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Diana Bolatova

Mathematical modeling of infectious diseases and impact of vaccination

THESIS
Presented in Partial Fulfillment for the
Degree of Master of Science in Scientific Mathematics
(degree code: 7M05401)
Department of Mathematics and Natural Sciences
Faculty of Engineering and Natural Sciences

Supervisor: **Shirali Kadyrov**

Kaskelen, 2023

SDU University
Faculty of Engineering and Natural Sciences
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Assistant Professor, PhD Akhmedov R.

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Topic of the thesis:

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Abstract

The world is changing and evolving these days, and the various germs and viruses that surround us are also changing and evolving. For this reason, it is essential to choose the best strategy for combating these infections while preserving the health as much as possible. This coursework uses a fundamental mathematical term in bio-mathematics which is a basic reproduction number R_0. It is a significant epidemiological term illustrating the number of infected people by one sick individual, hence giving the idea of a possible epidemics. Another thing to investigate in this coursework is a numerical approximation of the epidemic model under various scenarios to examine the model from a mathematical perspective. The following project covers the following topics: vaccination strategy, stability theory, mathematical biology, modeling of epidemics, optimization problems, and Python simulation. According to the epidemic model, one of the best strategies for immunizing the populace is pulse vaccination. The Next Generation matrix approach and the Hartman-Grobman method are two linearization techniques.

Аңдатпа

Бұл күндері бүкіл әлем әртүрлі өзгерістермен бірге дамып, өзгеруде бізді қоршаған бактериялар мен вирустар; сондықтан дұрыс тәсілді табу өте маңызды мүмкіндігінше денсаулық жағдайын сақтай отырып, олармен күресу. Бұл курстық жұмыс эпидемиялық модельді математикалық тұрғыдан қарастырады негізгі репродукция деп аталатын маңызды эпидемиологиялық терминді қолдану арқылы қарау әр түрлі шарттармен оның саны және сандық жуықтауы. Келесі жобаның пәндеріне математикалық биология, динамикалық кіреді жүйелер, вакцинация стратегиясы, тұрақтылық теориясы, оңтайландыру мәселесі, модельдеу эпидемиялар және Python симуляциясы. Эпидемиялық модель импульстік вакцинацияны ең табыстылардың бірі ретінде зерттейді халықты вакцинациялаудың әдістері. Линеаризация әдісі деп аталады Хартман-Гробман әдісі және Келесі ұрпақ матрицалық әдісі ретінде болды негізгі көбейту саны үшін алгебралық өрнекті шығару үшін қолданылады. Python симуляциясын пайдаланып, модель параметрлерін өзгерте отырып, оны көруге болады модель коэффициенттерінің әсері негізгі көбейту мәніне қалай әсер етеді саны.

Аннотация

. В наши дни весь мир меняется и развивается вместе с мутацией различных бактерий и вирусов, окружающих нас; поэтому очень важно найти правильный подход для борьбы с ними, максимально сохраняя состояние здоровья. В данной курсовой работе модель эпидемии рассматривается с математической точки зрения, используя очень важный эпидемиологический термин, известный как базовая репродукция и его численное вычисление с разными значениями для параметров модели. Дисциплины данного проекта включают математическую биологию, динамические системы, стратегии вакцинации, теория устойчивости, задача оптимизации и компиьютерное моделирование на Python. Согласно модели эпидемии, импульсная вакцинация является одним из наиболее успешных методов при вакцинации населения. Метод линеаризации, называемый как метод Хартмана-Гробмана и матричный метод следующего поколения применяются для получения алгебраического выражения для базового числа воспроизводства. Используя симуляцию Python, изменяя параметры модели, можно увидеть как влияние коэффициентов модели показывает зависимость от значения базового воспроизводительного числа.

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Finally, I'd like to say thank you to my family, especially my parents, who helped me get born and have been spiritually supportive of me all my life. They were the ones who made me.

Table of contents

Nomenclature

α	rate of losing immunity
β	transmission rate
γ	recovery rate for all positive constants
λ	continuous vaccination rate
μ	natural death
ω	latent period of the disease
τ	period between two pulse vaccinations
θ	pulse vaccination rate
d	disease-induced death rate
A	newborn invariant
SIR	Susceptible Infectious Recovered

1. Introduction

In the last decades, uncertain situations have been occurring a lot which affect the life quality of people. Mathematical modelling is an essential tool to approximate the results of those situations and keep from the upcoming dangers. Bacteria, infections, and viruses are one of the major struggles of all the life beings on our planet, not only the human beings. Some of them have grown into disasters known as epidemics, the examples are Black Death, Yellow Fever, and etc. A highly contagious disease – COVID-19 killed around 7 million of people according to the World Health Organization (WHO), which pushes the government to find the optimal solution to these problem and similar ones in case or arising in the future.

In total, more than 7 million people have died as a result of COVID-19. The distinction between COVID 19-induced and acquired immunity has recently become clearer. Even while many individuals have great expectations for vaccines, only a small number of people feel that they will be a true success. They would also decrease the likelihood of hospitalization and mortality. Logistics, supply chain, budgetary, and political obstacles all contribute to the slow progress of vaccine development. To forecast hypothetical alternatives and tolerated reactions, decision-makers require instruments to aid in their planning. A few models have been created to forecast the number of disability-adjusted life years saved by immunization programs that are both effective and cost-effective. Each reproductive number will be examined in this study to determine the coverage of vaccination, the efficiency of vaccination, the time horizon for vaccination, and the likelihood of vaccine failure in different nations. In addition, the simulation will be used to evaluate the efficacy, reactivity, and natural immunity of various vaccine techniques. When developing vaccines, it is advised that both vaccine-induced immunity and natural immunity be included in the development process. The opposite is also true: the more frequently a vaccination is administered, the less effective it becomes over time.

Mathematical modeling is the key instrument while solving epidemics problems. The history begins from Daniel Bernoulli [7] who investigated the vaccination strategies for various diseases as a smallpox to prolong the life of vaccinated ones up to three years.

The essential source in mathematical modeling is the compartment theory introduced by Kermack and McKendrick [19] considering the 3 main parts of the epidemics in the population, so called as SIR: S – susceptible, I – infectious, R – recovered. These three SIR terms are connected through differential equations. In this study, the base of a mathematical modelling is the Kermack and McKendrick procedure.

Any method has its own advantages and disadvantages, it applies to the SIR model as

well, for instance, it does not include much details, making this method easy to calculate, but the absent terms regarding the birth and death do not provide the big detailed picture of the situation.

Not many parts of the disease progress are present in this model, vaccination was not investigated, as well as the exposed population which is the state of carrying the disease, but in fact not being infectious. Another part not included is the death case due to the disease, it was not studied before. Hence, the next mathematical models were enhanced to give a better picture on the infections. First, scientists came up with a SIRS model [3] taking an immune system of a recovered individual as an additional element. Secondly, SIS is a model opposite to SIRS with no immune system after getting rid of an infection. Thirdly, the vaccination idea was included to halt the further spread of the disease in SIV [10]. Lastly, the incubation concept is investigated in the SEIR model [9]. As it can be illustrated, there are many different variations of the epidemiological model to be constructed to take into account all the possible outcomes and progress of the disease, however, it's important not to over complicate it so that it is possible to solve and provide a detailed analysis.

Furthermore, the sick population is the part of the SEIR model that was studied carefully in 2020 by many epidemiologists due to the well-known pandemic of COVID-19, therefore, infectious individuals were investigated in terms of the symptoms' appearance. That is why some papers included symptomatic and asymptomatic groups into the mathematical model analysis [2].

Any model in biomathematics has the most significant attribute which is a basic reproduction number denoted as R_0 contributing much to find out the effectiveness of the given model by calculating the speed of the virus spread among the population. Ronald Ross and Alfred Lotka were first to consider this parameter in their scientific works [27], while in 1952 another scientist George MacDonald made a valuable contribution in the first use of the reproduction number in epidemiology denoting it as a reproduction rate - Z_0 [23].

Definition 1. *The basic reproduction number R_0 describes the average possible number of infected outcomes produced by one contagious individual.*

To differentiate the possible outcomes of the disease spread through the numerical approach, the reproduction number is calculated to find out whether the epidemics will continue progressing at a high speed, disappear, or it will neither decrease nor increase.

According to [23], there are three main possible effects for R_0:

- $R_0 < 1$: the disease does not spread, since the sick person infects less than one individual;
- $R_0 = 1$: population number is stable, with no fluctuations in its size because each infected case transmits the disease to only one person;
- $R_0 > 1$: the disease causes the epidemics due to the quick spread rate in the population, since each contagious case generates more than one case, which means the exponential growth.

To have a better understanding of the reproduction number, there are a few values for the most common epidemic viruses provided below:

- influenza is a so-called flu, a contagious infection affecting the respiratory system caused by the influenza virus itself, and R_0 varies from 0.9 to 2.1 according to [8];
- Ebola is a virus spreading in West Africa between human beings that can be transmitted from the wild animals, while R_0 is from 1.5 up to 2.5 [1];
- COVID-19 is significantly one of the most dangerous viruses causing deaths to the millions of people and a huge impact on the whole world in all aspects of life, so the reproduction number R_0 in this case has a greater range from 2.5 to 6.0 [30].

The value of R_0 is a varying parameter being affected by such factors as the health care system, geographical situation, population density and etc.

1.1 Problem Statement and Research Objectives

At the moment, there is no widely accepted best practice for dealing with epidemics that manifest themselves over time. The ideal vaccine method for a constrained time-varying SEIR (Susceptible, Exposed, Infected, and Recovered) disease model is established through the use of restricted optimum control problems. Seasonal variations in the incidence coefficient, as well as monotonic losses in effective immunological capacity and monotonic changes in vaccine yield, are all taken into consideration in the calculation. At each time step, the limits imposed by vaccination levels, vulnerable populations, and vaccine supplies are taken into consideration, as control constraints imposed by pure regulation, pure state, and mixed state control.

1.2 Research Significance and Novelty

The novelty of this research project is in considering the SIR model with two vaccination parameters known as a pulse vaccination θ and a continuous vaccination coefficient λ.

In the next chapter the basics is discussed with a few necessary theorems that will be applied while showing the result.

To test the hypothesis, the analytical solution to the provided system is obtained. Then, it was numerically approximated by investigating several cases:

- no vaccination;
- pulse vaccination presence;
- continuous vaccination presence;
- both types of vaccination consideration.

Afterwards, the conclusion is drawn for which case is better to implement and what values are suitable for the system to work.

1.3 Thesis Outline

The first chapter is an Introduction devoted to the evolution of SIR mathematical modeling and its application to discover the disease flow. In the next chapter the model is formulated by introducing the considered coefficients and its effect on the solutions. Afterwards, analytical solution and numerical approximation on Python are introduced with a discussion part in the end.

2. Literature Review

2.1 Theoretical Foundation and History

To begin with, it is necessary to define the term "mathematical model." A mathematical depiction of a real-world scenario is a concrete expression of mathematical visualization, and it is sometimes referred to as a tangible embodiment of mathematical visualization in its various forms. This has led to the ability to show math problems in a way that looks like a picture by using diagrams and planar curves that are based on analytic solutions for three-dimensional simple figures like cylinders, spheres, and pyramids. [31, 13, 24]

There are many ways to stop and control the spread of infectious diseases, but each has its own benefits. Vaccination, medicine, self-isolation, quarantine, and preventative treatment are all good ways to do this.

As the title suggests, prophylaxis is a series of acts designed to prevent the spread of an infectious disease from one person to another. Hand washing and wearing a mask, for example, can both assist in keeping the virus at a distance. Treatment, whether it is in the form of medication or bed rest, is intended to cure or slow the progression of the illness. There are a plethora of medications available to treat or mitigate the impact of infectious infections. In this category are therapies that are comprehensive in nature, such as those used to treat malaria and tuberculosis. Another method that has been employed successfully in HIV and genital herpes patients is the reduction of symptoms, but not totally eradicating the disease.

Dead microbes can also be infused into the body as a treatment for this illness, which is a different approach. Vaccination is used, but the vaccine bodies are recognized by the human body as foreign particles and are removed from the body. Because of this, the human body produces antibodies against them, which serves to protect that person against the introduction of similar germs into his or her body in the future. A lot of people in the community have been vaccinated, so they can't get the disease again. This results in herd immunity, which stops the spread of disease.

The introduction of vaccines has resulted in important medical advancements. There has been a big change in the world because people have been immunized. Diseases like cholera and smallpox have been eliminated or almost eliminated. There are certain disadvantages to vaccination, including the fact that it does not provide total disease protection. As a result, it is possible that someone will become infected again even if they have previously been immunized against the disease. Antibodies created within the organism are no longer functional since

macrobiotics are capable of changing their composition. This is demonstrated by the ability of cold and influenza viruses to evolve in a spectacular manner. A vaccination's capacity to protect against specific diseases is referred to as its "vaccine efficacy".

Among the most important measures taken to prevent the disease from spreading further are quarantine and isolation, which require separating an affected person from the rest of the population. It is important to understand the difference between these two notions because quarantine protects healthy and potentially contagious people, whereas isolation protects the individuals who have been contaminated. The second method is more widely used and has proven to be effective in the treatment of a wide range of conditions. During the SARS outbreak in 2002–2003, the quarantine approach was implemented as the first line of defense in an emergency situation to contain the infection. Also known as "controlled reproduction numbers", these are numbers that are calculated via the use of proprietary mathematical models and control methodologies.

Initially, epidemiological models were constructed by two scientists Kermack and McKendrick in 1927 [20]. Now there are many various specific epidemiological models differing from one disease to another, while the most general type is SEIRS model [29, 11]. Considering this model in detail, there are 4 important subdivisions: S - susceptible, E - exposed, I - infected, and R - recovered. Moreover, there are many variations of generic model such as SIR model, SI model [26] and SIS model [22]. Transmissions across classes and population size fluctuations, such as births and deaths, are described by a set of differential equations depending on time of all variables in the population.

2.2 Mathematics in Biology

For many years, the principal subjects of mathematical interest were physics, astrophysics, and astronomy. However, lately there are many applications of mathematics in different areas, such as mathematical biology, statistics in psychology, applied statistical methods in bio-science, actuarial mathematics in finance, engineering mathematics, cryptography, and etc.

It is well-known fact that mathematics is the key science to all the disciplines starting from the linguistics and sociology, up to physics and biology. Mathematics provides the structure of different patterns in the surrounding world.

The first application of logical structure in biology was made by the Italian scientist Giovanni Borelli in the end of the 17th century [15], where he investigated the movement trajectory of animals and people via geometric methods.

There is a variety of mathematical instruments to be used in mathematical biology, for instance, linear and non-linear differential equations, functional analysis, linear algebra theory, applied statistical methods, and software applications. Vaccination strategy was investigated on smallpox by another Italian scientist-physicist Giovanni Borelli in 1766 in his work [6].

One of more recent works on mathematical models is considered the study of D'Arcy Thompson, where he investigated the growth patterns of various animals and plants, their structure

and models in 1917 [28] in his work.

Therefore, mathematics is the essential tool for modeling biology phenomena and organic systems using the analysis and theory approach with numerical approximation. The most important mathematical component in biology is dynamical systems that is explained in details in the next section.

2.3 Dynamical systems

A *dynamical system* in mathematics is a model expressing the change of a variable, or a set of different variables. They are usually applied to investigate the evolution of the process in biology, engineering, chemistry, economics, and more.

There are three main components of a dynamical system, which are:

- state space: the system is described in all states that it can represent; variables and dimensions are used, where each specific state is given by the concrete point;
- time evolution: the system is expressed via differential or difference equations, describing system's behaviour showing the system change over time;
- trajectory: the state space is structured by the path which is followed over time; the solution to the system of differential equations is the trajectory starting from the initial conditions state.

Many mathematical terms are applied in dynamical systems such as stability analysis, periodicity, chaos theory, and etc. The analysis is considered as linear and nonlinear with respect to variables, system can be discrete or continuous. Another type is whether they are deterministic or stochastic.

The fundamental idea of these systems are attractors, which are the states that systems approach as the time passes. Attractors are different terms as fixed points, limit cycles, and other concepts.

An *evolutionary rule* is a concept in mathematical modeling expressing the idea of a system or population changing as the time passes. It is described using functions or mathematical laws illustrating the behaviour of different states.

In mathematics, the idea of a *state* is expressed with n variables $x_1,\ x_2,\ ...,\ x_n$ taking any real values and the rule describing the change over time:

$$\frac{dy_i}{dt} = Y_i(x_1,\ x_2,\ ...,\ x_n), \quad for\ \ i = 1, 2, ..., n$$

where the unknowns $x_1,\ x_2,\ ...,\ x_n$ denote the system's state at each moment of time.

One of the founders of dynamical system theory was an influential French scientist Henri Poincare in 19th century. He made a considerable contribution to chaos theory about complex systems and its dynamics. Since Poincare studied celestial mechanics in the example of planets using three-body problem and mathematical modeling [25] in 1890.

Nowadays, the idea of dynamical systems is spread in all scientific disciplines such as physics, chemistry, biology, astronomy, economics, and etc. In this work, its application in biology is investigated, to be more precise, the virus behaviour in the population and the vaccination strategy to fight it in a more efficient way.

2.4 Mathematical model

Mathematical modeling is a procedure of illustrating mathematical simulations of real-life processes, which can be analyzed, optimized, and investigated further. Modeling is constructed using equations, initial conditions, available data and different algorithms. Mathematical modeling is applied everywhere, since it can help to predict or study future phenomena.

The models can be divided into main categories according to mathematical criteria.

1. **Deterministic vs. Stochastic Models:** Deterministic models are constructed with precise mathematical equations expressing the behaviour and depending on initial conditions, so the uncertainty is not present. While, stochastic models are the opposite of deterministic ones illustrating the randomness and random variables in the system.

2. **Continuous vs. Discrete Models:** Continuous models represent the systems constantly changing over time, therefore, differential equations are widely used in this type. On the other hand, discrete models describe the systems that change in discrete time intervals, so the abrupt change is investigated in this case.

3. **Static vs. Dynamic Models:** Static models illustrate the system at a specific time not studying its progress over period of time, which is used for snapshot-like models. Dynamic models express systems and processes changing over time.

4. **Linear vs. Nonlinear Models:** Linear models consider relationships between variables in a linear way, while nonlinear systems illustrate the product, division of the given variables which gives a better understanding of the real-world situations.

Since it is challenging to construct systems corresponding to real-life problems, mathematical models are approximate and not the exact simulation but as close as it can be.

2.5 Epidemiology

Epidemic is a wide spread of the disease affecting the significant number of people causing various factors and emergency situations. Epidemiology is the scientific area studying the impact of infectious diseases, transmission, patterns and the causes. There are significant factors influencing the flow describe in an Epidemiological Framework:

1. Disease agent: the cause of the epidemic such a bacteria, some virus, or an unknown parasite is an important subject in mathematical modeling, taking into consideration its transmission parameter, incubation period, and etc.

2. Host Population: the susceptible population carrying the disease is the host population, while factors include the immune system, genetics, geography, overall health conditions, age, and etc.

3. Environment: the surrounding situation, conditions play a crucial role, such that the disease agent can either grow, survive, or disappear depending on the temperature, weather conditions, humidity, and etc.

There are many factors influencing the flow of the epidemics, the most significant ones are:

1. transmission procedure: the way disease is spread matters considerably the epidemics, there are such modes as respiratory, vector-borne and other mechanisms;

2. incubation period is time gap between interaction with pathogen and the symptoms' appearance; this period matters in the spread of the disease; the less incubation period is, the faster epidemics ends;

3. basic reproduction number R_0: the crucial epidemiological value for control measures representing the number of infected people from one given individual; if R_0 is greater than 1, then the epidemics might develop; if it is less than 1, the disease will disappear; the information about reproduction number is provided with more detaiiles in the section 2.6;

4. vaccination strategy and immunity: people with strong immune system either after recovering from the disease, or after getting the vaccine do not let the spread of the virus further, preventing the epidemics;

5. social factors: population movements from places to places, hygiene habits, interactions between individuals, health norms play a significant role in the development of the epidemics;

6. public health functioning: the epidemic is affected a lot by the public health actions as isolation of infected population, testing the sick individuals, lockdown, hospital facilities;

7. traveling and movement around the globe: people changing locations from one country to another can spread the virus significantly causing the world pandemics;

8. environment conditions: atmosphere around the individual can play a considerable role in transmission and increasing the infection like malaria or dengue, since temperature, humidity are not negligible.

Considering the human history, the epidemics is the crucial episode leading to significant change in the population, immune system, country's economics, and other drastic consequences. The innovative technologies and modern medicine are not able to provide the cure from the epidemics. Regarding the economics conditions, the treatment, medical drugs, rehabilitation,

effective care of infected population requires the huge amount of money to support. Therefore, one of the main research goals is to assist the individuals in the country, which includes the enhancement of life quality, building strong immune system and not letting the infectious disease to develop further.

The main idea is to decrease the influence of epidemics using the mathematical models which can assist to illustrate the virus spread and manage the methods to effectively deal with it. The first pioneers on this path were Kermack W. O. and McKendrick A. G. by introducing the essential document in 1927 [19] with the first epidemic mathematical model. Their work was considered as the SIR model, where S - susceptible, I - infected, R - recovered population. The important condition taken into account is that total number of people is constant for some city as Kermack and McKendrick assumed. The city individuals were classified into three main compartments: people who are healthy but are prone to the disease, sick individuals carrying the disease, and healthy recovered people immune to the virus. The algorithm is worked out in a way that susceptible become infected, then recovered, which can be clearly seen from the flow diagram provided below:

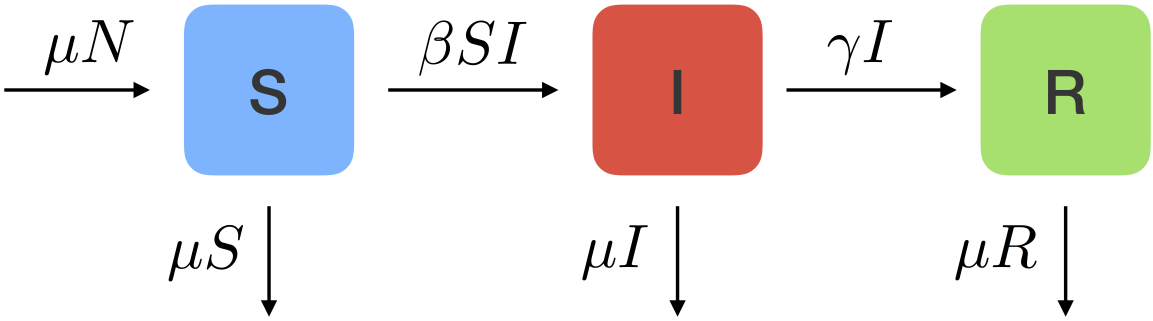


Figure 2.1: Classical SIR model

In the model provided 2.1, the greek letters express the parameters, where μ is natural death coefficient, β is the proportion of people becoming infected, γ is the recovery rate, μN is the newborn individuals considered as the susceptible when they born.

The SIR model was the foundation for other research works to investigate the well-known viruses as influenza which was the case for Baroyan and Rvachev [5] in the second half of the nineteenth century. However, the work became not effective later due to an incorrectly predicted date of the influenza epidemic which did not occur even later. The every day movements of people to different cities influenced the immune system of the whole population, hence, the susceptible individuals should be analyzed in another way and separately for each city.

The virus attacks the susceptible proportion of people and launches the antibodies to work against the unknown agents. The fighters of human body have a little delay to identify the unfamiliar virus and to start fighting, which is a favour to the virus taking its time to increase its number and bringing more destruction to the immune system. To facilitate the antibodies efforts, there was introduced such a medical innovation as the vaccination tool. It assists the virus battle in a global way by increasing and replacing the real antibodies, which provides a

significant assist to overcome with the disease. However, the new types of infections continue appearing and spreading more and some proportion of population do not share the same opinion on vaccination being useful and effective tool as the scientist have concluded.

In order to obtain a more precise mathematical interpretation of the SIR model, different scientists started working on the its further development. For instance in the study "Population Biology" [18] in 2013, mathematical ecologist and professor Alan Hastings made a research on ecology of populations.

In the book of Odo Diekmann and Hans Johan Andre Peter Heesterbeek in 2000 [12], the epidemics mathematical model is investigated on the example of population biology. Stochastic analysis is the key tool to find the connections between compartments.

Elena Gubar and Quanyan Zhu made a remarkable contribution to the epidemic investigation of optimal control of epidemic procedures in the case of multi-strain in 2017 [17] and optimal control for influenza modeling in 2013 [16].

The influenza epidemic was the major issue studied by many scientist including Kolesin I. D. and Zhitkova E. M. in 2015 [21] using the three-wave cycle model with asymptomatic compartment in the infected population.

By far the most significant variable in epidemiology is the basic reproduction number illustrating the potential of the disease to spread among population of a country or of the world. There are two main methods to compute the value of this parameter described in the next sections.

2.6 Basic reproduction number and the methods to calculate it

The basic reproduction number is a crucial parameter in mathematical biology to study the epidemiological analysis and understanding the behaviour of the system in the long term. The classical methods to investigate this parameter is a stability analysis and linearization method. The relevance of the approach is determined by the type of the systems being linear or nonlinear, its structure, and the specifics of the disease. The most applicable mathematical procedures to compute the reproduction number R_0 involve the following:

1. **Linearization and Jacobian Matrix:** the significant part is to identify the disease-free equilibrium value and approximate the nonlinear differential system by linear equations around the equilibrium point. The next step is to compute Jacobian Matrix illustrating the linearized system. After calculating the eigenvalues of Jacobian matrix, they are used to find out the equilibrium point's stability, while R_0 is considered to be the greatest eigenvalue of the matrix.

2. **Next-Generation Matrix (NGM) Method:** is a more general approach of the main linearization method. The requirement is to build a matrix illustrating the next generation of sick population generated by one sick person. Hence, the value of the basic reproduction number is computed following the procedure given before and defined as the spectral radius of the considered matrix. The models studying multiple infectious groups of the population are

the main examples of Next-Generation Matrix application.

3. **Poincaré-Bendixson Theorem:** has an application for two-dimensional systems that are considering the limit dynamics of different paths to recognize the states for limit cycles presence. The Poincaré-Bendixson Theorem has a great application in the case of long-term behaviour of infectious disease systems, taking into account the periodic equations or oscillations.

3. Methodology

3.1 Modeling

Taking the initial model SEIR model with Exposed compartment:

$$\begin{cases} \frac{dS}{dt} = A - \beta S(t)I(t) - \mu S(t) - \lambda S(t) + \alpha R(t) \\ \frac{dE}{dt} = \beta S(t)I(t) - \mu E(t) - \beta e^{-\mu\omega} S(t-\omega)I(t-\omega) \\ \frac{dI}{dt} = \beta e^{-\mu\omega} S(t-\omega)I(t-\omega) - (\mu + d + \gamma)I(t) \\ \frac{dR}{dt} = \gamma I(t) + \lambda S(t) - (\mu + \alpha)R(t) \end{cases}$$

$$\begin{cases} S(t^+) = S(t) - \theta S(t) \\ E(t^+) = E(t) \\ I(t^+) = I(t) \\ R(t^+) = R(t) + \theta S(t) \end{cases}$$

Since $N = S + E + I + R$, by changing the variable, $E = N - S - I - R$, the SIR model takes the following form:

$$\begin{cases} \frac{dS}{dt} = A - \beta S(t)I(t) - \mu S(t) - \lambda S(t) + \alpha R(t) \\ \frac{dI}{dt} = \beta e^{-\mu\omega} S(t-\omega)I(t-\omega) - \mu I(t) - dI(t) - \gamma I(t) \\ \frac{dR}{dt} = \gamma I(t) + \lambda S(t) - \mu R(t) - \alpha R(t) \\ \frac{dN}{dt} = A - \mu N(t) - dI(t) \end{cases}$$

$$\begin{cases} S(t^+) = S(t) - \theta S(t) \\ I(t^+) = I(t) \\ R(t^+) = R(t) + \theta S(t) \\ N(t^+) = N(t) \end{cases}$$

The system can be described using the flow diagram presented below, where the arrows show the direction of the single individual to become susceptible, then infected, and in the end recovered. However, in this research work, the infectious diseases are considered in a way that the recovered person can become prone to the disease again by getting the virus which means

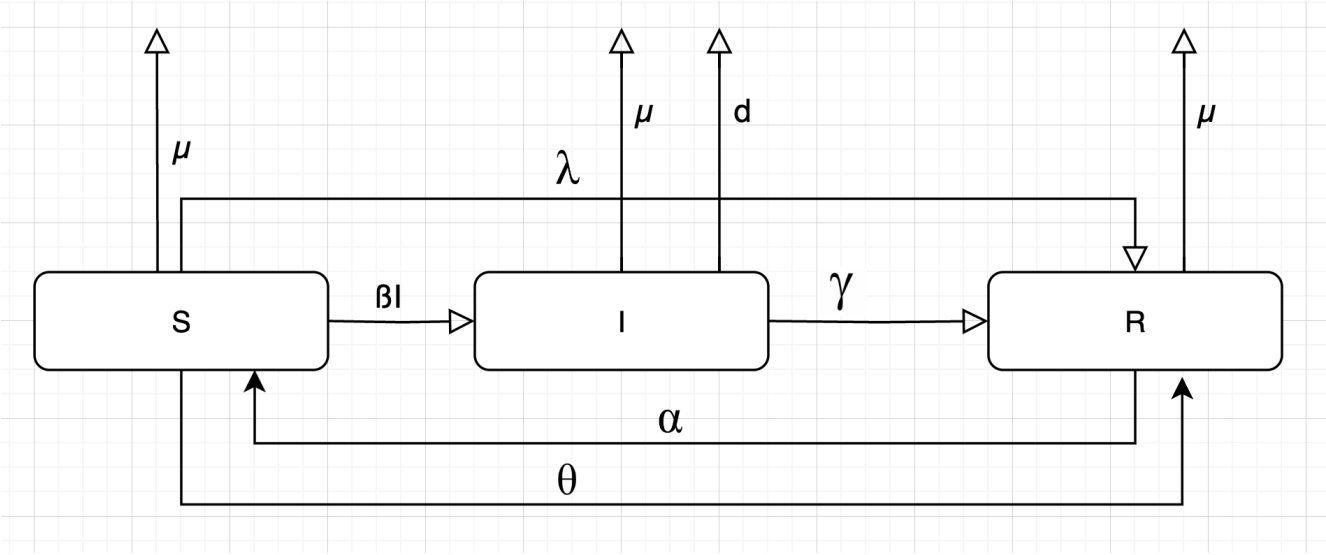


Figure 3.1: Flow diagram for SIR model

that there is no a strong immune system protecting people from the disease. Another thing to pay an attention is the vaccination parameters θ and λ that point from susceptible to recovered compartment by making the individuals immune to the disease. Other parameters are standard and its definitions are explained in the table.

Parameters	Meaning
μ	natural death
A	newborn invariant
α	rate of losing immunity
β	transmission rate
γ	recovery rate for all positive constants
d	disease-induced death rate
τ	period between two pulse vaccinations
ω	latent period of the disease ($\omega > 0$)
θ	pulse vaccination rate $\in (0, 1)$
λ	continuous vaccination rate

Lemma 3.1.1. For a differential system with an impulse parameter:

$$\begin{cases} \frac{du}{dt} = a - bu(t), & t \neq k\tau \\ u(t^+) = u(t) - \theta u(t), & t = k\tau \end{cases}$$

for $a > 0, b > 0, 0 < \theta < 1$, there is a unique periodic solution of the system which is greater than zero 3.1.1:

$$\tilde{u} = \frac{a}{b} + \left(u^* - \frac{a}{b}\right) e^{-b(t-k\tau)}, \quad k\tau < t \leq (k+1)\tau,$$

which is globally asymptotically stable, where $u^* = \frac{a}{b}\frac{(1-\theta)(1-e^{-b\tau})}{1-(1-\theta)e^{-b\tau}}$

Proof: considering the system 3.2 and integrating the first equation between the two pulses, the result presented below is obtained:

$$\frac{du}{dt} = a - bu(t)$$

$$\int_{k\tau}^{(k+1)\tau} \frac{du}{a - bu(t)} = \int_{k\tau}^{(k+1)\tau} dt$$

$$-\frac{1}{b} ln|a - bu(t)|\Big|_{k\tau}^{(k+1)\tau} = t\Big|_{k\tau}^{(k+1)\tau}$$

$$-\frac{1}{b}\left[ln\Big|a - bu((k+1)\tau)\Big| - ln|a - bu(k\tau)|\right] = (k+1)\tau - k\tau$$

$$-\frac{1}{b} ln\left|\frac{a - bu((k+1)\tau)}{a - bu(k\tau)}\right| = \tau$$

$$\left|\frac{a - bu((k+1)\tau)}{a - bu(k\tau)}\right| = e^{-b\tau}$$

$$a - bu((k+1)\tau) = \big(a - bu(k\tau)\big)e^{-b\tau}$$

$$u((k+1)\tau) = \frac{a}{b} - \frac{1}{b}\Big(a - bu(k\tau)\Big)e^{-b\tau}$$

$$u((k+1)\tau) = \frac{a}{b} + \left(u(k\tau) - \frac{a}{b}\right)e^{-b\tau}$$

Expressing $(k+1)\tau$ as t, τ as $t - k\tau$, the expression becomes:

$$u(t) = \frac{a}{b} + \left(u(k\tau)) - \frac{a}{b}\right)e^{-b(t-k\tau)}$$

Since the system 3.1.1 is non-autonomous, then using the second equation, the stroboscopic map can be constructed such that:

$$u((k+1)\tau) = (1-\theta)\left[\frac{a}{b} + \left(u(k\tau) - \frac{a}{b}\right)e^{-b\tau}\right] \triangleq f(u(k\tau))$$

In order to find the equilibrium point, use the theorem $f(u) = u$ from Gao, Chen: [14]

$$u^* = (1-\theta)\left[\frac{a}{b} + \left(u^* - \frac{a}{b}\right)e^{-b\tau}\right]$$

$$\frac{u^*}{(1-\theta)} - u^* e^{-b\tau} = \frac{a}{b} - \frac{a}{b}e^{-b\tau}$$

$$u^*\left[\frac{1 - e^{-b\tau}(1-\theta)}{(1-\theta)}\right] = \frac{a}{b}\big(1 - e^{-b\tau}\big)$$

$$u^* = \frac{a}{b}\frac{(1-e^{-b\tau})(1-\theta)}{1-e^{-b\tau}(1-\theta)}$$

From Cull, the solution is globally asymptotically stable, then periodic solution of system 3.1.1 is following the same trajectory behaviour.

3.2 Disease-Free Periodic Solution

Considering the last equation in system 2, the total size of the whole population gives the following:

$$\frac{dN}{dt} = A - \mu N(t) - dI(t)$$

Therefore, it can be concluded that $A-(\mu+d)N(t) \leq \frac{dN}{dt} \leq A-\mu N(t)$, which means that:

$$\frac{A}{\mu+d} \leq \liminf_{t\to\infty} N(t) \leq \limsup_{t\to\infty} N(t) \leq \frac{A}{\mu}$$

$N(t)$ is bounded by a constant $\frac{A}{\mu}$, then all solutions are uniformly bounded, according to [4]. Then, it is sufficient to construct a bounded feasible set:

$$\Omega = \left\{(S,I,R,N) \in \mathbb{R}_+ : N \leq \frac{A}{\mu}\right\}$$

The set Ω is positively invariant with respect to the initial system and the model is well-posed.

To investigate the disease-free periodic solution, the limiting system is discussed taking into account that $\limsup_{t\to\infty} N(t) = \frac{A}{\mu}$:

$$R(t) = \frac{A}{\mu} - S(t)$$

The reduced form of the initial system can be presented as:

$$\begin{cases} \frac{dS}{dt} = \frac{A}{\mu}(\mu+\alpha) - S(t)(\mu+\alpha+\lambda), \ t \neq k\tau \\ S(t^+) = S(t) - \theta S(t), \ \ t = k\tau \end{cases}$$

By applying the Lemma 3.1.1 to the limiting system, the calculations can be made:

$$\frac{dS^*}{dt} = A - (\mu+\lambda)S^*(t) + \alpha\left(\frac{A}{\mu} - S^*(t)\right) \text{ for } t \neq k\tau$$

$$S(t^+) = (1-\theta)S^*(t) \text{ if } t = k\tau \tag{3.1}$$

$$\int_0^t \frac{dS^*}{A + \frac{A\alpha}{\mu} - S^*(t)(\mu + \lambda + \alpha)} = \int_0^t dt$$

$$-\frac{1}{\mu + \lambda + \alpha} ln \left| A + \frac{A\alpha}{\mu} - S^*(t)(\mu + \lambda + \alpha) \right| \Bigg|_0^t = t \Big|_0^t$$

$$ln \left| A + \frac{A\alpha}{\mu} - S^*(t)(\mu + \lambda + \alpha) \right| - ln \left| A + \frac{A\alpha}{\mu} - S^*(0)(\mu + \lambda + \alpha) \right| = -t(\mu + \lambda + \alpha)$$

$$\frac{\left| A + \frac{A\alpha}{\mu} - S^*(t)(\mu + \lambda + \alpha) \right|}{\left| A + \frac{A\alpha}{\mu} - S^*(0)(\mu + \lambda + \alpha) \right|} = e^{-t(\mu + \lambda + \alpha)}$$

$$-S^*(t)(\mu + \lambda + \alpha) = \left(A\left(1 + \frac{\alpha}{\mu}\right) - S^*(0)(\mu + \lambda + \alpha) \right) e^{-t(\mu + \lambda + \alpha)} - A - \frac{A\alpha}{\mu}$$

$$S^*(t) = S(0)e^{-t(\mu + \lambda + \alpha)} - \frac{A(\mu + \alpha)}{\mu(\mu + \lambda + \alpha)} e^{-t(\mu + \lambda + \alpha)} + \frac{A\mu + A\alpha}{\mu(\mu + \lambda + \alpha)} \tag{3.2}$$

for $0 < t < \tau$

Let's denote

$$X = \frac{A(\mu + \alpha)}{\mu(\mu + \lambda + \alpha)}$$

Rewriting 3.2:

$$S^*(t) = S(0)e^{-t(\mu + \lambda + \alpha)} - Xe^{-t(\mu + \lambda + \alpha)} + X$$

$$S^*(t) = (S(0) - X)e^{-t(\mu + \lambda + \alpha)} + X \tag{3.3}$$

Equation 3.3 should be periodic.

Taking 3.1, to find the the equilibrium point:

$$S(t) = (1 - \theta)((S^* - X)e^{-t(\mu + \lambda + \alpha)} + X) \tag{3.4}$$

Applying the Lemma from [4] and solving for S^*:

$$\frac{S^*}{1 - \theta} = S^* e^{-t(\mu + \lambda + \alpha)} - Xe^{-t(\mu + \lambda + \alpha)} + X$$

$$S^* \left(\frac{1}{1 - \theta} - e^{-t(\mu + \lambda + \alpha)} \right) = X - Xe^{-t(\mu + \lambda + \alpha)}$$

$$S^* \frac{1 - (1 - \theta)e^{-t(\mu + \lambda + \alpha)}}{1 - \theta} = X(1 - e^{-t(\mu + \lambda + \alpha)})$$

$$S^* = \frac{X(1-\theta)(1-e^{-t(\mu+\lambda+\alpha)})}{1-(1-\theta)e^{-t(\mu+\lambda+\alpha)}}$$

According to Lemma 3.1.1, there is a unique positive τ-periodic solution presented by the following formula:

$$S^*(t) = \frac{A(\mu+\alpha)}{\mu(\mu+\alpha+\lambda)} + \left(S^* - \frac{A(\mu+\alpha)}{\mu(\mu+\alpha+\lambda)}\right)e^{-(\mu+\alpha+\lambda)(t-k\tau)}, \quad k\tau < t \leq (k+1)\tau,$$

where $S^* = \frac{A(\mu+\alpha)}{\mu(\mu+\alpha+\lambda)} \frac{(1-\theta)(1-e^{-(\mu+\alpha+\lambda)\tau})}{1-(1-\theta)e^{-(\mu+\alpha+\lambda)\tau}}$

It can be concluded that recovered compartment oscillates as susceptible part with the same period τ. Hence, the disease-free equilibrium solution takes the following form:

$$E_0(t) = (S^*(t), 0, \frac{A}{\mu} - S^*(t))$$

3.3 Basic Reproduction Number

The basic reproduction number can't be calculated by the next generation matrix method because the system is not continuous, therefore, the linearization technique at $E_0(t)$ is used first.

$$\frac{dI}{dt} = \beta e^{-\mu\omega} S^*(t-\omega)I(t-\omega) - (\mu+d+\gamma)I(t)$$

Let $i(t) = \beta e^{-\mu\omega} S^*(t-\omega)I(t-\omega)$ express the rate of infected individuals for some time t:

$$\frac{dI}{dt} = i(t) - (\mu+d+\gamma)I(t)$$

$$\frac{dI}{dt} + (\mu+d+\gamma)I(t) = i(t)$$

By multiplying both sides by $e^{(\mu+d+\gamma)t}$, the expression becomes:

$$\frac{dI}{dt}e^{(\mu+d+\gamma)t} + (\mu+d+\gamma)I(t)e^{(\mu+d+\gamma)t} = i(t)e^{(\mu+d+\gamma)t}$$

The left hand side can be written as the derivative:

$$\frac{d}{dt}\left[e^{(\mu+d+\gamma)t}I(t)\right] = e^{(\mu+d+\gamma)t}i(t)$$

Taking the integral of the last equation from 0 to t:

$$\int_0^t \frac{d}{ds}\left[e^{(\mu+d+\gamma)s}I(s)\right]ds = \int_0^t e^{(\mu+d+\gamma)s}i(s)ds$$

$$\left[e^{(\mu+d+\gamma)s}I(s)\right]\Big|_0^t = \int_0^t i(s)e^{(\mu+d+\gamma)s}ds$$

$$e^{(\mu+d+\gamma)t}I(t) - I(0) = \int_0^t i(s)e^{(\mu+d+\gamma)s}ds$$

$$I(t) = I(0)e^{-(\mu+d+\gamma)t} + \int_0^t i(s)e^{-(\mu+d+\gamma)(t-s)}ds$$

Making a change of variable t to $t-\omega$, the last equation takes the form:

$$I(t-\omega) = I(0)e^{-(\mu+d+\gamma)(t-\omega)} + \int_0^{t-\omega} i(s)e^{-(\mu+d+\gamma)(t-\omega-s)}ds$$

Multiplying the last equation by $\beta e^{-\mu\omega}S^*(t-\omega)$:

$$\begin{aligned} i(s) = {} & \beta e^{-\mu\omega}S^*(t-\omega)I(0)e^{-(\mu+d+\gamma)(t-\omega)} \\ & + \beta e^{-\mu\omega}S^*(t-\omega)\int_0^{t-\omega} i(s)e^{-(\mu+d+\gamma)(t-\omega-s)}ds, \end{aligned}$$

Changing one more variable $s = t - x$, the next equation is as follows:

$$\begin{aligned} i(s) = {} & \beta e^{-\mu\omega}S^*(t-\omega)I(0)e^{-(\mu+d+\gamma)(t-\omega)} \\ & - \beta e^{-\mu\omega}S^*(t-\omega)\int_t^{\omega} i(t-x)e^{-(\mu+d+\gamma)(t-\omega-(t-x))}dx, \end{aligned}$$

$$\begin{aligned} i(s) = {} & \beta e^{-\mu\omega}S^*(t-\omega)I(0)e^{-(\mu+d+\gamma)(t-\omega)} \\ & + \beta e^{-\mu\omega}S^*(t-\omega)\int_{\omega}^{t} i(t-x)e^{-(\mu+d+\gamma)(x-\omega)}dx, \end{aligned}$$

The last equation takes the form of:

$$i(t) = i_0(t) + \int_0^t K(t,x)i(t-x)dx,$$

where $i_0(t) = \beta e^{-\mu\omega}S^*(t-\omega)I(0)e^{-(\mu+d+\gamma)(t-\omega)}$,

$$K(t,x) = \begin{cases} 0, & \text{if } x < \omega \\ \beta e^{-\mu\omega}S^*(t-\omega)e^{-(\mu+d+\gamma)(x-\omega)}, & \text{if } x \geq \omega \end{cases}$$

Defining the linear operator $L : \mathbb{R} \to \mathbb{R}$:

$$L : v(t) \mapsto \int_0^{\infty} K(t,x)v(t-x)dx$$

3.4 Calculating R_0

$K(t,x)$ can be expressed as $K(t,x) = c(t)G(x)$, where $c(t) = \beta e^{-\mu\omega}S^*(t-\omega)$,

$$G(x) = \begin{cases} 0, & \text{if } x < \omega \\ e^{-(\mu+d+\gamma)(x-\omega)}, & \text{if } x \geq \omega \end{cases}$$

Since the basic reproduction number plays a role of a greatest eigenvalue of the matrix, then using the linear algebra theory, it can be shown that the spectral radius represents the biggest value of the eigenvalue. In order to find the basic reproduction number $R_0 = r(L)$, the following eigenvalue problem can be solved:

$$\int_0^\infty K(t,x)u(t-x)dx = R_0u(t),\ u \in \mathbb{R}$$

$$c(t)\int_0^\infty G(x)u(t-x)dx = R_0u(t),\ u \in \mathbb{R} \tag{3.5}$$

$$c(t)\int_0^\infty e^{-(\mu+d+\gamma)(x-\omega)}u(t-x)dx = R_0u(t),\ u \in \mathbb{R}$$

The equation above is differentiated first:

$$R_0u'(t) = c'(t)\int_\omega^\infty e^{-(\mu+d+\gamma)(x-\omega)})u(t-x)dx + c(t)\int_\omega^\infty e^{-(\mu+d+\gamma)(x-\omega)}u'(t-x)dx$$

$$\begin{aligned} R_0u'(t) &= c'(t)\int_\omega^\infty e^{-(\mu+d+\gamma)(x-\omega)})u(t-x)dx + c(t)\int_\omega^\infty e^{-(\mu+d+\gamma)(x-\omega)}u'(t-x)dx \\ &= c'(t)\frac{R_0u(t)}{c(t)} + c(t)\int_\omega^\infty e^{-(\mu+d+\gamma)(x-\omega)}u'(t-x)dx, \end{aligned}$$

Then the last expression is integrated by parts:

$$\begin{aligned} U &= e^{-(\mu+d+\gamma)(x-\omega)} & dU &= -(\mu+d+\gamma)e^{-(\mu+d+\gamma)(x-\omega)}dx \\ dV &= u'(t-x)dx & V &= -u(t-x) \end{aligned} \tag{3.6}$$

$$\begin{aligned} UV - \int_\omega^\infty VdU &= -e^{-(\mu+d+\gamma)(x-\omega)}u(t-x)\Big|_\omega^\infty - \int_\omega^\infty u(t-x)(\mu+d+\gamma)e^{-(\mu+d+\gamma)(x-\omega)}dx \\ &= e^{-(\mu+d+\gamma)(\omega-\omega)}u(t-\omega) - \textstyle\int_\omega^\infty u(t-x)(\mu+d+\gamma)e^{-(\mu+d+\gamma)(x-\omega)}dx \\ &= u(t-\omega) - (\mu+d+\gamma)\textstyle\int_\omega^\infty u(t-x)e^{-(\mu+d+\gamma)(x-\omega)}dx \\ &= u(t-\omega) - (\mu+d+\gamma)\frac{R_0u(t)}{c(t)} \end{aligned}$$

Going back to $R_0u'(t)$ expression:

$$\begin{aligned} R_0u'(t) &= c'(t)\frac{R_0u(t)}{c(t)} + c(t)u(t-\omega) - c(t)(\mu+d+\gamma)\frac{R_0u(t)}{c(t)} \\ &= c'(t)\frac{R_0u(t)}{c(t)} + c(t)u(t-\omega) - (\mu+d+\gamma)R_0u(t), \end{aligned}$$

Dividing both sides of the last expression by $R_0u(t)$, it becomes:

$$\frac{u'(t)}{u(t)} = \frac{c'(t)}{c(t)} + \frac{c(t)}{R_0}\frac{u(t-\omega)}{u(t)} - (\mu+d+\gamma)$$

Taking into account that $u(0) = u(\tau)$ and $c(0) = c(\tau)$ and integrating both sides of the last equation from 0 to τ, it becomes:

$$\int_0^\tau \frac{u'(t)}{u(t)}dt = \int_0^\tau \frac{c'(t)}{c(t)}dt + \int_0^\tau \frac{c(t)}{R_0}\frac{u(t-\omega)}{u(t)}dt - \int_0^\tau (\mu+d+\gamma)dt$$

$$ln|u(t)|\Big|_0^\tau = ln|c(t)|\Big|_0^\tau + \int_0^\tau \frac{c(t)}{R_0}\frac{u(t-\omega)}{u(t)}dt - (\mu+d+\gamma)\Big|_0^\tau$$

$$ln|u(\tau)| - ln|u(0)| = ln|c(\tau)| - ln|c(0)| + \int_0^\tau \frac{c(t)}{R_0}\frac{u(t-\omega)}{u(t)}dt - (\mu+d+\gamma)\tau$$

$$(\mu+d+\gamma)\tau = \frac{1}{R_0}\int_0^\tau c(t)\frac{u(t-\omega)}{u(t)}dt$$

$$R_0 = \frac{\int_0^\tau c(t)\frac{u(t-\omega)}{u(t)}dt}{(\mu+d+\gamma)\tau}$$

For the case, when $\omega = 0$, the following expression is obtained after the simplification:

$$R_0 = \frac{\int_0^\tau c(t)dt}{(\mu+d+\gamma)\tau}$$

3.5 Numerical approximation of R_0

Basic reproduction number depends on two pulse vaccination coefficients such as τ and θ, therefore, the numerical approach is considered to check the dependence on these two parameters, which is the discretization method.

The discretization approach is a procedure of transforming the continuous functions or expressions into discrete intervals to calculte them using computer software. So the finite set of values are used to get an answer close to the original system's solution.

From Equation 3.5:

$$R_0 u(t) = c(t) \int_0^\infty G(x) u(t-x) dx$$

$$R_0 u(t) = c(t) \int_\omega^\infty G(x) u(t-x) dx$$

$$R_0 u(t) = c(t) \int_\omega^\infty e^{-(\mu+d+\gamma)(x-\omega)} u(t-x) dx$$

Making a change of variable $t - x = s$:

$$\begin{aligned} R_0 u(t) &= -c(t) \int_{t-\omega}^{-\infty} e^{-(\mu+d+\gamma)(t-s-\omega)} u(s) ds \\ &= c(t) \int_{-\infty}^{t-\omega} e^{-(\mu+d+\gamma)(t-s-\omega)} u(s) ds, \end{aligned}$$

Dividing the integral into two parts and discretizing the second part:

$$R_0 u(t) = -c(t) \left(\int_0^{t-\omega} e^{-(\mu+d+\gamma)(t-\omega-s)} u(s) ds + \sum_{n=0}^{\infty} \int_{-\tau(n+1)}^{-\tau n} e^{-(\mu+d+\gamma)(t-\omega-s)} u(s) ds \right)$$

$$= -c(t) \left(\int_0^{t-\omega} e^{-(\mu+d+\gamma)(t-\omega-s)} u(s) ds + \sum_{n=0}^{\infty} \int_0^{\tau} e^{-(\mu+d+\gamma)(t-\omega+(n+1)\tau-s)} u(s) ds \right)$$

The integral and summation sign can be swapped to notice that:

$$\sum_{n=0}^{\infty} e^{-(\mu+d+\gamma)(t-\omega+(n+1)\tau-s)} = \frac{e^{-(\mu+d+\gamma)(t-\omega+\tau-s)}}{1 - e^{-(\mu+d+\gamma)\tau}}$$

The result is as follows:

$$R_0 u(t) = -c(t) \left(\int_0^{t-\omega} e^{-(\mu+d+\gamma)(t-\omega-s)} u(s) ds + \int_0^{\tau} \frac{e^{-(\mu+d+\gamma)(t-\omega+\tau-s)}}{1 - e^{-(\mu+d+\gamma)\tau}} u(s) ds \right)$$

$$\int_0^{\tau} \frac{e^{-(\mu+d+\gamma)(t_i-\omega+\tau-s)}}{1 - e^{-(\mu+d+\gamma)\tau}} u(s) ds = \lim_{N\to\infty} \frac{\tau}{N} \sum_{j=0}^{N-1} \frac{e^{-(\mu+d+\gamma)(t_i-\omega+\tau-t_j)}}{1 - e^{-(\mu+d+\gamma)\tau}} Y_j$$

If $i < k$:

$$\int_0^{t_i-\omega} e^{-(\mu+d+\gamma)(t-\omega-s)} u(s) ds = \lim_{N\to\infty} \frac{\tau}{N} \sum_{j=0}^{i-k} e^{-(\mu+d+\gamma)(t_i-\omega-t_j)} Y_j$$

If $i \geq k$:

$$\int_0^{t_i-\omega} e^{-(\mu+d+\gamma)(t_i-\omega-s)}u(s)ds = -\int_{\tau+t_i-\omega}^{\tau} e^{-(\mu+d+\gamma)(t_i-\omega+\tau-s)}u(s)ds$$

$$= \lim_{N\to\infty} -\frac{\tau}{N}\sum_{j=N+i-k}^{N-1} e^{-(\mu+d+\gamma)(t_i-\omega+\tau-t_j)}Y_j$$

$$\rho_0 Y = AY$$

$$A_{ij} = \frac{c(t_i)\tau e^{-(\mu+d+\gamma)(t_i-\omega+\tau-t_j)}}{N(1-e^{-(\mu+d+\gamma)\tau})} + \frac{c(t_i)\tau}{N}\cdot D,$$

where

$$D = \begin{cases} e^{-(\mu+d+\gamma)(t_i-\omega-t_j)}, & \text{if } i > k \text{ and } j \leq i-k, \\ 0, & \text{if } i > k \text{ and } j > i-k, \\ e^{-(\mu+d+\gamma)(t_i-\omega+\tau-t_j)}, & \text{if } i \leq k \text{ and } j \geq N+i-k \\ 0, & \text{if } i \leq k \text{ and } j < N+i-k. \end{cases}$$

$$\int_0^{\infty} G(x)u(t-x)dx = \int_0^t \hat{G}(t-x)u(x)dx + \int_t^{\tau} \hat{G}(t-x+\tau)u(x)dx$$

4. Results and Discussion

The mathematical modeling of an infectious disease is constructed from two approaches which are analytical method and numerical approximation. In the first part of the analysis, the analytical solution provided the formula for the most significant term in mathematical biology is a basic reproduction number R_0. The detailed significant analysis of the main terms included pulse vaccination coefficient θ, another continuous vaccination parameter λ and the disease transmission rate β which were remarkably affecting the value of the most important parameter in epidemiological analysis - reproduction number R_0. In the next sections, the outcomes interpretation, the novelty of the research, the contributions and limitations of the work are discussed in a great detail. The last thing is the suggestion idea to investigate in the next research work.

First of all, the SIR model was plotted without vaccination effect, as it can be clearly seen from the Figure 4.1a, the infectious compartment is increasing meaning there is an epidemic among the population. To have a closer look at the infectious part, another graph was analyzed on the Figure 4.1b. Since there is a disease epidemic, now the vaccination parameter can be added to check the effectiveness of pulse and continuous vaccination coefficients.

Moreover, the reproduction number values are calculated for S^* and for the general model itself which are 1.999 and 2.003, respectively, verifying the virus spread causing the epidemic.

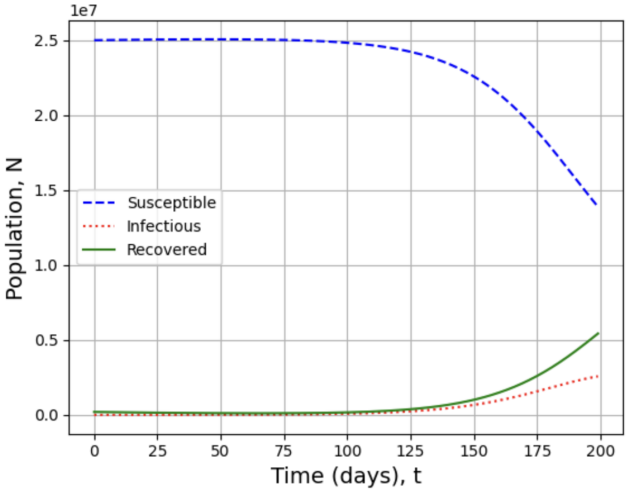
After understanding the overall trend of the SIR model and infectious compartment, parameters θ and λ are added to compare the disease flow.

By adding the pulse vaccination compartment, there is an additional θ coefficient which equals to 0.185 on the Figure 4.2a. While the significant value of the SIR model - the reproduction number for the overall model is 0.994 corresponding the condition for the disease to die out.

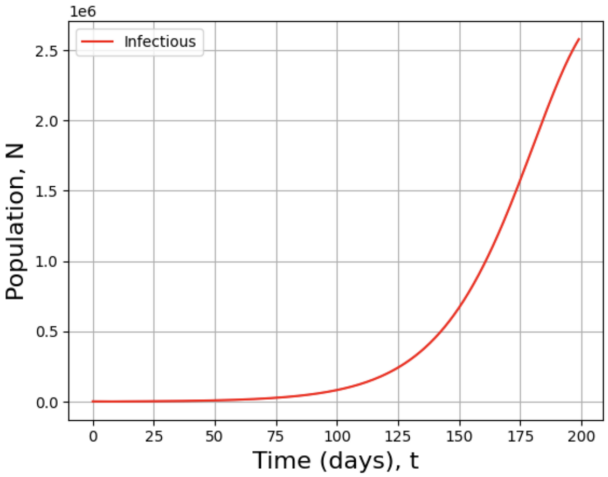
Taking a closer look at the SIR model, the zigzag trend can be noticed that expresses the pulse vaccination making the number of Susceptible and Recovered compartments increase and decrease abruptly for the same extent, respectively.

The number of infected population increases during the 200 days period 4.2b, however, on a long-term basis, it is going to decrease which is proved by the calculated value of the basic reproduction number.

The following figures 4.3a and 4.3b show the case for continuous vaccination rate $\lambda = 0.013$ expressing the 1.3 percent of the population to be continuously vaccinated. Even though, the graph illustrates the increase in infectious compartment, the reproduction number for S^* is

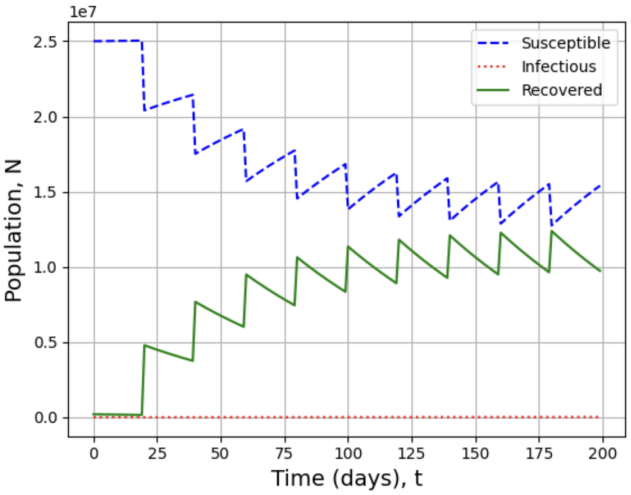


(a) SIR model

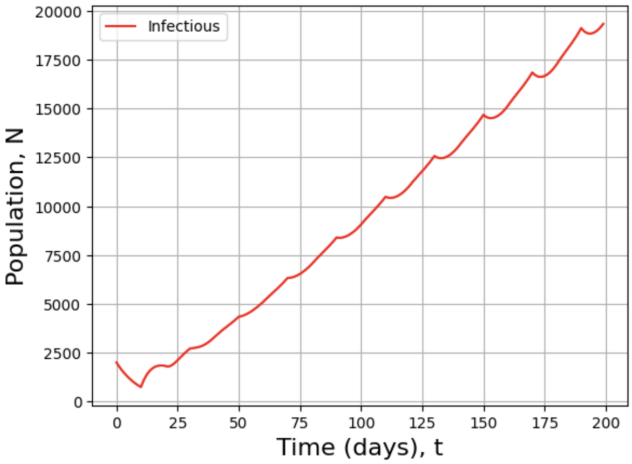


(b) Infectious population

Figure 4.1: No vaccination for $\theta = 0.0$, $\lambda = 0.0$.

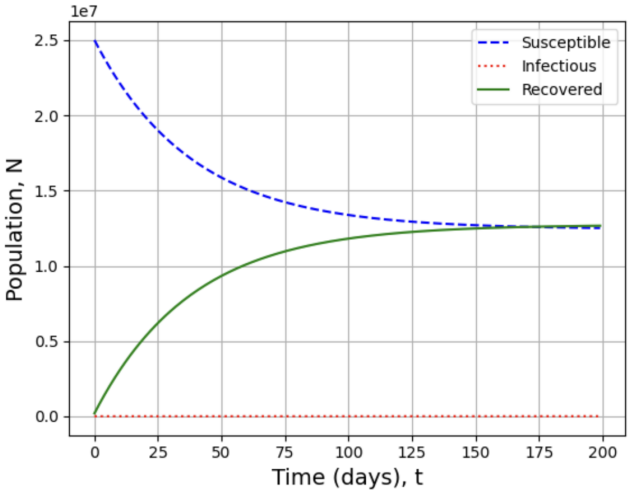


(a) SIR model

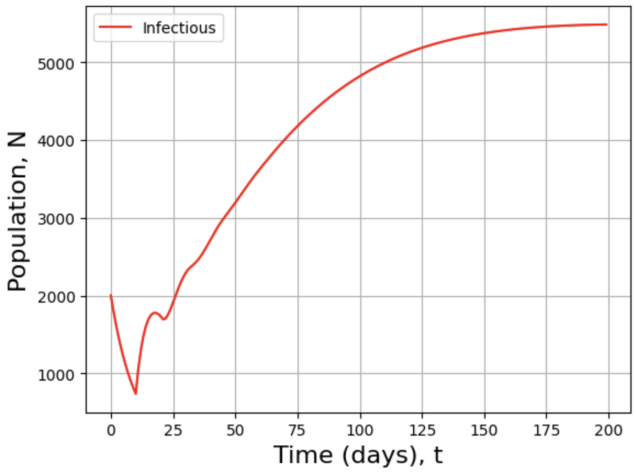


(b) Infectious population

Figure 4.2: Pulse vaccination for $\theta = 0.185$, $\lambda = 0.0$.

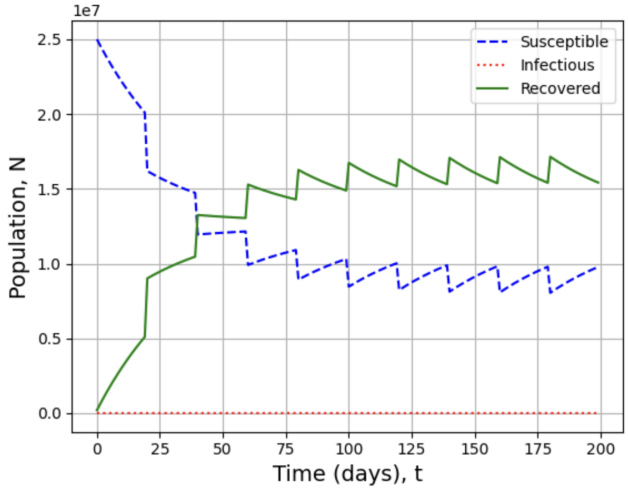


(a) SIR model

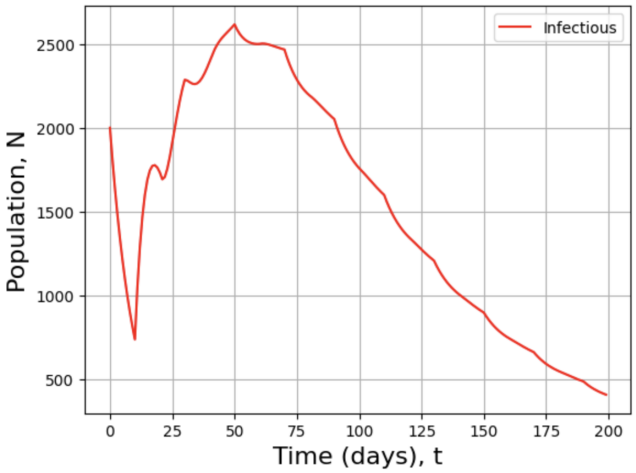


(b) Infectious population

Figure 4.3: Continuous vaccination for $\theta = 0.0$, $\lambda = 0.013$.



(a) SIR model



(b) Infectious population

Figure 4.4: Both vaccinations for $\theta = 0.185$, $\lambda = 0.013$.

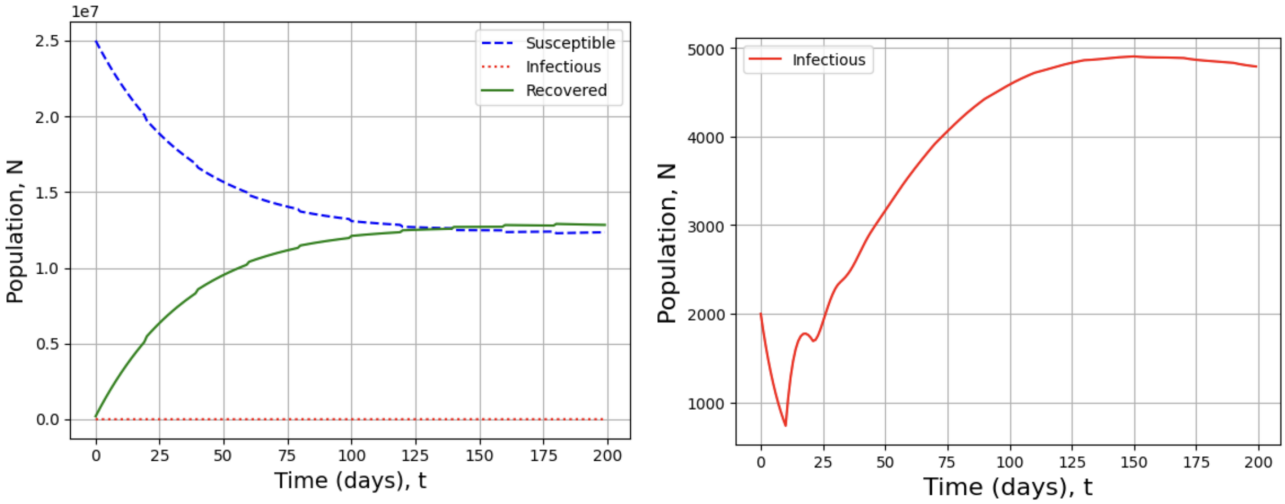
0.989, while for the general model is $R_0 = 0.991$.

The last case to analyze is the presence of both vaccination parameters that obviously decrease the flow of the disease giving the basic reproduction number being equal to 0.6297 on figures 4.4a and 4.4b.

However, even decreasing the pulse vaccination parameter θ twice to the value of 0.09 and λ remaining unchanged still gives the case when the disease dies out with $R_0 = 0.9698$ being less than 1. The described situation can be observed from the next two graphs attached above on the Figures 4.5a and 4.5b.

From the detailed analysis provided above from Figures 4.1a-4.5b, it can be observed that vaccination idea is a beneficial process for the whole population considering susceptible ones. It offers many advantages in ceasing the further spread of the given virus, a few reasons for vaccinating the population are provided with details below:

- transmission rate decreases: since the susceptible individuals become recovered by getting



(a) SIR model

(b) Infectious population

Figure 4.5: Both vaccinations for $\theta = 0.09$, $\lambda = 0.013$.

either the pulse vaccination, or the continuous vaccination, the virus is not able to attach to these people; therefore, the disease will slowly reduce its transmission rate β resulting in a smaller value of a reproduction number R_0 and dying out the disease;

- herd immunity: it is crucial that vaccination procedure provides the whole population with a protection in a sense of a herd immunity meaning that the majority of people are strong enough not to get infected again; the epidemics will stop by decreasing the value of R_0;

- change of a disease trajectory: vaccination is an artificial way of dealing with the virus that affects the dynamics in a huge extent by decreasing the number of infected cases and giving the cure to the society.

5. Conclusion

The investigation of the delayed SEIRS model presented in this study introducing the pulse vaccination parameter while changing the size of the considered population. The idea was to add another coefficient for continuous vaccination λ and study how it affects the flow of the disease from the infectious compartment point of view and the value of the reproduction number R_0 hence describe the progress of the epidemics.

In the paper by [4], the pulse vaccination influence in the epidemiological model is investigated, while the continuous vaccination parameter is not considered. By adding the λ parameter, it has been investigated that the main formula for the basic reproduction number R_0 remains unchanged, since any vaccination parameter does not affect the infectious compartment. Therefore, the analytical process of solving the SIR system was very identical to Bai. However, finding the disease-free equilibrium became a little different procedure because of λ being present in the susceptible and recovered compartments. To find the important term R_0, the next generation matrix method was not possible to be applied since an initial system was discontinuous. Therefore, the linearization method is used with respect to the disease-free periodic solution E_0. After the extended analysis, the system was presented in a form of a matrix that can be solved by calculating the greatest eigenvalue so called a spectral radius. It can be concluded that R_0 is same for continuous vaccination.

Having a closer look at the numerical approximation of R_0, the λ term made a significant impact in this case which have been seen from the graphs illustrated above. It was challenging to find such a transmission rate value for β so that R_0 is greater than 2 meaning there is an epidemic among the population, meanwhile, the disease can die out when adding the vaccine parameters that should make R_0 less than 1. By finding the proper value for β being 0.19 with $R_0 = 2.003$, the pulse vaccination coefficient θ was added by taking the value of 0.185 and giving the R_0 value being equal to 0.994 which is less than 1. Another situation was the following to consider the same transmission rate β being 0.19 with a different vaccination strategy - continuous vaccination case $\lambda = 0.013$ resulting in $R_0 = 0.989$ being less than 1, hence the disease dies out. The last scenario was to combine the two vaccines θ and λ taking the values as in separate cases with the same transmission rate β, and it resulted in a basic reproduction number R_0 to be 0.6297 which is much better than then previous two situations. Moreover, the model can be enhanced by decreasing θ to 0.09 to get $R_0 = 0.9698$ that is still less than 1.

Therefore, adding the separate vaccination parameter corresponding to continuous vaccina-

tion case, the considered SIR model tends to get rid of the disease which have been understood from R_0 values and attached graphs.

The transmission parameter β has to be constant while adding θ and λ which was difficult to find the appropriate reproduction number.

As a further research on this model, the elasticity parameter can be considered to check the degree of sensitivity of a specific variable, in this case, the reproduction number R_0.

A. Appendix A

The code used to run the numerical approximation for reproduction number R_0 can be found below:

```
import numpy as np
import scipy.optimize as optimization
import pandas as pd
import matplotlib.pyplot as plt
import scipy.integrate
import math
```

```
# parameters

#Initial Conditions
N0=25000000 #total population
S0=N0 #initial condition
I0=2000 #initial condition
R0=200000 #initial condition
Lambda=1000 #recruitment rate of population
mu=0.00004 #natural death rate
d=0.015 #death due to epidemic
delta=0.08 #recovery rate
beta=0.19 #transmission rate
alfa=0.0127 #rate of losing immunity
eta=0.001 #saturation rate
w=20 #vaccination period
tau=10 #incubation period
theta=0.009 #vaccination rate
lammbda=0.013 #continuous vaccination rate
```

```
Lambda/mu
```

```
24999999.999999996
```

Figure A.1: Parameters.

```
numdays = 200
time=range(numdays)

S=[]
I=[]
R=[]
N=[]
S.append(S0)
I.append(I0)
R.append(R0)
N.append(N0)

def f(t):
    if t<tau:
        return 0
    else:
        return beta*S[t-tau]*I[t-tau]*math.exp(-mu*tau)/N0
dt=1
for t in range(numdays-1):
    if ((t+1)%w != 0):
        S.append(S[t]+(Lambda-(beta*S[t]*I[t])/N0-(mu+lammbda)*S[t]+alfa*R[t])*dt)
        I.append(I[t]+(f(t)-(mu+d+delta)*I[t])*dt)
        R.append(R[t]+(delta*I[t]-(mu+alfa)*R[t]+lammbda*S[t])*dt)
        N.append(N[t]+(Lambda-mu*N[t]-d*I[t])*dt)
    else:
        S.append(S[t]+(Lambda-beta*S[t]*I[t]/N0-(mu+lammbda)*S[t]+alfa*R[t]-theta*S[t])*dt)
        I.append(I[t]+(f(t)-(mu+d+delta)*I[t])*dt)
        R.append(R[t]+(delta*I[t]-(mu+alfa)*R[t]+lammbda*S[t]+theta*S[t])*dt)
        N.append(N[t]+(Lambda-mu*N[t]-d*I[t])*dt)


plt.plot(time, S,color='b', label='Susceptible', linestyle='dashed')
plt.plot(time, I,color='r', label='Infectious', linestyle='dotted')
plt.plot(time, R,color='g', label='Recovered')
plt.grid()
plt.legend()
plt.xlabel('Time (days), t',fontsize=14)
plt.ylabel('Population, N',fontsize=14)
#plt.savefig('Vaccine_u.png',bbox_inches='tight', dpi=300)
plt.show()
```

Figure A.2: Plotting SIR model.

```
plt.plot(time, I,color='r', label='Infectious')

plt.grid()
plt.legend()
plt.xlabel('Time (days), t',fontsize=16)
plt.ylabel('Population, N',fontsize=16)
plt.show()
```

Figure A.3: Plotting I.

```
#DFE w-periodic solution
S_star=Lambda*(mu+alfa)*(1-theta)*(1-np.exp(-(mu+alfa+lammbda)*w))/(mu*(mu+alfa+lammbda)*(1-(1-theta)*np.exp(-(mu+alfa+lammbda)*w)))
def SS(t):
    #k=np.ceil(t/w)-1
    return Lambda*(mu+alfa)/(mu*(mu+alfa+lammbda))+(S_star-Lambda*(mu+alfa)/(mu*(mu+alfa+lammbda)))*np.exp(-(mu+alfa+lammbda)*t)

II=0

def RR(t):
    return Lambda/mu-SS(t)
```

g(t)=bSI/(N+nS)

```
#define g(t) the partial of f w.r.t I if f=bSI/(N+nS)
def c(t):
    return beta*np.exp(-mu*tau)*SS(t-tau)/N0
```

```
#g(t)/(mu+d+delta)
```

```
Rep=beta*(Lambda*(mu+alfa)/(mu*(mu+alfa+lammbda))*w+(S_star-Lambda*(mu+alfa)/(mu*(mu+alfa+lammbda)))*(1/(mu+alfa+lammbda))*
          (1-np.exp(-(mu+alfa+lammbda)*w)))/(N0*w*(mu+d+delta))
Rep
```

```
0.9724119025504703
```

```
#reproduction for S'=Lambda-beta*S*I/N0-mu*S; I'=beta*S*I/N0-(mu+d+delta)I
(Lambda/mu)*beta/(N0*(mu+d+delta))
```

```
1.9991582491582487
```

```
def tt(i):
    return i*w/N
```

Figure A.4: Calculation of S^*.

```
N=1000

w=w*(1+10**(-10))
S_star=Lambda*(mu+alfa)*(1-theta)*(1-np.exp(-(mu+alfa+lammbda)*w))/(mu*(mu+alfa+lammbda)*(1-(1-theta)*np.exp(-(mu+alfa+lammbda)*w)))

k=0
while tt(k) <= tau:
    k=k+1
k=k-1

A=np.zeros((N,N))
for i in range(N):
    for j in range(N):
        M=c(tt(i))*(w/N)*np.exp(-(mu+d+delta)*(tt(i)-tau+w-tt(j)))/(1-np.exp(-(mu+d+delta)*w))
        if ((i > k) and (j <= i-k)):
            A[i,j]=M+c(tt(i))*(w/N)*np.exp(-(mu+d+delta)*(tt(i)-tau-tt(j)))

        elif ((i <= k) and (j>N+i-k)):
            A[i,j]=M-c(tt(i))*(w/N)*np.exp(-(mu+d+delta)*(tt(i)-tau+w-tt(j)))

        else:
            A[i,j]=M

e_val,e_vec=np.linalg.eig(A)
max(abs(e_val))
```

```
0.9697662583268555
```

Figure A.5: Reproduction Number.

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