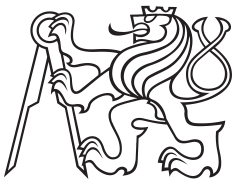
Master Thesis



Czech Technical University in Prague

F3

Faculty of Electrical Engineering
Department of Control Engineering

Epidemiological modeling and control

Harun Zalihic

Supervisor: doc. Kristian Hengster-Movric, PhD
May 2022

Acknowledgements

I thank the CTU in Prague for being a very good alma mater, and doc. Kristian Hengster-Movric PhD, for his support during this work.

Declaration

I declare that this work is all my own work and I have cited all sources I have used in the bibliography.

Prague, May 2022.

Prohlašuji, že jsem předloženou práci vypracoval samostatně, a že jsem uvedl veškerou použitou literaturu.

V Praze, Máj 2022.

Abstract

We will investigate the mathematical epidemiological models, while considering both the batch and networked compartmental models. Different means of controlling the course of epidemics will be considered, where the pharmacological and non-pharmacological interventions will be distinguished. Lyapunov theory of compartmental non-negative systems will be used for proving the stability of the disease-free equilibrium globally, while linearization will be used locally. Moreover, we will formulate current public health challenges as feedback control problems. Specially developed models for SARS-CoV-2 will be investigated. In the end, we will test the applicability of designed controls in light of incomplete data.

Keywords: epidemiological models, modeling, control, COVID-19

Supervisor: doc. Kristian Hengster-Movric, PhD
Karlovo namesti,
13,
12000 Praha 2

Abstrakt

Budeme zkoumat matematické epidemiologické modely, přičemž vezmeme v úvahu jak dávkové, tak síťové kompartmentové modely. Budou uvažovány různé způsoby kontroly průběhu epidemií, přičemž budou rozlišeny intervence farmakologické a nefarmakologické. Ljapunovova teorie kompartmentálních nezáporných systémů bude použita pro pokus o prokázání stability bezchorobné rovnováhy pro globální závěry, zatímco linearizace pro lokální závěry. Kromě toho budeme formulovat aktuální výzvy v oblasti veřejného zdraví jako problémy kontroly zpětné vazby. Budou zkoumány speciálně vyvinuté modely pro SARS-CoV-2. Na závěr vyzkoušíme použitelnost navržených ovládacích prvků ve světle neúplných dat.

Klíčová slova: epidemiologické modely, modelování, kontrola, COVID-19

Překlad názvu: Epidemiologické modelování a řízení

Contents

Figures

Tables

Chapter 1

Introduction

Diseases have always been an important part of human history. Right from the start of recorded history there have been epidemics that have caused many deaths before disappearing, sometimes returning years later, and sometimes diminishing in severity as populations develop immunity.

Even in the ancient past there were epidemics. The Antonine Plague (Plague of Galen) [12] of 165 to 180 AD, was the first pandemic impacting the Roman Empire. It is belived the plague was smallpox, although measles has also been suggested. Afterwards, the Plague of Cyprian [13] was a pandemic from about 249 to 262 AD that afflicted the Roman Empire. The agent of this plague is not known, but the suspects are smallpox, pandemic influenza, and viral hemorrhagic fever. The plague of Justinian [14] of 541 to 549 AD. This plague afflicted the entire Mediterranen Basin, Europe, and the Near East. Justinianic plague was bubonic plague. These pandemics have made a huge impact on the societys and cultures which makes it even more pressing to understand the effects of pandemic in the modern world today.

The Black Death [16](also known as the Pestilence, the Great mortality or the Plague) was a bubonic plague pandemic that affected Afro-Eurasia from 1346 to 1353. It is the deadliest pandemic in recorded human history, causing the deaths of 75- 200 million of people in Eurasia and North Africa, with a peak in Europe from 1347 to 1351.

Cholera [15] pandemics have occurred multiple times in the last 200 years, with the first pandemic originating in 1817. Concern about colera epidemics only grew when the European cities grew beyond the scale without having a proper sewerage system. As a result the Sanitation movement was founded which significantely improved the quality of life in European and American cities.

1918 influenza pandemic, also known as the "Spanish flu" [18], was an exceptionally deadly global pandemic. Estimates of deaths ranges from 17 million to 50 million, and possibly as high as 100 million.

The start of more recent pandemics was in 2002 with SARS-CoV-1 [17], which caused severe acute respiratory syndrome. Later in 2009 a pandemic of Swine flu happened which lasted until 2010. Covid-19 [19] or the coronavirus disease is a contagious disease caused by the SARS-CoV-2 virus. This epidemic that is still ongoing and the one that caused around 6 million deaths in the world.

Beside epidemics, there are also diseases that become endemic in some populations. At the present it seems that the Covid-19 could become endemic disease, since some countries are already declaring it an endemic disease (Spain).

1.1 History

In 1662 John Graunt, a London haberdasher, published his book "Natural and Political Observations made upon the Bills of the Mortality", and in doing so established the field of epidemiology. Graunt brought to light a diversity of facts about human life and disease that had not previously been appreciated.

The first model of mathematical epidemiology is considered to have appeared in the work of the Daniel Bernoulli (1700-1782) on inoculation against smallpox. Variolation, essentially inoculation with a mild strain, was introduced as a way to produce lifelong immunity against smallpox, but with a small risk of infection and death. There was heated debate about variolation, and Bernoulli was led to study the question of whether variolation was beneficial. His approach was to calculate the increase in life expectancy if smallpox could be eliminated as a cause of death [10].

An additional contribution to the knowledge on disease transmission process was obtained by the study of the temporal and spatial pattern of cholera cases in the 1855 epidemic in London by John Snow [9], who was able to pinpoint the Broad Street water pump as the source of the infection.
For us to be able to describe a mathematical model for the spread of a communicable disease, it is necessary to make some assumptions about the means of spreading infection. The modern view is that diseases are spread by the contact of humans through a virus or bacteria's.

W.H. Hamer was the founder of the idea that the spread of the infection should depend on the number of susceptible individuals and the number of infective individuals [4]. Hamer suggested a mass action law for the rate of new infections, and this idea has been basic in compartmental models since that time. It is worth noting that the foundations of the entire approach to epidemiology based on compartmental models were laid, not by mathematicians, but by public health physicians. Kermack and McKendrick in 1927 introduced the basic compartmental model as means to describe the

transmission of communicable disease. However, in order to describe this model, first the compartmental model in general will be described.

1.2 Comparmental models

Compartmental systems are a subclass of non-negative dynamical systems primarily governed by physical conservation laws, such as conservation of mass, energy, fluid, etc., pertaining to exchanges between different parts of the system -subsystems, compartments. Usually, each compartment is modelled as kinetically homogeneous, presuming instant perfect mixing of the content within it. Compartment contents are modeled as non-negative variables of state. The conservation laws imply evolution of the whole system's state on a non-negative orthant $\mathbb{R}^n$. Moreover, together with dissipation and transport of mass, energy or information, one finds an analogy of compartmental systems' dynamics to system thermodynamics. Compartmental models can be found in biological, social, medical, chemical, ecological, economic, demographic, queuing systems, LSS and stochastic (probabilistic) systems, as well as in telecommunications, transportation, power systems, heat transfer systems, (system) thermodynamics, structural vibration systems, to name just a few areas of application. Nonlinear non-negative compartmental systems exhibit rich dynamics, possibly even deterministic chaos. Property of compartmental models is that they can have non-isolated equilibria. By definition, such equilibria cannot be asymptotically stable. Instead, comparable notions useful for compartmental systems are convergence and *semistability*; wherein all limit points are Lyapunov stable but convergence to a particular limit point depends on initial conditions.
In *semistability* one thus has dependence of the final asymptotic steady-state on the precise initial state: a trajectory starting close to one non-isolated equilibrium point may very well end up, (converge), to another equilibrium point close to the original one. In fact, *semistability* implies Lyapunov stability and asymptotic stability implies *semistability*.

For such specialized model structures and stability notions, special stability guarantees are available. For example, non-oscillatory and only monotonic solutions can be guaranteed for compartmental systems under dissipativity. In considering passivity and dissipativity for compartmental systems, linear supply rates are of interest, which is not conventionally the case for general dynamical systems [1]. Characteristics of non-negative compartmental systems are:

- mass-action kinetics,
- directed flows and time-delays,
- non-negative inputs-constrained control space, e.g u $\in$[0,1],
- partial stability, semistability,

- convex linear programming problems,
- constrained optimization

1.2.1 Kermack-McKendrick epidemics models

Simple model introduced by Kermack and McKendrick in 1927 in order to describe the transmisson of communicable disease. The Kermack-McKendrick model is a non-negative compartmental model, based on relatively simple assumptions on the rates of flow between different classes of members of the population. The COVID-19 epidemic revived interest in epidemic models, which had been largely ignored.

To model an epidemic, we divide the population into three compartments S, I, and R. We let $S(t)$ represent the number of individuals who are susceptible to the disease, that is, who are not infected at time t. $I(t)$ stands for the number of infected individuals, assumed infectious and able to spread the disease by contact with susceptibles. $R(t)$ represents the number of individuals who were infected and then removed from the possibility of being infected again. Removal can be carried out through isolation from the rest of the population, or through immunization against infection, or through recovery from the disease or through death caused by the disease. The terminology SIR will be used to describe a disease that confers immunity against re-infection, to indicate the flow of individuals from the susceptible class S to the infective class I to the removed class R. Epidemics are usually diseases of this type. There are even models in case when once infected individuals is again susceptible to a diseases. The terminology SIS is used to describe one of those models. Usually, diseases caused by a virus are of SIR type while diseases caused by bacteria are of SIS type.

More complicated models are possible, for example, there are SEIR and SEIS models, with an exposed period between being infected and becoming infective, moreover, there are epidemics models with even more compartments, like SIDARTHE which was developed for the COVID-19 [5].

The general model includes the dependence of infectivity on the age of infection, that is, the time since becoming infected. What is often called the Kermack-McKendrick epidemic model is actually a special case of this general model introduced by Kermack and McKendrick in their 1927 paper.

The time t is the independent variable in these compartmental models. These models are initially formulated as differential equations, since the rates of transfer between compartments are explained mathematically as derivatives with respect to time of the sizes of the compartments. The assumption is made that the epidemic process is deterministic, that is,the behaviour of population is determined completely by its history and by the rules which describes the model. When formulating models in regard of the derivatives of the sizes of each compartment we assume that the number of members in the compartment is a differentiable function of time [2].

1.3 Simple Kermack-McKendrick Model

Starting point of the study will be the simple SIR disease model, or otherwise known as the special case of the model proposed by Kermack and McKendrick in 1927

$$\begin{aligned} \dot{S} &= -\beta SI \\ \dot{I} &= \beta SI - \alpha I \\ \dot{R} &= \alpha I. \end{aligned} \tag{1.1}$$

These are the assumptions of the SIR model:

- an average member of the population makes contact which are enough to transmit infection with βN others per unit time, where N represent total population size.
- infected leave the infective class at the rate αI per unit time.
- in this model there is no departure or entry into the population, and the population size is constant with the size N.

Important note for the SIR disease model is $N = S+I+R$. Since the assumption of a recovery proportional to the infectives has no clear epidemiological meaning, we will need to give it a more detailed mathematical explanation. The term "cohort" of members will represent the members who were all infected at one time, while the u(s) will denote the members who are still infective s-time units after having been infected [2]. The assumption says that α of these leave the infective class in unit time then

$$u^{'} = -\alpha u, \tag{1.2}$$

and the solution of this differential equation is

$$u(s) = u(0)e^{-\alpha s}. \tag{1.3}$$

As a result, it can be seen that those who remain infective s-time units after becoming infective is $e^{-\alpha s}$, so that the length of the infective period is distributed exponentially with mean $\int_0^\infty e^{-\alpha s} ds = 1/\alpha$, and this is what the second assumption really assumes.
This model can be only represented with the first two equations, or the R equation can be dropped since R is determined from S and I

$$\begin{aligned} \dot{S} &= -\beta SI \\ \dot{I} &= \beta SI - \alpha I, \end{aligned} \tag{1.4}$$

with the initial conditions $S(0) = S_0,\ I(0) = I_0,\ S_0 + I_0 = N$ [2].
In the Figure 1.1 the susceptible, infective and recovered compartment for the SIR uncontrolled model can be seen. The behaviour of the system is nicely shown, while the infectives are increasing the susceptible are decreasing until

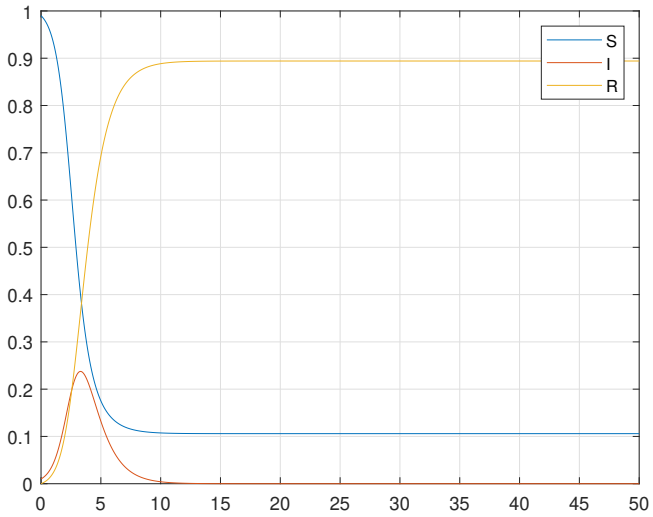


Figure 1.1: Uncontrolled SIR model.

there are not enough susceptible that would keep "feeding" the infectives. The big question with epidemics models is, when the small number of infectives is introduced into a population, will this number of infectives cause an epidemic. Since epidemics model are part of non-negative compartmental, then this model makes sense only as long $S(t)$ and $I(t)$ remain non-negative. It can be observed that $\dot{S} < 0$ for all t and $\dot{I} > 0$ if and only if $S_0 > \alpha/\beta$. As a result I increases so long as $S > \alpha/\beta$ but since S decreases for all t, I in the end decreases and reaches zero. The conclusion is that if $S_0 < \alpha/\beta$, I decreases to zero (no epidemic), while if $S_0 > \alpha/\beta$, I first increases to a maximum attained when α/β and then decreases to zero (epidemic). Quantity $\beta S_0/\alpha$ is called the basic reproduction number R_0. Basic reproduction number determines if there is an epidemic or not, if $R_0 < 1$ the infection dies out, while if $R_0 > 1$ there is an epidemic. The definition of the R_0 is that it represents the number of secondary infections caused by a single infective introduced into a whole susceptible population of size $N \approx S_0$ over the course of the infection of this single infective [2]. In this case an infective makes βN contacts in unit time, all of which are susceptible and thus produce new infections, and the mean infective period is $1/\alpha$, therefore the basic reproduction number is actually $\beta N/\alpha$. This can be easily shown in the Matlab simulink simulation. If the population is $N = 1$, then the maximum value the S_0 can have is 1, then the case of having no epidemics is provided if $R_0 < 1$ or $\beta/\alpha < 1$, which can be seen in the Figure 1.1. However in the Figure 1.2, the case when the infected are first increasing and after some time are decreasing, can be seen, or in other words the epidemic case. In the case of the population being $N=$ 1, then the S_0 can have the value 1 at the maximum. If the reproduction number is $R_0 > 1$ then the no epidemics case is satisfied if $\beta/\alpha > 1$, or in other words, if the rate of infection is less then rate of recovery then the spread stops.

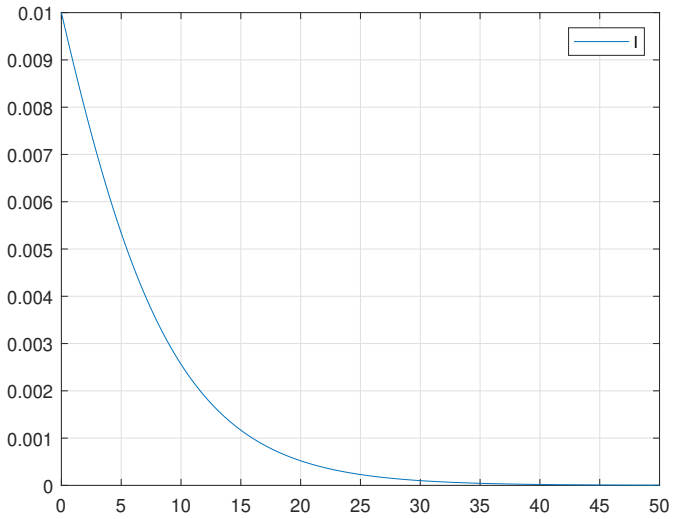


Figure 1.2: The number of infected in non-epidemic case.

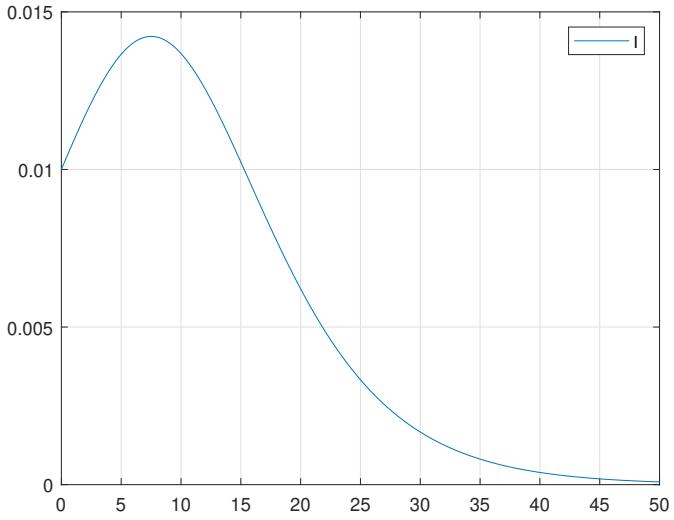


Figure 1.3: The number of infected in epidemic case.

1.4 Network epidemics models

To introduce network epidemics models, first, the network theory will be introduced. Network theory can be described as a link of graphs to real-world phenomena. The graph represents a set of mutually interconnected objects. In graph theory, objects are usually called nodes or vertices, while

the connections between nodes are usually called edges. In epidemiology, it can be simply referred to as individuals and their contacts. To simulate epidemics over a network of contacts, we need to record the infection status of all individuals. The easiest way of doing it, is by defining a vector for the infection status, in which the i-th element describes whether the i-th individual (node) of the network is infected.

In contrast to batch epidemics models, network epidemics models are based on a detailed study of mixing patterns in populations and assume a great deal of knowledge about the contact structure. This makes the parameter estimation and model validation that much more difficult for the network models. Network models divide a whole population into subgroups having different contact patterns to give very detailed predictions including the effects of various management strategies that treat various segments of the population differently. For the simple SIR model, if we are speaking in the terms of network epidemics dynamics each graph node is endowed with a population, s_i,x_i,r_i, $i = 1, 2, ...N$, the dynamics of which is influenced from its neighboring nodes, in this way we can model the contact of populations from different cities, regions, countries, or different groups in a population. While network models can give very detailed predictions, they have some big disadvantages. For a detailed network model, simulations take a long time and it makes it difficult to examine a significant range of parameter values, and also it is difficult to determine the sensitivity concerning the parameters of the model. The following are examples of network epidemics models:

1. nSI:

$$\dot{s}_i = -\beta s_i \sum_j A_{ij} x_j$$

$$\dot{x}_i = \beta s_i \sum_j A_{ij} x_j$$

NOTE: If the case is that s_i, x_i refers to a single individual, then this individual is either susceptible or infected, indeed one individual cannot infect itself. Therefore, it can be easily seen that it makes perfect sense to have $A_{ii} = 0$. However if the s_i, x_i refer to the batch i (city, region, age group), then one can have infection from the same batch (for example from the same city), and different fractions of the same batch can be susceptible or infected.

2. nSIR:

$$\dot{s}_i = -\beta s_i \sum_j A_{ij} x_j$$

$$\dot{x}_i = \beta s_i \sum_j A_{ij} x_j - \gamma x_i$$

$$\dot{r}_i = \gamma x_i$$

Constraint $s_i + x_i + r_i = 1, \forall i$.

1.5 The Next Generation Matrix

The next generation matrix comes from the idea of calculating a matrix whose (i, j) entry is the number of secondary infections caused in compartment i by an infected individual in compartment j. If the assumption is that there are n disease compartments and m non-disease compartments, and if $x \in \mathbb{R}^n$ and $y \in \mathbb{R}^m$ are the sub-populations in each of these compartments. Moreover, if the $\mathcal{F}_i$ represents the rate at which the i-th disease compartment is increased by a secondary infection, and if the $\mathcal{V}_i$ represent the rate at which disease progression, death and recovery decrease the i-th compartment [2]. Therefore the model can be written in the form

$$\begin{aligned} \dot{x}_i &= \mathcal{F}_i(x, y) - \mathcal{V}_i(x, y), \ i = 1, ..., n, \\ \dot{y}_j &= g_j(x, y), j = 1, ..., m. \end{aligned} \tag{1.5}$$

The following assumptions on $\mathcal{F}$ and $\mathcal{V}$ are made:

- $\mathcal{F}_i(x, y) \geq 0, \ \forall x, y > 0 \ and \ i = 1, ..., n,$
- $\mathcal{V}_i(x, y) \geq 0, \ whenever \ x_i = 0, \ i = 1, ..., n,$
- $\sum_{i=1}^{n} \mathcal{V}_i(x, y) \geq 0, \ \forall x, y > 0.$

After linearizing the model at a disease-free equilibrium and coming to some conclusions as the result, the matrix $K = FV^{-1}$, which will be called the next generation matrix is obtained.
The F and V are $n \ x \ n$ matrices

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

The element of the next generation matrix K_{ij} represent the expected total number of secondary infections produced in infective compartment i during the evolution of the system due to infected individuals from infective compartment j. The next generation matrix is a non-negative matrix and $R_0 = \rho(FV^{-1})$, the basic reproduction number is the Perron-Frobenius eigenvalue of the next generation matrix. The related non-negative Perron eigenvector $\omega \succeq 0$, $FV^{-1}\omega = \rho(FV^{-1})\omega$, gives the relative initial index case distribution over infective compartments conducive to the greatest number of secondary infections per generation. According to the Perron-Forbenius theorem, as a result if the positive matrix FV^{-1} is irreducible, then the reproduction number is a simple eigenvalue.

Chapter 2

Models with non-pharmacological interventions

Epidemics models or non-negative compartmental models can be easily modified to models with interventions or models with multiple compartments that represent different scenarios. Interventions in the epidemiological model can be non-pharmacological, like quarantine and isolation, and contact restrictions or pharmacological, like vaccines. Important note is that the conclusions made for the simple Kermack-McKendrick (SIR) epidemic model also hold for the more complicated compartmental models. These models can be seen in [2], and they can incorporate vaccination, or quarantine and isolation, asymptomatic and symptomatic cases of disease, etc. As a part of the models with non-pharmacological interventions, the modified SIR, and the model with quarantine and isolation will be explained in the next section.

2.1 Modified SIR

In the SIR model, the effect of the contact restrictions can be implemented with β chosen as a function of the proportion of the number of infected in the form of $\beta(i) = \beta_0(i - i_0)^{2n}$, where the number of infected can be simply kept as small as requested where it could be limited by i_0, beside this, the limit is set on the function that if $i > i_0$, the function is 0, as shown in the Figure 2.1. This representation of the restrictions is ideal, since in the real case the restrictions are imposed based on the past number of infected individuals, which can only be imperfectly known, and maintained at a constant level for a period of time, rather than reacting instantaneously to the changing number of infected individuals.

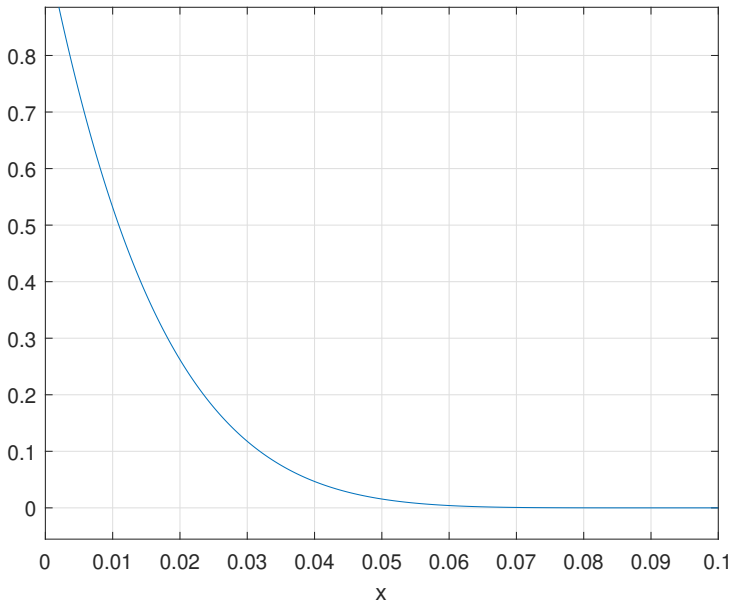


Figure 2.1: Beta as a function of the proportion of infected.

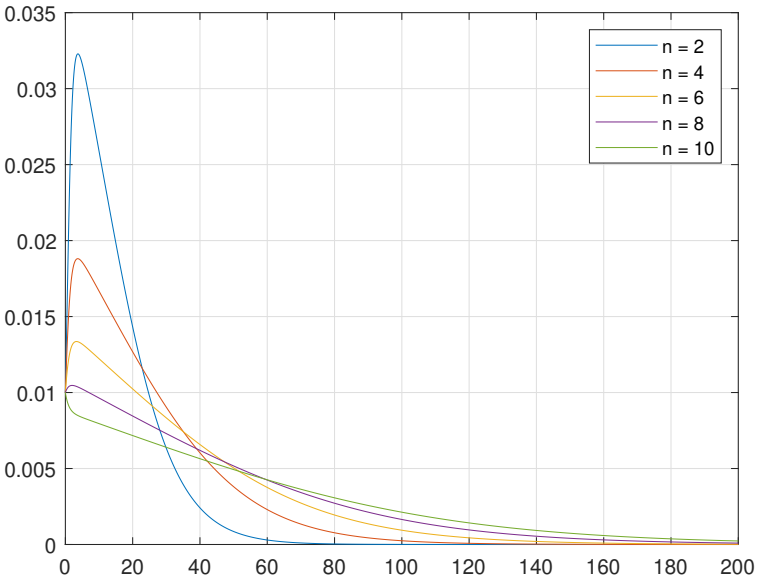


Figure 2.2: Evolution of the number of infected for different power of the polynomial.

The higher the power in the polynomial, the faster the polynomial goes close to zero, however the influence on the epidemic will be that it will last longer. As shown in the Figure 3.2. for the large enough power of the polynomial it is possible to accomplish the stability of a disease free equilibrium, however

the duration of the epidemic is prolonged. To make the restrictions more

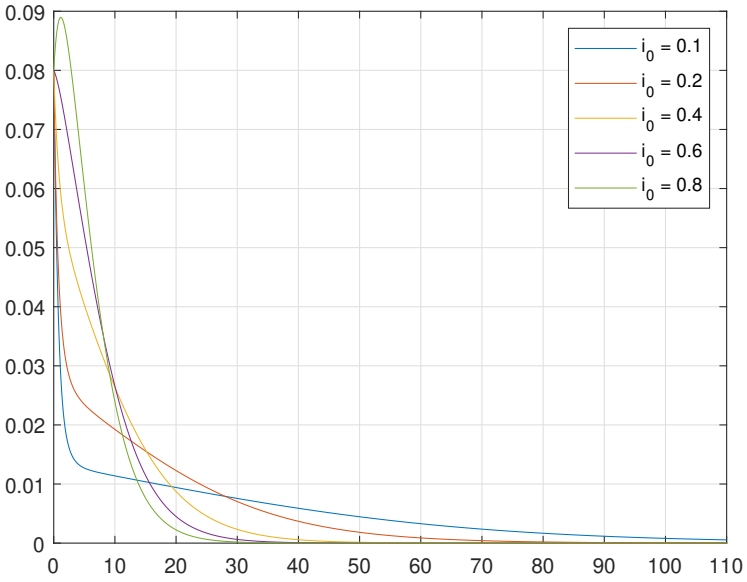


Figure 2.3: Infected for variated i_0.

realistic, the delay can be added to the calculation of the beta coefficient. In reality the detection of the current number of infected individuals is not immediate, moreover the restrictions are always implemented based on the previous number of infective members. In the Figure 3.4 and Figure 3.5 the

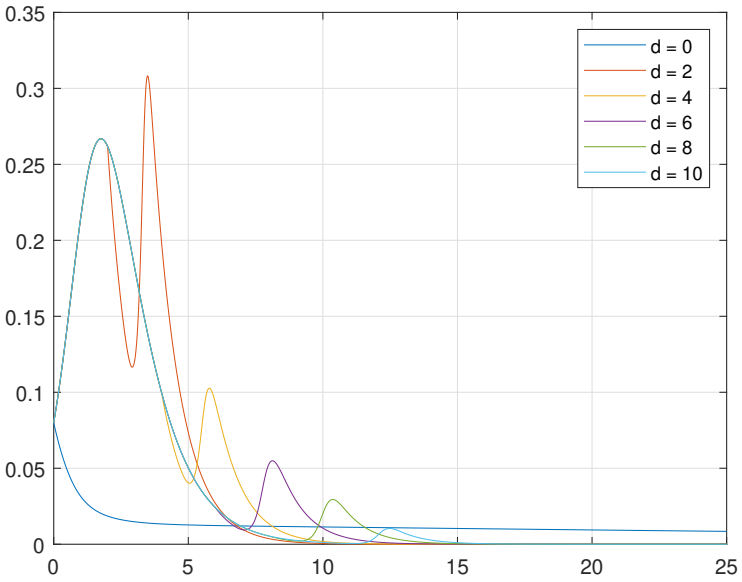


Figure 2.4: Infected in SIR model with different delay.

d represent how long the delay is, and it can be seen how the delay influences the behaviour of the system. Even for the relatively short delay the behaviour changes from a non-epidemic case to an epidemic case.

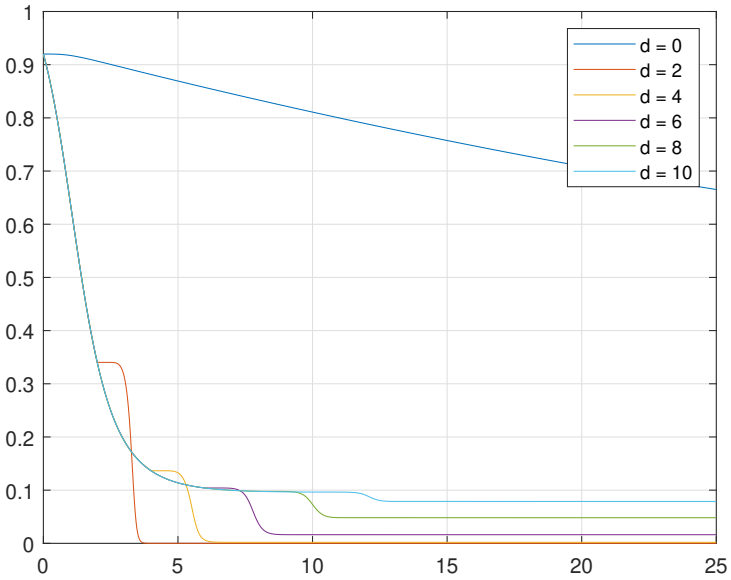


Figure 2.5: Susceptible in SIR model with different delay.

2.2 Quarantine and Isolation Model

In case when vaccination is not available, especially in the outbreak of a new disease, isolation of diagnosed infectives and quarantine of people who are suspected of having been infected, are the only control measures. The model is originally developed for the modeling the SARS epidemic of 2002-03, and it is called SEQIJR model [2]. SEQIJR model consists of the following equations

$$\begin{aligned}
\dot{S} &= -\beta S(\epsilon_E E + \epsilon_E \epsilon_Q + I + \epsilon_J J) \\
\dot{E} &= \beta S(\epsilon_E E + \epsilon_E \epsilon_Q + I + \epsilon_J J) - (\kappa_E + \gamma_Q)E \\
\dot{Q} &= \gamma_Q E - \kappa_Q Q \\
\dot{I} &= \kappa_E E - (\alpha_I + \gamma_J)I \\
\dot{J} &= \kappa_Q Q + \gamma_J I - \alpha_J J \\
\dot{R} &= \alpha_I I + \alpha_J J.
\end{aligned} \tag{2.1}$$

Compartment S represents susceptible, E stands for exposed members to the infection, Q represents quarantined members, I represents infected members and J represents isolated members. In this model the exposed members may be infective with infectivity reduced by a factor ϵ_E $(0 \leq \epsilon_E \leq 1)$. Exposed

members who are not isolated become infective at rate κ_E, while they became quarantined at a proportional rate γ_Q in unit time. Quarantinte is not perfect, but it reduces the contact rate by a factor ϵ_Q. Detection of the infecitves is done at a proportional rate γ_J. Infectives that are detected become isolated. Isolation is not perfect and there may still be transmission of disease by isolated members with an infectivity factor of ϵ_J. The rate at which quarantined members develop symptoms and become isolated is represented by κ_Q. Parameters α_I and α_J represent the infectives that leave the infecitve class, and isolated members that leave isolation class respectively. In this model the parameters γ_Q and γ_J are control parameters, however the parameters ϵ_Q and ϵ_J depend on the how perfect quarantine and isolation are, and thus also control measures in some sense [2].

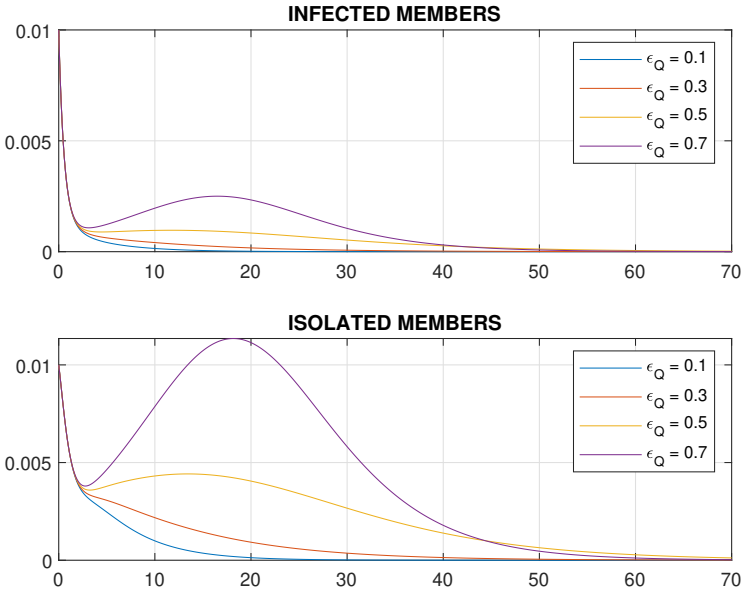


Figure 2.6: Quarantine model

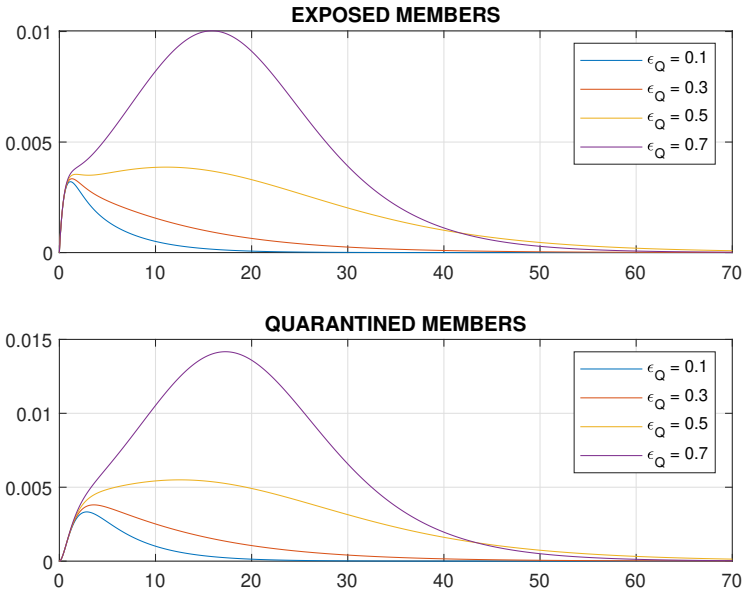


Figure 2.7: Quarantine model

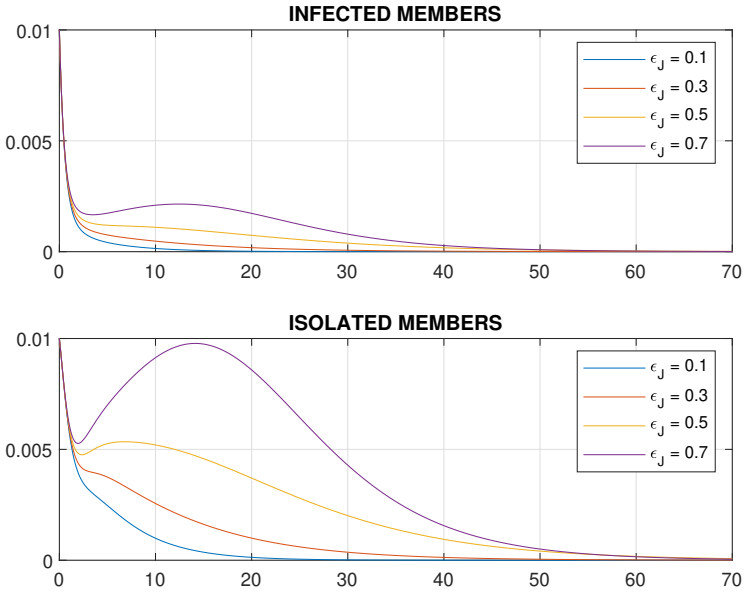


Figure 2.8: Quarantine model

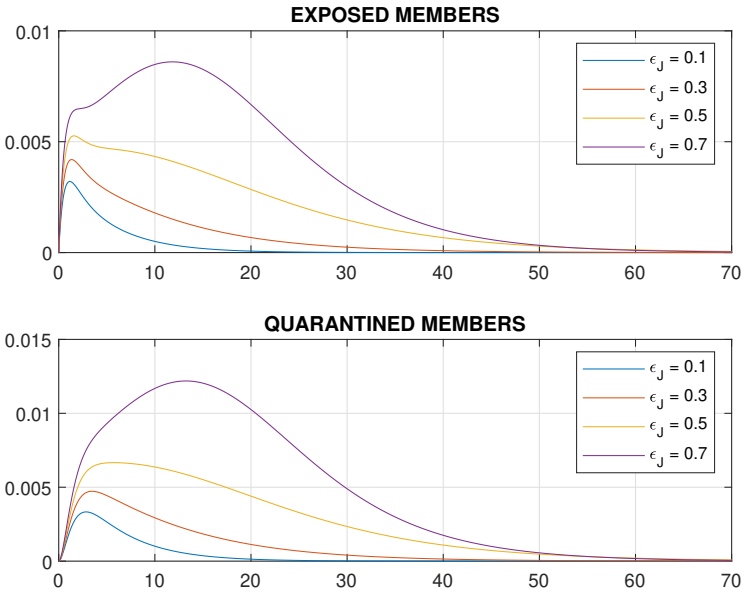


Figure 2.9: Quarantine model

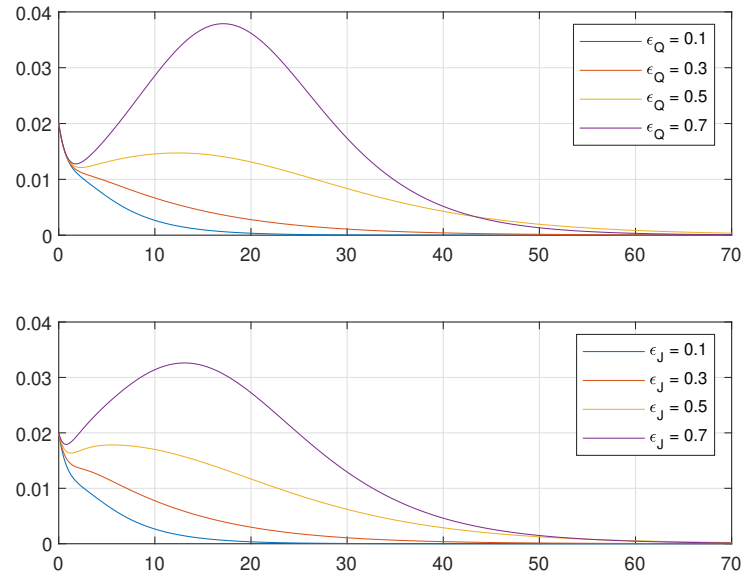


Figure 2.10: Sum of exposed, quarantined, infected and isolated members

In the figures 2.6, 2.7, 2.8 and 2.9, the infective compartments of the model are observed based on the perfection of quarantine and isolation. Based on these results from the simulation it can be concluded that the perfection of the quarantine has more impact on the number of members in infective compartments, in other words to control an epidemic it is more important to

have perfect quarantine then isolation.

2.3 The next generation matrix of the Quarantine-isolation model

The infective compartments in the model 2.2 are E, Q, I and J, while the non infective are S and R. The $\mathcal{F}$ and $\mathcal{V}$ can be written as

$$\mathcal{F} = \begin{bmatrix} \beta S(\epsilon_E E + \epsilon_E \epsilon_Q Q + I + \epsilon_J J) \\ \gamma_Q E \kappa_E E \kappa_Q Q + \gamma_J I \end{bmatrix}, \tag{2.2}$$

and

$$\mathcal{V} = \begin{bmatrix} (\kappa_E + \gamma_Q)E \\ \kappa_J Q \\ (\alpha_I + \gamma_J)I \\ \alpha_J J \end{bmatrix}; \tag{2.3}$$

as a result F and V are

$$F = \begin{bmatrix} \beta\epsilon_E S & \beta\epsilon_E\epsilon_Q S & \beta S & \beta\epsilon_J S \\ \gamma_Q & 0 & 0 & 0 \\ \kappa_E & 0 & 0 & 0 \\ 0 & \kappa_Q & \gamma_J & 0 \end{bmatrix}, \tag{2.4}$$

$$V = \begin{bmatrix} \kappa_E + \gamma_Q & 0 & 0 & 0 \\ 0 & \kappa_J & 0 & 0 \\ 0 & 0 & \alpha_I + \gamma_J & 0 \\ 0 & 0 & 0 & \alpha_J \end{bmatrix}, \tag{2.5}$$

$$V^{-1} = \begin{bmatrix} \frac{1}{\kappa_E+\gamma_Q} & 0 & 0 & 0 \\ 0 & \frac{1}{\kappa_J} & 0 & 0 \\ 0 & 0 & \frac{1}{\alpha_I+\gamma_J} & 0 \\ 0 & 0 & 0 & \frac{1}{\alpha_J} \end{bmatrix}, \tag{2.6}$$

and finally the next generation matrix for the quarantine-isolation model is

$$K_L = FV^{-1} = \begin{bmatrix} \frac{\beta\epsilon_E S}{\kappa_E+\gamma_Q} & \frac{\beta\epsilon_E\epsilon_J S}{\kappa_J} & \frac{\beta S}{\alpha_I+\gamma_J} & \frac{\beta\epsilon_J S}{\alpha_J} \\ \frac{\gamma_Q}{\kappa_E+\gamma_Q} & 0 & 0 & 0 \\ \frac{\kappa_E}{\kappa_E+\gamma_Q} & 0 & 0 & 0 \\ 0 & \frac{\kappa_Q}{\kappa_J} & \frac{\gamma_J}{\alpha_I+\gamma_J} & 0 \end{bmatrix}. \tag{2.7}$$

Important note is that the basic reproduction number is actually the Perron-Forbenius eigenvalue. The next generation matrix of quarantine-isolation model has 4 eigenvalues, of which one is 0, one is positive, and the other two are complex conjugate pair. By the Perron-Forbenius theorem, the Perron-Forbenius eigenvalue in this case is the positive eigenvalue. Since the expression for this eigenvalue is complex and quite long it is not written here.

Chapter 3

Models with pharmacological interventions

Vaccination models are a special case of models with pharmacological interventions. There are other types of pharmacological interventions (treatments), however since in the ongoing epidemic (COVID-19) the treatments are not widely available, models with vaccination are more interesting. In the next section vaccination model will be explained as well as the model when the new strain of the disease is introduced in the population.

3.1 Vaccination model

The vaccination model is taken from the [2]. The effects of vaccination can be modeled in different ways, depending whether the vaccination is preformed before the likely outbreak of an epidemic, as it is done before the "flu" season, or during the ongoing epidemic (like in the COVID-19). First, the vaccination model that has a fraction of the population vaccinated before epidemic is considered. The resulting model is

$$\begin{aligned} \dot{S}_U &= -\beta S_U(I_U + \delta I_V) \\ \dot{S}_V &= -\sigma\beta S_V(I_U + \delta I_V) \\ \dot{I}_U &= \beta S_U(I_U + \delta I_V) - \alpha_U I_U \\ \dot{I}_V &= \sigma\beta S_V(I_U + \delta I_V) - \alpha_V I_V \\ \dot{R} &= \alpha_V I_V + \alpha_V I_V, \end{aligned} \tag{3.1}$$

The initial conditions are as follows $S_U(0)$, $S_V(0)$, $I_U(0)$ and $I_V(0)$, where they represent the fraction of the population that is not infected and not vaccinated, the fraction of the population that is not infected and vaccinated, the fraction of the population that is infected and not vaccinated and the fraction of the population that is infected and vaccinated. The parameter σ represents how much the vaccinated members have susceptibility to infection reduced. Parameter σ can have values $0 \leq \sigma \leq 1$, with $\sigma = 0$ describes a perfectly effective vaccine, and $\sigma = 1$ describing a vaccine that has no effect at all. The assumption is also made that the vaccinated members who are infected have infectivity reduced by a factor δ. The parameters α_U, α_V represent the recovery rate of the infected unvaccinated individuals and

infected vaccinated individuals respectively. There are two different recovery rates because it can be assumed that the vaccinated individuals have a better recovery rate then those who are not vaccinated.

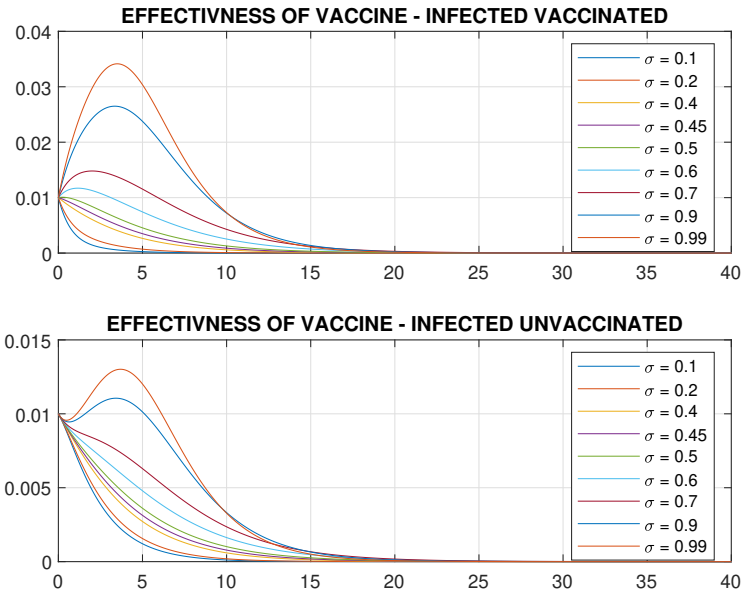


Figure 3.1: Effectiveness of the vaccine in a vaccination model.

The Figure 3.1 shows how the effectiveness of vaccine impacts the model. It is clear that it is possible to accomplish stable disease-free equilibrium if the vaccine is effective enough. It affects both the vaccinated and unvaccinated individuals.

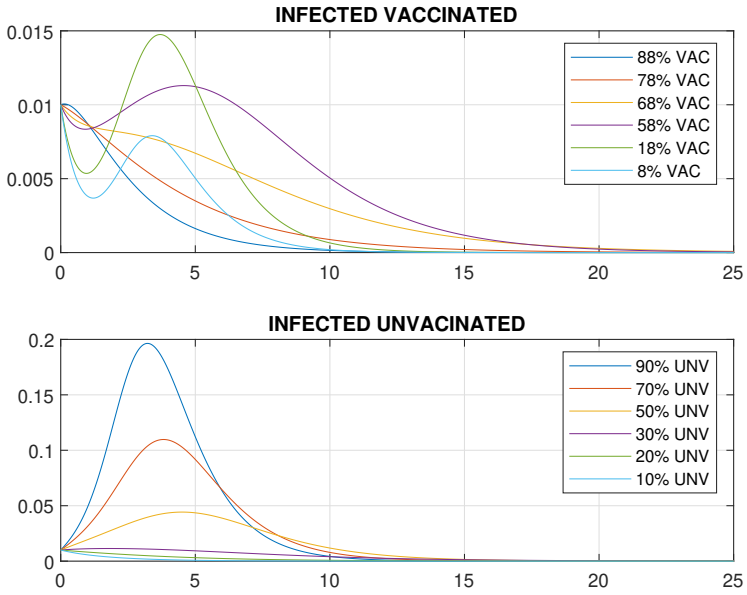


Figure 3.2: Percentage of the population vaccinated before the epidemic

In the Figure 3.2 the results are shown based on the percentage of the vaccinated population. The number of the infected vaccinated and unvaccinated both will be affected by this. It can be also seen that stable disease-free equilibrium can be accomplished.

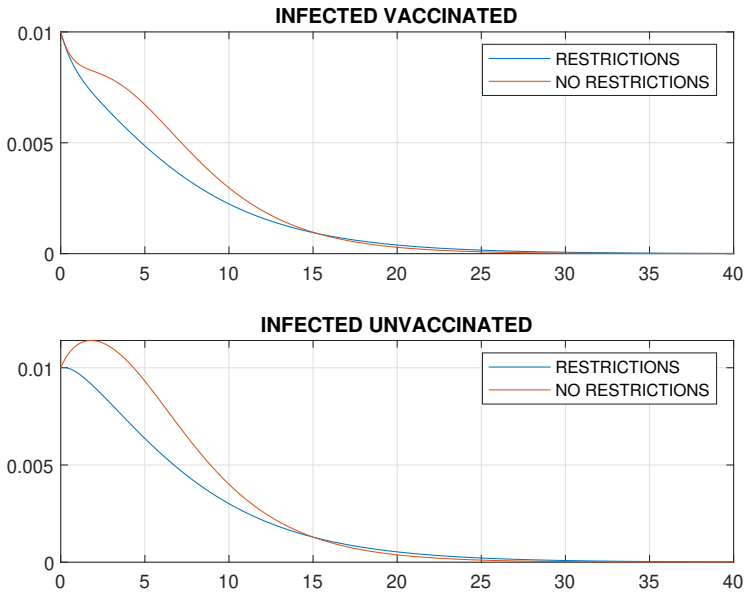


Figure 3.3: Impact of restrictions in vaccination model

In the Figure 3.3 it shows the result when the ideal contact restrictions are

implemented in the model as explained in the modified SIR model. Obviously the restrictions will help with controlling the epidemic.

3.2 The next generation matrix of the Vaccination model

In the model 3.1 the infective compartments are I_U and I_V, while the non infective ones are S_U and S_V, so $\mathcal{F}$ can be

$$\mathcal{F} = \begin{bmatrix} \beta S_U I_U + \beta\delta S_U I_V \\ \sigma\beta S_V (I_U + \delta I_V) \end{bmatrix} \tag{3.2}$$

and

$$\mathcal{V} = \begin{bmatrix} \alpha_U I_U \\ \alpha_V I_V \end{bmatrix} \tag{3.3}$$

as a result F and V will be

$$F = \begin{bmatrix} \beta S_U & \beta\delta S_U \\ \sigma\beta S_V & \sigma\beta\delta S_V \end{bmatrix}, \tag{3.4}$$

$$V = \begin{bmatrix} \alpha_U & 0 \\ 0 & \alpha_V \end{bmatrix}, \tag{3.5}$$

$$V^{-1} = \begin{bmatrix} \frac{1}{\alpha_U} & 0 \\ 0 & \frac{1}{\alpha_V} \end{bmatrix}. \tag{3.6}$$

Then the next generation matrix can be calculated as $K_L = FV^{-1}$

$$K_L = FV^{-1} = \begin{bmatrix} \frac{\beta S_U}{\alpha_U} & \frac{\beta\delta S_U}{\alpha_V} \\ \frac{\sigma\beta S_V}{\alpha_U} & \frac{\sigma\beta\delta S_V}{\alpha_V} \end{bmatrix}. \tag{3.7}$$

As described in the section 1.5, important property of the next generation matrix is that the Perron-Forbenius eigenvalue of the next generation matrix is the basic reproduction number. Therefore:

$$K_L - \lambda I = \begin{bmatrix} \frac{\beta S_U}{\alpha_U} - \lambda & \frac{\beta\delta S_U}{\alpha_V} \\ \frac{\sigma\beta S_V}{\alpha_U} & \frac{\sigma\beta\delta S_V}{\alpha_V} - \lambda \end{bmatrix}, \tag{3.8}$$

then the characteristic polynomial is

$$\lambda(\lambda - \frac{\beta S_U}{\alpha_U} - \frac{\sigma\delta\beta S_V}{\alpha_V}). \tag{3.9}$$

Based on the Perron-Forbenius theorem, the Perron-Forbenius eigenvalue is $\lambda = \frac{\beta S_U}{\alpha_U} + \frac{\sigma\beta S_V}{\alpha_V}$, as described the basic reproduction number is the Perron-Forbenius eigenvalue, therefore

$$R_0 = \frac{\beta S_U}{\alpha_U} + \frac{\sigma\beta S_V}{\alpha_V}. \tag{3.10}$$

It is known that the basic reproduction number determines if there is an epidemic or not. If the $R_0 < 1$ the infection dies out. Therefore, in this case, in order for the infection to die out the following condition needs to be satisfied

$$R_0 = \frac{\beta S_U}{\alpha_U} + \frac{\sigma \beta S_V}{\alpha_V} < 1. \tag{3.11}$$

3.3 New strain introduced

It is important to consider the model when the new strain or version of the disease is introduced. This can be seen in the recent outbreak of different strains of COVID-19, like Omicron, or Delta variant of a COVID-19. The new strain of a disease can significantly impact the epidemic dynamics, especially in case of pharmacological intervention such as vaccine, if the vaccine is less efficient for the new strain of the disease.

The model when the new strain is introduced reads

$$\begin{aligned}
\dot{S}_U &= -S_U(\beta_1(I_{U1} + \delta I_{V1}) + \beta_2(I_{U2} + \delta I_{V2})) \\
\dot{S}_V &= -S_V(\beta_1\sigma_1(I_{U1} + \delta I_{V1}) + \beta_2\sigma_2(I_{U2} + \delta I_{V2})) \\
\dot{I}_{U1} &= S_U(\beta_1(I_{U1} + \delta I_{V1})) - \alpha_U I_{U1} \\
\dot{I}_{U2} &= S_U(\beta_2(I_{U2} + \delta I_{V2})) - \alpha_U I_{U2} \\
\dot{I}_{V1} &= S_V(\beta_1\sigma_1(I_{U1} + \delta I_{V1}) - \alpha_V I_{V1} \\
\dot{I}_{V2} &= S_V(\beta_2\sigma_2(I_{U2} + \delta I_{V2}) - \alpha_V I_{V2},
\end{aligned} \tag{3.12}$$

where the compartments are mostly the same as in the model 3.1, the main difference is in the subscripts 1 and 2, where the compartments and parameters with subscript 1 represent the first variant of the disease while the subscript 2 represent the strain of the disease. In this model the infected members by one variant of the disease cannot be infected with the other variant at the same time. In the figure 2.9 in the legend the 'I' stands for infected members,'VAC' for vaccinated members while the 'UNV' is for unvaccinated members, the 'S' is for the susceptible members and the 1 represents the original variant of the disease while the 2 is for new variant the one that can be more infectious. It can be seen in the Figure 2.9 when the epidemic is almost finished, when the small amount of the infective members with the new strain is introduced there is a peak in the infected members.[3]

3.4 Discrete vaccination model

To make a vaccination model more realistic, firstly the time is discretized, and the model consists of the following equations

$$S_U[t+1] = S_U[t] - \beta C S_U[t](I_U[t] + \delta I_V[t])$$

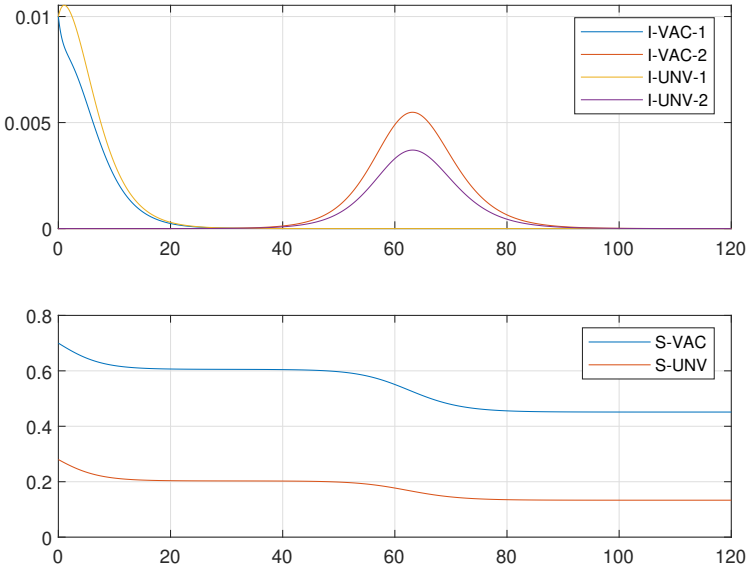


Figure 3.4: New strain model

$$S_V[t+1] = S_V[t] - \sigma\beta C S_V[t](I_U[t] + \delta I_V[t])$$

$$I_U[t+1] = I_U[t] + \beta C S_U[t](I_U[t] + \delta I_V[t]) - \alpha_U I_U[t] \tag{3.13}$$

$$I_V[t+1] = I_V[t] + \sigma\beta C S_V[t](I_U[t] + \delta I_V[t]) - \alpha_V I_V[t]$$

Beside this modification to the model 3.1, the population is split into three age groups (children, adults, seniors). The reason behind this is because it is known that SARS-CoV-2 differently impact children, adults and seniors [7]. In comparison with the previous models, the β is now 3x3 matrix as well as the parameter C, where C represents contact matrix, while the β is transmission matrix [6]. The transmission matrix β is assumed to have the following structure

$$\beta = \begin{bmatrix} \beta_1 & \beta_2 & \beta_2 \\ \beta_2 & \beta_3 & \beta_4 \\ \beta_2 & \beta_4 & \beta_5 \end{bmatrix} \tag{3.14}$$

where β_1 is a transmission probability between two children, β_2 is a transmission probability between children and adults or seniors, β_3 is a transmission probability between two adults, β_4 transmission probability between seniors and adults and β_5 is transmission probability between seniors [6]. In [6] parameters β_1, β_2, β_3, β_4, and β_5 are estimated by fitting the model to data on age-specific cumulative numbers of confirmed cases.
The contact matrix is expressed as a sum of the four specific contact matrices describing daily numbers of contacts at home (C_H), school (C_S), work (C_W),

and other types of contacts (C_O) [6]:

$$C_H = \begin{bmatrix} 1.52 & 0.67 & 0.036 \\ 2.84 & 2.05 & 0.20 \\ 0.93 & 0.58 & 0.75 \end{bmatrix}, \quad C_S = \begin{bmatrix} 4.77 & 0.20 & 0.0014 \\ 1.81 & 0.33 & 0.0075 \\ 0.022 & 0.019 & 0.022 \end{bmatrix}$$

$$C_W = \begin{bmatrix} 0.085 & 0.19 & 1.4 \cdot 10^{-5} \\ 0.42 & 5.28 & 9.4 \cdot 10^{-5} \\ 1.75 \cdot 10^{-5} & 0.00012 & 4 \cdot 10^{-5} \end{bmatrix}, \; C_O = \begin{bmatrix} 1.61 & 0.78 & 0.24 \\ 1.10 & 3.94 & 1.01 \\ 0.15 & 0.89 & 0.93 \end{bmatrix}$$

To make the model even more realistic, the decision making for the contact restrictions is based on the *risk index*, which is derived for the SARS-CoV-2. The risk index adds up points for the values of four *risk indicators*. These are:

1. the number of infected individuals in the last 14 days
2. the number of seniors that have been contracted in the last 14 days
3. the calculation of the reproduction number (if the virus is spreading in the population)
4. the average positivity of tests over the last 7 days

The risk index scale from 0 to 100, based on the points assigned to each of the indicators. In the [8] it shows how the actual contact restrictions for the SARS-CoV-2 were implemented in the Czech Republic based on the value of risk index. Considering the table in [8], similar contact restrictions were implemented in the model 3.3, in sense of lowering the values in the contact matrix based on the value of risk index. Moreover to make the model even more realistic the measures were held the same for some time. In Figure 3.5 the results can be seen, which are in some sense expected since the biggest proportion of infectives are unvaccinated members. It is worth mentioning, that the biggest transmission factor is for the adults, which as a result can be seen in the Figure 3.5 where the largest proportion of infectives are unvaccinated adults, moreover the vaccinated adults contribute a greater proportion of infectives than unvaccinated infected children.

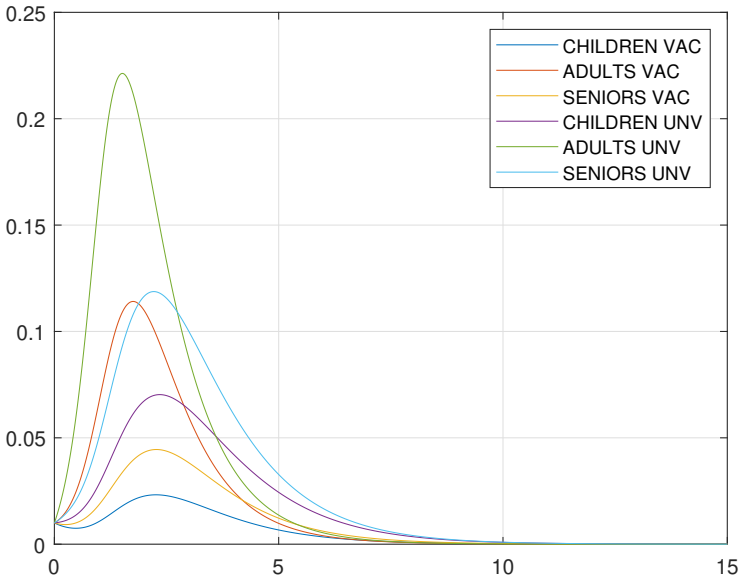


Figure 3.5: Infected vaccinated and unvaccinated splited into age cohorts

Chapter 4

Stability of a disease-free equilibrium

As in any controlled dynamical system, stability, global and asymptotic are of crucial interest, which in case of epidemics model is the stability of the disease free invariant set $i = 0$. Sometimes it can be concluded from the system parameters, but in general cases Lyapnov stability analysis is needed. An important note is that the epidemic systems are compartmental system, which is a subclass of non-negative dynamical systems.

4.1 Lyapunov analysis for non-negative compartmental systems

Non-negative compartmental systems defined by continuous-time dynamics

$$\dot{x} = f(x),\ x \in \mathbb{R}^n_+, \tag{4.1}$$

have their states evolving in the non-negative orthant $\mathbb{R}^n_+$if and only if $x_i = 0$, $f_i \geq 0, \forall x \in \mathbb{R}^n_+, \forall i$. Such dynamical systems are called essentially non-negative. Linear non-negative dynamical systems in continuous-time

$$\dot{x} = Mx,\ x \in \mathbb{R}^n_+, \tag{4.2}$$

necessarily have a Z-matrix [11] M. Such systems allow for special forms of Lyapunov functions, which allows us to simplify the Lyapunov analysis, where as in general this is not the case. One of those functions are so called linear copositive Lyapunov functions

$$V(x) = w^T x > 0,\ w \succ 0, \tag{4.3}$$

$$\dot{V}(x) = w^T f(x) < 0. \tag{4.4}$$

Furthermore, since in epidemics models considering fractions of the total constant population, the system state is restricted to a face of a n-simplex, which is itself $(n-1)$-simplex, those are compact subsets so an even more general conditions of LaSalle's invariant principle apply to guarantee global asymptotic stability of various invariant sets therein contained

$$V(x) = w^T x \geq 0,\ w \succeq 0, \tag{4.5}$$

$$\dot{V}(x) = w^T f(x) \leq 0. \tag{4.6}$$

This approach for the stability analysis can be shown on simple SIR epidemic model. Using Lyapunov methods, the stability and the convergence to the SIR disease-free equilibrium state $i = 0$, can be proven. Using linear Lyapunov functions $V_1(s, i, r) = s + i$ or $V_2 = i$, appropriate for positive compartmental systems with states in $\mathbb{R}^n_+$. After computing the derivative of the Lyapunov function the result is:

$$\dot{V}_1 = \dot{s} + \dot{i} = -\dot{r} = -\gamma i, \tag{4.7}$$

simply by looking the function 5.7 it can be concluded by Lasalle's invariance principle, that it converges to $i = 0$ equilibrium set for all $\gamma > 0$. However this function disregards the transfer between the susceptible and infected and takes into account only clearing of the infected to recovered. The second function is the proper function for the stability of $i = 0$ invariant set, more characteristic of the partial stability Lyapunov function. Furthermore, the derivative of the second Lyapunov function is

$$\dot{V}_2 = \dot{i} = (\beta s - \gamma)i, \tag{4.8}$$

given that $0 \leq s \leq 1$, $\dot{V}_2 = (\beta s - \gamma)i < 0$ for $\gamma > \beta$, again implying convergence by Lasalle's invariance principle to $i = 0$ for $r_0 < 1$. Important note is that the Lyapunov results are sufficient and not necessary.

4.2 Lyapunov analysis for vaccination model

Lyapunov analysis of the vaccination model 4.1 is done as it is described in the Section 5.1. Since the vaccination model is non-negative compartmental model Lyapunov linear functions can be used. Linear Lyapunov function for the model 4.1 is

$$V = I_U + I_V. \tag{4.9}$$

From the definition of the model it is known that $0 \leq I_U \leq 1$ and $0 \leq I_V \leq 1$. Moreover the Lyapunov function defined in the 5.9 is $0 \leq V \leq 1$.
The derivative of the Lyapunov function 5.9 is

$$\dot{V} = \dot{I}_U + \dot{I}_V \tag{4.10}$$

$$\dot{V} = \beta S_U(I_U + \delta I_V) - \alpha_U I_U + \sigma\beta S_V(I_U + \delta I_V) =$$

$$= I_U(\beta S_U + \sigma\beta S_V - \alpha_U) + I_V(\beta\delta S_U + \sigma\beta\delta S_V - \alpha_V)$$

Since the $0 \leq S_U \leq 1$ and $0 \leq S_V \leq 1$, and if the total population is 1 then $S_U + S_V + I_U + I_V + R = 1$ then $\dot{V}$ can never be as big as when the $S_U = 1$, $S_V = 1$, $I_U = 1$ and $I_V = 1$, which from the definition of the model is not possible.
So if the values of the S_U, S_V, I_U, I_V are replaced with 1. Then

$$\beta + \sigma\beta - \alpha_U + \beta\delta + \sigma\beta\delta - \alpha_V < 0$$

Then for the $\dot{V} < 0$ it is satisfied when

$$\beta < \frac{\alpha_U + \alpha_V}{1 + \sigma + \delta + \sigma\delta}. \tag{4.11}$$

4.3 Linearization of the model with quarantine and isolation at the disease-free equilibrium

Since model with quarantine and isolation is a nonlinear system it is useful to linearize the said model at the disease-free equilibrium. Disease-free equilibrium is the point $(N, 0, 0, 0, 0)$, however to simplify calculation $N = 1$. The linearization of 2.1 at the disease-free equilibrium has the system matrix

$$\begin{bmatrix} \epsilon_E\beta - (\kappa_E + \gamma_Q) & \epsilon_E\epsilon_Q\beta & \beta & \epsilon_J\beta \\ \gamma_Q & -\kappa_Q & 0 & 0 \\ \kappa_E & 0 & -(\alpha_I + \gamma_J) & 0 \\ 0 & \kappa_Q & \gamma_J & -\alpha_J \end{bmatrix}.$$

The characteristic polynomial of the corresponding matrix is a fourth degree polynomial. In order to check the behaviour of eigenvalues it is easier to keep all but one parameter fixed to obtain dependence on it alone.

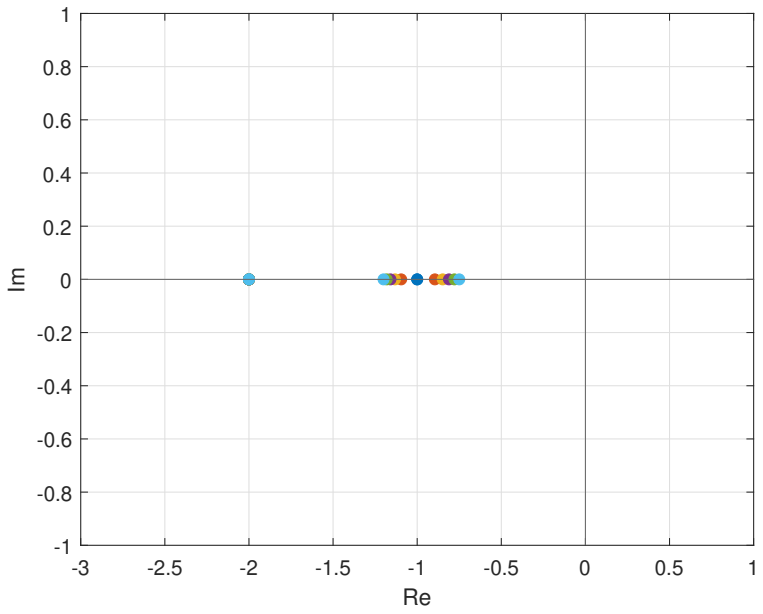


Figure 4.1: Variation of β.

In the figures the points with the same colors represent the eigenvalues for some value of varying parameter.

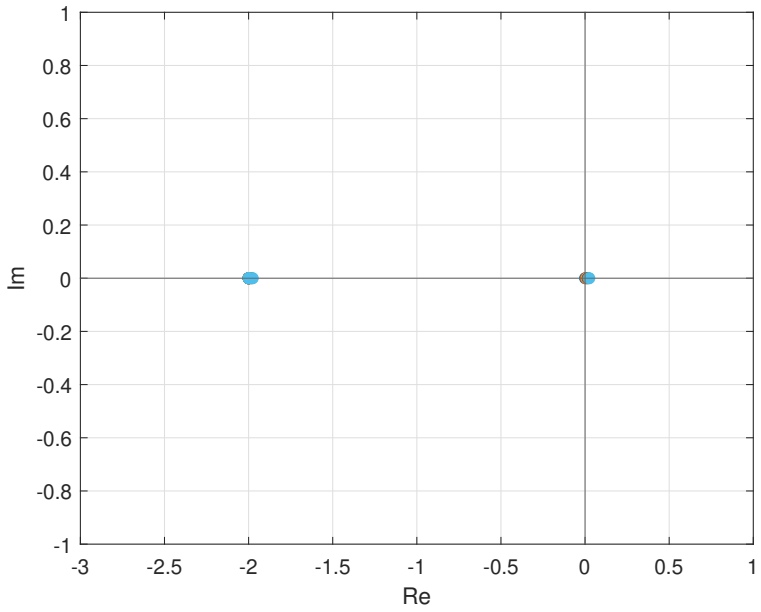


Figure 4.2: Variation of ϵ_E.

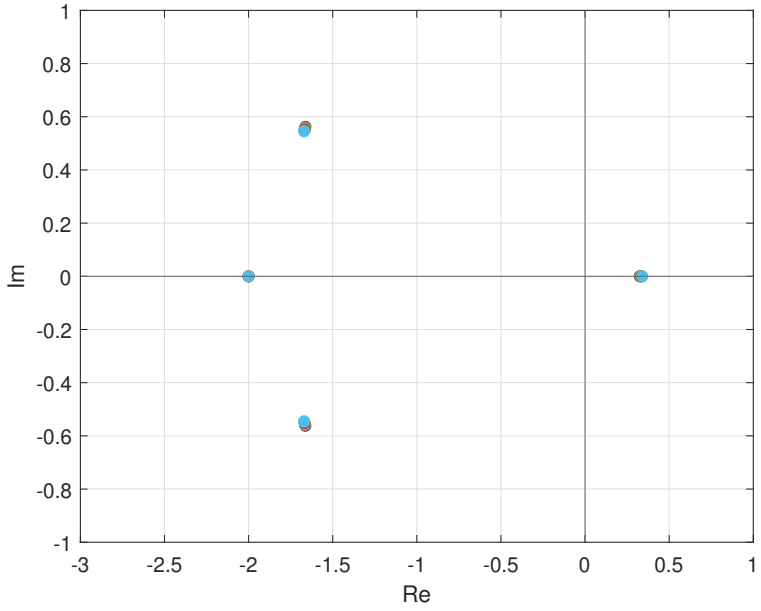


Figure 4.3: Variation of ϵ_Q.

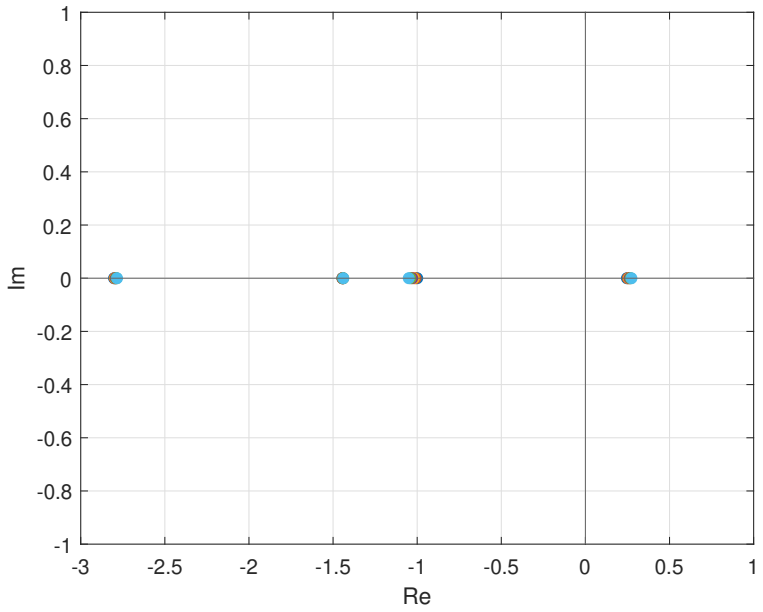


Figure 4.4: Variation of ϵ_J.

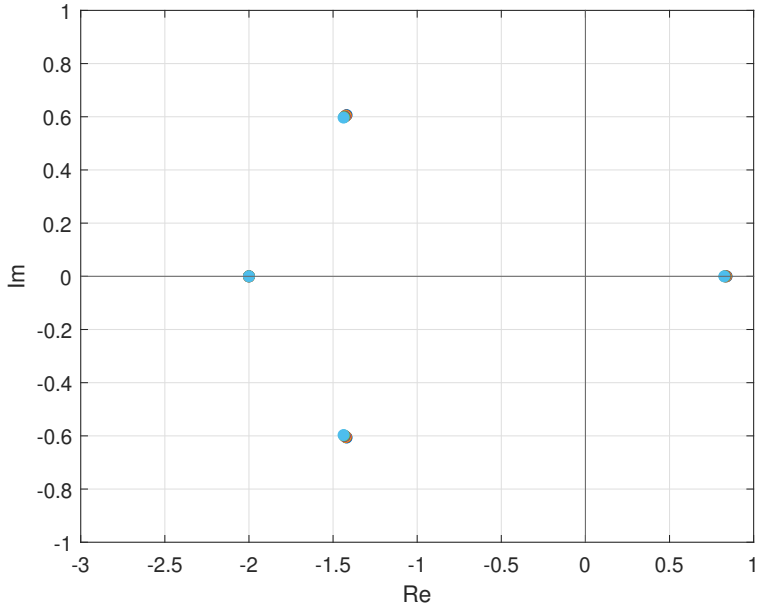


Figure 4.5: Variation of κ_E.

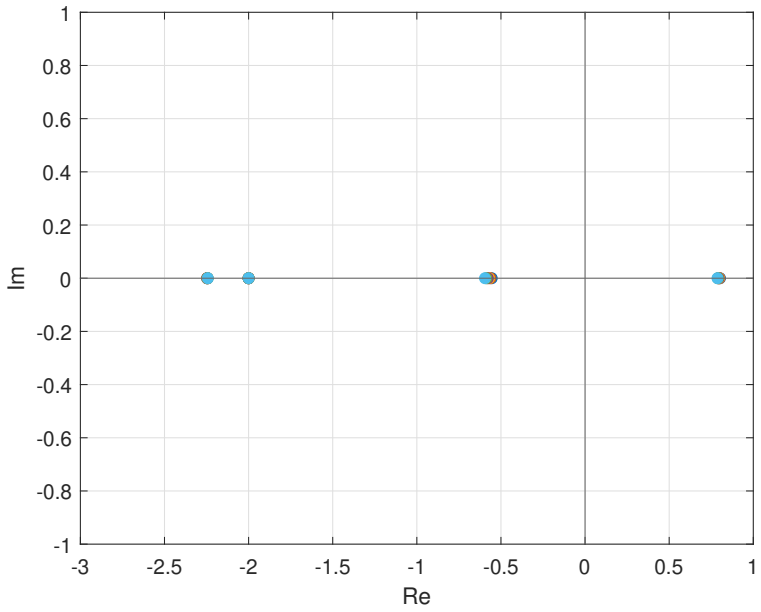


Figure 4.6: Variation of κ_Q.

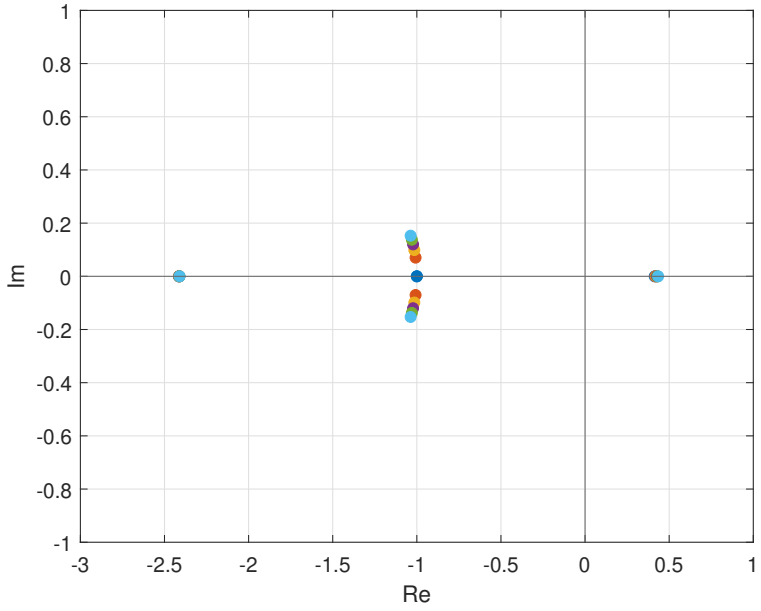


Figure 4.7: Variation of γ_Q.

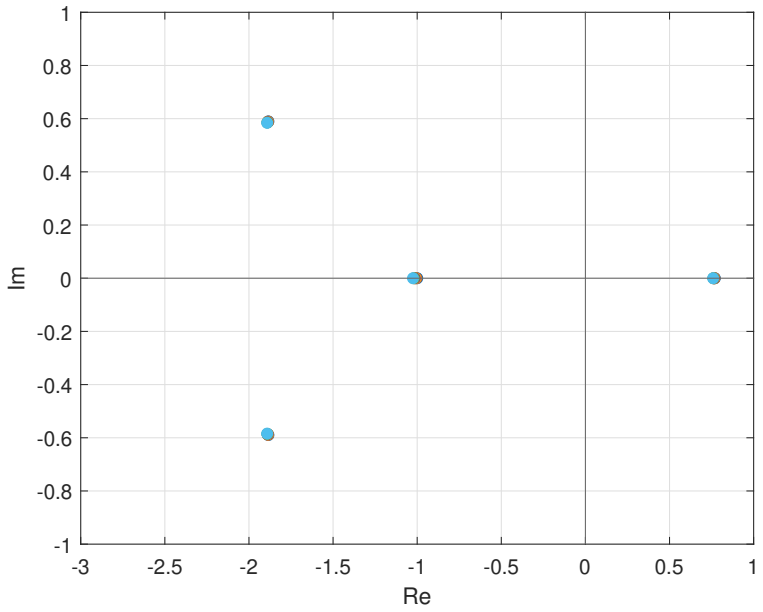


Figure 4.8: Variation of γ_J.

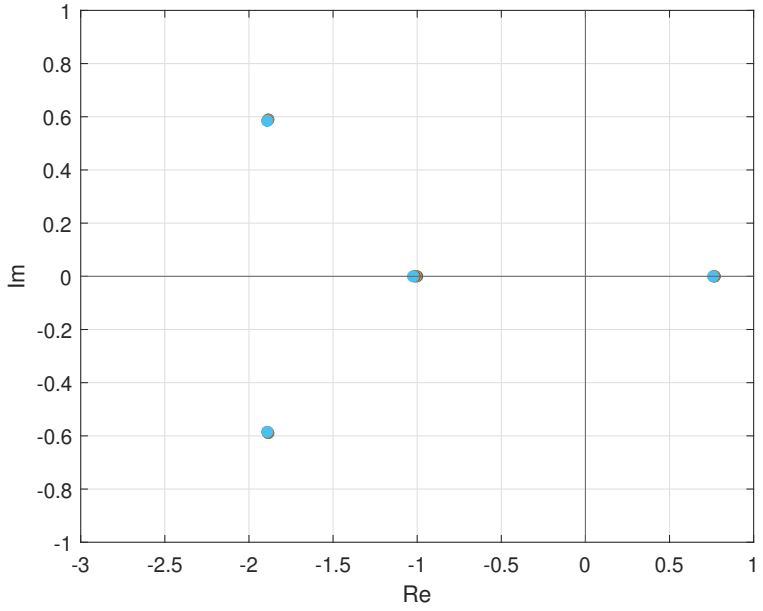


Figure 4.9: Variation of α_I.

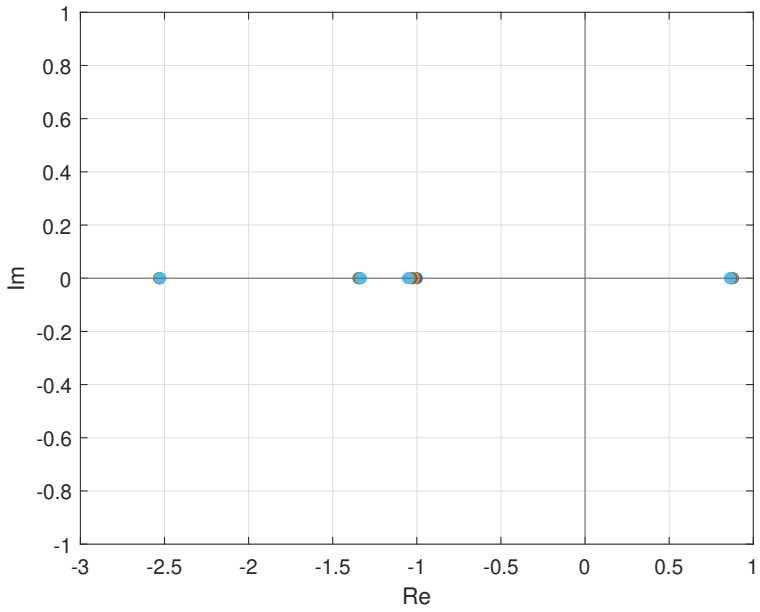


Figure 4.10: Variation of α_J.

By definition, all of the eigenvalues have to have negative real part in order to have stable disease-free equilibrium. Therefore, the biggest influence on the model has parameter β, since it moves the eigenvalues along x-axis (real axis). Other parameter mostly do not have that big influence on the model as it can be seen in the figures. Important note is that from the linearization of the quarantine-isolation model we can only make conclusions locally and not globally.

The Figure 4.7, and Figure 4.8 do not show that much sensitivity to the regarded parameters, but parameters γ_Q and γ_J represent control parameters in the model 2.1. Even though it seems that parameters ϵ_Q and ϵ_J do not have a big influence, however, they represent control measures in some sense, since they explain how perfect quarantine and isolation are.

Chapter 5

Models developed for COVID-19

5.1 SIDARTHE

SIDARTHE model was developed for the COVID-19 epidemic in Italy [5]. In this model the total population is partitioned into eight stages:

1. S - susceptible
2. I - infected (asymptomatic infected, undeteceted)
3. D - diagnosed (asymptomatic infected, detected)
4. A - ailing (symptomatic infected, undetected)
5. R - recognised (symptomatic infected, detected)
6. T - threatened (infected with life-threatening symptoms, detected)
7. H - healed (recoverd)
8. E - extinct (dead).

The SIDARTHE model consists of the following differential equations

$$\begin{aligned}
\dot{S}(t) &= -S(t)(\alpha I(t) + \beta D(t) + \gamma A(t) + \delta R(t)) \\
\dot{I}(t) &= S(t)(\alpha I(t) + \beta D(t) + \gamma A(t) + \delta R(t)) - (\epsilon + \zeta + \lambda) I(t) \\
\dot{D}(t) &= \epsilon I(t) - (\eta + \rho) D(t) \\
\dot{A}(t) &= \zeta I(t) - (\theta + \mu + \kappa) A(t) \\
\dot{R}(t) &= \eta D(t) + \theta A(t) - (\nu + \xi) R(t) \\
\dot{T}(t) &= \mu A(t) + \nu R(t) - (\sigma + \tau) T(t) \\
\dot{H}(t) &= \lambda I(t) + \rho D(t) + \kappa A(t) + \xi R(t) + \sigma T(t) \\
\dot{E}(t) &= \tau T(t)
\end{aligned} \tag{5.1}$$

The parameters $\alpha, \beta, \gamma, \delta$ represent the transmission rate because of the contacts between a *Susceptible* member and an $Infected$, a *Diagnosed*, an

Ailing, and *Recognised* member. The characteristics of these parameters is that they are modifiable by social distancing policies. Parameters ϵ and θ denote the probability rate of detection, relative to asymptomatic and mildly symptomatic cases respectively. The rate at which infected members develop symptoms, aware and not aware of being infected is represented with parameters ζ and η respectively. Parameters μ and ν respectively denote the rate at which undetected and detected infected subjects develop life-threatening symptoms. The mortality rate is captured by parameter τ. Recovery of the five infected classes is represented by $\lambda, \kappa, \xi, \rho$ and σ. Model parameters are based on the evolution of the epidemic in Italy in the period from the February 20, 2020 to March 12, 2020.

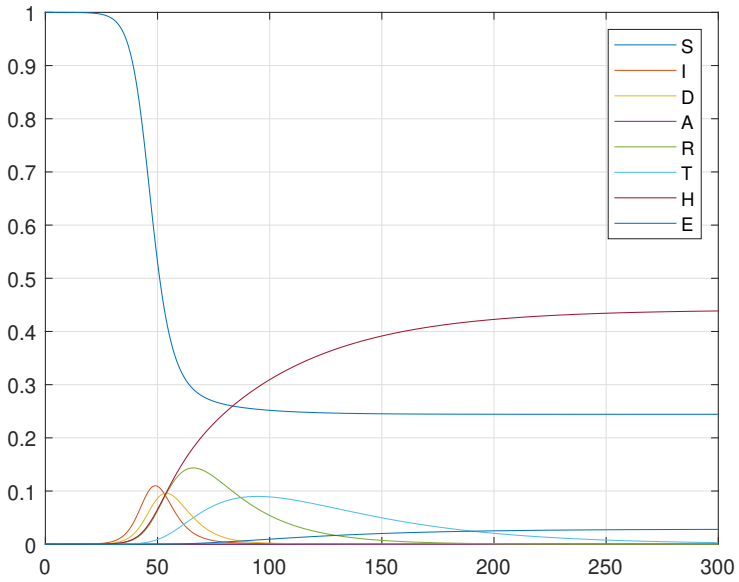


Figure 5.1: Uncontrolled SIDARTHE.

The Figure 5.1 shows how the epidemic proceeds in every compartment based on the estimated parameters as well as the initial conditions in [5]. In each of the figures, Figure 5.1, Figure 5.2, Figure 5.3, nice property of *Threatened* compartment is shown. Clearly, at the beginning of the epidemic it is not possible to have threatened members, they need to develop severe symptoms which takes time.

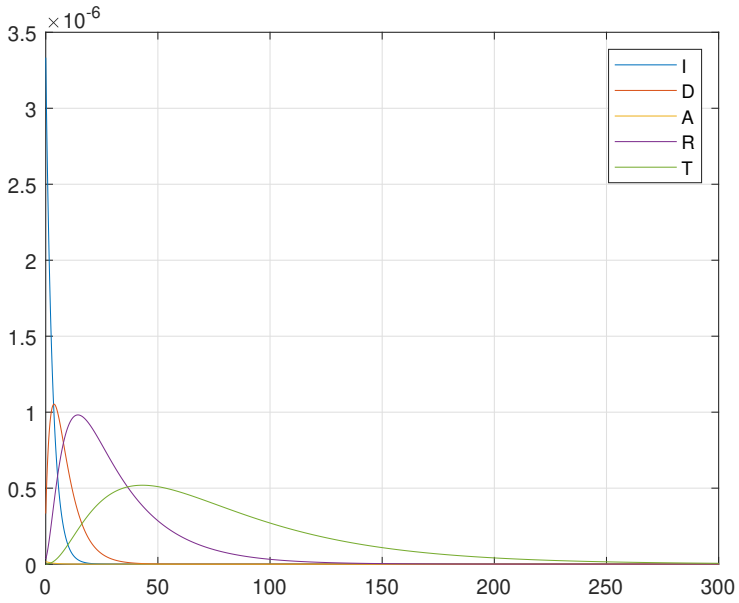


Figure 5.2: SIDARTHE ideal restrictions.

In the Figure 5.2 the infected compartments of the SIDARTHE model are shown. To try and accomplish stable disease-free equilibrium the ideal restrictions, similar to those in the modified SIR model, are implemented. In SIDARTHE model, instead of having one infective compartment (like in SIR), there are 5 infective compartments (I, D, A, R, T. Since in the SIR model there is only one transmission factor β, in SIDARTHE there are several of them α, β, γ, δ. Therefore, the contact restrictions are made based on the sum of every infective compartment. Based on the simulations, the best possible scenario is shown in the Figure 5.2, showing that no matter how ideal restrictions are, with the initial conditions and parameters developed in [5] it is not possible to accomplish stable disease-free equilibrium with restrictions.

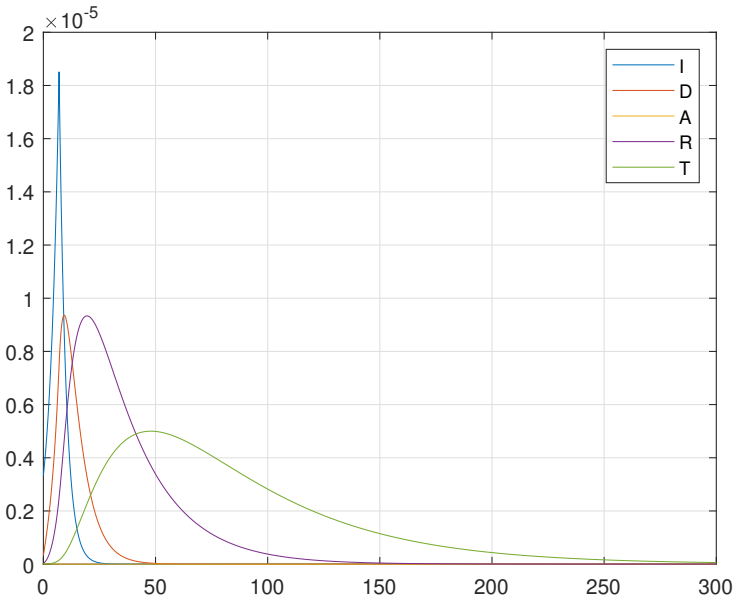


Figure 5.3: SIDARTHE realistic restrictions.

To make restrictions more realistic, in comparison to the ideal restrictions the restrictions are made based on the calculation of the moving average of the sum of all infective compartments, moreover the delay is added in the implementation of the restrictions in the population. Comparing the two figures it can be seen that there is an increase in all of the infective compartments as expected.

5.2 Model H

In [6][20] the model is developed for COVID-19 outbreak in the Czech Republic. The model consists of the following discrete-time equations

$$
\begin{aligned}
S[t+1] &= S[t] - \lambda S[t] \\
E[t+1] &= E[t] + \lambda S[t] - \sigma E[t] \\
I_a[t+1] &= I_a[t] + (1-p_s)\sigma E[t] - \gamma_a I_a[t] \\
I_p[t+1] &= I_p[t] + p_s \sigma E[t] - \xi I_p[t] \\
I_h[t+1] &= I_h[t] + (1-p_T)\xi I_p[t] - \gamma_s I_h[t] \\
I_s[t+1] &= I_s[t] + p_T \xi I_p[t] \\
R[t+1] &= R[t] + \gamma_a I_a[t] + \gamma_s[t],
\end{aligned}
\tag{5.2}
$$

where the probabilities with which individuals leave the respective model class is represented by parameter σ, ξ, γ_a and γ_s. In the model 5.2. the λ is defined as:

$$\lambda = \beta C \frac{r_\beta I_a[t] + r_\beta I_p[t] + r_c I_h[t] + r_c I_s[t]}{N[t]}. \tag{5.3}$$

Here, β and C are defined the same as in the model 3.3. Compartment S represents susceptible, E stands for exposed individuals, I_a represents infected asymptomatic, I_p represents presymptomatic individuals (individuals before developing symptoms), I_s stands for the infected individuals that undergo testing, while the I_h are infected individuals that decide not to undergo the testing and instead stay at home. The compartment R represents the recovered individuals. The r_β is a factor reducing the infection transmission probability for an asymptomatic individual, relative to a symptomatic one and r_c is a factor reducing contact rate of a symptomatic individual relative to asymptomatic one. In this model the same restrictions were implemented as in the model 3.3, where the risk index was calculated and based on the value of this risk index the decision on the restrictions was made. In each of the figures, Figure 5.4, Figure 5.5, Figure 5.6, the blue color represents children, red is for adults, and yellow for seniors.

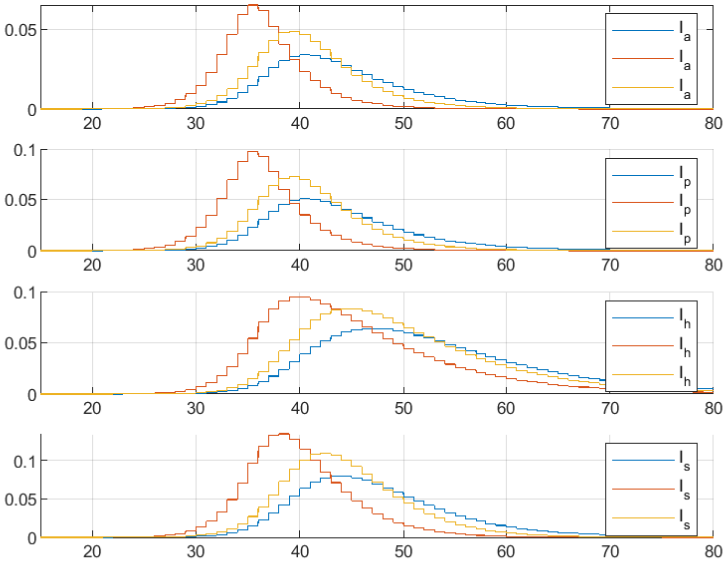


Figure 5.4: Uncontrolled Model H.

In the Figure 5.4, uncontrolled Model H is shown. In every infective compartment the most infected are adults, which is expected since they have the biggest transmission factor.

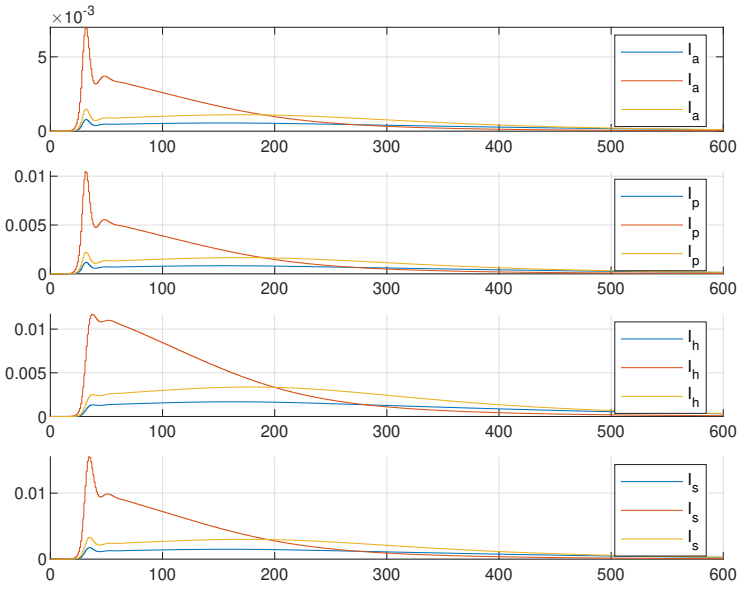


Figure 5.5: Model H ideal contact restrictions.

Figure 5.5 shows infective compartments when the ideal contact restriction is implemented in the model. By the ideal contact restrictions, it is considered the ideal contact restrictions as explained in the modified SIR model. Even in this case it is not possible to achieve the stability of a disease-free equilibrium, however it is possible to limit the maximum number of infected individuals. Comparing this result, with the results in the Figure 5.4 it is noticeable, by implementing the ideal contact restrictions, the duration of the epidemic is significantly extended.

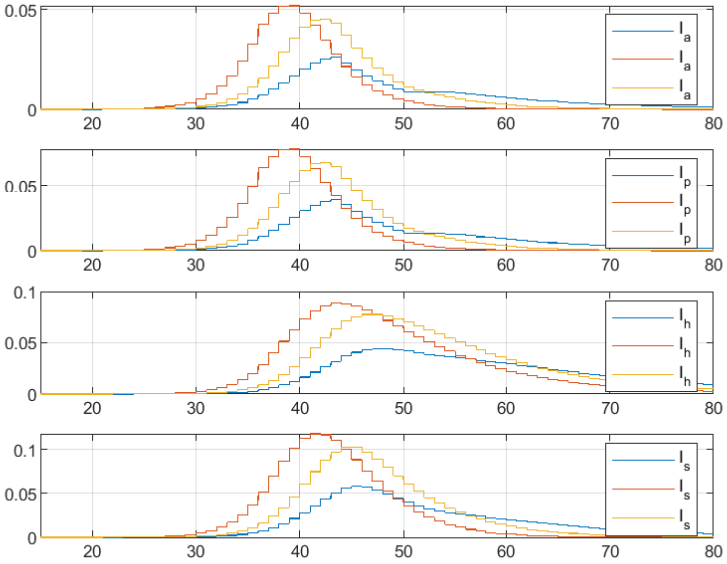


Figure 5.6: Model H real contact restrictions.

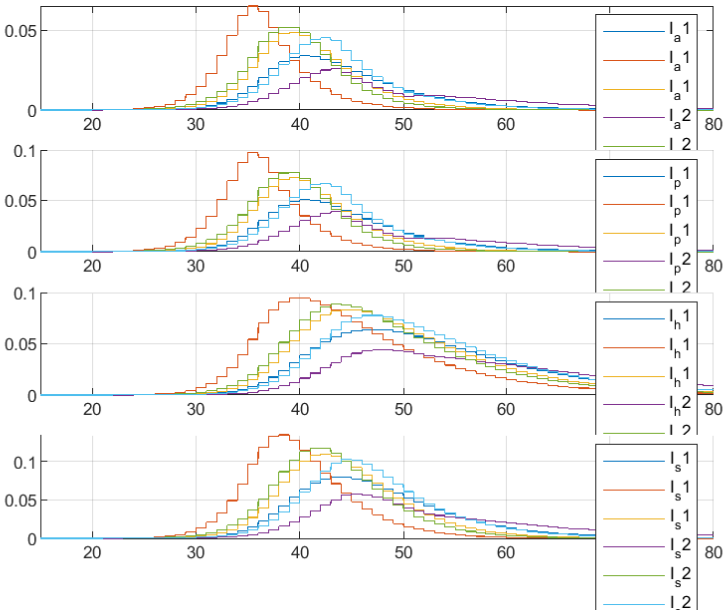


Figure 5.7: Model H overlapped Figures 5.4 and 5.6.

In Figure 5.7 the overlapped results from Figure 5.4 and 5.6 is shown so it is easier to notice differences.In the legend, the ones with number 1 are from the results from Figure 5.4, while the ones with 2 are from Figure 5.6 Definitely with real restrictions the maximum number of infectives will be lowered and it will delay the peak of the infected.

Chapter 6

Robustness of the models

The robustness of the models is tested based on incomplete data, specifically if the ideal contact restrictions are based on the incorrect number of the infective members. In reality this is unavoidable, since detection of infected members is not 100% reliable.

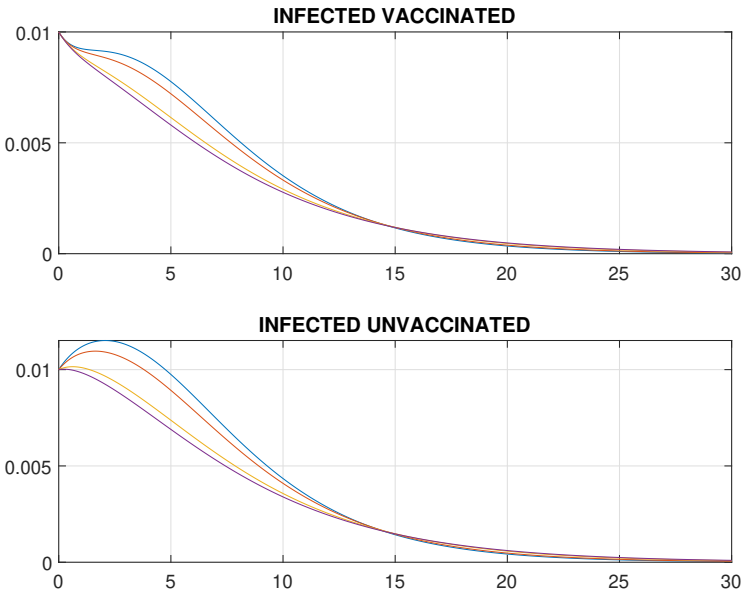


Figure 6.1: Vaccination model

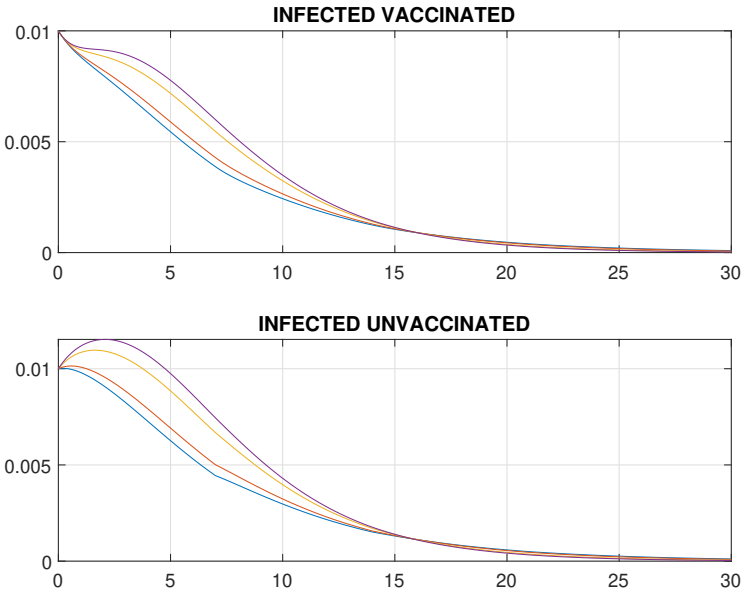


Figure 6.2: Vaccination model holding restrictions for some time

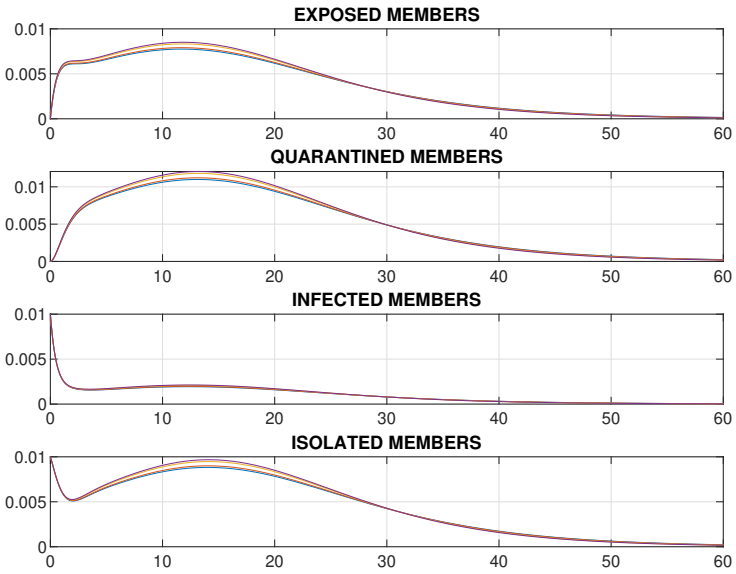


Figure 6.3: Quarantine-isolation model

When the ideal contact restrictions are decided based on the incorrect number of the infective members is shown in Figures 6.1, Figure 6.2, and Figure 6.3 for different models. In reality, this approach can represent when the tests are false negative, or when someone decides not to get tested. Based on these results, the quarantine-isolation model seems more robust to the

incomplete data, than the vaccination model. In the vaccination model, the case when there is unstable disease-free equilibrium is possible. Moreover, it seems that the infected unvaccinated members are more affected by the incomplete data.

Chapter 7

Conclusion

Mathematical epidemiological models became more observed since the SARS-CoV-2 epidemic. It became clear in order to control epidemics some controls were needed. Different types of models and controls were considered, like pharmacological and non-pharmacological interventions. Obviously, it depends on the features of the disease what interventions are needed, and how "aggressive" they need to be. As seen, epidemiological models are easily modifiable to the needs we want. The reason why some simpler models were considered is because they are quite easy to understand, they show qualitatively correct dynamics, and they also highlight important properties of the course of epidemics.

An important property of epidemiological models is the basic reproduction number R_0, more specifically if the $R_0 < 1$ the infection dies out, on the other hand, if the R_0 there is an epidemic. The basic reproduction number in the simple model is a ratio between infectivity and recovery rates. By increasing the rates of recovery rate, for example with medication or treatment, or decreasing the infectivity rate, one can hope to push $R_0 < 1$ and thereby stop an epidemic outbreak. When looking at the R_0 (3.11) of the vaccination model 3.1 it is noticeable that susceptible vaccinated members increase the R_0 factor but multiplied with the parameter σ. Therefore, the lower the σ the less influence susceptible vaccinated have. It was already explained, the parameter σ represents vaccine effectiveness, therefore the more effective vaccine the lower is R_0. This property is shown in Figure 3.1, where with enough effective vaccines it is possible to achieve stable disease-free equilibrium.

For the non-pharmacological interventions, the modified SIR model and Quarantine-isolation model were considered. In these models, the ideal restrictions were implemented as a function of the proportion of the number of infected, in order to try and stabilize disease-free equilibrium. It is shown that it is possible to control epidemics with this kind of contact restriction implemented in the model, however, this is the ideal case. In order to make these restrictions more realistic, the delay in the implementation of contact restrictions was added. A delay in the model definitely influences the course of the epidemic, and it can go from stable disease-free equilibrium to unstable disease-free equilibrium.

The models specifically developed for the SARS-CoV-2, shows us that it is

not possible to accomplish stable-disease equilibrium, even with ideal contact-restrictions. With contact restrictions, we can try to limit the maximum number of the infected, but we need to keep in mind that this will cause an extended duration of the epidemic. If we want to try and accomplish stable disease-free equilibrium we need some kind of pharmacological treatment in order to battle COVID-19. Morever, it is impossible to process all the testing of the infected individuals, in time in order to provide appropriate restrictions.

Bibliography

[1] Wassim M. Haddad, Vijay Sekhar Chellaboina, Qing Hui, *Nonnegative and Compartmental Dynamical Systems*, Princeton University Press, Princeton and Oxford, 2010.

[2] Fred Brauer, Carlos Castillo-Chavez, *Mathematical Models for Communicable Diseases*, CBMS-NSF Regional.

[3] Cameron Nowzari, Victor M. Preciado, George J. Pappas,*Analysis and Control of Epidemics: A survey of spreading processes on complex networks*, IEEE Control Systems Magazine, February 2011, pp. 26-46. DOI 10.1109/MCS.2015.2495000 Conference Series in Applied Mathematics, 2012. doi.org/10.1137/1.9781611972429.

[4] Hamer W.H. Epidemic disease in England - the evidence of variability and of persistence. The Lancet. 1906;167:733–738.

[5] G. Giordano, F. Blanchini, R. Bruno, P. Colaneri, A.D. Filippo, A.D. Matteo, M. Colaneri, COVID-19 IRCCS San Matteo Pavia Task Force. *A SIDARTHE Model of COVID-19 Epidemic in Italy.*

[6] J. Smyčka, R. Levisnky, E. Hromadkova, M. Šoltes, J. Šlerka, V. Tuček, J. Trnka, M. Šmid, M. Zajiček, T. Diviak, R. Neruda, P. Vidnerova and L. Berec. *Delays, masks, the elderly, and schools: first COVID-19 wave in Czech Republic.*

[7] N. G. Davies,et al.,Nature Medicine26, 1205 (2020).

[8] *Measures*, Ministerstvo zdravotnictvi Ceske Republiky. https://share.uzis.cz/s/9A8eFndtSM8H5yf/download/covid-pes-matice-opatreni.pdf.

[9] Johnson S. *Riverhead Books.* New York,: 2006. The ghost map.

[10] Bernoulli D. Mercure de Paris; 1760. Réflexions sur les avantages de l'inoculation. p. 173.

[11] ZihuaQu, *Cooperative control of dynamical systems: applications to autonomous vehicles*, 2009 Springer Science Business Media.

[12] *Antonine Plague*, From Wikipedia, the free encyclopedia, https://en.wikipedia.org/wiki/Antonine$_{P}lague$

[13] *Plague of Cyprian*, From Wikipedia, the free encyclopedia, https://en.wikipedia.org/wiki/Plague$_{o}f_{C}yprian$

[14] *Plague of Justinian*, From Wikipedia, the free encyclopedia, https://en.wikipedia.org/wiki/Plague$_{o}f_{J}ustinian$

[15] *History of cholera*, From Wikipedia, the free encyclopedia, https://en.wikipedia.org/wiki/History$_{o}f_{c}holera$

[16] *Black Death*, From Wikipedia, the free encyclopedia, https://en.wikipedia.org/wiki/Black$_{D}eath$

[17] *Severe acute respiratory syndrome coronavirus 1*, From Wikipedia, the free encyclopedia, https://en.wikipedia.org/wiki/Severe$_{a}cute_{r}espiratory_{s}yndrome_{c}oronavirus_{1}$

[18] *Spanish flu*, From Wikipedia, the free encyclopedia, https://en.wikipedia.org/wiki/Spanish$_{f}lu$

[19] *COVID-19*, From Wikipedia, the free encyclopedia, https://cs.wikipedia.org/wiki/Covid-19

[20] Ludek Berec *Model H: Predicting dynamics of hospitalizedCOVID-19 patients.*

MASTER‘S THESIS ASSIGNMENT

I. Personal and study details

Student's name: **Zalihic Harun** Personal ID number: **498110**

Faculty / Institute: **Faculty of Electrical Engineering**

Department / Institute: **Department of Control Engineering**

Study program: **Cybernetics and Robotics**

Branch of study: **Cybernetics and Robotics**

II. Master’s thesis details

Master’s thesis title in English:

Epidemiological modelling and control

Master’s thesis title in Czech:

Epidemiologické modelování a řízení

Guidelines:

Investigate models of mathematical epidemiology; consider both batch and networked compartmental models. Study different means of controlling the course of epidemics; distinguish between pharmacological and non-pharmacological interventions. Under appropriate control actions, attempt to prove stability of the disease-free equilibrium in investigated models. Use compartmental nonnegative systems Lyapunov theory for global, or linearization for local conclusions. More generally, formulate current public health challenges as feedback control problems; achieve local or global stability of the disease-free state. Consider specify limitations, if any, on implementability of such control actions, (as regards to e.g. theoretical observability of the systems’ states, or practical availability of information). Explore various epidemics models to see which formulation lends itself most readily to feedback control.
1. Study batch epidemiological models. Consider the stability of a disease-free equilibrium in uncontrolled systems.
2. Study networked epidemiological models. Formulate a stability condition for the total disease-free equilibrium.
3. Consider different means of controlling batch and networked models; incorporate effects of quarantine, social contact restrictions and vaccination into the models.
4. Formulate the stabilization of a disease-free equilibrium in batch and networked models as feedback control problems. Design the stabilizing feedback controls assuming the state of the system is fully known.
5. Test the applicability of designed controls in light of incomplete data. Look into robustness of the closed-loop stability to uncertainties in the available information.

Bibliography / sources:

[1] Fred Brauer, Carlos Castillo-Chavez, Mathematical Models for Communicable Diseases, CBMS-NSF Regional Conference Series in Applied Mathematics, 2012. doi.org/10.1137/1.9781611972429
[2] Cameron Nowzari, Victor M. Preciado, George J. Pappas, Analysis and Control of Epidemics: A survey of spreading processes on complex networks, IEEE Control Systems Magazine, February 2011, pp. 26-46. DOI 10.1109/MCS.2015.2495000
[3] Jia Li, Fred Brauer, Continuous-Time Age-Structured Models in Population Dynamics and Epidemiology, In book: Mathematical Epidemiology, April 2008, DOI: 10.1007/978-3-540-78911-6_9
[4] Wassim M. Haddad, Vijay Sekhar Chellaboina, Qing Hui, Nonnegative and Compartmental Dynamical Systems, Princeton University Press, Princeton and Oxford, 2010.

Name and workplace of master's thesis supervisor:

doc. Kristian Hengster-Movric, Ph.D. Department of Control Engineering FEE

Name and workplace of second master's thesis supervisor or consultant:

Date of master's thesis assignment: **13.02.2022** Deadline for master's thesis submission: **20.05.2022**

Assignment valid until:
by the end of summer semester 2022/2023

doc. Kristian Hengster-Movric, Ph.D.	prof. Ing. Michael Šebek, DrSc.	prof. Mgr. Petr Páta, Ph.D.
Supervisor's signature	Head of department's signature	Dean's signature

III. Assignment receipt

The student acknowledges that the master's thesis is an individual work. The student must produce his thesis without the assistance of others, with the exception of provided consultations. Within the master's thesis, the author must state the names of consultants and include a list of references.

.	
Date of assignment receipt	Student's signature