Review: Spatial Gene Drives and Pushed Genetic Waves by Tanaka, Stone, and Nelson

The authors' work develops a population genetics model for how the frequency of a gene-drive allele changes in time as constrained by its selection coefficient relative to the wild-type allele. The authors find that within the range $0.5 < s < 0.697$, the gene-drive allele can either overtake the wild population or go extinct contingent on the spatial distribution of the mutants. The authors extend the basic model to a two-dimensional system to show that these results still apply when the alleles are undergoing planar expansion.

- **What questions does this work answer?** This work specifies the range of selection coefficients over which the spatial extent of a population of gene-drive mutants (with perfect conversion efficiency) determines whether the mutants overtake the wild-type population or go extinct. Specifically the authors find that within the range $0.5 < s < 0.697$, gene drive fixation is tunable.
- **Why are these questions important?** This question is important because it provides a simple model for how gene-drive expansion can be controlled when the gene-drive allele has a lower fitness than the wild-type allele. Understanding the constraints on gene-drive allele expansion or extinction can allow genetic engineers to better tune genetically modified organisms for a controllable release into the population.
- **How does the work answer these questions?** The work answers this question by using deviations from the Hardy-Weinberg equilibrium to derive a differential equation for the gene-drive allele frequency $q(t)$ as it depends on the selection coefficient s. This selection coefficient is defined according to $f_{\text{drive}} = f_0(1-s)$ where f_0 is the fitness of the wild-type allele.
- **What are applications to systems/problems?** This work can be applied to population genetics systems where one is interested in how a gene-drive allele changes the distribution of the allele frequency in the population.

Originality Disclaimer: These notes represent this writer's most faithful attempt at interpreting many of the results in [1] and thus do not at all represent any original work on the part of this writer.

1 Introduction: Review of Genetics

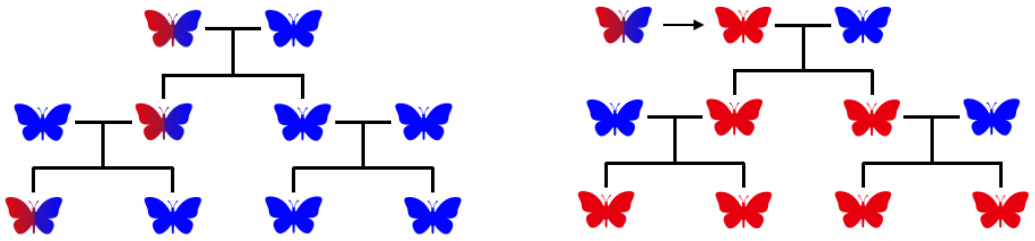
Before we discuss gene-drive inheritance, it is worthwhile to review Mendelian inheritance.

Let's say you are a microbiologist who has managed to engineer a mosquito which is homozygous in a mutant allele A. The wild-type mosquito, is in turn, homozygous in the wild allele a. You release this homozygous mutant mosquito into a population of wild-type mosquitos, and you want to know what proportion of this mutant mosquito's Nth generation offspring contain the mutant allele. We can answer this question by constructing a Punnet square for each mating possibility of the AA mutant and its offspring. When the AA mutant mates with the aa wild-type, all of the resulting offspring are heterozygous Aa mutants. Thus all of these first generation offspring contain the mutant A allele. This situation is shown in the Punnet square below

	A	A
a	Aa	Aa
a	Aa	Aa

(Mendelian Inheritance) (1)

Now, when any one of these offspring mates with another aa wild-type mosquito, the resulting offspring would be 50% Aa heterozygotes and 50% aa heterozygotes. Therefore, there is a 50% chance that



(a) (b)

Figure 1: (a) By Mendelian inheritance, if we have a heterozygous Aa mutant mating with a population of homozygous aa wild-types, then, by the second generation, only $1/4$ of the mutant's offspring will have the mutant allele A. (b) By gene-drive inheritance, if we have a heterozygous $A_{\text{gd}}a$ mutant—which converts to the homozygous $A_{\text{gd}}A_{\text{gd}}$ mutant by the action of the gene-drive—mating with a population of homozygous wild-types, then all of the the mutant's offspring will be homozygous in A_{gd}.

the offspring of the first generation of Aa will carry the A allele. We can repeat these arguments over many generations so that after N generations the fraction of the original AA's offspring which contain the A allele is $1/2^{N-1}$. This result assumes that all of the mutant offspring can reproduce in each generation. Thus we see that as generations pass, the proportion of the original mutant's offspring which carry the mutant allele gradually decays to zero. This is shown in Fig. 1a for two generations.

Gene drives radically alter this situation. The effect of a gene drive is to convert a heterozygous mutant into a mutant homozygous in the gene-drive allele[1]. Thus, if we take A_{gd} to be the mutant allele engineered as a gene-drive allele, then the corresponding allele on its partner chromosome would convert to A_{gd} as well. This means if we have the aa wildtype mating with the $A_{\text{gd}}A_{\text{gd}}$ mutant, the resulting offspring would be $A_{\text{gd}}a$ before the action of gene drive, and $A_{\text{gd}}A_{\text{gd}}$ after the action of the gene drive. Functionally, since the gene drive acts within the chromosomes on time scales much shorter than the organism's generation time, we can simply take the resulting offspring to all be homozygotes in A_{gd}. The Punnet square for this situation would be

	A_{gd}	A_{gd}
a	$A_{\text{gd}}A_{\text{gd}}$	$A_{\text{gd}}A_{\text{gd}}$
a	$A_{\text{gd}}A_{\text{gd}}$	$A_{\text{gd}}A_{\text{gd}}$

(Gene-drive Inheritance) (2)

Thus, after each generation, 100% of the original mutant's offspring have the mutant allele. The fact that this structure of inheritance (depicted for two generations in Fig. 1b) leads the offspring to completely convert to the genotype of one parent is why some call this situation **super-Mendelian inheritance** [2].

There is no free lunch however. Incorporating the gene-drive allele into an organism's genome typically results in a fitness cost relative to the fitness of the wild-type. That is, if f_0 is the fitness of the wild-type, and f_{gd} is the fitness of the gene-drive mutant then we have

$$f_{\text{gd}} = f_0(1 - s) \tag{3}$$

where $0 \leq s \leq 1$ is the selection coefficient. Since the gene-drive mutant has a lower fitness, it reproduces more slowly than the wild-type, and thus it is not absolutely the case that the the gene-drive allele will fix in population. The principal question Tanaka *et. al.* sought to answer is how exactly does selection affect the fixation of the gene-drive allele? For what selection coefficients does fixation never occur, always occur, or only sometimes occur? To answer these questions the authors made use of the Hardy-Weinberg principle.

[1] In the next subsection, we will discuss the exact mechanism by which a gene drive achieves this transformation, but for our purposes it suffices to take this change as fact.

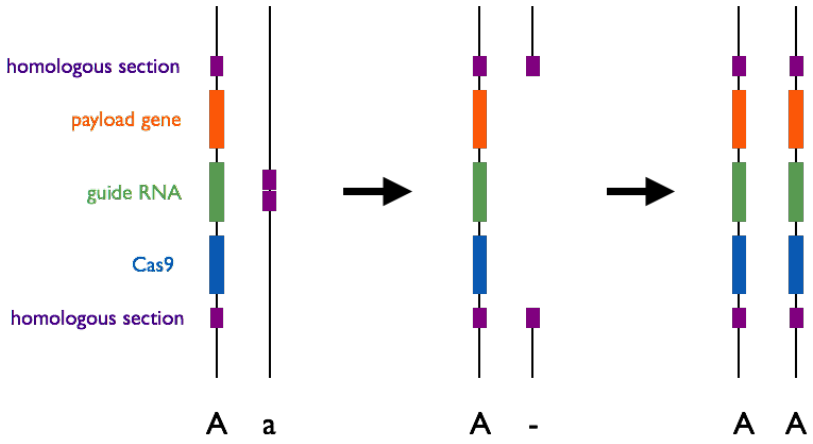


Figure 2: Schematic of how a gene drive replicates itself in the partner chromosome. The gene-drive allele translates a Cas9 protein which then cuts the partner DNA at a site dictated by the transcribed guide RNA. The cell repairs the cleaved gene by copying the uncut gene (the gene drive) into the sections of the cleaved gene that match the homologous sections framing the gene drive. Image recreated based on one by Thomas Julo [CC BY-SA 4.0 (http://creativecommons.org/licenses/by-sa/4.0)], via Wikimedia Commons.

1.1 *How Gene Drives Work

As an addendum to these results of the paper, we discuss in more detail how a gene drive converts heterozygous alleles into alleles homozygous in the gene-drive allele. An understanding of this mechanism starts with an understanding of the components which make up the gene drive. A gene drive consists of three principal components [3]:

- **Cas9 gene:** codes for the Cas9 protein which cuts DNA at a specific site determined by the guide RNA
- **Guide RNA gene:** transcribed into the guide RNA which forms a complex with the Cas9 protein. The guide RNA is engineered to bind to the specific section of the homologous DNA so that the Cas9 cuts the DNA at that site.
- **Payload gene:** desired gene we wish to propagate. In a sense, the Cas9 and guide RNA are like a truck and the payload gene is the cargo we're trying to transport into the homologous chromosome.

Framing these three sections of genes are two sections of DNA which, when joined together, are homologous to a section of the partner chromosome. These homologous sections are needed to ensure that when the gene-drive allele is copied into the partner allele, we end up with two identical genes. After Cas9 cuts the partner DNA, the cell repairs the cut DNA by copying the gene drive into the partner DNA; this copying process is called homologous DNA repair. In this way, we end up with two gene-drive alleles. The process of gene-drive duplication is presented as a schematic in Fig. 2.

2 Hardy-Weinberg Principle

One of the important simplifying assumptions in models of population genetics is **random mating**. Under random mating, we assume a population of organisms with various genotypes is well-mixed so that no organism in a specific location experiences a different collection of neighbors relative to another organism at some far off location. Consequently, the probability that a particular organism will mate with another organism of a certain genotype is simply equal to the frequency of that genotype. This random mating assumption is fundamental to what is known as the Hardy-Weinberg principle:

Hardy-Weinberg (H-W) principle: Under random mating (and for organisms that are diploid in a certain gene) the frequencies of the genotypes AA, Aa, and aa are q^2, $2pq$, and p^2, respectively, where q is the allele frequency of A and p is the allele frequency of a. [4]

By probability normalization, we have $q + p = 1$, and an important result of the H-W principle is that these allele frequencies remain the same for all generations when we neglect selection, mutations, genetic drift, and gene flow. We can see this latter fact through a calculation which when generalized allows us to derive the central differential equation of the paper.

Let's say our population has the three genotypes AA, Aa, and aa occurring with frequencies q^2, $2pq$ and p^2, respectively. We want to know the allele frequency of A in the next generation of the population. To do so precisely, we would need to know how these various genotypes reproduce which in turn entails knowing their individual fitnesses. Consistent with the assumptions of the H-W principle (specifically the no-selection assumption), we will take all genotypes to have the fitness f_0. We can summarize this system with the following table:

Genotype	Frequency	Fitness
AA	q^2	f_0
Aa	$2pq$	f_0
aa	p^2	f_0

The analysis of this system will be somewhat trivial, but we work through it completely to provide a model solution for the future cases. By the definition of fitness, and given the fitnesses listed in the table, we know that the AA, Aa, and aa organisms survive in the ratio $f_0 : f_0 : f_0$. Consequently, the ratio of the organisms $AA : Aa : aa$ in the next generation is

$$q^2 f_0 : 2pq f_0 : p^2 f_0, \tag{4}$$

which are simply the standard H-W ratios. The ratio of the number of A alleles and to the number of a alleles in this subsequent generation is therefore

$$q^2 f_0 + \tfrac{1}{2} 2pq f_0 : p^2 f_0 + \tfrac{1}{2} 2pq f_0, \tag{5}$$

where the factors of $\frac{1}{2}$ come from the fact that Aa has half of a full complement of A alleles and half of a full complement of a alleles. We can define $\langle f_A \rangle$ and $\langle f_a \rangle$ as the mean fitness of the A and a alleles, respectively, so that the ratio Eq.(5) can be written as $\langle f_A \rangle : \langle f_a \rangle$. To obtain the absolute allele frequencies in this new generation, we need to normalize the terms in these ratios by the total percentage of organisms which survive into the next generation. This is simply the **mean fitness** of the population:

$$\langle f \rangle = q^2 f_0 + 2pq f_0 + p^2 f_0. \tag{6}$$

We can now find the allele frequency of A in the next generation by dividing the surviving percentage of next-generation organisms with the A allele by the surviving percentage of all next-generation organisms. Denoting this new frequency as q', we have

$$q' = \frac{\langle f_A \rangle}{\langle f \rangle} = \frac{q^2 f_0 + \frac{1}{2} 2pq f_0}{q^2 f_0 + 2pq f_0 + p^2 f_0} = q, \tag{7}$$

where we used the identity $q + p = 1$. Thus, we find that the when all genotypes have the same fitness (that is, when there is zero selection), the allele frequencies remain the same from generation to generation. This result is as we expect at a H-W equilibrium.

2.1 Hardy-Weinberg with selection

We want to repeat the calculation which introduced this section except now we will incorporate a fitness cost for the AA genotype. We parameterize this fitness cost through a selection coefficient s which is between 0

and 1. The fitnesses of of the AA, Aa, and aa genotypes are denoted as $f_0(1-s)$, f_0, and f_0, respectively. We can thus construct the following summary table:

Genotype	Frequency	Fitness
AA	q^2	$f_0(1-s)$
Aa	$2pq$	f_0
aa	p^2	f_0

We want to know the allele frequency of A in the next generation. Computing $\langle f_A\rangle/\langle f\rangle$ for this population, we find

$$q' = \frac{\langle f_A\rangle}{\langle f\rangle} = \frac{q^2 f_0(1-s) + \frac{1}{2}2pqf_0}{q^2(1-s)f_0 + 2pqf_0 + p^2 f_0} = \frac{q(1-sq)}{1-sq^2}. \tag{8}$$

Since $q^2 < q$, we find that $q' < q$. This means that the frequency of the A allele decreases in each new generation generation, and over time, this allele will be eliminated from the population. This result is consistent with the framing of this system: Since we incorporated a selective disadvantage for being homozygous in A, fewer and fewer A alleles survive into subsequent generations, and the A allele eventually goes extinct.

2.2 Hardy Weinberg with selection and gene drives

Finally, we want to consider the case which is of concern to the paper: selection plus gene drives. Reviewing the motivation, gene drives function to convert partner alleles to gene-drive alleles so that heterozygotes become homozygotes. However, there is often a selective disadvantage to this conversion process. We denote our mutant allele as A_{gd} to signify that it is now a gene-drive allele. Let's say that the fitness of the genotypes $A_{\text{gd}}A_{\text{gd}}$ (homozygous gene-drive mutant) and aa (wild-type) are $f_0(1-s)$ and f_0, respectively; we do not specify the fitness of the $A_{\text{gd}}a$ genotype because in a moment we will see that it does not matter. At the start of one generation, we assume we still have the H-W frequencies. Our summary table is then

Genotype	Frequency	Fitness
$A_{\text{gd}}A_{\text{gd}}$	q^2	$f_0(1-s)$
$A_{\text{gd}}a$	$2pq$	–
aa	p^2	f_0

However, we note that the function of the gene drive is to convert all $A_{\text{gd}}a$ genotypes into $A_{\text{gd}}A_{\text{gd}}$ genotypes. Therefore, prior to the new generation the system is more correctly represented by

Genotype	Frequency	Fitness
$A_{\text{gd}}A_{\text{gd}}$	$q^2 + 2pq$	$f_0(1-s)$
aa	p^2	f_0

where we added the former $A_{\text{gd}}a$ frequencies to the $A_{\text{gd}}A_{\text{gd}}$ frequencies. We are now ready to answer our previous question: What are the allele frequencies of A_{gd} in the next generation? Working through the standard calculation, we find

$$q' = \frac{\langle f_A\rangle}{\langle f\rangle} = \frac{(q^2+2pq)f_0(1-s)}{(q^2+2pq)(1-s)f_0 + p^2 f_0} = \frac{(1-s)q(2-q)}{1-sq(2-q)}. \tag{9}$$

In a sense, Eq.(9) is the fundamental theoretical result of the paper. However, the equation does not lend itself to an easy interpretation of how selection affects the long-time dynamics of the frequency of A_{gd}. To obtain such an interpretation we will need to replace these discrete-generation dynamics with continuous -time dynamics.

3 Dynamics of gene-drive allele frequency

With Eq.(9), we can determine the gene-drive allele frequency in the next generation the frequency in this generation and the mutant's selection coefficient. However, to analyze the space of possible evolutions it is better to express this result as a differential equation. We do so through the derivative definition

$$q' - q \equiv \tau_g \frac{dq}{dt}, \tag{10}$$

where τ_g is the generation time of the organism. We then find

$$\tau_g \frac{dq}{dt} = \frac{(1-s)q(2-q)}{1-sq(2-q)} - q = \frac{q(-sq^2 + (3s-1)q + (1-2s))}{1-sq(2-q)}. \tag{11}$$

We can express this result more simply by solving the quadratic equation in the parentheses of the numerator. Doing so, we find the solutions

$$q_\pm = \frac{3s-1 \pm \sqrt{(3s-1)^2 + 4s(1-2s)}}{2s} = \frac{3s-1 \pm (1-s)}{2s} \longrightarrow \begin{cases} q_+ = 1 \\ q_- = \dfrac{2s-1}{s} \end{cases}. \tag{12}$$

We thus have the differential equation

$$\boxed{\tau_g \frac{dq}{dt} = \frac{-sq(q-q_+)(q-q_-)}{1-sq(2-q)} = \frac{sq(1-q)(q-q^*)}{1-sq(2-q)},} \tag{13}$$

where $q^* \equiv (2s-1)/s$. Eq.(13) is the paper's starting point for analyzing how the gene-drive frequency evolves in time. To study this evolution, the authors perceptively introduced a potential function. Writing Eq.(13) as

$$\frac{dq}{dt} + \frac{\partial}{\partial q} U(q,s) = 0, \tag{14}$$

the potential function $U(q,s)$ is defined as

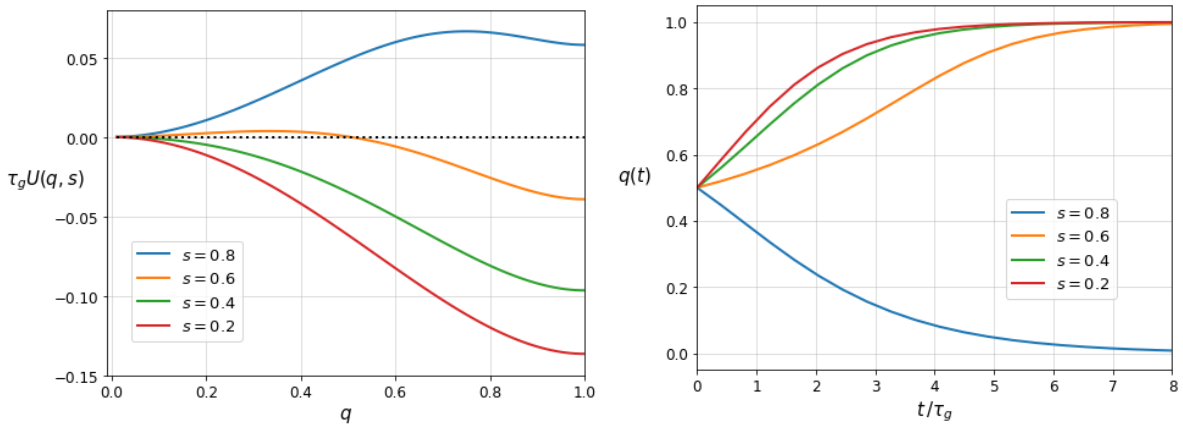
$$U(q,s) \equiv -\frac{1}{\tau_g} \int_0^q dq' \, \frac{sq'(1-q)(q'-q^*)}{1-sq'(2-q')}. \tag{15}$$

Inspecting Eq.(15), we can infer that the system has a local minimum at $q = 1$ and, when $s \geq 1/2$, a local maximum and a local minimum at $q = (2s-1)/s$ and $q = 0$, respectively. Thus, there are two local minima only when q^* exists or equivalently when $s \geq 1/2$. Plotting $U(q,s)$ for various selection coefficients can yield a qualitative understanding of what constraints define the system's time evolution. In Fig. 3a, we see that for $s < 0.5$ the system always evolves to $q = 1$. For $s > 0.5$, the system evolves to mutant fixation $(q = 1)$, if $q(t=0) > (2s-1)/s$ and to mutant extinction if $q(t=0) < (2s-1)/s$. In Fig. 3b, we provide examples of this result by solving Eq.(13) directly for the selection coefficients listed in Fig. 3a.

We note that these results only apply when Eq.(13) is the governing differential equation of the system. In the next section, when we incorporate spatial variations into the mutant-allele frequency, we will find that the system does not always evolve to the energetically favorable local minimum suggested by Fig. 3a.

4 Diffusion in 1D

Having considered a well-mixed system, the authors then consider how spatial variations change the dynamics of the mutant-allele frequency. To explore these dynamics, they assume that the mutants spatially



(a) (b)

Figure 3: Plots of potential landscape and allele frequency. We can determine the long-time dynamics of a well-mixed system by plotting $U(q,s)$ for a given value of s and beginning our trajectory at $q(0)=q_0$ on the relevant curve. The system then "rolls down the hill" until it reaches its local minimum at $q=0$ or $q=1$. This interpretation is affirmed by the allele-frequency vs. time plots in (b).

propagate through diffusion, so that Eq.(13) must be transformed into

$$\frac{\partial q}{\partial t} = D\frac{\partial^2 q}{\partial x^2} + \frac{sq(1-q)(q-q^*)}{1-sq(2-q)}, \tag{16}$$

where the probability $q(t)$ was promoted to a probability density $q(x,t)$. Exploring the properties of solutions to Eq.(19), the authors postulate an initial gaussian profile for the allele frequency,

$$q(x,0) = ae^{-x^2/b^2}, \tag{17}$$

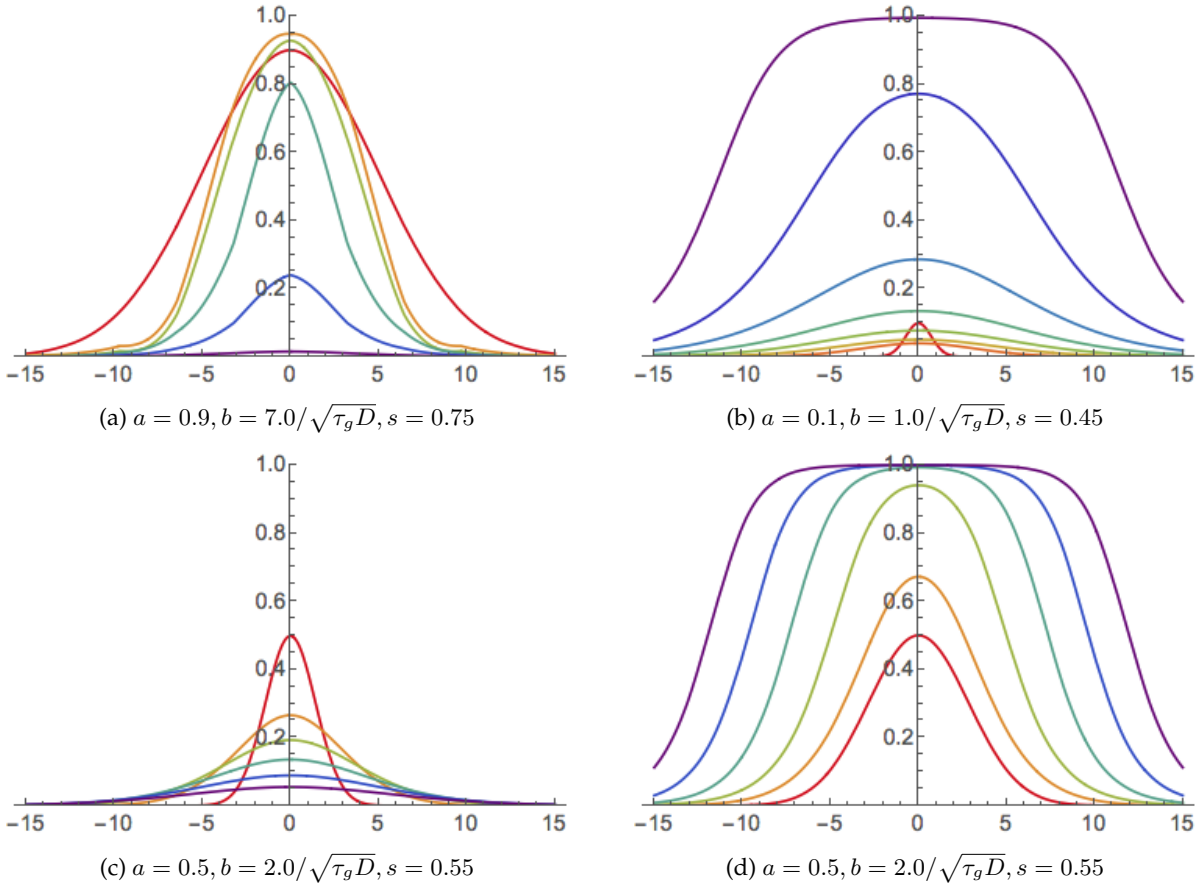
and determine how this profile changes in time contingent on the parameter values a, b, and s. Representative solutions are shown in Fig. 4. Comparing Fig. 4a and Fig. 4b, we see that for a sufficiently low selection coefficient, the mutant allele always fixes regardless of the size of its initial distribution, and, conversely, for a sufficiently high selection coefficient the mutant allele always goes extinct. Just how low and how high is suggested by Fig. 4c and Fig. 4d. For a selection coefficient of $s=0.55$, the mutant allele fixes contingent on the width of its initial distribution with larger widths associated with fixation and smaller widths with extinction. Thus although, $s=.45$ is associated with automatic fixation and $s=.75$ is associated with automatic extinction, $s=.55$ is in a range in which fixation is tunable.

4.1 Tunable Fixation/Extinction Regime

The authors find that the the regime in which the system does not automatically evolve to extinction or to fixation is defined by

$$0.5 < s < 0.697 \qquad \text{(Tunable fixation/extinction regime).} \tag{18}$$

For this range of selection coefficients, whether the mutant allele fixes or not depends on its initial spatial distribution $q(x,0)$ and specifically that distribution's spatial extent. Roughly, if the distribution is narrow when the system is in this tunable regime, the mutant allele will go extinct, and if the distribution is wide, the mutant allele will fix. The authors make these notions of "narrow" and "wide" quantitative by specifi-



(a) $a = 0.9, b = 7.0/\sqrt{\tau_g D}, s = 0.75$

(b) $a = 0.1, b = 1.0/\sqrt{\tau_g D}, s = 0.45$

(c) $a = 0.5, b = 2.0/\sqrt{\tau_g D}, s = 0.55$

(d) $a = 0.5, b = 2.0/\sqrt{\tau_g D}, s = 0.55$

Figure 4: Solutions to Eq.(19) for various initial gaussian distributions. The curves proceed in time by steps of $\Delta t = 5.0\tau_g$ from red to violet. We note that for (a), the allele frequency density at first expands before contracting and going extinct.

cally computing the initial distribution which defines the boundary between fixation and extinction (Shown for various selection coefficients as solid lines in Fig. 5 of the paper). In general, the authors find that higher selection coefficients require taller and wider initial critical distributions for long-time fixation to be achieved.

The authors determine Eq.(18) by first noting that $q = 1$ is both an absolute minimum and the only local minimum of Eq.(15) when $s < 0.5$. Thus for $s < 0.5$, the system will always evolve to mutant fixation. However, for $s \geq 0.5$, $q = 0$ also becomes a local minimum and there is a chance that the system will evolve to extinction. Whether this evolution occurs depends on the sign of $U(1, s)$. Specifically, [5] showed that the speed of the waves in diffusive systems of the kind governed by Eq.(19) is proportional to $U(1, s)$. For $U(1, s) < 0$ the waves propagate forward and for $U(1, s) > 0$ the waves propagate backward. While fixation in the case of forward propagation is determined by the initial density (i.e., sufficiently narrow initial densities can still be driven to extinction), in the case of backward propagation the system is always driven to extinction. Thus the value of s which determines whether the wave propagates forward to swamp the population or backward to extinction is $U(1, s) = 0$. Computing the value of s which satisfies this condition, the authors find $s_{\text{max}} = 0.697$. Therefore, for $s > s_{\text{max}}$, the mutant allele is always driven to extinction[2]

[2]The preceding explanation is somewhat different from that which is given in the author's text, but is consistent with their first reference.

4.2 Diffusion in 1D with Selection Barriers

The authors slightly modify their boundary-value problem to include a "selection barrier" some distance away from the initial distribution. The selection barrier consists of a small spatial region where the selection coefficient of the mutant changes to some value close to 1. The authors choose a barrier with $s = 0.958$ located within the domain $[25\sqrt{\tau_g D}, 27\sqrt{\tau_g D}]$. For this barrier, the authors find that a mutant allele distribution with $s = 0.479 < 0.5$ can propagate past the distribution, but a mutant allele distribution with $s = 0.542$ cannot.

5 Diffusion in 2D

In the final section, the authors extend their analysis to two dimensional systems. Diffusion is presumed to be isotropic so that the equation they analyze is

$$\frac{\partial q}{\partial t} = D\left(\frac{\partial^2 q}{\partial x^2} + \frac{\partial^2 q}{\partial x^2}\right) + \frac{sq(1-q)(q-q^*)}{1-sq(2-q)}. \tag{19}$$

The authors find that provided the impeding selection barrier has gaps through which the wave can propagate, a wave with $s < 0.5$ always overtakes the system. Conversely, a wave with $0.5 < s < 0.697$ only overcomes selection barriers if these barriers have gaps which are larger than the width of the wave's distribution.

6 Concluding Comments

In this paper, the authors analyze how a gene drive affections the population dynamics of diffusing mutants. Their main results are encapsulated by the differential equation Eq.(13) and the inequality Eq.(18), the latter of which is part of a larger set of inequalities which determines whether the mutant fixes or goes extinct.

$$\begin{aligned} s \leq 0.5 &: \text{ Fixation} \\ 0.5 < s < 0.697 &: \text{ Tunable fixation/extinction} \\ s \geq 0.697 &: \text{ Extinction} \end{aligned}$$

We note that the above conditions only apply when we assume complete conversion efficiency for the gene drive; the authors consider the implications of incomplete conversion in an appendix. For $s \leq 0.5$ the mutant allele always fixes, the interpretation being that in this regime the gene drive mechanism is strong enough to outweigh any reproductive disadvantage relative to the wild-type. For $s \geq 0.697$ the mutant allele always goes extinct, for its fitness is too low to allow propagation of the gene-drive relative to the wild-type allele. In the regime $0.5 < s < 0.697$, the mutant allele fixes or goes extinct contingent on the size of its initial density profile. For sufficiently large profiles the gene-drive mutant fixes and for small profiles the mutant goes extinct. The critical profile demarcating the boundary between these two regimes is found numerically in the paper.

7 Transcriber's Comments

The objective of these notes was to take the main results of the paper and explain them in the writer's own words. In this section, we outline some lingering questions left over from the analysis in the paper.

- **Incorporating mutations and genetic drift:** This model assumes that the gene-drive mechanism is the

only one which converts wild-type alleles into mutant-alleles. How would the results change if they were applied to finite size populations where genetic drift was relevant? How would a small mutation rate affect these results?

  - In the last section of the appendix, the authors do consider the effects of fluctuations due to finite population sizes, but they conclude that for mosquitos the effects are small enough to be ignored.

- **Three-dimensional system with selection barriers:** The final section of the paper considers how a two dimensional system is affected by porous selection barriers. It is worth asking how these results would extend to three-dimensional systems of the kind which could be engineered in the wild.

- **Controlling the selection coefficient:** A main result of the paper is that a gene-drive mutant is in the tunable fixation/extinction regime provided its selection coefficient is within a certain range. But the selection coefficient is an effective parameter which includes all phenotypical characteristic of the organism which affect its fitness. Could such a parameter be reliably "engineered" for an organism, and if it is engineered how could this value be protected against genetic mutations and other effects which naturally change fitness?

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