Homework 3: Doom by Deleterious Drive?

Mathematical Genetics
Fall 2019

Consider a diploid locus with alleles $D$ and $d$. Suppose that $D$ causes meiotic drive such that a fraction $\frac{1}{2} + \delta$ of gametes produced by a heterozygote $Dd$ parent are $D$ and $\frac{1}{2} - \delta$ are $d$. The parameter $\delta$ measures the segregation distortion caused by $D$.

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 genotype frequencies of $DD$, $Dd$, and $dd$ are, respectively, $P_{DD} = p^2$, $P_{Dd} = 2pq$, and $P_{dd} = q^2$.

Assume that $D$ is a deleterious recessive such that $DD$ homozygotes have relative fitness $1 - s$, with selection coefficient $s > 0$ whereas both $Dd$ and $dd$ genotypes have relative fitness 1.

A. Explain why the respective genotype frequencies $P^*_DD$ and $P^*_Dd$ of $DD$ and $Dd$ among the parents surviving selection are

\[
P^*_DD = \frac{p^2(1 - s)}{\bar{w}}
\]
\[
P^*_Dd = \frac{2pq}{\bar{w}}
\]

where the mean relative fitness is

\[\bar{w} = 1 - p^2s.\] (1)

B. Use part A to show that the frequency of $D$ among the gametes produced by the parents is

\[\hat{p}^* = \frac{p(1 - ps + q2\delta)}{1 - p^2s}\]

C. The next generation is formed by random mating with allele frequencies $\hat{p}^*$ and $\hat{q}^* = 1 - \hat{p}^*$ so the resulting offspring are in Hardy-Weinberg proportions with frequencies $p' = \hat{p}^*$ and $q' = \hat{q}^*$ of $D$ and $d$, respectively. Use part B to show that the per generation rate of evolution of this recessive deleterious drive allele is

\[\Delta p = p' - p = \frac{pq(2\delta - ps)}{1 - p^2s}\]

D. Use part C to argue that $\hat{p}$, the non-zero equilibrium frequency of $D$, is

\[\hat{p} = \frac{2\delta}{s}\] (2)
Why does (2) only make sense if $s \geq 2\delta$ and what does this condition mean biologically? What is the equilibrium frequency if $s < 2\delta$? Explain.

E. Using equation (2), show that the mean relative fitness (1) at equilibrium assuming $s \geq 2\delta$ is

$$\hat{w} = 1 - \frac{4\delta^2}{s} \tag{3}$$

Explain why the equilibrium mean fitness is $\hat{w} = 1 - s$ if $s < 2\delta$.

F. Suppose the mean absolute fitness of the population, $\bar{W}$, is $R$ times the relative mean fitness (1), that is

$$\bar{W} = R\hat{w} = R(1 - p^2s)$$

where $R > 1$ is the per generation, per capita growth rate of the population before introduction of the deleterious gene drive. Assuming $s \geq 2\delta$, note that the gene drive will cause eradication if

$$\bar{W} = R \left(1 - \frac{4\delta^2}{s}\right) < 1.$$ 

From this show that $\delta_{\text{doom}},$ the minimum segregation distortion of a recessive deleterious gene drive required for eradication, is

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

*Extra Credit.* Does $0 < s < 2\delta$ guarantee eradication? Explain.

G. Graph $\delta_{\text{doom}}$ as a function of $s$ for a slow-growing population ($R = 1.05$) and for a fast-growing population ($R = 2$). Compare the curves to each other and compare both to the line $\delta = s/2$ (Why?). Discuss how these results could be used in the design of a gene drive engineered for eradication.