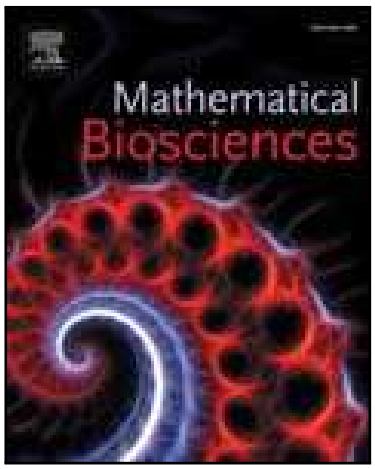

Models to assess how best to replace dengue virus vectors with Wolbachia-infected mosquito populations

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Highlights

- Now various strains of *Wolbachia*-infected vectors are released in dengue areas.
- Models with and without augmentation for dengue control are proposed.
- Stability analysis shows there are backward bifurcations and multiple attractors.
- Initial values and release methods affect the success of population replacement.
- Suitable *Wolbachia* and release methods are needed for the control of dengue virus.

Models to assess how best to replace dengue virus vectors with *Wolbachia*-infected mosquito populations

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Abstract

Dengue fever is increasing in importance in the tropics and subtropics. Endosymbiotic *Wolbachia* bacteria as novel control methods can reduce the ability of virus transmission. So, many mosquitoes infected with *Wolbachia* are released in some countries so that strategies for population replacement can be fulfilled. However, not all of these field trails are successful, for example, releases on Tri Nguyen Island, Vietnam in 2013 failed. Thus, we evaluated a series of relevant issues such as (a) why do some releases fail? (b) What affects the success of population replacement? And (c) Whether or not augmentation can block the dengue diseases in field trials. If not, how we can success be achieved? Models with and without augmentation, incorporating the effects of cytoplasmic incompatibility (CI) and fitness effects are proposed to describe the spread of *Wolbachia* in mosquito populations. Stability analysis revealed that backward bifurcations and multiple attractors may exist, which indicate that initial quantities of infected and uninfected mosquitoes, augmentation methods (timing, quantity, order and frequency) may affect the success of the strategies. The results show that successful population replacement will rely on selection of suitable strains of *Wolbachia* and careful design of augmentation methods.

Keywords: Backward bifurcation, Fitness effects, Augmentation order,

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Augmentation quantity, Augmentation times

1. Introduction

The mosquito-borne diseases, dengue fever and dengue hemorrhagic fever, are among the leading causes of illness in the tropics and subtropics such as the Americas, Southeast Asia, the Western Pacific, Africa and the Eastern Mediterranean, mostly in urban and semi-urban areas, with up to 380 million infections estimated to occur annually [1]. People may be infected with dengue more than once because it is caused by any one of four related viruses transmitted by mosquitoes, especially *Aedes aegypti* and *Aedes albopictus* [2]. There are no antiviral therapies or vaccines available to prevent infection with dengue, so control of mosquitoes remains the most effective protective measure for dengue prevention [3, 4]. However, the traditional use of insecticides as a control measure is often prohibitively expensive and environmental undesirable; moreover, it may lead to insecticide resistance [3].

Therefore, it is necessary to search for novel technologies to break dengue transmission cycles [5, 6]. At present, exploitation of *Wolbachia* bacteria is a promising method for manipulation of mosquito vectors. *Wolbachia* are maternally transmitted endosymbiotic bacteria, estimated to infect up to 65% of insect species and approximately 28% of the surveyed mosquito species [7, 8]. The bacteria live within testes and ovaries of their hosts and are passed from one generation to the next through the hosts' eggs; thus, they can interfere with the insects' reproductive mechanisms, causing phenomena such as cytoplasmic incompatibility (CI), parthenogenesis and feminization of genetic males. Appearances of these phenotypes depend on the host species and *Wolbachia* types. CI causes uninfected females that mate with infected males to rarely produce fertile eggs, while infected females are not affected. This gives infected females an advantage and helps the bacteria to spread quickly through a mosquito population [9, 10, 11, 12].

Two strategies to develop *Wolbachia* for biological control of dengue virus

have been proposed [13]. Different strategies lead to the selection of different strains of *Wolbachia* and methods for augmentation (pulse), which involves the supplemental release of infected mosquitoes. Relatively small seedings may be released at a critical time of the season (inoculative release) or millions may be released (inundative release) when the density of infected individuals is too low [14, 15]. Population suppression (mosquitoes dying out) based on CI occurs if only infected males are inundatively released, as in the case of the successful suppression of *Culex pipiens* populations in field tests [16, 17]. Some strains of *Wolbachia* can shorten the mosquitoes' lives, indirectly preventing viral maturation and transmission [18]. Furthermore others can not only successfully spread within mosquito populations but also act as a 'vaccine' for the mosquitoes to stop them from replicating and transmitting many types of viruses including dengue virus [19, 20]. So the strategies of population replacement (ensuring uninfected mosquitoes are replaced by infected ones) based on CI mechanisms and matrilineal inheritance, have been proposed involving inoculative releases of infected mosquitoes [19, 20, 21, 22].

Many mathematical models have been investigated for the spread of *Wolbachia* infection [23, 28, 29, 30, 31, 32, 33, 34]. A continuous-time model for the behaviour of one and two strains of *Wolbachia* within a single well-mixed population has been studied which demonstrated the Allee effect and founder control. Patchy persistence of the two strains has been shown in a discrete spatial model [23, 28]. Delay differential equations analyze how the reproductive advantage offsets the fitness costs for the success of population replacement [32]. Moreover, birth-pulse models of *Wolbachia*-induced CI have studied the effect of different density dependent death rate functions on different strategies for control of dengue virus [34].

At present dengue diseases, being among the leading causes of illness in the tropics and subtropics, have attracted close attention all over the world. After receiving government approval and support from the local community, researchers in many countries aim to release mosquitoes implanted with different strains of *Wolbachia* bacteria to block the spread of dengue virus. The first

releases were of mosquitoes infected with wMel *Wolbachia* (strong anti-dengue properties and low fitness costs) in Yorkeys Knob and Gordonvale in north-eastern Australia in 2011 [20]. Subsequentially, in Tri Nguyen Island, Vietnam, two types of *Wolbachia*-infected mosquitoes involving wMelPop (reducing mosquito lifespan) and wMel were released in April 2013, which failed, and in May 2014 (on going), respectively [35]. In communities around Yogyakarta, Indonesia, mosquitoes infected with wMel *Wolbachia* were also released in January 2014.

At present, over the next 30 years 7 million dengue cases are reported in Brazil. Today the country leads the world in the number of dengue cases with 3.2 million cases and 800 deaths reported during 2009-2014 [36]. Ten thousand mosquitoes will be released there once a week for three to four months. The first release was in September 2014 in Tubiacanga, in the north of Rio de Janeiro, to block the spread of dengue virus. Three more neighbourhoods will be targeted next, and large scale studies to evaluate the effect of the strategy are planned for 2016. In addition, further trials are also planned for Colombia [36]. It is useful to generalize analysis of the strategies for possible application in other countries with high-prevalence areas of dengue diseases. For instance, countries such as Malaysia, Singapore and China reported more cases in 2014 when compared to the same period in 2013 [37].

However, not all of field trails are successful in different countries, thus, interesting issues arise including (a) why did some releases fail in the end? (b) What affects the success of population replacement? (c) Whether or not augmentation can block dengue diseases in field trials, such as in Brazil? If not, how we can it be done successfully? In this study, we focus on answering these questions through mathematical models. Firstly, a continuous four-dimensional mosquito model with *Wolbachia*-induced CI is proposed and simplified as a two-dimensional model, because the ratio of males to females in each state is assumed to be identical. Secondly, we analyze the existence and stability of equilibria, and the conditions of backward bifurcations in three cases. The results show that the zero equilibrium is always unstable, which indicates population eradi-

cation will not be achieved, so only population replacement will be considered. If forward bifurcation occurs, the condition of the threshold $R_0 > 1$ ensures the success of population replacement naturally. However, as the threshold value R_0 may be very small when the mosquito population begins to become infected with *Wolbachia*, it is unlikely for R_0 to be larger than one in practice. Therefore it is weakened by the existence of backward bifurcation. When the fitness cost is large enough, there exists a backward bifurcation which is very important in disease control. So we discuss the basins of attraction of the two attractors and analyze how the parameter space impacts on the success of control strategies without augmentation. Thirdly, regarding the release of infected mosquitoes, models with finite and infinite augmentation are considered to analyze the effects of the initial densities of mosquitoes, augmentation timings, augmentation quantities and numbers of augmentations on the success of population replacement in the general case. The results show that suitable strains of *Wolbachia* should be selected and augmentation methods should be carefully designed for successful population replacement.

2. Models and methods

2.1. Mosquito population models

The total population of mosquitoes $N(t)$ is subdivided into four classes, uninfected females F_U, infected females F_I, uninfected males M_U and infected males M_I. It is assumed that both infected and uninfected individuals have the same natural birth rate b and natural death rate d, specify that the death rates are density dependent. And the offspring have a proportion f of females. The bacterium is mostly passed from infected females to their offspring. But the transmission is usually not perfect in nature, occurring with a probability $\tau \in (0, 1]$. The effect of the CI mechanism results in zygotic death of potential offspring with a probability $q \in [0, 1]$ when an infected male mates with an uninfected female, while all other crosses are unaffected.

Generally, compared with uninfected ones, mosquitoes infected with *Wolbachia* may suffer a fitness cost which is assumed as equal or larger than zero in [28, 29]. However, a fitness cost is not inevitable as there may be some fitness advantages in mosquitoes infected with *Wolbachia*, which allows them to spread more easily and establish themselves in field trails [38, 39, 40, 41]. So in this work, we consider that infected individuals may undergo an additional fitness effects $D(d + D > 0)$, such as fitness cost or $(D > 0)$ or fitness benefit $(D < 0)$ depending on the mosquito species and *Wolbachia* strains.

Therefore, the size of mosquito vector populations can be described by the following differential equations [28]

$$\begin{cases} \frac{dF_I(t)}{dt} = f\tau bF_I - (d+D)NF_I, \\ \frac{dF_U(t)}{dt} = fb(1-\tau)F_I + fbF_U(1-\frac{qM_I}{M_U+M_I}) - dNF_U, \\ \frac{dM_I(t)}{dt} = (1-f)\tau bF_I - (d+D)NM_I, \\ \frac{dM_U(t)}{dt} = (1-f)b(1-\tau)F_I + (1-f)bF_U(1-\frac{qM_I}{M_U+M_I}) - dNM_U. \end{cases} \tag{1}$$

In general, the main dengue mosquito vector species in China have $1:1$ sex ratios, for Aedes aegypti [24] and Ae. albopictus [25], and we assumed that the ratio of infected males to infected females is the same as the ratio of uninfected males to uninfected females, i.e. $M_I/F_I = M_U/F_U$. So after one or two generations, the ratio of males to females in each state is identical. However, there is evidence that a $1:1$ sex ratio may not pertain always [26] and in other insects infection with Wolbachia may indeed distort sex ratios [27]. If further research shows this to be the case in dengue vectors then modifications to our models will be needed in future and the effects of varying sex ratios investigated. Then we can simplify the above model by considering the entire infected and uninfected populations denoted by I and U, respectively, and re-scale suitable parameters, as follows:

$$\begin{cases} \frac{dI}{dt} = \tau bI - (d+D)(I+U)I \doteq F_1(I,U), \\ \frac{dU}{dt} = (1-\tau)bI + bU(1-\frac{qI}{I+U}) - d(I+U)U \doteq G_1(I,U). \end{cases} \tag{2}$$

The above model has been studied in the literature [28, 29]. However, the existence and stability of all possible equilibria of model (2) have not been solved

completely so far, and this is one of our main purposes. Consequently, some interesting biological implications concerning vector population replacement will be discussed in more detail in this paper.

Note that both

$$\lim_{(I,U)\to(0,0)} F_1(I,U) = 0 \text{ and } \lim_{(I,U)\to(0,0)} G_1(I,U) = 0$$

hold true, thus we can define $F_1(0,0) = G_1(0,0) = 0$, confirming that both of the functions F_1 and G_1 are continuous on the closure of $R^2 = \{(I,U)|I \geq 0, U \geq 0\}$. Therefore, the trivial equilibrium $E_{10}^* = (0,0)$ always exists in model (2).

The other equilibria of model (2) satisfy the following equations:

$$\begin{cases} F_1(I^*,U^*) = 0, \\ G_1(I^*,U^*) = 0. \end{cases} \tag{3}$$

Solving the above equations with respect to I^* and U^*, there are three other equilibria: boundary equilibrium $E_{11}^* = (0, b/d)$ and two interior equilibria $E_{1i}^*(i = 2, 3)$, where

$$E_{12}^* = \left(\frac{b\tau}{d+D} \frac{-B-\sqrt{\Delta}}{2A}, \frac{b\tau}{d+D} \frac{-B+\sqrt{\Delta}-2\tau D}{2A} \right)$$

and

$$E_{13}^* = \left(\frac{b\tau}{d+D} \frac{-B+\sqrt{\Delta}}{2A}, \frac{b\tau}{d+D} \frac{-B-\sqrt{\Delta}-2\tau D}{2A} \right)$$

with

$$\Delta = B^2 - 4AC,\ A = q(d+D),\ B = -(q(d+D)+\tau D) \text{ and } C = (d+D) - d\tau.$$

The positivity of all possible equilibria will be addressed in coming subsections. Moreover, the stability of some equilibria of model (2) can not be easily discussed directly, so we need to employ the following equivalent system.

2.2. The equivalent model of model (2)

Equilibrium E_{10}^* cannot be linearized in model (2), so its local stability cannot be studied directly. In addition, it is difficult to determine whether the eigenvalues of E_{1j}^* $(j = 2, 3)$ are less than zero or not, because of their complex forms. So we expand model (2) on a whole axis by studying the transformed model (ξ, U) with $\xi = I/(I + U) \in [0, 1)$ (the ratio of infected individuals to the total population) to understand the stability of E_{1j}^* $(j = 0, 1, 2, 3)$. Every nonzero equilibrium will possess one corresponding equilibrium in the transformed model. However, E_{10}^* may have three corresponding equilibria in the transformed model.

According to the above variable conversion, the equivalent model (ξ, U) of model (4) has the following form:

$$\begin{cases} \frac{d\xi}{dt} = \xi(-bq\xi^2 + bq\xi + b\tau - b - DU) \doteq F_2(\xi, U), \\ \frac{dU}{dt} = \frac{b(1-\tau)U\xi}{1-\xi} + bU(1 - q\xi) - \frac{dU^2}{1-\xi} \doteq G_2(\xi, U). \end{cases} \tag{4}$$

In this section, we first study the four boundary equilibria of model (4). They are denoted as $E_{20}^0 = (0, 0)$, $E_{20}^1 = (\xi_{01}, 0)$, $E_{20}^2 = (\xi_{02}, 0)$ and $E_{21}^* = (\xi_1, U_1) = (0, \frac{b}{d})$, where

$$\xi_{01,02} = \frac{q \mp \sqrt{\Delta_1}}{2q}$$

with $\Delta_1 = q^2 - 4q(1 - \tau) > 0$.

Note that for E_{10}^*, the second variable U of corresponding equilibria will be zero in the transformed model (4). So the three equilibria E_{20}^i (i=0,1,2) correspond to the equilibrium E_{10}^* of model (2).

The endemic equilibria of model (4) are solutions of

$$\begin{cases} \xi(-bq\xi^2 + bq\xi + b\tau - b - DU) = 0, \\ \frac{b(1-\tau)U\xi}{1-\xi} + bU(1 - q\xi) - \frac{dU^2}{1-\xi} = 0. \end{cases} \tag{5}$$

In order to obtain positive solutions of (5), we eliminate U using the second equation of (5) and substitute it into the first equation, then we have the following equation:

$$A\xi^2 + B\xi + C = 0. \tag{6}$$

This equation may have two positive roots

$$\xi_{2,3} = \frac{-B \mp \sqrt{\Delta}}{2A}$$

when $\Delta > 0$. So the two interior equilibria are

$$E_{22}^* = \left(\xi_2, \frac{b\tau}{d+D} \frac{-B + \sqrt{\Delta} - 2\tau D}{2A} \right),$$
$$E_{23}^* = \left(\xi_3, \frac{b\tau}{d+D} \frac{-B - \sqrt{\Delta} - 2\tau D}{2A} \right).$$

The three equilibria $E_{2j}^*(j = 1, 2, 3)$ of model (4) correspond to $E_{1j}^*(j = 1, 2, 3)$ of model (2), respectively.

2.3. Stability analysis of equilibria for models (4) and (2)

At first, we can utilize the Jacobian matrix of models (4) and (2) to determine the stability of equilibria $E_{1j}^*(j = 1, 2, 3)$ (see Appendix A for details). For convenience, the stability condition of E_{11}^* is denoted $-b\,(1 - \tau + D/d) = 0$ as $R_0 \doteq \tau - D/d = 1$, then E_{11}^* is locally stable provided that $R_0 < 1$. The stability of equilibria E_{12}^* and E_{13}^* are determined by whether the eigenvalues are strictly negative or not. However, the local stability of equilibrium E_{10}^* cannot be studied directly, because E_{10}^* cannot be linearized in model (2). So its stability is transported to analyze the three equilibria $E_{20}^i(i = 0, 1, 2)$ of the equivalent model (4). If we denote the eigenvalues of boundary equilibria of model (4) as λ_1 and λ_2, by a similar method as for model (2), their stabilities can be obtained as shown in Table 1.

Therefore, for the stability of boundary equilibria of models (4) and (2), we have the following main results.

Theorem 2.1. *For model (2), E_{11}^* is locally asymptotically stable if $R_0 < 1$, and unstable if $R_0 > 1$. For model (4), $E_{20}^i(i = 0, 1, 2)$ are unstable when they exist, therefore, for model (2), zero equilibrium E_{10}^* is unstable.*

Based on Theorem 2.1, E_{10}^* is always unstable which indicates that it is impossible to prevent the spread of dengue virus by eradicating mosquito populations. Indeed, it is also unlikely, and not necessarily desirable, that the mosquitoes could be eradicated in practice. Therefore, population replacement, an alternative and more effective strategy, will be addressed in this paper. To do this, we first need to analyze the stability of interior equilibria for models (2) and (4).

In order to understand the existence and stability of equilibria of models (4) and (2) in more detail, we choose D, τ and q as bifurcation parameters to address the regions of existence and stability of equilibria for the two models. For convenience, three key curves are defined as

$$L_1 : B = 0,\ L_2 : B^2 - 4AC = 0,\ L_3 : R_0 = 1.$$

In practice, the fitness advantages and disadvantages may be balanced out (i.e. $D = 0$) for mosquitoes infected with some *Wolbachia* [1, 41]. Other *Wolbachia* may have perfect transmission rates from infected females to their offspring (i.e., $\tau = 1$), which may lead to complete population replacement in mosquito populations [34]. Therefore, to comprehend how the three critical parameters D, τ and q affect the success of population replacement, we address the following three scenarios.

Case 1: Fitness cost $D = 0$.

In this case, the righthand function $F_2(I, U)$ of equivalent model (4) is independent of variable U. Interior equilibria of original model (2) are changed as $E_{12}^* = (I_2^*, U_2^*)$ and $E_{13}^* = (I_3^*, U_3^*)$, with

$$I_2^* = U_3^* = \frac{b\tau(q - \sqrt{\Delta_1})}{2dq} \text{ and } I_3^* = U_2^* = \frac{b\tau(q + \sqrt{\Delta_1})}{2dq}$$

and $\Delta_1 > 0$ indicates that both I_2^* and I_3^* are positive.

While in the equivalent model (4), they are simplified as $E_{22}^* = (\xi_2, U_2^*)$ and $E_{23}^* = (\xi_3, U_3^*)$, with

$$\xi_{2,3} = \frac{q \mp \sqrt{\Delta_1}}{2q}.$$

By estimating the eigenvalues of $E^*_{2i}(i = 2, 3)$ for model (4), the stability of $E^*_{2i}(i = 2, 3)$ and their corresponding equilibria $E^*_{1i}(i = 2, 3)$ of model (2) were determined as shown in Table 2.

In this case, the three lines (L_1, L_2 and L_3) divide the τ and q parameter space into five regions as shown in Fig. 2(A). Only Ω_{11} and Ω_{12} are meaningful regions for the existence of equilibria. Especially, the two attractors E^*_{11} and E^*_{13} (or E^*_{22} and E^*_{23}) coexist in region Ω_{12}, coinciding in line L_2. Detailed descriptions for each region are shown in Table 3.

According to the above stability analysis, we have the following main results.

Theorem 2.2. *For model (2), when there is no fitness cost, i.e. $D = 0$, there are at most four equilibria, E^*_{10}, E^*_{11}, E^*_{12} and E^*_{13}.*
(1) If $\Delta_1 > 0$, then E^*_{11} and E^*_{13} are locally stable, while the other two are unstable. The solution stabilizes at E^*_{11} provided that the initial ratio $\xi_0 \in (0, \xi_{01})$ and any U_0; the solution stabilizes at E^*_{13} provided that the initial ratio $\xi_0 \in (\xi_{01}, 1)$ and any U_0.
(2) If $\Delta_1 = 0$, then E^*_{12} and E^*_{13} collide together as $(b\tau/(2d), b\tau/(2d))$, and only E^*_{11} is locally stable.
(3) If $\Delta_1 < 0$, then two interior equilibria disappear, and E^*_{11} is locally stable.

Based on the above Theorem, there exists an Allee effect which means that low initial ratios of infected individuals to the total population ($\xi_0 < \xi_{01}$) are driven to the extinction of infected ones, but high initial ratios of infected individuals to the total population ($\xi_0 > \xi_{01}$) can survive for infected ones as shown in Fig. 1. So in this case, in order to achieve the population replacement, the initial ratio of the infected individuals should be larger than ξ_{01}.

Case 2: Perfect transmission $\tau = 1$.

In this special case, interior equilibria of the original model (2) are changed to

$$E_{12}^* = \left(\frac{bD}{q(d+D)^2}, \frac{b(q(d+D)-D)}{q(d+D)^2}\right), E_{13}^* = \left(\frac{b}{d+D}, 0\right).$$

Similarly, by estimating the eigenvalues of $E_{1i}^*(i=2,3)$ for model (2), their stabilities are determined. The three lines (L_1, L_2 and L_3) divide the D and q parameter space into many regions. Only $\Omega_{2k}(k=1,2,3,4)$ are meaningful regions for the existence of equilibria. Especially, the two attractors E_{11}^* and E_{13}^* (or E_{22}^* and E_{23}^*) coexist in region Ω_{23}, coinciding in line L_2. Detailed descriptions for each region are shown in Table 3.

Therefore, we have the following main results.

Theorem 2.3. *For model (2), when there is perfect transmission $\tau = 1$, there are at most four equilibria, E_{10}^*, E_{11}^*, E_{12}^* and E_{13}^*. E_{11}^* is locally stable provided that $D > 0$; E_{12}^* is unstable when it exists; E_{13}^* is locally stable provided that $D < qd/(1-q)$.*

According to the above Theorem, if the fitness cost $D < 0$, then only E_{13}^* is stable. Thus, the population replacement may be realized completely for the control of dengue diseases.

Case 3: General situation $D \neq 0, \tau \neq 1$.

In this case, it is difficult to determine the stability of interior equilibria, so we first concentrate on the existence of backward bifurcation, which is important in the control of dengue virus just as it is in the control of epidemics in general. Note that, $C \leq 0$ if and only if $R_0 \geq 1$ which is necessary in the following.

(i) Let $d + D = 0$, *i.e.*, $D = -d < 0$. (6) is a linear equation with a unique root $\xi = -C/B$, which is positive if and only if $R_0 > 1$. Thus if $d + D = 0$ there is a unique endemic equilibrium provided that $R_0 > 1$ which approaches zero as $R_0 \to 1$ while there is no endemic equilibrium if $R_0 < 1$. In this case it is impossible to have a backward bifurcation at $R_0 = 1$.

(ii) Let $d + D > 0$, *i.e.*, $D > -d$. If $B > 0$, then (6) is quadratic and there is a unique positive root when $R_0 > 1$; while there is no root when $R_0 \leq 1$. If $B < 0$, there is a unique positive root for (6) when $R_0 > 1$; a unique positive

root $\xi = -B/A$ when $R_0 = 1$; two positive roots ξ_2 and ξ_3 when $R_0^c < R_0 < 1$; no positive root when $R_0 < R_0^c$, where

$$R_0^c \doteq 1 - \frac{(q(d+D)+\tau D)^2}{4dq(d+D)}.$$

Here R_0^c can be obtained when $\xi_2 = \xi_3$, *i.e.*, $B^2 - 4AC = 0$.

Therefore, we have the following main results.

Theorem 2.4. *Model (4) exhibits a backward bifurcation when $R_0^c < R_0 < 1$ if $B < 0$. Consequently, model (2) has a backward bifurcation when $R_0^c < R_0 < 1$ under the same conditions owing to equivalence between models (2) and (4).*

Consider that the three parameters D, τ and q are critical to the success of population replacement, and backward bifurcation is important to endemic control, so in the following we address how the three parameters affect the occurrence of backward bifurcation.

We can obtain an explicit expression of D in terms of parameters q, d and τ for the existence of backward bifurcation at $R_0 = 1$. According to the expression of R_0 and B, inequality $B < 0$ is equivalent to $D > -dq$. So the backward bifurcation occurs at $R_0 = 1$ if and only if $D > -dq$. In other words, when the fitness cost $D > -dq$, backward bifurcation will take place as shown in Figs. 4(A) and 5(A), which means D is one of the factors leading to backward bifurcation. When $D \leq -dq$, then the backward bifurcation will change to forward as shown in Fig. 4(B).

Note that if $D > -dq$, there is a backward bifurcation at $R_0 = 1$, then there are two endemic equilibria for an interval of R_0 from a threshold value R_0^c defined by $B^2 - 4AC = 0$ to $R_0 = 1$. In order to calculate R_0^c, substituting the expressions of A, B and C into $B^2 - 4AC = 0$ yields a quadratic of τ:

$$D^2\tau^2 + 2q(3dD + 2d^2 + D^2)\tau + q(q-4)(d+D)^2 = 0. \tag{7}$$

Solving (7) with respect to τ yields

$$\tau_{1,2} = \frac{\left(-qD - 2qd \mp \sqrt{q^2dD + q^2d^2 + qD^2}\right)(d+D)}{D^2}.$$

Note that $B < 0$ and $R_0 < 1$ are equivalent to

$$\frac{-q(d+D)}{D} < \tau < \frac{d+D}{d}.$$

So $\tau_c = \tau_2$ and

$$R_0^c = \tau_c - \frac{D}{d}.$$

Similarly, we have the following results on the existence of backward bifurcations for Cases 1 and 2 as shown in Fig. 5.

Lemma 2.1. For model 2, in Case 1, there exists a backward bifurcation when $R_0^c < R_0 < 1$, with $R_0^c = \tau_c = 1 - q/4$; in Case 2, there exists a backward bifurcation when $R_0^c < R_0 < 1$, with $R_0^c = 1 - D_c/d = 1 - q/(1-q)$.

Similarly, the three lines (L_1, L_2 and L_3) divide the D and q parameter space into five regions as shown in Fig. 2(A). Only $\Omega_{3k}(k = 1, 2, 3, 4, 5, 6, 7)$ are meaningful regions for the existence of equilibria. Especially, the two attractors E_{11}^* and E_{13}^* (or E_{22}^* and E_{23}^*) coexist in region Ω_{33}, coinciding in line L_2. Detailed descriptions for each region are shown in Table 3.

Theorem 2.5. *For model (4), when $R_0 > 1$, the unique endemic equilibrium E_{23}^* is locally stable if $0 < q < \min\{4(1-\tau), -D/(d+D)\} \leq 1$.*

The proof of Theorem 2.5 is shown in Appendix B. Consequently, for model (2), there are the same stability conditions for the unique endemic equilibrium E_{13}^*.

Theorem 2.6. *For model (4), when $B < 0$ and $R_0^c < R_0 < 1$, if one of the following two conditions hold true:*
(i) If $D < 0$ and $-D/d < q < \min\{4(1-\tau), -D/(d+D)\} \leq 1$.
(ii) If $D > 0$, $q_1 < q < \min\{4(1-\tau), q_2\}$ and (C.1).
Then E_{23}^* is locally asymptotically stable. E_{22}^* is an unstable saddle provided that (C.2) holds.

Where (C.1), (C.2) and the proof of Theorem 2.6 are shown in Appendix C. Consequently, for model (2), there are the same stability conditions for the endemic equilibria E_{12}^* and E_{13}^*.

2.4. Modelling augmentation

At present, dengue diseases are giving rise to close attention all over the world. Some field trials (releases of mosquitoes implanted with different strains of *Wolbachia* bacteria) have been planned to achieve population replacement and block the spread of dengue virus in many countries including Australia, Vietnam, Indonesia and Brazil. However, not all of these releases can or will succeed.

We assume that initial populations of mosquitoes will have very low numbers infected with *Wolbachia*, so it is difficult for them to be established in the field trails which means $R_0 < 1$. Therefore, in the following, we focus on whether population replacement can be success under a lower value R_0. According to the above section, when backward bifurcation occurs, the solutions of model (2) from different initial values have different stable states, i.e. some solutions can stabilize at E_{11}^*, while others will stabilize at E_{13}^*, which depends on where the initial values lie in the basins of attraction of the two attractors, which indicates that strategies of population replacement may either succeed or fail in the end. So we focus on the existence of backward bifurcation in parameter space, and then alter their dynamics by introducing infected mosquitoes so that their orbit is within the desired zone, i.e., the grey areas in Figs. 2, 3 and 6. If this can be achieved, then the control measures will be successful. Without loss of generality, the releases of infected mosquitoes occurs at times $T_1, T_2, ..., T_k$ and augmentation (pulse) quantities $\theta_i > 0 (i = 1, 2, ..., k$, k being finite and infinite), with the same ratio of infected females to males as in the original model (2).

Then a model with augmentation is proposed as follows:

$$\begin{cases} \left.\begin{aligned} &\tfrac{dI}{dt} = \tau bI - (d+D)(I+U)I, \\ &\tfrac{dU}{dt} = (1-\tau)bI + bU(1-\tfrac{qI}{I+U}) - d(I+U)U, \end{aligned}\right\} t \neq T_i, \\ \left.\begin{aligned} &I(T_i^+) = I(T_i) + \theta_i, \\ &U(T_i^+) = U(T_i), \end{aligned}\right\} t = T_i, \end{cases} \tag{8}$$

where T_i^+ denotes the moment after pulse releases at time T_i, and they are nearly equal. The items $I(T_i^+)$ and $U(T_i^+)$ denote the mosquito densities of the infected and uninfected ones at time T_i after pulse releases, and we have $I(T_i^+) > 0$ and $U(T_i^+) > 0$.

Model (8) is employed to investigate how the augmentation time T_i and the augmentation quantity θ_i affect the success of population replacement.

3. Results and discussion

In this section, we will focus on the biological implications of all the main results shown in previous sections. In particular, we carry out numerical investigations for the models with and without augmentation strategies to address all the questions arising in the introduction section. To do this, we choose different parameter sets for illustrations only in the following due to our current lack of any real parameter values. In order to overcome this weakness, the wide ranges of all parameters related to mosquitoes and human actions have been chosen for sensitivity analysis, which allows us to address how the key parameter changes affect on the successful strategies of population replacement. Thus, the main results obtained here can be used to evaluate the effectiveness of different control tactics and to provide the qualitative information on the control of dengue vectors. So that suitable strains of *Wolbachia* and careful design of augmentation methods can be selected for the successful control of dengue virus.

3.1. Backward bifurcation

In epidemic models, when the bifurcation leading from a disease free equilibrium to an endemic equilibrium is forward, a basic reproduction number is a

threshold in a sense, i.e. a disease is persistent if it is greater than one, and dies out if it is below one. However, if a backward bifurcation occurs, the basic reproduction number does not describe the necessary elimination effort any more; rather it is replaced by a critical value at the turning point. In the control of dengue disease, it is desired to realize the population replacement as much as possible to block the replication of dengue virus, in other words, the outbreak of mosquitoes infected with *Wolbachia* benefit dengue control. Thus, it is important to identify backward bifurcations to obtain the threshold for the outbreak of *Wolbachia* infected mosquitoes.

According to detailed analysis of the stability of models (2) and (4), some useful quantitative results of backward or forward bifurcation can be described as follows.

Case 1: Fitness cost $D = 0$. Note that $D > -qd$ is satisfied in this case, thus forward bifurcation cannot occur at all, only backward bifurcation can appear in parameter region Ω_{12} as shown in Figs. 2(A) and 5(A). So for any initial values, the solutions of model (2) either stabilize at E^*_{11} or E^*_{13}, which depends on the relationship between initial values and the unstable manifold as shown in Figs. 1 and 2(B).

Case 2: Perfect transmission $\tau = 1$. Based on Theorem 2.4, if parameters lie in region Ω_{23}, backward bifurcation occurs as shown in Figs. 3(A) and 5(B). So for any initial values, the solutions of model (2) either stabilize at E^*_{11} or E^*_{13}, which depends on the relationship between initial values and the unstable manifold as shown in Fig. 3(B). While if the parameter values lie in regions Ω_{21} and $\Omega_{22}(D < 0)$, the backward bifurcation is replaced by a forward bifurcation, which implies that for any initial values, the solutions of model (2) finally stabilize at E^*_{13} provided that $R_0 > 1$, so population replacement is completely achieved.

Case 3: General situation $D \neq 0, \tau \neq 1$**.** Similarly, if the parameter values lie in region Ω_{33} (see Fig. 6(A)), backward bifurcation occurs as shown in Figs.

4(A) and 5(A). So for any initial values, the solutions of model (2) either stabilize at E_{11}^* or E_{13}^*, which depends on the relationship between initial values and the unstable manifold as shown in Figs. 7 and 8. Especially, when fitness cost $D > 0$, it is interesting that as D increases (from $0, 0.1, 0.2, 0.3, 0.4$ to $D^* = 0.7$), the threshold values R_0^c decrease and the regions of backward bifurcations become narrow until they disappear, as shown in Fig. 5(A). While if parameter values lie in regions Ω_{31} and Ω_{32}, the backward bifurcation is replaced by a forward bifurcation as shown in Fig. 4(B), which indicates population replacement can be partially fulfilled provided that $R_0 > 1$.

3.2. Multiple attractors

In order to explain the steady sates of the solutions for model (2) from different initial values when backward bifurcation occurs, we consider the basins of attraction of the two attractors E_{11}^* and E_{13}^* in their coexistence regions in three cases as shown in Figs. 2(B), 3(B) and 6(B), respectively.

In Fig. 2(B), the critical parameter values ($\tau = 0.9,\ q = 0.8$) are chosen from the region Ω_{22}, the other parameter values are the same as in Fig. 2(A). The two regions are separated by an unstable manifold $U_0 = (1 - \xi_{01})I_0/\xi_{01}$ (or $\xi_0 = \xi_{01}$), the grey and white regions are the basins of attraction of E_{13}^* and E_{11}^*, respectively, which indicates that for any initial values (I_0, U_0) , the solutions of model (2) will finally stabilize at E_{13}^* (or E_{11}^*), then two types of mosquitoes will coexist (or the infected ones will die out), which means that the population replacement can be partly realized (or fail).

In Fig. 3(B), parameter values are the same as in Fig. 3(A). The two regions are separated by the unstable manifold. The initial values (I_0, U_0) from the grey (or white) region, the solutions of model (2), will finally stabilize at E_{13}^* (or E_{11}^*), then uninfected mosquitoes are totally replaced by infected ones (or infected ones die out), which means that the population replacement can be completely realized (or fail).

Similarly, in Fig. 6(B), parameter values are the same as in Fig. 6(A). The two regions are separated by an unstable manifold. Only the initial values

(I_0, U_0) from the grey region, solutions of model (2) will finally stabilize at E^*_{13}, then uninfected mosquitoes are partly replaced by infected ones, which means that the population replacement is either partly realized or fails.

Note that the size of the basin of attraction of E^*_{13} increases from Cases 2, 1 and 3, respectively. So for Cases 1 and 3, the probability of solutions stabilizing to E^*_{13} are larger than that for Case 2. However, compared to Case 2 which can realize uninfected mosquitoes being totally replaced by infected ones, in Cases 1 and 3, they only realize the coexistence of the two types of mosquitoes. Therefore, in practice, we should balance the two sides, and different control aims may lead to the selection of different stains of *Wolbachia* bacteria. For example, if total population replacement is needed to control dengue disease, then the *Wolbachia* bacteria with perfect transmission rate is selected.

3.3. Control strategies without augmentation

For the control of dengue disease in epidemic areas, for example in Brazil, whether or not dengue disease is controlled successfully is determined by different parameter spaces and initial densities of two types of mosquitoes. Based on these facts, it is critical to consider the following three issues.

Firstly, in practice, in order to block the spread of dengue diseases, three key parameters (rate of zygotic death from CI q, fitness cost D and transmission rate τ) of different stains of *Wolbachia* in the target mosquitoes should be estimated at first. Next, appropriate strains should be selected to make sure that the three parameters lie in those regions that ensure the existence of E^*_{13}, as shown in Figs. 2(A), 3(A), 6(A) and Table 3. For example, the meaningful regions for the three cases are Ω_{12}, $\Omega_{2k}(k = 1, 2, 3)$ and $\Omega_{3k}(k = 1, 2, 3)$, respectively.

Secondly, different types of bifurcation (here forward and backward) may lead to different control strategies. So the type of bifurcation should be estimated clearly in each parameter region. When the effect of the fitness benefit is weak, i.e., $-d < D < -dq$, forward bifurcation occurs, so the threshold R_0 being unity is a strict threshold for the control of the disease: The infected mosquito will die out provided that $R_0 < 1$, and otherwise it will tend to break out.

For instance, the regions with forward bifurcation occurring are $\Omega_{2k}(k = 1, 2)$ and $\Omega_{3k}(k = 1, 2)$, respectively. Hence, for any initial values (I_0, U_0) from the regions, the solutions of model (2) finally stabilize at E^*_{13} provided that $R_0 > 1$ which indicates that the strategy of population replacement can be realized without augmentation. However, when the effect of fitness cost is strong, i.e. $D > -dq$, the backward bifurcation will take place when $R^c_0 < R_0 < 1$. For instance, the regions with backward bifurcation occurring are Ω_{12}, Ω_{23} and Ω_{33}, respectively. In this case, whether the strategy of population replacement can be achieved or not depends on the initial values (I_0, U_0). From Figs. 2(B), 3(B) and 6(B), if the initial densities of infected and uninfected mosquitoes lie in the grey region, population replacement may be realized in spite of a lack of control, and the levels of replacement depend on the different strains of *Wolbachia* bacteria. While if the initial densities of two types of mosquitoes lie in the white region, if there is no other control, the strategy of population replacement will fail in the end.

Thirdly, the more the degree of population replacement, the more is the benefit for controlling the dengue virus. Note that the total number of mosquitoes in equilibrium E^*_{13} is $I^*_{13} + U^*_{13} = b\tau/d$. If E^*_{13} exists and is locally stable in parameter space (see Table 3), it is desirable to make the number of infected ones (or uninfected ones) be as large (or small) as possible, which helps realization of population replacement for the control of dengue disease. In Case 2, if E^*_{13} exists and is locally stable, uninfected individuals will be totally replaced by infected ones, so it is unnecessary to make the number of infected mosquitoes as large as possible. In Case 1, the effects of parameters on the values I^*_{13} are similar to results presented by [34], which shows that the larger the natural birth rate b, rate of zygotic death from CI q and the probability of transmission from infected mother to offspring τ and the shorter the natural death rate d make dengue control more effective. In Case 3, the smaller the fitness cost D benefits dengue control, and the other parameters produce similar results to those in Case 1.

3.4. Control strategies with augmentation

According to the above section, in order to realize population replacement without augmentation, the strains of *Wolbachia* should be carefully evaluated at first, such that the existence of interior equilibria are possible and the threshold value R_0 is larger than one. However, the initial population of infected mosquitoes may be very low in numbers, so that the threshold value R_0 may be very small. Therefore, to answer the series of issues in the introduction, we focus on whether or not some strains of *Wolbachia* can realize population replacement under a relatively weak threshold condition $R_0^c < R_0 < 1$ (i.e. a backward bifurcation occurs). To do this, a key question is how augmentation can be applied such that the densities of infected and uninfected mosquitoes lie in desired regions, i.e., the grey areas in Figs. 2, 3 and 6, in other words, the basin of attraction of attractor E_{11}^* moves to that of E_{13}^*. Without loss of generality, we mainly analyze the effects of initial values, augmentation timings, augmentation quantities and number of augmentation events (or augmentation quantities and augmentation periods) on the solutions of model (8) in Case 3, when the number of augmentations is finite (or infinite), the other two cases can be discussed similarly. For convenience, denote T_{1j} and $\theta_{1j}(j = 1, 2, ..., k)$ as the pulse times and the quantities vectors released in j pulses, respectively.

Note that if some strains of *Wolbachia* are selected such that parameter values lie in the nonexistence regions of E_{13}^* (i.e. $R_0 < 1$ or $R_0 < R_0^c$ depending on forward or backward bifurcation, respectively), no matter how many infected mosquitoes are released, the strategies of population replacement will fail in the end. This possibly explains why the releases of mosquitoes infected with wMel in Tri Nguyen Island failed.

3.4.1. Augmentation at finite times

In order to show the effects of the initial values, pulse timings and pulse quantities on the solutions of model (8) with finite impulsive augmentation (here one, two and three pulses considered), only a single factor is changed, the other two factors being the same (see Figs. 9, 10 and 11). For easy comparison, in the

following figures, the initial densities of the uninfected mosquitoes are fixed and the black dotted lines denote the solutions of model (8) without augmentation. The parameter values are the same as in the corresponding figures.

Figs. 9(A), (C), 10(A) and 11(A) show that if the initial density of infected mosquitoes or the pulse quantity are too low, the releases cannot realize population replacement at all (see green solution curves). However, if the initial density of the infected ones or the pulse quantity increases, after many pulses, the densities of the two types of mosquitoes will lie in the basin of attraction of E_{13}^*, and then population replacement will succeed in the end. Moreover, the more the increase of the initial infected mosquitoes or of the pulse quantity, the easier it is to realize the replacement (i.e. the solutions stabilize faster at E_{13}^*), for example from magenta, blue to red solution curves in sequence.

Figs. 9(B), 10(B) and 11(B) show that too early or too late implementations of population replacement strategies cannot succeed at all (medium yellow or green solution curves), which implies that there may exist a most appropriate pulse time for the releases of infected mosquitoes. For convenience, we only consider the pulse time in the solutions of model (8) with one pulse. Other finite pulses can be analyzed similarly. When different pulse time points are selected, the detailed effects of them on the solutions of model (8) are shown in Fig. 12. The best pulse time is when the solution curve begins to be plain (i.e., the black solid line in Fig. 12(A)). The more pulse time points near it, the easier and the faster the solutions of model (8) is stabilization at E_{13}^*. If pulse time points are far from it, the solutions may in turn stabilize at E_{11}^* (here at times T_1, T_2, T_8, T_9) which lead to failure of population replacement. In Fig. 12(B), we give examples to verify our results. When pulse releases take place at three times T_3, T_5 and T_7, respectively, at time T_5, the solution of model (8) is the easiest and fastest to stabilize at E_{13}^* (see blue, red solid and magenta solution curves). In addition, when the pulse quantity increases to 0.35, and with pulses at times T_2 and T_8, the solutions of model (8) stabilize at E_{13}^*.

Figs. 10(C) and 11(C) illustrate three main points. Firstly, with the same pulse quantity, different pulse sequences may lead to entirely different results

(see the magenta and green solution curves). Secondly, if the strategies of population replacement can be achieved under some given pulse quantity, then with an increase of the pulse quantity at some pulse times, the more likely is realization of population replacement (see the magenta, blue and red solution curves). Thirdly, if the strategies of population replacement fail under some given pulse quantity, then only an increase of enough pulse quantity can realize population replacement (see the green, medium yellow and blue solution curves).

In order to show how the number of impulsive augmentations affect the strategies of population replacement, under the same pulse quantity, model (8) with different numbers of pulses is considered. In Fig. 13, with a single pulse, control strategies cannot be achieved, while with two or even three pulses, the control strategies may be realized better.

According to the above discussion, by finite augmentations of infected mosquitoes to block dengue diseases in some countries (for example in Brazil), the following advice is useful for realizing population replacement as far as possible in the high-incidence season of dengue.

- *Wolbachia* should be monitored and selected carefully at first regarding the existence of a backward bifurcation and the density of infected mosquitoes under stable state (I_{13}^*) being as large as possible.

- Initial densities of infected and uninfected mosquitoes and the pulse quantities are large enough so that population replacement can be achieved, and the higher they are, the easier and faster will it be to realize the replacement. Augmentation should be carried out at as near to the suitable time as possible. Too early or too late timings will lead to failure.

- In spite of the augmentation timings being the same, the sequence of augmentations of different quantities may substantially affect the success or failure of strategies. If the first pulse is carried out as near to the suitable time as possible and with a relative large quantity, the greater the chance of successful population replacement. In the same region of

pulse timing and pulse quantity, it is beneficial to population replacement when the number of pulses is increased.

3.4.2. Augmentation at infinite times

In practice, it is easier to implement control measures when releases are periodic rather than aperiodic. So in the following, we consider how periodic augmentation impacts on the implementation of population replacement. For convenience, pulse period and pulse quantity are denoted by T and θ, respectively in model (8).

Figs. 14(A) and (B) show that the pulse quantity is too low to realize population replacement (see green solution curve), as the pulse quantity increases, it is much easier and faster to achieve stability at a period solution with larger amplitude (see magenta, blue and red solution curves). Similar results are shown in Figs. 14(C) and (D) for when the pulse quantity is fixed and pulse period decreases.

Therefore, for the releases of infected mosquitoes in the fight against dengue disease in Brazil, releases with large pulse quantity and short period are required in the high-incidence season of dengue, so that population replacement can achieved as soon as possible to suppress the replication of dengue virus in mosquitoes.

3.5. Further work

In this paper, we focused on the augmentation quantity with the same ratio of infected females to males as in the original model (2). However, in practice, seasonal fluctuations in releases of infected mosquitoes will lead to different ratios of females to males. Secondly, females and males whether infected with *Wolbachia* or not may have different fates when they mate due to the CI mechanism and matrilineal inheritance. Moreover, as reported in the China Daily on Nov 10, 2014 [42], dengue fever has afflicted the whole of Guangdong Province in China particularly severely this year, with more than 42,000 cases reported by Nov 2. The fever is spread via bites from female mosquitoes, and the males do

not bite. *Wolbachia* has a special effect of sterility on the *Aedes aegypti* mosquito based on CI. Therefore, only the male mosquitoes infected with *Wolbachia* will be released in March and April on Shazai Island in Guangdong province in a trial aimed at sterilizing the mosquitoes that transmit diseases like dengue fever (population suppression). To achieve the best outcome, five Wolbachia-carrying male mosquitoes should be released for each uninfected wild male mosquito on the island. Further trials will be conducted in Jiangmen, Guangdong province, and in Hainan province. Therefore, model (1) can not be reduced to the simple model (2) any more, and the more realistic four-dimensional impulsive model should be developed to study how different sex ratios of the infected mosquitoes released may affect the strategies of population suppression and replacement. Whether or not the strategy of population suppression can be realized in Guangdong province remains to be seen. If not, how we can success be achieved?

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Appendix A. Stability of $E^*_{1j}(j = 1, 2, 3)$ of model (2)

In the neighbourhood of equilibria, the dynamics of model (2) are determined by the linearization

$$\dot{X} = JX \tag{A.1}$$

with Jacobian matrix J as the linear counterpart and $X = (I, U)$. By simple calculation, the Jacobian matrix J at (I, U) is given by

$$J(I,U) = \begin{pmatrix} b\tau - (d+D)(2I+U) & -(d+D)I \\ (1-\tau)b - \frac{bqU^2}{(I+U)^2} - dU & b(1 - \frac{qI}{I+U} + \frac{qIU}{(I+U)^2}) - d(I+2U) \end{pmatrix}. \tag{A.2}$$

The Jacobian matrix of model (2) at E^*_{11} takes the form of

$$\begin{pmatrix} b\tau - \frac{b(d+D)}{d} & 0 \\ b((1-\tau) - q - 1) & -b \end{pmatrix}.$$

where $(\star)$ is not necessary for the stability analysis, so we omit it.

Since the eigenvalues are

$$\lambda^1_{11} = b\tau - \frac{b(d+D)}{d} \leq 0, \quad \lambda^2_{11} = -b < 0.$$

Note that $\lambda^1_{11} \leq 0$ is equivalent to

$$R_0 \doteq \tau - \frac{D}{d} \leq 1,$$

so $R_0 = 1$ if and only if $\tau = 1$ (perfect transmission) and $D = 0$ (no fitness cost for infection). So for model (2), E^*_{11} is locally asymptotically stable if $R_0 < 1$, and unstable if $R_0 > 1$.

Combination (3) and (A.2), Jacobian matrices J at $E^*_{1i}(i = 2, 3)$ are simplified as

$$J_{E^*_{1i}} = \begin{pmatrix} -(d+D)I^* & -(d+D)I^* \\ \frac{q(d+D)^2}{b\tau^2}U^{*2} - dU^* + (1-\tau)b & \frac{q(d+D)^2}{b\tau^2}I^*U^* - dU^* - (1-\tau)b\frac{I^*}{U^*} \end{pmatrix}. \tag{A.3}$$

By simple calculation, eigenvalues of E_{12}^* are

$$\lambda_{12}^i = \frac{-P_1 \pm \sqrt{P_1^2 + 4N_1}}{2} \quad (i = 1, 2),$$

where

$$\begin{aligned} P_1 &= \tfrac{b}{4q(d+D)^2}[\Delta - (2q(d+D) + 4D\tau)\sqrt{\Delta} + (q^2 + 4q\tau - 4q + 3\tau^2)D^2 \\ &+ (2dq^2 + 12dq\tau - 8bq)D + d^2q^2 + 8q\tau d^2 - 4qd^2], \end{aligned} \tag{A.4}$$

and

$$N_1 = \frac{b^2\tau\sqrt{\Delta}\left(q(d+D) + D\tau - \sqrt{\Delta}\right)}{2q(d+D)^2}.$$

Similarly, eigenvalues of E_{13}^* are

$$\lambda_{13}^i = \frac{-P_2 \pm \sqrt{P_2^2 + 4N_2}}{2} \quad (i = 1, 2),$$

where

$$\begin{aligned} P_2 &= \tfrac{b}{4q(d+D)^2}[\Delta + (2q(d+D) + 4D\tau)\sqrt{\Delta} + (q^2 + 4q\tau - 4q + 3\tau^2)D^2 \\ &+ (2dq^2 + 12dq\tau - 8bq)D + d^2q^2 + 8q\tau d^2 - 4qd^2], \end{aligned} \tag{A.5}$$

and

$$N_2 = \frac{-b^2\tau\sqrt{\Delta}\left(q(d+D) + D\tau + \sqrt{\Delta}\right)}{2q(d+D)^2}.$$

Therefore, the types of equilibria E_{12}^* and E_{13}^* and their stability are determined according to whether or not their eigenvalues are strictly negative.

Appendix B. The proof of Theorem 2.5

The local stability of endemic equilibria of model (4) when $R_0 > 1$. The Jacobian matrix of model (4) is

$$J(\xi, U) = \begin{pmatrix} bq\xi(1-2\xi) & -D\xi \\ \frac{(1-\tau)bU - dU^2}{(1-\xi)^2} - bqU & \frac{(1-\tau)b\xi - 2dU}{1-\xi} + b(1-q\xi) \end{pmatrix}. \tag{B.1}$$

Combining nonzero coordinate values for endemic equilibria and (5), the Jacobian matrix of model (4) is simplified as

$$J(\xi,U)=\begin{pmatrix} bq\xi(1-2\xi) & -D\xi \\ \left(\frac{-b(1-q\xi)}{1-\xi}-bq\right)\left(\frac{-bq\xi^2+bq\xi+b\tau-b}{D}\right) & \frac{-d}{1-\xi}\left(\frac{-bq\xi^2+bq\xi+b\tau-b}{D}\right) \end{pmatrix}. \tag{B.2}$$

So

$$\begin{aligned} detJ &= \tfrac{b\xi^2(q\xi^2-q\xi+1-\tau)(-2q(d+D)\xi+q(d+D)+D)}{D(1-\xi)}, \\ trJ &= \tfrac{b(2qD\xi^3+(dq-3qD)\xi^2+q(D-d)\xi+d(1-\tau))}{D(1-\xi)}. \end{aligned} \tag{B.3}$$

Note that $R_0>1$ is equivalent to $C<0$, according to the expression of C, we have $D<-d(1-\tau)<0$. Therefore $detJ$ is positive if and only if

$$(q\xi^2-q\xi+1-\tau)(-2q(d+D)\xi+q(d+D)+D)<0.$$

For convenience, denote

$$f_1(\xi)=q\xi^2-q\xi+1-\tau,\ f_2(\xi)=-2q(d+D)\xi+q(d+D)+D,$$

then we have

$$f_1(\xi)>f_1(\frac{1}{2})=\frac{-q}{4}-\tau+1.$$

For simplicity, we only focus on the case of $f_1(\xi)>0$ for all the ξ, i.e., $q<4(1-\tau)$. Similarly, we can analyze the stability conditions when $f_1(\xi)<0$ for some ξ.

Solving $f_2(\xi)=0$ with respect to ξ yields

$$\xi^*=\frac{q(d+D)+D}{2q(d+D)}.$$

$\xi_3>\xi^*$ holds true naturally when $D<0$. So $detJ>0$ if $f_1(\frac{1}{2})>0$ and $f_2(0)<0$, i.e.,

$$0<q<\min\left\{4(1-\tau),\frac{-D}{(d+D)}\right\}\leq 1.$$

In addition, trJ is negative if and only if

$$2qD\xi^3 + (dq - 3qD)\xi^2 + q(D-d)\xi > \frac{-d(1-\tau)}{\xi}.$$

Denote

$$f_3(\xi) = 2qD\xi^3 + (dq - 3qD)\xi^2 + q(D-d)\xi,\ f_4(\xi) = \frac{-d(1-\tau)}{\xi}.$$

$f_3(0) = q(D-d) < 0$, $\lim_{\xi\to 0} f_4(\xi) = -\infty$. Solving $f_3(\xi) = 0$ with respect to ξ yields two roots $(D-d)/(2D) > 1/2$ and 1. Thus, $trJ < 0$ holds true naturally. By the Routh-Hurwitz criterion, we complete the proof of Theorem 2.5.

Appendix C. The proof of Theorem 2.6

There are two endemic equilibria $E^*_{2i}(i = 2, 3)$ when $R_c < R_0 < 1$, then $D > -d(1-\tau)$. Let J_i be the Jacobian matrix at $E^*_{2i}(i = 2, 3)$. Note that

$$\xi_3 = \frac{-B + \sqrt{\Delta}}{2A} > \frac{-B}{2A},$$

and $\Delta > 0$. For convenience, we only focus on the case of $f_1(\xi) > 0$ for all the ξ, i.e., $q < 4(1-\tau)$.

When $D < 0$, as in the similar proof of Theorem 2.5, then E^*_{23} is locally asymptotically stable if

$$\frac{-D}{d} < q < \min\left\{4(1-\tau), \frac{-D}{(d+D)}\right\}.$$

When $D > 0$, note that $f_2(\xi_3) > 0$ provided that $\xi_3 > \xi^*$. Substituting the formulae of ξ_3 and ξ^* into the above inequality yields $q_1 < q < q_2$, with

$$q_{1,2} = \frac{-B_1 \mp \sqrt{B_1^2 - 4A_1C_1}}{2A_1},$$

$A_1 = (d+D),\ B_1 = 6d\tau D + 4d^2\tau + 2\tau D^2 - 8dD - 4d^2 - 4D^2,\ C_1 = (2\tau - 1)D^2.$

Thus $detJ_3 > 0$ if $q_1 < q < q_2$ hold true.

From (B.3), trJ_3 is negative if $\xi(f_3(\xi_3)-f_4(\xi_3)) < 0$ holds true. Substituting the formulae of ξ_3 and ξ^* into the above inequality yields

$$q\tau D(d+D)(qD+d\tau+3\tau D)+2\tau^3D^3+\left(q\tau(d+D)^2+2qd\tau(d+D)+2\tau^2D^2\right)$$
$$\sqrt{\Delta_1} < (d+D)(6q\tau D(d+D)+q^2d^2\tau+2q(d+D)\sqrt{\Delta}). \tag{C.1}$$

On the other hand,

$$\xi_2 = \frac{-B-\sqrt{\Delta}}{2A}.$$

From (B.3) $detJ_2 < 0$ if and only if

$$\frac{f_1(\xi_2)f_2(\xi_2)}{D} < 0.$$

Substitution of ξ_2 into the above inequality yields

$$(\tau D-\sqrt{\Delta}+D)(\tau D-\sqrt{\Delta}-q(d+D)) > 0. \tag{C.2}$$

So E_{22}^* is a saddle provided (C.2). Therefore, we complete the proof of Theorem 2.6.

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Table Legends

Table 1: Stability of the equilibria $E_{20}^{i}(i=0,1,2)$ of model (4). (S∼Stable, U∼Unstable).

Model (4)	E_{20}^{0}	E_{20}^{1}	E_{20}^{2}
Eigenvalues $\lambda_i(i=1,2)$	$-b(1-\tau)<0$	$\frac{b\sqrt{\Delta_1}(q-\sqrt{\Delta_1})}{2q}>0$	$\frac{-b\sqrt{\Delta_1}(q+\sqrt{\Delta_1})}{2q}<0$
	$b>0$	$b\tau>0$	$b\tau>0$
Stability	U	U	U

Table 2: Stability of equilibria $E_{2i}^{*}(i=1,2,3)$ of model (4) and their corresponding equilibria E_{1i}^{*} of model (2) in Case 1. (S∼Stable, U∼Unstable).

Model (4)	E_{21}^{*}	E_{22}^{*}	E_{23}^{*}
Eigenvalues $\lambda_i(i=1,2)$	$-b(1-\tau)<0$	$\frac{b(\sqrt{\Delta_1}-q+4(1-\tau))}{2}>0$	$\frac{b(-\sqrt{\Delta_1}-q+4(1-\tau))}{2}<0$
	$-b<0$	$-b\tau<0$	$-b\tau<0$
Stability	S	U	S
Model (2)	E_{11}^{*}	E_{12}^{*}	E_{13}^{*}
Stability	S	U	S

Table 3: Parameter regions for the existence and stability of equilibria $E^*_{ij}(i = 1, 2, j = 1, 2, 3)$ of models (2) and (4) in the three cases. Each region denoted as $\Omega_{jk}(j = 1, 2, 3, k = 1, 2, 3, 4, 5, 6, 7)$. (S∼Stable, U∼Unstable, ×∼ Nonexistence).

Regions	Ω_{j1}	Ω_{j2}	Ω_{j3}	Ω_{j4}	Ω_{j5}	Ω_{j6}	Ω_{j7}
Case 1	E^*_{i1}(S)	E^*_{i1}(S)					
	$E^*_{i2}(\times)$	E^*_{i2}(U)					
	$E^*_{i3}(\times)$	E^*_{i3}(S)					
Case 2	E^*_{i1}(U)	E^*_{i1}(U)	E^*_{i1}(S)	E^*_{i1}(S)			
	$E^*_{i2}(\times)$	$E^*_{i2}(\times)$	E^*_{i2}(U)	$E^*_{i2}(\times)$			
	E^*_{i3}(S)	E^*_{i3}(S)	E^*_{i3}(S)	$E^*_{i3}(\times)$			
Case 3	E^*_{i1}(U)	E^*_{i1}(U)	E^*_{i1}(S)	E^*_{i1}(S)	E^*_{i1}(S)	E^*_{i1}(S)	E^*_{i1}(S)
	$E^*_{i2}(\times)$	$E^*_{i2}(\times)$	E^*_{i2}(U)	$E^*_{i2}(\times)$	$E^*_{i2}(\times)$	$E^*_{i2}(\times)$	$E^*_{i2}(\times)$
	E^*_{i3}(S)	E^*_{i3}(S)	E^*_{i3}(S)	$E^*_{i3}(\times)$	$E^*_{i3}(\times)$	$E^*_{i2}(\times)$	$E^*_{i2}(\times)$

Figure Legends

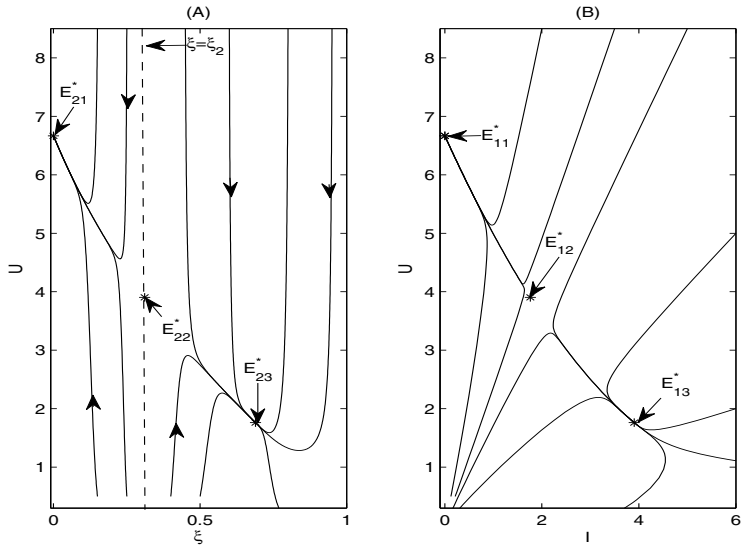

Figure 1: The effects of different initial values on the solutions of models (4) and (2) when $D = 0$. The parameter values are fixed as follows: $b = 2, \tau = 0.85, d = 0.3, q = 0.7$, then $E_{21}^* = (0.3110, 3.9042)$ and $E_{23}^* = (0.6890, 1.7624)$. When the initial infected ratio $\xi_0 < \xi_2$, the solutions of models (4) (or (2)) will stabilize at E_{21}^* (or E_{11}^*), when the initial infected ratio $\xi_0 > \xi_2$, the solutions will stabilize at E_{23}^* (or E_{13}^*).

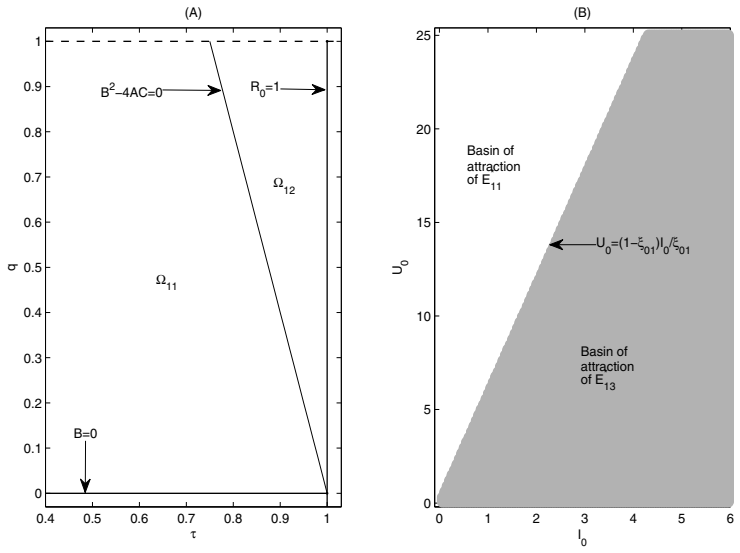

Figure 2: The existence and stability of equilibria $E^*_{ij}(i = 1, 2, j = 1, 2, 3)$ of models (2) and (4) (A) and basins of attraction of equilibria $E^*_{1j}(j = 1, 3)$ for model (2) (B) when $D = 0$. The baseline parameter values are fixed as follows: $b = 2, d = 0.3$, and critical parameters values fixed as $\tau = 0.9,\ q = 0.8$ in (B).

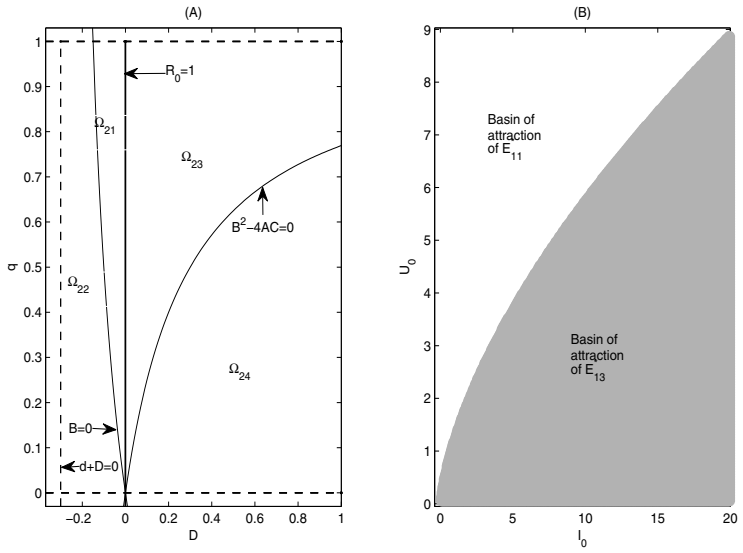

Figure 3: The existence and stability of equilibria $E^*_{ij}(i = 1, 2, j = 1, 2, 3)$ of models (2) and (4) (A) and basins of attraction of equilibria $E^*_{1j}(j = 1, 3)$ for model (2) (B) when $\tau = 1$. The baseline parameter values are the same as Fig. 2, and critical parameters values fixed as $D = 0.2,\ q = 0.8$ in (B).

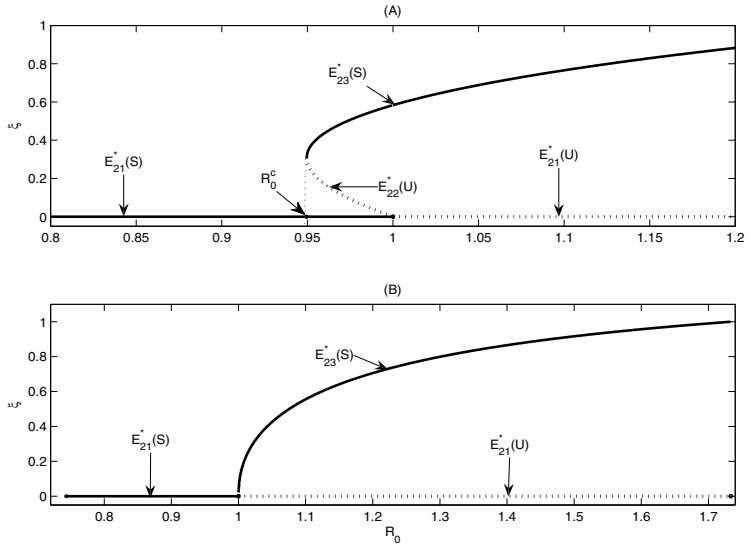

Figure 4: The bifurcation diagrams of infected ratio at equilibria versus R_0 for model (4) with different D values. The parameter values are fixed as follows: $b = 2, d = 0.3, \tau = 0.8, q = 0.7$. (A) Backward bifurcation with two interior equilibria when $D = -0.1$ and $R_0 < 1$. (B) With D reducing from -0.1 to -0.22, the backward bifurcation changes to a forward bifurcation.

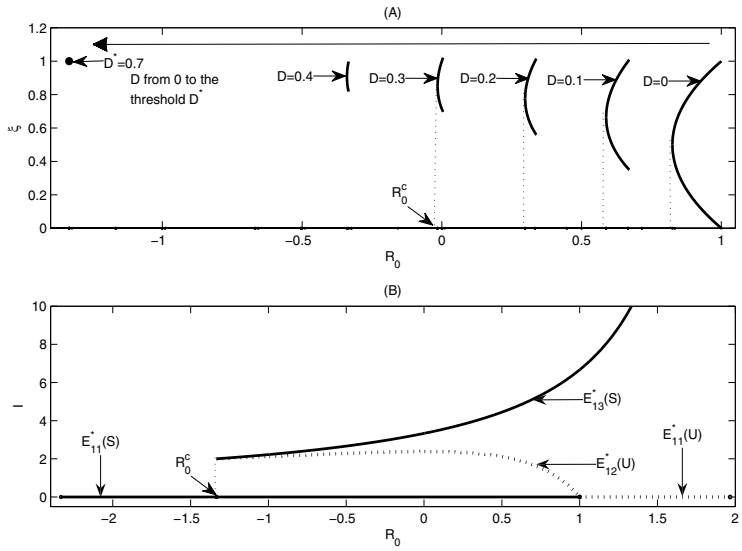

Figure 5: The bifurcation diagrams of infected ratio at equilibria versus R_0 for model (4) with $D \geq 0$ and $\tau = 1$, respectively. The parameter values are fixed as follows: $b = 2, d = 0.3, q = 0.7$. (A) Backward bifurcations occur with D increasing from 0 to 0.7 respectively with $\tau = 0.7$. (B) Backward bifurcation with two interior equilibria when $\tau = 1$ and $R_0 < 1$.

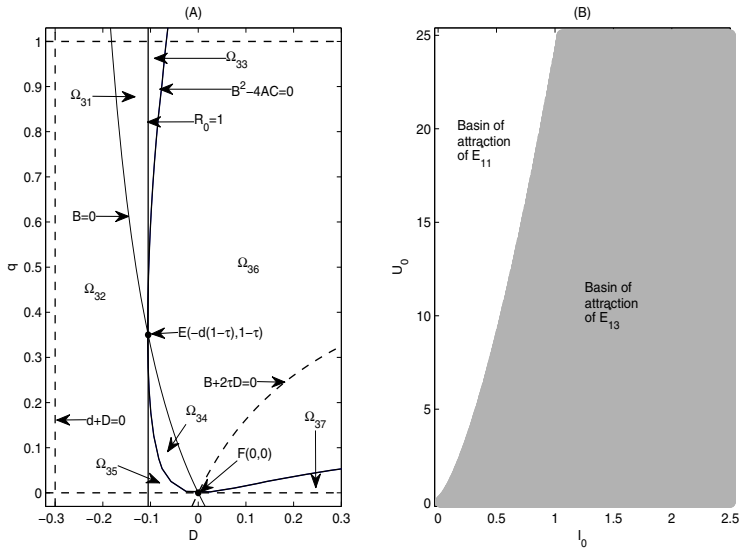

Figure 6: The existence and stability of equilibria $E^*_{ij}(i = 1, 2, j = 1, 2, 3)$ of models (2) and (4) (A) and basins of attraction of equilibria $E^*_{1j}(j = 1, 3)$ for model (2) (B) when in general case. The baseline parameter values are fixed as follows: $b = 2, d = 0.3, \tau = 0.65$, and critical parameters values fixed as $\tau = 0.9,\ q = 0.8$ in (B).

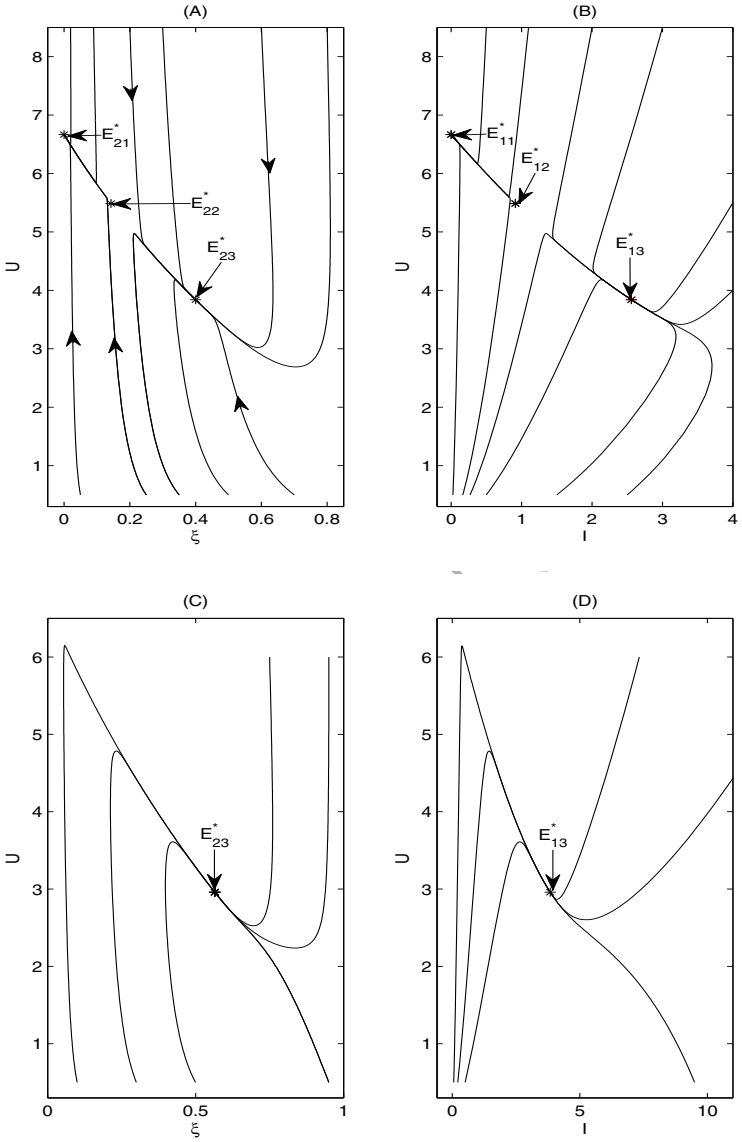

Figure 7: The effects of different initial values on the solutions of models (4) and (2) when $-dq < D < 0$. The baseline parameter values are the same as in Fig. 1 and $D = -0.1$. (A)-(B): There is an unstable manifold for models (4) or (2) such that some initial values will stabilize at E_{23}^* or E_{13}^*, while others will stabilize at E_{21}^* or E_{11}^*, given $\tau = 0.64$. Unstable equilibrium of model (7) $E_{22}^* = (0.1429, 5.4857)$, the unstable manifold moves to the right in this case, compared with $D = 0$. (C)-(D): The unstable manifold disappears, and all initial values will stabilize at E_{23}^* or E_{13}^*, given $\tau = 0.68$.

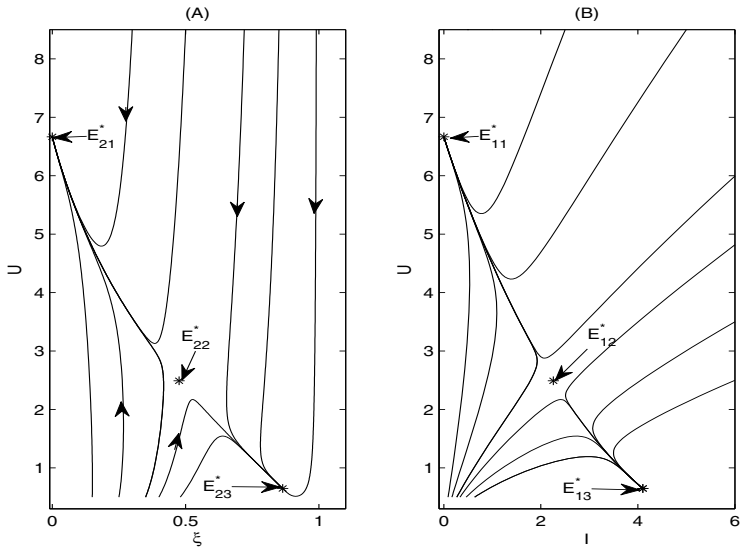

Figure 8: The effects of different initial values on the solutions of models (4) and (2) when $D > 0$. The baseline parameter values are the same as in Fig. 1 and $D = 0.1$. There is an unstable manifold for models (4) or (2) such that some initial values will stabilize at E^*_{23} or E^*_{13}, while others will stabilize at E^*_{21} or E^*_{11}, given $\tau = 0.64$. Unstable equilibrium of model (4) $E^*_{22} = (0.4755, 2.4916)$, unstable manifold moves to the left in this case, compared with $D = 0$.

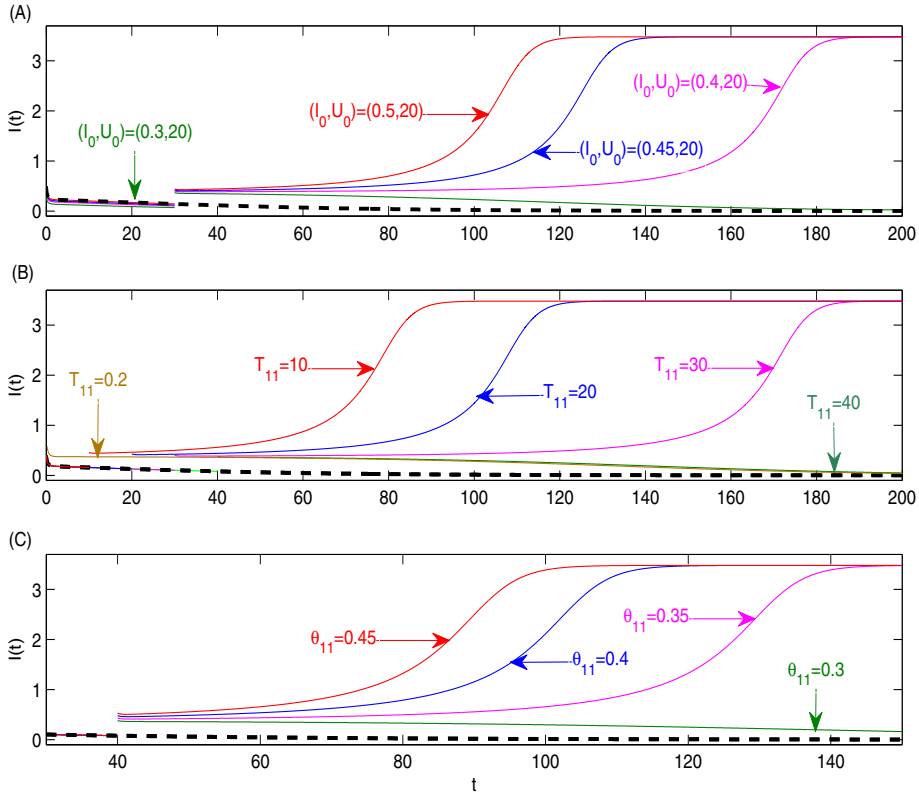

Figure 9: The effects of initial values (A), pulse timings (B) and pulse quantities (C) on the solutions of model (8) with one pulse in the general case. The baseline parameter values are fixed as the same as those in Fig. 6(B). In (A) $T_{11} = [30], \theta_{11} = [0.3]$, in (B) $(I_0, U_0) = (0.4, 20)$, $\theta_{11} = [0.3]$, and in (C) $(I_0, U_0) = (0.4, 20)$, $T_{11} = [40]$.

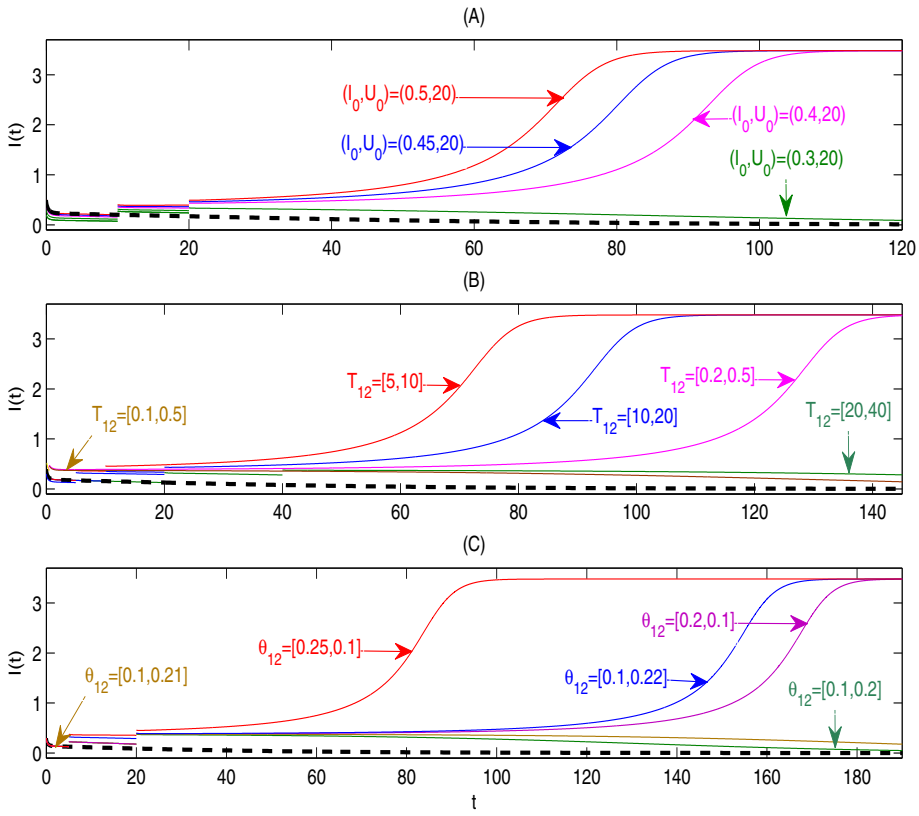

Figure 10: The effects of initial values (A), pulse timings (B) and pulse quantities (C) on the solutions of model (8) with two pulses in the general case. The baseline parameter values are fixed as the same as those in Fig. 6(B). In (A) $T_{12} = [10, 20], \theta_{12} = [0.2, 0.1]$, in (B) $(I_0, U_0) = (0.4, 20), \theta_{12} = [0.2, 0.1]$, and in (C) $(I_0, U_0) = (0.3, 20), T_{12} = [5, 20]$.

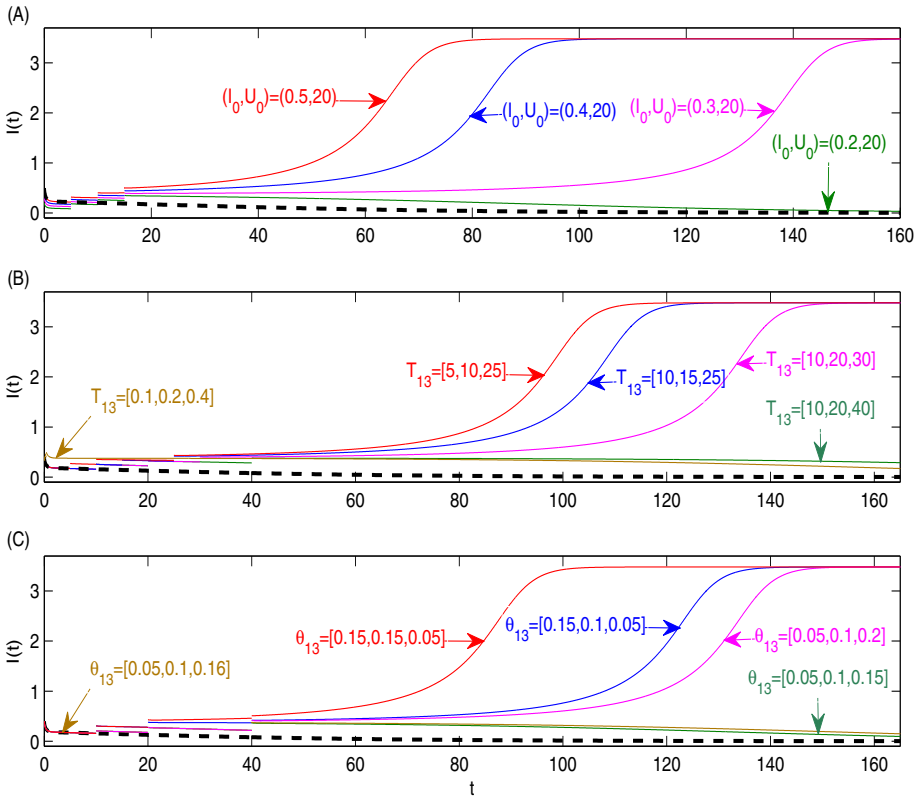

Figure 11: The effects of initial values (A), pulse timings (B) and pulse quantities (C) on the solutions of model (8) with three pulses in the general case. The baseline parameter values are fixed as the same as those in Fig. 6(B). In (A) $T_{13} = [5, 10, 15], \theta_{13} = [0.1, 0.1, 0.1]$, in (B) $(I_0, U_0) = (0.4, 20), \theta_{13} = [0.1, 0.1, 0.1]$, and in (C) $(I_0, U_0) = (0.4, 20), T_{13} = [10, 20, 40]$.

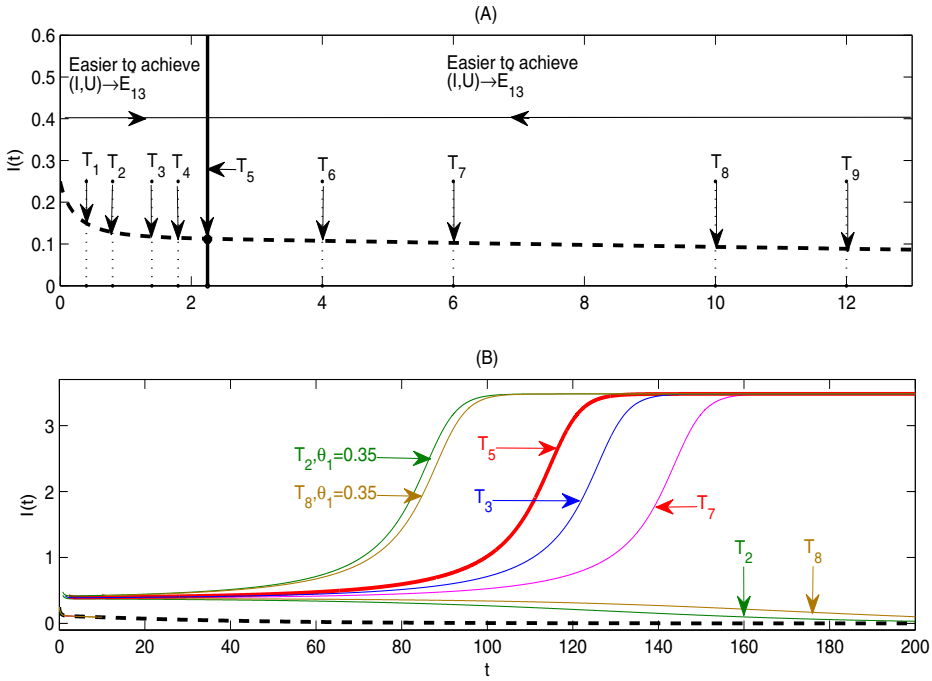

Figure 12: (A) The detailed effect of pulse timings on the solutions of (8) in the general case with one pulse and $(I_0, U_0) = (0.25, 20), \theta_{11} = [0.3]$. The baseline parameter values are fixed as the same as those in Fig. 6(B). When pulse timings are selected from $[0.4, 0.8, 1.4, 1.8, 2.25, 4, 6, 10, 12]$, respectively, only the first and last two timings fail to stabilize at E^*_{13}. (B) The solutions of models (8) with different pulse timings and pulse quantities in (A).

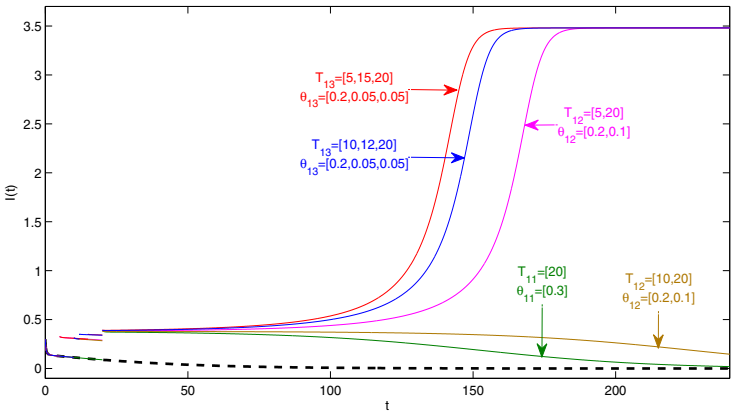

Figure 13: The effects of pulse sequences and numbers of pulses on the solutions of (8) in the general case. The baseline parameter values are fixed as the same as those in Fig. 6(B). Initial value and total quantity are fixed as $(I_0, U_0) = (0.3, 20), \theta = 0.3$, respectively.

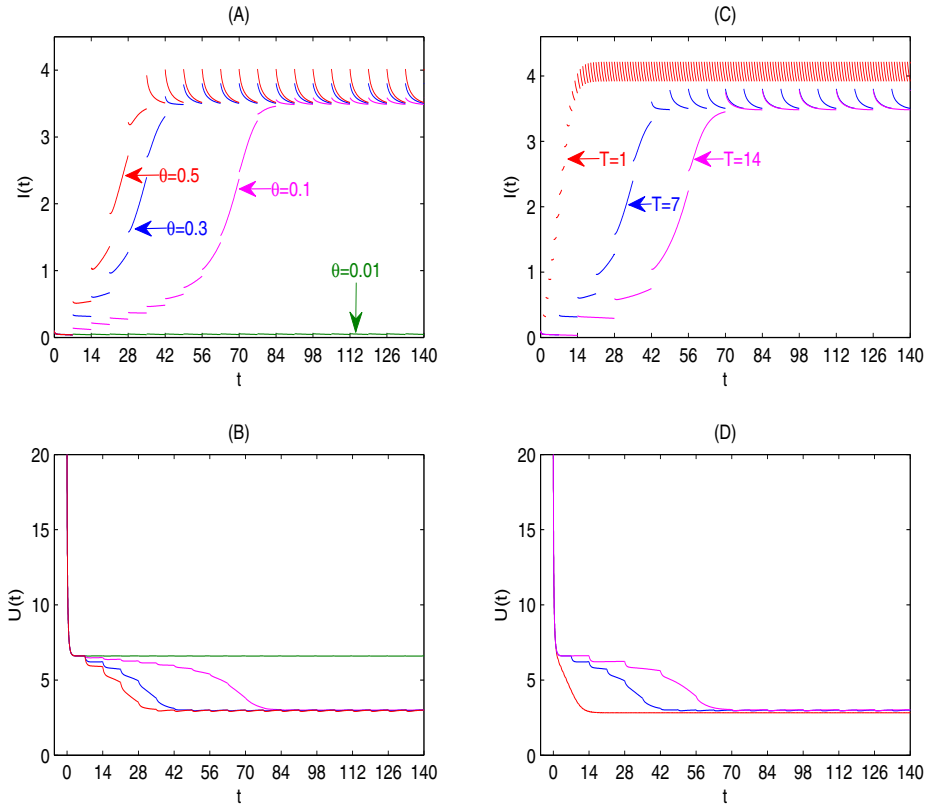

Figure 14: The effects of pulse quantities (A) and pulse periods (B) on the solutions of model (8) with infinite pulses in the general case. The baseline parameter values are fixed as the same as those in Fig. 6(B). Initial value is fixed as $(I_0, U_0) = (0.1, 20)$. In (A) pulse period $T = 7$ and in (B) pulse quantity $\theta = 0.3$.