Wolbachia spread dynamics in stochastic environments

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ARTICLE INFO

ABSTRACT

Dengue fever is a mosquito-borne viral disease with 100 million people infected annually. A novel strategy for dengue control uses the bacterium *Wolbachia* to invade dengue vector *Aedes* mosquitoes. As the impact of environmental heterogeneity on *Wolbachia* spread dynamics in natural areas has been rarely quantified, we develop a model of differential equations for which the environmental conditions switch randomly between two regimes. We find some striking phenomena that random regime transitions could drive *Wolbachia* to extinction from certain initial states confirmed *Wolbachia* fixation in homogeneous environments, and mosquito releasing facilitates *Wolbachia* invasion more effectively when the regimes transit frequently. By superimposing the phase spaces of the ODE systems defined in each regime, we identify the threshold curves below which *Wolbachia* invades the whole population, which extends the theory of threshold infection frequency to stochastic environments.

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1. Introduction

Dengue fever is a mosquito-borne disease caused by dengue virus infection. In the tropical and subtropical countries, as many as 100 million people are infected annually (Calisher, 2005; Kyle and Harris, 2008). In Guangzhou, the largest metropolitan area in southern China, we have just witnessed the largest outbreak of dengue fever from July to November in 2014. More than 30,000 cases were reported during that period (Long et al., 2015). Since there is no vaccine or effective medication available, eliminating the transmission vector *Aedes albopictus* by spraying insecticides or other means has been the primary dengue control strategy in Guangzhou. Although heavy applications of insecticides may rapidly reduce mosquito densities to mitigate the epidemics, it causes severe environmental damage and provides only a short-term solution as shown by the resurgence of dengue in Brazil, China, Cuba, and Singapore (Kyle and Harris, 2008; Ooi et al., 2006).

A novel strategy for dengue control uses *Wolbachia*, a maternally inherited endosymbiotic bacterium whose infection in *Aedes* mosquitoes may block transmission of dengue (Bian et al., 2010; Iturbe-Ormaetxe et al., 2011). Its invasion into natural field populations seeding with infected mosquitoes is facilitated by a mechanism called cytoplasmic incompatibility (CI), which causes death of the embryos of uninfected females mated with infected males (Hoffmann and Turelli, 1997; Laven, 1956). This has made the spreading dynamics of *Wolbachia* a reemerging hot topic since the earlier systematic studies of Caspari and Watson (1959), and Hoffmann et al. (1990); Turelli and Hoffmann (1995). Many interesting models of difference or differential equations have been developed to investigate the temporal and spatial *Wolbachia* spreading dynamics; see (Farkas and Hinow, 2010; Hancock et al., 2011; Huang et al., 2015; Jansen et al., 2008; Keeling et al., 2003; Turelli, 2010; Zheng et al., 2014) and the references therein.

For *Wolbachia* fixation in natural areas, it is crucial to determine the minimum number of infected mosquitoes released and the period across which releases need to be carried out. It is indeed an emerging need as recent experiments have indicated that *Wolbachia* infection often brings a fitness cost, either by shortening the host's mean lifespan, or by reducing the egg's viability (McMeniman et al., 2009; Walker et al., 2011; Xi et al., 2006). However, modeling accurately *Wolbachia* spread dynamics is a formidable task since *Aedes* mosquitoes live in different stages in open areas where exact rates of immigration are never clearly known, and most mosquito breeding sites are cryptic and can not easily be identified (Hancock et al., 2011). There are further challenges because the dependence of the birth and death rates on temperature and rainfall is often unclear. To develop a model that

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is analytically tractable, it is mandatory to ignore some affecting factors (Turelli, 2010; Zheng et al., 2014).

In most previous studies, it was assumed that the habitat environmental conditions for insects remain constant. However, mosquitoes live in a heterogeneous environment whose dynamical behavior varies accordingly when the living conditions such as temperature and precipitation fluctuate in nature. In this paper, we develop a mathematical model of a closed population of infected and uninfected mosquitoes living in a heterogeneous environment to assess the release rates and durations for *Wolbachia* fixation. We make the following basic assumptions suggested by the recent empirical data (McMeniman et al., 2009; Walker et al., 2011; Yeap et al., 2011), see also (Huang et al., 2015; Zheng et al., 2014):

(1) *Perfect maternal transmission*: If the mother is infected by *Wolbachia*, then all the offsprings are also infected.

(2) *Complete CI*: If infected male crosses with uninfected female, zygotic death due to CI occurs certainly.

(3) *Equal sex determination*: The probability that each newly eclosing adult is male (or female) is 50%.

We remark that both perfect maternal transmission and complete CI were observed in McMeniman et al. (2009) where the *Wolbachia* strain wMelPop was microinjected into naturally uninfected *A. aegypti* embryos (JCU strain). One purified mosquito cell line, PGYP1, has remained persistently infected by wMelPop (100 % infection frequency) until last assayed generation. Complete CI was confirmed by the finding that no eggs hatched from more than 2, 500 embryos obtained from crosses between male PGYP1 and uninfected JCU females. In Walker et al. (2011), three stably infected *A. aegypti* lines, MGYP1, MGYP2 and MGYP3, were generated independently and each line was 100% infected from generations 2–8 after infection. Further experimental evidences supporting (1) and (2) have been given in Bian et al. (2013), Yeap et al. (2011).

We include only adult mosquitoes in our model. Let $x_F(t)$ denote the number of infected reproductive females at time $t \geq 0$, and $x_M(t)$ the number of infected males. Similarly, let $y_F(t)$ denote the number of uninfected females, and $y_M(t)$ the number of uninfected males. Then the total number is $z = x_F + x_M + y_F + y_M$. Since the reproduction has a strong dependence on environmental conditions, we use $\mathcal{A}_0(t)$ and $\mathcal{B}_0(t)$ to denote the birth rates of infected and uninfected mosquitoes, respectively. It has been recorded that the oviposition rate of *A. aegypti* increases almost linearly in temperature from 15°C to 30°C and peaks at 30°C, and the pre-adult maturation rate increases almost linearly in temperature from 12°C to 35°C and peaks at 35°C (Chen and Hsieh, 2012; Focks and Barrera, 2007; Yang et al., 2009). In contrast, no significant change in the death rate of *A. aegypti* was observed in the same range of temperatures (Chen and Hsieh, 2012; Focks and Barrera, 2007; Yang et al., 2009). Assume that the per capita decay rates increase with the total population size z due to the overcrowding effect. We let c denote the decay rate constant of infected adults, and d the decay rate constant of uninfected adults. Based on our basic assumptions, we obtain, for infected mosquitoes

$$\frac{dx_F}{dt} = \frac{1}{2}\mathcal{A}_0(t)x_F - czx_F, \qquad \frac{dx_M}{dt} = \frac{1}{2}\mathcal{A}_0(t)x_F - czx_M, \qquad (1.1)$$

and for uninfected mosquitoes

$$\begin{aligned}
\frac{dy_F}{dt} &= \frac{1}{2}\mathcal{B}_0(t)y_F \frac{y_M}{x_M + y_M} - dzy_F, \\
\frac{dy_M}{dt} &= \frac{1}{2}\mathcal{B}_0(t)y_F \frac{y_M}{x_M + y_M} - dzy_M.
\end{aligned} \qquad (1.2)$$

The term $y_M/(x_M + y_M)$ represents the mating probability between uninfected females and males, which equals the proportion of eggs
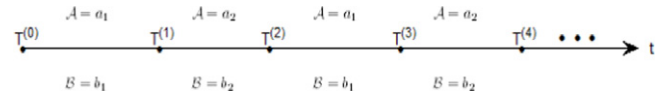

Fig. 1. The switching of the birth rates $\mathcal{A}(t)$ and $\mathcal{B}(t)$ between two different environmental regimes.

laid by the uninfected females that can be hatched successfully due to complete CI. Denote

$$x(t) = x_F(t) + x_M(t), \qquad y(t) = y_F(t) + y_M(t),$$
$$\mathcal{A}(t) = \frac{1}{2}\mathcal{A}_0(t), \qquad \mathcal{B}(t) = \frac{1}{2}\mathcal{B}_0(t).$$

Then by adding the equations in (1.1), and the equations in (1.2), we derive

$$\begin{cases}
\dfrac{dx}{dt} = x\left[\mathcal{A}(t) - c(x+y)\right], \\
\dfrac{dy}{dt} = y\left[\mathcal{B}(t)\dfrac{y}{x+y} - d(x+y)\right].
\end{cases} \qquad (1.3)$$

When $\mathcal{A}(t)$ and $\mathcal{B}(t)$ are constants, (1.3) reduces to the ODE system recently studied in Zheng et al. (2014).

In order to quantify the impact of the heterogeneous environment on the *Wolbachia* spread dynamics, we assume that the environment in the mosquito habitat transits randomly between n regimes as time moves on, and the birth rates take constant values in each regime. In this paper, we focus on $n = 2$. Let

$$0 = T^{(0)} < T^{(1)} < T^{(2)} < \cdots < T^{(n)} < \cdots$$

be the jump points when the environment switches between the two regimes (see Fig. 1). We set

$$\mathcal{A}(t) = \begin{cases}
a_1, & t \in [T^{(2n-2)}, T^{(2n-1)}), \quad n = 1, 2, \ldots, \\
a_2, & t \in [T^{(2n-1)}, T^{(2n)}), \quad n = 1, 2, \ldots,
\end{cases}$$

and

$$\mathcal{B}(t) = \begin{cases}
b_1, & t \in [T^{(2n-2)}, T^{(2n-1)}), \quad n = 1, 2, \ldots, \\
b_2, & t \in [T^{(2n-1)}, T^{(2n)}), \quad n = 1, 2, \ldots.
\end{cases}$$

We assume that the durations $S_n = T^{(n)} - T^{(n-1)}$ are independently and exponentially distributed with the rates $\lambda_1 > 0$ for odd n, and $\lambda_2 > 0$ for even n. Since the environmental changes make similar impact on the birth rates for the infected and uninfected mosquitoes (Wiwatanaratanabutr and Kittayapong, 2006), we assume further that

$$a_1 > a_2, \qquad b_1 > b_2. \qquad (1.4)$$

One of the most convenient quantities for measuring the infection level in the mixed population is the *infection frequency* defined by

$$p(t) = \frac{x(t)}{x(t) + y(t)}. \qquad (1.5)$$

Clearly, $0 \leq p \leq 1$ by its definition. $p = 1$ corresponds to *Wolbachia* fixation, for which all mosquitoes are infected; $p = 0$ corresponds to *Wolbachia* extinction for which no mosquito is infected. In the classical studies (Caspari and Watson, 1959; Hoffmann et al., 1990; Turelli and Hoffmann, 1995), some sufficient conditions have been specified under which the fate of *Wolbachia* spread is determined by a threshold value p^*: Any initial infection frequency $p_0 > p^*$ across all life stages leads to *Wolbachia* fixation, and $p_0 < p^*$ leads to *Wolbachia* extinction. The theory has been extended to incorporate important details of the insect's life history, immigration, spatial movement, and age-structure (Hancock et al., 2011; Turelli, 2010). When the infection does not alter the death