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Gene drive through a landscape: Reaction–diffusion models of population suppression and elimination by a sex ratio distorter

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ABSTRACT

Some genes or gene complexes are transmitted from parents to offspring at a greater-than-Mendelian rate, and can spread and persist in populations even if they cause some harm to the individuals carrying them. Such genes may be useful for controlling populations or species that are harmful. Driving-Y chromosomes may be particularly potent in this regard, as they produce a male-biased sex ratio that, if sufficiently extreme, can lead to population elimination. To better understand the potential of such genes to spread over a landscape, we have developed a series of reaction–diffusion models of a driving-Y chromosome in 1-D and radially-symmetric 2-D unbounded domains. The wild-type system at carrying capacity is found to be unstable to the introduction of driving-Y males for all models investigated. Numerical solutions exhibit travelling wave pulses and fronts, and analytical and semi-analytical solutions for the asymptotic wave speed under bounded initial conditions are derived. The driving-Y male invades the wild-type equilibrium state at the front of the wave and completely replaces the wild-type males, leaving behind, at the tail of the wave, a reduced- or zero-population state of females and driving-Y males only. In our simplest model of a population with one life stage and density-dependent mortality, wave speed depends on the strength of drive and the diffusion rate of Y-drive males, and is independent of the population dynamic consequences (suppression or elimination). Incorporating an immobile juvenile stage of fixed duration into the model reduces wave speed approximately in proportion to the relative time spent as a juvenile. If females mate just once in their life, storing sperm for subsequent reproduction, then wave speed depends on the movement of mated females as well as Y-drive males, and may be faster or slower than in the multiple-mating model, depending on the relative duration of juvenile and adult life stages. Numerical solutions are shown for parameter values that may in part be representative for *Anopheles gambiae*, the primary vector of malaria in sub-Saharan Africa.

1. Introduction

Many selfish genetic elements are able to spread and persist in populations not because they increase the survival or reproduction of individuals carrying them, but because they contrive to bias their transmission from parents to offspring above the Mendelian norm (Burt and Trivers, 2006; Werren, 2011). This phenomenon is often called gene drive, and examples of such genes include gamete killers, meiotic drivers, B chromosomes, transposable elements, and homing endonuclease genes. Because they can spread through populations even if they cause some harm to the organism, gene drive systems may be useful as tools to help control pest populations (Sinkins and Gould, 2006; Alphey, 2014; Burt, 2014).

Amongst the first selfish genes to be investigated for population control was the driving-Y chromosome (or, more precisely, male determining region) found naturally in some *Aedes aegypti* mosquito populations, which in some crosses is transmitted to more than 90% of progeny, the vast majority being sons (Craig et al., 1960; Hickey and Craig, 1966a,b). Such a gene might be expected to increase in frequency, rendering the entire population male-biased, which in turn could lead to suppression or even elimination (Hamilton, 1967). It turned out that most populations with the driving-Y also have resistant alleles, and sex ratios in nature are not severely biased (Wood and Newton, 1991). A similar phenomenon has been observed in *Culex pipiens* mosquitoes (Sweeny and Barr, 1978), but otherwise Y drive has rarely been reported from nature (Helleu et al., 2015). In mosquitoes, Y drive occurs because the development of X-bearing sperm is somehow disrupted; the molecular details are currently unknown, but cytological observations show that it is associated with breakage of the X chromosome during male meiosis (Newton et al., 1976). Recently, it

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has been demonstrated in *Anopheles gambiae* mosquitoes that a synthetic gene construct that expresses an enzyme that specifically cleaves the X chromosome during male meiosis results in the Y chromosome being transmitted to up to 95% of progeny (Galizi et al., 2014). In principle, inserting such a construct onto the Y chromosome could result in a synthetic driving-Y.

Models of random-mating populations have shown that a driving-Y chromosome can invade a population from an arbitrarily low frequency (i.e., there is no invasion threshold); that if it increases from low frequency it will go to fixation, replacing the non-driving-Y (i.e., simple models do not allow a stable intermediate equilibrium frequency); and that the population will be eliminated if the male bias is sufficiently extreme (Hamilton, 1967; Clark, 1987; Deredec et al., 2008, 2011). The dynamics of a driving-Y in spatially structured populations has been much less studied (Hamilton, 1967). North et al. (2013) used individual-based simulations of mosquitoes, each with an explicit location on a landscape, and showed it was still possible to get population elimination with a driving-Y.

Reaction–diffusion equations have been widely used to model biological invasions, both for beneficial mutations replacing a wild-type allele and for species invading a landscape (Fisher, 1937; Kolmogorov et al., 1937; Skellam, 1951; Andow et al., 1990; Shigesada and Kawasaki, 1997; Hastings et al., 2005). In these models a sufficiently localized initial condition can evolve into a travelling waveform that propagates with an asymptotically constant velocity. The wave connects a stable equilibrium state (at the tail of the wave, where the mutant gene has completely replaced the wild-type gene, or species abundance has gone to its carrying capacity) with an unstable state (at the tip of the wave, with the mutation or species absent). These methods have also been used to model the spread of maternally inherited *Wolbachia* bacteria that cause cytoplasmic incompatibility, in which case complex dynamics such as bifurcation, threshold, and Bartonian waves have been identified (Turelli and Hoffmann, 1991; Schofield, 2002; Barton and Turelli, 2011). Reaction–diffusion equations have also been used to model the sterile insect release method and exhibit travelling extinction waves (Lewis and van den Driessche, 1993).

In this paper, we apply reaction–diffusion equations to model the spatial spread of a driving-Y chromosome causing a population crash, and investigate how its spread through the population is affected by the dynamics of population suppression or extinction. In Section 2, we describe the mathematical approach that we use to analyse our systems of partial differential equations and delay PDEs. A series of models is then presented with successively more complex life histories: a one life-stage basic model (Section 3.1); a two life-stage model with immobile juveniles (Section 3.2); and the most complex model for which females mate once only at a male density-dependent rate (Section 3.3). These enhancements add significantly more complexity compared to the Fisher–KPP equation: time delay, up to seven dependent variables, differences in dispersal rate for different types, and an Allee effect. For each model, we calculate travelling waveform solutions and the linear spreading velocity of the travelling waves under bounded initial conditions. In Section 4, we extend the most complex model to two dimensions and apply it to the spatial spread of a driving-Y chromosome in *An. gambiae* mosquito populations, calculating wave speed and other characteristics that are useful in designing release strategies for disease control. In Section 5, we compare results for different models and implications for pest eradication strategies and discuss model assumptions and possible extensions.

2. Mathematical approach

We model the release of driving-Y males into a wild-type population using a series of deterministic, nonlinear reaction–diffusion PDEs and delay PDEs of the form:

$$\frac{\partial \boldsymbol{U}(x,t)}{\partial t} = \mathbf{D}\cdot\frac{\partial^2 \boldsymbol{U}(x,t)}{\partial x^2} + \boldsymbol{f}\left(\boldsymbol{U}(x,t), \boldsymbol{U}(x,t-T_J)\right) \tag{1}$$

where the vector $\boldsymbol{U}(x,t)$ represents the population densities and other dependent variables. Dispersal is based on a local random movement of individuals through space, with the population density flux governed by Fick's first law. We allow different diffusivities for the various types (driving-Y and wild-type males, females) so that we can investigate the role of each in dispersal, where $\mathbf{D} = \text{diag}[\![D_i]\!]$ is the diagonal diffusivity matrix with D_i denoting the diffusivity for type i. We model an unbounded, homogeneous domain in one spatial dimension for simplicity, although the results are extended to two spatial dimensions (radially-symmetric) in Section 4. The vector function $\boldsymbol{f}\left(\boldsymbol{U}(x,t), \boldsymbol{U}(x,t-T_J)\right)$ represents the non-linear growth and death terms, and models with two life stages include a time delay T_J due to the immobile juvenile stage. The homogeneous equilibrium states of (1), $\boldsymbol{U_{eq}}$, are the non-negative solutions of $\boldsymbol{f}\left(\boldsymbol{U}(x,t) = \boldsymbol{U_{eq}}, \boldsymbol{U}(x,t-T_J) = \boldsymbol{U_{eq}}\right) = 0$, equivalent to setting the spatial and time derivatives in (1) to zero.

We introduce the driving-Y male into the homogeneous wild-type equilibrium state $\boldsymbol{U_0} = \{U_{01}, \ldots, U_{0n}\}$, where n is the number of different types or dependent variables (up to seven). For each model, we calculate the full numerical solution of the non-linear PDEs (1) using the Method of Lines, combined with the Method of Steps for models with time delay (Bellen and Zennaro, 2003). We show that travelling population density waves are established that connect $\boldsymbol{U_0}$ at the tip of the wave with an equilibrium state $\boldsymbol{U_1} = \{U_{11}, \ldots, U_{1n}\}$ behind the wave.

We now describe how we calculate the linear stability of the equilibrium states and derive analytical and semi-analytical expressions for the asymptotic wave speed by linearizing (1) around the relevant equilibrium state. We consider bounded perturbations of the dependent variables $\boldsymbol{U}(x,t)$ around $\boldsymbol{U_0} = \{U_{01}, \ldots, U_{0n}\}$. For models with time delay $T_J \neq 0$, we need to consider displacements from equilibrium that persist over an interval of at least the longest time delay, which in our system is T_J. We thus introduce localized (bounded in space) perturbations of $\boldsymbol{U}(x,t)$ from its equilibrium value $\boldsymbol{U_0}$ both at times t and $t - T_J$:

$$\boldsymbol{\delta U}(x,t) = \boldsymbol{U}(x,t) - \boldsymbol{U_0} \quad \text{and} \quad \boldsymbol{\delta U}(x,t-T_J) = \boldsymbol{U}(x,t-T_J) - \boldsymbol{U_0}.$$

We then linearize the system of Eqs. (1), recognizing that $\boldsymbol{f}(\boldsymbol{U_0}) = 0$ (since at equilibrium the growth and death terms are balanced), to obtain:

$$\frac{\partial\, \boldsymbol{\delta U}(x,t)}{\partial t} = \mathbf{D}\cdot\frac{\partial^2 \boldsymbol{\delta U}(x,t)}{\partial x^2} + \mathbf{J^0}\cdot\boldsymbol{\delta U}(x,t) + \mathbf{J^{T_J}}\cdot\boldsymbol{\delta U}(x,t-T_J) \tag{2}$$

where the two Jacobian matrices $\mathbf{J^0} = [\![\frac{\partial f_i}{\partial U_j(x,t)}]\!]$ and $\mathbf{J^{T_J}} = [\![\frac{\partial f_i}{\partial U_j(x,t-T_J)}]\!]$ are both calculated at the equilibrium point $\boldsymbol{U_0}$.

We now introduce the spatial Fourier transform and temporal Laplace transform of the dependent variables, with $\widehat{\boldsymbol{\delta U}}(k,t)$ representing the spatial Fourier transformed variables and $\widetilde{\boldsymbol{\delta U}}(k,\omega)$ representing the doubly-transformed variables, defined below for $k \in \mathbb{C}$ and $\omega \in \mathbb{C}$:

$$\widetilde{\boldsymbol{\delta U}}(k,\omega) = \int_0^\infty e^{i\omega t}\, \widehat{\boldsymbol{\delta U}}(k,t)\,dt = \frac{1}{\sqrt{2\pi}}\int_0^\infty\int_{-\infty}^\infty e^{-ikx+i\omega t}\,\boldsymbol{\delta U}(x,t)\,dx\,dt.$$