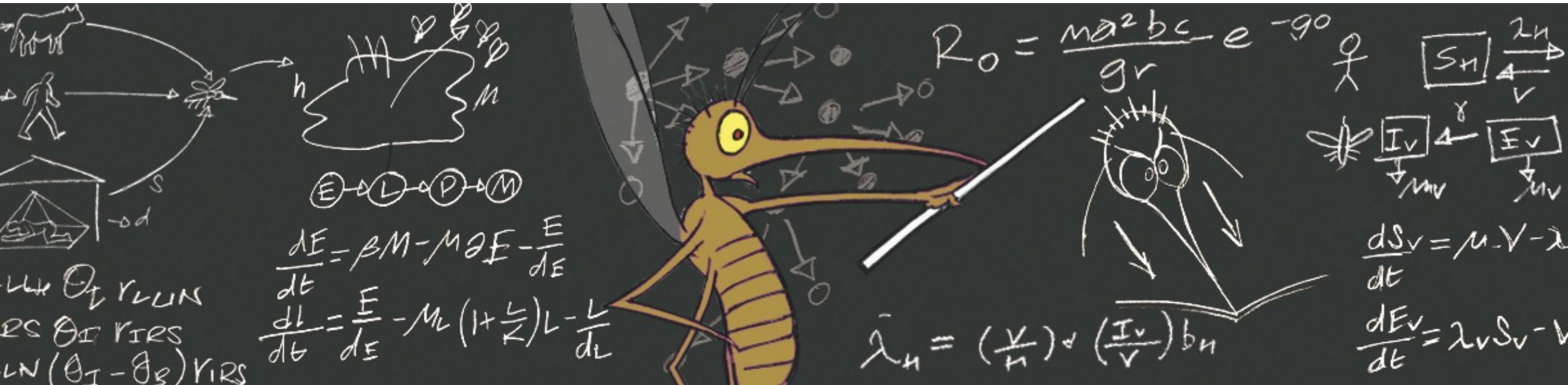
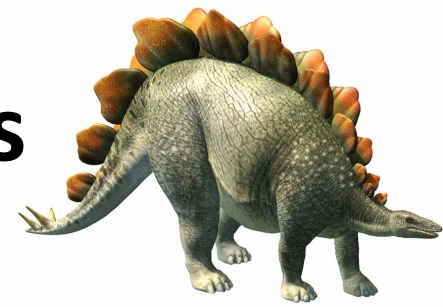


Modeling needs for gene drive mosquito projects

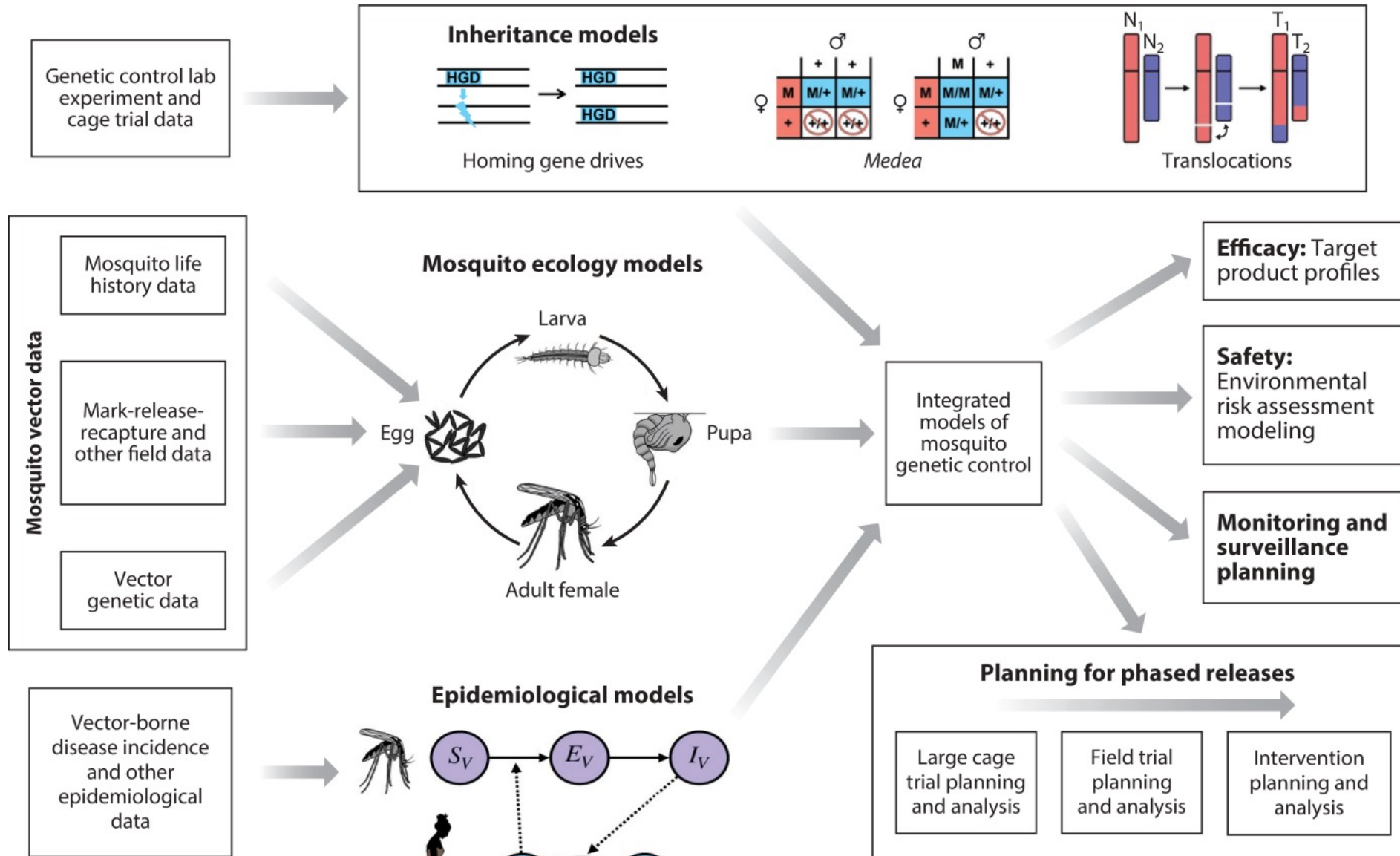
Gene Drive Research Forum 2024



John Marshall
Divisions of Epidemiology & Biostatistics
School of Public Health
University of California, Berkeley
john.marshall@berkeley.edu

Berkeley Public Health

Overview



- Marshall JM, North AR (2023) Mosquito Gene Drives & Malaria
- Raban R, Marshall JM *et al.* (2023) Annual Review of Genetics

Target product profiles

Model specification:

Product parameters:

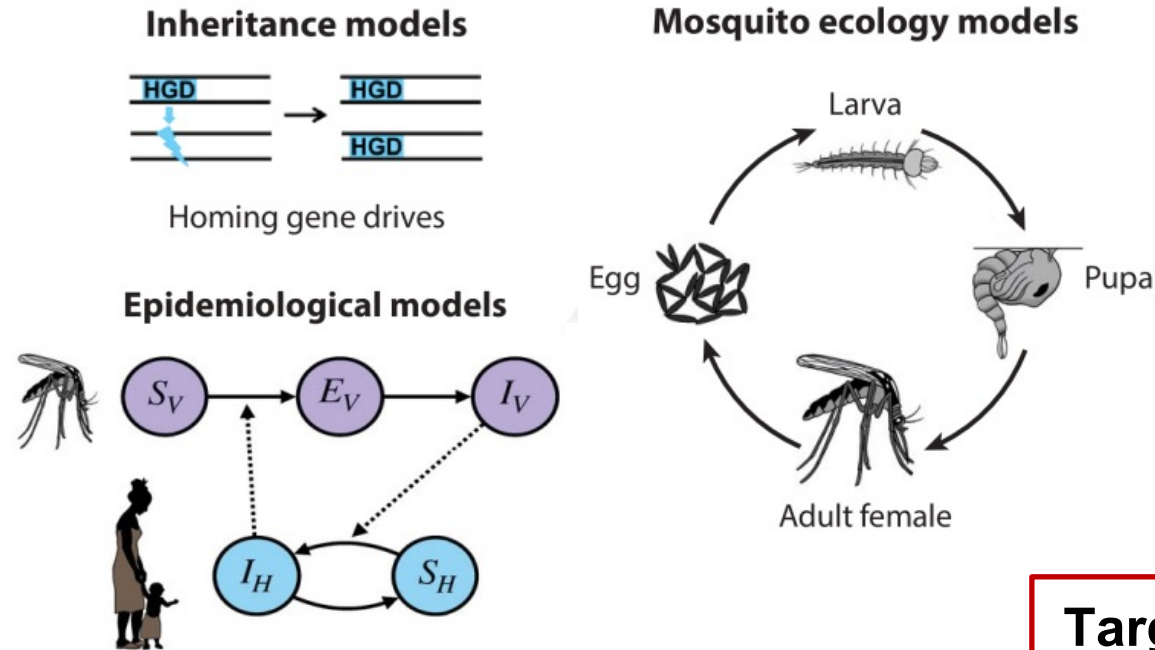
- Homing rate
- Resistance generation rate
- Fecundity/mating cost of gene drive allele
- Fecundity/mating cost of resistance allele
- Efficacy of transmission blocking*

Intervention parameters:

- Number of mosquitoes per release
- Number of releases

Setting:

- Initially, potential field sites
- Eventually, locations where gene drive may spread



Target product profile:

- Product & intervention parameters that satisfy outcomes of interest

Outcomes of interest:

- >20-50% reduction in prevalence
- >20-50% reduction in clinical incidence
- Impact within <6-12 months
- Duration of impact of >2-3 years

TP13 population replacement construct

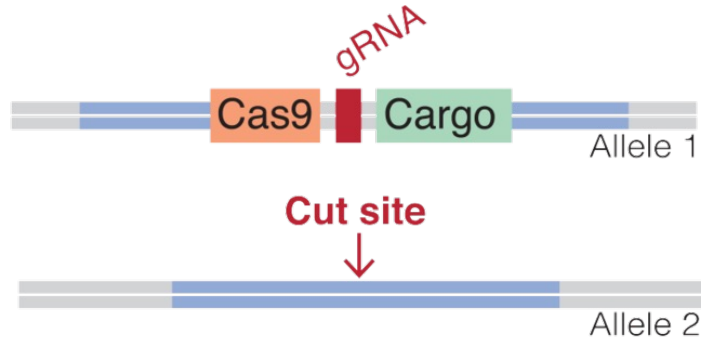
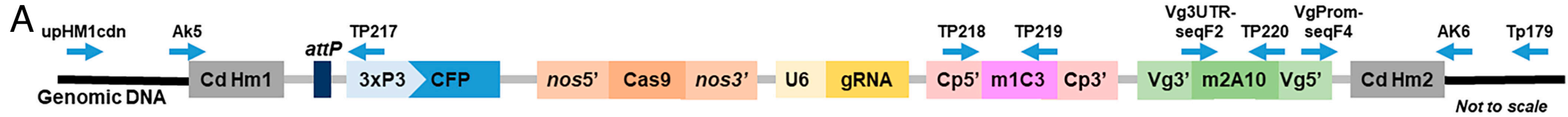
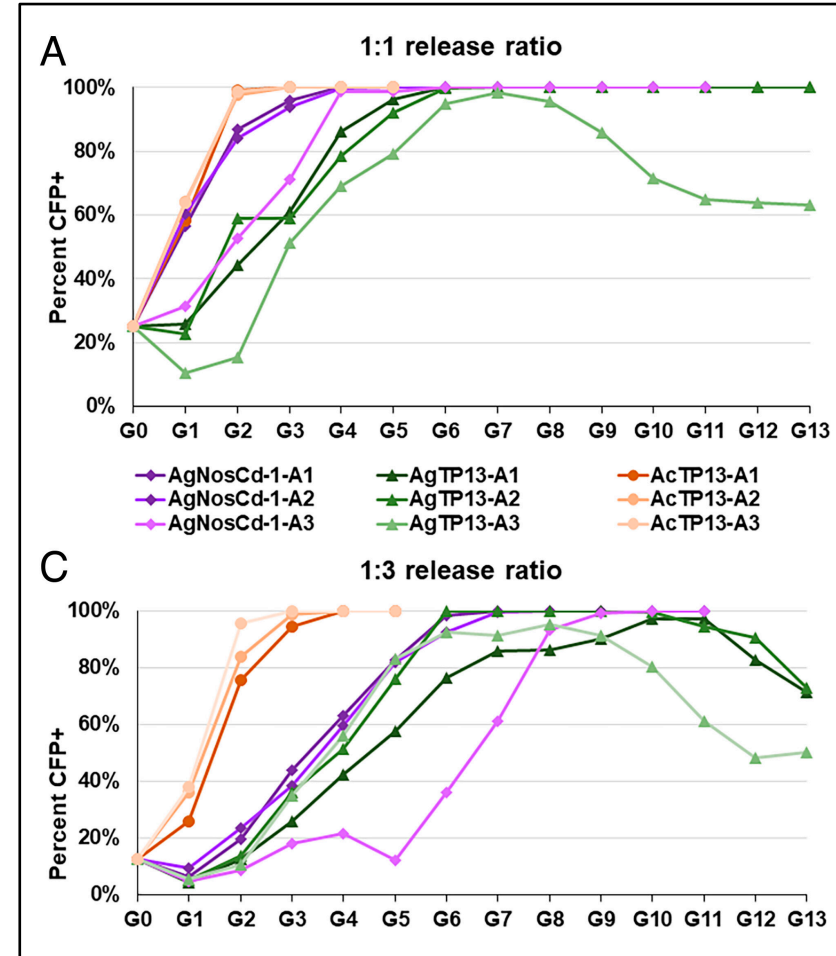


Table 1.
Gene-drive and eye phenotypes

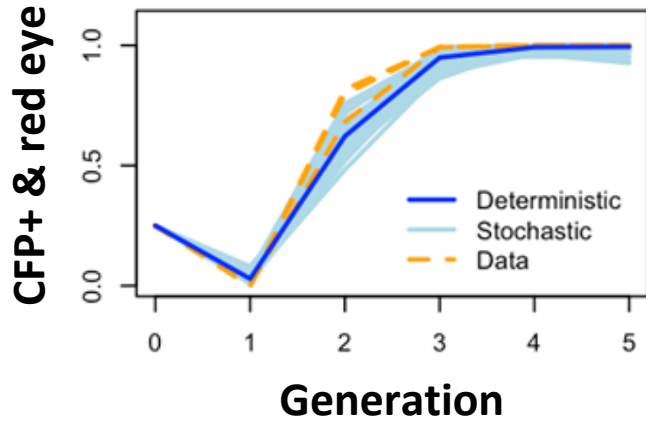
AcTP13	
Female-founder lineages [†]	
♀ 97.8% (1,472/1,507)	
♂ 100% (235/235)	♀ 97.5% (197/202)



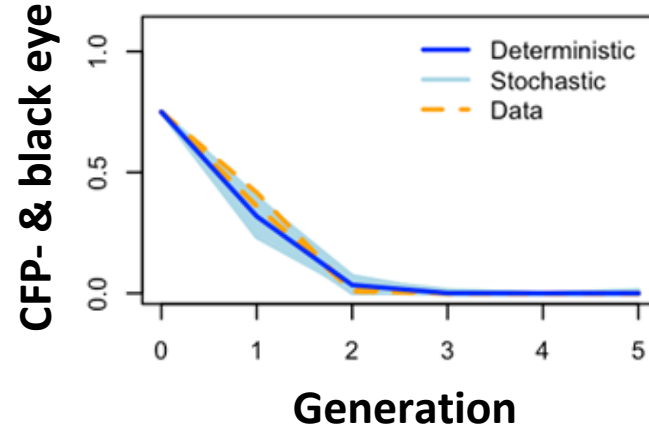
- Carballar-Lejarazú R, Dong Y, Pham TB, Tushar T, Corder RM *et al.* (2023) PNAS

Fitness-related parameters

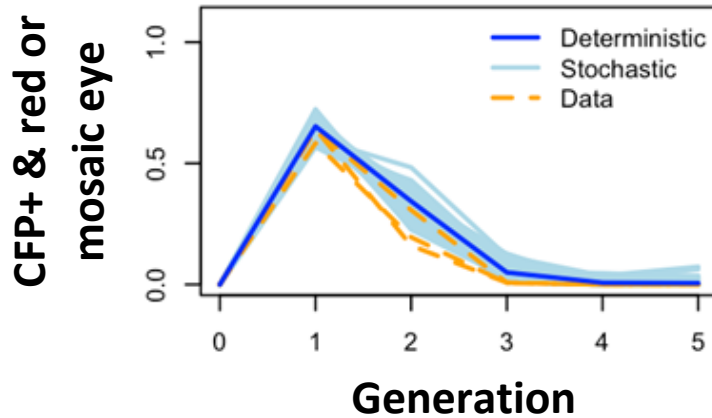
Genotypes: HH, HB



Genotypes: WW,
WR, RR, RB



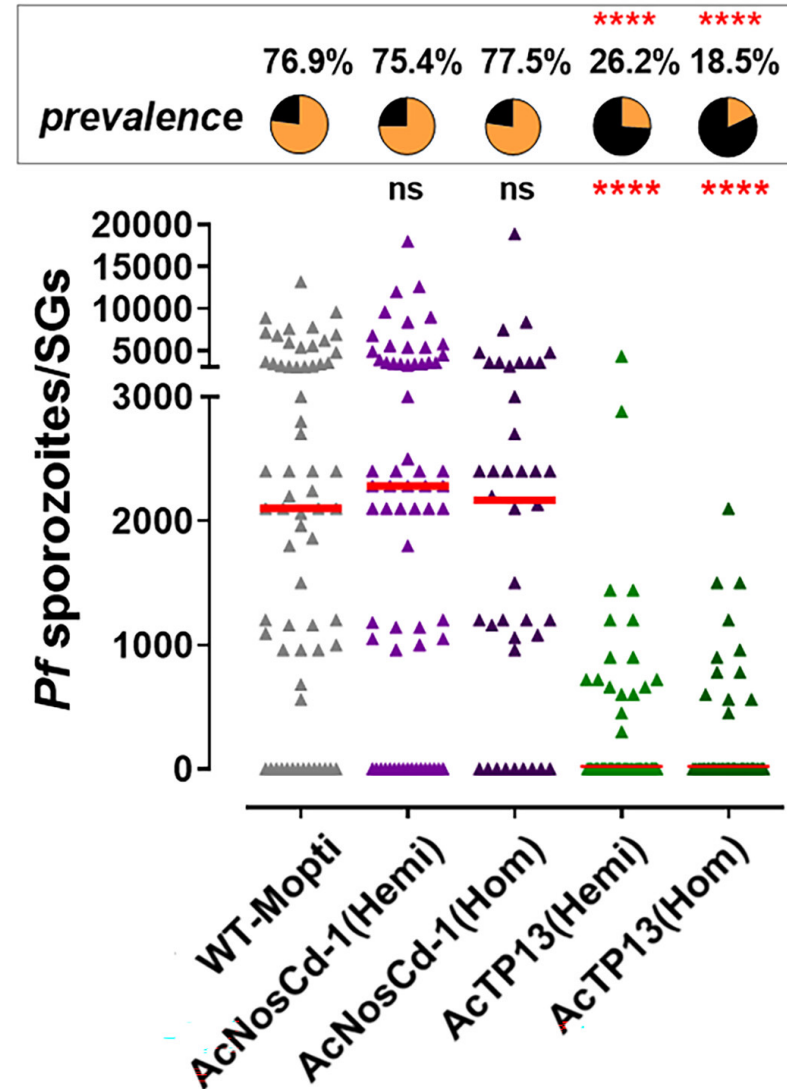
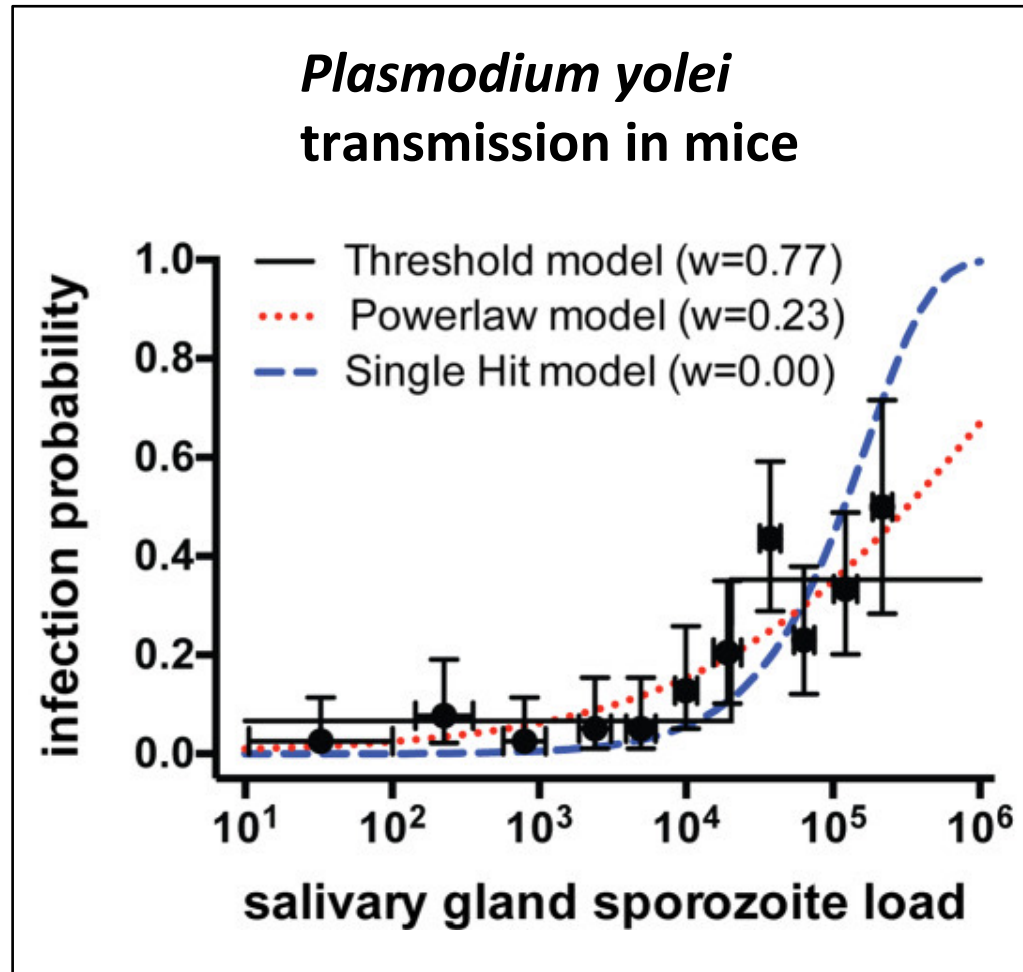
Genotypes: HW, HR



Parameter	AcTP13 (<i>An. coluzzii</i>)	
	Prior	Posterior
p_H^M	97.8% (88.3% – 100%)	97.9% (82.5% – 99.9%)
p_H^F	98.4% (94.4% – 99.999%)	98.5% (94.8% – 99.8%)
p_B^F	N/A	N/A
m_{HH}	1.04 (0.99 – 1.10)	1.05 (0.99 – 1.10)
m_H	1.78 (1.60 – 1.96)	1.78 (1.60 – 1.96)
f_{HH}	-	2.42 (0.85 – 3.67)
f_H	-	2.15 (1.24 – 3.82)

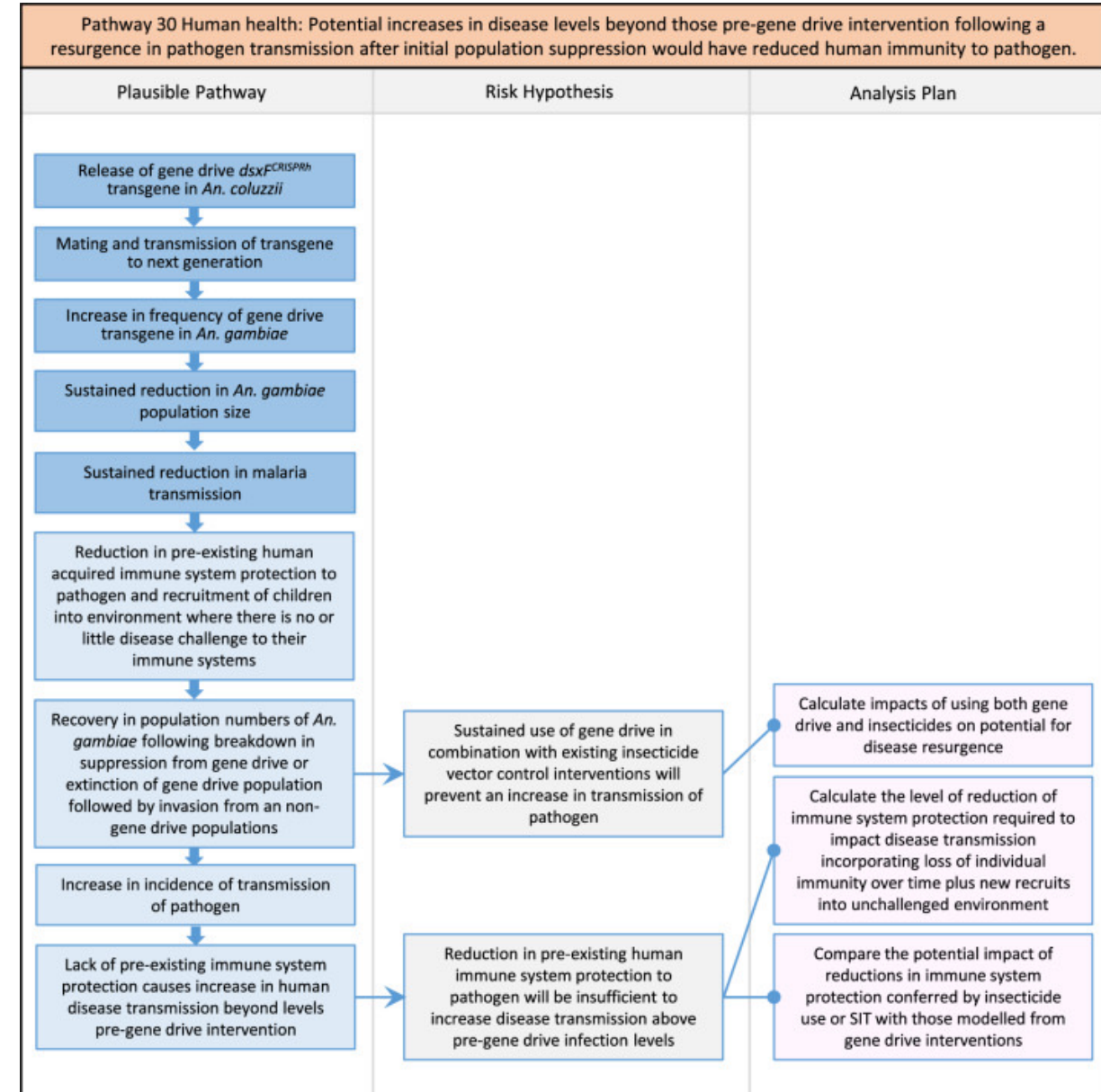
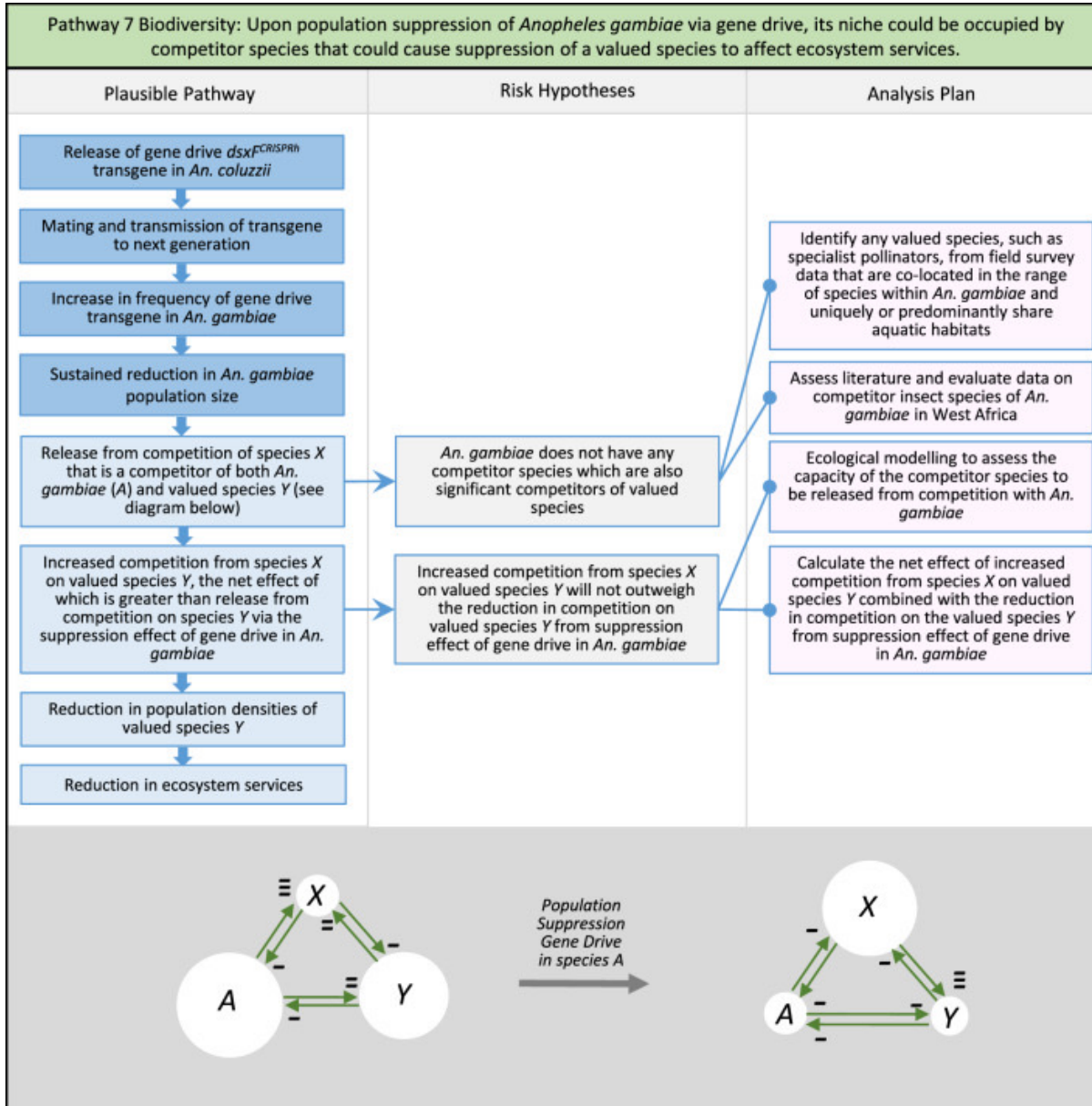
- Carballar-Lejarazú R, Dong Y, Pham TB, Tushar T, Corder RM *et al.* (2023) PNAS

Malaria transmission probability



- Aleshnick M, Ganusov VV, Nasir G, Yenokyan G *et al.* (2020) PLoS Pathogens
- Carballar-Lejarazú R, Dong Y, Pham TB, Tushar T, Corder RM *et al.* (2023) PNAS

Environmental risk assessment

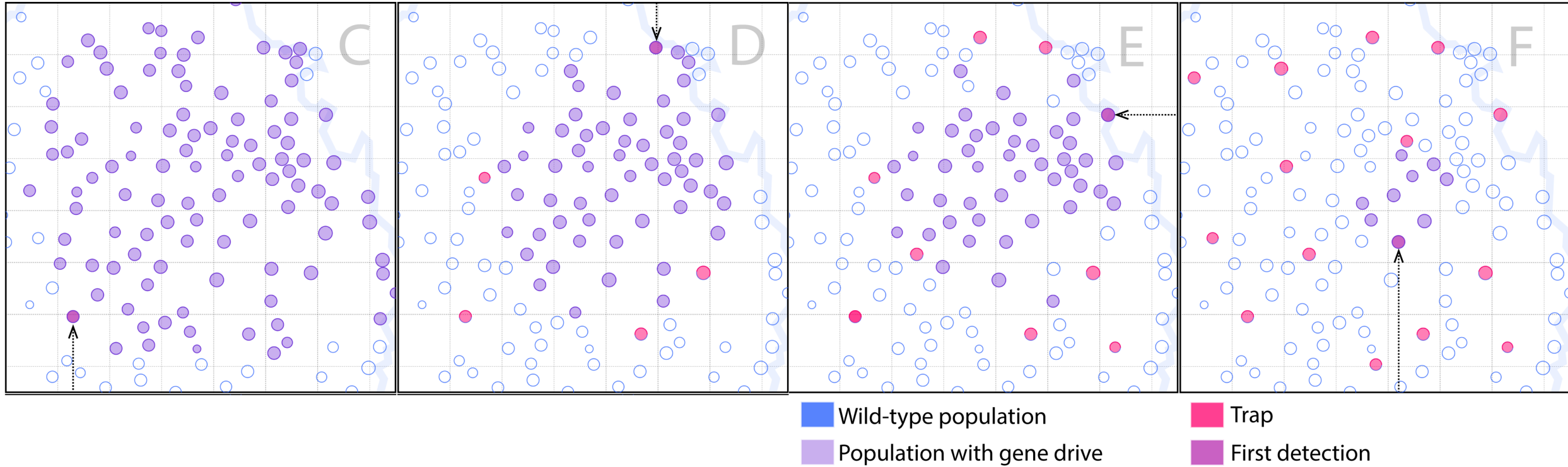


ERA modeling requires more ecological realism

Type of stressor/ interaction	EFSA 2013 characteristic	Implemented in GD models					
		Other models	North et al.	Skeeter Buster	MGDriveE	SLiM3	
Abiotic factors	Temperature	✓	✓	✓	×	×	
	Humidity	✓	✓	✓	×	×	
	Climatic/geographical barriers	✓	✓	✓	✓	✓	
Biotic characteristic TO related	Distribution (before and after release)	✓	✓	✓	✓	✓	
	Fitness	✓	✓	✓	✓	✓	
	Reproductive biology (fertility and fecundity) before and after release	✓	✓	✓	✓	✓	
	Dispersal	✓	✓	✓	✓	✓	
	Population size, structure, sex ratio (before and after GM release)	✓	✓	✓	✓	✓	
	Reduction in efficiency/resistance development against GM	✓	×	×	✓	✓	
	Changes in interactions (behavioural, genetic) between GMO and TO	×	×	×	×	×	
	Interactions with other species (non-target organisms)	Hybridization	×	×	×	×	×
		Pathogens (altered transmission range and frequency), increased vector competence	✓	×	×	✓	×
		Adverse effects due to “low quality GM insects” e.g. increased human biting rate or disease transmission	×	×	×	×	×
Prey		×	×	×	×	×	
Predators/predation		×	×	×	×	×	
Symbionts		✓ ⁵	×	×	✓ ⁵	×	
Hosts (plants, animals)		×	×	×	✓	×	
Parasites, pathogens		×	×	×	✓	×	
Trophic level/food web effects		×	×	×	×	×	
Competitors (abundance, species composition)		×	×	×	×	×	
Ecosystem services	×	×	×	×	×		
Toxins/allergens associated with GMO	×	×	×	×	×		

- Frieß JL, Lalyer CR, Giese B, Simon S, Otto M (2023) Ecological Modelling

Surveillance as a cost driver



- Rašić G, Lobo NF, Jeffrey Gutiérrez EH, Sánchez C. HM, Marshall JM (2022) *Frontiers in Genetics*

Optimal density & layout of traps

MGSurvE 0.7.2.0

Latest version

```
pip install MGSurvE
```

Released: Aug 11, 2022

MGSurvE

Navigation

- Project description
- Release history
- Download files

Project links

- Homepage

Statistics

GitHub statistics:

- Stars: 0
- Forks: 1
- Open issues/PRs: 0

View statistics for this project via [Libraries.io](#), or by using [our public dataset on Google BigQuery](#)

Project description

MGSurvE: Mosquito Gene Surveillance

MGSurvE is a project that optimizes mosquito traps' placement in complex heterogeneous landscapes in an effort to minimize the time to detection of genetic variants of interest.

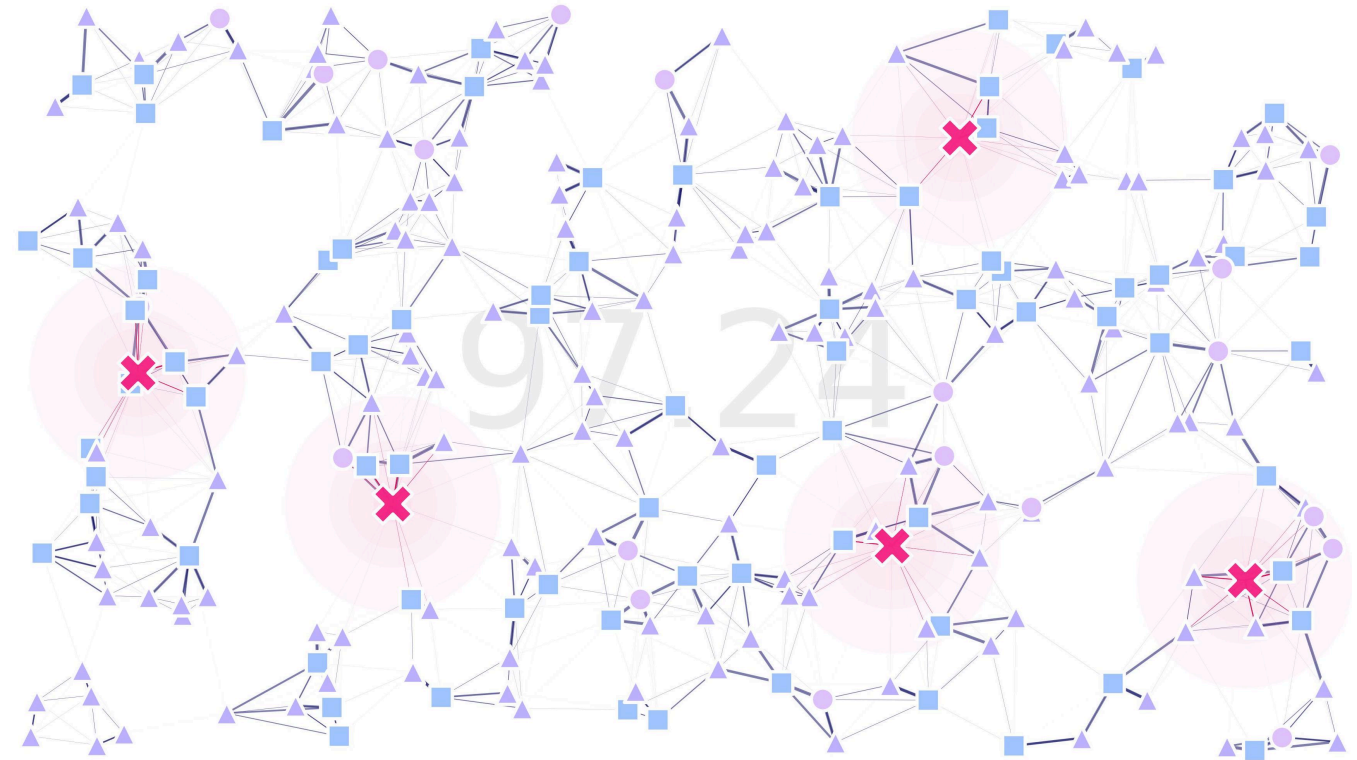
Please have a look at the [documentation](#) for more info and our [pypi](#) package for detailed [installation instructions](#), and [tutorials](#).

python 3.9 | 3.10 | pypi package 0.7.2.0 | docker img v0.7.2.0 | PyTests passing | Flake8 passing | CondaEnv passing | License GPLv3 | Open Source? Yes!

To install the package's latest stable version run (usage of [anaconda](#) for environment management is strongly recommended):

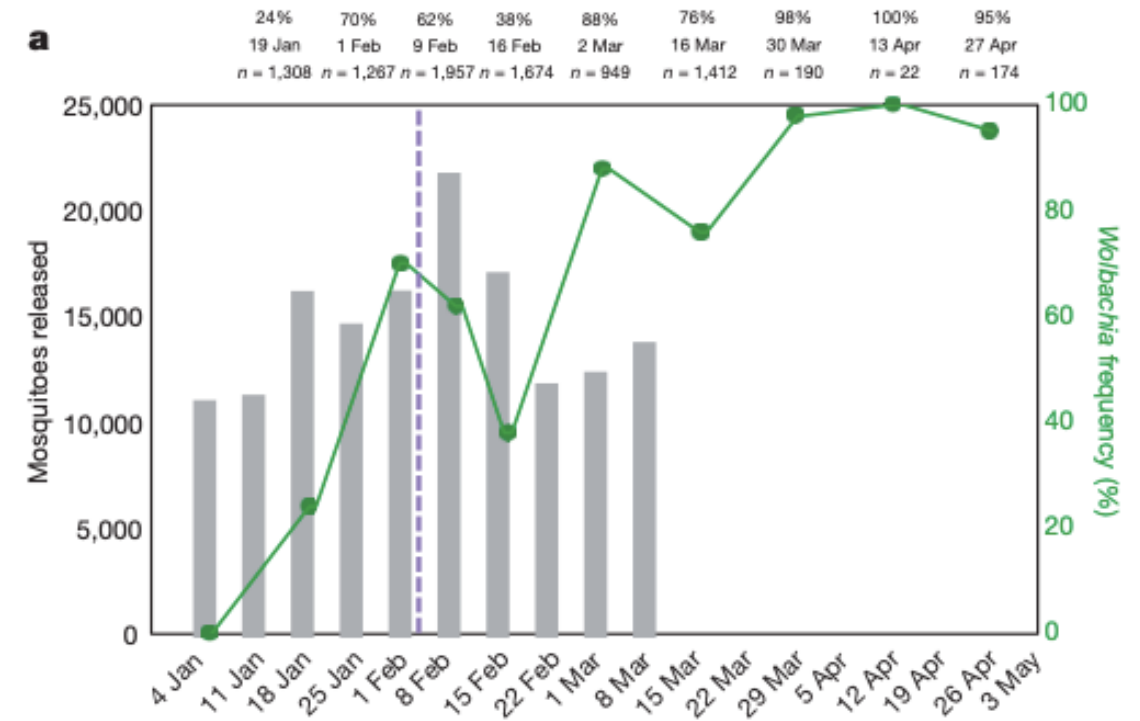
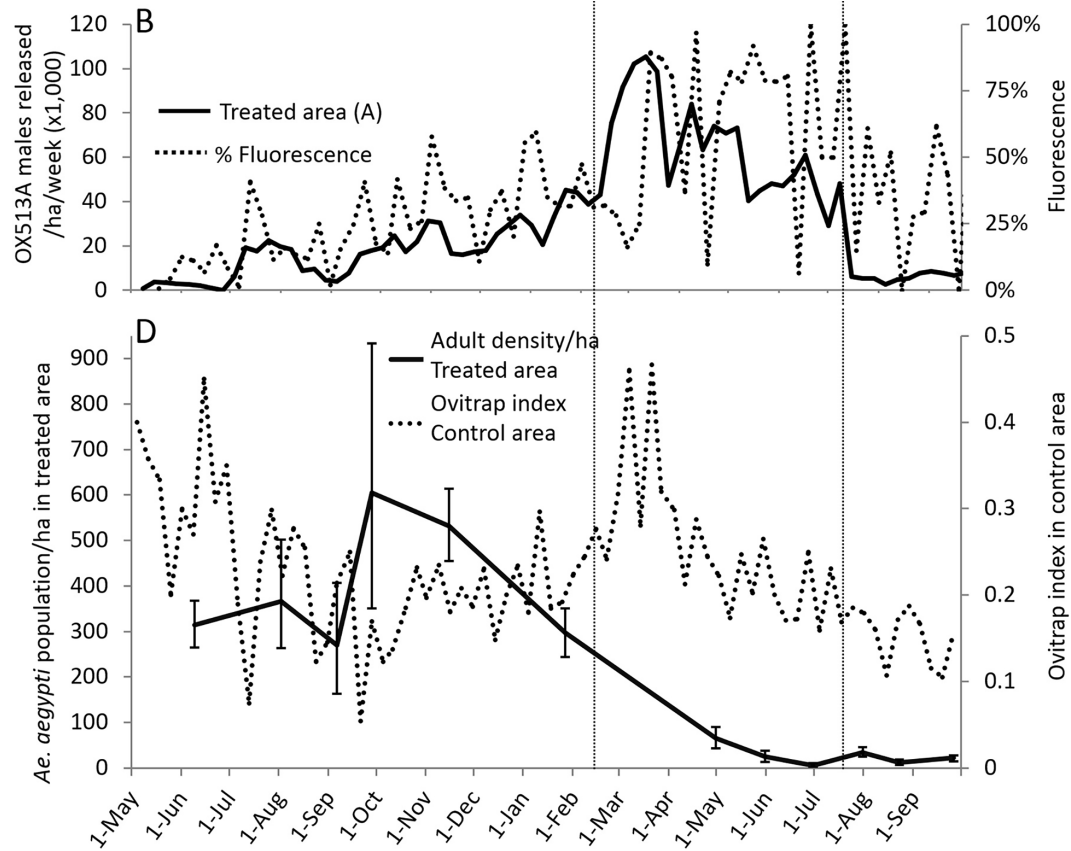
```
pip install MGSurvE
```

MGSurvE requires the installation of the [DEAP](#) optimization package, which should be installed automatically with our previous `pip` command. This package can also be installed with `conda install deap`, if needed; or by having a look at [DEAP's documentation](#) for additional methods. Please have a look at our [installation instructions](#) for common issues with some of the dependencies. Alternatively, pre-build images from [our Dockerhub](#) can be pulled and used to avoid dependencies issues.



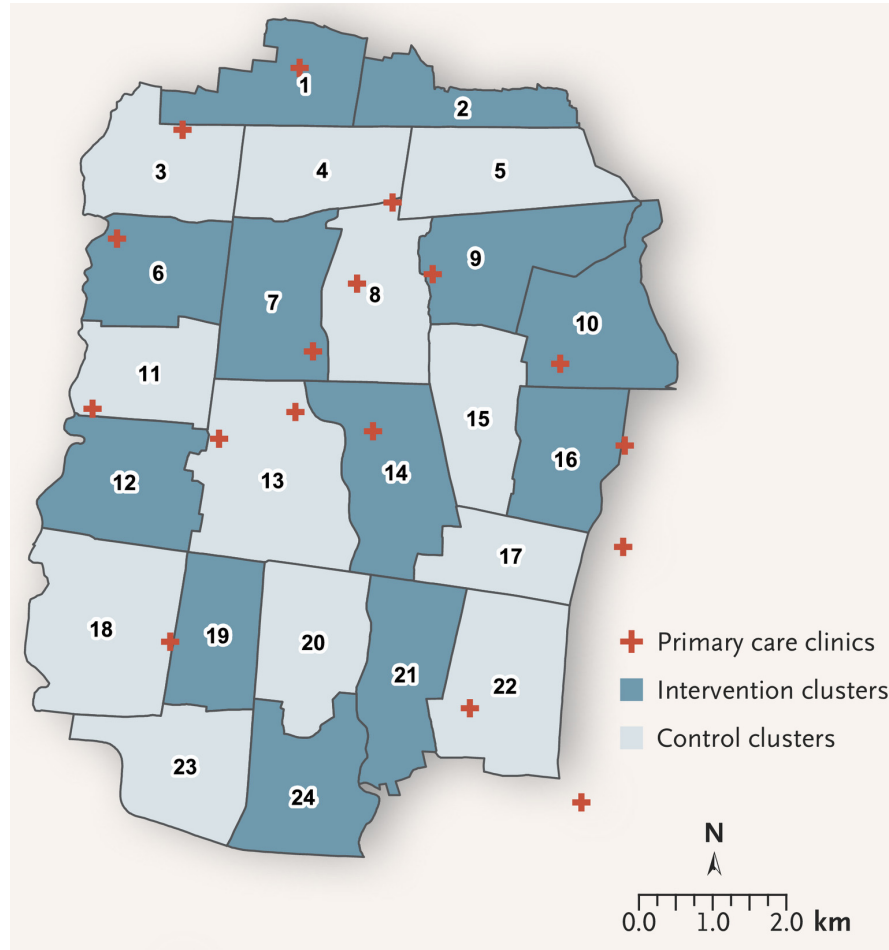
- Sánchez C. HM, Smith DL, Marshall JM (2023) <https://pypi.org/project/MGSurvE/>

Monitoring to infer fitness costs during a trial

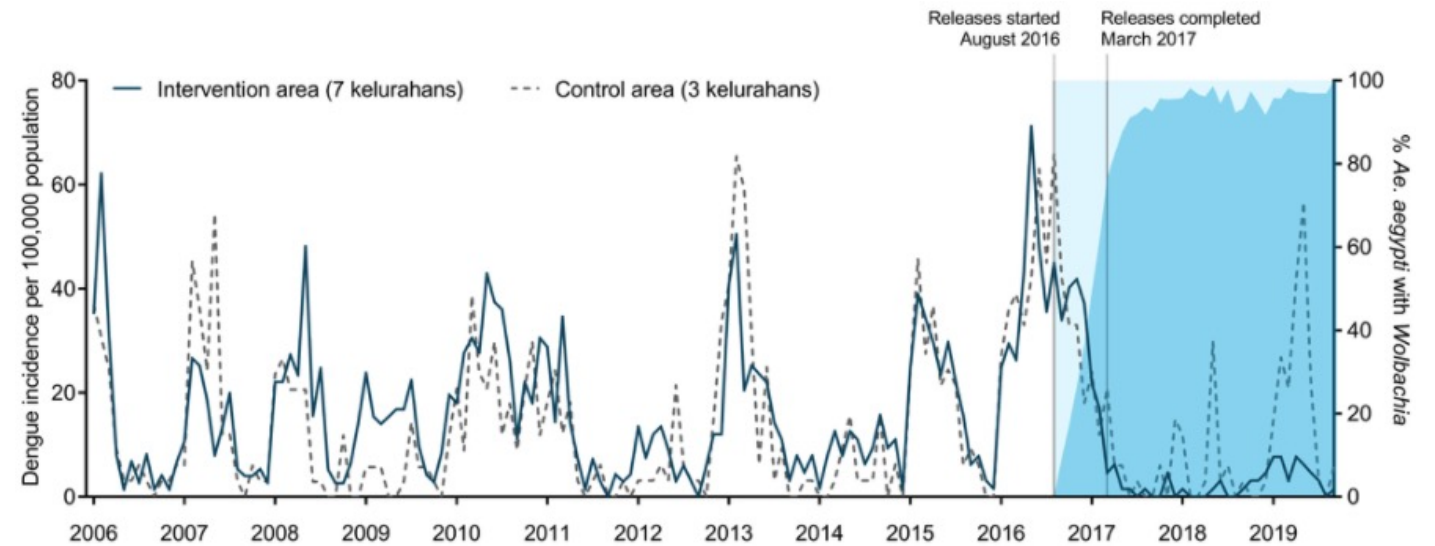
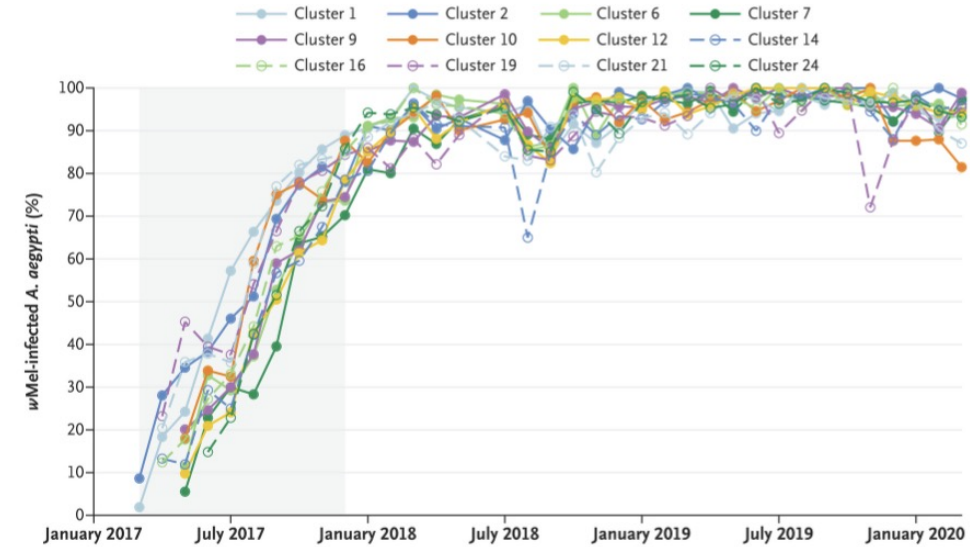


- Hoffmann AA, Montgomery BL, Popovici J *et al.* (2011) Nature
- Carvalho DO, McKemey AR, Garziera L *et al.* (2015) PLoS Negl Trop Dis

Field trial modeling: *Wolbachia* as a case study

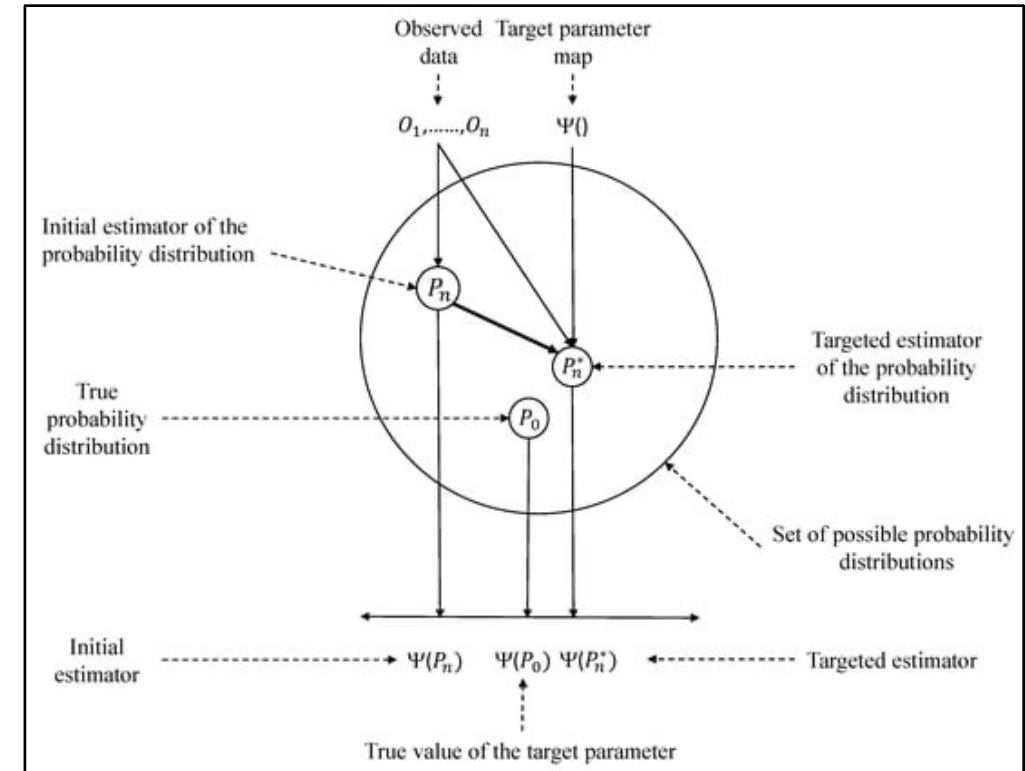
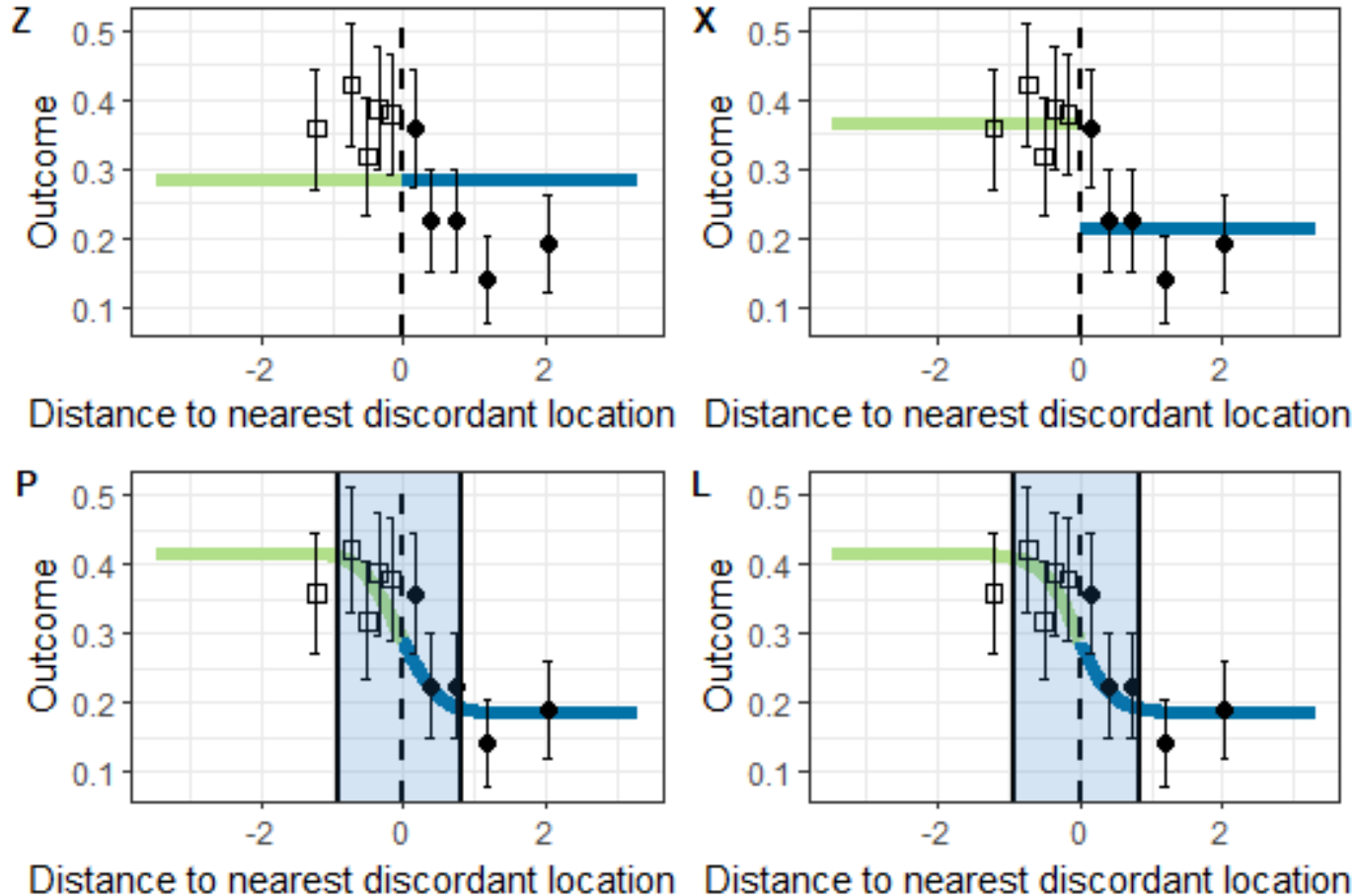


A Intervention Clusters



- Utarini A, Indiani C, Ahmad RA, Tantowiyojo W *et al.* (2021) *New England J Medicine*

Field trial modeling: Spillover & TMLE



- Smith T, Multerer L, Silkey M (2024) <https://cran.r-project.org/web/packages/CRTspat/>
- van der Laan MJ, Rubin D (2006) Targeted Maximum Likelihood Learning

Recap

1. Target product profiles:

- Determine when technology is ready for the field
- Some parameters can't be measured prior to release
- Parameter requirements may depend on others

2. Risk assessment:

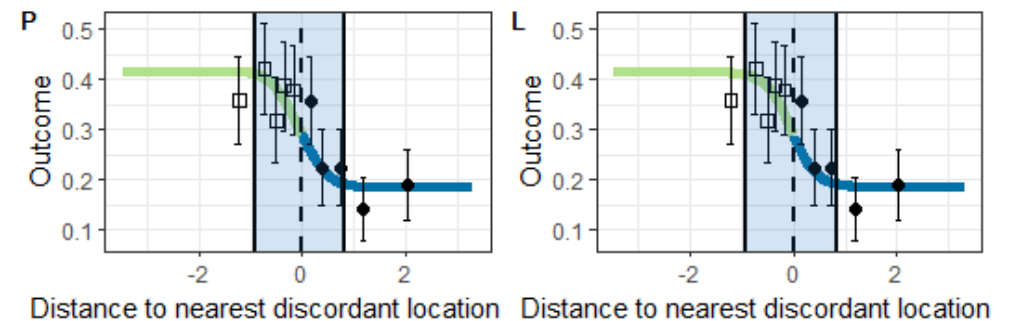
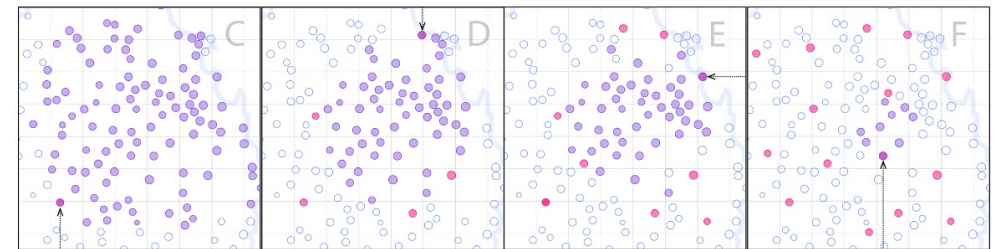
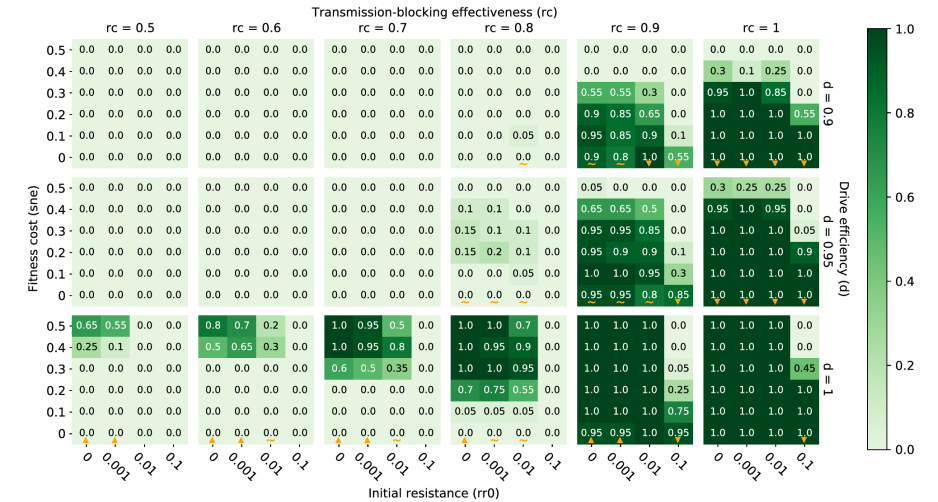
- A subset of identified risks are suited to modeling
- More ecological realism is needed

3. Monitoring & surveillance:

- Surveillance is expected to be a cost driver & requires efficient design
- Monitoring should infer fitness costs early in a trial

4. Field trial design:

- *Wolbachia* provides a case study, with differences
- Exploring new techniques to extract more power from field trial data



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LAB MEMBERS:

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