COMPLEX WOLBACHIA INFECTION DYNAMICS IN MOSQUITOES WITH IMPERFECT MATERNAL TRANSMISSION

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ABSTRACT. Dengue, malaria, and Zika are dangerous diseases primarily transmitted by *Aedes aegypti*, *Aedes albopictus*, and *Anopheles stephensi*. In the last few years, a new disease control method, besides pesticide spraying to kill mosquitoes, has been developed by releasing mosquitoes carrying bacterium *Wolbachia* into the natural areas to infect the wild population of mosquitoes and block disease transmission. The bacterium is transmitted by infected mothers and the maternal transmission was assumed to be perfect in virtually all previous models. However, recent experiments on *Aedes aegypti* and *Anopheles stephensi* showed that the transmission can be imperfect. In this work, we develop a model to describe how the imperfect maternal transmission affects the dynamics of *Wolbachia* spread. We establish two useful identities and employ them to find sufficient and necessary conditions under which the system exhibits monomorphic, bistable, and polymorphic dynamics. These analytical results may help find a plausible explanation for the recent observation that the *Wolbachia* strain *w*MelPop failed to establish in the natural populations in Australia and Vietnam.

1. **Introduction.** *Aedes aegypti*, *Aedes albopictus*, and *Anopheles stephensi*, are the primary vectors of some life-threatening mosquito-borne diseases such as dengue, malaria, and Zika. Since there are no effective vaccines available for these diseases, current controls mostly rely on environmental management by destructing vector breeding sites physically or chemically. Unfortunately, the chemical method of spraying pesticides causes severe environmental pollution and induces mosquito's insecticide resistance.

The study on the interaction of *Wolbachia* and mosquitoes has flourished due to the groundbreaking work [1, 2, 37, 38, 39, 40], which paved an avenue for a biologically safe method of mosquito-borne disease control [5, 10, 17, 18]. As expected,

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Wolbachia can block the replication of viruses such as dengue and Zika inside the mosquitoes [1, 37, 38, 39, 40] and confer resistance to the human malaria parasite *Plasmodium falciparum* [2]. In mosquitoes, maternally transmitted *Wolbachia* is associated with cytoplasmic incompatibility (CI), *i.e.*, the reduced hatch rate of embryos produced from fertilization of uninfected ova by sperm from *Wolbachia* infected males. Infected females therefore have a reproductive advantage, allowing *Wolbachia* to spread in polymorphic populations [4, 9, 14].

An appealing strategy is to release a large number of *Wolbachia* infected males in the natural area so that the CI mechanism can drive all the mated females sterile and the whole population can be suppressed. However, a complete population suppression requires a nearly perfect separation of males from infected females, which exerts tremendous challenges in extending this technology over large areas. An alternative strategy to meet the challenge is to seed the natural population with infected mosquitoes, both male and female, so the reproductive advantage for infected females induced by CI and the high maternal transmission rate can drive *Wolbachia* infected mosquitoes to replace the wild population. For the success of population replacement, it is critical to identify the *release threshold*: above which *Wolbachia* will invade all mosquitoes, but below which it will be wiped out [4, 9, 12, 34].

Some earlier mathematical models making use of difference equations have played an instrumental role in determining the release threshold for *Wolbachia* fixation in non-overlapping populations in laboratory [4, 9]. Inspired by its great potential to eliminate the mosquito-borne diseases, modeling *Wolbachia* spread dynamics parameterized by laboratory or field data [7, 11, 14, 23, 27, 36] has emerged as a hot topic for extensive studies. There have been models of ordinary [8, 22, 29], delayed differential equations [41] built to explore the subtle relations between *Wolbachia* invasion and important parameters. Such parameters include: (i) the maternal transmission rate ($1 - \mu$, where μ is the rate of uninfected ova produced by infected females); (ii) the intensity of CI (s_h, the reduced egg-hatch produced by matings between infected males and uninfected females), (iii) the fecundity cost/benefit of infected females relative to uninfected females. More recent models have also considered the impact of environmental heterogeneity and mosquito diffusion in space by stochastic equations [19] and reaction-diffusion equations [20, 21].

In most of the current theoretical studies on *Wolbachia* spreading dynamics in mosquitoes, it was assumed that maternal transmission is perfect ($\mu = 0$), and CI is complete ($s_h = 1$) which are supported by recent findings in mosquitoes. For example, maternal transmission loss was not observed for both the WB1 in *Aedes aegypti* and the wAlbA, wAlbB in *Aedes albopictus* together with complete CI [1, 37, 38, 39, 40]: examinations from crosses of uninfected Waco females and infected WB1 males showed that no egg hatch resulted from >3800 eggs [39]. In 2013, the LB1 infection was successfully established in an important malaria vector, *Anopheles stephensi* [2]. Again, of 8087 eggs resulting from crosses between LB1 females and the naturally uninfected LIS males, only 1.2% hatched, and the 100% maternal transmission efficiency was confirmed by fluorescence in situ hybridization (FISH) in self-crossing LB1 mosquitoes, while the data on maternal transmission efficiency in outcrossing (LB1 females × LIS males) is absent.

However, imperfect maternal transmission ($\mu > 0$) has been repeatedly documented in nature with respect to the *w*Ri, *w*Ru infection in *Drosophila simulans* [3, 23, 24, 32], and the *w*Mel in *Drosophila melanogaster* [14]. In *D. simulans*,

data indicates that uninfected ova produced by the wRi infected females are susceptible to CI. However, the wRu in *D. simulans* and the wMel in *D. melanogaster* cause weak or non-CI. Hence, among-female variation of *Wolbachia* deposition in ova seems to be generally associated with among-male variation in the effect of *Wolbachia* on sperm in *Drosophila*. For systematic studies on *Wolbachia* spreading in *D. simulans*, we refer the readers to Hoffmann and Turelli's work since 1990s [15, 16, 30, 31, 32, 33, 34] in which both *Wolbachia* infidelity and partial CI were identified.

It was predominantly believed that the maternal transmission of *Wolbachia* in mosquitoes is perfect. However, a very recent study [28] demonstrates that high temperatures (26-37°C) can induce both imperfect maternal transmission and incomplete CI of *Wolbachia* in *Aedes aegypti*, the primary vector of dengue. Imperfect maternal transmission was also observed in a recent study on the spread of *Wolbachia* strain LB1 in *Anopheles stephensi*, along with a confirmed complete CI in [2]. The findings in [2] show that self-crossing LB1 produces significantly lower hatching ($\sim$52.4%) than the outcrossing of LB1 females with uninfected males ($\sim$80%) and uninfected self-crossing ($\sim$90%), see Fig.1(B) in [2]. With the potential of a *Wolbachia*-based intervention for vector control on mosquito-borne diseases, we develop a model with complete CI and imperfect maternal transmission, and present a detailed mathematical analysis on the dynamics of *Wolbachia* spread. The main purpose of this manuscript is to dissect the effect of imperfect maternal transmission on *Wolbachia* spreading, which has not been studied in the existing literature.

To proceed, we divide the mosquitoes into four classes: uninfected females U_F, infected females I_F, uninfected males U_M, and infected males I_M. Assume that $U_F : U_M = I_F : I_M$ and hence the population can be formally considered hermaphroditic. Let I and U denote the total numbers of infected, and uninfected mosquitoes, respectively, *i.e.*, $I = I_F + I_M$ and $U = U_F + U_M$. Let $\mu \in (0, 1)$ be the proportion of uninfected ova produced by an infected female. Following [22, 41], we let b_U denote the average number of offspring produced by one uninfected female. Let δ_U denote the constant death rate for uninfected mosquitoes. For generality, we introduce b_I and δ_I as the corresponding parameters for infected mosquitoes as *Wolbachia* infection usually modifies the fitness and the longevity [25, 35] of the host. CI arises when an uninfected ova, born from infected females or uninfected females, is fertilized by the sperm from an infected male. Then, with complete CI between I_M and U_F [1, 2, 35, 39] and random mating, no uninfected adult progeny will be observed from the crossing of $I_F \times I_M$. Uninfected adult progeny still arise from the crossing $I_F \times U_M$ due to imperfect transmission. With random mating, the chance of a female crossing with U_M is $U_M/(I_M + U_M) = U/(I + U)$, and the chance of a female crossing with I_M is $I_M/(I_M + U_M) = I/(I + U)$. The latter one is also the probability of CI-occuring. Our model takes the form

$$\frac{dI}{dt} = b_I I \cdot \frac{I}{I + U} + b_I(1 - \mu)I \cdot \frac{U}{I + U} - \delta_I I(I + U), \tag{1}$$

$$\frac{dU}{dt} = b_I \mu I \cdot \frac{U}{I + U} + b_U \cdot U \cdot \left(1 - \frac{I}{I + U}\right) - \delta_U U(I + U). \tag{2}$$

In (2), the first term accounts for the birth of uninfected progeny from infected mothers, and the second term accounts for the birth from uninfected mothers, who have a probability $I/(I + U)$ to mate with infected males, and a contribution to the birth reduced by a factor $1 - I/(I + U) = U/(I + U)$ due to complete CI.

If we apply the rescaling

$$x = \frac{\delta_U}{b_U} I, \quad y = \frac{\delta_U}{b_U} U, \quad s = b_U\, t, \quad \beta = \frac{b_I}{b_U}, \quad \delta = \frac{\delta_I}{\delta_U}, \tag{3}$$

and rewrite $d \cdot /ds$ as $d \cdot /dt$, then we can transform (1)-(2) into

$$\frac{dx}{dt} = \beta \frac{x^2}{x+y} + \beta(1-\mu)\frac{xy}{x+y} - \delta x(x+y) := f(x,y), \tag{4}$$

$$\frac{dy}{dt} = \beta\mu\frac{xy}{x+y} + \frac{y^2}{x+y} - y(x+y) := g(x,y). \tag{5}$$

In [41], we studied the case of perfect maternal transmission (*i.e.*, $\mu = 0$), and included the average waiting time τ from parent mating to the emergence of reproductive progeny as a time delay in the model. We proved that when $\delta = 1$, *i.e.*, the infection does not alter the mean life span, *Wolbachia* can spread into the whole population as long as the infection frequency stays strictly above a threshold value for a period no less than the reproductive period τ. Interestingly, we also found that such a threshold value of infection frequency cannot be well defined for $\delta \neq 1$. For the reduced system without maturation delay, we obtained sharp estimates on a threshold curve determined by the population sizes of both infected and uninfected mosquitoes. This is different from a differential equation for the fraction of *Wolbachia*-infected mosquitoes [29], with the assumptions of constant population size and perfect maternal transmission of *Wolbachia*, where the threshold infection frequency is unique.

The remaining part of this paper is divided into three sections. In Section 2, we prove invariance and boundedness of solutions to system (4)-(5), and present two useful identities together with additional preliminary results. These help us study the global dynamics in Section 3 and prove that the system can exhibit monomorphic, bistable, and polymorphic dynamics, and give sufficient and necessary conditions for each case. Imperfect maternal transmission could lead to infinitely many polymorphic states, see Theorem 3.1. Also, our discussions in Section 4 highlights some challenges associated with the release of *w*MelPop.

2. **Preliminaries.**

2.1. **Invariance and boundedness.** Noticing that $f(x,y) \to 0$ and $g(x,y) \to 0$ as $(x,y) \to (0,0)$, we can extend the domain of system (4)-(5) to including $(0,0)$ by defining $f(0,0) = g(0,0) = 0$. Then the system has the origin $E_0 = (0,0)$ as an equilibrium point. It is obvious that the x-axis, the y-axis, the first quadrant $\mathbb{R}_+^2 := \{(x,y) : x \geq 0, \ y \geq 0\}$ and its interior set $\mathbb{R}_{+0}^2 := \{(x,y) : x > 0, y > 0\}$ are all invariant sets of (4)-(5). For application purpose, we restrict our discussion on the first quadrant $\mathbb{R}_+^2$ only.

Lemma 2.1. *Every solution of (4)-(5) initiated from the first quadrant is bounded. Moreover, for each (x_0, y_0) with $x_0 \geq 0$ and, $y_0 \geq 0$,*

$$\omega(x_0, y_0) \subset \{(x,y) : 0 \leq x \leq \beta(2-\mu)/\delta, \ 0 \leq y \leq \beta\mu + 1\}, \tag{6}$$

where $\omega(x_0, y_0)$ is the set of limit points of solutions of (4)-(5) initiated from (x_0, y_0).

Proof. Let $x(t)$ and $y(t)$ be solutions of (4)-(5) with $x_0 \geq 0$, $y_0 \geq 0$. It is seen that

$$x'(t) < \beta x + \beta(1-\mu)x - \delta x^2 = \delta x\left[\frac{\beta(2-\mu)}{\delta} - x\right].$$

Hence $x'(t) < 0$ when $x(t) > \beta(2-\mu)/\delta$, implying immediately that

$$\limsup_{t\to\infty} x(t) \le \beta(2-\mu)/\delta.$$

Similarly, if $y(t) > \beta\mu + 1$, then

$$y'(t) < (\beta\mu + 1)y - y^2 = y(\beta\mu + 1 - y) < 0,$$

and so $\limsup_{t\to\infty} y(t) \le \beta\mu + 1$ and (6) is verified. □

2.2. **The equilibrium points.** Besides E_0, system (4)-(5) always admits a *Wolbachia*-fixation equilibrium point $E_1 = (\beta/\delta, 0)$ and a *Wolbachia*-free equilibrium point $E_2 = (0, 1)$. Interior equilibria (x, y), if any, are the intersections of the x-nullcline $f(x, y) = 0$ and the y-nullcline $g(x, y) = 0$, that is

$$\Gamma_x : \quad \beta x + \beta(1-\mu)y = \delta(x+y)^2, \tag{7}$$

$$\Gamma_y : \quad \beta\mu x + y = (x+y)^2. \tag{8}$$

Multiplying (8) by δ and then comparing the resulting equation with (7), we see that Γ_x and Γ_y coincide if and only if

$$(C1): \quad \mu\delta = 1, \quad \text{and} \quad \beta(1-\mu) = \delta.$$

When (C1) is not satisfied, we subtract (7) by the product of (8) with δ and obtain

$$\beta(1-\mu\delta)x = \big[\delta - \beta(1-\mu)\big]y. \tag{9}$$

Lemma 2.2. *System (4)-(5) admits interior equilibrium points if and only if one of the following conditions holds:*
(C2): $\mu\delta > 1$, and $\beta(1-\mu) > \delta$;
(C3): $\mu\delta < 1$, and $\beta(1-\mu) < \delta$.
In this case, there is exactly one interior equilibrium point given by $E^* = (x^*, y^*)$ with

$$x^* = \frac{\beta\mu + k}{(1+k)^2}, \qquad y^* = \frac{k(\beta\mu + k)}{(1+k)^2}, \tag{10}$$

where

$$k := \frac{\beta(1-\mu\delta)}{\delta - \beta(1-\mu)}. \tag{11}$$

Proof. If the system admits interior equilibrium point (x, y), then (9) implies $k > 0$, so one of (C2) and (C3) must hold. On the other hand, either (C2) or (C3) gives $k > 0$ and (9) becomes $y = kx$. By inserting it into (8) we derive the expressions of x^* and y^* as in (10). □

If none of (C1)-(C3) holds, then system (4)-(5) does not admit any interior equilibrium point. For convenience of later discussion, we classify the remaining cases as the following 6 cases.
(C4): $\mu\delta < 1$, and $\beta(1-\mu) > \delta$;
(C5): $\mu\delta < 1$, and $\beta(1-\mu) = \delta$;
(C6): $\mu\delta = 1$, and $\beta(1-\mu) > \delta$;
(C7): $\mu\delta > 1$, and $\beta(1-\mu) < \delta$;
(C8): $\mu\delta > 1$, and $\beta(1-\mu) = \delta$.
(C9): $\mu\delta = 1$, and $\beta(1-\mu) < \delta$.

2.3. **The Jacobian matrix and two auxiliary functions.** As $f(x, y) > 0$ and $g(x, y) > 0$ when both $x > 0$ and $y > 0$ are sufficiently small, $E_0(0, 0)$ is a repeller. To determine the stability of other equilibria, we first compute the determinant and the trace of the Jacobian matrix [13] of system (4)-(5):

$$\mathbf{J} = \begin{pmatrix} \beta - \beta\mu \cdot \dfrac{y^2}{(x+y)^2} - \delta(2x+y) & -\beta\mu \cdot \dfrac{x^2}{(x+y)^2} - \delta x \\[4mm] (\beta\mu - 1) \cdot \dfrac{y^2}{(x+y)^2} - y & \beta\mu \cdot \dfrac{x^2}{(x+y)^2} + \dfrac{y(2x+y)}{(x+y)^2} - (x+2y) \end{pmatrix}. \tag{12}$$

At $E_1(\beta/\delta, 0)$ and $E_2(0, 1)$, direct calculations give

$$\mathbf{J}(E_1) = \begin{pmatrix} -\beta & -\beta(\mu+1) \\ 0 & \beta(\mu\delta-1)/\delta \end{pmatrix}, \quad \mathbf{J}(E_2) = \begin{pmatrix} \beta(1-\mu) - \delta & 0 \\ \beta\mu - 2 & -1 \end{pmatrix}$$

and at $E^*(x^*, y^*)$ by using $y^* = kx^*$ we find

$$\mathbf{J}(E^*) = \begin{pmatrix} \beta - \dfrac{\beta\mu k^2}{(k+1)^2} - \delta(2+k)x^* & -\dfrac{\beta\mu}{(k+1)^2} - \delta x^* \\[4mm] (\beta\mu-1) \cdot \dfrac{k^2}{(k+1)^2} - kx^* & \dfrac{\beta\mu}{(k+1)^2} + \dfrac{k(k+2)}{(k+1)^2} - (1+2k)x^* \end{pmatrix}.$$

Lemma 2.3. *(i) At E^*, we have*

$$\det J(E^*) = \frac{\beta k}{(k+1)^2} \left[\frac{\beta(1-\mu)}{\delta} \cdot \mu\delta - 1 \right]. \tag{13}$$

(ii) The trace of J at E^* is

$$\operatorname{tr} J(E^*) = \frac{-k^2 + (1-\beta)k - \beta}{(k+1)^2}. \tag{14}$$

Proof. Write $J(E^*) = (J_{ij})_{2\times 2}$. By using the definition of x^* we obtain

$$\begin{aligned} J_{11} &= \beta - \frac{\beta\mu k^2}{(k+1)^2} - \delta(2+k)\frac{\beta\mu + k}{(1+k)^2} \\ &= \frac{1}{(k+1)^2}\left[\beta(k+1)^2 - \beta\mu k^2 - \delta(2+k)(\beta\mu + k) \right] \\ &= \frac{1}{(k+1)^2}\left[(\beta(1-\mu) - \delta)k^2 + (2\beta - \beta\mu\delta - 2\delta)k + \beta(1 - 2\mu\delta) \right]. \end{aligned}$$

By the definition of k in (11), we have the identity

$$\left[\beta(1-\mu) - \delta \right] k = -\beta(1 - \mu\delta),$$

and hence J_{11} can be further reduced to

$$\begin{aligned} J_{11} &= \frac{1}{(k+1)^2}\left[-\beta(1 - \mu\delta)k + (2\beta - \beta\mu\delta - 2\delta)k + \beta(1 - 2\mu\delta) \right] \\ &= \frac{1}{(k+1)^2}\left[(\beta - 2\delta)k + \beta(1 - 2\mu\delta) \right]. \end{aligned}$$

The other three entries J_{12}, J_{21} and J_{22} can be simplified similarly, and $J(E^*)$ is reduced to

$$J(E^*) = \frac{1}{(k+1)^4} \begin{pmatrix} (\beta - 2\delta)k + \beta(1 - 2\mu\delta) & -\delta k - \beta\mu(1+\delta) \\ k\left[(\beta\mu - 2)k - \beta\mu \right] & k\left[-k + (1 - 2\beta\mu) \right] \end{pmatrix}.$$

(i) For notation simplicity, instead of calculating $\det J(E^*)$, we compute

$$\bar{J} := \frac{(k+1)^4}{k} \det J(E^*),$$

and then

$$
\begin{aligned}
\bar{J} &= \big[(\beta - 2\delta)k + \beta(1 - 2\mu\delta)\big] \cdot \big[-k + (1 - 2\beta\mu)\big] \\
&\quad + \big[\delta k + \beta\mu(1 + \delta)\big] \cdot \big[(\beta\mu - 2)k - \beta\mu\big] \\
&= -\beta(1 - \mu\delta)k^2 + \big[(\beta\mu)^2\delta + (\beta\mu)^2 + 3\beta\mu\delta - 2\beta^2\mu - 2\beta\mu - 2\delta\big]k \\
&\quad + 3(\beta\mu)^2\delta + \beta - (\beta\mu)^2 - 2\beta^2\mu - 2\beta\mu\delta.
\end{aligned}
$$

Note that (11) is equivalent to each of the following two identities

$$\delta k = \beta(1 - \mu)k + \beta(1 - \mu\delta), \tag{15}$$

$$\beta\mu\delta = \beta + \big[\beta(1 - \mu) - \delta\big]k, \tag{16}$$

which help us simplify $\bar{J}$ to the following

$$
\begin{aligned}
\frac{1}{\beta}\bar{J} &= -(1 - \mu\delta)k^2 + \Big\{\beta\mu + \mu\big[\beta(1 - \mu) - \delta\big]k + \beta\mu^2 + 3\mu\delta - 2\beta\mu - 2\mu\Big\}k \\
&\quad -2(1 - \mu)k - 2(1 - \mu\delta) + 3\mu\Big\{\beta + \big[\beta(1 - \mu) - \delta\big]k\Big\} \\
&\quad +1 - \beta\mu^2 - 2\beta\mu - 2\mu\delta \\
&= (\beta\mu - \beta\mu^2 - 1)k^2 + 2(\beta\mu - \beta\mu^2 - 1)k + (\beta\mu - \beta\mu^2 - 1) \\
&= (\beta\mu - \beta\mu^2 - 1)(k + 1)^2 = \Big[\frac{\beta(1 - \mu)}{\delta} \cdot \mu\delta - 1\Big](k + 1)^2.
\end{aligned}
$$

Therefore

$$\det J(E^*) = \frac{k}{(k+1)^4}\bar{J} = \frac{\beta k}{(k+1)^2}\Big[\frac{\beta(1 - \mu)}{\delta} \cdot \mu\delta - 1\Big].$$

(ii) Again, by using of (15), $\mathrm{tr}J^*$ can be simplified to

$$
\begin{aligned}
\mathrm{tr}J^* &= J_{11} + J_{22} \\
&= \frac{1}{(k+1)^2}\Big[(\beta - 2\delta)k + \beta(1 - 2\mu\delta) - k^2 + (1 - 2\beta\mu)k\Big] \\
&= \frac{1}{(k+1)^2}\Big[-k^2 + (\beta - 2\delta + 1 - 2\beta\mu)k + \beta(1 - 2\mu\delta)\Big] \\
&= \frac{1}{(k+1)^2}\Big[-k^2 + (\beta + 1 - 2\beta\mu)k - 2\delta k + \beta(1 - 2\mu\delta)\Big] \\
&= \frac{1}{(k+1)^2}\Big[-k^2 + (\beta + 1 - 2\beta\mu)k - 2\beta(1 - \mu)k \\
&\quad -2\beta(1 - \mu\delta) + \beta(1 - 2\mu\delta)\Big] \\
&= \frac{1}{(k+1)^2}\Big[-k^2 + (1 - \beta)k - \beta\Big].
\end{aligned}
$$

This completes the proof. $\qquad\square$

Lemma 2.4. *Assume that $\gamma(t) = (x(t), y(t))$ is a solution of (4)-(5) in $\mathbb{R}^2_{+0}$, let*

$$z(t) = \ln\Big(x^{1/\delta}(t)y^{-1}(t)\Big). \tag{17}$$

Then the derivative of $z(t)$ satisfies

$$z'(t) = \frac{\beta}{\delta}(1 - \mu\delta)\frac{x}{x+y} + \left[\frac{\beta(1-\mu)}{\delta} - 1\right]\frac{y}{x+y}. \tag{18}$$

Proof. By rewriting $z(t) = (1/\delta)\ln x(t) - \ln y(t)$ and taking derivatives, we find

$$
\begin{aligned}
z'(t) &= \frac{f(x,y)}{\delta x} - \frac{g(x,y)}{y} \\
&= \frac{\beta}{\delta}\frac{x}{x+y} + \frac{\beta(1-\mu)}{\delta}\frac{y}{x+y} - \frac{\beta\mu x}{x+y} - \frac{y}{x+y} \\
&= \frac{\beta}{\delta}(1 - \mu\delta)\frac{x}{x+y} + \left[\frac{\beta(1-\mu)}{\delta} - 1\right]\frac{y}{x+y}.
\end{aligned}
$$

This completes the proof. $\qquad\square$

For fixed constant $c > 0$, we denote by L_c the ray $y = cx$, $x > 0$. Also for a solution $\gamma(t) = (x(t), y(t))$ of (4)-(5) in $\mathbb{R}^2_{+0}$, let $l_c(t) = cx(t) - y(t)$. Obviously, if $\gamma(t) = (x(t), y(t)) \in L_c$, then $l_c(t) = 0$. Moreover, we have

Lemma 2.5. *For fixed constant $c > 0$ and any solution $(x(t), y(t))$ of (4)-(5) in $\mathbb{R}^2_{+0}$, we have*

$$l'_c(t)|_{L_c} = y\left[(\delta - 1)\frac{f(x,y)}{\delta x} + z'(t)\right]. \tag{19}$$

Proof. By interchanging cx with y when necessary, we obtain from (4)-(5) that

$$
\begin{aligned}
&l'_c(t)|_{L_c} \\
&= c\left[\frac{\beta x^2}{x+y} + \beta(1-\mu)\frac{xy}{x+y} - \delta x(x+y)\right] - \left[\beta\mu\frac{xy}{x+y} + \frac{y^2}{x+y} - y(x+y)\right] \\
&= y\left[\frac{\beta x}{x+y} + \beta(1-\mu)\frac{y}{x+y} - \delta(x+y) - \beta\mu\frac{x}{x+y} - \frac{y}{x+y} + (x+y)\right] \\
&= y\left[\beta(1-\mu) - \frac{y}{x+y} - (\delta-1)(x+y)\right] \\
&= y\left\{(\delta-1)\left[\frac{\beta}{\delta} - \frac{\beta\mu}{\delta}\frac{y}{x+y} - (x+y)\right] + \beta(1-\mu) - \frac{y}{x+y}\right. \\
&\quad \left. + \frac{\beta\mu(\delta-1)}{\delta}\frac{y}{x+y} - \frac{\beta(\delta-1)}{\delta}\right\} \\
&= y\left\{(\delta-1)\left[\frac{\beta}{\delta} - \frac{\beta\mu}{\delta}\frac{y}{x+y} - (x+y)\right]\right. \\
&\quad \left. + \left[\frac{\beta}{\delta} - \frac{\beta\mu}{\delta}\frac{y}{x+y} - \beta\mu\frac{x}{x+y} - \frac{y}{x+y}\right]\right\} \\
&= y\left\{(\delta-1)\left[\frac{\beta}{\delta} - \frac{\beta\mu}{\delta}\frac{y}{x+y} - (x+y)\right] + \frac{\beta}{\delta}(1-\mu\delta)\frac{x}{x+y}\right. \\
&\quad \left. + \left[\frac{\beta(1-\mu)}{\delta} - 1\right]\frac{y}{x+y}\right\}.
\end{aligned}
$$

By applying the relation (18) and

$$\frac{\beta}{\delta} - \frac{\beta\mu}{\delta}\frac{y}{x+y} - (x+y) = \frac{f(x,y)}{\delta x},$$

the proof is completed. $\qquad\square$

3. **Stability of equilibria.** $E_0(0,0)$ is always a repeller since $f(x,y) > 0$ and $g(x,y) > 0$ when both $x > 0$ and $y > 0$ are sufficiently small. In this section, we shall analyze the stability of equilibria and the global dynamics of system (4)-(5). The primary tool in our proof is (13) and (14) in Lemma 2.3, differential identities (18) in Lemma 2.4, and (19) in Lemma 2.5.

3.1. **The degenerate case (C1).** Assume that (C1) holds. Then both E_1 and E_2 are degenerate since $J(E_1)$ and $J(E_2)$ have zero as their eigenvalues. Furthermore, system (4)-(5) is reduced to

$$\frac{dy}{dx} = \frac{y}{\delta x}, \tag{20}$$

and the two nullclines defined in (7) and (8) are identical. All points on this coincident nullcline in $\mathbb{R}^2_{+0}$, including E_1 and E_2 on the boundary, are equilibrium points.

Theorem 3.1. *Let (C1) hold. Let $(x(t), y(t))$ be the solution of (4)-(5) initiated from $(x_0, y_0) \in \mathbb{R}^2_{+0} \setminus \Gamma_y$. Then*

$$y = y_0 \left(\frac{x}{x_0} \right)^{1/\delta}, \tag{21}$$

and $(x(t), y(t)) \to (x_+, y_+)$ as $t \to +\infty$, where $(x_+, y_+) \in \mathbb{R}^2_{+0}$ is the only intersecting point of (21) and the coincident nullcline Γ_y.
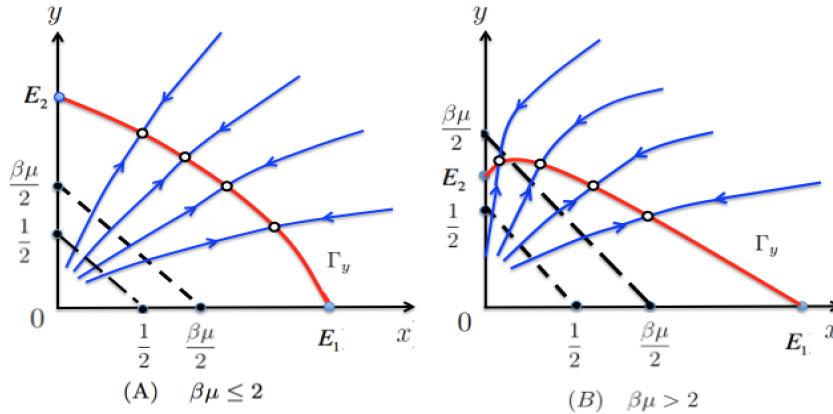

FIGURE 1.   *The phase portrait in the degenerate case.* (A) When $\beta\mu \leq 2$, the curve Γ_y stays in the domain $x + y > \beta\mu/2$ as a decreasing curve connecting E_1 and E_2. (B) When $\beta\mu > 2$, the curve Γ_y starts from E_2 in the domain $1/2 < x + y < \beta\mu/2$, increases first and then intersects the line $x + y = \beta\mu/2$ to enter the domain $x + y > \beta\mu/2$, and remains in this domain as a decreasing curve until reaching E_1. In both cases, given the initial value $(x_0, y_0) \in \mathbb{R}^2_{+0} \setminus \Gamma_y$, solution of (4)-(5) tends to the unique intersecting point (the hollow point) of the curve (21) and the nullcline Γ_y.

Proof. The relation (21) is easily derived by solving (20) with the initial condition. The only non-trivial part in the proof of the remaining conclusions is to show that (21) intersects the nullcline Γ_y (or Γ_x as they are identical) exactly once at $(x_+, y_+) \in \mathbb{R}^2_{+0}$.

Let $(x, y) \in \Gamma_y \cap \mathbb{R}^2_{+0}$. Since

$$\beta(1 - \mu) = \delta = \frac{1}{\mu} \quad \Longrightarrow \quad \beta\mu = \frac{1}{1 - \mu} > 1,$$

it holds that

$$x + y < \beta\mu x + y = (x + y)^2 < \beta\mu x + \beta\mu y, \quad 1 < x + y < \beta\mu.$$

Now if $\beta\mu \leq 2$, by taking derivative with respect to x on both sides of (8), we have

$$\frac{dy}{dx} = -\frac{2(x + y) - \beta\mu}{2(x + y) - 1} < 0.$$

Hence y decreases in x along Γ_y in $\mathbb{R}^2_{+0}$, and the increasing curve (21) intersects it exactly once for $x_+ \in (0, \beta\mu)$, see Figure 1-(A).

If $\beta\mu > 2$, then E_2 lies between $(0, \beta\mu/2)$ and $(0, 1/2)$, and Γ_y increases from E_2 until hitting the straight line $x + y = \beta\mu/2$, then decreases until reaching E_1 (See Figure 1-(B)). We only need to prove that if (21) cuts Γ_y within $1/2 < x+y < \beta\mu/2$, then it can cut only once. To the end, it suffices to prove that the slope of the tangent line to the curve (21) is always greater than the slope of the tangent line to Γ_y at possible intersecting points when $1/2 < x + y < \beta\mu/2$, *i.e.*,

$$\frac{y}{\delta x} > \frac{\beta\mu - 2(x + y)}{2(x + y) - 1}. \tag{22}$$

Actually, by using $\mu\delta = 1$ and the expression of Γ_y, we have

$$\begin{aligned}
(22) \quad &\Leftrightarrow \quad y\big[2(x + y) - 1\big] > \delta x\big[\beta\mu - 2(x + y)\big] \\
&\Leftrightarrow \quad 2y(x + y) - y > \beta x - 2\delta x(x + y) \\
&\Leftrightarrow \quad 2(x + y)(y + \delta x) > \beta x + y \\
&\Leftrightarrow \quad 2(x + y)^2(y + \delta x) > (\beta x + y)(x + y) \\
&\Leftrightarrow \quad 2(y + \beta\mu x)(y + \delta x) > (y + \beta x)(y + x) \\
&\Leftrightarrow \quad y^2 + \big[2\delta + 2\beta\mu - \beta - 1\big]xy + \beta x^2 > 0.
\end{aligned}$$

The last inequality always holds for case (C1) due to

$$\beta = \frac{\delta}{1 - \mu} = \frac{1}{\mu(1 - \mu)} > 1,$$

and hence

$$2\delta + 2\beta\mu - \beta - 1 = 2\beta(1 - \mu) + 2\beta\mu - \beta - 1 = \beta - 1 > 0.$$

This completes the proof. $\qquad\square$

3.2. Polymorphism and bistability.

The following theorem shows that Condition (C2) leads to a polymorphic scenario.

Theorem 3.2. *Let (C2) hold. Then both E_1 and E_2 are saddle points, and the interior equilibrium point $E^*(x^*, y^*)$ is globally asymptotically stable: for each point $(x, y) \in \mathbb{R}^2_{+0}$, $\omega(x, y) = E^*$.*

Proof. Both E_1 and E_2 are saddle points since their Jacobian matrix have one positive and one negative eigenvalue. By (13), $\det J(E^*) > 0$. Meanwhile, we have

$$\mu\delta > 1 \Rightarrow \delta > 1 \Rightarrow \beta(1-\mu) > \delta > 1 \Rightarrow \beta > \frac{1}{1-\mu} > 1, \tag{23}$$

and hence,

$$tr J(E^*) = \frac{-k^2 + (1-\beta)k - \beta}{(k+1)^2} < 0.$$

Thus E^* is locally asymptotically stable. To prove its global stability, it suffices to show that there is no closed orbits. Take

$$B(x,y) = 1/(xy^2) > 0 \tag{24}$$

in $\mathbb{R}^2_{+0}$. The divergence of the vector field (Bf, Bg) satisfies

$$\begin{aligned}
&\nabla \cdot (Bf, Bg) \\
&= \frac{\partial}{\partial x}\left[\frac{\beta x}{y^2(x+y)} + \frac{\beta(1-\mu)}{y(x+y)} - \frac{\delta(x+y)}{y^2}\right] \\
&\quad + \frac{\partial}{\partial y}\left[\frac{\beta\mu}{y(x+y)} + \frac{1}{x(x+y)} - \frac{x+y}{xy}\right] \\
&= \frac{\beta}{y(x+y)^2} - \frac{\beta(1-\mu)}{y(x+y)^2} - \frac{\delta}{y^2} - \beta\mu\frac{x+2y}{y^2(x+y)^2} - \frac{1}{x(x+y)^2} + \frac{1}{y^2} \\
&= -\beta\mu\left[\frac{x}{y^2(x+y)^2} + \frac{1}{y(x+y)^2}\right] - \frac{1}{x(x+y)^2} + \frac{1-\delta}{y^2} < 0
\end{aligned}$$

which declares nonexistence of closed orbits in $\mathbb{R}^2_{+0}$ by the Dulac's criterion [13]. □

The following theorem indicates that (C3) corresponds to a bistable scenario.

Theorem 3.3. *Assume that (C3) holds. Then the unique interior equilibrium point $E^*(x^*, y^*)$ is a saddle point, and E_1 and E_2 are locally asymptotically stable. Moreover, denoting by $y = h(x)$ the stable manifold of E^*, $h(x)$ is continuous and increasing, and is the separatrix that defines the basins of attraction of E_1 and E_2 in $\mathbb{R}^2_{+0}$, and it lies between $h_0(x)$ and $h_1(x)$, where*

$$h_0(x) = \frac{y^*}{x^*}x, \quad h_1(x) = y^*\left(\frac{x}{x^*}\right)^{1/\delta}. \tag{25}$$

Proof. Condition $\mu\delta < 1$ (resp. $\beta(1-\mu) < \delta$) in (C3) implies that $J(E_1)$ (resp. $J(E_2)$) has two negative eigenvalues, and hence both E_1 and E_2 are locally asymptotically stable under (C3). Moreover, $\det J(E^*) < 0$ by (13), and hence E^* is a saddle point.

Noticing that along $y = cx$, (18) implies that

$$z'(t)|_{y=cx} = \frac{\beta(1-\mu\delta) - [\delta - \beta(1-\mu)]c}{\delta(1+c)}. \tag{26}$$

We have

$$z'(t)|_{y=cx} = 0 \Leftrightarrow c = k; \quad z'(t)|_{y=cx} < 0 \Leftrightarrow c > k; \quad z'(t)|_{y=cx} > 0 \Leftrightarrow c < k. \tag{27}$$

By (19), we have

$$l'_k(t)|_{L_k} = y(\delta - 1)\frac{f(x,y)}{\delta x}.$$

There are three cases to consider.

(i) $\delta = 1$. Then $l'_k(t)|_{L_k} \equiv 0$, implying that $L_k : y = kx$ consists of solution curves of system (4)-(5), which also serves as the stable manifold of E^*.

(ii) $\delta > 1$. Consider the domain

$$\mathcal{D}_1 = \big\{(x,y) : 0 < x < x^*, \; h_0(x) < y < h_1(x)\big\}.$$

We claim that $\mathcal{D}_1$ is *negatively* invariant with respect to the dynamics of (4)-(5). In fact, on its upper boundary where $y = h_1(x)$, (27) implies that $z'(t) < 0$. On its lower boundary $y = h_0(x)$,

$$l'_k(t)|_{L_k} = y(\delta - 1)\frac{f(x,y)}{\delta x} > 0.$$

It follows that solutions of system (4)-(5) initiated within $\mathcal{D}_1$ other than the origin and E^* will leave this region in finite time and stay outside thereafter.

Similarly, consider

$$\mathcal{D}_2 = \big\{(x,y) : x > x^*, \; h_1(x) < y < h_0(x)\big\}.$$

Then we have $l'_k(t)|_{L_k} < 0$ on its upper boundary $y = h_0(x)$, and $z'(t) > 0$ on the lower boundary $y = h_1(x)$. Consequently, the stable manifold of E^* must locate inside $\mathcal{D}_1$ and $\mathcal{D}_2$ and (2) is verified.

(iii) $\delta < 1$. By using the same argument as above, the negative invariance of

$$\mathcal{D}_3 = \big\{(x,y) : 0 < x < x^*, \; h_1(x) < y < h_0(x)\big\}$$

and

$$\mathcal{D}_4 = \big\{(x,y) : x > x^*, \; h_0(x) < y < h_1(x)\big\}$$

could be proved by dissecting the sign of $l'_k(t)|_{L_k}$ and $z'(t)$ on the boundaries. $\square$

3.3. **Monomorphism.**

Theorem 3.4. *Assume that one of the Conditions (C4), (C5) and (C6) holds. Then E_1 is globally asymptotically stable: for each point $(x,y) \in \mathbb{R}^2_{+0}$, $\omega(x,y) = E_1$.*

Proof. From (18), $z'(t) > 0$ always holds for these 3 cases, showing that (4)-(5) does not have any non-trivival periodic solution. We claim that E_2 could not be the ω-limit set of the trajectory $(x(t), y(t))$ initiated from $\mathbb{R}^2_{+0}$. For cases (C4) and (C6), it is trivial since E_2 is a hyperbolic saddle point with the stable manifold on the y-axis. However, E_2 becomes non-hyperbolic for case (C5), whose local stability cannot be determined by the Jacobian matrix approach. In this case, since $z'(t) > 0$, it holds that $z(t) > z(0)$ for all $t > 0$, and so E_2 cannot be an ω-limit point. Hence, $\omega(x,y) = E_1$ by the classical Poincaré-Bendixson theorem [13]. $\square$

Theorem 3.5. *Assume that one of the Conditions (C7), (C8) and (C9) holds. Then E_2 is globally asymptotically stable in the sense that for each point $(x,y) \in \mathbb{R}^2_{+0}$, $\omega(x,y) = E_2$.*

Proof. It is easily seen that $z'(t) < 0$ for all cases, which again implies that (4)-(5) does not have non-trivial periodic solution. The equilibrium point E_1 could not be the ω-limit set of any trajectory $(x(t), y(t))$ in $\mathbb{R}^2_{+0}$ for cases (C7) and (C8) since it is a hyperbolic saddle point with the stable manifold on the x-axis. For case (C9), since $z'(t) < 0$, it holds that $z(t) < z(0)$ for all $t > 0$, and so E_1 cannot be an ω-limit point. Hence, $\omega(x,y) = E_2$ by the classical Poincaré-Bendixson theorem [13]. $\square$

4. Discussion.

4.1. **Polymorphism, bistability and monomorphism.** The asymptotic behavior of the *Wolbachia* spreading dynamics in a mixed population of infected and uninfected mosquitoes depends strongly on the life parameters modified by the *Wolbachia* infection. We classify the system parameters into Cases (C1) to (C9) and identify their correspondence to three different scenarios:

Polymorphism: Theorems 3.1 and 3.2 show that the mixed population remains polymorphic for which both infected and uninfected mosquitoes coexist when (C1) or (C2) holds. If the degenerate case (C1) occurs, then the ultimate coexistent state may change with the initial infection level. When (C2) occurs, the asymptotic population size is independent of the initial value and the infection frequency at the steady-state is $x^*/(x^* + y^*)$.

Bistability: For case (C3), Theorem 3.3 offers a sharp threshold given by the separatrix $y = h(x)$ on the initial values for successful *Wolbachia* invasion. If *Wolbachia* does not alter the longevity of the mosquito, *i.e.*, $\delta = 1$, then the stable manifold of E^* coincides with $h_0(x) \equiv h_1(x)$, see Figure 2-(A). If $\delta \neq 1$, then $y = h(x)$ is nested by the straight line $y = h_0(x)$ and the curve $y = h_1(x)$, see Figure 2-(B) ($\delta < 1$) and Figure 2-(C) ($\delta > 1$). For these three cases, the solution initiated below $y = h(x)$ approaches *Wolbachia* fixation equilibrium point E_1, while the solution initiated above $y = h(x)$ approaches *Wolbachia* free equilibrium point E_2.
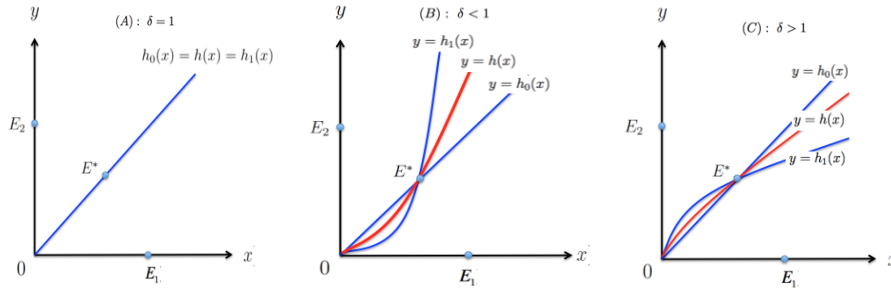

FIGURE 2. The separatrices $y = h(x)$ are sandwiched by $y = h_0(x)$ and $y = h_1(x)$.

Monomorphism: Theorem 3.4 implies that under either (C4) or (C5) or (C6), for any initial positive release, the *Wolbachia* infected mosquitoes will eventually replace the wild ones. Theorem 3.5 shows that under either (C7) or (C8) or (C9), *Wolbachia* infection will fail to establish, regardless of the number of initial release.

With perfect maternal transmission rate, *i.e.*, $\mu_1 = \mu_2 = 0$, system (4)-(5) is reduced to

$$\frac{dx}{dt} = \beta x - \delta x(x + y), \tag{28}$$

$$\frac{dy}{dt} = \frac{y^2}{x + y} - y(x + y) \tag{29}$$

for which only (C3), (C4) and (C5) can occur. When $\beta/\delta \geq 1$, the environment is more favorable (or at least equally favorable) for infected mosquitoes, and we say that *Wolbachia* infection has a *fitness benefit*. In this case, system (28)-(29) only

admits the *Wolbachia* free equilibrium point E_2 and the *Wolbachia* replacement equilibrium point E_1. Theorem 3.4 for Cases (C4) or (C5) shows that successful *Wolbachia* spreading is ensured from any initial release above 0 for the fitness benefit case. When $\beta < \delta$, we say that the infection has a *fitness cost*, and besides E_1 and E_2, there is a unique interior equilibrium point of system (28)-(29) which is a saddle point. Theorem 3.3 for Case (C3) displays bistable dynamics for the fitness cost case. These results are in line with the results in [41] which also include the corresponding results in [41] as special cases.

Comparing to perfect maternal transmission, the imperfect maternal transmission generates richer dynamics. To see this, we fix β and δ and consider separately the fitness cost case (i): $\beta \leq \delta$, and the benefit case (ii): $\beta > \delta$. We explore the impact of $\mu > 0$ in terms of its relation with two critical values

$$\nu_1 = \frac{1}{\delta}, \quad \nu_2 = 1 - \frac{\delta}{\beta}.$$

The detailed outcomes in different cases are shown in Figure 3. For example, in the fitness cost case (i), small μ corresponds to the bistable case (C3). However, increasing μ leads to (C9) and (C7), for which all solutions are attracted to E_2, and *Wolbachia* will be eventually wiped out, no matter how many infected mosquitoes are initially released. Thus, we see a transition from the bistable state to the monomorphic state E_2 as μ increases. In the fitness benefit case (ii) with $\nu_1 < \nu_2$, small μ corresponds to (C4) and (C6), for which all solutions converge to E_1: *Wolbachia* infected mosquitoes will eventually replace the wild ones, as long as $\mu < \nu_1$. But when μ is large, (C4) is replaced by (C2), (C8) and (C7) consecutively, which again implies the failure of the release because all solutions converge to E_2. Thus, there is also a transition of convergences to equilibria when $\mu > 0$ is increased: transition from convergence to the replacement equilibrium E_1 to convergence to E^* (the unique positive equilibrium, giving a unique polymorphic outcome), and finally to the failure equilibrium E_2. This is *in contrast to the transition in (i)* which is a transition from the bistable state to the monomorphic state E_2.

4.2. **Success or failure: Review on some recent releases.** We consider two *Wolbachia* strains, the benign *w*Mel and the virulent *w*MelPop, of *Aedes aegypti* in Australia. It was found that *w*Mel caused only 10% longevity reduction and no significant fecundity cost [35], but *w*MelPop decreased the longevity of infected female mosquitoes by ~50% and resulted in a fecundity cost of ~56% [25]. By using the laboratory data in [25, 35], we estimated the birth rates b_I and b_U from the oviposition rate, egg hatching rate and survival rate of larvae to adults, as well as the death rates δ_I and δ_U from the half-life of adults [41]. We found that $b_U = 0.3976$ and $\delta_U = 8.5034 \times 10^{-6}$, and for the benign *Wolbachia* strain *w*Mel: $b_I = 0.3976$, $\delta_I = 9.4482 \times 10^{-6}$, and for the virulent *Wolbachia* strain *w*MelPop: $b_I = 0.2154$, $\delta_I = 1.4172 \times 10^{-5}$. These parameter values lead to

$$\beta = \frac{0.3976}{0.3976} = 1, \quad \delta = \frac{9.4482 \times 10^{-6}}{8.5034 \times 10^{-6}} \approx 1.1111$$

for the benign *w*Mel, and

$$\beta = \frac{0.2154}{0.3976} \approx 0.5418, \quad \delta = \frac{1.4172 \times 10^{-5}}{8.5034 \times 10^{-6}} \approx 1.6667$$
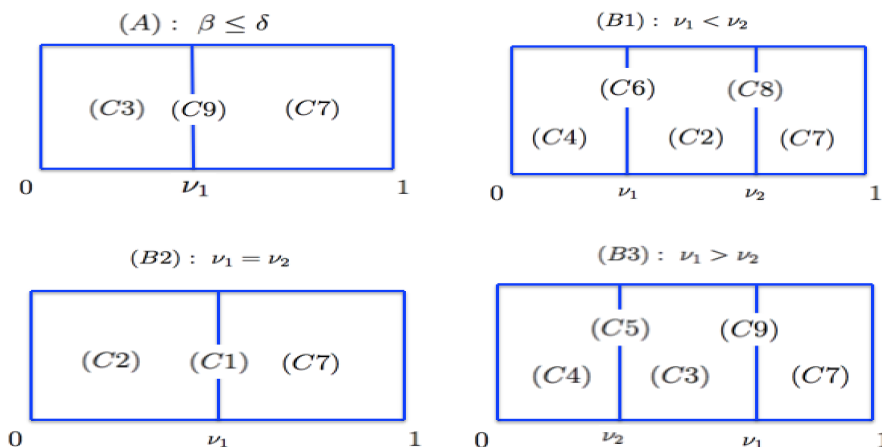
for the virulent *w*MelPop.

FIGURE 3. *Dynamics complexity induced by imperfect maternal transmission.* (A) When $\beta \leq \delta$, small μ corresponds to bistable case (C3). Increasing μ leads to (C9) and (C7), and the positive solutions converge to the monomorphic state E_2. (B) When $\beta > \delta$, we consider three subclasses. (B1): $\nu_1 < \nu_2$. As μ increases, (C4), (C6), (C2), (C8) and (C7) occur consecutively, and the system transits from the monomorphic state E_1 to the polymorphic state E^* and finally the monomorphic state E_2. (B2): When $\nu_1 = \nu_2$, only (C1), (C2) and (C7) can occur. The system is polymorphic at E^* when $\mu < \nu_1$, and is monomorphic at E_2 when $\mu > \nu_1$. (B3): $\nu_1 > \nu_2$. As μ increases, (C4), (C5), (C3), (C9) and (C7) occur one after another, and the system transits from the monomorphic state E_1 to the bistable state and finally the monomorphic state E_2.

In 2011, the *Wolbachia* strain wMel was introduced into *Aedes aegypti* populations in some northern Australian field sites [17] and had almost completely replaced wild mosquitoes for more than 3 years [10, 18]. Since September 2014, the wMel mosquitoes were released in two neighborhoods in Brazil [5]: Tubiacanga in Rio de Janeiro (2014-2015) and Jurujuba in Niteroi (2015) to reduce dengue transmission. Successful or ongoing field trials also include the wMel release in January 2014 in Indonesia, and in May 2015 in Colombia. Achievements of these field trials have been so encouraging that the strategy is becoming a worldwide plan to combat Zika and other mosquito-borne viruses.

In contrast to the effective and sustainable invasion of the wMel release in Australia, the 2013 wMelPop trial in central Vietnam (Tri Nguyen, Hon Mieu Island) [26] was a failure: wMelPop could be established transiently, but not persistently, in any of the two sites. The failure was largely attributed to the virulent property of the wMelPop that causes the infected mosquitoes to have a shorter lifespan ($\delta = 1.6667 > 1$) and produce fewer offspring than the wild ones ($\beta = 0.5418 < 1$).

We can claim that maternal transmission leakage even makes a transient establishment of *Wolbachia* in the wild mosquito population a big challenge. Consider again the wMelPop strain as an example. Given the uninfected mosquito's density y_0 and the leakage rate μ, if the maternal transmission leakage occurs, then

(4)-(5) determines a unique *Wolbachia* release threshold $x_0 = x_0(y_0, \mu)$. We plot the ratio x_0/y_0 against the leakage rate in the left panel in Figure 4. It displays a steep elevation of the threshold ratio x_0/y_0 for a successful *Wolbachia* invasion as the leakage μ increases from 0.3 to 0.5, and reaches as high as 16 when $\mu = 0.5$. Furthermore, should the leakage is accompanied by incomplete CI as shown in [28], the scenario is even more discouraging. It was shown in [28] that, among 1848 eggs from the crossing of uninfected females and wMelPop-infected males, 301 (16.31%) hatched. This leads to a reduction of the CI intensity s_h from $s_h = 1$ in (4)-(5) to $s_h = 0.8369$. With the incorporation of incomplete CI, the model is modified to

$$\frac{dx}{dt} = \beta \frac{x^2}{x+y} + \beta(1-\mu)\frac{xy}{x+y} - \delta x(x+y), \tag{30}$$

$$\frac{dy}{dt} = \beta\mu\frac{xy}{x+y} + y \cdot \left(1 - s_h \cdot \frac{x}{x+y}\right) - y(x+y). \tag{31}$$

Again, we can determine the unique threshold value $x_0 = x_0(y_0, \mu, s_h)$. In this case, a small increase on the leakage rate could bring a catastrophic failure of *Wolbachia* release. As shown in the right panel in Figure 4, the threshold ratio is as large as 7 when $\mu = 0.15$. Further increase of the leakage rate from 0.15 to 0.25 results in an augment of 6-fold on the threshold ratio. If $\mu = 0.3$, we found that even if the ratio is as large as 200, *Wolbachia* will be wiped out. Our example highlights some challenges associated with releasing wMelPop, which is in line with the results in [26, 28].
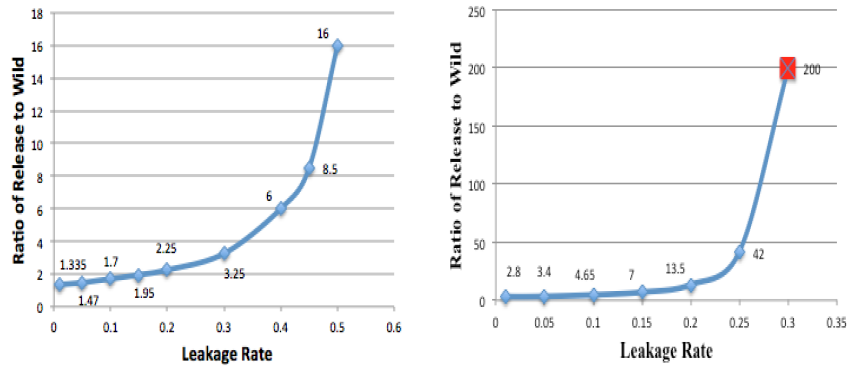

FIGURE 4. The maternal transmission leakage hinders the *Wolbachia* invasion. (Left) Fix $y_0 = 0.02$, we plot the ratio of x_0 to y_0 against the leakage rate $\mu = 0.01, 0.05, 0.1, 0.15, 0.2, 0.3, 0.4, 0.45$ and 0.5 for the leakage case (4)-(5). (Right) The combination of negative effects of imperfect maternal transmission and incomplete CI could make *Wolbachia* invasion impossible. Again, fix $y_0 = 0.02$ and $s_h = 0.8369$. When the leakage rate is 0.15, the incomplete CI mechanism leads the threshold ratio increase from 1.95 to 7. Worse than that, when the leakage rate is 0.3, the ratio as high as 200 is still insufficient to ensure successful *Wolbachia* invasion.

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