Dynamics of Structured Equations of Infectious Diseases

Foteini Stoila

M.Sc. Thesis

September 2022

This Thesis is dedicated to
Silia, Eleanna, Nick & Luna

MASTER THESIS COMMITTEE

Prof. Gerassimos Barbatis

Dr. Vasiliki Bitsouni (co-supervisor)

Prof. Ioannis G. Stratis (supervisor)

Contents

Abstract

From the smallpox model of Daniel Bernoulli in 1760 to recent COVID-19 pandemic, Mathematics have been used in population biology to explain and predict the infectious diseases outbreaks. With infectious diseases being a leading cause of death worldwide, particularly in low income countries, especially in young children, the study of population models and especially, structured population models in Epidemiology remains an urgent need. Structured equations distinguish individuals from one another according to characteristics such as age, location, status, and movement.

This M.Sc. Thesis is an introduction to the Mathematical Models of Epidemiology. The central theme is the study of various epidemiological models, based on which an infectious disease can develop and spread in a closed population. So, we will present and analyze such models of ordinary differential equations and structured epidemiological models of partial differential equations to explain how these characteristics affect the dynamics of the models and consequently the epidemiological processes.

Περίληψη

Από το μοντέλο ευλογιάς του Daniel Bernoulli το 1760 έως την πρόσφατη πανδημία COVID-19, τα Μαθηματικά έχουν χρησιμοποιηθεί στην Πληθυσμιακή Βιολογία για να εξηγήσουν και να προβλέψουν τα ξεσπάσματα μολυσματικών ασθενειών. Με τις μολυσματικές ασθένειες να αποτελούν την κύρια αιτία θανάτου παγκοσμίως, ιδιαίτερα στα μικρά παιδιά σε χώρες χαμηλού εισοδήματος, η μελέτη μοντέλων πληθυσμού και ιδιαίτερα μοντέλων «με διάκριση πληθυσμού κατά ένα χαρακτηριστικό» στην Επιδημιολογία παραμένει επιτακτική ανάγκη. Οι εξισώσεις των τελευταίων μοντέλων διακρίνουν τα άτομα το ένα από το άλλο σύμφωνα με χαρακτηριστικά όπως η ηλικία, ο τόπος κατοικίας, η κοινωνικο-οικονομική κατάσταση και οι μετακινήσεις.

Η παρούσα μεταπτυχιακή διπλωματική εργασία αποτελεί μια εισαγωγή στα Μαθηματικά Μοντέλα Επιδημιολογίας. Κεντρικό θέμα είναι η μελέτη διαφόρων επιδημιολογικών μοντέλων, βάσει των οποίων μπορεί να αναπτυχθεί και να εξαπλωθεί μια λοιμώδης νόσος σε έναν κλειστό πληθυσμό. Έτσι, θα παρουσιάσουμε και θα αναλύσουμε τέτοια μοντέλα συνήθων διαφορικών εξισώσεων και επιδημιολογικά μοντέλα μερικών διαφορικών εξισώσεων για να εξηγήσουμε πώς αυτά τα χαρακτηριστικά επηρεάζουν τη δυναμική των μοντέλων και κατά συνέπεια τις επιδημιολογικές διαδικασίες.

Chapter 1

Introduction

1.1 Historical note

Every year, millions of people all over the world die of infectious diseases, like influenza, smallpox, tuberculosis, HIV etc. Diseases cause more deaths in the world than anything else, even wars and famines. The study of epidemics dates back a long time ago, from the plague of Athens (440 - 428 BC) and the Black Death (14th century), to AIDS, SARS and the most recent COVID-19. It has led to a wide variety of epidemiological models and explanations for the cause and the spread of epidemics.

Some historic pandemics

- Plague of Justinian, from 541 to 542, killed approximately half of Europe's population.

- The Black Death of 1347 to 1352 killed 25 million in Europe over 5 years. The plague reduced the old world population from an estimated 450 million to between 350 and 375 million in the 14th century.

- The introduction of smallpox, measles, and typhus to the areas of Central and South America by European explorers during the 15th and 16th centuries caused pandemics among the native inhabitants. Between 1518 and 1568 disease pandemics are said to have caused the population of Mexico to fall from 20 million to 3 million.

- The first European influenza epidemic occurred between 1556 and 1560, with an estimated mortality rate of 20%.

- Smallpox killed an estimated 60 million Europeans during the 18th century (approximately 400,000 per year). Up to 30% of those infected, including 80% of the children under 5 years of age, died from the disease, and one-third of the survivors went blind.

- In the 19th century, tuberculosis killed an estimated one-quarter of the adult population of Europe; by 1918 one in six deaths in France were still caused by TB.

- The influenza pandemic of 1918 (or the Spanish flu) killed 25–50 million people (about 2% of world population of 1.7 billion). Today influenza kills about 250,000 to 500,000 worldwide each year.

- The COVID-19 pandemic, also known as the coronavirus pandemic, is an ongoing global pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The novel virus was first identified from an outbreak in Wuhan, China, in December 2019. Attempts to contain it there failed, allowing the virus to spread worldwide. The World Health Organization (WHO) declared a Public Health Emergency of International Concern on 30 January 2020 and a pandemic on 11 March 2020. As of 5 April 2022, the pandemic had caused more than 494 million cases and 6.17 million deaths, making it one of the deadliest in history.

1.2 A brief description

The study of the occurrence of a disease is called *epidemiology*. An *epidemic* is an unusually large disease outbreak. If it persists in a population, it is called *endemic*. The spread of an infectious disease involves factors which are related to the disease, such as the infectious agent, the latent and the infectious period, the infectiousness etc. It also involves social, demographic, geographic and economic factors.

Epidemic models are of great importance since their main goal is to predict the evolution over time of an infectious disease. We focus on the population of the infected individuals of the host species and not on the populations of the pathogens (such as viruses or bacteria). In general, we consider that pathogens invade and grow within an individual faster than the infection is transmitted from one individual to another.

A question that arises in any case of epidemic is, given some parameters, the initial number of infectives and the total size of the population, whether the infection will spread or not, and if it does, how it evolves over time and when it will start to decline. For this, we focus on the deterministic models for the single outbreak, on the endemic infections and mainly, on the age structured models that are more realistic related to the progression of the disease.

The purpose of the mathematical modeling of epidemics is to identify the patterns of disease, logically describe such events, and provide tools for the investigation of treatment, for the prevention methods, for estimating the level of population vaccination and generally for the control of the disease.

The origin of the models in interest is the early 20th century. Important works are these of Ross (1916) [46], Ross and Hudson (1917) [47], [48], Kermack and McKendrick (1927) [33], and Kendall (1956) [34].

For extensive discussion of topics in Mathematical Biology, the reader may refer to the corresponding bibliography: [3], [9], [10], [12], [13], [16], [17], [18], [20], [22], [23], [24], [25], [26], [27], [28], [29], [30], [32], [35], [40], [41], [42], [43], [44], [45], [50], [51]. For topics related to ODEs, the reader can refer to the bibliography: [2], [5], [6], [8], [11], [19], [49], while for topics related to PDEs: [1], [4], [21]. For topics related in general with concepts and techniques of Applied Mathematics, one can see: [7], [38], [39]. As for topics related with concepts and techniques of Integral Equations, one can see [14], [36], [52], [53], while for integrodifferential equations [15], [37].

1.3   Some simple models

There are some basic types of models for infectious diseases which are spread by direct contact of individuals in a population. Such simple models are

- SI models, where the infected individuals cannot be cured. Schematically

$$S \to I$$

- SIR models, where the infected individuals acquire immunity. Schematically

$$S \to I \to R$$

- SIS models, where the infected individuals do not acquire immunity, but after recovery they become susceptible again. Schematically

$$S \to I \to S$$

- SEIR models, where the infected individuals cannot transmit the disease for some time, that is the disease is latent. Schematically

$$S \to E \to I \to R$$

where

S represents the individuals that are susceptible

I represents the individuals that are infected

R represents the individuals that are recovered, and

E represents the individuals that are infected but they can not transmit the disease

Starting with the classic SIR model named after W.O. Kermack and A.G. McKendrick, which has been the main tool for analyzing epidemics, we focus on deterministic models, first for a single outbreak and then on endemic infections. They are the classical models for epidemic description, which are expressed as initial value problems based on ODEs.

Subsequently, the models are structured by class-age, that is the time elapsed since an individual becomes infected, which are expressed as initial value problems based on PDEs.

In all cases, the basic reproduction number is estimated and the the behavior of most of the solutions is determined.

Chapter 2

Deterministic Models

There are some basic types of deterministic models, which are formulated as initial value problems of systems of ODEs. Their mathematical analyses are elementary, but they provide concepts, intuition and basis for examining more sophisticated models.

2.1 Basic elements and notations

When we are interested in the infection spread at the population level, we take into account that the timescale of the pathogen invasion dynamics and the growth within the host, is negligible compared to the timescale of infection transmission from an individual to another. At first, we consider a disease such that we can divide the population into distinct epidemiological classes:

- the *susceptibles* S, those who are healthy and they can be infected, with $S(t)$ the corresponding number of susceptibles at time t,

- the *infectious*, or *infective*, or *infected* I, those who have the disease and they can transmit it, with $I(t)$ the corresponding number of infectious at time t.

- the *recovered* R, those who have had the disease, or they are immune or they have been isolated, with $R(t)$ the corresponding number of recovered at time t,

- the *exposed* E, that is, the *incubation class* which consists of the infected individuals, with the disease being latent between the time an individual is infected and the time he/she becomes infectious, with $E(t)$ the corresponding number of exposed individuals at time t.

In order to describe the transmission and the progression of the disease, we assume that

- susceptibles are infected after getting in contact with an infectious,

- transitions to classes other than the infectives depend on the progression of the infection within an individual and not on the interactions between individuals,

- the size of the population is very large (typical of deterministic population size).

2.2 SIR models

2.2.1 The classic Kermack - McKendrick model

Let $S(t)$ the number of susceptibles, $I(t)$ the number of infectious and $R(t)$ the number of recovered. We have the following assumptions

i. The rate of removal of the susceptibles is proportional to the number of the susceptibles and the infectious, namely

$$\frac{dS}{dt} = -\beta SI,$$

where $\beta > 0$ is a constant. It is the per capita rate at which susceptibles become infected, that is, the rate that the infective class increases (*force of infection*).

ii. The rate of removal of infectious to the recovered is proportional to the number of infectious, namely,

$$\frac{dR}{dt} = \gamma I,$$

where $\gamma > 0$ is a parameter called *recovery* or *removal rate* and its reciprocal $\frac{1}{\gamma} = \tau$ is a measure of the average time spent in the infectious state (*average infectious period*).

iii. The period of incubation is considered negligible.

iv. It is just likely for an individual to get in contact with another.

Considering all these assumptions we get the classic (1927) *Kermack - McKendrick model*, [33],

$$\frac{dS}{dt} = -\beta SI, \tag{2.1a}$$

$$\frac{dI}{dt} = \beta SI - \gamma I, \tag{2.1b}$$

$$\frac{dR}{dt} = \gamma I, \tag{2.1c}$$

where $\beta > 0$ and $\gamma > 0$ are the infection rate and the removal rate of infectious, respectively.

Adding the equations (2.1a)-(2.1c) and integrating the resulting equation, we get the total population size N

$$\frac{dS}{dt} + \frac{dI}{dt} + \frac{dR}{dt} = 0 \quad \Rightarrow \quad S(t) + I(t) + R(t) = N, \tag{2.2}$$

where

$$S(0) = S_0 > 0, \quad I(0) = I_0 > 0, \quad R(0) = 0, \tag{2.3}$$

are the initial numbers of the susceptibles, the infectious and the recovered, respectively.

The threshold phenomenon

Consider a population consisting of $I(0) = I_0$ infectives and $S(0) = S_0$ susceptibles.

From (2.1b), given β, γ, S_0 and I_0, we get

$$\left[\frac{dI}{dt}\right]_{t=0} = I_0(\beta S_0 - \gamma) \quad \begin{cases} > 0 \\ < 0 \end{cases} \quad \text{if} \quad S_0 \quad \begin{cases} > \dfrac{\gamma}{\beta} \\ < \dfrac{\gamma}{\beta} \end{cases} . \tag{2.4}$$

From (2.1a) we have

$$\frac{dS}{dt} \leq 0 \Rightarrow S \leq S_0.$$

If $S_0 < S_c = \dfrac{\gamma}{\beta}$, then $S < \dfrac{\gamma}{\beta}$, and

$$\frac{dI}{dt} = I(\beta S - \gamma) \leq 0, \quad \forall \quad t \geq 0 \tag{2.5}$$

so $I(t) < I_0$ as $t \to \infty$. That is, the population of infectious decreases and an epidemic can be avoided (the infection dies out).

If $S_0 > S_c = \dfrac{\gamma}{\beta}$, then

$$\frac{dI}{dt} \geq 0, \quad \text{so} \quad I(t) > I_0 \quad \text{for some} \quad t > 0,$$

that is, the population of infectious initially increases and an epidemic may occur. So, we have the *threshold phenomenon*.

The critical parameter $\rho = \dfrac{\gamma}{\beta}$ is called the *relative removal rate* and its reciprocal $\sigma = \dfrac{\beta}{\gamma}$ is called the *contact rate* of the infection. We define the basic *reproduction number* of the infection

$$R_0 = \frac{\beta S_0}{\gamma},$$

which is a very important number in epidemiology. It is defined as the average number of secondary infections by a single infective individual during the infection,

in a population of susceptibles. It measures the maximum reproductive potential for an infectious disease. The value $R_0 > 1$ indicates that the infection growth is positive, $R_0 = 1$ indicates flattening of the infection, while $R_0 < 1$ indicates that the outbreak will gradually disappear.

Indicatively, the value of R_0 for various infectious diseases is shown in the following table:

DISEASE	R_0
Measles	12.0 - 18.0
Chickenpox	10.0 - 12.0
COVID-19 (Omicron variant)	9.4 - 9.6
Polio	5.0 - 7.0
COVID-19 (Delta variant)	5.0 - 5.2
Smallpox	3.5 - 6.0
COVID-19 (Alpha variant)	4.0 - 5.0
HIV/AIDS	2.0 - 5.0
SARS	2.0 - 4.0
Common cold	2.0 - 3.0
Monkeypox	1.5 - 2.7
Influenza (1918 pandemic strain)	1.9 - 2.1
Ebola (2014 outbreak)	1.4 - 1.8
Influenza (2009 pandemic strain)	1.3 - 2.0
Influenza (seasonal strains)	1.2 - 1.4

In reality, both β and γ are functions of time since they change with hygiene, lockdown, medication, vaccination, and other measures. However, the biggest limitation of this model is that it assumes these parameters to be constant. Likewise, it is worthwhile to compute and track the reproductive number at all time points instead of computing only at the beginning. This tracking can be very helpful because it shows whether the epidemic is increasing ($R > 1$) or decreasing ($R < 1$) and hence, corrective measures can be taken.

Dividing (2.1b) by (2.1a), we get

$$\frac{dI}{dS} = -\frac{(\beta S - \gamma)I}{\beta S I} = -1 + \frac{\gamma}{\beta S}. \quad (I \neq 0) \tag{2.6}$$

Since all the singularities lie on the $I = 0$ axis, we consider $I \neq 0$. We can get the (S, I) phase plane trajectories by integrating (2.6)

$$I + S - \frac{\gamma}{\beta} \ln S = const. = c.$$

Using (2.3) we get

$$c = I_0 + S_0 - \frac{\gamma}{\beta} \ln S_0,$$

so

$$I + S - \frac{\gamma}{\beta} \ln S = I_0 + S_0 - \frac{\gamma}{\beta} \ln S_0 \quad \Rightarrow \quad I = N - S + \frac{\gamma}{\beta} \ln \frac{S}{S_0}, \tag{2.7}$$

where $I_0 + S_0 = N, R(0) = 0$, and for $t > 0$ we have $0 \leq S(t) + I(t) < N, R(t) > 0$. Figure 2.1 illustrates the susceptibles - infectious phase plane trajectories.
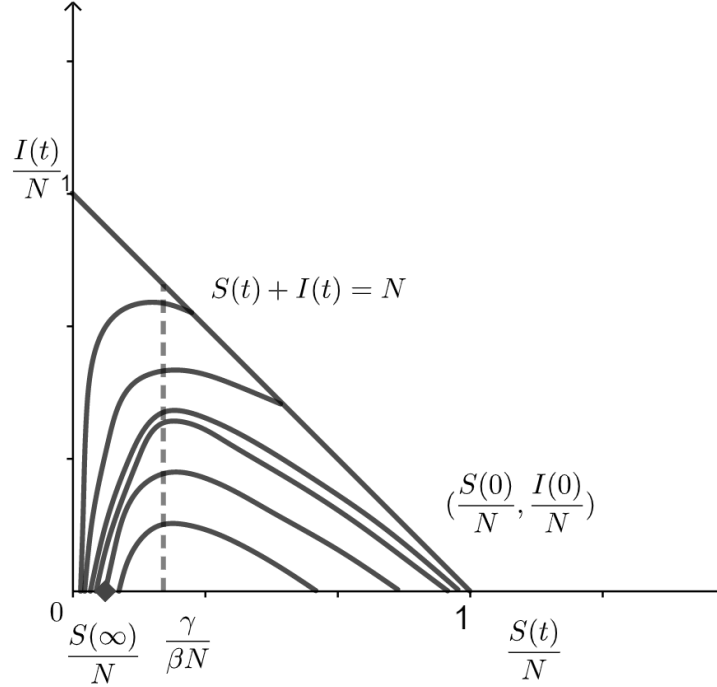

Figure 2.1: Phase plane trajectories for problem (2.1).

One of the questions that arise is how severe an epidemic that bursts can be. First, we can calculate the maximum I, from (2.5)

$$\frac{dI}{dt} = 0 \quad \Rightarrow \quad I(\beta S - \gamma) = 0 \quad \Rightarrow \quad S = \frac{\gamma}{\beta}$$

so (2.7) becomes

$$I_{max} = N - \frac{\gamma}{\beta} + \frac{\gamma}{\beta} \ln \left(\frac{\gamma}{\beta S_0} \right). \tag{2.8}$$

From (2.1a) $\dfrac{dS}{dt} < 0, \quad S \neq 0, \quad I \neq 0$, that is, S decreases. Dividing (2.1a) by (2.1c), we get

$$\frac{dS}{dR} = -\frac{\beta S}{\gamma}$$
$$\Rightarrow S = S_0 \exp \left(-\frac{\beta R}{\gamma} \right) \geq S_0 \exp \left(-\frac{\beta N}{\gamma} \right) > 0 \tag{2.9}$$
$$\Rightarrow 0 < S(\infty) \leq N.$$

Since the infectious population decreases as $t \to \infty$, that is, $I(\infty) = 0$, we get from (2.2)

$$S(\infty) = S_0 \exp\left[-\frac{\beta R(\infty)}{\gamma}\right]$$

$$\Rightarrow S(\infty) = S_0 \exp\left[-\frac{\beta(N - S(\infty))}{\gamma}\right], \tag{2.10}$$

so, $S(\infty)$ is the positive root of (2.10).

The total number of infected individuals is

$$I_{total} = I_0 + S_0 - S(\infty). \tag{2.11}$$

It is clear that $I(t) \to 0$ and $S(t) \to S(\infty) > 0$.

In order to apply a model to actual epidemic situations, it is important to know the removal rate of the infectious to the recovered, that is $\dfrac{dR}{dt}$. So, from (2.9), (2.2) and (2.1c), we get

$$\frac{dR}{dt} = \gamma I = \gamma(N - R - S) = \gamma\left(N - R - S_0 \exp\left[-\frac{\beta R}{\gamma}\right]\right), \quad R(0) = R_0. \tag{2.12}$$

If $\dfrac{\beta R}{\gamma}$ is small (that is, a small epidemic), we approximate (2.12) by

$$\frac{dR}{dt} = \gamma\left[N - S_0 + \left(\frac{\beta S_0}{\gamma} - 1\right)R - \frac{S_0 R^2 \beta^2}{2\gamma^2}\right],$$

[33], which ends up to the solution

$$R(t) = \frac{\beta^2}{S_0}\left[\left(\frac{\beta S_0}{\gamma} - 1\right) + \alpha \tanh\left(\frac{\alpha \gamma t}{2} - \phi\right)\right]$$

$$\alpha = \left[\left(\frac{\beta S_0}{\gamma} - 1\right)^2 + \frac{2\beta^2 S_0(N - S_0)}{\gamma^2}\right]^{1/2}, \quad \phi = \frac{\tanh^{-1}\left(\frac{\beta S_0}{\gamma} - 1\right)}{\alpha} \tag{2.13}$$

and then

$$\frac{dR}{dt} = \frac{\gamma \alpha^2 \gamma^2}{2\beta^2 S_0} \sec h^2\left(\frac{\alpha \gamma t}{2} - \phi\right) \tag{2.14}$$

with three parameters, that is, $\dfrac{\alpha^2 \gamma^3}{2\beta^2 S_0}$, $\alpha\gamma$, and ϕ.

If $\dfrac{\beta R}{\gamma}$ is large, we determine $R(t)$ solving numerically (2.12).

Summarizing, there are the following limitations of the classical SIR model:

1. Generally, the SIR model assumes all parameters β, γ, and R_0 to be constant, while in real scenario, these parameters would be changing with time.

2. The solution to the model is computed numerically and hence, the model has limited tracking and prediction ability.

3. The initial infected population $I(0)$ is small at the beginning of the epidemic. At the end of the epidemic, its final value should be zero, i.e., $I(\infty) = 0$, which is not ensured in the classical SIR model.

4. The initial removed population is $R(0) = 0$, because there is no recovery at the very beginning of the epidemic. Once the epidemic is over, there must be complete removal by recovery and deaths. Thus, $R(\infty) = K$, where $K = \int_0^\infty I(t)dt$, is the total size of the population infected over the entire period of the epidemic. However, this is also not ensured in the classical SIR model.

5. The initial susceptible population, $S(0) = N - I(0)$, is close to the total population N. Since $\dfrac{dS(t)}{dt} \leq 0$ is a negative-valued function of time, $S(t) \geq 0$ is also a decreasing function of time. Therefore, its final value must be zero, i.e., $S(\infty) = 0$. However, this is not ensured in the classical SIR model.

2.2.2   A more realistic scenario

In a more realistic scenario the parameters that denote the per capita rate at which susceptibles become infected and the rate at which infectives recover from disease are functions of time t. Let

- $\lambda(t)$ = the per capita rate at which susceptibles become infected (*force of infection*). It is related to the mechanisms individuals contact each other and to the infectivity of the pathogen that causes the disease.

- $\gamma(t)$ = the rate at which infectives recover from disease, (*removal rate*). It is inherent in the disease progression in each infected individual.

In order to conclude in a simple form of the force of infection adopted by the most models, we make the following assumptions

i. the population is mixing homogeneously,

ii. the whole population is active,

iii. the contact rate is independent of the size of the active population,

iv. all contacts with infectives are equally infectious.

So, we get

$$\lambda(t) = c(t)\chi\frac{I(t)}{N(t)} \quad \Rightarrow \tag{2.15}$$

$$\lambda(t) = \frac{\beta}{N}I(t), \tag{2.16}$$

where

- $c(t)$ = the per capita contact rate, that is the average number of contacts per individual per unit time

- χ = infectiousness of one contact with an infectious, which shows the *probability of transmission per contact of an infectious with a susceptible.*

- $\beta = c\chi$ = the average number of individuals infected in unit time, given that the contact rate c is constant.

- $N(t) = S(t) + I(t) + R(t) = N$ = total population, and it is a parameter of the problem.

- $\dfrac{I(t)}{N(t)}$ = **prevalence**, denotes the probability that a random contact is infective.

- $j(t) = \lambda(t)S(t)$ = **incidence**, that is the number of new infections at time t

We also assume, as in the simplest form of the SIR model, that the progression of the disease is the same in any infective individual, and that the probability for an individual to recover in any time is independent of how long he has been infected. So, the removal rate, which measures the average fraction of individuals that recover per unit time, is a constant. Furthermore, the probability for an individual to be still infectious for time t after he was infected is

$$\Pi(t) = e^{-\gamma t},$$

and, the average duration of the infection, namely the *infectious period* is

$$\tau = \frac{1}{\gamma}.$$

Assuming that there are no births or deaths in the population during the epidemic outbreak due to demographic dynamics or the disease, that is the demographic changes are negligible, the SIR model is sketched in Figure 2.2 and it is described by the following system of ODEs:

$$\frac{dS}{dt} = -\lambda(t)S(t), \tag{2.17a}$$

$$\frac{dI}{dt} = \lambda(t)S(t) - \gamma I(t), \tag{2.17b}$$

$$\frac{dR}{dt} = \gamma I(t), \tag{2.17c}$$

where

$$S(0) = S_0 > 0, \quad I(0) = I_0 > 0, \quad R(0) = 0, \quad \text{and} \quad N(t) = S_0 + I_0 + R_0 = N, \quad t \geq 0.$$
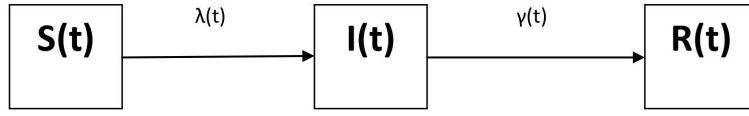
Figure 2.2: The SIR model for diseases which impart immunity. Suscptibles are infected at a rate $\lambda(t)$ and infected individuals recover at a rate $\gamma(t)$.

Using (2.16) for the force of infection, the (2.17) becomes

$$\frac{dS}{dt} = -\frac{\beta}{N}I(t)S(t), \tag{2.18a}$$

$$\frac{dI}{dt} = \frac{\beta}{N}I(t)S(t) - \gamma I(t), \tag{2.18b}$$

$$\frac{dR}{dt} = \gamma I(t). \tag{2.18c}$$

Concerning the duration of the infection as time unit, the susceptibles, the infectives and the recovered as fractions of the total population N, and renaming $\tilde{t}$ as t, we can scale the system with the transformation

$$t \mapsto \tilde{t} = \gamma t, \quad S \mapsto u = \frac{S}{N}, \quad I \mapsto \nu = \frac{I}{N}, \quad R \mapsto w = \frac{R}{N}, \tag{2.19}$$

and finally, we get

$$\frac{du}{dt} = -R_0 u(t)\nu(t), \qquad\qquad u(0) = u_0, \tag{2.20a}$$

$$\frac{d\nu}{dt} = R_0 u(t)\nu(t) - \nu(t), \qquad\qquad \nu(0) = \nu_0, \tag{2.20b}$$

$$\frac{dw}{dt} = \nu(t), \qquad\qquad w(0) = w_0, \tag{2.20c}$$

where

$$R_0 = \frac{c\chi}{\gamma} \tag{2.21}$$

is the *basic reproduction number*, and u_0, ν_0, w_0 are the initial conditions for which we have

$$u_0 > 0, \quad \nu_0 > 0, \quad w_0 \geq 0, \quad u_0 + \nu_0 + w_0 = 1. \tag{2.22}$$

The system (2.20) has a unique positive solution. Furthermore, for any solution we have $u(t) + \nu(t) + w(t) = 1$. From (2.20a) we get

$$\frac{du}{dt} < 0 \tag{2.23}$$

that is, $u(t)$ is a decreasing function, so

$$u(t) \to u_\infty \geq 0 \quad \text{as} \quad t \to +\infty \tag{2.24}$$

In addition, from (2.20c) and the initial conditions (2.22) we get

$$w(t) - w(0) = \int_0^t \nu(s)ds \quad \Rightarrow \quad w(t) = w_0 + \int_0^t \nu(s)ds = 1 - u(t) - \nu(t) \le 1$$

$$\text{so} \quad \int_0^\infty \nu(s)ds < +\infty \quad \text{and}$$

$$\nu(t) \to \nu_\infty = 1 - u_\infty - \int_0^\infty \nu(s)ds + w_0 \le 1, \quad \text{as} \quad t \to +\infty$$

$$\Rightarrow \quad \nu(t) \to 0 \quad \text{as} \quad t \to +\infty$$

since $\nu(t)$ is integrable in $(0, +\infty)$ and it converges.

Although we conclude that the number of susceptible individuals is reduced to u_∞ and that the epidemic extincts, we are interested in the way it behaves. Consider (2.20b)

$$\frac{d\nu}{dt} = R_0 u(t)\nu(t) - \nu(t) = (R_0 u(t) - 1)\nu(t),$$

and let

u_0 : the initial susceptible fraction,

$R_0 u_0$: the initial number of secondary cases produced by a single infectious, which must be greater than 1, in order for an epidemic to breaks out.

$R_0 u(t)$: the number of individuals infected as the infection goes on. Since $u(t)$ decreases, $R_0 u(t)$ decreases too. So, there is t^* such that $R_0 u(t^*) = 1$, and for $t > t^*$ it becomes $R_0 u(t) < 1$.

So,

$$\text{if} \quad R_0 u_0 \le 1 \quad \Rightarrow \quad \frac{d\nu}{dt} < 0 \quad \text{for} \quad t > 0,$$

$$\text{if} \quad R_0 u_0 > 1 \quad \Rightarrow \quad \begin{array}{l} \dfrac{d\nu}{dt} > 0 \quad \text{for} \quad t < t^*, \\[2mm] \dfrac{d\nu}{dt} < 0 \quad \text{for} \quad t > t^*, \end{array}$$

respectively. So, $\nu(t)$ maximizes at t^*, when $R_0 u(t^*) = 1$. The corresponding *threshold criterion* for an outbreak, that is, an epidemic occurs if and only if

$$R_0 u_0 > 1 \tag{2.27}$$

At the same time t^*, the fraction of susceptibles becomes

$$u(t^*) = \frac{1}{R_0}. \tag{2.28}$$

For $t > t^* \quad \Rightarrow \quad u(t) < u(t^*)$ the infection is no longer maintained.
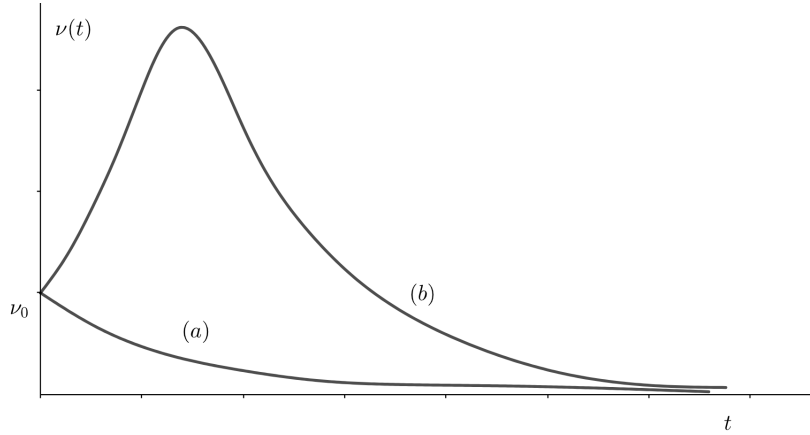
Figure 2.3: Solution for problem (2.20) and the threshold condition for an outbreak. (a) If $R_0 u_0 < 1$, the infective fraction $\nu(t)$ decreases, independently the initial fraction ν_0. (b) If $R_0 u_0 > 1$, the infective fraction increases before dying out; the maximum prevalence occurs at t^* such that $R_0 u(t^*) = 1$.

The *size of the epidemic*, that is the fraction of individuals that has been infected during the epidemic, if $\nu_0 \approx 0$, is

$$w_\infty - w_0 = 1 - u_\infty - (1 - u_0 - \nu_0) = u_0 + \nu_0 - u_\infty \approx u_0 - u_\infty.$$

In order to estimate the final size of the fraction of susceptibles u_∞, we work on (2.20a), and we have

$$u(t) = u_0 e^{-R_0 \int_0^t \nu(s)ds},$$

where

$$\int_0^t \nu(s)ds = 1 - u(t) - \nu(t) - w_0,$$

concluding that

$$u(t) = u_0 e^{-R_0(1-u(t)-\nu(t)-w_0)}, \tag{2.29}$$

from which we get

$$\nu - \frac{1}{R_0} \ln u + u = c, \tag{2.30}$$

where the constant

$$c = \nu_0 + u_0 - \frac{1}{R_0} \ln u_0$$

depends on the initial values. Figure 2.4 illustrates a (u, ν) phase plane trajectories.

Also, as $t \to \infty$,

$$u_\infty = u_0 e^{-R_0(1-u_\infty-w_0)}. \tag{2.31}$$

Define

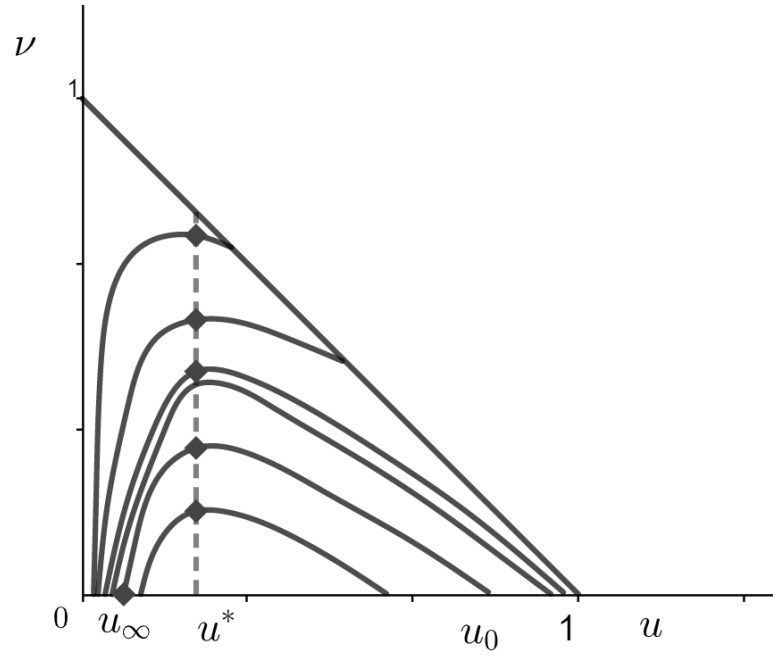$$H(z) := z - u_0 e^{-R_0(1-z-w_0)}. \tag{2.32}$$

Figure 2.4: Phase plane trajectories for problem (2.20). Different trajectories (2.30) are drawn for the same value of R_0 and different values of the constant. The feasible region is the triangle delimited by the line $u + \nu = 1$. The curves are described from right to left. At the critical value u^* for which $R_0 u^* = 1$, the infected fraction u begins to decrease. If a solution starts at a point with $u_0 < u^*$, there is no epidemic outbreak. Each curve ends on the u axis, at $u = u_\infty$.

Then u_∞ is a root of $H(z)$ in $[0, u_0]$ and, since

$$u(t) \searrow \quad \Rightarrow \quad u_\infty < u_0,$$

we have

$$H(0) < 0, \quad H(u_0) > 0 \quad \text{and} \quad H''(z) < 0, \forall z,$$

hence, (2.32) has the unique solution u_∞ in the interval $(0, u_0)$.

Plotting the function $H(z)$, we come to some conclusions about the size of u_∞ and the way threshold influences it, and so,

(a) if

$$R_0 u_0 < 1 \Rightarrow u_\infty \to u_0,$$

(b) if

$$R_0 u_0 > 1 \Rightarrow u_\infty \to 0.$$
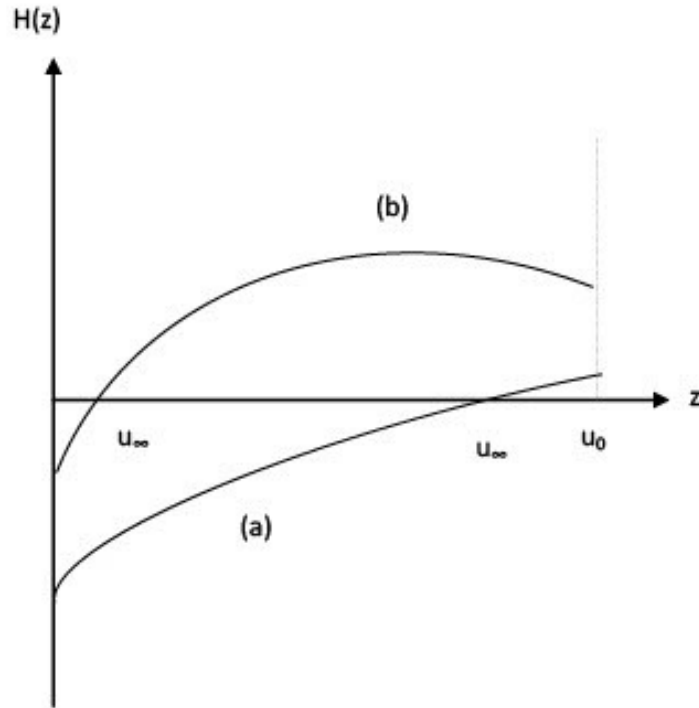
Figure 2.5: H(z) graph and the final size of the susceptible fraction (a) if $R_0 < 1$ and (b) if $R_0 > 1$.

The pandemic case

In case that an infection enters a population with no immunity, i.e.

$$w_0 = 0, \quad u_0 \approx 1, \quad \nu_0 << 1,$$

the function (2.32) gets the form

$$H(z) := z - u_0 e^{-R_0(1-z)}. \tag{2.33}$$

From the corresponding plots 2.6, 2.7, we have that as $u_0 \to 1, \nu_0 \to 0$, the size u_∞ that the susceptible fraction finally gets, is the root of

$$z - e^{-R_0(1-z)} = 0. \tag{2.34}$$

Particularly, we have the *threshold theorem for a pandemic*

- if $R_0 \leq 1$ then $u_\infty = 1$, i.e as $\nu_0 \to 0 \Rightarrow \nu_\infty \to 0$,

Figure 2.6: The pandemic case if $R_0 < 1$.

Figure 2.7: The pandemic case if $R_0 > 1$.

- if $R_0 > 1$ then u_∞ is the smallest solution to (2.34), which means that as $\nu_0 \to 0 \Rightarrow \nu_\infty \to \tilde{w}_\infty = 1 - \tilde{u}_\infty > 0$. This represents t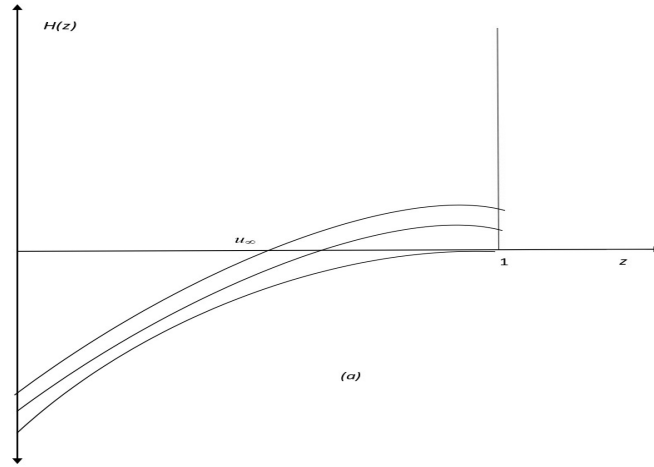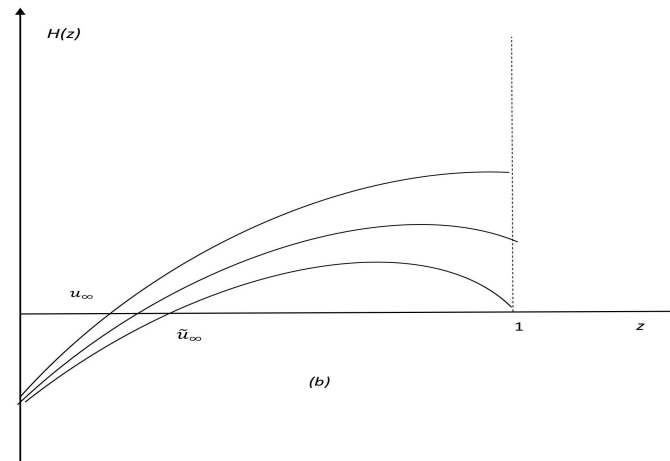he population fraction that recovers after an infection is introduced by a very small fraction of infected in a population consisting of susceptibles.

The quantity w_∞ is a function of R_0.

The parameter R_0, which defines the final impact of a pandemic, along with the knowledge of the initial immune fraction w_0, it defines the final impact of any epidemic, as u_∞ is a root of (2.32). Linearizing (2.20b) near an initial condition (u_0, ν_0) we have

$$\frac{d\nu}{d\tilde{t}} \approx (R_0 u_0 - 1)\nu(\tilde{t}).$$

The fraction of infected has exponential initial growth, and knowing the parameter R_0 and the susceptible fraction we can determine whether or not an epidemic can

be avoided.

2.2.3 The SIR model with demography

There are cases that we are interested in exploring the longer-term persistence and endemic dynamics of an infectious disease. Two different mechanisms may lead to disease endemicity. One of them is the demographic processes, especially the new-borns susceptibles, and the other is related to diseases that do not impart immunity.

In order to analyze the effect of demographic dynamics, we consider the SIR model with a simple Malthusian dynamics included. Assuming that

- births and deaths have the same rate μ in any class, which does not depend on the disease (then, $\dfrac{1}{\mu}$ years is the natural host "lifespan"), and so the population size does not change through time,

- the newborns enter the susceptible class,

a more generalized SIR model is:

$$\frac{dS}{dt} = \mu N - \frac{\beta}{N} S(t) I(t) - \mu S(t), \tag{2.35a}$$

$$\frac{dI}{dt} = \frac{\beta}{N} S(t) I(t) - \gamma I(t) - \mu I(t), \tag{2.35b}$$

$$\frac{dR}{dt} = \gamma I(t) - \mu R(t), \tag{2.35c}$$

Since $R(t) = N - S(t) - I(t)$ we get the reduced system

$$\frac{dS}{dt} = \mu N - \frac{\beta}{N} S(t) I(t) - \mu S(t), \tag{2.36a}$$

$$\frac{dI}{dt} = \frac{\beta}{N} S(t) I(t) - \gamma I(t) - \mu I(t), \tag{2.36b}$$

where

$$S(0) = S_0 \geq 0, \quad I(0) = I_0 \geq 0,$$

the initial conditions.

In this case, the total exit rate from the class of infectives is $\gamma + \mu$, and so, the number of secondary infections in a population consisting of susceptibles, namely, the reproduction number R_0, is given by

$$R_0 = \frac{c\chi}{\gamma + \mu},$$

and it is smaller than R_0 for a closed population, because the average time an individual is infectious, $\tau = \dfrac{1}{\gamma + \mu}$, is reduced by the natural mortality rate.

In order to scale the system we perform the transformation

$$t \mapsto \tilde{t} = (\gamma + \mu)t, \quad S \mapsto u = \frac{S}{N}, \quad I \mapsto \nu = \frac{I}{N}, \quad R \mapsto w = \frac{R}{N},$$

and then we have

$$\frac{du}{dt} = \alpha(1 - u(t)) - R_0 u(t)\nu(t), \tag{2.37a}$$

$$\frac{d\nu}{dt} = (R_0 u(t) - 1)\nu(t), \tag{2.37b}$$

where

$$\alpha = \frac{\mu}{\gamma + \mu} \tag{2.38}$$

is the demographic mortality.

The equilibrium state

From (2.37a) and (2.37b) we get

$$\begin{aligned}\frac{du}{dt} = 0 \\ \frac{d\nu}{dt} = 0\end{aligned} \quad \Rightarrow \quad \begin{aligned}\alpha(1 - u^*) - R_0 u^* \nu^* = 0 \\ (R_0 u^* - 1)\nu^* = 0\end{aligned} \quad \Rightarrow$$

- $u^* = 1, \quad \nu^* = 0$, the disease free equilibrium F, which always exists, and

- $u^* = \dfrac{1}{R_0}, \quad \nu^* = \alpha\left(1 - \dfrac{1}{R_0}\right)$, the endemic equilibrium E, which is feasible for $R_0 > 1$, and it belongs to the region $\{u \geq 0, \nu \geq 0, u + \nu \leq 1\}$.

Linearizing (2.37), we have the Jacobian matrix

$$J = \begin{pmatrix} -\alpha - R_0\nu & -R_0 u \\ R_0\nu & R_0 u - 1 \end{pmatrix}.$$

i. At $F \equiv (1, 0)$, it becomes

$$J(F) = \begin{pmatrix} -\alpha & -R_0 \\ 0 & R_0 - 1 \end{pmatrix}.$$

The corresponding eigenvalues are

$$\lambda_1 = -\alpha \quad \text{and} \quad \lambda_2 = R_0 - 1,$$

so,

for $R_0 < 1$, the equilibrium F is asymptotically stable,

for $R_0 > 1$, the equilibrium F is unstable.

ii. At $E \equiv \left(\dfrac{1}{R_0}, \alpha \left(1 - \dfrac{1}{R_0} \right) \right)$, which exists only for $R_0 > 1$, the Jacobian matrix becomes

$$J(E) = \begin{pmatrix} -\alpha R_0 & -1 \\ \alpha(R_0 - 1) & 0 \end{pmatrix},$$

for which

$$\text{trace} J(E) = -\alpha R_0 < 0, \quad \text{and} \quad \det J(E) = \alpha(R_0 - 1) > 0,$$

so, the corresponding eigenvalues have negative real parts, and consequently, equilibrium E is asymptotically stable.

The computation of the eigenvalues of $J(E)$ leads to the characteristic polynomial

$$\lambda^2 + \alpha R_0 \lambda + \alpha(R_0 - 1) = 0,$$

from which

$$\lambda_\pm = \frac{-\alpha R_0 \pm i\sqrt{4\alpha R_0 - \alpha^2 R_0^2 - 4\alpha}}{2},$$

for $R_0 \in (R_0^-, R_0^+)$, where

$$R_0^\pm = \frac{2}{\alpha} \left(1 \pm \sqrt{1 - \alpha} \right) > 1.$$

The approximate time ($\tilde{T} = 2\pi/\omega$ in the scaled time units) elapsed from one maximum to another, and the corresponding damping of the solution after one oscillation, Δ, can be taken by the eigenvalues $\lambda_\pm = b \pm i\omega$.

$$T = \frac{2\pi\tau}{\omega} = \frac{4\pi}{(\mu + \gamma)\sqrt{4\alpha R_0 - \alpha^2 R_0^2 - 4\alpha}}, \tag{2.39}$$

and

$$\Delta = e^{b\tilde{T}} = e^{-\alpha R_0 \tilde{T}/2}. \tag{2.40}$$

For most diseases in common, $\alpha \approx 10^{-2} - 10^{-4}$, that is, the average period an individual is infected is much sorter than the average life - time. Thus, $R_0^- \approx 1 + \dfrac{\alpha}{4} \approx 1$, and $R_0^+ \approx \dfrac{4}{\alpha}$ is very large, so the convergence to equilibrium will be oscillatory.

Returning to the original variables, and since $S^* + I^* + R^* = N$, the free and the endemic equilibrium result

- *disease free equilibrium* $(S^*, I^*, R^*) = (N^*, 0, 0)$,

- *endemic equilibrium*

$$(S^*, I^*, R^*) = \left(\frac{N}{R_0}, \quad \frac{\mu}{\beta}(R_0 - 1)N, \quad \left[1 - \frac{1}{R_0} - \frac{\mu}{\beta}(R_0 - 1) \right] N \right),$$

respectively.

2.3   SIS models (without immunity)

2.3.1   The simplest SIS model

Some infectious diseases, such as influenza, sexually transmitted infections, etc, do not confer immunity upon recovery. Individuals from infectives return to susceptible class and they can be infected many times throughout their lives. This class of models is called SIS and they can be schematically described as in Figure 2.8.
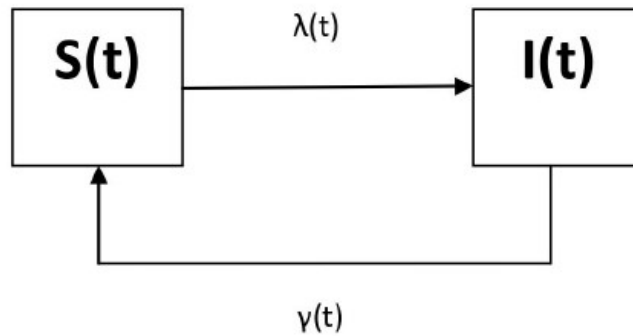
Figure 2.8: The SIS model for diseases which do not impart immunity. Susceptibles are infected at a rate $\lambda(t)$ and infected individuals become susceptible at a rate $\gamma(t)$.

The simplest SIS model can be described by the system of the ordinary differential equations:

$$\frac{dS}{dt} = -\frac{\beta}{N}S(t)I(t) + \gamma I(t), \tag{2.41a}$$

$$\frac{dI}{dt} = \frac{\beta}{N}S(t)I(t) - \gamma I(t), \tag{2.41b}$$

The difference between this and the SIR model is that the recovered individuals instead of passing to recovered class R, they return to the susceptible class S at a rate γI. Assuming that there are no deaths due to the disease, and that the population total size is constant, we get from (2.41)

$$\frac{dS}{dt} + \frac{dI}{dt} = 0 \quad \Rightarrow \quad S(t) + I(t) = S(0) + I(0) = N,$$

with $S(0) = S_0 > 0$ and $I(0) = I_0 > 0$ as initial conditions.

Since $S = N - I$ and using (2.41a), equation (2.41b) gives

$$\frac{dI}{dt} = \frac{\beta}{N}(N - I)I - \gamma I = (\beta - \gamma)I - \frac{\beta}{N}I^2 = (\beta - \gamma)I\left(1 - \frac{I}{(1 - \frac{\gamma}{\beta})N}\right), \qquad (2.42)$$

which is a logistic differential equation of the form

$$\frac{dI}{dt} = rI\left(1 - \frac{I}{K}\right)$$

with $r = \beta - \gamma$ and $K = (1 - \frac{\gamma}{\beta})N$.

If $\beta - \gamma < 0 \quad \Rightarrow \quad \frac{\beta}{\gamma} < 1 \quad \Rightarrow \quad \frac{dI}{dt} \leq 0$, then $I(t) \to 0$, as $t \to \infty$.

If $\beta - \gamma > 0 \quad \Rightarrow \quad \frac{\beta}{\gamma} > 1 \quad \Rightarrow \quad \frac{dI}{dt} \geq 0$, then $I(t) \to \left(1 - \frac{\gamma}{\beta}\right)N$, as $t \to \infty$.

The dimensionless quantity $R_0 = \frac{\beta}{\gamma}$ is the *basic reproduction number* for the disease, and the value $R_0 = 1$ defines a threshold. So,

- If $R_0 < 1$, the infection dies out, and the equilibrium $(S^*, I^*) = (N, 0)$ is called the *disease - free equilibrium*.

- If $R_0 > 1$, the infection spreads, $I = \left(1 - \frac{1}{R_0}\right)N \Rightarrow S = \frac{N}{R_0}$, and the equilibrium $(S^*, I^*) = \left(\frac{N}{R_0}, \left(1 - \frac{1}{R_0}\right)N\right)$ is called an *endemic equilibrium*.

A different approach

We can come to the same conclusions using the dimensionless variables as in previous cases. The equation for the infectious fraction (ν) becomes

$$\frac{d\nu}{dt} = R_0(\nu^* - \nu(t))\nu(t),$$

and the endemic state, which exists only for $R_0 > 1$, is

$$\nu^* = 1 - \frac{1}{R_0}.$$

One can see that it increases as R_0 increases.

From the above equation for $\frac{d\nu}{dt}$, we get

- if $R_0 \leq 1$ then $\frac{d\nu}{dt} < 0$ and $\nu(t) \to 0$ as $t \to +\infty$,

- if $R_0 > 1$ then $\nu(t) \to \nu^*$ as $t \to +\infty$.

As shown in Figure 2.9, in this case the extinction of the disease is opposed to the existence of a globally attractive endemic state ν^*.
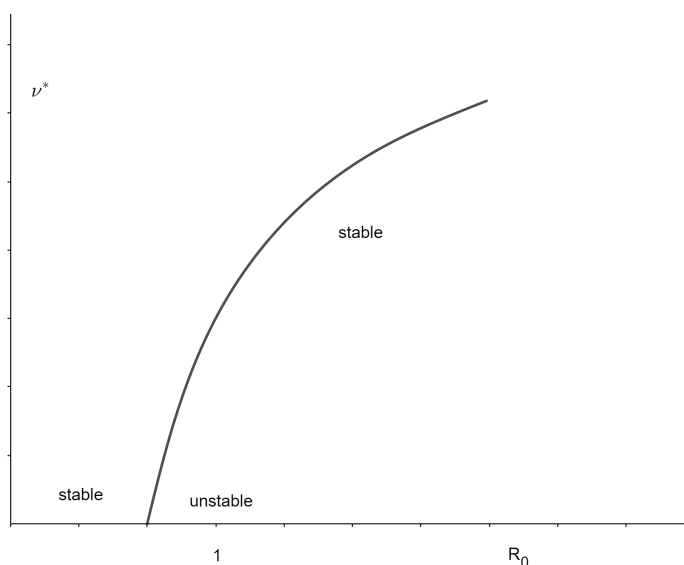
Figure 2.9: The infected fraction w_0 as a function of R_0.

2.3.2   The SIS model with demography

Consider a disease from which infectives recover without immunity and that includes demography (that is, births and deaths). Let

- Λ be the birth rate per unit time,

- μ be a death rate in each class,

- γ be a removal rate from the infective class through recovery or disease death.

Then, a simple SIS model with demography is

$$
\begin{aligned}
\frac{dS}{dt} &= \Lambda N - \frac{\beta}{N}S(t)I(t) - \mu S(t) + \gamma I(t), \\
\frac{dI}{dt} &= \frac{\beta}{N}S(t)I(t) - \gamma I(t) - \mu I(t).
\end{aligned}
\tag{2.43}
$$

Working as in SIS model without demography and assuming constant population size, it is easy to verify that the *basic reproduction number* R_0 is

$$
R_0 = \frac{\beta}{\gamma + \mu} \; .
$$

If $R_0 < 1$, the system has only the disease free equilibrium, which is asymptotically stable.
If $R_0 > 1$, there is the endemic equilibrium, which is asymptotically stable too.

2.4   SEIR models

In a more general model pathogen load is very low, so it can't be transmitted to other susceptibles, that is the infected individuals are exposed before becoming infective. In other words they are in the incubation phase. The length of this period depends on the disease.

Let σ be the constant rate that the exposed individuals become infective, then the average duration of the latent period is $\dfrac{1}{\sigma}$. An SEIR model with demography is given by the following equations

$$\frac{dS}{dt} = \mu N - (\frac{\beta}{N}I + \mu)S, \tag{2.44a}$$

$$\frac{dE}{dt} = \frac{\beta}{N}SI - (\mu + \sigma)E, \tag{2.44b}$$

$$\frac{dI}{dt} = \sigma E - (\mu + \gamma)I, \tag{2.44c}$$

$$\frac{dR}{dt} = \gamma I - \mu R. \tag{2.44d}$$

Adding the above equations we conclude that

$$S + E + I + R = N,$$

so, using the relation

$$R = N - (S + E + I)$$

we can reduce the system to a 3-dimensional equivalent system.

As with previous disease models, the SEIR model has a disease free equilibrium solution $(1, 0, 0, 0)$ and an endemic equilibrium solution (S^*, E^*, I^*, R^*), which is of greater interest and it is is given by

$$S^* = \frac{(\mu + \gamma)(\mu + \sigma)}{\beta\sigma}N = \frac{N}{R_0}, \tag{2.45a}$$

$$E^* = \frac{\mu(\mu + \gamma)}{\beta\sigma}(R_0 - 1)N, \tag{2.45b}$$

$$I^* = \frac{\mu}{\beta}(R_0 - 1)N, \tag{2.45c}$$

with

$$R^* = N - (S^* + E^* + I^*).$$

The *reproduction number* R_0 is defined as

$$R_0 = \frac{\beta\sigma}{(\mu + \sigma)(\mu + \gamma)}.$$

It can be shown that for $R_0 > 1$ the disease free equilibrium is unstable and the endemic equilibrium is stable.

2.5   Venereal diseases

For most of the sexually transmitted diseases the incubation period is usually short. For the models here, we assume that the population consists of two interacting classes, males and females. An individual of one class transmits the infection to an individual of the other class. So, we divide the population into:

- Susceptible males S and females S^*,

- Infectious males I and females I^*,

- Recovered males R and females R^*.

In the simplest form, i.e., in case that no recovered individual can return to susceptibles, the infection dynamics is figured in Figure 2.10.
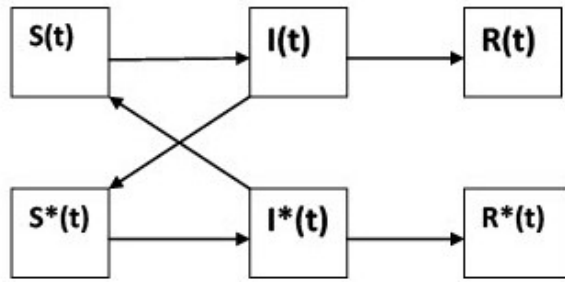
Figure 2.10: An individual of one class transmits the infection to an individual of the other class. No recovered individual can become susceptible.

An even simpler model that involves only susceptibles and infectious, is a criss-cross SI model, which schematically is figured in Figure 2.11.

In this model we assume that the infectious that have recovered, rejoin the susceptibles.

Let N and N^* be the total size of male and female population respectively. Then

$$S(t) + I(t) = N, \quad S^*(t) + I^*(t) = N^*. \tag{2.46}$$

We consider that the decrease rate of male susceptibles is proportional to the male susceptibles and the female infectious. So, we get

$$\frac{dS}{dt} = -\beta S(t)I^*(t) + \gamma I(t), \quad \frac{dS^*}{dt} = -\beta^* S^*(t)I(t) + \gamma^* I^*(t), \tag{2.47a}$$

$$\frac{dI}{dt} = \beta S(t)I^*(t) - \gamma I(t), \quad \frac{dI^*}{dt} = \beta^* S^*(t)I(t) - \gamma^* I^*(t), \tag{2.47b}$$
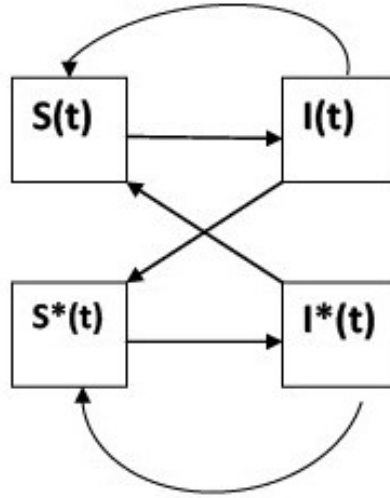
Figure 2.11: The criss - cross SI model.

where $\beta, \gamma, \beta^*, \gamma^*$ positive parameters, and

$$S(0) = S_0, \quad I(0) = I_0, \quad S^*(0) = S_0^*, \quad I^*(0) = I_0^*, \tag{2.48}$$

the given initial conditions.

Using (2.46) in (2.47) we get

$$\begin{aligned}
\frac{dI}{dt} &= \beta I^*(N - I) - \gamma I, \\
\frac{dI^*}{dt} &= \beta^* I(N^* - I^*) - \gamma^* I^*,
\end{aligned} \tag{2.49}$$

for the equilibrium points we have

$$\begin{aligned}
\beta I^*(N - I) - \gamma I &= 0, \\
\beta^* I(N^* - I^*) - \gamma^* I^* &= 0,
\end{aligned} \tag{2.50}$$

so

$$I = I^* = 0,$$

and

$$I_s = \frac{\beta \beta^* N N^* - \gamma \gamma^*}{\beta^* \gamma + \beta^* \beta N^*}, \quad I_s^* = \frac{\beta \beta^* N N^* - \gamma \gamma^*}{\beta \gamma^* + \beta^* \beta N^*}.$$

Setting

$$\rho = \frac{\gamma}{\beta}, \quad \rho^* = \frac{\gamma^*}{\beta^*},$$

we get

$$I_s = \frac{N N^* - \rho \rho^*}{\rho + N^*}, \quad I_s^* = \frac{N N^* - \rho \rho^*}{\rho + N^*}. \tag{2.51}$$

For the existence of non negative equilibrium points, it should be

$$NN^* - \rho\rho^* > 0 \quad \Leftrightarrow \quad \frac{NN^*}{\rho\rho^*} > 1 \quad \Leftrightarrow \quad \frac{\beta N}{\gamma}\frac{\beta^* N^*}{\gamma^*} > 1.$$

The interpretation for this condition is that if every man is susceptible, then $\frac{\beta N}{\gamma}$ is the average number of men that are infected by a woman for the period she is infectious. The corresponding quantity $\frac{\beta^* N^*}{\gamma^*}$ refers to women.

2.6 R_0: herd immunity, vaccination, estimation

The parameter R_0, the basic reproduction number, may be considered as the threshold beyond which the infection manages to enter the disease free-state. If $R_0 > 1$, the entrance of a single infective into a disease free but fully susceptible population, can make an infection endemic. In case that the number of individuals in susceptible class is too low at the beginning an epidemic outbreak is not going to happen. That is in case that part of the population is immune, and it is called *herd immunity*. Since newborn individuals enter the susceptible class, or the immunity declines over time, herd immunity cannot be maintained for long time.

Another effective measure in order to protect a population from an infection, is vaccination, which is not always available. The purpose of vaccination is to maintain the reproduction number below 1, so herd immunity can be guaranteed. So, the knowledge of R_0 can help us to estimate the size of vaccinated fraction.

Assume a total susceptible population and an available vaccine. If the vaccine has worked for fraction

$$w_0 \geq 1 - \frac{1}{R_0},$$

and the vaccinated individuals are immune (effectively vaccinated) before the infective agent enters the population, then the fraction of susceptibles becomes

$$u_0 = (1 - w_0) \leq \frac{1}{R_0} \iff R_0 u_0 \leq 1,$$

and an epidemic is avoided.

Many times, measures such as restriction of gathering or topical lock-downs, can be taken for the reduction of contact rate. Let ρ be a factor that reduces the average of contacts to $\tilde{c} = \rho c$. Then, the basic reproduction number becomes

$$\tilde{R}_0 = \rho R_0,$$

and an epidemic will be avoidable if and only if

$$\tilde{R}_0 \leq 1 \iff \rho \leq \frac{1}{R_0}.$$

Assuming that a fraction p is effectively vaccinated, (2.37a) becomes

$$\frac{du}{dt} = \alpha(1 - p - u(t)) - R_0 u(t)\nu(t).$$

If $p < 1 - \dfrac{1}{R_0}$, the fraction of infected at the endemic equilibrium becomes

$$\nu^* = \alpha\left(1 - p - \frac{1}{R_0}\right).$$

If $p \geq 1 - \dfrac{1}{R_0}$, the infection free state becomes asymptotically stable. The threshold value

$$p_c = 1 - \frac{1}{R_0},$$

is called the *critical vaccination ratio*. It indicates that in order to eradicate an infectious disease, we have to reach the effective vaccination fraction.

In general, since R_0 depends on contact rates and the probability of infecting contacts, a direct measurement of it is very difficult. There are a few methods for estimating R_0, but they require data coming from previous epidemics. That is not always useful, especially under the threat of a new infection outbreak.

2.7 Distributed infection period & variable infectiousness

In case of modeling diseases that have a non negligible incubation period or in cases of long - lasting infections where the infectiousness and the probability that an individual recovers or dies differ considering the time since one is being infected, it is important to take into account this time, called *infection period*.

Starting with the SIR model (2.17), we replace $I(t)$ with the incidence $j(t)$, i.e. the number of new infections at time t. So, (2.18b) becomes

$$\frac{dI}{dt} = j(t) - \gamma I(t) \quad \Rightarrow$$

$$I(t) = \int_{-\infty}^{t} \Pi(t - s)j(s)ds, \tag{2.52}$$

where $\Pi(t)$ is the probability an individual is still infectious after time t since the infection. Using (2.16) we get for the incidence

$$j(t) = \frac{c\chi}{N}I(t)S(t),$$

and we convert the system in integro-differential system

$$\frac{dS}{dt} = -j(t), \qquad\qquad S(0) = S_0, \tag{2.53a}$$

$$j(t) = S(t)\int_{-\infty}^{t} \frac{c\chi}{N}\Pi(t - s)j(s)ds, \qquad j(t) = \phi(t) \quad t \in (-\infty, 0]. \tag{2.53b}$$

It is clear that the system at time t depends on the past history of the incidence, weighted by the probability $\Pi(t)$ computed at the time $(t-s)$ elapsed since infection.

Modifying the probability $\Pi(t)$ and replacing the constant infectiousness χ with one that depends on the time elapsed since infection, we can get a kernel

$$K(t) = \frac{c}{N}\chi(t)\Pi(t),$$

and the model becomes

$$\frac{dS}{dt} = -j(t), \qquad\qquad\qquad S(0) = S_0, \qquad\qquad (2.54a)$$

$$j(t) = S(t)\int_{-\infty}^{t} K(t-s)j(s)ds, \qquad j(t) = \phi(t) \quad t \in (-\infty, 0]. \qquad (2.54b)$$

(2.54b) is a Volterra convolution equation.

(2.54b) through (2.54a) gives

$$\frac{1}{S(t)}\frac{dS(t)}{dt} = -\int_{-\infty}^{t} K(t-s)j(s)ds = \int_{0}^{t} K(t-s)\frac{dS(t)}{dt}ds - \int_{-\infty}^{0} K(t-s)\phi(s)ds.$$

Integrating the above equation in $(0,\infty)$, and using $u(t) = \dfrac{S(t)}{N}, u_\infty = \dfrac{S_\infty}{N}$, we get

$$\begin{aligned}
\ln\left(\frac{u_\infty}{u_0}\right) &= \int_0^{+\infty}\int_0^{t} K(t-s)\frac{dS}{ds}dsdt - \int_0^{+\infty}\int_{-\infty}^{0} K(t-s)\phi(s)dsdt \\
&= \int_0^{+\infty}\frac{dS}{ds}\int_s^{+\infty} K(t-s)dtds - \Lambda_0 = R_0(u_\infty - u_0) - \Lambda_0,
\end{aligned} \qquad (2.55)$$

where

$$R_0 = \int_0^{+\infty} K(s)ds = c\int_0^{+\infty} \chi(s)\Pi(s)ds, \qquad\qquad (2.56)$$

$$\Lambda_0 = \int_0^{+\infty}\int_{-\infty}^{0} K(t-s)\phi(s)dsdt,$$

are the basic reproduction number and the probability an individual of susceptible class is getting infected by one of the original class of infectives, respectively. In case of constant infectiousness and removal rate, R_0 and Λ_0 become

$$R_0 = c\chi\int_0^{+\infty} e^{-\gamma s}ds = \frac{c\chi}{\gamma},$$

$$\Lambda_0 = \frac{c\chi}{N}\int_0^{+\infty}\int_{-\infty}^{0} e^{-\gamma(t-s)}\phi(s)dsdt = \frac{R_0}{N}\int_{-\infty}^{0} e^{\gamma s}\phi(s)ds. \qquad (2.57)$$

So

$$\Lambda_0 = R_0\nu_0. \qquad\qquad (2.58)$$

From (2.55) we get

$$u_\infty = u_0 e^{-R_0(u_0 - u_\infty) - \Lambda_0}. \qquad\qquad (2.59)$$

When χ and γ are constant (2.59) gives (2.31).

In case of pandemic, $(w_0 = 0, \Lambda_0 \ll 1)$, (2.59) comes as root of (2.34) (R_0 from (2.56)).

As in the previous case, we approximate the fraction of susceptibles $u(t)$ by the number of susceptibles initially (u_0). (2.54b) becomes

$$j(t) = u_0 N \int_{-\infty}^{t} K(t-s)j(s)ds, \tag{2.60}$$

We are looking for roots of the form $j(t) = e^{\lambda t}$, so if we plug into (2.60) we get

$$e^{\lambda t} = u_0 N \int_{-\infty}^{t} K(t-s)e^{\lambda s}ds \quad \Rightarrow$$
$$e^{\lambda t} = u_0 N \int_{0}^{+\infty} K(s)e^{\lambda(t-s)}ds \quad \Rightarrow$$
$$1 = u_0 N \int_{0}^{+\infty} e^{-\lambda s}K(s)ds,$$

which is a characteristic equation for λ called the *Lotka characteristic equation*[28], and for which we know that it has a unique real solution α^*. So, we have

$$j(t) \approx j(0)e^{\alpha^* t}.$$

Furthermore, α^* is positive if and only if

$$u_0 N \int_{0}^{+\infty} K(s)ds = R_0 u_0 > 1.$$

So, the threshold condition determines the outbreak of an epidemic with initial exponential growth at a rate α^*.

Chapter 3

Age-Structured Models

3.1 The age of the disease

It is not always easy for an infected to perceive his condition, since one of the last stages in the development of a disease is the onset of symptoms. This means that the "disease clock", that it is activated in an individual the moment she/he gets infected, effects in different ways the mechanism an infection is transmitted, since it may run for a long time. That is why it is of vital importance to take it into account in epidemic modeling.

3.2 The classical Kermack - McKendrick model

There are many cases that we have to consider of the individual age in order to estimate how vulnerable and infectious a disease can be (*demographic age*). In some other cases we consider that age is the time elapsed since the individual infected (*class-age*). In some epidemic models, where a drug is used, we consider that age is the time within the drug users class.

In case we are modeling a long-lasting disease for which infected individuals have different possibilities to recover or die, and their infectiousness depends on the time they were infected, it is important to consider class-age. Assuming a single outbreak of an epidemic through a short time period so that demographic changes can be neglected, we consider a population that is closed, without migration, and that there are no births or deaths from natural causes (the "disease clock" is faster the demographic processes). So, the population size N is constant, and it is divided into the three distinct classes of susceptibles, infectious and recovered individuals. Furthermore, in this case the infectious class is structured by class-age, and we denote by

- $S(t)$ = the number of susceptibles at time t,

- $i(\theta, t)$ = the class-age density of the infected individuals (that is, the distribution of the infected with respect to θ),

- $R(t)$ = the number of recovered individuals at time t.

Note that $\theta \in [0, \theta_\dagger]$ is the *class-age*, that is, the time elapsed since infection, and $\theta_\dagger$ is the maximum duration of infection. Obviously, all the above must satisfy

$$S(t) + I(t) + R(t) = N, \quad \forall \quad t \geq 0,$$

where

$$I(t) = \int_0^{\theta_\dagger} i(\theta, t)d\theta,$$

is the total number of infected.

We also consider the following parameters

- $\gamma(\theta)$ = class-age specific removal rate,

- $\lambda(t)$ = per capita infection rate at time t (force of infection).

The number of infectious with class-age in the interval $[\theta, \theta + d\theta]$ that move into the the class of recovered during the time interval $[t, t + dt]$, is

$$\gamma(\theta)i(\theta, t)d\theta dt$$

The average number of susceptibles that become infectious per unit time, that is the *incidence rate*, is

$$\lambda(t)S(t)$$
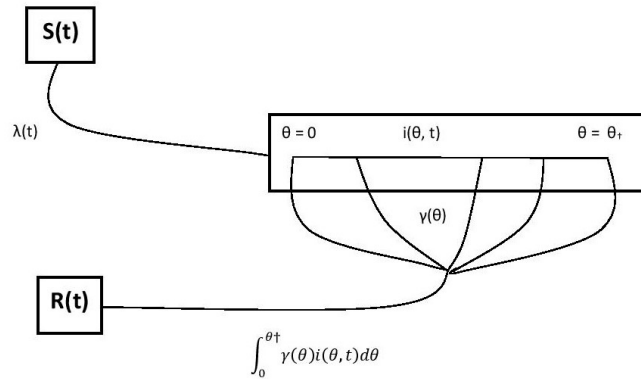
Figure 3.1: Kermack- McKendrick model. Susceptibles are infected at a rate $\lambda(t)$ and enter the class of infective individuals at class - age $\theta = 0$. Infective individuals progress through the disease and exit their class at a rate $\gamma(\theta)$ dependent on the class - age, to enter the recovered class.

Extending the form of the unstructured case for the *force of infection*, we have

$$\lambda(t) = \int_0^{\theta_\dagger} \lambda_0(\theta)i(\theta, t)d\theta, \tag{3.1}$$

where

$$\lambda_0(\theta) = \frac{c(\theta)\chi(\theta)}{N}, \tag{3.2}$$

with the *per capita contact rate* and the *infectiousness* possibly depend on the progression of the disease. The simplest extension from ODEs to class - age structured model is

$$\frac{dS}{dt} = -\lambda(t)S(t), \tag{3.3a}$$

$$\frac{\partial i(\theta,t)}{\partial t} + \frac{\partial i(\theta,t)}{\partial \theta} + \gamma(\theta)i(\theta,t) = 0, \tag{3.3b}$$

$$i(0,t) = \lambda(t)S(t), \tag{3.3c}$$

$$\frac{dR}{dt} = \int_0^{\theta_\dagger} \gamma(\theta)i(\theta,t)d\theta, \tag{3.3d}$$

with

$$S(0) = S_0, \quad i(\theta,0) = i_0(\theta), \quad R(0) = R_0.$$

the initial conditions.

The progression of the disease that is described by (3.3b), and the condition (3.3c) which is a non-local boundary condition that models the input of new infectives at age $\theta = 0$, are derived from the balance equation

$$\int_0^{\theta+h} i(\sigma,t+h)d\sigma = \int_0^\theta i(\sigma,t)d\sigma + \int_t^{t+h} \lambda(\sigma)S(\sigma)d\sigma - \int_0^h \int_0^{\theta+s} \gamma(\sigma)i(\sigma,t+s)d\sigma ds, \tag{3.4}$$

where the term

$$\int_t^{t+h} \lambda(\sigma)S(\sigma)d\sigma$$

gives the input of new infectives in the interval $[t, t+h]$. Since

$$\int_0^{\theta+s} \gamma(\sigma)i(\sigma,t+s)d\sigma$$

is the number of infected individuals that recover at the time $t+s$ with class-age less than or equal to $\theta + s$, the term

$$\int_0^h \int_0^{\theta+s} \gamma(\sigma)i(\sigma,t+s)d\sigma ds$$

gives the loss from the initial group of $\int_0^\theta i(\sigma,t)d\sigma$ individuals through the time interval $[t, t+h]$.

Differentiating (3.4) with respect to h and setting $h = 0$, we get

$$i(\theta,t) + \int_0^\theta i_t(\sigma,t)d\sigma = \lambda(t)S(t) - \int_0^\theta \gamma(\sigma)i(\sigma,t)d\sigma,$$

whereby, setting $\theta = 0$, we have

$$i(0,t) = \lambda(t)S(t).$$

Differentiating the above equation with respect to θ, we get

$$i_\theta(\theta,t) + i_t(\theta,t) + \gamma(\theta)i(\theta,t) = 0.$$

During the whole process, we consider the following minimal assumptions that the functions λ and γ are assumed to satisfy in order to be biologically significant

$$\gamma(\theta) \geq 0, \quad \lambda_0(\theta) \geq 0 \quad \text{a.e. in} \quad [0,\theta_\dagger], \tag{3.5a}$$

$$\gamma \in L^1_{loc}[0,\theta_\dagger), \quad \int_0^{\theta_\dagger} \gamma(\sigma)d\sigma = +\infty, \tag{3.5b}$$

$$\lambda_0 \in L^\infty(0,\theta_\dagger), \quad \lambda_0(\theta) > 0 \quad \text{a.e. in} \quad [\theta_1,\theta_2]. \tag{3.5c}$$

We define the *recovery probability*

$$B(\theta) = e^{-\int_0^\theta \gamma(\sigma)d\sigma}, \quad \theta \in [0,\theta_\dagger],$$

that is the probability for an individual to recover after being infected for θ units of time. It must be $B(\theta_\dagger) = 0$. Then,

$$L = \int_0^{\theta_\dagger} B(\theta)d\theta.$$

is the mean value of the time-infected of an individual.

We set

$$q(\theta,t) = e^{\int_0^\theta \gamma(\sigma)d\sigma}i(\theta,t) = \frac{i(\theta,t)}{B(\theta)}, \tag{3.6}$$

which satisfies

$$\frac{\partial q(\theta,t)}{\partial t} + \frac{\partial q(\theta,t)}{\partial \theta} = 0, \tag{3.7a}$$

$$q(0,t) = \lambda(t)S(t), \tag{3.7b}$$

$$q(\theta,0) = q_0(\theta) := e^{\int_0^\theta \gamma(\sigma)d\sigma}i_0(\theta), \tag{3.7c}$$

where

$$i_0(\theta) = i(\theta,0),$$

and

$$i(0,t) = \lambda(t)S(t) := \sigma(t)$$

is the *incidence*, that is the number of infectives in the unit of time.

Assuming $\sigma(t)$ is given, then q can be viewed as the solution to the first-order partial differential equation (3.7a) in the strip $\{\theta \in [0,\theta_\dagger], t \geq 0\}$, with the boundary conditions (3.7b) on the half-line $\{\theta = 0, t > 0\}$ and (3.7c) on the segment $\{\theta \in [0,\theta_\dagger], t = 0\}$. By integrating the equation along the characteristic lines $t - \theta = constant$, as sketched in Figure 3.2, we see that q has the following form

$$q(\theta,t) = \phi(\theta - t),$$

where ϕ is determined by the boundary conditions. So,

$$q(\theta, t) = \begin{cases} q_0(\theta - t), & \theta \geq t, \\ \sigma(t - \theta), & \theta < t, \end{cases}$$

which via (3.6) provides the formula for $i(\theta, t)$

$$i(\theta, t) = \begin{cases} i_0(\theta - t)\dfrac{B(\theta)}{B(\theta - t)}, & \theta \geq t, \\ i(0, t - \theta)B(\theta), & \theta < t. \end{cases}$$
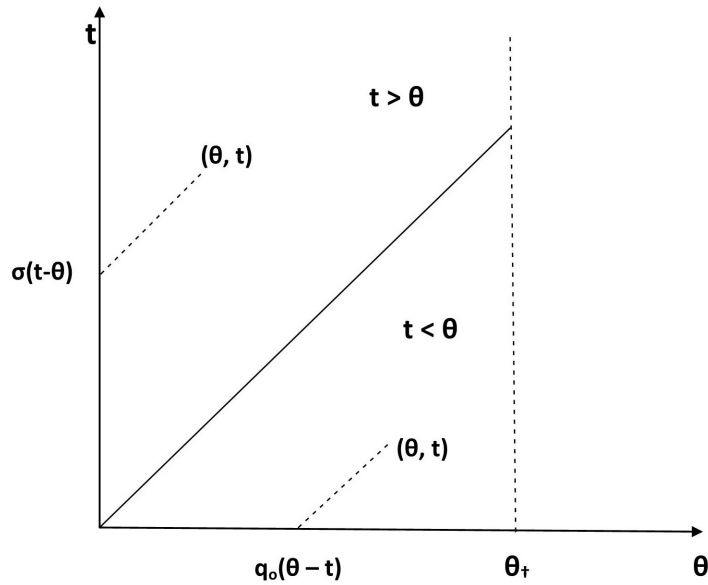
Figure 3.2: Integration of the first-order partial equation (3.7a) along the characteristic lines $t - \theta = const$.

For the *incidence* $\sigma(t)$ we have

$$\sigma(t) = \left[\int_0^{\theta_\dagger} \lambda_0(\theta) i(\theta, t) d\theta \right] S(t)$$

$$= \left[\int_0^t \lambda_0(\theta) B(\theta) \sigma(t - \theta) d\theta + \int_t^\infty \lambda_0(\theta) \frac{B(\theta)}{B(\theta - t)} i_0(\theta - t) d\theta \right] S(t),$$

where λ_0, B, i_0 are extended by zero outside of $[0, \theta_\dagger]$. Thus, (3.3) becomes

$$\begin{cases} \dfrac{dS(t)}{dt} = -\sigma(t), \\ \sigma(t) = \left[\int_0^t A(t - s)\sigma(s) ds + F(t) \right] S(t), \end{cases} \tag{3.8}$$

where

$$\begin{cases} A(t) = \lambda_0(t)B(t), \\ F(t) = \int_0^\infty \lambda_0(t+s)\dfrac{B(t+s)}{B(s)}i_0(s)ds, \end{cases} \tag{3.9}$$

with $S(0) = S_0 > 0$ as initial condition.

A solution to the system is a pair $\sigma \in C(R_+), S \in C^1(R_+)$.

The following Theorems and Propositions are from [27].

Theorem 3.2.1. *Let* (3.5) *be satisfied and let* $i_0 \in L^1(0, \theta_\dagger), i_0(\theta) \geq 0$. *Then, problem* (3.8) - (3.9) *has a unique solution.*

Proof. We transform (3.8) into a single equation. Since

$$\frac{dS(t)}{dt} = -\left[\int_0^t A(t-s)\sigma(s)ds + F(t) \right] S(t),$$

we have

$$S(t) = e^{-\left[\int_0^t A_1(t-s)\sigma(s)ds + F_1(t) \right]}, \tag{3.10}$$

where

$$A_1(t) = \int_0^t A(s)ds \geq 0, \quad F_1(t) = \int_0^t F(s)ds \geq 0.$$

Then (3.8) is equivalent to the integral equation

$$\sigma(t) = S_0 \left[\int_0^t A(t-s)\sigma(s)ds + F(t) \right] e^{-\left[\int_0^t A_1(t-s)\sigma(s)ds + F_1(t) \right]}. \tag{3.11}$$

This equation can be solved as usual by proving convergence of the iterates

$$\sigma^{k+1}(t) = S_0 \left[\int_0^t A(t-s)\sigma^k(s)ds + F(t) \right] e^{-\left[\int_0^t A_1(t-s)\sigma^k(s)ds + F_1(t) \right]},$$

initialized by $\sigma^0 \equiv 0$. Indeed, since F, F_1 are non-negative, continuous, and bounded on $[0, +\infty)$, while A, A_1 are non-negative a.e., and belong to $L^\infty(\mathbb{R}_+)$, we have

$$\sigma^k \in C(\mathbb{R}_+); \quad 0 \leq \sigma^k(t) \leq S_0 \parallel F \parallel_\infty e^{S_0 \parallel A \parallel_\infty t}.$$

Moreover, we can prove the estimate

$$|\sigma^{k+1}(t) - \sigma^k| \leq \frac{C^k T^k}{k!} \parallel \sigma^1 - \sigma^0 \parallel_C,$$

for any $T > 0$, and prove convergence. Thus, existence and uniqueness of a continuous σ follows exactly as in the case of the total birth rate. Finally, from (3.10), we obtain $S(t)$, so the pair (σ, S) is a solution to (3.8). $\qquad \square$

The outbreak and the extinction of an epidemic

Theorem 3.2.2. *Let (σ, S) be the solution to (3.3) provided by Theorem 3.2.1. Then,*

$$\lim_{t\to+\infty} \sigma(t) = 0, \quad \lim_{t\to+\infty} S(t) = S_\infty, \tag{3.12}$$

where S_∞ satisfies

$$S_\infty = S_0 \exp\Big[(S_\infty - S_0) \int_0^\infty A(s)ds + \int_0^\infty F(s)ds\Big]. \tag{3.13}$$

Proof. We note that from (3.3) we get

$$S(t) = S_0 - \int_0^t \sigma(s)ds > 0,$$

so that

$$\int_0^\infty \sigma(s)ds \le S_0, \tag{3.14}$$

and

$$\lim_{t\to+\infty} S(t) = S_\infty = S_0 - \int_0^\infty \sigma(s)ds \ge 0.$$

Also,

$$F(t) = 0 \quad \text{for} \quad t > \theta_\dagger,$$
$$A(t) = 0 \quad \text{for} \quad t > \theta_\dagger,$$

so that, since $\sigma \in L^1(0, +\infty)$ by (3.14), we have

$$\lim_{t\to+\infty} \int_0^t A(t-s)\sigma(s)ds = 0.$$

In conclusion, passing to the limit in (3.11), we prove (3.12).

Concerning the final size of the susceptible class, from (3.10) we obtain

$$S(t) = S_0 \exp\Big[\int_0^t A_1(t-s)\frac{dS(t)}{dt}ds + F_1(t)\Big]$$
$$= S_0 \exp\Big[\int_0^t A(s)S(t-s)ds + F_1(t) - A_1(t)S_0\Big],$$

because $\sigma(t) = -\dfrac{dS(t)}{dt}$. Thus, passing to the limit, we have (3.13). □

From the above, it comes that finally, for a single epidemic, the infection dies out and the class of susceptibles is not decreased by the infection. We have,

$$\lim_{t\to+\infty} I(t) = \lim_{t\to+\infty} \int_0^{\theta^\dagger} i(\theta, t)d\theta = \lim_{t\to+\infty} \int_0^\infty \sigma(t-\theta)B(\theta)d\theta = 0,$$

and from (3.13) we obtain $S_\infty > 0$.

In order to determine a threshold value for the infection maintenance, we define the *basic reproduction number* as

$$\mathscr{R}_0 = \int_0^{\theta\dagger} c(\theta)\chi(\theta)B(\theta)d\theta = N \int_0^{\theta\dagger} A(\theta)d\theta, \qquad (3.15)$$

which still represents the number of secondary infections an individual produces as long as he is infected, and it is involved in the threshold condition for the infection outbreak.

Proposition 3.2.1. *Under the assumptions of Theorem 3.2.1, let (σ, S) be the solution to (3.3). Then, σ is either identically zero, or eventually positive. If, in addition*

$$\lambda_0(\theta) > 0 \quad a.e \ in \quad [0, \theta_f], \qquad (3.16)$$

then $\sigma(t)$ is positive for all $t \geq 0$.

Proof. If σ is not identically zero, let

$$\sigma(t) > 0 \quad \text{for} \quad t \in [\alpha, \beta].$$

Then, for $t \in [\alpha + \theta_1, \beta + \theta_2]$ and $\theta_2 > \alpha + \theta_1 - \beta$, we have

$$\sigma(t) \geq S(t) \int_0^t A(t-\theta)\sigma(\theta)d\theta \geq S(t) \int_\alpha^{t\wedge\beta} A(t-\theta)\sigma(\theta)d\theta$$

$$\geq S(\beta+\theta_2) \min_{\theta\in[\alpha,\beta]} \sigma(\theta) \int_\alpha^{t\wedge\beta} A(t-\theta)d\theta$$

$$= S(\beta+\theta_2) \min_{\theta\in[\alpha,\beta]} \sigma(\theta) \int_{0\vee(t-\beta)}^{t-\alpha} \lambda_0(\theta)B(\theta)d\theta > 0,$$

where we have used the facts that $(\theta_1, \theta_2) \cap (\theta \vee (t-\beta), t-\alpha) \neq \varnothing$ and $S(\beta+\theta_2) > 0$.

Iterating this argument, we see that

$$\sigma(t) > 0 \quad \text{for} \quad t \in [\alpha + n\theta_1, \beta + n\theta_2],$$

for any positive integer n and, consequently, $\sigma(t)$ is eventually positive.

Let now (3.16) be satisfied, then $F(0) > 0$ and, consequently, $\sigma(0) > 0$. If $\sigma(t)$ vanishes somewhere, there must exist a t_0 such that

$$\sigma(t_0) = 0, \quad \sigma(t) > 0 \quad \text{for} \quad t \in [0, t_0).$$

Then,

$$0 = \sigma(t_0) = S(t_0) \left[\int_0^{t_0} A(t_0 - s)\sigma(s)ds + F(t_0) \right]$$

$$\geq S(t_0) \int_0^{t_0} A(t_0 - s)\sigma(s)ds > 0,$$

which is impossible. Hence, it must be $\sigma(t) > 0$ for all $t \geq 0$. $\qquad\square$

We define
$$I_k = [k\theta_\dagger, (k+1)\theta_\dagger], \quad 1 \le k \in \mathbb{Z},$$
and
$$m_k = \min_{t \in I_k} \sigma(t), \quad M_k = \max_{t \in I_k} \sigma(t), \quad S_k = S(k\theta_\dagger).$$
We have the following

Proposition 3.2.2. *Under the assumptions of Theorem 3.2.1, let (σ, S) be the solution to (3.3). If σ is not identically zero, then*
$$M_k > 0, \quad \forall k \ge 0, \quad and \quad m_k > 0 \quad eventually.$$

If (3.16) *is satisfied, then $m_k > 0, \quad \forall k \ge 0$.*

Proof. Since $F(t)$ is not identically zero on $[0, \theta_\dagger]$, neither is $\sigma(t)$, and we have $M_0 > 0$.

Assume $M_k > 0$ and let $[\alpha, \beta] \subset I_k$ be such that $\sigma(t) > 0$ on $[\alpha, \beta]$. Then, by the proof of Proposition 3.2.1, $\sigma(t) > 0$ on $[\alpha + n\theta_1, \beta + n\theta_2]$. Because it is possible to find n such that $(k+1)\theta_\dagger < \alpha + n\theta_1 < (k+2)\theta_\dagger$, then $\sigma(t) > 0$ somewhere in I_{k+1} and consequently, also $M_{k+1} > 0$.

The last part of the result is a direct consequence of Proposition 3.2.1. $\square$

In the following Theorem, the conditions concerning the outbreak of an epidemic are quoted.

Theorem 3.2.3. *Let assumptions* (3.5) *and* (3.16) *be satisfied, and let (σ, S) be the solution to* (3.3), *provided by Theorem 3.2.1. Then, for $k > 0$ we have*

$$M_k < M_{k-1} \quad if \quad \mathscr{R}_0 \frac{S_k}{N} < 1, \tag{3.17}$$

$$m_k > m_{k-1} \quad if \quad \mathscr{R}_0 \frac{S_{k+1}}{N} > 1. \tag{3.18}$$

Moreover, in the second case, we have

$$\mathscr{R}_0 \frac{S_\infty}{N} < 1. \tag{3.19}$$

Proof. Let $k > 0$ and $t \in I_k$; then
$$\sigma(t) = S(t) \int_0^{\theta_\dagger} A(s)\sigma(t-s)ds,$$
and, since $(t-s) \in I_k \cup I_{k-1}$ for $s \in [0, \theta_\dagger]$, it follows that
$$\sigma(t) \le S(t) \int_0^{\theta_\dagger} A(s)ds \quad (M_k \vee M_{k-1}),$$

and

$$M_k \leq \mathscr{R}_0 \frac{S_k}{N} \quad (M_k \vee M_{K-1}),$$

so that, since $M_k > 0$, we have

$$M_k \quad < \quad (M_k \vee M_{k-1}),$$

and (3.17) is proved. The proof of (3.18) is analogous. Concerning (3.19), assume, by contradiction, that $\mathscr{R}_0 \frac{S_k}{N} > 1$, for all k. Then, by (3.18), the sequence m_k is increasing, which is impossible by (3.12). $\qquad \square$

The last theorem describes the way an epidemic evolves through time intervals of length $\theta_\dagger$. For example, the epidemic will not maintain if the number of susceptibles is under the threshold value $\frac{N}{\mathscr{R}_0}$ at the end of the first interval.

3.3   SI age-dependent model

There are some diseases, such as herpes, for which infectives remain infective for life, but do not affect the life span. In these cases, the appropriate models are SI models, which are the simplest, since they can be described with only two individual classes.

We assume an infectious disease for which there is no incubation period neither cure. Let θ be the age from exposure to the disease. Then, we can divide the population into two classes, the *susceptibles*, $S(t)$, and the *infectious*, $i(\theta, t)$. As above, the population of the susceptibles, after the exposure to the infection, decreases at a rate

$$\frac{dS}{dt} = -\lambda(t)S(t) \quad \Rightarrow \quad \frac{dS}{dt} = -\left[\int_0^{\theta_\dagger} \lambda_0(\theta)i(\theta,t)d\theta\right]S(t), \quad S(0) = S_0, \qquad (3.20)$$

where, as above, $\lambda_0(\theta) = \dfrac{c(\theta)\chi(\theta)}{N}$ indicates the infectiousness of the infectious, and $\theta_\dagger$ is the time that an individual can be infectious. Obviously,

$$\frac{dS}{dt} \leq 0 \quad \Rightarrow \quad S(t) \to S(\infty), \quad \text{where} \quad 0 \leq S(\infty) \leq S_0.$$

For the population of infectious $i(\theta, t)$ we have

$$\frac{\partial i}{\partial t} + \frac{\partial i}{\partial \theta} = -\gamma(\theta)i(\theta, t). \qquad (3.21)$$

For the boundary conditions, we have

- at time $t = 0$, there is a number of infectious $i(0, \theta) = i_0(\theta)$,

- at $\theta = 0$, the rate of new infectious is equal to the rate that the susceptible population decreases, that is $\dfrac{dS}{dt}$.

So,

$$i(\theta, 0) = i_0(\theta),$$
$$i(0, t) = -\frac{dS}{dt}, \quad t > 0. \tag{3.22}$$

For the model which consists of the equations (3.20) - (3.22), $i_0(\theta), S_0$ are given, and $\gamma(\theta), \lambda(t)$ are considered to be known.

Let $\mathscr{R}_0$ be the number of initial susceptibles we expect to be infected by each infectious, then

$$\mathscr{R}_0 = S_0 \int_0^{\theta_\dagger} \lambda_0(\theta) i(\theta, t) B(\theta) d\theta, \tag{3.23}$$

where $B(\theta) = e^{-\int_0^a \gamma(\sigma)d\sigma}$ is the probability of an initial infectious surviving to age θ. If $\mathscr{R}_0 > 1$, the infection will spread. If $\mathscr{R}_0 < 1$, the infection will not spread. So, $\mathscr{R}_0 = 1$ is the threshold value for an epidemic.

3.4   The SIS model

In order to study those cases that lead to disease endemicity within the same context of class - age structure, we consider the structured version of the SIS model, and then we investigate the existence of endemic steady states and their stability. Starting with the modification of the structured SIR model, we get the equation system

$$\frac{dS}{dt} = -\lambda(t)S(t) + \int_0^{\theta_\dagger} \gamma(\theta) i(\theta, t) d\theta, \tag{3.24a}$$

$$\frac{\partial i(\theta, t)}{\partial t} + \frac{\partial i(\theta, t)}{\partial \theta} + \gamma(\theta) i(\theta, t) = 0, \tag{3.24b}$$

$$i(0, t) = \lambda(t)S(t), \tag{3.24c}$$

with the initial conditions

$$S(0) = S_0, \quad i(\theta, 0) = i_0(\theta),$$

and the force of infection

$$\lambda(t) = \int_0^{\theta_\dagger} \lambda_0(\theta) i(\theta, t) d\theta.$$

Let

$$I(t) = \int_0^{\theta_\dagger} i(\theta, t) d\theta$$

be the total number of infectives. Integrating (3.24b) with respect to θ, we have

$$\frac{dI(t)}{dt} + i(\theta_\dagger, t) - i(0, t) + \int_0^{\theta_\dagger} \gamma(\theta) i(\theta, t) d\theta = 0 \Rightarrow$$
$$\frac{dI(t)}{dt} = \lambda(t)S(t) - \int_0^{\theta_\dagger} \gamma(\theta) i(\theta, t) d\theta.$$
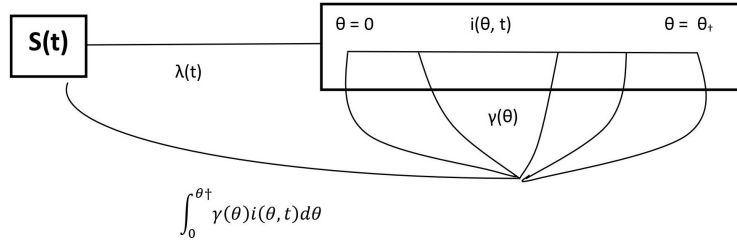
Figure 3.3: The SIS model with age structure. Susceptibles are infected at a rate $\lambda(t)$ and enter the class of infective individuals at class - age $\theta = 0$. Infective individuals progress through the disease and exit their class at a rate $\gamma(\theta)$ dependent on the class - age to go back to the susceptible class.

Considering (3.24a), we have

$$\frac{d\left(S(t) + I(t)\right)}{dt} = 0 \Rightarrow$$

$$S(t) + I(t) = N = const. \tag{3.25}$$

So, we can reduce the problem (3.24) to a single equation in terms of the variable

$$u(\theta, t) = \frac{i(\theta, t)}{N}.This is$$

$$u_t(\theta, t) + u_\theta(\theta, t) + \gamma(\theta)u(\theta, t) = 0, \tag{3.26a}$$

$$u(0, t) = \left(1 - \int_0^{\theta_\dagger} u(\theta, t)d\theta\right) \int_0^{\theta_\dagger} c(\theta)\chi(\theta)u(\theta, t)d\theta, \tag{3.26b}$$

$$u(\theta, 0) = u_0(\theta). \tag{3.26c}$$

3.4.1 Endemic state and stability

Except for the trivial solution $u^* \equiv 0$, which corresponds to the disease-free state, we look for nonzero endemic steady-states. These must be the solutions of

$$u'(\theta) + \gamma(\theta)u(\theta) = 0, \tag{3.27a}$$

$$u(0) = \left(1 - \int_0^{\theta_\dagger} u(\theta)d\theta\right) \int_0^{\theta_\dagger} c(\theta)\chi(\theta)u(\theta)d\theta. \tag{3.27b}$$

Then, from (3.27a) we get

$$u'(\theta) = -\gamma(\theta)u(\theta) \quad \Rightarrow \quad u^*(\theta) = u^*(0)e^{-\int_0^\theta \gamma(\sigma)d\sigma} \quad \Rightarrow \quad u^*(\theta) = u^*(0)B(\theta).$$

Then, (3.27b) gives

$$u^*(0) = \left(1 - \int_0^{\theta_\dagger} u^*(0)B(\theta)d\theta\right)\int_0^{\theta_\dagger} c(\theta)\chi(\theta)u^*(0)B(\theta)d\theta$$

$$\Rightarrow \quad 1 = \left(1 - u^*(0)\mathscr{B}\right)\mathscr{R}_0 \tag{3.28}$$

where

$$\mathscr{B} = \int_0^{\theta_\dagger} B(\theta)d\theta,$$

and

$$\mathscr{R}_0 = \int_0^{\theta_\dagger} c(\theta)\chi(\theta)B(\theta)d\theta,$$

is the *basic reproduction* number. From (3.28)

$$u^*(0) = \frac{1}{\mathscr{B}}\left(1 - \frac{1}{\mathscr{R}_0}\right),$$

so,

$$u^*(\theta) = \frac{1}{\mathscr{B}}\left(1 - \frac{1}{\mathscr{R}_0}\right)B(\theta)$$

is the unique endemic steady state, provided that

$$\mathscr{R}_0 > 1,$$

i.e., the threshold condition is satisfied.

Linearizing (3.26) at u^* we get

$$w_t(\theta, t) + w_\theta(\theta, t) + \gamma(\theta)w(\theta, t) = 0, \tag{3.29a}$$

$$w(0, t) = \left(1 - \int_0^{\theta_\dagger} u^*(\theta)d\theta\right)\int_0^{\theta_\dagger} c(\theta)\chi(\theta)w(\theta, t)d\theta$$

$$- \int_0^{\theta_\dagger} c(\theta)\chi(\theta)u^*(\theta)d\theta \int_0^{\theta_\dagger} w(\theta, t)d\theta, \tag{3.29b}$$

$$w(\theta, 0) = w_0(\theta). \tag{3.29c}$$

Then, we have the eigenvalue problems for the disease-free equilibrium $(u^* = 0)$ and for the endemic one $(\mathscr{R}_0 > 1)$ respectively.

For the disease-free equilibrium we set $u^*(\theta) = 0$, and we have

$$\begin{cases} (i) & \lambda w(\theta) + \gamma(\theta)w(\theta) = 0, \\ (ii) & w(0) = \int_0^{\theta_\dagger} c(\theta)\chi(\theta)w(\theta)d\theta, \end{cases} \tag{3.30}$$

and, for the endemic equilibrium we set $u^*(\theta) = \frac{1}{\mathscr{B}}\left(1 - \frac{1}{\mathscr{R}_0}\right)B(\theta)$, in (3.29b) and

we have

$$
\begin{aligned}
w(0) &= \left(1 - \int_0^{\theta_\dagger} \frac{1}{\mathscr{B}} \left(1 - \frac{1}{\mathscr{R}_0}\right) B(\theta) d\theta\right) \int_0^{\theta_\dagger} c(\theta)\chi(\theta)w(\theta) d\theta \\
&\quad - \int_0^{\theta_\dagger} c(\theta)\chi(\theta) \frac{1}{\mathscr{B}} \left(1 - \frac{1}{\mathscr{R}_0}\right) B(\theta) d\theta \int_0^{\theta_\dagger} w(\theta) d\theta \\
&= \int_0^{\theta_\dagger} c(\theta)\chi(\theta)w(\theta) d\theta - \frac{\mathscr{R}_0 - 1}{\mathscr{R}_0 \mathscr{B}} \int_0^{\theta_\dagger} B(\theta) d\theta \int_0^{\theta_\dagger} c(\theta)\chi(\theta)w(\theta) d\theta \\
&\quad - \frac{\mathscr{R}_0 - 1}{\mathscr{R}_0 \mathscr{B}} \int_0^{\theta_\dagger} c(\theta)\chi(\theta)B(\theta) d\theta \int_0^{\theta_\dagger} w(\theta) d\theta \\
&= \int_0^{\theta_\dagger} c(\theta)\chi(\theta)w(\theta) d\theta - \frac{\mathscr{R}_0 - 1}{\mathscr{R}_0} \int_0^{\theta_\dagger} c(\theta)\chi(\theta)w(\theta) d\theta \\
&\quad - \frac{\mathscr{R}_0 - 1}{\mathscr{B}} \int_0^{\theta_\dagger} w(\theta) d\theta,
\end{aligned}
$$

so, we conclude

$$
\begin{cases}
(i) & \lambda w(\theta) + \gamma(\theta)w(\theta) = 0, \\
(ii) & w(0) = \frac{1}{\mathscr{R}_0} \int_0^{\theta_\dagger} c(\theta)\chi(\theta)w(\theta) d\theta - \frac{\mathscr{R}_0 - 1}{\mathscr{B}} \int_0^{\theta_\dagger} w(\theta) d\theta.
\end{cases}
\tag{3.31}
$$

Setting

$$
K_0(t) = \frac{c(t)\chi(t)B(t)}{\mathscr{R}_0}, \quad K_1(t) = \frac{B(t)}{\mathscr{B}},
\tag{3.32}
$$

and normalizing the kernels so that $\widehat{K}_0(0) = \widehat{K}_1(0) = 1$, the eigenvalue problems lead to the characteristic equations

$$
1 = \mathscr{R}_0 \widehat{K}_0(\lambda),
\tag{3.33}
$$

and

$$
1 = \widehat{K}_0(\lambda) - (\mathscr{R}_0 - 1)\widehat{K}_1(\lambda),
\tag{3.34}
$$

respectively.

It is proved that, if $\mathscr{R}_0 < 1$ the disease-free state is asymptotically stable, and if $\mathscr{R}_0 > 1$ it is unstable. That is, $\mathscr{R}_0 = 1$ is the critical value where the endemic arises, since it is the value that the disease-free equilibrium loses its stability. In addition, the endemic steady state is stable at least as long as $\mathscr{R}_0 > 1$ is close enough to 1, that is, it inherits the stability that the disease-free equilibrium loses. For values of $\mathscr{R}_0$ that are larger, and depending on the kernels $K_0(t)$ and $K_1(t)$ form, destabilization of endemic steady-state may occur.

3.5   The basic SIR model

3.5.1   Modeling variable populations

Demographic changes may be responsible for disease endemicity through the introduction of newborn susceptibles. We also need to study the ways the population

size and the epidemiological classes affect the mechanisms of contact. In the seminal SIR model Kermack and McKendrick assumed a contact mechanism based on the mass-action law, expressed by the form (3.1) and (3.2) of the per capita infection rate λ. Taking into account the variability of the population size due to demographic changes and the increased mortality rates due to the disease, we introduce a general form of *infection rate*

$$\lambda(t) = \int_0^{\theta_\dagger} \frac{\mathscr{C}(\theta, N(t))}{N(t)} \chi(\theta) i(\theta, t) d\theta, \tag{3.35}$$

where

- $N(t) = S(t) + I(t) + R(t)$,

- χ = the variable infectivity,

- $\mathscr{C}(\theta, x)$ = the number of contacts per individual of class - age θ per unit time, when the total size of the active population is x.

We assume for the contact rate

$$\mathscr{C}(\theta, x) = c(\theta)\mathscr{K}(x), \tag{3.36}$$

where the function $\mathscr{K}$ is a function such that

$$\mathscr{K}(\cdot) \in C^1(\mathbb{R}_+), \quad \mathscr{K}(x) \geq 0, \quad \mathscr{K}'(x) \geq 0, \quad \mathscr{K}'(0) > 0. \tag{3.37}$$

So, the force of infection gets the constitutive form:

$$\lambda(t) = \frac{\mathscr{K}(N(t))}{N(t)} \int_0^{\theta_\dagger} \varphi(\theta) i(\theta, t) d\theta, \tag{3.38}$$

with kernel

$$\varphi(\theta) = c(\theta)\chi(\theta),$$
$$\varphi(\theta) \geq 0 \quad a.e. \quad in \quad [0, \theta_\dagger],$$
$$\varphi \in L^\infty(0, \theta_\dagger), \quad \varphi(\theta) > 0 \quad a.e. \quad in \quad [\theta_1, \theta_2].$$

Considering a simple demographic process, where the rate that individuals enter the susceptible class and the mortality rate are constant, we introduce

- Λ = the number of individuals who enter the susceptible-class per unit time.

- μ = the rate at which individuals die, not due to the disease (natural per capita mortality rate).

- v = the rate at which infected individuals die due to the disease, namely the per capita mortality due to the disease.

So, Λ and μ are related to all relevant input and output mechanisms and not only to births and deaths, and v is the possible lethal effect of the disease.

3.5.2   The extended Kermack - McKendrick SIR model

All the above assumptions may be included into an extended Kermack - McKendrick model of the form:

$$\frac{dS}{dt} = \Lambda - \lambda(t)S(t) - \mu S(t), \tag{3.39a}$$

$$\frac{\partial i(\theta,t)}{\partial t} + \frac{\partial i(\theta,t)}{\partial \theta} + \gamma(\theta)i(\theta,t) + (\mu + \nu)i(\theta,t) = 0, \tag{3.39b}$$

$$i(0,t) = \lambda(t)S(t), \tag{3.39c}$$

$$\frac{dR}{dt} = \int_0^{\theta_\dagger} \gamma(\theta)i(\theta,t)d\theta - \mu R(t), \tag{3.39d}$$

with the initial conditions

$$S(0) = S_0 > 0, \quad i(\theta,0) = i_0(\theta) \not\equiv 0, \quad R(0) = R_0 \geq 0,$$

where λ is given by (3.38) and $\gamma(\theta)$ is the age-specific per capita removal rate.

Integrating (3.39b) with respect to θ, for $0 \leq \theta \leq \theta_\dagger$, we have

$$\int_0^{\theta_\dagger} \frac{\partial i(\theta,t)}{\partial t}d\theta = -\int_0^{\theta_\dagger} \frac{\partial i(\theta,t)}{\partial \theta}d\theta - \int_0^{\theta_\dagger} \gamma(\theta)i(\theta,t)d\theta - (\mu + \nu)\int_0^{\theta_\dagger} i(\theta,t)d\theta,$$

and using (3.39c) we get

$$\frac{dI(t)}{dt} = \lambda(t)S(t) - \int_0^{\theta_\dagger} \gamma(\theta)i(\theta,t)d\theta - (\mu + \nu)I(t). \tag{3.40}$$

The total population dynamics is

$$\frac{dN(t)}{dt} = \Lambda - \mu N(t) - \nu I(t), \tag{3.41}$$

with

$$N(0) = S_0 + R_0 + \int_0^{\theta_\dagger} i_0(\theta)d\theta,$$

as initial condition.

Considering that

$$R(t) = N(t) - S(t) - I(t),$$

and using (3.39a) and (3.40), we can replace (3.39d) by (3.41). So the problem becomes

$$\frac{dS}{dt} = \Lambda - \lambda(t)S(t) - \mu S(t), \tag{3.42a}$$

$$\frac{\partial i(\theta,t)}{\partial t} + \frac{\partial i(\theta,t)}{\partial \theta} + \gamma(\theta)i(\theta,t) + (\mu + \nu)i(\theta,t) = 0, \tag{3.42b}$$

$$i(0,t) = \lambda(t)S(t), \tag{3.42c}$$

$$\frac{dN}{dt} = \Lambda - \mu N(t) - \nu I(t). \tag{3.42d}$$

As in previous case, we can transform the above system into an integrodifferential system, using the disease incidence $\sigma(t)$. Integration along characteristics gives

$$
i(\theta, t) = \begin{cases} i_0(\theta - t)e^{-(\mu+\nu)t}\dfrac{B(\theta)}{B(\theta - t)}, \theta \geq t, \\ \sigma(t - \theta)e^{-(\mu+\nu)\theta}B(\theta), \quad \theta < t \end{cases} \tag{3.43}
$$

where $B(\theta)$ is the *recovery probability*. Then, the problem becomes

$$
\frac{dS}{dt} = \Lambda - \mu S(t) - \sigma(t), \tag{3.44a}
$$

$$
\frac{dI}{dt} = \sigma(t) - \int_0^t A_1(t - s)\sigma(s)ds - F_1(t) - (\mu + \nu)I(t), \tag{3.44b}
$$

$$
\frac{dN}{dt} = \Lambda - \mu N(t) - \nu I(t), \tag{3.44c}
$$

$$
\sigma(t) = S(t)\frac{\mathscr{K}(N(t))}{N(t)}\left[\int_0^t A_2(t - s)\sigma(s)ds + F_2(t)\right], \tag{3.44d}
$$

with

$$
A_1(t) = e^{-(\mu+\nu)t}\gamma(t)B(t), \quad A_2(t) = e^{-(\mu+\nu)t}\varphi(t)B(t),
$$

$$
F_1(t) = e^{-(\mu+\nu)t}\int_0^\infty \gamma(t + s)\frac{B(t + s)}{B(s)}i_0(s)ds,
$$

$$
F_2(t) = e^{-(\mu+\nu)t}\int_0^\infty \varphi(t + s)\frac{B(t + s)}{B(s)}i_0(s)ds,
$$

where γ, φ, B, i_0 are extended by zero outside $[0, \theta_\dagger]$.

From theory, there exists a unique global solution of (3.44), such that the functions

$$
S, \quad S', \quad I, \quad N, \quad N' \quad \text{and} \quad \sigma
$$

are continuous, and they satisfy

$$
\sigma(t) \geq 0, \quad S(t) \geq 0, \quad I(t) \geq 0, \quad N(t) \geq S(t) + I(t) \geq 0.
$$

Solving (3.44a) we get

$$
S(t) = S_0 e^{-\mu t} + \frac{\Lambda}{\mu}(1 - e^{-\mu t}) - \int_0^t e^{-\mu(t-s)}\sigma(s)ds, \tag{3.45}
$$

and therefore

$$
\limsup_{t \to +\infty} \int_0^t e^{-\mu(t-s)}\sigma(s)ds \leq \frac{\Lambda}{\mu},
$$

and from (3.44c) we get

$$
N(t) = N(0)e^{-\mu t} + \frac{\Lambda}{\mu}(1 - e^{-\mu t}) - \nu \int_0^t e^{-\mu s}I(t - s)ds, \tag{3.46}
$$

and hence

$$\limsup_{t\to+\infty} N(t) \le \frac{\Lambda}{\mu}.$$

We also have

$$\limsup_{t\to+\infty} \int_0^t A_2(t-s)\sigma(s)ds \le \| \varphi \|_\infty \limsup_{t\to+\infty} \int_0^t e^{-\mu(t-s)}\sigma(s)ds \le \| \varphi \|_\infty \frac{\Lambda}{\mu},$$

and $S(t) \le N(t)$, so

$$\limsup_{t\to+\infty} \sigma(t) < +\infty. \tag{3.47}$$

So, we get the following theorem

Theorem 3.5.1. *Let the assumptions*

$$\gamma \in L^1_{loc}([0,\theta_\dagger)), \quad \gamma(\theta) \ge 0, \quad a.e. \ in \ \ [0,\theta_\dagger] \quad \int_0^{\theta_\dagger} \gamma(\sigma)d\sigma = +\infty,$$

$$\varphi \in L^\infty(0,\theta_\dagger), \quad \varphi(\theta) \ge 0 \quad a.e. \ in \ \ [0,\theta_\dagger], \quad \varphi(\theta) > 0 \quad a.e. \ \ in \ \ [\theta_1,\theta_2], \tag{3.48}$$

$$\mathscr{K}(\cdot) \in C^1(\mathbb{R}_+), \quad \mathscr{K}(x) \ge 0, \quad \mathscr{K}'(x) \ge 0, \quad \mathscr{K}'(0) > 0,$$

hold, and let (S,I,N,σ) *be the solution to* (3.44)*. If*

$$\mathscr{K}\left(\frac{\Lambda}{\mu}\right) \int_0^{\theta_\dagger} e^{-(\mu+\nu)\theta}\varphi(\theta)B(\theta)d\theta < 1, \tag{3.49}$$

then,

$$\lim_{t\to+\infty} I(t) = \lim_{t\to+\infty} \sigma(t) = 0, \quad \lim_{t\to+\infty} N(t) = \lim_{t\to+\infty} S(t) = \frac{\Lambda}{\mu}. \tag{3.50}$$

Proof. By (3.44d) we have

$$\sigma(t) \le \mathscr{K}(N(t))\left[\int_0^t A_2(t-s)\sigma(s)ds + F_2(t)\right],$$

and since

$$\limsup_{t\to+\infty} \int_0^t A_2(t-s)\sigma(s)ds \le \int_0^\infty A_2(s)ds \limsup_{t\to+\infty} \sigma(t),$$

we see that

$$\limsup_{t\to+\infty} \sigma(t) \le \mathscr{K}\left(\frac{\Lambda}{\mu}\right) \int_0^\infty A_2(s)ds \times \limsup_{t\to+\infty} \sigma(t),$$

so that, from (3.47) and (3.49), we have

$$\lim_{t\to+\infty} \sigma(t) = 0.$$

From this relation and (3.43), we have

$$\lim_{t\to+\infty} I(t) = \lim_{t\to+\infty} \int_0^{\theta_\dagger} e^{-(\mu+\nu)\theta}B(\theta)\sigma(t-\theta)d\theta = 0.$$

Finally, using (3.45) and (3.46), these last limits imply that

$$\lim_{t\to+\infty} N(t) = \lim_{t\to+\infty} S(t) = \frac{\Lambda}{\mu}. \tag{3.51}$$

$$\square$$

We should note that the parameter

$$\mathscr{R}_0 = \mathscr{K}\left(\frac{\Lambda}{\mu}\right) \int_0^{\theta_\dagger} e^{-(\mu+\nu)\theta} \varphi(\theta) B(\theta) d\theta, \tag{3.52}$$

is the *basic reproduction number* of the epidemic, that is (3.49) is a threshold criterion. As in previous cases, $\mathscr{R}_0$ gives the average number of new infections that an infective will produce in an active population of size $\frac{\Lambda}{\mu}$. Furthermore, the *disease-free* equilibrium of model (3.39) is

$$S^* = N^* = \frac{\Lambda}{\mu}, \quad i^*(\theta) \equiv 0.$$

Thus, we have the following result:
If $\mathscr{R}_0 < 1$, the epidemic extincts asymptotically and the population approaches the disease - free state.

It is expected that if $\mathscr{R}_0 > 1$, the disease-free state is unstable. So, it is a condition for the existence of non - trivial stationary states.

3.5.3 Endemic states for SIR model

Looking for positive stationary solutions to problem (3.42) is like we are looking for solutions $(S^*, i^*(\theta), N^*)$ to the following problem:

$$\Lambda - \mu S - \lambda S = 0, \tag{3.53a}$$

$$i'(\theta) + \gamma(\theta)i(\theta) + (\mu + \nu)i(\theta) = 0, \quad i(0) = \lambda S, \tag{3.53b}$$

$$\Lambda - \mu N - \nu I = 0, \tag{3.53c}$$

$$\lambda = \frac{\mathscr{K}(N)}{N} \int_0^{\theta_\dagger} \varphi(\theta)i(\theta)d\theta, \tag{3.53d}$$

$$I = \int_0^{\theta_\dagger} i(\theta)d\theta. \tag{3.53e}$$

The disease-free equilibrium $\left(\frac{\Lambda}{\mu}, 0, \frac{\Lambda}{\mu}\right)$ is a solution to (3.53). To study the endemic states of the disease, that is the existence of non - trivial solutions $(i^*(\theta) \not\equiv 0)$, we set the incidence at the endemic state $\sigma = \lambda S$. From (3.53b) we have

$$i(\theta) = \sigma e^{-(\mu+\nu)\theta} B(\theta), \tag{3.54}$$

and substituting it into (3.53) we get

$$\Lambda - \mu S - \sigma = 0, \tag{3.55a}$$

$$\Lambda - \mu N - \nu \mathscr{B}\sigma = 0, \tag{3.55b}$$

$$\frac{S\mathscr{K}(N)\mathscr{B}_\varphi}{N} = 1, \tag{3.55c}$$

$$I = \lambda S\mathscr{B}, \tag{3.55d}$$

where

$$\mathscr{B} = \int_0^{\theta_\dagger} e^{-(\mu+\nu)\theta} B(\theta) d\theta, \quad \mathscr{B}_\varphi = \int_0^{\theta_\dagger} \varphi(\theta) e^{-(\mu+\nu)\theta} B(\theta) d\theta, \tag{3.56}$$

In case that $\nu = 0$, that is the disease does not affect the population mortality, so (3.42d) is independent of the other equations in (3.42), and the endemic equilibrium becomes

$$S^* = \frac{\Lambda}{\mu \mathscr{K}\left(\frac{\Lambda}{\mu}\right) \mathscr{B}_\varphi}, \quad \sigma^* = \Lambda\left(1 - \frac{1}{\mu \mathscr{K}\left(\frac{\Lambda}{\mu}\right) \mathscr{B}_\varphi}\right), \quad N^* = \frac{\Lambda}{\mu}. \tag{3.57}$$

Furthermore, we want

$$\sigma^* > 0 \quad \Rightarrow \quad \mathscr{R}_0 = \mathscr{K}\left(\frac{\Lambda}{\mu}\right) \mathscr{B}_\varphi > 1. \tag{3.58}$$

If $\nu > 0$, then from (3.55b) we get

$$\sigma = \frac{1}{\nu \mathscr{B}} \left(\Lambda - \mu N\right),$$

and then (3.55a) gives

$$S = \frac{1}{\nu \mathscr{B}} \left(N - (1 - \nu \mathscr{B}) \frac{\Lambda}{\mu}\right).$$

Since we want positive σ and S, we get $N \in \left((1 - \nu \mathscr{B}) \frac{\Lambda}{\mu}, \frac{\Lambda}{\mu}\right)$. Substituting the above equations into (3.55c) we get

$$1 = \frac{1}{\nu \mathscr{B}} \left(1 - (1 - \nu \mathscr{B}) \frac{\Lambda}{\mu N}\right) \mathscr{K}(N) \mathscr{B} \varphi. \tag{3.59}$$

which is an equation of single variable N.

The right hand side of (3.59) is increasing and positive for N in the interval that lies, so the equation has a unique solution (N^*) if and only if (3.58) is satisfied. Thus, corresponding to it, from (3.55) for total disease-incidence and susceptibles respectively, we get

$$\sigma^* = \frac{1}{\nu \mathscr{B}}(\Lambda - \mu N^*), \quad S^* = \frac{1}{\nu \mathscr{B}} \left(N^* - (1 - \nu \mathscr{B}) \frac{\Lambda}{\mu}\right). \tag{3.60}$$

So,

$$I^* = \frac{1}{\nu}(\Lambda - \mu N^*).$$

Theorem 3.5.2. *Let assumption* (3.48) *hold. If* $\mathscr{R}_0 < 1$, *system* (3.42) *admits only the disease - free equilibrium*

$$\left(\frac{\Lambda}{\mu}, 0, \frac{\Lambda}{\mu}\right),$$

which is asymptotically stable. If $\mathscr{R}_0 > 1$, *there exists a unique endemic equilibrium,*

$$(S^*, \sigma^* e^{-(\mu+\nu)\theta} B(\theta), N^*),$$

where (S^*, σ^*, N^*) *are given by* (3.57) *or* (3.60) *depending on the value of* ν.

In order to analyze the stability of the endemic steady - state, we linearize (3.42) at the endemic state $(S^*, i^*(\theta), N^*)$ and we are looking for solutions of the form

$$e^{\lambda t}(S_0, y(\theta), N_0).$$

Furthermore, setting

$$\Psi(x) = \frac{\mathscr{K}(x)}{x},$$

we get the eigenvalue problem

$$\lambda S_0 + \lambda^* S_0 + \mu S_0 + S^* \Psi'(N^*) \sigma^* \mathscr{B}_\varphi N_0 + S^* \Psi(N^*) \int_0^{\theta_\dagger} \varphi(\theta) y(\theta) d(\theta) = 0, \quad (3.61\text{a})$$

$$\lambda y(\theta) + y'(\theta) + \gamma(\theta) y(\theta) + (\mu + \nu) y(\theta) = 0, \quad (3.61\text{b})$$

$$y(0) = \lambda^* S_0 + S^* \Psi'(N^*) \sigma^* \mathscr{B}_\varphi N_0 + S^* \Psi(N^*) \int_0^{\theta_\dagger} \varphi(\theta) y(\theta) d\theta = 0, \quad (3.61\text{c})$$

$$\lambda N_0 + \mu N_0 + \nu \int_0^{\theta_\dagger} y(\theta) d\theta = 0. \quad (3.61\text{d})$$

From (3.61b) we get

$$y(\theta) = y(0) e^{-\lambda \theta} e^{-(\mu+\nu)\theta} B(\theta),$$

and we substitute into (3.61a), (3.61c) and (3.61d) to conclude

$$(\lambda + \mu) S_0 + y(0) = 0, \quad (3.62)$$

$$- \beta S_0 + (1 - \widehat{K}_0(\lambda)) y(0) - S^* \Psi'(N^*) \sigma^* \mathscr{B} \varphi N_0 = 0, \quad (3.63)$$

$$\nu \mathscr{B} \widehat{K}_1(\lambda) y(0) + (\lambda + \mu) N_0 = 0, \quad (3.64)$$

where the kernels $K_0(t)$ and $K_1(t)$ have the form

$$K_0 = \frac{\varphi(t) e^{-(\mu+\nu)t} B(t)}{\mathscr{B}_\varphi}, \quad K_1(t) = \frac{e^{-(\mu+\nu)t} B(t)}{\mathscr{B}}, \quad \beta = \frac{\sigma^*}{S^*},$$

that is, they are like those for the SIS model. The computation of the determinant of the system leads to the characteristic equation

$$(\lambda + \mu)^2 \left[1 - \widehat{K}_0(\lambda) + \frac{\nu S^* \Psi'(N^*) \mathscr{B} \mathscr{B}_\varphi \sigma^* \widehat{K}_1(\lambda) + \beta}{\lambda + \mu} \right] = 0. \quad (3.65)$$

For $\lambda = -\mu$, the above equation has a double negative real root. For

$$1 = \widehat{K}_0(\lambda) - \frac{\nu S^* \Psi'(N^*) \mathscr{B} \mathscr{B}_\varphi \sigma^* \widehat{K}_1(\lambda) + \beta}{\lambda + \mu}, \quad (3.66)$$

we have, if $\nu = 0$, that

$$\widehat{K}_0(\lambda) = \frac{\lambda + \mu + \beta}{\lambda + \mu}. \quad (3.67)$$

If there is a root $\overline{\lambda}$ with positive real part, then it should be

$$|\widehat{K}_0(\overline{\lambda})| < 1,$$

and

$$\left| \frac{\overline{\lambda} + \mu + \beta}{\overline{\lambda} + \mu} \right| > 1,$$

that is, $\overline{\lambda}$ is *not* a root of (3.67).

If $\nu > 0$ sufficiently small, the endemic state is stable. Destabilization may occur for sufficiently large ν.

Chapter 4

Conclusions

Epidemics are a serious problem for the world's population. Each year millions of people die from infectious diseases.

Mathematical models can help us understand the spread and the spatial distribution of the diseases that lead to an epidemic and predict the spread or eradication of it. The important parameters which determine the outbreak of an epidemic are the initial size of susceptible individuals S_0, the infection rate λ of a disease (*force of infection*), and the *removal rate* γ (the rate of isolation or mortality or acquisition of immunity). These, along with the contact rates and the probability of infecting contacts, determine the *basic reproduction number* R_0, which constitutes the threshold criterion for the spread or elimination of an epidemic.

Several times, it is of particular interest to study the cases in which a disease ends up becoming endemic. We arrive at such conclusions by searching for endemic equilibrium points and their stability.

In practice, many of the factors that determine the above parameters are difficult to calculate or measured directly and therefore the exact prediction of the evolution of an epidemic becomes impossible.

Nevertheless, mathematical models can help authorities be more effectively prepared to deal with the consequences of a possible epidemic. They can also help us find the optimal strategies for the vaccination of the population. For these reasons, they are important tools that are worth studying and developing.

Bibliography

[1] Ακρίβης Γ. Δ., Αλικάκος Ν. Δ. (2017) *Μερικές Διαφορικές Εξισώσεις*, 2η εκδ., Σύγχρονη Εκδοτική.

[2] Αλικάκος Ν. Δ., Καλογερόπουλος Γ. Η. (2011) *Συνήθεις Διαφορικές Εξισώσεις*, 2η εκδ., Σύγχρονη Εκδοτική.

[3] Γιαλελής Ν., Μπιτσούνη Β., Στρατής Ι. Γ. (2022) *Μια Εισαγωγή στην Μαθηματική Βιολογία*, Αποθετήριο Ελληνικών Ακαδημαϊκών Ηλεκτρονικών Συγγραμμάτων και Βοηθημάτων Κάλλιπος, *υπό συγγραφή.*

[4] Μπιτσούνη Β. (2020) *Μερικές Διαφορικές Εξισώσεις*, Σημειώσεις Παραδόσεων, Τμήμα Μαθηματικών, ΕΚΠΑ.
   https://eclass.uoa.gr/modules/document/?course=MATH524

[5] Στρατής Ι. Γ. (1992) *Μια Εισαγωγή στην Ποιοτική Θεωρία των Συνήθων Διαφορικών Εξισώσεων*, Σημειώσεις Παραδόσεων, Τμήμα Μαθηματικών, ΕΚΠΑ.

[6] Arnold V. I. (1992) *Ordinary Differential Equations*, Springer.

[7] Bender C. M., Orszag S. A. (1999) *Advanced Mathematical Methods for Scientists and Engineers I: Asymptotic Methods and Perturbation Theory*, Springer.

[8] Boyce W. E., DiPrima R. C., Meade D. B. (2017) *Elementary Differential Equations and Boundary Value Problems*, 11th ed., John Wiley and Sons.

[9] Brauer F., Castillo-Chavez C. (2001) *Mathematical Models in Population Biology and Epidemiology*, Springer.

[10] Brauer F., Driessche P., Wu J. (2008) *Mathematical Epidemiology*, Springer

[11] Braun M. (1993) *Differential Equations and their Applications: An Introduction to Applied Mathematics*, 4th ed., Springer.

[12] Chou C.-S., Friedman A. (2016). *Introduction to Mathematical Biology - Modeling, Analysis, and Simulations*, Springer.

[13] Cohen, J. E. (2004) Mathematics is Biology's next microscope, only better; Biology is Mathematics' next Physics, only better. *PLoS Biology* **2**, e439.

[14] Corduneanu C. (2008) *Principles of Differential and Integral Equations*, AMS, 2nd ed.

[15] Cushing J. M. (1977) *Integrodifferential Equations and Delay Models in Population Dynamics*, Springer.

[16] Cushing J. M. (1998) *An Introduction to Structured Population Dynamics*, SIAM.

[17] Diekmann O., Heesterbeek H., Britton T. (2013) *Mathematical Tools for Understanding Infectious Disease Dynamics*, Princeton University Press.

[18] Diekmann O., Heesterbeek J. A. P., Metz, J. A. J. (1990) On the definition and the computation of the basic reproduction ratio R_0 in models for infectious diseases in heterogeneous populations, *Journal of Mathematical Biology* **28**, 365-382.

[19] Dumortier, F., Llibre, J., Artés, J. C. (2006) *Qualitative Theory of Planar Differential Systems*, Springer-Verlag.

[20] Edelstein-Keshet L. (2005) *Mathematical Models in Biology*, SIAM.

[21] Evans L. C. (2010) *Partial Differential Equations*, 2nd ed., AMS.

[22] Friedman A. (2012) PDE problems arising in Mathematical Biology, *Networks and Heterogeneous Media* **7**, 691-703.

[23] Friedman A. (2018) *Mathematical Biology - Modeling and Analysis*, SIAM.

[24] Garfinkel A., Shevtsov J., Guo Y. (2017) *Modeling Life: The Mathematics of Biological Systems*, Springer.

[25] Iannelli M. (1994) *Mathematical Theory of Age-Structured Population Dynamics*, Giardini.

[26] Iannelli M., Martcheva M., Milner F. A. (2005) *Gender-Structured Population Modeling*, SIAM.

[27] Iannelli M., Milner F. (2017) *The Basic Approach to Age-Structured Population Dynamics*, Springer.

[28] Iannelli M., Pugliese A. (2014) *An Introduction to Mathematical Population Dynamics: Along the Trail of Volterra and Lotka*, Springer.

[29] Ingalls B. P. (2013) *Mathematical Modeling in Systems Biology: An Introduction*, MIT Press.

[30] Jones D. S., Plank M. J., Sleeman B. D. (2009) *Differential Equations and Mathematical Biology*, 2nd ed., CRC Press.

[31] Kanwal R. P. (2013) *Linear Integral Equations - Theory & Technique*, Birkhäuser, 2nd ed.

[32] Keeling M. J., Rohani P. (2011) *Modeling Infectious Diseases in Humans and Animals*, Princeton University Press.

[33] Kermack W. O., McKendrick A. G. (1927) Contributions to the mathematical theory of epidemics, *Proceedings of Royal Society of London, Series A* **115**, 700-721.
http://www.math.utah.edu/~bkohler/Journalclub/kermack1927.pdf

[34] Kendall D. G. (1956) Deterministic and Stochastic epidemics in closed populations, *Proceedings of the Third Berkeley Symposium on Mathematical Statistics and Probability: Contributions to Biology and Problems of Health.* **149**–**165**.
https://www.degruyter.com/document/doi/10.1525/9780520350717-011/html

[35] Kot M. (2001) *Elements of Mathematical Ecology*, Cambridge University Press.

[36] Kress R. (2014) *Linear Integral Equations*, Springer, 3rd ed.

[37] Lakshmikantham V., Rama Mohana Rao M. (1995) *Theory of Integrodifferential Equations*, Gordon and Breach.

[38] Lin C. C., Segel L. A. (1988) *Mathematics Applied to Deterministic Problems in the Natural Sciences*, SIAM.

[39] Logan J. D. (2013) *Applied Mathematics*, 4th ed., Wiley.

[40] Logan J. D., Wolesensky W. R. (2009) *Mathematical Methods in Biology*, Wiley.

[41] Lotka A. J. (1925) *Elements of Physical Biology*, Williams and Wilkins.
https://archive.org/details/elementsofphysic017171mbp/mode/2up

[42] Martcheva M. (2015) *An Introduction to Mathematical Epidemiology*, Springer.

[43] Murray J. D. (2011) *Mathematical Biology. I: An Introduction*, 3rd ed., Springer.

[44] Murray J. D. (2011) *Mathematical Biology. II: Spatial Models and Biomedical Applications*, 3rd ed., Springer.

[45] Otto S. P., Day T. (2011) *A Biologist's Guide to Mathematical Modeling in Ecology and Evolution*, Princeton University Press.

[46] Ross R. (1916) An application of the theory of probabilities to the study of a priori pathometry. - Part I, *Proceedings of the Royal Society of London, Series A*, **92**, 204–230.
https://royalsocietypublishing.org/doi/10.1098/rspa.1916.0007

[47] Ross R., Hudson H. (1917), An application of the theory of probabilities to the study of a priori pathometry. - Part II, *Proceedings of the Royal Society of London, Series A*, **93**, 212–225.
https://royalsocietypublishing.org/doi/10.1098/rspa.1917.0014

[48] Ross R., Hudson H. (1917) An application of the theory of probabilities to the study of a priori pathometry. - Part III, *Proceedings of the Royal Society of London, Series A*, **93**, 225–240.
https://royalsocietypublishing.org/doi/10.1098/rspa.1917.0014

[49] Schaffer D. G., Cain J. W. (2018) *Ordinary Differential Equations: Basics and Beyond*, Springer.

[50] Segel L. A. (1984) *Modeling Dynamic Phenomena in Molecular and Cellular Biology*, Cambridge University Press.

[51] Segel L. A., Edelstein-Keshet L. (2013) *A Primer on Mathematical Models in Biology*, SIAM.

[52] Wazwaz A.-M. (2011) *Linear and Nonlinear Integral Equations, Methods and Applications*, Springer.

[53] Zemyan S. M. (2012) *The Classical Theory of Integral Equations*, Springer.