INTRODUCTION

In situations where evolution can occur over timescales that are short compared to the time it takes to disperse alleles across the population by migration, modelling based on the assumption of panmixia is often inadequate. Frameworks that explicitly incorporate spatial structure therefore must be used to accurately predict evolutionary dynamics in such scenarios (Barton et al., 2002, 2010; Battey et al., 2020; Feder et al., 2019; Hart et al., 2017; Kozakiewicz et al., 2018; Ladau & Eloe-Fadrosh, 2019; Wright, 1943).

Taking the idea of rapid evolution to an extreme, CRISPR gene drives can, in principle, spread through a population in just a few generations due to super-Mendelian inheritance (Alphey, 2014; Burt, 2006).
by wild-type recolonization from connected demes, whereas long-term population suppression occurred more reliably in seasonally stable areas. This often proceeded in irregular cycles, preventing complete population suppression by the drive. These examples demonstrate that the incorporation of explicit spatial structure in a gene drive population model can give rise to qualitatively new types of behaviour that are not observed in idealized panmictic population models, yet which could dramatically alter the ultimate outcome of a drive release.

In this study, we systematically explore how a population model that explicitly incorporates continuous space affects the dynamics and outcome of a suppression gene drive release. We show that a dynamic phenomenon we term “chasing,” which is similar to the pattern of local eradication followed by recolonization observed in previous studies (Bull et al., 2019; North et al., 2019, 2020), can lead to long-term, unstable coexistence between drive and wild-type alleles. We analyse the propensity of different types of suppression drives to produce such chasing dynamics and show how this phenomenon depends on the ecological and demographic parameters of the population.

2 | METHODS

2.1 | Suppression drive strategies

We studied four gene drive strategies for population suppression, each of which is capable of rapid population elimination in a panmictic model.

2.2 | Female fertility homing drive

This is a CRISPR/Cas9 homing drive that cleaves the wild-type allele of a heterozygote in the germline and then copies itself into that location by homology-directed repair. We assume that the drive allele is placed inside a haplosufficient but essential female fertility gene, inactivating the gene by its presence. Drive homozygous females (or females with any combination of drive alleles and resistance alleles that also disrupt the target gene) are sterile. As the drive increases in frequency, an accumulation of sterile females causes the population to collapse. If cleavage repair takes place by end-joining rather than homology-directed repair (in the germline as an alternative to homology-directed repair or in the embryo due to maternally deposited Cas9), guide RNA (gRNA) target sites are often mutated. This typically creates a nonfunctional version of the target gene (called an “r2” resistance allele) that can no longer be cleaved. Such r2 resistance alleles do not typically pose major issues for this drive, because they usually do not prevent population elimination, even though they reduce overall drive efficiency. A more severe problem is posed by “r1” resistance alleles, mutations that prevent targeting by gRNAs and preserve target gene function. However, the formation rate of r1 alleles can be reduced by using multiple
gRNAs (Champer, Oh, et al., 2020) or a highly conserved target site that cannot tolerate mutations (Kyrou et al., 2018). In a recent experiment, a female fertility homing drive like the one we model here was successful in rapidly eliminating small cage populations of Anopheles gambiae (Kyrou et al., 2018).

2.3 | Both-sex fertility homing drive

This drive is similar to the female fertility homing drive except that the drive resides in a gene that is required for both female and male fertility. Such a drive may be easier to engineer in some species if it uses a more common type of target gene. We also considered a variant of this drive that targets another common type of gene where disrupted alleles are recessive lethal, with lethality at the embryo stage.

2.4 | Driving Y

The third suppression system is a Driving Y chromosome, which involves inserting the drive on the Y chromosome. In the "X-shredder" variant we consider here, the drive cleaves sites located on the X chromosome during meiosis (North et al., 2013, 2019). With a high cleavage rate, most X chromosomes in the germline of a drive-carrying male are destroyed, resulting in most viable sperm containing the Y chromosome. As the drive spreads, the sex-ratio becomes increasingly male-biased until the number of females is so low that the population collapses. While this drive has been well studied theoretically, it has proven difficult to engineer due to low expression rates of transgenes on the Y chromosome (although autosomal X-shredders have been successfully developed Galizi et al., 2014, 2016).

2.5 | Toxin–antidote dominant sperm (TADS) suppression drive

This drive does not spread by homing but relies on toxin–antidote principles to increase in frequency. Here, the “toxin” is the Cas9 with gRNAs targeting an essential spermatogenesis gene for disruption, and the “antidote” is a recoded, cleavage-resistant copy of this gene that is included in the drive allele (Champer et al., 2020). The target gene is specifically expressed after meiosis I in males, with this expression being critical for spermatogenesis (Champer, Kim, et al., 2020). The drive allele resides in a recessive male fertility gene, disrupting the gene with its presence and causing sterility in male drive homozygotes. When Cas9 cleavage is repaired (by either end-joining or by homology-directed repair with a disrupted allele as a template), this typically creates a loss-of-function mutation. Sperm exposed to the toxin will thus not mature unless they are “rescued” by the drive. The drive spreads mainly through male heterozygotes, and the population declines as homozygous males accumulate. Maternal Cas9 activity helps this drive by creating more disrupted target alleles that will be removed from the population. Like the Driving Y system, a TADS suppression drive may prove difficult to engineer, in this case because it requires a highly specific target gene.

2.6 | Simulation model

To study the expected population dynamics of these four suppression drives, we created a simulation model of a sexually reproducing diploid population evolving over discrete, nonoverlapping generations. All simulations were implemented in the forward-in-time genetic simulation framework SLiM, version 3.2.1 (Haller & Messer, 2019).

Gene drive processes take place in the germline prior to reproduction. To reduce the run-time of our simulations, we model the gene drive in only the individuals that have reproduced. The following rules take place independently when generating each of their gametes. First, for the female fertility homing drive and both-sex fertility homing drive, a wild-type allele in a parent that also carries a drive allele is converted to a resistance allele with a probability equal to 1 – drive efficiency (we set drive efficiency = 0.95 as default, assuming an effective Cas9 promoter (Kyrou et al., 2018)). These resistance alleles disrupt the target gene unless otherwise specified. If not converted into a resistance allele, a wild-type allele is then converted into a drive allele with a probability equal to the homology-directed repair success rate (set to 0.99 in all cases in this study). The allele remains wild-type if neither of these events occur. However, if an offspring’s mother possessed a drive allele and the offspring still has remaining wild-type target sites (regardless of which parent these came from), then they may be converted into resistance alleles as a result of maternal Cas9 activity in the embryo. This occurs with a probability equal to the embryo resistance rate, which was set to 0.05 for all homing drives, a rate corresponding to a good Cas9 promoter (Kyrou et al., 2018).

For the Driving Y, a wild-type allele represents an intact X chromosome. If a father possesses a driving Y chromosome, the X chromosome is shredded at a probability equal to the drive efficiency (set to 0.99 by default for this drive). This occurs independently in each germline cell. A sperm that contains a shredded X chromosome is not viable, so we ensure that offspring cannot ultimately receive a shredded X (by generating a new offspring genotype if this takes place). If the offspring inherits a drive allele, then it is male, and if it inherits an intact wild-type X chromosome from their father, it is female.

For the TADS suppression drive, parents pass down two alleles. The first represents the target spermatogenesis gene, and the second represents the drive site (which is either a drive allele or a functional male fertility gene). A wild-type target gene in a parent that also has a drive allele is disrupted with a probability equal to the drive efficiency (set to 0.99 by default for this drive), independently in each gamete. Because a sperm with a disrupted target gene cannot
mature without also carrying the recoded copy of the drive, we en-
sure than an offspring cannot inherit both a disrupted target gene
and a nondrive allele from a drive-carrying father (by generating a
new offspring genotype if this takes place). For this system, addi-
tional Cas9 cleavage in the embryos of drive-carrying mothers does
not hamper drive performance and is in fact desirable. Thus, we as-
sume a Cas9 promoter that results in high cleavage activity in both
the germline and the embryo, with the embryo cut rate set at 95% of
the drive efficiency.

2.7 | Panmictic population model

We first implemented these simulations in a panmictic population,
assuming the following life cycle. Generations begin with
reproduction. Each nonsterile female randomly samples a male from
the population. Once sampled, a male’s probability of becoming the
mate is equal to 0.5, multiplied by his genotype-based fitness. This
method was used to simplify computational requirements compared
to assigning each male a fitness value at the outset, while ensuring
that the probability of being chosen remains proportional to each
male’s fitness. Genotype-based fitness is equal to the square root
of the product of both chromosomes’ fitness values, such that
drive homozygotes (or drive-carrier males for the Driving Y) have a
fitness equal to the drive fitness (set to 0.95 by default), while drive
heterozygotes have fitness equal to the square root of this value.
When investigating inbreeding effects, we scale this probability
such that male siblings become more or less likely to be selected
than unrelated males. Each female has up to 20 attempts to find a
mate based on this sampling and fitness-evaluation process. If she
fails to find a mate after 20 attempts, or if she selects a sterile male
he does not possess any wild-type or functional r1 resistance alleles
in the both-sex sterile homing drive, or he has two drive alleles or
two disrupted TADS target genes and no drive alleles in the
TADS suppression drive), then she will not reproduce. This mating
behaviour is representative of mosquito populations where females
typically only mate once (Degner & Harrington, 2016; Pondovie-
e et al., 2008).

In the panmictic population model, once a female has chosen a
mate, we scale her fecundity to \( \omega_i = \omega_0 \beta / ((\beta - 1)N/K + 1) \),
where \( N \) is the population size, \( \beta \) specifies the low-density growth rate
of the population, \( K \) is the carrying capacity and \( \omega_0 \) is the
fecundity based on her genotype fitness. We then draw the number of her
offspring from a binomial distribution with \( n = 50 \) and \( p = \omega_i / 25 \),
representing 50 eggs with independent survival (with 50 probably
approaching the upper limit of the number of offspring a success-
ful female could have under permissive conditions, and allowing a
reasonably sized distribution of the possible number of offspring
when the low-density growth rate is at its maximum and density com-
petition is low). This density dependence produces logistic growth
dynamics and should push the population toward carrying capacity
(in the absence of a suppression drive). If the population size is near
capacity, fecundity should tend towards \( \omega_i \approx 1 \), resulting in two
offspring on average. However, if the population size is lower than
capacity, females will tend to produce more than two offspring. We
chose a value of \( \beta = 6 \) as the default low-density growth rate, based
on estimates of the Anopheles rate that ranges between 2 and 12
(Deredec et al., 2011).

Simulations were initialized by allowing an initial wild-type pop-
ulation of \( K = 50,000 \) individuals to evolve over 10 generations to
reach an equilibrium. Then, drive-carriers, heterozygous for a drive
and wild-type allele, were released at a frequency of 1% of the total
population. For the Driving Y, only male drive carriers were released,
while releases comprised males and females at equal proportions for
all other drives.

2.8 | Two-dimensional spatial model

We extended our model into continuous space by tracking every
individual’s position across a 1 × 1 square landscape. The generation
cycle begins with reproduction. However, rather than sampling
any male from the population as a potential mate, females are now
restricted to sampling from within a radius specified by the migration
value, which we set to 0.04 by default. If the female cannot find a
suitable mate within this radius, she cannot reproduce. In this
model, we assume that density regulation is local. In particular,
we define a carrying density, \( \rho_c = K/\text{total area,} \) and then compare
this value to the local density, \( \rho_i \), around a female, defined as the
density of individuals within a circle of radius 0.01 around her. This
interaction function is inspired by mosquito larval competition,
in which all larvae in the same pool of water compete (hence the
interaction function not declining by distance up to the interaction
radius of 0.01), but larvae in adjacent pools cannot reach each other
and thus do not compete (the interaction function is zero above the
interaction radius). However, we do not explicitly model such bodies
of water with larva.

The fitness of the female is then scaled to \( \omega_i = \omega_0 \beta / ((\beta - 1) \rho_i / \rho_c + 1) \), where \( \beta \) represents the low-density growth rate of the population. This model allows females in a less
densely populated area to have higher fitness due to less compe-
tition for resources. Finally, the number of offspring is drawn from
a binomial distribution with \( n = 50 \) and \( p = \omega_i / 25 \), so females with
no genotype-based fitness disadvantage will average 2\( \beta \) offspring in
areas of very low density. Such density-dependence could represent
reduced competition at various stages of the life cycle, depending
on the biological system. For mosquitoes, the benefits of reduced
competition are primarily at the larval phase.

Offspring genotypes are obtained according to the same sup-
pression drive mechanisms as in the panmictic model. Once an off-
spring’s genotype is determined, the individual is displaced from the
position of its mother in a random direction by a random distance
drawn from a normal distribution with mean zero and standard devi-
ation equal to the migration value (producing an average displacement
equal to the migration value * \( \sqrt{\pi}/2 \)). Coordinates that fall outside of
the arena are redrawn until they fall within the boundaries.
Our spatial simulations were initialized by randomly scattering a population of \( K = 50,000 \) wild-type individuals (the population capacity, which is allowed to vary only in Figure S8) across the landscape. We then allowed the population to equilibrate for 10 generations before releasing drive heterozygotes (or drive-carrying males in the Driving Y) at 1% of the total population frequency in a central circle of radius 0.01.

### 2.9 Analyses of simulation outcomes

In our simulations, we recorded allelic frequencies, population size, and the frequency of sterile males and females at the end of every generation. We allowed each simulation to run for 1,000 generations, but stopped the simulation earlier if the population was eliminated. The drive allele was lost while wild-type individuals were still present, \( r1 \) resistance alleles evolved and prevented the spread of the drive (by reaching 10% total frequency - a level that we found to ensure continued invasion of the resistance allele in the population), or the drive was fixed but the population was not eliminated within 10 generations (this only occurred when an inefficient Driving Y fixed in the population and was considered to be an "equilibrium" outcome).

To quantify the degree of clustering in the spatial population model at any given time step, we calculated Green's coefficient (Green, 1966). We first divided the landscape into an 8 x 8 grid of equal-sized square cells and counted the number of wild-type homozygote individuals, \( n_i \), in each cell. Green's coefficient is then defined as \( G = (\bar{s}^2/n - 1)/(N - 1) \), where \( n \) and \( s^2 \) are the mean and variance, respectively, of the individual cell counts, and \( N \) denotes the total population size. If individuals are randomly distributed over the space according to a Poisson distribution, then \( n \) and \( s^2 \) should be equal, yielding \( G = 0 \). Clustering of individuals in space leads to \( s^2 > n \), and thus \( G > 0 \). The maximum value is \( G = 1 \), specifying a scenario in which all individuals are located within a single cell. Values of \( G \) between 0 and 1 allow quantification of the degree of spatial clustering in the population. Note that we only count wild-type homozygotes in our estimation of \( G \), as we found this to produce a larger dynamic range than when all individuals were included.

Based on the inferred time-series \( G(t) \) and \( N(t) \) in a simulation run, we developed an ad-hoc procedure to decipher if and when chasing occurred for instances where the drive did not fix and reach an equilibrium population. The drive initially clears the population radically from the centre of the landscape, causing wild-type individuals to become increasingly clustered around the edges. This results in increasing \( G(t) \) and decreasing \( N(t) \). However, when wild-type individuals escape to low-density areas and rebound, starting a chase, this pattern is reversed. We aimed to capture this scenario by identifying the first maximum in Green's coefficient and minimum of wild-type allele count (with monotonic decrease or increase, respectively, required for three generations on either side of the extremum) after the population had declined by at least 20% from its starting size. This indicates the point when wild-type individuals start to increase again, and clustering of wild-type individuals starts to decrease due to the expanding wild-type population during a chase. If there was an extremum in both, we considered a chase to have occurred. We considered the lowest generation of the two extrema to be the generation that chasing began. We tested this method by visually identifying the generation in which a chase began and comparing our visual detection to this automated test. Under a wide variety of parameters and with all types of drive, our algorithm was able to correctly identify the start of a chase within a few generations at most and matched the results of visually identifying the start of the chase in 100% of approximately 100 test cases with 50% chasing. Only in "borderline" areas of the parameter space where a chase lasted only a few generations did the algorithm occasionally fail to detect chasing, and only in similar situations did it produce false positives (both at rates of approximately 10% over 50 trials). Because these chases were invariably short and occurred in regions of the parameter space where chasing was unlikely in the first place, we considered these errors to be of minimal consequence to the general conclusions of our paper. An example of Green's coefficient and population size during a chase is provided in Figure S1.

### 2.10 Smoothing

In some specified figures, curves were smoothed to reduce noise from the limited number of simulations by displaying the weighted average of a data point and three adjacent points on either side (at weights of 75%, 37.5% and 18.75%, decreasing based on distance to the centre point). Near the ends in regions of rapid change, the number of data points used for smoothing on either side was equal to the number of data points between the point in question and the end point (zero for the end point) using the same weighting system.

### 2.11 Data generation

Simulations were run on the computing cluster at the Department of Computational Biology at Cornell University. Data processing and analytics were performed in Python, and figures were prepared in R. All SLiM files for the implementation of these suppression drives and data are available on GitHub (https://github.com/MesserLab/Chasing).

### 3 RESULTS

#### 3.1 Dynamics of suppression drives in panmictic populations

We analysed four different suppression drive strategies in this study. The first two strategies are homing-type drives, targeting either a female or both-sex fertility gene. The former has already been demonstrated in Anopheles (Kyrour et al., 2018). The third is a Driving Y chromosome, based on an X-shredder allele. The fourth is a TADS
FIGURE 1  Dynamics of suppression gene drives in our panmictic and spatial models. (a) Drive heterozygotes (drive-carrying males for the Driving Y) were released at 1% frequency into a panmictic population of wild-type individuals, and the drive allele frequency and population size were tracked for each generation until the population size reached zero. The data displayed are averages for 20 simulations. (b) Drive heterozygotes (drive-carrying males for the Driving Y) were released in a 0.01 radius circle into the middle of the spatial population. Outcomes were tracked for 1,000 generations for each simulation. The suppression rate specifies the proportion of simulations where the population was eliminated. Drive fitness and drive efficiency were varied on the left; low-density growth rate and migration value were varied on the right. Each point represents the average of at least 20 simulations.
suppression drive (Champer, Kim, et al., 2020) (see Methods for details of the different drive mechanisms).

In our panmictic population model, each of the drives, in idealized form, quickly increased in frequency after release and eliminated the population (Figure 1a), consistent with previous findings (Beaghton et al., 2017; Derec et al., 2011; Lambert et al., 2018). This remained true even if we assumed somewhat imperfect drives. For example, if drive efficiency and drive fitness were reduced to 0.8, each drive still successfully eliminated the population, although somewhat more slowly. Similarly, each drive can tolerate higher low-density growth rates (values of up to 12), despite the fact that increasing this parameter makes it more difficult for a drive to ultimately eliminate a population, given that a higher growth rate allows production of larger numbers of offspring when population size is small. The only exception to this within the parameter range that we considered is the Driving Y, which usually fails to suppress the population when \( 1/(1 - \text{drive efficiency}) \) is less than the low-density growth rate. This is consistent with modeling showing that fixation of such a drive allele often results in a reduction in the equilibrium population size instead of complete population suppression (Beaghton et al., 2017; Huang et al., 2007; North et al., 2013).

3.2 Suppression is less effective in spatially continuous populations

Panmictic population models can help us understand the basic dynamics of a gene drive, but real-world populations are usually structured, with individuals moving over a continuous landscape. To better understand how the dynamics of a suppression drive may be affected by such factors, we implemented a spatial simulation model in which individuals inhabit a two-dimensional arena. In this model, mates are chosen locally, offspring disperse a limited distance from their parents and population density is controlled by local competition. The level of localization can be varied in our simulations by the migration value parameter, which determines both the average dispersal distance of offspring and the radius over which mates can be selected. This model is generic, with arbitrary units for distance, thus allowing it to potentially provide general insights into the dynamics of suppression gene drive systems in spatially continuous populations (although several parameter ranges are inspired by mosquitoes—see Methods).

Figure 1b shows that the ability to eliminate the population is substantially reduced in our spatial model. As we varied drive efficiency and fitness values between 0.8 and 1.0 (representing high-efficiency drives), low-density growth rate between 2 and 12 (inspired by Anopheles data17), and migration value between 0.01 and 0.06, only the TADS drive was able to consistently eliminate the population within 1,000 generations. While the female sterile homing drive generally performed better than the both-sex sterile homing drive and the Driving Y system, all three of these strategies failed over large areas of the parameter space tested. For example, none of these three drives was able to reliably eliminate the population when drive efficiency was below 0.9 or when the migration value was below 0.03. Note that even at the lower migration level in our model (0.01), the drive would always reach the corners of the 1 × 1 arena well before (within 200 generations) the simulation was concluded after 1,000 generations.

3.3 Chasing dynamics accounts for the majority of drive failure in the spatial model

We wanted to test what causes drive failure in the spatial model. For the Driving Y, it is known that even in panmictic models, elimination can fail when drive efficiency is low and low-density growth rate is high, despite the drive allele becoming fixed in the population (Beaghton et al., 2017; Huang et al., 2007; North et al., 2013). This occurs when enough X chromosomes escape shredding in each generation for the resulting females to be able to maintain the population. We observed such an equilibrium in our spatial model of the Driving Y as well (Figure S2), but this mechanism does not fully explain drive failure over the whole parameter range, nor does it account for any failures of the other drive types. Another possible scenario is that failure is due to loss of the drive, which allows the wild-type population to rebound afterwards. We found that this indeed occurred in some cases (Figures S3 and S4), particularly for the both-sex sterile homing drive. However, this was too infrequent to account for the high failure rate.

Instead, we found that in most of the cases of drive failure, both drive and wild-type alleles coexisted in the population. Closer analysis of the spatiotemporal dynamics of drive carriers and wild-type individuals in these scenarios revealed an interesting pattern we term “chasing,” which is characterized by large fluctuations in population density over time and space (Figure 2). Chasing occurs when the drive has cleared substantial parts of the population, creating empty areas into which wild-type individuals can then escape from drive-populated areas. Because of limited competition in those areas, the wild-type population rebounds there quickly. Drive alleles then move in from the perimeter of the recolonized area, “chasing” the wild-type alleles and eventually suppressing the population in that area again. Meanwhile, wild-type alleles ahead of the drive are still recolonizing empty regions, preserving the chasing dynamics. Several videos illustrating chasing behaviour in our simulations for different drive types are available on YouTube (tinyurl.com/y5vjsfy2).

Note that chasing is different from equilibrium scenarios that can also lead to coexistence of drive and wild-type, such as observed for the Driving Y in both panmictic and spatial scenarios. In equilibrium scenarios of our model, overall population density is approximately uniform across space, and local drive allele frequencies are similar across all regions. By contrast, chasing is characterized by unstable strong clustering of individuals in space, with often substantial allele frequency differences between clusters and large fluctuations in cluster sizes and locations over time and space. The availability of empty spatial areas is critical to bring about these dynamics. Thus,
chasing is fundamentally a spatial phenomenon that cannot occur in panmictic models.

To detect whether chasing has occurred at any point in a given simulation run, we developed a statistical test based on the longitudinal analysis of population size changes and measures of spatial clustering (see Methods). We find that chasing is generally common in areas of the parameter space where the drive struggles to eliminate the population (Figures S5 and S6), although these ranges do not overlap exactly (compare with Figure 1b).

**Figure 3** shows the results of these analyses, revealing complex dependencies of drive outcomes on individual parameters and pronounced differences between drive types. In general, the TADS suppression drive was the only system that remained effective across the full range of parameters tested, except when the migration value was very low. The female-sterile homing drive also performed well but was still unable to induce population elimination for much of the parameter space. The Driving Y and both-sex sterile homing drives were generally less effective. The both-sex sterile homing drive in particular showed low performance because it was often lost from the population, usually after an initial period of chasing. A variant of this drive that induces lethality instead of sterility showed broadly similar performance (Figure S7, Supporting Information Results).

Drive efficiency had a dramatic effect on the success rate, even though we only considered drives with efficiency levels at or above 80% (high efficiency drives).

For the female-sterile homing drive, as efficiency increased, long-term chasing outcomes were replaced with elimination after
chasing, which in turn was eventually replaced with elimination without chasing. For the both-sex sterile drive, as efficiency increased, long-term chasing outcomes became less common and elimination after chasing became more common. However, the rate at which the drive was lost also increased before declining again when drive efficiency approached 100%. For the Driving Y, higher drive efficiency prevented equilibrium outcomes (when the drive became fixated, but did not chase or eliminate the population), but even for its optimal efficiency, which was somewhat below 100%, this drive did not achieve elimination in all simulations, unlike TADS or the female
sterile homing drive. In some simulations at this optimal level, elimination was rapid, but it usually occurred after a period of chasing. Increasing drive fitness generally shifted outcomes toward higher elimination rates for all drives, but this effect was of considerably lower magnitude than the effect of increasing drive efficiency in the parameter space we considered.

In addition to drive parameters, ecological parameters also had notable effects on outcome rates. Increasing the migration value generally increased the rate of elimination outcomes, consistent with the fact that higher migration should make the spatial model more similar to a panmictic model. A similar effect of migration was seen in simulations of cyclically dominant three-component systems, where high migration resulted in one class eventually dominatining (Frey, 2010). Higher low-density growth rates generally decreased the rate of elimination outcomes while increasing the rate of chasing outcomes, although the rate at which the drive was lost was also reduced. We found that changing the boundary of our arena to an unbounded toroidal space decreased the rate of successful elimination after chasing (Figure S8, Supporting Information Results). The overall population density had little effect on outcomes (Figure S9, Supporting Information Results), but chasing became far more common with even a modest increase in arena size (Figure S10).

3.5 | Impact of chasing on suppression potential

To better understand the impact of chasing on the overall goal of population suppression, we first examined the duration of chasing in runs where the population was eliminated after a chase (Figures S11 and S12). We found that in areas of parameter space where chasing was common, the time interval of chasing tended to be longer, usually several hundred generations. Where chasing was less common, the time interval of chasing tended to be shorter, comprising only a few generations before complete suppression.

The objective of a suppression drive could still be partially fulfilled even without achieving elimination if the population size is sufficiently reduced. This often occurs in chasing scenarios. To determine the magnitude of population reduction, we analysed the average population size during chasing, regardless of final outcome, over a range of parameters (Figures S13 and S14). In general, the migration value had a dominant effect, and when chasing was more common, the average population size during chasing was typically higher. Nonetheless, population reductions by a factor of 2–3 were common. When chasing was less common, the average population size was even smaller. The average Green’s coefficient during the chase was found to be lower when chasing was more common, indicating the presence of a greater number of chasing clusters at any given time (Figures S15 and S16, Supporting Information Results). This is consistent with predator–prey models in which higher dispersion resulted in larger “chasing” structures (Chang et al., 2019), as well as simulations of cyclically dominant three-component systems (Frey, 2010).

3.6 | The effect of inbreeding on chasing

Previous studies have found that inbreeding can pose a substantial obstacle to the spread of gene drive (Bull, 2017; Bull et al., 2019). To test whether these results extend to our spatial model and explore possible connections to the chasing phenomenon, we studied how varying the probability of mating between siblings affected drive outcomes in our spatial model (Figure 4). Consistent with previous results, we found that increased inbreeding (achieved in our model by increasing the preference for choosing a sibling as a mate) resulted in a reduced likelihood of elimination and more chasing. Similarly, if individuals had a reduced sibling mating rate, successful elimination became more likely. This was also observed when we reduced fecundity when mating occurred between siblings, representing the effects of inbreeding depression (Figures S17 and S18).

3.7 | Chasing can lead to drive failure by resistance allele formation

Cleavage repair by end-joining or incomplete homology-directed repair can lead to the formation of resistance alleles that do not match the drive’s gRNAs and are thus immune to future cleavage (Champer et al., 2017; Gantz et al., 2015; Hammond et al., 2015). Thus far, we have only considered resistance alleles that disrupt the target gene function, which usually do not have a drastic impact on the success rate of a suppression drive. However, some resistance alleles could preserve the function of the target gene and ultimately stop a suppression drive from spreading. Such function-preserving mutations are known as “r1” resistance alleles (Champer et al., 2017). A recent study in Anopheles was able to prevent the formation of r1 alleles in small population cages (Kyrou et al., 2018), but it is unclear exactly to what degree r1 allele formation can be mitigated.

To test the potential impact of r1 resistance alleles on drive outcomes, we varied the r1 resistance rate for the two homing drives in our model, which would be most prone to forming such alleles (Figure 5a). The r1 rate here specifies the fraction of resistance alleles that become r1 alleles. We did not see a substantial impact of resistance in our model with K = 50,000 individuals for r1 rates below $10^{-5}$, while for rates above $10^{-3}$, outcomes were dominated by resistance. Notably, in drive failures at intermediate r1 rates, the first r1 alleles usually arose well after the drive had started chasing, suggesting that if chasing had not occurred, such alleles would probably not have been able to prevent elimination.

This underlines the importance of chasing dynamics. Even temporary chasing raises the effective number of wild-type alleles (by allowing wild-type alleles to increase in number rapidly when moving into empty space) that must be converted by the drive before successful population elimination occurs, with each conversion possibly resulting in an r1 allele that may ultimately prevent elimination and allow the population to rebound. This is in stark contrast to panmictic models of these drives (Figure 5b), where r1 alleles can only thwart drive systems when occurring at much higher rates.
In our models thus far, we have investigated the outcomes resulting from a single drive release in the centre of the arena. However, more successful outcomes could potentially be obtained by adjusting the release strategy of the drive. To investigate this, we first modelled releases of drive-carrying individuals over the entire area, rather than in a small circle in the centre of the arena. This did not substantially change outcomes aside from speeding the rate at which the drive successfully suppressed or entered a chasing regime, although a random release did somewhat reduce the chance that a both-sex homing suppression drive would be lost (Figure 6). On the other hand, the rate of an inefficient (substantially reduced efficiency parameters) TADS drive underdoing chasing before suppression was increased.

We next varied the size of the randomly distributed release between 0.01% and 10% of the initial population. In this range, drive outcomes were largely unchanged (Figure S19). However, at low frequencies (corresponding to approximately five to 10 individuals), the inefficient TADS drive had a higher chance of being lost before chasing occurred.

We also investigated the possibility of performing repeated releases, varying the number of generations in between releases. Repeated releases substantially reduced the chance of chasing before suppression for the female-sterile homing drive, especially when the interval size was very small (Figure 6) and the release size was large (Figures S20 and S21). These same factors also reduced the duration of chasing (Figure S22). However, for the both-sex sterile homing drive and the Driving Y, releases were needed every generation to see a substantial improvement in drive outcomes. For the inefficient TADS drive, repeated releases actually increased the chance of chasing to occur. This drive is not susceptible to chasing.
in the first place, but because it has inefficient drive parameters (in the form assessed here), the release of drive heterozygotes adds a substantial number of wild-type alleles to the population, which then take additional time to be removed, a prerequisite for complete suppression. It is plausible that inefficient versions of the other drive types (in terms of reduced total cut rates) would suffer similarly under repeated release regimes.

4 | DISCUSSION

In this study, we demonstrated that suppression gene drives in spatially continuous populations can experience a phenomenon we term chasing dynamics, which often prevents complete population elimination by the drive. This phenomenon occurs when wild-type individuals move into areas previously cleared by the drive, where they can rebound quickly due to low levels of initial competition. Drive alleles then follow and chase wild-type alleles across the landscape. These dynamics can lead to long-term, unstable coexistence of drive and wild-type alleles in the population.

The consequences of chasing could potentially impact the decision to deploy a suppression drive. At a minimum, chasing may delay complete suppression, often by a substantial time interval, while more robust chasing can persist perpetually, depending on drive and environmental parameters. Moreover, the larger sizes of most realistic populations compared to those we modelled here provide more possibilities for a chasing situation to start. The overall population size can still be reduced substantially during chasing, yet continuous conversion of wild-type alleles may eventually result in the formation of functional resistance alleles. If such alleles do arise, population size can rebound quickly.

The definition of chasing we employed in this study is qualitative in nature, and we hope that future studies can develop a formal definition that would allow us to better understand how and when chasing is initiated. Simulations in one-dimensional space suggest that a chase can start by local elimination of the drive, thereby opening a migration route for wild-type individuals to recolonize empty areas. However, it is also possible for wild-type individuals to directly permeate an expanding wave of the drive to reach empty areas behind the wave that have been cleared by the drive (Figures S23 and S28, Supporting Information Results).

Chasing dynamics bear resemblance to a variety of qualitatively similar phenomena that have been previously described in other dynamic systems. For example, it could be argued that chasing is similar to a spatial game of "rock–paper–scissors" with drive individuals, wild-type individuals and empty space as the three elements of the system, where each tends to replace another one (albeit with "empty space" being a passive element in our model, rather than an equal
actor as in the rock–paper–scissors analogy). It has previously been shown that in a spatial game of rock–paper–scissors, cyclical dynamics can arise where no particular element always dominates (Benaim & Schreiber, 2019; Frey, 2010; González-Díaz et al., 2013; Hódsági & Szabó, 2019; Muyinda et al.; Toupo et al.; Voit & Meyer-Ortmanns.; Yan et al., 2020). Dynamics akin to chasing have been observed in other biological systems such as coral reef invertebrates (Jackson & Buss, 1975) and bacterial populations (Kerr et al., 2002). In the latter case, three cyclically competing strains were able to form coexisting patches, with each patch chasing another type. However, when the population was well mixed (analogous to our panmictic model), one strain always dominated (Kerr et al., 2002). Chasing dynamics also show similarity to the loss of parasites in a range expansion scenario (Phillips et al., 2010), in that wild-type alleles can move ahead of the drive during chasing.

Perhaps most obviously, the chasing of wild-type alleles by a suppression gene drive invokes a conceptual analogy to classical predator–prey systems, where spatial structure was found to generally promote the coexistence of areas dominated by predators, prey and empty space (Chang et al., 2019; Donalson & Nisbet, 1999; Gilpin & Feldman, 2017; Huang et al., 2019, 2019.). However, it is not yet clear whether a one-to-one mapping between these systems is indeed possible. For instance, cyclical dynamics can naturally arise in both panmictic predator–prey and rock–paper–scissors systems, but not in the panmictic models of the suppression drives we investigated, where only noncyclical equilibria (at least for relative drive and wild-type frequencies) or elimination of one allele type are possible. This indicates that spatial structure may play a more critical role in facilitating chasing dynamics for a suppression gene drive than for the cyclical dynamics observed in some predator–prey models.

**Figure 6** The effect of drive release pattern on suppression outcomes in continuous space. Drive heterozygotes (drive-carrying males for the Driving Y) were released randomly into a wild-type population at a level corresponding to 1% of the total population size. The proportion of different simulation outcomes is shown. The release interval specifies the full number of generations between releases in which no release occurs (a value of 0 corresponds to releases every generation). “S” represents a single random release (no continuous releases) and “C” represents a single central release. To show a greater dynamic range of outcomes, some default parameters were modified (female sterile homing drive: efficiency and fitness was reduced to 0.92, migration value was reduced to 0.035 and low-density growth rate was increased to 8; Driving Y: migration value was reduced to 0.0325; TADS suppression drive: efficiency and fitness was reduced to 0.8, migration value was reduced to 0.02, and low-density growth rate was increased to 12). Curves were obtained by averaging at least 100 simulation runs for each tested parameter value and then smoothed as described in the Methods to reduce noise.
Outcomes consistent with chasing behaviour have already been observed in other models of suppression gene drives in structured populations (Bull et al., 2019; North et al., 2019, 2020). In these studies, it was suggested that the drive efficiency should be high enough to avoid stochastic drive loss but should not be so high that the drive eliminates patches of wild-type alleles and itself before being able to spread to an adjacent region. This contrasts with our findings in continuous space, where except for the Driving Y, drives with maximum efficiency generally were most effective at achieving complete population suppression. One reason could be the very different models used in these studies, which did not include continuous space. Rather, wild-type colonization and suppression by the drive was a discrete event in each area, and a reduced rate of suppression would thus allow the drive to more efficiently invade adjacent populations.

Compared to our continuous-space model with local dispersal, the amount of chasing in a real-world population could possibly be increased by long-distance dispersal (by water, wind, human transportation, etc.), because this could make it easier for wild-type individuals to escape into empty areas far away from any drive-carrying individuals, where they could then expand quickly. Note that this long-range process is different from simply increasing the migration rate, which tended to reduce chasing by allowing drive individuals to more quickly disperse into local wild-type populations, thereby preventing them from reaching low-density areas far away from any drive individuals. Environmental variation, such as those that affect migration and low-density growth rates, may also facilitate chasing if regions exist with ecological parameters that are more amenable to chasing, which could then serve as “seeds” for recurrent, temporary expansions of wild-type individuals into surrounding areas that are less amenable to chasing. In a study of gene drive suppression in a network of linked panmictic demes, chasing-like behaviour was more frequent in areas with strong seasonality, and long-range dispersal did not have a large effect on suppression outcomes (North et al., 2019, 2020).

We found that the propensity of chasing is substantially affected by both drive performance and ecological parameters. In general, even modest reductions in drive fitness and efficiency greatly increased the likelihood of chasing and reduced the chance of successful elimination. However, the optimal efficiency for the Driving Y (X-shredder) was somewhat less than 100%, as seen in a previous study (North et al., 2019). In our model, this may be because the drive suppresses rapidly, and slightly reduced efficiency could prevent local stochastic loss of the drive, thereby making it harder for wild-type individuals to pass the drive and recolonize previously cleared empty areas to start a new chase. Higher migration values significantly shifted the range of outcomes in favour of elimination and reduced chasing propensity, consistent with the fact that this should generally shift the spatial model closer to the panmictic model. The low-density growth rate parameter usually had a smaller effect compared to others in reducing chasing. However, in simulations where the low-density growth rate was very low, we often saw a stochastic loss of the drive when the numbers of drive and wild-type individuals had reached low levels. Additionally, chasing was substantially inhibited, consistent with the notion that density-dependence is a critical prerequisite for chasing. In our model, the low-density growth rate parameter directly specifies the growth rate in the absence of competition, but it more generally determines the strength of density-based interactions (a value of 1 eliminates density dependence). Thus, the low-density growth rate is the driving force behind the advantage of wild-type alleles in low-density regions. Density-independent systems or those with just weak density dependence are thus unlikely to experience chasing or similar phenomena.

The drive types we investigated had markedly different effectiveness in their ability to suppress populations in continuous space. Understanding the underlying reasons for this poses an interesting topic for future study. Our initial analysis suggests that stochastic factors and the “thickness” of the advancing drive wave may play a key role in these differences (Table S1, Figures S29–S31, see the “Comparative analysis of drive types” section in the Supporting Information Results for additional results and discussion of this topic). One clear conclusion is that homing-type suppression drives should be targeted to an essential but haplolethal gene that affects only one sex (such as a female fertility gene), given that the both-sex drive had a substantially higher tendency to chase and also suffered from higher stochastic loss of the drive in our spatial model. The female fertility homing drive, on the other hand, performed quite well when it had high efficiency, which is promising given that such drives have already been constructed in Anopheles gambiae (Kyrou et al., 2018). The Driving Y (based on an X-shredder and very similar to a TADS-based Driving Y chromosome (Champer, Kim, et al., 2020)) also performed worse than the female sterile homing drive. TADS suppression had the highest effectiveness of all drive types we tested. If suitable gene targets for such a system can be identified, this could enable the development of drives that can both minimize resistance alleles with multiplexed gRNAs (a useful strategy but with substantial limitations in homing-type drives (Champer, Oh, et al., 2020)) and achieve complete suppression over a large range of parameters.

In addition to suppression drives, similar chasing behaviour could probably also arise for modification-type gene drives in continuous space populations under specific circumstances. In this case, the three cyclical classes would be wild-type alleles, resistance alleles that carry fitness costs and even more costly drive alleles.

Evolution of an increased tendency for inbreeding has been suggested as a mechanism by which populations could avoid the suppressive effects of a gene drive (Bull et al., 2019), and our studies in continuous space support this notion. We found that higher levels of inbreeding can indeed substantially reduce the effectiveness of the drive by increasing the likelihood of chasing. However, inbreeding avoidance (and inbreeding depression) can actually work in favour of the drive. In many real-world target populations, these latter effects could play an important role in determining the likelihood of drive success, and because suppression could occur rapidly, there may be insufficient time for the evolution of strategies that increase inbreeding in the population.

Overall, we have shown that suppression gene drives can exhibit rich dynamics in spatially continuous populations with a wide range of
possible outcomes. In particular, the chasing effect could be a primary means by which a population can escape elimination by a drive. Thus, to accurately predict the outcome of a suppression strategy, detailed population models should be utilized that incorporate realistic levels of spatial structure across all relevant scales.

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AUTHOR CONTRIBUTIONS
J.C. and P.W.M. conceived the study. I.K.K. and S.E.C. generated the computational framework. I.K.K. carried out the study. J.C. and I.K.K. wrote the initial draft of the manuscript, with additional revisions by P.W.M. All authors made comments on drafts and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT
All SLiM files for the implementation of these suppression drives and data are available on GitHub (https://github.com/MesserLab/Chasing).

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

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