

Dynamics of Doom: a Lethal Gene Drive

Dick Gomulkiewicz Steve Krone

Fall 2019

Consider a diploid locus with alleles D and d . Let p be the frequency of D and $q = 1 - p$ the frequency of d among newly formed zygotes, which we assume are formed via random union of the gametes produced by surviving parents, that is, the usual Hardy-Weinberg proportions.

Suppose that D causes meiotic drive such that a fraction $\frac{1}{2} + \delta$ of the gametes produced by a heterozygote Dd parent are D and $\frac{1}{2} - \delta$ are d . The parameter δ measures the segregation distortion caused by D . We have $0 \leq \delta \leq \frac{1}{2}$, and $\delta = 0$ gives the usual Mendelian segregation ratio.

We now *also* assume that D is a lethal (or sterile) recessive, which means that none of the DD zygotes survive to adulthood (or are completely sterile). The frequency of Dd heterozygotes and dd homozygotes among the surviving (fertile) parents is

$$P_{Dd}^* = \frac{2pq}{\bar{w}} \quad (1)$$

where

$$\bar{w} = 2pq + q^2 = q(1 + p) \quad (2)$$

is the mean *relative* fitness. The frequency of the only other surviving/fertile genotype, dd , is $1 - P_{Dd}^*$.

The frequency of D among the gametes produced by the parents completely depends on the heterozygotes:

$$p^* = \left(\frac{1}{2} + \delta\right) \cdot P_{Dd}^* = \frac{2pq\left(\frac{1}{2} + \delta\right)}{q(1 + p)} \quad (3)$$

Evolutionary dynamics The next generation is formed by random mating, which is equivalent to random union of gametes but with allele frequencies p^* and $q^* = 1 - p^*$. The resulting offspring are in Hardy-Weinberg proportions with frequencies $p' = p^*$ and $q' = 1 - p'$ of D and d , respectively. The rate of evolution of this recessive lethal gene drive is thus

$$\begin{aligned} \Delta p &= p' - p = \frac{2pq\left(\frac{1}{2} + \delta\right)}{q(1 + p)} - p \\ &= \frac{p(2\delta - p)}{1 + p} \end{aligned} \quad (4)$$

Equilibrium The effect of D on survival is directly opposed by its segregation distortion. The forces balance when $\Delta p = 0$ which, from (4), occurs at non-zero equilibrium allele frequency

$$\hat{p} = 2\delta \tag{5}$$

Note that \hat{p} increases from 0 to 1 as the distortion δ ranges from 0 to $\frac{1}{2}$.

Drive to Doom The mean relative fitness (2) at equilibrium is

$$\hat{w} = \hat{q}(1 + \hat{p}) = (1 - 2\delta)(1 + 2\delta) = 1 - 4\delta^2 \tag{6}$$

This shows that the mean fitness declines quadratically with the strength of segregation distortion δ . Note that a perfect gene drive, $\delta = \frac{1}{2}$, would reduce mean fitness all the way to zero, that is, it would cause population extinction.

Lethal gene drives don't have to cause perfect segregation distortion (or be completely lethal) to achieve eradication. Indeed, it is sufficient for a drive to push the finite growth rate—mean *absolute* fitness—of the population below 1.

The mean absolute fitness of the population, \bar{W} , is proportional to its relative mean fitness (2), that is

$$\bar{W} = R\bar{w} = Rq(1 + p) \tag{7}$$

for some some constant $R > 1$. R can be thought of as the original geometric growth rate of the population before a lethal gene drive is introduced into it.

An introduced gene drive will cause eradication if $\bar{W} < 1$ for some frequency of the drive allele. This goal can be achieved if the mean absolute fitness at equilibrium is less than 1, that is, if

$$\hat{W} = R\hat{w} = R(1 - 4\delta^2) < 1.$$

Rearranging this shows that the minimum distortion of a recessive lethal gene drive required for eradication, δ_{doom} , is

$$\delta_{\text{doom}} = \frac{1}{2} \sqrt{\frac{R-1}{R}}. \tag{8}$$