Evolutionary models of Z-linked synthetic suppression gene drives

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Abstract

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Keywords:

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Introduction

Here is a reference (e.g. Holman et al. 2018), and here's a link to a figure (**??**).

Aims: - Compare low and high cost shredders ability to suppress the pop. High cost spreads worse since Z*W females have fewer offspring, but it also means fewer offspring are born! - Local vs global release? - mosqutio/butterfly vs worm vs bird - effect of m/f dispersal and patch structure - is the Z conversion needed for spread? - effect of male weighting and softness of selection on females

Methods

Overview

We model a population of dioecious diploids, living in a landscape containing k discrete habitat patches. The species has ZW sex determination, and we model the demography and evolution of the population following the release of an engineered Z-linked allele that is capable of W-shredding in females (which it does at rate p_{shred}) and/or gene conversion in males (at rate p_{conv}). Our principle aim is to identify the key factors that determine whether the Z-linked genetic element (hereafter Z*) causes extinction of the population. The model is a stochastic individual-based simulation, and was written in R. An accompanying website presents well-annotated code used to run the model and generate all the figures (link).

Genetics and inheritance

Individuals in the model carry one sex-linked locus and 2 autosomal loci. Males carry two of three possible Z-linked alleles: the engineered gene drive allele (Z*), a wild-type Z allele (Z+), or a resistant allele that is immune to gene conversion by the gene drive (Zr). Females carry one of these Z-linked alleles, plus either a wild-type W chromosome (W+), or a resistant W chromosome that is immune to being shredded by the Z-linked gene drive (Wr). The A/a autosomal locus carries alleles a and A, where the A allele is dominant and confers immunity to gene drive (e.g. W-shredding) in females. The B/b autosomal locus carries alleles b and B, where B is dominant and confers immunity to gene drive (e.g. gene conversion) in males.

We assume that the A/a and B/b loci are unlinked and display normal diploid Mendelian inheritance. Inheritance of the sex chromosomes is Mendelian, except in certain genotypes that inherited a single Z*. Provided they do no carry a resistant Wr chromosome or at least one A allele, females carrying Z* produce a fraction $\frac{1}{2}(1 + p_{shred})$ of Z-bearing gametes and $\frac{1}{2}(1 - p_{shred})$ W-bearing gametes, and thus have a male-biased offspring sex ratio if $p_{shred} > 0$ (representing W-shredding or some other mechanism of Z-linked segregation distortion that operates in females). Similarly, provided that they do not carry a resistant Zr allele or at least one B allele, males carrying the Z* gene drive produce a fraction $\frac{1}{2}(1 + p_{conv})$ gametes

bearing the Z* allele and $\frac{1}{2}(1 - p_{conv})$ gametes with the Z+ allele, where $p_{conv} > 0$ indicates Z-linked transmission bias in males (e.g. because of a CRISPR-*Cas9* gene drive that mediates gene coversion).

Breeding

To begin the breeding phase of the lifecycle, we first determine the number of offspring produced by each female in the meta-population. The expected fecundity of each female is determined by three factors: her genotype, the density of males and females in the local patch and/or the meta-population, and global parameters in the model.

Specifically, we define local density in patch i as $d_{local,i} = f_i + \delta m_i$, where δ is a global parameter that scales the relative importance of the number of males in the patch (m_i), relative to the number of females (f_i). Similarly, we define global density as $d_{global} = f + \delta m$. When $0 < \delta < 1$, males contribute less to density than the equivalent number of females, while $\delta > 1$ indicates the reverse; δ encompasses sex differences in phenotypes like resource use, competitive ability, and behaviour. For example, we might expect $\delta < 1$ in species where males and females utilise different environmental niches, and $\delta > 1$ in species with strong inter-locus sexual conflict.

We then calculate the density experienced by a female in patch i as $d_i = \alpha d_{local,i} + (1-\alpha) d_{global}$, where α scales the relative importance of local and global density in limiting the number of offspring produced. We assume that fecundity decreases with d_i following a Richards model REF, such that the expected fecundity of females in patch i with genotype j is

$$E(F_{i,j}) = w_j F_{max}(1 - (\frac{d_i}{K})^q)$$

, where w_j is the fitness of genotype j (range: 0-1). The remaining terms are model parameters: F_{max} controls the maximal possible fecundity, K controls the carrying capacity, and q determines the shape of the relationship (linear, concave, or convex) between d_i and $E(F_{i,j})$. Finally, we determine the actual number of offspring produced by each female genotype in each patch by randomly sampling from a Poisson distribution with $\lambda = N_{i,j} E(F_{i,j})$.

Next, we select fathers for each offspring. In a patch containing n male genotypes, the probability that a male of genotype j is the father of any given offspring is

$$p_{i,j} = \frac{m_i w_j}{\sum_{j=1}^{n} m_i w_j}$$

, such that males with high fitness (relative to the average fitness of all males in the patch) are more likely to sire offspring. This formulation means that we assume that both sexes potentially reproduce with multiple different partners.

Finally, we randomly generate a genotype for each resulting offspring, based on the genotypes of its parents and the associated expected zygote frequencies. Offspring are born in the same patch as their parents, and the parental generation is removed from the population

after reproducing (i.e. we assume discrete, non-overlapping generations). Female and male offspring disperse to another patch with probabilities x_f and x_m respectively. We model two types of dispersal, in separate simulations: local dispersal, in which offspring move to one of the two neighbouring patches with equal probability (recalling that the k patches are arranged linearly in a ring), or global dispersal, in which dispersing offspring can land in any of the other patches.

Running the simulation

We first initialise the population, with specified (typically low or zero) frequencies for the Zr, Wr, A and B alleles. We then iterated the population for 100 generations of burn-in, to allow the population to reach its equilibrium size and genotypic composition. We then introduce $m_{release}$ males with the genotype Z*Z*aabb, representing the release into the wild of a laboratory-reared strain homozygous for the driving Z and for autosomal factors conferring susceptibility to drive. In some simulations, all the Z*Z*aabb males were released in a single patch, while in others the $m_{release}$ males were randomly and evenly divided across all k patches. We continued to cycle through the lifecycle (birth, migration, breeding, death) until either A) the driving Z* allele went extinct, B) the population went extinct, C) the Wr chromosome went to fixation (making population suppression impossible), D) the Z* allele fixed, but failed to cause population extinction, or E) 400 generations had elapsed. We recorded which of these five outcomes occurred, as well as the allele frequencies, population size, and sex ratio at each generation.

Results

- Note that when females hardly migrate, the Wr is slow to spread across patches. It only has a good invasion probability if Z* is present, otherwise it's neutral or costly

Discussion

Acknowledgements

So long, and thanks for all the fish!

References

Holman, L., D. Stuart Fox, and C. E. Hauser. 2018. The gender gap in science: How long until women are equally represented? PLoS Biology 16:e2004956.

Supporting information