ORIGINAL ARTICLE

MOLECULAR ECOLOGY WILEY

Gene drives for vertebrate pest control: Realistic spatial modelling of eradication probabilities and times for island mouse populations

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Abstract

Invasive alien species continue to threaten global biodiversity. CRISPR-based gene drives, which can theoretically spread through populations despite imparting a fitness cost, could be used to suppress or eradicate pest populations. We develop an individual-based, spatially explicit, stochastic model to simulate the ability of CRISPR-based homing and X chromosome shredding drives to eradicate populations of invasive house mice (*Mus muculus*) from islands. Using the model, we explore the interactive effect of the efficiency of the drive constructs and the spatial ecology of the target population on the outcome of a gene-drive release. We also consider the impact of polyandrous mating and sperm competition, which could compromise the efficacy of some gene-drive strategies. Our results show that both drive strategies could be used to eradicate large populations of mice. Whereas parameters related to drive efficiency and demography strongly influence drive performance, we find that sperm competition following polyandrous mating is unlikely to impact the outcome of an eradication effort substantially. Assumptions regarding the spatial ecology of mice influenced the probability of and time required for eradication, with short-range dispersal capacities and limited mate-search areas producing 'chase' dynamics across the island characterized by cycles of local extinction and recolonization by mice. We also show that highly efficient drives are not always optimal, when dispersal and mate-search capabilities are low. Rapid local population suppression around the introduction sites can cause loss of the gene drive before it can spread to the entire island. We conclude that, although the design of efficient gene drives is undoubtedly critical, accurate data on the spatial ecology of target species are critical for predicting the result of a gene-drive release.

KEYWORDS
CRISPR, homing drive, Island conservation, pest eradication, spatial model, X-shredder

1 | INTRODUCTION

Invasive alien species threaten biodiversity worldwide (Lovell et al., 2021) and are significant contributors to extinctions on islands (Blackburn et al., 2004; Burbidge & Manly, 2002; Clavero & García-Berthou, 2005; Russell & Kueffer, 2019; Russell et al., 2017). As the majority of recent extinction events have occurred on islands, they are critical targets for conservation efforts (Jones et al., 2016). Eradicating invasive alien species has been used successfully as a conservation tool to prevent further extinctions and restore species diversity. Successful eradications have been achieved on more than 1000 islands (DIISE, 2018; Holmes et al., 2019), and the response of native species has generally been positive to these eradication efforts (Jones et al., 2016). Unfortunately, long-term negative impacts have also been reported for a few species that were affected by the control methods used (Courchamp et al., 2003; Jones et al., 2016). Unwanted consequences to nontarget organisms associated with classical control methods, such as poison baiting, trapping or hunting (Howarth, 1991), make CRISPR-based gene-drive approaches an enticing alternative for eradicating invasive alien species. Gene drives are designed to be species specific, unlike most toxicant-based methods, and they can potentially be developed in any laboratory with appropriate transgenesis expertise (Esvelt et al., 2014; Godwin et al., 2019; Leitschuh et al., 2018; Oh et al., 2021; Webber et al., 2015).

A CRISPR-based 'homing' gene drive is a transgene composed of Cas9 endonuclease and gRNA expression constructs, inserted at the genomic site targeted by the gRNA, which induces double-stranded DNA breaks. This double-stranded break on the homologous chromosome is repaired through homology-directed repair, thereby copying the drive construct and converting heterozygotes to homozygotes and distorting Mendelian inheritance patterns (Burt, 2003; Gantz & Bier, 2015; Pfitzner et al., 2020; Windbichler et al., 2011). If the homing event is restricted to the germline, drives that disrupt genes related to sex determination, fertility or viability can be spread despite the obvious costs, and could potentially be used to drive populations to extinction (Deredec et al., 2008; Galizi et al., 2014, 2016; Kyrou et al., 2018; Prowse et al., 2017, 2018, 2019; Windbichler et al., 2008). The relative ease with which an invasive drive construct could spread through populations is potentially a high risk associated with this new technology (Webber et al., 2015). Accidental spread of the drive to nontarget populations remains a valid concern (Esvelt et al., 2014; Golnar et al., 2021; Noble et al., 2018; Webber et al., 2015).

Invasive house mice (*Mus muculus*) on isolated islands are an ideal model system for the development of genetic biocontrols for several reasons. Invasive rodents, including house mice, are recognized as the primary driver of many extinctions on islands (Angel et al., 2009; Godwin et al., 2019; Howald et al., 2007; Towns et al., 2006; Wanless et al., 2007). Geographic isolation, often combined with low levels of human movement, reduces the probability of gene flow to other areas. Moreover, house mice are the only introduced mammal on many islands, which effectively eliminates the possibility of gene flow to other species through hybridization. House mice also have strong negative impacts on the islands they have invaded (Angel et al., 2009; Jones et al., 2016), so eradicating mice from islands using gene-drive technologies is potentially a low-risk, high-gain option (Champer, Oakes, et al., 2021; Champer, Kim, et al., 20121; Godwin et al., 2019; Howald et al., 2007; Leitschuh et al., 2018; Webber et al., 2015).

Despite some promising empirical data (Grunwald et al., 2019), efficient germline homing in mice is yet to be developed (Pfitzner et al., 2020; Singh et al., 2015). Further, a major obstacle to the development of CRISPR-based gene drives that require homing is the action of DNA repair pathways other than homology-directed repair. When the DNA break affected by the Cas9/gRNA complex is repaired through Non Homologous End Joining (NHEJ), a small deletion or insertion mutation (indel) usually results, creating a drive-resistant allele, which could subsequently inhibit drive spread (Champer et al., 2017; Esvelt et al., 2014; Unckless et al., 2017). Although Prowse et al. (2017, 2018) showed using *in silico* modelling that multiplexed gRNAs could overcome the evolution of resistance, this strategy has never been tested empirically in mice (Champer et al., 2020). Therefore, there is considerable interest in alternative drive strategies that do not require homing and are less likely to produce resistant genotypes.

One promising strategy is a CRISPR-based construct inserted within the Y chromosome that targets the X chromosome for deletion. This X-shredding drive (also known as 'driving Y') suppresses the population by biasing offspring sex ratios towards males so that females become increasingly limiting. Theoretical models suggest that this strategy could be effective for population eradication (Beaghton et al., 2016; Deredec et al., 2008, 2011; Eckhoff et al., 2017; Hamilton, 1967; Prowse et al., 2019). Encouragingly, autosomal X-shredding drives have been demonstrated in mosquito germlines (Galizi et al., 2014, 2016; Windbichler et al., 2008), and Y chromosome X-shredding activity has been achieved in mouse zygotes (Zuo et al., 2017).

Theoretical models have been particularly important to understand the key factors that influence the spread of gene drives, since empirical studies in the wild are not yet possible. Models that provide realistic representations of the target pest species are essential to understand the factors that influence the spread of gene drives (Golnar et al., 2021). One common omission of previous modelling efforts is the spatial structure that is characteristic of wild populations. When spatial dynamics are explicitly taken into account, gene-drive parameters that achieve eradication in panmictic populations often fail due to rapid local extinction, followed by wild-type recolonization (Eckhoff et al., 2017; North et al., 2013, 2019). These perpetual cycles of local drive extinction and wild-type invasion, also known as 'chase dynamics', could delay or even prevent eradication (Champer, Oakes, et al., 2021).

Considering the importance of spatial dynamics in predicting the success of a pest species management programme using gene drives, it is necessary to model dispersal and/or mate-search movements of individuals with realistic functions that capture the complexity

of dispersal observed in nature (Travis & French, 2000). Commonly used simplifications in spatial models, such as fixed-term dispersal rates, dispersing only to neighbouring patches, or random dispersal to any other patches are over simplifications (Travis & French, 2000). Density-dependent dispersal is ubiquitous in nature (Amarasekare, 2004; Matthysen, 2005; Travis & French, 2000), but the relationship between density and dispersal is not always positive (Matthysen, 2005; Travis & French, 2000). Dispersal rate often decreases with increasing abundance in various taxa (Matthysen, 2005; Travis & French, 2000) including small rodents (Denomme-Brown et al., 2020; Diffendorfer, 1998; Ims & Andreassen, 2005; Lambin, 1994; Lin & Batzli, 2001; Rehmeier et al., 2004; Smith & Batzli, 2006; Van Hooft et al., 2008). Moreover, dispersal distances tend to be longer when densities are low (Boonstra, 1989; Jones et al., 1988; Russell et al., 2005; Sandell et al., 1990). Both positive density-dependent dispersal and negative density-dependent dispersal are reported in house mice (Berry & Jakobson, 1974; DeLong, 1967). Typically in saturated populations, mice disperse is less than 70 m (Pocock et al., 2005) and shows high spatial fidelity (Liechti et al., 2020). However, experimental releases show that individuals tend to move longer distances when they are rare (ca. 400 m, MacKay et al., 2019). Movement distances up to 970 m are reported for house mice (Moro & Morris, 2000).

Dispersal patterns during range expansions, including biological invasions, can be very different to those in a saturated population (Travis & Dytham, 2002). Typically, there is strong selection for increasing dispersal abilities during range expansion (e.g. Phillips et al., 2006), which results in evolution of negative density-dependent dispersal Travis et al. (2009). It follows that inferring dispersal patterns from stationary or saturated populations for use in models of population eradication are unlikely to capture how invasive species behave when they are reduced to low densities. Spatial models that investigate eradications should incorporate more realistic dispersal algorithms that capture the dispersal dynamics when the populations are saturated, as well as when they are sparsely populated. Over simplistic dispersal functions could lead to not only sceptical acceptance of the model's results (Travis & French, 2000), but also to inaccurate predictions about eradication probabilities or times to eradication.

Polyandry, where a female can mate with multiple males within a breeding cycle, is also largely overlooked in theoretical models of gene-drive spread, despite the possibility of competition between the sperm of wild-type and gene-drive carrying individuals. Any impact of the drive construct on the number or mobility of an animal's sperm could affect the drive's spread (Deredec et al., 2008). In *Drosophila*, for example, a naturally occurring sex-ratio drive (the 'SR drive') destroys Y-bearing sperm and distorts the sex ratio towards females, but polymorphism is maintained in the population because drive-carrying males produce fewer, lower quality sperm (Price et al., 2008). This 'sperm disadvantage' becomes particularly important when females mate with multiple males; in natural populations where polyandry is higher, the frequency of the SR drive is lower (Pinzone & Dyer, 2013; Price et al., 2014). Theoretical models

also suggest that polyandry could pose a problem for spread of the SR drive (Holman et al., 2015; Taylor & Jaenike, 2002). Polyandry is common in house mice (Firman & Simmons, 2008a; Manser et al., 2017, 2020) and reduces the spread of the *t* haplotype, another naturally occurring drive (Manser et al., 2017, 2020).

Here, we develop an individual-based, spatially explicit, stochastic model that extends a family of individual-based models used previously to study speciation in various taxa (Birand et al., 2012; Duenez-Guzman et al., 2009; Gavrilets & Vose, 2005, 2007, 2009; Gavrilets et al., 2007; Sadedin et al., 2009). Using the model, we investigate the effectiveness of two gene-drive strategies, a CRISPR-based homing drive and a Y-chromosome-linked X chromosome shredding drive, for eradicating invasive house mice from islands. To ensure a realistic island simulation, we considered the invasive mouse population on Antipodes Island in New Zealand, which has recently been eradicated using poison baiting (Horn et al., 2019). With an area of ~2000 ha, Antipodes Island was home to ~200,000 mice before their eradication (Russell, 2012). Using a hypothetical island of similar size and mouse density, we explore the consequences of the efficiency of the drive constructs, together with the mating and dispersal patterns of the target mouse population, on the outcome of a simulated gene-drive release. With the ability to model large, spatially dynamic population sizes (~20,000 individuals) and overlapping generations, our model provides realistic estimates of the probability of successful eradication and expected times to achieve eradication under different simulation assumptions.

2 | METHODS

2.1 | Model

For the purposes of our model, the entities are individuals that occupy a rectangular array of patches that together form a hypothetical island. Patches hold multiple individuals; however, individuals are not restricted to a single patch but utilize multiple patches. Individuals are diploid and have genetically controlled autosomal traits and sex chromosomes. A single breeding cycle is considered as a time-step, which is composed of the following events: (1) mate search, (2) mating, (3) density-dependent reproduction, (4) natal dispersal, (5) survival and (6) breeding dispersal. There are multiple breeding cycles (n_c) per year and generations are overlapping. Individuals can go through a number of breeding cycles provided that they survive until they reach a maximum age (age_m).

2.1.1 | (1) Mate search

All females mate, unless there are no males present within their mate-search area determined by mate-search distance parameter D_m, or if they are infertile due to the lack of a functional fertility gene (see *Strategy 1—Homing drive* below). A female starts searching for males within her central patch and randomly chooses one male to

mate with from those present in that patch. If no males are present, the search continues incrementally with distance in the neighbouring patches until a male mate is found. All patches of equal distance have the same probability of being chosen during the mate search. Females retain their central patch within a breeding cycle, irrespective of whether they find a mate.

2.1.2 | (2) Mating

Females can mate with a single male or with multiple males (n_m) in a single breeding cycle depending on the probability of multiple mating (p_m), and the number of males present in the female's central patch. Multiple mating in a breeding cycle is not possible unless there are at least two males in the female's central patch. Note that females choose males randomly, which could mean that some males can mate multiple times in a single breeding cycle, whereas others may not mate at all.

2.1.3 | (3) Density-dependent reproduction

Fertility is density-dependent. The number of offspring from each mated female is drawn from a Poisson distribution with mean parameter v as given by the discrete-time Beverton–Holt model (Kot, 2001):

$$v = \frac{b}{1 + [(b/2) - 1][N/K]} \tag{1}$$

where b is the average number of offspring of females in the absence of density-dependent regulation; N and K are the population size and the carrying capacity in a female's central patch respectively.

Under polyandrous mating, the paternity of each individual offspring is determined based on a probability assigned to each of the possible fathers. We modelled sperm competition through mating order, sperm count, or both (Figure 1). The first male's advantage of siring offspring is determined by the probability p_{fs}. For gene-drive strategies that affect the sperm count (see *Strategy 2—X-shredding drive* below), the probability of siring an offspring is reduced compared to that of the wild-type male by a sperm disadvantage coefficient d_s. The sex of each offspring is determined by the sex chromosomes inherited from parents.

2.1.4 | (4) Natal dispersal

All offspring are assumed to survive and become subadults since the density-dependent reproduction function (Eq. 1) implicitly incorporates offspring mortality. Before joining the mating pool as adults in the next breeding cycle, a subadult can leave its maternal patch and disperse to a new patch within distance D_n to establish
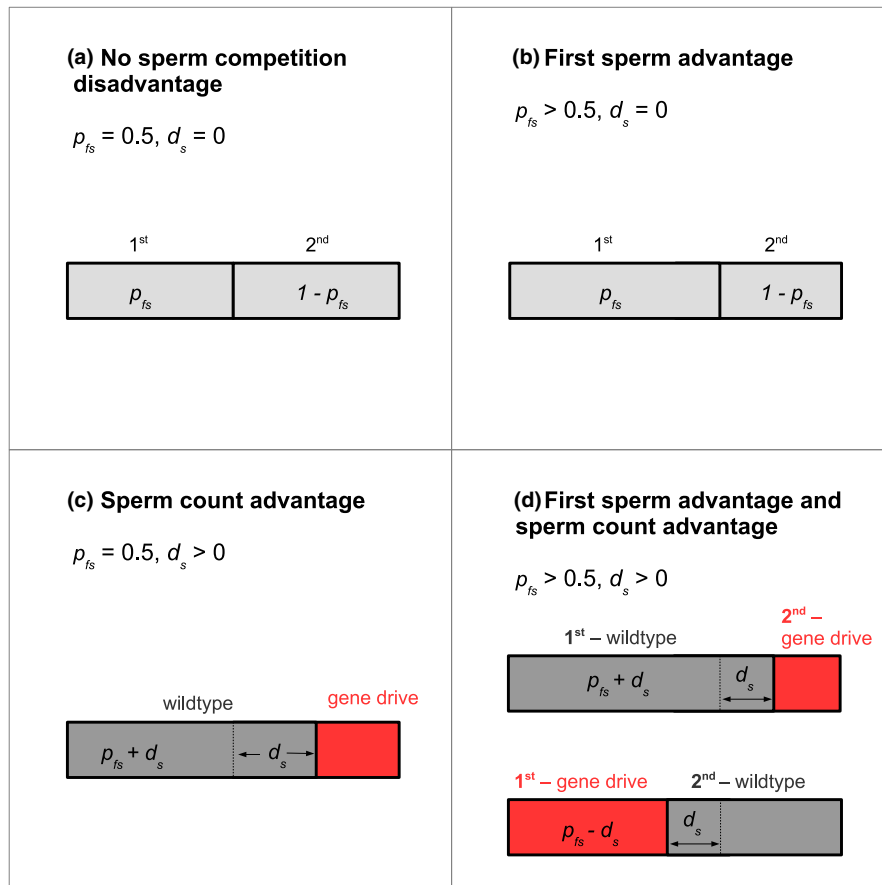

FIGURE 1 Possible scenarios for sperm competition. (a) There is no sperm competition if the first male's probability of siring the offspring is $p_{fs} = 0.5$, and if there is no disadvantage based on sperm count, $d_s = 0$. (b) The first male's sperm has an advantage when $p_{fs} > 0.5$ and $d_s = 0$, irrespective of his or the second male's genotype. (c) The probability of siring an offspring is reduced for gene-drive carrying males compared to that of wild-type males, when $d_s > 0$ due to the sperm count, irrespective of the order they have mated. d) Both the order of mating and the sperm count affects the probabilities of siring when $p_{fs} = 0.5$ and $d_s > 0$. The first male's advantage is exaggerated if it is a wild-type individual and the second male carries the gene drive. Conversely, the first male's advantage is reduced if the reverse is true

a mate-search area before its first breeding attempt (Section 1 above). We assumed that natal dispersal is both distance and negative density dependent, and the probability of dispersing to distance δ is calculated as:

$$P(\delta) = \exp\left[\left(a\frac{\delta}{D_n} - c\frac{N_r}{K_r}\right)^2\right] \qquad (2)$$

where a and c are dispersal and density coefficients respectively; D_n is the maximum distance that a subadult could disperse; N_r is the population size, and K_r is the carrying capacity, where both are both calculated by summing across all the patches within distance D_n. The probabilities are normalized to sum to one for each dispersing individual (see Figure S1a). All patches of equal distance have the same probability of being chosen irrespective of their direction. Also note that the number of patches available is reduced according to the number of neighbouring patches at the landscape boundaries.

The negative density-dependent dispersal function ensures that when the population size is close to carrying capacity, the probability of dispersing long distances is low (Figure S1a). We tested two additional natal dispersal functions. First, we assumed that natal dispersal is both distance and positive density dependent:

$$P(\delta) = \exp\left[\left(a\frac{\delta}{D_n} - \left(1 - c\frac{N_r}{K_r}\right)\right)^2\right] \qquad (3)$$

which implies the reverse of our default dispersal function (Eq. 2); that is, when the population size is close to carrying capacity, the probability of dispersing long distances is higher and subadults tend to move longer distances (see Figure S1b) to establish new mate-search areas, but when density is low, individuals tend to stay in their patches, or move shorted distances. Second, we assumed that natal dispersal is random within distance D_n.

2.1.5 | (5) Survival of adults

Survival of adults is implemented using a fixed probability of surviving ω to the next breeding cycle. To incorporate the possibility of an additional fitness cost imposed by a drive, the survival probability of gene-drive carrying individuals is reduced further by a multiplicative constant ω_d.

2.1.6 | (6) Breeding dispersal

Surviving adults can establish new mate-search areas with a new central patch within distance D_b (Harts et al., 2016). The probability of moving a distance δ is both distance and negative density dependent and is calculated as Eq. 2 (for simplicity, we assume that the maximum distances for natal dispersal, breeding dispersal and

mate-search distance parameter are physiologically constrained to be equal, and determined by D, that is $D_n = D_b = D_m = D$).

The negative density-dependent dispersal function (Figure S1a) ensures that when the population size is close to carrying capacity, individuals (subadults or adults) tend to retain the same central patch for natal and breeding dispersal, and form long-term stable communities (e.g. Liechti et al., 2020). At low densities, the probability of picking a distant patch to centre its new mate-search area is higher, which can be justified by an individual's imperative to move large distances to find mates when local density is nearly zero (e.g. MacKay et al., 2019; Nathan et al., 2015; Russell et al., 2005). Another common way of modelling this type of dispersal behaviour is to assume a constant proportion of dispersing individuals in the population that would experience higher mortality in their new patches with increasing distance and/or density (e.g. Champer, Oakes, et al., 2021).

2.2 | Suppression strategies

We explored the spread of two gene-drive strategies, the homing and X-shredding drives.

2.2.1 | Strategy 1—Homing drive

The homing drive is a CRISPR-based drive that is positioned in an exon of a haplosufficient female fertility gene (e.g. prolactin), generating a loss-of-function mutation. The fertility gene is autosomal and is present in both females and males. Deactivation of the gene occurs in the germline in both sexes; however, the gene is required only in females. If both copies of the gene are deactivated, she is considered infertile. The probability of successful homing of the drive is given by $p_C(1-p_N)$, where p_C is the probability of a successful cut, and p_N the probability of NHEJ. If homing fails due to NHEJ, the resulting allele can be functional with probability $p_C p_N(1-p_L)$, or nonfunctional with probability $p_C p_N p_L$, where p_L is the probability of loss of gene function following NHEJ. The probability that no DNA cutting occurs is $1-p_C$.

2.2.2 | Strategy 2—X-shredding drive

The X-shredding drive is a CRISPR-based drive located on the Y chromosome and cuts the X chromosome with probability p_x at multiple locations beyond repair during spermatogenesis. X-bearing sperm are destroyed, and eggs are predominantly fertilized by Y-bearing sperm, causing disproportionately more male offspring. Destroying the X-bearing sperm could potentially reduce the sperm count of males that carry the gene drive, which in turn could reduce their competitive ability against sperm from wild-type males (see mating section above). The X-shredding drive is inherited by male offspring only. We assumed that inviable X-bearing sperm do not reduce the availability of eggs to viable Y-bearing sperm by pseudofertilization

and that breaks in the X chromosome cannot be repaired by joining the two cleaved ends. Lastly, we assume that the evolution of alternative pathways of sex determination is unlikely.

2.3 | Parameters and initial conditions

Where available, model parameters are based on empirical data (Table 1). We assumed that the average number of offspring (b) produced by a female in the absence of density-dependent regulation in each breeding cycle is 6 (Murphy & Nathan, 2021). The maximum age (age_m) of individual mice is assumed as 2 years (Elliott et al., 2015; Murphy & Nathan, 2021); even though few simulated mice survive to that age and the survival probabilities specified (ω) effectively determine the age distribution of mice in the population (see Table

TABLE 1 Parameters of the model. For sensitivity analyses (SA), parameter combinations are drawn from a uniform distribution (U) or uniform discrete distribution (U_d) using Latin hypercube sampling

Parameter	Baseline value	SA
Life history		
Average number of offspring (b)	6	
Maximum age (age_m)	2	
Number of breeding cycles in a year (n_c)	6	
Dispersal coefficient (a)	1	
Density coefficient (c)	1	
Natal and breeding dispersal distance (D)	5	$U_d(1, 8)$
Drive fitness (ω_d)	1	$U(0.7, 1)$
Probability of survival (ω)	0.1	$U(0.1, 0.8)$
Carrying capacity per patch (K)	40	
Polyandry		
Probability of multiple mating (p_m)	0.2	$U(0, 0.8)$
Number of males mated per breeding cycle (n_m)	2	
Probability of first male siring an offspring (p_{fs})	0.5	$U(0.5, 0.8)$
Sperm disadvantage coefficient (d_s)	0.2	$U(0, 0.2)$
Inoculation		
Number of inoculation sites	16	
Number of gene-drive carrying individuals inoculated (N_i)	8	
Number of releases over time (n_t)	1	
Gene-drive parameters, Strategy I - Homing drive		
Probability of NHEJ (p_N)	0.02	$U(0, 0.1)$
Probability of loss of function after NHEJ (p_L)	0.999	$U(0.99, 1)$
Probability of successful cut (p_C)	1	$U(0.9, 1)$
Gene-drive parameters, Strategy II - X-shredding drive		
Probability of Y-drive shredding the X chromosome (p_x)	0.96	$U(0.9, 1)$

S1). Lastly, based on observed intervals between litters (Murphy & Nathan, 2021), we assumed that the number of breeding cycles in a year (n_c) is 6. However, the actual number of litters a female produces during her lifetime depends on the number of breeding cycles she survives, and the random offspring number drawn from the Poisson distribution (Eq. 1) each breeding cycle. When that number is zero, which is often the case near carrying capacity, the female skips a breeding cycle without producing offspring.

Under polyandrous mating, we assumed that the females can mate with up to two males ($n_m = 2$) in a breeding cycle, since generally two sires are observed within litters of field-caught pregnant females that show multiple paternity (Firman & Simmons, 2008a). The probability of the first male siring an offspring, $p_{fs} = 0.5$, means that there is no advantage to the first male, since the probability of the second male siring an offspring then becomes $1 - p_{fs} = 0.5$ (Figure 1). Higher values of p_{fs} represent a first male advantage (Firman & Simmons, 2008b; Sutter & Lindholm, 2016; Sutter et al., 2016). The probability of siring offspring could also be affected by sperm count. We therefore used a sperm disadvantage coefficient (d_s) to reduce a gene-drive carrying male's probability of siring offspring when competing against a wild-type male, irrespective of the mating order (Figure 1).

Our hypothetical island is ~2000 with ~200,000 mice. We assumed that the island is comprised of $64 \times 64 = 4096$ patches, each of which roughly corresponds to a 70 m × 70 m space. We initiated each patch with 20 males and 20 females, and allowed the population to reach ~200,000 individuals before introducing gene-drive carrying individuals. In order to keep the overall population size on the island stable under different demographic parameterizations before inoculation, we adjusted the per-patch carrying capacity (K) together with survival probabilities ω. In a classical sense, the carrying capacity of the island is ~200,000 individuals, and K only affects population size through reproduction (see Eqn. 1).

In order to calibrate the dispersal distances D on our hypothetical island, we checked the time it would take for a few individuals to successfully colonize the entire island. We assumed that four individuals invade the top, middle and bottom patches on the left edge of the island (twelve individuals in total), and we recorded the first time when an individual reached the right edge of the island with various maximum dispersal distances (D) and natal dispersal functions (Figure S3). Maximum dispersal distances $D \geq 4$ with negative density-dependent and random dispersal functions, and $D \geq 5$ with positive density-dependent function allow for the colonization of the entire island in 2–3 years, which fits with the historical invasion of the Antipodes island at the start of the 20th Century (Taylor, 2006). The maximum dispersal abilities $D = [4,7]$ in the model correspond to [240,560] m in the wild, which are within the reported ranges in literature (Moro & Morris, 2000; Nathan et al., 2015).

After a burn-in period of two years, the simulated island is inoculated with males carrying one of the gene-drive constructs detailed above. We modelled a single release into 16 patches distributed systematically across the island, with eight gene-drive carrying individuals ($N_i = 8$) released into each patch (i.e. a total of 128 individuals).

Such 'patchy' inoculations are more effective and generally require the release of fewer gene-drive carrying individuals to achieve success when compared to a single point release strategy (Huang et al., 2011). Following their release to particular patches, gene-drive carrying individuals randomly choose a patch within distance *D*, as described in the step 6 above, and join the pool of available males for mating. As described in step 1 of the model, females choose males randomly among all the available males, which implies that some gene-drive carrying males may not be chosen for mating.

We ran simulations for a maximum of 300 breeding cycles (50 years), but terminated simulation runs once populations were successfully eradicated. The model is coded using C programming language.

2.4 | Sensitivity analysis

We performed a global sensitivity analysis for each gene-drive strategy modelled to investigate the relative influence of parameters on the probability of successful eradication and the time to eradication. In each case, we created 10,000 unique parameter combinations from parameter ranges given in Table 1 using Latin hypercube sampling (randomLHS, R package lhs Carnell, 2020). We ran a single simulation for each parameter sample to maximize the coverage of the parameter space while minimizing computational effort (Prowse et al., 2016). Finally, we examined the influence of parameter inputs using Boosted Regression Tree models (BRT; R package *dismo* Hijmans et al., 2011) that we fitted to the sensitivity analysis output using the function gbm.step from the R package 'dismo' with the following settings: learning rate: 0.01, which determines contribution of each tree to the growing model; bag fraction: 0.75, which determines the proportion of the data to be selected at random without replacement from the full training set; tree complexity: 3, which determines the fitting of interactions; and fivefold cross-validation (Elith et al., 2008). *k*-fold cross-validation evaluates the model performance on *k*−1 subsets of the training data and then calculate the average prediction error rate, and repeats this process until each of the *k* subsets has served as the test set (Elith et al., 2008).

We used binomial error distribution for the probability of eradication, and Poisson error distribution for time to eradication (Elith et al., 2008). We labelled simulation outcomes as unsuccessful for the binomial error distribution if the drive was lost, resistant genotypes emerged, or eradication did not occur within the number of breeding cycles simulated, even though the population was suppressed to a new stable level. To investigate the influence of parameters on the time to eradication, we only used simulations when eradication was successfully achieved.

3 | RESULTS

Our simulations indicated that both the CRISPR-based homing drive and the X-shredding drive could be used to eradicate a population of ~200,000 mice from an island with size ~2000 ha. After inoculation of the population with 128 gene-drive carrying males, the drive constructs spread rapidly to the subsequent generations through reproduction, and to new areas through dispersal. For simulations in which mice were eradicated successfully, the population either declined rapidly and smoothly to extinction (Figure 2); or extinction occurred later after chase dynamics produced successive waves of local extinction and recolonization (Figure 3). Initial population decline was equally rapid in simulations where eradication was eventually unsuccessful due to evolution of resistance (Figure 4).

For both gene-drive strategies, parameters related to drive efficiency strongly affected the probability of successful eradication (Figure 5a,b). For the homing drive, the probability of eradication depended largely on the probabilities of NHEJ (p_N) and of loss of function of the target gene following NHEJ (p_L). Even low p_N could thwart the simulated eradication attempt when p_C was less than one, because functional resistant alleles were likely to evolve and spread rapidly through the target population (Figure 6a). Only when p_L was very close to one, NHEJ became less important since the target gene usually became nonfunctional after NHEJ. With low p_N, and high p_L, a homing drive could achieve eradications in less than 5 years (Figure 2). When p_L <1, as p_N increases, after an initial suppression the population is likely to bounce back to pre-inoculation size very quickly due to the evolution of resistance (Figure 4).

We found that the X-shredding drive could also be an effective tool for population eradication, achieving high levels of suppression very quickly after introduction to the population (Figure 3). However, the probability of X chromosome shredding (p_x) strongly influenced the probability of eradication (Figure 5b). For p_x < 0.85, the drive failed to eradicate the mouse population (Figure 7a,b); instead, it suppressed the population to a new stable equilibrium, because the production of female offspring continued due to inefficient shredding. Interestingly, a higher X chromosome shredding efficiency did not always translate into a higher probability of eradication (Figure 7a,b), mostly due to spatial dynamics (see below).

For both gene-drive strategies, the survival probability ω of mice each breeding cycle was the primary determinant of the time to eradication, rather than parameters governing the efficiency of the drive construct (Figure 5a,b). Lower survival probabilities translated into less generational overlap, faster turnover between generations, and hence a faster spread of the drive (also see Table S1). For both the strategies modelled, it was possible to achieve complete eradication of ~200,000 mice in <10 years with survival probabilities lower than 0.4 per breeding cycle (Figure 8).

Assumptions on space use by mice, including the mate-search and dispersal distances, affected the simulation outcomes in more subtle ways. This was most obvious for the X-shredding strategy, which could not be affected by the evolution of drive-resistant alleles (Figure 5a,b). For example, the seemingly counterintuitive finding of reduced probabilities of eradication with very high X-shredding efficiencies (Figure 7a,b) is explained because, with p_x close to one, low dispersal capacity and limited mate-search areas, the drive could cause rapid local population decline and extinction
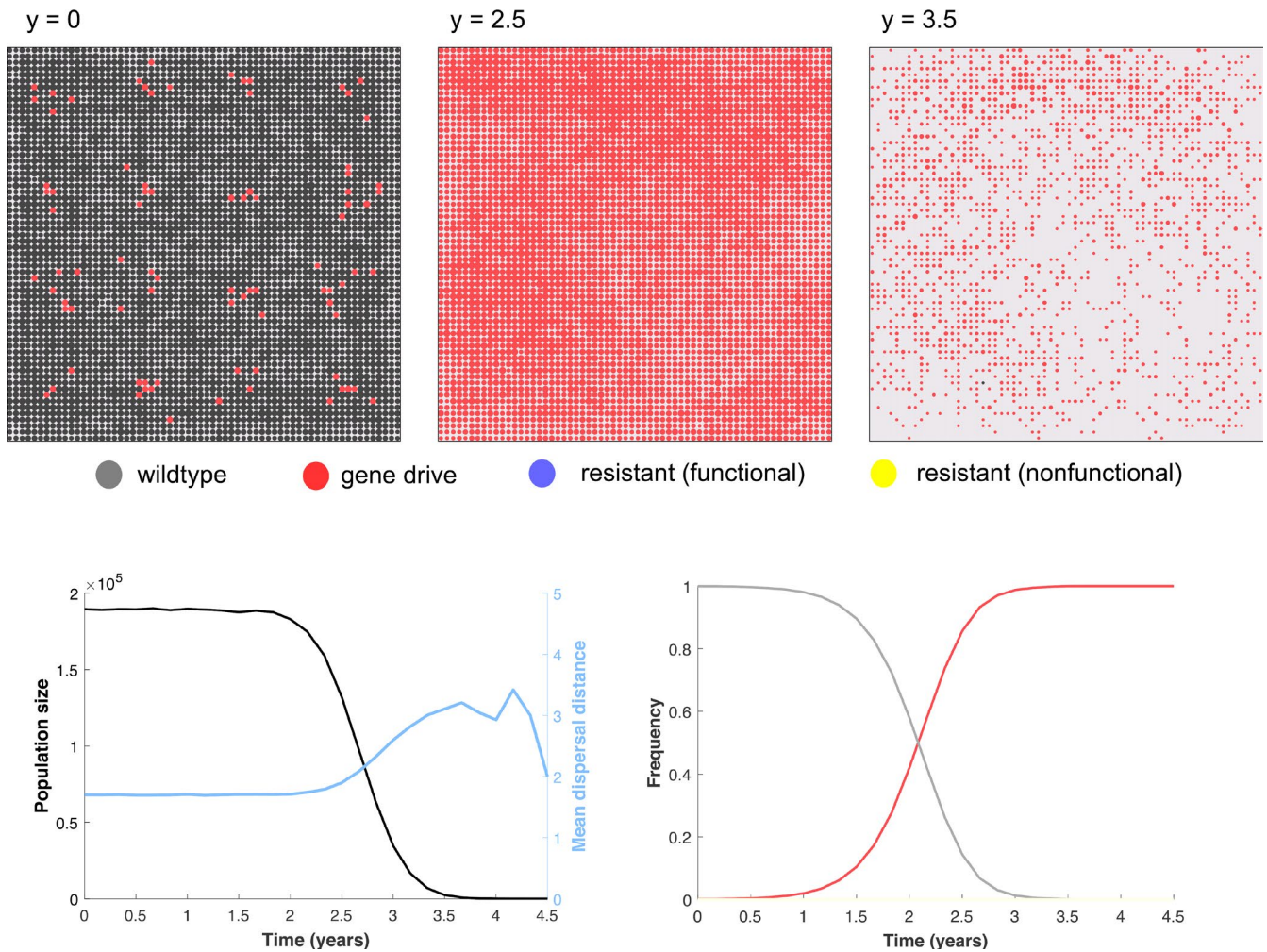
FIGURE 2 Progression of a simulation for the homing drive. Upper panel shows the distribution of the mouse population across each patch of the island through time, starting with the inoculation of gene-drive carrying individuals. Populations in patches are represented as circles, the size of which is proportional to the population size in that patch. The grey circles represent patches that contain wild-type individuals only. The colour changes as soon as the population has at least one individual with another genotype, which are presented below the plots. If multiple genotypes, other than the wild type are present, the colour represents the most dominant genotype. Empty patches appear as light grey. In the lower panel, the plot on the left shows the overall population size on the island through time, and the mean dispersal distance as it changes with density. The plot on the right shows the frequencies of wild-type and gene-drive carrying individuals, using the same colours as in the upper panel unless noted otherwise. At the time of inoculation ($y = 0$), gene-drive carrying individuals dispersed from their inoculation patches before breeding. Within a few years, the gene drive spread through the entire island, causing the rapid suppression and eventual eradication of the population in 4.5 years. The maximum population size was 189,786. (Parameter values that differed from values presented in 1 are: $p_N = 0.01$, $p_C = 0.9$, $p_{fs} = 0.7$, $d_s = 0$; see Supplementary Materials Online for a video of the simulation)

before spreading to neighbouring areas. Hence, the drive could be lost entirely in which case eradication failed (Figure 9a), or might 'chase' after the wild-type individuals that recolonized empty patches (Figure 9b). Less efficient drives (but with $p_x > 0.85$) resulted in higher probabilities of eradication (Figure 7b). Similarly, an efficient homing drive with low levels of NHEJ (p_N) did not guarantee the eradication success when dispersal was low (Figure 6b). Efficient drives could still be lost before spreading with $D = [4,7]$, corresponding to 240–560 m. in the wild, which are the biologically relevant dispersal abilities. Dispersal and mate-search distances also had high influence on the time to eradication, which is expected due to the influence of 'chasing' behaviour. Based on the predictions using the best number of trees derived from the BRT models fitted to the

sensitivity analysis output, the expected time to eradication for the homing drive increased from 5.63 years to 8.06 years when D was changed from 8 to 1.

Maximum dispersal distance D was more important for simulation outcomes than the shape of the natal dispersal function used (see Figure S4). Within the realistic dispersal distances described in *Parameters and initial conditions*, different natal dispersal functions did not substantially impact the probability of eradication or the time to eradication, although random dispersal consistently results in slightly shorter estimates of times to eradication. For shorter dispersal distances, positive density-dependent dispersal restricts dispersal ranges further at low densities, resulting in no eradication or longer times to eradication. Negative density-dependent dispersal,
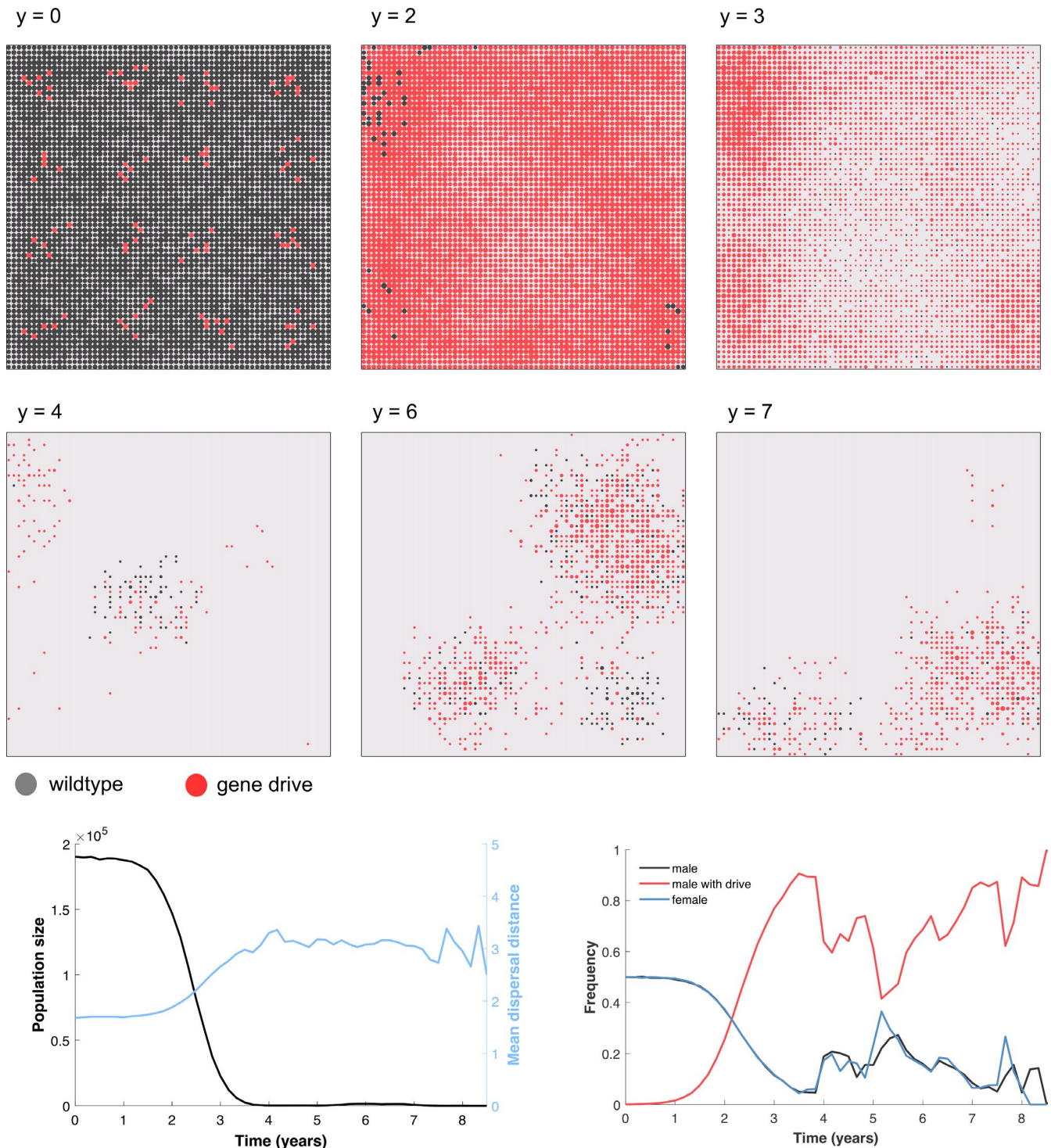
FIGURE 3 Progression of a sample simulation for the X-shredding drive (see Figure 2 for details). After inoculation, gene-drive individuals (red) are produced rapidly, suppressing the population in less than four years. Even though the overall population size remained low, complete eradication took four more years while drive-carrying individuals 'chased' wild-type individuals. The maximum population size was 190,476. (With p_x =1, p_{fs} =0.7; see Supplementary Materials Online for a video of the simulation)

which we think best captures the dispersal behaviour of mice more realistically, resulted in Gaussian-like distribution of dispersal events (Figure S2) with long-distance dispersal events becoming increasingly likely only when the population size was significantly reduced (~5% of its maximum size).

The parameters related to polyandry (probability of multiple mating, p_m) and sperm competition (probability of first male siring an offspring, p_{fs}, and sperm disadvantage coefficient, d_s) had very little influence on the eradication success of both the strategies (Figure 5a,b). For the homing drive, we considered the effect
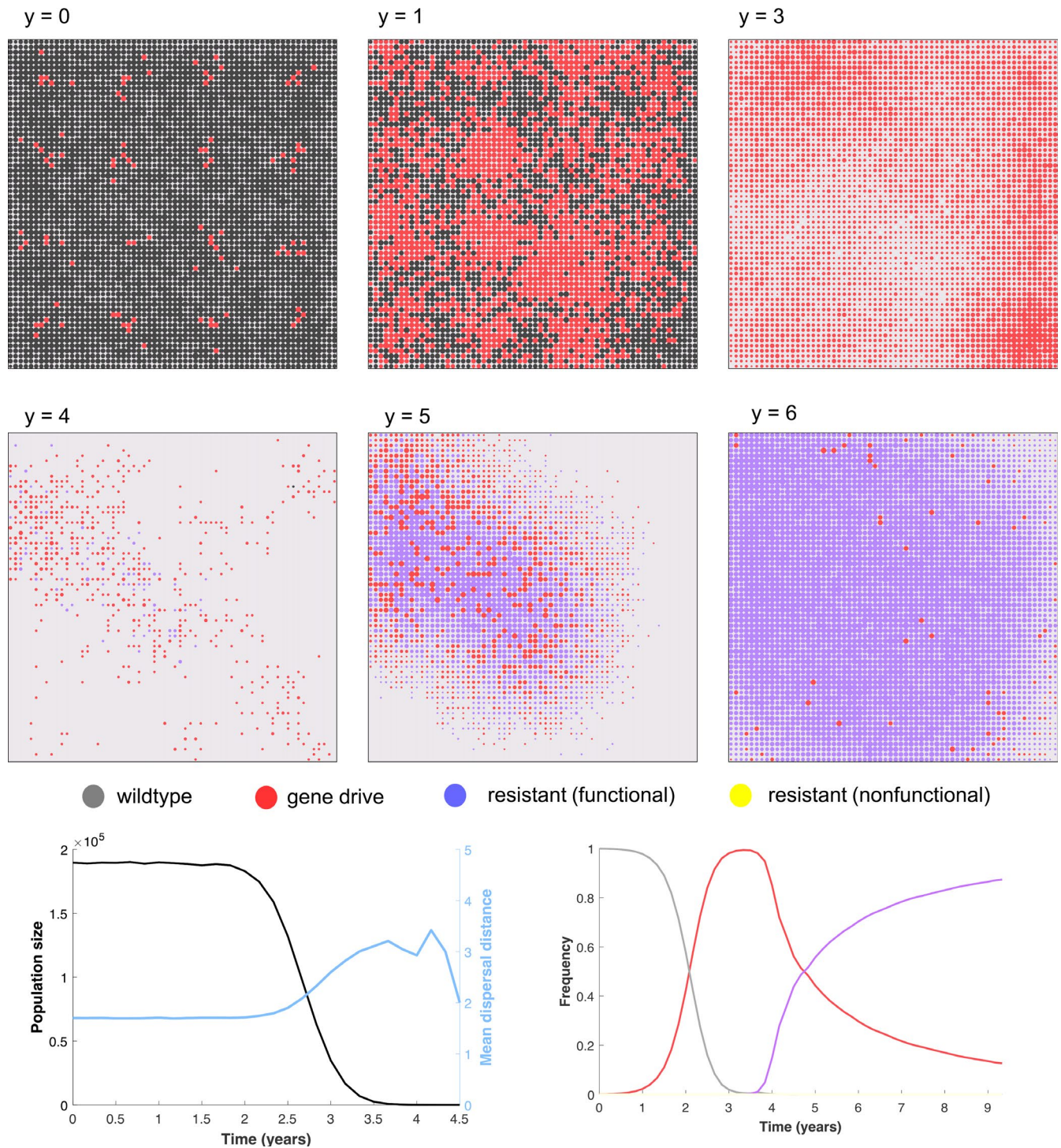
FIGURE 4 Progression of a sample simulation for the homing drive, where gene drive-resistant genotypes emerged (see Figure 2 for details). After inoculation, gene-drive carrying individuals (red) spread in the landscape and suppressed the population in three years. Around the same time, both functional (purple) and nonfunctional (yellow; visible in frequency plot only) resistant genotypes emerged; the former spread rapidly and the population size bounced back to pre-inoculation size. The maximum population size was 189,786. (With p_c =0.9, p_{fs} =0.7, d_s =0; see Supplementary Materials Online for a video of the simulation)

of first-sperm advantage only and found that it did not change the time to eradication with increasing levels of polyandry, nor with increasing first-sperm advantage (Figure 10a). For the X-shredding drive, we considered the effects of sperm competition through both first-sperm advantage and sperm count, and again found that

they did not substantially influence the probability of eradication (Figure 5b). Further, sperm competition governed through the sperm count delayed eradications only when the probability of polyandry (p_m) was very high (Figure 10b). Adding first-sperm advantage as an additional mechanism for sperm competition did not change this

FIGURE 5 Relative influence of parameters on the probability of eradication, and the time to eradication when successful, from Boosted Regression Tree models fit to the sensitivity analysis output for the homing drive (a) and X-shredding drive (b) strategies. Parameter abbreviations are provided in Table 1. (a) For the homing drive, probabilities of NHEJ (p_N) and loss of function after NHEJ (p_L) strongly influenced the probability of eradication; whereas, the survival probability (ω) per breeding cycle was the most important determinant of the time to eradication (when successful). (b) For the X-shredding drive, the efficiency of shredding p_x strongly influenced the probability of eradication, followed by the survival probability ω and dispersal distance D. All three also strongly influenced the expected time to eradication

(a)

(b)
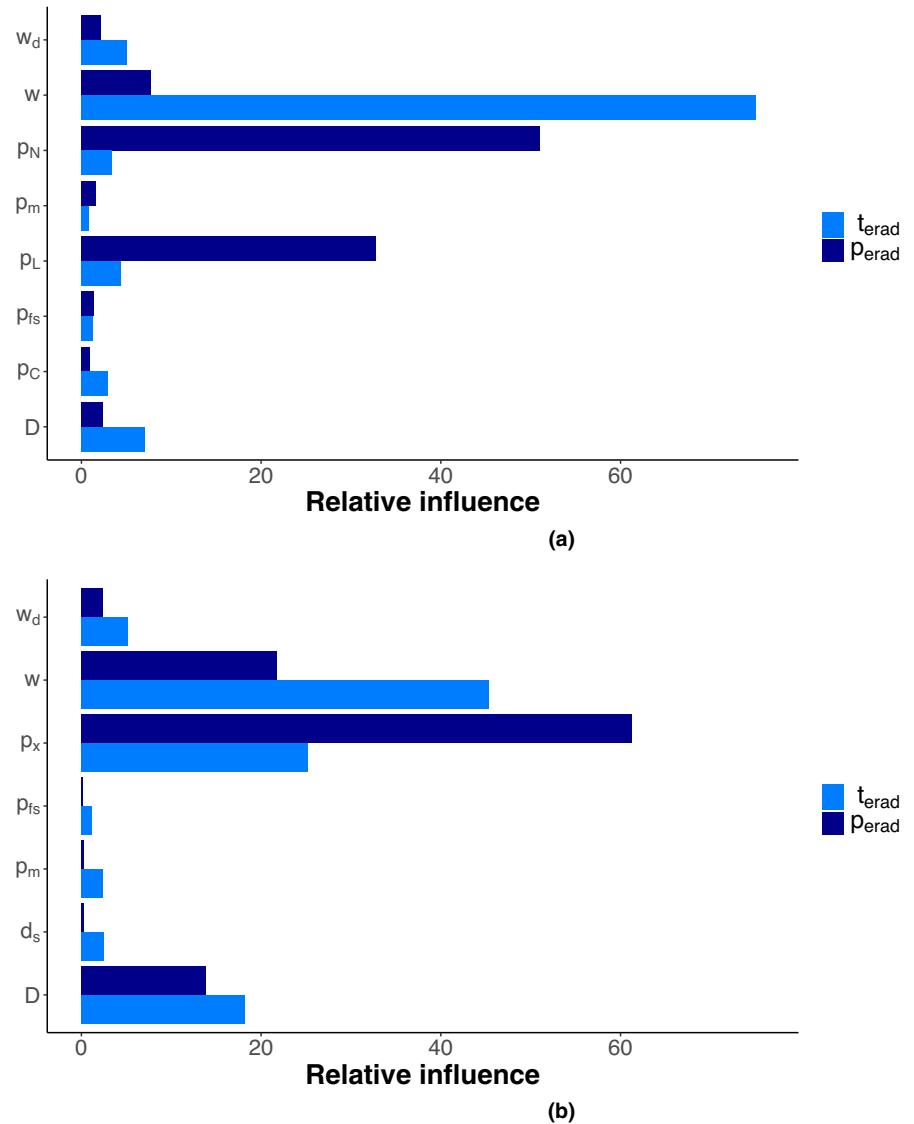
pattern (Figure 10b). With moderate levels of polyandry (p_m =0.4), eradication was delayed due to increased competitive advantage of the wild-type sperm over sperm from gene-drive carrying males with a lower sperm count (Figure 10c). Surprisingly, even when the wild-type sperm was afforded an absolute competitive advantage (d_s =0.5, p_{fs} =0), eradication could still be successful (Figure 10c).

4 | DISCUSSION

Over the last two decades, there has been substantial theoretical and empirical research interest in the development of genetic biocontrol technologies, including CRISPR-based gene drives designed to bias sex ratios or disrupt genes required for reproduction or development (Burt, 2003; Esvelt et al., 2014). Our individual-based, spatially explicit models suggest that gene drives could be used to eradicate invasive house mice from islands, but also highlight the critical importance of animal dispersal in governing the spread of gene drives through spatially structured populations,

which in turn impacts the probability of achieving eradication and the expected time to eradication.

Although many modelling studies have considered the efficacy of different gene-drive strategies to suppress or eradicate wild pest populations, to date most models have been nonspatial and thereby assuming a single panmictic pest population (e.g. Prowse et al., 2017, 2018, 2019) and/or have focused on nonmammalian pests (e.g. Eckhoff et al., 2017; North et al., 2013, 2019). Recently, however, Champer, Oakes, et al. (2021) used a spatially explicit model to consider the ability of three gene-drive strategies (two homing drives and an X-linked Y-shredder drive) to eradicate relatively small populations of mice (c. ~4000 individuals). In contrast, our study was motivated by a large invasive mouse population on an island home to 200,000 mice before their eradication. Our model shows that the two gene-drive strategies tested—a self-replicating homing drive that deactivates a haplosufficient fertility gene and a Y-drive that shreds the X chromosome in the male germline—could feasibly be used to eradicate 200,000 mice from an island of this size. An eradication could be achieved with inoculation of 128 gene-drive carrying
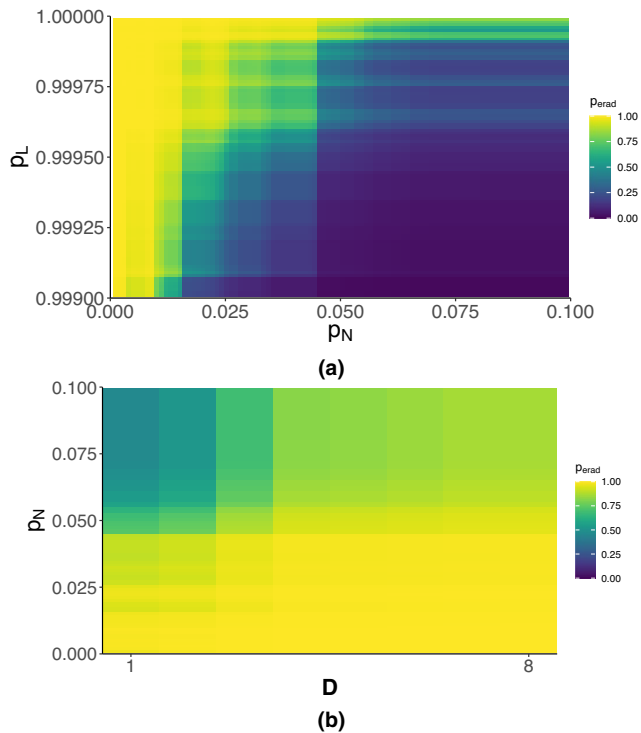
FIGURE 6 The expected probability of successful eradication (p_{erad}) using the homing drive, based on predictions from the Boosted Regression Tree model used for sensitivity analysis. (a) The influence of NHEJ (p_N) and loss of function after NHEJ (p_L), and (b) the influence of dispersal distance (D) and p_N, when p_L =1 (With p_m = 0 for both plots)

FIGURE 7 The expected probability of successful eradication (p_{erad}) using the X-shredding drive, based on predictions from the Boosted Regression Tree model used for sensitivity analysis. (a) The interaction between the X-shredding efficiency (p_x) and survival probability (w), and (b) between p_x and dispersal distance (D). (With p_m =0 for both plots)

FIGURE 8 Survival probabilities (ω) versus the expected time to eradication for the homing and X-shredding drives, based on predictions from the Boosted Regression Tree model used for sensitivity analysis. Both strategies achieved similar eradication times which were strongly influenced by the probability of survival (ω). (With p_m =0 for both strategies)

individuals, which is also encouraging since the cost of rearing gene-drive carrying individuals would be the main contributor to the cost of deploying this new technology (Atkinson et al., 2007).

Similar to previous nonspatial (Prowse et al., 2017, 2018; Wilkins et al., 2018) and spatial (Champer, Oakes, et al., 2021) models, our results indicate that the performance of a homing drive that disrupts a haplosufficient gene required for female reproduction is substantially reduced if gene mutations develop due to Non Homologous End Joining (NHEJ). If the NHEJ repair pathway is activated following a successful DNA cut at the target locus, rather than homology-directed repair, this can produce an allele that is resistant to future cutting by the Cas9/gRNA complex (e.g. Figure 4). Unless loss of function of the target gene is guaranteed following NHEJ, the drive can fail to eradicate the target population even if the probability of NHEJ is low (Figures 5a and 6a). Therefore, ensuring the expressed protein structure is sufficiently altered after NHEJ to prevent its effective function is an essential design requirement for the success of the homing gene drive.

In our simulations, the X chromosome shredding Y-drive achieved rapid eradication of the mouse population by biasing offspring sex ratios towards males (e.g. Figure 3). This strategy is an attractive alternative to homing drives for mouse population suppression since germline homing in mammals seems difficult to achieve (Grunwald et al., 2019; Pfitzner et al., 2020; Prowse et al., 2019). Since the Y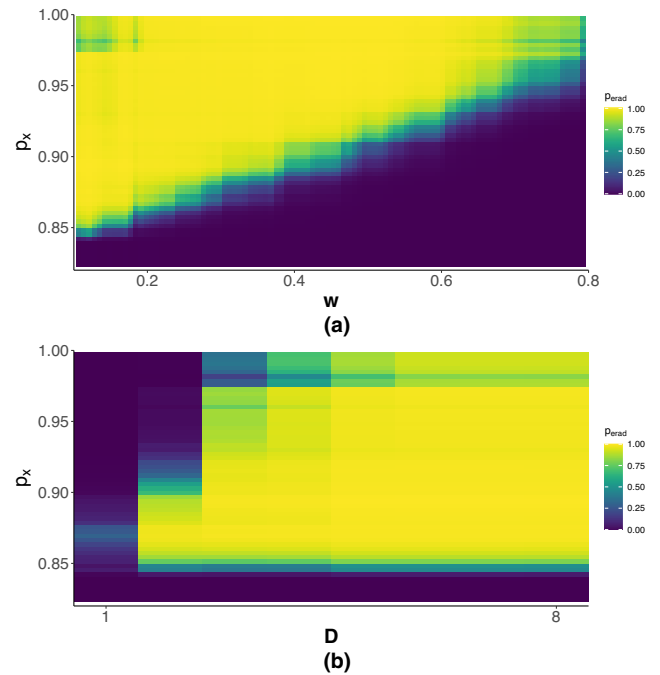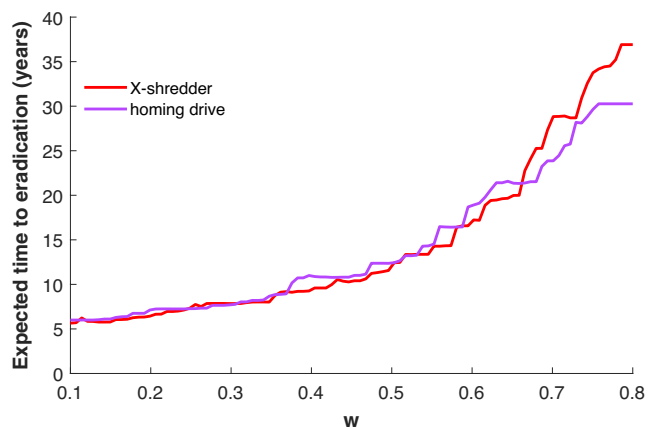-drive does not rely on homology-directed repair, a large number of sites could be targeted simultaneously with one or more gRNAs, which makes evolution of resistance unlikely (Champer, Oakes, et al., 2021; Champer et al., 2020; Prowse et al., 2017, 2018). Although the X chromosome shredding efficiency of this drive is a strong determinant of its efficacy (Figure 7a), if shredding is too efficient, this drive can be lost locally before it is able to spread widely (Figure 9a) or eradication can be delayed by repeated cycles of local
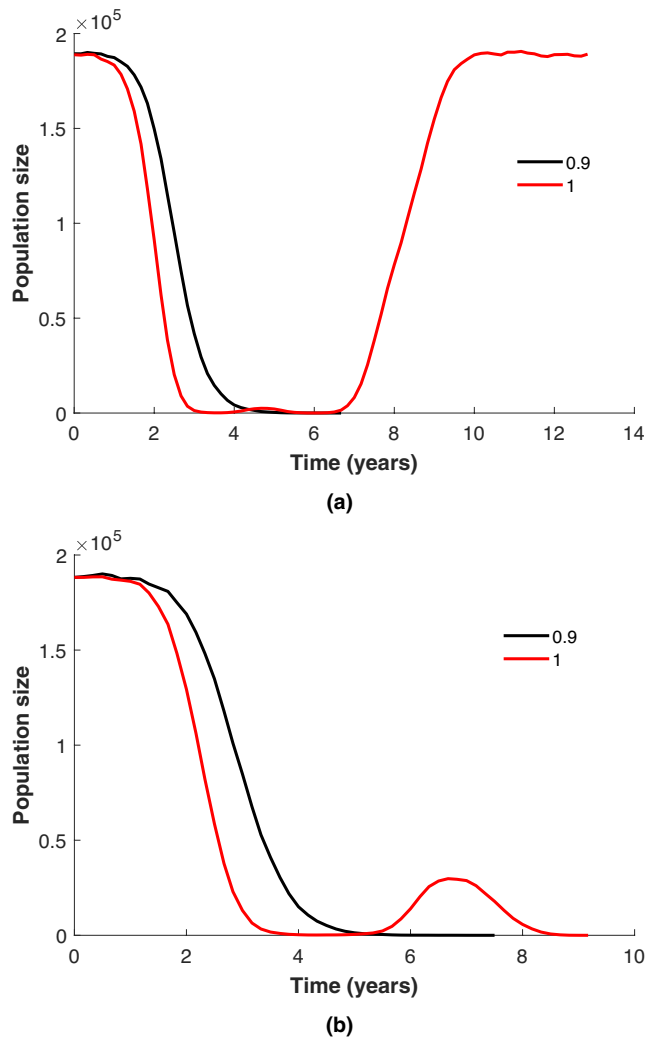
(a)

(b)

FIGURE 9 Population sizes through time in two sets of simulations for the X-shredding drive when only the probability of shredding (p_x) is altered in each set. Populations declined more quickly under perfect shredding ($p_x = 1$, red lines), and caused either: (a) the loss of the gene drive before it could spread to the other parts of the island, allow the population to rebound; or (b) 'chasing' after the wild type and delaying eradication. In contrast, with a less efficient drive ($p_x = 0.9$, black lines) eradication was successful in both scenarios. (With $p_{fs} = 0.7$ in a; $D = 4$, $p_{fs} = 0.5$, $d_s = 0.2$ in b)

drive extinction and wild-type recolonization, which is known as 'chase dynamics' (e.g. Figures 3 and 9a). Previous spatially explicit models for mosquitos also suggest that suppression is higher for intermediate cleavage rates (Champer, Oakes, et al., 2021; Eckhoff et al., 2017; North et al., 2013, 2019). Since this effect is more pronounced when mate-search and dispersal distances are low, reliable data on the spatial ecology of a target species, especially when they are sparsely populated, will be required to predict the outcomes of deploying this technology in the field. We suggest historical (or experimental, e.g. Nathan et al., 2015) records of invasions, and/or data on individual movements at the invasion front, could provide
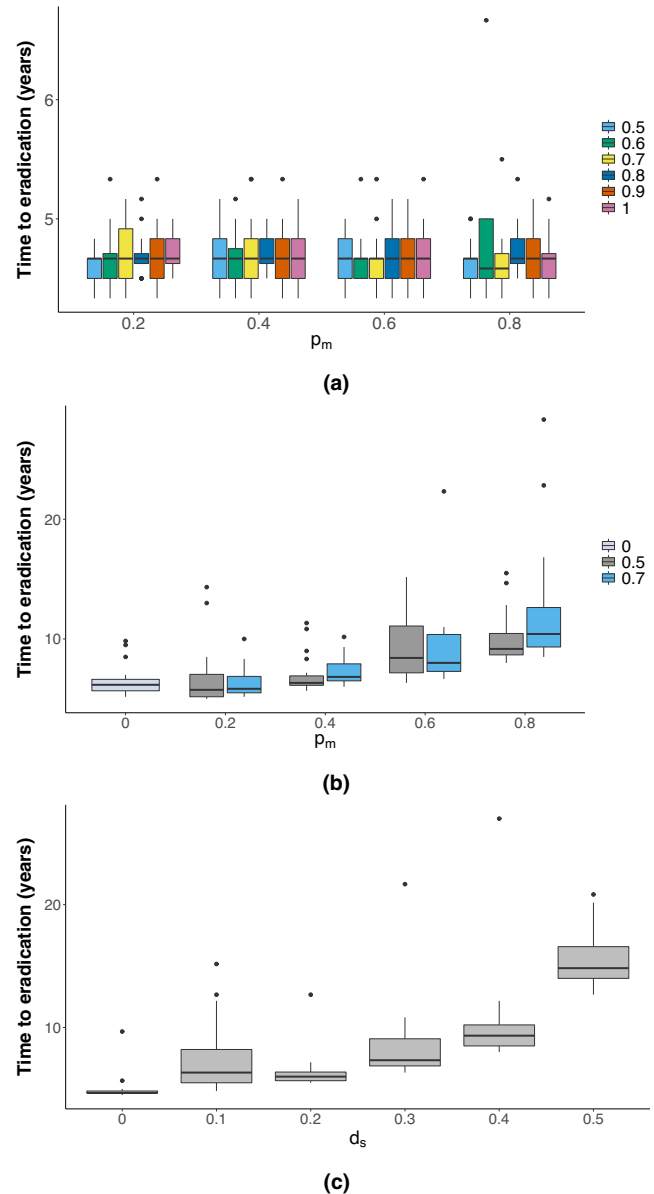

(a)

(b)

(c)

FIGURE 10 The effect of polyandry and sperm competition on the time to eradication based on 20 simulations for each parameter combination presented. (a) The probability of multiple mating (p_m) had no effect on the time to eradication for the homing drive, where sperm competition was based on first-sperm advantage only ($p_{fs} > 0.5$; values represented in different colours). (b) Increasing the probability of multiple mating (p_m) resulted in longer eradication times with the X-shredding drive, when sperm competition was based on the sperm count (grey boxes, $d_s = 0.2$, $p_{fs} = 0.5$). Adding a first-sperm advantage did not affect the results (blue boxes, $p_{fs} = 0.7$). (c) With moderate levels of polyandry ($p_m = 0.4$), decreasing the competitive advantage of the gene-drive carrying sperm further (due to a reduced sperm count) extended the time to eradication. (With $p_N = 0.01$, $p_C = 0.9$ for the homing drive and $p_x = 0.95$ for the X-shredding drive.) In the boxplots, the upper, middle and lower hinges correspond to the 25th, 50th and 75th percentiles respectively. The whiskers are within 1.5 interquartile range, and data beyond the end of the whiskers are outliers

much-needed information on mate-search behaviours and dispersal distances at low population densities.

Naturally occurring drives (e.g. the SR drive in *Drosophila*, the *t* haplotype in house mice) are negatively affected by polyandry (Manser et al., 2017, 2020; Pinzone & Dyer, 2013; Price et al., 2014), and therefore, polyandry could restrict the efficiency of synthetic gene drives used for population control (Deredec et al., 2008; Holman et al., 2015; Manser et al., 2019; Taylor & Jaenike, 2002). Polyandry is common in house mice (Firman & Simmons, 2008a), and sperm competition due to polyandry could be particularly important if the competitive ability of sperm from gene-drive carriers is reduced. For the X-shredding drive, sperm production is essentially halved in male carriers. However, our results concur with those of Deredec et al. (2008) and suggest that polyandry will have little impact on suppression drives unless polyandry is extremely common or the sperm of gene-drive carriers are substantially disadvantaged relative to the sperm of wild-type males (e.g. Manser et al., 2020).

The observed frequency of multiple paternity in field-caught pregnant females is 0.23–0.26 (Dean et al., 2006; Firman & Simmons, 2008a). The frequencies are likely to be lower in the surviving offspring. In our model, the observed frequency of multiple paternity in the surviving offspring (density-dependent reproduction) is around half of the probability of multiple mating, that is $p_m/2$. This suggests that setting $p_m = 0.4$ in the model should reflect the empirical data on multiple paternity. If we assume that sperm count translates directly into fertilization probabilities, the expected reduction in fertilization ability due to halving of sperm count (e.g. X-shredding drive) would reduce the male's siring probability from 1/2 to 1/3, when competing with a wild-type male. This corresponds to a sperm disadvantage coefficient $d_s = 1/6$, which in turn delays eradication only slightly (Figure 10c). An encouraging observation is that even when the wild-type sperm has the absolute competitive advantage ($d_s = 0.5$), the X-shredding drive could still produce successful simulated eradications.

In summary, our spatially explicit model demonstrates that an X chromosome shredding Y-drive could prove an efficient biocontrol strategy that achieves eradication in similar timeframe as that achieved by a homing drive. In fact, the X-shredding drive could prove to be a more attractive alternative, since this strategy does not rely on an effective homing mechanism which to date has proven difficult to achieve in mice. Although sperm production is essentially halved in males that carry an X-shredding drive, we find this cost will have little effect on the probability of eradication or time to eradication assuming up to moderate levels of polyandry. Finally, and in contrast to expectations from panmictic population models, slightly inefficient X chromosome shredding efficiency is predicted to improve eradication outcomes once spatial dynamics are taken into account.

AUTHOR CONTRIBUTIONS

All authors designed the research. A.B. developed the computer code and produced the results. A.B. and T.A.A.P. carried out the analyses of data. A. B. wrote the initial draft of the manuscript, with additional revisions by T.A.A.P. All authors provided comments and gave final approval for publication.

DATA AVAILABILITY STATEMENT

C code is available from the Dryad Digital Repository (https://doi.org/10.5061/dryad.wstqjq2p0).

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