(t^* + k\tau) > I(t^*)e^{ck} \to \infty$ as $k \to \infty$. This result contradicts the restriction (in this constant-population model) that $I(t) \leq 1$ for all t. Therefore we conclude that $I(t)$ is not less than $\bar{I}$ for all large t. If $I(t) \geq \bar{I}$ for all large t, then the permanence condition is satisfied automatically. The only other option is if $I(t)$ oscillates about $\bar{I}$ indefinitely.

In the oscillatory case, suppose now that $I(t_3) = \bar{I}$ for some $t_3 > t_2$ and that σ is the smallest positive constant such that $I(t_3 + \sigma) = \bar{I}$ and $I(t) \neq \bar{I}$ for $t \in (t_3, t_3 + \sigma)$.

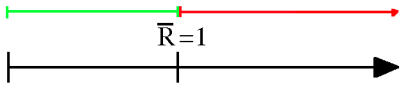

Fig. 5.2: Results on threshold values for bilinear incidence non-delay system.

- If $\sigma < \tau$ then since $I'(t) > -(\mu+\gamma)I(t)$ we have $I(t) > I(t_3)e^{-(\mu+\gamma)\sigma} = \bar{I}e^{-(\mu+\gamma)\sigma} > \bar{I}e^{-(\mu+\gamma)\tau} > 0$ for $t \in (t_3, t_3+\sigma)$.
- If $\sigma \geq \tau$ then let $\sigma = a\tau + b$ where $a, b \in \mathbb{Z}, a > 0$ and $b = \sigma \mod \tau$. We know from the above for $t \in (t_3, t_3 + a\tau]$ that $I(t) > I(t_3)e^{ca}$. Then for $t \in (t_3 + a\tau, t_3 + \sigma)$ we have $I(t) > I(t_3 + a\tau)e^{-(\mu+\gamma)b} > \bar{I}e^{ca}e^{-(\mu+\gamma)\tau} > \bar{I}e^{-(\mu+\gamma)\tau}$.

Since $t_3 > t_2$ was arbitrary then this result is true between any two times at which $I(t) = \bar{I}$. Therefore we have shown that if $\bar{\mathcal{R}} > 1$ then $I(t) > \bar{I}e^{-(\mu+\gamma)\tau} > 0$ for all $t > t_2$. Therefore the disease is permanent.

□

For $\bar{\mathcal{R}}$ close to 1, $\bar{I}$ and correspondingly $\bar{I}e^{-(\mu+\gamma)\tau}$ are very small. The important point, however, is that this bound is strictly positive so the disease is permanent. Suppose $\bar{I}e^{-(\mu+\gamma)\tau} \approx 0.0002$, in a population of one million individuals (and we need large populations to assume the model is continuous) this bound still translates into at least 200 infected at any given time.

Figure 5.2 summarizes the results so far for threshold values for System (5.8) (with common incidence term βSI). We have found that the time average $\bar{\mathcal{R}} = 1$ is the crucial threshold above which the disease is permanent and below which it is eradicated.

Now we look to extend our results to the general incidence delay model.

General Incidence

In the previous section we were able to show that if $\bar{\mathcal{R}} > 1$ the disease is permanent in the bilinear incidence non-delay model; now we consider general incidence, that is, the system (4.14) in the limit as $r \to 0$:

$$\begin{cases} S' &= \mu(1-S) - g(I,t)S \\ I' &= g(I,t)S - (\mu+\gamma+\alpha)I \quad t \neq k\tau, \quad k \in \mathbb{Z} \\ R' &= \gamma I - \mu R. \end{cases}$$

$$\begin{cases} S(k\tau) &= (1-p)S(k\tau^-) \\ I(k\tau) &= I(k\tau^-) \qquad\qquad t = k\tau \\ R(k\tau) &= R(k\tau) + pS(k\tau^-) \end{cases}$$

First we define the time-average $\bar{\lambda} := \frac{1}{\tau}\int_0^\tau \lambda(t)dt$. Then we again define $\bar{I}$ based on $\bar{\mathcal{R}}$:

$$\bar{I}(t) = \frac{\mu}{\lambda(t)}\left(\bar{\mathcal{R}} - 1\right). \tag{5.12}$$

This time we have that $\bar{I}$ is a function of t, but we notice that $\bar{I}$ from Equation (5.9) in the bilinear incidence subsection is a special case of the above, with $\lambda(t) \equiv \beta$.

Again we have that if $\bar{\mathcal{R}} > 1$ then $\bar{I}(t) > 0$ for all t. The main issue with general incidence arises from our constant-population model; as in the previous subsection we will look to show that $I(t)$ does not stay below $\bar{I}(t)$ forever beyond some threshold time, but if we can have $\bar{I}(t) \geq 1$ then we will find a contradiction. Such a case would arise if for some t we had $\lambda(t) \leq \mu(\bar{\mathcal{R}} - 1)$. As such we impose the restriction

$$\lambda(t) > \mu(\bar{\mathcal{R}} - 1) \tag{5.13}$$

for all $t \in [0, \tau]$, that is, $\lambda(t)$ cannot oscillate with too large an amplitude. ($\lambda(t)$ is just part of a bound for $\partial g(0,t)/\partial I$, however, so this does not directly restrict the amplitude of oscillation on $g(I,t)$.) If this condition is satisfied we will have that $\bar{I}(t)$ remains a valid compartment population. We note however that just because $\bar{I}(t) > 1$ for some t does not mean that $I(t)$ will be; we could have the case of oscillation about $\bar{I}(t)$, and so could have $I(t)$ remain less than one even if $\bar{I}(t)$ does not always.

Extending the bilinear incidence result to the time-varying incidence, we get that $\bar{\mathcal{R}} > 1 \Rightarrow \bar{\mathcal{R}}^* > 1$:

Claim 5. *Define $\bar{S}$ as the periodic solution to the system*

$$\begin{aligned} S'(t) &= \mu - (\mu + \lambda(t)\bar{I})S \quad = \mu - \mu\bar{\mathcal{R}}S, \quad t \neq k\tau \\ S(k\tau) &= (1-p)S(k\tau^-) \end{aligned} \tag{5.14}$$

Then if $\bar{\mathcal{R}} > 1$, we have

$$\bar{\mathcal{R}}^* := \frac{1}{\tau}\int_0^\tau \frac{\lambda(t)}{\mu+\gamma}\bar{S}(t)dt \quad > 1. \tag{5.15}$$

Proof. Although the incidence varies with time, the DE for $\bar{S}(t)$ has constant coefficients so we can easily integrate between pulses as before. We get the following values for the thresholds $\bar{\mathcal{R}}$ and $\bar{\mathcal{R}}^*$:

$$\begin{aligned} \bar{\mathcal{R}} &= \tfrac{1}{\mu+\gamma}\cdot\tfrac{1}{\tau}\textstyle\int_0^\tau \lambda(t)\tilde{S}(t)dt &&= \tfrac{1}{\mu+\gamma}\cdot\tfrac{1}{\tau}\textstyle\int_0^\tau \lambda(t)\left[1 - \frac{p}{1-(1-p)e^{-\mu\tau}}e^{-\mu(t-k\tau)}\right]dt \\ \bar{\mathcal{R}}^* &= \tfrac{1}{\mu+\gamma}\cdot\tfrac{1}{\tau}\textstyle\int_0^\tau \lambda(t)\bar{S}(t)dt &&= \tfrac{1}{\mu+\gamma}\cdot\tfrac{1}{\tau}\textstyle\int_0^\tau \lambda(t)\frac{1}{\bar{\mathcal{R}}}\left[1 - \frac{p}{1-(1-p)e^{-\mu\bar{\mathcal{R}}\tau}}e^{-\mu\bar{\mathcal{R}}(t-k\tau)}\right]dt \end{aligned}$$

So we have

$$\begin{aligned}\bar{\mathcal{R}}^* &= \frac{1}{\bar{\mathcal{R}}}\left[\bar{\mathcal{R}} + \frac{1}{\mu+\gamma}\cdot\frac{1}{\tau}\int_0^\tau \lambda(t)\left(\frac{p}{1-(1-p)e^{-\mu\tau}}e^{-\mu t} - \frac{p}{1-(1-p)e^{-\mu\bar{\mathcal{R}}\tau}}e^{-\mu\bar{\mathcal{R}}t}\right)dt\right] \\ &> 1 + \frac{1}{\bar{\mathcal{R}}}\cdot\frac{1}{\mu+\gamma}\cdot\frac{p}{1-(1-p)e^{-\mu\tau}}\cdot\frac{1}{\tau}\int_0^\tau \lambda(t)\left(e^{-\mu t} - e^{-\mu\bar{\mathcal{R}}t}\right)dt\end{aligned}$$

Since $\bar{\mathcal{R}} > 1$, $e^{-\mu t} - e^{-\mu\bar{\mathcal{R}}t} > 0$, and therefore $\bar{\mathcal{R}}^* > 1$. □

Theorem 22. *If $\bar{\mathcal{R}} > 1$ in System (5.4) then the disease is permanent.*

Remark. Theorem 21 is the special case of Theorem 22 with $g(I,t) = \lambda(t)I$ and $\lambda(t) \equiv \beta$. We presented it first so the initial analysis was simpler.

Proof. Proceeding as in the previous theorem, given $\bar{\mathcal{R}} > 1$, we assume that $I(t)$ stays "small" for all large t and look for a contradiction. Again following [27], assume there exists $t_1 > 0$ such that $I(t) < \bar{I}$ for all $t > t_1$. Then $S' = \mu - \mu S - g(I,t)S > \mu - (\mu + \lambda(t)I)S > \mu - (\mu + \lambda(t)\bar{I})S$ for $t > t_1$. Comparing to the system (5.14) we see that for any $\epsilon > 0$, there exists $t_2 > t_1$ such that $S(t) > \bar{S}(t) - \epsilon$ for all $t > t_2$. Choose ϵ small enough so that $\bar{\mathcal{R}}^* > 1 + \epsilon\frac{\bar{\lambda}}{\mu+\gamma}$. With β replaced by $\lambda(t)$ we follow the exact same derivation as for the bilinear incidence to get

$$\begin{aligned}I(t^*+\tau) &> I(t^*)e^{(\mu+\gamma)\int_{t^*}^{t^*+\tau}\frac{\lambda(t)}{\mu+\gamma}\left(\bar{S}(s)-\epsilon\right)-1\ ds} \\ &= I(t^*)e^{(\mu+\gamma)\left(\bar{\mathcal{R}}^* - \left[1+\epsilon\frac{\bar{\lambda}}{\mu+\gamma}\right]\right)\tau}\end{aligned}$$

Since the exponent is a strictly positive constant (for small enough ϵ, that is, for t large enough), we get $I(t^*+\tau) > I(t^*)$ for any $t^* > t_2$. In particular, define $c := (\mu+\gamma)\left(\bar{\mathcal{R}}^* - \left[1+\epsilon\frac{\bar{\lambda}}{\mu+\gamma}\right]\right)\tau$ and we get $I(t^*+k\tau) > I(t^*)e^{ck} \to \infty$ as $k \to \infty$. This result contradicts the restriction (in this constant-population model) that $I(t) \le 1$ for all t. Therefore we conclude that $I(t)$ is not less than $\bar{I}(t)$ for all large t.

Again, $I(t) \ge \bar{I}(t)$ for all large t, then the permanence condition is satisfied automatically. Otherwise, in the oscillatory case, suppose now that $I(t_3) = \bar{I}(t_3)$ for some $t_3 > t_2$ and that σ is the smallest positive constant such that $I(t_3+\sigma) = \bar{I}(t_3+\sigma)$ and $I(t) \ne \bar{I}(t)$ for $t \in (t_3, t_3+\sigma)$.

- If $\sigma < \tau$ then since $I'(t) > -(\mu+\gamma)I(t)$ we have $I(t) > I(t_3)e^{-(\mu+\gamma)\sigma} = \bar{I}(t_3)e^{-(\mu+\gamma)\sigma} > \bar{I}(t_3)e^{-(\mu+\gamma)\tau} > 0$ for $t \in (t_3, t_3+\sigma)$.
- If $\sigma \ge \tau$ then let $\sigma = a\tau + b$ where $a, b \in \mathbb{Z}, a > 0$ and $b = \sigma \mod \tau$. We know from the above for $t \in (t_3, t_3+a\tau]$ that $I(t) > I(t_3)e^{ca} = \bar{I}(t_3)e^{ca}$. Then for $t \in (t_3+a\tau, t_3+\sigma)$ we have $I(t) > I(t_3+a\tau)e^{-(\mu+\gamma)b} > \bar{I}(t_3)e^{ca}e^{-(\mu+\gamma)\tau} > \bar{I}(t_3)e^{-(\mu+\gamma)\tau}$.

Since $t_3 > t_2$ was arbitrary then this result is true between any two times at which $I(t) = \bar{I}(t)$. Recall $\bar{I}(t)$ is periodic and known so $\bar{I}(t_3)$ is a known, fixed value. Therefore we have shown that if $\bar{\mathcal{R}} > 1$ then $I(t) > \bar{I}(t)e^{-(\mu+\gamma)\tau} > 0$ for all $t > t_2$. Therefore the disease is permanent.

□

Thus we see that Figure 5.2 also summarizes the results for threshold values for System (5.4) (with general incidence term $g(I,t)S$). We have found that the time average $\bar{\mathcal{R}} = 1$ (defined as the period-average of the ratio of the coefficients of $I'(t)$, whatever the incidence) is the crucial threshold above which the disease is permanent and below which it is eradicated.

In the next subsection we give some simulations. Then in Section 5.2 we look to extend our results to the bilinear incidence delay model (4.7) and, if possible, the general incidence delay model (4.14).

5.1.3 Simulations

For our simulations we use the Matlab DDE solver dde23, explained by Shampine and Thompson in [67], even for ODE simulations (we simply set the delay to zero). For initial conditions we set $R(0) = 0$ and since we consider a normalized total population, we choose $S(0) = 0.5 = I(0)$.

We try to use physically realistic values for the parameters. The values consistently used are as listed in Table 5.1. The time unit is one year.

Parameters	
μ	$\frac{1}{70}$
τ	1
p	0.2
γ	2

Table 5.1: Parameters held constant during simulations.

$\mu = 1/70$ corresponds to an average life expectancy of 70 years. The pulse vaccination campaign is assumed to run once every year, with a conservative estimate of only 20% vaccination coverage.

Without delay, by solving System (5.4) with bilinear incidence $g(I,t) = \beta I$ for varying values of γ, we found that a longer recovery period $\frac{1}{\gamma}$ led to a higher infection peak population and longer-lasting epidemic. The results are shown in Figure 5.3. In order to increase the likelihood of a severe epidemic (with all other factors held constant), then, we set $\gamma = 2$ (a recovery period of 6 months) in subsequent simulations. For many diseases of interest (*e.g.* influenza, measles) this

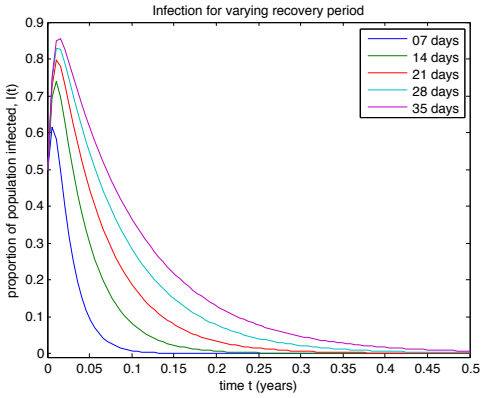

Fig. 5.3: Infective population in bilinear incidence SIR model with varying recovery period $1/\gamma$.

assumed recovery period is far longer than the real value, but we want to increase the visibility of the epidemic in these simulations.

Simulation results with varying values of $\bar{\mathcal{R}}$ are displayed in Figures 5.4 and 5.5, confirming the theoretical results for the bilinear incidence model without delay.

5.1.4 Model Adaptations: Vaccine Waning

In the event that the vaccine wanes, that is, the immunity conferred by vaccination is not permanent, then we will have the new model

$$\begin{aligned} S' =& \mu(1-\theta) - \mu S - g(I,t)S + \delta V \\ & \dots \\ V' =& \mu\theta - (\mu+\delta)V \end{aligned} \tag{5.16}$$

The addition of vaccine waning forces the model to be more cyclical (before, births could cause new susceptible individuals but at a very slow rate relative to the dynamics of the epidemic), but it does not directly affect the differential equation for $I(t)$. Thus if we can find out how the waning will affect the disease-free equilibrium solution $\tilde{S}(t)$ then we may be able to proceed as before from there.

The model (4.1) from [17], as with many epidemic models in the literature, expects a constant population $N(t) \equiv N$ which is normalized to $N = 1$, that is, the compartments are fractions of the population. Thus we notice

$$\begin{aligned} V &= 1 - S - I - R \\ &\leq 1 - S \end{aligned}$$

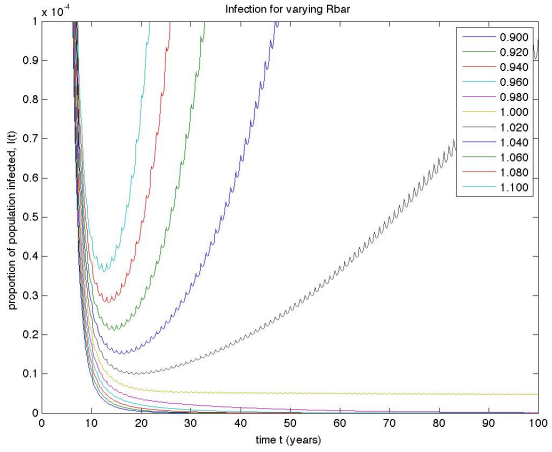

Fig. 5.4: Infective population for $\bar{\mathcal{R}}$ linearly spaced between 0.90 and 1.10.

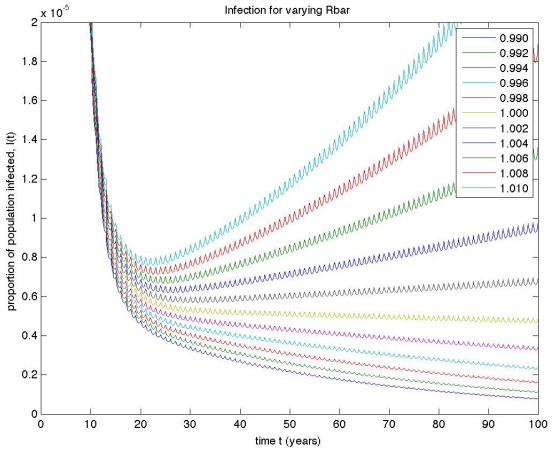

Fig. 5.5: $I(t)$ for $\bar{\mathcal{R}}$ linearly spaced between 0.99 and 1.01. Note difference in scale.

$$\begin{aligned}\Rightarrow S' &\leq \mu(1-\theta) - \mu S - g(I,t)S + \delta(1-S)\\ &\leq \mu(1-\theta) - \mu S + \delta(1-S)\\ &= [\mu(1-\theta)+\delta] - [\mu+\delta]S.\end{aligned}$$

We can use the pulse vaccination lemma to get

$$\begin{aligned}\tilde{S}_\delta(t) &= \frac{\mu(1-\theta)+\delta}{\mu+\delta} + \left(\frac{(\mu(1-\theta)+\delta)(1-p)(1-e^{-(\mu+\delta)\tau}}{(\mu+\delta)(1-(1-p)e^{-(\mu+\delta)\tau})} - \frac{\mu(1-\theta)+\delta}{\mu+\delta}e^{-(\mu+\delta)(t-k\tau)}\right)\\ &= \frac{\mu(1-\theta)+\delta}{\mu+\delta}\left[1+\left(\frac{(1-p)(1-e^{-(\mu+\delta)\tau})}{(1-(1-p)e^{-(\mu+\delta)\tau})}-1\right)e^{-(\mu+\delta)(t-k\tau)}\right]\\ &= \frac{\mu(1-\theta)+\delta}{\mu+\delta}\left[1-p\frac{e^{-(\mu+\delta)(t-k\tau)}}{(1-(1-p)e^{-(\mu+\delta)\tau})}\right].\end{aligned}$$

Then we note that for any $x > 0$

$$\begin{aligned}\mu+\delta &> \mu\\ e^{-(\mu+\delta)x} &< e^{-\mu x}\\ 1-(1-p)e^{-(\mu+\delta)x} &> 1-(1-p)e^{-\mu x}.\end{aligned}$$

So the numerator of the second term of $\tilde{S}_\delta$ is less than that of $\tilde{S}$, while the denominator is larger.

So the entire fraction in the second term is smaller for $\tilde{S}_\delta$ and we get that

$$\left[1 - p\frac{e^{-(\mu+\delta)(t-k\tau)}}{(1-(1-p)e^{-(\mu+\delta)\tau})}\right] > \left[1 - p\frac{e^{-\mu(t-k\tau)}}{(1-(1-p)e^{-\mu\tau})}\right]. \tag{5.17}$$

Then we consider the coefficients of $\tilde{S}_\delta$ ($\frac{\mu(1-\theta)+\delta}{\mu+\delta}$) and $\tilde{S}$ ($\frac{\mu(1-\theta)}{\mu}$):

$$\begin{aligned}\frac{\mu(1-\theta)}{\mu} &= 1-\theta, \quad \text{while} \\ \frac{\mu(1-\theta)+\delta}{\mu+\delta} &= \frac{\mu+\delta-\mu\theta}{\mu+\delta} = 1 - \frac{\mu}{\mu+\delta}\theta > 1-\theta\end{aligned}$$

From consideration of both factors of $\tilde{S}_\delta$ (the coefficient and the brackets) we get $\tilde{S}_\delta > \tilde{S}$. This result is as expected because physically if the vaccine could wear off, more susceptibles would become available leading to a more difficult process of eradicating the disease.

However we may now use the same process as in [17] to get the sufficient condition for eradication

$$\frac{1}{\tau}\int_0^\tau \lambda(t)\tilde{S}_\delta(t)dt \leq \mu + r. \tag{5.18}$$

That is, we now have

$$\begin{aligned}I' &= g(I,t)S - (\mu+r)I \\ &\leq [\lambda S - (\mu+r)]I \\ &\leq [\lambda(\tilde{S}_\delta + \epsilon) - (\mu+r)]I \quad \text{eventually,}\end{aligned}$$

so if the above condition (5.18) on the period-average is met the disease will be eradicated as $t \to \infty$.

5.2 Eradication and Permanence with Delay

5.2.1 Eradication in Delay Model with small $\mathcal{R}$

We consider (4.14) without disease mortality ($\alpha = 0$), reproduced here:

$$\begin{cases} S' &= \mu\,(1-S) - g(I,t)S \\ E' &= g(I,t)S - g(\ I(t-r), t-r\ )e^{-\mu r}S(t-r) - \mu E \\ I' &= g(\ I(t-r), t-r\ )e^{-\mu r}S(t-r) - (\mu+\gamma)I \\ R' &= \gamma I - \mu R \end{cases} \quad t \neq k\tau, \quad k \in \mathbb{Z}$$
$$\begin{cases} S(k\tau) &= (1-p)S(k\tau^-) \\ E(k\tau) &= E(k\tau^-) \\ I(k\tau) &= I(k\tau^-) \\ R(k\tau) &= R(k\tau) + pS(k\tau^-) \end{cases} \quad t = k\tau \tag{5.19}$$

This model is a combination of the delay model in [27] and the general incidence model in [17]. As in Section 4.3.1, the $e^{-\mu r}$ factor arises from natural deaths over the course of the latent period. In this general case we have that

$$E(t) = \int_{t-r}^{t} g(I(s), s)e^{-\mu(t-s)}S(s)ds.$$

We analyze the model based on the methods described in Section 4.3.1. The delay does not affect $S(t)$ directly, so we can say $S' \leq \mu(1-S)$ and look at an ODE comparison system

$$\begin{aligned} x' &= \mu(1-x), & t \neq k\tau \\ x(t) &= (1-p)x(t^-), & t = k\tau \end{aligned}$$

Using the procedure outlined after Lemma 1 of Section 4.3.1 we get that for any $\epsilon > 0$, $S(t) \leq \tilde{S}(t) + \epsilon$ eventually where $\tilde{S}(t)$ is the periodic solution defined by Equation (5.3). Then

$$\begin{aligned} I' &= g(I(t-r), t-r)e^{-\mu r}S(t-r) - (\mu + r + \alpha)I \\ &\leq [\lambda(t-r)e^{-\mu r}(\tilde{S}(t-r) + \epsilon)]I(t-r) - [\mu+\gamma]I(t) \end{aligned}$$

Because the delay term has positive coefficient we can use a comparison system with equality in the derivative:

$$y' = [\lambda(t-r)e^{-\mu r}(\tilde{S}(t-r) + \epsilon)] \cdot y(t-r) - [\mu+\gamma] \cdot y(t) \tag{5.20}$$

and get that if $I(t) = y(t)$ for $t \in [-r, 0]$, then $I(t) \leq y(t)$ for all $t \geq 0$. We define

$$\mathcal{R}(t) = \frac{\lambda(t)e^{-\mu r}\tilde{S}(t)}{\mu + \gamma}. \tag{5.21}$$

The question then is about the long-term behaviour of $y(t)$. We can use the Razumikhin approach of Theorem 13 by defining

$$V(t, y_t) := y_t^2(0) + (\mu + \gamma)\int_{-r}^{0} y_t^2(s)ds \tag{5.22}$$

$$= y^2(t) + (\mu + \gamma)\int_{t-r}^{t} y^2(s)ds \tag{5.23}$$

where $y_t(\sigma) = y(t + \sigma), \sigma \in [-r, 0]$. Theorem 13 is reprinted here:

Theorem 23. *Let w, W, and W_1 be continuous nondecreasing functions on $[0, H)$ which are zero at 0 and positive on $(0, H)$. Let $\|F(t, \psi)\| \leq B$ for some constant $B > 0$ for all $(t, \psi) \in (\alpha, \infty) \times C_D$. If there exists a functional V on $(\alpha, \infty) \times C_D$ such that*

1. *$V(t, \psi) \geq w(\|\psi(0)\|)$,*
2. *$V(t, \psi) \leq W(\|\psi\|_r)$, and*
3. *whenever $(t_0, \phi) \in (\alpha, \infty) \times C_D$ and $x = x(.; t_t, \phi)$ on $[t_0 - r, \beta_1)$ one has $\frac{d}{dt}V(t, x_t) \leq -W_1(\|x(t)\|)$ for $t_0 \leq t < \beta_1$,*

then the trivial solution of $x'(t) = F(t, x_t)$ is uniformly asymptotically stable.

Here $\mathcal{C}_D = C([-r, 0], D)$ where D is an open set in $\mathbb{R}$ (since y is a scalar). We are looking at Equation (5.20) so $F(t, \psi) = [\lambda(t-r)e^{-\mu r}(\tilde{S}(t-r)+\epsilon)]\psi(-r)-[\mu+\gamma]\psi(0)$. Note $\lambda(t)$ and $\tilde{S}(t)$ are periodic and bounded. Then, while we could theoretically have $D = \mathbb{R}$, if we have $D = (-H, H)$ we have $\|f(t, \psi)\| \leq H\left(\max_t \lambda(t)(\max_t \tilde{S}(t) + \epsilon) + [\mu + \gamma]\right) =: B$.

Let $a(u) = u^2$, then a is a class-$\mathcal{K}$ function for $u \geq 0$ and $V(t, y_t) \geq y^2(t) = y_t^2(0) = a(y_t(0)) \Rightarrow$ the first condition of "positive definiteness" is satisfied. The difference here is that we are considering V as a functional and not a function, but the condition is still based on $y(t)$, that is, on the current time. The second condition is easily met as well:

$$\begin{aligned} V(t, y_t) &:= y^2(t) + (\mu + \gamma)\int_{t-r}^{t} y^2(s)ds \\ &\leq \|y_t\|_r^2 + (\mu + \gamma)\int_{t-r}^{t} \|y_t\|_r^2 ds \\ &= \|y_t\|_r^2(1 + (\mu + \gamma)r) \end{aligned}$$

Then for the third condition, we take the derivative along solutions y of (5.20):

$$\begin{aligned}
\frac{dV}{dt} &= 2y(t)y'(t) + (\mu+\gamma)\left[y^2(t) - y^2(t-r)\right] \\
&= 2y(t)\left(\left[\lambda(t-r)e^{-\mu r}(\tilde{S}(t-r)+\epsilon)\right]y(t-r) - [\mu+\gamma]y(t)\right) + (\mu+\gamma)\left[y^2(t) - y^2(t-r)\right] \\
&= 2y(t)\left[\lambda(t-r)e^{-\mu r}(\tilde{S}(t-r)+\epsilon)\right]y(t-r) - (\mu+\gamma)\left[y^2(t) + y^2(t-r)\right] \\
&\leq 2|y(t)y(t-r)|\left[\lambda(t-r)e^{-\mu r}(\tilde{S}(t-r)+\epsilon)\right] - (\mu+\gamma)\left[y^2(t) + y^2(t-r)\right] \\
&\leq \left[y^2(t) + y^2(t-r)\right]\left[\lambda(t-r)e^{-\mu r}(\tilde{S}(t-r)+\epsilon)\right] - (\mu+\gamma)\left[y^2(t) + y^2(t-r)\right] \\
&= \left[y^2(t) + y^2(t-r)\right]\left[\lambda(t-r)e^{-\mu r}(\tilde{S}(t-r)+\epsilon) - (\mu+\gamma)\right] \\
&\leq y^2(t)\left[\lambda(t-r)e^{-\mu r}(\tilde{S}(t-r)+\epsilon) - (\mu+\gamma)\right]
\end{aligned}$$

For the simple functional we're using, we can just drop $y^2(t-r)$ at the end of dV/dt, so long as $\lambda(t)e^{-\mu r}\tilde{S}(t) - (\mu+\gamma) < 0$ for all t. That is, so long as $\mathcal{R}(t) < 1$ for all t, we recover the same threshold condition as usual; although our functional depended on y_t, that dependence was simple enough that the derivative dependence could be reduced to a dependence on y at the current time level, $y(t)$. (Note that because of the strict inequality, we will still have $\lambda(t)e^{-\mu r}(\tilde{S}(t)+\epsilon) - (\mu+\gamma) < 0$ if ϵ is small enough.)

In this theorem we are so far only able to look at a condition based on the maximum value of the functions $\lambda(t)$ and $\tilde{S}(t)$. That is, we needed $\mathcal{R}(t) < 1$ for all t. Is there some result such as in Section 5.1 we can find based on if, say, the *average* value of $\mathcal{R}$ is less than 1? This question will be addressed in the next subsection.

5.2.2 Eradication with Delay

We again consider model (5.19).The delay does not affect $S'(t)$ directly, so we proceed as before to get that for any $\epsilon > 0$, $S(t) \leq \tilde{S}(t) + \epsilon$ eventually where $\tilde{S}(t)$ is as in Equation (5.3). Then

$$\begin{aligned}
I' &= g(I(t-r), t-r)e^{-\mu r}S(t-r) - (\mu + r + \alpha)I \\
&\leq [\lambda(t-r)e^{-\mu r}(\tilde{S}(t-r)+\epsilon)]I(t-r) - [\mu+\gamma]I(t)
\end{aligned}$$

We would like to use a Razumikhin-style approach by defining a positive definite, decrescent functional V satisfying the conditions of Theorem 13. In the process of choosing one, however, we instead find a different useful functional: define

$$\tilde{V}(t, I_t) := I(t) + \int_{t-r}^{t} g(I, s)(\tilde{S}(s)+\epsilon)e^{-\mu r}ds, \tag{5.24}$$

Then we would have that $\tilde{V}(t, I_t) \geq I(t) = \|I_t(0)\|$ and $\tilde{V}(t, I_t) \leq \|I_t\|_r \left[1 + \int_{t-r}^{t} \lambda(s)(\tilde{S}(s) + \epsilon)e^{-\mu(t-s)}ds\right]$, satisfying the first two conditions of Theorem 13. Depending on $\lambda(t)$, though, the third condition is not immediately apparent. Even with bilinear incidence we only get $V' \leq -w_1(I(t))$ if $\beta e^{-\mu r}\tilde{S}(t) < \mu + \gamma$ for *all* $t \in [0, \tau]$.

Instead we decide to look at bounds on the delay. Because the delay term has positive coefficient we again use the comparison system (5.20) with equality in the derivative:

$$y' = [\lambda(t-r)e^{-\mu r}(\tilde{S}(t-r) + \epsilon)] \cdot y(t-r) - [\mu + \gamma] \cdot y(t) \tag{5.25}$$

and get that if $I(t) = y(t)$ for $t \in [-r, 0]$, then $I(t) \leq y(t)$ for all $t \geq 0$.

We can apply the theorems of Section 3.2.3 to the periodic delay system (5.20) (used as a comparison system for $I'(t)$) as follows. We use the same idea as in Example 34-3 of [18]. Rewrite Equation (5.20) as

$$\begin{aligned} y'(t) &= \lambda(t-r)e^{-\mu r}(\tilde{S}(t-r) + \epsilon) \cdot y(t-r) - (\mu + \gamma) \cdot y(t) \\ &= [\lambda(t-r)e^{-\mu r}(\tilde{S}(t-r) + \epsilon) - (\mu + \gamma)] \cdot y(t) + \lambda(t-r)e^{-\mu r}(\tilde{S}(t-r) + \epsilon) \cdot [y(t-r) - y(t)] \\ &=: a(t)y(t) + h(t, y_t) \end{aligned}$$

Despite the shift in t by $-r$, since both $\lambda(t)$ and $\tilde{S}(t)$ are known we define the coefficient $a(t)$ of the $y(t)$ term as a function of the current time t only. We are interested in solutions of the linear part of (5.20),

$$x'(t) = a(t)x(t) = \left[\lambda(t-r)e^{-\mu r}(\tilde{S}(t-r) + \epsilon) - (\mu + \gamma)\right] x(t). \tag{5.26}$$

(Note that $a(t)$ would generally be a matrix-valued function, but here in our scalar equation we have $a : \mathbb{R} \mapsto \mathbb{R}$.)

Since shifting $\lambda(t)$ and $\tilde{S}(t)$ does not affect their time-average over a pulse period τ, from Section 5.1.1 we know that if $\bar{\mathcal{R}} < 1$, then the trivial solution of (5.26) is UAS. We now want to apply Theorem 15 to the DE for $y(t)$.

Eradication under Small Delay

For condition *(i)* of Theorem 15, we notice

$$\begin{array}{rcl} \|f(t, y_t) - f(t, \tilde{y}_t)\| & = & \| \lambda(t-r)e^{-\mu r}(\tilde{S}(t-r) + \epsilon)[y(t-r) - \tilde{y}(t-r)] \quad - \quad (\mu + \gamma)[y(t) - \tilde{y}(t)] \| \\ & \leq & \lambda(t-r)e^{-\mu r}(\tilde{S}(t-r) + \epsilon) \cdot \|y(t-r) - \tilde{y}(t-r)\| \quad + \quad (\mu + \gamma) \cdot \|y(t) - \tilde{y}(t)\| \\ & \leq & \left(\lambda(t-r)e^{-\mu r}(\tilde{S}(t-r) + \epsilon) + (\mu + \gamma)\right) \|y_t - \tilde{y}_t\|_r \end{array}$$

so if we take

$$K = \lambda^M e^{-\mu r}(\tilde{S}^M + \epsilon) + (\mu + \gamma)$$

where $\lambda^M := \max_{t\in[0,\tau]} \lambda(t)$ (and recall $\tilde{S}^M$ is defined similarly), then the global Lipschitz condition is satisfied.

For condition *(ii)*, notice that $\|y(t-r) - y(t)\| \leq \max_{-r\leq s\leq 0}\|y'(t)\|r = \|y'_t\|_r r$. So for $h(t, y_t) = \lambda(t-r)e^{-\mu r}(\tilde{S}(t-r) + \epsilon)[y(t-r) - y(t)]$ we have

$$\|h(t, y_t)\| \leq \lambda(t-r)e^{-\mu r}(\tilde{S}(t-r) + \epsilon)\|y'_t\|_r r$$

Define

$$N := r\lambda^M e^{-\mu r}(\tilde{S}^M + \epsilon)K,$$

then we have

$$\begin{aligned}\|h(t, y_t)\| &\leq r\lambda(t-r)e^{-\mu r}(\tilde{S}(t-r) + \epsilon)\|y'_t\|_r \\ &\leq r\lambda^M e^{-\mu r}(\tilde{S}^M + \epsilon)\|y'_t\|_r \\ &= N\frac{\|y'_t\|_r}{K}.\end{aligned}$$

Condition *(ii)* is then satisfied so long as

$$\begin{aligned} & r\lambda^M e^{-\mu r}(\tilde{S}^M + \epsilon)K = N < \frac{\eta}{M} \\ \Rightarrow\ & r\ \lambda^M e^{-\mu r}(\tilde{S}^M + \epsilon)\left(\lambda^M e^{-\mu r}(\tilde{S}^M + \epsilon) + (\mu + \gamma)\right) < \epsilon\alpha e^{-\tau(a^M + \epsilon\alpha)} \end{aligned} \tag{5.27}$$

where $\alpha := \frac{1}{\tau}\int_{t_0}^{t_0+\tau} \lambda(t)dt$, $a^M = \max_{t\in[0,\tau]}|\lambda(t)(\tilde{S}(t) + \epsilon) - (\mu + \gamma)|$, and η and M were obtained in Section 5.1.1. We can choose ϵ to be arbitrarily small. Assuming we can satisfy this inequality then for small enough delay the periodic delay system is also uniformly asymptotically stable.

Note that in (5.27) we have returned to a condition on the maximum of the functions $\lambda(t)$ and $\tilde{S}(t)$, but the weaker condition on the time-average of these functions was useable for the asymptotic stability of the linear part.

From earlier we have that $M := e^{(a^M + \epsilon\alpha)\tau}$ and $\eta := \epsilon\alpha = \epsilon\frac{1}{\tau}\int_{t_0}^{t_0+\tau} \lambda(t)dt$. The condition then becomes

$$r < \frac{e^{-(a^M + \epsilon\alpha)\tau}}{\lambda^M e^{-\mu r}(\tilde{S}^M + \epsilon)} \cdot \frac{\epsilon\frac{1}{\tau}\int_{t_0}^{t_0+\tau} \lambda(t)dt}{\lambda^M e^{-\mu r}(\tilde{S}^M + \epsilon) + (\mu + \gamma)}$$

where $\epsilon > 0$ is fixed but arbitrary (we could and maybe should choose it as large as we like).

Simulation results for bilinear incidence agree with the theoretical work in this section, even for relatively large delay. Figure 5.6 displays infective populations with $\bar{\mathcal{R}} = 0.90$ over a short

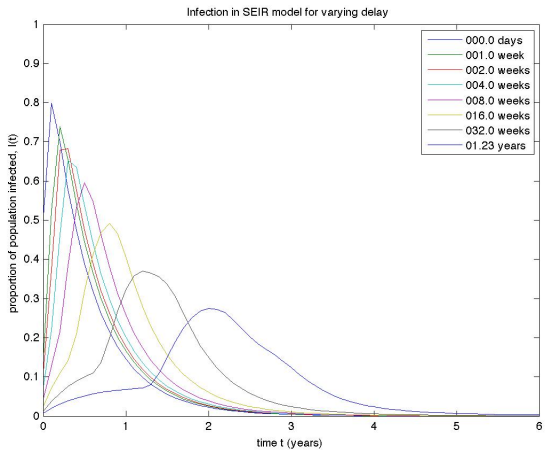

Fig. 5.6: Infective population for varying r with $\bar{\mathcal{R}} = 0.90$.

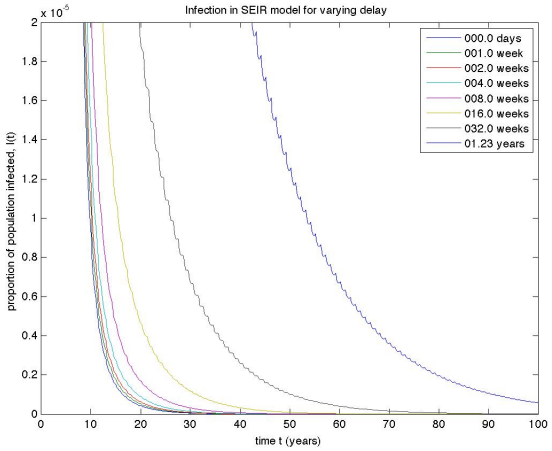

Fig. 5.7: Smaller scale of Figure 5.6 with t over 100 years.

time (6 years) for varying delays; despite the coarse time scale, we see that the infections all appear to die out. Figure 5.7 extends these results to 100 years with a much smaller y-axis scale. We see that even to 10^{-5} the infectives appear to be dying out, although longer delay does appear to defer the eradication.

Comparison to Model without Pulse Vaccination

If there was no pulse vaccination (PV) in System (4.7) then the threshold condition for eradication would reduce to $1 > \mathcal{R}_0 := \frac{\beta e^{-\mu r}}{\mu+\gamma}$. Comparing this condition to $\bar{\mathcal{R}} < 1$ and using our knowledge of $\tilde{S}$ we see that $\bar{\mathcal{R}} = \mathcal{R}_0 \int_0^\tau \tilde{S}(t)dt = \mathcal{R}_0 \cdot \left[1 - \frac{p}{1-(1-p)e^{-\mu\tau}} \cdot \frac{1-e^{-\mu\tau}}{\mu\tau}\right]$ ($\tilde{S}$ is given explicitly in (5.3) and easily integrated). For the parameter values used in our simulation (see Table 5.1 of Section 5.2.3) we have $\bar{\mathcal{R}} \approx \mathcal{R}_0[1 - 0.94] << \mathcal{R}_0$ so we expect eradication in the PV model for values that would not lead to eradication otherwise. Figure 5.8, with $\bar{\mathcal{R}} = 1.10$, confirms that with PV the infection dies out more quickly, while the susceptible population is kept small.

5.2.3 Permanence with Delay: Simulations

Determining the effects of delay on permanence is unfortunately more difficult than eradication, so we turn to simulation results for now.

To obtain the figures in this section, as well as Figures 5.6 and 5.7, we again use the Matlab DDE solver dde23. For initial conditions, we pick $R(0) = 0$. We choose an exponentially growing

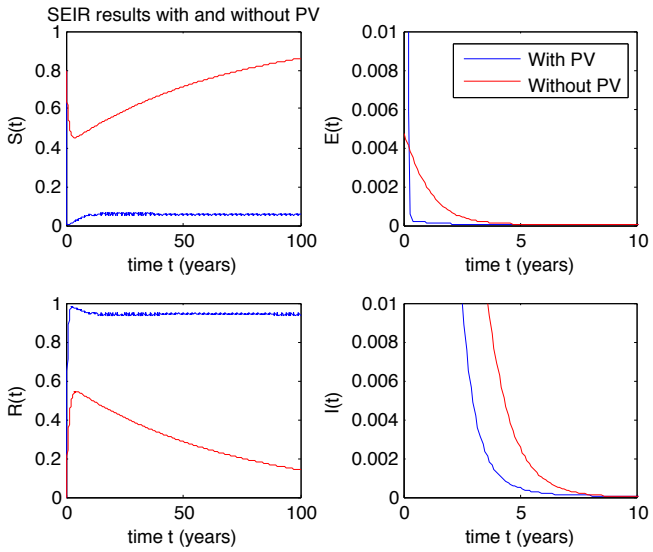

Fig. 5.8: Bilinear incidence SEIR model, $\bar{\mathcal{R}} = 1.1$, with and without pulse vaccination.

infective population $I(t) = be^{\mu t}$ for $t \in [-r, 0]$, an exponentially shrinking susceptible population $S(t) = ae^{-\mu t}$ for $t \in [-r, 0]$, and we determine $E(0)$ based on Equation 4.8, reprinted here for $t = 0$:

$$E(0) = \int_{-r}^{0} \beta e^{\mu s} S(s) I(s) ds. \tag{5.28}$$

We choose $a = 0.8$ and b is then fixed because we need $S(0) + E(0) + I(0) = 1$.

We use the parameter values from Table 5.1 of Section 5.1. with delay $r = 5$ days to consider the SEIR model (4.7) for different values of $\bar{\mathcal{R}}$, that is, we are varying β.

Like for the SIR model, in Figure 5.9 we again see that when $\bar{\mathcal{R}} \leq 1$ the disease appears to be dying off. (The $\bar{\mathcal{R}} = 1$ case was not discussed in this project but in reality would be pathological.) "Zooming in," in Figure 5.10 we see that even for values of $\bar{\mathcal{R}}$ very near to 1, $\bar{\mathcal{R}} = 1$ appears to be the threshold above which the disease eventually stops decreasing over time, and below which the disease dies out.

In Figure 5.6 of Section 5.2.2 we set $\bar{\mathcal{R}} = 0.90$ and ran simulations for varying delay. Figure 5.11 repeats this process for $\bar{\mathcal{R}} = 1.10$, that is, under conditions that would lead to endemic disease if there were no delay. Comparing Figure 5.6 to Figure 5.11 we note that in the short term the effects of the value of $\bar{\mathcal{R}}$ are barely distinguishable. Over the longer term, however, (comparing Figures 5.7 and 5.12) we see that $\bar{\mathcal{R}} = 1.10$ leads to a clearly endemic disease state with infected fraction on the order of 10^{-3}, while $\bar{\mathcal{R}} = 0.90$ leads to eradication, at least to the order of 10^{-5}.

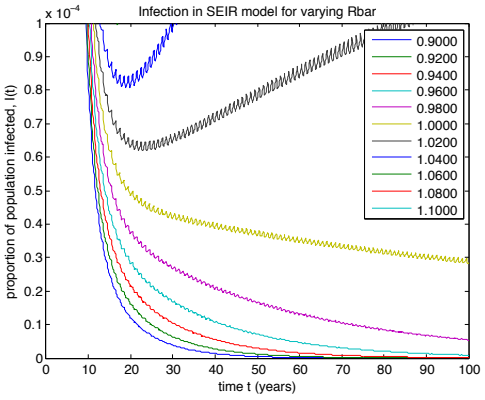

Fig. 5.9: Infective population in delay model for $\bar{\mathcal{R}}$ linearly spaced between 0.90 and 1.10.

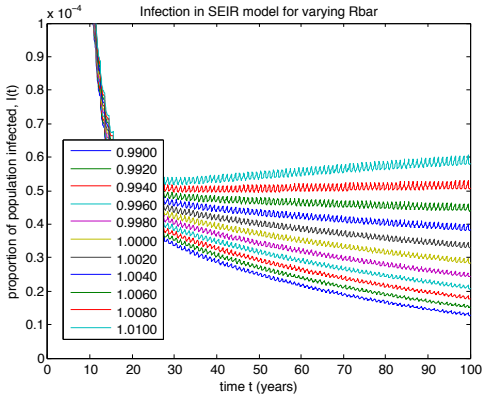

Fig. 5.10: $I(t)$ for $\bar{\mathcal{R}}$ linearly spaced between 0.99 and 1.01. Note difference in scale.

In Figures 5.6, 5.7, 5.11, and 5.12 the maximum delay was still only about 64 weeks. Without delay $\bar{\mathcal{R}} = 1$ was a sharp threshold between eradication and permanence, and it appears from these figures that it may be so for delay as well. In Figure 5.13 we set $\bar{\mathcal{R}} = 1$ and vary the delay between 2 and 9 years. While the trajectory of the infective population becomes very erratic, it doesn't seem as though the delay has upset the threshold yet. It may still be the case for larger delays, though.

All of these simulations were run for a bilinear incidence model; future work involves extension to time-varying incidence $g(I, t)$.

5.2.4 Model Adaptations: Accidental Vaccination of Exposed Class

Suppose we are implementing a pulse vaccination campaign aimed at vaccinating a fraction p of the susceptible population with each pulse. Those in the exposed or even infective classes, however, may not be showing symptoms yet: individuals move from E to I after the *latent* period during which they are not contagious. The so-called *incubation* period, however, is the time until an individual shows symptoms, and may be greater than the latent period, so there could be infectives not yet showing symptoms. Therefore there is a possibility the campaign will inadvertently vaccinate some exposed or infective individuals.

Without structure based on age or spatial distribution, though, these models (such as (5.8) and (5.19)) are assuming a homogeneous distribution of the population. In particular the mass-action incidence βSI does so, but even the more general $g(I, t)S$ assumes even mixing. Thus if we are aiming to vaccinate a fraction p of S, we may in fact end up also vaccinating a fraction p

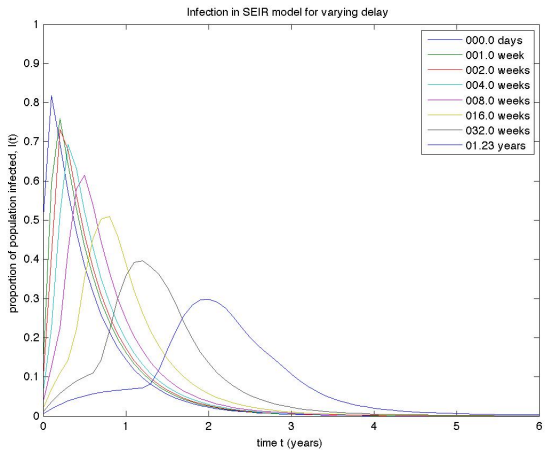

Fig. 5.11: Infective population for varying r with $\bar{\mathcal{R}} = 1.10$.

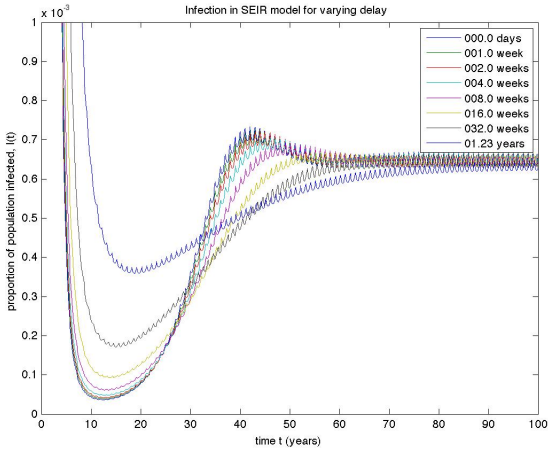

Fig. 5.12: Smaller scale of Figure 5.11 with t extended over 100 years.

of E and I as well. The PV part of model (5.19) could become:

$$\begin{aligned} S(k\tau) &= (1-p)S(k\tau^-) \\ E(k\tau) &= (1-p)E(k\tau^-) \\ I(k\tau) &= (1-p)I(k\tau^-) \\ R(k\tau) &= R(k\tau^-) + p[S(k\tau^-) + E(k\tau^-) + I(k\tau^-)] \end{aligned}$$

Note that this model assumes that the vaccination can somehow help to treat or cure the exposed and infective people, or maybe that exposed and infective individuals can be identified by the campaign and treated quickly. In the next subsections we consider the mathematical ramifications in such a case.

It may be more likely that the pulse does not affect E or I at all; in that case, we are still vaccinating the fraction p of S that we were planning on, but unfortunately resources are being wasted in giving vaccinations to those for whom it is too late. In terms of policy-making and cost-effectiveness it is important to not waste resources.

Models without delay

In a non-delay model similar to (4.5), with rate δ leaving the latent period, we have introduced discontinuity into E and I (not just their derivatives), but the compartments are still piecewise continuous. Between pulses we can apply the same analyses as before; at the pulses, the factor $0 \leq (1-p) \leq 1$ only serves to help decrease the infective populations.

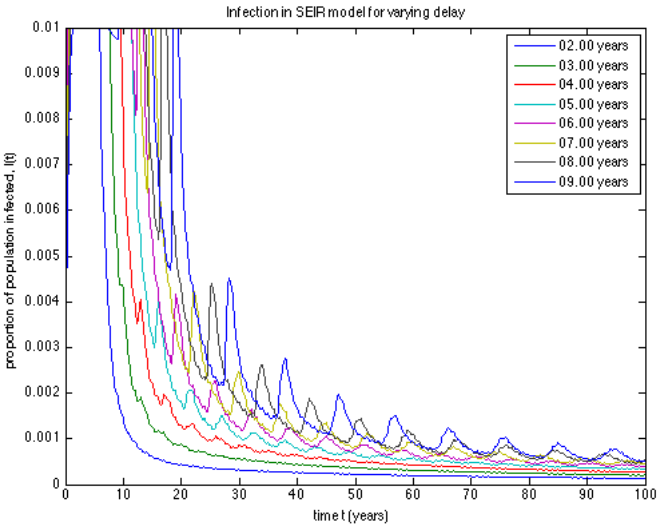

Fig. 5.13: Infective population for varying r with $\bar{\mathcal{R}} = 1.0$.

That is, we can still use the usual bounds $S' \leq \mu(1-\theta) - \mu S$ and find that we have the same globally attractive disease-free solution as obtained in [17] and [27]. In an SIR model without an exposed class, since everything in $I'(t)$ depends on only the current time t, for $t \neq k\tau$ we can again use the bounds $I'(t) \leq [\lambda(\tilde{S} + \epsilon) - (\mu + r)]I$ eventually to show that $I(t)$ is decreasing between pulses: by the condition (4.6) we have $I' < 0$. With an exposed class we can use the Lyapunov function approach as in [17]. Then at the pulses we have $I(k\tau)$ instantaneously decreasing further, and so we get that inadvertent treatment does not adversely affect the eradication of the disease.

In fact, even if only exposed individuals were likely to attend vaccination campaigns (and so $I(t)$ remained continuous and unchanged at the pulses), we would use the Lyapunov function approach with $L := \frac{\delta}{\delta - \gamma}E + I$ to get:

$$\begin{aligned} L' =& \frac{\delta}{\delta - \gamma}\left[g(I,t)S - (\mu + \delta)E\right] + \delta E - (\mu + \gamma)I \\ =& \dots \\ =& \frac{\delta}{\delta - \gamma}g(I,t)S - (\mu + \gamma)L \\ \leq& \frac{\delta}{\delta - \gamma}\left[\lambda(\tilde{S} + \epsilon) - \frac{\delta - \gamma}{\delta}(\mu + \gamma)\right]L \end{aligned}$$

Between pulses everything is exactly as before; at the pulses $I(t)$ is not directly affected, while $L(t)$ is only decreased because of the $(1-p)E$. Hence we still have $I(t) \to 0$ as $t \to \infty$.

A problem may arise, however, if instead of aiming to vaccinate a proportion p of the susceptibles, we determined say what that fraction would be in hard numbers and aimed to vaccinate that many (as a fraction of the total population N). That is, say we estimate a population of $1,000,000$ is 60% susceptible. Then we try to vaccinate 50% of the susceptibles, translating it into a goal of $300,000$ people. However, if use this hard number and vaccinate the set amount of people, we could have exposed or even infected people skewing the data and only wind up vaccinating less than 50% of the susceptibles. How much such an issue would affect the total depends on how large the exposed and infective populations are - at the verge of an outbreak, when many could be infected without knowing it yet, it would have more of an effect than if a disease is under control and a nearly-negligible number of people have it.

Mathematically, say we aim to vaccinate a total pS of the population. Assuming an equal distribution of S, E, and I, we could have

$$\begin{aligned} pS &= \bar{p}S + \bar{p}E + \bar{p}I \\ \Rightarrow p &= \bar{p}\left[1 + \frac{E+I}{S}\right] \\ \bar{p} &= \frac{p}{\left[1 + \frac{E+I}{S}\right]} \end{aligned}$$

Then we are only vaccinating a smaller fraction $\bar{p}$ of S, since $\frac{E+I}{S} > 0$. So long as the eradication condition (period-average) holds with the resulting larger $\tilde{S}_{\bar{p}}$ we will still have eradication, but campaign failure or ineffectiveness could otherwise result.

Models with Delay: Physical Well-Posedness

An important model issue becomes apparent with the accidental pulse treatment of exposed populations. Figure 5.14 shows the exposed population in the bilinear incidence SEIR model (4.7) with delay, with and without pulse treatment of $E(t)$. With pulse treatment, that is, removing a fraction p of $E(t)$ every τ time units, the population clearly becomes negative. Pulse removal of a fraction of E affects its DE only through the small $-\mu E$ term; the $-\beta S(t-r)I(t-r)$ term still causes a large decrease which, as shown in the figure, can drive E below zero.

In the model, we can see by integrating that $E(t) = \int_{t-r}^{t} \beta e^{-\mu(t-s)} I(s)S(s)ds$, but this result does not come across in the simulations (and incorporating it directly will lead to issues near the pulse times). Future work may need to involve incorporating the integral equation into the simulations.

We note that without pulse treatment of $E(t)$ the model remains well-defined and the set Ω_4 is invariant. Even with pulse treatment we have that (S, I) remain in $\{(S, I) : 0 \leq S, I; S + I \leq 1\}$, and it is only $R(t)$ that may be growing greater than 1. We further note that pulse treatment

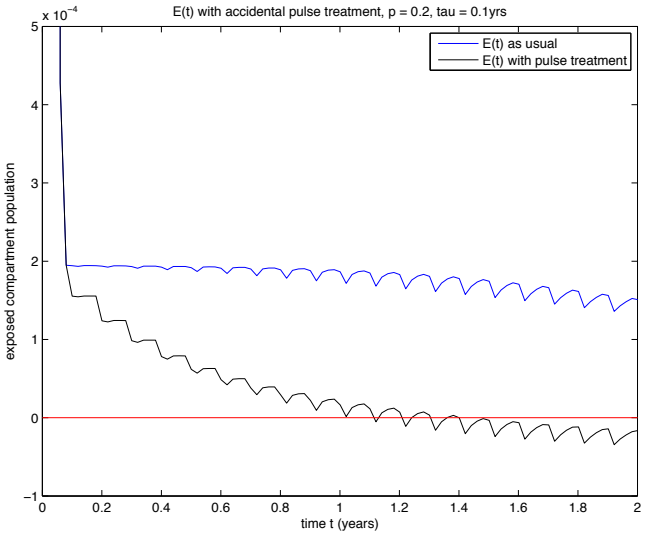

Fig. 5.14: $E(t)$ with and without pulse treatment.

may be unrealistic, at least on the same order as the pulse vaccination is effective; it is at least unlikely that the vaccines will spontaneously cure the entire fraction p of $E(t)$.

5.3 Existence of Periodic Solutions

We have so far been trying to look at the time-average of the coefficients of our non-autonomous bounding equation for $I'(t)$,

$$x'(t) = (e^{-\mu r}\lambda(t-r)\tilde{S}(t-r))x(t-r) - (\mu+\gamma)x(t). \tag{5.29}$$

An alternative method, used in many references (such as Cheng and Zhang [10] and Yan [79]), is to look for the existence of periodic solutions to Equation (5.29). In Appendix A we adapt theorems from [79] for equations of the form

$$\begin{cases} y'(t) = h(t, y(t)) - \eta f(t, y(t-\tau(t)), & t \in \mathbb{R}, t \neq t_k \\ y(t_k^+) - y(t_k^-) = \xi I_k(t_k, y(t_k - r(t_k))), & k \in \mathbb{Z} \end{cases} \tag{5.30}$$

to equations with opposite sign in the derivative of y. Then we are able to apply these theorems to find a threshold $\mathcal{R}_{per}$ below which there can be no periodic solution of (5.29). Our hope is that $\mathcal{R}_{per} < \mathcal{R}^*$, sharpening our current results. Unfortunately, when we compare this threshold $\mathcal{R}_{per}$ to $\mathcal{R}^*$ we find that it is almost surely larger, for reasonably physical choices of parameters, by a fair margin. Appendix A gives much more detail.

Chapter 6

Models with Varying Total Population Size

In this section we look to generalize our threshold results from the previous section to time-varying populations. For consistency we will use models with the common bilinear and standard incidences in order to illustrate the time-varying methods. We will use systems without delay for the most part, since we have shown in Section 5.2 that for small delay, uniform asymptotic stability of the non-delay system implies UAS of the delay system. We will discuss the effects of time-varying populations on the results in the previous section, then in Sections 6.3 and 6.4 we will look at generalizations to other incidence forms.

In the sections where $N(t)$ is not constant we will introduce the disease death rate α, that is, $I'(t) = \ldots - (\mu + \gamma + \alpha)I$. In the previous work we have always assumed $\alpha = 0$.

6.1 Constant Non-normalized Population $N \neq 1$

As explained in Section 2.2.3, in Systems (5.4) and (5.19) the initial term in the DE for $S'(t)$, "$\mu \cdot 1$", arose from the constant population size which was normalized to 1. With a time-varying population $N(t)$ we might instead assume, for example, that the births are proportional to N ("$\mu \cdot N$"), or proportional to some carrying capacity K. This assumption, however, leads to a necessary change in the bilinear incidence model, as described in Hethcote [36]: in particular, we use the standard incidence $\beta \frac{SI}{N}$ described in Section 2.2.3.

This new incidence does not mean that our prior calculations were wrong, however. If we

take the SIR model with standard incidence:

$$\begin{cases} S' &= \mu(N-S) - \beta\frac{I}{N}S \\ I' &= \beta\frac{I}{N}S - (\mu+\gamma)I \qquad\qquad t \neq k\tau \\ R' &= \gamma I - \mu R \end{cases}$$
$$\begin{cases} S(k\tau) &= (1-p)S(k\tau^-) \\ I(k\tau) &= I(k\tau^-) \qquad\qquad t = k\tau \\ R(k\tau) &= R(k\tau^-) + pS(k\tau^-) \end{cases} \tag{6.1}$$

and make the change of variables $s = \frac{S}{N}, i = \frac{I}{N}, r = \frac{R}{N}$, then dividing each equation of System (6.1) by N we get

$$\begin{cases} \frac{S'}{N} &= \mu\frac{N-S}{N} - \beta\frac{S}{N}\frac{I}{N} \\ \frac{I'}{N} &= \beta\frac{S}{N}\frac{I}{N} - (\mu+\gamma)\frac{I}{N} \\ \frac{R'}{N} &= \gamma\frac{I}{N} - \mu\frac{R}{N} \end{cases} \Rightarrow \begin{cases} s' &= \mu(1-s) - \beta si \\ i' &= \beta si - (\mu+\gamma)i \\ r' &= \gamma i - \mu r. \end{cases}$$

Because the pulse vaccination reaches a proportion of the susceptible population S, it reaches the same proportion of s:

$$\begin{aligned} S(k\tau) &= (1-p)\cdot S(k\tau^-) \\ N(k\tau)s(k\tau^+) &= (1-p)\cdot N(k\tau^-)s(k\tau^-) \\ \Rightarrow s(k\tau) &= (1-p)\cdot s(k\tau^-) \end{aligned}$$

since $N(t)$ remains unchanged across the pulse times.

This system (6.1) is equivalent to System (5.8) that we have been analyzing (the same result holds for the SEIR model). Thus in the constant-population model we can assume $N \neq 1$.

Our threshold results from previous sections still hold; for example, we notice that we still have $S'(t) \geq \mu N - \mu S$ where N is a constant. The comparison theorem with equality, by Lemma 1, leads to the globally attractive periodic solution

$$\tilde{S}_N(t) = \frac{\mu N}{\mu}\left[1 - \frac{p}{(1-(1-p)e^{-\mu\tau})}e^{-\mu(t-k\tau)}\right], \quad k\tau \leq t < (k+1)\tau,$$

and we realize that $\tilde{S}_N(t) = N\cdot\tilde{S}(t)$ where $\tilde{S}(t)$ is as we have been using in previous sections. Then we note from (6.1) that eventually

$$\begin{aligned} I'(t) &< \beta\frac{\tilde{S}_N + \epsilon}{N}I - (\mu+\gamma)I \\ &= \beta(\tilde{S} + \epsilon')I - (\mu+\gamma)I \end{aligned}$$

and so our results depending on $\bar{\mathcal{R}}$, which was based on $\tilde{S}$, are still crucial in leading to eradication of the system. Even though we are looking at the exact number of infectives rather than the proportion of the population, we easily reduce the system to a DE with the exact same coefficients (besides the arbitrarily small ϵ, ϵ') as when we analyzed the normalized model. The other results for the normalized system similarly carry over to when $N \neq 1$.

There may be issues if we build a model with births dependent on $N(t)$ but keep the bilinear incidence, because the simple change of variables no longer tranforms the system to the familar system 5.8. If $N(t) \equiv N$ then the issue is handled in the next section in the same way as with a carrying capacity. Otherwise the analysis is trickier; non-constant, non-logistic N, as well as extensions to other incidence forms such as the general incidence $g(I, t)$, will be looked at in Sections 6.3 and 6.4.

6.2 Carrying Capacity K

Assuming a constant birth rate A is equivalent to a carrying capacity K with $A = \mu K$. (Alternatively, if the birth rate b is different from the death rate μ, we may have really decided that $A = bK'$ for some K'. Since we are dealing with constants, however, we can just assume the factor of μ instead.) The differential equation for the total population then becomes

$$N' = \mu K - \mu N - \alpha I. \tag{6.2}$$

This approach is common in literature concerning pulse vaccination with time-varying total population size [26, 54, 57, 76, 81, 83]. There is an unfortunate issue with the model definition: without an equation of the form $N' = N \cdot f(N)$ for some f, we have that $N = 0$ is no longer an equilibrium point and a population can arise from nothing. In this section, however, we do not aim to fix the problem; rather, we continue our survey of the pulse vaccination literature and concern ourselves with the effects of this pseudo-logistic approach on the pulse vaccination approach outlined in Section 4.3.1.

In the analysis, the difference amounts to merely an extra factor of K in the resulting equations. That is, in Lemma 1 we have $a = \mu K$ instead of just μ, and then with $b = \mu$ again we have the resulting periodic solution

$$\begin{aligned} \tilde{S}_K(t) &= \frac{\mu K}{\mu}\left[1 - \frac{p}{(1-(1-p)e^{-\mu\tau})}e^{-\mu(t-k\tau)}\right], \quad k\tau \leq t < (k+1)\tau. \\ &= K\tilde{S}(t) \end{aligned}$$

We do need to take into account the fact that the population is no longer normalized, though, in which case we should again revert to using the standard incidence $\beta\frac{S}{N}I$.

Using Lemma 1 we get $S(t) \leq \tilde{S}_K(t) + \epsilon$ eventually, resulting in the bounding equation for I':

$$I' \leq \left[\beta \frac{1}{N}(\tilde{S}_K + \epsilon) - (\mu + \gamma + \alpha)\right] I$$

The $1/N$ factor could prove to be a problem if $N \to 0$, but thanks to the boundedness of the population in a logistic model we are alright:

- If $\alpha = 0$ then $N(t) \geq \min\{N_0, K\}$ for all $t \geq t_0$.
- If $\alpha \neq 0$ then since $I \leq N$ we have $N' = \mu(K - N) - \alpha I \geq \mu\left[K - (1 + \frac{\alpha}{\mu})N\right] > 0$ if $N < \frac{K}{1+\alpha/\mu}$, that is, the set $\{N \in \mathbb{R}_+ |\ N \geq \frac{K}{1+\alpha/\mu}\}$ is attractive.

Thus we have $N(t) \geq N_m := \min(N_0, \frac{K}{1+\alpha/\mu})$ (where α can be 0) for all $t \geq 0$, so $1/N \leq 1/N_m$. Then

$$\begin{aligned} I' &\leq \left[\beta \frac{1}{N_m}(\tilde{S}_K + \epsilon) - (\mu + \gamma + \alpha)\right] I \\ &= \left[\beta \frac{K}{N_m}(\tilde{S} + \epsilon') - (\mu + \gamma + \alpha)\right] I. \end{aligned}$$

We can use conditions on the time-varying "coefficient" in brackets to determine sufficient conditions for eradication of the disease as before; we will find that we need the possibly more strict condition

$$\left(\frac{1}{\tau}\int_0^\tau \frac{\beta \tilde{S}(t)}{\mu + \gamma + \alpha} dt\ =\right)\ \ \bar{\mathcal{R}} < \frac{N_m}{K} \leq 1. \tag{6.3}$$

In the case where $N_0 > K$ and there are no disease-related deaths ($\alpha = 0$ so it does not show up in the denominator of $\bar{\mathcal{R}}$), we immediately get the same eradication condition as we did for the normalized system.

Additionally, we note that for any $\epsilon_0 > 0$, as $t \to \infty$, $N(t)$ grows greater than $\frac{K}{1+\alpha/\mu} - \epsilon_0$. So as $t \to \infty$ our condition on $\bar{\mathcal{R}}$ becomes $\bar{\mathcal{R}} < \frac{1}{1+\alpha/\mu} - \epsilon_0 < 1$. Whether the amount of time it takes for the system to reach this proximity to K is reasonable compared to the time scale of the disease likely depends on the specific parameters.

In the pulse vaccination literature, even in models with a varying population, the change to standard incidence is not frequently used. Suppose that instead of switching to the standard incidence we look at a carrying capacity model with bilinear incidence; Gao *et. al.* [26] and Zhang *et. al.* [83] consider such models (with more complications added). In this case the condition for eradication reduces to

$$I' \leq \Big(\beta(\tilde{S}_K + \epsilon) - (\mu + \gamma + \alpha)\Big) I \quad \Rightarrow \quad \bar{\mathcal{R}} < \frac{1}{K}$$

for eradication. $\bar{\mathcal{R}}$ is the same as in (6.3), which is as we always define it besides the α term. This way the K factor of the coefficients of I in I' is more obvious:

$$I' \leq (\mu + \gamma + \alpha)\left(K\bar{\mathcal{R}} - 1\right) I.$$

Unless disease deaths cause $N(t) \to 0$ we can generally assume that N and K are on approximately the same order of magnitude (or will grow close). If we do not use the standard incidence to include the additional factor of N, then instead of needing to be less than 1, our threshold value $\bar{\mathcal{R}}$ must now be less than $1/K$. Depending on the value of K this may be a restrictive assumption, although it may be implicit; in [26], [83], [57], and [76], the carrying capacity is represented by a constant birth term A. Rather than setting $A = \mu K$ and simplifying the μ factors where possible, following through leads to the restriction $\bar{\mathcal{R}}_A < 1$ where $\bar{\mathcal{R}}_A = A\bar{\mathcal{R}}$ (or similar). With A just considered as another parameter the threshold is less obviously restrictive, but if we consider it as a product of μ with a population on the same order as N the dependence is clearer. If we use empirical data from prior epidemics to get a rough estimate of the basic reproduction number $\mathcal{R}_0$ (described in Section 2.4), this issue could cause a large change in our successive estimate of β. So, if we plan to use such empirical estimates to make predictions with our more complicated model, we need to be careful to ensure that the estimates agree with the model.

As described in the previous section on non-normalized constant N, we could also use the bilinear incidence with a birth rate proportional to N. Similarly to using carrying capacity K we would derive the condition $\bar{\mathcal{R}} < 1/N$ for eradication. If we have not normalized the total population then N might be a very large number indeed.

We note that all of our sample models in this section have been SIR models with no delay. These models were chosen for their simplicity, but for at least a small delay we note that the results carry over; as shown in Section 5.2, if the trivial solution of $x'(t) = [a(t) - b(t)]x(t)$ is uniformly asymptotically stable, then for small enough delay r we will also have that the trivial solution of $x'(t) = a(t)x(t-r) - b(t)x(t) = [a(t) - b(t)]x(t) + a(t)[x(t-r) - x(t)]$ is UAS as well.

For permanence in the standard incidence model with births proportional to K, we note that $N(t) \leq N^M := \max(K, N_0)$ (regardless of the value of α). In fact, as $t \to \infty$ we have that for any $\epsilon_1 > 0$, there exists $t_1 > 0$ such that $N(t) < K + \epsilon_1$ for all $t > t_1$, that is, $N^M \to K + \epsilon_1$. (Clearly $t_1 = t_0$ if $N_0 \leq K$.)

We can follow the same process as in earlier sections to look at permanence by defining

$$\bar{I}(t) := N(t)\frac{\mu}{\beta}(\bar{\mathcal{R}} - 1)$$

Note if $N_0 > 0$ then $N(t) > 0$ for all future time, so if $\bar{\mathcal{R}} > 1$ then $\bar{I}(t) > 0$ in the non-trivial case. We also note that this definition of $\bar{I}(t)$ is in agreement with our definition in earlier sections; if we define $I = Ni$, then we see that $\bar{I}(t) = N(t)\bar{i}$ where $\bar{i}$ is the value defined in [27]. If $N(t) \equiv 1$ then $\bar{I}(t)$ and $\bar{i}$ are interchangeable.

We also define $\bar{\mathcal{R}}^*$ in terms of $\bar{\mathcal{R}}$ (the time-average coefficient ratio) as before.

Claim 6. *If $\bar{\mathcal{R}}^* > N^M/K$ we have disease permanence.*

Proof. Suppose $\bar{\mathcal{R}}^* > \frac{N^M}{K}$ for all t greater than some t_1. Assume that $I(t) < \bar{I}(t)$ for all large t. Then for $t > t_1$,

$$S' = \mu K - \mu S - \beta \frac{I}{N} S \quad > \mu K - \mu S - \mu(\bar{\mathcal{R}} - 1)S \quad = \mu K - \mu \bar{\mathcal{R}} S,$$

which taken together with the pulse vaccination gives $S(t) > \bar{S}_K(t) - \epsilon = K\bar{S}(t) - \epsilon$ eventually. Then

$$I' = \beta \frac{S}{N} I - (\mu + \gamma + \alpha) I > \left[\frac{K}{N^M} \beta (\bar{S} + \epsilon) - (\mu + \gamma + \alpha) \right] I$$

eventually. From the process in Section 5.1.2 we see that $I(t) \to \infty$, leading to a contradiction. Therefore if the period-average of the brackets is positive we either have $I(t) > \bar{I}(t)$ for all t, where

$$\bar{I}(t) = N(t) \frac{\mu}{\beta} (\bar{\mathcal{R}} - 1) \geq \frac{K}{1 + \alpha/\mu} \frac{\mu}{\beta} (\bar{\mathcal{R}} - 1) =: \bar{I}_m,$$

and so the disease will be permanent, or otherwise $I(t)$ oscillates about $\bar{I}(t)$.

In the oscillatory case, we follow the same process as in Section 5.1.2. Suppose that $I(t_2) = \bar{I}(t_2)$ for some $t_2 > t_1$ and that σ is the smallest positive constant such that $I(t_2 + \sigma) = \bar{I}(t_2 + \sigma)$ and $I(t) \neq \bar{I}(t)$ for $t \in (t_2, t_2 + \sigma)$.

- If $\sigma < \tau$ then since $I'(t) > -(\mu + \gamma) I(t)$ we have $I(t) > I(t_2) e^{-(\mu+\gamma)\sigma} = \bar{I}(t_2) e^{-(\mu+\gamma)\sigma} > \bar{I}_m e^{-(\mu+\gamma)\tau} > 0$ for $t \in (t_2, t_2 + \sigma)$.
- If $\sigma \geq \tau$ then let $\sigma = a\tau + b$ where $a, b \in \mathbb{Z}, a > 0$ and $b = \sigma \mod \tau$. We know from the above for $t \in (t_2, t_2 + a\tau]$ that $I(t) > I(t_2) e^{ca}$. Then for $t \in (t_2 + a\tau, t_2 + \sigma)$ we have $I(t) > I(t_2 + a\tau) e^{-(\mu+\gamma)b} > I(t_2) e^{ca} e^{-(\mu+\gamma)\tau} = \bar{I}(t_2) e^{ca} e^{-(\mu+\gamma)\tau} > \bar{I}_m e^{-(\mu+\gamma)\tau}$.

Since $t_2 > t_1$ was arbitrary then this result is true between any two times at which $I(t) = \bar{I}(t)$. Therefore we have shown that if $\bar{\mathcal{R}}^* \frac{K}{N^M} > 1$ then $I(t) > \bar{I}_m e^{-(\mu+\gamma)\tau} > 0$ for all $t > t_1$. Therefore the disease is permanent.

□

Remark. As $t \to \infty$, if $N_0 > K$ then $N(t) \to K$, so this condition becomes $\bar{\mathcal{R}}^* > 1$. (That is, for any $\epsilon > 0$ there exists t_3 large enough that $N(t) < K + \epsilon$ for all $t > t_3$. Then considering t_3 as our new initial point, we have $N^M = K + \epsilon$ and for small enough ϵ, if $\bar{\mathcal{R}}^* > 1$ then by the strictness of the inequality $\bar{\mathcal{R}}^* > 1 + \frac{\epsilon}{K} = \frac{N^M}{K}$.) If $N_0 \leq K$ then $N^M/K \leq 1$ so $\bar{\mathcal{R}}^* > 1 \Rightarrow \bar{\mathcal{R}}^* > N^M/K$. The condition $\bar{\mathcal{R}}^* > 1$ works in both cases.

We proved earlier that $\bar{\mathcal{R}} > 1 \Rightarrow \bar{\mathcal{R}}^* > 1$, therefore with a carrying capacity we in fact keep the permanence threshold $\bar{\mathcal{R}} > 1$. When we mentioned in Section 6.1 that the permanence results carry over from $N = 1$ to general constant N, the proof is analogous to the above (and indeed simpler since there are no ratios with N and K to deal with).

6.3 Exponentially-varying Total Population Size

We consider the more general model

$$\begin{cases} S' &= bN - \mu S - g(N, S, I, t) \\ I' &= g(N, S, I, t) - (\mu + \gamma + \alpha)I \\ R' &= \gamma I - \mu R \end{cases} \tag{6.4}$$

with pulse vaccination as in (6.1). We will analyze this model in order to discuss the effects of a total population $N(t)$ that does not approach a carrying capacity.

First we note that

$$N' = (b - \mu)N - \alpha I. \tag{6.5}$$

Because $N(t)$ varies with time we cannot apply the PV method of Gao *et. al.* ([27]) directly; without a constant births term we cannot integrate as before, and so we do not obtain the disease-free periodic solution $\tilde{S}(t)$ which helps us lower the eradication threshold. When $N(t) \equiv N$, though, we were able to change variables to the population fractions, which led to the normalized type of model so often used in the literature. We apply the same method here with later adjustments for the non-constancy of $N(t)$. Cooke and van den Driessche, and later Li, use this population fraction method [12, 47], but to our knowledge the technique hasn't been used to allow for a more generalized population in a pulse vaccination model.

Let $s = S/N$, $i = I/N$, $r = R/N$. Then model (6.4) becomes

$$\begin{cases} (Ns)' &= bN - \mu(Ns) - g(N, Ns, Ni, t) \\ (Ni)' &= g(N, Ns, Ni, t) - (\mu + \gamma + \alpha)(Ni) \\ (Nr)' &= \gamma(Ni) - \mu(Nr) \end{cases} \tag{6.6}$$

$$\Rightarrow \begin{cases} N's + Ns' &= bN - \mu Ns - g(N, Ns, Ni, t) \\ N'i + Ni' &= g(N, Ns, Ni, t) - (\mu + \gamma + \alpha)Ni \\ N'r + Nr' &= \gamma Ni - \mu Nr. \end{cases} \tag{6.7}$$

Rearranging and dividing by $N(t)$,

$$\begin{cases} s' &= b - \mu s - \frac{1}{N} g(N, Ns, Ni, t) - s\frac{N'}{N} \\ i' &= \frac{1}{N} g(N, Ns, Ni, t) - (\mu + \gamma + \alpha)i - i\frac{N'}{N} \\ r' &= \gamma i - \mu r - r\frac{N'}{N}. \end{cases} \tag{6.8}$$

From (6.5) we have $N'/N = [(b-\mu)N - \alpha I]/N = b - \mu - \alpha i$. Substituting into the above,

$$\begin{cases} s' &= b - \mu s - \frac{1}{N} g(N, Ns, Ni, t) - bs + \mu s + \alpha si \\ i' &= \frac{1}{N} g(N, Ns, Ni, t) - \mu i - \gamma i - \alpha i - bi + \mu i + \alpha i^2 \\ r' &= \gamma i - \mu r - br + \mu r + \alpha ir \end{cases}$$

$$\Rightarrow \begin{cases} s' &= b - bs - \frac{1}{N} g(N, Ns, Ni, t) + \alpha si \\ i' &= \frac{1}{N} g(N, Ns, Ni, t) - (b + \gamma + \alpha)i + \alpha i^2 \\ r' &= \gamma i - br + \alpha ir. \end{cases} \tag{6.9}$$

The pulse vaccination still reaches the same proportion p of s as it does of S, as explained in Section 6.1.

In this subsection we assume $\alpha = 0$ (no deaths due to the disease); in the next subsection we deal with the nonzero case. If $\alpha = 0$ we are left with this inequality for s':

$$\begin{aligned} s' &\leq b - bs, \quad t \neq k\tau \\ s(k\tau^+) &= (1-p)s(k\tau). \end{aligned}$$

Using a comparison system for $x(t)$ with equality in the derivative, we find that $s(t) \leq x(t)$ and use Lemma 1 to find $x(t) \to \tilde{s}_b(t)$ as $t \to \infty$, where

$$\tilde{s}_b(t) = 1 - \frac{p}{1 - (1-p)e^{-b\tau}} e^{-b(t-k\tau)}$$

for $t \in (k\tau, (k+1)\tau]$. That is, rather than finding a disease-free periodic solution dependent on the death rate μ, we see that the solution depends instead on the birth rate. The important point, though, is that this solution is despite the fact that $N(t)$ varies! While we couldn't find a periodic solution bounding $S(t)$ (depending on whether $N(t)$ shrinks or grows), we have found one for the susceptible proportion $s(t)$.

We can now use this bound on $s(t)$ (that $s(t) < \tilde{s}_b(t) + \epsilon$ eventually for any $\epsilon > 0$) in our equation for i'. For example, if we use the standard incidence rate $g(N, S, I, t) = \beta\frac{SI}{N}$,

$$\begin{aligned} i' &= \frac{1}{N}\beta\frac{(Ns)(Ni)}{N} - (b+\gamma)i \\ &< \left[\beta(\tilde{s}_b(t) + \epsilon) - (b+\gamma)\right] i \end{aligned} \tag{6.10}$$

Whether or not the model includes delay (unless in the susceptible class) is basically irrelevant up to this point. (We say "basically" because for latent delay we would need to include an exposed class E, and the equation for i' would involve $g(\ N(t-r), S(t-r), I(t-r), t-r\ )$.) Assuming g is increasing in s, once we obtain the upperbound equation for i' we can find conditions under which $i \to 0$. For example, with standard incidence in (6.4) (bilinear incidence in (6.9)) then we find, as per d'Onofrio [17], that $\frac{\beta}{b+\gamma}\int_0^\tau \tilde{s}_b(t)dt < 1 \Rightarrow$ the disease is eradicated. With a delay model we can at least use the threshold $\mathcal{R}^* = \frac{\beta}{b+\gamma}\max_{t\in[0,\tau]}\tilde{s}_b(t)$ as in [27].

We note, however, that just because $i \to 0$ does not mean that $I \to 0$. In fact, if N is growing to ∞, we could have $I \to \infty$. Hethcote and van den Driessche explain that the definition of "persistence" of the disease is that $i \geq i_L > 0$ for some bound i_L [38]; thus if we find sufficient conditions for $i \to 0$ in (6.10) then we avoid persistence even if infective individuals remain. In our previous persistence proofs we either had constant $N(t)$ (so S, I, R and s, i, r were interchangeable) or $N(t)$ was bounded above and below, so we avoided the pitfall of looking at the wrong infective measure.

We further note that $N(t)$ varies only exponentially in the above models; given the nature of the compartmental models, $N'(t)$ is prescribed for us. We could assume some other time evolution for $N(t)$ and work backwards to construct the appropriate model, but logistic and exponential models seem adequate when looking at a single noninteracting population.

6.4 Extensions: Eradication with Disease Mortality and Cyclical Models

In the previous subsection we obtained System (6.9) from a SIR model, then proceeded to assume that $\alpha = 0$ in order to show that we can still find conditions for disease eradication in a general time-varying model.

Here we assume that $\alpha > 0$ and consider the changes to the threshold conditions. Then we consider cyclical models in which removal is not permanent (individuals in R return to S through immunity waning).

If $\alpha > 0$ then in (6.9) we have a term in s' that depends on i. If this term, αsi, was negative we could "drop" it when we drop the incidence term, to get $s' \geq b - bs$; unfortunately it is positive. We can exploit the fact, though, that we are dealing with population fractions: that is, we can use $i \leq 1$. A tighter bound may be possible but this method is a good first step. If $b > \alpha$ we obtain the equation

$$\begin{aligned} s' &\leq b - (b-\alpha)s, \\ s(k\tau^+) &= (1-p)s(k\tau), \end{aligned}$$

from which we again use Lemma 1 to get that $s(t) < \tilde{s}_{\alpha b}(t) + \epsilon$ eventually, where

$$\tilde{s}_{\alpha b}(t) = \frac{b}{b-\alpha}\left[1 - \frac{p}{1-(1-p)e^{-(b-\alpha)\tau}}e^{-(b-\alpha)(t-k\tau)}\right].$$

If $b < \alpha$, our system for $s(t)$ is of the form

$$\begin{aligned} s' &\leq b + as, \quad t \neq k\tau \\ s(k\tau^+) &= (1-p)s(k\tau), \end{aligned} \tag{6.11}$$

where $a = \alpha - b > 0$. Lemma 1 for the existence and global attractivity of $\tilde{s}_b(t)$ needed an equation of the form $x' = c_1 - c_2 x$ where $c_1, c_2 > 0$ so we cannot apply the result here. Instead, we proceed as we did when originally finding $\tilde{S}(t)$ in Lemma 1: multiply by the integrating factor e^{-at} and integrate between pulses to get

$$s(t) = \left[s(k\tau) + \frac{b}{a}\right]e^{a(t-k\tau)} - \frac{b}{a}$$

for $t \in [k\tau, (k+1)\tau)$. For an equilibrium solution we want $s(k\tau) = s((k+1)\tau) = (1-p)s((k+1)\tau^-)$. If we define

$$f(s) = (1-p)\left(\left[s + \frac{b}{a}\right]e^{a\tau} - \frac{b}{a}\right) \tag{6.12}$$

then we are looking for a fixed point $s* = f(s^*)$. Using this condition in (6.12) and isolating:

$$s^* = \frac{b}{a} \cdot \frac{(1-p)(e^{a\tau}-1)}{1-(1-p)e^{a\tau}}.$$

If we have an periodic solution then s^* will be its minimum. In order for a physically-valid (disease-free equilibrium) periodic solution to exist we thus need $s^* > 0$; looking at the denominator, this condition translates to $(1-p)e^{a\tau} < 1$ or equivalently

$$a < \frac{-1}{\tau}\ln(1-p)$$

(since $p < 1$, this condition does not force $a < 0$).

Looking at the problem an alternate way, in order for any periodic solution (strictly positive or otherwise) to be attractive, we need $f(s)$ to be a contraction mapping. Specifically, $f'(s) = (1-p)e^{a\tau} < 1 \Rightarrow a < \frac{-1}{\tau}\ln(1-p)$ again.

The $b = \alpha$ case is pathological but proceeding the same way we find that $s(t) = b(t-k\tau)+s(k\tau)$ for $t \in [k\tau, (k+1)\tau)$, so for a periodic solution we need $s^* = h(s^*) = (1-p)(b\tau + s^*)$. h is also a contraction mapping since $0 < p < 1$ so a periodic solution exists and is globally attractive.

In terms of our original model parameters, then, we find that if $b \geq \alpha$ then a positive periodic solution exists and is globally attractive, and we have now extended it so that if $\alpha > b$ we still have a globally attractive positive periodic solution of (6.11) so long as

$$\alpha < b + \frac{1}{\tau} \ln \frac{1}{1-p}. \tag{6.13}$$

If α is very large then we expect the disease deaths to remove infectives from the population quickly, and the births are not frequent enough to replenish the population. As $N(t) \to 0$ the susceptible population $S(t)$ is squeezed to 0 with it and $s(t)$ cannot sustain a periodic solution.

Regardless of the parameters, so long as they satisfy $\alpha \in \left(0, b + \frac{1}{\tau} \ln \frac{1}{1-p}\right)$, then once we find an upperbound for $s(t)$ we have

$$\begin{aligned} i' &= \frac{1}{N} g(N, Ns, Ni, t) - (b + \gamma + (1-i)\alpha) i \\ &\leq \frac{1}{N} g(N, Ns, Ni, t) - (b + \gamma) i, \end{aligned}$$

and so long as g is increasing in Ns we can find conditions on a comparison DE with equality to see when $i \to 0$. A sharper bound might be possible by keeping α explicitly in i'. We have not ignored the parameter, however, because it features in $\tilde{s}_{\alpha b}$. Depending on the form of g we can still find conditions on the eradication of the disease despite the disease deaths and time-varying $N(t)$.

Similarly, suppose we have a cyclical model such as a SIRS model, in which immunity wanes in an exponential distribution: $S' = \ldots + \delta R$, $R' = \ldots - \delta R$. The proportional model becomes

$$\begin{cases} s' &= b - bs - \frac{1}{N} g(N, Ns, Ni, t) + \alpha si + \delta r \\ i' &= \frac{1}{N} g(N, Ns, Ni, t) - (b + \gamma + \alpha) i + \alpha i^2 \\ r' &= \gamma i - (b + \delta) r + \alpha i r. \end{cases}$$

$$\begin{cases} s(k\tau^+) &= (1-p) s(k\tau) \\ i(k\tau^+) &= i(k\tau) \\ r(k\tau^+) &= r(k\tau) + p s(k\tau) \end{cases}$$

Since $r, i \leq 1$,

$$s' \leq (b + \delta) - (b - \alpha) s \tag{6.14}$$

which together with the pulse vaccination leads to $s(t) < \tilde{s}_{\alpha b \delta} + \epsilon$ eventually, where

$$\tilde{s}_{\alpha b \delta}(t) = \frac{b + \delta}{b - \alpha} \left[1 - \frac{p}{1 - (1-p) e^{-(b-\alpha)\tau}} e^{-(b-\alpha)(t - k\tau)} \right].$$

The replenishing of susceptibles due to δ means that the coefficient $\frac{b+\delta}{b-\alpha}$ of $\tilde{s}_{\alpha b\delta}(t)$ is larger than that of $\tilde{s}_{\alpha b}(t)$, $\frac{b}{b-\alpha}$, which is in turn larger than the coefficient ($= 1$) of $\tilde{s}_b(t)$. While it seems like disease deaths could contribute to the eradication of the disease, a likely reason why the coefficient of $\tilde{s}_{\alpha b}(t)$ is in fact greater than one (with a corresponding increase in $\bar{\mathcal{R}}_{\alpha b}$) is that disease deaths decrease both I and N by the same number. The total susceptible population S stays the same (when a disease death occurs) so the susceptible fraction s increases; recall we have changed variables to population fractions, not totals.

While the cyclical model can lead to richer dynamics that may be skipped in this analysis, we at least find that the time-varying $N(t)$ does not keep us from finding a periodic eventual upper bound for $s(t)$. Then we can find some manner of conditions under which $i \to 0$.

In terms of permanence, for a general incidence term the analysis may be unclear, but if we can follow the same procedure as for bilinear incidence then disease deaths and vaccine waning do not affect our analysis. That is, we assume $i <$ some $\bar{i}$ for all future t, then bound s' from below: if g is increasing in i, we say $s' \geq b - bs - g(N, Ns, N\bar{i}, t) + \alpha si + \delta s$ and we can in fact just drop the last two terms ($s' \geq b - bs - g(N, Ns, N\bar{i}, t)$) and continue as in earlier sections: find a lower bound for $s(t)$ and substitute it into i'.

Again a tighter bound may be desired or at least possible, but in an intuitive sense, disease deaths and vaccine waning help improve the chances of persistence so we can ignore their "helpful" effects and still find conditions for permanence. Similarly when we substitute our resulting lowerbound s_m for s into i' to get $i' \geq \frac{1}{N} g(N, Ns_m, Ni, t) - (b + \gamma + \alpha)i + \alpha i^2$, we can drop the αi^2 term.

6.5 Extensions: Delay Models with Standard Incidence

In the previous sections of this chapter we have been considering models without delay, mostly for brevity because when we look at the total population's derivative, the delay terms cancel out. In this section we deal with the issues that arise in changing variables to switch from standard incidence to bilinear incidence in a delay model.

Basically, to go from the non-delay, standard incidence model to the normalized bilinear model, we simply divided both sides of the equation by $N(t)$. If N is constant then there are no problems in applying this approach to a delay model.

Delay in $E(t)$

If $N(t)$ is not constant, we obtain the following SEIR model:

$$\begin{cases} S' &= bN - \mu S - \beta \frac{SI}{N} \\ E' &= \beta \frac{SI}{N} - \beta e^{-\mu r} \frac{S(t-r)I(t-r)}{N(t-r)} \\ I' &= \beta e^{-\mu r} \frac{S(t-r)I(t-r)}{N(t-r)} - (\mu + \gamma + \alpha)I \\ R' &= \gamma I - \mu R \end{cases} \tag{6.15}$$

with the usual pulse vaccination applied.

Again let $s = S/N$, $e = E/N$, $i = I/N$, $r = R/N$. Then model (6.15) becomes

$$\begin{cases} (Ns)' &= bN - \mu(Ns) - \beta \frac{(Ns)(Ni)}{N} \\ (Ne)' &= \beta \frac{(Ns)(Ni)}{N} - \beta e^{-\mu r} \frac{(N(t-r)s(t-r))(N(t-r)i(t-r))}{N(t-r)} - \mu(Ne) \\ (Ni)' &= \beta e^{-\mu r} \frac{(N(t-r)s(t-r))(N(t-r)i(t-r))}{N(t-r)} - (\mu + \gamma + \alpha)(Ni) \\ (Nr)' &= \gamma(Ni) - \mu(Nr) \end{cases} \tag{6.16}$$

Expanding the left-hand-side derivatives, rearranging, and dividing by $N(t)$ we get

$$\Rightarrow \begin{cases} s' &= b - bs - \beta si + \alpha si \\ e' &= \beta si - \beta e^{-\mu r} s(t-r)i(t-r) \frac{N(t-r)}{N(t)} - be + \alpha ei \\ i' &= \beta e^{-\mu r} s(t-r)i(t-r) \frac{N(t-r)}{N(t)} - (b + \gamma + \alpha)i + \alpha i^2 \\ r' &= \gamma i - br + \alpha ir \end{cases} \tag{6.17}$$

(Regardless of the delay term, we have $N' = (b - \mu)N - \alpha I$.) The analysis plays out almost identically to the non-delay case except for the $N(t-r)/N(t)$ factor in the incidence term. Instead of considering the compartment derivatives which have delay, we focus only on s' for now.

From the equation for s' we get $s(t) < \tilde{s}_{\alpha b}(t) + \epsilon$ eventually for any $\epsilon > 0$, where $\tilde{s}_{\alpha b}$ is as in Section 6.4. So $S(t) = N(t)s(t) < N(t)(\tilde{s}_{\alpha b}(t) + \epsilon)$ eventually; now we return to the equation for I' (the "big" I, the total infective population) and substitute this bound.

$$I' = \beta e^{-\mu r} \frac{S(t-r)I(t-r)}{N(t-r)} - (\mu + \gamma + \alpha)I \tag{6.18}$$

$$< \beta e^{-\mu r} \frac{N(t-r)\tilde{s}_{\alpha b}(t-r)I(t-r)}{N(t-r)} - (\mu + \gamma + \alpha)I \tag{6.19}$$

$$= \beta e^{-\mu r} \tilde{s}_{\alpha b}(t-r)I(t-r) - (\mu + \gamma + \alpha)I \tag{6.20}$$

$$\tag{6.21}$$

Using the methods of Gao *et.al.* applied to this equation, then, we find that if the threshold

$$\mathcal{R}^* = \frac{\beta e^{-\mu r} \tilde{s}_{\alpha b}^M}{\mu + \gamma + \alpha} < 1 \tag{6.22}$$

then $I(t) \to 0$ [27]. The important thing to note is that $N(t)$ may not be bounded, so $I(t) \to 0$ does not mean that the infective fraction $i(t)$ vanishes if $N(t)$ is shrinking as well. (If $N(t)$ shrinks too much, though, we will not be able to approximate the population as continuous, so the case becomes pathological.) Hence we may still use the change to fractional variables for this delay equation, but must be careful about our interpretation of the results.

Note we could use this method even without pulse vaccination, by using the relationship $S(t-r)/N(t-r) \leq 1$ to get rid of the $N(t-r)$ in the denominator of the term in $I'(t)$.

Delay in Other Compartments

In the above model, the delay occurred in $E(t)$, and we were basically able to ignore it and move on to the compartment of interest $I(t)$. If instead the delay occurred in $I(t)$, for example

$$I' = \beta \frac{SI}{N} - \beta e^{-\mu r} \frac{S(t-r)I(t-r)}{N(t-r)} - (\mu + \alpha)I, \tag{6.23}$$

then we could not use an upperbound on S to get rid of the $N(t-r)$ in the denominator, because the term with this factor is negative. Similarly with a delay in $R(t)$ we could have

$$R' = \gamma I - \gamma e^{-\mu r} I(t-r) - \mu R, \tag{6.24}$$

or with an exposed class (without delay) and a delay in $I(t)$ we could have

$$I' = \kappa E - \kappa e^{-\mu r} E(t-r) - (\mu + \alpha)I, \tag{6.25}$$

all with negative delay terms and with resulting fractional equations such as

$$r' = \gamma i - \gamma e^{-\mu r} i(t-r) \frac{N(t-r)}{N(t)} - \mu r + \frac{N'}{N} r. \tag{6.26}$$

The $N(t-r)/N(t)$ ratio is still a problem, but we can at least use the bounds

$$\begin{array}{rcl} (b-\mu-\alpha)N(t) & \leq N'(t) \leq & (b-\mu)N(t), \\ N_0 e^{(b-\mu-\alpha)t} & \leq N(t) \leq & N_0 e^{(b-\mu)t} \end{array} \tag{6.27}$$

and so

$$e^{-\alpha t} \cdot e^{-(b-\mu-\alpha)r} = \frac{e^{(b-\mu-\alpha)(t-r)}}{e^{(b-\mu)t}} \leq \frac{N(t-r)}{N(t)} \leq \frac{e^{(b-\mu)(t-r)}}{e^{(b-\mu-\alpha)t}} = e^{-(b-\mu)r} \cdot e^{\alpha t}. \tag{6.28}$$

Dealing with solutions to such a system is beyond the scope of this thesis, but we can at least use the bound on this ratio as a start.

Chapter 7

Switched Systems: Models with Standard Incidence and Switched Contact Rate

In Section 5.1 we looked at pulse vaccination together with, in some cases, delay. We considered a periodic bound $\lambda(t)$ for the contact rate, as in [17], in order to allow for more general models than the usual standard and bilinear incidences. The nonautonomy of the system, however, led to some difficulty in finding results for the delay systems.

In this section we will consider standard incidence models with a piecewise constant contact rate, in order to approximate a periodic parameter but still allow for more explicit results. Specifically, we follow the method of Liu and Stechlinski and use a switched contact rate $\beta_{\sigma(t)}$, where $\sigma(t) \in \{1, 2, \ldots, m\}$ is a periodic switching rule [52, 53].

The main aim of this section is to look at switched systems with impulsive behaviour and delay. As stated, we have already considered impulsive behaviour and delay together; in Section 7.2 we look to combine switched (non-delay) systems with impulsive behaviour, then in Sections 7.3.1 and 7.3.2 we add delay.

7.1 Introduction to Switched Systems

For brevity, in this section we consider a basic SI model such as that of Kermack and McKendrick in (2.2), reproduced here [44]:

$$\begin{cases} S' &= -\beta SI \\ I' &= \beta SI - \gamma I \end{cases} \tag{7.1}$$

The contact rate β is a constant value in this model. Suppose we instead use a piecewise constant for β, then we would in fact have $\beta = \beta(t)$ and our epidemic model becomes nonautonomous. For simplicity, suppose that $\beta(t)$ only takes on two values, β_1 and β_2. Suppose $\beta(t)$ "jumps" to β_1 at times $t = t_{2k}$ and jumps to β_2 at times $t = t_{2k+1}$. Then we have defined $\beta(t)$ by

$$\beta(t) = \begin{cases} \beta_1, & t \in [t_{2k}, t_{2k+1}) \\ \beta_2, & t \in [t_{2k+1}, t_{2k+2}) \end{cases} \tag{7.2}$$

for $k \in \mathbb{Z}$. The notation $\beta = \beta(t)$ is a bit misleading in this case, then, because it implies that β could vary a lot over time instead of just being piecewise constant. Instead we use the notation $\beta = \beta_{\sigma(t)}$ where

$$\sigma(t) = \begin{cases} 1, & t \in [t_{2k}, t_{2k+1}) \\ 2, & t \in [t_{2k+1}, t_{2k+2}). \end{cases} \tag{7.3}$$

is a "switching rule" [53]. Our initial model (7.1) then becomes

$$\begin{cases} S' &= -\beta_\sigma SI \\ I' &= \beta_\sigma SI - \gamma I \end{cases} \tag{7.4}$$

which is made up of two subsystems,

$$\begin{cases} S' &= -\beta_i SI \\ I' &= \beta_i SI - \gamma I \end{cases} \tag{7.5}$$

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

These concepts easily generalize to larger numbers of subsystems: we simply specify $\sigma(t) \in \{1, \ldots, m\}$ to get a switched system made up of m subsystems. For general switching between m subsystems, the switch times will not follow the easy rule $t_{even} \Rightarrow \beta_1, t_{odd} \Rightarrow \beta_2$ that occurs for $m = 2$. Instead we denote by t_k the switch times ($k \in \mathbb{Z}$).

In the remainder of this chapter we will look at switched systems where the switching parameter is the contact rate β and the switching rule $\sigma(t)$ is periodic with period T. We denote by T_k the time spent by $\sigma(t)$ at index $k \in \{1, \ldots, m\}$, where $\sum_{k=1}^{m} T_k = T$. We assume that $\sigma(t)$ switches *away* from k at switch times t_k; that is, $\sigma(t) = k$ for $t \in [t_{k-1}, t_k) = [t_k - T_k, t_k)$.

We assume σ cycles consecutively through the numbers $\{1, \ldots, m\}$, but the values $\beta_{\sigma(t)}$ do not have to be sequential by any means; we could have $\beta_i > \beta_{i+1}$, or $\beta_i = \beta_j$ for some $i \neq j$, depending on what best matches the situation we are trying to model. For example, we might set $\beta_1 = 2$ in winter, $\beta_2 = 1.5$ in spring, $\beta_3 = 1$ in summer, and $\beta_4 = 1.5$ again in the fall.

Existence and Uniqueness of Solutions

In this chapter we will look at switched systems with both delay and non-delay models. We will consider the non-delay models as a special case of the delay ones, in which $r = 0$.

As with the impulsive behaviour of the pulse vaccination, the switching of β_σ will cause discontinuities. If we consider our model to be

$$\begin{aligned} x'(t) &= f_{\sigma(t)}(t, x_t), \quad t \neq \tau_k, \quad t \geq t_0 \\ \Delta x(t) &= \mathcal{I}(t, x_{t^-}), \quad t = \tau_k, \quad t > t_0 \end{aligned} \tag{7.6}$$

then $\mathcal{I}$ models the pulse vaccination while $f_{\sigma(t)}$ models the changing contact rate $\beta_{\sigma(t)}$ by switching between systems f_i, $i = 1, \ldots, m$. (Here we use f_σ for brevity, but f_σ is not a completely general function; we are specifically considering a compartmental epidemic model, so we have $f_\sigma(t, \psi) = g_\sigma(t, \psi(0), \psi(-r))$ where g is the right-hand side of the epidemic model we are interested in.)

Over any finite time interval, the switching introduces only a finite number of discontinuities in $f_{\sigma(t)}$. Drawing on Section 3.3 we thus find that $f_{\sigma(t)}(t, \psi)$ is still composite-PC, that is, piecewise continuous when considered as a composite function of t, for piecewise continuous ψ. $f_{\sigma(t)}$ still satisfies a Lipschitz condition in $x(t)$ and $x(t - r)$, and is still quasi-bounded ($f_{\sigma(t)}$ jumps at the switch times $t = t_k$ but only to a subsystem with different finite parameters). Therefore we have that there exists a unique solution to (7.6) on the domain of definition of $f_{\sigma(t)}$.

Alternatively, we could simply consider the solution to (7.6) separately on the intervals $[t_{k-1}, t_k - r), [t_k - r, t_k), [t_k, t_{k+1} - r)$, and so on (assuming $T_k > r$ for $i = 1, \ldots, m$; the point is we look at intervals upon which all parameters, $\beta_{\sigma(t)}, \beta_{\sigma(t-r)}$, *etc.* are constant). Then upon each interval the system has no discontinuities besides the pulse vaccination, and we know from Section 3.3 of the existence, continuation, and uniqueness of a solution in such a case. Piecing the intervals together we have piecewise-continuous initial conditions x_t for each interval, but this is handled since f_σ is composite-PC.

7.2 Switched Contact Rate with Pulse Vaccination

7.2.1 Eradication with $\tau = T$

In this section we sharpen the results of Liu and Stechlinski [53].

We consider the constant-population model with standard incidence,

$$\begin{cases} S' &= \mu(N-S) - \beta_\sigma \frac{SI}{N} \\ I' &= \beta_\sigma \frac{SI}{N} - (\mu+\gamma)I \quad , \qquad t \neq k\tau \\ R' &= \gamma I - \mu R. \end{cases} \tag{7.7}$$

$$\begin{cases} S(k\tau) &= (1-p)S(k\tau^-) \\ I(k\tau) &= I(k\tau^-) \\ R(k\tau) &= R(k\tau^-) + pS(k\tau^-) \end{cases}$$

In [53] Liu and Stechlinski consider nearly the same model:

$$\begin{cases} s' &= \mu(1-s) - \beta_\sigma si \\ i' &= \beta_\sigma si - (\mu+\gamma)i \ , \qquad t \neq k\tau \\ r' &= \gamma i - \mu r. \end{cases} \tag{7.8}$$

$$\begin{cases} s(k\tau^+) &= (1-p)s(k\tau) \\ i(k\tau^+) &= (1-p)i(k\tau) \\ r(k\tau^+) &= r(k\tau) + ps(k\tau) + pi(k\tau) \end{cases}$$

Because they consider a normalized constant-population model we express the compartments as population fractions $s = S/N$, *etc.*, so $s + i + r = 1$. This change of variables is explained in detail in Section 6.1. The only other differences in the model are that we consider right-continuous populations (for consistency with earlier discussions), while in [53] the authors use left-continuous; and in [53] the pulse vaccination also affects $i(t)$ (by way of treatment).

Liu and Stechlinski state the following result:

Theorem 24. *([53], Thm. 3.3) Given the ratios*

$$\mathcal{R}_i := \frac{\beta_i}{\mu+\gamma}, \tag{7.9}$$

if the switching rule $\sigma(t)$ is periodic and

$$\frac{\ln(1-p)}{(\mu+\gamma)T} + \frac{\sum_{i=1}^m \mathcal{R}_i T_i}{T} < 1, \tag{7.10}$$

then the solution of (7.8) converges to the disease-free periodic solution $(s,i,r) = (\tilde{s}, 0, 1-\tilde{s})$.

The $\ln(1-p)/((\mu+\gamma)T)$ term of (7.10) comes from the pulse treatment of the infective class [53]. The disease-free solution $\tilde{s}(t)$ follows directly from Lemma 1 and the pulse vaccination procedure of Section 4.3.1: as in Equation (5.3) we have

$$\tilde{s}(t) = 1 - \frac{p}{1-(1-p)e^{-\mu\tau}} e^{-\mu(t-k\tau)}, \quad t \in (k\tau, (k+1)\tau]. \tag{7.11}$$

We continue with the lower-case $\tilde{s}$ because we are looking at population fractions in Equation (7.8). We will show that we can tighten the threshold for eradication using the disease-free periodic solution $\tilde{s}$ (as in [27]), although we do not consider the $\ln(1-p)/((\mu+\gamma)T)$ impulsive treatment term.

Claim 7. *Define the new ratios*

$$\mathcal{R}_i^* := \frac{\beta_i \tilde{s}^M}{\mu+\gamma}, \tag{7.12}$$

where $\tilde{s}^M = \max_{t\in[0,\tau]} \tilde{s}(t)$. *If the switching rule* $\sigma(t)$ *is periodic and*

$$\frac{\sum_{i=1}^m \mathcal{R}_i^* T_i}{T} < 1, \tag{7.13}$$

then the solution of (7.7) converges to the disease-free periodic solution $(S,I,R) = (N\tilde{s}, 0, N(1-\tilde{s}))$.

Proof. In [53] the authors use the fact that

$$\begin{aligned} i' &= [\beta_i s - (\mu+\gamma)]i \\ &\leq [\beta_i - (\mu+\gamma)]i \end{aligned}$$

since $0 \leq s \leq 1$.

We instead make the change of variables $s = S/N, i = I/N, r = R/N$ in (7.7) so our model looks just like (7.8) besides the direction of continuity and the pulse treatment of $i(t)$. We use Lemma 1 to say that there exists $t_1 > t_0$ such that

$$\begin{cases} s' & \leq \mu(1-s) \\ s(k\tau) & = (1-p)s(k\tau^-) \end{cases} \qquad \Rightarrow \qquad s(t) < \tilde{s}(t) + \epsilon$$

for all $t > t_1$, for any $\epsilon > 0$. Then

$$\begin{aligned} i' &= [\beta_i s - (\mu+\gamma)]i \\ &\leq [\beta_i(\tilde{s}+\epsilon) - (\mu+\gamma)]i \end{aligned} \tag{7.14}$$

eventually, where ϵ is arbitrarily small so the strict inequality in our threshold condition (7.13) will cause it to be irrelevant (see explanation in Section 5.1). The remainder of the proof is identical to that in [53]; thus we find that if

$$\frac{\sum_{i=1}^m \mathcal{R}_i^* T_i}{T} = \tilde{s}^M \frac{\sum_{i=1}^m \mathcal{R}_i T_i}{T} < 1, \tag{7.15}$$

where again $\tilde{s}^M = \max_{t\in[0,\tau]} \tilde{s}(t)$, then the disease will be eradicated. □

The main importance of this claim is that $\tilde{s}^M$ can be very small indeed: for $\mu = 1/70, \tau = 4, p = 0.2$ we have $\tilde{s}^M \approx 0.227$; for $p = 0.8, \tilde{s}^M = 0.069$. We see that pulse vaccination can very quickly decrease the susceptible population, and we take advantage of this result.

7.2.2 Eradication with $\tau = nT$

If the pulse vaccination period is an integer multiple of the switching period, and if condition (7.13) is satisfied, then we will still have eradication of the disease.

If (7.13) is not satisfied then we may still be able to satisfy a looser bound on the $\mathcal{R}_i$.

Claim 8. *Suppose $\sigma(t)$ is periodic with period T and the pulse vaccination period is $\tau = nT$. If*

$$\frac{1}{\tau}\int_0^\tau \tilde{s}(t)\mathcal{R}_{\sigma(t)}dt < 1, \tag{7.16}$$

where $\mathcal{R}_{\sigma(t)} = \beta_{\sigma(t)}/(\mu+\gamma)$ as in [53]. Then the disease will be eradicated.

Proof. From the strict inequality in (7.16), pick ϵ small enough so that

$$\frac{1}{\tau}\int_0^\tau (\tilde{s}(t)\mathcal{R}_{\sigma(t)} - 1)dt < -2\epsilon\beta_{av}, \tag{7.17}$$

where $\beta_{av} = \int_0^{nT}\beta_{\sigma(t)}dt = n\int_0^T \beta_{\sigma(t)}dt$.

Starting with $t = t_1$ where t_1 is large enough so that

$$I'(t) < [\beta_{\sigma(t)}(\tilde{s}(t)+\epsilon) - (\mu+\gamma)]I(t), \tag{7.18}$$

for $t \geq t_1$, from the above we get that

$$\frac{d}{dt}\left(I(t)\exp\left\{-\int_{t_1}^t (\mu+\gamma)(\mathcal{R}_{\sigma(\theta)}(\tilde{s}(\theta)+\epsilon)-1)d\theta\right\}\right) < 0. \tag{7.19}$$

In particular, integrate from t_1 to $t_1+\tau$ to get

$$\begin{aligned}
I(t_1+\tau) &< I(t_1)\exp\left\{\int_{t_1}^{t_1+\tau}(\mu+\gamma)(\mathcal{R}_{\sigma(\theta)}(\tilde{s}(\theta)+\epsilon)-1)d\theta\right\} \\
&< I(t_1)\exp\left\{\int_{t_1}^{t_1+\tau}(\mu+\gamma)(\mathcal{R}_{\sigma(\theta)}\tilde{s}(\theta)-1)d\theta + \epsilon\int_{t_1}^{t_1+\tau}(\mu+\gamma)\mathcal{R}_{\sigma(\theta)}d\theta\right\} \\
&< I(t_1)\exp\{(\mu+\gamma)(-2\epsilon\beta_{av}+\epsilon\beta_{av}\} \\
&< I(t_1)\exp\{-(\mu+\gamma)\epsilon\beta_{av}\}
\end{aligned}$$

by (7.17) since $\tau = nT$ and $\sigma(t)$ and $\tilde{s}(t)$ have periods which divide τ. Define $c := \exp\{-(\mu+\gamma)\epsilon\beta_{av}\} < 1$, then integrating over successive intervals we find that $I(t_1+k\tau) < I(t_1)c^k \to 0$ as $k \to \infty$. By the proof in Section 5.1 we have that the disease-free solution is uniformly asymptotically stable.

□

7.3 Switched Contact Rate SEIR Model with Pulse Vaccination and Delay

We consider the constant-population model with standard incidence,

$$\begin{cases} S' &= \mu N - \mu S - \beta_\sigma \frac{SI}{N} \\ E' &= \beta_\sigma \frac{SI}{N} - \beta_{\sigma(t-r)} \frac{S(t-r)I(t-r)}{N(t-r)} - \mu E \\ I' &= \beta_{\sigma(t-r)} \frac{S(t-r)I(t-r)}{N(t-r)} - (\mu+\gamma)I \\ R' &= \gamma I - \mu R. \end{cases}, \qquad t \neq k\tau \tag{7.20}$$

$$\begin{cases} S(k\tau) &= (1-p)S(k\tau^-) \\ E(k\tau) &= E(k\tau^-) \\ I(k\tau) &= I(k\tau^-) \\ R(k\tau) &= R(k\tau^-) + pS(k\tau^-) \end{cases}$$

As explained in Section 6.5, because N is constant we may again make the change of variables to population fractions, and be left with the bilinear incidence model

$$\begin{cases} S' &= \mu - \mu S - \beta_\sigma SI \\ E' &= \beta_\sigma SI - \beta_{\sigma(t-r)} S(t-r)I(t-r) - \mu E \\ I' &= \beta_{\sigma(t-r)} S(t-r)I(t-r) - (\mu+\gamma)I \\ R' &= \gamma I - \mu R. \end{cases}, \qquad t \neq k\tau \tag{7.21}$$

$$\begin{cases} S(k\tau) &= (1-p)S(k\tau^-) \\ E(k\tau) &= E(k\tau^-) \\ I(k\tau) &= I(k\tau^-) \\ R(k\tau) &= R(k\tau^-) + pS(k\tau^-) \end{cases}$$

where each of S, E, I, R is less than or equal to 1. We stick with the uppercase letters out of consistency with the work in Chapter 5.

We make the assumption that $T_i > r$ for $i = 1..m$. This assumption may be restrictive physically, but it simplifies the analysis; also, since the T_i are usually on the order of months or seasons, and the latent period is likely on the order of days, in practice the assumption can easily hold.

7.3.1 2 Subsystems

In this section we assume $\sigma(t) \in \{1, 2\}$ (that is, $m = 2$) and we look to find conditions, which lead to disease eradication, on the average ratio of the parameters of $I'(t)$ (including $\tilde{S}$) over one

period T of $\sigma(t)$.

Definition of $V(t)$

We have that

$$I'(t) \leq \beta_{\sigma(t-r)} e^{-\mu r} \tilde{S}^M I(t-r) - (\mu+\gamma) I(t). \tag{7.22}$$

Use the comparison equation

$$x'(t) = \beta_{\sigma(t-r)} e^{-\mu r} \tilde{S}^M x(t-r) - (\mu+\gamma) x(t). \tag{7.23}$$

By the comparison theorem, $I(t) \leq x(t)$ and since $I(t) \geq 0$, if we can show $x(t) \to 0$ then by squeeze theorem $I(t) \to 0$ as well.

We define

$$V(t) := \frac{1}{\mu+\gamma} \left(x(t) + \int_{t-r}^{t} \beta_{\sigma(s)} e^{-\mu r} \tilde{S}^M x(s) ds \right) \tag{7.24}$$

Then

$$\begin{aligned}
(\mu+\gamma) V'(t) &= x'(t) + \frac{d}{dt} \left(\int_{t-r}^{t} \beta_{\sigma(s)} e^{-\mu r} \tilde{S}^M x(s) ds \right) \\
&= \beta_{\sigma(t-r)} e^{-\mu r} \tilde{S}^M x(t-r) - (\mu+\gamma) x(t) + \beta_{\sigma(t)} e^{-\mu r} \tilde{S}^M x(t) \\
&\quad - \beta_{\sigma(t-r)} e^{-\mu r} \tilde{S}^M x(t-r) \\
&= \left[\beta_{\sigma(t)} e^{-\mu r} \tilde{S}^M - (\mu+\gamma) \right] x(t) \\
\Rightarrow V'(t) &= \left[\frac{\beta_{\sigma(t)} e^{-\mu r}}{\mu+\gamma} \tilde{S}^M - 1 \right] x(t)
\end{aligned}$$

We define

$$\mathcal{R}^*_{\sigma(t)} = \frac{\beta_{\sigma(t)} e^{-\mu r}}{\mu+\gamma} \tilde{S}^M \tag{7.25}$$

Then we get

$$V'(t) = [\mathcal{R}^*_{\sigma(t)} - 1] x(t) \tag{7.26}$$

Since $\sigma(t) = i$ for $t \in [t_{i-1}, t_i]$, we define $\mathcal{R}^*_i := \mathcal{R}^*_{\sigma(t)}$ for $t \in [t_{i-1}, t_i]$. Then

$$V'(t) = [\mathcal{R}^*_i - 1] x(t) \quad \text{for } t \in [t_{i-1}, t_i]. \tag{7.27}$$

Define $T_i = t_i - t_{i-1}$. Initially we let $m = 2$, that is, $\sigma(t) \in \{1, 2\}$. Suppose

$$(\mathcal{R}^*_i - 1) T_i + (\mathcal{R}^*_{i+1} - 1) T_{i+1} < 0. \tag{7.28}$$

In the case where $r = 0$ we know that the disease will be eradicated. We now look for restrictions in the delay case.

Proof $V(t) \to 0$

For brevity we let

$$\tilde{\beta}_\sigma(t) := \beta_{\sigma(s)} e^{-\mu r} \tilde{S}^M. \tag{7.29}$$

For $t \in [t_{i-1}, t_i)$,

$$\begin{aligned} V'(t) &= [\mathcal{R}_i^* - 1]x(t) \\ &= [\mathcal{R}_i^* - 1]\left[(\mu+\gamma)V(t) - \int_{t-r}^{t} \beta_{\sigma(s)} e^{-\mu r} \tilde{S}^M x(s) ds\right] \\ \Rightarrow \frac{d}{dt}\left[V(t)e^{-(\mu+\gamma)(\mathcal{R}_i^*-1)t}\right] &= -(\mathcal{R}_i^* - 1)e^{-(\mu+\gamma)(\mathcal{R}_i^*-1)t} \int_{t-r}^{t} \tilde{\beta}_{\sigma(s)} x(s) ds. \end{aligned}$$

Integrating from t_{i-1} to t,

$$\begin{aligned} V(t)e^{-(\mu+\gamma)(\mathcal{R}_i^*-1)t} &- V(t_{i-1})e^{-(\mu+\gamma)(\mathcal{R}_i^*-1)t_{i-1}} \\ &= -\int_{t_{i-1}}^{t} \left((\mathcal{R}_i^* - 1)e^{-(\mu+\gamma)(\mathcal{R}_i^*-1)\theta} \int_{\theta-r}^{\theta} \tilde{\beta}_{\sigma(s)} x(s) ds\right) d\theta \\ V(t) &= V(t_{i-1})e^{(\mu+\gamma)(\mathcal{R}_i^*-1)(t-t_{i-1})} \\ &\quad - (\mathcal{R}_i^* - 1)e^{(\mu+\gamma)(\mathcal{R}_i^*-1)t} \int_{t_{i-1}}^{t} \left(e^{-(\mu+\gamma)(\mathcal{R}_i^*-1)\theta} \int_{\theta-r}^{\theta} \tilde{\beta}_{\sigma(s)} x(s) ds\right) d\theta \end{aligned}$$

Thus, recalling that $T_i = t_i - t_{i-1}$, we find

$$\begin{aligned} V(t_i) &= V(t_{i-1})e^{(\mu+\gamma)(\mathcal{R}_i^*-1)(t_i-t_{i-1})} \\ &\quad - (\mathcal{R}_i^* - 1)e^{(\mu+\gamma)(\mathcal{R}_i^*-1)t_i} \int_{t_{i-1}}^{t_i} \left(e^{-(\mu+\gamma)(\mathcal{R}_i^*-1)t} \int_{t-r}^{t} \tilde{\beta}_{\sigma(s)} x(s) ds\right) dt \\ &= V(t_{i-1})e^{(\mu+\gamma)(\mathcal{R}_i^*-1)T_i} \\ &\quad - (\mathcal{R}_i^* - 1)e^{(\mu+\gamma)(\mathcal{R}_i^*-1)t_i} \int_{t_{i-1}}^{t_i} \left(e^{-(\mu+\gamma)(\mathcal{R}_i^*-1)t} \int_{t-r}^{t} \tilde{\beta}_{\sigma(s)} x(s) ds\right) dt \end{aligned}$$

Nothing in the above analysis depends on our assumption (7.28). Thus we can apply the same

process on $[t_i, t_{i+1}]$ to get

$$V(t_{i+1}) = V(t_i)e^{(\mu+\gamma)(\mathcal{R}^*_{i+1}-1)T_{i+1}} \tag{7.30}$$
$$- (\mathcal{R}^*_{i+1}-1)e^{(\mu+\gamma)(\mathcal{R}^*_{i+1}-1)t_{i+1}} \int_{t_i}^{t_{i+1}} \left(e^{-(\mu+\gamma)(\mathcal{R}^*_{i+1}-1)t} \int_{t-r}^{t} \tilde{\beta}_{\sigma(s)} x(s) ds \right) dt$$
$$= V(t_{i-1})e^{(\mu+\gamma)[(\mathcal{R}^*_i-1)T_i+(\mathcal{R}^*_{i+1}-1)T_{i+1}]}$$
$$- (\mathcal{R}^*_i-1)e^{(\mu+\gamma)(\mathcal{R}^*_i-1)t_i}e^{(\mu+\gamma)(\mathcal{R}^*_{i+1}-1)T_{i+1}} \int_{t_{i-1}}^{t_i} \left(e^{-(\mu+\gamma)(\mathcal{R}^*_i-1)t} \int_{t-r}^{t} \tilde{\beta}_{\sigma(s)} x(s) ds \right) dt$$
$$- (\mathcal{R}^*_{i+1}-1)e^{(\mu+\gamma)(\mathcal{R}^*_{i+1}-1)t_{i+1}} \int_{t_i}^{t_{i+1}} \left(e^{-(\mu+\gamma)(\mathcal{R}^*_{i+1}-1)t} \int_{t-r}^{t} \tilde{\beta}_{\sigma(s)} x(s) ds \right) dt \tag{7.31}$$

We are still dealing with the case $m = 2$, so given the period T of the switching signal $\sigma(t)$ we have that $V(t_{i+1}) = V(t_{i-1+m}) = V(t_{i-1} + T)$. If we can show $V(t_{i-1+m}) \leq \eta V(t_{i-1})$ for some $\eta < 1$ then we can show that the switched system is uniformly asymptotically stable.

If both $\mathcal{R}^*_i$ and $\mathcal{R}^*_{i+1}$ are less than 1, the disease will be eradicated - we may use a common Lyapunov function

$$V(t) = \frac{1}{\mu+\gamma} \left(x(t) + \int_{t-r}^{t} \beta^M e^{-\mu r} \tilde{S}^M x(s) ds \right) \tag{7.32}$$

to prove it, where β^M is the largest β_i. If both $\mathcal{R}^*_i$ and $\mathcal{R}^*_{i+1}$ are greater than 1, the disease will remain permanent: we can use a common "Lyapunov functional" using the smallest value of β_i to prove the disease persists by the method Gao *et. al.* used in [27]. Thus we are interested in the case where one of the ratios is less than 1 while the other is greater. (To generalize, in systems with $m > 2$ we are interested in the cases when the $\mathcal{R}^*_i$'s are not all greater or all less than 1).

WLOG we assume that $\mathcal{R}^*_i < 1 < \mathcal{R}^*_{i+1}$. Then the second term of (7.30) is positive (we are subtracting a negative) while the third term is negative. We are interested in an upper bound on $V(t_{i+1})$; thus we drop the third term to find

$$V(t_{i+1}) \leq V(t_{i-1})e^{(\mu+\gamma)[(\mathcal{R}^*_i-1)T_i+(\mathcal{R}^*_{i+1}-1)T_{i+1}]} \tag{7.33}$$
$$- (\mathcal{R}^*_i-1)e^{(\mu+\gamma)(\mathcal{R}^*_i-1)t_i}e^{(\mu+\gamma)(\mathcal{R}^*_{i+1}-1)T_{i+1}} \int_{t_{i-1}}^{t_i} \left(e^{-(\mu+\gamma)(\mathcal{R}^*_i-1)t} \int_{t-r}^{t} \tilde{\beta}_{\sigma(s)} x(s) ds \right) dt$$

At this point we would like to factor the above inequality. The first term is a function of $V(t_{i-1})$ but we need to find such a factor in the second term somehow. One method would be to use $\int_{t-r}^{t} \tilde{\beta}_{\sigma(s)} x(s) ds = (\mu+\gamma)V(t) - x(t)$ by definition of V and use $V(t) \leq V(t_{i-1})$ on $[t_{i-1}, t_i]$ to further simplify; following through with the t-integral, however, we eventually find the inequality

$$V(t_{i+1}) \leq e^{(\mu+\gamma)(\mathcal{R}^*_{i+1}-1)T_{i+1})} V(t_{i-1}). \tag{7.34}$$

The exponent is positive due to our assumption above so this method does not help us to prove that $V(t) \to 0$.

Instead, by the definition of $V(t)$ we also have $x(t) \leq (\mu+\gamma)V(t)$ for all t. On $[t_{i-1}, t_i)$ we have $V'(t) = (\mathcal{R}_i^* - 1)x(t) \leq 0$ so $x(t) \leq (\mu+\gamma)V(t) \leq (\mu+\gamma)V(t_{i-1})$ for $t \in [t_{i-1}, t_i]$. Similarly on $[t_{i-1} - r, t_{i-1})$ we have $V'(t) = (\mathcal{R}_{i-1}^* - 1)x(t) = (\mathcal{R}_{i+1}^* - 1)x(t) \geq 0$ since $m = 2$, so $V(t) \leq V(t_{i-1})$. Thus $x(t) \leq (\mu+\gamma)V(t) \leq (\mu+\gamma)V(t_{i-1})$ for $t \in [t_{i-1} - r, t_i]$, and so

$$\int_{t_{i-1}}^{t_i} \left(e^{-(\mu+\gamma)(\mathcal{R}_i^*-1)\theta} \int_{t-r}^{t} \tilde{\beta}_{\sigma(s)} x(s) ds \right) dt \leq (\mu+\gamma)V(t_{i-1}) \int_{t_{i-1}}^{t_i} \left(e^{-(\mu+\gamma)(\mathcal{R}_i^*-1)t} \int_{t-r}^{t} \tilde{\beta}_{\sigma(s)} ds \right) dt$$
$$\leq V(t_{i-1}) \cdot e^{-(\mu+\gamma)(\mathcal{R}_i^*-1)t_i} \cdot (\mu+\gamma) \left[\frac{\tilde{\beta}_i + \tilde{\beta}_{i+1}}{2} r^2 + \tilde{\beta}_i r (T_i - r) \right].$$

The double integral is evaluated by factoring out an upper bound on the exponential term, then splitting the dt integral into two, one from t_{i-1} to $t_{i-1} + r$ and one from $t_{i-1} + r$ to t_i. Then in the former we split the ds integral into two, one from $t - r$ to t_{i-1} and one from t_{i-1} to t. Including this bound in (7.33) we get

$$\begin{aligned}
V(t_{i+1}) &\leq V(t_{i-1}) e^{(\mu+\gamma)[(\mathcal{R}_i^*-1)T_i + (\mathcal{R}_{i+1}^*-1)T_{i+1}]} \\
&\quad - (\mathcal{R}_i^* - 1) e^{(\mu+\gamma)(\mathcal{R}_i^*-1)t_i} e^{(\mu+\gamma)(\mathcal{R}_{i+1}^*-1)T_{i+1}} \int_{t_{i-1}}^{t_i} \left(e^{-(\mu+\gamma)(\mathcal{R}_i^*-1)\theta} \int_{t-r}^{t} \tilde{\beta}_{\sigma(s)} x(s) ds \right) dt \\
&\leq V(t_{i-1}) e^{(\mu+\gamma)[(\mathcal{R}_i^*-1)T_i + (\mathcal{R}_{i+1}^*-1)T_{i+1}]} \\
&\quad - (\mathcal{R}_i^* - 1) e^{(\mu+\gamma)(\mathcal{R}_{i+1}^*-1)T_{i+1}} V(t_{i-1})(\mu+\gamma) \left[\frac{\tilde{\beta}_i + \tilde{\beta}_{i+1}}{2} r^2 + \tilde{\beta}_i r (T_i - r) \right] \\
&= V(t_{i-1}) \cdot e^{(\mu+\gamma)[(\mathcal{R}_i^*-1)T_i + (\mathcal{R}_{i+1}^*-1)T_{i+1}]} \cdot \\
&\quad \left(1 + (1 - \mathcal{R}_i^*)(\mu+\gamma) e^{(\mu+\gamma)(1-\mathcal{R}_i^*)T_i} \left[\frac{\tilde{\beta}_i + \tilde{\beta}_{i+1}}{2} r^2 + \tilde{\beta}_i r (T_i - r) \right] \right)
\end{aligned} \tag{7.35}$$

Define

$$\begin{aligned}
\eta &:= e^{(\mu+\gamma)[(\mathcal{R}_i^*-1)T_i + (\mathcal{R}_{i+1}^*-1)T_{i+1}]} \\
&\quad \cdot \left(1 + (1 - \mathcal{R}_i^*)(\mu+\gamma) \cdot e^{(\mu+\gamma)(1-\mathcal{R}_i^*)T_i} \left[\frac{\tilde{\beta}_i + \tilde{\beta}_{i+1}}{2} r^2 + \tilde{\beta}_i r (T_i - r) \right] \right),
\end{aligned} \tag{7.36}$$

then we are interested in if $\eta < 1$. The second factor (in round brackets) is greater than 1 since $\mathcal{R}_i^* < 1$ and all other values are positive. The first factor, $e^{(\mu+\gamma)[(\mathcal{R}_i^*-1)T_i + (\mathcal{R}_{i+1}^*-1)T_{i+1}]}$, must be less than 1 if we are to have $\eta < 1$, which agrees with Assumption (7.28). In fact, since $\eta < 1$ is

sufficient for eradication, we get the restriction

$$
\begin{aligned}
&(\mu+\gamma)[(\mathcal{R}_i^*-1)T_i+(\mathcal{R}_{i+1}^*-1)T_{i+1}] \\
&\qquad < \ln\left(1+(1-\mathcal{R}_i^*)(\mu+\gamma)\cdot e^{(\mu+\gamma)(1-\mathcal{R}_i^*)T_i}\left[\frac{\tilde{\beta}_i+\tilde{\beta}_{i+1}}{2}r^2+\tilde{\beta}_i r(T_i-r)\right]\right)^{-1} \\
\Rightarrow\ &\frac{\mathcal{R}_i^*T_i+\mathcal{R}_{i+1}^*T_{i+1}}{T} \\
&\qquad < 1-\frac{1}{(\mu+\gamma)T}\ln\left(1+(1-\mathcal{R}_i^*)(\mu+\gamma)e^{(\mu+\gamma)(1-\mathcal{R}_i^*)T_i}\cdot r\cdot\left[\frac{\tilde{\beta}_i+\tilde{\beta}_{i+1}}{2}r+\tilde{\beta}_i(T_i-r)\right]\right)
\end{aligned}
$$

Define

$$
\zeta := (1-\mathcal{R}_i^*)(\mu+\gamma)^2 e^{(\mu+\gamma)(1-\mathcal{R}_i^*)T_i}\cdot\left[\frac{\mathcal{R}_i^*+\mathcal{R}_{i+1}^*}{2}r+\mathcal{R}_i^*(T_i-r)\right] \tag{7.37}
$$

then $\zeta > 0$ and we have the slightly more understandable condition for eradication

$$
\sum_{j=1}^{2}\frac{\mathcal{R}_j^*T_j}{T} < 1-\frac{1}{(\mu+\gamma)T}\ln(1+r\zeta). \tag{7.38}
$$

We note that if $r=0$ we recover the non-delay eradication threshold (7.28).

This condition is rather complicated, but we note that it can definitely be achieved; for example, if we take $\mathcal{R}_1^*=1/3$, $\mathcal{R}_2^*=1.5$, $T_1=T_2=0.5$, and as in simulations we have $\mu=1/70$, $\gamma=2$, $r=5/365$, $\tau=4$, then we get that the left-hand side is equal to 0.9167 while the right-hand side of the condition is equal to 0.9938. Even with a much larger delay, say $r=50/365$, we get that the right-hand side is equal to $0.9183 > 0.9167$ (the left side is independent of r). Note that by choosing the $\mathcal{R}_i^*$ we can ignore the dependence on β_i and on the pulse vaccination proportion p; those parameters both affect the $\mathcal{R}_i^*$ but we are only interested in their combination.

Proof $I(t)\to 0$

While the uniform asymptotic stability of $I(t)$ may not be evident, we can clearly find that $I(t)$ is asymptotically stable by squeeze theorem. That is,

$$
0 \le I(t) \le x(t) \le (\mu+\gamma)V(t) \to 0 \text{ as } t\to\infty.
$$

7.3.2 m Subsystems

The indices are more complicated when there are more than 2 subsystems, but the general principle is the same. We integrate $V(t)$ over successive switch intervals to get $V(t_{i+m})$ as a

function of $V(t_i)$. We drop the negative terms to get an upper bound on $V(t_{i+m})$ and bound the remaining terms using $V(t_i)$. If the period-average of the parameters of $I'(t)$ (including the max $\tilde{S}^M$ of $\tilde{S}(t)$) is less than 1 we find that $V(t_{i+m}) \leq \eta V(t_i)$ where η depends on our interval but is < 1 eventually.

For brevity we define

$$f(i) := \int_{t_{i-1}}^{t_i} \left(e^{-(\mu+\gamma)(\mathcal{R}_i^*-1)t} \int_{t-r}^{t} \tilde{\beta}_{\sigma(s)} x(s) ds \right) dt. \tag{7.39}$$

Starting from $t = t_i$ and integrating successively, we get

$$\begin{aligned}
V(t_{i+1}) &= V(t_i)\exp\{(\mu+\gamma)(\mathcal{R}_{i+1}^*-1)T_{i+1}\} \\
&\quad - (\mathcal{R}_{i+1}^*-1)f(i+1)\exp\{(\mu+\gamma)(\mathcal{R}_{i+1}^*-1)t_{i+1}\}, \\
V(t_{i+2}) &= V(t_i)\exp\{(\mu+\gamma)[(\mathcal{R}_{i+1}^*-1)T_{i+1} + (\mathcal{R}_{i+2}^*-1)T_{i+2}]\} \\
&\quad - (\mathcal{R}_{i+1}^*-1)f(i+1)\exp\{(\mu+\gamma)[(\mathcal{R}_{i+1}^*-1)t_{i+1} + (\mathcal{R}_{i+2}^*-1)T_{i+2}]\} \\
&\quad - (\mathcal{R}_{i+2}^*-1)f(i+2)\exp\{(\mu+\gamma)(\mathcal{R}_{i+2}^*-1)t_{i+2}\}, \ \textit{etc.}
\end{aligned}$$

Continuing this way we find

$$\begin{aligned}
V(t_{i+k}) &= V(t_i)\exp\left\{ (\mu+\gamma)\sum_{j=1}^{k}(\mathcal{R}_{i+j}^*-1)T_{i+j} \right\} \\
&\quad - (\mathcal{R}_{i+1}^*-1)f(i+1)\exp\left\{ (\mu+\gamma)\left((\mathcal{R}_{i+1}^*-1)t_{i+1} + \sum_{j=2}^{k}(\mathcal{R}_{i+j}^*-1)T_{i+j} \right) \right\} \\
&\quad \vdots \\
&\quad - (\mathcal{R}_{i+k}^*-1)f(i+k)\exp\left\{ (\mu+\gamma)(\mathcal{R}_{i+k}^*-1)t_{i+k} \right\},
\end{aligned}$$

that is,

$$\begin{aligned}
V(t_{i+k}) &= V(t_i)\exp\left\{ (\mu+\gamma)\sum_{j=1}^{k}(\mathcal{R}_{i+j}^*-1)T_{i+j} \right\} \\
&\quad - \sum_{h=1}^{k}(\mathcal{R}_{i+h}^*-1)f(i+h)\exp\left\{ (\mu+\gamma)\left((\mathcal{R}_{i+h}^*-1)t_{i+h} + \sum_{j=h+1}^{k}(\mathcal{R}_{i+j}^*-1)T_{i+j} \right) \right\}
\end{aligned} \tag{7.40}$$

for any $k \in \mathbb{Z}$.

In particular, after one period we find

$$V(t_{i+m}) = V(t_i)\exp\left\{(\mu+\gamma)\sum_{j=1}^{m}(\mathcal{R}^*_{i+j}-1)T_{i+j}\right\} \tag{7.41}$$
$$-\sum_{h=1}^{m}(\mathcal{R}^*_{i+h}-1)f(i+h)\exp\left\{(\mu+\gamma)\left((\mathcal{R}^*_{i+h}-1)t_{i+h}+\sum_{j=h+1}^{m}(\mathcal{R}^*_{i+j}-1)T_{i+j}\right)\right\}.$$

In the subtracted terms, the exponential factors are clearly all positive, as are the $f(i+h)$ (since they are integrals of positive quantities). The $\mathcal{R}^*_{i+h}-1$ factors are what can change the sign of the terms. We drop the terms for which $\mathcal{R}^*_{i+1}>1$ to find the following upper bound on $V(t_{i+m})$:

$$V(t_{i+m}) \le V(t_i)\exp\left\{(\mu+\gamma)\sum_{j=1}^{m}(\mathcal{R}^*_{i+j}-1)T_{i+j}\right\} \tag{7.42}$$
$$+\sum_{\substack{h=1\\ \mathcal{R}^*_{i+h}<1}}^{m}(1-\mathcal{R}^*_{i+h})f(i+h)\exp\left\{(\mu+\gamma)\left((\mathcal{R}^*_{i+h}-1)t_{i+h}+\sum_{j=h+1}^{m}(\mathcal{R}^*_{i+j}-1)T_{i+j}\right)\right\}.$$

If we can find the terms in the second line in terms of $V(t_i)$ then we may be able to reach conclusions about the asymptotic behaviour of V.

To do so, we first notice that for $h\in\{1,\dots,m\}$ such that $\mathcal{R}^*_{i+h}<1$,

$$f(i+h) \le e^{-(\mu+\gamma)(\mathcal{R}^*_{i+h}-1)t_{i+h}}\int_{t_{i+h-1}}^{t_{i+h}}\left(\int_{t-r}^{t}\tilde{\beta}_{\sigma(s)}x(s)ds\right)dt, \tag{7.43}$$

and so the first term in the round brackets in (7.42) is cancelled to obtain

$$V(t_{i+m}) \le V(t_i)\exp\left\{(\mu+\gamma)\sum_{j=1}^{m}(\mathcal{R}^*_{i+j}-1)T_{i+j}\right\} \tag{7.44}$$
$$+\sum_{\substack{h=1\\ \mathcal{R}^*_{i+h}<1}}^{m}(1-\mathcal{R}^*_{i+h})\int_{t_{i+h-1}}^{t_{i+h}}\left(\int_{t-r}^{t}\tilde{\beta}_{\sigma(s)}x(s)ds\right)dt\cdot\exp\left\{(\mu+\gamma)\sum_{j=h+1}^{m}(\mathcal{R}^*_{i+j}-1)T_{i+j}\right\}.$$

Then we use the fact that on any switch interval $[t_{k-1},t_k]$ in which $\mathcal{R}_k<1$, $V(t_k)\le V(t_{k-1})$ (since $V'(t)=(\mathcal{R}^*_{\sigma(t)}-1)x(t)$). On intervals in which $\mathcal{R}_k>1$, we still have

$$V'(t)\le(\mathcal{R}_k-1)(\mu+\gamma)V(t)\Rightarrow V(t)\le V(t_{k-1})\exp\{(\mu+\gamma)(\mathcal{R}_k-1)(t-t_{k-1})\}.$$

So for $t \in [t_{i+k-1} - r, t_{i+k}]$,

$$x(t) \leq (\mu+\gamma)V(t) \leq (\mu+\gamma)V(t_i)\exp\left\{(\mu+\gamma)\sum_{\substack{j=1\\ \mathcal{R}^*_{i+j}>1}}^{k}(\mathcal{R}^*_{i+j}-1)T_{i+j}\right\}. \tag{7.45}$$

Substituting (7.45) into (7.44),

$$\begin{aligned} V(t_{i+m}) \leq V(t_i)\exp\left\{(\mu+\gamma)\sum_{j=1}^{m}(\mathcal{R}^*_{i+j}-1)T_{i+j}\right\} \\ + V(t_i)\sum_{\substack{h=1\\ \mathcal{R}^*_{i+h}<1}}^{m}(1-\mathcal{R}^*_{i+h})\bar{f}(i+h)\exp\left\{(\mu+\gamma)\sum_{j=h+1}^{m}(\mathcal{R}^*_{i+j}-1)T_{i+j}\right\} \end{aligned} \tag{7.46}$$

where

$$\bar{f}(i+h) := (\mu+\gamma)\,\exp\left\{(\mu+\gamma)\sum_{\substack{j=1\\ \mathcal{R}^*_{i+j}>1}}^{h}(\mathcal{R}^*_{i+j}-1)T_{i+j}\right\}\int_{t_{i+h-1}}^{t_{i+h}}\left(\int_{t-r}^{t}\tilde{\beta}_{\sigma(s)}ds\right)dt \tag{7.47}$$

is a positive constant. Factoring (7.46), and leaving out the bounds of integration for brevity,

$$\begin{aligned} V(t_{i+m}) &\leq V(t_i)\cdot\exp\left\{(\mu+\gamma)\sum_{j=1}^{m}(\mathcal{R}^*_{i+j}-1)T_{i+j}\right\} \\ &\quad\cdot\left[1+\sum_{\substack{h=1\\ \mathcal{R}^*_{i+h}<1}}^{m}(1-\mathcal{R}^*_{i+h})\bar{f}(i+h)\exp\left\{-(\mu+\gamma)\sum_{j=1}^{h}(\mathcal{R}^*_{i+j}-1)T_{i+j}\right\}\right] \\ &= V(t_i)\cdot\exp\left\{(\mu+\gamma)\sum_{j=1}^{m}(\mathcal{R}^*_{i+j}-1)T_{i+j}\right\}\cdot[\ 1+ \\ &\quad\sum_{\substack{h=1\\ \mathcal{R}^*_{i+h}<1}}^{m}(1-\mathcal{R}^*_{i+h})(\mu+\gamma)\iint\tilde{\beta}_{\sigma(s)}ds\ dt\cdot\exp\left\{-(\mu+\gamma)\sum_{\substack{j=1\\ \mathcal{R}^*_{i+j}<1}}^{h}(\mathcal{R}^*_{i+j}-1)T_{i+j}\right\}] \end{aligned} \tag{7.48}$$

and so

$$V(t_{i+m}) \leq V(t_i) \cdot \exp\left\{(\mu+\gamma)\sum_{j=1}^{m}(\mathcal{R}_{i+j}^{*}-1)T_{i+j}\right\} \cdot \eta \tag{7.49}$$

where η is the factor in square brackets above. We are assuming for $i = \{1, \ldots, m\}$ that $\mathcal{R}_i^*$ is strictly greater or less than one, and treating the $\mathcal{R}_i^* = 1$ case as pathological. As before, the double integral is equal to

$$r \cdot \left[\frac{\tilde{\beta}_{i+h} + \tilde{\beta}_{i+h-1}}{2} r + \tilde{\beta}_i(T_i - r)\right]. \tag{7.50}$$

As in the $m = 2$ case, if we can show $V(t_{i+m}) \leq \xi V(t_i)$ for some $\xi < 1$ then $V(t_{i+km}) \leq \xi^k V(t_i) \to 0$ as $k \to \infty$. The factor η in the above is clearly greater than 1, so the exponential factor must certainly be less than 1 if we are to have $\xi < 1$. We thus extend Assumption 7.28 to

$$\sum_{i=1}^{m} \mathcal{R}_i^* T_i < T. \tag{7.51}$$

If $r = 0$ then this condition is sufficient. If $r \neq 0$ (that is, there is delay) then we must instead have the stronger condition

$$\sum_{i=1}^{m} \frac{\mathcal{R}_i^* T_i}{T} < 1 - \frac{1}{(\mu+\gamma)T} \cdot \tag{7.52}$$

$$\ln\left(1 + \sum_{\substack{h=1 \\ \mathcal{R}_{i+h}^{*}<1}}^{m} (1-\mathcal{R}_{i+h}^{*})(\mu+\gamma)\iint \tilde{\beta}_{\sigma(s)} ds dt \cdot \exp\left\{(\mu+\gamma)\sum_{\substack{j=1 \\ \mathcal{R}_{i+j}^{*}<1}}^{h} (1-\mathcal{R}_{i+j}^{*})T_{i+j}\right\}\right)$$

which is sufficient for the asymptotic stability of the disease-free equilibrium: that is, as $k \to \infty$, $V \to 0$. By squeeze theorem we have $0 \leq I(t) \leq x(t) \leq (\mu+\gamma)V(t) \to 0$ as before, so the disease is eradicated eventually.

We note that our boundaries on the $V(t_{i+h})$ are not tight, and in fact we lead to the conclusion (as seen in 7.48) that the $\mathcal{R}_i^*$ which are less than 1 actually contribute to the size of η! This result agrees with our previous analysis for $m = 2$, though; in both cases we note that as $r \to 0$ then we recover the delay-free restriction seen in [53].

7.4 Switched Contact Rate in Other Models

Our delay analysis so far has always dealt with a SEIR model with delay in the exposed class. In this section we look at extensions to other models. As in Sections 7.3.1 and 7.3.2, we assume

the total population N is constant in order to avoid the change-of-variable problems described in Section 6.5.

7.4.1 Delay in $I(t)$

We consider a normalized population model (obtained from a standard incidence, constant-population model) of the form

$$\begin{cases} S' &= \mu(1-S) - \beta_\sigma SI \\ I' &= \beta_\sigma SI - \beta_{\sigma(t-\omega)} e^{-\mu\omega} S(t-\omega) I(t-\omega) - \mu I \qquad t \neq k\tau \\ R' &= \beta_{\sigma(t-\omega)} e^{-\mu\omega} S(t-\omega) I(t-\omega) - \mu R. \end{cases} \tag{7.53}$$

$$\begin{cases} S(k\tau) &= (1-p) S(k\tau^-) \\ I(k\tau) &= I(k\tau^-) \\ R(k\tau) &= R(k\tau^-) + pS(k\tau^-) \end{cases}$$

As usual we first proceed by applying Lemma 1 to the equation for S' to find that $S(t)$ is bounded above by the disease-free solution which starts at the same initial value; then, since $\tilde{S}$ attracts all disease-free solutions, we as usual find that $S(t)$ becomes arbitrarily close to $\tilde{S}(t)$ from above. Then in I' we have

$$\begin{aligned} I' &< \beta_\sigma(\tilde{S}+\epsilon) I - \beta_{\sigma(t-\omega)} e^{-\mu\omega} S(t-\omega) I(t-\omega) - \mu I \\ &\leq \Big(\beta_\sigma(\tilde{S}+\epsilon) - \mu\Big) I. \end{aligned}$$

By dropping the delay term entirely, we obtain an ODE for $I(t)$ almost identical (besides the missing γ) to equation (7.14). We are justified mathematically in dropping this term; define

$$\begin{aligned} f(t,\psi) &= \beta_\sigma S(t)\psi(0) - \beta_{\sigma(t-\omega)} e^{-\mu\omega} S(t-\omega)\psi(-\omega) - \mu\psi(0), \\ g(t,\psi) &= \Big(\beta_\sigma(\tilde{S}^M+\epsilon) - \mu\Big)\psi(0). \end{aligned}$$

g satisfies the quasimonotone condition from [69] and, while we do not know $S(t-\omega)$, we know it is positive and so the subtracted delay term in f is positive. Then $f(t,\psi) \leq g(t,\psi)$ (for large enough t) for all $\psi \in \mathcal{PC}_{mathcalR_+}$, so from Theorem 16 we are able to compare $I(t)$ to the solution of $x' = \Big(\beta_\sigma(\tilde{S}+\epsilon) - \mu\Big) x$ [69]. Then if $x \to 0$ we can use squeeze theorem to show $I \to 0$ as well.

Just like in Claim 7 we define the ratios

$$\mathcal{R}_i^* := \frac{\beta_i \tilde{S}^M}{\mu},$$

where $\tilde{S}^M = \max_{t\in[0,\tau]} \tilde{S}(t)$. We again find that if the switching rule $\sigma(t)$ is periodic and if

$$\frac{\sum_{i=1}^{m} \mathcal{R}_i^* T_i}{T} < 1 \tag{7.54}$$

then $x \to 0$ and so the disease will be eradicated. The proof is identical to that in Claim 7 (which uses [53]) except for the lack of a γ term in the denominators of the $\mathcal{R}_i$.

Remark. While mathematically we have only "dropped γ," the physical ramifications are important. By entirely ignoring the delay term in I' we are ignoring recovery from the disease, with the only way left to leave the infective class being through natural deaths. The condition (7.58) is in fact very restrictive (we could have $\mu \approx 1/70$ while $\gamma \approx 2$ or greater, so $1/(\mu+\gamma) < 1/2$ while $1/\mu = 70$). The other parameters of the system would need to be much greater to ensure eradication under this analysis; basically our condition is that we need each infective individual to die of natural causes before they pass on the infection! We can at least take comfort that the pulse vaccination very quickly decreases the susceptible population, so the chance an infective will pass on the infection is greatly decreased.

A much sharper bound could likely be obtained if we instead considered the entire delay differential equation for I'.

7.4.2 Delay in $R(t)$

We again consider a normalized population model (obtained from a standard incidence, constant-population model) with non-permanent immunity, of the form

$$\begin{cases} S' &= \mu(1-S) - \beta_\sigma SI + \gamma e^{-\mu h} I(t-h) \\ I' &= \beta_\sigma SI - (\mu+\gamma)I \qquad\qquad t \neq k\tau \\ R' &= \gamma I - \gamma e^{-\mu h} I(t-h) - \mu R. \end{cases} \tag{7.55}$$

$$\begin{cases} S(k\tau) &= (1-p)S(k\tau^-) \\ I(k\tau) &= I(k\tau^-) \\ R(k\tau) &= R(k\tau^-) + pS(k\tau^-) \end{cases}$$

In this model the recovered individuals lose their immunity after a time h, and return to the susceptible compartment.

Here we have a simple ODE for I', so as long as we can find some sort of bound on $S(t)$, we should be able to find thresholds easily. The difficulty of course arises with the delay term in S'.

The simplest way is to ignore the delay part entirely and use the fact that we are dealing with population fractions; then $\gamma e^{-\mu h} I(t-h) \leq \gamma e^{-\mu h}$ and we are looking at a pulse vaccination

system for S of the form

$$\begin{aligned} S' &\leq (\mu + \gamma e^{-\mu h}) - \mu S, \quad t \neq k\tau \\ S(k\tau) &= (1-p)S(k\tau^-) \end{aligned} \tag{7.56}$$

Just like in Section 6.4, we can use a comparison system with equality to apply Lemma 1 and find that eventually $S(t) < \tilde{S}_\gamma(t) + \epsilon$, where

$$\tilde{S}_\gamma(t) = \frac{\mu + \gamma e^{-\mu h}}{\mu}\left[1 - \frac{p}{1-(1-p)e^{-\mu\tau}} e^{-\mu(t-k\tau)}\right].$$

Then we define

$$\mathcal{R}_i^* = \frac{\beta_i \tilde{S}_\gamma^M}{\mu + \gamma} \tag{7.57}$$

and proceed as in Section 7.2 to get eradication so long as [53]

$$\frac{\sum_{i=1}^m \mathcal{R}_i^* T_i}{T} < 1. \tag{7.58}$$

Alternatively we could try to include the delay in S'. It seems as though keeping the $I(t-h)$-dependence will be difficult, since we would have two coupled equations for S' and I' (rather than being able to deal with S first then use the result in I'). Instead we can use the fact that

$$I(t) \leq N(t) - S(t) = 1 - S(t), \tag{7.59}$$

to get

$$\begin{aligned} S' &\leq \mu(1-S) - \beta_\sigma SI + \gamma e^{-\mu h}(1 - S(t-h)) \\ &= (\mu + \gamma e^{-\mu h}) - (\mu S + \gamma e^{-\mu h} S(t-h)) - \beta_\sigma SI \\ &\leq (\mu + \gamma e^{-\mu h}) - (\mu S + \gamma e^{-\mu h} S(t-h)). \end{aligned}$$

This bound on S' is similar to (7.56) but with the extra negative term $-\gamma e^{-\mu h} S(t-h)$, so we expect to find S decreases more or at least faster when we include the delay term.

7.5 Switched System Simulations

For all of the following simulations we use the Matlab DDE solver dde23. We have so far used this solver's event-finder to halt the integration at pulse vaccination times; now we use it to find the parameter switch times as well.

We again use the initial conditions $R(0) = 0$, $I(t) = be^{\mu t}$ for $t \in [-r, 0]$, $S(t) = ae^{-\mu t}$ for $t \in [-r, 0]$, and we determine $E(0)$ based on Equation 4.8, reprinted here (with switching) for $t = 0$:

$$E(0) = \int_{-r}^{0} \beta_{\sigma(s)} e^{\mu s} S(s) I(s) ds. \tag{7.60}$$

As before, we choose $a = 0.8$ and b is then fixed because we need $S(0) + E(0) + I(0) = 1$. We assume that the parameter switching still occurs in the initial condition functions, and still assume that the delay is small compared to the switch times (so $r < T_i$, $i = 1..m$). Thus we use β_m in the initial condition (since $\sigma(t) = m$ for $t \in [-T_m, 0] \supset [-r, 0]$) and then switch to β_1 starting at $t = 0$.

7.5.1 Delay in $E(t)$

In this subsection we look at simulations for the delayed SEIR model with pulse vaccination and switching parameter β_σ, System (7.21), that we studied in Section 7.3.

$\frac{1}{T}\sum_{i=1}^{m} \mathcal{R}_i^* T_i$ near 1

In Figures 7.1 - 7.4 we look at systems in which the time average $\frac{1}{T}\sum_{i=1}^{m} \mathcal{R}_i^* T_i$ is close to 1. The interpulse period is $\tau = 4$, the pulse vaccination proportion is $p = 0.6$, and the delay is $r = 5/365$, otherwise the parameters are as in Table 2.2. The first two figures have $\frac{1}{T}\sum_{i=1}^{m} \mathcal{R}_i^* T_i = 0.9875$, and the next pair have $\frac{1}{T}\sum_{i=1}^{m} \mathcal{R}_i^* T_i = 1.0125$. On the same scale as in Figure 7.3, the solution in Figures 7.1 - 7.2 looks almost identical. It is when we look extremely closely, as in Figures 7.2 and 7.4, that we see eradication on one side of the threshold and permanence on the other. Therefore our experimental results seem to support our theoretical ones.

Comparison to Model without Pulse Vaccination

In Section 7.3 we looked at $\frac{1}{T}\sum_{i=1}^{m} \mathcal{R}_i^* T_i$ near 1, where the $\mathcal{R}_i^*$ are as defined in (7.12). In terms of the $\mathcal{R}_i$ defined in (7.9),

$$\mathcal{R}_i^* = \tilde{s}^M \cdot \mathcal{R}_i.$$

In this section we set $\mathcal{R}_i$ and compare the solutions with and without pulse vaccination.

In Figures 7.5 - 7.8 we have $\frac{1}{T}\sum_{i=1}^{m} \mathcal{R}_i T_i = \frac{1}{4}(26+1+5+12) = 11$. For our specific parameter values, however, we have that $\tilde{S}^M \approx 0.0893$, and so $\frac{1}{T}\sum_{i=1}^{m} \mathcal{R}_i^* T_i \approx (11)(0.0893) = 0.9819 < 1$. We see the eradication of the disease in the pulse vaccination case (Figure 7.8), while without it the disease clearly remains endemic (Figure 7.6). We can also clearly see how much lower the susceptible population is kept by pulse vaccination.

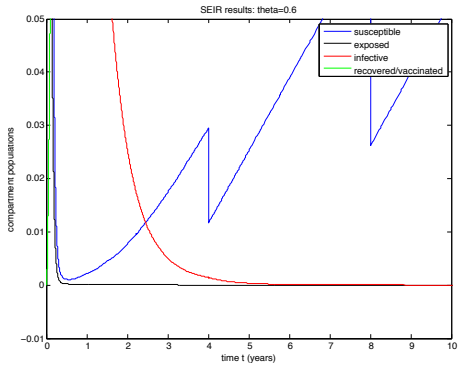

Fig. 7.1: SEIR delay model with $T = 1$, $T_i = 0.25$, $i = 1..4$, $\mathcal{R}_i = [1, 0.9, 1.1, 0.95]^T$.

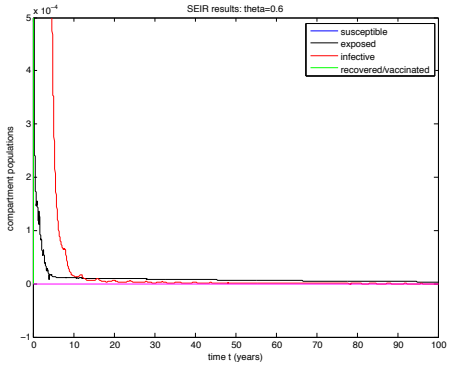

Fig. 7.2: SEIR delay model of Figure 7.1 on a smaller scale.

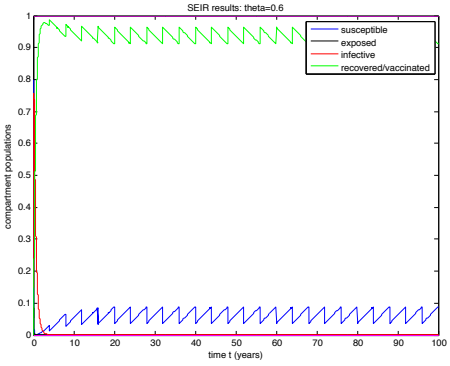

Fig. 7.3: SEIR delay model with $T = 1$, $T_i = 0.25$, $i = 1..4$, $\mathcal{R}_i = [1, 0.9, 1.1, 1.05]^T$.

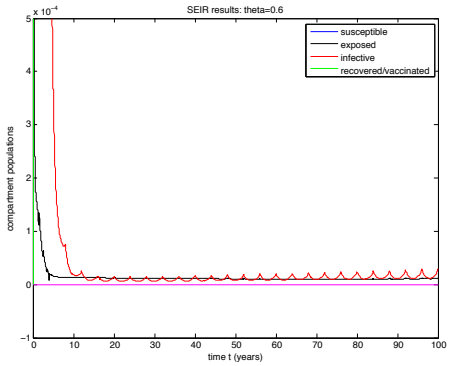

Fig. 7.4: SEIR delay model of Figure 7.3 on a smaller scale.

7.5.2 Application to Measles Modelling

Finally, we wish to see how our results compare to real-life data. The SEIR model with delay in E that we have been using, System (7.21), is well-suited qualitatively to model measles: there is permanent immunity, low death rate (in developed countries), and there are studies available on the relevant parameters. Figure 7.9 shows typical population movement between compartments.

Table 7.1 lists common parameter values in the literature. From Anderson and May we have that the incubation period is 9-12 days and the duration of infectiousness is 5-7 days [3]. We need to pick an exact number for r (one of the limitations of our delay model) so we choose the midpoint, $r = 10.5/365$ years (simulations in Chapter 5 showed that for small delays the results will not be affected much). Another limitation is the exponential distribution of the recovery rate

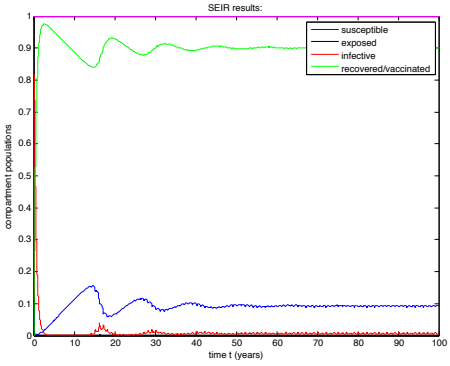

Fig. 7.5: SEIR delay model with $T = 1$, $T_i = 0.25$, $i = 1..4$, $\mathcal{R}_i = [26, 1, 5, 12]^T$.

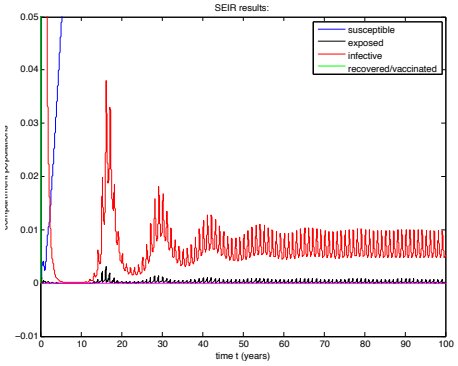

Fig. 7.6: SEIR delay model of Figure 7.5 on a smaller scale.

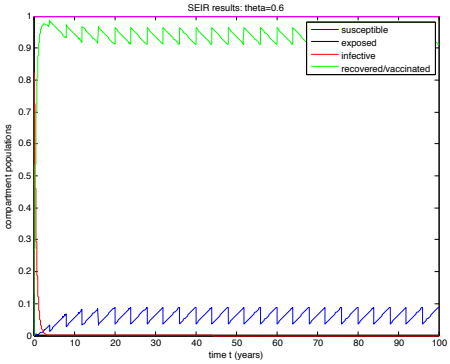

Fig. 7.7: SEIR delay model in Figure 7.5 with pulse vaccination.

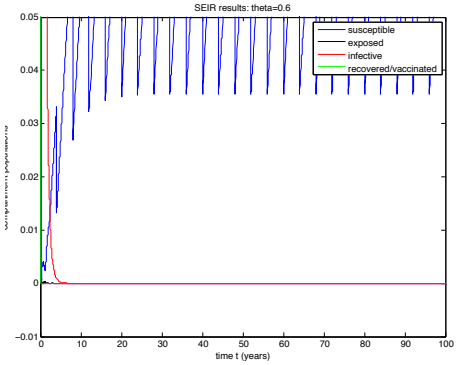

Fig. 7.8: SEIR delay model of Figure 7.7 on a smaller scale.

γ that we have assumed - with such a small distribution of infectious period [3] we could be better off with a fixed delay. With an exponential parameter, we could choose $1/\gamma = 6/365 \approx 1/61$ to match the average duration of infectiousness from [3]. From Kalivianakis *et.al.*, though, we have that a common value in the literature is $\gamma = 100$ [43], so in our simulations we split the difference between the two γ values and set $\gamma = 80$. Kalivianakis *et.al.* also state that commonly $\mu = 1/50$ and $\beta_{av} \approx 1800$ [43], so we will choose our switching values β_i accordingly.

In particular, we choose the values in Table 7.2. We assume that children and students returning to school have skyrocketing contact rates, while the lower density of the winter holidays lowers it again. Over the spring and summer we assume the combination of warm weather and, later, low density, lower the rate again. Since children may pass on disease to their parents we extrapolate to the general population.

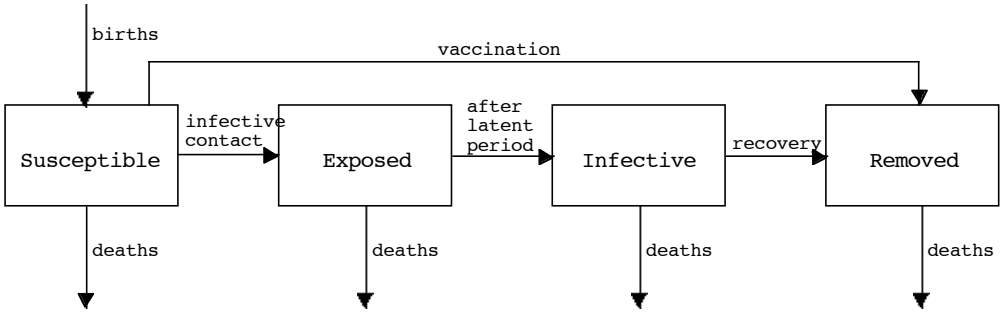

Fig. 7.9: Population movement in a measles compartmental model

Parameter	Range
Incubation period	9-12 days
Infectious period	5-7 days
Recovery rate	100 years^{-1}
Life expectancy	50 years
Average contact rate	1800 years^{-1}

Table 7.1: Common measles parameter values.

Figure 7.10 gives empirical results for measles cases in Ontario between the years 1950 and 1960. The data for this figure was obtained from the International Infectious Disease Data Archive [20].

We first attempt to find the solution to our switched SEIR delay model (without pulse vaccination) with the above parameter values. Unfortunately we find our solution accumulates error to the point of crashing. This instability is typically the result of the large difference in parameter sizes, such as $\mu = 2 \times 10^{-2}$ while $\beta = 1.8 \times 10^{3}$. It seems that our choice of DDE solver may not be able to handle the stiff problem well. While we would like to model the real-life situation as closely as possible, we will instead try to scale down some of the larger values while still seeing if we can approximate the shape of the graph in Figure 7.10. It is possible that our large value for γ, together with the large β, is causing steep changes in the graph. Instead we try smaller values for both γ and β: we take $\gamma = 2$ as before (although this implies an unusually long average recovery period) and accordingly scale the β_i in Table 7.2 by 1/40 as well. In future work we would like to investigate other numerical DDE solvers to see if they are better suited to stiff problems.

Figure 7.11 shows the trajectory over 10 years of the infective population under the new parameter assumptions.

Clearly the real-life data would have stochastic variation which our deterministic model cannot match. Of more concern is that our model falls quickly into a near-periodic state, which does not

i	β_i	T_i	Reason
1	4000	0.3	Fall (start of school)
2	500	0.1	Rest over holidays
3	3100	0.1	Return to school
4	500	0.5	Weather improves, summer vacation

Table 7.2: Switching parameter values.

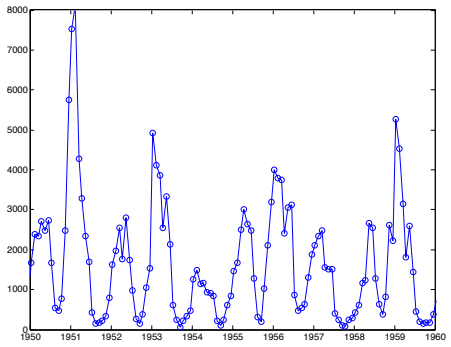

Fig. 7.10: Measles cases in Ontario, 1950-1960.

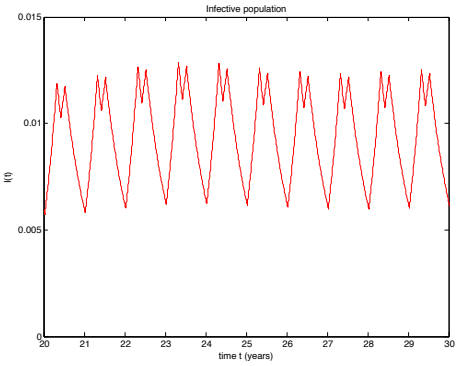

Fig. 7.11: SEIR model with physically realistic values.

allow for qualitative change in the incidence, contradicting empirical data in which the period of the epidemics may change over time [21]; Earn explains that despite the variance we model in β, over time all parameters (birth rate, life expectancy, *etc.*) will drift. These parameter changes can often be expressed, through a change of variables, as a change in β. Hence our fixed periodic choice for β will lead to much less erratic solutions than in real-life [21].

This section teaches us that while we may have a strong theoretical background for our model, accurate parameter estimation is very important. A switching parameter may do a very good job of modelling a time-varying parameter, but in any model it is difficult to take into account the drift of parameters over time.

Chapter 8

Conclusions and Future Work

8.1 Conclusions

In this work we have strengthened the results of d'Onofrio in [17] for non-delay models to show that if the time average $\bar{\mathcal{R}} < 1$ the disease-free solution is *uniformly* asymptotically stable, and we have shown that if $\bar{\mathcal{R}} > 1$ the disease is permanent.

We have extended the results for bilinear incidence delay models of Gao et. al. in [27] to determine that, for small delay, if $\bar{\mathcal{R}} < 1$ in a general incidence model the disease will be eradicated. We have confirmed our bilinear incidence results with simulations. We have considered the existence of periodic solutions to a pulse vaccination campaign model using existing theory on periodic solutions. We were not able to sharpen our cutoffs for eradication or permanence.

We explained different types of time-varying total population size, and their effects on a pulse vaccination solution. We explained why it is usually reasonable to assume a model with time-varying total population has a normalized population, by showing how we can change variables to a system where the compartments are fractions of the total population. The result also applied to constant-population delay systems. When changing from standard incidence to bilinear incidence in delay systems, we discussed a way to estimate the effect of time-varying N.

We extended the work of Stechlinski and Liu [52] on switched systems to include the decreased susceptibles in a pulse vaccination model. We then extended the results to a switched system with pulse vaccination and time delay, first with two subsystems and then to a general number of subsystems. We supported our theory with simulation results, and tried to apply the model to a real-life measles example. Additionally we looked at models with delay in other compartments than $E(t)$.

8.2 Future Directions

In future work, we would like to find results for time-varying parameters. With pulse vaccination we frequently find an eventual upper bound $\tilde{S}(t)$ for the susceptible population $S(t)$: even with a constant contact rate β, then, we would like to be able to treat $\beta\tilde{S}(t)$ as a time-varying coefficient of $I(t)$ and find threshold results based on the time-average of this coefficient. For non-delay systems we can easily find such results. In Section 5.1, however, we tried to generalize the periodic time-varying incidence results of d'Onofrio [17] to delay systems, but in the case of large delays we had to revert to looking at the maximum of this coefficient. In future work we would like to investigate whether this bound (a threshold value based on $\tilde{S}^M$) can be tightened until it is based on the period-average.

We would like to investigate optimum pulse vaccination timing. We are interested in the optimum inter-pulse time, and also the best time to start the campaign; if we have an incidence $\leq \lambda(t)\tilde{S}(t)$, then we may be able to shift $\tilde{S}(t)$ so the product with $\lambda(t)$ is minimized.

Some of our results for systems with delay were approximations, which we would like to improve upon; for example, when the delay was in the infective period (Section 7.4.1), we merely dropped the delay term. We would like to analyze this model completely, including the delay.

We would like to investigate any stabilizing effect of the delay. In Section 7 we discuss eradication of the disease, but permanence was more elusive, so we did not find an exact cutoff between eradication and permanence that we would have in a non-delay model. We want to investigate whether the delay may be helping to stabilize the disease-free equilibrium.

We would also like to look at more models with time-varying total population $N(t)$. In Chapter 6 we discuss such models, but most of the systems we analyze either have constant population or are transformable (by switching to population fractions) into a constant-population model. If we include disease deaths, for example, then we would have to take into account the size of $N(t)$ and we would like to include more simulations that do so. We would also like to look at models with a constant immigration term in addition to births proportional to N.

Finally we would like to apply our methods to real-life data. In Section 7.5.2 we consider measles epidemic data, and have some issues with our DDE solver; we would like to try other solvers and to improve our results, and in particular to see if the approach of Earn is applicable to our models [21]. We would also like to do the same with other diseases, such as those which do not confer permanent immunity, and their relevant models.

APPENDICES

Appendix A

Existence of Periodic Solutions

In Chapter 5 we have so far been trying to look at the time-average of the coefficients of our non-autonomous bounding equation for $I'(t)$,

$$x'(t) = (e^{-\mu r}\lambda(t-r)\tilde{S}(t-r))x(t-r) - (\mu+\gamma)x(t) \tag{A.1}$$

An alternative method, used in many references such as (Cheng and Zhang [10], and Yan [79]), is to look for the existence of periodic solutions to Equation (A.1). In this Appendix we follow the methods of Yan [79] and compare our results to those thresholds obtained previously. First we summarize the relevant assumptions and results from [79], then we apply the results to Equation (A.1).

A.1 Summary of Yan, 2007 [79]

In [79] we consider a general impulsive delay differential equation with parameters η and ξ:

$$\begin{cases} y'(t) = h(t, y(t)) - \eta f(t, y(t-\tau(t)), & t \in \mathbb{R}, t \neq t_k \\ y(t_k^+) - y(t_k^-) = \xi I_k(t_k, y(t_k - r(t_k))), & k \in \mathbb{Z} \end{cases} \tag{A.2}$$

We make the following assumptions on the model [79]:

(i) $\eta > 0$, $\xi \geq 0$

(ii) $\{t_k\}, k \in \mathbb{Z}$, is an increasing sequence of real numbers with $\lim_{k\to\pm\infty} t_k = \pm\infty$

(iii) $h, f : \mathbb{R} \times \mathbb{R}_+ \mapsto \mathbb{R}_+$ satisfy Caratheodory conditions (that is, $h(t, y)$ and $f(t, y)$ are locally Lebesgue measurable in t for each fixed y and are continuous in y for each fixed t) and are τ-periodic functions in t. Moreover, $f(t, y) > 0$ for all t and $y > 0$. $r : \mathbb{R} \mapsto \mathbb{R}$ is a locally bounded Lebesque measurable τ-periodic function.

(iv) There exist τ-periodic functions $a_1, a_2 : \mathbb{R} \mapsto \mathbb{R}_+$ with $\int_0^\tau a_1(t)dt > 0$ which are locally bounded and Lebesgue measurable so that $a_1(t)y \leq h(t, y) \leq a_2(t)y$ for all $y > 0$ and $\lim_{y\to 0^+} \frac{h(t,y)}{y}$ exists.

(v) $I_k : \mathbb{R} \times \mathbb{R}_+ \mapsto \mathbb{R}, k \in \mathbb{Z}$, satisfy Caratheodory conditions and are τ-periodic functions in y and there exists an integer ρ such that $I_{k+\rho}(t_{k+\rho}, y) = I_k(t_k, y), t_{k+\rho} = t_k + \tau, k \in \mathbb{Z}$. Moreover, $I_k(t, 0) = 0$ for all $k \in \mathbb{Z}$.

(vi) p and q (to be used later) are positive bounded Lebesgue measurable τ-periodic functions that are bounded away from zero.

We define the following values:

$$\bar{\delta}_i = e^{-\int_0^\tau a_i(t)dt},\ i = 1, 2, \quad \bar{\alpha} = \frac{\bar{\delta}_2}{1 - \bar{\delta}_2}, \quad bar\beta = \frac{1}{1 - \bar{\delta}_1}, \quad \bar{\sigma} = \frac{\bar{\alpha}}{\bar{\beta}}$$

As in [79] we define a Banach space $E = \{y(t) : \mathbb{R} \to \mathbb{R} | y(t)$ is continuous in (t_k, t_{k+1}), $y(t_k^+)$ and $y(t_k^-)$ exist, $y(t_k^-) = y(t_k), k \in \mathbb{Z}$, and $y(t + \tau) = y(t)\}$ with the norm $\|y\|_\tau = \sup_{-\leq t\leq\tau} |y(t)|$. Define $K = \{y \in E | y(t) \geq \bar{\sigma}\|y\|_\tau, t \in [0, \tau]\}$, then K is a cone because

Yan *et. al.* define an operator $\bar{T} : K \to K$ by

$$(\bar{T}y)(t) = \eta \int_t^{t+\tau} \bar{G}(t, s) f(s, y(s - r(s)))ds + \xi \sum_{t\leq t_k<t+\tau} G(t, t_k) I_k(t_k, y(t_k - r)) \tag{A.3}$$

where

$$\bar{G}(t, s) = \left(e^{-\int_s^t \frac{h(u,y(u))}{y(u)}du}\right)\left(1 - e^{-\int_0^\tau \frac{h(u,y(u))}{y(u)}du}\right)^{-1}. \tag{A.4}$$

They prove the following lemma for their system (A.2). This system is close to the equation (A.1) we wish to study, besides the sign of the terms. We will first state the lemma given by Yan *et. al.*, then prove the analogue for equation (A.1).

Lemma 2. *Assume that $(i) - (v)$ hold. Then $\bar{T} : K \to K$ is well defined, and the existence of a positive τ-periodic solution of (A.2) is equivalent to the existence of a non-zero fixed point of T in K.*

We then define

$$\begin{array}{lll} \underline{f}(y) = \min_{0\le t\le\tau} \frac{f(t,y)}{p(t)y}, & f_0 = \lim_{y\to 0^+} \underline{f}(y), & f_\infty = \lim_{y\to\infty} \underline{f}(y), \\ \underline{I}(y) = \min_{0\le t\le\tau, 0\le k\le\rho} \frac{I_k(t,y)}{q(t)y}, & I_0 = \lim_{y\to 0^+} \underline{I}(y), & I_\infty = \lim_{y\to\infty} \underline{I}(y), \\ P = \int_0^\tau p(t)dt, & Q = \sum_{0\le t_k\le\tau} q(t_k). & \end{array} \tag{A.5}$$

Then we have the following theorem:

Theorem 25. *[79] Assume that $(i)-(vi)$ hold and each of $f_0, f_\infty, I_0, I_\infty$ is not zero. Then there exists $\epsilon > 0$ such that for all η, ξ satisfying $\alpha\sigma\epsilon(\eta P + \xi Q) > 1$, (A.2) has no positive periodic solution.*

A.2 Application of [79] Methods to System 5.19

The linear autonomous bounding DDE we have for $I'(t)$, Equation (A.1), is similar to System (A.2) except for the sign of the two terms. Yan *et. al.* note in their conclusion that the results of their paper may be similarly applied to such an equation; [79] in this section we prove this assertion and show that the above theorems apply in the special case of Equation (A.1). We note also that the pulse vaccination in the model (5.19) does not affect $I'(t)$ directly, but we continue to use it in the proofs since it accommodates the discontinuities in $I'(t)$. Setting $\xi = 0$ recovers equation (A.1).

We begin by noting that Equation (A.1) is of the form

$$\begin{cases} y'(t) = -h(t, y(t)) + \eta f(t, y(t-\tau(t))), & t \in \mathbb{R}, t \ne t_k \\ y(t_k^+) - y(t_k^-) = \xi I_k(t_k, y(t_k - r(t_k))), & k \in \mathbb{Z}. \end{cases} \tag{A.6}$$

where $h(t, y(t)) = (\mu+\gamma)y(t)$, $r(t) \equiv r$, $\eta f(t, y(t-r)) = \lambda(t-r)\tilde{S}(t-r)y(t-r)$, and $I_k(t_k, y(t_k - r)) \equiv 0$.

A.2.1 Theorems from [79] Applied to Equation (A.6)

We require the same assumptions $(i)-(vi)$ for Equation (A.6); that is, for example, we still have that $h : \mathbb{R}\times\mathbb{R}_+ \to R_+$, we just now have the negative sign "out front" in the DE.

Again we define a Banach space $E = \{y(t) : \mathbb{R} \to \mathbb{R} | y(t)$ is continuous in (t_k, t_{k+1}), $y(t_k^+)$ and $y(t_k^-)$ exist, $y(t_k^+) = y(t_k), k \in \mathbb{Z}$, and $y(t+\tau) = y(t)\}$ with the norm $\|y\|_\tau = \sup_{-\tau\le t\le 0}|y(t)|$. Notice that we have "tweaked" the definition slightly to make $y(t)$ everywhere continuous from the right instead of the left. If the pulse vaccination does not directly affect the infected class in

our SEIR model ($I_k \equiv 0$ so $I(t)$ is continuous but its derivative has jump discontinuities) then even in our more general equation (A.6) we can assume $y(t)$ is continuous everywhere and it will still apply in the case of interest.

For Equation (A.6) we will need to define $\bar{G}(t,s)$ and the other parameters slightly differently. We show the derivation in order to explain.

We begin with the continuous part if (A.6). Rearranging:

$$\begin{aligned} y'(t) &= -h(t,y(t)) + \eta f(t, y(t-r)), \quad t \in \mathbb{R}, t \neq t_k \\ y'(t) + \frac{h(t,y(t))}{y(t)} y(t) &= \eta f(t, y(t-r)) \\ \frac{d}{dt}\left(y(t) e^{\int_0^t \frac{h(u,y(u))}{y(u)} du} \right) &= \eta f(t, y(t-r)) e^{\int_0^t \frac{h(u,y(u))}{y(u)} du} \end{aligned}$$

As with a linear ODE, we want to integrate from t to $t+\tau$, so the left hand side will give us $y(t)$ explicitly and we can rearrange to isolate it. However $y(t)$ has jump discontinuities that we must take into account. Integrating the left hand side, we see that

$$\begin{aligned} &\int_t^{t+\tau} \frac{d}{ds}\left(y(s) e^{\int_0^s \frac{h(u,y(u))}{y(u)} du} \right) ds \\ &\quad = \int_t^{t_k^-} \frac{d}{ds}\left(y(s) e^{\int_0^s (h/y) du} \right) ds + \int_{t_k}^{t_{k+1}^-} \frac{d}{ds}\left(y(s) e^{\int_0^s (h/y) du} \right) ds + \dots \\ &\qquad \dots + \int_{t_{k+\rho-1}}^{t+\tau} \frac{d}{ds}\left(y(s) e^{\int_0^s (h/y) du} \right) ds \\ &\quad = \left[y(t_k^-) e^{\int_0^{t_k^-} (h/y) du} - y(t) e^{\int_0^t (h/y) du} \right] + \left[y(t_{k+1}^-) e^{\int_0^{t_{k+1}^-} (h/y) du} - y(t_k) e^{\int_0^{t_k} (h/y) du} \right] + \dots \\ &\qquad \dots + \left[y(t+\tau) e^{\int_0^{t+\tau} (h/y) du} - y(t_{k+\rho-1}) e^{\int_0^{tk+\rho-1} (h/y) du} \right] \\ &\quad = y(t+\tau) e^{\int_0^{t+\tau} (h/y) du} - y(t) e^{\int_0^t (h/y) du} - \sum_{t < t_k \leq t+\tau} e^{\int_0^{t_k} (h/y) du} \left[y(t_k) - y(t_k^-) \right] \end{aligned}$$

since $e^{\int_0^{t_k^-} (h/y) du} = e^{\int_0^{t_k} (h/y) du}$. Hence we find

$$\begin{aligned} y(t+\tau) e^{\int_0^{t+\tau} (h/y) du} - y(t) e^{\int_0^t (h/y) du} &= \eta \int_t^{t+\tau} e^{\int_0^s (h/y) du} f(s, y(s-r)) ds \\ &\quad + \sum_{t < t_k \leq t+\tau} e^{\int_0^{t_k} (h/y) du} \xi I_k(t_k, y(t_k - r(t_k))) \end{aligned}$$

Now we are interested in the possibility of periodic solutions, so we assume $y(t)$ is τ-periodic. That is, $y(t+\tau) = y(t)$, so in the above we get

$$y(t)\left[e^{\int_0^{t+\tau}(h/y)du} - e^{\int_0^t (h/y)du}\right] = \eta\int_t^{t+\tau} e^{\int_0^s (h/y)du} f(s, y(s-r))ds + \sum_{t<t_k\le t+\tau} e^{\int_0^{t_k}(h/y)du}\xi I_k(t_k, y)$$

$$y(t)\left[e^{\int_0^t (h/y)du}\right]\left[e^{\int_0^\tau (h/y)du} - 1\right] = \eta\int_t^{t+\tau} e^{\int_0^s (h/y)du} f(s, y(s-r))ds + \sum_{t<t_k\le t+\tau} e^{\int_0^{t_k}(h/y)du}\xi I_k(t_k, y)$$

$$\Rightarrow y(t) = \eta\int_t^{t+\tau} \frac{e^{\int_0^s (h/y)du}}{e^{\int_0^t (h/y)du}\left[e^{\int_0^\tau (h/y)du} - 1\right]} f(s, y(s-r))ds$$

$$+ \sum_{t<t_k\le t+\tau} \frac{e^{\int_0^{t_k}(h/y)du}}{e^{\int_0^t (h/y)du}\left[e^{\int_0^\tau (h/y)du} - 1\right]}\xi I_k(t_k, y)$$

$$= \eta\int_t^{t+\tau} G(t,s) f(s, y(s-r))ds + \xi\sum_{t<t_k\le t+\tau} G(t,t_k) I_k(t_k, y)$$

where we define

$$G(t,s) = \left(e^{\int_t^s \frac{h(u,y(u))}{y(u)}du}\right)\left(e^{\int_0^\tau \frac{h(u,y(u))}{y(u)}du} - 1\right)^{-1}. \tag{A.7}$$

Continuing to use $a_1(t) = \mu + \gamma = a_2(t)$, by choosing

$$(\delta_1 = \delta_2 =)\ \delta = e^{+\int_0^\tau a_1(t)dt}, \quad \alpha = \frac{1}{\delta - 1}, \quad \beta = \frac{\delta}{\delta - 1}, \quad \sigma = \frac{\alpha}{\beta}$$

then similarly to before we have $\alpha \le G(t,s) \le \beta$.

Define $K = \{y \in E | y(t) \ge \sigma\|y\|_\tau, t \in [0,\tau]\}$, then K is again a cone. Similarly to Yan *et. al.* we define an operator $T : K \to K$ by

$$(Ty)(t) = \eta\int_t^{t+\tau} G(t,s) f(s, y(s-r(s)))ds + \xi\sum_{t<t_k\le t+\tau} G(t,t_k) I_k(t_k, y(t_k - r(t_k))) \tag{A.8}$$

Notice we have changed the position of the strict inequality in match our right-continuous general system (A.6).

We now prove the Lemma 2 for System (A.6). Yan *et. al.* prove the case for System (A.2) in [79] and the proof is nearly the same.

Proof. Assume $(i) - (v)$ hold.

First we show that $T : K \to K$ is well-defined; that is, $(Ty)(t)$ is defined for any $y \in K$ and $(Ty)(t) \in K$. Recall that $K \subset E$ and any $y \in E$ is τ-periodic.

Because f is Lebesgue measurable in t (and in particular, given the special case (A.1) we have f is piecewise continuous in t), the integral in the definition of $(Ty)(t)$ may be evaluated for any t. $(Ty)(t)$ is continuous for $t \in (t_k, t_{k+1})$ and we have that $(Ty)(t_k^+)$ and $(Ty)(t_k^-)$ exist (just by taking the limit of $(Ty)(t)$ as t approaches t_k from the right and left, respectively). We also have $(Ty)(t_k^+) = (Ty)(t_k)$ (for Equation (A.1) we have $t_k = k\tau$ so

$$\begin{aligned}(Ty)(t_k^+) &= \eta \int_{t_k^+}^{t_k^+ + \tau} G(t_k^+, s) f(s, y(s - r(s)))ds + \xi G(t_k^+, t_{k+1}) I_{k+1}(t_{k+1}, y(t_{k+1} - r)) \\ &= \eta \int_{t_k}^{t_k + \tau} G(t_k, s) f(s, y(s - r(s)))ds + \xi G(t_k, t_{k+1}) I_{k+1}(t_{k+1}, y(t_{k+1} - r)) = (Ty)(t_k),\end{aligned}$$

while the second term of $(Ty)(t_k^-)$ is $\xi G(t_k^-, t_k) I_k(t_k, y(t_k - r)))$.

As long as we can show τ-periodicity of Ty we will then have that $Ty \in E$ for any $y \in K$. To do so, we simply need to use the τ-periodicity of y, f, I_k, and G: take any $y \in K$, then for any $t \in \mathbb{R}$,

$$\begin{aligned}(Ty)(t+\tau) &= \eta \int_{t+\tau}^{t+2\tau} G(t+\tau, s) f(s, y(s - r(s)))ds + \xi \sum_{t+\tau < t_k \le t+2\tau} G(t+\tau, t_k) I_k(t_k, y(t_k - r(t_k))) \\ &= \eta \int_{t}^{t+\tau} G(t+\tau, u+\tau) f(u+\tau, y(u+\tau - r(u+\tau)))du + \xi \sum_{t < t_k \le t+\tau} G(t+\tau, t_k) I_k(t_k, y(t_k - r)) \\ &= \eta \int_{t}^{t+\tau} G(t, u) f(u+\tau, y(u+\tau - r(u+\tau)))du + \xi \sum_{t < t_k \le t+\tau} G(t+\tau, t_k) I_k(t_k, y(t_k - r)) \\ &= \eta \int_{t}^{t+\tau} G(t, u) f(u, y(u - r(u)))du + \xi \sum_{t < t_k \le t+\tau} G(t, t_k) I_k(t_k, y(t_k - r(t_k))) \\ &= (Ty)(t).\end{aligned}$$

To get the second line we just make the substitution $u = s - \tau$; to get the third we use the fact that the integral in $G(t, s)$ is from t to s and its integrand is τ-periodic; and to get the fourth line we use the fact that f and y (if $y \in K$) are τ-periodic. For the Σ term we use the perodicity of I_k and the t_k in Assumption (v). Hence we have shown $Ty \in E$.

Now we look to show that $Ty \in K$; it remains to be shown that $(Ty)(t) \ge \sigma \|Ty\|_\tau$ for any $t \in [0, \tau]$, where $\sigma = \alpha/\beta$ as defined before. But for any $y \in K$, since $0 \le \alpha \le G(t, s)$ for

$t, s \in [0, \tau]$, we have

$$(Ty)(t) \geq \alpha \left[\eta \int_t^{t+\tau} f(s, y(s - r(s)))ds + \xi \sum_{t<t_k\leq t+\tau} I_k(t_k, y(t_k - r(t_k))) \right]$$
$$= \sigma\beta \left[\eta \int_t^{t+\tau} f(s, y(s - r(s)))ds + \xi \sum_{t<t_k\leq t+\tau} I_k(t_k, y(t_k - r(t_k))) \right]$$

since $G(t, s) \leq \beta$. For any t we have

$$|(Ty)(t)| \leq \beta \left[\eta \int_t^{t+\tau} f(s, y(s - r(s)))ds + \xi \sum_{t<t_k\leq t+\tau} I_k(t_k, y(t_k - r(t_k))) \right]$$

but since f and $y \in K$ are $\tau-$*periodic* we have that $f(t, y(t-r(t)))$ is τ-periodic so its integral over one period is constant. Similarly by Assumption (v) we have that $\sum_{t<t_k\leq t+\tau} I_k(t_k, y(t_k - r(t_k)))$ is constant because as soon as $t = t_k$ we no longer include $I_k(t_k, y(t_k - r(t_k)))$ in the sum, but we do include $I_{k+\rho}(t_{k+\rho}, y(t_{k+\rho} - r(t_{k+\rho}))) = I_k(t_k, y(t_{k+\rho} - r(t_{k+\rho})))$ and $t_{k+\rho} = t_k + \tau$ so $y(t_{k+\rho} - r(t_{k+\rho}))) = y(t_k - r(t_k)))$.

So we have $|(Ty)(t)| \leq \beta \left[\eta \int_t^{t+\tau} f(s, y(s - r(s)))ds + \xi \sum_{t<t_k\leq t+\tau} I_k(t_k, y(t_k - r(t_k))) \right]$ for all $t \in [0, \tau]$, and so $\|Ty\|_\tau \leq \beta \left[\eta \int_t^{t+\tau} f(s, y(s - r(s)))ds + \xi \sum_{t<t_k\leq t+\tau} I_k(t_k, y(t_k - r(t_k))) \right]$ as well. Thus we have

$$(Ty)(t) \geq \sigma\beta \left[\eta \int_t^{t+\tau} f(s, y(s - r(s)))ds + \xi \sum_{t<t_k\leq t+\tau} I_k(t_k, y(t_k - r(t_k))) \right]$$
$$\geq \sigma\|Ty\|_\tau$$

which proves that $Ty \in K$. Therefore $T : K \to K$ is well defined.

Finally we prove that there exists a positive τ-periodic solution of (A.6) $\iff$ there exists a non-zero fixed point of T in K. Again we follow [79] very closely.

[$\Rightarrow$] Suppose that $y(t)$ is a positive periodic solution of (A.6). Then, following our above derivation of $G(t, s)$ we see that $(Ty)(t) = y(t)$.

[$\Leftarrow$] Suppose $y \in K$ and $Ty = y$ with $y \neq 0$. Then for any $t \neq t_k$,

$$\begin{aligned}
y'(t) &= ((Ty)(t))' \\
&= \left(\eta \int_t^{t+\tau} G(t,s) f(s, y(s - r(s)))ds + \xi \sum_{t<t_k\leq t+\tau} G(t,t_k) I_k(t_k, y(t_k - r(t_k))) \right)' \\
&= \left(e^{-\int_0^t (h/y)du} \eta \int_t^{t+\tau} \frac{e^{\int_0^s (h/y)du}}{\left[e^{\int_0^\tau (h/y)du} - 1\right]} f(s, y(s - r(s)))ds + \xi \sum_{t<t_k\leq t+\tau} G(t,t_k) I_k(t_k, y(t_k - r(t_k))) \right)' \\
&= \frac{h(t, y(t))}{y(t)} (Ty)(t) + \eta \left[G(t, t+\tau) \cdot f(t+\tau, y(t+\tau - r(t+\tau))) - G(t,t) \cdot f(t, y(t - r(t))) \right] \\
&= h(t, y(t)) + \eta \left[G(t, t+\tau) - G(t,t) \right] \cdot f(t, y(t - r(t)))
\end{aligned}$$

where the Σ term disappeared because it is constant in t as discussed earlier. We then note that

$$\begin{aligned}
G(t, t+\tau) - G(t,t) &= \frac{e^{\int_t^{t+\tau} \frac{h(u,y(u))}{y(u)} du}}{e^{\int_0^\tau \frac{h(u,y(u))}{y(u)} du} - 1} - \frac{e^{\int_t^t \frac{h(u,y(u))}{y(u)} du}}{e^{\int_0^\tau \frac{h(u,y(u))}{y(u)} du} - 1} \\
&= \frac{e^{\int_0^\tau \frac{h(u,y(u))}{y(u)} du}}{e^{\int_0^\tau \frac{h(u,y(u))}{y(u)} du} - 1} - \frac{1}{e^{\int_0^\tau \frac{h(u,y(u))}{y(u)} du} - 1} \quad = 1.
\end{aligned}$$

So we see that for $t \neq t_k$, $y'(t) = h(t, y(t)) + \eta f(t, y(t - r(t)))$, satisfying the first part of (A.6). At the impulse times, that is, for any $t = t_j$,

$$\begin{aligned}
y(t_j) - y(t_j^-) &= (Ty)(t_j) - (Ty)(t_j^-) \\
&= \eta \int_{t_j}^{t_j+\tau} [G(t_j, s) - G(t_j^-, s)] f(s, y(s - r(s)))ds \\
&\quad + \xi \left[\sum_{t_j<t_k\leq t_j+\tau} G(t_j, t_k) I_k(t_k, y(t_k - r(t_k))) - \sum_{t_j^-<t_k\leq t_j^-+\tau} G(t_j^-, t_k) I_k(t_k, y(t_k - r(t_k))) \right] \\
&= \xi \left[G(t_j, t_j+\tau) I_{j+\rho}(t_j + \tau, y(t_j + \tau - r(t_j + \tau))) - G(t_j^-, t_j) I_j(t_j, y(t_j - r(t_j))) \right] \\
&= \xi \left[G(t_j, t_j+\tau) - G(t_j^-, t_j) \right] I_j(t_j, y(t_j - r(t_j)) \\
&= \xi I_j(t_j, y(t_j - r(t_j))
\end{aligned}$$

The term with coefficient η is 0 since the integral in $G(t,s)$ means $G(t_j, s) = G(t_j^-, s)$. The quantity in brackets $G(t_j, t_j+\tau) - G(t_j^-, t_j) = 1$ as explained above, since $G(t_j, t_j) = G(t_j^-, t_j)$.

So the second part of (A.6) is also satisfied. Therefore y is τ-periodic and we have shown it is a solution of (A.6).

Therefore the existence of a positive periodic solution of (A.6) is equivalent to the existence of a fixed point of T in K.

□

As in [79] we define a few more quantities:

$$\bar{f}(y) = \max_{0\le t\le\tau} \frac{f(t,y)}{p(t)y}, \quad \bar{I}(y) = \max_{0\le t\le\tau, 0\le k\le\rho} \frac{I_k(t,y)}{q(t)y}$$

where $p, q : \mathbb{R} \to \mathbb{R}_+$ satisfy Assumption (vi). Following [79] we define the quantities $P = \int_0^\tau p(t)dt$ and $Q = \sum_{0\le t_k<\tau} q(t_k)$, and the notations:

$$\begin{array}{ll} f^0 = \lim_{y\to 0^+} \sup \bar{f}(y) & f^\infty = \lim_{y\to\infty} \sup \bar{f}(y) \\ I^0 = \lim_{y\to 0^+} \sup \bar{I}(y) & I^\infty = \lim_{y\to\infty} \sup \bar{I}(y) \end{array}$$

We restate and proof a non-existence proof given in [79]:

Theorem 26. *Assume that Assumptions $(i)-(vi)$ hold and that each of $f^0, f^\infty, I^0, I^\infty$ is finite. Then there exists $\epsilon > 0$ such that for all η, ξ satisfying*

$$\epsilon \cdot \beta(\eta P + \xi Q) < 1, \tag{A.9}$$

Equation (A.6) has no positive τ-periodic solution.

Proof. A similar theorem in which each of $f^0, f^\infty, I^0, I^\infty$ is nonzero is proved in [79]. We adapt their proof in order to prove the above theorem.

Let $\epsilon_0 > \max\{f^0, f^\infty, I^0, I^\infty\} < \infty$. We note, for example, that

$$\lim_{y\to 0^+} \frac{f(t,y)}{p(t)y} = f^0 < \epsilon_0 \Rightarrow f(t,y) \le \epsilon_0 p(t) y$$

for small enough y. The same result applies for I_k and for "large enough" y using the f^∞ limit. Hence from the limit definitions of $f^0, f^\infty, I^0, I^\infty$ we see that there exist positive constants $r_1 < r_2$ such that

$$\begin{array}{llll} f(t,y) \le \epsilon_0 \cdot p(t)y & I_k(t,y) \le \epsilon_0 \cdot q(t)y & \text{for } y \in [0, r_1], t \in [0,\tau], 0 \le k < \rho \\ f(t,y) \le \epsilon_0 \cdot p(t)y & I_k(t,y) \le \epsilon_0 \cdot q(t)y & \text{for } y \in [r_2, \infty), t \in [0,\tau], 0 \le k < \rho \end{array}$$

We have bounds on f and I_k for small and large y; what remains is to consider $y \in [r_1, r_2]$. Since this interval is closed, $y \ge r_1 > 0$ and $p(t), q(t)$ are bounded away from 0, we define

$$\epsilon = \max\left\{\epsilon_0, \quad \max_{y\in[r_1,r_2], t\in[0,\tau]} \frac{f(t,y)}{p(t)y}, \quad \max_{y\in[r_1,r_2], t\in[0,\tau], 0\le k<\rho} \frac{I_k(t,y)}{q(t)y}\right\}.$$

Then $f(t,y) \leq \epsilon \cdot p(t)y, I_k(t,y) \leq \epsilon \cdot q(t)y$ for $y \in \mathbb{R}_+$ and for all $t \in [0,\tau]$ with $0 \leq k < \rho$.

Under these conditions we assume the existence of a positive τ-periodic solution $\tilde{y}(t)$ and look for a contradiction. From Lemma 2 we have that any postive τ-periodic solution of (A.6) is equivalent to a fixed point of $T : K \to K$, which means

$$\begin{aligned}
\tilde{y}(t) = (T\tilde{y})(t) &= \eta \int_t^{t+\tau} G(t,s) f(s, \tilde{y}(s - r(s)))ds + \xi \sum_{t<t_k\leq t+\tau} G(t,t_k) I_k(t_k, \tilde{y}(t_k - r(t_k))) \\
&\leq \beta \left[\eta \int_t^{t+\tau} f(s, \tilde{y}(s - r(s)))ds + \xi \sum_{t<t_k\leq t+\tau} I_k(t_k, \tilde{y}(t_k - r(t_k))) \right] \\
&\leq \beta \left[\eta \int_t^{t+\tau} \epsilon \cdot p(s)\tilde{y}(s - r(s))ds + \xi \sum_{t<t_k\leq t+\tau} \epsilon \cdot q(t_k) y(t_k - r(t_k)) \right] \\
&\leq \epsilon\beta \|\tilde{y}\|_\tau \left[\eta \int_t^{t+\tau} p(s)ds + \xi \sum_{t<t_k\leq t+\tau} q(t_k) \right] \\
&= \epsilon\beta \|\tilde{y}\|_\tau [\eta P + \xi Q] \\
&< \|\tilde{y}\|_\tau
\end{aligned}$$

So for any $t \in [0,\tau]$ we have $\tilde{y}(t) < \|\tilde{y}\|_\tau$, *i.e.* $\|\tilde{y}\|_\tau < \|\tilde{y}\|_\tau$. This contradiction proves that we can't have a positive τ-perodic solution $\tilde{y}(t)$ if all of f^0, f^∞, I^0, and I^∞ are finite.

□

A.2.2 Application to SEIR model and Equation (A.1)

Equation (A.1) is of the form (A.6) with

$$\begin{aligned}
r(t) &\equiv r \\
\eta f(t, y(t - r(t))) &= e^{-\mu r}\lambda(t - r)\tilde{S}(t - r)y(t - r)) \\
h(t, y(t)) &= (\mu + \gamma)y(t) \\
t_k &= k\tau \\
I_k(k\tau, y(k\tau - r)) &\equiv 0.
\end{aligned}$$

The impulsive behaviour in this model affects the susceptible population and leads to the factor of $\tilde{S}(t)$; however, while it causes discontinuity in the time derivative of the infected population, the impulses do not affect the continuity of the population itself. That is, $y(t)$ is continuous everywhere. Since $I_k \equiv 0$ for all $k \in \mathbb{Z}$, we might as well set $\xi = 0$ for this model for brevity.

Lemma 2 applies to System (A.1) because assumptions $(i) - (vi)$ are satisfied in this special case:

(i) $\eta > 0$, $\xi \geq 0$: η is assumed to be a constant included in $\lambda(t)$.

(ii) Set $t_k = k\tau \in \mathbb{R}$ for $k \in \mathbb{Z}$. Then $\{t_k\}$ is an increasing sequence and $\lim_{k\to\pm\infty} t_k = \pm\infty$.

(iii) h is constant and therefore Lebesgue measurable and τ-periodic in t, and h is linear and therefore continuous in y for each fixed t. $f(t, y(t-r)) = e^{-\mu r}\lambda(t-r)\tilde{S}(t-r)y(t-r) > 0$ for $y > 0$ and is continuous in y for fixed t; f is discontinuous but Lebesgue measurable in t since $\tilde{S}$ is piecewise continuous in t. $r(t) \equiv r$ is clearly Lebesgue measurable and τ-periodic since it is constant.

(iv) If we set $a_1(t) \equiv \mu + \gamma \equiv a_2(t)$ then $a_1(t)y \leq h(t, y) \leq a_2(t)y$ for all y since we in fact have equality. These constant functions a_1, a_2 are therefore τ-periodic and we have $\lim_{y\to 0^+} \frac{h(t,y)}{y} = \lim_{y\to 0^+}(\mu + \gamma) = \mu + \gamma$.

(v) $I_k(t, y) \equiv 0$ for all $k \in \mathbb{Z}$ so we have that the $\{I_k\}$ satisfy Caratheodory conditions trivially. If we take $\rho = 1$ then $I_{k+\rho}(t_{k+\rho}, y) = I_k(t_k, y) = 0$, and $t_{k+\rho} = t_{k+1} = (k+1)\tau = t_k + \tau, k \in \mathbb{Z}$.

(vi) Take $p(t) = \frac{1}{\eta}e^{-\mu r}\lambda(t-r)\tilde{S}(t-r)$ and $q(t) \equiv q > 0$, then p and q are positive bounded Lebesgue measurable τ-periodic functions that are bounded away from zero (assuming $\lambda(t) > 0$ for all t).

For (A.1) we have

$$\frac{f(t, y}{p(t)y} = \frac{1}{\eta} \cdot \frac{e^{-\mu r}\lambda(t-r)\tilde{S}(t-r)}{p(t)}.$$

Take $p(t) = c \cdot \frac{1}{\eta}e^{-\mu r}\lambda(t-r)\tilde{S}(t-r)$ for some constant c and we get $\bar{f} = 1/c$ is constant. Then $f^0 = f^\infty = 1/c$.

Since $I_k \equiv 0$ we have for any strictly positive $q(t)$ and $y(t)$ that $\bar{I} = \frac{0}{q(t)y} = 0$, so $I^0 = I^\infty = 0$.

Therefore we have that $f^0, f^\infty, I^0, I^\infty$ are all finite. By Theorem 26 we have that if

$$\epsilon \cdot \beta(\eta P + \xi Q) < 1, \tag{A.10}$$

where

$$\begin{aligned}\epsilon &= \max\left\{\epsilon_0, \quad \max_{y\in[r_1,r_2],t\in[0,\tau]} \frac{f(t,y)}{p(t)y}, \quad \max_{y\in[r_1,r_2],t\in[0,\tau],0\leq k<\rho} \frac{I_k(t,y)}{q(t)y}\right\} \\ &= \max\left\{\epsilon_0, \quad \frac{1}{c}, \quad 0\right\} > \frac{1}{c},\end{aligned}$$

then we cannot have a positive periodic solution to (A.1).

In particular for this system (A.1), $P = \int_0^\tau \frac{c}{\eta} e^{-\mu r}\lambda(t-r)\tilde{S}(t-r)dt$ and since $\xi = 0$, condition (A.10) tells us that we need

$$\begin{aligned} & \frac{1}{c}\cdot\beta(\eta\int_0^\tau \frac{c}{\eta}e^{-\mu r}\lambda(t-r)\tilde{S}(t-r)dt) < 1 \\ \Rightarrow \quad & \beta\int_0^\tau e^{-\mu r}\lambda(t-r)\tilde{S}(t-r)dt < 1 \end{aligned} \tag{A.11}$$

Recall that

$$\beta = \max_{t,s\in[0,\tau]} G(t,s) = \frac{e^{(\mu+\gamma)\tau}}{e^{(\mu+\gamma)\tau}-1} = \frac{1}{1-e^{-(\mu+\gamma)\tau}};$$

that is, condition A.11 means that we have the condition

$$\mathcal{R}_{per} := \int_0^\tau \frac{e^{-\mu r}\lambda(t-r)\tilde{S}(t-r)}{1-e^{-(\mu+\gamma)\tau}}\, dt < 1 \tag{A.12}$$

A.3 Comparison of new threshold $\mathcal{R}_{per}$ to $\mathcal{R}^*$

At the beginning of this chapter we discussed the threshold value $\mathcal{R}^*$ defined by Gao *et. al.* in [27]. For a general incidence rate $g(t,I) \le \lambda(t)I(t)$ we have the corresponding value

$$\mathcal{R}^* = \frac{e^{-\mu r}\max_{t\in[0,\tau]}\lambda(t)\tilde{S}(t)}{\mu+\gamma}. \tag{A.13}$$

For $g(I,t) = \beta I$ we have $\max_{t\in[0,\tau]}\lambda(t)\tilde{S}(t) = \beta\tilde{S}^M$ so we recover the $\mathcal{R}^*$ from [27]. For brevity we let $(\lambda\tilde{S})^M := max_{t\in[0,\tau]}\lambda(t)\tilde{S}(t)$.

How does our new threshold $\mathcal{R}_{per}$ compare to $\mathcal{R}^*$? We would hope that this threshold below which periodic solutions cannot occur would help us to determine when the disease will be eradicated. Although we do not know for certain that the absence of a periodic solution for an infected population necessitates the eradication of the infection, in this section we shall unfortunately see that such theory is unnecessary. Even if it were true, we will show that $\mathcal{R}_{per} > \mathcal{R}^* > \bar{\mathcal{R}}$, so $\mathcal{R}_{per} < 1 \Rightarrow \mathcal{R}^* < 1$.

In order to show this, we consider the possibility that $\mathcal{R}_{per} < \mathcal{R}^*$. If this case is true, we have

$$\frac{\int_0^\tau e^{-\mu r}\lambda(t-r)\tilde{S}(t-r)dt}{1-e^{-(\mu+\gamma)\tau}} < \frac{e^{-\mu r}(\lambda\tilde{S})^M}{\mu+\gamma}$$

Dividing both sides by τ and denoting by $(\lambda\tilde{S})_{av}$ the average of $\lambda(t)\tilde{S}(t)$ over one period τ,

$$\begin{aligned} \frac{(\lambda\tilde{S})_{av}}{1-e^{-(\mu+\gamma)\tau}} &< \frac{(\lambda\tilde{S})^M}{(\mu+\gamma)\tau} \\ \Rightarrow \frac{(\mu+\gamma)\tau}{1-e^{-(\mu+\gamma)\tau}} &< \frac{(\lambda\tilde{S})^M}{(\lambda\tilde{S})_{av}} \end{aligned} \tag{A.14}$$

The right-hand side is independent of γ. We consider the left-hand side as a function of γ, $F(\gamma) = (\mu+\gamma)\tau/(1-e^{-(\mu+\gamma)\tau})$. Taking the derivative,

$$\begin{aligned} F'(\gamma) &= \frac{\tau(1-e^{-(\mu+\gamma)\tau}) - (+\tau e^{-(\mu+\gamma)\tau})(\mu+\gamma)\tau}{(1-e^{-(\mu+\gamma)\tau})^2} \\ &= \frac{\tau\left[1-e^{-(\mu+\gamma)\tau} - (\mu+\gamma)\tau e^{-(\mu+\gamma)\tau}\right]}{(1-e^{-(\mu+\gamma)\tau})^2} \end{aligned}$$

$F'(\gamma) = 0$ only when the quantity in square brackets is zero. Considering the function $G(x) = 1 - e^{-x} - xe^{-x}$, we see that $G(x) = 0$ only if $1-(1+x)e^{-x} = 0 \Rightarrow e^x = 1+x \Rightarrow x = 0$. For $x > 0$, $e^x > 1+x$ so $G(x) > 0\ \forall x > 0$. Since all of our parameters in our epidemic model are nonnegative, $(\mu+\gamma)\tau \geq 0$ always. That is, $F(\gamma)$ is always increasing in γ. If we are ever to satisfy the condition (A.14), it must certainly be satisfied when $\gamma = 0$.

We use the parameters from our simulations in Table 5.1 in Section 5.2.3 and a constant contact rate $\lambda(t) \equiv \beta$ (here β is the contact rate from earlier sections, not the value $\max G(t,s)$). We find

$$\frac{(\mu+\gamma)\tau}{1-e^{-(\mu+\gamma)\tau}} = 2.3244, \quad \frac{(\lambda\tilde{S})^M}{(\lambda\tilde{S})_{av}} = 1.1108$$

These values were for $\tau = 1$, a physically rather small interpulse period of one year. Setting $\tau = 4$ (for example for a mass measles vaccination campaign every 4 years) we get

$$\frac{(\mu+\gamma)\tau}{1-e^{-(\mu+\gamma)\tau}} = 8.0597, \quad \frac{(\lambda\tilde{S})^M}{(\lambda\tilde{S})_{av}} = 1.1099$$

Suppose instead we are vaccinating a large proportion $p = 0.80$ of the susceptible population with each vaccination campaign, and suppose that the campaigns are frequent, that is $\tau = 0.5$ years. Then we find

$$\frac{(\mu+\gamma)\tau}{1-e^{-(\mu+\gamma)\tau}} = 1.5867, \quad \frac{(\lambda\tilde{S})^M}{(\lambda\tilde{S})_{av}} = 1.6653$$

A strong but infrequent vaccination campaign on its own, however, is not enough ($\tau = 1, p = 0.8 \Rightarrow$ LHS $= 2.3244$, RHS $= 1.6640$). We also note that for a recovery period of one week ($\gamma = 365/7$) with the other parameters as in Table 5.1 we have the right-hand side $= 1.1108$ still (it is independent of γ), while the LHS $= 52.1571$. So it seems unlikely that for a physical campaign, with a recovery period on an order less than years, that we will ever have

$$\frac{(\mu+\gamma)\tau}{1-e^{-(\mu+\gamma)\tau}} < \frac{(\lambda\tilde{S})^M}{(\lambda\tilde{S})_{av}}$$

as we require for our new bound $\mathcal{R}_{per}$ to be an improvement on $\mathcal{R}^*$.

References

[1] Z. Agur, L. Cojocaru, G. Mazor, R.M. Anderson, and Y.L. Danon. Pulse mass measles vaccination across age cohorts. *Proceedings of the National Academy of Sciences*, 90:11698–11702, 1993. 16, 55

[2] M.E. Alexander and S.M. Moghadas. Periodicity in an epidemic model with a generalized non-linear incidence. *Mathematical Biosciences*, 189:75–96, 2004. 54, 55, 59

[3] Roy M. Anderson and Robert M. May. Population biology of infectious disease: Part i. *Nature*, 280(2):361–367, August 1979. 23, 127, 128

[4] H.R. Babad. Predicting the impact of measles vaccination in england and wales: model validation and analysis of policy options. *Epidemiol. Infect.*, 114:319–344, 1995. 16, 55

[5] N.T.J. Bailey and C. Alff-Steinberger. Improvements in the estimation of the latent and infectious periods of a contagious disease. *Biometrika*, 57(1):141–153, 1970. 58

[6] George Ballinger and Xinzhi Liu. Existence and uniqueness results for impulsive delay differential equations. *Dynamics of Continuous, Discrete and Impulsive Systems*, 5:579–591, 1999. 35, 42, 43, 44, 45, 52

[7] Fred Brauer and Carlos Castillo-Chavez. *Mathematical Models in Population Biology and Epidemiology*. Springer, 2001. 6, 8, 10, 15, 53, 58

[8] Stavros Busenberg and Kenneth L. Cooke. Periodic solutions of a periodic nonlinear delay differential equation. *SIAM Journal on Applied Mathematics*, 35(4):704–721, 1978. 53

[9] Vincenzo Capasso and Gabriella Serio. A generalization of the Kermack-McKendrick deterministic epidemic model. *Mathematical Biosciences*, 42:43–61, 1978. 53, 54

[10] Sui Sun Cheng and Guang Zhang. Existence of positive periodic solutions for non-autonomous functional differential equations. *Electronic Journal of Differential Equations*, 2001(59):1–8, 2001. 92, 134

[11] Kenneth L. Cooke and James L. Kaplan. A periodicity threshold theorem for epidemics and population growth. *Mathematical Biosciences*, 31:87–104, 1976. 23, 53, 59, 60

[12] Kenneth L. Cooke and P. van den Driessche. Analysis of an SEIRS epidemic model with two delays. *Journal of Mathematical Biology*, 35:240–260, 1996. 2, 10, 60, 64, 99

[13] Ciro A. de Quadros, Jon K. Andrus, Jean-Marc Olive, and Carlyle Guerra de Macedo. Polio eradication from the western hemisphere. *Annual Review of Public Health*, 13:239–53, 1992. 16

[14] O. Diekmann, J.A.P. Heesterbeek, and J.A.J. Metz. On the definition and the computation of the basic reproduction ratio r0 in models for infectious diseases in heterogeneous populations. *Journal of Mathematical Biology*, 28:365–382, 1990. 13

[15] O. Diekmann, J.A.P. Heesterbeek, and J.A.J. Metz. The legacy of Kermack and McKendrick. Centrum voor Wiskunde en Informatica Report, 1991. 53

[16] Alberto d'Onofrio. Mixed pulse vaccination strategy in epidemic model with realistically distributed infectious and latent times. *Applied Mathematics and Computation*, 151:181–187, 2004. 59

[17] Alberto d'Onofrio. Vaccination policies and nonlinear force of infection: Generalization of an observation by Alexander and Moghadas (2004). *Applied Mathematics and Computation*, 168:613–622, 2005. 2, 55, 56, 57, 58, 62, 63, 64, 66, 68, 78, 80, 81, 90, 101, 107, 131, 132

[18] Rodney David Driver. *Ordinary and Delay Differential Equations*. Springer-Verlag, 1977. 36, 37, 38, 39, 40, 41, 45, 58, 66, 84

[19] Jonathan Dushoff. Incorporating immunological ideas in epidemiological models. *Journal of Theoretical Biology*, 180:181–187, 1996. 7

[20] David J.D. Earn. International Infectious Disease Data Archive. 129

[21] David J.D. Earn. *Mathematical Biology*, volume 14, chapter Mathematical Epidemiology of Infectious Diseases. IAS / Park City Mathematics Series, 2009. 4, 16, 20, 22, 130, 132

[22] David J.D. Earn, Pejman Rohani, and Bryan T. Grenfell. Persistence, chaos and synchrony in ecology and epidemiology. *Proceedings of the Royal Society B*, 265:7–10, 1998. 10

[23] Neil M. Ferguson, D. James Nokes, and Roy M. Anderson. Dynamical complexity in age-structured models of the transmission of the measles virus: Epidemiological implications at high levels of vaccine uptake. *Mathematical Biosciences*, 138:101–130, 1996. 7

[24] Sunita Gakkhar and Kuldeep Negi. Pulse vaccination in SIRS epidemic model with non-monotonic incidence rate. *Chaos, Solitons and Fractals*, 35:626–638, 2008. 55, 62

[25] Shujing Gao, Lansun Chen, Juan J. Nieto, and Angela Torres. Analysis of a delayed epidemic model with pulse vaccination and saturation incidence. *Vaccine*, 24:6037–6045, 2006. 55, 60, 62

[26] Shujing Gao, Lansun Chen, and Zhidong Teng. Impulsive vaccination of an SEIRS model with time delay and varying total population size. *Bulletin of Mathematical Biology*, 69:731–745, 2007. 59, 62, 64, 65, 95, 96, 97

[27] Shujing Gao, Lansun Chen, and Zhidong Teng. Pulse vaccination of an SEIR epidemic model with time delay. *Nonlinear Analysis: Real World Applications*, 9:599–607, 2008. 2, 59, 60, 61, 62, 64, 66, 67, 68, 71, 73, 76, 81, 90, 97, 99, 101, 106, 111, 116, 131, 145

[28] Shujing Gao, Zhidong Teng, Juan J. Nieto, and Angela Torres. Analysis of an SIR epidemic model with pulse vaccination and distributed time delay. *Journal of Biomedicine and Biotechnology*, 2007. 59, 62

[29] Shujing Gao, Zhidong Teng, and Dehui Xie. The effects of pulse vaccination on SEIR model with two time delays. *Applied Mathematics and Computation*, 201:282–292, 2008. 60, 62

[30] Shujing Gao, Zhidong Teng, and Dehui Xie. Analysis of a delayed SIR epidemic model with pulse vaccination. *Chaos, Solitons and Fractals*, 40:1004–1011, 2009. 59, 60, 62

[31] Nicholas C. Grassly and Christophe Fraser. Seasonal infectious disease epidemiology. *Proceedings of the Royal Society B*, 273:2541–2550, 2006. 21

[32] Hans Heesterbeek. *Ecological Paradigms Lost: Routes of Theory Change*, volume 2, chapter The Law of Mass-Action in Epidemiology: A Historical Perspective, pages 81–105. Elsevier, 2005. 19, 53

[33] J.M. Heffernan, R.J. Smith, and L.M. Wahl. Perspectives on the basic reproductive ratio. *Journal of the Royal Society Interface*, 2:281–293, 2005. 12, 13, 14, 15

[34] Herbert W. Hethcote. Qualitative analysis of communicable disease models. *Mathematical Biosciences*, 28:335–356, 1976. 53

[35] Herbert W. Hethcote. An immunization model for a heterogeneous population. *Theoretical Population Biology*, 14:338–349, 1978. 53

[36] Herbert W. Hethcote. The mathematics of infectious diseases. *Society for Industrial and Applied Mathematics Review*, 42(4):599–653, December 2000. 10, 11, 93

[37] Herbert W. Hethcote, Harlan W. Stech, and P. van den Driessche. Nonlinear oscillations in epidemic models. *SIAM Journal on Applied Mathematics*, 40(1):1–9, February 1981. 60

[38] Herbert W. Hethcote and P. van den Driessche. An SIS epidemic model with variable population size and a delay. *Journal of Mathematical Biology*, 34:177–194, 1995. 64, 101

[39] Jing Hui and Lansun Chen. Impulsive vaccination of SIR epidemic models with nonlinear incidence rates epidemic models with nonlinear incidence rates. *Discrete and Continuous Dynamical Systems - Series B*, 4(3):595–605, August 2004. 55

[40] Jing Hui and Deming Zhu. Global stability and periodicity on SIS epidemic models with backward bifurcation. *Computers and Mathematics with Applications*, 50:1271–1290, 2005. 10

[41] Yu Jiang, Huiming Wei, Xinyu Song, Liquan Mei, Guanghui Su, and Suizheng Qiu. Global attractivity and permanence of a delayed SVEIR epidemic model with pulse vaccination and saturation incidence. *Applied Mathematics and Computation*, 213:312–321, 2009. 59, 60, 62

[42] Jianjun Jiao, Lansun Chen, and Shaohong Cai. An SEIRS epidemic model with two delays and pulse vaccination. *Journal of Systems Science and Complexity*, 21:217–225, 2008. 60, 62

[43] Mini Kalivianakis, Sipko L.J. Mous, and Johan Grasman. Reconstruction of the seasonally varying contact rate for measles. *Mathematical Biosciences*, 124:225–234, 1994. 128

[44] W.O. Kermack and A.G. McKendrick. A contribution to the mathematical theory of epidemics. *Proceedings of the Royal Society of London Series A*, 115(772):700–721, Aug 1927. 6, 53, 107

[45] Andrei Korobeinikov. Lyapunov functions and global stability for SIR and SIRS epidemiological models with non-linear transmission. *Bulletin of Mathematical Biology*, 30:615–626, 2006. 54

[46] Yang Kuang. *Delay Differential Equations with Applications in Population Dynamics*. Academic Press Inc., 1993. 18, 23, 24, 58

[47] Michael Y. Li, John R. Graef, Liancheng Wang, and János Karsai. Global dynamics of a SEIR model with varying total population size. *Mathematical Biosciences*, 160:191–213, 1999. 2, 10, 99

[48] Tong Li, Yi Li, and Herbert W. Hethcote. Periodic traveling waves in SIRS endemic models. *Mathematical and Computer Modelling*, 49:393–401, 2009. 60

[49] Shaoying Liu, Yongzhen Pei, Changguo Li, and Lansun Chen. Three kinds of TVS in a SIR epidemic model with saturated infectious force and vertical transmission. *Applied Mathematical Modelling*, 33:1923–1932, 2009. 19, 54

[50] Xinzhi Liu. Advanced ODEs: Course notes for AM 751. University of Waterloo, September 2009. 26, 28, 29, 31, 32, 33

[51] Xinzhi Liu. Amath 851: Stability theory and applications. Transcribed lecture notes, University of Waterloo, January - April 2011. 29, 30, 31

[52] Xinzhi Liu and Peter Stechlinski. Multi-city disease models with time-varying contact rate and transport-related infection. 2008. 21, 66, 107, 131

[53] Xinzhi Liu and Peter Stechlinski. Pulse and constant control schemes for epidemic models with seasonality. *Nonlinear Analysis: Real World Applications*, 12:931–946, 2011. 2, 107, 108, 109, 110, 111, 112, 122, 124, 125

[54] Youquan Luo, Shujing Gao, and Shuixian Yan. Pulse vaccination strategy in an epidemic model with two susceptible subclasses and time delay. *Applied Mathematics*, 2:57–63, 2011. 55, 59, 60, 62, 64, 65, 95

[55] C. Connell McCluskey. A model of HIV/AIDS with staged progression and amelioration. *Mathematical Biosciences*, 181:1–16, 2003. 7

[56] Xinzhu Meng and Lansun Chen. Global dynamical behaviors for an SIR epidemic model with time delay and pulse vaccination. *Taiwanese Journal of Mathematics*, 12(5):1107–1122, August 2008. 59, 60, 62

[57] Xinzhu Meng, Lansun Chen, and Huidong Cheng. Two profitless delays for the SEIRS epidemic disease model with nonlinear incidence and pulse vaccination. *Applied Mathematics and Computation*, 186:516–529, 2007. 55, 60, 62, 95, 97

[58] Xinzhu Meng, Lansun Chen, and Zhitao Song. Global dynamics behaviors for new delay SEIR epidemic disease model with vertical transmission and pulse vaccination. *Applied Mathematics and Mechanics*, 28(9):1259–1271, 2007. 59, 62

[59] Xinzhu Meng, Lansun Chen, and Bo Wu. A delay SIR epidemic model with pulse vaccination and incubation times. *Nonlinear Analysis: Real World Applications*, 11:88–98, 2010. 22, 60, 62

[60] Xinzhu Meng, Jianjun Jiao, and Lansun Chen. Two profitless delays for an SEIRS epidemic disease model with vertical transmission and pulse vaccination. *Chaos, Solitons and Fractals*, 40:2114–2125, 2009. 60, 62

[61] Hiroshi Nishiura. Early efforts in modeling the incubation period of infectious diseases with an acute course of illness. *Emerging Themes in Epidemiology*, 4(2), 2007. 7

[62] D. James Nokes and Jonathan Swinton. The control of childhood viral infections by pulse vaccination. *IMA Journal of Mathematics Applied in Medicine and Biology*, 12:29–53, 1995. 16, 55

[63] D. James Nokes and Jonathan Swinton. Vaccination in pulses: A strategy for global eradication of measles and polio? *Trends in Microbiology*, 5(1):14–19, January 1997. 16, 55

[64] Guoping Pang and Lansun Chen. A delayed SIRS epidemic model with pulse vaccination. *Chaos, Solitons and Fractals*, 34:1629–1635, 2007. 59, 60, 62

[65] Yongzhen Pei, Shaoying Liu, Shujing Gao, Shuping Li, and Changguo Li. A delayed SEIQR epidemic model with pulse vaccination and the quarantine measure. *Computers and Mathematics with Applications*, 58:135–145, 2009. 59, 60, 62

[66] Lisa Sattenspiel and Carl P. Simon. The spread and persistence of infectious diseases in structured populations. *Mathematical Biosciences*, 90:341–366, 1988. 7

[67] L.F. Shampine and S. Thompson. Solving delay differential equations with dde23. March 2000. 77

[68] Boris Shulgin, Lewi Stone, and Zvia Agur. Pulse vaccination strategy in the SIR epidemic model. *Bulletin of Mathematical Biology*, 60:1123–1148, 1998. 16, 55, 62

[69] Hal L. Smith. *Monotone Dynamical Systems: An Introduction to the Theory of Competitive and Cooperative Systems*, volume 41 of *Mathematical Surveys and Monographs*. American Mathematical Society, 1995. 42, 63, 123

[70] Xinyu Song, Yu Jiang, and Huiming Wei. Analysis of a saturation incidence SVEIRS epidemic model with pulse and two time delays. *Applied Mathematics and Computation*, 314:381–390, 2009. 55, 60, 62

[71] P. van den Driessche and James Watmough. A simple SIS epidemic model with a backward bifurcation. *Mathematical Biology*, 40:525–540, 2000. 54

[72] P. van den Driessche and James Watmough. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Mathematical Biosciences*, 180:29–48, 2002. 13

[73] Wendi Wang. Global behavior of an SEIRS epidemic model with time delays. *Applied Mathematics Letters*, 15:423–428, 2002. 60

[74] Xia Wang, Youde Tao, and Xinyu Song. Analysis of a pulse vaccination strategy in SIRVS epidemic model. *Communications in Nonlinear Science and Numerical Simulation*, 14:2747–2756, 2009. 55, 62

[75] Xia Wang, Youde Tao, and Xinyu Song. Pulse vaccination on SEIR epidemic model with nonlinear incidence rate. *Applied Mathematics and Computation*, 210:398–404, 2009. 55, 60, 62

[76] Chunjin Wei and Lansun Chen. A delayed epidemic model with pulse vaccination. *Discrete Dynamics in Nature and Society*, page 12, 2008. 59, 60, 62, 64, 65, 95, 97

[77] Huiming Wei, Yu Jiang, Xinyu Song, G.H. Su, and S.Z. Qiu. Global attractivity and permanence of a SVEIR epidemic model with pulse vaccination and time delay. *Journal of Computational and Applied Mathematics*, 229:302–312, 2009. 59, 60, 62

[78] Rui Xu and Zhien Ma. Global stability of a delayed SEIRS epidemic model with saturation incidence rate. *Nonlinear Dynamics*, 61:229–239, 2010. 54, 55, 59, 60

[79] Jurang Yan. Existence of positive periodic solutions of impulsive functional differential equations with two parameters. *Journal of Mathematical Analysis and Applications*, 327:854–868, 2007. ix, 92, 134, 135, 136, 138, 140, 142

[80] James A. Yorke, Herbert W. Hethcote, and Annett Nold. Dynamics and control of the transmission of gonorrhea. *Journal of the American Sexually Transmitted Diseases Association*, 5(2), April/June 1978. 53

[81] Tailei Zhang and Zhidong Teng. An impulsive delayed SEIRS epidemic model with saturation incidence. *Journal of Biological Dynamics*, 2(1):64–84, January 2008. 10, 55, 62, 95

[82] Tailei Zhang and Zhidong Teng. Pulse vaccination delayed SEIRS epidemic model with saturation incidence. *Applied Mathematical Modelling*, 32:1403–1416, 2008. 55, 62

[83] Tailei Zhang and Zhidong Teng. Extinction and permanence for a pulse vaccination delayed SEIRS epidemic model. *Chaos, Solitons and Fractals*, 39:2411–2425, 2009. 60, 62, 65, 95, 96, 97

[84] Xiao-Bing Zhang, Hai-Feng Huo, Xiao-Ke Sun, and Qiang Fu. The differential susceptibility SIR epidemic model with stage structure and pulse vaccination. *Nonlinear Analysis: Real World Applications*, 11:2634–2646, 2010. 59, 60, 62

[85] Xiao-Bing Zhang, Hai-Feng Huo, Xiao-Ke Sun, and Qiang Fu. The differential susceptibility SIR epidemic model with time delay and pulse vaccination. *J Appl Math Comput*, 34:287–298, 2010. 55, 59, 60, 62

[86] Zhong Zhao, Lansun Chen, and Xinyu Song. Impulsive vaccination of SEIR epidemic model with time delay and nonlinear incidence rate. *Mathematics and Computers in Simulation*, 79:500–510, 2008. 59, 60, 62