Mathematische Modelle für die Ausbreitung von Infektionskrankheiten

Mathematical Models for the Spread of Infectious Diseases

Vorwissenschaftliche Arbeit verfasst von

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Abstract

Diese Arbeit befasst sich mit der mathematischen Modellierung der Ausbreitung von Infektionskrankheiten. Infektionskrankheiten sind Krankheiten, die von Erregern verursacht werden und sich von Individuum zu Individuum verbreiten können. Laut der Weltgesundheitsorganisation (WHO) sind 23% aller Todesfälle des Jahres 2012 auf Infektionskrankheiten zurückzuführen. Das Modellieren von Infektionskrankheiten ist Teil der Epidemiolgie. Gewonnene Informationen können verwendet werden, um Epidemien vorherzusagen und Gegenmaßnahmen zu evaluieren.

Zuerst wird das SIR Modell vorgestellt. Dabei wird die Population in drei Gruppen aufgeteilt: die Gesunden, die Infizierten und die nicht mehr Infizierten. Die nicht mehr Infizerten sind Individuen, die verstorben oder gesund und dadurch immun geworden sind. Das SIR Modell beschreibt, wie sich die Größe dieser Gruppen über die Zeit verändert. Danach werden zwei Variationen des Modells beschrieben. Die erste Variation erlaubt die Modellierung von Inkubationszeiten, indem zum Beispiel die Infektionsrate davon abhängt, wie lange ein Individuum schon krank ist. Dieses Modell wird daraufhin zur Simulation einer Masern-Epidemie verwendet. Diese Simulation basiert auf Daten der WHO. Die zweite Variation des SIR Modells inkludiert Geburts- und Sterbeprozesse. Für die betrachteten Modelle werden die Gleichgewichte und deren Stabilität berechnet. Die Modelle werden mit der Programmiersprache R durch Differnzengleichungen berechnet.

Preface

When I was looking for a topic for my VWA I just happened to be reading the book "Games of Life" by Karl Sigmund. It is a book discussing some aspects of mathematical modelling of biology (biomathematics). Intrigued by the book and being interested in biology and mathematics, I went to a mathematics teacher discussing possible VWA topics in the broad field of biomathematics. I narrowed down the topic to the modelling of infectious diseases. After I found some literature on the topic, I programmed simple simulations and ultimately decided to choose the topic.

I want to thank all people who supported me during the writing of my VWA. Especially I want to thank Professor Glantschnig for supervising my VWA, reviewing the manuscript and for many helpful suggestions and my father for always being open to answer any of the questions concerning the mathematics. For reading and reviewing my paper I want to thank my mother, my grandparents and my sister. Thanks for the great support.

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Essentially, all models are wrong,
but some are useful

George E. P. Box (1919-2013)

1. Introduction

In 2012 23% of all deaths worldwide were caused by infectious diseases (*WHO | The top 10 causes of death*, n.d.). Infectious diseases are diseases caused by pathogens that are spread from individual to individual. The pathogens are microorganisms such as, for example, bacteria, viruses, fungi and parasites. Recovery from disease caused by certain pathogens results in permanent immunity to the diseases (Palm & Medzhitov, 2009).

Modelling the spread of infectious diseases is part of the field of epidemiology. The World Health Organization (WHO) defines epidemiology as "...the study of the distribution and determinants of health-related states or events (including disease), and the application of this study to the control of diseases and other health problems." (*WHO | Epidemiology*, n.d.).

Multiple models have been derived to simulate the spread of infectious diseases. In agent-based models, every single individual and its interactions are simulated. Compartment models on the other hand only consider the amount of, for example, healthy, infected and recovered individuals. Furthermore, the models can be divided into stochastic and deterministic models. Deterministic models have a unique solution for a specific set of parameters, while stochastic models include at least one random variable. Models can be of differing complexity, some include vital dynamics as birth and death rates (Hethcote, 1976), public health interventions (Riley et al., 2003), vaccination programs (Shulgin, Stone, & Agur, 1998) and seasonal changes (Stone, Olinky, & Huppert, 2007).

Information gained by the modelling of the spread of infectious diseases is used to predict epidemics and pandemics (Fraser et al., 2009; Legrand, Grais, Boelle, Valleron, & Flahault, 2007) and to evaluate tactics to prevent or stop epidemics and pandemics, for example with vaccination programs (Shulgin et al., 1998; Bernoulli & Blower, 2004) or with public health interventions (Riley et al., 2003).

The remainder of this paper is structured as follows: In Section 2, a classical, basic dynamic model and two of its variations are introduced. With one of these models a measles is simulated. In the third section, equilibria are calculated for the models and their stability is analyzed. In the fourth section, numerical examples for the

models are given. The paper finishes with a discussion. Programs used for the computations are written in the programming language R (R Core Team, 2015) and are included in the appendix. Only equations that are referred to later on in the paper are numbered.

2. SIR models to describe the time course of infections in a population

2.1. **The basic SIR model**

The SIR model divides the population into three disjoint groups or compartments, consisting of

- susceptible (S),
- infected (I) and
- removed (R)

individuals.

Individuals in the S-compartment can be infected by the disease when meeting infected individuals. If they are infected, they are moved to the I-compartment. The individuals in the I-compartment are infected and are contagious. They can infect individuals in the S-compartment. If individuals from the I-compartment recover or die, they are moved to the R-compartment. The R-compartment contains individuals that have recovered from the disease or have died. They are permanently immune and not contagious. The state variables S_t, I_t and R_t denote the number of susceptible, infected and removed individuals at time $t = 0, 1, 2, \ldots$. The total size of the population is $N = S_t + I_t + R_t$. If $N = 1$ the size of the state variables can be interpreted as the relative frequency of susceptible, infected and removed individuals.

There are two ways to look at this model: With discrete time and continuous time. Discrete time means that time is divided into steps, for example hours, days or weeks. Infection and recovery only occurs at those steps. In the continuous time model time progresses continuously. In this paper only discrete time models are considered. The basic SIR model described here is a discrete time version of the continuous time model in (Ma, 2009). It is a general model which is able to model the basic epidemic dynamics of infectious diseases. For this model the following is assumed:

- An individual becomes contagious one time step after infection and continues being so until it is removed.
- All infected individuals have the same probability to recover; the recovery rate is therefore not influenced by how long an individual has been infected. The earliest an infected individual can recover is one time step after infection.

Consider a specific susceptible and infected individual. Let β denote the probability that the two meet and the susceptible individual becomes infected. There

are $S_t I_t$ possible pairs of susceptible and infected individuals. Therefore the number of newly infected individuals is given by $S_t I_t \beta$. We assume that the probability of two specific individuals meeting is indirectly proportional to the population size N. This is the case if, for example, individuals meet at random.
Let γ be the recovery rate. It is defined as the probability for an infected individual to recover and become immune during one time step. The number of newly recovered individuals per unit of time is the product of γ and the number of infected individuals I_t. Resulting from this the difference equations for the basic SIR model can be derived:

$$\begin{aligned} S_{t+1} - S_t &= -S_t I_t \beta \\ I_{t+1} - I_t &= S_t I_t \beta - I_t \gamma \\ R_{t+1} - R_t &= I_t \gamma \end{aligned} \tag{1}$$

Note that the population size $N = S_t + I_t + R_t$ always remains constant. The flow of individuals from compartment to compartment can be visualized with the flow diagram in Figure 1. An R program to calculate results for this model can be found in Appendix A.

$$\boxed{\text{S}} \xrightarrow{SI\beta} \boxed{\text{I}} \xrightarrow{R\gamma} \boxed{\text{R}}$$

FIGURE 1. A flow diagram illustrating the movement of individuals between the compartments for the basic SIR model (1).

2.2. **A SIR model with changing infection and recovery rates**

Models with changing infection and recovery rates allow to model diseases with incubation times. In the first part of this section the general model is discussed, in the second part a special case simulating a measles epidemic is considered.

2.2.1. *Description of the model*

Kermack and McKendrick proposed a model with changing infection and recovery rates (Kermack & McKendrick, 1927). In this model the infection and the recovery rate for each individual depends on the time an individual has been infected. This is achieved by creating a separate subcompartment for each time step which includes all newly infected individuals and defining a specific infection and recovery rate for each subcompartment.
For example the subcompartment $I_{t,\theta}$ denotes the number of infected individuals at

time t that have been infected for $\theta = 0, 1, 2, \ldots$ time steps. Thus, after n time steps $I_{t,\theta}$ becomes $I_{t+n,\theta+n}$. This model is represented by the flow diagram in Figure 2.

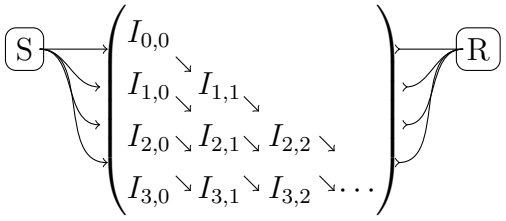

FIGURE 2. A flow diagram for a SIR model with incubation times and changing recovery rates showing the different subcompartments. Each letter represents a compartment. S is the compartment of susceptible individuals. If a susceptible individual is infected at a time step t it moves to the $I_{t,0}$ compartment. It includes only the newly infected individuals at the time step t. At each time step t some individuals from the compartments $I_{t,\theta}$ can be removed (if they recover or die). All remaining individuals move from the compartments $I_{t,\theta}$ to the compartments $I_{t+1,\theta+1}$. If an infected individual is removed, it is moved to the compartment R.

Let γ_θ denote the removal rate for the individuals infected for θ time steps. Then the number of removed individuals from one subcompartment changes at each time step according to

$$I_{t+1,\theta+1} - I_{t,\theta} = -I_{t,\theta}\gamma_\theta.$$

When considering n time steps the number of removed individuals in one subcompartment is

$$I_{t+n,\theta+n} - I_{t,\theta} = -\sum_{i=0}^{n} I_{t+i,\theta+i}\gamma_{\theta+i}.$$

The total number of newly recovered individuals from all subcompartments at time $t+1$ is given by

$$R_{t+1} - R_t = \sum_{\theta=0}^{t} I_{t,\theta}\gamma_\theta.$$

The number of susceptible individuals at a time step t is equal to the size of the total population N minus the number of all individuals that have ever been infected. Note that all individuals that are removed, were infected at some point in time such

that

$$S_t = N - \sum_{i=0}^{t} I_{i,0}.$$

Note that this equation is only true if no individuals obtain immunity by other means than recovery from infection. To calculate $I_{t,0}$, the number of newly infected individuals at time t, the varying infection rate must be taken into account. This results in the equation

$$I_{t+1,0} = S_t \sum_{\theta=0}^{t} I_{t,\theta}\beta_\theta \,,$$

where β_θ denotes the infection rate for the individuals infected for θ turns. Thus, the number of newly infected individuals at any time step $t+1$ is the product of the number of susceptible individuals at the time point t and the sum of the number of infected individuals in each subcompartment multiplied by their specific infection rate β_θ. This leads to the model equations

$$\begin{aligned} S_{t+1} - S_t &= -S_t \sum_{\theta=0}^{t} I_{t,\theta}\beta_\theta \\ I_{t+1} - I_t &= S_t \sum_{\theta=0}^{t} I_{t,\theta}\beta_\theta - \sum_{\theta=0}^{t} I_{t,\theta}\gamma_\theta \\ R_{t+1} - R_t &= \sum_{\theta=0}^{t} I_{t,\theta}\gamma_\theta, \end{aligned} \tag{2}$$

where I_t denotes the total number of infected individuals at a time step t, disregarding the time they have been infected already. An R program to calculate results for this model can be found in Appendix B.

2.2.2. *Modelling a measles epidemic*

Measles is an infectious disease that is highly contagious. It is caused by the measles virus and killed about 132, 200 people worldwide in 2015. There is a vaccine for measles. In 2015 85% of infants worldwide were vaccinated. The vaccination program has resulted in a reduction of 79% in measle deaths in comparison to the year of 2000 (*WHO | Measles*, n.d.).

Measles has an incubation time of about 10 days. After the incubation time the infected individuals develop a high fever which lasts for 4 to 7 days. About 14 days after the infection a distinctive rash develops which lasts around 6 days (*WHO | Measles*, n.d.). We say an individual is "removed" if it either recovers and is permanently immune or dies. In this model both the recovered and the deceased individuals are in the removed compartment.

Here a measles epidemic is modeled with a a SIR model with changing infection and recovery rates (2). Hours are used as time steps for the difference equations, therefore all constants are given as rates per hour.
For this simulation typical parameters for simulating the spread of measles are used: During the incubation time of 10 days (240 hours) the recovery rate is $\gamma = 0$ and infection rate is $\beta = 0$. When the fever breaks out in the individual, the infection rate is $\beta = 0.21/N$ (Shulgin et al., 1998; Engbert & Drepper, 1994) and the removal rate is $\gamma = 0$. When the rash develops around 14 days after the infection, the infection rate drops to $\beta = 0/N$ because the disease is likely to be recognized and the contact to other individuals will be restricted.
The length of the incubation time is modeled with a normal distribution with a mean of 240 hours and a standard deviation of 12 hours. The appearance of the rash 4 days after the fever is therefore also normally distributed with a mean of 336 hours and a standard deviation of 12 hours. Furthermore, the length of the disease is also normally distributed with a mean of 396 hours and a standard deviation of 18 hours. The mean and the standard deviation were chosen such that the time intervals given for different the stages of the disease in (*WHO | Measles*, n.d.) have a length of four standard deviations such that the time of the occurrence of the stage of the illness lies inside the interval for about 95% of the individuals. The resulting infection rate over time β_θ and the average length of the illness is visualized in Figure 3.

Two scenarios are considered. In the first scenario (left graph of Figure 4), most individuals are susceptible few are infected and none are removed. In the second scenario (right graph of Figure 4), the vaccination rate is considered. Around 85% of the population is vaccinated and the vaccine grants immunity in around 95% of vaccinated individuals. This number depends on the age at which the individual was vaccinated and whether the individual received one or two doses of the vaccine (World Health Organization, 2009). The relative frequency of susceptible individuals is represented by the green line, the red line represents the relative frequency of infected individuals and the blue line shows the relative frequency of removed individuals over time.
In the first scenario, the disease quickly spreads and the entire susceptible population is used up. Eventually, the disease dies out due to the lack of susceptible individuals and the entire population becomes removed.
Since measles is a very infectious disease even the high vaccination rate in the second scenario is not high enough to stop the spread of the disease. In the second scenario the disease spreads slower than in the first and takes longer to die out. The

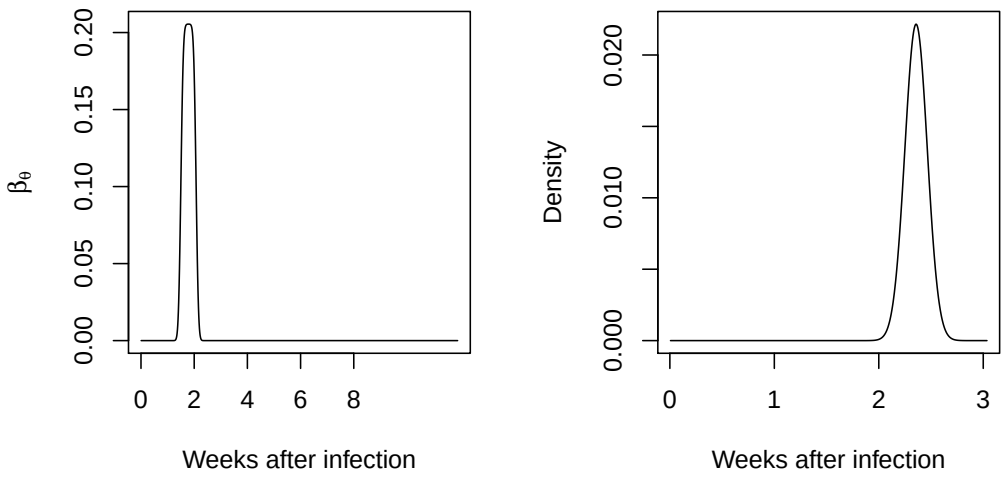

FIGURE 3. The left graph shows the infection rate β_θ for an individual over the course of its infection. During the incubation time $\beta_\theta = 0$ after the incubation time the infection rate rises up to $\beta_\theta = 2.1$. When the rash develops around 14 days after the infection and the disease is recognized the infection rate falls back to $\beta_\theta = 0$. The right graph shows a density function illustrating the average time after infection after which an infected individual recovers. The graphs were created with the R program in Appendix B.

entire susceptible population is used up and the disease dies out leaving a totally removed population. The WHO states that 95% of the population in each district must be vaccinated with two doses of the vaccines against measles to prevent an epidemic (World Health Organization, 2009). Modelling a measles epidemic with 95% removed individuals confirms this statement.

In (Shulgin et al., 1998; Engbert & Drepper, 1994) a separate birth and death process is additionally considered but since the birth and death rate is only 0.000002 and has practically no impact on the dynamic, it is dropped here for simplicity. Furthermore, the incubation time in (Engbert & Drepper, 1994) is simulated using the SEIR model which is an extension of the SIR model with an additional compartment for the individuals in the incubation period. The model with changing infection and recovery rates is more flexible for simulating this incubation period. It allows for a variation of specific incubation times and times of removal. The SEIR model on the other hand uses the average probability of the disease breaking out in an individual in the incubation period (compartment E) and the average probability of an infected individual being removed. This is a simplification and is therefore less accurate.

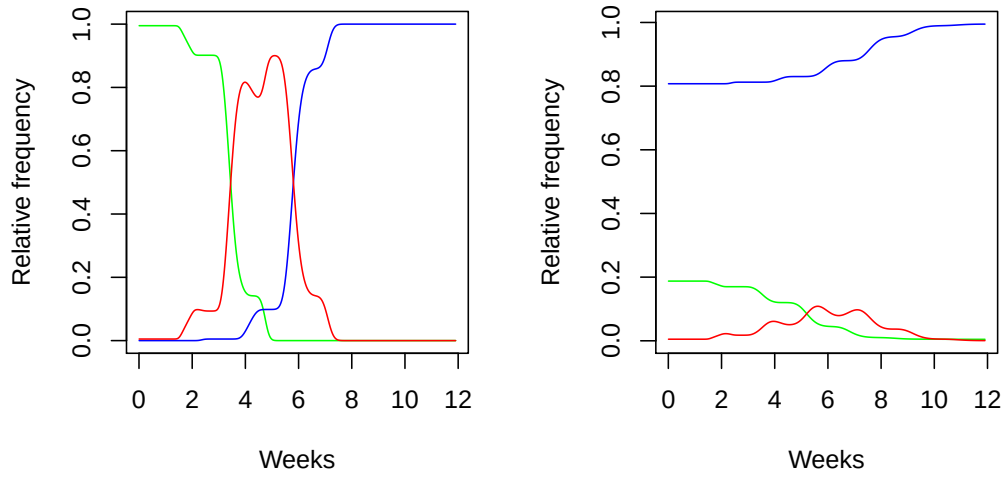

FIGURE 4. The left graph shows the first scenario with 99.5% susceptible, 0.5% infected and 0% removed individuals at the start of the epidemic. The right graph shows the second scenario where 85% of the population is vaccinated. At the start there are 18.75% susceptible 0.5% infected and 80.75% removed individuals. In both graphs the disease is modeled with the SIR model with changing infection and recovery rates (2). The lines represent the relative frequency of susceptible (green), infected (red) and removed (blue) individuals. The graphs were created with the R program in Appendix B.

2.3. **A SIR model with birth and death rates**

Another extension of the basic SIR model includes birth and death rates. An example of a model with birth and death rates is discussed in (Allen, 1994) and in (Ma, 2009). It is assumed that the birth rate $\mu > 0$ equals the death rate. Therefore the total population size N remains constant so that $S_t + I_t + R_t = N$. All newborn individuals are susceptible. This results in the following model:

$$\begin{aligned} S_{t+1} - S_t &= -S_t I_t \beta + \mu(N - S_t) \\ I_{t+1} - I_t &= S_t I_t \beta - I_t \gamma - \mu I_t \\ R_{t+1} - R_t &= I_t \gamma - \mu R_t = N - S_{t+1} - I_{t+1} \end{aligned} \tag{3}$$

The death rate is a constant and is not affected by whether an individual is infected, susceptible or removed. In this model the removed compartment only represents recovered individuals and not deceased ones. The deceased compartment is separate and not modeled here since deceased individuals do not interact with the living. Note that $\mu + \gamma \leq 1$, for if it were greater, then the number of infected individuals could

become negative, which is impossible. The flow of individuals from compartment to compartment is depicted in Figure 5. An R program to calculate results for this model can be found in Appendix C.

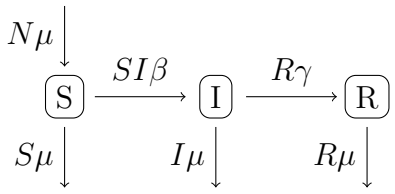

FIGURE 5. Flow diagram for a SIR model with birth and death rates, described by the equations (3), showing the flow of individuals from compartment to compartment.

3. Equilibria and their stability

3.1. **Definition and computation of equilibria**

When considering the behavior of such models it is interesting to look at equilibria. An equilibrium is a state in which all the state variables S, I and R remain constant over time. The number of susceptible, infected and removed individuals stays the same.

$$S_{t+1} = S_t$$

$$I_{t+1} = I_t$$

$$R_{t+1} = R_t$$

Consider first the basic SIR model (1) and let $\beta > 0$ and $\gamma > 0$. The equilibria and their stability are calculated with the help of the computer algebra system Maxima (Maxima, 2014). We show that there are only disease-free equilibria. To calculate these equilibria we need to solve the equations

$$-S_t I_t \beta = 0, +S_t I_t \beta - I_t \gamma = 0, I_t \gamma = 0.$$

Since we defined $\beta > 0$ and $\gamma > 0$ it follows that I_t must be equal to 0. No individuals are infected and therefore the disease does not spread and the number of susceptible and removed individuals remains constant.

Similarly, the equilibria for model (2) with incubation time and changing recovery rates have to satisfy

$$-S_t \sum_{\theta=0}^{t} I_{t,\theta}\beta_\theta = 0, S_t \sum_{\theta=0}^{t} I_{t,\theta}\beta_\theta - \sum_{\theta=0}^{t} I_{t,\theta}\gamma_\theta = 0, \sum_{\theta=0}^{t} I_{t,\theta}\gamma_\theta = 0.$$

Also for this model there are only disease-free equilibria. Only susceptible and removed individuals are present in the equilibria and their numbers do not change.

The model (3) with birth and death rates can have more than one equilibrium. Equilibria for this model satisfy

$$-S_t I_t \beta + \mu(N - S_t) = 0, S_t I_t \beta - I_t \gamma - \mu I_t = 0, I_t \gamma - \mu R_t = 0. \tag{4}$$

Thus we have three equations with three unknowns, the state variables S_t, I_t and R_t. But since we can express R_t as $R_t = N - S_t - I_t$ we are left with only two unknowns and three equations.

If we assume $I_t = 0$ and substitute it into the first equation we receive $\mu(N - S_t) = 0$ and since $\mu > 0$, it is clear that $S = N$. Thus, all individuals are susceptible and

the disease is not present. When we assume $I_t > 0$, then $S_t I_t \beta - I_t \gamma - \mu I_t = 0$ can be rearranged to $S_t = (I_t \gamma - \mu I_t)/I_t \beta$ and this simplifies to $S_t = (\gamma - \mu)/\beta$. If we now substitute $(\gamma - \mu)/\beta$ for S in one of the remaining equations, for example $-S_t I_t \beta + \mu(N - S_t) = 0$, we get $-(\gamma+\mu)I\beta/\beta + \mu N - \mu(\gamma+\mu)/\beta = 0$. This simplifies and rearranges to $I = (\mu N \beta - \mu^2 - \mu\gamma)/(\beta\mu + \beta\gamma)$.

As established, the set of equations (4) has two solutions,

$$\begin{aligned} \bar{S} &= N \\ \bar{I} &= 0 \\ \bar{R} &= 0 \end{aligned} \tag{5}$$

and

$$\begin{aligned} \bar{S}^* &= \frac{\mu + \gamma}{\beta} \\ \bar{I}^* &= \frac{\mu N \beta - \mu^2 - \mu\gamma}{\beta\mu + \beta\gamma} \\ \bar{R}^* &= \frac{-\mu\gamma - \gamma^2 + \beta\gamma N}{\beta\gamma + \beta\mu} = N - \bar{S} - \bar{I}\,. \end{aligned} \tag{6}$$

The second solution is only an equilibrium if the values of all the state variables $\bar{S}^*, \bar{I}^*, \bar{R}^*$ are greater or equal to zero and smaller or equal to N. This is the case if $R_0 \geq 1$, where

$$R_0 = (\beta N)/(\mu + \gamma).$$

Note that $\bar{S}^* = N/R_0$ and if $R_0 < 1$ then $\bar{S}^*$ is greater than N, which is not possible. R_0 is called the the basic reproduction number and can be interpreted as the number of individuals infected by one infected individual within a totally susceptible population during the time the individual is infected. Its estimation can be used to characterize the spread of diseases (Chowell, Viboud, Simonsen, & Moghadas, 2016; Aparicio & Pascual, 2007). If $R_0 < 1$ only the disease-free equilibria exist.

3.2. **Stability of equilibria for the SIR model (3) with birth and death rates**

An equilibrium can be locally asymptotically stable or unstable. A locally stable equilibrium is an equilibrium where the state variables converge back to the equilibrium after a small perturbation. In contrast if an unstable equilibrium is perturbed it may not revert back to the equilibrium.

According to (Ma, 2009) for $R_0 \leq 1$ the disease-free equilibrium is stable and for $R_0 \geq 1$ the second equilibrium (6) is stable. At $R_0 = 1$ the second equilibrium (6)

is the same as the disease-free equilibrium.

To determine the stability we have to determine the eigenvalues of the Jacobian matrix at the point of the equilibrium (Barbarossa, 2011). The equilibria are stable if the absolute values of all their eigenvalues are smaller than 1 and unstable when any of the absolute values of their eigenvalues is greater than 1. If the absolute value of the eigenvalues is equal to 1 the stability is not determined by the eigenvalues (Barbarossa, 2011). The model (3) can also be rewritten as

$$\begin{aligned} S_{t+1} &= S_t - S_t I_t \beta + \mu(N - S_t) \\ I_{t+1} &= I_t + S_t I_t \beta - I_t \gamma - \mu I_t \\ R_{t+1} &= R_t + I_t \gamma - \mu R_t = N - S_{t+1} - I_{t+1}. \end{aligned} \tag{7}$$

To calculate the Jacobian matrix at the point of the equilibrium, we first take the derivative of the functions on the right hand side of (7) with respect to the variables S, I, R (for simplicity the index t is dropped here) and obtain

$$\begin{pmatrix} \frac{\partial(S - SI\beta + \mu(N-S))}{\partial S} & \frac{\partial(S - SI\beta + \mu(N-S))}{\partial I} & \frac{\partial(S - SI\beta + \mu(N-S))}{\partial R} \\ \frac{\partial(I + SI\beta - I\gamma - \mu I)}{\partial S} & \frac{\partial(I + SI\beta - I\gamma - \mu I)}{\partial I} & \frac{\partial(I + SI\beta - I\gamma - \mu I)}{\partial R} \\ \frac{\partial(R + I\gamma - \mu R)}{\partial S} & \frac{\partial(R + I\gamma - \mu R)}{\partial I} & \frac{\partial(R + I\gamma - \mu R)}{\partial R} \end{pmatrix}. \tag{8}$$

This simplifies to

$$\begin{pmatrix} 1 - I\beta - \mu & -S\beta & 0 \\ I\beta & 1 + S\beta - \mu - \gamma & 0 \\ 0 & \gamma & 1 - \mu \end{pmatrix}. \tag{9}$$

The eigenvalues of this matrix are the roots of the characteristic polynomial:

$$(1 - \mu - \lambda)(1 - \mu - \lambda - \beta I)(1 - \mu - \lambda - \gamma + \beta S) + (1 - \mu - \lambda)\beta^2 IS \tag{10}$$

To calculate the characteristic polynomial, we need to subtract λ from the functions in the first diagonal of the matrix and then take the determinant of the resulting matrix. To calculate the roots of the characteristic polynomial, we have to solve the equation

$$(1 - \mu - \lambda)(1 - \mu - \lambda - \beta I)(1 - \mu - \lambda - \gamma + \beta S) + (1 - \mu - \lambda)\beta^2 IS = 0\,. \tag{11}$$

When calculating the roots of the polynomial we can easily see that is has a root at $\lambda = 1 - \mu$. To calculate its further roots we assume that $\lambda \neq 1 - \mu$ and divide (11) by $(1 - \mu - \lambda)$. If we expand the result, we have a quadratic equation:

$$\beta\mu I + \beta\lambda I + \beta\gamma I - \beta I - \beta\mu S - \beta\lambda S + \beta S + \mu^2 + 2\mu\lambda + \mu\gamma - 2\mu + \lambda^2 + \lambda\gamma - 2\lambda - \gamma + 1 = 0$$

The solutions of this quadratic equation are

$$(2-2\mu-\gamma-\beta I+\beta S+\sqrt{\beta^2S^2-(2\gamma\beta+2\beta^2I)S+\beta^2I^2-2\gamma\beta I+\gamma^2})/2$$

and

$$(2-2\mu-\gamma-\beta I+\beta S-\sqrt{\beta^2S^2-(2\gamma\beta+2\beta^2I)S+\beta^2I^2-2\gamma\beta I+\gamma^2})/2.$$

Thus, to summarize, the eigenvalues are

$$\begin{aligned}\lambda_1 &= \frac{2-2\mu-\gamma-\beta I+\beta S+\sqrt{\beta^2S^2-(2\gamma\beta+2\beta^2I)S+\beta^2I^2-2\gamma\beta I+\gamma^2}}{2}\\ \lambda_2 &= \frac{2-2\mu-\gamma-\beta I+\beta S-\sqrt{\beta^2S^2-(2\gamma\beta+2\beta^2I)S+\beta^2I^2-2\gamma\beta I+\gamma^2}}{2}\\ \lambda_3 &= 1-\mu.\end{aligned} \tag{12}$$

Now we can substitute the values we obtained for I and S at the points of the equilibria into the eigenvalue formulas and simplify the result. For the disease-free equilibrium (5) we get the following equations:

$$\begin{aligned}\lambda_1 &= 1-\mu-\gamma+\beta N\\ \lambda_2 &= 1-\mu\\ \lambda_3 &= 1-\mu\end{aligned} \tag{13}$$

We can easily see that λ_1 in (13) is only smaller or equal to 1 when $R_0 \leq 1$ since $R_0 = \beta N/(\mu+\gamma)$ and λ_1 is smaller or equal to 1 for $\beta N \leq \mu+\gamma$. This also makes sense from a biological standpoint; if an infected individual on average infects less then one other individual during the cause of its infection, the disease will die out. For the second equilibrium, if we substitute $R_0(\mu+\gamma)$ for βN in (12) we get

$$\begin{aligned}\lambda_1 &= \frac{2-\mu R_0+\sqrt{\mu}\sqrt{\mu {R_0}^2+(-4\gamma-4\mu)\,R_0+4\mu+4\gamma}}{2}\\ \lambda_2 &= \frac{2-\mu R_0-\sqrt{\mu}\sqrt{\mu {R_0}^2+(-4\gamma-4\mu)\,R_0+4\mu+4\gamma}}{2}\\ \lambda_3 &= 1-\mu\end{aligned} \tag{14}$$

I was not able to show that the absolute values of λ_1 and λ_2 (14) are smaller or equal to 1 for all $R_0 \geq 1$ because the eigenvalues can become complex numbers. However, for specific values the eigenvalues can be calculated. The stability of the equilibria can therefore be determined for specific values of μ, γ, β and N.

4. Numerical examples

For the model (3) with birth and death rates three scenarios, with different values of the basic reproduction number R_0 are considered (Table 1).

Scenario	R_0	μ	γ	β	N	Figure
Low	0.48	0.01	0.2	$0.1/N$	1	6
Medium	1.11	0.04	0.05	$0.1/N$	1	8
High	3.33	0.01	0.02	$0.1/N$	1	7

Table 1. The three scenarios considered for model (3). The terms Low, Medium, High reflect to the basic reproduction number R_0.

The equilibria and their stability and corresponding eigenvalues for the different scenarios are shown in Table 2.

Scenario	Equilibrium	Eigenvalues	Stable
Low	$(1, 0, 0)$	$(0.89, 0.99, 0.99)$	yes
Medium	$(1, 0, 0)$	$(1.01, 0.96, 0.96)$	no
	$(0.90, 0.04, 0.06)$	$(0.97, 0.99, 0.96)$	yes
High	$(1, 0, 0)$	$(1.07, 0.99, 0.99)$	no
	$(0.3, 0.23, 0.47)$	$(0.98 - 0.02i, 0.98 + 0.02i, 0.99)$	yes

Table 2. The equilibria, their eigenvalues and stability properties in the scenarios in Table 1.

Figure 6 shows solution paths for the low reproduction number scenario. The graphs show how the state variables S and I converge to $S = N$, $I = 0$ and $R = 0$ for different initial values of S and I.

The left graph of Figure 6 depicts multiple sets of initial conditions in one graph, but does not show how quickly the state variables approach the equilibrium.

The right graph of Figure 6 allows only one set of initial conditions but shows how quickly the state variables approach the equilibrium. The disease-free equilibrium is stable, this can also be proven by calculating the eigenvalues. The absolute value of the specific eigenvalues for this disease-free equilibrium are all smaller than 1. (See Table 2)

Note that the initial values in the left graph of Figure 6 can only lie in the marked triangle because the sum of all susceptible and infected individuals can not be greater than the size of the total population ($S + I \leq N$).

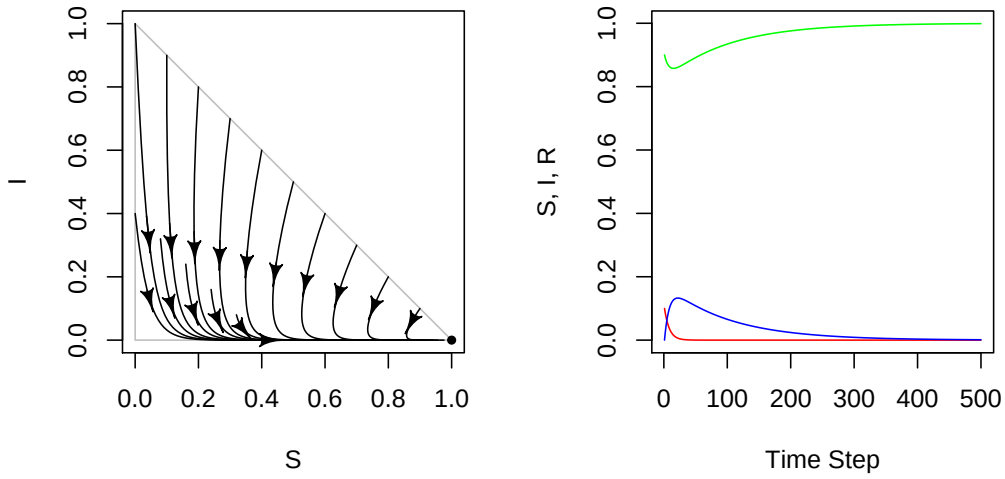

FIGURE 6. Solutions for the low basic reproduction number scenario with $R_0 < 1$ (in this simulation $R_0 = 0.48$). The parameter values used are $\mu = 0.01$, $\gamma = 0.2$, $\beta = 0.1/N$ and $N = 1$. The left graph shows solution paths in the SI plane for several initial conditions. The right graph shows the size of the compartments over time. The lines represent the relative frequency of susceptible (green), infected (red) and removed (blue) individuals. The graphs were created with the R program in Appendix C.

Figure 7 shows solution paths for the high reproduction number scenario. In the left graph it can be seen that the state variables spiral towards the equilibrium. The right graph shows the state variables oscillating towards the equilibrium. Two of the eigenvalues for the stable equilibrium are complex and therefore the values of the state variables oscillate towards the equilibrium (Barbarossa, 2011).

In Figure 8 solution paths for the medium reproduction number scenario with only real eigenvalues are plotted. Since the eigenvalues for this equilibrium are real the values for the state variables do not oscillate around the equilibrium.

Finally, Figure 9 shows solutions for the classical SIR model (1). The parameter values used in this simulation are $\gamma = 0.03$, $\beta = 0.1/N$ and $N = 1$. Since there are no birth and death rates, only disease-free equilibria exist. They are marked by the thick line in the left graph. Both graphs show that the state variables converge towards one of these disease-free equilibria.

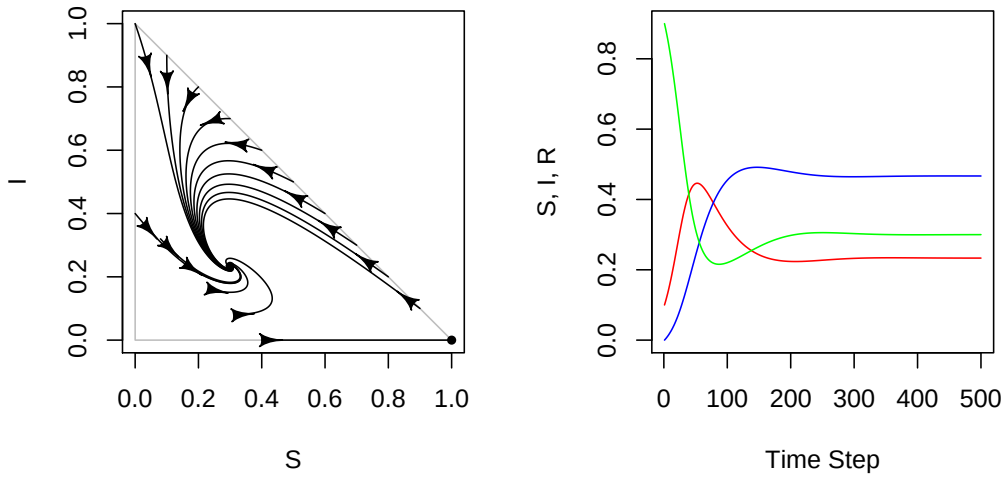

FIGURE 7. Solutions for the high basic reproduction number scenario with $R_0 > 1$ (in this simulation $R_0 = 3.33$) and two complex eigenvalues. The parameter values used are $\mu = 0.01$, $\gamma = 0.02$, $\beta = 0.1/N$ and $N = 1$. The left graph shows solution paths in the SI plane for several initial conditions. The right graph shows the size of the compartments over time. Legend see Figure 6. The graphs were created with the R program in Appendix C.

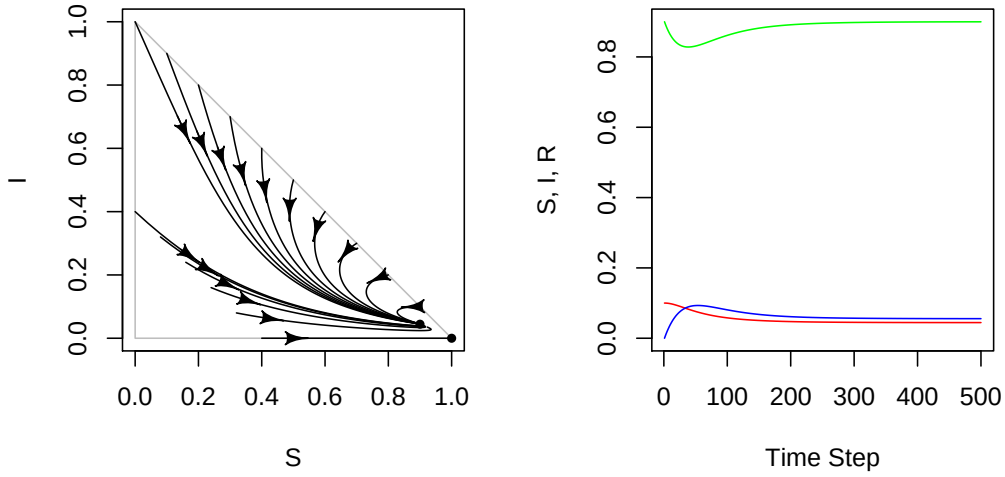

FIGURE 8. Solutions for the medium basic reproduction number scenario with $R_0 > 1$ (in this simulation $R_0 = 1.11$) and real eigenvalues. The parameter values used are $\mu = 0.04$, $\gamma = 0.05$, $\beta = 0.1/N$ and $N = 1$. The left graph shows solution paths in the SI plane for several initial conditions.The right graph shows the size of the compartments over time. Legend see Figure 6. The graphs were created with the R program in Appendix C.

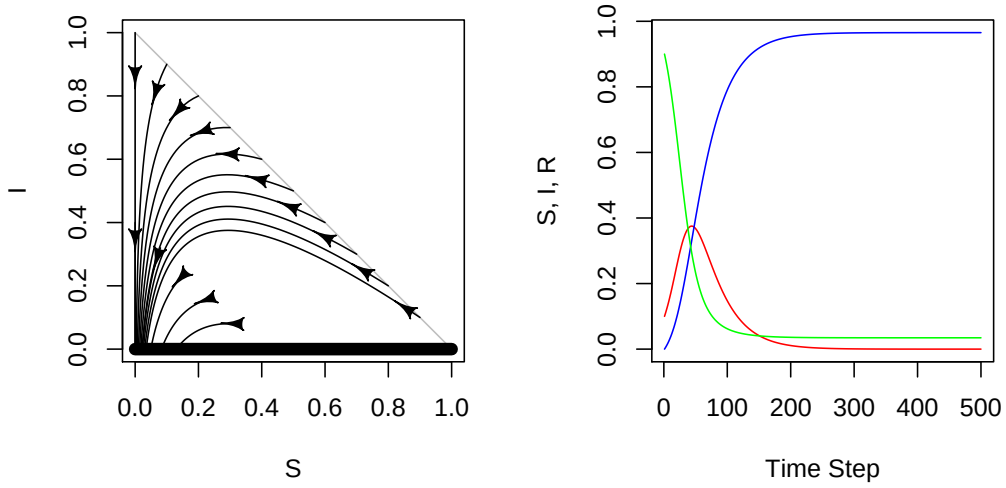

FIGURE 9. Solutions for a classical SIR model (1). The parameter values used are $\gamma = 0.03$, $\beta = 0.1/N$ and $N = 1$. The left graph shows solution paths in the SI plane for several initial conditions. The right graph shows the size of the compartments over time. Legend see figure 6. The graphs was created with the R program in Appendix A.

5. Discussion

At first a quick introduction to the basic SIR model (1) was described. Then the Kermack and McKendrick model (2), a model were the infectivity and the recovery rate of an infected individual are influenced by how long the individual has been infected was discussed and an example simulating a measles epidemic was described. In addition, a model with birth and death rates (3) was introduced. Then the equilibria for the discussed models and their stability were analyzed. In the model with birth and death rates (3) R_0 was identified as a determining factor as to whether a non disease-free equilibrium exists. The calculations were than checked for specific sets of parameters and initial conditions by numerical examples.

These models have several limitations.

- All individuals have the same probability of meeting each other.
- Most populations are not homogeneous and variables as the infectivity and the recovery rate therefore may vary.
- Neither age nor sex is regarded.
- The models only work for large groups of individuals, in small groups stochastic models have to be used because random variables can have a big impact in small populations.

The information obtained by the modelling of infectious diseases can be used to predictions whether and how an epidemic will occur and the efficiency of interventions such as vaccination programs to stop an epidemic can be calculated beforehand.

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1 A flow diagram illustrating the movement of individuals between the compartments for the basic SIR model (1). 8

2 A flow diagram for a SIR model with incubation times and changing recovery rates showing the different subcompartments. Each letter represents a compartment. S is the compartment of susceptible individuals. If a susceptible individual is infected at a time step t it moves to the $I_{t,0}$ compartment. It includes only the newly infected individuals at the time step t. At each time step t some individuals from the compartments $I_{t,\theta}$ can be removed (if they recover or die). All remaining individuals move from the compartments $I_{t,\theta}$ to the compartments $I_{t+1,\theta+1}$. If an infected individual is removed, it is moved to the compartment R. 9

3 The left graph shows the infection rate β_θ for an individual over the course of its infection. During the incubation time $\beta_\theta = 0$ after the incubation time the infection rate rises up to $\beta_\theta = 2.1$. When the rash develops around 14 days after the infection and the disease is recognized the infection rate falls back to $\beta_\theta = 0$. The right graph shows a density function illustrating the average time after infection after which an infected individual recovers. The graphs were created with the R program in Appendix B. 12

4 The left graph shows the first scenario with 99.5% susceptible, 0.5% infected and 0% removed individuals at the start of the epidemic. The right graph shows the second scenario where 85% of the population is vaccinated. At the start there are 18.75% susceptible 0.5% infected and 80.75% removed individuals. In both graphs the disease is modeled with the SIR model with changing infection and recovery rates (2). The lines represent the relative frequency of susceptible (green), infected (red) and removed (blue) individuals. The graphs were created with the R program in Appendix B. 13

5 Flow diagram for a SIR model with birth and death rates, described by the equations (3), showing the flow of individuals from compartment to compartment. 14

6 Solutions for the low basic reproduction number scenario with $R_0 < 1$ (in this simulation $R_0 = 0.48$). The parameter values used are $\mu = 0.01$, $\gamma = 0.2$, $\beta = 0.1/N$ and $N = 1$. The left graph shows solution paths in the SI plane for several initial conditions. The right graph shows the size of the compartments over time. The lines represent the relative frequency

of susceptible (green), infected (red) and removed (blue) individuals. The graphs were created with the R program in Appendix C. 20

7 Solutions for the high basic reproduction number scenario with $R_0 > 1$ (in this simulation $R_0 = 3.33$) and two complex eigenvalues. The parameter values used are $\mu = 0.01$, $\gamma = 0.02$, $\beta = 0.1/N$ and $N = 1$. The left graph shows solution paths in the SI plane for several initial conditions. The right graph shows the size of the compartments over time. Legend see Figure 6. The graphs were created with the R program in Appendix C. 21

8 Solutions for the medium basic reproduction number scenario with $R_0 > 1$ (in this simulation $R_0 = 1.11$) and real eigenvalues. The parameter values used are $\mu = 0.04$, $\gamma = 0.05$, $\beta = 0.1/N$ and $N = 1$. The left graph shows solution paths in the SI plane for several initial conditions.The right graph shows the size of the compartments over time. Legend see Figure 6. The graphs were created with the R program in Appendix C. 21

9 Solutions for a classical SIR model (1). The parameter values used are $\gamma = 0.03$, $\beta = 0.1/N$ and $N = 1$. The left graph shows solution paths in the SI plane for several initial conditions. The right graph shows the size of the compartments over time. Legend see figure 6. The graphs was created with the R program in Appendix A. 22

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2 The equilibria, their eigenvalues and stability properties in the scenarios in Table 1. 19

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:

Appendices

Appendix A. R program for the basic SIR model (1)

```
#Observed time steps
time = 500

#Total number of individuals
N = 100

#Probability of recovery of an infected individual at each time step
y = 0.01

#defining the infection rate
beta = 0.1 / N

#Making a vectors for each compartment
S = c(rep(0,time))
I = c(rep(0,time))
R = c(rep(0,time))

#Defining starting positions
S[1] = 99
I[1] = 1
R[1] = N - S[1] - I[1]
#Defining a counting variable for the loop.
tc = 1
while (time > tc)
  #opening loop
{
  tc = tc + 1
```

```
  #Defining the equations
  S[tc] = S[tc - 1] - S[tc - 1] * I[tc - 1] * beta
  I[tc] = I[tc - 1] + S[tc - 1] * I[tc - 1] * beta - I[tc - 1] * y
  R[tc] = R[tc - 1] + I[tc - 1] * y
}
#closing loop

#Ploting the vectors
plot(
  I, type = "l",col = "red",ylim = c(min(S,I,R), max(S,I,R)), xlab = "Time
Step",ylab = "S, I, R"
)
lines(R, type = "l",col = "blue")
lines(S, type = "l", col = "green")
par(mfrow = c(1,1))
```

Appendix B. R program for the model (2) with changing infection and recovery rates (parameter values are chosen for measles)

```
tt = 2000#time steps observed

#making vectors for the recovery and infection rate
rec = c(rep(0, tt))
inf = c(rep(0, tt))

rc = 1

rec[1] = 0
eps = 10 ^ (-10)
while (rc < tt) {
  #opening loop
  rc = rc + 1
  flag = pnorm(rc,mean = 396,sd = 18) > 1 - eps
  rec[rc] = ifelse(flag,1, dnorm(rc,mean = 396,sd = 18) / (1 - pnorm(rc
-
```

```
1,mean = 396,sd = 18)))#defining specific recovery rates for each time
step an individual has been infected
}#closing loop

#sum(rec[1:510]*(1-c(0,pnorm(1:509,mean=396,sd=18))))

rc = 0
while (rc < tt) {
  #opening loop
  rc = rc + 1
  inf[rc] = pnorm(rc,mean = 252,sd = 12) * (1 - pnorm(rc,mean = 348,sd
=
                                                    12)) * 1800 / 8760
/ N#defining specific infection rates for each time step an individual
has been infected
}#closing loop


measles = function(Sx,Ix,Rx) {
  #making vectors for the state variables S and R
  S = c(rep(0, tt))
  R = c(rep(0, tt))
  iv = c(rep(0, tt))
  I = matrix(0,ncol = tt, nrow = tt)
  #defining the initial values for the compartments
  S[1] = Sx
  I[1,1] = Ix
  R[1] = Rx
  N = S[1] + I[1,1] + R[1]


  rc = 1
  rec[1] = 0
  eps = 10 ^ (-10)
  while (rc < tt) {
```

```
    #opening loop
    rc = rc + 1
    flag = pnorm(rc,mean = 396,sd = 18) > 1 - eps
    rec[rc] = ifelse(flag,1, dnorm(rc,mean = 396,sd = 18) / (1 - pnorm(rc
-

  1,mean = 396,sd = 18)))#defining specific recovery rates for each time
step an individual has been infected
  }#closing loop

  #sum(rec[1:510]*(1-c(0,pnorm(1:509,mean=396,sd=18))))

  rc = 0
  while (rc < tt) {
    #opening loop
    rc = rc + 1
    inf[rc] = pnorm(rc,mean = 252,sd = 12) * (1 - pnorm(rc,mean = 348,sd
=
                                                          12)) * 1800 /
8760 / N#defining specific infection rates for each time step an individual
has been infected
  }#closing loop


  ic = 0
  tc = 0
  while (tc < tt - 1) {
    #opening loop
    tc = tc + 1
    #defining the equations
    S[tc + 1] = S[tc] - S[tc] * sum(I[tc,] * inf)
    R[tc + 1] = R[tc] + sum(I[tc,] * rec)
    I[tc + 1,1] = S[tc] * sum(I[tc,] * inf)
    ic = 0
    while (ic < tc) {
      #opening loop
```

```
      ic = ic + 1
      I[tc + 1,ic + 1] = I[tc,ic] - I[tc,ic] * rec[ic] #one of the equations:
removes individuals from the subcompartments

    }#closing loop
  }#closing loop
  icc = 0
  while (icc < tt) {
    #opening loop
    icc = icc + 1
    iv[icc] = sum(I[icc,]) #filling a vector with the total nuber of infected
for each time step taking the sum off all subcompartments
  }#closing loop
  plot(
    S, type = "l", col = "green", ylim = c(min(S,iv,R), max(S,iv,R)),xlab
= "Weeks",ylab =
      "Relative frequency", xaxt = "n"
  )
  axis(1,at = c(0,2,4,6,8,10,12) * 7 * 24,labels = c(0,2,4,6,8,10,12))
  lines(R, type = "l", col = "blue")
  lines(iv, type = "l", col = "red")
  #abline(v=c(240*1:8),col="gray")
}
#plots the grath for the 2 scenarios
pdf(file = "~/Desktop/rplots/kermackmckendrikvac.pdf",width = 7, height
=
      3.5)
par(pty = "s",mfrow = c(1,2),mar = c(4, 4, 1, 2) + 0.1)
measles(0.995,0.005,0)
measles(0.1875,0.005,0.8075)
dev.off()
#plots the grath with \beta and the average time until removal
pdf(file = "~/Desktop/rplots/kermackmckendrikrecinf.pdf",width = 7, height
=
      3.5)
par(pty = "s",mfrow = c(1,2),mar = c(4, 4, 1, 2) + 0.1)
```

```
plot(
  inf,type = "l", xlab = "Weeks after infection",
  ylab = expression(beta[theta]),xaxt =
    "n"
)
axis(1,at = c(0,2,4,6,8) * 7 * 24,labels = c(0,2,4,6,8))
plot(
  dnorm(1:510,mean = 396,sd = 18),type = "l",xlab = "Weeks after infection",
  ylab = "Density",xaxt =
    "n"
)
axis(1,at = c(0,1,2,3) * 7 * 24,labels = c(0,1,2,3))
dev.off()
```

Appendix C. R Program for the model (3) with birth and death rates

The R program for the graphs 6, 7 and 8 with the parameter values for graph 6:

```
library(shape)
#Observed time steps
time = 200
#Making a vectors for each compartment
S = c(rep(0,time))
I = c(rep(0,time))
R = c(rep(0,time))

#Total number of individuals
N = 1

#defining birth/death rate
mu = 0.01

#Probability of recovery of an infected individual at each time step
y = 0.2

#defining beta
beta = 0.1 / N
```

```
#pdf(file = "~/Desktop/rplots/Rs1.pdf",width=7, height=3.5)

#defining the plot layout
par(pty = "s",mfrow = c(1,2),mar = c(4, 4, 1, 2) + 0.1)

#plotting the left plot
plot(S,I,type = "l",ylim = c(0,N), xlim = c(0,N))
lines(c(0,1,0,0),c(1,0,0,1),col = "grey")

#defining counting variable
Nt = N
while (Nt >= 0)
  #opening loop {
  #Defining the initial positions
S[1] = N - Nt
I[1] = Nt
R[1] = N - S[1] - I[1]
#Defining a counting variable
tc = 1
while (time > tc)
  #opening loop
{
  tc = tc + 1
  #Defining the equations
  S[tc] = S[tc - 1] - S[tc - 1] * I[tc - 1] * beta + mu * (I[tc - 1] +
                                                             R[tc - 1])
  I[tc] = I[tc - 1] + S[tc - 1] * I[tc - 1] * beta - I[tc - 1] * y - mu
*
    I[tc - 1]
  R[tc] = R[tc - 1] + I[tc - 1] * y - mu * R[tc - 1]
}#closing loop
lines(S,I)
i = 5
Nt = Nt - N / 10
```

```
if (Nt > 0) {
  Arrows(S[i],I[i],S[i + 1],I[i + 1],arr.length = 0.3)
}
}
Nt = N
while (Nt >= 0) {
  #Defining starting positions
  S[1] = N * 0.4 - Nt * 0.4
  I[1] = Nt * 0.4
  R[1] = N - S[1] - I[1]
  #Defining a counting variable for the loop.
  tc = 1
  while (time > tc)
    #opening loop
  {
    tc = tc + 1
    #Defining the equations
    S[tc] = S[tc - 1] - S[tc - 1] * I[tc - 1] * beta + mu * (I[tc - 1]
+ R[tc -

      1])
    I[tc] = I[tc - 1] + S[tc - 1] * I[tc - 1] * beta - I[tc - 1] * y -
mu *
      I[tc - 1]
    R[tc] = R[tc - 1] + I[tc - 1] * y - mu * R[tc - 1]
  }
  #closing loop
  lines(S,I)
  i = 5
  Nt = Nt - N / 5
  Arrows(S[i],I[i],S[i + 1],I[i + 1],arr.length = 0.3)
}

points(1,0,pch = 20)
points((mu + y) / beta,(mu * N * beta - mu ^ 2 - mu * y) / (beta * y +
beta *
```

```
                                                                  mu),pch =
20)



#Observed time steps
time = 500
#Making a vectors for each compartment
S = c(rep(0,time))
I = c(rep(0,time))
R = c(rep(0,time))

#Ploting the vectors
R0 = beta * N / (mu + y)

#Defining starting positions
S[1] = 0.9
I[1] = 0.1
R[1] = N - S[1] - I[1]
#Defining a counting variable for the loop.
tc = 1
while (time > tc)
  #opening loop
{
  tc = tc + 1

  #Defining the equations
  S[tc] = S[tc - 1] - S[tc - 1] * I[tc - 1] * beta + mu * (I[tc - 1] +
R[tc -

    1])
  I[tc] = I[tc - 1] + S[tc - 1] * I[tc - 1] * beta - I[tc - 1] * y - mu
*
    I[tc - 1]
  R[tc] = R[tc - 1] + I[tc - 1] * y - mu * R[tc - 1]
}
```

```
#closing loop

#Ploting the vectors
plot(
  I, type = "l",col = "red",ylim = c(min(S,I,R), max(S,I,R)), xlab = "Time
Step",ylab = "S, I, R"
)
lines(R, type = "l",col = "blue")
lines(S, type = "l", col = "green")
par(mfrow = c(1,1))

#dev.off()
```