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Integrating gene drives with established pest controls to mitigate spillover risk

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Abstract

Gene drives are artificial genetic constructs that bias their own inheritance, enabling them to spread through a population and offering a promising way to control disease vectors and invasive species. While gene drives can potentially eradicate target populations, their unintended spillover into nontarget populations poses substantial ecological concerns. Here, we develop a general methodological framework to examine how integrating gene drives with established pest control methods, such as pesticide application and sterile-male release, can mitigate spillover risk. In this framework, we develop an optimal control model that identifies treatment strategies with minimum total costs of eradication, accounting for direct treatment expenditures and potential damage from spillover. We show that pesticides are most cost-effective at the intermediate stage of eradication when gene drives have already slowed population growth but do not yet substantially suppress the population. For sterile-male release, however, we observe two distinct types of optimal strategies, with the optimal choice depending on parameter values: intensive early-stage releases or mild later-stage releases. Using established pest controls also relaxes requirements for gene drive design, favoring milder suppressive effects as the treatment intensifies. Although spillover risk is hard to quantify in real-world contexts, the proposed approach identifies the maximum relative reduction in the spillover risk attainable with a given level of treatment effort.

KEYWORDS
bioeconomics, cost-efficiency, gene drive, optimal control, pesticides, spillover risk, sterile males

INTRODUCTION

Pest populations such as disease-vector species, crop-damaging species, and invasive species cause significant ecological and economic damage. Over the last

Adam Lampert and Gili Greenbaum contributed equally and should be considered co-last authors. The order of these two authors was decided by lottery.

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century, several pest control methods have been developed, including chemical pesticides, the release of sterile males, and biological control methods. Another approach currently being developed involves the use of gene drives—genetic elements that violate standard Mendelian inheritance laws (Alphey et al., 2020) and can spread rapidly in populations (Burt, 2003; Deredec et al., 2008; Unckless et al., 2015). Suppression gene drives, which can reduce population size either by imposing fitness costs on their carriers or by skewing the sex ratio, are being explored as promising tools to suppress harmful populations. Such gene drives are currently being developed for weeds (Barrett et al., 2019; Liu et al., 2024; Oberhofer et al., 2024) and rodents (Gierus et al., 2022; Manser et al., 2019; Pfitzner et al., 2020) and have reached advanced stages of laboratory experiments in mosquitoes (Hammond et al., 2021; Hammond & Galizi, 2017; Nolan, 2021). However, despite its potential, gene drive technology raises substantial concerns (Esvelt & Gemmell, 2017; Frieß et al., 2023; Hartley et al., 2022; Jiang & Wang, 2024; Schwartz et al., 2025), including the risk of unintended spillover of gene drive alleles to nontarget populations, which might severely damage ecosystems (Kim et al., 2023; Noble et al., 2018; Oye et al., 2014; Webber et al., 2015). Therefore, approaches for mitigating spillover risk must be developed for gene drive technology to move toward field application.

The dynamics of populations carrying gene drives have been modeled in numerous theoretical studies (reviewed in Dhole et al., 2020; Frieß et al., 2023; Kim et al., 2023) that have focused on conditions under which spillover occurs and explored how to mitigate it. For example, several studies have identified ranges of gene drive characteristics (fitness cost, conversion rate, etc.) that result in threshold-dependent spread, when the drive can invade only if introduced above a certain frequency, reducing risk of unintentional introductions (Burt, 2003; Deredec et al., 2008; Leftwich et al., 2018; Unckless et al., 2015). Other studies have explored sophisticated genetic architectures that may allow gene drive confinement to limited geographic localities (Champer et al., 2020; Noble et al., 2019; Zhu & Champer, 2023), or how gene drive sensitivity to environmental conditions can be leveraged to mitigate spillover risk (Girardin et al., 2019; Harris & Greenbaum, 2023; Marshall & Akbari, 2018; Tanaka et al., 2017). Recent studies have coupled evolutionary (allele frequency) dynamics with demographic (population size) dynamics (Beaghton & Burt, 2022; Girardin & Débarre, 2021; Harris & Greenbaum, 2023; Kläy et al., 2023). This is particularly important for gene drives aimed at suppressing populations, as the interplay between demographic and evolutionary processes may strongly affect spillovers. The inclusion of demography in gene drive models also opens the possibility for modeling how other processes that affect population sizes, such as traditional control measures, can interact with the dynamics of gene drives.

While most previous studies have considered gene drive as the only control measure applied, it is often advantageous to combine several control measures together. Combining several controls is a common practice in established pest control, where treatment schemes involving pesticide application, sterile-male release, and pheromone-based mating disruption have repeatedly proven effective in the field (Bansal et al., 2024; Gutierrez et al., 2019; Horner et al., 2020; Kittayapong et al., 2019), and theory has been developed for various such combinations (Barclay, 1980; Lampert & Liebhold, 2021; Larramendy & Soloneski, 2012; Tang & Cheke, 2008). Therefore, integrating gene drives with established control measures may open avenues to leverage their interactions, enhancing both environmental responsibility and cost-effectiveness of pest management.

Here, we examine the potential of complementing gene drives with two key established pest controls: pesticide application and sterile-male release. Our goal is to develop a general framework to identify the optimal treatment strategies—the timing and intensity of different interventions that minimize the total costs of eradication over time, considering both direct expenditures and expected damage due to spillover. Specifically, we consider the simplified assumption that the cost of spillover is proportional to the total number of gene drive carriers through the entire eradication process. Accordingly, the numerical results are intended to reveal qualitative and comparative optimization patterns rather than predict outcomes for a particular species or release program. This cost minimization approach, known as bioeconomic modeling, has become common for established pest controls; however, it remains almost overlooked in gene drive models, with only a few simulation studies incorporating cost (e.g., assessing health care outcomes related to insecticide-treated nets and vaccinations [Hancock et al., 2024; Metchanun et al., 2022]). In addition to identifying optimal treatment strategies for given gene drives, we examine how these strategies depend on biological and economic parameters, including gene drive configurations and population growth rates.

MODEL AND METHODS

Demographic gene drive model

We model a single isolated target population, such as an island population. To model spillover, we do not explicitly model neighboring populations (e.g., mainland

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population), but we assume that gene drive carriers may unintentionally escape to nontarget populations. To study how to combine multiple control methods optimally, we developed a model that incorporates both evolutionary dynamics (i.e., changes in the frequency of the gene drive allele) and demographic dynamics (i.e., changes in the population density) of a target population. As a baseline for evolutionary dynamics, we use a canonical model of a homing gene drive with gametic conversion that is expected to reach fixation when released in a population (Deredec et al., 2008; Unckless et al., 2015). As a baseline for the demographic dynamics, we use a standard discrete-time model of population growth under intraspecific competition (Beverton & Holt, 1957). We first describe the dynamics of a population in which a gene drive is deployed without additional controls, and in the following subsection, we describe how additional pest controls, such as pesticides and sterile males, modify the dynamics.

We consider a random-mating diploid population with nonoverlapping generations. Spillover of the gene drive to nontarget populations might occur, but we do not model other populations explicitly. We consider a single locus with two alleles: wild-type allele and gene drive allele. We assume that the gene drive allele reduces the fitness of its carriers with relative fitness cost s and dominance h, such that gene drive homozygotes have fitness $1-s$, heterozygotes have fitness $1-hs$, and wild-types have fitness 1. To model the gene drive mechanism, we assume that heterozygotes are converted to gene drive homozygotes with probability c; we assume that conversion occurs during gamete formation, in accordance with current empirical data (Grunwald et al., 2019; Kyrou et al., 2018). Under these conditions, the frequency of the gene drive allele, q_t, can be formulated as (Deredec et al., 2008; Unckless et al., 2015)

$$q_{t+1} = \frac{q_t^2(1-s) + q_t(1-q_t)(1-hs)(1+c)}{\overline{w}_t}, \quad (1)$$

where the numerator sums the contribution of the genotypes in terms of gene drive alleles, and the denominator represents the mean population fitness, $\overline{w}_t = q_t^2(1-s) + 2q_t(1-q_t)(1-hs) + (1-q_t)^2$. We show in Appendix S1 that Equation (1), which was previously derived by considering gene drive frequency alone, also applies to the setup explicitly considering both gene drive frequency and population density. Depending on the gene drive configuration (s, c, h), these dynamics can result in several outcomes: fixation of the gene drive, loss of the gene drive, a stable equilibrium with both gene drive and wild-type alleles present, or bistability with either fixation or loss of the gene drive—depending on initial conditions (Deredec et al., 2008; Unckless et al., 2015). Here, we focus on configurations that result in fixation of the gene drive allele regardless of its initial frequency.

To model the impact of gene drives on the population density, we adjust a standard population growth model to account for the reduced fitness of the gene drive carriers. Specifically, we assume that, in the absence of gene drive carriers, the population grows according to the Beverton–Holt model (Beverton & Holt, 1957), which is a standard discrete-time analog of the continuous logistic model:

$$n_{t+1} = \frac{rn_t}{1+(r-1)n_t}, \quad (2)$$

where n_t is the population density at time t (relative to the carrying capacity) and r is the intrinsic growth rate without intraspecific competition of a population of wild-type individuals. In turn, as the proportion of the gene drive allele in the population increases, fewer individuals survive and reproduce; therefore, we model the population growth rate to be proportional to the mean population fitness and modify the Beverton–Holt model accordingly (full derivation in Appendix S1):

$$n_{t+1} = \frac{rn_t\overline{w}_t}{1+(r-1)n_t}. \quad (3)$$

For a wild-type population, which has a mean fitness of $\overline{w}_t = 1$, Equation (3) reduces to Equation (2). In the presence of the gene drive, $\overline{w}_t < 1$, and the population grows slower and may even decline.

Dynamics under additional pest controls

The dynamics in Equation (3) model the population size under the impact of the gene drive spread, without any additional interventions. Next, we extend the model by incorporating established pest controls: pesticides and sterile males. For pesticides, we assume that a certain amount of chemical pesticides removes a fixed fraction of the population (Clark, 2010; Lampert & Liebhold, 2021). As a scaled unit, we consider a single pesticide application to be the amount that reduces the population size by half. We denote the number of pesticide application units used at time t as P_t ($P_t \geq 0$), and we adjust Equation (3) to incorporate pesticide application:

$$n_{t+1} = \frac{rn_t\overline{w}_t}{1+(r-1)n_t} \times \left(\frac{1}{2}\right)^{P_t}. \quad (4)$$

Next, we model the effect of sterile-male releases on the dynamics. We denote the amount of sterile males released at time t as M_t ($M_t \geq 0$), measured in units of

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fractions of the carrying capacity to match the scaling of population density n_t. Assuming a 1:1 sex ratio and that each female mates once, the proportion of females encountering a fertile mate is $\frac{n_t/2}{n_t/2+M_t}=\frac{n_t}{n_t+2M_t}$ (Knipling, 1959; Lampert & Liebhold, 2021; Sawyer et al., 1987). We can adjust the numerator in Equation (3) by this proportion to formulate the population size after sterile-male release:

$$n_{t+1}=\frac{rn_t\overline{w}_t}{1+(r-1)n_t}\times\frac{n_t}{n_t+2M_t}. \quad (5)$$

Finally, when both pesticides and sterile males are applied to a population with a gene drive, the joint effect of the three control measures can be formulated as

$$n_{t+1}=\frac{rn_t\overline{w}_t}{1+(r-1)n_t}\times\frac{n_t}{n_t+2M_t}\times\left(\frac{1}{2}\right)^{P_t}. \quad (6)$$

Formulating spillover risk mitigation as an optimal control problem

To examine how to optimally combine gene drives with the established pest control methods, we formulate an optimal control problem. Optimization is needed because using established pest controls bears a trade-off: They speed up eradication and thereby reduce the number of potential gene drive carriers escaping to nontarget populations (Figure 1) but inevitably increase the costs of eradication.

Our objective is, therefore, to minimize the *net present cost* (NPC)—the total costs of eradication over time, which include (1) the cost of spillover, (2) the amount invested in pesticides, and (3) the amount invested in sterile males. We define the spillover risk as the probability of a spillover event. In turn, the cost of spillover is the expected cost of damage due to spillover, which equals the spillover risk times the expected cost due to a spillover event. We assume, for simplicity, that (1) the spillover risk is proportional to the expected number of escaped gene drive carriers and (2) the expected number of escaped gene drive carriers is proportional to the total number of gene drive carriers in the target population, summed over all generations (Figure 1). Note that, when considering potential escapees, we equally account for all gene drive carriers, both homozygotes and heterozygotes, and use the Hardy–Weinberg genotype frequencies:

$$n_{D,t}=n_t\left(q_t^2+2q_t(1-q_t)\right). \quad (7)$$

In turn, the amount invested in additional pest controls is proportional to pesticide application in each

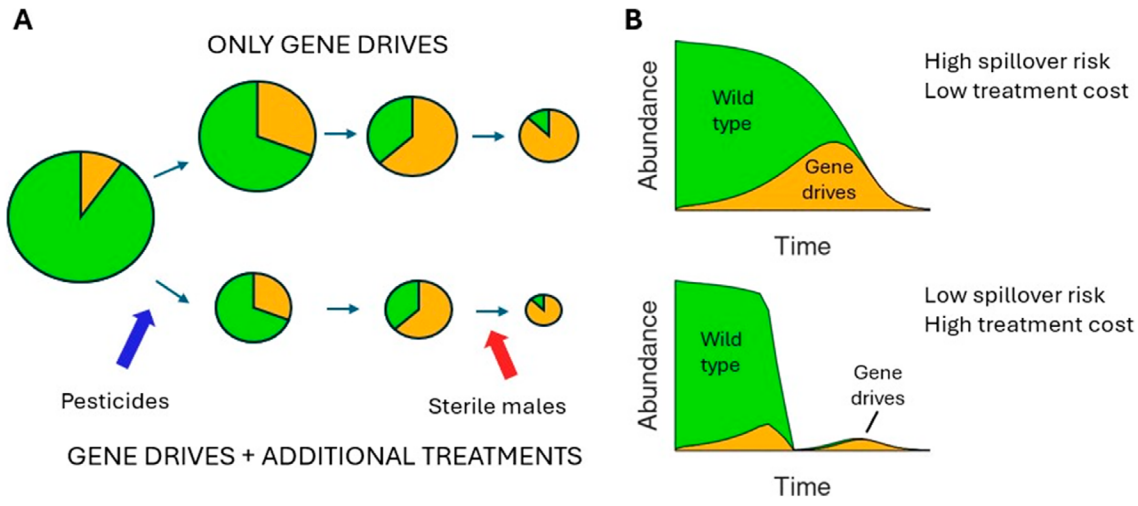


FIGURE 1 Illustration of the gene drive dynamics, with and without additional treatment methods. (A) Circles represent the population at different times throughout the treatment process (from left to right) or following different treatment scenarios (upper row vs. bottom row). Circle sizes represent population size, and their colors represent the genetic composition (orange is gene drives, green is wild-type). In both top and bottom rows, gene drives spread over time (the orange area becomes larger relative to the green area), and the population shrinks until it vanishes (circle sizes decrease over time). The top row demonstrates the dynamics without additional treatment (no pesticides and no sterile males). In the bottom row, pesticides and sterile males are introduced at different stages to speed up the eradication process. (B) Demonstrated are the abundances of the gene drive carriers and the wild-type individuals during eradication, without (top row) and with (bottom row) additional treatments. Spillover risk is proportional to the total number of gene drive carriers over time, represented approximately by the orange area in the population dynamics plots. Adding established pest controls (e.g., pesticides, sterile males) accelerates population suppression and thereby reduces spillover risk compared to using gene drives alone (top row vs. bottom row). However, these additional interventions incur their own costs, and minimizing the total cost can be optimized by controlling the timing and intensity of treatment application.

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generation, P_t, and sterile-male release in each generation, M_t. Thus, the NPC is given by

$$\mathrm{NPC} = \sum_{t=1}^{\infty} (C_S n_{D,t} + C_P P_t + C_M M_t), \quad (8)$$

where C_S is the damage per unit of potential escapees (the unit here is the number of gene drive carriers equal to the carrying capacity), C_P is the cost per unit of pesticide application, and C_M is the cost per unit of sterile-male release. Note that we do not consider discounting in Equation (8), since eradication is assumed to be rapid and the difference between present and delayed expenditures is negligible. Note that the constant coefficient C_S can be viewed as the product of two components: (1) the probability of each individual escaping, and (2) the expected damage caused by each escaped gene drive carrier. Therefore, higher C_S values could result from higher migration rates to nontarget populations or from greater valuation of spillover-induced damages. We scale all three cost coefficients in Equation (8) to that of spillover and thereby remain with only two cost ratios: $\alpha = C_P/C_S$ and $\beta = C_M/C_S$; hereafter, these cost ratios are referred to as the *per-unit treatment costs*. Higher α and β values imply higher costs of pesticides and sterile males, respectively, relative to the cost of spillover. Although the absolute values of C_P and C_M can be quantified in some situations (Lampert, 2024; Lampert & Liebhold, 2021), the value of C_S is largely unknown and hard to estimate. Thus, to keep our study general and applicable to various real-world cases, we consider a wide range of α and β values. For each combination of α and β values, we find the minimum achievable total spillover risk and express it as a function of the total investment in the other control methods. This multiple-objective optimization approach allows the examination of the full range of possibilities, not only for a certain choice of the relative cost. Our optimization procedure is conducted through a dynamic programming approach (Mangel & Clark, 1988), described in detail in Appendix S2.

Model parameterization

We focus on "successful" suppression gene drives, which invade the target population regardless of their initial frequency and eventually eradicate it. For tractability, most results shown here are for a gene drive with configuration $(s, c, h) = (0.7, 0.9, 0.5)$ deployed in a population with intrinsic growth rate $r = 2$. This baseline parameter set is chosen as a plausible species-averaged configuration. We also examine deviations from this baseline parameter set by varying the gene drive's fitness cost s (ranging from 0.3 to 1), conversion rate c (ranging from 0.8 to 1), and dominance h (ranging from 0 to 1), as well as the population's intrinsic growth rate r (ranging from 1.1 to 10). When varying these parameters, we consider only settings that result in unconditional gene drive spread and population eradication. For example, with a conversion rate of $c = 0.9$, dominance $h = 0.5$, and growth rate $r = 2$ (the baseline parameter set), we consider fitness costs ranging from $s = 0.5$ (below which the gene drive suppresses but does not eradicate the population) to $s = 0.95$ (above which the gene drive fails to spread). The results of sensitivity analysis provided in Appendix S3 show that deviations from the baseline parameter set do not qualitatively change the main conclusions, even when several parameters simultaneously substantially depart from the baseline configuration.

We mainly report results for a standard deployment scenario, where a small number of gene drive homozygotes ($q_0 = 0.01$) are introduced into a large population stable at the carrying capacity ($n_0 = 1$); however, to understand which population states require additional treatments, we also explore the whole space of possible initial conditions, with both q_0 and n_0 ranging from 0.01 to 1. Since it is unclear how spillover damage should be quantified, we examine a range of scenarios, from the cost of spillover being negligible relative to that of treatment ($\alpha, \beta \to \infty$) to it being immeasurably large ($\alpha, \beta = 0$).

RESULTS

Pesticide applications are most cost-efficient during peak gene drive abundance

First, we investigate the optimal strategies for combining gene drives with pesticide application. Our results show that, if the per-unit treatment cost α is below a certain threshold (i.e., treatment is relatively cheap), the optimal strategy is to rapidly lower the population size with pesticides ($\alpha = 0$ in Figure 2A). Above this threshold, however, the optimal treatment strategy utilizes both gene drives and pesticides, with pesticide application starting a few generations after the gene drive release (Figure 2A). As α increases further, the optimal strategies utilize pesticide applications only later on and become milder in their intensity. Finally, if α is above an even higher threshold, pesticide applications are no longer cost-effective, and the optimal strategy is to allow gene drives to lead to eradication without further intervention.

These results demonstrate that pesticide application is most cost-effective in the middle phase of eradication. The primary reason for this is that gene drive carriers—

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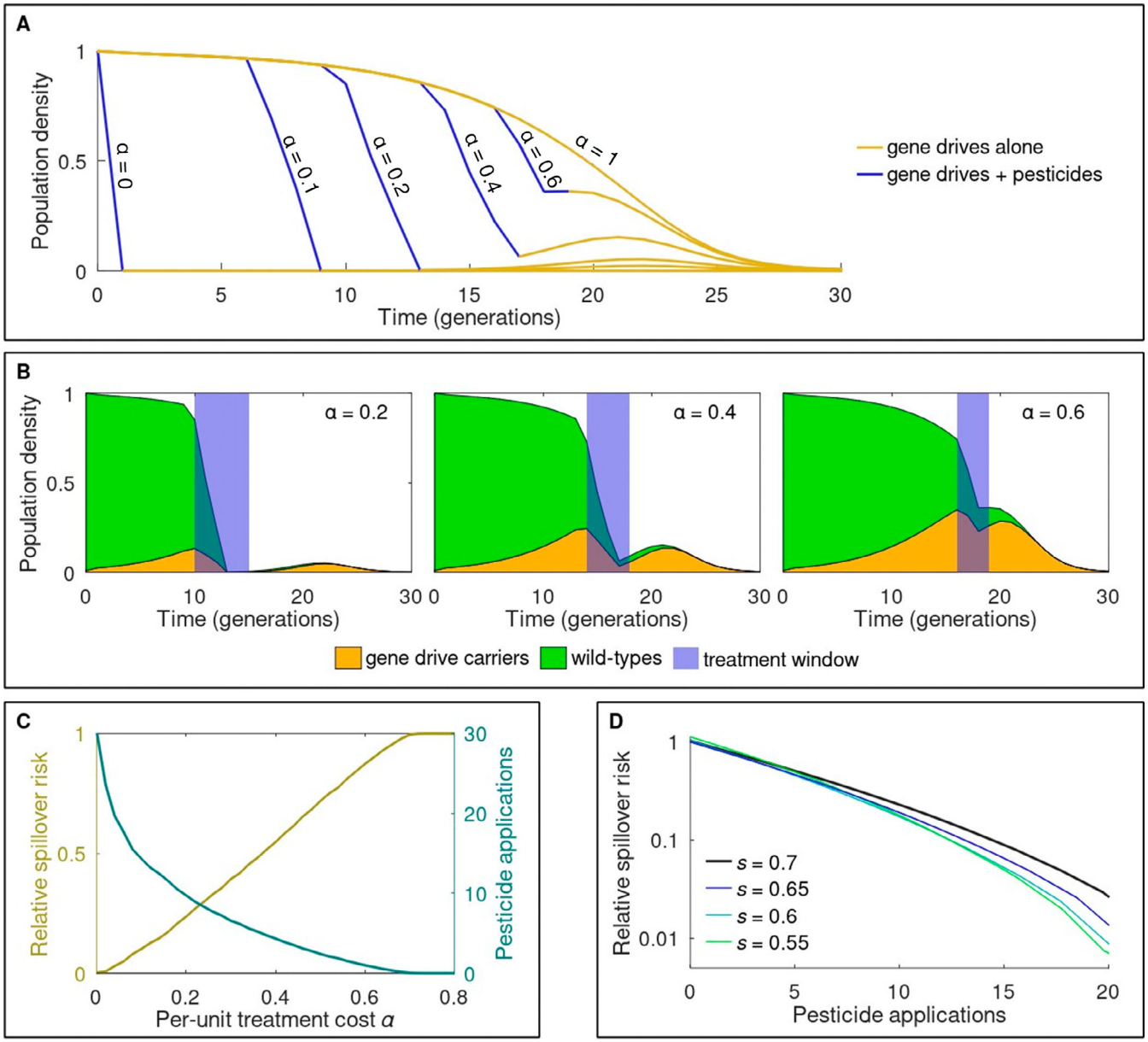


FIGURE 2 Optimal strategies for combining gene drive deployment with pesticide application. (A) Demonstrated are population dynamics under optimal pesticide application for different per-unit treatment costs (α), where the dynamics follow Equations (1) and (4). Each curve corresponds to a certain value of α denoted next to it. Population density is defined as population size relative to carrying capacity. (B) Demonstrated are genotype dynamics and treatment time windows for the optimal strategies for three values of α. (C) Relative spillover risk and total pesticide application following the optimal solution as functions of α. (D) Spillover-treatment curves, showing the minimum spillover risk achievable with the available amount of pesticides, for different values of s. Spillover risk shown on the y-axis is relative to the spillover risk of the baseline gene drive ($s = 0.7$) under no pesticide treatment. The curves are obtained by identifying the optimal treatment strategy for numerous values of α and computing relative spillover risk against total pesticide application. Parameters: $c = 0.9$, $h = 0.5$, $r = 2$; in (A–C) $s = 0.7$. Initial conditions are $n_0 = 1$ and $q_0 = 0.01$.

the source of spillover—become abundant at the intermediate stages (at the early stages, they are rare because the gene drive frequency is still low, whereas at late stages, they are rare because the population size is already small). Since the number of gene drive carriers is a key component of the objective function (Equations 7 and 8), the intermediate stages require the strongest intervention. A complementary reason for this is the change in the population's growth rate, which not only follows gene drive spread but also shifts upon interventions, given density-dependent demographic dynamics (Equation 6). At early stages, a high growth rate requires repeated pesticide applications and incurs additional costs. At late stages, when low-fitness gene drive carriers are abundant,

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the gene-drive-induced negative growth rate ensures eradication without pesticides. Thus, pesticide applications are cost-effective when the number of gene drive carriers (and hence the spillover risk) would reach its peak under the no-treatment scenario; as pesticide application becomes cheaper (lower α values), the treatment time window broadens (Figure 2B).

Following the optimal solution, as the per-unit treatment cost increases, the total amount of pesticide application decreases, while the relative spillover risk increases (Figure 2C). Specifically, the curve showing the resulting spillover as a function of the total pesticide application (Figure 2D) represents a Pareto front, in which one cannot obtain a solution that both requires fewer pesticide applications and results in lower spillover. The obtained spillover-treatment curve is convex, suggesting diminishing marginal efficiency from increasing pesticide application (Figure 2D), where each value of α results in a particular choice of total investment along the Pareto front. Our sensitivity analysis shows that the obtained spillover-treatment curves are qualitatively similar for a wide range of parameter values (Appendix S3: Figure S1).

Notably, cost-effectiveness can further be improved if the gene drive configuration is also subject to optimization. A key parameter that substantially affects gene drive dynamics is its fitness cost, s (Deredec et al., 2008; Unckless et al., 2015). Since gene drives with higher s values spread more slowly but suppress the population more strongly, an optimal fitness cost s^* must exist that minimizes the number of gene drive carriers over eradication (de Jong, 2017) and hence also the spillover risk. This optimal fitness cost should depend on both the gene drive configuration and demographic parameters, and particularly the intrinsic growth rate, because the latter determines the speed of population suppression once gene drive has spread. Comparison of spillover-treatment curves across various s values shows that, when the total pesticide application is zero, the optimal fitness cost for the growth rate of $r = 2$ is $s^* \approx 0.65$, slightly below the baseline configuration ($s = 0.7$). As intervention intensity increases, the optimal fitness cost tends to decrease (Figure 2D). Thus, combining gene drives with pesticide application favors gene drives with lower fitness costs, which could provide additional risk mitigation, especially under moderate-to-strong interventions.

Sterile-male strategies shift abruptly from weak to strong treatment regimes

Next, we consider the combination of gene drives with sterile-male release. Similarly to pesticides, for higher per-unit treatment cost β, the optimal strategy results in smaller total sterile-male release and higher relative spillover risk (Figure 3). However, we observe two qualitatively different types of optimal strategies which shift abruptly as β surpasses a critical threshold β_c—a behavior not observed for pesticides. For $\beta < \beta_c$, the optimal strategy is to release a large number of sterile males already during the first few generations following the gene drive release (Figure 3A, trajectories on the left). For higher β values (closer to the threshold), the releases start later and stop earlier, resulting in fewer sterile males being released overall. For $\beta > \beta_c$, the optimal strategy changes to minimal, if any, release of sterile males at a later stage, preceding the final stage where gene drive completes eradication alone (Figure 3A, trajectories on the right).

Not only do treatment strategies shift abruptly at $\beta = \beta_c$, but also the two outcomes following the optimal solution: total sterile-male release and relative spillover risk. The abrupt transition leaves a region of the spillover-treatment curve uncovered because optimal strategies with intermediate sterile-male release do not emerge (Figure 3, dashed segments in the right panels). This implies that the curve is concave in that region, and therefore, there is no value of the marginal cost β for which it is optimal to choose treatment from that region. The range of unobserved releases depends on parameter values; for example, it is narrower under lower fitness costs (Figure 3B) and under lower intrinsic growth rates (Figure 3C); qualitatively similar results are obtained with different parameters (Appendix S3: Figure S2).

The observed qualitative difference between pesticides and sterile males—gradual versus abrupt changes in optimal strategies—can be considered from the perspective of population states requiring treatment. The interplay between population dynamics and intervention efficacy can be visualized on a phase plane, where axes represent the abundances of gene drive and wild-type alleles. Irrespective of gene drive presence, pesticides are more effective in large populations, where each application removes more individuals, whereas sterile males are more effective in small ones, where their fraction relative to the wild-type counterparts is higher (Lampert & Liebhold, 2021). This general pattern is superimposed with drive-specific population dynamics, in particular changes in growth rate along the population's trajectory. Adding pesticides is cost-efficient if the population is sufficiently large and gene drive frequencies are intermediate. Moreover, pesticides are cost-effective in a narrower range of population densities if the per-unit treatment cost increases. On the phase plane, the above-mentioned conditions outline a triangular area adjacent to the hypotenuse; the area progressively contracts with α, gradually reducing the proportion of the population's

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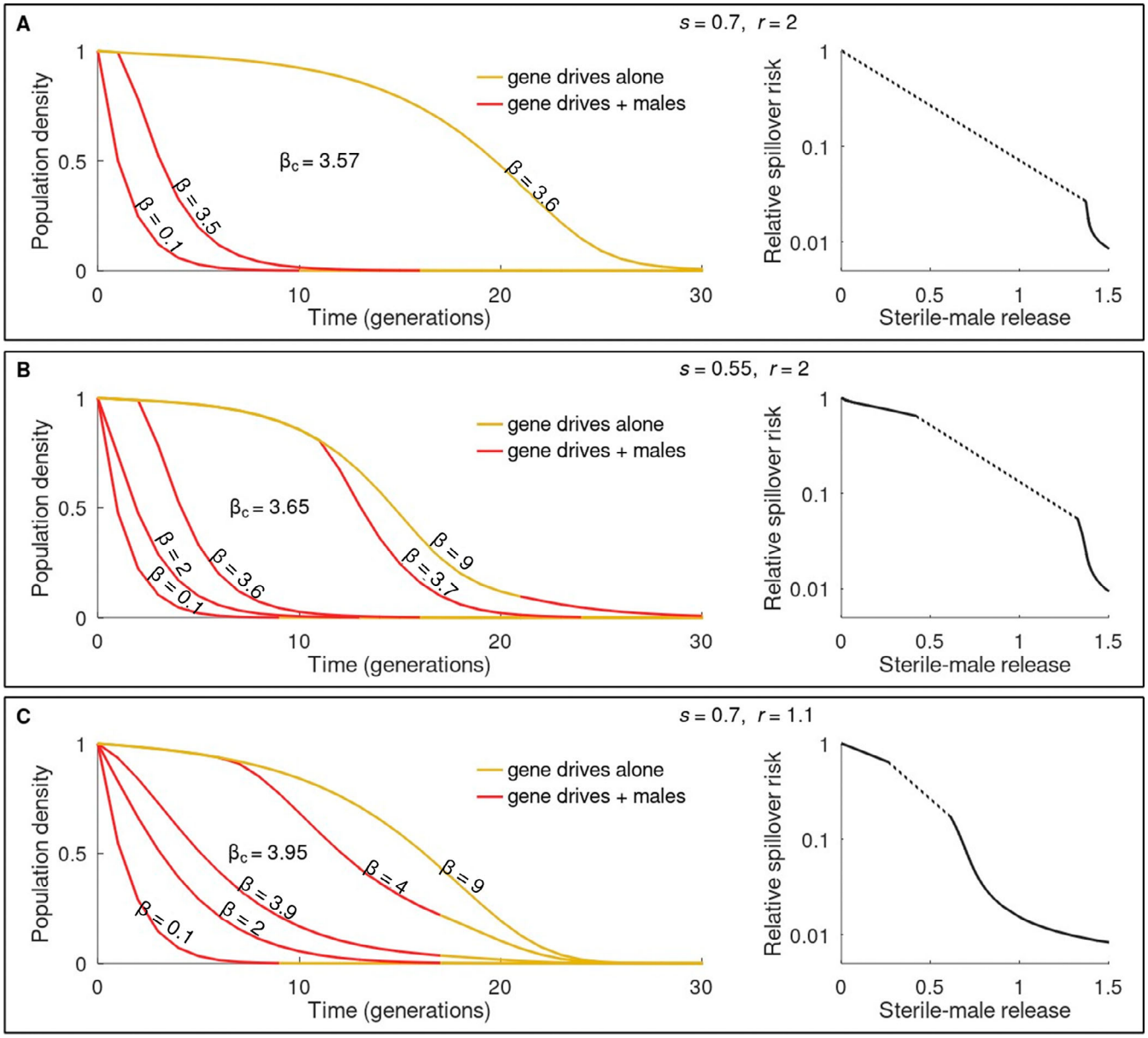


FIGURE 3 Optimal strategies for combining gene drive deployment with sterile-male release. Each box (A–C) shows optimal solutions for a different choice of the parameters r and s. In each box, the left panel shows the population dynamics under optimal sterile-male release for different per-unit treatment costs (β), denoted next to each curve, where the dynamics follow Equations (1) and (5). At a critical value β_c, the optimal treatment strategies change abruptly (the value of β_c is noted between the relevant curves). Population density is defined as population size relative to carrying capacity. The right panels report the spillover-treatment curve, showing the minimum relative spillover risk achievable with available amount of sterile males. Sterile-male release is defined as the number of sterile males relative to the wild-type carrying capacity. The dashed segments show ranges of sterile-male release that cannot be chosen as the optimal solution. Parameters: $c = 0.9$ and $h = 0.5$. Initial conditions: $n_0 = 1$ and $q_0 = 0.01$.

trajectory that intersects it (Figure 4A, blue). In contrast, adding sterile males appears cost-efficient when the population is small enough or the gene drive frequency is low. These conditions contour a drop-shaped area adjacent to the left edge of the phase plane (Figure 4B). The area moves downward with β, so at a critical β value, the entire trajectory shifts from lying inside (Figure 4B, left) to lying mostly outside (Figure 4B, right) this area.

For combined optimal treatments, pesticides are used early and sterile males later

Finally, we study a more general scenario, where both pesticides and sterile males can be used to mitigate spillover risk. Because we are now considering two possible interventions, we consider both per-unit treatment costs:

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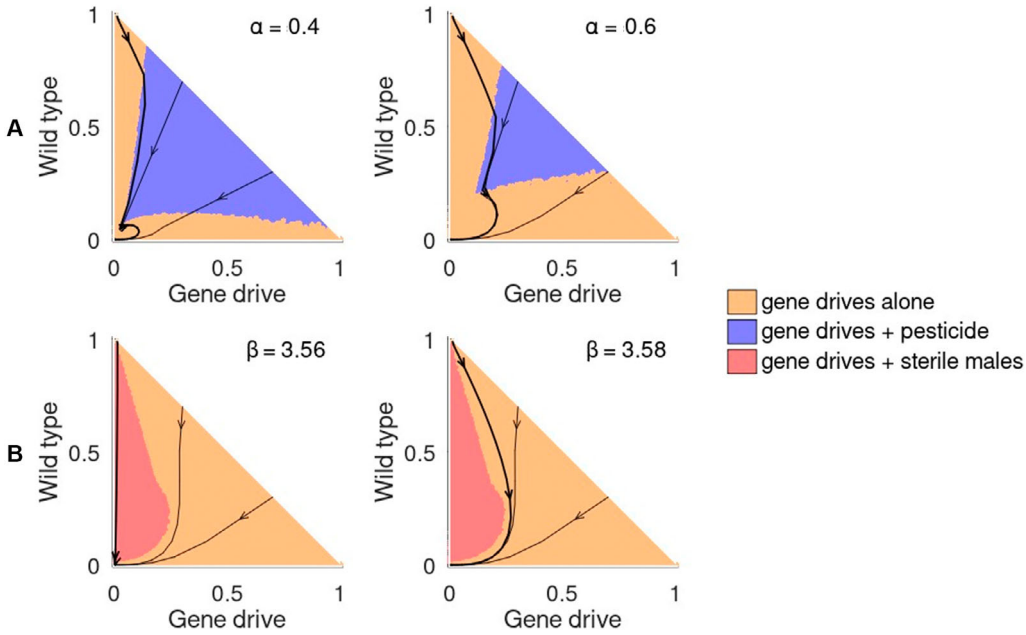


FIGURE 4 Population phase diagrams for gene drives combined with another treatment method. (A) Combining gene drives with pesticide application (Equation 4). (B) Combining gene drives with sterile-male release (Equation 5). The background colors denote states where gene drives are used alone (orange) or combined with pesticides (blue) or sterile males (red). For the shown gene drive configuration in (B), the critical per-unit treatment cost of sterile males is $\beta_c \approx 3.57$ (as in Figure 3A), and the two phase diagrams show scenarios slightly below (left) and slightly above (right) the threshold. Axes represent abundances of the two alleles relative to the carrying capacity. The black curves show the population's trajectories starting at different initial conditions (the bold curve corresponds to the initial conditions considered throughout most of the paper). Parameters: $c = 0.9$, $s = 0.7$, $h = 0.5$, and $r = 2$.

α for pesticide application and β for sterile-male release. The ratio between these two parameters, $\gamma = \alpha/\beta$, determines whether a single treatment method or their combination is favored. Specifically, we observe two thresholds, γ_1 and γ_2 ($\gamma_1 \le \gamma_2$), where pesticides are cost-effective when the ratio γ is below the upper threshold ($\gamma \le \gamma_2$) and sterile males when γ is above the lower threshold ($\gamma \ge \gamma_1$). Thus, both treatment methods should be applied only in the intermediate range $\gamma_1 \le \gamma \le \gamma_2$ (Appendix S2: Equation S4).

We found that when the per-unit treatment cost of one control method is low (relative to the other method and to the cost of spillover), only this method complements gene drive deployment. This scenario is demonstrated in the top row and left column of Figure 5: Sterile males are never used when $\alpha = 0.01$, whereas pesticides are never used when $\beta = 0.1$ (excluding the top-left panel, where α and β differ the least). Conversely, when the per-unit treatment cost of a method is substantially higher than that of the other method, it is abandoned, and the resulting pattern mirrors using the cheaper method alone. For example, the right column in Figure 5 resembles the pesticides-only scheme (Figure 4A), while the bottom row aligns with the males-only scheme (Figure 4B).

When both methods are affordable enough to be considered, but not cheap enough to be used alone, the optimal treatment strategy typically consists of several stages. In that case, pesticides are applied to initially suppress the population. Later, sterile males are released to sustain the population at a low density until gene drives have spread sufficiently. From that point onward, gene drives complete the eradication process alone. This sequence is demonstrated in the trajectories passing from blue through magenta to red and ultimately anchoring in the orange area on the phase plane in Figure 5.

Importantly, whenever the optimal treatment strategies involve both treatments, pesticide application starts immediately, without the lag often observed when pesticide application cannot be complemented by subsequent sterile-male release. This demonstrates the advantage of leveraging the synergy between different treatments: The possibility of conducting later stages of eradication more effectively, provided by sterile males, also enables earlier use of pesticides and thereby improves performance of the whole process.

Pesticide application before gene drive release may provide an additional advantage

In the previous sections, we assumed that gene drives are released into a population that has reached its carrying capacity and that treatments can be applied from that

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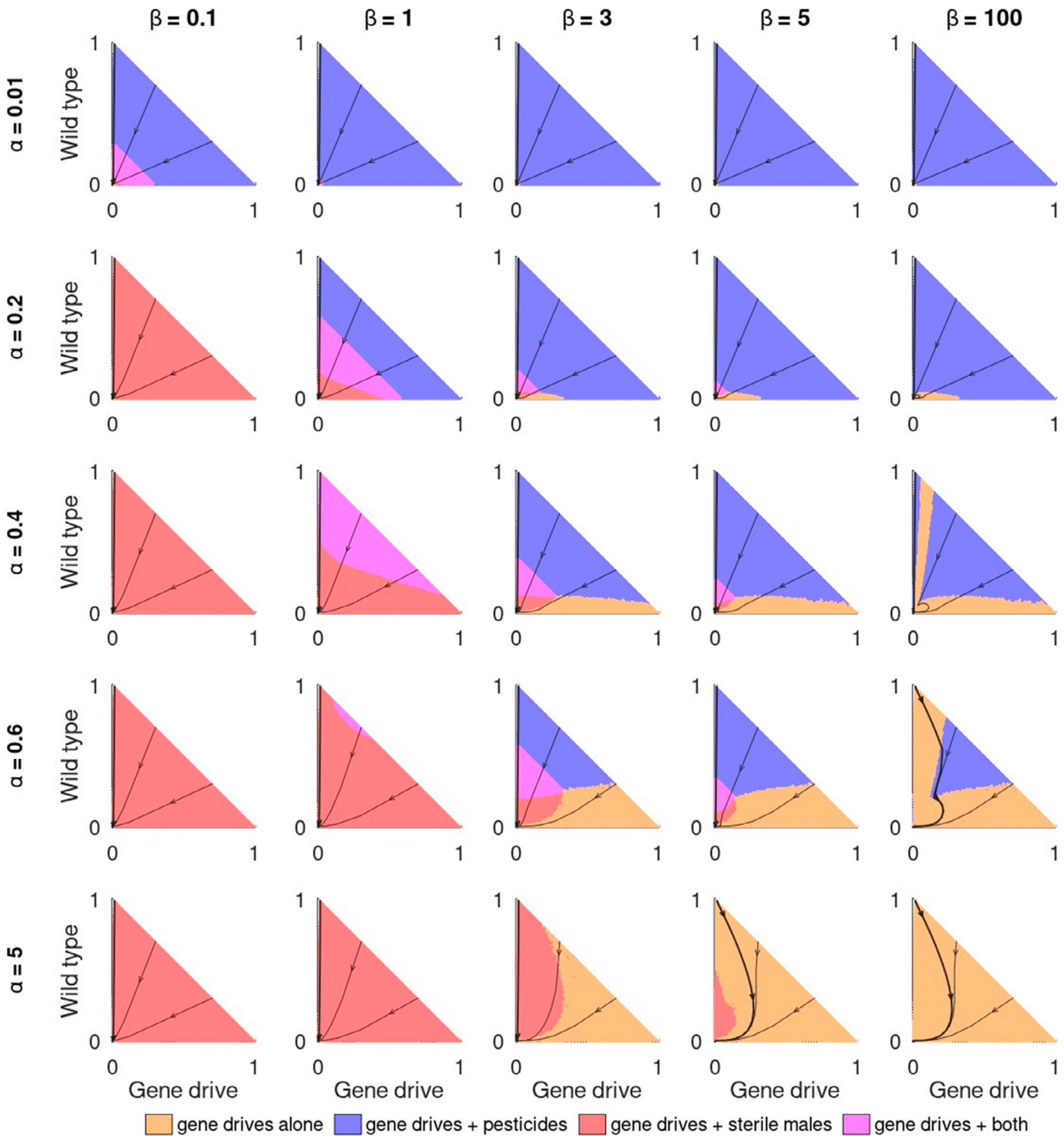


FIGURE 5 Population phase diagrams for cases in which both pesticides and sterile males can be used. Axes represent abundances of the two alleles: gene drive (x-axis) and wild-type (y-axis). The background colors denote states where gene drives are used alone (orange) or combined with additional treatments: pesticides (blue), sterile males (red), or both (magenta). The black curves show the population's trajectories starting at different initial conditions (the bold curve corresponds to the standard deployment scheme). Parameters: $c = 0.9$, $s = 0.7$, $h = 0.5$, and $r = 2$.

point onward. Another possibility for using established pest controls is preliminary treatment—suppressing the wild-type population before introducing gene drives. For consistency and to examine the effect of preliminary treatment alone (with all other factors remaining the same), we do not alter the initial number of gene drive carriers (although increasing this number may also increase eradication efficiency). Here, we examine the

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potential advantage of preliminary treatment with respect to pesticide application, because sterile-male release is most cost-efficient in already suppressed populations (see "*Sterile-male strategies shift abruptly from weak to strong treatment regimes*"). The intensity of preliminary pesticide application is subject to optimization due to an inherent trade-off: It facilitates eradication because gene drives start spreading from a higher initial frequency (as the population is already suppressed), but it requires additional investments. Notably, the timing of preliminary pesticide application does not require optimization, because it must always be most efficient to apply pesticides right before the gene drive release (earlier treatment would allow partial population recovery by the time the gene drives are released and is therefore wasteful). Thus, here we optimize the intensities of possibly applying pesticides both prior and subsequent to the gene drive release, extending the results above.

Our results show that, when pesticides are relatively cheap (low values of α), the total cost is minimized when the preliminary application of pesticides is intense, and the population density after this preliminary application is low (Figure 6A). In such cases, because the same amount of gene drive carriers is introduced to a relatively small population, gene drive frequency is initially high, leading to rapid eradication and low spillover risk. However, when pesticides are expensive, with values of α above a certain threshold, the optimal strategy does not include preliminary treatment (Figure 6B).

DISCUSSION

In this study, we developed a modeling framework for investigating the potential of integrating gene drives with established pest control methods to minimize the total cost of eradication, accounting for both direct treatment costs and expected damage due to spillover. This framework allows incorporating gene drive deployment into multiple-treatment schemes, controlling for direct expenditures and potential damage of spillovers. Our results show that both pesticide application and sterile-male release can substantially limit spillover, and we demonstrated how the optimal treatment strategy depends on biological (gene drive configuration and population growth rate) and economic (costs of interventions) parameters. Nevertheless, the optimal use of treatment methods, combined with gene drives, differs qualitatively between methods, with pesticides applied optimally to coincide with higher abundance of gene drive carriers, whereas sterile-male releases have two types of optimal application regimes, one early and intensive and one late and minimal.

Following the optimal strategy, regardless of the per-unit treatment costs, we observed a time point after which pesticide or sterile-male interventions should cease, and gene drives finalize eradication alone (see Figures 2A and 3). This occurs because, when the gene drive is sufficiently frequent, the population density monotonically decreases, eventually leading to a reduction in gene drive carrier abundance. In turn, the population density is already low (and so is the abundance of

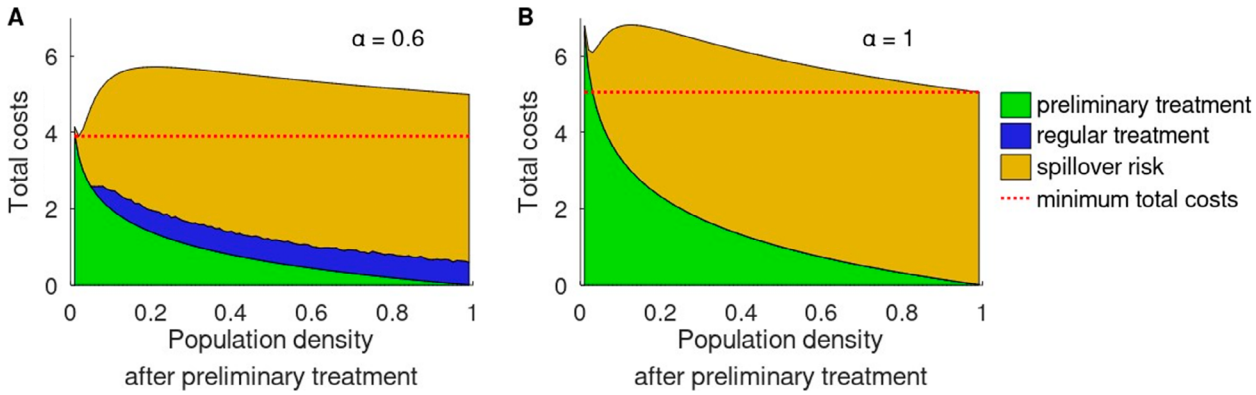


FIGURE 6 Optimal strategies for minimizing the total costs of eradication when pesticides can be applied both before and after gene drive release. Shown are the total costs of eradication as a function of population density after preliminary treatment, assuming optimal pesticide application from gene drive release onward. Population density is defined as population size relative to carrying capacity. The colors represent the components of the total cost: preliminary pesticide application (green), regular pesticide application (blue), and cost of spillover (orange). Shown are two qualitatively different results, corresponding to the optimal solutions for different choices of α (dotted red lines): (A) Intense preliminary pesticide application is optimal, as seen in the total cost reaching its minimum at low population density (around 0.02); and (B) Having no preliminary treatment is optimal, as seen in the minimum cost occurring at population density 1 (carrying capacity). Parameters: $c = 0.9$, $s = 0.7$, $h = 0.5$, $r = 2$, and initial condition is $n_{D,0} = 0.01$.

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gene drive carriers), and therefore, the marginal benefit of additional treatment becomes lower. This result aligns with previous findings in ecological restoration, where intervention occurs during intermediate stages and halts toward full recovery (Lampert & Hastings, 2014, 2019). In both cases, interventions move the system into a state from which the desired outcome, whether eradication or recovery, can be reached through system-internal dynamics alone, making additional treatments unwarranted. Additionally, we observed cases in which optimal strategies did not include established pest controls at the early stages of eradication. This occurs because, at early stages, when gene drives have only been introduced and have yet to substantially spread, spillover risk is still low, while the population growth rate is still high. Therefore, applying treatments during early stages would not substantially reduce the total spillover risk, and the population would be able to recover rapidly from the treatment.

Our study revealed an important distinction between pesticide applications and sterile-male releases in terms of their optimal use in combination with gene drives. With the increasing per-unit cost of pesticides, their total application gradually declined (see Figure 2C). In contrast, a threshold value of the per-unit cost of sterile males emerged, which discriminates two types of strategies: (1) intensive releases of sterile males starting from the earliest stages (Figure 3A, trajectories on the left) and (2) limited, cheap releases at late stages of eradication (Figure 3A, trajectories on the right). If both established pest controls complement gene drives, then pesticides should be applied first, when the population density is high, and sterile males released later, when the population density becomes lower (Figure 5). Similar temporal separation was previously reported for the optimal combination of treatment methods without gene drives (Lampert & Liebhold, 2021), and it occurs because pesticides are most cost-effective at higher population densities, whereas sterile males are most cost-effective at lower population densities, where their proportion is high enough to ensure predominant mating with sterile rather than wild males (Fister et al., 2013; Lampert & Liebhold, 2021).

Our general approach was to identify treatment strategies optimal in terms of total costs of eradication, including costs of both treatment and spillover. At the same time, the posed problem can be viewed as a multiple-objective optimization problem, with the number of gene drive carriers and expenditures on treatments being the two targets requiring simultaneous minimization. Assigning per-unit costs to these two targets and merging them into a single objective function—the total costs of eradication—would fall under the weighted-sum method of handling multiple-objective optimization. The total expenditure on treatment and the total spillover risk jointly form the Pareto front, visualized as spillover-treatment curves in Figures 2D and 3 (right panels). Such curves provide a useful practical tool because they eliminate the need to explicitly consider the per-unit treatment cost, which is often difficult to quantify. They demonstrate the best one could hope for: No solution exists that is both cheaper and results in lower spillover than any point on the Pareto front (Gunantara, 2018). Note that the spillover-treatment curves (Pareto fronts) obtained for pesticides are continuous and convex, implying that any point on the Pareto front results from a unique value of the per-unit treatment cost, α (Figure 2D). However, the spillover-treatment curves for sterile males contain separate segments, separated by dashed lines (Figure 3, right panels), indicating regions that do not exhibit the optimal solution for any value of β. Specifically, in these regions, the Pareto front is concave, implying that no value in that segment could be optimal.

One of the challenges in examining gene drive dynamics as a part of an optimal control problem is that the damage due to spillover is difficult to quantify. Therefore, our goal was not to assess absolute damage, but rather to evaluate the extent to which integrating established pest control methods can reduce spillover risk. We adopted a cautious approach, preferring to overestimate the risk rather than underestimate it, and therefore, we focused on gene drives that inevitably spread through populations, even though threshold-dependent drives (Greenbaum et al., 2021; Leftwich et al., 2018) and other designs of localization (Champer et al., 2020; Noble et al., 2019; Zhu & Champer, 2023) may be safer in terms of spillover. Because optimal strategies combining gene drives with other controls have not been previously investigated, we employed a simplified model for tractability. For simplicity, we consider the expected cost of damage due to spillover to be proportional to the total number of gene drive carriers over time. In particular, we assumed that population members have the same probability of escaping (though migration from the peripheries may be easier than from the core) and that each escaped gene drive carrier has the same potential to cause damage. Even where consequences depend primarily on whether any escape occurs, rather than on the number of escapees, the probability of at least one escape remains monotonic in cumulative carrier abundance under the constant independent-escape assumption, where the underlying assumption is that the probability of a spillover event remains small. Thus, the metric preserves the ranking of strategies for a given treatment effort, although absolute probabilities and cost-weighted optima require an explicit escape and consequence model. Also, our model does not incorporate

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stochasticity (Camm & Fournier-Level, 2025; Li & Champer, 2023), spatial structure (Beeton et al., 2022; Greenbaum et al., 2021; Harris & Greenbaum, 2023; North et al., 2020), type of selection (soft vs. hard; Harris & Greenbaum, 2023), or environmental sensitivity (Dhole et al., 2020; Kim et al., 2023). Nevertheless, our modeling approach is flexible and can be extended in future studies to include these and other biological and ecological features.

Another important aspect that should be considered in future models is the possibility of functional resistance to gene drive evolving along the course of eradication, which poses an additional risk in gene drive deployment that can be formulated as a cost, similar to how we treated spillover risk. Functional resistance may relate to spillover risk in complex ways: on the one hand, resistance may act as a natural safety mechanism, buffering spillover (Noble et al., 2018; Unckless et al., 2017), while on the other hand, it might result in stable polymorphism and prolonged persistence of gene drive carriers (Cook et al., 2022). Because the use of established pest controls may affect both suppression and resistance evolution, optimal strategies might utilize the advantages of different controls to minimize the different risks. Another aspect that could affect dynamics and should be incorporated into models is the sex-specificity of the gene drive. While most currently developed gene drive architectures target genes that cause sex-specific fitness costs (Gantz et al., 2015; Hammond et al., 2016; Kyrou et al., 2018), previous models have provided indication that the sex-averaged and two-sex models, generally, behave qualitatively similarly in terms of evolutionary dynamics (de Jong, 2017), suggesting that results presented here are reasonable first-order approximations to those expected with sex-specific drives. However, explicitly accounting for sex differences may improve estimation of costs and outcomes under some ecological scenarios.

Another issue limiting quantitative estimation of the risk of gene drive spillover is that it is species- and context-specific, and assessing these risks in natural settings is difficult. Previous modeling work has demonstrated the importance of considering various ecological features in spillover assessment, such as population structure (Birand et al., 2022; Gierus et al., 2022; Hancock et al., 2024; Pan & Champer, 2023), dispersal patterns (Champer et al., 2021; Hancock et al., 2024; Pan & Champer, 2023), mating system (Dhole et al., 2020; Sutter et al., 2021), interspecific transmission (Boëte, 2025; Connolly et al., 2023), etc. In light of these considerations, islands are currently viewed as a potential setting for initial field trials for deployment of gene drives for control of mosquito or rodent populations (Lanzaro et al., 2023). In these field trials, gene drives will need to be fine-tuned to locally fixed island-specific alleles (Oh et al., 2021; Sudweeks et al., 2019), and to enable adaptive, timely corrective actions (Connolly et al., 2024). Thus, if control methods such as pesticides and sterile males are to be integrated into these field trials, system-specific models should utilize the generalized framework presented here to investigate how they could cost-effectively improve the outcomes and reduce spillover risk under the specific parameters and settings of the trial. Such models could provide information for addressing the question "What level of spillover risk reduction is achievable with a given treatment budget?" while the acceptable level of residual risk must ultimately be determined in each specific case by relevant regulators and decision makers.

The framework presented here integrates spillover risk considerations into optimal pest management. Our goal is to develop a general framework that will allow for qualitative assessment of the potential benefits from combining gene drives with different established pest controls, rather than evaluating specific scenarios. Quantifying the probabilities of spillover events and their consequences will likely always involve many uncertainties. Nevertheless, our modeling approach is useful and practically applicable because the spillover-treatment curves it generates do not require cost estimates but assess the maximum relative reduction in spillover risk achievable with available resources (e.g., number of pesticide applications or sterile males). Thus, the integrated treatment schemes developed in this study clarify our understanding of how spillover risk can be mitigated using available resources and treatment types. Combining gene drives with tested and approved population control methods may help alleviate environmental damage and ease regulatory barriers that currently hinder the adoption of gene drives as a tool for addressing urgent public-health challenges.

AUTHOR CONTRIBUTIONS

Sviatoslav R. Rybnikov conducted the analysis and wrote the manuscript. Adam Lampert and Gili Greenbaum conceptualized, supervised, and wrote the manuscript. Adam Lampert and Gili Greenbaum contributed equally to the study, with the ordering of these authors determined via lottery.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Code (Rybnikov et al., 2026) is available in Dryad at https://doi.org/10.5061/dryad.1ns1rn997. An interactive version of the model dynamics is available through the modelRxiv repository (Harris et al., 2025) at: https://modelrxiv.org/model/JKcLuU.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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