

Supplementary Information

Controlling Invasive Rodents via Synthetic Gene Drive and the Role of Polyandry

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1 Text S1 Polyandry and Sperm Competition with an Arbitrary Number of Mating 2 Partners

3 **Polyandry** Let $f_{n,k}$ denote the frequency of a female mating with n males of which k are drive
4 males. To calculate $f_{n,k}$, we need to know the probability that a female mates with n mating
5 partners (where $n \in \{1 \dots n_{max}\}$), which we determine with parameter ϕ_n (with $\sum_1^n \phi_n = 1$). We
6 assume here that the mating process is random. Because we only have two types of (fertile) males,
7 the probability that a female encounters k t -Sry males in her sample of n mating partners follows
8 a binomial distribution. For a given mating combination n, k , we thus have

$$f_{n,k} = \phi_n \binom{n}{k} y^k (1-y)^{n-k}. \quad (S1)$$

9 For example, the probability that a female encounters two drive males ($k = 2$) if she mates with
10 three males overall ($n = 3$) will be $f_{3,2} = \phi_3 3y^2(1-y)$.

11 **Sperm Competition and Gene Drive** The *genotypic outcome* of a given mating combination n, k
12 will depend on the probability of fertilization by a t sperm, denoted by $p_{n,k}$. It depends on the
13 level of gene drive s (where $s = 0.5$ denotes Mendelian inheritance and $s = 1$ represents complete
14 drive) and sperm competitiveness r (see below). w/t and w/w males contribute the fraction
15 $\frac{k}{n}$ and $\frac{n-k}{n}$, respectively, to the sperm pool (viable and non-viable). However, we assume that
16 only r of a $D_w D_{Sry}$ male's sperm is viable, of which a fraction s carries the driver. Parameter r
17 hence defines $D_w D_{Sry}$ male sperm competitiveness relative to $D_w D_w$ wildtype males (whose sperm
18 competitiveness equals unity). It is thus a measure of sperm precedence at fertilisation, also referred
19 to as the loading of the sperm raffle. If all viable sperm have an equal fertilization probability, $p_{n,k}$
20 will be the fraction of viable t -Sry sperm $\frac{k}{n}sr$ divided by the total number of sperm $(1-k) + kr$.
21 We thus have

$$p_{n,k} = \frac{kdr}{n - k + kr}. \quad (S2)$$

22 If there are only drive males in a given male sample, $p_{n,k=n} = s$. Likewise, if all males are wildtype
23 males, $p_{n,k=0} = 0$. Hence, a drive male's reduced sperm competitiveness (r) is only relevant if males
24 of both genotypes are in the sample ($0 < k < n$ for $n > 1$). We can now calculate p , defined as
25 the probability that a given ova is fertilised by t -Sry sperm over all possible matings, which is simply
26 sum of the probability of D_t fertilisation of a particular mating $p_{n,k}$ weighed by possible mating

combinations $f_{n,k}$:

$$p_{n_{\max}} = \sum_{n=1}^{n_{\max}} \sum_{k=0}^n f_{n,k} p_{n,k}. \quad (\text{S3})$$

For the polyandry model used in the main text, we consider a simple scenario where females either mate with one male (at frequency $1 - \psi$) or two males (at frequency ψ). We can recover p_1 and p_2 from the main text by solving equations S1–S3 for $n_{\max} = 2$, $\phi_1 = 1 - \psi$, and $\phi_2 = \psi$.

Figure S1 illustrates how the number of mating partners n_{\max} , drive male frequency in the population y , and drive male sperm competitiveness r affect the probability of drive fertilisation p .

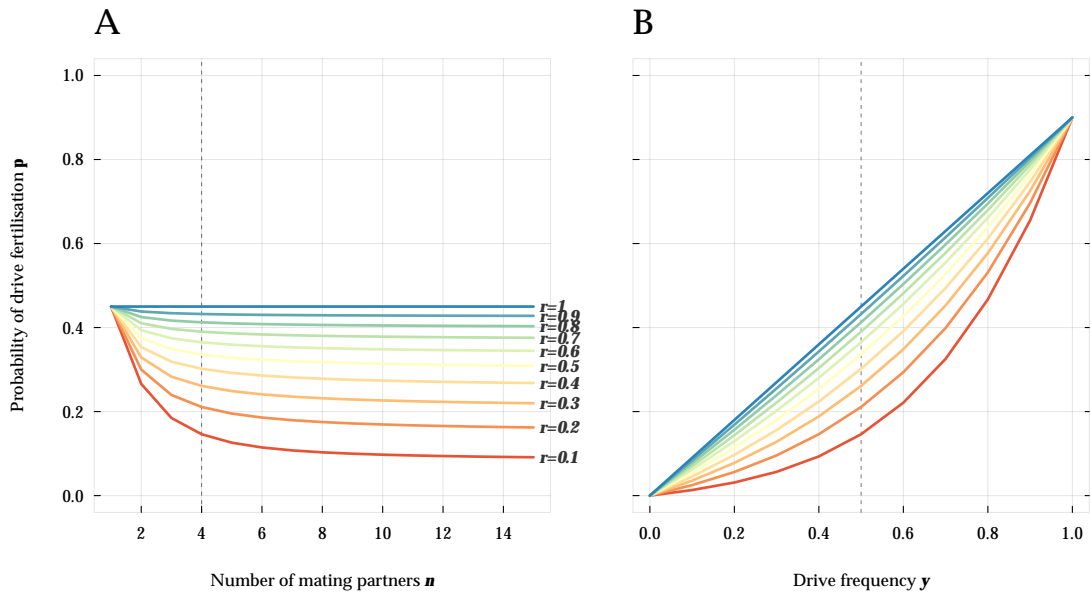


Figure S1. Polyandry and sperm competition reduce the probability that a female is fertilised by drive sperm. A. Polyandry is more effective if the number of mating partners n is high, although the marginal reduction in p gets smaller with every additional mating partner n . The different coloured lines represent varying levels of drive male sperm competitiveness r (colour gradient). The frequency of drive males in the population equals $y = 0.5$. B. Polyandry is less effective if the frequency of drive males is increased, as sperm competition is only relevant if drive males compete against wildtype males. The colour gradient again represents different levels of drive male sperm competitiveness r .

33 Text S2 Analytical Results — Single Release

34 In the case of a single release ($\mu = 0$), our system of differential equations ?? simplifies to

$$\begin{aligned}\frac{dN}{dt} &= bW - (m_1 + m_2 N)N \\ \frac{dW}{dt} &= bW \frac{1-p}{2} - (m_1 + m_2 N)W \\ \frac{dD}{dt} &= bW \frac{p}{2} - (m_1 + m_2 N)D\end{aligned}\tag{S4}$$

35 where $p = s \frac{D}{W+D}$ under monandry.

36 **Fixed points** The system S4 will reach a longterm equilibrium $\{\hat{N}, \hat{W}, \hat{D}\}$ if $\frac{dN}{dt} = \frac{dW}{dt} = \frac{dD}{dt} = 0$.

37 We have the following three solutions

$$\begin{aligned}\hat{N} &= \frac{\frac{b}{2} - m_1}{m_2}, \quad \hat{W} = \frac{\frac{b}{2} - m_1}{2m_2}, \quad \hat{D} = 0 \\ \hat{N} &= 0, \quad \hat{W} = 0, \quad \hat{D} = 0 \\ \hat{N} &= -\frac{m_1}{m_2}, \quad \hat{W} = 0, \quad \hat{D} = D\end{aligned}\tag{S5}$$

38 of which only the first two are biologically feasible, as the third equilibrium requires negative mortality
39 rates to produce $\hat{N} > 0$. The first equilibrium point describes a population where the driver is absent
40 and the population is at carrying capacity. The second equilibrium corresponds to the trivial case
41 where the population is not sustainable in the first place.

42 **Stability** The first equilibrium has the following three stability eigenvalues: $r_1 = -\frac{b}{2}$, $r_2 = m_1 -$
43 $\frac{b}{2}$, $r_3 = -\frac{b}{2}(1 - s)$. As expected, the population is viable if birth rates outweigh baseline death
44 rates ($m_1 < \frac{b}{2}$). Moreover, and as mentioned in the main text, we can have $r_3 = 0$ as the leading
45 eigenvalue when drive is complete ($s = 1$), which will change the dynamics of the system altogether,
46 as the driver can be maintained stably in the population.

47 Text S3 Analytical Results — Continued Release under Monandry

48 To simplify equilibrium calculations under continued release ($\mu > 0$), we rearrange the system
 49 slightly. Let D' denote the number of drive carrying 'females' $XYwt$ in the population. We can now
 50 write the system as the following three differential equations

$$\begin{aligned}\frac{dW}{dt} &= bW \frac{1-p}{2} - (m_1 + m_2 N) W \\ \frac{dD}{dt} &= bW \frac{p}{2} - (m_1 + m_2 N) D + \mu \\ \frac{dD'}{dt} &= bW \frac{p}{2} - (m_1 + m_2 N) D'\end{aligned}\tag{S6}$$

51 where the total population is now given as $N = 2W + D + D'$. We again search for equilibria by
 52 setting $\frac{dW}{dt} = \frac{dD}{dt} = \frac{dD'}{dt} = 0$. In the case of monandry, we get two biologically feasible solutions:

$$\begin{aligned}\hat{D}_1 &= \frac{-m_1 + \sqrt{m_1^2 + 4m_2\mu}}{2m_2}, \hat{W}_1 = 0, \hat{D}'_1 = 0 \\ \hat{D}_2 &= \frac{2\mu}{b(1-s)}, \hat{W}_2 = \text{complicated expression}^*, \Delta\hat{D}_2 = \text{complicated expression}^*\end{aligned}\tag{S7}$$

53 *available on supplementary Maple file.

54 **The eradication equilibrium and its stability** As in the case a single release, the first equilib-
 55 rium $\{\hat{W}_1, \hat{D}_1, \hat{D}'_1\}$ describes the (desired) outcome where the population is successfully eradicated
 56 ($\hat{W}_1 = 0$). Of the three eigenvalues of the Jacobian matrix, $r_{1,2,3}$, at the equilibrium point (see sup-
 57 plementary Maple file), only one can take on positive values ($r_1 = \frac{(1-s)b - m_1 - \sqrt{m_1^2 + 4m_2\mu}}{2}$). We can
 58 thus calculate the critical release rate μ_1^* at which the eradication equilibrium becomes attracting
 59 as the point where the leading eigenvalues r_1 becomes negative ($r_1 < 0$ if $\mu > \mu_1^*$). In other words,
 60 if release rates exceed μ_1^* , wildtype animals can no longer invade a population. Solving $r_1 = 0$ and
 61 replacing m_2 with $\frac{\frac{b}{2} - m_1}{K}$ (see Text S2), we have

$$\mu_1^* = \frac{K \frac{b}{2} (1-s) \left((1-s) \frac{b}{2} - m_1 \right)}{4R},\tag{S8}$$

62 where R denotes the baseline reproductive rate $R = \frac{b}{2} - m_1$. Also note that μ_1^* is a linear function
 63 of carrying capacity K , the standardised release rate $\mu_{\text{std},1}^* = \frac{\mu_1^*}{K}$ will hence be independent of
 64 population size K .

The internal equilibrium and its stability The second, internal equilibrium corresponds to the case where both drive and wildtype individuals stably coexist. Although solutions for \hat{W}_2 and \hat{D}'_2 exist, they are unwieldy and offer little insight. However, note that the dynamics of drive males D and 'females' D' only differ by the fact that males are released into the population while drive 'females' D' are not. More formally, at equilibrium, we have $\Delta\hat{D} = \hat{D} - \hat{D}' = \frac{\mu}{m_1 + m_2 N}$. Together with the fact that D' cannot take on negative values, this implies that $0 \leq \hat{D}' \leq \hat{D}$ for biologically relevant parameter values ($\mu, m_1, m_2 \geq 0$). As a plausible approximation, we can thus examine stability of the two boundaries where $\hat{D}' = 0$ or $\hat{D}' = D$. Note that this argument is mathematically not strictly correct, as $0 \leq \hat{D}' \leq \hat{D}$ does not guarantee that the stability eigenvalues or critical release thresholds are also sandwiched between those two cases (because they may depend non-monotonically on D'). They may nevertheless serve as a useful, plausible approximation.

- In the first boundary case where $D' = 0$, our differential equation system reduces to

$$\begin{aligned}\frac{dW}{dt} &= bW \frac{1-p}{2} - (m_1 + m_2 N) W \\ \frac{dD}{dt} &= bW \frac{p}{2} - (m_1 + m_2 N) D + \mu\end{aligned}\tag{S9}$$

where, importantly, $N = 2W + D$ (since $D' = 0$). System S9 is much easier to handle, and allows us to calculate the two eigenvalues of the Jacobian matrix at the internal equilibrium (see Supplementary Maple file). Once again, we can calculate critical release rate μ_2^* where the equilibrium becomes unstable and the population collapses. We have

$$\mu_2^* = \frac{K \frac{b}{2} (1-s) \left(2bs - R - \sqrt{4bs(2bs - R)} \right)}{R},\tag{S10}$$

with $R = \frac{b}{2} - m_1$. Note that μ_2^* is again independent of carrying capacity K when standardised $\mu_{\text{std},2}^* = \frac{\mu_2^*}{K}$.

- In the second boundary case where $D' = D$ we have system S9 with the important difference that $N = 2W + 2D$ (since $D' = D$). We can again calculate the critical release rate μ_3^* using the approach used above (Supplementary Maple file). We have

$$\mu_3^* = \frac{KR(1-s)}{8s}.\tag{S11}$$

86 **Testing approximate solutions** To assess the accuracy of the two approximate solutions, we com-
 87 pared them against numerical solutions based on the full equation system (see Figure S2). For all
 88 parameter combinations considered, the two analytical approximations μ_2^* , μ_3^* predict numerically
 89 calculated release thresholds relatively accurately. Numerically calculated release thresholds were
 90 indeed placed inside the interval of the two boundary cases $[\mu_2^*, \mu_3^*]$. Moreover, the critical release
 91 rate for the eradication equilibrium μ_1^* was smaller than μ^* for the internal equilibrium for all param-
 92 eter values considered ($\mu_1^* < \mu_3^* < \mu_2^*$). Hence, at least for the parameter space examined, we can
 93 distinguish three qualitatively different dynamics as release rates of drive animals μ into the target
 94 population are increased.

- 95 1. If release rates μ are sufficiently low such that $\mu < \mu_1^*$, the internal equilibrium is stable and
 96 the eradication equilibrium unstable. The resident population is sustainable.
- 97 2. At intermediate release rates where $\mu_1^* < \mu < \mu_3^*$ we have a bistable system where both the
 98 internal and the eradication equilibrium are stable. Note that the existence of bistability also
 99 implies that examining the stability criteria of the eradication equilibrium (invasion criteria),
 100 which is mathematically straightforward, is *not* sufficient to predict population eradication.
- 101 3. If release rates are sufficiently large such that $\mu > \mu_2^*$ the internal equilibrium is repellent
 102 and eradication is stable. The population collapses. Note that, because we had $\mu_1^* < \mu_2^*$ for
 103 all combinations considered, the condition $\mu > \mu_2^*$ was both a sufficient and necessary for a
 104 successful eradication.

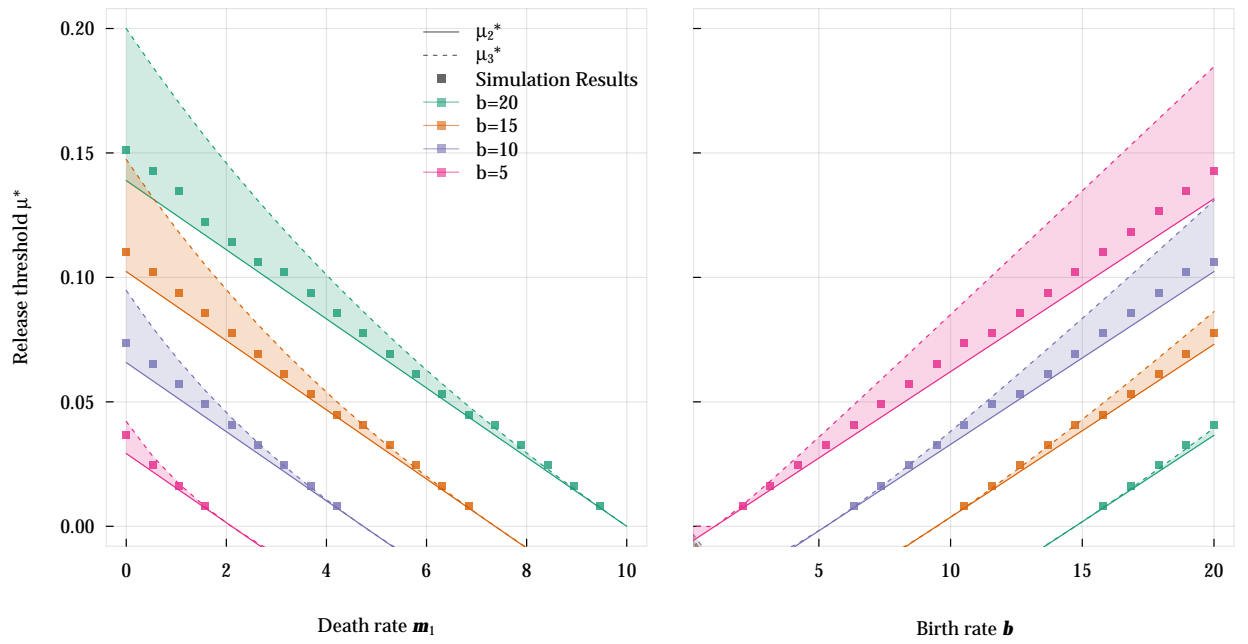


Figure S2. The critical release effort μ_{std}^* required to push a population to eradication as a function of birthrate b and death rate m_1 based on analytical approximation (solid and dotted line for μ_2^* and μ_3^* , respectively) and numerical calculation (squared dots). Drive strength in both panels is $s = 0.9$.

105 Text S4 Differential survival and mate choice

106 In this section, we analyse the effect of differential survival rates between genotypes and precop-
 107 ulatory mate choice on a) the success of *t-Sry* release campaign and b) on the strength of the
 108 polyandry effect explored in the main text. Because all four genotypes now have different fitness,
 109 we have to track them separately. We have the following equation system

$$\begin{aligned}
 \frac{dW_X}{dt} &= bW_X \frac{1-p}{2} - (m_1 + m_2 N) W_X \\
 \frac{dW_Y}{dt} &= bW_X \frac{1-p}{2} - (1 + s_m) (m_1 + m_2 N) W_Y \\
 \frac{dD_X}{dt} &= bW_X \frac{p}{2} - (1 + s_m + s_t) (m_1 + m_2 N) D_X \\
 \frac{dD_Y}{dt} &= bW_X \frac{p}{2} - (1 + s_m + s_t + s_{2Sry}) (m_1 + m_2 N) D_Y + \mu.
 \end{aligned}
 \tag{S12}$$

110 Population size N is again given as the sum of all four genotypes: $N = W_X + W_Y + D_X + D_Y$.

111 **Differential survival** Here, s_i represent survival differences between the different genotypes. They
 112 quantify the survival cost (or benefit if $s_i < 0$) of being (phenotypically) male (s_m), carrying the t
 113 haplotype (s_t), and the cost of carrying an extra copy of the *Sry* (s_{2Sry}).

114 The top panels in Figure S3 illustrate the effect of t related survival costs s_t on the required
 115 release effort to eradicate the population μ_{std}^* , and how that relationship is affected by polyandry
 116 levels ψ (the primary focus of this manuscript). As expected, required release efforts increase with
 117 increasing survival costs of the driver. Interestingly, the independent effects of survival (moving
 118 horizontally on upper panels in Fig. S3) and polyandry (moving vertically on upper panels in Fig.
 119 S3) are nearly identical, at least for the parameter combinations considered. Additionally, it appears
 120 that the two effects are close to additive.

121 In Figure S4, we investigate the impact of a survival cost on being phenotypically male (s_m)
 122 and of carrying an extra copy of the *Sry* gene s_{2Sry} on release dynamics. s_m has only very small
 123 effects on required release rates μ_{std}^* . This is because the success of the drive construct *mainly*
 124 depends on how competitive *t-Sry* males are *relative* to wildtype males, which is independent of
 125 overall male survival. In fact, lower male survival in some cases even decreases the required release
 126 effort because it creates decreased (density-dependent) competition on reproductive females. The

fact that the dynamics are dominated by the fitness contrast between drive and wildtype males also explains why the cost of carrying an extra S_{ry} $s_{2S_{ry}}$ is nearly identical to s_t (as the survival difference between drive and wildtype males is $s_t + s_{2S_{ry}}$, as reflected in the symmetry in right panel in Figure S4 with respect to the diagonal).

Mate choice We further explore the possibility that females have a precopulatory mating preference (preexisting or evolved), most likely to avoid drive carrying males. Let α measure the fixed relative strength of females to avoid matings with drive males. The probability of mating with a drive male f_t is given as

$$f_t = y \frac{1 - \alpha}{1 - \alpha y}. \quad (\text{S13})$$

where the denominator $y(1 - \alpha) + (1 - y) = 1 - \alpha y$ is a normalising constant that ensures that the probabilities of the two possible matings (W and D) add up to 1. Hence, females avoid drive males in the spectrum where $0 < \alpha < 1$, $\alpha = 0$ represents random mating, and $\alpha < 0$ would denote a preference for drive males. Substituting f_t for y in Equation 2, we then have

$$p_2 = f_t s \left(1 - \psi(1 - f_t) \frac{1 - r}{1 + r} \right). \quad (\text{S14})$$

The lower three panels in Fig. S3 show the effects of mate choice on required release efforts. Again, as expected, more animals need to be released if resident females avoid drive males. Note that mate avoidance becomes particularly problematic from an intervention perspective if drive male avoidance is strong ($\alpha > 0.6$). Again, there are no clear interactive effects with polyandry ψ .

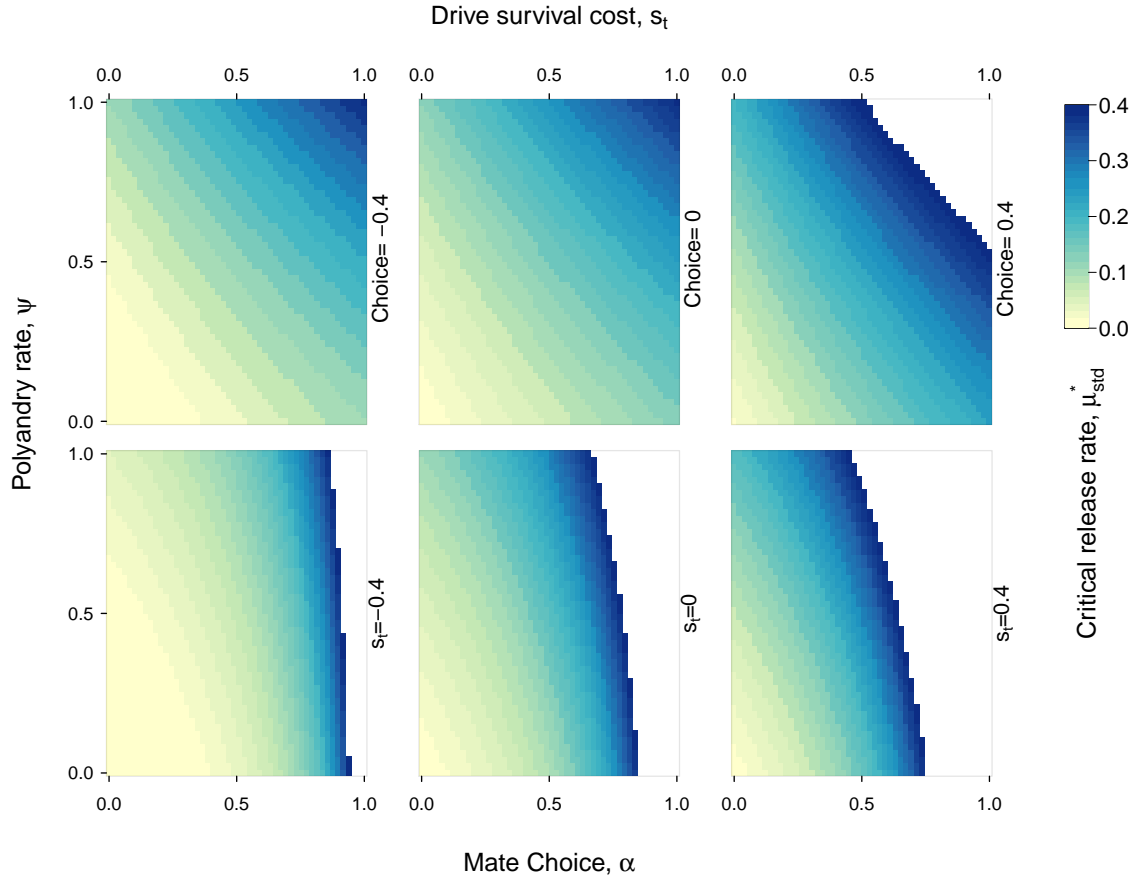


Figure S3. The critical release effort μ_{std}^* required to eradicate a population as a function of the survival cost of the driver s_t , mate choice against the driver α , and polyandry rate ψ . The three upper panels focus on drive survival costs s_t for three different levels of mate choice ($\alpha = -0.4, 0, 0.4$). The three lower panels focus on mate choice for three levels of drive survival cost ($s_t = -0.4, 0, 0.4$). The white area represent parameter combination where the required release rate exceeded the range considered ($\mu_{std}^* > 0.4$). Remaining parameter values for all panels: $s = 0.9$, $r = 0.2$, $s_m = 0$, $s_{2sry} = 0$, $b = 4$, $m_1 = 1$, $K = 1000$.

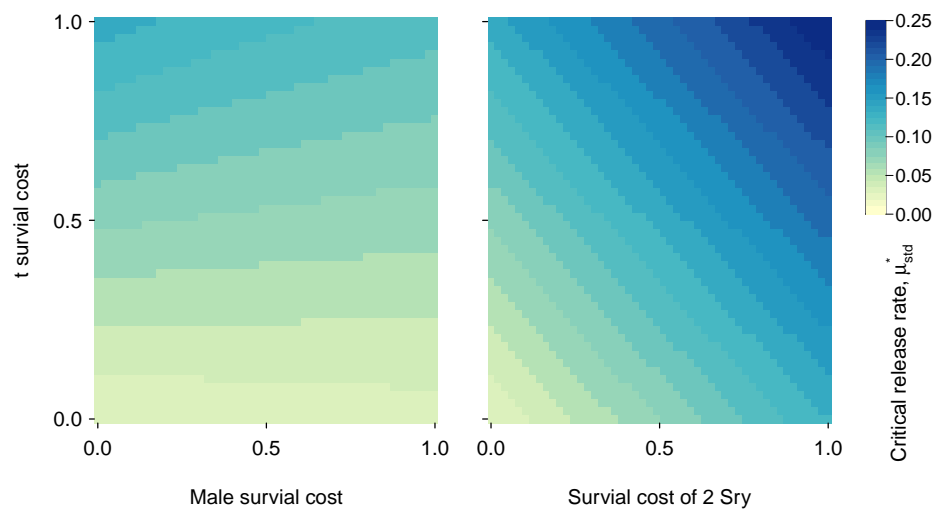


Figure S4. The critical release effort μ_{std}^* required to eradicate a population as a function of the survival cost of the driver s_t , the survival cost of being (phenotypically male) s_m , and the cost of carrying an extra copy of the *Sry* gene. Remaining parameter values for all panels: $s = 0.9$, $r = 0.2$, $\psi = 0$, $\alpha = 0$, $b = 4$, $m_1 = 1$, $K = 1000$.

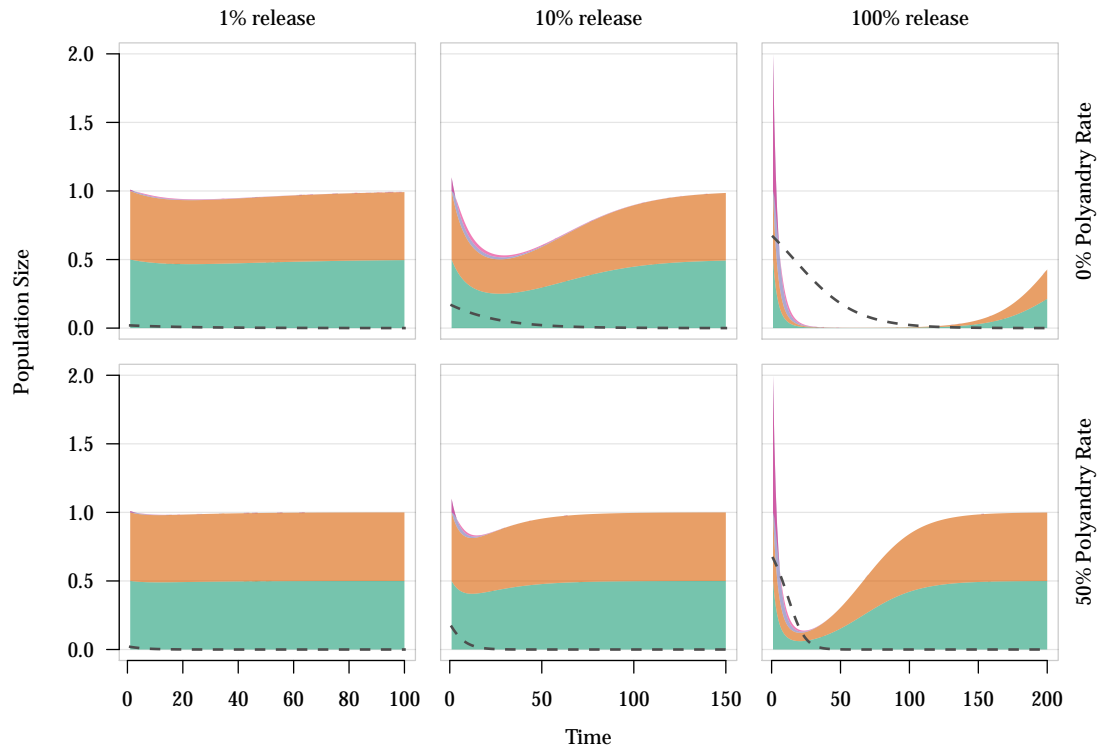


Figure S5. The number of wildtype males and females (W in green and orange), t -Sry males (D in violet) and t -Sry 'females' (pink) as a proportion of carrying capacity K after a single release of drive individuals into the population. The dotted line represents the drive frequency in the population. Columns represent different release efforts (number of males release as a proportion of carrying capacity K). The two rows depict a monandry ($\psi = 0$) and a polyandry ($\psi = 0.5, r = 0.2$) scenario, respectively. The driver cannot eradicate the population in any of the scenarios shown. Remaining parameter values: $s = 0.9, b = 0.9, m_1 = 0.4, K = 1000$