Pulse vaccination of a time-delayed SIRS epidemic model with nonlinear incidence rate

by

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Abstract

This work deals with an application of pulse vaccination for a varying size of the population of time-delayed $SIRS$ epidemic model. The dynamics of the infectious disease depends on the threshold value, R_0, known as the basic reproduction number. In the classical epidemic models, this value is evaluated by means of the next generation matrix. However, this method does not work for non-autonomous systems. Since we consider the pulse vaccination strategy for epidemic models our system is naturally non-autonomous. We follow the general approach to derive R_0 in terms of spectral radii of Poincare maps. Further, we show the existence of an infectious-free periodic solution and its global attractiveness for $R_0 < 1$ and the persistence of infectious disease for $R_0 > 1$.

Thesis Supervisor: Ardak Kashkynbayev
Title: Assistant Professor

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Contents

Chapter 1

Introduction

Nowadays health improvement became a worldwide topic being discussed all around and this is not surprising, as people are naturally concerned to live healthy long lives. People can prevent some diseases beforehand by leading healthy lifestyle. However, there are outbreaks of disease, that cannot be treated by usual therapies. For instance, the most recent meningitis, appeared in several countries in Summer 2018 [1], infected a substantial portion of the population before it disappeared. Hence, the epidemiology studies the determinants of health-related states of the specified population and applies the knowledge to control occurred health problems [13]. Overall, epidemiology studies behavior of infectious diseases, while mathematical modeling of epidemics helps to predict the threshold of an epidemics. This threshold parameter plays an important role in describing the behaviour of disease and controlling it.

Epidemiological models were first introduced by Kermack and McKendrick in 1927 [29]. Since then there were published numerous studies and few more progress in formulating different models for various types of infectious diseases. The general form of the model is $SEIRS$ model [43, 9], which consists of 4 epidemiological vital subgroups and mix homogeneously: S - susceptible, E - exposed, I - infected and R - recovered. Other models like SIR model, SI model [34] or SIS model [19, 33] are all just particular cases of the general model. All these models are formed as deterministic in structure models in this work. It is described as the transfer between them, including all the modifications in population size as births and deaths, are

modelled in a system of differential equations governing the time-evolution of each compartment value.

This broad studies in epidemiology means there is wide spread of infectious disease that demands for effective programs to control the infections. There are many types of vaccinating approaches to appose the diseases. Although there are traditional methods of controlling disease spread, including $SVIR$, $SVEIR$ [28], where class V stands for vaccinated population, we will analyze influence of pulse vaccination [35, 37], which is one of the effective strategies to control infectious diseases. The aim of the pulse vaccination strategy (PVS)[27] is to reduce the number of susceptibles as much as possible based on repeated vaccinating actions of a population at the infection rise until the spread of it has been stopped. For this reason we choose the epidemic model that satisfies this situation most. For instance, if we take an SIR models after vaccination acts, recovered individuals will gain total immunity to the pathogen. In $SIRS$ models, recovered population loses the immunity over time, and individuals may become susceptible again.

1.1 Guide to Thesis

The thesis work is structured in the following way:

Chapter 2 This chapter provides a general background how the epidemic models are constructed; all the terms used and important main concepts are introduced. The theory of constructing models based on differential equations, derivation of threshold parameter and disease control methods are discussed in details.

Chapter 3 In this chapter the stability concepts and theorems, comparison theorems and theorems for uniqueness and existence of solutions to differential equations are provided.

Chapter 4 This chapter is our research results chapter. We formulate our epidemic model related to general incidence terms and time-delay in differential equations with a particular focus on periodic vaccination strategy. We first show some initial results using literature to obtain a certain threshold, to analyze the global asymptotic stability of the disease-free periodic solution (DFPS) of the model. The concept of deriving the R_0 uses spectral radius approach for impulsive delay differential equations. Furthermore, we prove the permanence of the infection with delay if the parameter is not below the threshold. The work includes some Lemmas about periodicity, as we vaccinate the population at constant time periodically.

Chapter 5 In this chapter we conclude the work done and share some ideas for future work.

1.2 Motivation

The application of pulse vaccination to certain population with a vaccination-preventable disease is the whole image of current situation. To describe the details, we construct an $SIRS$ epidemic model, where the recovered population at some rate becomes susceptible again. But the main event is the transmission rate of susceptibles to infected compartment - the incidence rate. This work is focused on generalization of nonlinear incidence rate for $SIRS$ epidemic model.

We have already described the purpose of observing the $SIRS$ model with time delay. So, now we will discuss the aim of generalizing the term of incidence. The incidence rate is the interaction between susceptible individuals with infected ones at some rate to count how many people are becoming infected and transferring to infectious class. We denote it $f(S, I)$, which covers all other nonlinear incidences that are mentioned in academic papers before. However, this function $f(S, I)$ must hold some important conditions [30]. The first is that if there is no interaction between these two populations, there will no incidence function considered as: $f(S, 0) = f(0, I) = 0$. The whole infected population is recovered at all means there is no one who can infect the population. Otherwise, if all of the population is infected, there will be no infectious interaction between S and I classes. The second one is that both of the compartments are increasing or mathematically it is written as $\frac{dS}{dt} > 0, \frac{dI}{dt} > 0$ means the function $f(S, I)$ is always increasing with respect to S and I. These two assumptions keep the constructed model physically more reasonable: without infection, there can be no transmission, and there may not be vice verse transmission (when susceptible individual after contacting an infectious one cannot take away the disease). The third assumption describes the concavity property, which means that, when there is an outbreak of the disease and it spreads among the population we can notice an exponential growth of the infected population in the very beginning part of the epidemics. However, as the population is bounded, and the vaccination is repeatedly applied to susceptible class, at some point the population size becomes saturated.

To make our model more realistic, we take into consideration time-delay - τ, which is the period between the contact with an infection and the onset of symptoms. Takeuchi discusses a delayed equation for the incidence rate in I's factor, but not in S; that is the incidence term is $f(S(t), I(t-\tau))$ [24]. For example, the current rate of new infective people depends on the current number of susceptible people and upon the current number of infective mosquitoes. With latency period of τ, the current number of infective mosquitoes depends on the number of infective people τ time units ago. This kind of incidence rate depends on the susceptible individuals host at this given moment t, and infectives at the moment $t - \tau$.

The strategy of periodic vaccination with bilinear incidence rate was recently observed by Z. Bai [5]. Although the bilinear function is natural assumption to be used for the homogeneously mixing population, for example, the saturated incidence rate is more reasonable to be considered for some specific diseases. Because it is normal that there are either successful or unsuccessful number of infectious contacts between S and I and the number of successful ones may saturate at high infective levels. It depends on the amount of crowded infective individuals or the protection measures by the susceptible individuals. Also the dependence on I may be nonlinear, for example a saturation incidence term such as $\dfrac{\beta SI}{(1+cI)}$ [44], where $c > 0$. The contact rate still increases as I increases, but the growth is $1 + cI$ largest when I is very close to 0 and approaches a positive limit from below for large I.

Overall, the general function for nonlinear incidence rates covers both bilinear and saturated incidence rates. This $f(S, I)$ allows far more general incidence rates than the usual bilinear term, while bilinear incidence rate is the special case $f(S, I) \equiv \beta SI$.

The aim is to show that this function $f(S, I)$ is generalized form of all nonlinear incidence rates that welcome assumptions above. Despite it is complicated to study more general form of the incidence function, this may lead to richer dynamics and to more widely applicable results in the future.

Chapter 2

Modeling of Epidemics

2.1 Basic compartmental model

A few epidemic models are basically constructed using susceptible and infected groups of population. Depending on disease and the immune system of the population the model can be expanded to recovered class. To describe some fundamentals in epidemic models, consider a population - N, which is affected by a contagious disease. At time t, individuals in this population are classified into two homogeneously mixing compartments according to the disease state: susceptible - S and infected - I classes as in flowchart below (2.1). The Figure (2.1) illustrates a transmission of infection among this specified population and called SI model.

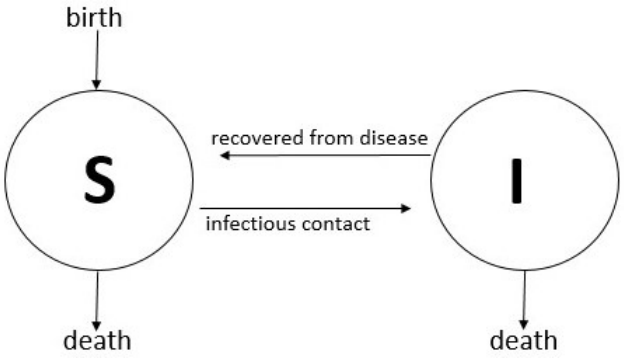


Figure (2.1) Transmission of disease through the population

Consider a case when infection transmits directly and from which there is no

recovery.

$$\frac{dS}{dt} = \Lambda - \beta SI - \mu S$$
$$\frac{dI}{dt} = \beta SI - (\mu + d)I$$

The population size in this SI model changes with a natural mortality rate, μ, and a disease-induced mortality d. As we see a susceptible individual transfers to infected group of population after the contact with disease. This contact happens in terms of bilinear incidence rate, βSI. There are some regular modifications in population size that may either enlarge by natural births and immigration that is represented as Λ, and leave the population besides natural death reasons, by deaths caused by disease, emigration and individuals with complete recovery resulted with lasting immunity after an infection agent. Moreover, we mostly accept that the births automatically enters the susceptible class assuming that immune of newborns may not prevent disease at all in the womb.

In case there is recovered class: if the individual recovers from infection with immunity, he passes to recovered population. The compartment of recovered class mostly does not include any analysis as it does not affect the dynamics of suceptibles and infectives [29].

Let us make an analysis on a Kermack and McKendrick's [7, 3] differential equation-based model that describes movement of disease in a simplest way. There are assumptions on this model that the population size is constant as it has no recruitment and natural death rates (we do not consider disease-induced death rate), and all the rates of transmission of disease are constant and has no specific duration of infection in an individual. Thus, the system of differential equations are as following:

$$\begin{cases} S' = -\beta SI, \\ I' = \beta SI - \delta I, \\ R' = \delta I, \end{cases} \tag{2.1}$$

where the term βSI is the incidence rate that defines the individual transfer depending

on infection, and term δI moves individuals from infectious class to recovered.

Since $N = N(t)$ is a constant number defining the total size of population at time t, we get this number by summarizing all classes as

$$N = S(t) + I(t) + R(t). \tag{2.2}$$

The initial size of population is measured at $t = 0$, where all classes are also at their initial stage. They are denoted as $S(0) = S_0, I(0) = I_0$, $R(0) = R_0$ and $S_\infty = \lim_{t\to\infty} S(t)$ and $I_\infty = \lim_{t\to\infty} I(t) = 0$, with initial population is obtained by their sum: $N = S(0) + I(0) + R(0)$. Therefore, taking derivatives of the equation (2.2) at time t, to see the change of rate at this time and get

$$N'(t) = S'(t) + I'(t) + R'(t) = 0.$$

In the Kermack - McKendrick epidemic model (2.1) the susceptible compartment is assumed to be decreasing, $\dfrac{dS}{dt} < 0, \forall t > 0$, except the initial condition when $t = 0$.

So here comes out the question: if the size of susceptibles is assumed to be decreasing, will the epidemic infect all the population?

First of all, let us know how the number of infected individuals changes [22]. If we are able to estimate maximum size of I for an infectious disease that is just entering the population, we may know when the amount of infectives will begin to decline.

$$\frac{dI}{dS} = \frac{\beta SI - \delta I}{-\beta SI} = \frac{\delta}{\beta S} - 1.$$

Once we see that this is a simple separable differential equation, all that is needed to solve it is to integrate both sides and we obtain

$$I = -S + \frac{\delta}{\beta} \ln S + C.$$

If our population will be perturbed by infection from 0, when $I_0 \approx 0$ and $S_0 \approx N$,

then

$$I_0 + S_0 - \frac{\delta}{\beta}\ln S_0 = C = I_\infty + S_\infty - \frac{\delta}{\beta}\ln S_\infty$$
$$\Rightarrow \frac{\beta}{\delta} = \frac{\ln N - \ln S_\infty}{N - S_\infty}.$$

When we try to estimate the maximum number of infectives, we analize the change of rate at time t, $\frac{dI}{dt} = 0$, i.e. $S(t) = \frac{\delta}{\beta}$ [6]

$$I = -\frac{\delta}{\beta} + \frac{\delta}{\beta}\ln\frac{\delta}{\beta} + S_0 + I_0 - \frac{\delta}{\beta}\ln S_0.$$

So, this result is maximum number of infected individuals that can be reached in the epidemic. It is known that R_0 represents basic reproduction number, which represents the number of secondary infections caused by a single infective in a wholly susceptible population [22]. Further in the Section (2.3) R_0 for the system (2.1) will be derived.

$$\log(S_\infty) = R_0(S_\infty - 1)$$

Looking to an implicit equation for S_∞, we see that it defines the amount of S at final stage of the epidemic. When $R_0 > 1$, this equation has exactly two roots, and only one of them is in the interval of $(0, 1)$. Let us define this equation as

$$\varphi = R_0(S_\infty - 1) - \log(S_\infty).$$

φ has different values depending on values of $\log(S_\infty)$. $\log(S_\infty) = 1$ always satisfies the $\varphi = 0$, at the time the $R_0 > 1$, the other solution of $\varphi = 0$ is general value of the final size. However, if $R_0 < 1$, the only value that satisfies equation (2.1) is $\log(S_\infty) = 1$, which means that everyone will still be susceptible at the final stage of epidemic, i.e. no infected individual. As R_0 gets larger, the final amount of the infected population gets larger as well.

The conclusion is that a fraction of the population will escape infection, which is $S_\infty < 1$.

2.2 Parameters and the Incidence Rate

Following parameters listed in Table (2.2) are consistently used in construction of epidemic models. The compartment transfer, entrance and exit rates are all included in this table. In addition, we listed some other parameters that will be used later in this work for delayed equations and pulse vaccination.

	Parameters
λ -	recruitment rate
μ -	natural death rate
d -	disease induced death rate
β -	contact rate (infection rate)
τ -	latent period (in delay models)
α -	rate of loosing immunity
T -	time until recovered (in delay models)
θ -	vaccination rate (constant)
δ -	recovery rate
R_0 -	basic reproduction number

Table (2.2). Common model parameters.

There is a common assumption that the movements between compartments are governed by parameters like μ, δ, and α in a deterministic model. It has been shown in [10] that these terms distribute the waiting times of transmissions between compartments exponentially. For example, the transfer rate δI corresponds to $P(t) = e^{\delta t}$ as

$$\frac{dI}{dt} = -\delta I$$
$$\frac{I(t)}{I(0)} = e^{-\delta t}, \forall t \geq 0.$$

This is the fraction that is still in the infective class t units after entering this class and $1/\delta$ as the mean waiting time.

One of vital parameters is the incidence rate shown in Figure (2.1) that is defined as the infection rate of susceptible individuals through their contacts with infectives. So, it is the number of new cases per unit time. Returning to the system of Kermack and McKendrick, if $S(t)$ and $I(t)$ are the number of susceptibles and infectives at

time t respectively, and N is the total population size, then $\frac{S(t)}{N}$ and $\frac{I(t)}{N}$ [7] are the fractions for S and I. Let β be the average number of infectious contacts between individuals per unit time and assume that this contact rate β is constant and does not depend on the population size N. So, $\frac{\beta IS}{N}$ is the number of new cases per unit time amongst the $S = N$ susceptibles. This form of incidence function is called the standard incidence rate, because it is formulated from the basic principles has just shown from [6]. This kind of the incidence rate depends on the relative frequency $\frac{I}{N}$ of infectives. Comparing to the bilinear incidence rate βSI we see that we must have $\beta = \beta N$, that is a mass-action model implicitly predicts that the average number of contacts per person will be larger in a larger population.

There are many different forms of incidence rates that are possible and may be commonly used. The dependence on I may be nonlinear, for example, or the incidence may be time-dependent or incorporate density effects.

2.3 Reproduction Number

Let us continue on analyzing Kermack and McKendrick's simple bilinear incidence model (2.1). Suppose that we have a system in which there are multiple discrete types of infected individuals and there is a value that describes whether or not disease can invade into the population in a steady state with the completely susceptible population. This case is called disease-free equilibrium (DFE) [25], where the fact that amount of susceptible individuals decreases due to the process of infection is ignored. So, in the analysis of simplest models as (2.1), it has become common practice to consider next generation process to derive basic reproduction number R_0 [18, 11].

We consider the case when an epidemic does not occur and the number of infected individuals neither increase or decrease, i.e, $R_0 = 1$. This is the steady state when

we equalize our infected compartment to zero, $\frac{dI}{dt} = 0$.

$$\frac{dI}{dt} = \beta SI - \delta I = 0$$
$$\beta SI - \delta I = 0$$
$$\frac{\beta SI}{\delta} = I$$

At DFE state nearly everyone is susceptible as $S \approx 1$. Substituting $S = 1$, we come to the following result

$$R_0 = \frac{\beta}{\delta}.$$

If $R_0 < 1$ then an infective is not producing enough new infections to replace, and consequently the disease will die out.

Recognition of reproduction number as in Kermack and McKendrick's model, is the simplest case and far from physical conditions. Also it may not always be so easily obtained as in the system (2.1).

There is a straightforward extension of the theory for obtaining basic reproduction number [8, 11, 21]. For the another method, we consider a heterogeneous population where the individuals can be subdivided into n epidemiologically different infected host types. We use a standard approach of generation process to analyze if the infectious population increases or decreases. Firstly, we define the $n \times n$ next generation matrix $\mathbf{G}$, in which the matrix consists of the ijth element that represent the transmission and spread of the infection from one generation to the next [18]. This element is defined as basic reproduction number, where type i is a susceptible population contacted by a single infected individual of type j. For example, consider the next generation matrix $\mathbf{G}$, which consists of two parts: A and B^{-1} like

$$\mathbf{G} = AB^{-1}$$

Assuming A_i is the term of the newly infected individuals, and the B_i defines trans-

ferred infectious individuals from one class to another. x_0 is the DFE points.

$$A = \left[\frac{\partial A_i(x_0)}{\partial x_j}\right] \quad \text{and} \quad B = \left[\frac{\partial B_i(x_0)}{\partial x_j}\right]$$

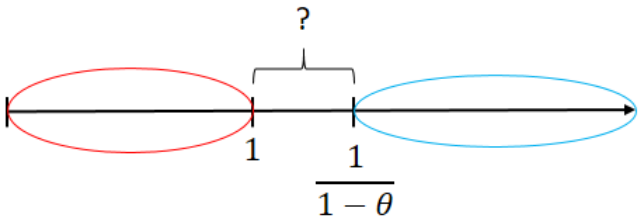
By calculating matrix $\mathbf{G}$, where each element is the expected number of secondary infections and R_0 is the value obtained as the dominant eigenvalue of this next generation matrix.

The efficiency of next generation matrix is proven by time as it is used in many research papers and it has several properties from a mathematical standpoint. It is non-negative and guarantees a single, unique eigenvalue which is positive, real, and strictly greater than all the others. This leading eigenvalue of the matrix $\mathbf{G}$ is known as R_0.

However, most of the scientific literature in case of the coexistence of time delays and application of pulse vaccinations, the method accepts the idea of deriving two thresholds in a concept of basic reproduction number: R^* and R_*. Because of the complex dynamical behaviours it becomes very difficult to study threshold agenda. Thus, it is important to prove whether $R^* < 1$ then the disease-free periodic solution holds global attractiveness or $R_* > 1$, where the disease stays permanent. In [15] the authors defined those two threshold numbers

$$R^* \quad \text{and} \quad R_* = (1-\theta)R^*$$

where θ is a pulse vaccination fraction. Meanwhile, we can rewrite R_* as $R^* > \dfrac{1}{1-\theta}$.



Upper and lower threshold values for R^* and R_*.

The Figure (2.3) clearly shows the "gap" that occurs after analysis made, which makes some doubts in its relevance. If these two thresholds are appropriate to make analysis on disease spread, then what happens in between of these thresholds R^*, R_*.

From the theory of mathematical epidemiology, we know that the persistence and extinction of the disease are directly depend on the compartment of infected individuals. For time-delayed models with pulse vaccination, the infectious variables are also following the idea of analyzing the DFE state. However, in such models the infectious compartment $\frac{dI}{dt}$ is periodic equation and linearization in infectious variables of these models at a disease-free periodic solution satisfy a periodic functional differential equation. For the models with similar characteristics listed above we applied approach of spectral radius to derive our threshold value.

In general, the idea of defining R_0 with the method of spectral radius of the next generation matrix was firstly introduced by Diekmann et al. [11]. It is an extension of next generation matrix approach, where R_0 is the spectral radius of matrix $\mathbf{G}$ [20] as $R_0 = r(\mathbf{G})$.

There are numerous works on the threshold dynamics of periodic models. For instance, Zhao and Xu [43] studied the global persistence and extinction of a periodic competitive model in terms of spectral radii of the Poincaré maps associated with linear periodic delay equations. The results were obtained in two values R^* and R_* as we discussed before. More recently Zhao established new work [40] on the theory of R_0 for a large class of periodic delayed models and applied it to a specific periodic model ($SEIR$ model) with incubation period.

Besides these works there is a research paper established by Z.Bai [5] on a single basic reproduction number for a associated periodic equations with impulsive effects. He considered a specific incidence rate, which is bilinear, while we try to obtain R_0 in terms of spectral radius for generalized incidence rate.

2.4 Control Methods

Modelling epidemics can be used in theory to determine how severe an epidemic or outbreak may be; however, the goal in public policy and in epidemiology is to try to influence the outcome of such problems. We want to use control methods to limit the severity of outbreaks or, ideally, to prevent them all. There are different control methods available, such as quarantine, travel restrictions, or most commonly vaccination. It is recently stated fact that in some circumstances a periodic vaccination strategy can be a more efficient use of limited immunization resources than continuous vaccination effort [23].

In general, the point of vaccination in real life is to confer immunity to an individual so they can fight off the disease if they are exposed to it. If we take a population, the vaccination will decrease the size of the susceptible compartment, ideally below the threshold, otherwise, there can be an outbreak. Vaccination can be applied in different ways, while we analyze the effects of pulse vaccination.

2.4.1 Pulse Vaccination

In comparison with continuous vaccination instead of constantly vaccinating an extremely large proportion of all newborn susceptibles, the pulse vaccination [35] strategy is concentrated on applying vaccination at a fraction θ of the entire susceptible population in a single pulse, administrated every T times. Pulse vaccination provides with an immunity to θS individuals, who are as a consequence, transferred to the recovered class of the population [23]. In our case, we assume that recovered population may lose the immunity after some time at rate α and again becomes susceptible. There is a pause immediately after each pulse vaccination, and the system further makes a progress from its new initial state. From this point the system is left without vaccination until the next vaccinating acts.

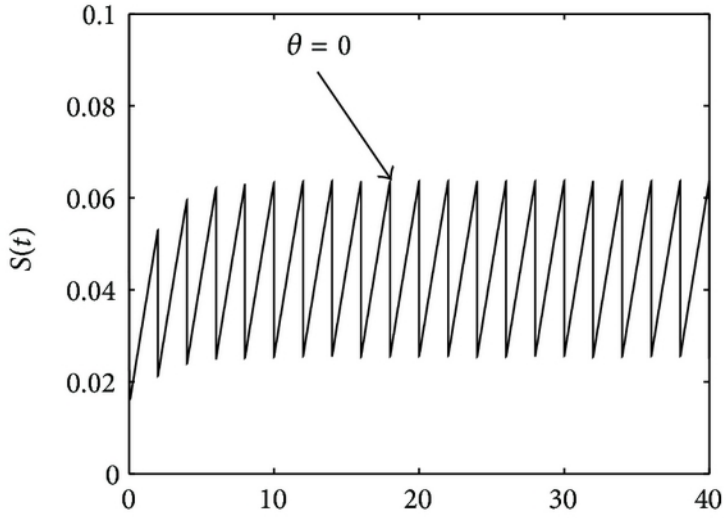


Figure (2.4.1). The dynamics of a model with pulse vaccination.

In the Figure (2.4.1) above we see the dynamics of vaccinating the susceptible population. The mechanism of action of pulse vaccination begins with an unvaccinated population in which infection is at its endemic equilibrium (for example, at $S = S^*$)[27]. On the average of $R_0 = 1$, despite the long term the infection is neither increasing or decreasing. If θS individuals are transferred to recovered class, there will be new susceptible fraction - S_t, which represents the number of susceptibles after some period of time. This means that at time t amount of susceptibles will be considerably lower than at the initial equilibrium like $S_t < S^*$ and the reproduction number will fall below the threshold, in our case it is 1. Thus, because of the reducing the amount of susceptibles to recovered class, the infection will initially decline *sharply* [37], which is one of the key attractions of pulse vaccination. To prevent infection from rising again or in other words, to prevent $R_0 > 1$, a further pulse must be applied when $S_t = S^*$, and not later.

However, in our work we try to to apply vaccination strategy while there is no disease at all, at disease free state. Then the amount of susceptible population may yield to a unique periodic solution or we call it disease-free periodic solution (DFPS). These results lead us to make analysis depending on DFPS. It is clear that we may know if this fixed and periodic vaccination strategy is effective looking to the dynamics

of disease free periodic solution [26].

For example, in [35], there are cases of practical application of pulse vaccination to polio and measles in South America and the United Kingdom, respectively. Earn [13] explains, for example, that measles incidence tends to go through periodic cycles, and conjectures that a global pulse vaccination campaign could force the incidence levels to be synchronized between different areas, so when the infective population falls in the troughs between epidemics there is a higher chance that stochastic effects will eradicate the disease. If the campaign is merely local there is more chance of the disease being re-imported from other areas. So, recovered people might be infected again.

Chapter 3

Differential Equations Theory

We have already mentioned that we use deterministic structuring to construct our model for infectious diseases. Such models are often formulated in terms of a system of differential equations, where time is confirmed in continuity or difference equations in discrete time. This explains what happens on the average at the population scale. A solution of a deterministic model is a function of time or space and is generally uniquely dependent on the initial data. If we look through the epidemic models listed previously, they are all constructed in a system of ordinary differential equations (ODE). The time-dependence was fully considered at a current time t. It means that the incidence was dependent on the populations at time t, as were the other transfer terms and the entrance and exit terms to the populations.

However, every physical process needs some time, which involves time delays. It is reasonable to use delays in equations as it leads to more realistic modeling. Even for vaccination strategies, it might take some time to show up the effect as the recipient builds immunity. During the discussions of fundamentals of simple epidemic models, we assumed that transmission of infection is distributed exponentially, which is unreasonable in physical situations. Hence, in such cases we use a delay differential equation.

Additionally, as we are periodically vaccinating our population, the state of infection among population may vary depending on each period. That is why, we describe such models in a system of impulsive differential equations.

3.1 Delay differential equations

In this section we discuss basic important theorems for a delay differential equations to understand the operations in the main chapter.

$$x'(t) = f(t, x_t) \tag{3.1}$$

with initial condition

$$x_{t_0} = \phi,$$

is delayed function, where $x(t) : J \to \mathbb{R}^n$, and the function $x_t : [-\tau, 0] \to \mathbb{R}^n$ is defined by

$$x_t(c) = x(t + c),\ c \in [-\tau, 0],$$

and variable c represents the delay interval.

3.1.1 Linearization

In analysis of nonlinear systems the key moment is to determine whether the equilibrium points are stable or not. The classical method of determining the stability is to linearize the system about the equilibrium point and to determine exponential rates of growth and decay for the associated linear system.

Let a function $f : C \to C^n$ is said to be linear if it satisfies

$$f(a\phi + b\varphi) = af(\phi) + bf(\varphi), \quad \phi, \varphi \in C, a, b \in \mathbb{C},$$

and bounded if there exists $K > 0$ such that

$$|f(\phi)| \leq K||\phi||,\ \phi \in C.$$

In this section we are aimed to consider some properties of linear delay differential equation (3.1). Moreover, we assume that the funtion f is bounded and linear.

So, let us consider an important example with a discrete-delay case with A and

B as $n \times n$ matrices that consequently lead to boundness of f. Finally, the equation (3.1) takes the form

$$x'(t) = Ax(t) + Bx(t - \tau).$$

Equation (3.1) is clearly an autonomous system so we may as well restrict initial data to prescribing the values of x on $[-\tau, 0]$:

$$x(t) = \phi(t),\ -\tau \leq t \leq 0, \text{ where } \phi \in C.$$

We analyzed our function f on boundness, that satisfies a global Lipschitz condition [36] that will be discussed in the next section.

3.1.2 Existence and Uniqueness

For further work we use the notation $C := C([\tau, 0], \mathbb{R}^n)$ as shorthand for the set of continuous functions from $[\tau, 0]$ to $\mathbb{R}^n$. Given a set D that we define it as $C_D := C([\tau, 0], D)$. For $-\tau, 0 \in \mathbb{R}$ with $-\tau < 0$ and $D \subset \mathbb{R}^n$, following [] we define the set of piecewise-continuous functions from $[-\tau, 0]$ to D by $PC := PC([-\tau, 0], \mathbb{R}^n)$ and $PC_D := PC([-\tau, 0], D)$.

Definition 3.1.1 *[31] For a function $\phi \in PC$, $||\phi||_\tau := sup_{\tau \leq c \leq 0}||\phi(c)||$ ($||.||_\tau$ is a norm on PC).*

Definition 3.1.2 *[12] (Lipschitzian) Given $f : J \times C_D \to \mathbb{R}^n$, and a subset $U \subset J \times C_D$, if there exists $K \geq 0$ such that*

$$|f(t, \phi_1) - f(t, \phi_2) \leq K||\phi_1 - \phi_2||_\tau$$

for any (t, ϕ_1) and $(t, \phi_2) \in U$, then we say f satisfies a Lipschitz condition on U with Lipschitz constant K. f is locally Lipschitzian in U if, given any $(t, \phi) \in J \times C_D$, there exists a neighbourhood of (t, ϕ) in which f is Lipschitzian.

Theorem 3.1.1 *[31](Uniqueness) Suppose U is an open set in $\mathbb{R} \times C$, $f : U \to \mathbb{R}^n$ is continuous, and $f(t, \phi)$ is Lipschitz in ϕ in each compact set in Ω. If $(\delta, \phi) \in U$, then there is a unique solution of (3.1) through (δ, ϕ).*

Theorem 3.1.2 *[12] Local Existence. Let $f : [t_0, \alpha) \times C_D \to \mathbb{R}^n$ satisfy the continuity condition and be locally Lipschitzian. Then, for each $\phi \in C_D$, the system* (3.1) *has a unique solution on $[t_0 - \tau, t_0 + \delta)$ for some $\delta > 0$.*

Theorem 3.1.3 *[31] (Existence). In* (3.1)*, suppose U is an open subset in $\mathbb{R} \times C$ and f is continuous on U. If $(\delta, \phi) \in U$, then there is a solution of* (3.1) *passing through (δ, ϕ).*

3.1.3 Comparison Theorem

First of all let us define $\phi, \xi \in C := C([-\tau, 0], \mathbb{R}^n)$, and a function f is said to satisfy the quasimonotone condition if whenever $\phi \leq \xi$ and $\phi_i(0) = \xi_i(0)$ for some $i \in \{1, 2, ..., n\}$, we have that $f_i(\phi) \leq f_i(\xi)$.

Theorem 3.1.4 *[12] Let $J \in \mathbb{R}$ be open. Let $f, g : J \times C \to R^n$ be continuous, Lipschitz on each compact subset of $J \times C$, and assume either f or g satisfies the quasimonotone condition. Assume also that $f(t, \phi) \leq g(t, \phi), \forall (t, \phi) \in JC$.*

If $(t, \phi), (t, \xi) \in J \times C$ satisfy $\phi \leq \xi$, then

$$x(t; t_0, \phi, f) \leq x(t; t_0, \xi, g)$$

holds for all $t \geq t_0$ for which both are defined.

3.2 Impulse differential equations

Delay differential equations have similar conditions to ODEs for existence and uniqueness, just slightly more complicated. The same is true for impulsive delay differential equations (IDDEs). We follow V. Lakshmikantham and D. Bainov's book [32].

We consider the model of an evolution process described by a system of differential equations as

$$\begin{aligned} x' &= f(t, x_t), \quad t \neq kT,\ t \geq t_0 \\ \Delta x &= \mathcal{I}(t, x_t^-), \quad t = kT,\ t > t_0. \end{aligned} \tag{3.2}$$

with the same initial condition of (3.1), where $f, \mathcal{I} : J \times PC_D \to R^n$, the initial time is $t_0 \in J$, and $\Delta x(t) = x(t^+) - x(t)$. There are some assumptions on impulses:

(A1) pulse times kT are fixed and head off to ∞;

(A2) impulses do not send solutions outside of the domain of f;

(A3) the solutions $x(t)$ of the impulsive differential system is left continuous at kT , $k \in \mathbb{N}$, that is, $x(T) = \lim_{h \to 0^+} x(T - h) = x(T)$.

3.2.1 Discontinuities

Although the total population is unchanged, pulse vaccination necessarily introduces some discontinuity into the compartment populations. Even if there is no discontinuity in the initial condition function ϕ, after the first pulse time t there will be discontinuity that occurs through derivatives as .

$$S(t^+) = (1 - \theta)S(t)$$

which is continuous from the left [32].

Let us consider piecewise-continuous function $x(t)$ as

$$x(t) = \begin{cases} 0, \, t \in [-\tau, 0) \\ 1, \, t \in [0, \tau]. \end{cases}$$

To show continuity of x_t with respect to $||.||_\tau$. Take c as $t_1 \in [-\tau, 0]$:

$$\begin{aligned} x_{t_1}(c) - x_{t_2}(c) &= x(t_1 + s) - x(t_2 + s) \\ &= x(t_1 - t_1) - x(t_2 - t_1) \\ &= x(0) - x(-(t_1 - t_2) = 1 - 0 \\ &\Rightarrow ||x_{t_1} - x_{t_2}||_\tau \geq ||x_{t_1}(c) - x_{t_2}(c)|| = 1. \end{aligned}$$

Let us consider a system of differential equations to construct a model [47]

$$\begin{cases} \left.\begin{aligned} \frac{dS}{dt} &= \Lambda - \mu S(t) - \beta S(t)I(t) + \alpha R(t), \\ \frac{dI}{dt} &= \beta S(t)I(t) - \beta S(t-\tau)I(t-\tau) - \mu E(t), \\ \frac{dE}{dt} &= \beta S(t-\tau)I(t-\tau) - (\mu + d + \delta)I(t), \\ \frac{dR}{dt} &= \delta I(t) - \mu R(t) - \alpha R(t), \end{aligned}\right\} t \neq kT, k \in \mathbb{N} \\ \left.\begin{aligned} \Delta S(t) &= -\theta S(t), \\ \Delta I(t) &= 0, \\ \Delta E(t) &= 0, \\ \Delta R(t) &= \theta S(t) \end{aligned}\right\} t = kT, k \in \mathbb{N} \end{cases} \tag{3.3}$$

There is a Lemma from [15] to derive disease-free periodic solution for the model (3.3).

Lemma 3.2.1 *[15] Let consider the following impulsive system*

$$\begin{cases} \frac{du}{dt} = a - bu(t), \quad t \neq kT \\ \Delta u(t) = -\theta u, \quad t = kT \end{cases}$$

where $a > 0, b > 0, 0 < \theta < 1$. Then there exists a unique positive periodic solution of the above system

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

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

Rearranging the equation above, we get

$$\begin{aligned}
\tilde{u}(t) &= \frac{a}{b} + \left(\frac{a}{b} \frac{(1-\theta)(1-e^{-b})}{1-(1-\theta)e^{-b}} - \frac{a}{b} \right) e^{-b(t-k)} \\
&= \frac{a}{b} + \left(\frac{a}{b} \frac{(1-\theta)(1-e^{-b})}{(1-(1-\theta)e^{-b})} - \frac{a(1-(1-\theta)e^{-b})}{b(1-(1-\theta)e^{-b})} \right) e^{-b(t-k)} \\
&= \frac{a}{b} + \left(\frac{a(1-\theta)(1-e^{-b}) - a(1-(1-\theta)e^{-b})}{b(1-(1-\theta)e^{-b})} \right) e^{-b(t-k)} \\
&= \frac{a}{b} \left[1 - \frac{\theta}{(1-(1-\theta)e^{-b(t-kT)})} e^{-b(t-kT)} \right], \ kT \leq t < (k+1)T.
\end{aligned}$$

If the impulsive behaviour is $u(t^+) = (1-\theta)u(t)$, the time interval becomes $kT < t \leq (k+1)T$. The lemma may be proven by integrating between pulses from kT to t, then requiring $(1-\theta)\tilde{u}((k+1)T) = \tilde{u}(kT)$ for the periodic solution [15]. Define a function f as $(1-\theta)[\frac{a}{b} + (u - \frac{a}{b})e^{-bT}]$, then the periodic solution is found to be globally asymptotically stable because f is a contraction mapping.

3.2.2 Existence and Uniqueness

Theorem 3.2.1 *Continuation. Assume f is composite - PC, quasi-bounded, and continuous in its second variable. Let $(t_0,) \in J \times PC_D$ and let $x = x(t_0,)$ be any solution of* (3.2).

A functional $f : J \times PC_D \to \mathbb{R}^n$ is said to be locally Lipschitz in its second variable if for each $t_0 \in J$ and $\alpha_1 > 0$ with $[t_0, t_0 + \alpha_1] \subset J$, and for each compact set FD there exists some $K > 0$ such that $f(t, \phi)f(t, \varphi) \leq K||\phi_1\varphi||_\tau$ for all $t \in [t_0, t_0 + \alpha_1]$ and $\phi, \varphi \in PC$.

Theorem 3.2.2 *Uniqueness. Assume that $f : J \times PC_D \to R^n$ is composite-PC and locally Lipschitz in its second variable. Then there exists at most one solution of* (3.2) *on $[t_0 - \tau, t_0 + \alpha_2)$ where $0 < \alpha_2 \leq \infty$ and $[t_0, t_0 + \alpha_2) \subset J$.*

The Theorem (3.2.2) also states that there is at most one solution for the system (3.2) on a general interval $[t_0, t_0 + \alpha_1) \in J$ where $0 < \alpha_1 \leq \infty$. In particular, we can also use $[t_0, \infty)$, the right-maximal interval for our epidemic model system.

Therefore there exists a unique solution to the delayed SIR epidemic model with pulse vaccination, for all $t \in \mathbb{R}^+$, that is, for all time in the future.

3.2.3 Comparison Theorem

To prove the comparison theorem of impulsive differential inequalities, we need to specify the notation of extremal solution of

$$\begin{cases} u' = g(t,u),\ t \neq kT,\ u(t_0) = u_0, \\ u(t^+) = \phi_k(t),\ t = kT,\ kT > t_0 \geq 0 \end{cases} \tag{3.4}$$

where $g \in C[\mathbb{R}_+ \times \mathbb{R}, \mathbb{R}]$, $\phi_k : \mathbb{R} \to \mathbb{R}$.

Definition 3.2.1 *Let $y(t) = y(t, t_0, u_0)$ be a solution of (3.4) on $[t_0, t_0 + a)$. Then $r(t)$ is said to be the maximal solution of (3.4) if for any solution $u(t) = u(t, t_0, u_0)$ of (3.4) existing on $[t_0, t_0 + a)$, the inequality*

$$u(t) \leq y(t),\ t \in [t_0, t_0 + a) \tag{3.5}$$

holds. A minimal solution $r(t)$ may be defined similarly by reversing the inequality (3.5).

Now we can come to the Comparison Theorem.

Theorem 3.2.3 *[32] Assume the assumptions (3.2) hold. Suppose that*

(i) $D_{x(t)}$=$x(t)$ $\phi_k(u)$ is non-decreasing in u and for each $k \in \mathbb{N}$,

$$\begin{cases} D_{x(t)} \leq g(t, x(t)),\ t \neq kT,\ x(t_0) \leq u_0, \\ x(t^+) \leq \phi_k(t),\ t = kT; \end{cases}$$

(ii) $y(t)$ is the maximal solution of (3.4) existing on $[t_0, \infty)$.

Then,

$$x(t) \leq y(t),\ t_0 \leq t < \infty.$$

3.3 Poincaré map

The idea of reducing the the study of continuous time systems to the study of an associated discrete time system or simply to maps is due to Poincaré. We use the Poincaré map because it preserves many properties of periodicity and quasi-periodicity of orbits of the original system. This property has a lower-dimensional state space and often used for analyzing the original system in a simpler way.

Let us consider the simple ordinary differential equation from [42]

$$y = \dot{x},\ x \in \mathbb{R}^n. \tag{3.6}$$

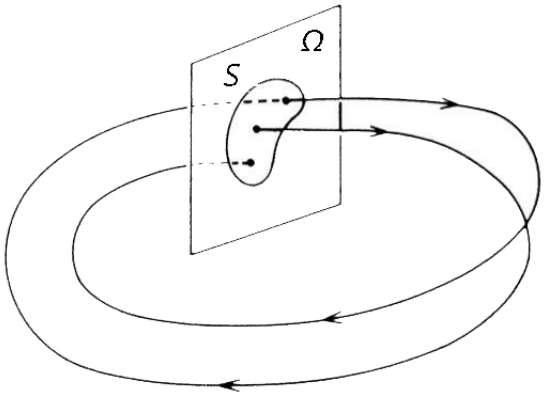


Figure (3.3) The Poincaré map for a periodic orbit.

The function $y : J \to R^n$ is C^r on some open set $J \subset R^n$. Let $\phi(t, \dot{)}$ denote the flow generated by (3.6). Suppose that (3.6) has a periodic solution of period T which we denote by $\phi(t, x_0)$, where $x_0 \in R^n$ is any point through which this periodic solution passes as $\phi(t+T, x_0) = \phi(t, x_0))$. Let Ω be an $n1$ dimensional surface transfers to the vector field at x_0; we refer to Ω as a cross-section to the vector field (3.3). From the literature we have $\phi(t, x)$ is C^r if $f(x)$ is C^r. Then we can have an open set $S \subset \Omega$, where the point that starts in set S returns to Ω in a time close to T. This process of associated points in S with the points of first return to set Ω is called the Poincaré

map, which we denote by P as following

$$P : S \to \Omega$$
$$x \to \phi(t(x), x)$$

where $t(x)$ is the time of first return of the point x to Ω. Note that, by construction, we have $t(x_0) = T$ and $P(x_0) = x_0$.

Therefore, a fixed point $x \in S$ corresponds to periodic orbit, and the period n point of P as $P^n(x) = x$ also corresponds to periodic orbit as $P^i(x) \in V, i = 1, , n)$. This means that the flow passes through the Ω n times before closing, as shown in Figure (3.3).

There are several advantages of using this technique, while we study ordinary differential equations, when we try to reduce the dimension, to study global dynamics and etc.

In dimensional reduction, when we construct the Poincaré map it involves the elimination of at least one of the variables of the given problem resulting in the study of a lower dimensional problem. Further, in lower dimensional problems, i.e. dimension ≤ 4, for the global dynamics of the system the numerically computed Poincaré maps provide an insightful display.

Chapter 4

SIRS Model with General Nonlinear Incidence Rate

4.1 Model Formulation

In this chapter we study delayed $SIRS$ model in consideration of pulse vaccination system. This is a population, which divided into four classes, the susceptible ones, infectious and recovered group denoted by S, I and R respectively. Here is the flowchart of infection in $SIRS$ model.

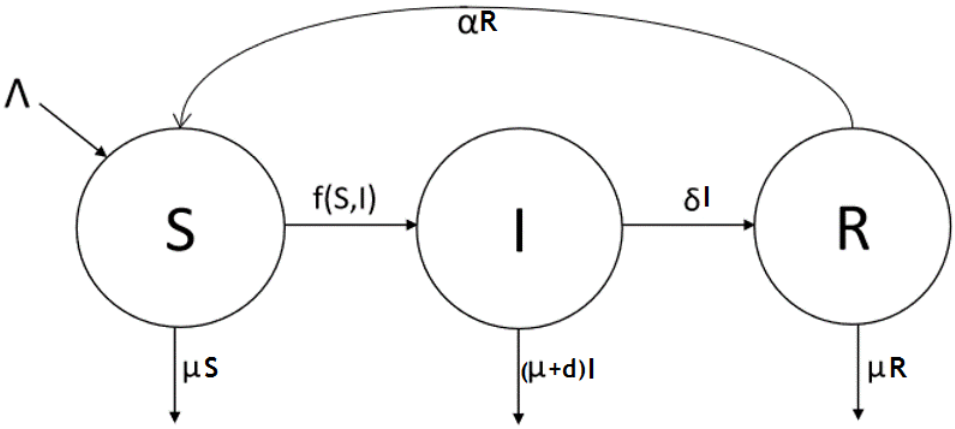


Figure (4.1). Transmission of infection in $SIRS$ epidemic model.

The differential equation-based model for Figure (4.1) is as following:

$$\begin{cases} \left.\begin{aligned} \frac{dS}{dt} &= \Lambda - \mu S(t) - f(S(t), I(t-\tau)) + \alpha R(t), \\ \frac{dI}{dt} &= f(S(t), I(t-\tau)) - (\mu + d + \delta) I(t), \\ \frac{dR}{dt} &= \delta I(t) - \mu R(t) - \alpha R(t), \end{aligned} \right\} t \neq kTa, k \in \mathbb{N} \\ \left.\begin{aligned} \Delta S(t) &= -\theta S(t), \\ \Delta I(t) &= 0, \\ \Delta R(t) &= \theta S(t), \end{aligned} \right\} t = kT, k \in \mathbb{N} \end{cases} \tag{4.1}$$

where $\Delta x(t) = x(t^+) - x(t)$, the coefficients $\Lambda-$ recruitment rate of population, $\mu-$ the natural death rate, $\alpha-$ the rate of losing immunity and $\delta-$ the recovery rate are all positive constants. Also infectious compartment has extra disease-related death rate denoted as d. As our model has time delay, τ is the latent period of the disease and T is also constant, which means period between two pulse vaccinations, while $\theta \in (0, 1)$ is the fraction of susceptible ones who are successfully vaccinated at times $t = kT$. We denote by $C(X, Y)$ and $PC(X, Y)$ the set of continuous and piecewise continuous functions from a topological set X to a topological set Y, respectively. Further, let us define $C_T(\mathbb{R})$ be the ordered Banach space of all continuous and T - periodic functions from $\mathbb{R}$ to $\mathbb{R}$ equipped with the norm $||u|| = \max_i |u_i|$. For a function $x \in C([-\tau, \nu], \mathbb{R}^n)$, $\nu > 0$, we define $x_t \in C([-\tau, 0], \mathbb{R}^n)$ for. by $x_t(c) = x(t + c)$, for all $c \in [-\tau, 0]$, $t \in [0, \nu]$.

We consider the system (4.1) with the following initial conditions

$$S(\xi) = \phi_1(\xi),\ I(\xi) = \phi_2(\xi),\ R(\xi) = \phi_3(\xi), \tag{4.2}$$

where $\phi_1, \phi_3 \in PC([-\tau, 0], \mathbb{R}), \psi_2 \in C([-\tau, 0], \mathbb{R})$ and satisfy $\phi_1(0) > 0, \phi_2(0) \geq 0$, and $\phi_3(0) \geq 0$. It worth mentioning that Theorem 1.2.3 and Theorem 1.2.4 in [14] yield that the system (4.1) supplemented with the initial condition (4.2) has a unique solution for $t \geq 0$.

Further, we will assume that the following conditions hold for the function f in

system (4.1):

(C1) $f(S,0) = f(0,I) = 0$;

(C2) $f(S,I)$ is always positive, continuous, differentiable and monotonically increasing i.e., $\dfrac{\partial f(S,I)}{\partial S} > 0$ and $\dfrac{\partial f(S,I)}{\partial I} > 0$ for all $S > 0$ and $I \geq 0$;

(C3) $f(S,I)$ is concave with respect to I i.e., $\dfrac{\partial^2 f(S,I)}{\partial I^2} \leq 0$ for all $S, I > 0$.

From the ***(C3)*** assumption, our incidence function $f(S,I)$ is bounded.

4.2 The Basic Reproduction Number

The total size of population is determined as $N(t) = S(t) + I(t) + R(t)$. Summing all equations in the system (4.1) yields

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

Thus, it follows that $\Lambda - (\mu + d)N(t) \leq \dot{N}(t) \leq \Lambda - \mu N(t)$. From the last inequality one can conclude

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

Hence, it is sufficient to consider the system (4.1) in a biologically feasible closed set

$$\Omega = \Big\{(S,I,R) \in \mathbb{R}_+ \Big| \, 0 \leq S + I + R \leq \frac{\Lambda}{\mu}\Big\}.$$

It can easily be verified that the set Ω is positively invariant with respect to (4.1), i.e., any solution of (4.1) starting in Ω remains in this closed set for $t \geq 0$.

Next, we show the existence of the disease-free periodic solution, where the the group of infectious is considered to be absent from the population, i.e., $I(t) = 0$ for all $t \geq 0$. Thus, in the limiting system one has

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

since $\limsup_{t\to\infty} N(t) = \dfrac{\Lambda}{\mu}$. Therefore, the system (4.1) in the limiting system reduces to

$$\begin{cases} \dfrac{dS}{dt} = \Big(\dfrac{\Lambda}{\mu} - S(t)\Big)(\alpha+\mu), & t \neq kT \\ \Delta S(t) = -\theta S, & t = kT. \end{cases} \tag{4.3}$$

By means of Lemma 3.2.1, it follows that the system (4.3) has a unique positive $T-$periodic solution given by the following formula.

$$\tilde{S}(t) = \frac{\Lambda}{\mu} + \left(S^* - \frac{\Lambda}{\mu}\right)e^{-\mu(t-\omega)}\ , \ kT < t \leq (k+1)T,$$

where $S^* = \dfrac{\Lambda}{\mu}\dfrac{(1-\theta)(1-e^{-\mu T})}{(1-(1-\theta)e^{-\mu T})}$. Further, $\tilde{S}(t)$ is globally asymptotically stable by Lemma 3.2.1.

Thus, it follows that the group of recovered population oscillates with the same period T. Consequently, the system (4.1) always has a disease-free periodic solution

$$E_0 = \left(\tilde{S}(t), 0, \frac{\Lambda}{\mu} - \tilde{S}(t)\right).$$

In order to analyze the dynamics of the epidemic model (4.1) it is important to find the threshold value R_0, so-called the basic reproduction number. Since the system (4.1) is discontinuous, R_0 cannot be obtained by the next generation matrix technique [41]. However, we note that more general approach in turns of the spectral radius is applied to derive R_0. For more details we refer to the paper by Zhao [46]. To this end, we linearize the system (4.1) around the disease-free periodic solution E_0 to obtain the following linear periodic functional differential equation [17] for the infected population.

$$\frac{dI}{dt} = \frac{\partial f(\tilde{S}(t), 0)}{\partial I} I(t-\tau) - (\mu + d + \delta)I(t). \tag{4.4}$$

Let $\Phi(t,s)$ be the principal fundamental matrix, $\Phi(s,s) = 1$, for all $s \in \mathbb{R}$, of the following linear ordinary differential equation.

$$\frac{dI}{dt} = -(\mu + d + \delta)I(t). \tag{4.5}$$

It is straightforward to see that $\Phi(t,s) = e^{-(t-s)(\mu+d+\delta)}$, for all $t \geq s$. Let us further define $g(t) := \dfrac{\partial f(\tilde{S}(t),0)}{\partial I}$ and an operator Π as $\Pi(t)\varphi = g(t)\varphi(-\tau)$ for any $\varphi \in C([-\tau,0],\mathbb{R})$.

One can show that $\Pi(t)\varphi = \displaystyle\int_{-\tau}^{0} d_\eta[\sigma(t,\eta)]\varphi(\eta)$, $\forall t \in \mathbb{R}$, $\varphi \in C([-\tau,0],\mathbb{R})$, where $\sigma(t,\eta)$ is the normalized function satisfying

$$\sigma(t,\eta) = \begin{cases} -g(t), & \eta \leq -\tau, \\ 0, & \text{otherwise.} \end{cases}$$

By the virtue of the condition (**C2**), it follows that Π and $\sigma(t,\eta)$ satisfy all requirements in Section (4.2) of [46]. Thus, we define two linear operators on C_T as follows.

$$\mathcal{M}y(t) = \Pi(t)\left(\int_0^\infty \Phi(t+\cdot, t-s+\cdot)y(t-s+\cdot)\,ds\right), \forall t \in \mathbb{R},\ y \in C_T,$$

and

$$\mathcal{N}y(t) = \int_0^\infty \Phi(t,t-s)\Pi(t-s)y(t-s+\cdot)\,ds,\ \forall t \in \mathbb{R},\ y \in C_T.$$

Note that the spectral radii of the operators $\mathcal{M}$ and $\mathcal{N}$ are equal. To see this, let us consider two bounded linear operators U and V on C_T given by

$$Uy(t) = \int_0^\infty \Phi(t,t-s)y(t-s)\,ds \text{ and } Vy(t) = \Pi(t)y_t,\ y \in C_T.$$

Then it follows that $\mathcal{M} = V \circ U$ and $\mathcal{N} = U \circ V$. Thus, the operators $\mathcal{M}$ and $\mathcal{N}$ have the equal spectral radius. Therefore following the procedures in [46], we conclude that the basic reproduction number is defined either as the spectral radius of the operator $\mathcal{M}$ or the operator $\mathcal{N}$, i.e., $R_0 := r(\mathcal{M}) = r(\mathcal{N})$. Let us continue with $R_0 = r(\mathcal{M})$.

Observe that

$$\begin{aligned}\mathcal{M}y(t) &= \Pi(t)\left(\int_0^\infty \Phi(t+\cdot, t-s+\cdot)y(t-s+\cdot)\,ds\right)\\ &= g(t)\int_0^\infty \Phi(t-\tau, t-s-\tau)y(t-s-\tau)\,ds\\ &= g(t)\int_\tau^\infty \Phi(t-\tau, t-s)y(t-s)\,ds\\ &= g(t)\int_\tau^\infty e^{-(\mu+d+\delta)(s-\tau)}y(t-s)ds.\end{aligned}$$

Thus, R_0 satisfies the following eigenvalue problem.

$$R_0 y(t) = g(t)\int_\tau^\infty e^{-(\mu+d+\delta)(s-\tau)}y(t-s)ds.$$

Differentiating the last equation yields

$$\begin{aligned}R_0 y'(t) &= g(t)\int_\tau^\infty e^{-(\mu+d+\delta)(s-\tau)}y'(t-s)ds + g'(t)\int_\tau^\infty e^{-(\mu+d+\delta)(s-\tau)}y(t-s)ds\\ &= -g(t)e^{-(\mu+d+\delta)(s-\tau)}y(t-s)\Big|_\tau^\infty - g(t)(\mu+d+\delta)\int_\tau^\infty e^{-(\mu+d+\delta)(s-\tau)}y(t-s)ds\\ &+\frac{g'(t)}{g(t)}g(t)\int_\tau^\infty e^{-(\mu+d+\delta)(s-\tau)}y(t-s)ds\\ &= g(t)y(t-\tau) - (\mu+d+\delta)R_0 y(t) + \frac{g'(t)}{g(t)}R_0 y(t).\end{aligned}$$

The last equations leads to

$$\frac{y'(t)}{y(t)} = \frac{g'(t)}{g(t)} + \frac{g(t)}{R_0}\frac{y(t-\tau)}{y(t)} - (\mu+d+\delta).$$

Observe that $y(T) = y(0)$ and $g(T) = g(0)$. Integrating the last expression from 0 to T yields

$$R_0 = \frac{\displaystyle\int_0^T g(t)\frac{y(t)}{y(t)}dt}{T(\mu+d+\gamma)} = \frac{\displaystyle\int_0^T \frac{\partial f(\tilde{S}(t),0)}{\partial I}\frac{y(t-\tau)}{y(t)}dt}{T(\mu+d+\gamma)}.$$

In the absence of time-delay, $\tau = 0$, the last formula yields [4]

$$R_0 = \frac{\displaystyle\int_0^T \frac{\partial f(\tilde{S}(t), 0)}{\partial I} dt}{T(\mu + d + \gamma)}.$$

Note that the operator $\mathcal{M}$ can be rewritten as

$$\mathcal{M}y(t) = \int_0^\infty K(t, s)y(t - s)ds, \tag{4.6}$$

where the kernel function $K(t, s)$ is given by

$$K(t, s) = \begin{cases} g(t - s + \tau)e^{-(\mu+d+\delta)(s-\tau)}, & \text{if } s \geq \tau, \\ 0, & \text{if } s < \tau. \end{cases}$$

4.3 Global Attractiveness

Let us define for any $\phi \in C([-\tau, 0], \mathbb{R})$, an operator $P(t)$ such that $P(t)\phi = u_t(\phi)$ is the unique solution of the the system (4.4). Then, it follows that $P := P(T)$ is the Poincare map of the system (4.4). In what follows, Theorem 2.1 in [46] becomes an auxiliary results for our further discussion. Thus, we include it here.

Lemma 4.3.1 *[46] Let $r(P)$ be a spectral radius of P. Then sign(R_0-1) = sign$(r(P)-1)$, i.e., R_0 and $r(P)$ have the same threshold value.*

1. *$R_0 = 1$ if and only if $r(P) = 1$.*
2. *$R_0 < 1$ if and only if $r(P) < 1$.*
3. *$R_0 > 1$ if and only if $r(P) > 1$.*

Lemma 4.3.2 *[46] Let $\mu = \dfrac{\ln r(P)}{T}$, then there exists a positive, T- periodic function $v(t)$ such that $e^{\mu t}v(t)$ is a positive solution of the system (4.4).*

Theorem 4.3.1 *The disease-free periodic solution of system (4.1) $\left(\tilde{S}(t), 0, \dfrac{\Lambda}{\mu} - \tilde{S}(t)\right)$ be globally attractive if $R_0 < 1$, then the disease-free periodic solution E_0 is globally attractive for system (4.1) in $PC([-\tau, 0], \mathbb{R}^3_+)$.*

Proof. So let us assume P_ϵ be a Poincare map of the following perturbed linear periodic equation, as from the Lemma (4.3.1) we have $R_0 < 1$ if and only if $r(P) < 1$.

$$\frac{dI}{dt} = \frac{\partial f(\tilde{S}(t) + \epsilon, 0)}{\partial I} I(t - \tau) - (\mu + d + \delta) I(t). \tag{4.7}$$

We fix a sufficiently small number $\epsilon > 0$, such that $r(P_\epsilon) < 1$ since this expression $\lim_{\epsilon \to 0} r(P_\epsilon) = r(P) < 1$ holds. Using the proof of the Lemma (4.3.2) from [5], for the perturbed linear equation (4.7) it yields to the existence of solution $e^{\mu_\epsilon t} v_\epsilon(t)$, where $\mu_\epsilon = \dfrac{\ln r(P_\epsilon)}{T} < 0$. Let $\dfrac{\partial f(\tilde{S}(t), 0)}{\partial I} = A(t)$ and $(\mu + d + \delta) = B(t)$, where $B(t) \in C_T$ and $A(t) > 0,\ \forall\ t \geq 0$ is a piece-wise continuous periodic function with discontinuity at each kT, where $k \in \mathbb{N}$. So, let $v(t, \phi) = (S(t), I(t), R(t))$ is the solution of the system (4.1), which satisfies to the expression $v_0 = \phi$. Then we consider following comparison equation for the obtained inequality from the first equation of system (4.1): $\dfrac{dS}{dt} \leq (\alpha + \mu)(\dfrac{\Lambda}{\mu} - \bar{S}(t))$.

$$\begin{cases} \dfrac{d\bar{S}}{dt}(t) = (\alpha + \mu)(\dfrac{\Lambda}{\mu} - \bar{S}(t)),\ t \neq kT \\ \Delta \bar{S}(t) = -\theta \bar{S}(t),\ t = kT \end{cases}$$

Using the Lemma (3.2.1) the system above admits a positive periodic solution $\bar{S}^*(t)$, which is globally asymptotically stable. By the comparison theorem for impulsive differential equations [32], there exists an integer $k_1 > 0$ such that

$$S(t) < \bar{S}(t) < \bar{S}^*(t) + \epsilon, \quad kT < t \leq (k+1)T,\ k > k_1.$$

There exists $k_2 > k_1$ such that $t > t_1 := k_2 T + \tau$.

$$\frac{dI}{dt} \leq \frac{\partial f(\tilde{S}(t) + \epsilon, 0)}{\partial I} I(t - \tau) - (\mu + d + \delta) I(t),$$

$$I(t) \leq K e^{\mu_\epsilon t} u_\epsilon(t),\ \text{for all } t \geq t_1$$

From the inequality above we conclude that

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

Further, we take any small number $\epsilon_1 > 0$, there is a k_3 such that $k_3T > k_2T + \tau$ and $I(t) < \epsilon_1, \forall t > k_3T$. From the equation N' obtained by summation of all compartments we get

$$\begin{aligned}\frac{dN}{dt} &= \Lambda - (\mu S(t) + \mu I(t) + \mu R(t)) - dI(t)\\ &> \Lambda - \mu N(t) - d\epsilon_1, \text{ for } t > k_2T.\end{aligned}$$

$$N(t) \geq \frac{\Lambda - d\epsilon_1}{\mu} - \epsilon_1.$$

As this fixed constant ϵ_1 is sufficiently small, by $\limsup_{t\to\infty} N(t) \leq \frac{\Lambda}{\mu}$ and

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

$$I(t) < \epsilon_1 \quad \text{and} \quad N(t) > \frac{\Lambda}{\mu} - \epsilon_1, \quad \text{for} \quad t > k_3T. \tag{4.8}$$

Using these expressions in (4.8), we obtain such inequality

$$\begin{aligned}\frac{dS}{dt} &= \Lambda - f(S,I) - \mu S + \alpha(N - S - I) \geq \Lambda - f(S,\epsilon_1) - \mu S(t) + \alpha\left(\frac{\Lambda}{\mu} - \epsilon_1 - S(t) - \epsilon_1\right)\\ &= \left(\Lambda + \frac{\alpha\Lambda}{\mu} - f(\frac{\Lambda}{\mu} + \epsilon_1, \epsilon_1) - 2\alpha\epsilon_1\right) - (\alpha + \mu)S(t).\end{aligned}$$

If we rewrite the right hand side of the inequality above in an impulsive system form, it will have globally stable periodic solution $\tilde{S}_{\epsilon_1}$ by the Lemma (3.2.1). Comparing with the initial inequality

$$\frac{dS}{dt} \leq (\alpha + \mu)(\frac{\Lambda}{\mu} - S(t)),$$

we apply comparison theorem

$\tilde{S}_{\epsilon_1} \leq S(t) > \tilde{S}(t) + \epsilon,\ kT < t < (k+1)T, k > k_4.$

And as the ϵ_1 is chosen arbitrarily small, $\lim_{\epsilon_1 \to 0} \tilde{S}_{\epsilon_1}(t) = \tilde{S}(t)$. Then it follows from comparison inequality above that

$$\lim_{t\to\infty} S(t) = \tilde{S}(t).$$

Thus, by using equations above we can obtain $\lim_{t\to\infty}(R(t) - (\frac{\Lambda}{\mu} - \tilde{S}(t))) = 0.$

Theorem 4.3.2 *If $R_0 > 1$, then there is a $p > 0$ such that every positive solution $u(t,\phi) = (S(t), I(t), R(t))$ of (1) satisfies $\liminf_{t\to\infty} I(t) \geq p$, for large enough value of t and any $\phi \in PC([-\tau, 0], \mathbb{R}^3_+)$, where $\phi_2(0) > 0$.*

Proof. In case where $R_0 > 1$, by Lemma (4.3.1) we have $r(P) > 1$. Let P_γ be the Poincare map of the perturbed equation below

$$\frac{dI}{dt} = \left(\frac{\partial f(\tilde{S}(t), 0)}{\partial I} - \gamma\right) I(t-\tau) - (\mu + d + \delta) I(t). \tag{4.9}$$

We take sufficiently small number $\gamma > 0$, such that $r(P_\gamma) > 1$ and $\gamma < \inf \tilde{S}(t)$, for all $t \geq 0$ as $\lim_{\gamma\to 0} r(P_\gamma) = r(P) > 1$.

Applying the Lemma (4.3.2), we obtain a positive solution $e^{\mu_\gamma t} v_\gamma(t)$ of (4.9), where $v_\gamma(t)$ is a positive T- periodic function and $\mu_\gamma = \dfrac{\ln r(P_\gamma)}{T} > 0$.

$$\begin{cases} \dfrac{d\bar{S}}{dt}(t) = \left(\Lambda + \dfrac{\alpha\Lambda}{\mu} - f(\dfrac{\Lambda}{\mu} + \epsilon, \epsilon) - 2\alpha\epsilon\right) - (\alpha + \mu)S(t), \quad t \neq kT \\ \Delta\bar{S}(t) = -\theta\bar{S}(t), \quad t = kT \end{cases}$$

From the Lemma (3.2.1), this system admits a positive periodic solution $\tilde{S}_\epsilon(t)$. This solution is said to be globally asymptotically stable if $\lim_{\epsilon\to 0}(\tilde{S}_\epsilon(t) - \tilde{S}(t)) = 0$. Thus

we fix sufficiently small number ϵ, which is positve. such that

$$\tilde{S}_\epsilon(t) > \tilde{S}(t) - \frac{\gamma}{2}, \text{ for all } t \geq 0. \tag{4.10}$$

We fix a small number $\eta > 0$ such that $\eta < \min\{\frac{\mu}{\Lambda}\epsilon, \epsilon\}$.

Let us consider that $I(t) < \eta$ for all $t \geq t_0$, where $t_0 > 0$. Now it follows there is a positive number η, such that $I(t) < \eta < \epsilon$ and

$$\frac{dN}{dt} = \Lambda - \mu N(t) - dI(t) > \Lambda - \mu N(t) - d\epsilon$$

Then there is a t_1, such that $t_0 < t_1$

$$N(t) \geq \frac{\Lambda - d\epsilon}{\mu} - \epsilon, \ \forall \ t \geq t_2$$

When for any $t \geq t_1, t \neq kT$

$$\frac{dS}{dt} > \left(\Lambda + \frac{\alpha\Lambda}{\mu} - f(\frac{\Lambda}{\mu} + \epsilon, \epsilon) - 2\alpha\epsilon\right) - (\alpha + \mu)S(t).$$

By standard comparison theorem and combining with the (4.10) inequality, we get that there exists $t_2 > t_1$ such that

$$S(t) \geq \bar{S}(t) > \tilde{S}_\epsilon(t) - \frac{\gamma}{2} > \tilde{S}_\epsilon(t) - \gamma, \ \forall t \geq t_3. \tag{4.11}$$

$$\begin{aligned}
\frac{dI}{dt} &= f(S, I(t-\tau)) - (\mu + d + \delta)I(t) \\
&\geq f(\tilde{S}(t), I(t-\tau)) - (\mu + d + \delta)I(t) \\
&\geq (\frac{\partial f(\tilde{S}, 0)}{\partial I} - \gamma)I(t-\tau) - (\mu + d + \delta)I(t).
\end{aligned}$$

If we choose positive number K_2 such that

$$I(t) \geq K_2 e^{\mu_\gamma t} v_\gamma(t) \quad \text{and} \quad K_2 e^{\mu_\gamma t} v_\gamma(t) < \eta, \text{ for } t \in [t_2, t_3].$$

Then there exists $t_4 > t_3$ such that $\eta \leq I(t) < \epsilon$, for $t \in [t_3, t_4]$ by comparison theorem

[36] which contradicts our assumption.

Since we checked the claim, we can follow these two possible assumptions:

(i) $I(t) \geq \eta$ for all possible large number t

(ii) $I(t)$ oscillates about η for all possible large t.

It is clear that for the (i) we will be already done with this Theorem. So, we have to discuss about (ii) to show our Theorem is true. Let us define $p = min\left\{\frac{\eta}{2}, \eta e^{-(\mu+d+\delta)\tau}\right\}$. Let us take $\underline{t}$ and $\overline{t}$ such that

$$I(\underline{t}) = I(\overline{t}) = \eta,\ I(t) < \eta,\ \forall\, t \in (\underline{t}, \overline{t}),$$

where $\underline{t}$ is considered to be sufficiently large to satisfy

$$S(t) > \tilde{S}(t) - \gamma,\ \forall\, t \in [\underline{t}, \overline{t}]. \tag{4.12}$$

The function $I(t)$ is uniformly continuous for any $t \geq 0$ since the infectious compartment $(I'(t))$ of our model (4.1) is bounded for all $t \geq 0$ as was mentioned before. Hence, there is a $t^* \in (0, \tau)$ such that $I(t) \geq \frac{\eta}{2}$ for $[\underline{t}, \underline{t} + t^*]$. Consequently, we consider all possible cases.

i) If $\overline{t} - \underline{t} \leq t^*$, then $I(t) > \frac{\eta}{2}$, $\forall\, t \in [\underline{t}, \overline{t}]$.

ii) If $t^* < \overline{t} - \underline{t} \leq \tau$, then $I(t) \geq e^{-(\mu+d+\delta)\tau} = \eta e^{-(\mu+d+\delta)\tau}$ for $t \in [\underline{t}, \overline{t}]$ since $I'(t) \geq -(\mu + d + \delta)I(t)$ and $I(\underline{t}) = \eta$.

iii) If $\overline{t} - \underline{t} > \tau$, we obtain $I(t) \geq e^{-(\mu+d+\delta)\tau} = \eta e^{-(\mu+d+\delta)\tau}$ for $t \in [\underline{t}, \underline{t} + \tau]$. Then we have to do the same for $t \in [\underline{t} + \tau, \overline{t}]$.

Suppose it will not give $I(t) \geq e^{-(\mu+d+\delta)\tau}$ for that t in (iii) then there is a $t_1^* > 0$ such that $I(t) \geq \eta e^{-(\mu+d+\delta)\tau}$ for all $t \in [\underline{t}, \underline{t} + \tau + t_1^*]$.

$$I(\underline{t} + \tau + t_1^*) = \eta e^{-(\mu+d+\delta)\tau},\ I(t) < \eta e^{-(\mu+d+\delta)\tau},\ \forall\, 0 < t - (\underline{t} + \tau + t_1^*) << 1.$$

From the (4.12) we have

$$\frac{dI}{dt} > (\frac{\partial f(\tilde{S}(t),0)}{\partial I} - \gamma)I(t-\tau) - (\mu+d+\delta)I(t),\ \forall\, 0 < t - (\underline{t}+\tau+t_1^*) << 1.$$

Choose a number $K_3 > 0$ such that

$$I(t) \geq K_3 e^{\mu_\gamma t} v_\gamma(t),\ \forall t \in [\underline{t}+t_1^*, \underline{t}+\tau+t_1^*]$$

and $\min\limits_{\forall t\in[0,\tau]} K_3 e^{\mu_\gamma(\underline{t}+t_1^*)} v_\gamma(t) \geq e^{-(\mu+d+\delta)\tau}$.

Applying comparison theorem implies to

$$I(t) \geq e^{-(\mu+d+\delta)\tau},\ \forall\, 0 < t - (\underline{t}+\tau+t_1^*) << 1$$

that is obvious contradiction to the assumption. Thus, we get $I(t) \geq p,\ \forall t \in [\underline{t}, \overline{t}]$ and as this interval for time t was chosen arbitrarily, we can conclude that

$$I(t) \geq p,\ \forall t > 0\,(\text{large enough } t).$$

Chapter 5

Conclusions and Future Work

5.1 Conclusion

In this work, we have established and then analyzed a non-autonomous $SIRS$ type of epidemic model by vaccinating periodically. We have extended the work by Z.Bai [5] which was analyzed on threshold dynamics for delayed $SEIRS$ model with a pulse vaccination. In his work he obtained sharp persistence results considering bilinear incidence function, while we are generalizing this function with incidence rate of a more general form $f(S, I)$.

Further, we have shown existence and derivation of a threshold parameter for the system of periodic equations, which determines uniform persistence of the disease and whether it dies out. We then examined a general compartmental disease transmission model with pulse intervention, and investigated the basic reproduction number defined by the spectral radius of Poincaré maps associated with linear periodic delay equations. This result extends the main results of the autonomous system [41] and the periodic system [40, 39]. Our main results show that the disease-free periodic solution of system (4.1) is globally asymptotically stable if $R_0 < 1$, otherwise, the disease is persistent.

We discussed either constant and time-varying total population sizes. Then we explained why it is unreasonable to assume the population size to be constant. That is why, we considered a model with time-varying total population that has a nor-

malized population that shows how we can change variables to a system where the compartments are fractions of the total population. Moreover, in $SIRS$ model, recovered individuals lose their immunity over time and pulse vaccination solution is more effective for such conditions.

5.2 Future work

In our model (4.1) we considered time-varying total population $N(t)$, that welcomes some constant modifications in total amount of individuals. In Chapter 2 we discussed different models with both constant population size and time-varying total population. We would like to analyze more epidemic models with non-constant population size as it more realistic to take in account demographic changes.

In such models we include recruitment rate, which is responsible for new-comers to the population. Almost, all models that have appeared in the scientific literature use either constant, Λ, or proportional, rN, recruitment rates. These cases, where fixed number of individuals are entering the population per unit time or when their amount is equal to the proportional to total size of individuals are more applicable in a small populations. Thus, we would like to consider more reasonable assumption when the number of new-comers increases with population size but saturates at specific level which is a result of resource limitations. This case is widely known as logistic entrance rate.

In addition, in our future studies we would like to look at the cost-effectiveness of pulse vaccination. So that we could use vaccine properly and without waste, we aim to find optimum inter-pulse time, and also the best time to start the campaign.

Finally, we aim to publish a paper describing the results of our research that are to be supported with simulations. Additionally, we would like to apply our model to specific disease that do not confer permanent immunity.

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