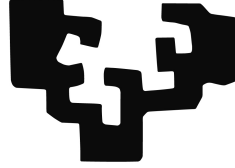


ON SOME NEW MATHEMATICAL MODELS FOR INFECTIVE DISEASES:
ANALYSIS, EQUILIBRIUM, POSITIVITY AND VACCINATION CONTROLS

eman ta zabal zazu



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Introduction

1.1 Preliminaries

An epidemic model is a mathematical description of the behavior of a population when it interacts with a specific disease. The main objective for creating a mathematical model is to understand the impact of the disease over the population at a global state, predict, and eventually, discuss the best way of interacting with such diseases in order to remove or lessen their effects. There are multiple agents that can be responsible for the apparition of a disease, and they are organized in different categories: When a disease can be developed because of the transmission from another sick individual, such as AIDS or common cold, it is called infectious disease, whereas the non-infectious diseases can be developed without such interactions, and it is usually associated to a existing predisposition, environmental causes or specific lifestyles.

This does not mean that those categories cannot overlap; for example, cirrhosis and liver cancer is firmly associated with contracting and developing hepatitis (an infectious diseases), although contracting this diseases is not necessary for the cirrhosis or the cancer to happen [1].

In other diseases, the variables derived from the ecosystem of the agents of infection can affect the parameters of the model to a level where they are of no use [3]. Such are the cases of the infectious diseases, caused by "macroparasites" such as flukes or helminths are not taken into account, as the environment of the host and the number of the agents of infection have so much influence that the complexity of the models are increased up to a level where the parameters involving the diseases cannot be properly described. Thus, the most successful mathematical models focus on the "fast" transmitted infectious diseases, where the within-host density of the pathogens is ignored and the life cycle of the pathogen is not relevant to the model. Typical epidemic diseases studied are influenza, pertussis, standard cough, tuberculosis, smallpox, malaria, dengue, diphtheria, etc [2].

The mechanic of these epidemic diseases share a set of common parameters characterized by the transmission of the illness from infected individuals to uninfected ones, and typically have some periods of time where the illness has not external symptoms (incubation period) but the patients become infective to others. Later one, the infected present external symptoms of different kinds and intensity depending on the particular disease and individuals and becomes able to transmit the disease to others (infectious). After a certain illness-dependent period of time, the infected population

can become recovered population, in the sense that the disease is removed from the hosts.

The epidemic models are referred to by acronyms which refer to the various kinds of populations being considered.

The "susceptible" subpopulation (S) are the portion of population individuals of the total population which could become infected.

The "infected" subpopulation (E) are those with the disease still without symptoms, also called the "exposed".

The "infectious" subpopulation (I) are those with external symptoms and an infectious capacity.

The "recovered" subpopulation (R) also sometimes referred to as the "removed by immunity" or the "immune" or the "recovered" are those which are infection-free.

Some epidemic models also include an extra subpopulation called the "vaccinated" subpopulation (V).

The sum of all the subpopulation i.e. the total population (N).

In this way, we have the following typical models with different degrees of complexity:

- SI (susceptible/ infectious) models
- SIR (susceptible/infectious/ recovered) models
- SEIR (susceptible /infected /infectious/recovered) models
- SVEIR (susceptible/vaccinated/ infected/infectious/recovered) models

The models can consider a forcing function called the vaccination function which is also often referred to by (V_c). These basic models will be explained in detail in the following sections. Usually, a typical epidemic model can be describe with a flow diagram similar to the one from figure 1.1.

The blue arrows represent the transitions between the different subpopulations. The dotted arrow represent the influence of certain subpopulations on the transitions between them. The development of the disease is sequential, and it goes from susceptible to recovered through all the stages.

Given the specific nature of the disease and the reaction of the immunity system of the host, some variants of the above models include a new final "S" in its corresponding acronym (cf. SEIRS), as the final stage of the disease goes back from recovered to susceptible. Depending on the velocity of the process and the impact on the health of the sick population, the fluctuations on the total population can be taken into account. Thus, the rate of production of newborns and the death rates are taken into account although, for simplicity, sometimes the population is assumed constant and these parameters omitted.

There are several methods to reduce, in statistical terms the probability of infection over the population and the spread of the disease. Many of them involve removing certain amount of susceptible or infected individuals from the population (culling), or isolation of the known infected from the rest of the healthy individuals (quarantine).

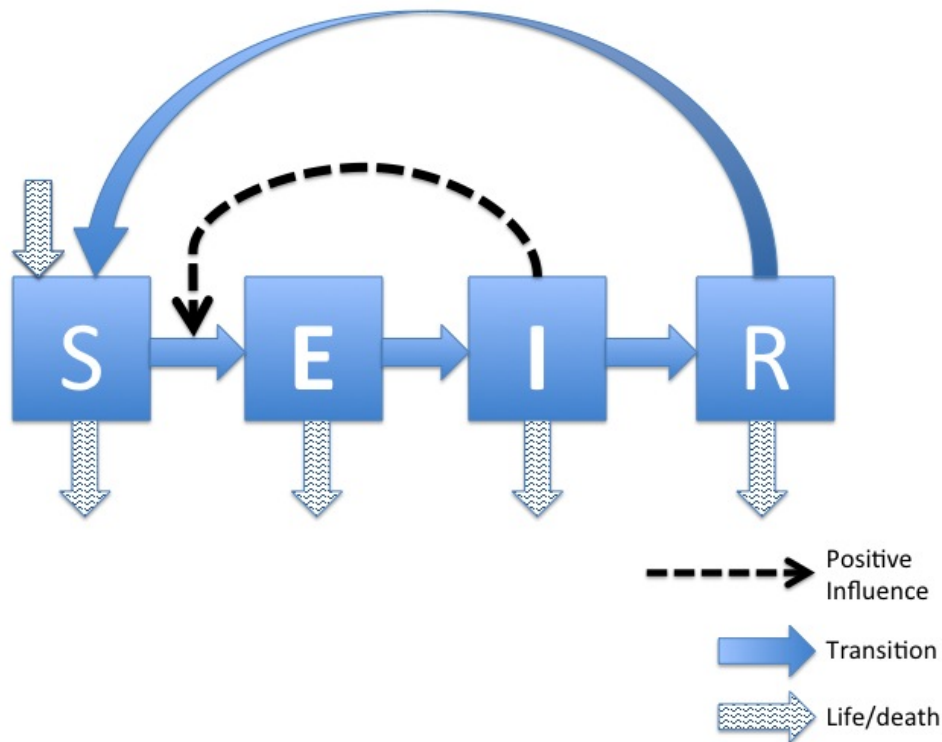


Figure 1.1: A representation of a SEIRS epidemic model, in which the transition between subpopulations and the rates of birth and death are taken into account

Medicine has a long history with this forms of disease control which in our models would become control laws. They are generic and can be applied when the information about the disease is minimal. However the resources needed using these ways are not always affordable and other methods less intrusive are needed. Thus, vaccination is considered a control law so that there are several possible strategies can be applied: constant vaccination and impulsive vaccination, being these vaccinations controlled by laws based on feedback information of the subpopulations, etc.

The vaccination control laws can include observers to estimate the subpopulations in order to synthesize the controls based on them. An important fact to be taken into account concerning vaccination is the following: Epidemic models are never (state) controllable under any vaccination control law and, equivalently, epidemic models are always (state) uncontrollable so that there is no control law which allows to take simultaneously all the subpopulations to suited prescribed final values in finite time. The intuitive reason for uncontrollability is that epidemic models describe transitions in-between the subpopulations and typically an individual which becomes infected, provided it does not die, passes along all the disease phases through time so that this makes impossible to accomplish with controllability in the usual sense. However, it must be noted that the property of "output controllability" is a feasible objective if the output is defined with some combination of subpopulation. For instance, if the output

is the sum of infected+infectious, it can be fixed as output controllability objective to fix to zero this output. If it is defined as the sum of the susceptible+immune, it can be fixed as output controllability objective to fix this output to the total population. This doctoral thesis is devoted to discuss some properties on the dynamics of several classes of SIRS, SEIRS and SVEIRS epidemic models. The major relevance is given to the local (around the equilibrium points) and global stability properties as well as to the vaccination rules which are implemented in order to asymptotically remove the disease and /or to improve their transient behavior towards to its practical annihilation. Epidemic models can be developed with either un-normalized subpopulations or with normalized ones (the total population is unity and the subpopulations are fractions of unity whose sum equalizes unity). In the second case, the evolution through time of the subpopulations is interpreted as a percentage of a quantity of individuals for each subpopulation at each time instant. Other properties of interest in the context of differential equations for continuous-time or discrete-time difference equations systems are:

- i) Global/local stability: The total stability of the population is irrelevant for normalized models since all the subpopulations are bounded for all time. In the case of un-normalized models, it is of interest in the case that the total population is unbounded.
- ii) Global/local asymptotic (partial) stability: It is relevant for both kinds models in the sense that the infected and infectious subpopulations are suited to asymptotically converge to zero. Equivalent, the sum of all the other subpopulations converges asymptotically to the whole population.
- iii) Permanence of the infection: It is related to the case when the infected/infectious subpopulations cannot be removed. If the model is permanent for any initial condition then its disease-free equilibrium point (i.e. that which has zero infected and infectious subpopulations) cannot be asymptotically stable. The disease-free equilibrium point is discussed more in detail in the following subsections of this chapter.
- iv) Positivity of the solution: Just because of coherency related to the problem nature, the epidemic models do not admit negative subpopulations.

1.1.1 Pseudomass-action and mass-action models

The first thing needed in order to describe the spread of an epidemic in a mathematical formalism is a proper definition of the force of infection. The force of infection is defined as the probability of transmission of a disease per unit of time to a susceptible individual. Then, the number of infected people per unit of time would be λX , being X the number of susceptible individuals and λ the force of infection. Assuming that the population suffering the epidemic is homogeneously mixed and move through the space where the epidemic is happening, the probability of interaction with sick individuals should be equally distributed. Thus, for a susceptible individual with an average of C_r contacts per unit of time with other individuals, a fraction of those

interactions would be with infected individuals $I = Y/N$, where Y is the number of infectious individuals and N the total population. During a small time interval δt , the number of interaction with infected population would be $\delta t C_r I/N$. The probability of contagion due to one of these interactions is defined as a constant P_C , so $1 - P_C$ is the probability of not contracting the disease in that specific contact. If the contacts are independent, the probability of not contracting the disease in that small time interval would be

$$(1 - \delta q) = (1 - P_C)^{\delta t C_r Y/N} \quad (1.1)$$

So the probability of contagion in that time would be $\delta q = 1 - (1 - P_C)^{\delta t C_r Y/N}$. The parameter beta is defined as $\beta = -C_r \log(1 - P_C)$ so that $\delta q = 1 - e^{-\beta \delta t Y/N}$ and the force of infection, defined as $\delta \lambda / \delta t$ is reduced to :

$$\lambda = \frac{\delta q}{\delta t} = (1 - e^{-\beta \delta t Y/N}) / \delta t = \beta Y/N + O(\delta t) \quad (1.2)$$

As $\delta t \rightarrow 0$, the term $O(\delta t) \rightarrow 0$. Then, the total rate of transmission of the susceptible subpopulation can be described as

$$\frac{dX}{dt} = -\lambda X = -\beta XY/N \rightarrow \frac{dS}{dt} = \dot{S} = -\beta SI \quad (1.3)$$

The mode of transmission can vary depending in how the contact rate is assumed to work [8]. The approach given in equation (1.3) is called "frequency dependent", and is based upon the assumption that contact rate does not depend on the size, but on the density of the subpopulations. This simple model is inspired in the concentration of molecules in a chemical reaction, to which the law of mass action applies [4] [5] [6] [7]. In a sense, this correspond to our expectations, as the average interactions of an individual in a city with a population of order 10.000.000 is not 1000 times higher than C_r in a small city of 10.000. The etiquette of "mass action" model has been a matter of confusion over the years for many epidemiologists as, in many human diseases, the size of the population and the density are usually equivalent (the area of action of the epidemic is considered constant) and the size of the total population is not affected by it significantly . As a result, the diverse approaches on the transmission mechanisms have conflictive nomenclature, and sometimes "mass action" is confused with "pseudo-mass action" models, in which the contact rate C_r depends on the density of the population [9]. The "pseudo-mass action" model considers that an increase in the density of populations results in an increase of the contact rate and thus, the number of infections, and the force of infection is defined as $\lambda = \beta Y$ instead of the one from equation (1.2). Other approaches to the transmission of the disease may present a middle point between both models, by having a saturation factor in which the value of the contact rate increases with the density of the subpopulations, until it reaches a maximum and tends to a constant value. In general, the difference between both models is only relevant when the population size fluctuates significantly; otherwise, the parametrization of β absorbs the $1/N$ term and the notation is quite similar, as seen in equation (1.3).

1.2 Characterization of the epidemic models

The models are described by a set of parameters, some of them being dependent on the species dealt with and some of them of the particular illness.

1.2.1 Terminology and main parameters

The following is a summary of the notation used in this and the next sections.

b_1/ν , b_3 : Birth rates of the population, a constant one (b_1/ν) and a population-dependent one (b_3). The birth rate is related to the population that is born/introduced to the population per unity of time, on average. It is measured as population per unity of time for b_1/ν time and plain unity of time⁻¹ for b_3 . Usually *years*⁻¹ is used as a measure of time and the number of individuals a measure of the size of the population, although both can vary when necessary.

b_2/μ : Natural death rate of any subpopulation. The death rate is related to the death of individuals/retired from the population due to old age and causes non-related to the disease. As the birth rate b_1/ν , the death rate is measured as population per unity of time and, when necessary, has the same value such that the total population remains constant. It is proportional to the inverse of the average life-span of a healthy individual in that population.

γ : Ratio of transition to recovered from infected subpopulation (I → R). It is proportional to the inverse of the time, on average, of recovery from the disease.

α : Extra death rate caused by the disease in the infected (*I*) subpopulation. As in the natural death rate, it is proportional to the inverse life-span, on average, of an individual affected by the disease.

τ : Average time of transition from exposed to infected (E → I) subpopulations. A similar parameter is sometimes used, analogous to γ and α , using the inverse of τ to define the parameter

κ , which is the ratio of transition from exposed to infected subpopulation.

ω : Average time of transition from immune to susceptible subpopulations (R → S).

β : Disease transmission constant. As defined in previous section, it is measured depending on the type formulations used for the model.

η : A saturation constant related to a transmission of the disease and incidence rate alternative to the pseudo mass and mass action models.

δ : A diminishing factor related to the disease transmission in the vaccinated subpopulation in contrast to that corresponding to the susceptible one.

V_c : Fraction of the population which is vaccinated since birth ($V_c \in [0, 1]$).

R_0 : Basic reproduction number, it is defined as the average number of secondary cases generated from an average primary case in an entirely susceptible subpopulation. This parameter is derived from the models, and it is fundamental for

the understanding the nature of the diseases and their evolution through time.

This parameter will be explained in more detail in the following sections.

A series of typical models are now presented in order to describe the more general characteristics observed in this context.

The SI epidemic model First, it is presented a model with the minimal number of subpopulations possible to describe an epidemic: A susceptible and an infectious subpopulation. It is assumed that the disease has a chronic component that affects the health of the hosts, so their average life expectancy is reduced. The dynamic of the subpopulations is described in figure 1.2 and in the following equations:

$$\frac{dS(t)}{dt} = \dot{S}(t) = \nu - \beta S(t)I(t) - \mu S(t) \quad (1.4)$$

$$\frac{dI(t)}{dt} = \dot{I}(t) = \beta S(t)I(t) - (\mu + \alpha)I(t) \quad (1.5)$$

Even though the model presented is quite simple, the non-linear βSI term makes analytical study of the solutions of $S(t)$ and $I(t)$ expressions futile. However, that does not mean that some analytical study is not possible. By setting to zero the equations (1.4) and (1.5) it is obtained the values of the subpopulations where, if there is no perturbation, will remain in the same state indefinitely. The equilibrium states obtained for this model are two, one where the disease is prevalent and another where it has been eradicated, which will be defined as endemic equilibrium (END) $[S^*, I^*] = [\frac{\alpha+\mu}{\beta}, \frac{\nu}{\alpha+\mu} - \frac{\mu}{\beta}]$ and disease-free equilibrium (DFE) $[S^*, I^*] = [\nu/\mu, 0]$, respectively.

Also, it is seen that if the susceptible subpopulation is below $S_0 = S_{END}^* = (\mu + \alpha)/\beta$ it is obtained from the equation (1.5) that

$$\dot{I}(t) = I(t)(\beta S(t) - (\mu + \alpha)) \leq 0 \quad \forall S(t) \leq S_0 \quad (1.6)$$

So it is seen that an analysis of the parameters of the disease can predict, partially but significantly, the evolution of the epidemic.

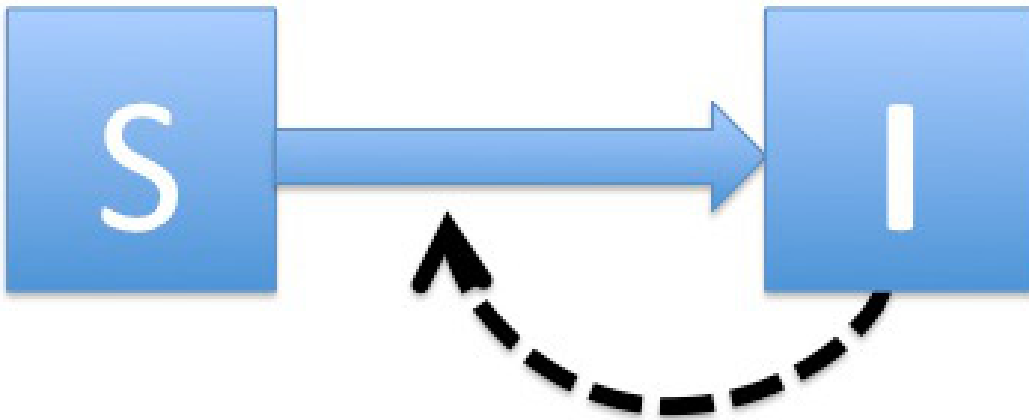


Figure 1.2: A Simple SI epidemic model

The SIR epidemic model The idea of "closed population" is introduced in this model, where the effects of demographics, i.e., migration of population, death or newborn individuals are discarded. The scenario presented is a large population in which a low level of infectious agent is introduced, and the epidemic spreads fast enough so that none of the demography is relevant to the evolution of the disease. The contact rate is frequency dependent and the population is assumed homogeneous mixed, so that the equations for the dynamics is defined as

$$\frac{dS(t)}{dt} = \dot{S}(t) = -\beta S(t)I(t) \quad (1.7)$$

$$\frac{dI(t)}{dt} = \dot{I}(t) = \beta S(t)I(t) - \gamma I(t) \quad (1.8)$$

$$\frac{dR(t)}{dt} = \dot{R}(t) = \gamma I(t) \quad (1.9)$$

A diagram of the model is shown at fig 1.3. After an initial state before interacting with the disease, the susceptible subpopulation goes to an infectious stage which last, on average γ^{-1} . Then the disease carry on and reach the final recovered state, immune to the disease. The solution of the model is obtained numerically as the non linear term βSI , again , does not facilitate obtaining an analytical solution. As in

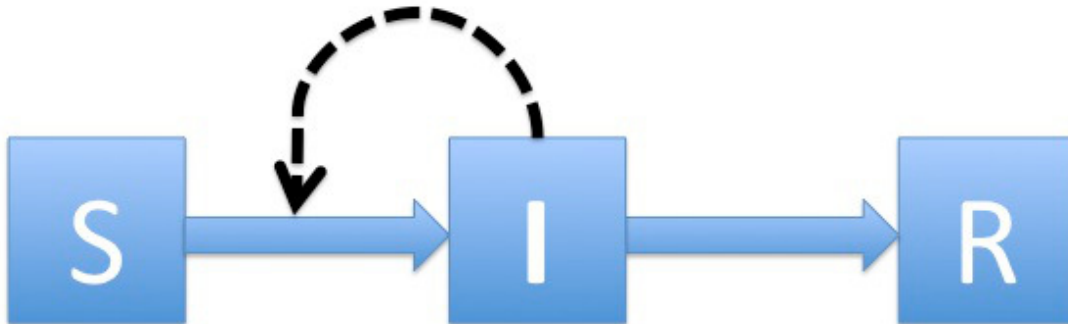


Figure 1.3: A Simple SIR epidemic model

the previous model, an analysis of the parameters can be made so that the threshold susceptible subpopulation is defined as

$$\dot{I}(t) = I(\beta S_0 - \gamma) \leq 0 \quad \rightarrow \quad S_0 = \gamma/\beta \quad (1.10)$$

SEIR epidemic model The SEIR model is based on a SIR model, but in this model it is taken into account as a relevant parameter the time between the host being exposed to the pathogen to the time where the host is considered infectious. Thus the new subpopulation is introduced. The dynamic of the SEIR model, as seen in figure 1.4 is similar to the SI and SIR model, with a stage between the susceptible and the infectious subpopulation and a disease relevant to the demography of the population. This exposed subpopulation will have a transition rate which, in this case, will be proportional to the inverse of the mean time of the latent period of

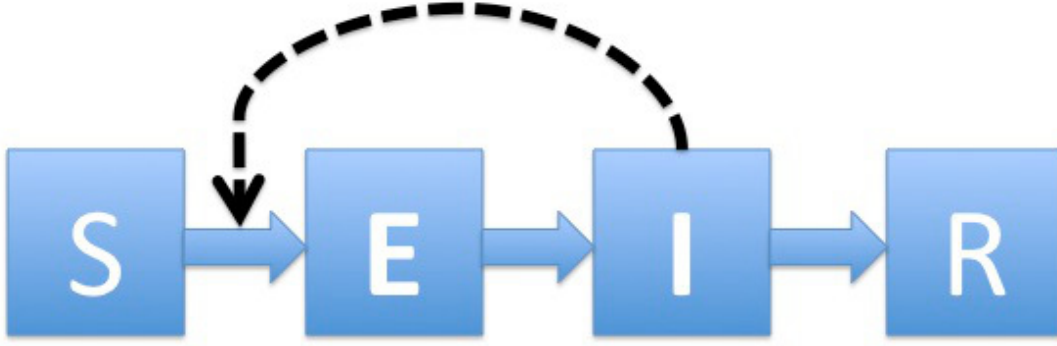


Figure 1.4: A Simple SEIR epidemic model

infection.

$$\dot{S}(t) = \nu - \beta S(t)I(t) - \mu S(t) \quad (1.11)$$

$$\dot{E}(t) = \beta S(t)I(t) - (\kappa + \mu)E(t) \quad (1.12)$$

$$\dot{I}(t) = \kappa E(t) - (\gamma + \alpha + \mu)I(t) \quad (1.13)$$

$$\dot{R}(t) = \gamma I(t) - \mu R(t) \quad (1.14)$$

An analysis of the parameters produce two equilibrium states. A DFE state

$$[S_{DFE}^*, E_{DFE}^*, I_{DFE}^*, R_{DFE}^*] = [\nu/\mu, 0, 0, 0]$$

and an END state

$$\begin{bmatrix} S_{END}^* \\ E_{END}^* \\ I_{END}^* \\ R_{END}^* \end{bmatrix} = \begin{bmatrix} \frac{(\alpha+\gamma+\mu)(\kappa+\mu)}{\beta\kappa} \\ \frac{\nu}{\kappa+\mu} - \frac{\mu(\alpha+\gamma+\mu)}{\beta\kappa} \\ \frac{\kappa\nu}{(\alpha+\gamma+\mu)(\kappa+\mu)} - \frac{\mu}{\beta} \\ \frac{\gamma\kappa\nu}{\mu(\alpha+\gamma+\mu)(\kappa+\mu)} - \frac{\gamma}{\beta} \end{bmatrix}$$

Observe that, depending on the disease, the parameters for the characterization can be bigger than the demographic parameters in various orders of magnitude, and the latent period time be small enough so that the previous SIR model is a simplified version of a fast acting SEIR one.

SVEIR epidemic model The final example presented here increases the complexity of the model a step further, as the susceptible subpopulation is divided into two different subpopulations: the normal susceptible subpopulation, in which the hosts are not protected against infection, and the vaccinated subpopulation, in which the immune system of the hosts has been stimulated so that their response is more positive. Thus, the way this subpopulations is affected from the disease is different, as it may reach a complete immunity without the need to suffer the effects of the infection or becoming a vector of the diseases itself. In fig 1.5, the evolution of the epidemic is presented. Usually, the vaccinated subpopulation enters in these dynamics due to different vaccination strategies. Sometimes, a flux from the susceptible to the vaccination subpopulation appears describing a vaccination campaign acting on the whole

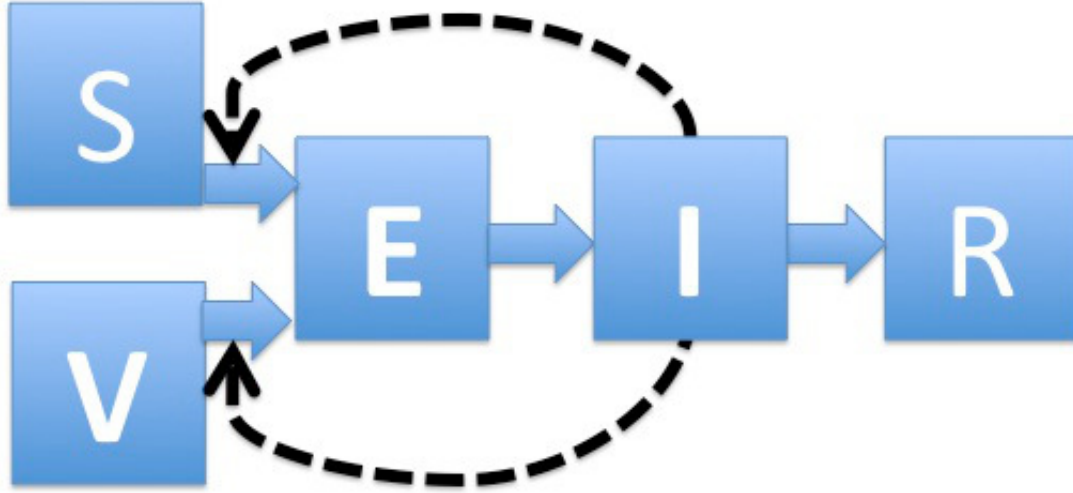


Figure 1.5: A Simple SVEIR epidemic model

susceptible individuals, Other times, the vaccination only acts on the newborns or the population migrating into the area of the epidemic. In this case, the equations describing the dynamics are

$$\dot{S}(t) = \nu(1 - V_c) - \beta S(t)I(t) - \mu S(t) \quad (1.15)$$

$$\dot{V}(t) = \nu V_c - \delta \beta S(t)I(t) - (\gamma_1 + \mu)V(t) \quad (1.16)$$

$$\dot{E}(t) = \beta(1 + \delta)S(t)I(t) - (\kappa + \mu)E(t) \quad (1.17)$$

$$\dot{I}(t) = \kappa E(t) - (\gamma + \mu + \alpha)I(t) \quad (1.18)$$

$$\dot{R}(t) = \gamma I(t) + \gamma_1 V(t) - \mu R(t) \quad (1.19)$$

As in the previous models, observe that a wise choose in the parameters can simplify this model into one like in the previous here presented. However this does not mean that every model has the same force of infection, as it will be seen in the following chapters. Saturation rates in the infection, complex networks of interaction between subpopulations and other approaches when modeling the mechanics of the disease affects the way it is designed. The prediction of the evolution of the disease based on the parameters on this model require a more complex analysis than in the more simple models, and it will be explained in the following section.

1.3 The basic reproduction number

The examples of a threshold susceptible subpopulation of the previous section can be differently interpreted as a condition of the relative removal rate of the disease to be small enough to spread. The inverse of the relative removal rate is called basic reproduction number or reproductive number, usually represented as R_0 . The R_0 is defined, from an epidemiologist perspective [10], as the average number of secondary

cases arising from an average primary case in an entirely susceptible population. The basic reproduction number is used to study the global impact that a disease can produce on a population, as a $R_0 > 1$ would mean that the number of individuals infected will increase with respect to the previous generation of infected individuals, and a $R_0 < 1$ would mean the opposite, which is a decrement in that number. R_0 is then obtained by multiplying the average infectious time of an individual with the average rate of infection of an infected individual in a disease-free population.

From a mathematical perspective, however, this alone infected individual in a disease-free population is considered a perturbation of the DFE state, one of the many possible small changes made on a equilibrium state. Then, given the differential equations governing the dynamic of these models, the general effect of any perturbation on the evolution of the system when it is in an equilibrium state can be calculated. Assume that the system for a generic epidemic with n different subpopulations N_i , $i = 1, 2, \dots, n$, corresponding to the different stages of the disease, is defined by the equations

$$\frac{dN_i}{dt} = f_i(N_1, N_2, \dots, N_n) \quad , i = 1, 2, \dots, n \quad (1.20)$$

Then, the DFE state correspond to the state where $f_i(N_1^*, N_2^*, \dots, N_n^*) = 0 \quad \forall i = 1, 2, \dots, n$ and the subset of N_j, N_{j+1}, \dots, N_n where the infection is present is equal to zero. Then, for a small perturbation on any subpopulation, the evolution can be approximately predicted using a multivariable taylor series of the functions around the DFE state. From equation (1.20)

$$\dot{\vec{N}}(\vec{N}) = \dot{\vec{N}}(\vec{N}^* + \vec{\epsilon}) = \dot{\vec{N}}(\vec{N}^*) + \vec{\epsilon}^T D\dot{\vec{N}}|_{\vec{N}^*} = \vec{\epsilon}^T J|_{\vec{N}^*} \quad (1.21)$$

being $\vec{N} = [N_1, N_2, \dots, N_n]^T$, $\dot{\vec{N}} = [f_1(\vec{N}), f_2(\vec{N}), \dots, f_n(\vec{N})]^T$, and the Jacobian matrix J defined as

$$J_{i,j} = \left. \frac{\partial f_i}{\partial N_j} \right|_{\vec{N}^*} \quad \rightarrow \quad J = \begin{bmatrix} \frac{\partial f_1^*}{\partial N_1} & \frac{\partial f_1^*}{\partial N_2} & \dots & \frac{\partial f_1^*}{\partial N_n} \\ \frac{\partial f_2^*}{\partial N_1} & \frac{\partial f_2^*}{\partial N_2} & \dots & \frac{\partial f_2^*}{\partial N_n} \\ \dots & \dots & \dots & \dots \\ \frac{\partial f_n^*}{\partial N_1} & \frac{\partial f_n^*}{\partial N_2} & \dots & \frac{\partial f_n^*}{\partial N_n} \end{bmatrix} \quad (1.22)$$

Then, the tendency of change of the system, when the disturbance is small and is approximated at first order, is characterized by the Jacobian matrix J . The sign of the eigenvalues of this matrix will determine the tendency of these disturbances to increase or decrease over time. The eigenvalues λ_i are defined as the solutions of $\det(\lambda I - J) = 0$. If all the real parts of λ_i , $i = 1, 2, \dots, n$ are less than zero then the system will react decreasing the subpopulations which have risen and increase the subpopulations which have dropped, until it reaches again the DFE. Thus, it can be said that the equilibrium state is, at least, locally stable.

The reproduction number is a manifestation of all the eigenvalues of the Jacobian matrix at the disease free equilibrium. Consider a SIR model as in the previous section with a death and a newborn rates μ and ν respectively. The characteristic

Jacobian matrix would be

$$J = \begin{bmatrix} -\beta I^* - \mu & -\beta S^* & 0 \\ \beta I^* & \beta S^* - (\mu + \gamma) & 0 \\ 0 & \gamma & -\mu \end{bmatrix} \quad (1.23)$$

and the polynomial derived from $\det(\lambda I - J) = 0$ would be

$$(\lambda + \mu)(-\beta S^* - \gamma - \lambda - \mu)(\lambda + \mu) + \beta I^*(\gamma + \lambda + \mu) = 0 \quad (1.24)$$

which, in the case of the DFE becomes

$$(S_{DFE}^* \beta - \gamma - \lambda - \mu)(\lambda + \mu)^2 = 0 \quad (1.25)$$

So the eigenvalues are $\lambda = \{-\mu, -\mu, \beta S_{DFE}^* - (\gamma + \mu)\}$. The negativity of the first two eigenvalues are trivial, while the condition of negativity for the third one correspond to a S_{DFE}^* below a threshold as seen in the previous section. The reproduction number, then, is constructed from the condition of negativity of this eigenvalue, as $\beta S_{DFE}^* < \gamma + \mu$ is equivalent to $\frac{\beta S_{DFE}^*}{\gamma + \mu} = R_0 < 1$.

The study of the equilibrium can also extend to the study of the endemic equilibrium, in which the reproduction number can also be a useful parameter for determine the stability of this point. In this example, the equation from equation (1.24) can be rearranged as a function of R_0

$$(\lambda + \mu)(\lambda^2 + \mu R_0 \lambda + (\mu + \gamma)\mu(R_0 - 1)) = 0 \quad (1.26)$$

so the eigenvalues for the endemic equilibrium are

$$\lambda = \left\{ -\mu, \frac{-\mu R_0 - \sqrt{(\mu R_0)^2 - 4(R_0 - 1)\mu(\mu + \gamma)}}{2}, \frac{-\mu R_0 + \sqrt{(\mu R_0)^2 - 4(R_0 - 1)\mu(\mu + \gamma)}}{2} \right\} \quad (1.27)$$

so for $R_0 < 1 \rightarrow R_0 - 1 < 0$, the third eigenvalue $\lambda_3 = \frac{1}{2}\mu R_0(-1 + \sqrt{1 + \xi})$, being $\xi > 1$ so λ_3 will be positive and thus the equilibrium is unstable. As you can see, the role of the reproduction number when studying the disease is not only confined to make predictions about the disease-free state. R_0 is also a parameter useful when studying other equilibrium states of the diseases, where the initial definition made by epidemiologists cannot be applied to those specific situations.

A terminology note We want to point out that in the English literature, we use the article "An" if the word "epidemic" follows after the model acronym. For instance, "An SEIR epidemic model". We change "an" to the usual "a" if the word "epidemic" is not written after the acronym. For instance, "A SEIR model". This is the standard notation for the case in the literature on the subject.

1.4 Contents of the Thesis

The content of this work is now briefly described.

Chapter 2 Chapter 2 is devoted to the study of the equilibrium points, boundedness and positivity of an SVEIRS epidemic model under constant regular vaccination. That is, it is discussed the main properties of a model which includes a vaccinated population and, furthermore, a constant vaccination control term. First at all the disease-free and endemic equilibrium points of the model are discussed, as well as their positivity and stability. Then, a set of simulations is made, and the chapter concludes with some remarks and recommendations for the current model.

Chapter 3 Chapter 3 relies on a general SVEIRS epidemic model under regular and adaptive vaccination. There are three kinds of vaccination strategies, namely, the constant (or regular) one, an impulsive one implemented at constant time intervals and a mixed one, i.e. there are vaccination impulses at variable inter-vaccination time intervals. The study of this chapter relies in a certain sense and adapted, "ad hoc" for this kind of problem, with former studies of Professors Mellado, Dormido, De la Sen and others in the context of proposing adaptive sampling laws for signal adaptation so as either to improve the transient responses or to keep a similar performance as for constant sampling by smaller sampling effort (i.e. with the use of less samples along the whole evaluated time interval). It is presented an exhaustive comparative simulation study, including an evaluation with a real parameterization of a pertussis disease, showing the efficacy of the adaptive vaccination with variable inter-vaccination times interval over the regular strategies. A complete stability study is also allocated in an appendix.

Chapter 4 Chapter 4 is devoted to the study of limit periodic oscillations in a SEIRS model. Typically, this behavior is associated to the case when global stability is guaranteed but none of the equilibrium points is globally asymptotically stable. The local stability of the equilibrium points is studied in detail. An analysis based on Fourier methods is given for the case of periodic vaccination and periodic infective rate. This is a typical situation appropriate for the analysis of seasonal diseases like, for instance, influenza. The study is completed with the periodic equilibrium states obtained for this situation, and some simulations of the dynamics of these systems.

Chapter 5 Chapter 5 considers an extended SIRS model with several (n) infective stages all taken from a common susceptible population. The various infective stages have successive starting points along time. This model treats to extend the typical SEIR sequential model to a more general interpretation, where a disease may remain dormant on an individual during a period of time and become again infectious, or the treatment of a disease may reduce the infectivity or the mortality of a disease after medication, or increase as a tolerance to the treatment is developed by the sick hosts. Since there are multiple infective stages, the presence of a specific exposed subpopulation is not considered. This role can be assimilated to any stage of the disease, depending on how the parameters are chosen. Several variants of the model related to the presence or not of delays are considered in the study. Also, there is a parallel study for a closed model formulated in the discrete context. Some simulations are also given and discussed.

Chapter 6 Chapter 6 is devoted to several aspects which have been studied along the period of this thesis but with either different analysis methods or more specific models. Therefore, it is included in this last chapter. In particular, the themes in this chapters cover the study of a disease propagation with temporal immunity, described by a SIRS (susceptible plus infected plus recovered populations) epidemic model and a simple SEIRS model. Another part of the this chapter is devote to the construction of a discrete model from the continuous SEIRSS model. Some variations on the vaccination control strategies have been implemented on those models. Specifically, some feedback and constant vaccination laws based on partial stability techniques by considering the manifold defined by the zero exposed and infectious subpopulations; also, an observer-based vaccination law are developed for the SEIR model. A control technique based on a model linearization approach is used to design the vaccination strategy in order to eradicate the infection from the population. Moreover, the controlled system is guaranteed to be positive and stable under such vaccination control strategy. A detailed simulation example is given for validating the theoretical results relative to the stability and positivity of the controlled system while guaranteeing the eradication of the epidemics.

Chapter 7 In Chapter 7 it is presented a conclusion to the studies made in this thesis, and new perspectives and potential uses for the health care, being it focused on humans or any other type of hosts susceptible to diseases. Future projects are also comented

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On the equilibrium points, boundedness and positivity of a SVEIRS model under constant regular constrained vaccination

This chapter discusses the disease-free and endemic equilibrium points of a SVEIRS mathematical model for disease propagation. The positivity of the five subpopulations in the model is discussed as well as the boundedness of the total population. The model takes also into consideration the natural population growing and the mortality associate to the disease as well as the lost of immunity of newborns. It is assumed that there are two finite delays affecting to the susceptible, recovered, exposed and infected subpopulation dynamics. The conditions for the stability of the disease-free equilibrium are studied and tested in a simulation.

2.1 Introduction

Important control problems nowadays related to Life Sciences are the control of ecological models like those of population evolution as Beverton-Holt model, Hassell model, Ricker model etc. via the online adjustment of the species environment carrying capacity, that of the population growth or that of the regulated harvesting quota as well as the disease propagation via vaccination control [1]- [6]. In a set of papers, several variants and generalizations of the Beverton-Holt model (standard time-invariant, time-varying parameterized, generalized model or modified generalized model) have been investigated at the levels of stability, cycle-oscillatory behavior, permanence and control through the manipulation of the carrying capacity [1]-[5]. The design of related control actions has been proved to be important in those papers at the levels, for instance, of aquaculture exploitation or plague fighting. On the other hand, the literature about epidemic mathematical models is exhaustive in many books and papers [7]-[20]. The sets of models include the most basic ones [13], [10], namely:

- i) SI- models where not removed- by immunity subpopulation is assumed. In other words, only susceptible and infected subpopulations are assumed.
- ii) SIR-models, which include susceptible, infected and removed- by immunity subpopulations.
- iii) SEIR-models where the infected subpopulations is split into two ones (namely, the 'infected' which incubate the disease but do not still have any disease symptoms and the 'infectious' or 'infective' which do exhibit the external disease symptoms).

The three above models have two possible major variants, namely, the 'pseudo-mass action' models, and the 'true-mass action' models (density dependant and non-dependant), although there are other many variants of the above, for instance, including vaccination of different kinds: constant [18] impulsive [21], [22], [23], discrete-time etc., incorporating point or distributed delays [20], [23], oscillatory behaviors [14] etc. It also should be noted that variants of such models become considerably simpler for the disease transmission among plants [13], [10]. Some generalizations involve the use of a mixed regular continuous-time and impulsive vaccination control strategies for generalized time-varying epidemic model which is subject to point and distributed either constant or time-varying delays [17], [20], [24]-[26].

Other well-known types of epidemic models are the so-called SVEIRS epidemic models which incorporate the dynamics of a vaccinated subpopulation and the 'infected' subpopulation without external symptoms of the SEIR-type models is replaced with an 'exposed' subpopulation subject to a certain dynamics [17], [23], [26].

Thus, in the context of SVEIRS models, the infected and infectious subpopulations of the SEIR models are joined in a single 'infected' subpopulation $I(t)$ while there is an exposed subpopulation $E(t)$ present in the model. This chapter is focused on the existence and some properties of disease-free and endemic equilibrium points of a SVEIRS model, while it is subjected to an eventual constant regular vaccination rather than to an impulsive vaccination type. Some issues about boundedness and positivity of the model are also investigated.

2.2 The SVEIRS model

Figure 2.1 describe the interactions between the subpopulations of the SVEIRS epidemic model, with regular constant vaccination. The equations describing this interactions are:

$$\dot{S}(t) = b(1 - S(t)) - \beta \frac{S(t)I(t)}{1 + \eta S(t)} + \gamma I(t - \omega) e^{-b\omega} + \nu(1 - V_c)N(t) \quad (2.1)$$

$$\dot{V}(t) = \nu V_c N(t) - \delta \beta \frac{V(t)I(t)}{1 + \eta V(t)} - (\gamma_1 + b)V(t) \quad (2.2)$$

$$E(t) = \beta \int_{t-\tau}^t \left(\frac{S(u)I(u)}{1 + \eta S(u)} + \delta \frac{V(u)I(u)}{1 + \eta V(u)} \right) e^{b(u-t)} du \quad (2.3)$$

$$\begin{aligned} \dot{I}(t) = & \beta \left(\frac{S(t-\tau)}{1 + \eta S(t-\tau)} + \frac{\delta V(t-\tau)}{1 + \eta V(t-\tau)} \right) I(t-\tau) e^{-b\tau} \\ & - (\gamma + b + \alpha) I(t) \end{aligned} \quad (2.4)$$

$$\dot{R}(t) = -bR(t) + \gamma_1 V(t) + \gamma (I(t) - I(t - \omega) e^{-b\omega}) \quad (2.5)$$

where S, V, E, I and R are, respectively, the susceptible, vaccinated, exposed, infected (or infective or infectious) and recovered (or removed-by-immunity) subpopulations, N is the total population being the sum of the above ones, $V_c \in [0, 1]$ is a constant vaccination action. There are potential latent and immune periods denoted by τ and

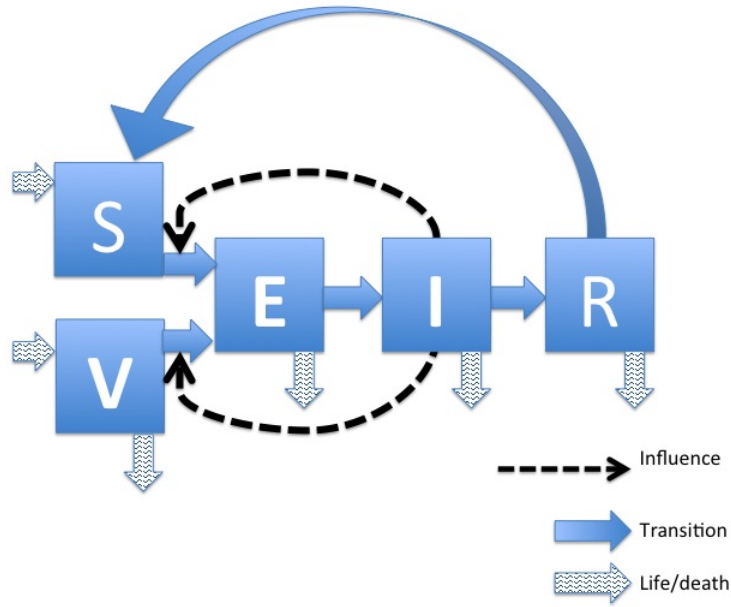


Figure 2.1: SVEIRS epidemic model

ω , respectively, which are internal delays in the dynamic epidemic model (2.1)-(2.5), b is the natural birth rate and death rate of the population. The parameter $\nu < b$ takes into account a vaccination action on newborns which decreases the incremental susceptible subpopulation through time, γ_1 is the average rate for vaccines to obtain immunity and move into recovered subpopulation, β (disease transmission constant) and $\delta\beta$ are, respectively, the average numbers for contacts of an infective with a susceptible and an infective with a vaccinated individual per unit of time, [23], [17]. The periodic impulsive, rather than regular, vaccination action proposed in [23] can be obtained from equations (2.1)-(2.5) with $V_c = 0$ and a regular impulsive vaccination period consisting of a culling action on the susceptible plus the corresponding increase of the vaccinated subpopulation. It should be pointed out that the epidemic model delays, representing here the latent and immune periods, parameterize the epidemic model apart from the role they play through the delayed model state in the dynamics and thus in the trajectory solution. This phenomenon is not very common in standard time-delay systems, where delays do not play usually a relevant role in the parameterizations, but only in the state-trajectory solution through the delayed state dynamics, [28]-[30]. It should be pointed out that the use of mathematical models supported by electronics instrumentation is also very relevant for the study of biological process, such as models of blood circulation, because of its facility for discretized implementation of real testing experiments [31]. Take into account that epidemic models are not controllable in the sense that all the subpopulations cannot be simultaneously governed [32]. Therefore, the main vaccination objective is to reduce the infected subpopulation as faster and as close to zero as possible [6],[27]. In this chapter it is investigated the disease-free and endemic equilibrium points, their

local stability properties and, under optional constrained vaccination, the positivity and boundedness properties of the state-trajectory solutions.

2.3 The disease-free equilibrium point

The potential existence of a disease-free equilibrium point is now discussed which asymptotically removes the disease if $\nu < b$.

Proposition 2.1. *Assume that $\nu < b$. Then, the disease-free equilibrium point $E^* = I^* = 0$ fulfills*

$$\begin{aligned} R^* &= \frac{\nu\gamma_1 V_c N^*}{b(\gamma_1 + b)} = \frac{\nu\gamma_1 V_c}{(b - \nu)(b + \gamma_1)} = \gamma_1 \frac{(b - \nu(1 - V_c))N^* - b}{b(\gamma_1 + b)} \\ V^* &= \frac{\nu V_c N^*}{\gamma_1 + b} = \frac{(b - \nu(1 - V_c))N^* - b}{\gamma_1 + b} \\ S^* &= 1 + \frac{\nu N^*(1 - V_c)}{b} = 1 + \frac{\nu(1 - V_c)}{b - \nu} \end{aligned}$$

with $N^* = \frac{b}{b - \nu}$ so that $V^* + R^* = \frac{\nu V_c N^*}{b} = \frac{\nu V_c}{b - \nu}$.

Two particular disease-free equilibrium points are $S^* = N^* = \frac{b}{b - \nu}$, $E^* = I^* = V^* = 0$ if $V_c = 0$, and $S^* = 1$, $V^* = \frac{\nu N^*}{(\gamma_1 + b)}$, $R^* = \frac{\nu\gamma_1}{(\gamma_1 + b)(b - \nu)}$, $E^* = I^* = 0$ if $V_c = 1$.

If $\nu \geq b$ then there is no disease-free equilibrium point.

Proof.

The equilibrium points are calculated by zeroing equations (2.1), (2.2), (2.4) and (2.5) and making identical to a disease-free equilibrium value, which leads to:

$$b - \left(b + \frac{\beta I^*}{1 + \eta S^*} \right) S^* + \gamma I^* e^{-b\omega} + \nu N^*(1 - V_c) = 0 \quad (2.6)$$

$$- \left(\frac{\delta \beta I^*}{1 + \eta V^*} + \gamma_1 + b \right) V^* + \nu N^* V_c = 0 \quad (2.7)$$

$$E^* - \frac{\beta}{b} (1 - e^{-b\tau}) \left(\frac{S^*}{1 + \eta S^*} + \frac{\delta V^*}{1 + \eta V^*} \right) I^* = 0 \quad (2.8)$$

$$\beta e^{-b\tau} \left(\frac{S^*}{1 + \eta S^*} + \frac{\delta V^*}{1 + \eta V^*} \right) I^* - (\gamma + b + \alpha) I^* = 0 \quad (2.9)$$

$$\gamma_1 V^* - b R^* + \gamma (1 - e^{-b\omega}) I^* = 0 \quad (2.10)$$

Thus, the disease-free equilibrium point satisfies the constraints:

$$E^* = I^* = 0 \quad (2.11)$$

$$b(1 - S^*) + \nu N^*(1 - V_c) = 0 \rightarrow S^* = 1 + \frac{\nu N^*(1 - V_c)}{b} \quad (2.12)$$

$$\gamma_1 V^* - bR^* = 0 \rightarrow V^* = \frac{bR^*}{\gamma_1} \quad (2.13)$$

$$-(\gamma_1 + b)V^* + \nu N^*V_c = 0 \rightarrow V^* = \frac{\nu N^*V_c}{\gamma_1 + b} = \frac{bR^*}{\gamma_1} \quad (2.14)$$

$$N^* = S^* + V^* + R^* = 1 + \frac{\nu N^*V_c}{b} + \left(1 + \frac{b}{\gamma_1}\right) R^* \quad (2.15)$$

$$\begin{aligned} &= 1 + \frac{\nu N^*V_c}{b} + \left(1 + \frac{b}{\gamma_1}\right) + \frac{\nu N^*V_c}{b} \\ &= \frac{b + \nu N^*}{b} \end{aligned} \quad (2.16)$$

$\rightarrow N^* = \frac{b}{b - \nu}$, provided that $\nu < b$

The proof follows directly from the above equations. \square

Remark 2.2.

Note from equation (2.9) that the identity $\frac{S^*}{1 + \eta S^*} + \frac{\delta V^*}{1 + \eta V^*} = \frac{\gamma + b + \alpha}{\beta} e^{b\tau}$ has always to be fulfilled by endemic equilibrium points, if any, but non-necessarily by disease-free equilibrium points for which $I^* = 0$. Note also that if $\gamma_1 = b$ then $R^* = V^* = \frac{\nu V_c N^*}{2b} = \frac{\nu V_c}{2(b - \nu)}$. If $\nu = 0$, as in the particular case of impulsive-free SVEIRS model obtained from that discussed in other works [23], [17], then the disease-free equilibrium satisfies $E^* = V^* = I^* = R^* = 0$, $N^* = S^* = 1$. In such a case, the model can be ran out with population normalized to unity. Note that the recovered subpopulation increases at the equilibrium as the vaccination increases while the susceptible one decreases.

Note that the exposed subpopulation at the equilibrium defined by equation (2.3) can be equivalently described by a differential equation obtained by applying the Leibniz differentiation rule under the integral symbol to yield:

$$\dot{\tilde{E}}(t) = -b\tilde{E}(t) + \beta \left(\frac{S^*}{1 + \eta S^*} + \frac{\delta V^*}{1 + \eta V^*} \right) (\tilde{I}(t) - \tilde{I}(t - \omega) e^{-b\omega}) \quad (2.17)$$

Note also from the equalities of Proposition 2.1 that

$$\frac{S^*}{1 + \eta S^*} + \frac{\delta V^*}{1 + \eta V^*} = K^* := \frac{b - \nu V_c}{(1 + \eta)b - \nu(1 + \eta V_c)} + \frac{\delta \nu b V_c}{(\gamma_1 + b)(b - \nu) + \eta \nu b V_c} \quad (2.18)$$

Also, since $\max(S^*, V^*) \leq N^* = \frac{b}{b - \nu}$, the following relation in equation (2.19) follows irrespective of the vaccination V_c , provided that the transmission constant is sufficiently small, satisfying $\beta = (\gamma + b + \alpha - \epsilon_\beta) e^{b\tau} \frac{b(1 + \eta) - \nu}{b(1 + \delta)} \leq (\gamma + b + \alpha) e^{b\tau} \frac{b(1 + \eta) - \nu}{b(1 + \delta)}$ for some real constant $0 \leq \epsilon_\beta < \gamma + b + \alpha$:

$$\frac{S^*}{1 + \eta S^*} + \frac{\delta V^*}{1 + \eta V^*} \leq \frac{1 + \delta}{N^{*-1} + \eta} = \frac{b(1 + \delta)}{b(1 + \eta) - \nu} = \frac{(\gamma + b + \alpha - \epsilon_\beta) e^{b\tau}}{\beta} \quad (2.19)$$

The local stability of the disease-free equilibrium point independent of the sizes of the delays τ and ω is discussed in the sequel for the particular case of sufficiently small β satisfying equation (2.19) and for the general case of equation (2.18). Also, the local asymptotic stability of the disease-free equilibrium point is guaranteed by that of the linearized incremental system around it. The linearized model around the equilibrium becomes to be defined from equations (2.1)-(2.2), (2.17) and (2.4)-(2.5) by the state vector $\tilde{x}(t) := \left(\tilde{S}(t), \tilde{V}(t), \tilde{E}(t), \tilde{I}(t), \tilde{R}(t) \right)^T$ which satisfies the differential equation system:

$$\tilde{x}(t) := A_0^* \tilde{x}(t) + A_\tau^* \tilde{x}(t - \tau) + A_\omega^* \tilde{x}(t - \omega) \quad ; \quad \tilde{x}(0) = \tilde{x}_0 \quad (2.20)$$

where

$$A_0^* = A_{0d}^* + \tilde{A}_0^* \quad (2.21)$$

$$:= \begin{bmatrix} \nu(1-V_c) - b & \nu(1-V_c) & \nu(1-V_c) & \nu(1-V_c) - \frac{\beta S^*}{1+\eta S^*} & \nu(1-V_c) \\ \nu V_c & \nu V_c - (\gamma_1 + b) & \nu V_c & \nu V_c - \frac{\delta \beta V^*}{1+\eta V^*} & \nu V_c \\ 0 & 0 & -b & \beta \left(\frac{S^*}{1+\eta S^*} + \frac{\delta V^*}{1+\eta V^*} \right) & 0 \\ 0 & 0 & 0 & -(\gamma + b + \alpha) & 0 \\ 0 & \gamma_1 & 0 & \gamma & -b \end{bmatrix} \quad (2.22)$$

$$= \begin{bmatrix} \nu(1-V_c) - b & \nu(1-V_c) & \nu(1-V_c) & \nu(1-V_c) - \frac{\beta(b+\nu(1-V_c)N^*)}{b+\eta(b+\nu(1-V_c)N^*)} & \nu(1-V_c) \\ \nu V_c & \nu V_c - (\gamma_1 + b) & \nu V_c & \nu V_c - \frac{\delta \beta \nu V_c N^*}{\gamma_1 + b + \eta \nu V_c N^*} & \nu V_c \\ 0 & 0 & -b & (\gamma + b + \alpha - \bar{\epsilon}_\beta) e^{b\tau} & 0 \\ 0 & 0 & 0 & -(\gamma + b + \alpha) & 0 \\ 0 & \gamma_1 & 0 & \gamma & -b \end{bmatrix} \quad (2.23)$$

for sufficiently small transmission constant β if equation (2.19) holds for some positive real constant $\bar{\epsilon}_\beta > \epsilon_\beta$ where the diagonal and non-diagonal matrix additive decomposition \tilde{A}_0^* is given from equation (2.23) by

$$\tilde{A}_{0d}^* := \begin{bmatrix} \nu(1-V_c) - b & 0 & 0 & 0 & 0 \\ 0 & \nu V_c - (\gamma_1 + b) & 0 & 0 & 0 \\ 0 & 0 & -b & 0 & 0 \\ 0 & 0 & 0 & -(\gamma + b + \alpha) & 0 \\ 0 & 0 & 0 & 0 & -b \end{bmatrix} \quad (2.24)$$

$\tilde{A}_0^* := A_0^* - A_{0d}^*$ obtained from equations (2.23)-(2.24), so that its off-diagonal part is identical to that of A_{0d}^* while the diagonal is identically zero, and the matrices A_τ^* and A_ω^* are entry-wise defined by:

$$\begin{aligned} (A_\tau^*)_{4,4} &= \gamma + b + \alpha - \bar{\epsilon}_\beta \\ (A_\omega^*)_{1,4} &= \gamma e^{-b\omega} \\ (A_\omega^*)_{5,4} &= -\gamma e^{-b\omega} \\ (A_\omega^*)_{3,4} &= -(\gamma + b + \alpha - \bar{\epsilon}_\beta) e^{b(\tau-\omega)} \end{aligned} \quad (2.25)$$

with all the remaining entries being zero. The following inequalities apply for equivalent norms of vectors and square matrices M of dimension or, respectively, order n :

$$n^{-1} \|M\|_2 \leq n^{-1/2} \|M\|_\infty \leq \|M\|_2 \leq n^{1/2} \|M\|_1 \leq n \|M\|_2 \quad (2.26)$$

Thus, one gets from the above inequalities from equation (2.26) that

$$\|A_\tau^*\|_2 + \|A_\omega^*\|_2 \leq \sqrt{5} (\|A_\tau^*\|_\infty \|A_\omega^*\|_\infty) \leq \sqrt{5} (\gamma + b + \alpha) \max [1, e^{b(\tau-\omega)}] \leq \bar{\gamma} \quad (2.27)$$

where

$$\bar{\gamma} = \begin{cases} \sqrt{5} (\gamma + b + \alpha) & \text{if } \tau \leq \omega \\ \sqrt{5} (\gamma + b + \alpha) e^{b(\tau-\omega)} & \text{if } \tau > \omega \end{cases} \quad (2.28)$$

Note from equation (2.28) that $\sqrt{5} (\gamma + b + \alpha) e^{b(\tau-\omega)} \leq b - b_0$ for a given b and any given positive real constant $b_0 < b$ if $(\gamma + b + \alpha)$ and $(\tau - \omega)$, if positive, are small enough such that, equivalently,

$$-\infty \leq \frac{1}{2} \ln(5) + \ln(\gamma + b + \alpha) + b(\tau - \omega) \leq \ln(b - b_0) \quad (2.29)$$

Thus, one gets from equations (2.27)-(2.29)

$$\|A_\tau^*\|_2 + \|A_\omega^*\|_2 \leq \bar{\gamma} \leq b - b_0 \quad (2.30)$$

It can be use from L' Hopital rule the following limit relations in the entries (1, 4) and (2, 4) of \tilde{A}_0^* :

$$\frac{\beta (b + \nu (1 - V_c) N^*)}{b + \eta (b + \nu (1 - V_c) N^*)} \rightarrow \frac{\beta}{1 + \eta}; \quad \frac{\delta \beta \nu V_c N^*}{\gamma_1 + b + \eta \nu V_c N^*} \rightarrow 0 \text{ as } b \rightarrow \infty \quad (2.31)$$

if the remaining parameters remain finite and then $N^* = S^* = 1$ and $E^* = I^* = V^* = R^* = 0$ from Proposition 2.1. By continuity with respect to parameters, for any sufficiently large $M \in \mathbf{R}_+$, $\exists \epsilon_{1,2} = \epsilon_{1,2}(M) \in \mathbf{R}_+$ with $\epsilon_{1,2} \rightarrow 0$ as $t \rightarrow \infty$ such that for $b \geq M$:

$$\frac{\beta (b + \nu (1 - V_c) N^*)}{b + \eta (b + \nu (1 - V_c) N^*)} \leq \frac{\beta + \epsilon_1}{1 + \eta}; \quad \frac{\delta \beta \nu V_c N^*}{\gamma_1 + b + \eta \nu V_c N^*} \leq \epsilon_2 \quad (2.32)$$

and, one gets for \tilde{A}_0^* being obtained from equations (2.22)-(2.24),

$$\left| \tilde{A}_0^* \right| = \begin{bmatrix} 0 & \nu(1 - V_c) & \nu(1 - V_c) & \left| \nu(1 - V_c) - \frac{\beta + \epsilon_1}{1 + \eta} \right| & \nu(1 - V_c) \\ \nu V_c & 0 & \nu V_c & |\nu V_c - \epsilon_2| & \nu V_c \\ 0 & 0 & 0 & (\gamma + b + \alpha - \bar{\epsilon}_\beta) e^{b\tau} & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & \gamma_1 & 0 & \gamma & 0 \end{bmatrix} \quad (2.33)$$

and for the parameter b being large enough such that it satisfies:

$$b \geq \max \left(\frac{1}{\tau} \max \left(\ln \left(\frac{\gamma + \gamma_1}{\gamma + b + \alpha} \right), \ln \left(\frac{4 \max(1, \nu)}{\gamma + b + \alpha} \right) \right), b_a \right) \quad (2.34)$$

with b_a being some existing real positive constant, depending on the vaccination constant V_c , such that $\nu(1 - V_c) \geq \frac{\beta + \epsilon_1}{1 + \eta}$, it follows from inspection of equations (2.32)-(2.33) that $\|\tilde{A}_0^*\| \leq (\gamma + b + \alpha) e^{b\tau}$. Using again equations (2.26)-(2.27), it follows that the following close constraint to equation (2.29):

$$\begin{aligned} -\infty &\leq \frac{1}{2} \ln(5) + \ln(\gamma + b + \alpha) + b(\tau - \omega) \\ &\leq \frac{1}{2} \ln(5) + \ln(\gamma + b + \alpha) + b\tau + \ln(1 + e^{-b\omega}) \leq \ln(b - b_0) \end{aligned} \quad (2.35)$$

guarantees

$$\begin{aligned} \|A_\tau^*\|_2 + \|A_\omega^*\|_2 + \|\tilde{A}_0^*\|_2 &\leq \sqrt{5} \left(\|A_\tau^*\|_\infty + \|A_\omega^*\|_\infty + \|\tilde{A}_0^*\|_\infty \right) \\ &\leq \sqrt{5} (\gamma + b + \alpha) (\max(1, e^{b(\tau - \omega)}) + e^{b\tau}) \leq \bar{\gamma}_1 \end{aligned} \quad (2.36)$$

where

$$\bar{\gamma}_1 (> \bar{\gamma}) = \begin{cases} \sqrt{5} (\gamma + b + \alpha) (1 + e^{b\tau}) & \text{if } \tau \leq \omega \\ \sqrt{5} (\gamma + b + \alpha) e^{b\tau} (1 + e^{-b\omega}) & \text{if } \tau > \omega \end{cases} \quad (2.37)$$

On the other hand, note that the linearized system equations (2.20)-(2.25) is asymptotically stable if and only if

$$\text{Det} \left(sI - A_{0d}^* - \tilde{A}_0^* - \tilde{A}_\tau^* e^{-\tau s} - \tilde{A}_\omega^* e^{-b\omega} \right) \neq 0 \quad \forall s \in C_{0+} := \{s \in C : \text{Res} \geq 0\} \quad (2.38)$$

which is guaranteed under the two conditions below:

- i) $\text{Det}(sI - A_{0d}^*) \neq 0$, $\forall s \in C_{0+}$, equivalently, A_{0d}^* is a stability matrix
- ii) The l_2 -matrix measure $\mu_2(A_{0d}^*)$ of (A_{0d}^*) is negative, and, furthermore, the following constraint holds

$$\bar{\gamma}_1 \leq b - \max(|\gamma_1 - \nu V_c|, \nu(1 - V_c))$$

which guarantees the above stability condition ii) via equations (2.36)-(2.37) if is sufficiently small to satisfy equation (2.19) and, furthermore,

$$\begin{aligned} \|A_\tau^*\|_2 + \|A_\omega^*\|_2 + \|\tilde{A}_0^*\|_2 &\leq \sqrt{5} (\gamma + b + \alpha) (\max(1, e^{b(\tau - \omega)}) + e^{b\tau}) \leq \bar{\gamma}_1 \\ &< |\mu_2(A_{0d}^*)| = \frac{1}{2} |\lambda_{\max}(A_{0d}^* + A_{0d}^{*T})| = |\lambda_{\max}(A_{0d}^*)| \\ &= b - \max(|\gamma_1 - \nu V_c|, \nu(1 - V_c)) \end{aligned} \quad (2.39)$$

The following result is proven from Proposition 2.1, the above asymptotic stability conditions for the linearized incremental system around the disease-free equilibrium point, which implies the local asymptotic stability of the nonlinear one from equations (2.1)-(2.5) about the equilibrium point, and the related former discussion for being small enough fulfilling equation (2.19):

Proposition 2.3. *Assume that $\beta \leq (\gamma + b + \alpha)e^{b\tau} \frac{b(1+\eta)\nu}{b(1+\delta)}$. Then it exists a sufficiently large $b > \max(|\gamma_1 - \nu V_c|, \nu(1 - V_c))$ such that the disease-free equilibrium point is locally asymptotically stable for any constant vaccination $V_c \in [0, 1]$ and a sufficiently small amount $(\gamma + b + \alpha)$, a sufficiently small delay τ and a sufficiently small difference delay $(\tau - \omega)$ (this being applicable if) such that equation (2.39) holds.*

An alternative result to Proposition 2.3 concerned with the asymptotic stability of the linearized SVEIRS model (and then the local asymptotic of that of the nonlinear SVEIR model) around the disease-free equilibrium for sufficiently small delays based on their parameterized quotient is given and proven in Appendix B. The result and its proof are based on an existence theorem of the first destabilizing delay and the use of the Jacobian matrix of the linearized system around the disease-free equilibrium. A more general related result can be obtained from equation (2.18), rather than from equation (2.19), without involving any "a priori" constraint on the transmission constant. By using equation (2.18), the following changes appear in the parameterization (2.22)-(2.25) of the linearized system around the disease-free equilibrium with the auxiliary real constant being defined in (2.18):

$$\left(\tilde{A}_{0d}^*\right)_{34} = \beta K^*, (A_\tau^*)_{44} = \beta e^{-b\tau} K^*, (A_\omega^*)_{34} = -\beta e^{-b\omega} K^* \quad (2.40)$$

The basic relation from equation (2.36) used for stability independent of the delays in Proposition 2.3 becomes accordingly modified as follows:

$$\begin{aligned} \|A_\tau^*\|_2 + \|A_\omega^*\|_2 + \|\tilde{A}_0^*\|_2 &\leq \sqrt{5} \left(\|A_\tau^*\|_\infty + \|A_\omega^*\|_\infty + \|\tilde{A}_0^*\|_\infty \right) \\ &\leq \sqrt{5} \left(\beta (1 + e^{-b\tau}) K^* + e^{-b\omega} \max(\gamma, \beta K^*) \right) \end{aligned} \quad (2.41)$$

$$\leq \sqrt{5} \left(\frac{2\beta}{1+\eta} + \max\left(\gamma, \frac{\beta}{1+\eta}\right) \right) \leq \tilde{\gamma}_1 \text{ (as } b \rightarrow \infty) \quad (2.42)$$

where (2.41) holds for any positive parameter b and equation (2.42) holds as such a parameter tends to infinity and also for a sufficiently large parameter b since $K^* \rightarrow \frac{1}{1+\eta} < 1$ as $b \rightarrow \infty$ from (2.18). Thus, for a sufficiently large $b_M \in \mathbb{R}_+$ and $b \geq b_M$, $\tilde{\gamma}_1$ may be taken as follows:

$$\tilde{\gamma}_1 = \sqrt{5} \max\left(\frac{2\beta}{1+\eta} + \gamma, \frac{3\beta}{1+\eta}\right) \quad (2.43)$$

and the former stability sufficient condition (2.39), derived from (2.19), is modified as follows for the general case from (2.18):

$$\|A_\tau^*\|_2 + \|A_\omega^*\|_2 + \|\tilde{A}_0^*\|_2 \leq \sqrt{5} \left(\frac{2\beta}{1+\eta} + \max\left(\gamma, \frac{\beta}{1+\eta}\right) \right) \leq \tilde{\gamma}_1 \quad (2.44)$$

$$\leq b - \max(|\gamma_1 - \nu V_c|, \nu(1 - V_c)) \quad (2.45)$$

Proposition 2.4. *Assume that $b > \max(b_M, \max(|\gamma_1 - \nu V_c|, \nu(1 - V_c)))$ and equation (2.45) holds. Then it exists a sufficiently large $b_M \in \mathbb{R}_+$ such that the disease-free equilibrium point is locally asymptotically stable for any constant vaccination $V_c \in [0, 1]$ such that (2.45) holds.*

Note that the statement of Propositions 2.3-2.4 guarantee the local stability of the disease-free equilibrium point under its existence condition of Proposition 2.1 requiring $\nu < b$.

2.4 Endemic equilibrium points and some characterizations

The existence of endemic equilibrium points which keep alive the disease propagation is now discussed:

Proposition 2.5. *Assume that $\omega > 0$. Then, the following properties hold:*

- i) *Assume $\beta \geq \frac{\eta e^{b\tau}(\gamma+b+\alpha)}{1+\delta}$ for $V_c > 0$ and $\beta \geq \eta e^{b\tau}(\gamma+b+\alpha)$ for $V_c = 0$. It exists at least one endemic equilibrium point at which the susceptible, vaccinated, infected, exposed and recovered subpopulations are positive and the vaccinated population is zero if and only if $V_c = 0$ (i.e. in the absence of vaccination action). Furthermore, such an equilibrium point satisfies the constraints:*

$$\begin{aligned} E^* &= \frac{\beta}{b} (1 - e^{-b\omega}) \left(\frac{S^*}{1 + \eta S^*} + \frac{\delta V^*}{1 + \eta V^*} \right) I^* > 0 \\ \min \left(S^* + \delta V^*, \frac{1 + \delta}{\eta} \right) &\geq \frac{S^*}{1 + \eta S^*} + \frac{\delta V^*}{1 + \eta V^*} = \frac{\gamma + b + \alpha}{\beta e^{-b\tau}} > 0 \\ R^* &= \frac{\gamma_1 V^* + \gamma (1 - e^{-b\omega}) I^*}{b} \geq \frac{\gamma (1 - e^{-b\omega}) I^*}{b} > 0 \end{aligned}$$

- ii) *If the transmission constant is small enough satisfying $\beta < \bar{\beta} := \frac{\eta e^{b\tau}(\gamma+b+\alpha)}{1+\delta}$ for $V_c > 0$ and $\beta < \eta e^{b\tau}(\gamma+b+\alpha)$ for $V_c = 0$ then there is no reachable endemic equilibrium point.*

Proof.

The endemic equilibrium point is calculated as follows:

$$0 = \beta e^{-b\tau} \left(\frac{S^*}{1 + \eta S^*} + \frac{\delta V^*}{1 + \eta V^*} \right) - (\gamma + b + \alpha) \quad (2.46)$$

$$E^* = \frac{\beta}{b} (1 - e^{-b\omega}) \left(\frac{S^*}{1 + \eta S^*} + \frac{\delta V^*}{1 + \eta V^*} \right) I^* > 0 \quad (2.47)$$

with

$$E^* > 0, \quad I^* > 0 \quad (2.48)$$

$$\left(\frac{S^*}{1 + \eta S^*} + \frac{\delta V^*}{1 + \eta V^*} \right) = \frac{(\gamma + b + \alpha)}{\beta e^{-b\tau}} > 0 \quad (2.49)$$

(since, otherwise, the above disease-free equilibrium point would be being considered). $S^* > 0$ since, otherwise, the following contradiction would follow:

$$0 < b + \gamma I^* e^{-b\omega} + \nu N^* (1 - V_c) = 0 \quad (2.50)$$

$V^* = 0$ if and only if $V_c = 0$, since otherwise for $V_c > 0$ and $V^* = 0$, it would follow that $\nu N^* V_c = 0$ which is only possible in the disease-free equilibrium point if the total population is extinguished, which is a contradiction at the endemic point.

$$R^* = \frac{\gamma_1 V^* + \gamma(1 - e^{-b\omega}) I^*}{b} \geq \frac{\gamma(1 - e^{-b\omega}) I^*}{b} > 0 \text{ for } \omega \neq 0 \quad (2.51)$$

Property (i) has been proven. Property (ii) follows from the fact that the second separate condition for the endemic equilibrium point in Property (i) fails if

$$\frac{1}{1 + \eta} < \frac{e^{b\tau} (\gamma + b + \alpha)}{\beta} \text{ for } V_c = 0$$

$$\frac{1 + \delta}{1 + \eta} < \frac{(\gamma + b + \alpha)}{\beta e^{-b\tau}} \text{ for } V_c > 0$$

since $S^* = V^* = 0$ is impossible at the endemic equilibrium point from such second condition of Property (i). Hence, the proof of Property (ii). \square

Remark 2.6.

Note that if $\omega = 0$ then it follows from (2.3) and (2.8) that $E(t) = E^* = 0; \forall t \in \mathbb{R}_{0+}$ so that the SVEIRS model from equations (2.1)-(2.5) becomes a simpler SVIRS one without specification of the exposed subpopulation dynamics.

Remark 2.7.

Note that, under the constraints in Proposition 2.5(ii) for $\alpha_S^{-1} + \alpha_V^{-1} + \alpha_E^{-1} + \alpha_I^{-1} + \alpha_R^{-1} = 1$, being $\alpha_S = N^*/S^*$, $\alpha_V = N^*/V^*$, $\alpha_E = N^*/E^*$, $\alpha_I = N^*/I^*$, $\alpha_R = N^*/R^*$, if there is no reachable endemic equilibrium point because $\beta < \bar{\beta}$, then the solution trajectory of equations (2.1)-(2.5) can only either converge to the disease-free equilibrium point, provided that it is at least locally asymptotically stable, or to be bounded (converging or not) to an oscillatory solution, or to diverge to an unbounded total population depending on the values of the parameterization of the model from equations (2.1)-(2.5).

Note that the endemic free transmission constant upper-bound $\bar{\beta}$ increases as η , τ and $(\gamma + b + \alpha)$ increase and also as δ decreases. If $V_c > 0$ then it follows from Proposition 2.5 that there exist positive constants $\alpha_S, \alpha_V, \alpha_E, \alpha_I$ and α_R satisfying $\alpha_S^{-1} + \alpha_V^{-1} + \alpha_E^{-1} + \alpha_I^{-1} + \alpha_R^{-1} = 1$ such that the endemic equilibrium points, if any, satisfy the constraints:

$$N^* = \alpha_S S^* = \alpha_V V^* = \alpha_E E^* = \alpha_I I^* = \alpha_R R^* \quad (2.52)$$

so that, one gets from (2.51) that

$$R^* = \frac{\gamma_1/\alpha_V + \gamma(1 - e^{-b\omega})/\alpha_I}{b} \alpha_R R^* = \frac{\gamma_1 \alpha_I + \gamma(1 - e^{-b\omega}) \alpha_V}{b \alpha_I \alpha_V} \alpha_R R^* \quad (2.53)$$

$$\frac{\beta}{b} (1 - e^{-b\omega}) \frac{1 + \delta}{1 + \eta} \leq \frac{E^*}{I^*} = \frac{\alpha_I}{\alpha_E} = \frac{\beta}{b} (1 - e^{-b\omega}) \left(\frac{S^*}{1 + \eta S^*} + \frac{\delta V^*}{1 + \eta V^*} \right)$$

$$\leq \frac{\beta}{b} (1 - e^{-b\omega}) \frac{1 + \delta}{\eta} \quad (2.54)$$

if $\min(S^*, V^*) \geq 1$, otherwise, only the upper-bounding constraint holds strictly in equation (2.54). Moreover, equations (2.6) and (2.46) may be equivalently written, respectively, as

$$b - \left(b + \frac{\beta\alpha_S S^*}{\alpha_I(1 + \eta S^*)} \right) S^* + \gamma \frac{\alpha_S}{\alpha_I} S^* e^{-b\omega} + \nu\alpha_S S^* (1 - V_c) = 0 \quad (2.55)$$

$$\frac{\alpha_V V^*}{\alpha_S + \alpha_V \eta V^*} + \frac{\delta V^*}{1 + \eta V^*} = \frac{\gamma + b + \alpha}{\beta e^{-b\tau}} \quad (2.56)$$

Equation (2.53) is equivalent, since $R^* > 0$ at the endemic equilibrium point, to

$$\frac{\gamma_1 \alpha_I \alpha_R + \gamma (1 - e^{-b\omega}) \alpha_V \alpha_R}{b \alpha_I \alpha_V} = 1 \quad (2.57)$$

Equation (2.55) is equivalent to

$$\begin{aligned} & [\alpha_S \eta (\nu \alpha_I (1 - V_c) + \gamma e^{-b\omega}) + \beta \alpha_S - b \alpha_I \eta] S^{*2} \\ & + [\alpha_S (\gamma e^{-b\omega} + \nu \alpha_I (1 - V_c)) + b \alpha_I (\eta - 1)] S^* + b \alpha_I = 0 \end{aligned} \quad (2.58)$$

Equation (2.58) is an algebraic equation of real coefficients of the form

$$aS^{*2} + dS^* + c = 0 \text{ with } c > 0$$

Such an equation has two positive real roots if $a > 0$, $d < 0$ and $d^2 \geq 4ac$ and one positive real root if $a < 0$ and $d > 0$. Thus, since there is a nonzero susceptible subpopulation at an endemic equilibrium point then either (2.59)-(2.61) below hold:

$$\alpha_S \eta (\nu \alpha_I (1 - V_c) + \gamma e^{-b\omega}) + \beta \alpha_S > b \alpha_I \eta \quad (2.59)$$

$$\alpha_S (\gamma e^{-b\omega} + \nu \alpha_I (1 - V_c)) < b \alpha_I (1 - \eta) \text{ provided that } \eta < 1 \quad (2.60)$$

$$[\alpha_S \gamma e^{-b\omega} + \nu \alpha_I (1 - V_c) + b \alpha_I (\eta - 1)]^2 \geq 4b \alpha_I [\alpha_S \eta (\nu \alpha_I (1 - V_c) + \gamma e^{-b\omega}) + \beta \alpha_S - b \alpha_I \eta] \quad (2.61)$$

or, alternatively,

$$\beta < \frac{\alpha_I}{\alpha_S} b \eta - (\nu \alpha_I (1 - V_c) + \alpha e^{-b\omega}) \eta = \frac{\eta}{I^*} [b S^* - (\nu N^* (1 - V_c) + \gamma e^{-b\omega})] \quad (2.62)$$

and

$$b < \frac{\alpha_S (\gamma e^{-b\omega} + \nu \alpha_I (1 - V_c))}{\alpha_I (1 - \eta)} = \frac{\gamma e^{-b\omega} I^* + \nu N^* (1 - V_c)}{S^* (1 - \eta)} \quad (2.63)$$

with $\eta < 1$ hold. On the other hand, the equation in (2.56) is equivalent to

$$\alpha_V \beta_0 (1 + \eta V^*) V^* + \delta \beta_0 V^* (\alpha_S + \eta \alpha_V V^*) = (1 + \eta V^*) (\alpha_S + \eta \alpha_V V^*) \quad (2.64)$$

where $\beta_0 := \frac{\beta e^{-b\tau}}{\gamma + b + \alpha}$ so that (2.64) is of the form

$$aV^{*2} + dV^* + c \equiv \eta(\eta - (1 + \delta)\beta_0)\alpha_V V^{*2} + (\alpha_V(\eta - \beta_0) + (\eta - \delta\beta_0)\alpha_S)V^* + \alpha_S = 0$$

(2.65)

Now, a close reasoning to that used for the susceptible endemic equilibrium component is applied to (2.65) to construct the subsequent reasoning for a potential nonzero vaccinated subpopulation at most two possibly existing endemic equilibrium points. Note that either

$$\begin{aligned}
\alpha_V \eta (\eta - (1 + \delta) \beta_0) &> 0 \iff \beta_0 < \frac{\eta}{1 + \delta}, \\
\alpha_V (\eta - \beta_0) + \alpha_S (\eta - \delta \beta_0) &= \eta (\alpha_V + \alpha_S) - \beta_0 (\alpha_V + \delta \alpha_S) < 0 \\
&\iff \beta_0 > \eta \frac{\alpha_V + \alpha_S}{\alpha_V + \delta \alpha_S} \\
&\iff \beta > \eta \frac{\alpha_V + \alpha_S}{\alpha_V + \delta \alpha_S} (\alpha + b + \alpha) e^{b\tau}
\end{aligned} \tag{2.66}$$

and

$$(\alpha_V (\eta - \beta_0) + \alpha_S (\eta - \delta \beta_0))^2 > 4 (\eta - (1 + \delta) \beta_0) \eta \alpha_V \alpha_S \tag{2.68}$$

or, alternatively,

$$\begin{aligned}
\alpha_V \eta (\eta - (1 + \delta) \beta_0) &< 0 \iff \beta_0 > \frac{\eta}{1 + \delta} \\
\alpha_V (\eta - \beta_0) + \alpha_S (\eta - \delta \beta_0) &> 0 \\
&\iff \beta_0 < \eta \frac{\alpha_V + \alpha_S}{\alpha_V + \delta \alpha_S} \\
&\iff \beta < \eta \frac{\alpha_V + \alpha_S}{\alpha_V + \delta \alpha_S} (\alpha + b + \alpha) e^{b\tau}
\end{aligned} \tag{2.69}$$

However, note that (2.67)-(2.68) imply that

$$\eta \frac{\alpha_V + \alpha_S}{\alpha_V + \delta \alpha_S} < \beta_0 = \frac{\beta e^{-b\tau}}{\alpha + b + \alpha} < \frac{\eta}{1 + \delta} \tag{2.71}$$

which is well-posed if and only if $\delta < \frac{-\alpha_S}{\alpha_V} < 0$ which contradicts the positivity of the parameter δ . As a result, only the alternative constraints (2.69)-(2.70) need to be considered with a non-zero vaccinated subpopulation at the endemic equilibrium point which is always the case under a nonzero regular constant vaccination $V_c \leq 1$. The above discussion concerning the endemic equilibrium point is summarized as follows:

Proposition 2.8. *Assume that $V_c \in (0, 1]$ and that $\beta \geq (\alpha + b + \alpha) \frac{\eta e^{b\tau}}{1 + \delta}$ so that $N^* = \alpha_S S^* = \alpha_V V^* = \alpha_E E^* = \alpha_I I^* = \alpha_R R^*$ for some positive constants $\alpha_S, \alpha_V, \alpha_E, \alpha_I$ and α_R . Then, it exists at least one endemic equilibrium point, and at most two endemic equilibrium points, with all the corresponding subpopulations being positive and the following parametrical constraints hold:*

$$\alpha_S^{-1} + \alpha_V^{-1} + \alpha_E^{-1} + \alpha_I^{-1} + \alpha_R^{-1} = 1, \quad \alpha_I / \alpha_E \leq \frac{\beta}{b} (1 - e^{-b\omega}) \frac{1 + \delta}{\eta} \tag{2.72}$$

Also, the constants α_S, α_I and α_V satisfy either (2.59)-(2.61), or (2.62)-(2.63), and (2.69)-(2.70).

Remark 2.9.

Note that if $\min(S^*, V^*) \geq 1$ then

$$(\gamma + b + \alpha) e^{b\tau} \frac{\eta}{1 + \delta} \leq \beta \leq (\gamma + b + \alpha) e^{b\tau} \frac{1 + \eta}{1 + \delta} \quad (2.73)$$

This implies that the coefficient 'a' in (2.65) is non-positive. If $a = 0$ then

$$V^* = \frac{\alpha_S}{|\alpha_V (\eta - \beta_0) + (\eta - \delta\beta_0) \alpha_S|} > 0 \text{ if } \alpha_V (\eta - \beta_0) + (\eta - \delta\beta_0) \alpha_S < 0$$

This implies that $\beta_0 > \eta \frac{\alpha_V + \alpha_S}{\alpha_V + \delta\alpha_S}$ which is compatible with equation (2.73) if

$$\beta \geq (\gamma + b + \alpha) \eta e^{b\tau} \max \left(\frac{1}{1 + \delta}, \frac{\alpha_V + \alpha_S}{\alpha_V + \delta\alpha_S} \right) \quad (2.74)$$

and $\eta \leq \frac{\alpha_V + \alpha_S}{\alpha_V + \delta\alpha_S}$, so that $\eta \frac{\alpha_V + \alpha_S}{\alpha_V + \delta\alpha_S} \leq \frac{1 + \eta}{1 + \delta}$.

Also, if $a < 0$ then $\beta < \eta \frac{\alpha_V + \alpha_S}{\alpha_V + \delta\alpha_S} e^{b\tau} (\gamma + b + \alpha)$ from (2.70) which is coherent with (2.73) if

$$\beta \leq (\gamma + b + \alpha) e^{b\tau} \min \left(\frac{1 + \eta}{1 + \delta}, \eta \frac{\alpha_V + \alpha_S}{\alpha_V + \delta\alpha_S} \right) \quad (2.75)$$

since $\frac{1}{1 + \delta} \leq \frac{\alpha_V + \alpha_S}{\alpha_V + \delta\alpha_S}$ for any $\delta > 0$, $\min(\alpha_V, \alpha_S) > 1$.

The existence of a unique endemic equilibrium point under zero vaccination is dealt with in Appendix C.

2.5 About infection propagation, the uniform boundedness of the total population and the positivity of the subpopulations

This section discusses briefly the monotone increase of the infected subpopulation and the boundedness of the total population as well as the positivity of the model:

Proposition 2.10.

If the infection propagates through with the infected subpopulation being non-decreasing then $\frac{S(\sigma)}{1 + \eta S(\sigma)} + \frac{\delta V(\sigma)}{1 + \eta V(\sigma)} \geq \frac{\gamma + b + \alpha}{\beta} e^{b\sigma}, \forall \sigma \in (t^* - 2\tau, t^* - \tau)$

Proof.

Note from (2.4) that for $t \in (t^* - 2\tau, t^*)$

$$\dot{I}(t) > 0 \Leftrightarrow \frac{I(t)}{I(t - \tau)} < \frac{\beta e^{-b\tau}}{\gamma + b + \alpha} \left(\frac{S(t - \tau)}{1 + \eta S(t - \tau)} + \frac{\delta V(t - \tau)}{1 + \eta V(t - \tau)} \right)$$

and if, furthermore, $I(t) \geq I(t - \tau)$ for $t \in (t^* - \tau, t^*)$, thus

$$1 \leq \frac{I(t)}{I(t - \tau)} < \frac{\beta e^{-b\tau}}{\gamma + b + \alpha} \left(\frac{S(t - \tau)}{1 + \eta S(t - \tau)} + \frac{\delta V(t - \tau)}{1 + \eta V(t - \tau)} \right)$$

□

Now, rewrite (2.3) in differential equivalent form by using Leibniz' s rule as follows:

$$\dot{E}(t) = -bE(t) + \beta \left[\left(\frac{S(t)}{1 + \eta S(t)} + \frac{\delta V(t)}{1 + \eta V(t)} \right) - \left(\frac{S(t - \omega)}{1 + \eta S(t - \omega)} + \frac{\delta V(t - \omega)}{1 + \eta V(t - \omega)} \right) e^{-b\omega} \right] \quad (2.76)$$

Proposition 2.11. *Assume that $\nu < b$. Then, the following properties hold provided that the SVEIR epidemic model (2.1)-(2.5) has non-negative solution trajectories of all the subpopulations for all time:*

- i) *Assume furthermore that $\psi := e^{\nu\tau} + \frac{\beta(1+\delta)(1-e^{-(b-\nu)\tau})}{\eta(b-\nu)} e^{-b\tau} < 1$. Then, the total population is uniformly bounded for all time, irrespective of the susceptible and vaccinated subpopulations, for any bounded initial conditions and*

$$\limsup_{t \rightarrow \infty} N(t) \leq \frac{1 - e^{-(b-\nu)\tau}}{b - \nu} (1 - \psi)^{-1} < \infty$$

- ii) *Assume that the transmission constant is large enough satisfying*

$$\beta \geq \frac{1}{1 + \delta} \sup_{t \in \mathbb{R}_{0+}} \left(\frac{b\eta(1 + \eta)}{\eta e^{-b\omega} I(t - \omega) - (1 + \eta)e^{-b\tau} I(t - \tau)} \right)$$

subject to $\frac{\eta}{1 + \eta} > e^{b(\omega - \tau)}$ and $\omega < \tau$. Then $N : \mathbb{R}_{0+} \rightarrow \mathbb{R}_{0+}$ is monotone decreasing and of negative exponential order so that the total population exponentially extinguishes as a result.

Proof.

Consider the SVEIRS model in differential form described in equations (2.1)-(2.2), (2.4)-(2.5) and (2.76). Summing up the five equations, one gets directly:

$$\begin{aligned} \dot{N}(t) &= (\nu - b)N(t) + b - \alpha I(t) \\ &+ \beta \left[\left(\frac{S(t - \tau)}{1 + \eta S(t - \tau)} + \frac{\delta V(t - \tau)}{1 + \eta V(t - \tau)} \right) e^{-b\tau} I(t - \tau) \right. \\ &\left. - \left(\frac{S(t - \omega)}{1 + \eta S(t - \omega)} + \frac{\delta V(t - \omega)}{1 + \eta V(t - \omega)} \right) e^{-b\omega} I(t - \omega) \right] \end{aligned} \quad (2.77)$$

$$\begin{aligned} &\leq (\nu - b)N(t) + b + \beta \left(\frac{S(t - \tau)I(t - \tau)}{1 + \eta S(t - \tau)} + \frac{\delta V(t - \tau)I(t - \tau)}{1 + \eta V(t - \tau)} \right) e^{-b\tau} \\ &\leq (\nu - b)N(t) + b + \beta \frac{1 + \delta}{\eta} e^{-b\tau} I(t - \tau) \\ &\leq \nu - bN(t) + b + \beta \frac{1 + \delta}{\eta} e^{-b\tau} N(t - \tau) \end{aligned} \quad (2.78)$$

since

$$\frac{S(t)}{1 + \eta S(t)} + \frac{\delta V(t)}{1 + \eta V(t)} \leq \frac{1 + \delta}{\eta}; \forall t \in \mathbb{R}_{0+}$$

Then, $N(t) \leq \psi \left(\sup_{t - \tau \leq \sigma \leq t} N(\sigma) + \frac{b(1 - e^{-(b-\nu)\tau})}{b - \nu} \right) < \infty; \forall t \in \mathbb{R}_{0+}$ and Property (i) follows since $\psi < 1$. Two cases are now discussed separately concerning the proof of Property 2.11(ii):

- i) Note that if the solution trajectory is positive subject to $\min(S(t), V(t)) \geq 1$ (equivalently if $\max(S^{-1}(t), V^{-1}(t)) \leq 1$) then

$$0 < \frac{1 + \delta}{1 + \eta} \leq \frac{S(t)}{1 + \eta S(t)} + \frac{\delta V(t)}{1 + \eta V(t)} \leq \frac{1 + \delta}{\eta} \quad (2.79)$$

so that one gets:

$$\begin{aligned} \dot{N}(t) &\leq (\nu - b)N(t) - \alpha I(t) + \left(b - \beta \left[\frac{1 + \delta}{1 + \eta} I(t - \omega) e^{-b\omega} - \frac{1 + \delta}{\eta} I(t - \tau) e^{-b\tau} \right] \right) \\ &\leq -(b - \nu)N(t) - \alpha I(t) \leq -(b - \nu)N(t) < 0 \end{aligned} \quad (2.80)$$

if $N(t) > 0$ since $b > \nu$ and $N(t) = 0$ if and only if $N(t) = I(t) = 0$ since $\beta \geq \frac{1}{1 + \delta} \frac{b\eta(1 + \eta)}{\eta e^{-b\omega} I(t - \omega) - (1 + \eta) I(t - \tau) e^{-b\tau}} > 0$ provided that $\frac{\eta}{1 + \eta} > e^{b(\omega - \tau)}$ with $\omega < \tau$. Then

$$N(t) \leq e^{-(b - \nu)t} N(0) < N(t'); \forall t, t' < t \in \mathbb{R}_{0+}$$

- ii) If $\max(S(t), V(t)) \leq 1$ (equivalently, if $\min(S^{-1}(t), V^{-1}(t)) \geq 1$) then

$$0 < \frac{1 + \delta}{1 + \eta} \leq \frac{S(t)}{1 + \eta S(t)} + \frac{\delta V(t)}{1 + \eta V(t)} \leq \frac{1 + \delta}{1 + \eta} \leq \frac{1 + \delta}{\eta} \quad (2.81)$$

so that (2.80) still holds and the same conclusion arises. Thus, Property (ii) is proven. \square

A brief discussion about positivity is summarized in the next result:

Proposition 2.12. *Assume that $V_c \in [0, 1]$. Then, the SVEIRS epidemic model from equations (2.1)-(2.5) is positive in the sense that no subpopulation is negative at any time, if its initial conditions are non-negative and the vaccinated subpopulation exceeds a certain minimum measurable threshold in the event that the recovered population is zero as follows: $V(t) \geq \max\left(\frac{\gamma}{\gamma_1} I(t - \omega) e^{-b\omega} - I(t), 0\right)$ if $R(t) = 0$. The susceptible, vaccinated, exposed and infected subpopulations are non-negative for all time irrespective of the above constraint. If, in addition, Proposition 2.11 (i) holds then all the subpopulations of the SVEIRS model are uniformly bounded for all time. Proof.*

First note that all the subpopulations are defined by continuous- time differentiable functions from (2.1)-(2.5). Then, if any subpopulation is negative, it is zero at some previous time instant. Assume that $S(\sigma) \geq 0$ for $\sigma < t$ and $S(t) = 0$ at some time instant t . Then from (2.1):

$$\dot{S}(t) = b + \gamma I(t - \omega) e^{-b\omega} + \nu(1 - V_c)N(t) \geq 0; \forall V_c \in [0, 1]$$

Thus, $S(t^+) \geq 0$. As a result, $S(t)$ cannot reach negative values at any time instant. Assume that $V(\sigma) \geq 0$ for $\sigma < t$ and $V(t) = 0$ at some time instant t . Then, $\dot{V}(t) =$

$\nu V_c N(t) \geq 0$ from (2.2) so that $V(t^+) \geq 0$. As a result, $V(t)$ cannot reach negative values at any time. $E(t) \geq 0$ for any time instant t from (2.3). Assume that $I(\sigma) \geq 0$ for $\sigma < t$ and $I(t) = 0$ at some time instant t . Then, $\dot{I}(t) \geq 0$ from (2.4). As a result, $I(t)$ cannot reach negative values at any time. Finally, assume that $R(\sigma) \geq 0$ for $\sigma < t$ and $R(t) = 0$ at some time instant t . Thus, $\dot{R}(t) = \gamma_1 V(t) + \gamma (I(t) - I(t - \omega)e^{-b\omega}) \geq 0$ from equation (2.5) if $V(t) \geq \max\left(\frac{\gamma}{\gamma_1} I(t - \omega)e^{-b\omega} - I(t), 0\right)$. Thus, if $V(t) \geq \max\left(\frac{\gamma}{\gamma_1} I(t - \omega)e^{-b\omega} - I(t), 0\right)$ when $R(t) = 0$ then all the subpopulations are uniformly bounded, since they are non-negative and the total population $N(t)$ is uniformly bounded from Proposition 2.11 (i). \square

2.6 Simulation results

This Section contains some simulation examples which are concerned with the existence and allocation of disease-free and endemic equilibrium points. The objective of these examples is to numerically show the potential existence of both types of equilibrium points and that the calculated values for their coordinates are given by the presented expressions. The particular values for the equilibrium points as well as the time taken by the model to converge to them depend on the specific choice of the parameter values which correspond to the particular disease under study and the species being considered in the epidemic model. For a different parameterization, these values would be different. Also, simulations have been run for a long time interval in order to show that the reached steady-state values are true equilibrium points. The parameters of the epidemic model are: $b = 0.05 \text{ days}^{-1}$, $1/\alpha = 1/\gamma = 200 \text{ days}$, $1/\gamma_1 = 15 \text{ days}$, $\beta_1 = \beta/2$, $\delta = \beta_1/\beta$, $\tau = 6 \text{ days}$, $\eta = 0.5$ and $\omega = 10 \text{ days}$. It can be pointed that in the case that the parameters for a particular epidemic model are unknown they can be estimated from the analysis of population data by using, either statistical methods [33], [34], or heuristic methods [35], or adaptive methods by using either batch or recursive parametrical estimation algorithms. See, for instance the works in [36], [37] being updated from collected real measured data on the subpopulations through time.

2.6.1 Disease-free equilibrium point

Consider now $\beta = 0.0166 \text{ days}^{-1}$ and $\nu = 0.2b$ and the initial subpopulations $S(0) = 250$, $V(0) = 150$, $E(0) = 150$, $I(0) = 250$, $R(0) = 200$. The two particular cases corresponding to $V_c = 0$ and $V_c = 1$ in Section 2.3 will be studied separately. Thus, the following simulations have been obtained for the SVEIR system from equations (2.1)-(2.5) and $V_c = 0$. Figure 2.3 shows a zoom on the equilibrium point reached by the model in Figure 2.2.

Note from Figures 2.2 and 2.3 that the vaccinated, exposed, infected and removed-

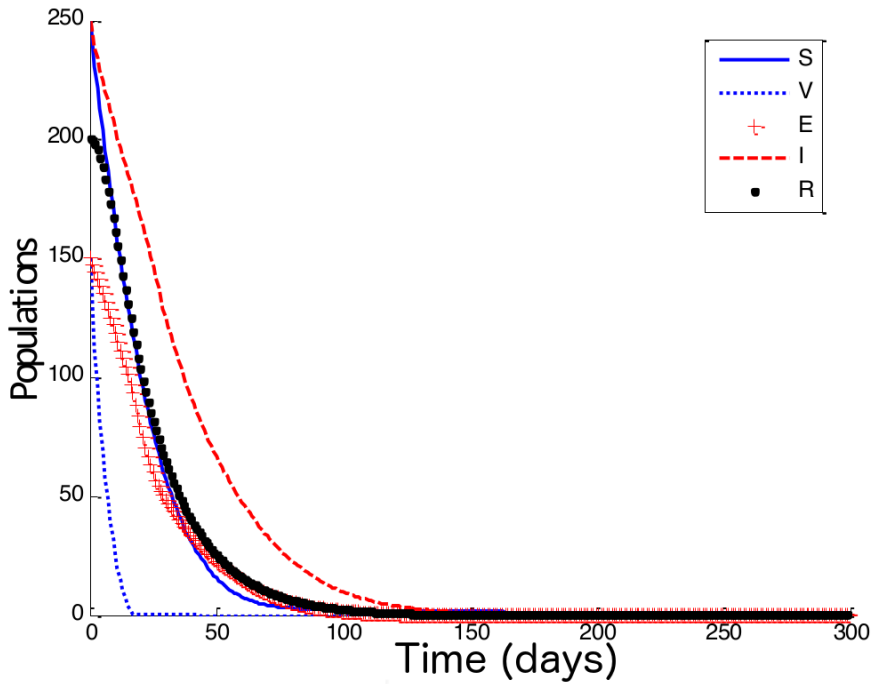


Figure 2.2: Solution trajectories for $V_c = 0$

by-immunity (recovered) populations converge to zero. This situation corresponds to the case when the disease is naturally eradicated from the population. On the other hand, the susceptible presents a different dynamics, converging to a non-zero equilibrium point. Figure 2.3 shows that the vaccinated, exposed, infectious and recovered populations are actually zero (which is represented by the superimposed graphics) while the susceptible converges to 1.25. Furthermore, these values correspond to the ones stated in Proposition 2.1 for $V_c = 0$, since all the populations vanish except the susceptible which converges to $S^* = \frac{b}{b-\nu} = 1.25$. If $V_c = 1$ then the solution trajectories converge to the equilibrium point as depicted in Figure 2.4.

In this case, only the exposed and infected tend to zero while the remaining subpopulations tend to the values calculated in Proposition 2.1 when $V_c = 1$:

$$S^* = 1, \quad V^* = \frac{\nu b}{(\gamma_1 + b)(b - \nu)} = 0.107$$

$$R^* = \frac{\nu \gamma_1}{(\gamma_1 + b)(b - \nu)} = 0.14 \quad E^* = I^* = 0$$

2.6.2 Endemic equilibrium point

In order to study the endemic equilibrium point, the value of β is changed now to a new value $\beta = 0.099$ satisfying the condition $\beta \geq \eta e^{b\tau} (\gamma + b + \alpha)$ stated in Proposition 2.5(i) for $V_c = 0$ and $\nu = 0.65b$. Thus, the model trajectory solutions are

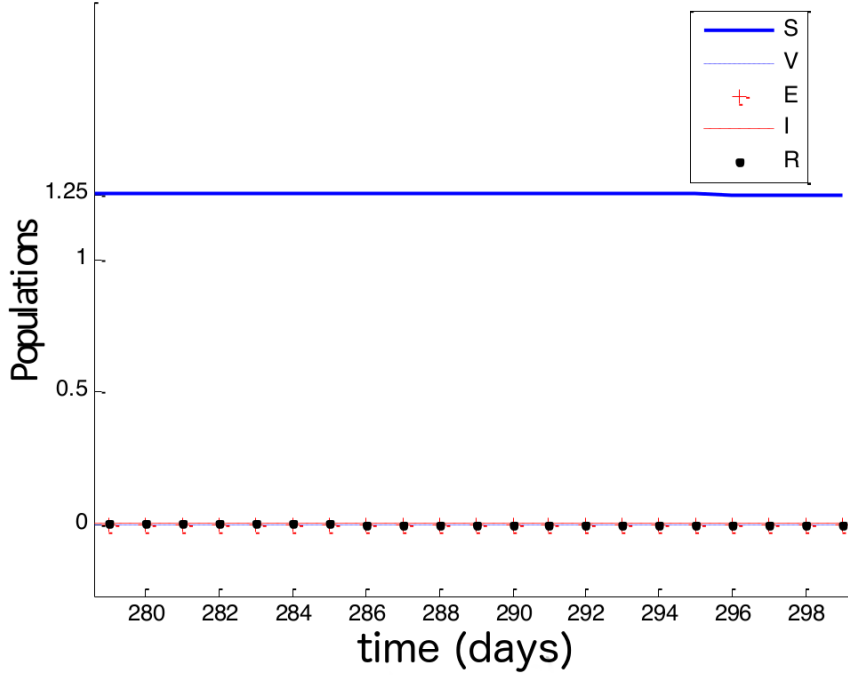


Figure 2.3: Zoom on the solution trajectories for the disease-free equilibrium point for $V_c = 0$

depicted in Figure 2.5:

A zoom on Figure 2.5 will show the equilibrium point of the system as represented in Figure 2.6. Figure 2.6 shows that there is an endemic equilibrium point, associated to non-zero populations of exposed and infectious, whose coordinates in view of Proposition 2.5(i) satisfy the constraints

$$E^* = \frac{\beta}{b}(1 - e^{-b\omega})\left(\frac{S^*}{1 + \eta S^*} + \frac{\delta V^*}{1 + \eta V^*}\right)I^* = 0.7$$

$$R^* = \frac{\gamma_1 V^* + \gamma(1 - e^{-b\omega})I^*}{b} = 0.043$$

while the remaining variables, which are not given explicitly in Proposition 2.5(i), are $I^* = 1.1$, $V^* = 0$ and $S^* = 1.38$. Thus, the validity of the results is numerically verified.

2.6.3 The epidemic model versus the evolution of fractional subpopulations

It is interesting to discuss the practical use of the model with fractional or percentage of populations with respect to a total population by making the model to be more versatile. Such fractions of the partial total populations can be taken, for instance, with respect to the initial total population of the habitat under study or with respect to that of the disease-free equilibrium. Note that in time-varying models or even

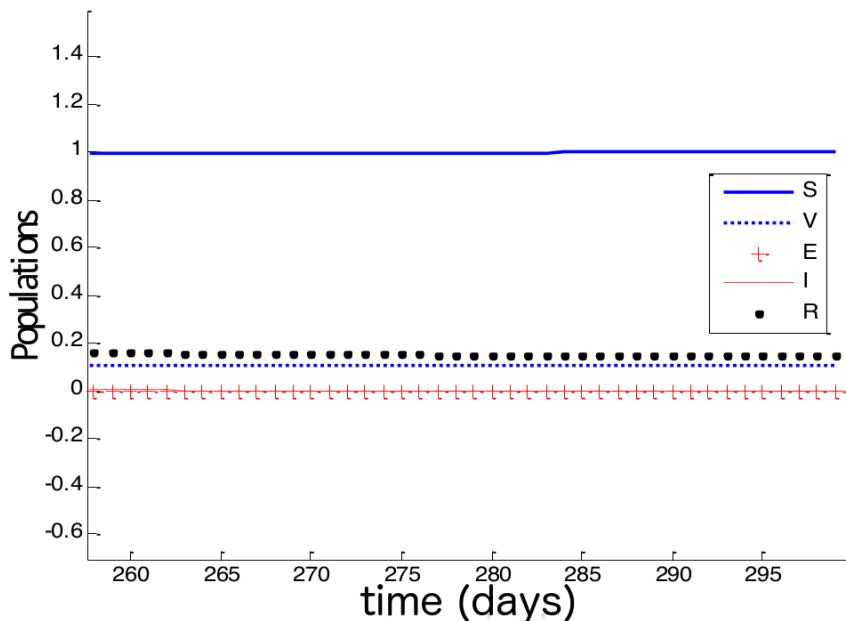


Figure 2.4: Disease-free equilibrium point for $V_c = 1$

in time-invariant ones with external interchange of population, newborn vaccination strategy or mortality associated with the disease, it can happen that overshoots and undershoots with respect to the unit Heaviside function of some of the total population evolution through time can occur. The reason is that the total population is not necessarily constant. The percentages of the subpopulations can be manipulated by using initial conditions in the model which are themselves percentages or by using absolute values of subpopulations and then displaying the percentage evolution of the subpopulations through time. A numerical simulation is made with initial conditions $S(0) = 25$, $V(0) = 15$, $E(0) = 15$, $I(0) = 25$, $R(0) = 20$. The parameters of the model are $b = 0.075 \text{ days}^{-1}$, $\nu = 0.995b < b$ and $N(0) = N^* = S^* = \frac{b}{b-\nu} = 200$. The results are depicted in Figure 2.7 and Figure 2.8 for $V_c = 0$ and $V_c = 1$, respectively. Figure 2.9 displays a zoom of the final evolution of the vaccinated and recovered subpopulations towards the disease-free equilibrium for $V_c = 1$.

2.7 Conclusions

The disease-free and endemic equilibrium points of a modified epidemic SVEIRS model of true-mass action type are studied, taking into account the loss of immunity of newborns. It contains potential latent and immune periods, which are internal delays in the model, and the total population is not considered constant, in general. A constant regular vaccination forcing term is incorporated to interchange numbers

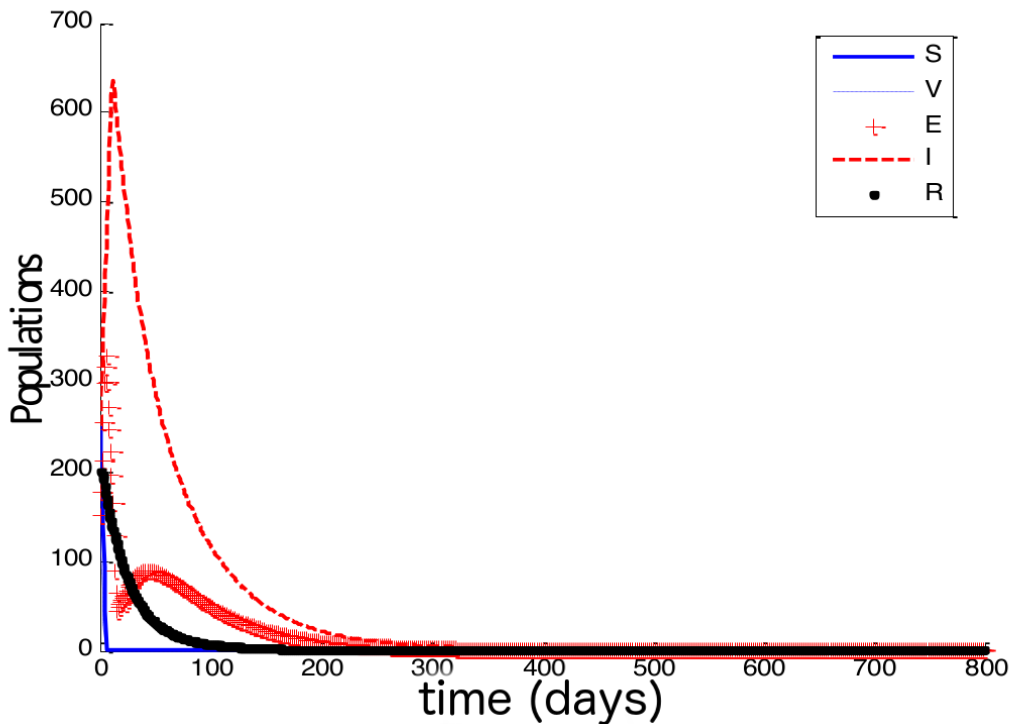


Figure 2.5: Solution trajectories converging to an endemic equilibrium point

of susceptible and vaccinated subpopulations. The incorporation of such term is one of the main novelties of the proposed SVEIRS model since they do not incorporate usually such a vaccination action . The existence and uniqueness of a disease-free equilibrium point as well as that of an endemic equilibrium point have been proven, and also, conditions of positivity and stability have been formulated and proven for reasonable constraints on the parameterization. A reproduction number-like threshold has been computed to elucidate the maintenance of the local asymptotic stability of the disease-free equilibrium for sufficiently small delays in the model. Roughly speaking, the disease-free equilibrium stability margin increases with the value of the constant vaccination while it decreases as the disease transmission constant increases. The main vaccination recommendation is to increase the constant vaccination effort as much as possible to a threshold value being compatible with the stability of the disease-free equilibrium point given by the threshold previously calculated. This strategy has a triple joint objective, namely,

- i) to increase the recovered subpopulation at a stable disease-free equilibrium point while jointly decreasing the susceptible one
- ii) to increase the effective value of the disease transmission constant being compatible with the stability of such an equilibrium, and
- iii) to avoid the convergence of the trajectory solutions to the endemic equilibrium point for larger values of the transmission constant compared to the case of absence of vaccination.

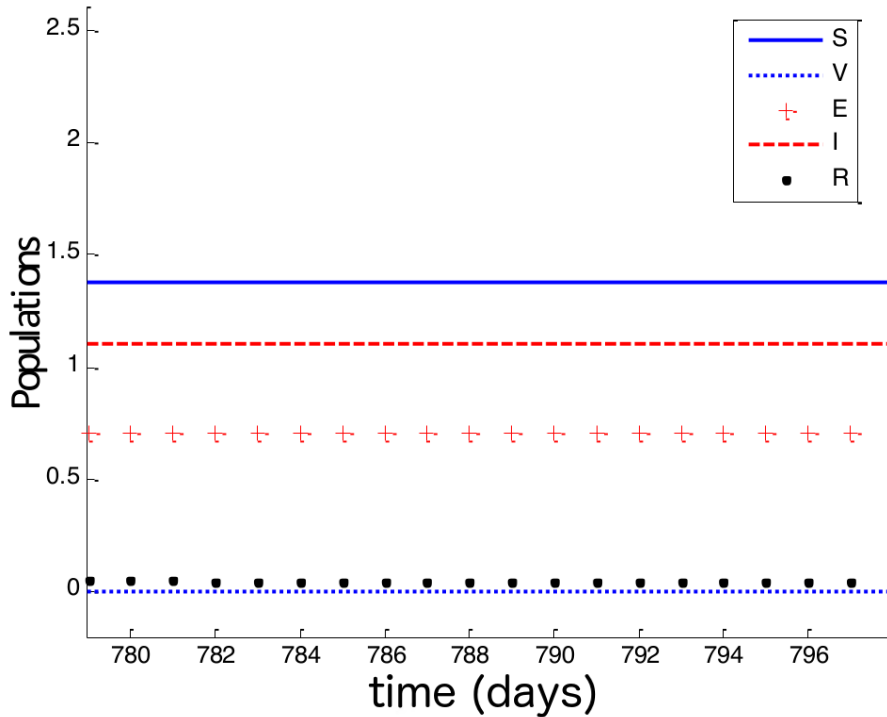


Figure 2.6: Zoom of the solution trajectories showing the endemic equilibrium point

After thinking in the use of the model in a practical way, provided that either the disease-free equilibrium point or the various formulas defining such an equilibrium are known, it is considered the followings:

- i) First, the concept that the susceptible, vaccinated and recovered disease-free equilibrium subpopulations are multiplicative coefficients of a given standard testing total population while, obviously, the exposed and infected populations are zero at a such stable disease-free equilibrium. This is a logical strategy to evaluate the subpopulations evolving through time, since their values are not ensured to be integer numbers without incorporating a discrete quantization model.
- ii) Secondly, to study the model simulations with values for the initial susceptible, vaccinated and recovered subpopulations being close to their corresponding above mentioned equilibrium coefficients, while the exposed and infected subpopulations are initially close to zero, but nonzero, (otherwise, the infection would never appear and propagate).
- iii) Run the model evolution through time. The total and the various subpopulations are calculated at any time instant with the various multiplicative coefficients applied to the standard testing population. This set up would be a logic scenario to model common infectious diseases since, in these situations, the exposed and infected subpopulations remain for all time within small deviations with respect

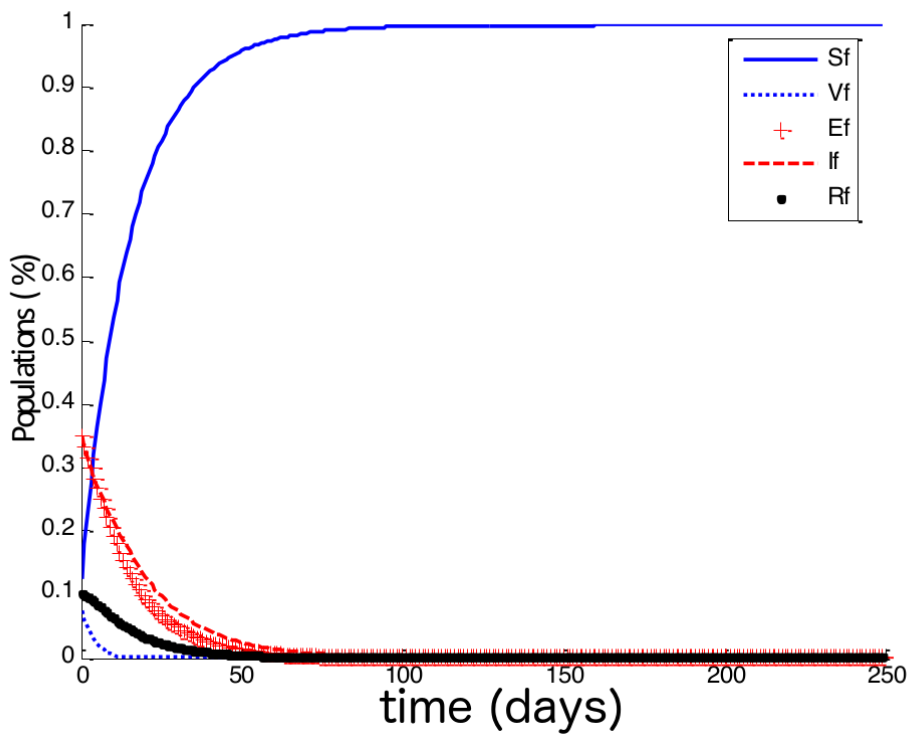


Figure 2.7: Percentages of populations evolving to the disease-free equilibrium point for $V_c = 0$

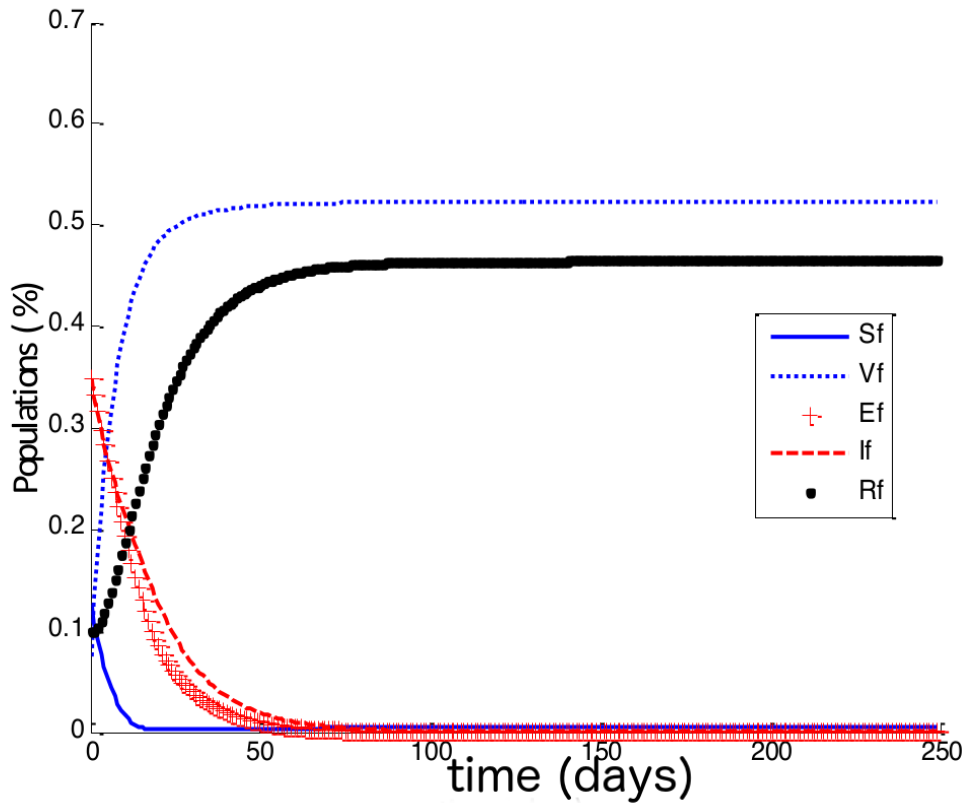


Figure 2.8: Percentages of populations evolving to the disease-free equilibrium point for $V_c = 1$

to the whole population under study.

A relevant extension of this formalism could be devoted to the incorporation of the hybrid modeling by a simultaneous consideration of both discrete-time modeling (for instance, for the dynamic of the system) and continuous time-modeling (for instance, for the vaccination effort). Hybrid systems are of greater interest in different problems of Control Theory because of their ability to a combined treatment of the formal accommodation and use of models which have continuous-time and discrete-time (or eventually digital) coupled dynamics or for the use of discrete-controllers operating on continuous time systems [38], [39], [40].

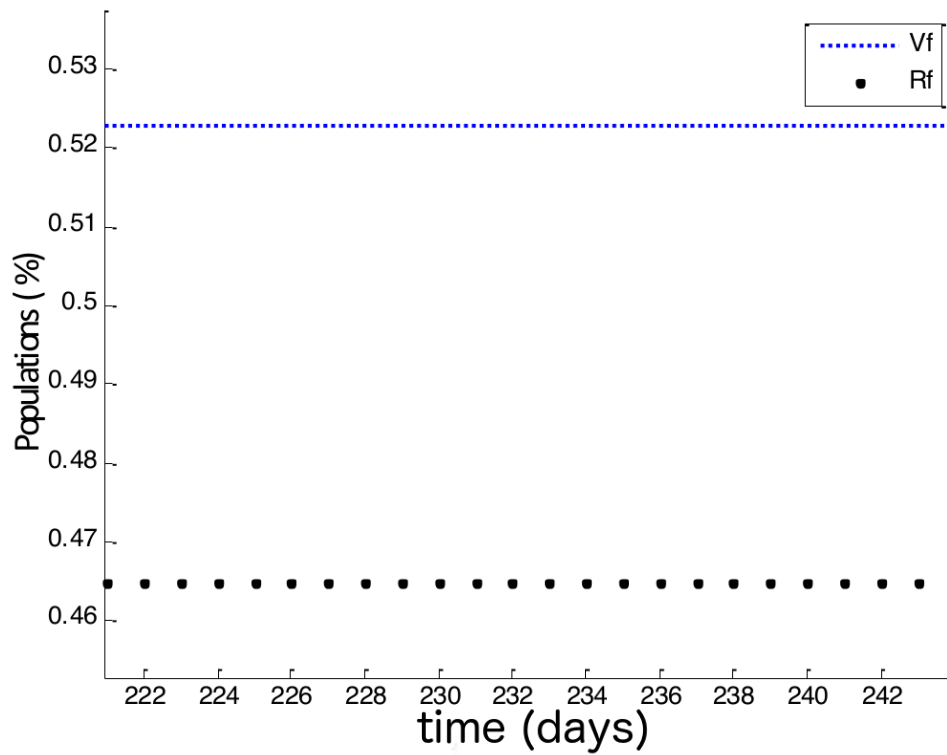


Figure 2.9: Zoom of the final evolution of the fractional vaccinated and recovered subpopulations towards the disease-free equilibrium point for $V_c = 1$

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On a generalized SVEIRS epidemic model under regular and adaptive impulsive vaccination

In this chapter, a SVEIRS model for a generic disease with incubation and recovered stages is proposed. It incorporates a vaccinated subpopulation, which presents a partial immunity to the disease. A study of the stability, periodic solutions and impulsive vaccination design is made in the SVEIRS model under impulsive and non-impulsive vaccination strategies. The effect of a regular impulsive vaccination on the evolution of the subpopulations is first studied and then, a non-regular impulsive vaccination strategy is introduced, based on an adaptive control law that changes the frequency and quantity of applied vaccines. Numerical simulations will show the efficiency of the later vaccination strategies and the rapid reduction of the infectious subpopulation over time, compared to a regular impulsive vaccinations with constant values.

3.1 Introduction

There is a network of interactions that define the spreading of any infectious disease. It usually involves different types of susceptible and infectious subpopulations [1]-[5] as well as the transitions between them. These transitions and the system dynamics derived from them strongly depend on the type of disease and the circumstances in which it is transmitted, such as the number of different hosts susceptible to the infection and the development of the infectious disease in each of those subpopulations [6]. Infectious disease have been modeled and described in many papers both in the absence of vaccination and with different vaccination strategies. The use of impulsive vaccination is also considered, and several design methods are provided to adjust both the inter-vaccination time period and the fraction of vaccinated population. Also, a reproduction number is developed to describe the stability of the periodic regime. Consequently, the resulting mathematical model introduces two types of susceptible subpopulation with different incidence rates of contagion: the susceptible and the vaccinated subpopulation [7]-[10]. Moreover, there are two classes of infected subpopulations since the infectious process is divided in two stages. The primary stage assumes that the infectious agent is already inside the host but remains latent and non-infectious. At the secondary stage the host develops the disease and becomes symptomatic and infectious [11], [12]. Finally, the host recovers from the disease and becomes immune to the disease for a certain time after becoming susceptible again. When only a regular non-impulsive vaccination is applied the dynamics of the SVEIR model asymptotically leads the state variables of the system (subpopulations) to ei-

ther a disease-free equilibrium (DFE) regime or an endemic one. The reached final state depends on the model parameters, i.e., the propagated disease. This study is focused on the stability of the DFE point. A regular impulsive vaccination is added to the regular non-impulsive one, in order to avoid a permanence of the infectious subpopulation. In this way, this oscillating state can be maintained around the DFE point and the induced periodicity is studied under these circumstances. Furthermore, non-regular impulsive vaccination strategies will be developed in order to improve the disease removal when the DFE point is unstable or if the disease prevalence decreases slowly, when the DFE point is stable. Consequently, a regime where the infectious subpopulation tends to zero will be obtained. Such vaccination strategies will be based on adaptive control techniques: The rules for generating the impulsive vaccinations are updated based on those used formerly for signal adaptation [13]-[19], but whose application in disease control and vaccination is novel. In this sense, a closed loop control system governs the vaccination impulses, each one characterized by a vaccination rate θ (the fraction of vaccinated subpopulation at that impulse), and an inter-vaccination period t_v (the time until the next impulse is applied). In this sense, various laws for updating t_v or θ and their capabilities to lead the system to the desired state will be presented and discussed.

The chapter is organized as follows. In section 3.2 the mathematical model of the disease is presented giving a significance to all the parameters included in it. Section 3.3 studies the equilibrium points of the dynamics without impulsive vaccination and establishes the stability of such points by defining a regular reproduction number [6]. The stability of the disease-free state of a set of regular impulsive vaccinations, with constants θ and t_v , is discussed in section 3.4, and all the preceding theoretical results are verified through simulations in section 3.5. First, a simulation for a regular non-impulsive vaccination system, and then simulations for a set of regular impulsive systems are developed. In section 3.6 a set of adaptive sampling laws are defined, namely, each vaccination action θ or t_v is set to a certain range of values, based on the available data of susceptible and infectious subpopulation measures [20]-[23]. In the first part, the adaptive laws involves a constant inter-vaccination time interval t_v , while the vaccination rate θ is updated. In the last part, however, t_v is adjusted in real time while the vaccination rate θ remains constant. After applying the two proposed different adaptive sampling laws, one adjusting the θ and the other adjusting t_v , the efficiency of this research is compared to the regular impulsive vaccination in section 3.7, and in section 3.8, the SVEIR model will be used to describe a possible outbreak of pertussis and the evolution of the disease applying different vaccination strategies. Final conclusions will be presented in section 3.9.

3.1.1 Notation

The model is described in the following terms:

- i) **Parameters.** Here it is presented all the parameters involving the epidemic model. Observe that all the parameters are non-negative.
 - b_1, b_3 : Birth rates of the population, a constant one (b_1) and a population-dependent one (b_3).

- b_2 : Natural death rate of any subpopulation.
- γ, γ_1 : Ratio of transition to recovered from infected (I→ R) and vaccinated (V→ R) subpopulations, respectively.
- α : Extra death rate caused by the disease in the infected (I) subpopulation.
- τ : Average time of transition from exposed to infected (E→ I) subpopulations.
- ω : Average time of transition from immune to susceptible subpopulations (R→ S).
- β : Disease transmission constant.
- η : Constant saturation related to the transmission of the disease which defines the incidence rate.
- δ : A diminishing factor related to the disease transmission in the vaccinated subpopulation in contrast to that corresponding to the susceptible one.
- V_c : Fraction of the population which is vaccinated since birth ($V_c \in [0, 1]$).
- t_v : Time intervals between two consecutive impulsive vaccinations.
- θ : Vaccination rate or the fraction of the susceptible subpopulation affected by the impulsive vaccination.

ii) **Vaccination Strategies.** Three different vaccination strategies can be applied to the SVEIR model:

- Regular non-impulsive vaccination: This vaccination strategy is applied at all time instants to a fraction V_c of the arriving (newborn) susceptible subpopulation. This strategy can be applied alone or complementary to the other two.
- Regular impulsive vaccination: This vaccination strategy is applied to a constant fraction θ of the susceptible subpopulation at uniformly distributed time instants, i.e., at time instant nt_v , with $n \in \mathbb{N}$ and a constant $t_v > 0$.
- Non-regular impulsive vaccination: This vaccination strategy is applied to a time-varying fraction $\theta(t_i)$ of the susceptible subpopulation at non-uniformly distributed time instants t_i with $i \in \mathbb{N}$.

3.2 The model

A generic model of five subpopulations is proposed, similar to the one of the previous chapter, where the full immunity acquired by vaccination has been replaced with the same temporal immune response derived from experiencing the disease. This model is, in turn, based on simpler SIR and SVEIR epidemic models [4, 7, 12],[24]-[26]. The term ω is called to the delay from the moment one individual recovers and acquires the immunity to the moment such an individual becomes susceptible to the disease again (susceptible subpopulation). The second delay τ is defined from the time instant when the host becomes infected to that when it becomes infective to

others. Also, it is assumed that the recovered subpopulation presents an immunity to the disease obtained through two different ways: either it is acquired after recovering from the disease or it is induced by vaccination. This vaccination is administered regularly to a fraction of newborn individuals that depend on the total population and, at specific moments in time, to a fraction of the susceptible subpopulation by means of an impulsive vaccination strategy. Both transitions, from vaccinated and infectious subpopulations to the recovered one, lead to an immunity indistinguishable from each other. The natural death rate b_2 is the inverse of the life expectancy, and the rates γ and γ_1 are the inverse of the average times of transition from infectious to immune and from vaccinated to immune subpopulations, respectively. The infectious incidence rate in the susceptible subpopulation is proportional to β and depends on $I(t)$ and $S(t)$. Due to the effects of the impulsive vaccination, there is a great variation in the number of the susceptible individuals, so a saturation factor, similar to some other previous true mass action-type models [3, 27], is introduced in order to maintain a reasonable infection rate irrespective of the value of $S(t)$ is high or low. This saturation factor is proportional to $\frac{1}{1+\eta S(t)}$ with $\eta \in \mathbb{R}$, $\eta > 0$. A similar incidence rate occurs in the vaccinated subpopulation with the parameter β reduced by a diminishing factor $\delta \in [0, 1)$, which implies the reduced possibility of a successful contagion to the disease in this subpopulation, and a saturation factor analogous to that of the susceptible subpopulation given by $\frac{1}{1+\eta V(t)}$. The SVEIRS model with delays is described by the following equations:

$$\begin{aligned} \dot{S}(t) = & b_1 - b_2 S(t) - \frac{\beta S(t) I(t)}{1+\eta S(t)} \\ & + e^{-b_2 \omega} (\gamma I(t - \omega) + \gamma_1 V(t - \omega)) + b_3 (1 - V_c) N(t) \end{aligned} \quad (3.1)$$

$$\dot{V}(t) = -\delta \frac{\beta V(t) I(t)}{1+\eta V(t)} - \gamma_1 V(t) - b_2 V(t) + b_3 V_c N(t) \quad (3.2)$$

$$\dot{E}(t) = \beta \left[\frac{S(t) I(t)}{1+\eta S(t)} + \delta \frac{V(t) I(t)}{1+\eta V(t)} - e^{-b_2 \tau} \left(\frac{S(t-\tau) I(t-\tau)}{1+\eta S(t-\tau)} + \delta \frac{V(t-\tau) I(t-\tau)}{1+\eta V(t-\tau)} \right) \right] - b_2 E(t) \quad (3.3)$$

$$\dot{I}(t) = \beta e^{-b_2 \tau} \left(\frac{S(t-\tau) I(t-\tau)}{1+\eta S(t-\tau)} + \delta \frac{V(t-\tau) I(t-\tau)}{1+\eta V(t-\tau)} \right) - (b_2 + \alpha + \gamma) I(t) \quad (3.4)$$

$$\dot{R}(t) = \gamma_1 V(t) + \gamma I(t) - (\gamma I(t - \omega) + \gamma_1 V(t - \omega)) e^{-b_2 \omega} - b_2 R(t) \quad (3.5)$$

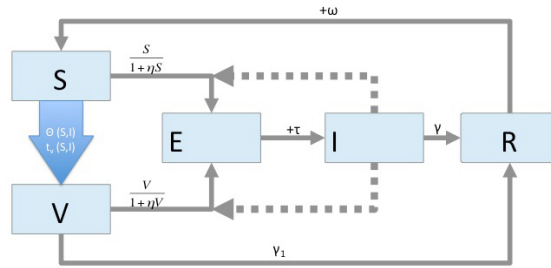


Figure 3.1: A block diagram of the SVEIRS model

$$\begin{cases} S(t^+) = (1 - \theta)S(t) \\ V(t^+) = V(t) + \theta S(t) \\ E(t^+) = E(t) & \text{if } t = nt_v \text{ (} n = 1, 2, 3, \dots \text{)} \\ I(t^+) = I(t) & \theta \in [0, 1] \\ R(t^+) = R(t) \end{cases} \quad (3.6)$$

with $N(t) = S(t) + V(t) + E(t) + I(t) + R(t)$ being the total population. Equation (3.6) is an impulsive function representing a vaccination campaign acting periodically on a fraction ($0 \leq \theta \leq 1$) of the susceptible subpopulation, which is converted into vaccinated subpopulation. A visual representation of the model structure can be seen at figure 3.1 where all the transition between subpopulations are represented through arrows, and the influence of the disease on those transitions is depicted by dashed arrows. Through the chapter the notation for the left limit at the impulse time instants nt_v^- will be simply denoted by nt_v . The parameters ω and τ are the internal delays at (3.1),(3.5) and (3.3),(3.4) respectively. The above model is different from other models [3] not only due to the distinct growth and death rates involved, but also because an additional population-dependent birth rate is considered and vaccination is administered to a fraction of the newborn. Furthermore, note that the presence of delays is often relevant in dynamic systems [12],[23],[26], and the migrations from vaccinated and infectious to the susceptible subpopulation (through the temporary immune recovered subpopulation) are taken into account.

3.3 Disease-free equilibrium point with no impulsive vaccination

In order to study the equilibrium points, first the SVEIRS model will be developed with regular non-impulsive vaccination, i.e., $\theta = 0$ in (3.6), and a constant vaccination rate V_c applied. Let S^*, V^*, E^*, I^*, R^* be the respective subpopulations at the eventual equilibrium points, i.e: $\lim_{t \rightarrow \infty} (S(t), V(t), E(t), I(t), R(t))^T = (S^*, V^*, E^*, I^*, R^*)^T$. Since the values of the subpopulations at an equilibrium point are constant, delay-dependency disappears at the equilibrium so that $\lim_{t \rightarrow \infty} I(t - \tau) = \lim_{t \rightarrow \infty} I(t - \omega) = \lim_{t \rightarrow \infty} I(t) = I^*$ and $\lim_{t \rightarrow \infty} E(t - \tau) = \lim_{t \rightarrow \infty} E(t) = E^*$. The model equations (3.1)-(3.5)

lead to:

$$\begin{cases} b_1 - b_2 S^* - \frac{\beta S^* I^*}{1+\eta S^*} + (\gamma I^* + \gamma_1 V^*) e^{-b_2 \omega} + b_3(1 - V_c) N^* & = 0 \\ -\delta \frac{\beta V^* I^*}{1+\eta V^*} - \gamma_1 V^* - b_2 V^* + b_3 V_c N^* & = 0 \\ (1 - e^{-b_2 \tau}) \beta \left(\frac{S^*}{1+\eta S^*} + \delta \frac{V^*}{1+\eta V^*} \right) I^* - b_2 E^* & = 0 \\ e^{-b_2 \tau} \beta \left(\frac{S^*}{1+\eta S^*} + \delta \frac{V^*}{1+\eta V^*} \right) I^* - (b_2 + \alpha + \gamma) I^* & = 0 \\ (1 - e^{-b_2 \omega}) (\gamma_1 V^* + \gamma I^*) - b_2 R^* & = 0 \\ \dot{S}^* + \dot{V}^* + \dot{E}^* + \dot{I}^* + \dot{R}^* = b_1 - (b_2 - b_3) N^* - \alpha I^* & = 0 \end{cases} \quad (3.7)$$

for the purpose of obtaining the respective subpopulations at the equilibrium points. By assuming the condition of non-negativity for all subpopulations, i.e.,

$$(S^*, V^*, E^*, I^*, R^*)^T \geq 0$$

the solution of the equation (3.7) reveals a set of points at which the equilibrium is reached. A solution of (3.7) such that $I^* \neq 0$ is defined as an endemic equilibrium point and, if $I^* = 0$ then it can be said that it is a disease-free equilibrium point. The model discussed here presents only one disease-free equilibrium (DFE) point, where $I^* = 0$ and $E^* = 0$. The values of the susceptible, vaccinated and recovered subpopulation as well as the total population at such DFE point are obtained from the equations in (3.7) by introducing $I^* = E^* = 0$. In this way:

$$N^* = \frac{b_1}{b_2 - b_3} \quad (3.8)$$

$$S^*(\omega) = \frac{b_1}{b_2} \left[1 + \frac{b_3}{b_2 - b_3} \left(1 + V_c \left(\frac{e^{-b_2 \omega} \gamma_1}{b_2 + \gamma_1} - 1 \right) \right) \right] \quad (3.9)$$

$$V^* = V_c \frac{b_3 b_1}{(\gamma_1 + b_2)(b_2 - b_3)} \quad (3.10)$$

$$R^*(\omega) = \frac{(1 - e^{-b_2 \omega})}{b_2} \gamma_1 V^* = V_c \frac{b_1}{b_2} \frac{b_3 \gamma_1 (1 - e^{-b_2 \omega})}{(\gamma_1 + b_2)(b_2 - b_3)} \quad (3.11)$$

Observe that the susceptible and recovered subpopulation depend on the ω delay.

3.3.1 Linearization

Proposition 3.1. *The following properties hold:*

- i) *The DFE point $(S^*(\omega), V^*, 0, 0, R^*(\omega))^T$ of the system (3.1)-(3.5) is locally asymptotically stable for any delays $\tau' \in (\tau - \Delta\tau, \tau + \Delta\tau)$ and $\omega' \in (\omega - \Delta\omega, \omega + \Delta\omega)$ for $\Delta\tau \in [0, \Delta\tau^*)$, $\Delta\omega \in [0, \Delta\omega^*)$, with sufficiently small $\Delta\tau^*$ and $\Delta\omega^*$, if $b_2 > b_3$ and $\alpha + \gamma_1 + b_2 > \beta e^{-b_2 \tau} \left(\frac{S^*(\omega)}{1+\eta S^*(\omega)} + \delta \frac{V^*}{1+\eta V^*} \right)$.*
- ii) *The DFE point $(S^*(0), V^*, 0, 0, R^*(0))^T$ of the system (3.1)-(3.5) is locally asymptotically stable for any delays $\tau \in [0, \tau^*)$ and $\omega \in [0, \omega^*)$, with small enough τ^* and ω^* , if $b_2 > b_3$ and*

$$\alpha + \gamma_1 + b_2 > \beta \left(\frac{S^*(0)}{1+\eta S^*(0)} + \delta \frac{V^*}{1+\eta V^*} \right).$$

Proof.

First, the dynamic equations are linearized (3.1)-(3.5) around the DFE point by means of the associated Jacobi matrix $\mathbf{J} = [J_{ij}] = \left[\frac{\partial x_i}{\partial x_j} \right]$ for $i, j \in \{1, 2, \dots, 5\}$ with $x_1 \equiv S$, $x_2 \equiv V$, $x_3 \equiv E$, $x_4 \equiv I$ and $x_5 \equiv R$ evaluated at the DFE point. The eigenvalues of this matrix are obtained by calculating the roots of the characteristic equation:

$$\text{Det}(\lambda I - \mathbf{J}) = 0 \quad (3.12)$$

Such eigenvalues are given by:

$$\lambda_i = \{-b_2, -b_2, -b_2 - \gamma_1, -b_2 + b_3, \beta e^{-b_2\tau} \left(\frac{S^*(\omega)}{1 + \eta S^*(\omega)} + \delta \frac{V^*}{1 + \eta V^*} \right) - (b_2 + \alpha + \gamma)\} \quad (3.13)$$

where $S^*(\omega)$ and V^* at the DFE point are given in (3.9) and (3.10) respectively. The real part of all the eigenvalues of the Jacobi matrix must be less than zero so that the linearized model around the DFE point is asymptotically stable, which means that this point is locally stable in the non-linear model. Note that all parameters of the model are always defined as positive or zero for any infectious disease. Thus, the DFE point is locally asymptotically stable around some given delays τ and ω if

$$b_3 - b_2 < 0 \quad (3.14)$$

$$\beta e^{-b_2\tau} \left(\frac{S^*(\omega)}{1 + \eta S^*(\omega)} + \frac{\delta V^*}{1 + \eta V^*} \right) - (b_2 + \alpha + \gamma) < 0 \quad (3.15)$$

Since the eigenvalues of the Jacobian matrix are continuous functions of all its entries, there are sufficiently small delay perturbations $\Delta\tau^*$ and $\Delta\omega^*$ which guarantee the local stability of the DFE point for any delays $\tau' \in (\tau - \Delta\tau, \tau + \Delta\tau)$ and $\omega' \in (\omega - \Delta\omega, \omega + \Delta\omega)$ for all $\Delta\tau \in [0, \Delta\tau^*)$, $\Delta\omega \in [0, \Delta\omega^*)$. Hence, Property (i).

In the same way, if $\omega = 0$ and $\tau = 0$ the stability conditions follow from a well known result in general theory of time-delay systems [18]. Just in this sense, the stability conditions of the equilibrium point for zero delays

$$\alpha + \gamma_1 + b_2 > \beta \left(\frac{S^*(0)}{1 + \eta S^*(0)} + \delta \frac{V^*}{1 + \eta V^*} \right); \quad b_2 > b_3 \quad (3.16)$$

directly guarantee the stability for small delays $\tau \in [0, \tau^*]$ and $\omega \in [0, \omega^*]$. Hence, Property (ii). \square

Remark 3.2.

If $\alpha + \gamma + b_2 < \beta \left(\frac{S^*(0)}{1+\eta S^*(0)} + \delta \frac{V^*}{1+\eta V^*} \right)$ then the DFE point is unstable for zero and sufficient small delays $\tau \in [0, \tau^*]$ and $\omega \in [0, \omega^*]$, as it would happen if $b_2 < b_3$ which would also imply negative subpopulations. If $\alpha + \gamma + b_2 = \beta \left(\frac{S^*(0)}{1+\eta S^*(0)} + \delta \frac{V^*}{1+\eta V^*} \right)$ and $b_2 > b_3$ then the linearized system around the DFE point is critically stable. Finally, if $b_2 = b_3$ then $I^* = \frac{b_1}{\alpha} \neq 0$ from (3.7). As a consequence, the system does not possess a DFE point.

Remark 3.3.

Proposition 3.1 (i) establishes the conditions to have a DFE point asymptotically locally stable for delays ω, τ . The first condition (3.14) implies that the population does not grow exponentially as the death rate is greater than the population-related birth rate. The parameters from the second condition (3.15) can be rearranged so it can be obtained:

$$R_0 = \frac{\beta e^{-b_2 \tau}}{b_2 + \alpha + \gamma} \left(\frac{S^*(\omega)}{1 + \eta S^*(\omega)} + \delta \frac{V^*}{1 + \eta V^*} \right) \quad (3.17)$$

where $S^(\omega)$ and V^* at the DFE point are given in (3.9) and (3.10) respectively. The parameter R_0 defined through (3.17) is referred to the basic reproduction number, which is defined in epidemic research as the expected number of secondary infections derived per infected individual $\beta e^{-b_2 \tau} \left(\frac{S^*(\omega)}{1 + \eta S^*(\omega)} + \delta \frac{V^*}{1 + \eta V^*} \right)$ during the average course of the infectious phase of the disease $(b_2 + \gamma + \alpha)^{-1}$ [31]-[33]. Since $S^*(\omega) = S^*(V_c, b_1, b_2, b_3, \omega, \gamma_1)$ and $V^* = V^*(V_c, b_1, b_2, b_3, \gamma_1)$ the reproduction number will be $R_0(\beta, b_1, b_2, b_3, \delta, \eta, \alpha, \gamma, \gamma_1, \omega, \tau)$ and will give us information about the local stability around the DFE point, as condition from (3.15) is equivalent to $R_0 < 1$. A consequence from Proposition 3.1 follows below.*

Remark 3.4.

If $R_0 > 1$ then the DFE point is locally unstable, as it would happen if $b_2 < b_3$, which would also imply negative subpopulations. If $R_0 = 1$ and $b_2 > b_3$ then the linearized system around the DFE point is critically stable.

3.4 Regular impulsive vaccination around the disease-free equilibrium point

The behavior of the model under a regular impulsive vaccination is studied in this section. The main motivation is to mitigate and, potentially, eradicate the infection from the host population when the DFE point is unstable under a regular non-impulsive vaccination strategy. The regular impulsive vaccination is characterized by a constant vaccination rate θ and a constant inter-vaccination time interval t_v . This vaccination strategy is applied to an auxiliary model constructed from the original model (3.1)-(3.6), in which there are not infected subpopulations: $E(t) = 0$ and $I(t) = 0 \quad \forall t \geq t_0$, being t_0 the hypothetical time instant at which the disease has been eradicated. The results obtained in this auxiliary model would be analogous to the SVEIRS model when it hypothetically tends to the disease-free state. The dynamic equations for this

reduced model are:

$$\begin{cases} \dot{S}'(t) = b_1 - b_2 S'(t) + b_3(1 - V_c)N'(t) + \gamma_1 V'(t - \omega)e^{-b_2 \omega} \\ \dot{V}'(t) = -\gamma_1 V'(t) - b_2 V'(t) + b_3 V_c N'(t) \\ \dot{R}'(t) = \gamma_1(V'(t) - V'(t - \omega)e^{-b_2 \omega}) - b_2 R'(t) \end{cases} \quad \forall t \neq nt_v \quad (3.18)$$

and

$$\begin{cases} S'(t^+) = (1 - \theta)S'(t) \\ V'(t^+) = V'(t) + \theta S'(t) \quad \theta \in [0, 1] \\ R'(t^+) = R'(t) \end{cases} \quad \forall t = nt_v \quad (3.19)$$

The equation of the total population in such a disease-free situation is:

$$\dot{N}'(t) = \dot{S}'(t) + \dot{V}'(t) + \dot{R}'(t) = b_1 - (b_2 - b_3)N'(t) \quad (3.20)$$

Such a total population presents a time evolution given by

$N'(t) = N^* - (N^* - N_0)e^{-(b_2 - b_3)t}$ where N_0 denotes the initial value $N'(0) \geq 0$. By supposing that $b_2 > b_3$, it follows that $\lim_{t \rightarrow \infty} N'(t) = N^*$ and the system reaches the DFE state where the total population N^* is given by (3.8).

The solution of these simplified equations (3.18)-(3.19) will be found under a periodic impulsive vaccination showing that they exhibit a periodic steady regimen of period $T = T(m, \sigma) = mt_v + \sigma$, with $\sigma \in [0, t_v)$, $m \in \mathbb{N} \cup \{0\} \triangleq \mathbb{N}_0$. Furthermore, the maximum values of the susceptible and vaccinated subpopulations will be obtained within such a periodic regime. Proposition 3.5 establishes that the period $T(m, \sigma)$ of such a solution must be always a multiple of t_v . and that such period is always t_v .

Proposition 3.5. *The following properties hold*

- i) *For a general periodic solution of (3.18)-(3.19) with a time period $T = T(m, \sigma) = mt_v + \sigma$ it is required that $\sigma = 0$.*
- ii) *There is a unique general solution with time period $T(1, 0) = t_v$. This solution would be, from (i) that with the smallest time period.*

Proof.

Assuming that the solutions of (3.18)-(3.19) exhibits a periodic behavior and that the period is given by $T(m, \sigma)$, with $\sigma \neq 0$, this would imply that, for any $n_1 \in \mathbb{N}$, $S(n_1 t_v) = S((n_1 + m)t_v + \sigma)$. However, while the susceptible subpopulation is required by the dynamic equation in (3.18) to show an impulse at $t = n_1 t_v$, this impulse is not present at $t' = (n_1 + m)t_v + \sigma$ since $(n_1 + m)t_v < t' < (n_1 + m + 1)t_v$. Therefore, periodicity is not reached if $\sigma \neq 0$. Hence Property (i).

The demonstration of Property (ii) is omitted here due to length constraints. This proof is included in Appendix D, and shows that the generic $T(n, 0)$ solution is unique and based on a superposition of $T(1, 0)$ solutions which, from Property (i), would be the solution with the smallest period. Hence Property(ii). \square

In order to simplify the notation, a redefinition is made to the variables for the vaccinated and susceptible subpopulations within the interval between two consecutive impulses after a large enough time so that they have reached the periodic regime and $\lim_{t \rightarrow \infty} N(t) = N^*$. In such a situation, the susceptible and vaccinated subpopulations can be denoted by:

$$\forall \{i, r\} \in \mathbb{N}_0, \tau \in [0, t_v) \rightarrow \begin{cases} S_i(\tau) \triangleq \lim_{r \rightarrow \infty} S'(\tau + (i+r)t_v) \\ V_i(\tau) \triangleq \lim_{r \rightarrow \infty} V'(\tau + (i+r)t_v) \end{cases} \quad (3.21)$$

where (3.8) and (3.10) has been taken into account. Once that it is known that $\{S_i(\tau) = S_j(\tau), V_i(\tau) = V_j(\tau)\} \forall i, j \in \mathbb{N}$ the equations in (3.18) at the periodic regime can be rearranged by using (3.21). In this way, the dynamics of the vaccinated subpopulation (3.2) is described by:

$$\dot{V}_i(\tau) = (\gamma_1 + b_2)(V^* - V_i(\tau)) \quad (3.22)$$

On the other hand the dynamics of the susceptible subpopulation (3.1) is rewritten as a two part equation due to the discontinuity derived from the delay $\omega = kt_v + xt_v$, being $k \in \mathbb{N}_0$ and $x \in [0, 1) \cap \mathbb{R}$, namely:

$$\dot{S}_i(\tau) = \begin{cases} b_2(S^*(\omega) - S_i(\tau)) + \gamma_1(V_i(0^+) - V^*)e^{-b_2\omega - (b_2 + \gamma_1)(\tau - (1-x)t_v)} & 0 \leq \tau < xt_v \\ b_2(S^*(\omega) - S_i(\tau)) + \gamma_1(V_i(0^+) - V^*)e^{-b_2\omega - (b_2 + \gamma_1)(\tau - xt_v)} & xt_v \leq \tau < t_v \end{cases} \quad (3.23)$$

where V^* and $S^*(\omega)$ are the values of the susceptible and vaccinated subpopulations from (3.9) and (3.10) respectively. It can be seen from these equations that in the periodic regime $\dot{S}_i(\tau) > 0$ and $\dot{V}_i(\tau) < 0$ if $S_i(\tau) < S^*$ and $V_i(\tau) > V^* \quad \forall \tau \in (0, t_v)$. This means that the susceptible subpopulation is continuously increasing, while the vaccinated subpopulation is continuously decreasing, within the time interval $[jt_v, (j+1)t_v)$ for any $j \in \mathbb{N}$ and large enough such that the model dynamics has reached the stationary periodic regime. Therefore, the maximum values of both subpopulations will be:

$$\begin{aligned} \max_{0 \leq \tau < t_v} \{S_i(\tau)\} &= S_i(t_v) = \frac{S_i(0^+)}{1 - \theta} \\ \max_{0 \leq \tau < t_v} \{V_i(\tau)\} &= V_i(0^+) \end{aligned} \quad (3.24)$$

where the values for $V_i(0^+)$, $S_i(0^+)$ are defined as:

$$\begin{aligned} S_i(0^+) &= S_0 = \frac{s_1(1 - \theta)}{s_2 - e^{b_2(xt_v - \omega)}\theta s_3} \\ V_i(0^+) &= V^* + \frac{s_1\theta}{(s_2 - e^{b_2(xt_v - \omega)}\theta s_3)(1 - e^{-(b_2 + \gamma_1)t_v})} \end{aligned} \quad (3.25)$$

with s_1 , s_2 and s_3 given by:

$$\begin{aligned} s_1 &= (e^{b_2 t_v} - 1) (e^{(b_2 + \gamma_1) t_v} - 1) S^*(\omega) \\ s_2 &= (e^{(b_2 + \gamma_1) t_v} - 1) (e^{b_2 t_v} - (1 - \theta)) \\ s_3 &= (e^{\gamma_1 x t_v} + e^{(b_2 + \gamma_1) t_v} - e^{(b_2 + x \gamma_1) t_v} - 1) \end{aligned} \quad (3.26)$$

The subpopulations $S'(t)$ and $V'(t)$ in the auxiliary model will be, respectively, above the values $S(t)$ and $V(t)$ of the original SVEIRS model. When the disease is permanent, i.e. $\liminf_{t \rightarrow \infty} \{S'(t) - S(t)\} \geq 0$ and $\liminf_{t \rightarrow \infty} \{V'(t) - V(t)\} \geq 0$ if $I(t) > 0$ and $E(t) > 0$, the values from the auxiliary model is used in (3.24) to define the impulsive reproduction number $R(\theta, t_v)$ as:

$$R(\theta, t_v) = \frac{\beta e^{-b_2 \tau}}{\gamma + b_2 + \alpha} \left(\max_{0 \leq t < t_v} \left\{ \frac{S_i(t)}{1 + \eta S_i(t)} \right\} + \max_{0 \leq t < t_v} \left\{ \delta \frac{V_i(t)}{1 + \eta V_i(t)} \right\} \right) \quad (3.27)$$

$$R(\theta, t_v) = \frac{\beta e^{-b_2 \tau}}{\gamma + b_2 + \alpha} \left(\frac{S_i(t_v)}{1 + \eta S_i(t_v)} + \delta \frac{V_i(0^+)}{1 + \eta V_i(0^+)} \right) \quad (3.28)$$

Now the dynamic equation for the infectious subpopulation from (3.4) is studied. For a sufficiently large time $t \geq t' = n_0 t_v$, $n_0 \in \mathbb{N}$, so that (3.21) is fulfilled, it can be established an upper-bound for the growth of the infectious subpopulation, namely :

$$\begin{aligned} \dot{I}(t) &\leq \beta e^{-b_2 \tau} \left(\max_{t' \leq t < t' + t_v} \left\{ \frac{S(t)}{1 + \eta S(t)} + \frac{\delta V(t)}{1 + \eta V(t)} \right\} \right) I(t - \tau) - (\gamma + b_2 + \alpha) I(t) \\ &\leq \beta e^{-b_2 \tau} \left(\max_{t' \leq t < t' + t_v} \left\{ \frac{S(t)}{1 + \eta S(t)} \right\} + \max_{t' \leq t < t' + t_v} \left\{ \frac{\delta V(t)}{1 + \eta V(t)} \right\} \right) I(t - \tau) - (\gamma + b_2 + \alpha) I(t) \\ &\leq \beta e^{-b_2 \tau} \left(\max_{t' \leq t < t' + t_v} \left\{ \frac{S'(t)}{1 + \eta S'(t)} \right\} + \max_{t' \leq t < t' + t_v} \left\{ \frac{\delta V'(t)}{1 + \eta V'(t)} \right\} \right) I(t - \tau) - (\gamma + b_2 + \alpha) I(t) \\ \dot{I}(t) &\leq \beta e^{-b_2 \tau} \left(\max_{0 \leq t < t_v} \left\{ \frac{S_i(t)}{1 + \eta S_i(t)} \right\} + \max_{0 \leq t < t_v} \left\{ \frac{\delta V_i(t)}{1 + \eta V_i(t)} \right\} \right) I(t - \tau) - (\gamma + b_2 + \alpha) I(t) \\ \dot{I}(t) &\leq (\gamma + b_2 + \alpha) (R(\theta, t_v) I(t - \tau) - I(t)) \end{aligned} \quad (3.29)$$

The interpretation given to the impulsive reproduction number $R(\theta, t_v)$ is intuitively analogous to the standard reproduction number R_0 from (3.17), but under a more complex regular impulsive vaccination instead of only a regular non-impulsive vaccination V_c . It leads to the identification of the parameters which make the model presents a stable oscillation around the DFE point under an impulsive vaccination strategy when $R_0 > 1$, i.e., when the DFE point is unstable with the application of only a regular non-impulsive vaccination V_c .

The following result in proposition 3.6 is addressed to give conditions for guaranteeing that the infectious subpopulation converges asymptotically to zero provided that $R(\theta, t_v) < 1$.

Proposition 3.6. *If $R(\theta, t_v) < 1$ then $I(t) \rightarrow 0$ as $t \rightarrow \infty$.*

Proof.

For all $t > 0$, it is known from (3.4) that:

$$\dot{I}(t) = aI(t) + b(t)I(t - \tau) \quad (3.30)$$

being $a = -(\alpha + b_2 + \gamma)$ and $b(t) = \frac{\beta e^{-b_2 \tau} S(t-\tau)}{1+\eta S(t-\tau)} + \delta \frac{\beta e^{-b_2 \tau} V(t-\tau)}{1+\eta V(t-\tau)}$. At a sufficient large t , it is known from (3.28) that

$$|b(t)|/|a| \leq R(\theta, t_v) < 1 \quad (3.31)$$

and then $\lim_{t \rightarrow \infty} I(t) = 0$ is obtained from [19]. \square

Proposition 3.7. *If $\theta = 0$ (i.e., in the absence of impulsive vaccination) then the impulsive reproduction number $R(0, t_v)$ becomes the standard, non-impulsive, reproduction number, i.e., $R(0, t_v) = R_0$, and implies that the stability at the DFE point when $R_0 < 1$ is not only local, but also globally asymptotically stable.*

Proof.

As $\theta = 0$, $R(0, t_v) = \frac{\beta e^{-b_2 \tau}}{\gamma + b_2 + \alpha} \left(\frac{S^*(\omega)}{1 + \eta S^*(\omega)} + \delta \frac{V^*}{1 + \eta V^*} \right) = R_0 < 1$. Then, from proposition 3.6, it is deduced $\lim_{t \rightarrow \infty} I(t) = 0$. The dynamic for the exposed subpopulation from (3.3) becomes $\dot{E}(t) \rightarrow -b_2 E(t)$, so that $\lim_{t \rightarrow \infty} E(t) = 0$ since $b_2 > 0$. Then, the susceptible, vaccinated and recovered subpopulations reach their values in (3.9)-(3.11) at the DFE point. \square

3.5 Numerical simulations with regular impulsive vaccination

3.5.1 Parameter Settings

In order to check if the reproduction number R_0 is equally valid in the periodic stationary regime of the non linear SVEIRS model, a simulation of the dynamics of the disease is made for a given set of initial conditions during a sufficient time to obtain a stationary regime, and the results are studied. It has been decided to use a student version of MATLAB ©7.11.0 (R2010)b Language for setting different values for the model parameters, displaying the solution data, and performing the technical computing, while the Simulink block-module environment from Matlab resolves the dynamics of the SVEIRS model (3.1)-(3.5). The Simulink system is designed using such equations, plus the following restriction that guarantees the non-negativity of the subpopulations:

$$\text{If } X_i(t_0) < 0 \rightarrow X_i(t_0) = 0 \quad \forall t_0 \quad (3.32)$$

The proposed SVEIRS model is now tested numerically for a given parameterization. A real case study for pertussis is later on discussed in section 3.8. The average life span is established as 70 years, so $b_2^{-1} = 70 \text{ years}$. It is defined $b_3 < b_2$, as the population would grow exponentially otherwise, and choose $b_1^{-1} = b_3^{-1} = 140 \text{ years}$ in order to have a disease-free total population equal to 1 ($N^* = \frac{b_1}{b_2 - b_3} = 1$). The vaccination parameters are set $V_c = 1$ and $\delta = 0.2$ while the saturation constant $\eta = 0.18$. For the transition rate from vaccinated to recovered subpopulation it is chosen five months of partial immunity before getting a total one in the recovered state, so $\gamma_1^{-1} = (\frac{150}{365}) \text{ years}$. The extra death rate for the infected is 0.5 months^{-1} , so $\alpha^{-1} = (\frac{2}{12}) \text{ years}$. About the parameters τ , ω and γ , a range of possible values from the data available [34]-[39] will be taken in order to study further the dynamics of the epidemic:

- $\tau = 0.04\text{-}4 \text{ years}$ (15-1500 days)
- $\omega = 1\text{-}100 \text{ years}$
- $\gamma = 12.2\text{-}2.4 \text{ years}^{-1}$

Finally, a value of the disease transmission constant β is chosen so the reproduction number reach a value higher than one, since as it is seen in (3.17), the reproduction number R_0 is directly proportional to β .

3.6 Vaccination strategies

3.6.1 Non-regular impulsive vaccination strategy with adaptable vaccination rate θ

After proving the convenience of a regular impulsive vaccination, it is studied the implantation of a more sophisticated impulsive vaccination strategy. Two concepts are introduced: the concept of vaccination cost (VC), directly related to the treatment and the number of consumed vaccines, and the disease cost (DC), related to the quantity of infected subpopulation over time. The main purpose is to guarantee the health of the population while minimizing both DC and VC costs. A constant interval t_v between consecutive impulsive vaccination time instants is chosen, with a vaccination rate varying according to different rules within the range $\theta \in [0, 1]$. The notation for the time varying vaccination rate will be $\theta_i = \theta(it_v) = \theta(t_i)$. Also, the normalization of the infectious and susceptible subpopulation with respect to the total population N^* at the DFE point, i.e., $I'(t) = I(t)/N^*$, $S'(t) = S(t)/N^*$ are used for defining the rules which on-line adjust θ_i .

Vaccination Rate updating rule based on Infectious subpopulation Quantity (VR-IQ)

This strategy updates the impulsive vaccination rate θ_i by using a rule based on the quantity of infectious subpopulation. As $R(\theta, t_v)$ is a strictly decreasing function with respect to $\theta \in [0, 1]$ i.e. $\frac{\partial R(\theta, t_v)}{\partial \theta} < 0$, there is only one value of θ corresponding to a given value of $R(\theta, t_v)$ with t_v being constant. Moreover, Proposition 3.6 establishes that if the impulsive reproduction number is smaller than 1 the disease is guaranteed

to be eradicated, i.e., if $R(\theta, t_v) < 1$ then $\lim_{t \rightarrow \infty} I(t) = 0$. Such a result is used in the following way. Given a set of values for the SVEIRS model parameters, a fixed value for t_v is chosen such that $R(0, t_v) \geq 1$ and $R(1, t_v) < 1$. Then, a database of $R(\theta, t_v)$ for $\theta \in [\theta_{min}, 1]$ is built, where $\theta_{min} = \arg\{\theta \in [0, 1] | R(\theta, t_v) = 1\}$ by taking into account (3.24), (3.25) and (3.28).

The aim of the VR-IQ rule is to increment the impulsive vaccination rate if the infectious subpopulation exceeds a predefined size in order to reduce it. For such purpose, the law used for updating such vaccination rate at each vaccination time instant is given by:

$$\theta_i = \arg\{\theta | R(\theta, t_v) = 1 + g_i(R(1, t_v) - 1)\} \quad (3.33)$$

where g_i is an auxiliary value given by:

$$g_i = \begin{cases} 1 & \text{if } \log_{10}[I'(t_i)] > 0 \\ 1 - \left| \frac{\log_{10}[I'(t_i)]}{C_I} \right| & \text{if } \log_{10}[I'(t_i)] \in [-C_I, 0] \\ 0 & \text{if } \log_{10}[I'(t_i)] < -C_I \end{cases} \quad (3.34)$$

with $I'(t_i)$ being the normalized infectious subpopulation at the moment before the vaccination time instant t_i , and $C_I > 0$ a predefined constant. Note that the vaccination rate θ_i takes the minimum value θ_{min} when the infectious subpopulation is very small, namely, $I'(t_i) < 10^{-C_I} \ll 1$ if C_I is large enough. In other words, $\theta_i = \theta_{min}$ when the infection is near to be eradicated.

Vaccination Rate updating rule based on Susceptible subpopulation Quantity (VR-SQ)

Two different rules will be used in order to update the value θ_i based on the susceptible subpopulation. The first one (VR-SQ₁) is similar to the rule VR-IQ. The main difference between them is that the subpopulation accountable in the rule VR-SQ₁ for setting the vaccination rate θ_i is not the infectious one, but the susceptible one. By taking into account that the contagion rate is directly proportional to the susceptible subpopulation from (3.1)-(3.5), the updating rule for θ_i has to maintain the susceptible subpopulation below a small upper-bound. For such purpose, the law used to update the impulsive vaccination rate is given by:

$$\theta_i = \arg\{\theta | R(\theta, t_v) = 1 + g_i(R(1, t_v) - 1)\} \quad (3.35)$$

where the auxiliary value g_i is:

$$g_i = \begin{cases} 1 & \text{if } \log_{10}[S'(t_i)] > 0 \\ 1 - \left| \frac{\log_{10}[S'(t_i)]}{C_S} \right| & \text{if } \log_{10}[S'(t_i)] \in [-C_S, 0] \\ 0 & \text{if } \log_{10}[S'(t_i)] < -C_S \end{cases} \quad (3.36)$$

with a predefined constant $C_S > 0$ and $S'(t_i)$ the value of the normalized susceptible subpopulation at the moment before the impulsive vaccination time instant t_i . Note

that θ_i takes the minimum value when $S'(t_i) < 10^{-C_S}$, i.e., when the susceptible subpopulation is very small if a suitable value for C_S is chosen.

In the second rule (VR-SQ₂) the values θ_i are updated by using an explicit function of the susceptible subpopulation at the impulsive vaccination time instants:

$$\theta_i = 1 - \frac{1}{1 + aS'(t_i)} \quad \text{with } a \geq 0 \quad (3.37)$$

Vaccination rate updating rule based on the Infectious subpopulation Growth (VR-IG)

In this case, the impulsive vaccination rate θ_i is slightly increased or decreased from the previous value at each impulsive vaccination time instant with a function that depends on the growth of the infectious subpopulation, namely:

$$\begin{aligned} \bar{\theta}_{i+1} &= \theta_i + \Delta\theta_i \\ \Delta\theta_i &= \text{sign}[\dot{I}'(t_i)] \left| \log_{10} \left[\left| \dot{I}'(t_i) \right| \right] \right| / C_I \\ \theta_{i+1} &= \begin{cases} 0 & \text{if } \bar{\theta}_{i+1} < 0 \\ \bar{\theta}_{i+1} & \text{if } \bar{\theta}_{i+1} \in [0, 1] \\ 1 & \text{if } \bar{\theta}_{i+1} > 1 \end{cases} \end{aligned} \quad (3.38)$$

with a predefined constant $C_I > 0$. Here, $\dot{I}'(t_i)$ can be estimated in practice in two ways, namely:

- i) $\dot{I}'(t_i)$ can be the growth of the normalized infectious subpopulation at the time of the impulse, or
- ii) $\dot{I}'(t_i)$ can be replaced by $\frac{I'(t_i) - I'(t_{i-1})}{t_v}$, i.e., the difference between the normalized infectious subpopulation just before the current impulse time instant (t_i) and just before the previous one (t_{i-1}) divided by the constant inter-vaccination time interval (t_v). Such a measure can be used as a suitable approximation to the true growth $\dot{I}'(t_i)$.

Vaccination Rate updating rule based on the Susceptible subpopulation Growth (VR-SG)

The θ_i rate, like in the VR-IG rule, is readjusted at each vaccination impulse time instant, but the purpose here is to react against the increase of the susceptible subpopulation with an increase of the impulsive vaccination rate, given that it indicates that the disease is still present:

$$\bar{\theta}_{i+1} = \theta_i + \Delta\theta_i, \quad \Delta\theta_i = C_S \dot{S}'(t_i) \quad (3.39)$$

$$\theta_{i+1} = \begin{cases} 0 & \text{if } \bar{\theta}_{i+1} < 0 \\ \bar{\theta}_{i+1} & \text{if } \bar{\theta}_{i+1} \in [0, 1] \\ 1 & \text{if } \bar{\theta}_{i+1} > 1 \end{cases} \quad (3.40)$$

with a predefined constant $C_S > 0$. Here $\dot{S}'(t_i)$, as the $\dot{I}'(t_i)$ before, can be

- (1) the growth of the normalized susceptible subpopulation at the time of the impulse, or
- (2) it can be replaced by $\frac{S'(t_i) - S'(t_{i-1})}{t_v}$, i.e., the difference between two data of the normalized susceptible subpopulation, one just before the current impulse time instant (t_i) and the other just before the previous impulse (t_{i-1}), divided by the constant inter-vaccination time interval (t_v).

3.6.2 Non-regular impulsive vaccination strategy with adaptable inter-vaccination time intervals

In the second approach for obtaining an optimization of the vaccination and disease costs related to a disease, a set of rules for updating the time period $t_v(i)$ from the current vaccination time instant to the next one is developed while the impulsive vaccination rate θ remains constant. Again, the infectious and susceptible subpopulations are normalized with respect to the total population N^* at the DFE point. As the inter-vaccination time interval is time-varying, it is defined now the current vaccination time instant as the sum of all preceding inter-vaccination time intervals,

namely, $t_i = \sum_{j=1}^i t_v(j)$, where $t_v(j) = t_j - t_{j-1}$ for $j \in \mathbb{N}$ and $t_v(1) = t_1 - t_0 = t_1$ since $t_0 = 0$, i.e., since the initial time instant is denoted by t_0 .

Inter-Vaccination time Intervals updating rule based on Infectious subpopulation Quantity (IVI-IQ)

The inter-vaccination time interval, as θ in the VR-IQ rule, depends on the quantity of infectious subpopulation. Analogous to the previous methods, it is created a database of $R(\theta, t_v)$ between a maximum and a minimum t_v . The more convenient time interval t_v is chosen within the range $t_v \in [t_v^{min}, t_v^{max}]$ with t_v^{min} such that $R(\theta, t_v^{min}) < 1$ for a prefixed θ . The fact that $R(\theta, t_v)$ decreases as the inter-vaccination time interval does is taken into account, since $\frac{\partial R(\theta, t_v)}{\partial t_v} > 0 \forall t_v$ for a constant θ . Furthermore, from Proposition 3.6 an impulsive vaccination reproduction number $R(\theta, t_v) < 1$ will guarantee $\lim_{t \rightarrow \infty} I(t) = 0$, so in order to decrease the infectious subpopulation the impulsive vaccination time intervals will be reduced as the infectious subpopulation exceeds a predefined size. For such purpose, the following rule is used:

$$t_v(i+1) = \text{arg}\{t_v \in [t_v^{min}, t_v^{max}] | R(\theta, t_v) = 1 + g_i(R(\theta, t_v^{min}) - 1)\} \quad (3.41)$$

where the auxiliary function g_i is given by:

$$g_i = \begin{cases} 1 & \text{if } \log_{10} [I'(t_i)] > 0 \\ 1 - \left| \frac{\log_{10} [I'(t_i)]}{C_I} \right| & \text{if } \log_{10} [I'(t_i)] \in [-C_I, 0] \\ 0 & \text{if } \log_{10} [I'(t_i)] < -C_I \end{cases} \quad (3.42)$$

with a predefined constant $C_I > 0$, and where $I'(t_i)$ is the normalized infectious subpopulation at the moment before the vaccination time instant.

Inter-Vaccination time Intervals updating rule based on Susceptible subpopulation Quantity (IVI-SQ)

As in the previous VR-SQ₁ and VR-SQ₂ rules, two alternative ways are now proposed to update the time interval between consecutive impulsive vaccinations. The first rule (IVI-SQ₁) is defined as the IVI-IQ one, with the difference that the subpopulation used for measuring the state of the disease propagation is not the infectious one, but the susceptible one. The aim is to reduce the susceptible subpopulation by vaccination so the following law is used for updating the inter-vaccination time intervals:

$$t_v(i+1) = \text{arg}\{t_v \in [t_v^{\min}, t_v^{\max}] | R(\theta, t_v) = 1 + g_i(R(\theta, t_v^{\min}) - 1)\} \quad (3.43)$$

where g_i is given by:

$$g_i = \begin{cases} 1 & \text{if } \log_{10} [S'(t_i)] > 0 \\ 1 - \left| \frac{\log_{10}[S'(t_i)]}{C_S} \right| & \text{if } \log_{10} [S'(t_i)] \in [-C_S, 0] \\ 0 & \text{if } \log_{10} [S'(t_i)] < -C_S \end{cases} \quad (3.44)$$

with a predefined constant $C_S > 0$, and $S'(t_i)$ being the value of the normalized susceptible subpopulation at the moment before the impulsive vaccination time instant. The second rule (IVI-SQ₂) used to update the inter-vaccination time intervals is:

$$t_v(i+1) = t_v^{\min} + \frac{(t_v^{\max} - t_v^{\min})}{1 + aS'(t_i)} \quad \text{with } a \geq 0 \quad (3.45)$$

Inter-Vaccination time Intervals updating rule based on Infectious subpopulation Growth (IVI-IG)

In this case, the inter-vaccination time interval $t_v(i+1)$ is slightly increased or decreased from the previous one at each impulsive vaccination time instant with a rule based on the growth of the infectious subpopulation. In this sense, the following adjusting law is proposed:

$$\Delta t_v(i) = \text{sign}[\dot{I}'(t_i)] \left| \log_{10} \left[\left| \dot{I}'(t_i) \right| \right] \right| / C_I \quad (3.46)$$

$$\bar{t}_v(i+1) = t_v(i) - \Delta t_v(i) \quad (3.47)$$

$$t_v(i+1) = \begin{cases} t_v^{\min} & \text{if } \bar{t}_v(i+1) < t_v^{\min} \\ \bar{t}_v(i+1) & \text{if } \bar{t}_v(i+1) \in [t_v^{\min}, t_v^{\max}] \\ t_v^{\max} & \text{if } \bar{t}_v(i+1) > t_v^{\max} \end{cases}$$

with $C_I > 0$ being a predefined constant. $\dot{I}'(t_i)$ can be

- i) the growth of the normalized infectious subpopulation at the time of the impulse, or
- ii) $\dot{I}'(t_i)$ can be replaced by $\frac{I'(t_i) - I'(t_{i-1})}{t_v(i)}$, i.e., the difference between the normalized infectious subpopulation just before the current impulse time instant (t_i) and just before the previous one (t_{i-1}) divided by the inter-vaccination time interval ($t_v(i) = t_i - t_{i-1}$). Such a measure can be used as a suitable approximation to the true growth $\dot{I}'(t_i)$.

Inter-Vaccination time Intervals updating rule based on Susceptible subpopulation Growth (IVI-SG)

Here $t_v(i)$, like in the IVI-IG rule of the previous section, is readjusted at each impulsive vaccination time instant, although the proposed adaptation law is based on the susceptible subpopulation instead of the infectious one. Now, an increase of the susceptible subpopulation gives place to a decrease of the time interval between impulsive vaccination time instants, namely:

$$\Delta t_v(i) = C_S \dot{S}'(t_i) \quad (3.48)$$

$$\bar{t}_v(i+1) = t_v(i) - \Delta t_v(i) \quad (3.49)$$

$$t_v(i+1) = \begin{cases} t_v^{min} & \text{if } \bar{t}_v(i+1) < t_v^{min} \\ \bar{t}_v(i+1) & \text{if } \bar{t}_v(i+1) \in [t_v^{min}, t_v^{max}] \\ t_v^{max} & \text{if } \bar{t}_v(i+1) > t_v^{max} \end{cases}$$

with $C_S > 0$ a predefined constant. $\dot{S}'(t_i)$ can be

- i) the growth of the normalized susceptible subpopulation at the time of the impulse, or
- ii) replaced by $\frac{S'(t_i) - S'(t_{i-1})}{t_v(i)}$, i.e., the difference between two data points of the normalized susceptible subpopulation, one just before the current impulse time instant (t_i) and the other just before the previous impulse (t_{i-1}), divided by the inter-vaccination time interval ($t_v(i) = t_i - t_{i-1}$).

3.7 Efficient method for coherency in the comparison of non-regular impulsive vaccination strategies against regular ones

The impact of the different rules for updating the vaccination rate θ_i and the time interval $t_v(i)$ from sections 3.6.1 and 3.6.2 is studied. For such purpose, a simulation of an outbreak is run, beginning with initial conditions near the DFE point plus a small fraction of infectious subpopulation. It is set a constant time interval $t_v = 1$ for the adaptive laws adjusting the time-varying rate θ_i in section 3.6.1 and a constant vaccination rate $\theta = 0.05$ for the adaptive laws adjusting the time-varying inter-vaccination time intervals within a range of $t_v(i) \in (0.46, 1.50)$ in section 3.6.2. The parameters of the system are set as those used in section 3.4 giving place to a reproduction number $R_0 = 1.25$ associated to an unstable DFE point. The reproduction number R_0 is also small enough so the impulsive reproduction number $R(\theta, t_v)$ achieves values under 1 given the proposed range for θ and t_v . The disease cost is defined as $DC = A \int_0^{t_f} I(t) dt$, related to the value of the infectious subpopulation during the simulation time, and the vaccination cost is defined as $VC = V_1 + V_2$.

- i) The first part $V_1 = \int_0^{t_f} b_3 V_c N(t) dt$ is related to the amount of newborns vaccinated during the simulation from 0 to t_f and it is proportional to the constant vaccination rate V_c .
- ii) The second part $V_2 = \sum_{i=1}^n \theta_i S(t_i)$ is related to the total amount of vaccinated individuals by means of impulsive vaccinations, with n being the number of impulsive vaccinations during the simulation.

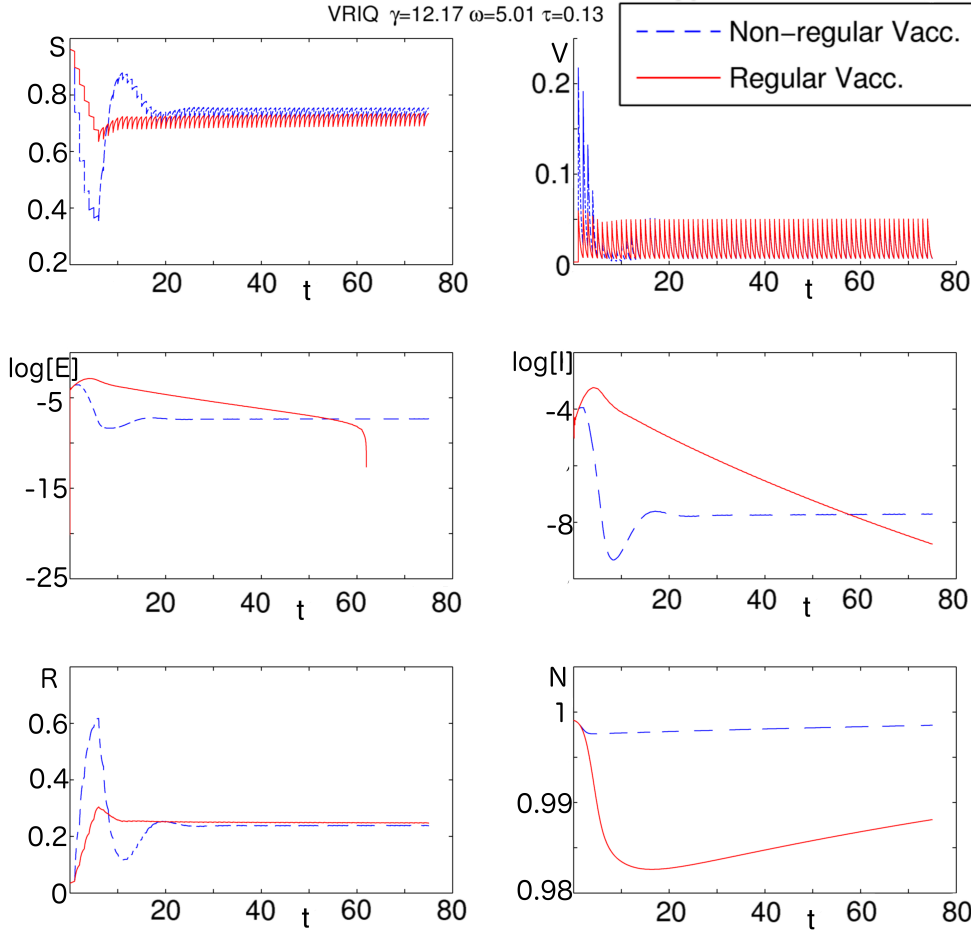


Figure 3.2: A comparison between the model dynamics with a non-regular impulsive vaccination with a VR-IQ strategy and a regular impulsive vaccination with the same Vaccination Cost.

After running the simulation and gathering information about the dynamics of the non-regular impulsive vaccination strategy and their DC and VC, the simulation is re-run again, now using a regular impulsive vaccination strategy with constant vaccination parameters θ and t_v . The data from the non-regular impulsive vaccination strategy will be used to get the most approximate vaccination parameters so the regular impulsive vaccination presents a VC comparable to the non-regular one. In this sense, a regular impulsive vaccination strategy of constants rates θ_m and inter-vaccination time intervals t_m will be applied, where θ_m and t_m are defined by the data

registered from the vaccination rate θ_i and the inter-vaccination time intervals of the non-regular impulsive vaccination strategies of section 3.6.1 and 3.6.2 respectively. Namely:

$$\theta_m = \frac{\sum_{i=1}^n S(t_i)\theta_i}{\sum_{i=1}^n S(t_i)}, t_m = \frac{1}{n} \sum_{i=1}^n t_v(i) \quad (3.50)$$

i.e., t_m is the average value of the inter-vaccination time intervals in the simulation corresponding to the strategies of Section 3.6.2 and θ_m is and average value of the vaccination rate corresponding to strategies of section 3.6.1 pondered with the susceptible subpopulation at the impulsive instants. The results show the differences over 70 years of simulation of the susceptible and the vaccinated subpopulations between the regular and the VR-IQ strategy, as it can be seen at the 1st and 2nd graphic of figure 3.2. The change of rate between the vaccinated and susceptible subpopulations has a direct impact in the evolution of the recovered and exposed subpopulations (3rd and 5th graphic) which subsequently, shapes the value of the infectious subpopulation as is seen in the 4th graphic dropping to depreciable amounts at ($I < 10^{-7}$) so that the disease is considered effectively controlled. Finally, the value of the total population (6th graphic) is influenced by the extra death derived from the disease. The velocity of the disease decrement is also very important, as the disease cost DC can be too high if the infectious subpopulation presents high values for a long time. It is seen that the infectious subpopulation reaches an acceptable minimum level more rapidly when the VR-IQ is applied instead of the regular impulsive vaccination. The death rate related to the disease is proportional to the number of infectious subpopulation, so the disease cost (DC) will give us also the total number of deaths caused by the disease after the simulation time, namely, $DC = A \int_0^{t_f} I(t)dt = A'[Death\ by\ disease]$, where A and A' are some positive constants.

It can be seen at figure 3.3 the consequences of the different dynamics induced in figure 3.2 for the regular impulsive vaccination and the non-regular impulsive one using the VR-IQ rule. Both strategies have similar vaccination cost but they differ clearly in the disease cost. In this sense, the mortality by causes related to the infection is higher when a regular impulsive vaccination is used instead of a non-regular one with the VR-IQ rule. Table 3.1 present the death numbers after 70 years for each vaccination strategy against a regular impulsive vaccination with the same VC.

It can be seen in table 3.1 that, with the exceptions of the IVI-IG₂ and the VR-SG rules, the non-regular impulsive vaccination strategies are more effective and are able to control more rapidly an outbreak than the regular impulsive vaccination one. A better visualization of the costs of these strategies can be seen in figure 3.4. In these graphics, the vaccination and disease costs corresponding to different non-regular impulsive vaccination strategies are compared to the costs of several regular impulsive vaccination strategies. For such purpose, two set of simulations are developed. The first set (discontinuous line) uses the same value for the inter-vaccination time intervals ($t_v = 1$) and different constants values for θ , one value for each simulation The

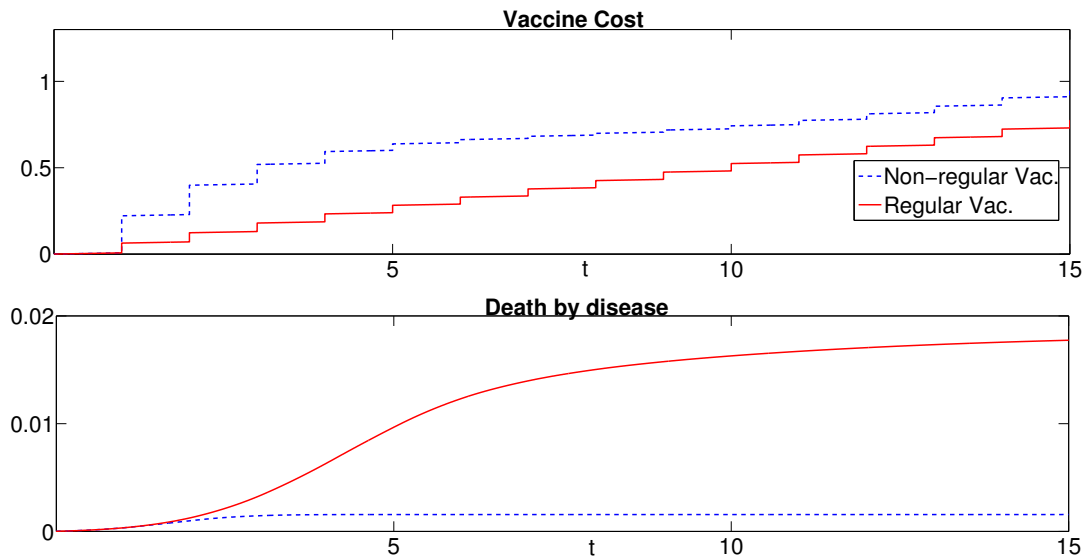


Figure 3.3: Vaccination cost and number of deaths by infection versus time for a non-regular impulsive vaccination with VR-IQ strategy and a regular impulsive vaccination.

second (continuous lines) uses a constant value for θ and different constant values for t_v within $t_v \in (0.4 - 1.5)$, one value of θ for each line ($\theta = \{0.05, 0.25, 0.45, 0.65\}$). The most adequate non-regular impulsive vaccination strategy can be identified in the graphic as the costs decreases in both axis. The non-regular impulsive vaccination rate strategies based on the VR-IQ rules clearly present the minimum VC and the fastest decrement of the infectious subpopulation minimizing DC.

3.8 Vaccination strategies on a known disease: Pertussis

After proving the efficiency of the vaccination strategies in a generic disease, the method is applied to a specific disease so it can be tested in a simulation of an actual disease. The pertussis (whooping cough) has been chosen as it presents a temporary immunity while it still has a significant death ratio [35], [36] so all the parameters are suitable to the SVEIRS model. According to the available data of pertussis, these model parameters are: $\tau = 8 \text{ days}$, $\omega = 12 \text{ years}$, $\gamma^{-1} = 15 \text{ days}$, $\gamma_1^{-1} = 4 \text{ days}$. A small mortality rate associated to the disease is given by $\alpha^{-1} = 3.8 \text{ years}$, while the parameters independent of the disease, such as the characteristic growth and death rate of the population, the newborn vaccination rate and the saturation parameters for the vaccine and susceptible subpopulation remain the same as in the previous simulation ($b_2^{-1} = 70 \text{ years}$, $b_1^{-1} = b_3^{-1} = 140 \text{ years}$, $V_c = 1$, $\delta = 0.2$, $\eta = 0.18$). The disease transmission constant β is set so that the reproduction number is $R_0 = 1.5$.

Vacc. Strategy	Deaths (Non-Regular)	Deaths (Regular)
VR-IQ $-C_I\epsilon(4 - 12)$	$10^{-3} - 8 \times 10^{-3}$	$9 \times 10^{-3} - 13 \times 10^{-3}$
VR-SQ ₁ $-C_S\epsilon(.04 - .12)$	$5 \times 10^{-4} - 2 \times 10^{-4}$	$9 \times 10^{-3} - 12 \times 10^{-3}$
VR-SQ ₂ $-a \in (1.3 - 4)$	$5 \cdot 10^{-4} - 6 \times 10^{-4}$	$7 \times 10^{-4} - 10 \times 10^{-4}$
VR-IG ₁ $-C_I\epsilon(40 - 120) - \dot{I}'$	$\sim 5 \times 10^{-4}$	$5 \times 10^{-4} - 50 \times 10^{-4}$
VR-IG ₂ $-C_I\epsilon(40 - 120) - \frac{\Delta I'}{\Delta t}$	$\sim 5 \times 10^{-4}$	$5 \times 10^{-4} - 40 \cdot 10^{-4}$
VR-SG ₁ $-C_S\epsilon(10 - 90) - \dot{S}'$	$5 \times 10^{-4} - 28 \times 10^{-4}$	$5 \times 10^{-4} - 14 \times 10^{-4}$
VR-SG ₂ $-C_S\epsilon(10 - 90) - \frac{\Delta S'}{\Delta t}$	$5 \times 10^{-4} - 15 \times 10^{-4}$	$5 \times 10^{-4} - 14 \times 10^{-4}$
IVI-IQ $-C_I\epsilon(50 - 125)$	$3 \times 10^{-3} - 3.5 \times 10^{-3}$	$4 \times 10^{-3} - 6 \times 10^{-3}$
IVI-SQ ₁ $-C_S\epsilon(2 - 6)$	$2.85 \times 10^{-3} - 2.87 \times 10^{-3}$	$2.9 \times 10^{-3} - 3.1 \times 10^{-3}$
IVI-SQ ₂ $-a \in (0.67 - 1.67)$	$2 \times 10^{-2} - 6 \times 10^{-2}$	$2 \times 10^{-2} - 6 \times 10^{-2}$
IVI-IG ₁ $-C_I\epsilon(25 - 62) - \dot{I}'$	$0.9 \times 10^{-2} - 1.7 \times 10^{-2}$	$2.2 \times 10^{-2} - 2.3 \times 10^{-2}$
IVI-IG ₂ $-C_I\epsilon(25 - 62) - \frac{\Delta I'}{\Delta t}$	$3 \times 10^{-3} - 6 \cdot 10^{-3}$	$14 \cdot 10^{-3} - 30 \times 10^{-3}$
IVI-SG ₁ $-C_S\epsilon(0.67 - 1.67) - \dot{S}'$	$27 \cdot 10^{-3} - 28 \cdot 10^{-3}$	$3.4 \cdot 10^{-3} - 3.8 \times 10^{-3}$
IVI-SG ₂ $-C_S\epsilon(0.67 - 1.67) - \frac{\Delta S'}{\Delta t}$	$2.9 \cdot 10^{-3} - 3.1 \cdot 10^{-3}$	$2.82 \cdot 10^{-3} - 2.85 \cdot 10^{-3}$

Table 3.1: Deaths for different strategies.

Initial conditions are set near to the DFE ($S(0) = S^*$, $V(0) = V^*$ and $R(0) = R^*$) plus a small perturbation of infected subpopulation ($I(0) = 0.0001N^*$). First, given the same initial conditions, it is compared the DC and VC (see section 3.7) of a non-regular impulsive vaccination strategy with an adaptive vaccination rate θ_i to the DC and VC derived from a regular vaccination strategy. The VR-IQ strategy from Section 3.6.1 is chosen, in which an impulse vaccination is administered annually ($t_v = 1$) to a fraction θ_i of the susceptible subpopulation, which can vary between 0 and 1. It is seen in figure 3.5 that when the non-regular strategy is applied the DC, proportional to the deaths resulting from pertussis, is reduced substantially (56%), while the VC, derived from the number of vaccines administered, is only slightly increased (4%). Another comparison is made between a non-regular impulsive vaccination strategy with adaptive inter-vaccination time intervals and a regular impulsive vaccination strategy. The IVI-IG vaccination rule based on the infectious population growth from section 3.6.2 is chosen, in which an impulsive vaccination is administered at a constant rate to the susceptible subpopulation ($\theta = 0.05$) varying the interval between the impulses from 5 to 18 months ($t_v \in [0.41, 1.5]$), and compare the DC and VC to a regular vaccination strategy with the same vaccination rate and an inter-vaccination time interval which would be the average obtained from the non-regular IVI-IG strategy. It can be seen at figure 3.6 the result in terms of vaccines administered over time and extra deaths resulting from pertussis, which are proportional to the VC and DC respectively. It can be seen that when the non-regular strategy is applied, the DC is reduced approximately to a 19% while the VC only increases a 5%. The difference of the vaccinated subpopulation between the impulsive vaccination with adaptive time intervals and the regular one can be seen at figure 3.7. Observe that in the case of the non-regular impulsive vaccination, a pattern of intensive vaccination emerges at intervals concurring with the average immunity time.

3.9 Conclusion

Theoretically valid impulsive vaccination strategies are presented and studied in order to eradicate an infectious disease. A new impulsive reproduction number is developed here, related to the inter-vaccination time interval and the impulsive vaccination rate. The impulsive reproduction number gives us a first method for studying the stability of periodic solutions for subpopulations around the DFE point when such an equilibrium point is unstable with a regular non-impulsive vaccination strategy. It is the basis for controlling contagious diseases by means of prevention actions and for describing the model and the usefulness of the application of regular or non-regular (adaptive) impulsive vaccination strategies. The model may present an unstable disease-free equilibrium point under regular non-impulsive vaccination, but if a certain impulsive vaccination is applied, the system reaches a disease-free periodic state. Although the values of the subpopulations are constantly adjusted by impulsive vaccination, both the steady state oscillation reached under the regular impulsive vaccination and the DFE state have virtually eradicated the infected subpopulation. A non-regular adjustable vaccination strategy is proposed based on a set of rules that update the vaccination rate at each vaccination instant, which are uniformly distributed in time. Another set of rules maintain the vaccination rate constant and update the inter-vaccination time intervals. Both alternatives improve the result about the eradication of the disease compared with the results obtained with a regular impulsive vaccination. In the case of pertussis, the disease cost is reduced substantially at the expense of a small increase in the vaccination cost.

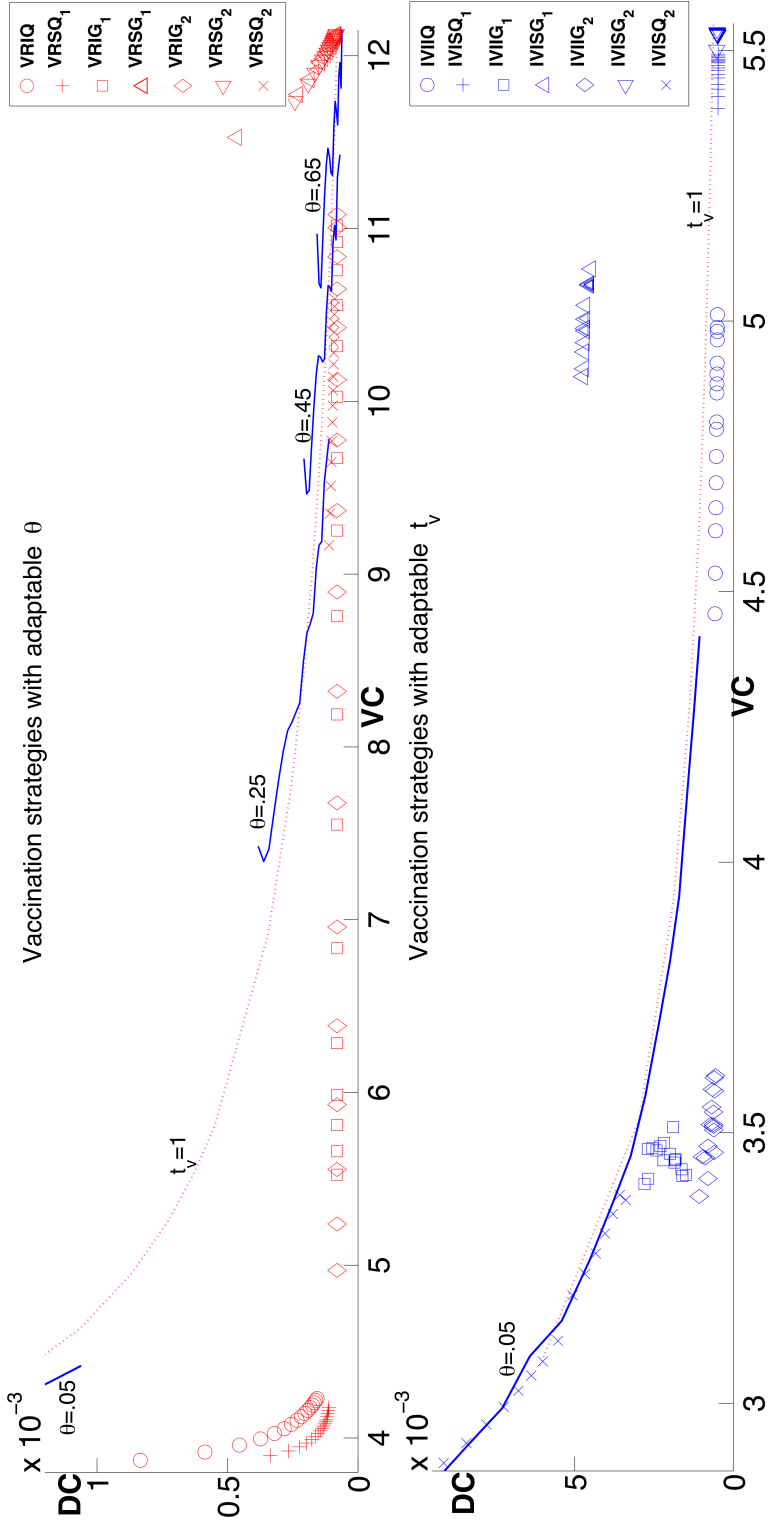


Figure 3.4: A disposition of the different DC (Assuming $A=1$) and VC values for the vaccination strategies with the constants C_I and C_S from Table 3.1. The graphic of the top presents the vaccination strategies from section 3.6.1, while the graphic of the bottom presents the strategies from section 3.6.2. The discontinuous line in both graphics represents the DC/VC values of a regular impulsive vaccination with $t_v = 1$ for $\theta \in (0, 1)$. The continuous lines represent the cost values associated to regular impulsive vaccination with different $t_v \in (0.4, 1.5)$, for a set of different values of $\theta = \{0.05, 0.25, 0.45, 0.65\}$.

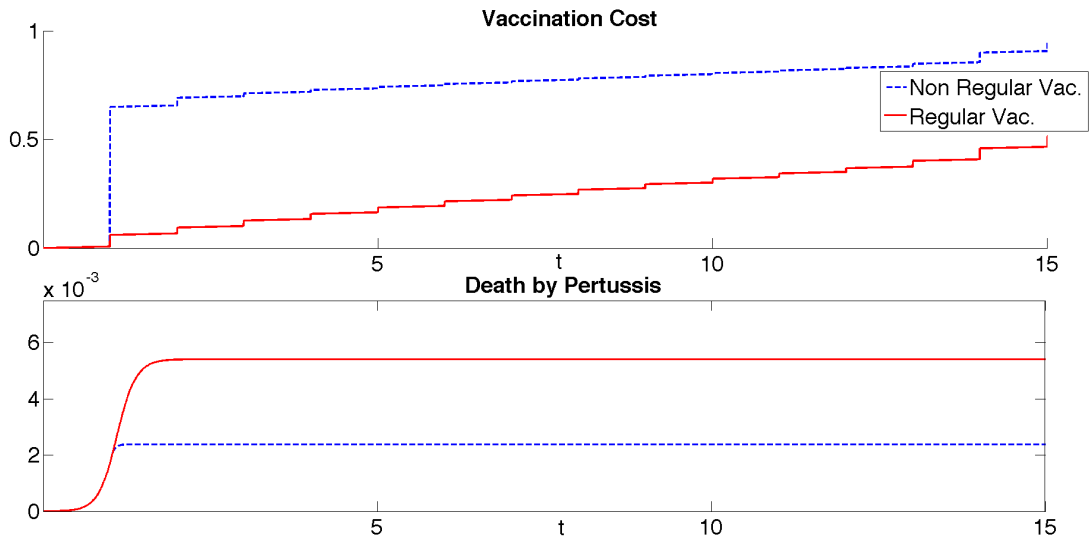


Figure 3.5: Vaccination cost and number of deaths by infection versus time for a regular and a non-regular impulsive vaccination strategy (VR-IQ).

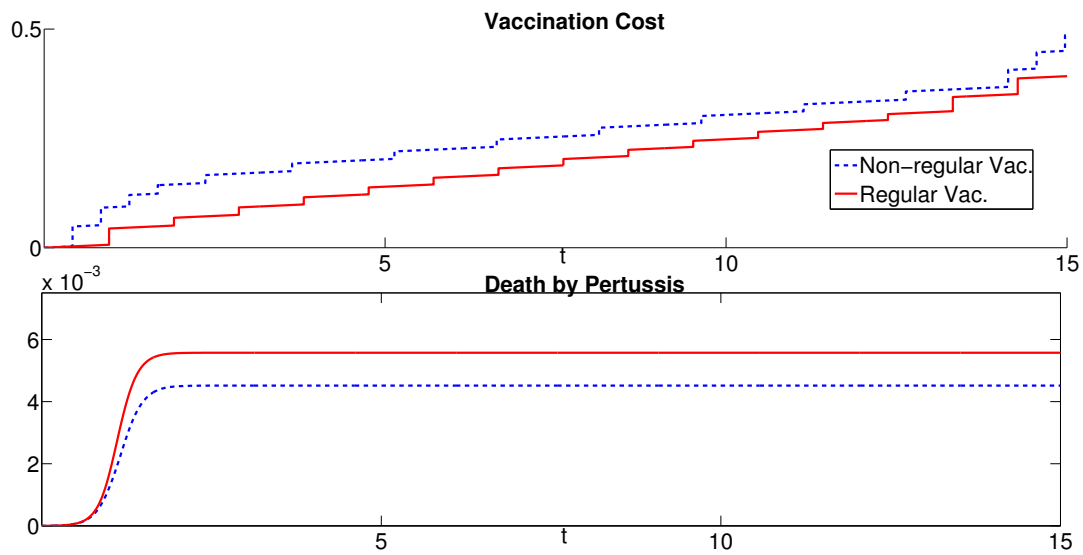


Figure 3.6: Vaccination cost and number of deaths by infection versus time for a regular and a non-regular impulsive vaccination strategy (IVI-IG).

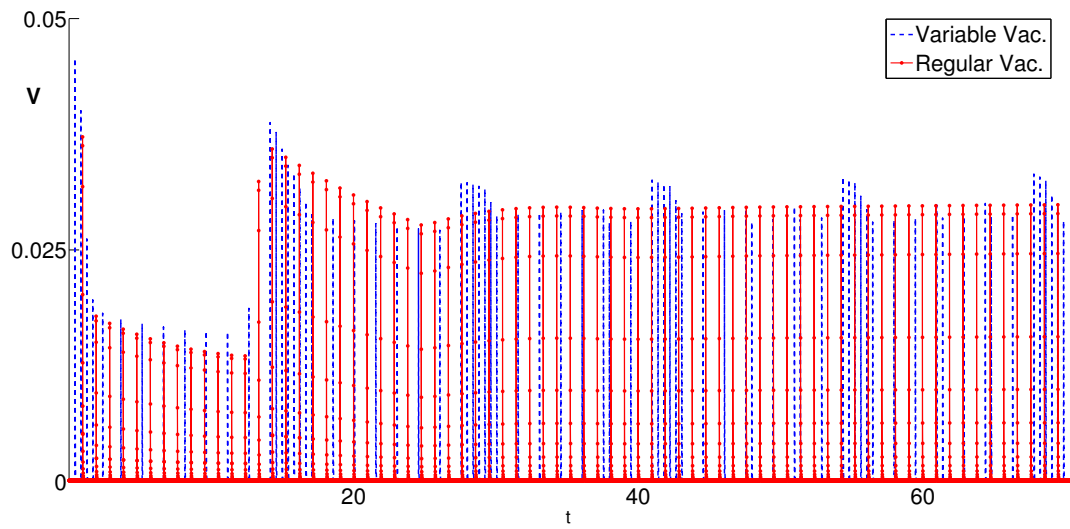


Figure 3.7: Evolution over time (years) of vaccinated subpopulation from initial conditions near to DFE, given a regular and a non-regular impulsive vaccination strategy (IVI-IG).

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Limit periodic solutions of a SEIRS mathematical model for non-lethal infectious disease

In this chapter, the equilibrium states of a simple SEIRS model of an infectious disease with variable parameters are analysed. The SEIRS model with a delay is presented under a set of parameters varying periodically, characteristic to the seasonality of the disease. The final equilibrium state, determined by these parameters, is obtained with a general method, proposed in this chapter, based on a Fourier analysis of the dynamics of the subpopulations. Then the stability of these equilibrium states for a general and some particular cases will be contemplated, and simulations will be made in order to confirm the predictions.

4.1 Introduction

The real impact a disease may produce on a population is usually difficult to estimate. The complex interactions between the sick and the healthy individuals that get infected play an important role in this uncertainty. Also, the conditions of this disease transmission may not be always the same as the season changes, or the immunity of the population may be boosted with vaccines, so the predictions become even more problematic. However, on big populations, a mathematical model representing the different possible stages of the disease can be a great aid in order to make a quantitative analysis of its evolution over time [1]-[3]. In this context, the whole population is classified in different subpopulations based on the status of each individual, with respect to the disease. The dynamics of such subpopulations can be described with multiple models, from simple equations with constant parameters [4], [5] to big complex models with many different subpopulations [6]-[10] and variable parameters over time [11], [2]. Sometimes these variable parameters represent a disease with a seasonal transmission rate or a disease being treated with a vaccination strategy applied only at specific moments of the year. Thus, the analysis of these mathematical models can be helpful to determine the best control strategy against the infection of new individuals [12], [13].

In this chapter, a SEIRS model is introduced based on a simplified version of the SVEIR model of previous chapters and other works studied in [14] and [15], [6]-[10]. As the vaccinated subpopulation is omitted, the effects of the saturation on the disease transmission are discarded. The purpose of this simplification is to obtain a less complicated formula for the values for the endemic subpopulations, so an analysis of the oscillatory regime can be made. The SEIRS model presents a disease with

two different stages: The first stage affects to the subgroup of the population which has been exposed and infected, but has not fully developed the disease yet. The second stage arises from the previous latent state to a fully developed one, in which all symptoms are present and the disease is infectious. The recovered state refers to the moment when the disease is defeated by the organism and becomes immune for a certain period of time, before it becomes susceptible to the disease again[16]-[18]. In this model it is also applied a vaccination strategy to the newborns which immunizes them from the disease without having to suffer from it. The strategy can be constant or adapt to the state of the disease. In this chapter, the simplest disposition of the SEIRS parameters will be studied in first place, analyzing the model under a constant vaccination and disease transmission rate. The equilibrium points and their stability will be obtained and discussed. Then, the new equilibrium states and their stability will be obtained after introducing a periodic vaccination rate $V_c(t+T) = V_c(t)$ which immunizes a fraction of the susceptible subpopulation, and a periodic disease transmission rate $\beta(t+T) = \beta(t)$. The predictions from the theory will be verified in the following simulations.

4.1.1 Notation

Parameters

- b_1, b_3 : Birth rates of the population, a constant one (b_1) which produces susceptible individuals and another one with an access to vaccination (b_3) producing a fraction (V_c) of immune individuals.
- b_2 : Natural death rate of any subpopulation.
- V_c : Fraction of the population which is vaccinated since birth ($V_c \in [0, 1]$). It can be constant through time or present a periodicity $V_c(t+T) = V_c(t)$.
- β : Transmission rate of the disease. It can be constant through time or present a periodicity $\beta(t+T) = \beta(t)$.
- κ : Transition rate from the latent disease at the exposed subpopulation to the infectious subpopulation ($E \rightarrow I$).
- γ : Transmission rate from the infectious subpopulation to the recovered subpopulation ($I \rightarrow R$).
- ω : Average time of transition from immune to susceptible subpopulation.

4.2 The SEIRS model

Figure 4.1 represents the dynamics of an infectious disease, which can be described by the equations:

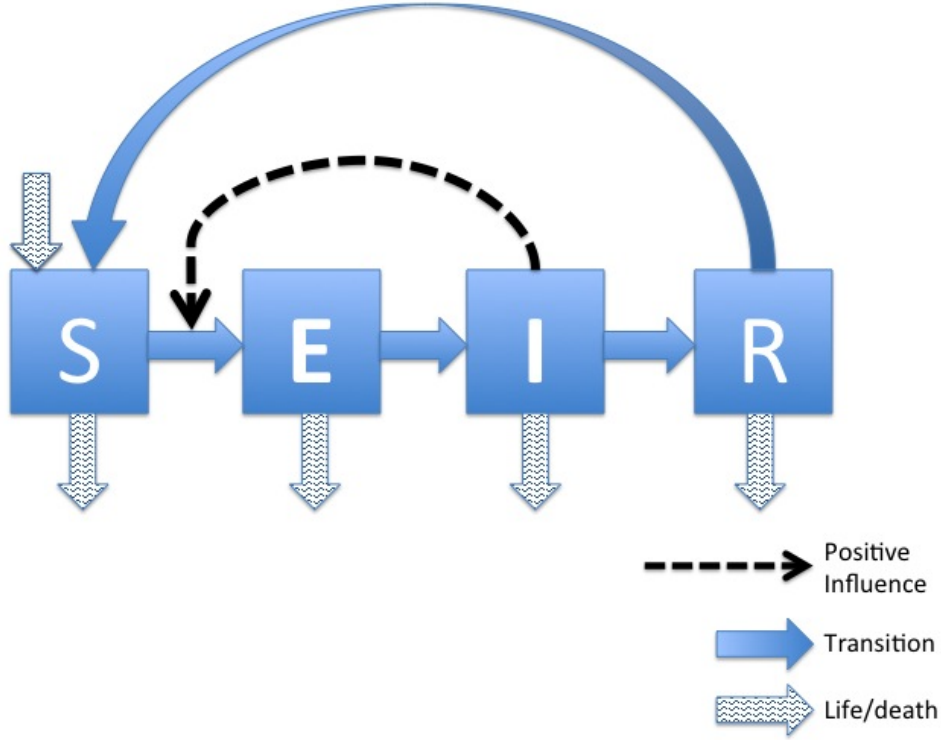


Figure 4.1: The SEIRS epidemic model

$$\dot{S}(t) = b_1 + b_3(1 - V_c(t)) - \beta(t)S(t)I(t) + \gamma I(t - \omega)e^{-b_2\omega} - b_2S(t) \quad (4.1)$$

$$\dot{E}(t) = \beta(t)S(t)I(t) - (b_2 + \kappa)E(t) \quad (4.2)$$

$$\dot{I}(t) = \kappa E(t) - (b_2 + \gamma)I(t) \quad (4.3)$$

$$\dot{R}(t) = b_3V_c(t) + \gamma(I(t) - I(t - \omega)e^{-b_2\omega}) - b_2R(t) \quad (4.4)$$

Observe that there is no additional death rate for the infectious subpopulation, as the disease is non lethal. Therefore, the dynamics of the total population $S(t) + E(t) + I(t) + R(t) = N(t)$ is described as:

$$\dot{N}(t) = b_1 + b_3 - b_2N(t) \quad (4.5)$$

The final total population tends to:

$$N^* = \frac{b_1 + b_3}{b_2} \quad (4.6)$$

This model holds an important interaction between the susceptible, exposed and infectious subpopulations, whose dynamics are independent from the recovered subpopulation. Observe also that, under conditions $S(0) \geq 0$, $E(0) \geq 0$, $I(0) \geq 0$, if the time t_E is defined

$$t_E = \{t | E(t) = 0 \wedge S(t_0) \geq 0 \wedge I(t_0) \geq 0 \forall t_0 \leq t\} \quad (4.7)$$

then, from equation (4.2) $\dot{E}(t_E) = \beta S(t_E)I(t_E) \geq 0$, so the first of the three (S, E, I) subpopulations to be negative cannot be the exposed one. In the same way, if the time t_I is defined

$$t_I = \{t | I(t) = 0 \wedge S(t_0) \geq 0 \wedge E(t_0) \geq 0 \forall t_0 \leq t\} \quad (4.8)$$

then, from equation (4.3) $\dot{I}(t) = \kappa E(t_I) \geq 0$, therefore the infectious subpopulation cannot be the first subpopulation to be negative either. Finally for the susceptible subpopulation the time t_S is defined as

$$t_S = \{t | S(t) = 0 \wedge E(t_0) \geq 0 \wedge I(t_0) \geq 0 \forall t_0 \leq t\} \quad (4.9)$$

such that from equation (4.1) $\dot{S}(t_S) = b_1 + b_3(1 - V_c(t_S)) + \gamma e^{-b_2\omega} I(t_S - \omega) \geq 0$. Therefore, neither the exposed or infected nor the susceptible subpopulation will be the first negative subpopulation of the three. Thus, one deduces that $S(t) < 0$ is impossible for any $t \geq 0$.

From equations (4.5) and (4.6), the evolution of the total population is defined as

$$N(t) = N(0)e^{-b_2t} + N^*(1 - e^{-b_2t}) \quad (4.10)$$

The maximum value of the total population will be defined as $N_{max} = \max\{N(0), N^*\}$ and given N_{max} it is determined a new value $R_m = \frac{\gamma e^{-b_2\omega}}{b_2 - \gamma e^{-b_2\omega}} N_{max}$, and defined the time instant :

$$t_R = \{t | R(t) = -R_m\} \quad (4.11)$$

As the infectious subpopulation is defined non-negative, it is obtained that

$$\min_{t \in (0, t_R)} (I(t) - e^{-b_2\omega} I(t - \omega)) \geq \min_{t \in (0, t_R)} (I(t)) - e^{-b_2\omega} \max_{t \in (0, t_R)} (I(t)) \geq -(N_{max} - R_m) \quad (4.12)$$

so

$$\begin{aligned} \dot{R}(t_R) &\geq -b_2 R(t_R) + \gamma \min_{t \in (0, t_R)} (I(t) - e^{-b_2\omega} I(t - \omega)) + b_3 V_c(t_R) \geq b_3 V_c(t_R) \\ &\geq -b_2 R(t_R) - \gamma \max_{t \in (0, t_R)} (e^{-b_2\omega} I(t - \omega)) + b_3 V(t_R) \geq b_3 V(t_R) \end{aligned} \quad (4.13)$$

Therefore, the recovered subpopulation will never reach a value below the value defined as $-R_m$.

4.3 Equilibrium points under a constant V_c and β

4.3.1 Disease free equilibrium

Given the equations in (4.1)-(4.4) and constant values for the vaccination V_c and the infectious rate β , let $\{S^*, E^*, I^*, R^*\}$ be the subpopulations at the equilibrium point, i.e.: $\lim_{t \rightarrow \infty} (S(t), E(t), I(t), R(t))^T = (S^*, E^*, I^*, R^*)^T$.

Since the subpopulation values are constant at this point, the delay dependence disappears as $\lim_{t \rightarrow \infty} I(t - \omega) = \lim_{t \rightarrow \infty} I(t) = I^*$, and equations (4.1)-(4.4) become:

$$\begin{cases} b_1 + b_3(1 - V_c) - \beta S^* I^* - b_2 S^* + \gamma I^* e^{-b_2 \omega} & = 0 \\ \beta S^* I^* - (b_2 + \kappa) E^* & = 0 \\ \kappa E^* - (b_2 + \gamma) I^* & = 0 \\ b_3 V_c + \gamma(1 - e^{-b_2 \omega}) I^* - b_2 R^* & = 0 \end{cases} \quad (4.14)$$

These equations present two possible solutions representing two equilibrium points. One of them is free from the disease as subpopulations E and I are equal to zero, and the other one presents an endemic state with a permanent infected subpopulation. First it is consider the disease-free equilibrium (DFE) point, where $E^* = I^* = 0$ and the final state from equation (4.14) is used to obtain the values of the subpopulations:

$$S^* = S_{dfe} = \frac{b_1 + b_3(1 - V_c)}{b_2} \quad (4.15)$$

$$E^* = E_{dfe} = 0 \quad (4.16)$$

$$I^* = I_{dfe} = 0 \quad (4.17)$$

$$R^* = R_{dfe} = \frac{b_3 V_c}{b_2} \quad (4.18)$$

Local Stability of the DFE point

Proposition 4.1.

The DFE equilibrium point is locally asymptotically stable for any delay $\omega \in [0, \omega^*)$ for some small enough ω^* , if $R_0 = \frac{S_{dfe} \beta \kappa}{(b_2 + \kappa)(b_2 + \gamma)} < 1$.

Proof.

First, the dynamic equations (4.14) around the DFE point are linearized by means of the associated Jacobi matrix $\mathbf{J} = [J_{ij}] = \left[\frac{\partial x_i}{\partial x_j} \right]$ for $i, j \in \{1, 2, 3, 4\}$, with $x_1 \equiv S$, $x_2 \equiv E$, $x_3 \equiv I$ and $x_4 \equiv R$ evaluated at the DFE point.

Such a Jacobi matrix is defined as

$$\mathbf{J}|_{x_{dfe}} = \begin{pmatrix} -b_2 & 0 & -\beta S_{dfe} + \gamma e^{-b_2 \omega} & 0 \\ 0 & -(b_2 + \kappa) & \beta S_{dfe} & 0 \\ 0 & \kappa & -(b_2 + \gamma) & 0 \\ 0 & 0 & \gamma(1 - e^{-b_2 \omega}) & -b_2 \end{pmatrix} \quad (4.19)$$

The eigenvalues of the Jacobi matrix are obtained by calculating the roots of the characteristic equation:

$$\text{Det}(\lambda I - \mathbf{J}) = 0 \quad (4.20)$$

Such eigenvalues are given by:

$$\lambda_i = \left\{ -b_2, -b_2, \frac{-(2b_2 + \gamma + \kappa) - \sqrt{(\gamma - \kappa)^2 + 4\beta\kappa S_{dfe}}}{2}, \right. \\ \left. \frac{-(2b_2 + \gamma + \kappa) + \sqrt{(\gamma - \kappa)^2 + 4\beta\kappa S_{dfe}}}{2} \right\} \quad (4.21)$$

The real part of λ_i must be negative so that the linearized system is asymptotically stable and the SEIRS model locally stable. The eigenvalues λ_1 , λ_2 and λ_3 are defined always negative, as all parameters are positive. However, the fourth eigenvalue λ_4 is only defined negative if $(2b_2 + \gamma + \kappa) > \sqrt{(\gamma - \kappa)^2 + 4\beta\kappa S_{dfe}}$. This inequality can be rearranged as:

$$R_0 = \frac{\beta\kappa S_{dfe}}{(b_2 + \kappa)(b_2 + \gamma)} < 1 \quad (4.22)$$

Since the eigenvalues of the Jacobian matrix are continuous functions of all its entries, there is a sufficiently small delay perturbation ω^* which guarantee the local stability of the DFE point for any delay $\omega \in [0, \omega^*)$. \square

4.3.2 Endemic equilibrium

From the equations in (4.14) it is obtained the subpopulations at endemic equilibrium point, namely:

$$S^* = S_{end} = \frac{(b_2 + \kappa)(b_2 + \gamma)}{\beta\kappa} \quad (4.23)$$

$$E^* = E_{end} = \frac{b_2(b_2 + \gamma)(S_{dfe} - S_{end})}{\kappa(\beta S_{end} - \gamma e^{-b_2\omega})} \quad (4.24)$$

$$I^* = I_{end} = \frac{b_2(S_{dfe} - S_{end})}{\beta S_{end} - \gamma e^{-b_2\omega}} \quad (4.25)$$

$$R^* = R_{end} = R_{dfe} + \frac{\gamma(1 - e^{-b_2\omega})(S_{dfe} - S_{end})}{\beta S_{end} - \gamma e^{-b_2\omega}} \quad (4.26)$$

Observe that the term $\beta S_{end} - \gamma e^{-b_2\omega}$ will be defined positive, since all parameters are defined positive, so it is obtained

$$\beta S_{end} - \gamma e^{-b_2\omega} = \frac{(b_2 + \kappa)(b_2 + \gamma)}{\kappa} - \gamma e^{-b_2\omega} \quad (4.27) \\ = \gamma(1 - e^{-b_2\omega}) + b_2 \left(1 + \frac{b_2 + \gamma}{\kappa} \right) \geq 0$$

A sufficient condition for the positivity of the recovered subpopulation at the equilibrium point, and necessary and sufficient for the positivity of the exposed and infectious, is that $S_{dfe} \geq S_{end}$ or, equivalently, $R_0 = \frac{S_{dfe}}{S_{end}} \geq 1$ (at $R_0 = 1$ the subpopulations becomes the ones of the DFE point). Observe that since the exposed and infectious subpopulations have been proven to be positive or zero, there is only one possible equilibrium point when $R_0 < 1$, which is the DFE.

Local stability of the Endemic Point

Proposition 4.2.

The endemic equilibrium point is locally asymptotically stable for $\omega \in [0, \omega^*)$ for some ω^* small enough, if $R_0 = \frac{S_{df}e^{\beta\kappa}}{(b_2+\kappa)(b_2+\gamma)} > 1$.

Proof.

As in the DFE point of the proposition 4.1, the dynamic equations from (4.14) is linearized around the endemic point, by means of the associated Jacobi matrix $\mathbf{J} = [J_{ij}] = [\frac{\partial \dot{x}_i}{\partial x_j}]$ for $i, j \in \{1, 2, 3, 4\}$ with $x_1 \equiv S$, $x_2 \equiv E$, $x_3 \equiv I$ and $x_4 \equiv R$ evaluated at such an endemic point.

The Jacobi matrix is given by

$$\mathbf{J}|_{x_{end}} = \begin{pmatrix} -\frac{b_2\Phi}{\Lambda} & 0 & -\Lambda & 0 \\ \frac{b_2(\Phi-\Lambda)}{\Lambda} & -(b_2 + \kappa) & \Lambda + \gamma e^{-b_2\omega} & 0 \\ 0 & \kappa & -(b_2 + \gamma) & 0 \\ 0 & 0 & \gamma(1 - e^{-b_2\omega}) & -b_2 \end{pmatrix} \quad (4.28)$$

being $\Lambda = \beta S_{end} - \gamma e^{-b_2\omega}$ and $\Phi = \beta S_{end} R_0 - \gamma e^{-b_2\omega}$. The eigenvalues of this matrix are obtained by calculating the roots of the characteristic equation:

$$\text{Det}(\lambda I - \mathbf{J}) = F(\lambda) = 0 \quad (4.29)$$

In order to have a locally asymptotically stable state, the four roots of the equation λ_i from the solutions $F(\lambda_i) = 0$ must have a negative real part.

$$F(\lambda) = (\lambda + b_2) \left(\lambda^3 + (b_2 \frac{\Phi}{\Lambda} + 2b_2 + \gamma + \kappa) \lambda^2 + b_2(2b_2 + \kappa + \gamma) \frac{\Phi}{\Lambda} \lambda + b_2 \kappa (\Phi - \Lambda) \right) = 0 \quad (4.30)$$

A characteristic root is $\lambda_1 = -b_2$. The remaining equation is equivalent to $g(\lambda) = b_2 \kappa \Lambda (p - 1) + \alpha p b_2 \lambda + (\alpha + p b_2) \lambda^2 + \lambda^3$, being $\alpha = (2b_2 + \gamma + \kappa)$ and $p = \phi/\Lambda$. For $R_0 < 1$, which implies that $p < 1$, coefficients have different signs, implying that at least there is a non negative root of $g(\lambda)$. The Routh-Hurwitz criterion [19, 20] says that for $p > 1$, i.e. $R_0 > 1$, all roots present a negative real part so the system is locally asymptotically stable. Thus, since the eigenvalues of the Jacobian matrix are continuous functions of all its entries, there is sufficiently small delay perturbation ω^* which guarantee the local stability of the endemic point for any delay $\omega \in [0, \omega^*)$. \square

4.4 Equilibrium states under a periodic vaccination $V_c(t)$ and infectious rate $\beta(t)$

In this section, a periodic vaccination $V_c(t)$ and a periodic transmission rate $\beta(t)$ are applied to the SEIRS model. This periodic variables can be described using the

Fourier series formalism as:

$$\beta(t) = \sum_{n=-\infty}^{\infty} \beta_n e^{i(n\rho t)} \quad (4.31)$$

$$V_c(t) = \sum_{n=-\infty}^{\infty} V_n e^{i(n\rho t)} \quad (4.32)$$

being the frequency related to the seasonal periodicity T , $\rho = \frac{2\pi}{T}$. The dynamic of the subpopulations at the periodic equilibrium state would be also described in the same way, namely:

$$\begin{cases} S^*(t) = \sum_{n=-\infty}^{\infty} S_n e^{i(n\rho t)} \\ E^*(t) = \sum_{n=-\infty}^{\infty} E_n e^{i(n\rho t)} \\ I^*(t) = \sum_{n=-\infty}^{\infty} I_n e^{i(n\rho t)} \\ R^*(t) = \sum_{n=-\infty}^{\infty} R_n e^{i(n\rho t)} \end{cases} \quad (4.33)$$

The dynamic equations from (4.1)-(4.4) are applied to the periodic equilibrium state from 4.14

$$\begin{cases} (b_1 + b_3)\delta_n - b_3 V_n - Q_n - b'_n S_n + \gamma e^{-b'_n \omega} I_n = 0 \\ Q_n - (b'_n + \kappa) E_n = 0 \\ \kappa E_n - (b'_n + \gamma) I_n = 0 \\ b_3 V_n + \gamma(1 - e^{-b'_n \omega}) I_n - b'_n R_n = 0 \end{cases} \quad (4.34)$$

where $b'_n = b_2 + in\rho$ and

$$\delta_n = \begin{cases} 1 & \text{if } n = 0 \\ 0 & \text{if } n \neq 0 \end{cases} \quad (4.35)$$

Being

$$Q_n = \sum_{j=-\infty}^{\infty} \beta_j P_{n-j} \quad (4.36)$$

$$\text{and } P_n = \sum_{j=-\infty}^{\infty} S_j I_{n-j} \quad (4.37)$$

Then, the solution for each subpopulation and each coefficient is:

$$\begin{cases} S_n = \frac{\delta_n(b_1 + b_3) - b_3 V_n}{b'_n} - \frac{\Upsilon_n Q_n}{b'_n \alpha_n} \\ E_n = \frac{Q_n}{\kappa + b'_n} \\ I_n = \frac{Q_n}{\alpha_n} \\ R_n = \frac{b_3 V_n}{b'_n} + \frac{\gamma(1 - e^{-b'_n \omega})}{\alpha_n b'_n} Q_n \end{cases} \quad (4.38)$$

being $\alpha_n = \frac{(b'_n + \kappa)(b'_n + \gamma)}{\kappa}$ and $\Upsilon_n = \alpha_n - \gamma e^{-b'_n \omega}$. The DFE solution, where $E_n = I_n = 0 \forall n$, will lead to $Q_n = 0$ and the definition of the DFE coefficients as:

$$\begin{cases} S_n^{dfe} &= \frac{\delta_n(b_1 + b_3) - b_3 V_n}{b'_n} \\ E_n^{dfe} &= 0 \\ I_n^{dfe} &= 0 \\ R_n^{dfe} &= \frac{b_3}{b'_n} V_n \end{cases} \quad (4.39)$$

Observe that both in the DFE and in the endemic equilibrium solution, the equations for the coefficient shows that $S_n + E_n + I_n + R_n = \delta_n N^*$. Observe also that the general solution for a situation where there is a permanent infected subpopulation $E \neq 0$ and $I \neq 0$ is not trivial, as each Q_n contains infinite terms; however, Q_n are negligible after certain number $n > n_0$, as they converge to zero (See Appendix E). This fact can be used in order to calculate the coefficients for the subpopulations using diverse numerical simulation works.

4.5 Local stability of the equilibrium states

Proposition 4.3.

The DFE equilibrium state is locally asymptotically stable for any delay $\omega \in [0, \omega^*)$ and some small enough ω^* , if $R_0(t) = \frac{S_{dfe}(t)\beta(t)\kappa}{(b_2 + \kappa)(b_2 + \gamma)} < 1 \forall t$.

Proof.

First, dynamic equations from (4.1)-(4.4) are linearized around the DFE state by means of the associated Jacobi matrix $\mathbf{J} = [J_{ij}] = \left[\frac{\partial x_i}{\partial x_j} \right]$ for $i, j \in \{1, 2, 3, 4\}$, with $x_1 \equiv S$, $x_2 \equiv E$, $x_3 \equiv I$ and $x_4 \equiv R$ evaluated at the DFE. The columns of such Jacobi matrix are given by

$$\mathbf{J}|_{x_{dfe}} = \begin{pmatrix} -b_2 & 0 & -\beta(t)S_{dfe}(t) + \gamma e^{-b_2 \omega} & 0 \\ 0 & -(b_2 + \kappa) & \beta(t)S_{dfe}(t) & 0 \\ 0 & \kappa & -(b_2 + \gamma) & 0 \\ 0 & 0 & \gamma(1 - e^{-b_2 \omega}) & -b_2 \end{pmatrix} \quad (4.40)$$

The eigenvalues of this matrix are obtained by calculating the roots of the characteristic equation :

$$\text{Det}(\lambda I - \mathbf{J}) = 0 \quad (4.41)$$

Such eigenvalues are given by:

$$\lambda_i = \left\{ -b_2, -b_2, \frac{-(2b_2 + \gamma + \kappa) - \sqrt{(\gamma - \kappa)^2 + 4\beta(t)\kappa S_{dfe}(t)}}{2}, \frac{-(2b_2 + \gamma + \kappa) + \sqrt{(\gamma - \kappa)^2 + 4\beta(t)\kappa S_{dfe}(t)}}{2} \right\} \quad (4.42)$$

The real part of λ_i must be negative so that the linearized system is asymptotically stable and the SEIRS model locally stable. The eigenvalues λ_1 , λ_2 and λ_3 are defined always negative, as all parameters are positive. However, the fourth eigenvalue λ_4 is only defined negative if $(2b_2 + \gamma + \kappa) > \sqrt{(\gamma - \kappa)^2 + 4\beta(t)\kappa S_{dfc}(t)}$. This inequality can be rearranged as :

$$R_0(t) = \frac{\beta(t)\kappa S_{dfc}(t)}{(b_2 + \kappa)(b_2 + \gamma)} < 1 \quad (4.43)$$

Since the eigenvalues of the Jacobian matrix are continuous functions of all its entries, there is sufficiently small delay perturbation ω^* which guarantee the local stability of the DFE state for any delay $\omega \in [0, \omega^*)$. \square

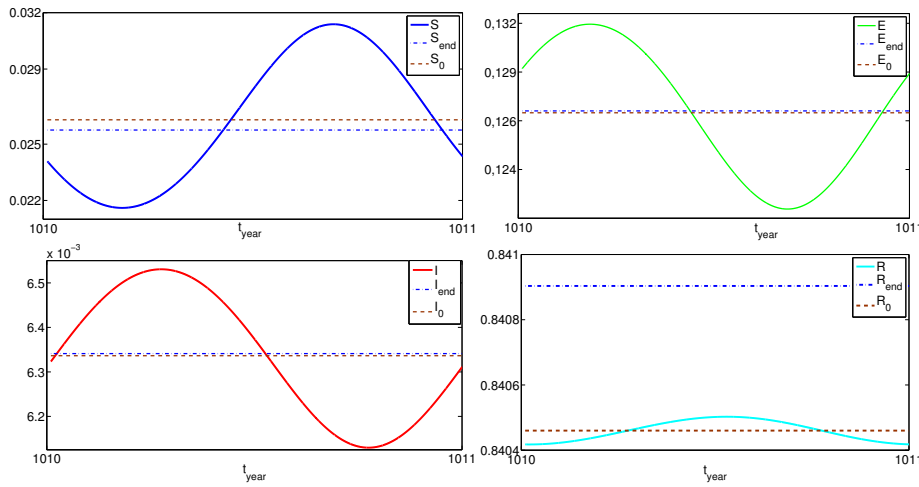


Figure 4.2: The graphics shows the final periodic state of the subpopulations under a $R_0(t) > 1$ (endemic). The dotted lines represent the expected subpopulation given the constant average parameters ($\{SEIR\}_{end}$), and the average values of the subpopulations ($\{SEIR\}_0$) respectively.

4.6 Simulation

A simulation of the model is presented in this section. The SEIRS model is implemented in a Simulink environment integrated in Matlab, with initial parameters for the mortality rate $b_2 = 1/70 \text{ years}^{-1}$ and the natality rates $b_1 = b_3 = 1/140 \text{ years}^{-1}$, so the final population from equation (4.5) would be equal to 1 at the equilibrium ($N^* = 1$).

The transition rate from the exposed subpopulation to the infectious one is $\kappa = 0.5 \text{ years}^{-1}$, the transition rate from the infectious subpopulation to the recovered one is set to $\gamma = 10 \text{ years}^{-1}$, and the average time of immunity is set to $\omega = 10 \text{ years}$.

A series of simulations are presented with different parameters for the transmission rate of the disease β and the vaccination strategy V_c , in order to show the evolution of the subpopulations over time given a reproduction number R_0 higher and below 1. The initial conditions for all simulations will be closed to the DFE point:

$S(0) = S_{dfe}$, $E(0) = 0$, $R(0) = R_{dfe}$ and $I(t) = 0.001N^* \forall t \in (-\omega, 0)$ from equations (4.5) and (4.15)-(4.18).

After the simulation has ran a time long enough, the evolution of the dynamics of the subpopulations reaches the final stable equilibrium state and results can be analyzed. The simplest model is characterized in figure 4.2, where it can be seen the final oscillatory state of the subpopulations given a variable sinusoidal vaccination $V_c(t) = 0.5(1 + \cos(\rho t))$ and a variable disease transmission rate $\beta(t) = 400(1 + 0.5\cos(\rho t))$, being $\rho = 2\pi \text{ rad/year}$, so that during the warm seasons the transmission rate drops to zero, and the maximum values exhibits at the beginning and the ending of the year (the colder season). It should be noted that the equilibrium state is the endemic equilibrium state, as predicted by section 4.5, since $R_0(t) > 1 \forall t$. After analyzing the

Table	Simulated	Predicted
S_0	.0263	.0263
E_0	.1269	.1269
I_0	.0063	.0063
R_0	.8404	.8404
$ S_1 $	2.7×10^{-3}	2.7×10^{-3}
$ E_1 $	2.4×10^{-3}	2.4×10^{-3}
$ I_1 $	0.1×10^{-3}	0.1×10^{-3}
$ R_1 $	0.3×10^{-3}	0.3×10^{-3}
$ S_2 $	1.144×10^{-4}	1.144×10^{-4}
$ E_2 $	1.12×10^{-4}	1.12×10^{-4}
$ I_2 $	0.03×10^{-4}	0.03×10^{-4}
$ R_2 $	0.004×10^{-4}	0.004×10^{-4}
$ S_3 $	2.06×10^{-6}	2.06×10^{-6}
$ E_3 $	2.04×10^{-6}	2.04×10^{-6}
$ I_3 $	0.05×10^{-6}	0.05×10^{-6}
$ R_3 $	0.03×10^{-6}	0.02×10^{-6}

Table 4.1: Coefficients of the Fourier series corresponding to the figure 4.2

coefficients from the simulations at the periodic states, a comparison is made with the coefficients predicted numerically from the parameters, using a Newton-Raphson method considering a set of $2n+1$ coefficients, with n large enough so that the coefficients $\{S_{n_0}, E_{n_0}, I_{n_0}, R_{n_0}\}$ are negligible for $|n_0| > n$ and a seed value defined by the endemic equilibrium point derived from the average transmission rate (β_0) and the average vaccination rate (V_0). The table 4.1 present the values of first coefficients of the Fourier series for the simulations. Observe the significant decrease of the coefficients and the accuracy of the predictions, presenting errors with negligible values. These errors can be attributed not to the predictions, but to the errors derived from running the simulation, as the time-step must be approachable in computation

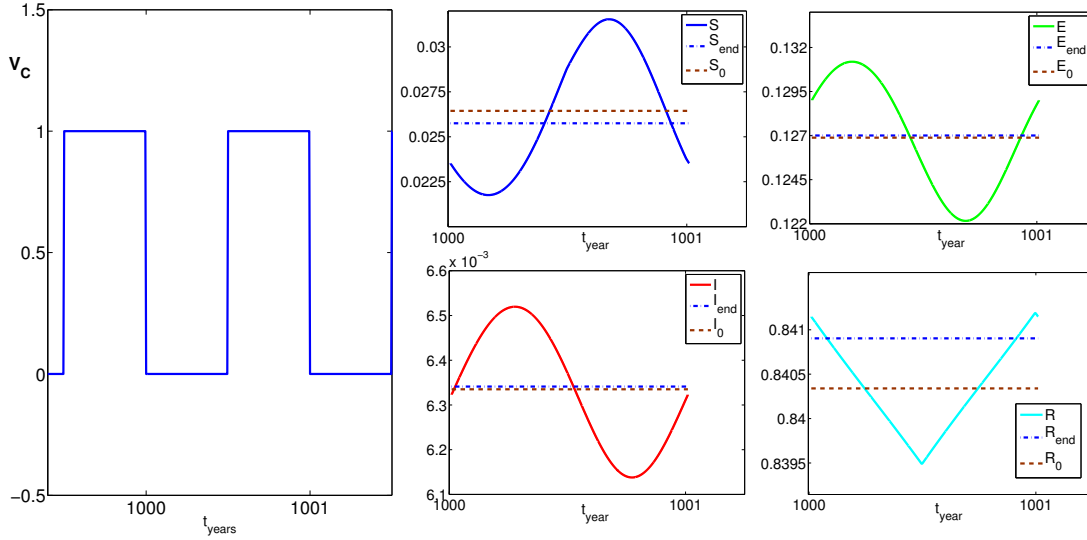


Figure 4.3: At the left side, the periodic vaccination strategy. At the right side, the final periodic states of the subpopulations reached under a vaccination $V_c(t) = 1 - \Theta(\sin(2\pi t))$ and $\beta = 400(1 + 0.5\cos(\rho t))$ ($R_0(t) > 1$).

terms.

In figure 4.3 it is shown the periodic state derived from a more complex vaccination strategy, which can be seen at the left graphic to be a step function whose values changes during a year between 1 and 0 and disease transmission rate $\beta(t) = 400(1 + 0.5\cos(\rho t))$, with $\rho = 2\pi$.

At figure 4.4 the final periodic state for an impulsive vaccination $V_c(t) = -\sum_{n=0}^{\infty} \theta S(t) \delta(t - nT)$, is presented for $\beta = 800$. As in the previous figure, the values of the coefficients for the final periodic states obtained from both the numerical predictions and the simulation are the same with a relative error $\epsilon \leq 10^{-5}$.

The importance of the moment to apply the vaccination in terms of introducing the appropriate phase in the vaccination function is shown at figure 4.5, where it is obtained the maximum and the average infectious subpopulation of an endemic equilibrium state defined, as in figure 4.2, by a disease transmission rate $\beta(t) = 400(1 + 0.5\cos(\rho t))$ and vaccination rate $V_c(t) = 0.5(1 + \cos(\rho t + \Phi))$. In this case, the different phases between the maximum vaccination rate and the maximum disease transmission rate Φ , is revealed to be important, as it can change the effectivity of the vaccination in an appreciable way.

4.7 Conclusions

A model describing four subpopulations with a periodic vaccination strategy and transmission rate either constant or periodic have been developed and studied. A

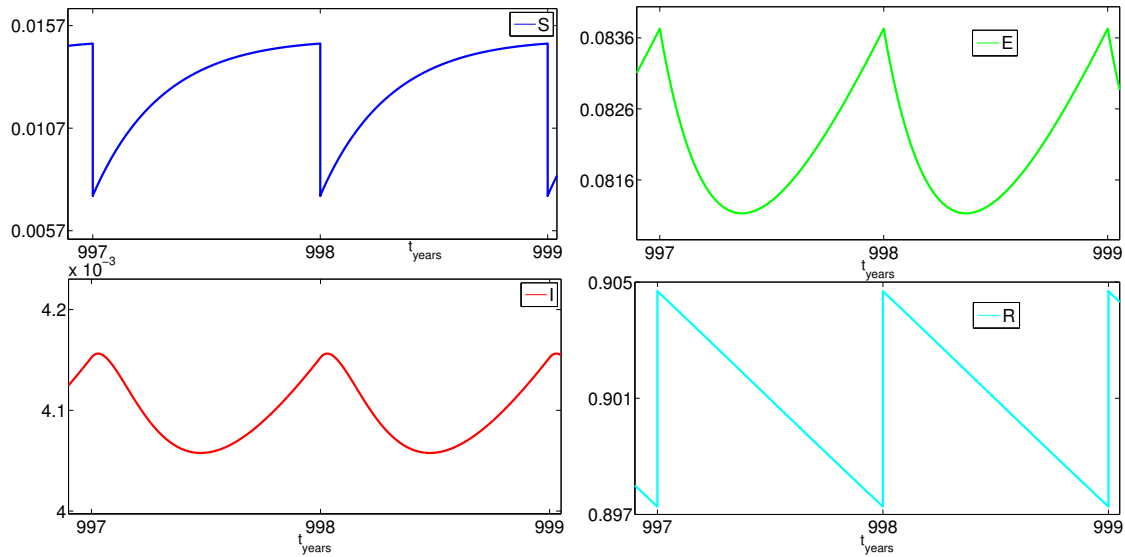


Figure 4.4: Final periodic states of the subpopulations reached under an impulsive vaccination for $\beta = 800$ and $V_c(t) = -\sum_{n=0}^{\infty} \theta S(t) \delta(t - nT)$, being $\theta = 1/2$.

generic periodicity has been introduced in order to describe the major number of possible situations, related to the presence of a control vaccination strategy against a seasonality in the transmission of the disease. A reproduction number, describing the stability of the equilibrium states of the dynamics of the subpopulations is obtained when the parameters of the model remain constant, and the stability of the disease-free equilibrium is further studied from the generic model. The numerical predictions for a periodic endemic state is confirmed by the simulations. The relevance of the work presented in this chapter is reflected on the versatility of the method, as it sets the basis for studying any type of vaccination strategy, as could be a quadratic wave representing different campaigns during the year, or even a peak in V_c , representing a massive punctual vaccination as it could happen in a potential emergency vaccination of the whole population. An analogous study could be done to the transmission rate, which can present also a complex seasonality, like migration paths or weather seasons, and predict the best prevention action and vaccination strategy in order to optimize them and minimize the impact of the disease.

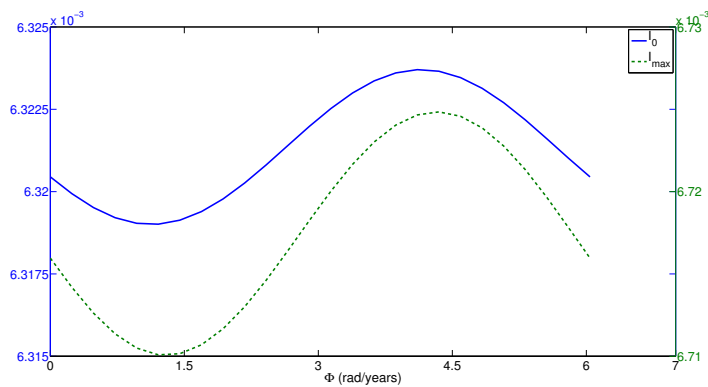


Figure 4.5: Maximum and average values of the infectious subpopulation equilibrium state for $V_c(t) = 0.5(1 + \cos(2\pi t + \Phi))$ and $\beta = 400(1 + 0.5\cos(2\pi t))$ ($R_0(t) > 1$) under different phases Φ .

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On the Positivity and Stability of a new SI_nRS Epidemic Model

This chapter proposes an extended SEIR model, being referred to as SI_nRS -model. The physical interpretation of the SI_nRS model is that the dynamics of the disease exhibits n different stages in which the infectivity and the mortality rates vary as the hosts of the disease go through the process of recovery, with a characteristic average time at each stage. The model includes n successive stages of infectious subpopulations, each one acting as the exposed subpopulation for the next infectious stage, in a cascade global disposal of infectious stages. Internal delays are introduced, which characterize the time intervals of the coupling of the susceptible dynamics with the infectious populations of the various cascade infectious stages. Then, an increasing delay is set as the stages index increases from 1 to n in the coupled dynamic action on each of those infectious stages. In order to study the stability, the concept of next generation matrix is introduced to obtain easily the reproduction number from large matrices used to describe this model.

5.1 Introduction

There is a very relevant interest in the literature concerning different aspects of dynamics of populations and related biological modeling issues including their positivity, stability, controllability and observability and appropriate design of control rules for such models. The interest is twofold, namely:

- i) On one hand, they have an undoubted mathematical interest because of the rich nonlinear dynamics they can exhibit, which makes its analysis nontrivial in most cases,
- ii) on the other hand they have relevant interests in the real world concerning aspects such that health, resource exploitation or rationalization of the labor management force towards economical issues.

The related models are based on differential, difference or hybrid ordinary or functional equations, eventually including internal delayed dynamics (i.e. delays in the state) or external delays (i.e. delays in the forcing action, if any), [11], [14], [18], [20], [25], [26], [31], [34]. The delays can be, in general, modeled as point-delays or as distributed delays and as constant or as time-varying delays. The background literature on the various involved subjects is exhaustive. In that context, important interest has been devoted to models of interaction of species versus their habitat, such as, for instance, the various Beverton-Holt models and some related generalizations, with their intrinsic problems of positivity, equilibrium analysis, stability, oscillatory solutions and their control. See, for instance, [1]-[2] and references therein. Impor-

tant attention is paid to the study of their inverse models and their control which are equivalent to the initial direct ones while being much more tractable mathematically, [1]-[2]. Control rules through the online design of the habitat carrying capacity have been dealt with, and applied in, aqua-culture exploitation, [1]. Logistic equations, predator-prey models and related oscillatory regimes have been also studied in the background literature (see, for instance, [3]-[5]). Epidemic models of various kinds ranging from very elementary to sophisticated have received and still receive important attention. The literature is exhaustive (see, for instance, [6]-[35]). There is also a wide variety of extended models available built with combinations and extensions of the above ones. The main properties dealt with are the calculation and related stability analysis of the disease-free and endemic equilibria, the infection permanence, which leads to the impossibility of reaching the disease-free equilibrium, and the positivity of the trajectories whose combined analysis with the boundedness of the total population leads to the internal stability [10], [13], [14], [16], [18], [19] of the whole model implying the boundedness of all the subpopulations [20]-[25], [28], [29], [35]. The control action on an epidemic model is performed through vaccination rules which can be of different types, for instance, constant or based either on linear or nonlinear feedback of some measurable or known subpopulations. Vaccination laws can also be of an impulsive nature (in practice, acting with large efforts along very short periods of time) or of a combined regular/impulsive nature, [14], [22]-[29], [31]. In particular, the technique of adaptive sampling to design the relevant vaccination time instants is combined with the design of vaccination rules in [28] so as to increase the vaccination performance towards the disease eradication. It has to be pointed out that epidemic models are essentially uncontrollable so that it is not possible to drive simultaneously, via a vaccination rule, all the subpopulations to prefixed arbitrary values in finite prefixed time intervals since the total population is a constrain for all time for the sum of all the subpopulations, [14], [22], [31]. However, most of the models are output controllable, or at least output stabilizable, with the outputs being defined "ad hoc" by either the infected and/or infectious subpopulations or the susceptible plus the immune subpopulations, those defined to be the output of the dynamic system, if necessary. The relevant idea in the epidemic models is that there is a transfer in-between subpopulations along the infection process (from there, their uncontrollability). The agent transmitting the infection is a quadratic dynamics of the susceptible and infected population with some either constant or functional factor (the incidence rate) which depends on a parameter or functional factor (the coefficient transmission rate) which depends on each infectious disease and the population nature, [8], [18]. There is a very basic parameter to analyze, called the basic reproduction number, which can have two interpretations, namely:

- i) If it ranges from zero to one, the disease-free equilibrium point is asymptotically stable and the infection asymptotically vanishes without requiring any external action on the system. In this case, the Jacobian matrix of the dynamics of the epidemic model defining the linearized state- trajectory has all its eigenvalues in the stable region. If it exceeds one the disease-free equilibrium is unstable so that the state trajectories can converge asymptotically to the endemic equilibrium or

exhibit an oscillatory behavior.

- ii) The infection cannot progress if the reproduction number is less than one since the minimum available initial infected population to propagate the disease is below its critical value for spreading.

However, the explicit expression of the reproduction number is neither direct nor easy to obtain in sophisticated epidemic models. Therefore more advanced techniques, based on the so called next generation matrix, have been proposed to define such reproduction number [32]-[35]. More recent studies on epidemic models are described in [38, 39]. The importance of demographics are takes into account in [38], while the stability of the equilibrium points of a delayed disease is described in [39]. This chapter addresses the concept of the next generation matrix for a new proposed extended SEIR model referred to as SI_nRS model with delays where there are n -successive stages of infectious subpopulations, each one acting at the exposed subpopulation of the next infectious stage in a cascade global disposal. Since the susceptible subpopulation is common to all infectious stages, its impact on each of those stages is modeled with an increasing delay as the infectious stage index increases from 1 to n . A second model is used without the above delay. A continuous-time model and a related discrete-time are presented and discussed. The physical interpretation of the SI_nRS models is that the incubating period of any disease is not identical for all the susceptible individuals so that they can become infected at different times. So, each of the infectious stages is an infectious class which includes a certain number of individuals which become infected at times centered about a reference average time instant which is considered common for the whole group. The stability analysis is performed by defining a basic reproduction number from an *ad hoc* next generation matrix for this model. The basic properties which are proved are the following:

- i) All the trajectories remain bounded since the differential equations system is non-negative, in the sense that all the subpopulations are non-negative for all time, and the total population is uniformly bounded for all time.
- ii) If the defined basic reproduction number is less than one then the disease-free equilibrium point is globally asymptotically stable as it is proved through the definition and use of a Lyapunov function. In this case, the endemic equilibrium point is locally unstable and, furthermore, it is unfeasible since it is not compatible with the system positivity.
- iii) If such a basic reproduction number is equal to one then the endemic equilibrium does not exist as such since it is identical to the disease-free equilibrium and then globally stable since the system is positive and the total population is uniformly bounded for all time so that none of the subpopulation can be unbounded.
- iv) If the basic reproduction number exceeds one then the disease-free equilibrium point is locally unstable.

5.2 The Model

This section contains the description and main properties of the introduced models. Previous models of multi-staged infectious diseases have been described in [37] including: a) the so-called epidemic models with multi-stage infectious period where the susceptible population influences the first infectious stage, that one the second infectious stage and so on; b) the epidemic models with several types of infective subpopulations which are influenced in a parallel disposal and all of them have transitions to a unique removed population; c) the epidemic among a number of homogeneous groups (each susceptible group generates its own SIR model). It can be considered, in a general context, that the structure proposed in this paper lies in the first of the above classes of the multi-stage models. Figure 5.1 describes in general terms the dynamic of the subpopulations that will be introduced in the following section.

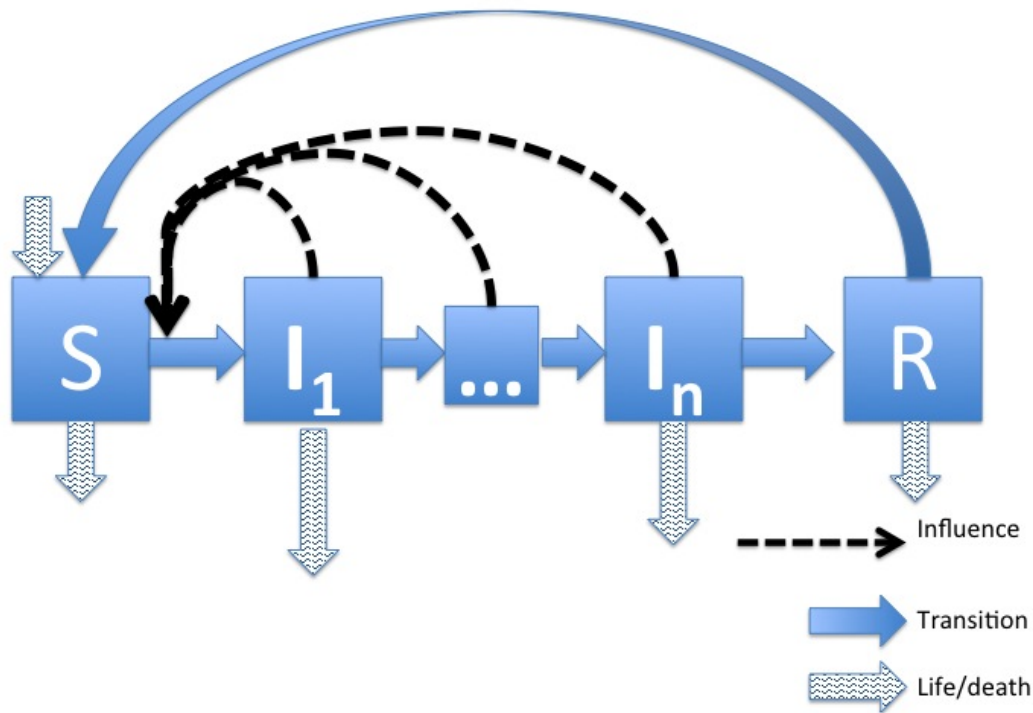


Figure 5.1: The dynamic of a generic staged SI_nRS epidemic model

5.2.1 SI_nRS Model with no delays

The proposed model is described as a succession of infectious stages of the disease, each one with a characteristic infectivity rate β_i . The susceptible individuals go through each infected subpopulation until they reach the recovered subpopulation, immune to the disease for a certain time until they become susceptible again. The susceptible population is born at a rate ν while the death rate of each infectious

subpopulation is $\mu_i = b + \xi_i$, being b the natural death rate of the population and ξ_i the mortality rate associated to the disease at each infectious stage. The transition rate from the i -th infectious subpopulation to the next one as well as the transition rate from the last infectious subpopulation to the recovered one are denoted by γ_i , while the transition from the recovered to the susceptible is γ_{n+1} . All the parameters are assumed to be positive so as to possess full physical meaning. The equations for the dynamics of the subpopulations are coupled as follows:

$$\dot{S}(t) = \nu - \left(b + \sum_{j=1}^n \beta_j I_j(t) \right) S(t) + R(t) \gamma_{n+1} \quad (5.1)$$

$$\dot{I}_1(t) = S(t) \sum_{j=1}^n \beta_j I_j(t) - (\mu_1 + \gamma_1) I_1(t) \quad (5.2)$$

$$\dot{I}_m(t) = \gamma_{m-1} I_{m-1}(t) - (\mu_m + \gamma_m) I_m(t) \quad \forall m = 2, 3, \dots, n \quad (5.3)$$

$$\dot{R}(t) = \gamma_n I_n(t) - (b + \gamma_{n+1}) R(t) \quad (5.4)$$

where the S and R are the susceptible and recovered subpopulations and the I_i are the various infectious subpopulations corresponding to the different infection stages. For notation simplicity, the vector \mathbf{x} is defined as

$$\mathbf{x}(t) = (I_1(t), I_2(t), \dots, I_n(t), R(t), S(t))^T \quad (5.5)$$

Now the positivity, existence of equilibrium points and stability are studied for this model.

Positivity and boundedness

Proposition 5.1. *All the subpopulations remain non-negative for all time for any given non-negative initial conditions, $x_i \geq 0 \forall i \in [1, \dots, n+2]$ and all $t \geq 0$.*

Proof.

Let $t_s > 0$ be so that $S(t_s) = 0$ and $R(t_s), I_i(t_s) \geq 0 \forall i \in [1, \dots, n]$. Then, from equation (5.2)

$$\dot{S}(t_s) = \nu + R(t_s) \gamma_{n+1} \geq 0 \quad (5.6)$$

Now, let $t_1 > 0$ be so that $I_1(t_1) = 0$ and $S(t_1), I_i(t_1) \geq 0 \forall i \in [2, \dots, n]$. Then, from equation (5.2)

$$\dot{I}_1(t_1) = S(t_1) \sum_{j=2}^n \beta_j I_j(t_1) \geq 0 \quad (5.7)$$

For the next $(n-1)$ infectious subpopulations the same operation is made: let $t_j > 0$ be so that $I_j(t_j) = 0$ and $S(t_j), I_i(t_j) \geq 0 \forall i \neq j$. Then, from equation (5.2)

$$\dot{I}_j(t_j) = \gamma_{j-1} I_{j-1}(t_j) \geq 0 \quad (5.8)$$

Finally, let $t_r > 0$ so that $R(t_r) = 0$ and $S(t_r), I_i(t_r) \geq 0, \forall i \in [1, \dots, n]$. Then, from equation (5.2)

$$\dot{R}(t_r) = \gamma_n I_n(t_r) \geq 0 \quad (5.9)$$

Since it has been proven that none of the subpopulations will have a negative derivative at any time instant when they vanish and the rest of the subpopulations are non-negative, then all the subpopulations must have non-negative values for all time. \square

Not only does the epidemic system possess non-negative solutions under non-negative initial conditions but also the total population and all the subpopulations are bounded for all time with a uniform finite upper-bound as it is discussed in the subsequent two results:

Proposition 5.2. *The total population $\sum_{i=1}^{n+2} x_i(t) = N(t)$ is finitely upper-bounded for any given non-negative initial conditions.*

Proof.

If all the equations (5.1)-(5.4) are summed up, it is obtained:

$$\dot{N}(t) = \nu - bN(t) - \sum_{j=1}^n \xi_j I_j(t) \quad (5.10)$$

Since Proposition 5.1 guarantees the non-negativity of subpopulations and all the parameters are assumed to be positive. Then, as $\xi_j \geq 0$ and $I_j(t) \geq 0$ for all time $t \geq 0$, $\sum_{j=1}^n \xi_j I_j(t) \geq 0$ for all $t \geq 0$, and

$$\dot{N}(t) = \nu - bN(t) - \sum_{j=1}^n \xi_j I_j(t) \leq \nu - bN(t) \quad (5.11)$$

The solution to the differential inequality from equation (5.11) is given by:

$$N(t) \leq e^{-bt} N(0) + \frac{\nu}{b} (1 - e^{-bt}) \leq \max \left(N(0), \frac{\nu}{b} \right) \quad (5.12)$$

for all $t \geq 0$. Thus, the total population is finitely upper-bounded and the proposition is proved. \square

Corollary 5.3. *All the subpopulations are finitely upper-bounded for all time for any given non-negative initial conditions, obeying the constraints $x_i(t) \leq N(0)e^{-bt} + N_{dfe}^* (1 - e^{-bt}) \quad \forall i \in [1, 2, \dots, n+2]$, where $N_{dfe}^* = \frac{\nu}{b}$ is the total population at the disease-free equilibrium.*

Equilibrium points

The equilibrium points are obtained by zeroing the left-hand side of equations (5.2), resulting in:

$$\begin{aligned} 0 &= \nu - \left(b + \sum_{j=1}^n \beta_j I_j(t) \right) S(t) + R(t) \gamma_{n+1} \\ 0 &= S(t) \sum_{j=1}^n \beta_j I_j(t) - (\mu_1 + \gamma_1) I_1(t) \\ 0 &= \gamma_{m-1} I_{m-1}(t) - (\mu_m + \gamma_m) I_m(t) \quad \forall m = 2, 3, \dots, n \\ 0 &= \gamma_n I_n(t) - (b + \gamma_{n+1}) R(t) \end{aligned} \quad (5.13)$$

This system possesses in general two solutions. The first one is the disease-free equilibrium point (DFE) in which the infectious and recovered subpopulations vanish so that the susceptible becomes the total population N_{dfe}^*

$$\begin{aligned} S_{dfe}^* &= \frac{\nu}{b} \\ I_{i,dfe}^* &= 0 \quad \forall i \in [1, 2, \dots, n] \\ R_{dfe}^* &= 0 \end{aligned} \tag{5.14}$$

and the endemic equilibrium point (END), described as:

$$\begin{aligned} S_{end}^* &= \left(\sum_{i=1}^n \beta_i \Lambda_i \right)^{-1} \\ I_{1,end}^* &= \frac{(1 + b/\gamma_{n+1}) \left(-b + b \sum_{j=1}^n (\beta_j \Lambda_j) \right)}{(b/\gamma_{n+1} + \sum_{j=1}^n \mu_j \Lambda_j)(\mu_1 + \gamma_1) \sum_{j=1}^n \beta_j \Lambda_j} = \frac{(b/\gamma_{n+1} + 1)b (S_{dfe}^* - S_{end}^*)}{(b/\gamma_{n+1} + \sum_{j=1}^n \mu_j \Lambda_j)(\mu_1 + \gamma_1)} \\ I_{m,end}^* &= \frac{\gamma_{m-1}}{\gamma_m + \mu_m} I_{m-1,end}^* \quad \forall m \in [2, 3, \dots, n] \\ R_{end}^* &= \frac{\gamma_n}{b + \gamma_{n+1}} I_{n,end}^* \end{aligned} \tag{5.15}$$

being $\Lambda_i = \frac{\prod_{j=1}^{i-1} \gamma_j}{\prod_{j=1}^i (\mu_j + \gamma_j)}$. Note that if $S_{end}^* > S_{dfe}^*$, then $I_m^* < 0 \quad \forall m \in [1, 2, 3, \dots, n]$, so

the endemic equilibrium is not feasible so that the only reachable equilibrium point is the disease-free equilibrium point. In the next section, it is seen that this situation corresponds to the reproduction number R_0 to be less than one. Once the expressions of both equilibrium points are obtained, it is possible to discuss their equilibrium in the next section.

Stability analysis: Next generation matrix

The local stability of the DFE point is proved in this section after introducing the reproduction number R_0 , which is the average number of new cases that produce an infected individual during the average duration of the disease. In order to find this number easily, a next-generation matrix with small domain is constructed as follows: The Jacobi matrix defined around the disease-free equilibrium is composed of four different submatrices: F , Σ , A and C

$$\begin{aligned} \mathbf{J} &= \left. \frac{\partial \dot{\mathbf{x}}}{\partial \mathbf{x}} \right|_{dfe} = \begin{pmatrix} F - \Sigma & 0 \\ A & C \end{pmatrix} \\ &= \begin{pmatrix} (\beta_1 S_{dfe} - (\mu_1 + \gamma_1)) & \beta_2 S_{dfe} & \dots & \beta_{n-1} S_{dfe} & \beta_n S_{dfe} & 0 & 0 \\ \gamma_1 & -(\mu_2 + \gamma_2) & \dots & 0 & 0 & 0 & 0 \\ \dots & \dots & \dots & \dots & \dots & \dots & \dots \\ 0 & 0 & \dots & -(\mu_{n-1} + \gamma_{n-1}) & 0 & 0 & 0 \\ 0 & 0 & \dots & \gamma_{n-1} & -(\mu_n + \gamma_n) & 0 & 0 \\ -\beta_1 S_{dfe} & -\beta_2 S_{dfe} & \dots & -\beta_{n-1} S_{dfe} & -(\beta_n S_{dfe} - \gamma_n) & -(b + \gamma_{n+1}) & 0 \\ 0 & 0 & \dots & 0 & 0 & 1\gamma_{n+1} & -b \end{pmatrix} \end{aligned}$$

where the important submatrix would be the transmission matrix F , representing the appearance of new infections, defined as :

$$F = \begin{pmatrix} \beta_1 S_{dfe} & \beta_2 S_{dfe} & \dots & \beta_{n-1} S_{dfe} & \beta_n S_{dfe} \\ 0 & 0 & \dots & 0 & 0 \\ \dots & \dots & \dots & \dots & \dots \\ 0 & 0 & \dots & 0 & 0 \\ 0 & 0 & \dots & 0 & 0 \end{pmatrix} \quad (5.16)$$

while Σ would be defined as :

$$\Sigma = \begin{pmatrix} (\mu_1 + \gamma_1) & 0 & \dots & 0 & 0 \\ -\gamma_1 & (\mu_2 + \gamma_2) & \dots & 0 & 0 \\ \dots & \dots & \dots & \dots & \dots \\ 0 & 0 & \dots & (\mu_{n-1} + \gamma_{n-1}) & 0 \\ 0 & 0 & \dots & -\gamma_{n-1} & (\mu_n + \gamma_n) \end{pmatrix}$$

and represents the remaining transitions of the infected subpopulation unrelated to the infection such as the deaths, or the transition from recovered to susceptible. Then, the inverse of that matrix Σ^{-1} would represent the average time in which a subpopulation stays in an infected state. The next generation matrix will be then defined as $\mathbf{K} = -\mathbf{F}\Sigma^{-1}$, and the reproduction number R_0 correspond to the spectral radius of \mathbf{K} . Thus, the spectral radius is given by:

$$\rho(\mathbf{K}) = R_0 = \sum_{i=1}^n \frac{\beta_i S_{dfe}^* \prod_{j=1}^{i-1} \gamma_j}{\prod_{j=1}^i (\gamma_j + \mu_j)} = S_{dfe}^* \sum_{i=1}^n \beta_i \Lambda_i = \frac{S_{dfe}^*}{S_{end}^*} \quad (5.17)$$

Thus, the stability of the disease-free equilibrium point is directly related to this spectral radius. In this way, it will be locally asymptotically stable when $R_0 < 1$, while $R_0 > 1$ will imply instability of such DFE point [35]. Studies of epidemic models with a parallel disposal of several submodels of susceptible-infectious-recovered subpopulations have proven that for $R_0 > 1$, the endemic point is locally asymptotically stable [40]. Remember that it has been proven in previous section, equation (5.15), that if $R_0 < 1$ the only reachable point is the disease-free equilibrium, which is also locally asymptotically stable. If $R_0 = 1$, both equilibrium points coincide (see equation (5.15)).

5.2.2 Discrete SI_nRS Model with no delays

This section considers the discrete-time counterpart of the continuous-time model from equations (5.1)-(5.4). In the discrete framework notation the subpopulations are written as $x_m(t) = x_k^m$, for any time $t \in [k\tau, (k+1)\tau)$. The discrete model, will be based on the continuous one from equations (5.1)-(5.4), with a step size $\tau > 0$. Thus, it is defined the change $\dot{\mathbf{x}}_k \rightarrow \frac{\mathbf{x}_{k+1} - \mathbf{x}_k}{\tau}$, with $\mathbf{x}_k = (I_k^1, I_k^2, \dots, I_k^n, R_k, S_k)$, as in

the continuous subpopulations from equation (5.5). Therefore, it is obtained:

$$\begin{aligned}
S_{k+1} &= \tau\nu - \left(1 - \tau b + \sum_{j=1}^n \tau\beta_j I_k^j\right) S_k + R_k \tau\gamma_{n+1} \\
R_{k+1} &= \gamma_n I_k^n + (1 - \tau b - \tau\gamma_{n+1}) R_k \\
I_{k+1}^1 &= S_k \sum_{j=1}^n \tau\beta_j I_k^j + (1 - \tau\mu_1 - \tau\gamma_1) I_k^1 \\
I_{k+1}^m &= \tau\gamma_{m-1} I_k^{m-1} + (1 - \tau\mu_m - \tau\gamma_m) I_k^m
\end{aligned} \tag{5.18}$$

Proposition 5.4. *The discrete system described in (5.18) is non-negative for any non-negative initial conditions if the step size τ is small enough to satisfy*

$$\tau \leq \min[\tau_1, \tau_2, \tau_3, \dots, \tau_{n+2}] \tag{5.19}$$

with $\tau_{m+2}^{-1} = \mu_m + \gamma_m \quad \forall m \in [1, \dots, n]$, $\tau_2^{-1} = b + \gamma_{n+1}$, and $\tau_1^{-1} = b + n\beta_M(N_1 + \nu/b)$, being $\beta_M = \max_{1 \leq j \leq n} [\beta_j]$ and N_1 the initial total population.

Proof.

Given a set of non-negative subpopulations at the k^{th} -sample, from the second equation of (5.18) it can be deduced that:

$$R_{k+1} = R_k(1 - \tau(b + \gamma_{n+1})) + \gamma_n I_k^n \geq R_k(1 - \tau(b + \gamma_{n+1})) \tag{5.20}$$

Then, $R_{k+1} \geq 0$ if $\tau \leq \tau_2$.

The same method can be applied for guaranteeing the non-negativity of $I_{k+1}^m \quad \forall m \in [1, \dots, n]$. From the third and fourth equations at (5.18), it is deduced that:

$$I_{k+1}^m \geq (1 - \tau(\mu_m + \gamma_m)) I_k^m \quad \forall m \in [1, \dots, n] \tag{5.21}$$

Then, $I_{k+1}^m \geq 0 \quad \forall m \in [1, \dots, n]$ if $\tau \leq \min_{1 \leq m \leq n} [\tau_{m+2}]$.

In order to guarantee the non-negativity of the susceptible subpopulation first it is set a maximum value for N_k . From (5.18)

$$S_{k+1} + R_{k+1} \sum_{j=1}^n I_{k+1}^j = N_{k+1} = \nu\tau + N_k(1 - b\tau) - \sum_{j=1}^n I_k^j(\mu_j - b) \tag{5.22}$$

$$N_{k+1} \leq \nu\tau + N_k(1 - b\tau) \tag{5.23}$$

$$N_{k+1} \leq (1 - b\tau)^{k-1} N_1 + \nu\tau \frac{1 - (1 - b\tau)^k}{b\tau} \tag{5.24}$$

then $\forall k \geq 1$, it can be said that

$$\begin{aligned}
N_{k+1} &\leq \max[(1 - b\tau)^{k-1} N_1] + \max\left[\nu\tau \frac{1 - (1 - b\tau)^k}{b\tau}\right] \\
&= N_1 + \frac{\nu}{b}
\end{aligned} \tag{5.25}$$

So from the first equation at (5.18) it is known that:

$$S_{k+1} \geq \left(1 - \tau \left(b + \sum_{j=1}^n \beta_j I_k^j\right)\right) S_k \tag{5.26}$$

Then, given that $I_k^j \leq N_k \quad \forall k, j > 0$; it is defined $\tau_1 = \frac{1}{b + \beta_M(N_1 + \nu/b)}$ so that the susceptible subpopulation remains non-negative if

$$\tau \leq \tau_1 = \frac{1}{b + \beta_M(N_1 + \nu/b)} \leq \frac{1}{b + \sum_{j=1}^n \beta_j I_k^j}$$

Thus, for a step size $\tau \leq \min[\tau_1, \tau_2, \tau_3, \dots, \tau_m]$, the system remains positive. \square

The equilibrium points are obtained by making $x_{k+1} = x_k = x^*$ in equation (5.18):

$$\begin{aligned} S^* &= \tau \nu - \left(1 - \tau b + \sum_{j=1}^n \tau \beta_j I^{j*} \right) S^* + R^* \tau \gamma_{n+1} \\ R^* &= \gamma_n I^{n*} + (1 - \tau b - \tau \gamma_{n+1}) R^* \\ I^{*1} &= S^* \sum_{j=1}^n \tau \beta_j I^{j*} + (1 - \tau \mu_1 - \tau \gamma_1) I^{*1} \\ I^{*m} &= \tau \gamma_{m-1} I^{m-1*} + (1 - \tau \mu_m - \tau \gamma_m) I^{m*} \quad \forall m = 2, 3, \dots, n \end{aligned} \tag{5.27}$$

The solutions of the above system of equations are the same as in the continuous-time case and given by equations (5.14) and (5.15) for the disease-free and endemic equilibrium points, respectively. A next generation matrix approach for discrete models is made so that the Jacobian matrix evaluated at the disease-free equilibrium

$$\mathbf{J} = \frac{\partial \mathbf{x}_{k+1}}{\partial \mathbf{x}_k} \tag{5.28}$$

$$\mathbf{x}_{k+1} - \mathbf{x}_{dfe} = \mathbf{J} (\mathbf{x}_k - \mathbf{x}_{dfe}) \tag{5.29}$$

The Jacobian takes the form

$$\mathbf{J} = \mathbb{I} - \begin{pmatrix} \tau(\mu_1 + \gamma_1 - \beta_1 S_{dfe}) & -\beta_2 S_{dfe} \tau & \dots & -\beta_{n-1} S_{dfe} \tau & -\beta_n S_{dfe} \tau & 0 & 0 \\ -\tau \gamma_1 & \tau(\mu_2 + \gamma_2) & \dots & 0 & 0 & 0 & 0 \\ \dots & \dots & \dots & \dots & \dots & \dots & \dots \\ 0 & 0 & \dots & \tau(\mu_{n-1} + \gamma_{n-1}) & 0 & 0 & 0 \\ 0 & 0 & \dots & -\tau \gamma_{n-1} & \tau(\mu_n + \gamma_n) & 0 & 0 \\ \beta_1 S_{dfe} \tau & \beta_2 S_{dfe} \tau & \dots & \beta_{n-1} S_{dfe} \tau & (\beta_n S_{dfe} - \gamma_n) \tau & (b + \gamma_{n+1}) \tau & 0 \\ 0 & 0 & \dots & 0 & 0 & \tau \gamma_{n+1} & \tau b \end{pmatrix} \tag{5.30}$$

The Jacobian can be separated in four submatrices as follows:

$$\mathbf{J} = \begin{pmatrix} F - \Sigma & 0 \\ A & C \end{pmatrix} \tag{5.31}$$

where the two relevant $n \times n$ submatrices are the fertility submatrix, related to the new infections and represented as F , and the transition submatrix Σ , with the same dimensions, related to the transition of the individuals between the different subpop-

ulations:

$$\Sigma = \begin{pmatrix} \tau(\mu_1 + \gamma_1) & 0 & \dots & 0 & 0 \\ -\tau\gamma_1 & \tau(\mu_2 + \gamma_2) & \dots & 0 & 0 \\ \dots & \dots & \dots & \dots & \dots \\ 0 & 0 & \dots & \tau(\mu_{n-1} + \gamma_{n-1}) & 0 \\ 0 & 0 & \dots & -\tau\gamma_{n-1} & \tau(\mu_n + \gamma_n) \end{pmatrix} - \mathbb{I} \quad (5.32)$$

$$F = \begin{pmatrix} \beta_1 S_{dfe}\tau & \beta_2 S_{dfe}\tau & \dots & \beta_{n-1} S_{dfe}\tau & \beta_n S_{dfe}\tau \\ 0 & 0 & \dots & 0 & 0 \\ \dots & \dots & \dots & \dots & \dots \\ 0 & 0 & \dots & 0 & 0 \\ 0 & 0 & \dots & 0 & 0 \end{pmatrix} \quad (5.33)$$

A simple calculation with the Jacobian matrix results into an equivalent decomposition of the whole linearization about the equilibrium system into two complete subsystems, one describing the infection progress while the other one expresses the disease-free subpopulation dynamics as follows:

$$\begin{aligned} \mathbf{y}_{k+1} &= (F - \Sigma) \mathbf{y}_k \\ \mathbf{l}_{k+1} &= A\mathbf{y}_k + C\mathbf{l}_k \end{aligned} \quad (5.34)$$

The term $\Sigma_{i,j}$ represents the fraction of the individuals from the j^{th} infected subpopulation that will survive and move to the i^{th} . Because of these demographic interpretations, from Perron-Froebenius theory on the maximum modulus [36], it is set the parameters so that the column sum of Σ and the maximum moduli of its eigenvalues are less than one, i. e. $\rho[\Sigma] < 1$, so as to exclude the case of an immortal population. Then, it can be established for the vector of initial infectious individuals that $\lim_{k \rightarrow \infty} (-\Sigma)^k \mathbf{y}_0 = 0$. Then, the next generation matrix Q can be defined as the sum of the infections ever produced by the infected individuals at t_k for all the time they remain infectious, which would be $F\mathbf{y}_k$ at t_k , $-F\Sigma\mathbf{y}_k$ at t_{k+1} , $F\Sigma^2\mathbf{y}_k$ at t_{k+2} ad infinitum:

$$Q\mathbf{y}_k = F(\mathbf{y}_k - \Sigma\mathbf{y}_k + \Sigma^2\mathbf{y}_k - \Sigma^3\mathbf{y}_k + \Sigma^4\mathbf{y}_k \dots)$$

Q represents the distribution of all infections accumulated during the lifespan of the infectious population:

$$Q = F(I - \Sigma + \Sigma^2 - \Sigma^3 + \Sigma^4 \dots) = F(I + \Sigma)^{-1}$$

Then the basic reproduction number is defined as the spectral radius of the Q matrix $R_0 = \rho[Q] = \rho[F(I + \Sigma)^{-1}]$. The spectral radius of the $F - \Sigma$ is defined as $\rho[F - \Sigma] = r$. It is proven in [36] that either $r = R_0 = 1$ or $1 < r < R_0$ or $1 > r > R_0 > 0$, so the stability of the disease-free equilibrium is determined by the value of R_0 . In this model the reproduction number is obtained as

$$R_0 = \sum_{i=1}^n \frac{\tau \beta_i S_{dfe} \prod_{j=1}^{i-1} \tau \gamma_j}{\prod_{j=1}^i \tau (\gamma_j + \mu_j)} = \frac{S_{dfe}}{S_{end}} \quad (5.35)$$

Thus, the disease-free equilibrium state will be locally stable when the reproduction number is less than 1, and unstable otherwise. From known previous calculations of the stability of a similar models in [35]-[36], this decomposition technique for stability analysis can be compared to the previous chapter for the SEIRS model, which is an specific version of a continuous SI_nRS model in which $n = 2$, $\beta_1 = 0$, $\mu_1 = \mu_2 = b$ and $\gamma_1 = \kappa$. From the definition in equation (5.35), it is obtained $R_0 = \frac{\beta_2 S_{df} e^{\kappa}}{(b+\kappa)(b+\gamma_2)}$, which agrees with the study of the eigenvalues of the Jacobian matrix in a continuous-time model [22].

5.2.3 SI_nRS Model with delays

Construction of the model

A new model is proposed based on the previous one in which the transition rates between subpopulations are substituted by delays, implying that each individual must stay at each stage of the infection during a certain period of time (latent period) before recovery. Such time periods are defined as $\tau_i = \gamma_i^{-1}$ for the infectious stages of the disease and $\tau_R = \gamma_{n+1}^{-1}$ for the recovered state. The model also preserves the infectivity mechanism of the previous one, in which all the infectious subpopulations affect the infection of the first stage at different rates. For notational abbreviation in the subsequent exposition it is now defined the function $f(\omega) = S(\omega) \sum_{j=1}^n \beta_j I_j(\omega)$.

Thus, the value of the infected subpopulation I_1 at a certain time t is defined by the ratio of the people that became infected at time $\omega < t$ that has not passed to the I_2 infectious subpopulation yet. In order to calculate the total amount, consider the probability:

$$1 - \int_0^{t-\omega} \rho_1(\xi) d\xi = \int_{t-\omega}^{\infty} \rho_1(\xi) d\xi \quad (5.36)$$

being $\rho_1(\xi)$ the probability distribution of the transition $I_1 \rightarrow I_2$ plus the probability to stay alive after time $t - \omega$, which would be equal to $e^{\mu_1(\omega-t)}$. An integration $\omega \in (-\infty, t)$ is made in order to obtain the value of the subpopulation at the instant t resulting in:

$$I_1(t) = \int_{-\infty}^t \left(\int_{t-\omega}^{\infty} \rho_1(\xi) d\xi \right) f(\omega) e^{\mu_1(\omega-t)} d\omega \quad (5.37)$$

Given the above integral function of the first stage of the infectious subpopulations, its derivative through time is easily obtained as

$$\dot{I}_1(t) = f(t) - \mu_1 I_1(t) - \int_0^{\infty} \rho_1(\omega) f(t-\omega) e^{-\mu_1 \omega} d\omega \quad (5.38)$$

Since in this case the probability of transition is equal to zero before the latent time interval τ_1 occurs, and is equal to 1 after it, the probability distribution of transition is defined as $\rho_1(\omega) = \delta(\omega - \tau_1)$, so that equation (5.38) transforms to:

$$\dot{I}_1(t) = f(t) - \mu_1 I_1(t) - e^{-\mu_1 \tau_1} f(t - \tau_1) \quad (5.39)$$

As the rate of death in the subpopulation $I_1(t)$ corresponds to $-\mu_1 I_1(t)$, it is inferred that the term $e^{-\mu_1 \tau_1} f(t - \tau_1)$ corresponds to the rate of transition from $I_1(t)$ to $I_2(t)$. Then, the value of the people that arrive at I_2 at $\omega < t$ would be $e^{-\mu_1 \tau_1} f(\omega - \tau_1)$, and I_2 at certain time would be written as

$$I_2(t) = \int_{-\infty}^t \left(\int_{t-\omega}^{\infty} \rho_1(\xi) d\xi \right) e^{\mu_2(\omega-t)} e^{-\mu_1 \tau_1} f(\omega - \tau_1) d\omega.$$

For any subpopulation $m \in [1, 2, \dots, n]$, it can be written that

$$I_m(t) = e^{-\mu_m t} \int_{-\infty}^t \left(\int_{t-\omega}^{\infty} \rho_m(\xi) d\xi \right) C_{m-1} f(\omega - T_{m-1}) e^{\mu_m \omega} d\omega \quad (5.40)$$

For the recovered subpopulation the same technique is used, so that the dynamic of R over time can be written as:

$$R(t) = e^{-\mu_R t} \int_{-\infty}^t \left(\int_{t-\omega}^{\infty} \rho_R(\xi) d\xi \right) C_n f(\omega - T_n) e^{\mu_R \omega} d\omega$$

with $C_i = \prod_{j=1}^i e^{-\mu_i \tau_j}$, $C_{n+1} = C_n e^{-\mu_R \tau_R}$ and $T_i = \sum_{j=1}^i \tau_j$, $T_{n+1} = T_n + \tau_R$. The dynamic equations of the subpopulations are then defined as:

$$\begin{aligned} \dot{S}(t) &= \nu - bS(t) - f(t) + C_{n+1} f(t - T_{n+1}) \\ \dot{R}(t) &= C_n f(t - T_n) - C_{n+1} f(t - T_{n+1}) - \mu_R R(t) \\ \dot{I}_m(t) &= C_{m-1} f(t - T_{m-1}) - C_m f(t - T_m) - \mu_m I_m(t) \quad \forall m \in [1, 2, \dots, n] \end{aligned} \quad (5.41)$$

where, as in the previous model, ν is the constant birth rate, and the fully immune recovered subpopulation eventually becomes susceptible again after the period of time τ_R .

Positivity and boundedness

Proposition 5.5. *The model from equation (5.41) is non-negative for any initial non negative conditions. Thus,*

$$\mathbf{x}_i(\omega) \geq 0; \forall m = 1, 2, \dots, n+2 \quad \forall \omega \in (-\infty, t_0) \quad (5.42)$$

which implies $\mathbf{x}_i(t) \geq 0; \forall m = 1, 2, \dots, n+2 \quad \forall t \in [t_0, \infty)$.

Proof.

Since $\beta_i \geq 0$, it is then deduced from equation (5.42) that $f(\omega) = S(\omega) \sum_{j=1}^n \beta_j I_j(\omega) \geq 0 \forall \omega \in (-\infty, t_0)$. Assume that

$$\exists \lambda > 0 | S(t_0 + \lambda) = 0, I_m(t) \geq 0 \quad \forall m = 1, 2, \dots, n+1; \quad \forall t \in [t_0, t_0 + \lambda)$$

then, from (5.41) at the time $t_0 + \lambda$

$$\dot{S}(t_0 + \lambda) = \nu + C_{n+1} f(t_0 + \lambda - T_{n+1}) > 0$$

therefore, the subpopulation S will not be the first subpopulation to be negative. From (5.40) assume that $\exists t_1 \geq t_0$ such that $I_m(t_1) = 0$ for the first time, and the

value $\zeta \geq 0$ as small as desired such that $I(t_1 - \zeta) > 0$; $I(t_1 + \zeta) < 0$. Then it can be said that

$$\begin{aligned} I_m(t_1 + \zeta) &= \int_{-\infty}^{t_1 - \zeta} \left(\int_{t_1 - \zeta - \omega}^{\infty} \rho_m(\xi) d\xi \right) C_{m-1} f(\omega - T_{m-1}) e^{\mu_m(\omega - (t_1 - \zeta))} d\omega \\ &\quad + \int_{t_1 - \zeta}^{t_1 + \zeta} \left(\int_{t_1 + \zeta - \omega}^{\infty} \rho_m(\xi) d\xi \right) C_{m-1} f(\omega - T_{m-1}) e^{\mu_m(\omega - (t_1 + \zeta))} d\omega \end{aligned} \quad (5.43)$$

Since $f(t_1 - \zeta) \geq 0$, and knowing that $f(t)$ is continuous and derivable for all t , from the mean value theorem it can be deduced that

$$\begin{aligned} \lim_{\zeta \rightarrow 0} I_m(t_1 + \zeta) &\geq \int_{t_1 - \zeta}^{t_1 + \zeta} \left(\int_{t_1 + \zeta - \omega}^{\infty} \rho_m(\xi) d\xi \right) C_{m-1} f(\omega - T_{m-1}) e^{\mu_m(\omega - (t_1 + \zeta))} d\omega \\ &\geq C_{m-1} f(t_1 - T_{m-1}) e^{\mu_m(\omega - t_1)} 2\zeta \geq 0 \end{aligned} \quad (5.44)$$

which is in direct contradiction with the original assumption of $I(t_1 - \zeta) > 0$; $I(t_1 + \zeta) < 0$. Then as $S(\omega)$ is not negative before $t_1 \geq 0$, the term $f(\omega)$ will remain non-negative. $\forall \omega \in (-\infty, t_1 + \zeta^+)$. Therefore, neither the infectious nor the susceptible subpopulation will be the first one to have a negative value. The same method can be applied to demonstrate that the recovered subpopulation will not be the first to have a negative value either. Then, $x_i(t) \geq 0 \forall i = [1, \dots, n + 2]$ holds for all time for any given non-negative initial conditions. \square

Since the lower bound of the subpopulations is established as 0, an upper bound for all the subpopulations is set in the following proposition.

Proposition 5.6. $S(t) \leq N_{dfe}$, $I_m(t) \leq N_{dfe}$, $R(t) \leq N_{dfe}$ $N_{dfe} = \sum_{i=1}^{n+2} \mathbf{x}_i^*_{dfe} = \nu/b$, for

any given initial conditions $\sum_{i=1}^{n+2} \mathbf{x}_i(0) = N(0) \leq \nu/b$.

Proof.

The dynamic of $N(t)$ is obtained from (5.41): $\dot{N}(t) = \nu - bN(t) - \sum_{i=1}^n I_i(t) (\mu_i - b)$. As $\mu_i \geq b \forall i = [1, 2, \dots, n]$, and given the previous boundary of non negativity from Proposition 5.5, it can be seen that for any $t_0 | N(t_0) = \nu/b$, $\dot{N}(t_0) = -\sum_{i=1}^n I_i(t) (\mu_i - b) \leq 0$.

Thus, $N(t) \leq \nu/b \forall t > t_0$. Then, for each subpopulation

$$\mathbf{x}(t) = (S(t), I_1(t), I_2(t), \dots, I_n(t), R(t))^T$$

it is established that

$$x_i(t) = N(t) - \sum_{j \neq i}^{n+2} x_j(t) \leq \nu/b - \sum_{j \neq i}^{n+2} x_j(t) \leq \nu/b; \forall t > t_0$$

\square

Equilibrium points

The existence of equilibrium points in the model is now studied. The dynamics of the subpopulation described in (5.41) is zero at the equilibrium points, so that

$$\begin{aligned} 0 &= b(\nu/b - S^*) - f^*(1 - C_{n+1}) \\ 0 &= f^*(C_{m-1} - C_m) - \mu_m I_m^* \\ 0 &= f^*(C_n - C_{n+1}) - \mu_R R^* \end{aligned} \quad (5.45)$$

being $f^* = S^* \left(\sum_{j=1}^n \beta I_j^* \right)$. Two equilibrium points are obtained and result to be

$$\begin{aligned} S_{dfe}^* &= \nu/b \\ I_{dfe}^* &= 0 \\ R_{dfe}^* &= 0 \end{aligned} \quad (5.46)$$

and

$$\begin{aligned} S_{end}^* &= \left(\sum_{j=1}^n (\beta_j \eta_j) \right)^{-1}, \\ I_{i\,end}^* &= \Gamma \eta_i \quad \forall i \in [1, \dots, n] \\ R_{end}^* &= \Gamma \eta_{n+1} \end{aligned} \quad (5.47)$$

with $\eta_j = \frac{C_{j-1} - C_j}{\mu_j}$ and $\Gamma = \frac{b \left(\nu/b - \left(\sum_{j=1}^n (\beta_j l_j) \right)^{-1} \right)}{1 - C_{n+1}}$. Note that $1 \geq C_1 \geq C_2 \geq \dots \geq C_{i-1} \geq C_i \geq \dots \geq C_{n+1} \geq 0$ and $\mu_j \geq 0 \quad \forall j$, so $\eta_j \geq 0 \quad \forall j$. Given any non-negative initial conditions, the endemic equilibrium point would not be reachable if $S_{end}^* = \left(\sum_{j=1}^n (\beta_j l_j) \right)^{-1} > \nu/b$, as Γ and $I_{i\,end}^*$ would be < 0 . Take into account that if $S^* = \nu/b$, $\mathbf{x}_{end} = \mathbf{x}_{dfe}$, the endemic and the disease-free equilibrium are the same, so there is only one equilibrium point in the system.

Stability of the disease-free equilibrium (DFE) point

The local stability of the DFE point is proved in this section after introducing the reproduction number R_0 , the average number of new cases that produce an infected individual during the average duration of the disease. In order to find this number easily, a next-generation matrix with small domain [35] is constructed as follows.

First, the vector of the subpopulations is reorganized as in (5.5), so that the Jacobian matrix around the DFE point can be properly written as:

$$\mathbf{J} = \frac{\partial \dot{\mathbf{x}}}{\partial \mathbf{x}} \Big|_{dfe} = \begin{pmatrix} F - \Sigma & 0 \\ A & C \end{pmatrix} \quad (5.48)$$

where F is the transmission matrix, representing the appearance of new infections $F_{ij} = C_{i-1} \beta_j$, while Σ represent the remaining transitions of the subpopulation which are unrelated directly to the infection, such as the deaths, or the transition from recovered subpopulation to susceptible subpopulation.

Then, the next generation matrix is given by $K = -\mathbf{F}\mathbf{\Sigma}^{-1}$. The submatrices composing the Jacobian are:

$$F - \Sigma = S_{dfe}^* \begin{pmatrix} (C_0 - C_1)\beta_1 & (C_0 - C_1)\beta_2 & \dots & (C_0 - C_1)\beta_{n-1} & (C_0 - C_1)\beta_n \\ (C_1 - C_2)\beta_1 & (C_1 - C_2)\beta_2 & \dots & (C_1 - C_2)\beta_{n-1} & (C_1 - C_2)\beta_n \\ \dots & \dots & \dots & \dots & \dots \\ (C_{n-1} - C_n)\beta_1 & (C_{n-1} - C_n)\beta_2 & \dots & (C_{n-1} - C_n)\beta_{n-1} & (C_{n-1} - C_n)\beta_n \\ (C_n - C_{n+1})\beta_1 & (C_n - C_{n+1})\beta_2 & \dots & (C_n - C_{n+1})\beta_{n-1} & (C_n - C_{n+1})\beta_n \end{pmatrix} - \begin{pmatrix} \mu_1 & 0 & \dots & 0 & 0 \\ 0 & \mu_2 & \dots & 0 & 0 \\ \dots & \dots & \dots & \dots & \dots \\ 0 & 0 & \dots & \mu_{n-1} & 0 \\ 0 & 0 & \dots & 0 & \mu_n \end{pmatrix} \quad (5.49)$$

$$A = S_{dfe}^* \begin{pmatrix} (C_n - C_{n+1})\beta_1 & (C_n - C_{n+1})\beta_2 & \dots & (C_n - C_{n+1})\beta_{n-1} & (C_n - C_{n+1})\beta_n \\ -(C_0 - C_{n+1})\beta_1 & -(C_0 - C_{n+1})\beta_2 & \dots & -(C_0 - C_{n+1})\beta_{n-1} & -(C_0 - C_{n+1})\beta_n \end{pmatrix} \quad (5.50)$$

$$C = \begin{pmatrix} -b & 0 \\ 0 & -b \end{pmatrix} \quad (5.51)$$

so the transmission and transition matrices are defined as :

$$\mathbf{F}_{ij} = (C_{i-1}\beta_j) S_{dfe}^* \quad (5.52)$$

$$\Sigma_{ij} = (\mu_i\delta_{ij} + C_i\beta_j S_{dfe}^*) \quad (5.53)$$

$\forall i, j = 1, \dots, n$. The element K_{ij} is the number of new cases generated in the stage of the disease i by one infected case who has just arrived from the stage of the disease j . Then, the dominant eigenvalue of the next generation matrix K would correspond to the reproduction number R_0 . However, it is possible in this case to construct a small domain next generation matrix [35] K_S with a lower dimension than K , from which it will be much easier to obtain this dominant eigenvalue. Since

- i) \mathbf{R} is a matrix whose rows are linearly independent vectors spanning the rows of \mathbf{F} and
- ii) \mathbf{C} is a matrix whose columns are linearly independent vectors spanning the columns of \mathbf{F} then $\mathbf{F} = \mathbf{C}\mathbf{R}$,

and the small domain next generation matrix will be defined as $\mathbf{K}_S = -\mathbf{R}\mathbf{\Sigma}^{-1}\mathbf{C}$. In this case $\mathbf{C} = (C_0, C_1, C_2, \dots, C_{n-1})^T$ and $\mathbf{R} = (\beta_1, \beta_2, \dots, \beta_n)$, so

$$K_S = -(\beta_1, \beta_2, \dots, \beta_n) \mathbf{\Sigma}^{-1} \begin{pmatrix} C_0 \\ C_1 \\ \dots \\ C_{n-1} \end{pmatrix} = \frac{\sum_{i=1}^n \frac{\beta_i C_{i-1}}{\mu_i}}{b/\nu + \sum_{i=1}^n \frac{\beta_i C_i}{\mu_i}} = R_0 \quad (5.54)$$

since that $\dim(K_S) = 1$, the dominant eigenvalue of K_S would be R_0 . Note that $K_S = R_0$ implies that if $R_0 \leq 1$, then $\left(\sum_{i=1}^n \frac{\beta_i (C_{i-1} - C_i)}{\mu_i} \right)^{-1} = S^* \geq S_{dfe}^*$, which is also the condition of reachability of the endemic equilibrium, as stated in the previous section.

Proposition 5.7. *The DFE is globally asymptotically stable if $R_0 < 1$*

Proof.

A candidate for a Lyapunov function Φ is defined as $\Phi = \phi_1 + \phi_2 + \phi_3$, being the auxiliary functions ϕ_1, ϕ_2, ϕ_3 defined as:

$$\phi_1 = \sum_{i=1}^n \left(\frac{\beta_i}{\mu_i} I_i(t) \right) \quad (5.55)$$

$$\phi_2 = - \sum_{i=1}^n \frac{\beta_i}{\mu_i} C_i \int_{t-T_i}^{t-T_{i-1}} f(\omega) d\omega \quad (5.56)$$

$$\phi_3 = \sum_{i=1}^n \frac{\beta_i (C_{i-1} - C_i)}{\mu_i} \int_{t-T_{i-1}}^t f(\omega) d\omega \quad (5.57)$$

now, ϕ_3 is positive definite $\forall t$, since $f(\omega) \geq 0 \forall \omega$, $\beta_i \geq 0$, $b_i > 0$ and $C_{i-1} > C_i = C_{i-1} e^{-b_i \tau_i} \forall i = 1, 2, \dots, n$. To verify the positivity of $\phi_1 + \phi_2$, consider the definition of the infectious subpopulation from (5.40) and the probability transition function $\rho_i(\xi) = \delta(\xi - \tau_i)$.

It is then established that

$$I_i(t) = C_{i-1} \int_{-\infty}^t \theta(\omega + \tau_i - t) f(\omega - T_{i-1}) e^{\mu_i(\omega - t)} d\omega$$

This integral function can be reconfigured as

$$I_i(t) = C_{i-1} \int_{-\infty}^{t-T_{i-1}} \theta(\omega' + T_i - t) f(\omega') e^{\mu_i(\omega' + T_{i-1} - t)} d\omega' \quad (5.58)$$

$$= C_{i-1} \int_{t-T_i}^{t-T_{i-1}} f(\omega) e^{\mu_i(\omega - (t-T_{i-1}))} d\omega \quad (5.59)$$

$$= C_i \int_{t-T_i}^{t-T_{i-1}} f(\omega) e^{\mu_i(\omega - (t-T_i))} d\omega \quad (5.60)$$

Given this definition of $I_i(t)$, the parameter $\sigma_i(t)$ is defined as

$$\sigma_i(t) = I_i(t) - C_i \int_{t-T_i}^{t-T_{i-1}} f(\omega) d\omega = C_i \int_{t-T_i}^{t-T_{i-1}} f(\omega) (e^{\mu_i(\omega - (t-T_i))} - 1) d\omega \quad (5.61)$$

Since $f(\omega) \geq 0$ and $(e^{\mu_i(\omega - (t-T_i))} - 1) \geq 0 \forall \omega \in [t - T_i, t - T_{i-1}]$, it is deduced that $\sigma_i(t) \geq 0 \forall t, \forall i \in [1, \dots, n]$. Then $\phi_1(t) + \phi_2(t) = \sum_{i=1}^n \frac{\beta_i}{\mu_i} \sigma_i(t) \geq 0 \forall t$ and $\phi_3(t) \geq 0 \forall t$.

Thus the non-negativity of the Φ function is proven. The function Φ is equal to zero for $I_i(\omega) = 0 \forall i = 1, \dots, n, \forall \omega \in [t - T_n, t]$. Then the derivative over time $\dot{\Phi} = \dot{\phi}_1 + \dot{\phi}_2 + \dot{\phi}_3$

is calculated as:

$$\begin{aligned}\dot{\Phi} &= \sum_{i=1}^n \frac{\beta_i}{\mu_i} (C_{i-1}f(t - T_{i-1}) - C_i f(t - T_i) - b_i I_i(t)) \\ &+ \sum_{i=1}^n \frac{\beta_i}{\mu_i} C_i (f(t - T_i) - f(t - T_{i-1})) \\ &+ \sum_{i=1}^n \frac{\beta_i (C_{i-1} - C_i)}{\mu_i} (f(t) - C_i f(t - T_{i-1}))\end{aligned}$$

$\dot{\Phi} = \sum_{i=1}^n \frac{\beta_i (C_{i-1} - C_i)}{\mu_i} f(t) - \beta_i I_i(t) = f(t) \left(\frac{S(t) - S^*}{S^* S(t)} \right)$. For $R_0 < 1 \rightarrow S^* > \nu/b \geq S(t)$, so $\dot{\Phi} = 0$ for $I_i = 0 \forall i = 1, \dots, n$ and $\dot{\Phi} < 0$ otherwise from equation (5.41). Thus the proposition is proved. \square

Stability of the endemic equilibrium point (END) model with n=1

For simple models, i.e., models with only one or two infectious subpopulations, a study of the stability of their endemic points is also made. The model is linearized around the endemic point and the eigenvalues of the Jacobi matrix are obtained. The function $f(\lambda)$ is defined as:

$$f(\lambda) = \text{Det}[\lambda I - \mathbf{J}] = 0 \quad (5.62)$$

with \mathbf{J} the 3x3 Jacobi matrix from (5.41), defined at the endemic equilibrium point from (5.47):

$$\mathbf{J} = \left. \frac{\partial \dot{\mathbf{x}}}{\partial \mathbf{x}} \right|_{end} \quad (5.63)$$

The solutions of $f(\lambda) = (-b + \lambda)(b\mu_1(S_{dfe}^*/S_{end}^* - 1) + bS_{dfe}^*/S_{end}^*\lambda + \lambda) = 0$ are

$$\lambda_1 = -b \quad (5.64)$$

$$\lambda_2 = A - \sqrt{A^2 + B} \quad (5.65)$$

$$\lambda_3 = A + \sqrt{A^2 + B} \quad (5.66)$$

respectively, with $A = \frac{-bS_{dfe}^*}{2S_{end}^*}$ and $B = -b\mu_1(\frac{S_{dfe}^*}{S_{end}^*} - 1)$. Since $b > 0$ and $\frac{S_{dfe}^*}{S_{end}^*} > 0$, λ_1 and λ_2 are defined negative. The third solution will be defined negative $\lambda_3 < 0$ if $|A| > |\sqrt{A^2 + B}| \rightarrow |A^2| > |A^2 + B| \rightarrow B < 0$, which is satisfied for $\frac{S_{dfe}^*}{S_{end}^*} > 1$ or, as it is shown in previous section, when $R_0 > 1$.

Stability of the endemic equilibrium point (END) model with n=2

For n=2 (i.e. there are two infectious subpopulations) a function $g(\lambda)$ will be defined as in (5.62), this time with \mathbf{J} a 4x4 jacobi matrix from the susceptible, the recovered, and the two stages of the infectious subpopulations.

$$g(\lambda) = (b + \lambda)(g_0 + g_1\lambda + g_2\lambda^2 + g_3\lambda^3)$$

with

$$g_0 = b\mu_1\mu_2\left(\frac{S_{dfe}^*}{S_{end}^*} - 1\right) \quad (5.67)$$

$$g_1 = b(\mu_1 + \mu_2)\frac{S_{dfe}^*}{S_{end}^*} - bX \quad (5.68)$$

$$g_2 = (\mu_1 + \mu_2 + b\frac{S_{dfe}^*}{S_{end}^*}) - X \quad (5.69)$$

$$g_3 = 1 \quad (5.70)$$

being $X = \frac{\mu_1\mu_2(\beta_1(1-C_1)+\beta_2(C_1-C_2))}{(\beta_1(1-C_1)\mu_2+\beta_2(C_1-C_2))\mu_1}$. The first eigenvalue is trivially obtained as $\lambda = -b$. The other eigenvalues will not be directly obtained, as it is only needed to demonstrate that their real part is negative in order to prove the local asymptotic stability of the model. The Routh-Hurwitz criterion [41][42] says that in order to have all the solutions of $g(\lambda_i) = 0$ on the left half plane, the coefficients of g must satisfy the following conditions:

$$g_i > 0 \forall i = 0, 1, 2, 3$$

$$g_1g_2 > g_3g_0$$

Both conditions can be satisfied once that the limits of the X parameter are established. Given $\mu_M = \max[\mu_1, \mu_2]$ and $\mu_m = \min[\mu_1, \mu_2]$ then

$$\frac{\mu_1\mu_2(\beta_1(1-C_1) + \beta_2(C_1-C_2))}{\mu_M(\beta_1(1-C_1) + \beta_2(C_1-C_2))} \leq X \leq \frac{\mu_1\mu_2(\beta_1(1-C_1) + \beta_2(C_1-C_2))}{\mu_m(\beta_1(1-C_1) + \beta_2(C_1-C_2))} \quad (5.71)$$

$$\mu_m \leq X \leq \mu_M \quad (5.72)$$

so that, for $R_0 > 1 \rightarrow \frac{S_{dfe}^*}{S_{end}^*} > 1$, it is deduced that the coefficients are positive:

$$0 < b\mu_1\mu_2\left(\frac{S_{dfe}^*}{S_{end}^*} - 1\right) = g_0 \quad (5.73)$$

$$0 < b\left(\mu_m\frac{S_{dfe}^*}{S_{end}^*} + \left(\frac{S_{dfe}^*}{S_{end}^*} - 1\right)\mu_M\right) \leq g_1 \quad (5.74)$$

$$0 < (\mu_m + b\frac{S_{dfe}^*}{S_{end}^*}) \leq g_2 \quad (5.75)$$

$$0 < 1 = g_3 \quad (5.76)$$

And the lower limit of the second condition is defined as:

$$g_1g_2 - g_1g_0 \geq \min[g_1]\min[g_2] - g_3g_0 = b\frac{S_{dfe}^*}{S_{end}^*}\left(\mu_m\left(b\frac{S_{dfe}^*}{S_{end}^*} + \mu_m\right) + b\left(\frac{S_{dfe}^*}{S_{end}^*} - 1\right)\mu_M\right) > 0 \quad (5.77)$$

so all the real parts of the eigenvalues are negative and the equilibrium endemic point is locally asymptotically stable as long as $R_0 > 1$.

5.2.4 Discrete SI_nR Model with delay

The dynamic equation (5.41) is approximated to $\dot{\mathbf{x}}_k \rightarrow \frac{\mathbf{x}_{k+1} - \mathbf{x}_k}{\tau}$, being $\mathbf{x}_k = (I_k^1, I_k^2, \dots, I_k^m, R_k, S_k)^T$ the vector of the subpopulations to obtain a discrete-time counterpart of the continuous-time model. The notation for any subpopulation at the time interval $t \in [k\tau, (k+1)\tau)$ is established as $x_m(t) = x_k^m$. Thus, it is obtained the analogous discrete equations to the model from (5.18):

$$\begin{aligned}
S_{k+1} &= \tau\nu - \left(1 - \tau b + \sum_{j=1}^n \tau\beta_j I_k^j\right) S_k + D_{n+1} S_{k-\sigma_{n+1}} \sum_{j=1}^n \tau\beta_j I_{k-\sigma_{n+1}}^j \\
R_{k+1} &= D_n S_{k-\sigma_n} \sum_{j=1}^n \tau\beta_j I_{k-\sigma_n}^j - D_{n+1} S_{k-\sigma_{n+1}} \sum_{j=1}^n \tau\beta_j I_{k-\sigma_{n+1}}^j + (1 - \tau b) R_k \\
I_{k+1}^m &= D_{m-1} S_{k-\sigma_{m-1}} \sum_{j=1}^n \tau\beta_j I_{k-\sigma_{m-1}}^j - D_m S_{k-\sigma_m} \sum_{j=1}^n \tau\beta_j I_{k-\sigma_m}^j + (1 - \tau\mu_m) I_k^m \quad \forall m \in [2, ..n] \\
I_{k+1}^1 &= S_k \sum_{j=1}^n \tau\beta_j I_k^j + (1 - \tau\mu_1) I_k^1 - D_1 S_{k-\sigma_1} \sum_{j=1}^n \tau\beta_j I_{k-\sigma_1}^j
\end{aligned} \tag{5.78}$$

with $\sigma_i = \sum_{j=1}^i N_j$ and $D_i = \prod_{j=1}^{i-1} e^{-\mu_j N_j \tau}$, being N_i the rounded half down value for $\tau_i/\tau \quad \forall i \in [1, \dots, n]$. Now, at the equilibrium point, the delays are not relevant, while the dynamic equation at the equilibrium can be rewritten as:

$$\begin{aligned}
S^* &= \tau\nu - (1 - \tau b) S^* + (D_{n+1} - 1) S^* \sum_{j=1}^n \tau\beta_j I^{j*} \\
R^* &= (D_n - D_{n+1}) S^* \sum_{j=1}^n \tau\beta_j I^{j*} + (1 - \tau b) R^* \\
I^{m*} &= (D_{m-1} - D_m) S^* \sum_{j=1}^n \tau\beta_j I^{j*} + (1 - \tau\mu_m) I^{m*} \quad \forall m \in [2, ..n] \\
I^{1*} &= (1 - D_1) S^* \sum_{j=1}^n \tau\beta_j I^{j*} + (1 - \tau\mu_1) I^1
\end{aligned} \tag{5.79}$$

The reproduction number will be obtained again with a next generation matrix method as in the previous section, so the value would be

$$K_S = R_0 = \frac{\sum_{i=1}^n \frac{\beta_i D_{i-1}}{\mu_i \tau}}{b/\nu\tau + \sum_{i=1}^n \frac{\beta_i D_i}{\mu_i \tau}} \tag{5.80}$$

which is similar to the reproduction number from the continuous model, with the only difference of the D_i constants instead of the previous C_i . However, given their similar

origins and values, the properties exhibited in both set of constants will be the same, in the sense that $0 \leq C_n \leq C_{n-1} \leq \dots \leq C_1 \leq 1$ such as $0 \leq D_n \leq D_{n-1} \leq \dots \leq D_1 \leq 1$. Given the same SI_nRS model with the same characteristics, the values of the reproduction number will be very similar too.

5.3 Simulation

A set of Matlab simulations are made based on the models described in the previous section, in order to contrast the predictions on their respective endemic and disease-free equilibrium states. A large enough number of infectious subpopulations is chosen, $n = 3$, so the stability of the models will be tested regarding their reproduction numbers. A common initial conditions are set to all the susceptible subpopulations in the disease-free equilibrium plus a 0.1 of that value of infected subpopulation at the first stage of the disease. For exposition and calculations convenience, the mortality rate b and the birth rate ν will be both taken equal to the inverse of the average lifespan of a human $b = \nu = \frac{1}{70} \text{ year}^{-1}$. The mortality rate of the three stages of the infection will be $\mu_1 = 2b$, $\mu_2 = 3b$, $\mu_3 = 3b/2$, and the average time in which an individual spends in each stage will be 19, 29 and 61 days respectively.

When simulating the discrete models, an appropriate time step size is chosen in order to guarantee the non-negativity of model with no delays. As for the discrete model with delays, given that non-negativity of the subpopulations in the continuous model has been proved in Proposition 5.5, an algorithm is established during the simulation so that the discrete dynamics approximates to the continuous one in any critical positivity points. A loop in which the following point is evaluated is introduced, acting over the time step size. While any of the subpopulations of the next point present a negativity $x_{k+1,i} < 0$ for any $i \in [1, \dots, n + 2]$, then the step size is reduced $\tau_k^j = \lambda \tau_j^{k-1}$, with j being the j^{th} loop iteration, $\tau_k^0 = \tau_k$ and $\lambda \in (0, 1)$. Another loop is set after this resetting the time step size $\tau_k^j = \lambda^{-1} \tau_k^{j-1}$ while the next point is non-negative or the time step size is equally or below the original value.

5.3.1 SI_3RS model with no delays

Given the parameters previously commented, the transition ratios between the different subpopulations are obtained as the inverse of their average times during each stage. Thus, $\gamma_1 = 365/19 \text{ year}^{-1}$, $\gamma_2 = 365/29 \text{ year}^{-1}$, $\gamma_3 = 365/61 \text{ year}^{-1}$, and the final transition from recovered to susceptible again will be set as $\gamma_4 = 365/670 \text{ year}^{-1}$. Given a value of the transition rates $\bar{\beta} = (7\beta_0, 4\beta_0, 7\beta_0)$ the reproduction number is set to 0.5 and 1.5 respectively. For the continuous model, two graphics representing the evolution of each subpopulation for both situations are presented in figure 5.2 and figure 5.3. while for the discrete model, a step time τ is set to 0.1 years and the simulations are run with the same parameters. The results of these simulations are presented in figure 5.4 and figure 5.5.

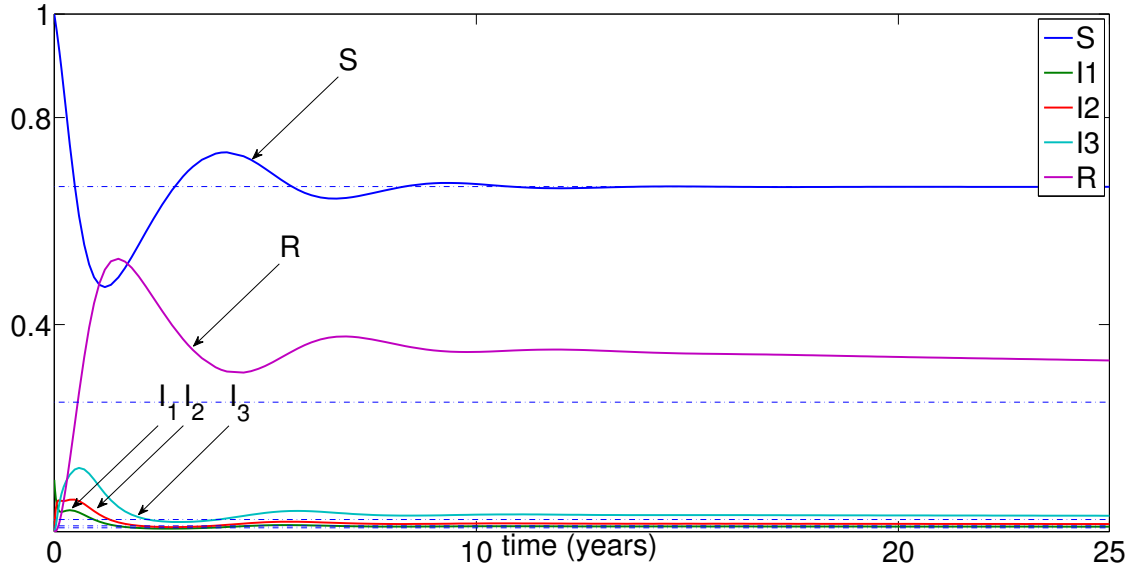


Figure 5.2: Dynamic of the subpopulations for $R_0 = 1.5$. The dotted lines represent the predicted endemic values.

5.3.2 SI_3RS model with delays

The common parameters are set as in the previous cases, but in this case the delayed times will be equal to their respective average times $\tau_1 = 19/365$ years, $\tau_2 = 29/365$ years and $\tau_3 = 61/365$ years. The delay of the transition between the recovered to the susceptible subpopulation will be changed from $610/365$ to $80/365$ years in order to let the simulation achieve the equilibrium at a reasonable time. The values of the transmission rates will maintain their proportionality, but the range of the possible reproduction number is not so wide as in the previous case. Their values are changed to now be $R_0 = 1.01$ and $R_0 = 0.92$ respectively. The evolution of the subpopulations are presented in figure 5.6 and figure 5.7. In the discrete model, the same time step as before is fixed to $\tau = 0.1$ years. The evolution of the subpopulations for each reproduction number can be seen in figure 5.8 and figure 5.9 respectively.

Observe that the subpopulations rapidly tend to the disease-free equilibrium point in figure 5.9. While it is seen that the discrete time and continuous time models reach the same final states when the conditions are equal, it is also been noticed the irregularity of the dynamics in the discrete models over the continuous. This fact reveals that the discretization procedure along with the time step must be selected carefully prior to simulate the discrete-time model.

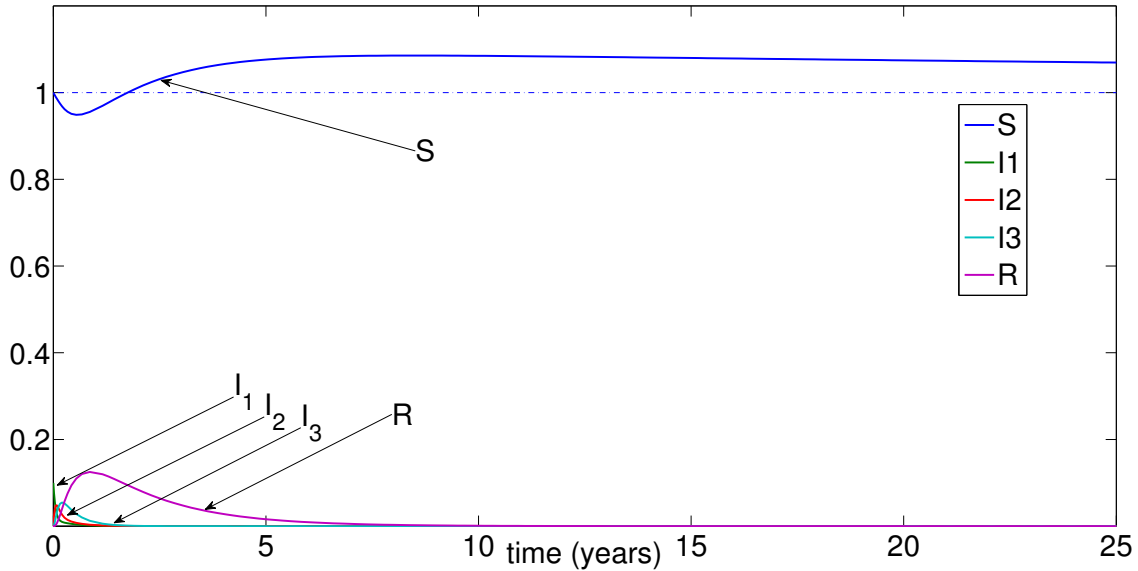


Figure 5.3: Dynamics of the subpopulations for $R_0 = 0.5$. The dotted line represents the predicted disease-free value of the susceptible subpopulation.

5.4 Conclusions

A model of a disease spreading with multiple infectious stages has been studied in depth. The next generation techniques have been proven to be quite useful when operating with models with complex interactions as in the variations of the model presented in this work. The reproduction numbers obtained in each case have also proven to predict correctly the final stable state of the subpopulations when they are properly simulated. The simulations have also shown that the different discretizations of a continuous model can cause significant discrepancies in the resulting dynamics. An appropriate integration step should be considered taking this into account as well as other factors like the computation time available, or, if the model is being used in a controlled system, the available time for data acquisition.

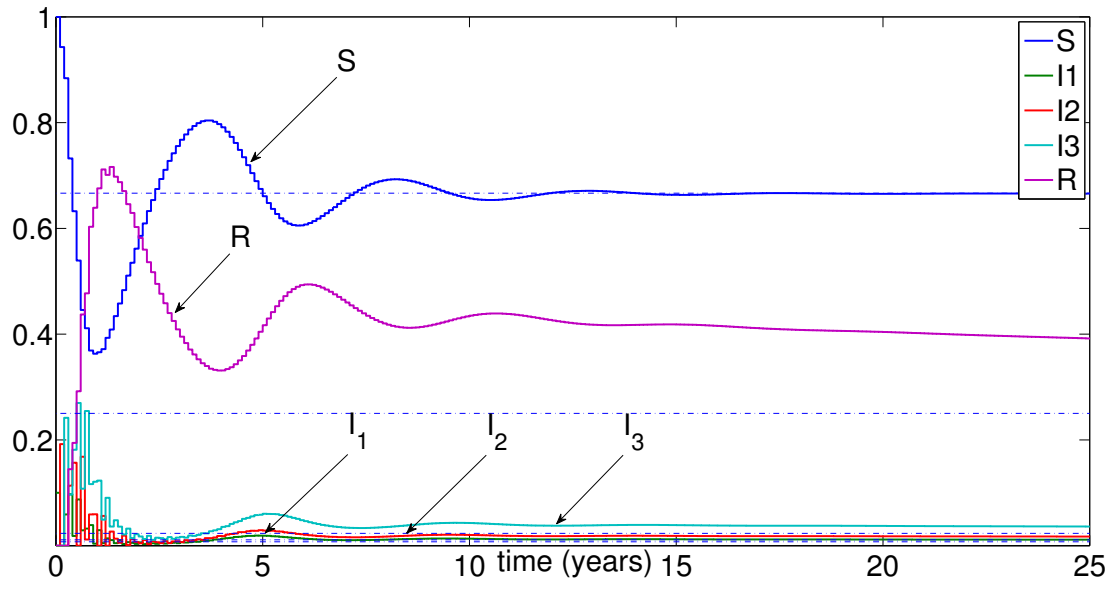


Figure 5.4: Dynamics of the subpopulations for $R_0 = 1.5$. The dotted lines represents the predicted endemic values.

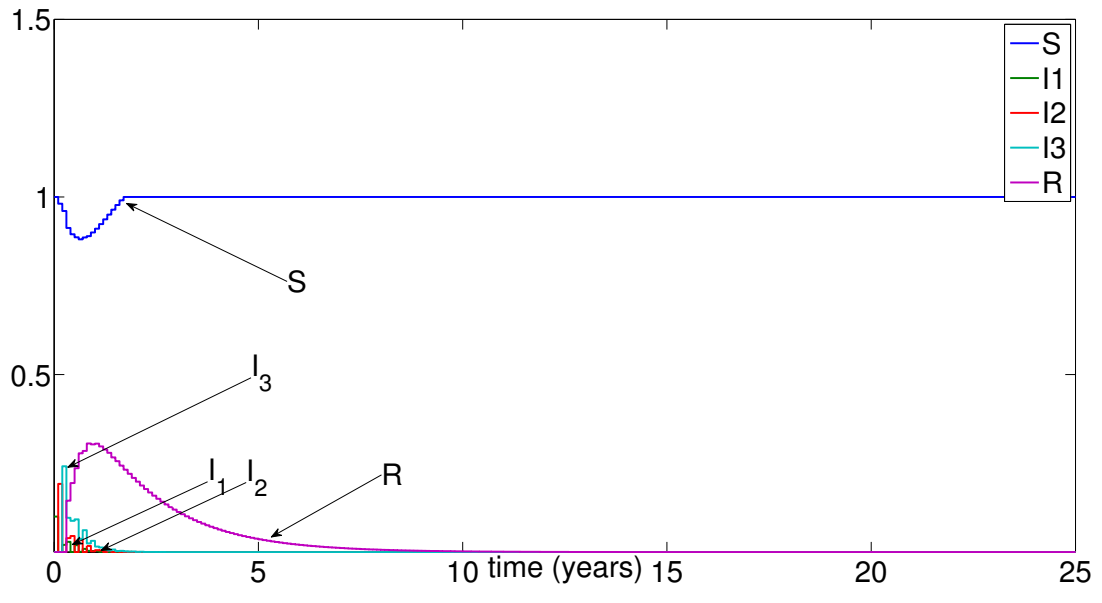


Figure 5.5: Dynamics of the subpopulations for $R_0 = 0.5$.

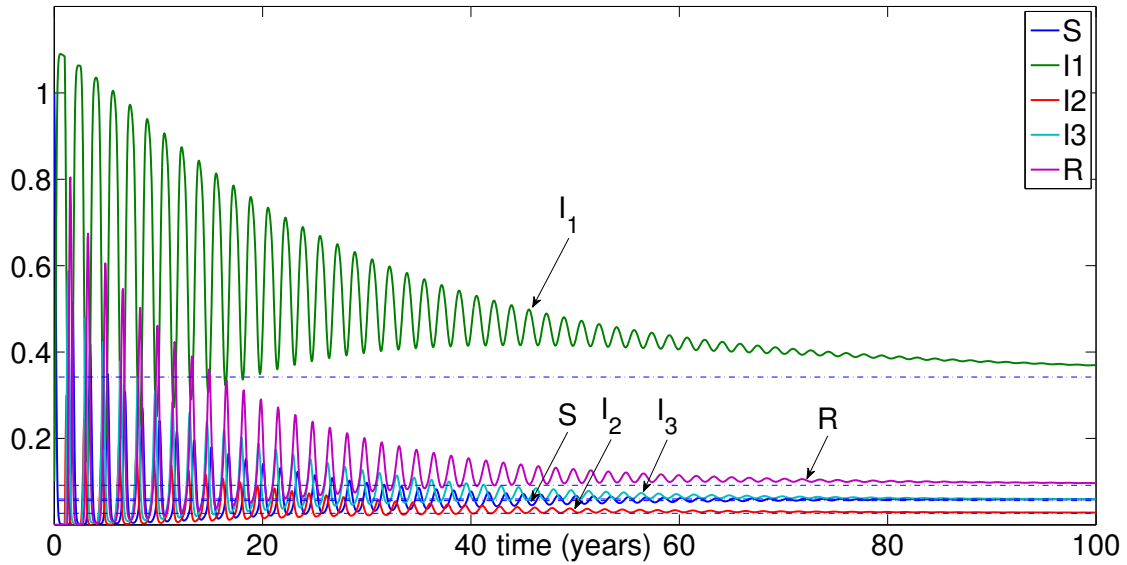


Figure 5.6: Dynamics of the subpopulations for the SI_3RS model for $R_0 = 1.01$. The dotted lines represent the predicted endemic values.

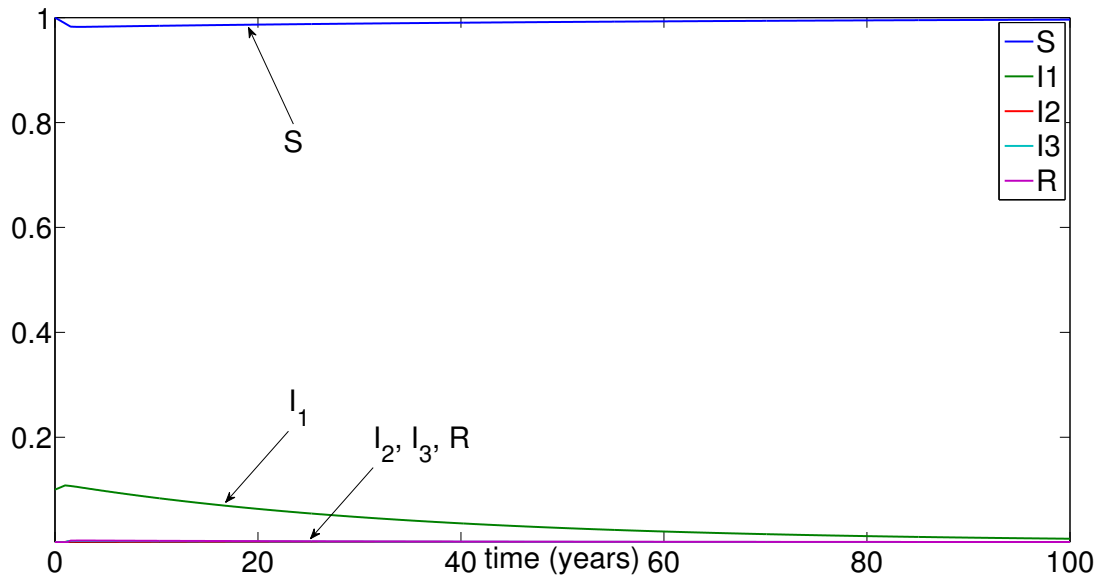


Figure 5.7: Dynamics of the subpopulations for the SI_3RS model for $R_0 = 0.92$. Observe that the subpopulations rapidly tend to the disease-free equilibrium.

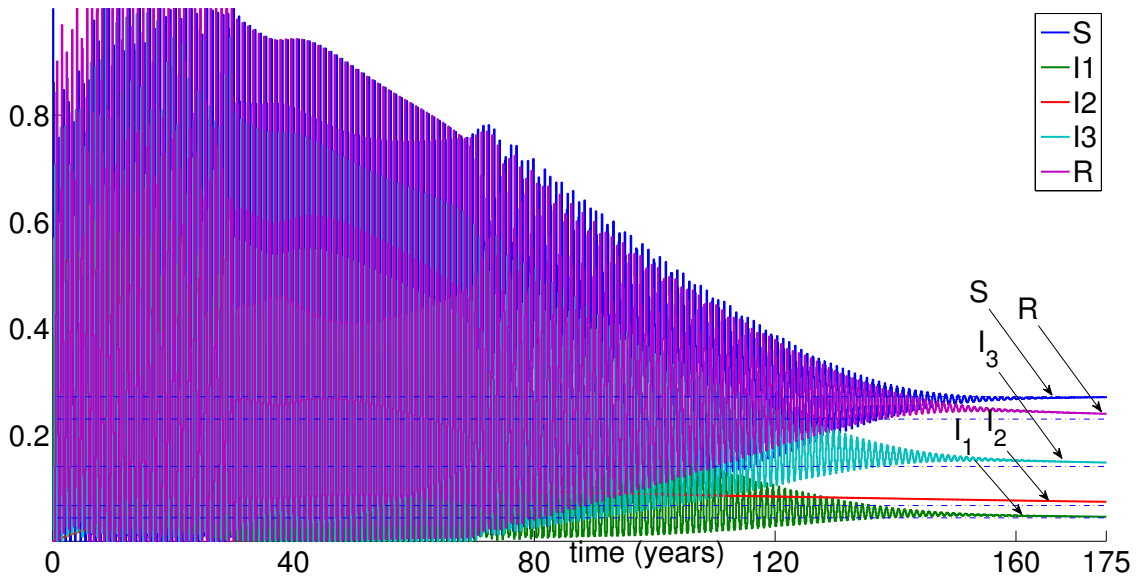


Figure 5.8: Dynamics of the different subpopulations of the discrete delayed SI_3RS model for $R_0 = 1.01$. The dotted lines represent the predicted endemic values.

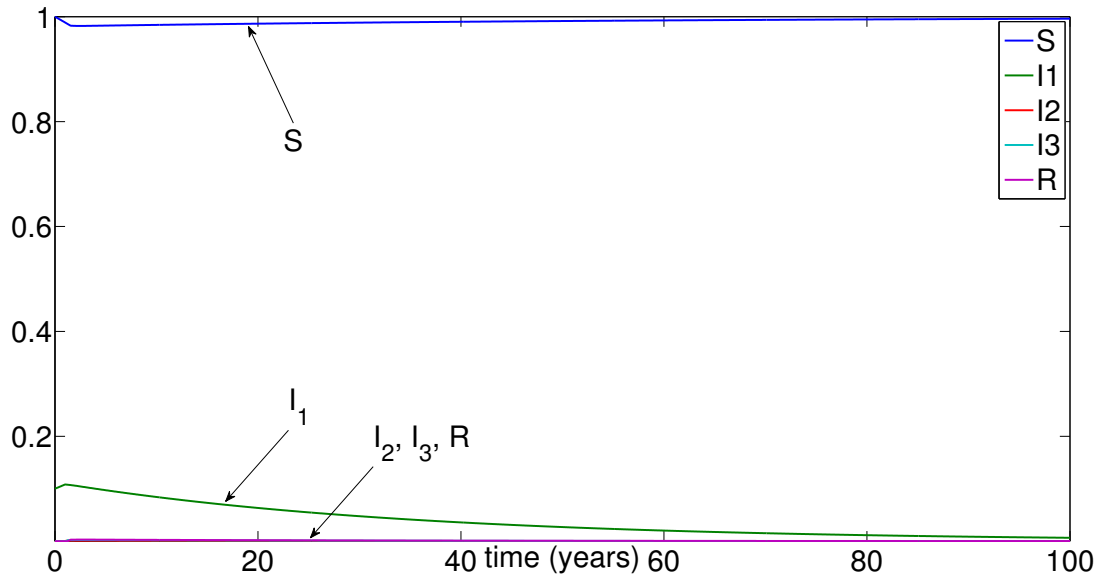


Figure 5.9: Dynamics of the subpopulations of the SI_3RS discrete delayed model for $R_0 = 0.92$.

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Feedback vaccination control for SIRS and SEIRS epidemic models: Partial stability, observer design and linealization-based techniques

This chapter deals with control topics in the context applied to epidemic models: Linearization-based techniques, observer design, partial stability and some discretization techniques. The topics here presented take part of the Phd work under financial support by the Spanish Ministry of Economy and Competitiveness, the Basque Government and the Faculty of Science and Technology of UPV/EHU, and are unified in this chapter because of the difficulty of including them in the former chapters or as individual ones. The propagation of a disease is described by a series of SEIRS and SIRS epidemic models. Some feedback vaccination law control techniques will be used in order to design a strategy to eradicate the infection from the population optimally. Those laws are based on different concepts, such as partial stability (ensuring the boundedness of the infectious and infected in order to get the disease under control), observer-based or discrete models. The partial stability of the models will be studied in the vaccination-free case. Moreover, the controlled systems are guaranteed to be positive and stable under such a vaccination control strategy. Simulation examples illustrates the theoretical results relative to the stability and positivity of the controlled system while guaranteeing the eradication of the epidemics, along with some comparison with previous vaccination laws.

6.1 Introduction

In order to understand the persistence of the infection in a host population, the development of numerical tools has been crucial. Furthermore, the analysis of mathematical models describing epidemics spreading allows us to obtain valuable knowledge of underlying aspects of the disease and make decisions regarding vaccination policies, establishment of quarantines, and so on. In this way, a large number of mathematical models have been proposed [1], as well as constant, regular and/or impulsive vaccination strategies have appeared in several researches [2]-[7]. Many specific features regarding these models have been studied in many works, such as the presence of bifurcations [8], oscillating behavior [2] and existence of waves [11]. However, the stability of the model has been by far the most important property to be studied [8],[9]-[16]. Typically, global stability is the main stability property to be analyzed [12]- [14], [16]. Global stability is referred to the boundedness of all the variables

composing the model as time goes by. Nevertheless, this approach seems to be quite conservative for the study of epidemics since a globally stable model would never capture a potential natural increase of a population, which would lead to diverging subpopulations. It is also worth noting that, from an epidemic point of view, it is only needed the boundedness (and eventually the convergence to zero) of the infected and infectious subpopulations regardless the behavior of the other ones, which are not directly suffering from the disease. Thus, if global stability is required, the analysis and conditions found may not be applicable to situations where the total population grows. This is a great inconvenience since the model may be globally unstable because the susceptible or the immune diverge while no specific information is obtained for the infected and infectious, which are the most important subpopulations from an epidemic point of view.

The concept of partial stability [17] is introduced and applied to controlled epidemic model with different types of nonlinear incidence rates. Partial stability focus on the analysis of the infected subpopulations and their boundedness, regardless the behavior of the other variables, including a potential natural increase of the total population. Also it is introduced other regular vaccination strategy, based on a feedback control law for exact input-output linearization, combined with an observer, as in [5], [6]. The observer is designed to estimate on-line the susceptible and the infected (or exposed) populations since such measures are not available in a real situation where only the infectious population is measurable. The estimates provided by the observer are used to synthesize the control law instead of the true susceptible and infected populations. Other potential situation is that the parameters of the epidemic model are not fully known what may be circumvented by using adaptive control strategies [18]. Also, although conventional epidemiology has used continuous models [1],[19],[20]-[30], partially because of the mathematical analysis is simpler, there are some advantages on applying discrete models [31]-[34], as the data from the subpopulation are not instantly obtained, and the possible actions made in order to restrain the disease may require certain time to be accomplished.

In this last chapter, a series of studies concerning this and other methods of disease eradication through vaccination are introduced to a series of SIRS and SEIR epidemic models. First, the continuous model are analyzed, and the subpopulations dynamics examined to verify if they have a behavior coherent with a real population. Then a series of feedback-type vaccination control laws are implemented in order to eradicate the illness.

The two different types are studied separately: First, a generic SEIR model is introduced, and control laws based on the partial stability frame through a Lyapunov-type adapted [17],[35] and observers are designed and implemented. Then, the study of the continuous model is combined with the study of the discrete model, which is constructed in order to run the simulations with diverse vaccination strategies. Several simulations of the dynamics of the subpopulations are made for each model and vaccination strategy, with the diseases being eradicated at different rates depending on the chosen parameters. Finally, a normalized SIRS epidemic model is introduced, to circumvent the complexity from the fact that the whole population may be varying, increasing or decreasing in time. Moreover, such a normalized model is used to syn-

thesize the vaccination control law, which ensures the eradication of the infection from the host population and the positivity of the normalized SIRS model as well as the original SIRS epidemic model. The approach considers the possibility of the susceptible subpopulation converging and not converging to zero, as it happened in previous vaccination control laws, [9],[36]. Simulation results showing the usefulness of the proposed approach are included and a comparison with respect other feedback-type vaccination strategies is performed.

6.2 SEIR Model and problem formulation

6.2.1 Model description

Consider the SEIR epidemic model with vaccination described by :

$$\dot{S}(t) = -\mu S(t) + \omega R(t) - \varphi(S, E, I, R)(t) + \nu N(t)(1 - V(t)) \quad (6.1)$$

$$\dot{E}(t) = \varphi(S, E, I, R)(t) - (\mu + \kappa)E(t) \quad (6.2)$$

$$\dot{I}(t) = -(\mu + \gamma)I(t) + \kappa E(t) \quad (6.3)$$

$$\dot{R}(t) = -(\mu + \omega)R(t) + \gamma I(t) + \nu N(t)V(t) \quad (6.4)$$

where $S(t)$, $E(t)$, $I(t)$ and $R(t)$ denote the subpopulations of susceptible, exposed, infectious and immune respectively.

$N(t)$ denotes the total population at time t (i.e. $N(t) = S(t) + E(t) + I(t) + R(t)$), μ is the rate of deaths from causes unrelated to the infection, ν denotes the birth rate and ω is the rate of losing immunity. The typically non-linear function $\varphi(S, E, I, R)$ is referred to as the disease incidence rate. When $\varphi(S, E, I, R) = \beta S(t)I(t)$ it is said to be the bilinear incidence rate; when $\varphi(S, E, I, R) = \varphi_1(S, E, I, R) = \beta \frac{S(t)I(t)}{N(t)}$ it is said to be the standard incidence rate and when $\varphi(S, E, I, R) = \varphi_2(S, E, I, R) = \frac{\beta S(t)I(t)}{1 + \alpha S(t)}$ or $\varphi(S, E, I, R) = \frac{\beta S(t)I(t)}{1 + \alpha I(t)}$ it is said to be the saturated incidence rate, where β is the transmission constant and α is the saturation coefficient. κ^{-1} and γ^{-1} are, respectively, the average durations of the latent and infective periods. All the above parameters are assumed to be positive so as to represent a real situation. The total population dynamics at time t can be calculated by summing up all the equations (6.1)-(6.4), leading to:

$$\dot{N}(t) = (\nu - \mu)N(t) \quad (6.5)$$

It can be deduced from equation (6.5) that the total population is constant when $\nu = \mu$, increases when $\nu > \mu$ and decreases when $\nu < \mu$. The relation between μ and ν also determines the existence or not of equilibrium points as the following proposition for incidence rate φ_1 shows:

Proposition 6.1. *The equilibrium points of the system of equations (6.1)-(6.4) with incidence rate φ_1 and $V(t) = 0$ are given by:*

i) *If $\nu \neq \mu$ then, the only equilibrium point is given by $S^* = E^* = I^* = R^* = 0$. This point represents the case of total population extinction.*

ii) *If $\nu = \mu$, the total population is constant, i.e. $N(t) = N = N(0) = S(0) + E(0) + I(0) + R(0)$ and there are two equilibrium points given by:*

- *$S^* = N, E^* = I^* = R^* = 0$, i.e., the total population becomes susceptible.*
-

$$S^* = \frac{(\mu + \kappa)(\mu + \gamma)}{\kappa\beta} N \quad (6.6)$$

$$E^* = \frac{(\mu + \omega)(\mu + \gamma)(\kappa\beta - (\mu + \gamma)(\mu + \kappa))}{\kappa\beta((\mu + \gamma + \kappa)(\mu + \omega) + \gamma\kappa)} N \quad (6.7)$$

$$I^* = \frac{(\mu + \omega)(\kappa\beta - (\mu + \gamma)(\mu + \kappa))}{\beta((\mu + \gamma + \kappa)(\mu + \omega) + \gamma\kappa)} N \quad (6.8)$$

$$R^* = \frac{(\kappa\beta - (\mu + \gamma)(\mu + \kappa))}{\beta((\mu + \gamma + \kappa)(\mu + \omega) + \gamma\kappa)} N \quad (6.9)$$

Proof.

Part ii) was proved in [37] and, therefore, it is only necessary to prove i). Thus, the equilibrium point implies, in particular, that equation (6.5) zeroes. Hence, there is:

$$\dot{N}(t) = 0 = (\nu - \mu)N(t) \quad (6.10)$$

Since $\nu - \mu \neq 0$, then $N(t) = 0$ is the only possibility of equilibrium which implies that $S^* = E^* = I^* = R^* = 0$. \square

Thus, as equation (6.5) reveals, this model is able to describe the case when the total population experiences a natural increase. Moreover, if $\nu > \mu$ global stability of the epidemic model from equations (6.1)-(6.4) will not hold. However, from an epidemic point of view, it is not needed all the populations to be bounded, just the infected, $E(t)$, and infectious, $I(t)$. Hence, in this paper the use the concept of partial stability is used to study the stability of the SEIR epidemic model given by equations (6.1)-(6.4) rather than the concept of global stability. An introduction to partial stability is given in the next subsection.

6.2.2 Partial stability of systems

The problem of partial stability is referred to the problem of studying the stability of a system restricted only to a part of the variables (but not all). Pioneering results in this field have been made by Rumyantsev [38], but a large number of researches have subsequently contributed to the field through years.

Now, a brief introduction to the partial stability problem is provided. Consider a

nonlinear dynamic system $\dot{x}(t) = f(x)$ with state vector $x(t)$ decomposed in the form:

$$x(t)^T = [y(t)^T \quad z(t)^T] \quad (6.11)$$

in such a way that the nonlinear system can be written as:

$$\dot{y}(t) = Y(y(t), z(t)), \quad \dot{z}(t) = Z(y(t), z(t)) \quad (6.12)$$

Consider also that the origin $x(t)^T = 0 = [0 \quad 0]$ is an equilibrium point. If the equilibrium point is located at other position it can be placed at the origin by a coordinates transformation. Thus, the concept of partial stability reads:

Definition 6.2. *An equilibrium position $x = 0$ of the system from equation (6.12) is:*

- i) locally y -stable if, for any $\epsilon > 0$, there exists a $\delta(\epsilon) > 0$ such that $\|x_0\| < \delta$ implies $\|y(t)\| < \epsilon$ for all $t \geq t_0$ with x_0 denoting the initial condition,*
- ii) locally asymptotically y -stable if it is locally y -stable and furthermore $y(t) \rightarrow 0$ as $t \rightarrow \infty$.*
- iii) globally asymptotically y -stable if the asymptotically y -stability holds for any bounded initial condition $\|x_0\|$.*

The intuitive meaning of Definition 6.2 is that the partial state variables in y are bounded for all time for a bounded initial condition of the full state regardless the tendency of the variables in z . This is an important issue since it allows us to study the behavior of just a subset of all the state variables as is convenient in epidemic models. The design of the vaccination control law will be based on the partial stability frame. One of the main tools to analyze the partial stability of a nonlinear system is the extension of the classical Lyapunov theorems to this concept [17], [35]. Thus, the following proposition 6.3 holds:

Proposition 6.3. *For system from equation (6.12), assume that there exists a function L satisfying:*

$$L(x) \geq a(\|y\|) \quad (6.13)$$

$$\dot{L}(x) \leq 0 \quad (6.14)$$

where $a(\cdot)$ denotes any continuous increasing function with argument $\|y(t)\|$. Then, the equilibrium position $x = 0$ of the system from equation (6.12) is y -stable.

The meaning of proposition 6.3 is that if a positive definite function is used only in the variables y , the Lyapunov theorem will be able to prove the partial stability of just those variables. Thus, this result will be used to design a novel vaccination control law.

6.3 Partial Stability of the Vaccination-Free model

This section is devoted to the study of the partial stability of the vaccination-free system (i.e. when $V = 0$ in Equations (6.1) and (6.4)). The work from [36] proved that Equations (6.1)-(6.4) lead to non-negative solutions for all $t \geq 0$ if $V = 0$. It will be proved that the infected and infectious may still be bounded for all time when the total system does not exhibit a global stability property. Hence, a further insight into the dynamics of the overall system is gained. The following proposition holds:

Proposition 6.4. *The nonlinear system from equation (6.1)-(6.4) is (E, I) -stable for any set of positive parameters with $\alpha \geq 1$ and incidence rate φ_1 or φ_2 provided that $(\mu + \kappa)(\mu + \gamma) - \beta\kappa \geq 0$.*

Proof.

Since $N = S + E + I + R$ and the system is non-negative (see [37]), then $S/N \leq 1$ and $\varphi_1(S, E, I, R) = \beta \frac{IS}{N} \leq \beta I$. In addition, since $\alpha \geq 1$ then $1 + \alpha S > S$ and $\frac{S}{1+S} < 1$. Hence, $\varphi_2(S, E, I, R) = \beta I \frac{S}{1+S} < \beta I$. Thus, regardless of the incidence rate, equation (6.2) can be upper-bounded as:

$$\dot{E}(t) \leq \beta I(t) - (\mu + \kappa)E(t) \quad (6.15)$$

Now, equations (6.3) and (6.15) form a system of linear differential inequalities whose stability can be stated through the comparison principle by analyzing the stability of the dynamics matrix:

$$A = \begin{pmatrix} -(\mu + \kappa) & \beta \\ \kappa & -(\mu + \gamma) \end{pmatrix} \quad (6.16)$$

whose characteristic equation is:

$$\det(sI - A) = s^2 + (2\mu + \kappa + \gamma)s + (\mu + \kappa)(\mu + \gamma) - \beta\kappa \quad (6.17)$$

According to the Routh-Hurwitz criterion [39], [40], all the coefficients in equation (6.17) must be non-negative in order to make the dynamics matrix stable. Since all the parameters of the model are assumed to be positive, $(2\mu + \kappa + \gamma)$ is trivially positive and it is only needed to require that:

$$(\mu + \kappa)(\mu + \gamma) - \beta\kappa \geq 0 \quad (6.18)$$

and the proposition is proved. \square

Notice that the system may still be (E, I) -stable despite $\nu > \mu$, which implies that some of the other variables diverge. Furthermore, the following corollary may be obtained:

Corollary 6.5. *The system from equations (6.1)-(6.4) is (E, I) -stable for both incidence rates provided that all the parameters are positive, $\alpha \geq 1$ and $\mu + \gamma \geq \beta$.*

Proof.

Since $\mu + \kappa > \kappa$, then equation (6.18) can be satisfied if $\mu + \gamma \geq \beta$. \square

Corollary 6.5 provides an insight concerning when the epidemics is bounded despite any natural increasing of the population (global instability). As it has been established, μ represents the rate of deaths for causes unrelated to the infection, γ the rate at which a new infective losses its infectivity and β the rate of new infectious. Thus, when people die soon and the latent period is small compared to the transmission velocity (I.e. $\mu + \gamma > \beta$), the infected and infectious subpopulations (E,I) are bounded. Hence, the application of partial stability gives another insight in the analysis of the model, and relates stability properties with more practical issues.

6.4 Vaccination laws based on partial stability

In this section a series of feedback-type vaccination control laws applied on the different proposed models will be designed starting from the concept of partial stability. Thus, the objective of the control is not to stabilize all the variables of the system, but only (E, I)-stabilize the system regardless the other variables.

6.4.1 Partial stability-based vaccination law based on recovered subpopulation

For this, Lyapunov's type proposition 6.3 will be used to prove that:

Proposition 6.6. *The vaccination law given by:*

$$V(t) = 1 + \frac{\omega}{\nu N(t)} R(t) \quad (6.19)$$

(E, I)-stabilizes the system of equations (6.1)-(6.4) for any set of positive parameters and any incidence rate. Furthermore, $S(t), E(t), I(t) \rightarrow 0$ as $t \rightarrow \infty$.

To perform the proof of proposition 6.6 it will be needed the following result:

Proposition 6.7. *The solution of the system of Equations (6.1)-(6.4) under the vaccination law from equation (6.19) satisfies $S(t), E(t), I(t), R(t) \geq 0$ for all $t \geq 0$ for any incidence rate and any set of positive parameters provided that $S(0), E(0), I(0), R(0) \geq 0$.*

Proof.

It is firstly proved that the total population remains non-negative for all time. Thus, from equation (6.5) have:

$$N(t) = e^{\nu - \mu} N(0) \geq 0 \quad (6.20)$$

since $N(0) = S(0) + E(0) + I(0) + R(0) \geq 0$. Now it will be proved that the susceptible are non-negative. For this, notice that both incidence rates φ_1 and φ_2 can be expressed as $\varphi = \varphi'(S, E, I, R) \cdot S(t)$. Thus equation (6.1) under vaccination law (6.19) takes the form:

$$\dot{S}(t) = -(\mu + \varphi'(S, E, I, R))S(t) \quad (6.21)$$

Now a proof by contradiction will be made: Assume that there exists a time instant t^* such that $S(t^*) < 0$. Thus, since $S(t)$ is a continuous function, there must be a time instant $t_S < t^*$ such that $S(t_S) = 0$. However, equation (6.21) implies $\dot{S}(t_S) = 0$, deducing that $S(t) = 0$ for all $t \geq t_S$. Thus, this contradicts the existence of such t^* and the susceptible cannot become negative. A case-based reasoning will be used to prove the non-negativeness of E and I . For this, recall that the incidence rates can also be expressed as $\varphi = \varphi'(S, E, I, R) \cdot I(t)$, i.e. φ vanishes when I vanishes. Thus, assume that there exists a time instant t_{EI} such that $E(t_{EI}) = I(t_{EI}) = 0$. Hence, equations (6.2) and (6.3) imply that $\dot{E}(t_{EI}) = \dot{I}(t_{EI}) = 0$ and $E(t) = I(t) = 0$ for all $t \geq t_{EI}$. This means that when both variables vanish simultaneously, they remain in zero for all time onwards. Now, define the following time instants:

$$t_E = \{t | E(t) = 0 \wedge I(t) > 0 \wedge S(t) > 0\} \quad (6.22)$$

$$t_I = \{t | I(t) = 0 \wedge E(t) > 0\} \quad (6.23)$$

$$t_{E2} = \{t | E(t) = 0 \wedge I(t) > 0 \wedge S(t) = 0\} \quad (6.24)$$

These time instants can be interpreted as the time instants when one variable E or I zeroes. Notice that in all cases it is supposed that the other variable is positive since as it has been proved before, if both variables vanish simultaneously, they remain in zero for the rest of the time. Thus, for t_E , there is $I(t_E) > 0$ and:

$$\dot{E}(t_E) = \varphi(S, E, I, R) = \varphi^*(S, E, I, R) \cdot I(t_E) > 0 \quad (6.25)$$

implying that E does not become negative, but tends to be positive again, while for t_I there is $E(t_I) > 0$ and:

$$\dot{I}(t_I) = \kappa E(t_I) > 0 \quad (6.26)$$

implying that I does not become negative, but it tends to be positive again. Now, from the definition of t_{E2} , the equations $\dot{E}(t) = 0$ and $\dot{I}(t) = -(\mu + \gamma)I(t)$ are established for all $t \geq t_{E2}$ implying:

$$I(t) = e^{-(\mu+\gamma)(t-t_{E2})} I(t_{E2}) \geq 0 \quad (6.27)$$

for all $t \geq t_{E2}$. Hence, both variables E and I remain non-negative for all time. Finally, the explicit solution of equation (6.4) under vaccination law from equation (6.19) can be written as:

$$R(t) = e^{-\mu t} R(0) + \int_0^t e^{-\mu(t-\tau)} [\gamma I(\tau) + \nu N(\tau)] d\tau \geq 0 \quad (6.28)$$

which is non-negative for $R(0) \geq 0$ since the rest of variables S, E, I and N have been proved to be non-negative. Thus, the proposition is proved. \square

Now, it can be proven proposition 6.6.

Proof. of proposition 6.6.

Consider the partially positive function:

$$L(t) = S(t) + E(t) + I(t) \quad (6.29)$$

$L(t)$ is positive definite in S , E and I from proposition 6.7 but it is not a positive definite function in the complete state $x = [S \ E \ I \ R]$. The time derivative of equation (6.29) is calculated as:

$$\begin{aligned} \dot{L} &= \dot{S}(t) + \dot{E}(t) + \dot{I}(t) \\ &= -\mu S(t) + \omega R(t) + \nu N(t)(1 - V(t)) \\ &\quad -\mu E(t) - (\mu + \gamma)I(t) \end{aligned} \quad (6.30)$$

If equation (6.19) is introduced into (6.30) one obtains:

$$\dot{L}(t) = -\mu S(t) - \mu E(t) - (\mu + \gamma)I(t) \leq 0 \quad (6.31)$$

Thus, the conditions for applying proposition 6.3 are met, and therefore, S , E and I are bounded for all time. Furthermore, while any of the variable S , E , I are positive, $\dot{L}(t) < 0$, implying that L decreases continually until it arrives to $S = E = I = 0$. Hence, all these variables converge to zero, proving the theorem. \square

Therefore, the epidemics is eradicated while the rest of variables evolve. Appreciate the rationale behind the vaccination law from equation (6.19). It is designed in order to cancel the positive terms appearing in equation (6.30) so as to make the derivative of L negative semidefinite (in the complete state). Furthermore, this design technique would not be used if a Lyapunov function in the complete state (e.g. $L = S + E + I + R$) would be proposed, since the vaccination function $V(t)$ disappears when all the subpopulations are summed up. In consequence, the partial stability approach has also provided a practical vaccination design tool. Moreover, the proposition 6.6 also proves the convergence of the susceptible to zero despite now the only interest are in the infected and infectious subpopulations. Finally, note that the vaccination control law holds for any kind of incidence rate since its particular value is canceled when summing up the equations for \dot{S} and \dot{E} . Therefore, the vaccination strategy holds for general nonlinear incidence rate equations.

6.4.2 Partial stability-based vaccination law based on susceptible subpopulation

Another vaccination law is designed, this time for the φ_1 specifically. This vaccination law considers a partial Lyapunov candidate function composed of only the exposed and infectious subpopulations, instead of including the immune subpopulation. This fact substantially modifies the design of the control law since the vaccination function does not appear explicitly in the Lyapunov function derivative, so that the design is indirectly carried out by controlling the subpopulation of susceptible. In the end the susceptible subpopulation is required to converge to a certain reference value located

on a safety band that allows the natural vanishment of the epidemic. The starting point of this vaccination law is the definition of the partial Lyapunov candidate function:

$$L(E(t), I(t)) = E(t) + I(t) \quad (6.32)$$

Note that this function does not contain all the state vector components, but only a subset of them. Therefore, it can be regarded as just a partial Lyapunov function. Its time derivative is given by (where the standard incidence rate has already been used):

$$\dot{L}(t) = \beta \frac{S(t)I(t)}{N_0} - \mu E(t) - (\mu + \gamma)I(t) \quad (6.33)$$

It can be noticed that the vaccination function $V(t)$ does not appear in equation (6.33). However, it can be rewritten from equation (6.33) as:

$$\dot{L}(t) = \left(\frac{\beta S(t)}{N_0} - (\mu + \gamma) \right) I(t) - \mu E(t) \quad (6.34)$$

If the subpopulations were positive, the Lyapunov candidate function from equation (6.32) would have negative-definite derivative if $\left(\frac{\beta S(t)}{N_0} - (\mu + \gamma) \right) \leq -\epsilon < 0$ for a given $\epsilon > 0$. Therefore, if the susceptible subpopulation satisfied:

$$S(t) \leq S_{ref,\epsilon} = \frac{N_0}{\beta} (\mu + \gamma - \epsilon) \quad (6.35)$$

then the time derivative from equation (6.34) would be negative and the exposed and infectious subpopulations would vanish according to proposition 6.3. In this way the control objective has been converted into attaining $S(t) \leq S_{ref,\epsilon}$. The notation $S_{ref,\epsilon}$ points out the fact that the reference value for the susceptible subpopulation depends on the choice of ϵ .

Remark 6.8. *Note that $S_{ref,\epsilon} \geq 0$ (since it acts as a reference population or threshold and must be non-negative) implies $(\mu + \gamma - \epsilon) \geq 0$, i.e. $0 < \epsilon \leq (\mu + \gamma)$.*

The controller design is based on feedback linearization, [36], while the objective is to attain $S(t) \leq S_{ref,\epsilon}$. For this purpose, consider the tracking error:

$$\tilde{S}(t) = S_{ref,\epsilon} - S(t) \quad (6.36)$$

With this notation, the control law reads:

$$\bar{V}(t) = V_{cancel}(t) + V_{linear\ dynamics}(t) \quad (6.37)$$

where:

$$V_{cancel}(t) = \frac{1}{\mu N_0} \left(\mu N_0 - \beta \frac{S(t)I(t)}{N_0} + \omega R(t) \right) \quad (6.38)$$

$$V_{linear\ dynamics}(t) = \frac{1}{\mu N_0} \left(-\mu S_{ref,\epsilon} - \Xi \tilde{S}(t) \right) \quad (6.39)$$

with $\Xi > 0$ denoting the minimum rate at which the susceptible subpopulation must converge to the reference value $S_{ref,\epsilon}$. Vaccination law (6.37) has two parts; the first one ($V_{cancel}(t)$) is in charge of canceling the nonlinear dynamics of the susceptible subpopulation given by equation (6.1) while the second one ($V_{linear\ dynamics}(t)$) specifies the desired linear dynamics for the closed-loop. The substitution of the vaccination law from equation (6.37) in equation (6.1) leads to the closed-loop system for the susceptible subpopulation (taking into account that $\nu = \mu$ and the total population is constant, i.e. $N(t) = N_0$ for all $t \geq 0$):

$$\dot{\tilde{S}}(t) = -(\mu + \Xi)\tilde{S}(t) \quad (6.40)$$

whose solution is given by:

$$\tilde{S}(t) = e^{-(\mu+\Xi)t}\tilde{S}(0) \quad (6.41)$$

Thus, $\tilde{S}(t) \rightarrow 0$ as $t \rightarrow \infty$. However, it is preferable to force $\tilde{S}(t) \rightarrow 0$ only when $S(t) \geq S_{ref,\epsilon}$ since when $S(t) < S_{ref,\epsilon}$, the time derivative $\dot{L}(t)$ is already negative and no external action is necessary. Therefore, the control law may be simplified to:

$$V(t) = \begin{cases} \bar{V}(t) & \text{if } S(t) \geq S_{ref} \text{ and } \bar{V}(t) \geq 0 \\ 0 & \text{otherwise} \end{cases} \quad (6.42)$$

where the fact that the control law cannot be negative has also been included. The proposed control law from equation (6.42) is able to make the susceptible subpopulation converge to the reference value $S_{ref,\epsilon}$ and eradicate the exposed and infectious subpopulations, as it is stated in the following part of the chapter.

Remark 6.9. *The convergence rate of the tracking error to zero when the vaccination law (6.37) is applied is given by $(\mu + \Xi)$ according to equation (6.41).*

Remark 6.10. *When $S(t) > S_{ref,\epsilon}$, then $\tilde{S}(t) < 0$ from equation (6.36). Therefore, $\dot{\tilde{S}}(t) > 0$ means that $\tilde{S}(t)$ grows implying that the susceptible subpopulation decreases and approaches $S_{ref,\epsilon}$. The higher the value of $\tilde{S}(t) > 0$ is, the faster the susceptible subpopulation tends to the reference value.*

Remark 6.11. *The susceptible subpopulation reference value is related to the well-known critical immunization threshold, framed now within the partial stability theory.*

As in the previous vaccination law, it must be proved that equation (6.32) is a properly defined Lyapunov function, i.e. $L(0, 0) = 0$ and $L(E, I) \geq 0$. The first statement is obvious while the second one is proved in two stages. When $S(t) < S_{ref,\epsilon}$ the vaccination law equals zero and the system is vaccination free. In 6.7 it is proved that the vaccination free system is non-negative for any set of positive parameters and any non-negative at all time. When $S(t) \geq S_{ref,\epsilon} \rightarrow S(t) \geq 0$ the positivity of E and I is proven on the same principles as in proposition 6.6. Thus, the analysis of the closed-loop stability can be made and enable us to state the following theorem:

Proposition 6.12. $L(E, I) = E(t) + I(t)$ is a positive-definite function in $(E(t), I(t))$ under vaccination law from equation (6.42).

In order to prove the stability of the closed-loop it is also needed the following fact.

Lemma 6.13. If $S(t) > S_{ref,\epsilon}$, then the control law from equation (6.42) makes $\tilde{S}(t)$ converge to zero non-slower than $(\mu + \Xi)$.

Proof.

When $S(t) > S_{ref,\epsilon}$ and $\bar{V}(t) > 0$, then the tracking error dynamics is given by equation (6.40), implying that $\tilde{S}(t)$ converges to zero at a rate of $(\mu + \Xi)$ as equation (6.41) shows. On the other hand, when $S(t) > S_{ref,\epsilon}$ and $\bar{V}(t) \leq 0$ then $V(t) = 0$ as the result of projection in equation (6.42). Under these circumstances, $\dot{S} = -\dot{\tilde{S}}$ since $S_{ref,\epsilon}$ is constant in equation (6.36) and equation (6.1) can be re-written as:

$$\begin{aligned} \dot{\tilde{S}}(t) &= \mu S(t) - \omega R(t) + \varphi(S, E, I, R) \\ &\quad - \nu N(t) + N(t)V(t) \end{aligned} \quad (6.43)$$

Now, let's denote as $\dot{\tilde{S}}(t)_{V^+}$, $\dot{\tilde{S}}(t)_{V^-}$ and $\dot{\tilde{S}}(t)_{V^0}$ the derivatives of the tracking error when the vaccination function $V(t)$ in equation (6.43) is positive, negative and no vaccination is applied, respectively. Thus, following chain of inequalities is presented:

$$\dot{\tilde{S}}(t)_{V^-} < \dot{\tilde{S}}(t)_{V^0} < \dot{\tilde{S}}(t)_{V^+} \quad (6.44)$$

If the control law is zero when $S(t) > S_{ref,\epsilon}$ then $\bar{V}(t)$ is negative or zero and this is the reason why the vaccination $V(t)$ is equated to zero. According to the chain from equation (6.44) this fact means that the convergence rate chosen for the closed-loop is smaller than the natural tendency of the susceptible subpopulation to decrease (given by $\dot{\tilde{S}}(t)_{V^0}$). As a consequence, a value of $\bar{V}(t) < 0$ and $V(t) = 0$ in this case implies that the susceptible subpopulation is converging to the reference value faster than when the control action is taken. Therefore, the proposition is proved. \square

Lemma 6.13 means that when the vaccination law is zero and $S(t) > S_{ref,\epsilon}$, the susceptible subpopulation naturally converges to the reference value. This fact will help us prove the stability of the closed-loop system. Finally, the last result needed is given in Lemma 6.14

Lemma 6.14. The set $\mathcal{S} = \{0 \leq S(t) \leq S_{ref,0} = S_{ref,\epsilon=0}, E(t), I(t), R(t) \geq 0\}$ is invariant under the vaccination law from equation (6.42) with a prescribed $0 < \epsilon \leq (\mu + \gamma)$.

Proof.

It will be proved that once the susceptible subpopulation belongs to the set \mathcal{S} , it is confined there by the action of the vaccination law from equation (6.42). The proof is based on considering two separate cases: $S_{ref,0} \geq S(t) \geq S_{ref,\epsilon}$ and $S(t) < S_{ref,\epsilon}$. When $S_{ref,\epsilon} \leq S(t) \leq S_{ref,0}$ then the control law acts and the closed loop equation is given by equation (6.40) that makes the error signal converge monotonously to zero.

Therefore, for any value belonging to that interval the susceptible subpopulation converges to $S_{ref,\epsilon} \in \mathcal{S}$ and the whole trajectory belongs to \mathcal{S} .

On the contrary, assume that $S(t) < S_{ref,\epsilon}$. Since $S(t)$ is a continuous variable it must cross $S_{ref,\epsilon}$ when it tries to arrive the border of the set \mathcal{S} (taking into account that proposition 6.7 proves that it cannot become negative). Thus, if the susceptible subpopulation tries to get out the set there must be a time instant t_c such that $S(t_c) = S_{ref,\epsilon}$. At this precise time, the control law acts and the closed-loop equation reads:

$$\dot{\tilde{S}}(t) = -(\mu + \Xi)\tilde{S}(t) \tag{6.45}$$

with $\tilde{S}(t_c) = 0$. The solution to equation (6.45) is $\tilde{S}(t) = 0$ for $t \geq t_c$ and the susceptible subpopulation remains in \mathcal{S} . Thus, the set is invariant and the proposition is proved. \square

Now the stability of the closed-loop can be proved.

Proposition 6.15. *$E(t), I(t)$ converge asymptotically to zero under the action of control law from equation (6.42) with a prescribed $0 < \epsilon \leq (\mu + \gamma)$ for any set of positive parameters and any initial conditions $S(0), E(0), I(0), R(0) \geq 0$.*

Proof.

Consider the Lyapunov candidate function $L = E(t) + I(t)$ with the vaccination law given by equation (6.42). This function is positive-definite as proved in proposition 6.12. Its time derivative is given by equation (6.34). If $S(0) < S_{ref,\epsilon}$ then the susceptible subpopulation remains within the set \mathcal{S} (Lemma 6.14) and the time derivative is negative definite since the exposed and infectious subpopulations are non-negative (proposition 6.7). Thus, $E(t)$ and $I(t)$ converge to zero asymptotically according to proposition 6.3. On the other hand, if $S(0) > S_{ref,\epsilon}$, then the closed-loop equation is given by equation (6.40) and the susceptible subpopulation converges to $S_{ref,\epsilon}$ either $V(t) = \bar{V}(t)$ or $V(t) = 0$ as Lemma 1 claims. Thus there exists a finite time t_s such that $S_{ref,\epsilon} < S(t_s) < S_{ref,0}$ i.e. $S(t_s) \in \mathcal{S}$. Since the set \mathcal{S} is invariant and within that set the Lyapunov candidate function is negative-definite then $E(t)$ and $I(t)$ converge asymptotically to zero. Thus, the proposition is proved. \square

Proposition 6.15 proves that the vaccination law from equation (6.42) is capable of removing the epidemics from the population taking into account that the only interest is to vanish the exposed and infectious subpopulations. Furthermore, the vaccination control is well-defined in the sense that it provides always non-negative values for the control.

6.5 Observed-based Vaccination

It turns out that while the assumption of the knowledge of the total population N is not quite restrictive in practice, the knowledge of partial populations of susceptible, infected, infectious and immune may be considered severely restrictive. If the partial

initial populations are unknown then their evolution through time cannot be computed in a closed form from the differential system of (6.1)-(6.4). A practical solution to circumvent the problem might be to estimate them based on percentages of the total population through time from experimental knowledge of the disease propagation. Another solution may be to estimate them online by using an on-line observer. This solution is focused on in the current manuscript by using a SEIR-estimation algorithm (observer) of the SEIR model with a standard incidence rate φ_1 , which estimates through time the individual populations being involved. The vaccination strategy is obtained as a control strategy from the data supplied by the observer through time. Such a strategy does not require the knowledge of the partial populations to organize and perform the vaccination strategy. The estimates of the various individual populations are denoted by the same notations as the real populations with hat superscripts, namely \hat{S} , \hat{E} , \hat{I} and \hat{R} . Thus, consider the SEIR-type observer for the SEIR model with φ_1 as follows:

$$\begin{aligned}
\dot{\hat{S}}(t) &= -\hat{\mu}\hat{S}(t) + \hat{\omega}\hat{R}(t) - \hat{\beta}\frac{\hat{S}(t)\hat{I}(t)}{N} + \hat{\mu}N(1 - V(t)) \\
\dot{\hat{E}}(t) &= \hat{\beta}\frac{\hat{S}(t)\hat{I}(t)}{N} - (\hat{\mu} + \hat{\kappa})\hat{E}(t) \\
\dot{\hat{I}}(t) &= -(\hat{\mu} + \hat{\gamma})\hat{I}(t) + \hat{\kappa}\hat{E}(t) \\
\dot{\hat{R}}(t) &= -(\hat{\mu} + \hat{\omega})\hat{R}(t) + \hat{\gamma}\hat{I}(t) + \hat{\mu}NV(t)
\end{aligned} \tag{6.46}$$

subject to initial conditions $\hat{S}(0) \geq 0$, $\hat{E}(0) \geq 0$, $\hat{I}(0) \geq 0$ and $\hat{R}(0) \geq 0$ under the constant through time estimated population constraint equalizing the true one, i.e.,

$$\begin{aligned}
N &= N(0) = \hat{S}(t) + \hat{E}(t) + \hat{I}(t) + \hat{R}(t) \\
&= \hat{S}(0) + \hat{E}(0) + \hat{I}(0) + \hat{R}(0)
\end{aligned} \tag{6.47}$$

$\forall t \in \mathbb{R}_{0+}$ and the vaccination law $V : \mathbb{R}_{0+} \rightarrow \mathbb{R}_{0+}$ given by:

$$V(t) = \frac{1}{\hat{\mu}N} \left(\lambda_1\hat{S}(t) + \lambda_2\hat{E}(t) + \lambda_3\hat{I}(t) + \lambda_4\hat{R}(t) + \lambda_5\hat{S}(t)\hat{I}(t) + gN \right) \tag{6.48}$$

In the above estimated SEIR-model, $\hat{\mu}$ is the estimated rate of deaths from causes unrelated to the infection, $\hat{\omega}$ is the estimated rate of losing immunity, $\hat{\beta}$ is the estimated transmission constant (with the total number of infections per unity of time at time t being $\hat{\beta}\hat{S}(t)\hat{I}(t)/N$), $\hat{\kappa}^{-1}$ and $\hat{\gamma}^{-1}$ are finite and, respectively, the estimated average durations of the latent and infective periods. The above parameter estimates can be done, through the use of available "a priori" knowledge, to be identical to the true values if those ones are known or estimated on-line from data measurements. Through this chapter, it has been assumed that those estimated parameters are fixed but not necessarily identical to the true parameters and all of them are non-negative. The substitution of equation (6.48) in equation (6.46) yields the following combined observer-controller for the SEIR-model:

$$\dot{\hat{x}}(t) = \hat{A}(t)\hat{x}(t) + \hat{b} \tag{6.49}$$

where

$$\hat{x}(t) = [\hat{S}(t) \hat{E}(t) \hat{I}(t) \hat{R}(t)]^T, \quad (6.50)$$

$$\hat{b} = [(\hat{\mu} - g)N \ 0 \ 0 \ gN]^T \text{ and} \quad (6.51)$$

$$\hat{A}(t) = \quad (6.52)$$

$$\begin{pmatrix} -(\hat{\mu} + \lambda_1 + (\hat{\beta}_1 + \lambda_5) \hat{I}(t)) & -\lambda_2 & -\lambda_3 & \hat{\omega} - \lambda_4 \\ \hat{\beta}_1 \hat{I}(t) & -(\hat{\mu} + \hat{\kappa}) & 0 & 0 \\ 0 & \hat{\kappa} & -(\hat{\mu} + \hat{\gamma}) & 0 \\ \lambda_1 + \lambda_5 \hat{I}(t) & \lambda_2 & \hat{\gamma} + \lambda_3 & -(\hat{\mu} + \hat{\omega} - \lambda_4) \end{pmatrix}$$

with $\hat{\beta}_1 = \hat{\beta}/N$. The substitution of equation (6.48) into equation (6.46) yields the following SEIR observer-based vaccination controlled SEIR-model:

$$\dot{x}(t) = A(t)x(t) + B(t)\hat{x}(t) + b \quad (6.53)$$

where

$$x(t) = [S(t) \ E(t) \ I(t) \ R(t)]^T \quad (6.54)$$

$$b = \left[\left(1 - \frac{g}{\hat{\mu}}\right) \mu N \ 0 \ 0 \ \frac{g\mu N}{\hat{\mu}} \right]^T \quad (6.55)$$

$$A(t) = \begin{pmatrix} -(\mu + \beta_1) \hat{I}(t) & 0 & 0 & \omega \\ \beta_1 \hat{I}(t) & -(\mu + \kappa) & 0 & 0 \\ 0 & \kappa & -(\mu + \gamma) & 0 \\ 0 & 0 & \gamma & -(\mu + \omega) \end{pmatrix} \quad (6.56)$$

with $\beta_1 = \beta/N$ and

$$B(t) = \left(\frac{\mu}{\hat{\mu}}\right) \begin{pmatrix} -(\lambda_1 + \lambda_5) \hat{I}(t) & -\lambda_2 & -\lambda_3 & -\lambda_4 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ \lambda_1 + \lambda_5 \hat{I}(t) & \lambda_2 & \lambda_3 & \lambda_4 \end{pmatrix} \quad (6.57)$$

The systems from equations (6.49)-(6.52) and (6.53)-(6.57) may be compacted as an extended system as follows:

$$\dot{\bar{x}}(t) = \bar{A}(t)\bar{x}(t) + \bar{b} \quad (6.58)$$

where

$$\bar{x}(t) = [\hat{x}^T(t) \ \tilde{x}^T(t)]^T, \quad (6.59)$$

$$\bar{b} = [\hat{b}^T \ \tilde{b}^T]^T \text{ and} \quad (6.60)$$

$$\bar{A} = \begin{pmatrix} \hat{A}(t) & 0 \\ A(t) - \hat{A}(t) + B(t) & A(t) \end{pmatrix} \quad (6.61)$$

with $\tilde{x}(t) = x(t) - \hat{x}(t)$ being the observation error, and a parametrical error defined by:

$$\tilde{b} = b - \hat{b} = \left(\frac{\mu}{\hat{\mu}} - 1\right) N[\hat{\mu} - g \ 0 \ 0 \ g]^T \quad (6.62)$$

It is direct to see that $\|\tilde{b}\| \leq \epsilon$ for any given real $\epsilon \geq 0$, with

$$\|\tilde{b}\| = |(\mu/\hat{\mu}) - 1|N\sqrt{(\hat{\mu} - g)^2 + g^2}$$

being the Euclidean norm of \tilde{b} , if $|\mu - \hat{\mu}| \leq \hat{\mu}\epsilon/(N\sqrt{(\hat{\mu} - g)^2 + g^2})$. Decompose

$$\begin{aligned} A(t) &= A_0 + \Delta A(t) \\ \hat{A}(t) &= \hat{A}_0 + \Delta \hat{A}(t) \\ A(t) - \hat{A}(t) + B(t) &= B_0 + \Delta B(t) \end{aligned} \quad (6.63)$$

where A_0 , \hat{A}_0 and B_0 are constant matrices and the non-unique decompositions from equation (6.63) are as follows:

$$A_0 = \begin{pmatrix} -(\mu + \beta_1 I_r) & 0 & 0 & \omega \\ 0 & -(\mu + \kappa) & 0 & 0 \\ 0 & \kappa & -(\mu + \omega) & 0 \\ 0 & 0 & \gamma & -(\omega + \mu) \end{pmatrix} \quad (6.64)$$

$$\hat{A}_0 = \begin{pmatrix} -(\hat{\mu} + \lambda_1 + (\hat{\beta}_1 + \lambda_5) \hat{I}_r) & -\lambda_2 & -\lambda_3 & \hat{\omega} - \lambda_4 \\ 0 & -(\hat{\mu} + \hat{\kappa}) & 0 & 0 \\ 0 & \hat{\kappa} & -(\hat{\mu} + \hat{\gamma}) & 0 \\ \lambda_1 + \lambda_5 \hat{I}_r & \lambda_2 & \hat{\gamma} + \lambda_3 & -(\hat{\mu} + \hat{\omega} - \lambda_4) \end{pmatrix}$$

$$\Delta A(t) = \begin{pmatrix} \beta_1(I_r - I(t)) & 0 & 0 & 0 \\ \beta_1 I_r & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \text{ and} \quad (6.65)$$

$$\Delta \hat{A}(t) = \begin{pmatrix} (\hat{\beta}_1 + \lambda_5)(\hat{I}_r - \hat{I}(t)) & 0 & 0 & 0 \\ \hat{\beta}_1 \hat{I}(t) & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ \lambda_5(\hat{I}(t) - \hat{I}_r) & 0 & 0 & 0 \end{pmatrix} \quad (6.66)$$

for any given prefixed constant values $I_r \geq 0$ and $\hat{I}_r \geq 0$. Moreover,

$$\Delta B(t) = A(t) - \hat{A}(t) + B(t) - B_0 \quad (6.67)$$

$$= \begin{pmatrix} -\tilde{\mu} - f_1(t) + f_2(t) - b_{011} & k'_2 & k'_3 & \tilde{\omega} + k'_4 \\ f_1(t) - b_{021} & -(\tilde{\kappa} + \tilde{\mu}) & 0 & 0 \\ 0 & \tilde{\kappa} & -(\tilde{\mu} + \tilde{\gamma}) & 0 \\ -f_2(t) & -k'_2 & \tilde{\gamma} - k'_3 & -(\tilde{\mu} + \tilde{\omega} + k'_4) \end{pmatrix}$$

with

$$f_1(t) = \beta_1 I(t) - \hat{\beta}_1 \hat{I}(t), \quad (6.68)$$

$$f_2(t) = (1 - (\mu/\hat{\mu}))(\lambda_1 + \lambda_5 \hat{I}(t)), \quad (6.69)$$

$$k'_i = (1 - \mu/\hat{\mu})\lambda_i, \text{ for } i = 1, 2, 3, 4, \quad (6.70)$$

$$\tilde{\mu} = \mu - \hat{\mu}, \quad \tilde{\kappa} = \kappa - \hat{\kappa}$$

$$\tilde{\gamma} = \gamma - \hat{\gamma}, \quad \tilde{\omega} = \omega - \hat{\omega}$$

with b_{011} and b_{021} being, respectively, the coefficients in the first and the second row of the first column of matrix $B \in \mathbb{R}^{4 \times 4}$. The rest of the coefficients of such matrix are identically zero. In this way, $\bar{A}(t)$ is decompose as follows:

$$\bar{A}(t) = \bar{A}_0 + \tilde{\tilde{A}}_0(t) \text{ with} \quad (6.71)$$

$$\bar{A}_0(t) = \begin{pmatrix} \hat{A}_0(t) & 0 \\ B_0 & A_0 \end{pmatrix} \text{ and } \tilde{\tilde{A}}_0 = \begin{pmatrix} \Delta \hat{A}(t) & 0 \\ \Delta B(t) & \Delta A(t) \end{pmatrix} \quad (6.72)$$

If A_0 and \hat{A}_0 are stability (or Hurwitz) matrices then the block triangular matrix \bar{A}_0 is also a stability matrix with stability abscissa $(-\rho)$ subject to the constraint $\max\{Re(\lambda_i(A_0)), Re(\lambda_i(\hat{A}_0))\} \leq -\rho < 0$ where the first inequality is non strict if there is some multiple eigenvalue of \bar{A}_0 .

6.5.1 Stability of the observed-based Vaccination law

A simple inspection shows that A_0 is a stability matrix if

$$\det(sI_4 - A_0) = (s + \mu + \beta_1 I_r)(s + \mu + \kappa)(s + \mu + \gamma)(s + \mu + \omega)$$

where I_4 denotes the 4-order identity matrix, is Hurwitz. Also, \hat{A}_0 is a stability matrix if $\det(sI_4 - \hat{A}_0) = \hat{d}(s) + (\lambda_1 + \lambda_5 \hat{I}_r) \hat{n}(s)$ has all its zeros in $Re(s) < 0$ where:

$$\begin{aligned} \hat{n}(s) &= (\lambda_4 - \hat{\omega})(s + \hat{\mu} + \hat{\kappa})(s + \hat{\mu} + \hat{\gamma}) \\ \hat{d}(s) &= (s + \hat{\mu} + \lambda_1 + (\hat{\beta}_1 + \lambda_5) \hat{I}_r)(s + \hat{\mu} + \hat{\kappa})(s + \hat{\mu} + \hat{\gamma})(s + \hat{\mu} + \hat{\omega} - \lambda_4) \end{aligned} \quad (6.73)$$

Assume that $\hat{d}(s)$ is a Hurwitz polynomial, that is, $\lambda_4 < (\hat{\mu} + \hat{\omega})$, $(\hat{\mu} + \lambda_1 + (\hat{\beta}_1 + \lambda_5) \hat{I}_r) > 0$, $\hat{\omega} + \hat{\kappa} > 0$ and $\hat{\mu} + \hat{\gamma} > 0$ and define $\hat{h}(s) \triangleq (\lambda_1 + \lambda_5 \hat{I}_r) \hat{n}(s) / \hat{d}(s)$.

Note that:

$$\begin{aligned} \det(sI_4 - \hat{A}_0) &= \hat{d}(s) + (\lambda_1 + \lambda_5 \hat{I}_r) \hat{n}(s) = 0 \\ \rightarrow 1 + \hat{h}(s) &= 0 \end{aligned} \quad (6.74)$$

has all its solutions in $Re(s) < 0$ if and only if $\|\hat{h}\|_\infty < 1$ since $\hat{d}(s)$ is a Hurwitz polynomial, where $\|\hat{h}\|_\infty$ is the H_∞ -norm of the transfer function $\hat{h}(s)$.

Since \bar{A}_0 is block-triangular and constant then the following result is direct.

Assertion 6.16. \bar{A}_0 is a stability matrix if and only if $\mu + \beta_1 I_r > 0$, $\mu + \kappa > 0$, $\mu + \gamma > 0$, $\mu + \omega > 0$ and $\hat{h} \in RH_\infty$ (i.e. $\lambda_4 < \hat{\mu} + \hat{\omega}$, $\hat{\mu} + \lambda_1 + (\hat{\beta}_1 + \lambda_5) \hat{I}_r > 0$, $\hat{\mu} + \hat{\kappa} > 0$ and $\hat{\mu} + \hat{\gamma} > 0$) with $\|\hat{h}\|_\infty < 1$.

From remark 6.16 and Gronwall's Lemma [41], it follows.

Assertion 6.17. The matrix function $\bar{A}(t)$ is stable if \bar{A}_0 is a stability matrix and, furthermore, $\rho > \sup_{t \in \mathbb{R}_{0+}} \{\|\tilde{\tilde{A}}_0(t)\|\}$ where $(-\rho) < 0$ is the stability abscissa of the matrix \bar{A}_0 .

Note that the Euclidean norm of \bar{b} may be directly calculated from those of \hat{b} and \tilde{b} using equations (6.51) and (6.62) leading to:

$$\|\bar{b}\| \leq \frac{(\hat{\mu} + |\mu - \hat{\mu}|)N}{\hat{\mu}} \sqrt{(\hat{\mu} - 2g)\hat{\mu} + 2g^2} \quad (6.75)$$

Note that $\rho_0 \triangleq \rho - \sup_{t \in \mathbb{R}_0^+} \{\|\tilde{A}_0(t)\|\} > 0$ so that $(-\rho_0) < 0$ is larger than the maximum of the stability abscissas of $\bar{A}(t)$ for $t \in \mathbb{R}_0^+$ if assertion 6.17 holds.

Assertion 6.18. *If assertion 6.17 holds then any solution of the forced system (6.58)-(6.72) satisfies the following inequality:*

$$\begin{aligned} \|\bar{x}(t)\| &\leq M(t) = \lambda_0 e^{-\rho_0 t} \left(\|\bar{x}(0)\| + \|\bar{b}\| \int_0^t e^{\rho_0 \tau} d\tau \right) \\ &\rightarrow \frac{\lambda_0 (\hat{\mu} + |\mu - \hat{\mu}|) N}{\rho_0 \hat{\mu}} \sqrt{(\hat{\mu} - 2g)\hat{\mu} + 2g^2} \end{aligned} \quad (6.76)$$

as $t \rightarrow \infty$, for some real constant $\lambda_0 \geq 1$, and the corresponding sub-states of $\bar{x}(t)$ satisfy:

$$\begin{aligned} \|\hat{x}(t)\| &\leq \hat{M}(t) = \lambda_0 e^{-\rho_0 t} \left(\|\hat{x}(0)\| + \|\hat{b}\| \int_0^t e^{\rho_0 \tau} d\tau \right) \\ &\rightarrow \frac{\lambda_0}{\rho_0} N \sqrt{(\hat{\mu} - 2g)\hat{\mu} + 2g^2} \end{aligned} \quad (6.77)$$

and

$$\begin{aligned} \|\tilde{x}(t)\| &\leq \tilde{M}(t) = \lambda_0 e^{-\rho_0 t} \left(\|\tilde{x}(0)\| + \|\tilde{b}\| \int_0^t e^{\rho_0 \tau} d\tau \right) \\ &\rightarrow \frac{\lambda_0 |\mu - \hat{\mu}| N}{\rho_0 \hat{\mu}} \sqrt{(\hat{\mu} - 2g)\hat{\mu} + 2g^2} \end{aligned} \quad (6.78)$$

as $t \rightarrow \infty$.

Note that $\|\tilde{x}(t)\| \rightarrow 0$ as $t \rightarrow \infty$ either if $\hat{\mu} = \mu$ (and then $\|\hat{x}(t)\| \rightarrow \frac{\lambda_0}{\rho_0} N \sqrt{(\mu - 2g)\mu + 2g^2}$ as $t \rightarrow \infty$ and, if in addition, $g = 0$ then $\|\hat{x}(t)\| \rightarrow \frac{\lambda_0 \mu N}{\rho_0}$ as $t \rightarrow \infty$) or if $\hat{\mu} = g = 0$ (and then $\|\hat{x}(t)\| \rightarrow 0$ as $t \rightarrow \infty$).

Finally, $x(t)$ satisfy:

$$\|x(t)\| \leq \|M(t)\| \rightarrow \frac{\lambda_0 (\hat{\mu} + |\mu - \hat{\mu}|) N}{\rho_0 \hat{\mu}} \sqrt{(\hat{\mu} - 2g)\hat{\mu} + 2g^2} \quad (6.79)$$

as $t \rightarrow \infty$ from the definition of b in equation (6.55). However, this upper-bound can be improved if a version of assertion 6.17 applied to the matrix function $A(t)$ leads to a smaller ratio of its corresponding constants than the ratio λ_0/ρ_0 of the whole extended system.

6.5.2 Positivity of the observed-based vaccination law

Positive systems are those having non-negative solutions in the sense that all the state components are non-negative for all time, provided that the initial condition and control are both non-negative [42]. Because of the nature of the SEIR epidemic model from equation (6.1), it is required to be a positive system for the implemented

vaccination law. The extended SEIR system has a unique solution for each initial state given by:

$$\bar{x}(t) = e^{\bar{A}_0 t} \left(\bar{x}(0) + \int_0^t e^{-\bar{A}_0 \tau} \left(\tilde{\bar{A}}_0(\tau) \bar{x}(\tau) + \bar{b} \right) d\tau \right) \quad (6.80)$$

From equations (6.49) and (6.53) the SEIR solution and its estimate through the observer are uniquely given by:

$$\hat{x}(t) = e^{\hat{A}_0 t} \left(\hat{x}(0) + \int_0^t e^{-\hat{A}_0 \tau} \left(\Delta \hat{A}_0(\tau) \hat{x}(\tau) + \hat{b} \right) d\tau \right) \quad (6.81)$$

and

$$x(t) = e^{A_0 t} \left(x(0) + \int_0^t e^{-A_0 \tau} \left(\Delta A_0(\tau) x(\tau) + B(\tau) \hat{x}(\tau + b) \right) d\tau \right) \quad (6.82)$$

respectively. In principle, it is apparently non necessary to require in addition that the estimation algorithm or the extended system be positive. The following notation is used for the theoretical results in this section. $x \in \mathbb{R}_{0+}^n$ is a positive real n-vector in the usual sense that all its components are non-negative. This can be also denoted by $x > 0$ if $x \neq 0$. In the same way, $A \in \mathbb{R}_{0+}^{n \times n}$ (or $A > 0$) is a positive real n-matrix in the usual sense that all its entries are non-negative. A square real matrix A is a Metzler matrix if and only if all its off-diagonal entries are non-negative and then its associate exponential matrix function is positive.

Assertion 6.19. *The following properties hold:*

i) *Assume that A_0 and \hat{A}_0 are Metzler matrices,*

$$\Delta A(t) > 0, \quad b + B(t)\hat{x}(t) \geq 0 \quad \text{and} \quad \Delta \hat{A}(t) > 0 \quad \forall t \in \mathbb{R}_{0+}$$

and $b > 0$ and $\hat{b} > 0$. Then $[x^T(0) \hat{x}^T(0)]^T > 0$ implies that $x(t) > 0$ and $\hat{x}(t) > 0 \quad \forall t \in \mathbb{R}_{0+}$. In other words, the extended system of state $[x^T(0) \hat{x}^T(0)]^T$ is positive.

ii) *Assume that in Property (i) \hat{A}_0 fails to be a Metzler matrix because of the value λ_1 or λ_5 in its (4,1) entry. Then, for initial conditions $\hat{x}(0) > 0$ which make $\hat{x}(t)$ to be non positive, $x(t)$ can fail to be positive for all time for some $x(0) > 0$ and some such λ_1 or λ_5 with sufficiently large absolute values.*

Remark 6.20. *It is required for modeling coherency that both the epidemic SEIR-model and its observer be positive dynamic systems. The condition of non-negative of $b + B(t)\hat{x}(t) \geq 0 \quad \forall t \in \mathbb{R}_{0+}$ in assertion 6.19 requires $g \geq 0$ and $(\hat{\mu} - g)N \geq (\lambda_1 + \lambda_5 \hat{I}(t))\hat{S}(t) + \lambda_2 \hat{E}(t) + \lambda_3 \hat{I}(t) + \lambda_4 \hat{R}(t) \geq -gN \quad \forall t \in \mathbb{R}_{0+}$, which may be guaranteed by choosing the controller gains under the knowledge $N = \sum_{i=1}^4 \hat{x}_i(t) \quad \forall t \in \mathbb{R}_{0+}$.*

The requirement that \hat{A}_0 be a Metzler matrix is guaranteed if $\lambda_2 = 0$, $-\hat{\gamma} \leq \lambda_3 \leq 0$, $0 \leq \lambda_4 \leq \hat{\omega}$ and $\lambda_1 + \lambda_5 \hat{I}_r \geq 0$. The condition that $\hat{b} > 0$ is guaranteed if $0 \leq g \leq \hat{\mu}$.

Finally, $\min_{t \in \mathbb{R}_{0+}} \{\Delta \hat{A}(t)\} > 0$ is guaranteed if λ_5 is such that $(\hat{\beta}_1 + \lambda_5) \left(\hat{I}_r - \max_{t \in \mathbb{R}_{0+}} \{\hat{I}(t)\} \right) \geq$

0 and $\lambda_5 \left(\min_{t \in \mathbb{R}_{0+}} \{\hat{I}(t)\} - \hat{I}_r \right) \geq 0$ are fulfilled. Such conditions require that $0 \geq \lambda_5 \geq -\hat{\beta}_1$. In this way the observer is a positive system. This restricts the generality of the choice of the gains in the vaccination control law from equation (6.48). However, if the requirement for the observer to be positive is removed then it is only needed that the SEIR model is positive under a modified vaccination law from equation (6.48) by requiring the weaker condition that $0 \leq g \leq \hat{\mu}$ and $\min\{\kappa, \omega, \gamma\} \geq 0$ and $I_r \geq \max_{t \in \mathbb{R}_{0+}} I(t)$.

Note that while assertion 6.19 (i) is of sufficiency-type to guarantee positivity, the lack of all the joint above conditions in assertion 6.19 (ii) refer to a necessary condition for positivity in such cases. Note also that the positivity and a total population equal to N for all time implies necessary global stability, so that it can be said the following:

Assertion 6.21. *If assertion 6.19 (i) holds then the extended SEIR-model (i.e. the combined SEIR-model plus its observer) is globally stable if all the initial populations and their estimates are non-negative. Furthermore all the susceptible, infected, infectious and immune populations and their estimates are upper-bounded by N and the sum of all the populations and that of their estimates is equal to N at any time. The converse is not true, in general, so that if the extended SEIR-model is stable under assertion 6.17 then that model is not necessarily positive.*

6.6 The reproduction number in the vaccination strategy

Another take of the model from equations (6.1)-(6.4) is studied in this section, using the predictions on the stability of the equilibrium points of the model from the reproduction number associated to the parameters. A discretized version of the model is presented in order to present a more realistic version of the data acquisition needed to perform adaptive vaccination strategies. For this version of the model, the disease incidence rate is chosen to be the bilinear function $\varphi = \beta S(t)I(t)$, and the acquired immunity to remain permanent, so it is set $\omega = 0$. Also, the birth rate is detached from the dependence on the total population $\nu \rightarrow \mu/N(t)$. The death rate is then set to be equal to the birth rate $\mu = \nu$ so that the population is not continuously increasing or decreasing and the dynamics of the total population $S + E + I + R = N$ can be described as

$$\dot{N}(t) = \mu(1 - N(t)) \tag{6.83}$$

which is independent of the disease, and tends to $\lim_{t \rightarrow \infty} N(t) = N^* = 1$. The nonlinear dynamics derived from these interactions is presented in the following equations:

$$\dot{S}(t) = \mu(1 - V(t) - S(t)) - \beta S(t)I(t) \quad (6.84)$$

$$\dot{E}(t) = \beta S(t)I(t) - (\mu + \kappa)E(t) \quad (6.85)$$

$$\dot{I}(t) = \kappa E(t) - (\mu + \gamma)I(t) \quad (6.86)$$

$$\dot{R}(t) = \mu V(t) + \gamma I(t) - \mu R(t) \quad (6.87)$$

In order to simplify the notation, a real continuous and time-differentiable vector function $\mathbf{x} : [0, \infty) \rightarrow \mathbb{R}^4$ is defined as

$$\mathbf{x}(t) = (S(t), E(t), I(t), R(t))^T$$

Equilibrium states and conditions of stability for a constant vaccination strategy V

It is considered here the solutions to the population dynamics, given a constant bounded vaccination strategy $V(t) = V \in [0, 1] \forall t \geq 0$. An equilibrium state where the values for the infectious and exposed subpopulations are zero is called disease-free equilibrium (DFE) while, if the exposed or infectious present positive values, is called the endemic equilibrium (END). Let $\lim_{t \rightarrow \infty} \mathbf{x}(t) = \mathbf{x}^*$ so that $\lim_{t \rightarrow \infty} \dot{\mathbf{x}}(t) = (0, 0, 0, 0)^T$. Then, from equations (6.84)-(6.87) it is obtained the following equations for the equilibrium points:

$$\begin{cases} \mu(1 - V) - \beta S^* I^* - \mu S^* & = 0 \\ \beta S^* I^* - (\mu + \kappa) E^* & = 0 \\ \kappa E^* - (\mu + \gamma) I^* & = 0 \\ \mu V + \gamma I^* - \mu R^* & = 0 \end{cases} \quad (6.88)$$

Two possible solutions are derived from (6.88) as in proposition 6.1, the disease free equilibrium (DFE) point and the endemic (END) point:

$$\mathbf{x}_{dfe}^* = (S_{dfe}, 0, 0, R_{dfe})^T \quad (6.89)$$

$$\mathbf{x}_{end}^* = \left(S_{end}, \frac{\mu(S_{dfe} - S_{end})}{\mu + \kappa}, \frac{\mu\kappa(S_{dfe} - S_{end})}{(\mu + \kappa)(\mu + \gamma)}, R_{dfe} - \frac{\gamma\kappa(S_{dfe} - S_{end})}{(\mu + \kappa)(\mu + \gamma)} \right)^T \quad (6.90)$$

with $S_{dfe} = 1 - V$, $R_{dfe} = V$ and $S_{end} = \frac{(\mu + \kappa)(\mu + \gamma)}{\beta\kappa}$. An important parameter when studying the stability of these possible solutions is the reproduction number R_0 , defined in epidemic research as the average number of infections per infected individual per the duration of the infectious phase:

$$R_0 \equiv \frac{\beta\kappa S_{dfe}}{(\mu + \kappa)(\mu + \gamma)} \quad (6.91)$$

However there can be periodic behaviors that are solutions to the SEIR model from (6.84)-(6.87), in which $\lim_{t \rightarrow \infty} \dot{\mathbf{x}}(t) \neq (0, 0, 0, 0)^T$. In the following propositions the reproduction number is used to discuss this possibility in addition to the stability of the equilibrium points.

Proposition 6.22. *Consider the proposed SEIR model from equations (6.84)-(6.87) under positive initial conditions:*

$$\mathbf{x}_i(0) \geq 0; \forall i = 1, 2, 3, 4$$

with a bounded vaccination $V(t) \in [0, 1] \forall t \geq 0$. Then, the equilibrium regime defined as $\lim_{t' \rightarrow \infty} \mathbf{x}(t' + t) = \mathbf{x}^*(t) \forall t \in \mathbb{R}$ holds the property:

$$\mathbf{x}_i^*(t) \leq 1; \forall i = 1, 2, 3, 4 \forall t \geq 0 \quad (6.92)$$

Proof.

The time evolution of the total population is derived from (6.83) as

$$N(t) = (N(0) - 1) e^{-\mu t} + 1$$

Thus, at the equilibrium regime, the sum of all the subpopulation must be one, i.e., $\sum_{i=1}^4 \mathbf{x}_i^*(t) = \lim_{t' \rightarrow \infty} N(t' + t) = 1$. It is established from proposition 6.7 the positivity of each subpopulation, so the following inequality is fulfilled:

$$0 \leq \mathbf{x}_i^*(t) = 1 - \sum_{\substack{j=1 \\ j \neq i}}^4 \mathbf{x}_j^*(t); \forall i = 1, 2, 3, 4 \quad (6.93)$$

which leads to $1 \geq \sum_{\substack{j=1 \\ j \neq i}}^4 \mathbf{x}_j^*(t) \geq \max_{j \neq i} [\mathbf{x}_j^*(t)]; \forall j, i = 1, 2, 3, 4$.

Hence $\mathbf{x}_i^*(t) \leq 1; \forall i = 1, 2, 3, 4; \forall t$. □

Proposition 6.23. *Consider the proposed SEIR model from equations (6.84)-(6.87), with a constant bounded vaccination strategy $V(t) = V \in [0, 1]$ and a time t_0 so that the exposed and infectious subpopulation are zero, i.e., $E(t_0) = I(t_0) = 0$. Then, the SEIR model will reach the DFE point.*

Proof.

It is deduced from (6.85)-(6.86) that if $I(t_0) = E(t_0) = 0$, then $\dot{I}(t) = \dot{E}(t) = 0 \forall t > t_0$. The following simplifications for the susceptible and recovered subpopulations are given as auxiliary equations of the dynamics to be used in the theoretical analysis:

$$\dot{S}(t) = \mu(1 - V - S(t)) \quad (6.94)$$

$$\dot{R}(t) = \mu(V - R(t)) \quad \forall t > t_0 \quad (6.95)$$

Then the time evolution of the susceptible and recovered subpopulations is given by the following equations:

$$\begin{aligned} \forall t \geq t_0 \\ S(t) &= (1 - V) + (S(t_0) - (1 - V))e^{-\mu(t-t_0)} \end{aligned} \quad (6.96)$$

$$R(t) = (R(t_0) - V)e^{-\mu(t-t_0)} + V \quad (6.97)$$

Hence, $\lim_{t \rightarrow \infty} \mathbf{x}(t) = (1 - V, 0, 0, V)^T = \mathbf{x}_{dfe}^*$. \square

Proposition 6.24. *Consider the proposed SEIR model (6.84)-(6.87) under positive initial conditions:*

$$\mathbf{x}_i(0) \geq 0; \forall i = 1, 2, 3, 4$$

through a bounded vaccination $V(t) \in [0, 1] \forall t \geq 0$ and $R_0 < 1$. Then, there is no periodic endemic solution for the SEIR model.

Proof.

A proof by contradiction is given here. Assume that there is a periodic solution $\mathbf{x}^*(t)$ where $\mathbf{x}_2^*(t) \geq m_e$, $\mathbf{x}_3^*(t) \geq m_i \forall t$, with $m_e, m_i > 0$. Then the following inequality is established from equation (6.84):

$$\dot{S}^*(t) \leq \mu (S_{dfe} - S^*(t) (1 + \beta m_i / \mu)) \quad (6.98)$$

The dynamic equation of an auxiliary function $S'(t)$ is defined as:

$$\dot{S}'(t) = \mu (S_{dfe} - S'(t) (1 + \beta m_i / \mu)) \quad (6.99)$$

whose solution is given by:

$$S'(t) = \frac{S_{dfe} + e^{-(\mu + \beta m_i)t} ((1 + \beta m_i) S'(0) - S_{dfe})}{1 + \beta m_i / \mu} \quad (6.100)$$

The difference $\Delta S^*(t) = S^*(t) - S'(t)$ between $S^*(t)$ and the auxiliary function $S'(t)$ is used then to define the following inequality:

$$\Delta \dot{S}^*(t) = \dot{S}^*(t) - \dot{S}'(t) \leq -(\mu + \beta m_i) (S^*(t) - S'(t)) \quad (6.101)$$

which leads to $\Delta S^*(t) \leq \Delta S^*(0) e^{-(\mu + \beta m_i)t}$. As $\mu + \beta m_i > 0$, it can be deduced that $\lim_{t \rightarrow \infty} \Delta S^*(t) \leq 0$, and it is known from propositions 6.7 and 6.22 that $S(t)$ is finite and bounded, so the following inequality holds

$$\limsup_{t \rightarrow \infty} [S^*(t)] \leq \lim_{t \rightarrow \infty} S'(t) = \frac{S_{dfe}}{1 + \beta m_i / \mu} \quad (6.102)$$

Given the periodicity of the solution, the integral on a time period τ of any subpopulation derivative will be zero:

$$\int_t^{t+\tau} \dot{\mathbf{x}}_i^*(t') dt' = \mathbf{x}_i^*(t + \tau) - \mathbf{x}_i^*(t) = 0; \forall i = 1, 2, 3, 4$$

Then from equations (6.85) and (6.86), it is defined

$$\kappa \bar{E} - (\mu + \gamma) \bar{I} = 0 \quad (6.103)$$

$$\beta \bar{S} \bar{I} - (\mu + \kappa) \bar{E} = 0 \quad (6.104)$$

being $\bar{I} = \int_t^{t+\tau} I(t') dt'$, $\bar{E} = \int_t^{t+\tau} E(t') dt'$ and $\bar{S} \bar{I} = \int_t^{t+\tau} S(t') I(t') dt'$ the average values at the periodic equilibrium. Let us combine equations (6.103) and (6.104) to obtain the following:

$$\frac{\beta \kappa \bar{S} \bar{I}}{(\mu + \kappa)(\mu + \gamma) \bar{I}} = 1 \quad (6.105)$$

Given that $\max_{t \leq \tau' \leq t+\tau} [S^*(\tau')] \bar{I} \geq \bar{S} \bar{I} \geq \min_{t \leq \tau' \leq t+\tau} [S^*(\tau')] \bar{I}$, it is established:

$$\frac{\beta \kappa \max_{t \leq \tau' \leq t+\tau} [S^*(\tau')]}{(\mu + \kappa)(\mu + \gamma)} \geq 1 \geq \frac{\beta \kappa \min_{t \leq \tau' \leq t+\tau} [S^*(\tau')]}{(\mu + \kappa)(\mu + \gamma)} \quad (6.106)$$

Then, as $m_i > 0$ it is known from equation (6.102) that $\max_{t \leq \tau' \leq t+\tau} [S^*(\tau')] \leq \frac{S_{dfe}}{1 + \beta m_i / \mu} < S_{dfe}$, which leads to the following inequality:

$$\frac{\beta \kappa S_{dfe}}{(\mu + \kappa)(\mu + \gamma)} > \frac{\beta \kappa \max_{t \leq \tau' \leq t+\tau} [S^*(\tau')]}{(\mu + \kappa)(\mu + \gamma)} \geq 1 \quad (6.107)$$

However, it is stated that $R_0 = \frac{\beta \kappa S_{dfe}}{(\mu + \kappa)(\mu + \gamma)} < 1$, which lies in direct contradiction of (6.107). Hence, a periodic solution with a permanent presence of the disease is not possible for $R_0 < 1$. \square

Proposition 6.25. *Consider the proposed SEIR model (6.84)-(6.87) under positive initial conditions:*

$$\mathbf{x}_i(0) \geq 0; \forall i = 1, 2, 3, 4$$

with a bounded constant vaccination $V(t) = V \in [0, 1]$.

Then, the DFE equilibrium point is unstable if $R_0 > 1$.

Proof.

First, the dynamic equations (6.84)-(6.87) are linearized around the DFE point by means of the associated Jacobi matrix $\mathbf{J} = [J_{ij}] = \left[\frac{\partial \mathbf{x}_i}{\partial \mathbf{x}_j} \right]$ for $i, j \in \{1, 2, 3, 4\}$ evaluated at the DFE point. Such a Jacobi matrix is given by:

$$\mathbf{J}|_{\mathbf{x}_{dfe}} = \begin{pmatrix} -\mu & 0 & -\beta S_{dfe} & 0 \\ 0 & -(\mu + \kappa) & \beta S_{dfe} & 0 \\ 0 & \kappa & -(\mu + \gamma) & 0 \\ 0 & 0 & \gamma & -\mu \end{pmatrix} \quad (6.108)$$

The eigenvalues of this matrix are obtained by calculating the roots of the characteristic equation $\text{Det}(\lambda I - \mathbf{J}) = G(\lambda)$, which results in the following:

$$\lambda_i = \left\{ -\mu, -\mu, \frac{-(2\mu + \gamma + \kappa) - \sqrt{(\gamma - \kappa)^2 + 4\beta\kappa S_{dfe}}}{2}, \frac{-(2\mu + \gamma + \kappa) + \sqrt{(\gamma - \kappa)^2 + 4\beta\kappa S_{dfe}}}{2} \right\} \quad (6.109)$$

If any eigenvalue λ_i has a positive real part, the system is locally unstable. The real part of the eigenvalues λ_1 , λ_2 and λ_3 is negative, as the parameters involved are defined positive. However, the real part of the fourth eigenvalue λ_4 is positive if $(2\mu + \gamma + \kappa) < \sqrt{(\gamma - \kappa)^2 + 4\beta\kappa S_{dfe}}$. This inequality can be rearranged as:

$$\frac{\beta\kappa S_{dfe}}{(\mu + \kappa)(\mu + \gamma)} > 1 \quad (6.110)$$

Hence, from equation (6.91) it is established that for $R_0 > 1$ the DFE point is unstable. \square

Proposition 6.26. *Consider the proposed SEIR model (6.84)-(6.87) under positive initial conditions:*

$$\mathbf{x}_i(0) \geq 0; \forall i = 1, 2, 3, 4$$

with a bounded constant vaccination $V(t) = V \in [0, 1]$. Then, the END equilibrium point is locally asymptotically stable if $R_0 > 1$.

Proof.

As in the DFE point of proposition 6.25, the dynamic equations from (6.84)-(6.87) is linearized around the endemic point, by means of the associated Jacobi matrix $\mathbf{J} = [J_{ij}] = \left[\frac{\partial \mathbf{x}_i}{\partial \mathbf{x}_j} \right]$ for $i, j \in \{1, 2, 3, 4\}$ evaluated at the endemic point. Such a Jacobi matrix is given by:

$$\mathbf{J}|_{\mathbf{x}_{end}} = \begin{pmatrix} -\mu R_0 & 0 & -\beta S_{end} & 0 \\ \mu(R_0 - 1) & -(\mu + \kappa) & \beta S_{end} & 0 \\ 0 & \kappa & -(\mu + \gamma) & 0 \\ 0 & 0 & \gamma & -\mu \end{pmatrix} \quad (6.111)$$

The eigenvalues of this matrix are obtained by calculating the roots of the characteristic equation $\text{Det}(\lambda I - \mathbf{J})$, i.e. :

$$\begin{aligned} \text{Det}(\lambda I - \mathbf{J}) &= (\lambda + \mu) (\lambda^3 + (\mu R_0 + 2\mu + \gamma + \kappa)\lambda^2 + \\ &\quad + \mu(2\mu + \kappa + \gamma)R_0\lambda + \beta S_{end}\mu\kappa(R_0 - 1)) \end{aligned} \quad (6.112)$$

In order to have a locally asymptotically stable state, the four roots of λ_i from the solutions of $\text{Det}(\lambda_i I - \mathbf{J}) = 0$ must have a negative real part. A characteristic root is found directly $\lambda_1 = -\mu$, while the Routh-Hurwitz criterion [39], [40] tells us that all the roots of the remaining characteristic equation $\beta S_{end}\mu\kappa(R_0 - 1) + \alpha\mu R_0\lambda + (\alpha +$

$R_0\mu)\lambda^2 + \lambda^3 = 0$, being $\alpha = 2\mu + \kappa + \gamma$, present a negative real part if the following coefficients derived from the polynomial are positive: $\alpha + \mu R_0$, $\beta\kappa S_{end}(R_0 - 1)$ and $\mu \left(\alpha R_0 + \frac{\beta\kappa S_{end}(R_0-1)}{\mu R_0 + \alpha} \right)$. Hence, for $R_0 > 1$, the END equilibrium point is locally asymptotically stable. \square

Propositions 6.22-6.26 emphasize the importance of the value of R_0 in order to describe the properties of the equilibrium states of the model. Two only possible non-periodic stable states are established and the reproduction number serves as a switch between them, a fact that is used in the following sections.

6.6.1 Discretization of the SEIR model

Even though the continuous model has proven to be excellent for describing the dynamics of the subpopulations for a fixed set of parameters, an interactive vaccination law based on a feedback loop requires a continuous data acquisition and the ensuing vaccination adjustment. As a result, the SEIR model is discretized with a ZOH (zero-order hold) in order to adapt to the common minimum reaction time T , which is taken as the sampling time. Two different SEIR models are used. The primary model is the discretized version of the non-linear SEIR model given by equations (6.84)-(6.87), while the secondary model is a linearized version of the primary one, associated to the Jacobi matrix evaluated at a state given by the initial conditions. The primary model, more precise and complex, is chosen to represent the dynamics of the populations under a specific vaccination law. The secondary model would give the same analytical result as the primary one with a reasonable accuracy at a given range, with the advantage of being simpler and more manageable. Such a model is employed for the development of the control signal that gives the values for the vaccination strategies, which are also applied to the primary model. Given that the values of the subpopulations in this linearized model will eventually diverge from the principal model, it will be periodically reset and linearized with the current data from the subpopulation of the primary model. Two different non-regular vaccination strategies are chosen for the secondary model, both based on a linear relation between the vaccination and the susceptible subpopulation:

Let V_0 and V_1 be two auxiliary functions defined as:

$$V_0 = \begin{cases} 1 - \frac{1}{R_0} & \text{if } R_0 \geq 1 \\ 0 & \text{if } R_0 < 1 \end{cases} \quad (6.113)$$

and

$$V_1 = \frac{1 + V_0}{2} \quad (6.114)$$

where V_0 is the minimum possible vaccination in which $R_0 \leq 1$ given a constant rate, and V_1 an arbitrary vaccination rate between V_0 and 1. A reactive vaccination law is defined as:

$$V(k) = V_0 + (V_1 - V_0)S(k) \quad (6.115)$$

where $V(k)$ and $S(k)$ are, respectively, the values of the vaccination rate and the susceptible subpopulation of the secondary model at the time t_k . Such a vaccination strategy would interpret a possible decrement of the susceptible subpopulation as a sign of infection, increasing their value. Contrary to the reactive strategy, a preventive vaccination law is defined as:

$$V(k) = V_1 + (V_0 - V_1)S(k) \quad (6.116)$$

being $V(k)$ and $S(k)$ the vaccination rate and the secondary susceptible subpopulation at time t_k . This vaccination law increases the vaccination rate for high values of the susceptible subpopulation as a preventing action since all individual within the susceptible subpopulation can potentially become infectious. Observe that the evaluation and application of the vaccination rate once the data of the susceptible subpopulation is collected is presumed to be instant for all practical purposes. Observe also that for a susceptible subpopulation in the range $S(k) \in [0, 1]$, any possible vaccination provided by the reactive and preventive laws would lead to a reproduction number below 1.

6.7 Simulations and discussion of the proposed strategies

In this section, a series of mathematical models implemented in a Matlab environment are defined and the results shown, in order to illustrate the theoretical results stated in the models of previous sections.

6.7.1 Partial stability-based vaccination control based on recovered subpopulation

The following parameters have been used for the simulations of a model with standard incidence rate $\varphi = \varphi_1(S, E, I, R) = \beta \frac{S(t)I(t)}{N(t)}$, and a vaccination law as in equation (6.19) :

$$\begin{aligned} \mu^{-1} &= 200 \text{ days}, & \kappa^{-1} &= 2.2 \text{ days} \\ \omega^{-1} &= 15 \text{ days}, & \gamma &= \kappa \\ \nu^{-1} &= 150 \text{ days} & \beta &= 1.66 \text{ days}^{-1} \end{aligned}$$

The initial conditions are given by $S(0) = 400, E(0) = 150, I(0) = 250$ and $R(0) = 200$. Notice that since ν^{-1} is smaller than μ^{-1} , then the total population increases through time. These parameters have been chosen so as to illustrate the theoretical results in a short-time simulation. The total simulation period is 50 days. Figure 6.1 shows the evolution of the disease in the absence of vaccination. There are two significant facts that deserve commentary. The first one is that there is a number of infected and infectious through time, i.e. the disease does not disappear in a natural way. Note that according to proposition 6.1 there is not an equilibrium point and

thus, the values of the subpopulations always change through time. The other one is that the model is not globally bounded since the total population diverges, as Figure 6.2 confirms. Thus, a vaccination policy is applied to this model in order to make the infectious and infected vanish. Figure 6.3 depicts the evolution of the

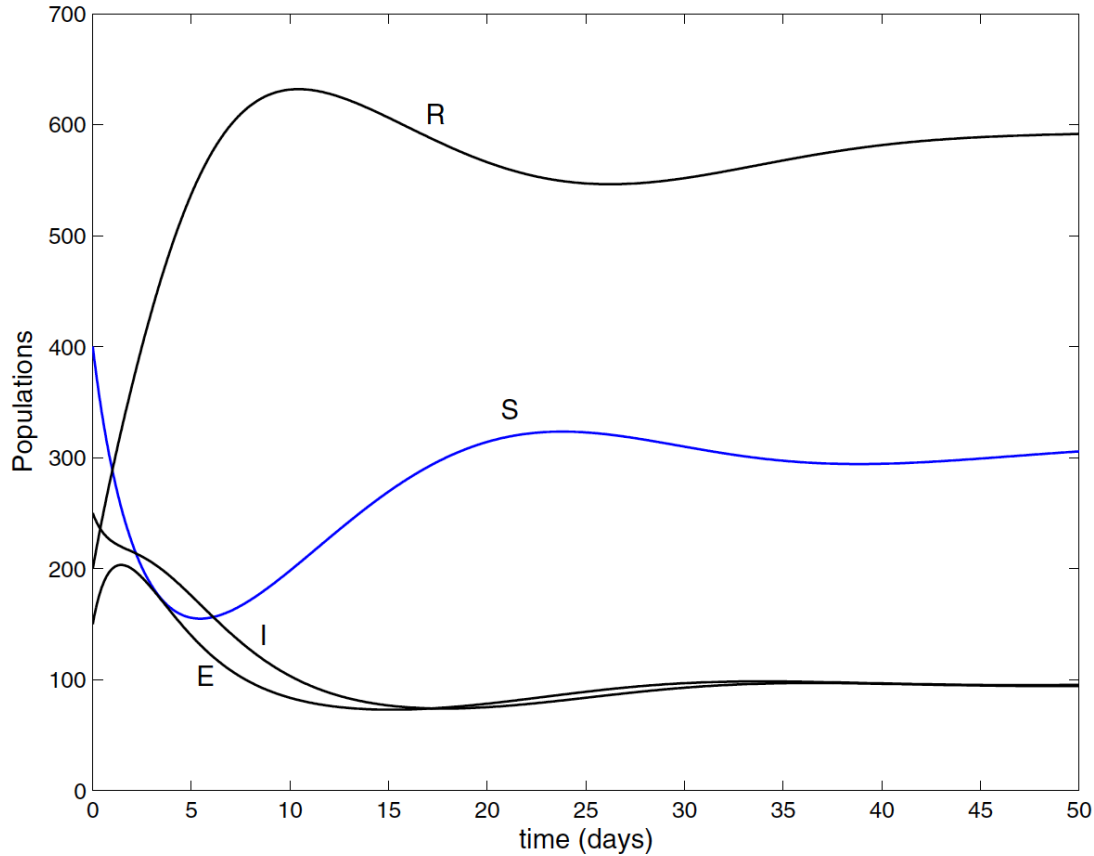


Figure 6.1: Dynamics of the system without vaccination.

disease when the vaccination law from equation (6.19) is applied to the system. Thus, the susceptible, infected and infectious converge to zero while the total population tends to be immune, as proposition 6.6 states. Figure 6.4 shows a zoom on the final period of the simulation. It can be verified that the infective and infectious are already zero while the susceptible tends to zero. The rate at which the susceptible tends to zero is given by μ once the infective and infected subpopulations have vanished. Since this value is in general small, then the convergence of the susceptible to zero is slow. Finally, Figure 6.5 shows the vaccination law. Note that the total population is still not bounded since Figure 6.3 shows the immune diverging. Hence, the vaccination control law does not try to globally stabilize the system but only the variables corresponding to the epidemics, i.e. it only tries to partially stabilize the system.

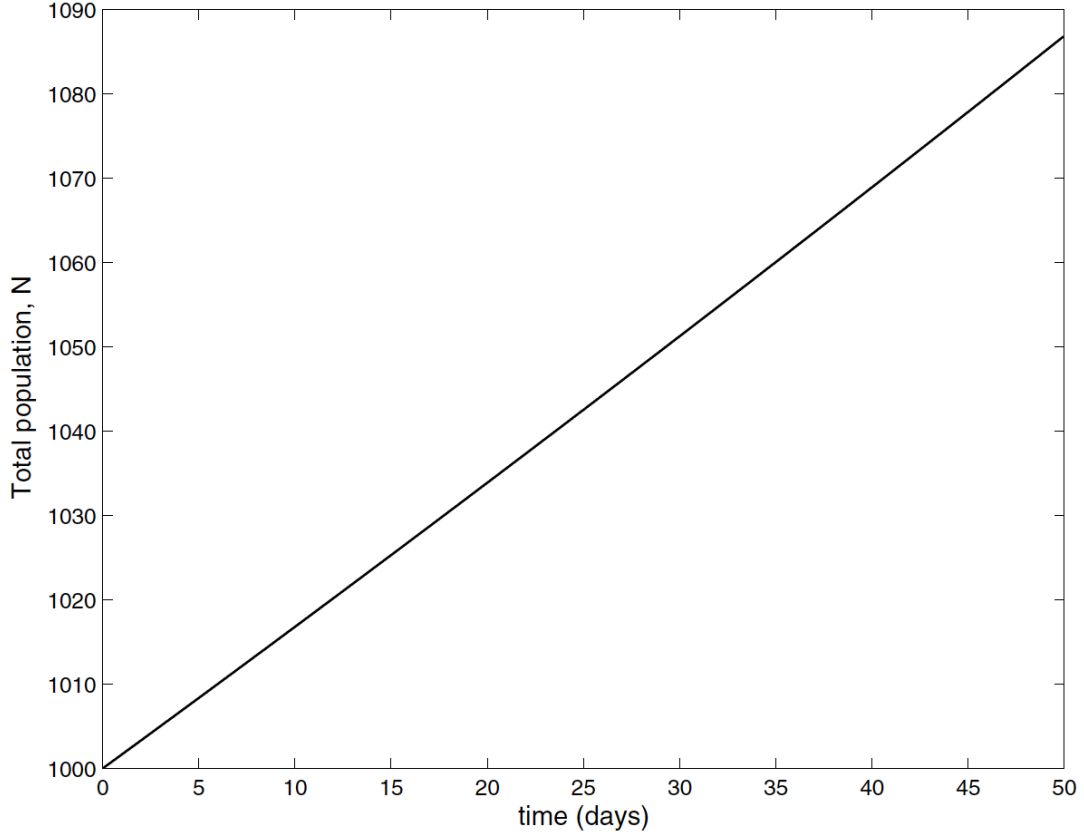


Figure 6.2: Dynamics of the total population, N , without vaccination.

A comparison with other vaccination laws

In this section, a comparative study of the proposed control law with respect to others recently proposed in the literature is done. Under this concrete model, three indexes will be used in order to perform the comparison:

- The total Vaccination cost (VC) is defined here as:

$$VC = \int_0^{T_{final}} N(t)V(t)dt \quad (6.117)$$

where T_{final} denotes the final time of simulation, which in this case is 50 days.

- The maximum value of the control (MV):

$$MV = \max\{V(t)|t \geq 0\} \quad (6.118)$$

- The time in days needed to eradicate the illness (TE):

$$TE = \min\{t_0|I(t_0) < 1 \text{ and } I(t) < 1 \forall t \geq t_0\} \quad (6.119)$$

The lower all the above values are, the better the control law is. Moreover, three control laws will be used for comparison. The one proposed in [9] and two proposed

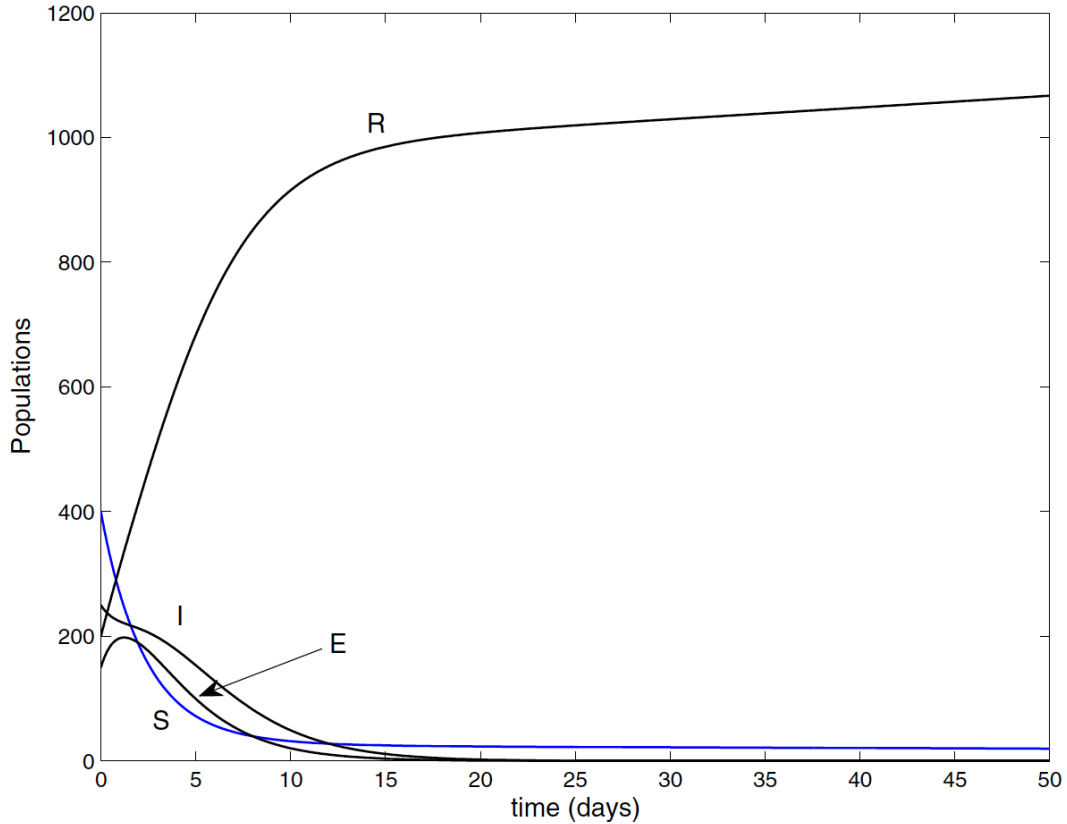


Figure 6.3: Dynamics of the system with the proposed vaccination.

in [36] through equations (26b) and (69) introduced therein. The obtained results are condensed in Table (6.1). The free design parameters of the compared control laws

	VC	MV	TE
Proposed	$5.252 \cdot 10^5$	10.93	22.58
[9]	$5.371 \cdot 10^5$	11.08	22.83
[36] Eq. (26b)	$5.407 \cdot 10^5$	11.04	22.91
[36] Eq. (69)	$5.233 \cdot 10^5$	20.21	22.75

Table 6.1: Comparison between different vaccination laws

have been adjusted in order to obtain a similar time to eradicate the illness, TE, among all of them. In this way, the comparison will be fair since the same performance with respect to infectious vanishing is used for all of them. The first conclusion is that all the control laws offer a similar behavior once fixed the TE parameter. The only one to offer a distinct value is the last one which possesses a larger peak value for the control law, MV.

Hence, the proposed control law is slightly better than the others. However, the approach has the advantage that its derivation and proof of stability and convergence is much easier than those made in [9] and [36]. Hence the presented approach is more

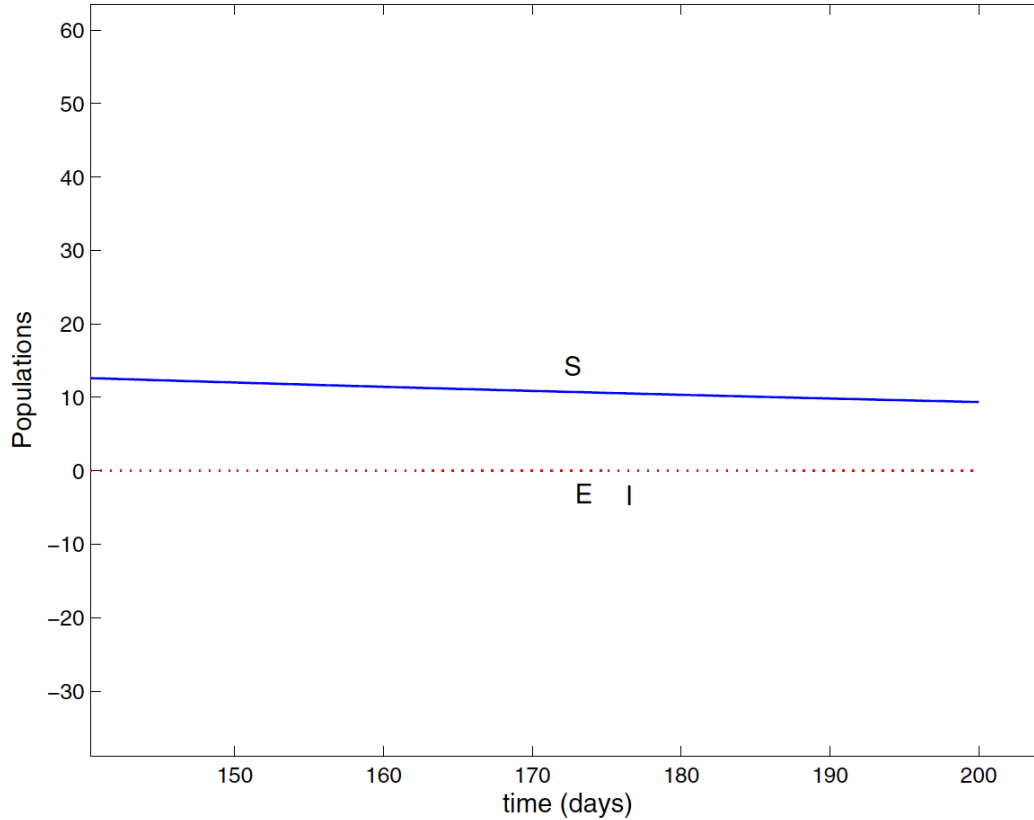


Figure 6.4: Zoom on a large-term simulation of the controlled system.

convenient than a classical global-stability frame to deal with this problem.

6.7.2 Partial stability-based vaccination law based on susceptible subpopulation

For the control law defined in section (6.4.2), another simulation is introduced. The actual parameters for the model φ_1 are given by:

$$\begin{aligned} \mu^{-1} &= 255 \text{ days}, & \kappa^{-1} &= 2.2 \text{ days}, \\ \omega^{-1} &= 15 \text{ days}, & \gamma &= \kappa, \\ \nu &= \mu, & \beta &= 1.66 \text{ days}^{-1} \end{aligned}$$

The parameters of the model are taken from an outbreak of influenza in a British boarding school in late 70's [43], [44], where the μ parameter has been modified in such a way that a short-term simulation is enough to show the dynamic behavior of the system. The initial conditions are $S(0) = 450$, $E(0) = 150$, $I(0) = 300$ and $R(0) = 100$ for a total population of $N_0 = 1000$ individuals. The parameters of the controller are $\Xi^{-1} = 100$ days and $\epsilon = \frac{\mu + \gamma}{2}$. The dynamic of the vaccination-free system is depicted in Figure 6.6. It can be noticed that the epidemic is persistent and there are a number of exposed and infectious in the equilibrium. Under these

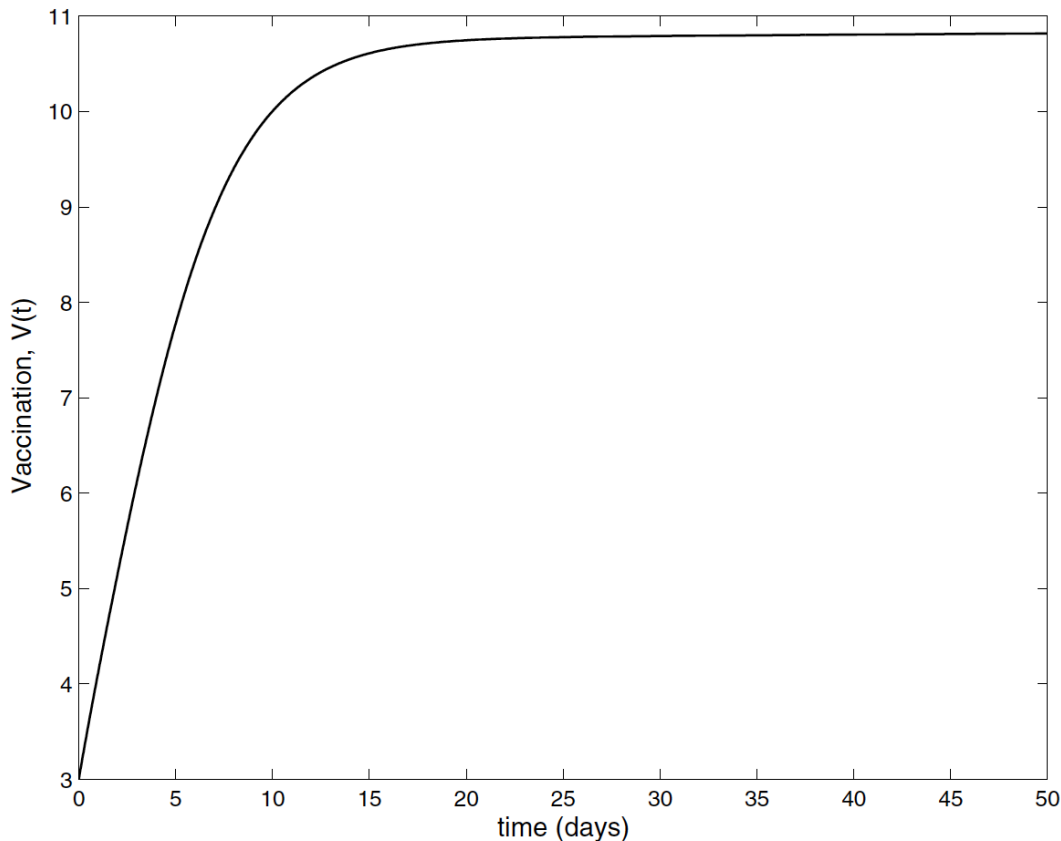


Figure 6.5: Vaccination function, $V(t)$.

circumstances, the vaccination control policy from (6.42) is applied to the system to obtain the closed-loop dynamics depicted in Figure 6.7.

Figure 6.7 shows that the exposed and infectious subpopulations converge to zero eradicating the epidemic from society asymptotically. Furthermore, the susceptible subpopulation converges to the reference value. In this way, it is not necessary to vaccinate the whole population since the susceptible subpopulation does not converge to zero as previous works enforce [9], [36]. Figure 6.8 depicts the vaccination effort needed to achieve the control objective. It is shown that the vaccination effort is zero during the first steps of disease spreading. This happens because the susceptible subpopulation decreases in a natural way at the beginning faster than the selected convergence rate, the non-saturated vaccination law $\bar{V}(t)$ is negative as figure 6.9 shows and no vaccination is needed to reduce the number of susceptible individuals. Notice that despite $V(t)$ vanishes, the susceptible subpopulation decreases in time, as stated in Lemma 6.13.

Finally, a sensitivity analysis is performed on the behavior of the closed-loop. To this end the parameter Ξ has been varied from $\Xi^{-1} = 10$ days to $\Xi^{-1} = 100$ days. The results are depicted in Figures 6.10 and 6.11. As expected, the larger Ξ is the faster the convergence of the susceptible subpopulation to the reference value is. On the other hand a faster convergence rate requires a larger vaccination effort. Thus, the

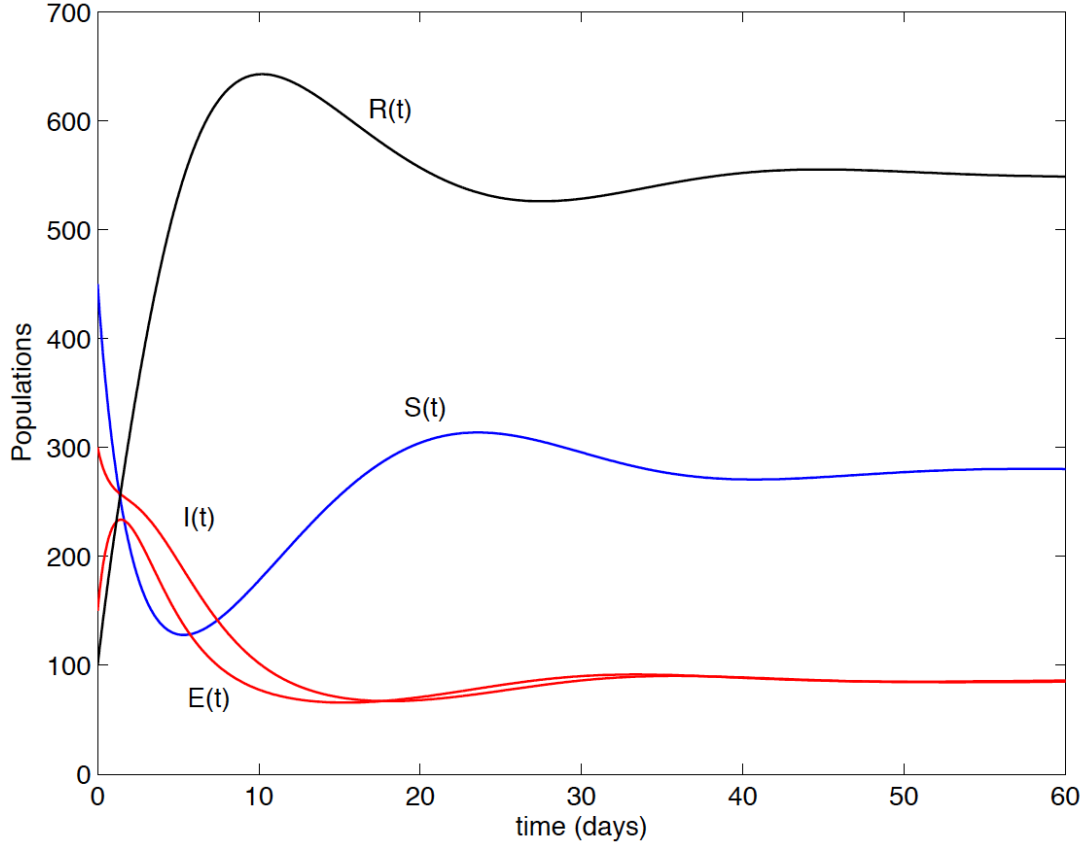


Figure 6.6: Dynamics of the subpopulations of a vaccination-free system based on a standard incidence rate model.

vaccination also increases as Ξ enlarges. A particular tuning for Ξ would then appear as a trade-off between celerity in epidemic eradication and vaccination capacity.

6.7.3 Simulation of an observed-based vaccination law

The observed-based vaccination law is also studied in a SEIR model described by the following parameters taken from an influenza outbreak [45]:

$$\begin{aligned} \mu^{-1} &= 25550 \text{ days} & \kappa^{-1} &= \gamma^{-1} = 2.2 \text{ days}, \\ \omega^{-1} &= 15 \text{ days} & \text{and } \beta &= 1.66 \text{ days}^{-1}. \end{aligned}$$

The initial conditions are given by $S(0) = 400$, $E(0) = 150$, $I(0) = 250$, and $R(0) = 200$ individuals so that the total population is $N(0) = 1000$ individuals. The observer from equation (6.46) is used to estimate the partial populations for all time since they are not measurable. The initial estimates are $\hat{S}(0) = 250$, $\hat{E}(0) = \hat{I}(0) = 150$, and $\hat{R}(0) = 450$ individuals. Moreover, an estimation of the values of the unknown true model parameters is used to parameterize the observer. Such estimates are:

$$\begin{aligned} \hat{\mu}^{-1} &= 23550 \text{ days} & \hat{\kappa}^{-1} &= \hat{\gamma}^{-1} = 2 \text{ days}, \\ \hat{\omega}^{-1} &= 14 \text{ days} & \text{and } \hat{\beta} &= 1.46 \text{ days}^{-1}. \end{aligned}$$

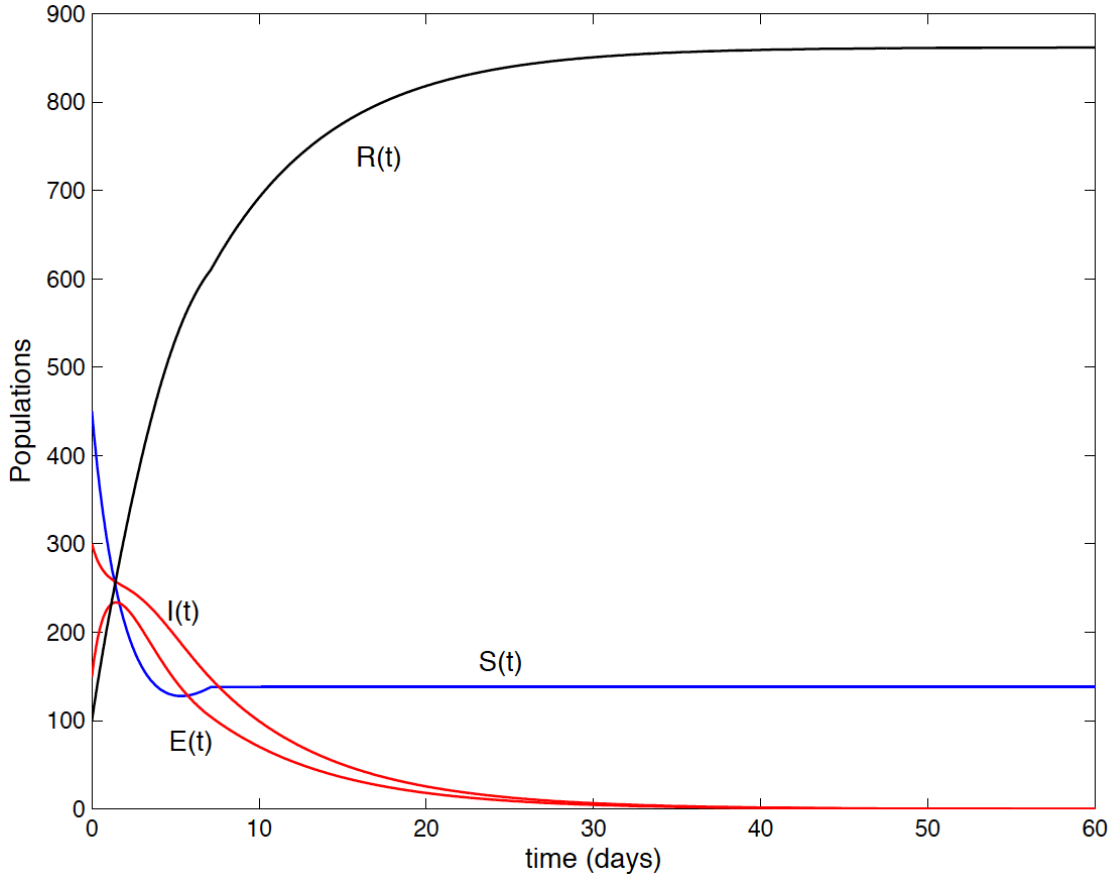


Figure 6.7: Dynamics of the subpopulations with the vaccination control law from equation (6.42) applied .

A vaccination strategy given by equation (6.48) is introduced in the system. The following values have been used for the control gains: $\lambda_1 = 1$, $\lambda_2 = -0.1$, $\lambda_3 = -\hat{\gamma}$, $\lambda_4 = 0.95$, $\lambda_5 = -\hat{\beta}_1$ and $g = \hat{\mu}$. Figure 6.12 shows the time-evolution of the populations. Figure 6.13 shows the error between the observation and the real states. Figure 6.12 does not only show that the SEIR-model is globally stable regardless the observation error depicted in Figure 6.13 but also that the observer-based control law eradicates the infective and infectious, while the immune almost reaches to be the total population N . A small number of susceptible still appear in the steady-state.

However, this behavior is much better than that obtained with the combined SEIR-model and observer system without vaccination where a number of infective and infectious appear as it can be seen in Figure 6.14. In summary, this example points out the improvement in the eradication of an infection disease if a vaccination control law based on an observer for the SEIR-model is applied compared with the results obtained in a free vaccination case. Note also that the true partial populations are bounded for all time, i.e., the combined SEIR control-observer model is stable. However, it is not a positive system since the control gain $\lambda_2 = -0.1$ makes \hat{A}_0 not be a Metzler matrix, so the observer is not a positive system (remark 6.20). This fact is

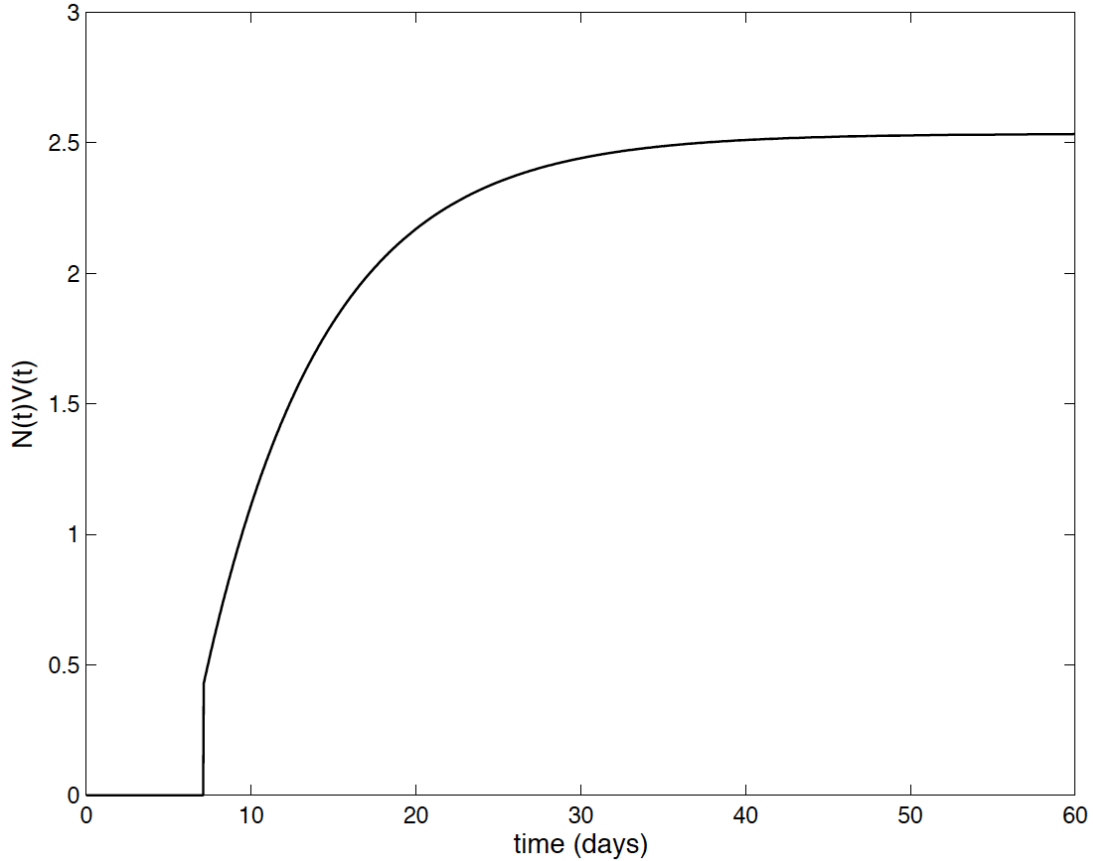


Figure 6.8: Vaccination effort $N(t)V(t)$ with the control policy from equation (6.42) applied.

according to the theoretical result pointed out in assertion 6.21.

6.7.4 Simulation of vaccination laws on a discretized SEIR model

A simulation of the discretized SEIR model from equations (6.84)-(6.87) is made applying two vaccination laws: the reactive vaccination law and the preventive vaccination law from equations (6.115) and (6.116) respectively. The two Simulink models run simultaneously recreating the outbreak of a disease with no permanent immunity, both associated to a set of parameters from a measles infection [46], so initial conditions are set up to a normalized population of $S(0) = 0.99$, $E(0) = R(0) = 0$, and $I(0) = 0.01$. The transition rate from the exposed to the infectious and from the infectious to the recovered are defined by mere weeks, hence the values are $\kappa = 14/365 \text{ year}^{-1}$ and $\gamma = 14/365 \text{ year}^{-1}$ respectively, while the birth-death rate is set with the average natural death rate of humans in a first world country $\nu = 1/70 \text{ year}^{-1}$. The infectivity rate β is set so the reproduction number from equation (6.91) is above 1, namely $R_0 = 1.6$. Both the primary and secondary models are discretized with a sample time $T = 0.05 \text{ year}$, while the matrix for the dynamics of the secondary model and the divergences from the primary one are reset each year. Under this conditions, fig-

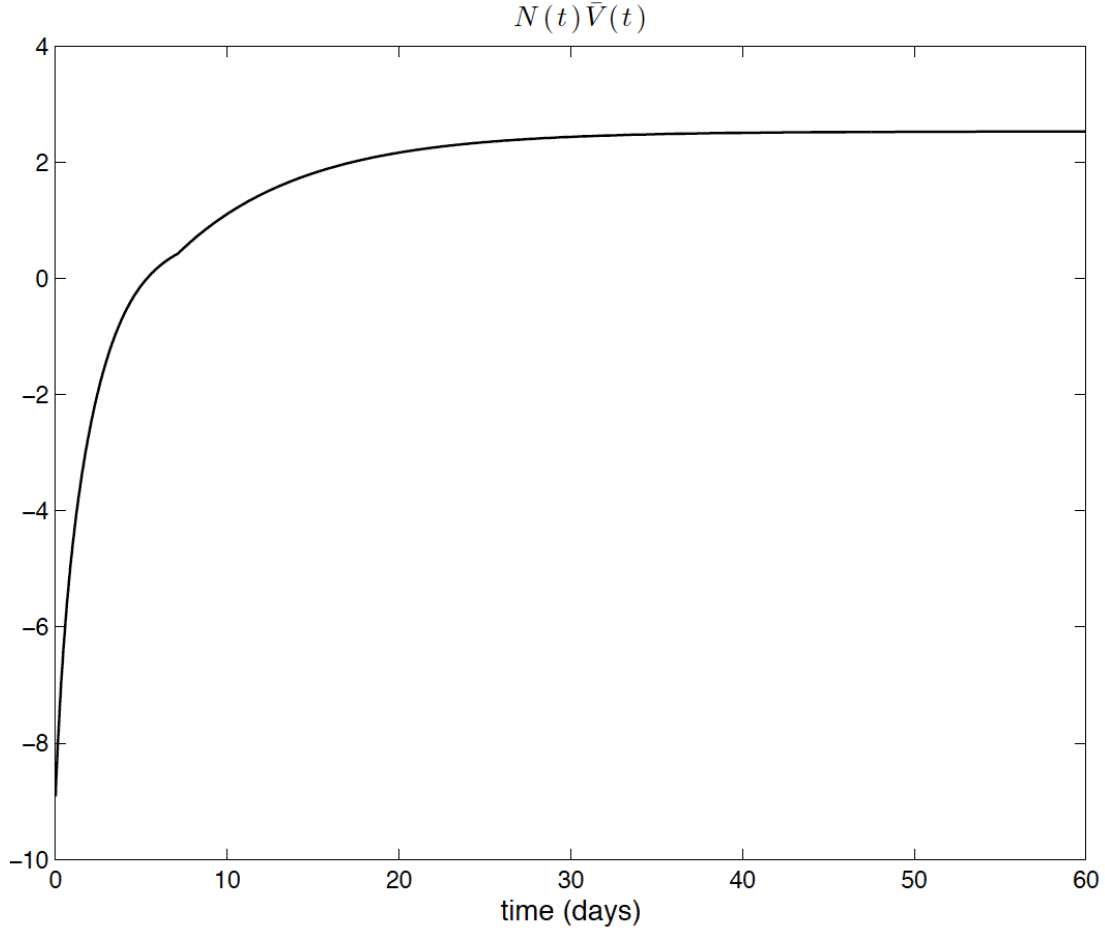


Figure 6.9: Non-saturated vaccination effort $N(t)\bar{V}(t)$ with the control policy from (6.37) applied.

Figure 6.15 presents the dynamics of the subpopulations when a preventive vaccination strategy is applied, while a closer look of the initial evolution of the subpopulations and the vaccination rate can be seen at figure 6.16 and figure 6.17 respectively. The effectivity of the strategies tested in these simulations are measured according to the vaccination cost (VC) and disease cost (DC), defined as the total number of vaccines used, in this case as

$$VC = \nu \sum_{k=0}^{k_f} V_k$$

and the total of infectious subpopulation present during the simulation:

$$DC = \sum_{k=0}^{k_f} I_k$$

The cost of both feedback-loops strategies from equations (6.115) and (6.116) obtained for a 20 years simulation are compared to the costs of applying, under the

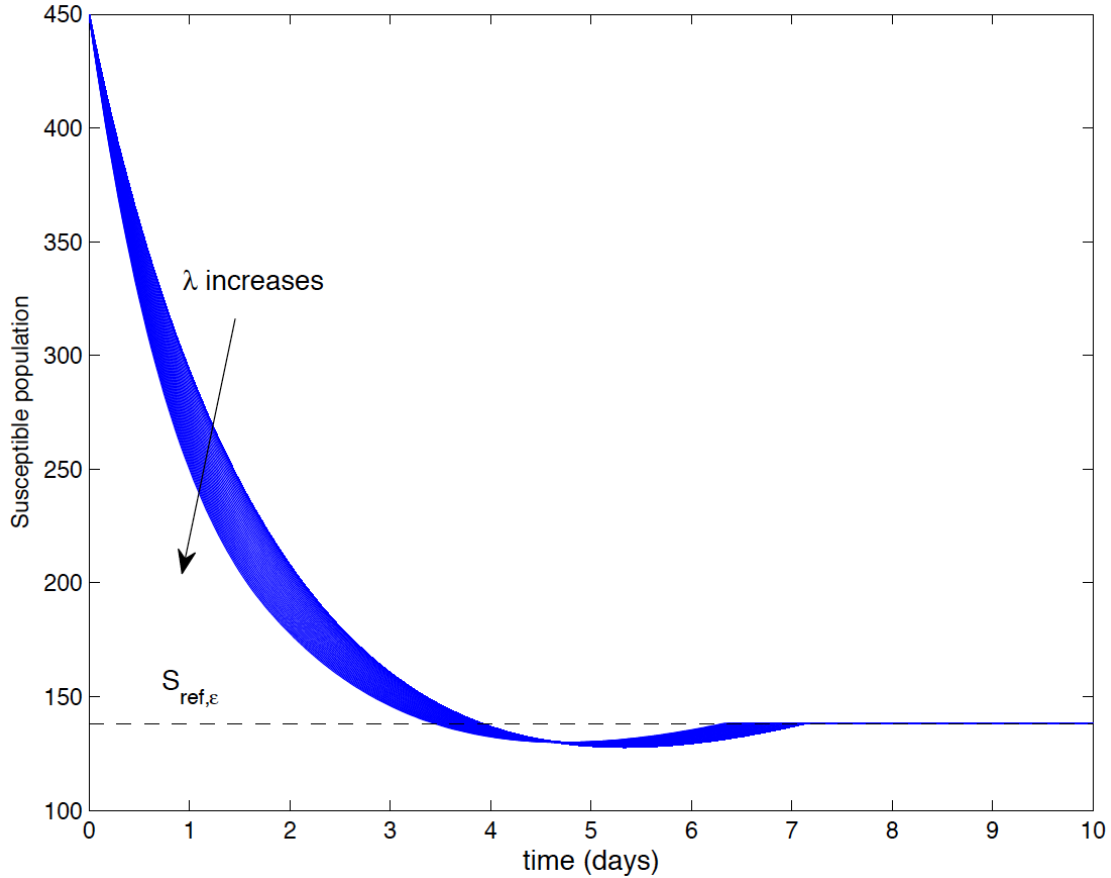


Figure 6.10: Behavior of the susceptible subpopulation as λ varies.

same circumstances, open-loop vaccination rules for different constant vaccination rates ranging between V_0 and V_1 in figure 6.18. Although the subtle differences in the vaccination costs due to the dynamics of the subpopulations cannot be seen clearly in figure 6.18, the relation between the VC and DC for the different vaccination strategies can be seen properly at figure 6.19, where the preventive strategy shows to be more efficient than a constant vaccination, as it shows a lower DC for what would be the same VC, while the contrary happens with the reactive strategy, as the VC required for reaching a certain DC is higher than the regular vaccination.

6.8 SIRS epidemic model and problem formulation

Here it is proposed a SIRS epidemic model with normalized subpopulations, and a vaccination strategy is introduced based on a linearization control techniques of the mapping from the vaccination control to the infected population. The main differences of the current model with respect to the previous ones is the simplification of the infected subpopulations into one, and the fact that the mortality from causes relative to the infection is appreciable in the population. Also, the birth and mortality

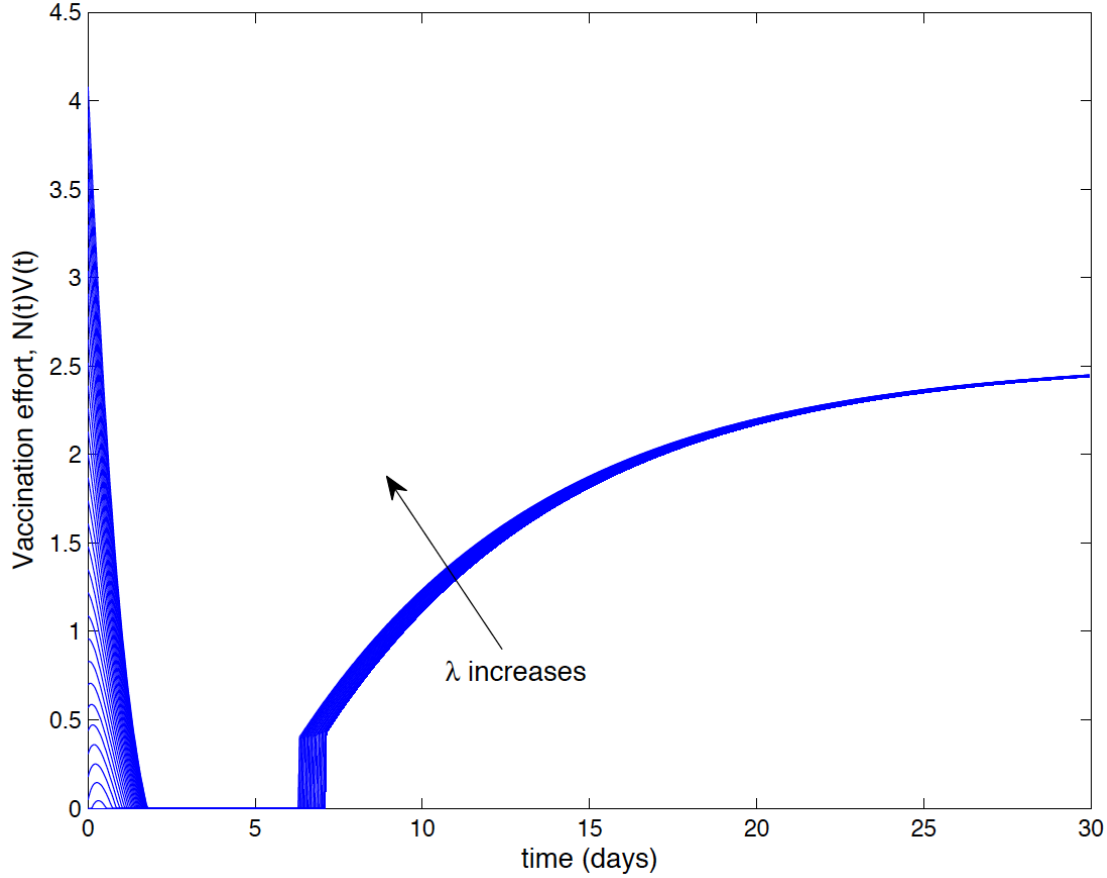


Figure 6.11: Behavior of the vaccination effort as λ varies.

from nature causes may be different so that the whole host population may be time-varying. The sum of all the subpopulations in a normalized SIRS epidemic model is invariable 1. Such a normalized model is obtained from the original SIRS one via a suitable variables change. Moreover, it is used to synthesize the vaccination control law which will ensure the eradication of the infection from the host population and the positivity of the normalized SIRS model as well as the original SIRS epidemic model. Finally, the described control strategy may be extended to more complex epidemical models which consider more population categories than those presented in the SIRS model. In this sense, vaccinated, quarantine, susceptible population with different risk of catching infection, asymptomatic or symptomatic infected populations have been considered in other compartmental models for describing the propagation of infectious diseases within a host population [47]-[49].

Notation:

$\mathbb{R}_+ \triangleq (0, \infty) \cap \mathbb{R}$ is the set of strictly positive real numbers and $\mathbb{R}_{0+} \triangleq \mathbb{R}_+ \cup \{0\}$.

$\mathbb{R}_- \triangleq (-\infty, 0) \cap \mathbb{R}$ is the set of strictly negative real numbers and $\mathbb{R}_{0-} \triangleq \mathbb{R}_- \cup \{0\}$.

\mathbb{R}_+^2 is the first open real quadrant and \mathbb{R}_{0+}^2 is the first closed real quadrant.

\mathbb{R}_-^2 is the third open real quadrant and \mathbb{R}_{0-}^2 is the third closed real quadrant.

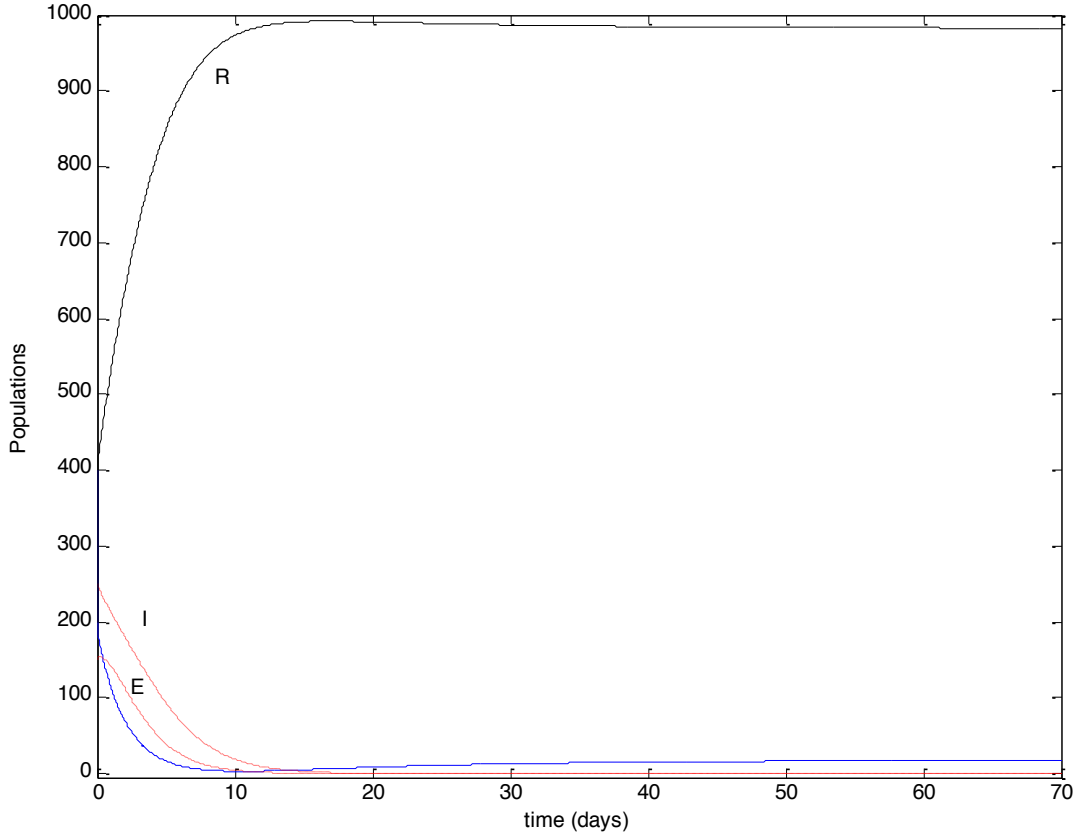


Figure 6.12: Evolution of the populations with standard incidence rate and vaccination-based observer from equation (6.48).

6.8.1 SIRS epidemic model

Let $S(t)$, $I(t)$ and $R(t)$ be, respectively, the susceptible, infected and recovered or removed-by-immunity subpopulations at time t . Consider a time-invariant SIRS epidemic model given by:

$$\dot{S}(t) = -\mu S(t) + \omega R(t) - \beta \frac{S(t)I(t)}{N(t)} + \nu N(t)[1 - V(t)] \quad (6.120)$$

$$\dot{I}(t) = -(\mu + \gamma)I(t) + \beta \frac{S(t)I(t)}{N(t)} \quad (6.121)$$

$$\dot{R}(t) = -(\mu + \omega)R(t) + \gamma(1 - \rho)I(t) + \nu N(t)V(t) \quad (6.122)$$

subject to initial conditions $S(0) \geq 0$, $I(0) \geq 0$ and $R(0) \geq 0$ under a vaccination function $V : \mathbb{R}_{0+} \rightarrow \mathbb{R}_{0+}$. In this SIRS model, as in the previous SEIR models, $N(t) \geq 0$ is the total population at any time instant $t \in \mathbb{R}_{0+}$, $\mu > 0$ is the death rate from natural causes unrelated to the infection, $\nu > 0$ is the birth rate, $\omega > 0$ is the rate of losing immunity, $\beta > 0$ is the transmission constant (with a standard incidence rate

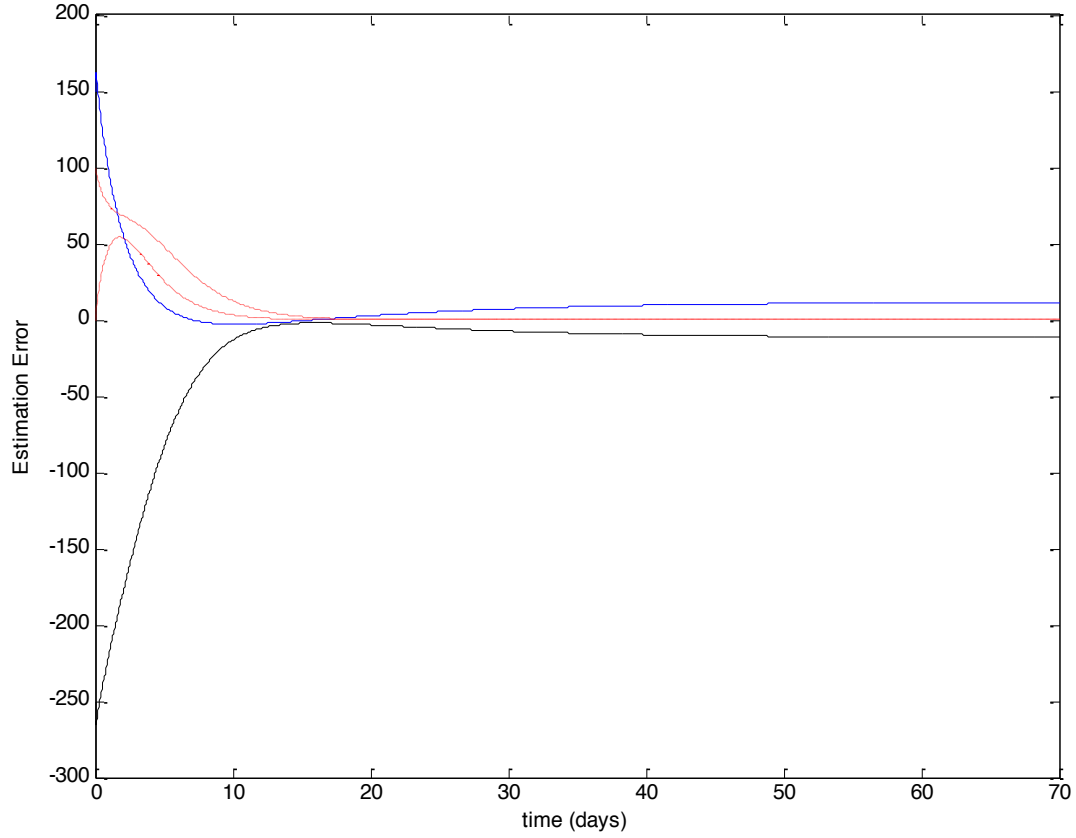


Figure 6.13: Evolution of the observation error with vaccination.

$\beta S(t)I(t)/N(t)$, $\gamma > 0$ is the recovery rate (or $\gamma^{-1} > 0$ the average duration of the infective period) and $\rho \in [0, 1)$ is the probability of death from infection causes. The total population dynamics is obtained by summing-up equations from (6.120)-(6.122) yielding:

$$\dot{N}(t) = \dot{S}(t) + \dot{I}(t) + \dot{R}(t) = (\nu - \mu)N(t) - \rho\gamma I(t) \quad (6.123)$$

so that the total population is time-varying.

6.8.2 Normalized SIRS epidemic model

The SIRS model from equations (6.120)-(6.122) is normalized with respect to the whole population by using the following variables change:

$$s(t) = \frac{S(t)}{N(t)}; \quad i(t) = \frac{I(t)}{N(t)}; \quad r(t) = \frac{R(t)}{N(t)} \quad (6.124)$$

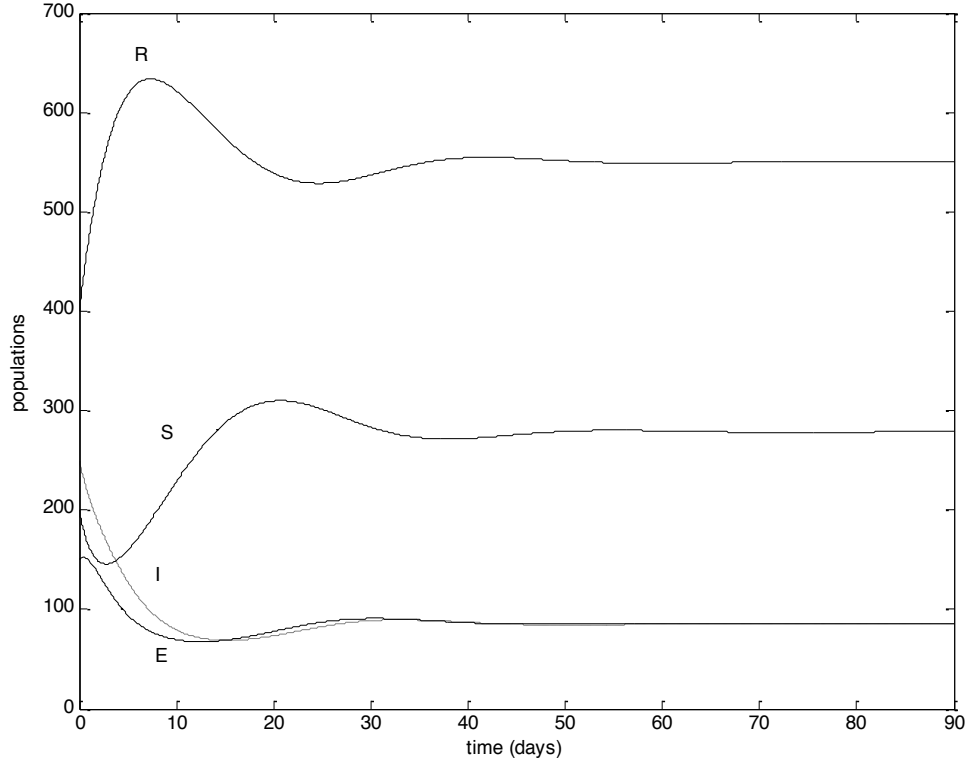


Figure 6.14: Evolution of the actual population through time in the vaccination-free case.

By introducing this variables change in equations (6.120)-(6.122), it is obtained the normalized SIRS model given by:

$$\dot{s}(t) = -\nu s(t) + \omega r(t) + (\rho\gamma - \beta) s(t)i(t) + \nu[1 - V(t)] \quad (6.125)$$

$$\dot{i}(t) = -(\nu + \gamma) i(t) + \beta s(t)i(t) + \rho\gamma i(t)^2 \quad (6.126)$$

$$\dot{r}(t) = -(\nu + \omega) r(t) + \gamma(1 - \rho) i(t) + \rho\gamma i(t)r(t) + \nu V(t) \quad (6.127)$$

By summing-up equations (6.125)-(6.127), it follows that $\dot{s}(t) + \dot{i}(t) + \dot{r}(t) = 0$ so that $s(t) + i(t) + r(t) = 1$ for all time irrespective of the vaccination function.

6.9 Design of a linealization-based control vaccination law in the SIRS model

The main control objective is that the infected population asymptotically tends to zero as $t \rightarrow \infty$, so the infection is eradicated from the population, while guaranteeing the positivity of the controlled system. A vaccination control law based on a static-state feedback linearization strategy is developed for achieving such a control

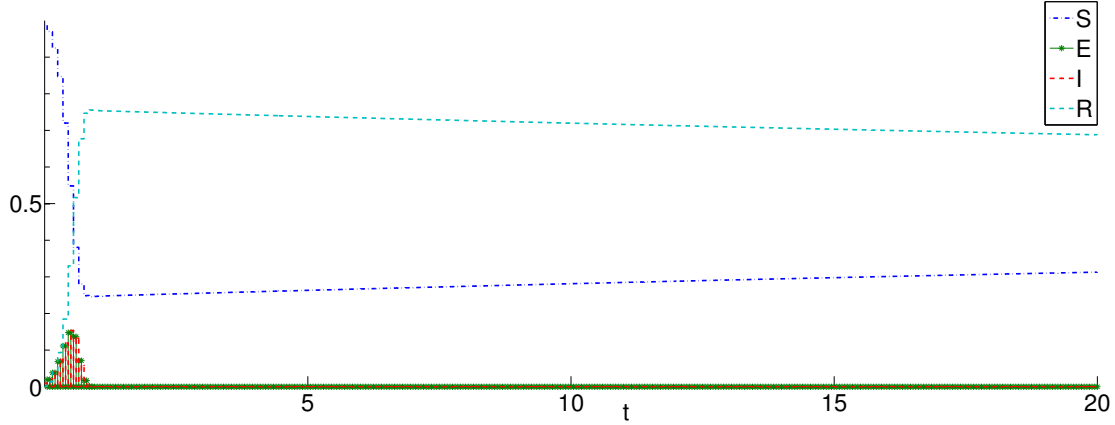


Figure 6.15: Evolution of the subpopulations for the discretized SEIR model with a preventive vaccination strategy and $R_0=1.6$

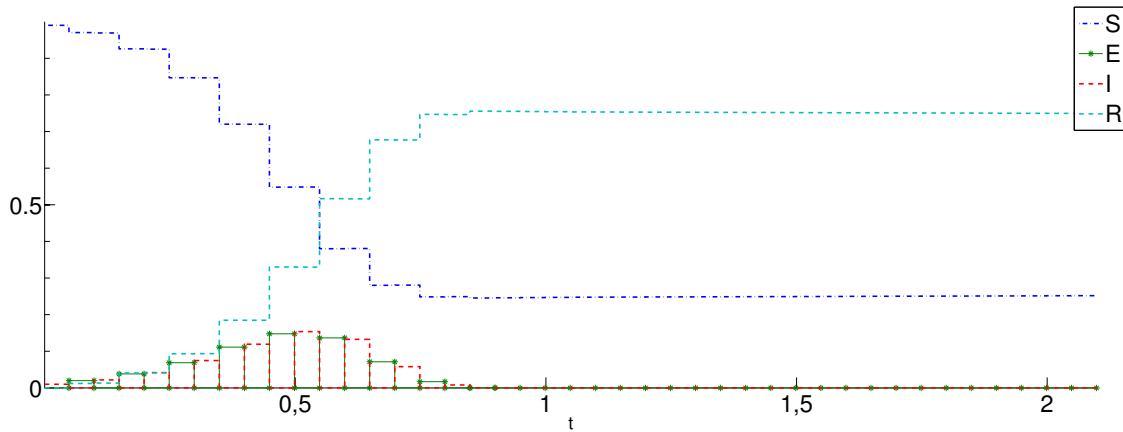


Figure 6.16: An amplified view of figure (6.15). The initial evolution of the subpopulations for a preventive vaccination strategy with $R_0=1.6$

objective. This technique requires a nonlinear coordinate transformation, based on the Lie derivatives Theory in the system representation [50]. The dynamics equations (6.125)-(6.127) of the normalized SIRS model can be equivalently written as the following nonlinear control affine system:

$$\dot{x}(t) = f(x(t)) + g(x(t))u(t); \quad y(t) = h(x(t)) \quad (6.128)$$

where $y(t) = i(t) \in \mathbb{R}_{0+}$, $u(t) = V(t) \in \mathbb{R}_{0+}$ and $x(t) = [i(t) \ s(t)] \in \mathbb{R}_{0+}^2$ are considered, respectively, the output signal, the input signal and the state vector of the system $\forall t \in \mathbb{R}_{0+}$, and $r(t) = 1 - s(t) - i(t)$ has been used, with:

$$f(x(t)) = \begin{bmatrix} -(\nu + \omega)i(t) + \beta s(t)i(t) + \rho\gamma i^2(t) \\ -(\nu + \omega)s(t) - \omega i(t) + (\rho\gamma - \beta)s(t)i(t) + \nu + \omega \end{bmatrix} \in \mathbb{R}^2 \quad (6.129)$$

$$g(x(t)) = [0 \ -\nu]^T \in \mathbb{R}_{0-}^2; \quad h(x(t)) = i(t) \in \mathbb{R}_{0+}$$

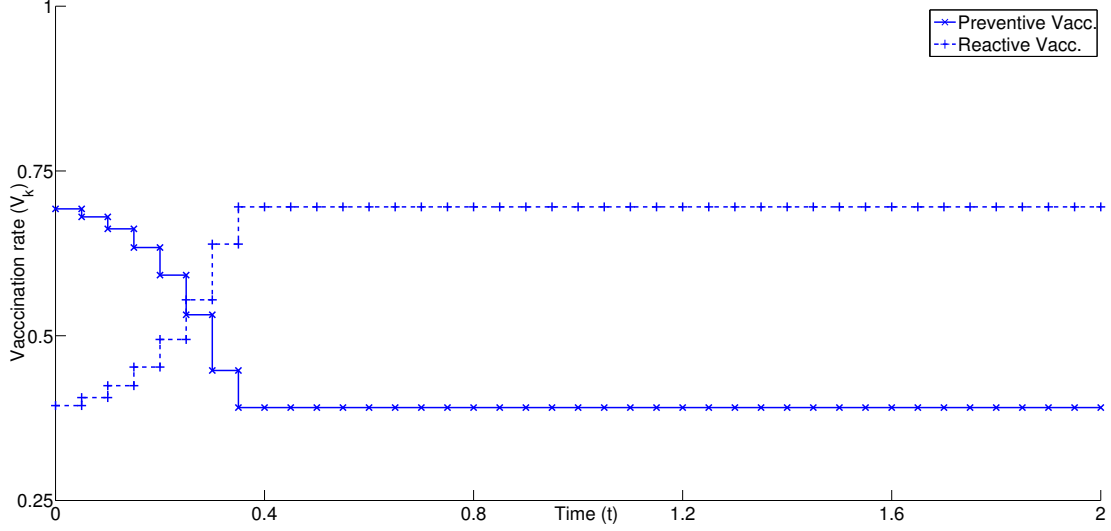


Figure 6.17: Initial vaccination rate for the discretized SEIR model based on the preventive and reactive vaccination with $R_0=1.6$

The first step to apply a coordinate transformation based on the Lie derivation is to determine the relative degree of the system. For such a purpose, the following definitions are taken into account:

- i) $L_f^k h(x(t)) \triangleq \frac{\partial(L_f^{k-1}h(x(t)))}{\partial x} f(x(t))$ is the k th-order Lie derivative of $h(x(t))$ along $f(x(t))$ with $L_f^0 h(x(t)) \triangleq h(x(t))$ and
- ii) the relative degree r of the system is the number of times that the output must be differentiated to obtain the input explicitly, i.e., the number r so that $L_g L_f^k h(x(t)) = 0$ for $k < r - 1$ and $L_g L_f^{r-1} h(x(t)) \neq 0$.

From equation (6.129), $L_g h(x(t)) = 0$ while $L_g L_f h(x(t)) = -\nu\beta i(t)$, so the relative degree of the system is 2 in $D \triangleq \{[i, s]^T \in \mathbb{R}_{0+}^2 \mid i \neq 0\}$, i.e., $\forall x \in \mathbb{R}_{0+}^2$ except in the singular surface $i = 0$ of the state space where the relative degree is not well-defined. Since the relative degree of the system is exactly equal to the dimension of the state space for any $x \in D$, the nonlinear coordinate change

$$\bar{i}(t) = L_f^0 h(x(t)); \quad \bar{s}(t) = L_f h(x(t)) = -(\nu + \gamma)i(t) + \beta s(t)i(t) + \rho\gamma i^2(t) \quad (6.130)$$

allows to represent the model in the so-called normal form in a neighborhood of any $x \in D$. Namely:

$$\dot{\bar{x}}(t) = \bar{f}(\bar{x}(t)) + \bar{g}(\bar{x}(t))u(t); \quad y(t) = h(\bar{x}(t)) \quad (6.131)$$

where $\bar{x}(t) = [\bar{i}(t) \quad \bar{s}(t)]^T$ and:

$$\begin{aligned} \bar{f}(\bar{x}(t)) &= [\bar{s}(t) \quad \phi(\bar{x}(t))]^T; \quad \bar{g}(\bar{x}(t)) = [0 \quad -\nu\beta\bar{i}(t)]^T h(\bar{x}(t)) = \bar{i}(t) = i(t) \\ \phi(\bar{x}(t)) &= (\beta - \nu - \gamma)(\omega + \nu)\bar{i}(t) - (\nu + \omega)\bar{s}(t) + (\rho\gamma(2\nu + \omega + \gamma) - \beta(\nu + \omega + \gamma))\bar{i}^2(t) \\ &\quad + (2\rho\gamma - \beta)\bar{s}(t)\bar{i}(t) + \frac{\bar{s}^2(t)}{\bar{i}(t)} - \rho\gamma(\rho\gamma - \beta)\bar{i}^3(t) \end{aligned} \quad (6.132)$$

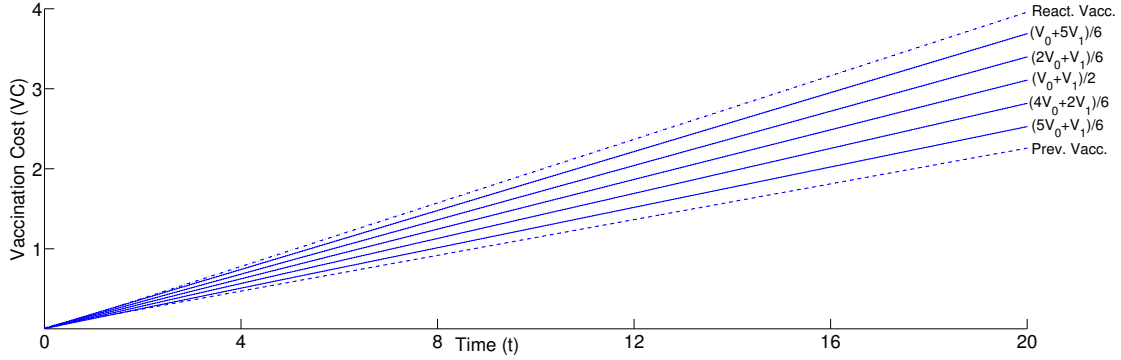


Figure 6.18: Vaccination cost over time for both the preventive and reactive vaccination strategies (dotted lines) and a set of constant vaccination rates (continuous lines)

The following result being relative to the input-output linearization of the system is established.

Proposition 6.27. *The state feedback control law*

$$u(t) = \frac{-L_f^2 h(x(t)) - \lambda_0 h(x(t)) - \lambda_1 L_f h(x(t))}{L_g L_f h(x(t))} \quad (6.133)$$

where λ_0 and λ_1 are the controller tuning parameters, induces the linear closed-loop dynamics

$$\ddot{y}(t) + \lambda_1 \dot{y}(t) + \lambda_0 y(t) = 0 \quad (6.134)$$

around any point $x \in D$.

Proof.

The state equation for the closed-loop system

$$\begin{bmatrix} \dot{\bar{i}}(t) \\ \dot{\bar{s}}(t) \end{bmatrix} = \begin{bmatrix} \bar{s}(t) \\ \phi(\bar{x}(t)) - L_f^2 h(x(t)) - \lambda_0 \bar{i}(t) - \lambda_1 \bar{s}(t) \end{bmatrix} \quad (6.135)$$

is obtained by introducing the control law from equation (6.133) in (6.131), and taking into account the fact that $L_g L_f h(x(t)) = -\nu \beta \bar{i}(t) = -\nu \beta \bar{i}(t) \neq 0 \quad \forall x \in D$ and the coordinate transformation from equation (6.130). Also, it follows that $L_f^2 h(x(t)) = \phi(\bar{x}(t))$ by direct calculations. Thus, the state equation of the closed-loop system in the state space defined by $\bar{x}(t)$ can be written as:

$$\dot{\bar{x}}(t) = A \bar{x}(t) \text{ with } A = \begin{bmatrix} 0 & 1 \\ -\lambda_0 & -\lambda_1 \end{bmatrix} \quad (6.136)$$

Furthermore, the output equation of the closed-loop system is $y(t) = C \bar{x}(t)$ with $C = [1 \ 0]$ since $y(t) = i(t) = \bar{i}(t)$. From equation (6.136) and the closed-loop output equation, it follows that:

$$\ddot{y} = \ddot{\bar{i}}(t) = \dot{\bar{s}}(t) = -\lambda_0 \bar{i}(t) - \lambda_1 \bar{s}(t) = -\lambda_0 y(t) - \lambda_1 \dot{y}(t) \rightarrow \ddot{y}(t) + \lambda_1 \dot{y}(t) + \lambda_0 y(t) = 0$$

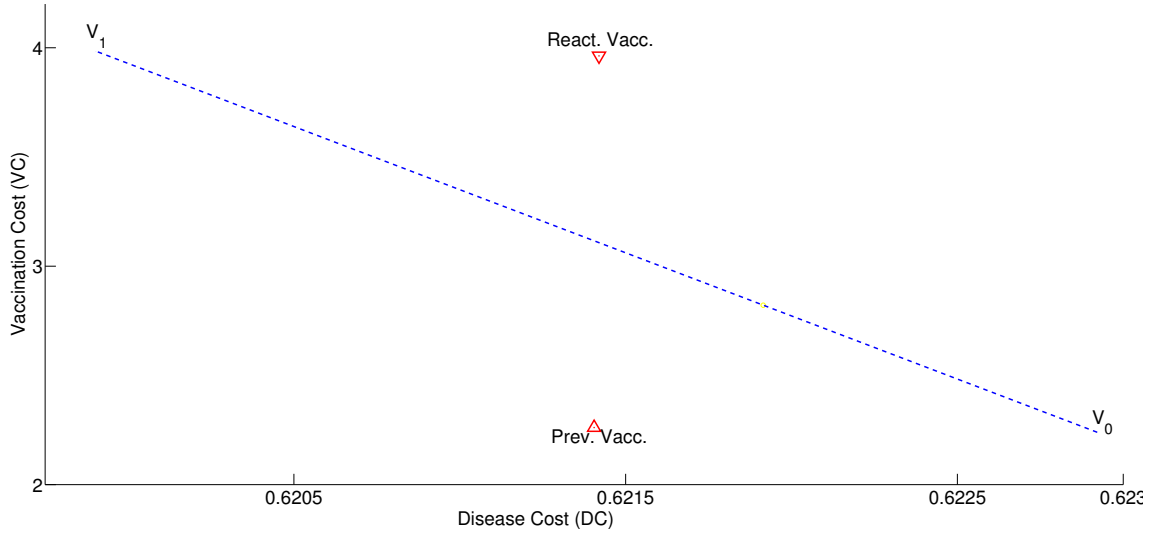


Figure 6.19: VC and DC for different constant vaccinations (dotted line) ranging between V_1 and V_0 . Upside triangle correspond to the preventive vaccination strategy, while the downside triangle to the reactive vaccination strategy.

$$(6.137)$$

□

Remark 6.28. *The roots of the characteristic polynomial $P(s) = s^2 + \lambda_1 s + \lambda_0$ corresponding to the closed-loop dynamics from equation (6.134) are given by $p_{1,2} = \frac{-\lambda_1 \pm \sqrt{\lambda_1^2 - 4\lambda_0}}{2}$. Then, the stability of the closed-loop dynamics is guaranteed if the control parameters are choosing strictly positive so that such roots have real parts being strictly negative. Moreover, such choice implies the exponential convergence to zero of the output variable $i(t) = \bar{i}(t)$ as time tends to infinity and, as a consequence, the eradication of the infection from the host population. However, the control parameters choice has also to guarantee the positivity of the susceptible, infected and recovered populations for all time as the system nature requires. This constraint implies that the model variables $i(t)$ and $s(t)$ have to be such that $i(t) + s(t) \in [0, 1] \forall t \in \mathbb{R}_{0+}$ so that $r(t) \in [0, 1] \forall t \in \mathbb{R}_{0+}$ in view of the constraint $i(t) + s(t) + r(t) = 1 \forall t \in \mathbb{R}_{0+}$. Such a positivity property implies additional conditions to be satisfied by the controller parameters λ_0 and λ_1 . This analysis is carried out in subsection 6.9.1 below.*

6.9.1 Control parameters choice

The application of the control law from equation (6.133), obtained from the exact input-output linearization strategy, makes the closed-loop dynamics of the normalized infected population be given by equation (6.134). Such a dynamics depends on the

control parameters λ_0 and λ_1 . Such parameters have to be appropriately chosen in order to guarantee the following suitable properties:

- i) the stability and positivity of the controlled SIRS model,
- ii) the eradication of the infection, i.e., the asymptotic convergence of $i(t)$ to zero as time tends to infinity and
- iii) the non-negativity of the vaccination function for all time.

The following theorems related to the choice of the controller tuning parameters in order to meet such properties are proven.

Proposition 6.29. *Assume that the initial condition $x(0) = [i(0) \ s(0)]^T \in \mathbb{R}_{0+}^2$ fulfills $i(0) \in [0, 1]$, $s(0) \in [0, 1]$ and $i(0) + s(0) \in [0, 1]$. Moreover, both roots p_1 and p_2 of the characteristic polynomial $P(s)$ associated with the closed-loop dynamics from equation (6.134) are of strictly negative real part via an appropriate choice of the free-design controller parameters λ_0 and λ_1 . Then, the control law from equation (6.133) guarantees the exponential stability of the transformed controlled SIRS model from equations (6.131)-(6.132).*

Moreover, the normalized SIRS model from (6.125)-(6.127) has the following properties: $i(t)$, $s(t)i(t)$ and $s(t) + r(t)$ are bounded for all time, $i(t) \rightarrow 0$, $s(t) + r(t) \rightarrow 1$ and $s(t)i(t) \rightarrow 0$ exponentially as $t \rightarrow \infty$, and $i(t) = o(1/s(t))$.

Proof.

The dynamics of the normalized controlled SIRS model from equation (6.134) can be equivalently written with the state equation from (6.136) and the output equation $y(t) = C\bar{x}(t)$, where $C = [1 \ 0]$, by taking into account that $y(t) = \bar{i}(t)$ and $\dot{y}(t) = \bar{s}(t)$. The initial condition $\bar{x}(0) = [\bar{i}(0) \ \bar{s}(0)]^T$ in such a realization is bounded, since it is related to $x(0)$ via the coordinate transformation from equation (6.130), and $x(0)$ is bounded. Such a controlled model is exponentially stable since the eigenvalues of the matrix A are the roots p_1 and p_2 of $P(s)$, which are assumed to be in the open left-half complex plane. Then, the state vector $\bar{x}(t)$ exponentially converges to zero as $t \rightarrow \infty$, while being bounded for all time. It implies that $i(t)$ is bounded for all time and converges exponentially to zero as $t \rightarrow \infty$ from the boundedness and exponential convergence to zero of $\bar{x}(t)$ as $t \rightarrow \infty$, since $i(t) = \bar{i}(t)$. Furthermore, the boundedness of $s(t) + r(t)$ for all time and its exponential convergence to unity as $t \rightarrow \infty$ are derived from the boundedness of $i(t)$, the exponential convergence to zero of $i(t)$ as $t \rightarrow \infty$ and the fact that $i(t) + s(t) + r(t) = 1 \ \forall t \in \mathbb{R}_{0+}$.

Finally, from the second equation of (6.130), it follows that $i(t)s(t)$ is bounded and it exponentially converges to zero as $t \rightarrow \infty$ from the boundedness and exponential convergence to zero of $i(t)$ and $\bar{x}(t)$ as $t \rightarrow \infty$. The facts that $i(t) \rightarrow 0$ and $s(t)i(t) \rightarrow 0$ as $t \rightarrow \infty$ imply directly that $i(t) = o(1/s(t))$. \square

Proposition 6.30. *Assume that the parameters and the initial condition of a SIRS*

epidemic model describing the propagation of an epidemic disease satisfy that:

$$\begin{aligned} N(0) > 0; \beta > \max\{\nu + \gamma, 2\rho\gamma\}; 0 < \frac{\nu + \gamma(1 - \rho i(0))}{\beta} < s(0) \leq 1 \\ 0 \leq i(0) < \min\left\{\frac{\beta - \nu - \gamma}{\beta - \rho\gamma}, \frac{(\beta - \nu - \gamma)(\nu + \omega)}{(\beta - \rho\gamma)(\nu + \gamma + \omega) - \rho\gamma\nu}\right\} < 1 \end{aligned} \quad (6.138)$$

If a vaccination strategy based on the control law from equation (6.133) with the tuning parameters λ_0 and λ_1 chosen such that the poles p_1 and p_2 of the controlled normalized system are reals and satisfy:

$$\begin{aligned} -(\nu + \gamma(1 - \rho\epsilon i(0))) < p_1 < \min\{0, \mu - \nu\}; \\ p_2 = \frac{1}{\epsilon - 1}(\epsilon p_1 + \nu + \gamma - \beta s(0) - \rho\gamma i(0)) < p_1 \end{aligned} \quad (6.139)$$

for some real parameter $\epsilon \in (1, \epsilon_{max})$ where the upper bound is given by:

$$\epsilon_{max} = \min\left\{\frac{\nu + \gamma}{\rho\gamma i(0)}, \frac{\beta s(0) + \rho\gamma i(0)}{p_1 + \nu + \gamma}, \bar{\epsilon}_1(p_1), \bar{\epsilon}_2(p_1)\right\} \quad (6.140)$$

with:

$$\begin{aligned} \bar{\epsilon}_1(p_1) &= \begin{cases} \frac{(\beta s(0) + \rho\gamma i(0) - \nu - \gamma)p_1 - g_1(\cdot)}{p_1^2 - g_1(\cdot)}; & \text{if } p_1^2 < g_1 \\ \infty & \text{otherwise;} \end{cases} \\ \bar{\epsilon}_2(p_1) &= \begin{cases} \frac{g_2(\cdot)(\beta s(0) + \rho\gamma i(0) - \nu - \gamma)}{g_2(\cdot)p_1 + (\beta s(0) + \rho\gamma i(0) - \nu - \gamma - p_1)g_3(\cdot)i(0)}; & \text{if } p_1 > -\frac{g_3(\cdot)i(0)(\beta s(0) + \rho\gamma i(0) - \nu - \gamma)}{g_2(\cdot) - g_3(\cdot)i(0)} \\ \infty & \text{otherwise} \end{cases} \end{aligned} \quad (6.141)$$

where

$$\begin{aligned} g_1(\beta, \nu, \gamma, \rho) &= \beta(\beta - \nu - 2\rho\gamma) + \rho\gamma(\nu + \gamma) \\ g_2(\beta, \nu, \gamma, \rho) &= (\beta - \nu - \gamma)(\nu + \omega) \\ g_3(\beta, \nu, \gamma, \rho) &= (\beta - \rho\gamma)(\nu + \gamma + \omega) - \rho\gamma\nu \end{aligned}$$

then:

- i) The normalized populations are non-negative $\forall t \in \mathbb{R}_{0+}$, i.e., $0 \leq i(t) \leq 1$, $0 \leq s(t) \leq 1$ and $0 \leq r(t) \leq 1$, $\forall t \in \mathbb{R}_{0+}$,
- ii) the populations $I(t), S(t), R(t)$ and $N(t)$ are non-negative $\forall t \in \mathbb{R}_{0+}$,
- iii) the epidemics is eradicated from the population, i.e., $I(t)$ tends asymptotically to zero as $t \rightarrow \infty$ and
- iv) the vaccination control function is non-negative $\forall t \in \mathbb{R}_{0+}$, i.e., $u(t) = V(t) \geq 0 \forall t \in \mathbb{R}_{0+}$.

Proof.

i) The dynamics of the normalized controlled SIRS model from (6.134) can be equivalently written with the state equation (6.136) and the output equation $y(t) = C\bar{x}(t)$, where $C = [1 \ 0]$, by taking into account that $y(t) = \bar{i}(t)$ and $\dot{y}(t) = \bar{s}(t)$. From such realization and taking into account the first equation (6.130) it follows that:

$$i(t) = \bar{i}(t) = y(t) = c_1 e^{p_1 t} + c_2 e^{p_2 t} \quad (6.142)$$

$\forall t \in \mathbb{R}_{0+}$ for some constants c_1 and c_2 being dependent on the initial conditions $y(0) = \bar{i}(0)$ and $\dot{y}(0) = \bar{s}(0)$, and where p_1 and p_2 denote the eigenvalues of A , i.e., the roots of the characteristic polynomial $P(s) = s^2 + \lambda_1 s + \lambda_0$, which may be fixed to desired values by appropriately adjusting the control parameters λ_1 and λ_0 . The values $\bar{i}(0)$ and $\bar{s}(0)$ are related to the initial conditions of the normalized SIRS model in its original realization, i.e., in the state space defined by $x(t) = [i(t) \ s(t)]^T$ via equation (6.130). In this way, the constants c_1 and c_2 can be obtained by solving the following set of linear equations:

$$\begin{aligned} y(0) &= \bar{i}(0) = c_1 + c_2 = i(0); \\ \dot{y}(0) &= \bar{s}(0) = c_1 p_1 + c_2 p_2 = -(\nu + \gamma)i(0) + \beta s(0)i(0) + \rho \gamma i^2(0) \end{aligned} \quad (6.143)$$

where equations (6.130) and (6.142) have been used. One obtains directly from equation (6.143) and by taking into account the assignment of p_2 in (6.139) that:

$$c_1 = \frac{\beta s(0)i(0) + \rho \gamma i^2(0) - (p_2 + \nu + \gamma)i(0)}{p_1 - p_2} = \epsilon i(0), \quad c_2 = i(0) - c_1 = (1 - \epsilon)i(0) \quad (6.144)$$

Then, it follows from equations (6.142) and (6.144) that:

$$i(t) = \epsilon i(0) (e^{p_1 t} - e^{p_2 t}) + i(0) e^{p_2 t} \geq 0 \quad \forall t \in \mathbb{R}_{0+} \quad (6.145)$$

since $e^{p_1 t} - e^{p_2 t} \geq 0 \ \forall t \in \mathbb{R}_{0+}$ as the constraints from equations (6.138)-(6.140) says that $p_2 < p_1 < 0$. From equations (6.130), (6.142), (6.144) and the facts that $\bar{s}(t) = \dot{y}(t)$ and $0 \leq i(t) \leq \epsilon i(0) e^{p_1 t}$, which implies that $0 \leq i^2(t) \leq \epsilon^2 i^2(0) e^{2p_1 t} \leq \epsilon^2 i^2(0) e^{p_1 t}$ since $p_1 < 0$, it follows that:

$$\begin{aligned} \beta s(t)i(t) &= \bar{s}(t) + (\nu + \gamma)i(t) - \rho \gamma i^2(t) \geq \epsilon i(0) (p_1 + \nu + \gamma - \rho \gamma \epsilon i(0)) e^{p_1 t} \\ &+ (1 - \epsilon) i(0) (p_2 + \nu + \gamma) e^{p_2 t} \geq 0 \end{aligned} \quad (6.146)$$

$\forall t \in \mathbb{R}_{0+}$, since $p_1 + \nu + \gamma - \rho \gamma \epsilon i(0) \geq 0$ from equation (6.139), $\epsilon > 1$ and:

$$p_2 + \nu + \gamma = \frac{\epsilon (p_1 + \nu + \gamma) - \beta s(0) - \rho \gamma i(0)}{\epsilon - 1} < 0 \quad (6.147)$$

by taking into account equation (6.139) and the fact that $\epsilon < \frac{\beta s(0) + \rho \gamma i(0)}{p_1 + \nu + \gamma}$ from equation (6.140). The fact that $i(t) \geq 0 \ \forall t \in \mathbb{R}_{0+}$ and equation (6.146) implies that $s(t) \geq 0 \ \forall t \in \mathbb{R}_{0+}$, since $\beta > 0$. From the fact that $i(t) + s(t) + r(t) = 1 \ \forall t \in \mathbb{R}_{0+}$ and equation (6.130), it follows that:

$$r(t) = 1 - i(t) - s(t) = \frac{(\beta - \nu - \gamma)i(t) - (\beta - \rho \gamma)i^2(t) - \bar{s}(t)}{\beta i(t)} \quad (6.148)$$

$\forall t \in \mathbb{R}_{0+}$, and then:

$$\begin{aligned} \beta i(t)r(t) &= (\beta - \nu - \gamma)i(0) (\epsilon e^{p_1 t} + (1 - \epsilon)e^{p_2 t}) \\ &- (\beta - \rho \gamma)i^2(0) (\epsilon e^{p_1 t} + (1 - \epsilon)e^{p_2 t})^2 - i(0) (p_1 \epsilon e^{p_1 t} + p_2 (1 - \epsilon)e^{p_2 t}) \end{aligned} \quad (6.149)$$

$\forall t \in \mathbb{R}_{0+}$ by taking into account equations (6.142), (6.144) and that $\bar{s}(t) = \frac{d}{dt}(i(t))$. By introducing the expression from equation (6.139) for p_2 in (6.149), one obtains that:

$$\beta i(t)r(t) = f_1(t) - f_2(t) - f_3(t) \quad (6.150)$$

$\forall t \in \mathbb{R}_{0+}$ where:

$$\begin{aligned} f_1(t) &= \epsilon(\beta - \nu - \gamma - p_1) i(0) e^{p_1 t} \\ f_2(t) &= ((\epsilon - 1)\beta + \beta s(0) + \rho\gamma i(0) - \epsilon(\nu + \gamma + p_1)) i(0) e^{p_2 t} \\ f_3(t) &= (\beta - \rho\gamma) i^2(0) (\epsilon e^{p_1 t} + (1 - \epsilon) e^{p_2 t})^2 \end{aligned} \quad (6.151)$$

Note that $f_i(t) \geq 0 \forall t \in \mathbb{R}_{0+}$, for $i \in \{1, 2, 3\}$, from equations (6.138)-(6.140), and that all of them are monotone decreasing functions which exponentially decrease to zero as time tends to infinity since $p_2 < p_1 < 0$. Moreover, both f_2 and f_3 decrease faster than f_1 so that the initial constraint $f_1(0) - f_2(0) - f_3(0) = \beta i(0)r(0) \geq 0$ implies that $f_1(t) - f_2(t) - f_3(t) = \beta i(t)r(t) \geq 0 \forall t \in \mathbb{R}_{0+}$. Then, $r(t) \geq 0 \forall t \in \mathbb{R}_{0+}$ is deduced from the fact that $i(t) \geq 0 \forall t \in \mathbb{R}_{0+}$ as it was previously proven. Finally, the facts that $i(t) \geq 0$, $r(t) \geq 0$, $s(t) \geq 0$ and $i(t) + r(t) + s(t) = 1 \forall t \in \mathbb{R}_{0+}$ directly imply that $0 \leq i(t) \leq 1$, $0 \leq s(t) \leq 1$ and $0 \leq r(t) \leq 1 \forall t \in \mathbb{R}_{0+}$.

ii) From equation (6.123) it follows that:

$$\begin{aligned} \frac{\dot{N}(t)}{N(t)} = \nu - \mu - \rho\gamma i(t) &\rightarrow d[\ln(N(t))] = (\nu - \mu - \rho\gamma i(t)) dt \\ &\rightarrow N(t) = N(0) e^{(\nu - \mu)t - \rho\gamma \int_0^t i(\tau) d\tau} \end{aligned} \quad (6.152)$$

so the total population $N(t) \geq 0 \forall t \in \mathbb{R}_{0+}$ since $N(0) > 0$. Then, $0 \leq I(t) \leq N(t)$, $0 \leq S(t) \leq N(t)$ and $0 \leq R(t) \leq N(t) \forall t \in \mathbb{R}_{0+}$ from equation (6.124) taking into account that $0 \leq i(t) \leq 1$, $0 \leq s(t) \leq 1$ and $0 \leq r(t) \leq 1 \forall t \in \mathbb{R}_{0+}$.

iii) From equations (6.124), (6.142) and (6.152) it follows that:

$$\begin{aligned} I(t) &= N(0) i(0) (\epsilon e^{p_1 t} + (1 - \epsilon) e^{p_2 t}) \\ &\cdot \exp \left\{ (\nu - \mu)t - \rho\gamma i(0) \left(\frac{\epsilon}{p_1} (e^{p_1 t} - 1) + \frac{1 - \epsilon}{p_2} (e^{p_2 t} - 1) \right) \right\} \quad \forall t \in \mathbb{R}_{0+} \end{aligned} \quad (6.153)$$

and then:

$$\lim_{t \rightarrow \infty} \{I(t)\} = N(0) i(0) e^{\rho\gamma i(0) \frac{\epsilon(p_2 - p_1) + p_1}{p_1 p_2}} \lim_{t \rightarrow \infty} \{(\epsilon e^{p_1 t} + (1 - \epsilon) e^{p_2 t}) e^{(\nu - \mu)t}\} \quad (6.154)$$

As a consequence, the infected population tends exponentially to zero as time tends to infinity, and then the infection is eradicated from the host population, since $p_2 < p_1 < 0$ and $p_1 < \mu - \nu$ from equation (6.139).

iv) The control law from equation (6.133) can be equivalently written as:

$$u(t) = \frac{\phi(\bar{x}(t)) + \lambda_0 \bar{i}(t) + \lambda_1 \bar{s}(t)}{\beta \nu \bar{i}(t)} \quad (6.155)$$

in the state space defined by $\bar{x}(t) = [\bar{i}(t) \ \bar{s}(t)]^T$. One can obtain by direct calculations, and taking into account equation (6.132), that:

$$\begin{aligned} u(t) &= \frac{1}{\beta\nu\bar{i}^2(t)} \{(\beta - \nu - \gamma)(\nu + \omega)\bar{i}^2(t) - (\nu + \omega)\bar{i}(t)\bar{s}(t) \\ &\quad - [(\beta - \rho\gamma)(\nu + \gamma + \omega) - \rho\gamma\nu]\bar{i}^3(t) - (\beta - 2\rho\gamma)\bar{s}(t)\bar{i}^2(t) \\ &\quad + \bar{s}^2(t) + \rho\gamma(\beta - \rho\gamma)\bar{i}^4 + \lambda_0\bar{i}^2(t) + \lambda_1\bar{s}(t)\bar{i}(t)\} \end{aligned} \quad (6.156)$$

The normalized infected population $\bar{i}(t)$ presents a unique maximum value at the time instant t^* when $\dot{\bar{i}}(t^*) = \dot{\bar{s}}(t^*) = 0$ as it can be deduced from equation (6.145). Furthermore, from equations (6.130) and (6.138), the fact that $\dot{\bar{i}}(0) = \dot{\bar{s}}(0) = i(0)[\beta s(0) + \rho\gamma i(0) - \nu - \gamma] > 0$ is implied. As a consequence, one knows that $\bar{s}(t) > 0 \ \forall t \in [0, t^*)$ and $\bar{s}(t) \leq 0 \ \forall t \in [t^*, \infty)$. In the following the proof of the non-negativity of $u(t)$ is split into two parts. First, when $\bar{s}(t) > 0$, i.e., $\forall t \in [0, t^*)$, one can deduce that:

$$\begin{aligned} u(t) &\geq \frac{1}{\beta\nu\bar{i}^2(t)} \{ \lambda_0\bar{i}^2(t)\lambda_1\bar{s}(t)\bar{i}(t) + \bar{s}^2(t) \\ &\quad - [\beta(\beta - \nu - 2\rho\gamma) + \rho\gamma(\nu + \gamma)]\bar{i}^3(t) + (\beta - \rho\gamma)^2\bar{i}^4(t) \} \end{aligned} \quad (6.157)$$

by taking into account that $-\bar{s}(t) \geq (\beta - \rho\gamma)\bar{i}^2(t) - (\beta - \nu - \gamma)\bar{i}(t)$ from equation (6.148) and the facts that $r(t) \geq 0$, $i(t) = \bar{i}(t) \geq 0 \ \forall t \in \mathbb{R}_{0+}$ and $\beta > 2\rho\gamma$ from equation (6.138). From equation (6.157), if $g_1(\beta, \nu, \gamma, \rho) = \beta(\beta - \nu - 2\rho\gamma) + \rho\gamma(\nu + \gamma) \leq 0$ then $u(t) > 0 \ \forall t \in [0, t^*)$. Otherwise, it follows that:

$$\begin{aligned} u(t) &> \frac{1}{\beta\nu\bar{i}^2(t)} \{ [p_1 p_2 - g_1(\cdot)]\bar{i}^2(t) + \lambda_1\bar{s}(t)\bar{i}(t) + \bar{s}^2(t) + (\beta - \rho\gamma)^2\bar{i}^4(t) \} \\ &= \frac{1}{\beta\nu\bar{i}^2(t)} \left\{ \frac{[p_1^2 - g_1(\cdot)]\epsilon - p_1[\beta s(0) + \rho\gamma i(0) - \nu - \gamma] + g_1(\cdot)\bar{i}^2(t)}{\epsilon - 1} \right. \\ &\quad \left. + \lambda_1\bar{s}(t)\bar{i}(t) + \bar{s}^2(t) + (\beta - \rho\gamma)^2\bar{i}^4(t) \right\} \end{aligned} \quad (6.158)$$

where $\lambda_0 = p_1 p_2$ and equation (6.139) have been used. From equation (6.158), if $p_1^2 \geq g_1(\cdot)$ then $u(t) > 0 \ \forall t \in [0, t^*)$ since $p_1 < 0$, $\epsilon > 1$ and $\beta s(0) + \rho\gamma i(0) - \nu - \gamma > 0$ from equation (6.138). Otherwise, from equation (6.158) it follows that:

$$u(t) > \frac{1}{\beta\nu\bar{i}^2(t)} \{ \lambda_1\bar{s}(t)\bar{i}(t) + \bar{s}^2(t) + (\beta - \rho\gamma)^2\bar{i}^4(t) \} > 0 \ \forall t \in [0, t^*) \quad (6.159)$$

by using the upper-bound $\bar{\epsilon}_1(p_1)$ defined in equation (6.141). In summary, $u(t) > 0 \ \forall t \in [0, t^*)$ irrespective of the value of $g_1(\cdot)$ and p_1 whenever p_1 and ϵ satisfy equations (6.139) and (6.140).

Now, when $\bar{s}(t) \leq 0$, i.e., $\forall t \in [t^*, \infty)$, from equation (6.156) one obtains that:

$$u(t) \geq \frac{1}{\beta\nu\bar{i}^2(t)} \{ (\beta - \nu - \gamma)(\nu + \omega)\bar{i}^2(t) - [(\beta - \rho\gamma)(\nu + \omega + \gamma) - \rho\gamma\nu]\bar{i}^3(t) + \bar{s}^2(t) + \lambda_0\bar{i}^2(t) + \lambda_1\bar{s}(t)\bar{i}(t) \} \quad (6.160)$$

where $\beta > 2\rho\gamma$ from equation (6.138) has been used. By direct calculations, it follows that:

$$\bar{s}^2(t) + \lambda_0\bar{i}^2(t) + \lambda_1\bar{s}(t)\bar{i}(t) = \epsilon(\epsilon - 1)(p_1 - p_2)^2\bar{i}^2(t)e^{(p_1+p_2)t} \geq 0 \quad (6.161)$$

$\forall t \in [t^*, \infty)$, where $\lambda_0 = p_1 p_2$, $\lambda_1 = -(p_1 + p_2)$, $\epsilon > 1$, equation (6.145) and $\dot{i}(t) = \bar{s}(t)$ have been used. Then, from equation (6.160):

$$\begin{aligned} u(t) &\geq \frac{1}{\beta\nu} \{(\beta - \nu - \gamma)(\nu + \omega) - [(\beta - \rho\gamma)(\nu + \gamma + \omega) - \rho\gamma\nu]\bar{i}(t)\} \quad (6.162) \\ &= \frac{1}{\beta\nu} [g_2(\cdot) - g_3(\cdot)\bar{i}(t)] \quad \forall t \in [t^*, \infty) \end{aligned}$$

where equation (6.141) has been used. If $g_3(\cdot) \leq 0$ then $u(t) \geq \frac{(\beta - \nu - \gamma)(\nu + \omega)}{\beta\nu} > 0 \quad \forall t \in [t^*, \infty)$ from equation (6.162) by using the fact that $\beta > \nu + \gamma$ from equation (6.138). Otherwise, i.e., if $g_3(\cdot) > 0$ then $h(t) = g_2(\cdot) - g_3(\cdot)\bar{i}(t)$ reaches its minimum value at the time instant t^* when $\bar{i}(t) = i(t)$ reaches its maximum value. Such a minimum value is given by:

$$h(t^*) = g_2(\cdot) - g_3(\cdot)i(0)[\epsilon e^{p_1 t^*} + (1 - \epsilon)e^{p_2 t^*}] = g_2(\cdot) - g(\cdot)i(0)\epsilon \left(1 - \frac{p_1}{p_2}\right) e^{p_1 t^*} \quad (6.163)$$

where the fact that $e^{p_2 t^*} = \frac{\epsilon p_1}{(\epsilon - 1)p_2} e^{p_1 t^*}$ since $\dot{i}(t^*) = \bar{s}(t^*) = 0$ has been used. From introducing the relation between p_1 and p_2 of equation (6.139) in (6.163), one obtains:

$$\begin{aligned} h(t^*) &\geq g_2(\cdot) - g_3(\cdot)i(0)\epsilon \frac{\beta s(0) + \rho\gamma i(0) - \nu - \gamma - p_1}{\beta s(0) + \rho\gamma i(0) - \nu - \gamma - \epsilon p_1} \\ &= \frac{p_1 [g_2(\cdot) - g_3(\cdot)i(0)]\epsilon}{\beta s(0) + \rho\gamma i(0) - \nu - \gamma - \epsilon p_1} \quad (6.164) \\ &\quad + \frac{[\beta s(0) + \rho\gamma i(0) - \nu - \gamma]g_2(\cdot) - \epsilon g_3(\cdot)i(0)[\beta s(0) + \rho\gamma i(0) - \nu - \gamma]}{\beta s(0) + \rho\gamma i(0) - \nu - \gamma - \epsilon p_1} \end{aligned}$$

If $p_1 \leq \frac{g_3(\cdot)i(0)[\nu + \gamma - \beta s(0) - \rho\gamma i(0)]}{g_2(\cdot) - g_3(\cdot)i(0)}$ then $h(t) \geq h(t^*) \geq \frac{\beta s(0) + \rho\gamma i(0) - \nu - \gamma}{\beta s(0) + \rho\gamma i(0) - \nu - \gamma - \epsilon p_1} g_2(\cdot) > 0 \quad \forall t \in [t^*, \infty)$ for any $\epsilon > 1$, where the facts that $p_1 < 0$, $\beta s(0) + \rho\gamma i(0) - \nu - \gamma > 0$ and $g_2(\cdot) - g_3(\cdot)i(0) > 0$ from equations (6.138)-(6.139) have been used. Otherwise, i.e., if $\frac{g_3(\cdot)i(0)[\nu + \gamma - \beta s(0) - \rho\gamma i(0)]}{g_2(\cdot) - g_3(\cdot)i(0)} < p_1 < 0$, then $h(t) \geq h(t^*) > 0 \quad \forall t \in [t^*, \infty)$ from using the upper-bound $\bar{\epsilon}_2(p_1)$ defined in equation (6.141) for ϵ . In summary, $u(t) > 0 \quad \forall t \in [t^*, \infty)$ irrespective of the value of $g_3(\cdot)$ whenever p_1 and ϵ satisfy the constraints in equations (6.139) and (6.140). This fact completes the proof that $u(t) > 0 \quad \forall t \in \mathbb{R}_{0+}$ irrespective of the values for $g_1(\cdot)$ and $g_3(\cdot)$ if p_1 and ϵ satisfy the constraints in equations (6.139) and (6.140). \square

Remark 6.31. *The constraints in equations (6.138) relative to the initial conditions and the parameters of the SIRS model are fulfilled for the majority of the epidemic diseases. On one hand, the disease transmission constant β is usually much higher than both the birth rate ν and the recovery rate γ so that the constraint about β in equations (6.138) can be considered. On the other hand, at the beginning of the infection propagation the number of infected individuals is usually small enough and the almost population is susceptible so that the conditions in equations (6.138) relative to $i(0)$ and $s(0)$ are satisfied.*

Remark 6.32. *The process to select the desired poles p_1 and p_2 , via a suitable choice of ϵ , is the following. First, once one knows or has estimated the values for the parameters ν, β, ω, ρ and γ corresponding to the propagation of a specific epidemics, a value for p_1 such that $-(\nu + \gamma) < p_1 < 0$ is chosen. Then, the upper bounds in equations (6.140)-(6.141) for the parameter ϵ can be computed in order to choose a value for ϵ satisfying $\epsilon \in (1, \epsilon_{max})$.*

6.10 Simulation results of the SIRS model

An example based on the rabbit hemorrhagic disease in United Kingdom is considered to illustrate the theoretical results presented in the paper [51]. An initial population of $N(0) = 1000$ rabbits is used. Such an epidemics can be described by the SIRS model from equations (6.120)-(6.123) with the parameter values:

$$\begin{aligned} \mu &= 0.01 \text{ days}^{-1}, & \nu &= 0.017 \text{ days}^{-1} \\ \beta &= 0.936 \text{ days}^{-1}, & \omega &= 0.0333 \text{ days}^{-1} \\ \gamma &= 0.0125 \text{ days}^{-1} & \text{and } \rho &= 0.9314 \end{aligned}$$

Such values are commonly used in the literature [51], [1]. The main characteristic of such an infection is its high mortality, note the value of the probability of dying from the infection ($\rho = 0.9314$) close to 1. The initial conditions for the individual populations are given by: $S(0) = 990$, $I(0) = 10$ and $R(0) = 0$. Two sets of simulation results are presented to compare the time evolution of the populations within the SIRS mathematical model in two different situations, namely:

- i) when no vaccination control actions are applied and
- ii) when a vaccination based on the described feedback input-output linearization control technique is applied.

6.10.1 Evolution of the disease without vaccination

The time evolution of the system populations in the free-vaccination case, i.e. if $V(t) = 0 \forall t \in \mathbb{R}_{0+}$ is displayed in Figure 6.20. The population of rabbits disappears because of the high mortality of the infection as it can be seen in this figure. As a consequence, a vaccination strategy has to be applied if the eradication of the epidemics is required while guaranteeing the persistence of the rabbits.

6.10.2 Epidemics evolution with a feedback control law

First, note that the considered initial condition and the parameters of the SIRS model for the propagation of the rabbit hemorrhagic disease satisfy the constraints in equations (6.138). Then, the control law given by equations (6.133), or equivalently written

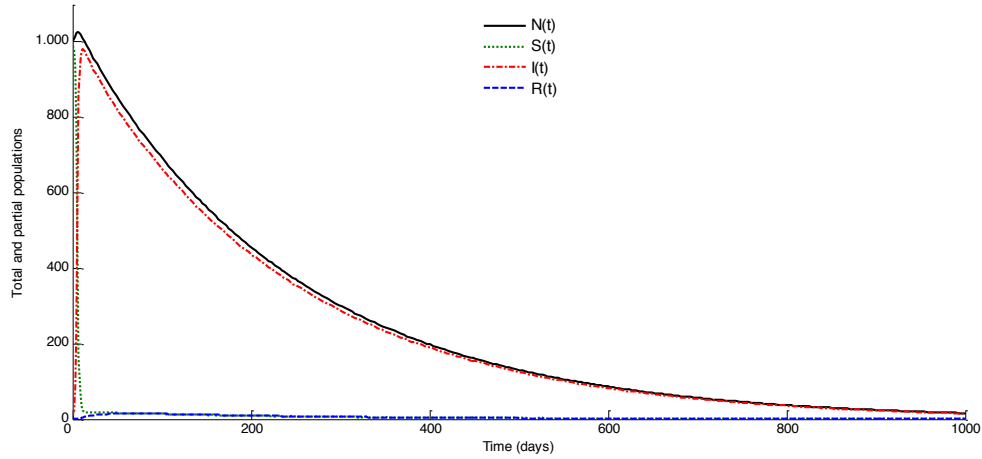


Figure 6.20: Time evolution of the total and partial (susceptible, infected and recovered) populations without vaccination.

as in equation (6.155), can be applied in order to eradicate the epidemics while guaranteeing the non-negativity of the populations and the vaccination control function. The free-design controller parameters $\lambda_0 = p_1 p_2$ and $\lambda_1 = -(p_1 + p_2)$, where p_1 and p_2 are the desired roots for the characteristic polynomial $P(s)$ associated with the closed-loop dynamics, are prefixed in the following way. The desired dominant root p_1 is chosen satisfying the constraint $-(\nu + \gamma) < p_1 < 0$, namely, $p_1 = -\nu = -0.017$. Then, the upper bound in equation (6.140) for the value of ϵ is calculated, namely $\epsilon_{max} = 1.0186$.

The theoretical results developed in Section 6.9 prove that a choice of $\epsilon \in (1, 1.086)$ is sufficient to guarantee the non-negativity of the populations and the vaccination control function in the controlled SIRS model as well as the eradication of the infectious disease. For such purpose, the value $\epsilon = 1.018$ is chosen. Such a choice for p_1 and ϵ determines the value for the root p_2 by the relation in equation (6.139), namely, $p_2 = -50.809$. Also, the values $\lambda_0 = p_1 p_2 = 0.8638$ and $\lambda_1 = -(p_1 + p_2) = 50.826$ for the control law are derived from such a procedure.

The time evolution of the respective populations is displayed in Figures 6.21 and 6.22 while the vaccination control function is shown in Figures 6.23.

The vaccination control action achieves the control objectives as it is seen in Figure 6.21, 6.22 and 6.23. In this sense, the infection is eradicated from the population since the infected population exponentially converges to zero as Figure 6.21 shows. Also, all of the partial populations, the whole population and the vaccination control function are non-negative for all time. Such properties are coherent with the results proved in proposition 6.30. A consequence of the vaccination control action is that the total population of the rabbits monotonically grows through time in a fast way, like it occurs in absence of disease, as it can be seen in Figure 6.22. These simulation results point out the improvement of the use of a vaccination strategy in order to guarantee a suitable growth of the rabbit population against a high mortality infectious disease.

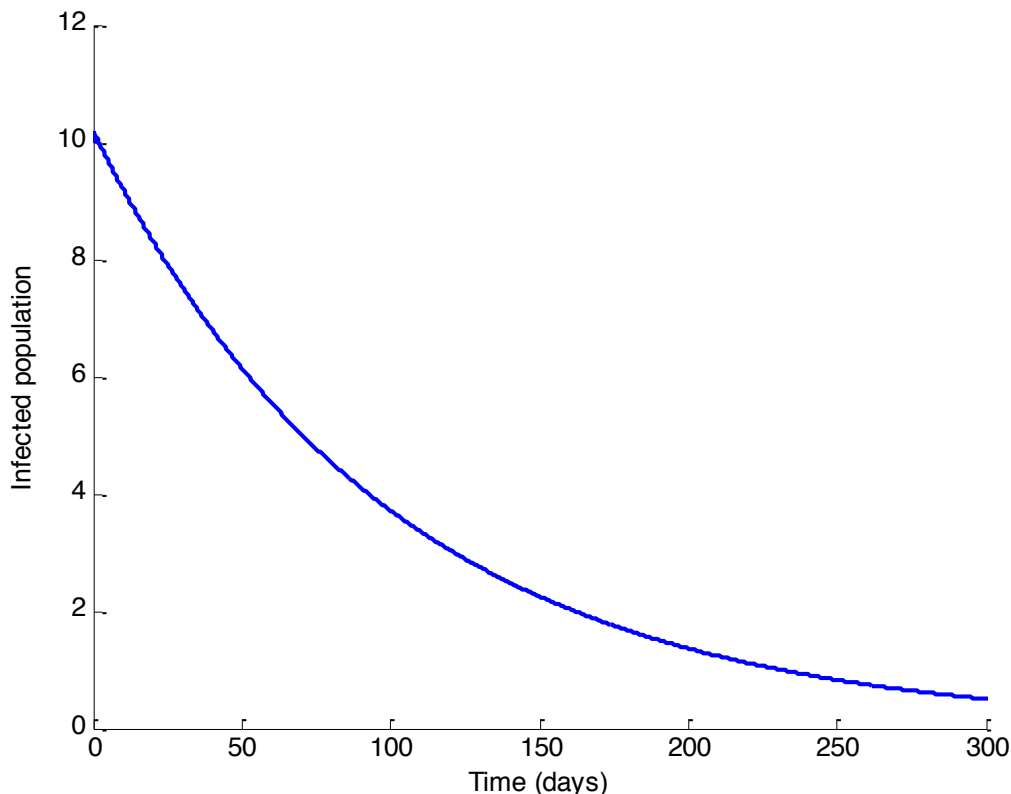


Figure 6.21: Evolution of the infected population with vaccination.

Remark 6.33. *The conditions in proposition 6.30 are sufficient but non necessary to ensure the positivity of the controlled model. Concretely, the upper-bounds $\bar{\epsilon}_1(p_1)$ and $\bar{\epsilon}_2(p_1)$ are sufficient to guarantee the non-negativity of the vaccination function $V(t)$ for all time. However, such upper-bounds can be relaxed in the current example by taking into account the results obtained from an exhaustive simulation work. In such work, the non-negativity of the vaccination control function is maintained for all time although the value of the free design parameter ϵ is not smaller than $\epsilon_{max} = 1.0186$. In this context, the following section analyzes the influence of the parameter ϵ in the controlled system dynamics.*

6.10.3 Influence of the control free-design parameter ϵ in the time evolution of the disease

Again, the rabbit hemorrhagic disease is considered for this study and the same dominant pole is chosen for the controlled system dynamics, namely, $p_1 = -\nu = -0.017$. Four different values for the parameter ϵ are considered, namely, $\epsilon = 1.018$ (which corresponds to the non-dominant pole of the closed-loop dynamics located in $p_2 = -50.809$), $\epsilon_2 = 1.5$ ($p_2 = -1.8455$), $\epsilon_3 = 2$ ($p_2 = -0.9313$) and $\epsilon_4 = 5$ ($p_2 = -0.2456$)

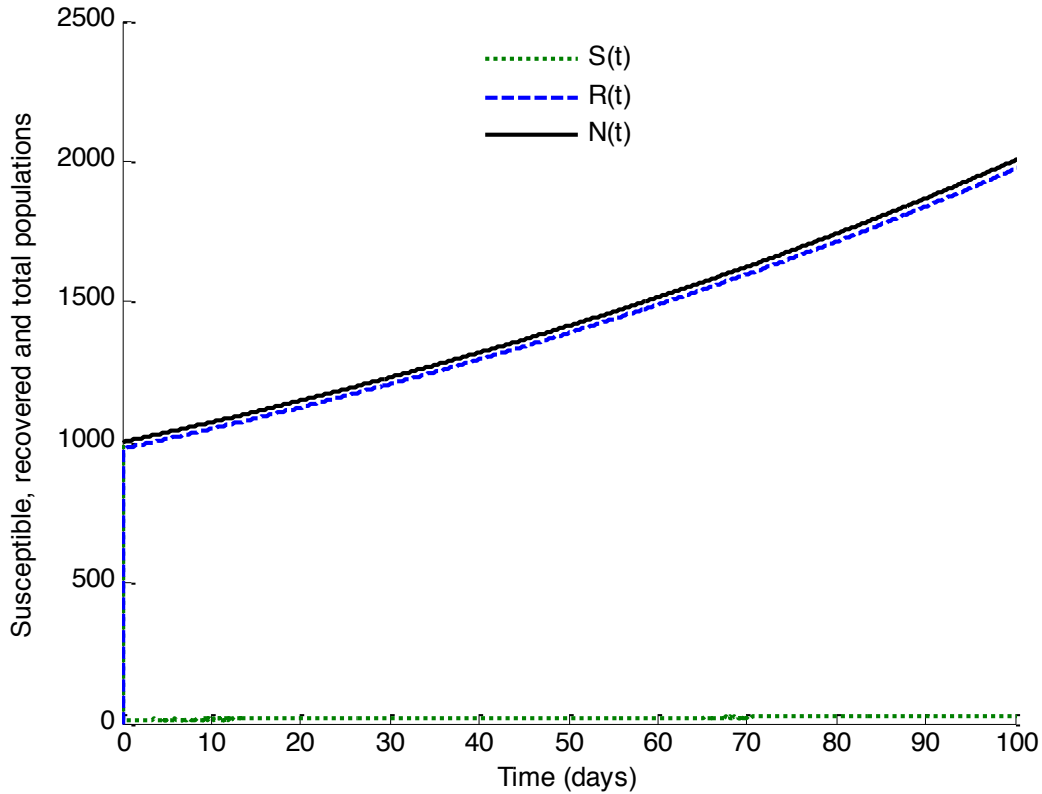


Figure 6.22: Evolution of the susceptible, recovered and total populations with vaccination.

for analyzing the influence of such a parameter, and then the influence of the pole p_2 via the relation in equation (6.139) in the controlled system dynamics. Figures 6.24 display the time evolution of the infected and total populations for the four different values of ϵ . The infected population increases until it reaches a maximum value and then it exponentially decreases to zero as time tends to infinity. Moreover, such a maximum value is smaller and is reached earlier as smaller the parameter ϵ is. In this sense, a value for $\epsilon > 1$ and closed to unity is convenient for a fast eradication of the infection from the host population. On other hand, the influence of ϵ in the time evolution of the total population is less appreciable. The total population exponentially increases in a fast way in all cases. Figures 6.25 display the time evolution of the vaccination control function for the different values of ϵ . One can see that the vaccination control function takes a large value at the initial time instant and then it decreases until reaching a quasi-stationary regime where its value is maintained below a small threshold for any of the considered values of ϵ . The magnitude of the vaccination control function at such an initial time instant is larger as smaller the parameter ϵ is. Moreover, the vaccination control function shows an oscillatory behavior in the quasi-stationary regime if a value of ϵ closed to unity (concretely if $\epsilon = \epsilon_1$) is used while it does not oscillate if $\epsilon \geq 1.5$. As a consequence, a value for

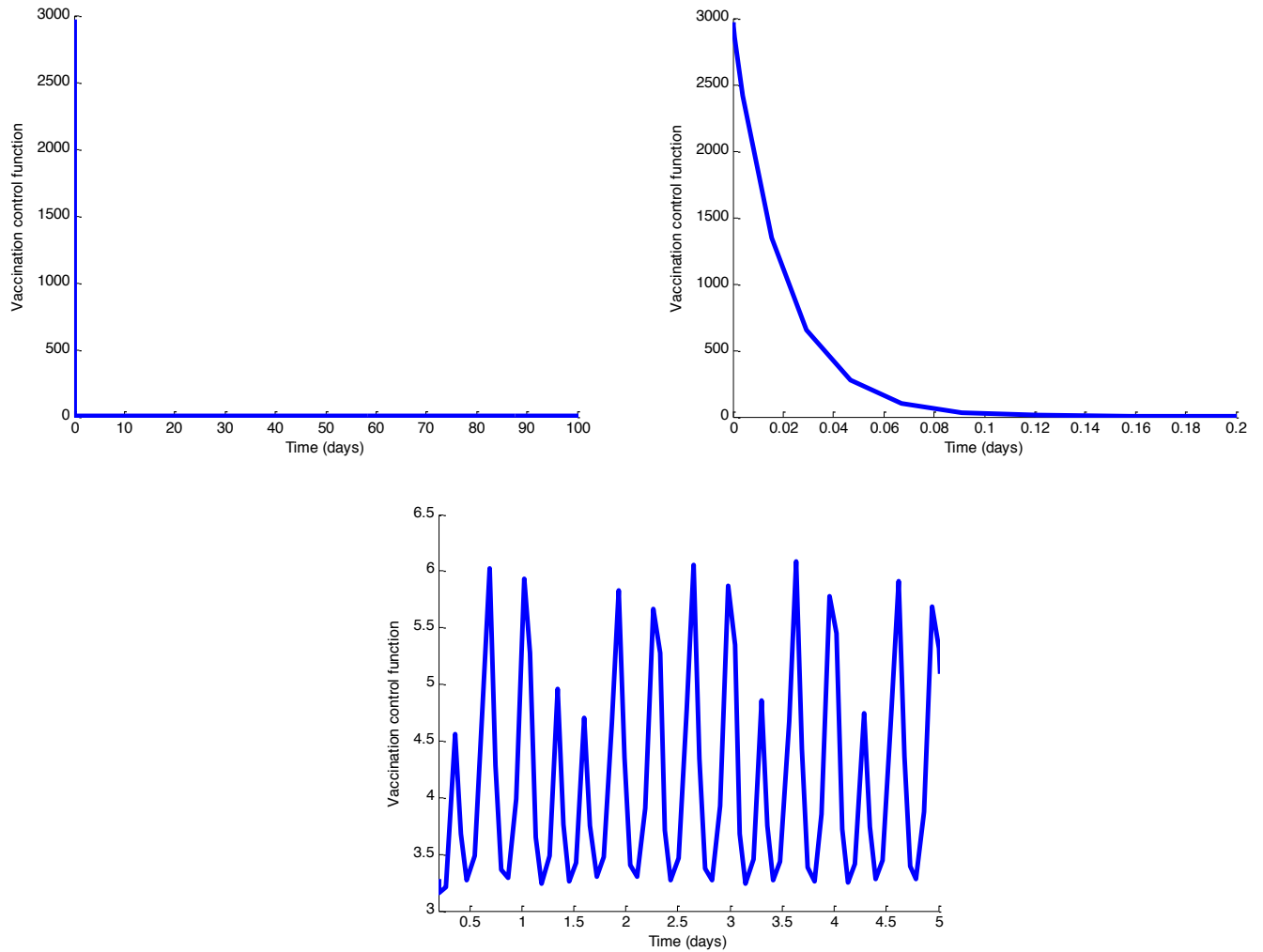


Figure 6.23: Evolution of the vaccination control function in three different time ranges.

ϵ large enough so that the maximum of the vaccination control function does not exceed a prescribed threshold can be interesting in order to minimize the cost of the treatment of the infection by means of vaccines application. However, a large value of ϵ implies a non appropriate time evolution of the infected population as it has been previously discussed in relation to Figures 6.24. As a consequence, a tradeoff between the treatment cost and the evolution of the epidemics has to be taken into account when choosing the value of the parameter ϵ used to generate the vaccination control function.

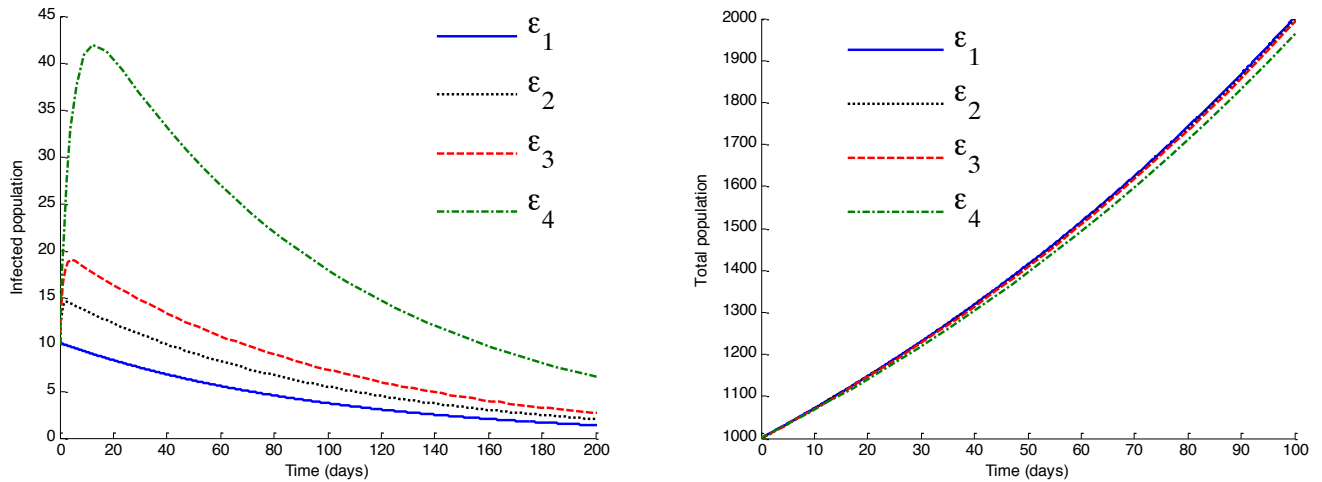


Figure 6.24: Evolution of the infected and total populations with different values of the parameter ϵ used to generate the vaccination function.

6.11 Conclusions

A set of models of diseases spreading over large populations have been established, based indifferent works on the matter. Vaccination control strategies based on feedback input-output linearization, partial stability and observer operators have been proposed to fight against the propagation of these epidemics within the hosts populations. The simulations of the strategies here presented acting on the SEIR and SIRS epidemic models show the different efficiencies of the possible vaccination campaigns overall, in particular the partial stability provides a meaningful analysis of the problem since it only focuses on the behavior of some of the variables (infected and infectious) instead of the complete population. Thus, it can capture the situation when a natural increase of the population occurs which would not lead to a global stability property. In addition, a feedback-type vaccination control law has been designed from the concept of partial stability through adapted Lyapunov-type methods. Since the Lyapunov function is only set up from the exposed and infectious subpopulations, its time-derivate does not contain the vaccination function $V(t)$ so that it has to be indirectly defined through an appropriate definition of a reference value for the susceptible subpopulation.

These theoretical results are complemented with some simulation results to illustrate the operation of the control law and its usefulness. The proposed techniques in this chapter open a new line to design vaccination strategies, where it is not required that the susceptible subpopulation converge to zero to guarantee the eradication of the epidemic disease, but just to stay below a prescribed threshold. Also, as not all the individuals have to be vaccinated, it theoretically provides an economic saving from other approaches. Future researches in the subject are going to deal with the combination of this control technique with the design of an observer to estimate the susceptible and infected populations when their true data are not available as it

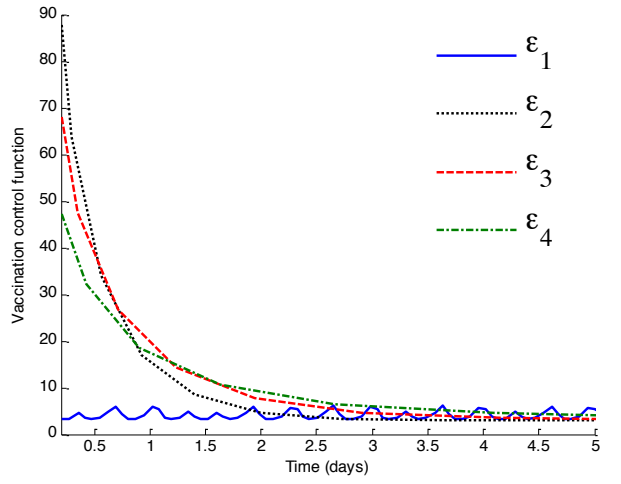
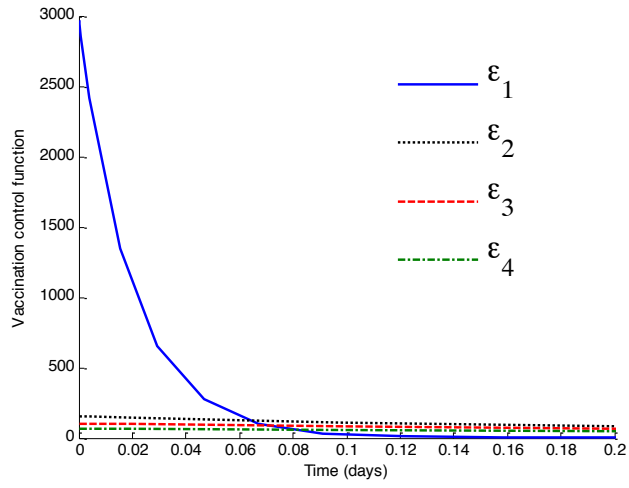


Figure 6.25: Evolution of the vaccination function with different values of the parameter ϵ used to generate the vaccination function

usually occurs in a real situation.

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Conclusions, perspectives and future works

The fact that the computation power used in epidemic simulations is not as demanding as in other types of modelization, such as weather prediction or aerodynamic engineering, proves that this is not a limiting factor for improving our models. There is lots of space in that area to grow. However, the main weakness and/or criticism it can be made to epidemic modelling has always been the lack of good data supporting the model.

The increase of connectivity and personal data collection, on the human side, and the increasingly cheaper sensor for monitoring livestock and nature may bring a change into that. Even though the concerns over the privacy of individuals are rightly raised, our focus centers on the potential benefits of the data acquisition. As a remarkable example, the multinational company Google has recently opened "www.google.com/flutrends" in which the flu activity is linked to the frequency of appearance of certain key words in their search engine. Given the large number of people using google, the data sample is big enough and distributed enough to show, with a good approximation, how many people in that area may be affected by the disease, with the advantage over other monitoring techniques of being at real-time and more source over other techniques of vigilance.

Other examples less ethical conflictive include monitoring of the position, temperature and ph of the digestive tract of a large cattle herd, geo-tagging the movements and dispersion in big animal migrations. Data provided by this new technological advances could be the tipping point of disease dynamic research, and improve significantly the reaction time when fighting an emerging epidemic. Living up to the challenges of the upcoming plagues is not only a matter of social responsibility, but survivalism. Under this situations, the work here presented is a good basis to understand and fight diseases in a world where the flow of data is continuously increasing. We have included most types of infectious diseases, not categorized in any case by biological terms, but by the relation of the affected host to the population. A compendium of all the possible interactions made between individuals suffering from an infectious disease, have been described mathematically, including temporal or permanent immune response, a variable population, different mortality, recovery and infection rate, depending on the chosen characterization. Even more, the counter measures to the spreading of the disease are also integrated in the models so the different vaccination strategies, being it continuous over time or an action in a specific moment, are also represented in this models. The equilibrium points deduced from these models and their stability is analyzed mathematically. After the study through several simulations of the dynamics over time of these models the conclusions suggest that a vaccination strategy adapted with feedback from the quantity of infected and infectious individuals can be more efficient in terms of cost vaccines adminis-

tered over number of infectious people treated. These strategies are compared to the regular ones, in which there is no outside influence on the rate and/or frequency of vaccination. So, given the capabilities of these methods, we consider several proposals to continue with this work in the future:

- To introduce other methods of disease control similar to the ones used to develop vaccination control, such as culling and quarantine, in which a selection of the population is retired from the population instead of being immunized.
- To introduce the concept of migration on the models. The importance of the migration could vary from a simple new parameter representing the introduction of new individuals in the subpopulations to creating a "metapopulation", which is a set of populations, each one with their own dynamic, interacts between each other depending on the spatial analysis of the location of such subpopulations.
- To obtain discrete models based on the given and discussed continuous-time ones. The simple idea is to approximate the left-hand-sides containing first-order derivatives by incremental discrete one-step values associated with a running sampling period. All those models can be analyzed from a point of view of equilibrium points, their stability properties and local and global asymptotic stability properties. A further extension would be to consider different kinds of vaccination laws like constant vaccination or feedback vaccination or even culling-time vaccination. All the relevant suited stability and positivity properties can be obtained and evaluated.
- A second kind of discrete models could be got by using zero-order holds, first-order holds or partial rate corrector holds for vaccination on the continuous-time models. It turns out that these models are distinct from those of the above extension proposal since they imply an external control action with a modified device. For instance, a zero-order hold has the effect of taking a piecewise constant vaccination law being constant in-between sampling instants. The relevant stability and positivity properties can be also discussed for those classes of models and "ad hoc" vaccination laws can be proposed.
- Comparative studies between those kinds of discrete models and the continuous ones counterparts can be performed analytically and through numerical simulation. Note that it can be interesting to use those models so as to decrease computational effort related to their continuous counterparts since the magnitude of the sampling period in this kind of application is not very critical so that it can be chosen rather large, for instance, of the order of days.
- All those discrete models can be revisited and extended in the multi-stage infective context in the guidelines of chapter 5 with a wide comparative study with the single stage and continuous-time counterparts.
- Generalization of all the above studies to time-varying models with eventual time-varying infective rate and seasonal migrations.
- The possible existence and characterization of periodic solutions can be also investigated for those new models for the case when no equilibrium point be

asymptotically stable, for instance, in the context of some time-varying model parameterizations or under periodic infective transmission parameter of the illness.

A series of publications have been derived from this work

"On the Equilibrium Points, Boundedness and Positivity of a Sveirs Epidemic Model under Constant Regular Constrained Vaccination"

Manuel De, La Sen, Asier Ibeas, Santiago Alonso-Quesada, Raul Nistal.
Informatica 01/2011; 22(3):339-370

"An observer-based vaccination law for a SEIR epidemic model"

M. De la Sen, S. Alonso-Quesada, A. Ibeas, R. Nistal.
Proceedings of International Conference on Database and Data Mining (ICDDM 2011); 01/2011.

"On the Equilibrium Points, Boundedness and Positivity of a SVEIRS Epidemic Model Under Constant Regular Vaccination"

M. De la sen, S. Alonso-Quesada, R. Nistal, A. Ibeas.
International Conference on Electrical, Control and Computer Engineering, Pahang; 06/2011.

"Periodic solutions of a generalized SVEIR Epidemic model under impulsive periodic Vaccination"

Raul Nistal, Manuel de la Sen, Santiago Alonso-Quesada.
IASTED Biomedical Engineering Conference; 02/2012.

"Partial stability of controlled SEIR epidemic models"

A. Ibeas, M. de la Sen, S. Alonso-Quesada, R. Nistal.
Control Conference (ECC), 2013 European; 01/2013.

"A vaccination strategy based on linearization control techniques for fighting against epidemic diseases propagation"

Santiago Alonso-Quesada, Manuel De La Sen, Asier Ibeas, Raul Nistal.
Advances in Difference Equations 01/2013; 2013(1):2013:364. DOI:10.1186/1687-1847-2013-364.

"Limit Periodic Solutions of a SEIR Mathematical Model for Non-lethal Infectious Disease"

Raul Nistal, Manuel de la Sen, Santiago Alonso-Quesada.
Applied Mathematical Sciences 01/2013; 7:773-789.

"Periodic equilibrium states in a SEIR mathematical model of an infectious non-lethal disease"

Raul Nistal, Manuel De La Sen, Santiago Alonso-Quesada, Asier Ibeas.
2013 25th Chinese Control and Decision Conference, CCDC 2013, Guiyang; 05/2013.

"On the Periodic Solutions of a Generalized SVEIR Model under Impulsive Vaccination"

R.Nistal, M. De la Sen, S. Alonso-Quesada, A. Ibeas.

Applied Mathematical Sciences 01/2014; 8(15):701-715. DOI:10.12988/ams.2014.312714.

"On a generalized SVEIR epidemic model under regular and adaptive impulsive vaccination"

Raul Nistal, Manuel De La Sen, Santiago Alonso-Quesada, Asier Ibeas.

Nonlinear Analysis: Modelling and Control 01/2014; 19(1):83-108.

"A nonlinear SEIR epidemic model with feedback vaccination control"

Raul Nistal, Manuel De la Sen, Santiago Alonso-Quesada, Asier Ibeas.

13 th European Control Conference, Strasbourg; 06/2014.

"On the Stability and Equilibrium Points of Multistaged SI(n)R Epidemic Models"

Raul Nistal, Manuel De La Sen, Santiago Alonso-Quesada, Asier Ibeas, Aitor J Garrido.

Discrete Dynamics in Nature and Society 01/2015; 2015(1):1-15.

APPENDIX A

Solution trajectory of the SVEIRS model

The solution trajectories of the SVEIRS differential model from equations (2.1)-(2.5) are given below. Equation (2.1) yields:

$$S(t) = e^{-\int_0^t (b + \beta \frac{I(\xi)}{1 + \eta S(\xi)}) d\xi} S(0) + \int_0^t e^{-\int_\xi^t (b + \beta \frac{I(\kappa)}{1 + \eta S(\kappa)}) d\kappa} (\gamma I(\xi - \omega) e^{-b\omega} + \nu(1 - V_c) N(\xi) + b) d\xi \quad (\text{A.1})$$

Equation (2.2) yields:

$$V(t) = e^{-\int_0^t (b + \delta\beta \frac{I(\xi)}{1 + \eta V(\xi)}) d\xi} V(0) + \nu V_c \int_0^t e^{-\int_\xi^t (b + \delta\beta \frac{I(\kappa)}{1 + \eta V(\kappa)}) d\kappa} N(\xi) d\xi \quad (\text{A.2})$$

Equation(2.3) is already in integral form. Equation(2.4) yields:

$$I(t) = e^{-(\gamma + b + \alpha)t} I(0) + \beta e^{-b\tau} \int_0^t e^{(\gamma + b + \alpha)\xi} \left(\frac{S(\xi - \tau)}{1 + \eta S(\xi - \tau)} + \frac{\delta V(\xi - \tau)}{1 + \eta V(\xi - \tau)} \right) I(\xi - \tau) d\xi \quad (\text{A.3})$$

Equation(2.5) yields:

$$R(t) = e^{-bt} \left[R(0) + \int_0^t e^{b\xi} (\gamma_1 V(\xi) + \gamma I(\xi) - I(\xi - \omega) e^{-b\omega}) d\xi \right] \quad (\text{A.4})$$

APPENDIX B

Disease-free equilibrium stability for sufficiently small delays with quotient parameterization

The following alternative result to Proposition 2.3 is based on an existence of the first sufficiently small destabilizing delay size of the linearized system around the equilibrium, provided that the linearized zero-delay model is asymptotically stable around the disease-free equilibrium point.

Proposition B.1. *Assume that $b > \nu$ and*

$$R_{p0} = \beta \left(\frac{b - \nu V_c}{b - \nu + \eta(b - \nu V_c)} + \frac{\delta b \nu V_c}{(b + \gamma_1)(b - \nu) + \eta b \nu V_c} \right) \frac{1}{\gamma + b + \alpha} < 1$$

Then, the SVEIRS epidemic model is locally asymptotically stable around the disease-free equilibrium point for $\tau = \lambda\omega$; $\forall \omega \in [0, \omega^)$, any prefixed $\lambda \in \mathbb{R}_+$ and some $\omega^* \in \mathbb{R}_+$, if the so-called reproduction number satisfies the following constraint:*

$$R_p(\lambda, \omega^*) := \beta e^{-b\lambda\omega^*} \left(\frac{b - \nu V_c}{b - \nu + \eta(b - \nu V_c)} + \frac{\delta b \nu V_c}{(b + \gamma_1)(b - \nu) + \eta b \nu V_c} \right) \frac{1}{\gamma + b + \alpha} < 1$$

For any prefixed, $(\lambda, \omega) \in \mathbb{R}_+^2$, the above property holds for sufficiently small disease transmission constant that satisfies:

$$\beta < e^{b\lambda\omega^*} (\lambda + b + \alpha) \left(\frac{b - \nu V_c}{b - \nu + \eta(b - \nu V_c)} + \frac{\delta b \nu V_c}{(b + \gamma_1)(b - \nu) + \eta b \nu V_c} \right)^{-1}$$

Proof.

Consider the linearized system about the disease-free equilibrium point of state vector $\tilde{x}(t) := \left(\tilde{S}(t), \tilde{V}(t), \tilde{E}(t), \tilde{I}(t), \tilde{R}(t) \right)^T$ characterized in Proposition 2.1 which satisfies the differential system (2.20) which becomes for $x^*(t) = x^*(t - \tau) = x^*(t - \omega)$:

$$\tilde{x}(t) = A^*(t, \omega) \tilde{x}(t) = (A_0^* + A_\tau^* + A_\omega^*) \tilde{x}(t); \quad \tilde{x}(0) = \tilde{x}_0 \quad (\text{B.1})$$

where $A^*(\tau, \omega) = \frac{\partial \tilde{x}}{\partial \tilde{x}^T} \Big|_{(S^*, V^*, 0, 0, R^*)^T}$ is the Jacobian matrix of equations (2.1) (2.5) at the disease-free equilibrium point. Define the delay quotient $\lambda = \tau/\omega$ for $\omega \neq 0$, resulting in $\lambda = \infty$ if $\omega = 0$ and $\tau \neq 0$, with such a definition modified as $\lambda = 0$ if $\tau = \omega = 0$. Then, there is a bijective mapping from the Jacobian matrix $A^*(\tau, \omega)$ to $\overline{A}^*(\lambda, \omega)$, for a such a definition of λ , for any triple $(\tau, \omega, \lambda) \in \mathbb{R}_{0+}^3$ where:

$$\overline{A}^*(\lambda, \omega) := \begin{pmatrix} (1 - V_c)\nu - b & (1 - V_c)\nu & (1 - V_c)\nu & (1 - V_c)\nu - \frac{\beta S^*}{1 + \eta S^*} + \gamma e^{-b\omega} & (1 - V_c)\nu \\ \nu V_c & \nu - (b + \gamma_1) & \nu V_c & \nu V_c - \frac{\delta \beta V^*}{1 + \eta V^*} & \nu V_c \\ 0 & 0 & -b & \beta (1 - e^{-b\omega}) \left(\frac{S^*}{1 + \eta S^*} + \frac{\delta V^*}{1 + \eta V^*} \right) & 0 \\ 0 & 0 & 0 & \beta e^{-b\lambda\omega} \left(\frac{S^*}{1 + \eta S^*} + \frac{\delta V^*}{1 + \eta V^*} \right) - (\gamma + b + \alpha) & 0 \\ 0 & \gamma_1 & 0 & 1 - e^{-b\omega} \gamma & -b \end{pmatrix}$$

The eigenvalues of $\overline{A^*}(\lambda, \omega)$ are:

$$\beta e^{-b\lambda\omega} \left(\begin{array}{c} (-b, -b, -(b + \gamma_1), \nu - b, \\ \frac{(b - \nu V_c)}{b - \nu + \eta(b - \nu V_c)} + \frac{\delta b \nu V_c}{(b + \gamma_1)(b - \nu) + \eta b \nu V_c} - (\gamma + b + \alpha) \end{array} \right)$$

Assume that is a stability matrix so that the above matrix has eigenvalues of negative real parts, i.e. $b > \nu$, and

$$R_p(\lambda, \omega) := \beta e^{-b\lambda\omega} \left(\frac{b - \nu V_c}{b - \nu + \eta(b - \nu V_c)} + \frac{\delta b \nu V_c}{(b + \gamma_1)(b - \nu) + \eta b \nu V_c} \right) \frac{1}{\gamma + b + \alpha} < 1$$

Thus the linearized system about the disease-free equilibrium is asymptotically stable and the nonlinear one is locally asymptotically stable for zero delays $\omega = 0$, $\tau = \lambda\omega = 0$ ($\lambda = 0$). By continuity arguments of the eigenvalues with respect to the parameters, for any prefixed $\lambda \in \mathbb{R}^+$, there exist $\omega^* \in \mathbb{R}^+$ and $\tau^* = \lambda\omega^* \in \mathbb{R}^+$ such that the linearized system about the disease-free equilibrium is asymptotically stable and also the nonlinear one is locally asymptotically stable for $\tau = \lambda\omega$; $\forall \omega \in [0, \omega^*)$, that is if $b > \nu$ and the reproduction number

$$R_p(\lambda, \omega^*) := \frac{\beta e^{-b\lambda\omega^*}}{\gamma + b + \alpha} \left(\frac{b - \nu V_c}{b - \nu + \eta(b - \nu V_c)} + \frac{\delta b \nu V_c}{(b + \gamma_1)(b - \nu) + \eta b \nu V_c} \right) < 1$$

If $R_p(\lambda, \omega^*) \geq 1$ then the linearized system is either critically stable or unstable. \square

Remark B.2.

Note that for small model delays, the disease-free equilibrium stability margin decreases as the transmission constant increases for a given vaccination term. However, the modification of the value of the vaccination effort to a new appropriate value can compensate a certain increase of the transmission constant to still keep the disease-free equilibrium point stability.

APPENDIX C

Allocation of a unique endemic equilibrium point for the vaccination-free case $V_c = 0$

This appendix contains the location of the endemic equilibrium points in the special case corresponding to $V_c = 0$ so that equation (2.7) implies $V^* = 0$. Furthermore, equation (2.9) yields for the endemic point:

$$\frac{\beta e^{-b\tau}}{\gamma + b + \alpha} \left(\frac{S^*}{1 + \eta S^*} \right) = 1 \quad (\text{C.1})$$

Then the value of S^* can be obtained:

$$S^* = \frac{\gamma + b + \alpha}{\beta e^{-b\tau} - (\gamma + b + \alpha)\eta} \quad (\text{C.2})$$

In order to obtain a positive value for S^* the constraint $\beta > \eta e^{b\tau} (\gamma + b + \alpha)$ must be satisfied which is the one required in proposition 2.5(i) for the presence of an endemic equilibrium point. The remaining variables can be deduced from equations (2.6), (2.8) and (2.10) by using the value of the total population in the equilibrium is the sum of all partial populations at such an equilibrium point. Hence, the total population in the equilibrium is obtained by zeroing the left-hand side of equation (2.77), i.e.:

$$0 = \nu - bN^* + b - \alpha I^* + \beta \frac{S^* I^*}{1 + \eta S^*} (e^{-b\tau} - e^{-b\omega}) \quad (\text{C.3})$$

Thus,

$$N^* = \frac{b}{b - \nu} + \frac{1}{b - \nu} \left[\beta \frac{S^* I^*}{1 + \eta S^*} (e^{-b\tau} - e^{-b\omega}) - \alpha \right] I^* \quad (\text{C.4})$$

$$= \frac{b}{b - \nu} + \frac{1}{b - \nu} [(\gamma + b + \alpha) (e^{-b\tau} - e^{-b\omega}) - \alpha] I^* \quad (\text{C.5})$$

On the other hand, equation (2.8) together with (C.2) implies that:

$$E^* = \frac{\gamma + b + \alpha}{b} (e^{b\tau} - e^{b(\tau - \omega)}) I^* \quad (\text{C.6})$$

and equation (2.10) becomes

$$R^* = \frac{\gamma}{b} (1 - e^{-b\omega}) I^*$$

for $V_c = 0$. The total population is then given using (C.1)-(C.6) by:

$$N^* = \frac{b}{b-\nu} + \frac{1}{b-\nu} [(\gamma + b + \alpha) (1 - e^{b(\tau-\omega)}) - \alpha] I^* \quad (\text{C.7})$$

$$\begin{aligned} &= \frac{\gamma + b + \alpha}{\beta e^{-b\tau} - \eta(\gamma + b + \alpha)} + \frac{(\gamma + b + \alpha) (e^{b\tau} - e^{b(\tau-\omega)}) I^*}{b} \\ &+ I^* + \frac{\gamma}{b} (1 - e^{-b\omega}) I^* \end{aligned} \quad (\text{C.8})$$

and the value of I^* is given by:

$$I^* = \frac{(\gamma + b + \alpha) b (b - \nu) - b^2 \beta (e^{-b\tau} - (\gamma + b + \alpha) \eta)}{(\beta e^{-b\tau} - (\gamma + b + \alpha) \eta) [(\nu (1 - e^{-b\omega}) - b) (\gamma + b + \alpha) e^{b\tau} + \nu (b + \gamma) + \gamma (b - \nu) e^{-b\omega}]} \quad (\text{C.9})$$

Thus, the remaining components of the endemic equilibrium point, which is seen to be unique, are given by (C.6) and (C.7) by using (C.8):

$$\begin{aligned} E^* &= \frac{(\gamma + b + \alpha) (e^{b\tau} - e^{b(\tau-\omega)})}{(\beta e^{-b\tau} - (\gamma + b + \alpha) \eta)} \\ &\times \frac{(\gamma + b + \alpha) (b - \nu) - b (\beta e^{-b\tau} - (\gamma + b + \alpha) \eta)}{[(\nu (1 - e^{-b\omega}) - b) (\gamma + b + \alpha) e^{b\tau} + \nu (b + \gamma) + \gamma (b - \nu) e^{-b\omega}]} \end{aligned} \quad (\text{C.10})$$

$$\begin{aligned} R^* &= \frac{\gamma (1 - e^{-b\omega})}{(\beta e^{-b\tau} - (\gamma + b + \alpha) \eta)} \\ &\times \frac{(\gamma + b + \alpha) (b - \nu) - b (\beta e^{-b\tau} - (\gamma + b + \alpha) \eta)}{[(\nu (1 - e^{-b\omega}) - b) (\gamma + b + \alpha) e^{b\tau} + \nu (b + \gamma) + \gamma (b - \nu) e^{-b\omega}]} \end{aligned} \quad (\text{C.11})$$

APPENDIX D

Periodic disease-free solutions of a generalized delayed model under impulsive vaccination

Proposition D.1. *There is a unique general periodic solution of equations (3.18)-(3.19) with time period $T = T(1, 0) = t_v$. This solution would be, from Proposition 3.5 (i), that with the smallest time period.*

Proof.

Assuming that a generalized periodic solution of equations (3.18)-(3.19) with time period $T(n, 0) = nt_v$ exists, the possible values for n are obtained. In order to simplify the notation, it is defined the variables for the vaccinated and susceptible subpopulations within the interval between two consecutive impulses after a large enough time so that they have reached the periodic regime and the total population is constant, namely $N(t) = N_{dfe}^*$. The susceptible and vaccinated subpopulations in such a situation can be denoted by:

$$\forall \{i, r\} \in \mathbb{N}_0 \triangleq \mathbb{N} \cup \{0\}, \tau \in [0, t_v) \rightarrow \begin{cases} S_i(\tau) \triangleq \lim_{r \rightarrow \infty} S'(\tau + (i+r)t_v) \\ V_i(\tau) \triangleq \lim_{r \rightarrow \infty} V'(\tau + (i+r)t_v) \end{cases} \quad (\text{D.1})$$

The periodicity requires that :

$$S_{i+n}(\tau) = S_i(\tau) \quad , \quad V_{i+n}(\tau) = V_i(\tau), \quad \forall \tau \in [0, t_v) \quad (\text{D.2})$$

Also, the delayed vaccinated subpopulation term of equation (3.18) for $\omega = kt_v + xt_v$, where $k \in \mathbb{N}_0$ and $x \in [0, 1) \cap \mathbb{R}$, can be written as:

$$V_i(\tau - \omega) = V_i(\tau - ((k+x)t_v)) = \begin{cases} V_{i-(k+1)}(\tau + (1-x)t_v) & 0 \leq \tau < xt_v \\ V_{i-k}(\tau - xt_v) & xt_v \leq \tau < t_v \end{cases} \quad (\text{D.3})$$

and with this equation the susceptible subpopulation dynamics in the periodic state can be written as:

$$\dot{S}_i(\tau) = \begin{cases} b_1 - b_2 S_i(\tau) + \gamma_1 V_{i-(k+1)}(\tau + (1-x)t_v) e^{-b_2 \omega} \\ \quad + b_3 (1 - V_c) N_{dfe}^* & 0 \leq \tau < xt_v \\ b_1 - b_2 S_i(\tau) + b_3 (1 - V_c) N_{dfe}^* + \gamma_1 V_{i-k}(\tau - xt_v) e^{-b_2 \omega} & xt_v \leq \tau < t_v \end{cases} \quad (\text{D.4})$$

while the equation for the dynamics of the vaccinated subpopulation is:

$$\dot{V}_i(\tau) = -\gamma_1 V_i(\tau) - b_2 V_i(\tau) + b_3 V_c N_{dfe}^* \quad (\text{D.5})$$

By solving this equation between two consecutive impulses, one obtains:

$$V_i(\tau) = (V_i(0^+) - V_{dfe}^*)e^{-(b_2+\gamma_1)\tau} + V_{dfe}^* = V_{dfe}^*(1 - e^{-(b_2+\gamma_1)\tau}) + V_i(0^+)e^{-(b_2+\gamma_1)\tau} \quad (\text{D.6})$$

with V_{dfe}^* defined in equation (3.10). Then, using this result, it is obtained the time-evolution for the periodic solution of the susceptible subpopulation from (D.4):

$$S_i(\tau) = \begin{cases} \begin{aligned} &e^{-b_2(t+\omega)} (V_{dfe}^*(e^{b_2t} - 1)\gamma_1/b_2 \\ &+ (V_{i-(k+1)}(0^+) - V_{dfe}^*)e^{-(b_2+\gamma_1)(\tau+(1-x)t_v)}(1 - e^{\gamma_1\tau}) \\ &+ (1 - e^{-b_2\tau})S_{dfe}^* + e^{-b_2\tau}S_i(0^+) \end{aligned} & 0 \leq \tau < xt_v \\ \begin{aligned} &e^{-b_2(t+\omega)} ((V_{i-k}(0^+) - V_{dfe}^*)e^{b_2xt_v}(1 - e^{\gamma_1(xt_v-\tau)}) \\ &+ (V_{i-(k+1)}(0^+) - V_{dfe}^*)e^{-(b_2+\gamma_1)t_v(1-x)}(1 - e^{-\gamma_1xt_v}) \\ &(1 - e^{-b_2\tau})S_{dfe}^* + e^{-b_2\tau}S_i(0^+) + e^{-b_2(t+\omega)}V_{dfe}^*(e^{b_2t} - 1)\gamma_1/b_2 \end{aligned} & xt_v \leq \tau < t_v \end{cases} \quad (\text{D.7})$$

with S_{dfe}^* defined in equation (3.9). From the equations of (3.19) and the time evolutions (D.6),(D.7) at $\tau = t_v$, it can be described the relation between the different values of the subpopulations after different impulses as:

$$\begin{cases} S_i(0^+) = (1 - \theta)S_{i-1}(t_v) \\ S_i(t_v) = aS_i(0^+) + bV_{i-k}(0^+) + cV_{i-(k+1)}(0^+) + d \\ V_i(t_v) = C_{v0} + C_{v1}V_i(0^+) \\ V_i(0^+) = V_{i-1}(t_v) + \theta S_{i-1}(t_v) \end{cases} \quad (\text{D.8})$$

being $C_{v1} = e^{-(b_2+\gamma_1)t_v}$, $C_{v0} = V_{dfe}^*(1 - C_{v1})$ and $a = e^{-b_2t_v}$, $b = C_{v1}e^{-b_2(\omega-xt_v)}(e^{\gamma_1t_v} - e^{\gamma_1xt_v})$, $c = aC_{v1}e^{-b_2(\omega-xt_v)}(e^{\gamma_1xt_v} - 1)$ and $d = (1-a)S_{dfe}^* - (b+c+(1-a)e^{-b_2\omega}\gamma_1/b_2)V_{dfe}^*$. As is seen in equation (D.2) the relations in equation (D.8) describe a n-cycle. Then, such equations can be presented in matrix form:

$$\begin{pmatrix} S_1(0^+) \\ S_2(0^+) \\ \vdots \\ S_n(0^+) \end{pmatrix} = (1 - \theta)\mathbf{R} \begin{pmatrix} S_1(t_v) \\ S_2(t_v) \\ \vdots \\ S_n(t_v) \end{pmatrix} \quad (\text{D.9})$$

$$\begin{pmatrix} S_1(t_v) \\ S_2(t_v) \\ \vdots \\ S_n(t_v) \end{pmatrix} = a \begin{pmatrix} S_1(0^+) \\ S_2(0^+) \\ \vdots \\ S_n(0^+) \end{pmatrix} + b\mathbf{R}^k \begin{pmatrix} V_1(0^+) \\ V_2(0^+) \\ \vdots \\ V_n(0^+) \end{pmatrix} + c\mathbf{R}^{k+1} \begin{pmatrix} V_1(0^+) \\ V_2(0^+) \\ \vdots \\ V_n(0^+) \end{pmatrix} + \begin{pmatrix} d \\ d \\ \vdots \\ d \end{pmatrix} \quad (\text{D.10})$$

$$\begin{pmatrix} V_1(0^+) \\ V_2(0^+) \\ \vdots \\ V_n(0^+) \end{pmatrix} = \mathbf{R} \left(\begin{pmatrix} V_1(t_v) \\ V_2(t_v) \\ \vdots \\ V_n(t_v) \end{pmatrix} + \theta \begin{pmatrix} S_1(t_v) \\ S_2(t_v) \\ \vdots \\ S_n(t_v) \end{pmatrix} \right) \quad (\text{D.11})$$

$$\begin{pmatrix} V_1(t_v) \\ V_2(t_v) \\ \vdots \\ V_n(t_v) \end{pmatrix} = \begin{pmatrix} C_{v0} \\ C_{v0} \\ \vdots \\ C_{v0} \end{pmatrix} + C_{v1} \begin{pmatrix} V_1(0^+) \\ V_2(0^+) \\ \vdots \\ V_n(0^+) \end{pmatrix} \quad (\text{D.12})$$

with the row switching matrix $\mathbf{R} = \begin{pmatrix} 0 & 0 & \dots & 0 & 1 \\ 1 & 0 & \dots & 0 & 0 \\ 0 & 1 & \dots & 0 & 0 \\ \vdots & \vdots & \dots & \vdots & \vdots \\ 0 & 0 & \dots & 1 & 0 \end{pmatrix}$ which satisfies $\mathbf{R} \begin{pmatrix} 1 \\ 1 \\ \vdots \\ 1 \end{pmatrix} = \begin{pmatrix} 1 \\ 1 \\ \vdots \\ 1 \end{pmatrix}$.

The equations from equations (D.12) and (D.11) are rearranged using equation (D.10), so it is obtained:

$$\begin{aligned} \begin{pmatrix} V_1(0^+) \\ V_2(0^+) \\ \vdots \\ V_n(0^+) \end{pmatrix} &= \mathbf{R} \begin{pmatrix} C_{v0} \\ C_{v0} \\ \vdots \\ C_{v0} \end{pmatrix} + C_{v1} \mathbf{R} \begin{pmatrix} V_1(0^+) \\ V_2(0^+) \\ \vdots \\ V_n(0^+) \end{pmatrix} + \theta \mathbf{R} \begin{pmatrix} S_1(t_v) \\ S_2(t_v) \\ \vdots \\ S_n(t_v) \end{pmatrix} \quad (\text{D.13}) \\ &= \mathbf{R} \begin{pmatrix} C_{v0} \\ C_{v0} \\ \vdots \\ C_{v0} \end{pmatrix} + C_{v1} \mathbf{R} \begin{pmatrix} V_1(0^+) \\ V_2(0^+) \\ \vdots \\ V_n(0^+) \end{pmatrix} \\ &+ \theta \mathbf{R} \left(a \begin{pmatrix} S_1(0^+) \\ S_2(0^+) \\ \vdots \\ S_n(0^+) \end{pmatrix} + \mathbf{R}^k (b\mathbf{I} + c\mathbf{R}) \begin{pmatrix} V_1(0^+) \\ V_2(0^+) \\ \vdots \\ V_n(0^+) \end{pmatrix} + \begin{pmatrix} d \\ d \\ \vdots \\ d \end{pmatrix} \right) \end{aligned}$$

Then it is obtained the values of the susceptible subpopulation after the impulsive time instants in relation to the values of the vaccinated subpopulation at such time instants:

$$\begin{pmatrix} S_1(0^+) \\ S_2(0^+) \\ \vdots \\ S_n(0^+) \end{pmatrix} = \frac{1}{\theta a} \left((\mathbf{R}^{-1} - C_{v1}\mathbf{I} - \theta \mathbf{R}^k (b\mathbf{I} + c\mathbf{R})) \begin{pmatrix} V_1(0^+) \\ V_2(0^+) \\ \vdots \\ V_n(0^+) \end{pmatrix} - (C_{v0+}\theta d) \begin{pmatrix} 1 \\ 1 \\ \vdots \\ 1 \end{pmatrix} \right) \quad (\text{D.14})$$

Note that if $\theta = 1$ then, from equation (D.9), it is known that $S_i(0^+) = 0 \forall i \in \mathbb{N}$, and it follows from equation (D.14) that:

$$(C_{v0} + d) \begin{pmatrix} 1 \\ 1 \\ \vdots \\ 1 \end{pmatrix} = (\mathbf{R}^{-1} - C_{v1}\mathbf{I} - \mathbf{R}^k (b\mathbf{I} + c\mathbf{R})) \begin{pmatrix} V_1(0^+) \\ V_2(0^+) \\ \vdots \\ V_n(0^+) \end{pmatrix} \quad (\text{D.15})$$

It is defined a matrix \mathbf{M}_0 as:

$$\mathbf{M}_0 = (C_{v0+}d)^{-1} (\mathbf{R}^{-1} - C_{v1}\mathbf{I} - \mathbf{R}^k (b\mathbf{I} - c\mathbf{R})) \quad (\text{D.16})$$

Note that the sum of all the elements which compose any row in the matrices $\mathbf{R}^k, \forall k \in \mathbb{Z}$, is equal to 1. Such a fact implies that :

$$\mathbf{M}_0 \begin{pmatrix} 1 \\ 1 \\ \dots \\ 1 \end{pmatrix} = \begin{pmatrix} m_0 \\ m_0 \\ \dots \\ m_0 \end{pmatrix} \quad (\text{D.17})$$

being $m_0 = \frac{1-C_{v1}-b-c}{C_{v0}+d}$. As \mathbf{M}_0 is row-equivalent to \mathbf{I} , it is known from Chapter 3-[38] that:

$$\exists \mathbf{M}_0^{-1} \rightarrow \mathbf{M}_0^{-1} \mathbf{M}_0 \begin{pmatrix} 1 \\ 1 \\ \dots \\ 1 \end{pmatrix} = \begin{pmatrix} 1 \\ 1 \\ \dots \\ 1 \end{pmatrix} \quad (\text{D.18})$$

Then, from equation (D.15) it is obtained:

$$\begin{pmatrix} V_1(0^+) \\ V_2(0^+) \\ \dots \\ V_n(0^+) \end{pmatrix} = \mathbf{M}_0^{-1} \begin{pmatrix} 1 \\ 1 \\ \dots \\ 1 \end{pmatrix} = \frac{1}{m_0} \begin{pmatrix} 1 \\ 1 \\ \dots \\ 1 \end{pmatrix} \quad (\text{D.19})$$

proving that $\{V_j(0^+) = V_i(0^+), S_j(0^+) = S_i(0^+)\}, \forall i, j \in \mathbb{N}$, for $\theta = 1$.
If $\theta \neq 1$, then the values of $S_i(t_v)$ and $V_i(t_v)$ can be found from equations (D.9) and (D.12), respectively, and by applying them on equation (D.11) it follows that:

$$\begin{pmatrix} V_1(0^+) \\ V_2(0^+) \\ \dots \\ V_n(0^+) \end{pmatrix} = \mathbf{R} \begin{pmatrix} C_{v0} \\ C_{v0} \\ \dots \\ C_{v0} \end{pmatrix} + C_{v1} \mathbf{R} \begin{pmatrix} V_1(0^+) \\ V_2(0^+) \\ \dots \\ V_n(0^+) \end{pmatrix} + \frac{\theta}{1-\theta} \begin{pmatrix} S_1(0^+) \\ S_2(0^+) \\ \dots \\ S_n(0^+) \end{pmatrix} \quad (\text{D.20})$$

Then, by applying (D.14) in equation (D.20) it can be obtained:

$$\begin{pmatrix} V_1(0^+) \\ V_2(0^+) \\ \dots \\ V_n(0^+) \end{pmatrix} = \left(C_{v0} - \left(\frac{C_{v0} + \theta d}{a(1-\theta)} \right) \right) \begin{pmatrix} 1 \\ 1 \\ \dots \\ 1 \end{pmatrix} + \left(C_{v1} \mathbf{R} + \left(\frac{\mathbf{R}^{-1} - C_{v1} \mathbf{I} - \theta \mathbf{R}^{k+1} (b \mathbf{R}^{-1} + c \mathbf{I})}{a(1-\theta)} \right) \right) \begin{pmatrix} V_1(0^+) \\ V_2(0^+) \\ \dots \\ V_n(0^+) \end{pmatrix} \quad (\text{D.21})$$

so the values of the vaccinated subpopulation after the impulsive time instants are defined as:

$$\begin{pmatrix} V_1(0^+) \\ V_2(0^+) \\ \dots \\ V_n(0^+) \end{pmatrix} = \left[C_{v0} - \left(\frac{C_{v0} + \theta d}{a(1-\theta)} \right) \right] \left[\mathbf{I} - \left(C_{v1} \mathbf{R} + \left(\frac{\mathbf{R}^{-1} - C_{v1} \mathbf{I} - \theta \mathbf{R}^k (b \mathbf{I} + c \mathbf{R})}{a(1-\theta)} \right) \right) \right]^{-1} \begin{pmatrix} 1 \\ 1 \\ \dots \\ 1 \end{pmatrix} \quad (\text{D.22})$$

It is defined a matrix \mathbf{M} as:

$$\mathbf{M} = \left[C_{v0} - \left(\frac{C_{v0} + \theta d}{a(1-\theta)} \right) \right]^{-1} \left[\mathbf{I} - \left(C_{v1} \mathbf{R} + \left(\frac{\mathbf{R}^{-1} - C_{v1} \mathbf{I} - \theta \mathbf{R}^{k+1} (b \mathbf{R}^{-1} + c \mathbf{I})}{a(1-\theta)} \right) \right) \right]$$

(D.23)

Note that the sum of all the elements which compose any row in the matrices $\mathbf{R}^k, \forall k \in \mathbb{Z}$, is equal to 1. Such a fact implies that :

$$\mathbf{M} \begin{pmatrix} 1 \\ 1 \\ \vdots \\ 1 \end{pmatrix} = m \begin{pmatrix} 1 \\ 1 \\ \vdots \\ 1 \end{pmatrix} \quad (\text{D.24})$$

being $m = \left(1 - C_{v1} - \frac{1 - C_{v1} - \theta(b+c)}{a(1-\theta)}\right) / \left(C_{v0} - \left(\frac{C_{v0} + \theta d}{a(1-\theta)}\right)\right)$. Since, as in the previous demonstration, \mathbf{M} is row equivalent to \mathbf{I} , then it is known from Chapter 3- [38] that is invertible so that:

$$\exists \mathbf{M}^{-1} \rightarrow \mathbf{M}^{-1} \mathbf{M} \begin{pmatrix} 1 \\ 1 \\ \vdots \\ 1 \end{pmatrix} = \begin{pmatrix} 1 \\ 1 \\ \vdots \\ 1 \end{pmatrix} \quad (\text{D.25})$$

so the values of the vaccinated subpopulation after the regular impulsive vaccination instants are:

$$\begin{pmatrix} V_1(0^+) \\ V_2(0^+) \\ \vdots \\ V_n(0^+) \end{pmatrix} = \mathbf{M}^{-1} \begin{pmatrix} 1 \\ 1 \\ \vdots \\ 1 \end{pmatrix} = \frac{1}{m} \begin{pmatrix} 1 \\ 1 \\ \vdots \\ 1 \end{pmatrix} \quad (\text{D.26})$$

and, from (D.14), the susceptible subpopulation after such impulsive instants are:

$$\begin{pmatrix} S_1(0^+) \\ S_2(0^+) \\ \vdots \\ S_n(0^+) \end{pmatrix} = \frac{1}{a\theta} \left[\frac{1 - C_{v1} - \theta(b+c)}{m} - (C_{v0} + \theta d) \right] \begin{pmatrix} 1 \\ 1 \\ \vdots \\ 1 \end{pmatrix} \quad (\text{D.27})$$

In summary, it is established that, either if $\theta = 1$ or $\theta \in (0, 1)$ the values of the susceptible and vaccinated subpopulations just after any impulsive vaccination instant at the periodic regime will be the same, i.e : $\{S_i(0^+) = S_j(0^+), V_i(0^+) = V_j(0^+)\}, \forall i, j \in \mathbb{N}$. As the time evolutions of the susceptible and the vaccinated subpopulations within the time period between any two consecutive impulsive vaccination instants depend only in such initial values (see (D.7) and (D.6)) then $\{S_i(\tau) = S_j(\tau), V_i(\tau) = V_j(\tau)\}, \forall \tau \in [0, t_v), \forall j, i \in \mathbb{N}$. The matrices \mathbf{M} and \mathbf{M}_0 are invertible so this solution is unique for any $T(n, 0) = nt_v$. It can be seen in (3.20) that, if $b_2 > b_3$, after a sufficiently large time t_0 the total population reaches a constant value $N(t) = N^* \forall t > t_0$, so the recovered subpopulation $R_i(\tau) = N_{df_e}^* - (S_i(\tau) + V_i(\tau))$ must also present the same periodicity that the susceptible and vaccinated subpopulations. Therefore, from equations (D.26) and (D.27), the solution of the generalized periodic solution of the subsystem of subpopulations S', V' and R' is periodic and present the smallest periodic solution with time period $T(1, 0)$. \square

APPENDIX E

Convergence of the periodic solution coefficients of a SEIR model

The coefficients $\{S_n, E_n, I_n, R_n\}$ from equation (4.34) are studied as $n \rightarrow \infty$. As the subpopulations at the equilibrium $\{S^*(t), E^*(t), I^*(t), R^*(t)\}$ and $V_c(t), \beta(t)$ are defined real and bounded, from Bessel inequality it is known that

$$\frac{1}{T} \int_0^T \|V(t)\|^2 dt \geq \sum_{n=-\infty}^{\infty} \|V_n\|^2$$

$$\frac{1}{T} \int_0^T \|\beta(t)\|^2 dt \geq \sum_{n=-\infty}^{\infty} \|\beta_n\|^2$$

and

$$\frac{1}{T} \int_0^T \|\{S^*, E^*, I^*, R^*\}(t)\|^2 dt \geq \sum_{n=-\infty}^{\infty} \|\{S_n, E_n, I_n, R_n\}\|^2$$

so it is deduced that the coefficients for the vaccination and disease transmission rate and all the subpopulations must tend to zero as $|n|$ tends to infinity: Then, as $\lim_{n \rightarrow \infty} S_n = 0$, $\lim_{n \rightarrow \infty} E_n = 0$, $\lim_{n \rightarrow \infty} I_n = 0$ and $\lim_{n \rightarrow \infty} R_n = 0$, it is deduced from equation (4.37) and (4.36) that for all n :

$$P_n \leq \max_{-\infty < i < \infty} \{S_i\} \sum_{j=-\infty}^{\infty} I_j = S_0 I^*(0)$$

$$Q_n \leq \max_{-\infty < i < \infty} \{P_i\} \sum_{j=-\infty}^{\infty} \beta_j \leq S_0 I^*(0) \beta(0)$$

so from equation (4.34):

$$\lim_{n \rightarrow \infty} |S_n| \leq \lim_{n \rightarrow \infty} \frac{b_3 |V_n|}{\rho n} + \frac{|Q_n|}{\rho n} \leq \lim_{n \rightarrow \infty} \frac{S_0 I^*(0) \beta(0)}{\rho n} = 0$$

$$\lim_{n \rightarrow \infty} |I_n| = \lim_{n \rightarrow \infty} \frac{\beta \kappa |P_n|}{(\rho n)^2} \leq \lim_{n \rightarrow \infty} \frac{\beta \kappa S_0 I^*(0)}{(\rho n)^2} = 0$$

So, as the for P_n

$$\begin{aligned}
\lim_{n \rightarrow \infty} P_n &= \lim_{n \rightarrow \infty} \sum_{j=-\infty}^{\infty} S_{n-j} I_j \\
&= \lim_{n \rightarrow \infty} I_n S_0 + 2 \operatorname{Re} \left[\sum_{j=1}^{\infty} S_j I_{n-j} \right] \\
&= 2 \lim_{n \rightarrow \infty} \operatorname{Re} \left[\sum_{j=1}^{n/2-1} S_j I_{n-j} + \sum_{j=n/2}^{\infty} S_j I_{n-j} \right] + \lim_{n \rightarrow \infty} I_n S_0 \\
&\leq 2 \lim_{n \rightarrow \infty} \operatorname{Re} \left[I_{n/2} \sum_{j=1}^{n/2-1} S_{-j} + S_{n/2} \sum_{j=n/2}^{\infty} I_{n/2-j} \right] + \lim_{n \rightarrow \infty} I_n S_0 = 0
\end{aligned}$$

Also, for the Q_n from equation (4.36) it is deduced :

$$\begin{aligned}
\lim_{n \rightarrow \infty} Q_n &= \sum_{j=-\infty}^{\infty} \beta_j P_{n-j} \\
&= \beta_0 \lim_{n \rightarrow \infty} P_n + \lim_{n \rightarrow \infty} 2 \operatorname{Re} \left[\sum_{j=1}^{n/2-1} \beta_j P_{n-j} + \sum_{j=n/2}^{\infty} \beta_j P_{n-j} \right] \\
&\leq \beta_0 \lim_{n \rightarrow \infty} P_n + \lim_{n \rightarrow \infty} 2 \operatorname{Re} \left[P_{n/2} \sum_{j=1}^{n/2-1} \beta_j + \beta_{n/2} \sum_{j=n/2}^{\infty} P_{n-j} \right] = 0
\end{aligned}$$