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# Dynamics of Non-Autonomous SEIRS Models with General Incidence

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# Dedicatory

To João and Miguel
To Adelaide

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# Resumo

Consideramos modelos SEIRS com funções de incidência gerais dependendo dos suscetíveis, dos infeciosos e da população total, e analisamos esses modelos em diversos cenários: autónomo, não-autónomo geral e periódico. Em todas essas situações, analisamos a persistência forte e a extinção da doença. Além disso, abordamos os seguintes problemas: no caso autónomo, obtemos resultados sobre a existência e a estabilidade global do equilíbrio livre de doença e do equilíbrio endémico; no caso periódico, obtemos a estabilidade global da solução periódica livre de doença quando o número reprodutivo básico é inferior a um, e, usando o conhecido teorema de continuação de Mawhin, discutimos a existência de soluções periódicas endémicas; no caso não-autónomo geral, provamos que as nossas condições para persistência forte e extinção são robustas, no sentido em que se mantêm inalteradas para perturbações suficientemente pequenas dos parâmetros e das funções de incidência. Finalmente, consideramos uma versão do nosso modelo com duas variáveis de controle, vacinação e tratamento, e estudamos a existência e unicidade da solução do modelo de controle ótimo considerado. Algumas experiências computacionais ilustram os nossos resultados.

# Palavras-chave

Modelos epidemiológicos SEIRS; não-autónomo; periódico; persistência e extinção; estabilidade; controle ótimo.

# Resumo alargado

Neste trabalho, consideramos uma família de modelos SEIRS com incidência geral em diversos cenários. Os modelos considerados são da forma

$$\begin{cases} S' = \Lambda(t) - \beta(t)\,\varphi(S,N,I) - \mu(t)S + \eta(t)R \\ E' = \beta(t)\,\varphi(S,N,I) - (\mu(t)+\varepsilon(t))E \\ I' = \varepsilon(t)E - (\mu(t)+\gamma(t))I \\ R' = \gamma(t)I - (\mu(t)+\eta(t))R \\ N = S+E+I+R \end{cases}$$

onde $S$, $E$, $I$, $R$ representam, respetivamente, os compartimentos dos suscetíveis, latentes (infetados mas não infeciosos), infeciosos e recuperados e $N$ é a população total, $\Lambda(t)$ representa a taxa de natalidade, $\beta(t)\,\varphi(S,N,I)$ é a incidência da classe latente nos indivíduos suscetíveis, $\mu(t)$ são as mortes naturais, $\eta(t)$ representa a taxa de perda de imunidade, $\varepsilon(t)$ representa a taxa de infetividade e $\gamma(t)$ é a taxa de recuperação.

O estudo de modelos com funções de incidência gerais é importante para podermos destacar as características que são dependentes e independentes da forma destas funções. Esta foi a nossa principal motivação para a realização deste estudo.

Alguns dos problemas mais importantes na epidemiologia matemática incluem a obtenção das condições para a persistência e extinção da doença, a existência de soluções fixas e periódicas, o estudo da estabilidade e da existência de bifurcações. Em todos estes casos, o número reprodutivo básico, geralmente denotado por $\mathcal{R}_0$, e as suas generalizações desempenham um papel importante, em particular, permitem estabelecer uma fronteira entre a persistência e a extinção da doença. Mais precisamente, dizemos que os infeciosos se extinguem se para qualquer solução temos que $\lim\limits_{t\to+\infty} I(t) = 0$ e dizemos que os infeciosos são fortemente persistentes num conjunto $A$, se existir $K > 0$ tal que, para qualquer solução do sistema apresentado com condições iniciais em $A$, temos que $\liminf\limits_{t\to+\infty} I(t) \geq K > 0$. Definições similares podem ser feitas para os outros compartimentos.

No caso autónomo, Li, Muldowney e Driessche [20] estudaram um modelo já considerado em [14], onde se assume que a população é constante, as taxas de mortalidade e de nascimento são iguais e a função de incidência é da forma $\varphi(S,N,I) = g(I)S$ com $g$ classe $C^1$ verificando $|Ig'(I)| < I$. Eles obtiveram a estabilidade assintótica local do equilíbrio livre de doença quando $\mathcal{R}_0 < 1$ e a estabilidade global do equilíbrio endémico quando $\mathcal{R}_0 > 1$, assumindo que os parâmetros satisfazem $\eta > \varepsilon - \mu - \gamma$. Recentemente, Cheng e Yang [5] melhoraram o resultado de Li, Muldowney e Driessche completando o estudo da estabilidade global do equilíbrio endémico para todos os parâmetros. No nosso contexto, as taxas de natalidade e mortalidade não são consideradas constantes e as funções de incidência podem depender da população total.

No capítulo 1 consideramos parâmetros constantes, obtendo um modelo autónomo, e assumimos que as funções de incidência são duas vezes continuamente diferenciáveis. Este é o contexto em que mais informações podem ser obtidas sobre o nosso sistema. Há, em particular, uma forma geral desenvolvida em Driessche e Watmough [36] para obter o número reprodutivo básico $\mathcal{R}_0$ que é apresentado na secção 1.2. Na seção 1.3 obtemos uma importante região invariante que contém os equilíbrios do sistema, que também são calculados, e aplicamos a teoria geral da secção anterior ao nosso modelo, obtendo as regiões de estabilidade assintótica local do equilíbrio livre de doença e a região de persistência forte da doença. A estabilidade global é discutida na secção 1.4. No que respeita ao equilíbrio livre de doença, é provado nesta secção que é globalmente assintoticamente estável se o número reprodutivo básico é inferior ou igual a um e instável no caso contrário. Quando o número reprodutivo básico é maior que um, para funções de incidência da forma $\beta\varphi(S, N, I) = \beta C(N)Sg(I)$, a estabilidade assintótica global do equilíbrio endémico é também obtida, mas apenas assumindo recuperação permanente ($\eta = 0$). Os resultados de estabilidade nesta secção foram parcialmente inspirados em Safi e Garba [33]. Alguns exemplos ilustrativos dos resultados obtidos neste capítulo são apresentados na secção 1.5.

Assumirmos que os parâmetros são independentes do tempo não é muito realista em muitas situações. Em particular, o caso não-autónomo geral permite a discussão não só das flutuações sazonais periódicas, mas também de efeitos ambientais e demográficos não-periódicos. Como exemplo de tais efeitos, para algumas doenças, como a cólera e a febre amarela, sabe-se que o tamanho do período de latência pode diminuir com o aquecimento global [34]. Este tipo de fenómenos justifica o estudo de modelos com parâmetros não-periódicos.

No capítulo 2, tivemos como objetivo considerar um cenário o mais geral possível. Assim, nenhum comportamento especial foi estabelecido para os parâmetros, que se supõe serem apenas funções contínuas, limitadas e não-negativas, e nenhuma diferenciabilidade é assumida para as funções de incidência, que apenas se assume satisfazerem algumas propriedades numa parte especial do seu domínio. Apesar da generalidade assumida, na secção 2.2 foi possível obter condições para persistência e extinção. Quando as nossas condições determinam extinção, também obtivemos estabilidade assintótica global das soluções livres de doença. Como caso particular, temos o caso da incidência simples, $\varphi(S, N, I) = SI$, já considerada em artigos de Zhang e Teng [42] e de Kuniya e Nakata [30, 18]. Para a incidência simples, Zhang e Teng definem uma condição para persistência forte e uma condição para extinção baseada em algumas constantes que, mesmo no caso autónomo, não determinam a fronteira entre permanência e extinção. Para melhorar este resultado no caso periódico com incidência simples, Kuniya e Nakata [30] obtiveram condições baseadas em resultados gerais de Wang e Zhao [38] e, no caso não-autónomo geral com incidência simples, o resultado de Zhang e Teng foi melhorado em [18]. Neste trabalho, seguimos a abordagem em [18] para obtermos critérios explícitos de persistência forte e extinção no contexto não-autónomo para o nosso modelo de incidência geral. Naturalmente, o resultado de Kuniya e Nakata está incluído como um caso particular da nossa generalização como se pode ver na secção 2.3 onde vários exemplos são considerados. Em particular, nesta secção analisamos modelos com parâmetros não-autónomos dados por funções da forma $p(t) = c(1 + \alpha \cos(\omega t + \phi))$. Modelos com este tipo de parâmetros foram estudados por exemplo em [2, 23, 30, 18]. De realçar que a nossa generalização requer diversos argumentos adicionais não-triviais na prova dos resultados principais e auxiliares nas secções 2.1 e 2.2. Tal como em Kuniya e Nakata [18], não foi possível obter condições limite precisas, mesmo no caso autónomo. Noutro sentido, na secção 2.4, para funções de incidência diferenciáveis, provou-se que as nossas condições para permanência e extinção são robustas. Nomeadamente, provou-se que, se as nossas condições determinam persistência (respetivamente extinção) da doença então, para pequenas perturbações dos parâmetros no espaço das funções $C^1$ com a norma do supremo e pequenas perturbações da função de incidência num subconjunto adequado do conjunto das funções $C^1$, continuamos a ter persistência (respetivamente extinção). Os resultado deste capítulo estão incluídos no artigo [27].

Devido às frequentes mudanças sazonais que ocorrem na realidade, o caso periódico é muito importante. De facto, sabemos bem que várias doenças infeciosas exibem padrões sazonais de incidência. Um exemplo bem conhecido é suportado por dados semanais sobre o sarampo na Inglaterra e no País de Gales durante o período 1948-1968 [1]. Outros exemplos ocorrem em várias doenças da infância, tais como papeira, varicela, rubéola e tosse convulsa [26].

No capítulo 3 os parâmetros são periódicos com período comum e assumimos que as funções de incidência são continuamente diferenciáveis. Este é um contexto que é menos geral do que o do capítulo 2 e mais geral do que o do capítulo 1. Tal como no caso autónomo analisado no capítulo 1, existe um método geral para obter o número reprodutivo básico neste contexto. Este método desenvolvido por Wang e Zhao [38] é apresentado na secção 3.2 juntamente com resultados relacionados sobre persistência obtidos por Rebelo, Margueri e Bacaër [31]. Na secção 3.3 provamos a existência de uma única solução livre de doença e, aplicando a teoria geral descrita na secção anterior, estabelecemos nas secções 3.4 e 3.5 a estabilidade assintótica global da solução livre de doença, quando o número reprodutivo básico é menor que um, e a persistência dos infeciosos quando o número reprodutivo básico é maior que um. A existência de uma solução endémica periódica é estabelecida na secção 3.6, assumindo que o número reprodutivo básico é maior que um e outras condições adicionais. O nosso resultado baseia-se na teoria do grau, mais precisamente numa aplicação do teorema de continuação de Mawhin, e generaliza o resultado principal de Zhang, Liu e Teng [41] que considerou um modelo com funções de incidência simples e imunidade permanente. Embora a ideia de aplicar o teorema de continuação de Mawhin tenha sido retirada de [41], nós necessitamos de novos argumentos não triviais para lidar com o nosso caso, não só porque consideramos funções de incidência gerais, mas também porque permitimos imunidade temporária, o que nos obrigou a usar o modelo quadridimensional original em vez de um sistema reduzido como em [41]. Ilustramos os resultados neste capítulo na secção 3.7 considerando modelos com parâmetros periódicos da forma $p(t) = c(1 + \alpha \cos(\omega t + \phi))$.

Na realidade, a evolução do número de suscetíveis, expostos, infeciosos e recuperados depende de alguns fatores que podem ser controlados. Dois dos principais fatores são o tratamento de infeciosos e a vacinação de suscetíveis.

No capítulo 4, consideramos o efeito do tratamento e da vacinação no nosso modelo na forma de variáveis de controle e propomos um problema de controle ótimo num intervalo finito com funcional de custo na forma de Lagrange. Mais especificamente, consideramos duas variáveis de controle: tratamento, $\mathbb{T}$, e vacinação, $\mathbb{V}$. O tratamento é aplicado aos indivíduos infetados, movendo uma parte deles do compartimento dos infetados para o compartimento dos recuperados. A vacinação é aplicada aos indivíduos suscetíveis, também movendo uma parte deles para a classe dos recuperados. Portanto, adicionamos as variáveis de controle $\mathbb{T}$ e $\mathbb{V}$ ao sistema inicial no intervalo $t \in [t_0, t_f]$, obtendo o modelo de controle

$$\begin{cases} S' &= \Lambda(t) - \beta(t)\varphi(S,N,I) - \mu(t)S + \eta(t)R - \mathbb{V}S \\ E' &= \beta(t)\varphi(S,N,I) - (\mu(t) + \varepsilon(t))E \\ I' &= \varepsilon(t)E - (\mu(t) + \gamma(t))I - \mathbb{T}I \\ R' &= \gamma(t)I - \mu(t)R - \eta(t)R + \mathbb{T}I + \mathbb{V}S \\ N &= S + E + I + R \end{cases}$$

e consideramos o funcional de custo $\mathcal{J}$, dado por

$$\mathcal{J}(I, \mathbb{T}, \mathbb{V}) = \int_0^{t_f} \kappa_1 I + \kappa_2 \mathbb{T}^2 + \kappa_3 \mathbb{V}^2 dt, \ 0 < \kappa_1, \kappa_2, \kappa_3 < \infty.$$

Depois de apresentarmos o nosso problema na secção 4.1, provamos a existência de uma solução ótima na secção 4.2 e, depois de estabelecermos uma versão adequada do princípio máximo de Pontryagin na secção 4.3, obtemos a unicidade do controle ótimo num intervalo suficientemente pequeno na secção 4.4. A nossa abordagem segue os argumentos de Gaff e Schaefer [9] que consideraram um modelo autónomo e uma função de incidência particular. Além de considerarmos funções de incidência gerais, também admitimos parâmetros dependentes do tempo. Finalmente, na secção 4.5, apresentamos alguns resultados de simulação, obtidos para comparar um modelo autónomo com o correspondente modelo periódico.

# Abstract

We consider SEIRS models with general incidence functions depending on the susceptibles, the infectives and the total population, and we analyze this models in several scenarios: autonomous, general non-autonomous and periodic. In all this settings, we discuss the strong persistence and the extinction of the disease. Additionally, we address the following problems: in the autonomous setting, we obtain results on the existence and global stability of disease-free and endemic equilibriums; in the periodic setting, we obtain the global stability of disease-free periodic solution when the basic reproductive number is less than one, and, using the well-known Mawhin continuation theorem, we discuss the existence of endemic periodic solutions; in the general non-autonomous setting, we prove that our conditions for strong persistence and extinction are robust, in the sense that they are unchanged by sufficiently small perturbations of the parameters and the incidence functions. Finally, we consider a version of our model with two control variables, vaccination and treatment, and study the existence and uniqueness of solution of the optimal control model considered. Some computational experiences illustrate our results.

# Keywords

Epidemiological SEIRS models; non-autonomous; periodic; persistence and extinction; stability; optimal control.

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# Introduction

The study of compartmental epidemiological models has a long history that goes back to the construction of the SIR compartmental model of Kermack and Mckendrick [16] in 1927. Since then, compartmental models have been widely used in epidemiology and several different compartments have been considered, so that the models fit the different situations described.

The SEIR/SEIRS models are among the most studied models in epidemiology. In fact, in these models it is assumed that the population is divided in four compartments. Besides the infected, susceptible and recovered compartments in the SIR models, an exposed compartment is also considered in order to split the infected population in two groups: the individuals that are infected and can infect others (the infective class) and the individuals that are infected but are not yet able to infect others (the exposed or latent class). This division makes the model particularity suitable to include several infectious diseases like measles and, assuming vertical transmission, rubella [21]. If there is no recovery, the model is appropriate to describe diseases such as Chagas' disease [35]. It is also suitable to model diseases like hepatitis B and AIDS [21]. Although influenza can be modeled by a SEIRS model [6], due to the short latency period it is sometimes more convenient to use the simpler SIRS formulation [7]. Mathematically, the existence of more than one infected compartment brings some additional difficulties to the study of the model.

In this work we will consider a family of models with general incidence in several scenarios. Namely, we will consider models of the form

$$\begin{cases} S' = \Lambda(t) - \beta(t)\,\varphi(S,N,I) - \mu(t)S + \eta(t)R \\ E' = \beta(t)\,\varphi(S,N,I) - (\mu(t)+\varepsilon(t))E \\ I' = \varepsilon(t)E - (\mu(t)+\gamma(t))I \\ R' = \gamma(t)I - (\mu(t)+\eta(t))R \\ N = S+E+I+R \end{cases} \tag{1}$$

where $S$, $E$, $I$, $R$ denote respectively the susceptible, exposed (infected but not infective), infective and recovered compartments and $N$ is the total population, $\Lambda(t)$ denotes the birth rate, $\beta(t)\,\varphi(S,N,I)$ is the incidence into the exposed class of susceptible individuals, $\mu(t)$ are the natural deaths, $\eta(t)$ represents the rate of loss of immunity, $\varepsilon(t)$ represents the infectivity rate and $\gamma(t)$ is the rate of recovery. We should mention that the difference between SEIR and SEIRS models is related to immunity. If immunity is permanent after recovery ($\eta(t) = 0$) then there is no flow from the $R$ to the $S$ compartment and we have a SEIR model. Otherwise, if $\eta(t)$ is not identically zero, then there is a flow from the $R$ to the $S$ compartment and we have a SEIRS model.

Several different incidence functions have been considered to model the transmission in the context of SEIR/SEIRS models. In particular Michaelis-Menten incidence functions, that include the usual simple and standard incidence functions, have the form $\beta(t)\varphi(S,N,I) = \beta(t)C(N)SI/N$ and were considered, just to name a few references, in [37, 3, 11, 30, 18, 42]. The assumption that the incidence function is bilinear is seldom too simple and it is necessary to consider some saturation effect as well as other non-linear behaviors [24, 45]. The Holling Type II incidence, given by $\beta(t)\varphi(S,N,I) = \beta(t)SI/(1+\alpha I)$, is an example of an incidence function with saturation effect and was considered for instance in [33, 43]. Another popular type of incidence, given by $\beta(t)\varphi(S,N,I) = \beta(t)I^pS^q$, was considered in [17, 24, 13]. Also, a generalization of Holling Type II incidence, $\beta(t)\varphi(S,N,I) = \beta(t)SI^p/(1+\alpha I^q)$, was considered in [14, 32].

It is important to study models with general form for the incidence functions in order to highlight the features that are dependent and independent of the shape of these functions. This was our main motivation to undertake this study.

Some of the most important problems in mathematical epidemiology include the obtention of thresholds conditions for persistence and extinction of the disease, the existence of stationary and periodic solutions, stability and bifurcation analysis. In all these aspects the basic reproductive number, usually denoted by $\mathcal{R}_0$, and its generalizations play an important role, in particular to establish a threshold between persistence and extinction of the disease. More precisely, we say that the infectives go to extinction if for any solution we have $\lim\limits_{t\to+\infty} I(t) = 0$ and we say that the infectives are strongly persistent in some set $A$ if there is $K > 0$ such that, for any solution of (1) with initial conditions in $A$, we have $\liminf\limits_{t\to+\infty} I(t) \geq K > 0$. Similar definitions can be made for the others compartments.

In the autonomous situation, Li, Muldowney and Driessche [20] studied a model already considered in [14], where the population is assumed constant, equal death and birth rates are considered and the incidence function is of the form $\varphi(S,N,I) = g(I)S$ with $g$ of class $C^1$ and verifying $|Ig'(I)| < I$. They obtained the local asymptotic stability of the disease-free equilibrium when $\mathcal{R}_0 < 1$ and the global stability of the endemic equilibrium when $\mathcal{R}_0 > 1$, in the assumption that the parameters satisfy $\eta > \varepsilon - \mu - \gamma$. Recently, Cheng and Yang [5] improved Li, Muldowney and Driessche's result by completing the study of the global stability of the endemic equilibrium for all the parameters. In our context, the birth and death rates are not assumed constant and the incidence functions may depend on the total population.

In chapter 1 we consider constant parameter functions, obtaining an autonomous model, and the incidence functions are assumed to be twice continuously differentiable. This is the context where more information can be obtained about our system. There is, in particular, a general tool developed in Driessche and Watmough [36] to obtain the basic reproductive number $\mathcal{R}_0$ that is presented in section 1.2. In section 1.3 we obtain an important invariant region that contains the equilibriums of the system, that are also computed, and we apply the general tool of the previous section to our model, obtaining the regions of local asymptotic stability of the disease-free equilibrium and the region of strong persistence of the disease. The global stability is discussed in section 1.4. Concerning the disease-free equilibrium, it is proved in that section that it is globally asymptotically stable if the basic reproductive number is less or equal to one and unstable otherwise. When the basic reproductive number is greater than one, for incidence functions of the form $\beta\varphi(S,N,I) = \beta C(N)Sg(I)$, the global asymptotic stability of the endemic equilibrium is also obtained but only assuming permanent recovery ($\eta = 0$). The stability results in this section were partially inspired in Safi and Garba [33]. Some illustrative examples of the results obtained in this chapter are considered in section 1.5.

The assumption that the parameters are independent of time is not very realistic in many situations. In particular, the general non-autonomous setting allows the discussion not only of periodic seasonal fluctuations but also of environmental and demographic effects that are non periodic. As an example of such effects, for some diseases like cholera and yellow fever, it is known that the size of the latency period may decrease with global warming [34]. This type of phenomena leads to non-periodic parameters.

In chapter 2, we had the objective of considering a setting as general as possible. Thus, no special behavior was prescribed for the parameters, that are only assumed to be continuous, bounded and non-negative functions, and no differentiability is assumed for the incidence functions, that are only required to satisfy some properties on a special part of their domain. In spite of the assumed generality, it was possible in section 2.2 to obtain threshold conditions for persistence and extinction. When our conditions prescribe extinction, we also obtained global asymptotic stability of the disease-free solutions. A particular case of our setting is the case of mass-action incidence, $\varphi(S,N,I) = SI$, that was considered in papers by Zhang and Teng [42] and by Kuniya and Nakata [30, 18]. For mass action incidence, Zhang and Teng defined a condition for strong persistence and a condition for extinction based on the sign of some constants that, even in the autonomous setting, are not thresholds. To improve this result in the periodic mass action setting, Kuniya and

Nakata [30] obtained conditions based in general results by Wang and Zhao [38] and, in the general mass action non-autonomous setting, Zhang and Teng's result was improved in [18]. In this work we follow the approach in [18] to obtain explicit criteria for strong persistence and extinction in the non-autonomous setting for our general incidence model. Naturally, the result of Kuniya and Nakata is included as a particular case of our generalization as shown in section 2.3 where several examples are considered. In particular, we discuss in that section models with non-autonomous parameters given by functions of the form

$$p(t) = c(1 + \alpha \cos(\omega t + \phi)). \tag{2}$$

Models with this type of parameter functions were studied for instance in [2, 23, 30, 18]. It should be emphasized that our generalization requires several nontrivial additional arguments in the proof of the main and the auxiliary results in sections 2.1 and 2.2. Like in Kuniya and Nakata [18], it was not possible to obtain sharp thresholds as in the autonomous case. In another direction, in section 2.4, for differentiable incidence functions, it was proved that our conditions for permanence an extinction are robust. Namely, it was proved that, if our conditions determine persistence (respectively extinction) of the disease then, for small perturbations of the parameter functions in the space of $C^1$ functions with the supremum norm and small perturbations of the incidence function in some suitable subset of the set of $C^1$ functions, we still have persistence (respectively extinction). The results in this chapter are included in the article [27].

Due to the frequent seasonal changes that occur in practice, the periodic case is a very important one. In fact, it is well-known that several infectious diseases exhibit seasonal patterns of incidence. A well-known example is given by data on weekly measles notification in England and Wales during the period 1948-1968 [1]. Other examples occur in several childhood diseases such as mumps, chicken-pox, rubella and pertussis [26].

In chapter 3 the parameters are assumed periodic with a common period and the incidence functions are assumed continuously differentiable. This is a setting that is less general than the one in chapter 2 and more general than the one in chapter 1. Like in the autonomous case discussed in chapter 1, there is a general tool to obtain the basic reproductive number in this case. This tool developed by Wang and Zhao [38] is presented in section 3.2 together with related results about persistence obtained by Rebelo, Margueri and Bacaër [31]. In section 3.3 we prove the existence of a unique disease-free solution and, applying the general theory developed in the preceding section, we establish in sections 3.4 and 3.5 the global asymptotic stability of the disease-free solution, when the basic reproductive number is less than one, and the persistence of the infectives when the basic reproductive number is greater than one. The existence of a periodic endemic solution is obtained in section 3.6, assuming that the basic reproductive number is greater than one and some additional assumptions. Our result is based on degree theory, more precisely it relies on an application of Mawhin's continuation theorem, and generalizes the main result in Zhang, Liu and Teng [41] that considered a model with simple incidence functions and permanent immunity. Although the idea of applying Mawhin's continuation theorem was borrowed from [41], we need several nontrivial new arguments to deal with our case, not only because we consider general incidence functions, but also because we allow temporary immunity, which forced us to use the original four-dimensional system instead of a reduced system like in [41]. We will illustrate the results in this chapter in section 3.7 by considering models with periodic parameters of the form (2).

In practice, the evolution of the number of susceptible, exposed, infectives and recovered depends on some factors that can be controlled. Two of the main factors are the treatment of infectives and the vaccination of susceptibles.

In chapter 4, we consider the effect of treatment and vaccination to our model in the form of control variables and consider a free terminal point optimal control problem in a finite interval with cost functional in Lagrange form. More specifically, we consider two control variables: treatment, $\mathbb{T}$, and vaccination, $\mathbb{V}$. The treatment is applied to the infected individuals, moving a fraction of them from the infected compartment to the recovered compartment. The vaccination is applied to the susceptible individuals, also moving a fraction of them to the recovered class. Therefore, we will add the control variables $\mathbb{T}$ and $\mathbb{V}$ to system (1) in the interval $t \in [t_0, t_f]$, obtaining the control model

$$\left\{ \begin{array}{lcl} S' & = & \Lambda(t) - \beta(t)\varphi(S,N,I) - \mu(t)S + \eta(t)R - \mathbb{V}S \\ E' & = & \beta(t)\varphi(S,N,I) - (\mu(t) + \varepsilon(t))E \\ I' & = & \varepsilon(t)E - (\mu(t) + \gamma(t))I - \mathbb{T}I \\ R' & = & \gamma(t)I - \mu(t)R - \eta(t)R + \mathbb{T}I + \mathbb{V}S \\ N & = & S + E + I + R \end{array} \right. \tag{3}$$

and we consider the cost functional $\mathcal{J}$, given by

$$\mathcal{J}(I, \mathbb{T}, \mathbb{V}) = \int_0^{t_f} \kappa_1 I + \kappa_2 \mathbb{T}^2 + \kappa_3 \mathbb{V}^2 dt, \ 0 < \kappa_1, \kappa_2, \kappa_3 < \infty. \tag{4}$$

After introducing rigorously our problem in section 4.1, we prove the existence of an optimal solution in section 4.2 and, after stating a suitable version of Pontryagin's maximum principle in section 4.3, we obtain the uniqueness of the optimal control in a sufficiently small interval in section 4.4. Our approach follow the arguments in Gaff and Schaefer [9] that considered an autonomous model and a particular incidence function. In addition to considering general incidence functions, we also allow time-dependent parameters. Finally, in section 4.5, we present some simulation results, designed to compare an autonomous and a corresponding periodic model.

# Chapter 1

## Autonomous model

In this chapter we consider the autonomous version of problem (1), i.e. we assume that the parameter functions are constant.

### 1.1 Setting and Preliminaries

In this chapter we will make the following assumptions:

A1) The parameter functions are constant: $\Lambda(t)=\Lambda$, $\beta(t)=\beta$, $\mu(t)=\mu$, $\varepsilon(t)=\varepsilon$, $\eta(t)=\eta$ and $\gamma(t)=\gamma$ with $\Lambda,\beta,\mu>0$ and $\varepsilon,\eta,\gamma\geq 0$;

A2) Function $\varphi:(\mathbb{R}_0^+)^3\to\mathbb{R}$ is twice continuously differentiable and nonnegative;

A3) For each $0\leq S\leq \Lambda/\mu$ and $0\leq I\leq \Lambda/\mu$, the function $N\mapsto\varphi(S,N,I)$ is non-increasing, for each $0<I\leq N\leq\Lambda/\mu$ the function $S\mapsto\varphi(S,N,I)$ is increasing and, for all $N,S,I\geq 0$, we have $\varphi(0,N,I)=\varphi(S,N,0)=0$;

A4) For each $0<S\leq N\leq\Lambda/\mu$, the function

$$I\mapsto\begin{cases}\dfrac{\varphi(S,N,I)}{I} & \text{if} \quad 0<I\leq\Lambda/\mu\\[2mm] \dfrac{\partial\varphi}{\partial I}(S,N,0) & \text{if} \quad I=0\end{cases}$$

is non-increasing and not identically zero.

Several particular forms for $\varphi$ for particular SEIRS or SEIR models have been considered. For instance, in [22], for a SEIR autonomous model under different assumption than ours, an incidence of the form $\varphi(S,N,I)=SI/(1+bN)$ with $b>0$ was considered. Also for a SEIR autonomous model [20] a general incidence of the form $\varphi(S,N,I)=g(I)S$ satisfying $g\in C^1$, $g(I)>0$, $g(0)=0$ and $\Lambda=\mu$ was considered.

## 1.2 Thresholds for General Autonomous Models

In this section we present a tool, developed by Pauline van den Driessche and James Watmough in [36], to obtain thresholds for permanence and extinction of the disease in autonomous epidemiological models.

Assume that some population is divided into $n$ homogeneous compartments. To consider a general epidemic model for such population, we assume that $x_i$, $i = 1, \ldots, n$, denotes the number of individuals in compartment $i$. We assume that the first $m$ compartments contain infected individuals and that the last $n - m$ compartments are disease-free compartments. Let $X_s$ be the set of disease-free states:

$$X_s = \{(x_1, \ldots, x_n) : x_1 = \cdots = x_m = 0 \text{ and } x_{m+1}, \ldots, x_n \geq 0\}.$$

We denote by $\mathcal{F}_i(x)$ the rate of appearance of new infections in compartment $i$, by $\mathcal{V}_i^+(x)$ the rate of transfer of individuals into compartment $i$ by all other means and by $\mathcal{V}_i^-(x)$ the rate of transfer of individuals out of compartment $i$. We will write $\mathcal{F}(x) = (\mathcal{F}_1(x), \ldots, \mathcal{F}_n(x))$ and analogously $\mathcal{V}^+(x) = (\mathcal{V}_1^+(x), \ldots, \mathcal{V}_n^+(x))$ and $\mathcal{V}^-(x) = (\mathcal{V}_1^-(x), \ldots, \mathcal{V}_n^-(x))$. We will consider epidemic models of the form

$$x' = \mathcal{F}(x) - \mathcal{V}(x) := f(x), \tag{1.1}$$

where $x = (x_1, \ldots, x_n)$ and $\mathcal{V}(x) = \mathcal{V}^-(x) - \mathcal{V}^+(x)$, and verifying the following assumptions:

DW1) Functions $\mathcal{F}$, $\mathcal{V}^-$ and $\mathcal{V}^+$ are twice continuously differentiable;

DW2) If $x \geq 0$, then $\mathcal{F}_i(x), \mathcal{V}_i^-(x), \mathcal{V}_i^+(x) \geq 0$ for $i = 1, \ldots, n$;

DW3) For all $i = 1, \ldots, n$, if $x_i = 0$ then $\mathcal{V}_i^-(x) = 0$;

DW4) If $i > m$ then $\mathcal{F}_i(x) = 0$ ;

DW5) If $x \in X_s$ then $\mathcal{F}_i(x) = 0$ for $i = 1, \ldots, m$;

DW6) If $x \in X_s$ then $\mathcal{V}_i^+(x) = 0$ for $i = 1, \ldots, m$ ;

DW7) There is at least one equilibrium point in $X_s$ denoted by $x^*$;

DW8) All eigenvalues of $d(\mathcal{V}^+ - \mathcal{V}^-)_{x^*}$ have negative real part;

Assumptions DW2), DW3), DW4), DW5) and DW6) are according with the biological context inherent at this epidemiological model. We have the following Lemma:

Lemma 1.2.1 (Lemma 1 of [36]). If (1.1) satisfies DW1) to DW8), then

$$d\mathcal{F}_{x^*} = \begin{bmatrix} F & 0 \\ 0 & 0 \end{bmatrix} \quad \text{and} \quad d\mathcal{V}_{x^*} = \begin{bmatrix} V & 0 \\ J_3 & J_4 \end{bmatrix}$$

where $F$ and $V$ are the $m \times m$ matrices given by

$$F = \left[\frac{\partial \mathcal{F}_i}{\partial x_j}(x^*)\right]_{1\le i,j\le m} \quad \text{and} \quad V = \left[\frac{\partial \mathcal{V}_i}{\partial x_j}(x^*)\right]_{1\le i,j\le m}.$$

Further, $F$ is non-negative, $V$ is a non-singular M-matrix (i.e. a square real matrix whose off-diagonal entries are non-positive and all the eigenvalues have positive real part) and all eigenvalues of $J_4$ have positive real part.

Following [36], we define the basic reproductive ratio of (1.1), $\mathcal{R}_0$, as the spectral radius of the matrix $FV^{-1}$:

$$\mathcal{R}_0 = \rho(FV^{-1}) = \max\{|\lambda| : \lambda \text{ is an eigenvalue of } FV^{-1}\}.$$

We have the following theorem on the permanence and extinction of the disease:

Theorem 1.2.1 (Theorem 2 in [36]). If (1.1) satisfies DW1) to DW8) then the disease-free equilibrium $x^*$ is locally asymptotically stable if $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 > 1$.

## 1.3 Persistence and Extinction

We now consider the autonomous SEIRS model presented in section 1.1. Define the basic reproductive number for this model by

$$\mathcal{R}_0 = \frac{\varepsilon\beta}{(\gamma+\mu)(\mu+\varepsilon)} \partial\varphi/\partial I\,(\Lambda/\mu, \Lambda/\mu, 0). \tag{1.2}$$

We shall see that this number coincides with the one obtained by van den Drissche and Watmough's method.

Firstly we will see that there are important compact invariant sets for this model, namely the sets

$$\Delta = \{(S,E,I,R) \in (\mathbb{R}_0^+)^4 : N = S+E+I+R = \Lambda/\mu\}, \tag{1.3}$$

and

$$\Delta_0 = \{(S,E,I,R) \in (\mathbb{R}_0^+)^4 : N = S+E+I+R \le \Lambda/\mu\}.$$

The next lemma shows that these sets are forward invariant and that, for any solution of system (1), the total population always tends to $\Lambda/\mu$ as $t \to +\infty$.

Lemma 1.3.1. Assume that A1) holds. Then, the sets $\Delta$ and $\Delta_0$ are forward invariant and any solution, $(S(t), E(t), I(t), R(t))$, of (1) verifies

$$\lim_{t\to+\infty} N(t) = \lim_{t\to+\infty} S(t) + E(t) + I(t) + R(t) = \Lambda/\mu.$$

Proof. Adding the equations in system (1) we get the differential equation $N' = \Lambda - \mu N$ that has general solution $N(t) = C\,\mathrm{e}^{-\mu t} + \Lambda/\mu$. Letting $t \to +\infty$ we immediately conclude that $\lim_{t\to+\infty} N(t) = \Lambda/\mu$. It is also immediate that if $N(t_0) = \Lambda/\mu$ then $C = 0$ and thus $N(t) = \Lambda/\mu$ for all $t \geq t_0$. This establishes the forward invariance of the set $\Delta$. Assume now that $S(t_0) + E(t_0) + I(t_0) + R(t_0) \leq \Lambda/\mu$ for some $t_0 \in \mathbb{R}_0^+$. Then we have $\Lambda/\mu \geq N(t_0) = C\,\mathrm{e}^{-\mu t_0} + \Lambda/\mu$ and then $C \leq 0$. We conclude that $N(t) \leq \Lambda/\mu$ for all $t \geq t_0$ and that $\Delta_0$ is forward invariant. □

Note that, according to A1) and A2), the right end side of our system is continuous and locally Lipschitz and thus, by Picard–Lindelöf's theorem we have existence and uniqueness of (local) solution for our problem. By Lemma 1.3.1, every solution is global in the future. Next, we will discuss the existence of equilibrium points of the system.

Theorem 1.3.1. Assuming that A1) to A4) hold and that $\varepsilon > 0$, equation

$$\beta\varphi((\Lambda - bI)/\mu, \Lambda/\mu, I)/I - (\mu + \varepsilon)(\mu + \gamma)/\varepsilon = 0 \tag{1.4}$$

where $b = \mu((\mu + \eta + \varepsilon)(\mu + \gamma) + \varepsilon\eta)/(\varepsilon(\mu + \eta))$, has a unique solution in $]0, +\infty[$, $I^\#$, if $\mathcal{R}_0 > 1$ and no solutions in $]0, +\infty[$ if $\mathcal{R}_0 \leq 1$. We have the following:

1. if $\mathcal{R}_0 \leq 1$ then system (1) has exactly one equilibrium point, the disease-free equilibrium $e^* = (\Lambda/\mu, 0, 0, 0)$;

2. if $\mathcal{R}_0 > 1$ then system (1) has exactly two equilibrium points, the disease-free equilibrium $e^* = (\Lambda/\mu, 0, 0, 0)$ and the endemic equilibrium

   $$e^\# = (\Lambda/\mu - bI^\#/\mu, (\mu + \gamma)I^\#/\varepsilon, I^\#, \gamma I^\#/(\mu + \eta)),$$

   where $I^\#$ is the unique solution of (1.4).

Proof. The equilibrium points of system (1) are the solutions of

$$\begin{cases} \Lambda - \beta\,\varphi(S, N, I) - \mu S + \eta R = 0 \\ \beta\,\varphi(S, N, I) - (\mu + \varepsilon)E = 0 \\ \varepsilon E - (\mu + \gamma)I = 0 \\ \gamma I - (\mu + \eta)R = 0 \end{cases}.$$

We obtain immediately $E = (\mu+\gamma)I/\varepsilon$ and $R = \gamma I/(\mu+\eta)$. By the second equation we get $\beta\,\varphi(S,N,I) = (\mu+\varepsilon)E$. Therefore, using the first equation we get

$$\Lambda - (\mu+\varepsilon)E - \mu S + \eta R = 0 \quad \Leftrightarrow \quad S = \frac{1}{\mu}\left(\Lambda - bI\right),$$

where

$$b = \frac{(\mu+\varepsilon)(\mu+\gamma)}{\varepsilon} - \frac{\eta\gamma}{\mu+\eta}. \tag{1.5}$$

Finally, from the first equation

$$-\,\beta\,\varphi\left((\Lambda - bI)/\mu, \Lambda/\mu, I\right) + bI + \frac{\gamma\eta}{\mu+\eta}I = 0, \tag{1.6}$$

where we used the fact that, by Lemma 1.3.1, at any equilibrium point the total population must be $N = \Lambda/\mu$.

Define, for $I > 0$,

$$P(I) = -\beta\,\frac{\varphi\left((\Lambda - bI)/\mu, \Lambda/\mu, I\right)}{I} + b + \frac{\gamma\eta}{\mu+\eta}$$

and note that, for $I > 0$, equation (1.6) can be written in the form $P(I)I = 0$.

By A2) and A3) we have

$$\frac{\partial\varphi}{\partial N}(\Lambda/\mu, \Lambda/\mu, 0) = \lim_{h\to 0^+} \frac{\varphi(\Lambda/\mu, \Lambda/\mu + h, 0) - \varphi(\Lambda/\mu, \Lambda/\mu, 0)}{h} = \lim_{h\to 0^+} \frac{0}{h} = 0, \tag{1.7}$$

and similarly $\frac{\partial\varphi}{\partial S}(\Lambda/\mu, \Lambda/\mu, 0) = 0$, by A1) to A4) we obtain

$$\begin{aligned}
&\lim_{I\to 0^+} \frac{\varphi(\Lambda/\mu - bI/\mu, \Lambda/\mu, I)}{I} \\
&= \lim_{I\to 0^+} \frac{\varphi(\Lambda/\mu, \Lambda/\mu, I)}{I} \lim_{I\to 0^+} \frac{\varphi(\Lambda/\mu - bI/\mu, \Lambda/\mu, I)}{\varphi(\Lambda/\mu, \Lambda/\mu, I)} \\
&= \frac{\partial\varphi}{\partial I}(\Lambda/\mu, \Lambda/\mu, 0) \lim_{I\to 0^+} \frac{-\frac{b}{\mu}\frac{\partial\varphi}{\partial S}(\Lambda/\mu - bI/\mu, \Lambda/\mu, I) + \frac{\partial\varphi}{\partial I}(\Lambda/\mu - bI/\mu, \Lambda/\mu, I)}{\frac{\partial\varphi}{\partial I}(\Lambda/\mu, \Lambda/\mu, I)} \\
&= \frac{\partial\varphi}{\partial I}(\Lambda/\mu, \Lambda/\mu, 0) \left(1 - \frac{\frac{b}{\mu}\frac{\partial\varphi}{\partial S}(\Lambda/\mu, \Lambda/\mu, 0)}{\frac{\partial\varphi}{\partial I}(\Lambda/\mu, \Lambda/\mu, 0)}\right)
\end{aligned}$$

and thus

$$\lim_{I\to 0^+} \frac{\varphi(\Lambda/\mu - bI/\mu, \Lambda/\mu, I)}{I} = \frac{\partial\varphi}{\partial I}(\Lambda/\mu, \Lambda/\mu, 0). \tag{1.8}$$

We will now turn our attention to function $P$. We have, according to (1.8),

$$\begin{aligned}\lim_{I\to 0^+} P(I) &= \lim_{I\to 0^+} -\beta\,\frac{\varphi\left((\Lambda-bI)/\mu,\Lambda/\mu,I\right)}{I}+b+\frac{\gamma\eta}{\mu+\eta}\\ &= -\beta\,\frac{\partial\varphi}{\partial I}(\Lambda/\mu,\Lambda/\mu,0)+b+\frac{\gamma\eta}{\mu+\eta}\\ &= -\beta\,\frac{\partial\varphi}{\partial I}(\Lambda/\mu,\Lambda/\mu,0)+\frac{(\mu+\varepsilon)(\mu+\gamma)}{\varepsilon}\\ &= \frac{(\mu+\varepsilon)(\mu+\gamma)}{\varepsilon}\left(1-\mathcal{R}_0\right).\end{aligned} \tag{1.9}$$

Letting $c(I)=(\Lambda/\mu-bI,\Lambda/\mu,I)$, by A3) and A4), we have $\frac{\partial\varphi}{\partial I}(c(I))I-\varphi(c(I))\le 0$ and thus

$$\frac{\partial P}{\partial I}=-\beta\frac{-\frac{b}{\mu}\frac{\partial\varphi}{\partial S}(c(I))I+\frac{\partial\varphi}{\partial I}(c(I))I-\varphi(c(I))}{I^2}>0. \tag{1.10}$$

By (1.8) and (1.10), we conclude that there is $I>0$ such that $P(I)=0$ if and only if $\mathcal{R}_0>1$ and in this case there is a unique solution of $P(I)=0$. Call it $I^{\#}$. It is now easy to check that if $\mathcal{R}_0>1$ then (1.6) has two solutions, $I=0$ and $I=I^{\#}$, and if $\mathcal{R}_0\le 1$ then (1.6) has a unique solution, $I=0$. Thus if $\mathcal{R}_0>1$ then (1) has two solutions, $e^*$ and $e^{\#}$, and if $\mathcal{R}_0\le 1$ then (1) has a unique solution, $e^*$. □

Note that, when $\varepsilon=0$, we have $\mathcal{R}_0=0<1$ and $e^*$ is the unique equilibrium.

We have the theorem:

Theorem 1.3.2. Under assumptions A1) to A4), the disease-free equilibrium $e^*=(\Lambda/\mu,0,0,0)$ is locally asymptotically stable if $\mathcal{R}_0<1$ and unstable if $\mathcal{R}_0>1$, where $\mathcal{R}_0$ is the constant in (1.2).

Proof. To obtain our result we will use Theorem 1.2.1. Using the ordering $(x_1,x_2,x_3,x_4)=(E,I,S,R)$, we have the following:

$$\mathcal{F}=\begin{bmatrix}\beta\varphi(S,N,I)\\0\\0\\0\end{bmatrix}\quad \mathcal{V}^-=\begin{bmatrix}(\mu+\varepsilon)E\\(\mu+\gamma)I\\\beta\varphi(S,N,I)+\mu S\\(\mu+\eta)R\end{bmatrix}\quad \mathcal{V}^+=\begin{bmatrix}0\\\varepsilon E\\\Lambda+\eta R\\\gamma I\end{bmatrix}.$$

In our context $X_s=\{(E,I,S,R)\in(\mathbb{R}_0^+)^4: E=I=0\}$ and it is easy to see that conditions DW1) to DW6) hold. By Theorem 1.3.1, we have a (unique) disease-free equilibrium given by $e^*=(\Lambda/\mu,0,0,0)\in X_s$ and condition DW7) is verified. Since $\frac{\partial\varphi}{\partial S}(\Lambda/\mu,\Lambda/\mu,0)=\frac{\partial\varphi}{\partial N}(\Lambda/\mu,\Lambda/\mu,0)=0$, we have

$$d(\mathcal{V}^+-\mathcal{V}^-)_{e^*}=\begin{bmatrix}-(\mu+\varepsilon)&0&0&0\\\varepsilon&-(\mu+\gamma)&0&0\\0&-\beta\frac{\partial\varphi}{\partial I}(\Lambda/\mu,\Lambda/\mu,0)&-\mu&\eta\\0&\gamma&0&-(\mu+\eta)\end{bmatrix}.$$

We can easily compute the eigenvalues of this matrix: $\lambda_1 = -(\mu+\varepsilon)$, $\lambda_2 = -(\mu+\gamma)$, $\lambda_3 = -\mu$ and $\lambda_4 = -(\mu+\eta)$. By A1) all eigenvalues are negative and DW8) holds.

By (1.7) we conclude that $\partial\varphi/\partial N(\Lambda/\mu, \Lambda/\mu, 0) = 0$ and we can compute the matrices $F$ and $V$ for our model

$$F = \begin{bmatrix} 0 & \beta\dfrac{\partial\varphi}{\partial I}(\Lambda/\mu, \Lambda/\mu, 0) \\ 0 & 0 \end{bmatrix} \quad \text{and} \quad V = \begin{bmatrix} \mu+\varepsilon & 0 \\ -\varepsilon & \mu+\gamma \end{bmatrix}.$$

Some simple computation yield,

$$FV^{-1} = \begin{bmatrix} \dfrac{\beta\varepsilon\ \partial\varphi/\partial I(\Lambda/\mu, \Lambda/\mu, 0)}{(\mu+\varepsilon)(\mu+\gamma)} & \dfrac{\beta\ \partial\varphi/\partial I(\Lambda/\mu, \Lambda/\mu, 0)}{\mu+\gamma} \\ 0 & 0 \end{bmatrix}$$

and thus we obtain

$$\begin{aligned} \rho(FV^{-1}) &= \frac{\varepsilon\beta}{(\mu+\gamma)(\mu+\varepsilon)} \left|\partial\varphi/\partial I\,(\Lambda/\mu, \Lambda/\mu, 0)\right| \\ &= \frac{\varepsilon\beta}{(\mu+\gamma)(\mu+\varepsilon)} \partial\varphi/\partial I\,(\Lambda/\mu, \Lambda/\mu, 0) \\ &= \mathcal{R}_0, \end{aligned} \tag{1.11}$$

and the theorem follows from Theorem 1.2.1. □

## 1.4 Global Stability

In this section we will obtain the global stability of the disease-free equilibrium and, under the assumption that the incidence has some special form, we obtain the global stability of the endemic equilibrium.

Theorem 1.4.1. Assume that A1) to A4) hold. Then the disease-free equilibrium $e^*$ is globally asymptotically stable if $\mathcal{R}_0 < 1$, where $\mathcal{R}_0$ is the constant in (1.2).

Proof. We will first establish the global stability of $e^*$ in $\Delta$, the set defined in (1.3). Assume that $\varepsilon > 0$. From assumption A4), the function $\widetilde{\varphi}_{S,N} : [0, \Lambda/\mu] \to \mathbb{R}$ given by

$$\widetilde{\varphi}_{S,N}(I) = \begin{cases} \varphi(S, N, I)/I & \text{if} \quad 0 < I \le \Lambda/\mu \\ \dfrac{\partial\varphi}{\partial I}(S, N, 0) & \text{if} \quad I = 0 \end{cases}$$

is non-increasing and, according to A3), the function $\overline{\varphi}_{N,I} : [0, \Lambda/\mu] \to \mathbb{R}$ given by $\overline{\varphi}_{N,I}(S) = \varphi(S, N, I)$ is increasing. Thus, for any $I \in [0, \Lambda/\mu]$,

$$\varphi(\Lambda/\mu - bI/\mu, \Lambda/\mu, I) = \overline{\varphi}_{\Lambda/\mu,I}(\Lambda/\mu - bI/\mu) < \overline{\varphi}_{\Lambda/\mu,I}(\Lambda/\mu) = \widetilde{\varphi}_{\Lambda/\mu,\Lambda/\mu}(I)I,$$

where $b$ is given by (1.5). Note that

$$b = \frac{\mu(\mu+\varepsilon)}{\varepsilon} + \gamma\left(\frac{\mu+\varepsilon}{\varepsilon} - \frac{\eta}{\mu+\eta}\right) > \frac{\mu(\mu+\varepsilon)}{\varepsilon} > 0.$$

Therefore, by A4),

$$\varphi(\Lambda/\mu - bI/\mu, \Lambda/\mu, I) < \sup_{\delta\in[0,\Lambda/\mu]} \widetilde{\varphi}_{\Lambda/\mu,\Lambda/\mu}(\delta) I = \frac{\partial \varphi}{\partial I}(\Lambda/\mu, \Lambda/\mu, 0) I.$$

Consider the function $L : \Delta \to \mathbb{R}$ given by

$$L(S,E,I,R) = \frac{\varepsilon}{\mu+\varepsilon}E + I.$$

In the set $\Delta$ we have $N = \Lambda/\mu$ and thus, by A3) and A4), we have for $I > 0$

$$\begin{aligned}
L' &= \frac{\varepsilon}{\mu+\varepsilon}E' + I' \\
&= \frac{\varepsilon}{\mu+\varepsilon}(\beta\varphi(S,\Lambda/\mu,I) - (\mu+\varepsilon)E) + \varepsilon E - (\gamma+\mu)I \\
&= \frac{\varepsilon\beta\varphi(S,\Lambda/\mu,I)}{\mu+\varepsilon} - (\gamma+\mu)I \\
&\leq \frac{\varepsilon\beta\varphi(\Lambda/\mu,\Lambda/\mu,I)}{\mu+\varepsilon} - (\gamma+\mu)I \\
&= \left(\frac{\varepsilon\beta\widetilde{\varphi}_{\Lambda/\mu,\Lambda/\mu}(I)}{\mu+\varepsilon} - (\gamma+\mu)\right) I \\
&\leq \left(\frac{\varepsilon\beta}{\mu+\varepsilon}\frac{\partial\varphi}{\partial I}(\Lambda/\mu,\Lambda/\mu,0) - (\gamma+\mu)\right) I \\
&= (\gamma+\mu)(\mathcal{R}_0 - 1)I < 0,
\end{aligned}$$

since $\mathcal{R}_0 < 1$. Thus $L$ is a Lyapunov function for system (1) in $\Delta$ and $L' = 0$ if and only if $I = 0$. Therefore the largest compact invariant subset of $\Delta$ where $L' = 0$ is the set $\{(S,E,I,R) \in \Delta : E = I = 0\}$. By Lemma 1.3.1, the positive orbits of (1) are bounded and thus, by LaSalle's invariance principle, Theorem 6.4 in Chapter 2 of [19] (see also for instance [12, 44]), we conclude that

$$I(t) \to 0 \quad \text{as} \quad t \to +\infty. \tag{1.12}$$

Given $\delta > 0$ there is $T_\delta \in \mathbb{R}^+$ such that $0 < I(t) \leq \delta$ for all $t \geq T_\delta$. Thus

$$\begin{aligned}
E' &\leq \beta\frac{\varphi(\Lambda/\mu,\Lambda/\mu,I)}{I}I - (\mu+\varepsilon)E \\
&\leq \beta\frac{\partial\varphi}{\partial I}(\Lambda/\mu,\Lambda/\mu,0)\delta - (\mu+\varepsilon)E
\end{aligned}$$

and therefore

$$E(t) \leq \beta \frac{\frac{\partial \varphi}{\partial I}(\Lambda/\mu, \Lambda/\mu, 0)}{\mu + \varepsilon} \delta + C\,\mathrm{e}^{-(\mu+\varepsilon)t}$$

and, since $\delta > 0$ is arbitrary, we conclude that

$$E(t) \to 0 \quad \text{as} \quad t \to +\infty. \tag{1.13}$$

By (1.12) and (1.13), given $\delta > 0$ there is $T_\delta \in \mathbb{R}^+$ such that $I(t), E(t) \leq \delta$ for all $t \geq T_\delta$. By the fourth equation in system (1) we get

$$R' = \gamma I - (\mu + \eta)R \leq \gamma\delta - (\mu + \eta)R,$$

for all $t \geq T_\delta$. Thus, by comparison we get,

$$R(t) \leq C\,\mathrm{e}^{-(\mu+\eta)t} + \frac{\gamma\delta}{\mu + \eta}.$$

Since $\delta > 0$ is arbitrary, we conclude that

$$R(t) \to 0 \quad \text{as} \quad t \to +\infty. \tag{1.14}$$

Finally by (1.12), (1.13) and (1.14) we obtain

$$S(t) = N(t) - E(t) - R(t) - I(t) \to \Lambda/\mu - 0 - 0 - 0 = \Lambda/\mu, \tag{1.15}$$

as $t \to +\infty$, and we conclude that $e^* = (\Lambda/\mu, 0, 0, 0)$ is globally asymptotically stable in $\Delta$, assuming that $\varepsilon > 0$.

On the other hand, if $\varepsilon = 0$, we can easily check that the third equation in (1) assures that $I(t) \to 0$ as $t \to +\infty$ and thus, by a similar reasoning we can obtain (1.13), (1.14) and (1.15).

Now, let $q(t) = (S(t), E(t), I(t), R(t))$ be some solution of system (1) with initial condition $q_0 = (S(t_0), E(t_0), I(t_0), R(t_0)) = (S_0, E_0, I_0, R_0)$ contained in $(\mathbb{R}_0^+)^4 \setminus \Delta$. Since $N(t) \to \Lambda/\mu$ as $t \to +\infty$, we conclude that the $\omega$-limit of the orbit $q = \{q(t) : t \geq t_0\}$ must be contained in $\Delta$. Assume by contradiction that $a \in \Delta \setminus \{e^*\}$ is in the $\omega$-limit of $q$. Since $\{e^*\}$ is the $\omega$-limit of any orbit in $\Delta$, it follows that $\{e^*\}$ is the $\omega$-limit of the orbit $p$ contained in $\Delta$ and such that $p(0) = a$. By invariance of the $\omega$-limit, we conclude that the orbit $p$ is in the $\omega$-limit of $q$. Since the omega limit of $p$ is $\{e^*\}$, for any given $\delta > 0$ there must $t_\delta$ such that $\|p(t_\delta) - e^*\| < \delta/2$. Since $p(t_\delta)$ is in the $\omega$-limit of $q$ there must be $t_1$ such that $\|q(t_1) - p(t_\delta)\| < \delta/2$. Thus for any given $\delta > 0$ there is $t_1 > 0$ such that

$$\|q(t_1) - e^*\| \leq \|q(t_1) - p(t_\delta)\| + \|p(t_\delta) - e^*\| < \delta. \tag{1.16}$$

But, since $e^*$ is locally asymptotically stable, by Theorem 1.3.2, we conclude that there is some $\delta_1 > 0$ such that the $\omega$-limit of any orbit that enters the ball $B_{\delta_1}(e^*)$ is $\{e^*\}$. By (1.16) the orbit $q$ enters the ball $B_{\delta_1}(e^*)$ and we conclude that the $\omega$-limit of $q$ is $\{e^*\}$. A contradiction. Thus, $a$ is not in the $\omega$-limit of $q$. Since $\overline{B_{\delta_1}(e^*)}$ is compact, $q$ is bounded and thus the $\omega$-limit of $q$ is nonempty. We conclude that it must be equal to $\{e^*\}$. We conclude that $\{e^*\}$ is the $\omega$-limit of any orbit in $(\mathbb{R}_0^4)^+$ and thus $\{e^*\}$ is globally asymptotically stable in $(\mathbb{R}_0^4)^+$. □

Next, we will obtain a theorem on the global stability of the endemic equilibrium.

Theorem 1.4.2. Assume that A1) to A4) hold. Assume further that $\eta = 0$ and that $\varphi(S, N, I) = C(N)\psi(I)S$ with $I \mapsto \psi(I)$ increasing and $I \mapsto \psi(I)/I$ non-increasing. In these conditions, if $\mathcal{R}_0 > 1$, where $\mathcal{R}_0$ is the constant in (1.2), the endemic equilibrium $e^\#$ is globally asymptotically stable in

$$\Delta_1 := \{(S, E, I, R) \in \Delta : E > 0 \text{ or } I > 0\}. \tag{1.17}$$

Moreover, if $C(N) = 1$ then $e^\#$ is globally asymptotically stable in

$$\Delta_2 := \{(S, E, I, R) \in (\mathbb{R}_0^+)^4 : E > 0 \text{ or } I > 0\}. \tag{1.18}$$

Proof. Let $e^\# = (S^\#, E^\#, I^\#, R^\#)$ and consider the function $L : \mathcal{C} \to \mathbb{R}$, where $\mathcal{C} = \Delta_1$ or $\mathcal{C} = \Delta_2$, given by

$$\begin{aligned} L = {} & S - S^\# - S^\# \ln(S/S^\#) + E - E^\# - E^\# \ln(E/E^\#) \\ & + \frac{\mu + \varepsilon}{\varepsilon} \left[ I - I^\# - I^\# \ln(I/I^\#) \right]. \end{aligned}$$

First note that at the endemic equilibrium we have

$$\Lambda = \beta\varphi(S^\#, \Lambda/\mu, I^\#) + \mu S^\#, \quad \mu + \varepsilon = \frac{\beta\varphi(S^\#, \Lambda/\mu, I^\#)}{E^\#} \quad \text{and} \quad \frac{\mu + \gamma}{\varepsilon} = \frac{E^\#}{I^\#}$$

We have

$$\begin{aligned} L' &= S' - S^\# S'/S + E' - E^\# E'/E + \frac{\mu + \varepsilon}{\varepsilon} \left[ I' - I^\# I'/I \right] \\ &= \Lambda - \beta\varphi(S, N, I) - \mu S - \frac{S^\#}{S}(\Lambda - \beta\varphi(S, N, I) - \mu S) \\ &\quad + \beta\varphi(S, N, I) - (\mu + \varepsilon)E - \frac{E^\#}{E}(\beta\varphi(S, N, I) - (\mu + \varepsilon)E) \\ &\quad + \frac{\mu + \varepsilon}{\varepsilon} \left[ \varepsilon E - (\mu + \gamma)I - \frac{I^\#}{I}(\varepsilon E - (\mu + \gamma)I) \right] \end{aligned}$$

and thus

$$\begin{aligned}
L' &= \Lambda\left(1-\frac{S^\#}{S}\right)-\mu S\left(1-\frac{S^\#}{S}\right)+\beta S^\#\frac{\varphi(S,N,I)}{S}-\frac{(\mu+\varepsilon)(\mu+\gamma)}{\varepsilon}I\\
&\quad-\frac{E^\#\beta\varphi(S,N,I)}{E}+(\mu+\varepsilon)E^\#-\frac{(\mu+\varepsilon)I^\#E}{I}+\frac{(\mu+\varepsilon)(\mu+\gamma)}{\varepsilon}I^\#\\
&=\mu S^\#\left(2-\frac{S^\#}{S}-\frac{S}{S^\#}\right)-\beta\frac{S^\#}{S}\varphi(S^\#,\Lambda/\mu,I^\#)+\beta\varphi(S^\#,\Lambda/\mu,I^\#)\\
&\quad+\beta\varphi(S,N,I)S^\#/S-\beta\varphi(S^\#,\Lambda/\mu,I^\#)I/I^\#-\beta\varphi(S,N,I)E^\#/E\\
&\quad+\beta\varphi(S^\#,\Lambda/\mu,I^\#)-\beta\varphi(S^\#,\Lambda/\mu,I^\#)I^\#E/(E^\#I)+\beta\varphi(S^\#,\Lambda/\mu,I^\#).
\end{aligned}$$

Adding and subtracting

$$\beta\varphi(S^\#,\Lambda/\mu,I^\#)\quad\text{and}\quad\beta\frac{\left(\varphi(S^\#,\Lambda/\mu,I^\#)\right)^2IS}{\varphi(S,N,I)I^\#S^\#}$$

we get

$$\begin{aligned}
L' &= \mu S^\#\left(2-\frac{S^\#}{S}-\frac{S}{S^\#}\right)+\beta\varphi(S^\#,\Lambda/\mu,I^\#)\times\\
&\quad\times\left(4-\frac{S^\#}{S}-\frac{\varphi(S,N,I)E^\#}{\varphi(S^\#,\Lambda/\mu,I^\#)E}-\frac{I^\#E}{E^\#I}-\frac{\varphi(S^\#,\Lambda/\mu,I^\#)IS}{\varphi(S,N,I)S^\#I^\#}\right)\\
&\quad-\beta\varphi(S^\#,\Lambda/\mu,I^\#)+\beta\frac{\left(\varphi(S^\#,\Lambda/\mu,I^\#)\right)^2IS}{\varphi(S,N,I)I^\#S^\#}+\beta\frac{\varphi(S,N,I)S^\#}{S}\\
&\quad-\beta\frac{\varphi(S^\#,\Lambda/\mu,I^\#)I}{I^\#}.
\end{aligned}$$

Thus

$$\begin{aligned}
L' &= \mu S^\#\left(2-\frac{S^\#}{S}-\frac{S}{S^\#}\right)+\beta\varphi(S^\#,\Lambda/\mu,I^\#)\times\\
&\quad\times\left(4-\frac{S^\#}{S}-\frac{\varphi(S,N,I)E^\#}{\varphi(S^\#,\Lambda/\mu,I^\#)E}-\frac{I^\#E}{E^\#I}-\frac{\varphi(S^\#,\Lambda/\mu,I^\#)IS}{\varphi(S,N,I)S^\#I^\#}\right)\\
&\quad+(\Lambda-\mu S^\#)\left(-1+\frac{\varphi(S^\#,\Lambda/\mu,I^\#)IS}{\varphi(S,N,I)I^\#S^\#}+\frac{\varphi(S,N,I)S^\#}{\varphi(S^\#,\Lambda/\mu,I^\#)S}-\frac{I}{I^\#}\right)\\
&=\mu S^\#\left(2-\frac{S^\#}{S}-\frac{S}{S^\#}\right)+\beta\varphi(S^\#,\Lambda/\mu,I^\#)\times\\
&\quad\times\left(4-\frac{S^\#}{S}-\frac{\varphi(S,N,I)E^\#}{\varphi(S^\#,\Lambda/\mu,I^\#)E}-\frac{I^\#E}{E^\#I}-\frac{\varphi(S^\#,\Lambda/\mu,I^\#)IS}{\varphi(S,N,I)S^\#I^\#}\right)\\
&\quad+(\Lambda-\mu S^\#)\frac{IS}{\varphi(S,N,I)}\times\\
&\quad\times\left(\frac{\varphi(S,N,I)}{IS}-\frac{\varphi(S^\#,\Lambda/\mu,I^\#)}{I^\#S^\#}\right)\left(\frac{\varphi(S,N,I)S^\#}{\varphi(S^\#,\Lambda/\mu,I^\#)S}-1\right).
\end{aligned}$$

Using the fact that $x^2 + y^2 \geq 2xy$ (with equality if and only if $x = y$) we conclude that

$$2 - \frac{S^\#}{S} - \frac{S}{S^\#} \leq 0, \tag{1.19}$$

with equality if and only if $S = S^\#$. We claim that

$$4 - \frac{S^\#}{S} - \frac{\varphi(S,N,I)E^\#}{\varphi(S^\#,\Lambda/\mu,I^\#)E} - \frac{I^\# E}{E^\# I} - \frac{\varphi(S^\#,\Lambda/\mu,I^\#)IS}{\varphi(S,N,I)S^\# I^\#} \leq 0. \tag{1.20}$$

In fact we have

$$\begin{aligned}
&\frac{\varphi(S,N,I)E^\#}{\varphi(S^\#,\Lambda/\mu,I^\#)E} + \frac{\varphi(S^\#,\Lambda/\mu,I^\#)IS}{\varphi(S,N,I)S^\# I^\#} \\
&= \frac{\varphi(S,N,I)^2 E^\# S^\# I^\# + \varphi(S^\#,\Lambda/\mu,I^\#)^2 ESI}{\varphi(S^\#,\Lambda/\mu,I^\#)\varphi(S,N,I)S^\# I^\# E} \\
&\geq 2\frac{\sqrt{E^\# SI}}{\sqrt{S^\# I^\# E}}
\end{aligned}$$

and analogously

$$\frac{S^\#}{S} + \frac{I^\# E}{E^\# I} \geq 2\frac{\sqrt{S^\# I^\# E}}{\sqrt{E^\# SI}}$$

and thus

$$\begin{aligned}
&4 - \frac{S^\#}{S} - \frac{\varphi(S,N,I)E^\#}{\varphi(S^\#,\Lambda/\mu,I^\#)E} - \frac{I^\# E}{E^\# I} - \frac{\varphi(S^\#,\Lambda/\mu,I^\#)IS}{\varphi(S,N,I)S^\# I^\#} \\
&\leq 4 - 2\left(\frac{\sqrt{E^\# SI}}{\sqrt{S^\# I^\# E}} + \frac{\sqrt{S^\# I^\# E}}{\sqrt{E^\# SI}}\right) \leq 0,
\end{aligned}$$

establishing (1.20).

Since $\varphi(S,N,I) = C(N)\psi(I)S$ with $I \mapsto \psi(I)$ increasing and $I \mapsto \psi(I)/I$ non-increasing, for $(S,E,I,R) \in \Delta_1$ we have

$$\begin{aligned}
&\left(\frac{\varphi(S,N,I)}{IS} - \frac{\varphi(S^\#,\Lambda/\mu,I^\#)}{I^\# S^\#}\right)\left(\frac{\varphi(S,N,I)S^\#}{\varphi(S^\#,\Lambda/\mu,I^\#)S} - 1\right) \\
&= C(\Lambda/\mu)\left(\frac{\psi(I)}{I} - \frac{\psi(I^\#)}{I^\#}\right)\left(\frac{\psi(I)}{\psi(I^\#)} - 1\right) \leq 0.
\end{aligned} \tag{1.21}$$

By A3), Theorem 1.3.1, and since $(\mu+\gamma)I^\# = \varepsilon E^\#$, it is easy to check that we have equality in (1.19), (1.20) and (1.21) if and only if $S = S^\#$, $I = I^\#$ and $E = E^\#$. Therefore $L$ is a Lyapunov function in $\Delta_1$ if $\mathcal{R}_0 > 1$ and, since $I \mapsto \psi(I)$ is increasing and $I \mapsto \psi(I)/I$ is non-increasing, $L' = 0$ if and only if $S = S^\#$, $E = E^\#$ and $I = I^\#$. It follows that the largest compact invariant subset of $\Delta_1$ where $L' = 0$ is the set

$$\{(S,E,I,R) \in \Delta_1 : S = S^\#, E = E^\# \text{ and } I = I^\#\}.$$

According to Lemma 1.3.1, the positive orbits of (1) are bounded and thus, by LaSalle's invariance principle [19] (see also [44, 12]), we conclude that

$$S(t) \to S^{\#}, \quad E(t) \to E^{\#} \quad \text{and} \quad I(t) \to I^{\#} \tag{1.22}$$

as $t \to +\infty$. Therefore

$$\lim_{t\to+\infty} R(t) = \Lambda/\mu - \lim_{t\to+\infty} (S(t) + E(t) + I(t)) = \Lambda/\mu - S^{\#} - E^{\#} - I^{\#} = R^{\#}$$

and we conclude that $e^{\#}$ is globally asymptotically stable in $\Delta_1$.

Assuming now that $C(N) = 1$, for $(S, E, I, R) \in \Delta_2$ we have

$$\begin{aligned} &\left(\frac{\varphi(S,N,I)}{IS} - \frac{\varphi(S^{\#},\Lambda/\mu,I^{\#})}{I^{\#}S^{\#}}\right)\left(\frac{\varphi(S,N,I)S^{\#}}{\varphi(S^{\#},\Lambda/\mu,I^{\#})S} - 1\right) \\ &= \left(\frac{\psi(I)}{I} - \frac{\psi(I^{\#})}{I^{\#}}\right)\left(\frac{\psi(I)}{\psi(I^{\#})} - 1\right) \le 0. \end{aligned} \tag{1.23}$$

Reasoning like before, we conclude that $e^{\#}$ is globally asymptotically stable in $\Delta_2$. □

Note in particular that Theorem 1.4.2 shows that, when $\eta = 0$ and $\mathcal{R}_0 > 1$, the endemic equilibrium is globally asymptotically stable in $\Delta_2$ for the Michaelis-Menten incidence functions.

## 1.5 Example

In this section we illustrate the obtained results in this chapter, by considering the particular model:

$$\begin{cases} S' = \Lambda - \beta SI - \mu S \\ E' = \beta SI - (\mu E + \varepsilon)E \\ I' = \varepsilon E - (\mu + \gamma)I \\ R' = \gamma I - \mu R \\ N = S + E + I + R \end{cases} . \tag{1.24}$$

Inspired in [30], we set $\Lambda = \mu = 2$, $\varepsilon = 1$, $\gamma = 0.02$ and consider the following initial conditions $S_0 = E_0 = I_0 = R_0 = 0.1$ (black lines). We assume that there is no loss of immunity and let $\eta = 0$. On the left-hand side of figure 1.1 we considered $\beta = 5.9$, and we can see that all trajectories approach the disease-free equilibrium $e^* = (1, 0, 0, 0)$ and thus that the disease goes to extinction. In this case, we have approximately $\mathcal{R}_0 = 0.9736 < 1$ and Theorem 1.4.1 confirms that, in fact, the disease-free equilibrium is globally asymptotically stable. On the right-hand side of figure 1.1 we now make $\beta = 6.9$, and we can see that the disease persists and that all trajectories approach the endemic equilibrium $e^{\#} \approx (0.8782, 0.081, 0.0402, 0.0004)$. In this case, we have approximately $\mathcal{R}_0 = 1.1386 > 1$ and Theorem 1.4.1 states that the endemic equilibrium is globally asymptotically stable. The red and cyan lines correspond respectively to solutions with the following initial conditions: $S_0 = 0.08$, $E_0 = 0.07$, $I_0 = 0.12$, $R_0 = 0.13$ and $S_0 = 1.99$, $E_0 = 0.09$, $I_0 = 0.05$, $R_0 = 0.25$.

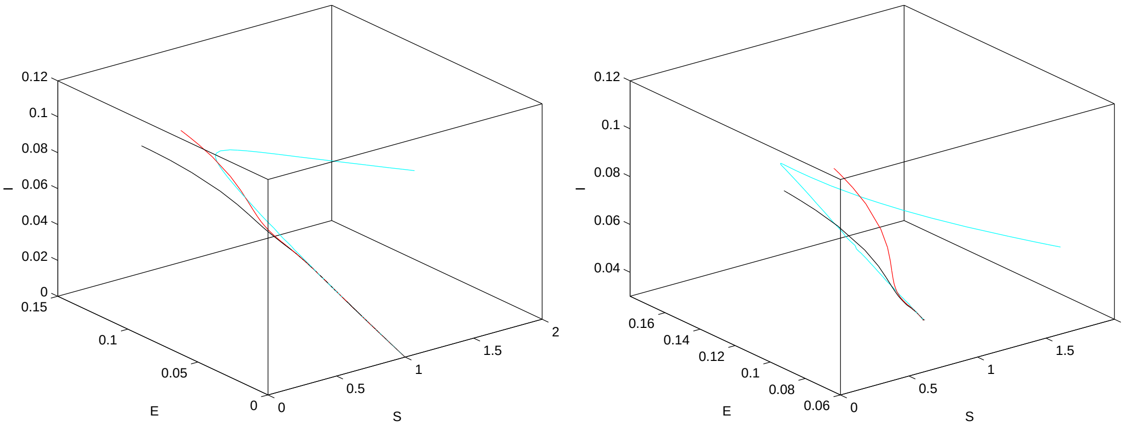


Figure 1.1: Disease Free Case and Endemic Case.

In figures 1.2 and 1.3 we present the trajectories of the infectives and the susceptibles for the above situations.

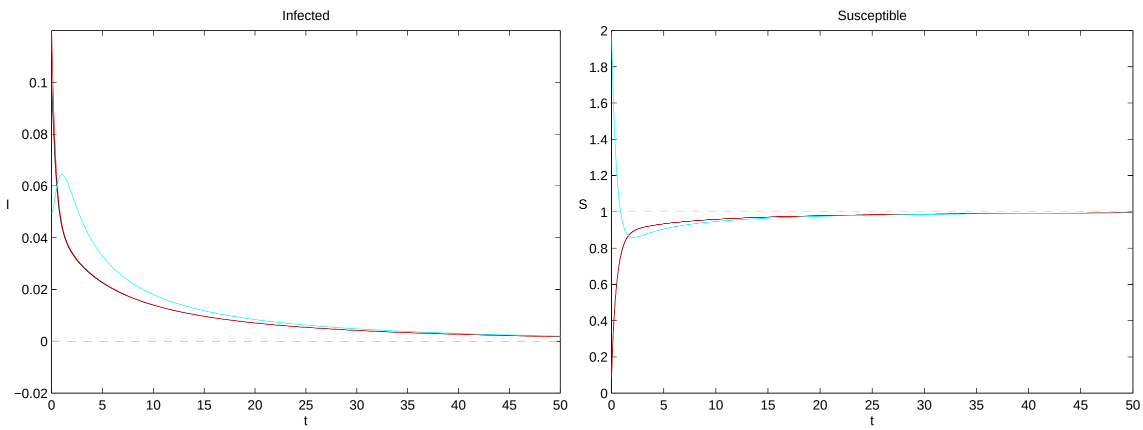


Figure 1.2: Disease Free Case.

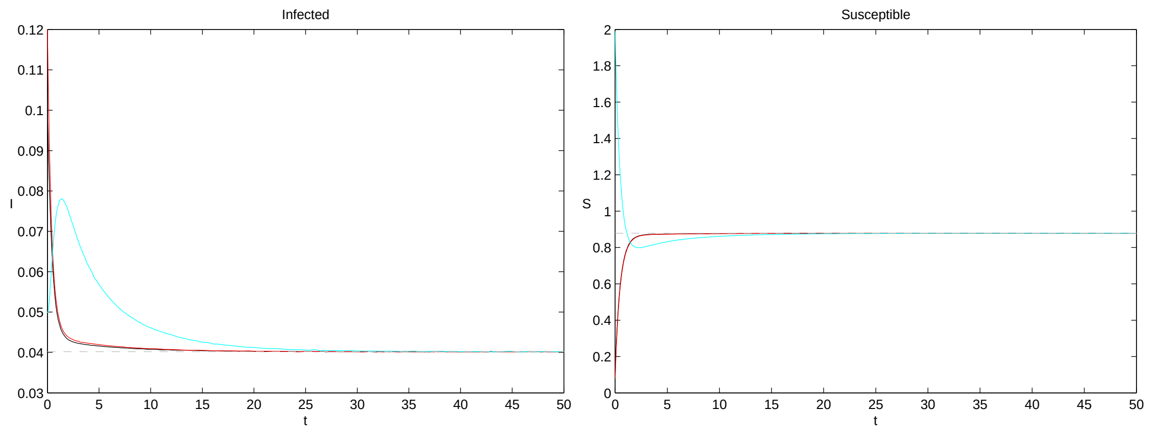


Figure 1.3: Endemic Case.

# Chapter 2

## Non-Autonomous Model

In this chapter we consider a general non-autonomous model, more precisely we will consider problem (1) assuming that the parameters are continuous bounded and nonnegative functions.

## 2.1 Setting and Preliminaries

Before presenting the assumptions considered on this chapter we need to introduce some notation. Given a continuous and bounded function $h : \mathbb{R}^+ \to \mathbb{R}$ we define

$$h^-_\omega = \liminf_{t\to+\infty} \frac{1}{\omega}\int_t^{t+\omega} h(s)\,ds \quad \text{and} \quad h^+_\omega = \limsup_{t\to+\infty} \frac{1}{\omega}\int_t^{t+\omega} h(s)\,ds,$$

and

$$h^u = \sup_{t\geq 0} h(t) \quad \text{and} \quad h^\ell = \inf_{t\geq 0} h(t).$$

For each $\delta$ and $\theta$ with $\delta > \theta \geq 0$ define the set

$$\Delta_{\theta,\delta} = \{(S,N,I) \in \mathbb{R}^3 \colon\ \theta \leq S \leq N \leq \delta \ \wedge\ 0 \leq I \leq N \leq \delta\}.$$

We will see that there is $K > 0$ such that, for any given solution $(S(t), E(t), I(t), R(t))$ of our system, the vector $(S(t), N(t), I(t))$ where $N(t) = S(t) + E(t) + I(t) + R(t)$ stays in the region $\Delta_{0,K}$ for every $t \in \mathbb{R}_0^+$ sufficiently large.

We will now state the assumptions about our system. We assume that:

NA1) The parameter functions $\Lambda$, $\mu$, $\beta$, $\eta$, $\varepsilon$ and $\gamma$ are continuous bounded and nonnegative real valued functions on $\mathbb{R}_0^+$, $\varphi$ is a continuous and nonnegative real valued function on $(\mathbb{R}_0^+)^3$ and there are $\omega_\mu, \omega_\Lambda, \omega_\beta > 0$ such that

$$\mu^-_{\omega_\mu} > 0,\ \Lambda^-_{\omega_\Lambda} > 0 \quad \text{and} \quad \beta^-_{\omega_\beta} > 0; \tag{2.1}$$

NA2) Letting $D > 0$ be the constant in 3) in Proposition 2.1.1 for each $0 \leq S \leq D$

and $0 \le I \le D$, the function $N \mapsto \varphi(S,N,I)$ is non-increasing, for each $0 \le I \le N \le D$ the function $S \mapsto \varphi(S,N,I)$ is non-decreasing, for each $0 \le I \le D$ the function $S \mapsto \varphi(S,S,I)$ is non-decreasing and $\varphi(0,N,I) = \varphi(S,N,0) = 0$;

NA3) For each $0 \le S \le N \le D$, where $D > 0$ is the constant in 3) in Proposition 2.1.1, the limit

$$\lim_{I \to 0^+} \frac{\varphi(S,N,I)}{I}$$

exists and the convergence is uniform in $(S,N)$ verifying $0 \le S \le N \le D$;

NA4) For each $0 \le S \le N \le D$, where $D > 0$ is the constant in 3) in Proposition 2.1.1, the function

$$I \mapsto \begin{cases} \dfrac{\varphi(S,N,I)}{I} & \text{if} \quad 0 < I \le D \\ \displaystyle\lim_{I \to 0^+} \frac{\varphi(S,N,I)}{I} & \text{if} \quad I = 0 \end{cases}$$

is non-increasing;

NA5) Letting $D$ be the constant in 3) in Proposition 2.1.1, the following holds: given $\theta > 0$ there is $K_\theta > 0$ such that, for $(S_1,N,I),(S_2,N,I) \in \Delta_{\theta,D}$, we have

$$|\varphi(S_1,N,I) - \varphi(S_2,N,I)| \le K_\theta |S_1 - S_2| I,$$

and, for $(S_1,S_1,I),(S_2,S_2,I) \in \Delta_{\theta,D}$, we have

$$|\varphi(S_1,S_1,I) - \varphi(S_2,S_2,I)| \le K_\theta |S_1 - S_2| I.$$

Assume also that $\mathbb{R}^+ \ni \theta \mapsto K_\theta$ is a continuous function.

Note that by NA3) the function in NA4) is continuous and, since it is defined in a compact interval, it is bounded. Note also that by NA3) and NA4), there is $M > 0$ such that, for every $0 \le S \le N \le D$ and $0 \le I \le N \le D$, such that we have

$$\frac{\varphi(S,N,I)}{I} \le \lim_{\delta \to 0^+} \frac{\varphi(S,N,\delta)}{\delta} \le M < +\infty. \tag{2.2}$$

Additionally, if the function $\varphi$ is differentiable and for each $\theta \in ]0,D]$ there is $K_\theta > 0$ such that

$$\frac{\partial \varphi}{\partial S}(S,N,I) \le K_\theta I,$$

for all $(S,N,I) \in \Delta_{\theta,D}$, then NA5) holds.

As we will see, conditions NA1)–NA5) are verified in several usual examples.

We now state some simple facts about our system.

Proposition 2.1.1. Assume that NA1) to NA5) hold. Then we have the following:

1) all solutions $(S(t), E(t), I(t), R(t))$ of (1) with nonnegative initial conditions, $S(0), E(0), I(0), R(0) \geq 0$, are nonnegative for all $t \geq 0$;

2) all solutions $(S(t), E(t), I(t), R(t))$ of (1) with positive initial conditions, $S(0)$, $E(0)$, $I(0)$, $R(0) > 0$, are positive for all $t \geq 0$;

3) There is a constant $D > 0$ such that, if $(S(t), E(t), I(t), R(t))$ is a solution of (1) with nonnegative initial conditions, $S(0), E(0), I(0), R(0) \geq 0$, then

$$\limsup_{t \to +\infty} N(t) = \limsup_{t \to +\infty} (S(t) + E(t) + I(t) + R(t)) < D.$$

Proof. Properties 1) and 2) are consequence of the direction of the flow on the boundary of $(\mathbb{R}_0^+)^4$. Adding the first four equations in (1) we obtain

$$N' = \Lambda(t) - \mu(t)N.$$

By (2.1), there is $T \geq 0$ such that $\int_t^{t+\omega_\mu} \mu(s)\, ds \geq \frac{1}{2}\mu^-_{\omega_\mu}\omega_\mu$ for $t \geq T$. Thus, given $t_0 \geq T$ we have

$$\begin{aligned}
\int_{t_0}^t \mu(s)\, ds &\geq \int_{t_0}^{t_0 + \lfloor \frac{t-t_0}{\omega_\mu} \rfloor \omega_\mu} \mu(s)\, ds \\
&\geq \frac{1}{2}\mu^-_{\omega_\mu}\omega_\mu \lfloor \frac{t-t_0}{\omega_\mu} \rfloor \\
&\geq \frac{1}{2}\mu^-_{\omega_\mu}\omega_\mu \left( \frac{t-t_0}{\omega_\mu} - 1 \right) \\
&= \frac{1}{2}\mu^-_{\omega_\mu}(t-t_0) - \frac{1}{2}\mu^-_{\omega}\omega_\mu,
\end{aligned}$$

where $\lfloor a \rfloor$ denotes the integer part of $a$, and, setting $\mu_1 = \dfrac{1}{2}\mu^-_{\omega_\mu}$ and $\mu_2 = \dfrac{1}{2}\mu^-_{\omega_\mu}\omega_\mu$, we conclude that there are $\mu_1, \mu_2 > 0$ and $T > 0$ sufficiently large such that, for all $t \geq t_0 \geq T$ we have

$$\int_{t_0}^t \mu(s)\, ds \geq \mu_1(t-t_0) - \mu_2. \tag{2.3}$$

By (2.3) we have, for all $t \geq T$,

$$\begin{aligned}
N(t) &= \mathrm{e}^{-\int_{t_0}^t \mu(s)\, ds} N_0 + \int_{t_0}^t \mathrm{e}^{-\int_u^t \mu(s)\, ds} \Lambda(u)\, du \\
&\leq \mathrm{e}^{-\mu_1(t-t_0)+\mu_2} N_0 + \Lambda^u \int_{t_0}^t \mathrm{e}^{-\mu_1(t-u)+\mu_2}\, du \\
&= \mathrm{e}^{-\mu_1(t-t_0)+\mu_2} N_0 + \frac{\Lambda^u \mathrm{e}^{\mu_2}}{\mu_1} \left(1 - \mathrm{e}^{-\mu_1(t-t_0)}\right).
\end{aligned}$$

Therefore

$$\limsup_{t\to+\infty} N(t) < \limsup_{t\to+\infty} \left[ \mathrm{e}^{-\mu_1(t-t_0)+\mu_2} N_0 + \frac{\Lambda^u \mathrm{e}^{\mu_2}}{\mu_1} \left(1 - \mathrm{e}^{-\mu_1(t-t_0)}\right) \right] = \frac{\Lambda^u \mathrm{e}^{\mu_2}}{\mu_1}$$

and we obtain 3) setting $D = \Lambda^u \mathrm{e}^{\mu_2} / \mu_1$. □

By Proposition 2.1.1, for every $\delta > 0$ and every solution $(S(t), E(t), I(t), R(t))$ of our system, $(S(t), N(t), I(t))$ stays in the region $\Delta_{0,D}$ for all $t \in \mathbb{R}_0^+$ sufficiently large, where $D$ is given by 3) in Proposition 2.1.1. By 3) in Proposition 2.1.1, a similar argument to the one given bellow the proof of Lemma 1.3.1 assures that solutions are global in future.

## 2.2 Persistence and Extinction

To address the problem of persistence and extinction, we need to consider the following auxiliary differential equation

$$z' = \Lambda(t) - \mu(t)z. \tag{2.4}$$

The next result summarizes some properties of equation (2.4).

Proposition 2.2.1. Assume that NA1) holds. We have the following:

1) Given $t_0 \geq 0$, all solutions $z(t)$ of equation (2.4) with initial condition $z(t_0) \geq 0$ are nonnegative for all $t \geq 0$;

2) Given $t_0 \geq 0$, all solutions $z(t)$ of equation (2.4) with initial condition $z(t_0) > 0$ are positive for all $t \geq 0$;

3) All solutions of (2.4) are bounded and for any two solutions $z, z_1$ of (2.4) we have $|z(t) - z_1(t)| \to 0$ as $t \to +\infty$;

4) There is $L \geq 0$ and $T > 0$ such that if $t_0 \geq T$, $z(t)$ is a solution of (2.4) and $\tilde{z}(t)$ is a solution of
$$z' = \Lambda(t) - \mu(t)z + f(t) \tag{2.5}$$
with $f$ bounded and $\tilde{z}(t_0) = z(t_0)$ then
$$\sup_{t\geq t_0} |\tilde{z}(t) - z(t)| \leq L \sup_{t\geq t_0} |f(t)|;$$

5) There exists constants $m_1, m_2 > 0$ such that, for each solution of (2.4) with $z(0) = z_0 > 0$, we have

$$m_1 \le \liminf_{t \to \infty} z(t) \le \limsup_{t \to \infty} z(t) \le m_2.$$

Proof. Given $t_0 \ge 0$, the solution of (2.4) with initial condition $z(t_0) = z_0$ is given by

$$z(t) = \mathrm{e}^{-\int_{t_0}^t \mu(s)\,ds} z_0 + \int_{t_0}^t \mathrm{e}^{-\int_u^t \mu(s)\,ds} \Lambda(u)\,du \tag{2.6}$$

and thus, since $\Lambda(t) \ge 0$ for all $t \ge 0$, if $z_0 \ge 0$ we obtain $z(t) \ge 0$ for all $t \ge t_0$ and if $z_0 > 0$ we obtain $z(t) > 0$ for all $t \ge t_0$. This establishes 1) and 2).

By (2.1) (recalling (2.3)), there are $\mu_1, \mu_2 > 0$ sufficiently small and $t_0 > 0$ sufficiently large such that, for all $t \ge t_0$ we have

$$\begin{aligned} z(t) &= \mathrm{e}^{-\int_{t_0}^t \mu(s)\,ds} z_0 + \int_{t_0}^t \mathrm{e}^{-\int_u^t \mu(s)\,ds} \Lambda(u)\,du \\ &\le \mathrm{e}^{-\mu_1(t-t_0)+\mu_2} z_0 + \Lambda^u \int_{t_0}^t \mathrm{e}^{-\mu_1(t-u)+\mu_2}\,du \\ &= \mathrm{e}^{-\mu_1(t-t_0)+\mu_2} z_0 + \frac{\Lambda^u \mathrm{e}^{\mu_2}}{\mu_1}\left(1 - \mathrm{e}^{-\mu_1(t-t_0)}\right) \\ &\le \mathrm{e}^{\mu_2} z_0 + \frac{\Lambda^u \mathrm{e}^{\mu_2}}{\mu_1} \end{aligned} \tag{2.7}$$

and we conclude that $z(t)$ is bounded.

Let $z$ and $z_1$ be solutions of (2.4) with $z(t_0) = z_0$ and $z_1(t_0) = z_{0,1}$. By (2.6) and (2.1), there is $t_0 > 0$ such that, for $t \ge t_0$ we have

$$|z(t) - z_1(t)| = \mathrm{e}^{-\int_{t_0}^t \mu(s)\,ds} |z_0 - z_{0,1}| \le \mathrm{e}^{-\mu_1(t-t_0)+\mu_2} |z_0 - z_{0,1}|$$

and thus $|z(t) - z_1(t)| \to 0$ as $t \to +\infty$ and we obtain 3).

Subtracting (2.4) and (2.5) and setting $w(t) = \tilde{z}(t) - z(t)$, where $\tilde{z}$ is a solution of (2.4) and $z$ a solution of (2.5), with $z(t_0) = \tilde{z}(t_0)$, we obtain

$$w' = -\mu(t)w + f(t)$$

and thus, since $w(t_0) = \tilde{z}(t_0) - z(t_0) = 0$, we get again by (2.1) (and the computations in (2.3)), for $t_0$ sufficiently large

$$\begin{aligned} |\tilde{z}(t) - z(t)| = |w(t)| &= \int_{t_0}^t \mathrm{e}^{-\int_u^t \mu(s)\,ds} |f(u)|\,du \le \sup_{t \ge t_0} |f(t)| \int_{t_0}^t \mathrm{e}^{-\mu_1(t-u)+\mu_2}\,du \\ &= \frac{\mathrm{e}^{\mu_2}}{\mu_1} \sup_{t \ge t_0} |f(t)| \left(1 - \mathrm{e}^{-\mu_1(t-t_0)}\right) \le \frac{\mathrm{e}^{\mu_2}}{\mu_1} \sup_{t \ge t_0} |f(t)|, \end{aligned}$$

for all $t \geq t_0$, and setting $L = e^{\mu_2}/\mu_1$,we obtain 4).

By (2.1), for all $t > 0$ sufficiently large there is $\Lambda_1 > 0$ such that

$$\begin{aligned} z(t) &= \mathrm{e}^{-\int_{t-\omega_\Lambda}^t \mu(s)\,ds} z_0 + \int_{t-\omega_\Lambda}^t \mathrm{e}^{-\int_u^t \mu(s)\,ds} \Lambda(u)\,du \\ &\geq \int_{t-\omega_\Lambda}^t \mathrm{e}^{-\mu^u \omega_\Lambda} \Lambda(u)\,du \\ &\geq \Lambda_1 \mathrm{e}^{-\mu^u \omega_\Lambda} \end{aligned}$$

and thus $\liminf_{t\to+\infty} z(t) \geq \Lambda_1 \mathrm{e}^{-\mu^u\omega_\Lambda}$. By (2.7) we have $\limsup_{t\to+\infty} z(t) \leq \dfrac{\Lambda^u \mathrm{e}^{\mu_2}}{\mu_1}$ and we obtain 5). □

For $p > 0$ and $t > 0$, define the auxiliary functions

$$g_\delta(p,t,z) = \beta(t)\frac{\varphi(z,z,\delta)}{\delta} p + \gamma(t) - \left(1+\frac{1}{p}\right)\varepsilon(t), \tag{2.8}$$

$$h(p,t) = \gamma(t) - \left(1+\frac{1}{p}\right)\varepsilon(t),$$

$$b_\delta(p,t,z) = \beta(t)\frac{\varphi(z,z,\delta)}{\delta} p - \mu(t) - \varepsilon(t). \tag{2.9}$$

Consider also the function

$$W(p,t) = pE(t) - I(t).$$

For each solution $z(t)$ of (2.4) with $z(0) > 0$ and $\lambda > 0, p > 0$ we define

$$\mathcal{R}_e(\lambda,p) = \operatorname{Exp}\left[\limsup_{t\to+\infty} \int_t^{t+\lambda} \lim_{\delta\to 0^+} b_\delta(p,s,z(s))\,ds\right], \tag{2.10}$$

$$\mathcal{R}_p(\lambda,p) = \operatorname{Exp}\left[\liminf_{t\to+\infty} \int_t^{t+\lambda} \lim_{\delta\to 0^+} b_\delta(p,s,z(s))\,ds\right], \tag{2.11}$$

$$\mathcal{R}_e^*(\lambda,p) = \operatorname{Exp}\left[\limsup_{t\to+\infty} \int_t^{t+\lambda} \frac{\varepsilon(s)}{p} - \mu(s) - \gamma(s)\,ds\right], \tag{2.12}$$

$$\mathcal{R}_p^*(\lambda,p) = \operatorname{Exp}\left[\liminf_{t\to+\infty} \int_t^{t+\lambda} \frac{\varepsilon(s)}{p} - \mu(s) - \gamma(s)\,ds\right], \tag{2.13}$$

and finally

$$G(p) = \limsup_{t\to+\infty} \lim_{\delta\to 0^+} g_\delta(p,t,z(t)) \tag{2.14}$$

and

$$H(p) = \liminf_{t\to+\infty} h(p,t). \tag{2.15}$$

Note that, if the incidence function is differentiable, then the equations (2.10), (2.11) and (2.14) simplify. In fact, in this case, according to NA2) we have $\varphi(S,N,0)=0$, and thus

$$\lim_{\delta\to 0^+}\frac{\varphi(z(t),z(t),\delta)}{\delta}=\frac{\partial\varphi}{\partial I}(z(t),z(t),0).$$

The next lemma shows that the numbers $\mathcal{R}_e(\lambda,p)$, $\mathcal{R}_p(\lambda,p)$, and $G(p)$ above do not depend on the particular solution $z(t)$ of (2.4) with $z(0)>0$.

Lemma 2.2.1. Assume that NA1) to NA5) hold. We have the following:

1) Let $p>0$, $\varepsilon>0$ be sufficiently small and $0<\theta\le D$. If

$$a,b\in\,]\theta,D[\quad\text{and}\quad a-b<\varepsilon,$$

then

$$b_\delta(p,t,a)-b_\delta(p,t,b)<\beta^u K_\theta p\varepsilon. \tag{2.16}$$

2) The numbers $\mathcal{R}_p(\lambda,p)$ and $\mathcal{R}_e(\lambda,p)$ and $G(p)$ are independent of the particular solution $z(t)$ with $z(0)>0$ of (2.4).

Proof. Assume that $p>0$, $\varepsilon>0$ and $0<\theta\le D$, $a,b\in]\theta,D[$ and $a-b<\varepsilon$. We have, by NA5),

$$|\varphi(a,a,\delta)-\varphi(b,b,\delta)|\le K_\theta|a-b|\delta.$$

Therefore, if $a>b$ we have by NA2)

$$\beta(t)\frac{\varphi(a,a,\delta)}{\delta}-\beta(t)\frac{\varphi(b,b,\delta)}{\delta}\le\beta(t)K_\theta|a-b|=\beta(t)K_\theta(a-b)\le\beta^u K_\theta\varepsilon \tag{2.17}$$

and if $a\le b$, again by NA2),

$$\beta(t)\frac{\varphi(a,a,\delta)}{\delta}-\beta(t)\frac{\varphi(b,b,\delta)}{\delta}\le 0\le\beta^u K_\theta\varepsilon. \tag{2.18}$$

By (2.17) and (2.18) we have

$$b_\delta(p,t,a)-b_\delta(p,t,b)\le\beta^u K_\theta p\varepsilon$$

and we obtain (2.16).

On the other side, again by NA5), assuming that $p>0$, $\varepsilon>0$, $0\le\delta\le D$, $a,b\in]\theta,D[$ and $|a-b|\le\varepsilon$ we get

$$\beta(t)\frac{\varphi(a,a,\delta)}{\delta}-\beta^u K_\theta\varepsilon\le\beta(t)\frac{\varphi(b,b,\delta)}{\delta}\le\beta(t)\frac{\varphi(a,a,\delta)}{\delta}+\beta^u K_\theta\varepsilon,$$

and thus

$$b_\delta(p,t,a)-\beta^u K_\theta p\varepsilon\le b_\delta(p,t,b)\le b_\delta(p,t,a)+\beta^u K_\theta p\varepsilon. \tag{2.19}$$

We will now show that $\mathcal{R}_e(\lambda,p)$ and $\mathcal{R}_p(\lambda,p)$ are independent of the particular solution $z(t)$ of (2.4) with $z(0)>0$. In fact, letting $z_1$ be some solution of (2.4) with $z_1(0)>0$, by 5) in Proposition 2.2.1, we can choose $\theta_1>0$ such that $z(t),z_1(t)\geq\theta_1$ for all $t\geq T$. On the other hand, by 3) in Proposition 2.2.1, given $\varepsilon>0$ there is a $T_\varepsilon>0$ such that $|z(t)-z_1(t)|<\varepsilon$ for every $t\geq T_\varepsilon$. Letting $a=z(t)$ and $b=z_1(t)$ and computing the integral from $t$ to $t+\lambda$ in (2.19) we get

$$\left|\int_t^{t+\lambda}\lim_{\delta\to0^+}b_\delta(p,s,z_1(s))\,ds-\int_t^{t+\lambda}\lim_{\delta\to0^+}b_\delta(p,s,z(s))\,ds\right|\leq\lambda\beta^uK_{\theta_1}p\,\varepsilon,$$

for every $t\geq T_\varepsilon$. We conclude that, for every $\varepsilon>0$,

$$\begin{aligned}&\limsup_{t\to+\infty}\int_t^{t+\lambda}\lim_{\delta\to0^+}b_\delta(p,s,z_1(s))\,ds-\lambda\beta^uK_{\theta_1}p\,\varepsilon\\&\leq\limsup_{t\to+\infty}\int_t^{t+\lambda}\lim_{\delta\to0^+}b_\delta(p,s,z(s))\,ds\\&\leq\limsup_{t\to+\infty}\int_t^{t+\lambda}\lim_{\delta\to0^+}b_\delta(p,s,z_1(s))\,ds+\lambda\beta^uK_{\theta_1}p\,\varepsilon,\end{aligned}$$

and thus $\mathcal{R}_e(\lambda,p)$ is independent of the chosen solution. Taking $\liminf$ instead of $\limsup$, the same reasoning shows that $\mathcal{R}_p(\lambda,p)$ is also independent of the particular solution. Similar computations imply that $G(p)$ is also independent of the particular chosen solution. This proves the lemma. □

We will also use the next technical lemma in the proof of Theorem 2.2.1.

Lemma 2.2.2. Assume that NA1) to NA5) hold. Let $(S(t),E(t),I(t),R(t))$ be some solution of (1) with $S(T_0)>0$, $E(T_0)>0$, $I(T_0)>0$, $R(T_0)>0$ for some $T_0>0$. If there is a positive constant $p>0$ such that $G(p)<0$ or $H(p)>0$ then there exists $T\geq0$ such that either $W(p,t)\leq0$ for all $t\geq T$ or $W(p,t)>0$ for all $t\geq T$. Additionally, if there are positive constants $p,\lambda>0$ such that $G(p)<0$ or $H(p)>0$, $\mathcal{R}_p(\lambda,p)>1$ and $\mathcal{R}_p^*(\lambda,p)>1$, then there exists $T\geq0$ such that $W(p,t)\leq0$, for $t\geq T$.

Proof. Let us assume first that $G(p)<0$ and let $(S(t),E(t),I(t),R(t))$ be some solution of (1) with $S(T_0),E(T_0),I(T_0),R(T_0)>0$ for some $T_0>0$. Then there is $T_1>0$ such that $g_\delta(p,t,N(t))<0$ for all $t\geq T_1$ (note that $N(t)$ is a solution of (2.4)). By contradiction, assume also that there is no $T_2\geq T_1$ such that $W(p,t)\leq 0$ or $W(p,t)>0$ for all $t\geq T_2$. Therefore there is $s\geq T_1$ such that

$$W(p,s)=0\quad\Leftrightarrow\quad pE(s)=I(s)$$

and
$$\frac{dW}{dt}(p,s) \geq 0.$$

Since $s \geq T_1$ we have $\lim_{\delta \to 0^+} g_\delta(p,s,N(s)) < 0$. By NA2), NA3), NA4) and (2.8) we obtain

$$\begin{aligned}
0 &\leq \frac{dW}{dt}(p,s)\\
&= \frac{d}{dt}[pE(t) - I(t)]|_{t=s}\\
&= pE'(s) - I'(s)\\
&= p\left[\beta(s)\,\varphi(S(s),N(s),I(s)) - (\mu(s)+\varepsilon(s))E(s)\right] - \varepsilon(s)E(s) + (\mu(s)+\gamma(s))I(s)\\
&= \left[p\beta(s)\,\frac{\varphi(S(s),N(s),I(s))}{I(s)} + \mu(s) + \gamma(s)\right] I(s) - [p(\mu(s)+\varepsilon(s)) + \varepsilon(s)]E(s)\\
&\leq \left[p\beta(s)\lim_{\delta \to 0^+}\frac{\varphi(S(s),N(s),\delta)}{\delta} + \mu(s) + \gamma(s)\right] I(s) - \left[\mu(s) + \varepsilon(s) + \frac{\varepsilon(s)}{p}\right] pE(s)\\
&= \left[p\beta(s)\lim_{\delta \to 0^+}\frac{\varphi(S(s),N(s),\delta)}{\delta} + \gamma(s) - \varepsilon(s)\left(1 + \frac{1}{p}\right)\right] I(s)\\
&\leq \left[p\beta(s)\lim_{\delta \to 0^+}\frac{\varphi(N(s),N(s),\delta)}{\delta} + \gamma(s) - \varepsilon(s)\left(1 + \frac{1}{p}\right)\right] I(s)\\
&= \lim_{\delta \to 0^+} g_\delta(p,s,N(s))I(s) < 0
\end{aligned}$$

which contradicts the assumption. Thus, there is $T_2 \geq T_1$ such that $W(p,t) \leq 0$ or $W(p,t) > 0$ for all $t \geq T_2$.

Assume now that $H(p) > 0$ and let $(S(t), E(t), I(t), R(t))$ be some solution of (1) with $S(T_0), E(T_0), I(T_0), R(T_0) > 0$ for some $T_0 > 0$. Then there is $T_3 > 0$ such that $h(p,t) > 0$ for all $t \geq T_3$. By contradiction, assume also that there is no $T_4 \geq T_3$ such that $W(p,t) \leq 0$ or $W(p,t) > 0$ for all $t \geq T_4$. Therefore there is $s \geq T_3$ such that
$$W(p,s) = 0 \quad \Leftrightarrow \quad pE(s) = I(s)$$

and
$$\frac{dW}{dt}(p,s) \leq 0.$$

Since $s \geq T_3$ we have $h(p,s) > 0$. By NA2), NA4) and (2.8) we obtain

$$\begin{aligned}
0 &\geq \frac{dW}{dt}(p,s) \\
&= \frac{d}{dt}[pE(t) - I(t)]|_{t=s} \\
&= pE'(s) - I'(s) \\
&= p\,[\beta(s)\,\varphi(S(s),N(s),I(s)) - (\mu(s)+\varepsilon(s))E(s)] - \varepsilon(s)E(s) + (\mu(s)+\gamma(s))I(s) \\
&\geq [\mu(s)+\gamma(s)]\,I(s) - \left[\mu(s)+\varepsilon(s)+\frac{\varepsilon(s)}{p}\right] pE(s) \\
&= \left[\gamma(s) - \varepsilon(s)\left(1+\frac{1}{p}\right)\right] I(s) \\
&= h(p,s)I(s) > 0
\end{aligned}$$

which is a contradiction. Thus there is $T_4 \geq T_3$ such that $W(p,t) \leq 0$ or $W(p,t) > 0$ for all $t \geq T_4$. Assuming that $G(p) < 0$ or $H(p) > 0$, $\mathcal{R}_p(\lambda,p) > 1$ and $\mathcal{R}_p^*(\lambda,p) > 1$ for some $p, \lambda > 0$, by the previous arguments, we have $W(p,t) > 0$ for all $t \geq T_2$ or $W(p,t) \leq 0$ for all $t \geq T_2$. Suppose by contradiction that $W(p,t) > 0$ for all $t \geq T_2$. We have $E(t) > I(t)/p$ for all $t \geq T_2$. Then, by the third equation in (1) we have

$$\frac{d}{dt}I(t) > \varepsilon(t)\frac{1}{p}I(t) - (\mu(t)+\gamma(t))I(t) = [\varepsilon(t)\frac{1}{p} - \mu(t) - \gamma(t)]I(t)$$

and thus, for all $t \geq T_2$, we have

$$I(t) > I(T_2)\,\mathrm{e}^{\int_{T_2}^t \varepsilon(r)\frac{1}{p} - \mu(r) - \gamma(r)\,dr}.$$

Since $\mathcal{R}_p^*(\lambda,p) > 1$, by (2.13) we conclude that there is $\theta > 0$ and $T > 0$ such that, for all $t \geq T$, we have

$$\int_t^{t+\lambda} \varepsilon(r)\frac{1}{p} - \mu(r) - \gamma(r)\,dr > \theta.$$

Thus, for all $t > \max\{T_2, T\}$, we obtain $I(t) > I(T_2)\,\mathrm{e}^{(\frac{t-T_2}{\lambda}-1)\theta}$. Thus $I(t) \to +\infty$ and this contradicts the fact that $I(t)$ must be bounded. Then we must have $W(p,t) \leq 0$ and the lemma is proved. □

We now state our main theorem on the extinction and strong persistence of the infectives in system (1).

Theorem 2.2.1. Assume that NA1) to NA5) hold. We have the following for system (1).

1) If there are constants $\lambda > 0$ and $p > 0$ such that $\mathcal{R}_e(\lambda,p) < 1$, $\mathcal{R}_e^*(\lambda,p) < 1$ and $G(p) < 0$ then the infectives $I$ go to extinction.

2) If there are constants $\lambda > 0$ and $p > 0$ such that $\mathcal{R}_e(\lambda, p) < 1$, $\mathcal{R}_e^*(\lambda, p) < 1$ and $H(p) > 0$ then the infectives $I$ go to extinction.

3) If there are constants $\lambda > 0$ and $p > 0$ such that $\mathcal{R}_p(\lambda, p) > 1$, $\mathcal{R}_p^*(\lambda, p) > 1$ and $G(p) < 0$ then the infectives $I$ are strongly persistent in the set $\Delta_1$ in (1.17).

4) If there are constants $\lambda > 0$ and $p > 0$ such that $\mathcal{R}_p(\lambda, p) > 1$, $\mathcal{R}_p^*(\lambda, p) > 1$ and $H(p) > 0$ then the infectives $I$ are strongly persistent in the set $\Delta_1$ in (1.17).

5) In the assumptions of 1) or 2) the disease-free solution $(S(t), 0, 0, 0)$ is globally asymptotically stable.

Proof. Assume that there are constants $\lambda > 0$ and $p > 0$ such that $\mathcal{R}_e(\lambda, p) < 1$, $\mathcal{R}_e^*(\lambda, p) < 1$ and $G(p) < 0$ or $H(p) > 0$ and let $(S(t), E(t), I(t), R(t))$ be some solution of (1) with $S(T_0), E(T_0), I(T_0), R(T_0) > 0$ for some $T_0 > 0$.

Since $\mathcal{R}_e(\lambda, p) < 1$, by (2.10) we conclude that there is $T_1 \geq T$ and $\alpha > 0$such that

$$\int_t^{t+\lambda} \lim_{\delta \to 0^+} b_\delta(p, s, N(s))\, ds < -\alpha < 0,$$

for all $t \geq T_1$.

By 3) in Proposition 2.1.1, we may assume that $(S(t), N(t), I(t)) \in \Delta_{0,D}$ for $t \geq T_1$.

By Lemma 2.2.2 we have $W(p, t) > 0$ for all $t \geq T_1$ or $W(p, t) \leq 0$ for all $t \geq T_1$. Assume first that $W(p, t) > 0$ for all $t \geq T_1$. Since $I(T_0) > 0$, by 2) in Proposition 2.1.1 we have that $I(t) > 0$ for all $t \geq T_0$ and, by the second equation in (1), NA2), NA4) and (2.9), there is $T_2 \geq T_1$ such that

$$\begin{aligned} E'(t) &= \beta(t)\varphi(S(t), N(t), I(t)) - (\mu(t) + \varepsilon(t))E(t) \\ &= \beta(t)\frac{\varphi(S(t), N(t), I(t))}{I(t)} I(t) - (\mu(t) + \varepsilon(t))E(t) \\ &< \beta(t)\frac{\varphi(N(t), N(t), I(t))}{I(t)} pE(t) - (\mu(t) + \varepsilon(t))E(t) \\ &\leq \beta(t) \lim_{\delta \to 0^+} \frac{\varphi(N(t), N(t), \delta)}{\delta} pE(t) - (\mu(t) + \varepsilon(t))E(t) \\ &= \lim_{\delta \to 0^+} b_\delta(p, t, N(t))E(t) \end{aligned} \tag{2.20}$$

for all $t \geq T_2$. Thus, integrating (2.20) we obtain, using (2.2),

$$
\begin{aligned}
E(t) &\leq E(T_2)\,\mathrm{Exp}\left[\int_{T_2}^{t} \lim_{\delta\to 0^+} b_\delta(p,s,N(s))\,ds\right]\\
&= E(T_2)\,\mathrm{Exp}\left[\int_{T_2}^{T_2+\lambda\lfloor\frac{t-T_2}{\lambda}\rfloor} \lim_{\delta\to 0^+} b_\delta(p,s,N(s))\,ds + \right.\\
&\qquad\qquad \left. + \int_{T_2+\lambda\lfloor\frac{t-T_2}{\lambda}\rfloor}^{t} \lim_{\delta\to 0^+} b_\delta(p,s,N(s))\,ds\right]\\
&\leq E(T_2)\,\mathrm{Exp}\left[\int_{T_2}^{T_2+\lambda\lfloor\frac{t-T_2}{\lambda}\rfloor} \lim_{\delta\to 0^+} b_\delta(p,s,N(s))\,ds + \right.\\
&\qquad\qquad \left. + \int_{T_2+\lambda\lfloor\frac{t-T_2}{\lambda}\rfloor}^{t} \beta(s) \lim_{\delta\to 0^+} \frac{\varphi(N(s),N(s),\delta)}{\delta} p\,ds\right]\\
&< E(T_2)\,\mathrm{Exp}\left[-\alpha\lfloor\frac{t-T_2}{\lambda}\rfloor + \beta^u M p\lambda\right],
\end{aligned}
$$

for all $t \geq T_2$. We conclude that $0 \leq \limsup_{t\to+\infty} I(t) \leq p \limsup_{t\to+\infty} E(t) = 0$ assuming that $W(p,t) > 0$ for all $t \geq T_1$.

Assume now that $W(p,t) \leq 0$ for all $t \geq T_1$. By the third equation in (1) we have

$$
I'(t) \leq \varepsilon(t)I(t)/p - (\mu(t)+\gamma(t))I(t) = (\varepsilon(t)/p - \mu(t) - \gamma(t))I(t) \tag{2.21}
$$

for all $t \geq T_1$. Since $\mathcal{R}_e^*(\lambda,p) < 1$, by (2.12) we conclude that there are constants $\alpha_0 > 0$ and $T_3 \geq T_1$ such that

$$
\int_t^{t+\lambda} \varepsilon(s)/p - \mu(s) - \gamma(s)\,ds < -\alpha_0 < 0, \tag{2.22}
$$

for all $t \geq T_3$. Thus, by (2.21) and (2.22), we have

$$
I(t) \leq I(T_3)\,\mathrm{e}^{\int_{T_3}^{t} \varepsilon(s)/p-\mu(s)-\gamma(s)\,ds} \leq I(T_3)\,\mathrm{e}^{-\alpha_0\lfloor\frac{t-T_3}{\lambda}\rfloor + \frac{\lambda\varepsilon^u}{p}},
$$

for all $t \geq T_3$. We conclude that $I(t) \to 0$ and we obtain 1) and 2) in the theorem.

Assume now that there are constants $\lambda > 0$, $p > 0$ such that $\mathcal{R}_p(\lambda,p) > 1$, $\mathcal{R}_p^*(\lambda,p) > 1$ and $G(p) < 0$ or $H(p) > 0$ for all $t \geq T$ and let $(S(t),E(t),I(t),R(t))$ be some fixed solution of (1) with $S(T_0),E(T_0),I(T_0),R(T_0) > 0$ for some $T_0 > 0$.

Since $\mathcal{R}_p(\lambda,p) > 1$, by (2.11) and NA3) we conclude that there are constants $0 < \delta_2 \leq D$, $\alpha > 0$ and $T_4 > 0$ such that

$$
\int_t^{t+\lambda} \beta(s)\frac{\varphi(N(s),N(s),\delta)}{\delta} p - \mu(s) - \varepsilon(s)\,ds > \alpha > 0, \tag{2.23}
$$

for all $t \geq T_4$ and $0 < \delta \leq \delta_2$ and that $g_\delta(p, t, N(t)) < 0$ for all $t \geq T_5$ and $0 < \delta \leq \delta_2$. By Proposition 2.1.1, we may also assume that $(S(t), N(t), I(t)) \in \Delta_{0,D}$ for all $t \geq T_4$.

By (2.1) we can choose $\varepsilon_1 > 0$, $0 < \varepsilon_2 < \delta_2$, $\varepsilon_3 > 0$ and $0 < \alpha_1 < \alpha$ such that, for all $t \geq T_4$, we have

$$\int_t^{t+\lambda} \beta(s)M\varepsilon_2 - (\mu(s) + \varepsilon(s))\varepsilon_1 \, ds < -\alpha_1 \tag{2.24}$$

$$\int_t^{t+\lambda} \gamma(s)\varepsilon_2 - (\mu(s) + \eta(s))\varepsilon_3 \, ds < -\alpha_1 \tag{2.25}$$

$$\theta_1 = \frac{m_1}{2} - \varepsilon_1 - [1 + \beta^u M\lambda + \gamma^u\lambda]\varepsilon_2 - \varepsilon_3 > 0 \tag{2.26}$$

and

$$\kappa = K_{\theta_1}[\varepsilon_1 + [1 + \beta^u M\lambda + \gamma^u\lambda]\varepsilon_2 + \varepsilon_3] < \frac{\alpha}{2p\beta^u\lambda} \tag{2.27}$$

where $M$ is given by (2.2), $m_1$ is given by 5) in Proposition 2.2.1 and $K_{\theta_1}$ is given by NA5).

We will show that

$$\limsup_{t\to+\infty} I(t) > \varepsilon_2. \tag{2.28}$$

Assume by contradiction that it is not true. Then there exists $T_5 > T_4$ such that, for all $t \geq T_5$, we have

$$I(t) \leq \varepsilon_2. \tag{2.29}$$

Suppose that $E(t) \geq \varepsilon_1$ for all $t \geq T_5$. Then, by the second equation in (1), (2.2), NA4) and (2.24), we have for all $t \geq T_5$

$$\begin{aligned}
E(t) &= E(T_5) + \int_{T_5}^t \beta(s)\, \varphi(S(s), N(s), I(s)) - (\mu(s) + \varepsilon(s))E(s)\, ds \\
&= E(T_5) + \int_{T_5}^t \beta(s)\, \frac{\varphi(S(s), N(s), I(s))}{I(s)} I(s) - (\mu(s) + \varepsilon(s))E(s)\, ds \\
&\leq E(T_5) + \int_{T_5}^t \beta(s)M\varepsilon_2 - (\mu(s) + \varepsilon(s))\varepsilon_1 \, ds
\end{aligned}$$

and therefore

$$\begin{aligned}
E(t) \leq E(T_5) &+ \int_{T_5}^{T_5 + \lfloor \frac{t-T_5}{\lambda} \rfloor \lambda} \beta(s)M\varepsilon_2 - (\mu(s) + \varepsilon(s))\varepsilon_1 \, ds \\
&+ \int_{T_5 + \lfloor \frac{t-T_5}{\lambda} \rfloor \lambda}^t \beta(s)M\varepsilon_2 - (\mu(s) + \varepsilon(s))\varepsilon_1 \, ds \\
&< E(T_5) - \alpha_1 \lfloor \frac{t - T_5}{\lambda} \rfloor + \beta^u M\varepsilon_2\lambda
\end{aligned}$$

and thus $E(t) \to -\infty$ which contradicts 2) in Proposition 2.1.1. We conclude that there exists $T_6 \geq T_5$ such that $E(T_6) < \varepsilon_1$. Suppose that there exists a $T_7 > T_6$ such that $E(T_7) > \varepsilon_1 + \beta^u M \varepsilon_2 \lambda$. Then we conclude that there must exist $T_8 \in ]T_6, T_7[$ such that $E(T_8) = \varepsilon_1$ and $E(t) > \varepsilon_1$ for all $t \in ]T_8, T_7]$. Let $n \in \mathbb{N}_0$ be such that $T_7 \in [T_8 + n\lambda, T_8 + (n+1)\lambda]$. Then, by the second equation in (1), (2.2), (2.29) and (2.24) we have

$$\begin{aligned}
\varepsilon_1 + \beta^u M \varepsilon_2 \lambda &< E(T_7) \\
&= E(T_8) + \int_{T_8}^{T_7} \beta(s)\varphi(S(s), N(s), I(s)) - (\mu(s) + \varepsilon(s))E(s)\, ds \\
&\leq E(T_8) + \int_{T_8}^{T_7} \beta(s) M \varepsilon_2 - (\mu(s) + \varepsilon(s))\varepsilon_1\, ds \\
&\leq \varepsilon_1 - \alpha_1 n + \int_{T_8 + n\lambda}^{T_7} \beta^u M \varepsilon_2\, ds \\
&\leq \varepsilon_1 + \beta^u M \varepsilon_2 \lambda
\end{aligned}$$

and this is a contradiction. We conclude that, for all $t \geq T_7$ we have

$$E(t) \leq \varepsilon_1 + \beta^u M \varepsilon_2 \lambda. \tag{2.30}$$

Suppose that $R(t) \geq \varepsilon_3$ for all $t \geq T_9$. Then, by the fourth equation in (1), (2.29) and (2.25), we have for all $t \geq T_9$

$$\begin{aligned}
R(t) &= R(T_9) + \int_{T_9}^{t} \gamma(s)I(s) - (\mu(s) + \eta(s))R(s)\, ds \\
&\leq R(T_9) + \int_{T_9}^{t} \gamma(s)\varepsilon_2 - (\mu(s) + \eta(s))\varepsilon_3\, ds
\end{aligned}$$

and thus

$$\begin{aligned}
R(t) \leq R(T_9) &+ \int_{T_9}^{T_9 + \lambda \lfloor \frac{t - T_9}{\lambda} \rfloor} \gamma(s)\varepsilon_2 - (\mu(s) + \eta(s))\varepsilon_3\, ds \\
&+ \int_{T_9 + \lambda \lfloor \frac{t - T_9}{\lambda} \rfloor}^{t} \gamma(s)\varepsilon_2 - (\mu(s) + \eta(s))\varepsilon_3\, ds \\
&< R(T_9) - \alpha_1 \lfloor \frac{t - T_9}{\lambda} \rfloor + \gamma^u \varepsilon_2 \lambda
\end{aligned}$$

and therefore $R(t) \to -\infty$ which contradicts 2) in Proposition 2.1.1. We conclude that there exists $T_{10} \geq T_9$ such that $R(T_{10}) < \varepsilon_3$. Suppose that there exists $T_{11} \geq T_{10}$ such that $R(T_{11}) > \varepsilon_3 + \gamma^u \varepsilon_2 \lambda$. Then we conclude that there must exist $T_{12} \in ]T_{10}, T_{11}[$ such that $R(T_{12}) = \varepsilon_3$ and $R(t) > \varepsilon_3$ for all $t \in ]T_{12}, T_{11}]$. Let $n \in \mathbb{N}_0$ be such that $T_{11} \in [T_{12} + n\lambda, T_{12} + (n+1)\lambda]$. Then, by the fourth equation in (1), (2.29) and

(2.25) we have

$$\begin{aligned}\varepsilon_3+\gamma^u\varepsilon_2\lambda < R(T_{11}) &= R(T_{12})+\int_{T_{12}}^{T_{11}}\gamma(s)I(s)-(\mu(s)+\eta(s))R(s)\,ds\\ &\leq R(T_{12})+\int_{T_{12}}^{T_{11}}\gamma(s)\varepsilon_2-(\mu(s)+\eta(s))\varepsilon_3\,ds\\ &< \varepsilon_3-\alpha_1 n+\int_{T_{12}+n\lambda}^{T_{11}}\gamma^u\varepsilon_2\,ds\\ &\leq \varepsilon_3+\gamma^u\varepsilon_2\lambda\end{aligned}$$

and this is a contradiction. We conclude that, for all $t \geq T_{10}$ we have

$$R(t) \leq \varepsilon_3+\gamma^u\varepsilon_2\lambda. \tag{2.31}$$

By Lemma 2.2.2 there exists $T_{13} \geq T_{10}$ such that $pE(t) \leq I(t)$, for all $t \geq T_{13}$. According to the second equation in (1) and NA4) and recalling that by (2.29) and the assumptions we have $I(t) \leq \varepsilon_2 < \delta_2$, for all $t \geq T_{13}$ we get,

$$\begin{aligned}E'(t) &= \beta(t)\varphi(S(t),N(t),I(t))-(\mu(t)+\varepsilon(t))E(t)\\ &= \beta(t)\frac{\varphi(S(t),N(t),I(t))}{I(t)}I(t)-(\mu(t)+\varepsilon(t))E(t)\\ &\geq \beta(t)\frac{\varphi(S(t),N(t),\delta_2)}{\delta_2}I(t)-(\mu(t)+\varepsilon(t))E(t)\end{aligned} \tag{2.32}$$

By (2.29), (2.30) and (2.31), we have, for all $t \geq T_{13}$,

$$\begin{aligned}N(t)-S(t) = E(t)+I(t)+R(t) &\leq \varepsilon_1+\beta^u M\varepsilon_2\lambda+\varepsilon_2+\varepsilon_3+\gamma^u\varepsilon_2\lambda\\ &= \varepsilon_1+[1+\beta^u M\lambda+\gamma^u\lambda]\varepsilon_2+\varepsilon_3.\end{aligned} \tag{2.33}$$

On the other side, by 5) in Proposition 2.2.1, there is $T_{14} > T_{13}$ such that, for all $t \geq T_{14}$, we have $N(t) \geq m_1/2$. Therefore, for all $t \geq T_{14}$, we have by (2.33) and (2.26)

$$\begin{aligned}S(t) &\geq N(t)-\varepsilon_1-[1+\beta^u M\lambda+\gamma^u\lambda]\varepsilon_2-\varepsilon_3\\ &\geq \frac{m_1}{2}-\varepsilon_1-[1+\beta^u M\lambda+\gamma^u\lambda]\varepsilon_2-\varepsilon_3\\ &= \theta_1 > 0.\end{aligned}$$

Thus, by NA5), (2.33) and (2.27) we have

$$\begin{aligned}&|\varphi(S(t),N(t),\delta_2)-\varphi(N(t),N(t),\delta_2)|\\&\le K_{\theta_1}|S(t)-N(t)|\delta_2\\&\le K_{\theta_1}[\varepsilon_1+[1+\beta^u M\lambda+\gamma^u\lambda]\varepsilon_2+\varepsilon_3]\delta_2\\&=\kappa\delta_2,\end{aligned} \tag{2.34}$$

and thus

$$\varphi(N,N,\delta_2)-\kappa\delta_2\le\varphi(S,N,\delta_2)\le\varphi(N,N,\delta_2)+\kappa\delta_2. \tag{2.35}$$

Therefore, by (2.35), (2.29) (2.32), (2.33), (2.27), NA5) and since $pE(t)\le I(t)$, we obtain, for all $t\ge T_{14}$,

$$\begin{aligned}E'(t)&=\beta(t)\ \frac{\varphi(N(t),N(t),I(t))}{I(t)}\ I(t)-(\mu(t)+\varepsilon(t))E(t)\\&\ge\beta(t)\ \frac{\varphi(N(t),N(t),\delta_2)-\kappa\delta_2}{\delta_2}\ pE(t)-(\mu(t)+\varepsilon(t))E(t)\\&=\left[\beta(t)\frac{\varphi(N(t),N(t),\delta_2)}{\delta_2}-\beta(t)\kappa\right]pE(t)-(\mu(t)+\varepsilon(t))E(t)\\&=\left[\beta(t)\frac{\varphi(N(t),N(t),\delta_2)}{\delta_2}p-\beta(t)\kappa p-\mu(t)-\varepsilon(t)\right]E(t).\end{aligned} \tag{2.36}$$

Therefore, integrating (2.36) an using (2.23) and (2.27), we have

$$\begin{aligned}E(t)&\ge E(T_{14})\operatorname{Exp}\left[\int_{T_{14}}^t\beta(s)\frac{\varphi(N(s),N(s),\delta_2)}{\delta_2}p-\mu(s)-\varepsilon(s)-\beta^u\kappa p\,ds\right]\\&=E(T_{14})\operatorname{Exp}\left[\int_{T_{14}}^{T_{14}+\lambda\lfloor\frac{t-T_{14}}{\lambda}\rfloor}\beta(s)\frac{\varphi(N(s),N(s),\delta_2)}{\delta_2}p-\mu(s)-\varepsilon(s)-\beta^u\kappa p\,ds+\right.\\&\quad\left.+\int_{T_{14}+\lambda\lfloor\frac{t-T_{14}}{\lambda}\rfloor}^t\beta(s)\frac{\varphi(N(s),N(s),\delta_2)}{\delta_2}p-\mu(s)-\varepsilon(s)-\beta^u\kappa p\,ds\right].\end{aligned}$$

Thus, by (2.23) and (2.27),

$$\begin{aligned}E(t)&\ge E(T_{14})\ \operatorname{Exp}\left[(\alpha-\beta^u\kappa p\lambda)\lfloor\frac{t-T_{14}}{\lambda}\rfloor-(\mu^u+\varepsilon^u+\beta^u\kappa p)\lambda\right]\\&\ge E(T_{14})\ \operatorname{Exp}\left[\alpha/2\lfloor\frac{t-T_{14}}{\lambda}\rfloor-(\mu^u+\varepsilon^u+\beta^u\kappa p)\lambda\right]\end{aligned}$$

and we conclude that $E(t)\to+\infty$. This is a contradiction with the boundedness of $E$ established in Proposition 2.1.1. We conclude that $\limsup_{t\to+\infty} I(t)>\varepsilon_2$ holds.

Next we prove that

$$\liminf_{t\to+\infty} I(t)\ge\ell, \tag{2.37}$$

where $\ell > 0$ is some constant to be determined.

Similarly to (2.24)–(2.27), letting $\lambda_3 = k\lambda > 0$ with $k \in \mathbb{N}$ be sufficiently large and recalling (2.1), we conclude that there is $T_{15} \geq T_{14}$, $\varepsilon_1 > 0$, $\varepsilon_2 > 0$, $\varepsilon_3 > 0$ sufficiently small such that for all $t \geq T_{15}$ we have

$$N(t) = S(t) + E(t) + R(t) + I(t) < 2m_2, \tag{2.38}$$

$$\int_t^{t+\lambda_3} \beta(s)M\varepsilon_2 - (\mu(s) + \varepsilon(s))\varepsilon_1 \, ds < -2m_2, \tag{2.39}$$

$$\int_t^{t+\lambda_3} \gamma(s)\varepsilon_2 - (\mu(s) + \delta(s))\varepsilon_3 \, ds < -2m_2, \tag{2.40}$$

$$\int_t^{t+\lambda_3} \beta(s) \, \frac{\varphi(N(s), N(s), \delta_2)}{\delta_2} p - \mu(s) - \varepsilon(s) \, ds > k\alpha, \tag{2.41}$$

$$\theta_1 = \frac{m_1}{2} - \varepsilon_1 - [1 + \beta^u M\lambda + \gamma^u\lambda]\varepsilon_2 - \varepsilon_3 > 0,$$

$$\kappa = K_{\theta_1}[\varepsilon_1 + [1 + \beta^u M\lambda + \gamma^u\lambda]\varepsilon_2 + \varepsilon_3] < \min\left\{\frac{\alpha}{2\beta^u p\lambda}, \frac{2(\mu^u + \gamma^u)}{\beta^u p}\right\}, \tag{2.42}$$

where $\alpha$ is the constant in (2.23).

According to (2.28) there are only two possibilities: there exists $T > 0$ such that $I(t) \geq \varepsilon_2$ for all $t \geq T$ or $I(t)$ oscillates about $\varepsilon_2$.

In the first case we set $\ell = \varepsilon_2$ and we obtain (2.37).

Otherwise we must have the second case. Let $T_{17} \geq T_{16} > T_{15}$ be constants such that $W(p,t) \leq 0$, for all $t \geq T_{15}$ (we may assume this by Lemma 2.2.2) and that $I(T_{16}) = I(T_{17}) = \varepsilon_2$ and $I(t) < \varepsilon_2$ for all $t \in [T_{16}, T_{17}]$. Suppose first that $T_{17} - T_{16} \leq C + 2\lambda_3$ where $C$ satisfies

$$C \geq \frac{1}{\mu^u + \gamma^u} \left[(4\mu^u + 2\gamma^u + 2\varepsilon^u)\lambda_3 + \ln\frac{2}{\alpha k}\right], \tag{2.43}$$

From the third equation in (1) we have

$$I'(t) \geq -(\mu^u + \gamma^u)I(t). \tag{2.44}$$

Therefore, we obtain for all $t \in [T_{16}, T_{17}]$,

$$I(t) \geq I(T_{16}) \, \mathrm{e}^{-\int_{T_{16}}^t \mu^u + \gamma^u \, ds} \geq \varepsilon_2 \, \mathrm{e}^{-(\mu^u+\gamma^u)(C+2\lambda_3)} .$$

On the other hand, if $T_{17} - T_{16} > C + 2\lambda_3$ then, from (2.44) we obtain

$$I(t) \geq \varepsilon_2 \, \mathrm{e}^{-(\mu^u+\gamma^u)(C+2\lambda_3)},$$

for all $t \in [T_{16}, T_{16}+C+2\lambda_3]$. Set $\ell = \varepsilon_2 \,\mathrm{e}^{-(\mu^u+\gamma^u)(C+2\lambda_3)}$. We will show that $I(t) \geq \ell$ for all $t \in [T_{16}+C+2\lambda_3, T_{17}]$ and this establishes the result.

Suppose that $E(t) \geq \varepsilon_1$ for all $t \in [T_{16}, T_{16}+\lambda_3]$. Then, from the second equation in (1), (2.2), (2.38) and (2.39) we have

$$\begin{aligned} &E(T_{16}+\lambda_3) \\ &= E(T_{16}) + \int_{T_{16}}^{T_{16}+\lambda_3} \beta(s)\,\varphi(S(s),N(s),I(s)) - (\mu(s)+\gamma(s))E(t)\,ds \\ &\leq E(T_{16}) + \int_{T_{16}}^{T_{16}+\lambda_3} \beta(s)M\varepsilon_2 - (\mu(s)+\gamma(s))\varepsilon_1\,ds \\ &< 2m_2 - 2m_2 = 0, \end{aligned}$$

which is a contradiction with 1) in Proposition 2.1.1. Therefore, there exists a $T_{18} \in [T_{16}, T_{16}+\lambda_3]$ such that $E(T_{18}) < \varepsilon_1$. Then, as in the proof of (2.30) and using (2.39), we can show that $E(t) \leq \varepsilon_1 + \beta^u M \varepsilon_2 \lambda_3$, for all $t \geq T_{18}$. Also proceeding as in the proof of (2.31) and using (2.40) we may assume that $R(t) \leq \varepsilon_3 + \gamma^u \varepsilon_2 \lambda_3$ for all $t \geq T_{18}$.

By (2.44) we have

$$I(t) \geq I(T_{16})\,\mathrm{e}^{-\int_{T_{16}}^{t} \mu^u+\gamma^u\,ds} = I(T_{16})\,\mathrm{e}^{-(\mu^u+\gamma^u)(t-T_{16})} \geq \varepsilon_2\,\mathrm{e}^{-(\mu^u+\gamma^u)2\lambda_3} \tag{2.45}$$

for all $t \in [T_{16}+\lambda_3, T_{16}+2\lambda_3]$.

Assume that there exists a $T_{19} > 0$ such that $T_{19} \in [T_{16}+C+2\lambda_3, T_{17}]$, $I(T_{19}) = \ell$ and $I(t) \geq \ell$ for all $t \in [T_{16}, T_{19}]$ (otherwise the result is established). By (2.34) and (2.45) we have, for all $t \in [T_{16}+\lambda_3, T_{16}+2\lambda_3]$,

$$\begin{aligned} E'(t) &\geq \beta(t)\,\frac{\varphi(S(t),N(t),\delta_2)}{\delta_2} I(t) - (\mu^u+\varepsilon^u)E(t) \\ &\geq \beta(t)\left(\frac{\varphi(N(t),N(t),\delta_2)}{\delta_2} - \kappa\right)\varepsilon_2\,\mathrm{e}^{-(\mu^u+\gamma^u)2\lambda_3} - (\mu^u+\varepsilon^u)E(t), \end{aligned} \tag{2.46}$$

where $\kappa$ is given by (2.27). By (2.46), (2.41) and (2.42), we get

$$\begin{aligned}
&E(T_{16}+2\lambda_3)\\
&\geq e^{-(\mu^u+\varepsilon^u)\lambda_3}E(T_{16}+\lambda_3)+\int_{T_{16}+\lambda_3}^{T_{16}+2\lambda_3}\beta(s)\left(\frac{\varphi(N(s),N(s),\delta_2)}{\delta_2}-\kappa\right)\varepsilon_2\times\\
&\quad\times \mathrm{e}^{-(\mu^u+\gamma^u)2\lambda_3}\,e^{-(\mu^u+\varepsilon^u)(T_{16}+2\lambda_3-s)}\,ds\\
&\geq e^{-(\mu^u+\gamma^u)2\lambda_3}\int_{T_{16}+\lambda_3}^{T_{16}+2\lambda_3}\beta(s)\left(\frac{\varphi(N(s),N(s),\delta_2)}{\delta_2}-\kappa\right)\varepsilon_2\,\mathrm{e}^{-(\mu^u+\varepsilon^u)\lambda_3}\,ds\\
&\geq e^{-(3\mu^u+2\gamma^u+\varepsilon^u)\lambda_3}\varepsilon_2\int_{T_{16}+\lambda_3}^{T_{16}+2\lambda_3}\beta(s)\,\frac{\varphi(N(s),N(s),\delta_2)}{\delta_2}-\beta^u\kappa\,ds\\
&> e^{-(3\mu^u+2\gamma^u+\varepsilon^u)\lambda_3}\varepsilon_2\left(k\alpha/p-\beta^u\kappa\lambda_3\right)\\
&= e^{-(3\mu^u+2\gamma^u+\varepsilon^u)\lambda_3}\varepsilon_2\left(\alpha/p-\beta^u\kappa\lambda\right)k\\
&> e^{-(3\mu^u+2\gamma^u+\varepsilon^u)\lambda_3}\varepsilon_2\alpha k/(2p).
\end{aligned}\tag{2.47}$$

On the other side, by (2.36) we obtain

$$E'(t)\geq\left[\beta(t)\,\frac{\varphi(N(t),N(t),\delta_2)}{\delta_2}p-\beta(t)\kappa p-\mu(t)-\varepsilon(t)\right]E(t).\tag{2.48}$$

and thus, by (2.48),

$$\begin{aligned}
&\varepsilon_2\,\mathrm{e}^{-(\mu^u+\gamma^u)(C+2\lambda_3)}=I(T_{19})\geq pE(T_{19})\\
&\geq pE(T_{16}+2\lambda_3)\mathrm{Exp}\left[\int_{T_{16}+2\lambda_3}^{T_{19}}\beta(s)\frac{\varphi(N(s),N(s),\delta_2)}{\delta_2}p-\beta(s)\kappa p-\mu(s)-\varepsilon(s)\,ds\right]
\end{aligned}$$

and thus, letting $n=2+\lfloor\frac{T_{19}-T_{16}}{\lambda_3}\rfloor$

$$\begin{aligned}
&\varepsilon_2\,\mathrm{e}^{-(\mu^u+\gamma^u)(C+2\lambda_3)}\\
&\geq pE(T_{16}+2\lambda_3)\mathrm{Exp}\left[\int_{T_{16}+2\lambda_3}^{T_{16}+n\lambda_3}\beta(s)\frac{\varphi(N(s),N(s),\delta_2)}{\delta_2}p-\beta(s)\kappa p-\mu(s)-\varepsilon(s)\,ds\right.\\
&\quad\left.+\int_{T_{16}+n\lambda_3}^{T_{19}}\beta(s)\frac{\varphi(N(s),N(s),\delta_2)}{\delta_2}p-\beta(s)\kappa p-\mu(s)-\varepsilon(s)\,ds\right]
\end{aligned}$$

and therefore, by (2.47), (2.41) and (2.42), we have

$$\begin{aligned}
\varepsilon_2\,\mathrm{e}^{-(\mu^u+\gamma^u)(C+2\lambda_3)}&>pe^{-(4\mu^u+2\gamma^u+2\varepsilon^u)\lambda_3}\varepsilon_2\frac{\alpha k}{2p}\,\mathrm{e}^{(n-2)(\alpha k-\beta^u\kappa p\lambda_3)}\,\mathrm{e}^{-\beta^u\kappa p\lambda_3}\\
&>pe^{-(4\mu^u+2\gamma^u+2\varepsilon^u)\lambda_3}\varepsilon_2\frac{\alpha k}{2p}\,\mathrm{e}^{(n-2)\alpha k/2}\,\mathrm{e}^{-\beta^u\kappa p\lambda_3}\\
&>\frac{1}{2}e^{-(4\mu^u+2\gamma^u+2\varepsilon^u)\lambda_3}\varepsilon_2\alpha k\,\mathrm{e}^{-\beta^u\kappa p\lambda_3}\\
&>\frac{1}{2}e^{-(4\mu^u+2\gamma^u+2\varepsilon^u)\lambda_3}\varepsilon_2\alpha k\,\mathrm{e}^{-2(\mu^u+\gamma^u)\lambda_3}
\end{aligned}$$

and this implies that

$$C < \frac{1}{\mu^u + \gamma^u}\left[(4\mu^u + 2\gamma^u + 2\varepsilon^u)\lambda_3 + \ln\frac{2}{\alpha k}\right],$$

contradicting (2.43). This shows (2.37) and proves 3) and 4) in the theorem.

Now, to obtain the global asymptotic stability of the disease-free solution, we recall that, by (2.3), there are $\mu_1, \mu_2 > 0$ sufficiently small and $T > 0$ sufficiently large such that, for all $t \geq t_0 \geq T$ we have

$$-\int_{t_0}^{t} \mu(s)\, ds \leq -\mu_1(t - t_0) + \mu_2.$$

Assume that $\mathcal{R}_e(\lambda, p) < 1$, $\mathcal{R}_e^*(\lambda, p) < 1$ and $G(p) < 0$ or $H(p) > 0$. Let $(S(t), 0, 0, 0)$ be a disease-free solution of (1) with $S_1(t_0) = S_{1,0}$ and let $(S_1(t), E_1(t), I_1(t), R_1(t))$ with $S_1(t_0) = S_0$, $E_1(t_0) = E_0$, $I_1(t_0) = I_0$ and $R_1(t_0) = R_0$ be some solution of (1).

Since we are in the conditions of 1) or 2), for each $\varepsilon > 0$ there is $T_\varepsilon > 0$ such that $I_1(t) \leq \varepsilon$ for each $t \geq T_\varepsilon$. Therefore, using the second equation in (1), we get, for $t \geq T_\varepsilon$,

$$\begin{aligned} E_1'(t) &= \beta(t)\frac{\varphi(S_1(t), N_1(t), I_1(t))}{I_1(t)} I_1(t) - (\mu(t) + \varepsilon(t))E_1(t) \\ &\leq \beta^u M\varepsilon - \mu(t)E_1(t) \end{aligned}$$

and thus, for $t \geq t_0 \geq \max\{T, T_\varepsilon\}$, we have

$$\begin{aligned} E_1(t) &\leq \mathrm{e}^{-\int_{t_0}^{t} \mu(s)\, ds} E_0 + \int_{t_0}^{t} \beta^u M\varepsilon\, \mathrm{e}^{-\int_{u}^{t} \mu(s)\, ds}\, du \\ &\leq \mathrm{e}^{-\mu_1(t-t_0)+\mu_2} E_0 + \beta^u M\varepsilon \int_{t_0}^{t} \mathrm{e}^{-\mu_1(t-u)+\mu_2}\, du \\ &= \mathrm{e}^{-\mu_1(t-t_0)+\mu_2} E_0 + \frac{\beta^u M\, \mathrm{e}^{\mu_2}}{\mu_1}(1 - \mathrm{e}^{-\mu_1(t-t_0)})\varepsilon \end{aligned}$$

and, since $\varepsilon > 0$ is arbitrary, we conclude that

$$\limsup_{t\to+\infty} E_1(t) = 0. \tag{2.49}$$

Again, since we are in the conditions of 1) or 2), for each $\varepsilon > 0$ there is $T_\varepsilon > 0$ such that $I_1(t) \leq \varepsilon$ for each $t \geq T_\varepsilon$. Therefore, using the fourth equation in (1), we get, for $t \geq T_\varepsilon$,

$$R_1'(t) = \gamma(t)I_1(t) - (\mu(t) + \eta(t))R_1(t) \leq \gamma^u\varepsilon - \mu(t)R_1(t)$$

and thus, for $t \geq t_0 \geq \max\{T, T_\varepsilon\}$, we have

$$\begin{aligned} R_1(t) &\leq \mathrm{e}^{-\int_{t_0}^t \mu(s)\,ds} R_0 + \int_{t_0}^t \gamma^u \varepsilon \, \mathrm{e}^{-\int_u^t \mu(s)\,ds} \, du \\ &\leq \mathrm{e}^{-\mu_1(t-t_0)+\mu_2} R_0 + \gamma^u \varepsilon \int_{t_0}^t \mathrm{e}^{-\mu_1(t-u)+\mu_2} \, du \\ &= \mathrm{e}^{-\mu_1(t-t_0)+\mu_2} R_0 + \frac{\gamma^u \, \mathrm{e}^{\mu_2}}{\mu_1}(1-\mathrm{e}^{-\mu_1(t-t_0)})\varepsilon. \end{aligned}$$

Since $\varepsilon > 0$ is arbitrary, we conclude that

$$\limsup_{t\to+\infty} R_1(t) = 0. \tag{2.50}$$

Let $(S_1(t), E_1(t), I_1(t), R_1(t))$ be some solution of (1) and $(S(t), 0, 0, 0)$ be a disease free solution. Let $N_1(t) = S_1(t) + E_1(t) + I_1(t) + R_1(t)$. Since $N_1(t)$ and $S(t)$ are solutions of (2.4), we conclude by 3) in Proposition 2.2.1 that $|N_1(t) - S(t)| \to 0$ as $t \to +\infty$. Therefore

$$\begin{aligned} &\limsup_{t\to+\infty} |S_1(t) - S(t)| \\ &= \limsup_{t\to+\infty} |N_1(t) - E_1(t) - I_1(t) - R_1(t) - S(t)| \\ &\leq \limsup_{t\to+\infty} (\, |N_1(t) - S(t)| + E_1(t) + I_1(t) + R_1(t)\,) = 0. \end{aligned} \tag{2.51}$$

By (2.49), (2.50) and (2.51) and since $I_1(t) \to 0$ as $t \to +\infty$, we obtain 5) in the theorem. □

## 2.3 Examples

Example 2.3.1 (Autonomous case). Let $\Lambda(t) = \Lambda > 0$, $\mu(t) = \mu > 0$, $\eta(t) = \eta \geq 0$, $\varepsilon(t) = \varepsilon \geq 0$, $\gamma(t) = \gamma \geq 0$ and $\beta(t) = \beta > 0$ in (1) and assume that NA1) to NA4) hold. It is easy to see that $z(t) = \Lambda/\mu$ is a solution of (2.4) with positive initial condition in this case. Letting

$$L_{\varphi,\Lambda,\mu} = \lim_{\delta\to 0^+} \frac{\varphi(\Lambda/\mu, \Lambda/\mu, \delta)}{\delta}, \tag{2.52}$$

we have

$$G(p) = \beta p L_{\varphi,\Lambda,\mu} + \gamma - (1+1/p)\varepsilon,$$

$$H(p) = \gamma - \left(1 + \frac{1}{p}\right)\varepsilon,$$

$$\mathcal{R}_e(\lambda, p) = \mathcal{R}_p(\lambda, p) = \mathrm{Exp}\left[(\beta p L_{\varphi,\Lambda,\mu} - \mu - \varepsilon)\,\lambda\right],$$

and

$$\mathcal{R}_e^*(\lambda,p)=\mathcal{R}_p^*(\lambda,p)=\operatorname{Exp}\left[\left(\varepsilon/p-\mu-\gamma\right)\lambda\right].$$

Define

$$\mathcal{R}^A=\frac{\varepsilon\beta\, L_{\varphi,\Lambda,\mu}}{(\mu+\varepsilon)(\mu+\gamma)} \tag{2.53}$$

Note that, when $\varphi$ is differentiable, $L_{\varphi,\Lambda,\mu}=\partial\varphi/\partial I(\Lambda/\mu,\Lambda/\mu,0)$ and $\mathcal{R}^A=\mathcal{R}_0$, where $\mathcal{R}_0$ is the basic reproduction number in (1.2). The following result is a consequence of Theorem 2.2.1 in the autonomous case.

Corollary 2.3.1. Assume that NA1) to NA5) hold. We have the following for the autonomous system above.

1) If $\mathcal{R}^A<1$ then the infectives go to extinction;

2) If $\mathcal{R}^A>1$ then the infectives are strongly persistent;

3) If $\mathcal{R}^A<1$ the disease free equilibrium $(\Lambda/\mu,0,0,0)$ is globally asymptotically stable.

Proof. Assuming that $\mathcal{R}^A<1$ we have

$$\frac{\varepsilon\beta}{(\mu+\varepsilon)(\mu+\gamma)}L_{\varphi,\Lambda,\mu}<1$$

and thus for all $p>0$ such that

$$\frac{\varepsilon}{\mu+\gamma}<p<\frac{\mu+\varepsilon}{\beta L_{\varphi,\Lambda,\mu}},$$

we have

$$\frac{\varepsilon}{p}<\mu+\gamma \quad\Leftrightarrow\quad \frac{\varepsilon}{p}-\mu-\gamma<0 \quad\Leftrightarrow\quad \mathcal{R}_e^*(\lambda,p)<1$$

and also

$$\beta pL_{\varphi,\Lambda,\mu}<\mu+\varepsilon \quad\Leftrightarrow\quad \beta pL_{\varphi,\Lambda,\mu}-\mu-\varepsilon<0 \quad\Leftrightarrow\quad \mathcal{R}_e(\lambda,p)<1.$$

Since

$$G\left(\frac{\varepsilon}{\mu+\gamma}\right)=\beta L_{\varphi,\Lambda,\mu}\frac{\varepsilon}{\mu+\gamma}+\gamma-\left(1+\frac{\mu+\gamma}{\varepsilon}\right)\varepsilon=(\mathcal{R}^A-1)(\mu+\varepsilon)<0$$

and $G$ is continuous we conclude that there is $p>0$ satisfying $\mathcal{R}_e(\lambda,p)<1$, $\mathcal{R}_e^*(\lambda,p)<1$ and $G(p)<0$. Thus, by 1. in Theorem 2.2.1, the infectives go to extinction and we obtain 1).

Assuming now that $\mathcal{R}^A > 1$ we have

$$\frac{\varepsilon\beta}{(\mu+\varepsilon)(\mu+\gamma)} L_{\varphi,\Lambda,\mu} > 1$$

and thus, by the same reasoning, for all $p > 0$ such that

$$\frac{\varepsilon}{\mu+\gamma} > p > \frac{\mu+\varepsilon}{\beta L_{\varphi,\Lambda,\mu}},$$

we have $\mathcal{R}_e^*(\lambda, p) > 1$ and $\mathcal{R}_e(\lambda, p) > 1$. Since

$$G\left(\frac{\mu+\varepsilon}{\beta L_{\varphi,\Lambda,\mu}}\right) = \beta L_{\varphi,\Lambda,\mu}\frac{\mu+\varepsilon}{\beta L_{\varphi,\Lambda,\mu}} + \gamma - \left(1 + \frac{\beta L_{\varphi,\Lambda,\mu}}{\mu+\varepsilon}\right)\varepsilon = (\mu+\gamma)\left(1-\mathcal{R}^A\right) < 0$$

and $G$ is continuous we conclude that there is $p > 0$ satisfying $\mathcal{R}_e(\lambda, p) < 1$, $\mathcal{R}_e^*(\lambda, p) < 1$ and $G(p) < 0$. Thus, by 3. in Theorem 2.2.1, the infectives are strongly persistent and we obtain 2).

By 5) in Theorem 2.2.1 we obtain immediatly 3). □

For the model considered in [20], where incidence is given by $\varphi(S, N, I) = g(I)S$ with $g \in C^1$, $g(I) > 0$, $g(0) = 0$ and $\Lambda = \mu$, we recover the threshold obtained in that paper: $\mathcal{R}^A = \varepsilon\beta g'(0)/[(\mu+\varepsilon)(\mu+\gamma)]$.

Assuming constant parameter functions, that $\varphi$ is twice differentiable and also that NA1) to NA5) hold, we obtain an autonomous model satisfying A1) to A4) (with that additional assumption that $S \to \varphi(S, S, I)$ non-decreasing for $0 < I < D$). In this setting, Corollary 2.3.1 recovers the results in Theorem 1.3.2.

Example 2.3.2 (Asymptotically autonomous case). In this example we are going to consider the asymptotically autonomous model. That is, additionally to the assumptions on Theorem 2.2.1, we are going to assume for system (1) that the time-dependent parameters are asymptotically constant: $\mu(t) \to \mu$, $\eta(t) \to \eta$, $\varepsilon(t) \to \varepsilon$, $\gamma(t) \to \gamma$ and $\beta(t) \to \beta$ as $t \to +\infty$. Denoting by $F(t, S, E, I, R)$ the right hand side of (1) and by $F_0(S, E, I, R)$ the right hand side of the limiting system, i.e

$$\lim_{t\to+\infty} F(t, S, E, I, R) = F_0(S, E, I, R),$$

we also need to assume that the convergence is uniform on every compact set of $(\mathbb{R}_0^+)^4$ and we will also assume that $(S, E, I, R) \mapsto F(t, S, E, I, R)$ and $(S, E, I, R) \mapsto F_0(S, E, I, R)$ are locally Lipschitz functions.

There is a general setting that will allow us to study this case. Namely, let $f : \mathbb{R} \times \mathbb{R}^n \to \mathbb{R}$ and $f_0 : \mathbb{R}^n \to \mathbb{R}$ be continuous and locally Lipschitz in $\mathbb{R}^n$.

Assume also that the non-autonomous system

$$x' = f(t,x) \tag{2.54}$$

is asymptotically autonomous with limit equation

$$x' = f_0(x), \tag{2.55}$$

that is, assume that $f(t,x) \to f_0(x)$ as $t \to +\infty$ with uniform convergence in every compact set of $\mathbb{R}^n$. The following theorem is a particular case of a result established in [25]. Related results and applications can be found for example in [4, 29].

Theorem 2.3.1. Let $\Phi(t,t_0,x_0)$ and $\varphi(t,t_0,y_0)$ be solutions of (2.54) and (2.55) respectively. Suppose that $e \in \mathbb{R}^n$ is a locally stable equilibrium point of (2.55) with attractive region

$$W(e) = \left\{ y \in \mathbb{R}^n : \lim_{t\to+\infty} \varphi(t,t_0,y) = e \right\}$$

and that $W_\Phi \cap W(e) \neq \emptyset$, where $W_\Phi$ denotes the omega limit of $\Phi(t,t_0,x_0)$. Then $\lim\limits_{t\to+\infty} \Phi(t,t_0,x_0) = e$.

Using Theorem 2.3.1 we can obtain a result relating the asymptotically autonomous and the autonomous case.

Corollary 2.3.2. Assume the NA1) to NA5) hold and let $\mathcal{R}^A$ be the basic reproductive numbers of the limiting autonomous system, defined by (2.53). Then, if $\mathcal{R}^A < 1$, the infectives go to extinction in the limiting autonomous system.

Proof. When $\mathcal{R}^A < 1$, the set $(\mathbb{R}_0^+)^4$ is the attractive region for the disease-free equilibrium of system (1) and the omega limit of every orbit with initial condition in $(\mathbb{R}_0^+)^4$ of the asymptotically autonomous system is contained in $(\mathbb{R}_0^+)^4$. Thus, by Theorem 2.3.1 we obtain the result. □

Example 2.3.3 (Periodic model with constant $\Lambda$, $\mu$). Next we assume that some model coefficients are periodic functions with the same period, namely we assume that there is $\omega > 0$ such that, for all $t \geq 0$, we have $\eta(t) = \eta(t+\omega)$, $\varepsilon(t) = \varepsilon(t+\omega)$, $\gamma(t) = \gamma(t+\omega)$ and $\beta(t) = \beta(t+\omega)$. We also assume that $\mu$ and $\Lambda$ are constant functions and that NA1) to NA5) hold.

We have in his case

$$\mathcal{R}_e(\omega,p) < 1 \;\Leftrightarrow\; \limsup_{t\to+\infty} \int_t^{t+\omega} \beta(s)L_{\varphi,\Lambda,\mu} - (\mu+\varepsilon(s))\,ds < 0 \;\Leftrightarrow\; \left[p\bar{\beta}L_{\varphi,\Lambda,\mu} - \mu - \bar{\varepsilon}\right]\omega < 0$$

$$\mathcal{R}_e^*(\omega,p) < 1 \;\Leftrightarrow\; \limsup_{t\to+\infty} \int_t^{t+\omega} \varepsilon(s)/p - \mu - \gamma(s)\,ds < 0 \;\Leftrightarrow\; (\bar{\varepsilon}/p - \mu - \bar{\gamma})\,\omega < 0,$$

$$G(p) = \max_{t\in[0,\omega]} \left[\beta(t) p L_{\varphi,\Lambda,\mu} + \gamma(t) - (1+1/p)\varepsilon(t)\right],$$

$$H(p) = \min_{t\in[0,\omega]} \left[\gamma(t) - (1+1/p)\varepsilon(t)\right],$$

Define

$$R^{per} = \frac{\bar{\varepsilon}\,\bar{\beta}\,L_{\varphi,\Lambda,\mu}}{(\mu+\bar{\varepsilon})(\mu+\bar{\gamma})}$$

where $\bar{f} = \frac{1}{\omega}\int_0^\omega f(s)\,ds$ and $L_{\varphi,\Lambda,\mu}$ is given by (2.52). The following result is a consequence of Theorem 2.2.1 in this case.

Corollary 2.3.3. Assume the NA1) to NA5) hold. Then we have the following for the periodic system with constant $\mu$ and $\Lambda$.

1) If $G\left(\bar{\varepsilon}/(\mu+\bar{\gamma})\right) < 0$ or $H\left((\mu+\bar{\varepsilon})/(\bar{\beta}L_{\varphi,\Lambda,\mu})\right) > 0$ and $R^{per} < 1$ then the infectives go to extinction;

2) If $G\left((\mu+\bar{\varepsilon})/(\bar{\beta}L_{\varphi,\Lambda,\mu})\right) < 0$ or $H\left(\bar{\varepsilon}/(\mu+\bar{\gamma})\right) > 0$ and $R^{per} > 1$ then the infectives are strongly persistent.

Proof. By the same computations as in the proof of corollary 2.3.1 we conclude that $\mathcal{R}_e^{per} < 1$ if and only if there is

$$p \in I = \left(\frac{\bar{\varepsilon}}{\mu+\bar{\gamma}}, \frac{\mu+\bar{\varepsilon}}{\bar{\beta}L_{\varphi,\Lambda,\mu}}\right)$$

such that $\mathcal{R}_e(\lambda,p) < 1$ and $\mathcal{R}_e^*(\lambda,p) < 1$.

Moreover, by continuity of the functions $G$ and $H$, if

$$G\left(\frac{\bar{\varepsilon}}{\mu+\bar{\gamma}}\right) < 0 \quad \text{or} \quad H\left(\frac{\mu+\bar{\varepsilon}}{\bar{\beta}L_{\varphi,\Lambda,\mu}}\right) > 0$$

then there is $p \in I$ such that $G(p) < 0$ or $H(p) > 0$ and, by theorem 2.2.1, we obtain 1).

By similar arguments we obtain 2). □

As we will see in section 3.2, in [31] a method to obtain persistence in a general periodic epidemiological model relying in the spectral radius of some operator was obtained. Though our conditions are not thresholds in the periodic case, they have the advantage that can be easily computed.

To illustrate the above corollary we consider the following family of periodic models

$$\begin{cases} S' = \mu - \beta(1+b\cos(2\pi t))\,SI - \mu S + \eta R \\ E' = \beta(1+b\cos(2\pi t))\,SI - (\mu + \varepsilon(1+d\cos(2\pi t)))E \\ I' = \varepsilon(1+d\cos(2\pi t))E - (\mu + \gamma(1+k\cos(2\pi t)))I \\ R' = \gamma(1+k\cos(2\pi t))I - (\mu+\eta)R \\ N = S+E+I+R \end{cases} \tag{2.56}$$

where $|b| < 1$, $|d| < 1$ and $|k| < 1$. In [30] it was showed that for $\mu = 2$, $\varepsilon = 1$, $\gamma = 0.02$, $\eta = 0.1$, $\beta = 6.2$ and $b = 0.6$ and $d = k = 0$ the number $R^{per}$ is not a threshold. Our result is not applicable in this case since in this case $G\left(\varepsilon/(\mu+\gamma)\right) = G(0.49505) = 1.91089 > 0$.

It is easy to check that, for the system (2.56), letting $\beta$ and $b$ vary and $\mu = 2$, $\varepsilon = 1$, $\gamma = 0.02$, $\eta = 0.1$ and $d = k = 0$, we have that $R^{per} < 1$ (respectively $R^{per} > 1$) is equivalent to $\beta < 6.06$ (respectively $\beta > 6.06$), $G(\varepsilon/(\mu+\gamma)) < 0$ is equivalent to $\beta(1+|b|) < 6.06$, $G\left((\mu+\varepsilon)/(\beta L_{\varphi,\Lambda,\mu})\right) < 0$ is equivalent to $\beta > 9|b| + 6.06$ and $H\left(\varepsilon/(\mu+\gamma)\right) > 0$ and $H\left((\mu+\varepsilon)/(\beta L_{\varphi,\Lambda,\mu})\right) > 0$ are impossible. In the first plot in figure 2.1 we plot the region of parameters $(b, \beta)$ where corollary 2.3.3 is applicable and where we have extinction and permanence. In the first plot in figure 2.1, we include also a curve obtained numerically and corresponding to the threshold $R_0 = 1$. This curve was obtained using the method introduced in section 3.4 of [2]. Also in [2] (see equation (51)), it was shown that, for $d = k = 0$ and small $b$, we have

$$R_0 = \frac{\beta\varepsilon}{(\mu+\varepsilon)(\mu+\gamma)} + \frac{\beta\varepsilon b^2/2}{4\pi^2 + (2\mu+\varepsilon+\gamma)^2} + o(b^2). \tag{2.57}$$

In the second plot in figure 2.1 we plotted, for $b \in [-1, 0]$, the numerically obtained threshold (full) and the approximate threshold in (2.57) (dashed).

Using the parameters in [30] but letting $\gamma$ and $k$ vary, we consider $\mu = 2$, $\eta = 0.1$, $\varepsilon = 1$, $\beta = 6.2$ and $b = d = 0$, we conclude that $G(\varepsilon/(\mu+\gamma)) < 0$ is equivalent to $(2+\gamma)\left(3 - \gamma|k|\right) > 6.2$, $G\left((\mu+\varepsilon)/(\beta L_{\varphi,\Lambda,\mu})\right) < 0$ is equivalent to $\gamma(1+|k|) < 0.067$, $H\left(\varepsilon/(\mu+\gamma)\right) > 0$ is impossible and $H\left((\mu+\varepsilon)/(\beta L_{\varphi,\Lambda,\mu})\right) > 0$ is equivalent to $\gamma(1-|k|) > 3.067$. Additionally $R^{per} < 1$ is equivalent to $\gamma > 0.067$ and $R^{per} > 1$ is equivalent to $\gamma < 0.067$. In the first plot in figure 2.2 we plot the region of parameters $(k, \gamma)$ where corollary 2.3.3 is applicable and where we have extinction and permanence, as well as the numerical approximation of the threshold, obtained by the method introduced in [2].

Finally, letting $\varepsilon$ and $d$ vary and setting $\mu = 2$, $\gamma = 0.02$, $\eta = 0.1$, $\beta = 6.2$ and $b = k = 0$, we conclude that $R^{per} < 1$ is equivalent to $\varepsilon < 0.967$, $R^{per} > 1$ is equivalent to $\varepsilon > 0.967$, $G(\varepsilon/(\mu+\gamma)) < 0$ is equivalent to $2.069\varepsilon - 2 + |d|(\varepsilon + 2.02) < 0$, $G\left((\mu+\varepsilon)/(\beta L_{\varphi,\Lambda,\mu})\right) < 0$ is equivalent to $(2.02+\varepsilon)(2+\varepsilon) - (8.2+\varepsilon)\varepsilon(1 -$

$|d|) < 0$, $H(\varepsilon/(\mu+\gamma)) > 0$ is equivalent to $0.02 - (\varepsilon + 2.02)(1 + |d|) > 0$ and $H((\mu+\varepsilon)/(\beta L_{\varphi,\Lambda,\mu})) > 0$ is equivalent to $0.02-(1+6.2/(2+\varepsilon))\varepsilon(1+|d|) > 0$. In the second plot in figure 2.2 we plot the region of parameters $(d, \varepsilon)$ where corollary 2.3.3 is applicable and where we have extinction and permanence. We also plot the numerical approximation of the threshold, obtained by the method introduced in [2].

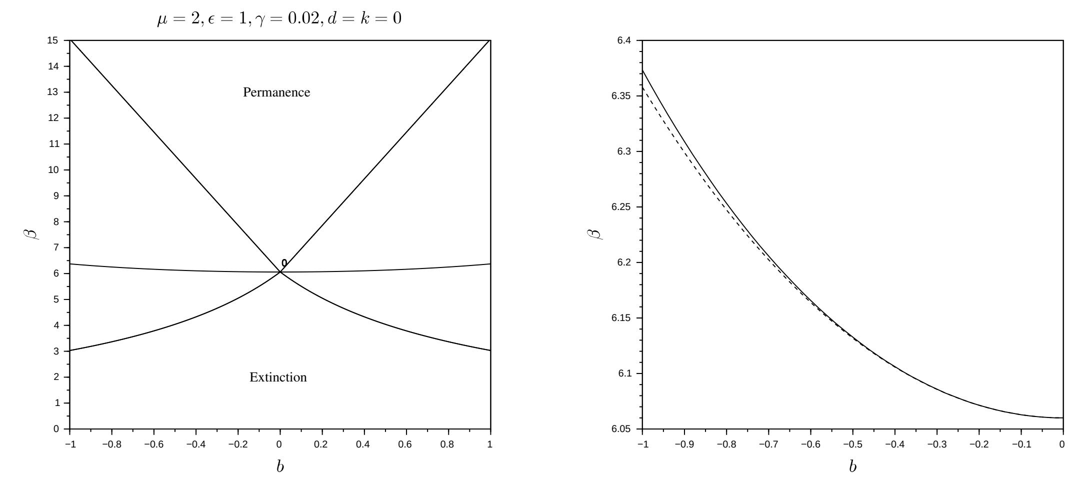


Figure 2.1: Regions of permanence and extinction for $(b, \beta)$ and approximated thresholds obtained numerically and given by (2.57).

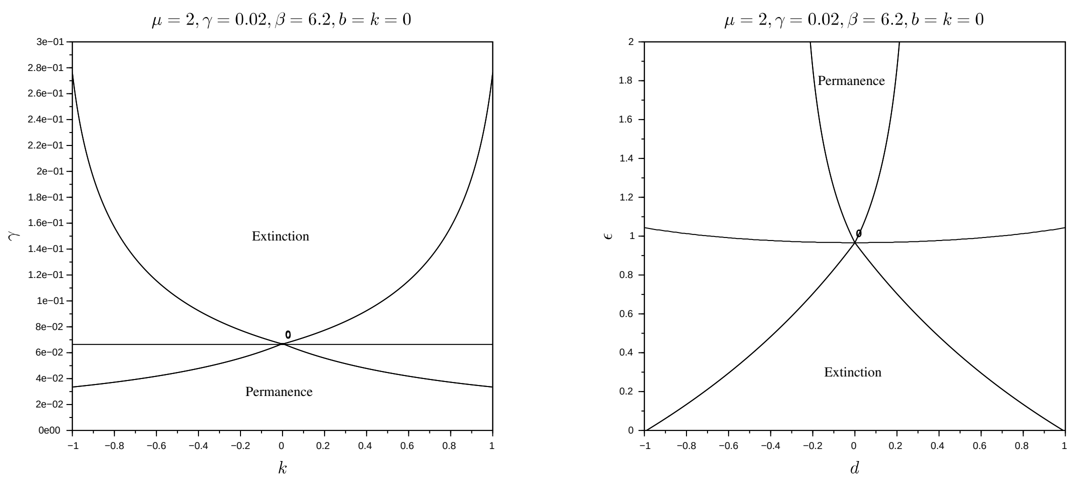


Figure 2.2: Regions of permanence and extinction for $(k, \gamma)$ and $(d, \varepsilon)$.

Example 2.3.4 (Michaelis-Menten contact rates). We consider the particular form for the incidence $\varphi(S, N, I) = C(N)\frac{SI}{N}$. We recall that these rates are called Michaelis-Menten contact rates were considered for instance in [40] and have as particular cases the standard incidence ($C(N) = 1$) and the simple incidence ($C(N) = N$).

We will assume that $\Lambda$ and $\mu$ are constant, that

$$N \mapsto C(N)/N \quad \text{is non-increasing} \tag{2.58}$$

and that, for each $\theta > 0$,

$$\|C(N_1) - C(N_2)\| \leq K_\theta \|N_1 - N_2\|. \tag{2.59}$$

We have

$$\begin{aligned}
\mathcal{R}_e(\lambda, p) < 1 \quad &\Leftrightarrow \quad \limsup_{t\to+\infty} \int_t^{t+\lambda} \beta(s)C(\Lambda/\mu)p - \mu - \varepsilon(s)\, ds < 0 \\
&\Leftarrow \quad pC(\Lambda/\mu) \limsup_{t\to+\infty} \int_t^{t+\lambda} \beta(s)\, ds - (\mu + \varepsilon_\lambda^-)\lambda < 0 \\
&\Leftrightarrow \quad \left[pC(\Lambda/\mu)\beta_\lambda^+ - \mu - \varepsilon_\lambda^-\right] \lambda < 0
\end{aligned}$$

$$\begin{aligned}
\mathcal{R}_e^*(\lambda, p) < 1 \quad &\Leftrightarrow \quad \limsup_{t\to+\infty} \int_t^{t+\lambda} \varepsilon(s)/p - \mu - \gamma(s)\, ds < 0 \\
&\Leftarrow \quad \left(\varepsilon_\lambda^+/p - \mu - \gamma_\lambda^-\right) \lambda < 0,
\end{aligned}$$

and analogously

$$\mathcal{R}_p(\lambda, p) > 1 \quad \Leftarrow \quad \left[pC(\Lambda/\mu)\beta_\lambda^- - \mu - \varepsilon_\lambda^+\right] \lambda > 0$$

and

$$\mathcal{R}_p^*(\lambda, p) > 1 \quad \Leftarrow \quad \left(\varepsilon_\lambda^-/p - \mu - \gamma_\lambda^+\right) \lambda > 0.$$

Define

$$\mathcal{R}_e^M(\lambda) = \frac{\varepsilon_\lambda^+ \beta_\lambda^+ C(\Lambda/\mu)}{(\mu + \varepsilon_\lambda^-)(\mu + \gamma_\lambda^-)} \quad \text{and} \quad \mathcal{R}_p^M(\lambda) = \frac{\varepsilon_\lambda^- \beta_\lambda^- C(\Lambda/\mu)}{(\mu + \varepsilon_\lambda^+)(\mu + \gamma_\lambda^+)}.$$

Corollary 2.3.4. Assume that NA1) to NA5) hold. We have the following for the Michaelis-Menten contact-rates with constant $\Lambda$ and $\mu$ and satisfying (2.58) and (2.59).

1) If $G(\varepsilon_\lambda^+/(\mu+\gamma_\lambda^-)) < 0$ or $H((\mu+\varepsilon_\lambda^-)/(C(\Lambda/\mu)\beta_\lambda^+)) > 0$ and $\mathcal{R}_e^M(\lambda) < 1$ for some $\lambda > 0$ then the infectives go to extinction;

2) If $G((\mu+\varepsilon_\lambda^-)/(C(\Lambda/\mu)\beta_\lambda^+)) < 0$ or $H(\varepsilon_\lambda^+/(\mu+\gamma_\lambda^-)) > 0$ and $\mathcal{R}_p^M(\lambda) > 1$ for some $\lambda > 0$ then the infectives are strongly persistent.

Proof. We begin by noting that

$$G(p) = \limsup_{t\to+\infty} [\beta(t)C(\Lambda/\mu)p - \gamma(t) - (1+1/p)\varepsilon(t)]$$
$$= \limsup_{t\to+\infty} \frac{\beta(t)C(\Lambda/\mu)p^2 - (\gamma(t)+\varepsilon(t))p - \varepsilon(t)}{p}$$

thus, there is $p > 0$ such that $G(p) < 0$ if and only if there is $p > 0$ such that $pG(p) < 0$. Since

$$\beta(t)C(\Lambda/\mu)p^2 - (\gamma(t)+\varepsilon(t))p - \varepsilon(t)$$

has two zeros, $a_0 \in \mathbb{R}^-$ and $a_1 \in \mathbb{R}^+$, and the coefficient of $p^2$ is positive, we conclude that there is $p > 0$ such that $G(p) < 0$ if and only if there is $p \in ]0, a_1[$ such that $G(p) < 0$.

By similar computations to the ones in the proof of corollary 2.3.1 we conclude that if there is $\lambda > 0$ such that $\mathcal{R}_e^M(\lambda) < 1$ then there is

$$p \in I = \left( \frac{\varepsilon_\lambda^+}{\mu + \gamma_\lambda^-}, \frac{\mu + \varepsilon_\lambda^-}{C(\Lambda/\mu)\beta_\lambda^+} \right)$$

such that $\mathcal{R}_e(\lambda, p) < 1$ and $\mathcal{R}_e^*(\lambda, p) < 1$. Thus, if $G(\varepsilon_\lambda^+/(\mu+\gamma_\lambda^-)) < 0$, we have $]0, a_1[ \cap I \neq \emptyset$. Therefore if $G(\varepsilon_\lambda^+/(\mu+\gamma_\lambda^-)) < 0$ there is $p > 0$ such that $\mathcal{R}_e(\lambda, p) < 1$, $\mathcal{R}_e^*(\lambda, p) < 1$ and $G(p) < 0$. Thus, by Theorem 2.2.1, the infectives go to extinction. On the other hand, since $H$ is continuous, if $H((\mu+\varepsilon_\lambda^-)/(C(\Lambda/\mu)\beta_\lambda^+)) > 0$ there is $p \in I$ such that $\mathcal{R}_e(\lambda, p) < 1$, $\mathcal{R}_e^*(\lambda, p) < 1$ and $H(p) > 0$. Therefore if $H((\mu+\varepsilon_\lambda^-)/(C(\Lambda/\mu)\beta_\lambda^+)) > 0$ there is $p > 0$ such that $\mathcal{R}_e(\lambda, p) < 1$, $\mathcal{R}_e^*(\lambda, p) < 1$ and $H(p) > 0$. Thus, by Theorem 2.2.1, the infectives go to extinction and we obtain 1).

By similar computations we get 2). □

In particular, setting $C(N) = N$ (mass-action incidence) we get

$$\mathcal{R}_e^M(\lambda) = \frac{\varepsilon_\lambda^+ \beta_\lambda^+ \Lambda/\mu}{(\mu+\varepsilon_\lambda^-)(\mu+\gamma_\lambda^-)} \quad \text{and} \quad \mathcal{R}_p^M(\lambda) = \frac{\varepsilon_\lambda^- \beta_\lambda^- \Lambda/\mu}{(\mu+\varepsilon_\lambda^+)(\mu+\gamma_\lambda^+)}.$$

and setting $C(N) = 1$ (standard incidence) we obtain

$$\mathcal{R}_e^M(\lambda) = \frac{\varepsilon_\lambda^+ \beta_\lambda^+}{(\mu+\varepsilon_\lambda^-)(\mu+\gamma_\lambda^-)} \quad \text{and} \quad \mathcal{R}_p^M(\lambda) = \frac{\varepsilon_\lambda^- \beta_\lambda^-}{(\mu+\varepsilon_\lambda^+)(\mu+\gamma_\lambda^+)}.$$

To illustrate the above corollary we consider the following family of nonperiodic models

$$\begin{cases} S' = \mu - \beta(1 + b(1 + \mathrm{e}^{-t})\cos(2\pi t))\, SI - \mu S + \eta R \\ E' = \beta(1 + b(1 + \mathrm{e}^{-t})\cos(2\pi t))\, SI - (\mu + \varepsilon)E \\ I' = \varepsilon E - (\mu + \gamma)I \\ R' = \gamma I - (\mu + \eta)R \\ N = S + E + I + R \end{cases}$$

It is easy to see that, in this case, $\beta_1^+ = \beta_1^- = \beta$ and thus

$$\mathcal{R}_e^M(1) = \mathcal{R}_p^M(1) = \frac{\varepsilon\beta}{(\mu + \varepsilon)(\mu + \gamma)}$$

The following figures show situations where we have strong persistence and extinction for the above model with different values for $\beta$ and $b$ and $\mu = 2$, $\varepsilon = 1$, $\gamma = 0.02$ and $\eta = 0.1$. For instance, for $\beta = 10$ and $b = 0.3$ we can see that $\mathcal{R}_p^M(1) = 1.65 > 1$ and $G(3/10) = -0.41 < 0$ and we conclude that we have strong persistence and for $\beta = 5$ and $b = 0.2$ we can see that $\mathcal{R}_e^M(1) = 0.82 < 1$ and $G(0.495) = -0.03 < 0$ and we conclude that we have extinction (see figure 2.3).

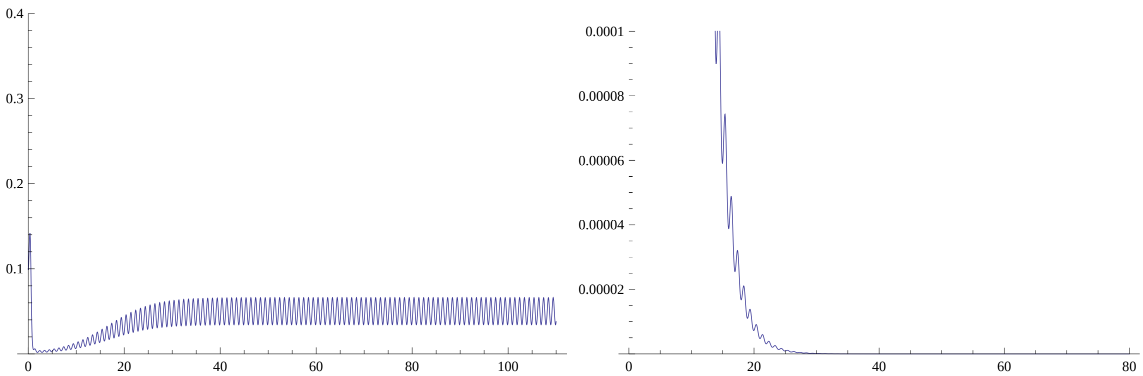


Figure 2.3: left: $\beta = 10$ and $b = 0.3$; right: $\beta = 5$ and $b = 0.2$.

## 2.4 Robustness

In this section we will discuss the robustness of the conditions $\mathcal{R}_e(\lambda, p) < 1$, $\mathcal{R}_e^*(\lambda, p) < 1$, $\mathcal{R}_p(\lambda, p) > 1$, $\mathcal{R}_p^*(\lambda, p) > 1$, $H(p) > 0$ and $G(p) < 0$, i.e., roughly speaking, if for sufficiently small perturbations of the parameters of our model in some admissible family of functions the conditions above are preserved. We will consider differentiable functions $\varphi$.

Consider the family of systems

$$\begin{cases} S' = \Lambda(t) - \beta_\tau(t)\,\varphi_\tau(S,N,I) - \mu(t)S + \eta_\tau(t)R \\ E' = \beta_\tau(t)\,\varphi_\tau(S,N,I) - (\mu(t)+\varepsilon_\tau(t))E \\ I' = \varepsilon_\tau(t)E - (\mu(t)+\gamma_\tau(t))I \\ R' = \gamma_\tau(t)I - (\mu(t)+\eta_\tau(t))R \\ N = S+E+I+R \end{cases}, \tag{2.60}$$

where $\tau \in [-\zeta,\zeta]$ and we assume that, making $\tau = 0$, we have $\varphi_0 = \varphi$, $\beta_0 = \beta$, $\eta_0 = \eta$, $\varepsilon_0 = \varepsilon$ and $\gamma_0 = \gamma$ and that, for $\tau = 0$ the parameters satisfy our assumptions (i.e. for $\tau = 0$ we have our original system (1) with assumptions NA1) to NA5)). We also assume that for each $\tau \in [-\zeta,\zeta]$ the parameter functions $\beta_\tau$, $\eta_\tau$, $\varepsilon_\tau$ and $\gamma_\tau$ are continuous and bounded in $\mathbb{R}_0^+$, that $\varphi_\tau$ is differentiable in $\Delta_{0,D}$ and that $\varphi_\tau(S,N,0) = 0$.

For $g : \mathbb{R}_0^+ \to \mathbb{R}$ denote by $\|\cdot\|_\infty$ the supremum norm (given by $\|g\|_\infty = \sup_{t\ge 0}|g(t)|$) and for $f : (\mathbb{R}_0^+)^3 \to \mathbb{R}$ denote by $\|\cdot\|_{\Delta_{0,D}}$ the $C^1$ norm of the restriction $f|_{\Delta_{0,D}}$:

$$\|f\|_{\Delta_{0,D}} = \max_{x\in\Delta_{0,D}} |f(x)| + \max_{x\in\Delta_{0,D}} \|d_x f\|.$$

Denote by $\mathcal{R}_e^\tau(\lambda,p)$, $\mathcal{R}_p^\tau(\lambda,p)$, $(\mathcal{R}_e^*)^\tau(\lambda,p)$, $\left(\mathcal{R}_p^*\right)^\tau(\lambda,p)$, $G_p^\tau(\lambda)$ and $H_p^\tau(\lambda)$, respectively the numbers (2.10), (2.11), (2.12), (2.13) (2.14) and (2.15) with respect to the system indexed $\tau$ in our family of models.

We have the following result on the robustness of conditions $\mathcal{R}_e(\lambda,p) < 1$, $\mathcal{R}_e^*(\lambda,p) < 1$, $\mathcal{R}_p(\lambda,p) > 1$, $\mathcal{R}_p^*(\lambda,p) > 1$, $H(p) > 0$ and $G(p) < 0$.

Theorem 2.4.1. Assume that $\|\beta_\tau - \beta\|_\infty$, $\|\eta_\tau - \eta\|_\infty$, $\|\varepsilon_\tau - \varepsilon\|_\infty$, $\|\gamma_\tau - \gamma\|_\infty$ and $\|\varphi_\tau - \varphi\|_{\Delta_{0,K}}$ converge to 0 as $\tau \to 0$. Then there is $L > 0$ such that, for all $\tau \in [-L,L]$, the numbers

$$|G^\tau(p) - G(p)|, \quad |H^\tau(p) - H(p)|, \quad |\mathcal{R}_e^\tau(\lambda,p) - \mathcal{R}_e(\lambda,p)|,$$

$$\left|\mathcal{R}_p^\tau(\lambda,p) - \mathcal{R}_p(\lambda,p)\right|, \quad |(\mathcal{R}_e^*)^\tau(\lambda,p) - \mathcal{R}_e^*(\lambda,p)| \quad \text{and} \quad \left|\left(\mathcal{R}_p^*\right)^\tau(\lambda,p) - \mathcal{R}_p^*(\lambda,p)\right|$$

converge to 0 as $\tau \to 0$.

Proof. Let $b_\delta^\tau$ denote the function in (2.9) with $\varphi$, $\beta$, and $\varepsilon$ replaced by $\varphi_\tau$, $\beta_\tau$, and $\varepsilon_\tau$ respectively. Let $\delta > 0$. We have that there is $L > 0$ such that for $\tau \in [-L,L]$ we have by assumption $\sup_{t\ge 0}|\beta_\tau(t) - \beta(t)| < \delta$ and thus $\beta_\tau(t) < \beta^u + \delta$ for all $t \ge 0$.

Write $B = \beta^u + \delta$. By (2.9) and (2.2) we have

$$\begin{aligned}
&|b^\tau_\delta(p,t,z(t)) - b_\delta(p,t,z(t))| \\
&= \left|\beta_\tau(t)\frac{\varphi_\tau(z(t),z(t),\delta)}{\delta}p - \mu(t) - \varepsilon_\tau(t) - \beta(t)\frac{\varphi(z(t),z(t),\delta)}{\delta}p + \mu(t) + \varepsilon(t)\right| \\
&\le |\beta_\tau(t)|\, p \left|\frac{\varphi_\tau(z(t),z(t),\delta) - \varphi(z(t),z(t),\delta)}{\delta}\right| \\
&\qquad + |\beta_\tau(t) - \beta(t)|\, p\frac{\varphi(z(t),z(t),\delta)}{\delta} + \|\varepsilon_\tau - \varepsilon\|_\infty \\
&\le Bp\left|\frac{\varphi_\tau(z(t),z(t),\delta) - \varphi(z(t),z(t),\delta)}{\delta}\right| + Mp\|\beta_\tau - \beta\|_\infty + \|\varepsilon_\tau - \varepsilon\|_\infty
\end{aligned} \tag{2.61}$$

Since for $\tau \in [-L, L]$, $\varphi_\tau$ is differentiable and $\varphi_\tau(S,N,0) = \varphi(S,N,0) = 0$, we get

$$\begin{aligned}
&|\varphi_\tau(z(t),z(t),\delta) - \varphi(z(t),z(t),\delta)| \\
&= \left|\frac{\partial \varphi_\tau}{\partial I}(z(t),z(t),0)\delta + r^\tau(\delta) - \frac{\partial \varphi}{\partial I}(z(t),z(t),0)\delta - r(\delta)\right| \\
&\le \left|\frac{\partial \varphi_\tau}{\partial I}(z(t),z(t),0) - \frac{\partial \varphi}{\partial I}(z(t),z(t),0)\right|\delta + |r^\tau(\delta)| + |r(\delta)|
\end{aligned} \tag{2.62}$$

where $r(\delta)/\delta \to 0$ and $r^\tau(\delta)/\delta \to 0$ as $\delta \to 0$. By (2.62) we obtain

$$\begin{aligned}
&\frac{|\varphi_\tau(z(t),z(t),\delta) - \varphi(z(t),z(t),\delta)|}{\delta} \\
&\le \left|\frac{\partial \varphi_\tau}{\partial I}(z(t),z(t),0) - \frac{\partial \varphi}{\partial I}(z(t),z(t),0)\right| + \frac{|r^\tau(\delta)|}{\delta} + \frac{|r(\delta)|}{\delta} \\
&\le \|\varphi_\tau - \varphi\|_{\Delta_{0,D}} + \frac{|r^\tau(\delta)|}{\delta} + \frac{|r(\delta)|}{\delta}
\end{aligned} \tag{2.63}$$

Thus, by (2.61) and (2.63) we get, for $t$ sufficiently big,

$$\begin{aligned}
&|b^\tau_\delta(p,t,z(t)) - b_\delta(p,t,z(t))| \\
&\le Bp\left|\frac{\varphi_\tau(z(t),z(t),\delta) - \varphi(z(t),z(t),\delta)}{\delta}\right| + Mp\|\beta_\tau - \beta\|_\infty + \|\varepsilon_\tau - \varepsilon\|_\infty \\
&\le Bp\left(\|\varphi_\tau - \varphi\|_{\Delta_{0,D}} + \frac{|r^\tau(\delta)|}{\delta} + \frac{|r(\delta)|}{\delta}\right) + Mp\|\beta_\tau - \beta\|_\infty + \|\varepsilon_\tau - \varepsilon\|_\infty.
\end{aligned}$$

Therefore

$$\begin{aligned}
&\lim_{\delta\to 0^+} |b^\tau_\delta(p,t,z(t)) - b_\delta(p,t,z(t))| \\
&\qquad \le Bp\|\varphi_\tau - \varphi\|_{\Delta_{0,D}} + Mp\|\beta_\tau - \beta\|_\infty + \|\varepsilon_\tau - \varepsilon\|_\infty.
\end{aligned}$$

Thus

$$\left|\int_t^{t+\lambda} \lim_{\delta\to 0^+} b_\delta^\tau(p,s,z(s)) - \lim_{\delta\to 0^+} b_\delta(p,s,z(s))\, ds\right|$$
$$\leq \int_t^{t+\lambda} \lim_{\delta\to 0^+} |b_\delta^\tau(p,s,z(s)) - b_\delta(p,s,z(s))|\, ds \leq \Theta(\tau),$$

where

$$\Theta(\tau) = \lambda B p \|\varphi_\tau - \varphi\|_{\Delta_{0,D}} + M p \lambda \|\beta_\tau - \beta\|_\infty + \lambda \|\varepsilon_\tau - \varepsilon\|_\infty.$$

Thus

$$\ln \mathcal{R}_e(\lambda,p) - \Theta(\tau) \leq \ln \mathcal{R}_e^\tau(\lambda,p) \leq \ln \mathcal{R}_e(\lambda,p) + \Theta(\tau)$$

and then

$$\mathcal{R}_e(\lambda,p)\, \mathrm{e}^{-\Theta(\tau)} \leq \mathcal{R}_e^\tau(\lambda,p) \leq \mathcal{R}_e(\lambda,p)\, \mathrm{e}^{\Theta(\tau)}$$

and sending $\tau \to 0$ we get

$$\lim_{\tau\to 0} \mathcal{R}_e^\tau(\lambda,p) = \mathcal{R}_e(\lambda,p).$$

Similarly we obtain also $\lim_{\tau\to 0} (\mathcal{R}_e^*)^\tau(\lambda,p) = (\mathcal{R}_e^*)(\lambda,p)$, $\lim_{\tau\to 0} \mathcal{R}_p^\tau(\lambda,p) = \mathcal{R}_p(\lambda,p)$, $\lim_{\tau\to 0} \left(\mathcal{R}_p^*\right)^\tau(\lambda,p) = (\mathcal{R}_p^*)(\lambda,p)$, $\lim_{\tau\to 0} G^\tau(p) = G(p)$ and $\lim_{\tau\to 0} H^\tau(p) = H(p)$. □

The following is an immediate corollary of Theorem 2.4.1 and shows that persistence, extinction and asymptotic stability of the disease free solutions persist for small enough perturbations of $\tau$ in our family of systems.

Corollary 2.4.1. There is $L > 0$ such that for all $\tau \in [-L, L]$ we have.

1) If there are constants $\lambda > 0$ and $p > 0$ such that $\mathcal{R}_e(\lambda,p) < 1$, $\mathcal{R}_e^*(\lambda,p) < 1$ and $G(p) < 0$ then the infectives $I$ go to extinction in system (2.60).

2) If there are constants $\lambda > 0$ and $p > 0$ such that $\mathcal{R}_e(\lambda,p) < 1$, $\mathcal{R}_e^*(\lambda,p) < 1$ and $H(p) > 0$ then the infectives $I$ go to extinction in system (2.60).

3) If there are constants $\lambda > 0$ and $p > 0$ such that $\mathcal{R}_p(\lambda,p) > 1$, $\mathcal{R}_p^*(\lambda,p) > 1$ and $G(p) < 0$ then the infectives $I$ are strongly persistent in system (2.60).

4) If there are constants $\lambda > 0$ and $p > 0$ such that $\mathcal{R}_p(\lambda,p) > 1$, $\mathcal{R}_p^*(\lambda,p) > 1$ and $H(p) > 0$ then the infectives $I$ are strongly persistent in system (2.60).

5) In the assumptions of 1. any disease-free solution $(S_1(t), 0, 0, R_1(t))$ is globally asymptotically stable in system (2.60).

# Chapter 3

## Periodic Model

In this chapter we consider the periodic version of problem (1), i.e. we assume that all the parameter functions are periodic functions with the same period.

## 3.1 Settings and Preliminaries

We will make the following assumptions:

P1) There is $\omega \geq 0$ such that $\Lambda$, $\mu$, $\beta$ and $\varepsilon$ are continuous and positive $\omega$-periodic real valued functions on $\mathbb{R}_0^+$ and that $\eta$ and $\gamma$ are continuous and nonnegative $\omega$-periodic real valued functions on $\mathbb{R}_0^+$;

P2) Function $\varphi : (\mathbb{R}_0^+)^3 \to \mathbb{R}$ is continuously differentiable;

P3) For $S, N, I \geq 0$ we have $\varphi(0, N, I) = \varphi(S, N, 0) = 0$;

P4) For $S, I > 0$ and $N \in \left[\Lambda^\ell/\mu^u, \Lambda^u/\mu^\ell\right]$ we have $c_1 \leq \varphi(S, N, I)/(SI) \leq c_2$;

P5) For $0 \leq I \leq N \leq \Lambda^u/\mu^\ell$, the function $\mathbb{R}_0^+ \ni S \mapsto \varphi(S, N, I)$ is non-decreasing, for $0 \leq S \leq N \leq \Lambda^u/\mu^\ell$, the function $\mathbb{R}_0^+ \ni I \mapsto \varphi(S, N, I)$ is non-decreasing and for $0 \leq S, I \leq N \leq \Lambda^u/\mu^\ell$ the function $\mathbb{R}_0^+ \ni N \mapsto \varphi(S, N, I)$ is non-increasing;

P6) For $0 \leq S \leq N \leq \Lambda^u/\mu^\ell$, the function $\mathbb{R}^+ \ni I \mapsto \varphi(S, N, I)/I$ is non-increasing.

We note that Proposition 2.1.1 still holds in our context.

We will consider in our periodic setting the periodic linear differential equation

$$z' = \Lambda(t) - \mu(t)z. \tag{3.1}$$

We recall that Proposition 2.2.1 furnishes some properties of this equation when $\Lambda(t)$ and $\mu(t)$ are bounded and thus it still holds when these parameter functions are periodic. In the present context we can add the following.

Lemma 3.1.1. Assume that condition P1) holds. Then we have the following:

1) for each solution $z(t)$ of (3.1) we have

$$\Lambda^\ell/\mu^u \leq \liminf_{t\to+\infty} z(t) \leq \limsup_{t\to+\infty} z(t) \leq \Lambda^u/\mu^\ell;$$

2) for each solution $z(t)$ of (3.1) with initial condition in $[\Lambda^\ell/\mu^u, \Lambda^u/\mu^\ell]$ we have $z(t) \in [\Lambda^\ell/\mu^u, \Lambda^u/\mu^\ell]$, for all $t \geq t_0$;

3) there is a unique periodic solution $z^*(t)$ of (3.1) in $\mathbb{R}^+$, this solution has period $\omega$ and is given by

$$z^*(t) = \frac{\int_0^\omega \Lambda(u)\,\mathrm{e}^{-\int_u^\omega \mu(s)\ ds}\ du}{1-\mathrm{e}^{-\int_0^\omega \mu(s)\,ds}}\,\mathrm{e}^{-\int_0^t \mu(s)\,ds} + \int_0^t \Lambda(u)\,\mathrm{e}^{-\int_u^t \mu(s)\ ds}\ du. \tag{3.2}$$

Proof. By the variation of the parameters formula we have that the unique solution of (3.1) with $z(0) = z_0$ is

$$z(t, z_0) = z_0\,\mathrm{e}^{-\int_0^t \mu(s)\,ds} + \int_0^t \Lambda(u)\,\mathrm{e}^{-\int_u^t \mu(s)\ ds}\ du.$$

Therefore we have

$$z(t, z_0) \leq z_0\,\mathrm{e}^{-\mu^\ell t} + \Lambda^u \int_0^t \mathrm{e}^{-\mu^\ell (t-u)}\ du = \left(z_0 - \Lambda^u/\mu^\ell\right)\mathrm{e}^{-\mu^\ell t} + \Lambda^u/\mu^\ell \tag{3.3}$$

and thus $\limsup_{t\to+\infty} z(t, z_0) \leq \Lambda^u/\mu^\ell$. Similarly,

$$z(t, z_0) \geq z_0\,\mathrm{e}^{-\mu^u t} + \Lambda^\ell \int_0^t \mathrm{e}^{-\mu^u (t-u)}\ du = \left(z_0 - \Lambda^\ell/\mu^u\right)\mathrm{e}^{-\mu^u t} + \Lambda^\ell/\mu^u \tag{3.4}$$

and thus $\liminf_{t\to+\infty} z(t, z_0) \geq \Lambda^\ell/\mu^u$. We obtain 1).

Let $z_0 \in [\Lambda^\ell/\mu^u, \Lambda^u/\mu^\ell]$. Since $z_0 - \Lambda^u/\mu^\ell \leq 0$ and $z_0 - \Lambda^\ell/\mu^u \geq 0$, by (3.3) and (3.4) we obtain 2).

By the invariance of $[\Lambda^\ell/\mu^u, \Lambda^u/\mu^\ell]$ established in 2), the map $P : [\Lambda^\ell/\mu^u, \Lambda^u/\mu^\ell] \to [\Lambda^\ell/\mu^u, \Lambda^u/\mu^\ell]$ given by $P(y) = z(\omega, y)$, where $z(t, y)$ denotes the unique solution of (3.1) with initial condition $z(0) = y$, is well defined. Since $P$ is a continuous function on the convex and compact set $[\Lambda^\ell/\mu^u, \Lambda^u/\mu^\ell]$, by Brower's fixed point theorem, we conclude that $P$ has a fixed point $y_0$. Thus $z(\omega, y_0) = y_0$.

By uniqueness of solution we have

$$z(\omega + t, y_0) = z(t, z(\omega, y_0)) = z(t, y_0) \tag{3.5}$$

and we can conclude that the solution of (3.1) with $z(0) = y_0$ is a $\omega$-periodic solution. Moreover, by (3.5) and the variation of the parameters formula, we obtain

$$y_0 = y_0 \, \mathrm{e}^{-\int_0^\omega \mu(s)\, ds} + \int_0^\omega \Lambda(u) \, \mathrm{e}^{-\int_u^\omega \mu(s)\ ds} \ du$$

and thus

$$y_0 = \frac{\int_0^\omega \Lambda(u) \, \mathrm{e}^{-\int_u^\omega \mu(s)\ ds} \ du}{1 - \mathrm{e}^{-\int_0^\omega \mu(s)\, ds}} \tag{3.6}$$

and we get (3.2). The uniqueness of the periodic solution follows from the global asymptotic stability of solutions proved in 3) in Proposition 2.2.1. We obtain 3). □

Since we have periodicity we can add some additional information to that in Proposition 2.1.1. In fact we have the following

Lemma 3.1.2. Assume that conditions P1) to P6) hold. Then:

1) If $(S(t), E(t), I(t), R(t))$ is a periodic solution of (1) verifying $S(t_0)$, $E(t_0)$, $I(t_0)$, $R(t_0) \geq 0$, then we have $\Lambda^\ell/\mu^u \leq N(t) \leq \Lambda^u/\mu^\ell$.

2) For any $\delta > 0$, and every solution $(S(t), E(t), I(t), R(t))$, there is $T_\delta > 0$ such that $(S(t), E(t), I(t), R(t))$ belongs to the set

$$\left\{(S, E, I, R) \in (\mathbb{R}_0^+)^4 : \Lambda^\ell/\mu^u - \delta \leq S + E + I + R \leq \Lambda^u/\mu^\ell + \delta\right\},$$

for all $t \geq T_\delta$.

Proof. We simply note that, adding the differential equations in (1), we get the equation $N' = \Lambda(t) - \mu(t)N$. By Lemma 3.1.1, we obtain the result. □

By 2) in Lemma 3.1.2, a similar argument to the one given bellow, the proof of Lemma 1.3.1 assures that solutions are global in future.

## 3.2 Thresholds for General Periodic Epidemiological Models

We will now present the periodic counterpart of the method presented in section 1.2 to obtain threshold conditions for general autonomous epidemiological models. This method, applicable to periodic models, was developed by Wendi Wang and Xiao-Qiang Zhao in [38].

Like in section 1.2, we still assume that the population is divided into $n$ homogeneous compartments. We continue denoting by $x_i$, $i = 1, \ldots, n$, the number of individuals in compartment $i$ with the first $m$ compartments being infected individuals and the last $n-m$ compartments being disease-free compartments. We still denote by $X_s$ the set of disease-free states. By $\mathcal{F}_i(t,x)$ we mean the rate of appearance of new infections in compartment $i$, by $\mathcal{V}_i^+(t,x)$ the rate of transfer of individuals into compartment $i$ by all other means and by $\mathcal{V}_i^-(t,x)$ the rate of transfer of individuals out of compartment $i$. These functions will now be assumed periodic in the first variable. We will consider an epidemic model of the form

$$x' = \mathcal{F}(t,x) - \mathcal{V}(t,x) := f(t,x), \tag{3.7}$$

where we have $\mathcal{F}(t,x) = (\mathcal{F}_1(t,x),\ldots,\mathcal{F}_n(t,x))$ and $\mathcal{V}(t,x) = \mathcal{V}^-(t,x) - \mathcal{V}^+(t,x)$ with $\mathcal{V}^+(t,x) = (\mathcal{V}_1^+(t,x),\ldots,\mathcal{V}_n^+(t,x))$ and $\mathcal{V}^-(t,x) = (\mathcal{V}_1^-(t,x),\ldots,\mathcal{V}_n^-(t,x))$ and $x = (x_1,\ldots,x_n)$. We will assume the following:

WZ1) Functions $\mathcal{F}_i(t,x)$, $\mathcal{V}_i^-(t,x)$ and $\mathcal{V}_i^+(t,x)$, $i=1,\ldots,n$, are nonnegative and continuous in $\mathbb{R}\times(\mathbb{R}_0^+)^n$ and continuously differentiable with respect to $x$;

WZ2) There is $\omega>0$ such that functions $\mathcal{F}_i(t,x)$, $\mathcal{V}_i^-(t,x)$ and $\mathcal{V}_i^+(t,x)$, $i=1,\ldots,n$, are periodic of period $\omega$ in $t$;

WZ3) If $x_i=0$ then $\mathcal{V}_i^-(t,x)=0$ for all $i=1,\ldots,n$;

WZ4) If $i>m$ then $\mathcal{F}_i(t,x)=0$ for all $t$;

WZ5) If $x\in X_s$, then $\mathcal{F}_i(t,x)=\mathcal{V}_i^+(t,x)=0$ for $i=1,\ldots,m$;

WZ6) Model (3.7) has a disease-free periodic solution $x^*=(0,\ldots,0,x_{m+1}^*,\ldots,x_n^*)$ with $x_i^*(t)>0$ for at least one index $i\in\{m+1,\ldots,n\}$ and all $t$;

WZ7) We have $\rho(\Phi_M(\omega))<1$ where, as usual, $\rho$ is the spectral radius, and $\Phi_M(t)$ is the monodromy matrix of the linear $\omega$-periodic system $z'=M(t)z$ where

$$M(t) = \left[\frac{\partial f_i}{\partial x_j}(t,x^*(t))\right]_{m+1\le i,j\le n};$$

WZ8) We have $\rho(\Phi_{-V}(\omega))<1$ where $\Phi_{-V}(t)$ is the monodromy matrix of the linear $\omega$-periodic system $z'=-V(t)z$ where

$$V(t) = \left[\frac{\partial \mathcal{V}_i}{\partial x_j}(t,x^*(t))\right]_{1\le i,j\le m}. \tag{3.8}$$

Similarly to the autonomous case, we have

$$d\mathcal{F}_x(t,x^*(t)) = \begin{bmatrix} F(t) & 0 \\ 0 & 0 \end{bmatrix} \quad \text{and} \quad d\mathcal{V}_x(t,x^*(t)) = \begin{bmatrix} V(t) & 0 \\ J(t) & -M(t) \end{bmatrix}$$

where $V(t)$ is given by (3.8) and $F(t)$ is the $m \times m$ matrix given by

$$F(t) = \left[\frac{\partial \mathcal{F}_i}{\partial x_j}(t, x^*(t))\right]_{1 \leq i,j \leq m}.$$

Furthermore, $F(t)$ is non-negative and $-V(t)$ is cooperative, i.e. the off-diagonal elements of $-V(t)$ are non-negative.

Denote by $Y(t,s)$, $t \geq s$, the evolution operator of the linear $\omega$-periodic system

$$y' = -V(t)y, \tag{3.9}$$

that is, for each $s$, the $m \times m$ matrix $Y(t,s)$ satisfies

$$\frac{d}{dt}Y(t,s) = -V(t)Y(t,s) \quad \text{and} \quad Y(s,s) = I,$$

for all $t \geq s$, $s \in \mathbb{R}$, where $I$ is the $m \times m$ identity matrix. Thus the monodromy matrix of (3.9), $\Phi_{-V}(\omega)$, equals $Y(\omega, 0)$.

We need to define an operator that will help us define the basic reproduction ratio in the present context. Denote by $C_\omega$ the Banach space of all $\omega$-periodic functions $\varphi : \mathbb{R} \to \mathbb{R}^m$ with the maximum norm $\|\cdot\|_\infty$. We define a linear operator $L : C_\omega \to C_\omega$, called the next infection operator, by

$$(L\phi)(t) = \int_0^\infty Y(t, t-a)F(t-a)\phi(t-a)\ da,$$

for all $t \in \mathbb{R}$ and $\phi \in C_\omega$. We can define now the basic reproduction ratio for the periodic epidemic model (3.7) as the spectral radius of $L$:

$$\mathcal{R}_0 = \rho(L).$$

The following theorem shows that $\mathcal{R}_0$ is in fact a threshold parameter for the permanence and extinction of the disease.

Theorem 3.2.1 (Theorem 2.2 in [38]). If (3.7) satisfies WZ1) to WZ8) then the disease-free periodic solution $x^*$ is locally asymptotically stable if $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 > 1$. Furthermore

1) $\mathcal{R}_0 = 1$ if and only if $\rho(\Phi_{F-V}(\omega)) = 1$;

2) $\mathcal{R}_0 < 1$ if and only if $\rho(\Phi_{F-V}(\omega)) < 1$;

3) $\mathcal{R}_0 > 1$ if and only if $\rho(\Phi_{F-V}(\omega)) > 1$.

To characterize better $\mathcal{R}_0$, we consider the space

$$C_\omega^+ = \{\varphi \in C_\omega : \varphi(t) \geq 0, \text{ for all } t \in \mathbb{R}\}$$

and, for $\lambda \in (0, +\infty)$, the linear $\omega$-periodic equation

$$w' = \left[-V(t) + \frac{F(t)}{\lambda}\right] w, \tag{3.10}$$

for $t \in \mathbb{R}$. Let $W(t, s, \lambda)$, $t \geq s$, $s \in \mathbb{R}$, be the evolution operator of system (3.10). We have the following result.

Theorem 3.2.2 (Theorem 2.1 in [38]). If (3.7) satisfies WZ1) to WZ8) then the following statements hold:

1) if there is $\lambda_0 > 0$ that solves $\rho(W(\omega, 0, \lambda)) = 1$ then $\mathcal{R}_0 > 0$;

2) if $\mathcal{R}_0 > 0$ then $\lambda = \mathcal{R}_0$ is the unique solution of $\rho(W(\omega, 0, \lambda)) = 1$;

3) $\mathcal{R}_0 = 0$ if and only if $\rho(W(\omega, 0, \lambda)) < 1$ for all $\lambda > 0$.

The next result gives conditions for persistence of the disease.

Theorem 3.2.3 (Theorem 3 in [31]). Assume that conditions WZ1) to WZ8) hold and that $\mathcal{R}_0 > 1$. Fix $j \in \{1, \ldots, m\}$ and assume also that:

1) there exists a compact set $K \subset (\mathbb{R}_0^+)^4$ which is positively invariant for the flow of system (1) and which is also an absorbing set for that flow, i.e., given $x_0 \in K$ and $s_0 \in \mathbb{R}$, we have $x(t, (x_0, s_0)) \in K$ for all $t \geq s_0$, and for any $x_0 \in (\mathbb{R}_0^+)^4$ and $s_0 \in \mathbb{R}$ there exists $t_1 \geq s_0$ such that for each $t \geq t_1$ we have $x(t, (x_0, s_0)) \in K$;

2) there exists $\tau \in [0, \omega)$ such that $F(\tau) - V(\tau)$ is irreducible and there exists $\varepsilon^* > 0$, $\lambda_1 : (0, \varepsilon^*) \to \mathbb{R}^+$ and $\lambda_2 : (0, \varepsilon^*) \to \mathbb{R}^+$, with $\lim_{\varepsilon \to 0^+} \lambda_1(\varepsilon) = 0$ and $\lim_{\varepsilon \to 0^+} \lambda_2(\varepsilon) = 1$, such that

   a) for all $\varepsilon \in (0, \varepsilon^*)$, for any solution $x(t)$ of (1) with initial condition $x(s) = x_s \in K$, if there exists $t_0 \geq s_0$ such that $x_j(t) \leq \varepsilon$ for each $t \geq t_0$ then there exists $t_1 \geq t_0$ such that $x_k(t) \leq \lambda_1(\varepsilon)$, for all $t \geq t_1$ and all $k \in \{1, \ldots, m\} \setminus \{j\}$;

   b) for all $\varepsilon \in (0, \varepsilon^*)$, for any solution $x(t)$ of (1) with initial condition $x(s) = x_s \in K$, if there exists $t_0 \geq s_0$ such that $\|y(t)\| \leq \varepsilon$, $y(t) = (x_1(t), \ldots, x_m(t))$, for each $t \geq t_0$, then there exists $t_1 \geq t_0$, such that $y' \geq (F(t)/\lambda_2(\varepsilon) - V(t))\, y$, for all $t \geq t_1$.

Then, system (1) is uniformly persistent with respect to $x_j$.

## 3.3 Existence and Stability of Disease-Free Periodic Solutions

Theorem 3.3.1. Assume that conditions P1) to P6) hold. Then system (1) admits a unique disease-free periodic solution given by $x^* = (S^*(t), 0, 0, 0)$, where $S^*$ is the unique periodic solution of (3.1). This solution has period $\omega$.

Proof. By Lemma 3.1.1, equation

$$S' = \Lambda(t) - \mu(t)S$$

with initial condition $S(0) = S_0 > 0$ admits a unique positive periodic solution $S^*(t)$, which is globally attractive. Since $R' = -(\mu(t) + \eta(t))R$ has general solution $R(t) = C\,\mathrm{e}^{-\int_0^t \mu(s)+\eta(s)\ ds}$, we conclude that for any periodic solution we must have $C = 0$. Thus system (1) admits an unique disease-free periodic solution given by $(S^*(t), 0, 0, 0)$. Since $S^*(t)$ is $\omega$-periodic, it follows that $(S^*(t), 0, 0, 0)$ is $\omega$-periodic. □

To apply the results in the previous section to our model we let $x = (x_1, x_2, x_3, x_4) = (E, I, S, R)$ and we can write system (1) in the form

$$x' = \mathcal{F}_S(t, x) - (\mathcal{V}_S^-(t, x) - \mathcal{V}_S^+(t, x))$$

where

$$\mathcal{F}_S(t, x) = \begin{bmatrix} \beta(t)\varphi(S, N, I) \\ 0 \\ 0 \\ 0 \end{bmatrix},$$

$$\mathcal{V}_S^-(t, x) = \begin{bmatrix} (\mu(t) + \varepsilon(t))E \\ (\mu(t) + \gamma(t))I \\ \beta(t)\varphi(S, N, I) + \mu(t)S \\ (\mu(t) + \eta(t))R \end{bmatrix}$$

and

$$\mathcal{V}_S^+(t, x) = \begin{bmatrix} 0 \\ \varepsilon(t)E \\ \Lambda(t) + \eta(t)R \\ \gamma(t)I \end{bmatrix}.$$

It is easy to see that conditions WZ1) to WZ5) are consequence of conditions P1) to P6). By Theorem 3.3.1, condition WZ6) holds.

Letting $x^* = (0, 0, S^*(t), 0)$ be the unique positive $\omega$-periodic solution given by Theorem 3.3.1, by P2) and P3) we have $\frac{\partial \varphi}{\partial N}(S^*(t), S^*(t), 0)$=0 and therefore

$$F_S(t) = \begin{bmatrix} 0 & \beta(t)\frac{\partial \varphi}{\partial I}(S^*(t), S^*(t), 0) \\ 0 & 0 \end{bmatrix}$$

and

$$V_S(t) = \begin{bmatrix} \mu(t) + \varepsilon(t) & 0 \\ -\varepsilon(t) & \mu(t) + \gamma(t) \end{bmatrix}.$$

Let $Y_S(t, s)$, $t \geq s$, be the evolution operator of the linear $\omega$-periodic system $y' = -V(t)y$, i.e. $Y_S(t, s)$ satisfies

$$\frac{d}{dt}[Y_S(t, s)] = \begin{bmatrix} -(\mu(t) + \varepsilon(t)) & 0 \\ \varepsilon(t) & -(\mu(t) + \gamma(t)) \end{bmatrix} Y_S(t, s) \tag{3.11}$$

for $t \geq s$, $s \in \mathbb{R}$. The next infection operator $L_S : C_\omega \to C_\omega$ becomes in our context

$$(L_S\varphi)(t) = \int_0^\infty Y_S(t, t-a)F_S(t-a)\varphi(t-a)\, da$$

and we define the basic reproduction ratio in our context by

$$\mathcal{R}_0 = \rho(L_S).$$

By Theorem 3.2.1 we get the following result.

Theorem 3.3.2. Assume that conditions P1) to P6) hold. Then, for system (1), the disease-free periodic solution $x^*$ is locally asymptotically stable if $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 > 1$. Furthermore

1) $\mathcal{R}_0 = 1$ if and only if $\rho(\Phi_{F_S - V_S}(\omega)) = 1$;

2) $\mathcal{R}_0 < 1$ if and only if $\rho(\Phi_{F_S - V_S}(\omega)) < 1$;

3) $\mathcal{R}_0 > 1$ if and only if $\rho(\Phi_{F_S - V_S}(\omega)) > 1$,

where $\Phi_{F_S - V_S}(t)$ is the fundamental matrix solution of the linear system

$$x' = (F_S(t) - V_S(t))x.$$

## 3.4 Global Stability of Disease-Free Periodic Solutions

We begin by defining some concepts. Let $A$ be an square matrix. We say that $A$ is cooperative if all its off-diagonal elements are non-negative and we say that $A$ is irreducible if it can not be placed into block upper-triangular form by simultaneous row/column permutations. To obtain the global stability of the disease-free periodic solution we need an auxiliary result.

Lemma 3.4.1 (Lemma 2.1 in [30]). Let $A(t)$ be a continuous, cooperative, irreducible and $\omega$-periodic matrix function, let $\Phi_A(t)$ be the fundamental matrix solution of

$$x' = A(t)x \tag{3.12}$$

and let $p = \frac{1}{\omega}\ln(\rho(\Phi_A(\omega)))$, where $\rho$ denotes the spectral radius. Then, there exists a positive $\omega$-periodic function $v(t)$ such that $\mathrm{e}^{pt}\, v(t)$ is a solution of (3.12).

We are now in conditions to state a result about the persistence of the infectives in our context.

Theorem 3.4.1. If conditions P1) to P6) hold, the disease-free $\omega$-periodic solution $x^* = (S^*(t), 0, 0, 0)$ of system (1) is globally asymptotically stable if $\mathcal{R}_0 < 1$.

Proof. By Theorem 3.3.2, if $\mathcal{R}_0 < 1$, then $x^*(t) = (S^*(t), 0, 0, 0)$, the disease-free $\omega$-periodic solution, is locally asymptotically stable. On the other hand, by 3) in Proposition 2.2.1, for any $\varepsilon_1 > 0$ there exists $T_1 > 0$ such that

$$S^*(t) - \varepsilon_1 \le N(t) \le S^*(t) + \varepsilon_1 \tag{3.13}$$

for $t > T_1$. Thus $S(t) \le N(t) \le S^*(t)+\varepsilon_1$ and $N(t) \ge S^*(t)-\varepsilon_1$. By conditions P2), P5) and P6) there is a function $\psi$ such that $\psi(\xi) \to 0$ as $\xi \to 0$ and

$$\begin{aligned}
\varphi(S(t), N(t), I(t)) &\le \varphi(S^*(t) + \varepsilon_1, S^*(t) - \varepsilon_1, I(t)) \\
&= \frac{\varphi(S^*(t) + \varepsilon_1, S^*(t) - \varepsilon_1, I(t))}{I(t)} I(t) \\
&\le I(t) \lim_{\delta \to 0^+} \frac{\varphi(S^*(t) + \varepsilon_1, S^*(t) - \varepsilon_1, \delta)}{\delta} \\
&= \frac{\partial \varphi}{\partial I}(S^*(t) + \varepsilon_1, S^*(t) - \varepsilon_1, 0)\ I(t) \\
&\le \left( \frac{\partial \varphi}{\partial I}(S^*(t), S^*(t), 0) + \psi(\varepsilon_1) \right) I(t),
\end{aligned}$$

for $t > T_1$. Therefore, by the second and third equations in (1), we have

$$\begin{cases} E' \le \beta(t) \left[ \dfrac{\partial \varphi}{\partial I}(S^*(t), S^*(t), 0)I + \psi(\varepsilon_1) I \right] - (\mu(t) + \varepsilon(t))E \\ I' = \varepsilon(t)E - (\mu(t) + \gamma(t))I \end{cases}.$$

Let

$$M_2(t) = \begin{bmatrix} 0 & \beta(t) \\ 0 & 0 \end{bmatrix}.$$

By Theorem 3.3.2 we conclude that $\rho(\Phi_{F_S-V_S}(\omega)) < 1$. Choose $\varepsilon_1 > 0$ such that $\rho(\Phi_{F_S-V_S+\psi(\varepsilon_1)M_2}(\omega)) < 1$ and consider the system

$$\begin{cases} u' = \beta(t)\left[\dfrac{\partial\varphi}{\partial I}(S^*(t), S^*(t), 0)v + \psi(\varepsilon_1)v\right] - (\mu(t)+\varepsilon(t))u \\ v' = \varepsilon(t)u - (\mu(t)+\gamma(t))v \end{cases},$$

or, in matrix language,

$$\begin{bmatrix} u' \\ v' \end{bmatrix} = (F_S(t) + V_S(t) + \psi(\varepsilon_1)M_2(t)) \begin{bmatrix} u \\ v \end{bmatrix}.$$

By Lemma 3.4.1 and the standard comparison principle, there are $\omega$-periodic functions $v_1$ and $v_2$ such that

$$E(t) \le v_1(t)\, \mathrm{e}^{pt} \quad \text{and} \quad I(t) \le v_2(t)\, \mathrm{e}^{pt},$$

where $p = \frac{1}{\omega}\ln(\rho(\Phi_{F-V+\psi(\varepsilon_1)M_2}(\omega)))$. We conclude that $I(t) \to 0$ and $E(t) \to 0$ as $t \to +\infty$. It follows that $R(t) \to 0$ as $t \to +\infty$. Thus, since $N(t) - S^*(t) \to 0$ as $t \to +\infty$ we conclude that

$$S(t) - S^*(t) = N(t) - S^*(t) - E(t) - I(t) - R(t) \to 0,$$

as $t \to +\infty$. Hence the disease-free periodic solution is globally asymptotically stable. The result follows. □

## 3.5 Persistence of the Infectives

Theorem 3.5.1. Assume that conditions P1) to P6) hold and that $\mathcal{R}_0 > 1$. Then system (1) is persistent with respect to $I$.

Proof. To prove the theorem we will use Theorem 3.2.3. It follows from Lemma 3.1.2 that condition 1) in Theorem 3.2.3 holds, letting the compact set $K$ be the set

$$K = \{(S,E,I,R) \in (\mathbb{R}_0^+)^4 : \Lambda^\ell/\mu^u \le S+E+I+R \le \Lambda^u/\mu^\ell\}$$

if $\Lambda$ or $\mu$ are not constant functions and

$$K = \{(S,E,I,R) \in (\mathbb{R}_0^+)^4 : \Lambda^\ell/\mu^u - \delta \leq S+E+I+R \leq \Lambda^u/\mu^\ell + \delta\},$$

for some $0 < \delta < \Lambda/\mu$, if $\Lambda$ and $\mu$ are constant functions.

Let $(S^*(t),0,0,0)$ be the disease free periodic solution of system (1). If there is $\delta > 0$ and $t_0 \in \mathbb{R}$ such that $I(t) \leq \delta$ for $t \geq t_0$ then, using P3) and P4), we have

$$R' \leq \gamma^u \delta - (\mu+\eta)^\ell R,$$

$$(S-S^*)' \leq -\beta(t)\varphi(S,N,I) - \mu(t)(S-S^*) + \eta^u R \leq -\mu(t)(S-S^*) + \eta^u R,$$
$$E' \leq \beta^u \varphi(S,N,I) - (\mu+\varepsilon)^\ell E \leq \beta^u c_2 S\delta - (\mu+\varepsilon)^\ell E$$

and

$$(S^*-S)' \leq \beta(t)\varphi(S,N,I) - \mu(t)(S^*-S) - \eta^u R \leq \beta^u c_2 S\delta - \mu(t)(S^*-S)$$

Thus, for $t$ sufficiently large, we have

$$R(t) \leq 2\delta \frac{\gamma^u}{(\mu+\gamma)^\ell} := k_1(\delta), \tag{3.14}$$

$$S(t) - S^*(t) \leq 2k_1(\delta)\frac{\eta^u}{\mu^\ell} := k_2(\delta), \tag{3.15}$$

$$E(t) \leq 2\delta \frac{c_2\beta^u(k_2(\delta)+S^*)^u}{(\mu+\varepsilon)^\ell} := k_3(\delta) \tag{3.16}$$

and

$$S^*(t) - S(t) \leq 2\delta \frac{c_2\beta^u(k_2(\delta)+S^*)^u}{\mu^\ell} := k_4(\delta). \tag{3.17}$$

Also, according to (3.13), we also have, for $t$ sufficiently large,

$$|S^*(t) - N(t)| \leq k_5(\delta), \tag{3.18}$$

with $k_5(\delta) \to 0$ as $\delta \to 0$.

Now, we will check assumption 2a) in Theorem 3.2.3. Assume that there exists $t_0 \in \mathbb{R}$ such that $I(t) \leq \delta$ for each $t \geq t_0$. From (3.16), there exists $t_3 \geq t_0$ such that for each $t \geq t_3$ we have $E(t) \leq k_3(\delta)$. So we obtain 2a) in Theorem 3.2.3 setting $\lambda_1(\delta) = k_3(\delta)$. Let us now check assumption 2b) in Theorem 3.2.3. Choose $\delta_1 > 0$ such that $k_4(\delta) < \min\limits_{t\in[0,\omega)} S^*(t)$ for all $0 < \delta < \delta_1$. Take $\delta \in (0,\delta_1)$ and suppose that there exists $t_0 \in \mathbb{R}$ such that $\|(E(t),I(t))\| \leq \delta$ for each $t \geq t_0$. Then (3.17) shows that there exists $t_4 \geq t_0$ such that $S(t) \geq S^*(t) - k_4(\delta)$ for $t \geq t_4$ and (3.18) shows that $N(t) \leq S^*(t) + k_5(\delta)$. Therefore, by P5), we get

$$\begin{cases} E' \geq \beta(t)\varphi(S^*(t) - k_4(\delta), S^*(t) + k_5(\delta), I) - (\mu(t) + \varepsilon(t))E \\ I' \geq \varepsilon(t)E - (\mu(t) + \gamma(t))I \end{cases}$$

and assumption 2b) holds with

$$\lambda_2(\delta) = \max_{t \in [0,\omega]} \frac{\partial\varphi/\partial I\,(S^*(t), S^*(t), 0)}{\varphi(S^*(t) - k_4(\delta), S^*(t) + k_5(\delta), \delta)/\delta}.$$

By Theorem 3.2.3 the result follows. □

## 3.6 Existence of Endemic Periodic Solutions

We need to define the numbers

$$\widetilde{R}_0^\ell = \frac{\beta^\ell \varepsilon^\ell L_\varphi}{(\mu+\varepsilon)^u(\mu+\gamma)^u} \quad \text{and} \quad \widetilde{R}_0^u = \frac{\beta^u \varepsilon^u L_\varphi}{(\mu+\varepsilon)^\ell(\mu+\gamma)^\ell}, \tag{3.19}$$

where

$$L_\varphi = \frac{1}{\omega}\int_0^\omega \frac{\partial\varphi}{\partial I}(z^*(t), z^*(t), 0)\, dt$$

and $z^*(t)$ is the $\omega$-periodic solution given by 3) in Lemma 3.1.1.

Note that, when our parameter functions are constant, we obtain

$$\widetilde{R}_0^\ell = \frac{\beta\varepsilon}{(\mu+\varepsilon)(\mu+\gamma)}\frac{\partial\varphi}{\partial I}(\Lambda/\mu, \Lambda/\mu, 0),$$

which is the basic reproductive number in (1.11) obtained for the autonomous case.

We need the following auxiliary result that will be used to show the existence and uniqueness of the solution of some algebraic equations in the proof of our main result. We will use the notation $\bar{f} = \frac{1}{\omega}\int_0^\omega f(s)\, ds$.

Lemma 3.6.1. Assume that condition P1) to P6) hold and $\widetilde{R}_0^\ell > 1$. Then there is a unique $r > 0$ that solves equation

$$\frac{\bar{\varepsilon}\bar{\beta}}{\bar{\mu}+\bar{\gamma}}\varphi\left(\bar{\Lambda}/\bar{\mu} - dr, \bar{\Lambda}/\bar{\mu}, r\right)/r - (\bar{\mu}+\bar{\varepsilon}) = 0, \tag{3.20}$$

where

$$d = \frac{(\bar{\mu}+\bar{\gamma})(\bar{\mu}+\bar{\varepsilon})(\bar{\mu}+\bar{\eta}) - \bar{\varepsilon}\bar{\gamma}\bar{\eta}}{\bar{\varepsilon}\bar{\mu}(\bar{\mu}+\bar{\eta})}. \tag{3.21}$$

This unique solution belongs to the interval $]0, \bar{\Lambda}/\bar{\mu}[$.

Proof. According to conditions P2), P3) and P6), the function $\psi : [0, \bar{\Lambda}/\bar{\mu}] \to \mathbb{R}$ given by

$$\psi(v) = \begin{cases} \dfrac{\bar{\varepsilon}\bar{\beta}}{\bar{\mu}+\bar{\gamma}} \dfrac{\varphi\left(\bar{\Lambda}/\bar{\mu} - dv, \bar{\Lambda}/\bar{\mu}, v\right)}{v} - (\bar{\mu}+\bar{\varepsilon}) & \text{if } 0 < v \le \bar{\Lambda}/\bar{\mu} \\ \dfrac{\bar{\varepsilon}\bar{\beta}}{\bar{\mu}+\bar{\gamma}} \dfrac{\partial \varphi}{\partial I}\left(\bar{\Lambda}/\bar{\mu}, \bar{\Lambda}/\bar{\mu}, 0\right) - (\bar{\mu}+\bar{\varepsilon}) & \text{if } v = 0 \end{cases}$$

is continuous and non-increasing and we have

$$\psi(0) = \left[\frac{\bar{\varepsilon}\bar{\beta}}{(\bar{\mu}+\bar{\gamma})(\bar{\mu}+\bar{\varepsilon})} \frac{\partial \varphi}{\partial I}\left(\bar{\Lambda}/\bar{\mu}, \bar{\Lambda}/\bar{\mu}, 0\right) - 1\right](\bar{\mu}+\bar{\varepsilon}) = \left(\overline{R}_0 - 1\right)(\bar{\mu}+\bar{\varepsilon}) > 0.$$

By P3), for the unique $d_0 \in ]0, \bar{\Lambda}/\bar{\mu}[$ satisfying $\bar{\Lambda}/\bar{\mu} - dd_0 = 0$, we get

$$\psi(d_0) = \left[\frac{\bar{\varepsilon}\bar{\beta}}{(\bar{\mu}+\bar{\gamma})(\bar{\mu}+\bar{\varepsilon})} \frac{\varphi\left(0, \bar{\Lambda}/\bar{\mu}, d_0\right)}{d_0} - 1\right](\bar{\mu}+\bar{\varepsilon}) = -(\bar{\mu}+\bar{\varepsilon}) < 0.$$

Thus, by Bolzano's theorem, there is $r \in ]0, d_0[\subset]0, \bar{\Lambda}/\bar{\mu}[$ that solves (3.20). Since

$$\psi'(v) = \frac{\bar{\varepsilon}\bar{\beta}}{\bar{\mu}+\bar{\gamma}} \frac{\left[-d\frac{\partial \varphi}{\partial S}(c(v)) + \frac{\partial \varphi}{\partial I}(c(v))\right] v - \varphi(c(v))}{v^2} < 0,$$

where $c(v) = (\bar{\Lambda}/\bar{\mu} - dv, \bar{\Lambda}/\bar{\mu}, v)$ (note that, by P6) we have $\frac{\partial \varphi}{\partial I}(c(v))v - \varphi(c(v)) < 0$ and by P5) we have $\frac{\partial \varphi}{\partial S}(c(v)) \ge 0$), we conclude that the solution is unique and the proof is complete. □

We also need to consider the matrix

$$\mathcal{M} = \begin{bmatrix} -\mu - K_{110} & -K_{010}q/p & -K_{011}r/p & (-K_{010}+\eta)\,s/p \\ K_{110}p/q & K_{010} & K_{011}r/q & K_{010}s/q \\ 0 & \mu+\gamma & -(\mu+\gamma) & 0 \\ 0 & 0 & \mu+\eta & -(\mu+\eta) \end{bmatrix} \tag{3.22}$$

where $r$ is the unique solution of (3.20),

$$p = \frac{\bar{\Lambda}}{\bar{\mu}} - \frac{(\bar{\mu}+\bar{\gamma})(\bar{\mu}+\bar{\varepsilon})(\bar{\mu}+\bar{\eta}) - \bar{\varepsilon}\bar{\gamma}\bar{\eta}}{\bar{\varepsilon}\bar{\mu}(\bar{\mu}+\bar{\eta})} r,$$

$q = (\bar{\mu}+\bar{\gamma})r/\bar{\varepsilon}$, $s = \bar{\gamma}r/(\bar{\mu}+\bar{\eta})$ and

$$K_{abc} = \bar{\beta}\left[a\frac{\partial \varphi}{\partial S}(p, \bar{\Lambda}/\bar{\mu}, r) + b\frac{\partial \varphi}{\partial N}(p, \bar{\Lambda}/\bar{\mu}, r) + c\frac{\partial \varphi}{\partial I}(p, \bar{\Lambda}/\bar{\mu}, r)\right].$$

In the following result, we obtain conditions for the existence of endemic periodic orbits. For each $\lambda \in (0,1)$, we need to consider the system

$$\begin{cases} S'_\lambda = \lambda(\Lambda(t) - \beta(t)\,\varphi(S_\lambda, N_\lambda, I_\lambda) - \mu(t)S_\lambda + \eta(t)R_\lambda) \\ E'_\lambda = \lambda(\beta(t)\,\varphi(S_\lambda, N_\lambda, I_\lambda) - (\mu(t) + \varepsilon(t))E_\lambda) \\ I'_\lambda = \lambda(\varepsilon(t)E_\lambda - (\mu(t) + \gamma(t))I_\lambda) \\ R'_\lambda = \lambda(\gamma(t)I_\lambda - (\mu(t) + \eta(t))R_\lambda) \\ N_\lambda = S_\lambda + E_\lambda + I_\lambda + R_\lambda \end{cases} \tag{3.23}$$

Consider the following condition:

P7) We have $\eta \equiv 0$ or or there is $k^\ell > 0$ such that $\liminf_{t\to+\infty} I_\lambda(t) \geq K^\ell$ for all $\lambda \in (0,1)$ and $t \in [0,\omega]$ in system (3.23).

Theorem 3.6.1. Assume that conditions P1) to P6) and P7) hold. Assume also that

1) $\mathcal{R}_0 > 1$;

2) $\widetilde{R}_0^\ell > \mu^u L_\varphi/(c_1 \Lambda^\ell)$;

3) $\det \mathcal{M} \neq 0$.

Then system (1) has an endemic $\omega$-periodic solution.

To obtain Theorem 3.6.1 we will use a well known result in degree theory, the Mawhin continuation theorem [10, 28].

Proof. If $\eta \equiv 0$, using the estimates that we will obtain, the theorem can be proved in a similar way to the main theorem in [41]. We will assume that $\eta$ is not identically zero. To prove theorem 3.6.1 we first need to give some definitions and state some well known facts. Let $X$ and $Z$ be Banach spaces.

Definition 1. A linear mapping $\mathcal{L} : D \subseteq X \to Z$ is called a Fredholm mapping of index zero if

1. $\dim \ker \mathcal{L} = \operatorname{codimIm} \mathcal{L} < \infty$;

2. $\operatorname{Im} \mathcal{L}$ is closed in $Z$.

Given a Fredholm mapping of index zero, $\mathcal{L} : D \subseteq X \to Z$ , it is well known that there are continuous projectors $P : X \to X$ and $Q : Z \to Z$ such that

1. $\operatorname{Im} P = \ker \mathcal{L}$;

2. $\ker Q = \operatorname{Im} \mathcal{L} = \operatorname{Im}(I - Q)$;

3. $X = \ker \mathcal{L} \oplus \ker P$;

4. $Z = \operatorname{Im}\mathcal{L} \oplus \operatorname{Im} Q$.

It follows that $\mathcal{L}|_{D\cap \ker P} : (I-P)X \to \operatorname{Im}\mathcal{L}$ is invertible. We denote the inverse of that map by $K_p$.

Definition 2. A continuous mapping $\mathcal{N} : X \to Z$ is called $L$-compact on $\overline{U} \subset X$, where $U$ is an open bounded set, if

1. $Q\mathcal{N}(\overline{U})$ is bounded;

2. $K_p(I-Q)\mathcal{N} : \overline{U} \to X$ is compact.

Since $\operatorname{Im} Q$ is isomorphic to $\ker\mathcal{L}$, there exists an isomorphism $\mathcal{J} : \operatorname{Im} Q \to \ker\mathcal{L}$.

We are now prepared to state the theorem that will allow us to prove theorem 3.6.1: Mawhin's continuation theorem [28].

Theorem 3.6.2. (Mawhin's continuation theorem) Let $X$ and $Z$ be Banach spaces, let $U \subset X$ be an open and bounded set, let $\mathcal{L} : D \subseteq X \to Z$ be a Fredholm mapping of index zero and let $\mathcal{N} : X \to Z$ be $L$-compact on $\overline{U}$. Assume that

1) for each $\lambda \in (0,1)$ and $x \in \partial U \cap D$ we have $\mathcal{L}x \neq \lambda\mathcal{N}x$;

2) for each $x \in \partial U \cap \ker\mathcal{L}$ we have $Q\mathcal{N}x \neq 0$;

3) $\deg(\mathcal{J}Q\mathcal{N}, U \cap \ker\mathcal{L}, 0) \neq 0$.

Then the operator equation $\mathcal{L}x = \mathcal{N}x$ has at least one solution in $D \cap \overline{U}$.

With the change of variables $S(t) = \mathrm{e}^{u_1(t)}$, $E(t) = \mathrm{e}^{u_2(t)}$, $I(t) = \mathrm{e}^{u_3(t)}$ and $R(t) = \mathrm{e}^{u_4(t)}$, system (1) becomes

$$\begin{cases} u_1' = \Lambda(t)\,\mathrm{e}^{-u_1} - \beta(t)\,\varphi(\mathrm{e}^{u_1}, w, \mathrm{e}^{u_3})\,\mathrm{e}^{-u_1} - \mu(t) + \eta(t)\,\mathrm{e}^{u_4-u_1} \\ u_2' = \beta(t)\,\varphi(\mathrm{e}^{u_1}, w, \mathrm{e}^{u_3})\,\mathrm{e}^{-u_2} - (\mu(t)+\varepsilon(t)) \\ u_3' = \varepsilon(t)\,\mathrm{e}^{u_2-u_3} - (\mu(t)+\gamma(t)) \\ u_4' = \gamma(t)\,\mathrm{e}^{u_3-u_4} - (\mu(t)+\eta(t)) \\ w = \mathrm{e}^{u_1} + \mathrm{e}^{u_2} + \mathrm{e}^{u_3} + \mathrm{e}^{u_4} \end{cases} \tag{3.24}$$

and if $(v_1(t), v_2(t), v_3(t), v_4(t))$ is a periodic solution of period $\omega$ of system (3.24) then $\left(\mathrm{e}^{v_1(t)}, \mathrm{e}^{v_2(t)}, \mathrm{e}^{v_3(t)}, \mathrm{e}^{v_4(t)}\right)$ is a periodic solution of period $\omega$ of system (1). For

$\lambda \in (0,1)$ consider the system

$$\begin{cases} u_1' = \lambda\left(\Lambda(t)\,\mathrm{e}^{-u_1} - \beta(t)\varphi(\mathrm{e}^{u_1}, w, \mathrm{e}^{u_3})\,\mathrm{e}^{-u_1} - \mu(t) + \eta(t)\,\mathrm{e}^{u_4-u_1}\right) \\ u_2' = \lambda\left(\beta(t)\varphi(\mathrm{e}^{u_1}, w, \mathrm{e}^{u_3})\,\mathrm{e}^{-u_2} - (\mu(t)+\varepsilon(t))\right) \\ u_3' = \lambda\left(\varepsilon(t)\,\mathrm{e}^{u_2-u_3} - (\mu(t)+\gamma(t))\right) \\ u_4' = \lambda\left(\gamma(t)\,\mathrm{e}^{u_3-u_4} - (\mu(t)+\eta(t))\right) \\ w = \mathrm{e}^{u_1} + \mathrm{e}^{u_2} + \mathrm{e}^{u_3} + \mathrm{e}^{u_4} \end{cases} . \tag{3.25}$$

By 1) in Lemma 3.1.1, if $(u_1(t), u_2(t), u_3(t), u_4(t))$ is periodic then

$$\frac{\Lambda^\ell}{\mu^u} \le w(t) \le \frac{\Lambda^u}{\mu^\ell}. \tag{3.26}$$

We will now prepare the setting where we will apply Mawhin's theorem. We will consider the Banach spaces $(X, \|\cdot\|)$ and $(Z, \|\cdot\|)$ where

$$X = Z = \{u = (u_1, u_2, u_3, u_4) \in C(\mathbb{R}, \mathbb{R}^4) : u(t) = u(t+\omega)\}$$

and

$$\|u\| = \max_{t\in[0,\omega]} |u_1(t)| + \max_{t\in[0,\omega]} |u_2(t)| + \max_{t\in[0,\omega]} |u_3(t)| + \max_{t\in[0,\omega]} |u_4(t)|.$$

Let $\mathcal{L} : D \subseteq X \to Z$, where $D = X \cap C^1(\mathbb{R}, \mathbb{R}^4)$, be defined by

$$\mathcal{L}u(t) = \frac{du(t)}{dt}$$

and $\mathcal{N} : X \to Z$ be defined by

$$\mathcal{N}u(t) = \begin{bmatrix} \Lambda(t)\,\mathrm{e}^{-u_1(t)} - \beta(t)\varphi(\mathrm{e}^{u_1}, w, \mathrm{e}^{u_3})\,\mathrm{e}^{-u_1(t)} - \mu(t) + \eta(t)\,\mathrm{e}^{u_4(t)-u_1(t)} \\ \beta(t)\varphi(\mathrm{e}^{u_1}, w, \mathrm{e}^{u_3})\,\mathrm{e}^{-u_2(t)} - (\mu(t)+\varepsilon(t)) \\ \varepsilon(t)\,\mathrm{e}^{u_2(t)-u_3(t)} - (\mu(t)+\gamma(t)) \\ \gamma(t)\,\mathrm{e}^{u_3(t)-u_4(t)} - (\mu(t)+\eta(t)) \end{bmatrix}.$$

Consider also the projectors $P : X \to X$ and $Q : Z \to Z$ given by

$$Pu = \frac{1}{\omega}\int_0^\omega u(t)\,dt \qquad \text{and} \qquad Qz = \frac{1}{\omega}\int_0^\omega z(t)\,dt.$$

Note that $\operatorname{Im} P = \ker \mathcal{L} = \mathbb{R}^4$, that

$$\ker Q = \operatorname{Im} \mathcal{L} = \operatorname{Im}(I-Q) = \left\{ z \in Z : \frac{1}{\omega}\int_0^\omega z(t)\,dt = 0 \right\},$$

that $\mathcal{L}$ is a Fredholm mapping of index zero (since $\dim\ker\mathcal{L} = \operatorname{codimIm}\mathcal{L} = 4$) and that $\operatorname{Im}\mathcal{L}$ is closed in $X$.

Consider the generalized inverse of $\mathcal{L}$, $\mathcal{K}_p : \operatorname{Im}\mathcal{L} \to D \cap \ker P$, given by

$$\mathcal{K}_p z(t) = \int_0^t z(s)\,ds - \frac{1}{\omega}\int_0^\omega \int_0^r z(s)\,ds\,dr,$$

the operator $Q\mathcal{N} : X \to Z$ given by

$$Q\mathcal{N}u(t) = \begin{bmatrix} \frac{1}{\omega}\int_0^\omega \frac{\Lambda(t)}{\mathrm{e}^{u_1(t)}} - \beta(t)\varphi(\mathrm{e}^{u_1}, w, \mathrm{e}^{u_3})\,\mathrm{e}^{-u_1(t)} + \frac{\eta(t)\,\mathrm{e}^{u_4(t)}}{\mathrm{e}^{u_1(t)}}\,dt - \bar{\mu} \\ \frac{1}{\omega}\int_0^\omega \beta(t)\varphi(\mathrm{e}^{u_1}, w, \mathrm{e}^{u_3})\,\mathrm{e}^{-u_2(t)}\,dt - (\bar{\mu} + \bar{\varepsilon}) \\ \frac{1}{\omega}\int_0^\omega \varepsilon(t)\,\mathrm{e}^{u_2(t)-u_3(t)}\,dt - (\bar{\mu} + \bar{\gamma}) \\ \frac{1}{\omega}\int_0^\omega \gamma(t)\,\mathrm{e}^{u_3(t)-u_4(t)}\,dt - (\bar{\mu} + \bar{\eta}) \end{bmatrix}.$$

and the mapping $\mathcal{K}_p(I-Q)\mathcal{N} : X \to D \cap \ker P$ given by

$$\mathcal{K}_p(I-Q)\mathcal{N}u(t) = A_1(t) - A_2(t) - A_3(t)$$

where

$$A_1(t) = \begin{bmatrix} \int_0^t \frac{\Lambda(s)}{\mathrm{e}^{u_1(s)}} - \beta(s)\varphi(\mathrm{e}^{u_1}, w, \mathrm{e}^{u_3})\,\mathrm{e}^{-u_1(s)} + \frac{\eta(s)\,\mathrm{e}^{u_4(s)}}{\mathrm{e}^{u_1(s)}} - \mu(s)\,ds \\ \int_0^t \beta(s)\varphi(\mathrm{e}^{u_1}, w, \mathrm{e}^{u_3})\,\mathrm{e}^{-u_2(s)} - (\mu(s) + \varepsilon(s))\,ds \\ \int_0^t \varepsilon(s)\,\mathrm{e}^{u_2(s)-u_3(s)} - (\mu(s) + \gamma(s))\,ds \\ \int_0^t \gamma(s)\,\mathrm{e}^{u_3(s)-u_4(s)} - (\mu(s) + \eta(s))\,ds \end{bmatrix},$$

$$A_2(t) = \begin{bmatrix} \frac{1}{\omega}\int_0^\omega\int_0^t \frac{\Lambda(s)}{\mathrm{e}^{u_1(s)}} - \beta(s)\varphi(\mathrm{e}^{u_1}, w, \mathrm{e}^{u_3})\,\mathrm{e}^{-u_1(s)} + \frac{\eta(s)\,\mathrm{e}^{u_4(s)}}{\mathrm{e}^{u_1(s)}} - \mu(s)\,ds\,dt \\ \frac{1}{\omega}\int_0^\omega\int_0^t \beta(s)\varphi(\mathrm{e}^{u_1}, w, \mathrm{e}^{u_3})\,\mathrm{e}^{-u_2(s)} - (\mu(s) + \varepsilon(s))\,ds\,dt \\ \frac{1}{\omega}\int_0^\omega\int_0^t \varepsilon(t)\,\mathrm{e}^{u_2(s)-u_3(s)} - (\mu(s) + \gamma(s))\,ds\,dt \\ \frac{1}{\omega}\int_0^\omega\int_0^t \gamma(t)\,\mathrm{e}^{u_3(s)-u_4(s)} - (\mu(s) + \eta(s))\,ds\,dt \end{bmatrix}$$

and

$$A_3(t) = \left[\frac{t}{\omega} - \frac{1}{2}\right] \left[\begin{array}{c} \displaystyle\int_0^\omega \frac{\Lambda(s)}{\mathrm{e}^{u_1(s)}} - \beta(s)\varphi(\mathrm{e}^{u_1}, w, \mathrm{e}^{u_3})\,\mathrm{e}^{-u_1(s)} + \frac{\eta(s)\,\mathrm{e}^{u_4(s)}}{\mathrm{e}^{u_1(s)}} - \mu(s)\,ds \\ \displaystyle\int_0^\omega \beta(s)\varphi(\mathrm{e}^{u_1}, w, \mathrm{e}^{u_3})\,\mathrm{e}^{-u_2(s)} - (\mu(s)+\varepsilon(s))\,ds \\ \displaystyle\int_0^\omega \varepsilon(s)\,\mathrm{e}^{u_2(s)-u_3(s)} - (\mu(s)+\gamma(s))\,ds \\ \displaystyle\int_0^\omega \gamma(s)\,\mathrm{e}^{u_3(s)-u_4(s)} - (\mu(s)+\eta(s))\,ds \end{array}\right].$$

It is immediate that $Q\mathcal{N}$ and $\mathcal{K}_p(I-Q)\mathcal{N}$ are continuous. An application of Ascoli-Arzela's theorem shows that $\mathcal{K}_p(I-Q)\mathcal{N}(\overline{\Omega})$ is compact for any bounded set $\Omega \subset X$. Since $Q\mathcal{N}(\overline{\Omega})$ is bounded, we conclude that $\mathcal{N}$ is $L$-compact on $\Omega$ for any bounded set $\Omega \subset X$.

Let $(u_1, u_2, u_3, u_4) \in X$ be some solution of (3.25) for some $\lambda \in (0,1)$ and, for $i = 1,2,3,4$ define

$$u_i(\xi_i) = \min_{t\in[0,\omega]} u_i(t) \qquad \text{and} \qquad u_i(\chi_i) = \max_{t\in[0,\omega]} u_i(t).$$

From the third equation in (3.25) we get,

$$\mathrm{e}^{u_2(\xi_2)-u_3(\xi_3)} \le \mathrm{e}^{u_2(\xi_3)-u_3(\xi_3)} = \frac{\mu(\xi_3)+\gamma(\xi_3)}{\varepsilon(\xi_3)} \le \frac{(\mu+\gamma)^u}{\varepsilon^\ell} \tag{3.27}$$

and

$$\mathrm{e}^{u_2(\chi_2)-u_3(\chi_3)} \ge \mathrm{e}^{u_2(\chi_3)-u_3(\chi_3)} = \frac{\mu(\chi_3)+\gamma(\chi_3)}{\varepsilon(\chi_3)} \ge \frac{(\mu+\gamma)^\ell}{\varepsilon^u}. \tag{3.28}$$

From the second equation in (3.25), P4), (3.19) and (3.27), we obtain

$$\begin{aligned} \mathrm{e}^{u_1(\xi_1)} \le \mathrm{e}^{u_1(\xi_2)} &= \frac{(\mu+\varepsilon)^u}{\beta^\ell} \frac{\mathrm{e}^{u_1(\xi_2)+u_3(\xi_2)}}{\varphi(\mathrm{e}^{u_1(\xi_2)}, w(\xi_2), \mathrm{e}^{u_3(\xi_2)})}\,\mathrm{e}^{u_2(\xi_2)-u_3(\xi_2)} \\ &\le \frac{(\mu+\varepsilon)^u}{\beta^\ell} \frac{\mathrm{e}^{u_1(\xi_2)+u_3(\xi_2)}}{\varphi(\mathrm{e}^{u_1(\xi_2)}, w(\xi_2), \mathrm{e}^{u_3(\xi_2)})} \frac{(\mu+\gamma)^u}{\varepsilon^\ell} \\ &\le \frac{(\mu+\varepsilon)^u(\mu+\gamma)^u}{c_1\beta^\ell\varepsilon^\ell} \\ &= L_\varphi/(c_1\widetilde{R}_0^\ell). \end{aligned} \tag{3.29}$$

and, by the second equation in (3.25), P4), (3.19) and (3.28), we get

$$\begin{aligned}
\mathrm{e}^{u_1(\chi_1)} \geq \mathrm{e}^{u_1(\chi_2)} &= \frac{(\mu+\varepsilon)^\ell}{\beta^u} \frac{\mathrm{e}^{u_1(\chi_2)+u_3(\chi_2)}}{\varphi(\mathrm{e}^{u_1(\chi_2)}, w(\chi_2), \mathrm{e}^{u_3(\chi_2)})} \mathrm{e}^{u_2(\chi_2)-u_3(\chi_2)} \\
&\geq \frac{(\mu+\varepsilon)^\ell}{\beta^u} \frac{\mathrm{e}^{u_1(\xi_2)+u_3(\xi_2)}}{\varphi(\mathrm{e}^{u_1(\xi_2)}, w(\xi_2), \mathrm{e}^{u_3(\xi_2)})} \frac{(\mu+\gamma)^\ell}{\varepsilon^u} \\
&\geq \frac{(\mu+\varepsilon)^\ell(\mu+\gamma)^\ell}{c_2\beta^u\varepsilon^u} \\
&= L_\varphi/(c_2\widetilde{R}_0^u).
\end{aligned} \tag{3.30}$$

Define

$$A_{1\xi} = L_\varphi/(c_1\widetilde{R}_0^\ell) \quad \text{and} \quad A_{1\chi} = L_\varphi/(c_2\widetilde{R}_0^u). \tag{3.31}$$

From the fourth equation in (3.25) we get

$$\mathrm{e}^{u_3(\xi_3)} \leq \mathrm{e}^{u_3(\chi_4)-u_4(\chi_4)+u_4(\chi_4)} = \frac{\mu(\chi_4)+\eta(\chi_4)}{\gamma(\chi_4)} \mathrm{e}^{u_4(\chi_4)} \leq \frac{(\mu+\eta)^u}{\gamma^\ell} \mathrm{e}^{u_4(\chi_4)} \tag{3.32}$$

and

$$\mathrm{e}^{u_3(\chi_3)} \geq \mathrm{e}^{u_3(\xi_4)-u_4(\xi_4)} \mathrm{e}^{u_4(\xi_4)} = \frac{\mu(\xi_4)+\eta(\xi_4)}{\gamma(\xi_4)} \mathrm{e}^{u_4(\xi_4)} \geq \frac{(\mu+\eta)^\ell}{\gamma^u} \mathrm{e}^{u_4(\xi_4)}. \tag{3.33}$$

Thus we obtain

$$\mathrm{e}^{u_4(\xi_4)} \leq \frac{\gamma^u}{(\mu+\eta)^\ell} \mathrm{e}^{u_3(\chi_3)} \qquad \text{and} \qquad \mathrm{e}^{u_4(\chi_4)} \geq \frac{\gamma^\ell}{(\mu+\eta)^u} \mathrm{e}^{u_3(\xi_3)}. \tag{3.34}$$

From the first equation in (3.25) we have

$$\beta(\chi_1)\varphi\left(\mathrm{e}^{(u_1(\chi_1))}, w(\chi_1), \mathrm{e}^{u_3(\chi_1)}\right) = \Lambda(\chi_1) - \mu(\chi_1)\,\mathrm{e}^{u_1(\chi_1)} + \eta(\chi_1)\,\mathrm{e}^{u_4(\chi_1)}.$$

Using (3.30) and (3.26), the right hand expression can be bounded by

$$\begin{aligned}
\Lambda(\chi_1) - \mu(\chi_1)\,\mathrm{e}^{u_1(\chi_1)} + \eta(\chi_1)\,\mathrm{e}^{u_4(\chi_1)} &\leq \Lambda^u - \mu^\ell\,\mathrm{e}^{u_1(\chi_1)} + \eta^u\,\mathrm{e}^{u_4(\chi_1)} \\
&\leq \Lambda^u + \eta^u \frac{\Lambda^u}{\mu^\ell}
\end{aligned} \tag{3.35}$$

and, by (3.30), we obtain

$$\begin{aligned}
\beta(\chi_1)\varphi\left(\mathrm{e}^{u_1(\chi_1)}, w(\chi_1), \mathrm{e}^{u_3(\chi_1)}\right) &\geq \beta^\ell c_1\,\mathrm{e}^{u_1(\chi_1)+u_3(\chi_1)} \\
&\geq \beta^\ell c_1 L_\varphi/(c_2\widetilde{R}_0^u)\ \mathrm{e}^{u_3(\xi_3)}.
\end{aligned} \tag{3.36}$$

By (3.35) and (3.36) we get

$$e^{u_3(\xi_3)} \le \frac{\Lambda^u + \eta^u \Lambda^u/\mu^\ell}{\beta^\ell c_1 L_\varphi/(c_2 \widetilde{R}_0^u)}. \tag{3.37}$$

Define

$$A_{3\xi} = \frac{\Lambda^u + \eta^u \Lambda^u/\mu^\ell}{\beta^\ell c_1 L_\varphi/(c_2 \widetilde{R}_0^u)}. \tag{3.38}$$

Again from the first equation in (3.25)

$$\beta(\xi_1)\varphi\left(e^{u_1(\xi_1)}, w(\xi_1), e^{u_3(\xi_1)}\right) = \Lambda(\xi_1) - \mu(\xi_1)\, e^{u_1(\xi_1)} + \eta(\xi_1)\, e^{u_4(\xi_1)}.$$

Since, by (3.29),

$$\begin{aligned}\Lambda(\xi_1) - \mu(\xi_1)\, e^{u_1(\xi_1)} + \eta(\xi_1)\, e^{u_4(\xi_1)} &\ge \Lambda^\ell - \mu^u\, e^{u_1(\xi_1)} + \eta^\ell\, e^{u_4(\xi_4)} \\ &\ge \Lambda^\ell - \mu^u L_\varphi/(c_1 \widetilde{R}_0^\ell)\end{aligned}$$

and

$$\begin{aligned}\beta(\xi_1)\varphi\left(e^{u_1(\xi_1)}, w(\xi_1), e^{u_3(\xi_1)}\right) &\le \beta^u c_2\, e^{u_1(\xi_1)+u_3(\xi_1)} \\ &\le c_2 \beta^u L_\varphi/(c_1 \widetilde{R}_0^\ell)\, e^{u_3(\chi_3)}\end{aligned}$$

we get

$$e^{u_3(\chi_3)} \ge \frac{\Lambda^\ell - \mu^u L_\varphi/(c_1 \widetilde{R}_0^\ell)}{c_2 \beta^u L_\varphi/(c_1 \widetilde{R}_0^\ell)}. \tag{3.39}$$

By hypothesis 2) we conclude that the right hand side of (3.39) is positive. Define

$$A_{3\chi} = \frac{\Lambda^\ell - \mu^u L_\varphi/(c_1 \widetilde{R}_0^\ell)}{\beta^u c_2 L_\varphi/(c_1 \widetilde{R}_0^\ell)}. \tag{3.40}$$

By hypothesis P7), there is $K^\ell > 0$ such that

$$\liminf_{t\to+\infty} I(t) \ge K^\ell. \tag{3.41}$$

Using (3.41), (3.26) and (3.34) we obtain bounds for $e^{u_4(t)}$, namely

$$e^{u_4(\xi_4)} \le \frac{\gamma^u}{(\mu+\eta)^\ell}\frac{\Lambda^u}{\mu^\ell} \qquad \text{and} \qquad e^{u_4(\chi_4)} \ge \frac{\gamma^\ell}{(\mu+\eta)^u}\, e^{u_3(\xi_3)} \ge \frac{\gamma^\ell}{(\mu+\eta)^u} K^\ell.$$

Define

$$A_{4\xi} = \frac{\gamma^u}{(\mu+\eta)^\ell}\frac{\Lambda^u}{\mu^\ell} \quad \text{and} \quad A_{4\chi} = \frac{\gamma^\ell}{(\mu+\eta)^u} K^\ell. \tag{3.42}$$

By the third equation in (1), (3.37) and (3.39) we get

$$e^{u_2(\xi_2)} \leq e^{u_2(\xi_3)-u_3(\xi_3)}\, e^{u_3(\xi_3)} \leq \frac{(\mu+\gamma)^u}{\varepsilon^\ell} A_{3\xi}$$

and

$$e^{u_2(\chi_2)} \geq e^{u_2(\chi_3)-u_3(\chi_3)}\, e^{u_3(\chi_3)} \geq \frac{(\mu+\gamma)^\ell}{\varepsilon^u} A_{3\chi}.$$

Using (3.38) and (3.40), we can establish bounds for $e^{u_2(t)}$. In fact, we have $e^{u_2(\xi_2)} \leq A_{2\xi}$ and $e^{u_2(\chi_2)} \geq A_{2\chi}$, where

$$A_{2\xi} = \frac{(\mu+\gamma)^u \left(\Lambda^u + \eta^u \Lambda^u/\mu^\ell\right)}{\varepsilon^\ell \beta^\ell c_1 L_\varphi/(c_2 \widetilde{R}_0^u)} \tag{3.43}$$

and

$$A_{2\chi} = \frac{(\mu+\gamma)^\ell \left(\Lambda^\ell - \mu^u L_\varphi/(c_1 \widetilde{R}_0^\ell)\right)}{\varepsilon^u \beta^u c_2 L_\varphi/(c_1 \widetilde{R}_0^\ell)}. \tag{3.44}$$

By (3.31), (3.38), (3.40), (3.42), (3.43), (3.44) we obtain, for $i = 1, \ldots, 4$,

$$u_i(\xi_i) \leq \ln A_{i\xi} \qquad \text{and} \qquad u_i(\chi_i) \geq \ln A_{i\chi}. \tag{3.45}$$

Integrating in $[0,\omega]$ the last three equations in (3.25) we obtain

$$\int_0^\omega \beta(t)\, \varphi\left(e^{u_1(t)}, w(t), e^{u_3(t)}\right) e^{-u_2(t)}\, dt = (\bar{\mu}+\bar{\varepsilon})\omega, \tag{3.46}$$

$$\int_0^\omega \varepsilon(t)\, e^{u_2(t)-u_3(t)}\, dt = (\bar{\mu}+\bar{\gamma})\omega \tag{3.47}$$

and

$$\int_0^\omega \gamma(t)\, e^{u_3(t)-u_4(t)} = (\bar{\mu}+\bar{\eta})\omega. \tag{3.48}$$

By (3.45) and (3.46) and using the fact that $\lambda \in (0,1)$, we get

$$\begin{aligned}
u_2(t) &= u_2(\xi_2) + \int_{\xi_2}^t u_2'(s)\, ds \leq u_2(\xi_2) + \int_0^\omega |u_2'(t)|\, dt \\
&= u_2(\xi_2) + \lambda \int_0^\omega \left|\beta(t)\, \varphi\left(e^{u_1(t)}, w(t), e^{u_3(t)}\right) e^{-u_2(t)} - (\mu(t)+\varepsilon(t))\right| dt \\
&\leq \ln A_{2\xi} + 2\int_0^\omega \beta(t)\, \varphi\left(e^{u_1(t)}, w(t), e^{u_3(t)}\right) e^{-u_2(t)}\, dt \\
&\leq \ln A_{2\xi} + 2(\bar{\mu}+\bar{\varepsilon})\omega,
\end{aligned}$$

and also

$$\begin{aligned} u_2(t) &\geq u_2(\chi_2) - \int_0^\omega |u_2'(t)|\, dt \\ &= u_2(\chi_2) - \lambda \int_0^\omega \left|\beta(t)\, \varphi\left(\mathrm{e}^{u_1(t)}, w(t), \mathrm{e}^{u_3(t)}\right) \mathrm{e}^{-u_2(t)} - (\mu(t) + \varepsilon(t))\right|\, dt \\ &\geq \ln A_{2\chi} - 2(\bar{\mu} + \bar{\varepsilon})\omega. \end{aligned}$$

By (3.45) and (3.47) and using the fact that $\lambda \in (0,1)$, we obtain

$$\begin{aligned} u_3(t) &\leq u_3(\xi_3) + \int_0^\omega |u_3'(t)|\, dt = u_3(\xi_3) + \lambda \int_0^\omega \left|\varepsilon(t)\, \mathrm{e}^{u_2 - u_3} - (\mu(t) + \gamma(t))\right|\, dt \\ &\leq \ln A_{3\xi} + 2 \int_0^\omega \varepsilon(t)\, \mathrm{e}^{u_2 - u_3}\, dt \leq \ln A_{3\xi} + 2(\bar{\mu} + \bar{\gamma})\omega, \end{aligned} \tag{3.49}$$

and also

$$\begin{aligned} u_3(t) &\geq u_3(\chi_3) - \int_0^\omega |u_3'(t)|\, dt = u_3(\chi_3) - \lambda \int_0^\omega \left|\varepsilon(t)\, \mathrm{e}^{u_2 - u_3} - (\mu(t) + \gamma(t))\right|\, dt \\ &\geq \ln A_{3\chi} - 2 \int_0^\omega \varepsilon(t)\, \mathrm{e}^{u_2 - u_3}\, dt \geq \ln A_{3\chi} - 2(\bar{\mu} + \bar{\gamma})\omega. \end{aligned}$$

Similarly, by (3.45) and (3.48) and using the fact that $\lambda \in (0,1)$, we conclude that

$$\begin{aligned} u_4(t) &\leq u_4(\xi_4) + \int_0^\omega |u_4'(t)|\, dt = u_4(\xi_4) + \lambda \int_0^\omega \left|\gamma(t)\, \mathrm{e}^{u_3 - u_4} - (\mu(t) + \eta(t))\right|\, dt \\ &\leq \ln A_{4\xi} + 2 \int_0^\omega \gamma(t)\, \mathrm{e}^{u_3 - u_4}\, dt \leq \ln A_{4\xi} + 2(\bar{\mu} + \bar{\eta})\omega \end{aligned}$$

and also that

$$\begin{aligned} u_4(t) &\geq u_4(\chi_4) - \int_0^\omega |u_4'(t)|\, dt = u_4(\chi_4) - \lambda \int_0^\omega \left|\gamma(t)\, \mathrm{e}^{u_3 - u_4} - (\mu(t) + \eta(t))\right|\, dt \\ &\geq \ln A_{4\chi} - 2 \int_0^\omega \gamma(t)\, \mathrm{e}^{u_3 - u_4}\, dt \geq \ln A_{4\chi} - 2(\bar{\mu} + \bar{\eta})\omega. \end{aligned}$$

Finally, integrating the first equation of (3.25) in $[0,\omega]$ and using (3.45) and (3.49), we obtain

$$\begin{aligned} \int_0^\omega \Lambda(t)\, \mathrm{e}^{-u_1} + \eta(t)\, \mathrm{e}^{u_4 - u_1}\, dt &= \int_0^\omega \beta(t)\, \varphi\left(\mathrm{e}^{u_1(t)}, w(t), \mathrm{e}^{u_3(t)}\right) \mathrm{e}^{-u_1(t)} + \mu(t)\, dt \\ &= \int_0^\omega \beta(t)\, \frac{\varphi\left(\mathrm{e}^{u_1(t)}, w(t), \mathrm{e}^{u_3(t)}\right)}{\mathrm{e}^{u_1(t) + u_3(t)}}\, \mathrm{e}^{u_3(t)} + \mu(t)\, dt \\ &\leq \left(\bar{\beta} c_2 A_{3\xi}\, \mathrm{e}^{-2(\bar{\mu} + \bar{\gamma})\omega} + \bar{\mu}\right) \omega, \end{aligned}$$

and thus

$$\begin{aligned}
u_1(t) &\le u_1(\xi_1) + \int_0^\omega |u_1'(t)|\,dt \\
&= u_1(\xi_1) + \lambda \int_0^\omega \left| \Lambda(t)\,\mathrm{e}^{-u_1} - \beta(t)\,\frac{\varphi\left(\mathrm{e}^{u_1}, w, \mathrm{e}^{u_3}\right)}{\mathrm{e}^{u_1+u_3}}\,\mathrm{e}^{u_3} - \mu(t) + \eta(t)\,\mathrm{e}^{u_4-u_1} \right| dt \\
&\le \ln A_{1\xi} + 2\int_0^\omega \Lambda(t)\,\mathrm{e}^{-u_1} + \eta(t)\,\mathrm{e}^{u_4-u_1}\,dt \\
&\le \ln A_{1\xi} + 2\left(\bar\beta c_2 A_{3\xi}\,\mathrm{e}^{-2(\bar\mu+\bar\gamma)\omega} + \bar\mu\right)\omega
\end{aligned}$$

and also

$$\begin{aligned}
u_1(t) &\ge u_1(\chi_1) - \int_0^\omega |u_1'(t)|\,dt \\
&= u_1(\chi_1) - \lambda \int_0^\omega \left| \Lambda(t)\,\mathrm{e}^{-u_1} - \beta(t)\,\frac{\varphi\left(\mathrm{e}^{u_1}, w, \mathrm{e}^{u_3}\right)}{\mathrm{e}^{u_1+u_3}}\,\mathrm{e}^{u_3} - \mu(t) + \eta(t)\,\mathrm{e}^{u_4-u_1} \right| dt \\
&\ge \ln A_{1\chi} - 2\int_0^\omega \Lambda(t)\,\mathrm{e}^{-u_1} + \eta(t)\,\mathrm{e}^{u_4-u_1}\,dt \\
&\ge \ln A_{1\chi} - 2\left(\bar\beta c_2 A_{3\xi}\,\mathrm{e}^{-2(\bar\mu+\bar\gamma)\omega} + \bar\mu\right)\omega.
\end{aligned}$$

Consider the algebraic system

$$\begin{cases}
\bar\Lambda\,\mathrm{e}^{-u_1} - \bar\beta\varphi(\mathrm{e}^{u_1}, w, \mathrm{e}^{u_3})\,\mathrm{e}^{-u_1} - \bar\mu + \bar\eta\,\mathrm{e}^{u_4-u_1} = 0 \\
\bar\beta\varphi(\mathrm{e}^{u_1}, w, \mathrm{e}^{u_3})\,\mathrm{e}^{-u_2} - \bar\mu - \bar\varepsilon = 0 \\
\bar\varepsilon\,\mathrm{e}^{u_2-u_3} - \bar\mu - \bar\gamma = 0 \\
\bar\gamma\,\mathrm{e}^{u_3-u_4} - \bar\mu - \bar\eta = 0
\end{cases}. \tag{3.50}$$

Multiplying the first equation by $\mathrm{e}^{u_1}$, the second by $\mathrm{e}^{u_2}$, the third by $\mathrm{e}^{u_3}$ and the fourth equation by $\mathrm{e}^{u_4}$ and adding the equations we conclude that any solution of this equation verifies

$$w = \frac{\bar\Lambda}{\bar\mu}.$$

Moreover, we conclude by simple computations that the solution of system (3.50) verifies

$$\mathrm{e}^{u_2} = \frac{\bar\mu + \bar\gamma}{\bar\varepsilon}\,\mathrm{e}^{u_3} = \frac{(\bar\mu+\bar\gamma)(\bar\mu+\bar\eta)}{\bar\varepsilon\bar\gamma}\,\mathrm{e}^{u_4} \tag{3.51}$$

and also

$$\mathrm{e}^{u_1} = \frac{\bar\Lambda}{\bar\mu} - \frac{(\bar\mu+\bar\gamma)(\bar\mu+\bar\varepsilon)(\bar\mu+\bar\eta) - \bar\varepsilon\bar\gamma\bar\eta}{\bar\varepsilon\bar\mu(\bar\mu+\bar\eta)}\,\mathrm{e}^{u_3}. \tag{3.52}$$

Thus, by the second equation in (3.50) we get

$$\frac{\bar\varepsilon\bar\beta}{\bar\mu+\bar\gamma}\,\varphi\left(\bar\Lambda/\bar\mu - d\,\mathrm{e}^{u_3}, \bar\Lambda/\bar\mu, \mathrm{e}^{u_3}\right)\mathrm{e}^{-u_3} - (\bar\mu+\bar\varepsilon) = 0, \tag{3.53}$$

where

$$d = \frac{(\bar{\mu}+\bar{\gamma})(\bar{\mu}+\bar{\varepsilon})(\bar{\mu}+\bar{\eta}) - \bar{\varepsilon}\bar{\gamma}\bar{\eta}}{\bar{\varepsilon}\bar{\mu}(\bar{\mu}+\bar{\eta})}. \tag{3.54}$$

By Lemma 3.6.1, (3.53) has a unique solution. Therefore, by (3.51) and (3.52) we conclude that the algebraic system (3.50) has a unique solution. Denote this solution by $p^* = (p_1^*, p_2^*, p_3^*, p_4^*)$. Let $M_0 > 0$ be such that $|p_1^*|+|p_2^*|+|p_3^*|+|p_4^*| < M_0$ and let

$$M_1 = \max\{|\ln A_{1\xi} + 2\left(\bar{\beta}c_2 A_{3\xi}\,\mathrm{e}^{-2(\bar{\mu}+\bar{\gamma})\omega} + \bar{\mu}\right)\omega|, |\ln A_{1\chi} - 2\left(\bar{\beta}c_2 A_{3\xi}\,\mathrm{e}^{-2(\bar{\mu}+\bar{\gamma})\omega} + \bar{\mu}\right)\omega|\},$$

$$M_2 = \max\{|\ln A_{2\xi} + 2(\bar{\mu}+\bar{\varepsilon})\omega|, |\ln A_{2\chi} - 2(\bar{\mu}+\bar{\varepsilon})\omega|\},$$

$$M_3 = \max\{|\ln A_{3\xi} + 2(\bar{\mu}+\bar{\gamma})\omega|, |\ln A_{3\chi} - 2(\bar{\mu}+\bar{\gamma})\omega|\},$$

and

$$M_4 = \max\{|\ln A_{4\xi} + 2(\bar{\mu}+\bar{\eta})\omega|, |\ln A_{4\chi} - 2(\bar{\mu}+\bar{\eta})\omega|\}.$$

Define

$$M = M_0 + M_1 + M_2 + M_3 + M_4.$$

We will apply Mawhin's Theorem in the open set

$$\Omega = \{(u_1,u_2,u_3,u_4) \in X : \|(u_1,u_2,u_3,u_4)\| < M\}.$$

Let $u \in \partial\Omega \cap \ker \mathcal{L} = \partial\Omega \cap \mathbb{R}^4$. Then $u$ is a constant function that we can identify with the vector $(u_1,u_2,u_3,u_4) \in \mathbb{R}^4$ with $\|u\| = M$ and

$$Q\mathcal{N}u := \begin{bmatrix} F_1(u) \\ F_2(u) \\ F_3(u) \\ F_4(u) \end{bmatrix} = \begin{bmatrix} \bar{\Lambda}\,\mathrm{e}^{-u_1} - \bar{\beta}\varphi(\mathrm{e}^{u_1}, w, \mathrm{e}^{u_3})\,\mathrm{e}^{-u_1} - \bar{\mu} + \bar{\eta}\,\mathrm{e}^{u_4-u_1} \\ \bar{\beta}\varphi(\mathrm{e}^{u_1}, w, \mathrm{e}^{u_3})\,\mathrm{e}^{-u_2} - \bar{\mu} - \bar{\varepsilon} \\ \bar{\varepsilon}\,\mathrm{e}^{u_2-u_3} - \bar{\mu} - \bar{\gamma} \\ \bar{\gamma}\,\mathrm{e}^{u_3-u_4} - \bar{\mu} - \bar{\eta} \end{bmatrix} \neq 0.$$

We conclude that

$$\begin{aligned} \deg(\mathrm{Id}\,Q\mathcal{N}, \partial\Omega \cap \ker L, (0,0,0,0)) &= \sum_{x \in (IdQ\mathcal{N})^{-1}(0,0,0,0)} \text{sign}\det d_x(\mathrm{Id}\,Q\mathcal{N}) \\ &= \text{sign}\det d_{p^*}(\mathrm{Id}\,Q\mathcal{N}) \\ &= \text{sign}\det \mathcal{M}, \end{aligned}$$

where $\mathcal{M}$ is the matrix in (3.22). By hypothesis 3) we have $\det \mathcal{M} \neq 0$. Thus

$$\deg(\mathrm{Id}\,Q\mathcal{N}u, \partial\Omega \cap \ker L, (0,0,0,0)) \neq 0.$$

According to Mawhin's continuation theorem, we conclude that equation $\mathcal{L}x = \mathcal{N}x$ has at least one solution in $D \cap \bar{U}$. Therefore, in the hypothesis of the theorem, we conclude that system (1) has at least one $\omega$-periodic solution and the result follows. □

Before presenting some corollaries of Theorem 3.6.1, we have to define the following number:

$$\overline{\mathcal{R}}_0 = \frac{\bar{\varepsilon}}{(\bar{\mu}+\bar{\varepsilon})(\bar{\mu}+\bar{\gamma})} \frac{1}{\omega} \int_0^\omega \beta(t) \frac{\partial \varphi}{\partial I}(z^*(t), z^*(t), 0)\, dt. \tag{3.55}$$

We have the corollary:

Corollary 3.6.1 (Michaelis-Menten incidence functions). Assuming that P7) holds, let $\varphi(S,N,I) = C(N)SI/N$ where $\mathbb{R}_0^+ \ni N \to C(N)$ is a continuously differentiable real valued function and $\mathbb{R}^+ \ni N \to C(N)/N$ is a non-increasing function. If $\mathcal{R}_0 > 1$ and

$$\widetilde{R}_0^\ell > \frac{L_\varphi \mu^u \Lambda^u}{C(\Lambda^u/\mu^\ell)\mu^\ell \Lambda^\ell}, \tag{3.56}$$

then system (1) has an endemic periodic solution of period $\omega$.

Proof. It is easy to see that the incidence functions considered satisfy hypothesis P2) to P6) with

$$c_1 = C(\Lambda^u/\mu^\ell)\mu^\ell/\Lambda^u \quad \text{and} \quad c_2 = C(\Lambda^\ell/\mu^u)\mu^u/\Lambda^\ell.$$

We are assuming that $\mathcal{R}_0 > 1$ and thus we have condition (1) in Theorem 3.6.1. Condition (3.56) corresponds to condition 2) in Theorem 3.6.1. It remains to verify condition 3). Some computations yield

$$\operatorname{sign}\det \mathcal{M} = \operatorname{sign}\left(\bar{\mu}\bar{\beta}\bar{\varepsilon}(\bar{\mu}+\bar{\eta})C(\bar{\Lambda}/\bar{\mu})\left(1 - 1/\overline{R}_0\right)\right) = 1.$$

Note that $1 - 1/\overline{\mathcal{R}}_0 \geq 1 - 1/\widetilde{R}_0^\ell > 0$ because

$$\begin{aligned}
\widetilde{R}_0^\ell &> \frac{\mu^u \Lambda^u}{C(\Lambda^u/\mu^\ell)\mu^\ell \Lambda^\ell} \frac{1}{\omega} \int_0^\omega \frac{C(z^*(t))}{z^*(t)} z^*(t)\, dt \\
&\geq \frac{\mu^u \Lambda^u}{C(\Lambda^u/\mu^\ell)\mu^\ell \Lambda^\ell} \frac{C(\Lambda^u/\mu^\ell)}{\Lambda^u/\mu^\ell} \Lambda^\ell/\mu^u = 1.
\end{aligned}$$

Therefore, the result follows from Theorem 3.6.1. □

The following is an immediate corollary of the previous one.

Corollary 3.6.2 (Simple incidence functions). Assuming that P7) holds, let $\varphi(S,N,I) = SI$. If $\mathcal{R}_0 > 1$ and

$$\frac{\beta^\ell \varepsilon^\ell \Lambda^\ell}{(\mu+\varepsilon)^u(\mu+\gamma)^u \mu^u} > 1 \tag{3.57}$$

then system (1) has an endemic periodic solution of period $\omega$.

Proof. Simply note that in this case we can take $c_1 = 1$ and use Corollary 3.6.1. □

Condition (3.57) in Corollary 3.6.2 is the same as the condition in Theorem 3.1 in [41] where it is discussed the existence of periodic orbits for a model with mass-action incidence and no disease induced mortality. When the disease induced mortality is set to zero (letting $\alpha \equiv 0$), the model considered in [41] becomes a particular case of ours, correspondig to set $\eta \equiv 0$ and $\varphi(S, N, I) = SI$ in our model. For the no disease induced mortality case, Corollary 3.6.2 recovers the main result in [41].

## 3.7 Example

In this section we illutrate the obtained results in this chapter, by considering the particular model:

$$\begin{cases} S' = \Lambda - \beta[1 + b\cos(2\pi t + \varphi)]\, SI - \mu S \\ E' = \beta[1 + b\cos(2\pi t + \varphi)]\, SI - (\mu + \varepsilon)E \\ I' = \varepsilon E - (\mu + \gamma)I \\ R' = \gamma I - \mu R \\ N = S + E + I + R \end{cases} . \tag{3.58}$$

We begin by obtaining an estimate for $\mathcal{R}_0$ in this case. We have in this case

$$F_S(t) = \begin{bmatrix} 0 & \beta[1 + b\cos(2\pi t + \varphi)]\Lambda/\mu \\ 0 & 0 \end{bmatrix} \quad \text{and} \quad V_S(t) = \begin{bmatrix} \mu + \varepsilon & 0 \\ -\varepsilon & \mu + \gamma \end{bmatrix}.$$

Since $V_S(t)$ is a constant and diagonal matrix, it is easy to check that, for $\gamma < \varepsilon$, we have

$$Y_S(s,t) = \begin{bmatrix} \mathrm{e}^{-(\mu+\varepsilon)(t-s)} & 0 \\ \dfrac{\varepsilon}{\gamma - \varepsilon}\left(\mathrm{e}^{-(\mu+\varepsilon)(t-s)} - \mathrm{e}^{-(\mu+\gamma)(t-s)}\right) & \mathrm{e}^{-(\mu+\gamma)(t-s)} \end{bmatrix}.$$

Thus, we can compute $Y_S(t, t-a)F_S(t-a)$. Namely we have

$$Y_S(t,t-a)F_S(t-a) = \begin{bmatrix} 0 & \mathrm{e}^{-(\mu+\varepsilon)a}\, \beta[1 + b\cos(2\pi(t-a) + \varphi)]\Lambda/\mu \\ 0 & \dfrac{\varepsilon\beta\Lambda}{\mu(\gamma-\varepsilon)}\left(\mathrm{e}^{-(\mu+\varepsilon)a} - \mathrm{e}^{-(\mu+\gamma)a}\right)[1 + b\cos(2\pi(t-a) + \varphi)] \end{bmatrix}.$$

Therefore, writing $\phi(t) = (\phi_1(t), \phi_2(t))$ for some $\phi \in C_\omega$ with $\omega = 1$, we obtain

$$
\begin{aligned}
(L\phi)(t) &= \int_0^{+\infty} Y_S(t, t-a) F_S(t-a) \phi(t-a) da \\
&= \int_0^{+\infty} \left( \frac{\Lambda\beta}{\mu} \mathrm{e}^{-(\mu+\varepsilon)a} [1 + b\cos(2\pi(t-a)+\varphi)] \phi_2(t-a), \right. \\
&\qquad \left. \frac{\varepsilon\beta\Lambda}{\mu(\gamma-\varepsilon)} \left(\mathrm{e}^{-(\mu+\varepsilon)a} - \mathrm{e}^{-(\mu+\gamma)a}\right) [1 + b\cos(2\pi(t-a)+\varphi)] \phi_2(t-a) \right)^T da.
\end{aligned}
$$

Using the fact that, for $k > 0$, we have

$$
\int_0^{+\infty} \mathrm{e}^{-ka} \cos(2\pi(t-a)+\varphi) da = \frac{k}{k^2 + 4\pi^2} \left( \cos(2\pi t + \varphi) + \frac{2\pi}{k} \sin(2\pi t + \varphi) \right),
$$

we obtain

$$
\begin{aligned}
\|(L\phi)\| &\le \max_{t\in[0,1]} |\phi_2(t)| \max_{t\in[0,1]} \left\| \int_0^{+\infty} \left( \frac{\Lambda\beta}{\mu} \mathrm{e}^{-(\mu+\varepsilon)a} [1 + b\cos(2\pi(t-a)+\varphi)], \right.\right. \\
&\qquad \left.\left. \frac{\varepsilon\beta\Lambda}{\mu(\gamma-\varepsilon)} \left(\mathrm{e}^{-(\mu+\varepsilon)a} - \mathrm{e}^{-(\mu+\gamma)a}\right) [1 + b\cos(2\pi(t-a)+\varphi)] \right)^T da \right\| \\
&\le \|\phi\| \max_{t\in[0,1]} \left\| \left( \frac{\Lambda\beta}{\mu} A(t), \frac{\Lambda\varepsilon\beta}{\mu(\gamma-\varepsilon)} (A(t) - B(t)) \right) \right\|
\end{aligned}
$$

where

$$
A(t) = \frac{1}{\mu+\varepsilon} + b\frac{\mu+\varepsilon}{(\mu+\varepsilon)^2 + 4\pi^2} \left( \cos(2\pi t + \varphi) + \frac{2\pi}{\mu+\varepsilon} \sin(2\pi t + \varphi) \right)
$$

and

$$
B(t) = \frac{1}{\mu+\gamma} + b\frac{\mu+\gamma}{(\mu+\gamma)^2 + 4\pi^2} \left( \cos(2\pi t + \varphi) + \frac{2\pi}{\mu+\gamma} \sin(2\pi t + \varphi) \right).
$$

Finally we get

$$
\|L\phi\| \le \|\phi\| \max_{t\in[0,1]} \max \left\{ \frac{\Lambda\beta}{\mu} |A(t)|, \frac{\Lambda\varepsilon\beta}{\mu|\gamma-\varepsilon|} |A(t) - B(t)| \right\}
$$

and thus, since the norm of the operator is an upper bound for the spectral radius we obtain:

$$
\mathcal{R}_0 = \rho(L) \le \|L\| \le \max_{t\in[0,1]} \max \left\{ \frac{\Lambda\beta}{\mu} |A(t)|, \frac{\Lambda\varepsilon\beta}{\mu|\gamma-\varepsilon|} |A(t) - B(t)| \right\}. \tag{3.59}
$$

Like in section 1.5, we set $\Lambda = \mu = 2$, $\varepsilon = 1$, $\gamma = 0.02$ and consider the following initial conditions $S_0 = E_0 = I_0 = R_0 = 0.1$ (black lines). We assume that there is no loss of immunity and let $\eta = 0$. To consider a periodic case, we begin by setting

$b = 0.1$, $\beta = 5.9$ and $\varphi = 0$ in (3.58).

Using (3.59) we can see that in this case $\mathcal{R}_0 \leq 0.98644 < 1$ and we conclude that the disease goes to extinction. We can see this in the right-hand side of figure 3.1.

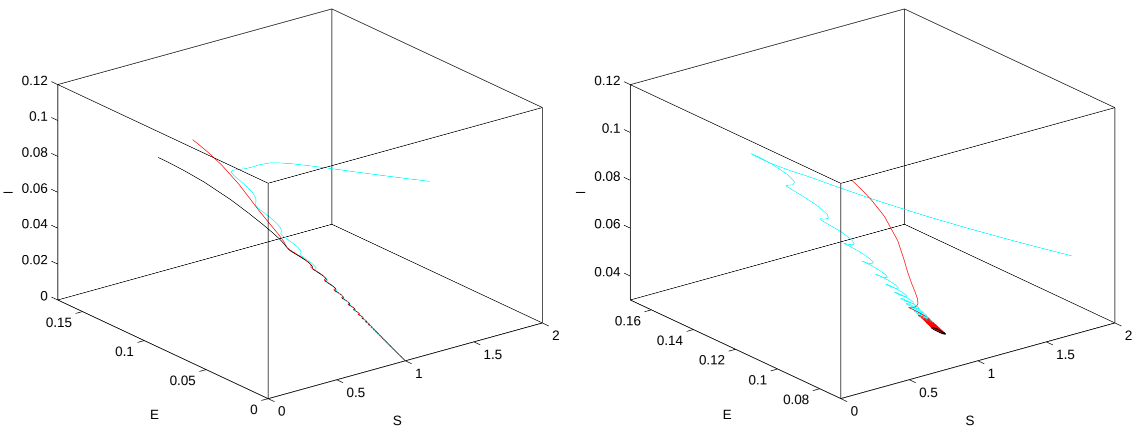


Figure 3.1: Disease-free case and endemic case for $b = 0.1$.

If we now consider a larger value for $b$, for instance if we set $b = 0.6$, estimate (3.59) gives $\mathcal{R}_0 < 1.05114$ not allowing any conclusion. As we will see, the disease still goes to extinction. In fact, a plot for this case can be seen on the left-hand side of figure 3.2 where we can see that all trajectories approach the disease-free equilibrium $e^* = (1, 0, 0, 0)$ and thus that the disease goes to extinction. In this case, the approximate formula (2.57) gives $\mathcal{R}_0 \approx 0.990017$ and we can see, according to Theorem 3.4.1, that in fact the disease goes to extinction.

On the right-hand side of figure 3.1, we let $b = 0.1$ and $\beta = 6.9$. We can see that the disease persists and that all trajectories approach an endemic periodic orbit. In this case, the approximate formula (2.57), gives $\mathcal{R}_0 = 1.13915 > 1$ and we have $\beta^\ell \varepsilon^\ell \Lambda^\ell / ((\mu + \varepsilon)^u (\mu + \gamma)^u \mu^u) = 1.02475 > 1$ confirming the existence of an endemic periodic orbit, according to Corollary 3.6.2.

If we increase the oscillations and set $b = 0.6$, the approximate formula (2.57), gives $\mathcal{R}_0 = 1.15782 > 1$. In this case Corollary 3.6.2 does not allow us to conclude that there is an endemic periodic orbit because $\beta^\ell \varepsilon^\ell \Lambda^\ell / ((\mu + \varepsilon)^u (\mu + \gamma)^u \mu^u) = 0.455446 < 1$. In spite of this, in the right-hand side of figure 3.2 we can see that the disease persists and that all trajectories approach an endemic periodic orbit. Note that the red and cyan lines correspond respectively to solutions with the following initial conditions: $S_0 = 0.08$, $E_0 = 0.07$, $I_0 = 0.12$, $R_0 = 0.13$ and $S_0 = 1.99$, $E_0 = 0.09$, $I_0 = 0.05$, $R_0 = 0.25$.

In figures 3.3 and 3.4 we present the trajectories of the infectives and the susceptibles for the situations described in figure 3.2.

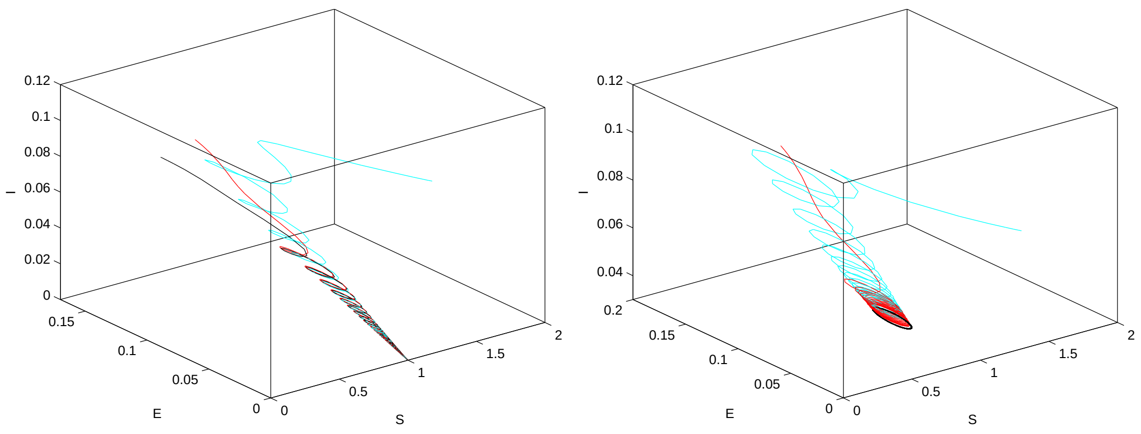


Figure 3.2: Disease Free Case and Endemic Case for $b = 0.6$.

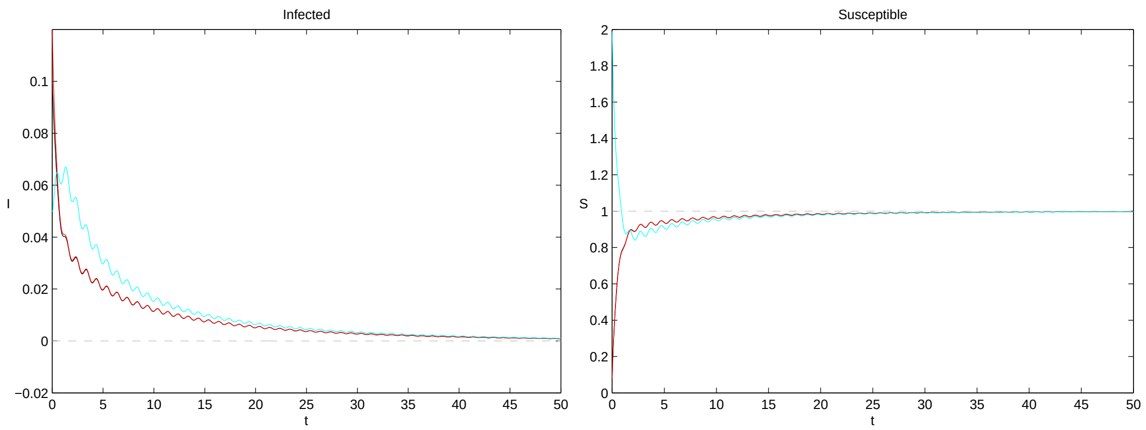


Figure 3.3: Disease Free Case.

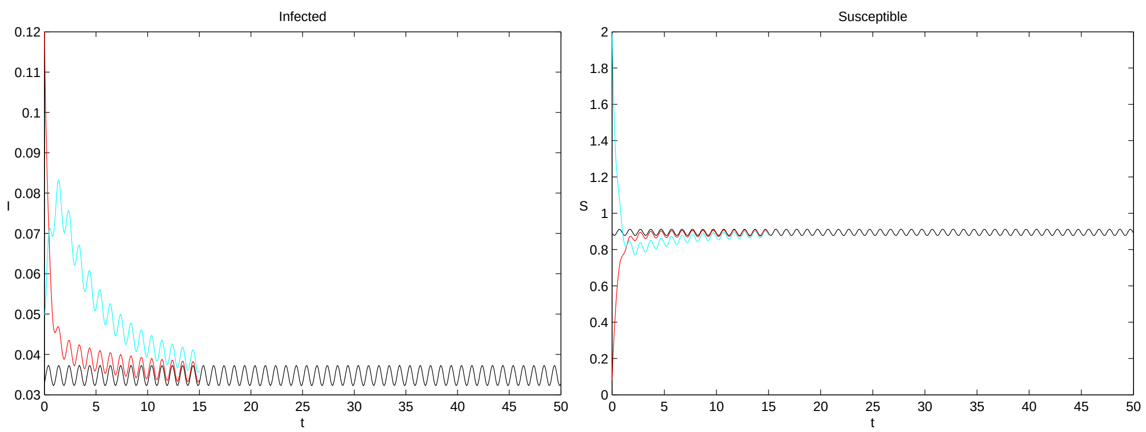


Figure 3.4: Endemic Case.

# Chapter 4

## Control Model

In this chapter we will add to our SEIRS model two control variables, vaccination and treatment, and discuss the obtained control model (3).

## 4.1 Setting and Preliminaries

We consider in this chapter problem (3) in the interval $[0, t_f]$ with $0 < t_f < \infty$. We assume that

C1) The parameter functions $\Lambda$, $\beta$, $\mu$, $\alpha$, $\eta$ and $\gamma$ are $\omega$-periodic and continuous on $[0, t_f]$;

C2) Function $\varphi$ is twice continuously differentiable;

C3) We have $\varphi(0, N, I) = \varphi(S, N, 0) = 0$.

Before stating our optimal control problem we will define in abstract what we mean by optimal control problem. This will allow us to introduce some notation and clarify our setting. We will follow [8].

Let $f : \mathbb{R} \times \mathbb{R}^n \times \mathbb{R}^m \to \mathbb{R}^n$, $f(t, x, u)$, be a continuous function with continuous first partial derivatives with respect to $x$ and let $\Phi : \mathbb{R} \times \mathbb{R} \times \mathbb{R}^n \times \mathbb{R}^n \to \mathbb{R}^k$, $\Phi(t_0, t_1, x_0, x_1)$, be a function of class $C^1$.

Let $U \subseteq \mathbb{R}^m$ be a closed set and $\mathcal{U}$ be a set of Lebesgue integrable functions $u$ with values in $U$ and defined on some interval $[t_0, t_1]$, which may differ for different elements of $\mathcal{U}$. A function $u \in \mathcal{U}$ will be called a control. For a control $u$ defined on $[t_0, t_1]$ the solution $x(t)$ of the differential equation

$$x' = f(t, x, u) \tag{4.1}$$

on the interval $[t_0, t_1]$ with initial condition $x(t_0) = x_0$ will be called the trajectory corresponding to the control $u$ and the initial condition $x_0$.

Notice that, in our context, by solution of (4.1) we mean an absolutely continuous function $x : [t_0, t_1] \to U$ such that

$$x(t) = x(t_0) + \int_{t_0}^{t} f(s, x(s), u(s))\ ds, \quad t_0 \leq t \leq t_1.$$

The value of $x(t)$ at time t is called the state of the system at time $t$. If $x(t)$ appears without mention in a formula it is always understood that a control $u$ and initial condition $x_0$ have been specified and that $x(t)$ is the trajectory corresponding to $u$ and $x_0$.

The first component of $\Phi$ evaluated at $(t_0, t_1, x_0, x_1)$, where $x(t)$ is a solution of (4.1),

$$\Phi_1(t_0, t_1, x_0, x_1), \tag{4.2}$$

is called the performance index or performance criterion of the system and will be denoted by $J(x_0, u)$ to emphasize the dependence on the initial state $x_0$ and control $u$:

$$J(x_0, u) = \Phi_1(t_0, t_1, x_0, x_1). \tag{4.3}$$

The next $k - 1$ components of $\Phi$ define end conditions for the trajectories of the system:

$$\Phi_j(t_0, t_1, x_0, x_1) = 0, \tag{4.4}$$

$j = 2, \ldots, k$. A pair $(x_0, u)$, consisting of an initial condition $x_0$ and a control $u$, will be called feasible if there is a solution $x(t)$ of (4.1) on $[t_0, t_1]$ with initial condition $x(t_0) = x_0$ satisfying the end conditions (4.4). Let $\mathcal{F}$ denote the class of feasible pairs $(x_0, u)$.

We are now in conditions to say that the optimal control problem is to find in the class $\mathcal{F}$ an element $(x_0, u)$ such that the corresponding performance index (4.2) is minimized. A pair $(x_0, u) \in \mathcal{F}$ for which $J$ achieves this minimum will be called an optimal initial condition and an optimal control.

The formulation of optimal control problem given above is usually called the Mayer formulation taking into account the form of the cost functional. When the cost functional has the form

$$J(x_0, u) = \int_{t_0}^{t_1} L(t, x(t), u(t))\ dt, \tag{4.5}$$

then we say that we have a Lagrange formulation for the optimal control problem.

In our context, we will consider a free terminal point problem, i.e. we will consider fixed initial and final times and fixed initial state. There will be no end conditions (and thus $\Phi$ reduces to $\Phi_1$) and we will consider the Lagrange formulation.

In the Lagrange formulation, the optimal control problem that we will consider corresponds to find an element $u$ that minimizes (4). In this formulation the function $f : \mathbb{R} \times \mathbb{R}^4 \times \mathbb{R}^2 \to \mathbb{R}^4$ is given by

$$f(t, W, Y) = (f_S(t, W, Y), f_E(t, W, Y), f_I(t, W, Y), f_R(t, W, Y)),$$

where $W = (S, E, I, R)$, $Y = (\mathbb{T}, \mathbb{V})$,

$$f_S(t, W, Y) = \Lambda(t) - \beta(t)\,\varphi(S, N, I) - \mu(t)\,S + \eta(t)\,R - \mathbb{V}S,$$

$$f_E(t, W, Y) = \beta(t)\,\varphi(S, N, I) - (\mu(t) + \varepsilon(t))\,E,$$

$$f_I(t, W, Y) = \varepsilon(t)\,E - (\mu(t) + \gamma(t))\,I - \mathbb{T}I$$

and

$$f_R(t, W, Y) = \gamma(t)\,I - \mu(t)\,R - \eta(t)\,R + \mathbb{T}I + \mathbb{V}S,$$

and the function $\Phi : \mathbb{R} \times \mathbb{R} \times \mathbb{R}^4 \times \mathbb{R}^4 \to \mathbb{R}$ is given by

$$\Phi(0, t_f, W_0, W_1) = \mathcal{J}(\mathbb{T}, \mathbb{V}) = \int_0^{t_f} \kappa_1 I + \kappa_2 \mathbb{T}^2 + \kappa_3 \mathbb{V}^2 dt.$$

In our context we set $\mathcal{F} = \{((S_0, E_0, I_0, R_0), (\mathbb{T}, \mathbb{V})) : (\mathbb{T}, \mathbb{V}) \in \Omega\}$ where

$$\Omega = \{(\tau, \nu) \in L^1(0, t) : (\tau(t), \nu(t)) \in [0, \tau_{max}] \times [0, \nu_{max}], \text{ for all } t \in [0, t_f]\}.$$

## 4.2 Existence of Solution

To establish the existence of solutions for our free terminal point optimal control problem, we will follow the third chapter in [8]. We consider the general optimal control problem in section 4.1 in Lagrange formulation and thus the cost functional is given by

$$J(x_0, u) = \int_{t_0}^{t_1} L(t, x(t), u(t))\; dt.$$

The following result is contained in Theorem III.4.1 and Corollary III.4.1 in [8].

Theorem 4.2.1 (Existence of solutions for control problems). Suppose that $f$ and $L$ are continuous and that there exist positive constants $C_1$ and $C_2$ such that, for $t \in \mathbb{R}$, $x, x_1, x_2 \in \mathbb{R}^n$ and $u \in \mathbb{R}^m$ we have

a) $\|f(t, x, u)\| \leq C_1(1 + \|x\| + \|u\|)$;

b) $\|f(t, x_1, u) - f(t, x_2, u)\| \leq C_2\|x_1 - x_2\|(1 + \|u\|)$.

c) $\mathcal{F}$ is non-empty;

d) $U$ is closed;

e) Letting $S = \{(t_0, t_1, x_0, x) : x \in \mathbb{R}^n\}$, there is $\mu_1 > inf J(x_0, u)$ and a compact set $S' \subseteq S$ such that if $e \in S$ and $J(x_0, u) \leq \mu_1$ then $e \in S'$;

f) $U$ is convex, $f(t, x, u) = \alpha(t, x) + \beta(t, x)u$ and $L(t, x, \cdot)$ is convex on $U$;

g) $L(t, x, u) \geq c_1|u|^\beta - c_2$, $c_1 > 0$, $\beta > 1$.

Then there exist $(x_0^*, u^*)$ minimizing $J$ on $\mathcal{F}$.

We will apply Theorem 4.2.1 to our problem in order to obtain an existence theorem. Namely, we have the following result:

Theorem 4.2.2. There exists an optimal control pair $(\mathbb{T}^*, \mathbb{V}^*)$ and a corresponding solution of the initial value problem (3), $(S^*, E^*, I^*, R^*)$, that minimizes the cost functional $\mathcal{J}$ in (4) over $\Omega$.

Proof. We will check that we are in the conditions of Theorem 4.2.1. Using C2) and C3), we immediately obtain a) and b). Conditions c) and d) are immediate from the definition of $\mathcal{F}$ and since $U = [0, \tau_{max}] \times [0, \nu_{max}]$. Condition e) is immediate.

Since the state equations are linearly dependent on the controls, we obtain f). Finally, $L$ is convex in the controls since is quadratic in the controls. Moreover,

$$L = k_1 I + k_2 \mathbb{T}^2 + k_3 \mathbb{V}^2 \geq \min\{k_2, k_3\}(\mathbb{T}^2 + \mathbb{V}^2) \geq \min\{k_2, k_3\}\|(\mathbb{T}, \mathbb{V})\|^2$$

and we establish g).

Thus the result follows from Theorem 4.2.1. □

## 4.3 Pontryagin's Maximum Principle

In this section we apply a version of Pontryagin's maximum principle for bounded controls to a slightly distinct version of our problem where the control space will be a smaller space. To do this it is necessary to replace the set $\mathcal{U}$ defined in section 4.1 by the set $\mathcal{V}$ consisting of left continuous piecewise continuous functions defined in $[t_0, t_1]$ and with values in $U$.

To state a result that will help us characterize the optimal controls for our problem, we need to define the Hamiltonian for the Free Terminal Point Problem in Lagrange formulation:

$$\mathcal{H}(t, x, u, p) = p_0 L(t, x, u) + \sum_{i=1}^{n} p_i(t) f_i(t, x, u), \tag{4.6}$$

where $p = (p_1, \ldots, p_n)$. The following result is a version of Pontryagin's Maximum Principle for the Free Terminal Point Problem given in Kamien and Schwartz [15].

Theorem 4.3.1 (Pontryagin's Minimum Principle). Let $L$, $f$, $\partial L/\partial x_j$ and $\partial f/\partial x_j$ be continuous for $i = 1, \ldots, n$ and let $u^*$ be an optimal control for the free terminal point problem in the Lagrange formulation.

Then there exists a constant $p_0$ and a continuous vector valued function $p : [t_0, t_1] \to \mathbb{R}^n$, $p(t) = (p_1(t), \ldots, p_n(t))$, such that

1) $(p_0, p(t)) \neq (0, 0)$, for all $t \in [t_0, t_1]$;

2) $\mathcal{H}(t, x^*(t), u^*(t), p(t)) \leq \mathcal{H}(t, x^*(t), u(t), p(t))$ for all $t \in [t_0, t_1]$;

3) $p_i'(t) = -\partial\mathcal{H}/\partial x_i(t, x^*(t), u^*(t), p(t))$ for all $i = 1, \ldots, n$ and all $t \in [t_0, t_1]$ that is a continuity point of $u^*(t)$;

4) $p_i(t_1) = 0$ for all $i = 1, \ldots, n$.

In our setting the Hamiltonian is given by

$$\begin{aligned}
&\mathcal{H}(t, (S, E, I, R), (\mathbb{T}, \mathbb{V}), p) \\
&= p_1 \left[\Lambda(t) - \beta(t)\varphi(S, N, I) - \mu(t) S + \eta(t) R - \mathbb{V}S\right] \\
&\quad + p_2 \left[\beta(t)\varphi(S, N, I) - (\mu(t) + \varepsilon(t)) E\right] \\
&\quad + p_3 \left[\varepsilon(t) E - (\mu(t) + \gamma(t)) I - \mathbb{T}I\right] \\
&\quad + p_4 \left[\gamma(t) I - \mu(t) R - \eta(t) R + \mathbb{T}I + \mathbb{V}S\right] + \kappa_1 I + \kappa_2 \mathbb{T}^2 + \kappa_3 \mathbb{V}^2.
\end{aligned}$$

Applying Theorem 4.3.1 to our problem we get the following result.

Theorem 4.3.2. Assuming that there is an optimal control pair $(\mathbb{T}^*, \mathbb{V}^*)$ and corresponding trajectory $(S^*, E^*, I^*, R^*)$ that minimizes the cost functional $\mathcal{J}$ in (4) over $\mathcal{V}$, there are functions $p_1$, $p_2$, $p_3$ and $p_4$ satisfying

$$p_1' = (p_1 - p_2)\beta(t)\left(\partial_1\varphi(S, N, I) + \partial_2\varphi(S, N, I)\right) + p_1(\mu(t) + \mathbb{V}) - p_4\mathbb{V} \tag{4.7}$$

$$p_2' = p_2(\mu(t) + \varepsilon(t)) - p_3\varepsilon(t), \tag{4.8}$$

$$\begin{aligned}
p_3' = {} & p_3(\mu(t) + \gamma(t) + \mathbb{T}) + (p_1 - p_2)\beta(t)\left(\partial_2\varphi(S, N, I) + \partial_3\varphi(S, N, I)\right) \\
& - p_4(\gamma(t) + \mathbb{T}) - \kappa_1,
\end{aligned} \tag{4.9}$$

$$p_4' = \mu(t) p_4 - \eta(t) p_1 + \eta(t) p_4, \tag{4.10}$$

with transversality conditions

$$p_1(t_f) = p_2(t_f) = p_3(t_f) = p_4(t_f) = 0. \tag{4.11}$$

Furthermore, the optimal control pair is given by

$$\mathbb{T}^* = \min\left\{\max\left\{0, \frac{I^*(p_3 - p_4)}{2k_2}\right\}, \tau_{max}\right\} \tag{4.12}$$

and

$$\mathbb{V}^* = \min\left\{\max\left\{0, \frac{S^*(p_1 - p_4)}{2k_3}\right\}, \upsilon_{max}\right\}. \tag{4.13}$$

Proof. We consider the Lagrange formulation of our problem and apply Theorem 4.3.1. Immediate computations show that equations (4.7) to (4.10) are consequence of 3) in Theorem 4.3.1 and that equation (4.11) is consequence of 4) in Theorem 4.3.1.

We will now characterize the controls. The general form for the optimality conditions on the set

$$\{t \in [0, t_f] : 0 < \mathbb{V}^*(t) < \nu_{max} \text{ and } 0 < \mathbb{T}^*(t) < \tau_{max}\}$$

are

$$0 = \frac{\partial \mathcal{H}}{\partial \mathbb{V}^*} = -p_1 S + p_4 S + 2k_3 \mathbb{V}^* \quad \text{and} \quad 0 = \frac{\partial \mathcal{H}}{\partial \mathbb{T}^*} = -p_3 I + p_4 I + 2k_2 \mathbb{T}^*,$$

and thus on this set

$$\mathbb{V}^* = \frac{(p_1 - p_4)S}{2k_3} \quad \text{and} \quad \mathbb{T}^* = \frac{(p_3 - p_4)I}{2k_2}.$$

If $t \in int\{t \in [0, t_f] : \mathbb{V}^*(t) = \nu_{max}\}$, then the necessary condition for optimal control is

$$0 \geq \frac{\partial \mathcal{H}}{\partial \mathbb{V}^*} = -p_1 S + p_4 S + 2k_3 \mathbb{V}^* \quad \Leftrightarrow \quad \frac{(p_1 - p_4)S}{2k_3} \geq \nu_{max}.$$

Analogously, if $t \in int\{t \in [0, t_f] : \mathbb{T}^*(t) = \tau_{max}\}$, then the necessary condition for optimal control is

$$0 \geq \frac{\partial \mathcal{H}}{\partial \mathbb{T}^*} = -p_3 I + p_4 I + 2k_2 \mathbb{T}^* \quad \Leftrightarrow \quad \frac{(p_3 - p_4)I}{2k_2} \geq \tau_{max}.$$

If $t \in int\{t \in [0, t_f] : \mathbb{V}^*(t) = 0\}$, then the necessary condition for optimal control is

$$0 \leq \frac{\partial \mathcal{H}}{\partial \mathbb{V}^*} = -p_1 S + p_4 S + 2k_3 \mathbb{V}^* \quad \Leftrightarrow \quad \frac{(p_1 - p_4)S}{2k_3} \leq 0.$$

Analogously, if $t \in int\{t \in [0, t_f] : \mathbb{T}^*(t) = 0\}$, then the necessary condition for optimal control is

$$0 \leq \frac{\partial \mathcal{H}}{\partial \mathbb{T}^*} = -p_3 I + p_4 I + 2k_2 \mathbb{T}^* \quad \Leftrightarrow \quad \frac{(p_3 - p_4)I}{2k_2} \leq 0.$$

Therefore we obtain (4.12) and (4.13). □

## 4.4 Uniqueness of the Optimal Control

In this section we will show that the optimality system, defined by the state equations, the initial conditions, the adjoint equations and the transversality conditions, is unique. The proof of this result is inspired on Gaff and Schaefer [9]. In this section $\partial_i$ denotes the partial derivative with respect to the $i$-th variable.

Theorem 4.4.1. For $T > 0$ sufficiently small, the optimality system is unique.

Proof. We assume that we have two optimality systems corresponding to trajectories and state equations $(S, E, I, R)$, $(p_1, p_2, p_3, p_4)$ and $(\bar{S}, \bar{E}, \bar{I}, \bar{R})$, $(\bar{p}_1, \bar{p}_2, \bar{p}_3, \bar{p}_4)$ and we will show that the two are the same, at least in some small interval. To achieve this we make the change of variables

$$S(t) = e^{\alpha t} s(t), \quad E(t) = e^{\alpha t} e(t), \quad I(t) = e^{\alpha t} i(t), \quad R(t) = e^{\alpha t} r(t)$$

and

$$p_1(t) = e^{-\alpha t} \phi_1(t), \quad p_2(t) = e^{-\alpha t} \phi_2(t), \quad p_3(t) = e^{-\alpha t} \phi_3(t), \quad p_4(t) = e^{-\alpha t} \phi_4(t).$$

Naturally, setting $n(t) = s(t) + e(t) + i(t) + r(t)$, we have

$$N(t) = S(t) + E(t) + I(t) + R(t) = \mathrm{e}^{\alpha(t)}\, n(t).$$

By Proposition 2.1.1, we can assume that the trajectories lie in a compact set $\Gamma$. Using the differentiability assumption C2) we get

$$\begin{aligned} &|\varphi(A, B, C) - \varphi(\bar{A}, \bar{B}, \bar{C})| \\ &\leq |\varphi(A, B, C) - \varphi(\bar{A}, B, C)| + |\varphi(\bar{A}, B, C) - \varphi(\bar{A}, \bar{B}, C)| \\ &\quad + |\varphi(\bar{A}, \bar{B}, C) - \varphi(\bar{A}, \bar{B}, \bar{C})| \\ &\leq M_1^u |A - \bar{A}| + M_2^u |B - \bar{B}| + M_3^u |C - \bar{C}|, \end{aligned} \tag{4.14}$$

where, since $\Gamma$ is compact, we have

$$M_i^u := \sup_{x\in\Gamma} |\partial_i \varphi| < +\infty, \quad i = 1,2,3. \tag{4.15}$$

Considering the first equation in (3) we get

$$\alpha e^{\alpha t} s + e^{\alpha t}\dot{s} = \Lambda - \beta\varphi(e^{\alpha t}s, e^{\alpha t}n, e^{\alpha t}i) - \mu e^{\alpha t}s + \eta e^{\alpha t} r - \mathbb{V} e^{\alpha t} s$$

and thus

$$\alpha s + \dot{s} = \frac{\Lambda}{e^{\alpha t}} - \frac{\beta}{e^{\alpha t}}\varphi(e^{\alpha t}s, e^{\alpha t}n, e^{\alpha t}i) - \mu s + \eta r - \mathbb{V}s.$$

Subtracting from the above equation the corresponding barred equation we obtain

$$\begin{aligned}\alpha(s-\bar{s}) + (\dot{s}-\dot{\bar{s}}) = &-\frac{\beta}{e^{\alpha t}}(\varphi(e^{\alpha t}s, e^{\alpha t}n, e^{\alpha t}i) - \varphi(e^{\alpha t}\bar{s}, e^{\alpha t}\bar{n}, e^{\alpha t}\bar{i})) - \mu(s-\bar{s})\\ &+ \eta(r-\bar{r}) - (\mathbb{V}s - \bar{\mathbb{V}}\bar{s}).\end{aligned}$$

Multiplying by $(s-\bar{s})$, integrating from 0 to $T$ and noting that $s(0) = \bar{s}(0)$ we have

$$\begin{aligned}&\frac{1}{2}(s(T)-\bar{s}(T))^2 + \alpha\int_0^T (s-\bar{s})^2 dt\\ &= -\int_0^T \frac{\beta}{e^{\alpha t}}(s-\bar{s})(\varphi(e^{\alpha t}s, e^{\alpha t}n, e^{\alpha t}i) - \varphi(e^{\alpha t}\bar{s}, e^{\alpha t}\bar{n}, e^{\alpha t}\bar{i}))dt\\ &\quad - \int_0^T \mu(s-\bar{s})^2 dt + \int_0^T \eta(s-\bar{s})(r-\bar{r})dt - \int_0^T (\mathbb{V}s - \bar{\mathbb{V}}\bar{s})(s-\bar{s})dt\end{aligned}$$

and by (4.14) we obtain

$$\begin{aligned}&\frac{1}{2}(s(T)-\bar{s}(T))^2 + \alpha\int_0^T (s-\bar{s})^2 dt\\ &\leq \int_0^T \frac{\beta}{e^{\alpha t}}|s-\bar{s}|(M_1^u|e^{\alpha t}s - e^{\alpha t}\bar{s}| + M_2^u|e^{\alpha t}n - e^{\alpha t}\bar{n}| + M_3^u|e^{\alpha t}i - e^{\alpha t}\bar{i}|)dt\\ &\quad - \int_0^T \mu(s-\bar{s})^2 dt + \int_0^T \eta(s-\bar{s})(r-\bar{r})dt - \int_0^T (\mathbb{V}s - \bar{\mathbb{V}}\bar{s})(s-\bar{s})dt\\ &= \int_0^T \beta|s-\bar{s}|(M_1^u|s-\bar{s}| + M_2^u|n-\bar{n}| + M_3^u|i-\bar{i}|)dt\\ &\quad - \int_0^T \mu(s-\bar{s})^2 dt + \int_0^T \eta(s-\bar{s})(r-\bar{r})dt - \int_0^T (\mathbb{V}s - \bar{\mathbb{V}}\bar{s})(s-\bar{s})dt\\ &= \int_0^T \beta M_1^u(s-\bar{s})^2 dt + \int_0^T \beta M_2^u|s-\bar{s}||n-\bar{n}|dt + \int_0^T \beta M_3^u|s-\bar{s}||i-\bar{i}|dt\\ &\quad - \int_0^T \mu(s-\bar{s})^2 dt + \int_0^T \eta(s-\bar{s})(r-\bar{r})dt - \int_0^T (\mathbb{V}s - \bar{\mathbb{V}}\bar{s})(s-\bar{s})dt\end{aligned}$$

and finally

$$\begin{aligned}
&\frac{1}{2}(s(T)-\bar{s}(T))^2+\alpha\int_0^T (s-\bar{s})^2dt \\
&\leq \beta^u {M_1}^u \int_0^T (s-\bar{s})^2 dt + \beta^u M_2^u \int_0^T (s-\bar{s})^2+(n-\bar{n})^2dt \\
&\quad + \beta^u {M_3}^u \int_0^T (s-\bar{s})^2+(i-\bar{i})^2 dt + \eta^u \int_0^T (s-\bar{s})^2+(r-\bar{r})^2dt \\
&\quad + \int_0^T K_1[(\mathbb{V}-\bar{\mathbb{V}})^2+2(s-\bar{s})^2]dt \\
&\leq C_1 \int_0^T (s-\bar{s})^2+(i-\bar{i})^2+(e-\bar{e})^2+(r-\bar{r})^2dt + K_1\int_0^T (\mathbb{V}-\bar{\mathbb{V}})^2dt,
\end{aligned}$$

where $K_1$ depends on the bounds for $\bar{s}$ and $\mathbb{V}$ and $C_1=\beta^u M_1^u+2\beta^u M_2^u+\beta^u M_3^u+\eta^u+2K_1$ (recall that $M_i^u$ is given by (4.15)).

We will use some estimates for $(\mathbb{V}-\bar{\mathbb{V}})^2$ and $(\mathbb{T}-\bar{\mathbb{T}})^2$ that will be obtained later. Namely, we have

$$(\mathbb{V}-\bar{\mathbb{V}})^2 \leq C_9[(s-\bar{s})^2+(\phi_1-\bar{\phi}_1)^2+(\phi_4-\bar{\phi}_4)^2], \tag{4.16}$$

where $C_9$ depends on bounds for $s$, $\bar{\phi}_1$ and $\bar{\phi}_4$, and

$$(\mathbb{T}-\bar{\mathbb{T}})^2 \leq C_{10}[(i-\bar{i})^2+(\phi_3-\bar{\phi}_3)^2+(\phi_4-\bar{\phi}_4)^2], \tag{4.17}$$

where $C_{10}$ depends on bounds for $i$, $\bar{\phi}_3$ and $\bar{\phi}_4$ (see equations (4.33) and (4.34)).

By (4.16) we obtain

$$\begin{aligned}
&\frac{1}{2}(s(T)-\bar{s}(T))^2+\alpha\int_0^T (s-\bar{s})^2dt \\
&\leq C_1 \int_0^T (s-\bar{s})^2+(i-\bar{i})^2+(e-\bar{e})^2+(r-\bar{r})^2dt \\
&\quad + K_1C_9\int_0^T (s-\bar{s})^2+(\phi_1-\bar{\phi}_1)^2+(\phi_4-\bar{\phi}_4)^2dt \\
&\leq (C_1+K_1C_9)\int_0^T (s-\bar{s})^2+(i-\bar{i})^2+(e-\bar{e})^2+(r-\bar{r})^2 \\
&\quad +(\phi_1-\bar{\phi}_1)^2+(\phi_4-\bar{\phi}_4)^2dt \\
&\leq (C_1+K_1C_9)\int_0^T \Phi(t)+\Psi(t)dt.
\end{aligned} \tag{4.18}$$

From the second equation in (3) we have

$$\begin{aligned}
&\frac{1}{2}(e(T)-\bar{e}(T))^2+\alpha\int_0^T(e-\bar{e})^2dt\\
&\leq\int_0^T\frac{\beta}{e^{\alpha t}}|e-\bar{e}||\varphi(e^{\alpha t}s,e^{\alpha t}n,e^{\alpha t}i)-\varphi(e^{\alpha t}\bar{s},e^{\alpha t}\bar{n},e^{\alpha t}\bar{i})|dt-\int_0^T(\mu+\varepsilon)(e-\bar{e})^2dt\\
&\leq\int_0^T\frac{\beta}{e^{\alpha t}}|e-\bar{e}|(M_1^u|e^{\alpha t}s-e^{\alpha t}\bar{s}|+M_2^u|e^{\alpha t}n-e^{\alpha t}\bar{n}|+M_3^u|e^{\alpha t}i-e^{\alpha t}\bar{i}|)dt\\
&\quad-\int_0^T(\mu+\varepsilon)(e-\bar{e})^2dt
\end{aligned}\tag{4.19}$$

and thus

$$\begin{aligned}
&\frac{1}{2}(e(T)-\bar{e}(T))^2+\alpha\int_0^T(e-\bar{e})^2dt\\
&\leq\int_0^T\beta|e-\bar{e}|(M_1^u|s-\bar{s}|+M_2^u|n-\bar{n}|+M_3^u|i-\bar{i}|)dt-\int_0^T(\mu+\varepsilon)(e-\bar{e})^2dt\\
&=\int_0^T\beta M_1^u|e-\bar{e}||s-\bar{s}|dt+\int_0^T\beta M_2^u|e-\bar{e}||n-\bar{n}|dt+\int_0^T\beta M_3^u|e-\bar{e}||i-\bar{i}|dt\\
&\quad-\int_0^T(\mu+\varepsilon)(e-\bar{e})^2dt
\end{aligned}\tag{4.20}$$

Using the fact that $xy\leq x^2+y^2$ we get

$$\begin{aligned}
&\frac{1}{2}(e(T)-\bar{e}(T))^2+\alpha\int_0^T(e-\bar{e})^2dt\\
&\leq\beta^uM_1^u\int_0^T(e-\bar{e})^2+(s-\bar{s})^2dt+\beta^uM_2^u\int_0^T(e-\bar{e})^2+(n-\bar{n})^2dt\\
&\quad+\beta^uM_3^u\int_0^T(e-\bar{e})^2+(i-\bar{i})^2dt\\
&\leq C_2\int_0^T(s-\bar{s})^2+(i-\bar{i})^2+(e-\bar{e})^2+(r-\bar{r})^2dt\\
&\leq C_2\int_0^T\Phi(t)+\Psi(t)dt,
\end{aligned}\tag{4.21}$$

where $C_2=\beta^uM_1^u+2\beta^uM_2^u+\beta^uM_3^u$.

Recalling that

$$(xy-\bar{x}\bar{y})(w-\bar{w})\leq C((x-\bar{x})^2+(y-\bar{y})^2+(w-\bar{w})^2),$$

with $C>0$ depending on the bounds for $\bar{x}$ and $y$, from the third equation in (3) we conclude that

$$\begin{aligned}
&\frac{1}{2}(i(T)-\bar{i}(T))^2+\alpha\int_0^T(i-\bar{i})^2dt\\
&=\int_0^T\varepsilon(i-\bar{i})(e-\bar{e})dt-\int_0^T(\mu+\gamma)(i-\bar{i})^2dt-\int_0^T(\mathbb{T}i-\bar{\mathbb{T}}\bar{i})(i-\bar{i})dt\\
&\le\varepsilon^u\int_0^T(i-\bar{i})^2+(e-\bar{e})^2dt+\int_0^T K_2[(\mathbb{T}-\bar{\mathbb{T}})^2+2(i-\bar{i})^2]dt\\
&\le C_3\int_0^T(i-\bar{i})^2+(e-\bar{e})^2dt+K_2\int_0^T(\mathbb{T}-\bar{\mathbb{T}})^2dt,
\end{aligned}$$

where $K_2$ depends on the bounds for $\bar{i}$ and $\mathbb{T}$ and $C_3=\varepsilon^u+2K_2$. Thus, by (4.17) we have

$$\begin{aligned}
&\frac{1}{2}(i(T)-\bar{i}(T))^2+\alpha\int_0^T(i-\bar{i})^2dt\\
&\le C_3\int_0^T(i-\bar{i})^2+(e-\bar{e})^2dt+K_2C_{10}\int_0^T(i-\bar{i})^2+(\phi_3-\bar{\phi}_3)^2+(\phi_4-\bar{\phi}_4)^2dt\\
&\le(C_3+K_2C_{10})\int_0^T(s-\bar{s})^2+(i-\bar{i})^2+(e-\bar{e})^2+(r-\bar{r})^2+(\phi_3-\bar{\phi}_3)^2\\
&\quad+(\phi_4-\bar{\phi}_4)^2dt\\
&\le(C_3+K_2C_{10})\int_0^T\Phi(t)+\Psi(t)dt.
\end{aligned}\tag{4.22}$$

From the fourth equation in (3) we conclude that

$$\begin{aligned}
&\frac{1}{2}(r(T)-\bar{r}(T))^2+\alpha\int_0^T(r-\bar{r})^2dt\\
&=\int_0^T\gamma(i-\bar{i})(r-\bar{r})dt-\int_0^T(\mu+\eta)(r-\bar{r})^2dt+\int_0^T(\mathbb{T}i-\bar{\mathbb{T}}\bar{i})(r-\bar{r})dt\\
&\quad+\int_0^T(\mathbb{V}s-\bar{\mathbb{V}}\bar{s})(r-\bar{r})dt\\
&\le\gamma^u\int_0^T(i-\bar{i})^2+(r-\bar{r})^2dt+\int_0^T K_3[(\mathbb{T}-\bar{\mathbb{T}})^2+(i-\bar{i})^2+(r-\bar{r})^2]dt\\
&\quad+\int_0^T K_4[(\mathbb{V}-\bar{\mathbb{V}})^2+(s-\bar{s})^2+(r-\bar{r})^2]dt\\
&\le C_4\int_0^T(s-\bar{s})^2+(i-\bar{i})^2+(r-\bar{r})^2dt+K_3\int_0^T(\mathbb{T}-\bar{\mathbb{T}})^2dt+K_4\int_0^T(\mathbb{V}-\bar{\mathbb{V}})^2dt,
\end{aligned}$$

where $K_3$ and $K_4$ depends on the bounds for $\bar{i}$, $\bar{s}$, $\mathbb{T}$ and $\mathbb{V}$ and $C_4=\gamma^u+K_3+K_4$.

Therefore, by (4.16) and (4.17) we obtain

$$\begin{aligned}
&\frac{1}{2}(r(T)-\bar{r}(T))^2+\alpha\int_0^T(r-\bar{r})^2dt\\
&\leq C_4\int_0^T(s-\bar{s})^2+(i-\bar{i})^2+(r-\bar{r})^2dt+K_3C_{10}\int_0^T(i-\bar{i})^2+(\phi_3-\bar{\phi}_3)^2\\
&\quad+(\phi_4-\bar{\phi}_4)^2dt+K_4C_9\int_0^T(s-\bar{s})^2+(\phi_1-\bar{\phi}_1)^2+(\phi_4-\bar{\phi}_4)^2dt\\
&\leq(C_4+K_3C_{10}+K_4C_9)\int_0^T(s-\bar{s})^2+(i-\bar{i})^2+(e-\bar{e})^2+(r-\bar{r})^2\\
&\quad+(\phi_1-\bar{\phi}_1)^2+(\phi_3-\bar{\phi}_3)^2+(\phi_4-\bar{\phi}_4)^2dt\\
&\leq(C_4+K_3C_{10}+K_4C_9)\int_0^T\Phi(t)+\Psi(t)dt.
\end{aligned} \tag{4.23}$$

By equation (4.7) we get

$$\begin{aligned}
-\alpha e^{-\alpha t}\phi_1+e^{-\alpha t}\dot{\phi}_1&=e^{-\alpha t}(\phi_1-\phi_2)\beta\left(\partial_1\varphi\left(e^{\alpha t}s,e^{\alpha t}n,e^{\alpha t}i\right)+\partial_2\varphi\left(e^{\alpha t}s,e^{\alpha t}n,e^{\alpha t}i\right)\right)\\
&\quad+e^{-\alpha t}\phi_1\left(\mu+\mathbb{V}\right)-e^{-\alpha t}\phi_4\mathbb{V}
\end{aligned}$$

and thus

$$\begin{aligned}
-\alpha\phi_1+\dot{\phi}_1&=(\phi_1-\phi_2)\beta\left(\partial_1\varphi\left(e^{\alpha t}s,e^{\alpha t}n,e^{\alpha t}i\right)+\partial_2\varphi\left(e^{\alpha t}s,e^{\alpha t}n,e^{\alpha t}i\right)\right)\\
&\quad+\phi_1\left(\mu+\mathbb{V}\right)-\phi_4\mathbb{V}.
\end{aligned} \tag{4.24}$$

Using C2) we get

$$\begin{aligned}
&|\phi_j\partial_i\varphi\left(e^{\alpha t}s,e^{\alpha t}n,e^{\alpha t}i\right)-\bar{\phi}_j\partial_i\varphi\left(e^{\alpha t}\bar{s},e^{\alpha t}\bar{n},e^{\alpha t}\bar{i}\right)|\\
&\leq|\phi_j\partial_i\varphi\left(e^{\alpha t}s,e^{\alpha t}n,e^{\alpha t}i\right)-\phi_j\partial_i\varphi\left(e^{\alpha t}\bar{s},e^{\alpha t}\bar{n},e^{\alpha t}\bar{i}\right)|\\
&\quad+|\phi_j\partial_i\varphi\left(e^{\alpha t}\bar{s},e^{\alpha t}\bar{n},e^{\alpha t}\bar{i}\right)-\bar{\phi}_j\partial_i\varphi\left(e^{\alpha t}\bar{s},e^{\alpha t}\bar{n},e^{\alpha t}\bar{i}\right)|\\
&=\phi_j|\partial_i\varphi\left(e^{\alpha t}s,e^{\alpha t}n,e^{\alpha t}i\right)-\partial_i\varphi\left(e^{\alpha t}\bar{s},e^{\alpha t}\bar{n},e^{\alpha t}\bar{i}\right)|+|\phi_j-\bar{\phi}_j||\partial_i\varphi\left(e^{\alpha t}\bar{s},e^{\alpha t}\bar{n},e^{\alpha t}\bar{i}\right)|\\
&=\phi_j\left[|\partial_i\varphi\left(e^{\alpha t}s,e^{\alpha t}n,e^{\alpha t}i\right)-\partial_i\varphi\left(e^{\alpha t}\bar{s},e^{\alpha t}n,e^{\alpha t}i\right)|+|\partial_i\varphi\left(e^{\alpha t}\bar{s},e^{\alpha t}n,e^{\alpha t}i\right)\right.\\
&\quad\left.-\partial_i\varphi\left(e^{\alpha t}\bar{s},e^{\alpha t}\bar{n},e^{\alpha t}i\right)|+|\partial_i\varphi\left(e^{\alpha t}\bar{s},e^{\alpha t}\bar{n},e^{\alpha t}i\right)-\partial_i\varphi\left(e^{\alpha t}\bar{s},e^{\alpha t}\bar{n},e^{\alpha t}\bar{i}\right)|\right]\\
&\quad+|\phi_j-\bar{\phi}_j||\partial_i\varphi\left(e^{\alpha t}\bar{s},e^{\alpha t}\bar{n},e^{\alpha t}\bar{i}\right)|\\
&\leq\phi_j[M_{i1}^u|e^{\alpha t}s-e^{\alpha t}\bar{s}|+M_{i2}^u|e^{\alpha t}n-e^{\alpha t}\bar{n}|+M_{i3}^u|e^{\alpha t}i-e^{\alpha t}\bar{i}|]\\
&\quad+|\phi_j-\bar{\phi}_j||\partial_i\varphi\left(e^{\alpha t}\bar{s},e^{\alpha t}\bar{n},e^{\alpha t}\bar{i}\right)|\\
&\leq\phi_j^u[M_{i1}^u e^{\alpha t}|s-\bar{s}|+M_{i2}^u e^{\alpha t}|n-\bar{n}|+M_{i3}^u e^{\alpha t}|i-\bar{i}|]+M_i^u|\phi_j-\bar{\phi}_j|
\end{aligned}$$

where, by C2) and since $\Gamma$ is compact, we have

$$M_{ij}^u:=\sup_{x\in\Gamma}|\partial_j\partial_i\varphi(x)|<+\infty,\quad i,j\in\{1,2,3\}. \tag{4.25}$$

Subtracting from equation (4.24) the corresponding barred equation we conclude that

$$\begin{aligned}
& -\alpha\phi_1+\dot{\phi}_1+\alpha\bar{\phi}_1-\dot{\bar{\phi}}_1 \\
&=\beta(\phi_1-\phi_2)\left(\partial_1\varphi\left(e^{\alpha t}s,e^{\alpha t}n,e^{\alpha t}i\right)+\partial_2\varphi\left(e^{\alpha t}s,e^{\alpha t}n,e^{\alpha t}i\right)\right)+\phi_1\left(\mu+\mathbb{V}\right)-\phi_4\mathbb{V} \\
&\quad-\beta(\bar{\phi}_1-\bar{\phi}_2)\left(\partial_1\varphi\left(e^{\alpha t}\bar{s},e^{\alpha t}\bar{n},e^{\alpha t}\bar{i}\right)+\partial_2\varphi\left(e^{\alpha t}\bar{s},e^{\alpha t}\bar{n},e^{\alpha t}\bar{i}\right)\right)-\bar{\phi}_1\left(\mu+\bar{\mathbb{V}}\right)+\bar{\phi}_4\bar{\mathbb{V}} \\
&=\beta\left[\phi_1\left(\partial_1\varphi\left(e^{\alpha t}s,e^{\alpha t}n,e^{\alpha t}i\right)+\partial_2\varphi\left(e^{\alpha t}s,e^{\alpha t}n,e^{\alpha t}i\right)\right)\right. \\
&\quad\left.-\bar{\phi}_1\left(\partial_1\varphi\left(e^{\alpha t}\bar{s},e^{\alpha t}\bar{n},e^{\alpha t}\bar{i}\right)+\partial_2\varphi\left(e^{\alpha t}\bar{s},e^{\alpha t}\bar{n},e^{\alpha t}\bar{i}\right)\right)\right] \\
&\quad-\beta\left[\phi_2\left(\partial_1\varphi\left(e^{\alpha t}s,e^{\alpha t}n,e^{\alpha t}i\right)+\partial_2\varphi\left(e^{\alpha t}s,e^{\alpha t}n,e^{\alpha t}i\right)\right)\right. \\
&\quad\left.-\bar{\phi}_2\left(\partial_1\varphi\left(e^{\alpha t}\bar{s},e^{\alpha t}\bar{n},e^{\alpha t}\bar{i}\right)+\partial_2\varphi\left(e^{\alpha t}\bar{s},e^{\alpha t}\bar{n},e^{\alpha t}\bar{i}\right)\right)\right] \\
&\quad+\mu(\phi_1-\bar{\phi}_1)+\phi_1\mathbb{V}-\bar{\phi}_1\bar{\mathbb{V}}-\phi_4\mathbb{V}+\bar{\phi}_4\bar{\mathbb{V}}.
\end{aligned}$$

Multiplying by $\phi_1-\bar{\phi}_1$ and integrating from 0 to $T$ we obtain

$$\begin{aligned}
& -\frac{1}{2}(\phi_1(0)-\bar{\phi}_1(0))^2-\alpha\int_0^T(\phi_1-\bar{\phi}_1)^2dt \\
&=\int_0^T\beta(\phi_1-\bar{\phi}_1)\left[\phi_1\left(\partial_1\varphi\left(e^{\alpha t}s,e^{\alpha t}n,e^{\alpha t}i\right)+\partial_2\varphi\left(e^{\alpha t}s,e^{\alpha t}n,e^{\alpha t}i\right)\right)\right. \\
&\quad\left.-\bar{\phi}_1\left(\partial_1\varphi\left(e^{\alpha t}\bar{s},e^{\alpha t}\bar{n},e^{\alpha t}\bar{i}\right)+\partial_2\varphi\left(e^{\alpha t}\bar{s},e^{\alpha t}\bar{n},e^{\alpha t}\bar{i}\right)\right)\right]dt \\
&\quad-\int_0^T\beta(\phi_1-\bar{\phi}_1)\left[\phi_2\left(\partial_1\varphi\left(e^{\alpha t}s,e^{\alpha t}n,e^{\alpha t}i\right)+\partial_2\varphi\left(e^{\alpha t}s,e^{\alpha t}n,e^{\alpha t}i\right)\right)\right. \\
&\quad\left.-\bar{\phi}_2\left(\partial_1\varphi\left(e^{\alpha t}\bar{s},e^{\alpha t}\bar{n},e^{\alpha t}\bar{i}\right)+\partial_2\varphi\left(e^{\alpha t}\bar{s},e^{\alpha t}\bar{n},e^{\alpha t}\bar{i}\right)\right)\right]dt \\
&\quad+\int_0^T\mu(\phi_1-\bar{\phi}_1)^2dt+\int_0^T(\phi_1-\bar{\phi}_1)(\phi_1\mathbb{V}-\bar{\phi}_1\bar{\mathbb{V}})dt \\
&\quad-\int_0^T(\phi_1-\bar{\phi}_1)(\phi_4\mathbb{V}-\bar{\phi}_4\bar{\mathbb{V}})dt.
\end{aligned} \tag{4.26}$$

Multiplying (4.26) by $-1$, we obtain

$$\begin{aligned}
& \frac{1}{2}(\phi_1(0)-\bar{\phi}_1(0))^2+\alpha\int_0^T(\phi_1-\bar{\phi}_1)^2dt \\
&\le\beta^u\int_0^T|\phi_1-\bar{\phi}_1|\left[|\phi_1\partial_1\varphi\left(e^{\alpha t}s,e^{\alpha t}n,e^{\alpha t}i\right)-\bar{\phi}_1\partial_1\varphi\left(e^{\alpha t}\bar{s},e^{\alpha t}\bar{n},e^{\alpha t}\bar{i}\right)|\right. \\
&\quad\left.+|\phi_1\partial_2\varphi\left(e^{\alpha t}s,e^{\alpha t}n,e^{\alpha t}i\right)-\bar{\phi}_1\partial_2\varphi\left(e^{\alpha t}\bar{s},e^{\alpha t}\bar{n},e^{\alpha t}\bar{i}\right)|\right]dt \\
&\quad+\beta^u\int_0^T|\phi_1-\bar{\phi}_1|\left[|\phi_2\partial_1\varphi\left(e^{\alpha t}s,e^{\alpha t}n,e^{\alpha t}i\right)-\bar{\phi}_2\partial_1\varphi\left(e^{\alpha t}\bar{s},e^{\alpha t}\bar{n},e^{\alpha t}\bar{i}\right)|\right. \\
&\quad\left.+|\phi_2\partial_2\varphi\left(e^{\alpha t}s,e^{\alpha t}n,e^{\alpha t}i\right)-\bar{\phi}_2\partial_2\varphi\left(e^{\alpha t}\bar{s},e^{\alpha t}\bar{n},e^{\alpha t}\bar{i}\right)|\right]dt \\
&\quad-\int_0^T(\phi_1-\bar{\phi}_1)(\phi_1\mathbb{V}-\bar{\phi}_1\bar{\mathbb{V}})dt+\int_0^T(\phi_1-\bar{\phi}_1)(\phi_4\mathbb{V}-\bar{\phi}_4\bar{\mathbb{V}})dt
\end{aligned}$$

and thus, by (4.15) and (4.25), we conclude that

$$\begin{aligned}
&\frac{1}{2}(\phi_1(0)-\bar{\phi}_1(0))^2+\alpha\int_0^T(\phi_1-\bar{\phi}_1)^2dt\\
&\le \beta^u\int_0^T|\phi_1-\bar{\phi}_1|\left[\phi_1^u(M_{11}^u e^{\alpha t}|s-\bar{s}|+M_{12}^u e^{\alpha t}|n-\bar{n}|+M_{13}^u e^{\alpha t}|i-\bar{i}|)\right.\\
&\quad+M_1^u|\phi_1-\bar{\phi}_1|+\phi_1^u(M_{21}^u e^{\alpha t}|s-\bar{s}|+M_{22}^u e^{\alpha t}|n-\bar{n}|+M_{23}^u e^{\alpha t}|i-\bar{i}|)\\
&\quad\left.+M_2^u|\phi_1-\bar{\phi}_1|\right]dt+\beta^u\int_0^T|\phi_1-\bar{\phi}_1|\left[\phi_2^u(M_{11}^u e^{\alpha t}|s-\bar{s}|+M_{12}^u e^{\alpha t}|n-\bar{n}|)+\right.\\
&\quad+M_{13}^u e^{\alpha t}|i-\bar{i}|)+M_1^u|\phi_2-\bar{\phi}_2|+\phi_2^u\left(M_{21}^u e^{\alpha t}|s-\bar{s}|+M_{22}^u e^{\alpha t}|n-\bar{n}|\right.\\
&\quad\left.\left.+M_{23}^u e^{\alpha t}|i-\bar{i}|\right)+M_2^u|\phi_2-\bar{\phi}_2|\right]dt-\int_0^T(\phi_1-\bar{\phi}_1)(\phi_1\mathbb{V}-\bar{\phi}_1\bar{\mathbb{V}})dt\\
&\quad+\int_0^T(\phi_1-\bar{\phi}_1)(\phi_4\mathbb{V}-\bar{\phi}_4\bar{\mathbb{V}})dt.
\end{aligned}$$

Finally we have

$$\begin{aligned}
&\frac{1}{2}(\phi_1(0)-\bar{\phi}_1(0))^2+\alpha\int_0^T(\phi_1-\bar{\phi}_1)^2dt\\
&\le \beta^u\phi_1^u e^{\alpha T}\left((M_{11}^u+M_{21}^u)\int_0^T(\phi_1-\bar{\phi}_1)^2+(s-\bar{s})^2dt+(M_{12}^u+M_{22}^u)\times\right.\\
&\quad\left.\times\int_0^T(\phi_1-\bar{\phi}_1)^2+(n-\bar{n})^2dt+(M_{13}+M_{23})^u\int_0^T(\phi_1-\bar{\phi}_1)^2+(i-\bar{i})^2dt\right)\\
&\quad+\beta^u(M_1^u+M_2^u)\int_0^T(\phi_1-\bar{\phi}_1)^2dt+\beta^u\phi_2^u e^{\alpha T}\left((M_{11}^u+M_{21}^u)\int_0^T(\phi_1-\bar{\phi}_1)^2\right.\\
&\quad+(s-\bar{s})^2dt+(M_{12}^u+M_{22}^u)\int_0^T(\phi_1-\bar{\phi}_1)^2+(n-\bar{n})^2dt+(M_{13}+M_{23})^u\times\\
&\quad\left.\times\int_0^T(\phi_1-\bar{\phi}_1)^2+(i-\bar{i})^2dt\right)+\beta^u(M_1^u+M_2^u)\int_0^T(\phi_1-\bar{\phi}_1)^2+(\phi_2-\bar{\phi}_2)^2dt\\
&\quad+\int_0^T K_5[(\mathbb{V}-\bar{\mathbb{V}}|)^2+2(\phi_1-\bar{\phi}_1)^2]dt+\int_0^T K_6[(\mathbb{V}-\bar{\mathbb{V}})^2+(\phi_4-\bar{\phi}_4)^2\\
&\quad+(\phi_1-\bar{\phi}_1)^2]dt\\
&\le C_5\int_0^T(s-\bar{s})^2+(e-\bar{e})^2+(i-\bar{i})^2+(r-\bar{r})^2+(\phi_1-\bar{\phi}_1)^2+(\phi_2-\bar{\phi}_2)^2\\
&\quad+(\phi_4-\bar{\phi}_4)^2dt+(K_5+K_6)\int_0^T(\mathbb{V}-\bar{\mathbb{V}})^2dt,
\end{aligned}$$

where $K_5$ and $K_6$ depends on the bounds for $\bar{\phi}_1$, $\bar{\phi}_4$ and $\mathbb{V}$ and

$$\begin{aligned}
C_5=&\ \beta^u\phi_1^u e^{\alpha T}\left((M_{11}^u+M_{21}^u)+2(M_{12}^u+M_{22}^u)+(M_{13}+M_{23})^u\right)\\
&+\beta^u\phi_2^u e^{\alpha T}\left((M_{11}^u+M_{21}^u)+2(M_{12}^u+M_{22}^u)+(M_{13}+M_{23})^u\right)\\
&+2\beta^u(M_1^u+M_2^u)+2K_5+K_6.
\end{aligned}$$

By (4.16) and (4.17) we obtain

$$\begin{aligned}
&\frac{1}{2}(\phi_1(0)-\bar{\phi}_1(0))^2+\alpha\int_0^T(\phi_1-\bar{\phi}_1)^2dt \\
&\le C_5\int_0^T(s-\bar{s})^2+(e-\bar{e})^2+(i-\bar{i})^2+(r-\bar{r})^2+(\phi_1-\bar{\phi}_1)^2 \\
&\quad+(\phi_2-\bar{\phi}_2)^2+(\phi_4-\bar{\phi}_4)^2dt \\
&\quad+(K_5+K_6)C_9\int_0^T(s-\bar{s})^2+(\phi_1-\bar{\phi}_1)^2+(\phi_4-\bar{\phi}_4)^2dt \qquad (4.27)\\
&\le (C_5+(K_5+K_6)C_9)\int_0^T(s-\bar{s})^2+(e-\bar{e})^2+(i-\bar{i})^2+(r-\bar{r})^2 \\
&\quad+(\phi_1-\bar{\phi}_1)^2+(\phi_2-\bar{\phi}_2)^2+(\phi_4-\bar{\phi}_4)^2dt \\
&\le (C_5+(K_5+K_6)C_9)\int_0^T\Phi(t)+\Psi(t)dt.
\end{aligned}$$

From equation (4.8) we have $-\alpha e^{-\alpha t}\phi_2+e^{-\alpha t}\dot{\phi}_2 = e^{-\alpha t}\phi_2(\mu+\varepsilon)-e^{-\alpha t}\phi_3\varepsilon$ and thus $-\alpha\phi_2+\dot{\phi}_2=\phi_2(\mu+\varepsilon)-\phi_3\varepsilon$. Subtracting from the above equation the corresponding barred equation one gets

$$-\alpha\phi_2+\dot{\phi}_2+\alpha\bar{\phi}_2-\dot{\bar{\phi}}_2=\left(\phi_2-\bar{\phi}_2\right)(\mu+\varepsilon)-\left(\phi_3-\bar{\phi}_3\right)\varepsilon,$$

and multiplying by $\phi_2-\bar{\phi}_2$ and integrating from 0 to $T$ we obtain

$$\begin{aligned}
&-\frac{1}{2}(\phi_2(0)-\bar{\phi}_2(0))^2-\alpha\int_0^T(\phi_2-\bar{\phi}_2)^2dt \\
&=\int_0^T\left(\phi_2-\bar{\phi}_2\right)^2(\mu+\varepsilon)\,dt-\int_0^T\left(\phi_2-\bar{\phi}_2\right)\left(\phi_3-\bar{\phi}_3\right)\varepsilon dt.
\end{aligned}$$

Multiplying by $-1$, we have, letting $C_6=\varepsilon^u$,

$$\begin{aligned}
\frac{1}{2}(\phi_2(0)-\bar{\phi}_2(0))^2+\alpha\int_0^T(\phi_2-\bar{\phi}_2)^2dt &\le C_6\int_0^T(\phi_2-\bar{\phi}_2)^2+(\phi_3-\bar{\phi}_3)^2dt \\
&\le C_6\int_0^T\Phi(t)+\Psi(t)dt.
\end{aligned} \qquad (4.28)$$

From equation (4.9) we conclude that

$$\begin{aligned}
-\alpha e^{-\alpha t}\phi_3+e^{-\alpha t}\dot{\phi}_3 &= e^{-\alpha t}\phi_3(\mu+\gamma+\mathbb{T})+e^{-\alpha t}(\phi_1-\phi_2)\beta(\partial_2\varphi\left(e^{\alpha t}s,e^{\alpha t}n,e^{\alpha t}i\right) \\
&\quad+\partial_3\varphi\left(e^{\alpha t}s,e^{\alpha t}n,e^{\alpha t}i\right))-e^{-\alpha t}\phi_4(\gamma+\mathbb{T})-\kappa_1
\end{aligned}$$

and thus

$$-\alpha\phi_3 + \dot{\phi}_3 = \phi_3\left(\mu+\gamma+\mathbb{T}\right) + (\phi_1-\phi_2)\beta(\partial_2\varphi\left(e^{\alpha t}s, e^{\alpha t}n, e^{\alpha t}i\right) + \partial_3\varphi\left(e^{\alpha t}s, e^{\alpha t}n, e^{\alpha t}i\right)) - \phi_4(\gamma+\mathbb{T}) - e^{\alpha t}\kappa_1.$$

Subtracting from the above equation the corresponding barred equation we obtain

$$\begin{aligned}
&- \alpha\phi_3 + \dot{\phi}_3 + \alpha\bar{\phi}_3 - \dot{\bar{\phi}}_3 \\
&= \phi_3\left(\mu+\gamma+\mathbb{T}\right) + (\phi_1-\phi_2)\beta\left(\partial_2\varphi\left(e^{\alpha t}s, e^{\alpha t}n, e^{\alpha t}i\right) + \partial_3\varphi\left(e^{\alpha t}s, e^{\alpha t}n, e^{\alpha t}i\right)\right) \\
&\quad - \phi_4(\gamma+\mathbb{T}) - e^{\alpha t}\kappa_1 - \bar{\phi}_3\left(\mu+\gamma+\bar{\mathbb{T}}\right) \\
&\quad - (\bar{\phi}_1-\bar{\phi}_2)\beta\left(\partial_2\varphi\left(e^{\alpha t}s, e^{\alpha t}n, e^{\alpha t}i\right) + \partial_3\varphi\left(e^{\alpha t}s, e^{\alpha t}n, e^{\alpha t}i\right)\right) + \bar{\phi}_4(\gamma+\bar{\mathbb{T}}) + e^{\alpha t}\kappa_1 \\
&= \beta\left[\phi_1\left(\partial_2\varphi\left(e^{\alpha t}s, e^{\alpha t}n, e^{\alpha t}i\right) + \partial_3\varphi\left(e^{\alpha t}s, e^{\alpha t}n, e^{\alpha t}i\right)\right)\right. \\
&\quad \left.-\bar{\phi}_1\left(\partial_2\varphi\left(e^{\alpha t}\bar{s}, e^{\alpha t}\bar{n}, e^{\alpha t}\bar{i}\right) + \partial_3\varphi\left(e^{\alpha t}\bar{s}, e^{\alpha t}\bar{n}, e^{\alpha t}\bar{i}\right)\right)\right] \\
&\quad - \beta\left[\phi_2\left(\partial_2\varphi\left(e^{\alpha t}s, e^{\alpha t}n, e^{\alpha t}i\right) + \partial_3\varphi\left(e^{\alpha t}s, e^{\alpha t}n, e^{\alpha t}i\right)\right)\right. \\
&\quad \left.-\bar{\phi}_2\left(\partial_2\varphi\left(e^{\alpha t}\bar{s}, e^{\alpha t}\bar{n}, e^{\alpha t}\bar{i}\right) + \partial_3\varphi\left(e^{\alpha t}\bar{s}, e^{\alpha t}\bar{n}, e^{\alpha t}\bar{i}\right)\right)\right] \\
&\quad + (\phi_3-\bar{\phi}_3)\left(\mu+\gamma\right) + \phi_3\mathbb{T} - \bar{\phi}_3\bar{\mathbb{T}} - (\phi_4-\bar{\phi}_4)\gamma - (\phi_4\mathbb{T} - \bar{\phi}_4\bar{\mathbb{T}}).
\end{aligned}$$

Multiplying by $\phi_3 - \bar{\phi}_3$ and integrating from 0 to $T$ we get

$$\begin{aligned}
&- \frac{1}{2}(\phi_3(0)-\bar{\phi}_3(0))^2 - \alpha\int_0^T(\phi_3-\bar{\phi}_3)^2dt \\
&= \int_0^T \beta(\phi_3-\bar{\phi}_3)\left[\phi_1\left(\partial_2\varphi\left(e^{\alpha t}s, e^{\alpha t}n, e^{\alpha t}i\right) + \partial_3\varphi\left(e^{\alpha t}s, e^{\alpha t}n, e^{\alpha t}i\right)\right)\right. \\
&\quad \left.-\bar{\phi}_1\left(\partial_2\varphi\left(e^{\alpha t}\bar{s}, e^{\alpha t}\bar{n}, e^{\alpha t}\bar{i}\right) + \partial_3\varphi\left(e^{\alpha t}\bar{s}, e^{\alpha t}\bar{n}, e^{\alpha t}\bar{i}\right)\right)\right] dt \\
&\quad - \int_0^T \beta(\phi_3-\bar{\phi}_3)\left[\phi_2\left(\partial_2\varphi\left(e^{\alpha t}s, e^{\alpha t}n, e^{\alpha t}i\right) + \partial_3\varphi\left(e^{\alpha t}s, e^{\alpha t}n, e^{\alpha t}i\right)\right)\right. \\
&\quad \left.-\bar{\phi}_2\left(\partial_2\varphi\left(e^{\alpha t}\bar{s}, e^{\alpha t}\bar{n}, e^{\alpha t}\bar{i}\right) + \partial_3\varphi\left(e^{\alpha t}\bar{s}, e^{\alpha t}\bar{n}, e^{\alpha t}\bar{i}\right)\right)\right] dt \\
&\quad + \int_0^T\left(\mu+\gamma\right)\left(\phi_3-\bar{\phi}_3\right)^2dt + \int_0^T(\phi_3-\bar{\phi}_3)(\phi_3\mathbb{T}-\bar{\phi}_3\bar{\mathbb{T}})dt \\
&\quad - \int_0^T\gamma(\phi_3-\bar{\phi}_3)(\phi_4-\bar{\phi}_4)dt - \int_0^T(\phi_3-\bar{\phi}_3)(\phi_4\mathbb{T}-\bar{\phi}_4\bar{\mathbb{T}})dt.
\end{aligned} \tag{4.29}$$

Multiplying (4.29) by $-1$, we obtain

$$
\begin{aligned}
&\frac{1}{2}(\phi_3(0)-\bar{\phi}_3(0))^2+\alpha\int_0^T(\phi_3-\bar{\phi}_3)^2dt\\
&\leq \beta^u\int_0^T|\phi_3-\bar{\phi}_3|\left[|\phi_1\partial_2\varphi\left(e^{\alpha t}s,e^{\alpha t}n,e^{\alpha t}i\right)-\bar{\phi}_1\partial_2\varphi\left(e^{\alpha t}\bar{s},e^{\alpha t}\bar{n},e^{\alpha t}\bar{i}\right)|\right.\\
&\quad\left.+|\phi_1\partial_3\varphi\left(e^{\alpha t}s,e^{\alpha t}n,e^{\alpha t}i\right)-\bar{\phi}_1\partial_3\varphi\left(e^{\alpha t}\bar{s},e^{\alpha t}\bar{n},e^{\alpha t}\bar{i}\right)|\right]dt\\
&\quad+\beta^u\int_0^T|\phi_3-\bar{\phi}_3|\left[|\phi_2\partial_2\varphi\left(e^{\alpha t}s,e^{\alpha t}n,e^{\alpha t}i\right)-\bar{\phi}_2\partial_2\varphi\left(e^{\alpha t}\bar{s},e^{\alpha t}\bar{n},e^{\alpha t}\bar{i}\right)|\right.\\
&\quad\left.+|\phi_2\partial_3\varphi\left(e^{\alpha t}s,e^{\alpha t}n,e^{\alpha t}i\right)-\bar{\phi}_2\partial_3\varphi\left(e^{\alpha t}\bar{s},e^{\alpha t}\bar{n},e^{\alpha t}\bar{i}\right)|\right]dt\\
&\quad+\gamma^u\int_0^T|\phi_3-\bar{\phi}_3||\phi_4-\bar{\phi}_4|dt-\int_0^T(\phi_3-\bar{\phi}_3)(\phi_3\mathbb{T}-\bar{\phi}_3\bar{\mathbb{T}})dt\\
&\quad+\int_0^T(\phi_3-\bar{\phi}_3)(\phi_4\mathbb{T}-\bar{\phi}_4\bar{\mathbb{T}})dt\\
&\leq \beta^u\int_0^T|\phi_3-\bar{\phi}_3|\left[\phi_1^u(M_{21}^u e^{\alpha t}|s-\bar{s}|+M_{22}^u e^{\alpha t}|n-\bar{n}|+M_{23}^u e^{\alpha t}|i-\bar{i}|)\right.\\
&\quad+M_2^u|\phi_1-\bar{\phi}_1|\\
&\quad\left.+\phi_1^u(M_{31}^u e^{\alpha t}|s-\bar{s}|+M_{32}^u e^{\alpha t}|n-\bar{n}|+M_{33}^u e^{\alpha t}|i-\bar{i}|)+M_3^u|\phi_1-\bar{\phi}_1|\right]dt\\
&\quad+\beta^u\int_0^T|\phi_3-\bar{\phi}_3|\left[\phi_2^u(M_{21}^u e^{\alpha t}|s-\bar{s}|+M_{22}^u e^{\alpha t}|n-\bar{n}|+M_{23}^u e^{\alpha t}|i-\bar{i}|)\right.\\
&\quad+M_2^u|\phi_2-\bar{\phi}_2|\\
&\quad\left.+\phi_2^u(M_{31}^u e^{\alpha t}|s-\bar{s}|+M_{32}^u e^{\alpha t}|n-\bar{n}|+M_{33}^u e^{\alpha t}|i-\bar{i}|)+M_3^u|\phi_2-\bar{\phi}_2|\right]dt\\
&\quad+\gamma^u\int_0^T(\phi_3-\bar{\phi}_3)^2+(\phi_4-\bar{\phi}_4)^2dt-\int_0^T(\phi_3-\bar{\phi}_3)(\phi_3\mathbb{T}-\bar{\phi}_3\bar{\mathbb{T}})dt\\
&\quad+\int_0^T(\phi_3-\bar{\phi}_3)(\phi_4\mathbb{T}-\bar{\phi}_4\bar{\mathbb{T}})dt
\end{aligned}
$$

and therefore

$$
\begin{aligned}
&\frac{1}{2}(\phi_3(0)-\bar{\phi}_3(0))^2+\alpha\int_0^T(\phi_3-\bar{\phi}_3)^2dt\\
&\leq \beta^u\phi_1^u e^{\alpha T}\Big((M_{21}^u+M_{31}^u)\int_0^T(\phi_3-\bar{\phi}_3)^2+(s-\bar{s})^2dt\\
&\quad+(M_{22}^u+M_{32}^u)\int_0^T(\phi_1-\bar{\phi}_1)^2+(n-\bar{n})^2dt+(M_{23}+M_{33})^u\int_0^T(\phi_3-\bar{\phi}_3)^2\\
&\quad+(i-\bar{i})^2dt\Big)+\beta^u(M_2^u+M_3^u)\int_0^T(\phi_3-\bar{\phi}_3)^2+(\phi_1-\bar{\phi}_1)^2dt\\
&\quad+\beta^u\phi_2^u e^{\alpha T}\Big((M_{21}^u+M_{31}^u)\int_0^T(\phi_3-\bar{\phi}_3)^2+(s-\bar{s})^2dt\\
&\quad+(M_{22}^u+M_{32}^u)\int_0^T(\phi_3-\bar{\phi}_3)^2+(n-\bar{n})^2dt\\
&\quad+(M_{23}+M_{33})^u\int_0^T(\phi_3-\bar{\phi}_3)^2+(i-\bar{i})^2dt\Big)\\
&\quad+\beta^u(M_2^u+M_3^u)\int_0^T(\phi_3-\bar{\phi}_3)^2+(\phi_2-\bar{\phi}_2)^2dt\\
&\quad+\gamma^u\int_0^T(\phi_3-\bar{\phi}_3)^2+(\phi_4-\bar{\phi}_4)^2dt+\int_0^T K_7[(\mathbb{T}-\bar{\mathbb{T}}|)^2+2(\phi_3-\bar{\phi}_3)^2]dt\\
&\quad+\int_0^T K_8[(\mathbb{T}-\bar{\mathbb{T}})^2+(\phi_4-\bar{\phi}_4)^2+(\phi_3-\bar{\phi}_3)^2]dt\\
&\leq C_7\int_0^T(s-\bar{s})^2+(e-\bar{e})^2+(i-\bar{i})^2+(r-\bar{r})^2\\
&\quad+(\phi_1-\bar{\phi}_1)^2+(\phi_2-\bar{\phi}_2)^2+(\phi_3-\bar{\phi}_3)^2+(\phi_4-\bar{\phi}_4)^2dt\\
&\quad+(K_7+K_8)\int_0^T(\mathbb{T}-\bar{\mathbb{T}})^2dt,
\end{aligned}
\tag{4.30}
$$

where $K_7$ and $K_8$ depends on the bounds for $\bar{\phi}_3$, $\bar{\phi}_4$ and $\mathbb{T}$ and

$$
\begin{aligned}
C_7=\;&\beta^u\phi_1^u e^{\alpha T}\left((M_{21}^u+M_{31}^u)+2(M_{22}^u+M_{32}^u)+(M_{23}+M_{33})^u\right)\\
&+\beta^u\phi_2^u e^{\alpha T}\left((M_{21}^u+M_{31}^u)+2(M_{22}^u+M_{32}^u)+(M_{23}+M_{33})^u\right)\\
&+2\beta^u(M_2^u+M_3^u)+\gamma^u+2K_7+K_8.
\end{aligned}
$$

Now, by (4.30) and (4.17) we obtain

$$
\begin{aligned}
\frac{1}{2}(\phi_3(0)-\bar{\phi}_3(0))^2+\alpha\int_0^T(\phi_3-\bar{\phi}_3)^2dt\leq C_7\int_0^T(s-\bar{s})^2+(e-\bar{e})^2\\
+(i-\bar{i})^2+(r-\bar{r})^2+(\phi_1-\bar{\phi}_1)^2+(\phi_2-\bar{\phi}_2)^2+(\phi_3-\bar{\phi}_3)^2\\
+(\phi_4-\bar{\phi}_4)^2dt+(K_7+K_8)C_{10}\int_0^T(i-\bar{i})^2+(\phi_3-\bar{\phi}_3)^2+(\phi_4-\bar{\phi}_4)^2dt
\end{aligned}
$$

and thus

$$\begin{aligned}
&\frac{1}{2}(\phi_3(0)-\bar{\phi}_3(0))^2+\alpha\int_0^T(\phi_3-\bar{\phi}_3)^2dt \\
&\le (C_7+(K_7+K_8)C_{10})\int_0^T(s-\bar{s})^2+(e-\bar{e})^2+(i-\bar{i})^2+(r-\bar{r})^2 \\
&\quad+(\phi_1-\bar{\phi}_1)^2+(\phi_2-\bar{\phi}_2)^2+(\phi_3-\bar{\phi}_3)^2+(\phi_4-\bar{\phi}_4)^2dt \\
&\le (C_7+(K_7+K_8)C_{10})\int_0^T\Phi(t)+\Psi(t)dt.
\end{aligned} \tag{4.31}$$

From equation (4.10) we conclude that $-\alpha e^{-\alpha t}\phi_4+e^{-\alpha t}\dot{\phi}_4=e^{-\alpha t}\phi_4(\mu+\eta)-e^{-\alpha t}\phi_1\eta$ and thus $-\alpha\phi_4+\dot{\phi}_4=\phi_4(\mu+\eta)-\phi_1\eta$. Subtracting from the above equation the corresponding barred equation, we obtain

$$-\alpha\phi_4+\dot{\phi}_4+\alpha\bar{\phi}_4-\dot{\bar{\phi}}_4=\left(\phi_4-\bar{\phi}_4\right)(\mu+\eta)-\left(\phi_1-\bar{\phi}_1\right)\eta.$$

Multiplying by $\phi_4-\bar{\phi}_4$ and integrating from 0 to $T$ we get

$$\begin{aligned}
&-\frac{1}{2}(\phi_4(0)-\bar{\phi}_4(0))^2-\alpha\int_0^T(\phi_4-\bar{\phi}_4)^2dt \\
&=\int_0^T\left(\phi_4-\bar{\phi}_4\right)^2(\mu+\eta)\,dt-\int_0^T\left(\phi_4-\bar{\phi}_4\right)\left(\phi_1-\bar{\phi}_1\right)\eta dt.
\end{aligned}$$

Multiplying by $-1$, we obtain

$$\begin{aligned}
\frac{1}{2}(\phi_4(0)-\bar{\phi}_4(0))^2+\alpha\int_0^T(\phi_4-\bar{\phi}_4)^2dt &\le \eta^u\int_0^T|\phi_4-\bar{\phi}_4||\phi_1-\bar{\phi}_1|dt \\
&\le C_8\int_0^T(\phi_1-\bar{\phi}_1)^2+(\phi_4-\bar{\phi}_4)^2dt \\
&\le C_8\int_0^T\Phi(t)+\Psi(t)dt,
\end{aligned} \tag{4.32}$$

where $C_8=\eta^u$.

We will now obtain the bounds for $\left(\mathbb{V}-\bar{\mathbb{V}}\right)^2$ and $\left(\mathbb{T}-\bar{\mathbb{T}}\right)^2$ announced in (4.16) and (4.17). We have

$$\begin{aligned}
\left(\mathbb{V}-\bar{\mathbb{V}}\right)^2 &= \left(\frac{e^{\alpha t}s}{2\kappa_3}(e^{-\alpha t}\phi_1-e^{-\alpha t}\phi_4)-\frac{e^{\alpha t}\bar{s}}{2\kappa_3}(e^{-\alpha t}\bar{\phi}_1-e^{-\alpha t}\bar{\phi}_4)\right)^2 \\
&= \frac{1}{4\kappa_3^2}(s\phi_1-s\phi_4-\bar{s}\bar{\phi}_1+\bar{s}\bar{\phi}_4)^2 \\
&= \frac{1}{4\kappa_3^2}(s(\phi_1-\bar{\phi}_1)+(s-\bar{s})\bar{\phi}_1+s(\bar{\phi}_4-\phi_4)+(-s+\bar{s})\bar{\phi}_4)^2
\end{aligned}$$

and thus

$$
\begin{aligned}
&\left(\mathbb{V}-\bar{\mathbb{V}}\right)^2\\
&=\frac{1}{4\kappa_3^2}((s(\phi_1-\bar{\phi}_1)+(s-\bar{s})\bar{\phi}_1)^2+2(s(\phi_1-\bar{\phi}_1)+(s-\bar{s})\bar{\phi}_1)\times\\
&\quad\times(s(\bar{\phi}_4-\phi_4)+(\bar{s}-s)\bar{\phi}_4)+(s(\bar{\phi}_4-\phi_4)+(\bar{s}-s)\bar{\phi}_4)^2)\\
&=\frac{1}{4\kappa_3^2}(s^2(\phi_1-\bar{\phi}_1)^2+2s\bar{\phi}_1(s-\bar{s})(\phi_1-\bar{\phi}_1)+\bar{\phi}_1^2(s-\bar{s})^2+2s^2(\phi_1-\bar{\phi}_1)(\bar{\phi}_4-\phi_4)\\
&\quad+2s\bar{\phi}_1(s-\bar{s})(\bar{\phi}_4-\phi_4)+2\bar{\phi}_4 s(s-\bar{s})(\bar{\phi}_1-\phi_1)-2\bar{\phi}_1\bar{\phi}_4(s-\bar{s})^2\\
&\quad+s^2(\bar{\phi}_4-\phi_4)^2+2\bar{\phi}_4 s(\bar{\phi}_4-\phi_4)(\bar{s}-s)+\bar{\phi}_4^2(\bar{s}-s)^2)\\
&\le\frac{1}{4\kappa_3^2}((4s\bar{\phi}_1+\bar{\phi}_1^2+4s\bar{\phi}_4+\bar{\phi}_4^2)(s-\bar{s})^2+(3s^2+2s\bar{\phi}_1+2s\bar{\phi}_4)(\phi_1-\bar{\phi}_1)^2\\
&\quad+(3s^2+2s\bar{\phi}_1+2s\bar{\phi}_4)(\bar{\phi}_4-\phi_4)^2)\\
&\le C_9[(s-\bar{s})^2+(\phi_1-\bar{\phi}_1)^2+(\phi_4-\bar{\phi}_4)^2]
\end{aligned}
\tag{4.33}
$$

where

$$C_9=\frac{1}{4\kappa_2^2}(4\max\{s\}\max\{\bar{\phi}_1,\bar{\phi}_4\}+\max\{\bar{\phi}_1\}^2+\max\{\bar{\phi}_4\}^2+3\max\{s\}^2).$$

Analogously we obtain

$$
\begin{aligned}
&\left(\mathbb{T}-\bar{\mathbb{T}}\right)^2\\
&=(\frac{e^{\alpha t}i}{2\kappa_2}(e^{-\alpha t}\phi_3-e^{-\alpha t}\phi_4)-\frac{e^{\alpha t}\bar{i}}{2\kappa_2}(e^{-\alpha t}\bar{\phi}_3-e^{-\alpha t}\bar{\phi}_4))^2\\
&=\frac{1}{4\kappa_2^2}(i\phi_3-i\phi_4-\bar{i}\bar{\phi}_3+\bar{i}\bar{\phi}_4)^2\\
&=\frac{1}{4\kappa_2^2}(i(\phi_3-\bar{\phi}_3)+(i-\bar{i})\bar{\phi}_3+i(\bar{\phi}_4-\phi_4)+(-i+\bar{i})\bar{\phi}_4)^2\\
&=\frac{1}{4\kappa_2^2}((i(\phi_3-\bar{\phi}_3)+(i-\bar{i})\bar{\phi}_3)^2+2(i(\phi_3-\bar{\phi}_3)+(i-\bar{i})\bar{\phi}_3)(i(\bar{\phi}_4-\phi_4)+(\bar{i}-i)\bar{\phi}_4)\\
&\quad+(i(\bar{\phi}_4-\phi_4)+(\bar{i}-i)\bar{\phi}_4)^2)\\
&=\frac{1}{4\kappa_2^2}(i^2(\phi_3-\bar{\phi}_3)^2+2i\bar{\phi}_3(i-\bar{i})(\phi_3-\bar{\phi}_3)+\bar{\phi}_3^2(i-\bar{i})^2+2i^2(\phi_3-\bar{\phi}_3)(\bar{\phi}_4-\phi_4)\\
&\quad+2i\bar{\phi}_3(i-\bar{i})(\bar{\phi}_4-\phi_4)+2\bar{\phi}_4 i(i-\bar{i})(\bar{\phi}_3-\phi_3)-2\bar{\phi}_3\bar{\phi}_4(i-\bar{i})^2\\
&\quad+i^2(\bar{\phi}_4-\phi_4)^2+2\bar{\phi}_4 i(\bar{\phi}_4-\phi_4)(\bar{i}-i)+\bar{\phi}_4^2(\bar{i}-i)^2)\\
&\le\frac{1}{4\kappa_2^2}((4i\bar{\phi}_3+\bar{\phi}_3^2+4i\bar{\phi}_4+\bar{\phi}_4^2)(i-\bar{i})^2+(3i^2+2i\bar{\phi}_3+2i\bar{\phi}_4)(\phi_3-\bar{\phi}_3)^2\\
&\quad+(3i^2+2i\bar{\phi}_3+2i\bar{\phi}_4)(\bar{\phi}_4-\phi_4)^2)\\
&\le C_{10}[(i-\bar{i})^2+(\phi_3-\bar{\phi}_3)^2+(\phi_4-\bar{\phi}_4)^2],
\end{aligned}
\tag{4.34}
$$

where

$$C_{10} = \frac{1}{4\kappa_2^2}(4\max\{i\}\max\{\bar{\phi}_3, \bar{\phi}_4\} + \max\{\bar{\phi}_3\}^2 + \max\{\bar{\phi}_4\}^2 + 3\max\{i\}^2).$$

We have finally all the bounds needed to prove our result. Define

$$\Psi(t) = (s(t) - \bar{s}(t))^2 + (e(t) - \bar{e}(t))^2 + (i(t) - \bar{i}(t))^2 + (r(t) - \bar{r}(t))^2$$

and

$$\Phi(t) = (\phi_1(t) - \bar{\phi}_1(t))^2 + (\phi_2(t) - \bar{\phi}_2(t))^2 + (\phi_3(t) - \bar{\phi}_3(t))^2 + (\phi_4(t) - \bar{\phi}_4(t))^2.$$

and observe that $\Psi(t) \geq 0$ and $\Phi(t) \geq 0$ for all $t$.

Adding equations (4.18), (4.21), (4.22), (4.23), (4.27), (4.28), (4.31) and (4.32), we obtain for the sum of left-hand sides

$$\frac{1}{2}\Psi(T) + \frac{1}{2}\Phi(0) + \alpha \int_0^T \Psi(T) + \Phi(T)dt$$

and thus

$$\begin{aligned} &\frac{1}{2}[\Psi(T) + \Phi(0)] + \alpha \int_0^T \Psi(T) + \Phi(T)dt \\ &\leq \tilde{C} \int_0^T \Psi(T) + \Phi(T)dt + \hat{C}e^{\alpha T} \int_0^T \Psi(T) + \Phi(T)dt \end{aligned}$$

which is equivalent to

$$\frac{1}{2}[\Psi(T) + \Phi(0)] + (\alpha - \tilde{C} - \hat{C}e^{\alpha T}) \int_0^T \Psi(T) + \Phi(T)dt \leq 0. \tag{4.35}$$

We now choose $\alpha$ so that

$$\alpha > \tilde{C} + \hat{C}$$

and note that $\frac{\alpha - \tilde{C}}{\hat{C}} > 1$. Subsequently, we choose $T$ such that

$$T < \frac{1}{\alpha} \ln\left(\frac{\alpha - \tilde{C}}{\hat{C}}\right).$$

Then,

$$\alpha T < \ln\left(\frac{\alpha - \tilde{C}}{\hat{C}}\right) \quad \Rightarrow \quad e^{\alpha T} < \frac{\alpha - \tilde{C}}{\hat{C}}.$$

It follows that $\alpha - \tilde{C} - \hat{C}e^{\alpha T} > 0$, so inequality (4.35) can hold if and only if, for all $t \in [0, T]$, we have $s(t) = \bar{s}(t)$, $e(t) = \bar{e}(t)$, $i(t) = \bar{i}(t)$, $r(t) = \bar{r}(t)$, $\phi_1(t) = \bar{\phi}_1(t)$,

$\phi_2(t) = \bar{\phi}_2(t)$, $\phi_3(t) = \bar{\phi}_3(t)$ and $\phi_4(t) = \bar{\phi}_4(t)$. But this is equivalent to $S(t) = \bar{S}(t)$, $E(t) = \bar{E}(t)$, $I(t) = \bar{I}(t)$, $R(t) = \bar{R}(t)$, $p_1(t) = \bar{p}_1(t)$, $p_2(t) = \bar{p}_2(t)$, $p_3(t) = \bar{p}_3(t)$ and $p_4(t) = \bar{p}_4(t)$.

With this, the uniqueness of the optimal control is established. □

## 4.5 Numerical Simulation

In what follows, the incidence into the exposed class of susceptible individuals and the birth function $\Lambda(t)$ are

$$\beta(t)\varphi(S,N,I) = 0.56(1 - \text{per}\,\cos(2\pi t + 0.26))SI$$

and

$$\Lambda(t) = 0.05 + 0.05\,\text{per}\,\cos(2\pi t),$$

with per $\in [0,1[$. The remaining parameter functions – $\mu(t)$, $\eta(t)$, $\varepsilon(t)$ and $\gamma(t)$ – are assumed constant. The values for the several parameters in this section were taken from [39] and [41] and are presented in Table 4.1. As mentioned before, the optimal control system consists in the states equations (the first four equations on system (3)), the initial conditions, the adjoint equations (4.7) to (4.10) and the transversality conditions (4.11) with the optimal equations (4.12) and (4.13) substituted into the state and adjoint equations. The state equations system and the adjoint equations system were solved numerically using the solver `ode45` of MATLAB, an explicit $4^{th}$ and $5^{th}$ order Runge-Kutta method. The state system is solved with the initial conditions of Table 4.1. The adjoint system is solved, as the previous system, after making the following change of variable:

$$t' = t_f - t. \tag{4.36}$$

The procedure can be described by the following algorithm:

Step 1: Let $i = 0$, $\mathbb{V}_i = 0$ and $\mathbb{T}_i = 0$;

Step 2: Let $i = i + 1$. The variables $S_i$, $E_i$, $I_i$ and $R_i$ are determined using the initial conditions and the vectors $\mathbb{V}_{i-1}$ and $\mathbb{T}_{i-1}$;

Step 3:
  i) Apply change of variable (4.36) to the adjoint system, to the state variables and to the control variables;
  ii) The adjoint variables $p_{1,i}$, $p_{2,i}$, $p_{3,i}$ and $p_{4,i}$ are computed solving the resulting adjoint system;

Step 4: Variables $\mathbb{V}_i$, $\mathbb{T}_i$ are updated according with formulas (4.12) and (4.13);

Step 5: If the relative error is smaller than a given tolerance ($< 1\%$) for all the variables, the algorithm stops.
Otherwise go to Step 2.

In table 4.1 we presents the values for the parameters of our system:

Table 4.1: Values of parameters used

| Name | Description | Value |
|---|---|---|
| $S_0$ | Initial susceptible population | 0.98 |
| $E_0$ | Initial exposed population | 0 |
| $I_0$ | Initial infective population | 0.01 |
| $R_0$ | Initial recovered population | 0.01 |
| $\mu$ | natural deaths | 0.05 |
| $\varepsilon$ | infectivity rate | 0.03 |
| $\gamma$ | rate of recovery | 0.05 |
| $\eta$ | rate of loss of immunity | 0.041 |
| $k_1$ | weight for number infected | 1 |
| $k_2$ | weight for treatment | 0.01 |
| $k_3$ | weight for vaccination | 0.01 |
| $\tau_{max}$ | maximum rate of treatment | 0.1 |
| $v_{max}$ | maximum rate of vaccination | 0.4 |

In each one of the figures 4.1 to 4.5, we present two plots side by side in order to be able to compare the controlled and uncontrolled situations as well as the autonomous and the periodic situations.

The behavior of our optimal control model with $per = 0$ (autonomous case) and $per = 0.8$, in both the controlled and the uncontrolled case, is represented in figure 4.1 and figure 4.2. We can observe that, if we apply treatment and vaccination (controlled case), the number of exposed and infected individuals is significatively lower, as expected. It can be seen that the susceptible and recovered classes have very different behavior in the controlled and uncontrolled situations. Additionally, we observe that the variation of both classes in the uncontrolled case is not significant.

In figure 4.3 and figure 4.4, we have the same trajectories as in figure 4.1 and figure 4.2. In these figures we can observe the effect of the periodicity of $\Lambda(t)$ and $\beta(t)$ in the different classes. The effect is perceptible in susceptible and exposed classes, since the periodic functions are present in these classes. With these results, we conjecture that the periodicity effect is "softened" in the transition between classes.

In figure 4.5 are represented the trajectories of treated individuals (left side) and of vaccinated individuals (right side). According to the optimal conditions, both trajectories go to zero when $t \to t_{final} = 25$. The periodicity effect is perceptible in the vaccinated variable, consequence of the fact that vaccination takes place in the susceptible class. Treatment occurs in the infective class and, as we have seen, in

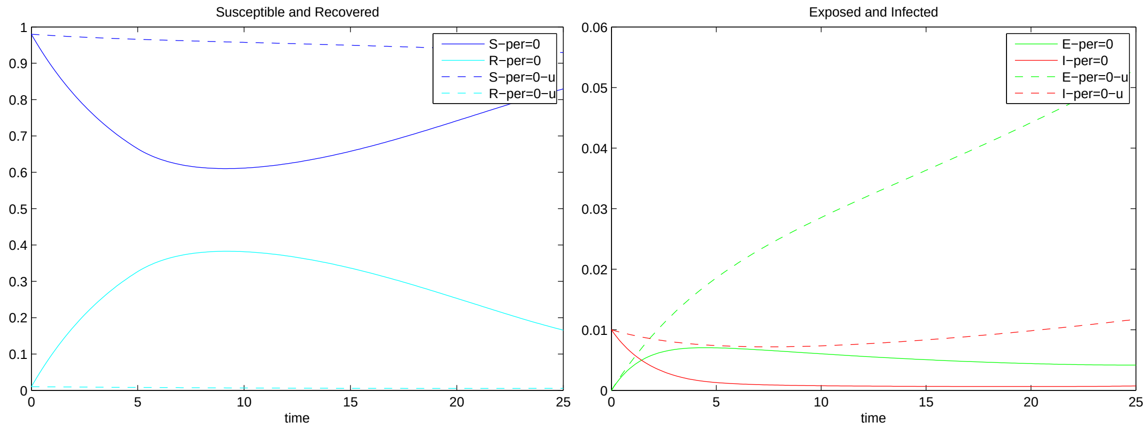


Figure 4.1: SEIRS model with $per = 0$: controlled and uncontrolled case.

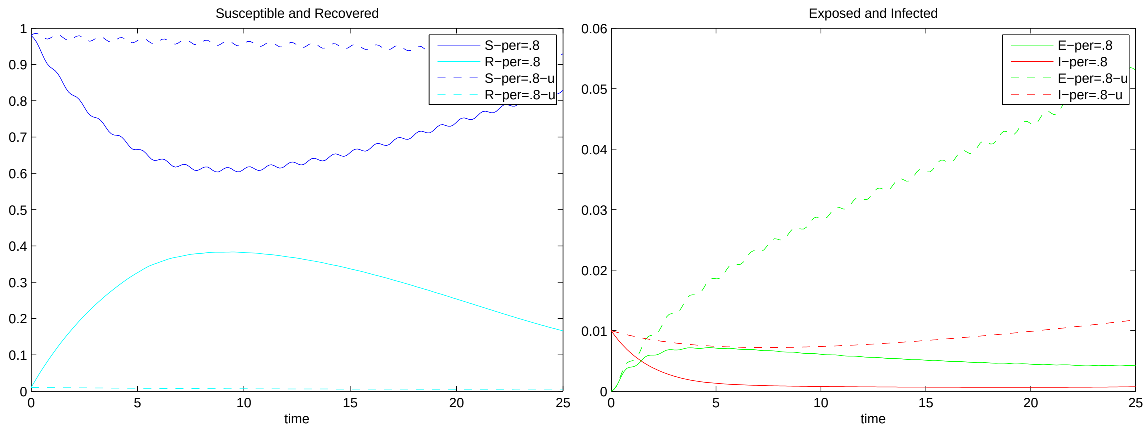


Figure 4.2: SEIRS model with $per = 0.8$: controlled and uncontrolled case.

this class the periodicity is not perceptible. As a consequence, periodicity it is only slightly perceptible in the treatment variable.

From figure 4.6 to figure 4.9, we present the behavior of infected, treated and vaccinated classes when we varied the parameters $\mu$, $\gamma$, $\varepsilon$ and $\eta$, respectively, maintaining, in each case, the initial values and the other parameters. In all figures we varied the respective parameter ($\mu$, $\gamma$, $\varepsilon$ and $\eta$ ) from 0 to 0.1 in steps of length 0.01.

Referring to figure 4.6, where the variation of $\mu$ is analysed, we can say that the effect of periodicity is more perceptible in the vaccinated variable than in the treatment variable for the reasons explained above. In the infected class, for low values of $\mu$ (low mortality) we can observe that the infected class increases. This is justified by the difference between birth and death.

Concerning figure 4.7, where we can observe the effect of the variation of $\gamma$, the effect of periodicity is analogous to the previous situation. The bigger the value of $\gamma$ the more the infected individuals recover and thus the faster the infected class decreases.

In figure 4.8, one can see the effect of the variation of $\varepsilon$. The effect of periodicity in this case is analogous to the effect of periodicity in the previous situations. When

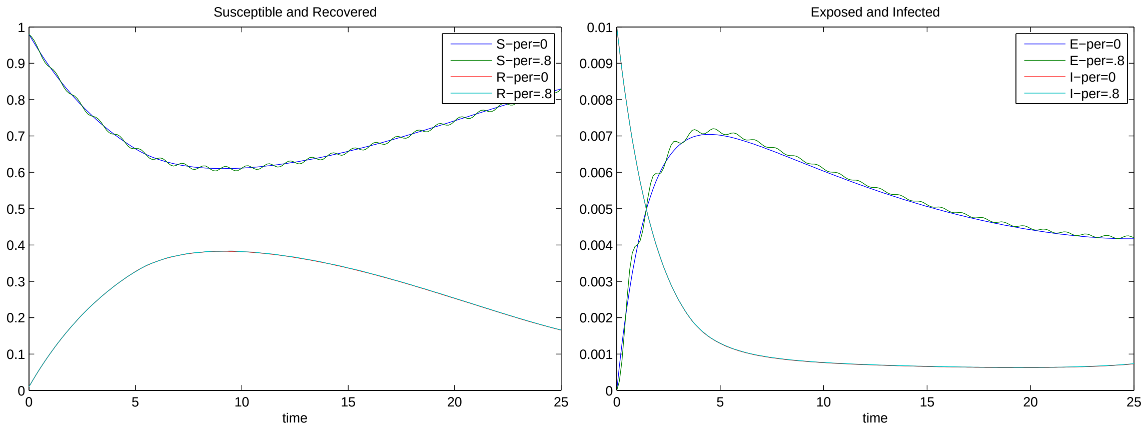


Figure 4.3: SEIRS model for controlled case: $per = 0$ and $per = 0.8$.

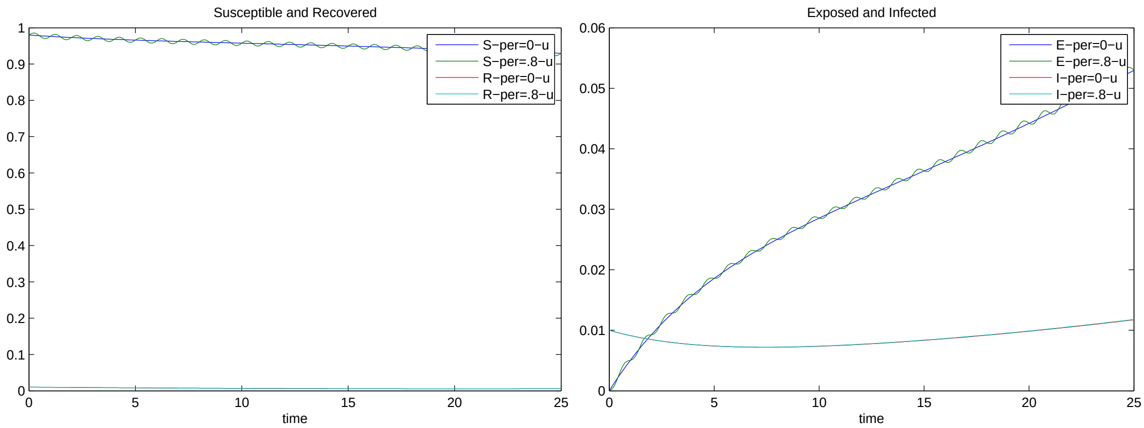


Figure 4.4: SEIRS model for uncontrolled case: $per = 0$ and $per = 0.8$.

we have a high value of $\varepsilon$, we have a faster transition of exposed individuals to the infected class and this is the reason why we can observe in figure 4.8 that increasing the value of $\varepsilon$ leads to an increase in the infected class.

Finally, in figure 4.9 the variation of $\eta$ is highlighted. We can conclude that the periodicity effect is similar to the previous considered scenarios, more perceptible in some situations that in others. The variation of $\eta$ is the one that less influences the behavior of the three variables considered in figure 4.9.

It is worth noting that, in the situations considered and range of parameters considered the experiments, maintaining all other parameters constant, the variation of $per$ has a very small effect on the obtained cost. Namely, we saw numerically that

$$\left| \mathcal{J}\left(I, \mathbb{T}, \mathbb{V}\right)\Big|_{per=v_1} - \mathcal{J}\left(I, \mathbb{T}, \mathbb{V}\right)\Big|_{per=v_2} \right| \leqslant 0.000329537,$$

for $v_1, v_2 \in \{0, 0.8\}$, where $\mathcal{J}\left(I, \mathbb{T}, \mathbb{V}\right)\Big|_{per=v_i}$, $i = 1, 2$, is the obtained total cost for two of our control problems differing only in the parameter $per$.

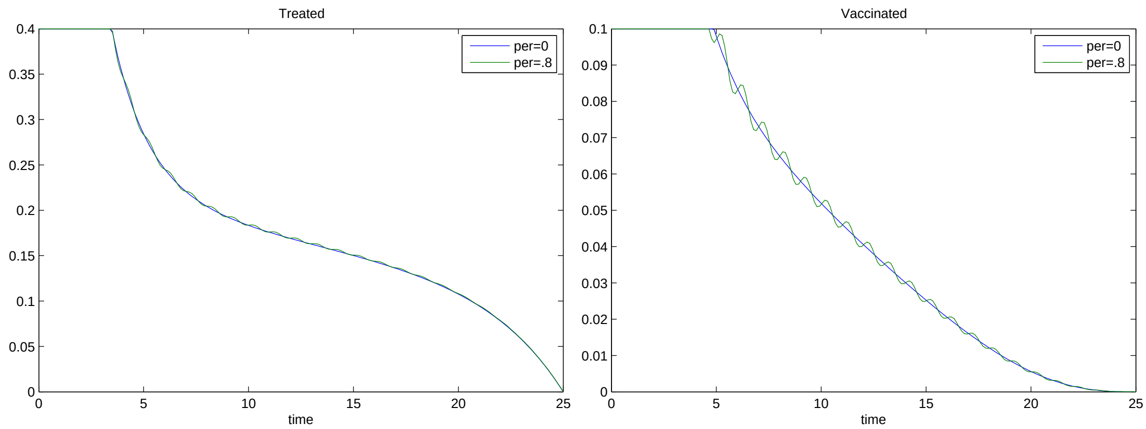


Figure 4.5: Treated and Vaccinated: $per = 0$ and $per = 0.8$.

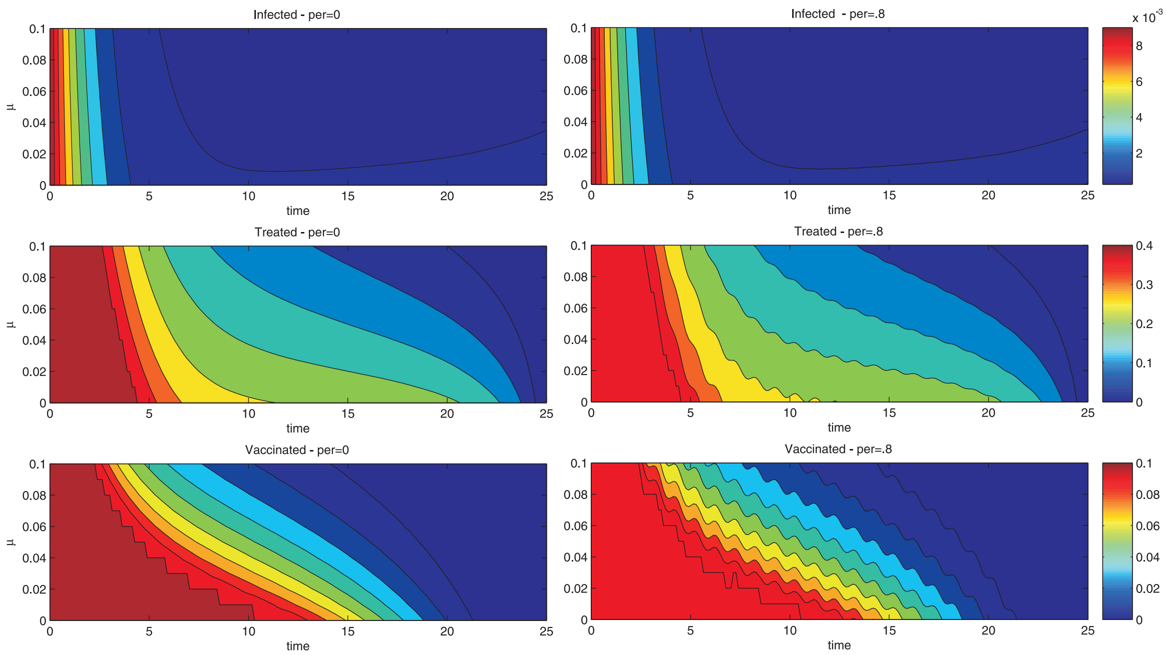


Figure 4.6: Infected, Treated and Vaccinated with the variation of $\mu$ from 0 to 0.1

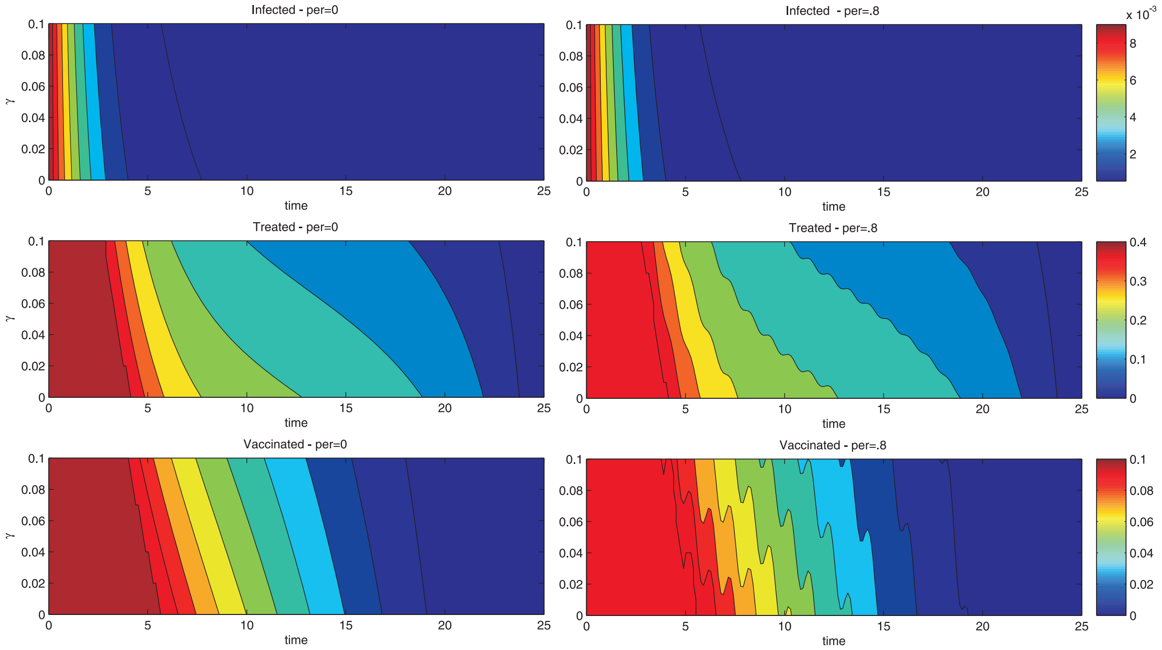


Figure 4.7: Infected, Treated and Vaccinated with the variation of $\gamma$ from 0 to 0.1

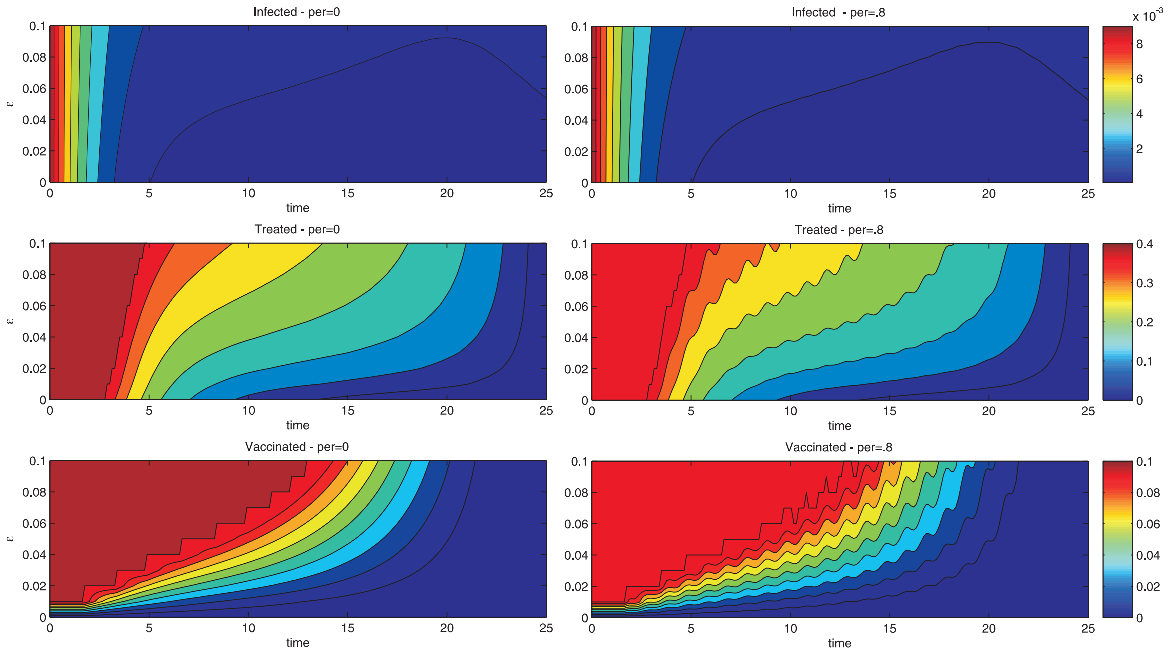


Figure 4.8: Infected, Treated and Vaccinated with the variation of $\varepsilon$ from 0 to 0.1

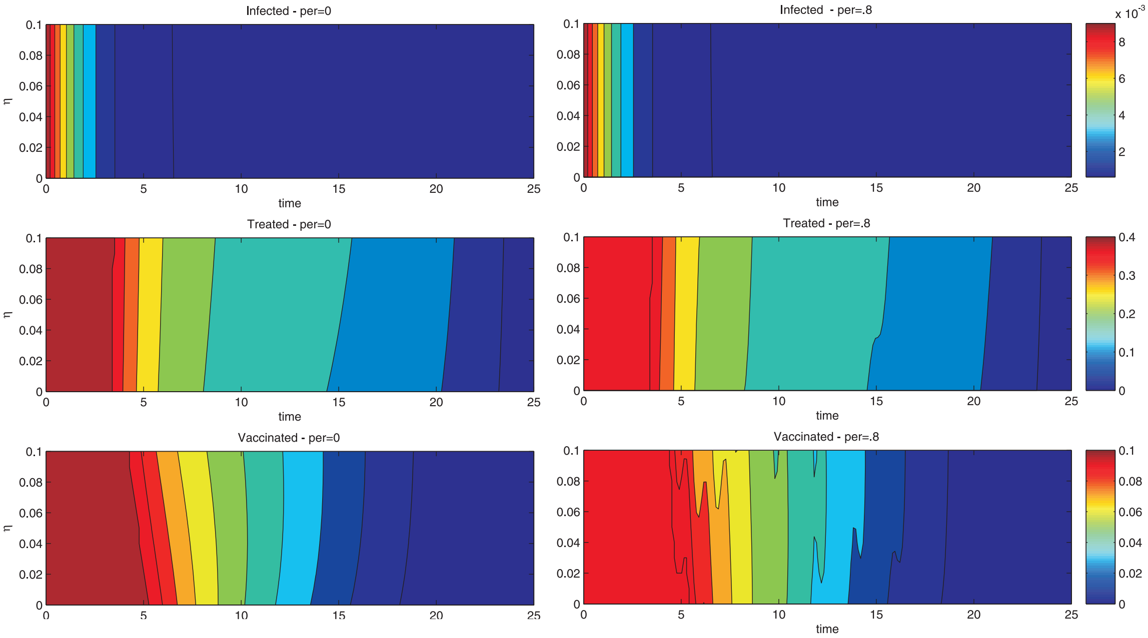


Figure 4.9: Infected, Treated and Vaccinated with the variation of $\eta$ from 0 to 0.1

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# Appendix A

## Attachments

### A.1 Matlab Code for Figures in Chapter 1

Figures 1.1, 1.2 and 1.3

```
clear all

global L B a u eta e g

    format short

    t=0

    L= 2;
    B=5.9;
    a=0;
    u= 2;
    eta= 0;
    e= 1;
    g= 0.02;

    S0=.1
    E0=.1
    I0=.1
    R0=.1
    OPTIONS=odeset('AbsTol',1e-10);
    w0=[S0,E0,I0,R0];
    [t,w]=ode113('sistema',[0,400],w0,OPTIONS);
    S=w(:,1); E=w(:,2); I=w(:,3); R=w(:,4);
    S1=S; E1=E; I1=I; R1=R;
    t1=t;

    for j=1 : length(t)
        aux_i(j)=0;
        aux_s(j)=1;
    end

    S0=.08
    E0=.07
    I0=.12
    R0=.13
    OPTIONS=odeset('AbsTol',1e-10);
    w0=[S0,E0,I0,R0];
    [t,w]=ode113('sistema',[0,400],w0,OPTIONS);
    S=w(:,1); E=w(:,2); I=w(:,3); R=w(:,4);
    S2=S; E2=E; I2=I; R2=R;
    t2=t;

    S0=1.99
    E0=.09
    I0=.05
    R0=.25
    OPTIONS=odeset('AbsTol',1e-10);
    w0=[S0,E0,I0,R0];
    [t,w]=ode113('sistema',[0,400],w0,OPTIONS);
    S=w(:,1); E=w(:,2); I=w(:,3); R=w(:,4);
    S3=S; E3=E; I3=I; R3=R;
    t3=t;

    figure
    plot(t1,S1,'k',t1,E1,'k--',t1,I1,'k.')
    axis ([0,5,0,2])
    xlabel ('t');
    legend ('S(t)','E(t)','I(t)')
    hold on
```

```
plot(t2,S2,'r',t2,E2,'r--',t2,I2,'r.')
hold on
plot(t3,S3,'c',t3,E3,'c--',t3,I3,'c.')

figure
plot(E1,I1,'k')
xlabel ('E(t)'); ylabel ('I(t)','Rotation',0.0)
hold on
plot(E2,I2,'r')
hold on
plot(E3,I3,'c')

figure
plot(S1,I1,'k')
xlabel ('S(t)'); ylabel ('I(t)','Rotation',0.0)
hold on
plot(S2,I2,'r')
hold on
plot(S3,I3,'c')

figure
plot3(S1,E1,I1,'k')
axis ([0,2,0,.15,0,.12])
xlabel ('S'); ylabel ('E'); zlabel ('I')
box on
hold on
plot3(S2,E2,I2,'r')
hold on
plot3(S3,E3,I3,'c')

figure
plot(t1,S1,'k')
title ('Susceptible')
xlabel ('t');
ylabel ('S','Rotation',0.0)
axis ([0,50,0,2])
hold on
plot(t2,S2,'r')
hold on
plot(t3,S3,'c')
hold on
plot(t1,aux_s,'--','Color',[.75 .75 .75])

figure
plot(t1,I1,'k')
title ('Infected')
xlabel ('t')
ylabel ('I','Rotation',0.0)
axis ([0,50,-0.02,0.12])
hold on
plot(t2,I2,'r')
hold on
plot(t3,I3,'c')
hold on
plot(t1,aux_i,'--','Color',[.75 .75 .75])
```

```
clear all

global L B a u eta e g

    format short

    t=0

    L= 2;
    B=6.9;
    a=0;;
    u= 2;
    eta= 0;
    e= 1;
    g= 0.02;

    S0=.1
    E0=.1
    I0=.1
    R0=.1
    OPTIONS=odeset('AbsTol',1e-10);
    w0=[S0,E0,I0,R0];
    [t,w]=ode113('sistema',[0,100],w0,OPTIONS);
    S=w(:,1); E=w(:,2); I=w(:,3); R=w(:,4);
    S1=S; E1=E; I1=I; R1=R;
    t1=t;

     for j=1 : length(t)
        aux_i(j)=.0402;
        aux_s(j)=.8782;
    end

    S0=.08
    E0=.07
    I0=.12
    R0=.13
    OPTIONS=odeset('AbsTol',1e-10);
    w0=[S0,E0,I0,R0];
    [t,w]=ode113('sistema',[0,100],w0,OPTIONS);
    S=w(:,1); E=w(:,2); I=w(:,3); R=w(:,4);
    S2=S; E2=E; I2=I; R2=R;
    t2=t;

    S0=1.99
    E0=.09
    I0=.05
    R0=.25
    OPTIONS=odeset('AbsTol',1e-10);
    w0=[S0,E0,I0,R0];
    [t,w]=ode113('sistema',[0,100],w0,OPTIONS);
    S=w(:,1); E=w(:,2); I=w(:,3); R=w(:,4);
    S3=S; E3=E; I3=I; R3=R;
    t3=t;

    figure
    plot(t1,S1,'k',t1,E1,'k--',t1,I1,'k.')
    axis ([0,5,0,2])
    xlabel ('t');
    legend ('S(t)','E(t)','I(t)')
    hold on
```

```
plot(t2,S2,'r',t2,E2,'r--',t2,I2,'r.')
hold on
plot(t3,S3,'c',t3,E3,'c--',t3,I3,'c.')

figure
plot(E1,I1,'k')
xlabel ('E(t)'); ylabel ('I(t)','Rotation',0.0)
hold on
plot(E2,I2,'r')
hold on
plot(E3,I3,'c')

figure
plot(S1,I1,'k')
xlabel ('S(t)'); ylabel ('I(t)','Rotation',0.0)
hold on
plot(S2,I2,'r')
hold on
plot(S3,I3,'c')

figure
plot3(S1,E1,I1,'k')
axis ([0,2,0.06,.18,0.03,.12])
xlabel ('S'); ylabel ('E'); zlabel ('I')
box on
hold on
plot3(S2,E2,I2,'r')
hold on
plot3(S3,E3,I3,'c')

figure
plot(t1,S1,'k')
title ('Susceptible')
xlabel ('t');
ylabel ('S','Rotation',0.0)
axis ([0,50,0,2])
hold on
plot(t2,S2,'r')
hold on
plot(t3,S3,'c')
hold on
plot(t1,aux_s,'--','Color',[.75 .75 .75])

figure
plot(t1,I1,'k')
title ('Infected')
xlabel ('t')
ylabel ('I','Rotation',0.0)
axis ([0,50,0.03,0.12])
hold on
plot(t2,I2,'r')
hold on
plot(t3,I3,'c')
hold on
plot(t1,aux_i,'--','Color',[.75 .75 .75])
```

```
function wprime=de4_rhs(t,w)
global L B a u eta e g

wprime=[L-B*(1+a*cos(2*pi*t))*w(1)*w(3)-u*w(1)+eta*w(4)
         B*(1+a*cos(2*pi*t))*w(1)*w(3)-(u+e)*w(2)
         e*w(2)-(u+g)*w(3)
         g*w(3)-(u+eta)*w(4)] ;
```

## A.2 Scilab Code for Figures in Chapter 2

Figures 2.1 and 2.2

```
clear;
mu=2; epsi=1; gamm=0.02; d=0; k=0;
function [dzdt]=f(t, z)
E=z(1)
I=z(2)
dzdt(1)=bet*(1+b*cos(2*%pi*t))*I-(mu+epsi*(1+d*cos(2*%pi*t)))*E
dzdt(2)=epsi*(1+d*cos(2*%pi*t))*E-(mu+gamm*(1+k*cos(2*%pi*t)))*I
endfunction
time=[0:0.01:1];
n=length(time);
blist=[-1:0.05:1];
for i=1:length(blist),
b=blist(i);
betmin=0.1;
betmax=10;
while betmax-betmin>0.000001,
bet=(betmax+betmin)/2;
sol1=ode([1;0],0,time,f);
column1=sol1(:,n);
sol2=ode([0;1],0,time,f);
column2=sol2(:,n);
MonodromyMatrix=[column1 column2];
FloquetMultiplier=max(real(spec([MonodromyMatrix])));
if FloquetMultiplier>1 then
betmax=bet;
else
betmin=bet;
end;
end;
threshold(i)=bet;
end;
plot2d(blist,threshold,rect=[min(blist) 0 max(blist) 15]);

t=linspace(-1,1,1000);
s=linspace(0,15,1000);
function z=epsi_ext(x, y),z=y*(1+abs(x))-6.06,endfunction
contour(t,s,epsi_ext,[0,0]);
function w=epsi_per(x, y),w=y-9*abs(x)-6.06,endfunction
contour(t,s,epsi_per,[0,0]);

xstring(0,2,"Extinction",0,0)
t=get("hdl")   //get the handle of the newly created object
t.font_foreground=1; // change font properties
t.font_size=3;
t.font_style=5;
t.text_box_mode = 'centered' ; // the text is now centered on [0,0.3].
t.alignment = 'center' ;
xstring(0,13,"Permanence",0,0)
t=get("hdl")   //get the handle of the newly created object
t.font_foreground=1; // change font properties
t.font_size=3;
t.font_style=5;
t.text_box_mode = 'centered' ; // the text is now centered on [0,1.8].
t.alignment = 'center' ;
```

```
clear;
mu=2; epsi=1; gamm=0.02; d=0; k=0;
function [dzdt]=f(t, z)
E=z(1)
I=z(2)
dzdt(1)=bet*(1+b*cos(2*%pi*t))*I-(mu+epsi*(1+d*cos(2*%pi*t)))*E
dzdt(2)=epsi*(1+d*cos(2*%pi*t))*E-(mu+gamm*(1+k*cos(2*%pi*t)))*I
endfunction
time=[0:0.01:1];
n=length(time);
blist=[-1:0.02:0];
for i=1:length(blist),
b=blist(i);
betmin=6;
betmax=6.4;
while betmax-betmin>0.0001,
bet=(betmax+betmin)/2;
sol1=ode([1;0],0,time,f);
column1=sol1(:,n);
sol2=ode([0;1],0,time,f);
column2=sol2(:,n);
MonodromyMatrix=[column1 column2];
FloquetMultiplier=max(real(spec([MonodromyMatrix])));
if FloquetMultiplier>1 then
betmax=bet;
else
betmin=bet;
end;
end;
threshold(i)=bet;
end;
plot2d(blist,threshold,rect=[min(blist) 6.05 max(blist) 6.4]);
appr=0.16501650-blist.^2/129.3576;
for j=1:length(blist),
approximate_beta_th(j)=1/appr(j);
end;
plot2d(blist,approximate_beta_th,style=5);
```

```
clear;
mu=2; epsi=1; bet=6.2; d=0; b=0;
function [dzdt]=f(t, z)
E=z(1)
I=z(2)
dzdt(1)=bet*(1+b*cos(2*%pi*t))*I-(mu+epsi*(1+d*cos(2*%pi*t)))*E
dzdt(2)=epsi*(1+d*cos(2*%pi*t))*E-(mu+gamm*(1+k*cos(2*%pi*t)))*I
endfunction
time=[0:0.001:1];
n=length(time);
galist=[-1:0.001:1];
for i=1:length(galist),
k=galist(i);
gammmin=0;
gammmax=0.1;
while gammmax-gammmin>0.001,
gamm=(gammmax+gammmin)/2;
sol1=ode([1;0],0,time,f);
column1=sol1(:,n);
sol2=ode([0;1],0,time,f);
column2=sol2(:,n);
MonodromyMatrix=[column1 column2];
FloquetMultiplier=max(real(spec([MonodromyMatrix])));
if FloquetMultiplier>1 then
gammmin=gamm;
else
gammmax=gamm;
end;
end;
threshold(i)=gamm;
end;
plot2d(galist,threshold,rect=[min(galist) 0 max(galist) 0.3]);

t=linspace(-1,1,100);
s=linspace(0,0.3,100);
function z=gamm_ext(x, y),z=(2+y)*(3-y*abs(x))-6.2,endfunction
contour(t,s,gamm_ext,[0,0])
function w=gamm_perm(x, y),w=y*(1+abs(x))-0.067,endfunction
contour(t,s,gamm_perm,[0,0])

xstring(0,0.15,"Extinction",0,0)
t=get("hdl")   //get the handle of the newly created object
t.font_foreground=1; // change font properties
t.font_size=3;
t.font_style=5;
t.text_box_mode = 'centered' ; // the text is now centered on [0,0.3].
t.alignment = 'center' ;
xstring(0,0.03,"Permanence",0,0)
t=get("hdl")   //get the handle of the newly created object
t.font_foreground=1; // change font properties
t.font_size=3;
t.font_style=5;
t.text_box_mode = 'centered' ; // the text is now centered on [0,1.8].
t.alignment = 'center' ;
```

```
clear;
mu=2; gamm=0.02; bet=6.2; k=0; b=0;
function [dzdt]=f(t, z)
E=z(1)
I=z(2)
dzdt(1)=bet*(1+b*cos(2*%pi*t))*I-(mu+epsi*(1+d*cos(2*%pi*t)))*E
dzdt(2)=epsi*(1+d*cos(2*%pi*t))*E-(mu+gamm*(1+k*cos(2*%pi*t)))*I
endfunction
time=[0:0.01:1];
n=length(time);
elist=[-1:0.01:1];
for i=1:length(elist),
d=elist(i);
epsimin=0.5;
epsimax=1.5;
while epsimax-epsimin>0.001,
epsi=(epsimax+epsimin)/2;
sol1=ode([1;0],0,time,f);
column1=sol1(:,n);
sol2=ode([0;1],0,time,f);
column2=sol2(:,n);
MonodromyMatrix=[column1 column2];
FloquetMultiplier=max(real(spec([MonodromyMatrix])));
if FloquetMultiplier>1 then
epsimax=epsi;
else
epsimin=epsi;
end;
end;
threshold(i)=epsi;
end;
plot2d(elist,threshold,rect=[min(elist) 0 max(elist) 2]);

t=linspace(-1,1,1000);
s=linspace(0,2,1000);
function z=epsi_ext(x, y),z=2.0693*y-2+(2.02+y)*abs(x),endfunction
contour(t,s,epsi_ext,[0,0]);
function w=epsi_per(x, y),w=(2.02+y)*(2+y)-(8.2+y)*y*(1-abs(x)),endfunction
contour(t,s,epsi_per,[0,0]);

xstring(0,0.3,"Extinction",0,0)
t=get("hdl")   //get the handle of the newly created object
t.font_foreground=1; // change font properties
t.font_size=3;
t.font_style=5;
t.text_box_mode = 'centered' ; // the text is now centered on [0,0.3].
t.alignment = 'center' ;
xstring(0,1.8,"Permanence",0,0)
t=get("hdl")   //get the handle of the newly created object
t.font_foreground=1; // change font properties
t.font_size=3;
t.font_style=5;
t.text_box_mode = 'centered' ; // the text is now centered on [0,1.8].
t.alignment = 'center' ;
```

## A.3 Matlab Code for Figures in Chapter 3

Figures 3.1, 3.2, 3.3 and 3.4

```
clear all

global L B a u eta e g

    format short

    t=0

    L= 2;
    B=5.9;
    a=0.1;
    u= 2;
    eta= 0;
    e= 1;
    g= 0.02;

    S0=.1
    E0=.1
    I0=.1
    R0=.1
    OPTIONS=odeset('AbsTol',1e-10);
    w0=[S0,E0,I0,R0];
    [t,w]=ode113('sistema',[0,400],w0,OPTIONS);
    S=w(:,1); E=w(:,2); I=w(:,3); R=w(:,4);
    S1=S; E1=E; I1=I; R1=R;
    t1=t;

    for j=1 : length(t)
        aux_i(j)=0;
        aux_s(j)=1;
    end

    S0=.08
    E0=.07
    I0=.12
    R0=.13
    OPTIONS=odeset('AbsTol',1e-10);
    w0=[S0,E0,I0,R0];
    [t,w]=ode113('sistema',[0,400],w0,OPTIONS);
    S=w(:,1); E=w(:,2); I=w(:,3); R=w(:,4);
    S2=S; E2=E; I2=I; R2=R;
    t2=t;

    S0=1.99
    E0=.09
    I0=.05
    R0=.25
    OPTIONS=odeset('AbsTol',1e-10);
    w0=[S0,E0,I0,R0];
    [t,w]=ode113('sistema',[0,400],w0,OPTIONS);
    S=w(:,1); E=w(:,2); I=w(:,3); R=w(:,4);
    S3=S; E3=E; I3=I; R3=R;
    t3=t;

    figure
    plot(t1,S1,'k',t1,E1,'k--',t1,I1,'k.')
    axis ([0,5,0,2])
    xlabel ('t');
    legend ('S(t)','E(t)','I(t)')
    hold on
```

```
plot(t2,S2,'r',t2,E2,'r--',t2,I2,'r.')
hold on
plot(t3,S3,'c',t3,E3,'c--',t3,I3,'c.')

figure
plot(E1,I1,'k')
xlabel ('E(t)'); ylabel ('I(t)','Rotation',0.0)
hold on
plot(E2,I2,'r')
hold on
plot(E3,I3,'c')

figure
plot(S1,I1,'k')
xlabel ('S(t)'); ylabel ('I(t)','Rotation',0.0)
hold on
plot(S2,I2,'r')
hold on
plot(S3,I3,'c')

figure
plot3(S1,E1,I1,'k')
axis ([0,2,0,.17,0,.12])
xlabel ('S'); ylabel ('E'); zlabel ('I')
box on
hold on
plot3(S2,E2,I2,'r')
hold on
plot3(S3,E3,I3,'c')

figure
plot(t1,S1,'k')
title ('Susceptible')
xlabel ('t');
ylabel ('S','Rotation',0.0)
axis ([0,50,0,2])
hold on
plot(t2,S2,'r')
hold on
plot(t3,S3,'c')
hold on
plot(t1,aux_s,'--','Color',[.75 .75 .75])

figure
plot(t1,I1,'k')
title ('Infected')
xlabel ('t')
ylabel ('I','Rotation',0.0)
axis ([0,50,-0.02,0.12])
hold on
plot(t2,I2,'r')
hold on
plot(t3,I3,'c')
hold on
plot(t1,aux_i,'--','Color',[.75 .75 .75])
```

```
clear all

global L B a u eta e g

    format short

    t=0

    L= 2;
    B=6.9;
    a=0.1;
    u= 2;
    eta= 0;
    e= 1;
    g= 0.02;

    S0=.1
    E0=.1
    I0=.1
    R0=.1
    OPTIONS=odeset('AbsTol',1e-10);
    w0=[S0,E0,I0,R0];
    [t,w]=ode113('sistema',[0,1000],w0,OPTIONS);
    S=w(length(w(:,1))-1000:length(w(:,1)),1);
    E=w(length(w(:,2))-1000:length(w(:,2)),2);
    I=w(length(w(:,3))-1000:length(w(:,3)),3);
    R=w(length(w(:,4))-1000:length(w(:,4)),4);
    S1=S; E1=E; I1=I; R1=R;
    t1=t(length(t)-1000:length(t));

    S0=w(length(w(:,1)),1);
    E0=w(length(w(:,2)),2);
    I0=w(length(w(:,3)),3);
    R0=w(length(w(:,4)),4);
    OPTIONS=odeset('AbsTol',1e-10);
    w0=[S0,E0,I0,R0];
    [t,w]=ode113('sistema',[0,50],w0,OPTIONS);
    S=w(:,1); E=w(:,2); I=w(:,3); R=w(:,4);
    S11=S; E11=E; I11=I; R11=R;
    t11=t;


    S0=.08
    E0=.07
    I0=.12
    R0=.13
    OPTIONS=odeset('AbsTol',1e-10);
    w0=[S0,E0,I0,R0];
    [t,w]=ode113('sistema',[0,15],w0,OPTIONS);
    S=w(:,1); E=w(:,2); I=w(:,3); R=w(:,4);
    S2=S; E2=E; I2=I; R2=R;
    t2=t;

    S0=1.99
    E0=.09
    I0=.05
    R0=.25
    OPTIONS=odeset('AbsTol',1e-10);
    w0=[S0,E0,I0,R0];
    [t,w]=ode113('sistema',[0,15],w0,OPTIONS);
```

```
S=w(:,1); E=w(:,2); I=w(:,3); R=w(:,4);
S3=S; E3=E; I3=I; R3=R;
t3=t;

figure
plot(t2,S2,'r',t2,E2,'r--',t2,I2,'r.')
axis ([0,5,0,2])
xlabel ('t');
legend ('S(t)','E(t)','I(t)')
hold on
plot(t3,S3,'c',t3,E3,'c--',t3,I3,'c.')
hold on
plot(t1,S1,'k',t1,E1,'k--',t1,I1,'k.')

figure
plot(E1,I1,'k')
xlabel ('E(t)'); ylabel ('I(t)','Rotation',0.0)
hold on
plot(E2,I2,'r')
hold on
plot(E3,I3,'c')

figure
plot(S2,I2,'r')
xlabel ('S(t)'); ylabel ('I(t)','Rotation',0.0)
hold on
plot(S3,I3,'c')
hold on
plot(S1,I1,'k')

figure
plot3(S2,E2,I2,'r')
axis ([0,2,.07,.17,.03,.12])
xlabel ('S'); ylabel ('E'); zlabel ('I')
box on
hold on
plot3(S3,E3,I3,'c')
hold on
plot3(S1,E1,I1,'k')

figure
plot(t11,S11,'k')
title ('Susceptible')
xlabel ('t');
ylabel ('S','Rotation',0.0)
axis ([0,50,0,2])
hold on
plot(t2,S2,'r')
hold on
plot(t3,S3,'c')

figure
plot(t11,I11,'k')
title ('Infected')
xlabel ('t')
ylabel ('I','Rotation',0.0)
axis ([0,50,.03,0.12])
hold on
plot(t2,I2,'r')
hold on
```

```
plot(t3,I3,'c')
```

```
clear all

global L B a u eta e g

    format short

    t=0

    L= 2;
    B=5.9;
    a=0.6;
    u= 2;
    eta= 0;
    e= 1;
    g= 0.02;

    S0=.1
    E0=.1
    I0=.1
    R0=.1
    OPTIONS=odeset('AbsTol',1e-10);
    w0=[S0,E0,I0,R0];
    [t,w]=ode113('sistema',[0,400],w0,OPTIONS);
    S=w(:,1); E=w(:,2); I=w(:,3); R=w(:,4);
    S1=S; E1=E; I1=I; R1=R;
    t1=t;

    for j=1 : length(t)
        aux_i(j)=0;
        aux_s(j)=1;
    end

    S0=.08
    E0=.07
    I0=.12
    R0=.13
    OPTIONS=odeset('AbsTol',1e-10);
    w0=[S0,E0,I0,R0];
    [t,w]=ode113('sistema',[0,400],w0,OPTIONS);
    S=w(:,1); E=w(:,2); I=w(:,3); R=w(:,4);
    S2=S; E2=E; I2=I; R2=R;
    t2=t;

    S0=1.99
    E0=.09
    I0=.05
    R0=.25
    OPTIONS=odeset('AbsTol',1e-10);
    w0=[S0,E0,I0,R0];
    [t,w]=ode113('sistema',[0,400],w0,OPTIONS);
    S=w(:,1); E=w(:,2); I=w(:,3); R=w(:,4);
    S3=S; E3=E; I3=I; R3=R;
    t3=t;

    figure
    plot(t1,S1,'k',t1,E1,'k--',t1,I1,'k.')
    axis ([0,5,0,2])
    xlabel ('t');
    legend ('S(t)','E(t)','I(t)')
    hold on
```

```
plot(t2,S2,'r',t2,E2,'r--',t2,I2,'r.')
hold on
plot(t3,S3,'c',t3,E3,'c--',t3,I3,'c.')

figure
plot(E1,I1,'k')
xlabel ('E(t)'); ylabel ('I(t)','Rotation',0.0)
hold on
plot(E2,I2,'r')
hold on
plot(E3,I3,'c')

figure
plot(S1,I1,'k')
xlabel ('S(t)'); ylabel ('I(t)','Rotation',0.0)
hold on
plot(S2,I2,'r')
hold on
plot(S3,I3,'c')

figure
plot3(S1,E1,I1,'k')
axis ([0,2,0,.17,0,.12])
xlabel ('S'); ylabel ('E'); zlabel ('I')
box on
hold on
plot3(S2,E2,I2,'r')
hold on
plot3(S3,E3,I3,'c')

figure
plot(t1,S1,'k')
title ('Susceptible')
xlabel ('t');
ylabel ('S','Rotation',0.0)
axis ([0,50,0,2])
hold on
plot(t2,S2,'r')
hold on
plot(t3,S3,'c')
hold on
plot(t1,aux_s,'--','Color',[.75 .75 .75])

figure
plot(t1,I1,'k')
title ('Infected')
xlabel ('t')
ylabel ('I','Rotation',0.0)
axis ([0,50,-0.02,0.12])
hold on
plot(t2,I2,'r')
hold on
plot(t3,I3,'c')
hold on
plot(t1,aux_i,'--','Color',[.75 .75 .75])
```

```
clear all

global L B a u eta e g

    format short

    t=0

    L= 2;
    B=6.9;
    a=0.6;
    u= 2;
    eta= 0;
    e= 1;
    g= 0.02;

    S0=.1
    E0=.1
    I0=.1
    R0=.1
    OPTIONS=odeset('AbsTol',1e-10);
    w0=[S0,E0,I0,R0];
    [t,w]=ode113('sistema',[0,1000],w0,OPTIONS);
    S=w(length(w(:,1))-10000:length(w(:,1)),1);
    E=w(length(w(:,2))-10000:length(w(:,2)),2);
    I=w(length(w(:,3))-10000:length(w(:,3)),3);
    R=w(length(w(:,4))-10000:length(w(:,4)),4);
    S1=S; E1=E; I1=I; R1=R;
    t1=t(length(t)-10000:length(t));

    S0=w(length(w(:,1)),1);
    E0=w(length(w(:,2)),2);
    I0=w(length(w(:,3)),3);
    R0=w(length(w(:,4)),4);
    OPTIONS=odeset('AbsTol',1e-10);
    w0=[S0,E0,I0,R0];
    [t,w]=ode113('sistema',[0,50],w0,OPTIONS);
    S=w(:,1); E=w(:,2); I=w(:,3); R=w(:,4);
    S11=S; E11=E; I11=I; R11=R;
    t11=t;


    S0=.08
    E0=.07
    I0=.12
    R0=.13
    OPTIONS=odeset('AbsTol',1e-10);
    w0=[S0,E0,I0,R0];
    [t,w]=ode113('sistema',[0,15],w0,OPTIONS);
    S=w(:,1); E=w(:,2); I=w(:,3); R=w(:,4);
    S2=S; E2=E; I2=I; R2=R;
    t2=t;

    S0=1.99
    E0=.09
    I0=.05
    R0=.25
    OPTIONS=odeset('AbsTol',1e-10);
    w0=[S0,E0,I0,R0];
    [t,w]=ode113('sistema',[0,15],w0,OPTIONS);
```

```
S=w(:,1); E=w(:,2); I=w(:,3); R=w(:,4);
S3=S; E3=E; I3=I; R3=R;
t3=t;

figure
plot(t2,S2,'r',t2,E2,'r--',t2,I2,'r.')
axis ([0,5,0,2])
xlabel ('t');
legend ('S(t)','E(t)','I(t)')
hold on
plot(t3,S3,'c',t3,E3,'c--',t3,I3,'c.')
hold on
plot(t1,S1,'k',t1,E1,'k--',t1,I1,'k.')

figure
plot(E1,I1,'k')
xlabel ('E(t)'); ylabel ('I(t)','Rotation',0.0)
hold on
plot(E2,I2,'r')
hold on
plot(E3,I3,'c')

figure
plot(S2,I2,'r')
xlabel ('S(t)'); ylabel ('I(t)','Rotation',0.0)
hold on
plot(S3,I3,'c')
hold on
plot(S1,I1,'k')

figure
plot3(S2,E2,I2,'r')
axis ([0,2,.0,.2,.03,.12])
xlabel ('S'); ylabel ('E'); zlabel ('I')
box on
hold on
plot3(S3,E3,I3,'c')
hold on
plot3(S1,E1,I1,'k')

figure
plot(t11,S11,'k')
title ('Susceptible')
xlabel ('t');
ylabel ('S','Rotation',0.0)
axis ([0,50,0,2])
hold on
plot(t2,S2,'r')
hold on
plot(t3,S3,'c')

figure
plot(t11,I11,'k')
title ('Infected')
xlabel ('t')
ylabel ('I','Rotation',0.0)
axis ([0,50,.03,0.12])
hold on
plot(t2,I2,'r')
hold on
```

```
plot(t3,I3,'c')
```

```
function wprime=de4_rhs(t,w)
global L B a u eta e g

wprime=[L-B*(1+a*cos(2*pi*t))*w(1)*w(3)-u*w(1)+eta*w(4)
         B*(1+a*cos(2*pi*t))*w(1)*w(3)-(u+e)*w(2)
         e*w(2)-(u+g)*w(3)
         g*w(3)-(u+eta)*w(4)] ;
```

## A.4 Matlab Code for Figures in Chapter 4

Figures 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8 and 4.9

```
function main

format long e

clear;  close all
clear all;

global per mu epsilon gama eta tfinal n alpha k1 k2 k3;

n=200;
j = 0;
tfinal = 25;

%mu variation

gama = .05;
epsilon = .03;
alpha = 0;
eta = 0.041;


for mu = 0:.01:.1
        per = 0;
        [t, y] = SEIR_bvp_control_bounds;

        j = j+1;
        ss = y(1,:); % ss = S(t)
        se = y(2,:); % se = E(t)
        si = y(3,:); % si = I(t)
        sr = y(4,:); % sr = R(t)
        sT = y(9,:); %Treatment
        sV = y(10,:); %Vaccination
        sp1 = y(5,:);
        sp2 = y(6,:);
        sp3 = y(7,:);
        sp4 = y(8,:);

        x=linspace(0,tfinal,n);

        vs=interp1 (t,ss,x,'spline');
        ve=interp1 (t,se,x,'spline');
        vi=interp1 (t,si,x,'spline');
        vr=interp1 (t,sr,x,'spline');
        vT=interp1 (t,sT,x,'spline');
        vV=interp1 (t,sV,x,'spline');
        vp1=interp1 (t,sp1,x,'spline');
        vp2=interp1 (t,sp2,x,'spline');
        vp3=interp1 (t,sp3,x,'spline');
        vp4=interp1 (t,sp4,x,'spline');
        mu;
        matriz_p0 (j, 1:n) = vi;
        matrizT_p0 (j, 1:n) = vT;
        matrizV_p0 (j, 1:n) = vV;

        aux_mu_p0 (j) = trapz (t,k1*si+k2*sT.^2+k3*sV.^2);
end

        mu = .05
        [t, y] = SEIR_bvp_control_bounds;
```

```
        ss = y(1,:); % ss = S(t)
        se = y(2,:); % se = E(t)
        si = y(3,:); % si = I(t)
        sr = y(4,:); % sr = R(t)
        sT = y(9,:); %Treatment
        sV = y(10,:); %Vaccination
        sp1 = y(5,:);
        sp2 = y(6,:);
        sp3 = y(7,:);
        sp4 = y(8,:);

        x=linspace(0,tfinal,n);

        vs=interp1 (t,ss,x,'spline');
        ve=interp1 (t,se,x,'spline');
        vi=interp1 (t,si,x,'spline');
        vr=interp1 (t,sr,x,'spline');
        vT=interp1 (t,sT,x,'spline');
        vV=interp1 (t,sV,x,'spline');
        vp1=interp1 (t,sp1,x,'spline');
        vp2=interp1 (t,sp2,x,'spline');
        vp3=interp1 (t,sp3,x,'spline');
        vp4=interp1 (t,sp4,x,'spline');
        mu;
        vetor_p0_s  = vs;
        vetor_p0_e  = ve;
        vetor_p0_i  = vi;
        vetor_p0_r  = vr;
        vetorT_p0 = vT;
        vetorV_p0 = vV;

        mu = .05
        [t, y] = SEIR_bvp_control_bounds_u;

        ss = y(1,:); % ss = S(t)
        se = y(2,:); % se = E(t)
        si = y(3,:); % si = I(t)
        sr = y(4,:); % sr = R(t)

        x=linspace(0,tfinal,n);

        vs=interp1 (t,ss,x,'spline');
        ve=interp1 (t,se,x,'spline');
        vi=interp1 (t,si,x,'spline');
        vr=interp1 (t,sr,x,'spline');
        mu;
        vetor_p0_s_u  = vs;
        vetor_p0_e_u  = ve;
        vetor_p0_i_u  = vi;
        vetor_p0_r_u  = vr;

j = 0;
for mu = 0:.01:.1
        per = .8;
        [t, y] = SEIR_bvp_control_bounds;

        j = j+1;
        ss = y(1,:); % ss = S(t)
        se = y(2,:); % se = E(t)
        si = y(3,:); % si = I(t)
```

```
        sr = y(4,:); % sr = R(t)
        sT = y(9,:); %Treatment
        sV = y(10,:); %Vaccination
        sp1 = y(5,:);
        sp2 = y(6,:);
        sp3 = y(7,:);
        sp4 = y(8,:);

        x=linspace(0,tfinal,n);

        vs=interp1 (t,ss,x,'spline');
        ve=interp1 (t,se,x,'spline');
        vi=interp1 (t,si,x,'spline');
        vr=interp1 (t,sr,x,'spline');
        vT=interp1 (t,sT,x,'spline');
        vV=interp1 (t,sV,x,'spline');
        vp1=interp1 (t,sp1,x,'spline');
        vp2=interp1 (t,sp2,x,'spline');
        vp3=interp1 (t,sp3,x,'spline');
        vp4=interp1 (t,sp4,x,'spline');
        mu;
        matriz_p08 (j, 1:n) = vi;
        matrizT_p08 (j, 1:n) = vT;
        matrizV_p08 (j, 1:n) = vV;

        aux_mu_p08 (j) = trapz (t,k1*si+k2*sT.^2+k3*sV.^2);
end


        mu = .05
        [t, y] = SEIR_bvp_control_bounds;

        ss = y(1,:); % ss = S(t)
        se = y(2,:); % se = E(t)
        si = y(3,:); % si = I(t)
        sr = y(4,:); % sr = R(t)
        sT = y(9,:); %Treatment
        sV = y(10,:); %Vaccination
        sp1 = y(5,:);
        sp2 = y(6,:);
        sp3 = y(7,:);
        sp4 = y(8,:);

        x=linspace(0,tfinal,n);

        vs=interp1 (t,ss,x,'spline');
        ve=interp1 (t,se,x,'spline');
        vi=interp1 (t,si,x,'spline');
        vr=interp1 (t,sr,x,'spline');
        vT=interp1 (t,sT,x,'spline');
        vV=interp1 (t,sV,x,'spline');
        vp1=interp1 (t,sp1,x,'spline');
        vp2=interp1 (t,sp2,x,'spline');
        vp3=interp1 (t,sp3,x,'spline');
        vp4=interp1 (t,sp4,x,'spline');
        mu;
        vetor_p08_s  = vs;
        vetor_p08_e  = ve;
        vetor_p08_i  = vi;
        vetor_p08_r  = vr;
```

```
        vetorT_p08 = vT;
        vetorV_p08 = vV;

        mu = .05
        [t, y] = SEIR_bvp_control_bounds_u;

        ss = y(1,:); % ss = S(t)
        se = y(2,:); % se = E(t)
        si = y(3,:); % si = I(t)
        sr = y(4,:); % sr = R(t)

        x=linspace(0,tfinal,n);

        vs=interp1 (t,ss,x,'spline');
        ve=interp1 (t,se,x,'spline');
        vi=interp1 (t,si,x,'spline');
        vr=interp1 (t,sr,x,'spline');
        mu;
        vetor_p08_s_u  = vs;
        vetor_p08_e_u  = ve;
        vetor_p08_i_u  = vi;
        vetor_p08_r_u  = vr;

        for j = 1:1:11
            max_aux_mu (j) = abs(aux_mu_p0(j)-aux_mu_p08(j));
        end
        max_mu = max (max_aux_mu);

        figure;
        plot (x, vetor_p0_s,'b', x, vetor_p0_e,'g',....
              x, vetor_p0_i,'r', x, vetor_p0_r,'c',...
              x, vetor_p0_s_u,'--b', x, vetor_p0_e_u,'--g',...
              x, vetor_p0_i_u,'--r', x, vetor_p0_r_u,'--c');
        title ('SEIRS')
        xlabel ('time')
        legend ('S-per=0','E-per=0','I-per=0','R-per=0',...
            'S-per=0-u','E-per=0-u','I-per=0-u','R-per=0-u')

        figure;
        plot (x, vetor_p0_s,'b', x, vetor_p0_r,'c',...
        x, vetor_p0_s_u,'--b', x, vetor_p0_r_u,'--c');
        title ('Susceptible and Recovered')
        xlabel ('time')
        legend ('S-per=0','R-per=0',...
            'S-per=0-u','R-per=0-u')

        figure;
        plot (x, vetor_p0_e,'g', x, vetor_p0_i,'r',...
        x, vetor_p0_e_u,'--g', x, vetor_p0_i_u,'--r');
        title ('Exposed and Infected')
        xlabel ('time')
        legend ('E-per=0','I-per=0',...
            'E-per=0-u','I-per=0-u')

%-----------------------------------------------------------------------%

        figure;
        plot (x, vetor_p08_s,'b', x, vetor_p08_e,'g',...
              x, vetor_p08_i,'r', x, vetor_p08_r,'c',...
              x, vetor_p08_s_u,'--b', x, vetor_p08_e_u,'--g',...
```

```
      x, vetor_p08_i_u,'--r', x, vetor_p08_r_u,'--c');
title ('SEIRS')
xlabel ('time')
legend ('S-per=.8','E-per=.8','I-per=.8','R-per=.8',...
    'S-per=.8-u','E-per=.8-u','I-per=.8-u','R-per=.8-u')

figure;
plot (x, vetor_p08_s,'b', x, vetor_p08_r,'c',...
x, vetor_p08_s_u,'--b', x, vetor_p08_r_u,'--c');
title ('Susceptible and Recovered')
xlabel ('time')
legend ('S-per=.8','R-per=.8',...
    'S-per=.8-u','R-per=.8-u')

figure;
plot (x, vetor_p08_e,'g', x, vetor_p08_i,'r',...
x, vetor_p08_e_u,'--g', x, vetor_p08_i_u,'--r');
title ('Exposed and Infected')
xlabel ('time')
legend ('E-per=.8','I-per=.8',...
    'E-per=.8-u','I-per=.8-u')

%------------------------------------------------------------------------%

figure;
plot (x, vetor_p0_s, x, vetor_p08_s,...
      x, vetor_p0_s_u, x, vetor_p08_s_u);
title ('Susceptible')
xlabel ('time')
legend ('per=0','per=.8','per=0-u','per=.8-u')

figure;
plot (x, vetor_p0_e, x, vetor_p08_e,...
      x, vetor_p0_e_u, x, vetor_p08_e_u);
title ('Exposed')
xlabel ('time')
legend ('per=0','per=.8','per=0-u','per=.8-u')

figure;
plot (x, vetor_p0_i, x, vetor_p08_i, x,...
      vetor_p0_i_u, x, vetor_p08_i_u);
title ('Infected')
xlabel ('time')
legend ('per=0','per=.8','per=0-u','per=.8-u')

figure;
plot (x, vetor_p0_r, x, vetor_p08_r, x,...
      vetor_p0_r_u, x, vetor_p08_r_u);
title ('Recovered')
xlabel ('time')
legend ('per=0','per=.8','per=0-u','per=.8-u')

figure;
plot (x, vetor_p0_s, x, vetor_p08_s,...
      x, vetor_p0_r, x, vetor_p08_r);
title ('Susceptible and Recovered')
xlabel ('time')
legend ('S-per=0','S-per=.8','R-per=0','R-per=.8')

figure;
```

```
    plot (x, vetor_p0_s_u, x, vetor_p08_s_u,...
          x, vetor_p0_r_u, x, vetor_p08_r_u);
    title ('Susceptible and Recovered')
    xlabel ('time')
    legend ('S-per=0-u','S-per=.8-u','R-per=0-u','R-per=.8-u')

    figure;
    plot (x, vetor_p0_e, x, vetor_p08_e,...
          x, vetor_p0_i, x, vetor_p08_i);
    title ('Exposed and Infected')
    xlabel ('time')
    legend ('E-per=0','E-per=.8','I-per=0','I-per=.8')

    figure;
    plot (x, vetor_p0_e_u, x, vetor_p08_e_u,...
          x, vetor_p0_i_u, x, vetor_p08_i_u);
    title ('Exposed and Infected')
    xlabel ('time')
    legend ('E-per=0-u','E-per=.8-u','I-per=0-u','I-per=.8-u')

    figure;
    plot (x, vetorT_p0, x, vetorT_p08);
    title ('Treated')
    xlabel ('time')
    legend ('per=0','per=.8')

    figure;
    plot (x, vetorV_p0, x, vetorV_p08);
    title ('Vaccinated')
    xlabel ('time')
    legend ('per=0','per=.8')

%------------------------------------------------------------------------%

    figure;
    [xt,yd]=meshgrid(0:tfinal/(n-1):tfinal,0:0.01:0.1);

    subplot (3,2,1);
    contourf(xt,yd, matriz_p0);
    title('Infected - per=0')
    xlabel ('time')
    ylabel ('\mu')

    subplot (3,2,2);
    contourf(xt,yd, matriz_p08);
    title('Infected  - per=.8')
    xlabel ('time')
    hp4 = get(subplot(3,2,2),'Position');
    colorbar('Position', [hp4(1)+hp4(3)+0.01  hp4(2)  0.02  hp4(4)])

    subplot (3,2,3);
    contourf(xt,yd, matrizT_p0);
    title('Treated - per=0')
    xlabel ('time')
    ylabel ('\mu')

    subplot (3,2,4);
    contourf(xt,yd, matrizT_p08);
    title('Treated - per=.8')
    xlabel ('time')
```

```
        hp4 = get(subplot(3,2,4),'Position');
        colorbar('Position', [hp4(1)+hp4(3)+0.01  hp4(2)  0.02  hp4(4)])

        subplot (3,2,5);
        contourf(xt,yd, matrizV_p0);
        title('Vaccinated - per=0')
        xlabel ('time')
        ylabel ('\mu')

        subplot (3,2,6);
        contourf(xt,yd, matrizV_p08);
        title('Vaccinated - per=.8')
        xlabel ('time')
        hp4 = get(subplot(3,2,6),'Position');
        colorbar('Position', [hp4(1)+hp4(3)+0.01  hp4(2)  0.02  hp4(4)])

%gama variation
j = 0;

mu = .05;
epsilon = .03;
alpha = 0;
eta = 0.041;

for gama = 0:.01:.1
        per = 0;
        [t, y] = SEIR_bvp_control_bounds;

        j = j+1;
        ss = y(1,:); % ss = S(t)
        se = y(2,:); % se = E(t)
        si = y(3,:); % si = I(t)
        sr = y(4,:); % sr = R(t)
        sT = y(9,:); %Treatment
        sV = y(10,:); %Vaccination
        sp1 = y(5,:);
        sp2 = y(6,:);
        sp3 = y(7,:);
        sp4 = y(8,:);

        x=linspace(0,tfinal,n);

        vs=interp1 (t,ss,x,'spline');
        ve=interp1 (t,se,x,'spline');
        vi=interp1 (t,si,x,'spline');
        vr=interp1 (t,sr,x,'spline');
        vT=interp1 (t,sT,x,'spline');
        vV=interp1 (t,sV,x,'spline');
        vp1=interp1 (t,sp1,x,'spline');
        vp2=interp1 (t,sp2,x,'spline');
        vp3=interp1 (t,sp3,x,'spline');
        vp4=interp1 (t,sp4,x,'spline');
        gama;
        matriz_p0 (j, 1:n) = vi;
        matrizT_p0 (j, 1:n) = vT;
        matrizV_p0 (j, 1:n) = vV;

        aux_gama_p0 (j) = trapz (t,k1*si+k2*sT.^2+k3*sV.^2);
end
```

```
j = 0;
for gama = 0:.01:.1
        per = .8;
        [t, y] = SEIR_bvp_control_bounds;

        j = j+1;
        ss = y(1,:); % ss = S(t)
        se = y(2,:); % se = E(t)
        si = y(3,:); % si = I(t)
        sr = y(4,:); % sr = R(t)
        sT = y(9,:); %Treatment
        sV = y(10,:); %Vaccination
        sp1 = y(5,:);
        sp2 = y(6,:);
        sp3 = y(7,:);
        sp4 = y(8,:);

        x=linspace(0,tfinal,n);

        vs=interp1 (t,ss,x,'spline');
        ve=interp1 (t,se,x,'spline');
        vi=interp1 (t,si,x,'spline');
        vr=interp1 (t,sr,x,'spline');
        vT=interp1 (t,sT,x,'spline');
        vV=interp1 (t,sV,x,'spline');
        vp1=interp1 (t,sp1,x,'spline');
        vp2=interp1 (t,sp2,x,'spline');
        vp3=interp1 (t,sp3,x,'spline');
        vp4=interp1 (t,sp4,x,'spline');
        gama;
        matriz_p08 (j, 1:n) = vi;
        matrizT_p08 (j, 1:n) = vT;
        matrizV_p08 (j, 1:n) = vV;

        aux_gama_p08 (j) = trapz (t,k1*si+k2*sT.^2+k3*sV.^2);
end

        for j = 1:1:11
            max_aux_gama (j) =abs(aux_gama_p0(j)-aux_gama_p08(j));
        end
        max_gama = max (max_aux_gama);

        figure;
        [xt,yd]=meshgrid(0:tfinal/(n-1):tfinal,0:0.01:0.1);

        subplot (3,2,1);
        contourf(xt,yd, matriz_p0);
        title('Infected - per=0')
        xlabel ('time')
        ylabel ('\gamma')

        subplot (3,2,2);
        contourf(xt,yd, matriz_p08);
        title('Infected  - per=.8')
        xlabel ('time')
        hp4 = get(subplot(3,2,2),'Position');
        colorbar('Position', [hp4(1)+hp4(3)+0.01  hp4(2)  0.02  hp4(4)])

        subplot (3,2,3);
        contourf(xt,yd, matrizT_p0);
```

```
        title('Treated - per=0')
        xlabel ('time')
        ylabel ('\gamma')

        subplot (3,2,4);
        contourf(xt,yd, matrizT_p08);
        title('Treated - per=.8')
        xlabel ('time')
        hp4 = get(subplot(3,2,4),'Position');
        colorbar('Position', [hp4(1)+hp4(3)+0.01  hp4(2)  0.02  hp4(4)])

        subplot (3,2,5);
        contourf(xt,yd, matrizV_p0);
        title('Vaccinated - per=0')
        xlabel ('time')
        ylabel ('\gamma')

        subplot (3,2,6);
        contourf(xt,yd, matrizV_p08);
        title('Vaccinated - per=.8')
        xlabel ('time')
        hp4 = get(subplot(3,2,6),'Position');
        colorbar('Position', [hp4(1)+hp4(3)+0.01  hp4(2)  0.02  hp4(4)])

%epsilon variation
j = 0;

mu = .05;
gama = .05;
alpha = 0;
eta = 0.041;

for epsilon = 0:.01:.1
        per = 0;
        [t, y] = SEIR_bvp_control_bounds;

        j = j+1;
        ss = y(1,:); % ss = S(t)
        se = y(2,:); % se = E(t)
        si = y(3,:); % si = I(t)
        sr = y(4,:); % sr = R(t)
        sT = y(9,:); %Treatment
        sV = y(10,:); %Vaccination
        sp1 = y(5,:);
        sp2 = y(6,:);
        sp3 = y(7,:);
        sp4 = y(8,:);

        x=linspace(0,tfinal,n);

        vs=interp1 (t,ss,x,'spline');
        ve=interp1 (t,se,x,'spline');
        vi=interp1 (t,si,x,'spline');
        vr=interp1 (t,sr,x,'spline');
        vT=interp1 (t,sT,x,'spline');
        vV=interp1 (t,sV,x,'spline');
        vp1=interp1 (t,sp1,x,'spline');
        vp2=interp1 (t,sp2,x,'spline');
        vp3=interp1 (t,sp3,x,'spline');
        vp4=interp1 (t,sp4,x,'spline');
```

```
        epsilon;
        matriz_p0 (j, 1:n) = vi;
        matrizT_p0 (j, 1:n) = vT;
        matrizV_p0 (j, 1:n) = vV;

        aux_epsilon_p0 (j) = trapz (t,k1*si+k2*sT.^2+k3*sV.^2);
end

j = 0;
for epsilon = 0:.01:.1
        per = .8;
        [t, y] = SEIR_bvp_control_bounds;

        j = j+1;
        ss = y(1,:); % ss = S(t)
        se = y(2,:); % se = E(t)
        si = y(3,:); % si = I(t)
        sr = y(4,:); % sr = R(t)
        sT = y(9,:); %Treatment
        sV = y(10,:); %Vaccination
        sp1 = y(5,:);
        sp2 = y(6,:);
        sp3 = y(7,:);
        sp4 = y(8,:);

        x=linspace(0,tfinal,n);

        vs=interp1 (t,ss,x,'spline');
        ve=interp1 (t,se,x,'spline');
        vi=interp1 (t,si,x,'spline');
        vr=interp1 (t,sr,x,'spline');
        vT=interp1 (t,sT,x,'spline');
        vV=interp1 (t,sV,x,'spline');
        vp1=interp1 (t,sp1,x,'spline');
        vp2=interp1 (t,sp2,x,'spline');
        vp3=interp1 (t,sp3,x,'spline');
        vp4=interp1 (t,sp4,x,'spline');
        epsilon;
        matriz_p08 (j, 1:n) = vi;
        matrizT_p08 (j, 1:n) = vT;
        matrizV_p08 (j, 1:n) = vV;

        aux_epsilon_p08 (j) = trapz (t,k1*si+k2*sT.^2+k3*sV.^2);
end

        for j = 1:1:11
            max_aux_epsilon(j) = abs(aux_epsilon_p0(j)-aux_epsilon_p08(j));
        end
        max_epsilon = max (max_aux_epsilon);

        figure;
        [xt,yd]=meshgrid(0:tfinal/(n-1):tfinal,0:0.01:0.1);

        subplot (3,2,1);
        contourf(xt,yd, matriz_p0);
        title('Infected - per=0')
        xlabel ('time')
        ylabel ('\epsilon')

        subplot (3,2,2);
```

```
        contourf(xt,yd, matriz_p08);
        title('Infected  - per=.8')
        xlabel ('time')
        hp4 = get(subplot(3,2,2),'Position');
        colorbar('Position', [hp4(1)+hp4(3)+0.01  hp4(2)  0.02  hp4(4)])

        subplot (3,2,3);
        contourf(xt,yd, matrizT_p0);
        title('Treated - per=0')
        xlabel ('time')
        ylabel ('\epsilon')

        subplot (3,2,4);
        contourf(xt,yd, matrizT_p08);
        title('Treated - per=.8')
        xlabel ('time')
        hp4 = get(subplot(3,2,4),'Position');
        colorbar('Position', [hp4(1)+hp4(3)+0.01  hp4(2)  0.02  hp4(4)])

        subplot (3,2,5);
        contourf(xt,yd, matrizV_p0);
        title('Vaccinated - per=0')
        xlabel ('time')
        ylabel ('\epsilon')

        subplot (3,2,6);
        contourf(xt,yd, matrizV_p08);
        title('Vaccinated - per=.8')
        xlabel ('time')
        hp4 = get(subplot(3,2,6),'Position');
        colorbar('Position', [hp4(1)+hp4(3)+0.01  hp4(2)  0.02  hp4(4)])

%eta variation
j = 0;

mu = .05;
epsilon = .03;
gama = .05;
alpha = 0;

for eta = 0:.01:.1
        per = 0;
        [t, y] = SEIR_bvp_control_bounds;

        j = j+1;
        ss = y(1,:); % ss = S(t)
        se = y(2,:); % se = E(t)
        si = y(3,:); % si = I(t)
        sr = y(4,:); % sr = R(t)
        sT = y(9,:); %Treatment
        sV = y(10,:); %Vaccination
        sp1 = y(5,:);
        sp2 = y(6,:);
        sp3 = y(7,:);
        sp4 = y(8,:);

        x=linspace(0,tfinal,n);

        vs=interp1 (t,ss,x,'spline');
        ve=interp1 (t,se,x,'spline');
```

```
        vi=interp1 (t,si,x,'spline');
        vr=interp1 (t,sr,x,'spline');
        vT=interp1 (t,sT,x,'spline');
        vV=interp1 (t,sV,x,'spline');
        vp1=interp1 (t,sp1,x,'spline');
        vp2=interp1 (t,sp2,x,'spline');
        vp3=interp1 (t,sp3,x,'spline');
        vp4=interp1 (t,sp4,x,'spline');
        eta;
        matriz_p0 (j, 1:n) = vi;
        matrizT_p0 (j, 1:n) = vT;
        matrizV_p0 (j, 1:n) = vV;

        aux_eta_p0 (j) = trapz (t,k1*si+k2*sT.^2+k3*sV.^2);
end

j = 0;
for eta = 0:.01:.1
        per = .8;
        [t, y] = SEIR_bvp_control_bounds;

        j = j+1;
        ss = y(1,:); % ss = S(t)
        se = y(2,:); % se = E(t)
        si = y(3,:); % si = I(t)
        sr = y(4,:); % sr = R(t)
        sT = y(9,:); %Treatment
        sV = y(10,:); %Vaccination
        sp1 = y(5,:);
        sp2 = y(6,:);
        sp3 = y(7,:);
        sp4 = y(8,:);

        x=linspace(0,tfinal,n);

        vs=interp1 (t,ss,x,'spline');
        ve=interp1 (t,se,x,'spline');
        vi=interp1 (t,si,x,'spline');
        vr=interp1 (t,sr,x,'spline');
        vT=interp1 (t,sT,x,'spline');
        vV=interp1 (t,sV,x,'spline');
        vp1=interp1 (t,sp1,x,'spline');
        vp2=interp1 (t,sp2,x,'spline');
        vp3=interp1 (t,sp3,x,'spline');
        vp4=interp1 (t,sp4,x,'spline');
        eta;
        matriz_p08 (j, 1:n) = vi;
        matrizT_p08 (j, 1:n) = vT;
        matrizV_p08 (j, 1:n) = vV;

        aux_eta_p08 (j) = trapz (t,k1*si+k2*sT.^2+k3*sV.^2);
end

        for j = 1:1:11
            max_aux_eta (j) = abs(aux_eta_p0(j)-aux_eta_p08(j));
        end
        max_eta = max (max_aux_eta);

        max_error = max ([max_mu max_gama max_epsilon max_eta]);
        disp (sprintf ('maximum error= %g',max_error));
```

```
        figure;
        [xt,yd]=meshgrid(0:tfinal/(n-1):tfinal,0:0.01:0.1);

        subplot (3,2,1);
        contourf(xt,yd, matriz_p0);
        title('Infected - per=0')
        xlabel ('time')
        ylabel ('\eta')

        subplot (3,2,2);
        contourf(xt,yd, matriz_p08);
        title('Infected  - per=.8')
        xlabel ('time')
        hp4 = get(subplot(3,2,2),'Position');
        colorbar('Position', [hp4(1)+hp4(3)+0.01  hp4(2)  0.02  hp4(4)])

        subplot (3,2,3);
        contourf(xt,yd, matrizT_p0);
        title('Treated - per=0')
        xlabel ('time')
        ylabel ('\eta')

        subplot (3,2,4);
        contourf(xt,yd, matrizT_p08);
        title('Treated - per=.8')
        xlabel ('time')
        hp4 = get(subplot(3,2,4),'Position');
        colorbar('Position', [hp4(1)+hp4(3)+0.01  hp4(2)  0.02  hp4(4)])

        subplot (3,2,5);
        contourf(xt,yd, matrizV_p0);
        title('Vaccinated - per=0')
        xlabel ('time')
        ylabel ('\eta')

        subplot (3,2,6);
        contourf(xt,yd, matrizV_p08);
        title('Vaccinated - per=.8')
        xlabel ('time')
        hp4 = get(subplot(3,2,6),'Position');
        colorbar('Position', [hp4(1)+hp4(3)+0.01  hp4(2)  0.02  hp4(4)])

end
```

```
function [t, y] = SEIR_bvp_control_bounds

format long e

global n tfinal mu gama epsilon alpha eta per k1 k2 k3 S0 E0 I0 R0 ...
    vcmax trmax;

disp('------------------------------------------------------------------------')
vcmax = 0.1;
trmax = 0.4;
ft = linspace(0, tfinal, n); % Generate t for Va and for Ta
Va = 0.0+0.*ft;
Ta = 0.0+0.*ft;

% Resolution of Boundary Value Problem (BVP)

options = odeset('RelTol',10^(-6),'AbsTol',10^(-6), 'Stats', 'on', ...
    'MaxStep',1/4);

k1 = 1;
k2 = 0.01;
k3 = 0.01;
S0 = .98;
E0 = 0;
I0 = .01;
R0 = .01;
ssa = Va; sea = Va; sia = Va; sra = Va;
p1a = Va; p2a = Va; p3a = Va; p4a = Va;

tspan = linspace(0,tfinal,n);
nn = 0; tol = 0.99; aux = 10;

y00 = [0 0 0 0];

while aux>tol && nn<50,

    nn = nn + 1; fprintf('iter = %g\n',nn);

    y0 = [S0 E0 I0 R0];
    sol1 = ode45(@(t,y) odes(t,y,ft,Va,Ta),tspan,y0,options);
    [y] = deval(sol1, tspan);

    disp(' ')
    ss = y(1,:); se = y(2,:); si = y(3,:); sr = y(4,:);

    fprintf(' - - - - - - - - - - - - - - - - \n');

    sol2 = ode45(@(t,y) odes2(t,y,ft,ss(end:-1:1),si(end:-1:1),...
        Va(end:-1:1),Ta(end:-1:1)),tspan,y00,options);
    [y2] = deval(sol2, tspan);
    y2=[y2(1,end:-1:1);y2(2,end:-1:1);y2(3,end:-1:1);y2(4,end:-1:1)];
    y = y2;
    fprintf('- - - - - - - - - - - - - - - - - - - - - - - - - - - - - -\n');

    Tax = Ta; Vax = Va;
    p1 = y(1,:); p2 = y(2,:); p3 = y(3,:); p4 = y(4,:);
    Va = (p1-p4).*ss/(2*k3); %Vaccination
    Ta = (p3-p4).*si/(2*k2); %Treatment

    [Va, Ta] = apara(Va,Ta);
```

```
     aux1 = max(abs(Vax-Va))/(max(abs(Va)))*100;
     aux2 = max(abs(Tax-Ta))/(max(abs(Ta)))*100;
     aux = max( aux1, aux2 );

     format short g
   [max(abs(ss-ssa))/(max(abs(ss))),...
   max(abs(se-sea))/(max(abs(se))), max(abs(si-sia))/(max(abs(si))),...
   max(abs(sr-sra))/(max(abs(sr))), max(abs(p1-p1a))/(max(abs(p1))),...
   max(abs(p2-p2a))/(max(abs(p2))), max(abs(p3-p3a))/(max(abs(p3))),...
   max(abs(p4-p4a))/(max(abs(p4)))]*100
    format long e
    ssa = ss; sea = se; sia = si; sra = sr;
    p1a = p1; p2a = p2; p3a = p3; p4a = p4;

     fprintf (' norma_vac = %g \n',aux1);
     fprintf (' norma_trat = %g \n',aux2);
    fprintf (' tol = %g \n',tol);
    disp(' ')
    fprintf('-----------------------------------------------------------\n');
    if nn>1 && aux>tol,
        Ta = ( Ta + Tax ) / 2;
        Va = ( Va + Vax ) / 2;
        fprintf('******** get average *********')
    end
end

t = tspan;
y=[ss;se;si;sr;p1;p2;p3;p4;Ta;Va];
end

% -------------------------------------------------------------------------

function yp = odes(t,y,ft,V0,T0)
% Definition of ODEs System
global mu eta gama epsilon alpha;

S = y(1); E = y(2);  I = y(3); R = y(4);

Va = interp1(ft, V0, t,'spline');
% Interpolate the data set (ft, Va) at times t
Ta = interp1(ft, T0, t,'spline');
% Interpolate the data set (ft, Ta) at times t

yp(1) = lambda(t)-beta(t)*S*I-mu*S+eta*R-Va*S;
yp(2) = beta(t)*S*I - (mu+epsilon)*E;
yp(3) = epsilon*E-(mu+alpha+gama)*I-Ta*I;
yp(4) = gama*I-mu*R-eta*R+Ta*I+Va*S;

yp = [yp(1); yp(2); yp(3); yp(4)];
end

% -------------------------------------------------------------


function yp = odes2(t,y,ft,S,I,V0,T0)
% Definition of ODEs System
global mu gama alpha epsilon eta k1;
```

```
p1 = y(1); p2 = y(2); p3 = y(3); p4 = y(4);

S = interp1(ft, S, t,'spline');
I = interp1(ft, I, t,'spline');
Va = interp1(ft, V0, t,'spline');
% Interpolate the data set (ft, Va) at times t
Ta = interp1(ft, T0, t,'spline');
% Interpolate the data set (ft, Ta) at times t

yp(1) = p1*(mu + beta(t)*I) - beta(t)*I*p2 + (p1-p4)*Va;
yp(2) = p2*(mu+epsilon)-p3*epsilon;
yp(3) = p3*(mu+gama+alpha)-gama*p4 +(p1-p2)*beta(t)*S ...
    +(p3-p4)*Ta-k1;
yp(4) = mu*p4-eta*p1+eta*p4;

yp = [-yp(1); -yp(2); -yp(3); -yp(4)];

end

% ------------------------------------------------------------

function [v1, v2] = apara(aux1,aux2)

global vcmax trmax

n1 = size(aux1, 2);
v1 = zeros(1, n1); v2 = v1;
for i = 1 : n1
    if aux1(i) < 0,
        v1(i) = 0.0;
    elseif aux1(i) > vcmax,
        v1(i) = vcmax;
    else
        v1(i) = aux1(i);
    end
    if aux2(i) < 0,
        v2(i) = 0;
    elseif aux2(i) > trmax,
        v2(i) = trmax;
    else
        v2(i) = aux2(i);
    end
end

end

% ------------------------------------------------------------

function beta = beta( t )
global per;
beta = .56 * (1 - per * cos( 2 * pi * t + 0.26 ) ) ;
end

% ------------------------------------------------------------

function lambda = lambda( t )
global per;
lambda = 0.05+0.05*per * cos( 2 * pi * t ) ;
end
```

```
% ------------------------------------------------------------
```

```
function [t, y] = SEIR_bvp_control_bounds_u

format long e

global n tfinal mu gama epsilon alpha eta per k1 k2 k3 S0 E0 I0 R0 ...
    vcmax trmax;

disp('------------------------------------------------------------------')
vcmax = 0;
trmax = 0;
ft = linspace(0, tfinal, n); % Generate t for Va and for Ta
Va = 0.0+0.*ft;
Ta = 0.0+0.*ft;

% Resolution of Boundary Value Problem (BVP)

options = odeset('RelTol',10^(-6),'AbsTol',10^(-6), 'Stats', 'on', ...
    'MaxStep',1/4);

k1 = 1;
k2 = 0.01;
k3 = 0.01;
S0 = .98;
E0 = 0;
I0 = .01;
R0 = .01;
ssa = Va; sea = Va; sia = Va; sra = Va;
p1a = Va; p2a = Va; p3a = Va; p4a = Va;

tspan = linspace(0,tfinal,n);
nn = 0; tol = 0.99; aux = 10;

y00 = [0 0 0 0];

    nn = nn + 1; fprintf('iter = %g\n',nn);

    y0 = [S0 E0 I0 R0];
    sol1 = ode45(@(t,y) odes(t,y,ft,Va,Ta),tspan,y0,options);
    [y] = deval(sol1, tspan);

    disp(' ')
    ss = y(1,:); se = y(2,:); si = y(3,:); sr = y(4,:);

    fprintf(' - - - - - - - - - - - - - - - - - \n');

    sol2 = ode45(@(t,y) odes2(t,y,ft,ss(end:-1:1),si(end:-1:1),...
        Va(end:-1:1),Ta(end:-1:1)),tspan,y00,options);
    [y2] = deval(sol2, tspan);
    y2=[y2(1,end:-1:1);y2(2,end:-1:1);y2(3,end:-1:1);y2(4,end:-1:1)];
    y = y2;

    fprintf('- - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -\n');

    Tax = Ta; Vax = Va;
    p1 = y(1,:); p2 = y(2,:); p3 = y(3,:); p4 = y(4,:);

     aux1 = max(abs(Vax-Va))/(max(abs(Va)))*100;
     aux2 = max(abs(Tax-Ta))/(max(abs(Ta)))*100;
     aux = max( aux1, aux2 );
```

```
      format short g
    [max(abs(ss-ssa))/(max(abs(ss))),...
    max(abs(se-sea))/(max(abs(se))), max(abs(si-sia))/(max(abs(si))),...
    max(abs(sr-sra))/(max(abs(sr))), max(abs(p1-p1a))/(max(abs(p1))),...
    max(abs(p2-p2a))/(max(abs(p2))), max(abs(p3-p3a))/(max(abs(p3))),...
    max(abs(p4-p4a))/(max(abs(p4)))]*100
     format long e
     ssa = ss; sea = se; sia = si; sra = sr;
     p1a = p1; p2a = p2; p3a = p3; p4a = p4;

      fprintf (' norma_vac = %g \n',aux1);
      fprintf (' norma_trat = %g \n',aux2);
     fprintf (' tol = %g \n',tol);
     disp(' ')
     fprintf('---------------------------------------------------------\n');
     if nn>1 && aux>tol,
         Ta = ( Ta + Tax ) / 2;
         Va = ( Va + Vax ) / 2;
         fprintf('******** get average *********')
     end

t = tspan;
y=[ss;se;si;sr;p1;p2;p3;p4;Ta;Va];
end

% ---------------------------------------------------------------------------

function yp = odes(t,y,ft,V0,T0)
% Definition of ODEs System
global mu eta gama epsilon alpha;

S = y(1); E = y(2);  I = y(3); R = y(4);

Va = interp1(ft, V0, t,'spline');
% Interpolate the data set (ft, Va) at times t
Ta = interp1(ft, T0, t,'spline');
% Interpolate the data set (ft, Ta) at times t

yp(1) = lambda(t)-beta(t)*S*I-mu*S+eta*R-Va*S;
yp(2) = beta(t)*S*I - (mu+epsilon)*E;
yp(3) = epsilon*E-(mu+alpha+gama)*I-Ta*I;
yp(4) = gama*I-mu*R-eta*R+Ta*I+Va*S;

yp = [yp(1); yp(2); yp(3); yp(4)];
end

% ---------------------------------------------------------------


function yp = odes2(t,y,ft,S,I,V0,T0)
% Definition of ODEs System
global mu gama alpha epsilon eta k1;

p1 = y(1); p2 = y(2); p3 = y(3); p4 = y(4);

S = interp1(ft, S, t,'spline');
I = interp1(ft, I, t,'spline');
Va = interp1(ft, V0, t,'spline');
% Interpolate the data set (ft, Va) at times t
Ta = interp1(ft, T0, t,'spline');
```

```
% Interpolate the data set (ft, Ta) at times t

yp(1) = p1*(mu + beta(t)*I) - beta(t)*I*p2 + (p1-p4)*Va;
yp(2) = p2*(mu+epsilon)-p3*epsilon;
yp(3) = p3*(mu+gama+alpha)-gama*p4 +(p1-p2)*beta(t)*S ...
    +(p3-p4)*Ta-k1;
yp(4) = mu*p4-eta*p1+eta*p4;

yp = [-yp(1); -yp(2); -yp(3); -yp(4)];

end

% ------------------------------------------------------------


function beta = beta( t )
global per;
beta = .56 * (1 - per * cos( 2 * pi * t + 0.26 ) ) ;
end

% ------------------------------------------------------------

function lambda = lambda( t )
global per;
lambda = 0.05+0.05*per * cos( 2 * pi * t ) ;
end

% ------------------------------------------------------------
```