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ESTIMATING THE UNKNOWN VARIABLES OF  
A SEIR MODEL AND A STABILITY ANALYSIS  
OF THE EQUILIBRIA OF THIS MODEL

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APPLIED TO MEASLES IN ENGLAND AND WALES

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D. R. CIRKEL  
s1918575

*University of Groningen*  
*Master's thesis mathematics*

*First supervisor:*  
PROF DR. E.C. WIT  
*Second supervisor:*  
PROF. DR. A.J. VAN DER SCHAFT



university of  
 groningen

faculty of science  
 and engineering



## **Abstract**

This thesis concerns the estimation of the unknown variables in a SEIR model applied to the disease measles. The method we suggest to find estimations of these variables uses window smoothing and yields in estimators for systems that are linear in the parameters. The derived method is implemented in R and used for an analysis on data of England and Wales from 1948 to 1966. A stability analysis of a disease-free equilibrium and an endemic equilibrium is made.



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# Chapter 1

## Introduction

### 1.1 Measles

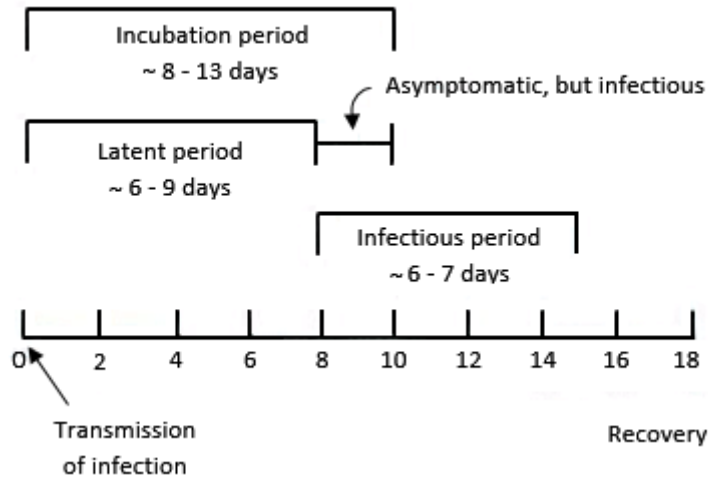
Measles is a highly contagious viral disease caused by an RNA virus in the genus Morbillivirus [4]. Even though the other viruses in the genus often infect humans and various animals, measles only infects humans and non-human primates [30].

The disease is most common among young children, although passive immunity to measles is passed on from recovered mothers to their offspring via maternal antibodies for about 4 months [9]. After infection of the host, the virus passes through a latent period of 6 to 9 days, pursued by an infectious period of 6 to 7 days [3].

The characteristic time scale of the transmission dynamics is thus around 2 weeks and can be found in Figure 1.1. The result of the infection is either death, or full recovery followed by lifelong immunity of the host.

Morbidity from measles is often highly due to fast transmissibility, although the disease itself rarely results in death of the host. However, in undeveloped countries, measles is still a major cause of mortality. The overwhelming majority (more than 95%) of measles deaths occur in countries with low per capita incomes and weak health infrastructures [38], since the combination of measles and malnutrition can be lethal.

Even though measles is a highly contagious viral disease, in 2014 about 85% of the world's children had been vaccinated by their first birthday, resulting in near extinction of the disease in some parts of the world [37].



**Figure 1.1:** *The characteristic course of measles after infection.*

## 1.2 Thesis outline

This thesis is organized as follows.

First, Chapter 2 explains the basic concepts of some compartmental models in epidemiology and then discusses a SEIR model that describes the change in compartment size due to measles, with the use of ordinary differential equations. In Chapter 3, the obtained data is described and it is discussed how this data leads to finding values for the observable parameters of our model. Chapter 4 includes a method for deriving stepwise time-course window estimators that leads to finding estimations of the non-observable parameters. In Chapter 5 the derived method is implemented in R and used for a data analysis in which the model from Chapter 2, together with the observable parameters from Chapter 3 and the non-observable estimated parameters from Chapter 4 is compared to real data. Furthermore, a stability analysis of a disease-free equilibrium and an endemic equilibrium of the SEIR model is discussed in Chapter 6.

This thesis is completed with a conclusion and discussion of the preceding chapters.



# Chapter 2

## The model

### 2.1 Basic SIR model

To obtain a better view of the spread of epidemic diseases we will use a mathematical model known as the SIR model. This model is based on a non-linear system of differential equations first published in a seminal paper by Kermack and McKendrick in 1927 [17].

#### 2.1.1 Characteristics and assumptions of the model

The SIR model focusses on illness caused by pathogen and followed by (usually life-long) immunity. We assume that a given population ( $\mathcal{N}$ ) can be divided into a couple categories: susceptible: those who are able to receive the disease ( $\mathcal{S}$ ), infectious: those who are infected and capable of passing on the disease ( $\mathcal{I}$ ) and recovered: those who successfully cleared the infection ( $\mathcal{R}$ ). We signify an individual as  $n$  and the number of the entire population at time  $t$  as  $N(t)$ . Even more, we denote the total amount of susceptible individuals in  $\mathcal{S}$  at time  $t$  as  $S(t)$ . Or, symbolically:

$$S(t) = \#n \in \mathcal{S},$$

Likewise,

$$\begin{aligned} I(t) &= \#n \in \mathcal{I}, \\ R(t) &= \#n \in \mathcal{R}. \end{aligned}$$

It is clear that  $N(t) = S(t) + I(t) + R(t)$ , since an individual is either susceptible, infectious, or recovered from the disease. Moreover, it is clear that  $N, S, I$  and  $R$  all are positive. We will sometimes refer to  $\mathcal{S}, \mathcal{I}$  and  $\mathcal{R}$  as ‘class  $S$ ’, ‘class  $I$ ’ and respectively ‘class  $R$ ’.

For convenience we will (for now) consider a closed population and not take population demographical factors such as births, natural deaths and migration in consideration. We assume there is a group of individuals in the susceptible class and at least one individual in the infectious class. The individuals from both these classes will mingle, causing contacted individuals in the susceptible class to get infected with a certain probability, which

subsequently moves them to the infectious class. Once moved to the infectious class, the newly infective individuals are able to contact more susceptible individuals and spread the disease. Based on some probabilistic process, the infectious individuals either die or recover. The latter results in moving the individual to the recovered class. The individual is now no longer infected. Depending on whether the disease results in immunity, the recovered individual may move back to the susceptible class. In this study, we will assume lifelong immunity holds.

To introduce the model equations we will draw on a few more assumptions. First, we will assume homogenous mixing: any individual is equally likely to contact any other individual in the population on a given day. Second, we will assume equal susceptibility and identical disease processes for every individual.

### 2.1.2 The model

Before the model equations can be introduced we need to define the transmission rate per susceptible individual or ‘force of infection’, which measures the per capita probability at which susceptible individuals incur the infection. We assume frequency dependent transmission, which is common for pathogens with heterogeneous contact structure [24]. This transmission rate is often denoted by  $\lambda$  [3], and equals  $\frac{\beta I}{N}$ , where  $\beta$  signifies a contact term. Its derivation can be found in Appendix A.

Now that we have derived the transmission term, we are able to write down ordinary differential equations, which will show the rate of change in compartment size, as follows

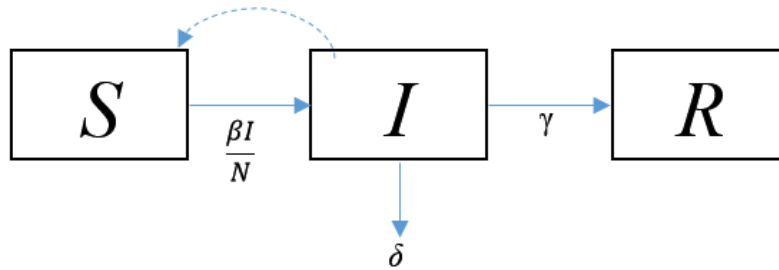
$$\begin{aligned}\dot{S}(t) &= -\lambda S(t) = -\frac{\beta I(t)}{N(t)} S(t), \\ \dot{I}(t) &= \frac{\beta I(t)}{N(t)} S(t) - (\gamma + \delta) I(t), \\ \dot{R}(t) &= \gamma I(t).\end{aligned}\tag{2.1}$$

The parameters  $\gamma$  and  $\delta$  are non-negative parameters that represent the rate at which individuals recover, or respectively die from the disease. Usually we are more interested in the average infectious period, which is given by  $\gamma^{-1}$ . We simplify the model by assuming these parameters are constant throughout the year and write the model without the time variable  $t$ . A graphical representation of a SIR model is given in Figure 2.1.

### 2.1.3 The basic reproduction number

Another measure of transmissibility is the basic reproduction number, denoted by  $R_0$ . It is one of the most important quantities in epidemiology, which will be elaborated on in Chapter 6. It is defined as:

*“The average number of secondary infections produced when one infected individual is introduced into a host population where everyone is susceptible.”*[3]



**Figure 2.1:** A basic SIR model. Here susceptible individuals become infected with the pathogen at rate  $\frac{\beta I}{N}$  and either recover from the disease at rate  $\gamma$  or die a disease-induced death at rate  $\delta$ .

To write down  $R_0$  mathematically, we view the basic reproduction number as the inverse of relative removal rate, which is found by considering

$$\begin{aligned} \dot{I} &= \frac{\beta I}{N} S - (\gamma + \delta) I \\ &= \left( \beta \frac{S}{N} - (\gamma + \delta) \right) I. \end{aligned}$$

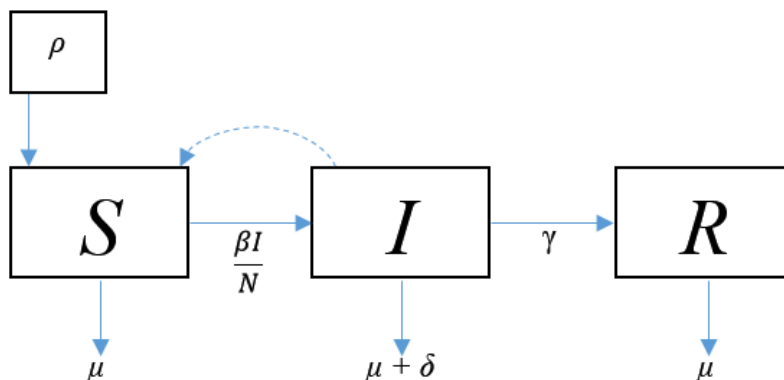
When the amount of susceptible individuals  $S$  is less than  $\frac{N(\gamma + \delta)}{\beta}$ , then  $\dot{I} < 0$  and the infection cannot sustain. The above ratio is known as the relative removal rate. Thus

$$R_0 = \frac{\beta}{N(\gamma + \delta)}.$$

If we assume the population is homogeneously mixed, then the number of secondary infections produced by an infected individual,  $R_0$ , will be linearly proportional to the probability that any random contact is with a susceptible individual [3]. Intuitively it makes sense that a new disease cannot invade if it has an average reproduction rate smaller than one. Clearly, the disease will not spread if the virus cannot successfully transmit to more than one susceptible individual. The importance of this quality will become clear in Chapter 6.

## 2.2 SIR model with demographics

In the previous section we have been exploring the basic framework of a SIR model without demographics. However, without the births of new susceptible individuals, every epidemic will lead to extinction of the infection. Thus, to get a more realistic model, we should take (at least some of) these demographical parameters in consideration.



**Figure 2.2:** A *SIR* model with population demography. The parameters  $\rho$  and  $\mu$  denote the recruitment and respectively the per capita natural death rate. Susceptible individuals become infected with the pathogen at rate  $\frac{\beta I}{N}$  and either recover from the disease at rate  $\gamma$  or die at rate  $\delta$  from the disease.

### 2.2.1 The model

The easiest way to fit the rate at which individuals suffer from natural mortality into this model is taking the average lifespan of an individual. We will denote this with  $\mu^{-1}$ , implying that the death rate of any individual is  $\mu$  at any point in time. Altogether, we will assume migration to be neglectable, while we add the birth- and death rates to the *SIR* model in (2.1) and attain the following:

$$\begin{aligned}\dot{S} &= \rho - \left( \frac{\beta I}{N} + \mu \right) S, \\ \dot{I} &= \frac{\beta I}{N} S - (\gamma + \delta + \mu) I, \\ \dot{R} &= \gamma I - \mu R.\end{aligned}$$

Here  $\rho$  equals the influx or recruitment of susceptible individuals and  $\mu$  is the per capita rate of natural deaths (i.e. every death that is not disease related). Both  $\rho$  and  $\mu$  are nonnegative values. We assume that all new-borns are susceptible and vertical transmission can be neglected. Usually  $\mu$  is an age-dependent parameter. However, since the high transmission rates of measles ensures that 95% of all people in (pre-vaccination) urban areas were infected by the age of 15, and essentially everybody by the age of 20 had either recovered from the disease or suffered a disease-induced death [1], we simplify the system by viewing the death rate as an age-*in*dependent parameter. These adjustments yield in a new, more accurate compartmental epidemic model, which is depicted schematically in Figure 2.2.

## 2.2.2 The basic reproduction number

By rewriting the second equation of the model as

$$\dot{I} = \left( \frac{\beta S}{N} - (\gamma + \delta + \mu) \right) I,$$

one can easily verify that the basic reproduction number is given by

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

## 2.3 SEIR model

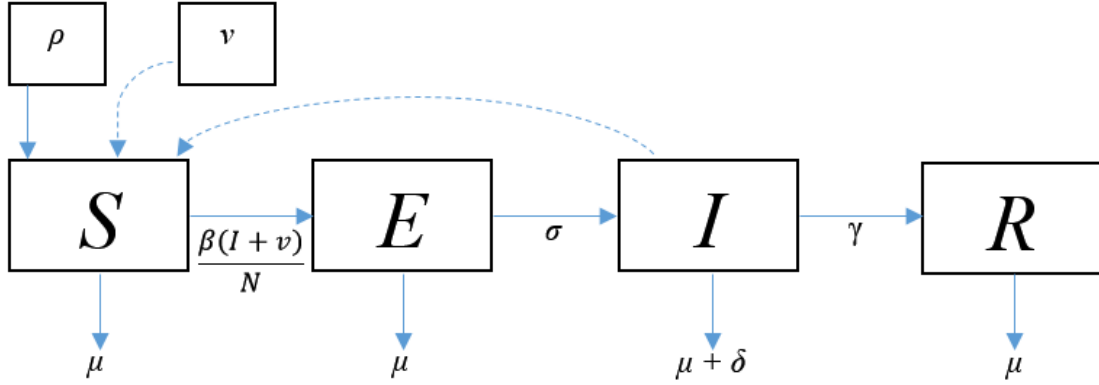
This section includes the alteration from the SIR-model with demographics to the SEIR-model as used in the remaining part of this thesis.

### 2.3.1 The model

For some diseases, such as the measles, the transmission occurs with a relatively small amount of pathogen entering the body. At this stage the pathogen needs to gain strength by reproducing rapidly and its affluence is at this point too low for transmission to different susceptible individuals to occur. Thus, there is a moment at which the susceptible individuals are infected, but are not yet infectious. We need to accommodate a new class for this group of the population, who we will label as ‘the exposed’ ( $\mathcal{E}$ ). Once the susceptible individuals get infected and enter the exposed class, they do not show any symptoms yet, as is shown in Figure 1.1. As soon as the pathogen’s abundance is high enough, it will start to spread and the individual will move into the infectious class. The amount of individuals in  $\mathcal{E}$  at time  $t$  is represented by  $E(t)$ . We apply this to our model and see the SIR model transform into a SEIR model as described by Anderson and May [3]:

$$\begin{aligned}\dot{S} &= \rho - \left( \frac{\beta(I+v)}{N} + \mu \right) S, \\ \dot{E} &= \frac{\beta(I+v)}{N} S - (\sigma + \mu) E, \\ \dot{I} &= \sigma E - (\gamma + \delta + \mu) I, \\ \dot{R} &= \gamma I - \mu R.\end{aligned}\tag{2.2}$$

The first new parameter in this system is  $\sigma$ , denoting the rate of exposed individuals moving to the infectious class. Here again, we are often more interested in  $\sigma^{-1}$ , the mean latent period. Moreover,  $\sigma$  is a positive constant. As a final adjustment, we implement a visiting impact  $v$ , as is done in [15], which allows a small group outside the modelled infected to infect the susceptible population. A graphical representation of this model can be found in Figure 2.3.



**Figure 2.3:** A SEIR model with population demography and influence from outside the modelled population. The parameters  $\rho$  and  $\mu$  denote the recruitment and respectively the per capita natural death rate. Susceptible individuals become infected with the pathogen at rate  $\frac{\beta(I+v)}{N}$ , become infectious at rate  $\sigma$  and either recover from the disease at rate  $\gamma$  or die at rate  $\delta$ . The variable  $v$  is a small amount of individuals from outside the population.

The reason for  $v$  becomes clear when one compares long-term data from a large island (such as Britain) with data from a smaller island (such as Iceland), which can be found in [3]. The measles virus survives endemically in a biennial cycle in England and Wales, while in Iceland the virus outbreak is triggered by travellers or immigrants and does not show an endemically biennial cycle. The susceptible and infected population in Iceland is simply not large enough for the long-term persistence of infection in the absence of repeated re-introduction. Hence, without allowing a small group outside the modelled infected to infect the susceptible population, the virus would die out [3]. Therefore, adding a small group of visitors will make the model more accurate.

The population size can still be determined by  $S(t) + E(t) + I(t) + R(t) = N(t)$ , since the original infectious group has merely been split into two. From this, one can conclude that  $N(t)$  can also be ascertained through

$$\dot{N} = \rho - \mu N - \delta I, \quad (2.3)$$

which is derived by adding the equations in system (2.2). From (2.3), it can be induced that if  $\rho$  is a constant term,

$$\rho - (\mu + \delta)N \leq \dot{N} \leq \rho - \mu N. \quad (2.4)$$

Note that since we are assuming lifelong immunity, the first three equations of (2.2) contain no  $R(t)$  terms, thus the fourth equation of the model is redundant and we can use  $S(t) + E(t) + I(t) + R(t) = N(t)$  to construct a reduction of (2.2) as

$$\begin{aligned}\dot{S} &= \rho - \left( \frac{\beta(I+v)}{N} + \mu \right) S, \\ \dot{E} &= \frac{\beta(I+v)}{N} S - (\sigma + \mu) E, \\ \dot{I} &= \sigma E - (\gamma + \delta + \mu) I.\end{aligned}\tag{2.5}$$

### 2.3.2 The basic reproduction number

To determine the reproduction number for the above SEIR model, more calculation is necessary. How we have found the quantity for  $R_0$  as

$$R_0 = \frac{\beta(\rho + v)\sigma}{N\mu(\mu + \sigma)(\gamma + \delta + \mu)},$$

can be found in Appendix B

## 2.4 Conclusion

Epidemical diseases, such as measles, can be described by compartmental models. The entire population can be split in different compartments, according to the state of an individual: susceptible to the disease ( $\mathcal{S}$ ), exposed, but not yet infectious ( $\mathcal{E}$ ), infectious ( $\mathcal{I}$ ) and recovered and immune ( $\mathcal{R}$ ). With the use of ordinary differential equations the change in compartment size of a SEIR model is described. Moreover, the basic reproduction number  $R_0$  is determined. The following chapter will focus on the data of the parameters of this model.

## Chapter 3

# The data

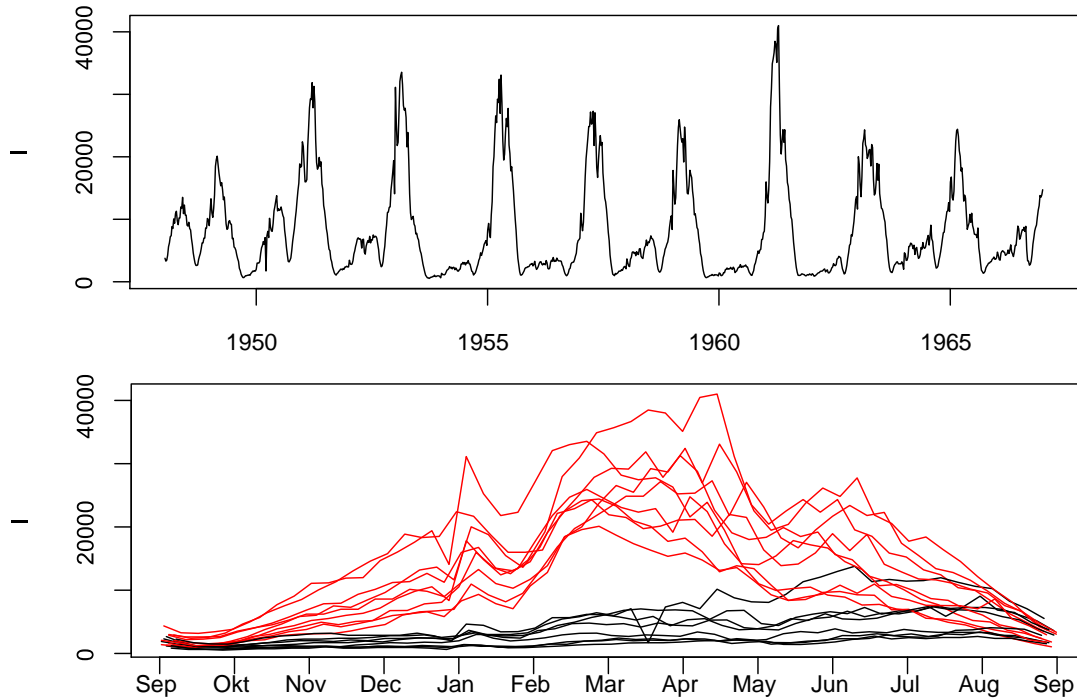
The majority of the parameters in model (2.5) are known, since they are directly observable or deducible from appropriate studies and data. This chapter will show how the data used in our model is found and/or derived. To ensure uniformity, all the parameters will be defined monthly. We will first discuss the reported cases of measles, after which the data of the virus and the host will be addressed.

### 3.1 The reported cases

The weekly reported cases of measles for England and Wales from 1948 through 1966 are reported by the Office of Population Censuses and Surveys, and are obtained from [7]. Every year, there are either 52 or 53 reports submitted. This is due to the fact that a year lasts slightly longer than 52 weeks. The case reports are shown in Figure 3.1. When viewing the data from Figure 3.1, it becomes clear that an epidemic usually starts in September. This is consistent with the beginning of a new school year, which is accompanied by an increase of contact for children. Therefore, we let the year start in September; e.g. we define the year 1949 as 1 September 1948 until 30 August 1949.

From 1951 until 1966 outbreaks of measles occurred every other year in the odd numbered years, with an exceedingly high amount in 1961. From 1948 to 1966 the average number of reported annual cases was around 426.000, with approximately 180.000 cases in low years, and 672.000 cases in high years. In high years, the largest number of cases of measles occurred during spring, while in low years the beginning of summer showed more reports. Moreover, it is assumed that the delay from diagnosis to the receipt of notification in the health department from England and Wales equals the delay of that in New York and Baltimore during the same period, which is estimated to be around 10 days [23]. This explains why the sudden drop in cases of measles as seen in Figure 3.1 occurs in August. About three weeks later than the actual start of the holidays in July. The minimum cases are usually reported in September and October.





**Figure 3.1:** Above: Weekly measles records from England and Wales from 1948 through 1966. Below: Weekly measles records from England and Wales throughout the year. The red lines correspond with the higher, odd numbered years, while the black lines equal the lower, even numbered years.

### 3.2 The virus

The latent period of measles is specified in [3], and is set around 6 to 9 days. Hence, we let  $\sigma = \frac{365}{12 \cdot 7,5}$  to find the monthly rate of exposed individuals moving in to the infectious class.

Likewise, the infectious period is known to be around 6 or 7 days [3], setting  $\gamma = \frac{365}{12 \cdot 6,5}$  as the monthly rate of which infected individuals move from the infectious state out of the model.

Furthermore, the yearly amount of measles induced deaths of Wales and England ( $d$ ) is reported by the Government of the United Kingdom [29]. The highest amount of disease-induced deaths was measured in 1959, with a total of 33 deaths, while the lowest was measured in 1965. That year, the disease only resulted in the deaths of two people. From this data, we define a monthly disease-induced death rate,  $\delta(t)$  as the ratio of measles induced deaths per year and the total reported measles of that year. That is,

$$\delta(t) = \frac{d(u)}{12 \sum_{t_u \leq t < t_{u+1}} I(t)},$$

where  $u = 1, \dots, 18$ , representing a year; e.g.  $t_1 = 1949, t_{18} = 1966$ .

### 3.3 The host

Population data from England and Wales was obtained from the Office of Population Censuses and Surveys, Medical Statistics Division [28] and provides yearly population counts from 1901 to 1992 divided in age groups. By simply adding the groups, one finds the total yearly population of England and Wales. From this data, a monthly average can be interpolated as

$$N(t_{u,w}) = N(t_{u-1}) + \frac{1}{2} \frac{N(t_u) - N(t_{u-1})}{t_{u,1} - t_{u-1,1}} (t_{u,w+1} + t_{u,w} - 2t_{u-1,1}),$$

where  $u = 1, \dots, 18$  and  $w = 1, \dots, 12$  represents a month in year  $u$ . For example,  $t_{1,1} =$  September 1948,  $t_{18,12} =$  August 1966.

Furthermore, the births of children in England and Wales from 1937 to 1999 were monthly gathered by the Office of National Statistics [27]. The mean age of infection of the disease was about 4 to 5 years [3]. Therefore, we will make use of the births 4 years preliminary to the year we are modelling, to make up for the 4 year gap of which children do not go to school. Thus, the amount of births at time  $t$ ,  $\rho(t)$ , is given by the number of births ( $b(t)$ ) of 4 years earlier. In other words,

$$\rho(t_{u,w}) = b(t_{u-4,w}),$$

where  $u = 1, \dots, 18$  and  $w = 1, \dots, 12$  represents a month in year  $u$ .

In [39], the life expectancy at birth from 1948 to 1966 of the entire United Kingdom is presented. Assuming this resembles the life expectancy solely of England and Wales, one can compute an average of  $\mu^{-1} = 70, 18$ . Thus, the monthly per capita death rate  $\mu$  equals  $\frac{1}{12 \cdot 70, 18}$ .

Moreover, we allow a small constant presence of 10 infectious visitors to be around, resulting in  $v = \frac{10}{12}$ .

# Chapter 4

## The method

Many of the epidemiological and demographic parameters in model (2.5) can be measured or derived directly by appropriate studies, as has been shown in Chapter 3. The contact rate  $\beta$ , however, combines a multitude of biological, social and environmental factors, and thus cannot be measured directly. Chapter 5 will be devoted to estimating this  $\beta$  on the basis of data, with the method described in this chapter. To do this, we will first lay down a theoretical framework. After this, the acquired knowledge will be applied to the SEIR model in order to complete the estimation strategy.

### 4.1 Theoretical framework

The method used to estimate  $\beta$  from the data is published by Vujačić, Dattner, González and Wit [34]. It focuses on the special class of non-linear systems that is linear in all its parameters and will result in an explicit form for the estimators.

Discrete data for  $I(t)$  can be collected over time. In particular, it can be assumed that during interval  $[0, T]$  we observe

$$Y(t_i) = I(t_i; \theta, x_0) + \varepsilon_i,$$

where  $i = 1, \dots, n$  and  $0 \leq t_1 \leq t_n = T$  represent equidistant points in time. The initial values are given by  $x_0 = x(0)$  and  $\theta = (\rho, \beta, v, \sigma, \gamma, \delta, \mu)^T$ . Furthermore,  $\varepsilon_i$  is the 4-dimensional column vector of noise during the measurements at time  $t_i$  and  $T$  equals either 52 or 53, depending on how many weekly reports are reported in the year. Since  $\beta$  and most of  $x_0$  are unknown, the values need to be estimated from the data.

Assuming that the model in (2.5) is linear in  $\beta$ , one can write

$$\dot{x}(t) = F(x(t); \theta) = g(x(t))\theta.$$

Vujačić, Dattner, González and Wit focussed on estimators of the parameters  $\theta$  and  $x_0$  that are obtained by minimizing

$$L(x_0, \theta) = \int_0^T \left\| \hat{x}(t) - x_0 - \int_0^t g(\hat{x}(s)) ds \theta \right\|^2 dt. \quad (4.1)$$

Here  $\hat{x}(t)$  is a stepwise estimator of the state  $x = (S, E, I)$ , denoted by  $\hat{x}(t) = (\hat{S}(t), \hat{E}(t), \hat{I}(t))^T$ , which will be discussed in more detail in section 4.2.1.

Define  $\omega = (x_0, \theta)^T$  and  $f(t) = (I_3; \int_0^t g(\hat{x}(s)) ds)$ , then (4.1) can be written as

$$\begin{aligned} L(\omega) &= \int_0^T \|\hat{x}(t) - \omega^T f(t)^T\|^2 dt \\ &= \int_0^T \|\hat{x}(t)\|^2 dt - \int_0^T \|\omega^T f(t)^T \hat{x}(t)\| dt + \int_0^T \|\omega^T f(t)^T f(t) \omega\| dt. \end{aligned} \quad (4.2)$$

Since  $\int_0^t g(\hat{x}(s)) ds$  is the integral of a piecewise constant function, it can be written as the finite sum

$$\sum_{i=1}^l (t_i - t_{i-1})g(\hat{x}(t_i)) + (t - t_l)g(\hat{x}(t_{l+1})), \quad t_l \leq t < t_{l+1}.$$

Throughout this thesis, we assume that the sums of the form  $\sum_{i=1}^l f_i$  equal zero for  $l = 0$ . Write the above summation as a matrix,  $\hat{G}(t)$ , such that

$$\begin{aligned} \hat{G}(t) \cdot e &= [(t_1 - t_0)g(\hat{x}(t_1)) \quad \dots \quad (t_l - t_{l-1})g(\hat{x}(t_l)) \quad (t - t_l)g(\hat{x}(t_{l+1}))] \cdot e \\ &= \sum_{i=1}^l (t_i - t_{i-1})g(\hat{x}(t_i)) + (t - t_l)g(\hat{x}(t_{l+1})), \quad t_l \leq t < t_{l+1}, \end{aligned}$$

where  $e = (1, \dots, 1)$  in  $\mathbb{R}^{l+1}$ .

Now, let  $F(t) = (TI_3; \hat{G})$  and  $\omega$  in equation (4.2) can be taken out of the integral.

$$L(\omega) = \omega^T \int_0^T F(t)^T F(t) dt \omega - 2\omega^T \int_0^T F(t)^T \hat{x}(t) dt + \int_0^T \|\hat{x}(t)\|^2 dt. \quad (4.3)$$

To obtain the argument of the minimum of  $L(\omega)$ , and thus  $\hat{\omega}$ , equation (4.3) is derived with respect to  $\omega$  and set to zero in order to get the following

$$2 \int_0^T F(t)^T F(t) dt \omega - 2 \int_0^T F(t)^T \hat{x}(t) dt = 0.$$

Hence, the minimizer of (4.3) is given by

$$\hat{\omega} = \left( \int_0^T F(t)^T F(t) dt \right)^{-1} \int_0^T F(t)^T \hat{x}(t) dt.$$

## 4.2 Method applied to the SEIR model

Considering the theoretical framework is discussed, we will now focus on applying acquired estimation strategy to the model (2.5). First, we will focus on the derivation of the time course window estimators. Second, the objective function  $L(\omega)$  will be adjusted, to match the SEIR model. Finally the estimation strategy will be illustrated.

### 4.2.1 Time course window estimators

In the previous section we have seen that in order to estimate  $\omega$ , we require knowledge of the time course window estimator

$$\hat{x}(t) = \begin{pmatrix} \hat{S}(t) \\ \hat{E}(t) \\ \hat{I}(t) \end{pmatrix},$$

yet  $I(t)$  is the only observable state. Therefore,  $\hat{E}(t)$  and  $\hat{S}(t)$  will have to be estimated. First, it will be shown how  $\hat{I}(t)$  is derived, after which the estimation of the other estimators will be shown.

A window estimator  $\hat{I}(t)$  is introduced, which is a stepwise function that estimates  $I(t)$  as the monthly mean of observations. To do so, our data is divided into 12 subintervals which contain at least 4 and at most 5 weeks of data. We denote the  $i$ -th subinterval as  $S_i$ , where  $i = 1, \dots, 12$ . Let  $S(t)$  denote the subinterval to which  $t$  belongs. That is, if  $t \in S_i$  then  $S(t) = S_i$ . Now the window estimator can be defined as the mean of the data of each subinterval

$$\hat{I}(t) = \frac{1}{|S(t)|} \sum_{t_j \in S(t)} Y(t_j), \quad t \in S(t).$$

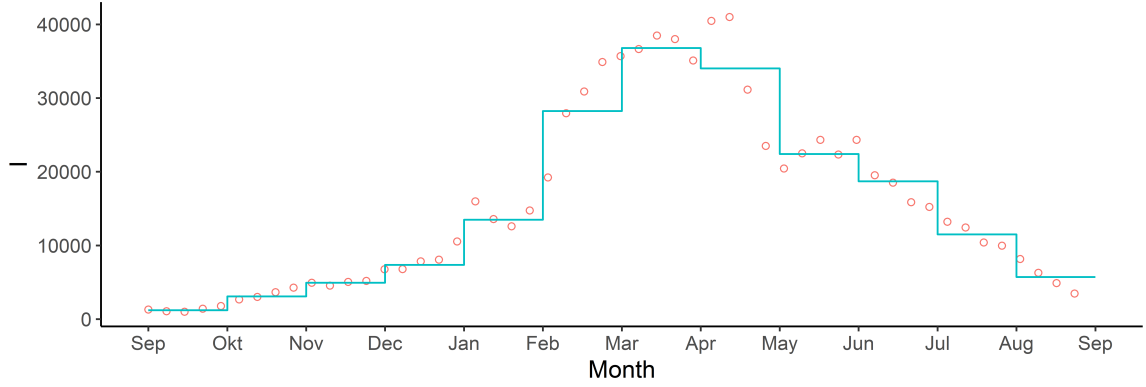
The results are shown in the Figure 4.1.

In contrast to the infected state,  $S(t)$  and  $E(t)$  are not observable states and therefore cannot be smoothed from data. However, we can simply say

$$\hat{E}(t) = \sum_{i=1}^{12} \hat{\varepsilon}_i 1_{\{t \in S_i\}}, \quad (4.4)$$

$$\hat{S}(t) = \sum_{i=1}^{12} \hat{\eta}_i 1_{\{t \in S_i\}}, \quad (4.5)$$

for some reasonable values of  $\varepsilon = (\varepsilon_1, \dots, \varepsilon_{12})$  and  $\eta = (\eta_1, \dots, \eta_{12})$ , and  $\varepsilon_1 = E_0$  and  $\eta_1 = S_0$ .



**Figure 4.1:** A plot of the reported causes of measles in the year 1961 in England and Wales, and the stepwise window estimator. The reported causes are shown by the red circles and the blue solid line is the window estimator.

## 4.2.2 The objective function

Applying equation (4.1) to the SEIR model described in section 2.3 gives us the following

$$\begin{aligned}
L(\omega) = & \int_0^T \left\| \widehat{I}(t) - I_0 - \int_0^t \sigma \widehat{E}(s) - (\gamma + \delta + \mu) \widehat{I}(s) ds \right\|^2 dt \\
& + \int_0^T \left\| \widehat{E}(t) - E_0 - \int_0^t \frac{\beta (\widehat{I}(s) + v)}{N(s)} \widehat{S}(s) - (\sigma + \mu) \widehat{E}(s) ds \right\|^2 dt \\
& + \int_0^T \left\| \widehat{S}(t) - S_0 - \int_0^t \rho - \left( \frac{\beta (\widehat{I}(s) + v)}{N(s)} + \mu \right) \widehat{S}(s) ds \right\|^2 dt. \quad (4.6)
\end{aligned}$$

We define  $\mathcal{J}(t)$  as the right term between the first brackets of (4.6). That is,

$$\mathcal{J}(t) := \int_0^t \sigma \widehat{E}(s) - (\gamma + \delta + \mu) \widehat{I}(s) ds.$$

Since this is the integral of a piecewise constant function, it can be rewritten as a finite sum. If we implement the definition of  $\widehat{E}(t)$  from equation (4.4) in the formula, we get

$$\begin{aligned}
\mathcal{J}(t) = & \sum_{i=1}^l (t_i - t_{i-1}) \left( \sigma \widehat{\varepsilon}_i - (\gamma + \delta + \mu) \widehat{I}_i \right) \\
& + (t - t_l) \left( \sigma \widehat{\varepsilon}_{l+1} - (\gamma + \delta + \mu) \widehat{I}_{l+1} \right), \quad t_l \leq t < t_{l+1}.
\end{aligned}$$

Therefore,

$$\begin{aligned}
\int_0^T \left[ \widehat{I}(t) - I_0 - \mathcal{J}(t) \right]^2 dt &= \int_0^T (\widehat{I}(t) - I_0)^2 - 2(\widehat{I}(t) - I_0)\mathcal{J}(t) + \mathcal{J}(t)^2 dt \\
&= \sum_{i=1}^k (t_i - t_{i-1})(\widehat{I}_i - I_0)^2 - 2 \sum_{i=1}^k (t_i - t_{i-1})(\widehat{I}_i - I_0) \left( \sum_{t_j < t_i} (t_j - t_{j-1})(\sigma \widehat{\varepsilon}_j - (\gamma + \delta + \mu)\widehat{I}_j) \right. \\
&\quad \left. + (t_i - t_{i-1}) \frac{\sigma \widehat{\varepsilon}_i - (\gamma + \delta + \mu)\widehat{I}_i}{2} \right) + \sum_{i=1}^k (t_i - t_{i-1}) \left( \sum_{t_j < t_i} (t_j - t_{j-1})(\sigma \widehat{\varepsilon}_j - (\gamma + \delta + \mu)\widehat{I}_j) \right)^2 \\
&\quad + \sum_{i=1}^k (t_i - t_{i-1})^2 (\sigma \widehat{\varepsilon}_i - (\gamma + \delta + \mu)\widehat{I}_i) \sum_{t_j < t_i} (t_j - t_{j-1})(\sigma \widehat{\varepsilon}_j - (\gamma + \delta + \mu)\widehat{I}_j) \\
&\quad + \sum_{i=1}^k \frac{1}{3} (t_i - t_{i-1})^3 (\sigma \widehat{\varepsilon}_i - (\gamma + \delta + \mu)\widehat{I}_i)^2. \tag{4.7}
\end{aligned}$$

The same can be done for  $\int_0^T \left[ \widehat{E}(t) - E_0 - \mathcal{E}(t) \right]^2 dt$  and  $\int_0^T \left[ \widehat{S}(t) - S_0 - \mathcal{S}(t) \right]^2 dt$  leading to a formula for  $L(\omega)$  which can be found in Appendix C.1.

In section 4.1 it is shown that  $L(\omega)$  can be written as

$$L(\omega) = \omega^T A \omega - 2\omega^T B + C,$$

for some matrices  $A, B$  and  $C$ . Minimizing  $L(\omega)$  will lead to an explicit form of  $\widehat{\omega}$ , namely

$$\widehat{\omega} = A^{-1}B.$$

The above shows us that the value of  $C$  is not significant in the calculation of  $\widehat{\omega}$ .

### 4.2.3 Estimation strategy

From (4.4), (4.5) and (4.6) it is clear that we need to estimate not only  $\beta$ ,  $E_0$  and  $S_0$ , but also  $\varepsilon$  and  $\eta$ . Unfortunately, then the second and third term of our objective function (4.6) are no longer linear. However, conditioned on each other, they are. Therefore, the following two steps are applied to ensure  $L(\omega)$  is linear during the computation.

#### Step 1

In order to find an estimation of all the above parameters an initial guess of  $\widehat{\psi} = (\widehat{\varepsilon}, \widehat{\eta})^T$  is generated from a uniform distribution over  $[0.1 \times 10^5]$  and respectively  $[0.1 \times 10^7]$ . First,  $\widehat{\psi}$  is kept fixed, while minimizing  $L$  with respect to  $\omega$ . Thus, one can write

$$L(\omega) = \omega^T A_p \omega - 2\omega^T B_p + C_p, \tag{4.8}$$

for some matrices  $A_p, B_p, C_p$ , which can be found in Appendix C.2, to obtain

$$\widehat{\omega} = A_p^{-1}B_p.$$

## Step 2

Second, the found estimator  $\widehat{\omega} = (\widehat{\beta}, \widehat{E}_0, \widehat{S}_0)^T$  is kept fixed, in order to minimize  $L$  with respect to  $\psi$ .

$$L(\psi) = \psi^T A_s \psi - 2\psi^T B_s + C_s, \quad (4.9)$$

for some (other) matrices  $A_s, B_s, C_s$ , which are elaborated in Appendix C.3. This leads to finding a new, better estimator  $\widehat{\psi}$ , by solving

$$\widehat{\psi} = A_s^{-1} B_s.$$

Now again, the new  $\widehat{\psi}$  will be kept fixed and the two steps described above can be repeated for a reasonable amount of iterations.

## 4.3 Conclusion

With the use of the method discussed by Vujačić, Dattner, González and Wit [34] the values that cannot be observed or deduced from appropriate studies and data, are estimated. The method focuses on the special class of non-linear systems that is linear in its parameters. The method can only be applied if all the states are observed, however only state  $I$  is observable. Therefore, primary the initial values of the states  $E$  and  $S$  are being guessed as  $\varepsilon_i$  and  $\eta_i$  for  $i = 1, \dots, 12$ . These values are being kept fixed and explicit estimates of  $\beta$ ,  $S_0$  and  $E_0$  are being found. Now, by keeping these estimates fixed, new, better values of the states  $E$  and  $S$  are found. These steps are repeated for a reasonable amount of times. Ultimately, the parameters are expected to converge to certain values.



# Chapter 5

## The results

This chapter will be devoted to listing the obtained results. In Appendix D one can view the R code used to obtain the content of this chapter. We will first address the parameters found by the optimization model. Subsequently, the results of a simulation study based on these parameters will be listed.

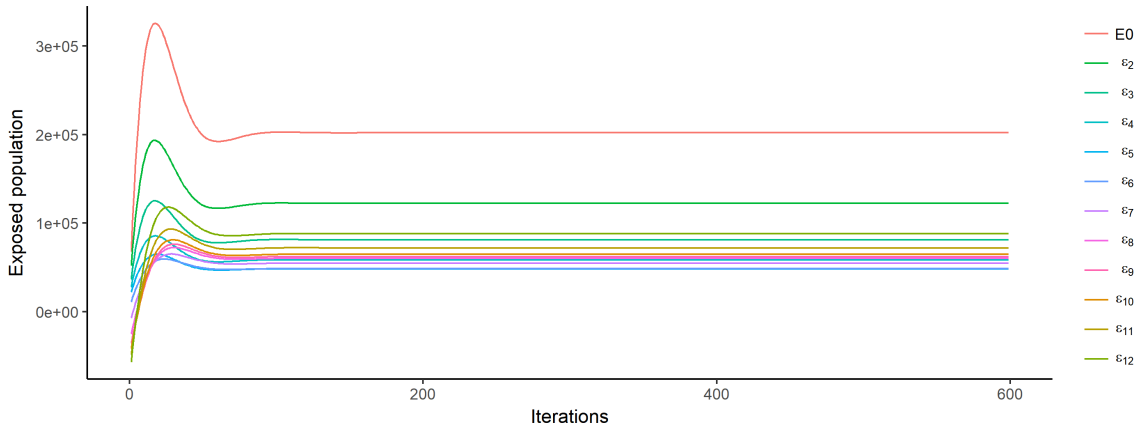
### 5.1 Finding the parameters

When we let the optimization model run for a reasonable amount of iterations, we find that the outcome is not as expected. At first glance, the values of  $\beta$ ,  $E_0$  and  $\varepsilon_i$  for  $i = 2, \dots, 12$  suggest to converge. However, this is not the case. Figures 5.1a,b show the development of the parameters belonging to the exposed population after (a) 600 and (b)  $10^5$  iterations, in which the divergence can be seen.

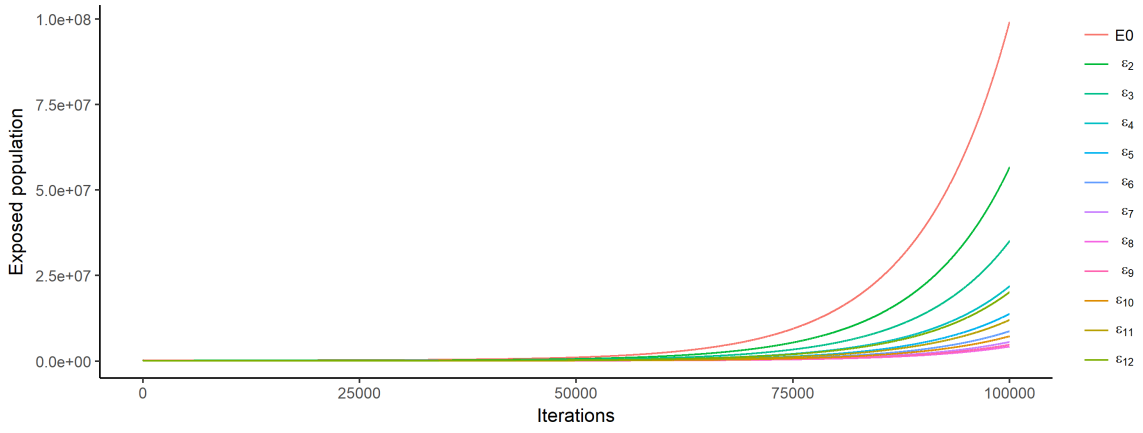
It appears that the values of  $S_0$  and  $\eta_i$  for  $i = 2, \dots, 12$  keep expanding, resulting in the undesirable outcome. The almost linear increasing values of  $S_0$  and  $\eta_i$  for  $i = 2, \dots, 12$  can be found in Figure 5.1c.

Since the estimation of  $S_0$  and  $\eta_i$  for  $i = 2, \dots, 12$  (and the other parameters) are dependent on each other, we have concluded there must be a bug in the determination of either of these parameters. To omit this, we have chosen to compute the value of  $S_0$  and treat it as a constant.

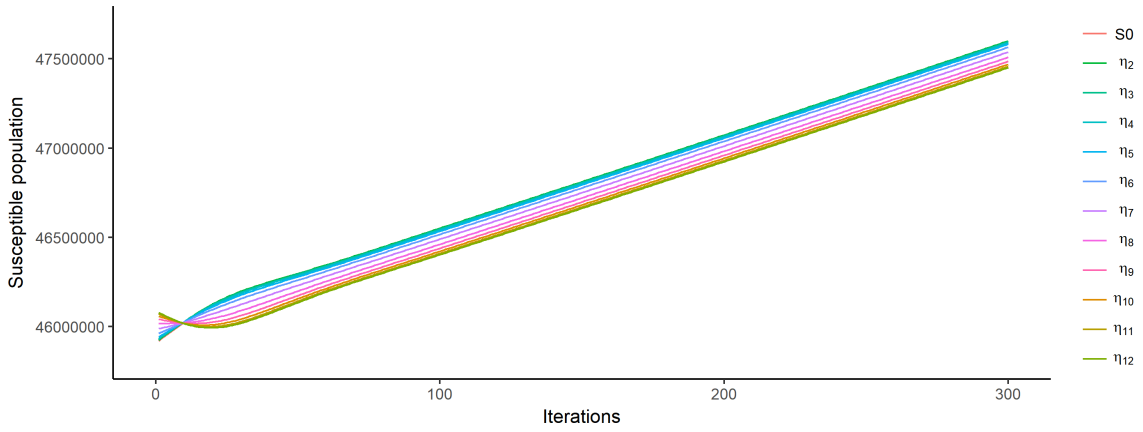
Fine and Clarckson (1982) argue that the total number of individuals susceptible to measles during the fifties and sixties in England and Wales remains relatively constant, around 4.5 million [10, 11]. Moreover, the same study shows that between 1950 and 1965 the amount of susceptibles in an average even year rises almost linearly from 4.5 million to 4.8 million, while during an average odd year this amount drops from 4.8 million to 4.3 million and then rises back to 4.5 million [11]. We assume this is similar for all years from 1948 to 1966 and let  $S_0$  equal 4.5 million during all even years and 4.8 million during odd years.



(a)

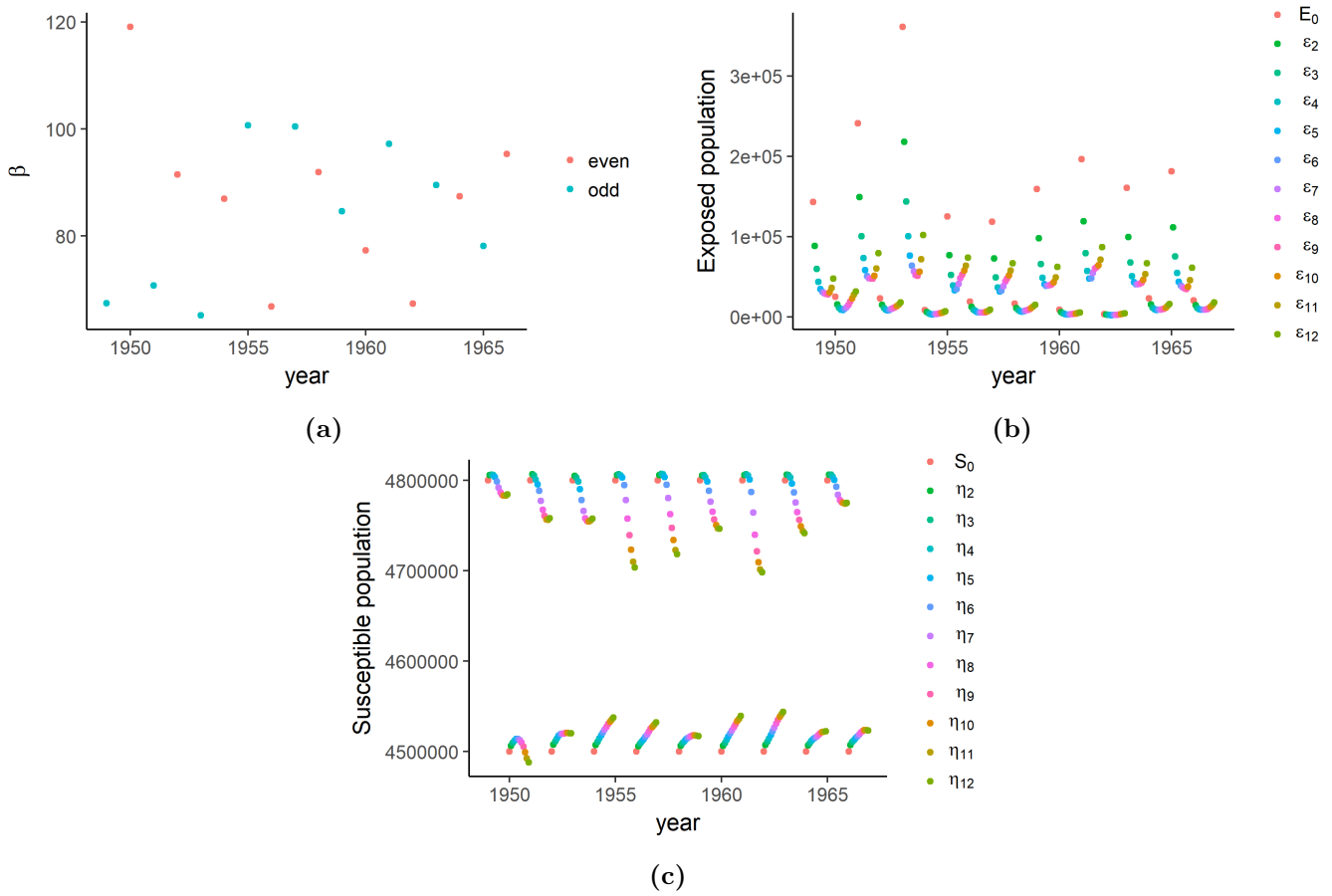


(b)



(c)

**Figure 5.1:** Plots with the estimation of the values of the parameters  $E_0$ ,  $\varepsilon_i$  for  $i = 2, \dots, 12$ ,  $S_0$  and  $\eta_i$  for  $i = 2, \dots, 12$  in the year 1961 plotted against a certain number of iterations. **(a):** The maximum of 300 iterations suggests convergence of the parameters belonging to the exposed population. **(b):** A maximum of  $10^5$  iterations shows the parameters belonging to the exposed population are actually diverging. **(c):** A plot with the increasing values of the estimation the parameters belonging to the susceptible population.



**Figure 5.2:** Three plots regarding the outcome of the parameters  $\hat{\omega} = (\hat{\beta}, \hat{E}_0, \hat{S}_0)^T$  and  $\hat{\psi} = (\hat{\epsilon}_1, \dots, \hat{\epsilon}_{12}; \hat{\eta}_1, \dots, \hat{\eta}_{12})^T$  from 1949 to 1966. **(a):** The estimated outcome of  $\beta$  for the years 1949 to 1966. The red dots represent even years, while the blue dots signify odd numbered years. **(b):** The estimated values of  $E_0$  and  $\epsilon_i$  for  $i = 2, \dots, 12$ . Every colour signifies a different  $\epsilon_i$ . **(c):** The estimated values of  $S_0$  and  $\eta_i$  for  $i = 2, \dots, 12$ . Every colour signifies a different  $\eta_i$ .

The adjusted model converges rapidly to an equilibrium state. The results can be found in Figure 5.2.

When viewing the transmission parameter in Figure 5.2a we see the value of this parameter lies between 60 and 120. This value seems to be nowhere near the values found in other studies ([6]:  $6.7 \cdot 10^{-4} - 1.6 \cdot 10^{-6}$ ; [8]:  $2 \cdot 10^{-6} - 4 \cdot 10^{-6}$ ; [34]:  $3.3 \cdot 10^{-7}$ ; [23]:  $7.25 \cdot 10^{-4} - 2.65 \cdot 10^{-5}$ ; [11]:  $2.4 \cdot 10^{-7}$ ). However, all of these studies have assumed  $N$  to be constant, and therefore included this value in  $\beta$ . Throughout every year, we let  $N$  equal the population at the start of that year and correct the transmission parameter for this term. Then the estimation of  $\beta$  lies between  $1.4 \cdot 10^{-6}$  and  $2.7 \cdot 10^{-6}$ , corresponding with the found literature.

There is no distinct correlation between the value of  $\beta$  and whether a year is odd or even numbered. However, when taking Figure 3.1 in account, it can be concluded that the even numbered years with a higher value of  $\beta$  have resulted in a relatively higher amount of infected individuals than the even numbered years with a low value of  $\beta$ . Considering the odd numbered years, no similar conclusion can be made.

Regarding the exposed population, Figure 5.2b clearly displays a distinction in the odd and even numbered years. As expected, the odd numbered years have a significant larger amount of exposed individuals, leading to a larger number of infected population.

Moreover, it can be seen that the number of exposed individuals decreases in the first half of the year, after which it increases. Again, during the even numbered years a correlation between the amount of exposed individuals and the amount of reported cases in Figure 3.1 can be seen. However, concerning the odd numbered years, no similar correlation can be found.

Considering the susceptible population, the fixed  $S_0$  is clearly visible. The changing value for the odd and even numbered years has a significant influence on the value of the parameters belonging to the susceptible population.

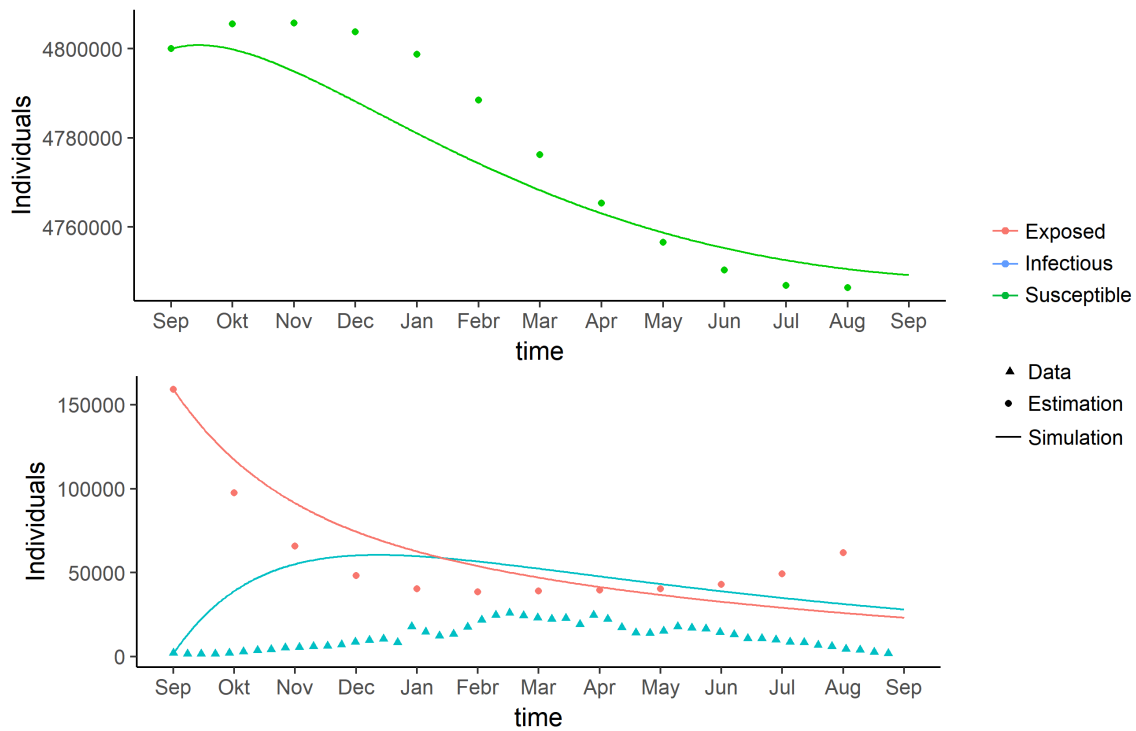
As expected, the amount of susceptible individuals reduces during odd numbered years, since more individuals move to the exposed and thereafter infectious state. Similarly, the amount of susceptible individuals during even numbered years decreases during the year (with the exception of 1950, an even year with an exceptional high amount of reported cases). Interestingly, with regard to the results from Fine and Clarkson (1982), the susceptible population does not decrease as much during odd numbered years, neither does it increase as much during even numbered years [11].

Furthermore, here again, the even numbered years show a correlation with the amount of exposed individuals and the amount of reported cases in Figure 3.1. Larger outbreaks leave fewer susceptible individuals. However, once more, such conclusions cannot be drawn regarding the odd numbered years.

## 5.2 Simulation

In order to verify the results of the previous section, a simulation has been made. The simulation follows the model (2.5) and the parameters from Chapter 3 and the previous section. The used code can be found in Appendix D. During the simulation the population  $N$  and the amount of births  $\rho$  are treated as constants by taking the average of a year.

The results of the simulation of the population applied to measles in 1959 are depicted in Figure 5.3. In the upper panel, the estimated number of susceptible individuals  $\eta_1, \dots, \eta_{12}$  are displayed with green dots, while the green solid line equals the outcome of the simulation based on the parameter estimate of  $\beta$ . In the lower panel the red dots represent the estimated number of exposed individuals  $\varepsilon_1, \dots, \varepsilon_{12}$ , the observed cases of measles are plotted as blue triangles, and the red and blue solid lines denote the simulated amount of exposed and infectious individuals.



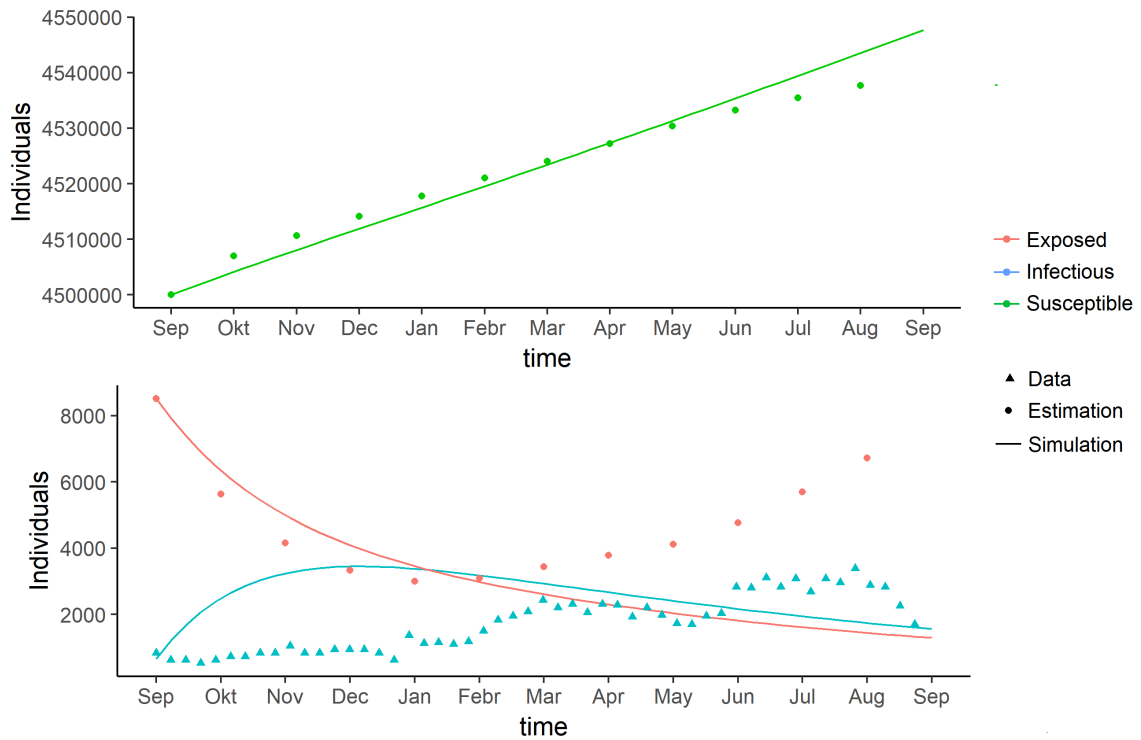
**Figure 5.3:** Plots with the number of exposed individuals (red), infectious individuals (blue) and susceptible individuals (green) in the year 1959. The solid lines are the outcome of the simulation based on the parameter estimates of  $\beta$ ,  $E_0$  and  $S_0$ , the dots display the solutions of the estimation of  $\eta_i$  and  $\varepsilon_i$  for  $i = 1, \dots, 12$  and the triangles represent the weekly reported cases of measles.

The simulated quantities do not correspond to the estimated and reported values of  $S$ ,  $E$  and  $I$  entirely. However, the main direction is comparable.

Regarding the susceptible population, in the first couple of months the simulation decreases the amount more rapid than the estimates, which can be accounted to the higher simulated values of  $E$  and ultimately  $I$ . The transition from undersimulating the estimates of  $S$  to overshooting the estimates of the susceptible population coincides nearly exactly with the transition from overshooting the estimates of the exposed population to undershooting the estimates of  $E$  in April.

The simulation results in nearly 4 times more infectious cases of measles as reported (viz. 2349591 instead of 610845). Moreover, a maximum amount of simulated infectious individuals is in December and January, while the actual summit lies between March and April.

The above trends can be found during the simulation any given odd numbered year. When changing to an even year, the simulation approaches the estimations better, as one can see in Figure 5.4. Here, the results of the simulation of the change in compartment groups in 1954 is given.



**Figure 5.4:** Plots with the number of exposed individuals (red), infectious individuals (blue) and susceptible individuals (green) in the year 1954. The solid lines are the outcome of the simulation based on the parameter estimates of  $\beta$ ,  $E_0$  and  $S_0$ , the dots display the solutions of the estimation of  $\eta_i$  and  $\varepsilon_i$  for  $i = 1, \dots, 12$  and the triangles represent the weekly reported cases of measles.

The simulation of the susceptible population is nearly exact and the amount of infectious individuals seems more fitting. Nevertheless, the peak of the epidemic is still simulated too early in the year and the simulation results in nearly 1.5 times as many infectious cases.

Similar as in odd numbered years, the simulated amount of exposed individuals is ever declining, in contrast to the estimated values.

### 5.3 Conclusion

The derived methods are implemented in R and used for a data analysis. During the analysis, the parameters did not converge as expected. To counter this,  $S_0$  has been kept fixed during the optimization. The estimated values of  $\beta$  are similar to the results found in other studies. The estimates of  $E$  and  $S$  are as expected. However, the estimates of the parameters belonging to the susceptible population do not decrease as brisk during odd numbered years, nor do they increase as fast during even numbered years as found in other studies.

In order to verify the found parameters, a simulation study has been made. The output of this simulation does not entirely fit the data of  $I$  and the estimated values of  $E$  and  $S$ . However, a comparison can be seen, especially during the even numbered years. Nevertheless, the simulation based on the estimates of the parameters  $\beta$ ,  $S_0$  and  $E_0$ , results in nearly four times more infectious cases of measles as reported during odd numbered years and 1.5 as many during even numbered years.

## Chapter 6

# Stability of the system

This chapter examines the stability of our SEIR model. First the equilibria of the SEIR model are determined. After this, the stability of these equilibria is proven. Subsequently, the stability of the SEIR model applied to measles is discussed. Here, the estimated parameters of the previous chapter will be implemented in order to make statements about the stability of the system.

Throughout this chapter it is assumed that  $v = 0$ . In section 6.2.2 we will discuss why we make this assumption and what kind of changes this generates to the stability of our model.

Subsequently, the birth rate  $\rho$  and the disease induced deathrate  $\delta$  are set fixed, which in turn ensures that the population size is constant<sup>1</sup>. This allows us to normalize our system with respect to  $N(t)$ ; i.e. now  $S(t), E(t), I(t)$  and  $R(t)$  denote, respectively, the fractions of the susceptible, the exposed, the infective and the recovered population. The adjusted model equals the following.

$$\begin{aligned}\dot{S} &= \rho - (\beta I + \mu) S, \\ \dot{E} &= \beta I S - (\sigma + \mu) E, \\ \dot{I} &= \sigma E - (\gamma + \delta + \mu) I,\end{aligned}\tag{6.1}$$

where one has to keep in mind that  $\rho$  is no longer the amount of births, but equals the birth rate.

Moreover, since  $\rho$  is now constant, equation (2.4) holds. Hence, the following is true

$$\frac{\rho}{\mu + \delta} \leq \liminf_{t \rightarrow \infty} N(t) \leq \limsup_{t \rightarrow \infty} N(t) \leq \frac{\rho}{\mu}.$$

Throughout this chapter we will therefore study (6.1) in the closed set

$$\Gamma = \{x = (S, E, I) \in \mathbb{R}_+^3 \mid S + E + I \leq \frac{\rho}{\mu}\}.$$

---

<sup>1</sup>There are, in our knowledge, only a couple of papers that focus on the stability analysis of different compartmental models with varying population size ([12, 14, 16, 19, 32]). They are mostly based on [20].



## 6.1 Theoretical framework

When the time-dependent ratios of  $S(t)$ ,  $E(t)$  and  $I(t)$  become constant, the disease reaches an equilibrium state which can be described as

$$\begin{cases} \dot{S} = \rho - (\beta I + \mu)S = 0, \\ \dot{E} = \beta IS - (\sigma + \mu)E = 0, \\ \dot{I} = \sigma E - (\gamma + \delta + \mu)I = 0, \end{cases} \quad (6.2)$$

From (6.2) we derive two equilibria. A disease-free equilibrium, which we will denote with  $x_0^*$  and an endemic equilibrium,  $x_e^*$ . Both will be examined in the following section.

### 6.1.1 Disease-free equilibrium

First, the simpler case is discussed: the disease-free equilibrium. It is clear that  $x_0^* = (S_0^*, 0, 0)$  is a solution of (6.2), where  $S_0^* = \frac{\rho}{\mu}$ . We shall exploit the same ideas developed by Li and Wang (2002) and examine the stability around  $x_0^*$  by following two propositions concerning the reproduction number [22].

**Proposition 1.** *The equilibrium  $x_0^*$  is globally asymptotically stable in  $\Gamma$  if  $R_0 \leq 1$ .*

*Proof.* Let us consider the following function

$$L(x) = E + \frac{\sigma + \mu}{\sigma} I.$$

Now,  $L(x) \geq 0$  for all  $x \neq x_0^*$ , where  $x \in \Gamma$ . Moreover,  $L(x_0^*) = 0$ . Its derivative along the system (6.1) is

$$\begin{aligned} \dot{L} &= \beta IS - \frac{(\sigma + \mu)(\gamma + \delta + \mu)}{\sigma} I \\ &= \left( \frac{\sigma \beta S}{(\sigma + \mu)(\gamma + \delta + \mu)} - 1 \right) \frac{(\sigma + \mu)(\gamma + \delta + \mu)}{\sigma} I. \end{aligned}$$

The rate of susceptible individuals in the entire population can never be larger than the rate of susceptible individuals at the disease free equilibrium. In other words,  $S \leq S_0 = \frac{\rho}{\mu}$ . In consequence, we can state

$$\begin{aligned} \dot{L} &\leq \left( \frac{\rho \sigma \beta}{\mu(\sigma + \mu)(\gamma + \delta + \mu)} - 1 \right) \frac{(\sigma + \mu)(\gamma + \delta + \mu)}{\sigma} I \\ &= (R_0 - 1) \frac{(\sigma + \mu)(\gamma + \delta + \mu)}{\sigma} I. \end{aligned} \quad (6.3)$$

Hence, if  $R_0 \leq 1$ , then  $\dot{L}(x) \leq 0$  for all  $(S, E, I) \in \Gamma$ , since the parameters in (6.3) are all positive. This implies that  $L(x)$  is a Lyapunov function for  $R_0 \leq 1$ . Therefore, under this condition, the equilibrium  $x_0^*$  is stable.

Since the equality holds when  $I = 0$  or  $R_0 = 1$ , we cannot prove global stability by means of Lyapunov's direct method alone. Therefore, we will use LaSalle's Invariance Principle, which implies that all paths in  $\Gamma$  approach the largest positively invariant subset of the set

$\Omega$ , where  $\dot{L}(x) = 0$ . In our case  $\dot{L}(x) = 0$  only if  $I = 0$  or  $(S, E, I) = x_0^*$ . The only positive invariant subset of the plane  $I = 0$  is the point  $x_0^*$ . Hence,  $x_0^*$  is the largest invariant set in  $\Omega = \{(S, E, I) \in \Gamma \mid \dot{L}(x) = 0\}$ . The global stability of  $x_0^*$ , when  $R_0 \leq 1$  immediately follows from LaSalle's Invariance Principle.  $\square$

**Proposition 2.** *The equilibrium  $x_0^*$  is an unstable saddle point in  $\Gamma$  if  $R_0 > 1$ .*

*Proof.* From Proposition 1 we know  $x_0^*$  is only stable in  $\Gamma$  if  $R_0 \leq 1$ . Furthermore, if  $R_0 > 1$ , then  $\dot{L}(x) > 0$  for  $x$  sufficient close to  $x_0^*$  in  $\Gamma$ , except when  $I = 0$ . Thus, any solutions in the system starting sufficiently close to  $x_0^*$  leave the neighbourhood of  $x_0^*$ . Except of those on the invariant  $S$ -axis, on which system (6.1) reduces to  $\dot{S} = \rho - \mu S$  and thus  $S(t) \rightarrow \frac{\rho}{\mu}$ , as  $t \rightarrow \infty$ .  $\square$

### 6.1.2 Endemic equilibrium

The endemic equilibrium is found by  $x_e^* = (S^*, E^*, I^*)$ , where

$$\begin{aligned} S^* &= \frac{\rho}{\mu R_0}, \\ E^* &= \frac{(\gamma + \delta + \mu)(R_0 - 1)\mu}{\beta\sigma}, \\ I^* &= \frac{\mu(R_0 - 1)}{\beta}. \end{aligned}$$

A derivation of the above equilibrium can be found in Appendix E.

The endemic equilibrium  $x_e^*$  is only in the first octant of the SEIR space when the contact number of (6.1) satisfies  $R_0 > 1$  [25]. Therefore, we will only consider this case. We will once again examine the stability of this equilibrium through two propositions, proving both local and global stability.

**Proposition 3.** *When  $R_0 > 1$ , the equilibrium  $x_e^*$  is locally asymptotically stable in  $\dot{\Gamma}$ .*

*Proof.* To prove local stability of  $x_e^*$  Lyapunov's first method is used. The Jacobian of model (6.1) at point  $x_e^*$  is given by

$$J(x_e^*) = \begin{pmatrix} -\beta I_e^* - \mu & 0 & -\beta S_e^* \\ \beta I_e^* & -(\sigma + \mu) & \beta S_e^* \\ 0 & \sigma & -(\gamma + \delta + \mu) \end{pmatrix} \quad (6.4)$$

$$= \begin{pmatrix} -\mu R_0 & 0 & -\frac{\beta\rho}{\mu R_0} \\ (R_0 - 1)\mu & -(\sigma + \mu) & \frac{\beta\rho}{\mu R_0} \\ 0 & \sigma & -(\gamma + \delta + \mu) \end{pmatrix}. \quad (6.5)$$

To prove the matrix is stable, it has to be shown all its eigenvalues have negative real parts. To do this, we write down the characteristic polynomial of (6.5) and set it to zero,

$$\det(I\lambda - J(x_e^*)) = \lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0. \quad (6.6)$$

Here

$$\begin{aligned}
a_1 &= \gamma + \delta + 2\mu + \mu R_0 + \sigma, \\
a_2 &= \mu R_0(\sigma + 2\mu + \gamma + \delta) + (\sigma + \mu)(\gamma + \delta + \mu) - \frac{\beta\rho\sigma}{\mu R_0}, \\
a_3 &= \mu R_0(\sigma + \mu)(\gamma + \delta + \mu) - \frac{\beta\rho\sigma}{R_0}.
\end{aligned} \tag{6.7}$$

Obviously,  $a_1 > 0$ . By verifying the Routh-Hurwitz conditions it will be shown that the eigenvalues of (6.5) have negative real parts. We construct the Routh Table, which can be found in table 6.1.

$\lambda^3$	1	$a_2$	0
$\lambda^2$	$a_1$	$a_3$	0
$\lambda^1$	$s_1$	0	0
$\lambda^0$	$a_3$	0	0

where  $s_1 = \frac{a_1 a_2 - a_3}{a_1}$ .

**Table 6.1:** The Routh Table belonging to (6.6).

In Appendix F it is shown that the signs of the first column are positive. Therefore, there are no sign changes, and consequently there are no poles of the characteristic equation in the right hand plane. Accordingly, it can be concluded that the equilibrium  $x_e^*$  is locally stable in  $\mathring{\Gamma}$  for  $R_0 > 1$ .  $\square$

Now that it is established that  $x_e^*$  is locally stable for  $R_0 > 1$ , it will be shown that all solutions of (6.1) in  $\mathring{\Gamma}$  converge to  $x_e^*$  when  $R_0 > 1$ , implying global stability of  $x_e^*$  in  $\mathring{\Gamma}$ .

**Proposition 4.** *When  $R_0 > 1$ , the equilibrium  $x_e^*$  is globally asymptotically stable in  $\mathring{\Gamma}$ .*

*Proof.* To establish global stability we shall make use of Theorem 5.1 of [18].

**Theorem 1.** *Assume that*

1. *there is a compact absorbing set  $K \subset \Gamma$  and system (6.1) has a unique equilibrium  $x_e^*$  in  $\mathring{\Gamma}$ ;*
2.  *$x_e^*$  is locally asymptotically stable;*
3. *system (6.1) satisfies the Poincaré-Bendixson Property;*
4. *each periodic orbit,  $\Omega$  of system (6.1) in  $\mathring{\Gamma}$  is orbitally asymptotically stable.*

*Then the unique equilibrium  $x_e^*$  is globally asymptotically stable in  $\mathring{\Gamma}$ .*

For models where the feasible region exists of a bounded cone, proving there is a compact absorbing set in that cone, equals proving that the system (6.1) is uniform persistent [36]. Clearly there exists a positive  $\alpha < 1$  such that

$$\liminf_{t \rightarrow \infty} x_i(t) \geq \alpha, \quad i = 1, 2, 3$$

holds for  $x_e^*$ . Above, we have seen that  $x_e^*$  exists and is locally asymptotically stable, thus condition (1) and (2) of Theorem 1 hold.

By examining equation (6.4) it can be verified that all non-diagonal elements of the Jacobian matrix of (6.1) are negative for  $\{x = (S, E, I) \in \mathbb{R}^3 \mid S \leq 0, E \geq 0, I \leq 0\}$ . Therefore, the system (6.1) is competitive and hence the model satisfies the Poincaré-Bendixson Property [31]. Thus, condition (3) of Theorem 1 holds too. It is left to show that each periodic orbit of system (6.1) in  $\mathring{\Gamma}$  is orbitally asymptotically stable. To do so, we will show  $\dot{z}(t) = \frac{\delta f^{[2]}}{\delta x}(p(t))z(t)$  is asymptotically stable, where  $\frac{\delta f^{[2]}}{\delta x}$  is the second additive compound matrix of the Jacobian matrix of (6.1).

The second additive compound matrix of a  $3 \times 3$  Jacobian matrix with  $J = (a_{ij})$  is given by

$$\frac{\delta f^{[2]}}{\delta x} = \begin{bmatrix} a_{11} + a_{22} & a_{23} & -a_{13} \\ a_{32} & a_{11} + a_{33} & a_{12} \\ -a_{31} & a_{21} & a_{22} + a_{33} \end{bmatrix}. [21]$$

Therefore the second additive compound matrix of the Jacobian of (6.1) equals the following

$$\frac{\delta f^{[2]}}{\delta x} = \begin{bmatrix} -\beta I - \mu - (\sigma + \mu) & \beta S & \beta S \\ \sigma & -\beta I - \mu - (\gamma + \delta + \mu) & 0 \\ 0 & \beta I & -(\sigma + \mu) - (\gamma + \delta + \mu) \end{bmatrix}.$$

Hence it results in the following system

$$\begin{aligned} \dot{X} &= -(\beta I + \sigma + 2\mu)X + \beta SY + \beta SZ \\ \dot{Y} &= \sigma X - (\beta I + \gamma + \delta + 2\mu)Y \\ \dot{Z} &= \beta IY - (\sigma + \gamma + \delta + 2\mu)Z. \end{aligned} \quad (6.8)$$

We will use Lyapunov's second method to prove stability of system (6.8). Suppose that  $(X(t), Y(t), Z(t))$  is a solution of this system, let  $(S, E, I) \in \Omega$  and consider the following Lyapunov function

$$L(X, Y, Z; S, E, I) = \sup \left\{ |X|, \frac{E}{I}(|Y| + |Z|) \right\}. \quad (6.9)$$

By the uniform persistence of condition (1) of Theorem 1, the orbit  $\Omega$  of the periodic solution  $(S, E, I)$  is at a positive distance from the boundary  $\delta\Gamma$ . Therefore we know there exists a  $c_1 > 0$  such that  $L(X, Y, Z; S, E, I) \geq c_1|(X, Y, Z)|$  for all  $(X, Y, Z) \in \mathbb{R}^3$  and  $(S, E, I) \in \Omega$ . Hence,  $L$  is a Lyapunov-candidate function.

The derivative of equation (6.9) is given by

$$\dot{L} = \sup \left\{ |\dot{X}|, \left( \frac{\dot{E}}{E} - \frac{\dot{I}}{I} \right) \frac{E}{I}(|Y| + |Z|) + \frac{E}{I}(|\dot{Y}| + |\dot{Z}|) \right\} \quad (6.10)$$

Using system (6.8) and the triangle inequality, we get

$$\begin{aligned} |\dot{X}| &= |-(\beta I + \sigma + 2\mu)X + \beta SY + \beta SZ| \\ &\leq -(\beta I + \sigma + 2\mu)|X| + \beta S(|Y| + |Z|). \end{aligned} \quad (6.11)$$

On the other hand,

$$\begin{aligned}
\frac{E}{I}(|\dot{Y}| + |\dot{Z}|) &= \frac{E}{I}(|\sigma X - (\beta I + \gamma + \delta + 2\mu)Y| + |\beta IY - (\sigma + \gamma + \delta + 2\mu)Z|) \\
&\leq \frac{E}{I}(\sigma|X| - (\beta I + \gamma + \delta + 2\mu)|Y| + \beta I|Y| - (\sigma + \gamma + \delta + 2\mu)|Z|) \\
&= \frac{E}{I}(\sigma|X| - (\gamma + \delta + 2\mu)|Y| - (\sigma + \gamma + \delta + 2\mu)|Z|).
\end{aligned}$$

Therefore,

$$\begin{aligned}
\left(\frac{\dot{E}}{E} - \frac{\dot{I}}{I}\right) \frac{E}{I}(|Y| + |Z|) + \frac{E}{I}(|\dot{Y}| + |\dot{Z}|) &\leq \left(\frac{\dot{E}}{E} - \frac{\dot{I}}{I}\right) \frac{E}{I}(|Y| + |Z|) \\
&+ \frac{E}{I}(\sigma|X| - (\gamma + \delta + 2\mu)|Y| - (\sigma + \gamma + \delta + 2\mu)|Z|). \tag{6.12}
\end{aligned}$$

Both (6.11) and (6.12) can be rewritten in the form  $aX + b\frac{E}{I}(|Y| + |Z|)$ , for some  $a$  and  $b$ .

$$(6.11) \leq -(\beta I + \sigma + 2\mu)|X| + \frac{\beta SI}{E} \frac{E}{I}(|Y| + |Z|),$$

$$\begin{aligned}
(6.12) &\leq \left(\frac{\dot{E}}{E} - \frac{\dot{I}}{I}\right) \frac{E}{I}(|Y| + |Z|) + \frac{E}{I}(\sigma|X| - (\gamma + \delta + 2\mu)|Y| - (\sigma + \gamma + \delta + 2\mu)|Z|) \\
&= \frac{E\sigma}{I}|X| + \left(\frac{\dot{E}}{E} - \frac{\dot{I}}{I} - (\gamma + \delta + 2\mu)\right) \frac{E}{I}|Y| + \left(\frac{\dot{E}}{E} - \frac{\dot{I}}{I} - (\sigma + \gamma + \delta + 2\mu)\right) \frac{E}{I}|Z| \\
&\leq \frac{E\sigma}{I}|X| + \left(\frac{\dot{E}}{E} - \frac{\dot{I}}{I} - (\gamma + \delta + 2\mu)\right) \frac{E}{I}(|Y| + |Z|).
\end{aligned}$$

Therefore, we can rewrite equation (6.10) as

$$\dot{L} \leq \max\{g_1, g_2\}L, \tag{6.13}$$

where

$$\begin{aligned}
g_1 &= -(\beta I + \sigma + 2\mu) + \frac{\beta SI}{E} \\
g_2 &= \frac{E\sigma}{I} + \frac{\dot{E}}{E} - \frac{\dot{I}}{I} - (\gamma + \delta + 2\mu).
\end{aligned}$$

Rewriting the second equation of (6.1) to  $\beta SI = \dot{E} + (\sigma + \mu)E$  and implementing this in  $g_1$  gives us

$$\begin{aligned}
g_1 &= -(\beta I + \sigma + 2\mu) + \frac{\dot{E} + (\sigma + \mu)E}{E} \\
&= \frac{\dot{E}}{E} - \beta I - \mu
\end{aligned}$$

However, if one implements the definition of  $\dot{I}$  from (6.1) into  $g_2$  the following occurs

$$\begin{aligned} g_2 &= \frac{E\sigma}{I} + \frac{\dot{E}}{E} - \frac{\sigma E - (\gamma + \delta + \mu)I}{I} - (\gamma + \delta + 2\mu) \\ &= \frac{\dot{E}}{E} - \mu. \end{aligned}$$

Clearly,  $\max\{g_1, g_2\} \leq \frac{\dot{E}}{E} - \mu$  and

$$\int_0^\omega \max\{g_1, g_2\} dt \leq \ln E|_0^\omega - \mu = -\mu,$$

by the periodicity of  $E$ . This relation and (6.13) imply that  $L(t) \rightarrow 0$  as  $t \rightarrow \infty$ . This again implies in turn that  $(X(t), Y(t), Z(t)) \rightarrow 0$  as  $t \rightarrow \infty$ . As a result, the second compound system is asymptotically stable, and thus condition (4) of Theorem 1 is verified. Therefore, it is proven that Theorem (1) holds.  $\square$

In conclusion, Table 6.2 lists the found results.

	$x_0^* = (S_0^*, 0, 0)$	$x_e^* = (S^*, E^*, I^*)$
$R_0 \leq 1$	GAS	NID
$R_0 > 1$	saddle	GAS

**Table 6.2:** Summary of stability results for model (6.1), where GAS stands for globally asymptotically stable and NID means not in the domain  $\Gamma$  or not an distinct equilibrium in  $\Gamma$ .

## 6.2 Stability of the SEIR model applied to measles

Now that the theoretical framework is exploited, we will apply the acquired knowledge to the SEIR model in the context of measles. We will first discuss the case that  $v = 0$ , after which the situation that  $v \neq 0$  will be addressed.

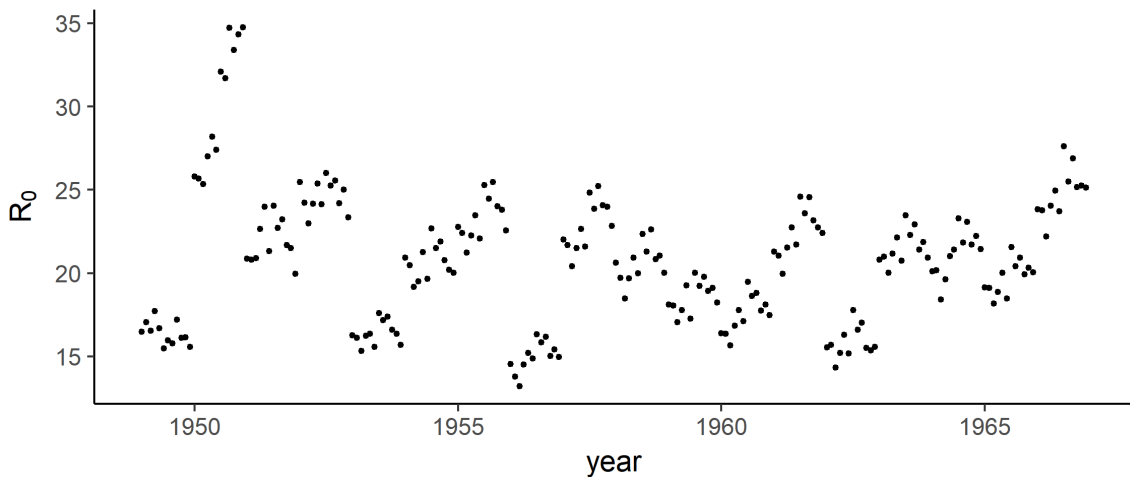
### 6.2.1 The case that $v = 0$

Here the stability of our system will be examined, by filling in our  $\hat{\beta}$  found in Chapter 5 and the parameters from Chapter 3 in the following formula

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

As one can see, the  $N^{-1}$ -term has been taken out of the definition of  $R_0$  as presented in 2.3.2. This is due to the fact that  $v = 0$  and  $\rho$  here equals the birthrate, and as a result has included this term.

At the start of this chapter we have assumed  $\delta$  and  $\rho$  are fixed, although throughout the other chapters we have seen that  $\delta$  and  $\rho$  are not constant during a year. Therefore, we have treated  $\delta$  and  $\rho$  as stepwise constants while determining  $R_0$ . The results from this calculation are presented in Figure 6.1.



**Figure 6.1:** *The value of  $R_0$  for every month from 1949 to 1966.*

It is clear that  $R_0$  is larger than 1, thus the system satisfies the conditions for stability of the endemic equilibrium. Specifically, the minimum and maximum of  $R_0$  are found to be 13.23 and 34.76, respectively. The year 1950 hosts the largest value of  $R_0$ , due to the rather small number of susceptible individuals and the relatively high number of outbreaks that year. That is, to obtain an equivalent outbreak size, the attack rate (thus the basic reproduction number) has to be higher in a population in with fewer susceptible individuals.

According to Anderson and May (1991, 1985) measles has an estimated basic reproduction number range of 12–18 [2, 3]. Thus, the found results are higher.<sup>2</sup> The cause of the increased values of  $R_0$  has to do with the higher number of simulated cases of infections in Section 5.2. After all, a higher basic reproduction number leads faster to more infections.

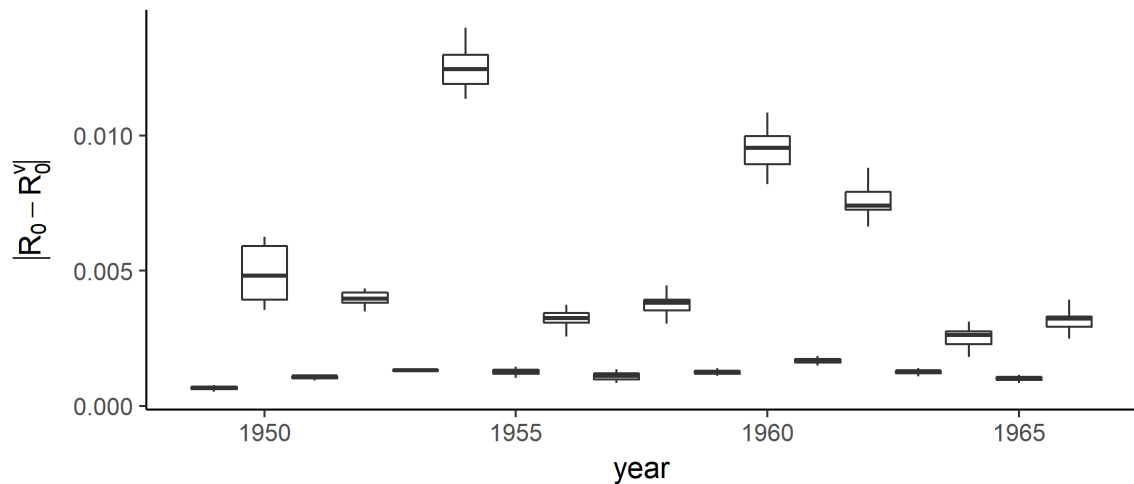
### 6.2.2 The case that $v \neq 0$ .

When assuming  $v \neq 0$ , determining the equilibria is not quite as simple as before. Even when  $I = 0$ , there is always a small presence of infectious people around. Hence, there is no chance for the disease to die out completely. Therefore, there is no disease-free equilibrium and we only consider the endemic equilibrium  $x_e^*$ . Its derivation can be found in Appendix G. When looking at this  $x_e^*$ , it is clear why we have chosen to let  $v$  equal zero.

In Chapter 3, the visitors impact  $v$  is set to ten individuals. However, since in this chapter we are measuring in ratios of the entire population, we set  $v = 2 \cdot 10^{-7}$ . Since  $v$  is so small, we expect our equilibrium point to move only minimal. Moreover, our propositions about stability are expected not to change.

In Figure 6.2 the distance from the value of  $R_0$  with  $v = 0$  and  $R_0^v$  with  $v = 2 \cdot 10^{-7}$  is plotted. This distance does not exceed a value of 0.014. Therefore, we conclude that  $R_0$  is still larger than one. This suggests that the SEIR system with  $v = 2 \cdot 10^{-7}$  has a stable

<sup>2</sup>There are some studies that suggest the basic reproduction rate of measles lies between 12–40. However, these studies all focus on an outbreak in a (partially) vaccinated population [26, 33, 35].



**Figure 6.2:** *Boxplots of the distance between  $R_0$  and  $R_0^v$  from 1949 to 1966.*

endemic equilibrium. However, without verifying the theorems and propositions of section 6.1 for this case, no hard conclusions can be drawn.

### 6.3 Conclusion

The stability of the SEIR model without the influence of visitors is examined. Local and global stability of the disease-free equilibrium is proved, provided that the reproduction number  $R_0 \leq 1$ . Likewise, local and global stability of the endemic equilibrium, provided that  $R_0 > 1$ , is proved. Furthermore, it has been proven that as long as  $R_0 > 1$ , the disease-free equilibrium becomes an unstable saddle point.

Concerning the SEIR model applied to measles, the basic reproduction number based on the estimates of  $\beta$  and  $x_0$  lies between 13 and 35. Therefore, the system satisfies the conditions for stability of the endemic equilibrium. The value of the basic reproduction number is higher than known by literature. This is in line with the high number of infected individuals as seen in the simulation.

Regarding the case that  $v \neq 0$ , only speculations can be made. That said, it is expected that the system will have a stable endemic equilibrium near the equilibrium point of the case where  $v = 0$ .



# Chapter 7

## Conclusion

### 7.1 Recapitulation

Epidemical diseases, such as measles, can be described by compartmental models. The entire population can be split in different compartments, according to the state of an individual: susceptible to the disease ( $\mathcal{S}$ ), exposed, but not yet infectious ( $\mathcal{E}$ ), infectious ( $\mathcal{I}$ ) and recovered and immune ( $\mathcal{R}$ ). With the use of ordinary differential equations the change in compartment size of this so-called SEIR model can be described. Moreover, the basic reproduction number  $R_0$  is determined.

Most of the parameters of this SEIR model can be observed or deduced from appropriate studies and data. However, the variables  $\beta$ ,  $S_0$ , and  $E_0$  are not. With the use of the method discussed by Vujačić, Dattner, González and Wit [34] these values are estimated. It focuses on the special class of non-linear systems that is linear in its parameters. The method uses window smoothing and yields in an explicit form of the estimators  $\beta$  and  $x_0$ .

The method can only be applied if all the states are observed, however only state  $I$  is observable. Therefore, primary the initial values of the states  $E$  and  $S$  are being guessed as  $\varepsilon_i$  and  $\eta_i$  for  $i = 1, \dots, 12$ . These values are being kept fixed and the mentioned method is used to find explicit estimates of  $\beta$ ,  $S_0$  and  $E_0$ . Now, by keeping these estimates fixed, new, better values of the states  $E$  and  $S$  are found. These steps are repeated for a reasonable amount of times. Ultimately, the parameters are expected to converge to certain values.

The derived method is implemented in R and used for a data analysis. During the analysis, the parameters did not converge as expected. To counter this,  $S_0$  has been kept fixed during the optimization. The estimated values of  $\beta$  are similar to the results found in other studies. The estimates of  $E$  and  $S$  are as expected. However, the estimates of the parameters belonging to the susceptible population do not decrease as brisk during odd numbered years, nor do they increase as fast during even numbered years as found in other studies.

In order to verify the found parameters, a simulation study has been made. The output of this simulation does not entirely fit the data of  $I$  and the estimated values of  $E$  and  $S$ . However, a comparison can be seen, especially during the even numbered years. Nevertheless, the simulation based on the estimates of the parameters  $\beta$ ,  $S_0$  and  $E_0$ , results in nearly

four times more infectious cases of measles as reported during odd numbered years and 1.5 as many during even numbered years.

In the last chapter the stability of the SEIR model without the influence of visitors is examined. Local and global stability of the disease-free equilibrium, provided that the reproduction number  $R_0 \leq 1$ , is proved with the use of Lyapunov's direct method and LaSalle's Invariance Principle. Furthermore, it has been proven that as long as  $R_0 > 1$ , the disease-free equilibrium becomes an unstable saddle point. Moreover, local and global stability of the endemic equilibrium, provided that  $R_0 > 1$ , is proved by means of Lyapunov's first method and Theorem 5.1 of [18].

Concerning the SEIR model applied to measles, the basic reproduction number based on the estimates of  $\beta$  and  $x_0$  lies between 13 and 35. Therefore, the system satisfies the conditions for stability of the endemic equilibrium. The value of the basic reproduction number is higher than known by literature. This is in line with the high number of infected individuals as seen in the simulation.

## 7.2 Conclusion

The method as exploited in this thesis has not lead to outcomes as expected. After treating  $S_0$  as a constant, the values of the estimates of  $\beta$  are similar as found in other studies. However, the simulation based on the found estimates of  $\beta$ ,  $E_0$  and the fixed  $S_0$ , does not match the data of  $I$  and estimates of  $E$  and  $S$  entirely. Neither does the basic reproductive number, computed by means of these estimated parameters, correspond to found literature.

The known propositions regarding stability of the endemic and disease-free equilibrium are proved for the SEIR model as described in this thesis without the influence of visitors. Without the assumption that  $v = 0$ , the disease-free equilibrium cannot exist. Furthermore, it is shown that the model without the influence of visitors satisfies the conditions for stability of the endemic equilibrium. It is discussed that the model with  $v \neq 0$  and  $v$  very small satisfies the conditions for stability of the endemic equilibrium.

## 7.3 Discussion

At first instance, the parameters in the optimization method did not converge. The parameters concerned with the susceptible population increased in value with each iteration. This is probably caused by a bug in  $A_p$ ,  $B_p$ ,  $A_s$  or  $B_s$ . Since the parameters are all correlated with each other it is assumed that even a single bug can have an impact on all the parameters. Since the bug could not be found, the divergence is omitted by fixing  $S_0$  values found in other studies.

Regarding the simulation, it is unclear why the outcome is not entirely similar to the estimates. It seems to be credible that the rather high estimated value of  $E_0$  is the culprit. During odd numbered years, the estimated value of  $E_0$  can be up to 30% of the entire amount of reported cases of that year. Even though some individuals do not get to the  $I$  state due to natural morbidity, it is still unlikely that the amount of exposed individuals at the beginning of the year is that high. Another possible cause could be that the fixed value

of  $S_0$  is not sufficiently accurate, but most likely, the deviant outcomes are being caused by the same bug that caused the parameters belonging to the susceptible population to increase.

Likewise, the basic reproduction number is higher than discussed in other studies. This is analogous to the high simulated number of infected individuals. That is to say, when the basic reproduction number is high, one individual will infect more susceptible individuals leading to more infected individuals and a larger outbreak. Consequently, when there is a large outbreak size, but a rather small group susceptible population, the basic reproduction number has to be higher.

## 7.4 Future research

Even though the method in this thesis gave us reasonable values of  $\beta$  and  $x_0$ , the output will not be extremely accurate, because of the assumption of a constant  $\beta$ . However, from the data it is clear that  $\beta$  varies throughout the year. It would be interesting to let the model work with the seasonal influence of  $\beta$ . In this section different methods to describe  $\beta$  with the influence of seasonal forcing are shown. We encourage each and everybody with interest in this subject to examine this.

### 7.4.1 $\beta$ as a stepwise constant

It is obvious that less contact with other individuals will reduce the chance of an individual getting infected. Since measles are a transmittable childhood disease, it makes sense that during the holidays children have a smaller chance of getting ill than when they are going to school. Therefore, we introduce a variable  $\beta(t)$  as a replacement for the constant parameter  $\beta$  in the differential equations in (2.5). This variable contact rate is given by

$$\beta(t) = \begin{cases} \beta_S & \text{on school days,} \\ \beta_H & \text{on non-school days,} \end{cases}$$

as is done in [5]. The parameter  $\beta_S$  ensures  $\beta(t)$  to be high on school days, while  $\beta_H$  causes  $\beta(t)$  to be low during holidays.

The value  $\beta_H$  is estimated on non-schooldays and  $\beta_S$  on schooldays. Due to the latent period of the disease, one should take in account that the measles have an incubation period of 8 to 13 days.

The data can be divided into two groups. Data during schooldays,  $I_S$ , which is taken from November to August, and  $I_H$  from September, October and August that year, representing data during non-schooldays. The estimators  $\widehat{I}(t)$ ,  $\widehat{E}(t)$  and  $\widehat{S}(t)$  can again be smoothed from the data, or estimated as is done in section 4.2.1. Once this is done,  $\widehat{\omega} = (\beta_S, \beta_H, I_0, E_0, S_0)^T$  can be estimated in a similar way to  $\widehat{\omega}$  as seen the section 4.2. The corresponding matrices can be determined. Particularly  $\widehat{\psi}$  can be estimated by adding a subscript ( $i$ ,  $j$ , or  $s$ ) to every  $\beta$  concurrent with the subscript of  $I$  immediately after that  $\beta$ . Keeping in mind that  $\beta_i$  equals  $\beta_S$  for  $i = 3, \dots, 11$  and respectively  $\beta_H$  for  $i = 1, 2, 12$ , one can insert this value into the original matrices  $A_s$  (C.3) and  $B_s$  (C.2), and find  $\widehat{\psi}$ .

### 7.4.2 $\beta$ as a spline

The approach described above is more accurate, but it still only has two values for  $\beta$ . A different approach to this statistical problem, is to write  $\beta$  similar to the definitions of  $\widehat{E}$  and  $\widehat{S}$ , found in equations (4.4) and (4.5). That is,

$$\beta(t) = \sum_{i=1}^{12} \beta_i 1_{\{t \in S_i\}}.$$

Writing  $\beta(t)$  as a spline, allows one to view  $\beta(t)$  as a function that is linear in  $\beta_i$  for all  $1 \leq i \leq 12$ . Thus, once more the model is linear in all its parameters. Hence, the estimation strategy as discussed in section 4.2 will again result in an explicit form of the estimators  $\widehat{\omega}$  and  $\widehat{\psi}$ . Now, however,  $\widehat{\omega}$  will result in a  $15 \times 1$  vector as

$$\widehat{\omega} = (\beta_1, \dots, \beta_{12}, E_0, S_0)^T.$$

Here again, the matrices  $A_p$  and  $B_p$  need to be changed entirely, while the matrices  $A_s$  and  $B_s$  can simply undertake the minor change of adding a subscript to  $\beta$  as is done above.

### 7.4.3 $\beta$ as a function

To view  $\beta$  as a function variable through time  $t$ , let

$$\beta(t) = \sum_{i=1}^{12} \beta_i t^{i-1}.$$

Writing  $\beta(t)$  like this, allows us to view  $\beta(t)$  as a function that is linear in  $\beta_i$  for all  $1 \leq i \leq 12$ . When applying this to (2.5), the model again is linear in all its parameters. Hence, the method discussed in section 4.1 will result in an explicit form for the estimators  $\widehat{\psi}$  and  $\widehat{\omega}$ , where  $\widehat{\omega}$  now denotes a vector of the form

$$\widehat{\omega} = (\beta_1, \dots, \beta_{12}, I_0, E_0, S_0)^T.$$

Even though the previous methods only account for minor changes in  $L(\psi, \omega)$ , the objective function analogous to this method changes a bit more, since every  $\beta_i$  in  $L(\omega)$  has to be written as

$$\sum_{r=1}^{12} \frac{1}{r} \beta_r (t_i - t_{i-1})^r.$$

Once more, the corresponding matrices can be determined and optimization problem can be solved.

### 7.4.4 Stability of the SEIR system for variations of $\beta$

When viewing  $\beta$  as a variable function, the properties that have been proven in this thesis cannot assumed to be true.

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# Appendix A

## Force of infection

Consider an individual  $n \in \mathcal{S}$ , who has an average of  $\tau$  contacts per unit time. Some of these contacts occur with infectious individuals, who are denoted by the ratio  $\frac{I}{N}$ , where  $I$  is the number of individuals in the infected class and  $N$  equals the number of individuals in the entire population. Then, during an interval of  $[t, t + \delta t]$  the susceptible individual will come in contact with  $\frac{\tau I}{N} \delta t$  infectious individuals. Define  $p$  as the probability of the susceptible individual actually acquiring the disease upon contact with an infected individual. Then  $1 - p$  is the chance of the individual eluding the pathogen.

Let  $\delta q$  be the chance of the individual to get infected after  $\frac{\tau I}{N} \delta t$  contacts. Now, the probability of the individual *not* receiving the illness following  $\frac{\tau I}{N} \delta t$  contacts can be defined as  $1 - \delta q$ . That is,

$$\begin{aligned} 1 - \delta q &= (1 - p)^{\frac{\tau I}{N} \delta t} \\ &= e^{\log(1-p) \frac{\tau I}{N} \delta t}. \end{aligned}$$

By expanding the exponential term and neglecting any higher order terms, one finds

$$\begin{aligned} 1 - \delta q &= 1 + \log(1 - p) \frac{\tau I}{N} \delta t \quad (+ \text{ h.o. terms}) \\ -\delta q &= \log(1 - p) \frac{\tau I}{N} \delta t \\ \frac{\delta q}{\delta t} &= \beta \frac{I}{N}, \end{aligned}$$

where  $\beta = -\tau \log(1 - p)$ . This parameter  $\beta$  is named the contact rate. Moreover, if we take the limit of the obtained equation as  $t$  tends to zero, it results in the following

$$\lim_{t \rightarrow 0} \frac{\delta q}{\delta t} = \frac{dq}{dt} = \beta \frac{I}{N}.$$

By the definition of  $q$ , the probability of the susceptible individual to get infected with the pathogen is now found, or in other words: we have found the per capita transmission term  $\lambda$ .



## Appendix B

# Reproductive number

An introduction of how to calculate  $R_0$  in compartmental population models is provided by [13]. We will follow this next generation matrix approach closely.

### B.1 Theoretical framework

Consider  $n$  compartments of which  $m$  are infected. Let  $F_i$  be given by the rate of appearance of new infections in compartment  $i$ , with  $i = 1, \dots, n$ . Additionally, let  $V_i = V_i^- - V_i^+$ , where  $V_i^-$  is the rate of relocation of individuals into the  $i$ -th compartment and  $V_i^+$  the relocation of individuals out of compartment  $i$ .

Now, let us consider the matrix  $G = FV^{-1}$ , where

$$F = \left[ \frac{\partial F_i(x_0)}{\partial x_j} \right]$$

and

$$V = \left[ \frac{\partial V_i(x_0)}{\partial x_j} \right].$$

Here  $j = 1, \dots, m$  and  $x_0$  equals the start of an epidemic. That is, one infected individual is introduced into a host population where everyone is susceptible. Then,  $R_0$  is the dominant eigenvalue of  $G$ .

### B.2 Method applied to the SEIR model

We consider the SEIR model as given in section 2.3. Since we are concerned with the population that spread the infection, only the exposed and the infected classes have to be taken in consideration. Then the number of ways that new infections can arise need to be appointed. Even though there are two disease states, there is only one way to create new infections:

$$F = \begin{bmatrix} 0 & \frac{\beta(\rho+v)}{N\mu} \\ 0 & 0 \end{bmatrix}.$$

Now, to find the number of ways that individuals can move between compartments

$$V = \begin{bmatrix} \mu + \sigma & 0 \\ -\sigma & \gamma + \delta + \mu \end{bmatrix}.$$

Now,  $R_0$  is the leading eigenvalue of

$$\begin{aligned} FV^{-1} &= \frac{1}{(\mu + \sigma)(\gamma + \delta + \mu)} \begin{bmatrix} 0 & \frac{\beta(\rho+v)}{N\mu} \\ 0 & 0 \end{bmatrix} \begin{bmatrix} \gamma + \delta + \mu & 0 \\ -\sigma & \mu + \sigma \end{bmatrix} \\ &= \begin{bmatrix} \frac{\beta(\rho+v)\sigma}{N\mu(\mu+\sigma)(\gamma+\delta+\mu)} & \frac{\beta(\rho+v)}{N\mu(\gamma+\delta+\mu)} \\ 0 & 0 \end{bmatrix}. \end{aligned}$$

Thus  $\det(IR_0 - FV^{-1}) = 0$ , and simple calculations show

$$R_0 = \frac{\beta(\rho + v)\sigma}{N\mu(\mu + \sigma)(\gamma + \delta + \mu)}.$$

## Appendix C

# Calculation of $L(\omega)$ , $B_p$ , $A_p$ , $B_s$ and $A_s$

### C.1 Derivation of $L(\omega)$

Implementing the definition of  $\int_0^T [\widehat{I}(t) - I_0 - \mathcal{J}(t)]^2 dt$  from equation (4.7) and the derivations of  $\int_0^T [\widehat{E}(t) - E_0 - \mathcal{E}(t)]^2 dt$  and  $\int_0^T [\widehat{S}(t) - S_0 - \mathcal{S}(t)]^2 dt$  in to the equation (4.6) of  $L(\omega)$  yields in:

$$\begin{aligned}
L(\omega, \psi) &= \int_0^T \left\| \widehat{I}(t) - I_0 - \int_0^t \sigma \widehat{E}(s) - (\gamma + \delta + \mu) \widehat{I}(s) ds \right\|^2 dt \\
&+ \int_0^T \left\| \widehat{E}(t) - E_0 - \int_0^t \frac{\beta (\widehat{I}(s) + v)}{N(s)} \widehat{S}(s) - (\sigma + \mu) \widehat{E}(s) ds \right\|^2 dt \\
&+ \int_0^T \left\| \widehat{S}(t) - S_0 - \int_0^t \rho - \left( \frac{\beta (\widehat{I}(s) + v)}{N(s)} + \mu \right) \widehat{S}(s) ds \right\|^2 dt \\
&= \sum_{i=1}^{12} (t_i - t_{i-1}) (\widehat{I}_i - I_0)^2 - 2 \sum_{i=1}^{12} (t_i - t_{i-1}) (\widehat{I}_i - I_0) \left( \sum_{j < i} (t_j - t_{j-1}) (\sigma \widehat{\varepsilon}_j - (\gamma + \delta + \mu) \widehat{I}_j) \right. \\
&\quad \left. + (t_i - t_{i-1}) \frac{\sigma \widehat{\varepsilon}_i - (\gamma + \delta + \mu) \widehat{I}_i}{2} \right) + \sum_{i=1}^{12} (t_i - t_{i-1}) \left( \sum_{j < i} (t_j - t_{j-1}) (\sigma \widehat{\varepsilon}_j - (\gamma + \delta + \mu) \widehat{I}_j) \right)^2 \\
&+ \sum_{i=1}^{12} (t_i - t_{i-1})^2 (\sigma \widehat{\varepsilon}_i - (\gamma + \delta + \mu) \widehat{I}_i) \sum_{j < i} (t_j - t_{j-1}) (\sigma \widehat{\varepsilon}_j - (\gamma + \delta + \mu) \widehat{I}_j) \\
&+ \sum_{i=1}^{12} \frac{1}{3} (t_i - t_{i-1})^3 (\sigma \widehat{\varepsilon}_i - (\gamma + \delta + \mu) \widehat{I}_i)^2
\end{aligned}$$

$$\begin{aligned}
& + \sum_{i=1}^{12} (t_i - t_{i-1})(\widehat{\varepsilon}_i - E_0)^2 - 2 \sum_{i=1}^{12} (t_i - t_{i-1})(\widehat{\varepsilon}_i - E_0) \left( \sum_{j<i} (t_j - t_{j-1}) \left( \frac{\beta(\widehat{I}_j + v)}{N_j} \widehat{\eta}_j - (\sigma + \mu) \widehat{\varepsilon}_j \right) \right. \\
& + \left. (t_i - t_{i-1}) \frac{\frac{\beta(\widehat{I}_i + v) \widehat{\eta}_i - (\sigma + \mu) \widehat{\varepsilon}_i}{2}}{2} \right) + \sum_{i=1}^{12} (t_i - t_{i-1}) \left( \sum_{j<i} (t_j - t_{j-1}) \left( \frac{\beta(\widehat{I}_j + v)}{N_j} \widehat{\eta}_j - (\sigma + \mu) \widehat{\varepsilon}_j \right) \right)^2 \\
& + \sum_{i=1}^{12} (t_i - t_{i-1})^2 \left( \frac{\beta(\widehat{I}_i + v)}{N_i} \widehat{\eta}_i - (\sigma + \mu) \widehat{\varepsilon}_i \right) \sum_{j<i} (t_j - t_{j-1}) \left( \frac{\beta(\widehat{I}_j + v)}{N_j} \widehat{\eta}_j - (\sigma + \mu) \widehat{\varepsilon}_j \right) \\
& + \sum_{i=1}^{12} \frac{1}{3} (t_i - t_{i-1})^3 \left( \frac{\beta(\widehat{I}_i + v)}{N_i} \widehat{\eta}_i - (\sigma + \mu) \widehat{\varepsilon}_i \right)^2 \\
& + \sum_{i=1}^{12} (t_i - t_{i-1})(\widehat{\eta}_i - S_0)^2 - 2 \sum_{i=1}^{12} (t_i - t_{i-1})(\widehat{\eta}_i - S_0) \left( \sum_{j<i} (t_j - t_{j-1}) \left( \rho_j - \left( \frac{\beta(\widehat{I}_j + v)}{N_j} + \mu \right) \widehat{\eta}_j \right) \right. \\
& + \left. (t_i - t_{i-1}) \frac{\rho_i - \left( \frac{\beta(\widehat{I}_i + v)}{N_i} + \mu \right) \widehat{\eta}_i}{2} \right) + \sum_{i=1}^{12} (t_i - t_{i-1}) \left( \sum_{j<i} (t_j - t_{j-1}) \left( \rho_j - \left( \frac{\beta(\widehat{I}_j + v)}{N_j} + \mu \right) \widehat{\eta}_j \right) \right)^2 \\
& + \sum_{i=1}^{12} (t_i - t_{i-1})^2 \left( \rho_i - \left( \frac{\beta(\widehat{I}_i + v)}{N_i} + \mu \right) \widehat{\eta}_i \right) \sum_{j<i} (t_j - t_{j-1}) \left( \rho_j - \left( \frac{\beta(\widehat{I}_j + v)}{N_j} + \mu \right) \widehat{\eta}_j \right) \\
& + \sum_{i=1}^{12} \frac{1}{3} (t_i - t_{i-1})^3 \left( \rho_i - \left( \frac{\beta(\widehat{I}_i + v)}{N_i} + \mu \right) \widehat{\eta}_i \right)^2. \tag{C.1}
\end{aligned}$$

## C.2 Derivation of $B_p$ and $A_p$

Missing out a few lines of algebra, equation (C.1) can be rewritten in the form (4.8) as

$$L(\omega) = \omega^T A_p \omega - 2\omega^T B_p + C_p,$$

for some  $C_p$ ,  $\omega = (\beta, E_0, S_0)^T$ , and  $B_p$  and  $A_p$  as specified below.

$$A_p = \begin{bmatrix} a & b & -b \\ b & c & 0 \\ -b & 0 & c \end{bmatrix},$$

where

$$\begin{aligned}
a &= \sum_{i=1}^{12} \frac{2}{3} (t_i - t_{i-1})^3 \left( \frac{\widehat{I}_i + v}{N_i} \right)^2 \widehat{\eta}_i^2 + 2(t_i - t_{i-1})^2 \left( \frac{\widehat{I}_i + v}{N_i} \right) \widehat{\eta}_i \sum_{j < i} (t_j - t_{j-1}) \left( \frac{\widehat{I}_j + v}{N_j} \right) \widehat{\eta}_j \\
&\quad + 2(t_i - t_{i-1}) \sum_{k, l < i} (t_k - t_{k-1})(t_l - t_{l-1}) \left( \frac{\widehat{I}_k + v}{N_k} \right) \widehat{\eta}_k \left( \frac{\widehat{I}_l + v}{N_l} \right) \widehat{\eta}_l, \\
b &= \frac{1}{2} \sum_{i=1}^{12} (t_i - t_{i-1}) \left( (t_i - t_{i-1}) \left( \frac{\widehat{I}_i + v}{N_i} \right) \widehat{\eta}_i + 2 \sum_{j < i} (t_j - t_{j-1}) \left( \frac{\widehat{I}_j + v}{N_j} \right) \widehat{\eta}_j \right), \\
c &= t_{12} - t_0.
\end{aligned}$$

$$B_p = \begin{bmatrix} a \\ b \\ c \end{bmatrix},$$

where

$$\begin{aligned}
a &= \sum_{i=1}^{12} (t_i - t_{i-1}) \left( (\widehat{\varepsilon}_i - \widehat{\eta}_i) \left( \frac{1}{2} (t_i - t_{i-1}) \left( \frac{\widehat{I}_i + v}{N_i} \right) \widehat{\eta}_i + \sum_{j < i} (t_j - t_{j-1}) \left( \frac{\widehat{I}_j + v}{N_j} \right) \widehat{\eta}_j \right) \right. \\
&\quad + (\rho_i - \mu \widehat{\eta}_i + (\sigma + \mu) \widehat{\varepsilon}_i) \left( \frac{1}{3} (t_i - t_{i-1})^2 \left( \frac{\widehat{I}_i + v}{N_i} \right) \widehat{\eta}_i + \frac{1}{2} (t_i - t_{i-1}) \sum_{j < i} (t_j - t_{j-1}) \left( \frac{\widehat{I}_j + v}{N_j} \right) \widehat{\eta}_j \right) \\
&\quad + \frac{1}{2} (t_i - t_{i-1}) \left( \frac{\widehat{I}_i + v}{N_i} \right) \widehat{\eta}_i \sum_{j < i} (t_j - t_{j-1}) (\rho_j - \mu \widehat{\eta}_j + (\sigma + \mu) \widehat{\varepsilon}_j) \\
&\quad \left. + \sum_{k, l < i} (t_k - t_{k-1})(t_l - t_{l-1}) (\rho_l - \mu \widehat{\eta}_l + (\sigma + \mu) \widehat{\varepsilon}_l) \left( \frac{\widehat{I}_k + v}{N_k} \right) \widehat{\eta}_k \right), \\
b &= \sum_{i=1}^{12} (t_i - t_{i-1}) \left( \left( 1 + \frac{1}{2} (t_i - t_{i-1}) (\sigma + \mu) \right) \widehat{\varepsilon}_i + \sum_{j < i} (t_j - t_{j-1}) (\sigma + \mu) \widehat{\varepsilon}_j \right), \\
c &= \sum_{i=1}^{12} (t_i - t_{i-1}) \left( \widehat{\eta}_i - \frac{1}{2} (t_i - t_{i-1}) (\rho_i - \mu \widehat{\eta}_i) - \sum_{j < i} (t_j - t_{j-1}) (\rho_j - \mu \widehat{\eta}_j) \right).
\end{aligned}$$

### C.3 Derivation of $B_s$ and $A_s$

Likewise, we can rewrite equation (C.1) in the form (4.9) as

$$L(\psi) = \psi^T A_s \psi - 2\psi^T B_s + C_s,$$

for some  $C_s$ ,  $\psi = (\varepsilon_1, \dots, \varepsilon_{12}, \eta_1, \dots, \eta_{12})^T$ , and  $B_s$  given by the following symmetric matrix.

$$A_s = \begin{bmatrix} a_1 & b_{1,2} & b_{1,3} & \dots & b_{1,12} & c_1 & d_{1,2} & d_{1,3} & \dots & d_{1,12} \\ b_{2,1} & a_2 & b_{2,3} & \dots & b_{2,12} & x_{2,1} & c_2 & d_{2,3} & \dots & d_{2,12} \\ b_{3,1} & b_{3,2} & a_3 & \dots & b_{3,12} & x_{3,1} & x_{3,2} & c_3 & \dots & d_{3,12} \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ b_{12,1} & b_{12,2} & b_{12,3} & \dots & a_{12} & x_{12,1} & x_{12,2} & x_{12,3} & \dots & c_{12} \\ c_1 & x_{1,2} & x_{1,3} & \dots & x_{1,12} & e_1 & f_{1,2} & f_{1,3} & \dots & f_{1,12} \\ d_{2,1} & c_2 & x_{2,3} & \dots & x_{2,12} & f_{2,1} & e_2 & f_{2,3} & \dots & f_{2,12} \\ d_{3,1} & d_{3,2} & c_3 & \dots & x_{3,12} & f_{3,1} & f_{3,2} & e_3 & \dots & f_{3,12} \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ d_{12,1} & d_{12,2} & d_{12,3} & \dots & c_{12} & f_{12,1} & f_{12,2} & f_{12,3} & \dots & e_{12} \end{bmatrix}. \quad (\text{C.2})$$

The components of matrix (C.2) equal the following.

$$\begin{aligned} a_i &= (t_i - t_{i-1})^2 \left( (\sigma^2 + (\sigma + \mu)^2) \left( (t_{12} - t_i) + \frac{1}{3}(t_i - t_{i-1}) \right) + (\sigma + \mu) \right) \\ &\quad + (t_i - t_{i-1}), \\ b_{i,j} &= b_{j,i} = \frac{1}{2}(t_i - t_{i-1})(t_j - t_{j-1}) \left( 2(\sigma + \mu) + (\sigma^2 + (\sigma + \mu)^2) \left( (t_i - t_{i-1}) + 2(t_{12} - t_i) \right) \right), \\ c_i &= -\frac{1}{2}(t_i - t_{i-1})^2 \left( \frac{\beta(\widehat{I}_i + v)}{N_i} \right) \left( 1 + \frac{2}{3}(t_i - t_{i-1})(\sigma + \mu) + 2(\sigma + \mu)(t_{12} - t_i) \right), \\ d_{i,j} &= d_{j,i} = -(t_i - t_{i-1})(t_j - t_{j-1}) \frac{\beta(\widehat{I}_i + v)}{N_i} (\sigma + \mu) \left( \frac{1}{2}(t_i - t_{i-1}) + (t_{12} - t_i) \right), \\ x_{i,j} &= x_{j,i} = -(t_i - t_{i-1})(t_j - t_{j-1}) \frac{\beta(\widehat{I}_j + v)}{N_j} \left( (\sigma + \mu) \left( \frac{1}{2}(t_i - t_{i-1}) + (t_k - t_i) \right) + 1 \right), \\ e_i &= (t_i - t_{i-1})^2 \left( \left( \frac{\beta(\widehat{I}_i + v)}{N_i} \right)^2 + \left( \frac{\beta(\widehat{I}_i + v)}{N_i} + \mu \right)^2 \right) \left( (t_{12} - t_i) + \frac{1}{3}(t_i - t_{i-1}) \right) \\ &\quad + (t_i - t_{i-1}) \left( 1 + (t_i - t_{i-1}) \left( \frac{\beta(\widehat{I}_i + v)}{N_i} + \mu \right) \right), \\ f_{i,j} &= f_{j,i} = \frac{1}{2}(t_i - t_{i-1})(t_j - t_{j-1}) \left( ((t_i - t_{i-1}) + 2(t_k - t_i)) \left( \left( \frac{\beta(\widehat{I}_j + v)}{N_j} + \mu \right) \left( \frac{\beta(\widehat{I}_i + v)}{N_i} + \mu \right) \right) \right. \\ &\quad \left. + \left( \frac{\beta(\widehat{I}_j + v)}{N_j} \right) \left( \frac{\beta(\widehat{I}_i + v)}{N_i} \right) \right) + 2 \left( \frac{\beta(\widehat{I}_j + v)}{N_j} + \mu \right). \end{aligned}$$

Furthermore, the vector  $A_s$  is given by

$$B_s = \begin{bmatrix} a_1 \\ a_2 \\ \vdots \\ a_{12} \\ b_1 \\ b_2 \\ \vdots \\ b_{12} \end{bmatrix}. \quad (\text{C.3})$$

Here the components of the vector equal

$$\begin{aligned} a_i &= (t_i - t_{i-1}) \left( \frac{1}{2}(t_i - t_{i-1})(\widehat{I}_i - I_0)\sigma + (\sigma + \mu)E_0 \right) + E_0 + \frac{1}{3}(t_i - t_{i-1})^2(\gamma + \delta + \mu)\sigma\widehat{I}_i \\ &\quad + (t_{12} - t_i)(\sigma + \mu)E_0 + \frac{1}{2}(t_i - t_{i-1})(\gamma + \delta + \mu)\sigma \sum_{j < i} (t_j - t_{j-1})\widehat{I}_j \\ &\quad + \sigma \sum_{s=i+1}^{12} (t_s - t_{s-1}) \left( (\widehat{I}_s - I_0) + \frac{1}{2}(t_s - t_{s-1})(\gamma + \delta + \mu)\widehat{I}_s \right) \\ &\quad + \sigma \sum_{s=1}^{12} (t_s - t_{s-1})(\gamma + \delta + \mu)\widehat{I}_s (t_{12} - t_{\max(i,s)}), \\ b_i &= (t_i - t_{i-1}) \left( \frac{1}{2}(t_i - t_{i-1}) \left( \left( \frac{\beta(\widehat{I}_i + v)}{N_i} + \mu \right) S_0 - \frac{\beta(\widehat{I}_i + v)}{N_i} E_0 \right) + S_0 + \frac{1}{2}(t_i - t_{i-1})\rho_i \right. \\ &\quad + \frac{1}{3}(t_i - t_{i-1})^2\rho_i \left( \frac{\beta(\widehat{I}_i + v)}{N_i} + \mu \right) + (t_{12} - t_i) \left( \left( \frac{\beta(\widehat{I}_i + v)}{N_i} + \mu \right) S_0 - \frac{\beta(\widehat{I}_i + v)}{N_i} E_0 \right) \\ &\quad + \left. \left( \frac{1}{2}(t_i - t_{i-1}) \left( \frac{\beta(\widehat{I}_i + v)}{N_i} + \mu \right) + 1 \right) \sum_{j < i} \rho_j (t_j - t_{j-1}) + \frac{1}{2} \left( \frac{\beta(\widehat{I}_i + v)}{N_i} + \mu \right) \sum_{s=i+1}^{12} \rho_s (t_s - t_{s-1})^2 \right. \\ &\quad + \left. \rho_i \sum_{s=1}^{12} (t_s - t_{s-1}) \left( \frac{\beta(\widehat{I}_s + v)}{N_s} + \mu \right) (t_{12} - t_{\max(i,s)}) \right). \end{aligned}$$

# Appendix D

## R code

Below one can find the R code that has been used in this thesis.

### D.1 Estimation

#### D.1.1 Matrix definition

```
#####  
##### DEFINITION Ap, Bp #####  
#####
```

```
Ap <- function(psi,t, v, mu, sigma, gamma, delta, rho, N, I,omega){  
  a = b = 0  
  psi<-c(omega[2], psi[1:11], omega[3], psi[12:22])  
  for (i in 1:12){  
    j=1  
    while(j<i) {  
      a <- a + 2 * (t[i+1]-t[i])^2 * ((I[i]+v)/N[i]) * psi[12+i] * (t[j  
        +1]-t[j]) * ((I[j]+v)/N[j]) * psi[12+j]  
      b <- b + (t[i+1]-t[i]) * (t[j+1]-t[j]) * ((I[j]+v)/N[j]) * psi[12+j]  
      j=j+1  
    }  
    k=1  
    while(k<i){  
      l=1  
      while(l<i){  
        a <- a + 2*(t[i+1]-t[i])*(t[k+1]-t[k])*(t[l+1]-t[l]) * ((I[k]+  
          v)/N[k]) * psi[12+k] * ((I[l]+v)/N[l]) * psi[12+l]  
        l=l+1  
      }  
      k=k+1  
    }  
  }  
  a <- a + (2/3) * (t[i+1]-t[i])^3 * ((I[i]+v)/N[i])^2 * psi[12+i]^2  
  b <- b + 0.5*(t[i+1]-t[i])^2*((I[i]+v)/N[i]) * psi[12+i]
```



```

}
c <- t[13] - t[1]
Ap <- matrix(c(a, b, -b, b, c, 0, -b, 0, c), nrow = 3)
return(Ap)
}

```

```

Bp <- function(psi, t, v, mu, sigma, gamma, delta, rho, N, I, omega){
  a = b = c = 0
  psi <- c(omega[2], psi[1:11], omega[3], psi[12:22])
  for (i in 1:12){
    j=1
    while(j<i) {
      a <- a + (t[i+1]-t[i]) * ((psi[i]-psi[12+i])*(t[j+1]-t[j]) * ((I[j]
        ]+v)/N[j])*psi[12+j] + 0.5*(t[i+1]-t[i])*(rho[i] - mu* psi
        [12+i] + (sigma + mu)*psi[i]) * (t[j+1]-t[j]) * ((I[j]+v)/N[j]
        ])*psi[12+j] + 0.5*(t[j+1]-t[j])*(rho[j] - mu* psi[12+j] +
        (sigma + mu)*psi[j]) * (t[i+1]-t[i]) * ((I[i]+v)/N[i])*psi[12+
        i])
      b <- b + (t[i+1]-t[i]) * ((t[j+1]-t[j])*(sigma + mu)*psi[j])
      c <- c - (t[i+1]-t[i]) * ((t[j+1]-t[j])*(rho[j] - mu* psi[12+j]))
      j=j+1
    }
    k=1
    while(k<i){
      l=1
      while(l<i){
        a <- a + (t[i+1]-t[i])*(t[k+1]-t[k])*(t[l+1]-t[l])*(rho[l]-mu*
          psi[12+l]+(sigma+mu)*psi[l]) * ((I[k]+v)/N[k])*psi[12+k]
        l=l+1
      }
      k=k+1
    }
    a <- a + (t[i+1]-t[i])^2 * (0.5*(psi[i]-psi[12+i]) * ((I[i]+v)/N[i]) *
      psi[12+i] + (rho[i] - mu*psi[12+i] + (sigma + mu)*psi[i])
      *(1/3)*(t[i+1]-t[i]) * ((I[i]+v)/N[i])*psi[12+i])
    b <- b + (t[i+1]-t[i]) * (psi[i] + 0.5*(t[i+1]-t[i])*(sigma + mu)
      )*psi[i])
    c <- c + (t[i+1]-t[i]) * (psi[12+i] - 0.5*(t[i+1]-t[i])*(rho[i] -
      mu*psi[12+i]))
  }
  Bp <- rbind(a, b, c)
  return(Bp)
}

```

```

#####
##### DEFINITION As, Bs #####
#####

```

```

As <- function(omega, t, v, mu, sigma, gamma, delta, rho, N, I){

```

```

omega<-c(omega[1], I[1], omega[2:3])
a = b = c = d = matrix(0, nrow = 12, ncol = 12)
for (i in 1:12){
  j=1
  while(j<i) {
    a[j, i] <- a[i, j] <- 0.5*(t[j+1]-t[j]) *((t[i+1]-t[i])^2 *(sigma
      ^2+ (sigma + mu)^2) + 2*(t[i+1]-t[i])*(sigma + mu) + 2*(t[i
      +1]-t[i])*(t[13]-t[i+1])*(sigma^2 +(sigma+mu)^2)) #b(i, j)
    b[j, i] <- c[i, j] <- -0.5*(t[j+1]-t[j]) *(t[i+1]-t[i])*(omega
      [1]*(I[i]+v)/N[i])*(sigma + mu)*((t[i+1]-t[i]) + 2*(t[13]-t[
      i+1])) #d(i, j)
    b[i, j] <- c[j, i] <- -0.5*(t[j+1]-t[j]) *(t[i+1]-t[i])*(omega
      [1]*(I[j]+v)/N[j])*((t[i+1]-t[i])*(sigma + mu) + 2 + 2*(t
      [13]-t[i+1])*(sigma+mu)) #x(i, j)
    d[j, i] <- d[i, j] <- 0.5*(t[j+1]-t[j]) *(t[i+1]-t[i]) *((t[i+1]-t
      [i])*((omega[1]*(I[i]+v)/N[i]) + mu)*((omega[1]*(I[j]+v)/N[
      j]) + mu) + (omega[1]*(I[i]+v)/N[i])*(omega[1]*(I[j]+v)/N[j
      ])) + 2*((omega[1]*(I[j]+v)/N[j]) + mu) + 2*(t[13]-t[i+1])
      *((omega[1]*(I[i]+v)/N[i])*(omega[1]*(I[j]+v)/N[j]) + (omega
      [1]*(I[i]+v)/N[i]) + mu)*((omega[1]*(I[j]+v)/N[j]) + mu)) #f
      (i, j)
    j=j+1
  }
  a[i, i] <- (t[i+1]-t[i])^2 *((sigma^2 + (sigma + mu)^2)*((t[13]-t[i
    +1]) + (1/3)*(t[i+1]-t[i])) + (sigma + mu)) + (t[i+1]-t[i]) #a
    (i)
  b[i, i] <- c[i, i] <- -0.5*(t[i+1]-t[i])^2 *(omega[1]*(I[i]+v)/N[i])
    *(1 + (2/3)*(t[i+1]-t[i])*(sigma + mu) + 2*(sigma + mu)*(t
    [13]-t[i+1])) #c(i)
  d[i, i] <- (t[i+1]-t[i])^2 *((omega[1]*(I[i]+v)/N[i])^2 + ((omega
    [1]*(I[i]+v)/N[i]) + mu)^2)*((t[13]-t[i+1]) + (1/3)*(t[i+1]-t[
    i])) + (t[i+1]-t[i])*(1 + (t[i+1]-t[i])*((omega[1]*(I[i]+v)/N[
    i]) + mu)) #e(i)
}
As <- rbind(cbind(a, b), cbind(c, d))
As<-As[-c(1,13),-c(1,13)]
return(As)
}

```

```

Bs <- function(omega, t, v, mu, sigma, gamma, delta, rho, N, I){
omega<-c(omega[1], I[1], omega[2:3])
a = b = matrix(0, nrow = 12, ncol = 1)
for (i in 1:12){
  a[i] <- (t[i+1]-t[i]) *(0.5*(t[i+1]-t[i])*((I[i]- omega[2])*sigma
    + (sigma + mu)*omega[3])+ omega[3] + (1/3)*(t[i+1]-t[i])^2 * (
    gamma + delta + mu)*sigma*I[i])
  b[i] <- (t[i+1]-t[i]) *(0.5*(t[i+1]-t[i])*((omega[1]*(I[i]+v)/N[i]
    + mu)*omega[4] - (omega[1]*(I[i]+v)/N[i])*omega[3]) + omega
    [4] + 0.5*(t[i+1]-t[i])*rho[i] + (1/3)*(t[i+1]-t[i])^2*rho[i
    ]*(omega[1]*(I[i]+v)/N[i] + mu) + (t[13]-t[i+1])*((omega[1]*(I
    [i]+v)/N[i] + mu)*omega[4] - (omega[1]*(I[i]+v)/N[i])* omega

```

```

    [3]))
  j=1
  while(j<i){
    a[i] <- a[i] + 0.5*(t[i+1]-t[i])^2*(gamma + delta + mu)*sigma *
      (t[j+1]-t[j])*I[j]
    b[i] <- b[i] + (t[i+1]-t[i])*(0.5*(t[i+1]-t[i])*(omega[1]*(I[i]+
      v)/N[i] + mu) + 1)*rho[j]*(t[j+1]-t[j])
    j=j+1
  }
  s=i+1
  while(s<=12){
    a[i] <- a[i] + (t[i+1]-t[i])*(t[s+1]-t[s])*((sigma + mu)*omega
      [3] + sigma*(I[s] - omega[2])) + 0.5*(t[s+1]-t[s])*sigma*(
      gamma + delta + mu)*I[s]
    b[i] <- b[i] + 0.5*(t[i+1]-t[i])*(omega[1]*(I[i]+v)/N[i] + mu)*
      rho[s]*(t[s+1]-t[s])^2
    s=s+1
  }
  s=1
  while(s<=12){
    a[i] <- a[i] + (t[i+1]-t[i])*sigma* (t[s+1]-t[s])* (gamma +
      delta + mu)*I[s] *(t[13]-t[max(i,s)+1])
    b[i] <- b[i] + (t[i+1]-t[i])*rho[i]*(t[s+1]-t[s])*(omega[1]*(I[s]
      ]+v)/N[s] + mu)*(t[13]-t[max(i,s)+1])
    s=s+1
  }
}
Bs <- rbind(a,b)
Bs <- Bs[-c(1,13)]
return(Bs)
}

```

### D.1.2 Optimization

```

library("gmp")

opt <- function(it, year){

#####
##### PARAMETERS #####
#####

  t <- seq(from=0, to=1, by=1/12)

  v <- 10/12
  mu <- 1/(70.18*12)
  sigma <- 365/(12 * 7.5)
  gamma <- 365/(12 * 6.5)

```

```

measles <- Data_measles[which(Data_measles$year >= ((year-1)
  *10000+6666) & Data_measles$year < (year*10000+6666)),]
delta <- Data_dis_death[which(Data_dis_death$year == year),]
  $count/(12 * sum(measles$count))
rho <- as.matrix(cbind(Data_birth[which(Data_birth$year == year
  -5),c(11:14)], Data_birth[which(Data_birth$year == year-4),c
  (3:10)]))

pop.0 <- sum(Data_pop[which(Data_pop$year == year-1),]$popcount
  )
pop <- sum(Data_pop[which(Data_pop$year == year),]$popcount)
N <- matrix(0, nrow = 12, ncol = 1)
for (i in 1:12){
  N[i] <- pop.0 + 0.5*(t[i+1]+t[i]-2*t[1])*(pop - pop.0)/(t
    [13]- t[1])
}

I <- matrix(0, nrow = 12, ncol = 1)
for (i in 1:12){
  I[i] <- sum(measles[which(measles$year >= ((year-1 + (i-1)
    /12)*10000+6666) & measles$year < ((year-1 + (i)/12)
    *10000+6666)),]$count)/length(measles[which(measles$year
    >= ((year-1 + (i-1)/12)*10000+6666) & measles$year < ((
    year-1 + (i)/12)*10000+6666)),]$count)
}

epsilon <- cbind(runif (12, 0,0.1*10^5))
eta <- cbind(runif (12, 0,0.1*10^7))
psi <- matrix(c(epsilon , eta),nrow=1)

omega<-c(0, psi [1] , psi [13])
psi <- psi[-c(1,13)]
S0 <- c(4.5*10^6, 4.6*10^6)

#####
##### OPTIMALIZATION #####
#####

fig <- matrix(0, nrow = 3+22, ncol = it -1)
k=1
while(k<it){

```

```

omega <- asNumeric(solve.bigq(as.bigq(Ap(psi, t, v, mu, sigma
, gamma, delta, rho, N, I, omega)), Bp(psi, t, v, mu, sigma,
gamma, delta, rho, N, I, omega)))
omega[3] <- S0[year%%2 + 1]

psi <- asNumeric(solve.bigq(as.bigq(As(omega, t, v, mu, sigma,
gamma, delta, rho, N, I)), Bs(omega, t, v, mu, sigma, gamma
, delta, rho, N, I)))

fig[,k] <- rbind(omega, psi)
rownames(fig) <- c("beta", "E0", "S0", "e1", "e2", "e3", "e4",
"e5", "e6", "e7", "e8", "e9", "e10", "e11", "S1", "s2",
"s3", "s4", "s5", "s6", "s7", "s8", "s9", "s10", "s11")

k=k+1
}
return(t(fig))
}

```

## D.2 Simulation

```

library(deSolve)
sim <- function(it, year){
#####
##### SEIR MODEL #####
#####
seir <- function(times, y, paras){
S <- y[1]
E <- y[2]
I <- y[3]
with(as.list(c(y, paras)), {
dS <- rho - (beta * (I + v)/N + mu)* S
dE <- (beta * (I + v)/N)*S - (sigma + mu) * E
dI <- sigma * E - (gamma + delta + mu) * I
result <- c(dS, dE, dI)
return(list(result))
})
}
#####
##### PARAMETERS #####
#####

v <- 10/12

```

```

mu <- 1/(12 *70.18)
sigma <- 365/(12 * 7.5)
gamma <- 365/(12 * 6.5)

measles <- Data_measles[which(Data_measles$year >= ((year-1)
*10000+6666) & Data_measles$year < (year*10000+6666)),]
delta <- Data_dis_death[which(Data_dis_death$year == year),]
$count/(12 * sum(measles$count))
rho <- as.matrix(cbind(Data_birth[which(Data_birth$year == year
-5),c(11:14)], Data_birth[which(Data_birth$year == year-4),c
(3:10)]))
rho <- mean(rho)

N <- sum(Data_pop[which(Data_pop$year == year-1),]$popcount)
I <- sum(measles[which(measles$year >= ((year-1)*10000+6666) &
measles$year < ((year-1 + 1/12)*10000+6666)),]$count)/length
(measles[which(measles$year >= ((year-1)*10000+6666) &
measles$year < ((year-1 + 1/12)*10000+6666)),]$count)

beta <- fig[it-1,1]
S.sim <- fig[it-1,3]
E.sim <- fig[it-1,2]
I.sim <- I
x.sim <- c(S.sim, E.sim, I.sim)
times <- seq(0,1, by = 1/52)
paras <- c(rho, beta, v, sigma, gamma, delta, N)

#####
##### SIMULATION #####
#####

out <- as.data.frame(lsoda(y = x.sim, times = times, func =
seir, parms = paras))
colnames(out) <- c("time", "S", "E", "I")
return(out)
}

```

## Appendix E

# The dynamic equilibrium

For  $x^* = (S^*, E^*, I^*)$  to be an equilibrium we need that  $f(x^*) = 0$ . In other words, it is necessary to find  $S^*, E^*$ , and  $I^*$ , such that our model equals zero. Let the right side of each of the three differential equations in system (2.5) equal zero, keeping in mind that the visitors impact  $v = 0$ , and obtain the following equations

$$\begin{cases} \rho - (\beta I + \mu)S & = 0, \\ \beta IS - (\sigma + \mu)E & = 0, \\ \sigma E - (\gamma + \mu + \delta)I & = 0. \end{cases}$$

Rewriting the third equation for  $E$  and implementing it in the second equation gives us

$$\begin{cases} \rho - (\beta I + \mu)S & = 0, \\ \beta IS - (\sigma + \mu)\frac{(\gamma + \mu + \delta)I}{\sigma} & = 0, \\ \frac{(\gamma + \mu + \delta)I}{\sigma} & = E. \end{cases} \quad (\text{E.1})$$

From the second equation it can be seen that

$$\left( \beta S - \frac{(\sigma + \mu)(\gamma + \mu + \delta)}{\sigma} \right) I = 0,$$

Thus either  $I^* = 0$ , which simply matches the disease-free equilibrium, or

$$\begin{aligned} S^* &= \frac{(\sigma + \mu)(\gamma + \delta + \mu)}{\beta\sigma} \\ &= \frac{\rho}{\mu R_0}. \end{aligned}$$

Implementing this in the first differential equation yields

$$\rho - (\beta I + \mu)\frac{\rho}{\mu R_0} = 0.$$

From which one can conclude that

$$I^* = \frac{\mu R_0 - \mu}{\beta}.$$

Implementing this  $I^*$  in the third equation of (E.1) makes it is clear that an equilibrium is found by

$$\begin{aligned} S^* &= \frac{\rho}{\mu R_0}, \\ E^* &= \frac{(\gamma + \delta + \mu)(R_0 - 1)\mu}{\beta\sigma}, \\ I^* &= \frac{\mu(R_0 - 1)}{\beta}. \end{aligned}$$



# Appendix F

## Routh table

Consider the following Routh Table.

$\lambda^3$	1	$a_2$	0
$\lambda^2$	$a_1$	$a_3$	0
$\lambda^1$	$s_1$	0	0
$\lambda^0$	$a_3$	0	0

where

$$\begin{aligned}
 a_1 &= \gamma + \delta + 2\mu + \mu R_0 + \sigma, \\
 a_2 &= \mu R_0(\sigma + 2\mu + \gamma + \delta) + (\sigma + \mu)(\gamma + \delta + \mu) - \frac{\beta\rho\sigma}{\mu R_0}, \\
 a_3 &= \mu R_0(\sigma + \mu)(\gamma + \delta + \mu) - \frac{\beta\rho\sigma}{R_0}, \\
 s_1 &= \frac{a_1 a_2 - a_3}{a_1}.
 \end{aligned}$$

By showing that the first column of the Routh table is positive, it is proven that the eigenvalues of (6.6) have negative real parts.

Since 1 and  $a_1$  are both positive, it suffices to show that  $s_1$  and  $a_3$  are both positive. We will start with proving  $a_3 > 0$ . Assume this is not true, then

$$\begin{aligned}
 a_3 &= \mu R_0(\sigma + \mu)(\gamma + \delta + \mu) - \frac{\beta\rho\sigma}{R_0} \leq 0 \\
 \mu R_0(\sigma + \mu)(\gamma + \delta + \mu) &\leq \frac{\beta\rho\sigma}{R_0}.
 \end{aligned}$$

Which is equal to

$$\frac{\mu R_0^2(\sigma + \mu)(\gamma + \delta + \mu)}{\beta\rho\sigma} \leq 1.$$

Or, when applying the definition of  $R_0$

$$\begin{aligned}
 \frac{R_0^2}{R_0} &\leq 1, \\
 R_0 &\leq 1.
 \end{aligned}$$

This leads to a contradiction, thus  $a_3$  is positive, if  $R_0 > 1$ .

Now, it is left to show that  $s_1 > 0$ , or, equivalently

$$a_1 a_2 > a_3. \quad (\text{F.1})$$

From (6.7) we get,

$$\begin{aligned} a_1 a_2 &= (\gamma + \delta + 2\mu + \mu R_0 + \sigma)(\mu R_0(\sigma + 2\mu + \gamma + \delta) + (\sigma + \mu)(\gamma + \delta + \mu) - \frac{\beta \rho \sigma}{\mu R_0}), \\ &= \underbrace{\mu R_0(\sigma + \mu)(\gamma + \delta + \mu) - \frac{\beta \rho \sigma}{R_0}}_{=a_3} + (\gamma + \delta + 2\mu + \sigma)(\sigma + \mu)(\gamma + \delta + \mu) + \\ &\quad (\gamma + \delta + 2\mu + \mu R_0 + \sigma)(\mu R_0(\sigma + 2\mu + \gamma + \delta)) - (\gamma + \delta + \mu + \mu R_0 + \sigma) \frac{\beta \rho \sigma}{\mu R_0}. \end{aligned}$$

Thus,  $a_1 a_2 = a_3 + r$ , where  $r$  denotes the residual term of the above equation. Showing that  $r > 0$  will proof that  $s_1 > 0$ . Let us assume  $r \leq 0$ , then

$$\begin{aligned} &(\gamma + \delta + 2\mu + \sigma)(\sigma + \mu)(\gamma + \delta + \mu) + (\gamma + \delta + 2\mu + \mu R_0 + \sigma)(\mu R_0(\sigma + 2\mu + \gamma + \delta)) \\ &\leq (\gamma + \delta + \mu + \mu R_0 + \sigma) \frac{\beta \rho \sigma}{\mu R_0}. \end{aligned}$$

Which is equal to stating

$$\begin{aligned} &(\gamma + \delta + 2\mu + \sigma)(\sigma + \mu)(\gamma + \delta + \mu) \frac{\mu R_0}{\beta \rho \sigma} + (\gamma + \delta + 2\mu + \mu R_0 + \sigma)(\sigma + 2\mu + \gamma + \delta) \frac{\mu^2 R_0^2}{\beta \rho \sigma} \\ &\leq \gamma + \delta + \mu + \mu R_0 + \sigma. \end{aligned}$$

The equation is expanded, after which the definition of  $R_0$  is implemented to get

$$\begin{aligned} &(\gamma + \delta + 2\mu + \sigma) \frac{R_0}{R_0} + 2 \frac{\mu R_0^2}{R_0} + ((\gamma + \delta + \mu)^2 + (\sigma + \mu)^2) \frac{\mu^2 R_0^2}{\beta \rho \sigma} \\ &\quad + (\sigma + 2\mu + \gamma + \delta) \frac{\mu^3 R_0^3}{\beta \rho \sigma} \leq \gamma + \delta + \mu + \mu R_0 + \sigma. \end{aligned}$$

Equivalently,

$$\mu + 2\mu R_0 + ((\gamma + \delta + \mu)^2 + (\sigma + \mu)^2) \frac{\mu^2 R_0^2}{\beta \rho \sigma} + (\sigma + 2\mu + \gamma + \delta) \frac{\mu^3 R_0^3}{\beta \rho \sigma} \leq \mu R_0.$$

By division through  $\mu R_0$  one easily gets

$$\frac{1}{R_0} + 2 + ((\gamma + \delta + \mu)^2 + (\sigma + \mu)^2) \frac{\mu R_0}{\beta \rho \sigma} + (\sigma + 2\mu + \gamma + \delta) \frac{\mu^2 R_0^2}{\beta \rho \sigma} \leq 1,$$

and subsequently,

$$\frac{1}{R_0} + ((\gamma + \delta + \mu)^2 + (\sigma + \mu)^2) \frac{\mu R_0}{\beta \rho \sigma} + (\sigma + 2\mu + \gamma + \delta) \frac{\mu^2 R_0^2}{\beta \rho \sigma} \leq -1.$$

However, since  $R_0 > 1$  and all the model parameters are positive, this leads to a contradiction. Thus,  $r > 0$ .

Hence, it is clear that the inequality (F.1) holds. Therefore, all the signs of the first column of the Routh Table 6.1 are positive, there are no sign changes, and consequently there are no poles of the characteristic equation in the right hand plane.

## Appendix G

# The dynamic equilibrium when $v \neq 0$

With the use of Matlab, an endemic equilibrium point for the model described in (2.5) is found. It is of the form  $x_{e^*} = (S_{e^*}^*, E_{e^*}^*, I_{e^*}^*)$ , where the components are given by

$$S_{e^*}^* = \frac{(\sigma + \mu)(\delta + \gamma + \mu)}{2\gamma\sigma(\beta\mu^3 + \beta\sigma\mu^2 + \beta\delta\mu^2 + \beta\gamma\mu^2 + \beta\delta\sigma\mu + \beta\gamma\sigma\mu) \left( \gamma\mu^3 - \gamma(\beta^2\delta^2\sigma^2v^2 + 2\beta^2\delta^2\sigma\mu v^2 + \beta^2\delta^2\mu^2v^2 + 2\beta^2\delta\gamma\sigma^2v^2 + 4\beta^2\delta\gamma\sigma\mu v^2 + 2\beta^2\delta\gamma\mu^2v^2 + 2\beta^2\delta\rho\sigma^2v + 2\beta^2\delta\rho\sigma\mu v + 2\beta^2\delta\sigma^2\mu v^2 + 4\beta^2\delta\sigma\mu^2v^2 + 2\beta^2\delta\mu^3v^2 + \beta^2\gamma^2\sigma^2v^2 + 2\beta^2\gamma^2\sigma\mu v^2 + \beta^2\gamma^2\mu^2v^2 + 2\beta^2\gamma\rho\sigma^2v + 2\beta^2\gamma\rho\sigma\mu v + 2\beta^2\gamma\sigma^2\mu v^2 + 4\beta^2\gamma\sigma\mu^2v^2 + 2\beta^2\gamma\mu^3v^2 + \beta^2\rho^2\sigma^2 + 2\beta^2\rho\sigma^2\mu v + 2\beta^2\rho\sigma\mu^2v + \beta^2\sigma^2\mu^2v^2 + 2\beta^2\sigma\mu^3v^2 + \beta^2\mu^4v^2 + 2\beta\delta^2\sigma^2\mu v + 4\beta\delta^2\sigma\mu^2v + 2\beta\delta^2\mu^3v + 4\beta\delta\gamma\sigma^2\mu v + 8\beta\delta\gamma\sigma\mu^2v + 4\beta\delta\gamma\mu^3v - 2\beta\delta\rho\sigma^2\mu - 2\beta\delta\rho\sigma\mu^2 + 4\beta\delta\sigma^2\mu^2v + 8\beta\delta\sigma\mu^3v + 4\beta\delta\mu^4v + 2\beta\gamma^2\sigma^2\mu v + 4\beta\gamma^2\sigma\mu^2v + 2\beta\gamma^2\mu^3v - 2\beta\gamma\rho\sigma^2\mu - 2\beta\gamma\rho\sigma\mu^2 + 4\beta\gamma\sigma^2\mu^2v + 8\beta\gamma\sigma\mu^3v + 4\beta\gamma\mu^4v - 2\beta\rho\sigma^2\mu^2 - 2\beta\rho\sigma\mu^3 + 2\beta\sigma^2\mu^3v + 4\beta\sigma\mu^4v + 2\beta\mu^5v + \delta^2\sigma^2\mu^2 + 2\delta^2\sigma\mu^3 + \delta^2\mu^4 + 2\delta\gamma\sigma^2\mu^2 + 4\delta\gamma\sigma\mu^3 + 2\delta\gamma\mu^4 + 2\delta\sigma^2\mu^3 + 4\delta\sigma\mu^4 + 2\delta\mu^5 + \gamma^2\sigma^2\mu^2 + 2\gamma^2\sigma\mu^3 + \gamma^2\mu^4 + 2\gamma\sigma^2\mu^3 + 4\gamma\sigma\mu^4 + 2\gamma\mu^5 + \sigma^2\mu^4 + 2\sigma\mu^5 + \mu^6 \right)^{\frac{1}{2}} + \gamma^2\mu^2 + \gamma\sigma\mu^2 + \gamma^2\sigma\mu + \delta\gamma\mu^2 - \beta\gamma\rho\sigma + \delta\gamma\sigma\mu + \beta\gamma^2\sigma v + \beta\gamma\mu^2v + \beta\gamma^2\mu v + \beta\delta\gamma\sigma v + \beta\delta\gamma\mu v + \beta\gamma\sigma\mu v \right) + \frac{\rho}{\mu},$$

$$\begin{aligned}
E_e^* = & -\frac{\mu(\delta + \gamma + \mu)}{2\gamma\sigma(\beta\mu^3 + \beta\sigma\mu^2 + \beta\delta\mu^2 + \beta\gamma\mu^2 + \beta\delta\sigma\mu + \beta\gamma\sigma\mu)} \left( \gamma\mu^3 + \gamma(\beta^2\delta^2\sigma^2v^2 + 2\beta^2\delta^2\sigma\mu v^2 \right. \\
& + \beta^2\delta^2\mu^2v^2 + 2\beta^2\delta\gamma\sigma^2v^2 + 4\beta^2\delta\gamma\sigma\mu v^2 + 2\beta^2\delta\gamma\mu^2v^2 + 2\beta^2\delta\rho\sigma^2v + 2\beta^2\delta\rho\sigma\mu v \\
& + 2\beta^2\delta\sigma^2\mu v^2 + 4\beta^2\delta\sigma\mu^2v^2 + 2\beta^2\delta\mu^3v^2 + \beta^2\gamma^2\sigma^2v^2 + 2\beta^2\gamma^2\sigma\mu v^2 + \beta^2\gamma^2\mu^2v^2 \\
& + 2\beta^2\gamma\rho\sigma^2v + 2\beta^2\gamma\rho\sigma\mu v + 2\beta^2\gamma\sigma^2\mu v^2 + 4\beta^2\gamma\sigma\mu^2v^2 + 2\beta^2\gamma\mu^3v^2 + \beta^2\rho^2\sigma^2 \\
& + 2\beta^2\rho\sigma^2\mu v + 2\beta^2\rho\sigma\mu^2v + \beta^2\sigma^2\mu^2v^2 + 2\beta^2\sigma\mu^3v^2 + \beta^2\mu^4v^2 + 2\beta\delta^2\sigma^2\mu v + 4\beta\delta^2\sigma\mu^2v \\
& + 2\beta\delta^2\mu^3v + 4\beta\delta\gamma\sigma^2\mu v + 8\beta\delta\gamma\sigma\mu^2v + 4\beta\delta\gamma\mu^3v - 2\beta\delta\rho\sigma^2\mu - 2\beta\delta\rho\sigma\mu^2 + 4\beta\delta\sigma^2\mu^2v \\
& + 8\beta\delta\sigma\mu^3v + 4\beta\delta\mu^4v + 2\beta\gamma^2\sigma^2\mu v + 4\beta\gamma^2\sigma\mu^2v + 2\beta\gamma^2\mu^3v - 2\beta\gamma\rho\sigma^2\mu - 2\beta\gamma\rho\sigma\mu^2 \\
& + 4\beta\gamma\sigma^2\mu^2v + 8\beta\gamma\sigma\mu^3v + 4\beta\gamma\mu^4v - 2\beta\rho\sigma^2\mu^2 - 2\beta\rho\sigma\mu^3 + 2\beta\sigma^2\mu^3v + 4\beta\sigma\mu^4v \\
& + 2\beta\mu^5v + \delta^2\sigma^2\mu^2 + 2\delta^2\sigma\mu^3 + \delta^2\mu^4 + 2\delta\gamma\sigma^2\mu^2 + 4\delta\gamma\sigma\mu^3 + 2\delta\gamma\mu^4 + 2\delta\sigma^2\mu^3 + 4\delta\sigma\mu^4 \\
& + 2\delta\mu^5 + \gamma^2\sigma^2\mu^2 + 2\gamma^2\sigma\mu^3 + \gamma^2\mu^4 + 2\gamma\sigma^2\mu^3 + 4\gamma\sigma\mu^4 + 2\gamma\mu^5 + \sigma^2\mu^4 + 2\sigma\mu^5 + \mu^6 \Big)^{\frac{1}{2}} \\
& + \gamma^2\mu^2 + \gamma\sigma\mu^2 + \gamma^2\sigma\mu + \delta\gamma\mu^2 - \beta\gamma\rho\sigma + \delta\gamma\sigma\mu + \beta\gamma^2\sigma v + \beta\gamma\mu^2v + \beta\gamma^2\mu v + \beta\delta\gamma\sigma v \\
& \left. + \beta\delta\gamma\mu v + \beta\gamma\sigma\mu v \right)
\end{aligned}$$

and

$$\begin{aligned}
I_e^* = & -\frac{\mu}{2\gamma(\beta\mu^3 + \beta\sigma\mu^2 + \beta\delta\mu^2 + \beta\gamma\mu^2 + \beta\delta\sigma\mu + \beta\gamma\sigma\mu)} \left( \gamma\mu^3 + \gamma(\beta^2\delta^2\sigma^2v^2 + 2\beta^2\delta^2\sigma\mu v^2 \right. \\
& + \beta^2\delta^2\mu^2v^2 + 2\beta^2\delta\gamma\sigma^2v^2 + 4\beta^2\delta\gamma\sigma\mu v^2 + 2\beta^2\delta\gamma\mu^2v^2 + 2\beta^2\delta\rho\sigma^2v + 2\beta^2\delta\rho\sigma\mu v \\
& + 2\beta^2\delta\sigma^2\mu v^2 + 4\beta^2\delta\sigma\mu^2v^2 + 2\beta^2\delta\mu^3v^2 + \beta^2\gamma^2\sigma^2v^2 + 2\beta^2\gamma^2\sigma\mu v^2 + \beta^2\gamma^2\mu^2v^2 \\
& + 2\beta^2\gamma\rho\sigma^2v + 2\beta^2\gamma\rho\sigma\mu v + 2\beta^2\gamma\sigma^2\mu v^2 + 4\beta^2\gamma\sigma\mu^2v^2 + 2\beta^2\gamma\mu^3v^2 + \beta^2\rho^2\sigma^2 \\
& + 2\beta^2\rho\sigma^2\mu v + 2\beta^2\rho\sigma\mu^2v + \beta^2\sigma^2\mu^2v^2 + 2\beta^2\sigma\mu^3v^2 + \beta^2\mu^4v^2 + 2\beta\delta^2\sigma^2\mu v + 4\beta\delta^2\sigma\mu^2v \\
& + 2\beta\delta^2\mu^3v + 4\beta\delta\gamma\sigma^2\mu v + 8\beta\delta\gamma\sigma\mu^2v + 4\beta\delta\gamma\mu^3v - 2\beta\delta\rho\sigma^2\mu - 2\beta\delta\rho\sigma\mu^2 + 4\beta\delta\sigma^2\mu^2v \\
& + 8\beta\delta\sigma\mu^3v + 4\beta\delta\mu^4v + 2\beta\gamma^2\sigma^2\mu v + 4\beta\gamma^2\sigma\mu^2v + 2\beta\gamma^2\mu^3v - 2\beta\gamma\rho\sigma^2\mu - 2\beta\gamma\rho\sigma\mu^2 \\
& + 4\beta\gamma\sigma^2\mu^2v + 8\beta\gamma\sigma\mu^3v + 4\beta\gamma\mu^4v - 2\beta\rho\sigma^2\mu^2 - 2\beta\rho\sigma\mu^3 + 2\beta\sigma^2\mu^3v + 4\beta\sigma\mu^4v \\
& + 2\beta\mu^5v + \delta^2\sigma^2\mu^2 + 2\delta^2\sigma\mu^3 + \delta^2\mu^4 + 2\delta\gamma\sigma^2\mu^2 + 4\delta\gamma\sigma\mu^3 + 2\delta\gamma\mu^4 + 2\delta\sigma^2\mu^3 + 4\delta\sigma\mu^4 \\
& + 2\delta\mu^5 + \gamma^2\sigma^2\mu^2 + 2\gamma^2\sigma\mu^3 + \gamma^2\mu^4 + 2\gamma\sigma^2\mu^3 + 4\gamma\sigma\mu^4 + 2\gamma\mu^5 + \sigma^2\mu^4 + 2\sigma\mu^5 + \mu^6 \Big)^{\frac{1}{2}} \\
& + \gamma^2\mu^2 + \gamma\sigma\mu^2 + \gamma^2\sigma\mu + \delta\gamma\mu^2 - \beta\gamma\rho\sigma + \delta\gamma\sigma\mu + \beta\gamma^2\sigma v + \beta\gamma\mu^2v + \beta\gamma^2\mu v + \beta\delta\gamma\sigma v \\
& \left. + \beta\delta\gamma\mu v + \beta\gamma\sigma\mu v \right).
\end{aligned}$$