Demographic feedbacks can hamper the spatial spread of a gene drive

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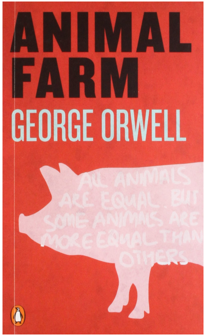
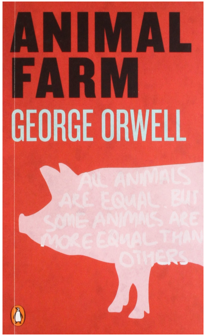
ANR-19-CE45-0009-01

Voir https://arxiv.org/abs/2101.11255
pour plus de détails !

MMB

January 2021


ANIMAL FARM
GEORGE ORWELL
ALL ANIMALS ARE EQUAL BUT SOME ANIMALS ARE MORE EQUAL THAN OTHERS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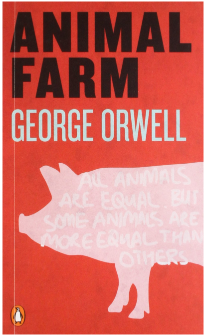
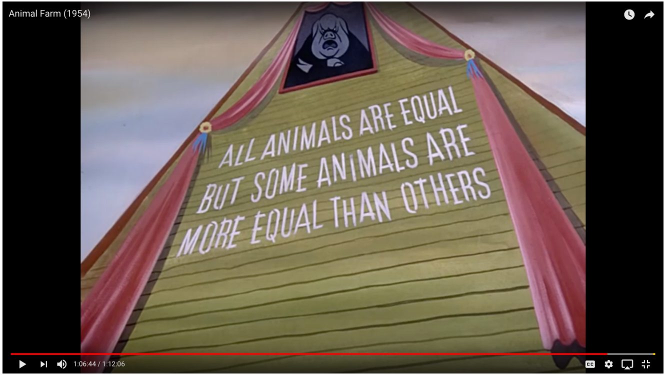
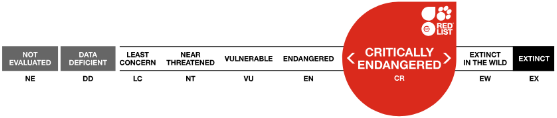




(c) Animal Farm (1954 movie), Youtube

All animals are equal…

(c) Andrew Suryono, Natl Geographic



(c) IUCN

Some animals are less equal than others

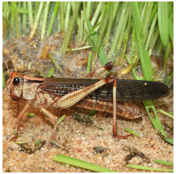

(c) J. Gathany/CDC


(c) Penarc, Wikipedia


(c) J. Gathany, CDC


(c) pestworld.org


(c) C. J. Sharp, Wikimedia


(c) H. Krisp, Wikimedia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Pest control

Mechanical, Physical

(c) www.publicdomainpictures.net

Chemical

(c) USDA, Wikimedia

Biological

(c) Fishbase

Pest control

Mechanical, Physical

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Chemical

(c) USDA, Wikimedia

Biological

(c) Fishbase

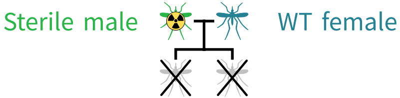
Genetic

"Dissemination, by mating or inheritance, of factors that reduce pest damage"

Alphey 2014, *Ann. Rev. Entomo.*

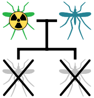
Genetic control of populations

Sterile Insect Technique

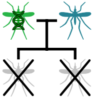


Genetic control of populations

Sterile Insect Technique

Sterile male  WT female

Sterile Insect Technique 2.0

GM male  WT female

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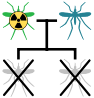
Sterile male  WT female

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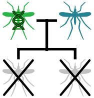
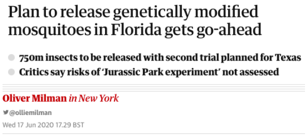
GM male  WT female



Plan to release genetically modified mosquitoes in Florida gets go-ahead

- 750m insects to be released with second trial planned for Texas
- Critics say risks of 'Jurassic Park experiment' not assessed

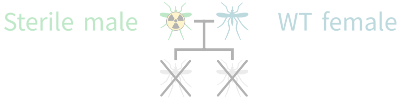
Oliver Milman *in New York*

@olliemilman

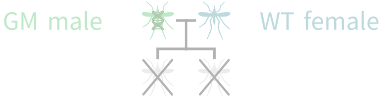
Wed 17 Jun 2020 17.29 BST

Genetic control of populations

Sterile Insect Technique

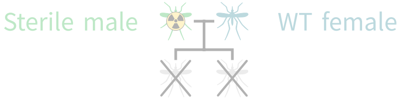


Sterile Insect Technique 2.0



Genetic control of populations

Sterile Insect Technique



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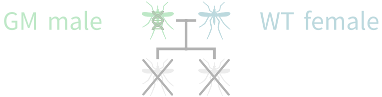
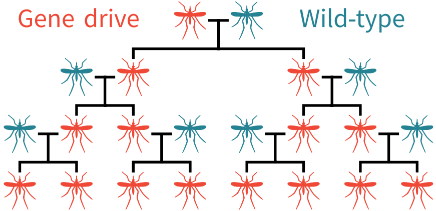
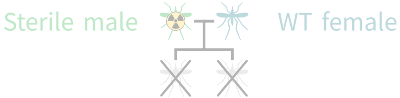


Gene Drive



Genetic control of populations

Sterile Insect Technique



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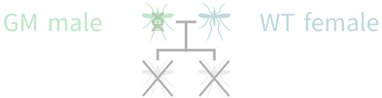

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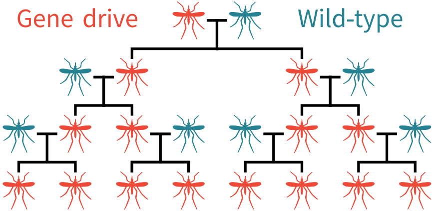
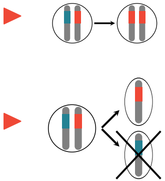
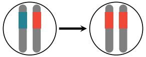


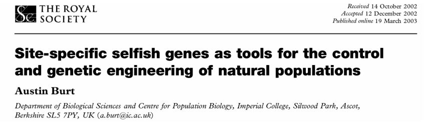


Champer *et al.* (2016)

Homing-based gene drive



- Homing endonuclease genes (HEG)



THE ROYAL SOCIETY

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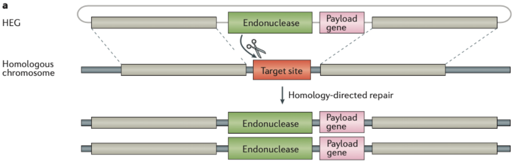
Site-specific selfish genes as tools for the control and genetic engineering of natural populations

Austin Burt

Department of Biological Sciences and Centre for Population Biology, Imperial College, Silwood Park, Ascot, Berkshire SL5 7PY, UK (a.burt@ic.ac.uk)



(c) Champer *et al.* (2016)

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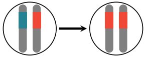

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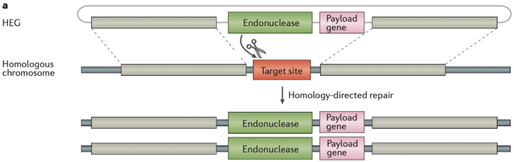


(c) Champer *et al.* (2016)

- RNA-guided gene drive

eLIFE elifesciences.org

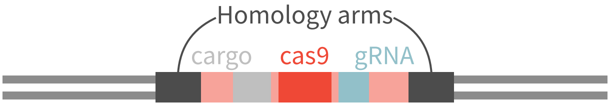
Concerning RNA-guided gene drives for the alteration of wild populations

DOI: 10.7554/eLife.03401.001

KEVIN M ESVELT*, ANDREA L SMIDLER, FLAMINIA CATTERUCCIA* AND GEORGE M CHURCH*

RNA-guided gene drive

Esvelt *et al.* 2014, *eLife*



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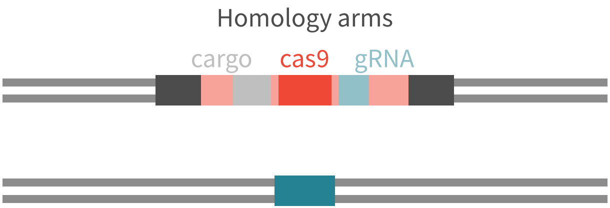

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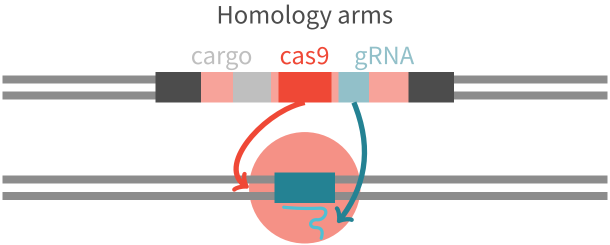

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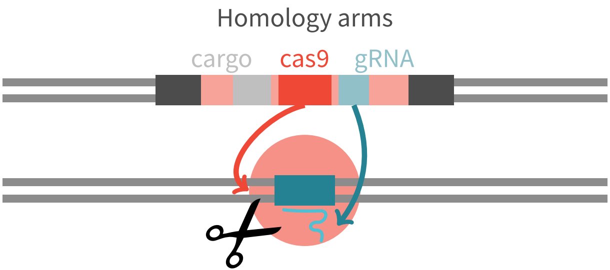

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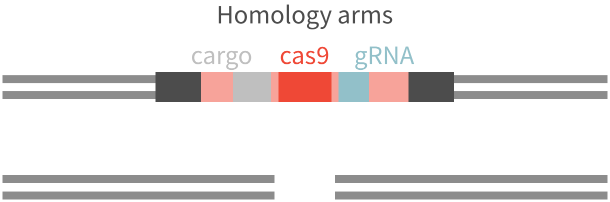

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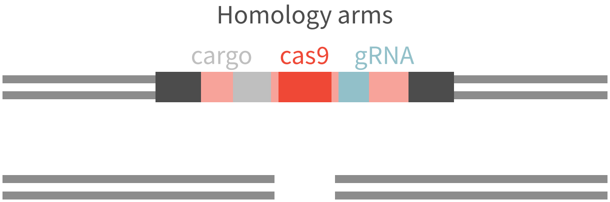

Homologous directed repair (HDR)

RNA-guided gene drive

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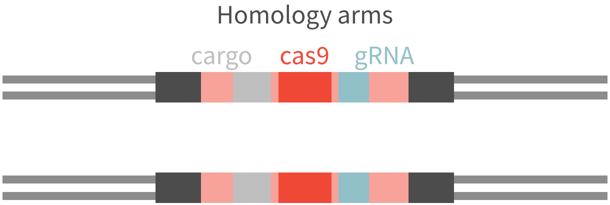
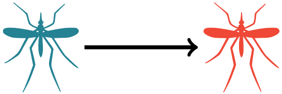
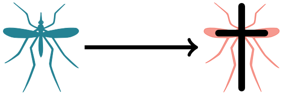


Types of drive

Modification drive



Eradication drive



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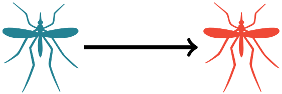

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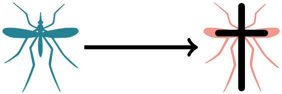
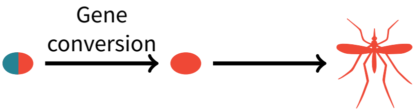
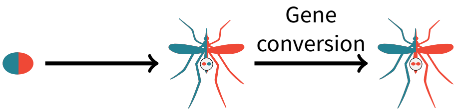


Timing of gene conversion

In the zygote (Z)



In the gonads (G)



Modelling a homing-based gene drive

Deredec *et al.* (2008)

Alleles

Wild-Type W, Drive D

Modelling a homing-based gene drive

Deredec *et al.* (2008)

Alleles

Wild-Type W, Drive D

Parameters

Fitnesses			
Genotype	WW	WD	DD
Fitness	1	$1 - h_D s_D$	$1 - s_D$

c_D Conversion efficiency

Modelling a homing-based gene drive

Deredec *et al.* (2008)

Alleles

Wild-Type W, Drive D

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Equations (Conversion in the zygote)

Allele frequencies

$$q_W = 1 - q_D,$$

$$q'_D = \frac{q_D^2(1 - s_D) + 2q_W q_D(c_D(1 - s_D) + \frac{1}{2}(1 - c_D)(1 - h_D s_D))}{1 - s_D q_D^2 - 2q_W q_D(c_D s_D + (1 - c_D)h_D s_D)}.$$

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Population size

$$N' = \min\left(\alpha \overline{w} N, K\right)$$

Modelling a homing-based gene drive

Equilibria

$q_D = 0$: drive allele is lost
$q_D = 1$: drive allele is fixed
$q_D = q_D^*$: intermediate drive frequency
$\rightarrow$ coexistence or bistability

Modelling a homing-based gene drive

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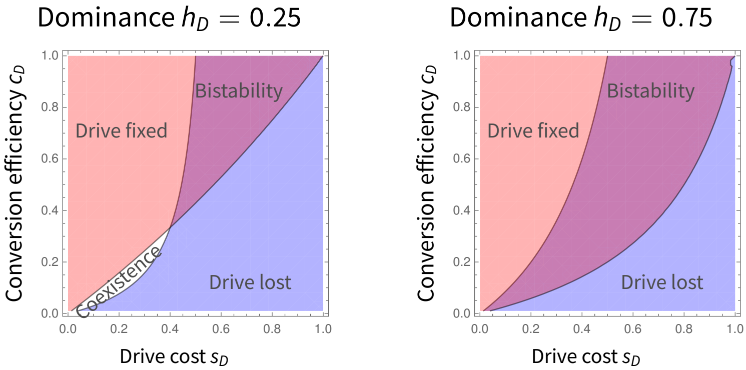

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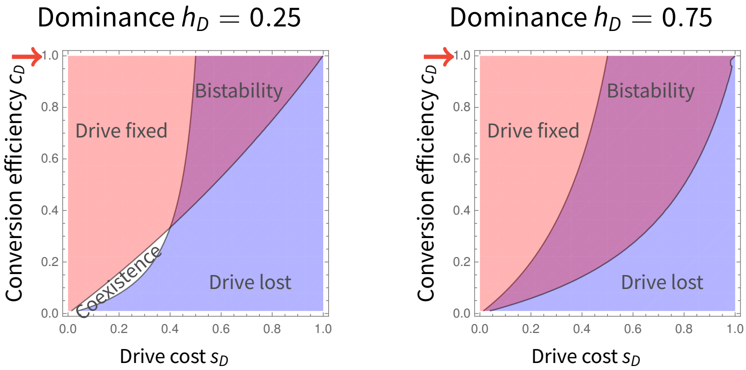
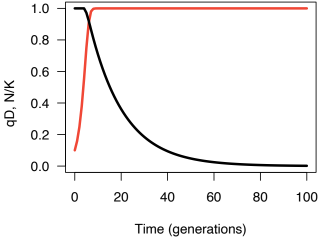


Modelling a homing-based gene drive

Drive fixation

Threshold-independent drive

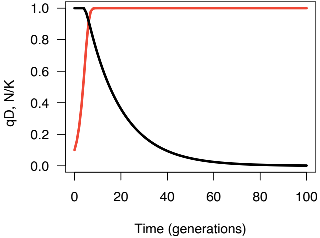


Legend:
drive frequency,
population size

Modelling a homing-based gene drive

Drive fixation

Threshold-independent drive



Legend:
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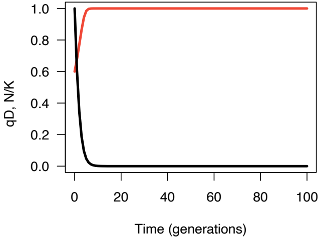
population size

Bistability

Threshold-dependent drive



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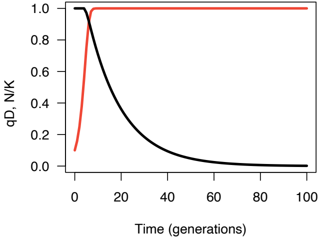

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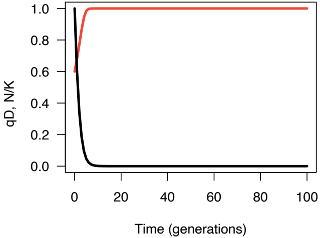
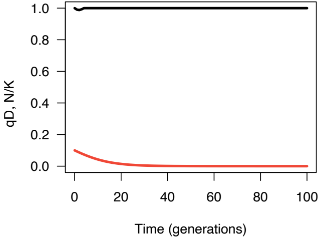
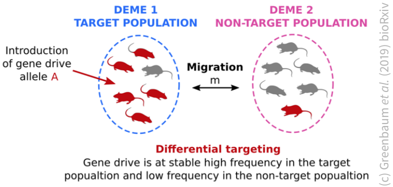




Spatial spread of threshold-dependent drives

- Potentially limited spread to non-target populations



Greenbaum *et al.* 2019

- Continuous space: “pushed wave” regime

Spatial spread of a homing-based drive

Tanaka et al. 2017, PNAS

Reaction-diffusion; Assuming perfect conversion ($c_D = 1$)

$$\tau_g \frac{\partial q}{\partial t} = \tau_g D \frac{\partial^2 q}{\partial x^2} + \frac{sq(1-q)(q-q^*)}{1-sq(2-q)}, \quad \text{where } q^* = \frac{2s-1}{s}$$

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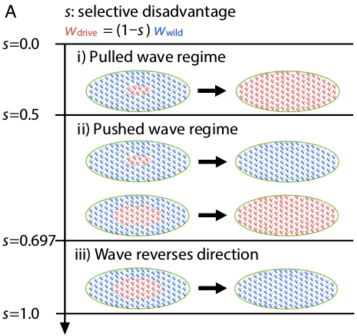

NB: $s < 0.5$ corresponds to the “Fixation” regime; $s > 0.5$ to the “Bistability” regime.

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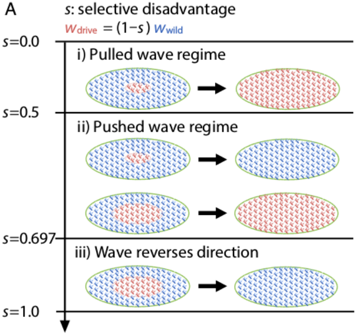

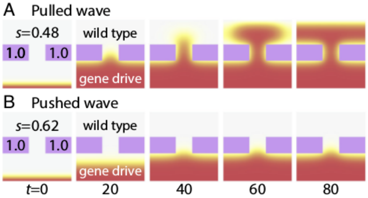

NB: $s < 0.5$ corresponds to the “Fixation” regime; $s > 0.5$ to the “Bistability” regime.

Reaction–diffusion model

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- Conversion rate $OD \to DD$: 100%
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Assumption: selection only acts on juvenile survival ($\delta_D = \beta_D = \mu_D = 1$, $\omega_D = 1 - s$)

Proportion–density variables

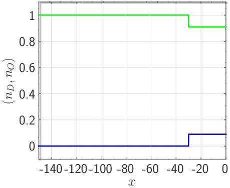
- $p(t,x)$: allelic proportion of gene drive
- $n(t,x)$: total population density
- $s \in [0,1]$: fitness cost of the gene drive population
- $r > 0$: Malthusian growth rate of the wild-type population

$$\begin{cases} \dfrac{\partial p}{\partial t} - \Delta p - 2\nabla\left(\ln n\right)\cdot\nabla p = \left(1 + r(1-n)\right) sp(1-p)\left(p - \dfrac{2s-1}{s}\right) \\ \dfrac{\partial n}{\partial t} - \Delta n = n\left(\left(1 - s + s(1-p)^2\right)\left(1 + r(1-n)\right) - 1\right) \end{cases}$$

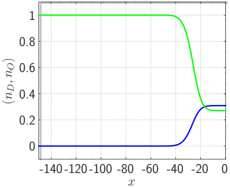
Stationary states

- $(p,n) = (0,1)$: no gene drive
- $(p,n) = \left(1, \max\left(1 - \frac{s}{r(1-s)}, 0\right)\right)$: fixated gene drive

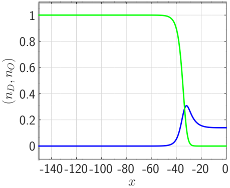
1D numerical simulations



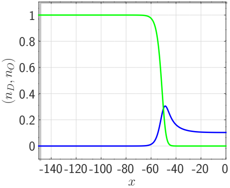
(a) $t = 0$



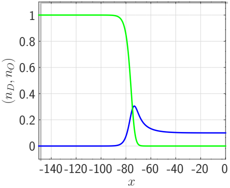
(b) $t = 20$



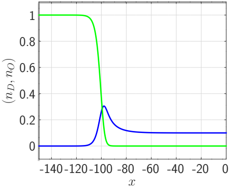
(c) $t = 40$



(d) $t = 80$



(e) $t = 140$

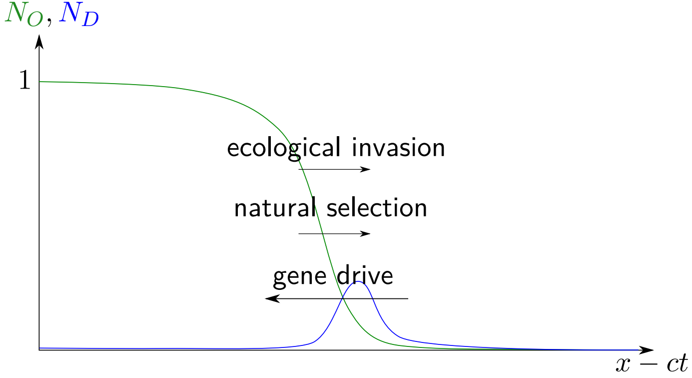


(f) $t = 200$

Figure: $n_D(t,x)$, $n_O(t,x)$, $r = 10/9$, $s = 0.5$ $\quad \left(1 - \frac{s}{r(1-s)} = 0.1\right)$

Traveling wave with speed c

$(n_D, n_O)(t,x) = (N_D, N_O)(x - ct)$ + conditions at infinity

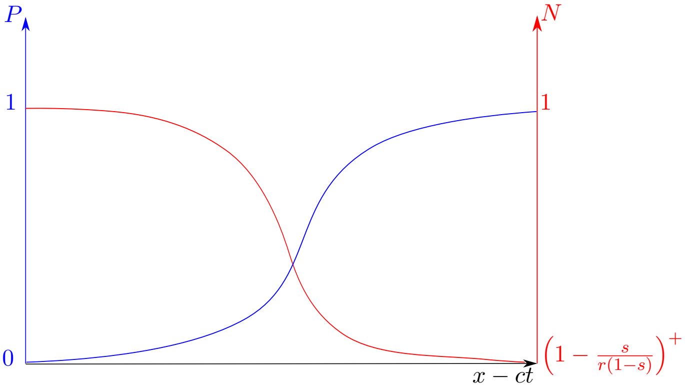


Q: sign of c as a function of r and s ?

A: numerical simulations, theoretical analysis

Traveling wave in proportion–density variables

$(p, n)(t, x) = (P, N)(x - ct)$ + conditions at infinity



Numerical observation: monotonic P and N

Pure population replacement: assumption constant n

$$\partial_t p - \Delta p = sp(1-p)\left(p - \frac{2s-1}{s}\right)$$

- Stability: $p = 1$ stable ; $p = 0$ stable iff $s > 1/2$ (reversibility)
- Sign of c: sign of $s - 2/3$ (viable iff $s < 2/3$)
- "Good" region: viable and reversible iff $1/2 < s < 2/3$

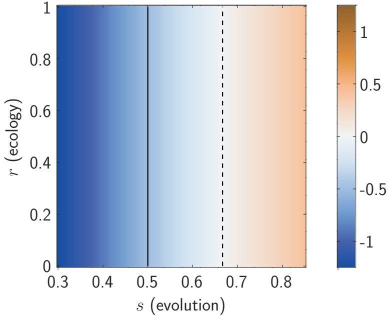


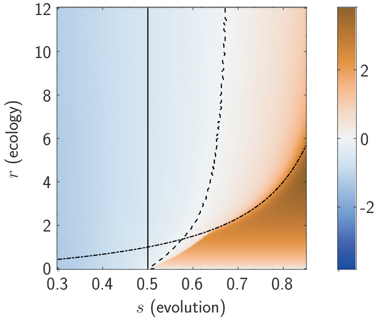
Figure: Values of $c_{s,r}$

— threshold 1-2-stability $s = 1/2$
- - level-line $\{c = 0\}$ $s = 2/3$

Partial suppression or total eradication

$$\begin{cases} \partial_t p - \Delta p - 2\nabla(\ln n)\cdot\nabla p = (r(1-n)+1)sp(1-p)\left(p - \frac{2s-1}{s}\right) \\ \partial_t n - \Delta n = n\left((1-s+s(1-p)^2)(r(1-n)+1)-1\right) \end{cases}$$

- "Good" region: reduced, larger nonviable region
- Eradication region ($1 < \frac{s}{r(1-s)}$): with a discontinuity in the nonviable region between retraction and nonexistence [num.]



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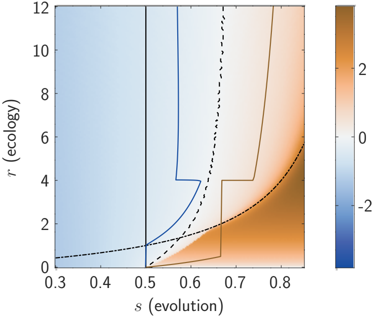

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— threshold 1-2-stability $s = 1/2$
- - level-line $\{c = 0\}$ [num.]
-·- eradication threshold $r = \frac{s}{1-s}$
– – known sign thresholds

Mathematical obstacles

$$\begin{cases} \partial_t p - \Delta p - 2\nabla\left(\ln n\right)\cdot\nabla p = (r(1-n)+1)sp(1-p)\left(p - \frac{2s-1}{s}\right) \\ \partial_t n - \Delta n = n\left(\left(1-s+s(1-p)^2\right)\left(r(1-n)+1\right)-1\right) \end{cases}$$

- Reaction term without monotonicity: no comparison principle
- Singularity as $n \to 0$

Same obstacles in variables n_D-n_O

Elements of proof

Sign of c under assumption of existence and monotonicity

- Monotonicity: $N = h(P)$, $h : [0,1] \to \left[\left(1 - \frac{s}{r(1-s)}\right)^+, 1\right]$
- Equation on P:

$$-cP' - P'' - 2\frac{h'(P)}{h(P)}|P'|^2 = (r(1-h(P))+1)sP(1-P)\left(P - \frac{2s-1}{s}\right)$$

- Change of variable (Nadin-Strugarek-Vauchelet, *J. Math. Biol.*, 2018):

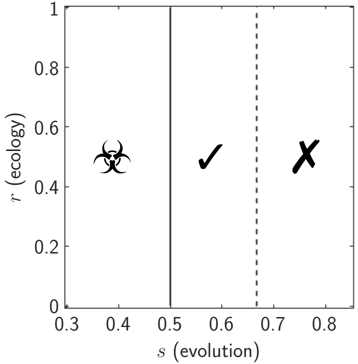
$$\operatorname{sgn}(c) = \operatorname{sgn}\left[-\int_0^1 h(\rho)^4 (r(1-h(\rho))+1)s\rho(1-\rho)\left(\rho - \frac{2s-1}{s}\right) \mathrm{d}\rho\right]$$

- Estimates

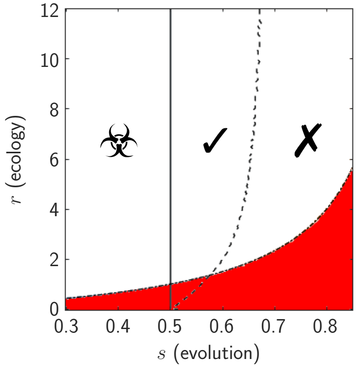
Nonexistence result: if $r \leq \frac{2s-1}{2(1-s)}$, by maximum principle

Conclusion

Summary



(a) Neglecting demography



(b) Accounting for demography

Figure: Gene drive regimes

☣: irreversible ; ✓: possible ; ✗: nonviable ; ■: eradication

Developments & perspectives

Developments not mentioned in this talk

- Sensibility analysis (parameters ω_D, β_D, μ_D)
- Density-dependent death rate
- Allee effect
- Stochasticity

Perspectives

- Existence, multiplicity, stability and monotonicity of traveling waves
- Limit $r \to +\infty$
- Better estimates of the sign of the speed
- Conversion in the germinal line instead of the egg
- Emergence and evolution of gene drive resistance (Champer *et al.*, *PLOS Genetics*, 2017 ; Unckless *et al.*, *Genetics*, 2017)

Gene drives may not work as advertised

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- Evolution of resistance

  Unckless et al. 2017 Genetics, Champer et al. 2017 PLOS Genetics, KaramiNejadRanjbara et al. 2018 PNAS

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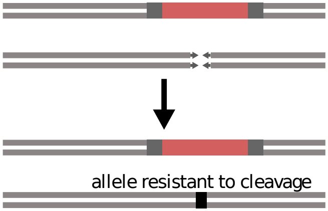
  - generation of resistance by Non Homologous End Joining



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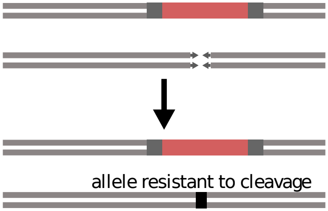

- Evolution of mating systems
  Bull 2017, Bull et al. 2019 Evolution, Medicine and Public Health

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Specific to gene drive

Generic

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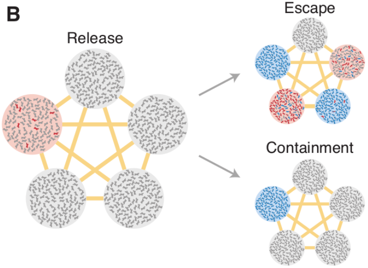

Noble et al. (2018) eLife

Generic

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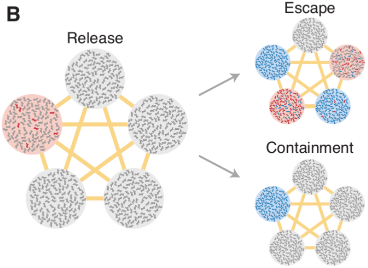

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  Horizontal gene transfer

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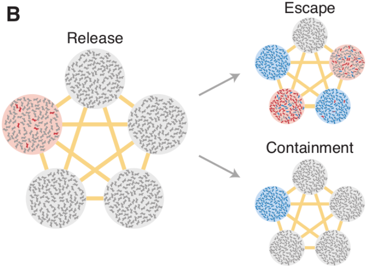

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Generic

- Ecosystem consequences of population suppression

Regulatory issues

Gene drive-modified organisms are living genetically modified organisms

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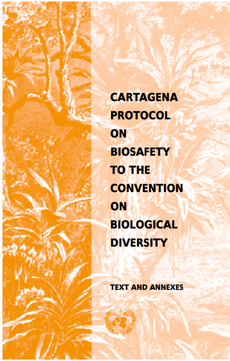

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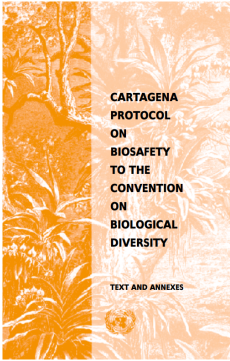

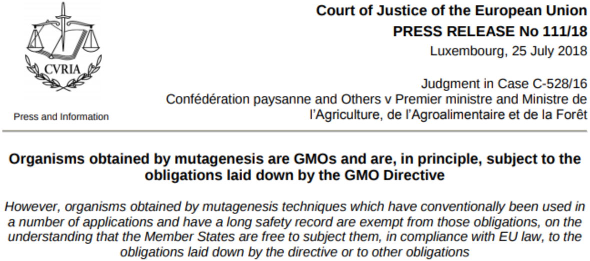

CVRIA

Press and Information

Court of Justice of the European Union
PRESS RELEASE No 111/18
Luxembourg, 25 July 2018

Judgment in Case C-528/16
Confédération paysanne and Others v Premier ministre and Ministre de l'Agriculture, de l'Agroalimentaire et de la Forêt

Organisms obtained by mutagenesis are GMOs and are, in principle, subject to the obligations laid down by the GMO Directive

However, organisms obtained by mutagenesis techniques which have conventionally been used in a number of applications and have a long safety record are exempt from those obligations, on the understanding that the Member States are free to subject them, in compliance with EU law, to the obligations laid down by the directive or to other obligations

Funding

Main funders of gene drive research:

1. DARPA Safe Genes program
2. Bill & Melinda Gates foundation Target Malaria

- Need for independent risk assessment

Ethics

- Gene drive vs. other methods of population control

Ethics

- Gene drive vs. other methods of population control
- Are the benefits worth the risks?

Ethics

- Gene drive vs. other methods of population control
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Ethics

- Gene drive vs. other methods of population control
- Are the benefits worth the risks?
- Deciding which species can be eradicated
- Modifying wild populations

Thanks for your attention!

https://arxiv.org/abs/2101.11255