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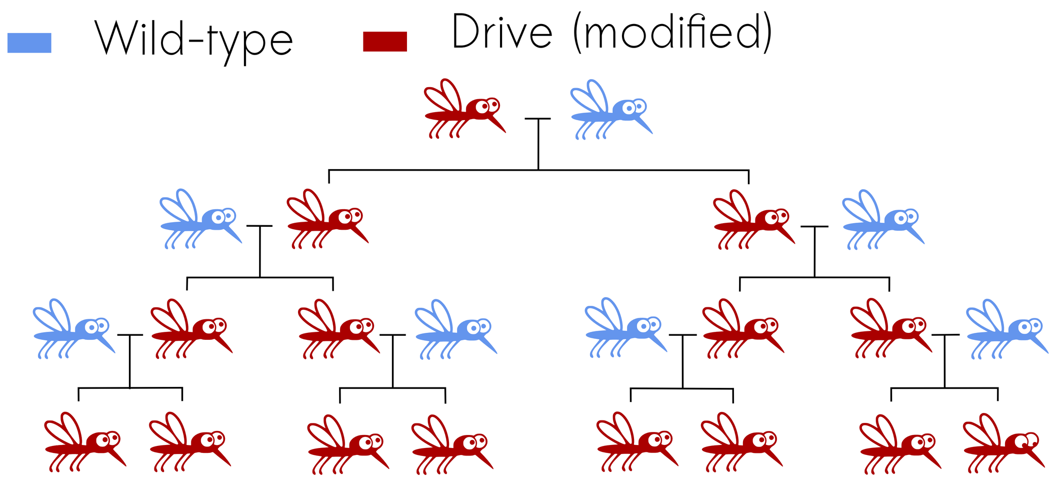
The importance of demography in gene drive mathematical models.

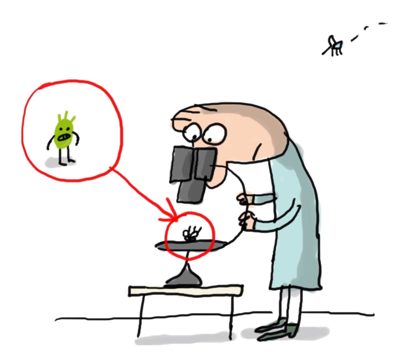
FIRST: WHAT IS GENE DRIVE ?

Gene drive is a genetic technology that biases the transmission of a targeted mutation by ensuring quasi-systematic inheritance to the offspring.



Example of a drive rapide propagation

Applications are diverse and numerous: eradicate insect-borne deseases, control invasive or pest species...

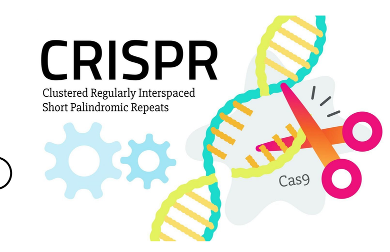


Develop mosquitoes resistance to Malaria

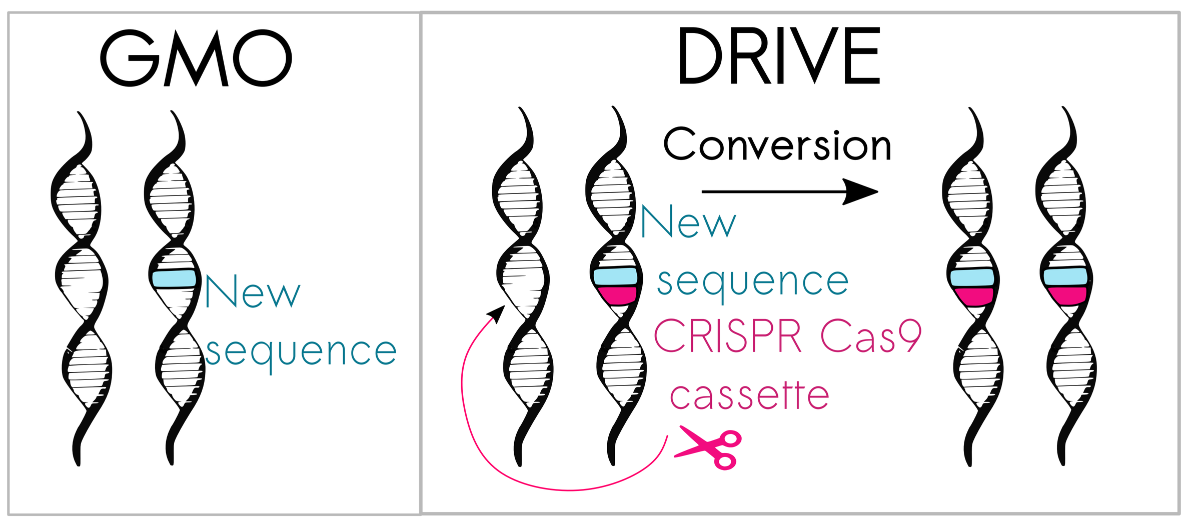
Preserve islands biodiversity

Eliminate wild resistance to herbicides

HOW DOES IT WORK?



CRISPR-Cas drive takes CRISPR-Cas GMO to another level. As we introduce a modification in the genome we also include the CRISPR cassette.



The cell then produces everything needed to copy the mutation.

MODEL WITH EARLY PERFECT CONVERSION

We study the propagation of gene drive with spatio-temporal models. The first one (below) considers perfect conversion in the zygote, resulting in the absence of heterozygous individuals. $n_D(t,x)$: wild-type density, $n_W(t,x)$: drive density, r: intrinsic growth rate, s: fitness disadvantage for drive.

Wild-type

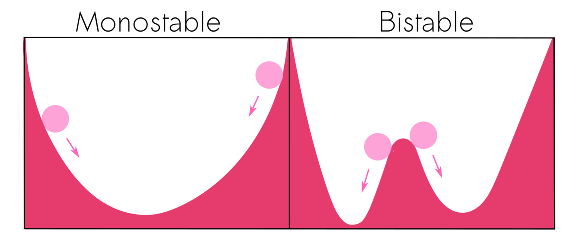
$$\partial_t n_W - \partial_{xx} n_W = 1 \left(r\,(1-n_D-n_W)+1\right) \frac{n_W^2}{n_W+n_D} - n_W$$

Drive Drive

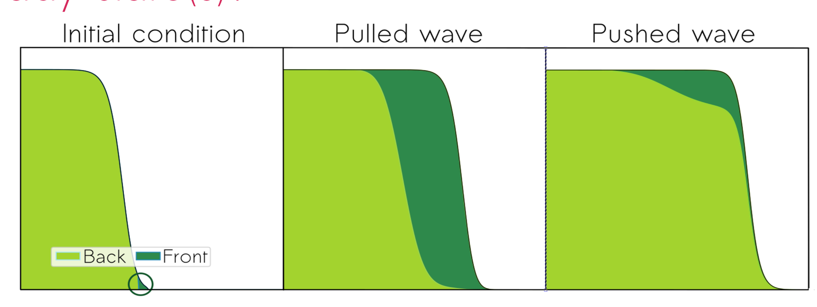
$$\underbrace{\partial_t n_D}_{\text{Variations in time}} - \underbrace{\partial_{xx} n_D}_{\text{Diffusion}} = \underbrace{(1-s)}_{\text{Fitness / Disadvantage}} \underbrace{\left(r\,(1-n_D-n_W)+1\right)}_{\text{Growth term}} \underbrace{\frac{n_D^2+2n_Dn_W}{n_W+n_D}}_{\text{Mating / Advantage (conversion)}} - \underbrace{n_D}_{\text{Mortality}}$$

1) Final equilibrium
What is left in the environment ?

2) Monostable or bistable wave
One or two stable steady state(s)?



3) Pulled or pushed wave, and speed?
Which individuals drive the movement?

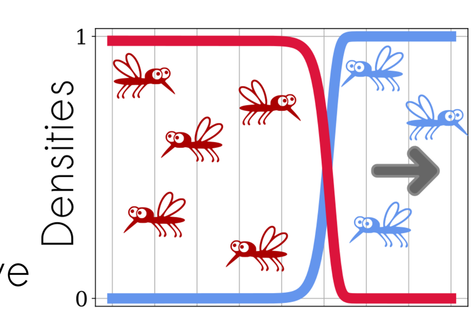


How important is it to consider demography?

We can rewrite the system above with $n = n_W + n_D$ and $p = n_D/(n_W + n_D)$:

$$\iff \begin{cases} \partial_t p - \partial_{xx} p - 2\,\partial_x(\log n).\partial_x p = \left(r\,(1-n)+1\right)\, s\, p\,(1-p)\,\left(p - \frac{2s-1}{s}\right) \\ \partial_t n - \partial_{xx} n = \left(r\,(1-n)+1\right)\left(1-s+s(1-p)^2\right)\, n - n \end{cases}$$

Most gene drive models in the literature focus on the proportion (only one equation on p) and assume a constant population size n. We wonder if this simplification is justified. To study this question we focus on travelling waves solutions (drawing on the right) and compare them over three criteria (see right column) for different values of the demographic parameter r. We observe significant differences, attesting the importance of demography.



Space (1D)

RESULTS

$r \to +\infty$ Model without demography [a]

$$\partial_t p - \partial_{xx} p = \frac{s\,p\,(1-p)\,\left(p-\frac{2s-1}{s}\right)}{1-s+s(1-p)^2}$$

	0 < s < 0.36	0.36 < s < 0.5	0.5 < s < 0.70	0.70 < s < 1
1)	Drive invasion			WT invasion
2)	Monostable		Bistable	
3)	Pulled wave	Pushed wave		

$r \to 0$ Nearly an SI epidemiological model [b]

$$\begin{cases} \partial_t p - \partial_{xx} p - 2\,\partial_x(\log n).\partial_x p = s\,p\,(1-p)\,\left(p - \frac{2s-1}{s}\right) \\ \partial_t n - \partial_{xx} n = s\,p\,(p-2)\,n \end{cases}$$

	0 < s < 0.36	0.36 < s < 0.5	0.5 < s < 0.70	0.70 < s < 1
1)	Drive invasion		No invasion	
2)	Monostable		Continuum	
3)	Pulled wave		No wave	

MODEL WITH EARLY OR LATE PARTIAL CONVERSION

In a second part, we consider a more realistic model: the conversion is not systematic anymore and takes place in the zygote or in the germline. The conversion rate c is between 0 and 1.

These changes result in two models more complex than the previous one, containing 3 equations as we now need to follow heterozygous individuals.

Early partial conversion occuring (in the zygote)

$$\begin{cases} \partial_t n_D - \partial_{xx} n_D = (1-s)(r\,(1-n)+1)\, \frac{c\,n_W n_H + 2\,c\,n_W n_D + (0.5\,c+0.25)\,n_H^2 + (c+1)\,n_H n_D + n_D^2}{n} - n_D \\ \partial_t n_H - \partial_{xx} n_H = (1-sh)(r\,(1-n)+1)\ \ (1-c)\,\frac{n_W n_H + 2\,n_W n_D + 0.5\,n_H^2 + n_H n_D}{n} - n_D \\ \partial_t n_W - \partial_{xx} n_W = (r\,(1-n)+1)\,\frac{n_W^2 + n_W n_H + 0.25\,n_H^2}{n} - n_W \end{cases}$$

c, 1-s

Two cases: (1-c) (1-h) < 0.5: possible bistability.
(1-c) (1-h) > 0.5: possible coexistence.

Late partial conversion occuring (in the germline)

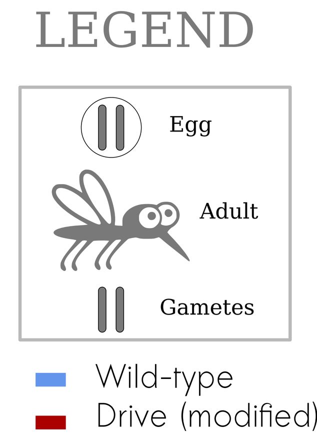
$$\begin{cases} \partial_t n_D - \partial_{xx} n_D = (1-s)(r\,(1-n)+1)\, \frac{0.25\,(1+c)^2\,n_H^2 + (1+c)\,n_H n_D + n_D^2}{n} - n_D \\ \partial_t n_H - \partial_{xx} n_H = (1-sh)(r\,(1-n)+1)\, \frac{(1+c)\,n_W n_H + 2\,n_W n_D + 0.5\,(1-c^2)\,n_H^2 + (1-c)\,n_H n_D}{n} - n_H \\ \partial_t n_W - \partial_{xx} n_W = (r\,(1-n)+1)\,\frac{n_W^2 + (1-c)\,n_W n_H + 0.25\,(1-c)^2\,n_H^2}{n} - n_W \end{cases}$$

1-sh, c

... with $n = n_D + n_H + n_W$.

Two cases: h > 0.5: possible bistability.
h < 0.5: possible coexistence.

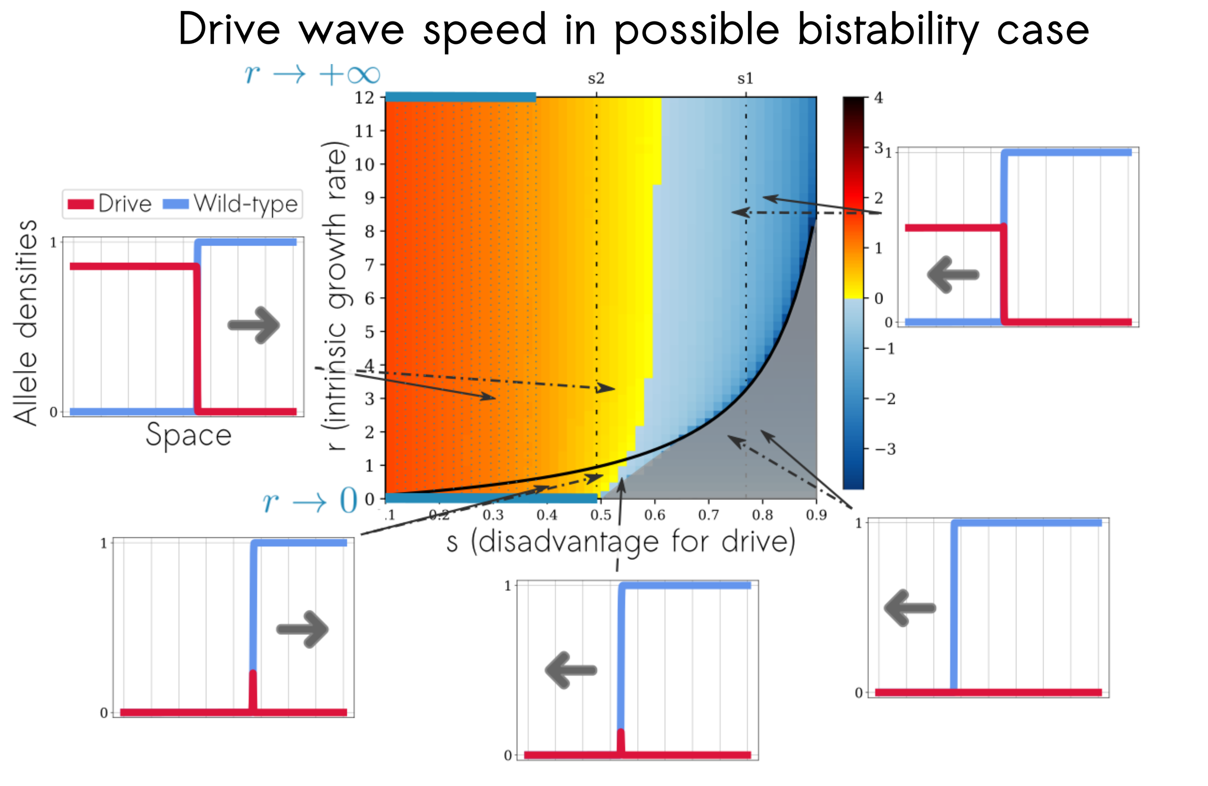
LEGEND



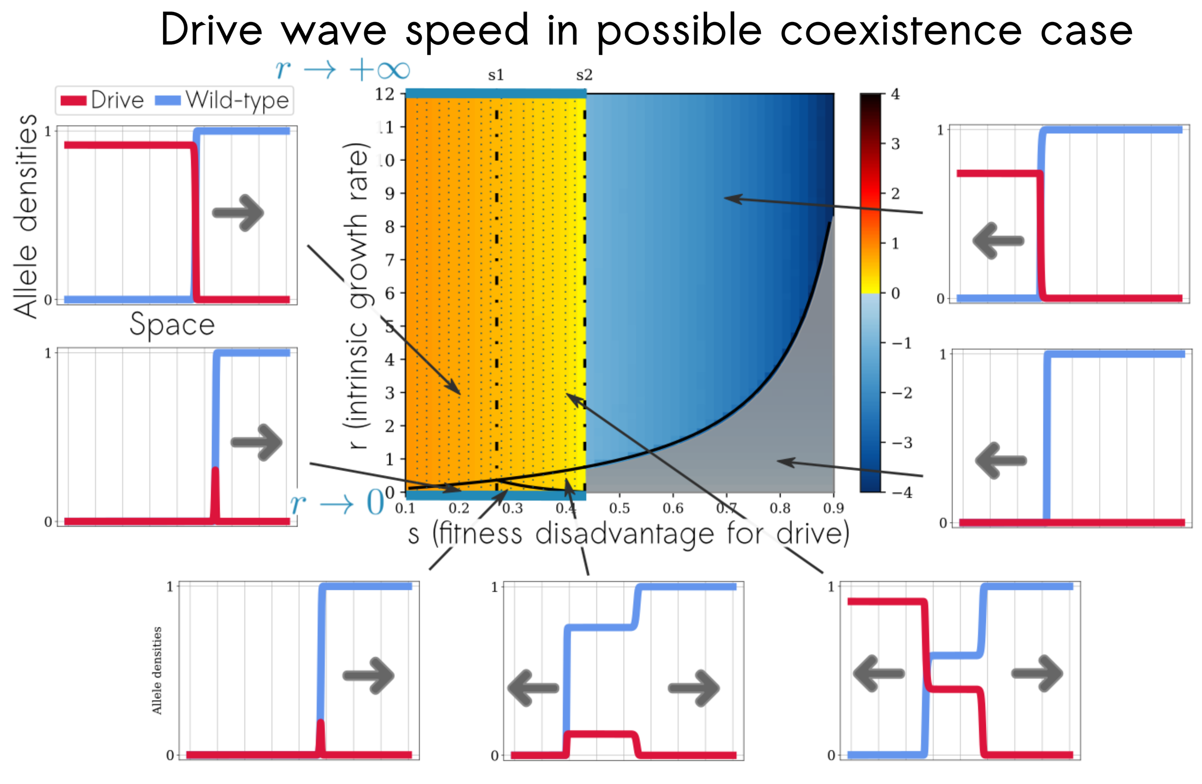
RESULTS

As the models are complex to study, we are searching for conditions implying a pulled monostable wave, again for $r \to +\infty$ and $r \to 0$. Those conditions are colored here below, on the heatmap of wave speed values:

Drive wave speed in possible bistability case



Drive wave speed in possible coexistence case



CONCLUSION

- Taking into account the variations in population size can drastically change the conclusion (which type invades, at which speed, etc...). It also indicates us if there will be an extinction event.

- However under certain conditions (see the results box on the left), the growth rate does not seem to impact the wave: similar waves are leading to totally different densities in the end.

SOURCES

(a) M. Strugarek and N. Vauchelet "Reduction to a Single Closed Equation for 2-by-2 Reaction-Diffusion Systems of Lotka-Volterra Type". *SIAM Journal on Applied Mathematics 76.5* (Jan. 2016), pp.2060-2080.
(b) J. Zhou et al. "Critical Traveling Waves in a Diffusive Disease Model". *Journal of Mathematical Analysis and Applications 476.2* (Aug. 2019), pp.522-538

Drawings come from https://www.1jour1actu.com/
Heatmaps were computed thanks to Migale, INRAE.