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The Epidemiology of Childhood Related Diseases: Stability Analysis and Optimal Control

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The Epidemiology of Childhood Related Diseases: Stability Analysis and Optimal Control

Abstract:

Abstract 1

Childhood related epidemics such as measles are characterized by: (i) short periodic outbreaks that may last for short periods of time, between two weeks and six months. (ii) The timescale of such epidemics is therefore shorter compared to the time scale of human population dynamics, since the human lifespan is 60 years on average. (iii) Vaccination plays a key role in controlling such diseases.

We analyzed an SIR model with periodic contact and vaccination rates. We aimed at stability of disease free equilibrium to obtain a criterion for determining optimal vaccination strategy. Two stability analysis tools are used. Floquet theory offered an orbital stability analysis for periodic orbit, while Singular perturbation theory gave an instantaneous stability result. The conditions obtained from stability analysis were used to define two optimal control problems.

From the analysis of the optimal control problems, it turns out that optimal vaccination should target at the instantaneous stability criterion. Focusing only on the Floquet multiplier as the criterion for disease control may lead to a situation where the instantaneous stability is not satisfied at some time points, even though orbital stability holds, leading to short time epidemics that that are not controlled.

Abstract 2

An age dependent model for Hepatitis B, with five compartments of individuals (Susceptibles, Latents, Infectious, Carriers and Immunes) is analysed. The model allows for vertical transmission and the newborns from carrier mothers who develop infection enter into the Latent class.

The aim is to investigate bi-stability scenario, that has been reported in literature for Hepatitis B models without age structure. The results point out that for scenarios when vertical transmission is not allowed for, the probability of development of carriers should depend on the force of infection Λ (in an increasing manner), for bi-stability to occur.

In the case when vertical transmission is allowed for, we show that if we hold the probability of carriage development $q(\Lambda)$ as a constant of force of infection Λ and ensure that no new susceptibles occur, that is, we hold $(\omega - \Omega)$ non-increasing (possibly through mass infant vaccination), then, we are not likely to have bi-stabiliy occurring in the system. The importance of analysis of bi-stability lies in its possible effect on vaccination campaigns since possible existence of two endemic equilibrium (low and high) may impact on disease control through a successful vaccination.

Keywords:SIR-epidemic models, Floquet Theory, Singular Perturbation Theory, Optimal Control and Vaccination Strategies, Stability and Bi-stability analysis, Hepatitis B, Force of Infection.

Zusammenfassung

Diese Arbeit untersucht optimale Impfstrategien für Kinderkrankheiten (u. a. Masern, Windpocken, Mumps, Röteln und Hepatitis B). Die Theorie umfasst die Stabilitätsanalyse eines epidemiologischen SIR Modells. Kontaktrate und Impfparameter wurden als periodisch angenommen. Eine Stabilitätsanalyse für das krankheitsfreie Gleichgewicht (triviale Lösung) wurde ausgeführt. Für periodische Systeme ist die Floquet Theorie der Standardansatz (Orbitale Stabilität).

Eine andere Vorgehensweise zur Analyse der Stabilität der trivialen Lösung lieferte die Singuläre Störungs-Theorie, die die unterschiedlichen Zeitskalen von Infektion und Populationsdynamik ausnutzt. Dies führt auf die Definition von Instantaner Stabilität. Die Ergebnisse ergeben parallel zwei Optimierungsprobleme, die zur Definition von optimalen Impfstrategien führen.

Wir definieren eine Menge von Lösungen für die Optimierungsprobleme und bieten Lösungskandidaten für jedes Optimierungsproblem, das zur Menge optimaler Lösungen gehört. Weiterhin wurden beide Kontrollszenarien (Orbitale und Instantaner Stabilität) simuliert.

Die Untersuchungen deuten an, dass es meistens besser ist das Instantaner Stabilitätskriterium anzuwenden, was zu einem fast optimalen Floquet Faktor führt. Die Fokussierung ausschließlich auf den Floquet Faktor (Orbitale Stabilität) kann zu Situationen führen, in denen die Instantaner Stabilität nicht gegeben ist und für einige Erkrankungen Kurzzeit-Epidemien auftreten können.

Der Abschnitt Hepatitis B ist eine Fallstudie. Eine altersstrukturiertes Hepatitis B Modell wurde analysiert. Motivation für diese Untersuchung ist eine früher veröffentlichte Arbeit zur Bi-Stabilität in Rahmen eines Modells ohne Altersstruktur. Wir betrachten insbesondere die Frage, ob Bi-stabilität im Wesentlichen durch Altersstruktur bedingt sein kann.

Summary

This work examines optimum vaccination strategies for childhood illnesses (such as chicken pox, mumps, German measles and hepatitis B). The theory involves the stability analysis of an epidemiological SIR Model. Contact rate and vaccination parameter were assumed as periodic. A stability analysis for the Disease Free State (trivial solution) was done. For periodically driven systems, the Floquet theory is the standard tool (leading to Orbital stability). Another approach to the analysis of the stability of the trivial solution was done by Singular Perturbations theory which uses the different time scales of disease infection and population dynamics. This leads to the definition of Instantaneous stability. The results lead in parallel, to two optimization problems from which we obtain optimum vaccination strategies. We define a set of solutions for the optimization problems and offer candidate solutions for every optimization problem which belongs to the set of optimal solutions. Furthermore both control scenarios (Orbital and Instantaneous stability) were simulated. The investigations indicate that it is mostly better to apply the

Instantaneous stability criterion which leads to an almost optimum Floquet factor. The focusing exclusively on the Floquet factor (Orbital stability) can lead to situations in which the Instantaneous stability is not satisfied and for some illnesses, short-term epidemics may occur. The segment on Hepatitis B is a case study. An age-structured hepatitis B model was analyzed. Motivation for this investigation is an earlier published work on Bi-stability in the case of a model without age structure. We look in particular at the question of whether Bi-stability can occur in the case of an age structured model.

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Munich, Germany — Nelson O. Onyango

September, 2010

To Mary, Natalie and Agneta.

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SECTION A:

A general childhood disease model of SIR type with periodic coefficients is analyzed. Stability analysis is done using standard tool of Floqúet theory which provides an averaging "orbital stability" criterion. We conjecture that such an averaging behavior may fail to capture short outbreaks in disease even when orbital stability is satisfied.

However an optional approach via Singular Perturbation theory provides an instantaneous stability criterion which has the capacity to capture such small outbreaks in diseases that may be unnoticed if one used an orbital criterion obtained from the Floqúet case.

Chapter 1

Introduction

1.1 Introduction

Vaccination is widely used in medicine to control the spread of many infectious diseases such as Measles, TB, Rubella, among others. The main concern is, "which vaccination policies are optimal?" Optimal in the sense of disease eradication with regard to associated costs.

This study is aimed at characterizing optimal vaccination strategies, given certain restricted costs. For instance, studies are ongoing to compare *Constant Vaccination Strategy* which involves vaccinating children homogenously over time to *Pulse vaccination Strategy*. Whether single dose or booster vaccination, if the doses are given randomly/uniformly in time to children in the population, then we still classify the policy as constant vaccination. Booster vaccination is done for instance in Finland and Sweden since 1982 and USA since 1989, where the MMR-(Measles, Mumps, Rubella) vaccine is administered at two age groups/levels, with 97-98% success [Alexander 2006, pp2]. An alternative strategy popularly referred to as Pulse Vaccination Strategy (PVS) is also know as vaccination campaign, or the case when vaccination is done for all children of an age group, e.g. 0-7years, in one particular day. Mathematical theory of pulse vaccination as studied by Agur [Agur 1993] is being widely investigated in Mathematics.

Mathematical theory in this work involves concepts form Pulse Vaccination and Vaccination days, as in [Agur 1993, Eichner 1995] and optimal vaccination in periodic setting, e.g., in [Anita 1998]. The idea of Vaccination days (where some special day is set aside to vaccinate certain age group of children) seem very effective, but the reasons are not completely clear. Some ideas to explain this phenomenon include:

(1) At vaccination days typically all children between say 2 and 7 years are vaccinated, irrespectively from the vaccination status; thus, children missed before have at each vaccination day the chance to be vaccinated; initial vaccination failures get a second chance to become immune; all vaccinateds receive a booster vaccination that ensures protection.

(2) There is a kind of resonance between periodic contact rate and periodic vaccination rate that yields a fast eradication of the disease (perhaps even before

herd immunity is reached).

(3) Vaccination is more effective if vaccination days are carefully spread in time (as in pulse vaccination), than randomly distributing them over time (like in Constant vaccination) [Agur 1993, Shulgin 1998].

We only address the last question, assuming that the disease is not present in the population. The aim is to stabilize the population against invasion of the disease using a given amount of vaccination doses per period. The tools used are those developed from works on models with age structure [Hadeler 1996a, Hadeler 1996b, Mueller 1998, Mueller 2000]. Interest is to apply the theories to model the spread of childhood diseases such as measles whose contact rates are periodic due to school terms, or seasonal changes, for instance.We determine stability conditions in terms of orbital and instantaneous stability and illustrate optimal vaccination policies with respect to the two stability criteria. The conjecture is that instantaneous stability offers a more appropriate tool to trace disease outbreaks and hence develop an effective vaccination policy for childhood diseases.

One requires mathematical tools to get an insight into biological problems such as spread and control of epidemics. Standard mathematical tools may be available for most problems. However, more work my need to be done, to get to the finer details of such problems.

A system of ODE's commonly referred to as SIR model in epidemiology, with periodic coefficients is analyzed. We assume the manifold $I(t) = 0$ holds and seek solutions on this manifold. Assuming a smooth flow, positive invariance and uniqueness of solutions is proved using Tangent conditions and Lipschitz conditions respectively. Assuming N(t)=S(t)+I(t)+R(t), the Quasimonotonicity (cooperative system) holds and uniqueness of solutions can be inferred.

As is standard with epidemiological models, we investigated the local stability of disease free state (the trivial solution). Stability of the disease free state indicates no infectives in the population. This is an indication of an effective vaccination campaign in a system with vaccination. For a system with periodic coefficients, Floquet Theory is the main tool of analysis. The results of Floquet theory gave us an orbital stability criterion.

We incorporated more biological reality in the modeling, by assuming that we have a fast time scale for disease compared to the time scale for the population dynamics. This holds for childhood diseases such as measles or chicken pox that have infective periods lasting short periods of time (e.g 2 weeks). Singular perturbation theory handles stability analysis for systems with different time scales. The results of singular perturbation theory gave us an instantaneous stability analysis criteria.

The work is organized as follow:

Chapter 1 introduces the model and its assumptions. Positive invariance and uniqueness of solutions are investigated for a standard case of solutions in C^1. Chapter 2 addresses the problem of stability analysis of the disease free state. In a

model with vaccination, a stable disease free state is an indicator of a successful vaccination effort. Orbital stability and instantaneous stability criterion are obtained via two alternative mathematical theorems. In chapter 3, the two stability control problems from chapter two are used to define two optimal control problems.

Problem 1.1.1 *For $\psi \in L^{\infty}_{+}(0,T)$, find the vaccination schedule that minimizes*

$$\tilde{\mathcal{F}}[\psi] = \frac{1}{T}\int_0^T \beta(\tau)\, S[\psi](\tau)\, d\tau$$

under the constraint that the number of vaccination doses $\tilde{C}[\psi] = C_0$ is given, where $\tilde{C}[\psi]$ is defined as

$$\tilde{C}[\psi] := \int_0^T \psi(\tau)\, S[\psi](\tau)\, d\tau.$$

Problem 1.1.2 *For $\psi \in L^{\infty}_{+}(0,T)$, find the vaccination schedule that minimizes*

$$\|R_v[\psi]\|_{L^\infty} = \left\| \frac{\beta(t) S[\psi](t)}{\alpha} \right\|_{L^\infty}$$

under the constraint that the number of vaccination doses $\tilde{C}[\psi] = C_0$ is given. Again,

$$\tilde{C}[\psi] := \int_0^T \psi(\tau)\, S[\psi](\tau)\, d\tau.$$

It turns out that the optimal control problem (1.1.1) is a classical optimal control problem, but the control problem (1.1.2), which involves minimizing a supremum of a function, does not fall into any class of standard classical optimal control problems unless with modifications. Since we are interested in comparisons of the two optimal control strategies, we chose to handle both problems in a similar manner, by defining a set $\mathfrak{S}$ from which we guarantee the existence of optimal solutions. Section (3.2) in chapter 3 is dedicated to characterizing the set of optimal solutions for both problems. In chapter 4, we illustrate candidate optimal control solutions for the two control problems. In chapter 5, we use the candidate solutions and simulate the vaccination strategies obtained from the two cases using a set of parameters that emulate measles epidemic.

Chapter 6 in Section B is rather a case study on Hepatitis B. Section A deals with a general theory for any childhood related diseaes. The chapter offers an example from Hepatitis B modeling with an aim at investigating a hypothesis that the contribution of carriers in the population leads to possible bi-stability scenario. The fixed point equation for the force of infection is used to investigate stability, a common approach used in the literature for age structured systems in epidemiology. The motivation is to justify, in an age structured model, the hypothesis of contribution of carriers for bi-stability as reported in an earlier published work [Medley 2001].

We prove this hypothesis for a case when no vertical transmission is allowed in our model.

Though we fail to prove the above hypothesis in a general case when vertical transmission is allowed for, we however show that if we hold the probability of carriage development $q(\Lambda)$ as a constant of the force of infection Λ and ensure, through mass infant vaccination, that no new susceptibles occur, i.e. $(\omega - \Omega)$ non-increasing, then we are not likely to have bi-stabiliy occuring in the system.

1.2 Definition of terminologies

(i) **SIR models:** These are epidemiological models that separate a population of (human) individuals into compartments, of susceptible people (those who do not have disease and are at risk of being infected if they meet infected people), infected people (who have the disease and can infect other people they come into contact with) and immune people (who have recovered from the disease and have some protection from infection). There are models that consider more compartments of infection including incubation, Carriage and even a return paths from Immune state to susceptible state.

(ii) **Optimal Vaccination:** Vaccination is the use of vaccines to prevent specific diseases. Optimal vaccination requires good management of available resources (money, time, personnel or any other costs considered) to achieve effective disease control, even without vaccinating the whole population.

(iii) **Vaccination Strategy:** An approach of applying vaccination doses. This can be studied in terms of vaccination doses used, number of immunes already induced in the population or the number of susceptibles still remaining in the population. In this study, the number of susceptibles in a population undergoing vaccination $S[\psi](t)$ will be used to classify vaccination strategies.

(iv) **Vaccination support:** Any time point in which vaccination is done. We expect the vaccination parameter $\psi(t) = 0$ outside the vaccination support.

(v) **Bistability:** Also understood as "hysteresis" in general bifurcation theory. It is a scenario where two non-trivial solutions co-exist for the same set of parameters in a system of equations representing some natural system.

1.3 Model and assumptions

We assume a SIR-model with vaccination. We consider a large population that is well mixed like the children of several large schools located close together (up to a certain degree, these are contradicting assumptions and a mathematical fiction).

We further assume that the immunes (who are immune either due to the disease itself or because of immunisation) are completely protected for the rest of their lives.

The contact rate $\beta = \beta(t)$ is assumed to be periodic with a period $\hat{T}$. We aim to control the disease by a periodic vaccination rate. Primarily from mathematical and practical reasons (annual periodicity) we assume the vaccination rate to be periodic with a period T that is a multiple of $\hat{T}$,

$$T = l\,\hat{T}, \qquad l \in \mathbb{N}.$$

We use b to denote the influx rate into the population, μ the exit rate (which may be rather related to the exit from the population compartment under consideration than to mortality) and α the recovery rate. Furthermore, the vaccination rate $\psi(t)$ is assumed in $L^\infty_+(0,T)$ (the non-negative L^∞ functions) as well as $\beta \in L^\infty_+(0,T)$. The contact rate is also assumed to be bounded away from zero, $\beta(t) \geq \underline{\beta} > 0$. All rates are non-negative, ($b \geq 0,\ \mu \geq 0$ and $\alpha \geq 0$). The standard SIR-model reads in this situation

$$\begin{aligned} \frac{d}{dt}S &= b - \mu S - \psi(t)S - \beta(t)S\,I \\ \frac{d}{dt}I &= -\mu I + \beta(t)S\,I - \alpha I \\ \frac{d}{dt}R &= -\mu R + \psi(t)S + \alpha I \end{aligned} \tag{1.1}$$

We now investigate the uninfected periodic solution and its stability; the proofs of the statements are rather standard but are nevertheless given for sakes of completeness.

Proposition 1.3.1 *For given $\psi \in L^\infty_+(0,T)$ there is a unique periodic solution with $I(t) \equiv 0$. All initial conditions with $I(0) = 0$ tend to this solution.*

Proof: If $I(0) = 0$ we find $I(t) = 0$ for all times, i.e. we are left with a linear set of equations. Since the equation for S is independent of that for R, we find

$$S(t) = e^{-\int_0^t \mu + \psi(\tau)\,d\tau} S(0) + b \int_0^t e^{-\int_\sigma^t \mu + \psi(\tau)\,d\tau}\,d\sigma = H(t)S(0) + b \int_0^t \frac{H(t)}{H(\sigma)}\,d\sigma$$

where we use the abbreviation $H(t) = \exp(-\int_0^t \mu + \psi(\tau)\,d\tau)$. We first look for the periodic solution, which is given by $S(T) = S(0)$, i.e.

$$S(0) = b\,\frac{H(T)}{1 - H(T)} \int_0^T \frac{1}{H(\sigma)}\,d\sigma.$$

Thus

$$S(t) = b\,\frac{H(T)}{1 - H(T)} \int_0^T \frac{H(t)}{H(\sigma)}\,d\sigma + b \int_0^t \frac{H(t)}{H(\sigma)}\,d\sigma$$

is the only candidate for a periodic solution.

It is straight forward to check that it is (the unique) periodic solution and attracts all trajectories: Let $S(t_0)$ be any solution, then $u(t) = S(t) - \hat{S}(t)$ satisfies $\dot{u} = -\mu u - \psi(t)u$, i.e. $u(t) = u(0)H(t) \to 0$ exponentially fast for $t \to \infty$.

□

Definition 1.3.1 *For $\psi \in L^\infty_+$ let $S[\psi] : [0,T] \to \mathbb{R}$ denote the susceptible component of the unique determined, periodic solution of (1.1) with $I(t) \equiv 0$,*

$$S[\psi](t) = b\,\frac{p(T)\Phi(T)}{1-p(T)\Phi(T)}\int_0^T \frac{p(t)\Phi(t)}{p(\sigma)\Phi(\sigma)}\,d\sigma + b\int_0^t \frac{p(t)\Phi(t)}{p(\sigma)\Phi(\sigma)}\,d\sigma$$

where we used the abbreviation $p(t) = \exp(-\mu t)$ and $\Phi(t) = \exp(-\int_0^t \psi(\tau)\,d\tau)$, s.t. $H(t) = p(t)\Phi(t)$.

1.4 Asymptotic behavior of I(t).

It is standard to show that stability of disease free state is achieved if the infective population, I(t) tends to zero asymptotically (for the reproductive number- R_0 less that unity) [Zhou 2003].

From the results of Floquet analysis in the next section, we observe that $R_0 < 1$ if

$$\int_0^T \beta(\tau)S[\psi](\tau)d\tau \le T(\mu+\alpha).$$

Proposition 1.4.1 *The Infectious population I(t) tends to zero asymptotically for $R_0 < 1$.*

Proof

$$\dot{I}(t) = -\{\mu+\alpha-\beta(t)S(t)\}I(t)$$

$$\begin{aligned}
I(t) &= I(0)\exp\left(-\int_0^t((\mu+\alpha)-\beta(\tau)S(\tau))d\tau\right)\\
&= I(0)\exp\left(-\int_0^t((\mu+\alpha)-\beta(\tau)S[\psi](\tau))d\tau - \int_0^t \beta(\tau)\left\{S[\psi](t)-S(\tau)\right\}d\tau\right)\\
&= I(0)\exp\left(-\int_0^t((\mu+\alpha)-\beta(\tau)S[\psi](\tau))d\tau\right)\exp\left(-\int_0^t \beta(\tau)\left\{S[\psi](t)-S(\tau)\right\}d\tau\right)\\
&= I(0)\exp\left(-\int_0^t((\mu+\alpha)-\beta(\tau)S[\psi](\tau))d\tau - \int_0^t \beta(\sigma)\tilde{S}\exp\left\{-\int_0^t(\mu+\psi(\tau))d\tau\right\}d\sigma\right)\\
&= I(0)P_0P_1
\end{aligned}$$

where

$$P_0 = \exp\left(-\int_0^t ((\mu+\alpha) - \beta(\tau)S[\psi](\tau))d\tau\right)$$

and

$$P_1 = \exp\left(-\int_0^t \beta(\sigma)\tilde{S}\exp\left\{-\int_0^t (\mu+\psi(\tau))d\tau\right\}d\sigma\right)$$

Note that as $t \to \infty, \quad \psi(t) \to \infty$.
Thus $\exp\left\{-\int_0^t(\mu+\psi(\tau))d\tau\right\} \to 0$ and $P_1 \to 1$.

We further investigate P_0.

We notice that if

$$\int_0^t \beta(\tau)S[\psi](\tau)d\tau \leq t(\mu+\alpha),$$

then P_0 is decreasing. I(t) cannot exponentially grow hence no possibility of outbreaks.

We proceed to show I(t) goes to zero. A quick note is that

$$\begin{aligned} P_0 &= \exp\left(-\int_0^t ((\mu+\alpha) - \beta(\tau)S[\psi](\tau))d\tau\right) \\ &= \exp\left(-\int_0^t ((\mu+\alpha)d\tau\right)\exp\left(\int_0^t \beta(\tau)S[\psi](\tau))d\tau\right) \\ &= \exp\left(-t(\mu+\alpha)\right)\exp\left(\int_0^t \beta(\tau)S[\psi](\tau))d\tau\right) \end{aligned}$$

As $t \to \infty, \quad \exp\left(-t(\mu+\alpha)\right) \to 0$ and $P_0 \to 0$.

Alternatively, let $t = nT+t_1$ and $0 \leq t_1 < T$ (n denotes the number of periodic circles as $I(t)$ is periodic). As $t \to \infty, \ n \to \infty$ as well, since $t = nT + t_1$.

$$\begin{aligned} P_0(t) &= \exp\left\{-\int_0^{nT} (\mu+\alpha) - \beta(\tau)S[\psi](\tau)d\tau + \int_{nT}^t (\mu+\alpha) - \beta(\tau)S[\psi](\tau)d\tau\right\} \\ &= P_0(nT)\exp\left\{-\int_0^{t_1} (\mu+\alpha) - \beta(\tau)S[\psi](\tau)d\tau\right\} \\ &\leq P_0(nT).Q \end{aligned} \tag{1.2}$$

$$\begin{aligned} P_0(nT) &= (P_0(T))^n \\ &= \exp\left(-n\int_0^T (\mu+\alpha) - \beta(\tau)S[\psi](\tau)d\tau\right) \\ &= \exp\left(-n\left(T(\mu+\alpha) - \tilde{\mathcal{F}}[\psi]\right)\right) \end{aligned}$$

where $\tilde{\mathcal{F}}[\psi] = \int_0^T \beta(t)S[\psi](t)\,dt$.

$$\exp\left\{-n\left(T(\mu+\alpha) - \tilde{\mathcal{F}}\right)\right\} \to 0 \qquad \text{as} \qquad n \to \infty,$$

$$P_0(nT) \longrightarrow 0 \qquad \text{as} \qquad n \longrightarrow \infty$$

and

$$P_0(t) \longrightarrow 0 \qquad \text{as} \qquad n \longrightarrow \infty.$$

Notice that Q in (1.2)remains bounded if $\int_0^{t_1} \beta(\tau)S[\psi](\tau)d\tau \leq t_1(\mu+\alpha)$.

Hence

$$\Rightarrow I(t) \to 0, \quad as \qquad t \to \infty.$$

□

1.5 Positive Invariance and Uniqueness of Solutions

Denote system (1.1) by the equation

$$\dot{y} = f(y),$$

where vector y denotes $(S, I, R)^T$. Assume $f \in C^r(0,\infty)$; $0 \leq r \leq \infty$, a smooth flow. We show that solutions to system (1.1) live in an invariant positive domain and are unique.

Theorem 1.5.1 *Consider the ODE system $\dot{y} = f(y)$, $y \in \mathbb{R}^3$, where $y = (S, I, R)^T$ and $f(y)$ continuous. Consider an invariant set $M \in \mathbb{R}^3_+$, for this system i.e., $y(0) \in M$, and $y(t) \in M$, $\forall\ t > 0$. By the tangent condition, suppose f : $[0, T]$ X $\overline{M} \mapsto \mathbb{R}^3$, and $n(z)$ defines the outer normal vector at z to set M, then; i) the closure of M is positively invariant if*

$$\langle n(z), f(t,z)\rangle \leq 0, \quad \forall t \in [0,T], \quad z \in \partial M,$$

ii) if the following Lipschitz condition holds, then $\dot{y} = f(y)$, $y(0) = y_0$, $y \in \mathbb{R}^n$, is uniquely solvable in $[0,\infty)$,

$$\langle (y_1 - y_2), (f(t,y_1) - f(t,y_2)\rangle \leq L|y_1 - y_2|^2$$

For proof, see [Wolfgang 2000, pp124]. □

Proposition 1.5.2 *Based on the assumptions of theorem (1.5.1), system (1.1) defined by the equation*

$$\dot{y} = f(y),$$

where vector y *denotes* $(S, I, R)^T$ *has solutions in a positively invariant set* $M \in \mathbb{R}^3$. *The solutions are unique.*

Proof:

Part(i)

Define three boundary points to M by

$$z = \{(\tilde{S}, \tilde{I}, 0), (\tilde{S}, 0, \tilde{R}), (0, \tilde{I}, \tilde{R})\}, \qquad \tilde{S}, \tilde{I}, \tilde{R} \geq 0.$$

Define corresponding outer normal vectors at these points by

$$n(z) = \{(0, 0, -1), (0, -1, 0), (-1, 0, 0)\}.$$

At each boundary point, the following condition should hold.

$$\langle n(z), f(t, z)\rangle \leq 0, \quad \forall t \in [0, T], z \in \partial M,$$

$$\begin{aligned} \langle (0,0,-1), (f_1(t,z), f_2(t,z), f_3(t,z))\rangle &= -f_3(t, \tilde{S}, \tilde{I}, 0) \\ &= -\psi(t)\tilde{S} - \alpha\tilde{I} \\ &< 0; \qquad \psi(t), \alpha, \tilde{S}, \tilde{I} \geq 0 \end{aligned}$$

$$\begin{aligned} \langle (0,-1,0), (f_1(t,z), f_2(t,z), f_3(t,z))\rangle &= -f_2(t, \tilde{S}, 0, \tilde{R}) \\ &= 0; \end{aligned}$$

$$\begin{aligned} \langle (-1,0,0), (f_1(t,z), f_2(t,z), f_3(t,z))\rangle &= -f_1(t, 0, \tilde{I}, \tilde{R}) \\ &= -b \\ &< 0; \qquad b \geq 0) \end{aligned}$$

??

Part (ii)

Lipschitz condition offers a sufficient condition for uniqueness of solutions, see e.g., [Wolfgang 2000, pp124] and [Chicone 1999, pp120].

We have, $y = (S, I, R)^T$, thus, $y_1 = (S_1, I_1, R_1)^T$, $y_2 = (S_2, I_2, R_2)^T$.

We show that given y_1 and y_2 that satisfy $\dot{y} = f(y)$,

$$\langle (y_1 - y_2), (f(t, y_1) - f(t, y_2))\rangle \leq L|y_1 - y_2|^2.$$

Let

$$\langle (y_1 - y_2), (f(t, y_1) - f(t, y_2))\rangle = Q,$$

then

$$
\begin{aligned}
Q &= (S_1 - S_2)[f_1(t, y_1) - f_1(t, y_2)] + (I_1 - I_2)[f_2(t, y_1) - f_2(t, y_2)] \\
&\quad +(R_1 - R_2)[f_3(t, y_1) - f_3(t, y_2)] \\
&= (S_1 - S_2)[(b - \mu S_1 - \psi(t)S_1 - \beta(t)S_1 I_1) - (b - \mu S_2 - \psi(t)S_2 - \beta(t)S_2 I_2)] \\
&\quad +(I_1 - I_2)[(-\mu I_1 + \beta(t)S_1 I_1 - \alpha I_1) - (-\mu I_2 + \beta(t)S_2 I_2 - \alpha I_2)] \\
&\quad +(R_1 - R_2)[(-\mu R_1 + \psi(t)S_1 + \alpha I_1) - (-\mu R_2 + \psi(t)S_2 + \alpha I_2)] \\
&= -(\mu + \psi(t))(S_1 - S_2)^2 - (\mu + \alpha)(I_1 - I_2)^2 - \mu(R_1 - R_2)^2 \\
&\quad +\psi(t)(R_1 - R_2)(S_1 - S_2) + \alpha(R_1 - R_2)(I_1 - I_2) \\
&\quad -\beta(t)(S_1 I_1 - S_2 I_2)\{(S_1 - S_2) - (I_1 - I_2)\} \qquad (1.3) \\
&\leq -(\mu + \beta(t)S_2)(S_1 - S_2)^2 - (\mu - \beta(t)I_1)(I_1 - I_2)^2 - (\mu - \psi(t) - \alpha)(R_1 - R_2)^2 \\
&\leq -\mu\{(S_1 - S_2)^2 + (I_1 - I_2)^2 + (R_1 - R_2)^2\} = L|y_1 - y_2|^2.
\end{aligned}
$$

Here, we need a continuous bounded Lipschitz function L, which we have approximated with μ . However, in the second last statement above,L is defined and finitely so if S_2, and I_1 or simply $S(t)$ and $I(t)$ are bounded functions and this follows since $S(t) + I(t) + R(t) = N(t)$, and we know that

$$\dot{N(t)} = b - \mu N(t),$$

such that $lim_{t\to\infty} N(t) = \frac{b}{\mu}$. The equation (1.3) is modified using
(i) $S_1 I_1 - S_2 I_2 = S_1 I_1 - S_2 I_1 + S_2 I_1 - S_2 I_2$.
(ii) $(S_1 - S_2)(I_1 - I_2) \leq (S_1 - S_2)^2 + (I_1 - I_2)^2$.

The solutions for (1.1) remain positive on the time interval $[0, T)$ and is unique, for some set of initial conditions. Positivity of solutions for SEIR type model is also illustrated in [Herzog 2004], for general cases and for quasi-monotone systems.

□

Theorem 1.5.3 Quasimonotonicity: *Consider an ODE system* $\dot{y} = f(t, y)$, $f : [0, \infty) X \mathbb{R}^3 \mapsto \mathbb{R}^3$. *Suppose f(t,y) is quasimonotone increasing and continuous, and there exists some continuous function* $L : [0, \infty) \mapsto \mathbb{R}$ *, a defined function g(.) and two possible solutions x and y, that satisfy the system, such that*

$$g(f(t, y) - f(t, x)) \leq L(t)g(y - x), \qquad \forall t \geq 0, \qquad x \leq y,$$

then $\dot{y} = f(t, y), \qquad y(0) = y_0$ *is uniquely solvable on* $[0, \infty)$.

Proposition 1.5.4 *The ODE system (1.1) is quasimonotone (cooperative) system and by theorem (1.5.3), the system is uniquely solvable and solutions live in a positively invariant corn* $\mathbb{R}^3_+$.

Proof: We make use of [Herzog 1998, Theorem 1] and the condition $N = S + I + R$.

$$\begin{aligned} \frac{d}{dt}S &= b - \mu S - \psi(t)S - \beta(t)S\,(N - S - R) \\ \frac{d}{dt}I &= -\mu I + \beta(t)S\,I - \alpha I \\ \frac{d}{dt}R &= -\mu R + \psi(t)S + \alpha I \end{aligned} \tag{1.4}$$

The general Jacobian matrix to the ODE system (1.4) reads,

$$J = \begin{pmatrix} -\mu - \psi - \beta(N - S - R) + \beta S & 0 & \beta S \\ \beta I & -\mu - \alpha - \beta S & 0 \\ \psi & \alpha & -\mu \end{pmatrix}$$

The off diagonal terms are positive, hence we have a cooperative system. By theorem (1.5.3), the system is uniquely solvable, and positivity in the positive corn $\mathbb{R}^3_+$ of solutions for this case, holds [Herzog 1998] .

□

Chapter 2

Stability Analysis

2.1 Orbital stability of periodic solution

We now investigate the stability of the solution in the full model. We use Floquet Theory, whose direct object of study is a linear differential equation with periodic coefficients [Ioos 1990].

Proposition 2.1.1 *The Floquet multipliers for the solution $S[\psi](t)$ read*

$$\rho_1 = e^{-\int_0^T \mu+\psi(\tau)\,d\tau}, \quad \rho_2 = e^{-\int_0^T \mu\,d\tau}, \quad \rho_3 = e^{-(\mu+\alpha)T+\int_0^T \beta(\tau)S[\psi](\tau)\,d\tau}.$$

Proof:

Consider the linearization of (1.1) around a periodic solution by setting

$$S(t) = s + S[\psi](t), \quad R(t) = r + \left(\frac{b}{\mu} - S[\psi](t)\right), \text{ and } I(t) = i + 0.$$

We find

$$\begin{aligned} \frac{d}{dt}s &= -\mu s - \psi(t)s - \beta(t)S[\psi](t)\,i \\ \frac{d}{dt}i &= -\mu i + \beta(t)S[\psi](t)\,i - \alpha i \\ \frac{d}{dt}r &= -\mu r + \psi(t)s + \alpha i \end{aligned} \tag{2.1}$$

A fundermental matrix of (2.1) consists of solutions satisfying the initial conditions $(1,0,0)^T$, $(0,1,0)^T$, and $(0,0,1)^T$.

Consider the initial condition $(0,0,1)^T$. We note that

$$i(t) = i(0)\exp\left\{-\int_0^t \mu + \beta(\tau)S[\psi](\tau) + \alpha d\tau\right\} = 0 \quad \text{since} \quad i(0) = 0$$

Then we consider the equation for $s(t)$, i.e.,

$$s(t) = s(0)\exp\left\{-\int_0^t \mu + \psi(\tau)d\tau\right\} - \int_0^t \exp\left\{-\int_\tau^r \mu + \psi(\tau)d\tau\right\}\beta(r)S[\psi](r)i(r)dr.$$

Since $i(t) = 0$ and $s(0) = 0$, $s(t) = 0\ \forall\ t$.

Finally,

$$r(t) = r(0)\exp\left\{-\int_0^t \mu\right\} + \int_0^t \exp\left\{-\int_0^r \mu\right\}(\psi(r)s(r)+\alpha i(r))dr = \exp\left\{-\int_0^t \mu\right\}$$

Hence we obtain the solution,

$$\begin{pmatrix} s \\ i \\ r \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 1 \end{pmatrix} e^{-\mu t}$$

In a similar manner, we obtain the other two solutions. All the three independent solutions with initial conditions $(0,0,1)^T$ $(1,0,0)^T$, and $(0,1,0)^T$ read,

$$\begin{pmatrix} s \\ i \\ r \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 1 \end{pmatrix} e^{-\mu t}, \qquad \begin{pmatrix} s \\ i \\ r \end{pmatrix} = \begin{pmatrix} \exp(-\int_0^t \mu + \psi(\tau)\, d\tau) \\ 0 \\ \int_0^t \exp(\mu(t-\tau))\,\psi(\tau)\exp(-\int_0^\tau \mu + \psi(\sigma)\, d\sigma)\, d\tau \end{pmatrix}$$

and

$$\begin{pmatrix} s \\ i \\ r \end{pmatrix} = \begin{pmatrix} * \\ \exp(-\int_0^t \mu + \alpha\, d\tau + \int_0^t \beta\, S[\psi](\tau)\, d\tau) \\ * \end{pmatrix}.$$

The Monodromy matrix $M(T)$, which is a fundamental matrix $\phi(t)$ of the linearized system, evaluated at time T(the period), has the form

$$\begin{pmatrix} \exp(-\int_0^T \mu + \psi(\tau)\, d\tau) & * & 0 \\ 0 & \exp(-\int_0^T \mu + \alpha\, d\tau + \int_0^T \beta\, S[\psi](\tau)\, d\tau) & 0 \\ * & * & \exp(-\int_0^T \mu\, d\tau) \end{pmatrix}$$

The entries (*) in the matrix are assumed equal to zero. The columns of the Monodromy matrix are defined by the three independent solutions, and the matrix is evaluated at period T. As $M(T)$ posseses a block structure, it is possible to read the spectrum from the diagonal entries, which therefore define the Floquet multipliers as ρ_1, ρ_2 and ρ_3. □

The local stability of the disease free equilibrium is satisfied if

$$|\rho_i| < 1 \quad i = 1, 2, 3.$$

That is, the eigen values should lie in a unit circle [Chicone 1999, Theorem 2.53, pp168]. Since the absolute value of ρ_1 and ρ_2 are less than one, therefore, local stability is determined by ρ_3, especially by the value of the average quantity $1/T\int_0^T \beta(t)S[\psi](t)\, dt$ and we are led to the following definition.

Definition 2.1.1 *Let* $\tilde{\mathcal{F}} : L^\infty_+ \to \mathbb{R}$,

$$\tilde{\mathcal{F}}[\psi] = \frac{1}{T}\int_0^T \beta(t)S[\psi](t)\, dt.$$

If $\tilde{\mathcal{F}}[\psi] < (\mu + \alpha)$ *then the uninfected periodic orbit is orbital stable.*

2.2 Instantaneous Stability Analysis

2.2.1 Fast Epidemic

Now we assume a different point of view. Consider a disease which is quite infectious but has a short infective period in comparison with the period of the contact- and vaccination rate. This situation may be given in cases like measles. Thus, β and α are both large. We may express this fact in introducing a small parameter ε,

$$\begin{aligned} \frac{d}{dt}S &= b - \mu S - \psi(t)S - \frac{1}{\varepsilon}\beta(t)S\,I \\ \frac{d}{dt}I &= -\mu I + \frac{1}{\varepsilon}\beta(t)S\,I - \frac{1}{\varepsilon}\alpha I \\ \frac{d}{dt}R &= -\mu R + \psi(t)S + \frac{1}{\varepsilon}\alpha I \end{aligned} \tag{2.2}$$

We want to know, if an epidemic is possible in this situation. It is important to be precise what the statement "an epidemic is possible" means. The idea is, that we start at time t_0 close to the uninfected periodic solution (especially with $I(t_0)$ nonzero, but small) and find - for short times - a trajectory that resembles the usual epidemic model in case that the reproduction number is larger than one, i.e. the trajectories resemble that of the ODE

$$s' = -\hat{\beta}s\,i, \quad i' = (\hat{\beta}s\,i - \hat{\alpha}i), \quad r' = \hat{\alpha}i.$$

It is well known that there is an invariant functional $x : \mathbb{R}^2 \to \mathbb{R}$ on these trajectories of the form

$$x(s,i) = -s + (\alpha/\beta)\ln(s) - i.$$

I.e., $x(s(t), i(t))$ is constant, or, equivalently, $i = -s + (\alpha/\beta)\ln(s) - x$ where $x < \max\{-s + (\hat{\alpha}/\hat{\beta})\ln(s) \,|\, s \in \mathbb{R}_+\} = x_0 = (\hat{\alpha}/\hat{\beta})(\ln(\hat{\alpha}/\hat{\beta}) - 1)$. We aim to apply Singular perturbation theory. The theory requires clearly separated time scales and an autonomous equation. Thus, we first (formally) decouple time and periodic functions and augment the state space with a variable $q \in [0, T]$ where we identify $q \equiv q \bmod T$, i.e. $q \in S^1$ (note that this variable lives in a compact set) and obtain

$$\begin{aligned} \frac{d}{dt}S &= b - \mu S - \psi(q)S - \frac{1}{\varepsilon}\beta(q)S\,I, \\ \frac{d}{dt}I &= -\mu I + \frac{1}{\varepsilon}\beta(q)S\,I - \frac{1}{\varepsilon}\alpha I \\ \frac{d}{dt}R &= -\mu R + \psi(q)S + \frac{1}{\varepsilon}\alpha I, \\ \frac{d}{dt}q &= 1 \end{aligned} \tag{2.3}$$

The time scale t of (2.3) is the time scale of the population dynamics. If we transform time to the fast time scale of the disease, using $t = \varepsilon\tau$ and dropping the equation for R since $R(t_0) = b/\mu - S[\psi](t_0)$ and equations for S, X and q do not depend on R, we obtain the new system,

$$\begin{aligned} \frac{d}{d\tau}S &= \varepsilon\{b - \mu S - \psi(q)S\} - \beta(q)S\,I, \\ \frac{d}{d\tau}I &= -\varepsilon\mu I + \beta(q)S\,I - \alpha I \\ \frac{d}{d\tau}q &= \varepsilon \end{aligned} \tag{2.4}$$

Taking $\varepsilon \to 0$, (2.4) becomes an SIR-model without population dynamics, from whose dynamics we obtain the constant relation $X = -S + (\alpha/\beta(q))\ln(S) - I$. Since X is constant on a fast system, it defines a slow variable in the context of Singular perturbation theory, and hence our choice of $X(q)$ to transform the system into a distinct fast-slow system.

2.2.2 Variable transformation.

We observe that system (2.3) mixes the slow time scales of population dynamics and vaccination with the fast dynamics of the epidemic. In order to use Singular perturbation theory, we need to separate the time scales explicitly using a transformation of variables.

The idea for a variable change is the following: on the fast time scale of the epidemic, q is fixed. Thus if $\varepsilon \to 0$, we expect a trajectory of (2.4) to follow a pure SIR-model without population dynamics or vaccination. That is, there is a relation between S and I of the following form

$$-S + (\alpha/\beta)\ln(S) - I = \text{constant}.$$

The SI-plane is fibred by these curves, indicating the time course of epidemics with different initial values. This observation gives rise to the definition

$$X = -S + (\alpha/\beta(q))\ln(S) - I$$

As $S, I \geq 0$, X assumes values only below the maximum of $-S + (\alpha/\beta(q))\ln(S)$. The maximum is assumed at $S = \beta(q)/\alpha$, and thus

$$X \leq X^* = -\beta(q)/\alpha + (\alpha/\beta(q))\ln(\beta(q)/\alpha).$$

On the fast time scale, X is constant. Instead of the SI-plane we investigate the system on the SX-plane.

We find

$$\begin{aligned}\frac{d}{dt}X &= -S' + \frac{\alpha\, S'}{\beta(q)S} - \frac{\alpha\beta'(q)\, q'}{\beta^2(q)}\ \ln(S) - I' \\ &= -b + \mu S + \psi(q)S + \frac{1}{\varepsilon}\beta(q)S\, I + \frac{\alpha\,[b - \mu S - \psi(q)S - \frac{1}{\varepsilon}\beta(q)S\, I]}{\beta(q)S} \\ &\quad -\frac{\alpha\beta'(q)\, q'}{\beta^2(q)}\ \ln(S) + \mu I - \frac{1}{\varepsilon}\beta(q)S\, I + \frac{1}{\varepsilon}\alpha I \\ &= -b + \mu S + \psi(q)S + \frac{\alpha\,[b - \mu S - \psi(q)S]}{\beta(q)S} - \frac{\alpha\beta'(q)\, q'}{\beta^2(q)}\ \ln(S) + \mu I\end{aligned} \tag{2.5}$$

From the definition of X we have

$$I = -S + (\alpha/\beta(q))\ln(S) - X$$

hence

$$\begin{aligned}\frac{d}{dt}X &= -b + \mu S + \psi(q)S + \frac{\alpha\,[b - \mu S - \psi(q)S]}{\beta(q)S} - \frac{\alpha\beta'(q)\, q'}{\beta^2(q)}\ \ln(S) \\ &\quad +\mu[-S + (\alpha/\beta(q))\ln(S) - X]\end{aligned} \tag{2.6}$$

Define

$$g(S,q) := \mu S + \psi(q)S + \frac{\alpha\,[b - \mu S - \psi(q)S]}{\beta(q)S} + \mu[-S + (\alpha/\beta(q))\ln(S)] \tag{2.7}$$

then

$$\frac{dX}{dt} = -b - \mu X + g(S,q) - \frac{\alpha\beta'(q)\, q'}{\beta^2(q)}\ \ln(S)$$

We thus obtain the transformed, slow system

$$\begin{aligned}\frac{dX}{dt} &= -b - \mu X + g(S,q) - \frac{\alpha\beta'(q)\, q'}{\beta^2(q)}\ \ln(S) \\ \varepsilon\frac{dS}{dt} &= \varepsilon[b - \mu S - \psi(q)S] - \beta(q)S\,[-S + (\alpha/\beta(q))\ln(S) - X] \\ \frac{dq}{dt} &= 1\end{aligned} \tag{2.8}$$

Since $\frac{dq}{dt} = 1$, we have,

$$\begin{aligned}\frac{dX}{dt} &= -b - \mu X + g(S,q) - \frac{\alpha\beta'(q)}{\beta^2(q)}\ \ln(S) \\ \varepsilon\frac{dS}{dt} &= \varepsilon[b - \mu S - \psi(q)S] - \beta(q)S\,[-S + (\alpha/\beta(q))\ln(S) - X] \\ \frac{dq}{dt} &= 1\end{aligned} \tag{2.9}$$

Using $\tau = t/\epsilon$, fast system reads

$$\begin{aligned} \frac{dX}{d\tau} &= \varepsilon[-b - \mu X + g(S,q) - \frac{\alpha\beta'(q)\,q'}{\beta^2(q)}\ \ln(S)] \\ \frac{dS}{d\tau} &= \varepsilon[b - \mu S - \psi(q)S] - \beta(q)S\,[-S + (\alpha/\beta(q))\ln(S) - X] \qquad (2.10) \\ \frac{dq}{d\tau} &= \varepsilon \end{aligned}$$

or

$$\begin{aligned} \frac{dX}{d\tau} &= \varepsilon[b - \mu X + g(S,q) - \frac{\alpha\beta'(q)\,\varepsilon}{\beta^2(q)}\ \ln(S)] \\ \frac{dS}{d\tau} &= \varepsilon[b - \mu S - \psi(q)S] - \beta(q)S\,[-S + (\alpha/\beta(q))\ln(S) - X] \qquad (2.11) \\ \frac{dq}{d\tau} &= \varepsilon \end{aligned}$$

Remark 2.2.1 Invariant Manifold $\{I = 0\}$

We know that in the original equation the plane $\{I = 0\}$ *is invariant. This is also true for the transformed system, as this is defined by a regular transformation. In the transformed system, this manifold, which we denote from now on by* M^**, is given by*

$$M^* = \{(S,I,q)\,|\,I = 0\} = \{(X,S,q)\,|\,-X - S + \alpha\,S/\beta(q) = 0\}.$$

The dynamics in the (S,I,q)*-system reads*

$$\begin{aligned} \frac{d}{dt}S &= b - \mu S - \psi(q)S \\ \frac{d}{dt}q &= 1 \end{aligned}$$

and $I = 0$*. As* I *resp.* X *is not involved in these equation, also in the transformed coordinates* (X,S,q) *the dynamics on this manifold is given by these very equations, where* X *is given by* $X = -S + \alpha\,S/\beta(q)$*.*

It is necessary to note, that neither the manifold nor the dynamics on the manifold depends on ε*. Thus, also in the limit of* $\varepsilon \to 0$ *(for the fast as well as for the slow system, see below), this manifold will be conserved.*

All feasible initial conditions $(S,I,q) \in \mathbb{R}_+ \times \mathbb{R}_+ \times [0,T]$ *correspond to points*

$$\{(X,S,q)\,|X \le -S + \alpha\,S/\beta(q) \in \mathbb{R}_+, q \in [0,T]\}.$$

2.2.3 Limiting fast and slow systems.

Fast system

Consider the fast system, taking ε to zero,

$$\begin{aligned} \frac{dX}{d\tau} &= 0 \\ \frac{dS}{d\tau} &= -\beta(q)S\left[-S + (\alpha/\beta(q))\ln(S) - X\right] \\ \frac{dq}{d\tau} &= 0 \end{aligned} \tag{2.12}$$

On the time scale of the fast process (the epidemics), the trajectory for S resembles that of a simple SIR-model without population dynamics. We determine the stationary states of S, if X and q are given and fixed. Either $S = 0$, or

$$X = -S + (\alpha/\beta(q))\ln(S).$$

As only $X \leq X^*$ is allowed for X, we find additional stationary points. Given q, the stationary points in the SX-plane are sketched in figure 2.1. The parameters used are $\beta(q) = 3$, $\alpha = 1$.The stability of the branches is indicted by the linestyle, where the dashed line indicates the unstable branch while the solid line indicates the stable branch. The arrows indicate the direction of the fast field.

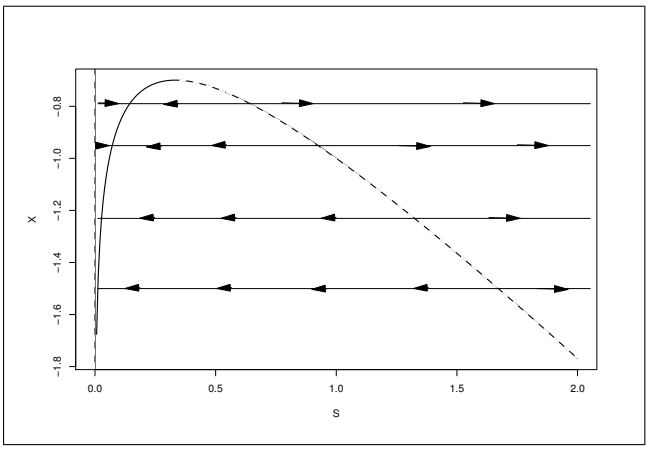

Figure 2.1: Solution branches on the SX-plane, including fast and slow manifolds.

Slow system

Consider the slow system, taking ε to zero,

$$\begin{aligned} \frac{dX}{dt} &= -b - \mu X + g(S,q) - \frac{\alpha\beta'(q)\,q'}{\beta^2(q)}\ \ln(S) \\ 0 &= \beta(q)S\left[-S + (\alpha/\beta(q))\ln(S) - X\right] \\ \frac{dq}{dt} &= 1. \end{aligned} \tag{2.13}$$

We are interested for the dynamics on the two unstable and the stable branch of stationary points.

Case 1: Unstable branch $S = 0$:

The function $g(S, q)$ becomes unbounded for $S \to 0$. Thus, this branch is not feasible. Neither can we compute for any solution $X(t)$ that defines the slow manifold.

Case 2: Unstable and stable branch $S > 0$:

On this branch, we have

$$X = -S + (\alpha/\beta(q)) \ln(S)$$

and hence

$$g(S,q) = \mu S + \psi(q)S + \frac{\alpha\,[b - \mu S - \psi(q)S]}{\beta(q)S} + \mu X \tag{2.14}$$

and thus

$$\begin{aligned} X' &= -b - \mu X + \mu S + \psi(q)S + \frac{\alpha\,[b - \mu S - \psi(q)S]}{\beta(q)S} + \mu X - \frac{\alpha\beta'(q)\,q'}{\beta^2(q)}\ \ln(S) \\ &= -b + \mu S + \psi(q)S + \frac{\alpha\,[b - \mu S - \psi(q)S]}{\beta(q)S} - \frac{\alpha\beta'(q)\,q'}{\beta^2(q)}\ \ln(S) \\ &= \frac{(-\beta(q)S + \alpha)[b - \mu S - \psi(q)S]}{\beta(q)S} - \frac{\alpha\beta'(q)\,q'}{\beta^2(q)}\ \ln(S) \qquad (2.15) \\ q' &= 1 \end{aligned}$$

One possibility is to express S in terms of X with help of the algebraic relation between X and S. As this is not explicitly possible, we use the other way: We express X' in terms of S and S' and derive an ODE for S' on this slow manifold.

$$X' = -S' - \frac{\alpha\beta'(q)q'}{\beta^2(q)} \ln(S) + \frac{\alpha}{\beta(q)S} S'$$

That is,

$$\begin{aligned} -S' - \frac{\alpha\beta'(q)q'}{\beta^2(q)} \ln(S) + \frac{\alpha}{\beta(q)S} S' &= \frac{(-\beta(q)S + \alpha)[b - \mu S - \psi(q)S]}{\beta(q)S} - \frac{\alpha\beta'(q)\,q'}{\beta^2(q)}\ \ln(S) \\ \Rightarrow \qquad S'\left(\frac{-\beta(q)S + \alpha}{\beta(q)S}\right) &= \frac{(-\beta(q)S + \alpha)[b - \mu S - \psi(q)S]}{\beta(q)S} \\ \Rightarrow \qquad S' &= b - \mu S - \psi(q)S \qquad (2.16) \end{aligned}$$

We thus have an explicit solution for $S(t)$ along the slow manifold, in the form,

$$S(t) = S(0) exp\left\{-\int_0^t \mu + \psi(q) dq\right\} + b \int_0^t exp\left\{-\int_\sigma^t \mu + \psi(q) dq\right\} d\sigma,$$

and from the relation

$$X = -S + (\alpha/\beta(q)) \ln(S) - I,$$

we substitute $S(t)$ and have an expression for $X(t)$.

2.2.4 Stability along slow manifold

From system (2.13), the slow manifold is given by

$$h(S) = -\beta(q)S\,[-S + (\alpha/\beta(q))\ln(S) - X].$$

In order to determine the stability along the slow manifold, we inspect the derivative of the slow manifold. The derivative reads

$$h'(S) = -\beta(q)[-S + (\alpha/\beta(q))\ln(S) - X] - \beta(q)S\,[-1 + (\alpha/\beta(q))/S]$$

and $h'(S) < 0 \Rightarrow$ stable branch. There are three solution branches for $h(S) = 0$. The first branch is $S = 0$. The graph $-S + (\alpha/\beta(q))\ln(S) = X$ has two solution branches for $0 < S < \alpha/\beta(q)$ herein referred to as the middle branch and $S > \alpha/\beta(q)$ which we refer to as the right hand outer branch.

(i) Since $h'(S) \to \infty$ for $S \to 0$, branch $S = 0$ is thus unstable.

(ii) Consider $-S + (\alpha/\beta(q))\ln(S) - X = 0$. If, $\beta(q) \neq 0$, and $S \neq 0$, then $h'(S) < 0$ if

$$[-1 + (\alpha/\beta(q))/S] > 1 \quad \Rightarrow \quad \beta(q)S/\alpha < 1,$$

from which we define R_0. This condition is satisfied in the middle branch only. The middle branch is thus stable, the right hand outer branch ($s > \alpha/\beta$)is unstable.

As we start in $\{(X, S)\,|\,X \leqq h(S)\}$, a perturbation close to the unstable branch will jump to the stable part via the fast field.

For ε positive but small, there is a time layer $\mathcal{O}(\varepsilon)$ and a trajectory of (2.11) that is ε-close to the lines $X =$constant, if we start close to the unstable branch of the invariant manifold M^*. This is possible for initial conditions $S(t_0) = S[\psi](t_0)$, $R(t_0) = b/\mu - S[\psi](t_0)$, and $I(t_0) > 0$, $I(t_0) = \mathcal{O}(\varepsilon)$ if and only if the curve $(S[\psi](q), I[\psi][q], q)$ enters the unstable part of M^*, i.e. iff $\|\beta(t)S[\psi](t)/\alpha\|_{L^\infty} > 1$.

We are led to the proposition.

Proposition 2.2.1 *For $\varepsilon > 0$ but sufficiently small, an epidemic is possible iff $\|\beta(t)S[\psi](t)/\alpha\|_{L^\infty} > 1$.*

2.3 Comparison: Floquet Theory vs Singular perturbation Theory

In figure(2.2), we illustrate that Orbital stability of the uninfected periodic solution may not play a role, but the instantaneous stability at a certain time point is the

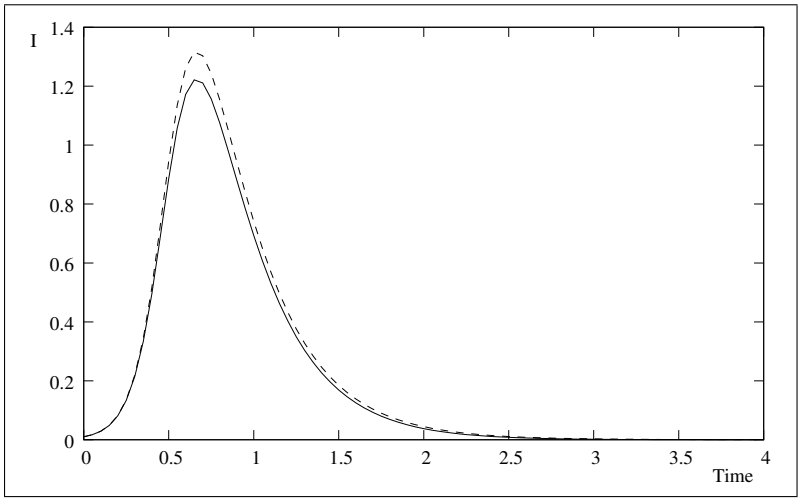

Figure 2.2: Epidemic scenario when Orbital stability holds, instantaneous stability fails in-between.

decisive criterion if or if not an epidemic may happen. The figure gives a simulation of an epidemic for time independent contact rate (dashed curve) and slowly varying, periodic contact rate (solid curve). Parameters used are $b = 0.05$, $\mu = 0.016666$, $\alpha = 1$, $\epsilon = 0.3$. For the constant case, $\beta = 1.4$ while for the varying case $\beta = 0.9 + \cos(t)0.5$. We define the instantaneous reproduction number as follows.

Definition 2.3.1 The instantaneous reproduction rate (in presence of vaccination) R_v is defined by

$$R_v(t) = \beta(t)S[\psi](t)/\alpha.$$

We call the uninfected periodic orbit instantaneously stable, if

$$\|R_v\|_{L^\infty} < 1.$$

Note, that R_v is not well defined for every time point, since β is an L^∞-function. However, $R_v \in L^\infty(0,T)$. We reach the following conclusion.

Proposition 2.3.1 *If the uninfected periodic orbit is instantaneously stable, it is also orbital stable. In general, it is not true that Orbital stability implies Instantaneous stability.*

On the first glance, the proposition seems to contradict itself. For ϵ small, but positive, we may look at the system under the point of view of Orbital stability

as well as under the point of view of instantaneous stability. There are situations, where orbital stability is given, while instantaneous stability is not. Thus, if we start close to the uninfected periodic orbit, we ultimately converge to this orbit though an epidemic outbreak is possible, as depicted in figure (2.2).

The reason for this seemingly contradiction is the fact, that orbital stability only implies that eventually the density of infectives tends to zero. In between, the number may (again and again, periodically) become quite large, s.t. an observer, who only consider the prevalence of disease locally has the impression that local outbreaks occur. However, these outbreaks become after each period T smaller and smaller and eventually fade out. The case of measles which has clearly shorter time scale relative to population dynamics would exhibit this scenario.

Let us consider the fate of a trajectory starting $\mathcal{O}(\varepsilon)$ close to the uninfected solution at time points, where this solution is instantaneously unstable. If the I component is sufficiently large, an instantaneous epidemic outbreak will happen. However, as time changes, we will reach a parameter region where $\beta(t)/\alpha(t) < 1$. At the latest here, the epidemic breaks down and the trajectory comes close to M^*. As the dynamics of the epidemic process is fast, we will find (for ε sufficiently small) that we are $e^{-1/\varepsilon}$-close to M^* if we enter next a parameter region where we have instantaneous instability. As we are very close to M^*, where $dI/dt = 0$, it takes a long time until the perturbation grows s.t. I is in the magnitude of $\mathcal{O}(\varepsilon)$, and another instantaneous epidemic occurs. Indeed, we will leave the instantaneous unstable part before this happens. This so-called slow passage effect yields the orbital stability of a trajectory $(S[\psi](t), 0, R[\psi](t))$ with instantaneous unstable parts.

Chapter 3

Optimal Vaccination Strategies

3.1 Definition of Optimal Control Problems

We assume as is often the case, that the budget for the control of the disease is restricted. During one period for vaccination we want to spend at most C_0 vaccination doses. The aim is to find a vaccination schedule that is as effective as possible. The idea is to get an impression what can be gained by optimization concepts, as an effective vaccination strategy. The efficiency may be measured in terms of orbital or instantaneous stability of disease free state.

Problem 3.1.1 *For $\psi \in L^\infty_+(0,T)$, find the vaccination schedule that minimizes*

$$\tilde{\mathcal{F}}[\psi] = \frac{1}{T}\int_0^T \beta(\tau)\, S[\psi](\tau)\, d\tau$$

under the constraint that the number of vaccination doses $\tilde{C}[\psi] = C_0$ is given, where $\tilde{C}[\psi]$ is defined as

$$\tilde{C}[\psi] := \int_0^T \psi(\tau)\, S[\psi](\tau)\, d\tau.$$

Problem 3.1.2 *For $\psi \in L^\infty_+(0,T)$, find the vaccination schedule that minimizes*

$$\|R_v[\psi]\|_{L^\infty} = \left\| \frac{\beta(t) S[\psi](t)}{\alpha} \right\|_{L^\infty}$$

under the constraint that the number of vaccination doses $\tilde{C}[\psi] = C_0$ is given. Again,

$$\tilde{C}[\psi] := \int_0^T \psi(\tau)\, S[\psi](\tau)\, d\tau.$$

Problem (3.1.1) can be formulated as a classical Maximum Principles problem. Considering all the details of the optimization problem(3.1.1), we define the following proposition.

Proposition 3.1.3 *Consider the population profiles $S[\psi](t)$, $I[\psi](t) \equiv 0$, $R[\psi](t)$. Define the set of optimal vaccination strategies,*

$$\Psi = \{\psi | 0 \le \psi \le \psi_{max};\ \psi \in L^\infty_+.\ \},$$

The optimal control problem is to minimize,

$$\mathcal{F}[\psi](t) = \int_0^T \beta(\tau) S[\psi](\tau) d\tau;$$

subject to

$$\dot{S}(t) = b - \mu S - \psi S; \quad S(0) = S(T)$$

$$\dot{C}(t) = \psi S; \quad C(0) = 0, C(T) = C$$

$$0 \leq \psi \leq \psi_{max}.$$

This problem is an optimal control problem with singular arc of infinite local order.

Proof:
Using the Minimization principle of Pontryagin, we define a Hamiltonian,

$$H(S, C, \lambda_1, \lambda_2, \psi) = \lambda_1(b - \mu S - \psi S) + \lambda_2 \psi S + \beta S,$$

which is affine in the control variable ψ, and can be written as,

$$H = H_0 + \psi H_1,$$

where $H_0 = \lambda_1(b - \mu S) + \beta S$, and $H_1 = (\lambda_2 - \lambda_1)S$.

This is a singular case of optimal control [Robbins 1967] with a singular arc when $\lambda_2 = \lambda_1$. The control variable ψ appears linearly in the Hamiltonian, thus its optimal value $\hat{\psi}$ will be piecewise constant function (A bang-bang control) [Neubert 2003, pp845] of the form;

$$\hat{\psi} = \begin{cases} 0, & \text{if} \quad \lambda_2 - \lambda_1 > 0; \\ \psi_{max}, & \text{if} \quad \lambda_2 - \lambda_1 < 0; \\ *, & \text{if} \quad \lambda_2 = \lambda_1. \end{cases}$$

One needs to know what happens when $H_1 = \lambda_2 - \lambda_1 = 0$, in a defined interval of time. To determine $\hat{\psi}$ in this interval, one needs to differentiate $H_1 = \lambda_2 - \lambda_1 = 0$, with respect to time t, until the derivative satisfies the condition

$$\frac{\partial}{\partial \psi} \left\{ \frac{d^{2p} H_1}{dt^{2p}} \right\} \neq 0,$$

where p defines the local order of the singular arc [Robbins 1967, pp849]. Taking the derivative of H_1 with respect to t, one fails to achieve the above condition for finite p. Hence, the (local) order of the singular arc in the optimization problem here is infinite.

□

Remark 3.1.1 *(i) It turns out that the control Problem (3.1.3) is a classical linear optimal control problem with a singular arc of infinite order. This problem has been already handled in literature [Baumann 1998]. However, the second problem of minimizing an essential supremum is not a straightforward classical optimization problem and may need reformulation to apply classical tools.*
(ii) To match the orbital optimization problem with the alternative instantaneous optimization problem, we choose to define a set of solutions that would guarantee existence of solutions for both optimal problems. We define the set as $\mathfrak{S}$.

3.2 Characterizing the set of Optimal Solutions

The worst strategies maximize $\tilde{\mathcal{F}}[\psi]$ and $\|R_v[\psi]\|_\infty$, respectively. We aim to prove existence for solutions. It turns out, that in general we do not find solutions for $\psi \in L^\infty_+$. We need to extend our search to a larger set.

The success of a vaccination program can be defined in terms of how many susceptible individuals are still in the population. An excellent vaccination program implies no susceptibles in the population. We study vaccination strategies in terms of a set of susceptible population profiles $\tilde{\mathfrak{S}} = \{S[\psi] \,|\, \psi \in L^\infty_+\} \subset L^\infty(0,T)$, whose closure we denote by $\mathfrak{S}$.

First we show the set of all population profiles originating from $\tilde{\mathfrak{S}}$ is bounded and compact. We also need to show that it is convex.

3.2.1 $\tilde{\mathfrak{S}}$ is bounded and compact

Proposition 3.2.1 *For any* $\psi \in L^\infty_+$ *we find uniform bounds for* $\|S[\psi]\|_{L^\infty}$ *and* $\tilde{C}[\psi]$, *i.e.,*

$$\|S[\psi]\|_\infty \leqq b/\mu$$

and

$$\tilde{C}[\psi] \leqq bT.$$

Proof:
The function $S[\psi](t)$ satisfies the differential inequality $\dot{S}[0](t) \leqq b - \mu S[0](t)$, under no vaccination and thus the solution of $\dot{\sigma} = b - \mu\sigma$ is a super-solution, where

$$S[0](t) := S[\psi](t)|_{\psi=0}.$$

This solution tends asymptotically to b/μ and $S[\psi](t)\|_{\psi\neq 0}$ stays periodic, bounded above by b/μ . Thus,

$$0 \leq S[\psi](t) \leq b/\mu \qquad \Rightarrow \qquad \|S[\psi]\|_\infty \leq b/\mu.$$

In order to estimate $\tilde{C}[\psi] = \int_0^T \psi(\tau)S[\psi](\tau)\,d\tau$, we integrate the differential equation for S, with respect to t over one period, ($I(t) \equiv 0$ assumed).

$$\begin{aligned} \frac{d}{dt}S[\psi](t) &= b - \mu S[\psi](t) - \psi(t)S[\psi](t) \\ \int_0^T \frac{d}{dt}S[\psi](t)dt &= \int_0^T b dt - \int_0^T \mu S[\psi](t)dt - \int_0^T \psi(t)S[\psi](t)dt \\ 0 &= bT - \mu \int_0^T S[\psi](t)dt - \tilde{C}[\psi] \end{aligned}$$

hence we find

$$\tilde{C}[\psi] = Tb - \mu \int_0^T S[\psi](t)\,dt \leq Tb$$

□

To investigate compactness, we use a remark [Evans 1998, pp274] that follows from sobolev embedding theorem in [Evans 1998, Theorem 1, pp272]. We start with both the remark and the theorem(without proof as this follows from the reference).

Theorem 3.2.2 *Assume* $\tilde{\mathfrak{S}} \subset \mathbb{R}^n$ *is open, bounded and Lipschitz domain, s.t.,* $\partial\tilde{\mathfrak{S}} \in C^1$. *Suppose* $1 \leq p \leq \infty$, *then*

$$W^{1,p}(\tilde{\mathfrak{S}}) \subset\subset L^q(\tilde{\mathfrak{S}})$$

for $1 \leq q < p^*$ *and* $p^* = \frac{np}{n-p}$.

Remark 3.2.1 *If* $p^* \to \infty$, *as* $p \to n$, *then*

(i)

$$W^{1,p}(\tilde{\mathfrak{S}}) \subset\subset L^p(\tilde{\mathfrak{S}})$$

for all $1 \leq p \leq \infty$.

(ii)

$$W_0^{1,p}(\tilde{\mathfrak{S}}) \subset\subset L^p(\tilde{\mathfrak{S}})$$

even if $\partial\tilde{\mathfrak{S}} \notin C^1$.

Using the above remark, we specify the following proposition.

Proposition 3.2.3 *The set* $\tilde{\mathfrak{S}} = \{S[\psi] \,|\, \psi \in L^\infty_+\} \subset L^\infty(0,T)$ *is a bounded subset in* $W^{1,1}(0,T)$ *and is precompact in* L^1.

Proof:
We already showed that $\|S[\psi]\|_\infty$ is uniformly bounded, and thus, we only consider the bounded interval $[0,T]$. $\|S[\psi]\|_1$ is also bounded in this interval. The norm of the derivative can be derived using the differential equation,

$$\begin{aligned}\int_0^T |\frac{d}{dt}S[\psi](t)|\,dt &\leq \int_0^T (b+\mu\, S[\psi](t))\,dt + \int_0^T \psi(t)\, S[\psi](t)\,dt \\ &= bT + \mu\|S[\psi]\|_1 + \tilde{C}[\psi].\end{aligned}$$

All the terms in the last line are uniformly bounded, i.e. $\tilde{\mathfrak{S}}$ is a bounded subset of $W^{1,1}(0,T)$. Since $W^{1,1}(0,T)$ is compact embedded in L^1, then $\tilde{\mathfrak{S}}$ is precompact in L^1 and its closure $\mathfrak{S}$ is a compact subset of L^1. □

Remark 3.2.2 *(1) Let* $\mathfrak{S}$ *be the closure of* $\tilde{\mathfrak{S}}$ *under the* L^1*-topology. Then,* $\mathfrak{S}$ *is a compact subset in* L^1. *Furthermore, since the* L^∞*-norm is bounded for all elements in* $\tilde{\mathfrak{S}}$, $\mathfrak{S}$ *is also a bounded subset of* L^∞.

(2) The cost functional $C : \tilde{\mathfrak{S}} \to \mathbb{R}$, $\Big(C(S[\psi]) := \tilde{C}[\psi]\Big)$ *has an unique extension* $C : \mathfrak{S} \to \mathbb{R}$, *since this functional can be represented as a function of* $\|S[\psi]\|_1$. *Since* C *is a bounded linear functional, and by Hahn-Banach theorem,* C *is continuous on* $\mathfrak{S}$.

(3) The vaccination effect functional $\mathcal{F} : \tilde{\mathfrak{S}} \to \mathbb{R}$, $\Big(\mathcal{F}(S[\psi]) := \tilde{\mathcal{F}}[\psi]\Big)$ *has an unique extension* $\mathcal{F} : \mathfrak{S} \to \mathbb{R}$, *since this functional depends on* $S[\psi]$ *only via*

$$\int_0^T \beta(\tau) S[\psi](\tau)\,d\tau$$

which is a continuous, linear functional w.r.t. the L^1*-topology.*

(4) We denote with C_∞ *the maximal possible costs. Since* $\mathfrak{S}$ *is compact and* C *continuous, the functional* C *assumes its maximum and the maximum* (C_∞) *is well defined.*

Theorem 3.2.4 *If $0 \leq C_0 \leq C_\infty$, the problem 3.1.1 has a solution in $\mathfrak{S}$, where C_0 denotes the number of vaccination doses, and C_∞ the maximum number of doses available for the vaccination program.*

Proof:
Since $0 \leq C_0 \leq C_\infty$, and since C is continuous, the set $\{S \in \mathfrak{S} \,|\, C(S) = C_0\}$ is non-empty and compact. Thus, the continuous functional $\mathcal{F}$ assumes its minimum within this set. □

Theorem 3.2.5 *We assume $\beta(t) \geq \underline{\beta} > 0$. If $0 \leq C_0 \leq C_\infty$, the problem 4.2.1 has a solution in $\mathfrak{S}$.*

Proof:
We aim to minimize

$$||R_v||_{L^\infty} = \text{supess}\{R_v\}.$$

It is possible to control $S(t)$ through vaccination, in order to minimize supess$\{R_v\}$.

Let m define the optimal value for αR_v under the usual cost constraint, where,

$$m = \inf_{S \in \mathfrak{S}} \; \underset{t \in (0,T)}{\text{supess}}\{\beta(t)S(t)\}.$$

The problem has a solution if we could find a profile $\beta(t)S(t)$ that corresponds to m.

Let $S_i \in \mathfrak{S}$ s.t. the values $m_i = \text{supess}_{t\in(0,T)}\, \beta(t)S_i(t)$ converge against m. Since $\mathfrak{S}$ is w.r.t. the L^1-topology compact, we find a subsequence of the S_i that converge in the L^1-norm to $\overline{S} \in \mathfrak{S}$.

We show that

$$\underset{t\in(0,T)}{\text{supess}}\, \beta(t)\overline{S}(t) \leq m. \tag{3.1}$$

If this is not the case, then there is an $\epsilon > 0$, s.t. $\text{supess}_{t\in(0,T)}\, \beta(t)\overline{S}(t) = m+\epsilon > m$. Hence, there is an measurable set $J \subset (0,T)$

$$J = \{t \in (0,T) \,|\, \beta(t)\overline{S}(t) > m + \epsilon/2\}$$

with measure larger than zero. For $i > n_0$, for some arbitrary $n_0 \in \mathbb{R}_+$ large enough, we have $m_i < m + \epsilon/2$. Hence,

$$\begin{aligned} \|\overline{S} - S_i\|_{L^1} &\geq \int_J |\overline{S} - S_i|\, dt = \int_J \overline{S} - S_i\, dt = \int_J \frac{1}{\beta(t)}(\beta(t)\overline{S}(t) - \beta(t)S_i(t))\, dt \\ &\geq \epsilon/2 \int_J \frac{1}{\beta(t)}\, dt \geq \frac{\epsilon\,|J|}{2\|\beta\|_\infty} > 0 \end{aligned}$$

in contradiction to the fact that the S_i tend to $\overline{S}$ in the L^1-norm. Thus, (3.1) holds and $\overline{S}$ is a solution of the problem. □

3.2.2 Convexity of $\mathfrak{S}$

We show that $\mathfrak{S}$ is convex and compact. According to the theorem of Krein and Milman, the extremal points structure the complete set. Consequently, we investigate this special set. The inside structure we obtain here is the centerpiece for later considerations about the structure of the optimal points in $\mathfrak{S}$.

Proposition 3.2.6 *The set $\tilde{\mathfrak{S}}$ is convex and so is its closure $\mathfrak{S}$.*

Proof: Let $S_\tau$and $S_i = S[\psi_i];\ i = 1, 2;\ \psi_i \in L^\infty_+$ be population profiles in $\mathfrak{S}$. We find an $\epsilon > 0$ with $S_i > \epsilon > 0$, i.e. also S_τ is bounded away from zero.

If $\mathfrak{S}$ is convex, then $S_\tau \in \mathfrak{S}$ can be expressed as a convex combination of $S_i \in \mathfrak{S} : i = 1, 2$.

$$S_\tau(t) = \tau S_1(t) + (1-\tau)S_2(t).$$

We check that $S_\tau \in \mathfrak{S}$, that is, it satisfies the original differential equation for $S(t)$ for some vaccination rate $\psi_\tau(t)$.

$$\begin{aligned}
\frac{d}{dt}S_\tau(t) &= \tau\frac{d}{dt}S_1(t) + (1-\tau)\frac{d}{dt}S_2(t) \\
&= \tau\left(b - \mu S_1(t) - \psi(t)S_1(t)\right) + (1-\tau)\left(b - \mu S_2(t) - \psi(t)S_2(t)\right) \\
&= b - \mu\left(\tau S_1(t) + (1-\tau)S_2(t)\right) - \tau\psi_1(t)S_1(t) - (1-\tau)\psi_2(t)S_2(t) \\
&= b - \mu S_\tau(t) - \psi_\tau S_\tau(t). \qquad (3.2)
\end{aligned}$$

where

$$\psi_\tau(t) = \frac{\tau\psi_1(t)S_1(t) + (1-\tau)\psi_2(t)S_2(t)}{S_\tau(t)} \qquad (3.3)$$

Since $\psi_i(t)$ and $S_i[\psi](t)$ are periodic functions, $\psi_\tau(t)$ linearly depends on periodic functions, hence it is periodic, and so is the solution $S_\tau(t)$.

We also show that $\psi_\tau \in L^\infty_+$.

$$\begin{aligned}
||\psi_\tau(t)||_{L^\infty} &= \left|\left|\frac{\tau\psi_1(t)S_1(t) + (1-\tau)\psi_2(t)S_2(t)}{S_\tau(t)}\right|\right|_{L^\infty} \\
&= \left|\left|\psi_1(t)\left(\frac{\tau S_1(t)}{S_\tau(t)}\right) + \psi_2(t)\left(\frac{(1-\tau)S_2(t)}{S_\tau(t)}\right)\right|\right|_{L^\infty} \\
&\leq ||\psi_1(t)||_{L^\infty} + ||\psi_2(t)||_{L^\infty} < \infty
\end{aligned}$$

Hence $S_\tau(t) \in \mathfrak{S}$. Since $\mathfrak{S}$ is the closure of a convex set, it is also convex.

Hence, $\mathfrak{S}$ is a convex and compact set. By the theorem of Krein-Milman [Yosida 1980, pp362], it can be characterized completely by the set of its extremal points $\Sigma(\mathfrak{S})$. □

3.2.3 Definition of Vaccination Support for $S[\psi](t) \in \mathfrak{S}$

In order to obtain a better inside structure of the set $\Sigma(\mathfrak{S})$ of extremal points, we define the vaccination-support of a population profile $S \in \mathfrak{S}$, i.e. we derive a criterion for these time points, where ψ does not vanish. If the rate ψ is in L^∞_+, we may use the differential equation, multiply this equation with a non-negative test function $\phi \in C^\infty_c(A,B)$ and integrate between arbitrary points (A,B) that is,

$$\int_A^B \phi(t)\frac{dS[\psi](t)}{dt}dt = b\int_A^B \phi(t)dt - \mu\int_A^B \phi(t)S[\psi](t)dt - \int_A^B \phi(t)\psi(t)S[\psi](t)dt.$$

We integrate the LHS by parts and note that $S[.](A) = S[.](B) = 0$ since A and B are boundary points of the function support. We then obtain

$$\int_A^B \phi(t)\psi(t)S[\psi](t)\,dt = \int_A^B (\phi'(t) - \mu\phi(t))\,S[\psi](t)\,dt + b\int_A^B \phi(t)\,dt =: H(S[\psi],\phi;A,B).$$

Then, H is (for A, B, ϕ given) a continuous functional on $\mathfrak{S}$. For a given $S \in \tilde{\mathfrak{S}}$ and given A, B, we find that H vanishes for all $\phi \in C^\infty_c(A,B)$ if and only if $\psi|_{(A,B)} = 0$ in $L^\infty : \psi|_{(A,B)} \in L^\infty$. We are led to the following definition.

Definition 3.2.1 *Let $S \in \mathfrak{S}$ and $\theta \subset [0,T)$ the set of points x so that $A < x < B$ exists, s.t.*

$$H(s,\phi;A,B) = 0 \qquad \forall \phi \in C^\infty_c(A,B), \quad \phi \geq 0.$$

The vaccination-support $supp_v(S)$ of the population profile S is defined as $[0,T)\setminus\theta$.

Remark 3.2.3 **(1)** If $\psi \in L^\infty_+$, this function can be interpreted as a generalized function, and thus $supp(\psi)$ is well defined. It is straight forward to see that $supp(\psi) = supp_v(S[\psi])$ through $H(s,\phi;A,B)$.

(2) Since $H(S,\phi;A,B)$ is non-negative for $\phi \geq 0$ and $S \in \tilde{\mathfrak{S}}$, this is also true for $S \in \mathfrak{S}$.

3.2.4 Continuity of $S[\psi](t)$ about discrete vaccination points.

In the next section, we will define candidate optimal vaccination strategies that vaccinate at discrete time points. We demonstrate that the functional $S[\psi](t)$ has well defined left hand and right hand limits at vaccination points, t_0. Consider following Lemmata:

Lemma 3.2.7 *Let* $t_0 \in [0,T]$ *be fixed and* $\varepsilon > 0$. *Define two functions,*

$$A_\varepsilon = ess\,sup\, S[\psi](t) | t \in [t_0, t_0+\varepsilon],$$

$$B_\varepsilon = ess\,inf\, S[\psi](t) | t \in [t_0, t_0+\varepsilon],$$

Then, for $0 < \varepsilon' < \varepsilon$

1. $A_\varepsilon \geq A_{\varepsilon'}$,

2. $B_\varepsilon \leq B_{\varepsilon'}$.

Proof:
The set,

$$\{t \in [t_0, t_0+\varepsilon'] | S[\psi](t) > A\} \subseteq \{t \in [t_0, t_0+\varepsilon] | S[\psi](t) > A\}$$

and

$$\mu\{t \in [t_0, t_0+\varepsilon'] | S[\psi](t) > A\} \leq \mu\{t \in [t_0, t_0+\varepsilon] | S[\psi](t) > A\}$$

$$\mu\{t \in [t_0, t_0+\varepsilon] | S[\psi](t) > A\} = 0 \Rightarrow \mu\{t \in [t_0, t_0+\varepsilon'] | S[\psi](t) > A\} = 0$$

$$\Rightarrow A | \mu\{t \in [t_0, t_0+\varepsilon] | S[\psi](t) > A\} = 0 \geq A | \mu\{t \in [t_0, t_0+\varepsilon'] | S[\psi](t) > A\} = 0$$

$$\Rightarrow A_\varepsilon \geq A_{\varepsilon'},$$

where $\mu\{.\}$ defines the measure of a set. Similarly,

$$B_\varepsilon \leq B_{\varepsilon'}.$$

Corollary 3.2.8 *It follows that,*

$$A_\varepsilon \geq A_{\varepsilon'} \geq B_{\varepsilon'} \geq B_\varepsilon$$

for arbitrarily small positive real values $\varepsilon' \leq \varepsilon$

Lemma 3.2.9 *The* $\lim_{\varepsilon \to 0} |A_\varepsilon - B_\varepsilon|$ *exists and is equal to zero.*

Proof
We know that $A_\varepsilon \geq A_{\varepsilon'} \geq B_{\varepsilon'} \geq B_\varepsilon$.
Thus $|A_\varepsilon - B_\varepsilon| \geq |A_{\varepsilon'} - B_{\varepsilon'}|$ for $\varepsilon' \leq \varepsilon$.
Define $\nabla(\varepsilon) := |A_\varepsilon - B_\varepsilon|$, monotonously increasing in ε.
Define $\delta = \liminf_{\varepsilon \to 0}\{\nabla(\varepsilon)\}$. We show that the limit exists for $\delta = 0$. Suppose $\delta > 0$. We know that for ε decreasing, A_ε is monotonously decreasing

and bounded function, B_ε is monotonously increasing and bounded function, hence the following limits exist:

$$lim_{\varepsilon\to 0}A_\varepsilon = A_0$$

and

$$lim_{\varepsilon\to 0}B_\varepsilon = B_0.$$

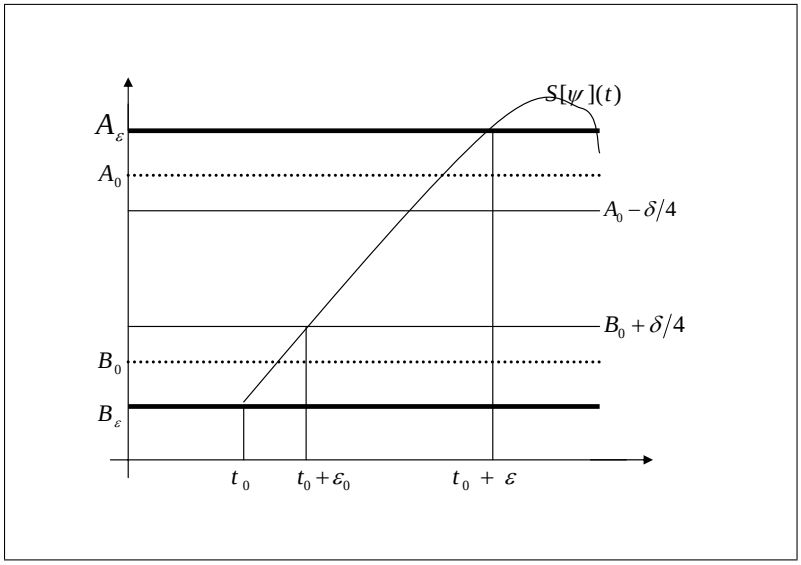

Figure 3.1: Limits of $S[\psi](t)$ w.r.t a vaccination point t_0.

Suppose $\delta > 0$. We have $S[\psi](t)$ monotonically increasing in $(t_0, t_0+\varepsilon)$. Since $B_0 > B_\varepsilon \,\forall\, t \in (t_0, t_0+\varepsilon), \exists\ \varepsilon_0 \in (0,\varepsilon)$ s.t. $S[\psi](t) \le B_0 + \delta/4$ in the interval $(t_0, t_0+\varepsilon_0)$, thus $S[\psi](t) \le A_0 - \delta/4$ in $(t_0, t_0+\varepsilon_0)$. Hence

$$\mu\{t \in [t_0, t_0+\varepsilon_0] | S[\psi](t) \ge A_0 - \delta/4\} = 0.$$

$$\Rightarrow A_{\tilde\varepsilon} \le A_0 - \delta/4 \ \ \forall\ \ \tilde\varepsilon \in (0, \varepsilon_0),$$

s.t. as $\tilde\varepsilon \to 0$, $A_0 \le A_0 - \delta/4$.
$\Rightarrow 0 \le -\delta/4$. $\Rightarrow \delta \le 0$, a contradiction. □

Lemma 3.2.10 $\lim_{\varepsilon\to 0-} |A_\varepsilon - B_\varepsilon|$ *exists and is equal to zero.*

Proof:
The proof parallels that of lemma (3.2.9), reversing time and changing the roles of the supremum and infimum. □

Proposition 3.2.11 *Consider any vaccination point* $t_0 \in [0,T]$. *Then the limits,* $lim_{t\to t_0+}S[\psi](t)$ *and* $lim_{t\to t_0-}S[\psi](t)$ *are well defined.*

Proof: It follows from lemma (3.2.7) to lemma (3.2.10) that the limit is well defined. □

Since $\mathfrak{S}$ is compact and convex, we characterize it by its set of extremal points.

3.2.5 The set of extremal points, $\Sigma(\mathfrak{S})$.

Proposition 3.2.12 *Let $M \subset [0,T)$ be a closed nonempty set, $M \subseteq \{supp_v(S)\}$. Define the map $\Delta : [0,T) \setminus M \to \mathbb{R}_+$ by*

$$\Delta(t) = \begin{cases} t - \max\{x \in M \,|\, x < t\} & \text{if} \quad \{x \in M \,|\, x < t\} \neq \emptyset \\ t + (T - \max\{x \in M\}) & \text{if} \quad \{x \in M \,|\, x < t\} = \emptyset \end{cases}.$$

Define the function $S^* \in L^\infty_+(0,T)$ by

$$S^*(t) = \begin{cases} 0 & ; t \in M \\ b/\mu(1 - e^{-\mu\Delta(t)}) & ; else \end{cases},$$

then $S^* \in \Sigma(\mathfrak{S})$.

Remark 3.2.4 Every compact subset of the space $\mathbb{R}^n$ is Lebesque measurable [Amann 2001, Theorem 5.1, pp41]. For M compact subset in $[0,T)$, then M is Lebesque measurable and for all time points $x \in M$, $S^* \in L^1$

Proof:

Step I: We show that $S^* \in \mathfrak{S}$.

We need to take care about the cyclic structure of $[0,T)$. Let $\hat{M} = \{x \in \mathbb{R} \,|\, \exists i \in \mathbb{Z} : x + i\,T \in M\}$.

Now we mollify M:

For $n \in \mathbb{N}$, we define the sequence of sets

$$M_n = \{t \in [0,T) \,|\, \min_{m \in \hat{M}}(|t - m|) \leq 1/n; \quad m \equiv x + iT; \quad i \in \mathbb{Z}\},$$

the rates $\psi_n = n^2\,\chi_{M_n}(t) \in L^\infty_+(0,T)$, periodically continued on $\mathbb{R}$ and denote $S_n = S[\psi_n]$.

Since $M_n \supset M$, then, $supp_v(S_n) \supset M$ and

$$\cap_{n \in \mathbb{N}} supp_v(S_n) = M.$$

Let $x \in M$.We show that there exists a sequence $S_n(x) \to 0$, $\forall\, x \in M$.

Considering the lower interval, $[x-1/n, x] \subset M_n$. Since $\psi_n \in L^\infty$, the function $S_n \in C^0$. Thus we are able to inspect the functions S_n at the point x.

$$\begin{aligned} 0 \le S_n(x) &= S_n(x-1/n)e^{-\int_{x-1/n}^{x}(\mu+\psi_n(t))\,dt} + b\int_{x-1/n}^{x} exp\left(-\int_t^x (\mu+\psi_n(t))\,dt\right)\,dt \\ &\le \frac{b}{\mu}e^{-\int_{x-1/n}^{x} n^2\,dt} + b\int_{x-1/n}^{x} exp\left(-\int_t^x n^2\,dt\right)\,dt \\ &= \frac{b}{\mu}e^{-n} + \frac{b}{n^2}(1-e^{-n}) \to 0 \quad \text{for } n\to\infty. \end{aligned}$$

We use the fact that $\lim_{t\to\infty} S[\psi](t) = b/\mu$ and that $S[\psi](t)$ has b/μ as its upper bound. Hence, we find that the convergence $S_n|_{M_n} \to S^* = 0|_M$ is pointwise and uniformly, $\sup_{x\in M}|S_n(x) - S^*(x)| \to 0$.

Now assume that $x \notin M$.

We show that there exists a sequence $S_n(x) \to S^*(x) = b/\mu(1-e^{-\mu\Delta(t)}),\ \forall\, x \notin M$.

Without restriction we assume that n is large enough to ensure $x \notin M_n$. Let $A = \max\{y \in M \,|\, y < x\}$. Then, $A_n = A + 1/n \in \partial M_n$, and $(A_n, x] \subset \mathbb{R}\setminus M_n$. Therefore, the functions S_n satisfy $S_n' = b - \mu S_n$ in $(A_n, x]$, in other words, $(A_n, x] \not\subset supp_v(S_n)$. We thus have $S_n(t) = b/\mu(1-e^{-\mu(t-A_n)})$ and $S^*(t) = b/\mu(1-e^{-\mu(t-A)})$ in $(A_n, x]$.

$$\begin{aligned} |S_n(x) - S^*(x)| &= S_n(x) - S^*(x) \\ &= \frac{b}{\mu}\exp\{-\mu t\}(\exp\{-\mu A\} - \exp\{-\mu A_n\}) \\ &\le \frac{b}{\mu}\exp\{-\mu t\}(\exp\{-\mu A\} - \exp\{-\mu(A+1/n)\}) \\ &= \frac{b}{\mu}\exp\{-\mu t\}\exp\{-\mu A\}(1-\exp\{-\mu/n\}) \\ &= 0; \quad n\to\infty \end{aligned}$$

A similar argument like above shows us that $S_n(A_n) \to 0$ for $n\to\infty$, uniformly for all right boundaries of connected components in M_n. Thus,

$$\lim_{n\to\infty}\sup_{x\in[0,T)}|S_n(x) - S^*(x)| \to 0$$

and hence also $\|S_n - S^*\|_{L^1} \to 0$.

Step II: We show that $s^* \in \Sigma(\mathfrak{S})$.

Consider a time point $x \in M$:

We know that both $\lim_{t\to x+} S^*(t)$and $\lim_{x\to x+} S_i(t)$ are defined for time points $x \in M$ where M is defined as a subset of the vaccination support of the susceptible population profile, as shown in proposition (3.2.11).

By definition,

$$\lim_{t\to x+} S^*(t) = 0,$$

and by convexity, we have

$$S^*(t) = \tau S_1(t) + (1-\tau)S_2(t);$$

From this expression and since

$$S_i(t) \geq 0; \quad \tau \in (0,1),$$

it is not possible that convexity holds unless

$$\lim_{t \to x+} S_i(t) = 0, \quad i = 1, 2.$$

(no sum of two non-negative numbers adds up to zero, unless the two numbers are both zero). This applies in an open interval $(A, B) \subseteq M$ s.t.

$$S^*(t)|_{(A,B)} = S_1(t)|_{(A,B)} = S_2(t)|_{(A,B)} = 0.$$

Thus for $x \in M$, S^* cannot be represented as a sum of two or more extremal points.

Now consider a time point $x \notin M$:

Choose an interval $(A, B) \notin M$ but such that $A \in \partial M$. (A, B) is then outside the vaccination support (hence $\psi = 0$)and thus $\frac{d}{dt}S_i = b - \mu S; \quad S_i(A) = 0$ and $\frac{d}{dt}S^* = b - \mu S^*; \quad S^*(A) = 0$.

Then, in $(A, B) \in \mathbb{R} \setminus M$,

$$S^*(t) = S_i(t) = \frac{b}{\mu}(1 - \exp\{-\mu \Delta t\}).$$

Thus S^* cannot again be represented as a sum of extremal points in $\mathfrak{S}$.

We conclude that S^* is itself an extremal point. □

Remark 3.2.5 *We know that $\mathfrak{S}$ is compact and bounded. Since $\Sigma(\mathfrak{S}) \subset \mathfrak{S}$, the closure of $\Sigma(\mathfrak{S})$ is compact. Thus, there is a sequence S_n^* that approximates $S^*[\psi] \in M$. Furthermore, any function in L^1 can be approximated by a sequence of step functions.*

Chapter 4

Candidate Optimal Vaccination Strategies

4.1 Candidate Optimal Strategies with respect to orbital stability

To get an inside look into the set of solutions, we offer a discrete (approximation) version of problem (3.1.1) and thus, redefine vaccination rate in terms of vaccination doses $u(t)$ instead of the vaccination rate $\psi(t)$.

Problem 4.1.1 *Consider $S[u](t)$, $R[u](t)$ as solutions to*

$$R[u](t) = b/\mu - S[u](t)$$

$$\frac{d}{dt}S[u](t) = b - \mu S[u](t) - \psi S[u](t).$$

Let

$$\mathfrak{U} = \{u | u = \sum_{i=1}^{n} d_i \delta(t - t_i) : \quad i = 1, 2, ..., n\}$$

Let furthermore, $C[u](t) = \int_0^T u(t)dt$ represent the cost of vaccination.

We aim to minimize,

$$\mathcal{F}[u](t) = \int_0^T \beta(\tau) S[u](\tau) d\tau$$

subject to,

$$S[u](t) \geq 0 \quad \forall \quad t \in [0, T]$$

$$R[u](t) = b/\mu - S[u](t)$$

and the costs $C[u](t)$ given.

First we show that we may go back and forth between representations of vaccination strategies by $\psi(t)$ and $u(t)$.

Lemma 4.1.2 *Consider on the one hand $\psi \in \Psi$ together with $S[\psi] \geq 0$ and on the other hand $\{u \in \mathfrak{U} | u = \sum_{i=1}^{n} d_i \delta(t-t_i)\}$ together with $S[u](t) \geq 0$. Given $\psi(t) \in \Psi_n$, we find $u \in \mathfrak{U}$ s.t. the periodic solution of $S[u] = S[\psi]$ is true. Conversely, if we have a non-negative solution $S[u]$ for $u = \sum_{i=1}^{n} d_i \delta(t-t_i)$, there is a strategy $\psi \in \Psi_n$ s.t. $S[u] = S[\psi]$ is true.*

Proof:

(a) Construction of u from ψ:

As $S[\psi]$ is $C^{\infty}([0,T] \setminus \{t_1, .., t_n\})$, the jump parameters $d_i = S[\psi](t_i-) - S[\psi](t_i+)$ are well defined. Furthermore, $d_i \geq 0$ due to the monotonicity of $S[\psi]$ between the vaccination points.

$$\frac{d}{dt} S[\psi](t) = b - \mu S[\psi] \quad t \neq t_i$$

On the other hand, for all time points $t = t_i$, we have equality since

$$S[\psi](t_i-) - S[\psi](t_i+) = d_i$$

and

$$S[u](t_i-) - S[u](t_i+) = d_i.$$

For all $t \neq t_i$,

$$\frac{d}{dt}(S[\psi](t) - S[u](t)) = -\mu(S[\psi](t) - S[u](t)).$$

and the solution converges to zero by uniqueness of solutions and we also have equality.

(b) Construction of ψ from u:

Define

$$d_i = S[u](t_i-) - S[u](t_i+).$$

Take the interval $(0, t_i)$, as $(t_i, t_i + 1)$ are assumed equal for all $i = 1, 2, ..., n$. The solution

$$\begin{aligned} S[\psi](t) &= S(0)exp\{-\int_0^t \mu + \psi(\tau)d\tau\} + b\int_0^t exp\{-\int_\sigma^t \mu + \psi(\tau)d\tau\}d\sigma \\ &= S(0)exp\{-t\mu - c_i\} + b\int_0^t exp\{-(t-\sigma)\mu - c_i\}d\sigma \\ &= S(0)exp\{-c_i\}\left\{exp\{-t\mu\} + b\int_0^t exp\{-(t-\sigma)\mu\}d\sigma\right\} \end{aligned}$$

$$S[\psi](t_i+) = e^{-c_i} S[\psi](t_i-). \tag{4.1}$$

Since d_i is the weight of the jump at t_i, we denote it by

$$d_i = S[\psi](t_i-) - e^{-c_i} S[\psi](t_i-) = S[\psi](t_i-) - S[\psi](t_i+)$$

Of course,

$$d_i = S[u](t_i-) - S[u](t_i+).$$

So,

$$S[\psi](t_i) = S[u](t_i).$$

Note that

$$e^{-c_i} = 1 - \frac{d_i}{S[\psi](t_i-)}.$$

Take $d_i = S[\psi](t_i-)$, indicating that everyone is vaccinated at t_i, then $c_i = \infty$.

In the alternative, consider

$$\psi(t) = \frac{1}{S[\psi]} \left\{ b - \mu S[\psi] - \frac{dS[\psi]}{dt} \right\}$$

If there exists a time point $t_i \in [0,T]$ s.t. $S[\psi](t_i+) = 0$, then $\psi(t_i)$ is large and

$$\begin{aligned} c_i = \int_{t_i-\epsilon}^{t_i+\epsilon} \psi(\tau)\, d\tau &= \int_{t_i-\epsilon}^{t_i+\epsilon} \frac{1}{S[\psi]} \{b - \mu S[\psi]\} d\tau - \int_{t_i-\epsilon}^{t_i+\epsilon} \left\{ \frac{1}{S[\psi]} \frac{dS[\psi]}{dt} \right\} d\tau, \\ &\simeq 0 - \{ln(S[\psi](t_i+)) - ln(S[\psi](t_i-))\} \\ &\simeq ln\left(\frac{S[\psi](t_i-)}{S[\psi](t_i+)} \right) \end{aligned}$$

As $S[\psi](t)$ is bounded,

$$\lim_{\varepsilon \to 0} \int_{t_i-\varepsilon}^{t_i+\varepsilon} b - \mu S(t)\, dt = 0.$$

This takes us back to (4.1) and we proceed similarly as above. □

We offer some clarification on $u(t)$. We consider $\psi S[\psi]$ as a given inhomogeneity, $u = \psi S[\psi]$. We also note that $u(t_i)$ is interpreted as the number of vaccination dosages used at time point t_i such that

$$u(t) = 0 \quad \forall \quad t \notin \{t_1, t_2, ..., t_n\}.$$

Furthermore, S is smooth outside the vaccination support and we consider the integral

$$\int_{t_i-\varepsilon}^{t_i+\varepsilon} \frac{d}{dt} S(t)\, dt = \int_{t_i-\varepsilon}^{t_i+\varepsilon} b - \mu S(t)\, dt + \int_{t_i-\varepsilon}^{t_i+\varepsilon} u(t) dt$$

As before, we assume

$$\int_{t_i-\varepsilon}^{t_i+\varepsilon} b - \mu S(t)\, dt = 0,$$

follows if we are close to vaccination time and the susceptible population approaches its maximum; $S[\psi] \approx b/\mu$. Thus $\varepsilon \to 0$,

$$S(t_i-) - S(t_i+) \quad = \quad \int_{t_i-\varepsilon}^{t_i+\varepsilon} u(t)dt$$

i.e., $u(t_i)$ reflects the number of vaccinations that take place at t_i. We may denote the total number of vaccination doses used as

$$u = \sum_{i=1}^{n} d_i \delta_{t_i}(t)$$

where $d_i = S(t_i-) - S(t_i+)$ are the number of vaccinated persons.

Lemma 4.1.3 *Let $u = \sum_{i=1}^{n} d_i \delta_{t_i}$ correspond to a strategy ψ, then the costs are $C[\psi] = \sum_{i=1}^{n} d_i$.*

Proof:

$$\begin{aligned} C[\psi] &= \int_0^T \psi(t) S[\psi](t)\, dt \\ &= -\int_0^T \frac{dS[\psi](t)}{dt}\, dt + bT - \mu \int_0^T S[\psi](t)\, dt \\ &= bT - \mu \int_0^T s[u](t)\, dt \end{aligned} \tag{4.2}$$

due to periodicity,

$$\int_0^T \frac{dS[\psi](t)}{dt}\, dt = 0. \tag{4.3}$$

Since

$$\frac{dS[u](t)}{dt} = b - \mu S[u](t) \; - \sum_{i=1}^{n} d_i \delta(t - t_i),$$

then,

$$\int_0^T \frac{dS[u](t)}{dt} dt = bT - \mu \int_0^T S[u](t)\, dt - \sum_{i=1}^{n} d_i$$

$$0 = C[\psi] - \sum_{i=1}^{n} d_i,$$

follows from (4.2) and (4.3) and thus,

$$C[\psi] = \sum_{i=1}^{n} d_i.$$

□

We intend to offer a reformulation of the functional $F : \Psi_n \to \mathbb{R}$. We show that the functional $F[u]$ can be written as some constant minus the sum of the effects of all vaccinations doses in a given vaccination strategy.

Proposition 4.1.4 *Define a function*

$$G(t) = \int_{\tau}^{\infty} \beta(t) e^{-\mu(t-\tau)}\, dt.$$

Then, the functional $F[.]$ for the problem (4.1.1) reads

$$F[u](t) := \int_0^T \beta(t) b/\mu\, dt - \int_0^T u(t) G(t)\, dt.$$

Proof: First, consider $\psi \in L^{\infty}_{+}$, and replace in the system (1.1) the vaccinateds $R(t)$ by a class of vaccinateds structured by time since vaccination.

Consider σ denotes $S[\psi]$ while $\rho(t,a)$ denotes an age structured immune group, $R[\psi](t,a)$, from which we obtain the marginal distribution $R[\psi](t)$.

$$\begin{aligned} \partial_t \sigma &= b - \mu\sigma - \psi\sigma \\ (\partial_t + \partial_a)\rho(t,a) &= -\mu\rho(t,a), \qquad \rho(t,0) = \psi(t)\sigma(t) = u(t) \\ \sigma(0) &= \sigma(T), \quad \rho(0,a) = \rho(T,a) \end{aligned}$$

As ψ is periodic, we may replace the periodic boundary conditions by the requirement that σ and ρ are globally bounded functions for $t \in \mathbb{R}$ and $a \in \mathbb{R}_+$. Then,

$$\frac{d}{dt}\left(\sigma(t) + \int_0^{\infty} \rho(t,a)\, da\right) = b - \mu\left(\sigma(t) + \int_0^{\infty} \rho(t,a)\, da\right).$$

Thus, for $t \to \infty$, we have

$$\left(\sigma(t) + \int_0^{\infty} \rho(t,a)\, da\right) \to b/\mu$$

and since we select the globally bounded, i.e. periodic, solution of the partial differential equation, the solution is invariant under a time shift of nT, $n \in \mathbb{N}.$, Thus, the limit can be replaced by equality,

$$\left(\sigma(t) + \int_0^{\infty} \rho(t,a)\, da\right) = b/\mu$$

hence

$$S[u](t) = b/\mu - R[u](t).$$

The PDE has a solution,

$$\rho(t,a) = u(t-a)e^{-\mu a}$$

which we integrate w.r.t a to obtain the marginal distribution

$$R[\psi](t) = \int_0^{\infty} \rho(t,a)\, da = \int_0^{\infty} u(t-a)e^{-\mu a} da.$$

The boundary condition is defined in terms of u in $u(t-a)$, we may define,

$$R[u](t) := \int_0^{\infty} u(t-a)e^{-\mu a} da$$

and $S[u](t) = b/\mu - R[u](t)$,

$$\begin{aligned} F[u] &:= \int_0^T \beta(t)S[u](t)dt \\ &= \int_0^T \beta(t)\left\{b/\mu - \int_0^\infty \rho(t,a)da\right\}dt \\ &= \int_0^T \beta(t)\left\{b/\mu - \int_0^\infty u(t-a)e^{-\mu a}da\right\}dt \\ &= P - Q \end{aligned}$$

where,

$$\begin{aligned} P &= \int_0^T \beta(t)b/\mu\, dt \\ Q &= \int_0^T \int_0^\infty \beta(t)u(t-a)e^{-\mu a}dadt \end{aligned}$$

Let $\tau = t - a$, then

$$\begin{aligned} Q &= \int_0^T \int_t^{-\infty} -\beta(t)u(\tau)e^{-\mu(t-\tau)}d\tau dt \\ &= \int_0^T \int_{-\infty}^t \beta(t)u(\tau)e^{-\mu(t-\tau)}d\tau dt \\ &= \int_0^T \left\{\int_0^t + \sum_{i=1}^\infty \int_{-iT}^{(-i+1)T}\right\} \beta(t)u(\tau)e^{-\mu(t-\tau)}d\tau dt \\ &= \int_0^T \int_0^t \beta(t)u(\tau)e^{-\mu(t-\tau)}d\tau dt \\ &\quad + \int_0^T \sum_{i=1}^\infty \int_{-iT}^{(-i+1)T} \beta(t)u(\tau)e^{-\mu(t-\tau)}d\tau dt \end{aligned}$$

Alternating the integrals,

$$\begin{aligned} Q &= \int_0^T \int_\tau^T \beta(t)u(\tau)e^{-\mu(t-\tau)}dtd\tau \\ &\quad + \sum_{i=1}^\infty \int_{-iT}^{(-i+1)T} \int_0^T \beta(t)u(\tau)e^{-\mu(t-\tau)}dtd\tau \\ &= \int_0^T \int_\tau^T \beta(t)u(\tau)e^{-\mu(t-\tau)}dtd\tau \\ &\quad + \sum_{i=1}^\infty \int_0^T \int_0^T \beta(t)u(\tau')e^{-\mu(t-\tau'+iT)}dtd\tau' \qquad (\tau' = \tau + iT) \\ &= \int_0^T \int_\tau^T \beta(t)u(\tau)e^{-\mu(t-\tau)}dtd\tau \\ &\quad + \sum_{i=1}^\infty \int_0^T \int_{iT}^{(i+1)T} \beta(t')u(\tau')e^{-\mu(t'-\tau')}dt'd\tau \qquad (t' = t + iT) \end{aligned}$$

Due to periodicity, $t' \equiv t, \quad \tau' \equiv \tau$ and we have,

$$\begin{aligned} Q &= \int_0^T \int_\tau^T \beta(t)u(\tau)e^{-\mu(t-\tau)}dtd\tau \\ &\quad + \int_0^T \sum_{i=1}^{\infty} \int_{iT}^{(i+1)T} \beta(t)u(\tau)e^{-\mu(t-\tau)}dtd\tau \\ &= \int_0^T \int_\tau^{\infty} \beta(t)u(\tau)e^{-\mu(t-\tau)}dtd\tau \end{aligned}$$

thus,

$$F[u] = \int_0^T \beta(t)b/\mu \, dt - \int_0^T u(t)G(t) \, dt$$

where

$$G(t) = \int_\tau^{\infty} \beta(t)e^{-\mu(t-\tau)} \, dt.$$

□

Corollary 4.1.5 *Consider the optimization problem restricted to Ψ_n, where the vaccination support is given by the points*

$$0 \leq t_1 < t_2 <, \cdots < t_n < T.$$

At least one optimal strategy (possibly not all) can be characterized by means of the function

$$G \in C^0([0,T], \mathbb{R}_+), \quad t \mapsto \int_t^{\infty} \beta(\tau)e^{-\mu(\tau-t)} \, d\tau.$$

That is, there is an optimal strategy of the restricted problem that satisfies the conditions:

1. *If $\{t_i | lim_{t \to t_i +} S[\psi](t) = 0\}$:= time when everyone is vaccinated and $\{t_j | lim_{t \to t_j +} S[\psi](t) \geq 0\}$:=time point where not everyone is vaccinated, then*

$$G(t_i) \geq G(t_j).$$

2. *If $\{t_i | lim_{t \to t_i +} S[\psi](t) = 0\}$:= everyone vaccinated, $\{t_{lo} | lim_{t \to t_{lo} +} S[\psi](t) > 0\}$:= part of the population vaccinated and*

$\{t_j | lim_{t \to t_j +} S[\psi](t) = S[\psi](t_j -)\} :=$ *no one vaccinated,*

then

$$G(t_i) \geq G(t_{l_0}) \geq G(t_j).$$

3. *In all points but one vaccination point, either the complete population is vaccinated or no one is vaccinated*

We already know that there is at least one optimal strategy. All we have to do is to show that there is one strategy among these that satisfies the three conditions listed above. The proof will be shown using the following lemmata.

We establish conditions that allow to move vaccination doses from one time point t_i to another time point t_j without changing the costs.

Lemma 4.1.6 *Consider ψ, $\psi' \in \Psi_n$ corresponding to $u = \sum_{i=1}^n d_i \delta_{t_i}$ respectively $u' = \sum_{i=1}^n d'_i \delta_{t_i}$. If $j, k \in \{1, .., n\}$ with $d_j > 0$, $S[u](t_k+) > 0$, then the strategy with $d'_k = d_k + \varepsilon$ and $d'_j = d_j - \varepsilon$ is feasible for all $\varepsilon \leq d_j$ s.t. $s[u'](t_k+) \geq 0$. If $G(t_j) \geq G(t_k)$, its possible to obtain $F[\psi'] \leq F[\psi]$ for $C[\psi'] = C[\psi]$. Furthermore, if $G(t_j) > G(t_k)$, then $F[\psi'] < F[\psi]$.*

Proof: First of all, due to Lemma (4.1.2), a strategy ψ' is feasible (i.e. there is a strategy ψ' that corresponds to u').

Next, as the costs do not change, $C(\psi) = \sum_{i=1}^n d_i = \sum_{i=1}^n d'_i = C[\psi']$.

Then,

$$\mathcal{F}[\psi] = \int_0^T \beta(t) b/\mu \, d\tau - \sum_1^n d_i G(t_i)$$

$$\mathcal{F}[\psi'] = \int_0^T \beta(t) b/\mu \, d\tau - \sum_1^n d'_i G(t_i)$$

$$\begin{aligned} \mathcal{F}[\psi] - \mathcal{F}[\psi'] &= -d_j G(t_j) - d_k G(t_k) + d'_j G(t_j) + d'_k G(t_k) \\ &= -G(t_j)(d_j - d'_j) - G(t_k)(d_k - d'_k) \\ &= -\varepsilon G(t_j) + \varepsilon G(t_k) \\ &= \varepsilon (G(t_k) - G(t_j)) \end{aligned}$$

$$\mathcal{F}[\psi] = \mathcal{F}[\psi'] - \varepsilon (G(t_k) - G(t_j)).$$

If $G(t_j) - G(t_k) \geq 0$ or $G(t_j) - G(t_k) \leq 0$ (depending on the case), the result follows. □

Now we show that there is an optimal strategy satisfying conditions (1)-(3) of corollary (4.1.5).

Lemma 4.1.7 *Consider a strategy ψ^* that satisfies condition 1 of corollary (4.1.5). There is an strategy $\psi' \in \Psi_n$ s.t. $C[\psi'] = C[\psi^*]$ and $F[\psi'] \leq F[\psi^*]$, that satisfies condition (1) of corollary (4.1.5).*

Proof:
By the said condition 1, if everyone is vaccinated at time point t_i, and part of the population vaccinated at t_j, then

$$G(t_i) \geq G(t_j).$$

By results of Lemma (4.1.6), we may reduce vaccination doses at time t_i and add the same amount at time t_j to obtain a new strategy ψ' for which $F[\psi'] \leq F[\psi^*]$. □

Lemma 4.1.8 *Consider a strategy ψ^* that satisfies conditions 1 and 2 of corollary (4.1.5). There is a strategy $\psi' \in \Psi_n$ s.t. $C[\psi'] = C[\psi^*]$, $F[\psi'] \leq F[\psi^*]$, that satisfies condition (1) and (2) of corollary (4.1.5).*

Proof:
Condition (2) reads: If t_{l_0} is one time point, where only a part of the population is vaccinated, t_i is a time point where everyone is vaccinated, t_j is a time point where no one is vaccinated, then

$$G(t_i) \geq G(t_{l_0}) \geq G(t_j).$$

We already know that there is an optimal strategy ψ' that satisfies condition 1 (Lemma 4.1.7). Then, in a similar manner, for $G(t_i) \geq G(t_{l_0})$ and $G(t_{l_0}) \geq G(t_j)$, we are able to find by means of Lemma (4.1.6) a better strategy than the optimal strategy ψ^*. □

Lemma 4.1.9 *There is an strategy $\psi' \in \Psi_n$ s.t. $C[\psi'] = C[\psi^*]$, $F[\psi'] \leq F[\psi^*]$, both satisfying condition (1), (2) and (3) of the corollary (4.1.5).*

Proof:
Condition (3) reads: In all points but one vaccination point, either the complete population is vaccinated or no one is vaccinated. We already know that there is an optimal strategy satisfying conditions (1) and (2). Consider the set of points, where all (or none) of the population is vaccinated. We are (via Lemma (4.1.6) allowed to move vaccination doses back and forth between these points, as $G(.)$ is necessarily the same for these time points. Thus, it is possible to satisfy condition (3). □

Corollary 4.1.10 *We define an optimal population profile using $G(t_i)$ and a constant g. It is possible to conclude: there is a real number g, s.t.*

i) $G(t_i) > g \quad \Rightarrow \quad$ *everyone is vaccinated in* t_i

ii) $G(t_i) < g \quad \Rightarrow \quad$ *no one is vaccinated in* t_i

iii) if only a part of the population is vaccinated in t_l, then $G(t_l) = g$.

The optimal vaccination strategy is given by,

$$\psi = c^{\infty}\delta_M + c\delta(t - t_i) + 0.\chi_{(0,T)\setminus(M\cap\{t_i\})}.$$

Here c^{∞} representing the number of doses that vaccinates all susceptibles at time $t \in M$ where $M = \{t|G(t) > g\}$ and $t_i = \{t|G(t) = g\}$ denotes time points when only part of the population is vaccinated.

4.1.1 Continuous limit

The idea now is to use the corollary (4.1.10) as starting point, to go to the limit, and to characterize in this way one optimal strategy of the full problem (in degenerate cases, there may be more than one optimal strategy, but it is sufficient for our purposes to characterize one strategy).

Ingredient 1: (Approximation by the step function)

Define

$$\Psi := \left\{ \psi \,\middle|\, supp_v(\psi) \subset \{0, T\};\ \psi \in L^{\infty}_{+} \right\}$$

and

$$\Psi_n := \left\{ \psi \in \Psi \,\middle|\, supp_v(\psi) \subset \{t_i | 0 \leq t_i \leq T;\ \ i = 1, 2, ..., n\} \right\}$$

Then, $\Psi_n \subset \Psi$, and the sequence of sets Ψ_n approximate Ψ. We claim that $\exists \psi_n \in \Psi_n : \quad s.t \quad \psi_n \rightarrow \psi$ in the topology of Ψ, $\quad \forall\ \psi \in \Psi$.

Proof: This is true, as step functions are dense in $L^1(\mathbb{B})$ for some measure space $\mathbb{B}$ [Mueller 1998]. □

Ingredient 2: (Cost constraint)

We can improve ingredient(1) by including a cost constraint:

We claim that $\exists\ \psi_n \in \Psi_n \cap \{C[\psi] \leq c\} :$ *s.t* $\psi_n \to \psi$ *in the topology of* $\Psi, \quad \forall\ \psi \in \Psi \cap \{C[\psi] \leq c\}$.

Proof: Let $\psi_n^* \in \Psi_n$ approximating $\psi \in \Psi$. As the costs are continuous, we know

$$\lim_{n\to\infty} C[\psi_n^*] = C[\psi] \leq c.$$

Thus, we may construct a strategy $\tilde{\psi}_n$ by an convex combination of ψ_n^* and the extremal strategy $\hat{\psi}_n \equiv 0$, such that $\tilde{\psi}_n \to \psi_n \in \Psi \cap \{C[\psi] \leq c\}$.

The $\hat{\psi}_n \equiv 0$ component will vanish for $n \to \infty$ and thus,

$$\lim_{n\to\infty} C[\lambda\psi_n^* + (1-\lambda)\hat{\psi}_n] = \lim_{n\to\infty} C[\lambda\psi_n^*] = \lambda C[\psi] \leq c; \quad 0 \leq \lambda \leq 1.$$

Thus, $\tilde{\psi}_n \to \psi$, and the statement is true. □

Ingredient 3: (The optimal strategy)

Let ψ_n^* *be an optimal strategy for the optimization problem for maximal cost restriction* c. *For* ψ_n^* *such that ingredients (1) and (2) are true, then* $\psi_n^* \to \psi^* \in \Psi$.

Proof: Assume there exists $\tilde{\psi}_n \to \tilde{\psi}$ an optimal strategy. By Lemma (4.1.6), it is possible to construct a strategy ψ_n^* by moving vaccination doses such that

$$C[\psi_n^*] \leq c, \qquad \mathcal{F}(\psi_n^*) \leq \mathcal{F}(\tilde{\psi}_n).$$

where

$$\mathcal{F}(\psi_n^*) \quad \forall \quad \psi_n \in \Psi_n.$$

is minimum. The sequence ψ_n^* converges to a point in $\psi^* \in \Psi$ by compactness. □

Remark 4.1.1 *If* $\beta(t)$ *has only a finite number of local minima and maxima in* $[0,T]$, *then* $G(t)$ *has a finite number of minima and maxima.*

Proposition 4.1.11 *Let*

$$\Gamma_g = \{t \in [0,T) \,|\, G(t) \geq g\}.$$

Then, Γ_g *consist of a finite number of closed intervals with a length larger zero, and a finite number of points. For any optimal vaccination strategy* ψ^*, *there is* $g \in \mathbb{R}$, *s.t.* $supp_v(\psi^*) = \Gamma_g$. *Within the closed intervals of size larger zero, everyone is vaccinated. We have only one point in the set of isolated points in* Γ_g *where only a part of the population is vaccinated.*

Remark 4.1.2 *As the points are isolated, there is only a finite number of points.*

Proof: As Ψ is compact, We know that there is a converging subsequence ψ_n^* that converges to $\psi^* \in \Psi$.

First, we show that there is $g \in \mathbb{R}$ s.t. $\text{supp}_v(\psi^*) = \Gamma_g$.

Due to corollary (4.1.10) and the ingredients (1) to (3), there is for all ψ_n a number $g_n \in \mathbb{R}$, s.t.

(i) $G(t_i) > g_n$, everyone is vaccinated at t_i,

(ii) $G(t_l) = g_n$, only a part of the population is vaccinated at t_l,

(iii) $G(t_i) < g_n$, no one is vaccinated.

We may chose a subsequence (of our converging sequence) such that $g_n \to g$. Thus, for all time points t_i with $G(t_i) > g + \varepsilon$ the vaccination strategies of the converging subsequence will vaccinate everyone. As for $n \to \infty$ the time points become dense in $\{t \,|\, G(t) > g + \varepsilon\}$ and ψ^* vaccinates everyone in this interval, for all $\varepsilon > 0$, hence also true for $\{t \,|\, G(t) > g\}$. As the vaccination support is closed, this is also true for the closure of the set $\{t \,|\, G(t) > g\}$. In this case, the last time point $t_N \in [0, T]$ corresponds to $\{t \,|\, G(t) = g\}$ as we intend to use the only the remaining vaccination doses at this point.

With a similar argument, we see that no one is vaccinated in $\{t \,|\, G(t) < g\}$. We have only an isolated point of Γ_g, where only a part of the population is vaccinated. □

4.2 Candidate Optimal Strategies w.r.t instantaneous stability

From the stability criterion derived from singular perturbation theory, we recall the following definition,

Definition 4.2.1 *Define the instantaneous reproduction rate (in presence of vaccination)* $R_v : [0, T] \to \mathbb{R}$ *by*

$$R_v(t) = \beta(t) S[\psi](t)/\alpha.$$

We call the uninfected periodic orbit instantaneously stable, if

$$\|R_v\|_{L^\infty} \leq \tilde{R} < 1, \quad \textit{for some constant } \tilde{R}.$$

We then define the optimal control problem,

Problem 4.2.1 *For $\psi \in L^{\infty}_{+}(0,T)$, find the vaccination schedule that minimizes $\|R_v[\psi]\|_{L^\infty} = ||\beta(t)S(t)||_{L^\infty}$ under the constraint that the number of vaccination doses $\tilde{C}[\psi] \leq C_\infty$ is given.*

We seek an infimum over $S[\psi]$ since we can control it through vaccination. If we consider an approximation of $\beta(t)$ with step functions $\beta_n(t)$ for $n = 1, 2, ..., N$; $t \in [0,T]$, then we would represent for each class of β_n;

$$\begin{aligned} \|R_v[\psi]\|_{L^\infty} &= ||\beta_n(t)S(t)||_{L^\infty} \\ &= |\beta_n|\,||S(t)||_{L^\infty} \end{aligned}$$

4.2.1 Rectangular contact rate.

It is possible to represent a two level contact rate to mimic school holidays, when contact rate is low by β_1 and school terms when the contact rate is higher by β_2, s.t.

$$\beta(t) = \begin{cases} \beta_1, & t \in [0, T_1]; \\ \beta_2, & t \in [T_1, T]. \end{cases}$$

where $\beta_1 > \beta_2$ and $\beta(t)$ is a periodic.

Figure (4.1) depicts instantaneous control scenario for $\beta(t) = \beta_i : \quad i = 1, 2$. The intervals $[0, T_1]$ and $[T_1, T]$ assumed fixed. However, $(\tau_1, \tau_2) \in supp_v(\psi)$ depends on the vaccination strategy used and may change.

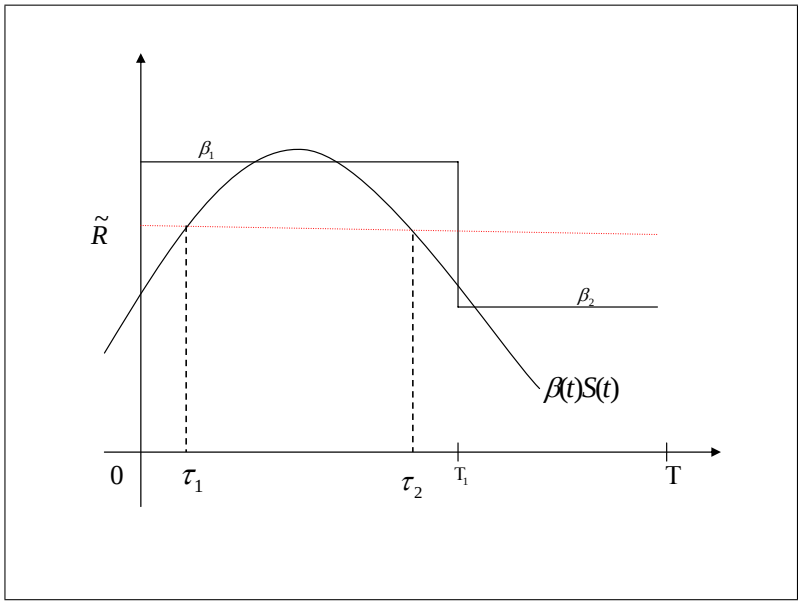

Figure 4.1: Sketch graph of $\beta(t)S[\psi](t)$ for two level of contact rate.

Proposition 4.2.2 *Assume that* C_∞ *being the maximum number of vaccination doses to be used in [0,T], is fixed. Let* ψ_{opt} *define a solution of problem (4.2.1) s.t* $\tilde{R} := ess\ sup\{\beta(t)S[\psi_{opt}](t)\}$. *For* ψ_{opt}, *we find*

$$\beta(t)S[\psi_{opt}](t) \geq \tilde{R} \quad \forall \quad t \in supp_v(\psi_{opt})$$

and

$$\beta(t)S[\psi_{opt}](t) < \tilde{R} \quad \forall t \in [0,T] \setminus supp_v(\psi_{opt}).$$

Then, the optimal problem has a solution in the set,

$$\Lambda = \{\psi | \psi = c_1\delta(t-\tau_1) + c_2\chi_{[\tau_1,\tau_2]} + c_3\chi_{[\tau_2,T]}\}$$

for some constants c_1, c_2, c_3.

Proof:

The intervals $[0,T_1]$ and $[T_1,T]$ are assumed fixed, being the beginning and the end of school terms, or weather seasons. They are the contact rate intervals. However, $(\tau_1,\tau_2) \in supp_v(\psi)$ depends on the vaccination strategy used.

Step 1:

We define the constants $c_i^* :\ i = 1,2,3$ corresponding to a a feasible optimal strategy ψ^* that is $S[\psi^*] \in \mathfrak{S}$. Below, we obtain $c_1^* = ln\left\{\frac{S[\psi](\tau_1-)}{S[\psi](\tau_1+)}\right\}$, $c_2^* = \frac{\beta_1 b}{\tilde{R}} - \mu$ and $c_3^* = 0$, for ψ^* optimal.

(i) We define c_1^* as the weight of a delta peak, an impulse vaccination input that either ensures $\beta(t)S[\psi](t) < \tilde{R}$, or fails to meet this target. If it fails, we define c_2^* as a uniform distribution over $[\tau_1,\tau_2]$ and vaccinate until $\beta(\tau_2)S[\psi](\tau_2) \leq \tilde{R}$. In $[0,T] \setminus [\tau_1,\tau_2]$, we have $c_3^* = 0$.

(ii) Consider the population at its equilibrium, i.e.,

$$\frac{dS(t)}{dt} = b - \mu S(t) - \psi(t)S(t) = 0$$

$$\psi(t) = \frac{1}{S(t)}\{b - \mu S(t)\}.$$

Take $|\beta_1|S[\psi](\tau_2) = \tilde{R}$ and c_2^* uniform over the same interval, hence

$$c_2^* = \frac{\beta_1 b}{\tilde{R}} - \mu.$$

At point τ_1, we have a delta peak. Consider the interval $[\tau_1 - \varepsilon, \tau_1 + \varepsilon]$ and $\psi(t) = c_1^* \delta(t - \tau_1)$,

$$\begin{aligned} S[\psi](t) &= S[.](\tau_1 - \varepsilon) \exp\left\{ - \int_{\tau_1 - \varepsilon}^{\tau_1 + \varepsilon} \mu + \psi(t) d\tau \right\} \\ &\quad + b \int_{\tau_1 - \varepsilon}^{\tau_1 + \varepsilon} \exp\left\{ - \int_{\sigma}^{\tau_1 + \varepsilon} \mu + \psi(t) d\tau \right\} d\sigma \\ &= e^{-c_1^*} S[\psi](\tau_1 -) \\ \Rightarrow S[\psi](\tau_1 +) &= e^{-c_1^*} S[\psi](\tau_1 -) \\ c_1^* &= ln \left\{ \frac{S[\psi](\tau_1 -)}{S[\psi](\tau_1 +)} \right\} \end{aligned}$$

Step 2:
Show that ψ^* is optimal.

Define any other optimal strategy $\tilde{\psi} \in \Psi$.

In $[0, T] \setminus [\tau_1, \tau_2]$, $\psi^* = 0$. We have two possibilities:

- the strategy $\tilde{\psi}$ either vaccinates no one in this interval,

$$S[\tilde{\psi}](t) = S[\psi^*](t),$$

- vaccinates at least someone in this interval, $S[\tilde{\psi}](t) < S[\psi^*](t)$.

$$\Rightarrow \quad S[\tilde{\psi}](t) \leq S[\psi^*](t) : \qquad t \in [T_1, T].$$

Consider $[\tau_1, \tau_2]$, we know that $||\beta(t) S[\psi^*](t)||_{L^\infty} \leq \tilde{R}$ and $C[\psi^*] \leq C[\psi]$, for all $\psi \in \Psi$. That there exists any strategy $C[\tilde{\psi}] \leq C[\psi^*]$ is a contradiction.

- ψ^* optimal implies it has the minimal cost i.e., $C[\psi^*] \leq C[\psi]$ for $\psi \in \Psi$, and we expect $S[\tilde{\psi}](t) \leq S[\psi^*](t)$. Furthermore, $S[\tilde{\psi}](t) \leq S[\psi^*](t)$, else we do not have control over $||S[\tilde{\psi}]\beta(t)||_{L^\infty}$.

Since $S[\tilde{\psi}](t) \leq S[\psi^*](t) : \qquad \forall \ t \in [0, T]$,
Hence, $C[\psi^*] \leq C[\tilde{\psi}]$, so ψ^* is optimal. □

4.2.2 Approximating contact rate by size $(n > 2)$ step function.

Now define $\beta(t)$ by

$$\beta_i : \ t \in [t_i, t_{i+1}], \ i = 0, 1, 2, ..., n.$$

The aim is to approximate $\beta(t)$ by a step function. Interest is the point(s) when $\hat{\beta} = max\{\beta(t)\}$, as this gives information on when $||\beta(t) S(t)||_{L^\infty}$ is large. We conjecture that $\{t_i \in [0, T] : \beta(t_i) = \hat{\beta}\} = [T_1, T_2] =: I_{max}$ is an ideal vaccination time.

Once we know the susceptible profile at $T_2 \in I_{max}$ and the vaccination doses used after this time point, then by the periodic nature of [0,T], we know the susceptible profile $\forall\, t \in [0, T]$. Hence the vaccination strategy is well known.

Proposition 4.2.3 *Define* $\beta_n(t) = \sum_{i=1}^{n} \beta_i \chi_{[t_i, t_i+1]}$. *For fixed maximum costs and* $\tilde{R} = ess\ sup\{\beta_n(t)S[\psi](t)\}$, *the optimal problem w.r.t instantaneous stability has a solution in the set*

$$\Lambda = \left\{ \psi | \psi = \sum_{i=1}^{n} c_1^{(i)} \delta(t - t_i) + c_2^{(i)} \chi_{[t_i - \tau_i^1, t_i]} + c_3^{(i)} \chi_{[t_i, t_i + \tau_i^2]} \right\}$$

s.t. for $\psi_{opt} \in \Psi$,

$$\beta(t)S[\psi_{opt}](t) \leq \tilde{R} \quad \forall \quad t \in supp_v(\psi_{opt})$$

$$\beta(t)S[\psi_{opt}](t) < \tilde{R} \quad \forall t \in [0, T] \setminus supp_v(\psi_{opt}).$$

Proof:

Step 1:

We construct a strategy $\psi^* \in \Psi$. Consider the interval $(t_{i_0}, t_{i_0} + 1)$ in which $\beta(t) = \hat{\beta}$. Assuming $(t_{i_0}, t_{i_0} + 1) \subset supp_v(S(t))$, then we know that $S(t_{i_0} + 1) = \frac{\tilde{R}}{\hat{\beta}.}$ As in the case of step size $n = 2$, we are able to define the constants $c_j^{(i_0)} : \quad j = 1, 2, 3$ in the interval $(t_{i_0}, t_{i_0} + 1)$ and by reconstruction, $c_j^i : \forall\ i = 1, 2, ...n : \ j = 1, 2, 3$ such that there is a strategy which meets the requirements of proposition (4.2.3).

Step 2:

We seek to know if the strategy ψ^* defined in step 1 is optimal. From the proof of optimal strategy using step size $n = 2$ for β, we can easily extend the same arguments for step size $n > 2$.

As a result ψ^* is optimal. □

4.2.3 Continuous Limit

We have approximated $\beta(t)S[\psi](t)$ by a series of step functions and now wish to go to the limit. Suppose $\beta_n(t)$ goes to the limit, i.e., $\beta_n(t) \to \beta(t)$ in L^∞. We seek to know if $\beta_n(t)S[\psi_n^*] \to \beta(t)S[\psi^*]$ in L^1.

Theorem 4.2.4 *Suppose* $\beta_n(t) \to \beta(t)$ *in* L^∞, $\psi_n \to \psi$ *in* Ψ, *and* $S[\psi_n](t) \to S[\psi](t)$ *in* L^1, *then* $\beta_n(t)S[\psi_n](t) \to \beta(t)S[\psi](t)$ *in* L^1.

$$\|\beta_n(t)S[\psi_n] - \beta(t)S[\psi]\|_{L^1} \to 0$$

Proof.

We show that

$$\begin{aligned}\|\beta_n S[\psi_n] - \beta S[\psi]\|_{L^1} &= \|(\beta_n - \beta)S[\psi_n] + \beta(S[\psi_n] - S[\psi])\|_{L^1} \\ &\leq \|(\beta_n - \beta)S[\psi_n]\|_{L^1} + \|\beta(S[\psi_n] - S[\psi])\|_{L^1} \\ &\leq \|(\beta_n - \beta)\|_{L^\infty}\|S[\psi_n]\|_{L^1} + \|\beta\|_{L^\infty}\|(S[\psi_n] - S[\psi])\|_{L^1} \\ &\to 0\end{aligned}$$

The RHS converges to zero since β and $\|\beta\|_{L^\infty}$ are assumed bounded, $\|(\beta_n - \beta)\|_{L^\infty} \to 0$, $\|S[\psi_n]\|_{L^1}$ is bounded since $S[\psi_n](t) \to S[\psi](t)$ in L^1, and $\|(S[\psi_n] - S[\psi])\|_{L^1} \to 0$. □

Corollary 4.2.5 *If $\beta_n \to \beta$ in L^∞, ψ_n^{opt} approximates an optimal strategy and solution to problem (4.2.1), then there is a converging subsequence $S[\psi_{n_l}^{opt}] \to S[\psi^{opt}]$ in $\mathfrak{S}$, where $S[\psi^{opt}]$ is a candidate optimal strategy with minimum costs.*

Proof:
We need theorem (4.2.4) and the compactness of $\mathfrak{S}$. Hence there exists an optimal strategy that can be approximated by a series of step functions. □

Corollary 4.2.6 *If β is piecewise continuous L^∞ function and has a unique maximum at time $\hat{t}$, then the optimal strategy is characterized by*

- *For $\hat{t} \in supp_v(\psi^{opt})$, $S[\psi^{opt}](\hat{t}+) = \tilde{R}/\hat{\beta}$,*
- *$\forall\ t \in supp_v(\psi^{opt})$, $S[\psi^{opt}](t+) = \tilde{R}/\beta(t+)$,*
- *$\forall\ t \notin supp_v(\psi^{opt})$, $S[\psi^{opt}](t+) < \tilde{R}/\beta(t+)$.*

Chapter 5

Simulation

We consider the case of measles as one of the childhood diseases. Most childhood diseases tend to have periodic outbreaks, occasioned by climatic factors and human contact rate patterns, among other factors. The school going childhood age has periodic contact due to school terms as one would expect higher contact rates during school days and lower contact rates during holidays. Pre-vaccination era records show a 2 year or less outbreak period for measles in most regions of the world, even in sub-sahara Africa (Niger case [Ferrari 2008]). But this has improved to a five year period in the post vaccination period. However, we use in this case a one year vaccination period to match it with the contact period.

In most regions where vaccination is efficiently done, the prevalence of measles has been kept very low. In European countries, the incidence rate has been kept at approximately 1 case per 1 million or even less. However, measles is endemic in parts of Africa and Asia, going by the World Health organization (WHO) reports.

Statistics for deaths from measles by worldwide region are as follows: There were about 311,000 deaths from measles in Africa in 2002, about 196,000 deaths from measles in South East Asia in 2002, about 6,000 deaths from measles in Europe in 2002, about 70,000 deaths from measles in Eastern Mediterranean in 2002 and about 28,000 deaths from measles in Western Pacific in 2002 (The World Health Report, WHO, 2004).

In table (5.1), we have reports of measles incidence by country from US Census Bureau, Population Estimates, 2004 and US Census Bureau, International Data Base, 2004. The cases here are the reported cases. Values for Africa might be higher, as many cases go unreported.

Going by the United Nations report [Reports 2007], life expectancy in Europe and specifically in Germany stood at 79.4 years about year 2007, hence a mortality rate of about 0.013 per year, while birth rate was 8.2 births per 1000. Consider a developing country like Kenya where the birth rate around year 2007 stood at 39.2 births per 1000 and a life expectancy of 54.1 years (corresponding to a mortality rate of 0.02 per year approximately).

We simulate control strategies for measles using the following parameters: A total population size N(t)=1 million was assumed. This is typical of most cities (or effective interacting populations) around the world. Measles incidence rate fluctuates even in endemic populations such as sub-sahara Africa and Asia. One could assume an incidence of any value between 0 and 3000 cases per 1 million [Reports 2007]. We used an incidence $I0 = 100$ for our simulations. The contact rate is considered

Select countries	Cases	Population	Incidence
Americas			
USA	107	293,655,405	1 in 2 million
Canada	11	32,507,874	-
Mexico	38	104,959,594	-
Africa			
Ethiopia	26	71,336,571	-
Kenya	12	32,982,109	3 in 1 million
Tanzania	13	36,070,799	-
Europe			
Austria	3	8,174,762	-
Czech Republic	0	1,0246,178	-
Germany	30	82,424,609	3 in 1 million
Hungary	3	10,032,375	-

Table 5.1: Measles incidence by country: US Census Bureau, Population Estimates, 2004 and US Census Bureau, International Data Base, 2004

Parameter	Symbol	Value(time unit=1year)
Contact/Vaccination period	T	1
Death rate	μ	0.0166
Birth rate	b= $10^6\mu$	16,600
Recovery rate	α	52
Measles Incidence	I0	0-3000

Table 5.2: Parameter values: Human population dynamics (not specific to any particular region) and Measles dynamics.

periodic and we used,

$$\beta(t) = \{0.5 + 0.5cos(2\pi t/T) + 5.0cos(4\pi t/T)\}\frac{\mu\alpha}{b - \alpha I0}$$

Contact rate period may depict the school term and school holiday behavior among school age children. During school term, the contact rate is higher and lower during holidays. If vaccination rate is made periodic, then we may antagonize the spread of the disease leading to effective control [Agur 1993]. The period $T = 1$ year was therefore used. Measles has a short infectious period, one to two weeks infection period. Hence the rate $\alpha = 52$ denotes one week infection period or $\alpha = 26$ for two weeks infection period.

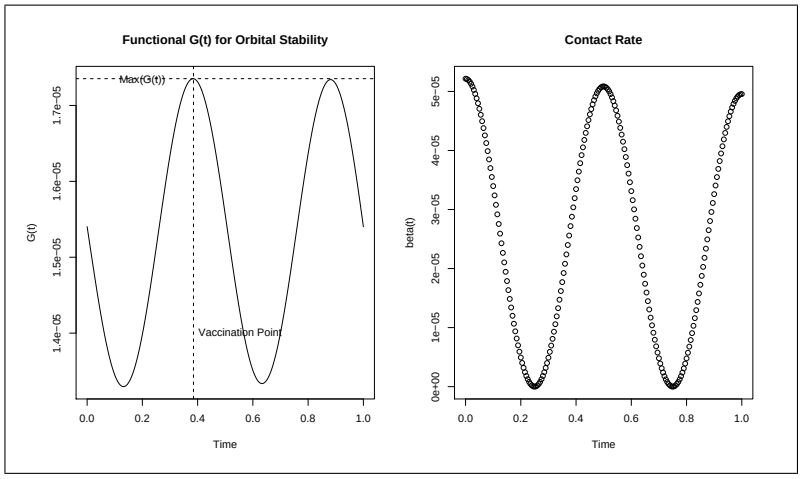

Figure 5.1: G(t), the threshold criterion from Orbital Stability and the simulated periodic contact rate.

Under orbital stability, the idea is to vaccinate when the functional $G(t)$ exceeds some maximum value. The maximum is depicted in figure (5.1) at which point, we have a vaccination time ($t_i \approx 0.3$) and ($t_i \approx 0.8$). We simulated a periodic contact rate $\beta(t)$ and notice that vaccination points come at time points when the vaccination rate is on the verge of increase. Under these circumstances, the idea is to concentrate vaccination doses at the time when the contact rate begins to increase, such as at the beginning of school terms. We observe the vaccination strategies under orbital stability criterion, where the function $G(t)$ is used (fig. 5.2). In this case the susceptible profile is given for the case when the vaccination profile vaccinates a fraction of susceptibles at vaccination time, and the vaccination profile empties the number of available susceptibles at vaccination time. We simulate the susceptible profile for the instantenious stability case, a case when vaccination is done when the functional R_v hits a maximum threshold (see figures (5.4) for $\mu = 1.66$ and (5.3) for $\mu = 0.0166$).

The aim was to distinguish between orbital stability criterion and instantaneous stability criterion. The hypothesis is that, for childhood diseases, we gain better

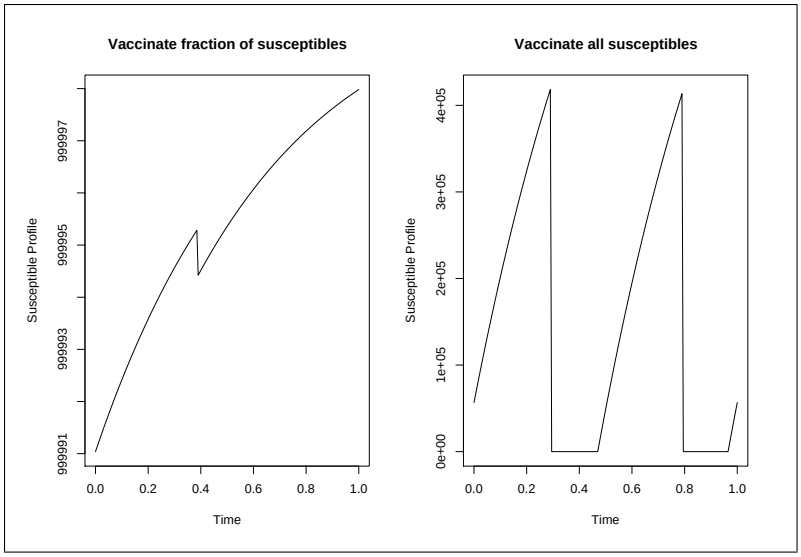

Figure 5.2: Susceptible profiles and vaccination time, under orbital stability.

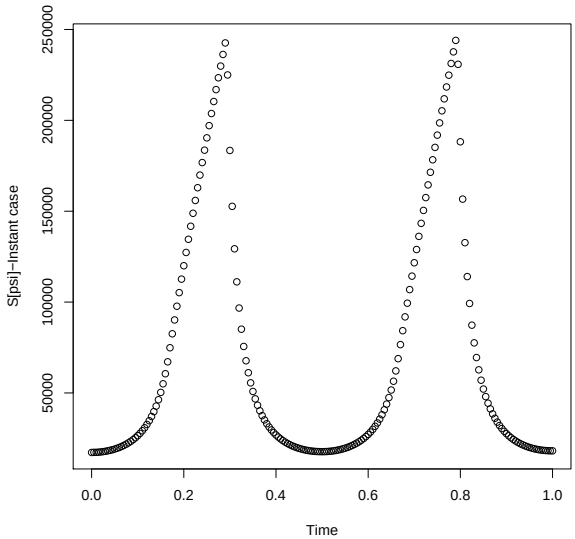

Figure 5.3: Susceptible population under the instantaneous vaccination strategy ($\mu = 1.66$).

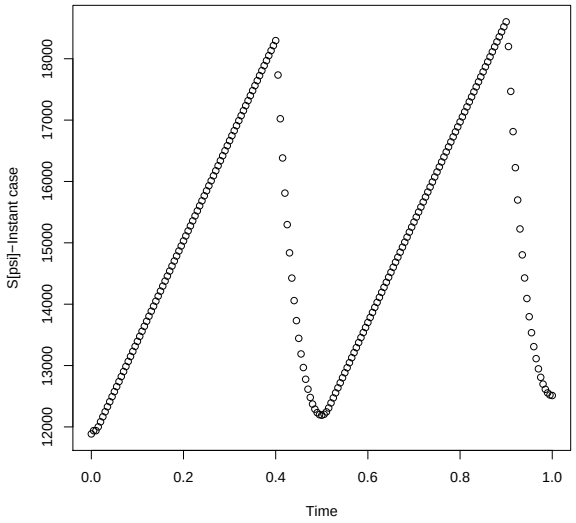

Figure 5.4: Susceptible population under the instantaneous vaccination strategy ($\mu = 0.0166$).

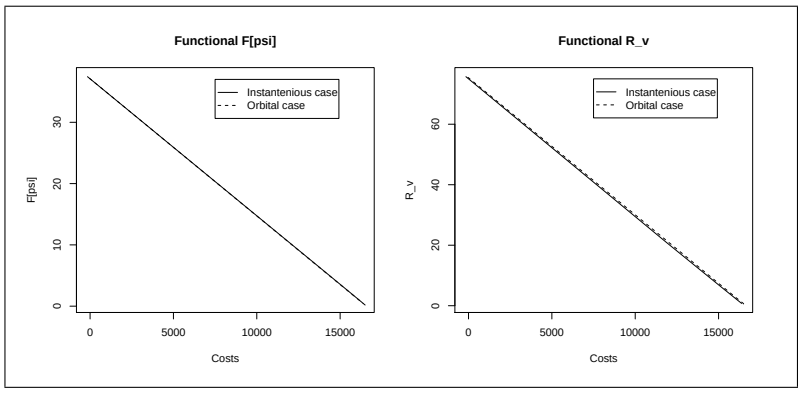

Figure 5.5: Costs for minimizing F[psi] and R_v for ($\mu = 0.166$)

control if we use instantaneous stability criterion to develop an optimal vaccination strategy than we do when we use orbital stability criterion.

Now we consider a real situation where the human lifespan or life expectancy is assumed to be 60 years. This corresponds to $\mu = 0.0166$. For such a case, the mortality is small but the life span is too large in comparison to the period (T) of contact and vaccination. The comparison of vaccination strategies under orbital and instantaneous stabilities give the results of figure (5.5). There is no clear difference between the two vaccination strategies, whether we use orbital or instantaneous stability criterion. This can be given the following interpretation: The precise time or phase at which a person is vaccinated will have only a small influence on the time course of the susceptible population at equilibrium dynamics; the person is protected for many periods, that is, the reduction of the susceptible population by a single vaccination is almost uniform in time. Therefore, the distribution of doses in time has only a little influence on the performance w.r.t. the different efficacy measures.

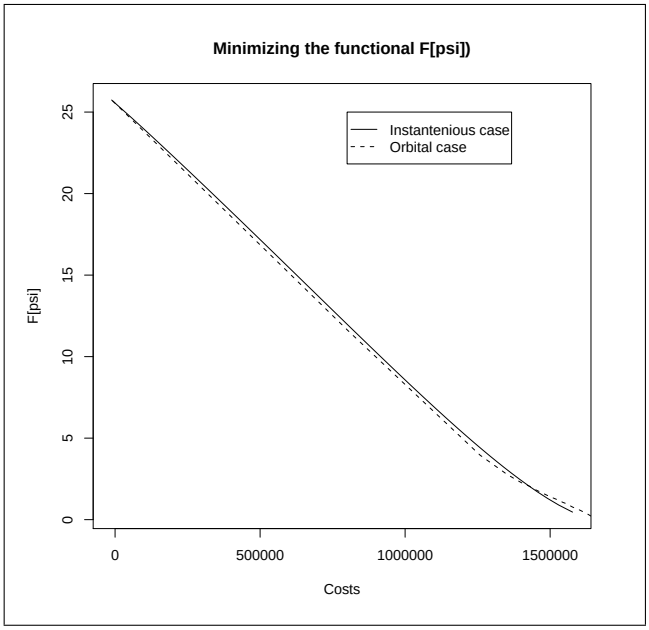

Figure 5.6: Costs required to minimize F[psi] under the two strategies ($\mu = 1.66$).

We consider a rather unrealistic situation. Suppose the human lifespan is short and almost equal to the period of vaccination. We consider $\mu = 1.66$ corresponding to a human lifespan of only 7 months. It is only when the lifespan is in the same magnitude or shorter than the period of vaccination that a vaccination dose achieves a local effect in time. Consider the results of figures (5.6) and (5.7), where $\mu = 1.66$ is used. In this case, the two stability criteria behave differently. Since the Floquét multiplier $\mathcal{F}[\psi]$ is an average over the complete period, it gives the same result for both instantaneous strategy and orbital strategy, i.e., it is not important at which time susceptibles are removed as long as the average value over [0,T] remains below

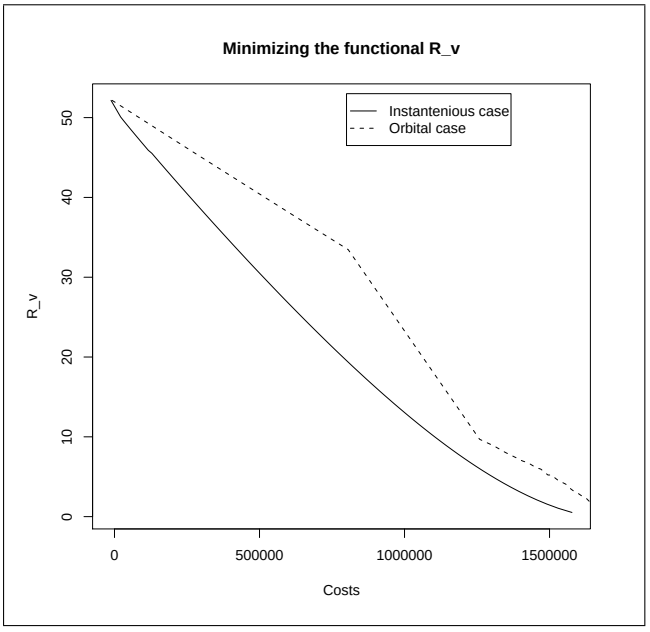

Figure 5.7: Costs required to minimize R_v under the two strategies ($\mu = 1.66$)

its threshold (fig. 5.6). But in the instantaneous stability criterion, there is a strong effect on when to vaccinate. It may be important to place the vaccination doses at any point when instantaneous stability is violated. We notice that instantaneous stability is reached with less vaccination doses when we choose to minimize the supremum R_v (fig. 5.7). The hypothesis that the instantaneous stability offers some benefit holds albeit in this extreme situation.

As a consequence and for practical purposes, these considerations and heuristical arguments seem to imply that it is better to target at the instantaneous stability criterion, as in most cases, this will lead to a Floquét multiplier that is close to the optimal Floquét multiplier. Focusing only on the Floquét multiplier may lead to a situation where the instantaneous stability is rather bad, and for some childhood diseases such as measles, short time epidemics may appear.

SECTION B:

In this section, we model a specific case of Hepatitis B, centering attention on the conditions that may lead to bi-stability in an age structured Hepatitis B model. Bi-stability is also called Hysteresis in Bifurcation theory. Bi-stability may offer a great challenge to vaccination campaign, since even in cases when vaccination is effective, the possibility of co-existence of higher and lower disease endemic states may complicate a vaccination effort aimed at disease control, as analyzed in literature such as Medley([Medley 2001]).

Chapter 6

Hepatitis-B: Bi-stability in an age structured model.

6.1 Introduction

The dynamics of Hepatitis B Virus (HBV) have been extensively studied for various regions in the world. A major classification of HBV world prevalence regions is as follows [Edmunds 1996]:

- Africa sub-sahara; where horizontal infection among lower age groups is the dominant form of transmission, together with perinatal transmission (mother to child transmission within the first year of the infant). The region is hyper-endemic (over 10% carrier prevalence) since more infection among children leads to more carrier prevalence.

- South East Asia where vertical transmission is reportedly more significant. Then other forms of childhood infection also contribute. This region is hyper-endemic as well.

- Europe and North Americas where only transmission among adults contribute to infection. Sexual contact and intra-venous drug use are the key contact pathways. The region is low-endemic as very few adults develop to carrier state after acute infection.

The model structure in this case largely depicts a scenario of a developing country where vertical transmission could play a role in transmission, immunization largely done at childbirth without screening and only heterosexual behavior in the community. The parameters also largely reflect those of developing countries.

Although the disease Hepatitis B (HepB) can be effectively vaccinated against, there are concerns about optimal vaccination against the disease. Recent developments in the dynamics of HepB virus indicate existence of complex dynamics such as endemic state bi-stability, that may be of great concern to vaccination efforts.

In the context of a developing country (Sub-Sahara Africa scenario), we examine causes for existence of bi-stable endemic scenario in an age structured model. This phenomenon has been observed in a model without age structure [Medley 2001]. The main result is that hyper-endemic populations, with high carrier prevalence are likely to exhibit bi-stable dynamics. Bi-stability may offer a great challenge to vaccination

campaign, since even in cases when vaccination is effective, the possibility of co-existence of higher and lower disease endemic states may complicate a vaccination effort aimed at disease control.

6.2 Model Structure

We develop a compartmental model in line with the formulation in [Edmunds 1996] which modeled a study in Gambia-Africa, a hyper-endemic region.

We define a as the age of an individual and t as time. The compartments in the model include: S(a,t) are Susceptibles, L(a,t) are Latent individuals including those infected but not yet infectious, I(a,t) are Acute Infected Individuals who are very infectious, but move on quickly to Chronic infectious state hence contribute less new infections. C(a,t) are Carriers who in some literature are referred to as chronic infectious [Zhao 2000]. They stay in this state for so long and contribute more to new infections than Acute infectious group. Finally R(a,t) are the Immunes, else refereed to as recovered individuals.

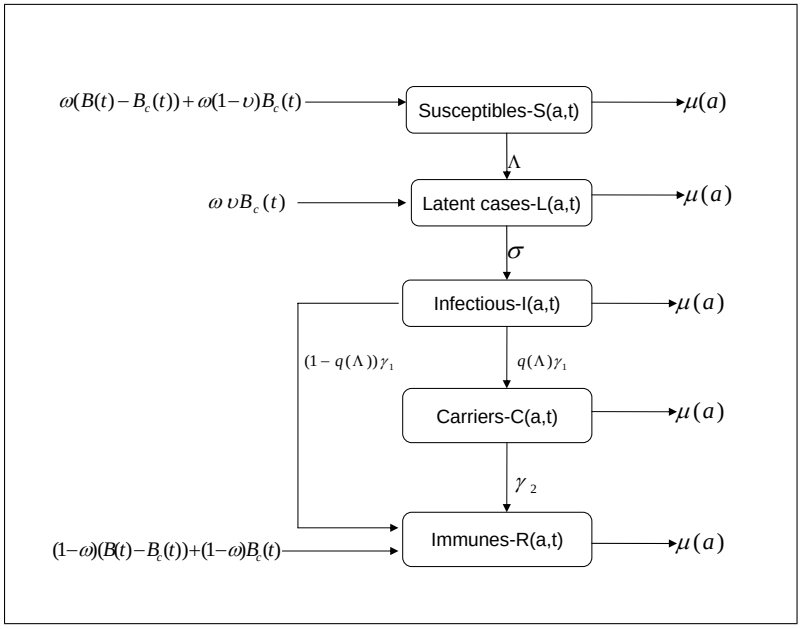

Figure 6.1: Flow chart of Hepatitis B virus(HBV) transmission.

The following parameters define movement among the compartments: $\Lambda(t)$ is the force of infection and varies with time; σ defines the rate of movement from latent state to infectious state; $q(\Lambda(t))$ is the probability that an individual who is infectious becomes a carrier, hence $(1 - q(\Lambda(t)))$ is the probability that such a person becomes immune; γ_1, γ_2 are recovery rates from infectious and carrier states respectively; $b(a)$ is the age dependent birth rate affecting boundary conditions into S(a,t), L(a,t) and R(a,t) states, while $\mu(a)$ denotes the instantaneous mortality rate

at age a.

Λ defines the force of infection and takes the form of standard incidence rate.

$$\Lambda(t) = \int_0^\infty k(a)\beta(b)\{I(b,t) + \alpha C(b,t)\}db/P(t) \tag{6.1}$$

where α is the infectiousness of carriers relative to acute infections and $P(t) = \int_0^\infty N(a,t)da$. This form of transmission kernel $k(a,b) = k(a)\beta(b)$ is refereed to in literature as the separable mixing case [Thieme 2003] and is very handy for our computations in the equation for force of infection. The case of separable mixing $k(a,b) = k(a)\beta(b)$ is also used in [Dietz 1983, Mueller 1998]. Other forms of transmission coefficient include constant case $\beta(a,a') = \beta$, and $k(a,b) = \beta(b)$ [Gripenberg 1983].

The total population is given by

$$N(a,t) = S(a,t) + L(a,t) + I(a,t) + C(a,t) + R(a,t) \tag{6.2}$$

and B(t) represents the total number of births, denoted by

$$B(t) = \int_0^\infty N(a,t)b(a)da. \tag{6.3}$$

The assumption that $a \in [0,\infty)$ as in equation (6.3) is often used for computation purposes, otherwise we know that an individuals age can never go beyond some upper limit $\bar{a}$. We assume that $\bar{a} = \infty$. $B_c(t)$ for total number of births due to carrier mothers is given by the equation

$$B_c(t) = \int_0^\infty C(a,t)b(a)da \tag{6.4}$$

Therefore $\{B(t) - B_c(t)\}$ represent births from non-carrier mothers. The model also assumes that vaccination is done to newborns only.

Given ω as the proportion of births that are not successfully immunized, $(1-\omega)$ defines immunization coverage for new born children. Suppose also that a proportion ν of newborns babies of carrier mothers develop carriage and (1-ν) such children do not develop carriage. We have the following increments into S, L and R classes, which define the boundary conditions in the model.

- $\omega(B(t) - B_c(t)) + \omega(1-\nu)B_c(t) = \omega(B(t) - \omega\nu B_c(t))$ into the Susceptible class,
- $\nu\omega B_c(t)$ into the Latent class,
- $(1-\omega)(B(t) - B_c(t)) + (1-\omega)B_c(t) = (1-\omega)B(t)$ increment into the the Immune class.

Under the above assumptions, we then describe the spread of Hepatitis B by the system of PDE's as

$$
\begin{aligned}
(\partial_t + \partial_a)S(a,t) &= -\Lambda S(a,t) - \mu S(a,t) \\
S(0,t) &= \omega \int_0^\infty (N(a,t) - \nu C(a,t))\, b(a) da \\
(\partial_t + \partial_a)L(a,t) &= \Lambda S(a,t) - \sigma L(a,t) - \mu L(a,t) \\
L(0,t) &= \nu\omega \int_0^\infty C(a,t) b(a) da \\
(\partial_t + \partial_a)I(a,t) &= \sigma L(a,t) - \gamma_1 I(a,t) - \mu I(a,t) \\
I(0,t) &= 0 \\
(\partial_t + \partial_a)C(a,t) &= q(\Lambda,a)\gamma_1 I(a,t) - \gamma_2 C(a,t) - \mu C(a,t) \\
C(0,t) &= 0 \\
(\partial_t + \partial_a)R(a,t) &= \gamma_2 C(a,t) + (1 - q(\Lambda,a))\gamma_1 I(a,t) - \mu R(a,t) \\
R(0,t) &= (1-\omega) \int_0^\infty N(a,t) b(a) da
\end{aligned}
\tag{6.5}
$$

In matrix form we denote this by,

$$
(\partial_t + \partial_a)X(a,t) = AX(a,t) - \mu(a)X(a,t); \quad X(a,0) = X_0(a), \tag{6.6}
$$

where $X(a,t) = (S(a,t), L(a,t), I(a,t), C(a,t), R(a,t))^T$ and A:=A(a,t) is a continuous matrix valued function.

Consider the fractions of the compartments in the model at age a and time t :

$$
s(a,t) := \frac{S(a,t)}{N(a,t)}, \quad l(a,t) := \frac{L(a,t)}{N(a,t)}, \quad i(a,t) := \frac{I(a,t)}{N(a,t)},
$$
$$
c(a,t) := \frac{C(a,t)}{N(a,t)}, \quad r(a,t) := \frac{R(a,t)}{N(a,t)}
$$

and we also define

$$
p(a,t) = \frac{N(a,t)}{P(t)} \rightarrow \quad p_0(a) = p(a),
$$

i.e., $p(a,t)$ has an asymptotic convergence [Webb 1985, Pruess 1984]

The total population has an exponential growth (we obtain this from the sum of the equations in the system (6.5))

$$
(\partial_t + \partial_a)N(a,t) = -\mu(a)N(a,t)
$$
$$
N(0,t) = \int_0^\infty b(a)N(a,t)da
$$

The projected susceptible population is thus obtained.

$$
\begin{aligned}
(\partial_t + \partial_a)S(a,t)/N(a,t) &= \frac{(\partial_t + \partial_a)S(a,t)}{N(a,t)} - \frac{S(a,t)}{N(a,t)} \frac{(\partial_t + \partial_a)N(a,t)}{N(a,t)} \\
&= \frac{-\Lambda S(a,t) - \mu(a)S(a,t)}{N(a,t)} - \frac{S(a,t)}{N(a,t)} \frac{-\mu(a)N(a,t)}{N(a,t)} \\
(\partial_t + \partial_a)s(a,t) &= -\Lambda s(a,t)
\end{aligned}
$$

Proceeding the same way, we obtain the projected system (6.7), which is independent of population dynamics. The birth rate however appears in the boundary conditions.

Define

$$\hat{b}(a) = \frac{N(a,t)b(a)}{\int_0^\infty N(a,t)b(a)da},$$

the system reads,

$$\begin{aligned}
(\partial_t + \partial_a)s(a,t) &= -\Lambda s(a,t) \\
s(0,t) &= \omega - \omega\nu \int_0^\infty c(a,t)\hat{b}(a)da \\
(\partial_t + \partial_a)l(a,t) &= \Lambda s(a,t) - \sigma l(a,t) \\
l(0,t) &= \nu\omega \int_0^\infty c(a,t)\hat{b}(a)da \\
(\partial_t + \partial_a)i(a,t) &= \sigma l(a,t) - \gamma_1 i(a,t) \\
I(0,t) &= 0 \\
(\partial_t + \partial_a)c(a,t) &= q(\Lambda)\gamma_1 i(a,t) - \gamma_2 c(a,t) \\
c(0,t) &= 0 \\
(\partial_t + \partial_a)r(a,t) &= \gamma_2 c(a,t) + (1 - q(\Lambda))\gamma_1 i(a,t) \\
r(0,t) &= 1 - \omega
\end{aligned} \tag{6.7}$$

6.3 Case without vertical transmission

Vertical transmission characterizes a situation where a fraction of newborns are born positive of the disease, having been infected at birth. In this setting, the parameter ν defines this fraction. If $\nu = 0$, then we do not have vertical transmission. For such a subcase ($\nu = 0$), we know from a general and similar case in [Inaba 1990] that if the initial age distributions are in L^1 and are non-negative, then the solutions exist globally, remain non-negative and stay in L^1. The semi-group methods are used to prove existence of solutions. The case of existence of solutions when vertical transmission exists is also worked out in [Inaba 2006], again using semi-group methods.

6.3.1 Fixed point equation for Λ

The equilibrium dynamics of model (6.7) can be classified using a fixed point equation for the force of infection. The fixed point equation reads,

$$\Lambda = \Lambda G(\Lambda),$$

and its solutions represent the trivial(disease free) or the non-trivial(endemic) equilibriums of the system.

$\Lambda = 0$ corresponds to the trivial solution, while solutions to $1 = G(\Lambda)$ correspond to the endemic equilibrium solutions. Bi-stable scenario occurs when $1 = G(\Lambda)$ has two endemic solutions.

We consider case without vertical transmission ($\nu = 0$). To evaluate $\Lambda(t)$, one needs solutions of $i(a,t)$ and $c(a,t)$. We use model (6.7) at its equilibrium and assume no time dependance,

$$\begin{aligned}
\frac{d}{da}s(a) &= -\Lambda k(a)s(a) \\
s(0) &= \omega \\
\frac{d}{da}l(a) &= \Lambda k(a)s(a) - \sigma l(a) \\
l(0) &= 0 \\
\frac{d}{da}i(a) &= \sigma l(a) - \gamma_1 i(a) \\
i(0) &= 0 \\
\frac{d}{da}c(a) &= q(\Lambda)\gamma_1 i(a) - \gamma_2 c(a) \\
c(0) &= 0 \\
\frac{d}{da}r(a) &= \gamma_2 c(a) + (1 - q(\Lambda))\gamma_1 i(a) \\
r(0) &= 1 - \omega
\end{aligned} \tag{6.8}$$

and

$$\begin{aligned}
\Lambda &= \int_0^\infty \beta(b)\{I(b) + \alpha C(b)\}db/P(t) \\
&= \int_0^\infty \beta(b)\frac{N(a,t)}{P(t)}\{i(b) + \alpha c(b)\}db \\
&= \int_0^\infty p(b)\beta(b)\{i(b) + \alpha c(b)\}db
\end{aligned} \tag{6.9}$$

To evaluate (6.9) for Λ, we make the following convenience transformation on (6.8), $\tilde{l} = l/\Lambda$, $\tilde{i} = i/\Lambda$ and $\tilde{c} = c/\Lambda$, removing Λ dependance in all equations except $s(a)$. Thus,

$$\begin{aligned}
\frac{d}{da}\tilde{l}(a) &= k(a)s(a) - \sigma\tilde{l}(a) \\
\tilde{l}(0) &= 0 \\
\frac{d}{da}\tilde{i}(a) &= \sigma\tilde{l}(a) - \gamma_1\tilde{i}(a) \\
\tilde{i}(0) &= 0 \\
\frac{d}{da}\tilde{c}(a) &= (q_0 + q_1(\Lambda))\gamma_1\tilde{i}(a) - \gamma_2\tilde{c}(a) \\
\tilde{c}(0) &= 0
\end{aligned} \tag{6.10}$$

Remark 6.3.1 *We define the operator* $K_j : L^1_+ \to L^1_+ : \quad j = 1, 2$ *and* $\hat{K}_j : L^1_+ \to \mathbb{R}_+ : \quad j = 1, 2$ *s.t.*

$$\begin{aligned}
x \to K_1[x] &:= \int_0^a \exp\{-\gamma_1(a-\tau_1)\}\,\sigma \int_0^{\tau_1} \exp\{-\sigma(\tau_1-\tau_0)\}\,x(\tau)d\tau_0 d\tau_1 \\
x \to K_2[x] &:= \int_0^a h(a,\tau_2) \int_0^{\tau_2} \exp\{-\gamma_1(\tau_2-\tau_1)\} \int_0^{\tau_1} \exp\{-\sigma(\tau_1-\tau_0)\}\,x(\tau)d\tau_0 d\tau_1 d\tau_2 \\
x \to \hat{K}_1[x] &:= k(a) \int_0^\infty \beta(b)p(b)K_1\left[x(\tau)\right] db \\
x \to \hat{K}_2[x] &:= k(a) \int_0^\infty \alpha\beta(b)p(b)K_2\left[x(\tau)\right] db
\end{aligned}$$

where $h(a,\tau_2) = \exp\{-\gamma_2(a-\tau_2)\}\,\sigma\gamma_1$.

Hence the solutions

$$\begin{aligned}
\tilde{i}(a) &= \omega \int_0^a \exp\{-\gamma_1(a-\tau_1)\}\,\sigma \int_0^{\tau_1} \exp\{-\sigma(\tau_1-\tau_0)\}\exp\{-\Lambda\tau_0\}d\tau_0 d\tau_1 \\
&= \omega K_1[\exp(-\Lambda\tau_0)]
\end{aligned}$$

and

$$\begin{aligned}
\tilde{c}(a) &= \omega q(\Lambda) \int_0^a h(a,\tau_2) \int_0^{\tau_2} \exp\{-\gamma_1(\tau_2-\tau_1)\}\,l(\tau_0,\tau_1)d\tau_1 d\tau_2 \\
&= \omega q(\Lambda) K_2[\exp(-\Lambda\tau_0)]
\end{aligned}$$

where $l(\tau_0,\tau_1) = \int_0^{\tau_1} \exp\{-\sigma(\tau_1-\tau_0)\}\exp\{-\Lambda\tau_0\}d\tau_0$ and replace the solutions in (6.9) to obtain

$$\begin{aligned}
\Lambda &= \Lambda k(a) \int_0^\infty \beta(b)p(b)\left\{\omega K_1[\exp\{-\Lambda\tau_0\}] + \alpha q(\Lambda)\omega K_2[\exp\{-\Lambda\tau_0\}]\right\} db \\
&= \Lambda\left\{\omega\hat{K}_1[\exp\{-\Lambda\tau_0\}] + \alpha q(\Lambda)\omega\hat{K}_2[\exp\{-\Lambda\tau_0\}]\right\} \\
&=: \Lambda G(\Lambda) \qquad (6.11)
\end{aligned}$$

This is the characteristic equation for the force of infection. Any non-negative root Λ of the characteristic equation corresponds to a stationary solution of the epidemic model. There is always a solution $\Lambda = 0$ satisfying (6.11) that corresponds to the trivial solution. In the center of our interest are endemic solutions, that is, solutions $\Lambda \neq 0$. In this case, these are solutions satisfying $G(\Lambda) = 1$ where,

$$G(\Lambda) = \left\{\omega\hat{K}_1[\exp\{-\Lambda\tau_0\}] + \alpha q(\Lambda)\omega\hat{K}_2[\exp\{-\Lambda\tau_0\}]\right\} \qquad (6.12)$$

The fixed point equation defines the next generation operator for the infective population and thus, if we set $\Lambda = 0$, then $G(\Lambda)|_{\Lambda=0}$ is defined as the *Basic Replacement Ratio* if the population is not under vaccination or the *Net Replacement Ratio* if there is vaccination [Thieme 2003]. We consider the following theorem[Thieme 2003, Theorem 22.1, pp350].

Theorem 6.3.1 *If $q(\Lambda)$ is chosen such that $G(\Lambda)$ is unimodal for $\Lambda \in \mathbb{R}+$, then $G(\Lambda)=1$ has two solutions if*

(i) $G(0) < 1$

(ii) $\exists\ \Lambda^* > 0$, *s.t.* $G(\Lambda^*) > 1$.

(iii) $\lim_{\Lambda\to\infty} G(\Lambda) = 0$

Lemma 6.3.2 *For* $\Lambda \in \mathbb{R}_+$,

$$\lim_{\Lambda\to\infty} G(\Lambda) = 0$$

Proof

$$\begin{aligned}\lim_{\Lambda\to\infty} G(\Lambda) &= \lim_{\Lambda\to\infty} \left\{\omega\hat{K}_1[\exp\{-\Lambda\tau_0\}] + \alpha q(\Lambda)\omega\hat{K}_2[\exp\{-\Lambda\tau_0\}]\right\} \\ &= \lim_{\Lambda\to\infty} \left\{\omega\hat{K}_1[\exp\{-\Lambda\tau_0\}]\right\} + \lim_{\Lambda\to\infty} \left\{\alpha q(\Lambda)\omega\hat{K}_2[\exp\{-\Lambda\tau_0\}]\right\} \\ &= 0\end{aligned}$$

This follows as $\hat{K}_i\ \forall\ i = 1, 2$ approaches zero exponentially fast as $\Lambda \to \infty$. This is independent of the form of $q(\Lambda)$.

□

Corollary 6.3.3 *If conditions in theorem (6.3.1) hold, then the model (6.8) has two endemic solutions if*

(i) $\omega\hat{K}_1[1] + \omega q(0)\alpha\hat{K}_2[1] < 1$,

(ii) $\exists\Lambda^* > 0,\ s.t.\ \ q(\Lambda^*) > \frac{(1-G(0))+\omega\hat{K}_1[1-\exp\{-\Lambda^*\tau_0\}]+\omega q(0)\alpha\hat{K}_2[1]}{\omega\alpha\hat{K}_2[1-\exp\{-\Lambda^*\tau_0\}]}$.

Proof
Since,

$$G(\Lambda) = \left\{\omega\hat{K}_1[\exp\{-\Lambda\tau_0\}] + \alpha q(\Lambda)\omega\hat{K}_2[\exp\{-\Lambda\tau_0\}]\right\},$$

then $G(0) < 1$ implies,
$G(0) = \omega\hat{K}_1[1] + \omega q(0)\alpha\hat{K}_2[1] < 1$.
If $\exists\ \Lambda^* > 0$, s.t. $G(\Lambda^*) > 1$, then,

$$G(\Lambda^*) = \left\{\omega\hat{K}_1[\exp\{-\Lambda^*\tau_0\}] + \alpha q(\Lambda^*)\omega\hat{K}_2[\exp\{-\Lambda^*\tau_0\}]\right\} > 1$$

and we obtain the expression of condition (ii) from the expression of $G(\Lambda^*)$.

□

6.4 Case with vertical transmission

We consider the model (6.7) at its equilibrium, when vertical transmission occurs at birth ($\nu \neq 0$), and denote

$$\Omega = \omega\nu \int_0^\infty c(a)\hat{b}(a)da.$$

$$\begin{aligned}
\frac{d}{da}s(a) &= -\Lambda k(a)s(a) \\
s(0) &= \omega - \Omega \\
\frac{d}{da}l(a) &= \Lambda k(a)s(a) - \sigma l(a) \\
l(0) &= \Omega \\
\frac{d}{da}i(a) &= \sigma l(a) - \gamma_1 i(a) \\
i(0) &= 0 \\
\frac{d}{da}c(a) &= q(\Lambda)\gamma_1 i(a) - \gamma_2 c(a) \\
c(0) &= 0 \\
\frac{d}{da}r(a) &= \gamma_2 c(a) + (1-q(\Lambda))\gamma_1 i(a) \\
r(0) &= 1 - \omega
\end{aligned} \tag{6.13}$$

Assume

$$K_3 := \sigma \int_0^a \exp\{-\gamma_1(a-\tau_1)\}\exp\{-\sigma\tau_1\}d\tau_1$$

and

$$K_4 := \gamma_1 \int_0^a \exp\{-\gamma_2(a-\tau_2)\}K_3 d\tau_2.$$

hence the solutions

$$\begin{aligned}
\tilde{i}(a) &= \int_0^a h(a,\tau_1)\left\{\Omega\exp\{-\sigma\tau_1\} + (\omega-\Omega)\int_0^{\tau_1}\exp\{-\sigma(\tau_1-\tau_0)\}\exp\{-\Lambda\tau_0\}d\tau_0\right\}d\tau_1 \\
&= \Omega K_3 + (\omega-\Omega)K_1[\exp(-\Lambda\tau_0)]
\end{aligned}$$

where

$h(a,\tau_1) = \exp\{-\gamma_1(a-\tau_1)\}\sigma$

and

$$\begin{aligned}
\tilde{c}(a) &= \gamma_1 q(\Lambda)\int_0^a \exp\{-\gamma_2(a-\tau_2)\}\tilde{i}(\tau_2)d\tau_2 \\
&= \Omega q(\Lambda)K_4 + (\omega-\Omega)q(\Lambda)K_2[\exp(-\Lambda\tau_0)]
\end{aligned}$$

Thus,

$$\begin{aligned}\Lambda &= \Lambda k(a)\int_0^\infty \beta(b)p(b)\left(\Omega K_3+(\omega-\Omega)K_1[\exp(-\Lambda\tau_0)]\right)db\\ &\quad +\Lambda k(a)\int_0^\infty \beta(b)p(b)\left(\alpha\Omega q(\Lambda)K_4+(\omega-\Omega)q(\Lambda)K_2[\exp(-\Lambda\tau_0)]\right)db\\ &= \Lambda\omega\left\{\hat{K}_1[\exp\{-\Lambda\tau_0\}]+\alpha q(\Lambda)\hat{K}_2[\exp\{-\Lambda\tau_0\}]\right\}\\ &\quad +\Lambda\Omega\left\{\hat{K}_3-\hat{K}_1[\exp\{-\Lambda\tau_0\}]+\alpha q(\Lambda)\left(\hat{K}_4-\hat{K}_2[\exp\{-\Lambda\tau_0\}]\right)\right\}\end{aligned} \tag{6.14}$$

However, we have additional information in

$$\begin{aligned}\Omega &= \omega\nu\int_0^\infty c(a)\hat{b}(a)da\\ &= \Lambda\omega\nu\int_0^\infty\left(\Omega q(\Lambda)K_4+(\omega-\Omega)q(\Lambda)K_2[\exp(-\Lambda\tau_0)]\right)\hat{b}(a)da\\ &= \Lambda\Omega\omega\nu q(\Lambda)K_5+\Lambda\omega\nu(\omega-\Omega)q(\Lambda)K_6[\exp(-\Lambda\tau_0)]\\ &= \Lambda\Omega\omega\nu q(\Lambda)\left\{K_5-K_6[\exp(-\Lambda\tau_0)]\right\}+\Lambda\omega^2\nu q(\Lambda)K_6[\exp(-\Lambda\tau_0)]\end{aligned} \tag{6.15}$$

where

$$K_5 := \int_0^\infty K_4\hat{b}(a)da$$

and

$$K_6 := \int_0^\infty K_2[\exp(-\Lambda\tau_0)]\hat{b}(a)da.$$

6.4.1 Fixed point equation for Λ

We now have a two dimensional case fixed point equation, with Λ and the new variable Ω. From (6.14) and (6.15), we form an eigenvalue problem,

$$\begin{pmatrix}\Lambda\\ \Omega\end{pmatrix} = A(\Lambda)\begin{pmatrix}\Lambda\\ \Omega\end{pmatrix} \tag{6.16}$$

where

$$A(\Lambda) = \begin{bmatrix}a_{11} & a_{12}\\ a_{21} & a_{22}\end{bmatrix}$$

$$a_{11} = \omega\left\{\hat{K}_1[\exp\{-\Lambda\tau_0\}]+\alpha q(\Lambda)\hat{K}_2[\exp\{-\Lambda\tau_0\}]\right\}$$

$$a_{12} = \Lambda\left\{\hat{K}_3-\hat{K}_1[\exp\{-\Lambda\tau_0\}]+\alpha q(\Lambda)\left(\hat{K}_4-\hat{K}_2[\exp\{-\Lambda\tau_0\}]\right)\right\}$$

$$a_{21} = \omega^2\nu q(\Lambda)K_6[\exp(-\Lambda\tau_0)]$$

$$a_{22} = \Lambda\omega\nu q(\Lambda)\left\{K_5-K_6[\exp(-\Lambda\tau_0)]\right\}$$

The eigen value problem (6.16) has a feasible solution (Λ^*, Ω^*) which corresponds to the eigen value 1.

Proposition 6.4.1 *If* $\Lambda \in \mathbb{R}_+$, *then* Ω *is well defined and positive for all parameters.*

Proof:

Consider two extreme cases of the model (6.13), one for which all newborns are disease free, and another in which all newborns are infected by disease. We also consider $S(a) + l(a) + i(a) + c(a) + r(a) = 1$, hence ignore the equation for $r(a)$. All the components $x = (s, l, i, c, r)^T$ of the system (6.13) are positive, i.e., $x(a) \geq 0$.

Case 1: Suppose $\omega - \Omega = 1$, all newborns enter susceptible class. Then $\Omega = 0$.

$$\begin{aligned}
\frac{d}{da}s_0(a) &= -\Lambda k(a)s_0(a) \\
s_0(0) &= 1 \\
\frac{d}{da}l_0(a) &= \Lambda k(a)s_0(a) - \sigma l_0(a) \\
l_0(0) &= 0 \\
\frac{d}{da}i_0(a) &= \sigma l_0(a) - \gamma_1 i_0(a) \\
i_0(0) &= 0 \\
\frac{d}{da}c_0(a) &= q(\Lambda)\gamma_1 i_0(a) - \gamma_2 c_0(a) \\
c_0(0) &= 0
\end{aligned} \tag{6.17}$$

Case 2: Suppose $\Omega = 1$ and $\omega - \Omega = 0$. All newborns enter the latent class,

$$\begin{aligned}
\frac{d}{da}s_1(a) &= -\Lambda k(a)s_1(a) \\
s_1(0) &= 0 \\
\frac{d}{da}l_1(a) &= \Lambda k(a)s_1(a) - \sigma l_1(a) \\
l_1(0) &= 1 \\
\frac{d}{da}i_1(a) &= \sigma l_1(a) - \gamma_1 i_1(a) \\
i_1(0) &= 0 \\
\frac{d}{da}c_1(a) &= q(\Lambda)\gamma_1 i_1(a) - \gamma_2 c_1(a) \\
c_1(0) &= 0
\end{aligned} \tag{6.18}$$

The general equation is given by

$$x = x_0(\omega - \Omega) + \Omega x_1$$

for all the components $x = (s, l, i, c, r)^T$. For example, if $\Omega = 0$ and $\omega - \Omega = 1$, then $x = x_0$. Similarly, if $\Omega = 1$ and $\omega - \Omega = 0$, then $x = x_1$.

Considering the equation for Ω,

$$\begin{aligned}\Omega &= \omega\nu \int_0^\infty c(a)\hat{b}(a)da \\ &= \omega\nu \int_0^\infty \{c_0(a)(\omega - \Omega) + \Omega c_1(a)\}\hat{b}(a)da \\ &= \frac{\omega^2\nu \int_0^\infty c_0(a)\hat{b}(a)da}{1 + \omega\nu \int_0^\infty (c_0(a) - c_1(a))\hat{b}(a)da} \end{aligned} \tag{6.19}$$

The numerator in (6.19) is positive, but we however need to investigate the denominator. If $0 \leq c_0(a), c_1(a) \leq 1, \quad c_0(a) \geq 0,$ we have $c_0(a) - c_1(a) > -c_1(a) > -1$. Hence, for $c_1(a) \leq 1$,

$$\begin{aligned} 1 + \omega\nu \int_0^\infty (c_0(a) - c_1(a))\hat{b}(a)da &\geq 1 - \omega\nu \int_0^\infty c_1(a)\hat{b}(a)da \\ &\geq 1 - \omega\nu \int_0^\infty \hat{b}(a)da \\ &= 1 - \omega\nu; \quad \int_0^\infty \hat{b}(a)da = 1. \\ &\geq 0 \end{aligned}$$

Hence Ω is positive and well defined over all parameter values.

□

Remark 6.4.1 *From lemma (6.3.2), we know that*

$$\lim_{\Lambda\to\infty} G(\Lambda) = 0,$$

hence

$$\lim_{\Lambda\to\infty} G_1(\Lambda) = \lim_{\Lambda\to\infty} \left\{ G(\Lambda) \left\{ 1 - \frac{\Omega}{\omega} \right\} + \frac{\Omega}{\Lambda} A \right\} = 0.$$

Proposition 6.4.2 Bi-stability. *Consider the eigen value problem (6.16).* $\Lambda = 0$ *satisfies the eigen value problem and corresponds to a trivial solution of model (6.7). Otherwise, there exists an equation* $G_1(\Lambda) = 1$ *defined by equation (6.21) whose solutions corresponds to a non-trivial solution of model (6.7).* $G_1(\Lambda) = 1$, *can only have more than one non-trivial solution if* $\omega - \Omega$ *is increasing in* Λ *and* $G_1(\Lambda) = 1$ *satisfies conditions of* $G(\Lambda) = 1$ *in theorem (6.3.1)*

Proof:

Suppose $G_1(\lambda)1$ statisfies conditions of theorem (6.3.1), then two non-trivial solutions can occur. We proceed to prove that if $\omega - \Omega$ is decreasing, then we can only have one non-trivial (endemic) solution utmost.

$$\begin{aligned}
\Lambda &= \int_0^\infty p(b)\beta(b)(i(b)+\alpha c(b))db \\
&= \int_0^\infty p(b)\beta(b)(\omega i_0(b)+\Omega(i_0(b)-i_0(b))+\alpha\omega c_o(b)+\alpha\Omega(c_0(b)-c_0(b))db \\
&= \int_0^\infty p(b)\beta(b)\{(\omega(i_0(b)+\alpha c_0(b))+\Omega[(i_0(b)-i_1(b))+\alpha(c_0(b)-c_1(b))]\}db \\
&= \int_0^\infty p(b)\beta(b)(\omega(i_0(b)+\alpha c_0(b))db+\Omega\int_0^\infty p(b)\beta(b)[(i_0(b)-i_1(b))+\alpha(c_0(b)-c_1(b))]db \\
&= \Lambda G(\Lambda) \\
&\quad +\frac{\omega^2\nu\int_0^\infty c_0(a)\hat{b}(a)da}{1+\omega\nu\int_0^\infty(c_0(a)-c_1(a))\hat{b}(a)da}\int_0^\infty p(b)\beta(b)[(i_0(b)-i_1(b))+\alpha(c_0(b)-c_1(b))]db \\
&= \Lambda G(\Lambda)-\frac{\omega}{1+\frac{(1-\omega\nu)+\omega\nu\int_0^\infty(1-c_1(a))\hat{b}(a)da}{\omega\nu\int_0^\infty c_0(a)\hat{b}(a)da}}(\Lambda G(\Lambda)/\omega-A) \qquad (6.20)
\end{aligned}$$

The fixed point equation (6.20) has a solution $\Lambda = 0$ or solutions Λ_i^* satisfying,

$$1 = G(\Lambda)\left\{1-\frac{\Omega}{\omega}\right\}+\frac{\Omega}{\Lambda}A := G_1(\Lambda) \qquad (6.21)$$

where

$$G(\Lambda) = \int_0^\infty p(b)\beta(b)(\omega(i_0(b)+\alpha c_0(b))db$$

$$\frac{\Omega}{\Lambda} = \frac{\omega}{\Lambda+\frac{(1-\omega\nu)+\omega\nu\int_0^\infty(1-c_1(a))\hat{b}(a)da}{\omega\nu\int_0^\infty\tilde{c}_0(a)\hat{b}(a)da}}$$

and

$$A = \int_0^\infty p(b)\beta(b)\{i_1(b)+c_1(b)\}db.$$

Note that $\tilde{c}_0(a)$ is monotonously decreasing in Λ and $c_1(a)$ does not depend on Λ. Hence Ω/Λ is decreasing in Λ.

If $q(\Lambda)$ independent of Λ, then $G(\Lambda)$ is monotonously decreasing in Λ.

$G_1(\Lambda) = 1$ has two solutions if

$$1-\frac{\Omega}{\omega} = \frac{\omega-\Omega}{\omega}$$

is increasing in Λ. □

We therefore reach the following conclusion. An increasing $(\omega - \Omega)$ implies an increase in the newborns who join the susceptible class. If we limit the increase in $(\omega - \Omega)$, then we reduce the possibility of two non-trivial solutions and by implication, no chances of bistable scenario. The possibility of reducing entry into susceptible class is through mass infant vaccination. In epidemiological terms, reducing the size of the susceptible class or entry into the susceptible class implies in the long run, that we will have reduced the numbers of individuals who can get infected (and hence individual who develop carriage) in the population.

The phenomenon of bi-stability for Hepatitis B model has been studied by Medley [Medley 2001] in a model without age structure. Medley [Medley 2001] observes that hyper-endemic populations, with high carrier prevalence are likely to exhibit bi-stable dynamics. We try to extend his arguments to an age structured model to further observe the causes of bi-stability. We note in the case when no vertical transmission is present in the model ($\nu = 0$), that $q(\Lambda)$ which represents the probability of infected individuals moving on to carrier state, is solely responsible for possible occurrence of bi-stability. If $q(\Lambda)$ does not depend on Λ, then bi-stability cannot occur as the equation $G(\Lambda) = 1$ can have only one solution in the maximum.

In line with results in literature and our results from the case without vertical transmission, we intended to show that even in the case with vertical transmission, bi-stability may result from effect of an additional force of infection, such as the situation caused by presence of carriers in Hepatitis B transmission. However, results for the case with vertical transmission show that other than just the role of carriers, the number of susceptibles in a population also plays a significant role. The arguments are complimentary and not contradictory.

Chapter 7

Discussion and Prospects.

Section A.

Stability analysis for periodic driven systems is done using standard tool of Floqúet theory. The averaging behavior that characterizes stability in the case of Floqúet theory, may be its shortcoming in dealing with childhood related diseases. Most childhood related diseases such as measles have short span of outbreaks, some outbreaks small especially in the post vaccination era and availability of treatment. We conjecture that stability analysis that returns an instantaneous stability criterion is more useful for control of childhood diseases than the orbital stability criterion. We show this through the simulations at the end of the first section.

We note some prospects of research based on this work:

(1) The work in this section involved an analysis of an SIR model with vaccination in periodic settings. The analysis was carried out on a manifold $I(t) = 0$. This scenario is true for the developed world where most childhood diseases are almost extinct or affect a very small population of people if at all. A measles epidemic would not affect more than 100 individuals before it is controlled. The scenario is different in a developing country; this assumption would not be realistic. It requires assuming an infective population that is non-zero, at least at an initial time.

(2) The optimal control problems were derived from Stability analysis conditions. The idea is that a successful vaccination campaign should ensure the disease is minimized or eradicated in a population. This is equivalent to the stability of the disease free state. Hence we derived conditions for stability of the disease free state, and used these conditions to define optimal control problems for vaccination. The technique we used to solve the control problems involved deriving a set of solutions($\mathfrak{S}$) that guarantees existence of optimal solutions. Since the set has infinitely many solutions, we derived candidate optimal solution strategies that belong to this set of solutions.

The optimal control problem derived from Orbital stability turns out to be a fine classical optimal control problem, "A Pontryagin Maximum Principle Optimal control problem with a singular arc with infinite local order." We did not tackle the problem fully in this direction and hence, one would wish to go

further using any classical techniques of handling such problems available in literature.

The optimal control problems derived from the instantaneous stability case does not fit into the classical methods as it involves controlling a supremum of a function. It would require certain modifications on the problem to fit it into any classical form, hence seek optimal solutions using classical techniques.

Section B.

The phenomenon of bi-stability for Hepatitis B model has been observed by Medley[Medley 2001] in a model without age structure. The main result in Medley's paper is that hyper-endemic populations, with high carrier prevalence are likely to exhibit bi-stable dynamics. This results concur with our case for a scenario when no vertical transmission is present in the model($\nu = 0$). We observe that if the probability of development of carriage $q(\Lambda)$ does not depend on force of infection Λ, then $G(\Lambda) = 1$ has only one solution in the maximum, implying no bi-stability.

In line with these results, we chose, in the case when vertical transmission is allowed for, to prove the following conjecture:

Remark 7.0.2 conjecture *Bi-stability can only be realized in the model when there is an additional influence of force of infection at later steps of disease progression other than at the first step of contact between susceptible and infected individuals. We expected that,*

1. *If $q(\Lambda(t))$:=the rate of development of carriers, does not depend on force of infection $\Lambda(t)$, then we cannot have a bi-stable scenario.*

2. *We conjecture that there is a Λ-dependent function $q(\Lambda)$ that leads to multiple equilibria.*

3. *Vertical transmission helps to reinforce the occurrence of a bi-stable condition.*

The proof is not complete with similar results. We however found out that $\omega - \Omega$ which is a boundary condition into the susceptible class, plays the key role in bi-stability.

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