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Existence of periodic solutions of a periodic SEIRS model with general incidence

Joaquim P. Mateus[a], César M. Silva[b,*]

[a] *Instituto Politécnico da Guarda, 6300-559 Guarda, Portugal*
[b] *Departamento de Matemática, Universidade da Beira Interior, 6201-001 Covilhã, Portugal*

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ABSTRACT

For a family of periodic SEIRS models with general incidence, we prove the existence of at least one endemic periodic orbit when some condition related to $\mathcal{R}_0$ holds. Additionally, we prove the existence of a unique disease-free periodic orbit, that is globally asymptotically stable when $\mathcal{R}_0 < 1$. In particular, our main result generalizes the one in Zhang et al. (2012). We also discuss some examples where our results apply and show that, in some particular situations, we have a sharp threshold between existence and non existence of an endemic periodic orbit.

1. Introduction

In the sequence of the model introduced by Li and Muldowney in [1], several works were devoted to the study of epidemic models with a latent class. In these models, besides the infected, susceptible and recovered compartments, an exposed compartment is also considered in order to split the infected population into 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 [2]. Additionally, if there is no recovery, the model is appropriate to describe diseases such as Chagas' disease [3]. This model can also be used to model diseases like hepatitis B and AIDS [2]. Even influenza can be modeled by a SEIRS model [4], although, due to the short latency period, it is sometimes more convenient to use the simpler SIRS formulation [5]. Mathematically, the existence of more than one infected compartment brings some additional challenges to the study of the model.

* Corresponding author.
E-mail addresses: jmateus@ipg.pt (J.P. Mateus), csilva@mat.ubi.pt (C.M. Silva).
URL: http://www.mat.ubi.pt/~csilva (C.M. Silva).

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In this work we focus on the existence and stability of endemic periodic solutions of a large family of periodic SEIRS models contained in the family of models already considered in [6]. Namely, we will consider models of the form

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

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, $\epsilon(t)$ represents the infectivity rate and $\gamma(t)$ is the rate of recovery. We assume that Λ, β, μ, η, ϵ and γ are periodic functions of the same period ω. Naturally, for biological reasons we will take the initial conditions in the set $\{(S,E,I,R) \in \mathbb{R}^4 : S,E,I,R \geq 0\}$.

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 [7–12]. 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 [13,14]. 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 [15,16]. Another popular type of incidence, given by $\beta(t)\varphi(S,N,I) = \beta(t)I^pS^q$, was considered in [17,13,18]. 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 [19,20]. All these incidence functions satisfy our hypothesis (see (P1) to (P6) in Section 2).

The search for periodic solutions and the study of their stability is a very important subject in epidemiology. In fact, in the non-autonomous context, periodic solutions play the same role as equilibriums in the autonomous context. Our main result shows that there exists a positive periodic solution of (1) whenever $\overline{\mathcal{R}}_0 > 1$, where $\overline{\mathcal{R}}_0$ is the basic reproductive number of the averaged system, $\inf_{(0,1]} \mathcal{R}_0^\lambda > 1$, where $\mathcal{R}_0^\lambda$, $\lambda \in (0,1]$, are the basic reproductive numbers of a family of systems related to system (1) and the determinant of some matrix is not zero, a technical condition required by our method of prove that consists in applying the famous Mawhin continuation theorem. We also prove that, when $\mathcal{R}_0 < 1$, there exists a unique disease-free periodic solution that is globally asymptotically stable. Here, $\mathcal{R}_0$ is given by the spectral radius of some operator, obtained by the method developed in [21] and $\mathcal{R}_0^1 = \mathcal{R}_0$. To obtain our result, it is fundamental to have a good result about persistence of the infectives. Fortunately, in [22] such result is obtained for general epidemiological models and applied to a mass-action SEIRS model. We use this result to obtain persistence in our general incidence case.

For mass-action incidence, in [23], it is discussed the existence of periodic orbits. It is shown there that, under some condition involving bounds for the periodic parameters, there exists at least a positive periodic orbit. The referred model differs from ours not only because it assumes a particular form for the incidence function, but also because it allows disease induced mortality and it assumes that immunity is permanent. When the disease induced mortality is set to zero (letting $\alpha \equiv 0$), that model becomes a particular case of ours. Thus, when there is no disease induced mortality, Corollary 4 in Section 4 generalizes the main result in [23].

Although the idea of applying Mawhin's continuation theorem was borrowed from [23], we need several nontrivial new arguments to deal with our case. In particular, because we allow temporary immunity, we were forced to use the original four-dimensional system instead of a reduced system.

2. Notation and preliminaries

In this section we will establish the assumptions on model (1) and state some results on threshold type conditions obtained in [6] for this model.

Given a bounded ω-periodic function $f : \mathbb{R}_0^+ \to \mathbb{R}$, we define $f^u = \max_{t\in[0,\omega]} f(t)$ and $f^\ell = \min_{t\in[0,\omega]} f(t)$. We will make the following assumptions:

(P1) There is $\omega \geq 0$ such that Λ, μ, β and ϵ are continuous and positive ω-periodic real valued functions on $\mathbb{R}_0^+$ and that η and γ are continuous, bounded and non-negative ω-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) There are $c_1, c_2 > 0$, such that, 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.

Notice that condition (P3) is biologically natural: if there are no infectives or no susceptibles, then there is no contact between susceptibles and infectives. One can also justify that the assumptions in (P5) are not unreasonable. For instance, if we increase the number of infectives (or the number of susceptibles) maintaining the total population then the contact between infectives and susceptibles must not decrease. On the other hand, it is not as easy to justify the technical conditions (P4) and (P6). Nevertheless we stress that our conditions are satisfied by a large family of incidence functions that include the most used ones.

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

$$z' = \Lambda(t) - \mu(t)z. \tag{2}$$

We have the following proposition whose proof is standard (see for instance Lemma 2.1 in [12]):

Lemma 1. *Assume that condition* (P1) *holds. Then we have the following:*

(1) *Given $t_0 \geq 0$, all solutions z of Eq. (2) with initial condition $z(t_0) \geq 0$ are nonnegative for all $t \geq 0$;*
(2) *Given $t_0 \geq 0$, all solutions z of Eq. (2) with initial condition $z(t_0) > 0$ are positive for all $t \geq 0$;*
(3) *Given any two solutions z, z_1 of (2) we have $|z(t) - z_1(t)| \to 0$ as $t \to +\infty$;*
(4) *For each solution $z(t)$ of (2) we have*

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

(5) *For each solution $z(t)$ of (2) 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 $t \geq t_0$;*
(6) *There is a unique periodic solution $z^*(t)$ of (2) in $\mathbb{R}^+$, this solution has period ω and is given by*

$$z^*(t) = \frac{\int_0^\omega \Lambda(u)\,\mathrm{e}^{-\int_u^\omega \mu(s)\,ds}\,du}{1 - \mathrm{e}^{-\int_0^\omega \mu(s)\,ds}}\,\mathrm{e}^{-\int_0^t \mu(s)\,ds} + \int_0^t \Lambda(u)\,\mathrm{e}^{-\int_u^t \mu(s)\,ds}\,du. \tag{3}$$

We now obtain some simple properties of system (1).

Lemma 2. *Assume that conditions* (P1)–(P6) *hold. Then:*

(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) *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* $\Lambda^\ell/\mu^u \leq N(t) \leq \Lambda^u/\mu^\ell$*.*
(4) *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. A simple analysis of the flow on the boundary of $(\mathbb{R}_0^+)^4$ allows one to conclude that (1) and (2) hold. To obtain the remaining conditions we note that, adding the differential equations in (1) we get the equation $N' = \Lambda(t) - \mu(t)N$. By Lemma 1, we easily obtain (3) and (4). □

By (P1) and (P2), 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. By (4) in Lemma 2, every solution is global in the future.

3. Existence and stability of disease-free periodic orbits

Theorem 1. *Assume that conditions* (P1)–(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* (2)*. This solution has period* ω*.*

Proof. By Lemma 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 a unique disease-free periodic solution given by $(S^*(t), 0, 0, 0)$. Since $S^*(t)$ is ω-periodic, it follows that $(S^*(t), 0, 0, 0)$ is ω-periodic. □

To obtain the basic reproductive number, we will use the general setting and the notation in [21] and, letting $x = (x_1, x_2, x_3, x_4) = (E, I, S, R)$, we can write system (1) in the form

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

where

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

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

and

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

It is easy tosee that conditions (A1)–(A5) in page 701 of [21] are consequence of conditions (P1)–(P6).

Letting $x^* = (0,0,S^*(t),0)$ be the unique positive ω-periodic solution of (1) given by Theorem 1, by (P2) and (P3) we have $\frac{\partial\varphi}{\partial N}(S^*(t),S^*(t),0)=0$ and therefore the matrices in (2.2) in [21] are given by

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

and

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

Denote by $Y(t,s)$, $t \geq s$, the evolution operator of the linear ω-periodic system $y' = -V(t)y$, i.e. $Y(t,s)$ is such that

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

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

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

and we define the basic reproduction ratio in our context by

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

By Theorem 2.2 in [21] we get the following result.

Theorem 2. *Assume that conditions* (P1)–(P6) *hold. Then, for system* (1)*, the disease-free periodic solution* x_0^* *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* $\rho(\Phi_{F-V}(\omega)) > 1$*,*

where $\Phi_{F-V}(t)$ *is the fundamental matrix solution of the linear system*

$$x' = (F(t)-V(t))x.$$

We begin by defining some concepts. Let A be a 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 cannot 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 (*Lemma 2.1 in [10]*). *Let $A(t)$ be a continuous, cooperative, irreducible and ω-periodic matrix function, let $\Phi_A(t)$ be the fundamental matrix solution of*

$$x' = A(t)x \tag{4}$$

and let $p = \frac{1}{\omega}\ln(\rho(\Phi_A(\omega)))$, where ρ denotes the spectral radius. Then, there exists a positive ω-periodic function $v(t)$ such that $\mathrm{e}^{pt}\, v(t)$ is a solution of (4).

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

Theorem 3. *If conditions* (P1)–(P6) *hold, the disease-free ω-periodic solution $x^* = (S^*(t), 0, 0, 0)$ of system (1) is globally asymptotically stable if $\mathcal{R}_0 < 1$.*

Proof. By Theorem 2, if $\mathcal{R}_0 < 1$, then $x^*(t) = (S^*(t), 0, 0, 0)$, the disease-free ω-periodic solution, is locally asymptotically stable. On the other hand, by (3) in Lemma 1, for any $\varepsilon_1 > 0$ there exists $T_1 > 0$ such that

$$S^*(t) - \varepsilon_1 \le N(t) \le S^*(t) + \varepsilon_1 \tag{5}$$

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 ψ 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 2 we conclude that $\rho(\Phi_{F-V}(\omega)) < 1$. Choose $\varepsilon_1 > 0$ such that $\rho(\Phi_{F-V+\psi(\varepsilon_1)M_2}(\omega)) < 1$ 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,

$$\begin{bmatrix} u' \\ v' \end{bmatrix} = (F(t) - V(t) + \psi(\varepsilon_1) M_2(t)) \begin{bmatrix} u \\ v \end{bmatrix}.$$

By Lemma 3 and the standard comparison principle, there are ω-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. □

4. Persistence of the infective compartment and existence of endemic periodic orbits

The next theorem shows that, when $\mathcal{R}_0 > 1$, the infectives are persistent. In fact, we will proof a slightly stronger result that will be useful later. For each $\lambda \in (0, 1]$, consider the system

$$\begin{cases} S' = \lambda\,(\Lambda(t) - \beta(t)\,\varphi(S, N, I) - \mu(t)S + \eta(t)R) \\ E' = \lambda\,(\beta(t)\,\varphi(S, N, I) - (\mu(t) + \epsilon(t))E) \\ I' = \lambda\,(\epsilon(t)E - (\mu(t) + \gamma(t))I) \\ R' = \lambda\,(\gamma(t)I - (\mu(t) + \eta(t))R) \\ N = S + E + I + R \end{cases} \tag{6}$$

and, for each $\lambda \in [0, 1]$, let $\mathcal{R}_0^\lambda$ be the basic reproductive number of (6). In particular, $\mathcal{R}_0^1 = \mathcal{R}_0$.

The proof of the result below consists in adapting the argument used in the first example in Section 3 of [22], where the case of a SEIRS model with simple incidence is considered, to our more general situation.

Theorem 4. *Assume that conditions* (P1)–(P6) *hold. Given* $\lambda \in (0, 1]$, *if* $\mathcal{R}_0^\lambda > 1$, *then system* (6) *is persistent with respect to* I. *In particular, if* $\mathcal{R}_0 > 1$ *then system* (1) *is persistent with respect to* I. *Moreover, if*

$$\inf_{\lambda \in (0,1]} \mathcal{R}_0^\lambda > 1, \tag{7}$$

there is $K^\ell > 0$ *such that* $\liminf_{t\to+\infty} I(t) > K^\ell$ *for any* $\lambda \in [0, 1]$ *and any solution* $(S(t), E(t), I(t), R(t))$ *of* (6) *with positive initial conditions.*

Proof. To prove the theorem we will use Theorem 3 in [22]. It follows from Lemma 2 that condition (A8) in Theorem 3 in [22] 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 Λ or μ are not constant functions and

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

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

Denote by $(S(t), E(t), I(t), R(t))$ a solution of (6) for some $\lambda \in (0, 1]$, with positive initial conditions, and let $(S^*(t), 0, 0, 0)$ be the disease free periodic solution of that system. If there is $\delta > 0$ and $t_0 \in \mathbb{R}$ such that $I(t) \le \delta$ for $t \ge t_0$ then, using (P3) and (P4), we have

$$\begin{aligned} &R' \le \lambda\gamma^u\delta - \lambda(\mu + \eta)^\ell R, \\ &(S - S^*)' \le -\lambda\beta(t)\varphi(S, N, I) - \lambda\mu(t)(S - S^*) + \lambda\eta^u R \le -\lambda\mu^\ell(S - S^*) + \lambda\eta^u R, \\ &E' \le \lambda\beta^u\varphi(S, N, I) - \lambda(\mu + \varepsilon)^\ell E \le \lambda\beta^u c_2 S\delta - \lambda(\mu + \varepsilon)^\ell E \end{aligned}$$

and

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

Additionally, for t sufficiently large, we have

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

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

$$E(t) \leq 2\delta \frac{c_2\beta^u(k_2(\delta)+S^*)^u}{(\mu+\varepsilon)^\ell} \leq 2\delta \frac{c_2\beta^u(k_2(\delta)+\Lambda^u/\mu^\ell)}{(\mu+\varepsilon)^\ell} := k_3(\delta) \tag{8}$$

and

$$S^*(t) - S(t) \leq 2\delta \frac{c_2\beta^u(k_2(\delta)+S^*)^u}{\mu^\ell} \leq 2\delta \frac{c_2\beta^u(k_2(\delta)+\Lambda^u/\mu^\ell)}{\mu^\ell} := k_4(\delta). \tag{9}$$

Also, according to (5), we also have, for t sufficiently large,

$$|S^*(t) - N(t)| \leq k_5(\delta), \tag{10}$$

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

Now, we will check assumptions (ii) and (iii) (a) in Theorem 3 in [22]. Assume that there exists $t_0 \in \mathbb{R}$ such that $I(t) \leq \delta$ for each $t \geq t_0$. From (8), 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 (iii) (a) in Theorem 3 in [22] setting $\eta(\delta) = k_3(\delta)$ and (i) holds since $\eta(\delta) \to 0$ as $\delta \to 0$. Let us now check assumptions (i) and (iii) (b) in Theorem 3 in [22]. Choose $\delta_1 > 0$ such that $k_4(\delta) < \min_{t\in[0,\omega)} S^*(t)$ 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 (9) 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 (10) 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 (iii) (b) in Theorem 3 in [22] holds with the function λ in that theorem replaced by

$$l_\lambda(\delta) = \max_{t\in[0,\omega]} \frac{\partial\varphi/\partial I\,(S^*(t), S^*(t), 0)}{\varphi(S^*(t) - k_4(\delta), S^*(t) + k_5(\delta), \delta)/\delta}. \tag{11}$$

Since $l_\lambda(\delta) \to 1$ as $\delta \to 0$ we conclude that (ii) in the referred theorem holds. We conclude that system (6) is persistent with respect to I.

Assume now that (7) holds. Then, since

$$\begin{aligned} l_\lambda(\delta) &= \max_{t\in[0,\omega]} \frac{\partial\varphi/\partial I\,(S^*(t), S^*(t), 0)}{\varphi(S^*(t) - k_4(\delta), S^*(t) + k_5(\delta), \delta)/\delta} \\ &\leq \max_{\xi\in[\Lambda^\ell/\mu^u, \Lambda^u/\mu^\ell]} \frac{\partial\varphi/\partial I\,(\xi, \xi, 0)}{\varphi(\xi - k_4(\delta), \xi + k_5(\delta), \delta)/\delta}, \end{aligned}$$

by (3) in Lemma 2, we can replace the function in (11) by

$$l(\delta) = \max_{\xi\in[\Lambda^\ell/\mu^u, \Lambda^u/\mu^\ell]} \frac{\partial\varphi/\partial I\,(\xi, \xi, 0)}{\varphi(\xi - k_4(\delta), \xi + k_5(\delta), \delta)/\delta}, \tag{12}$$

a function that is independent of λ. Note that $l(\delta) \to 1$ as $\delta \to 0^+$. According to the proof of Theorem 3 in [22], the function $l_\lambda(\delta)$ determines the constant K^ℓ such that $\liminf_{t\to+\infty} I(t) > K^\ell$ for each $\lambda \in (0,1]$ and each solution $(S(t), E(t), I(t), R(t))$ of (6). Since $l_\lambda(\delta)$ can be taken the same for each $\lambda \in (0,1]$, we can take the same constant K^ℓ for each $\lambda \in (0,1]$. The result follows. □

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. Define

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

Lemma 4. *Assume that conditions* (P1)–(P5) *hold and* $\overline{\mathcal{R}}_0 > 1$. *Then there is a unique* $r > 0$ *that solves equation*

$$\frac{\bar{\epsilon}\bar{\beta}}{\bar{\mu}+\bar{\gamma}}\varphi\left(\bar{\Lambda}/\bar{\mu}-dr,\bar{\Lambda}/\bar{\mu},r\right)/r-(\bar{\mu}+\bar{\epsilon})=0, \tag{13}$$

where

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

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

$$\psi(v)=\begin{cases}\dfrac{\bar{\epsilon}\bar{\beta}}{\bar{\mu}+\bar{\gamma}}\dfrac{\varphi\left(\bar{\Lambda}/\bar{\mu}-dv,\bar{\Lambda}/\bar{\mu},v\right)}{v}-(\bar{\mu}+\bar{\epsilon}) & \text{if } 0<v\le\bar{\Lambda}/\bar{\mu}\\[2mm] \dfrac{\bar{\epsilon}\bar{\beta}}{\bar{\mu}+\bar{\gamma}}\dfrac{\partial\varphi}{\partial I}\left(\bar{\Lambda}/\bar{\mu},\bar{\Lambda}/\bar{\mu},0\right)-(\bar{\mu}+\bar{\epsilon}) & \text{if } v=0\end{cases}$$

is continuous and non-increasing and we have

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

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

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

Thus, by Bolzano's theorem, there is $r\in]0,d_0[\subset]0,\bar{\Lambda}/\bar{\mu}[$ that solves (13). 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

$$\mathcal{M}=\begin{bmatrix}-\bar{\mu}-K_{110} & -K_{010}q/p & -K_{011}r/p & (-K_{010}+\eta)\,s/p\\ K_{110}p/q & K_{010} & K_{011}r/q & K_{010}s/q\\ 0 & \bar{\mu}+\bar{\gamma} & -(\bar{\mu}+\bar{\gamma}) & 0\\ 0 & 0 & \bar{\mu}+\bar{\eta} & -(\bar{\mu}+\bar{\eta})\end{bmatrix} \tag{14}$$

where r is the unique solution of (13),

$$p=\frac{\bar{\Lambda}}{\bar{\mu}}-\frac{(\bar{\mu}+\bar{\gamma})(\bar{\mu}+\bar{\epsilon})(\bar{\mu}+\bar{\eta})-\bar{\epsilon}\bar{\gamma}\bar{\eta}}{\bar{\epsilon}\bar{\mu}(\bar{\mu}+\bar{\eta})}r,\qquad q=(\bar{\mu}+\bar{\gamma})r/\bar{\varepsilon},\qquad s=\bar{\gamma}r/(\bar{\mu}+\bar{\eta})$$

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, using Mawhin's continuation theorem and our persistence result, we obtain conditions for the existence of endemic periodic orbits.

Theorem 5. *Assume that conditions* (P2)–(P6) *hold. Assume also that*

(1) $\overline{\mathcal{R}}_0 > 1$ *and* $\inf_{\lambda\in(0,1]} \mathcal{R}_0^\lambda > 1$*;*
(2) $\det \mathcal{M} \neq 0$.

Then system (1) *has an endemic* ω*-periodic solution.*

To obtain Theorem 5 we will use a well known result in degree theory, the Mawhin continuation theorem [24,25].

Proof. Before proving Theorem 5, 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. $\dim \ker \mathcal{L} = \operatorname{codim} \operatorname{Im} \mathcal{L} < \infty$;
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 5: Mawhin's continuation theorem [25].

Theorem 6 (*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

$$S(t) = \mathrm{e}^{u_1(t)}, \qquad E(t) = \mathrm{e}^{u_2(t)}, \qquad I(t) = \mathrm{e}^{u_3(t)} \quad \text{and} \quad R(t) = \mathrm{e}^{u_4(t)}, \tag{15}$$

system (1) becomes

$$\begin{cases} u_1' = \Lambda(t)\,\mathrm{e}^{-u_1} - \beta(t)\,\varphi(\mathrm{e}^{u_1}, w, \mathrm{e}^{u_3})\,\mathrm{e}^{-u_1} - \mu(t) + \eta(t)\,\mathrm{e}^{u_4-u_1} \\ u_2' = \beta(t)\,\varphi(\mathrm{e}^{u_1}, w, \mathrm{e}^{u_3})\,\mathrm{e}^{-u_2} - (\mu(t)+\epsilon(t)) \\ u_3' = \epsilon(t)\,\mathrm{e}^{u_2-u_3} - (\mu(t)+\gamma(t)) \\ u_4' = \gamma(t)\,\mathrm{e}^{u_3-u_4} - (\mu(t)+\eta(t)) \\ w = \mathrm{e}^{u_1} + \mathrm{e}^{u_2} + \mathrm{e}^{u_3} + \mathrm{e}^{u_4} \end{cases} \tag{16}$$

and if $(v_1(t), v_2(t), v_3(t), v_4(t))$ is a periodic solution of period ω of system (16) 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 ω of system (1). Consider also the system

$$\begin{cases} u_1' = \lambda\left(\Lambda(t)\,\mathrm{e}^{-u_1} - \beta(t)\varphi(\mathrm{e}^{u_1}, w, \mathrm{e}^{u_3})\,\mathrm{e}^{-u_1} - \mu(t) + \eta(t)\,\mathrm{e}^{u_4-u_1}\right) \\ u_2' = \lambda\left(\beta(t)\varphi(\mathrm{e}^{u_1}, w, \mathrm{e}^{u_3})\,\mathrm{e}^{-u_2} - (\mu(t)+\epsilon(t))\right) \\ u_3' = \lambda\left(\epsilon(t)\,\mathrm{e}^{u_2-u_3} - (\mu(t)+\gamma(t))\right) \\ u_4' = \lambda\left(\gamma(t)\,\mathrm{e}^{u_3-u_4} - (\mu(t)+\eta(t))\right) \\ w = \mathrm{e}^{u_1} + \mathrm{e}^{u_2} + \mathrm{e}^{u_3} + \mathrm{e}^{u_4}, \end{cases} \tag{17}$$

that can be obtained by applying the change of variables (15) to system (6).

By (4) in Lemma 1, if $(u_1(t), u_2(t), u_3(t), u_4(t))$ is periodic then

$$\frac{\Lambda^\ell}{\mu^u} \leq w(t) \leq \frac{\Lambda^u}{\mu^\ell}. \tag{18}$$

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

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

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

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

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 $\dim\ker\mathcal{L} = \operatorname{codim}\operatorname{Im}\mathcal{L} = 4$) 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

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

$t \in [0, \omega]$, the operator $Q\mathcal{N} : X \to Z$ given by

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

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

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

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

and

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

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 Ω for any bounded set $\Omega\subset X$.

Let $(u_1,u_2,u_3,u_4)\in X$ be some solution of (17) for some $\lambda\in(0,1)$ and, for $i=1,2,3,4$ define

$$u_i(\xi_i)=\min_{t\in[0,\omega]}u_i(t)\quad\text{and}\quad u_i(\chi_i)=\max_{t\in[0,\omega]}u_i(t).$$

From the third equation in (17) we get,

$$\mathrm{e}^{u_2(\xi_2)-u_3(\xi_3)}\le\mathrm{e}^{u_2(\xi_3)-u_3(\xi_3)}=\frac{\mu(\xi_3)+\gamma(\xi_3)}{\epsilon(\xi_3)}\le\frac{(\mu+\gamma)^u}{\epsilon^\ell}\tag{19}$$

and

$$\mathrm{e}^{u_2(\chi_2)-u_3(\chi_3)}\ge\mathrm{e}^{u_2(\chi_3)-u_3(\chi_3)}=\frac{\mu(\chi_3)+\gamma(\chi_3)}{\epsilon(\chi_3)}\ge\frac{(\mu+\gamma)^\ell}{\epsilon^u}.\tag{20}$$

From the second equation in (17), (P4) and (19), we obtain

$$\begin{aligned}\mathrm{e}^{u_1(\xi_1)}\le\mathrm{e}^{u_1(\xi_2)}&=\frac{(\mu+\epsilon)^u}{\beta^\ell}\frac{\mathrm{e}^{u_1(\xi_2)+u_3(\xi_2)}}{\varphi(\mathrm{e}^{u_1(\xi_2)},w(\xi_2),\mathrm{e}^{u_3(\xi_2)})}\,\mathrm{e}^{u_2(\xi_2)-u_3(\xi_2)}\\&\le\frac{(\mu+\epsilon)^u}{\beta^\ell}\frac{\mathrm{e}^{u_1(\xi_2)+u_3(\xi_2)}}{\varphi(\mathrm{e}^{u_1(\xi_2)},w(\xi_2),\mathrm{e}^{u_3(\xi_2)})}\frac{(\mu+\gamma)^u}{\epsilon^\ell}\\&\le\frac{(\mu+\epsilon)^u(\mu+\gamma)^u}{c_1\beta^\ell\epsilon^\ell}\end{aligned}$$

and, by the second equation in (17), (P4) and (20), we get

$$\begin{aligned}\mathrm{e}^{u_1(\chi_1)}\ge\mathrm{e}^{u_1(\chi_2)}&=\frac{(\mu+\epsilon)^\ell}{\beta^u}\frac{\mathrm{e}^{u_1(\chi_2)+u_3(\chi_2)}}{\varphi(\mathrm{e}^{u_1(\chi_2)},w(\chi_2),\mathrm{e}^{u_3(\chi_2)})}\,\mathrm{e}^{u_2(\chi_2)-u_3(\chi_2)}\\&\ge\frac{(\mu+\epsilon)^\ell}{\beta^u}\frac{\mathrm{e}^{u_1(\xi_2)+u_3(\xi_2)}}{\varphi(\mathrm{e}^{u_1(\xi_2)},w(\xi_2),\mathrm{e}^{u_3(\xi_2)})}\frac{(\mu+\gamma)^\ell}{\epsilon^u}\\&\ge\frac{(\mu+\epsilon)^\ell(\mu+\gamma)^\ell}{c_2\beta^u\epsilon^u}.\end{aligned}\tag{21}$$

Define

$$A_{1\xi} = \frac{(\mu+\epsilon)^u(\mu+\gamma)^u}{c_1\beta^\ell\epsilon^\ell} \quad \text{and} \quad A_{1\chi} = \frac{(\mu+\epsilon)^\ell(\mu+\gamma)^\ell}{c_2\beta^u\epsilon^u}. \tag{22}$$

From the fourth equation in (17) we get

$$\mathrm{e}^{u_3(\xi_3)} \le \mathrm{e}^{u_3(\chi_4)-u_4(\chi_4)+u_4(\chi_4)} = \frac{\mu(\chi_4)+\eta(\chi_4)}{\gamma(\chi_4)}\,\mathrm{e}^{u_4(\chi_4)} \le \frac{(\mu+\eta)^u}{\gamma^\ell}\,\mathrm{e}^{u_4(\chi_4)}$$

and

$$\mathrm{e}^{u_3(\chi_3)} \ge \mathrm{e}^{u_3(\xi_4)-u_4(\xi_4)}\,\mathrm{e}^{u_4(\xi_4)} = \frac{\mu(\xi_4)+\eta(\xi_4)}{\gamma(\xi_4)}\,\mathrm{e}^{u_4(\xi_4)} \ge \frac{(\mu+\eta)^\ell}{\gamma^u}\,\mathrm{e}^{u_4(\xi_4)}.$$

Thus we obtain

$$\mathrm{e}^{u_4(\xi_4)} \le \frac{\gamma^u}{(\mu+\eta)^\ell}\,\mathrm{e}^{u_3(\chi_3)} \quad \text{and} \quad \mathrm{e}^{u_4(\chi_4)} \ge \frac{\gamma^\ell}{(\mu+\eta)^u}\,\mathrm{e}^{u_3(\xi_3)}. \tag{23}$$

From the first equation in (17) 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 (21) and (18), the right hand expression can be bounded by

$$\begin{aligned}\Lambda(\chi_1) - \mu(\chi_1)\,\mathrm{e}^{u_1(\chi_1)} + \eta(\chi_1)\,\mathrm{e}^{u_4(\chi_1)} &\le \Lambda^u - \mu^\ell\,\mathrm{e}^{u_1(\chi_1)} + \eta^u\,\mathrm{e}^{u_4(\chi_1)} \\ &\le \Lambda^u + \eta^u\frac{\Lambda^u}{\mu^\ell}\end{aligned} \tag{24}$$

and, by (21), we obtain

$$\begin{aligned}\beta(\chi_1)\varphi\left(\mathrm{e}^{u_1(\chi_1)}, w(\chi_1), \mathrm{e}^{u_3(\chi_1)}\right) &\ge \beta^\ell c_1\,\mathrm{e}^{u_1(\chi_1)+u_3(\chi_1)} \\ &\ge \frac{\beta^\ell c_1(\mu+\epsilon)^\ell(\mu+\gamma)^\ell}{c_2\beta^u\epsilon^u}\,\mathrm{e}^{u_3(\xi_3)}.\end{aligned} \tag{25}$$

By (24) and (25) we get

$$\mathrm{e}^{u_3(\xi_3)} \le \frac{c_2(1+\eta^u/\mu^\ell)\Lambda^u\beta^u\epsilon^u}{c_1\beta^\ell(\mu+\epsilon)^\ell(\mu+\gamma)^\ell}. \tag{26}$$

By hypothesis (1) and Theorem 4, there is $K^\ell > 0$ such that

$$\liminf_{t\to+\infty} \mathrm{e}^{u_3(t)} \ge K^\ell. \tag{27}$$

Thus $\mathrm{e}^{u_3(t)} \ge K^\ell$. Define

$$A_{3\xi} = \frac{c_2(1+\eta^u/\mu^\ell)\Lambda^u\beta^u\epsilon^u}{c_1\beta^\ell(\mu+\epsilon)^\ell(\mu+\gamma)^\ell} \quad \text{and} \quad A_{3\chi} = K^\ell. \tag{28}$$

Using (27), (18) and (23) and again the fact that $\mathcal{R}_0 > 1$, we obtain bounds for $\mathrm{e}^{u_4(t)}$, namely

$$\mathrm{e}^{u_4(\xi_4)} \le \frac{\gamma^u}{(\mu+\eta)^\ell}\frac{\Lambda^u}{\mu^\ell} \quad \text{and} \quad \mathrm{e}^{u_4(\chi_4)} \ge \frac{\gamma^\ell}{(\mu+\eta)^u}\,\mathrm{e}^{u_3(\xi_3)} \ge \frac{\gamma^\ell}{(\mu+\eta)^u}K^\ell.$$

Define

$$A_{4\xi} = \frac{\gamma^u}{(\mu+\eta)^\ell}\frac{\Lambda^u}{\mu^\ell} \quad \text{and} \quad A_{4\chi} = \frac{\gamma^\ell}{(\mu+\eta)^u}K^\ell. \tag{29}$$

By the third equation in (1), (26) and (27) we get

$$\mathrm{e}^{u_2(\xi_2)} \le \mathrm{e}^{u_2(\xi_3)-u_3(\xi_3)}\,\mathrm{e}^{u_3(\xi_3)} \le \frac{(\mu+\gamma)^u}{\epsilon^\ell} A_{3\xi}$$

and

$$\mathrm{e}^{u_2(\chi_2)} \ge \mathrm{e}^{u_2(\chi_3)-u_3(\chi_3)}\,\mathrm{e}^{u_3(\chi_3)} \ge \frac{(\mu+\gamma)^\ell}{\epsilon^u} A_{3\chi}.$$

Using (28), we can establish bounds for $\mathrm{e}^{u_2(t)}$. In fact, we have $\mathrm{e}^{u_2(\xi_2)} \le A_{2\xi}$ and $\mathrm{e}^{u_2(\chi_2)} \ge A_{2\chi}$, where

$$A_{2\xi} = \frac{c_2(\mu+\gamma)^\ell(1+\eta^u/\mu^\ell)\Lambda^u\beta^u\epsilon^u}{c_1\epsilon^\ell\beta^\ell(\mu+\epsilon)^\ell(\mu+\gamma)^\ell} \tag{30}$$

and

$$A_{2\chi} = \frac{(\mu+\gamma)^\ell}{\epsilon^u} K^\ell. \tag{31}$$

By (22), (28), (29), (30), (31) we obtain, for $i = 1, \ldots, 4$,

$$u_i(\xi_i) \le \ln A_{i\xi} \quad \text{and} \quad u_i(\chi_i) \ge \ln A_{i\chi}. \tag{32}$$

Integrating in $[0,\omega]$ the last three equations in (17) we obtain

$$\int_0^\omega \beta(t)\,\varphi\left(\mathrm{e}^{u_1(t)}, w(t), \mathrm{e}^{u_3(t)}\right)\mathrm{e}^{-u_2(t)}\;dt = (\bar\mu+\bar\epsilon)\omega, \tag{33}$$

$$\int_0^\omega \epsilon(t)\,\mathrm{e}^{u_2(t)-u_3(t)}\;dt = (\bar\mu+\bar\gamma)\omega \tag{34}$$

and

$$\int_0^\omega \gamma(t)\,\mathrm{e}^{u_3(t)-u_4(t)} = (\bar\mu+\bar\eta)\omega. \tag{35}$$

By (32) and (33) and using the fact that $\lambda \in (0,1)$, we get

$$\begin{aligned} u_2(t) &= u_2(\xi_2) + \int_{\xi_2}^t u_2'(s)\,ds \le u_2(\xi_2) + \int_0^\omega |u_2'(t)|\,dt \\ &= u_2(\xi_2) + \lambda\int_0^\omega \left|\beta(t)\,\varphi\left(\mathrm{e}^{u_1(t)}, w(t), \mathrm{e}^{u_3(t)}\right)\mathrm{e}^{-u_2(t)} - (\mu(t)+\epsilon(t))\right|\,dt \\ &\le \ln A_{2\xi} + 2\int_0^\omega \beta(t)\,\varphi\left(\mathrm{e}^{u_1(t)}, w(t), \mathrm{e}^{u_3(t)}\right)\mathrm{e}^{-u_2(t)}\;dt \\ &\le \ln A_{2\xi} + 2(\bar\mu+\bar\epsilon)\omega, \end{aligned}$$

and also

$$\begin{aligned} u_2(t) &\ge u_2(\chi_2) - \int_0^\omega |u_2'(t)|\,dt \\ &= u_2(\chi_2) - \int_0^\omega \left|\beta(t)\,\varphi\left(\mathrm{e}^{u_1(t)}, w(t), \mathrm{e}^{u_3(t)}\right)\mathrm{e}^{-u_2(t)} - (\mu(t)+\epsilon(t))\right|\,dt \\ &\ge \ln A_{2\chi} - 2(\bar\mu+\bar\epsilon)\omega. \end{aligned}$$

By (32) and (34) and using the fact that $\lambda \in (0,1)$, we obtain

$$\begin{aligned} u_3(t) &\le u_3(\xi_3) + \int_0^\omega |u_3'(t)|\,dt = u_3(\xi_3) + \lambda\int_0^\omega \left|\epsilon(t)\,\mathrm{e}^{u_2-u_3} - (\mu(t)+\gamma(t))\right|\,dt \\ &\le \ln A_{3\xi} + 2\int_0^\omega \epsilon(t)\,\mathrm{e}^{u_2-u_3}\;dt \le \ln A_{3\xi} + 2(\bar\mu+\bar\gamma)\omega, \end{aligned} \tag{36}$$

and also

$$u_3(t) \geq u_3(\chi_3) - \int_0^\omega |u_3'(t)|\, dt = u_3(\chi_3) - \lambda \int_0^\omega \left|\epsilon(t)\, \mathrm{e}^{u_2-u_3} - (\mu(t)+\gamma(t))\right|\, dt$$
$$\geq \ln A_{3\chi} - 2\int_0^\omega \epsilon(t)\, \mathrm{e}^{u_2-u_3}\, dt \geq \ln A_{3\chi} - 2(\bar\mu + \bar\gamma)\omega.$$

Similarly, by (32) and (35) and using the fact that $\lambda \in (0,1)$, we conclude that

$$u_4(t) \leq u_4(\xi_4) + \int_0^\omega |u_4'(t)|\, dt = u_4(\xi_4) + \lambda \int_0^\omega \left|\gamma(t)\, \mathrm{e}^{u_3-u_4} - (\mu(t)+\eta(t))\right|\, dt$$
$$\leq \ln A_{4\xi} + 2\int_0^\omega \gamma(t)\, \mathrm{e}^{u_3-u_4}\, dt \leq \ln A_{4\xi} + 2(\bar\mu + \bar\eta)\omega$$

and also that

$$u_4(t) \geq u_4(\chi_4) - \int_0^\omega |u_4'(t)|\, dt = u_4(\chi_4) - \lambda \int_0^\omega \left|\gamma(t)\, \mathrm{e}^{u_3-u_4} - (\mu(t)+\eta(t))\right|\, dt$$
$$\geq \ln A_{4\chi} - 2\int_0^\omega \gamma(t)\, \mathrm{e}^{u_3-u_4}\, dt \geq \ln A_{4\chi} - 2(\bar\mu + \bar\eta)\omega.$$

Finally, integrating the first equation of (17) in $[0,\omega]$ and using (32) and (36), 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

$$\begin{aligned}u_1(t) &\leq u_1(\xi_1) + \int_0^\omega |u_1'(t)|\, dt \\ &= u_1(\xi_1) + \lambda \int_0^\omega \left|\Lambda(t)\, \mathrm{e}^{-u_1} - \beta(t)\, \frac{C(w)}{w}\, \mathrm{e}^{u_3} - \mu(t) + \eta(t)\, \mathrm{e}^{u_4-u_1}\right|\, dt \\ &\leq \ln A_{1\xi} + 2\int_0^\omega \Lambda(t)\, \mathrm{e}^{-u_1} + \eta(t)\, \mathrm{e}^{u_4-u_1}\, dt \\ &\leq \ln A_{1\xi} + 2\left(\bar\beta c_2 A_{3\xi}\, \mathrm{e}^{-2(\bar\mu+\bar\gamma)\omega} + \bar\mu\right)\omega\end{aligned}$$

and also

$$\begin{aligned}u_1(t) &\geq u_1(\chi_1) - \int_0^\omega |u_1'(t)|\, dt \\ &= u_1(\chi_1) - \lambda \int_0^\omega \left|\Lambda(t)\, \mathrm{e}^{-u_1} - \beta(t)\, \frac{C(w)}{w}\, \mathrm{e}^{u_3} - \mu(t) + \eta(t)\, \mathrm{e}^{u_4-u_1}\right|\, dt \\ &\geq \ln A_{1\chi} - 2\int_0^\omega \Lambda(t)\, \mathrm{e}^{-u_1} + \eta(t)\, \mathrm{e}^{u_4-u_1}\, dt \\ &\geq \ln A_{1\chi} - 2\left(\bar\beta c_2 A_{3\xi}\, \mathrm{e}^{-2(\bar\mu+\bar\gamma)\omega} + \bar\mu\right)\omega.\end{aligned}$$

Consider the algebraic system

$$\begin{cases}\bar\Lambda\, \mathrm{e}^{-u_1} - \bar\beta\varphi(\mathrm{e}^{u_1}, w, \mathrm{e}^{u_3})\, \mathrm{e}^{-u_1} - \bar\mu + \bar\eta\, \mathrm{e}^{u_4-u_1} = 0 \\ \bar\beta\varphi(\mathrm{e}^{u_1}, w, \mathrm{e}^{u_3})\, \mathrm{e}^{-u_2} - \bar\mu - \bar\epsilon = 0 \\ \bar\epsilon\, \mathrm{e}^{u_2-u_3} - \bar\mu - \bar\gamma = 0 \\ \bar\gamma\, \mathrm{e}^{u_3-u_4} - \bar\mu - \bar\eta = 0.\end{cases} \tag{37}$$

Multiplying the first equation by e^{u_1}, the second by e^{u_2}, the third by e^{u_3} and the fourth equation by 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 (37) verifies

$$\mathrm{e}^{u_2} = \frac{\bar{\mu}+\bar{\gamma}}{\bar{\epsilon}}\,\mathrm{e}^{u_3} = \frac{(\bar{\mu}+\bar{\gamma})(\bar{\mu}+\bar{\eta})}{\bar{\epsilon}\bar{\gamma}}\,\mathrm{e}^{u_4} \tag{38}$$

and also

$$\mathrm{e}^{u_1} = \frac{\bar{\Lambda}}{\bar{\mu}} - \frac{(\bar{\mu}+\bar{\gamma})(\bar{\mu}+\bar{\epsilon})(\bar{\mu}+\bar{\eta}) - \bar{\epsilon}\bar{\gamma}\bar{\eta}}{\bar{\epsilon}\bar{\mu}(\bar{\mu}+\bar{\eta})}\,\mathrm{e}^{u_3}. \tag{39}$$

Thus, by the second equation in (37) we get

$$\frac{\bar{\epsilon}\bar{\beta}}{\bar{\mu}+\bar{\gamma}}\,\varphi\left(\bar{\Lambda}/\bar{\mu} - d\,\mathrm{e}^{u_3}, \bar{\Lambda}/\bar{\mu}, \mathrm{e}^{u_3}\right)\mathrm{e}^{-u_3} - (\bar{\mu}+\bar{\epsilon}) = 0, \tag{40}$$

where

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

By Lemma 4, (40) has a unique solution. Therefore, by (38) and (39) we conclude that the algebraic system (37) 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

$$\begin{aligned}
M_1 &= \max\left\{\left|\ln A_{1\xi} + 2\left(\bar{\beta}c_2 A_{3\xi}\,\mathrm{e}^{-2(\bar{\mu}+\bar{\gamma})\omega} + \bar{\mu}\right)\omega\right|, \left|\ln A_{1\chi} - 2\left(\bar{\beta}c_2 A_{3\xi}\,\mathrm{e}^{-2(\bar{\mu}+\bar{\gamma})\omega} + \bar{\mu}\right)\omega\right|\right\},\\
M_2 &= \max\{|\ln A_{2\xi} + 2(\bar{\mu}+\bar{\epsilon})\omega|, |\ln A_{2\chi} - 2(\bar{\mu}+\bar{\epsilon})\omega|\},\\
M_3 &= \max\{|\ln A_{3\xi} + 2(\bar{\mu}+\bar{\gamma})\omega|, |\ln A_{3\chi} - 2(\bar{\mu}+\bar{\gamma})\omega|\},
\end{aligned}$$

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

$$Q\mathcal{N}u := \begin{bmatrix} F_1(u) \\ F_2(u) \\ F_3(u) \\ F_4(u) \end{bmatrix} = \begin{bmatrix} \bar{\Lambda}\,\mathrm{e}^{-u_1} - \bar{\beta}\varphi(\mathrm{e}^{u_1}, w, \mathrm{e}^{u_3})\,\mathrm{e}^{-u_1} - \bar{\mu} + \bar{\eta}\,\mathrm{e}^{u_4-u_1} \\ \bar{\beta}\varphi(\mathrm{e}^{u_1}, w, \mathrm{e}^{u_3})\,\mathrm{e}^{-u_2} - \bar{\mu} - \bar{\epsilon} \\ \bar{\epsilon}\,\mathrm{e}^{u_2-u_3} - \bar{\mu} - \bar{\gamma} \\ \bar{\gamma}\,\mathrm{e}^{u_3-u_4} - \bar{\mu} - \bar{\eta} \end{bmatrix} \neq 0.$$

We conclude that

$$\begin{aligned}
\deg(\mathrm{Id}\,Q\mathcal{N}, \partial\Omega \cap \ker L, (0,0,0,0)) &= \sum_{x \in (IdQ\mathcal{N})^{-1}(0,0,0,0)} \operatorname{sign}\det d_x(\mathrm{Id}\,Q\mathcal{N})\\
&= \operatorname{sign}\det d_{p^*}(\mathrm{Id}\,Q\mathcal{N})\\
&= \operatorname{sign}\det \mathcal{M},
\end{aligned}$$

where $\mathcal{M}$ is the matrix in (14). By hypothesis (2) 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 ω-periodic solution and the result follows. □

The following corollary shows that, when φ does not depend explicitly on the total population, the condition $\det \mathcal{M} \neq 0$ is always satisfied. Notice that, additionally to well known separable incidence functions such as the mass-action incidence, the next corollary includes also non-separable situations.

Corollary 1. *Let $\varphi(S,N,I) = \psi(S,I)$ and assume that it satisfies conditions* (P2)–(P6). *If condition* (1) *in Theorem 5 holds then system (1) has an endemic periodic solution of period ω.*

Proof. Some computations yield

$$\det \mathcal{M} = -\frac{(\bar{\eta}+\bar{\mu})(\bar{\gamma}+\bar{\mu})}{q}\left(\bar{\eta}s\frac{\partial\varphi}{\partial S}(p,\bar{\Lambda}/\bar{\mu},r) + \bar{\mu}r\frac{\partial\varphi}{\partial I}(p,\bar{\Lambda}/\bar{\mu},r)\right). \tag{41}$$

By (P4), (P5) and (41) we have $\det \mathcal{M} \neq 0$. Thus, condition (2) in Theorem 5 holds. The result follows from Theorem 5. □

The following is an immediate corollary of the previous one.

Corollary 2 (*Simple Incidence Functions*)**.** *Let $\varphi(S,N,I) = SI$. If condition* (1) *in Theorem 5 holds then system (1) has an endemic periodic solution of period ω.*

The next corollary shows that, in the case of Michaelis–Menten incidence, the condition $\det \mathcal{M} \neq 0$ is also always satisfied.

Corollary 3 (*Michaelis–Menten Incidence Functions*)**.** *Let $\varphi(S,N,I) = \frac{C(N)}{N}SI$ and assume that $N \mapsto C(N)$ is non-decreasing continuously differentiable and positive and that $N \to C(N)/N$ is non-increasing. If condition* (1) *in Theorem 5 holds then system (1) has an endemic periodic solution of period ω.*

Proof. In this case we have

$$\begin{aligned}\det \mathcal{M} &= -\frac{\bar{\beta}(\eta+\mu)(\gamma+\mu)}{q}\left(\frac{\partial\varphi}{\partial N}(p,\bar{\Lambda}/\bar{\mu},r)\,(\mu r+\eta s+\mu q+\mu s) + \eta s\frac{\partial\varphi}{\partial S}(p,\bar{\Lambda}/\bar{\mu},r) + \mu r\frac{\partial\varphi}{\partial I}(p,\bar{\Lambda}/\bar{\mu},r)\right)\\ &= -\frac{\bar{\beta}(\eta+\mu)(\gamma+\mu)}{q}\left(\frac{C'(\bar{\Lambda}/\bar{\mu})}{\bar{\Lambda}/\bar{\mu}}pr\,(\mu r+\eta s+\mu q+\mu s)\right.\\ &\qquad \left. - \frac{C(\bar{\Lambda}/\bar{\mu})}{\bar{\Lambda}^2/\bar{\mu}^2}pr\,(\mu r+\eta s+\mu q+\mu s) + \frac{C(\bar{\Lambda}/\bar{\mu})}{\bar{\Lambda}/\bar{\mu}}r(s\eta+p\mu)\right).\end{aligned}$$

Since $p < \bar{\Lambda}/\bar{\mu}$ and $r+q+s = \bar{\Lambda}/\bar{\mu} - p$, we have

$$\begin{aligned}\det \mathcal{M} = -\frac{\bar{\beta}(\eta+\mu)(\gamma+\mu)}{q}&\left(\frac{C'(\bar{\Lambda}/\bar{\mu})}{\bar{\Lambda}/\bar{\mu}}pr\,(\mu r+\eta s+\mu q+\mu s)\right.\\ &\left. + \frac{C(\bar{\Lambda}/\bar{\mu})}{\bar{\Lambda}/\bar{\mu}}r(p^2\bar{\mu}^2/\bar{\Lambda} + \eta s(1-p/(\bar{\Lambda}/\bar{\mu})))\right) < 0.\end{aligned}$$

Thus, $\det \mathcal{M} \neq 0$ and the result follows. □

Next, assuming that there is no loss of immunity, we obtain a corollary where an alternative condition for the existence of an endemic periodic orbit is given.

Corollary 4. *Assume that conditions* (P2)–(P6) *hold, that* $\overline{\mathcal{R}}_0 > 1$, *that* $\eta(t) = 0$ *for all* $t \geq 0$ *and that*

$$\frac{\Lambda^\ell \beta^\ell \varepsilon^\ell c_1}{\mu^u(\mu+\varepsilon)^u(\mu+\gamma)^u} > 1. \tag{42}$$

Then system (1) *has an endemic periodic solution of period* ω.

Proof. Since $\eta(t) = 0$ for all $t \geq 0$ we have, by the first equation in (6),

$$\mathrm{e}^{u_1(\chi_1)} \geq \frac{(\mu+\varepsilon)^\ell(\mu+\gamma)^\ell}{c_2\beta^u\varepsilon^u} \quad \text{and} \quad \mathrm{e}^{u_1(\xi_1)} \leq \frac{(\mu+\varepsilon)^u(\mu+\gamma)^u}{c_1\beta^\ell\varepsilon^\ell}.$$

Additionally

$$\begin{aligned} \Lambda(\xi_1)\,\mathrm{e}^{-u_1(\xi_1)} &= \beta(\xi_1)\varphi(\mathrm{e}^{u_1(\xi_1)}, w(\xi_1), \mathrm{e}^{u_3(\xi_1)})\,\mathrm{e}^{-u_1(\xi_1)} + \mu(\xi_1) \\ &= \beta(\xi_1)c_2\,\mathrm{e}^{u_3(\xi_1)} + \mu(\xi_1) \end{aligned}$$

and we conclude, using the hypothesis,

$$\begin{aligned} \mathrm{e}^{u_3(\xi_1)} &= \frac{\Lambda(\xi_1)\,\mathrm{e}^{-u_1(\xi_1)} - \mu(\xi_1)}{\beta(\xi_1)c_2} \geq \frac{\mu^u}{c_2\beta^u}\left(\frac{\Lambda^\ell}{\mu^u}\,\mathrm{e}^{-u_1(\xi_1)} - 1\right) \\ &\geq \frac{\mu^u}{c_2\beta^u}\left(\frac{c_1\Lambda^\ell\beta^\ell\varepsilon^\ell}{\mu^u(\mu+\varepsilon)^u(\mu+\gamma)^u} - 1\right) > 0. \end{aligned}$$

Thus, we can take

$$K^\ell = \frac{c_1\Lambda^\ell\beta^\ell\varepsilon^\ell}{\mu^u(\mu+\varepsilon)^u(\mu+\gamma)^u}$$

in (27) instead of the value obtained by Theorem 4. Note that (42) implies $\overline{\mathcal{R}}_0 > 1$ and we have the corollary. □

In [23] it is discussed the existence of periodic orbits for a model with mass-action incidence and disease induced mortality. When the disease induced mortality is set to zero ($\alpha \equiv 0$), the model considered in [23] becomes a particular case of ours. For the no disease induced mortality case, Corollary 4 improves the main result in [23]. Note that, for mass-action incidence, we can take $c_1 = 1$ in (42).

5. Examples

To illustrate our findings, in this section we will apply our results to some particular family of models.

Example 1. We consider a family of systems with incidence $\varphi(S, N, I) = SI/N$, with ω-periodic birth rate and loss of immunity rate and with all other parameters constant. Namely, we have the model

$$\begin{cases} S' = \Lambda(t) - \beta\,SI/N - \mu S - \eta(t)R \\ E' = \beta\,SI/N - \mu E + \epsilon E \\ I' = \epsilon E - (\mu+\gamma)I \\ R' = \gamma I - (\mu+\eta(t))R \\ N = S + E + I + R, \end{cases} \tag{43}$$

where $\Lambda(t+\omega) = \Lambda(t)$ and $\eta(t+\omega) = \eta(t)$. In this case, the matrices $F(t)$ and $V(t)$ are constant matrices and, by (ii) in Lemma 2.2 in [21], we have

$$\mathcal{R}_0 = \rho(FV^{-1}) = \frac{\beta\varepsilon}{(\mu+\varepsilon)(\mu+\gamma)} = \overline{\mathcal{R}}_0.$$

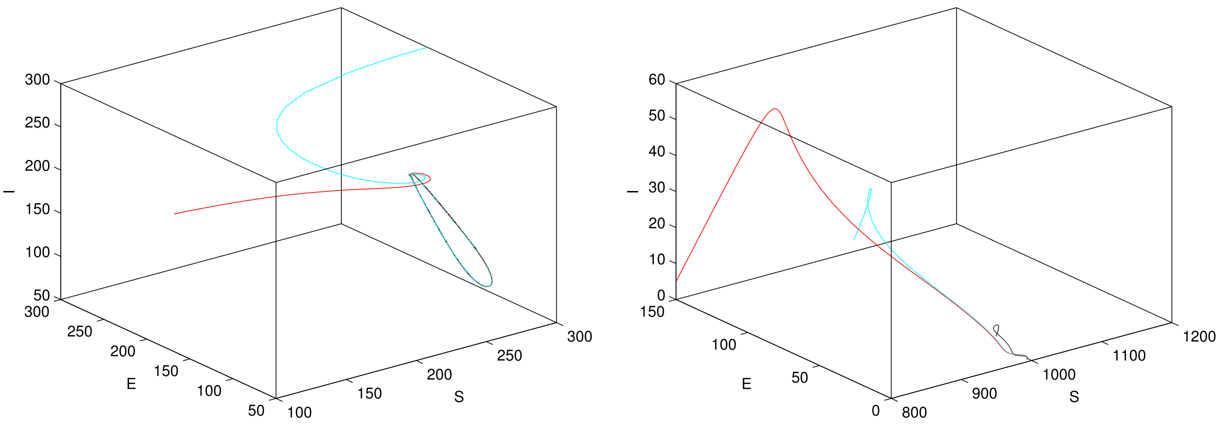

Fig. 1. Endemic case and disease-free case.

It is immediate that, in this case, $\mathcal{R}_0^\lambda = \mathcal{R}_0$ for all $\lambda \in (0,1]$. Thus for this family of models, Corollary 3 implies that $\mathcal{R}_0$ is a sharp threshold between existence and non existence of an endemic periodic orbit.

To obtain some numerical results we consider some particular values for the parameters taken from a real situation, the influenza epidemic occurred in an English boarding school in 1978, and described in the British medical journal "The Lancet", although, for some of the parameters, instead of a constant value we will consider a periodic function with that constant value as average. Namely, we consider $\gamma = \varepsilon = 1/2.2$, $\mu = 1/25\,550$, $\beta = 1.66$,

$$\eta(t) = 1/7(1 + 0.5\cos(2\pi t/365))$$

and we assume that $\Lambda(t) = 1000/25\,550$. For these parameters $\inf_{\lambda\in(0,1]} \mathcal{R}_0^\lambda = \mathcal{R}_0 = 3.65 > 1$ and $\det \mathcal{M} = -2.93 \neq 0$ (notice that, since $\inf_{\lambda\in(0,1]} \mathcal{R}_0^\lambda > 1$ and $\overline{\mathcal{R}}_0 > 1$, by Corollary 3 we already knew that $\det \mathcal{M} \neq 0$) and thus we have an endemic periodic orbit. In the left-hand side of Fig. 1 we plot the periodic orbit as well as the trajectories corresponding to the initial conditions $S(0) = 300$, $E(0) = 200$, $I(0) = 300$, $R(0) = 200$ and $S(0) = 150$, $E(0) = 250$, $I(0) = 150$, $R(0) = 450$. Changing β to 0.45 we obtain $\mathcal{R}_0 = 0.99 < 1$ and thus, by Theorem 3, we have extinction of the disease and all trajectories must approach the disease-free periodic orbit, that in this case is a disease-free equilibrium. In the right-hand side of Fig. 1 we plot the disease-free equilibrium as well as the trajectories corresponding to the initial conditions $S(0) = 980$, $E(0) = 15$, $I(0) = 5$, $R(0) = 0$ and $S(0) = 800$, $E(0) = 150$, $I(0) = 5$, $R(0) = 45$ and $S(0) = 900$, $E(0) = 75$, $I(0) = 25$, $R(0) = 0$.

In the left-hand side of Fig. 2 we plot the S, I and R components of the endemic periodic orbit corresponding to the endemic situation described above and on the right-hand side of Fig. 2 we plot the infective component of the solution for different trajectories corresponding to the disease-free situation described above. Next, we will try to get a better insight about condition (2) in Theorem 5, even though in the present situation $\det \mathcal{M} \neq 0$ is no additional restriction to $\inf_{\lambda\in(0,1]} \mathcal{R}_0^\lambda$ and $\overline{\mathcal{R}}_0 > 1$. Firstly, we let ε and β vary, maintaining the particular numerical values above for the other parameters, and, in the left-hand side of Fig. 3, plot the region where $\inf_{(0,1]} \mathcal{R}_0^\lambda > 1$ and the line $\det \mathcal{M} = 0$. Next, letting γ and β vary and maintaining the particular numerical values above for the other parameters, we plot in the right-hand side of Fig. 3 the region where $\inf_{\lambda\in(0,1]} \mathcal{R}_0^\lambda > 1$ and the line $\det \mathcal{M} = 0$.

Example 2. In model (1), assume that $\Lambda(t) = \Lambda_0 a(t)$ and $\mu(t) = \mu_0 a(t)$, with $a(t+\omega) = a(t)$, that $\beta(t) = \beta_0 b(t)$, $\varepsilon(t) = \varepsilon_0 b(t)$, $\gamma(t) = \gamma_0 b(t)$, $\beta(t) = \beta_0 b(t)$, with $b(t+\omega) = b(t)$, and that $\eta(t+\omega) = \eta(t)$. In

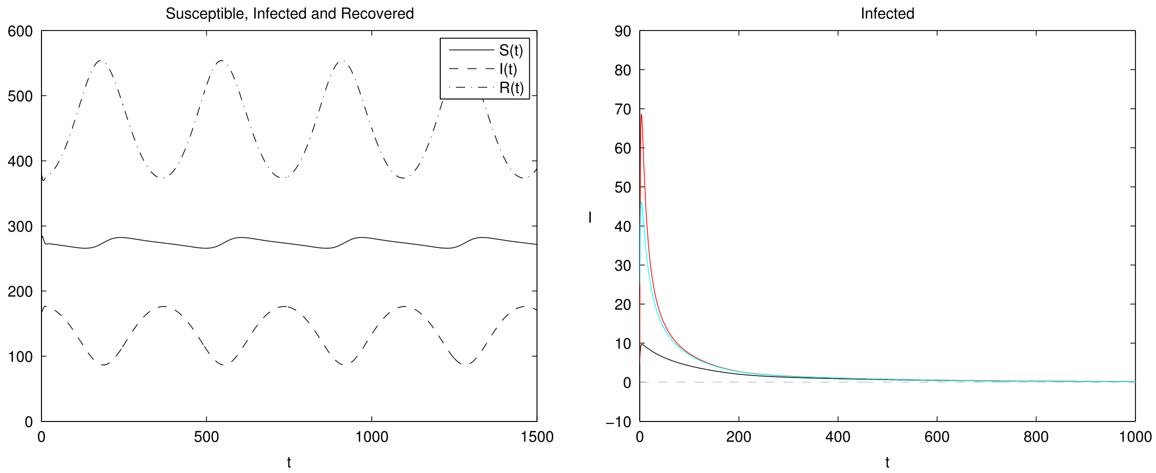

Fig. 2. Endemic orbit and infectives in the disease-free situation.

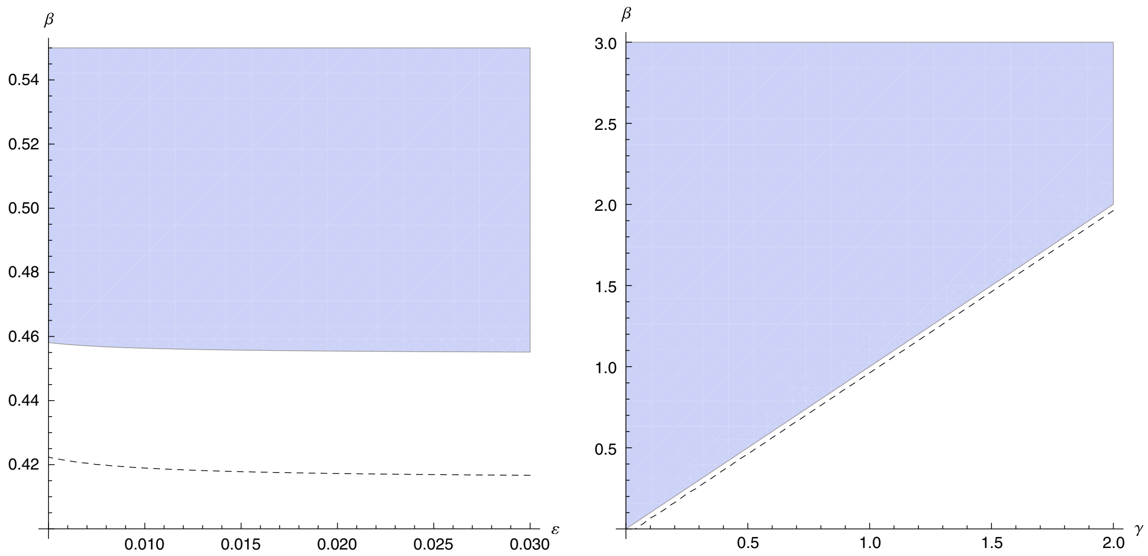

Fig. 3. Regions where Theorem 5 applies and condition $\det \mathcal{M} = 0$.

this case, for each $\lambda \in (0, 1]$, we have

$$\begin{aligned} B_{\lambda,\ell}(t) &:= F_\lambda(t)/\ell - V_\lambda(t) \\ &= \lambda \begin{bmatrix} -\mu_0 a(t) - \varepsilon_0 b(t) & \beta_0 \dfrac{\partial \varphi}{\partial I}(\Lambda_0/\mu_0, \Lambda_0/\mu_0, 0) b(t)/\ell \\ \varepsilon_0 b(t) & -\mu_0 a(t) - \gamma_0 b(t) \end{bmatrix}. \end{aligned}$$

Therefore

$$\begin{aligned} C_{\lambda,\ell}(t) &:= \int_0^t F_\lambda(s)/\ell - V_\lambda(s)\, ds \\ &= \lambda \begin{bmatrix} -\mu_0 \alpha_1(t) - \varepsilon_0 \alpha_2(t) & \beta_0 \dfrac{\partial \varphi}{\partial I}(\Lambda_0/\mu_0, \Lambda_0/\mu_0, 0) \alpha_2(t)/\ell \\ \varepsilon_0 \alpha_2(t) & -\mu_0 \alpha_1(t) - \gamma_0 \alpha_2(t) \end{bmatrix}, \end{aligned}$$

where

$$\alpha_1(t) = \int_0^t a(s)\,ds \quad \text{and} \quad \alpha_2(t) = \int_0^t b(s)\,ds.$$

In our conditions, it is easy to check that $B_{\lambda,\ell}(t)C_{\lambda,\ell}(t) = C_{\lambda,\ell}(t)B_{\lambda,\ell}(t)$. By Theorem 2.3 in [26] we conclude that

$$\begin{aligned}\Phi_{F_\lambda/\ell - V_\lambda}(\omega) &= Exp\left(\omega\lambda\begin{bmatrix} -(\bar{\mu}+\bar{\varepsilon}) & \bar{\beta}\dfrac{\partial\varphi}{\partial I}(\Lambda_0/\mu_0, \Lambda_0/\mu_0, 0)/\ell \\ \bar{\varepsilon} & -(\bar{\mu}+\bar{\gamma})\end{bmatrix}\right) \\ &= S^{-1}\begin{bmatrix} \mathrm{e}^{\omega\lambda p_+} & 0 \\ 0 & \mathrm{e}^{\omega\lambda p_-}\end{bmatrix} S,\end{aligned}$$

where

$$p_\pm = \frac{\lambda\omega(2\bar{\mu}+\bar{\varepsilon}+\bar{\gamma})}{2}\left(-1 \pm \sqrt{1 + \frac{4(\bar{\mu}+\bar{\varepsilon})(\bar{\mu}+\bar{\gamma})}{(2\bar{\mu}+\bar{\varepsilon}+\bar{\gamma})^2}(\mathcal{R}/\ell - 1)}\right),$$

where

$$\mathcal{R} = \frac{\varepsilon_0\beta_0\frac{\partial\varphi}{\partial I}(\Lambda_0/\mu_0, \Lambda_0/\mu_0, 0)}{(\mu_0+\varepsilon_0)(\mu_0+\gamma_0)}.$$

We conclude that

$$\rho(\Phi_{F_\lambda/\ell - V_\lambda}(\omega)) = 1 \quad \Leftrightarrow \quad \ell = \mathcal{R}$$

and thus, by (ii) in Theorem 2.1 in [21], we conclude that $\mathcal{R}_0^\lambda = \mathcal{R}_0 = \mathcal{R} = \overline{\mathcal{R}}_0$, for all $\lambda \in (0,1]$.

For this family of models, Theorem 5 implies that $\mathcal{R}_0$ is a sharp threshold between existence and non existence of an endemic periodic orbit.

To obtain some numerical results we again consider parameters inspired in the influenza epidemic occurred in an English boarding school in 1978, although, for some of the parameters, instead of a constant value we will consider a periodic function with that constant value as average. Namely, we consider $\gamma(t) = \varepsilon(t) = 1/2.2(1+0.1\cos(2\pi t/365))$, $\mu(t) = 1/25\,550(1+0.2\cos(2\pi t/365))$, $\beta(t) = 1.66(1+0.1\cos(2\pi t/365))$, $\eta(t) = 1/7(1+0.5\cos(2\pi t/365))$ and we assume that $\Lambda(t) = 1000/25\,550(1+0.2\cos(2\pi t/365))$. We consider again the incidence $\varphi(S,N,I) = SI/N$ (and thus $\partial\varphi/\partial I(\Lambda_0/\mu_0, \Lambda_0/\mu_0, 0) = 1$). In the left-hand side of Fig. 4 we can see a periodic orbit and the trajectories corresponding to the initial conditions $S(0) = 300$, $E(0) = 150$, $I(0) = 50$, $R(0) = 500$ and $S(0) = 500$, $E(0) = 100$, $I(0) = 25$, $R(0) = 375$. This is consistent with the fact that, in this case, $\inf_{\lambda\in(0,1]}\mathcal{R}_0^\lambda = \mathcal{R}_0 = \overline{\mathcal{R}}_0 = 3.65 > 1$ and $\det\mathcal{M} = -2.93 \neq 0$ (by Corollary 3 we already knew that $\det\mathcal{M} \neq 0$). On the other hand, letting now $\beta = 0.45$ we get $\mathcal{R}_0 = 0.99 < 1$ and, by Theorem 3, we conclude that we have extinction. This can be seen in the left-hand side of Fig. 4 where we plot the trajectories with the initial conditions $S(0) = 980$, $E(0) = 15$, $I(0) = 5$, $R(0) = 0$, $S(0) = 800$, $E(0) = 150$, $I(0) = 50$, $R(0) = 0$ and $S(0) = 900$, $E(0) = 75$, $I(0) = 25$, $R(0) = 0$.

In the left-hand side of Fig. 5 we plot the S, I and R components of the endemic periodic orbit corresponding to the endemic situation described above and on the right-hand side of Fig. 5 we plot the infective component of the solution for different trajectories corresponding to the disease-free situation described above.

Notice that the regions in Fig. 3 are also regions where Theorem 5 applies in the present context since $\inf_{\lambda\in(0,1]}\mathcal{R}_0^\lambda$ gives the same expression in this context and also $\det\mathcal{M} = 0$ is the same line since the average of the parameters in this case corresponds to the values of the parameters in the previous situations.

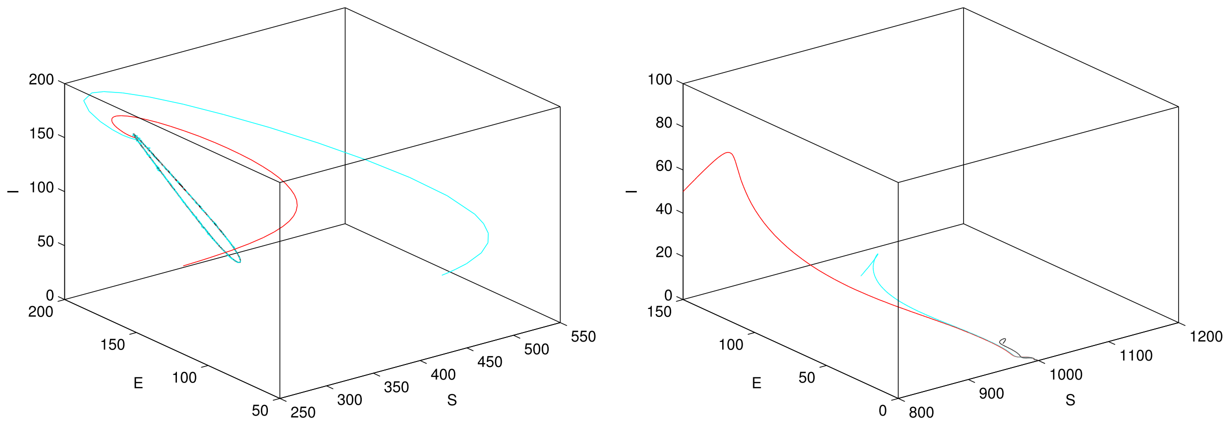

Fig. 4. Endemic case and disease-free case.

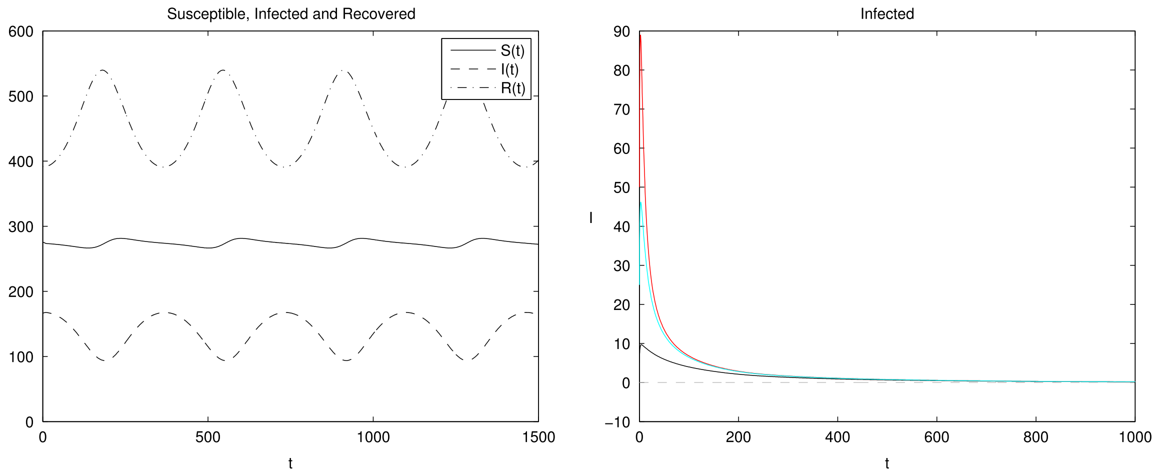

Fig. 5. Endemic orbit and infectives in the disease-free situation.

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Further reading

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