

IDEAS AND PERSPECTIVE

Incorporating ecology into gene drive modeling

Running title: Eco-evolutionary gene drive modeling

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Statement of authorship

JK, PWM, GG conceived the study and supervised the project. KDH, IKK, SS simulated and analyzed the model. All authors contributed substantially to writing.

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Abstract

Gene drive technology, in which fast-spreading engineered drive alleles are introduced into wild populations, represents a promising new tool in the fight against vector-borne diseases, agricultural pests, and invasive species. Due to the risks involved, gene drives have so far only been tested in laboratory settings while their population-level behavior is mainly studied using mathematical and computational models. The spread of a gene drive is a rapid evolutionary process that occurs over timescales similar to many ecological processes. This can potentially generate strong eco-evolutionary feedback that could profoundly affect the dynamics and outcome of a gene drive release. We therefore argue for the importance of incorporating ecological features into gene drive models. We describe the key ecological features that could affect gene drive behavior, such as population structure, life-history, environmental variation, and mode of selection. We review previous gene drive modeling efforts and identify areas where further research is needed. As gene drive technology approaches the level of field experimentation, it is crucial to evaluate gene drive dynamics, potential outcomes, and risks realistically by including ecological processes.

KEYWORDS:

eco-evolutionary dynamics | population structure | non-Mendelian inheritance | population genetics | eco-evolutionary modeling

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1 INTRODUCTION

2 Gene drives are engineered genetic constructs that can quickly spread desired alleles through a wild population. Advancements
3 in genetic engineering have led to concerted efforts to develop gene drives for controlling disease vectors (such as mosquitoes)
4 (Sinkins and Gould, 2006; Adelman et al., 2017), invasive species (Dearden et al., 2018), and agricultural pests (Neve, 2018;
5 Legros et al., 2021). Recently, several proof-of-principle studies have demonstrated the successful spreading of engineered gene
6 drive constructs through laboratory insect populations (Kyrou et al., 2018; Champer et al., 2020b; Adolfi et al., 2020). Potential
7 gene drive applications typically have the following goals: (i) phenotypic modification of individuals in a population, such
8 as changing their ability to transmit a disease without significantly affecting their fitness (*modification drive*), or (ii) suppression/eradication of a population through intentionally reducing the fitness or skewing the sex ratio of the population (*suppression drive*).
10

11 Gene drive technologies can employ different mechanisms to generate rapid spread in a population. With CRISPR-based
12 homing gene drives, for example, the drive allele can convert heterozygous germline cells for the drive allele to homozygous
13 cells by cleaving a specified sequence on the wild-type homologous chromosome and then copying itself into that position.
14 As a result, the drive allele will be passed on to offspring at a super-Mendelian ratio, which generates an evolutionary force
15 that allows the gene drive allele to increase exponentially in frequency in the population (Figure 1A). In addition to homing
16 drives, there are several other possible drive mechanisms, such as sex-linked drives (Galizi et al., 2016; Prowse et al., 2019) and
17 underdominance systems (Davis et al., 2001; Akbari et al., 2013; Champer et al., 2020a); for further details about the different
18 types of gene drives and their molecular mechanisms, we refer readers to reviews by Champer et al. (2016) and Hay et al. (2021).
19 While these different types of drives rely on distinct genetic mechanisms, the evolutionary dynamics they induce can often be
20 quite similar. Here, we primarily consider the basic homing gene drive design, but our description of their dynamics pertains to
21 many other gene drive mechanisms that can spread exponentially from a low introduction frequency.

22 In general, evolutionary processes are affected by their ecological context yet since they typically occur over much longer
23 timescales than ecological processes, we can often consider these processes separately. However, when evolution occurs rapidly,
24 feedback between evolutionary and ecological processes can significantly affect the dynamics and outcomes. In order to understand
25 rapid evolutionary dynamics, both ecological and evolutionary processes therefore must be considered simultaneously.
26 Gene drive spread represents an extreme case of such a rapid evolutionary process because gene drives can in principle sweep
27 through a population within just a few generations (Windbichler et al., 2011; Simoni et al., 2014; Gantz et al., 2015; Unckless
28 et al., 2015; Kyrou et al., 2018). In this case, the timescales of the ecological and evolutionary processes involved can be similar,
29 potentially generating strong feedback between ecology and evolution generated that may influence the outcomes of gene
30 drive deployments and affect the development of successful and safe deployment strategies. This eco-evolutionary dependence
31 is reinforced when considering the strong demographic and ecological changes that suppression drives are expected to induce.
32 Consequently, ecological factors can crucially affect the evolutionary dynamics of a gene drive.

33 An important concern with this new technology is the risk of unintended consequences, such as the spillover of a drive from
34 the target population into non-target populations or species (Esveld and Gemmell, 2017; Noble et al., 2018; Courtier-Orgogozo
35 et al., 2020). Therefore, gene drives have only been tested in laboratory settings, and our expectations about their behavior in
36 natural environments is based primarily on mathematical and computational modeling. Such studies have provided important
37 insights into the expected evolutionary dynamics of gene drives, allowing us to predict how fast and under what parameters
38 a drive could spread through a population (Burt, 2003; Derec et al., 2008; Unckless et al., 2015). However, when deployed
39 into wild populations, the outcome of a gene drive release could also be strongly affected by the ecology of the population in
40 question (Dhole et al., 2020).

41 In this Perspective, we provide a comprehensive overview of the key ecological features that could affect gene drive behavior
42 (Figure 1B). We center our efforts on incorporating these features into mathematical and computational models to elucidate the
43 complex interplay between ecological and evolutionary processes shaping gene drive dynamics. Gene drive models typically
44 track the frequency of a drive allele and evaluate the conditions for its spread, as well as the temporal or spatial properties
45 of its dynamics (sometimes the evolution and dynamics of resistance alleles are also tracked). We therefore focus on how
46 different ecological factors (green in Figure 1B) can affect the evolutionary dynamics of a gene drive allele (within blue region
47 in Figure 1B) across time and space. To demonstrate eco-evolutionary interactions in gene drives, we present several toy models
48 that incorporate various ecological features, and we re-examine results from previously published models.

49 POPULATION STRUCTURE

50 Modeling population structure and the spatial aspects of gene drive behavior is key to preparing for the use of this technology in
51 natural populations, because there are still many uncertainties about how gene drives behave in geographically structured popu-
52 lations and how their spread could be limited and confined. Without a sound theoretical understanding, coupled by experimental
53 validation, it will be difficult for researchers to design safe deployment plans and for governments and regulators to approve
54 the use of gene drives (Rašić et al., 2022). While much progress has already been made in modeling gene drive dynamics in
55 structured populations (e.g., see Dhole et al., 2020), many open questions still remain.

56 One of the main risks involved in gene drive deployment is the potential for spillover to non-target populations or regions (Oye
57 et al., 2014; Webber et al., 2015; Noble et al., 2018). Once deployed in wild populations, the self-copying genetic mechanism of
58 the gene drive allows the drive allele to rapidly spread through the target population; the same mechanism, however, makes the
59 gene drive very difficult to confine to a restricted geographic location. Therefore, modeling and understanding the behavior of
60 gene drives in a *spatial context* is crucial. Current spatial models seek to understand the spatiotemporal behavior of different gene
61 drives under different genetic mechanisms or ecological scenarios, and thereby aim to develop potential strategies for mitigating
62 the risks of spillover by determining conditions under which the spatial localization of the gene drive can be attained (Champer
63 et al., 2020c; Greenbaum et al., 2021; Harris and Greenbaum, 2022).

64 An important spatial aspect to consider is the meta-population behavior that would be initiated by suppression gene drives
65 in which populations become extinct due to the spread of the gene drive and the fitness burden it induces, but the regions they
66 occupy may subsequently be colonized by other populations. Extinction-colonization dynamics have been extensively studied
67 in ecological theory (Hanski, 1994; Hanski et al., 1999; Hanski and Gaggiotti, 2004), but have not yet been substantially incor-
68 porated into gene drive models. Migration dynamics in which the gene drive phenotype affects traits related to dispersal could
69 also influence the outcomes of gene drive dynamics (Runge and Lindholm, 2018, 2021). These spatial dynamics are expected
70 to generate eco-evolutionary feedbacks that would affect the spatial behavior of the gene drive and spillovers. Investigating
71 these dynamics would require modeling of dispersal evolution (Comins et al., 1980; Hovestadt et al., 2001; Murrell et al., 2002;
72 Greenbaum et al., 2022) in relation to gene drive spread.

73 The simplest model that incorporates population structure is, arguably, the discrete two-population model: a target popula-
74 tion within which the gene drive is released at an initial frequency, and a non-target population that is connected to the target
75 population through migration into which the gene drive might be transmitted and spread (Figure 2A). While this setup is highly
76 simplistic and often hardly realistic, it can serve as a tractable model for understanding the basic behavior of gene drives in a
77 spatial context, and may relate to scenarios where deployment is considered on an island or in an isolated region that is weakly
78 connected to the main range of the species. In this simple model, several types of behaviors can already be observed. Depending
79 on the type of drive and its parameters (such as its fitness cost, dominance, and conversion efficiency), the drive may not man-
80 age to spread in the target population, and consequently there is no spillover to the non-target population (*Failure* in Figure 2A).
81 In other cases, the gene drive spreads in the target population and always spills over to the non-target population, regardless of
82 how low the migration rates are (*Spillover* in Figure 2A). This occurs when the gene drive is always expected to increase in fre-
83 quency regardless of its frequency in the population. However, for threshold-dependent drives (i.e., drives that are only expected
84 to increase in frequency when present above their threshold frequency and decrease when below it), it is also possible that the
85 drive can spread in the target population while remaining at a low frequency in the non-target population (*Only target affected*
86 in Figure 2A). This behavior is typically restricted to cases in which the migration rates between the populations are fairly low
87 (below $m \approx 0.1$ in the model in Fig. 2A, but to achieve some robustness in parameter specifications typically below $m \approx 0.01$;
88 see Greenbaum et al. 2021). The simple two-population model therefore already illustrates the possibility of confining a gene
89 drive to a certain geographic location through tuning of the genetic parameters and mechanism of the drive (see examples in
90 Tanaka et al., 2017; Noble et al., 2018; Willis and Burt, 2021; Greenbaum et al., 2021; Harris and Greenbaum, 2022; Beaghton
91 and Burt, 2022; Gamez et al., 2021; Champer et al., 2020b).

92 With additional features added to this simplistic model, other types of gene drive behaviors can emerge. For example, when
93 explicitly adding demography to the two-population model, transient demographic bottlenecks or oscillations in population sizes
94 and gene drive frequencies may emerge (Harris and Greenbaum, 2022) (Figure 2A). These behaviors are caused by feedback
95 between the gene drive spread, demographic suppression caused by the gene drive, and migration rates. This example emphasizes
96 that incorporating eco-evolutionary feedbacks, even in simple models, can qualitatively change our understanding of gene drive
97 dynamics, and provide ideas for ways to mitigate spillover risks.

4

98 While discrete two-population models can already demonstrate several important principles of the effects of population struc-
99 ture on gene drive dynamics, it is often necessary to employ discrete multi-population models or continuous space models to
100 understand the spatial behavior of gene drives. For example, using the classic stepping stone model (Kimura and Crow, 1964),
101 one can demonstrate the relative effects of spatial short-distance dispersal and non-spatial long-distance dispersal on gene drive
102 spread. To demonstrate this, we present a stepping stone model that also integrates long-distance dispersal (Figure 2B). In this
103 toy model, short-distance dispersal rates determine the speed of the gene drive wave-front as it spreads through space. However,
104 even extremely small amounts of long-distance dispersal can qualitatively change the spread dynamics, generating a critical
105 threshold beyond which the gene drive overtakes the entire population very rapidly (dashed lines in Figure 2B). This toy model
106 demonstrates how elaborating classic models of population structure can be instructive on elements that could substantially alter
107 gene drive spread dynamics. Understanding these spatial behaviors is critical for evaluating the potential for spatially localized
108 gene drives, and for designing pre- and post-release monitoring programs (Rašić et al., 2022).

109 When the population structure is complex (e.g., high variability in connectivity between populations), it is also crucial to
110 consider the position of the target population in relation to the entire population structure. For example, it is important to under-
111 stand whether targeting central or well-connected populations changes the spread dynamics, compared to targeting peripheral
112 populations. To address these questions, which involve more complex and more realistic spatial organizations, network models
113 of population structure may be appropriate (Greenbaum and Fefferman, 2017). To demonstrate this point, we investigate a toy
114 model in which population structure is represented as a network (Fig. 2C). We compare the dynamics when deploying identical
115 gene drives in a peripheral population (orange in Fig. 2C) with deployment in a central population (purple). While most pop-
116ulations are rapidly overtaken by the gene drive allele when the release site is central, only a small fraction of populations are
117 affected when deployment is peripheral.

118 In addition to tracking the allele frequencies of the gene drive in space, these discrete spatial models are also useful for
119 understanding the spread of emerging resistance alleles, and for evaluating the risks that these would impede the spread of
120 the gene drive and become fixed in populations (Noble et al., 2018). Population structure can affect the critical population
121 size required for resistance alleles to emerge (Khatri and Burt, 2022), while the level of gene flow between populations is
122 expected to impact the spread of resistance alleles, similarly to its impact on gene drive spread. Higher gene flow can also
123 increase the generation of resistance alleles: non-homologous end joining (NHEJ) events can generate alleles that block the
124 CRISPR conversion mechanism by altering the target sequence. The likelihood of these events is dependent on the frequency
125 of heterozygotes (Unckless et al., 2017), which increases as a function of gene flow (Harris and Greenbaum, 2022). Thus,
126 considering both topology and the level of gene flow is important for understanding how certain types of population structure
127 could increase the probability of resistance alleles emerging.

128 Continuous-space models provide an alternative modeling framework for understanding the spatiotemporal dynamics of gene
129 drive spread. One particularly useful approach has been the analysis of reaction-diffusion equations to describe the spatial
130 dynamics of gene drives (Beaghton et al., 2016; Tanaka et al., 2017; Girardin et al., 2019; Girardin and Débarre, 2021), in which
131 the properties of gene drive “waves” can be studied analytically under different conditions (Tanaka et al., 2017). This has pro-
132 vided key insights into the necessary release thresholds of underdominance gene drives (Barton and Turelli, 2011), how the
133 wave speed changes with the gene drive mechanism (Tanaka et al., 2017; Paril and Phillips, 2022; Girardin and Débarre, 2021),
134 how the thickness of the wave impacts a suppression drive’s ability to eliminate a population (Paril and Phillips, 2022; Champer
135 et al., 2021), and how an artificial intervention barrier can block a gene drive wave (Girardin et al., 2019). Continuous-space
136 individual-based simulation models can incorporate more ecological features than analytical models and provide another promising
137 approach for investigating the spatial behavior of gene drives. These models display interesting outcomes (see examples in
138 Box 1), including dynamics that can be equated with extinction-colonization processes.

139 DEMOGRAPHIC DYNAMICS

140 Population size affects evolutionary processes and allele frequencies in many ways, such as through genetic drift and the rela-
141 tionship between selection and the effective population size. Evolutionary processes may also affect the population size, for
142 example through the fixation of adaptive or deleterious alleles. There are a number of aspects of demography that can be con-
143 sidered in modeling gene drive spread, including the population sizes prior to deployment, of the target population as well as
144 neighboring non-target populations, and the demographic effects of the gene drive itself as it spreads. The latter is of particu-
145 lar importance in suppression gene drives, which are designed to reduce growth rates and are expected to generate substantial

¹⁴⁶ demographic changes at the same timescale as the evolutionary dynamics of gene drive spread. Therefore, eco-evolutionary
¹⁴⁷ feedback between the changes in allele frequencies and changes in population sizes can shape the dynamics and outcomes of
¹⁴⁸ deployment (Girardin and Débarre, 2021; Kläy et al., 2022; Beaghton and Burt, 2022).

¹⁴⁹ Although the integration of demography into models can have a crucial effect on outcomes, the role of demography in the
¹⁵⁰ model is often dictated by the modeling approach and model design (Dhole et al., 2020). Early gene drive models focused
¹⁵¹ more on understanding the evolutionary spread of the gene drive in a single population (Burt, 2003; Derec et al., 2008),
¹⁵² while the demographic effects of the gene drive were considered as the reduction in growth rate caused by the gene drive
¹⁵³ (Derec et al., 2008). These models explicitly assume that demography will be influenced by the spread of the gene drive, but
¹⁵⁴ do not consider feedback from demographic changes to the evolutionary dynamics. This modeling approach is consistent with
¹⁵⁵ subsequent population genetic models of gene drive spread that attempt to identify evolutionary equilibria of the gene drive
¹⁵⁶ allele (Unckless et al., 2015; Greenbaum et al., 2021). Other modeling approaches, such as agent-based models (Noble et al.,
¹⁵⁷ 2018; Champer et al., 2020c) and reaction-diffusion systems (Beaghton et al., 2016; Tanaka et al., 2017), incorporate and track
¹⁵⁸ demographic changes directly. These approaches implicitly view evolutionary dynamics as a product of the interaction between
¹⁵⁹ the evolutionary spread of the gene drive and its demographic effects.

¹⁶⁰ Another perspective through which modeling the demographic effect of a gene drive can be viewed is the distinction between
¹⁶¹ soft and hard selection (Bell et al., 2021). Under soft selection, changes in the frequency of the allele depend only on its relative
¹⁶² fitness, and not on population size or density. Consequently, soft selection models (e.g., Derec et al. 2008; Unckless et al.
¹⁶³ 2015) only require tracking of the allele frequencies, and are therefore typically simpler and more tractable than hard selection
¹⁶⁴ models. In such models, demographic effects are considered a secondary effect caused by the spread of the gene drive. In hard
¹⁶⁵ selection models, on the other hand, the fitness of the gene drive allele directly affects individual survival.

¹⁶⁶ In modification gene drives, where the goal is typically not to induce a demographic effect but rather to simply spread the
¹⁶⁷ modifying allele, soft selection models are often appropriate. On the other hand, hard selection models are better suited for
¹⁶⁸ modeling suppression gene drives. This dichotomy, however, does not capture the full complexity of selection operating during
¹⁶⁹ gene drive deployment. In the initial phase of deployment, while the population is close to carrying capacity, the spread of
¹⁷⁰ the gene drive should depend primarily on the relative densities of the genotypes (i.e. individuals in the population will still
¹⁷¹ be in direct competition). Thus, during this phase, hard selection models should behave similarly to soft selection models. As
¹⁷² the population collapses, the reduction in population density can lead to decreased fitness through Allee effects (see Box 1), or
¹⁷³ altered gene flow in and out of the collapsing population (Harris and Greenbaum, 2022). This can, in turn, alter the evolutionary
¹⁷⁴ trajectory, leading to the collapse of the population, loss of the gene drive, or long-term persistence at an intermediate frequency.
¹⁷⁵ This transition from soft to hard selection over a short time scale complicates coherent modeling of the connection between the
¹⁷⁶ demographic and the evolutionary behaviors of gene drives, and demonstrates that more nuanced treatment of selection modes
¹⁷⁷ may be needed (Start, 2020; Bell et al., 2021).

¹⁷⁸ A sensible modeling approach to address this issue, perhaps, is to adopt more flexible modeling frameworks that can incor-
¹⁷⁹ porate a spectrum between hard and soft selection (Start, 2020; Bell et al., 2021). With tunable parameters that determine the
¹⁸⁰ mode of selection, it is possible to investigate the extent to which hard selection modeling is crucial in determining the out-
¹⁸¹ comes of gene drive deployment, and to identify where soft-selection modeling is sufficient (Harris and Greenbaum, 2022). For
¹⁸² instance, it is possible to model both evolutionary and demographic dynamics, tracking allele frequency and population size,
¹⁸³ and allow for different levels of interaction between these dynamics (as demonstrated by the toy model in Figure 2A lower-right
¹⁸⁴ panel). Another useful approach for modeling hard and soft selection is to accompany mathematical models with comparable
¹⁸⁵ individual-based simulation models. In individual-based models, fitness effects can become emergent properties of the sim-
¹⁸⁶ ulation rather than being explicitly modeled. Consequently, the mode of selection may change throughout the simulation, based
¹⁸⁷ on the ecological circumstances. Interaction between different selection pressures, such as the gene drive fitness effects coupled
¹⁸⁸ with predator-prey interactions, can also be relatively easily modeled (Liu et al., 2022). While individual-based models are less
¹⁸⁹ tractable than mathematical or simplified computational models, they may help to identify whether assumptions regarding the
¹⁹⁰ mode of selection are important in model interpretation.

¹⁹¹ ENVIRONMENTAL VARIATION

¹⁹² Evolutionary processes are affected by the environment in many ways, most notably through natural selection. Environmental
¹⁹³ variability, both temporal and spatial, can affect both the outcome and the spatiotemporal dynamics of evolutionary processes

(Débarre and Gandon, 2011; Bell et al., 2021). Therefore, changes in the expression and fitness cost of the gene drive allele due to environmental variation are important to model (Eckhoff et al., 2017). Many environmental factors could potentially affect the phenotypic expression of the gene drive allele, including abiotic factors such as temperature or presence of chemicals, and biotic factors such as food availability or presence of parasites, endosymbionts, and predators. When these environmental factors vary in space and time, the selection pressures and fitness costs affecting the gene drive allele will also vary.

Natural habitats are typically spatially heterogeneous in environmental conditions. This heterogeneity can affect the speed and characteristics of the spread of gene drives. We demonstrate this point by presenting an analysis of a toy model in Figure 4. This model is a simple elaboration of the stepping-stone model from Figure 2B, in which spatial heterogeneity is modeled as variability in the fitness cost imposed by the gene drive (s). For each population in the stepping-stone grid, s is sampled from a normal distribution with mean $\mu = 0.5$ and different standard deviations σ . This sampling of selection costs reflects different selection pressures experienced in different locations due to different local environments, and the variation of the sampled distribution reflects the level of environmental variation. We modeled a simple homing gene drive (as in Derec et al., 2008; Unckless et al., 2015). Analysis of the model shows that the gene drive spreads more rapidly and farther as the environmental variability is increased (Figure 4). The explanation for this behavior is that, when the fitness cost varies, the gene drive can spread faster through regions in which the fitness costs are relatively lower, and therefore arrive at peripheral locations faster. In other words, the gene drive can travel through “paths of low resistance” (lower fitness costs) in the landscape that are generated by environmental variability.

There are many ways in which this variability can be modeled, and different types of gene drives may respond differently to such variability, and these could be investigated in detail using similar modeling frameworks to the one we present here. In addition, the example in Figure 4 demonstrates how small refinement of existing models can greatly increase the scope of model outcomes and our understanding of the relationship between ecology and evolution in gene drive spread. Importantly, because most empirical studies of gene drives are conducted under presumably optimal environmental conditions, we have little empirical data on the behavior of gene drives under different environmental conditions; empirical studies under non-optimal but realistic conditions could provide important input as to the parametrization of environmental variation models.

Environmental variability between populations also has implications for spillovers. When the environment varies between two populations, the likelihood of spillover and the speed of spread may be affected by differential fitness costs (e.g., Figure 5, treating the two species as two populations). An aspect we have not considered in our simple models is temporal environmental variation, which could affect gene drive dynamics and outcomes as well. Temporal environmental changes can be regular and expected such as seasonal changes, but may also be random or idiosyncratic, which could be modeled in a similar manner as in Figure 4.

The presence of natural environmental variation further complicates the planning of gene drive releases by introducing an additional level of uncertainty to gene drive outcomes. However, artificially induced environmental variation affecting gene drive behavior could also be used advantageously. For example, it is conceivable that induced changes in the fitness cost of a suppression gene drive could be used to reverse the spread of the drive or to create a spatial barrier to its spread. Because spatial containment of gene drives, prevention of spillovers, and induced reversal of gene drive spread are important potential control measures, such induced environmental effects on gene drives have received some attention (e.g., Tanaka et al., 2017; Marshall and Akbari, 2018; Girardin et al., 2019). For instance, gene drives have been designed to produce sensitivity or resistance to a specific chemical or cue, which can be intentionally introduced into the environment (Chae et al., 2020; Vella et al., 2017; Eckhoff et al., 2017). If a gene drive is designed such that the presence of the chemical significantly increases the fitness costs associated with the drive allele, to the extent that it can no longer spread, such an induced environmental effect could be deployed locally to generate a barrier to the spread of the gene drive, or globally to reverse its spread. The potential for control of gene drive spread using this approach can be assessed through modeling; an analytical model that demonstrated the use of such mechanisms and considered spatial differential fitness cost has shown that inducing a non-continuous lethal region can prevent gene drive spillovers (Tanaka et al., 2017). In this case, however, the barrier works only for a narrow range of parameters and depends on the width of the gaps in the barrier. An interesting idea to induce spatial heterogeneity studied by mathematical modeling is releasing a gene drive and a genetic antidote drive in different spatial configurations (Girardin et al., 2019). This can generate a spatiotemporal predator-prey-like relationship, which could lead in some cases to coexistence of the gene drive allele and the antidote, and could potentially lead to an evolutionary arms-race between the gene drive and the antidote.

Environmental heterogeneity can also be used to control gene drives through temporal rather than spatial mechanisms. For example, heat-sensitive gene drive designs can generate a “temporal barrier”, which could be delayed or reversed with seasonal temperature changes (Oberhofer et al., 2021). Natural endosymbiont systems that have temperature-dependent phenotypes could

provide insights into important parameters and features to be incorporated into models of such phenomena. An additional possibility for the design of reversible gene drives is to generate a reduction in the conversion efficiency of the gene drive, rather than (or in combination with) an increase of the fitness cost in response to an environmental cue (Heffel and Finnigan, 2019). In other words, a genetic element that under certain environmental conditions would function as a drive, but under different conditions would not, or even serve as an “anti-drive” that favors inheritance of wild-type alleles. Such genetic constructs, as well as other constructs designed to contain the spread of gene drives such as “daisy chain” and “antidote” constructs (Vella et al., 2017; Marshall and Akbari, 2018; Dhole et al., 2019; Girardin et al., 2019; Heffel and Finnigan, 2019), are difficult to implement genetically or remain theoretical at this point, yet could provide key additional layers of safety and control in potential gene drive deployments. Models that integrate environmental variation are obviously critical for studying the effects of these novel gene drive designs.

255 MATING SYSTEM

256 Homing gene drives propagate in the population through conversion of heterozygous individuals into gene drive homozygotes.
257 Consequently, the effectiveness of gene drives depends on the manner in which heterozygotes are formed in the population,
258 and thus on the mating system of the organism in question (Leftwich et al., 2015; Sutter et al., 2021; Verma et al., 2023). In
259 cases where the drive allele is associated with some phenotypic characteristics that mate selection is acting on, through direct
260 expression or due to genetic linkage to the trait loci, fewer heterozygotes would be generated, and the number of conversion
261 events will be reduced. This can slow down the spread of the gene drive or even reverse its direction and lead to loss of the gene
262 drive allele. Indeed, for some naturally occurring gene drives, species have evolved to avoid mating with drive-carriers if they
263 can be reliably detectable through a specific trait (Lenington, 1991; Wilkinson et al., 1998). Despite having theoretical support
264 (Lande and Wilkinson, 1999; Reinhold et al., 1999; Manser et al., 2017b), empirical evidence for mate avoidance of natural drive
265 carriers is limited (Price and Wedell, 2008). Whether a population could evolve to detect and behaviorally reduce transmission
266 of a synthetic gene drive thus remains largely unknown. Given the timescale in which the gene drive spreads, an evolutionary
267 response in mating behavior needs to occur rapidly before the gene drive is fixed in order to affect gene drive dynamics. Therefore,
268 an evolutionary change in mating behavior is expected to be significant only if the genetic basis of the mating behavior has
269 sufficient (narrow-sense) heritability. A detailed understanding of the target population’s mating biology and identifying mating
270 traits that can be exploited for control could provide an effective gene drive design strategy; for example, a gene drive can be
271 engineered to manifest traits known to confer higher mating preference and thus mating success with wild-type individuals.

272 Drive-carrying males are often substantially compromised in their sperm competitive ability, and thereby paternity, due to
273 reduction in sperm number and quality (Haig and Bergstrom, 1995; Price and Wedell, 2008; Verspoor et al., 2020). In polyandrous
274 species, sperm competition alone can hinder the spread of the drive allele even in the absence of a mechanism for mate
275 choice (Wedell, 2013; Manser et al., 2020). Assuming the female’s mating success is determined as a function of the total num-
276 ber (or above a set threshold) of high fitness sperms, wild-type females can develop behavioral resistance by increasing their
277 rate of remating, which would reduce the transmission of the gene drive allele to the next generation. In response to a gene
278 drive, the mating system can evolve rapidly (e.g., within ten generations in a laboratory population (Price et al., 2008)) due to
279 the fitness cost of disrupted reproduction, especially with polyandry being a heritable trait (Haig and Bergstrom, 1995; Travers
280 et al., 2016). The number of rematings, however, cannot increase indefinitely. As the system evolves, the drive-carrying male
281 frequency and the sex ratio can change (especially for sex-ratio distorter drives); therefore, the evolution of polyandry and the
282 changes in mating rate over time require careful modeling efforts.

283 In wild populations, natural drive frequencies are usually observed to be lower in populations with polyandry than in pop-
284ulations with monoandry (Pinzone and Dyer, 2013; Wedell, 2013). This suggests that polyandry can protect populations from
285 extinction caused by gene drives (Price et al., 2010b). For example, the high rate of female remating in wild house mice has
286 been shown to limit the spread of *t* haplotype both in a controlled laboratory experiment (Manser et al., 2017a) and in a wild
287 population (Manser et al., 2020). However, whether polyandry, and other mating behaviors in general, has evolved in response
288 to natural drives and its interaction with other ecological or demographic factors requires further investigation.

289 Males can also evolve mitigation strategies against the reduced sperm competitive ability. Counteracting the evolution of
290 polyandry in females, non-drive carrying males can evolve reproductive traits that prevent females from remating (Price et al.,
291 2010a). Further, to compensate for the decrease in the sperm-competitiveness, the drive-carrying males can evolve to increase
292 their sperm production (Meade et al., 2019, 2020). The complex dynamics of coevolution of male and female mating and

reproduction strategies, sexual conflict, and sexual selection in the presence of gene drives requires more extended modeling. Incorporating evolutionary game theory (Simmons, 2001; Wedell et al., 2002; Parker and Pizzari, 2010) into gene drive modeling frameworks can be a fruitful approach for understanding such dynamics.

Two additional key mating choice behaviors that can potentially impact gene drive spread deployment strategies are inbreeding and assortative mating. Many of the proposed target species for a gene drive release display high levels of inbreeding (e.g., mosquitoes (Vazeille et al., 2001) and mice (Laurie et al., 2007)), which reduces the likelihood of mating between individuals with different genotypes, and specifically between wild-type individuals and gene drive-carrying individuals. Because the spread of gene drives requires heterozygotes, even a small level of inbreeding can significantly hinder gene drive propagation (Drury et al., 2017). Due to the fitness cost of gene drives, it is possible that a mating system that favors inbreeding will evolve as a response to the gene drive, allowing the wild-type allele to persist; strong inbreeding depression, however, can remove the fitness advantage of inbreeding and enable the spread of the gene drive (Bull, 2017; Bull et al., 2019). Modeling efforts have shown that these results are generally consistent across multiple gene drive architectures and parameters (Beaghton and Burt, 2022), species modeled (Drury et al., 2017; Faber et al., 2021; Grawelle et al., 2021), and spatial population structure (Champer et al., 2021).

Applications of gene drives have, thus far, focused mostly on diploid species, and opportunities in haplodiploid target species have not been explored in depth despite their prevalence among invasive species (McLaughlin and Dearden, 2019). For randomly mating haplodiploid populations, a modeling study suggests that while gene drive spread can occur, the speed of population suppression is greatly reduced and the resistance to the drive arises faster compared to diploid populations (Li et al., 2020). In contrast, nearly neutral or beneficial drive alleles can spread in haplodiploid populations at a level similar to that in diploid populations. Because haplodiploid species often display high levels of inbreeding (de la Filia et al., 2015), gene drives for haplodiploid populations are expected to exhibit further complexities, therefore requiring further theoretical study to understand their feasibility.

In addition to inbreeding, assortative mating is another important factor to consider in terms of its effects on gene drive spread. Assortative mating has been observed in many target species; for example, *Anopheles gambiae* displays assortative mating with regard to body-size (Maiga et al., 2012; Diabate and Tripet, 2015; Callahan et al., 2018), and wild rodents exhibit preferential mating behavior based on olfactory preference (Lenington, 1991; Manser et al., 2015). Under standard Mendelian inheritance, assortative mating alone does not alter allele frequencies over time (Jennings, 1916; Fisher, 1919; Wright, 1921), but only increases the population variance of the property on which the assortment is based (Crow and Felsenstein, 1968; Felsenstein, 1981). In general, assortative mating on a trait that is linked to the gene drive allele will reduce the occurrence of heterozygotes, because wild-type homozygotes will preferentially mate with other wild-type homozygotes rather than with gene drive homozygotes (or heterozygotes, unless the gene drive allele is recessive). This reduction in the heterozygotes in the population, relative to random mating, reduces the opportunities of the gene drive to convert heterozygotes to gene drive homozygotes, and therefore reduces the rate of spread of the gene drive. With dissassortative mating on a trait linked to the gene drive, the opposite would be true, and the gene drive is expected to spread faster.

In threshold-dependent gene drive systems (Hay et al., 2010; Ward et al., 2011; Dhole et al., 2018; Champer et al., 2020c), assortative mating can affect the threshold frequency (Huang et al., 2010; Khamis et al., 2020). For example, in a target species where age is an important factor of mating success, such as in *Aedes aegypti* (Sawadogo et al., 2013; Diabate and Tripet, 2015), ignoring the age-dependent mating preference can introduce biases in estimating the introduction threshold (Huang et al., 2009). In general, in the presence of assortative mating by age, the introduction threshold is highest when releasing old females because of their low fecundity, and lowest for young adults due to their high reproductive potential. In addition, single-age releases of only males can significantly hinder the spread of a gene drive compared to bi-sex releases due to the limited mating between the wild-type females and the introduced males (Huang et al., 2009, 2010). Further studies are also needed on how the gene drive dynamics interact with other evolutionary processes known to be affected by mate choice, such as hybrid speciation (Irwin, 2020), adaptive introgression (Chen and Pfennig, 2020), genetic swamping (Todesco et al., 2016), and reproductive isolation (Schumer et al., 2015).

337 LIFE HISTORY

338 Broadly, there are three key life stages in which the spread of the gene drive can be affected: gamete, zygote, and adult (Verma
339 et al., 2021). The primary effect of the mating system is at the adult stage, but it can also affect both the gametic and zygotic
340 phases through fertility selection (Verma et al., 2023). At what stage of the life cycle a gene drive acts and where its fitness costs

manifest can play an important role in the successful propagation of a gene drive (Deredec et al., 2008; Rode et al., 2019), as well as in the potential confinement of the drive allele to a target population in structured populations (Champer et al., 2020c; Greenbaum et al., 2021). For example, in a reaction–diffusion model with a driving-Y chromosome, the speed of the gene drive allele spread is reduced in the presence of a juvenile stage (in which insects are typically relatively immobile) and displays strong dependency on the relative duration of juvenile and adult life stages when coupled with mating system (Beaghton et al., 2016). Therefore, failure to incorporate life stages along with population structure can lead to an underestimation of important parameters, such as the introduction threshold in underdominance drives (Sánchez C. et al., 2020). The evaluation of relative fitness costs of the early-life traits and late-life traits and their interaction with other ecological factors can guide more effective population management strategies along the life cycle. Gene drive models incorporating many life history traits of target species have been extensively studied; for a comprehensive review, see Godfray et al. (2017).

A life stage that is important but understudied for gene drive applications is dormancy. Under environmental fluctuations, many organisms utilize reversible dormant states or “seedbanks” (Lennon and Jones, 2011). This life-history strategy results in age-structured populations and overlapping generations. Because of the existence of a metabolically inactive dormant state, mildly deleterious alleles can persist in a population for an extended period, reducing the rate of evolution and the efficiency of selective forces. When favorable reproductive opportunities arise and the dormant population is reactivated, the standing genetic variation of the population from the dormancy period can accelerate adaptive evolution, and in turn affect the dynamics and long-term stability of the population (Lennon et al., 2021). The seedbank, therefore, modifies the fundamental evolutionary and ecological forces acting on the population and acts as an evolutionary buffer for maintaining diversity under natural and anthropogenic disturbances (Cohen, 1966; Evans and Dennehy, 2005). Such a bet-hedging strategy can profoundly influence genetic diversity (Ellner and Hairston, 1994; Hedrick, 1995; Hairston and Kearns, 2002; Koopmann et al., 2017), demography (Rubio de Casas et al., 2015), recombination (Shoemaker and Lennon, 2018), and reproductive and migration rates (Tellier et al., 2011; Buoro and Carlson, 2014; Heinrich et al., 2018; Blath et al., 2021). Even in the absence of selection, the seedbank reduces the effect of genetic drift and can change patterns of genetic diversity and population demography (Kaj et al., 2001; Blath et al., 2015, 2020). With the increased interest in the application of gene drives to organisms with dormancy traits, such as many plants (Neve, 2018; Siddiqui et al., 2021), fungi (DiCarlo et al., 2015; Yan and Finnigan, 2018; Halder et al., 2019; Pennisi, 2020), bacteria (Valderrama et al., 2019), and animals (Wilsterman et al., 2021), it is crucial to consider how dormancy affects gene drive dynamics. Despite its importance and relevance, this ecological trait has so far been almost ignored in gene-drive modeling.

Proof-of-concept modeling studies of annual weeds have shown how a single life history trait of dormancy alone can have a significant impact on the success of gene drive spread for weed control (Barrett et al., 2019; Legros and Barrett, 2022). Under idealized conditions, simulation results showed that the presence of a seedbank substantially diminishes the fitness impact of the gene drive and thus increases the time to reach population suppression. Accordingly, the rate of gene drive spread depends on the duration of the seed dormancy. These results are in line with the view that dormancy acts as an evolutionary buffer for a population under selective pressure. Therefore, in addition to influencing the spread of the gene drive, dormancy can impede the evolution and spread of resistance alleles (Barrett et al., 2019).

While dynamics of gene drives with dormancy have been studied only under a simple idealized model of annual weeds, some general qualitative predictions can be made considering recent works on the population genetics of beneficial mutations in the presence of dormancy. Two fundamentally different models of dormancy have been proposed based on the average time individuals spend in the dormant state in comparison to the evolutionary timescale measured by the coalescent time (the expected time to the most recent common ancestor): “weak” seedbank (Kaj et al., 2001) that models dormancy induced by scheduled seasonality (e.g., plants or invertebrate species) and “strong” seedbank where individuals stochastically switch between active and dormant states (Blath et al., 2015, 2016) (e.g., bacteria). Under both models, the spread of a beneficial mutation has been investigated. Analytical (Koopmann et al., 2017; Heinrich et al., 2018) and simulation studies (Shoemaker and Lennon, 2018; Korfmann et al., 2023) have shown, under both models, that the efficacy of selection (both positive and negative) is reduced with dormancy and has strong dependence on the average time lineages spend in the dormant state and the size of the dormant population. These models have yet to be adjusted to incorporate gene drives but could be used as a modeling platform to initiate such investigations. Further modeling efforts incorporating other eco-evolutionary factors and their spatiotemporal variations in diverse target species will be needed to better understand the effect of dormancy and to design population control strategies that leverage life history traits. In particular, target species-specific life stage in which dormancy occurs (e.g., embryo, larva, pupa, or adult) and their mutation, mobility, and mortality during dormancy must be considered in gene drive modeling.

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390 Life history traits that depend on external environmental cues—such as mosquito diapause—can also be utilized for designing
391 gene drives and deployment strategies. For example, a modeling study of a gene drive mechanism incorporating a diapause-
392 specific promoter (Akbari et al., 2014) showed that if the gene drive spreads to fixation before the environmental cue causing
393 diapause appears (e.g., dry season), then population eradication can be achieved. Such environmental cue-dependent life-history-
394 specific gene drive strategies can be desirable because the genetic architecture can be designed to be species-specific, limiting
395 the potential for inter-species spillovers. Further, since the environmental cue activating the gene drive phenotype often has
396 a spatial dependency, such as altitude and geographic location, the effect of the population suppression by gene drive can be
397 confined to specific geographical regions (see *Environmental Variation* section).

398 INTER-SPECIES CROSSOVER

399 Inter-species mating events, in which individuals from different but closely-related species breed, are rare but do occur. Such
400 events can lead to the introgression of genetic material from one species into another (Edelman and Mallet, 2021; Harrison and
401 Larson, 2014; Mallet et al., 2016; Baack and Rieseberg, 2007). For example, in mosquitoes, one of the prime candidate species for
402 gene drive deployments, extensive introgression has been reported between different species (Alcorn and Kolls, 2015; Neafsey
403 et al., 2015; Wen et al., 2016; Niang et al., 2015; Bernardini et al., 2019; Pollegioni et al., 2023). If inter-species breeding would
404 result in gene drive introgression, and the introgressed allele would be able to achieve super-Mendelian inheritance also in the
405 non-target species, it could spread through this species as well (Connolly et al., 2021). Therefore, even though inter-species gene
406 flow is most often negligible between two species, a single inter-species breeding event may result in an inter-species gene drive
407 spillover. Such a spillover may have a significant effect on modification or suppression of a non-target species. It is unclear how a
408 gene drive construct engineered for one species would behave in another species, as this may depend on the construct and species
409 in question. Nevertheless, caution dictates that inter-species crossovers must be considered and modeled (Courtier-Orgogozo
410 et al., 2020; Hayes et al., 2018).

411 The inter-species crossover scenario is similar to the two-population spillover scenario, because what is being considered
412 is the transmission dynamics between two sets of individuals, populations, or species (see the toy model in Figure 5). There
413 are, however, important distinctions between the two cases. First, the gene flows rates between species are typically orders of
414 magnitude lower than between-population gene flow rates. Therefore, threshold-dependent gene drive designs, as discussed
415 above in the “population structure” section, may be a much more effective mitigating measure for inter-species spillovers than for
416 between-population spillovers. With low inter-species migration rates, the range of parameters resulting in confinement to the
417 target species may be large enough to provide robustness in terms of the precise parameter design of the gene drive (Greenbaum
418 et al., 2021).

419 Another important distinction between within- and between-species transmission is that the phenotypic expression of the gene
420 drive, as well as the genetic parameters, would likely be different in the genomic background of the non-target species. Because
421 the gene drive architecture was not designed and experimented in the non-target species, it is unclear whether the gene drive
422 allele will result in a lower fitness cost because the designed deleterious phenotype is less optimally expressed or in increased
423 fitness cost due to the incompatibility of the genetic construct with the new genomic background. If the fitness cost is increased
424 after introgressing to the new species, the rate of spread is expected to be reduced, and may even prevent the gene drive from
425 spreading at all (Figure 5B, orange curves). However, a more problematic scenario would be when the fitness cost is reduced in
426 the non-target species; in this case, the gene drive would be more invasive and spread faster than in the species it was designed
427 for (Figure 5B, purple curves). Therefore, whenever possible, it would be prudent to evaluate the fitness cost and efficiency of
428 the gene drive not only in the target species, but also in all other closely related and geographically overlapping species.

429 As demonstrated in the simple model in Figure 5, inter-species crossover can be modeled by integrating environmental variation
430 into two-species models. In this approach, the low-migration and high-environmental variation parameter regimes should
431 be the focus of investigation. Here, the environmental variation is both the difference in the environments of the two species, as
432 well as the difference in the genomic environment of the gene drive allele. These differences, therefore, can affect parameters
433 other than fitness, such as the dominance of the gene drive allele and the conversion efficiency of the gene drive mechanisms.
434 Other ecological features discussed here, such as mating system and life-history, may also differ between the species, and two-
435 species models that explore the effect of such differences could help us better understand the likelihood and consequences of
436 inter-species spillovers.

437 CONCLUSIONS AND FUTURE DIRECTIONS

438 In this Perspective, we have illustrated the important role eco-evolutionary interactions can play in the expected dynamics and
439 outcomes of gene drive releases. This strong coupling of ecological and evolutionary processes is a consequence of the rapid
440 nature of gene drive dynamics, in which population-level evolutionary changes can occur over the same timescales as ecological
441 processes. We have argued that it is therefore critical to incorporate ecological features and eco-evolutionary feedback into our
442 mathematical and computational models of gene drives, and we have proposed several strategies to this end. Importantly, given
443 the complex nature of eco-evolutionary interactions, models that seek to inform us on the role of ecology in gene drive spread
444 should be designed to answer specific questions and be as tractable as possible, rather than aiming for maximal realism.

445 We have highlighted a number of areas where integrating new mathematical and computational methodologies can aid in
446 addressing the ecological impacts on gene drive dynamics. In studying spatiotemporal gene drive dynamics, for example, ideas
447 and methods from network science can be used to model more realistic population structures, as has been done in the field of
448 ecological genetics (Dyer and Nason, 2004; Dyer, 2015; Greenbaum and Fefferman, 2017). Detailed geographic information
449 and explicit landscape features could be incorporated into system-specific landscape-genetic models (Manel et al., 2003; Storfer
450 et al., 2007; Manel and Holderegger, 2013) to investigate the outcomes of gene drive dynamics and evaluate interventions in a
451 realistic spatial setting (e.g., North et al., 2019, 2020; Selvaraj et al., 2020). Applying ecological extinction-colonization theory
452 to gene drives may provide insights into dynamics such as those described in Box 1. Finally, optimal control theory (Lenhart
453 and Workman, 2007; Rafikov et al., 2009; Lampert and Liebhold, 2021) combined with evolutionary game theory (Adami et al.,
454 2016) can provide insights into the optimal gene drive deployment strategy that accounts for both eco-evolutionary dynamics
455 and socioeconomic costs influencing the management and control of the target species. Importantly, since many theories and
456 modeling approaches are used to model gene drive dynamics, it is crucial to maintain as much compatibility and comparability
457 between models as possible. One way to achieve this is by demonstrating where model results converge or diverge between
458 newly published models and previous models.

459 Simulation-based models can also play a critical role in this context. With agent-based models, many ecological factors can
460 be incorporated so that eco-evolutionary feedback becomes an emergent property of the model rather than explicitly defined.
461 Such simulations will allow us to evaluate the robustness of mathematical models and systematically test their assumptions.
462 The advent of powerful, computationally efficient simulation frameworks such as SLiM (Haller and Messer, 2019, 2023), a
463 forward-in-time individual-based scripting environment for evolutionary simulations, allows us to model gene drive scenarios in
464 unprecedented detail. Several mosquito-specific simulation frameworks (e.g., EMOD (Eckhoff, 2011), Skeeter Buster (Legros
465 et al., 2012), and MGDrivE (Sánchez C et al., 2020)) are also already available in which the spread of a gene drive can be
466 modeled along with detailed aspects of the mosquito life cycle and disease transmission.

467 A key challenge will be determining the appropriate level of ecological complexity that needs to be included in a gene drive
468 model for any specific application, as the ideal model is typically the simplest one that still contains all relevant features. Yet,
469 how can we know which features will ultimately be relevant? This fundamental problem cannot be solved through modeling
470 alone but will require experiments and field studies to assess a model's accuracy in predicting the most important aspects of
471 the real-world system. Once a sufficiently accurate model has been identified, sensitivity analysis of its parameter space will be
472 needed to reveal which features are critical and which could be neglected without losing too much predictive accuracy. However,
473 such analyses become increasingly cumbersome as the number of parameters in a model increases. Recent work has suggested
474 promising new avenues to tackle this problem using supervised machine learning. For instance, in a study on the potential of
475 gene drives for suppressing invasive rodent populations, a complex eco-evolutionary simulation model was accompanied by an
476 adaptively trained meta-model, which enabled in-depth sensitivity analyses that would have been prohibitively time-consuming
477 using the underlying simulation model alone (Champer et al., 2022b). Such new statistical approaches can help us develop a better
478 understanding of a model's outcome space and identify the parameters that must be measured most accurately in experiments
479 or ecological field studies.

480 Ideally, the construction, parameterization, and evaluation of ecological gene drive models should be done at an early stage
481 in the development of gene drive projects. Early modeling efforts can help us assess the risks involved pre-deployment, guide
482 the design of the gene drive construct, and allow for the informed and coherent development of deployment strategies. As
483 projects progress and more specific ecological conditions become relevant, system-specific modeling should be carried out.
484 These system-specific models should focus on the ecological factors that have been predicted to have strong effects on gene drive
485 spread and are reported to be present and relevant in the system. In addition, field studies should be carried out to parameterize
486 the models in these key ecological features.

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BOX 1. Chasing dynamics and Allee effects in continuous space

Non-spatial panmictic models of suppression gene drives typically predict one of three outcomes in the absence of resistance to the drive (Beaghton et al., 2017; Prowse et al., 2017; Champer et al., 2021): (i) the gene drive allele spreads and successfully eradicates the population, (ii) the gene drive allele is lost, or (iii) the drive reaches a stable equilibrium frequency with wild-type alleles. In continuous space, however, a gene drive that would be predicted to successfully spread and eradicate the population in panmictic models may result in additional outcomes with distinct features. For instance, Champer et al. (2021) described a dynamic called “chasing”, where wild-type individuals recolonize low-density areas that the suppression drive had previously vacated. Here, wild-type individuals experience less competition and thus have an advantage in fecundity (Champer et al., 2021) or offspring survival (Birand et al., 2022; Champer et al., 2022a), which allows wild-type alleles to rapidly expand and recolonize uninhabited regions. In some cases, the gene drive allele “chases after” recolonizing wild-type alleles, while at the same time, new chasing cycles could start elsewhere in the landscape. This pattern is different from the static equilibrium outcome of panmictic models, because chasing is a state characterized by a large variance in population density over time and space (Figure 3A). Chasing cycles may persist indefinitely, could cause the loss of the drive allele after a while, or at least substantially delay the time until full population eradication. Similar chasing-like persistent oscillations can also emerge in spatial reaction-diffusion (Girardin and Débarre, 2021) and discrete (Harris and Greenbaum, 2022) models that incorporate demography through the same principle: wild-type alleles increasingly migrate to regions or populations in which the population has previously been suppressed by the gene drive.

Another outcome that emerges in continuous space models, resembling an Allee effect for the “gene drive population”, is the local success of a suppression drive followed by the drive eliminating itself before spreading to a sufficient amount of the target landscape to cause complete eradication (Figure 3B) (Birand et al., 2022; North et al., 2019). This situation is more likely to occur when the drive system is very efficient but the population is fragmented or sparsely distributed such that it is difficult for individuals carrying the gene drive to disperse from an initial site and encounter other individuals to mate with. In this scenario, the gene drive spreads rapidly, decreasing the population density locally, but then faces the Allee effect wherein gene drive allele carriers cannot find wild-type individuals to mate with. This leads to loss of the drive allele, while wild-type individuals are still present elsewhere. Chasing dynamics can contribute to this outcome since chasing tends to lower the population densities in various regions of the target space, but this outcome can also occur in the absence of chasing. In a panmictic model, in contrast, this phenomena would not be observed and such an efficient drive would be able to fully eliminate the population.

BOX 2. Glossary

- **Chasing.** A dynamic where wild-type individuals recolonize areas that a suppression drive has previously vacated. The gene drive allele “chases after” the wild-type alleles in space, and these cycles may persist indefinitely without fully eliminating the population.
- **Conversion rate/probability.** The efficiency in which a homing gene drive converts heterozygotes to gene drive homozygotes. Usually measured as the probability that conversion occurs in each reproduction event.
- **Fitness cost.** For suppression drives, the reduction in fitness is induced by the gene drive allele. This usually refers to homozygotes of the gene drive allele. For heterozygotes, the dominance of the gene drive allele also needs to be considered.
- **Gene drive wave front.** In spatial contexts of gene drive spread, the spread of the gene drive can be modeled as an advancing wave where the replacement of the wild-type allele by the drive allele occurs in a region that moves through space. The wave can be described by different properties, for example, by the speed in which the wave advances, or by the thickness of the wave (the region in which replacement of the wild-type allele by the gene drive allele occurs).
- **Modification drive.** A gene drive engineered to modify a certain phenotype without inducing population suppression.
- **Resistance allele.** An allele that prevents the gene drive from functioning. Resistance alleles can be additional alleles at the gene drive locus, arising through *de novo* mutation, standing genetic variation, or non-homologous end joining, but may also appear in other loci.
- **Spillover.** The spread of the gene drive allele beyond a target population or species through gene flow, followed by rapid increase in frequency in a non-target population/species.
- **Super-Mendelian inheritance.** An inheritance mode in a diploid locus in which one of the alleles has a probability higher than 50% of being transmitted to each offspring. This inheritance mode is a violation of the 50% inheritance probability of Mendel’s laws of inheritance.
- **Suppression drive.** A gene drive with an engineered allele that conveys a high fitness cost to its carrier. Suppression drives are intended to significantly reduce the size of the target population or even eliminate it.
- **Threshold-dependent drive.** A gene drive that spreads in a population only when its frequency in the population is above a threshold. Such gene drives can be generated through different mechanisms, such as when the balance of natural selection and super-Mendelian inheritance generate a non-stable equilibrium in the evolutionary dynamics or through genetic underdominance.

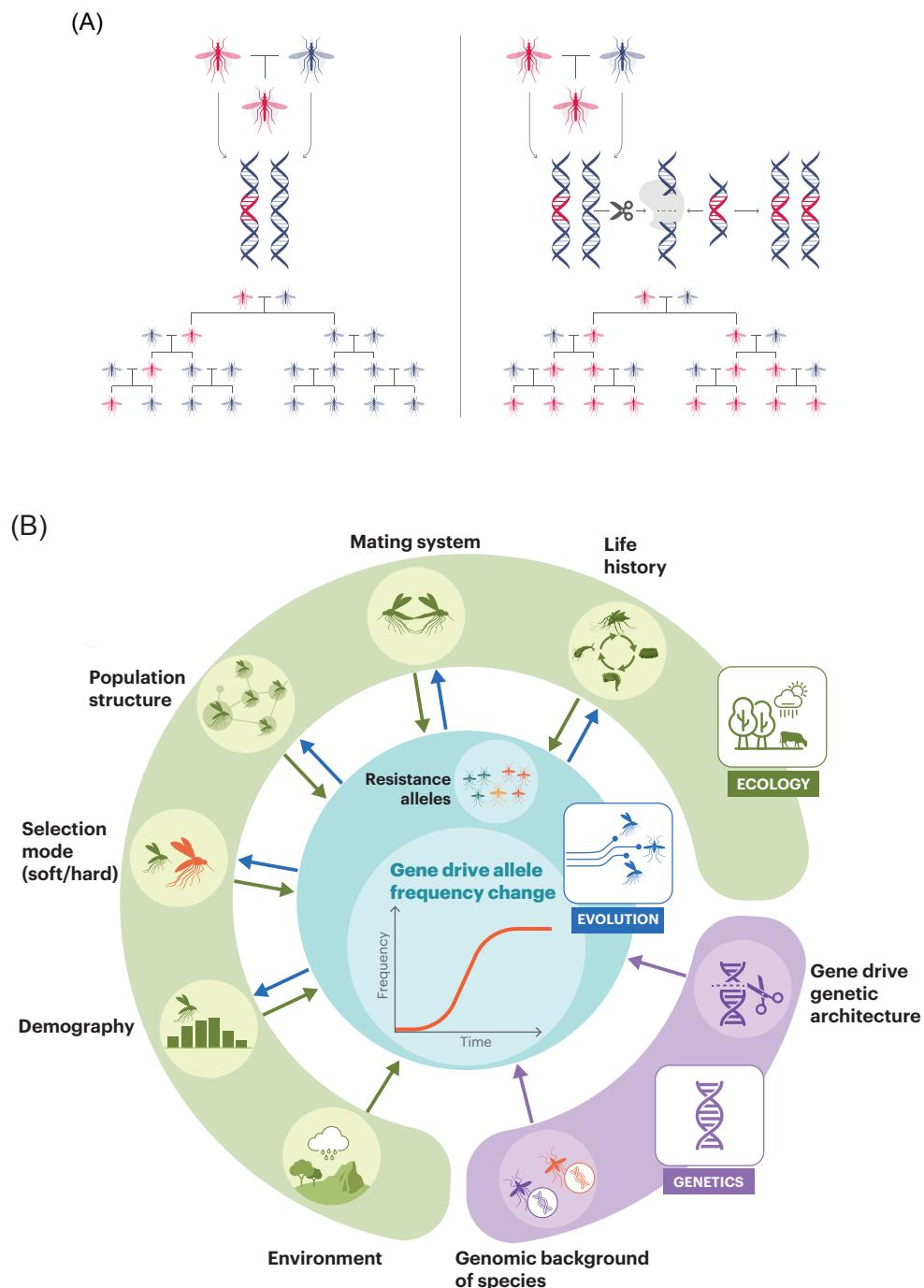


FIGURE 1 (A) Basic homing gene drive mechanism. Under standard Mendelian inheritance, a newly introduced allele (red) in a heterozygous individual has a 50% probability of being transmitted to any given offspring. Its average frequency in the population is expected to remain constant over time (left panel). In a CRISPR homing gene drive, the CRISPR endonuclease in the drive allele can cut the wild-type homologous chromosome (blue) at the targeted site. Homology-directed repair of such a cut will lead to copying of the drive allele onto the wild-type chromosome, converting a heterozygote to a homozygote for the gene drive allele. When this process occurs in the germline, it will bias the transmission of the drive allele to a higher-than-Mendelian (super-Mendelian) ratio. Such preferential inheritance can lead to a rapid spread of the drive allele even when it carries a fitness cost (right panel). (B) The main ecological features (in green) affecting the evolutionary dynamics (in blue). Genetic aspects (in purple) can also affect gene drive spread but fall outside the scope of this paper. The arrows describe the direction of an effect between different features. Most ecological features potentially generate eco-evolutionary feedback (bi-directional green and blue arrows) because the rapid evolutionary dynamics of gene drives occur at ecological time scales.

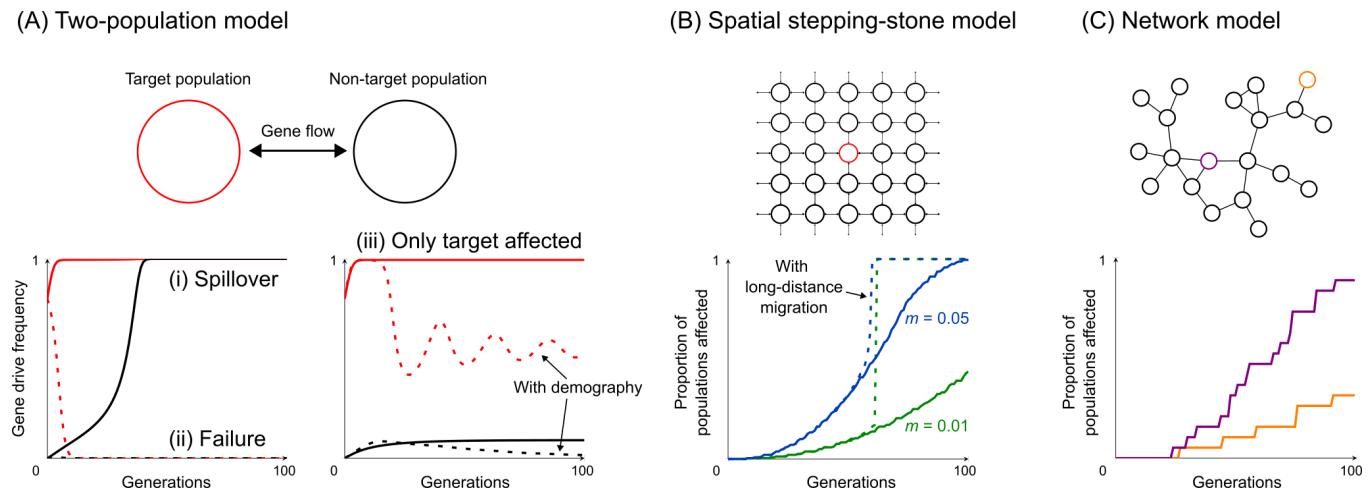


FIGURE 2 Models of gene drive dynamics incorporating discrete population structure. (A) A two-population model with a target population in red and a non-target population in black. In the panels below, three possible outcomes are shown. (i) *Spillover* (left panel, continuous lines), where both target and non-target populations are affected by the gene drive. (ii) *Failure* (left panel, dashed lines) where the gene drive is removed from the system. (iii) Only target population is affected (right panel). When adding demography to the model (dashed lines), other outcomes such as fluctuations, oscillations, and transient suppression may arise (model following Harris and Greenbaum (2022)). The different outcomes (i)–(iii) were generated by varying the fitness cost of the gene drive. (B) A spatial stepping-stone model, where the gene drive is released in the central position (in red), with short-distance (m across each edge) and long-distance (m_∞ independent of spatial configuration) migration rates. The panel below shows the proportion of populations to which the gene drive has spread (defined as populations with gene drive allele frequency > 0.5). Without long-distance migration (continuous lines), the short-distance migration rate m determines the speed-of-advance of the gene drive wave. With small amounts of long-distance migration ($m_\infty = 10^{-5}$, dashed lines), the behavior of the dynamics qualitatively changes, and the entire population is rapidly overtaken by the gene drive once a spatial threshold is breached. (C) A network model of population structure. Here, a central (purple) and peripheral (orange) release sites are considered. The more central the release site is in the population structure topology, the more populations are affected by the gene drive at a faster rate. The plots in panels A, B, and C can be reproduced interactively with user-defined model parameters using the modelRxiv platform: <https://modelrxiv.org/model/3O8d97> for panel A, <https://modelrxiv.org/model/nynewH> for panel B, and <https://modelrxiv.org/model/Ek9TEV> for panel C.

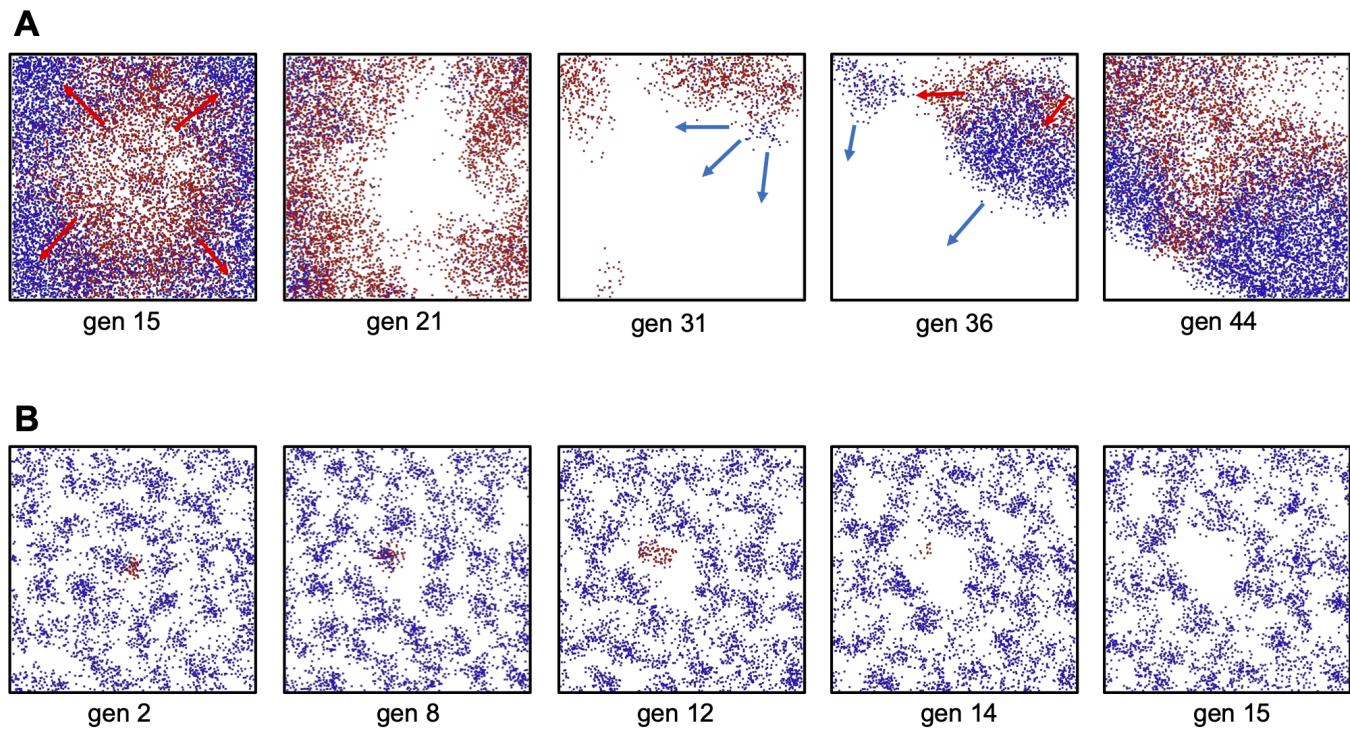


FIGURE 3 Snapshots from simulation runs of the continuous-space model from Champer et al. (2021), illustrating two different types of failure of suppression gene drives in continuous space models. Individuals carrying the gene drive allele are in red, and wild-type individuals are in blue. The gene drive is introduced in generation 0 into a single individual at the center of the landscape. (A) Depiction of the chasing phenomenon (model can be found at <https://github.com/MesserLab/Chasing/blob/master/Models/chasing.slim>). The drive first expands from the release site (red arrows). In generation 31, the population has been suppressed across large areas, but some wild-type individuals in the upper right corner now expand into uninhabited space and rapidly recolonize the area due to reduced competition (blue arrows). The gene drive “chases after” these wild-type dominated regions. By generation 44, the wild-type allele has recolonized much of the landscape, and the gene drive again spreads into these now wild-type dominated regions. (B) Allee effect leading to loss of the gene drive allele in a fragmented population (model can be found at https://github.com/MesserLab/Chasing/blob/master/Models/drive_loss.slim). Initially, an efficient suppression drive is spreading successfully in a local region. However, because of the patchiness of the population, it quickly eliminates all wild-types individuals in that local region, thereby resulting in loss of the gene drive allele by generation 15.

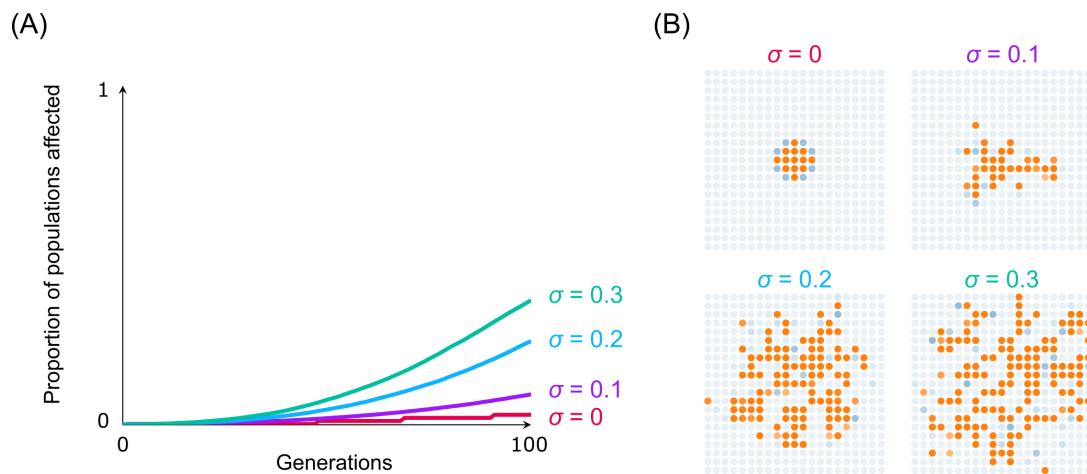


FIGURE 4 Model of gene drive dynamics incorporating environmental variation. The model follows the stepping stone model in Figure 2B but in each population, the gene drive experiences a different environment, modeled as a variation in the fitness cost imposed by the drive. For each population, this fitness cost s was sampled from a normal distribution with a mean of 0.5 and a standard deviation of σ . (A) The average proportion of populations affected by the gene drive (defined as frequency > 0.5) for different σ values. The average was taken across 100 replicates for each σ value. (B) Examples of snapshots of the gene drive spread after 100 generations for different σ values. Color shades denote gene drive frequency, and orange denotes frequency > 0.5 . With increased environmental variation, gene drives spread faster, and their spatial distributions becomes wider. The plots in panels A and B can be reproduced interactively with user-defined model parameters using the modelRxiv platform (<https://modelrxiv.org/model/8ennKo>).

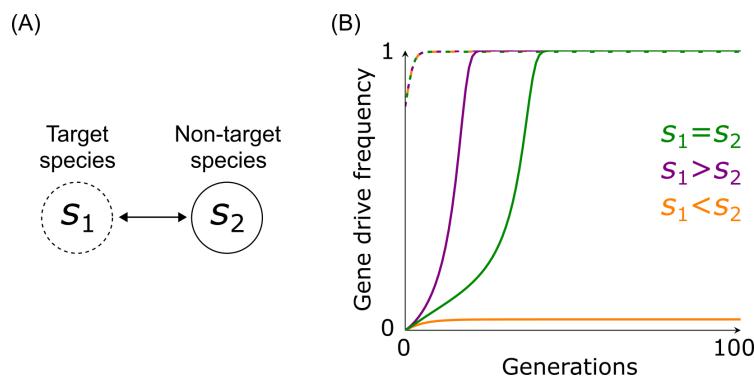
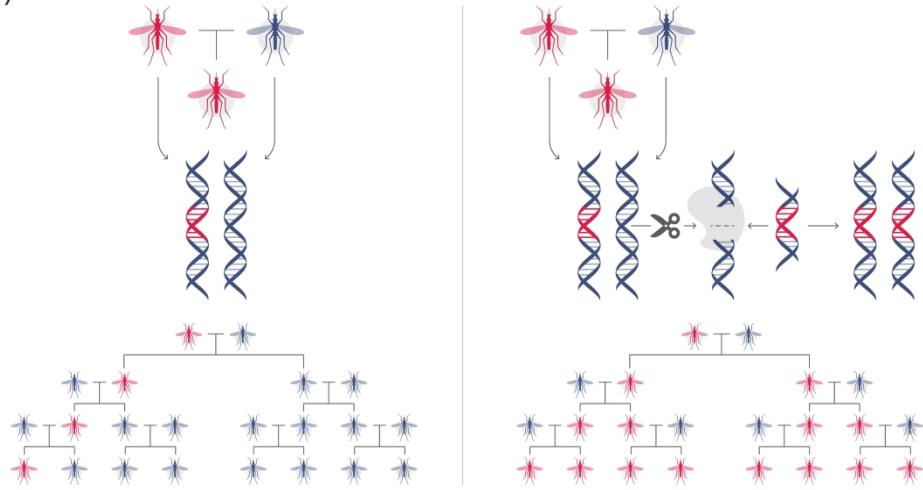


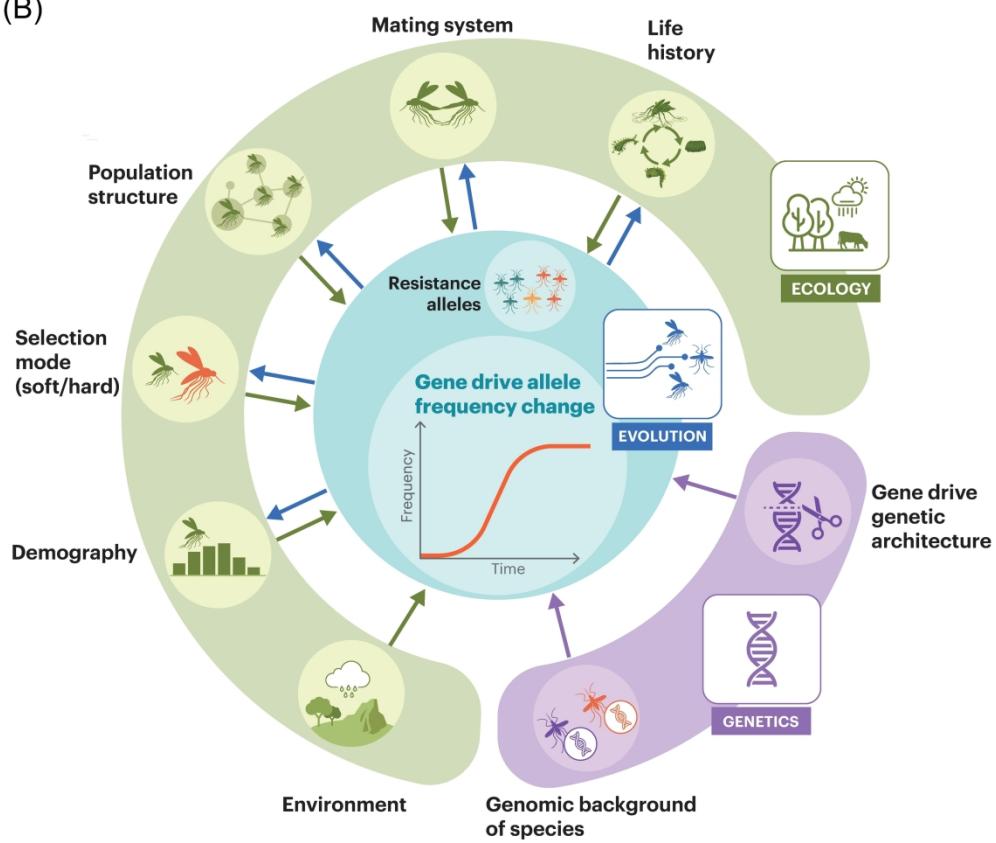
FIGURE 5 Model of gene drive inter-species crossover. (A) The model follows the two-population model in Figure 2A, but in each species, the gene drive fitness costs is different: s_1 in the target species (dashed lines) and s_2 in the non-target species (continuous lines). (B) The gene drive frequency in the two species for $s_1 = s_2 = 0.5$ in green, for $s_1 > s_2$ in purple ($s_1 = 0.5$, $s_2 = 0.4$), and for $s_1 < s_2$ in orange ($s_1 = 0.5$, $s_2 = 0.6$). Here, with higher fitness costs in the non-target species, the gene drive does not spill over, but in other cases it does. The plot in panel B can be reproduced interactively with user-defined model parameters using the modelRxiv platform (<https://modelrxiv.org/model/T7KW4p>).

(A)

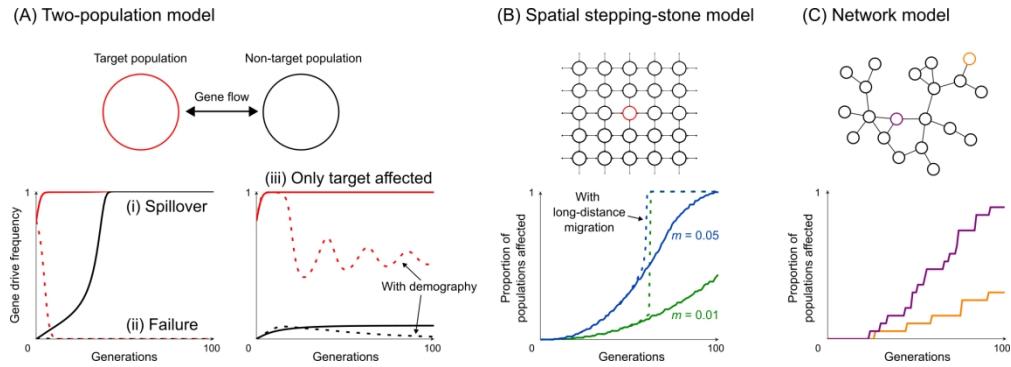


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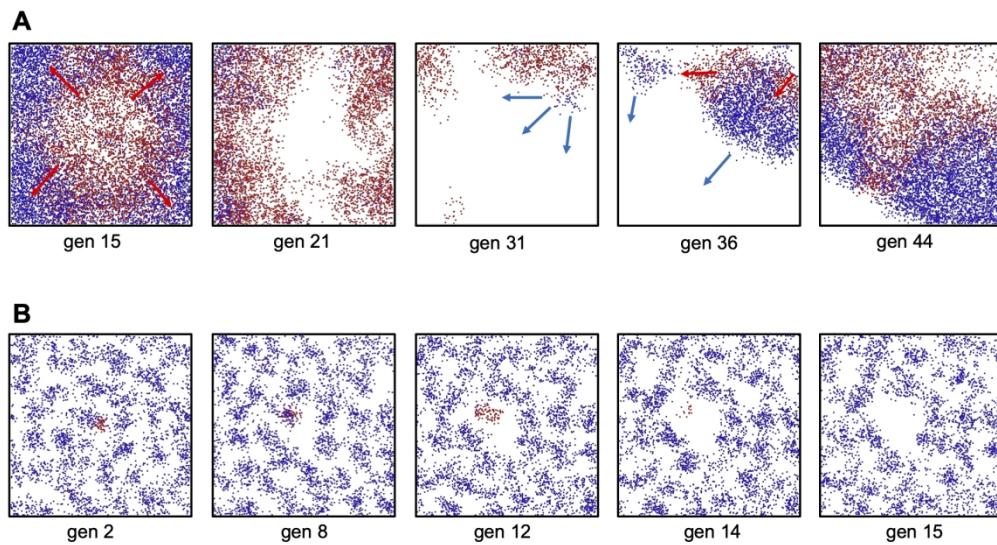
(B)



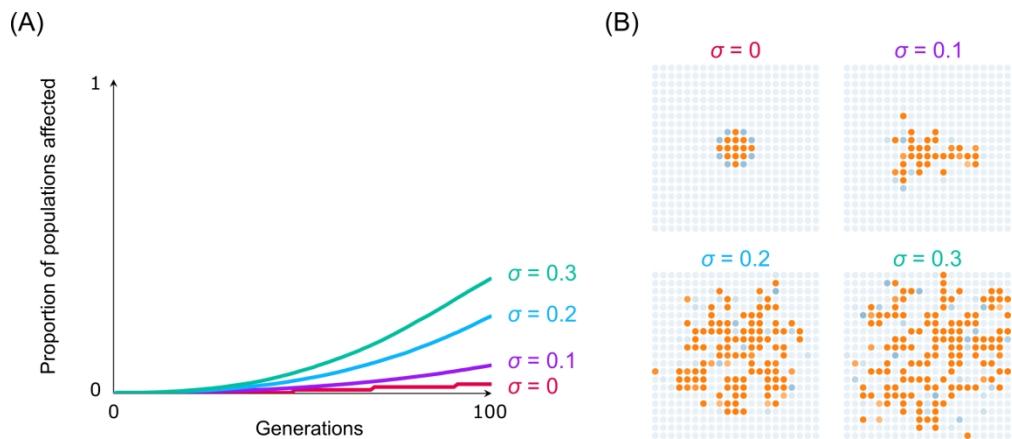
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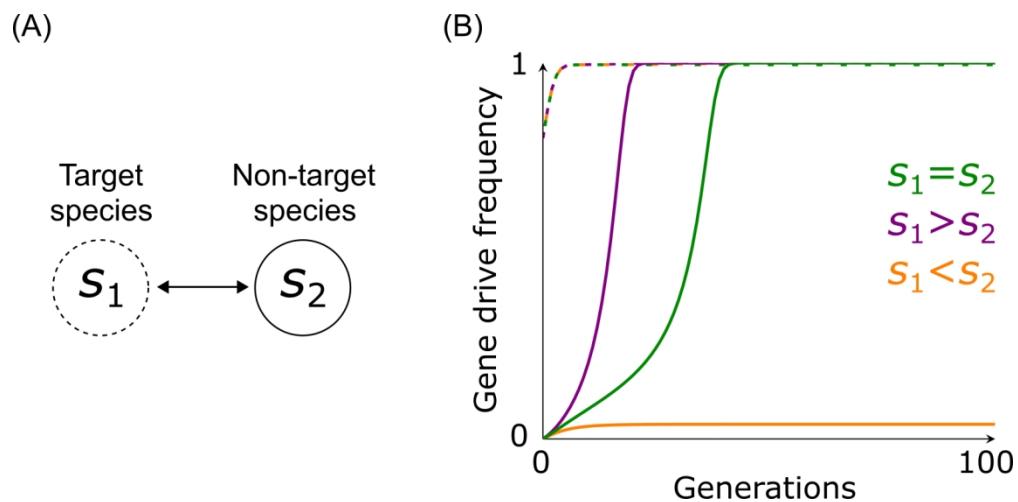
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