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Backward bifurcation for pulse vaccination

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ABSTRACT

We investigate an SIVS model with pulse vaccination strategy. First we compute the disease free periodic solution and prove its global asymptotic stability in the disease free subspace. We identify the corresponding control reproduction number R_c and prove that the disease free periodic solution is locally asymptotically stable if $R_c < 1$, and under some additional conditions it is globally asymptotically stable as well. For $R_c > 1$ we prove the uniform persistence of the disease. Our main result is that nontrivial endemic periodic solutions are bifurcating from the disease free periodic solution as R_c is passing through the threshold value one. A complete bifurcation analysis is provided for the associated nonlinear fixed point equation. We show that backward bifurcation of periodic orbits is possible for suitable parameter values, and give explicit conditions to determine whether the bifurcation is backward or forward. The main mathematical tools are comparison principles and Lyapunov–Schmidt reduction. Finally, we compare the pulse vaccination strategy with continuous vaccination, and illustrate that backward bifurcation occurs in more realistic models as well when pulse vaccination is applied.

1. Introduction

Vaccination is a common and effective strategy to control and to prevent the spread of communicable diseases, thus understanding the impact of various vaccination schemes on the transmission dynamics is of major public health concern. In compartmental models we divide the population being studied into several disjoint classes (*S*usceptible, *I*nfected, *V*accinated, *R*ecovered, etc.), and use differential equations to describe the transition of individuals among those classes. The basic reproduction number R_0 (corresponds to models of uncontrolled epidemics) and the control reproduction number R_c (corresponds to models where some control measure is applied) are key concepts in mathematical epidemiology, as they express the expected number of secondary infections caused by a single infective introduced into a wholly susceptible (or controlled) population.

Typically, the infection dies out if $R_c < 1$, and the disease remains endemic if $R_c > 1$. In most models, for $R_c < 1$ the disease free equilibrium is the unique steady state and there is a bifurcation at $R_c = 1$, when the disease free equilibrium loses its stability and a stable endemic equilibrium appears for $R_c > 1$. Such a transition of stability is called forward bifurcation. However, in some models the situation is very different: there exist multiple endemic equilibria for $R_c < 1$, even stable one. In this case, there may be a self-sustained epidemic even though the reproduction number is less than one. This situation is called backward bifurcation (see Fig. 1 for a sketch). The nature of this bifurcation has serious implications for disease control: in the first case, it is sufficient to apply a control measure such that R_c becomes less than one to eradicate the disease, while in the second case it is necessary to decrease R_c well below one to ensure that the disease will die out. In various vaccination models, backward bifurcation can appear if the vaccination is imperfect.

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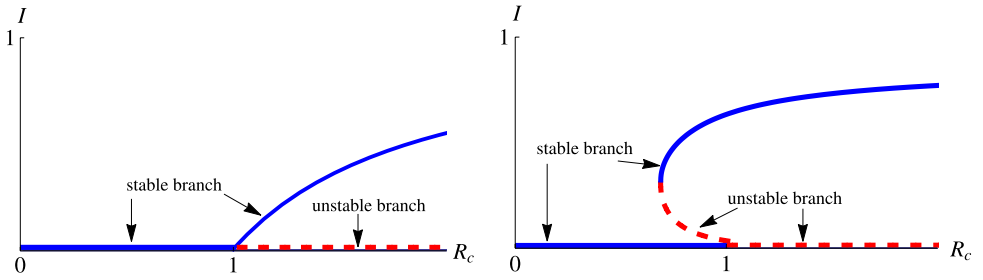

Fig. 1. The types of bifurcation appearing in simple SIVS model.

The susceptible–vaccinated–infected–removed–susceptible (SVIRS) model

$$\begin{cases} S'(t) = \Lambda(1-\Phi) + \omega_v V(t) + \omega_r R(t) - \dfrac{\beta I(t)}{N(t)} S(t) - \mu S(t), \\ V'(t) = \Lambda\Phi - (1-\psi)\dfrac{\beta I(t)}{N(t)} V(t) - (\omega_v + \mu) V(t), \\ I'(t) = \dfrac{\beta I(t)}{N(t)} S(t) + (1-\psi)\dfrac{\beta I(t)}{N(t)} V(t) - (\sigma_u + \mu) I, \\ R'(t) = \sigma_u I(t) - (\omega_r + \mu) R(t) \end{cases} \tag{1}$$

with waning immunity and imperfect cohort vaccination was analyzed in [1], where one can read the detailed explanation of the terms and parameters.

This model can be simplified if we replace the recruitment term Λ by $\mu N(t)$, then the recruitment and the mortality is balanced and the population size remains constant, what we can normalize to $N(t) = 1$ without loss of generality. The model further reduces if infected individuals do not develop natural immunity, and patients moving immediately to the susceptible class (this is the limit case when the length of immunity $1/\omega_r \to 0$, or equivalently $\omega_r \to \infty$). We replace cohort vaccination by continuous vaccination strategy, that is $\Phi = 0$, and a new parameter ϕ is introduced which describes the vaccination rate at which individuals are moving from the S-class to the V-class. By these simplifying assumptions and modifications, we arrive at the simple SIVS model studied by Brauer [2]:

$$\begin{cases} S'(t) = \mu - \beta S(t) I(t) - \mu S(t) + \gamma I(t) + \theta V(t) - \varphi S(t), \\ I'(t) = \beta S(t) I(t) - (\mu + \gamma) I(t) + \sigma\beta V(t) I(t), \\ V'(t) = \varphi S(t) - \sigma\beta V(t) I(t) - (\mu + \theta) V(t), \end{cases} \tag{2}$$

where we changed the notation ω_v to θ, σ_u to γ and $1-\psi$ to σ to follow the notation of [2] throughout this paper. In model (2), β is the transmission rate, μ is the birth and death rate, γ is the recovery rate, φ is the vaccination rate. The vaccination may reduce, but not completely eliminate susceptibility to infection: this is modeled by including a factor σ, $0 \le \sigma \le 1$. If $\sigma = 0$, the vaccine is perfectly effective, while $\sigma = 1$ means that the vaccine has zero effect. It is assumed that the vaccination loses effect at rate θ. In this model the constant population size $S(t) + I(t) + V(t) = 1$ is assumed. Brauer investigated this vaccination model and proved the existence of multiple endemic equilibria and backward bifurcation for suitable parameter values [2]. Backward bifurcation has been observed in different epidemic models in various contexts: for malaria [3], influenza [4], HSV-2 [5], Hepatitis B and C [6], chlamydia trachomatis [7], dengue [8], tuberculosis in [9] and general models with treatment [10].

Here we modify model (2), by replacing the continuous vaccination term by a pulse vaccination strategy. We study the resulting system of impulsive differential equations. The pulse scheme is a repeated application of the vaccine at distinct times, so we vaccinate a fraction φ of the susceptible population after each time T. It is known from [11–13], that sometimes pulse vaccination is more effective than continuous vaccination, therefore it is natural to investigate the dynamics and the backward–forward bifurcations of model (2) with pulse vaccination.

2. The model

Consider the following pulse vaccination model, based on (7):

$$\begin{cases} \begin{cases} S'(t) = \mu - \beta S(t) I(t) - \mu S(t) + \gamma I(t) + \theta V(t), \\ I'(t) = \beta S(t) I(t) - (\mu + \gamma) I(t) + \sigma\beta V(t) I(t), \qquad \text{if } t \ne nT, \\ V'(t) = -\sigma\beta V(t) I(t) - (\mu + \theta) V(t), \end{cases} \\ \begin{cases} S\left(nT^+\right) = (1-\varphi) S\left(nT^-\right), \\ I\left(nT^+\right) = I\left(nT^-\right), \qquad \text{if } t = nT. \\ V\left(nT^+\right) = V\left(nT^-\right) + \varphi S\left(nT^-\right), \end{cases} \end{cases} \tag{3}$$

where $n = 1, 2, \ldots$ is the period of pulse vaccination, nT^+ is the time, when we apply the n-th pulse, nT^- is the time, just before applying the n-th pulse. We may assume $S(t) + I(t) + V(t) = 1$, thus we can reduce system (3) to the following:

$$\begin{cases} S'(t) = \mu + \theta - \beta S(t)I(t) - (\mu + \theta)S(t) + (\gamma - \theta)I(t), \\ I'(t) = \beta S(t)I(t) - (\mu + \gamma)I(t) + \sigma\beta(1 - S(t) - I(t))I(t), \quad \text{if } t \neq nT, \\ \begin{cases} S\left(nT^+\right) = (1-\varphi)S\left(nT^-\right), \\ I\left(nT^+\right) = I\left(nT^-\right), \end{cases} \qquad \text{if } t = nT. \end{cases} \tag{4}$$

Due to the biological interpretation, we study (3) in the set

$$\Omega = \left\{(S, I, V) \in \mathbb{R}^3 : S + I + V = 1, S \geq 0, I \geq 0, V \geq 0\right\},$$

which is invariant (it can be seen from the right-hand side of (4)).

The more general form of an impulsive differential equation with fixed impulse times reads as

$$\begin{cases} x'(t) = f(x(t)), & t \neq t_i, \\ x\left(t_i^+\right) = J_i\left(x\left(t_i^-\right)\right), \end{cases}$$

where $\{t_i\}$ is monotone increasing and unbounded, $f : \mathbb{R}^n \to \mathbb{R}^n$ and $J_i : \mathbb{R}^n \to \mathbb{R}^n$ are continuous functions, $i = 1, 2, \ldots$. Impulsive differential equations naturally arise in many fields of mathematical biology: besides pulse vaccination, they can be applied for example to modeling chemotherapeutic treatment of tumors [14,15] or pest control [16].

In the context of disease transmission, there are several papers in the literature considering pulse vaccination strategy. The basic SIR model was extended by pulse vaccination in [13,17] and [18]. Exposed and carrier compartments were added in [19–21], where the global asymptotic stability of the disease free periodic solution was shown for $R_c < 1$. When $R_c > 1$, usually the system has permanence, which was proved in [22] with nonlinear incidence. The existence of a periodic endemic solution for $R_c > 1$ was established in [23] and [12] for somewhat different models. In the next sections, besides the usual results for the stability of the disease free periodic solution and persistence, we prove that in system (4) subthreshold nontrivial periodic endemic solutions may exist, via a backward bifurcation of periodic solutions from the disease free periodic solution at $R_c = 1$.

To the best of our knowledge, this is the first paper where backward bifurcation is proved for a pulse vaccination model.

3. Disease-free periodic solution

Lemma 1. *The unique disease-free periodic solution*

$$\begin{cases} \bar{S}(t) = 1 + e^{-(t-nT)(\mu+\theta)}\left(\dfrac{\left(1 - e^{-T(\mu+\theta)}\right)(1-\varphi)}{1 - (1-\varphi)e^{-T(\mu+\theta)}} - 1\right), \quad t \in (nT, (n+1)T), \\ \bar{S}(nT) = \dfrac{\left(1 - e^{-T(\mu+\theta)}\right)(1-\varphi)}{1 - (1-\varphi)e^{-T(\mu+\theta)}}, \\ \bar{I}(t) = 0, \quad t \geq 0, \end{cases} \tag{5}$$

of system (4) is globally asymptotically stable in the disease-free subspace.

Proof. First we calculate the disease-free periodic solution, i.e. we assume $I(t) = 0, t \geq 0$. Under this condition (4) simplifies to

$$\begin{cases} S'(t) = \mu + \theta - (\mu + \theta)S(t), \\ S\left(nT^+\right) = (1-\varphi)S\left(nT^-\right). \end{cases} \tag{6}$$

In the time interval $nT \leq t \leq (n+1)T$, system (6) has the solution

$$S(t) = 1 + e^{-(t-nT)(\mu+\theta)}(S(nT^+) - 1). \tag{7}$$

Let S_{n+1} the size of susceptible population after the $(n+1)$-th pulse, i.e. $S_{n+1} = S\left((n+1)T^+\right)$. From (7),

$$S_{n+1} = (1-\varphi)\left(1 + e^{-T(\mu+\theta)}(S_n - 1)\right) =: \psi(S_n).$$

The map ψ has a unique positive fixed point

$$S^* = \frac{\left(1 - e^{-T(\mu+\theta)}\right)(1-\varphi)}{1 - (1-\varphi)e^{-T(\mu+\theta)}}.$$

If $t \neq nT$,

$$\begin{aligned}\bar{S}(t) &= 1 + e^{-(t-nT)(\mu+\theta)}\left(\frac{\left(1-e^{-T(\mu+\theta)}\right)(1-\varphi)}{1-(1-\varphi)e^{-T(\mu+\theta)}} - 1\right)\\ &= 1 + e^{-(t+T-(n+1)T)(\mu+\theta)}\left(\frac{\left(1-e^{-T(\mu+\theta)}\right)(1-\varphi)}{1-(1-\varphi)e^{-T(\mu+\theta)}} - 1\right)\\ &= \bar{S}(t+T),\end{aligned}$$

and in case $t = nT$, $\bar{S}(t) = S^* = \bar{S}((n+1)T)$, so (5) is periodic with period T. Thus, (5) is a solution of system (4) not only in the time interval $[0, T)$, but also for all $t \geq 0$. Since (5) in the time interval $[0, T)$ is

$$\bar{S}(t) = 1 + e^{-t(\mu+\theta)}\left(\frac{\left(1-e^{-T(\mu+\theta)}\right)(1-\varphi)}{1-(1-\varphi)e^{-T(\mu+\theta)}} - 1\right),$$

$\left(\bar{S}(t), 0\right)$ is a solution of (4). From the above calculations, at $t = nT$ the pulse conditions are satisfied.

From $0 < \left(\psi'(S^*)\right)' = (1-\varphi)\left(e^{-T(\mu+\theta)}\right) < 1$, we obtain that S^* is a stable fixed point of ψ. Since ψ is a linear map, S^* is asymptotically stable. □

Analogously to the concept of the basic reproduction number, the control reproduction number is the expected number of secondary infections caused by a single infected individual introduced into a disease free population where some control measure is applied (in our case, vaccination). In our model, in the absence of the disease, the number of susceptibles is a T-periodic function, thus the control reproduction number can be expressed as the product of the mean infectious period $\left(\frac{1}{\mu+\gamma}\right)$ and the number of secondary infections generated per unit time, averaged over a period of length T. That is the transmission coefficient β multiplied by the average number of susceptibles in such a period (i.e. $\frac{1}{T}\int_0^T \bar{S}(u)du$) and additionally, since vaccination is not perfect, the average number of vaccinated individuals who contract the infection $\left(\sigma\frac{1}{T}\int_0^T\left(1-\bar{S}(u)\right)du\right)$, so we define

$$R_c := \frac{\beta}{\mu+\gamma}\left(\frac{1}{T}\int_0^T \bar{S}(u)du + \sigma\frac{1}{T}\int_0^T\left(1-\bar{S}(u)\right)du\right).$$

In the next theorem we show that R_c is indeed a stability threshold for the disease free periodic solution.

Theorem 1. *The disease-free periodic solution (5) is locally asymptotically stable, if $R_c < 1$ and unstable, if $R_c > 1$*

Proof. We linearize (4) around the disease-free periodic solution, so let

$$\begin{cases} S(t) = s(t) + \bar{S}(t), \\ I(t) = i(t) + \bar{I}(t), \end{cases}$$

and we obtain

$$\begin{cases} s'(t) = -\beta\bar{S}(t)i(t) - \mu s(t) + \gamma i(t) + \theta(-s(t) - i(t)), \\ i'(t) = \beta\bar{S}(t)i(t) - (\mu+\gamma)i(t) + \sigma\beta\left(1-\bar{S}(t)\right)i(t), \end{cases} \tag{8}$$

subject to the vaccination scheme

$$\begin{cases} s\left(T^+\right) = (1-\varphi)s\left(T^-\right), \\ i\left(T^+\right) = i\left(T^-\right). \end{cases} \tag{9}$$

We have to investigate the stability of equilibrium $(0, 0)$ of system (8). Consider the corresponding fundamental matrix

$$A(t) = \begin{pmatrix} s_1(t) & s_2(t) \\ i_1(t) & i_2(t) \end{pmatrix},$$

where $(s_1(t), i_1(t))$ and $(s_2(t), i_2(t))$ are solutions of (8) with initial values $(s_1(0), i_1(0))$ and $(s_2(0), i_2(0))$. Set

$$\begin{aligned} s_1(0) &= 1, \quad s_2(0) = 0, \\ i_1(0) &= 0, \quad i_2(0) = 1. \end{aligned}$$

To apply Floquet-theory, we calculate the monodromy matrix ($A(T)$ after we apply the first impulse), which is the following:

$$M := \begin{pmatrix} (1-\varphi)e^{-(\mu+\theta)T} & (1-\varphi)s_2(T) \\ 0 & e^{\int_0^T \beta\bar{S}(u) - (\mu+\gamma) + \sigma\beta\left(1-\bar{S}(u)\right)du} \end{pmatrix}.$$

Since the characteristic equation of M is

$$\left((1-\varphi)e^{-(\mu+\theta)T}-\lambda\right)\left(e^{\int_0^T \beta\bar{S}(u)-(\mu+\gamma)+\sigma\beta\left(1-\bar{S}(u)\right)du}-\lambda\right)=0,$$

we do not need to calculate $s_2(T)$. The eigenvalues of M are $\lambda_1=(1-\varphi)e^{-(\mu+\theta)T}$ and $\lambda_2=e^{\int_0^T \beta\bar{S}(u)-(\mu+\gamma)+\sigma\beta(1-\bar{S}(u))\,du}$. From the Floquet-theorem, the equilibrium $(0,0)$ is locally asymptotically stable, if the moduli of all eigenvalues are less than 1. It is obvious that $\lambda_1<1$, and $\lambda_2<1$ if and only if $\int_0^T \beta\bar{S}(u)-(\mu+\gamma)+\sigma\beta\left(1-\bar{S}(u)\right)du<0$, that is $\frac{1}{T}\int_0^T \bar{S}(u)+\sigma\left(1-\bar{S}(u)\right)du<\frac{\mu+\gamma}{\beta}$. This inequality can be rearranged as $R_c<1$. □

The next theorem states that under an additional condition, the disease-free periodic solution is globally asymptotically stable.

Theorem 2. *Suppose $\gamma-\theta\le 0$, then the disease-free periodic solution is globally asymptotically stable if $R_c<1$.*

Proof. If $\gamma-\theta\le 0$, then

$$S'(t)=\mu+\theta-\beta S(t)I(t)-(\mu+\theta)S(t)+(\gamma-\theta)I(t)\le\mu+\theta-(\mu+\theta)S(t),$$

so we consider the following comparison system:

$$\begin{cases}x'(t)=\mu-\mu x(t)+\theta-\theta x(t),\\ x\left(nT^+\right)=(1-\varphi)x\left(nT^-\right).\end{cases}\tag{10}$$

The disease-free periodic solution is a solution of this system and according to Lemma 1, the periodic solution $\bar{S}(t)$ is globally asymptotically stable. By the comparison principle [24], for all $\epsilon_1>0$ there exists an $m_1\ge 0$, such that

$$S(t)<\bar{S}(t)+\epsilon_1,\quad nT<t<(n+1)T,\quad nT\ge m_1T.$$

From the second equation of system (4), we have

$$I'(t)\le I(t)(\beta(1-\sigma)(\bar{S}(t)+\epsilon_1)-(\mu+\gamma-\sigma\beta)),\qquad nT\le t\le(n+1)T,\qquad nT\ge m_1T.$$

Then we consider the following comparison system:

$$\begin{cases}y'(t)=y(t)\left(\beta(1-\sigma)(\bar{S}(t)+\epsilon_1)-(\mu+\gamma-\sigma\beta)\right),\\ y\left(nT^+\right)=y\left(nT^-\right)\end{cases}\tag{11}$$

so, we have $y(t)\ge I(t)$ for large t. Integrating system (11) between pulses $[nT,(n+1)T]$, we obtain

$$y((n+1)T)=y(nT)e^{\int_{nT}^{(n+1)T}\beta(1-\sigma)(\bar{S}(t)+\epsilon_1)-(\mu+\gamma-\sigma\beta)\,dt}.$$

Using iteration step by step, we find

$$y(nT)=y_{m_1}e^{(n-m_1)\int_0^T\beta(1-\sigma)(\bar{S}(t)+\epsilon_1)-(\mu+\gamma-\sigma\beta)\,dt}$$

where $y_{m_1}=y\left(m_1T^+\right)>0$. Since $R_c\le 1$, i.e. $\frac{1}{T}\int_0^T\bar{S}(u)+\sigma\left(1-\bar{S}(u)\right)du<\frac{\mu+\gamma}{\beta}$, we can choose ϵ_1 sufficiently small, such that $\frac{1}{T}\int_0^T\bar{S}(u)+\sigma\left(1-\bar{S}(u)\right)+\epsilon_1\,du<\frac{\mu+\gamma}{\beta}$, then we obtain $\lim_{n\to\infty}y(nT)=0$. Thus, we know each solution of system (11)

$$y(t)=y(nT)e^{\int_{nT}^t\beta(1-\sigma)(\bar{S}(t)+\epsilon_1)-(\mu+\gamma-\sigma\beta)ds},\quad nT\le t\le(n+1)T$$

tends to zero, i.e. $\lim_{t\to\infty}y(t)=0$. So we have $\lim_{t\to\infty}I(t)=0$. Then, for any (sufficiently small) $\epsilon_2>0$ there exists $m_2\ge 0$, $m_2\in\mathbb{Z}$, $m_1<m_2$, such that $I(t)<\epsilon_2$ $(t>m_2T>m_1T)$.

Similarly, from the first equation of (4), we have $S'(t)>\mu-\beta S(t)\epsilon_2-\mu S(t)+\theta\left(1-S(t)-\epsilon_2\right)$. Next consider the comparison system

$$\begin{cases}z'(t)=\mu-\beta z(t)\epsilon_2-\mu z(t)+\theta\left(1-z(t)-\epsilon_2\right),\\ z\left(nT^+\right)=(1-\varphi)z\left(nT^-\right).\end{cases}$$

Similarly, we can calculate the unique periodic solution $\bar{z}(t)$ with period T and the fixed point z^*, which is globally asymptotically stable. The periodic solution $\bar{z}(t)$ is the following:

$$\begin{aligned}\bar{z}(t)=&\frac{\mu+\theta\left(1-\epsilon_2\right)}{\mu+\theta+\beta\epsilon_2}+e^{-(t-nT)(\mu+\theta+\beta\epsilon_2)}\frac{(1-\varphi)\frac{\mu+\theta(1-\epsilon_2)}{\mu+\theta+\beta\epsilon_2}\left(1-e^{-(\mu+\theta+\beta\epsilon_2)T}\right)}{1-(1-\varphi)e^{-(\mu+\theta+\beta\epsilon_2)T}}\\ &-e^{-(t-nT)(\mu+\theta+\beta\epsilon_2)}\frac{\mu+\theta\left(1-\epsilon_2\right)}{\mu+\theta+\beta\epsilon_2},\quad nT<t<(n+1)T.\end{aligned}$$

Let $z(t)$ be any solution of the comparison system with initial value $z_0 = z\left(0^+\right) > 0$. It follows from the comparison principle that any solution of system (4) with initial values $S_0 = S\left(0^+\right) = z_0 > 0$ and $I_0 = I\left(0^+\right) > 0$, there exists an $m_3 \geq 0$, $m_3 \in \mathbb{Z}$, $m_1 < m_2 < m_3$, such that

$$S(t) > \bar{z}(t) - \epsilon_2, \qquad nT < t < (n+1)T, \qquad nT > m_3 T.$$

Thus we have $\bar{z}(t) - \epsilon_2 < S(t) < \bar{S}(t) + \epsilon_1$, where $\bar{z}(t) \to \bar{S}(t)$ uniformly as $\epsilon_2 \to 0$. Because ϵ_1 and ϵ_2 are arbitrarily small we have $S(t) \to \bar{S}(t)$, as $t \to \infty$. Thus, $\bar{S}(t)$ is globally attractive, which implies the disease-free periodic solution is globally asymptotically stable. □

4. Persistence of the disease

Theorem 3. *If $R_c > 1$, then there exists a positive constant m_I, such that for any positive solution $I(t)$ of system (4), $\liminf_{t\to\infty} I(t) \geq m_I$, i.e. the disease is uniformly strongly persistent.*

Proof. We consider a solution (S, I) of system (4) and a constant $I^* \in (0, 1)$. Suppose there exists $t_0 > 0$, such that $I(t_0) < I^*$. Let $t_1 := \sup\{s : I(t_0 + u) < I^*, u < s\}$. This time interval of length t_1 can be finite or infinite. First, we prove t_1 is finite when I^* is appropriately chosen. Assume that $t_1 = \infty$. We see that $I(t) < I^*$ holds in interval $[t_0, \infty)$. Then, from the first equation of (4),

$$S'(t) > \mu - \beta I^* - \mu S(t) + \theta\left(1 - S(t) - I^*\right)$$

as $t \geq t_0$. We consider the following comparison system:

$$\begin{cases} w'(t) = \mu - \beta I^* - \mu w(t) + \theta\left(1 - w(t) - I^*\right), \\ w\left(nT^+\right) = (1-\varphi) w\left(nT^-\right), \\ w\left(\tilde{t}_0^+\right) = 0, \end{cases} \tag{12}$$

as $t > \tilde{t}_0$, where $\tilde{t}_0 := \left\lceil \frac{t_0}{T} \right\rceil T$. We can calculate the periodic solution $\bar{w}$ with period T and we can deduce (similarly as in Lemma 1) that this solution is globally asymptotically stable:

$$\begin{aligned} \bar{w}(t) = {} & \frac{\mu + \theta - (\beta + \theta) I^*}{\mu + \theta} \\ & + e^{-(\mu+\theta)(t-nT)} \frac{(1-\varphi)\frac{\mu+\theta-(\beta+\theta)I^*}{\mu+\theta}\left(1 - e^{-(\mu+\theta)T}\right)}{1 - (1-\varphi)e^{-(\mu+\theta)T}} \\ & - e^{-(\mu+\theta)(t-nT)} \frac{\mu + \theta - (\beta+\theta) I^*}{\mu + \theta}, \quad nT < t < (n+1)T. \end{aligned} \tag{13}$$

From the first equation of (4), we also get $S'(t) \leq \mu + \theta - (\mu + \theta) S(t) + |\gamma - \theta| I^*$, so we can consider the following comparison system:

$$\begin{cases} u'(t) = \mu + \theta - (\mu + \theta) u(t) + |\gamma - \theta| I^*, \\ u\left(nT^+\right) = (1-\varphi) u\left(nT^-\right), \\ u\left(\tilde{t}_0\right) = 1. \end{cases}$$

We compute the globally asymptotically stable, T-periodic solution $\bar{u}$:

$$\begin{aligned} \bar{u}(t) = {} & \frac{\mu + \theta + (\gamma - \theta) I^*}{\mu + \theta} \\ & + e^{-(\mu+\theta)(t-nT)} \frac{(1-\varphi)\frac{\mu+\theta+|\gamma-\theta|I^*}{\mu+\theta}\left(1 - e^{-(\mu+\theta)T}\right)}{1 - (1-\varphi)e^{-(\mu+\theta)T}} \\ & - e^{-(\mu+\theta)(t-nT)} \frac{\mu + \theta + |\gamma - \theta| I^*}{\mu + \theta}, \quad nT < t < (n+1)T. \end{aligned} \tag{14}$$

From the comparison principle, for any $\epsilon > 0$ there exists $t_2 > 0$, such that $\bar{u}(t) + \epsilon > u(t) \geq S(t) \geq w(t) > \bar{w}(t) - \epsilon$, as $t > \tilde{t}_0 + t_2$.

From the second equation of system (4), we obtain

$$I'(t) \geq I(t)\left(\beta\left(\bar{w}(t) - \epsilon\right) - (\mu + \gamma) + \sigma\beta\left(1 - \bar{u}(t) - \epsilon - I^*\right)\right)$$

if $t > \tilde{t}_0 + t_2$. Let $K^* \in \mathbb{Z}^+$, $K^* T > \tilde{t}_0 + t_2$ and integrating between pulses $[kT, (k+1)T]$ for $k > K^*$ yields

$$I((k+1)T) \geq I(kT) e^{\int_{kT}^{(k+1)T} \beta(\bar{w}(t)-\epsilon) - (\mu+\gamma) + \sigma\beta\left(1 - (\bar{u}(t)+\epsilon) - I^*\right) dt}, \tag{15}$$

then we obtain

$$I\left(\left(K^*+n\right)T\right) \geq I\left(K^*T\right)e^{n\int_0^T \beta(\bar{w}(t)-\epsilon)-(\mu+\gamma)+\sigma\beta\left(1-(\bar{u}(t)+\epsilon)-I^*\right)dt}.$$

Define $\alpha := \int_0^T \beta\left(\bar{w}(t)-\epsilon\right)-(\mu+\gamma)+\sigma\beta\left(1-(\bar{u}(t)+\epsilon)-I^*\right)dt$. We see from (13) and (14), that $\bar{w}(t)-\epsilon \to \bar{S}(t)$ and $\bar{u}(t)+\epsilon \to \bar{S}(t)$ as $\epsilon \to 0$ and $I^* \to 0$. If ϵ and I^* are sufficiently small, then from $R_c > 1$ we have that $\alpha > 0$. Thus $I\left(\left(K^*+n\right)T\right) \geq I\left(K^*T\right)e^{n\alpha} \to \infty$ as $n \to \infty$, which contradicts the boundedness of $I(t)$, therefore if I^* is sufficiently small, then $t_1 < \infty$.

Let us fix these previous ϵ and I^*, for which $t_1 < \infty$. Then two options remained: there exists a $t_3 > \tilde{t}_0 + t_2$, such that $I(t) \geq I^*$ for all $t \geq t_3$ or $I(t)$ oscillates about I^*. We begin with the second case: from the oscillatory property we can define an unbounded, monotone increasing sequence $\{\tau_i\}$ such that $\tau_i > \tilde{t}_0 + t_1$, $I(\tau_{2i}) < I^*$ and $I(\tau_{2i+1}) \geq I^*$. Choose an arbitrary τ_{2k}. Let $\tau_* := \inf\{\tau : \tau_{2k-1} < \tau < \tau_{2k}, I(\tau) \leq I^*\}$, $\tilde{\tau}_* := \left\lceil \frac{\tau_*}{T} \right\rceil T - \tau_*$ and similarly $\tau^* := \sup\{\tau : \tau_{2k} < \tau < \tau_{2k+1}, I(\tau) \leq I^*\}$, $\tilde{\tau}^* := \tau^* - \left\lfloor \frac{\tau^*}{T} \right\rfloor T$. Let $l := \min\left\{n \in \mathbb{N} : e^{-(2T+t_2)(\mu+\gamma+\sigma\beta)+n\alpha} > 1\right\}$. We see that $\tilde{\tau}_* < T$, $\tilde{\tau}^* < T$, and from the continuity of $I(t)$, we have $I(\tau_*) = I(\tau^*) = I^*$. There exists such an l, because $\alpha > 0$. We claim that $\tau^* - \tau_* < 2T + t_2 + lT$. Indirectly, assume that $\tau^* - \tau_* > 2T + t_2 + lT$. Then, from $I'(t) \geq -(\mu+\gamma+\sigma\beta)I(t)$, we have

$$I\left(\tau_* + \tilde{\tau}_* + \tilde{\tau}^* + t_2\right) \geq I^* e^{-\left(\tilde{\tau}_* + \tilde{\tau}^* + t_2\right)(\mu+\gamma+\sigma\beta)} > I^* e^{-(2T+t_2)(\mu+\gamma+\sigma\beta)}.$$

From the indirect assumption $I(\tau_* + \tilde{\tau}_* + \tilde{\tau}^* + t_2 + lT) < I^*$, but from (15) we obtain

$$\begin{aligned} I\left(\tau_* + \tilde{\tau}_* + \tilde{\tau}^* + t_2 + lT\right) &\geq I^* e^{-\left(\tilde{\tau}_* + \tilde{\tau}^* + t_2\right)(\mu+\gamma+\sigma\beta)} e^{l\alpha} \\ &> I^* e^{-(2T+t_2)(\mu+\gamma+\sigma\beta)} e^{l\alpha} > I^*, \end{aligned}$$

which is a contradiction.

Hence $\tau^* - \tau_* < 2T + t_2 + lT$ and $I(t) > I^* e^{-(2T+t_2+lT)(\mu+\gamma+\sigma\beta)}$ for $t \in (\tau_*, \tau^*)$, thus in the oscillatory case we can set $m_l := I^* e^{-(2T+t_2+lT)(\mu+\gamma+\sigma\beta)}$ and for any sufficiently large s for which $I(s) < I^*$, we have $I(s) > m_l$, since we can choose $\{\tau_i\}$ such that $s \in (\tau_{2k-1}, \tau_{2k+1})$ for some k.

Finally, if there exists a $t_3 > \tilde{t}_0 + t_1$, such that $I(t) > I^*$ for all $t > t_3$, then the same $m_l < I^*$ works as well as a lower estimate.

Note that m_l depends only on the fixed constants I^* and ϵ, thus we have strong uniform persistence. □

5. Forward and backward bifurcation of nontrivial endemic periodic solutions

In this section, we give conditions for the existence of endemic periodic solution of system (4). We follow the scheme of [14], however our bifurcation parameter is the vaccination rate φ, instead of the time-period T. Introduce the following notations: the solution vector is $X(t) := (S(t), I(t))$, the right-hand side of system (4) is $F(S, I) = (F_1(S, I), F_2(S, I))$, with components

$$(\mu - \beta SI - \mu S + \gamma I + \theta(1 - S - I), \beta SI - (\mu + \gamma)I + \sigma\beta(1 - S - I)I),$$

the impulsive effect is $\Theta(\varphi, (S, I)) = (\Theta_1(\varphi, (S, I)), \Theta_2(\varphi, (S, I)))$ with components

$$((1 - \varphi)S, I)$$

and the moments of impulses $t_i := iT$. Then system (4) has the form

$$S' = F_1(S, I), \tag{16}$$

$$I' = F_2(S, I), \tag{17}$$

$$S\left(t_i^+\right) = \Theta_1\left(\varphi, \left(S\left(t_i^-\right), I\left(t_i^-\right)\right)\right), \tag{18}$$

$$I\left(t_i^+\right) = \Theta_2\left(\varphi, \left(S\left(t_i^-\right), I\left(t_i^-\right)\right)\right). \tag{19}$$

From the notations above, we obtain $\Theta_1(\varphi, X) \neq 0$, if $S \neq 0$, $\Theta_2(\varphi, X) \neq 0$, if $I \neq 0$ and $F_2(S, 0) \equiv \Theta_2(\varphi, (S, 0)) \equiv \Theta_1(\varphi, (0, I)) \equiv 0$. Let Φ_t be the flow associated to (16)–(17): $X(t) = \Phi_t(X_0)$, $0 < t \leq T$, where $X_0 = X(0)$. Then $X(T) = \Phi_T(X_0) =: \Phi(X_0)$ and $X\left(T^+\right) = \Theta(\varphi, \Phi(X_0))$. Define the operator Ψ by

$$\Psi(\varphi, X) := (\Psi_1(\varphi, X), \Psi_2(\varphi, X)) = \Theta(\varphi, \Phi(X)), \tag{20}$$

and denote by $D_X\Psi$ the derivative of Ψ with respect to X. Then X is a T-periodic solution of (16)–(19) if and only if $\Psi(\varphi, X_0) = X_0$ and X_0 is exponentially stable, if $\rho(D_X\Psi) < 1$.

We use the notation $\bar{S}(t)$ for the locally asymptotically stable solution of (16), (18), with $I = 0$. Let us fix all parameters but φ and denote φ_0 the critical vaccination rate, which corresponds to $R_c = 1$. Let $\bar{S}_0(t)$ be the corresponding T-periodic

solution and denote by $\zeta(t) = \left(\overline{S_0}(t), 0\right)$ the T-periodic solution of system (16)–(19). From

$$D_X\Psi(\varphi, X) = D_X\Theta(\varphi, \Phi(X))D_X\Phi(X) = \begin{pmatrix} \frac{\partial\Theta_1(\varphi,X)}{\partial S} & \frac{\partial\Theta_1(\varphi,X)}{\partial I} \\ \frac{\partial\Theta_2(\varphi,X)}{\partial S} & \frac{\partial\Theta_2(\varphi,X)}{\partial I} \end{pmatrix} \begin{pmatrix} \frac{\partial\Phi_1(X)}{\partial S} & \frac{\partial\Phi_1(X)}{\partial I} \\ \frac{\partial\Phi_2(X)}{\partial S} & \frac{\partial\Phi_2(X)}{\partial I} \end{pmatrix},$$

at $X_0 = (x_0, 0)$ (where $x_0 = \overline{S_0}(0) = S^*$), we have the relation

$$D_X\Psi(\varphi_0, X_0) = D_X\Theta(\varphi_0, \Phi(X_0))\, D_X\Phi(X_0) = \begin{pmatrix} 1-\varphi_0 & 0 \\ 0 & 1 \end{pmatrix} \begin{pmatrix} \frac{\partial\Phi_1(X_0)}{\partial S} & \frac{\partial\Phi_1(X_0)}{\partial I} \\ 0 & \frac{\partial\Phi_2(X_0)}{\partial I} \end{pmatrix}.$$

From the variational equation associated to system (16)–(17),

$$\frac{d}{dt}\left(D_X\Phi_t(X_0)\right) = D_XF(\Phi_t(X))\, D_X\Phi_t(X)$$

with the initial condition $D_X\Phi_t(X_0) = \mathrm{Id}_{\mathbb{R}^2}$, we obtain

$$\begin{aligned} \frac{\partial\Phi_1(X_0)}{\partial S} &= e^{\int_0^T \frac{\partial F_1(\zeta(r))}{\partial S}\,dr}, \\ \frac{\partial\Phi_1(X_0)}{\partial I} &= \int_0^T e^{\int_u^T \frac{\partial F_1(\zeta(r))}{\partial S}\,dr} \frac{\partial F_1(\zeta(u))}{\partial I} e^{\int_0^u \frac{\partial F_2(\zeta(r))}{\partial I}\,dr}\,du, \\ \frac{\partial\Phi_2(X_0)}{\partial S} &= 0, \\ \frac{\partial\Phi_2(X_0)}{\partial I} &= e^{\int_0^T \frac{\partial F_2(\zeta(r))}{\partial I}\,dr}. \end{aligned}$$

We explore the bifurcation of nontrivial periodic solutions of system (16)–(19) near ζ. It is convenient for the computations to change the variables φ and X to $\bar\varphi$ and $\bar X$, such that $\varphi = \varphi_0 + \bar\varphi$ and $X = X_0 + \bar X$. In terms of new variables, the fixed point problem reads as

$$N\left(\bar\varphi, \bar X\right) = 0, \tag{21}$$

where $N\left(\bar\varphi, \bar X\right) = \left(N_1\left(\bar\varphi, \bar X\right), N_2\left(\bar\varphi, \bar X\right)\right) = X_0 + \bar X - \Psi\left(\varphi_0 + \bar\varphi, X_0 + \bar X\right)$. If $\left(\bar\varphi, \bar X\right)$ is the zero of N, then $X_0 + \bar X$ is the fixed point of $\Psi(\varphi_0 + \bar\varphi, \cdot)$. Since ζ is a T-periodic solution of (16)–(19), it is associated to the fixed point X_0 of $\Psi(\varphi_0, \cdot)$. From the stability of $\overline{S_0}(t)$ on the disease-free subspace, we get $1 - \left|(1-\varphi_0)\frac{\partial\Phi_1(X_0)}{\partial S}\right| \neq 0$. Let the derivative of N be given by the following matrix:

$$D_{\bar X}N\left(\bar\varphi, \bar X\right) = \begin{pmatrix} a' & b' \\ c' & d' \end{pmatrix}. \tag{22}$$

Let $a' = a_0, b' = b_0, c' = c_0, d' = d_0$ for $\left(\bar X; \bar\varphi\right) = ((0,0), 0)$:

$$\begin{aligned} a' &= 1 - \frac{\partial\Theta_1\left(\varphi_0 + \bar\varphi; X_0 + \bar X\right)}{\partial S}\frac{\partial\Phi_1\left(X_0 + \bar X\right)}{\partial S} - \frac{\partial\Theta_1\left(\varphi_0 + \bar\varphi; X_0 + \bar X\right)}{\partial I}\frac{\partial\Phi_2\left(X_0 + \bar X\right)}{\partial S}, \\ b' &= -\frac{\partial\Theta_1\left(\varphi_0 + \bar\varphi; X_0 + \bar X\right)}{\partial S}\frac{\partial\Phi_1\left(X_0 + \bar X\right)}{\partial I} - \frac{\partial\Theta_1\left(\varphi_0 + \bar\varphi; X_0 + \bar X\right)}{\partial I}\frac{\partial\Phi_2\left(X_0 + \bar X\right)}{\partial I}, \\ c' &= -\frac{\partial\Theta_2\left(\varphi_0 + \bar\varphi; X_0 + \bar X\right)}{\partial S}\frac{\partial\Phi_1\left(X_0 + \bar X\right)}{\partial S} - \frac{\partial\Theta_2\left(\varphi_0 + \bar\varphi; X_0 + \bar X\right)}{\partial I}\frac{\partial\Phi_2\left(X_0 + \bar X\right)}{\partial S}, \\ d' &= 1 - \frac{\partial\Theta_2\left(\varphi_0 + \bar\varphi; X_0 + \bar X\right)}{\partial S}\frac{\partial\Phi_1\left(X_0 + \bar X\right)}{\partial I} - \frac{\partial\Theta_2\left(\varphi_0 + \bar\varphi; X_0 + \bar X\right)}{\partial I}\frac{\partial\Phi_2\left(X_0 + \bar X\right)}{\partial I}, \end{aligned}$$

and from (22) we get

$$\begin{aligned} a_0 &= 1 - (1-\varphi_0)\frac{\partial\Phi_1(X_0)}{\partial S}, \\ b_0 &= -(1-\varphi_0)\frac{\partial\Phi_1(X_0)}{\partial I}, \\ c_0 &= 0, \\ d_0 &= 1 - \frac{\partial\Phi_2(X_0)}{\partial I}. \end{aligned}$$

Thus $c_0 = 0$ and $a_0 > 0$ from $(1-\varphi_0)\left(\frac{\partial \Phi_1(X_0)}{\partial S}\right) < 1$, which comes from the stability of $\bar{S}_0(t)$. The necessary condition for the bifurcation of nontrivial zeros of the function N is that the determinant of the Jacobian matrix $D_X N(0,(0,0))$ equals to zero. This reduces to $d_0 = 0$, which is equivalent to $R_c = 1$. Assume this condition holds and we now investigate sufficient condition for the existence of bifurcating nontrivial T-periodic solutions.

Since we assumed $\det(D_X N(0,(0,0))) = 0$, we cannot use the Implicit Function Theorem for giving variable X as a function of φ. We carry out a Lyapunov–Schmidt reduction to obtain a system of equations, where we can use the Implicit Function Theorem. In the following we use the terminology of [25]. Let $D_X N(0,(0,0)) = E$ be the matrix of a linear map.

Step 1.*Decompose the ambient space with the kernel and range of E.*

We have $\dim \mathrm{Ker}(E) = 1 = \text{co-dim}(\mathrm{Im}(E))$. We denote by P and Q the projections onto Ker(E) and Im(E) respectively, such that

$P\left(\mathbb{R}^2\right) = \mathrm{Ker}(E) = \mathrm{Span}\{Y_0\}$, where $Y_0 = \left(-\frac{b_0}{a_0}, 1\right)$,

$Q\left(\mathbb{R}^2\right) = \mathrm{Im}(E) = \mathrm{Span}\{I_0\}$, where $I_0 = (1,0)$, $(I-Q)\left(\mathbb{R}^2\right) = \mathrm{Span}\{(0,1)\}$.

Step 2. *Transfer this decomposition to the equation.*

It is obvious that for all $u \in \mathbb{R}^2$, $u = 0 \Leftrightarrow Q(u) = 0$ and $(I-Q)(u) = 0$. Thus we obtain $N\left(\bar{\varphi}, \bar{X}\right) = 0$ if and only if $Q\left(N\left(\bar{\varphi}, \bar{X}\right)\right) = 0$ and $(I-Q)\left(N\left(\bar{\varphi}, \bar{X}\right)\right) = 0$, so this is true if and only if $N_1\left(\bar{\varphi}, \bar{X}\right) = 0$ and $N_2\left(\bar{\varphi}, \bar{X}\right) = 0$. From the decomposition $\mathbb{R}^2 = \mathrm{Ker}(E) \oplus \mathrm{Im}(E)$, we have $\bar{X} = \alpha Y_0 + z I_0$, where $\alpha, z \in \mathbb{R}$ are unique. Thus (21) is equivalent to

$$N_1(\bar{\varphi}, \alpha Y_0 + z I_0) = 0, \qquad N_2(\bar{\varphi}, \alpha Y_0 + z I_0) = 0. \tag{23}$$

Step 3. Show that the first equation of (23) may be solved for all but one of the variables, using the Implicit Function Theorem.

From the first equation of (23), we have

$$\frac{\partial N_1(0,(0,0))}{\partial z} = \frac{\partial N_1(0,(0,0))}{\partial \bar{X}} \frac{\partial \bar{X}}{\partial z} = a_0 \neq 0.$$

Thus from the Implicit Function Theorem, there exists $\delta > 0$ sufficiently small and a unique, continuous function Z^*, such that

$$\begin{cases} Z^*(\bar{\varphi}, \alpha) = \left({z_1}^*(\bar{\varphi}, \alpha), 0\right), \\ Z^*(0,0) = (0,0), \\ N_1\left(\bar{\varphi}, \alpha Y_0 + Z^*(\bar{\varphi}, \alpha)\right) = 0 \end{cases} \tag{24}$$

for every $(\bar{\varphi}, \alpha)$, such that $|\alpha| < \delta$ and $|\bar{\varphi}| < \delta$, furthermore

$$\begin{aligned} \left.\frac{\partial {z_1}^*}{\partial \alpha}\right|_{(\bar{\varphi},\bar{\alpha})=(0,0)} &= -\left.\frac{\frac{\partial N_1}{\partial \alpha}}{\frac{\partial N_1}{\partial z}}\right|_{(\bar{\varphi},\bar{X})=(0,(0,0))} = -\left.\frac{\frac{\partial N_1}{\partial S}\frac{\partial S}{\partial \alpha} + \frac{\partial N_1}{\partial I}\frac{\partial I}{\partial \alpha}}{\frac{\partial N_1}{\partial S}\frac{\partial S}{\partial z}}\right|_{(\bar{\varphi},\bar{X})=(0,(0,0))} \\ &= -\left.\frac{\frac{\partial N_1}{\partial S}\left(\frac{-b_0}{a_0}\right) + \frac{\partial N_1}{\partial I}\frac{\partial I}{\partial \alpha}}{\frac{\partial N_1}{\partial S}}\right|_{(\bar{\varphi},\bar{X})=(0,(0,0))} = 0, \end{aligned} \tag{25}$$

so $\frac{\partial {z_1}^*(0,0)}{\partial \alpha} = 0$.

Step 4. Substitute the solution of first equation of (23) into the other equation.

Then $N\left(\bar{\varphi}, \bar{X}\right) = 0$ if and only if

$$\begin{aligned} f(\bar{\varphi}, \alpha) &= N_2\left(\bar{\varphi}, \alpha\left(-\frac{b_0}{a_0}, 1\right) + \left({z_1}^*(\bar{\varphi}, \alpha), 0\right)\right) \\ &= N_2\left(\bar{\varphi}, \left(-\frac{b_0}{a_0}\alpha + {z_1}^*(\bar{\varphi}, \alpha), \alpha\right)\right) = 0. \end{aligned} \tag{26}$$

We know that $f(\bar{\varphi}, \alpha)$ vanishes at $(0,0)$, thus it is necessary to compute higher order derivatives of $f(\bar{\varphi}, \alpha)$ up to the order i for which $D^i f(0,0) \neq 0$. Let us introduce the following variables:

$$\begin{cases} \eta(\bar{\varphi}) = \varphi_0 + \bar{\varphi}, \\ \eta_1(\bar{\varphi}, \alpha) = x_0 - \dfrac{b_0}{a_0}\alpha + {z_1}^*(\bar{\varphi}, \alpha), \\ \eta_2(\bar{\varphi}, \alpha) = \alpha. \end{cases}$$

The first partial derivatives of f.

We find

$$\begin{aligned} \frac{\partial f(\bar{\varphi}, \alpha)}{\partial \bar{\varphi}} &= \frac{\partial}{\partial \bar{\varphi}}\left(\eta_2 - \Theta_2(\eta, \Phi(\eta_1, \eta_2))\right) \\ &= -\frac{\partial \Phi_2(\eta_1, \eta_2)}{\partial S}\frac{\partial \eta_1}{\partial \bar{\varphi}} - \frac{\partial \Phi_2(\eta_1, \eta_2)}{\partial I}\frac{\partial \eta_2}{\partial \bar{\varphi}}, \end{aligned}$$

while

$$\frac{\partial \eta_2(\bar{\varphi},\alpha)}{\partial \bar{\varphi}} = 0,$$

for all $(\bar{\varphi},\alpha)$ and

$$\left.\frac{\partial \Phi_2(\eta_1,\eta_2)}{\partial S}\right|_{(\eta_1,\eta_2)=(0,0)} = 0,$$

thus $\frac{\partial f(0,0)}{\partial \bar{\varphi}} = 0$. On the other hand,

$$\begin{aligned}\frac{\partial f(\bar{\varphi},\alpha)}{\partial \alpha} &= \frac{\partial}{\partial \alpha}\left(\eta_2 - \Theta_2(\eta, \Phi(\eta_1,\eta_2))\right)\\ &= 1 - \left(\frac{\partial \Phi_2(\eta_1,\eta_2)}{\partial S}\left(-\frac{b_0}{a_0} + \frac{\partial z_1{}^*(\bar{\varphi},\alpha)}{\partial \alpha}\right) + \frac{\partial \Phi_2(\eta_1,\eta_2)}{\partial I}\right),\end{aligned}$$

but

$$\left.\frac{\partial \Phi_2(\eta_1,\eta_2)}{\partial S}\right|_{(\eta_1,\eta_2)=(0,0)} = 0,$$

and $d_0 = 1 - \frac{\partial \Phi_2(X_0)}{\partial I} = 0$ from our assumption, so $\frac{\partial f(0,0)}{\partial \alpha} = 0$.

Therefore, we obtain $Df(0,0) = (0,0)$.

We need compute the second-order derivatives, and we use the following forms of $\frac{\partial f(\bar{\varphi},\alpha)}{\partial \alpha}$ and $\frac{\partial f(\bar{\varphi},\alpha)}{\partial \bar{\varphi}}$:

$$\begin{aligned}\frac{\partial f(\bar{\varphi},\alpha)}{\partial \alpha} &= 1 - \left(\frac{\partial \Phi_2(\eta_1,\eta_2)}{\partial S}\left(-\frac{b_0}{a_0} + \frac{\partial z_1{}^*(\bar{\varphi},\alpha)}{\partial \alpha}\right) + \frac{\partial \Phi_2(\eta_1,\eta_2)}{\partial I}\right),\\ \frac{\partial f(\bar{\varphi},\alpha)}{\partial \bar{\varphi}} &= -\left(\frac{\partial \Phi_2(\eta_1,\eta_2)}{\partial S}\frac{\partial z_1{}^*(\bar{\varphi},\alpha)}{\partial \bar{\varphi}}\right).\end{aligned}$$

Second-order derivatives of f.

Let $A = \frac{\partial^2 f(0,0)}{\partial \bar{\varphi}^2}$, $B = \frac{\partial^2 f(0,0)}{\partial \alpha \partial \bar{\varphi}}$ and $C = \frac{\partial^2 f(0,0)}{\partial \alpha^2}$.

Calculation of A.

We have

$$\begin{aligned}\frac{\partial^2 f(\bar{\varphi},\alpha)}{\partial \bar{\varphi}^2} &= \frac{\partial}{\partial \bar{\varphi}}\left(\frac{\partial f(\bar{\varphi},\alpha)}{\partial \bar{\varphi}}\right)\\ &= -\frac{\partial z_1{}^*(\bar{\varphi},\alpha)}{\partial \bar{\varphi}}\left(\frac{\partial^2 \Phi_2(\eta_1,\eta_2)}{\partial S^2}\frac{\partial z_1{}^*(\bar{\varphi},\alpha)}{\partial \bar{\varphi}} + \frac{\partial^2 \Phi_2(\eta_1,\eta_2)}{\partial S \partial I}\frac{\partial \eta_2}{\partial \bar{\varphi}}\right) - \frac{\partial \Phi_2(\eta_1,\eta_2)}{\partial S}\frac{\partial^2 z_1{}^*(\bar{\varphi},\alpha)}{\partial \bar{\varphi}^2}.\end{aligned}$$

However,

$$\frac{\partial \eta_2(\bar{\varphi},\alpha)}{\partial \bar{\varphi}} = 0,$$

for all $(\bar{\varphi},\alpha)$ and

$$\left.\frac{\partial \Phi_2(\eta_1,\eta_2)}{\partial S}\right|_{(\eta_1,\eta_2)=(0,0)} = \left.\frac{\partial^2 \Phi_2(\eta_1,\eta_2)}{\partial S^2}\right|_{(\eta_1,\eta_2)=(0,0)} = 0,$$

so $A = \frac{\partial^2 f(\bar{\varphi},\alpha)}{\partial \bar{\varphi}^2} = 0$.

Calculation of C.

We have

$$\begin{aligned}\frac{\partial^2 f(\bar{\varphi},\alpha)}{\partial \alpha^2} &= \frac{\partial}{\partial \alpha}\left(\frac{\partial f(\bar{\varphi},\alpha)}{\partial \alpha}\right)\\ &= -\frac{\partial^2 \Phi_2(\eta_1,\eta_2)}{\partial S^2}\left(-\frac{b_0}{a_0} + \frac{\partial z_1{}^*(\bar{\varphi},\alpha)}{\partial \alpha}\right)^2 - 2\frac{\partial^2 \Phi_2(\eta_1,\eta_2)}{\partial S \partial I}\left(-\frac{b_0}{a_0} + \frac{\partial z_1{}^*(\bar{\varphi},\alpha)}{\partial \alpha}\right)\\ &\quad - \frac{\partial \Phi_2(\eta_1,\eta_2)}{\partial S}\frac{\partial^2 z_1{}^*(\bar{\varphi},\alpha)}{\partial \alpha^2} - \frac{\partial^2 \Phi_2(\eta_1,\eta_2)}{\partial I^2}.\end{aligned}$$

From (25), we deduce

$$\left.\frac{\partial z_1{}^*(\bar{\varphi},\alpha)}{\partial\alpha}\right|_{(\bar{\varphi},\alpha)=(0,0)}=0,$$

and

$$\left.\frac{\partial\Phi_2(\eta_1,\eta_2)}{\partial S}\right|_{(\eta_1,\eta_2)=(0,0)}=\left.\frac{\partial^2\Phi_2(\eta_1,\eta_2)}{\partial S^2}\right|_{(\eta_1,\eta_2)=(0,0)}=0,$$

so

$$\frac{\partial^2 f(\bar{\varphi},\alpha)}{\partial\alpha^2}=2\frac{\partial^2\Phi_2(\eta_1,\eta_2)}{\partial S\partial I}\frac{b_0}{a_0}-\frac{\partial^2\Phi_2(\eta_1,\eta_2)}{\partial I^2}=:C.$$

The following formulas were calculated also in [14]:

$$\frac{\partial^2\Phi_2(T,X_0)}{\partial S\partial I}=\int_0^T e^{\int_0^T\frac{\partial}{\partial I}F_2(\zeta(r))\,dr}\frac{\partial^2F_2(\zeta(u))}{\partial S\partial I}du,$$

$$\begin{aligned}\frac{\partial^2\Phi_2(T,X_0)}{\partial I^2}&=\int_0^T e^{\int_0^T\frac{\partial}{\partial I}F_2(\zeta(r))\,dr}\frac{\partial^2F_2(\zeta(u))}{\partial^2 I}du+\int_0^T\left\{e^{\int_u^T\frac{\partial}{\partial I}F_2(\zeta(r))\,dr}\frac{\partial^2F_2(\zeta(u))}{\partial S\partial I}\right\}\\&\quad\times\left\{\int_0^u e^{\int_p^u\frac{\partial}{\partial S}F_1(\zeta(r))\,dr}\frac{\partial F_1(\zeta(p))}{\partial I}e^{\int_0^p\frac{\partial}{\partial I}F_2(\zeta(r))\,dr}dp\right\}du.\end{aligned}$$

Calculation of B.

Some calculations give

$$\begin{aligned}\frac{\partial^2 f(\bar{\varphi},\alpha)}{\partial\alpha\partial\bar{\varphi}}&=\frac{\partial}{\partial\bar{\varphi}}\left(\frac{\partial f(\bar{\varphi},\alpha)}{\partial\alpha}\right)\\&=-\frac{\partial^2\Phi_2(\eta_1,\eta_2)}{\partial S^2}\frac{\partial z_1{}^*(\bar{\varphi},\alpha)}{\partial\bar{\varphi}}\left(-\frac{b_0}{a_0}+\frac{\partial z_1{}^*(\bar{\varphi},\alpha)}{\partial\alpha}\right)-\frac{\partial\Phi_2(\eta_1,\eta_2)}{\partial S}\frac{\partial^2 z_1{}^*(\bar{\varphi},\alpha)}{\partial\alpha\partial\bar{\varphi}}\\&\quad-\frac{\partial^2\Phi_2(\eta_1,\eta_2)}{\partial I\partial S}\frac{\partial z_1{}^*(\bar{\varphi},\alpha)}{\partial\bar{\varphi}}.\end{aligned}$$

On the other hand,

$$\left.\frac{\partial z_1{}^*(\bar{\varphi},\alpha)}{\partial\alpha}\right|_{(\bar{\varphi},\alpha)=(0,0)}=0,$$

and

$$\left.\frac{\partial\Phi_2(\eta_1,\eta_2)}{\partial S}\right|_{(\eta_1,\eta_2)=(0,0)}=\left.\frac{\partial^2\Phi_2(\eta_1,\eta_2)}{\partial S^2}\right|_{(\eta_1,\eta_2)=(0,0)}=0.$$

From (24) we know that $N_1(\bar{\varphi},\alpha)\equiv 0$ near $(0,0)$, thus

$$\begin{aligned}&\frac{\partial}{\partial\bar{\varphi}}\left(x_0+\left(-\frac{b_0}{a_0}\right)\alpha+z_1{}^*(\bar{\varphi},\alpha)-(1-\eta)\Phi_1(\eta_1,\eta_2)\right)=0,\\&\frac{\partial z_1{}^*(\bar{\varphi},\alpha)}{\partial\bar{\varphi}}-\left(-\Phi_1(\eta_1,\eta_2)+(1-\eta)\frac{\partial\Phi_1(\eta_1,\eta_2)}{\partial S}\frac{\partial z_1{}^*(\bar{\varphi},\alpha)}{\partial\bar{\varphi}}\right)=0.\end{aligned}$$

Evaluated at $(\bar{\varphi},\alpha)=(0,0)$, we have

$$\frac{\partial z_1{}^*(0,0)}{\partial\bar{\varphi}}=-\frac{\Phi_1(x_0,0)}{1-(1-\varphi_0)\frac{\partial\Phi_1(x_0,0)}{\partial S}}=-\frac{\Phi_1(x_0,0)}{a_0},$$

thus

$$\frac{\partial^2 f(\bar{\varphi},\alpha)}{\partial\alpha\partial\bar{\varphi}}=\frac{\partial^2\Phi_2(\eta_1,\eta_2)}{\partial I\partial S}\frac{\Phi_1(x_0,0)}{a_0}=:B.$$

From the calculations above, one has

$$D^2 f(0,0)(\bar{\varphi},\alpha)=2B\alpha\bar{\varphi}+C\alpha^2.$$

Therefore, we have

$$f(\bar{\varphi},\alpha)=\frac{\alpha}{2}\tilde{f}(\bar{\varphi},\alpha),$$

where

$$\tilde{f}(\bar{\varphi},\alpha)=2B\bar{\varphi}+C\alpha+\frac{1}{\alpha}o_{(\bar{\varphi},\alpha)}\left((|\bar{\varphi}|+|\alpha|)^2\right). \tag{27}$$

Furthermore, $\frac{\partial\tilde{f}(0,0)}{\partial\bar{\varphi}}=2B$ (resp. $\frac{\partial\tilde{f}(0,0)}{\partial\alpha}=C$). So, for $B\neq 0$ (resp. $C\neq 0$), we can use the Implicit Function Theorem, which gives us $\bar{\varphi}=\xi(\alpha)$ (resp. $\alpha=\lambda(\bar{\varphi})$), such that for all α (resp. $\bar{\varphi}$) near 0, $\tilde{f}(\xi(\alpha),\alpha)=0$ (resp. $\tilde{f}(\bar{\varphi},\lambda(\bar{\varphi}))=0$). Then, if $BC\neq 0$, we have $\frac{\alpha}{\bar{\varphi}}\simeq-\frac{C}{2B}$. In conclusion, $f(\bar{\varphi},\alpha)=0$ implies $\frac{\alpha}{\bar{\varphi}}\simeq-\frac{C}{2B}$. $BC=0$ does not determine the dynamical behavior; if $BC=0$, it is necessary to compute the third order derivative of f. Finally, we conclude the following theorem.

Theorem 4. *Consider the family of operators $\Psi(\varphi,X)$, defined in (20). As the parameter φ is passing through the critical value φ_0, a nontrivial fixed point appears near the fixed point X_0. The bifurcation is supercritical, if $BC<0$, and it is subcritical, if $BC>0$.*

When φ increases, then R_c decreases, so the supercritical bifurcation in the $\bar{\varphi}-\alpha$ plane means a backward bifurcation in the model. On the other hand, the subcritical bifurcation corresponds to a transcritical bifurcation.

Corollary 1. *The type of bifurcation in model (4) depends on the sign of BC: if $BC<0$ then there is a backward bifurcation, if $BC>0$ then there is a forward bifurcation of endemic periodic solutions from the disease-free periodic solution at $R_c=1$.*

6. Backward bifurcation in an HIV model with pulse vaccination

Similar arguments can be applied to more complex and realistic models as well. Here we consider an HIV model from [26], involving cohort and continuous vaccination strategies with imperfect vaccine, where we replaced the continuous vaccination by pulse vaccination:

$$\begin{cases}
X'(t)=(1-p)\Lambda-\mu X-\lambda X+\gamma V,\\
V'(t)=p\Lambda-\mu V-q\lambda V-\gamma V,\\
Y'(t)=\lambda X-(\mu+\sigma)Y, & \text{if } t\neq nT,\\
W'(t)=q\lambda V-(\mu+\theta\sigma)W,\\
A'(t)=\sigma Y+\theta\sigma W-(\mu+\alpha)A,\\
X\left(nT^+\right)=(1-\xi)X\left(nT^-\right),\\
V\left(nT^+\right)=V\left(nT^-\right)+\xi X\left(nT^-\right),\\
Y\left(nT^+\right)=Y\left(nT^-\right), & \text{if } t=nT,\\
W\left(nT^+\right)=W\left(nT^-\right),\\
A\left(nT^+\right)=A\left(nT^-\right).
\end{cases} \tag{28}$$

Here, following the notation of [26], $X(t), V(t), Y(t), W(t), A(t)$ denote the number of susceptible, vaccinated non-infected, unvaccinated infected, vaccinated infected, and being in the AIDS stage individuals at time t, respectively. The force of infection is $\lambda=\frac{\beta Y+s\beta W}{N}$, where $N(t)=X(t)+V(t)+Y(t)+W(t)$. For the detailed explanation of the model and its parameters we refer to [26], where an explicit criterion was given in terms of the model parameters for backward bifurcation in the case of continuous vaccination. We illustrate that the phenomenon of backward bifurcation can be observed for pulse vaccination as well. In Fig. 5(a), we used the same parameters as [26] (with the only modification which was necessary to define pulse vaccination), in a situation when the corresponding reproduction number is less than 1. One can observe the bistability of an endemic and a disease free state, thus backward bifurcation occurs similarly to [26]. In the case of Fig. 5(a), the pulse vaccination can be considered as only a small perturbation of the continuous case, however we can see that the phenomenon is more general: by a significant increase of the vaccination parameter ξ, one can still find the backward bifurcation as depicted in Fig. 5(b), where the disease can die out or can become periodically endemic, depending on the initial values. This suggests that backward bifurcation in pulse vaccination models is just as common as in continuous models, and our approach and analysis for system (4) can be extended to many more complex systems.

7. Discussion

We started with a simple SIVS model from [2] that exhibits backward bifurcation, and replaced the continuous vaccination by a pulse vaccination strategy. This way we obtained a system of impulsive differential equations, where the role of equilibria in the original system is taken over by periodic solutions. We calculated the disease-free periodic solution, and identified the control reproduction number R_c, which is, by Floquet-theory, shown to be a threshold quantity: if $R_c<1$, then the disease-free periodic solution is locally asymptotically stable, while it is unstable for $R_c>1$. By finding suitable comparison systems, we provided a global asymptotic stability result under an additional condition, while for $R_c>1$ we showed the strong uniform persistence of the infection. Our main result is the fully elaborated bifurcation analysis of system (4) at $R_c=1$, which is based on transforming the question into a fixed point problem of a nonlinear operator, and applying

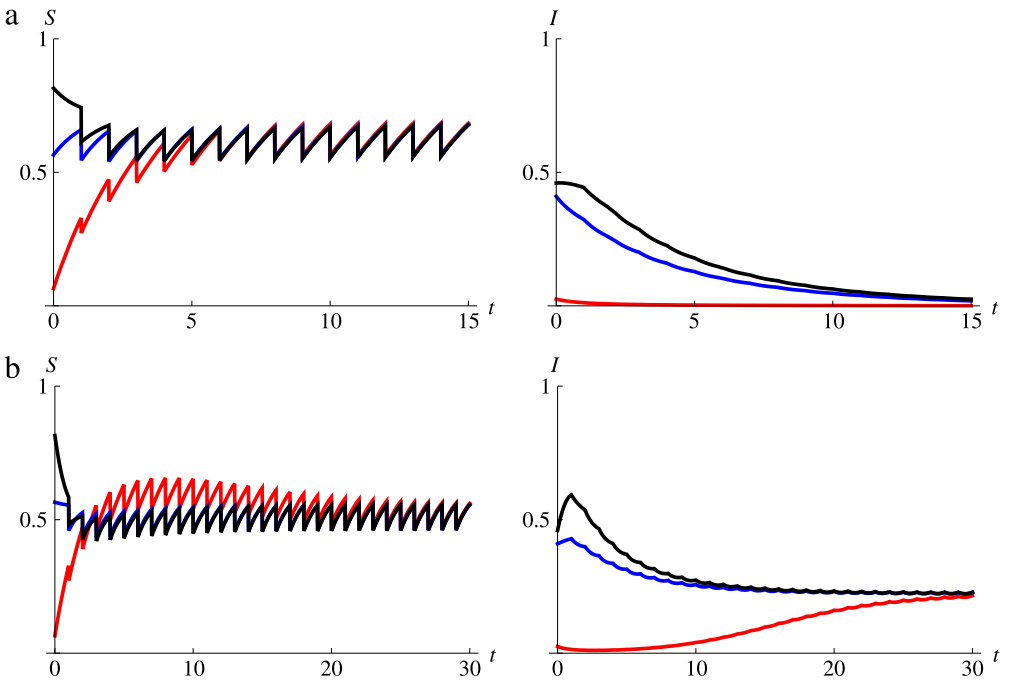

Fig. 2. Here $(\sigma, \gamma, \mu, \theta, \varphi, T) = (0.1, 0.89, 0.31, 0.01, 0.174, 1)$. In (a), $\beta = 1.55$ and $R_c = 0.86$: the disease-free periodic solution is globally stable. In (b), $\beta = 2.22$ and $R_c = 1.23$; the disease-free periodic solution is unstable and there is a stable endemic periodic solution.

Lyapunov–Schmidt reduction. The system can exhibit either forward or backward bifurcation of endemic periodic solutions branching from the disease-free periodic solution at $R_c = 1$, depending on the sign of an explicitly given expression, BC, what we can calculate for particular parameter settings to illustrate the theorem. For example, for $\sigma = 0.1$, $\gamma = 0.89$, $\theta = 0.01$, $T = 1$, $\varphi = 0.174$, $\mu = 0.31$, $\beta = 2.23$ and the other parameters are the same, then $BC = 2684.44 > 0$, thus there is a forward bifurcation at $R_c = 1$ (see Fig. 2). If $\mu = 0.01$, $\beta = 5.32$, and the other parameters are the same as in the previous case, then backward bifurcation occurs at $R_c = 1$ and the value of BC is -30.4828 (see Fig. 3). The bifurcation diagrams are depicted in Fig. 4. To identify a proper control strategy (that guarantees the eradication of the disease) by means of pulse vaccination, it is crucial to know whether we face a forward or a backward bifurcation.

For a comparison of the continuous and the pulse strategies we have to relate a continuous strategy to a corresponding impulsive strategy. We use a similar approach as in [11]. In the absence of the infection and neglecting demography, for the case of continuous vaccination the number of susceptible and vaccinated individuals are governed by the system

$$\begin{cases} S'(t) &= \theta V - pS, \\ V'(t) &= -\theta V + pS, \end{cases}$$

where p is the rate susceptibles get vaccinated. The solution with initial condition $S(0) = 1, V(0) = 0$ is $S_0(t) = \frac{\theta}{\theta+p} + \frac{p}{p+\theta}e^{-(p+\theta)t}$, $V_0(t) = \frac{p}{p+\theta} - \frac{p}{p+\theta}e^{-(p+\theta)t}$. Thus the number of vaccinated individuals in $[0, T]$ is $p\int_0^T S_0(t)dt < 1$. For the corresponding pulse vaccination strategy, the fraction ϕ of the susceptible population is vaccinated on this interval. Thus, for a given p (that specifies a continuous strategy), we associate a corresponding couple (ϕ, T) (that specifies an impulsive strategy), such that $\phi = p\int_0^T S_0(t)dt$ holds, then we use approximately the same amount of vaccines in the absence of the disease.

First, we numerically calculate and compare the reproduction numbers for such p and (φ, T). We find that for the parameter setting of Fig. 2(a), $R_{cc} = 0.857$ and $R_{cp} = 0.859$; for Fig. 2(b), $R_{cc} = 1.227$ and $R_{cp} = 1.23$; for Fig. 3(a), $R_{cc} = 0.648$ and $R_{cp} = 0.649$; for Fig. 3(b), $R_{cc} = 1.229$ and $R_{cp} = 1.23$; where we employed the notation R_{cc} and R_{cp} to distinguish the corresponding control reproduction numbers for the continuous and the pulse vaccination strategies. We conclude that the differences are very minor, thus essentially a given amount of vaccine gives the same reproduction number, regardless which vaccination strategy (continuous or impulsive) we apply.

Thus, in the case of forward bifurcation, both vaccination strategies require the same amount of vaccine to control the disease (i.e. to bring R_c below one). The situation is more delicate in the case of backward bifurcation, since then the threshold for certain disease eradication is not $R_c = 1$. In the situation of Fig. 4, we found numerically that the turning points of the bifurcation curves are basically the same (at $R_{cc} = 0.616$ vs. $R_{cp} = 0.615$). Hence, even in the case of backward bifurcation, to reduce the reproduction number to safe values requires the same effort.

However, there is an other factor that may be significant. When the disease is not controlled thus becomes endemic, which scheme does result in a smaller density of infected individuals? First consider the forward bifurcation case with

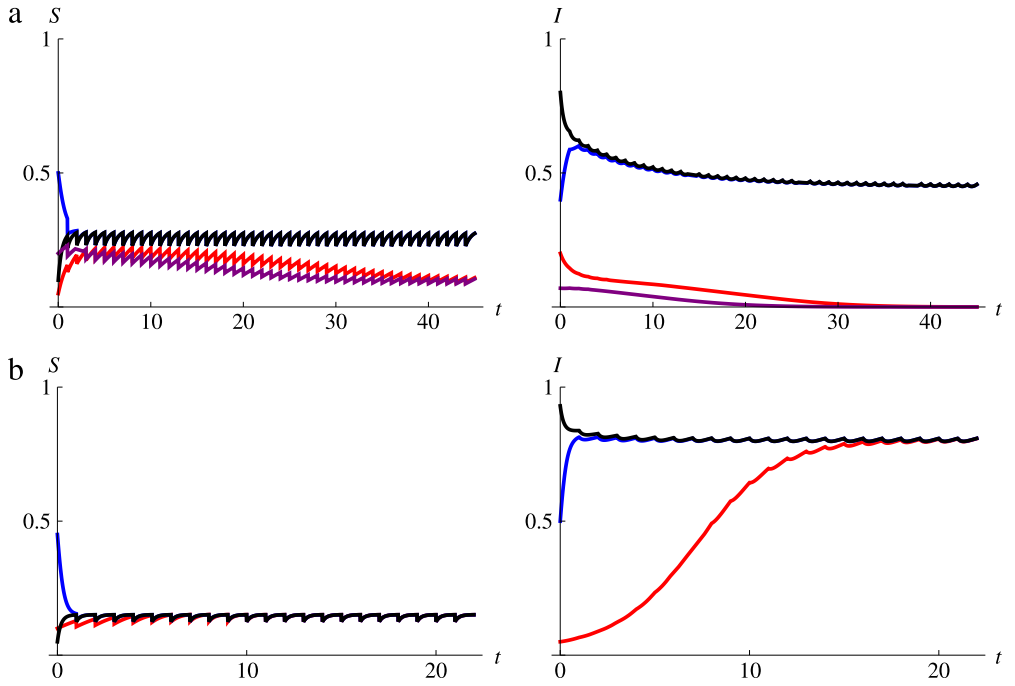

Fig. 3. Here $(\sigma, \gamma, \mu, \theta, \varphi, T) = (0.1, 0.89, 0.01, 0.01, 0.174, 1)$. In (a), $\beta = 3.15$ and $R_c = 0.65$: the disease-free periodic solution and an endemic periodic solution are both stable. In (b), $\beta = 5.97$ and $R_c = 1.23$; the disease-free periodic solution is unstable and there is a stable endemic periodic solution.

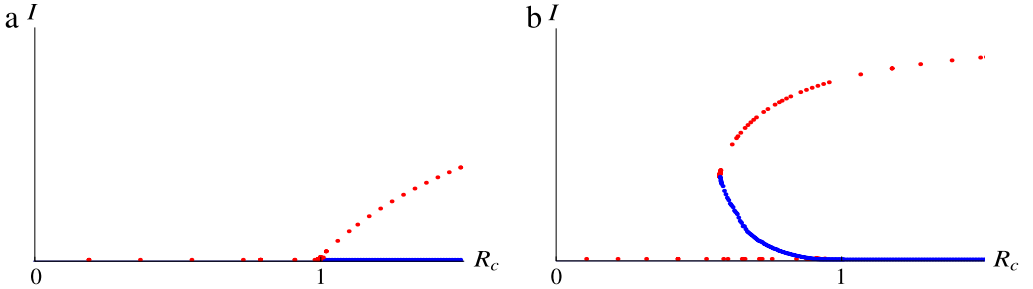

Fig. 4. (a) Numerically calculated bifurcation diagrams for the impulsive system. For $\sigma = 0.1, \gamma = 0.89, \mu = 0.31, \theta = 0.01, \varphi = 0.174, T = 1$, we have forward bifurcation. (b) For $\sigma = 0.1, \gamma = 0.89, \mu = 0.01, \theta = 0.01, \varphi = 0.174, T = 1$, we have backward bifurcation.

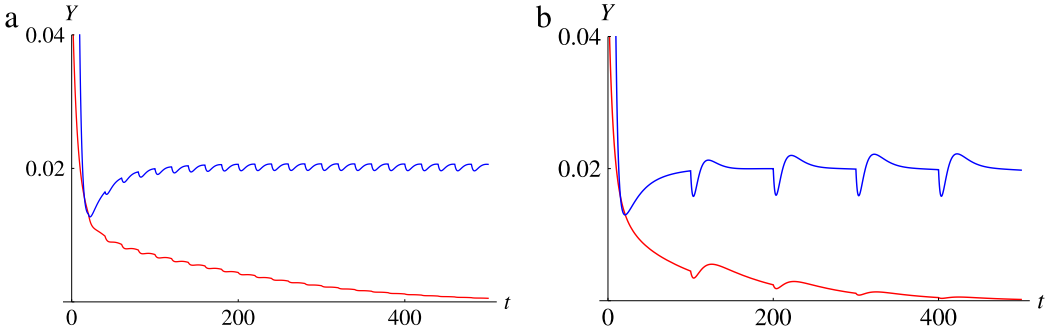

Fig. 5. (a) Simulations for system (28) from different initial values with parameter values taken from [26]: $\mu = 0.02, p = 0.999, s = 1.1, \xi = 0.09, \theta = 0.5, q = 0.99, \gamma = 0.09, \sigma = 0.36, \beta = 0.3, \alpha = 0.2, T = 20, \Lambda = 0.02$. (b) Here $\mu = 0.02, p = 0.999, s = 1.1, \xi = 0.4, \theta = 0.5, q = 0.99, \gamma = 0.09, \sigma = 0.36, \beta = 0.3, \alpha = 0.2, T = 100, \Lambda = 0.02$. The disease-free periodic solution and an endemic periodic solution are both stable in both cases.

$R_c = 1.23$ (parameters are chosen as before). Then the time average of the fraction of infected individuals for the impulsive system is 0.19, while the corresponding continuous strategy yields an endemic equilibrium 0.22. Thus here the pulse

vaccination strategy is beneficial, as the average number of infected individuals is reduced by 3% of the total population. On the other branches of the bifurcation curves, we find that for backward bifurcation at $R_c = 1.23$, the average of infected individuals is the same, 0.8 for both schemes, while at $R_c = 0.65$ this value is 0.44 vs. 0.45 (the latter is the pulse strategy). However, a numerical approximation of the bifurcation curve indicates that in the case of backward bifurcation, the unstable branch in the continuous case is below the unstable branch of the impulsive case, thus the basin of attraction of the eradication solution seems larger for the pulse vaccination strategy.

Overall, the qualitative behavior of the continuous and the impulsive SIVS systems are very similar. The numerical investigations suggest that pulse vaccination strategy is better only when the system has forward bifurcation and $R_c > 1$, because then it leads a lower endemic state, or when the system has backward bifurcation and $R_c < 1$ (because then it produces a larger basin of attraction for eradication). While the SIVS system is rather simplified, this is the first system for which backward bifurcation is proved under pulse vaccination strategy. Furthermore, our numerical investigations for the HIV model demonstrates that this phenomenon is rather general, and our discussion indicates that such considerations about the vaccination strategies can be important in realistic situations as well.

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