

Threshold-Dependent Gene Drives in the Wild: Spread, Controllability, and Ecological Uncertainty

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Gene drive technology could allow the intentional spread of a desired gene throughout an entire wild population in relatively few generations. However, there are major concerns that gene drives could either fail to spread or spread without restraint beyond the targeted population. One potential solution is to use more localized threshold-dependent drives, which only spread when they are released in a population above a critical frequency. However, under certain conditions, small changes in gene drive fitness could lead to divergent outcomes in spreading behavior. In the face of ecological uncertainty, the inability to estimate gene drive fitness in a real-world context could prove problematic because gene drives designed to be localized could spread to fixation in neighboring populations if ecological conditions unexpectedly favor the gene drive. This perspective offers guidance to developers and managers because navigating gene drive spread and controllability could be risky without detailed knowledge of ecological contexts.

Keywords: gene drives, conservation, uncertainty, modeling, biotechnology

Though humans have had a long history of controlling wild populations, it has been much harder to manipulate the genetics of these populations. Mendelian inheritance, wherein each sexually reproducing organism only passes about 50% of their genes to their offspring, practically guarantees that any allele introduced into a population would fail to spread to fixation unless it offered a substantial fitness benefit (figure 1a). In contrast, gene drives have the potential to overcome Mendelian inheritance by passing certain alleles to a majority of offspring (Burt 2003; Esvelt et al. 2014; NASEM 2016). This inheritance advantage causes the gene drive to spread through a population, even if the gene drive is otherwise deleterious to the organism's fitness (Figure 1b; Burt 2003; Unckless et al. 2015). Though some gene drives occur naturally, recent scientific interest has focused on engineering both natural and synthetic gene drives, which are often linked to a secondary gene of interest called a cargo gene. The possible applications of this technology are wide-ranging, from disease control (Sinkins and Gould 2006; Hammond et al. 2016), to agriculture (Scott et al. 2018), to conservation (Campbell et al. 2015; Piaggio et al. 2017; Prowse et al. 2017). For example, spreading disease resistance alleles into a vector population could limit infection rates to humans (Sinkins and Gould 2006; Hammond et al. 2016) and endangered species (Piaggio et al. 2017), spreading genes that limit the number of viable

offspring produced into a pest or invasive population could suppress and eradicate them (Deredec et al. 2008; Leitschuh et al. 2018), and spreading genes that increase climate tolerance into dispersal-limited species like corals could protect them from rapidly changing climatic conditions (Redford et al. 2014; Anthony et al. 2017; Piaggio et al. 2017). Unfortunately, although gene drives might make it easier to manage wild populations, the self-replicating feature of gene drives could be difficult to control, especially under conditions of uncertainty (NASEM 2016).

Though gene drives could allow population managers to drive a desired costly gene to fixation, biased inheritance could be less desirable when gene drives reach beyond a targeted, local population. Assuming that individuals who carry these gene drives disperse and mate freely, the spreading trait could have unanticipated impacts on neighboring populations, on entire species, or indirectly on surrounding ecological communities (NASEM 2016; Esvelt and Gemmell 2017; Noble et al. 2018). Recognizing these risks, innovators have already called for multiple safeguards that would reduce the risk of accidental release during research and development (Akbari et al. 2015; DiCarlo et al. 2015; NASEM 2016; Champer et al. 2019), reversal strategies that would limit or remove a gene drive from a wild population (Esvelt et al. 2014; Vella et al. 2017), or specialized drives that can be localized geographically (Esvelt et al. 2014;

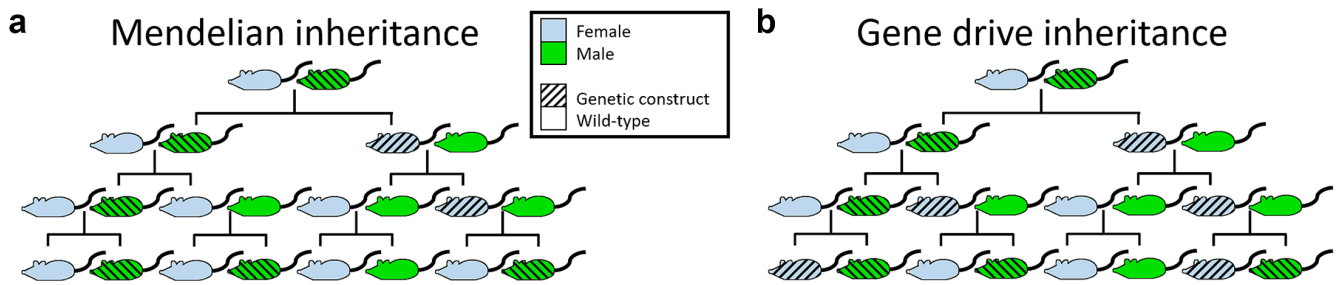


Figure 1. After several generations, the frequency of descendants carrying a dominant genetic construct depends on the inheritance rate of the construct. For standard Mendelian inheritance in (a), each offspring has a 50% chance of inheriting the construct. After three generations, only 1/8 of descendants will carry the construct. With a gene drive in (b), each offspring has a greater than 50% chance of inheriting the construct (5/6 in this example). With this inheritance advantage, a higher proportion of descendants will carry the construct after three generations. However, because inheritance is not 100%, some offspring will still inherit the wild-type variant.

Dhole et al. 2017; Sudweeks et al. 2019). At the same time, many researchers remain unconvinced that gene drives will work well enough to be effective in the wild, because an assortment of natural genetic, evolutionary, behavioral, and ecological obstacles could weaken their spread (Esvelt et al. 2014; Moro et al. 2018; Bull 2017; Manser et al. 2017; Wilkins et al. 2018; North et al. 2019). Thus, to ensure gene drives can spread through a population in the first place, innovators have been interested in countering the evolution of resistance and increasing the long-term fitness of gene drives (Marshall et al. 2017; Prowse et al. 2017; Unckless et al. 2017; Kyrou et al. 2018; Champer et al. 2018a).

To an outside observer, it might appear confusing that the science of gene drives is concurrently progressing toward techniques that both increase and decrease the long-term efficacy of gene drive spread in the wild. However, these goals are not mutually exclusive when we consider context; instead, they emphasize the inherent complexities of designing a gene drive that spreads well but only when and where we want it to spread. From modeling experience (Backus and Gross 2016; Backus 2017), we have reason to speculate that there is a trade-off between the ability of many gene drives to spread through a population on their own and our ability to control the spread of those gene drives. This paper focuses on this trade-off and the dangers of management approaches that might not account for the full range of biological contexts on gene drive spreading behavior. We argue that current uncertainties—at molecular and ecological scales—make balancing the trade-off between control and spread a risky proposition.

We begin by describing the trade-off between the long-term spreading behavior of two types of gene drives and the ability of a manager to control the spread. Next, we explain how the nonlinear nature of this trade-off could cause managers to be unprepared for starkly divergent outcomes, especially with uncertain ecological conditions. Using a conceptual example of a threshold-dependent synthetic *Medea* gene drive, we describe how a gene drive that might appear

safe could become highly risky when the uncertainty around this trade-off is ignored. Throughout this paper, we discuss this trade-off mostly in the context of standard gene drives, which spread indefinitely throughout most populations, and threshold-dependent gene drives, which only spread when they exist at frequencies above critical thresholds relative to the wild-type counterparts (both as defined by Min et al. (2018)). Because self-exhausting gene drives like Killer-Rescue (Gould et al. 2008) or Daisy-chain (Noble et al. 2019) systems are designed to be gradually lost from wild populations over time, they are unlikely to spread indefinitely.

Gene drive controllability

What makes a gene drive “controllable” or “safe” varies with context. In particular, stakeholder and cultural risk tolerance, economic costs, local ecological conditions, and genetics can change what is feasible and acceptable (NASEM 2016). Perhaps most simply, a controllable gene drive might be one that is designed to remain localized (Marshall and Hay 2012; Dhole et al. 2017; Marshall and Akbari 2018) or designed with the ability to halt and reverse spreading when necessary. For example, many gene drives could specifically be designed with modifications—like reversal and immunizing drives—that counteract undesired spreading if a gene drive disperses beyond its intended target population (Esvelt et al. 2014, Vella et al. 2017). However, these would require some level of monitoring, preparedness, and expectation that the gene drive could be present in a population. In these cases, controllability requires that managers of neighboring ecosystems would also need to be adequately informed and prepared for the potential risks of gene drives spreading. When these risks are greater and when there is higher potential of spreading beyond the target population, the costs and efforts that should be dedicated to countermeasures and monitoring would also increase.

Alternatively, the need for active control measures would be less demanding if there is negligible risk that a gene drive would spread into a non-target population in the first place.

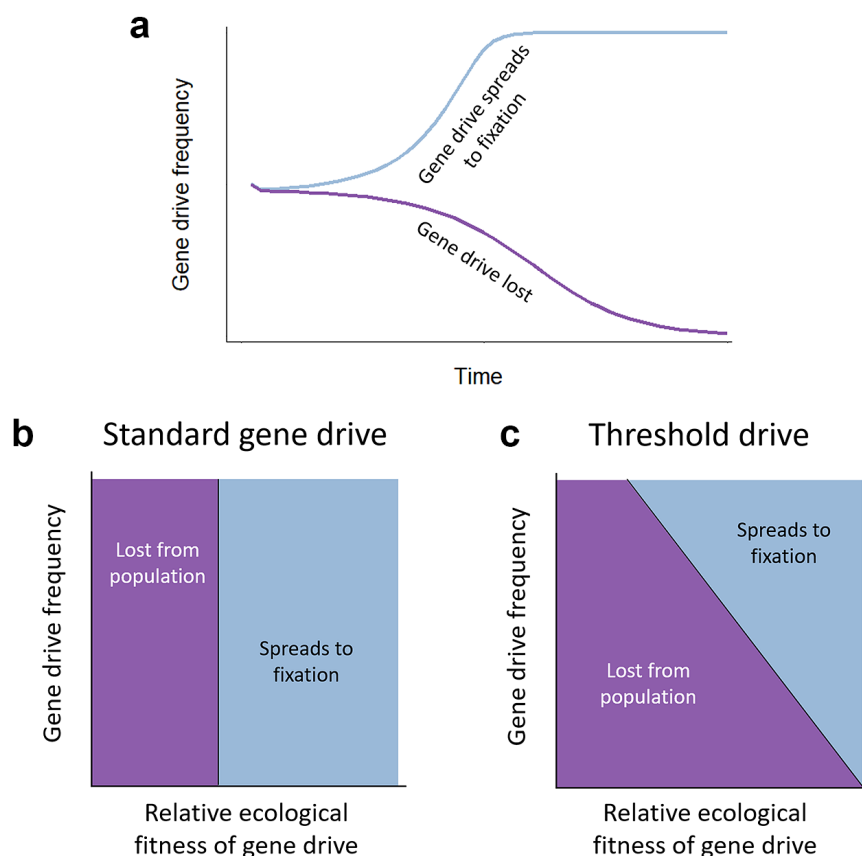


Figure 2. In standard and threshold gene drives, there are two general types of long-term dynamics that depend on frequency and fitness of the gene drive. All examples here are conceptual, not relating directly to any particular gene drive system. (a) Most gene drives will either spread to fixation or be lost from a population over time. (b) Regardless of frequency, standard gene drives spread to fixation with high relative fitness and are lost from a population with low relative fitness. (c) The long-term dynamics of threshold drives depend on both gene drive frequency and gene drive fitness. A threshold gene drive is more likely to spread with higher frequencies and lower fitness.

Therefore, we could argue that the ability to control a gene drive depends most strongly on the drive's expected long-term spreading behavior when and where it is not expected. With few exceptions, the spread of non-exhausting gene drives can follow two types of long-term dynamic patterns, which can change with gene drive fitness, frequency, ecology, and evolution. In general, gene drives with lower fitness are expected to be lost from a population over time and gene drives with higher fitness will spread to fixation (figure 2a). At some critical point in fitness, a gene drive can switch from one dynamic behavior to another.

Standard homing and meiotic gene drives would be difficult to control because they would spread to fixation through a population after a small number are released, as long as fitness costs associated with carrying the gene drive do not outweigh the inheritance advantage of the gene drive itself (figure 2b). While simple to implement, standard gene drives are difficult, if not impossible, to keep localized. If

even a small number of individuals emigrate from a target population or escape from a laboratory setting, they have the potential to spread to fixation wherever they arrive. Importantly, whether or not a standard gene drive spreads would depend on its fitness relative to the fitness of the specific local population. Therefore, just because a gene drive spreads in one population would not mean it spreads in all populations.

Alternatively, threshold (or frequency-dependent) gene drives might be considered more controllable, as they only spread to fixation if released into a population above some critical frequency (figure 2c). These include underdominance (Davis et al. 2001; Magori and Gould 2006; Reeves et al. 2014) and many synthetic *Medea*-like drives (Wade and Beeman 1994; Chen et al. 2007; Akbari et al. 2013; Akbari et al. 2014). When released into a population below that critical frequency, they should be lost over time. Since spreading dynamics depend on local population genetic frequencies, threshold drives could be easier to keep localized as long as there is limited gene flow between separate populations (Marshall and Hay 2012; Akbari et al. 2013; Buchman et al. 2018; Marshall and Akbari 2018). If this critical threshold frequency is substantially above 0, a small number of individuals carrying the gene drive dispersing to a new population should be unlikely to spread through its new population. Moreover, if managers want to reverse the spread

of the gene drive or remove a gene drive from any location, they could release enough wild-type individuals to push the population back below the critical threshold frequency (Akbari et al. 2013; Buchman et al. 2018). Importantly, critical thresholds depend partially on the gene drive's molecular construction, but also on the fitness of the individuals carrying the gene drive (Ward et al. 2010; Marshall and Hay 2012). In general, if there is a high fitness cost to carrying the gene drive, critical release thresholds would be high, but if the fitness cost is low, the thresholds can approach 0 (Ward et al. 2010). Again, these fitness costs are relative to the fitness of wild populations, so long-term spreading behavior can vary from population to population.

Unexpected dynamical shifts

While appealing from a controllability standpoint, threshold drives present a difficult trade-off. Since threshold values largely depend on gene drive fitness, developers could

influence these critical threshold frequencies by manipulating gene drive fitness costs. If critical threshold frequencies are too high, it would be logistically difficult and expensive to breed and release enough individuals for the gene drive to reach the critical frequency in all but a few small, isolated populations. On the other hand, low thresholds increase the chance that the gene drive could reach the critical frequency in neighboring non-target populations (Marshall and Hay 2012; Dhole et al. 2017). Thus, designing a threshold drive requires developers to balance how efficient or controllable they want the gene drive to be. For the sake of argument, we might consider a naïve, but straightforward, solution to this trade-off. That is, we might try to find a middle ground where a gene drive is fit enough to spread efficiently, but not so efficiently that countermeasures would prove difficult or impossible within a practical timeframe. This compromise might make intuitive sense if one imagines the relationship between gene drive fitness and controllability as linear: increasing spreadability simply decreases controllability in a proportional sense.

In contrast, relationships between gene drive efficiency and controllability could result in unexpected shifts in dynamical behavior. For both standard and threshold gene drives, theoretical models suggest that a small change in gene drive fitness would usually have a negligible impact on the spreading behavior of a gene drive, and thus have little impact on our ability to control the gene drive. However, in some situations, a small change in fitness could profoundly change the expected long-term dynamics. That is, there is a critical fitness threshold (in addition to frequency threshold in threshold-dependent gene drives) that could suddenly change dynamical behavior. When biological conditions are uncertain and difficult to predict, managers and developers could be unaware of these fitness thresholds, meaning that a gene drive that was originally envisioned to be localized might spread rapidly and uncontrollably throughout the entire range of the species if the threshold is lower than expected. Alternatively, a drive that might be designed to reach several subpopulations in a metapopulation might be restricted to a few subpopulations if the threshold is higher than expected. This type of sudden behavioral shift is characteristic of catastrophe theory, commonly discussed across many sciences, including ecology, genetics, and evolution (Scheffer et al. 2001). If ecological conditions could suddenly change a localized drive into an indefinitely self-propagating drive, the risk of accidental, uninhibited spread would likely outweigh any slight benefits of increased fitness.

Critical fitness thresholds offer a conceptual strategy to classify gene drives by spreading dynamics, but identifying these thresholds in practice would be far from straightforward because of the layers of uncertainty surrounding gene drives and ecology. As with most modeling insight, this threshold is apparent only through a substantial amount of abstraction and simplification. These limitations exemplify inherent structural uncertainty in our ability to predict long-term ecological dynamics. For example, seasonality,

predator–prey dynamics, mating dynamics, density dependence, stochasticity, and spatial structure are often taken for granted for the sake of simplicity (see variations in Deredec et al. 2011; Kaebnick et al. 2016; Eckhoff et al. 2017; Wilkins et al. 2018; Jansen et al. 2008, Tanaka et al. 2017 for more context), but we suspect that these dynamic processes might alter gene drive spreading patterns over time. Additionally, there will be some level of uncertainty around key biological parameters that govern the fitness of the gene drive. Parameters like gene drive inheritance rates might be somewhat precisely estimated from laboratory and simulated field trials, but realistic ecological conditions would be difficult to simulate in controlled environments. The ecological fitness of the gene drive will depend ultimately on the organism's survival ability (through foraging ability, predator avoidance, and lifespan), reproductive success (through sexual selection, fecundity, and fertility), and susceptibility to resistance (genetic, molecular, and behavioral), in addition to inherent randomness (Regan et al. 2002). Each of these biological components might independently reduce or favor the overall fitness of the organism. Thus, it will be difficult to confidently estimate long-term dynamics, especially as these uncertainties compound with one another.

Exploring uncertainty with a *Medea* drive

To demonstrate how ecological uncertainty can change expectations about gene drive spread, we consider a simple two-population variant of a model for a hypothetical synthetic *Medea* gene drive (see Akbari et al. 2014). This type of gene drive—found naturally on the *Tribolium* beetle (Beeman et al. 1992) with synthetic varieties for other species (Chen et al. 2007; Akbari et al. 2014)—links a gene that produces a toxin activated in mothers to a gene that produces an antidote activated as a zygote. Any offspring of a *Medea* mother that do not inherit a *Medea* gene drive will die. Therefore, heterozygotic mothers carrying the *Medea* gene drive will always produce offspring that carry the gene drive (though heterozygotic fathers do not have this constraint). When there are no fitness costs to carrying the *Medea* drive, the inheritance advantage drives the *Medea* drive to eventual fixation (Wade and Beeman 1994). However, with higher fitness costs, the *Medea* gene drive only spreads through a population if the frequency of *Medea* is above a critical threshold (Ward et al. 2010). These frequency thresholds also depend on migration rates, as gene flow of wild-type individuals from neighboring populations and dispersal of *Medea* away from the target population effectively reduces the local frequency of the gene drive (Marshall and Hay 2012). Other ecological and behavioral factors are also likely to influence spreading behavior further.

Even if fitness costs are high and migration is low, we argue that it could be risky to assume this *Medea* drive would remain localized. Though it is probably much more likely that ecological conditions would be unfavorable to gene drive carriers that migrate to new locations, we cannot ignore the possibility that ecology might instead favor

new immigrants. For example individuals that migrate from one population to another might introduce genetic diversity into a smaller, isolated second population. Therefore gene drives dispersing beyond a local population might temporarily have a relative fitness advantage because of frequency-dependent mating selection in favor of novel genotypes (Hughes et al. 2013), or they might benefit from offspring with hybrid vigor (Ebert et al. 2002) or other advantageous heritable traits carried over from other environments. To be clear, any of these advantages would be rare and quickly lost over time (if not closely linked to the *Medea* drive itself), but they could benefit the gene drive long enough to unexpectedly spread beyond the critical threshold. If a *Medea* drive is assumed to have a high fitness cost and this cost would only be higher in neighboring populations, developers might attempt to increase the genetic and ecological fitness of the gene drive while unaware of how close the gene drive is to threshold conditions given the ecological context.

Using figure 3, we demonstrate how relative ecological fitness, migration rates, and uncertainty can interact to result in three starkly different scenarios following the release of a *Medea* drive into the wild. Assuming the goal is to drive *Medea* to fixation locally in only one of two separate populations, we consider the release of enough males into the population so that 55% of males (post-release) are homozygous for *Medea* (figure 3a). Every generation, some percentage of individuals migrate bidirectionally. Individuals that carry *Medea* have some fitness cost. Over 200 generations, the relative fitness of *Medea* and the migration rate determines the long-term dynamics: whether the gene drive is lost from the system (under the critical threshold), spreads to fixation in only the target population (above the critical threshold in population 1), or spreads to fixation in both populations (above the threshold in both populations). In the first example of figure 3b, the triangle represents a *Medea* drive where individuals are expected to be only 75% as fit as their wild-type counterparts and migration occurs at a rate of 0.2% per generation. The ellipse around this point represents uncertainty in ecological conditions, caused by the inability to precisely estimate migration rates and relative fitness of organisms carrying the gene drive. Because gene drives usually impose an ecological fitness cost, we assume that there is a high chance that ecological fitness will be lower than expected, but there is also a small, but notable, chance that fitness could be higher than expected. If managers could be confident that the actual conditions fall somewhere within this ellipse, they would be fairly certain that the *Medea* drive would be localized, spreading to fixation only in the target population. In the second example of figure 3b, the solid circle could represent a *Medea* drive where developers might have further attempted to limit the fitness costs imposed on individuals carrying it, increasing the fitness to 90% of the wild-type counterpart. With the same amount of uncertainty as in the previous example, managers could not be as confident about the outcome after the *Medea* drive is released into the wild. In this case, even though fixation in only the

target population is the most likely outcome, there is some possibility that the ecological and behavioral context could cause the *Medea* drive to spread to fixation in the second population as well.

Even if threshold drives are restricted to islands or other seemingly isolated populations, humans have a long enough history of moving organisms, both intentionally and accidentally, that 0% migration cannot be guaranteed. If ecological conditions are uncertain and critical thresholds are not sufficiently high, managers of neighboring, non-target populations might not be prepared to react and counter a *Medea* invading their populations. Because a *Medea* drive with a fitness cost should be lost from a population when below a critical frequency, neighboring population managers would need access to additional wild-type individuals that they can introduce to counteract spreading dynamics. Whether this is feasible would depend on the quality of monitoring and whether there is access to breeding facilities. Moreover, it has already been suggested that early releases of self-propagating gene drives into the wild might explicitly incorporate additional genetic constraints to limit the scale of gene drive spread (Esvelt and Gemmill 2017), such as the use of locally fixed alleles (Sudweeks et al. 2019) or split drives (Champer et al. 2019) and daisy drives (Noble et al. 2019).

Because the spreading behavior of a gene drive is context dependent, it is also important to emphasize that a gene drive might shift dynamical spreading behavior as context changes over time. This shift is most evident with the evolution of resistance to gene drives (Champer et al. 2017; Marshall et al. 2017; Unckless et al. 2017; Kyrou et al. 2018; Champer et al. 2018a). For example, if a cargo gene linked to a *Medea* drive imposes an additional fitness cost to the organism, any mutations that inactivate or delete the cargo gene (but not the *Medea* itself) would rapidly spread through a population, outcompeting the original gene drive. Similarly, any genetically determined behaviors or mechanisms that reduce their likelihood to mate with individuals carrying the *Medea* drive would have a substantial fitness advantage over other females, increasing behavioral resistance over time (Bull 2017; Drury et al. 2017). Therefore, even if unexpected ecological conditions cause the *Medea* drive to reach critical threshold frequencies in neighboring populations, indefinite spread is likely to be temporary as long as resistance evolves and spreads in the long run. One important caveat to this is that eventual gene drive resistance is not equivalent to eventual gene drive absence. If evolved resistance occurs through the inactivation of the cargo gene but the rest of the drive remains intact, the resulting gene drive could spread through the population and remain indefinitely. While this would not have the same potential negative ecological impact as a non-mutated *Medea* drive spreading to fixation, it could carry negative social and cultural implications to affected publics (Esvelt et al. 2014; Noble et al. 2018).

Even if ecological conditions are unlikely to favor the long-term global spread of a threshold drive, the possible

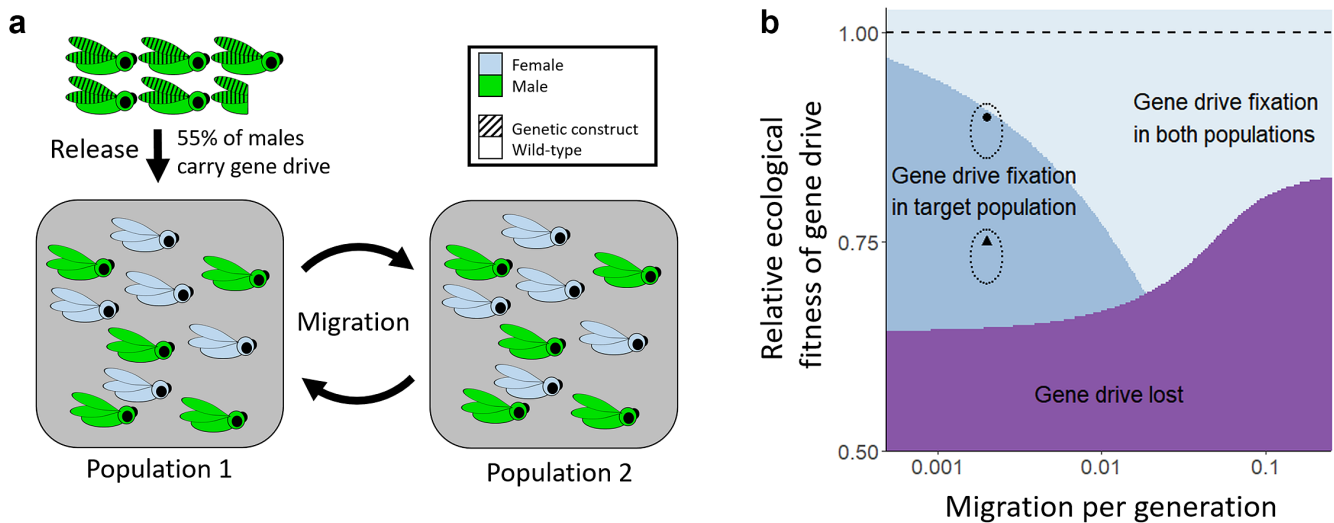


Figure 3. Example of long-term dynamics of a threshold-dependent *Medea* drive in a two-population system. The goal is to drive the *Medea* drive to fixation in one population without spreading to fixation in a neighboring population. (a) There are two populations, initially consisting of only wild-type individuals, and there is some bidirectional migration between the populations. Males that are homozygous for *Medea* are released into population 1 so that 55% percent of the males in population 1 will be carrying the *Medea* drive (roughly 1.22:1 ratio). Over several generations, these populations mate and migrate. (b) After 200 generations, the fate of the two-population system depends on the migration rate and the relative fitness of the gene drive. The filled circle and triangle represent two separate *Medea* drives that could be released into one population with an expected migration rate of 0.2% per generation. Ellipses around either point represent parameter uncertainty in both gene drive fitness and migration rates. Because gene drives are more likely to impose an ecological fitness cost on the organisms carrying them, there is a higher chance that ecological fitness would be lower than expected with only a small chance that ecological fitness is higher than expected. The triangle is a drive that was developed such that it has an expected relative fitness of 75% of wild-type counterparts. If the ecological dynamics of the system lie anywhere in the region of uncertainty, the gene drive will go to fixation in only the target population. The circle is a drive developed with a higher expected relative fitness of 90%. In this case, there is a small probability that *Medea* could drive to fixation in both populations.

ecological and social consequences of any unexpected spread beyond the local population could be severe. To avoid such surprises, we would instead advise that all gene drives, especially standard and threshold drives, should be developed with the recognition that local ecology, behavior, or other biological conditions, and not just genetics, could sometimes favor the gene drive. This perspective would advise developers and managers to be aware of and minimize uncertainty around situations where gene drives could disperse beyond target populations.

Navigating fitness, controllability, and uncertainties

There will always be uncertainty and error when estimating ecological conditions, so gene drive developers should acknowledge that long-term spreading behavior could differ from expectation. Uncertainty can shift the expected long-term model behavior, calling attention to the difficulty of knowing precisely whether the application of a particular gene drive in a given ecological environment will spread or not. At very high levels of uncertainty, it would be difficult to reliably assume that a particular gene drive is going to remain localized. Likewise, because a threshold drive could

fall below critical thresholds with some unexpected relative fitness cost, developers might plan for the need for repeated releases even when it is unlikely to be necessary, especially when failure is costly. Together, managers could account for this range of risks by preparing for all possible outcomes, especially when near threshold conditions. This assumption might make gene drives more difficult to implement, but could be a necessary precaution that could prevent unintentional ecological harm and economic costs. At the same time, we do not wish to discourage development and potential use of threshold drives, as they would be easier to control and would likely be more socially acceptable than standard gene drives (Min et al. 2018). Though we acknowledge that most previous suggestions that threshold drives could be localized have understandably been made with considerable caution (Marshall and Hay 2012; Akbari et al. 2013; Dhole et al. 2017), uncertainty in ecological dynamics might make acceptable parameter ranges for release too low to be practical in the near future (Jansen et al. 2008; Tanaka et al. 2017; Champer et al. 2018b).

These insights suggest two pragmatic agendas for gene drive research. First, although some of the most compelling

hurdles for developing gene drive technology revolve around overcoming the barriers of weak spreading potential (Unckless et al. 2017; Moro et al. 2018; Champer et al. 2018a), these barriers should be crossed with caution. Any research with the potential for environmental release, intentional or not, should include safeguards for all possible outcomes, ensuring that alternative control measures are readily available for neighboring populations. Second, modelers and ecologists must work together to characterize the uncertainties that might change the long-term spreading behavior of gene drives. Further research could help limit the number and severity of surprises during implementation, but we should also acknowledge that there will always be some level of irreducible uncertainty that we cannot predict. In the future, we may well improve accuracy and precision in our predictions about gene drives, but we should never confuse growing insight for perfect foresight. For now, while uncertainties remain large, we suggest moving research forward with humility, precaution (Kaebnick et al. 2016), and attention to the insights of models that challenge intuition.

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Supplemental material

Supplemental data are available at *BIOSCI* online.

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