Modelling homing suppression gene drive in haplodiploid organisms

Yiran Liu and Jackson Champer

Center for Bioinformatics, School of Life Sciences, Peking-Tsinghua Center for Life Sciences, Peking University, Beijing, 100871 People’s Republic of China

Cite this article: Liu Y, Champer J. 2022 Modelling homing suppression gene drive in haplodiploid organisms. Proc. R. Soc. B 289: 20220320.
https://doi.org/10.1098/rspb.2022.0320

Received: 18 February 2022
Accepted: 21 March 2022

Subject Category:
Biological applications

Subject Areas:
bioengineering, computational biology, evolution

Keywords:
suppression, haplodiploid, gene drive, modelling, continuous space, homing drive

Author for correspondence:
Jackson Champer
e-mail: jchamper@pku.edu.cn

Gene drives have shown great promise for suppression of pest populations. These engineered alleles can function by a variety of mechanisms, but the most common is the CRISPR homing drive, which converts wild-type alleles to drive alleles in the germline of heterozygotes. Some potential target species are haplodiploid, in which males develop from unfertilized eggs and thus have only one copy of each chromosome. This prevents drive conversion, a substantial disadvantage compared to diploids where drive conversion can take place in both sexes. Here, we study homing suppression gene drives in haplodiploids and find that a drive targeting a female fertility gene could still be successful. However, such drives are less powerful than in diploids and suffer more from functional resistance alleles. They are substantially more vulnerable to high resistance allele formation in the embryo owing to maternally deposited Cas9 and guide RNA and also to somatic cleavage activity. Examining spatial models where organisms move over a continuous landscape, we find that haplodiploid suppression drives surprisingly perform nearly as well as in diploids, possibly owing to their ability to spread further before inducing strong suppression. Together, these results indicate that gene drive can potentially be used to effectively suppress haplodiploid populations.

1. Introduction

Suppression gene drives have recently shown great promise for a variety of applications, in particular elimination of pest populations [1–4]. These genetic elements bias their own inheritance to increase in frequency in a population, eventually causing suppression by biasing the sex ratio or rendering enough individuals sterile or nonviable. Though the most rapid progress has been in Anopheles mosquitoes for reduction of vector-borne disease [5–7] (for which modification drives have also been developed [8–10]), suppression gene drives could also be used to remove invasive species or agricultural pests. Thus far, gene drives have been demonstrated in a variety of organisms, including yeast [11,12], flies [13–18], mice [19] and plants [20]. Most of these have been homing type drives, where a nuclease, usually CRISPR/Cas9, cuts a wild-type chromosome at a site-directed by its guide RNA (gRNA) [21]. The chromosome then undergoes homology-directed repair, which results in the drive alleles being copied to the target site. Since this occurs in the germline, the drive alleles will be inherited at an increased rate. However, if end-joining repair occurs instead than the wild-type site can mutate into a resistance allele, which cannot be converted to a drive allele [22–24]. These resistance alleles have the potential to slow or even stop the spread of a gene drive. The dynamics of such drives have been modelled extensively [16,25–29], which is particularly important for predicting the outcome of a real-world drive release.

Though many possible applications of gene drives have been considered [1–4], haplodiploid species have received little attention as possible targets. In these species, males develop from unfertilized eggs and thus only have one of each chromosome, which limits drive conversion in homing drives to females. So far, there has only been a single modelling studying assessing the possibilities for modification drives in haplodiploids [30]. The study concluded...
that homing drives could be effective, but they were always slower than in diploids, especially when drive performance was reduced. Though these results are promising in some situations, rapid suppression of haplodiploids is often desirable. This is especially true in well-known pest species such as invasive fire ants, which can cause human harm in addition to catastrophic damage to ecosystems and agricultural production [31,32]. In this species, CRISPR genome engineering has already been demonstrated [33], bringing the possibility of developing a gene drive closer to reality. Other major haplodiploid pests that could potentially be the target of a suppression drive include certain bark beetles, which are highly invasive and damaging to many natural forests and the lumber industry, and thrips, which cause major agricultural losses of potatoes, onions, cotton and other crops.

However, several drive mechanisms in diploids would not function in haplodiploids, particularly those that bias sex ratio or cause infertility or nonviability in males or in both males and females. Two studies attempted to develop models for haplodiploid suppression drives based on homing drives, but these lacked power to cause complete suppression on their own [34,35]. Our initial assessments indicated that of the established drive systems, only homing drives targeting haplosufficient but essential female fertility genes could cause strong suppression. In this study, we investigate this drive in detail, including its properties such as rate of spread and especially its overall suppressive power, comparing it to more well-studied but similar suppression drives in diploids. We find that embryo resistance and somatic cleavage activity can substantially reduce the efficiency of haplodiploid suppression drives, but over a wide parameter range, its performance is still nearly as good as diploid drives.

Additionally, many recent modelling studies of gene drive suppression have revealed unexpected complexity in spatially explicit scenarios. These scenarios could take the form of abstract patches [36], complex networks of linked panmictic populations [37,38] or arenas with continuous space [39–41]. In these simulations, the gene drive is often initially successful, eliminating the population in a particular region. However, this region can then be recolonized by wild-type individuals. The gene drive is still present in adjacent areas and moves in shortly afterwards, completing cycles of suppression and recolonization as the drive ‘chases’ wild-type alleles. Because even slightly weaker drives are more prone to suffering from such outcomes [39], a haplodiploid homing suppression drive might lose its ability to effectively suppress populations. We used our continuous space model to assess the performance of haplodiploid drives, but we found that it was only, on average, slightly more vulnerable to chosing than diploid drives of the same design and performance, still usually suppressing the population in a timely manner. In some areas of parameter space, the haplodiploid drive even had small advantages over the diploid version. These results indicate that homing suppression gene drives targeting female fertility genes are promising candidates for genetic control of haplodiploid pest species.

2. Methods

(a) Suppression drive strategy
In haplodiploids, females are derived from the diploid progeny, and unfertilized eggs become males. Here, we assess homing drives targeting female fertility genes for population suppression. In drive heterozygous females (males with only one chromosome cannot be heterozygous), the wild-type alleles will be converted into drive alleles in the germline through target cleavage followed by homology-directed repair using the drive as a template. This is the ‘drive conversion rate’ or ‘drive efficiency’. With such a drive, we target a haplosufficient but essential female fertility gene, leading to sterility in female drive homozygotes. The increasing frequency of drive alleles will result in accumulation of sterile drive homozygous females among the population, which can ultimately cause the population collapse.

However, there are two possible repair mechanisms after DNA cleavage, homology-directed repair and end-joining. If the cleaved target site is repaired by the latter mechanism, it may cause the site to be mutated, and such sites could not be cleaved by Cas9 in the future owing to sequence mismatch with the gRNA. Because these can no longer be converted to drive alleles, they are called ‘resistance alleles’. Most resistance alleles result in a non-functional target gene, which we called ‘r2’ alleles. Such alleles could contribute to female sterility but would also slow the drive. Females possessing only drive and/or non-functional resistance alleles are considered to be sterile in our model. Functional ‘r1’ resistance alleles, a more serious type, will almost always result in failure of a suppression drive. However, multiple gRNAs [16,42] and conserved target sites [5] could be used to limit the formation of functional resistance alleles (perhaps at the cost of drive conversion efficiency [16,42,43]), so we only explicitly modelled them in some of our simulations.

(b) Simulation model
The forward-in-time genetic simulation framework SLiM (v. 3.6) was used to perform all simulations [44]. In this study, we used code for diploids targeting X-linked loci to model haplodiploids since inheritance patterns in both situations are identical. The model is described in detail in a previous study [39]. In short, the sexually reproducing population in our model is 50,000 with a 1:1 sex ratio and discrete generations. This means that for each time step in the model, completely new individuals are generated in a single round of reproduction using density-dependent fecundity, with no individuals persisting from one generation to the next. Drive conversion and various fitness effects are modelled explicitly. In the spatial model, individuals migrate in even-field, bounded, dimensionless continuous space, experience density effects, finding mates and distributing offspring in only their local area. See the electronic supplementary material, Methods for full details of the models.

3. Results

(a) Characteristics of haplodiploid suppression drives
To assess the potential of a female fertility homing suppression drive in haplodiploids, we first compared drive characteristics between haplodiploids and diploids in panmictic populations. Our model uses discrete generations and simplified competition and life cycle characteristics. Competition is simply determined by the size of the total population compared to the carrying capacity, which affects female fecundity. Thus, rather than being representative of a particular species, it provides an easy way to focus on comparisons between drives with different performance parameters while still retaining minimal ecological features to ensure that the population has a stable carrying capacity.
Our default parameters (electronic supplementary material, table S1) approximately corresponded to a successfully constructed drive in *Anopheles* with reduced fitness costs [5], representing highly efficient but somewhat imperfect systems. The suppression drive targets a female fertility gene, causing females without wild-type alleles to be sterile (figure 1a). In diploids, wild-type alleles could be converted into drive alleles during the germline stage in both males and females (figure 1a), so that the drive frequency could increase rapidly (figure 1b). Males have only one chromosome in haplodiploids, so drive conversion can only be completed in females (figure 1a), resulting in a slower rate of increase (figure 1b). Thus, the haplodiploid drive could still eliminate the population, but this occurred later than in diploids (figure 1c). This delay was exacerbated in a small number of simulations in which stochastic effects allowed the wild-type population to temporarily rebound before ultimately being suppressed.

Aside from affecting the rate of increase of the drive (electronic supplementary material, figure S1 and accompanying text), various performance parameters can also affect genetic load, which is a characteristic that measures suppressive power on a target population. It measures the reduction in reproductive capacity in the population compared to an equivalent wild-type population. A genetic load of 0 means that the drive does not affect reproduction, while a genetic load of 1 means that the drive has stopped all reproduction in the population. Higher genetic loads will generally reduce the population size to a greater degree, but the exact level of reduction depends on complex species-specific and ecology-specific density dependence and other related factors [3]. Thus, when assessing the power of a suppression drive, genetic load provides a convenient measure to examine effects of the drive itself. Note that a drive with sufficiently high genetic load will have enough power to eliminate the population if the low-density growth rate is sufficiently low unless other factors intervene such as functional resistance alleles or spatial structure.

We measured the genetic load of the suppression drives between generations 50 and 150, at which point they had reached their long-term equilibrium frequency (electronic supplementary material, figure S2A). In general, the genetic load of diploid drives was higher than for haplodiploids (figure 2), though the haplodiploid drive was still able to reach high genetic load at high efficiency (figure 2a; electronic supplementary material, figure S2B). Variation in drive efficiency (figure 2a) and fitness (figure 2b) had similar effects on both drives, though the effect was somewhat larger in haplodiploids. However, the genetic load in haplodiploids fell off drastically if the embryo resistance was more than 0.6 (figure 2c), or if the relative fitness from somatic cleavage was less than 0.7 (figure 2d). This was not the case for diploid drives, though such drives would of course be slowed in these circumstances. This is because diploids support male drive,
which would be unaffected by either of these parameters, allowing the drive to continue increasing in frequency. If the drive can only increase in frequency in females, as in haplodiploids, it would lose all driving capacity if all drive-carrying offspring of females also have resistance alleles caused by high embryo resistance allele formation, or are unable to reproduce owing to fitness costs from high somatic cleavage rates. We also examined the germline resistance allele formation rate, but it has little effect on the genetic load (electronic supplementary material, figure S2C-D).

(b) Drive performance in continuous space

We next examined drive performance in a model with dimensionless continuous space, where density dependence, mating and offspring placement can now only occur locally. To focus on fundamental features of continuous space as related to drive, we again used a simple population genetic model in which local competition affects female fecundity. Previous studies indicated that suppression drives in continuous space could fail in several ways. In one, the genetic load would be insufficient to suppress the population, but because this also occurs in panmictic populations, we restricted our analysis to drives that would theoretically be able to suppress analogous panmictic populations. This included drives with at least 80% drive conversion rate and 80% fitness in homozygotes (with each drive allele contributing the square root of this fitness, and alleles having multiplicative fitness). A second mode of failure involves stochastic loss of the drive after the population size has been reduced owing to the drive, making stochastic effects more dominant (early stochastic loss of the drive before it had a chance to spread never occurred in our model). This can also occur in panmictic populations, but it is far more common in models of suppression drives in continuous space [39,45]. This is because individuals carrying unique alleles at low population densities may struggle to find nearby mates, which does not occur to nearly as great an extent in panmictic populations when all remaining individuals can potentially mate with each other. However, we found that this outcome was very rare for a female fertility homing suppression gene drive in haplodiploids, occurring in 0.29% of simulations (electronic supplementary material, figure S3).

Another more common mode of drive failure was ‘chasing’. This refers to a phenomenon in which some wild-type individuals escape from the drive and reach empty regions where the drive had previously eliminated the population [39]. Here, they experience reduced competition and are

![Figure 2. Effects of performance characteristics on the genetic load. The equilibrium genetic load is displayed for female fertility homing suppression drives with default performance characteristics and varying (a) drive conversion rate, (b) drive homozygote fitness, (c) embryo resistance allele formation rate, or (d) fitness cost in female heterozygotes owing to somatic CRISPR cleavage activity. Displayed data are the average from 200 simulations.](image-url)
able to have high numbers of offspring. The drive remains in contact with these wild-type groups, ‘chasing’ them and continuously causing suppression, but in many cases, the drive fails to ultimately eliminate the population, even after long periods of time. Chasing was quite common in our simulations of haplodiploids. This was not unexpected, given similar results in other types of drives [39] and given that our panmictic results that showed occasional rebound of the wild-type population (figure 1b,c). Movies showing short and long chases involving the haplodiploid drive can be found on GitHub (https://github.com/jchamper/ChamperLab/tree/main/Haplodiploid-Suppression-Modeling).

Specifically, when drive fitness, and more importantly, drive efficiency (representing the drive conversion rate), were high, the population was often suppressed without chasing (figure 3a; electronic supplementary material, figure S4A-B). However, it was more common for a period of chasing to occur prior to suppression (figure 3b). When both efficiency and fitness were low, chasing could persist for extended periods of time, with the population still in a chasing state after 1000 generations (figure 3c). With default parameters (electronic supplementary material, table S1), suppression could occur fairly quickly, though chasing could somewhat extend this (electronic supplementary material, figure S5). In simulations when chasing was avoided or minimized, suppression occurred quickly (figure 3d). However, time to suppression (figure 3d) was mostly controlled by the duration of chasing (figure 3e) when chasing became significant at lower efficiency and fitness, sometimes lasting several hundred generations.

In many cases, an outcome in which chasing persists could still provide benefits by reducing the population and its reproductive capacity. We measured this by tracking the average number of fertile females during a chase (figure 3f). This indicated that even an inefficient drive could reduce the population several-fold compared to its initial state. This reduction was greater for more efficient drives. However, for drives with very high efficiency, the average number of fertile females tended to be higher with greater variance (figure 3f).

Ecological characteristics can also influence the outcome of a suppression drive release. We thus varied the migration...
rate and the population growth rate at low densities, similarly tracking drive outcomes for an efficient drive (electronic supplementary material, figure S4C-D). Unlike most previously investigated drives, we found that the low-density growth rate had little effect in the range tested (figure 4; electronic supplementary material, figure S4D) (though eventually, high enough low-density growth rates would yield equilibrium outcomes in all situations, including panmictic populations). Migration rate had a similar effect as drive efficiency. When migration was high, suppression before chasing was common (figure 4a), followed by suppression after chasing for most of the parameter range (figure 4b). When very low, long-term chasing outcomes were common (figure 4c). However, most chasing was short and quickly ended in suppression at middle and high migration rates (figure 4d,e). When migration was low, the average population during a chase was higher (figure 4f).

Figure 4. Outcomes of a drive release in continuous space with varying migration rate and low-density growth rate. Female drive heterozygotes and drive males with default performance parameters and varying migration and low-density growth rate were released into the middle of a spatial population of 50 000 individuals. Outcome rates are displayed for (a) suppression without chasing, (b) suppression after a period of chasing, and (c) simulations in which chasing was still occurring at the end of the simulation. Also displayed is (d) the median time to suppression, (e) the average duration of chasing that eventually ended in suppression (blue represents parameter space where chasing did not end for 1000 generations in any simulation), and (f) the average number of fertile females during any type of chasing. Twenty simulations were assessed for each point in the parameter space.

c) Drive failure owing to functional resistance allele formation

One critical issue that CRISPR homing suppression gene drives must overcome is that of functional resistance. If such alleles form, they are highly likely to quickly spread in the population and prevent successful suppression [16,23,25,26,28,39,41]. To assess functional resistance alleles in haplodiploids, we allowed each new resistance allele to have a small chance of being functional, which would then allow reproduction for any female with the functional resistance (r1) allele. The range of this chance spanned from $10^{-6}$, in which r1 alleles
would almost never form in the simulations, up to $10^{-9}$, which could probably be achieved easily with even minimal effort towards finding conserved target sites or multiplexing with a single additional gRNA [16,43]. As with non-functional resistance alleles, they could not be converted to drive alleles. We expect haplodiploid drives to be more vulnerable to this, given the same rate of functional resistance allele formation. This is because haplodiploid drives have a 1:2 ratio for methods for drive increase (female germline) to methods of resistance allele formation (female germline and the embryos of drive females owing to maternally deposited Cas9 and gRNA), while diplodids have a higher 2:3 ratio (as above, but also drive increase and resistance allele formation in the male germline). This allows diplodids to increase in frequency a greater amount for the same amount of resistance allele formation, thus allowing for more total resistance allele formation by the time the drive has reached high enough frequency to eliminate the wild-type population. Stochastic effects seen in figure 1b,c can also increase the number of opportunities to form resistance alleles in haplodiploids compared to diplodids. Yet, despite these factors, the rate of drive failure owing to functional resistance allele formation was only modestly higher in haplodiploids in panmictic populations (figure 5), consistent with previous studies of modification drives [30]. However, when drive conversion rate is reduced, haplodiploid drives become less able to suppress the population and thus more vulnerable to formation of functional resistance alleles (electronic supplementary material, figure S10 and accompanying text).

In spatial populations, we expect that long periods of chasing would similarly increase the chance that functional resistance alleles could eventually develop, even if the rate of their formation would be at an acceptable level for panmictic populations in which suppression occurs quickly without chasing. This was previously demonstrated in diplodid drives [39]. Examining our haplodiploid drives, we see this same phenomenon, with half of resistance outcomes taking place when resistance alleles formed after chasing with our default parameters (electronic supplementary material, figure S11). When we allow drive conversion rate and the relative rate of functional resistance allele formation to vary, a pattern emerges in which chasing substantially increases the parameter range over which functional resistance alleles are likely to form (figure 6). Note that reductions in the drive conversion rate in these simulations do increase the absolute germline resistance allele formation rate (and therefore the functional resistance allele formation rate). This is generally consistent with the experimentally derived notion that resistance allele formation represents a prevalent alternative to successful drive conversion [7,16,22,43]. Overall, we find that reducing the relative rate of functional resistance allele formation is important, but that it may be equally important to keep drive conversion high, both to reduce the absolute rate of resistance allele formation and to prevent opportunities to form resistance alleles during chasing.

4. Discussion

While modification type homing drives have previously been extensively analysed in haplodiploid organisms [30], this study investigates the details of how such species could be suppressed by a gene drive. Our results show that this is possible in haplodiploid organisms and that a highly efficient drive can actually provide for very strong and successful suppression. This remains true even in more challenging environments involving continuous space where the ‘chasing’ phenomenon can slow or prevent suppression.

In haplodiploid organisms, the number of options for suppression gene drives is greatly reduced compared to diplodids. Previously developed sex-biasing strategies based on sex chromosomes such as X-shredders are certainly not possible, and even drives that do not rely on this will often lack the power needed to achieve high genetic loads. For example, homing drives targeting genes that are essential for both sexes or males would be eliminated quickly in males [34,35], and even toxin-antidote dominant embryo (TADE) [46,47] drives would lack the power for suppression. Our modelling using the same format as in this study indicates that all of these configurations cannot increase in frequency on their own (TADE suppression slightly increases in frequency in the first generation only as the population equilibrates) and can only maintain a frequency in ideal form. Any imperfections in fitness or drive efficiency result in the drive declining in frequency regardless of release size. Modified versions of these homing drive strategies could still provide some suppression [34,35]. Fortunately, we found that the strategy of targeting a haplosufficient but essential female-specific gene with a homing drive was still able to achieve high genetic load (and though we modelled a female fertility gene, results would be broadly similar with a female viability gene). This type of gene drive has been well studied, with the latest drives even circumventing functional resistance alleles by careful target site selection [5] or multiplexed gRNAs [42]. Because haplodiploid drives are somewhat more vulnerable to such functional resistance alleles, both methods would likely also be needed to avoid functional resistance in large, natural haplodiploid organisms.
populations. Fortunately, though, such methods should function with similarly high efficiency to their demonstrations in flies and mosquitoes, meaning that sufficiently low resistance drives could probably be generated if baseline drive conversion efficiency of the target species was acceptably high. However, our study indicates that homing suppression drives in haplodiploids would need to keep somatic activity and embryo resistance allele formation even lower than in diploid drives to be effective. Though a rigorous requirement, there is still some flexibility in the specific values, and previously constructed drives have already achieved low enough somatic activity in flies [42] and embryo resistance in mosquitoes [5].

Surprisingly, we found that in continuous space models, female fertility homing suppression drives perform nearly as well in haplodiploid species as in diploids. Though more vulnerable to chasing over a fair amount of the parameter space we investigated, chases in most of this region were short, meaning that ultimate differences between the drives were minimal. Haplodiploid drives even had some minor advantages in some circumstances, such as reduced rates of drive loss and less loss of efficiency when the low-density growth rate was high. A previous study indicated that drives with less powerful mechanisms tended to be far more vulnerable to chasing [39], but despite being unable to perform drive conversion in males to increase in frequency, this did not significantly apply to haplodiploid drives. This is perhaps because the drive can still diffuse quickly into wild-type populations but causes suppression more slowly than diploid drives, making it more difficult for pockets of wild-type individuals to stochastically avoid the drive in a chasing situation.

We note that our model is quite simplified compared to some realistic populations. We used discrete generations and simplified competition while avoiding complex life cycle characteristics that are typical of many species, especially many haplodiploid insects. In our spatial model, we only considered a bounded square and assumed spatial homogeneity. Our intention in this study was to present a basic overview of suppression drives in haplodiploids and how they differ from drives in diploids. However, this generality means that our conclusions are limited when considering specific species, particularly for predicting time intervals from a drive release to various outcomes. Life cycles, diverse landscapes, connectivity between populations, types of intraspecific and interspecific competition (and other interactions), seasonality, and other factors can all influence how a drive may spread through and suppress a population.

Unlike TADE suppression drives, powerful homing drives are unconfined, even in haplodiploid organisms. This is because they can increase rapidly in frequency
based on their drive allele conversion mechanism, even when initially present in a population at low frequency, allowing them to invade new populations with even small numbers of migrants. This may be undesirable in some situations such as targeted suppression of invasive populations. Tethered drive systems could provide a solution to this [48,49] and allow for confined drive in haplodiploids. Indeed, modelling shows that a toxin-antidote recessive embryonic drive, which could be used to confine a homing drive that lacks Cas9, would perform well at an X-linked locus [46], and it would have identical performance in haplodiploid species in other configurations [47] as well.

X-linked homing drives in diploids (which have been similarly neglected in previous modelling like haplodiploids) would also have similar performance to drives in haplodiploids [30], and our modelling is thus equally applicable to both. Normally, we would expect autosomal diploid suppression drives to have equal or superior performance to X-linked drives. However, our modelling in continuous space indicates there may be a narrow parameter space where an X-linked drive could provide a solution to this [48,49] as well.

Cas9, would perform well at an X-linked locus [46], and it would also have similar performance to drives in haplodiploids [30], and our modelling is thus equally applicable to both. Normally, we would expect autosomal diploid suppression drives to have equal or superior performance to X-linked drives. However, our modelling in continuous space indicates there may be a narrow parameter space where an X-linked drive would be preferred for avoiding long-term chasing of migrations. This may be undesirable in some situations as well.

While the development of gene drives in new species remains difficult, our results are nonetheless promising for future control of haplodiploid pests. Thus, studies developing CRISPR knock-in techniques in haplodiploid pest species, as well as characterization of germline promoter elements, female-specific target genes, and gRNA promoters can be considered high priority. As with diploids, ecological field investigations and more advanced modelling studies are also needed for accurate outcome predictions of gene drive deployment in specific species and regions of interest.

Data accessibility. All data and code are available on GitHub: https://github.com/jchamper/ChamperLab/tree/main/Haplodiploid-Suppression-Modeling.

Authors' contributions. Y.L.: conceptualization, formal analysis, investigation, methodology, software, validation, visualization, writing—original draft, writing—review and editing; J.C.: conceptualization, funding acquisition, project administration, supervision, visualization, writing—original draft, writing—review and editing.

Both authors gave final approval for publication and agreed to be held accountable for the work performed therein.

Conflict of interest declaration. We declare we have no competing interests.

Funding. This study was supported by laboratory startup funds from Peking University and the SLS-Qidong Innovation Fund.

Acknowledgements. Thanks to Samuel E. Champer and Isabel K. Kim for assistance with SLiM programming.

References

1. Hay BA, Oberhofer G, Guo M. 2021 Engineering the composition and fate of wild populations with gene drive. Annu. Rev. Entomol. 66, 407–434. (doi:10.1146/annurev-ento-020117-043154)

2. Bier E. 2021 Gene drives gaining speed. Nat. Rev. Genet. 23, 5–22. (doi:10.1038/s41576-021-00386-0)

3. Dhole S, Lloyd AL, Gould F. 2020 Gene drive dynamics in natural populations: the importance of density dependence, space, and sex. Annu. Rev. Ecol. Evol. Syst. 51, 503–531. (doi:10.1146/annurev-ecolsys-031120-101013)

4. Rode NO, Estoup A, Bourguet D, Courtier-Orgogozo V, Débarre F. 2019 Population management using gene drive: molecular design, models of spread dynamics and assessment of ecological risks. Conserv. Genet. 20, 671–690. (doi:10.1007/s10592-019-01165-5)

5. Kyono K, Hammond AM, Galizi R, Kranjac N, Burt A, Beaghton AK, Nolan T, Crisanti A. 2018 A CRISPR-Cas9 gene drive targeting doublesex causes complete population suppression in caged Anopheles gambiae mosquitoes. Nat. Biotechnol. 36, 1062–1066. (doi:10.1038/nbt.4245)

6. Simoni A et al. 2020 A male-biased sex-distorter gene drive for the human malaria vector Anopheles gambiae. Nat. Biotechnol. 38, 1054–1060. (doi:10.1038/s41587-020-0508-1)

7. Fuchs S et al. 2021 Resistance to a CRISPR-based gene drive at an evolutionarily conserved site is revealed by mimicking genotype fixation. PLoS Genet. 17, e1009790. (doi:10.1371/journal.pgen.1009790)

8. Carballar-Lejasazú R et al. 2020 Next-generation gene drive for population modification of the malaria vector mosquito, Anopheles gambiae. Proc. Natl Acad. Sci. USA 117, 22 805–22 814. (doi:10.1073/pnas.2012144117)

9. Adolphi A et al. 2020 Efficient population modification gene drive-rescue system in the malaria mosquito Anopheles stephensi. Nat. Commun. 11, 1–13. (doi:10.1038/s41467-020-19426-0)

10. Hoermann A, Tapanelli S, Capriotti P, Del Corso G, Masters EKG, Hubertewald T, Christophides GR, Windbichler N. 2021 Converting endogenous genes of the malaria mosquito into simple non-autonomous gene drives for population replacement. Elife 10, e58791. (doi:10.7554/eLife.58791)

11. Shapiro RS et al. 2018 A CRISPR–Cas9-based gene drive platform for genetic interaction analysis in Candida albicans. Nat. Microbiol. 3, 73–82. (doi:10.1038/s41556-017-0043-0)

12. Lewis IC, Yan Y, Finningan GC. 2021 Analysis of a Cas12a-based gene-drive system in budding yeast. Access Microbiol. 3, 000301. (doi:10.1093/acmi/0.000301)

13. Champer J, Lee E, Yang E, Liu J, Clark AG, Messer PW. 2020 A CRISPR homing gene drive targeting a haplolethal gene removes resistance alleles and successfully spreads through a cage population. Proc. Natl Acad. Sci. USA 117, 24 377–24 383. (doi:10.1073/pnas.2004373117)

14. Guichard A et al. 2019 Efficient allele-drive in Drosophila. Nat. Commun. 10, 1640. (doi:10.1038/s41467-019-09694-w)

15. Grunwald HA, Gantz VM, Poplawski G, Xu X-RS, Bier E, Cooper KL. 2019 Super-Mendelian inheritance mediated by CRISPR–Cas9 in the female mouse germ line. Nature 566, 105–109. (doi:10.1038/s41586-019-0875-2)

16. Zhang T, Mudgett M, Ramabhu R, Abramson B, Dai X, Michael TP, Zhao Y. 2021 Selective inheritance of target genes from only one parent of sexually reproduced F1 progeny in Arabidopsis. Nat. Commun. 12, 1–8. (doi:10.1038/s41467-021-24195-5)

17. Pickar-Oliver A, Gersbach CA. 2019 The next generation of CRISPR–Cas technologies and applications. Nat. Rev. Mol. Cell Biol. 20, 490–507. (doi:10.1038/s41580-019-0131-5)

18. Champer J, Reeves R, Oh SY, Liu C, Liu J, Clark AG, Messer PW. 2017 Novel CRISPR/Cas9 gene drive constructs reveal insights into mechanisms of resistance allele formation and drive efficiency in
genetically diverse populations. *PLoS Genet.* **13**, e1006796. (doi:10.1371/journal.pgen.1006796)

23. Hammond AM et al. 2017. The creation and selection of mutations resistant to a gene drive over multiple generations in the malaria mosquito. *PLoS Genet.* **13**, e1007039. (doi:10.1371/journal.pgen.1007039)

24. Pham TB et al. 2019. Experimental population modification of the malaria vector mosquito, *Anopheles stephensi*. *PLoS Genet.* **15**, e1008440. (doi:10.1371/journal.pgen.1008440)

25. Uckless RL, Clark AG, Messer PW. 2017 Evolution of resistance against CRISPR/Cas9 gene drive. *Genetics* **205**, 827–841. (doi:10.1534/genetics.116.197285)

26. Noble C, Olejarz I, Esselt K, Church G, Nowak M. 2017 Evolutionary dynamics of CRISPR gene drives. *Sci. Adv.* **3**, e1601964. (doi:10.1126/sciadv.1601964)

27. Beaghton AK, Hammond A, Nokan T, Grisanti A, Burt A. 2019. Gene drive for population genetic control: non-functional resistance and parental effects. *Proc. R. Soc B* **286**, 20191586. (doi:10.1098/rspb.2019.1586)

28. Prowse TAA, Caissay P, Ross JV, Pitcher C, Wittmann TA, Thomas P. 2017. Dodging silver bullets: good CRISPR gene-drive design is critical for eradicating exotic vertebrates. *Proc. R. Soc. B* **284**, 201710799. (doi:10.1098/rspb.2017.0799)

29. Wu SL, Bennett JB, Sánchez CHM, Dolgert AJ, León TM, Marshall JM. 2021. MGDrivE 2: a simulation framework for gene drive systems incorporating seasonality and epidemiological dynamics. *PLoS Comput. Biol.* **17**, e1009030. (doi:10.1371/journal.pcbi.1009030)

30. Li J, Aidlin Harari O, Doss A, Walling LL, Atkinson PW, Morin S, Tabashnik BE. 2020. Can CRISPR gene drive work in pest and beneficial haplodiploid species? *Evol. Appl.* **13**, 2392–2403. (doi:10.1111/eva.13032)

31. Vinson SB. 2013. Impact of the invasion of the imported fire ant. *Insect Sci.* **20**, 439–455. (doi:10.1111/1744-7917.2012.01572.x)

32. Lee CM, Lee D-S, Kwon T-S, Athar M, Park Y-S. 2021 Predicting the global distribution of *Solenopsis geminata* (*Hymenoptera: Formicidae*) under climate change using the MaxEnt model. *Insects* **12**, 229. (doi:10.3390/insects12030229)

33. Chiu Y-K, Hou J-C, Chang T, Huang Y-C, Wang J. 2020. Mutagenesis mediated by CRISPR/Cas9 in the red imported fire ant, *Solenopsis invicta*. *Insectes Soc.* **67**, 317–326. (doi:10.1007/s00040-020-00755-8)

34. Faber NR, Meiborg AB, Mcfarlane GR, Gorjanc G, Harpur BA. 2021. A gene drive does not spread easily in populations of the honey bee parasite *Varroa destructor*. *Apidologie* **1**, 1–16. (doi:10.11101/2021.04.30.442149)

35. Lester PJ, Bulgarella M, Batty JW, Dearden PK, Ghuilin J, Kean JM. 2020. The potential for a CRISPR gene drive to eradicate or suppress globally invasive social wasps. *Sci. Rep.* **10**, 1–13. (doi:10.1038/s41598-020-69259-6)

36. Bull JJ, Remien CH, Krone SM. 2019. Gene-drive-mediated extinction is thwarted by population structure and evolution of sib mating. *Evol. Med. Public Heal.* **2019**, 66–81. (doi:10.1093/emph/euz014)

37. North AR, Burt A, Godfray HCJ. 2020. Modelling the potential of genetic control of malaria mosquitoes at national scale. *BMJ Clin. Res.** **17**, 26. (doi:10.1186/s12915-019-0645-5)

38. North AR, Burt A, Godfray HCJ. 2020. Modelling the suppression of a malaria vector using a CRISPR-Cas9 gene drive to reduce female fertility. *BMJ Clin. Res.** **18**, 98. (doi:10.1186/s12915-020-00834-z)

39. Champer J, Kim IK, Champer SE, Clark AG, Messer PW. 2020. Performance analysis of novel toxin-antidote CRISPR gene drive systems. *BMJ Biol.** **18**, 27. (doi:10.1186/s12915-020-00761-2)

40. Champer J, Champer SE, Kim IK, Clark AG, Messer PW. 2020. Design and analysis of CRISPR-based underdominance toxin-antidote gene drives. *Evol. Appl.* **14**, 1052–1069. (doi:10.1111/eva.13180)

41. Dhole S, Lloyd AL, Gould F. 2019. Tethered homing gene drives: a new design for spatially restricted population replacement and suppression. *Evol. Appl.* **12**, 1688–1702. (doi:10.1111/eva.12827)

42. Metzloff M, Yang E, Dhole S, Clark AG, Messer PW, Champer J. 2021. Experimental demonstration of tethered gene drive systems for confined population modification or suppression. *bioRxiv*, 2021.05.29.446308. (doi:10.1101/2021.05.29.446308)