Theoretical Population Biology 115 (2017) 45–60

Contents lists available at ScienceDirect

Theoretical Population Biology

journal homepage: www.elsevier.com/locate/tpb

Deploying dengue-suppressing *Wolbachia*: Robust models predict slow but effective spatial spread in *Aedes aegypti*

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ARTICLE INFO

Article history:
Received 11 December 2016
Available online 12 April 2017

Keywords:
Population transformation
Population replacement
Bistable wave dynamics
Disease suppression
Zika
Biocontrol

ABSTRACT

A novel strategy for controlling the spread of arboviral diseases such as dengue, Zika and chikungunya is to transform mosquito populations with virus-suppressing *Wolbachia*. In general, *Wolbachia* transinfected into mosquitoes induce fitness costs through lower viability or fecundity. These maternally inherited bacteria also produce a frequency-dependent advantage for infected females by inducing cytoplasmic incompatibility (CI), which kills the embryos produced by uninfected females mated to infected males. These competing effects, a frequency-dependent advantage and frequency-independent costs, produce bistable *Wolbachia* frequency dynamics. Above a threshold frequency, denoted $\hat{p}$, CI drives fitness-decreasing *Wolbachia* transinfections through local populations; but below $\hat{p}$, infection frequencies tend to decline to zero. If $\hat{p}$ is not too high, CI also drives spatial spread once infections become established over sufficiently large areas. We illustrate how simple models provide testable predictions concerning the spatial and temporal dynamics of *Wolbachia* introductions, focusing on rate of spatial spread, the shape of spreading waves, and the conditions for initiating spread from local introductions. First, we consider the robustness of diffusion-based predictions to incorporating two important features of wMel-*Aedes aegypti* biology that may be inconsistent with the diffusion approximations, namely fast local dynamics induced by complete CI (*i.e.*, all embryos produced from incompatible crosses die) and long-tailed, non-Gaussian dispersal. With complete CI, our numerical analyses show that long-tailed dispersal changes wave-width predictions only slightly; but it can significantly reduce wave speed relative to the diffusion prediction; it also allows smaller local introductions to initiate spatial spread. Second, we use approximations for $\hat{p}$ and dispersal distances to predict the outcome of 2013 releases of wMel-infected *Aedes aegypti* in Cairns, Australia, Third, we describe new data from *Ae. aegypti* populations near Cairns, Australia that demonstrate long-distance dispersal and provide an approximate lower bound on $\hat{p}$ for wMel in northeastern Australia. Finally, we apply our analyses to produce operational guidelines for efficient transformation of vector populations over large areas. We demonstrate that even very slow spatial spread, on the order of 10–20 m/month (as predicted), can produce area-wide population transformation within a few years following initial releases covering about 20–30% of the target area.

1. Introduction

Wolbachia are maternally inherited endosymbionts, pervasive among arthropods (Weinert et al., 2015) and best known for reproductive manipulation (Werren et al., 2008). Their most widely documented reproductive manipulation is cytoplasmic incompatibility (CI) (Hoffmann and Turelli, 1997; Hamm et al., 2014), which kills embryos produced by *Wolbachia*-uninfected females mated to infected males. *Wolbachia*-infected females are compatible with both infected and uninfected males and generally produce only infected progeny. CI gives infected females a reproductive advantage that increases with the infection frequency. Consequently, CI-inducing *Wolbachia* can spread within and among populations, at least once they become sufficiently common that the CI-induced advantage overcomes any frequency-independent disadvantages (Caspari and Watson, 1959; Turelli and Hoffmann, 1991; Turelli, 2010; Barton and Turelli, 2011). Because *Wolbachia* are maternally transmitted, selection favors variants that increase the fitness of infected females (Turelli, 1994; Haygood and Turelli, 2009). Teixeira et al. (2008) and Hedges et al. (2008) discovered that *Wolbachia*-infected individuals are protected from some pathogens, including viruses. Pathogen protection is not universal (Osborne et al., 2009), and studies of both transient somatic *Wolbachia* transinfections (Dodson et al., 2014) and stable transinfections (Martinez et al.,

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http://dx.doi.org/10.1016/j.tpb.2017.03.003
0040-5809/

2014) suggest that *Wolbachia* can occasionally enhance susceptibility to pathogens. However, virus protection seems to be a common property of both natural and introduced *Wolbachia* infections (Martinez et al., 2014).

This anti-pathogen effect has revitalized efforts to use *Wolbachia* for disease control, an idea first proposed in the 1960s (Laven, 1967; McGraw and O'Neill, 2013). The disease-vector mosquito *Aedes aegypti* has been transinfected with two *Wolbachia* strains from *Drosophila melanogaster* (wMelPop, McMeniman et al., 2009 and wMel, Walker et al., 2011). Two isolated natural Australian *Ae. aegypti* populations have been transformed with wMel to suppress dengue virus transmission (Hoffmann et al., 2011), and these populations have remained stably transformed for more than four years (Hoffmann et al., 2014; S. L. O'Neill, pers. comm.). The dengue-suppressing phenotype of wMel-transinfected *Ae. aegypti*, first demonstrated in laboratory colonies (Walker et al., 2011), has been maintained, and possibly enhanced, after two years in nature (Frentiu et al., 2014). Recently, wMel has also been shown to block the spread of the Zika virus by *Ae. aegypti* (Dutra et al., 2016). *Anopheles stephensi* was also transinfected with *Wolbachia*, making them less able to transmit the malaria-causing parasite (Bian et al., 2013). *Wolbachia* transinfections are now being deployed for disease control in at least five countries (Australia, Vietnam, Indonesia, Brazil and Colombia, see the "Eliminate Dengue" website:http://www.eliminatedengue.com/program), with many more releases planned. We present simple approximation-based predictions to understand and aid the deployment of these transinfections.

Our mathematical analyses rest on bistable frequency dynamics for *Wolbachia* transinfections. Namely, the frequency-independent costs associated with introduced infections cause frequencies to decline when the infections are rare; but the frequency-dependent advantage associated with CI overcomes these costs when the infections become sufficiently common. As explained in the Discussion, bistability now seems implausible for naturally occurring *Wolbachia* infections (cf. Fenton et al., 2011; Kriesner et al., 2013; Hamm et al., 2014). However, we present several lines of evidence, including new field data, indicating that wMel transinfections in *Ae. aegypti* experience bistable dynamics in nature.

Why does bistability matter? As reviewed in Barton and Turelli (2011), bistability constrains which variants can spread spatially, how fast they spread, how difficult it is to initiate spread, and how easily spread is stopped. Roughly speaking, spatial spread can occur only if the critical frequency, denoted $\hat{p}$, above which local dynamics predict deterministic increase rather than decrease, is less than a threshold value near $1/2$. As discussed in Turelli (2010), $\hat{p}$ is determined by a balance between the frequency-dependent advantage provided by cytoplasmic incompatibility and frequency-dependent disadvantages associated with possible deleterious *Wolbachia* effects on fecundity, viability and development time. As $\hat{p}$ increases, the rate of predicted spatial spread slows to zero (then reverses direction), the area in which the variant must be introduced to initiate spread approaches infinity, and smaller spatial heterogeneities suffice to halt spread. Spatial dynamics depend on details of local frequency dynamics and dispersal that are not well understood empirically. This motivates our exploration of quantitative predictions using relatively simple but robust models that focus on three key biological phenomena, dispersal, deleterious fitness effects and cytoplasmic incompatibility.

We seek conditions under which minimal releases of dengue-suppressing *Wolbachia* transinfections achieve area-wide disease control by transforming a significant fraction of the vector population in a relatively short period. We focus on simple models to provide quantitative predictions and guidelines, and test the robustness of the predictions to long-distance dispersal. Our simple approximations make testable predictions that may be improved as additional data become available. Many parameters in detailed models will be difficult to estimate and are likely to vary in time and space. Our idealization is motivated by the scarce information concerning the ecology of disease vectors such as *Ae. aegypti*. For instance, the dynamics of introductions must depend on ecological factors such as density regulation (Hancock et al., 2011a,b). However, the ecology of *Ae. aegypti* is so poorly understood that increases in embryo lethality associated with CI might lead to either decreasing or increasing adult numbers (cf. Prout, 1980; Walsh et al., 2013; but see Hancock et al., 2016). As in Barton and Turelli (2011), we ignore these ecological complications and emphasize quantitative conclusions that depend on only two key parameters: σ, a measure of average dispersal distance, and $\hat{p}$, the unstable equilibrium frequency. We illustrate how these two parameters can be estimated from introduced-*Wolbachia* frequency data (producing predictions that can be cross-validated) and explore the robustness of the resulting predictions.

Our new analyses build on Barton and Turelli (2011), which used diffusion approximations to understand spatial and temporal dynamics. To determine the robustness of those diffusion-based predictions, which make mathematical assumptions that may not be consistent with the biology of *Wolbachia*-transinfected mosquitoes, we examine dispersal patterns that assign higher probabilities to long-distance (and very short-distance) dispersal. We ask how dispersal patterns affect wave speed, wave shape, and the conditions for initiating an expanding wave (Section 4). We use these new, more robust predictions to propose guidelines for field deployment of dengue-suppressing *Wolbachia*. This involves addressing new questions. For instance, Barton and Turelli (2011) determined the minimum area over which *Wolbachia* must be introduced to initiate spatial spread, but ignored the fact that near this critical size threshold, dynamics would be extremely slow. Effective field deployment requires initiating multiple waves to cover a broad area relatively quickly, given constraints on how many mosquitoes can be released. This requires understanding how transient dynamics depend on initial conditions. We synthesize data-based and model-based analyses of spatial spread to outline efficient strategies for area-wide transformation of vector populations (Section 7).

In addition to our theoretical results concerning predicted properties of spatial spread and near-optimal release strategies, we illustrate the theory with predictions concerning the outcome of wMel releases in Cairns, Australia in 2013 (Section 5). We also analyze some previously unpublished data from the 2011 releases reported in Hoffmann et al. (2011) to approximate a lower bound for $\hat{p}$ relevant to the Cairns releases (Section 6).

2. Mathematical background, models and methods

Our initial numerical analyses focus on testing the robustness of predictions presented in Barton and Turelli (2011). We first describe the diffusion approximations and results from Barton and Turelli (2011) before describing the alternative approximations and analyses. Next we describe the model used to analyze the new data we present. Finally we describe our approaches to approximating optimal release strategies.

2.1. Diffusion approximations, alternative dynamics and predictions

The simplest spatial model relevant to understanding *Wolbachia* frequency dynamics in space and time is a one-dimensional diffusion approximation:

$$\frac{\partial p}{\partial t} = \frac{\sigma^2}{2}\frac{\partial^2 p}{\partial x^2} + f(p), \tag{1}$$

where $f(p)$ describes local dynamics and $p(x, t)$ denotes the infection frequency at point x and time t, and σ denotes the standard