Abstract

BACKUS, GREGORY ALAN. Population Dynamics Models of Invasive Rodent Eradication with Gene Drive Technology. (Under the direction of Kevin Gross and Nick Haddad.)

Invasive rodents have caused considerable damage to island ecosystems, contributing to the extinction of several rare endemic species. To protect these unique ecosystems, rodents have been eradicated from hundreds of islands throughout the world. Unfortunately, eradication usually involves the heavy application of chemical toxicants that can harm and kill many non-target species. Genetic engineering could provide an alternative, species-specific eradication technique. One example would involve engineering a house mouse (*Mus musculus*) to carry a genetic construct that would cause a majority of its offspring to be male, many of which would be sterile. Releasing these genetically engineered mice to interbreed with an invasive population would reduce the number of fertile female mice in that population until no more remain.

I build and analyze a series of mathematical models to explore the population dynamics and population genetics of eradicating an invasive island-rodent population using the previously described genetic construct. First, I use a differential equation model that describes the spread of this suppressing gene drive through a density-dependent population. With this model, I highlight conditions under which the gene drive would eradicate the population. Particularly, if mice carrying the gene drive have a substantial survival advantage over their wild-type counterparts, the gene drive could spread through and eradicate a population with a single release. More likely, gene drive mice would have a fitness disadvantage, and eradication would require repeated releases of the gene drive into the population. I also use this model to show that increasing the speed and efficiency of eradication comes at the expense of a more disruptive transient impact on the surrounding ecosystem.

Next, I adjust the previous model to allow for the potential of heritable female mate choice. I find that preferential mating in favor of wild-type males could act as a form of gene drive resistance as it becomes more frequent in response to the gene drive. On an island, this resistance

could be countered with higher gene drive release rates, which could force the population to extinction before preferential mating has the opportunity to evolve. Alternatively, preferential mating could instead act in favor of gene drive males. Even when gene drive males have a survival cost, strong preferential mating in their favor could allow for the long-term persistence of a gene drive or even result in eradication.

Lastly, I construct and analyze a stochastic eradication model where mice are separated into a collection of discrete patches. Within this context, I simulate eradication in a variety of conditions by varying dispersal rates, number of patches, and the topology of patch connections. A balanced repeated release of the gene drive into every patch is most successful, but it would likely be infeasible without full knowledge of the population structure. If gene drives are not able to be released throughout the full spatial extent of the population, eradication is still possible, though less effective. The minimum number of areas necessary to release the gene drive depends on dispersal and patch topology.

Population Dynamics Models of Invasive Rodent Eradication with Gene Drive Technology

by
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Dedication

To Kyle and Cassidy.

You're both incredible sources of inspiration.

Biography

Greg was born in Vancouver, Washington in 1988. He eventually moved to Newfoundland for two years before ending up in southern Alabama in time for high school. There, he was lucky to be able to attend the Alabama School of Mathematics and Science where he first gained a true appreciation for math and biology. For his undergraduate career, Greg attended Bard College in the bustling up-state New York metropolis of Annandale-on-Hudson. At Bard, his coursework in ecology and mathematics led him to a senior project studying a mathematical model of the successional dynamics of a fragmented plant community. With a fancy liberal arts degree under his belt, he was accepted to the NC State Biomath program and later joined the Zoology program. With an IGERT fellowship, Greg became part of an interdisciplinary, collaborative cohort of graduate students exploring the intersection of genetic engineering and conservation. When he isn't busy writing a dissertation, Greg prefers to spend his time hiking, cooking, playing video games, and making music.

Acknowledgements

I would like to my advisor, Kevin Gross, who has allowed me to pursue my own research interests while providing engaged and exceptional guidance along the way. He has also had extreme patience in learning to understand my partially-developed thoughts while also helping me figure out the best way to translate these ideas on my own. Additionally, Nick Haddad, Jason Delborne, John Godwin, and Alun Lloyd have enriched my graduate school experience, each well beyond their roles as committee members. Fred Gould and several others also deserve plenty thanks for helping to organize IGERT and GES-related activities while also encouraging my interdisciplinary training.

Among those who have worked with me and encouraged me throughout my time at NC State, there is, of course, little distinction between who is a peer, a friend, or a colleague. Thanks should go out to, and certainly aren't limited to, Tim, Kelsey, Carl, Emi, Caroline, Andrew, Jake, Elizabeth, Michael, Megan, Mandi, Rene, and Jess (and everyone else I forgot because I'm an awful person). I'm also very appreciative to Jacob Spry and the rest of my friends outside of NC State who have provided plenty of support and friendship, even when I couldn't provide much in return. Similarly, I appreciate my family for putting up with throughout this process. Being so far away and busy, I've missed far too many events. And to Cassidy, who has provided so much throughout this process. This dissertation is ending in a much better place emotionally and intellectually thanks to you.

Honorable mentions can be awarded to both Cup-A-Joe and Coffee Haven (R.I.P.) and everyone who has worked in either in the last few years. Sure, I thanked them with plenty of business, but they deserve some credit for fueling a majority of this dissertation.

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Chapter 1

Introduction

1.1 Background

Islands account for a small amount of the world's land area, yet they contain a disproportionately large amount of the world's biodiversity (Myers et al., 2000). The rare, endemic species that have evolved to live in these island ecosystems are threatened by invasive rodents (Atkinson, 1985; Towns et al., 2006; Howald et al., 2007). To protect these rare species, rodents have been eradicated from hundreds of islands worldwide (Howald et al., 2007; DIISE, 2015), resulting in substantial conservation benefits (Bellingham et al., 2010; Jones et al., 2016). Rodents are usually eradicated with heavy applications of anticoagulant toxicants, especially on larger islands (Campbell et al., 2015). Unfortunately, these toxicants are not species-specific, as they can harm endemic species, livestock, pets, and even humans (Eason and Spurr, 1995; Glen et al., 2013; Campbell et al., 2015). Additionally, toxicant baits need to be distributed densely and widely over the full extent of island to ensure that every individual is exposed to the toxicant (Pott et al., 2015). Because of these limitations, there is an increasing demand for the development of new eradication techniques (Campbell et al., 2015).

Genetic engineering technology could provide an alternative invasive species eradication tool that is species-specific, capable of self-dispersing, and less harmful to the surrounding ecosystem (Campbell et al., 2015; Piaggio et al., 2017). To eradicate a population, an organism could be engineered to carry a gene construct that would manipulate sex ratios, reduce fertility, or reduce fecundity (Burt, 2003; Deredec et al., 2008; Alphey, 2014). This gene could be combined with a selfish genetic element that is normally inherited above the standard 50% Mendelian ratio, forming what is known as a gene drive. When organisms carrying this gene drive are released, they could interbreed and gradually suppress an undesired pest population. These techniques have been primarily developed within the past few decades as tools for managing insect pest populations (Alphey, 2014). However, there has been accelerating interest in adapting these techniques to control larger invasive vertebrate species (Esvelt et al., 2014; Thresher et al., 2014;

Jones et al., 2016), and especially for the eradication of invasive rodents from islands (Campbell et al., 2015; Piaggio et al., 2017). As gene drive techniques become increasingly entwined with conservation, it is important to re-evaluate these techniques from this new perspective.

1.2 Outline

I analyze a set of ecological models relating to the eradication of invasive rodent populations with a gene drive. The motivating system is a house mouse (*M. musculus*) that is capable of suppressing a population after it is engineered to carry a combination of just two genes in a single gene construct. First, an *Sry* gene, which codes for testis development, would be inserted into the autosome of a mouse. Any mouse that inherits an autosomal *Sry* gene will develop as a male regardless of its sex chromosomes, though XX mice would be sterile. This would be linked to a *t*-haplotype, a naturally occurring gene drive in mice. With this gene construct, the engineered mouse would have mostly male offspring. Repeatedly releasing engineered mice that carry this gene into a wild population should theoretically eradicate that population over time.

In Chapter 2, I build a basic differential equation model to describe the potential for this gene drive to spread through and eradicate a wild population of house mice. I use this model to show how the ability of this gene drive to spread changes with the relative death rate of gene drive mice. Because genetically manipulating an organism would usually be expected to impose a fitness cost, gene drive mice would likely need to be repeatedly released to eradicate a population. However, if gene drive mice have a substantial survival advantage, the gene drive could spread through and eradicate a population with a single release. I also use this model to demonstrate how faster eradication times could correspond with an increased intensity of transient ecological disruption on the island ecosystem.

In Chapter 3, I add female mate choice into the previous model by allowing females to have heritable preference to mate with either wild-type males or gene drive males. I explore the

evolutionary interaction between spread of gene drives and the responding change in preferential mating. When preference favors wild-type males, mating resistance can evolve to limit the spread of gene dives through the population. On the other hand, preference could also act in favor of gene drive males and increase the spread of the gene drive through the population.

These previous models assume that each mouse has an equal change of interacting with each other mouse in the population. However, rodent populations could realistically be separated into separate spatial or social patches. In chapter 4, I consider this population structure as I use a stochastic model to determine how a gene drive could spread through a metapopulation. Though I find that spatial structure is not important when gene drives are released evenly throughout the metapopulation, a completely balanced release strategy would be infeasible without full knowledge of the metapopulation structure. However, because gene drive mice are capable of spreading through a population on their own, an unbalanced release strategy could still be successful as long as the metapopulation is well connected and between-patch dispersal rates are high.

1.3 Other work

In addition to the work that I present within the main text of my dissertation, my Ph.D. experience was enriched by an interdisciplinary collaboration with other students who were also interested in the intersection of genetic engineering and conservation. This collaboration was funded thanks to an NSF-funded IGERT grant on Genetic Engineering and Society: The Case of Transgenic Pests. As a group project, we explored the complex scientific, ethical, and social issues related to releasing genetically engineered mice into an island ecosystem. Together, we created a website that highlights several of the possible implications and concerns surrounding the development of genetic engineering technology for conservation. This work can be found at `https://research.ncsu.edu/islandmice/`.

Also, Chapter 2 originally contained an additional analysis related to the releasing of gene drive mice in discrete pulses. As we condensed our results for the sake of publication, we removed that analysis from the submitted manuscript. However, that work is retained within this dissertation as Appendix B.

Chapter 2

Genetic engineering to eradicate invasive mice on islands: Modeling the efficiency and ecological impacts

Abstract [1]

Invasive rodents are usually eradicated from islands through the application of chemical toxicants that can harm surrounding ecosystems. A recently proposed alternative involves engineering a house mouse (*Mus musculus*) to carry a genetic construct that would cause a majority of its offspring to be male, many of which would be sterile. Releasing these genetically engineered mice to interbreed with an invasive population would reduce the number of fertile female mice until no more remain. We constructed a mathematical model to analyze the population dynamics of eradication with this genetically engineered mouse and determined its eradication efficiency through model analysis and simulations. Because genetically engineered mice would likely have a fitness disadvantage compared to wild mice, we found that they would need to be repeatedly released into the population to ensure complete eradication. However, if genetically engineered mice have a substantial survival advantage, we determined that the genetic construct could theoretically spread and eradicate a population after a single pulsed release onto the target island or after an engineered mouse escapes to a non-target location. Also, while the species specificity of genetic engineering avoids some of the non-target impacts of traditional eradication methods, ecological impacts could manifest indirectly. We compared several metrics to estimate potential transient impacts on the ecosystem and found that there is a trade-off between the speed of an eradication and the intensity of increased disruptive ecological interactions. Together, our results can inform safe and efficient ecological practices for eradication with developing genetic engineering technology.

[1] This chapter is published: Backus GA, Gross K. Genetic engineering to eradicate invasive mice on islands: Modeling the efficiency and ecological impacts. *Ecosphere* 7: e01589.

2.1 Introduction

Island ecosystems often include rare endemic species that are threatened by invasive species (Alcover et al., 1998; Aguirre-Muñoz et al., 2008). Rodents are common among island invasives and contribute to a large number of extinctions (Howald et al., 2007). From a conservation perspective, this creates a strong incentive to eradicate these non-native rodents from islands. Past rodent eradications have mostly been successful at removing the target species from the ecosystem (Howald et al., 2007) and have resulted in subsequent ecological recoveries (Aguirre-Muñoz et al., 2008; Croll et al., 2016; Jones et al., 2016). Unfortunately, eradication is a complex process that comes with a long set of problems and complications, many of which are the result of the most common eradication method that involves exposing islands to chemical toxicants (Campbell et al., 2015). The anticoagulant toxicants that are used can be lethal to non-target organisms (Howald et al., 2007; Campbell et al., 2015) and they kill through slow internal bleeding (Hoare and Hare, 2006), which can be a concern for animal welfare and public perception (Fitzgerald, 2009; Howald et al., 2010). Also, while rodenticides are effective at eradicating rodents on smaller islands, it can be logistically challenging to scale efforts with increased land area (Howald et al., 2007; Holmes et al., 2015). House mice (*Mus musculus*) are particularly difficult to eradicate with toxicants (Howald et al., 2007), as only 70% of full-island mouse eradications have been completely successful compared to 88% for all other rodent species (DIISE, 2015). These numerous drawbacks of rodenticide-driven eradication, especially for mice, motivate the search for alternative eradication techniques (Campbell et al., 2015).

Among the potential new tools for eradication, genetic engineering (GE) could provide a promising species-specific, non-lethal alternative. Though GE techniques have been primarily developed to manage insect pest populations (Burt, 2003; Deredec et al., 2008; Alphey, 2014), GE has been recently considered for managing a wider range of invasive species (Davis et al., 1999; Deredec et al., 2008; Gould, 2008; Hodgins et al., 2009; Thresher et al., 2014; Esvelt et al.,

2014; Campbell et al., 2015; Johnson et al., 2016; NAS, 2016). In general, these techniques would involve releasing GE organisms into an undesired population to gradually suppress and eradicate that population after several generations of interbreeding (Burt, 2003; Deredec et al., 2008; Alphey, 2014). The most prominently proposed population-suppressing GE techniques aim to manipulate offspring sex-ratios, such as female-specific RIDL (release of insects carrying dominant lethal) (Thomas et al., 2000), the Trojan female technique (Gemmell et al., 2013), and X-chromosome shredders (Deredec et al., 2008). By releasing enough of these sex-biasing GE organisms over a long enough period of time, the undesired population should reach the point where nearly all individuals are of one sex and the population cannot sustain itself (Hamilton, 1967). Sex-biasing GE constructs can be made more efficient though gene drives, which increase the rate of inheritance above the natural Mendelian rate of 50% (Burt, 2003; Esvelt et al., 2014). Increased transmission rates can reduce the number of GE organisms that need to be released and shorten the duration of eradication. Though much of the established theory on GE-assisted population suppression has been developed around the genetic, behavioral, and ecological characteristics of insects, the general theory could also apply to rodent species.

We focus on the eradication of invasive house mice with a recently proposed engineered genetic construct (Campbell et al., 2015), which we refer to as the *t-Sry* construct. The *t-Sry* mouse is engineered by linking two naturally occurring *M. musculus* genes that are not normally linked in the wild. One of these, the "sex-determining region (of the) Y" (*Sry*) gene, is found on most mammalian Y chromosomes. The gene is an essential component in the development of testes, though it has‘ no known role in spermatogenesis (Goodfellow and Lovell-Badge, 1993). Mice with two X chromosomes, which would usually develop as females, can be engineered to develop as males if they carry a copy of the *Sry* gene on an autosome. However, they would also be unable to reproduce lacking the ability to produce sperm (Koopman et al., 1991). The other component of the *t-Sry* construct is the *t*-haplotype (Dobrovolskaia-Zavadskaia and Kobozieff, 1927), which distorts transmission in male mice such that fathers with one copy of

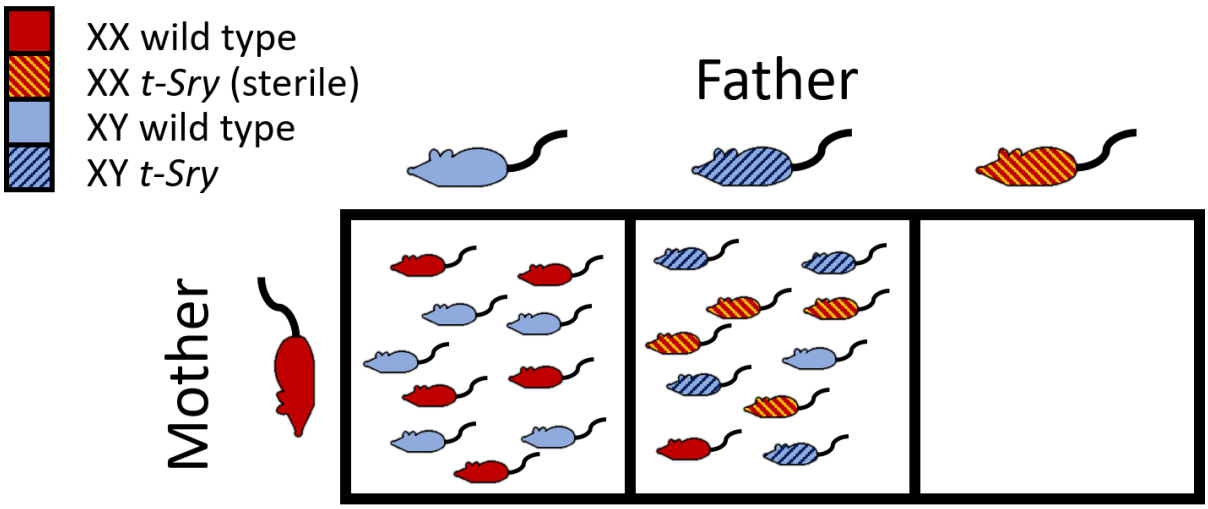

Figure 2.1 Diagram showing how the *t-Sry* construct spreads to offspring. All newborn mice must have a wild-type mother. When the father is wild-type, all offspring would be wild-type. Half of these would be male (XY) and the other half would be female (XX). When the father is a fertile *t-Sry* mouse (XY), more than half of the offspring ($\tau = 0.8$ in this example) would also carry the *t-Sry* construct. As before, half of all of these offspring would be XY and the other half would be XX. XX mice that carry the *t-Sry* construct would be phenotypically male, but would be sterile.

the *t*-haplotype can pass that copy of the *t*-haplotype to over 90% of their offspring (Schimenti, 2000). Linking the *Sry* gene and the *t*-haplotype together would cause most of the offspring of a genetically engineered *t-Sry* father either to carry the *t-Sry* construct or to be sterile (Figure 2.1). In theory, the *t-Sry* construct should reduce the number of fertile females and fully eradicate the mouse population after several generations of releasing and interbreeding, similar to autosomal X-chromosome shredders described in Deredec et al. (2008).

We explore several aspects of *t-Sry* mouse population dynamics and genetics to address some new concerns about the emerging use of GE for eradicating invasive rodents. First, we investigate how differences in engineered mouse survival rates can change the success and long-term dynamics of GE-driven eradication. In most situations, GE organisms would be expected to have a lower survival rate than their wild counterparts. This is because engineered genes tend to impose a fitness cost on individuals that carry them (Catteruccia et al., 2003; Marrelli

et al., 2006) and because the *t-Sry* construct would be engineered in lab mice that would not be adapted to surviving in island ecosystems (Miller et al., 2000). Some of these costs could be reduced by backcrossing laboratory-derived *t-Sry* mice with wild-derived varieties. However, *t-Sry* mice would likely lack some of the learned social and ecological behaviors that would be necessary to survive in a new environment. Thus, the *t-Sry* construct would most likely be lost from a population over time if it is not sustained by repeated releases of *t-Sry* mice, a quality referred to as self-limitation (Gould, 2008; Alphey, 2014).

Alternatively, we also consider the theoretical possibility that the *t-Sry* construct could be self-sustaining, in the sense that the GE construct would remain in the population without additional releases. There are a wide variety of wild *M. musculus* populations throughout the world, each with unique genetic traits (Miller et al., 2000; Chalfin et al., 2014), including differences in lifespan, maturation rates (Miller et al., 2000), and competitive ability (Cunningham et al., 2013). Additionally, some *M. musculus* populations could be theoretically less susceptible to climate stress, predators, or pathogens. A *t-Sry* mouse that is backcrossed to carry these beneficial traits could theoretically be more fit than other wild *M. musculus* populations. In such a situation, it might be possible to eradicate a population with only a single pulsed release of *t-Sry* mice. An unintentional escape of a mouse carrying a self-sustaining suppressive gene drive construct into a non-target population could cause widespread suppression and extinction, even to the ancestral *M. musculus* population (Esvelt et al., 2014). This emphasizes the need to understand how the fitness of a GE mouse can affect the persistence of an engineered gene in wild populations.

While direct population suppression from a GE construct would be species-specific (if no closely related rodent species are present), releasing *t-Sry* mice could disrupt the island ecosystem in other ways. *M. musculus* have an adaptive diet that has allowed them to exploit island ecosystems by preying on endemic plants, invertebrates, reptiles, and even seabird chicks (Angel et al., 2009). Invasive species can also attract and support populations of non-native predators

that would otherwise prey on rarer endemic species (Roemer et al., 2002; Howald et al., 2007). Eradication with the *t-Sry* construct would require adding more house mice into the ecosystem where wild house mice are already invasive, further intensifying these antagonistic interactions. Moreover, the number of GE mice that would need to be released to suppress a population could be considerable. The magnitude of these transient impacts would likely vary depending on the survival of *t-Sry* mice and their rate of release into the population.

Even though the increase in mouse population density would only be temporary during the beginning of the eradication process, its resulting effects on the ecosystem could be permanent (David et al., 2013; Esvelt et al., 2014), especially if the temporary increase in mouse density results in the extinction of a rare species. Namely, short-term impacts can have long-term ramifications. Despite this, while some have explored the ecological impacts of similar GE-driven population suppression techniques (Scott et al., 2002; Gould, 2008; Bonsall et al., 2010; Esvelt et al., 2014), few have considered the transient ecological impacts of forcing a population above natural levels (David et al., 2013). This is possibly because previous work has primarily focused on mosquitoes, which are usually thought to have a reasonably small role in their ecosystems (Godfray, 2013). Comparatively, invasive rodents can be very disruptive to non-native ecosystems (Howald et al., 2007), bringing into question what damage they could cause at greater than usual densities. Therefore, understanding how the relative survival and release rate of GE mice affect the population dynamics of a GE-assisted mouse eradication could help to limit temporary impacts on the ecosystem.

In this chapter, we address these issues by using a mathematical model to explore the dynamics and ecological impacts of eradicating a population of invasive mice with genetically engineered *t-Sry* mice. First, we identify the conditions under which this technique can successfully eradicate a population. In doing so, we consider the effects of survival on the long-term dynamics of *t-Sry* mice. This helps to determine the situations in which the construct is self-limiting or self-sustaining. Also, we create and analyze several metrics to quantify the temporary

negative ecological impacts that would ensue from the release of *t-Sry* mice. We compare these metrics over a number of different release strategies, varying the mortality and release rates of the *t-Sry* construct.

2.2 Methods

2.2.1 Model

Our model occurs over continuous time and continuous state space with overlapping generations. It is also density dependent with polygamous random mating, no migration, and no mutation. This model consists of a mouse population separated into four distinct groups based on whether or not individuals carry a Y chromosome and whether or not they carry the *t-Sry* construct. The state variables are the population densities of XX wild-type mice, $W_X(t)$; XY wild-type mice, $W_Y(t)$; XX *t-Sry* mice, $G_X(t)$; and XY *t-Sry* mice, $G_Y(t)$. The sum of all of these groups is the total population density, defined as $N(t) = W_X(t) + W_Y(t) + G_X(t) + G_Y(t)$. Because the *t-Sry* construct contains an *Sry* gene, which is partially responsible for male development in mice, the terms "male" and "female" could be somewhat ambiguous. Throughout the rest of this chapter, we use male to refer to mice that carry at least one functional copy of the *Sry* construct in some form (W_Y, G_X, and G_Y) and "female" to refer to mice that contain no copies of the *Sry* gene (W_X).

Without any genetically engineered mice, the population dynamics of this model should reflect a simplified natural mouse population. Therefore, this model is a standard logistic growth model (Verhulst, 1838) when it contains only wild-type mice. Several studies demonstrate that mouse birth rates decrease with greater population densities (Vandenbergh, 1987; Nathan et al., 2015). Specifically, when a large number of female mice are in close proximity, they will go into estrus less often (Vandenbergh, 1987). Thus, $a_1 > 0$ is the baseline per capita birth rate of females (or males) and $a_2 > 0$ is the rate at which this per capita birth rate declines with

increasing female density. Additionally, the per capita death rate should increase as the total population density increases because of overcrowding and resource limitation. Then $b_1 > 0$ is the baseline per capita death rate and $b_2 > 0$ is the rate at which the per capita death rate increases with increasing density. At an equal sex ratio, the equivalent logistic growth parameters are the growth rate $r = a_1 + b_1$ and the carrying capacity $K = 2\left(\frac{a_1 - b_1}{a_2 + 2b_2}\right)$ (Appendix A).

Adding *t-Sry* mice into the model requires further manipulations from basic two-sex logistic growth (Figure 2.1).

1. The genotype of any newborn mouse depends on the parental genotypes. All mice are born from a wild-type mother. However, both wild-type and *t-Sry* XY mice could be potential fathers. To focus on other dynamics, we do not consider mating preference in this model. With this simplification, the frequency of newborn mice with wild-type fathers is equal to the proportion of fertile male mice that are wild-type, $\frac{W_Y}{W_Y + G_Y}$. Similarly, the frequency of *t-Sry* fathers is $\frac{G_Y}{W_Y + G_Y}$. Hereafter, the frequency of *t-Sry* mice in the reproductive male population is defined as $\phi(t) = \frac{G_Y(t)}{W_Y(t) + G_Y(t)}$.

2. The XX *t-Sry* mouse is sterile and does not directly contribute to future births.

3. When the father carries the *t-Sry* construct, a biased proportion $0.5 \leq \tau \leq 1$ of offspring also inherit the construct. The other $1 - \tau$ inherit the wild-type counterpart allele.

4. The fitness of *t-Sry* mice is likely to be different from the wild-type mice of the island. This fitness difference could manifest in many ways (such as modifying the birth rate or chance of mating), but, for simplicity, we only alter the death rate of GE mice. Additionally, resource competition between wild and *t-Sry* mice could be modeled more explicitly (Russell et al., 2014), but we simplify these dynamics by assuming that each genotype's competitive ability is incorporated in its relative death rate. The change in the death rate of *t-Sry* mice is represented as c. Most likely, this would occur as an increase in the death

rate ($c > 0$). If *t-Sry* mice could be backcrossed with a highly competitive wild mouse, we are also interested in exploring the possibility of *t-Sry* mice with neutral ($c = 0$) or increased survival ($c < 0$).

5. New *t-Sry* XY mice are continuously added into the population at a rate of $\mu \geq 0$ per month.

If there is initially an equal sex ratio of wild-type mice, the model can be simplified into three equations. With some algebra (Appendix A), the final model is

$$\frac{dN}{dt} = 2\left((a_1 - a_2 W_X)W_X - (b_1 + b_2 N)\left(W_X + (c+1)\left(\frac{N}{2} - W_X\right)\right)\right) + \mu \tag{2.1}$$

$$\frac{dW_X}{dt} = ((a_1 - a_2 W_X)(1 - \tau\phi) - (b_1 + b_2 N))W_X \tag{2.2}$$

$$\frac{d\phi}{dt} = -((1-\tau)(a_1 - a_2 W_X) + c(b_1 + b_2 N))(1-\phi)\phi + \mu\frac{(1-\phi)^2}{W_X} \tag{2.3}$$

2.2.2 Analysis

Using this model, we determine both the long-run dynamics and transient impacts of releasing *t-Sry* mice into wild population. All analyses and simulations are conducted in Maple 18 and MATLAB 2015b, with a simple theoretical sample island beginning with a stable population at carrying capacity. Natural demographic parameters (Table 2.1) for wild-type mice (a_1, a_2, b_1, and b_2) are loosely derived from Nathan et al. (2015) where they were estimated for an experimental house mouse invasion, though we adjusted the density-dependent terms so the island would have a carrying capacity of $K = 1000$. Though the transmission distortion from the *t*-haplotype could take a wide range of values, reasonable manipulations this variable did not reveal any unique qualitative behavior. Therefore, we do not focus on this parameter within the context of this paper. This analysis uses a constant higher transmission distortion $\tau = 0.95$, roughly based on current lab studies (D. Threadgill and D. Kanavy, personal communication)

(Table 2.1). Instead, model analysis focuses on manipulating the mortality and release rate of *t-Sry* mice. These parameters aspects that can be more easily influenced by human control. Additionally, both mortality and release rate have a large effect on the qualitative behavior. Therefore, the model is analyzed over a wide range of *t-Sry* mouse death rates (c) and release rates (μ) (Table 2.1).

In the transient analysis, the minimum release rate needed for eradication, μ^*, is numerically solved for each set of parameter values. Eradication is then simulated with applicable release rates of *t-Sry* mice into a wild-type population at carrying capacity. These simulations continue until females are considered eradicated. Because the wild-type mice can only approach complete eradication but not actually reach it with this model, we consider wild-type mice to be eradicated when their density is below a small threshold ($W_X < 0.05$).

For each simulation, a variety of metrics are calculated (Figure 2.2.a). The first metric, t_{erad} is the time from the beginning of *t-Sry* release to the time that females are considered eradicated. Second, the total density of *t-Sry* mice that need to be released to complete eradication is calculated as μt_{erad}. Third, the maximum density of the population throughout a successful eradication is determined. Last, we create another metric, referred to as population excess, that combines both the time and magnitude of increasing the population density above its carrying capacity into a single quantity. For this, t_0 is the time that the first *t-Sry* mice are released and t_K is last time that the population is above carrying capacity. The population excess is then defined as $\int_{t_0}^{t_K} (N(t) - K)\, dt$ and is calculated with the trapezoidal method function in MATLAB (trapz).

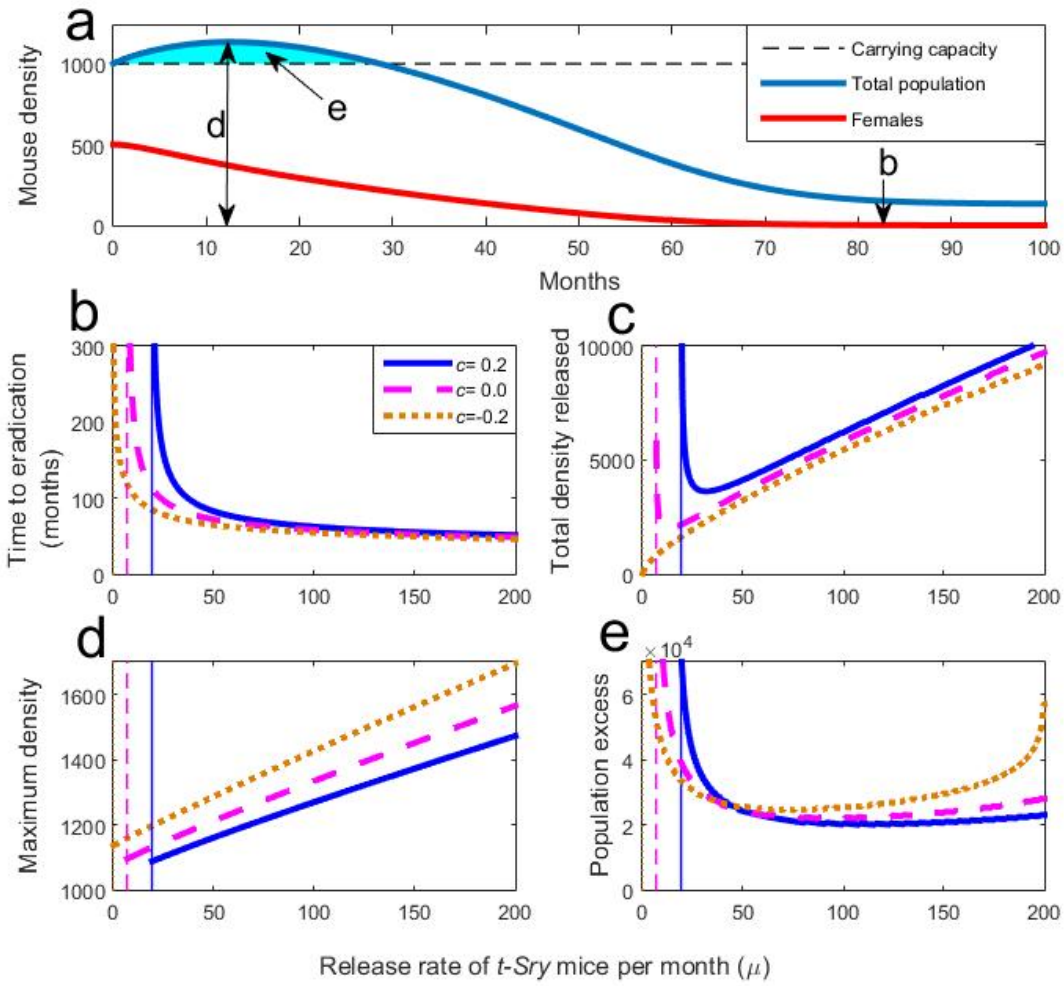

Figure 2.2 The efficiency and ecological impact of an eradication depend on both the change in death rate, c, and the release rate, μ, of *t-Sry* mice. Parameter values for these figures can be found in Table 2.1. (a) An example eradication via *t-Sry* mouse release illustrates the time to eradication, the maximum density, and the population excess. (b) The time to eradication decreases when the release rate increases and when *t-Sry* mice have greater mortality. (c) The total number of mice necessary to release before eradication is minimized for intermediate release rates. As *t-Sry* mouse mortality increases, so does the number of mice that need to be released. (d) The maximum density of mice increases as the release rate of *t-Sry* mice increases and decreases when *t-Sry* mortality increases. (e) Population excess is minimized for intermediate release rates. The dashed lines in (b-e) represent the critical release rate μ^*, below which eradication is impossible, and are colored to match their respective values of c

Table 2.1 Descriptions of all state variables and parameters used in the model

Parameter	Description	Values
a_1	Baseline per-capita birth rate	0.7 month^{-1}
a_2	Density dependence on birth rate	$9 \cdot 10^{-4}$ (mice/unit area)$^{-1}\cdot$ month^{-1}
b_1	Baseline per-capita death rate	0.2 month^{-1}
b_2	Density dependence on death rate	$5 \cdot 10^{-5}$ (mice/unit area)$^{-1}\cdot$ month^{-1}
c	Change in death rate of *t-Sry* mice	-0.2 to 0.2
τ	Transmission distortion of t-haplotype	0.95
μ	Release rate of fertile *t-Sry* mice	0 to 200 (mice/unit area)$^{-1}$

2.3 Results

2.3.1 Long-term dynamics

The long-run outcomes (stable equilibria) of the model demonstrate the conditions in which releasing *t-Sry* mouse can eradicate a mouse population. The number of long-run outcomes depend on the change in death rate, c, and the release rate, μ, of *t-Sry* mice. While all of these equilibria can be solved analytically, the formulae for most are complicated and do not provide much insight. Therefore, we present written and graphical descriptions.

When *t-Sry* mice are present, there can be either one or two potential long-run outcomes. If there are two stable equilibria, the model is bistable and the long-run outcome depends on initial conditions. One outcome, eradication, occurs when there are no female mice in the population and all males are *t-Sry* mice. Some mice would remain in the population, but because there are no females, the population would only be sustained from the continuous release rate of *t-Sry* mice, $\mu > 0$. Upon reaching this point, a population manager would stop releasing mice and the population would be completely eradicated after the remaining mice naturally die. This is a stable outcome for nearly all parameter values, with a few exceptions we describe later. Another outcome consists of a stable resident population of *t-Sry* mice coexisting with the

wild-type population.

Overall, eradication is always successful when *t-Sry* are released above a critical release rate μ^*, and eradication fails (approaching the coexistence outcome) when the release rate is below μ^*. In general, the value of μ^* is greater when *t-Sry* mice have a greater death rate. We describe three distinct types of long-run behavior in order of increasing values of c.

First, if *t-Sry* mice have a much lower death rate than wild-type mice, any release of *t-Sry* mice would lead to eradication (Figure 2.3.a). Specifically, there is a critical value for the change in mortality $c_1^* < 0$ below which the *t-Sry* construct is self-sustaining and it approaches fixation over time. Thus, if $c < c_1^*$, then $\mu^* = 0$ and any positive release rate results in eradication. With a single small pulsed release of *t-Sry* mice, the construct would spread through the population, leading to complete eradication even if no more *t-Sry* are released after the initial release pulse (Figure 2.4.a-b).

Next, there is another critical value for the change in mortality c_2^* (where $c_1^* \leq c_2^* \leq 0$). When c is between c_1^* and c_2^* a low release rate of *t-Sry* mice cannot eradicate a wild-type population that is initially at carrying capacity. In this case, $\mu^* > 0$ and when the release rate is below μ^*, the model is bistable. Under these conditions, an eradication attempt would result in a stable coexistence of both wild-type and *t-Sry* mice. With a larger release rate $\mu > \mu^*$, the wild-type population would be eradicated (Figure 2.3.b). However, as long as the change in death rate is between c_1^* and c_2^*, the *t-Sry* construct is still self-sustaining. Thus, if a population manager were to stop releasing mice after a small initial release, the *t-Sry* mice would remain in the population indefinitely, though the GE construct would not eradicate the wild-type population.

When the change in *t-Sry* mouse death rate is increased above c_2^*, the *t-Sry* construct is self-limiting. This contrasts with the previous case because the gene construct would eventually be lost from the population if it is not sustained by repeated releases. The self-limiting case is most likely to be realized as it occurs when *t-Sry* mice have a greater death rate or even a slightly smaller death rate than wild mice. Similar to the previous case, a smaller release $\mu < \mu^*$

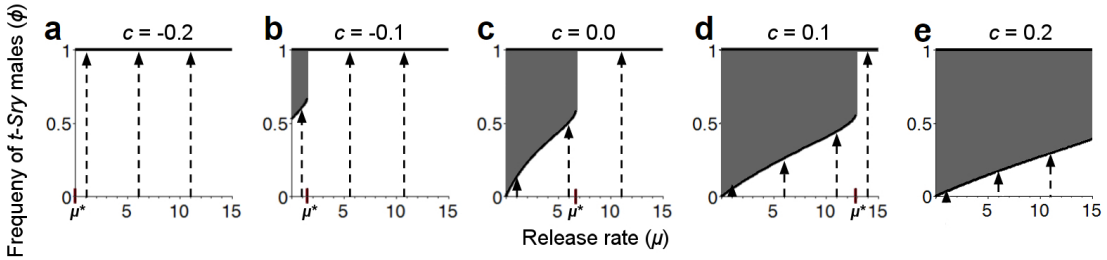

Figure 2.3 Simplified equilibrium diagrams in ϕ (frequency of *t-Sry* males) over μ (release rate of *t-Sry* mice) with different values of c (survival cost to *t-Sry* mice). Thick solid lines represent stable, attracting equilibria. In this example $c_1^* = -0.18$ and $c_2^* = -0.06$. An eradication attempt with a constant release rate μ would begin at the bottom of these diagrams (where $\phi = 0$). The population would change over time, following the dashed lines, by moving upward on this diagram until it reaches the first solid line stable equilibrium. It would remain there unless the release rate is changed. In (a), $c < c_1^*$ and the population would be eradicated in the long-run for any release rate. In (b), $c_1^* < c < c_2^*$, so the population would approach the coexistence state when $\mu < \mu^*$. Since the *t-Sry* construct is self-sustaining in this case, stopping release ($\mu = 0$) after some GE mice are in the population would result in the *t-Sry* mice remaining in the population indefinitely. The population would be eradicated if $\mu > \mu^{**}$. Each of (c), (d), and (e) represent cases where $c > c_2^*$. The population would approach coexistence state when $\mu < \mu^*$. The *t-Sry* construct would be lost from the population if *t-Sry* release was later stopped. When $\mu > \mu^*$, the population would be eradicated. Because $\mu^* = 19.2$ when $c = 0.2$, it is not shown in (e).

would not result in eradication, and it could even lead to an increase in the total population density as long as release continues (Figure 2.4.c-d). To reach eradication, one would need to release *t-Sry* mice at a high rate of $\mu > \mu^*$ (Figure 2.4.e-f). The value of μ^* increases as the death rate of *t-Sry* mice increases (Figure 2.3.c-e).

2.3.2 Transient analysis

The amount of time needed for a successful eradication decreases with greater release rates (Figure 2.2.b). Eradication time is most sensitive to changes in the release rate when the release rate is only slightly above the critical value μ^*. For larger release rates, increasing the release rate further still decreases the time to eradication, but with diminishing effect. These trends hold regardless of the death rate of the *t-Sry* mouse. However, releasing *t-Sry* mice with reduced death rates should eradicate a population more quickly than releasing *t-Sry* mice with an increased death rate. Thus, the quickest eradication would occur with highly competitive GE mice released at a high rate.

Changing the release rate can have varying effects on the total number of *t-Sry* mice that are necessary to release (Figure 2.2.c). Overall, an intermediate release rate above μ^* would minimize the number of mice that need to be released (except when $c < c_1^*$, where a single *t-Sry* mouse could theoretically lead to eradication). Additionally, the number of *t-Sry* mice needed for eradication is greater when *t-Sry* mice have increased mortality and less when they have decreased mortality.

The maximum population density increases almost linearly as the release rate increases (Figure 2.2.d). This near-linear relationship occurs regardless of the death rate of *t-Sry* mice. However, the maximum population density is greater when engineered mice have a lower mortality and less when they higher mortality. Therefore, the maximum density is minimized when *t-Sry* mice have increased death rates and are released into a population slowly.

Changing the release rate also has varying effects on the population excess. Overall, inter-

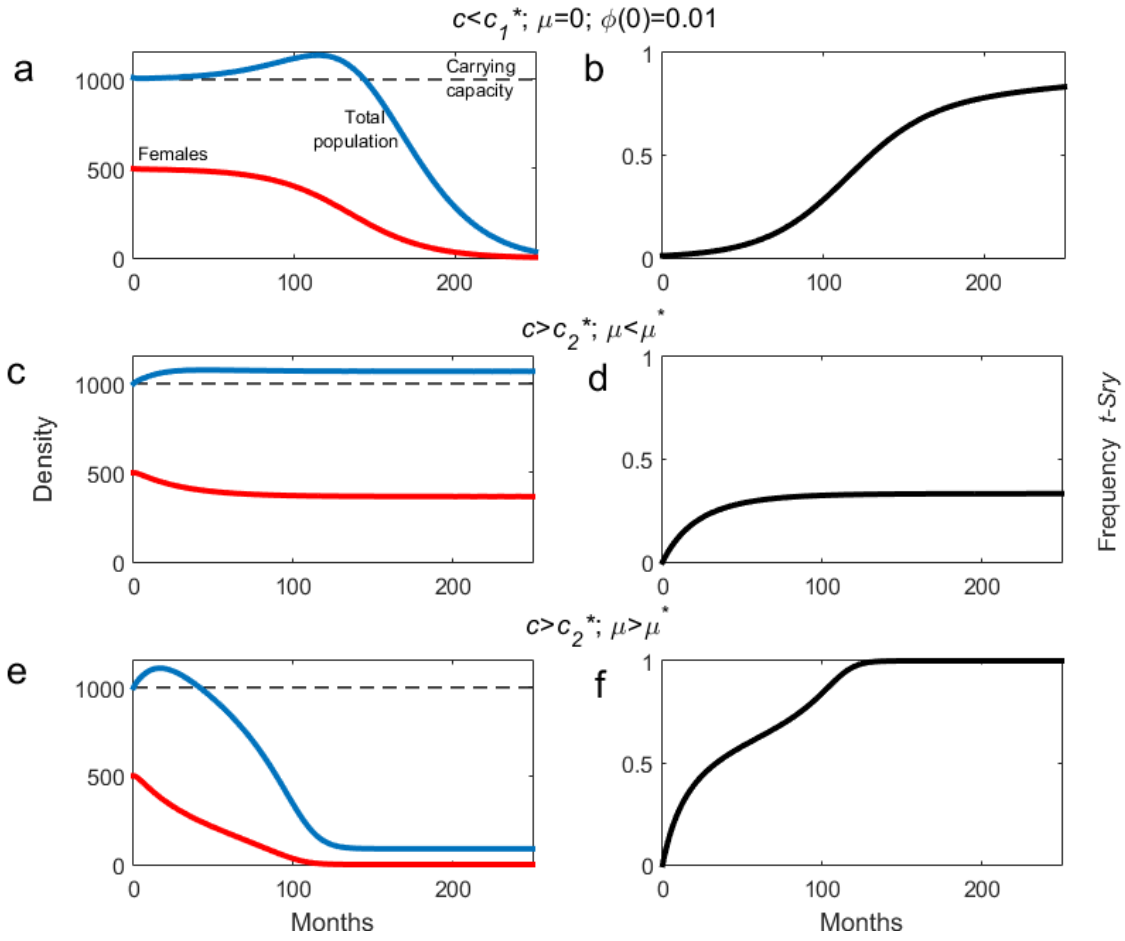

Figure 2.4 The success of three potential eradication attempts depends on the change in death rate, c, and the release rate, μ, of *t-Sry* mice. (a-b) A *t-Sry* mouse with a largely reduced death rate, $c = -0.2 < c_1^*$, can cause the population to be eventually eradicated with a single pulsed release. (c-d) With increased mortality $c = 0.1 > c_2^*$ and a low release rate of $\mu = 8$ mice per month, the population maintains a small stable frequency of *t-Sry* mice and lowers the number of female mice, but does not eradicate the population. (e-f) An increased death rate $c = 0.1 > c_2^*$ and a high release rate of $\mu = 20 > \mu^*$ mice per month increases the frequency of *t-Sry* males until $\phi = 1$ and decreases the number of wild-type females until they are no longer present ($W_X \equiv 0$). This leads to eventual eradication.

mediate values for the release rate minimize the population excess of *t-Sry* mice (Figure 2.2.e). The change in mortality has a different effect depending on the release rate of *t-Sry* mice. In particular, when *t-Sry* mice have a greater death rate, lower release rates will have high population excess. Because of the *t-Sry* mices reduced survival, the population must be forced above the carrying capacity (via continuous release of *t-Sry* mice) for a longer amount of time before the population density begins to decrease. However, this lower survival also decreases the population excess at higher release rates. Since the population reaches a sufficient number of *t-Sry* mice more rapidly, the excess mice will die off below the carrying capacity quickly.

2.4 Discussion

The use of gene drives for population suppression is not new (Burt, 2003; Deredec et al., 2008; Alphey, 2014), but we have presented and analyzed one of the first models that considers this technology specifically for a mammalian species. We have shown in theory that genetically engineered *t-Sry* mice can eradicate entire invasive populations of *Mus musculus*. In this model, when *t-Sry* mice are released into a population, they interbreed with wild island mice and produce mostly *t-Sry* offspring. Initially the population density increases as *t-Sry* are added. Over enough time, there would theoretically be no females left in the population because very few fertile female offspring are sired from increasingly common *t-Sry* fathers. Because the *t-Sry* construct would likely impose a survival cost and because transmission distortion will not be 100%, the gene construct would have a selective disadvantage and probably be lost from the population if *t-Sry* mice are not repeatedly released. In these situations, the *t-Sry* construct is self-limiting and *t-Sry* mice can only eradicate a population if they are released above a critical release rate. In some situations this critical release rate might be considerable, but it can be reduced by increasing the survival of *t-Sry* mice or by increasing the transmission distortion of the *t*-haplotype. If the survival of *t-Sry* mice could be greatly improved by backcrossing

them with highly competitive wild strains, however, the *t-Sry* construct could theoretically be self-sustaining. In these cases, the *t-Sry* construct could spread on its own and eradicate the population without sustained releases.

While these general qualitative trends are similar to previous models of sex-biasing gene drives in insects (most notably autosomal X-shredders, as in Deredec et al. (2008)), invasive rodents present a new and important set of ecological characteristics that must be considered as this technology develops. Because mice disrupt the ecosystems where they invade (Howald et al., 2007; Angel et al., 2009), it is worthwhile to determine release strategies that could reduce the additional ecological stress that comes from adding more GE mice to an island. We found that there is no optimal strategy for releasing *t-Sry* mice that would minimize all potential ecological impacts. High release rates of *t-Sry* mice with greater survival can eradicate a population of invasive mice relatively quickly, but also result in a large increase in the density of an ecologically disruptive population. A lower release rate and higher mortality of *t-Sry* mice, on the other hand, can reduce the maximum population density of mice throughout the eradication, though eradication might then take several additional years to complete. Thus, there is a trade-off between the duration and intensity of the transient ecological impacts of GE-assisted mouse eradication. Consequently, there is no "one size fits all" release strategy that applies to every island. Whether GE-assisted eradication should be faster or less disruptive would depend on the ecological sensitivities of threatened species in an islands ecological community.

We demonstrate how differences in the fitness of the GE mice, through modifying their death rate, could theoretically lead to striking differences in the ability of the *t-Sry* construct to spread and to be controlled. The dynamical consequences of *t-Sry* mice with substantially increased survival are particularly notable. Though this case is less likely to be realized outside of theory (at least initially), the potential for increased survival through backcrossing makes this a worthwhile consideration. With enough of a survival advantage, we have shown that the *t-Sry* construct could theoretically be self-sustaining. Without the need for repeated releases, a self-

sustaining *t-Sry* could eradicate a population more cheaply and quickly. Though this increased efficiency might seem appealing, this increased persistence would make eradication much more difficult to control. Worryingly, if a highly fit *t-Sry* mouse escapes from the target island, or even a breeding facility, the escaped GE mouse might be able to cause widespread suppression and extinction of non-target *M. musculus* populations. This presents a significant ecological, regulatory, and social risk to non-target areas (Esvelt et al., 2014). If such a *t-Sry* mouse were released, it would be necessary to contemplate measures to make a self-sustaining *t-Sry* construct more controllable. For example, carefully designed physical, molecular, and ecological barriers could limit spread of a gene construct to avoid accidental releases during development and production (Esvelt et al., 2014; Akbari et al., 2015). Also, currently established biosecurity measures to prevent rodent reinvasions after eradication (Russell et al., 2008; Harris et al., 2012) could be adapted to prevent *t-Sry* escape during an eradication. Additionally, a separate "reversal" gene drive could be engineered alongside the *t-Sry* construct to be released in case of an unintentional spreading event (Esvelt et al., 2014). Mice carrying this reversal drive would need to breed into the population to overwrite and nullify the suppressive effects of the *t-Sry* construct before eradication (Esvelt et al., 2014). In the more likely case where *t-Sry* mice have increased mortality, the *t-Sry* construct would be self-limiting. Without the ability to spread indefinitely on its own, a self-limiting construct would present far fewer risks. In short, a self-limiting construct is inherently reversible and therefore more easily controlled.

In this analysis, we focused on the dynamics that ensue when GE mice are released at a steady continuous rate into a population of entirely wild-type mice. Under most scenarios (specifically, when $c > c_1^*$, or when GE mice do not live substantially longer than wild-type mice), both eradication and coexistence of GE and wild-type mice are possible, though the eventual outcome will depend on the initial conditions. This bistability suggests the following possibility. Any successful eradication effort must begin with a release rate that exceeds the critical release rate, μ^*. However, as the proportion of fertile GE males grows, the release rate

of GE mice can eventually be reduced without jeopardizing the success of the eradication, as long as the dynamics stay within the basin of attraction of the eradication equilibrium. In other words, it is not absolutely necessary to maintain the initial high release rate throughout the eradication effort for the eradication to succeed. In practical terms, however, reducing the release rate without jeopardizing the eradication requires a confident knowledge of the exact location of the boundary that separates the basin of attraction for the eradication equilibrium from the basin of attraction for the coexistence equilibrium. We have not mapped that boundary here because it will depend sensitively on biological details that are specific to a particular eradication scenario. However, our simplified model at least suggests that a more flexible release schedule is possible. The flexibility to modify the release rate as the eradication unfolds contrasts with rodenticide-driven eradications, which tend to have rigid deployment schedules (Howald et al., 2007, 2010).

This model is based on the assumption that an undisturbed invasive mouse population would remain constant over time. However, many mouse population densities often increase throughout a breeding season, followed by declines once breeding subsides (Ferreira et al., 2006). Rodenticide-driven eradications can capitalize on these population cycles (Howald et al., 2007, 2010; Russell et al., 2011), as fewer individuals need to be eradicated when rodents are naturally less abundant. Sterility-based biological control methods in other rodents have also been shown to benefit from optimal timing throughout natural population cycles (Shi et al., 2002). Population cycles will likely influence the optimal timing of GE-assisted eradications as well. For example, releasing *t-Sry* into a population during the lowest point of an annual cycle would likely result in a greater proportion of *t-Sry* mice than if they were released at other times. Additionally, these GE male mice would be exposed to less competitive interference during lower points, making them less likely to die before mating. Optimal timing of GE mouse release could reduce the total eradication time while also decreasing the impact on the rest of ecosystem.

The release of GE mice could also be combined with other control methods in an integrated eradication strategy. There is precedent to this, as disease-driven biological control has successfully been combined with toxicants to eradicate other vertebrate species from islands (Parkes et al., 2014; Springer, 2016). An integrated approach with GE might begin by spreading rodenticide bait onto an island to reduce the population density without the intention of full eradication. Usually, rodenticide needs to be applied heavily over a wide area to ensure that bait is available to the full distribution rodents for enough time (Pott et al., 2015). However, because rodenticide would not need to guarantee 100% efficacy, fewer mice and non-target organisms would need to be killed than in a pure rodenticide eradication. Following rodenticide, *t-Sry* mice could be released onto the island in areas where the population is still extant to gradually eradicate the remaining population. Starting the release of *t-Sry* mice at a lower population density, the eradication would have a shorter duration and lower levels of population excess than a pure GE approach. Overall, both rodenticide and GE mice could reduce the negative impacts of the other. Despite the advantages of an integrated approach, its main barriers are likely to be regulatory. Rodenticide eradications are subject to strict regulation (Eason et al., 2010; Campbell et al., 2015), often requiring several years of planning to navigate (Howald et al., 2010). Bringing the release of GE animals into this framework would introduce additional complex regulatory standards into the process (Campbell et al., 2015). Also, this integrated approach would require some poisoning and killing of mice, partially negating the major animal welfare motivations behind developing *t-Sry* in the first place. A more detailed analysis into this integrated approach could provide more insight into whether this would be economically and ecologically viable.

We focused on the *t-Sry* mouse in this chapter because it is currently in development. However, our model can also inform rodent eradications with other gene drive systems. Among the alternative gene drives, CRISPR/Cas9 is one of the most promising (Jinek et al., 2012; Esvelt et al., 2014; Gantz and Bier, 2015). Unlike the *t*-haplotype, CRISPR would be applicable

to more invasive rodents than just *M. musculus* (Esvelt et al., 2014; Campbell et al., 2015), likely including the rat species *Rattus rattus*, *R. norvegicus*, and *R. exulans*. CRISPR and other engineered gene drives can also have greater transmission rates, increasing their ability to spread. Applying this to our model, we would expect these gene drives to reduce both the critical release rate and potential temporary ecosystem impacts. Additionally, compared to other gene drives, CRISPR can be fairly precise and manipulable despite being a relatively small gene construct (Jinek et al., 2012). This specificity and smaller size can decrease the survival cost that would normally be imposed on GE organisms, again increasing the ability of a construct to spread into a population. Both increased transmission distortion and lower fitness costs would even make it easier for these engineered gene drives to be self-sustaining.

Overall, gene drive assisted rodent eradication methods provide a targeted, non-lethal alternative to toxicants. With our model, we have addressed some basic ecological questions concerning the ability of GE construct to spread, while also demonstrating a tradeoff in the potential impacts on the ecosystem. Before this technology could be considered a viable alternative to rodenticides, future ecological studies will need to further explore the seasonality of mouse population dynamics, the spatial dynamics of release and the subsequent spread of gene constructs, and the trophic community dynamics on each particular targeted island. Additionally, while the spread of a GE construct to other rodent species is unlikely in the timeframe of eradication (through hybridization or horizontal gene transfer (Snow et al., 2005)), the consequences of such an event could be severe enough to lead to the extinction of a non-target species, warranting further research and investigation. Moreover, pathogens are more likely than genes to cross species boundaries. Because introducing lab-bred rodents to an island could unintentionally spread new pathogens to naïve endemic species, future research in this area would be critical.

These ecological questions exist alongside a set of new and complex genetic, evolutionary, behavioral, social, and regulatory ideas that come from engineering and releasing GE rodents

for eradication. Even if complications or setbacks in any of these research areas could limit the future of the t-Sry mouse or any other suppression gene drive rodent, the intersection of synthetic biology and conservation is only in its infancy and could have countless applications moving forward (Redford et al., 2013; Esvelt et al., 2014; Johnson et al., 2016; NAS, 2016). Therefore, our analysis of the temporary and long-term ecological impacts of *t-Sry* driven mouse eradication should help contribute and inform the ongoing evaluation of these issues.

Chapter 3

Resistance and persistence of a suppressing gene drive as a result of preferential mating

Abstract

Gene drives are genetic constructs that are inherited by offspring above the standard 50% ratio. There have been several recent proposals to use these gene drives as a species-specific tool for eradicating populations of invasive species. In one of these proposals, house mice (*Mus musculus*) would be engineered to carry a gene drive that would alter offspring sex ratio. If these mice are released into an invasive population, that population could be suppressed gradually until no females remain. Unfortunately, if enough wild females choose not to mate with males that carry the gene drive, eradication efforts might be resisted. On the other hand, females might preferentially mate with newly introduced gene drive males to increase the genetic variation in the population, accelerating the spread of the gene drive. To explore these ideas further, we constructed a population model of gene drive eradication where females can preferentially mate with either wild males or gene drive males. Also, mate choice is heritable in this model, allowing it to evolve over the course of an eradication attempt. We find that preferential mating that favors wild-type males becomes more frequent in response to gene drive mice that are added to the population. While this mate preference would reduce gene drive spread, it could be countered through higher release rates of the gene drive, which could force the population to eradication before preferential mating has the opportunity to evolve. Alternatively, preferential mating that favors gene drive males might allow a gene drive to persist in a population even when that gene drive imposes a survival cost. Thus, preferential mating could unexpectedly cause the long-term persistence of a gene drive or even result in eradication. This could cause considerable risk if the gene drive escaped to a non-target population.

3.1 Introduction

There has been a recent surge of interest in the potential to manipulate the genetic composition of wild populations for the benefit of conservation and pest control (Esvelt et al., 2014). Particularly, undesired populations could be suppressed gradually if individuals from that population are genetically engineered to have a reduced frequency of female offspring (Deredec et al., 2008). Unfortunately, it could take considerable effort to spread an engineered gene through a population, as engineered genes almost certainly impose a fitness cost on the organisms that carry them (Catteruccia et al., 2003). To overcome this fitness cost, a sex-altering gene could be combined with a selfish genetic element that is inherited above the standard Mendelian rate of 50% (Craig et al., 1960; Esvelt et al., 2014). Any genes that are linked to the selfish element should also be inherited by a majority of offspring. Together these genes create a "gene drive", which can spread through a population even at a cost to the organism (Burt, 2003; Unckless et al., 2015). Gene drives are not new (Craig et al., 1960; Burt, 2003), but recent developments have increased the accessibility of this technology. The discovery of the CRISPR/Cas9 system has been particularly consequential because, moreso than earlier counterparts, CRISPR/Cas9 is highly manipulable, precise, and applicable in a large number of species (Jinek et al., 2012; Gantz and Bier, 2015). Since this development, there has been accelerated interest in and concern over the possibility of directly manipulating the genomes of wild populations through the release of GE organisms (Burt, 2003; Esvelt et al., 2014; Oye et al., 2014; NAS, 2016).

Population suppressing gene drives were originally proposed to eliminate invertebrate pests like mosquitoes (Burt, 2003; Alphey, 2014). Since then, these ideas have been expanded to suppress invasive vertebrate populations (Thresher et al., 2014; Campbell et al., 2015; Johnson et al., 2016). Historically, invasive species have been controlled with heavy applications of chemical toxicants (Howald et al., 2007; Campbell et al., 2015) or through the release of natural predators, parasites, and pathogens (Messing and Wright, 2006). These approaches can be

expensive and have high potential for negative non-target impacts on other species (Campbell et al., 2015). Alternatively, a gene-drive-assisted eradication could provide a self-replicating, species-specific, non-lethal alternative to traditional methods. With such strong potential, the use of gene drives to eradicate wild populations presents its own risks. In some situations, a suppressing gene could be self-sustaining and spread to fixation on its own. This self-sustaining drive could cheaply and efficiently eradicate an undesired invasive population, but if this gene drive were to spread beyond the target population, it would have the potential to cause widespread eradication in other locations. In extreme cases, this could lead to the eradication of the invasive species' ancestral native population (Esvelt et al., 2014). To avoid this, conservation-focused gene drives would most likely be planned for release on islands or other isolated populations where biosecurity measures could limit the risk of escape (Campbell et al., 2015). Also, gene drives could specifically be designed with no intention of persisting in the wild. These weaker self-limiting gene drives would only eradicate a population through repeated releases of GE individuals over time (Alphey, 2014; Esvelt et al., 2014; Backus and Gross, 2016). Because of the reduced risks of accidental eradication, self-limitation would likely be a desired quality for any application in conservation biology.

The evolution of resistance is a major technical hurdle that could limit the practical application of releasing gene drives into wild populations. Evolution is expected to favor any traits that can help the population avoid the costs of gene drives (Burt, 2003; Esvelt et al., 2014; Bull, 2015; Lindholm et al., 2016). Depending on the type of gene drive and the species involved, resistance could take a variety of forms from the mutation of the gene drive itself to the natural selection of molecular mechanisms to that limit gene drive effectiveness (Alphey et al., 2011; Esvelt et al., 2014; Noble et al., 2016*b*). Importantly, nonrandom mating could theoretically lead to the behavioral resistance of gene drives in any species with some capacity for mate choice (Burt, 2003; Esvelt et al., 2014; Bull, 2015). If wild females are less likely to mate with males that carry gene drives, that gene drive would be less likely to spread to new offspring

and persist in the population. This form of preferential mating is not uncommon in the wild, as several species have adapted preferential mating behaviors that avoid the costs imposed by natural gene drives (Lenington et al., 1994; Johns et al., 2005; Manser et al., 2015). If this mating discrimination is genetically determined, evolution could favor this behavioral resistance and further limit the spread of the gene drive in the future. Though mating discrimination has been shown to limit the effectiveness of genetic pest management in several cases (McInnis et al., 1996; Itô and Yamamura, 2005; Jaenike et al., 2006), there has been surprisingly little effort to explain the dynamics of how behavioral resistance might evolve (Bull, 2017). This is especially important to consider as GE tools become more easily accessible across a wider variety of species with more complex mating systems.

While some concern has already been raised about the potential for mate choice to resist the spread of gene drives (Burt, 2003; Esvelt et al., 2014; Bull, 2015), there is a theoretical potential for nonrandom mating to instead act in favor of the individuals that carry gene drives. Because of the strong fitness costs associated with inbreeding (Charlesworth and Willis, 2009), wild animal populations are expected to avoid mating with close kin (Pusey and Wolf, 1996; Amos et al., 2001; Tregenza and Wedell, 2002; Lehmann et al., 2007). For example, female house mice have demonstrated pre-copulatory and post-copulatory mechanisms to avoid mating with closely related males (Yamazaki et al., 1976; Potts et al., 1991; Krackow and Matuschak, 1991; Firman and Simmons, 2008, 2015). Similarly, in some species, females have been shown to prefer mating with males that carry rare and novel phenotypes over males with more common phenotypes (Hughes et al., 1999; Singh and Sisodia, 2000; Kokko et al., 2007). It follows that preferential mating has the potential to favor novel introduced phenotypes, which would increase the rate that a suppressing gene drive spreads through a population. Though this preference would aid in eradication efforts, it could also increase the persistence of a gene drive that escapes from the target population. Especially if a gene drive was otherwise designed to be self-limiting, unexpected preferential mating in favor of GE males could be a major concern where there is

potential for the gene drive to spread to non-target populations.

In this chapter, we explore the possible consequences of nonrandom mating on gene-drive population suppression. If unexpected, wild female mating preference could have the potential to make gene drive eradication too difficult or too easy. Therefore, if gene drive eradication models do not account for female mate choice or the potential for it to evolve, some critical behavioral complications of eradication could be missing. Therefore, we construct and analyze a gene drive eradication model in which a genetically determined trait influences female mating preference between wild males and males that carry a suppressing gene drive. With this model, we describe possible long-term outcomes and behaviors with respect to the gene drive in a population where some females preferentially mate. Next, we explain the potential evolutionary interactions between a suppressing gene drive and preferential mating alleles. With these theoretical foundations, we simulate the release of gene drives into a population to determine how female mate choice can impact eradication efforts. Lastly, we simulate the population dynamics that follow a single pulsed release to explore how preferential mating can impact the persistence of a suppressing gene drive when it is not actively being released into a population.

3.2 Model

Our model is adapted from a continuous time, density-dependent population model of invasive house mouse (*Mus musculus*) eradication with a suppressing gene drive (Backus and Gross, 2016). The gene drive construct in this case is engineered to be carried on a male autosome. This construct consists of two genes that, when linked together in the genome of a male, cause nearly all of its offspring to develop phenotypically as male. Those that would normally develop as males would be unaffected while those that would normally be females would develop as sterile phenotypic males. The sex-ratio-altering gene is linked to a selfish genetic element that increases the rate of inheritance of the gene construct from a normal Mendelian frequency of

0.5 to an increased frequency of $\tau > 0.5$. Because this particular gene drive cannot be carried by a fertile female, no offspring will be born with two copies of the gene drive, so no individuals in this system will be homozygous for the gene drive. To suppress and eradicate a population, fertile males that carry the gene drive would be released to interbreed with the wild population. Over enough time, the density of females would be greatly reduced, eventually resulting in eradication (Backus and Gross, 2016).

To incorporate the evolution of female preference, we modify the previous model by assuming that female mate choice is somewhat genetically determined. Though mate choice would realistically be influenced by several genes, we simplify the model to consider only a single autosomal gene, independent of the gene drive locus, that influences female preference between mating with either wild-type or gene drive males. In this model, there are two possible alleles at this locus, preferential mating **C** and random mating **c**. While males also carry these alleles, both **C** and **c** are neutral to male behavior and fitness. Females that are homozygous for **c** do not have a preference between males and, therefore, choose to mate with males proportional to their frequencies in the population. Females that are homozygous for **C** do have mating preferences. In this case, preferential mating either increases or decreases the frequency of mating events between **CC** females and gene drive males relative to their proportions in the population. Depending on the dominance of **C**, heterozygous **Cc** females can have preference equal to or between either homozygous case.

Between sex chromosomes (XX and XY), presence of the gene drive construct, and female mate choice genotype ($\Gamma = \{\mathbf{CC}, \mathbf{Cc}, \mathbf{cc}\}$), there are 12 distinct genetic combinations that are represented in this model. However, we simplify our analysis by reducing the model to a subset of these combinations. If we assume that wild-type individuals initially exist at an equal sex ratio and that demographic rates (birth and death) are equivalent for both sexes, the equations governing the dynamics of both XX and XY wild-type individuals should be equivalent. Therefore, we describe the dynamics of both with the same equations. We represent

the density of wild-type females (or males) that carry preference genotype $k \in \Gamma$ with the state variable $W_k(t)$ and the density of fertile gene drive males that carry preference genotype $k \in \Gamma$ with the state variable $G_k(t)$ (Table 1). Since sterile XX gene drive males will not contribute their genes to future generations, their preference genotype is not directly relevant. However, these sterile males can contribute to density dependence, so we represent the total density of all sterile gene drive males with the state variable $S(t)$. Certain combinations of state variables are also useful for condensing notation. The total density of wild-type males (or females) is $W(t) = \sum_{j\in\Gamma} W_j(t)$, the total density of fertile gene drive males is $G(t) = \sum_{j\in\Gamma} G_j(t)$, and the total density of fertile males is $M(t) = W(t) + G(t)$. Overall, the total population density is $N(t) = 2W(t) + G(t) + S(t)$. The frequency of fertile gene drive males over the total number of fertile males is $\phi(t) = \frac{G(t)}{M(t)}$. The frequency of the preference genotype or allele k in the wild-type population is $\theta_{Wk}(t) = \frac{W_k(t)}{W(t)}$ and similarly for fertile gene drive males is $\theta_{Gk}(t) = \frac{G_k(t)}{G(t)}$.

When there are only wild-type individuals in the population, this model is constructed to resemble standard logistic growth (Verhulst, 1838). We define $a_1 > 0$ as the baseline per-capita birth rate of females (or males) and $a_2 > 0$ as the rate at which this per-capita birth rate declines with increasing density of females (Table 2). Additionally, the per capita death rate should increase as the total population density increases because of overcrowding and resource limitation. We define $b_1 > 0$ as the baseline per-capita death rate and $b_2 > 0$ as the rate at which the per-capita death rate increases with increasing population density. With a unique genetic background, the survival rate of gene drive individuals is likely different from the survival rate of wild-type individuals. This difference in survival is represented with the parameter c, modifying the death rate of individuals carrying the gene drive. The survival difference could (and most likely would) occur as a cost by increasing the death rate ($c > 0$). However, it could also occur as a survival advantage by decreasing the death rate ($c < 0$) or it could be neutral ($c = 0$). Because of the selfish-genetic element in the gene drive construct, a biased proportion $0.5 \leq \tau \leq 1$ of offspring should inherit the construct if the father is carrying it. The other $1 - \tau$

instead inherit the wild-type allele at that locus. Gene drive males carrying preference genotype $k \in \Gamma$ are continuously released into the population at a rate of $\mu_k \geq 0$ per month, with a total release rate of $\mu = \sum_{j \in \Gamma} \mu_j$ per month.

To represent female mate choice in this model, we separate the mating process into multiple functions. A female will likely have several opportunities to mate throughout her lifetime but this would need to occur within a limited window of mating receptiveness. During this window of receptiveness, a female must either choose a mate or fail to reproduce. For example, within a short time window, a preferentially mating (**CC**) female could encounter a male with which she does not prefer to mate. The female could either choose to mate with this male anyway or decline this opportunity to wait for a more preferred mate. This would continue until she either picks an acceptable mate or runs out of opportunities to mate (through death or ending her receptivity). Importantly, even though **cc** females have no preference between males, they need not mate with the first male they encounter. If there are many highly preferable males in a population, a high proportion of females should mate within their lifetime. On the other hand, if there are few males in a population (or the preferred type is rare), a low proportion of females should mate. To quantify this mate choice, we define two preference parameters $\gamma \geq 0$ and $\gamma_G \geq 0$. Overall, all females of any genotype will have base preference of γ for wild-type males. However, the preference of a female of genotype i for a gene drive male is

$$\gamma_{iG} = \begin{cases} \gamma_G, & \text{if } i = \text{CC} \\ h\gamma_G + (1-h)\gamma, & \text{if } i = \text{Cc} \\ \gamma, & \text{if } i = \text{cc} \end{cases}, \tag{3.1}$$

where $0 \leq h \leq 1$ is the dominance of the preferential mating allele. The proportion of females of genotype i that mate within their lifetime depends on the density of males in the population and the preference of females of genotype i for these males. This proportion η_i is based on a

cumulative distribution function of an exponential distribution over male density; that is

$$\eta_i = 1 - e^{-\rho(\gamma W + \gamma_{iG} G).} \tag{3.2}$$

where $\rho > 0$ is the mating receptivity of females. The male will also be important in determining the genotypes of the offspring that are born. Given that a female of genotype i does mate, the proportion of her offspring that come from a wild-type father is

$$\psi_i = \frac{\gamma W}{\gamma W + \gamma_{iG} G}, \tag{3.3}$$

while the proportion is $1 - \psi_i$ for a gene drive father. Lastly, each individual offspring resulting from a successful mating has mate choice genotypes that come from Mendelian combinations of the parents' genotypes. We define $g_{ij}(k)$ as the proportion of offspring that are preference genotype k for each mating between female of genotype i and male of genotype j (Figure C.1).

Altogether, each group changes in density over time with the differential equations

$$\frac{dW_k}{dt} = (a_1 - a_2 W)W \sum_{i \in \Gamma} \eta_i \theta_{Wi} \sum_{j \in \Gamma} g_{ij}(k) \left(\psi_i \theta_{Wj} + (1-\tau)(1-\psi_i)\theta_{Gj}\right) - (b_1 + b_2 N) W_k \tag{3.4}$$

$$\frac{dG_k}{dt} = (a_1 - a_2 W)W \sum_{i \in \Gamma} \eta_i \theta_{Wi} \sum_{j \in \Gamma} g_{ij}(k) \tau (1-\psi_i)\theta_{Gj} - (1+c)(b_1 + b_2 N) G_k + \mu_k \tag{3.5}$$

$$\frac{dS}{dt} = (a_1 - a_2 W)W \sum_{i \in \Gamma} \eta_i \theta_{Wi} \tau (1-\psi_i) - (1+c)(b_1 + b_2 N) S \tag{3.6}$$

for all $k \in \Gamma$.

3.3 Density-independent frequency model

Because the full density-dependent model requires keeping track of 7 state variables with 13 parameters, the full system is difficult to explore without numerical simulations. Before

Table 3.1 State variables and combinations of state variables

Notation	Definition
W_k	Density of wild-type males (or females) with genotype k
W	Density of wild-type males (or females)
G_k	Density of fertile gene drive males with genotype k
G	Density of fertile gene drive males
S	Density of sterile gene drive males
M	Density of all fertile males
N	Total population density
ϕ	Frequency of fertile gene drive males over all fertile males
θ_{Wk}	Frequency of preferential mating genotype (or allele) k over all wild-type individuals
θ_{Gk}	Frequency of preferential mating genotype (or allele) k over all fertile gene drive males

Table 3.2 Parameters and their default values.

Notation	Default value	Definition
a_1	0.7 month^{-1}	Baseline per capita birth rate
a_2	$9 \cdot 10^{-4}$ $(\text{mice (per unit area) month})^{-1}$	Strength of density dependence on birth rate
b_1	0.2 month^{-1}	Baseline per capita death rate
b_2	$5 \cdot 10^{-5}$ $(\text{mice (per unit area) month})^{-1}$	Strength of density dependence on death rate
c	varies	Survival cost of gene drive
τ	0.95	Transmission distortion of gene drive
μ	varies $\frac{\text{mice (per unit area)}}{\text{month}}$	Release rate of fertile gene drive males
γ	1	Baseline preference
γ_G	varies	Preference of **CC** females for gene drive males
h	0.5	Dominance of preferential mating allele **C**
ρ	0.007	Female receptiveness

performing any simulations, we can gain some preliminary insight by analyzing a simplified version of the model in greater detail. By making a few simplifications, the model can be reduced to two density-independent differential equations for the allele frequencies of preferential mating ($\theta_{W\mathbf{C}}$) and the gene drive (ϕ). With these two equations, we can explain some of the basic dynamics of the interactions between these two genes in the population.

First, we remove the density dependence of the basic demographic rates. By assuming that $a_2 = b_2 = 0$, the per-capita birth and death rates do not change with population density. In the full density dependent model, female mating success depends on whether the female can find a preferred mate within the time she is receptive. Thus, mating success would decrease when male density decreases. To remove this form of density dependence, we assume that females are always receptive by letting ρ approach an infinite value. In this case,

$$\lim_{\rho\to\infty} \eta_i = 1 - \lim_{\rho\to\infty} e^{(-\rho(\gamma W + \gamma_{iG} G))} = 1, \tag{3.7}$$

so that all females will mate within their lifespan. We assume that the preferential mating allele is always at Hardy-Weinberg equilibrium so that $\theta_{W\mathbf{CC}} = \theta_{W\mathbf{C}}^2$, $\theta_{W\mathbf{Cc}} = 2\theta_{W\mathbf{C}}(1 - \theta_{W\mathbf{C}})$, and $\theta_{W\mathbf{cc}} = (1 - \theta_{W\mathbf{C}})^2$ at any point in time. Also, we can assume that the transmission distortion of the gene drive is 100% effective such that $\tau = 1$. Thus, there is no gene flow from gene drive males into the wild-type population and we can disregard the frequency of $\mathbf{C}$ in gene drive males. Lastly, we restrict $\mu = 0$ and consider only cases where the gene drive may exist in the population, but is not actively being released.

To reduce notation, let

$$\omega_1(\phi) = \gamma(1 - \phi) + \gamma_G \phi > 0 \tag{3.8}$$

and

$$\omega_2(\phi) = \gamma(1 - \phi) + (h\gamma_G + (1 - h)\gamma)\phi > 0. \tag{3.9}$$

With some algebra (Appendix C), these assumptions allow us to simplify the model to a set of two equations

$$\frac{d\phi}{dt} = \phi(1-\phi)\left(a_1(\gamma_G - \gamma)(1-\phi)\theta_{W\mathbf{C}}\left(\frac{\theta_{W\mathbf{C}}}{\omega_1(\phi)} + \frac{2h(1-\theta_{W\mathbf{C}})}{\omega_2(\phi)}\right) - b_1 c\right) \tag{3.10}$$

$$\frac{d\theta_{W\mathbf{C}}}{dt} = \frac{a_1}{2}(\gamma - \gamma_G)\theta_{W\mathbf{C}}(1-\theta_{W\mathbf{C}})\left(\frac{\phi(1-\phi)}{\omega_2(\phi)}\right)\left(h(1-\theta_{W\mathbf{C}}) + \left(\frac{(1-h)\gamma}{\omega_1(\phi)}\right)\theta_{W\mathbf{C}}\right). \tag{3.11}$$

3.3.1 Basic dynamics

In the absence of any preferential mating, the spread of the gene drive ultimately depends on its relative survival cost, as

$$\frac{d\phi}{dt} = -b_1 c(1-\phi)\phi \tag{3.12}$$

when $\theta_{W\mathbf{C}} = 0$. That is, gene drive frequency will decrease until it is lost from the population when $c > 0$, gene drive frequency will increase until the population is eradicated when $c < 0$, and gene drive frequency will remain constant when $c = 0$. When there is preferential mating in the wild population, the spread of the gene drive also depends on direction of female preference. To demonstrate this, we define

$$A_1 = \phi(1-\phi)^2 a_1 \theta_{W\mathbf{C}}\left(\frac{\theta_{W\mathbf{C}}}{\omega_1(\phi)} + \frac{2h(1-\theta_{W\mathbf{C}})}{\omega_2(\phi)}\right) \tag{3.13}$$

When $0 < \phi < 1$, $\theta_{W\mathbf{C}} > 0$, each multiplicative term in A_1 is positive, so $A_1 > 0$. Thus, if wild-type males are preferred ($\gamma_G < \gamma$), then

$$\frac{d\phi}{dt} = (\gamma_G - \gamma)A_1 - b_1 c(1-\phi)\phi < -b_1 c(1-\phi)\phi, \tag{3.14}$$

when both the gene drive and preferential mating are extant but not at fixation. This shows

that gene drives are less successful at spreading through a population where wild-type males are preferred. Moreover, when preferential mating frequency is higher, the gene drive is even less successful at spreading through the population (Figure 3.1.a). Importantly, a gene drive that spreads in a randomly mating population could be lost from a population when there is a sufficiently high frequency of preferential mating favoring wild-type males. If preferential mating favors gene drive males instead, these trends are reversed.

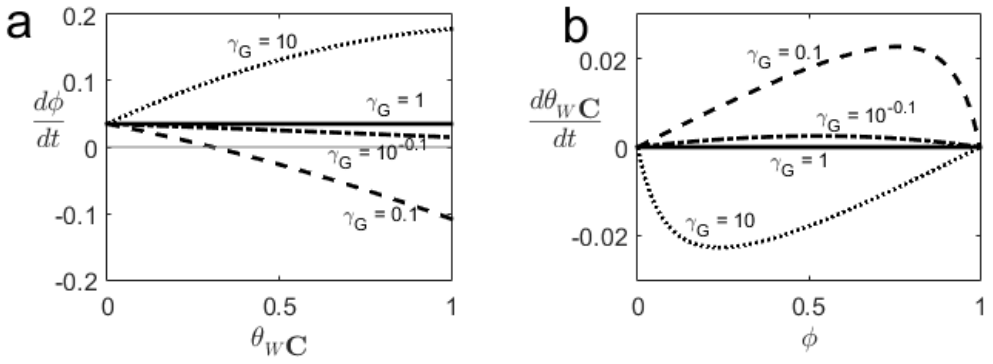

Figure 3.1 Instantaneous rates of change in allele frequencies. In each of these examples, the gene drive has a relative survival advantage at $c = -0.2$ and baseline preference is $\gamma = 1$. (a) The instantaneous rate of change in gene drive frequency at $\phi = 0.5$ as it changes with preferential mating direction, strength, and frequency. Solid line: Preference is neutral ($\gamma_G = 1$), so gene drive spread is not affected by $\theta_{W\mathbf{C}}$. Dotted line: Gene drive males are preferred ($\gamma_G = 10$), so gene drive spread increases with higher preferential mating frequency. Dash-dot line: Wild-type males are weakly preferred ($\gamma_G = 10^{-0.1}$), so gene drive spread decreases with higher preferential mating frequency. However, the gene drive always increases even when preferential mating is at fixation. Dashed line: Wild type males are strongly preferred ($\gamma_G = 0.1$). When $\theta_{W\mathbf{C}} > 0.31$, preferential mating is great enough that the gene drive decreases in frequency. (b) The instantaneous rate of change in preferential mating frequency at $\theta_{W\mathbf{C}} = 0.5$ as it changes with gene drive frequency and the direction and strength of preferential mating. When $\gamma_G > \gamma$, preferential mating always decreases in response to the gene drive. The magnitude of this decrease is largest at a low-intermediate gene drive frequency. When $\gamma_G < \gamma$, preferential mating always increases in response to the gene drive. The magnitude of this increase is largest at a high-intermediate gene drive frequency.

Within this model, preferential mating frequency should remain constant in an undisturbed population where no gene drive males are present. Indeed, we find $\phi = 0$ implies that $\frac{d\theta_{W\mathbf{C}}}{dt} = 0$.

Preferential mating frequency does change in response to the gene drive depending on the direction of the preference. To demonstrate this, we define

$$A_2 = \frac{a_1}{2}\theta_{W\mathbf{C}}(1-\theta_{W\mathbf{C}})\left(\frac{\phi(1-\phi)}{\omega_2(\phi)}\right)\left(h(1-\theta_{W\mathbf{C}}) + \left(\frac{(1-h)\gamma}{\omega_1(\phi)}\right)\theta_{W\mathbf{C}}\right). \tag{3.15}$$

When $0 < \phi < 1$ and $0 < \theta_{W\mathbf{C}} < 1$, each term of A_2 is positive, so $A_2 > 0$. Thus, if wild-type males are preferred ($\gamma_G < \gamma$), then

$$\frac{d\theta_{W\mathbf{C}}}{dt} = (\gamma - \gamma_G)A_2 > 0. \tag{3.16}$$

whenever both the gene drive and preferential mating are extant but not at fixation. Thus, preferential mating always increases in response to the gene drive when wild type males are preferred. Alternatively, preferential mating frequency always decreases in response to the gene drive when gene drive males are favored, as

$$\frac{d\theta_{W\mathbf{C}}}{dt} = (\gamma - \gamma_G)A_2 < 0. \tag{3.17}$$

when $0 < \phi < 1$, $0 < \theta_{W\mathbf{C}} < 1$, and $\gamma_G > \gamma$. Moreover, unless $\gamma_G = \gamma$, $\frac{d\theta_{W\mathbf{C}}}{dt} \neq 0$ for any point where $0 < \phi < 1$, $0 < \theta_{W\mathbf{C}} < 1$. Regardless of strength and direction of preference, the change in preferential mating frequency is greatest at intermediate gene drive frequencies (Figure 3.1.b).

3.3.2 Equilibrium analysis

Equilibria exist at any points where $\frac{d\phi}{dt} = \frac{d\theta_{W\mathbf{C}}}{dt} = 0$. From equations 3.10 and 3.11, we see that $\frac{d\phi}{dt}$ and $\frac{d\theta_{W\mathbf{C}}}{dt}$ are both a product of $\phi(1-\phi)$. Thus, the lines $\phi = 0$ and $\phi = 1$ are always equilibria regardless of parameter values. Throughout the rest of this chapter, the line $\phi = 0$ is referred to as the undisturbed equilibrium, as it corresponds to $\phi = \frac{G}{W+G} = 0$ where the gene

drive does not exist in the population. Also, the line $\phi = 1$ is referred to as the eradication equilibrium, as $\phi = \frac{G}{W+G} = 1$ is only possible when $W = 0$.

Any additional equilibria can be identified at the intersection of nullclines (curves where either $\frac{d\phi}{dt} = 0$ or $\frac{d\theta_{W\mathbf{C}}}{dt} = 0$). For $\theta_{W\mathbf{C}}$, these nullclines exist at $\phi = 0$, $\phi = 1$, $\theta_{W\mathbf{C}} = 0$ and $\theta_{W\mathbf{C}} = 1$. An internal nullcline exists for ϕ whenever the curve

$$\theta_{W\mathbf{C}} = -\frac{1}{2}\frac{h\omega_1(\phi)}{\omega_2(\phi) - 2h\omega_1(\phi)} \pm \frac{\sqrt{\left(a_1(\gamma_G - \gamma)(1-\phi)\left(\frac{2h}{\omega_2(\phi)}\right)\right)^2 + 4a_1(\gamma_G - \gamma)b_1c(1-\phi)\left(\frac{1}{\omega_1(\phi)} - \frac{2h}{\omega_2(\phi)}\right)}}{2\left(a_1(\gamma_G - \gamma)(1-\phi)\left(\frac{1}{\omega_1(\phi)} - \frac{2h}{\omega_2(\phi)}\right)\right)} \tag{3.18}$$

is a real number between $0 \leq \phi \leq 1$ and $0 \leq \theta_{W\mathbf{C}} \leq 1$. Importantly, if this nullcline exists, it represents the point where a gene drive would change from spreading to being lost from the population. When this nullcline exists, and intersects any of the $\theta_{W\mathbf{C}}$ nullclines it can alter the behavior of the system in a variety of ways.

If any gene drives are added to the population, the population will eventually approach either the undisturbed or eradication equilibria (except in the borderline case at $c = 0$). Before the population reaches one of these points, it can undergo substantial change as both the gene drive and preferential mating evolve in response to each other. This evolution depends on whether the gene drive has a survival cost or advantage and whether preferential mating favors gene drive or wild-type males. We explore all four combinations, but first define the general behavior of gene drive persistence.

3.3.2.1 Gene drive persistence

The persistence of the gene drive depends on its survival cost and the strength, direction, and frequency of preferential mating in the population. Overall, gene drive persistence can be described with four different general patterns in qualitative behavior. We explain these in increasing levels of persistence (Table 3.3). A gene drive is non-persistent if it decreases in frequency from its initial point toward the undisturbed equilibrium. This corresponds to the

Table 3.3 Qualitative behavior of gene drive drive frequency in increasing level of persistence.

Behavior	Gene drive spread after small release	Outcome
Non-persistence	Always $\frac{d\phi}{dt} < 0$	$\phi = 0$
Temporary persistence	First $\frac{d\phi}{dt} > 0$, then $\frac{d\phi}{dt} < 0$	$\phi = 0$
Coexisting persistence	Always $\frac{d\phi}{dt} > 0$	$0 < \phi < 1$
Eradicating and persistence	Always $\frac{d\phi}{dt} > 0$	$\phi = 1$

rapid loss of the gene drive from the population. A gene drive is temporarily persistent when it spreads through the population for some time, but it is ultimately lost as it approaches the undisturbed equilibrium. While this has the same outcome as the non-persistent case, it usually takes far longer to reach the undisturbed equilibrium. When the gene drive is coexistent and persistent, it will spread through a population toward an equilibrium $0 < \phi < 1$ where both the gene drive and wild-type coexist in the population. In the density-independent model, this is a borderline case that we do not explain in detail. Lastly, a gene drive is eradicating and persistent when it spreads through a population indefinitely toward the eradication equilibrium.

3.3.2.2 Low gene drive survival, wild-type males preferred

When the gene drive has a relative survival cost and preferential mating favors wild-type males, the gene drive is always non-persistent (Figure 3.2.a). The gene drive is always lost in these cases because it has a relative disadvantage in both survival and mate choice compared to wild-type males. Additionally, preferential mating frequency always increases in response to the gene drive. Therefore, even though the population will always return to the undisturbed equilibrium, it will reach this point with a higher preferential mating frequency than when it started.

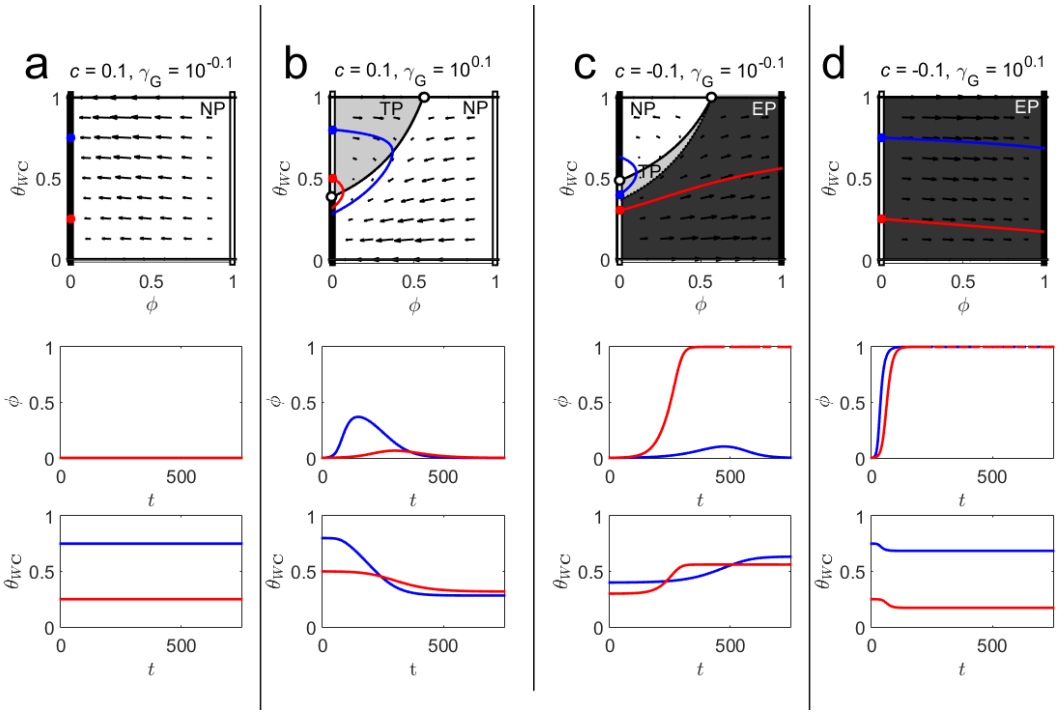

Figure 3.2 Top row: Phase planes of model behavior in four representative cases with gene drive frequency (ϕ) on the horizontal axis and preferential mating frequency ($\theta_{W\mathbf{C}}$) on the vertical axis. Arrows indicate the trajectory of the model at the corresponding values of ϕ and $\theta_{W\mathbf{C}}$. The lines at $\phi = 0$ and $\phi = 1$ are equilibria in all cases. These lines are filled where the equilibria are attracting and unfilled where the equilibria are unstable. The unfilled points in (b) and (c) are saddle point equilibria. Gene drive frequencies change in three different behavioral patterns. In regions that are white (and marked NP for non-persistence), the gene drive only decreases in frequency until it is lost from the population. In regions that are lightly shaded (and marked TP for temporary persistence), the gene drive initially increases in frequency before it reaches the non-persistent region and is eventually lost from the population. In regions that are darkly shaded (and marked EP for eradicating and persistent), the gene drive increases in frequency until the population is eradicated. Beginning at enlarged, colored points, the colored curves show example model behavior as it moves over the trajectories of state space. For each curve, gene drive frequency of gene drive is initially at $\phi = 0.001$ while the initial preferential mating frequency is chosen to show specific representative behaviors. Bottom rows: With the same examples as above, curves show the change in these frequencies over time. Within each vertical panel, color corresponds the same example throughout all three plots.

3.3.2.3 Low gene drive survival, gene drive males preferred

When the gene drive has a relative survival cost, but preferential mating favors gene drive males, the gene drive is always lost from the population. However, the population can follow

two general behaviors before it reaches the undisturbed equilibrium (Figure 3.2.b). In this case, the internal ϕ-nullcline from equation 3.18 exists. A saddle point equilibrium forms where the internal ϕ-nullcline intersects with the $\theta_{W\mathbf{C}}$-nullcline $\theta_{W\mathbf{C}} = 1$. The internal ϕ-nullcline also intersects the $\theta_{W\mathbf{C}}$-nullcline at $\phi = 0$ and at some point $0 < \theta^*_{W\mathbf{C}} < 1$, forming another saddle point equilibrium. Importantly, this second saddle point splits the undisturbed equilibrium in two. Because of this, the undisturbed equilibrium is attracting when $\theta_{W\mathbf{C}} < \theta^*$ and repelling when $\theta_{W\mathbf{C}} > \theta^*$.

There is a non-persistent region at any point in state space where preferential mating frequency is below this internal ϕ-nullcline and the gene drive frequency is above the nullcline. In this case, the gene drive frequency decreases because preferential mating is not strong enough or at a high enough frequency to maintain the gene drives in the population. At the same time, preferential mating frequency is also decreasing. The population attracts toward the undisturbed equilibrium where the gene drive no longer exists and preferential mating is at a lower frequency than it was initially.

There is also a temporarily persistent region in state space where gene drive frequency is below the internal nullcline and preferential mating is above the nullcline. In this case, preferential mating is initially strong enough to increase gene drive frequency. However, preferential mating frequency is decreasing throughout, eventually reaching the point where preferential mating can no longer sustain the gene drive. At this point, the population crosses the internal ϕ-nullcline into the previously described non-persistent region. Afterward, the gene drive and preferential mating frequencies decrease, approaching the undisturbed equilibrium. Because the preferential mating frequency is decreasing throughout, it will be at a much lower frequency than when it began.

Interestingly, no matter how strongly preferential mating favors gene drive males, the eradication equilibrium is never attracting when the gene drive has a survival cost. Under these conditions, the internal ϕ-nullcline always passes through the $\theta_{W\mathbf{C}} = 1$ at some point where

$\phi < 1$. Thus, there will always be some finite region between the internal ϕ-nullcline and the eradication equilibrium where the gene drive decreases in frequency. Because gene drive males have a survival cost, the gene drive only spreads through the population due to its mating advantage. Since the gene drive cannot maintain this advantage with an infinitesimally small frequency of females, the gene drive eventually stops spreading through the population at some point before the population is eradicated. While this is a logical outcome of our initial assumptions of density independence, it falls short of biological realism. Namely, an Allee effect would likely push the population to extinction when female density is low enough (Allee et al., 1949; Courchamp et al., 1999). This emphasizes the importance of the female mating success function η_i in our full density-dependent model.

3.3.2.4 High gene drive survival, wild-type males preferred

When the gene drive has a relative survival advantage and preferential mating favors wild type males, the state space of the model is split into three different regions (Figure 3.2.c). Under these conditions, the internal ϕ-nullcline exists and forms a saddle point equilibrium where it crosses the $\theta_{W\mathbf{C}}$-nullcline at $\theta_{W\mathbf{C}} = 1$. In this situation, the stable manifold flows from the undisturbed equilibrium to the saddle point over an internal trajectory. This stable manifold separates the temporarily persistent and eradicating persistent behaviors. The internal ϕ-nullcline also intersects the $\theta_{W\mathbf{C}}$-nullcline at $\phi = 0$ and at some point $0 < \theta^*_{W\mathbf{C}} < 1$, creating another saddle point equilibrium. Importantly, this second saddle point splits the undisturbed equilibrium in two. Because of this, the undisturbed equilibrium is unstable when $\theta_{W\mathbf{C}} < \theta^*$ and stable when $\theta_{W\mathbf{C}} > \theta^*$.

When preferential mating frequency is above the internal ϕ-nullcline and gene drive frequency is below this nullcline, the gene drive is non-persistent. In this case, preferential mating is at a high enough frequency that a gene drive with a survival advantage will not spread through the population. In this region, gene drive frequency always decreases while preferential

mating frequency always increases. Thus, the population attracts toward the undisturbed equilibrium where the gene drive no longer exists and preferential mating is at a higher frequency than when it began.

In the region between the internal ϕ-nullcline and the stable manifold, the gene drive is temporarily persistent. While gene drive frequency initially increases because of its survival advantage, preferential mating frequency is also increasing in response. Eventually, preferential mating in favor of wild-type males is frequent enough that the gene drive stops spreading. At this point, the population flows over the internal ϕ-nullcline and reaches the non-persistent region. Afterward, the gene drive decreases in frequency until the population ultimately ends up at the undisturbed equilibrium. Because the preferential mating frequency is increasing throughout, it will end at a much higher frequency than when it began.

Lastly, when preferential mating is below the stable manifold and gene drive frequency is above the stable manifold, the gene drive is eradicating and persistent. In this case, the gene drive has enough of a survival advantage that it can spread and eradicate the population despite a mating disadvantage. As the gene drive is spreading, preferential mating is increasing in frequency in response. However, even though females are becoming less likely to mate with gene drive males, the effect will not be strong enough to resist the spread of the gene drive.

3.3.2.5 High gene drive survival, gene drive males preferred

When the gene drive has a relative survival advantage and preferential mating favors gene drive males, the gene drive is eradicating and persistent in all cases (Figure 3.2.d). The gene drive always spreads because it has a relative advantage in both survival and mate choice compared to wild-type males. While the preferential mating frequency always decreases in response to the gene drive, it never changes the outcome because the gene drive would still be persistent and eradicating even when all females mate randomly.

3.4 Density-dependent model

3.4.1 Simulations

With the full density-dependent model, we used a numerical simulation approach to determine how the evolution of preferential mating could impact eradication attempts with gene drives. Additionally, we simulated single small pulses of gene drive males to determine how preferential mating evolution could impact gene drive persistence. These simulations were conducted with an ordinary differential equation solver (ode45) in Matlab 2015a.

Each simulation began at the undisturbed equilibrium with the wild type population at carrying capacity, which we solved numerically. We varied preferential mating from $\gamma_G = 0.1$ (when wild-type males are $10\times$ preferred) to $\gamma_G = 10$ (when gene drive males are $10\times$ preferred). To compare mate choice over several initial conditions, we varied initial frequency of preferential mating from $\theta_0 = 0$ to $\theta_0 = 1$. Genotype frequencies were distributed initially at Hardy-Weinberg equilibrium ($\theta_{W,\mathbf{CC}} = \theta_0^2$, $\theta_{W,\mathbf{Cc}} = 2\theta_0(1-\theta_0)$, $\theta_{W,\mathbf{cc}} = (1-\theta_0)^2$). We also varied gene drive survival cost from $c = 0.2$, where the gene drive would be self-limiting in the absence of preferential mating, to $c = -0.2$ where the gene drive would be self-sustaining to eradication. The remaining parameters were not the focus of our simulations and set to default values (Table 3.2).

3.4.2 Eradication

When females prefer to mate with wild-type males, eradication is more difficult as gene drives are behaviorally resisted (Figure 3.3). Thus, a release rate that is sufficient to eradicate a randomly mating population might not be sufficient to eradicate a preferentially mating population. Though increasing the release of gene drives would increase the rate of gene drive spread, it might also increase the evolutionary response in favor of preferential mating against the gene

drive. However, as long as the gene drive release rate is high enough, the population could be eradicated faster than preferential mating can evolve. Overall, this increases the minimum gene drive release rate that is needed to eradicate the population.

To show how preferential mating could affect eradication, we determined the minimum release rate of gene drive males that would be required for eradication for each set of parameter values and initial conditions described in 3.4.1. We made the assumption that prior to release, the gene drive males would be backcrossed with stock from the wild population over several generations. Therefore, the preferential mating genotype frequency in released gene drive males should resemble the initial frequency in the wild population, such that $\mu_k = \mu\theta_{W,k}(0)$ gene drive males per month.

We found the minimum release rate to be higher as higher initial frequencies of females had strong preferential mating in favor of wild-type males (Figure 3.4). On the other hand, when some females preferentially mated with gene drive males, the minimum release rate was reduced. With substantially high initial frequencies of females strongly preferring gene drive males, this minimum rate was as low as 0 gene drive males per month. At this point, a single pulse of gene drive males could eradicate the population without a sustained release. We elaborate on these ideas in the following section.

3.4.3 Persistence

To maintain control over the gene drive in the wild, a self-limiting gene drive is likely to be desirable within a conservation framework. With these self-limiting cases, there should be minimal concern over the long-term persistence of the gene drive if it spreads to a non-target population or if an eradication attempt needs to be stopped prior to completion. However, if preferential mating can allow a gene drive to persist in a population and even eradicate a population, the self-limiting nature of some gene drives might not be guaranteed.

To show how preferential mating could affect gene drive persistence, we simulated the dy-

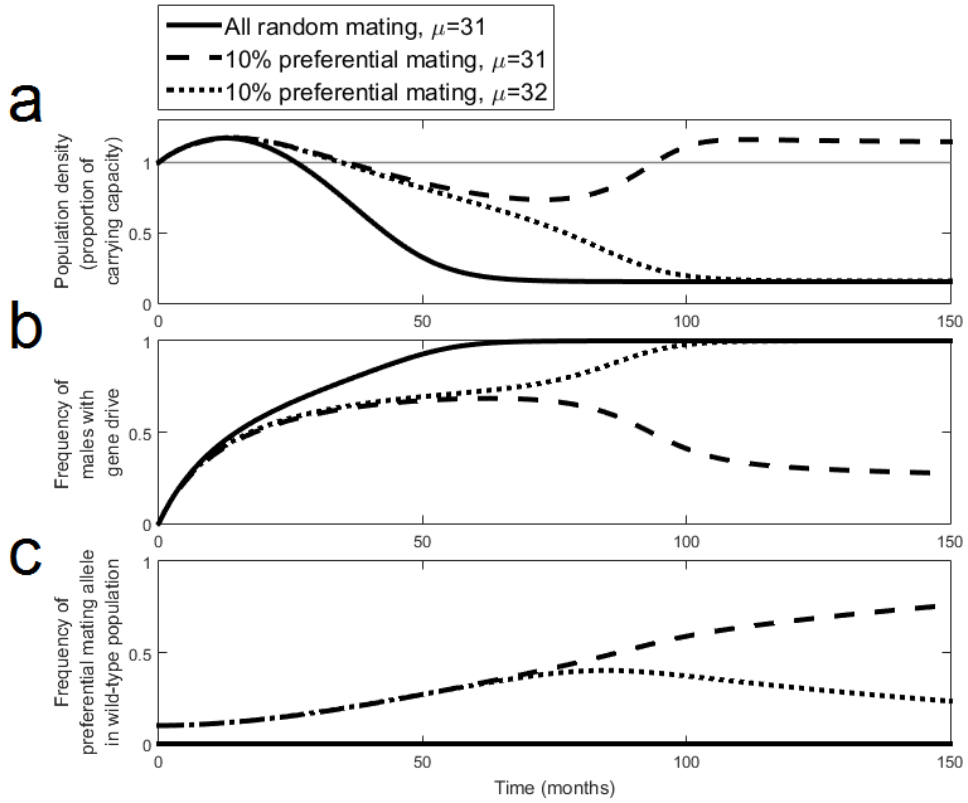

Figure 3.3 Three simulations of eradication attempts over various conditions where **CC** females have a strong preference to mate with wild type males ($\gamma_G = 0.1$ and $\gamma = 1$). In these examples, panel (a) shows the change in population density, (b) shows the change in the frequency of males carrying the gene drive, and (c) shows the change in frequency of the preferential mating allele in females. For comparison, the solid line represents a wild population without preferential mating. If gene drive males are released into this random mating population at a rate of $\mu = 31$ per month, the population is eradicated as the gene drive spreads to fixation. The dashed line represents a wild population where the preferential mating allele is initially at a frequency of $\theta_0 = 0.1$ and gene drive males are released into the population at a rate of $\mu = 31$ per month. After an initial increase in population density, the population declines as the gene drive spreads. Throughout this time, preferential mating increases in frequency, which decreases the spread of the gene drive. Eventually, the gene drive is resisted and the population density recovers despite maintaining the $\mu = 31$ per month release rate. The dotted line represents a wild population where the preferential mating allele is initially at frequency of $\theta_0 = 0.1$ but gene drive males are released into the population at a rate of $\mu = 32$ per month. In this case, the gene drive is released into the population fast enough that preferential mating does not completely resist the spread of the gene drive. Thus, the population is eventually eradicated.

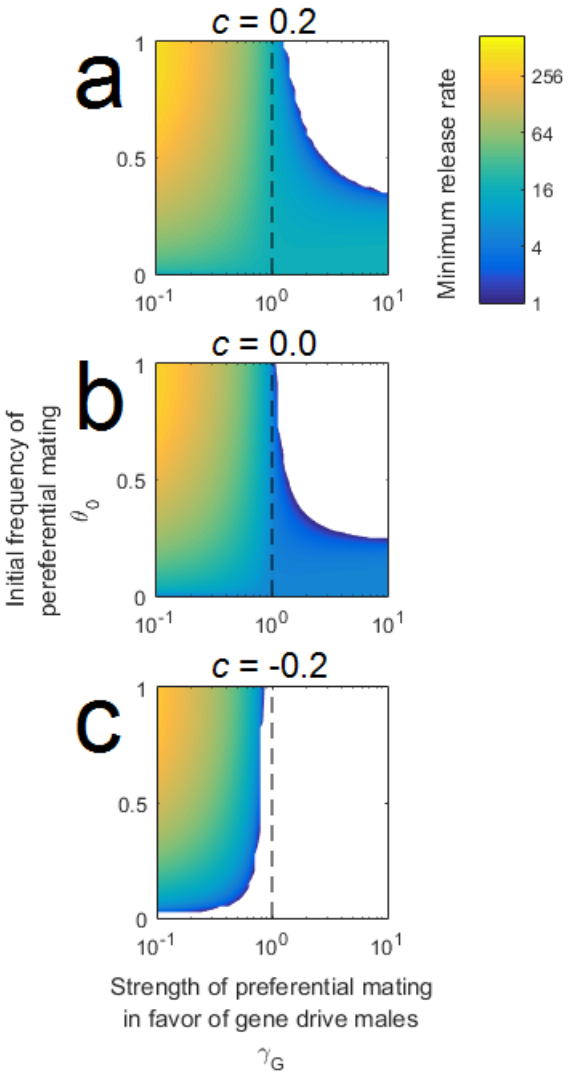

Figure 3.4 The minimum release rate necessary for eradication increases with a higher initial frequency of preferential mating in favor of wild-type males. The minimum release rate decreases with a higher initial frequency of preferential mating in favor of gene drive males. The color corresponds with the minimum release rate of gene drive males that is necessary to eradicate the population. Note the log2 scale on the color axis and the log10 scale on the horizontal axis. White areas have a minimum release rate of 0, such that any pulsed release of gene drives can result in eradication. The survival cost associated with carrying the gene drive is $c = 0.2$ in (a), $c = 0$ in (b), and $c = -0.2$ in (c). The dashed line represents neutral preferential mating when $\gamma_G = \gamma = 1$.

namics following small pulsed releases of gene drive males (1% of the carrying capacity) being added to an undisturbed population. These populations were simulated until the model asymptotically approached an equilibrium point. We classified the gene drive persistence behavior of each simulation by the equilibrium it asymptotically approached and the initial trajectory of the gene drive frequency (Table 3.3). If the population was eventually eradicated following the pulsed release, the gene drive was considered eradicating and persistent. We recorded the eradication time as total time it took for the population to reach a threshold around the eradication equilibrium ($W < 0.05$). If the gene drive was eventually lost from the population, the gene drive was non-persistent or temporarily persistent. We recorded the persistence time as the total time it took for the population to reach a threshold around the undisturbed equilibrium ($G < 0.05$).

We found that preferential mating in favor of wild-type males can decrease the persistence of gene drives, while preferential mating in favor of gene drive males can increase the persistence of gene drives (Figure 3.5). Thus, a gene drive that would eradicate the population under all random mating could become temporarily persistent or completely non-persistent if a high enough proportion of females prefer to mate with wild-type males (Figure 3.5.c). A gene drive that would be completely non-persistent when all females randomly mate can become temporarily persistent or even fully persistent and eradicating if a high enough proportion of females prefer to mate with gene drive males (Figure 3.5.a-b).

Notably unlike the density-independent model, this eradicating and persistent behavior is possible even when the gene drive imposes a survival cost. This is likely because in the density-dependent model, only some proportion of females mate within their lifetime ($\sum_i \eta_i < 1$). When male density is low, there could be few enough females successfully mating that the population would decrease even when no gene drive males are in the population. If the gene drive can suppress the population to this point, reduced female mating success could cause an Allee effect and push the population the rest of the way to eradication.

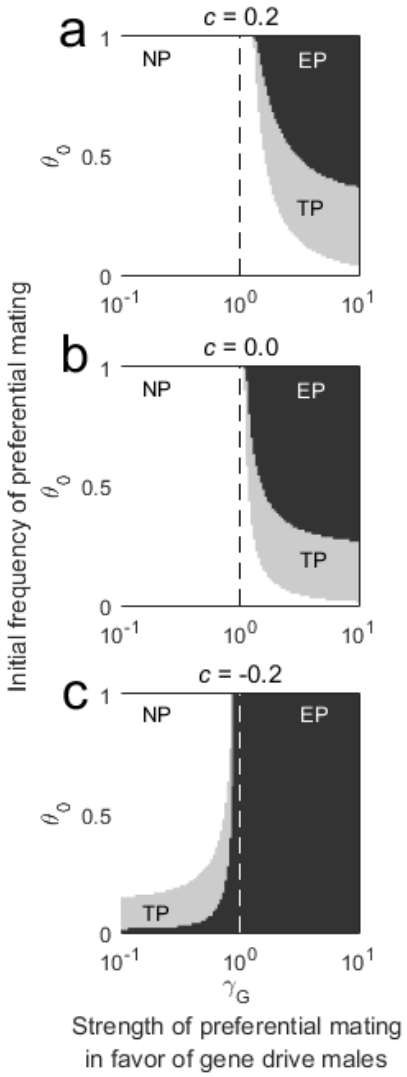

Figure 3.5 The qualitative behavior of a gene drive after a small pulse of gene drive males (1% of the carrying capacity) are added to a wild population at carrying capacity depends on several conditions. Note the log10 scale on the horizontal axis. The gene drive can be non-persistent (NP, white), temporarily persistent (TP, light gray), or eradicating and persistent (EP, dark gray). The dashed lines represent neutral preferential mating when $\gamma_G = \gamma = 1$. In (a), the gene drive has a survival cost $c = 0.2$, in (b), gene drive survival is neutral relative to the wild population $c = 0$, and in (c), the gene drive has a survival benefit $c = -0.2$.

Preferential mating not only changes the general qualitative behavior of gene drive persistence, but it can also have other important temporal effects. Particularly, in the subset of cases where the gene drive persists and eradicates the population, both the frequency and strength of female preference impact eradication time. Eradication is faster if preferential mating is strongly in favor of the gene drive and at a higher initial frequency (Figure 3.6.a,c,e). If preferential mating favors wild-type males yet the gene drive is still persistent and eradicating, weaker preference and lower frequencies of preferential mating result in faster eradication time (Figure 3.6.e)

Even when a gene drive is ultimately lost from the population, preferential mating can substantially increase gene drive persistence time. A gene drive that is completely non-persistent is lost from a population quickly, as it immediately decreases in frequency until it is lost from the population. In this case, gene drive persistence time is shorter when more females have stronger preference to mate with wild-type males (Figure 3.6.b,d,f). A gene drive that is temporarily persistent remains in the population longer, increasing in frequency before it is lost. The longest persistence times occur near the boundary between non-persistence and persistence. In these cases, the gene drive could theoretically persist at a relatively low frequencies with a small fitness advantage over wild mice. As preferential mating evolves in response, the relative mating success of gene drive males decreases. Eventually, the gene drive loses its fitness advantage and it is slowly lost from the population. The density-independent models can provide some additional insight into these long persistence times. For comparative cases, we can consider areas where the gene drive switches from non-persistent to temporary persistent behavior at low gene drive frequencies in the density-independent model. These regions are very close to a saddle point equilibrium (Figure 3.2.b-c) where trajectories of rates of change in allele frequencies are very small. Thus, any orbit that begins in the temporary persistent region near the saddle points would remain in a slow moving region as it eventually approaches the undisturbed equilibrium.

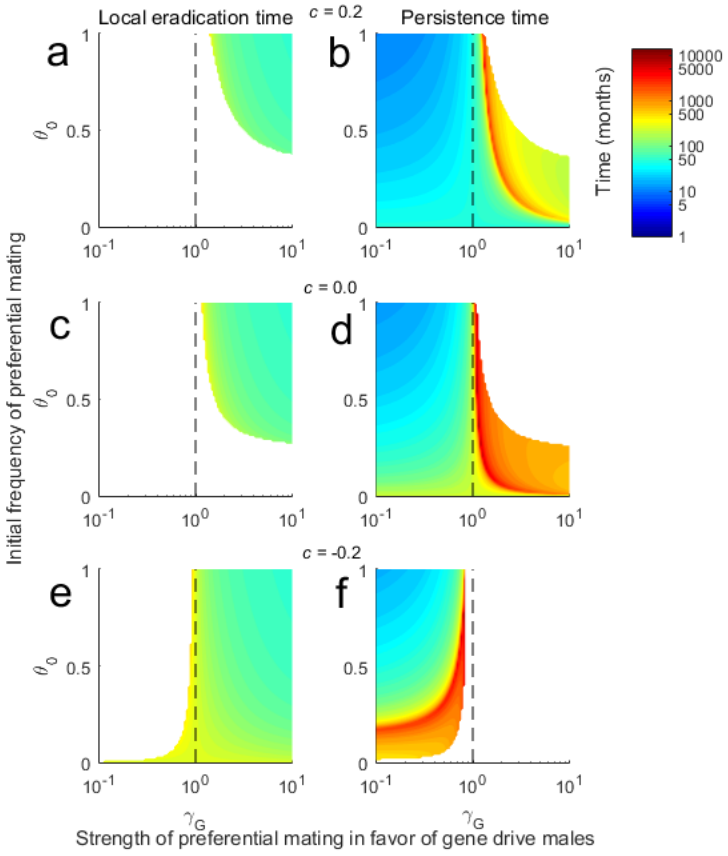

Figure 3.6 After a small pulse of fertile gene drive males ($G = 0.01K$) is added to a wild population at carrying capacity, the fate of the population and the gene drive could depend on several conditions. The colors correspond to the time it takes the population to reach threshold conditions for an outcome. Note the log10 scale on the color axis and the log10 scale on the horizontal axis. (a,c,e) Local eradication time as it changes with preferential mating strength and frequency. (b,d,f) Persistence time as it changes with preferential mating strength and frequency. In (a,b) gene drives have a survival cost $c = 0.2$, in (c,d) gene drives have neutral survival $c = 0.0$, and in (e,f) gene drives have a survival benefit $c = -0.2$. The dashed lines represent neutral preferential mating when $\gamma_G = \gamma = 1$.

3.5 Discussion

Our analysis suggests that preferential mating could have substantial impacts on the dynamics of population suppression gene drives. It has been suggested by many (Burt, 2003; Esvelt et al., 2014; Bull, 2015, 2017) that behavioral resistance could limit the spread and effectiveness of gene drives in wild populations. We confirm this idea by showing a reduction in the spread of a suppressing gene drive when females preferentially mate with wild males and avoid gene drive males. Additionally, when this preferential mating is heritable, it increases in frequency in response to the gene drive. Thus, the wild-type population gradually becomes more resistant to the gene drive over time. If enough females avoid mating with gene drive males, gene drives could stop spreading completely, even when they are continually released into the population. At this point, eradication would be stalled as the population density reverts back near its initial level and higher levels of behavioral resistance.

Within our model, eradication is always possible with a high enough release rate, as long as preferential mating does not completely exclude gene drive males. During the process of an eradication attempt, gene drive frequency should increase over time as it is continually released. However, if there is heritable preferential mating in favor of wild-type males, these preferential mating alleles should also be increasing in response to the gene drive. The success or failure of eradication depends on which of these alleles ultimately spreads through the population faster. Higher release rates should increase the chance that the gene drive prevails by not only artificially reinforcing the density of gene drives in the population, but by also reducing the relative proportion of wild-type males. Therefore, rapidly releasing gene drives at large densities can be an effective strategy to mitigate the impacts of behavioral resistance. Once the population is eradicated, the evolution of preferential mating is irrelevant (assuming no migration takes place).

This notion of increasing the release rate to reduce the impact of resistance could seem

counterintuitive, especially because pesticide resistance is understood to increase with heavier applications of pesticides (Denholm and Rowland, 1992). However, the suppressing gene drive described in this model is distinct from other control techniques for several important reasons. Firstly, it is important to keep in mind that these heavy release rates of gene drives do not mean to prevent the evolution of resistance completely. In fact, if heritable mate choice favors wild-type males, this behavioral resistance could actually spread faster at higher release rates. Instead, these heavy release rates of gene drives would be used to ensure that a population is eradicated before preferential mating has the chance to evolve. Unlike chemically-driven control methods, gene drive males directly become part of the population they are suppressing. Higher gene drive release rates could be used to counteract any reduction in mating success from preferential mating. Secondly, pesticides primarily decrease populations through killing or sterilizing after some direct interaction with the substance. Increasing the application rates of these pesticides can create a situation where nearly all individuals encounter the chemical, giving an extreme fitness advantage for those individuals that resist it. The suppressing gene drive described in this model, on the other hand, suppresses populations specifically through breeding. Females that avoid mating with gene drive males do have a selective advantage, but this advantage does not monotonically increase with higher densities of gene drive males in the population (Figure 3.1.b). Especially in cases where gene drive males greatly outnumber wild-type males, females that prefer wild-type males risk choosing a less preferred mate or not mating at all. Lastly, this suppressing gene drive is described within the context of an island. Because an island population should be relatively small (compared to a more global distribution of insect pests) and bounded, complete eradication is a realizable objective. Assuming strict biosecurity measures are in place, there should be little risk of resistant individuals emigrating and spreading resistance to non-target populations. Likewise, there should be little risk of new individuals immigrating and reestablishing the population with latent resistance genes.

We also show that the gene drive should spread through the population easier if preferential

mating instead favors gene drive males. More specifically, when females prefer mating with gene drive males, the minimum release rate necessary for eradication decreases while the gene drive's level of persistence increases. A gene drive that would require sustained releases under random mating could theoretically eradicate a preferentially mating population with only a single pulsed release. While this scenario would be ideal for eradicating a target population, it becomes problematic if the gene drive manages to spread to a non-target population. In that case, latent preferential mating in the non-target population could result in widespread extinction. Thus, biosecurity safeguards (Akbari et al., 2015) and sterilizing gene drives (Esvelt et al., 2014) should be readily available throughout development and release.

Like the gene drive described in this chapter, several theoretical gene drives under consideration would be specifically designed to be self-limiting (Gould et al., 2008; Legros et al., 2013; Alphey, 2014; Backus and Gross, 2016; Noble et al., 2016*a*). If one of these self-limiting gene drives were to escape the target population, they might cause a minimal amount of population disruption, but the gene drive would ultimately be expected to be lost from the population (Alphey, 2014; Noble et al., 2016*a*). Thus, when self-limitation is expected, it could be argued that this gene drive design is inherently safer and would need fewer safeguards than a self-sustaining drive. However, because preferential mating can allow an otherwise self-limiting gene drive to persist and eradicate a population, designed self-limitation might not necessarily be a viable safeguard on its own. Even so, there is an important distinction between gene drives that are persistent because they are specifically designed to be self-sustaining and gene drives that become persistent because of a relative fitness advantage in the local population. The former are expected to effectively spread through almost any population. While local ecology and behavior can limit the speed that these gene drives spread through a population, these self-sustaining gene drives would have a large enough fitness advantage that they would most likely persist regardless (unless resistance develops). In the latter case, the gene drive's persistence is the result of relative mating advantages (described in this chapter) or increased survival rates

(described in more detail in Backus and Gross (2016)). However, these advantages are relative to the local population, and they are unlikely to be universal. While females in one population might prefer to mate with gene drive males to their own detriment, there is no guarantee that a neighboring population, much less the global range of the species, would have the same mating preferences. Thus, global extinction is unlikely to result from an accidental escape of a gene drive designed for self-limitation, but it would be only a small consolation if several local eradication events occurred anyway.

Even if preferential mating in favor of gene drive males is not strong enough to cause a self-limiting gene drive to be persistent and eradicating, our model suggests that mate choice can greatly increase the amount of time that a gene drive would remain in a population. With the complex interaction between the gene drive and preferential mating, gene drives could persist temporarily. In this case the gene drive would initially spread through a population until they lose their relative advantage and the gene drive is ultimately lost. While the long-term outcome is the same whether a gene drive is lost from a population slowly or quickly, the impact on the population could be radically different between these cases. If the gene drive is lost from the population almost immediately, its impact on the population could be negligible. When a gene drive is temporarily persistent, on the other hand, it can reduce the local population density throughout the entire time it persists. Worryingly, even a small change in preferential mating parameters can lead to large changes in persistence time in some situations. Importantly, in the region of parameter space where persistence time is very sensitive to changes in preferential mating, the gene drive could have minimal direct impact on the population. Because the gene drive would only remain in the population at relatively low frequencies throughout its temporary persistence, it would not substantially reduce the density of a non-target population. On the other hand, when a gene drive is temporarily persistent but for a shorter period of time, the gene drive would initially spread through a population in a way that reflects a persistent and eradicating gene drive. This could considerably decrease the population density and cause more

population disruption, albeit for a shorter duration.

One of the biggest challenges for the future of gene drive technology could come from the difficulty in anticipating potential evolutionary responses to the gene drives (Bull, 2015). Even though population managers would be aware that mating behaviors could impact gene drive dynamics, the genetic and behavioral mechanisms governing these interactions are likely to be complex and difficult to diagnose beforehand. To estimate latent preferential mating in a target population, the mating preference of wild females from the target population could be quantified through mate choice experiments (Dougherty and Shuker, 2015), but it would be difficult to realistically replicate the mate choice that would occur in the ecological and behavioral conditions from the target island. Unfortunately, individual genes that influence mate choice would most likely be difficult to identify, even in species with genomes that are well understood (Chenoweth and Blows, 2006; Lindholm and Price, 2016). Realistically, eradication would be attempted with limited knowledge of wild mating behaviors. Therefore, countermeasures that avoid behavioral resistance in target populations and reduce over-persistence in non-target populations would need to be applicable for a wide range of preferential mating scenarios. Thus, even if a gene drive is expected to eradicate a population with a single release pulse, it should be repeatedly released into the population to ensure the population is eradicated before it is resisted. On the other end, even if males carrying a gene drive are not expected to survive without repeated releases, biosecurity measures should act as though they could persist indefinitely.

This model provides some insight to the possibility of behavioral responses to gene drives, but it has some limitations that might need to be addressed before extrapolating to real biological systems. First, mate choice is realistically influenced by several genes on several different loci (Chenoweth and Blows, 2006) and a quantitative genetic modeling approach could provide additional insight (Lande, 1982). Also, it might prove useful to break mating dynamics into more detailed components. Particularly, sexual selection could take place in both sexes at different stages in the mating process. This chapter addresses pre-copulatory mate choice in females,

yet male-male competition for mates could also play an important role in gene drive evolution. For example, outbred male house mice have been shown to greatly outperform inbred males in competition for females (Meagher et al., 2000). If preferential mating favors wild-type males, these preferred males could become more inbred and not fare as well in male-male competition. Polyandrous female house mice have also been shown to undergo post-copulatory mate choice to avoid producing offspring with fitness costs (Firman and Simmons, 2008; Manser et al., 2011). This can allow one male phenotype to dominate during male-male competition while females could select another phenotype after copulation. Lastly, this chapter addresses gene drives in the context of completely eradicating a population from a bounded island system. The suggestions for limiting the impacts of preferential mating evolution would likely change in other contexts. When controlling pest species in mainland ecosystems (Burt, 2003; Alphey, 2014), full eradication is not necessarily the objective. Especially if populations are widespread and migration is inevitable, high release rates of gene drive males could instead accelerate the evolution of behavioral resistance without eradicating that resistant population.

Gene drives are rapidly becoming better understood and their applications are far-reaching (Esvelt et al., 2014; NAS, 2016). Though conservation biology is one of the most promising avenues of gene drive application, it also has a lot to lose if gene drives are implemented poorly (Redford et al., 2013; Campbell et al., 2015; Webber et al., 2015; Johnson et al., 2016). Along these lines, we have shown that preferential mating could theoretically thwart gene drive eradication efforts by making gene drives too powerful or not powerful enough when we are naïve to its potential. Though we cannot completely mitigate the undesired evolution of preferential mating itself, we can be prepared for and reduce its impacts if it does appear.

Chapter 4

Eradicating a stochastic metapopulation with a gene drive

Abstract

Recent advances in genetic engineering technology have opened the door for new species-specific methods of eradicating invasive species. Among the proposed applications, a rodent could be engineered to carry a gene that alters the sex-ratio of their offspring with a gene drive that has greater than 50% inheritance. If this genetically engineered rodent was released into a wild invasive population, it could gradually reduce that population to extinction. One potential benefit of this strategy is the ability of genetically engineered rodents to disperse throughout the extent of a population on their own. Unfortunately, this same propensity for dispersal could also allow the invasive species to take refuge in certain areas before recolonizing areas of the population that were previously eradicated. In this chapter, I numerically investigate some of the ways that population structure could complicate gene drive eradication efforts by constructing and analyzing a continuous-time Markov model of eradication dynamics in a metapopulation. Using this model, I compare multiple eradication strategies over a range of metapopulations by varying dispersal rates, number of patches, and the topology of patch connections. Overall, a balanced repeated release of the gene drive into every patch was most successful and was not substantially affected by variations in metapopulation structure. However, because a completely balanced release strategy is contingent on full knowledge of the metapopulation structure, this strategy is unlikely to be feasible in reality. In the event that gene drives are not able to be released throughout the full spatial extent of the population, eradication could still be possible. The minimum number of areas necessary to release the gene drive depends on dispersal and patch topology.

4.1 Introduction

Invasive mammals are partially responsible for high numbers of extinctions in rare and unique island ecosystems throughout the world (Alcover et al., 1998; Aguirre-Muñoz et al., 2008; Doherty et al., 2016). To mitigate damage, these invasive species can be extirpated through highly coordinated eradication efforts, after which the affected ecosystem can recover (Aguirre-Muñoz et al., 2008; Croll et al., 2016; Jones et al., 2016). As of now, there is a wide range of available tools and strategies for managing invasive animals, including dispersing chemical toxicants (Howald et al., 2007; Campbell et al., 2015), spreading diseases (Singleton, 1994; Parkes et al., 2014), releasing predators (Hoddle, 2004; Saunders et al., 2010), and hunting (Carrion et al., 2011). However, most of these methods carry some risk of killing or harming other species in the surrounding ecological community, including those that eradication intends to protect (Campbell et al., 2015). Additionally, several of these methods are limited by economic cost, regulation, evolved resistance, and the land area of targeted islands (Campbell et al., 2015).

At the same time, recent advances in genetic engineering (GE) technology have opened the door to new invasive species eradication tools (Thresher et al., 2014; Campbell et al., 2015; Johnson et al., 2016; Piaggio et al., 2017). In the past, similar genetic engineering tools have been used to control wild insect pests (Burt, 2003; Alphey, 2014). Generally, these pest populations are gradually suppressed after they interbreed with released insects that carry a GE construct that alters sex ratios, reduces fecundity, or imposes other fitness costs on their offspring (Burt, 2003; Deredec et al., 2008; Alphey, 2014). Though lab-reared GE organisms are likely to have reduced fitness relative to a wild population (Catteruccia et al., 2003), the GE construct could suppress a population more efficiently when linked to a gene drive that is inherited by offspring above a standard Mendelian ratio of 50% (Lyttle, 1991; Burt, 2003; Esvelt et al., 2014). By releasing enough individuals with the eradication gene drive into the

population over enough time, the population could theoretically be eradicated after no viable females remain in the population. Currently, these same ideas are being adapted to eradicate invasive house mice (*Mus musculus*) from island populations (Campbell et al., 2015; Piaggio et al., 2017). By rearranging only two naturally occurring mouse genes, this gene drive mouse could theoretically eradicate a population when they are released into that population above a critical release rate (Backus and Gross, 2016).

A major disadvantage of traditional chemical toxicant based eradication comes from the need to spread the toxicant densely enough for the bait to be accessible to each individual of the invasive population (Pott et al., 2015). Gene drive organisms, on the other hand, can disperse through an island on their own, allowing them to reach areas beyond where they were originally released. Especially on large islands with steep and complex topography (Howald et al., 2007; Cuthbert et al., 2014), this self-dispersal might allow gene drive organisms to reach areas that would be difficult for population managers to reach with toxicant baits. At the same time, individuals from the wild population would also be dispersing around the island. Thus, an invasive species could be extirpated from one area before it is later recolonized from another area where the invasive population is still extant. Especially if some refuges go undetected during initial island population surveys, it could be difficult to plan eradication around this risk of recolonization. It is important to consider that separations in population structure might not only be physical, but populations could also be separated by mating and social structure. For example, wild house mice tend to form small, socially distinct demes that exchange individuals through occasional dispersal events (Noyes et al., 1982; Gerlach, 1996). Though a gene drive might ideally be released evenly throughout the full extent of a structured population, it would likely be difficult to achieve this in reality. Therefore, it is useful to determine how well gene drive eradication could fare when an even release is impractical.

Metapopulation ecology provides a theoretical framework to address complications of population structure in gene drive assisted eradication. In this context, an island invasive species

population could be broken down into a set of subpopulations that interact through migration and dispersal (Levins, 1969; Hanski and Gilpin, 1997). This is an alternative to viewing it as a panmictic population where every individual would have an equal chance of interacting with every other individual. Within a metapopulation framework, populations can persist regionally while a series of repeated extinction and colonization events occur locally (Levins, 1969). Because of this recolonization, a set of distinct subpopulations could persist longer than a single panmictic population when dispersal is high enough. However, if subpopulation dynamics are highly correlated to one another through a very high dispersal rate, recolonization would be unlikely to rescue an extinct subpopulation because neighboring subpopulations would be nearing extinction themselves (Heino et al., 1997). Overall, metapopulations tend to persist longest when dispersal rates are intermediate (Casagrandi and Gatto, 2006; Yaari et al., 2012). For pest management, this metapopulation context could be crucial, as recolonization of a locally extinct subpopulation might foil control efforts. Therefore, population suppression strategies within this context should emphasize techniques that limit the potential for recolonization.

To address how population structure could affect eradication of an invasive mammal from an island ecosystem with gene drive technology, I expand a previous model of gene drive assisted eradication (Backus and Gross, 2016) to incorporate metapopulation dynamics. In the original model, house mice (*M. musculus*) are engineered to carry a gene drive that alters offspring sex ratios. These mice are released into a population that is closed and panmictic. Depending on the relative survival of the engineered mouse compared to the wild population, the gene drive could either eradicate the population following a single release or require repeated releases over time. Within a metapopulation context, I determine how migration rates, number of patches, and patch connectedness can influence eradication success and efficiency. Additionally, I explore how eradication efficiency is affected by how evenly the gene drive is released onto the island. Lastly, I test the effectiveness of the gene drive over a range of randomly generated metapopulations. I use these random metapopulations to determine whether gene drives can remain successful

when certain patches are inaccessible.

4.2 Methods

4.2.1 Gene drive mouse

Within this paper, I focus on the eradication of an invasive *M. musculus* population with a recently proposed cisgenic gene drive construct (Campbell et al., 2015; Backus and Gross, 2016; Piaggio et al., 2017), engineered by linking two naturally occurring *M. musculus* genes that are not normally linked in the wild. First, the "sex-determining region (of the) Y" (*Sry*) gene is an essential component in testes development, though it has no known role in spermatogenesis (Goodfellow and Lovell-Badge, 1993). Mice with two X chromosomes, which would usually develop as females, can be engineered to develop as males when they carry a copy of the *Sry* gene on an autosome. However, these engineered XX males would be sterile, lacking the ability to produce sperm (Koopman et al., 1991). The other gene in this gene drive construct is the *t*-haplotype (Dobrovolskaia-Zavadskaia and Kobozieff, 1927), which distorts transmission in male mice such that fathers with one copy of the *t*-haplotype can pass that copy of the *t*-haplotype to over 90% of their offspring (Bauer et al., 2005). Linking the *Sry* gene and the *t*-haplotype together would cause most of the offspring of a genetically engineered father either to carry the GE construct or to be sterile.

Generally, this gene drive would not be expected to persist or eradicate a population because the gene drive would likely carry a fitness cost and because transmission distortion would not be complete (Backus and Gross, 2016). To eradicate the population, the gene drive would need to be repeatedly released into the population to overcome the overall fitness disadvantage. In this situation, the gene drive would considered self-limiting (Alphey, 2014). However, the engineered gene drive mice could be backcrossed with mice from a highly competitive wild population. Theoretically, this backcrossing could give the gene drive mice a relative fitness

advantage over a weakly competitive wild mouse population. If this advantage is large enough, the gene drive might be able to spread through and eradicate a population with a single release (Backus and Gross, 2016). In this situation the gene drive would be considered self-sustaining (Alphey, 2014).

4.2.2 Model

I constructed a stochastic, continuous-time Markov chain metapopulation model adapted from the gene drive mouse eradication model described in Backus and Gross (2016). This original model is a system of ordinary differential equations that describes how releasing gene drive mice into a population can impact mouse population density and population genetics over time. In the derived model I retain the basic ecological dynamics, but replace population density with population size, separate the population into a finite number of distinct subpopulations, and allow for demographic stochasticity.

This multi-patch model consists of a full island population subdivided into H distinct patches. Each patch $k \in \{1, .., H\}$ has a subpopulation of mice separated by sex and genotype into four different groups. These groups of mice are represented as discrete abundances with state variables $F_k(t)$ for wild-type females, $M_k(t)$ for wild-type males, $G_k(t)$ for gene drive males, and $S_k(t)$ for sterile males carrying the gene drive. Additionally, I define $N_k(t) = F_k(t) + M_k(t) + G_k(t) + S_k(t)$ as the total subpopulation size in patch k. These state variables change over time with events randomly generated using the so-called Gillespie algorithm (Doob, 1942; Kendall, 1950; Bartlett, 1953; Gillespie, 1976). Details of each event type are described below.

4.2.2.1 Events

4.2.2.1.1 Demographic events

At any given point in time, the next demographic event occurs at the end of an exponentially distributed time interval that depends on the number of mice in the population at the time. To satisfy the Markov property, the expected time interval between these demographic events is updated each time the metapopulation changes.

Assuming there is at least one male and one female in a subpopulation, the per capita birth rate is $a_1 > 0$ per month. At high female densities, female mice go into estrus less often (Vandenbergh, 1987). I represent this density dependence by decreasing the per capita birth rate in a subpopulation by $a_2 > 0$ per female per month. Overall, a birth in subpopulation k occurs at a rate

$$\lambda_k = \begin{cases} 2(a_1 - a_2 F_k)F_k, & \text{if } M_k + G_k > 0 \\ 0, & \text{otherwise.} \end{cases} \tag{4.1}$$

With this gene drive system, the sex and genotype of the offspring depends on the genotype of the father, chosen randomly from the local males in the subpopulation. For simplicity, mate choice is simplified so that females have no preferential mating between male genotypes. Thus, there is a probability of $\frac{M_k}{M_k+G_k}$ that the offspring's father is a wild-type male and a probability of $\frac{G_k}{M_k+G_k}$ that its father is a gene drive male. If the father is wild-type, the offspring would be a wild-type female with a probability of $\frac{1}{2}$ and wild-type male with a probability of $\frac{1}{2}$. However, if the father is a gene drive male, there is an extra-Mendelian probability of $0.5 \leq \tau \leq 1$ that the gene drive would be inherited. Overall, the offspring of a gene drive father would be a wild-type male with a probability of $\frac{1}{2}(1-\tau)$, a wild-type female with a probability of $\frac{1}{2}(1-\tau)$, a gene drive male with probability of $\frac{\tau}{2}$, and a sterile male with a probability of $\frac{\tau}{2}$.

The base per capita death rate of a wild-type mouse in a subpopulation is $b_1 > 0$ per month. Because of limited resources, the per capita death rate increases by $b_2 > 0$ per mouse per month

as the total subpopulation size increases. Gene drive mice can have a different death rate than wild-type mice, quantified as a change in the death rate $c > -1$. Because genetically engineered organisms tend to carry a fitness cost (Catteruccia et al., 2003), the survival difference would likely increase the death rate $c > 0$. However, there is theoretical potential for gene drive mice to have a reduced death rate relative to the local wild population (Backus and Gross, 2016), in which case $c < 0$. Put together, the overall death rate of a subpopulation is

$$\mu = (b_1 + b_2 N)(F + M + (1 + c)(G + S)). \tag{4.2}$$

4.2.2.1.2 Dispersal

Like demographic events, dispersal between patches could be implemented as a random event that occurs at a specified rate. However, if dispersal rate is very high, it could be computationally expensive to simulate extremely frequent dispersal events. To reduce the computation time of metapopulations with high dispersal, I simplify the model so that dispersal only occurs at the end of every simulated month. At these time points, every individual in every subpopulation has an independent probability m of dispersing to another patch. The total number of individuals dispersing from patch k each month is generated from a binomial random variable with mean mN_k. Depending on the metapopulation's topology, some subset of other patches will be connected to patch k. Each of the individuals that do disperse from patch k migrate independently into any one of these connected patches with equal probability.

In this paper, I represent patch dispersal topology (or connectivity) with a graph theoretical approach (as in Gillarranz and Bascompte (2011); Grilli et al. (2015)). The full metapopulation is an unweighted, connected graph with H nodes. Each subpopulation is represented by a node and each dispersal connection is an edge connecting two nodes (Figure 4.1). By only considering connected graphs, I restrict the analysis to metapopulations where any individual in patch k could reach any other patch in a finite number of dispersal events. Even with

this restriction, there is an intractably large number of unique topologies for metapopulations with many patches (greater than $3 \cdot 10^{19}$ for $H = 16$ (Stein and Stein, 1967)). To restrict the analysis further, I first consider two boundary cases (as in Earn et al. (2000) and Yaari et al. (2012)) In the stepping stone topology, each patch is connected to only two other patches, forming a ring-shaped metapopulation (Figure 4.1.a). In the fully connected topology, each patch is connected to every other patch (Figure 4.1.b). I also consider a collection of topologies randomly generated from an Erdős-Rényi model (Erdős and Rényi, 1959) (Figure 4.1.c-d). These graphs are created by considering each of the possible $H(H-1)$ unique pair of nodes. An edge is formed between each of these pairs with a probability of β. For each of these individual randomly-generated topologies, metapopulation connectedness is quantified using the graph density metric (Hanneman and Riddle, 2005). This is defined as

$$\frac{2(\text{number of edges in graph})}{H(H-1)}. \tag{4.3}$$

4.2.2.1.3 Release of gene drive males

When the gene drive is repeatedly released into the metapopulation, a total of $\gamma \in \mathbb{N}_0$ gene drive males are added into the entire metapopulation at the beginning of every month (immediately after dispersal). Each patch k receives some proportion $0 \leq \rho_k \leq 1$ of the γ gene drive males during each release event (where $\sum_{i=1}^{H} \rho_k = 1$).

Whether they are released repeatedly or in a single pulse, gene drive males are released into the metapopulation in three different arrangements in this paper. With a balanced release of gene drive males, each patch receives the same number of gene drive males during each release event, or $\rho_k = \frac{1}{H}$ for each patch k. In an unbalanced release, one patch receives a larger proportion $\frac{H+1}{2H}$ of gene drive males and the rest of the patches receive a smaller proportion

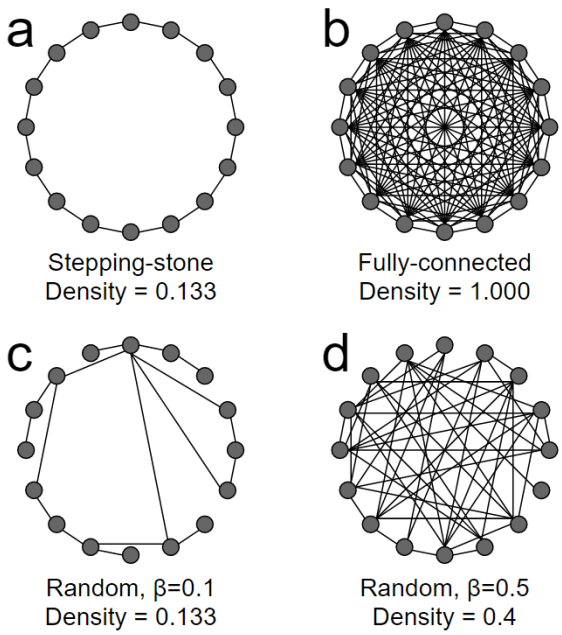

Figure 4.1 Metapopulation dispersal topology was determined with a graph theoretical approach. In this context, each node is a subpopulation. Any two subpopulations connected by an edge are directly connected through dispersal. Graph density is a simple measurement of how patches are connected to one another, defined in equation 4.3. (a) In a stepping stone metapopulation, an individual dispersing from any given patch can only migrate to one of two different neighboring patches. (b) In a fully-connected metapopulation, an individual dispersing from any given patch can migrate to any other patch with equal probability. (c-d) These metapopulations were generated as Erdős-Rényi random graphs. Each possible connection was formed with a probability of β.

$\frac{1}{2H}$. Lastly, with the all-in-one release strategy, all gene drive males are released into a single patch while no other patch receives any gene drive males. In this scenario, gene drive males can only enter non-target patches through dispersal events. For some simulations, I excluded certain patches from receiving any gene drive males during release. The gene drive males that would have been released into those excluded patches are randomly redistributed throughout the rest of the viable patches each at equal probability.

4.2.2.2 General simulation description

Each simulation of metapopulation eradication initially began with wild-type mice at a carrying capacity of $K_{mp} = 2^{10} = 1024$ mice in the total metapopulation. I chose this specific value because it can be divided evenly into $H = \{1, 2, 4, 8, 16\}$ patches, each with their own subpopulation carrying capacity of $K_k = K_{mp}/H$ mice. In the context of this model, the carrying capacity is the positive population size where only wild-type mice exist, the sex ratio is equal, and the birth rate is equal to the death rate. If every subpopulation has equal demographic parameters, I found that

$$\sum_{i=1}^{H}(\lambda_i - \mu_i) = 0 \tag{4.4}$$

when

$$K_{mp} = \sum_{i=1}^{H} K_i = \sum_{i=1}^{H} 2\left(\frac{a_1 - b_1}{a_2 + 2b_2}\right). \tag{4.5}$$

A simulation progresses by repeatedly generating events from the so-called Gillespie algorithm until it meets one of three stop conditions. One of these conditions, eradication, occurs as soon as no females exist in any of the subpopulations. When simulating a single release of gene drive males, a second stop condition, gene drive extinction, occurs as soon as no fertile gene drive males exist in any of the subpopulations. The final stop condition, non-eradication, occurs when $t > 600$, or 50 simulated years have passed and neither of the other stop conditions were met. This could be the result of the population reaching a coexistence equilibrium (Backus and Gross, 2016) or eradication taking too long to be practical.

4.2.2.3 Parameters

I used $a_1 = 0.7$ per month as the base per capita birth rate and $b_1 = 0.2$ per month as the base per capita death rate for each patch k. To scale density dependence so that the total island

carrying capacity is always $K_{mp} = 1024$ mice regardless of the number of subpopulations on the island (H), I used $a_2 = 8.7890625 \cdot 10^{-4} \cdot H$ per mouse per month and $b_2 = 4.8828125 \cdot 10^{-5} \cdot H$ per mouse per month. Throughout analysis, I kept $\tau = 0.95$ constant to represent a gene drive that has high, but not complete, transmission distortion. The remaining parameter values were selected to represent the range of qualitative behaviors that were found in the deterministic model. For each analysis, I selected specific values of survival cost c, release size γ, and release proportions ρ_k.

4.2.3 Analyses

4.2.3.1 One patch

I compared a single patch version of this stochastic metapopulation model to the deterministic model described in (Backus and Gross, 2016). This comparison was made to demonstrate whether the stochastic model reasonably resembles behaviors previously described in the deterministic model and to highlight any unique outcomes of stochasticity. For comparison, I assume that a unit of density from the deterministic model is equivalent to a single individual mouse in the stochastic model. Additionally, because the deterministic model can only asymptotically approach eradication or gene drive extinction, I use $F < 0.5$ and $G < 0.5$, respectively, as thresholds to determine analogous stopping stopping times in the deterministic model.

First, I simulated the population dynamics following a single release of gene drive males into a population of wild-type mice at carrying capacity. For each factorial combination of a range of survival costs ($c = -0.2$ to $c = 0.2$ by differences of 0.1) and initial gene drive release sizes (1 to 4048 mice by factors of 4), I simulated the stochastic model 1000 times and simulated the deterministic model once. I recorded the outcome of each simulation (from the stop condition that it met), and the time it took to reach this outcome.

Additionally, I simulated the population dynamics of repeatedly releasing gene drive males

into the population every month. For each factorial combination over a range of survival costs ($c = -0.2$ to $c = 0.2$ by differences of 0.2) and gene drive release rates (2 to 22 mice per month by differences of 2), I simulated the stochastic model 1000 times. I performed these simulations with the deterministic model as well, but with a finer set of continuous release rates between 0.01 and 22 mice per month (by differences of 0.01). Again, I recorded both the outcome of each simulation and the time it took to reach this outcome.

4.2.3.2 Two patches

To determine how migration and release arrangement would affect gene drive assisted eradication, I simulated a range of eradication attempts on a metapopulation consisting of two subpopulations. I was also interested in how these results might qualitatively change depending on whether eradication is driven by a single release of self-sustaining gene drive males or by repeatedly releasing self-limiting gene drive males. For both single release and repeated release scenarios, I picked representative cases where the population should be eradicated easily. When simulating single releases, I used 512 ($K_{mp}/2$) gene drive males with a survival advantage of $c = -0.2$. When simulating repeated releases, I used repeated pulse sizes of $\gamma = 64$ ($K_{mp}/16$) gene drive males every month with a survival cost of $c = 0.2$. For both types of gene drive eradication, I simulated the model 1000 times for each factorial combination over a range of dispersal probabilities ($m = 2^{-1}$ to $m = 2^{-12}$, decreasing in factors of 2) and three different release arrangements (balanced, unbalanced, and all-in-one). I recorded both the outcome of each simulation and the time it took to reach this outcome.

4.2.3.3 H patches

To determine how the number of patches in a metapopulation could impact eradication, I simulated eradication attempts divided into increasing numbers of separate subpopulations. With $H > 2$ patches, patch topology must also be considered, so I compared both stepping

stone and fully connected topologies (Figure 4.1.a,b). To reduce the complexity, I restricted the analysis to scenarios where gene drive males have a survival cost ($c = 0.2$) and are repeatedly released into the population in pulses of $\gamma = 64$ gene drive males. Instead of the larger set of dispersal rates from the previous analysis, I used a smaller set of high $m = 2^{-1}$, intermediate $m = 2^{-6}$, and low $m = 2^{-11}$ dispersal probabilities. I simulated the model 1000 times for each factorial combination of patch number, topology, release arrangement, and migration rate, and I recorded both the outcome of each simulation and the time it took to reach this outcome.

4.2.3.4 Random topologies and exclusion

Islands could have complex topography or undetected subpopulations, making it difficult to release gene drives into every subpopulation. In these cases, the dispersal and metapopulation topology could be crucial to determining how well the gene drive can reach and eradicate these excluded subpopulations. I was interested in what proportion of patches gene drive mice need to be released into to ensure eradication when population structure is unknown. To do so, I generated a set of connected 16-node random Erdős-Rényi graphs with edge connection probabilities randomly selected from a uniform distribution between $\beta = 0.1$ and $\beta = 0.5$. Then dispersal rates were randomly selected from 2^X where $X \sim \text{Uniform}(-1, -6)$. For each random metapopulation, a balanced release of 64 gene drive males per month was simulated until a stop condition was reached. Following this, eradication was simulated for the same metapopulation, but with a random patch excluded from gene drive release. This was repeated, excluding one additional random patch each time until all gene drive mice were released into the same patch. Using these simulations, I determined the maximum number of patches that could be excluded from each population while still yielding a successful eradication.

4.3 Results

4.3.1 One patch

With the one patch comparisons, the qualitative behavior of the stochastic model resembled the qualitative behavior of the deterministic model. First, when a single pulse of gene drive males was released into a population, the long-term behavior of the population largely depended on the gene drive survival cost in both deterministic and stochastic models. When at least sixteen gene drive males with a very high relative survival advantage ($c = -0.2$) were released into the population, that population is likely to be eradicated within 50 years in the stochastic model (Figure 4.2.a). This is similar to the deterministic model where any single release of gene drive males with a very high relative survival advantage ($c = -0.2$) eradicated the population within 50 years. When gene drive mice had a moderate relative survival advantage ($c = -0.1$), intermediate release sizes usually failed to eradicate the population within 50 years in the stochastic model (Figure 4.2.a). Similarly, when $c = -0.1$, the deterministic model always failed to eradicate the population after 50 years. When gene drive mice had neutral survival or survival disadvantages ($c \geq 0$), there was a high probability of gene drive extinction for all release sizes in the stochastic model (Figure 4.2.a). Comparatively, with these relative survival differences, the gene drive would always be lost from the population in the deterministic model. The models were notably different in the sensitivity of the overall outcome to initial gene drive single release size. In the deterministic model, the same outcome always occurred regardless of release size. With the stochastic model, larger releases were more likely to result in eradication and smaller releases were more likely to result in gene drive extinction. In both models, the release size of gene drive males had a qualitatively similar effect on the time it took to reach the long-term outcome. In cases where the population was eradicated, the eradication time decreased with increased release size (Figure 4.2.b). Also, in cases where the gene drive was

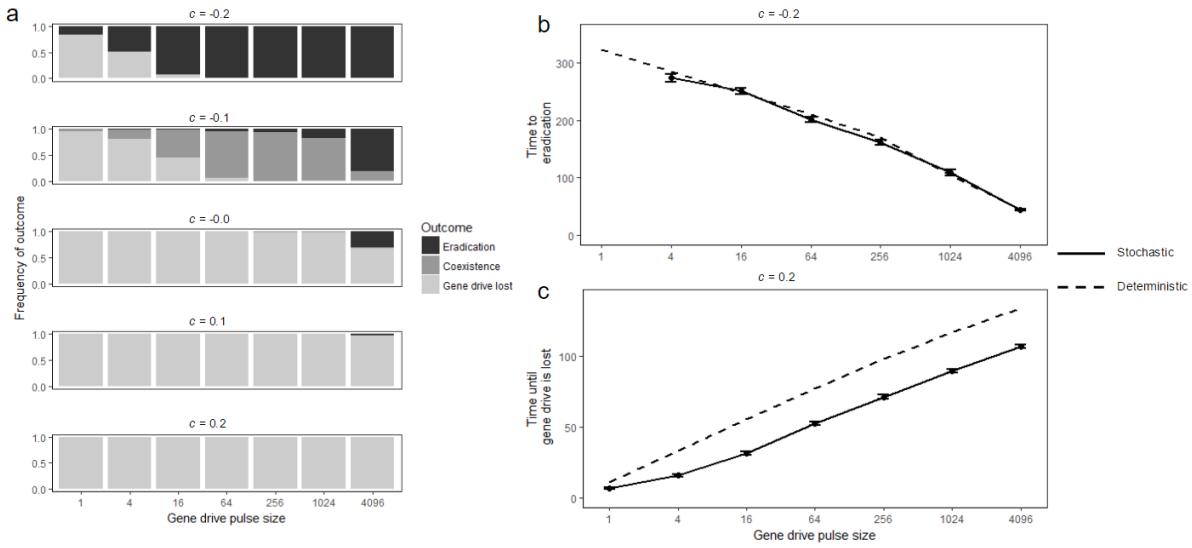

Figure 4.2 Simulation results following a single release of gene drive males into a single panmictic population. (a) The final outcome of the simulation depended on gene drive survival difference and pulse size. (b) Among the simulations where the gene drive had a survival advantage at $c = -0.2$ and the population was eradicated within 50 years, the mean eradication time (conditional on successful eradication) decreased as the gene drive release size increased for both the stochastic and deterministic models. A release of 1 gene drive male is not included since it occurred at a relatively low frequency. (c) Among the simulations where the gene drive had a survival difference cost at $c = 0.2$ and the population was eradicated within 50 years, the mean gene drive extinction time increased as the gene drive release size increased for the stochastic and deterministic models. Error bars represent 95% confidence intervals.

lost from the population, the gene drive extinction time increased with increased release size (Figure 4.2.c).

The long-term outcomes of both models were also similar when gene drives were repeatedly released into the population. With the deterministic model, the population was only eradicated when gene drive mice were released into the population above a critical release rate γ^* that depends on the relative survival of gene drive mice (Backus and Gross, 2016). In the stochastic model, probability of eradication increased as the release rate increased (Figure 4.3.a). Also in the stochastic model, non-eradication was the most probable outcome below the comparative deterministic γ^* and eradication was the most probable outcome above γ^*. Among the cases where the population was eradicated, the eradication time decreased with increased release rate for both models (Figure 4.3.b). Additionally, this eradication time was most sensitive to changes in release rate immediately above the critical release rate γ^*.

4.3.2 Two patches

A single release of 512 gene drive males with a survival advantage $c = -0.2$ into a two-patch metapopulation usually resulted in eradication, though all-in-one releases with very low migration rates were less successful (Table 4.1). Among these successful cases, eradication times were faster when dispersal was either low or high for either the balanced and unbalanced release arrangements. The greatest mean eradication time for either of these arrangements was at an intermediate dispersal probability (around $m = 2^{-8}$) (Figure 4.4.a). However, for the all-in-one release strategy, the mean eradication time increased as dispersal decreased. In general, the balanced release strategy eradicated the population faster than the unbalanced release, which was faster than the all-in-one release. All three release strategies converged at the highest dispersal rate $m = 0.5$, which had the minimum mean eradication time for each.

Repeatedly releasing 64 gene drive males with a survival disadvantage $c = 0.2$ into a two-patch metapopulation were always eradication for balanced and unbalanced release arrange-

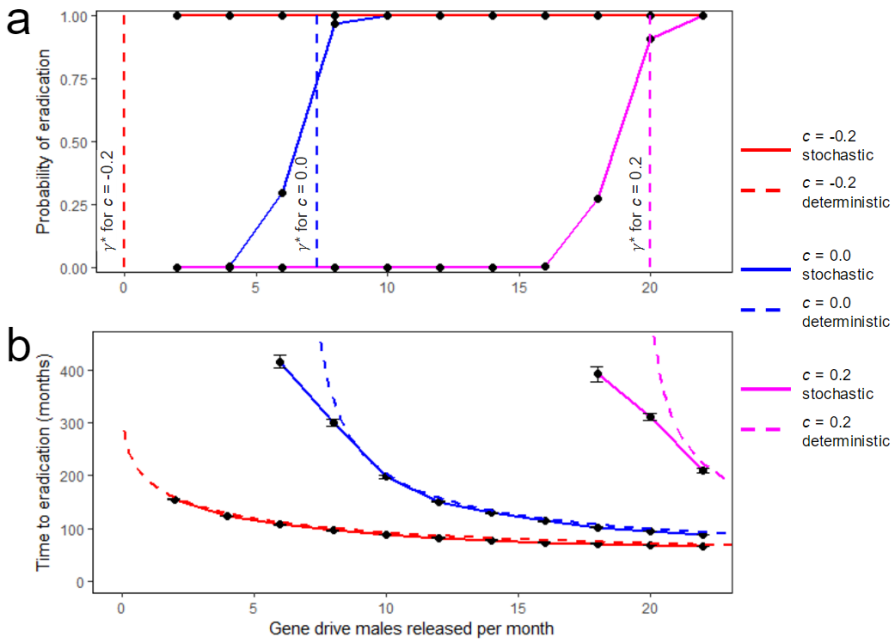

Figure 4.3 Simulation results following the repeated release of gene drive males into a single panmictic population. (a) Probability of eradication increased with higher release rates of gene drive males with a higher survival advantage. (b) Mean eradication time decreased with increased gene drive release rate. Error bars represent 95% confidence intervals.

Table 4.1 Eradication probabilities for single releases of 512 gene drive mice with a survival benefit $c = -0.2$ into two patches.

Dispersal	Balanced	Unbalanced	All-in-one
2^{-1}	0.993	0.994	0.995
2^{-2}	0.993	0.989	0.989
2^{-3}	0.986	0.986	0.989
2^{-4}	0.980	0.984	0.989
2^{-5}	0.983	0.977	0.984
2^{-6}	0.971	0.969	0.982
2^{-7}	0.977	0.960	0.957
2^{-8}	0.965	0.962	0.960
2^{-9}	0.967	0.962	0.951
2^{-10}	0.955	0.939	0.853
2^{-11}	0.966	0.956	0.560

Table 4.2 Eradication probabilities for repeated releases of 64 gene drive mice per month with a survival cost $c = 0.2$ into two patches.

Dispersal	Balanced	Unbalanced	All-in-one
2^{-1}	1	1	1
2^{-2}	1	1	1
2^{-3}	1	1	1
2^{-4}	1	1	1
2^{-5}	1	1	0.295
2^{-6}	1	1	0
2^{-7}	1	1	0
2^{-8}	1	1	0
2^{-9}	1	1	0
2^{-10}	1	1	0
2^{-11}	1	1	0

ments (Table 4.2). For the balanced release strategy, the mean eradication time was not affected by dispersal rate (Figure 4.4.b). With both the unbalanced and all-in-one release strategies, decreasing the dispersal rate increased the mean eradication time among simulations that resulted in eradication. The mean eradication time for the all-in-one release was most sensitive to decreasing dispersal rates and was unlikely to successfully eradicate the population when $m \leq 2^{-5}$ (Table 4.2). Again, the balanced release was quickest and the all-in-one strategy was slowest, and all three strategies converged at the highest dispersal rate of $m = 0.5$.

4.3.3 H patches

Each simulation in this set of simulations resulted in eradication. With repeated gene drive releases, the mean eradication time for balanced release arrangements was mostly not substantially affected by patch number, metapopulation topology, or dispersal rates (Figure 4.5). However, there was a slight increase in eradication at high patch numbers when dispersal was low and a slight decrease when dispersal was high. The mean eradication time of the unbalanced

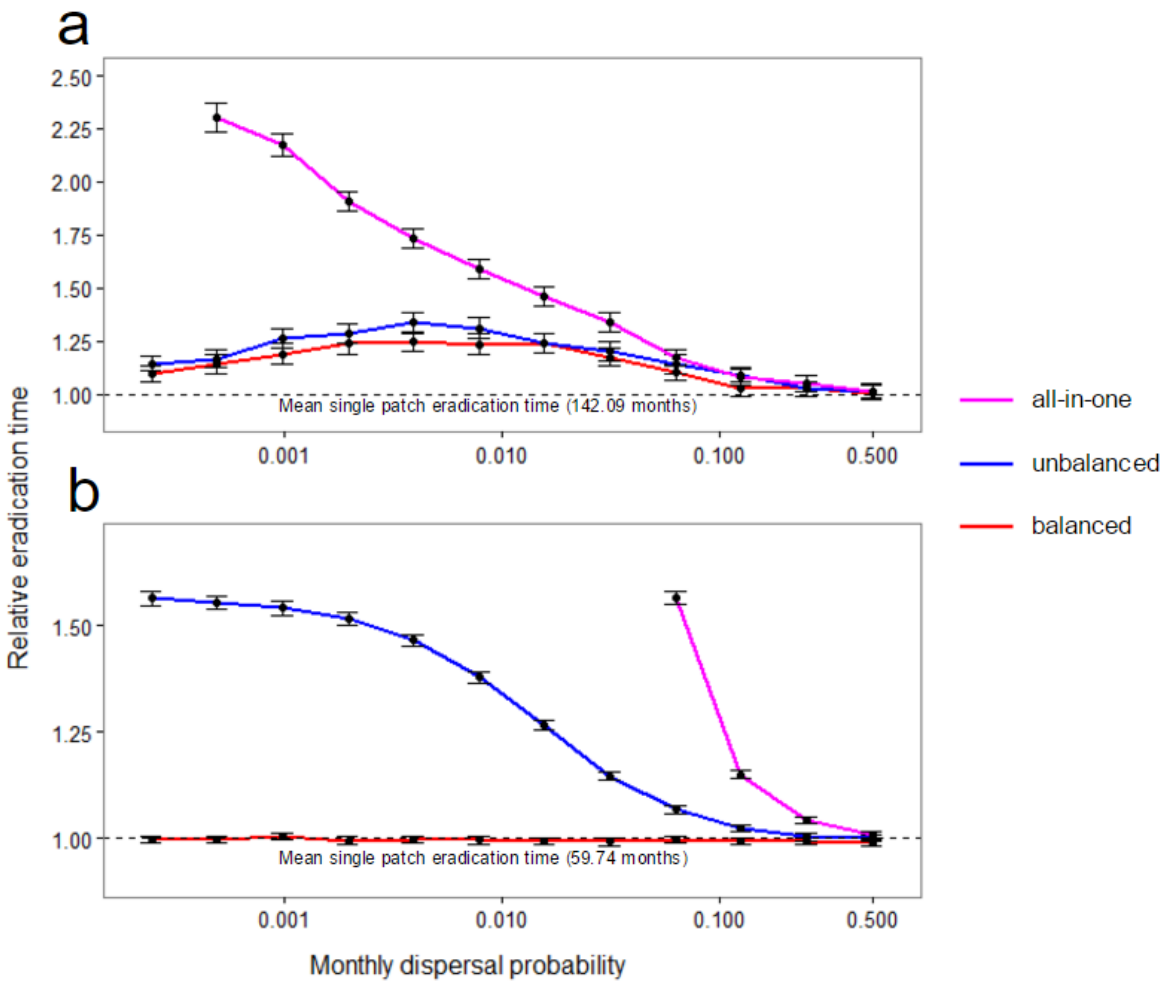

Figure 4.4 Mean eradication times of successful eradications relative to equivalent eradications of a single patch metapopulation. These eradication times are compared over dispersal probability (horizontal axis) and release strategy (line color). Error bars represent 95% confidence intervals. (a) Simulations following a single release of 512 gene drive males with a survival difference of $c = -0.2$. (b) Simulations of 64 gene drive males with a fitness difference of $c = 0.2$ being added to the metapopulation every month.

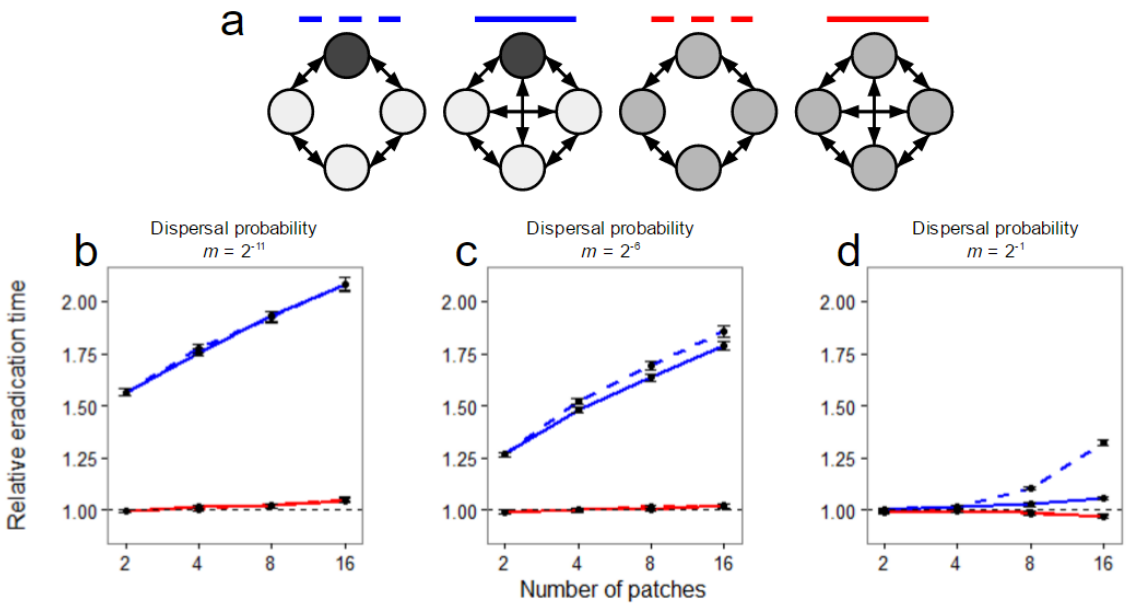

Figure 4.5 (a) Representation of four simulation designs for $H = 2, 4, 8, 16$ patches. In each simulation, 64 gene drive males with a survival cost $c = 0.2$ are released into the total metapopulation every month. Blue lines represent the unbalanced release arrangement where one patch receives $\left(\frac{H+1}{2H}\right) \cdot 64$ gene drive males per release and the other patches each receive $\left(\frac{1}{2H}\right) \cdot 64$ gene drive males per release. Red lines represent the balanced release arrangement where every patch receives $\frac{64}{H}$ gene drive males per release. Dashed lines represent a stepping-stone metapopulation toplogy while solid lines represent a fully-connected topology. (b-d) The mean eradication time of these four release strategies as it changed over the number of patches in the metapopulation relative to a single patch metapopulation. Each subsequent panel has a set of comparisons with increasing dispersal probabilities. Error bars represent 95% confidence intervals.

arrangement was always at least as long as the balanced arrangement, if not longer, for all parameter combinations. Also, the mean eradication time of unbalanced release was greater when the metapopulation had lower dispersal and more patches. Lastly, the eradication was slower with the stepping-stone topology than with the fully-connected topology. This effect of topology was greater with higher probability of dispersal and more patches in the metapopulation.

4.3.4 Random topologies and exclusion

With frequent dispersal and highly connected patches, a metapopulation could often be eradicated even if gene drive males are only released into a few patches (Figure 4.6.a). On the other extreme, when dispersal was low and metapopulation connection density was low, eradication was usually only possible when gene drive males were released into nearly every patch. In general, when the dispersal rate was lower, gene drive males needed to be released into more patches to ensure eradication. Similarly, when the metapopulation had lower connection density, gene drive males needed to be released into more patches to ensure eradication. Metapopulation topology was most influential to this minimum patch number when dispersal rates were higher (Figure 4.6.b).

4.4 Discussion

Eradication with gene drives should be most effective when gene drives are repeatedly released evenly throughout the full extent of the metapopulation. While this may not have be surprising, it is intriguing that the balanced release strategy was not strongly affected by dispersal rate, metapopulation topology, or the number of patches in the the metapopulation. More importantly, this balanced release strategy serves as an ideal point of comparison for limitations that might arise. Intriguingly, the unbalanced release arrangement was ultimately sufficient to eventually eradicate a metapopulation in most scenarios but its speed was more reliant on dispersal, topology, and number of patches.

While a balanced release might be desired, there are several reasons that it might not be possible to employ in practice. Especially on larger islands, it could be impractical and expensive to release the gene drive evenly throughout the entire extent of a population. When islands have steep cliffs, hills, mountains, or other complex topography, it could be difficult, if not impossible to reach certain subpopulations. Prior to eradication attempts, great effort is generally expended

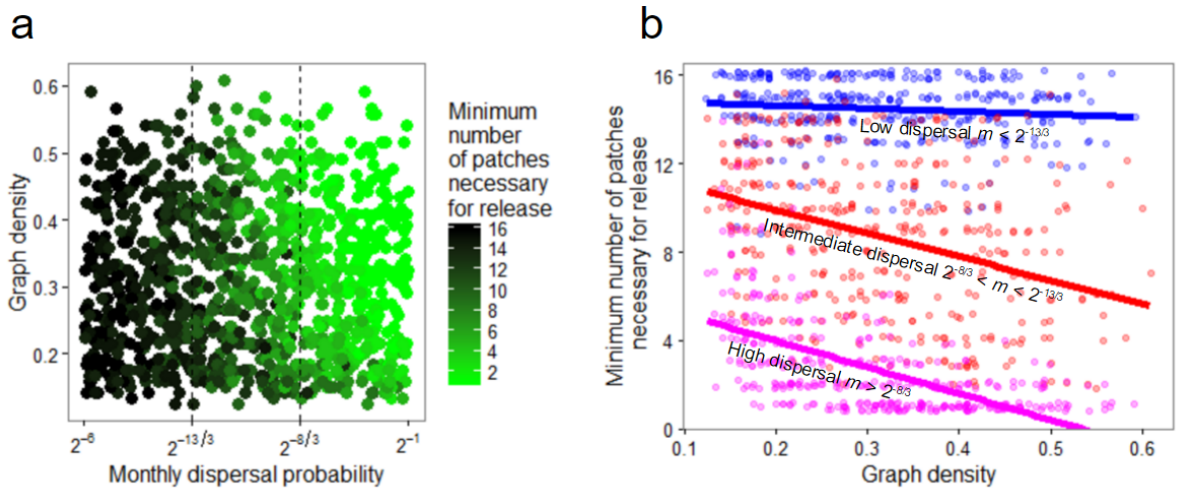

Figure 4.6 Summary of random exclusion simulations. In each simulation, 64 gene drive males with a survival cost $c = 0.2$ are released into the total metapopulation every month. (a) Each point represents the minimum number of patches necessary for release in a single randomly generated graph. Points that are shaded closer to the black end of the spectrum required release into nearly every patch in the metapopulation. Points that are shaded closer to the green end of the spectrum were possible to eradicate by releasing into very few patches. Dashed vertical lines delineate the three different levels of dispersal rate shown in the following panel. (b) As metapopulation connection density increased, the minimum number of patches necessary for release decreased. Each point represents the same set of random metapopulations from (a). While this effect was weak at low dispersal rates (blue), it is stronger for intermediate (red) and high (magenta) dispersal rates. Trendlines represent simple linear regression.

surveying small invasive mammal densities in various habitats throughout the spatial scale of an island (Russell et al., 2008; Ringler et al., 2014; Pott et al., 2015). However, detection is not always perfect with these methods, possibly leading to eradication failure (Howald et al., 2007). In any of these situations, gene drives could still be released into a representative subset of locations on the island. The success of this subset strategy would depend on the the ability of gene drive males to disperse to each of the un-targeted areas. Thus, if dispersal rates are low or patches are only weakly connected to one another, eradication could take substantially longer or even be unsuccessful.

One of the proposed benefits of gene drive eradication over a more traditional chemical toxicant driven approach is the ability to use it on an inhabited island without risk of chemical exposure (Campbell et al., 2015). Several invasive species subpopulations would likely live in and around human built structures (Oppel et al., 2011; Glen et al., 2013). If gene drive rodents were released into these areas, the rodent population density would temporarily increase above usual levels for some time (see Backus and Gross (2016)). These large increases in rodent density could pose a health risk to the public (Meerberg et al., 2009; Oppel et al., 2011) and make it difficult to achieve public support. To avoid this, one could consider excluding human developed areas from receiving releases of gene drive males so that rodents in developed areas would only be exposed to the gene drive through immigration from undeveloped areas. While this might limit the exposure of humans to rodents, the full island eradication would become dependent on dispersal. Ultimately, this would increase eradication time and could even cause eradication to be unsuccessful.

In a deterministic and panmictic population Backus and Gross (2016) demonstrated that if it is possible to engineer and breed gene drive rodents with a moderate competitive advantage over the wild population, the gene drive could theoretically spread through and eradicate a population with a single release. While this self-sustaining behavior could allow for effective eradication with minimal effort, it would be problematic if a gene drive escaped from the

island to a mainland population, potentially leading to widespread extinction events (Esvelt et al., 2014; Backus and Gross, 2016). Using gene drive rodents with an increased survival rate ($c = -0.2$), I have shown that this self-sustaining behavior remains possible within a stochastic metapopulaton context, though with a few notable exceptions. Because of demographic stochasticity, a very small single release of gene drive males is unlikely to eradicate a population. Fortunately, it is unlikely that this demographic stochasticity would be a major hindrance to eradication efforts, as eradication is around 90% probable when the release size is only increased to 16 gene drive males. Moreover, because it would be difficult for gene drive males to escape to mainland populations in large numbers, this demographic stochasticity would likely reduce the risk of escaped gene drive rodents to cause widespread extinction.

Interestingly, single releases of the self-sustaining gene drive were least effective when dispersal between patches occurred with an intermediate probability. Several other stochastic models suggest that metapopulations also tend to persist longest when dispersal occurs at intermediate rates (Harrison, 1991; Yaari et al., 2012; Casagrandi and Gatto, 2006). In these intermediate cases, dispersal is low enough that subpopulation dynamics are mostly independent from one another, lowering the chance that the extinction of neighboring subpopulations coincide. At the same time, if one subpopulation does become locally extinct, dispersal is high enough that individuals from neighboring patches would be likely to recolonize the extinct subpopulation. This recolonization of wild-type individuals from dissimilar subpopulations may have prolonged the persistence of the metapopulation in the single release simulations in this paper. Even though a self-sustaining gene drive could theoretically spread to eradication on its own, multiple releases of the gene drive could help to overcome the recolonization problem. By forcing each subpopulation to repeatedly receive the same influx of gene drive males, these subpopulations would be more likely to reach local eradication at similar times.

Because self-limiting gene drives are easier to control, they might be more likely than a self-sustaining variation to be implemented in the field (Alphey, 2014). However, a self-limiting

eradication gene drive would require high release rates and long eradication times. The complications of population structure could add to the list of drawbacks to self-limitation. Especially in metapopulations with low dispersal rates and low subpopulation connectedness, failing to release the gene drive into certain subpopulations could be detrimental to eradication efforts. These self-limiting gene drives cannot persist in a population without being replaced by repeated releases of gene drive males above some critical release rate. Any subpopulations that are excluded would also need to maintain that minimum rate entirely through dispersal without any direct releases. However, subpopulation exclusion would be less problematic when the gene drive is self-sustaining. Because a small number of individuals with a self-sustaining gene drive could eradicate a population without repeated releases, excluded subpopulations could be eradicated even when dispersal is rare. Overall, this might provide more incentive to develop self-sustaining gene drive eradication techniques.

While these results could be helpful when considering gene drive eradication within a spatial context, it is important to emphasize that these conclusions are not universal to all island ecosystems. Realistic population structures will be more complex and cryptic than the model presented in this paper. For example, males and females could disperse at different rates (Gerlach, 1996) and patch size and density are likely to be more heterogeneous (Ringler et al., 2014; Pott et al., 2015). However, these results suggest that gene drives can be a successful eradication tool in a variety of population structures as long as most areas are accessible to release or dispersal. Regardless, the self-dispersal of the gene drives should allow them to reach a wider spatial extent than chemical-based approaches.

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Appendices

Appendix A

Model formulation of eradication with *t-Sry* mice

The model described in equations 2.1-2.3 of the main text can be derived from a logistic growth model with a few modifications to describe *t-Sry* mouse dynamics. We build the model with four state variables of density, separated by sex chromosomes and genotype at the *t-Sry* locus (W_X: XX wild-type; W_Y: XY wild-type; G_Y: XX *t-Sry*; G_X: XY *t-Sry*). Refer to Table A.1 within this supplement for further description of the state variables and parameters that are used.

A.1 Wild-type only

First, we describe the model when only wild-type mice are present ($W_X > 0$, $W_Y > 0$, $G_X = G_Y = 0$) and *t-Sry* mice are not being added to the population ($\mu = 0$). Because the dynamics of birth and death need to be distinct later in the model construction, we separate the traditional growth rate r and carrying capacity K into smaller components. Density dependence in birth rate is determined by only the density of females in the population. Thus, $a_1 > 0$ is

the baseline per-capita birth rate of females (or males) and $a_2 > 0$ is the rate at which this per-capita birth rate declines with increasing female density. Density dependence on the death rate depends on the total population density. Thus, $b_1 > 0$ is the baseline per-capita death rate and $b_2 > 0$ is the rate at which the per -capita death rate increases with increasing density. In this situation, the population dynamics are described with just the two equations

$$\frac{dW_X}{dt} = (a_1 - a_2 W_X)W_X - (b_1 + b_2 N)W_X \tag{A.1}$$

$$\frac{dW_Y}{dt} = (a_1 - a_2 W_X)W_X - (b_1 + b_2 N)W_Y. \tag{A.2}$$

If we assume an equal sex ratio $W_X = W_Y$, we can derive the logistic growth equation (Verhulst, 1838). In this situation, $N = W_X + W_Y = 2W_X$. Thus,

$$\begin{aligned}
\frac{dN}{dt} &= \frac{d}{dt}(W_X + W_Y) = 2\frac{dW_X}{dt} \\
&= 2(a_1 - a_2 W_X)W_X - 2(b_1 + b_2 N)W_X \\
&= \left(a_1 - a_2 \frac{N}{2}\right) N - (b_1 + b_2 N)N \\
&= (a_1 - b_1)N - \left(\frac{a_2}{2} + b_2\right) N^2 \\
&= (a_1 - b_2)N \left(1 - \left(\frac{\frac{a_2}{2} + b_2}{a_1 - b_1}\right) N\right).
\end{aligned} \tag{A.3}$$

We then define the parameters

$$r = a_1 - b_1 \tag{A.4}$$

and

$$K = \frac{a_1 - b_1}{\frac{a_2}{2} + b_2} = 2\left(\frac{a_1 - b_1}{a_2 + 2b_2}\right). \tag{A.5}$$

Substituting these parameters into the previous equation, we have the logistic growth model

$$\frac{dN}{dt} = rN\left(1 - \frac{N}{K}\right). \tag{A.6}$$

A.2 Wild-type and *t-Sry* mice

Next, we describe a model that accounts for the presence of *t-Sry* mice ($G_X > 0$, $G_Y > 0$) and the release of *t-Sry* mice into the population ($\mu \geq 0$). Because all fertile females in the population are wild-type, all offspring that are born must inherit a wild-type allele from their mother. The other allele at the *t-Sry* locus depends on the father's genotype. All offspring that result from a mating between two wild-type parents results in wild-type offspring (half being XX and half being XY) (Table A.2). On the other hand, offspring from a *t-Sry* father can be either wild-type or *t-Sry*. In particular, a frequency $0.5 \leq \tau \leq 1$ of offspring will be *t-Sry* and $1 - \tau$ will be wild-type (in either case, half are XX and the other half are XY) (Table S2).

Death rates in *t-Sry* mice are similar to death rates in wild-type mice, except *t-Sry* death rates are multiplied by $1 + c$. *t-Sry* mice have decreased survival when $c > 0$ and increased survival when $c < 0$.

Lastly, XY *t-Sry* mice are continuously added into the population at a rate of μ per month. Altogether, the change in density over time is

$$\frac{dW_X}{dt} = (a_1 - a_2W_X)\left(\frac{W_Y}{W_Y + G_Y}\right)W_X \quad +(1-\tau)(a_1 - a_2W_X)\left(\frac{G_Y}{W_Y + G_Y}\right)W_X - (b_1 + b_2N)W_X \tag{A.7}$$

$$\frac{dW_Y}{dt} = (a_1 - a_2W_X)\left(\frac{W_Y}{W_Y + G_Y}\right)W_X \quad +(1-\tau)(a_1 - a_2W_X)\left(\frac{G_Y}{W_Y + G_Y}\right)W_X - (b_1 + b_2N)W_Y \tag{A.8}$$

$$\frac{dG_X}{dt} = \tau(a_1 - a_2W_X)\left(\frac{G_Y}{W_Y + G_Y}\right)W_X - (1+c)\,(b_1 + b_2N)\,G_X \tag{A.9}$$

$$\frac{dG_Y}{dt} = \underbrace{\qquad\qquad}_{\text{birth rate from wild-type fathers}} \quad \underbrace{\tau(a_1 - a_2W_X)\left(\frac{G_Y}{W_Y + G_Y}\right)W_X}_{\text{birth rate from } t\text{-}Sry \text{ fathers}} - \underbrace{(1+c)\,(b_1 + b_2N)\,G_Y}_{\text{death rate}} + \underbrace{\mu}_{\text{release rate}}. \tag{A.10}$$

A.3 Three equation model

To simplify this model to three equations, we can assume an initial equal sex ratio of male and female wild-type mice on the island. Any wild-type population that does not have an equal sex ratio would eventually approach an equal sex ratio, as $W_X = W_Y = \frac{K}{2}$ is the only stable attracting fixed point where wild mice maintain a positive population. Under this assumption $W_X = W_Y$ and $\frac{dW_X}{dt} = \frac{dW_Y}{dt}$. Therefore, we only need to analyze one of these variables to understand both. Additionally, we rewrite this model by defining two additional state variables adapted from the previous variables. First, the total population is defined as $N = W_X + W_Y + G_X + G_Y$. Second, the frequency of *t-Sry* mice in the reproductive male population is defined as $\phi = \frac{G_Y}{W_Y+G_Y}$.

Below, we demonstrate a more detailed step-by-step process of reformulating the model. Equations A.7-A.10 are reformulated to 2.1 (main text),

$$
\begin{aligned}
\frac{dN}{dt} &= \frac{dW_X}{dt} + \frac{dW_Y}{dt} + \frac{dG_X}{dt} + \frac{dG_Y}{dt} \\
&= (a_1 - a_2W_X)\left(\frac{W_Y}{W_Y+G_Y}\right)W_X + (1-\tau)(a_1 - a_2W_X)\left(\frac{G_Y}{W_Y+G_Y}\right)W_X - (b_1 + b_2N)W_X \\
&\quad + (a_1 - a_2W_X)\left(\frac{W_Y}{W_Y+G_Y}\right)W_X + (1-\tau)(a_1 - a_2W_X)\left(\frac{G_Y}{W_Y+G_Y}\right)W_X - (b_1 + b_2N)W_Y \\
&\quad + \tau(a_1 - a_2W_X)\left(\frac{G_Y}{W_Y+G_Y}\right)W_X - (1+c)\,(b_1 + b_2N)\,G_X \\
&\quad + \tau(a_1 - a_2W_X)\left(\frac{G_Y}{W_Y+G_Y}\right)W_X - (1+c)\,(b_1 + b_2N)\,G_Y + \mu \\
&= 2(a_1 - a_2W_X)\left(\frac{W_Y+G_Y}{W_Y+G_Y}\right)W_X \\
&\quad - (b_1 + b_2N)(W_X + W_Y - (1+c)(G_X + G_Y)) + \mu \\
&= 2(a_1 - a_2W_X)W_X - (b_1 + b_2N)(2W_X - (1+c)(N - 2W_X)) + \mu \\
&= 2\left((a_1 - a_2W_X)W_X - (b_1 + b_2N)\left(W_X + (c+1)\left(\frac{N}{2} - W_X\right)\right)\right) + \mu.
\end{aligned}
\tag{A.11}
$$

Equation A.7 is rewritten as Equation 2.2 (main text) using only the state variables N, W_X, and ϕ,

$$\begin{aligned}
\frac{dW_X}{dt} &= (a_1 - a_2 W_X)\left(\frac{W_Y}{W_Y + G_Y}\right) W_X + (1-\tau)(a_1 - a_2 W_X)\left(\frac{G_Y}{W_Y + G_Y}\right) W_X - (b_1 + b_2 N) W_X \\
&= (a_1 - a_2 W_X)\left(\frac{W_Y + (1-\tau) G_Y}{W_Y + G_Y}\right) W_X - (b_1 + b_2 N) W_X \\
&= (a_1 - a_2 W_X)((1-\phi) + (1-\tau)\phi) W_X - (b_1 + b_2 N) W_X \\
&= \left((a_1 - a_2 W_X)(1 - \tau\phi) - (b_1 + b_2 N)\right) W_X. \qquad \text{(A.12)}
\end{aligned}$$

Equations A.8 and A.10 are rearranged to form Equation 2.3 (main text) using the quotient rule of differentiation,

$$\begin{aligned}
\frac{d\phi}{dt} &= \frac{(W_Y + G_Y)\frac{dG_Y}{dt} - G_Y\left(\frac{dW_Y}{dt} + \frac{dG_Y}{dt}\right)}{(W_Y + G_Y)^2} \\
&= \frac{1}{W_Y + G_Y}\left(\frac{dG_Y}{dt} - \phi\left(\frac{dW_Y}{dt} + \frac{dG_Y}{dt}\right)\right) \\
&= \frac{1-\phi}{W_X}\left((1-\phi)\frac{dG_Y}{dt} - \phi\frac{dW_Y}{dt}\right) \\
&= \frac{1-\phi}{W_X}\left((1-\phi)\left((a_1 - a_2 W_X)\tau\phi W_X - (1+c)\left(b_1 + b_2 N\right) G_Y + \mu\right)\right. \\
&\qquad \left. - \phi\left((a_1 - a_2 W_X)(1-\tau\phi) W_X - (b_1 + b_2 N) W_Y\right)\right) \\
&= (a_1 - a_2 W_X)(1-\phi)\left(\tau(1-\phi)\phi - \phi(1-\tau\phi)\right)(1-\phi) \\
&\quad - (b_1 + b_2 N)((1-\phi)\phi(1+c) - \phi(1-\phi)) + (1-\phi)\mu\left(\frac{1-\phi}{W_X}\right) \\
&= (1-\phi)\phi(a_1 - a_2 W)(\tau - 1) - (1-\phi)\phi(b_1 - b_2 N)c + \mu\frac{(1-\phi)^2}{W_X} \\
&= -\left((1-\tau)(a_1 - a_2 W_X) + c(b_1 + b_2 N)\right)(1-\phi)\phi + \mu\frac{(1-\phi)^2}{W_X}. \qquad \text{(A.13)}
\end{aligned}$$

Table A.1 Descriptions of all state variables and parameters used in the model

State variable	Description
W_X	XX wild-type density
W_Y	XY wild-type density
G_X	XX *t-Sry* density
G_Y	XY *t-Sry* density
N	Total population density
ϕ	Frequency of *t-Sry* males
Parameter	**Description**
a_1	Baseline per capita birth rate
a_2	Strength of density dependence on birth rate
b_1	Baseline per capita death rate
b_2	Strength of density dependence on death rate
c	Change in death rate of *t-Sry* mice
τ	Transmission distortion of *t*-haplotype
μ	Release rate of fertile *t-Sry* mice

Table A.2 Birth rate of each offspring type (or total population) separated by the genotype of the father.

Offspring	Wild-type father	*t-Sry* father
XX wild-type: W_X	$(a_1 - a_2 W_X)\left(\frac{W_Y}{W_Y+G_Y}\right) W_X$	$(1-\tau)(a_1 - a_2 W_X)\left(\frac{G_Y}{W_Y+G_Y}\right) W_X$
XY wild-type: W_Y	$(a_1 - a_2 W_X)\left(\frac{W_Y}{W_Y+G_Y}\right) W_X$	$(1-\tau)(a_1 - a_2 W_X)\left(\frac{G_Y}{W_Y+G_Y}\right) W_X$
XX *t-Sry*: G_X	0	$\tau(a_1 - a_2 W_X)\left(\frac{G_Y}{W_Y+G_Y}\right) W_X$
XY *t-Sry*: G_Y	0	$\tau(a_1 - a_2 W_X)\left(\frac{G_Y}{W_Y+G_Y}\right) W_X$
Total: N	$2(a_1 - a_2 W_X)\left(\frac{W_Y}{W_Y+G_Y}\right) W_X$	$2(a_1 - a_2 W_X)\left(\frac{G_Y}{W_Y+G_Y}\right) W_X$

Appendix B

Discrete release pulses of *t-Sry* mice

A potential downside to eradication using *t-Sry* mice is that it requires the addition of more mice to the population. This would cause the population to increase above its carrying capacity, which would likely temporarily increase the ecological impact of mice on the island ecosystem. Therefore, this technique has the potential to cause more damage to ecosystems that it was meant to protect. We perform simulations of this model to quantify some of these ecological impacts. In Chapter 2, we consider eradications with a continuous release rate, as this scenario is easier to analyze mathematically. However, a realistic eradication schedule would involve multiple separated releases over time. Therefore, we also compare a separate approach where mice are periodically released in discrete pulses.

Simulations of discrete release pulses of *t-Sry* mice are run similarly to the continuous release in section 2.3.2. Because multiple releases would be most necessary when the *t-Sry* construct is self-limiting, we restrict the discrete release analysis to the case where $c = 0.1 > c_2^*$. Pulses of XY *t-Sry* mice are added into the population at specific intervals until wild-type females are nearly eradicated ($W_X < 0.05$). To keep these simulations comparable to a continuous release, the density of mice released per pulse and the interval length can be adjusted such that they have the same average monthly release rate, μ_{av}.

When *t-Sry* mice are released in frequent pulses, dynamics behave much like the continuous release scenarios. As releases become more infrequent, however, eradications take longer to complete despite the average monthly release rate being equivalent (Figure B.1). Increasing the time between releases further shows that there is a limit to the amount of time between releases that could result in a successful eradication. This maximum time between releases occurs because of the self-limiting nature of the *t-Sry* construct in these examples. The *t-Sry* mice that are added in a particular release pulse could be mostly lost from the population before the next pulse is released. Therefore, the population density would rebound, undoing the effect of suppression. This maximum time between releases increases as the average monthly release rate (μ_{av}) increases.

For transient impact metrics, discrete releases are similar to continuous releases when there are only short intervals between each release. However, all of these metrics increase as the time between releases increases. They continue to increase until they reach the maximum amount of time between releases. Overall, increasing the time between releases also increases the time it would take for a successful eradication (Figure B.1), the number of mice that need to be released, the maximum density, and the population excess.

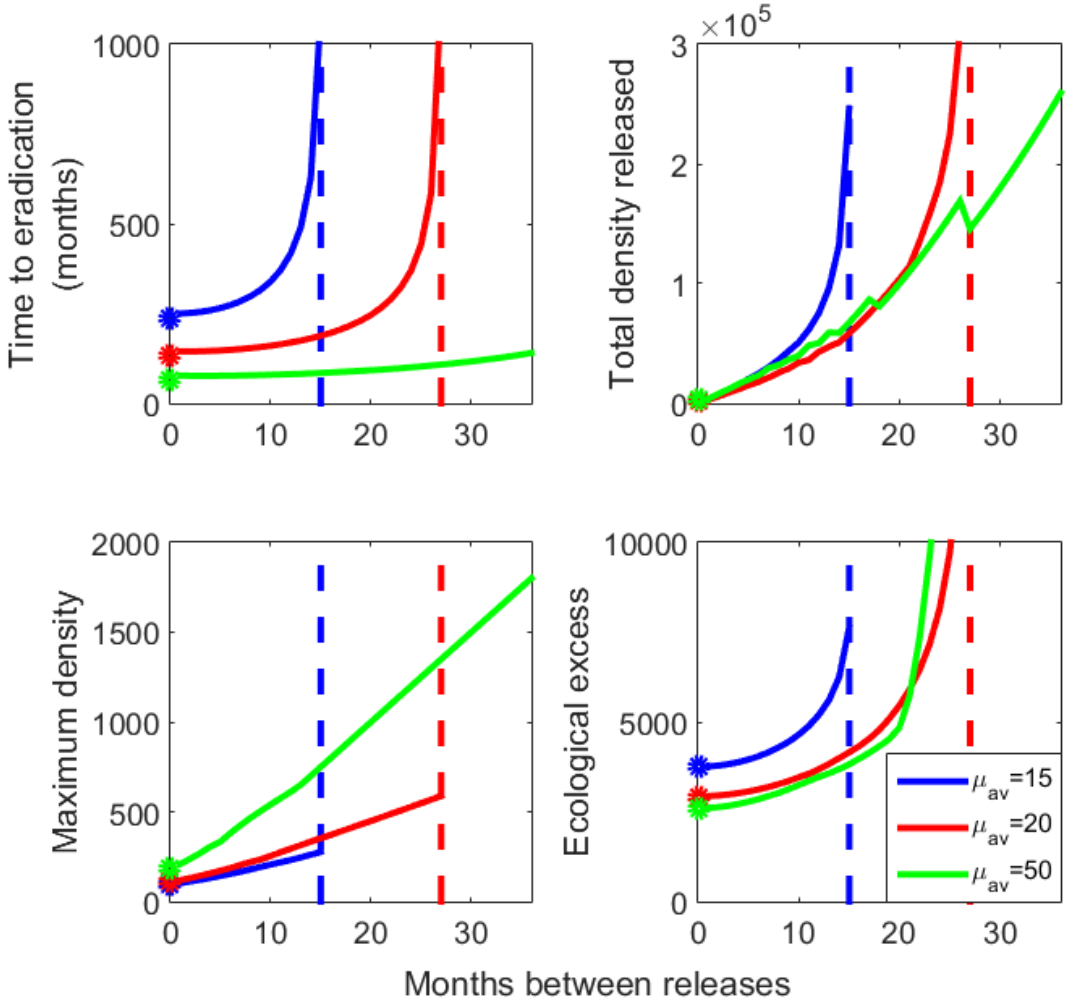

Figure B.1 With discrete releases pulses, the time to eradication increases with larger gaps between release. Additionally, each other metric increases with larger gaps between release. This holds for all three simulated average monthly release rates. Results for comparative continuous release rates of *t-Sry* mice are marked on the vertical axis. Vertical lines show the maximum amount of time between discrete releases that results in successful eradication for each average release rate.

Appendix C

Density-independent models of gene drive frequency and preferential mating frequency

Within this appendix, we provide a detailed explanation of how to derive the density-independent frequency equations (3.10-3.11) in the main text) from the full set of density-dependent equations (3.4-3.6 from Chapter 3). For reference, we begin with the equations

$$\frac{dW_k}{dt} = (a_1 - a_2 W)W \sum_{i\in\Gamma} \eta_i \theta_{Wi} \sum_{j\in\Gamma} g_{ij}(k) \left(\psi_i \theta_{Wj} + (1-\tau)(1-\psi_i)\theta_{Gj}\right) - (b_1 + b_2 N)W_k \tag{C.1}$$

$$\frac{dG_k}{dt} = (a_1 - a_2 W)W \sum_{i\in\Gamma} \eta_i \theta_{Wi} \sum_{j\in\Gamma} g_{ij}(k)\tau(1-\psi_i)\theta_{Gj} - (1+d)(b_1 + b_2 N)G_k + \mu_k \tag{C.2}$$

$$\frac{dS}{dt} = (a_1 - a_2 W)W \sum_{i\in\Gamma} \eta_i \theta_{Wi} \tau(1-\psi_i) - (1+d)(b_1 + b_2 N)S, \tag{C.3}$$

where $g_{ij}(k)$ is shown below in Figure C.1. For each combination of $i \in \Gamma$ and $j \in \Gamma$, we see that

$$\sum_{k \in \Gamma} g_{ij}(k) = g_{ij}(\mathbf{CC}) + g_{ij}(\mathbf{Cc}) + g_{ij}(\mathbf{cc}) = 1 \tag{C.4}$$

Offspring: k = CC		Father: *j*		
		CC	**Cc**	**cc**
Mother: *i*	**CC**	1	1/2	0
	Cc	1/2	1/4	0
	cc	0	0	0

Offspring: k = Cc		Father: *j*		
		CC	**Cc**	**cc**
Mother: *i*	**CC**	0	1/2	1
	Cc	1/2	1/2	1/2
	cc	1	1/2	0

Offspring: k = cc		Father: *j*		
		CC	**Cc**	**cc**
Mother: *i*	**CC**	0	0	0
	Cc	0	1/4	1/2
	cc	0	1/2	1

Figure C.1 The value of Mendelian inheritance ratios for offspring of genotype k, $g_{ij}(k)$, for each combination of mother genotype i and father genotype j.

We define gene drive frequency as $\phi = \frac{G}{W+G}$. To find the rate of change for ϕ, we need equations for $\frac{dG}{dt}$ and $\frac{d(W+G)}{dt}$. First, we find the rate of change in wild-type male density

$(W = W_{\mathbf{CC}} + W_{\mathbf{Cc}} + W_{\mathbf{cc}})$ as

$$\begin{aligned}
\frac{dW}{dt} &= \frac{dW_{\mathbf{CC}}}{dt} + \frac{dW_{\mathbf{Cc}}}{dt} + \frac{dW_{\mathbf{cc}}}{dt} \\
&= (a_1 - a_2 W) W \sum_{i \in \Gamma} \eta_i \theta_{Wi} \sum_{j \in \Gamma} g_{ij}(\mathbf{CC}) \left(\psi_i \theta_{Wj} + (1-\tau)(1-\psi_i)\theta_{Gj}\right) - (b_1 + b_2 N) W_{\mathbf{CC}} \\
&\quad + (a_1 - a_2 W) W \sum_{i \in \Gamma} \eta_i \theta_{Wi} \sum_{j \in \Gamma} g_{ij}(\mathbf{Cc}) \left(\psi_i \theta_{Wj} + (1-\tau)(1-\psi_i)\theta_{Gj}\right) - (b_1 + b_2 N) W_{\mathbf{Cc}} \\
&\quad + (a_1 - a_2 W) W \sum_{i \in \Gamma} \eta_i \theta_{Wi} \sum_{j \in \Gamma} g_{ij}(\mathbf{cc}) \left(\psi_i \theta_{Wj} + (1-\tau)(1-\psi_i)\theta_{Gj}\right) - (b_1 + b_2 N) W_{\mathbf{cc}} \\
&= (a_1 - a_2 W) W \sum_{i \in \Gamma} \eta_i \theta_{Wi} \sum_{j \in \Gamma} \left(\psi_i \theta_{Wj} \left(g_{ij}\mathbf{CC}\right) + g_{ij}(\mathbf{Cc}) + g_{ij}(\mathbf{cc})\right) \\
&\qquad\qquad + (1-\tau)(1-\psi_i)\theta_{Gj} \left(g_{ij}\mathbf{CC}\right) + g_{ij}(\mathbf{Cc}) + g_{ij}(\mathbf{cc}))) \\
&\quad - (b_1 + b_2 N)(W_{\mathbf{CC}} + W_{\mathbf{Cc}} + W_{\mathbf{cc}}) \\
&= (a_1 - a_2 W) W \sum_{i \in \Gamma} \eta_i \theta_{Wi} \sum_{j \in \Gamma} \left(\psi_i \theta_{Wj} + (1-\tau)(1-\psi_i)\theta_{Gj}\right) - (b_1 + b_2 N) W \\
&= (a_1 - a_2 W) W \sum_{i \in \Gamma} \eta_i \theta_{Wi} \left((\psi_i (\theta_{W\mathbf{CC}} + \theta_{W\mathbf{Cc}} + \theta_{W\mathbf{cc}})\right. \\
&\qquad\qquad \left. + (1-\tau)(1-\psi_i)(\theta_{G\mathbf{CC}} + \theta_{G\mathbf{Cc}} + \theta_{G\mathbf{cc}})\right) \\
&\quad - (b_1 + b_2 N) W \\
&= (a_1 - a_2 W) W \sum_{i \in \Gamma} \eta_i \theta_{Wi} \left(\psi_i + (1-\tau)(1-\psi_i)\right) - (b_1 + b_2 N) W. \qquad \text{(C.5)}
\end{aligned}$$

Similarly, the rate of change in density of all fertile gene drive males $(G = G_{\mathbf{CC}} + G_{\mathbf{Cc}} + G_{\mathbf{cc}})$ is

$$\begin{aligned}
\frac{dG}{dt} &= \frac{dG_{\mathbf{CC}}}{dt} + \frac{dG_{\mathbf{Cc}}}{dt} + \frac{dG_{\mathbf{cc}}}{dt} \\
&= (a_1 - a_2 W) W \sum_{i \in \Gamma} \eta_i \theta_{Wi} \tau (1 - \psi_i) - (1 + c)(b_1 + b_2 N) G + \mu. \qquad \text{(C.6)}
\end{aligned}$$

Together, the rate of change in all fertile male density ($M = W + G$) is

$$\begin{aligned}
\frac{dM}{dt} &= \frac{dW}{dt} + \frac{dG}{dt} \\
&= (a_1 - a_2 W)W \sum_{i \in \Gamma} \eta_i \theta_{Wi} \left(\psi_i + (1-\tau)(1-\psi_i)\right) + (a_1 - a_2 W)W \sum_{i \in \Gamma} \eta_i \theta_{Wi} \tau (1-\psi_i) \\
&\quad - (b_1 + b_2 N)W - (1+c)(b_1 + b_2 N)G + \mu \\
&= (a_1 - a_2 W)W \sum_{i \in \Gamma} \eta_i \theta_{Wi} \left(\psi_i + (1-\tau)(1-\psi_i) + \tau(1-\psi_i)\right) \\
&\quad - (b_1 + b_2 N)(W + (1+c)G) + \mu \\
&= (a_1 - a_2 W)W \sum_{i \in \Gamma} \eta_i \theta_{Wi} \left(\psi_i + (1-\psi_i)\right) - (b_1 + b_2 N)(W + (1+c)G) + \mu \\
&= (a_1 - a_2 W)W \sum_{i \in \Gamma} \eta_i \theta_{Wi} - (b_1 + b_2 N)(W + (1+c)G) + \mu
\end{aligned} \tag{C.7}$$

With these equations, we can derive $\frac{d\phi}{dt}$ with the quotient rule, as

$$\begin{aligned}
\frac{d\phi}{dt} &= \frac{d}{dt}\left(\frac{G}{M}\right) \\
&= \frac{M\frac{dG}{dt} - G\frac{dM}{dt}}{M^2} \\
&= \frac{M}{M^2}\left((a_1 - a_2W)W\sum_{i\in\Gamma}\eta_i\theta_{Wi}\tau(1-\psi_i) - (1+c)(b_1+b_2N)G + \mu\right) \\
&\quad - \frac{G}{M^2}\left((a_1 - a_2W)W\sum_{i\in\Gamma}\eta_i\theta_{Wi} - (b_1+b_2N)(W+(1+c)G) + \mu\right) \\
&= (a_1 - a_2W)(1-\phi)\sum_{i\in\Gamma}\eta_i\theta_{Wi}\tau(1-\psi_i) - (1+c)(b_1+b_2N)\phi + \frac{\mu}{M} \\
&\quad - (a_1 - a_2W)\phi(1-\phi)\sum_{i\in\Gamma}\eta_i\theta_{Wi} + \phi(b_1+b_2N)((1-\phi)+(1+c)\phi) - \phi\left(\frac{\mu}{M}\right) \\
&= (a_1 - a_2W)(1-\phi)\sum_{i\in\Gamma}\eta_i\theta_{Wi}\left(\tau(1-\psi_i) - \phi\right) \\
&\quad - \phi(b_1+b_2N)((1+c) - (1-\phi) - (1+c)\phi) + \frac{\mu}{M} - \phi\left(\frac{\mu}{M}\right) \\
&= (a_1 - a_2W)(1-\phi)\sum_{i\in\Gamma}\eta_i\theta_{Wi}\left(\tau(1-\psi_i) - \phi\right) - \phi(b_1+b_2N)(c(1-\phi)) + \left(\frac{1-\phi}{M}\right)\mu \\
&= (1-\phi)\left((a_1 - a_2W)\sum_{i\in\Gamma}\eta_i\theta_{Wi}\left(\tau(1-\psi_i) - \phi\right) - c\phi(b_1+b_2N) + \frac{\mu}{M}\right). \qquad \text{(C.8)}
\end{aligned}$$

We can also derive $\frac{d\theta_{Wk}}{dt}$ from the quotient rule, as

$$\begin{aligned}
\frac{d\theta_{Wk}}{dt} &= \frac{d}{dt}\left(\frac{W_k}{W}\right) \\
&= \frac{W\frac{dW_k}{dt} - W_k\frac{dW}{dt}}{W^2} \\
&= \frac{W}{W^2}\left((a_1 - a_2W)W\sum_{i\in\Gamma}\eta_i\theta_{Wi}\sum_{j\in\Gamma}g_{ij}(k)\left(\psi_i\theta_{Wj} + (1-\tau)(1-\psi_i)\theta_{Gj}\right) - (b_1+b_2N)W_k\right) \\
&\quad + \frac{W_k}{W^2}\left((a_1 - a_2W)W\sum_{i\in\Gamma}\eta_i\theta_{Wi}\left(\psi_i + (1-\tau)(1-\psi_i)\right) - (b_1+b_2N)W\right) \\
&= (a_1 - a_2W)\sum_{i\in\Gamma}\eta_i\theta_{Wi}\sum_{j\in\Gamma}g_{ij}(k)\left(\psi_i\theta_{Wj} + (1-\tau)(1-\psi_i)\theta_{Gj}\right) \\
&\quad - (a_1 - a_2W)\theta_{Wk}\sum_{i\in\Gamma}\eta_i\theta_{Wi}\left(\psi_i + (1-\tau)(1-\psi_i)\right) \\
&\quad - (b_1+b_2N)\theta_{Wk} + (b_1+b_2N)\theta_{Wk} \\
&= (a_1 - a_2W)\sum_{i\in\Gamma}\eta_i\theta_{Wi}\left(\sum_{j\in\Gamma}g_{ij}(k)\left(\psi_i\theta_{Wj} + (1-\tau)(1-\psi_i)\theta_{Gj}\right) - \theta_{Wk}\left(\psi_i + (1-\tau)(1-\psi_i)\right)\right) \\
&= (a_1 - a_2W)\sum_{i\in\Gamma}\eta_i\theta_{Wi}\sum_{j\in\Gamma}\left(g_{ij}(k) - \theta_{Wk}\right)\left(\psi_i\theta_{Wj} + (1-\tau)(1-\psi_i)\theta_{Gj}\right). \qquad \text{(C.9)}
\end{aligned}$$

Next, we let $\theta_{W\mathbf{C}} = \theta_{W\mathbf{CC}} + \frac{1}{2}\theta_{W\mathbf{Cc}}$ and $g_{ij}(\mathbf{C}) = g_{ij}(\mathbf{CC}) + \frac{1}{2}g_{ij}(\mathbf{Cc})$, as shown in Figure C.2. Then

$g_{ij}(\mathbf{C})$		Father: j		
		CC	**Cc**	**cc**
Mother: i	**CC**	1	3/4	1/2
	Cc	3/4	1/2	1/4
	cc	1/2	1/4	0

Figure C.2 The inheritance ratios of the C allele, $g_{ij}(\mathbf{C})$, for each combination of mother genotype i and father genotype j.

$$
\begin{aligned}
\frac{d\theta_{W\mathbf{C}}}{dt} &= \frac{\theta_{W\mathbf{CC}}}{dt} + \frac{1}{2}\frac{\theta_{W\mathbf{Cc}}}{dt} \\
&= (a_1 - a_2 W)\sum_{i\in\Gamma}\eta_i\theta_{Wi}\sum_{j\in\Gamma}\left(g_{ij}(\mathbf{CC}) - \theta_{W\mathbf{CC}}\right)\left(\psi_i\theta_{Wj} + (1-\tau)(1-\psi_i)\theta_{Gj}\right) \\
&\quad + \frac{1}{2}(a_1 - a_2 W)\sum_{i\in\Gamma}\eta_i\theta_{Wi}\sum_{j\in\Gamma}\left(g_{ij}(\mathbf{Cc}) - \theta_{W\mathbf{Cc}}\right)\left(\psi_i\theta_{Wj} + (1-\tau)(1-\psi_i)\theta_{Gj}\right) \\
&= (a_1 - a_2 W)\sum_{i\in\Gamma}\eta_i\theta_{Wi}\sum_{j\in\Gamma}\left(g_{ij}(\mathbf{CC}) - \theta_{W\mathbf{CC}} + \frac{1}{2}g_{ij}(\mathbf{Cc}) - \frac{1}{2}\theta_{W\mathbf{Cc}}\right)\left(\psi_i\theta_{Wj} + (1-\tau)(1-\psi_i)\theta_{Gj}\right) \\
&= (a_1 - a_2 W)\sum_{i\in\Gamma}\eta_i\theta_{Wi}\sum_{j\in\Gamma}\left(g_{ij}(\mathbf{C}) - \theta_{W\mathbf{C}}\right)\left(\psi_i\theta_{Wj} + (1-\tau)(1-\psi_i)\theta_{Gj}\right). \qquad \text{(C.10)}
\end{aligned}
$$

To create simple, density-independent versions of $\frac{d\phi}{dt}$ and $\frac{d\theta_{W\mathbf{C}}}{dt}$, we make the following assumptions:

1. $a_2 = b_2 = 0$
2. $\rho \to \infty \implies \lim_{\rho\to\infty}\eta_i = 1 - \lim_{\rho\to\infty} e^{(-\rho(\gamma W + \gamma_{iG}G))} = 1$
3. $\tau = 1$
4. $\mu = 0$
5. Hardy-Weinberg equilibrium:
   (a) $\theta_{W\mathbf{CC}} = \theta_{W\mathbf{C}}^2$
   (b) $\theta_{W\mathbf{Cc}} = 2\theta_{W\mathbf{C}}(1 - \theta_{W\mathbf{C}})$
   (c) $\theta_{W\mathbf{cc}} = (1 - \theta_{W\mathbf{C}})^2$

To reduce notation at this point, we define

$$\omega_1(\phi) = \gamma(1-\phi) + \gamma_G\phi > 0 \qquad \text{(C.11)}$$

and

$$\omega_2(\phi) = \gamma(1-\phi) + (h\gamma_G + (1-h)\gamma)\phi > 0. \qquad \text{(C.12)}$$

Thus, $\frac{d\phi}{dt}$ becomes

$$
\begin{aligned}
\frac{d\phi}{dt} &= (1-\phi)\left((a_1 - a_2 W)\sum_{i\in\Gamma}\eta_i\theta_{Wi}\left(\tau(1-\psi_i)-\phi\right) - c\phi(b_1+b_2N) + \frac{\mu}{M}\right) \\
&= (1-\phi)\left(a_1\sum_{i\in\Gamma}\theta_{Wi}\left(1-\psi_i-\phi\right) - c\phi b_1\right) \\
&= (1-\phi)\left(a_1\sum_{i\in\Gamma}\theta_{Wi}\left(\frac{\gamma_{iG}\phi}{\gamma(1-\phi)+\gamma_{iG}\phi}-\phi\right) - \phi b_1 c\right) \\
&= \phi(1-\phi)\left(a_1\sum_{i\in\Gamma}\theta_{Wi}\left(\frac{\gamma_{iG}}{\gamma(1-\phi)+\gamma_{iG}\phi}-1\right) - b_1 c\right) \\
&= \phi(1-\phi)\left(a_1\left(\theta_{W\mathbf{C}}^2\left(\left(\frac{\gamma_G}{\gamma(1-\phi)+\gamma_G\phi}\right)-1\right)\right.\right. \\
&\qquad +2\theta_{W\mathbf{C}}(1-\theta_{W\mathbf{C}})\left(\left(\frac{h\gamma_G+(1-h)\gamma}{\gamma(1-\phi)+(h\gamma_G+(1-h)\gamma)\phi}\right)-1\right) \\
&\qquad \left.\left.+(1-\theta_{W\mathbf{C}})^2\left(\frac{\gamma}{\gamma(1-\phi)+\gamma\phi}-1\right)\right) - b_1 c\right) \\
&= \phi(1-\phi)\left(a_1\left(\theta_{W\mathbf{C}}^2\left(\frac{\gamma_G-\gamma(1-\phi)-\gamma_G\phi}{\omega_1(\phi)}\right)\right.\right. \\
&\qquad +2\theta_{W\mathbf{C}}(1-\theta_{W\mathbf{C}})\left(\frac{h\gamma_G+(1-h)\gamma-\gamma(1-\phi)-(h\gamma_G+(1-h)\gamma)\phi}{\omega_2(\phi)}\right) \\
&\qquad \left.\left.+(1-\theta_{W\mathbf{C}})^2(1-1)\right) - b_1 c\right) \\
&= \phi(1-\phi)\left(a_1\left(\theta_{W\mathbf{C}}^2(1-\phi)\left(\frac{\gamma_G-\gamma}{\omega_1(\phi)}\right)\right.\right. \\
&\qquad \left.\left.+2\theta_{W\mathbf{C}}(1-\theta_{W\mathbf{C}})(1-\phi)\left(\frac{h\gamma_G+(1-h)\gamma-\gamma}{\omega_2(\phi)}\right)\right) - b_1 c\right) \\
&= \phi(1-\phi)\left(a_1(1-\phi)\theta_{W\mathbf{C}}\left(\theta_{W\mathbf{C}}\left(\frac{\gamma_G-\gamma}{\omega_1(\phi)}\right)+2(1-\theta_{W\mathbf{C}})\left(\frac{h(\gamma_G-\gamma)}{\omega_2(\phi)}\right)\right) - b_1 c\right) \\
&= \phi(1-\phi)\left(a_1(\gamma_G-\gamma)(1-\phi)\theta_{W\mathbf{C}}\left(\frac{\theta_{W\mathbf{C}}}{\omega_1(\phi)}+\frac{2h(1-\theta_{W\mathbf{C}})}{\omega_2(\phi)}\right) - b_1 c\right). \qquad \text{(C.13)}
\end{aligned}
$$

Also, $\frac{d\theta_{W\mathbf{C}}}{dt}$ becomes

$$
\begin{aligned}
\frac{d\theta_{W\mathbf{C}}}{dt} &= (a_1 - a_2 W) \sum_{i\in\Gamma} \eta_i \theta_{Wi} \sum_{j\in\Gamma} \left(g_{ij}(\mathbf{C}) - \theta_{W\mathbf{C}}\right) \left(\psi_i \theta_{Wj} + (1-\tau)(1-\psi_i)\theta_{Gj}\right) \\
&= a_1 \sum_{i\in\Gamma} \sum_{j\in\Gamma} \left(g_{ij}(\mathbf{C}) - \theta_{W\mathbf{C}}\right) \psi_i \theta_{Wj} \theta_{Wi} \\
&= a_1 \Bigg(\left((1-\theta_{W\mathbf{C}})\, \theta_{W\mathbf{C}}^4 + \left(\frac{3}{4} - \theta_{W\mathbf{C}}\right) 2\theta_{W\mathbf{C}}^3 (1-\theta_{W\mathbf{C}}) + \left(\frac{1}{2} - \theta_{W\mathbf{C}}\right) \theta_{W\mathbf{C}}^2 (1-\theta_{W\mathbf{C}})^2 \right) \psi_{\mathbf{CC}} \\
&\quad + \left(\left(\frac{3}{4} - \theta_{W\mathbf{C}}\right) 2\theta_{W\mathbf{C}}^3 (1-\theta_{W\mathbf{C}}) + \left(\frac{1}{2} - \theta_{W\mathbf{C}}\right) 4\theta_{W\mathbf{C}}^2 (1-\theta_{W\mathbf{C}})^2 + \left(\frac{1}{4} - \theta_{W\mathbf{C}}\right) 2\theta_{W\mathbf{C}}^2 (1-\theta_{W\mathbf{C}})^2 \right) \psi_{\mathbf{Cc}} \\
&\quad + \left(\left(\frac{1}{2} - \theta_{W\mathbf{C}}\right) \theta_{W\mathbf{C}}^2 (1-\theta_{W\mathbf{C}})^2 + \left(\frac{1}{4} - \theta_{W\mathbf{C}}\right) 2\theta_{W\mathbf{C}}^2 (1-\theta_{W\mathbf{C}})^2 + (0 - \theta_{W\mathbf{C}})\,(1-\mathbf{C})^4 \right) \psi_{\mathbf{cc}} \Bigg) \\
&= a_1 \Bigg(\left(\theta_{W\mathbf{C}}^4 - \theta_{W\mathbf{C}}^5\right) \psi_{\mathbf{CC}} + \left(\frac{3}{4}\theta_{W\mathbf{C}}^3 - \frac{7}{2}\theta_{W\mathbf{C}}^4 + 2\theta_{W\mathbf{C}}^5\right) \psi_{\mathbf{CC}} + \left(\frac{1}{2}\theta_{W\mathbf{C}}^2 - 2\theta_{W\mathbf{C}}^3 + \frac{5}{2}\theta_{W\mathbf{C}}^4 - \theta_{W\mathbf{C}}^5\right) \psi_{\mathbf{CC}} \\
&\quad + \left(\frac{3}{4}\theta_{W\mathbf{C}}^3 - \frac{7}{2}\theta_{W\mathbf{C}}^4 + 2\theta_{W\mathbf{C}}^5\right) \psi_{\mathbf{Cc}} + \left(2\theta_{W\mathbf{C}}^2 - 8\theta_{W\mathbf{C}}^3 + 10\theta_{W\mathbf{C}}^4 - 4\theta_{W\mathbf{C}}^5\right) \psi_{\mathbf{Cc}} \\
&\quad + \left(\frac{1}{2}\theta_{W\mathbf{C}} - \frac{7}{2}\theta_{W\mathbf{C}}^2 + \frac{15}{2}\theta_{W\mathbf{C}}^4 - \frac{13}{2}\theta_{W\mathbf{C}}^4 + 2\theta_{W\mathbf{C}}^5\right) \psi_{\mathbf{Cc}} + \left(\frac{1}{2}\theta_{W\mathbf{C}}^2 - 2\theta_{W\mathbf{C}}^3 + \frac{5}{2}\theta_{W\mathbf{C}}^4 - \theta_{W\mathbf{C}}^5\right) \psi_{\mathbf{cc}} \\
&\quad + \left(\frac{1}{2}\theta_{W\mathbf{C}} - \frac{7}{2}\theta_{W\mathbf{C}}^2 + \frac{15}{2}\theta_{W\mathbf{C}}^4 - \frac{13}{2}\theta_{W\mathbf{C}}^4 + 2\theta_{W\mathbf{C}}^5\right) \psi_{\mathbf{cc}} + \left(-\theta_{W\mathbf{C}} + 4\theta_{W\mathbf{C}}^2 - 6\theta_{W\mathbf{C}}^3 + 4\theta_{W\mathbf{C}}^4 - \theta_{W\mathbf{C}}^5\right) \psi_{\mathbf{cc}} \Bigg) \\
&= a_1 \left(\left(\frac{1}{2}\psi_{\mathbf{Cc}} - \frac{1}{2}\psi_{\mathbf{cc}}\right) \theta_{W\mathbf{C}} + \left(\frac{1}{2}\psi_{\mathbf{CC}} - \frac{3}{2}\psi_{\mathbf{Cc}} + \psi_{\mathbf{cc}}\right) \theta_{W\mathbf{C}}^2 + \left(-\frac{1}{2}\psi_{\mathbf{CC}} + \psi_{\mathbf{Cc}} - \frac{1}{2}\psi_{\mathbf{cc}}\right) \theta_{W\mathbf{C}}^3 + 0\theta_{W\mathbf{C}}^4 + 0\theta_{W\mathbf{C}}^5 \right) \\
&= a_1 \theta_{W\mathbf{C}} \Bigg(\frac{1}{2}\left(\psi_{\mathbf{Cc}} - \psi_{\mathbf{cc}}\right) - \left(\psi_{\mathbf{Cc}} - \psi_{\mathbf{cc}}\right) \theta_{W\mathbf{C}} + \frac{1}{2}\left(\psi_{\mathbf{Cc}} - \psi_{\mathbf{cc}}\right) \theta_{W\mathbf{C}}^2 \\
&\qquad + \frac{1}{2}\left(\psi_{\mathbf{CC}} - \psi_{\mathbf{Cc}}\right) \theta_{W\mathbf{C}} - \frac{1}{2}\left(\psi_{\mathbf{CC}} - \psi_{\mathbf{Cc}}\right) \theta_{W\mathbf{C}}^2 \Bigg) \\
&= \frac{a_1}{2} \theta_{W\mathbf{C}} \left(\left(\psi_{\mathbf{Cc}} - \psi_{\mathbf{cc}}\right) (1-\theta_{W\mathbf{C}})^2 + \left(\psi_{\mathbf{CC}} - \psi_{\mathbf{Cc}}\right) \theta_{W\mathbf{C}} (1-\theta_{W\mathbf{C}}) \right) \\
&= \frac{a_1}{2} \theta_{W\mathbf{C}} (1-\theta_{W\mathbf{C}}) \Big(\left(\psi_{\mathbf{Cc}} - \psi_{\mathbf{cc}}\right) (1-\theta_{W\mathbf{C}}) + \left(\psi_{\mathbf{CC}} - \psi_{\mathbf{Cc}}\right) \theta_{W\mathbf{C}} \Big)
\end{aligned}
\tag{C.14}
$$

We solve

$$
\begin{aligned}
\psi_{\mathbf{CC}} - \psi_{\mathbf{Cc}} &= \frac{\gamma(1-\phi)}{\omega_1(\phi)} - \frac{\gamma(1-\phi)}{\omega_2(\phi)} \\
&= \gamma(1-\phi) \left(\frac{\omega_2(\phi) - \omega_1(\phi)}{\omega_1(\phi)\omega_2(\phi)} \right) \\
&= \gamma(1-\phi) \left(\frac{\gamma(1-\phi) + (h\gamma_G + (1-h)\gamma)\phi - \gamma(1-\phi) - \gamma_G\phi}{\omega_1(\phi)\omega_2(\phi)} \right) \\
&= \gamma(1-\phi) \left(\frac{h\gamma_G\phi + \gamma\phi - h\gamma\phi - \gamma_G\phi}{\omega_1(\phi)\omega_2(\phi)} \right) \\
&= \gamma\phi(1-\phi) \left(\frac{(1-h)(\gamma - \gamma_G)}{\omega_1(\phi)\omega_2(\phi)} \right) \\
&= (1-h)\gamma(\gamma - \gamma_G) \left(\frac{\phi(1-\phi)}{\omega_1(\phi)\omega_2(\phi)} \right)
\end{aligned}
\tag{C.15}
$$

and

$$\begin{aligned}
\psi_{\mathbf{Cc}} - \psi_{\mathbf{cc}} &= \frac{\gamma(1-\phi)}{\omega_2(\phi)} - (1-\phi) \\
&= (1-\phi)\left(\frac{\gamma - \omega_2(\phi)}{\omega_2(\phi)}\right) \\
&= (1-\phi)\left(\frac{\gamma - \gamma(1-\phi) - (h\gamma_G + (1-h)\gamma)\phi}{\omega_2(\phi)}\right) \\
&= (1-\phi)\left(\frac{\gamma\phi - h\gamma_G\phi - \gamma\phi + h\gamma\phi}{\omega_2(\phi)}\right) \\
&= \phi(1-\phi)\left(\frac{h(\gamma - \gamma_G)}{\omega_2(\phi)}\right) \\
&= h(\gamma - \gamma_G)\left(\frac{\phi(1-\phi)}{\omega_2(\phi)}\right). \qquad \text{(C.16)}
\end{aligned}$$

Substituting these into the previous equation, we find

$$\begin{aligned}
\frac{d\phi}{dt} &= \frac{a_1}{2}\theta_{W\mathbf{C}}(1-\theta_{W\mathbf{C}})\Big((\psi_{\mathbf{Cc}} - \psi_{\mathbf{cc}})(1-\theta_{W\mathbf{C}}) + (\psi_{\mathbf{CC}} - \psi_{\mathbf{Cc}})\theta_{W\mathbf{C}}\Big) \\
&= \frac{a_1}{2}\theta_{W\mathbf{C}}(1-\theta_{W\mathbf{C}})\Bigg(\left(h(\gamma - \gamma_G)\left(\frac{\phi(1-\phi)}{\omega_2(\phi)}\right)\right)(1-\theta_{W\mathbf{C}}) \\
&\qquad + \left((1-h)\gamma(\gamma - \gamma_G)\left(\frac{\phi(1-\phi)}{\omega_1(\phi)\omega_2(\phi)}\right)\right)\theta_{W\mathbf{C}}\Bigg) \\
&= \frac{a_1}{2}(\gamma - \gamma_G)\theta_{W\mathbf{C}}(1-\theta_{W\mathbf{C}})\left(\frac{\phi(1-\phi)}{\omega_2(\phi)}\right)\left(h(1-\theta_{W\mathbf{C}}) + \left(\frac{(1-h)\gamma}{\omega_1(\phi)}\right)\theta_{W\mathbf{C}}\right) \qquad \text{(C.17)}
\end{aligned}$$