Transmission Dynamics of an Infectious Disease with Treatment

by

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Abstract

In an infectious disease with a long infectious period (which can be the entire life for some diseases), the infectivity of individuals may change due to different reasons. For example, infected individuals may receive treatment and their level of infectivity can reduce depending on the efficacy of the treatment. Or, infected individuals may change their behaviour and reduce their activity once the disease is diagnosed, leading to a reduction of their infectivity. Treated individuals may stop getting treatment, and return to the infective class at a rate depending on how long they have been receiving treatment.

In this thesis, a compartmental model consisting of three compartments (susceptibles, infectives and treated infectives) is formulated to study the effect of treatment on the transmission dynamics of a disease. Continuous and discrete treatment-age-structured models are derived and the asymptotic behaviour of the system is studied and the basic reproduction number is determined.

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Contents

List of Tables

Chapter 1

Introduction

"Prevention is the most important application of epidemiology and epidemiology is the principal pillar of prevention."[10]

Epidemiologists divide preventive strategies into two groups: reducing *risk factors*[1] and preventive treatments. Examples of reducing risk factors include: increasing hygiene standards, for example in tuberculosis, providing unpolluted resources when there is an environmental reservoir, for instance in cholera and controlling the infective agents (vectors), for example mosquitoes in malaria [10]. Immunization is one of the most effective preventive treatments to control the spread of infectious diseases. This can be done through vaccination and in this case, the efficacy of the vaccine is an important factor. The disease transmission is affected by a reduction in the incidence of the infectious disease. Preventive (drug) treatments are used when there is no vaccine available and in some cases they have both preventive and curative effects (drug treatments in malaria [10] and antiviral treatment in influenza [1]).

[1] A variable associated with an increased risk of disease or infection

On the other hand, some curative treatments have indirect preventive effects and they influence the transmission of infectious diseases. These effects are similar to that of vaccination and they reduce the incidence of the disease, so the efficacy of treatment plays an important role. In particular, in the absence of vaccine the preventive effects of treatments can be remarkable. For example, Highly Active Antiretroviral Therapy (HAART) has become a preventive strategy to control HIV, because of its effects on reducing the transmission of HIV, in addition to the reduction of the mortality (see [14, 18] and references therin).

Considering the important role of treatment in transmission dynamics of infectious diseases, mathematical modellers have studied the effect of treatment in various ways [1, 4, 8, 11, 14, 18, 20, 21]. In some models, treated individuals are assumed to be partially recovered, i.e., a fraction of treated population recover with immunity and the others return to the infective compartment but it is assumed that treated individuals can not infect the others [1]. Some models assume a reduced infectivity for treated individuals [4]. A number of models are developed to study the treatment effects for specific diseases such as HIV/AIDS [14] and HCV [11].

The aim of this thesis is to study the effect of treatment in an SI model where the infective individuals remain infectious for the rest of their life for example HIV/AIDS. We assume that the *infectivity* of treated individuals is reduced depending on how long they have been receiving treatment, and by *infectivity* we mean “the probability of transmission given a contact between a susceptible and an infective individual” [6]. The idea is similar to the model studied by Hyman and Li in [8], where they have considered an infection-age structured model with treatment and assuming that the activity level and the infectivity of infected population depend on the age of infection. Here we assume that the infectiousness of infective individuals who are not getting treatment is a constant and it varies when they start getting treatment. We also suppose that the treated individuals may stop getting treatment and return to the infective class at a rate that depends on the age of treatment. The emphasis of this model is on studying the positive effect of treatment (efficacy and duration) and the negative effect of interrupting the treatment on reducing the incidence of an infectious disease. The model is formulated and analysed with both continuous and discrete age of treatment structure. For the continuous case, different approaches are used and some results on stability of the disease free equilibrium point are given. In the discrete case, the local and global stability of the disease free equilibrium point and the existence of the endemic equilibrium point are discussed.

The thesis organization is as follows: Chapter 2 covers the basic theory of ordinary and delay differential equations and some results in mathematical epidemiology; in Chapter 3, the model is formulated and justified using several approaches; Chapter 4 is dedicated to the analysis of the model including the local stability of the disease free equilibrium point and derivation of the threshold value, the basic reproduction number; a discrete age-structured model is formulated in Chapter 5 and the local and global stability analysis are given; Chapter 6 summarises previous chapters and gives concluding remarks.

Chapter 2

Preliminaries

2.1 Mathematical Preliminaries

The essential mathematical tools used in this thesis are presented in this section. Some basic theory of ordinary (ODE) and delay differential equations (DDE) including the fundamental theorem of existence and uniqueness, the flow defined by ODE's and DDE's and the local stability of equilibrium points are given.

2.1.1 Ordinary Differential Equations

Throughout this section, E is an open subset of $\mathbb{R}^n$, $x_0 \in E$ is given and $f : E \to \mathbb{R}^n$ is a vector field on E. The proof of theorems of this section can be found in [12].

Autonomous ODE's An autonomous system of ordinary differential equations is given by

$$x'(t) = f(x(t)), \tag{2.1}$$

where $f : E \to \mathbb{R}^n$ does not depend explicitly on t. If the vector field $f = (f_1, \cdots, f_n)$ is differentiable at x_0, then the derivative of f at x_0 is a linear operator defined by

$$Df = [\frac{\partial f_i}{\partial x_j}], \tag{2.2}$$

which is called the *Jacobian matrix*.

Assume the initial time $t_0 = 0$ and suppose I is an interval containing 0. The following system is called an *initial value problem (IVP)*:

$$x'(t) = f(x(t)), \tag{2.3a}$$

$$x(0) = x_0. \tag{2.3b}$$

Definition 2.1. *Consider System* (2.1) *and let f be continuous. Then $x(t)$ is a solution of* (2.1) *on I if it satisfies $x'(t) = f(x(t))$ for all $t \in I$. $x(t)$ is a solution to the IVP* (2.3) *if it satisfies $x(0) = x_0$.*

We need the following definition to state the fundamental theorem of existence and uniqueness.

Definition 2.2. *$f : E \to \mathbb{R}^n$ is said to satisfy a* Lipschitz condition *on E if there exists a constant $K \geq 0$ such that*

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

for all $x, y \in E$. f is said to satisfy a locally Lipschitz condition *if for all $x_0 \in E$ there* *exist δ and $K_0 \geq 0$ such that*

$$|f(x) - f(y)| \leq K_0|x - y|$$

for all $x, y \in N(x_0, \delta)$, a neighbourhood of x_0 of size δ.

Remark 2.1. *If $f \in C^1(E)$, then f is Lipschitz on E.*

Theorem 2.2. *(Fundamental Theorem of Existence and Uniqueness) Let $f \in C^1(E)$, then there exists $a > 0$ such that the IVP (2.3) has a unique solution on $I = [-a, a]$.*

Consider the initial value problem (2.3). Let f be continuously differentiable on E and let $\Phi(t, x_0)$ be the solution of (2.3) defined on its maximal interval of existence I. The flow of (2.3) is defined by

$$\Phi_t(x_0) = \Phi(t, x_0), \quad \text{for all} \quad t \geq 0.$$

The flow of (2.3) satisfies the following properties:

- $\Phi_0(x) = x, \quad \forall x \in E$;
- $\Phi_s(\Phi_t(x)) = \Phi_{s+t}(x)$ for all $s, t \in \mathbb{R}_+$;
- $\Phi_{-t}(\Phi_t(x)) = x$.

A fixed point of the flow Φ_t defined by (2.3) is a point $x^* \in \mathbb{R}^n$ such that $\Phi_t(x^*) = x^*$ for all $t \geq 0$.

Definition 2.3. *The point $x^* \in \mathbb{R}^n$ is called an* equilibrium point *of (2.1) if $f(x^*) = 0$, i.e., x^* is a fixed point of the flow of (2.1).*

In the rest of this section, we assume that $x^* = 0$, since $0 \neq x^* \in \mathbb{R}^n$ is an equilibrium point of (2.1) if and only if $y^* = 0$ is the equilibrium point of the following system:

$$y'(t) = f(y(t))$$

where $y(t) = x(t) - x^*$.

In the theory of ordinary differential equations, x^* is called a *stable* equilibrium point if the solutions with an initial value near the origin stay close to it, as time goes to infinity, and it is called *asymptotically stable* if it is stable and the solutions approach to x^*. The mathematical definition is given below.

Definition 2.4. *Suppose $x^* = 0$ is an equilibrium point of equation (2.1).*

- *The point $x^* = 0$ is* stable *if for any $\epsilon > 0$, there is $\delta = \delta(\epsilon) > 0$ such that*

$$\forall x_0 \in E, \quad |x_0| < \delta \Longrightarrow |x(t)| < \epsilon, \quad \forall t > 0.$$

- *The point $x^* = 0$ is* asymptotically stable *if it is stable and* "attractive"*, i.e., there exists $\delta > 0$ such that*

$$|x_0| < \delta \Rightarrow |x(t)| \to 0 \quad as \quad t \to \infty.$$

Let $U \subseteq E$ be the set of all initial values $x_0 \in \mathbb{R}^n$ such that the solution of the IVP (2.3) exists and converges to $x^* = 0$. If $U \neq E$, then $x^* = 0$ is *locally asymptotically stable* (LAS) and if $U = E$, it is called *globally asymptotically stable* (GAS) with respect to E.

Linearization Principle One way to study the asymptotic behaviour of System (2.1), is the local analysis of the system near the equilibrium points. Let $f(0) = 0$ and consider the linear system

$$x'(t) = Ax(t), \tag{2.4}$$

where $A = Df(0)$ is the Jacobian matrix of f evaluated at 0, defined in (2.2).

Theorem 2.3. *Consider the linear system* (2.4). *The equilibrium point* $x^* = 0$ *is locally asymptotically stable if all eigenvalues of* A *have negative real part, and unstable if there is an eigenvalue with positive real part.*

The following theorem shows that the behaviour of system (2.1) near $x^* = 0$ is determined by the behaviour of the linear system (2.4).

Theorem 2.4. *(Hartman-Grobman) Let* f *be a* C^1 *vector field on* E *containing the origin, and* Φ_t *be the flow generated by System* (2.1). *Let* $x^* = 0$ *be the equilibrium point of* (2.1) *and assume all eigenvalues of* $A = Df(0)$ *have non zero real part. Then there exist open sets* V *and* W *containing the origin and a homeomorphism* $h : V \to W$ *that maps trajectories of* (2.1) *close to the origin to trajectories of* (2.4) *near the origin, preserving the parametrization, i.e., for all* $x_0 \in V$, *there exists an open interval* I_0 *containing zero such that*

$$h \circ \Phi_t(x_0) = e^{At}h(x_0), \quad \forall x_0 \in V, t \in I_0,$$

where

$$e^{At} = \sum_{k=0}^{\infty} \frac{(At)^k}{k!}.$$

The system (2.4) is called the *linearization* of system (2.1) about the equilibrium point $x^* = 0$.

2.1.2 Delay Differential Equations

Proofs of theorems throughout this section can be found in [7].

Delay differential equations are a type of functional differential equations where the evolution of the system depends not only on the current state of the system but also on its past history.

A delay differential equation can be written as

$$x'(t) = f(x(t), x(t-\tau))$$

for a single, discrete delay $\tau \in \mathbb{R}_+$,

$$x'(t) = f(x(t), x(t-\tau_1), \ldots, x(t-\tau_n))$$

for multiple delays $\tau_1, \ldots, \tau_n \in \mathbb{R}_+$, and

$$x'(t) = f\left(x(t), \int_{t-\tau}^{t} x(s)ds\right)$$

for a distributed (or continuous) delay, where $\tau \in \mathbb{R}_+$.

Let $\tau \geq 0$ be given and $C := C([-\tau, 0], \mathbb{R}^n)$ be the Banach space of continuous functions on the closed interval $[-\tau, 0]$ with the supremum norm $\|\phi\| = \sup\limits_{-\tau\leq\theta\leq 0} |\phi(\theta)|$. For $\alpha > 0$ and $t_0 \in \mathbb{R}$, let $x : [t_0 - \tau, t_0 + \alpha] \to \mathbb{R}^n$ be continuous. For $t \in [t_0, t_0 + \alpha)$, let $x_t \in C$ be defined by

$$x_t(\theta) = x(t+\theta), \quad t \in [t_0, t_0 + \alpha). \tag{2.5}$$

Using this notation, a delay differential equation can be written as

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

Example 2.5. *Consider the following equation*

$$x'(t) = ax(t) + bx(t - \tau)$$

where $a, b \in \mathbb{R}$ are constants. This equation can be written as follows

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

where $f : C \to \mathbb{R}$ is a continuous function defined by

$$f(\phi) = a\phi(0) + b\phi(-\tau).$$

In the rest of this section the initial time t_0 is assumed to be zero, unless otherwise stated.

Definition 2.5. *An initial value problem (IVP) of a delay differential equation is given by the following relation*

$$x'(t) = f(x_t), \quad t \geq 0, \tag{2.6a}$$

$$x_0 = \phi \in C. \tag{2.6b}$$

A solution on $[0, \alpha]$ is a continuous function $x : [-\tau, \alpha] \to \mathbb{R}^n$ such that $x : [0, \alpha] \to \mathbb{R}^n$ is differentiable and satisfies equation (2.6a).

The function $\phi \in C$ in the above IVP is called the initial data, corresponding to the initial value in ordinary differential equations. Since, in a system of delay differential equations, the rate of change of the system depends on the state of the system at previous times, the initial value $x(0)$ does not provide enough information to study the IVP. So we need to know the values of x on the interval $[-\tau, 0]$.

Remark 2.6. *The function $x : [-\tau, \alpha] \to \mathbb{R}^n$ is a solution of the IVP* (2.6) *if it satisfies the following integral equation*

$$x(t) = \phi(0) + \int_0^t f(x_s)ds.$$

Proof. Assume $x : [-\tau, \alpha] \to \mathbb{R}^n$ satisfies the equation (2.6); integrating both sides of the equation from 0 to t, we have

$$\begin{aligned} \int_0^t x'(s)ds = \int_0^t f(x_s)ds \Leftrightarrow x(t) - x(0) &= \int_0^t f(x_s)ds \\ \Leftrightarrow x(t) &= \phi(0) + \int_0^t f(x_s)ds. \end{aligned}$$

Conversely, if $x(t)$ satisfies the above integral equation, differentiating both sides, we will get equation (2.6). □

If $\tau = 0$ in (2.6), then we have the ordinary differential equation $x'(t) = f(x)$ and the initial data ϕ will be the initial value for the ODE. The following example illustrates a simple delay differential equation and connects the concepts here to the corresponding concepts in ODE.

Example 2.7 (Delayed Negative Feedback)**.** *Consider the equation*

$$\begin{aligned} x'(t) &= -x(t-\tau), \\ x_0 &= 1. \end{aligned} \tag{2.7}$$

With the notation in (2.5)*, the above equation can be written as*

$$x'(t) = -x_t(-\tau),$$
$$x_0(\theta) = 1, \quad -\tau \leq \theta \leq 0.$$

For $0 \leq t \leq \tau$*, we have* $-\tau \leq t - \tau \leq 0$ *and therefore* $x'(t) = -x(t-\tau) = -1$ *which is an ODE with initial value* $x(0) = 1$*. Solving this ODE we get*

$$x(t) = 1 - t, \quad 0 \leq t \leq \tau.$$

For $\tau \leq t \leq 2\tau$*, we solve the equation* $x'(t) = -x(t-\tau) = -(1-(t-\tau))$ *and we get*

$$\begin{aligned} x(t) &= x(\tau) + \int_\tau^t -(1-(s-\tau))ds \\ &= 1 - t + \frac{(t-\tau)^2}{2}, \quad \tau \leq t \leq 2\tau, \end{aligned}$$

and for $(n-1)\tau \leq t \leq n\tau$ *we get the following*

$$x(t) = 1 + \sum_{k=1}^{n} (-1)^k \frac{[t-(k-1)\tau]^k}{k!}.$$

Numerical simulations of this solution shows that for a small delay ($\tau = 0.25$*) the solution is close to the solution of the ODE* $x'(t) = -x(t)$ *with the initial value* $x(0) = 1$*. For values greater than* e^{-1} *the behavior is very different compared to the ODE and the solution oscillates [15].*

The method used in this example is called the *method of steps.* It can be shown that $x(t)$ is C^0 on $(-\tau, \infty)$, C^1 on $(0, \infty)$ and C^n on $((n-1)\tau, \infty)$, thus $x(t)$ is getting smoother on each step.

Existence, Uniqueness, Continuation and Continuous Dependence

The fundamental theorem of delay differential equations states that continuity of the function $f : C \to \mathbb{R}^n$ is enough to have existence of the solution to the IVP (2.6) and gives a necessary condition for uniqueness of the solution. First we state the definition of a *locally Lipschitz* operator on C, which is similar to the Definition 2.2.

Definition 2.6. *The function $f : C \to \mathbb{R}^n$ is* locally Lipschitz *if for all $\phi \in C$, there exist $\delta > 0$ and $M > 0$ such that*

$$|f(\phi) - f(\psi)| \leq M\|\phi - \psi\|$$

for all $\psi \in C$ with $\|\phi - \psi\| < \delta$.

Definition 2.7. *Let X and Y be Banach spaces. The function $f : X \to Y$ is called* completely continuous *if f is continuous and $f(X) \subseteq Y$ is precompact, i.e., $\overline{f(X)}$ is compact.*

Theorem 2.8 (Schauder's Fixed Point Theorem)**.** *If X is a convex and closed subset of a Banach space B and $T : X \to X$ is completely continuous, then T has a fixed point in X.*

Theorem 2.9. *Assume $f : C \to \mathbb{R}^n$ is continuous:*

(i) Existence: for any $\phi \in C$ the IVP

$$\begin{aligned} x'(t) &= f(x_t), \\ x_0 &= \phi, \end{aligned} \tag{2.8}$$

has a solution on $[-\tau, \alpha]$ for $\alpha > 0$;

(ii) Uniqueness: if $f : C \to \mathbb{R}^n$ is locally Lipschitz, then the solution is unique on $[-\tau, \alpha]$;

(iii) Continuation: if we further assume that f maps bounded sets in C to the bounded sets in $\mathbb{R}^n$, then we either have $\alpha = \infty$ or $\lim_{t \to \alpha^-} |x(t)| = \infty$;

(iv) Continuous dependence: $x_t^{(\phi)}$, the state of system with the initial data ϕ and at time t, is continuous with respect to all variables (t, ϕ) that is: for all $\phi \in C$, if $[-\tau, \alpha)$ is the maximal interval of existence of the solution x^ϕ, then for all $\epsilon > 0$, $\alpha^* \in (0, \alpha)$, there exists $\delta > 0$ such that for all $\phi^* \in C$ with $\|\phi^* - \phi\| < \delta$, the solution x^{ϕ^*} exists on $[-\tau, \alpha)$ and for all $t, \tilde{t} \in [0, \alpha^*]$ with $|t - \tilde{t}| < \delta$ we have $\|x_{\tilde{t}}^{\phi^*} - x_t^\phi\| < \epsilon$.

Solution Semiflow and Dynamical System Property

Consider the IVP (2.6). For every $\phi \in C$, let x^ϕ be the solution through ϕ. Assume $f : C \to \mathbb{R}^n$ is completely continuous and satisfies enough smoothness conditions so that the solution $x^\phi(t)$ is continuous with respect to (ϕ, t). As ordinary differential equations define a dynamical system on $\mathbb{R}^n$, a delay differential equation generates a dynamical system on the function space C. The state of the system associated to the equation (2.6) at time $t \geq 0$ is the function $x_t^\phi \in C$.

Definition 2.8. *Assume that the solution $x^\phi : [-\tau, \infty) \to \mathbb{R}^n$ of the IVP (2.6) exists for all $t \geq 0$. Define $\Phi : [0, \infty) \times C \to C$ by the following relation*

$$\Phi(t, \phi) = x_t^\phi.$$

Φ is called a semi-flow on C and satisfies the following properties:

(a) Φ is continuous;

(b) $\Phi(0, \phi) = \varphi$*;*

(c) $\Phi(t, \Phi(s, \phi)) = \Phi(t + s, \phi)$ *for all* $t, s \geq 0$*.*

Definition 2.9. *The set* $\gamma^+(\phi) = \{\Phi(t, \phi), t \geq 0\}$ *is called the positive orbit of* Φ *through* ϕ*. A set* D *is said to be an* invariant set *for* Φ*, if* $\Phi(t, D) = D$ *for all* $t \geq 0$*. The* ω*-limit set of* $\phi \in C$ *is defined to be*

$$\omega(\phi) = \bigcap_{s \geq 0} \overline{(\gamma^+(\Phi(s, \phi)))}.$$

The ω*-limit set of* $B \subseteq C$ *is*

$$\omega(B) = \bigcap_{s \geq 0} \overline{(\gamma^+(\Phi(s, B)))}.$$

It can be seen that $\omega(\phi) = \{\psi \in C, \exists t_n \to \infty, x^{\phi}_{t_n} \to \psi, t \to \infty\}$.

Theorem 2.10. *The* ω*-limit set* $\omega(\phi)$ *is nonempty, compact, connected and invariant and we have*

$$dist(x^{\phi}_t, \omega(\phi)) \to 0, t \to \infty.$$

Equilibria and their Stability

Let $x(t) = x^* \in \mathbb{R}^n$ be the solution given in Theorem 2.9 to the IVP (2.6), then for all $t \geq 0$ we have $x^{\phi}_t = x^*$, so x^* is a fixed point of the system.

Definition 2.10. *The solution* x^* *is said to be an* equilibrium point *of the delay differential Equation* (2.6) *if* $f(x^*) = 0$ *for all* $t \geq 0$*.*

Without loss of generality, we can assume that $x^* = 0$, since the point $\hat{x} \in \mathbb{R}^n$ is an equilibrium point of Equation (2.6) if and only if $y^* = 0$ is an equilibrium point of the equation

$$y'(t) = g(t, y_t), \quad t \geq 0$$
$$y_0 = \psi \in C,$$

where $y(t) = x(t) - \hat{x}$.

Definition 2.11. *Suppose $x^* = 0$ is an equilibrium point of*

$$\begin{aligned} x'(t) =& f(x_t), \quad t \geq t_0 \\ x_{t_0} =& \phi, \end{aligned}$$

- *The point $x^* = 0$ is* stable *if for any $t_0 \geq 0$ and $\epsilon > 0$, there is $\delta = \delta(t_0, \epsilon) > 0$ such that*

$$\forall \phi \in C, \quad \|\phi\| < \delta \Longrightarrow \|x_t^{(t_0,\phi)}\| < \epsilon, \quad \forall t > t_0.$$

- *The point $x^* = 0$ is* asymptotically stable *if it is stable and* "attractive" *in the sense that for any t_0, there exists $\delta(t_0) > 0$ such that*

$$\|\phi\| < \delta_0 \Rightarrow x_t^{(t_0,\phi)} \to 0 \quad as \quad t \to \infty.$$

- *The point $x^* = 0$ is* uniformly stable *if δ is independent of t_0 and it is* uniformly asymptotically stable *if it is uniformly stable and uniformly attractive, that is, there exists a $\delta > 0$ such that*

$$\forall \epsilon > 0 \quad \exists T(\epsilon) : \|\phi\| < \delta \Rightarrow \|x_t^{(t_0,\phi)}\| < \epsilon,$$

for $t \geq t_0 + T$ and for every t_0.

- *The point $x^* = 0$ is* globally exponentially stable *if for any $\phi \in C$ there exist $\lambda > 0$*

and $M \geq 1$ such that

$$\|x_t^{(t_0,\phi)}\| < M\|\phi\|e^{-\lambda(t-t_0)}, t \geq t_0.$$

In other words, the equilibrium point is stable if for an initial data close to $x = 0$, the state of the system for all $t \geq t_0$ remains close to it, depending on the initial time t_0, and it is attractive if the state of the system approaches $x = 0$ as time goes to infinity and if it is approaching exponentially fast and with any initial data, then we have globally exponentially stability. Different types of the equilibrium points defined above are quite similar to the corresponding types for ODE's.

Linear Stability Linear delay differential equations are studied here and for this purpose strongly continuous semi-groups are introduced. Spectral properties are investigated for some examples and finally the stability of nonlinear systems is discussed using the linearization principle. The results are not used directly in the thesis but they are foundations of the linear stability of delay differential equations. Proof of the theorems can be found in [3].

Consider the linear delay differential equation

$$x'(t) = L(x_t), \tag{2.9}$$

where $L : C \to \mathbb{R}^n$ is a bounded linear operator.

Definition 2.12. *Let X be a Banach space and $T(t) : X \to X$ be a bounded linear operator for all $t \geq 0$. The family $(T(t))_{t\geq 0}$ is called a* stongly continuous semi-group *if it satisfies the following properties:*

(1) $T(0) = Id$;

(2) $T(t+s) = T(t)T(s)$ *for all* $t, s \geq 0$;

(3) the map $t \mapsto T(t)x$ *is continuous for all* $x \in X$.

Let $(T(t))_{t\geq 0}$ be a strongly continuous semigroup on X. Let $D(A) \subseteq X$ be the set of all $x \in X$ for which the following limit exists:

$$Ax = \lim_{h\to 0} \frac{T(h)(x) - x}{h}.$$

Th map $A : D(A) \to X$ is called the *infinitesimal generator* of the strongly continuous semi-group $(T(t))_{t\geq 0}$, and we denote it by $(A, D(A))$.

Lemma 2.11. *A generator* $(A, D(A))$ *of a strongly continuous semigroup* $(T(t))_{t\geq 0}$ *has the following properties:*

(i) $A : D(A) \to X$ *is a linear operator;*

(ii) $T(t)x \in D(A)$ *for* $x \in D(A)$ *and*

$$\frac{d}{dt}T(t)x = T(t)Ax = AT(t)x \quad \textit{for all} \quad t \geq 0;$$

(iii) For all $t \geq 0$, $\quad x \in X$

$$\int_0^t T(s)xds \in D(A);$$

(iv) the following identities hold for every $t \geq 0$

$$\begin{aligned} T(t)x - x &= A \int_0^t T(s)x ds \quad \textit{if} \quad x \in X \\ &= \int_0^t T(s)Axds \quad \textit{if} \quad x \in D(A). \end{aligned}$$

Theorem 2.12. *Let* $(A, D(A))$ *be the generator of a strongly continuous semigroup* $(T(t))_{t\geq 0}$ *on a Banach space* X. *Then* $(A, D(A))$ *is a closed operator and* $\overline{D(A)} = X$. *Additionally, if* $(S(t))_{t\geq 0}$ *is another semigroup with generator* $(A, D(A))$, *then* $S(t) = T(t)$ *for all* $t \geq 0$.

Definition 2.13. *Let* $(T(t))_{t\geq 0}$ *be a strongly continuous semigroup on a Hilbert space* H. *The operator* $(A, D(A))$ *is called* dissipative *if*

$$\Re\langle Ax, x\rangle \leq 0, \quad \textit{for all} \quad x \in D(A).$$

Proposition 2.13. *Let* $(T(t))_{t\geq 0}$ *be a strongly continuous semigroup. Then there exist constants* $w \in \mathbb{R}$ *and* $M \geq 1$ *such that*

$$\|T(t)\| \leq Me^{wt}, \quad \textit{for all} \quad t \geq 0.$$

Consider the linear equation (2.9) and for $t \geq 0$, define the operator $T(t) : C \to C$ by

$$T(t)\phi = x_t^{\phi} \in C. \tag{2.10}$$

Remark 2.14. *The relation* (2.10) *defines a strongly continuous semigroup on* C.

Proof. We show that the properties in definition 2.12 are satisfied:

- $T(0) = Id : C \to C$, since $T(0)\phi = x_0^{\phi} = \phi$.

- To show $T(t+s) = T(t)T(s)$, let $t, s \geq 0$, then

$$\begin{aligned} T(t+s)\phi &= x^{\phi}_{t+s} \\ &= x^{x^{\phi}_s}_t \\ &= T(t)T(s)\phi. \end{aligned}$$

- The map $t \mapsto T(t)\phi$ is continuous for all $\phi \in C$ since $x : [-\tau, \alpha] \to \mathbb{R}^n$ is continuous: fix $\phi \in C$. For $\epsilon > 0$ there exists $\delta_1 > 0$ such that for all $\theta_1, \theta_2 \in [-\tau, \alpha]$ with $|\theta_2 - \theta_1| < \delta_1$ we have

$$|x(\theta_2) - x(\theta_1)| < \epsilon.$$

Let $\delta \leq \delta_1$ and $t_1, t_2 \in [0, \alpha]$ such that $|t_2 - t_1| < \delta$, then

$$|(t_2 + \theta) - (t_1 + \theta)| < \delta \leq \delta_1, \quad \text{for all} \quad -\tau \leq \theta \leq 0$$

and therefore

$$|x(t_2 + \theta) - x(t_1 + \theta)| < \epsilon, \quad \text{for all} \quad -\tau \leq \theta \leq 0.$$

thus

$$\begin{aligned} \|x^{\phi}_{t_2} - x^{\phi}_{t_1}\| &= \sup_{-\tau \leq \theta \leq 0} |x^{\phi}_{t_2}(\theta) - x^{\phi}_{t_1}(\theta)| \\ &= \sup_{-\tau \leq \theta \leq 0} |x(t_2 + \theta) - x(t_1 + \theta)| < \epsilon. \end{aligned} \tag{2.11}$$

So we have

$$|t_2 - t_1| < \delta \Longrightarrow \|T(t_2)\phi - T(t_1)\phi\| < \epsilon.$$

□

Remark 2.15. *The generator* $(A, D(A))$ *is given by*

$$D(A) = \{\phi \in C^1([-\tau, 0], \mathbb{R}^n) : \phi'(0) = L\phi\}$$
$$A(\phi) = \phi'$$

Proof. The generator $A(\phi)$ is given by the following limit:

$$A(\phi) = \lim_{h\to 0} \frac{T(h)\phi - \phi}{h}$$

For $\theta < 0$, we have

$$\begin{aligned} A\phi(\theta) &= \lim_{h\to 0} \frac{x_h^{\phi}(\theta) - \phi(\theta)}{h} \\ &= \lim_{h\to 0} \frac{x^{\phi}(\theta + h) - \phi(\theta)}{h} \\ &= \lim_{h\to 0} \frac{\phi(\theta + h) - \phi(\theta)}{h} \\ &= \phi'(\theta) \end{aligned}$$

and for $\theta = 0$,

$$\begin{aligned} A\phi(\theta) &= \lim_{h\to 0} \frac{x^{\phi}(h) - \phi(0)}{h} \\ &= \lim_{h\to 0} \frac{\phi(0) + \int_0^h Lx_s ds - \phi(0)}{h} \\ &= L\phi. \end{aligned}$$

□

Definition 2.14. *Let* $A : X \to X$ *be a linear operator on a Banach space* X*. The* resolvant set $\rho(A)$ *is defined to be the values* $\lambda \in \mathbb{C}$ *for which* $\lambda I - A$ *is invertible and the inverse operator is bounded and its domain is dense in* X*. The complement of* $\rho(A)$ *is called the spectrum of* A*, denoted by* $\sigma(A)$*. The spectrum of* A *consists of three type of values:*

- *Residual spectrum:*

$$R\sigma(A) = \{\lambda \in \sigma(A) : (\lambda I - A)^{-1} \textit{exists but its domain is not dense in } X\}$$

- *Continuous spectrum:*

$$C\sigma(A) = \{\lambda \in \sigma(A) : (\lambda I - A)^{-1} \textit{has a dense domain but is not bounded}\}$$

- *Point spectrum:*

$$P\sigma(A) = \{\lambda \in \sigma(A) : \lambda I - A \quad \textit{is not invertible}\}.$$

Let $\lambda \in P\sigma(A)$, then $(\lambda I - A)\phi = 0$ has a non trivial solution in $D(A)$

$$\begin{aligned}(\lambda I - A)\phi = 0 &\Leftrightarrow \lambda\phi(0) = L(e^{\lambda \cdot}\phi(0)) \\ &\Leftrightarrow [\lambda I - L(e^{\lambda \cdot})]\phi(0) = 0 \\ &\Leftrightarrow \det[\lambda I - L(e^{\lambda \cdot})] = 0.\end{aligned}$$

This proves the following theorem.

Theorem 2.16. $\lambda \in P\sigma(A)$ *if and only if* $\det[\lambda I - L(e^{\lambda \cdot})] = 0$.

The equation $\det[\lambda I - L(e^{\lambda \cdot})] = 0$ is called the *characteristic equation* associated to the linear system (2.9).

Example 2.17.
- *Discrete delay: Consider the equation given in Example 2.5. The characteristic equation is given by*

$$\lambda + a - be^{-\lambda\tau} = 0.$$

- *Distributed delay: Consider the following distributed delay equation:*

$$x'(t) = \int_0^t x(t-s)ds.$$

The characteristic equation is given by

$$\lambda = \int_0^\infty e^{-\lambda s} ds.$$

For both of the above examples, the distribution of roots can be very complicated.

The following theorem gives the relation between roots of the characteristic equation and the stability of the trivial equilibrium point.

Theorem 2.18. *If there exists $\lambda \in P\sigma(A)$ such that $\Re(\lambda) > 0$, then the trivial solution $x^* = 0$ is unstable and if $\Re(\lambda) < 0$ for all $\lambda \in P\sigma(A)$, then $x^* = 0$ is locally asymptotically stable.*

Stability using Lyapunov Functionals Let $f : C \to \mathbb{R}^n$ be completely continuous and consider the delay differential equation of (2.6). Let $\mathcal{K}$ denote the set of continuous and strictly increasing functions $w : \mathbb{R}_+ \to \mathbb{R}_+$ with $w(0) = 0$, which are called $\mathcal{K}$-class functions.

Definition 2.15. *Let $V : C \to \mathbb{R}^n$ be a continuous functional. The derivative of V along the solutions of equation (2.6) is given by the following relation:*

$$\dot{V}(\phi) = \limsup_{t \to 0^+} \frac{1}{t}(V(x_t^\phi) - V(x_0^\phi)).$$

V is called a Lyapunov function on a set $G \subseteq C$ relative to (2.6), if it is continuous on the closure $\bar{G}$ of G and $\dot{V} \le 0$ on G.

Let

$$S = \{\phi \in \bar{G} : \dot{V}(\phi) = 0\}$$

$$W = \text{largest set in } S \text{ that is invariant with respect to the system.}$$

Theorem 2.19. *Suppose $f : C \to \mathbb{R}^n$ is continuous, maps bounded sets in C to the bounded sets in $\mathbb{R}^n$ and that $f(0) = 0$. Assume there exists a continuous functional $V : C \to \mathbb{R}^n$ and continuous nondecreasing functions u, v, $w : \mathbb{R}^+ \to \mathbb{R}^+$ such that $u(0) = v(0) = 0$ and $u(s), v(s) > 0$ for all $s > 0$. Further assume that*

(i) $u(|\phi(0)|) \leq V(\phi) \leq V(\|\phi\|)$;

(ii) $\dot{V}(\phi) \leq -w(|\phi(0)|)$,

then $x = 0$ is stable. Additionally, if $w(s) > 0$ for all $s > 0$, then $x = 0$ is asymptotically stable.

Theorem 2.20. *If V is a Lyapunov function on $G \subseteq C$ and x_t^ϕ is a bounded solution of equation (2.6) which remains in G, then $x_t^\phi \to W$ as $t \to \infty$.*

Theorem 2.21. *Assume $w_1, w_2 \in \mathcal{K}$ and $w_3 : \mathbb{R}_+ \to \mathbb{R}_+$ is a continuous, nondecreasing function. If there exists a continuous function $V : \mathbb{R} \times \mathbb{R}^n \to \mathbb{R}_+$ such that*

(i) $w_1(|x|) \leq V(t, x) \leq w_2(|x|)$,

(ii) $\dot{V}(t, \phi(0)) \leq -w_3(|\phi(0)|)$ *if* $V(t + s, \phi(s)) \leq V(t, \phi(0))$, $s \in [-\tau, 0]$,

then $x = 0$ is uniformly stable.

Theorem 2.22. *Suppose the conditions of Theorem 2.21 are satisfied and $w_3(s) > 0$ for $s > 0$. If there exists a continuous nondecreasing function $p(s) > s$ for $s > 0$ such that* *condition (ii) in theorem 2.21 is replaced by*

$$\dot{V}(t,\phi(0)) \leq -w_3(|\phi(0)|), \quad V(t+s,\phi(s)) < p(V(t,\phi(0))), \quad s \in [-\tau, 0],$$

then $x = 0$ is uniformly asymptotically stable. If $w_1(s) \to \infty$ as $t \to \infty$, then the solution $x = 0$ is a global attractor of the system.

Theorem 2.23. *If V is a Lyapunov function on $U_\ell = \{\phi \in C : V(\phi) < \ell\}$ and there is a constant $K = K(\ell)$ such that $|\phi(0)| < K$ for all $\phi \in U_\ell$, then $\phi \in U_\ell$ implies $x_t^\phi \to W$ as $t \to \infty$.*

Corollary 2.24. *Let $V : C \to \mathbb{R}$ be continuous and there exist functions $a(r)$ and $b(r)$ such that $a(r) \to \infty$ as $t \to \infty$ and*

$$\begin{aligned} a(|\phi(0)|) &\leq V(\phi), \\ \dot{V}(\phi) &\leq -b(|\phi(0)|). \end{aligned} \tag{2.12}$$

Then the solution $x = 0$ is stable and all solutions are bounded. If, additionally $b(r)$ is positive definite, then all solutions converge to zero as $t \to \infty$.

Example 2.25. *Consider the following delay equation:*

$$x'(t) = ax^3(t) + bx^3(t-\tau) \tag{2.13}$$

where a and b are constants and $a \neq 0$. Let

$$V(\phi) = -\frac{\phi^4(0)}{2a} + \int_{-\tau}^{0} \phi^6(\theta)d\theta$$

then the derivative of V with respect to equation (4) *is given by*

$$\dot{V}(\phi) = -[\phi^6(0) + \frac{2b}{a}\phi^3(0)\phi^3(-\tau) + \phi^6(-\tau)].$$

V is a Lyapunov function on C if $|b| \leq |a|$.

2.2 Mathematical Epidemiology

This section contains the basic concepts and some commonly used methodologies in mathematical epidemiology.

2.2.1 Compartmental Models

In modelling the spread of infectious diseases, the population is divided into several compartments. Here we demonstrate an example: in an SIR model, there are three compartments:

- Susceptibles: individuals who are not yet infected and are susceptible of being infected if they are exposed;
- Infectives: individuals that are infected and can spread the disease;
- Removed: individuals who have been infected and have been removed by quarantine, or have recovered and have immunity to the disease, or have died because of the disease.

Other compartments may be introduced, based on the model being studied, such as Latent, Exposed, Treated and so on. In the following S, I and R are the number of susceptibles, infectives and recovered individuals, respectively. We assume that the total population is large, so that we can consider the variables as continuous functions of time. Here we assume that $N = S(t) + I(t) + R(t)$ is constant and we consider the fractions $S^*(t) = S(t)/N$, $I^*(t) = I(t)/N$ and $R^*(t) = R(t)/N$. For simplicity of notation we denote these fractions by the same letters S, I and R. The following system of ordinary differential equations describes an SIR model with vital dynamics (birth and death):

$$S'(t) = d - dS(t) - \beta S(t)I(t) \tag{2.14a}$$

$$I'(t) = \beta S(t)I(t) - dI(t) - \gamma I(t) \tag{2.14b}$$

$$R'(t) = \gamma I(t) - dR(t) \tag{2.14c}$$

The equation for R can be omitted, since it does not affect the system (the total population N is constannt so $R'(t) = -(S'(t) + I'(t))$). The birth rate and death rate are assumed to be the same and are denoted by d; β is the transmission rate and is defined as follows [19]:

Definition 2.16. *The* per capita *transmission rate is the rate of efficient contacts which is given by product of infection probability p and the total number of contacts per unit time C.*

Individuals leave the infective compartment at rate γ, so the mean infection period is $1/\gamma$. The term $\beta S(t)I(t)$ represents the incidence, i.e., the number of new infection cases arising per unit time [6] (*mass action incidence*), and depends on the size of susceptible and infective populations, meaning that if the number of individuals in each compartment is twice larger, then the number of new infections will be four times larger, with the same transmission rate. The key assumption for mass action incidence is that the infective and susceptible populations are uniformly mixed.

Remark 2.26. *The term* $\lambda(t) = \beta I(t)$ *is also called the* force of infection, *which is defined to be the probability per unit of time for susceptibles to become infected, and is obtained by summing all contribution of infectives [6]. For the general case the incidence of the disease is given by* $S(t)\lambda(t)$.

In the analysis of System (2.14), we are interested in determining the stability of the disease free equilibrium point, where the disease dies out, i.e., when $I = 0$ and therefore $(S, I, R) = (N, 0, 0)$. One of the main goals, in the analysis of epidemiological models, is to find a threshold value for the stability of the disease free equilibrium point. This value is called the *basic reproduction number*, denoted by $\mathcal{R}_0$, which is defined as follows [6]:

Definition 2.17. ***(Basic Reproduction number)*** *The* basic reproduction number *is the expected number of secondary cases produced in a population of susceptible individuals by one infected individual during his/her effective infectious period.*

The disease free equilibrium point is locally asymptotically stable if $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 > 1$. This means that if an infected individual can infect less than one person during the infection period, the disease dies out and if the number of secondary infections is more than one, then the disease invades the population. By linearizing System (2.14) about the disease free equilibrium point, we get $\mathcal{R}_0 = \beta/(d + \gamma)$.

Remark 2.27. *Another expression for the basic reproduction is given by* $\mathcal{R}_0 = \iota\bar{t}$, *where* ι *is the transmission rate (or infectivity) and* $\bar{t}$ *is the mean time spent in the infective compartment. For example in the* SIR *model,* $\bar{t} = \frac{1}{\gamma+d}$ *and* $\iota = \beta$. *If the infectivity of individuals vary with time (or with the age of infection, treatment, etc.), then* ι *will be the sum over the infectivity of individuals.*

2.2.2 The Next Generation Operator Method

There are different methods to compute the basic reproduction number. One of the well known methods is the method of *next generation operator* [5].

Suppose the population N is divided into two types of compartments: disease and non disease compartments. Let $x = (x_1, \cdots, x_n) \in \mathbb{R}^n$ and $y = (y_1, \cdots, y_m) \in \mathbb{R}^m$ denote the disease and non disease compartments, respectively ($x = I$ and $y = (S, R)$ in the SIR model of previous section). Consider the following system of ordinary differential equations describing the disease transmission:

$$x_i' = (\mathcal{F}_i - \mathcal{V}_i)(x, y) \quad 1 \leq i \leq n \tag{2.15a}$$

$$y_j' = g_j(x, y) \quad 1 \leq j \leq m \tag{2.15b}$$

and let the feasible set $\mathcal{D}$ be given by

$$\mathcal{D} = \{(x, y) \in \mathbb{R}^{n+m} : x_1 + \cdots + x_n + y_1 + \cdots + y_m = 1\}$$

Assume

(A1) $\mathcal{F}_i(0, y) = 0$, $\mathcal{V}_i(0, y) = 0$ for all $y \geq 0$ and $1 \leq i \leq n$ (this means that new infections are only caused by a host infective and there is no immigration of infectives);

(A2) $\mathcal{F}_i(x, y) \geq 0$ for all $x, y \geq 0$ ($\mathcal{F}$ shows the new infections and it can not be negative);

(A3) $\mathcal{V}_i(x, y) \leq 0$ for $x_i = 0$ (there is only inflow to an empty compartment);

(A4) $\sum_{i=1}^{n} \mathcal{V}_i(x, y) \geq 0$ (this sum is the total outflow of all disease compartments)

(A5) the system $g_j'(0, y) = 0$ has a unique solution, y_0, which is asymptotically stable.

These assumptions ensure that the disease free equilibrium point exists and the model is well posed.

Let F and V be the following matrices

$$F = \frac{\partial \mathcal{F}_i}{\partial x_j}(0, y_0), \quad V = \frac{\partial \mathcal{V}_i}{\partial x_j}(0, y_0).$$

The linear stability of System (2.15) is determined by the linear stability of the following system

$$x' = (F - V)(x). \tag{2.16}$$

Definition 2.18. *A real matrix M is called an M-matrix if it is a Z-matrix, i.e., $m_{ij} \leq 0$ for $i \neq j$, and if it can be written in the form $M = sI - B$, for B non negative and $s > \rho(B)$, where $\rho(B)$ is the spectral radius of B defined by*

$$\rho(B) = \max\{|z| : z \quad \textit{is an eigenvalue of} \quad B\}.$$

From assumptions $(A1) - (A5)$, we can see that F and V are non negative and V is a M-matrix.

Lemma 2.28. *If F is non negative and V is a non negative M-matrix, then eigenvalues of $F - V$ have negative real parts if and only if $\rho(FV^{-1}) < 1$.*

Theorem 2.29. *Consider the system given by (2.15). The disease free equilibrium point is locally asymptotically stable if $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$, where $\mathcal{R}_0 = \rho(FV^{-1})$.*

Global Stability of the DFE Let $f(x, y) := (F - V)(x) - \mathcal{F}(x, y) + \mathcal{V}(x, y)$. For global stability of the DFE we have the following theorems [16].

Theorem 2.30. *If $f(x,y) \geq 0$ in $\mathcal{D}$ and $F \geq 0$, $V^{-1} \geq 0$ and $\mathcal{R}_0 \leq 1$, then $L(x) = \omega^T V^{-1} x$ is a Lyapunov function for the model* (2.15) *on $\mathcal{D}$.*

Theorem 2.31. *Let $\mathcal{D}$ be positively invariant under the flow of* (2.15) *and suppose the disease free system has a unique equilibrium point which is GAS in $\mathbb{R}^m_+$. Assume $f(x) \geq 0$ with $f(0) = 0$, $F, V^{-1} \geq 0$ and $V^{-1}F$ is irreducible. Then the following results hold*

(i) *If $\mathcal{R}_0 < 1$, then the DFE is GSA in $\mathcal{D}$;*

(ii) *If $\mathcal{R}_0 > 1$, then the DFE is unstable and the system* (2.15) *is persistent and there exists at least one endemic equilibrium point.*

Table 2.1: Table of symbols

Symbol	Meaning
ODE	ordinary differential equation
DDE	delay differential equation
DFE	disease free equilibrium point
Id	identity function
$\Re$	real part
d	birth/death rate
β	transmission rate
φ	treatment rate
$1-\sigma(a)$	age-dependent treatment efficacy
$\theta(a)$	age-dependent rate of returning to infective class

Chapter 3

Treatment-Age Structured Model

In this chapter, we formulate a model to study the transmission dynamics of infectious diseases with treatment, using different approaches. We start with a system of equations consisting of integro-differential and partial differential equations with non zero initial and boundary conditions (direct approach). Then we transform this system to a single delay-integro-differential equation. We also look at the problem from a survival point of view and formulate the model using survival functions and finally we have a discrete age structured model where the treated infective compartment is divided into n age of treatment classes to get a system of ordinary differential equations. Here we construct the foundation of the model, which will remain the same throughout this chapter.

The population is divided into three compartments:

- *Susceptible* individuals have no immunity to the disease and are infected if they come into an infecting contact with an infected individual. The number of such individuals at time t is denoted $S(t)$.
- *Infectious* individuals are actively spreading the disease. Their number is $I(t)$.

- *Treated infectious* individuals are infectious but are undergoing treatment. The effect of treatment (in addition to its curative effects) is to reduce the infectiousness of these individuals to susceptible individuals. Their number is denoted by $I_T(t)$.

We refer to compartments and to individuals in the compartments using just the letters used to denote the number of individuals in the compartments. The compartments I and I_T represent the *infected* compartments. The total population in the system is

$$N = S + I + I_T.$$

We also make the following assumptions, some of which will be discussed in more detail later.

1. Birth occurs at the *per capita* rate b dependent on the total population N. There is no vertical transmission of the disease, so that all birth takes place in the susceptible compartment.

2. Death occurs at the *per capita* rate d in each compartment.

3. Birth and death occur at the same rate, which we denote d.

4. The disease cannot be cured; once infected (and infectious), individuals remain infectious for the entire duration of their life.

5. Some individuals infectious with the disease undergo treatment. The rate at which infectious individuals are treated is the *per capita* rate φ.

6. Treatment reduces the infectiousness of those treated. The efficacy of treatment in reducing infectiousness is $1 - \sigma(a)$, where $a \in \mathbb{R}_+$ is the length of time that

individuals have been treated for. We assume σ is a non-decreasing, piecewise C^1 function of a.

7. Individuals undergoing treatment might interrupt their treatment and thus proceed back to the regular infectious compartment. The rate at which they do so is $\theta(a)$; see below.

Assumption 6 is related to the effect and duration of treatment and assumes that treatment reduces infectiousness. There has been a considerable amount of debate on this subject, both in the biological and modelling communities. The issue is complicated by the fact that infectiousness, efficiency and the like are notions that concern individuals but that are mostly observed at the community level.

In Assumption 7, the rate at which treated individuals return to the infective compartment depends on how long they have been treated for. If we consider the age of treatment, the rate is a non-decreasing and piecewise C^1 function of the age of treatment, denoted by $\theta(a)$.

We will also consider a survival function $P(a)$ which is defined to be the fraction of treated individuals who are still in treated class a unit time after entering. More details on survival function $P(a)$ and its relation with the rate $\theta(a)$ will be given in section 3.3.

3.1 Direct Approach

Here we assume that the rate at which individuals interrupt their treatment is denoted by $\theta(a)$ and depends on the length of time $a \in \mathbb{R}_+$ they have been undergoing treatment for. Therefore we consider the duration of time treated infectious individuals have been receiving treatment for, and instead of using the variable $I_T(t)$, we use the variable $I_T(a,t)$, where $a \in \mathbb{R}_+$ is the *age of treatment* and $t \in \mathbb{R}_+$ is time. Following the literature, we say that the model is *structured* in terms of age-of-treatment. The flow diagram of this model is shown in Figure 3.1.

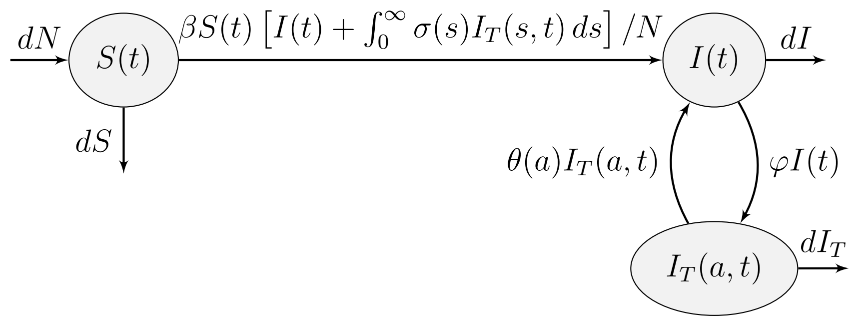

Figure 3.1: Flow diagram for the model.

Let $I_T(a,t)$ be the density of treated infectious individuals at time t with age of treatment a; thus, the number of treated individuals with age of treatment between a_1 and a_2 at time t is given by

$$\int_{a_1}^{a_2} I_T(s,t)ds,$$

and the total population of I_T at time t is

$$I_T(t) = \int_0^\infty I_T(a,t)da.$$

We have the following system of equations

$$\frac{dS}{dt} = dN - dS(t) - \frac{S(t)}{N}\lambda(t) \tag{3.1a}$$

$$\frac{dI}{dt} = \frac{S(t)}{N}\lambda(t) - dI(t) - \varphi I(t) + \int_0^\infty \theta(s) I_T(s,t)ds \tag{3.1b}$$

$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a}\right) I_T(a,t) = -(\theta(a) + d) I_T(a,t) \tag{3.1c}$$

under the boundary condition

$$I_T(0,t) = \varphi I(t) \tag{3.1d}$$

and the initial condition

$$S(0), I(0) > 0, I_T(a,0) = \psi(a), a \in \mathbb{R}_+, \tag{3.1e}$$

where β is the transmission rate constant, and $\lambda(t)$ is the force of infection given by

$$\lambda(t) = \beta(I(t) + \int_0^\infty \sigma(s) I_T(s,t) ds).$$

Note that $\sigma(a)$ is a piecewise C^1 function and $\sigma(a) = 1$ means that the treated individuals have the same level of the infectivity that the infective individuals have. The efficacy of the treatment is defined by $\epsilon(a) = 1 - \sigma(a)$, so $\epsilon(a) = 0$ means that the treatment is not efficient and therefore does not reduce the level of infectivity.

Remark 3.1. *Here we assume that* $\lim_{a \to \infty} \psi(a) = 0$. *This is biologically reasonable since initially treated individuals either move to the infected class or they die, eventually.*

3.2 Transformation to a Delay Differential Equation

In this section we reformulate the model by reducing it to a delay differential equation. We use the method of characteristics [9].

Let $M(a,t) = I_T(a,t)$ with $M(0,t) = \varphi I(t)$, $M(a,0) = \psi(a)$ and define $\tilde{M}(s) = M(a(s), t(s))$.

Differentiating $\tilde{M}$ with respect to s, we get

$$\frac{d\tilde{M}}{ds} = \frac{\partial P}{\partial a}\frac{da}{ds} + \frac{\partial P}{\partial t}\frac{dt}{ds}.$$

If the curves $\alpha(s) = (a(s), t(s))$ in the at plane are given by the condition

$$\frac{dt}{ds} = \frac{da}{ds} = 1,$$

then we have the following ODE for $\tilde{M}(s)$, which is equivalent to the Equation (3.1c):

$$\frac{d\tilde{M}}{ds} = -(d + \theta(a(s)))\tilde{M}.$$

So, if the value of $\tilde{M}$ is known for (a_0, t_0), then we have

$$\tilde{M}(s) = M(a_0, t_0)e^{-\int_{a_0}^{a_0+s}(d+\theta(v))dv}.$$

For $a > t$, let $t_0 = 0$, $a_0 \geq 0$,

$$\begin{aligned} M(a,t) &= M(a_0, 0)e^{-\int_{a_0}^{a_0+s}(d+\theta(v))dv} \\ &= \psi(a-t)e^{-\int_{a-t}^{a}(d+\theta(v))dv} \\ &= \psi(a-t)e^{-dt-\int_{a-t}^{a}\theta(v)dv} \end{aligned}$$

and for $a \leq t$ let $a_0 = 0$, $t_0 \geq 0$,

$$\begin{aligned} M(a,t) &= M(0, t_0)e^{-\int_{0}^{s}(d+\theta(v))dv} \\ &= \varphi I(t-a)e^{-\int_{0}^{a}(d+\theta(v))dv} \\ &= \varphi I(t-a)e^{-da-\int_{0}^{a}\theta(v)dv}. \end{aligned}$$

Thus we have the following expression for $I_T(a,t)$:

$$I_T(a,t) = \begin{cases} \varphi I(t-a)e^{-da-\int_0^a \theta(v)dv}, & 0 \le a \le t, \\ \psi(a-t)e^{-dt-\int_{a-t}^a \theta(v)dv}, & t < a. \end{cases} \tag{3.2}$$

Remark 3.2. *From* (3.2)*, by taking limit of* $I_T(a,t)$ *for* $t < a$*, we can see that* $\lim_{a\to\infty} I_T(a,t) = 0$.

Lemma 3.3. *The total population N is constant.*

Proof. We show that $\frac{dN}{dt} = 0$. Since $N = S(t) + I(t) + \int_0^\infty I_T(s,t)ds$ we have

$$\begin{aligned}
\frac{dN}{dt} = 0 \quad &\Leftrightarrow \quad S'(t) + I'(t) + \int_0^\infty \frac{\partial}{\partial t} I_T(s,t)ds = 0 \\
&\Leftrightarrow \quad dN - dS(t) - \frac{S(t)}{N}\lambda(t) + \frac{S(t)}{N}\lambda(t) - dI(t) - \varphi I(t) \\
&\qquad + \int_0^\infty \theta(s) I_T(s,t)ds + \int_0^\infty \frac{\partial}{\partial t} I_T(s,t)ds = 0 \\
&\Leftrightarrow \quad d(N - S(t) - I(t)) - \varphi I(t) + \int_0^\infty \theta(s) I_T(s,t)ds - d\int_0^\infty I_T(s,t)ds \\
&\qquad - \int_0^\infty \theta(s) I_T(s,t)ds - \int_0^\infty \frac{\partial}{\partial s} I_T(s,t)ds = 0 \\
&\Leftrightarrow \quad -\varphi I(t) - \int_0^\infty \frac{\partial}{\partial s} I_T(s,t)ds = 0 \\
&\Leftrightarrow \quad -\varphi I(t) - \lim_{a\to\infty} I_T(a,t) + I_T(0,t) = 0
\end{aligned}$$

and the last equality holds since $\lim_{a\to\infty} I_T(a,t) = 0$. □

Let $S^*(t) = S(t)/N$, $I^*(t) = I(t)/N$ and $I_T^*(a,t) = I_T(a,t)/N$ be proportions, which we denote with the same letters S, I and I_T. Using the formula given above for $I_T(a,t)$, (3.1) can be written as

$$\begin{aligned}
\frac{dS}{dt} &= d - dS(t) - \beta S(t)\bigg(I(t) + \int_0^t \varphi\sigma(s)e^{-ds-\int_0^s \theta(u)du} I(t-s)ds \\
&\quad + \int_t^\infty \sigma(s)\psi(s-t)e^{-dt-\int_{s-t}^s \theta(u)du}ds\bigg) \qquad (3.3a)\\
\frac{dI}{dt} &= \beta S(t)\bigg(I(t) + \int_0^t \varphi\sigma(s)e^{-ds-\int_0^s \theta(u)du} I(t-s)ds \\
&\quad + \int_t^\infty \sigma(s)\psi(s-t)e^{-dt-\int_{s-t}^s \theta(u)du}ds\bigg) - (d+\varphi)I(t) \\
&\quad + \int_0^t \varphi\theta(s)e^{-ds-\int_0^s \theta(u)du} I(t-s)ds + \int_t^\infty \theta(s)\psi(s-t)e^{-dt-\int_{s-t}^s \theta(u)du}ds. \qquad (3.3b)
\end{aligned}$$

Since

$$S(t) = 1 - I(t) - \int_0^\infty I_T(s,t)ds,$$

we reduce the number of equations to get the following delay-integro-differential equation

$$\begin{aligned}
\frac{dI}{dt} = \beta&\bigg(1 - I(t) - \int_0^t \varphi e^{-ds-\int_0^s \theta(u)du} I(t-s)ds - \int_t^\infty \psi(s-t)e^{-dt-\int_{s-t}^s \theta(u)du}ds\bigg) \\
&\bigg(I(t) + \int_0^t \varphi\sigma(s)e^{-ds-\int_0^s \theta(u)du} I(t-s)ds + \int_t^\infty \sigma(s)\psi(s-t)e^{-dt-\int_{s-t}^s \theta(u)du}ds\bigg) \\
&- (d+\varphi)I(t) + \int_0^t \varphi\theta(s)e^{-ds-\int_0^s \theta(u)du} I(t-s)ds + \int_t^\infty \theta(s)\psi(s-t)e^{-dt-\int_{s-t}^s \theta(u)du}ds.
\end{aligned} \qquad (3.4)$$

This equation is in the standard form of functional differential equations and by Theorem 2.9, there exists a unique solution defined for $t \in [0,\infty)$. Let

$$\frac{dI}{dt} = F(I_t),$$

then F is C^1 and therefore it is locally Lipschitz, so Theorem 2.9 applies.

If we assume $\psi(a) = 0$ in System (3.1), then $I_T(a,t) = 0$ for $a > t$ and we get the following delay-integro-differential equation

$$\begin{aligned}\frac{dI}{dt} &= \beta\big(1 - I(t) - \int_0^t \varphi e^{-ds-\int_0^s \theta(u)du} I(t-s)ds\big)\big(I(t) + \int_0^t \varphi\sigma(s)e^{-ds-\int_0^s \theta(u)du} I(t-s)ds\big) \\ &\quad - dI(t) - \varphi I(t) + \int_0^t \theta(s)\varphi e^{-ds-\int_0^s \theta(u)du} I(t-s)ds.\end{aligned} \tag{3.5}$$

3.3 Survival Function Approach

In this section, we assume $P(t)$ is the survival function for treated infective class, i.e, $P(t)$ is the fraction of treated individuals that are still in the treated class t unit times after starting the treatment. Define the random variable X to be the time spent in the treated infective compartment before returning to the infective compartment. The survival function of this random variable is given by

$$P(t) = Pr(X > t).$$

Assuming that treated infective individuals leave the treated compartment at rate $\theta(a)$, the survival in the treated compartment is given by

$$P(a) = e^{-\int_0^a \theta(v)dv},$$

and has the following properties:

(*i*) $0 \leq P(a) \leq 1$ for all $a \geq 0$;

(*ii*) $P(0) = 1$;

(*iii*) P is a monotone nonincreasing function

From (iii) one can see that $\lim_{a\to\infty} P(a)$ exists [13]. Here we additionally assume that $\int_0^\infty P(a)da < \infty$.

The exponential and the step functions are two important survival functions:

- Exponential function
$$P(t) = e^{-\eta t}$$

- Step function
$$P(t) = \begin{cases} 1 & \text{for } 0 \le t \le \tau; \\ 0 & \text{for } t > \tau. \end{cases}$$

We have the following system

$$\frac{dS}{dt} = dN - dS(t) - \frac{S(t)}{N}\lambda(t) \tag{3.6a}$$

$$I_T(t) = I_{T_0}(t) + \int_0^t \varphi(1 - S(u) - I_T(u))P(t-u)e^{-d(t-u)}du. \tag{3.6b}$$

where the force of infection $\lambda(t)$ is as follows

$$\lambda(t) = \beta\left(1 - S(t) - I_T(t) + \sigma(t)I_{T_0}(t) + \int_0^t \varphi(1 - S(u) - I_T(u))\sigma(t-u)P(t-u)e^{-d(t-u)}du\right),$$

and

$$I_{T_0}(t) = e^{-dt}\int_0^\infty I_T(0,u)\frac{P(u+t)}{P(u)}du. \tag{3.7}$$

Remark 3.4. *Consider the stage-age structure for I_T and assume that $I_T(a_0, t_0)$ is known. Let $a = a_0 + s$ and $t = t_0 + s$, then by integrating along the characteristics (similar to*

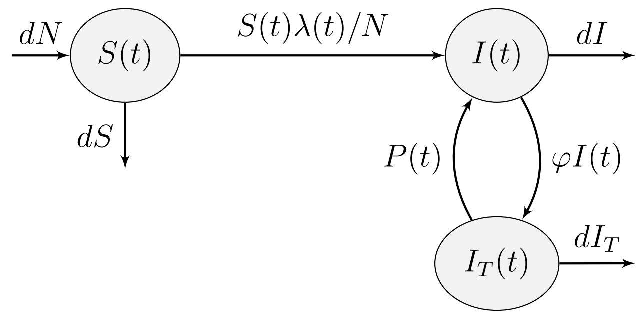

Figure 3.2: Flow diagram for the model formulated using a survival function

section 3.8) we get the following:

$$I_T(a,t) = I_T(a_0,t_0)e^{-ds}\frac{P(a_0+s)}{P(a_0)}$$

and therefore

$$I_T(a,t) = \varphi I(t-a)e^{-da}P(a) \quad \textit{for} \quad 0 \le a \le t \tag{3.8a}$$

$$I_T(a,t) = I_T(a-t,0)e^{-dt}\frac{P(a)}{P(a-t)} \quad \textit{for} \quad t \le a \le \infty, \tag{3.8b}$$

thus

$$\begin{aligned} I_T(t) = \int_0^\infty I_T(u,t)du = \int_0^t &\varphi(1-S(u)-I_T(u))P(t-u)e^{-d(t-u)}du \\ &+ e^{-dt}\int_0^\infty I_T(u,0)\frac{P(u+t)}{P(u)}du \end{aligned} \tag{3.9}$$

and we get the following expression for $I_{T_0}(t)$

$$I_{T_0}(t) = e^{-dt}\int_0^\infty I_T(u,0)\frac{P(u+t)}{P(u)}du. \tag{3.10}$$

Consider the fractions $S(t)/N$, $I(t)/N$ and $I_T(t)/N$ (denoted by the same letters S, I and I_T) to get the following system

$$\frac{dS}{dt} = d - dS(t) - S(t)\lambda(t) \tag{3.11a}$$

$$I_T(t) = I_{T_0}(t) + \int_0^t \varphi(1 - S(u) - I_T(u))P(t-u)e^{-d(t-u)}du. \tag{3.11b}$$

Before further analysis, we need to show that the model is well posed. Consider the region

$$\mathcal{D} = \{(S, I, I_T) : S, I, I_T \geq 0, \quad S + I + I_T = 1\}.$$

For the model to be biologically meaningful, $\mathcal{D}$ must be positively invariant under the flow of the system.

Theorem 3.5. *Solutions of System* (3.11) *with initial values* $S(0) > 0$, $I(0) > 0$ *and* $I_T(a, 0) \geq 0$ *remain in the region* $\mathcal{D}$.

Proof. Let $S(0) > 0$. Solving equation (3.11a) we get

$$S(t) = S(0)e^{-\int_0^t \lambda(s)ds - dt} + e^{-\int_0^t \lambda(s)ds - dt}\int_0^t de^{-\int_0^u \lambda(s)ds - du}du,$$

so $S(t)$ is positive for all t. Since $S(t) + I(t) + I_T(t) = 1$ we have

$$-\frac{dI}{dt} = \frac{dS}{dt} + \frac{dI_T}{dt}, \tag{3.12}$$

where

$$\frac{dI_T}{dt} = \frac{dI_{T_0}}{dt} + \varphi\big(1 - S(t) - I_T(t)\big) + \int_0^t \varphi I(u)e^{-d(t-u)}\big(P'(t-u) - dP(t-u)\big)du$$

and $P'(t-u)$ is the derivative of P with respect to t. Suppose $I(t) > 0$ on $[0, t_0)$ and $I(t_0) = 0$, then

$$\begin{aligned}
-\frac{dI((t_0)}{dt} &= d - dS(t_0) - \beta S(t_0)\left(\int_0^{t_0} \varphi I(u)\sigma(t_0-u)P(t_0-u)e^{-d(t_0-u)}du + \sigma(t_0)I_{T_0}(t_0)\right) \\
&\quad + \frac{dI_{T_0}(t_0)}{dt} + \int_0^{t_0} \varphi I(u)e^{-d(t_0-u)}\big(P'(t_0-u) - dP(t_0-u)du\big) \\
&= d\left(1 - S(t_0) - e^{-dt_0}\int_0^{\infty} I_T(0,u)\frac{P(t_0+u)}{P(u)}du - \int_0^{t_0} \varphi I(u)e^{-d(t_0-u)}P(t_0-u)du\right) \\
&\quad - \beta S(t_0)\left(\int_0^{t_0} \varphi I(u)\sigma(t_0-u)P(t_0-u)e^{-d(t_0-u)}du + \sigma(t_0)I_{T_0}(t_0)\right) \\
&\quad + e^{-dt_0}\int_0^{\infty} I_T(0,u)\frac{P'(t_0+u)}{P(u)}du + \int_0^{t_0} \varphi I(u)e^{-d(t_0-u)}P'(t_0-u)du
\end{aligned}$$

$$\begin{aligned}
&= -\beta S(t_0)\left(\int_0^{t_0} \varphi I(u)\sigma(t_0-u)P(t_0-u)e^{-d(t_0-u)}du + \sigma(t_0)I_{T_0}(t_0)\right) \\
&\quad + e^{-dt_0}\int_0^{\infty} I_T(0,u)\frac{P'(t_0+u)}{P(u)}du + \int_0^{t_0} \varphi I(u)e^{-d(t_0-u)}P'(t_0-u)du < 0.
\end{aligned}$$

Since we assumed P is non-increasing , $P'(t) \leq 0$. Therefore $\frac{dI((t_0)}{dt} > 0$ and $I(t) > 0$ for all t. From equation (3.11b) we can see that $I_T(t) > 0$ since $I(u)$, $P(t-u)$, and $e^{-d(t_0-u)}$ are all positive. Finally the condition $S + I + I_T = 1$ ensures that the solutions are bounded and this completes the proof. □

The proof provided here is similar to the proof given for an SI model with vaccination [2].

3.4 Discrete-Age-Structured Model

Consider the following treatment-age groups for the treated individuals:

$$I_T^i(t) = \int_{a_{i-1}}^{a_i} I(s,t)ds, \quad \text{for} \quad 1 \leq i \leq n,$$

where $0 = a_0 \leq a_1 \leq \cdots \leq a_{n-1} \leq a_n = a^*$. Assume the infectivity of each age group is reduced by σ_i and the rate of returning to the infective class for each age group is θ_i for $1 \leq i \leq n$. Suppose the individuals of age group I_T^i move to I_T^{i+1} at rate γ_i for $1 \leq i \leq n-1$. Let S, I and $I_T^i, \quad 1 \leq i \leq n$ be fractions, then we have the following

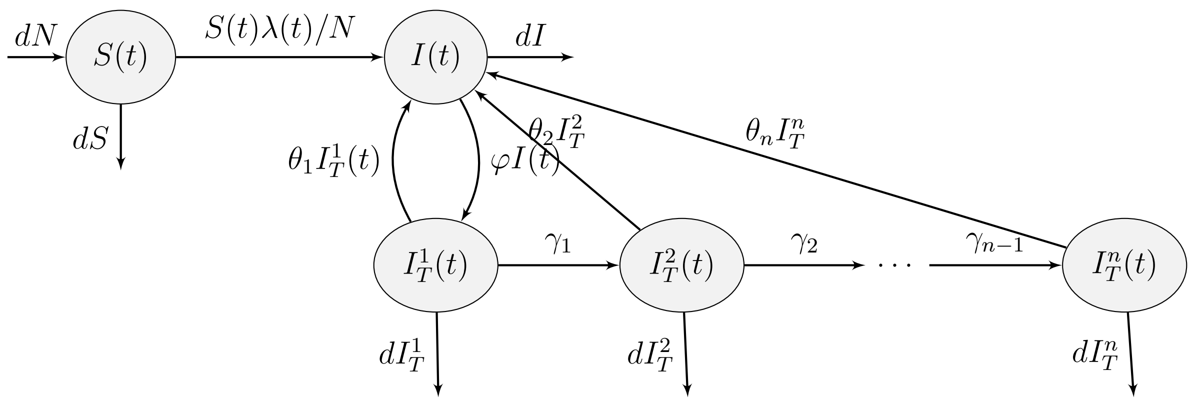

Figure 3.3: Flow diagram for the discrete age structured model.

equations:

$$\begin{aligned}
S'(t) &= d - dS(t) - S(t)\lambda(t) \\
I'(t) &= S(t)\lambda(t) + \sum_{i=1}^{n} \theta_i I_T^i(t) - (\varphi + d)I(t) \\
I_T^{1'}(t) &= \varphi I(t) - (\theta_1 + \gamma_1 + d)I_T^1(t) \\
I_T^{i'}(t) &= \gamma_{i-1} I_T^{i-1}(t) - (\theta_i + \gamma_i + d)I_T^i(t), \quad \text{for} \quad 2 \leq i \leq n-1 \\
I_T^{n'}(t) &= \gamma_{n-1} I_T^{n-1}(t) - (\theta_n + d)I_T^n(t)
\end{aligned} \tag{3.13}$$

where

$$\lambda(t) = \beta(I(t) + \sigma_1 I_T^1(t) + \cdots + \sigma_n I_T^n(t)).$$

Let $x = (x_1, \cdots, x_{n+1})$, y denote the disease and non disease compartments, respectively, and $\mathcal{D}$ be the feasible set for system (3.13)

$$\mathcal{D} = \{(x, y) \in \mathbb{R}^{n+2} : x_1 + x_2 + \cdots + x_{n+1} + y = 1\}.$$

Let $I = I_T^i = 0, \quad 1 \leq i \leq n$, then the disease free equilibrium point is given by $E_0 = (1, 0, \cdots, 0)$.

Chapter 4

Mathematical Analysis

The models derived in Chapter 3 using different approaches are analysed in this chapter. The stability of the disease free equilibrium and the treshold value, $\mathcal{R}_0$, are given for each method.

4.1 Direct Approach

Let S, I and I_T be fractions; then System (3.1) is equivalent to

$$\frac{dS}{dt} = d - dS(t) - S(t)\lambda(t) \tag{4.1a}$$

$$\frac{dI}{dt} = S(t)\lambda(t) - dI(t) - \varphi I(t) + \int_0^\infty \theta(s) I_T(s,t)ds \tag{4.1b}$$

$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a}\right) I_T(a,t) = -(\theta(a) + d) I_T(a,t). \tag{4.1c}$$

Let $I = I_T = 0$ to get the disease free equilibrium point $E_0 = (1, 0, 0)$. To linearize System (4.1) about E_0, let $u(t) = S(t) - 1$ and I and I_T be as before:

$$\frac{du}{dt} = -du(t) - \beta\left(\int_0^\infty \sigma(s) I_T(s,t)ds + I(t)\right) \tag{4.2a}$$

$$\frac{dI}{dt} = \beta\left(\int_0^\infty \sigma(s) I_T(s,t)ds + I(t)\right) - dI(t) - \varphi I(t) + \int_0^\infty \theta(s) I_T(s,t)ds \tag{4.2b}$$

$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a}\right) I_T(a,t) = -(\theta(a) + d) I_T(a,t) \tag{4.2c}$$

with the boundary condition

$$I_T(0,t) = \varphi I(t). \tag{4.2d}$$

Here we omitted the initial value, since we are interested in the long term behaviour of the system. Since $u(t)$ does not play a role in Equations (4.2b) and (4.2c), we can omit Equation (4.2a). Let

$$I(t) = \bar{I} e^{zt}, \quad I_T(a,t) = \bar{I}_T(a) e^{zt}.$$

Substituting these *ansatz* solutions in System (4.2), we get

$$z\bar{I} = (\beta - d - \varphi)\bar{I} + \beta \int_0^\infty \sigma(s)\bar{I}_T(s)ds + \int_0^\infty \theta(s)\bar{I}_T(s)ds$$

$$\bar{I}_T'(a) = -(\theta(a) + d + z)\bar{I}_T(a)$$

$$\bar{I}_T(0) = \varphi \bar{I}.$$

In the second equation $\bar{I}_T'(a) = \frac{d}{da}\bar{I}_T(a)$, i.e., the second equation is an ODE for $\bar{I}_T$. Solving the equation, we have

$$\bar{I}_T(a) = \varphi \bar{I} e^{-da - za - \int_0^a \theta(v)dv},$$

and substituting this in the first equation gives

$$z = (\beta - d - \varphi) + \int_0^\infty (\beta\sigma(s) + \theta(s))\varphi e^{-ds - zs - \int_0^s \theta(v)dv} ds. \tag{4.3}$$

Equation (4.3) is the characteristic equation for the System (3.1). In the next section the same characteristic equation will be obtained, so we leave the analysis of this equation for the next section.

4.2 Delay-Integro-Differential Equation

In this section, we study the equation obtained in Section 3.2 by transforming System (3.1) to a delay differential equation. Let $F(I(t))$ be the right hand side of the equation (3.5), so $dI/dt = F(I(t))$. Let $DF(0)$ be the *Fréchet* derivative of the operator F at the steady state $I = 0$, which is obtained by the formula:

$$DF(x)h = \lim_{r \to 0} \frac{F(x + rh) - F(x)}{r}.$$

Using this formula for $DF(0)$, we get

$$
\begin{aligned}
DF(0)I(t) &= \lim_{r\to 0}\frac{F(rI(t))-F(0)}{r}\\
&= \lim_{r\to 0}\frac{1}{r}\Bigg((\beta-d-\varphi)rI(t)+\int_0^t \varphi(\beta\sigma(s)+\theta(s))e^{-ds-\int_0^s\theta(u)du}rI(t-s)ds\\
&+\int_t^\infty(\beta\sigma(s)+\theta(s))\psi(s-t)e^{-dt-\int_{s-t}^s\theta(u)du}ds-r^2I^2(t)\\
&-rI(t)\big(\int_0^t(1+\sigma(s))\varphi e^{-ds-\int_0^s\theta(u)du}rI(t-s)ds\\
&+\int_t^\infty(1+\sigma(s))\psi(s-t)e^{-dt-\int_{s-t}^s\theta(u)du}ds\big)\\
&-\int_0^t \varphi e^{-ds-\int_0^s\theta(u)du}rI(t-s)ds\int_0^t\varphi\sigma(s)e^{-ds-\int_0^s\theta(u)du}rI(t-s)ds\\
&-\int_t^\infty \psi(s-t)e^{-dt-\int_{s-t}^s\theta(u)du}ds\int_t^\infty\sigma(s)\psi(s-t)e^{-dt-\int_{s-t}^s\theta(u)du}ds\\
&-\int_0^t \varphi e^{-ds-\int_0^s\theta(u)du}rI(t-s)ds\int_t^\infty\sigma(s)\psi(s-t)e^{-dt-\int_{s-t}^s\theta(u)du}ds\\
&-\int_0^t \varphi\sigma(s) e^{-ds-\int_0^s\theta(u)du}rI(t-s)ds\int_t^\infty\psi(s-t)e^{-dt-\int_{s-t}^s\theta(u)du}ds\\
&+\int_t^\infty(\beta\sigma(s)+\theta(s))\psi(s-t)e^{-dt-\int_{s-t}^s\theta(u)du}ds\\
&+\int_t^\infty \psi(s-t)e^{-dt-\int_{s-t}^s\theta(u)du}ds\int_t^\infty\sigma(s)\psi(s-t)e^{-dt-\int_{s-t}^s\theta(u)du}ds\Bigg)\\
&= \lim_{r\to 0}\Bigg((\beta-d-\varphi)I(t)+\int_0^t \varphi(\beta\sigma(s)+\theta(s))e^{-ds-\int_0^s\theta(u)du}I(t-s)ds-rI^2(t)\\
&-I(t)\big(\int_0^t(1+\sigma(s))\varphi e^{-ds-\int_0^s\theta(u)du}rI(t-s)ds\\
&+\int_t^\infty(1+\sigma(s))\psi(s-t)e^{-dt-\int_{s-t}^s\theta(u)du}ds\big)\\
&-\int_0^t \varphi e^{-ds-\int_0^s\theta(u)du}I(t-s)ds\int_0^t\varphi\sigma(s)e^{-ds-\int_0^s\theta(u)du}rI(t-s)ds\\
&-\int_0^t \varphi e^{-ds-\int_0^s\theta(u)du}I(t-s)ds\int_t^\infty\sigma(s)\psi(s-t)e^{-dt-\int_{s-t}^s\theta(u)du}ds\\
&-\int_0^t \varphi\sigma(s) e^{-ds-\int_0^s\theta(u)du}I(t-s)ds\int_t^\infty\psi(s-t)e^{-dt-\int_{s-t}^s\theta(u)du}ds\Bigg)
\end{aligned}
$$

$$
\begin{aligned}
&= (\beta - d - \varphi)I(t) + \int_0^t \varphi(\beta\sigma(s) + \theta(s))e^{-ds-\int_0^s \theta(u)du} I(t-s)ds \\
&\quad - I(t)\int_t^\infty (1+\sigma(s))\psi(s-t)e^{-dt-\int_{s-t}^s \theta(u)du}ds \\
&\quad - \int_0^t \varphi e^{-ds-\int_0^s \theta(u)du} I(t-s)ds \int_t^\infty \sigma(s)\psi(s-t)e^{-dt-\int_{s-t}^s \theta(u)du}ds \\
&\quad - \int_0^t \varphi\sigma(s) e^{-ds-\int_0^s \theta(u)du} I(t-s)ds \int_t^\infty \psi(s-t)e^{-dt-\int_{s-t}^s \theta(u)du}ds.
\end{aligned}
$$

Therefore the associated linear equation is obtained by setting $dI/dt = DF(0)I(t)$

$$
\begin{aligned}
\frac{dI}{dt} &= (\beta - d - \varphi)I(t) + \int_0^t \varphi(\beta\sigma(s) + \theta(s))e^{-ds-\int_0^s \theta(u)du} I(t-s)ds \\
&\quad - I(t)\int_t^\infty (1+\sigma(s))\psi(s-t)e^{-dt-\int_{s-t}^s \theta(u)du}ds \\
&\quad - \int_0^t \varphi e^{-ds-\int_0^s \theta(u)du} I(t-s)ds \int_t^\infty \sigma(s)\psi(s-t)e^{-dt-\int_{s-t}^s \theta(u)du}ds \\
&\quad - \int_0^t \varphi\sigma(s) e^{-ds-\int_0^s \theta(u)du} I(t-s)ds \int_t^\infty \psi(s-t)e^{-dt-\int_{s-t}^s \theta(u)du}ds.
\end{aligned} \tag{4.4}
$$

Let

$$
\begin{aligned}
b &= (\varphi + d - \beta), \\
K(s) &= \varphi(\beta\sigma(s) + \theta(s))e^{-ds-\int_0^s \theta(u)du}, \\
Q_1(t) &= \int_t^\infty (1+\sigma(s))\psi(s-t)e^{-dt-\int_{s-t}^s \theta(u)du}ds, \\
Q_2(t) &= \int_t^\infty \sigma(s)\psi(s-t)e^{-dt-\int_{s-t}^s \theta(u)du}ds, \\
Q_3(t) &= \int_t^\infty \psi(s-t)e^{-dt-\int_{s-t}^s \theta(u)du}ds,
\end{aligned} \tag{4.5}
$$

then (4.4) can be written as

$$
\begin{aligned}
\frac{dI}{dt} &= -(b + Q_1(t))I(t) + \int_0^t K(s)I(t-s)ds - Q_2(t)\int_0^t \varphi e^{-ds-\int_0^s \theta(u)du} I(t-s)ds \\
&\quad - Q_3(t)\int_0^t \varphi\sigma(s)e^{-ds-\int_0^s \theta(u)du} I(t-s)ds,
\end{aligned} \tag{4.6}
$$

which is a linear non-autonomous delay-integro-differential equation. The stability analysis of this equation is very complicated and we consider the case where the boundary condition is trivial, i.e., $I_T(a,0) = 0$.

Let $\psi(a) = 0$ in (4.4), then we get the following linear equation associated to (3.5) in section 3.2

$$\frac{dI}{dt} + bI(t) = \int_0^t K(s)I(t-s)ds, \tag{4.7}$$

where b and $K(s)$ are defined in (4.5).

The following theorem gives the stability of the DFE of the System (4.1) and the Equation (4.7).

Theorem 4.1. *Let*

$$\mathcal{R}_0 = \frac{\beta}{d}\,\frac{1 + \int_0^\infty \varphi\sigma(s)e^{-ds-\int_0^s \theta(v)dv}ds}{1 + \varphi\int_0^\infty e^{-ds-\int_0^s \theta(v)dv}ds}.$$

The disease free equilibrium point is locally asymptotically stable if $\mathcal{R}_0 < 1$ and unstable for $\mathcal{R}_0 > 1$.

Proof. Use the *ansatz* $I(t) = e^{zt}$ in Equation (4.7), then

$$ze^{zt} + be^{zt} = \int_0^\infty K(s)e^{z(t-s)}ds,$$

and after simplification we get the characteristic equation

$$z + b = \int_0^\infty K(s)e^{-zs}ds. \tag{4.8}$$

Suppose $\mathcal{R}_0 < 1$ and let $z = x + iy$, we show that all roots of the characteristic equation have negative real parts. Assume $x > 0$ and take the norm of both sides of (4.8)

$$\begin{aligned}|z + \varphi + d - \beta| &\leq \int_0^\infty K(s)|e^{-zs}|ds \\ &\leq \int_0^\infty K(s)ds,\end{aligned}$$

since $e^{-xs} < 1$ for $x > 0$,

$$(x + \varphi + d - \beta)^2 + y^2 \leq \left(\int_0^\infty K(s)ds\right)^2$$

and therefore

$$(x + \varphi + d - \beta)^2 - \left(\int_0^\infty K(s)ds\right)^2 < -y^2,$$

but

$$(x + \varphi + d - \beta)^2 - \left(\int_0^\infty K(s)ds\right)^2 > 0$$

for $x > 0$. To see this we need to show that

$$\varphi + d - \beta > \int_0^\infty K(s)ds,$$

for $\mathcal{R}_0 < 1$. Suppose this inequality does not hold, i.e.,

$$\varphi + d - \beta \leq \int_0^\infty K(s)ds,$$

equivalently

$$\varphi + d - \beta \leq \int_0^\infty (\beta\sigma(s) + \theta(s))e^{-ds - \int_0^s \theta(v)dv}ds,$$

hence

$$\beta + \int_0^\infty \beta\varphi\sigma(s)e^{-ds - \int_0^s \theta(v)dv}ds \geq \varphi + d - \int_0^\infty \varphi\theta(s)e^{-ds - \int_0^s \theta(v)dv}ds.$$

On the other hand we can see that

$$\begin{aligned}\varphi - \int_0^\infty \varphi\theta(s)e^{-ds-\int_0^s \theta(v)dv}ds &= \varphi\Big(1 - \int_0^\infty \theta(s)e^{-ds-\int_0^s \theta(v)dv}ds\Big)\\ &= \varphi\Big(1 - \lim_{r\to\infty}\int_0^r \theta(s)e^{-ds-\int_0^s \theta(v)dv}ds\Big)\end{aligned}$$

$$\begin{aligned}&= \varphi\Big(1 - \lim_{r\to\infty}\big(e^{-dr} - e^{-dr-\int_0^r \theta(v)dv}\\ &\quad + \int_0^r (de^{-ds} - de^{-ds-\int_0^s \theta(v)dv})ds\big)\Big)\\ &= \varphi d\int_0^\infty e^{-ds-\int_0^s \theta(v)dv}ds,\end{aligned}$$

therefore

$$\beta + \int_0^\infty \beta\varphi\sigma(s)e^{-ds-\int_0^s \theta(v)dv}ds \geq d + \varphi d\int_0^\infty e^{-ds-\int_0^s \theta(v)dv}ds,$$

which in turn implies that $\mathcal{R}_0 \geq 1$ and this is a contradiction. Thus all eigenvalues of the characteristic equation have negative real parts and by Theorem 2.18, the DFE is locally asymptotically stable.

For $\mathcal{R}_0 > 1$, we show that (4.8) has a positive real root. Let $f_1(x) = x + \varphi + d - \beta$ and $f_2(x) = \int_0^\infty K(s)e^{-xs}ds$. It is easy to see that $f_1(x)$ is increasing and $\lim_{x\to\infty} f_1(x) = \infty$ and $f_2(x)$ is non-increasing, since

$$f_2'(x) = -\int_0^\infty sK(s)e^{-xs}ds \leq 0$$

for all $x > 0$. Since $\mathcal{R}_0 > 1$ we have

$$\begin{aligned}d + \varphi - \int_0^\infty \varphi\theta(s)e^{-ds-\int_0^s \theta(v)dv}ds &= d + d\int_0^\infty \varphi e^{-ds-\int_0^s \theta(v)dv}ds\\ &< \beta + \int_0^\infty \beta\varphi\sigma(s)e^{-ds-\int_0^s \theta(v)dv}ds,\end{aligned}$$

thus

$$\varphi + d - \beta < \int_0^\infty K(s)ds,$$

equivalently $f_1(0) < f_2(0)$, therefore there exists $x > 0$ such that $f_1(x) = f_2(x)$, which means that the characteristic equation (4.8) has a positive real root. So the disease free equilibrium point is unstable. $\square$

4.3 Survival Function Approach

System (3.6) has the disease free equilibrium point $(S, I_T) = (1, 0)$. We discuss the stability by linearizing:

$$\frac{dS}{dt} = -dS(t) + \beta\left(S(t) + I_T(t) + \int_0^t \varphi(S(u) + I_T(u))\sigma(t-u)P(t-u)e^{-d(t-u)}du\right) \tag{4.9a}$$

$$I_T(t) = \int_0^t \varphi(-S(u) - I_T(u))P(t-u)e^{-d(t-u)}du. \tag{4.9b}$$

Using the *ansatz* $S(t) = C_1 e^{zt}$ and $I_T(t) = C_2 e^{zt}$

$$\begin{aligned} C_1\Big[Z - \beta\big(1 + \int_0^\infty \varphi\sigma(u)P(u)e^{-Zu}du\big)\Big] & -C_2\beta\big(1 + \int_0^\infty \varphi\sigma(u)P(u)e^{-Zu}du\big) & = 0 \\ C_1\int_0^\infty \varphi P(u)e^{-Zu}du & +C_2\big(1 + \int_0^\infty \varphi P(u)e^{-Zu}du\big) & = 0. \end{aligned}$$

where $Z = z + d$. For this system to have a non trivial solution, the determinant of coefficients must be zero. Therefore

$$\left[Z - \beta\left(1 + \int_0^\infty \varphi\sigma(u)P(u)e^{-Zu}du\right)\right]\left(1 + \int_0^\infty \varphi P(u)e^{-Zu}du\right)$$
$$+ \beta\left(1 + \int_0^\infty \varphi\sigma(u)P(u)e^{-Zu}du\right)\int_0^\infty \varphi P(u)e^{-Zu}du = 0.$$

This system leads to the following characteristic equation

$$Z - \beta\left(1 + \int_0^\infty \varphi\sigma(u)P(u)e^{-Zu}du\right) + Z\int_0^\infty \varphi P(u)e^{-Zu}du = 0. \tag{4.10}$$

Consider the special case where σ is constant, which means that the infectivity of the treated infective individuals is reduced by the same value for all ages. In this case, we have the following system:

$$\frac{dS}{dt} = d - dS(t) - \beta S(t)(I(t) + \sigma I_T(t)) \tag{4.11a}$$

$$I_T(t) = I_{T0}(t) + \int_0^t \varphi I(u)P(t-u)e^{-d(t-u)}du, \tag{4.11b}$$

where I_{T_0} is given in (3.7). Let $\bar{t}_1$ and $\bar{t}_2$ be the total average time in I and I_T class, respectively. Let

$$\lambda_1 = \beta, \quad \lambda_2 = \sigma\beta. \tag{4.12}$$

The basic reproduction number can be defined as the sum of the basic reproduction numbers associated to I and I_T, that are defined to be the product of λ_i and the total average time $\bar{t}_i$:

$$\mathcal{R}_0 = \lambda_1\bar{t}_1 + \lambda_2\bar{t}_2. \tag{4.13}$$

Let $\tilde{P} = \int_0^\infty P(u)e^{-du}du$. The average time spent in I is given by the following series:

$$\bar{t}_1 = \frac{1}{d+\varphi}\left(1 + \frac{\varphi}{d+\varphi}(1-d\tilde{P}) + \frac{\varphi^2}{(d+\varphi)^2}(1-d\tilde{P})^2 + \cdots\right) = \frac{1}{d(1+\varphi\tilde{P})}, \tag{4.14}$$

which is the average time spent in I on the first pass multiplied by the sum of probabilities of surviving I and I_T in the *ith* visit. Since the average time spent in both I and I_T is $1/d$ we have $\bar{t}_1 + \bar{t}_2 = 1/d$ and therefore

$$\bar{t}_2 = \frac{1}{d} - \frac{1}{d(1+\varphi\tilde{P})} = \frac{\varphi\tilde{P}}{d(1+\varphi\tilde{P})}. \tag{4.15}$$

Substituting these in (4.13) the basic reproduction number is given by

$$\mathcal{R}_0 = \lambda_1\bar{t}_1 + \lambda_2\bar{t}_2 = \frac{\beta}{d(1+\varphi\tilde{P})} + \frac{\sigma\beta\varphi\tilde{P}}{d(1+\varphi\tilde{P})} = \frac{\beta(1+\sigma\varphi\tilde{P})}{d(1+\varphi\tilde{P})}. \tag{4.16}$$

Conjecture 4.2. *The disease free equilibrium point is locally asymptotically stable if* $\mathcal{R}_0 < 1$ *and unstable if* $\mathcal{R}_0 > 1$.

Proof. The characteristic equation is given by

$$(z+d-\beta) + \varphi(z+d-\sigma\beta)\int_0^\infty P(u)e^{-(z+d)u}du = 0. \tag{4.17}$$

We show that if $\mathcal{R}_0 > 1$, then there exists a positive real root. Let x be real, then

$$(x+d-\beta) = -\varphi(x+d-\sigma\beta)\lim_{r\to\infty}\left(\int_0^r P(u)e^{-(d+x)u}du\right). \tag{4.18}$$

Define $f_1(x) = (x+d-\beta)$ and $f_2(x) = -\varphi(x+d-\sigma\beta)\lim\limits_{r\to\infty}\left(\int_0^r P(u)e^{-(d+x)u}du\right)$, then

$$
\begin{aligned}
f_1(0) &= (d-\beta), \\
f_2(0) &= -\varphi(d-\sigma\beta)\lim_{r\to\infty}\left(\int_0^r P(u)e^{-du}du\right)
\end{aligned}
$$

and

$$
\begin{aligned}
f_1(0)-f_2(0)<0 &\Leftrightarrow \beta\left(1+\sigma\varphi\int_0^\infty P(u)e^{-du}du\right) > d\left(1+\varphi\int_0^\infty P(u)e^{-du}du\right) \\
&\Leftrightarrow \frac{\beta(1+\sigma\varphi\tilde{P})}{d(1+\varphi\tilde{P})} > 1.
\end{aligned}
$$

We can see that $\lim\limits_{x\to\infty} f_1(x) = \infty$ and f_1 is an increasing function of x. On the other hand, f_2 is nonincreasing for $x > 0$,

$$
\begin{aligned}
f_2'(x) &= \lim_{r\to\infty}\left(\int_0^r (-\varphi P(u)e^{-(d+x)u} + \varphi u(x+d-\sigma\beta)P(u)e^{-(d+x)u})du\right) \\
&= -\lim_{r\to\infty}\left(\int_0^r \varphi P(u)e^{-(d+x)u}(1+u(\sigma\beta-d-x)du)\right) < 0,
\end{aligned}
$$

since

$$
\begin{aligned}
\lim_{r\to\infty}\left(\int_0^r P(u)e^{-(d+x)u}(1+u(\sigma\beta-d-x))du\right) = \lim_{r\to\infty}\Bigg((1+r(\sigma\beta-d-x))\int_0^r P(w)e^{-(d+x)w}dw \\
+(x+d-\sigma\beta)\int_0^r\int_0^u P(w)e^{-(d+x)w}dwdu\Bigg) > 0.
\end{aligned}
$$

For the last inequality, we can see that $(1+r(\sigma\beta-d-x))\int_0^r P(w)e^{-(d+x)w}dw \to +\infty$ for those values of $x > 0$ such that $x+d-\sigma\beta > 0$. Therefore $f_1(x) = f_2(x)$ has a positive root.

We also need to show that all roots of (4.17) have negative real parts for $\mathcal{R}_0 < 1$ and have not yet been able to do so. Thus, the proof is incomplete at the moment. $\square$

Remark 4.3. *Note that for two extreme values $\sigma = 1$ and $\sigma = 0$, we get $\mathcal{R}_0 = \beta/d$ and $\mathcal{R}_0 = \beta/d(1+\varphi\tilde{P})$. The case $\sigma = 1$ is similar to an SI model and $\sigma = 0$ is similar to an SIR model with relapse studied in [17].*

Next, we consider two special cases for $P(t)$: exponential and step functions.

Exponential Function The exponential function $P(t) = e^{-\theta t}$ reduces System (4.11) to a system of ordinary differential equations.

$$\frac{dS}{dt} = d - dS(t) - \beta S(t)(I(t) + \sigma I_T(t)) \tag{4.19a}$$

$$\frac{dI_T}{dt} = \varphi I(t) - (d+\theta)I_T(t) \tag{4.19b}$$

$$\frac{dI}{dt} = -\left(d - dS(t) - \beta S(t)(I(t) + \sigma I_T(t)) + \varphi I(t) - (d+\theta)I_T(t)\right). \tag{4.19c}$$

First, we find an expression for $\mathcal{R}_0$ using the next generation matrix. We have

$$\mathcal{F} = \begin{bmatrix} \beta S(t)(I(t) + \sigma I_T(t)) \\ 0 \end{bmatrix}, \quad \mathcal{V} = \begin{bmatrix} d - dS(t) + \varphi I(t) - (d+\theta)I_T(t) \\ -\varphi I(t) + (d+\theta)I_T(t) \end{bmatrix}$$

and

$$F = \begin{bmatrix} \beta & \sigma\beta \\ 0 & 0 \end{bmatrix}, \quad V = \begin{bmatrix} d+\varphi & -\theta \\ -\varphi & d+\theta \end{bmatrix}$$

therefore

$$FV^{-1} = \frac{1}{d(d+\varphi+\theta)} \begin{bmatrix} \beta(d+\theta) + \sigma\beta\varphi & \beta\theta + \sigma\beta(d+\varphi) \\ 0 & 0 \end{bmatrix}$$

Finally $\mathcal{R}_0$ is given by

$$\rho(FV^{-1}) = \frac{\beta(d+\theta) + \sigma\beta\varphi}{d(d+\varphi+\theta)}. \tag{4.20}$$

On the other hand the total average times in I and I_T are given by

$$\bar{t}_1 = \frac{d+\theta}{d(d+\theta+\varphi)}, \quad \bar{t}_2 = \frac{\varphi}{d(d+\theta+\varphi)} \tag{4.21}$$

so we get

$$\begin{aligned} \mathcal{R}_0 &= \lambda_1 \bar{t}_1 + \lambda_2 \bar{t}_2 \\ &= \beta \frac{d+\theta}{d(d+\theta+\varphi)} + \sigma\beta \frac{\varphi}{d(d+\theta+\varphi)} \\ &= \frac{\beta(d+\theta)+\sigma\beta\varphi}{d(d+\varphi+\theta)}. \end{aligned} \tag{4.22}$$

These results show that the basic reproduction number given by (4.16) is valid for the exponential function.

Step Function Consider the following function for $P(t)$:

$$P(t) = \begin{cases} 1 & \text{for } 0 \le t \le \tau; \\ 0 & \text{for } t > \tau. \end{cases}$$

Using this, for $t \ge \tau$, System (4.11) can be written as

$$\frac{dS}{dt} = d - dS(t) - \beta S(t)(I(t) + \sigma I_T(t)) \tag{4.23a}$$

$$I_T(t) = \int_{t-\tau}^{t} \varphi(1 - S(u) - I_T(u))e^{-d(t-u)}du \tag{4.23b}$$

since $I_{T_0}(t) = 0$ for $t \ge \tau$, and $\lambda(t) = \beta(I(t) + \sigma I_T(t))$, (4.23a) reduces to the following system of discrete delay equations:

$$\frac{dS}{dt} = d - dS(t) - \beta S(t)(I(t) + \sigma I_T(t)) \tag{4.24a}$$

$$\frac{dI_T}{dt} = \varphi(I(t) - e^{-d\tau} I(t-\tau)) - dI_T(t). \tag{4.24b}$$

For this step function, $\tilde{P} = \int_0^\tau e^{-du} du = (1 - e^{-d\tau})/d$ and from (4.16) we have

$$\mathcal{R}_0 = \frac{\beta(1 + \sigma\varphi\tilde{P})}{d(1 + \varphi\tilde{P})} = \frac{\beta(d + \sigma\varphi(1 - e^{-d\tau}))}{d(d + \varphi(1 - e^{-d\tau}))}. \tag{4.25}$$

The step survival function for treated infective compartment means that the individuals stay in this class for a fixed time τ after starting the treatment and then return to the infective class. Note that if there is no delay, i.e., $\tau = 0$, then $\mathcal{R}_0 = \beta/d$.

4.4 Discrete-Age-Structured Model

The analysis for local and global stability of the disease free equilibrium point is given in this section. The basic reproduction number is derived and existence of the endemic equilibrium point is discussed.

Here we use the method of next-generation-matrix to compute the basic reproduction number. First note that we can omit the first equation in (3.13), since $S(t) = 1 - I(t) -$

$\sum_{i=1}^{n} I_T^i(t)$. So we consider the following system

$$\begin{aligned}
I'(t) &= \beta(1 - I(t) - \sum_{i=1}^{n} I_T^i(t))\lambda(t) + \sum_{i=1}^{n} \theta_i I_T^i(t) - (\varphi + d)I(t) \\
I_T^{1'}(t) &= \varphi I(t) - (\theta_1 + \gamma_1 + d)I_T^1(t) \\
I_T^{i'}(t) &= \gamma_{i-1} I_T^{i-1}(t) - (\theta_i + \gamma_i + d)I_T^i(t), \quad \text{for} \quad 2 \le i \le n-1 \\
I_T^{n'}(t) &= \gamma_{n-1} I_T^{n-1}(t) - (\theta_n + d)I_T^n(t)
\end{aligned} \tag{4.26}$$

Let $x'(t) = G(x(t))$. The new infections and flow within and out of the infected compartments are given by

$$\mathcal{F} = \begin{bmatrix} \beta(1 - I(t) - \sum_{i=1}^{n} I_T^i(t))\lambda(t) \\ 0 \\ \vdots \\ 0 \end{bmatrix}, \quad \mathcal{V} = \begin{bmatrix} (\varphi + d)I(t) - \sum_{i=1}^{n} \theta_i I_T^i(t) \\ (\theta_1 + \gamma_1 + d)I_T^1(t) - \varphi I(t) \\ \vdots \\ (\theta_i + \gamma_i + d)I_T^i(t) - \gamma_{i-1} I_T^{i-1}(t) \\ \vdots \\ (\theta_n + d)I_T^n(t) - \gamma_{n-1} I_T^{n-1}(t) \end{bmatrix}$$

i.e., $G(x) = (\mathcal{F} - \mathcal{V})(x)$. The derivative of $\mathcal{F}$ and $\mathcal{V}$ at $x = 0$ are as follows

$$F = \begin{bmatrix} \beta & \beta\sigma_1 & \beta\sigma_2 & \dots & \beta\sigma_n \\ 0 & 0 & 0 & \dots & 0 \\ \vdots & \vdots & \vdots & & \vdots \\ 0 & 0 & 0 & \dots & 0 \end{bmatrix},$$

$$V = \begin{bmatrix} d+\varphi & -\theta_1 & -\theta_2 & \dots & -\theta_n \\ -\varphi & (\theta_1+\gamma_1+d) & 0 & \dots & 0 \\ 0 & -\gamma_1 & (\theta_2+\gamma_2+d) & \dots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \dots & -\gamma_{n-1} & (\theta_n+d) \end{bmatrix}.$$

Since F has only one nonzero row, we only need the first column of V^{-1} which is given below

$$V^{-1} = \frac{1}{D} \begin{bmatrix} \prod_{i=1}^{n-1}(\theta_i+\gamma_i+d)(\theta_n+d) & .. & .. & .. & .. \\ \varphi \prod_{i=2}^{n-1}(\theta_i+\gamma_i+d)(\theta_n+d) & .. & .. & .. & .. \\ \varphi\gamma_1 \prod_{i=3}^{n-1}(\theta_i+\gamma_i+d)(\theta_n+d) & .. & .. & .. & .. \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ \varphi\gamma_1\gamma_2\dots\gamma_{n-2}(\theta_n+d) & .. & .. & .. & .. \\ \varphi\gamma_1\gamma_2\dots\gamma_{n-1} & .. & .. & .. & .. \end{bmatrix}$$

where

$$\begin{aligned} D = {} & (d+\varphi)\prod_{i=1}^{n-1}(\theta_i+\gamma_i+d)(\theta_n+d) - \varphi\theta_1\prod_{i=2}^{n-1}(\theta_i+\gamma_i+d)(\theta_n+d) \\ & - \varphi\theta_2\gamma_1\prod_{i=3}^{n-1}(\theta_i+\gamma_i+d)(\theta_n+d) - \dots - \varphi\theta_{n-1}\gamma_1\gamma_2\cdots\gamma_{n-2}(\theta_n+d) \\ & - \varphi\theta_n\gamma_1\gamma_2\cdots\gamma_{n-1}. \end{aligned}$$

Theorem 4.4. *Let*

$$\begin{aligned}\mathcal{R}_0 = \rho(FV^{-1}) = \frac{\beta}{D}\Bigg(&\prod_{i=1}^{n-1}(\theta_i+\gamma_i+d)(\theta_n+d)\\ &+\varphi\sigma_1\prod_{i=2}^{n-1}(\theta_i+\gamma_i+d)(\theta_n+d)+\varphi\sigma_2\gamma_1\prod_{i=3}^{n-1}(\theta_i+\gamma_i+d)(\theta_n+d)\\ &+\cdots+\varphi\sigma_{n-1}\gamma_1\gamma_2\cdots\gamma_{n-1}(\theta_n+d)+\varphi\sigma_n\gamma_1\gamma_2\cdots\gamma_{n-1}\Bigg),\end{aligned} \tag{4.27}$$

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

Remark 4.5. *It is easy to see that*

$$\mathbf{1}V = d\mathbf{1}, \quad \textit{and} \quad \mathbf{1}V^{-1} = \frac{1}{d}\mathbf{1},$$

where $\mathbf{1} = (1, \ldots, 1)^T$. Let $\sigma_{min} \le \sigma_i \le \sigma_{max}$, for all $1 \le i \le n$, then we have the following bounds for $\mathcal{R}_0$

$$\frac{\beta\sigma_{min}}{d} \le \mathcal{R}_0 \le \frac{\beta\sigma_{max}}{d}.$$

Theorem 4.6. *The DFE is globally asymptotically stable if $\mathcal{R}_0 < 1$.*

Proof. By Theorems 2.30 and 2.31, we need to show that $F, V^{-1} \ge 0$, $V^{-1}F$ is irreducible and $f(x) \ge 0$ in $\mathcal{D}$, where $f(x) = (F - V - \mathcal{F} + \mathcal{V})(x)$. Note that we do not have a non disease compartment in System (4.26). From the results above, we can see that F and V^{-1} are nonnegative and V^{-1} is positive so $V^{-1}F$ is irreducible. To see that $f(x) \ge 0$ in

$\mathcal{D}$, note that we have

$$(F-V)(I, I_T^1, \cdots, I_T^n) = \begin{bmatrix} (\beta - d - \varphi)I(t) + \sum_{i=1}^{n}(\beta\sigma_i + \theta_i)I_T^i(t) \\ \varphi I(t) - (\theta_1 + \gamma_1 + d)I_T^1(t) \\ \vdots \\ \gamma_{i-1}I_T^{i-1}(t) - (\theta_i + \gamma_i + d)I_T^i(t) \\ \vdots \\ \gamma_{n-1}I_T^{n-1}(t) - (\theta_n + d)I_T^n(t) \end{bmatrix}$$

and therefore

$$f(I, I_T^1, \cdots, I_T^n) = (F - V - \mathcal{F} + \mathcal{V})(I, I_T^1, \cdots, I_T^n) = \begin{bmatrix} (I + \sum_{i=1}^{n} I_T^i)(I + \sum_{i=1}^{n} \sigma_i I_T^i) \\ 0 \\ \vdots \\ 0 \end{bmatrix}$$

which is a non negative matrix. So by Theorem 2.31, the DFE is globally asymptotically stable for $\mathcal{R}_0 < 1$. □

Existence of The Endemic Equilibrium Point By Theorem 2.31, there exists at least one endemic equilibrium point in the feasible set $\mathcal{D}$. To find the endemic equilibrium point we equate right hand side of (3.13) to zero:

$$\begin{aligned} 0 &= d - dS(t) - \beta S(t)\lambda(t) \\ 0 &= \beta S(t)\lambda(t) + \sum_{i=1}^{n} \theta_i I_T^i(t) - (\varphi + d)I(t) \\ 0 &= \varphi I(t) - (\theta_1 + \gamma_1 + d)I_T^1(t) \\ 0 &= \gamma_{i-1}I_T^{i-1}(t) - (\theta_i + \gamma_i + d)I_T^i(t), \quad \text{for} \quad 2 \le i \le n-1 \\ 0 &= \gamma_{n-1}I_T^{n-1}(t) - (\theta_n + d)I_T^n(t). \end{aligned} \tag{4.28}$$

From the third equation we get

$$I_T^1(t) = \frac{\varphi}{(\theta_1 + \gamma_1 + d)} I(t), \tag{4.29}$$

and for $2 \leq i \leq n-1$ we have

$$I_T^i(t) = \frac{\gamma_{i-1}}{\theta_i + \gamma_i + d} I_T^{i-1}(t).$$

Combining the two equations we get

$$I_T^i(t) = \frac{\varphi \prod_{k=1}^{i-1} \gamma_k}{\prod_{k=1}^{i} (\theta_k + \gamma_k + d)} I(t), \quad 2 \leq i \leq n-1, \tag{4.30}$$

and

$$I_T^n(t) = \frac{\varphi \prod_{k=1}^{n-1} \gamma_k}{(\theta_n + d) \prod_{k=1}^{n-1} (\theta_k + \gamma_k + d)} I(t). \tag{4.31}$$

Let $I_T^i(t) = A_i I(t)$ for $1 \leq i \leq n$ where

$$\begin{aligned} A_1 &= \frac{\varphi}{(\theta_1 + \gamma_1 + d)}, \\ A_i &= \frac{\varphi \prod_{k=1}^{i-1} \gamma_k}{\prod_{k=1}^{i} (\theta_k + \gamma_k + d)}, \quad 2 \leq i \leq n-1, \\ A_n &= \frac{\varphi \prod_{k=1}^{n-1} \gamma_k}{(\theta_n + d) \prod_{k=1}^{n-1} (\theta_k + \gamma_k + d)}, \end{aligned} \tag{4.32}$$

then using the first equation of (4.28) we have

$$I^* = \frac{\beta(1+\sum\limits_{i=1}^{n}\sigma_i A_i) - d(1+\sum\limits_{i=1}^{n} A_i)}{\beta(1+\sum\limits_{i=1}^{n}\sigma_i A_i)(1+\sum\limits_{i=1}^{n} A_i)}. \tag{4.33}$$

Let $E^* = (S^*, I^*, I_T^{1*}, \cdots, I_T^{n*})$ be the endemic equilibrium point where I^* is given by (4.33), $I_T^{i*} = A_i I^*$ and $S^* = 1 - I^*(1+\sum\limits_{i=1}^{n} A_i)$.

Lemma 4.7. *If $\mathcal{R}_0 > 1$, then E^* is the unique endemic equilibrium point in $\mathcal{D}$.*

Proof. To show that E^* is in $\mathcal{D}$, we only need to show $I^* > 0$ for $\mathcal{R}_0 > 1$, and $I^* > 0$ holds if

$$\beta(1+\sum_{i=1}^{n}\sigma_i A_i) - d(1+\sum_{i=1}^{n} A_i) > 0$$

$$\beta(1+\sum_{i=1}^{n}\sigma_i A_i) > d(1+\sum_{i=1}^{n} A_i)$$

$$\frac{\beta(1+\sum\limits_{i=1}^{n}\sigma_i A_i)}{d(1+\sum\limits_{i=1}^{n} A_i)} > 1.$$

A direct computation shows that $\mathcal{R}_0$ given by (4.27) is equal to the following

$$\mathcal{R}_0 = \frac{\beta(1+\sum\limits_{i=1}^{n}\sigma_i A_i)}{d(1+\sum\limits_{i=1}^{n} A_i)},$$

therefore $\mathcal{R}_0 > 1$ implies that $I^* > 0$. $\square$

The Jacobian matrix $DG(E^*)$ derived from System (4.26) is given by

$$DG(E^*) = \begin{bmatrix} -\varphi - d\mathcal{R}_0 + \frac{\beta}{\mathcal{R}_0} & B_1 & B_2 & .. & B_n \\ \varphi & -(\theta_1 + \gamma_1 + d) & 0 & .. & 0 \\ 0 & -\gamma_1 & -(\theta_2 + \gamma_2 + d) & .. & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & .. & 0 & -\gamma_{n-1} & -(\theta_n + d) \end{bmatrix}$$

where $B_\ell = \theta_\ell + d - d\mathcal{R}_0 + \frac{\beta\sigma_\ell}{\mathcal{R}_0}$, $1 \leq \ell \leq n$. To determine the local asymptotic stability of the endemic equilibrium point, we need to study the eigenvalues of this matrix. This is complicated and we have not progressed further at this moment. The result of $1,000,000$ numerical simulations, for random parameter values in appropriate parameter ranges, shows that all eigenvalues of the Jacobian matrix at the endemic equilibrium point have negative real parts, when $\mathcal{R}_0 > 1$ (919,478 cases), and this suggests that E^* is indeed locally asymptotically stable when $\mathcal{R}_0 > 1$.

Chapter 5

Discussions and Conclusions

In infectious diseases where there is no recovery (such as HIV/AIDS), treatment can have both curative and preventive effect and the preventive effect of treatment on reducing the incidence of the disease can be significant, in particular if there is no efficient vaccine available. The emphasis of the current work is on the influence of the duration and efficacy of treatment, and the possible negative effect of interrupting the treatment, on the disease transmission. For this purpose, a mathematical model was formulated to describe the transmission dynamics, using different approaches. Initially a system of integro-differential and partial differential equations was built and then it was transformed to a single delay-integro-differential equation. A survival function approach using a general form of survival function was developed and finally a discrete age structured model was formulated. All models were given in Chapter 3 to provide a comparison of different methods in the formulation of the model and to give a better understanding of the original model and the mathematical analysis.

For the stability analysis of the disease free equilibrium point, the first two models were studied by linearizing and the characteristic equation obtained for both methods was the same. The threshold value, $\mathcal{R}_0$, was given and it was proved that the DFE is locally asymptotically stable for $\mathcal{R}_0 < 1$ and unstable for $\mathcal{R}_0 > 1$. The proposed (but not verified) expression for $\mathcal{R}_0$ in the special case, where σ was assumed to be a constant function, in the survival function approach was similar to $\mathcal{R}_0$ given in general case for the other approaches. Both expressions of $\mathcal{R}_0$ agree with the value of $\mathcal{R}_0$ for a system of ODE when θ and σ are constants. Finally, the local and global stability of the DFE for the discrete age structured model were discussed. The expression for $\mathcal{R}_0$ was derived, using the method of next generation matrix, which is also similar to the previous results. The existence of a unique endemic equilibrium point was proved and numerical simulations were used to check the local stability of the EEP for $\mathcal{R}_0 > 1$.

In all approaches, the basic reproduction number depends on the parameter values $\sigma(a)$, φ and $\theta(a)$. The direct dependence of $\mathcal{R}_0$ on the value of $\sigma(a)$ suggests that by reducing $\sigma(a)$ (i.e., increasing the efficacy of the treatment $\epsilon(a) = 1 - \sigma(a)$) the basic reproduction number will decrease. Further analysis is required to study the dependence of $\mathcal{R}_0$ on the parameters φ and $\theta(a)$.

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