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PERSPECTIVE

Incorporating ecology into gene drive modelling

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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 behaviour 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 behaviour, such as population structure, life-history, environmental variation and mode of selection. We review previous gene drive modelling 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, eco-evolutionary modelling, non-Mendelian inheritance, population genetics, population structure

INTRODUCTION

Gene drives are engineered genetic constructs that can quickly spread desired alleles through a wild population. Advancements in genetic engineering have led to concerted efforts to develop gene drives for controlling disease vectors, such as mosquitoes (Adelman et al., 2017; Sinkins & Gould, 2006), invasive species (Dearden et al., 2018) and agricultural pests (Legros et al., 2021; Neve, 2018). Recently, several proof-of-principle studies have demonstrated the successful spreading of engineered gene drive constructs through laboratory insect populations (Adolfi et al., 2020; Champer, Yang, et al., 2020; Kyrou et al., 2018). Potential gene drive applications typically have the following goals: (i) phenotypic modification of individuals in a population, such 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*). *Box 1* explains the italicized terms that not all ecologists may be familiar with.

Gene drive technologies can employ different mechanisms to generate rapid spread in a population. With CRISPR-based homing gene drives, for example, the drive allele can convert heterozygous germline cells for the drive allele to homozygous cells by cleaving a specified sequence on the wild-type homologous chromosome and then copying itself into that position. As a result, the drive allele will be passed on to offspring at a super-Mendelian ratio, which generates an evolutionary force that allows the gene drive allele to increase exponentially in frequency in the population (Figure 1a). In addition to homing drives, there are several other possible drive mechanisms, such as sex-linked drives (Galizi

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BOX 1 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/efficiency**. 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 wavefront**. In spatial contexts of gene drive spread, the spread of the gene drive can be modelled 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-types alleles 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.

et al., 2016; Prowse et al., 2019) and underdominance systems (Akbari et al., 2013; Champer, Kim, et al., 2020; Davis et al., 2001); for further details about the different types of gene drives and their molecular mechanisms, we refer readers to reviews by Champer et al. (2016) and Hay et al. (2021). While these different types of drives rely on distinct genetic mechanisms, the evolutionary dynamics they induce can often be quite similar. Here, we primarily consider the basic homing gene drive design, but our description of their dynamics pertains to many other gene drive mechanisms that can spread exponentially from a low introduction frequency.

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

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

In this perspective, we provide a comprehensive overview of the key ecological features that could affect gene drive behaviour (Figure 1b). We centre our efforts on incorporating these features into mathematical and computational models to elucidate the complex interplay between ecological and evolutionary processes shaping gene drive dynamics. Gene drive models typically track the frequency of a drive allele and evaluate

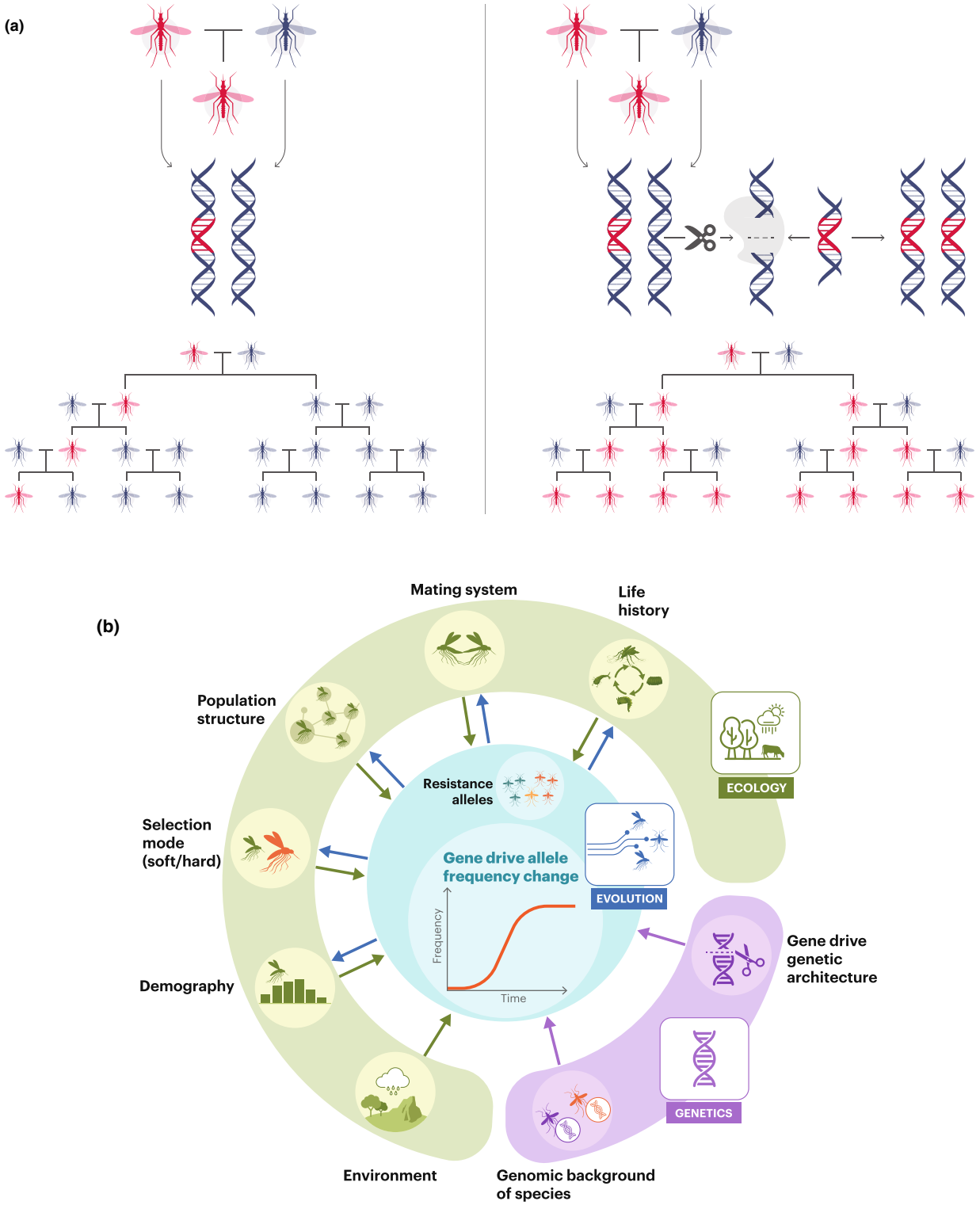

FIGURE 1 (a) Basic homing gene drive mechanism. Under standard Mendelian inheritance, a newly introduced allele (red) in a heterozygous individual has a 50% probability of being transmitted to any given offspring. Its average frequency in the population is expected to remain constant over time (left 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 timescales.

the conditions for its spread, as well as the temporal or spatial properties of its dynamics (sometimes the evolution and dynamics of *resistance alleles* are also tracked). We, therefore, focus on how different ecological factors (green in Figure 1b) can affect the evolutionary dynamics of a gene drive allele (within blue region in Figure 1b) across time and space. To demonstrate eco-evolutionary interactions in gene drives, we present several toy models that incorporate various ecological features, and we re-examine results from previously published models.

POPULATION STRUCTURE

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

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

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

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

With additional features added to this simplistic model, other types of gene drive behaviours can emerge. For example, when explicitly adding demography to the two-population model, transient demographic bottlenecks or oscillations in population sizes and gene drive frequencies may emerge (Harris & Greenbaum, 2022)

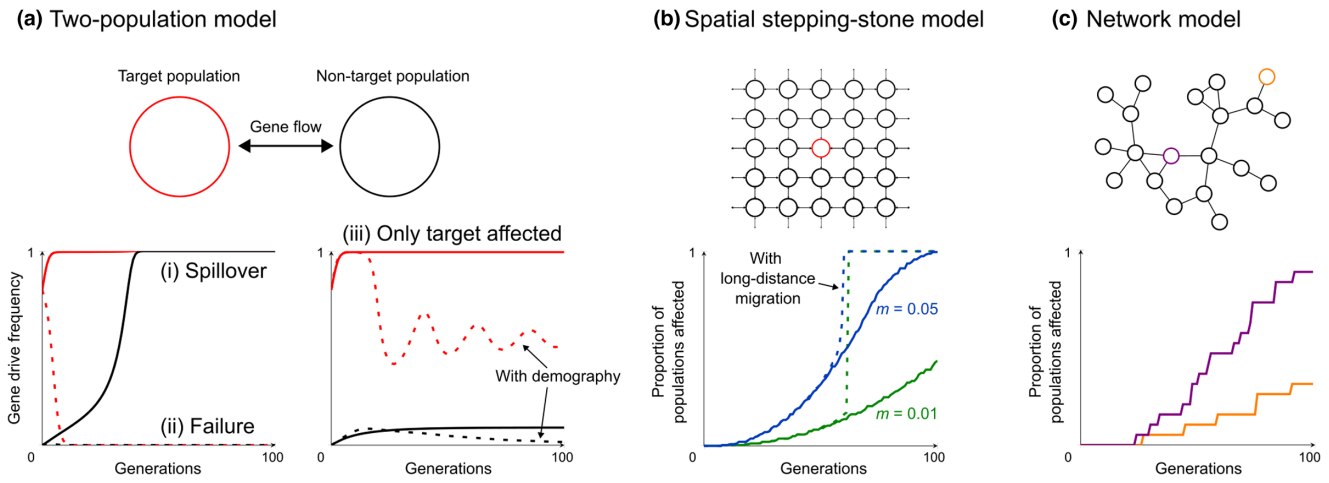

FIGURE 2 Models of gene drive dynamics incorporating discrete population structure. (a) A two-population model with a target population in red and a non-target population in black. In the panels below, three possible outcomes are shown. (i) *Spillover* (left panel, continuous lines) where both target 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 behaviour 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, 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–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 2a). These behaviours are caused by feedback between the gene drive spread, demographic suppression caused by the gene drive and migration rates. This example emphasizes that incorporating eco-evolutionary feedbacks, even in simple models, can qualitatively change our understanding of gene drive dynamics, and provide ideas for ways to mitigate spillover risks.

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

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

In addition to tracking the allele frequencies of the gene drive in space, these discrete spatial models are also useful for understanding the spread of emerging resistance alleles, and for evaluating the risks that these would

impede the spread of the gene drive and become fixed in populations (Noble et al., 2018). Population structure can affect the critical population size required for resistance alleles to emerge (Khatri & Burt, 2022), while the level of gene flow between populations is expected to impact the spread of resistance alleles, similarly to its impact on gene drive spread. Higher gene flow can also increase the generation of resistance alleles: non-homologous end-joining (NHEJ) events can generate alleles that block the CRISPR conversion mechanism by altering the target sequence. The likelihood of these events is dependent on the frequency of heterozygotes (Unckless et al., 2017), which increases as a function of gene flow (Harris & Greenbaum, 2022). Thus, considering both topology and the level of gene flow is important for understanding how certain types of population structure could increase the probability of resistance alleles emerging.

Continuous-space models provide an alternative modelling framework for understanding the spatiotemporal dynamics of gene drive spread. One particularly useful approach has been the analysis of reaction–diffusion equations to describe the spatial dynamics of gene drives (Beaghton et al., 2016; Girardin et al., 2019; Girardin & Débarre, 2021; Tanaka et al., 2017), in which the properties of gene drive 'waves' can be studied analytically under different conditions (Tanaka et al., 2017). This has provided key insights into the necessary release thresholds of underdominance gene drives (Barton & Turelli, 2011), how the wave speed changes with the gene drive mechanism (Girardin & Débarre, 2021; Paril & Phillips, 2022; Tanaka et al., 2017), how the thickness of the wave impacts a suppression drive's ability to eliminate a population (Champer et al., 2021; Paril & Phillips, 2022) and how an artificial intervention barrier can block a gene drive wave (Girardin et al., 2019). Continuous-space individual-based simulation models can incorporate more ecological features than analytical models and provide another promising approach for investigating the spatial behaviour of gene drives. These models display interesting outcomes (see examples in Box 2 and Figure 3), including dynamics that can be equated with extinction–colonization processes.

DEMOGRAPHIC DYNAMICS

Population size affects evolutionary processes and allele frequencies in many ways, such as through genetic drift and the relationship between selection and the effective population size. Evolutionary processes may also affect the population size, for example, through the fixation of adaptive or deleterious alleles. There are a number of aspects of demography that can be considered in modelling gene drive spread, including the population sizes prior to deployment, of the target population as well as neighbouring non-target populations, and the demographic effects of the gene drive itself as it spreads. The latter is of particular importance in suppression gene drives,

BOX 2 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; Champer et al., 2021; Prowse et al., 2017): (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, Kim, et al., 2022), 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 & Débarre, 2021) and discrete (Harris & 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, contrast, this phenomenon would not be observed and such an efficient drive would be able to fully eliminate the population.

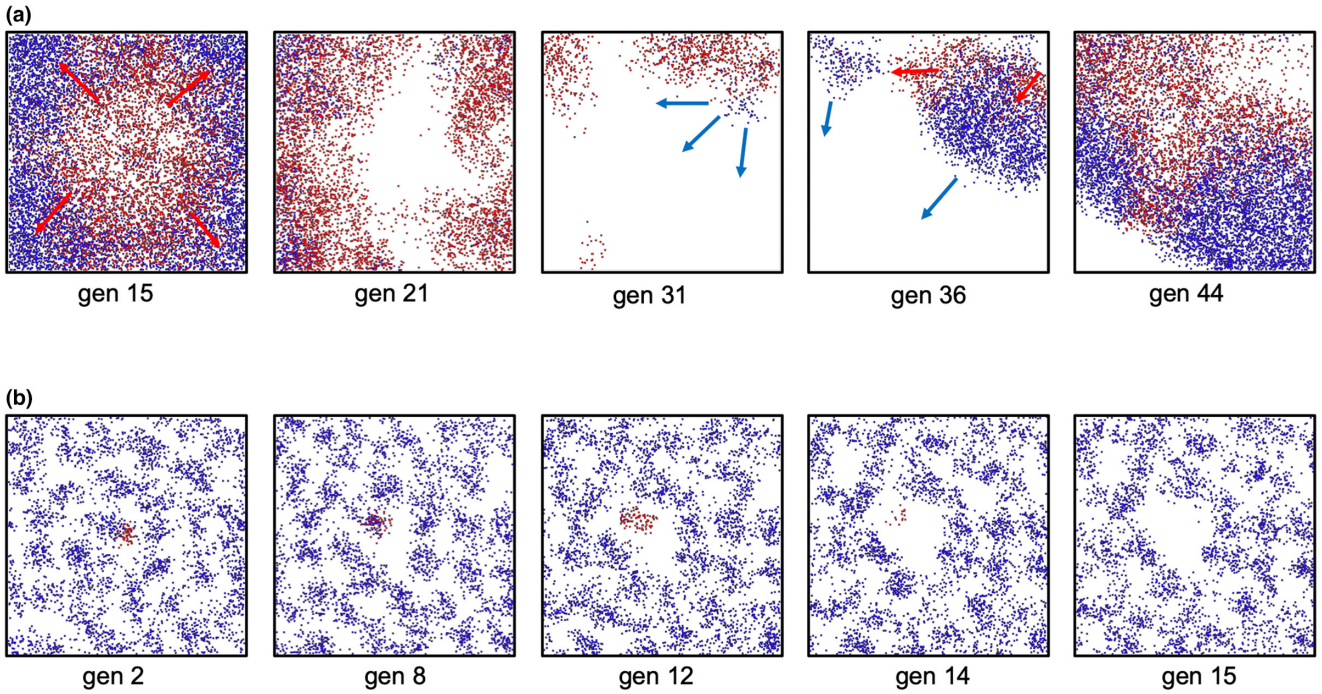

FIGURE 3 Snapshots from simulation runs of the continuous-space model from Champer et al. (2021), illustrating two different types of failure of suppression gene drives in continuous-space models. Individuals carrying the gene drive allele are in red, and wild-type individuals are in blue. The gene drive is introduced in generation 0 into a single individual at the centre 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-type individuals in that local region, thereby resulting in loss of the gene drive allele by generation 15.

which are designed to reduce growth rates and are expected to generate substantial demographic changes at the same timescale as the evolutionary dynamics of gene drive spread. Therefore, eco-evolutionary feedback between the changes in allele frequencies and changes in population sizes can shape the dynamics and outcomes of deployment (Beaghton & Burt, 2022; Girardin & Débarre, 2021; Kläy et al., 2022).

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

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

In modification gene drives, where the goal is typically not to induce a demographic effect but rather

to simply spread the modifying allele, soft selection models are often appropriate. On the other hand, hard selection models are better suited for modelling suppression gene drives. This dichotomy, however, does not capture the full complexity of selection operating during gene drive deployment. In the initial phase of deployment, while the population is close to carrying capacity, the spread of the gene drive should depend primarily on the relative densities of the genotypes (i.e. individuals in the population will still be in direct competition). Thus, during this phase, hard selection models should behave similarly to soft selection models. As the population collapses, the reduction in population density can lead to decreased fitness through Allee effects (see Box 2 and Figure 3), or altered gene flow in and out of the collapsing population (Harris & Greenbaum, 2022). This can, in turn, alter the evolutionary trajectory, leading to the collapse of the population, loss of the gene drive or long-term persistence at an intermediate frequency. This transition from soft to hard selection over a short timescale complicates coherent modelling of the connection between the demographic and the evolutionary behaviours of gene drives, and demonstrates that more nuanced treatment of selection modes may be needed (Bell et al., 2021; Start, 2020).

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

ENVIRONMENTAL VARIATION

Evolutionary processes are affected by the environment in many ways, most notably through natural selection. Environmental variability, both temporal and spatial, can affect both the outcome and the spatiotemporal dynamics of evolutionary processes (Bell et al., 2021; Débarre & Gandon, 2011). 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 modelled 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 modelled a simple homing gene drive (as in Deredec 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 behaviour 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 generated by environmental variability.

There are many ways in which this variability can be modelled, and different types of gene drives may respond differently to such variability, and these could be investigated in detail using similar modelling 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 behaviour 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 modelled 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 behaviour 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., Girardin et al., 2019; Marshall & Akbari, 2018; Tanaka et al., 2017). 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; Eckhoff et al., 2017; Vella 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 modelling; 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 modelling 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

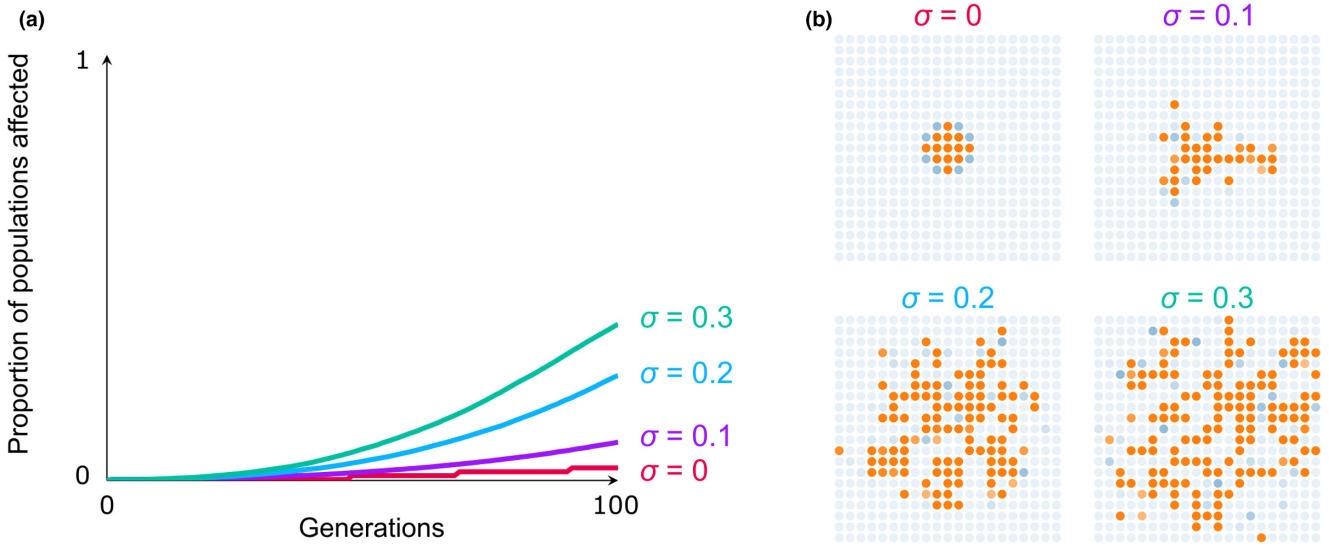

FIGURE 4 Model of gene drive dynamics incorporating environmental variation. The model follows the stepping-stone model in Figure 2b but in each population, the gene drive experiences a different environment, modelled as a variation in the fitness cost imposed by the drive. For each population, this 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. Colour shades denote gene drive frequency, and orange denotes frequency >0.5. With increased environmental variation, gene drives spread faster, and their spatial distributions become 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).

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 in the fitness cost in response to an environmental cue (Heffel & Finnigan, 2019). In other words, a genetic element under certain environmental conditions would function as a drive, but under different conditions would not, or even serve as an 'anti-drive' that favours 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 (Dhole et al., 2019; Girardin et al., 2019; Heffel & Finnigan, 2019; Marshall & Akbari, 2018; Vella et al., 2017), 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.

MATING SYSTEM

Homing gene drives propagate in the population through conversion of heterozygous individuals into gene drive homozygotes. Consequently, the effectiveness of gene drives depends on the manner in which heterozygotes are formed in the population, and thus on the mating system of the organism in question (Leftwich et al., 2015; Sutter et al., 2021; Verma et al., 2023). In cases where the drive allele is associated with some phenotypic characteristics that mate selection is acting on, through direct expression or due to genetic linkage to the trait loci, fewer heterozygotes would be generated and the number of conversion 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 drive allele. Indeed, for some naturally occurring gene drives, species have evolved to avoid mating with drive carriers if they can be reliably detected through a specific trait (Lenington, 1991; Wilkinson et al., 1998). Despite having theoretical support (Lande & Wilkinson, 1999; Manser, Lindholm, & Weissing, 2017; Reinhold et al., 1999), empirical evidence for mate avoidance of natural drive carriers is limited (Price & Wedell, 2008). Whether a population could evolve to detect and behaviourally reduce transmission of a synthetic gene drive thus remain largely unknown. Given the timescale in which the gene drive spreads, an evolutionary response in mating behaviour needs to occur rapidly before the gene drive is fixed in order to affect gene drive dynamics. Therefore, an evolutionary change in mating behaviour is expected to be significant only if the genetic basis of the mating behaviour has sufficient (narrow-sense) heritability. A detailed understanding of the target population's mating biology and identifying mating traits that can be exploited for control could provide an effective gene drive design strategy; for example, a gene drive can be engineered to manifest traits known to confer higher mating preference and thus mating success with wild-type individuals.

Drive-carrying males are often substantially compromised in their sperm competitive ability, and thereby paternity, due to reduction in sperm number and quality (Haig & Bergstrom, 1995; Price & Wedell, 2008; Verspoor et al., 2020). In polyandrous species, sperm competition alone can hinder the spread of the drive allele even in the absence of a mechanism for mate choice (Manser et al., 2020; Wedell, 2013). Assuming the female's mating success is determined as a function of the total number (or above a set threshold) of high-fitness sperms, wild-type females can develop behavioural resistance by increasing their rate of remating, which would reduce the transmission of the gene drive allele to the next generation. In response to a gene drive, the mating system can evolve rapidly (e.g., within 10 generations in a laboratory population (Price et al., 2008)) due to the fitness cost of disrupted reproduction, especially with polyandry being a heritable trait (Haig & Bergstrom, 1995; Travers et al., 2016). The number of rematings, however, cannot increase indefinitely. As the system evolves, the drive-carrying male frequency and the sex ratio can change (especially for sex-ratio distorter drives); therefore, the evolution of polyandry and the changes in mating rate over time require careful modelling efforts.

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

Males can also evolve mitigation strategies against the reduced sperm competitive ability. Counteracting the evolution of polyandry in females, non-drive-carrying males can evolve reproductive traits that prevent females from remating (Price, Hurst, & Wedell, 2010). Further, to compensate for the decrease in sperm competitiveness, the drive-carrying males can evolve to increase 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 require more extended modelling. Incorporating evolutionary game

theory (Parker & Pizzari, 2010; Simmons, 2001; Wedell et al., 2002) into gene drive modelling frameworks can be a fruitful approach to understanding such dynamics.

Two additional key mating choice behaviours 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 favours 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). Modelling efforts have shown that these results are generally consistent across multiple gene drive architectures and parameters (Beaghton & Burt, 2022), species modelled (Drury et al., 2017; Faber et al., 2021; Grewelle 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 & Dearden, 2019). For randomly mating haplodiploid populations, a modelling 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 (Callahan et al., 2018; Diabate & Tripet, 2015; Maïga et al., 2012), and wild rodents exhibit preferential mating behaviour based on olfactory preference (Lenington, 1991; Manser et al., 2015). Under standard Mendelian inheritance, assortative mating alone does not alter allele frequencies over time (Fisher, 1919; Jennings, 1916; Wright, 1921), but only increases the population variance of the property on which the assortment is based (Crow & 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 disassortative 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 (Champer, Zhao, et al., 2020; Dhole et al., 2018; Hay et al., 2010; Ward et al., 2011), 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* (Diabate & Tripet, 2015; Sawadogo et al., 2013), 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 & Pfennig, 2020), genetic swamping (Todesco et al., 2016) and reproductive isolation (Schumer et al., 2015).

LIFE HISTORY

Broadly, there are three key life stages in which the spread of the gene drive can be affected: gamete, zygote and adult (Verma 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 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, Zhao, et al., 2020; 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, Bennett, 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 & 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 favourable 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 & Dennehy, 2005). Such a bet-hedging strategy can profoundly influence genetic diversity (Ellner & Hairston, 1994; Hairston & Kearns, 2002; Hedrick, 1995; Koopmann et al., 2017), demography (Rubio de Casas et al., 2015), recombination (Shoemaker & Lennon, 2018) and reproductive and migration rates (Blath et al., 2021; Buoro & Carlson, 2014; Heinrich et al., 2018; Tellier et al., 2011). Even in the absence of selection, the seedbank reduces the effect of genetic drift and can change patterns of genetic diversity and population demography (Blath et al., 2015, 2020; Kaj et al., 2001). With the increased interest in the application of gene drives to organisms with dormancy traits, such as plants (Neve, 2018; Siddiqui et al., 2021), fungi (DiCarlo et al., 2015; Halder et al., 2019; Pennisi, 2020; Yan & Finnigan, 2018), 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 modelling.

Proof-of-concept modelling 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 & 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) 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 (Heinrich et al., 2018; Koopmann et al., 2017) and simulation studies (Korfmann et al., 2023; Shoemaker & Lennon, 2018) 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 modelling platform to initiate such investigations. Further modelling 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 modelling.

Life history traits that depend on external environmental cues—such as mosquito diapause—can also be utilized for designing gene drives and deployment strategies. For example, a modelling study of a gene drive mechanism incorporating a diapause-specific promoter (Akbari et al., 2014) showed that if the gene drive spreads to fixation before the environmental cue causing diapause appears (e.g., dry season), then population eradication can be achieved. Such environmental cue-dependent life-history-specific gene drive strategies can be desirable because the genetic architecture can be

designed to be species specific, limiting the potential for inter-species spillovers. Further, since the environmental cue activating the gene drive phenotype often has a spatial dependency, such as altitude and geographic location, the effect of the population suppression by the gene drive can be confined to specific geographical regions (see *Environmental Variation* section).

INTER-SPECIES CROSSOVER

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

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

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

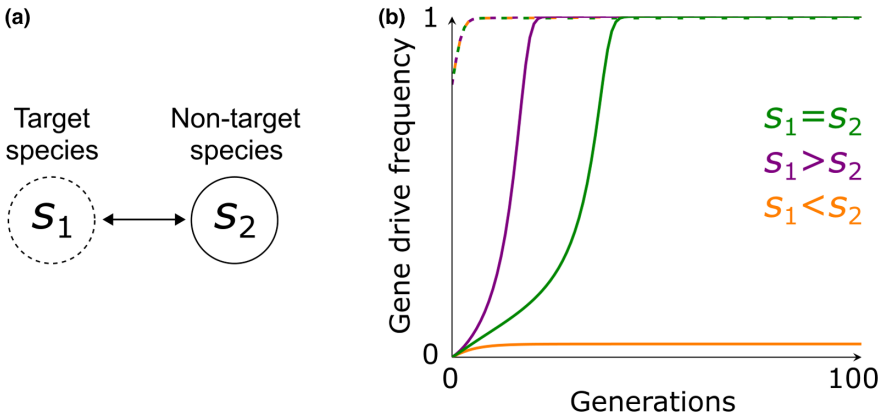

FIGURE 5 Model of gene drive inter-species crossover. (a) The model follows the two-population model in Figure 2a, but in each species, the gene drive fitness costs are different: s_1 in the target species (dashed lines) and s_2 in the non-target species (continuous lines). (b) The gene drive frequency in the two species for $s_1 = s_1 = 0.5$ in green, $s_1 > s_2$ in purple ($s_1 = 0.5$, $s_2 = 0.4$) and $s_1 < s_2$ in orange ($s_1 = 0.5$, $s_1 = 0.6$). 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).

fitness cost and efficiency of the gene drive not only in the target species but also in all other closely related and geographically overlapping species.

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

CONCLUSIONS AND FUTURE DIRECTIONS

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

We have highlighted a number of areas where integrating new mathematical and computational methodologies can aid in addressing the ecological impacts on gene drive dynamics. In studying spatiotemporal gene drive dynamics, for example, ideas and methods from network science can be used to model more realistic population structures, as has been done in the field of ecological genetics (Dyer, 2015; Dyer & Nason, 2004; Greenbaum & Fefferman, 2017). Detailed geographic information and explicit landscape features could be incorporated into system-specific landscape genetic models (Manel et al., 2003; Manel & Holderegger, 2013; Storfer et al., 2007) to investigate the outcomes of gene drive dynamics and evaluate interventions in a realistic spatial setting (e.g., North et al., 2019, 2020; Selvaraj et al., 2020). Applying ecological extinction–colonization theory to gene drives may provide insights into dynamics such as those described in Box 2 and Figure 3. Finally, optimal control theory (Lampert & Liebhold, 2021; Lenhart & Workman, 2007; Rafikov et al., 2009) combined with evolutionary game theory (Adami et al., 2016) can provide insights into the optimal gene drive deployment strategy that accounts for both eco-evolutionary dynamics and socioeconomic costs influencing the management and control of the target species. Importantly, since many theories and modelling approaches are used to model gene drive dynamics, it is crucial to maintain as much compatibility and comparability between models as possible. One way to achieve this is by demonstrating where model results converge or diverge between newly published models and previous models.

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

A key challenge will be determining the appropriate level of ecological complexity that needs to be included in a gene drive model for any specific application, as the ideal model is typically the simplest one that still contains all relevant features. Yet, how can we know which features will ultimately be relevant? This fundamental problem cannot be solved through modelling alone but will require experiments and field studies to assess a model's accuracy in predicting the most important aspects of the real-world system. Once a sufficiently accurate model has been identified, sensitivity analysis of its parameter space will be needed to reveal which features are critical and which could be neglected without losing too much predictive accuracy. However, such analyses become increasingly cumbersome as the number of parameters in a model increases. Recent work has suggested promising new avenues to tackle this problem using supervised machine learning. For instance, in a study on the potential of gene drives for suppressing invasive rodent populations, a complex eco-evolutionary simulation model was accompanied by an adaptively trained meta-model, which enabled in-depth sensitivity analyses that would have been prohibitively time consuming using the underlying simulation model alone

(Champer, Oakes, et al., 2022). Such new statistical approaches can help us develop a better understanding of a model's outcome space and identify the parameters that must be measured most accurately in experiments or ecological field studies.

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

AUTHOR CONTRIBUTIONS

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

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DATA AVAILABILITY STATEMENT

The models for Figures 2–5 can be accessed at https://doi.org/10.5061/dryad.8931zcrvr.

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