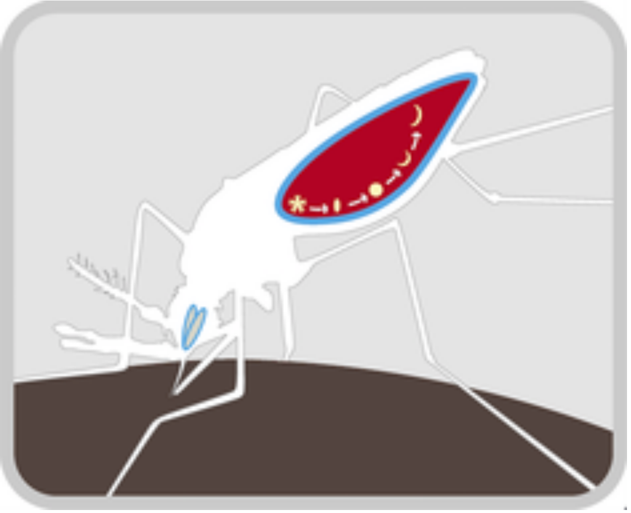
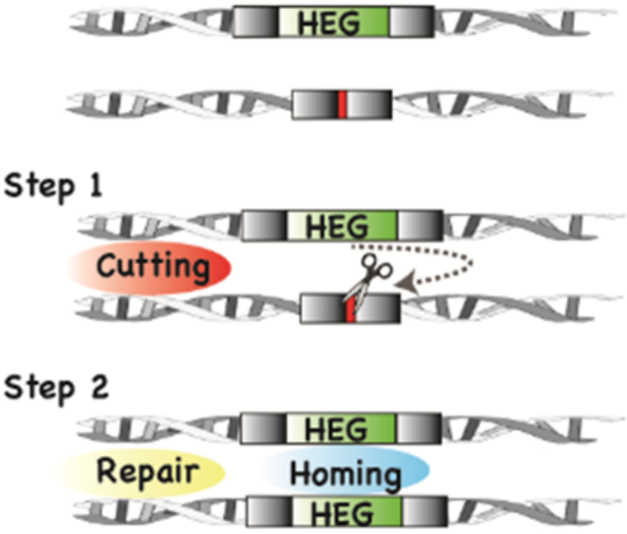
Harvard Medical School, 28th March 2018

Can malaria, dengue and Zika be controlled by CRISPR-based gene drive and other novel tools?

John M. Marshall

Divisions of Biostatistics & Epidemiology
School of Public Health, University of California, Berkeley

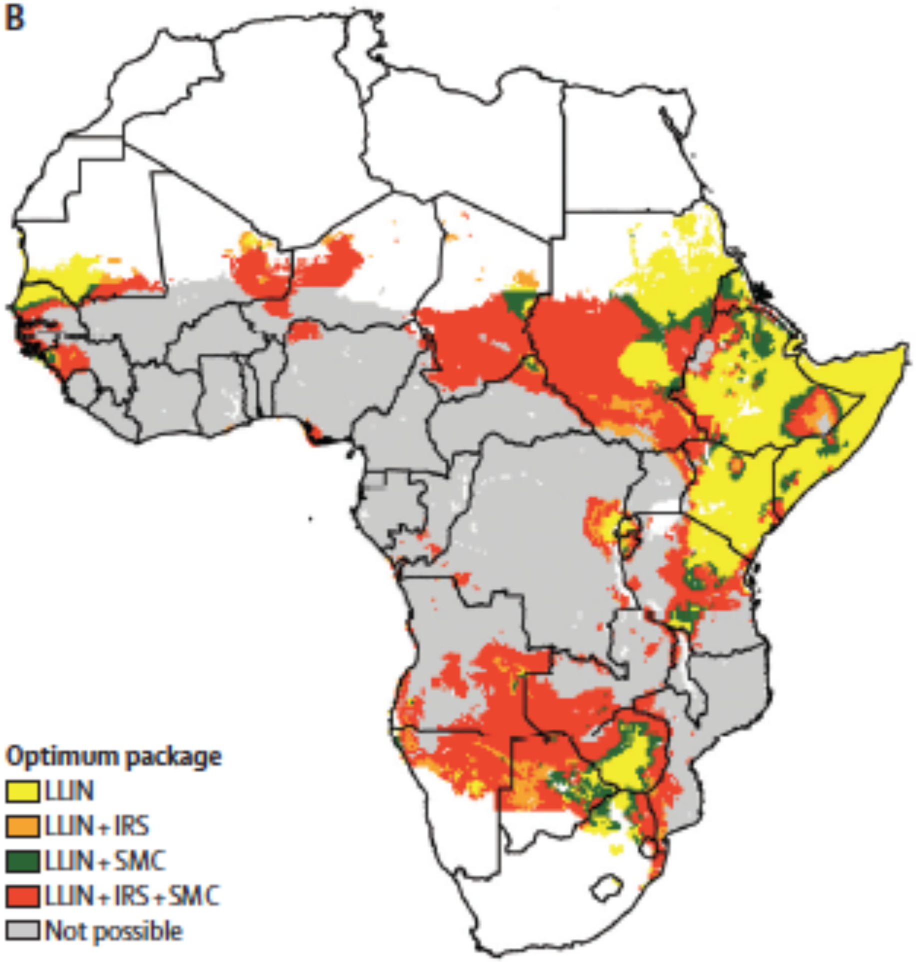




Berkeley School of Public Health

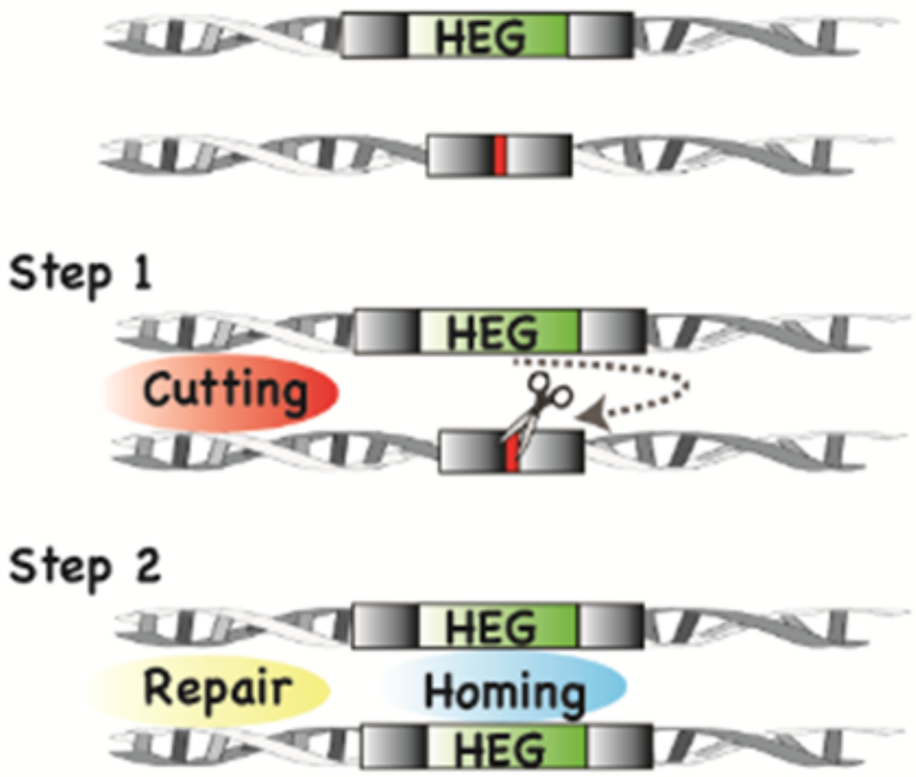
Estimating the most efficient allocation of interventions to achieve reductions in *Plasmodium falciparum* malaria burden and transmission in Africa: a modelling study

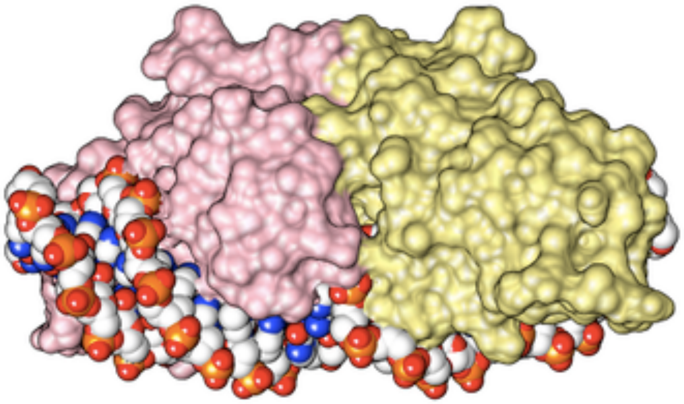
Patrick G T Walker, Jamie T Griffin, Neil M Ferguson, Azra C Ghani

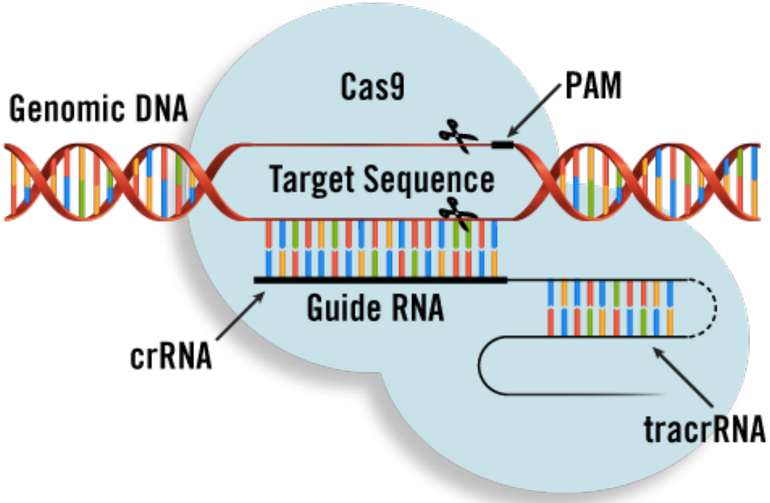


- Walker PGT, Griffin JT, Ghani AC (2016) Lancet Global Health 4: e474-e484.

Homing-based gene drive systems







Recent engineering successes

The mutagenic chain reaction: A method for converting heterozygous to homozygous mutations

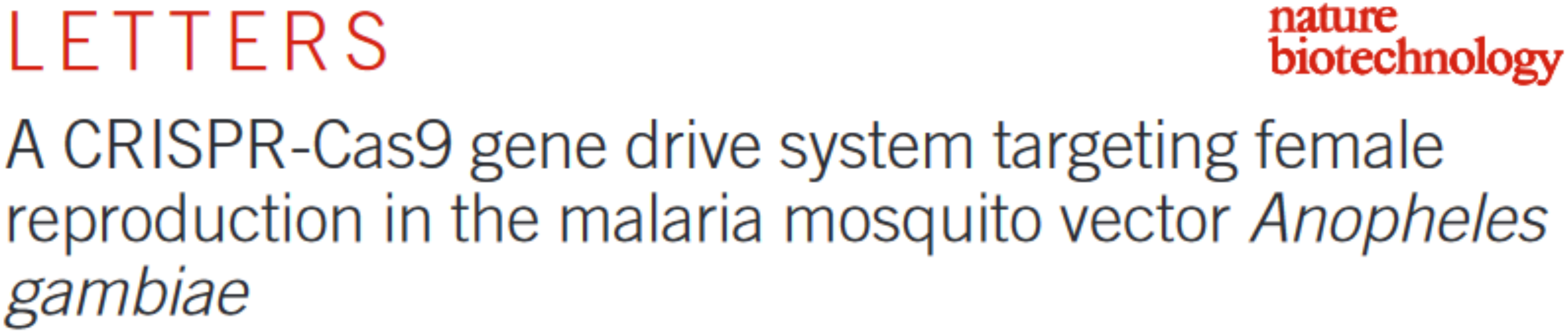
Valentino M. Gantz* and Ethan Bier*

Sciencexpress

PNAS

Highly efficient Cas9-mediated gene drive for population modification of the malaria vector mosquito *Anopheles stephensi*

Valentino M. Gantz[a,1], Nijole Jasinskiene[b,1], Olga Tatarenkova[b], Aniko Fazekas[b], Vanessa M. Macias[b], Ethan Bier[a,2], and Anthony A. James[b,c,2]



LETTERS

nature biotechnology

A CRISPR-Cas9 gene drive system targeting female reproduction in the malaria mosquito vector *Anopheles gambiae*

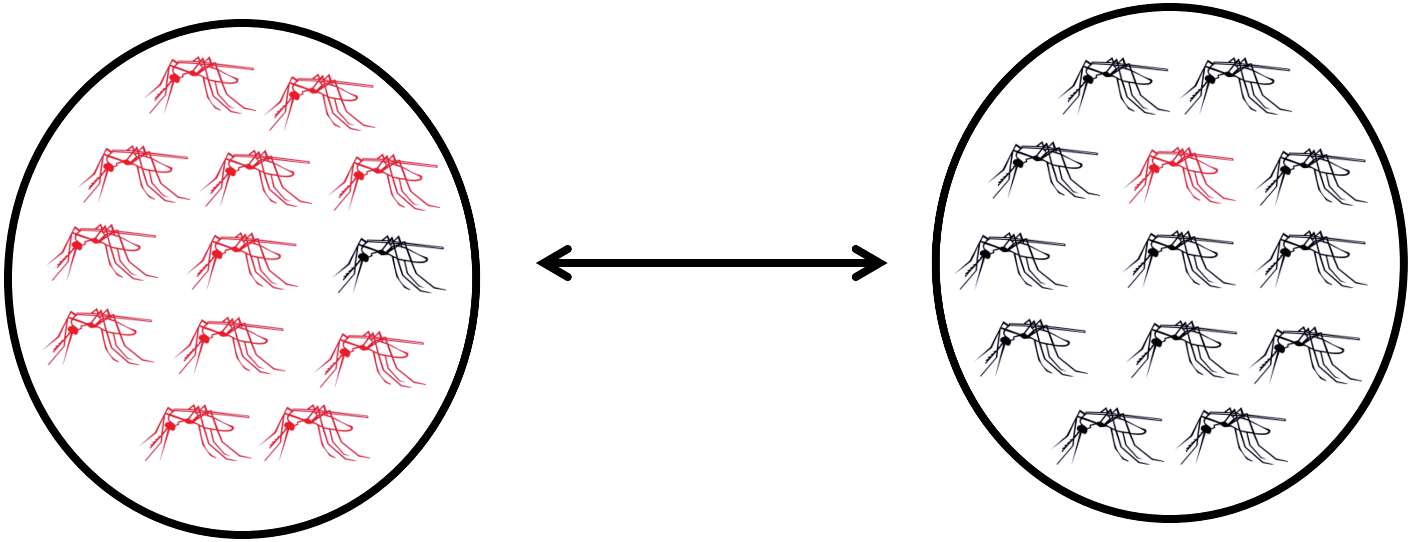
Q1. Is it possible to perform a confined trial of a gene drive system?

Banambani, Mali

7 km

~1% / gen

Doneguebougou, Mali



RESEARCH **Open Access**

Perspectives of people in Mali toward genetically-modified mosquitoes for malaria control

John M Marshall*[1], Mahamoudou B Touré[2], Mohamed M Traore[2], Shannon Famenini[3,4] and Charles E Taylor[3,4]

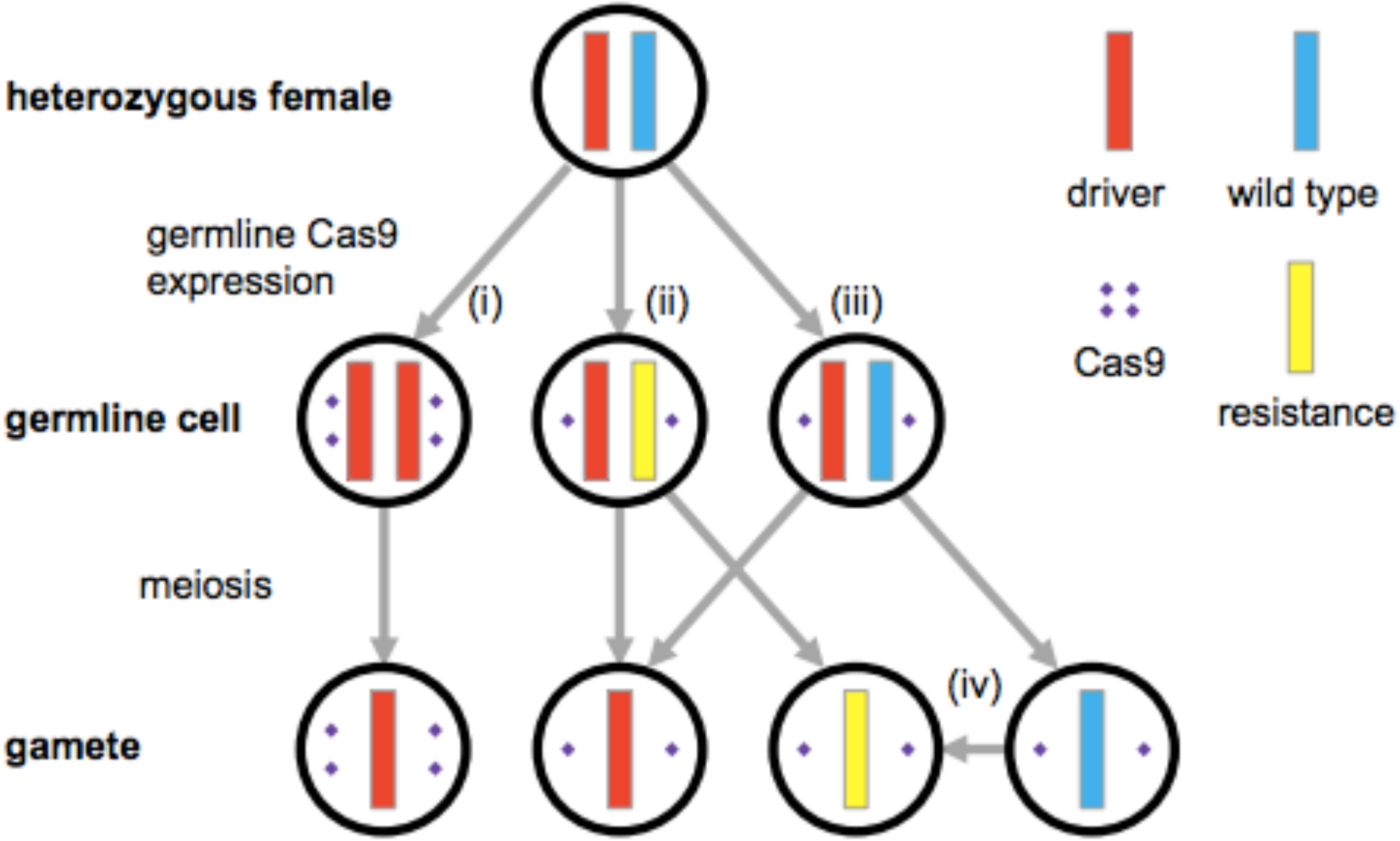
- **Public attitude surveys** in **Mali** suggest that people would like to see a **successful confined trial** before accepting a release:

"I would have to see an example of modified mosquitoes reducing malaria in another village before I believe this claim"

72-year-old man, Tienfala, Mali

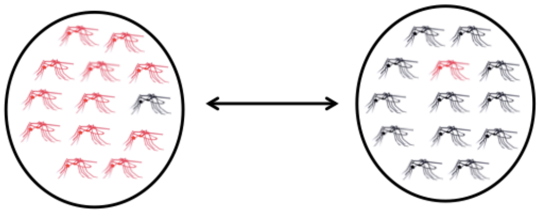
- Marshall JM, Toure MB, Traore MM, Famenini S, Taylor CE (2010) Malaria Journal 9: 128

Q2. Can CRISPR-based gene drive be effective at disease control on a wide scale?



- Champer J, Reeves R, Oh SY, Liu C, Liu J *et al.* (2017) PLoS Genetics 13: e1006796

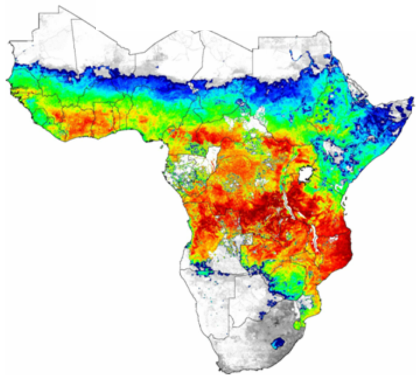
Talk outline



Overview

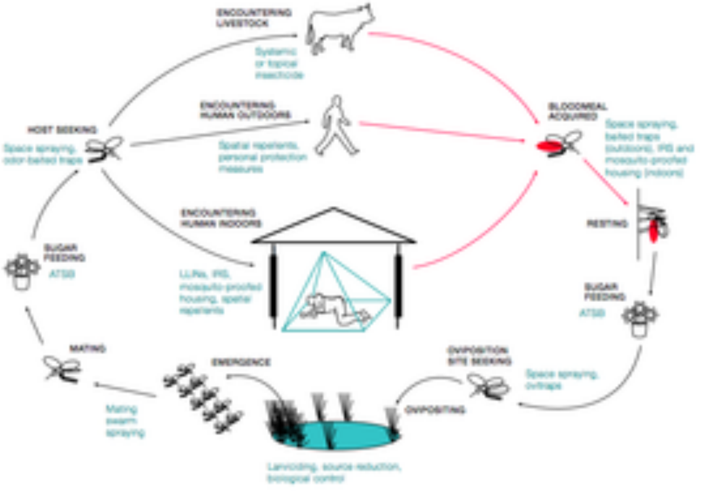
Q1. Is it possible to perform a confined trial of a gene drive system?

- Threshold-dependent gene drive systems
- Inferring patterns of mosquito dispersal



Q2. Can CRISPR-based gene drive be effective at disease control on a wide scale?

- Resistant allele generation
- Possible solutions involving guide RNA multiplexing



Q3. Which other novel vector control tools should we be prioritizing?

- Attractive toxic sugar baits (ATSB)
- Vector control optimization model (VCOM)

Conclusion

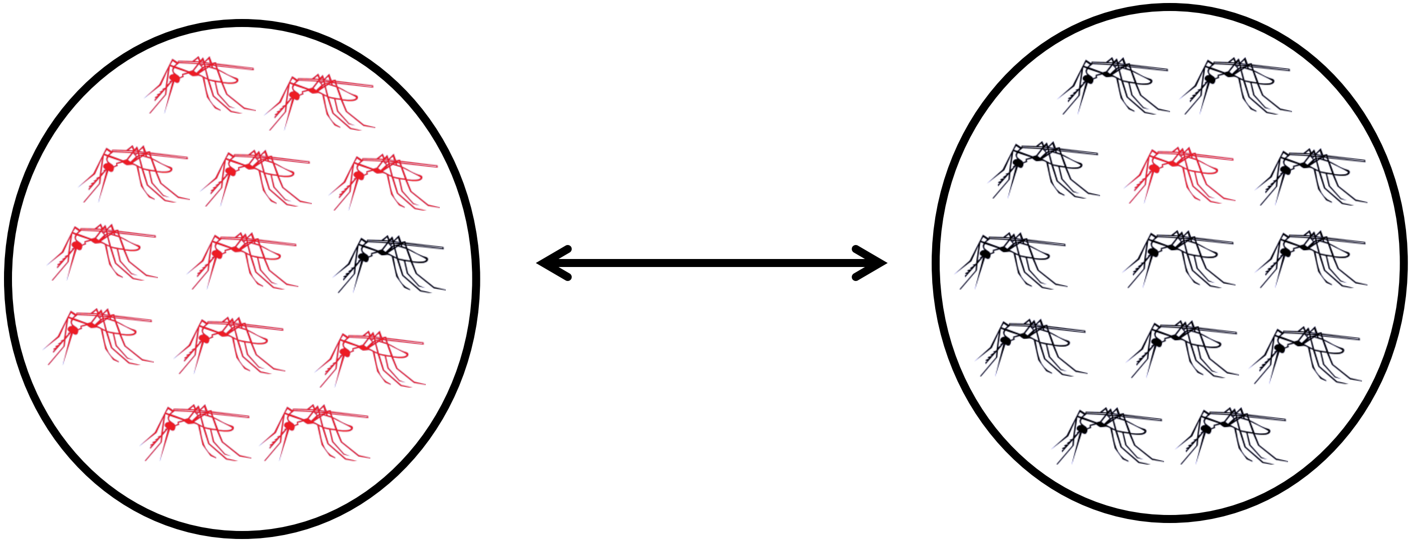
Q1. Is it possible to perform a confined trial of a gene drive system?

Banambani, Mali

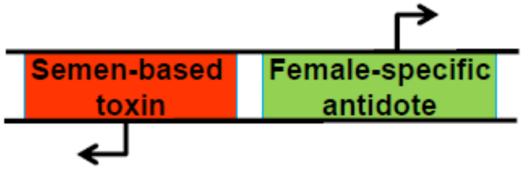
7 km

~1% / gen

Doneguebougou, Mali

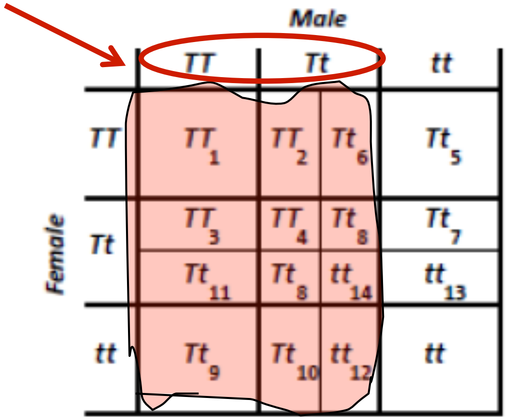


Semele

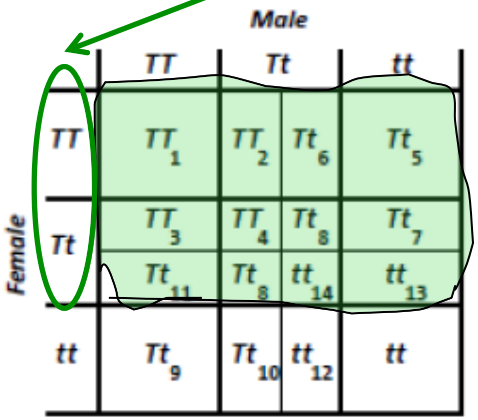


Transgenic males
produce **toxic semen**

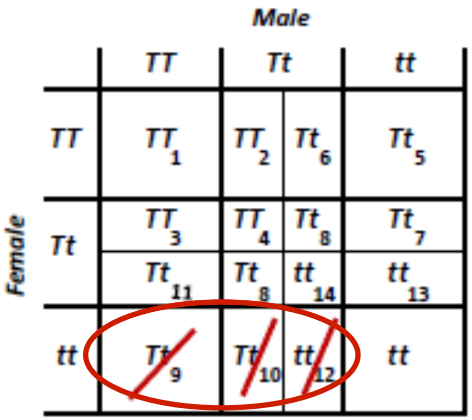
Transgenic females
produce **antidote**



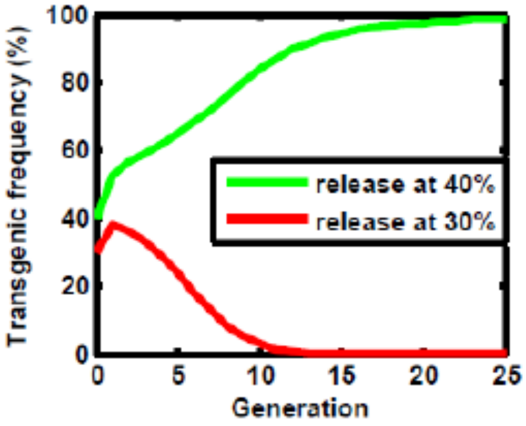
		Male		
Female		TT	Tt	tt
	TT	TT_1	TT_2 Tt_6	Tt_5
	Tt	TT_3 Tt_{11}	TT_4 Tt_8 Tt_8 tt_{14}	Tt_7 tt_{13}
	tt	Tt_9	Tt_{10} tt_{12}	tt



		Male		
Female		TT	Tt	tt
	TT	TT_1	TT_2 Tt_6	Tt_5
	Tt	TT_3 Tt_{11}	TT_4 Tt_8 Tt_8 tt_{14}	Tt_7 tt_{13}
	tt	Tt_9	Tt_{10} tt_{12}	tt



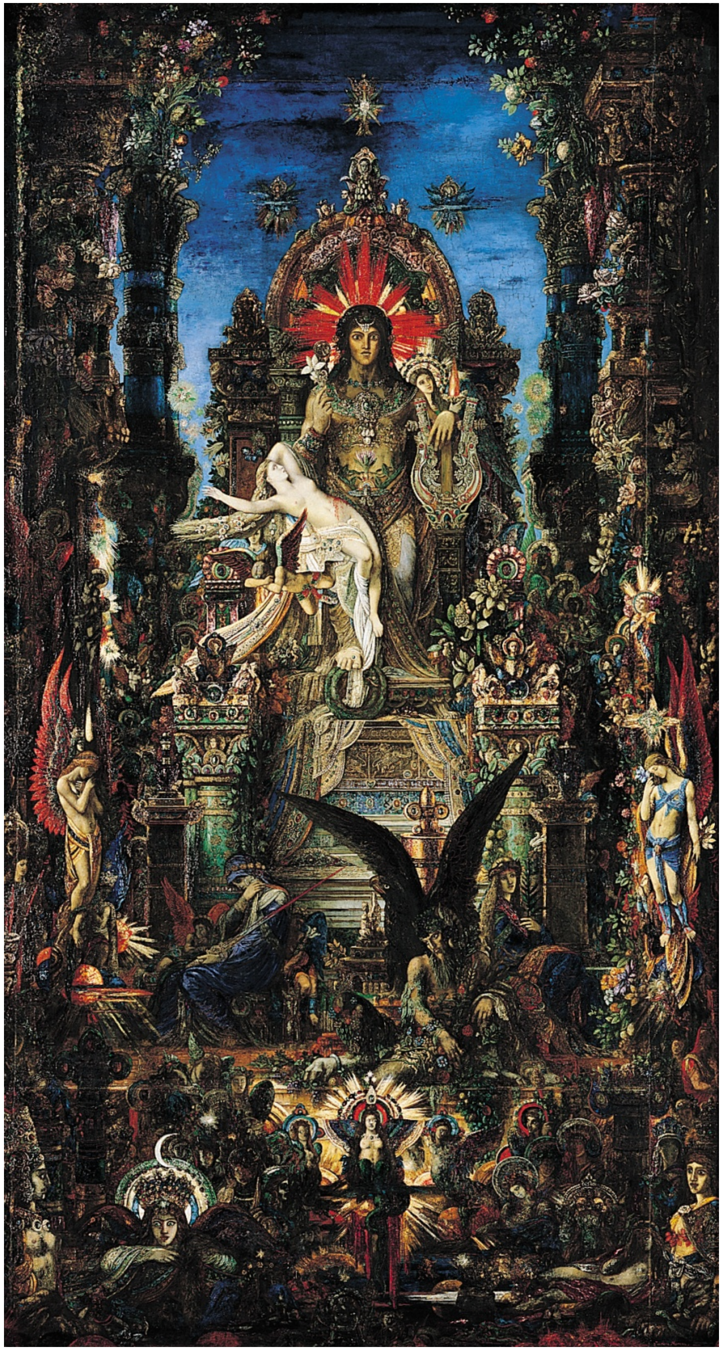
		Male		
Female		TT	Tt	tt
	TT	TT_1	TT_2 Tt_6	Tt_5
	Tt	TT_3 Tt_{11}	TT_4 Tt_8 Tt_8 tt_{14}	Tt_7 tt_{13}
	tt	$\cancel{Tt_9}$	$\cancel{Tt_{10}}$ $\cancel{tt_{12}}$	tt



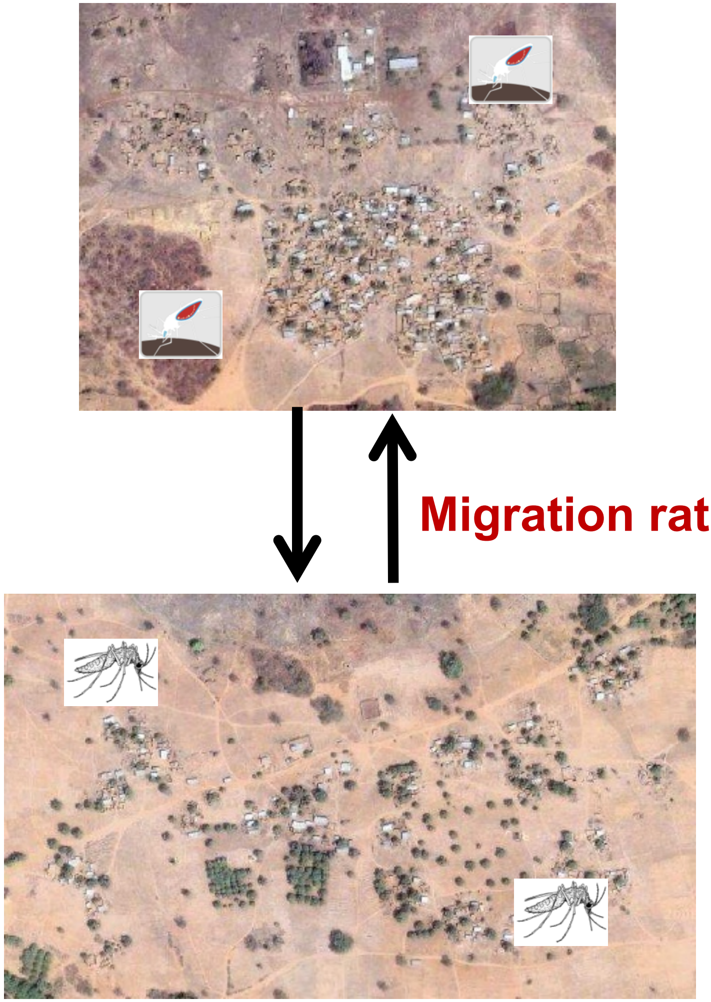
- A **release including females** results in **gene drive** (GM females are favored at high population frequencies).

- **Release threshold = 36.4%**:

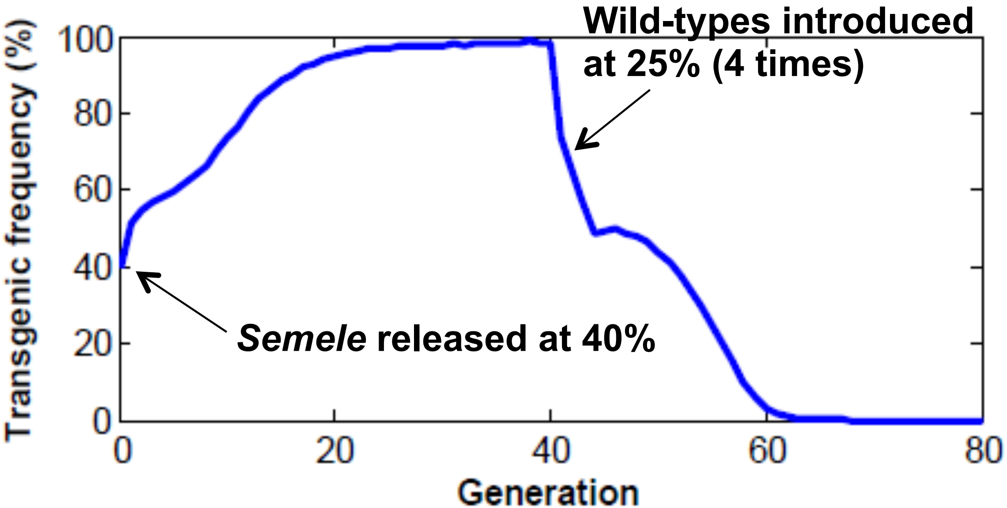
- Marshall JM, Pittman GW, Buchman A, Hay BA (2011) Genetics 187: 535-551.

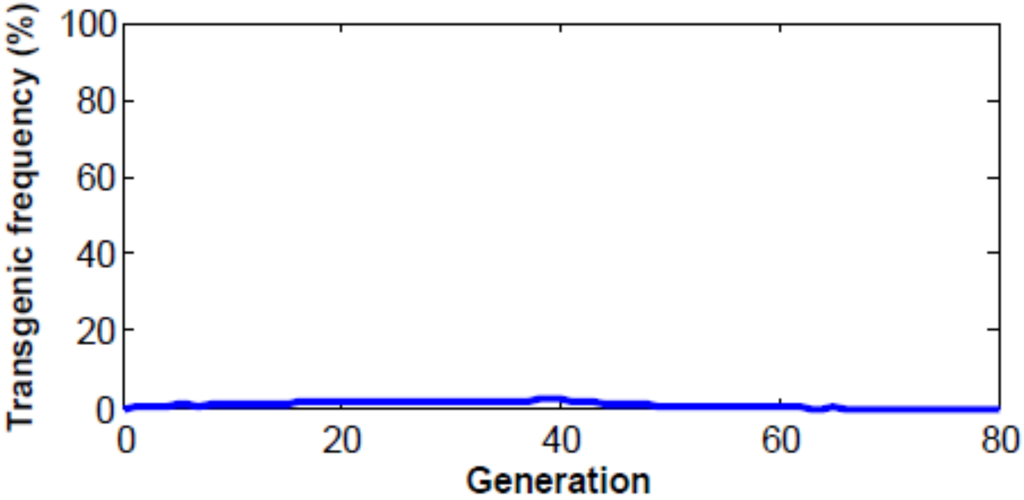


Introduction of *Semele* is predicted to be confineable and reversible



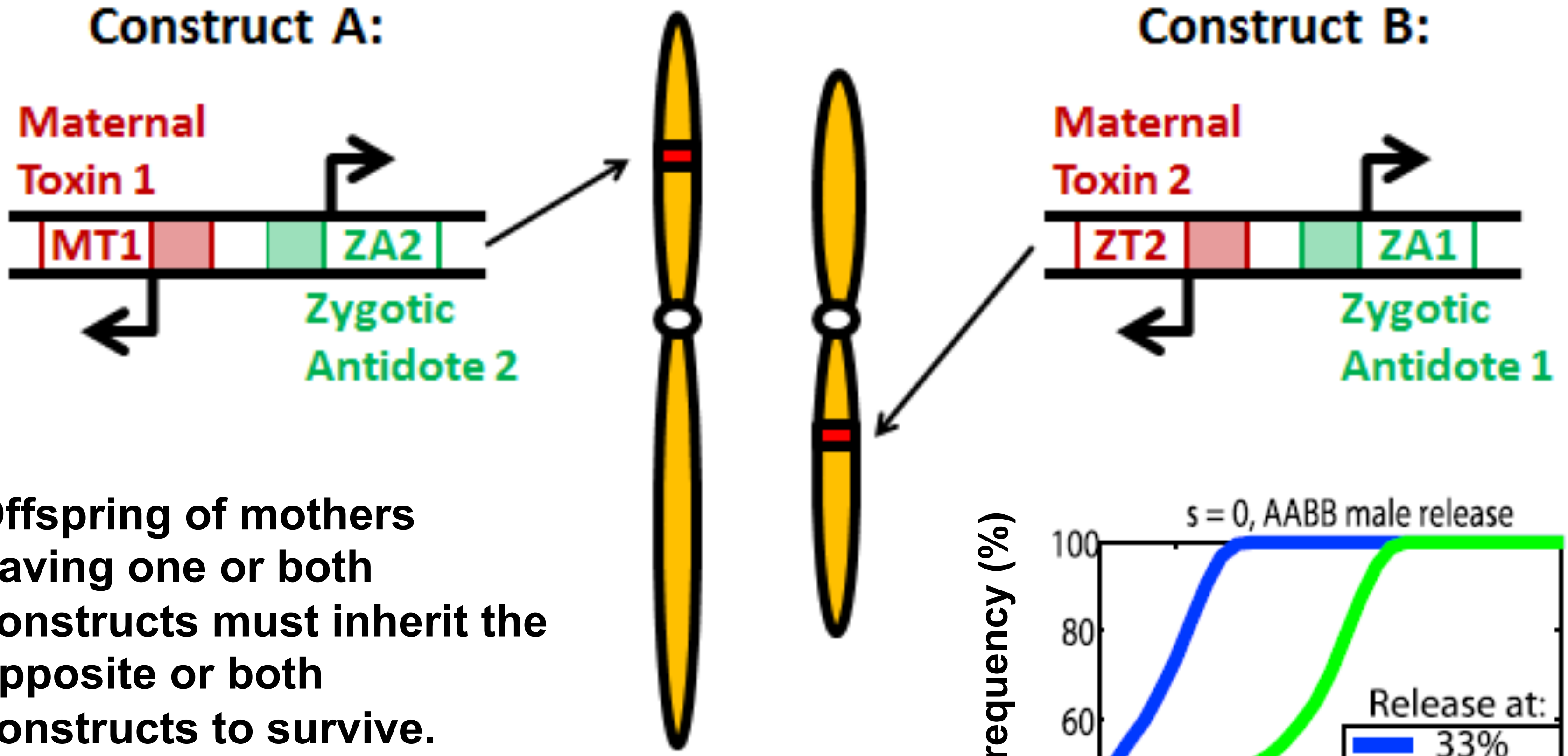
Migration rate = 1% /gen





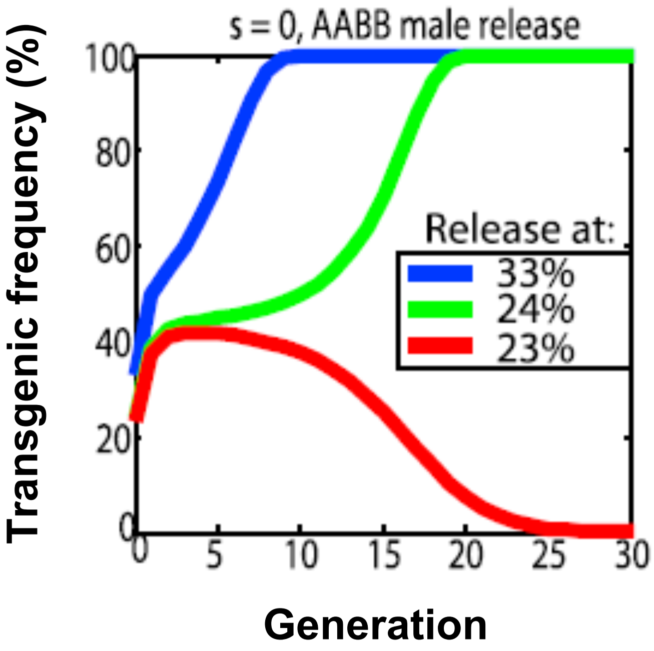
- Marshall JM, Pittman GW, Buchman A, Hay BA (2011) Genetics 187: 535-551.

UD$^{\mathrm{MEL}}$



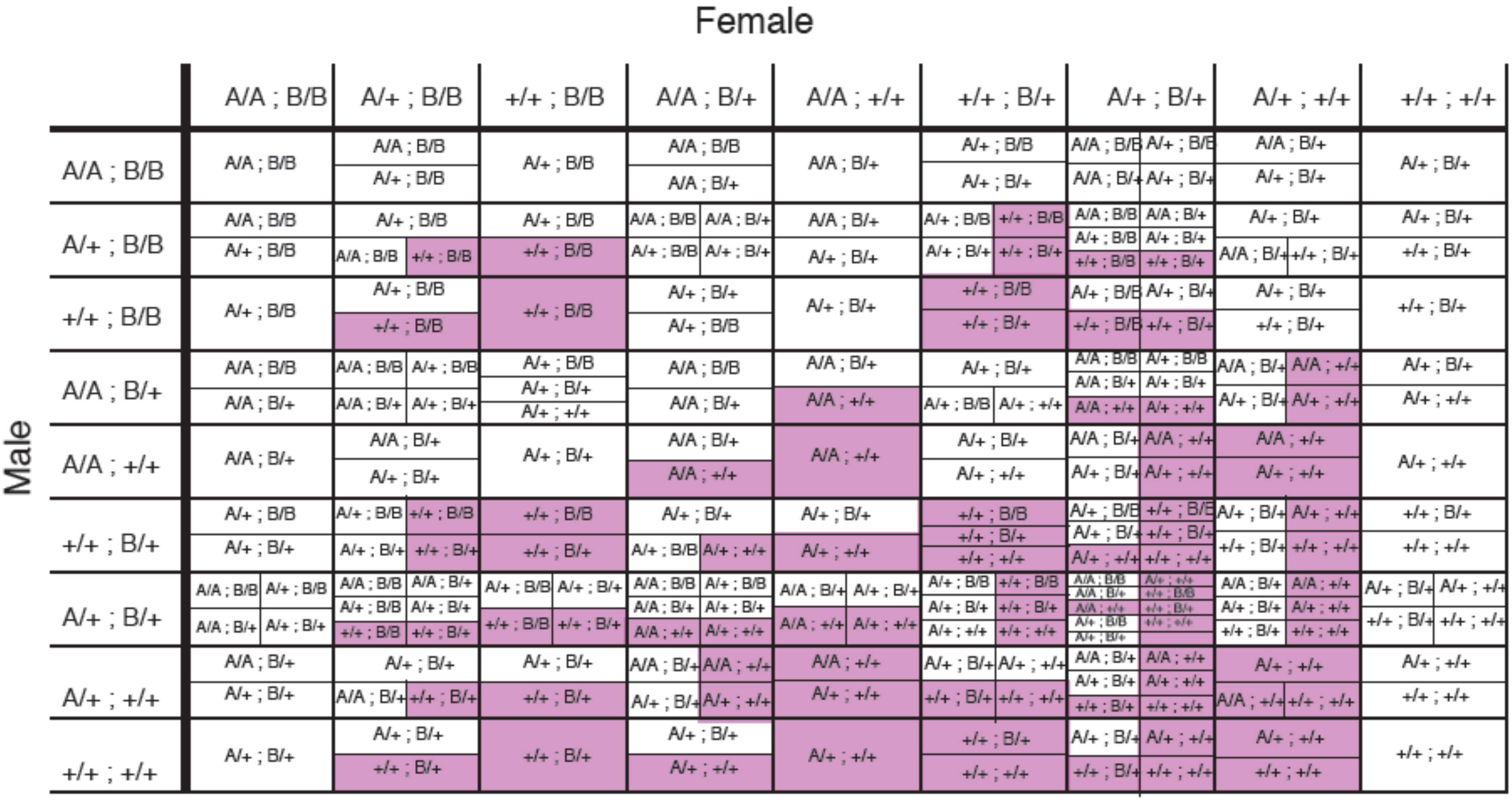
- **Offspring of mothers having one or both constructs must inherit the opposite or both constructs to survive.**

- This is **more likely** at **higher population frequencies (>24%)** leading to **frequency-dependent drive**.



- Akbari OS, Matzen KD, Marshall JM, Huang H *et al.* (2013) Current Biology 23: 671-677

Inheritance pattern of UD^{MEL}



Female

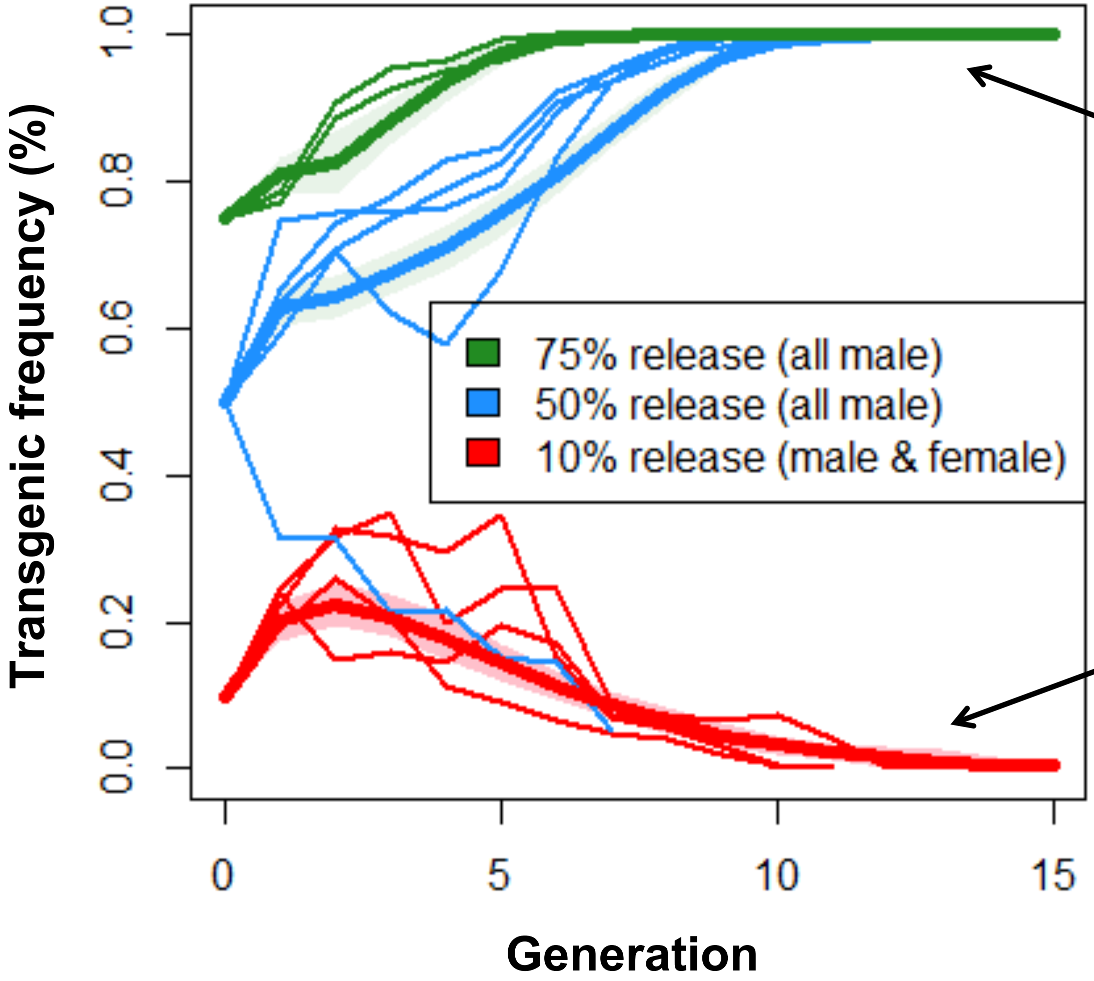
Male

	A/A ; B/B	A/+ ; B/B	+/+ ; B/B	A/A ; B/+	A/A ; +/+	+/+ ; B/+	A/+ ; B/+	A/+ ; +/+	+/+ ; +/+
A/A ; B/B	A/A ; B/B	A/A ; B/B A/+ ; B/B	A/+ ; B/B	A/A ; B/B A/A ; B/+	A/A ; B/+	A/+ ; B/B A/+ ; B/+	A/A ; B/B A/+ ; B/B A/A ; B/+ A/+ ; B/+	A/A ; B/+ A/+ ; B/+	A/+ ; B/+
A/+ ; B/B	A/A ; B/B A/+ ; B/B	A/+ ; B/B A/A ; B/B +/+ ; B/B	A/+ ; B/B +/+ ; B/B	A/A ; B/B A/A ; B/+ A/+ ; B/B A/+ ; B/+	A/A ; B/+ A/+ ; B/+	A/+ ; B/B +/+ ; B/B A/+ ; B/+ +/+ ; B/+	A/A ; B/B A/A ; B/+ A/+ ; B/B A/+ ; B/+ +/+ ; B/B +/+ ; B/+	A/+ ; B/+ A/A ; B/+ +/+ ; B/+	A/+ ; B/+ +/+ ; B/+
+/+ ; B/B	A/+ ; B/B	A/+ ; B/B +/+ ; B/B	+/+ ; B/B	A/+ ; B/+ A/+ ; B/B	A/+ ; B/+	+/+ ; B/B +/+ ; B/+	A/+ ; B/B A/+ ; B/+ +/+ ; B/B +/+ ; B/+	A/+ ; B/+ +/+ ; B/+	+/+ ; B/+
A/A ; B/+	A/A ; B/B A/A ; B/+	A/A ; B/B A/+ ; B/B A/A ; B/+ A/+ ; B/+	A/+ ; B/B A/+ ; B/+ A/+ ; +/+	A/A ; B/B A/A ; B/+	A/A ; B/+ A/A ; +/+	A/+ ; B/+ A/+ ; B/B A/+ ; +/+	A/A ; B/B A/+ ; B/B A/A ; B/+ A/+ ; B/+ A/A ; +/+ A/+ ; +/+	A/A ; B/+ A/A ; +/+ A/+ ; B/+ A/+ ; +/+	A/+ ; B/+ A/+ ; +/+
A/A ; +/+	A/A ; B/+	A/A ; B/+ A/+ ; B/+	A/+ ; B/+	A/A ; B/+ A/A ; +/+	A/A ; +/+	A/+ ; B/+ A/+ ; +/+	A/A ; B/+ A/A ; +/+ A/+ ; B/+ A/+ ; +/+	A/A ; +/+ A/+ ; +/+	A/+ ; +/+
+/+ ; B/+	A/+ ; B/B A/+ ; B/+	A/+ ; B/B +/+ ; B/B A/+ ; B/+ +/+ ; B/+	+/+ ; B/B +/+ ; B/+	A/+ ; B/+ A/+ ; B/B A/+ ; +/+	A/+ ; B/+ A/+ ; +/+	+/+ ; B/B +/+ ; B/+ +/+ ; +/+	A/+ ; B/B +/+ ; B/B A/+ ; B/+ +/+ ; B/+ A/+ ; +/+ +/+ ; +/+	A/+ ; B/+ A/+ ; +/+ +/+ ; B/+ +/+ ; +/+	+/+ ; B/+ +/+ ; +/+
A/+ ; B/+	A/A ; B/B A/+ ; B/B A/A ; B/+ A/+ ; B/+	A/A ; B/B A/A ; B/+ A/+ ; B/B A/+ ; B/+ +/+ ; B/B +/+ ; B/+	A/+ ; B/B A/+ ; B/+ +/+ ; B/B +/+ ; B/+	A/A ; B/B A/+ ; B/B A/A ; B/+ A/+ ; B/+ A/A ; +/+ A/+ ; +/+	A/A ; B/+ A/+ ; B/+ A/A ; +/+ A/+ ; +/+	A/+ ; B/B +/+ ; B/B A/+ ; B/+ +/+ ; B/+ A/+ ; +/+ +/+ ; +/+	A/A ; B/B A/+ ; +/+ A/A ; B/+ +/+ ; B/B A/A ; +/+ +/+ ; B/+ A/+ ; B/B +/+ ; +/+ A/+ ; B/+	A/A ; B/+ A/A ; +/+ A/+ ; B/+ A/+ ; +/+ +/+ ; B/+ +/+ ; +/+	A/+ ; B/+ A/+ ; +/+ +/+ ; B/+ +/+ ; +/+
A/+ ; +/+	A/A ; B/+ A/+ ; B/+	A/+ ; B/+ A/A ; B/+ +/+ ; B/+	A/+ ; B/+ +/+ ; B/+	A/A ; B/+ A/A ; +/+ A/+ ; B/+ A/+ ; +/+	A/A ; +/+ A/+ ; +/+	A/+ ; B/+ A/+ ; +/+ +/+ ; B/+ +/+ ; +/+	A/A ; B/+ A/A ; +/+ A/+ ; B/+ A/+ ; +/+ +/+ ; B/+ +/+ ; +/+	A/+ ; +/+ A/A ; +/+ +/+ ; +/+	A/+ ; +/+ +/+ ; +/+
+/+ ; +/+	A/+ ; B/+	A/+ ; B/+ +/+ ; B/+	+/+ ; B/+	A/+ ; B/+ A/+ ; +/+	A/+ ; +/+	+/+ ; B/+ +/+ ; +/+	A/+ ; B/+ A/+ ; +/+ +/+ ; B/+ +/+ ; +/+	A/+ ; +/+ +/+ ; +/+	+/+ ; +/+

2 Locus UD^{MEL} 81 dihybrid punnet Square

- Akbari OS, Matzen KD, Marshall JM, Huang H *et al.* (2013) Current Biology 23: 671-677

UD^{MEL} drive experiments agree with mathematical predictions & display threshold behavior



Drive to fixation occurs for releases that are

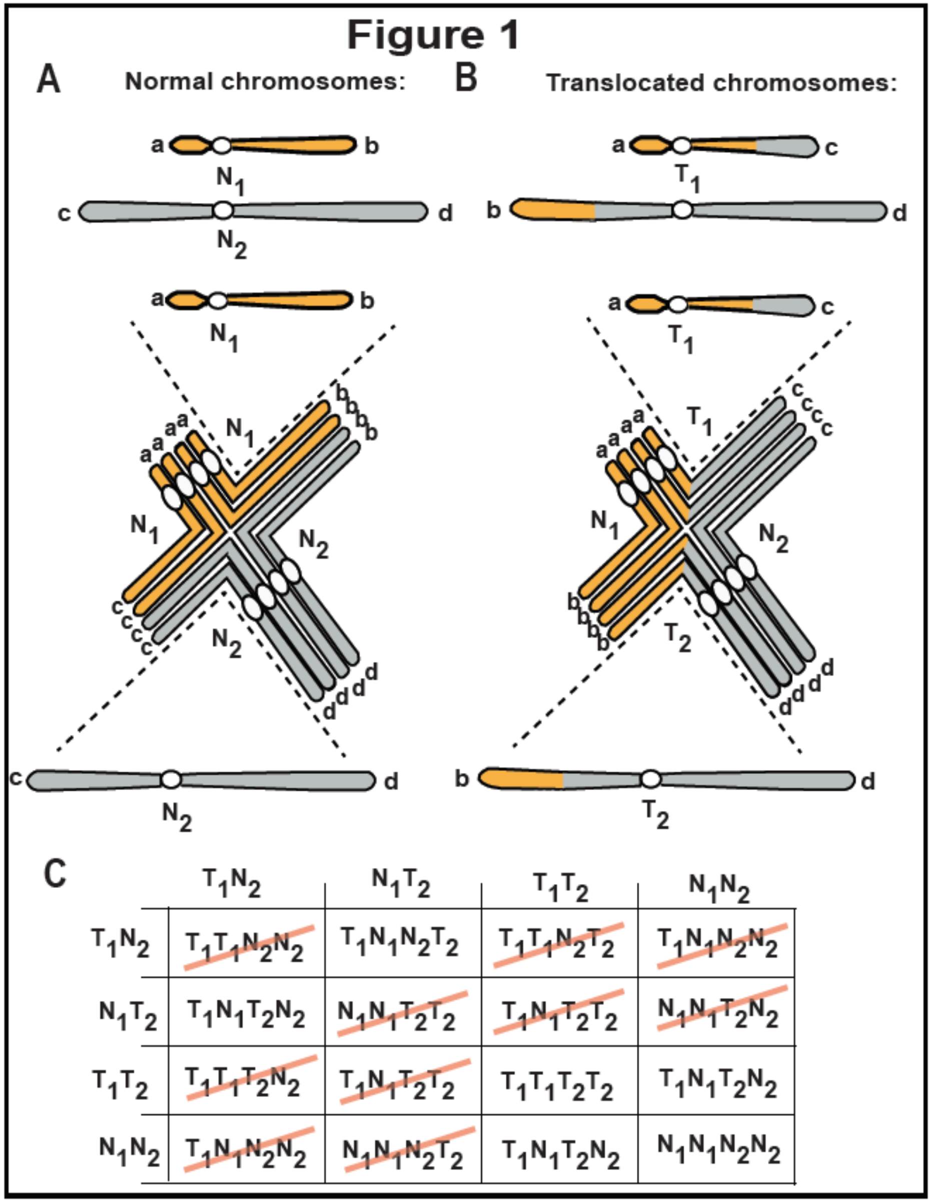
50% (or 75%) homozygous males for **UD^{MEL}** &
50% (or 25%) wild-type males & females

Elimination of the drive system is seen for releases that are

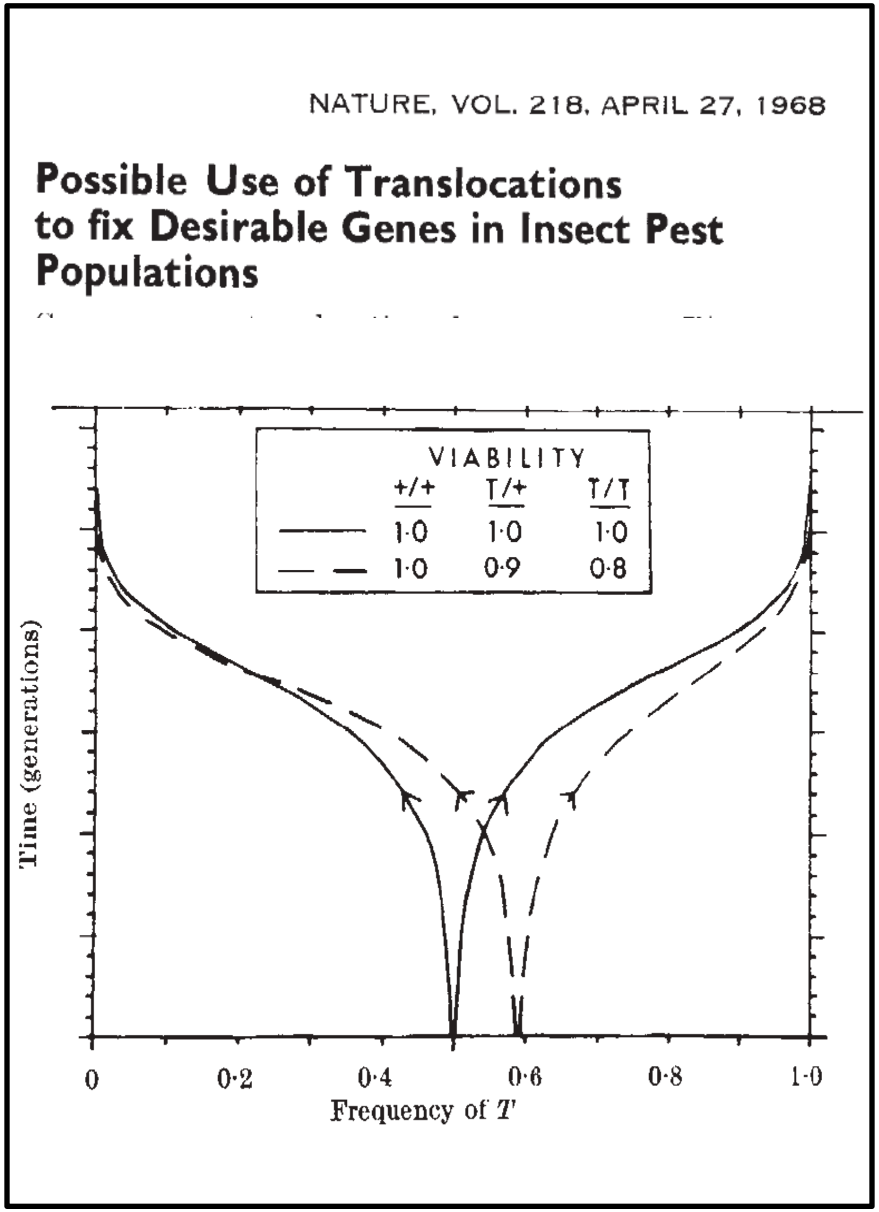
10% homozygous males for **UD^{MEL}** &
90% wild-type males & females

- Akbari OS, Matzen KD, Marshall JM, Huang H *et al.* (2013) Current Biology 23: 671-677

Translocations also display threshold dynamics



	T_1N_2	N_1T_2	T_1T_2	N_1N_2
T_1N_2	~~$T_1T_1N_2N_2$~~	$T_1N_1N_2T_2$	~~$T_1T_1N_2T_2$~~	~~$T_1N_1N_2N_2$~~
N_1T_2	$T_1N_1T_2N_2$	~~$N_1N_1T_2T_2$~~	~~$T_1N_1T_2T_2$~~	~~$N_1N_1T_2N_2$~~
T_1T_2	~~$T_1T_1T_2N_2$~~	~~$T_1N_1T_2T_2$~~	$T_1T_1T_2T_2$	$T_1N_1T_2N_2$
N_1N_2	~~$T_1N_1N_2N_2$~~	~~$N_1N_1N_2T_2$~~	$T_1N_1T_2N_2$	$N_1N_1N_2N_2$

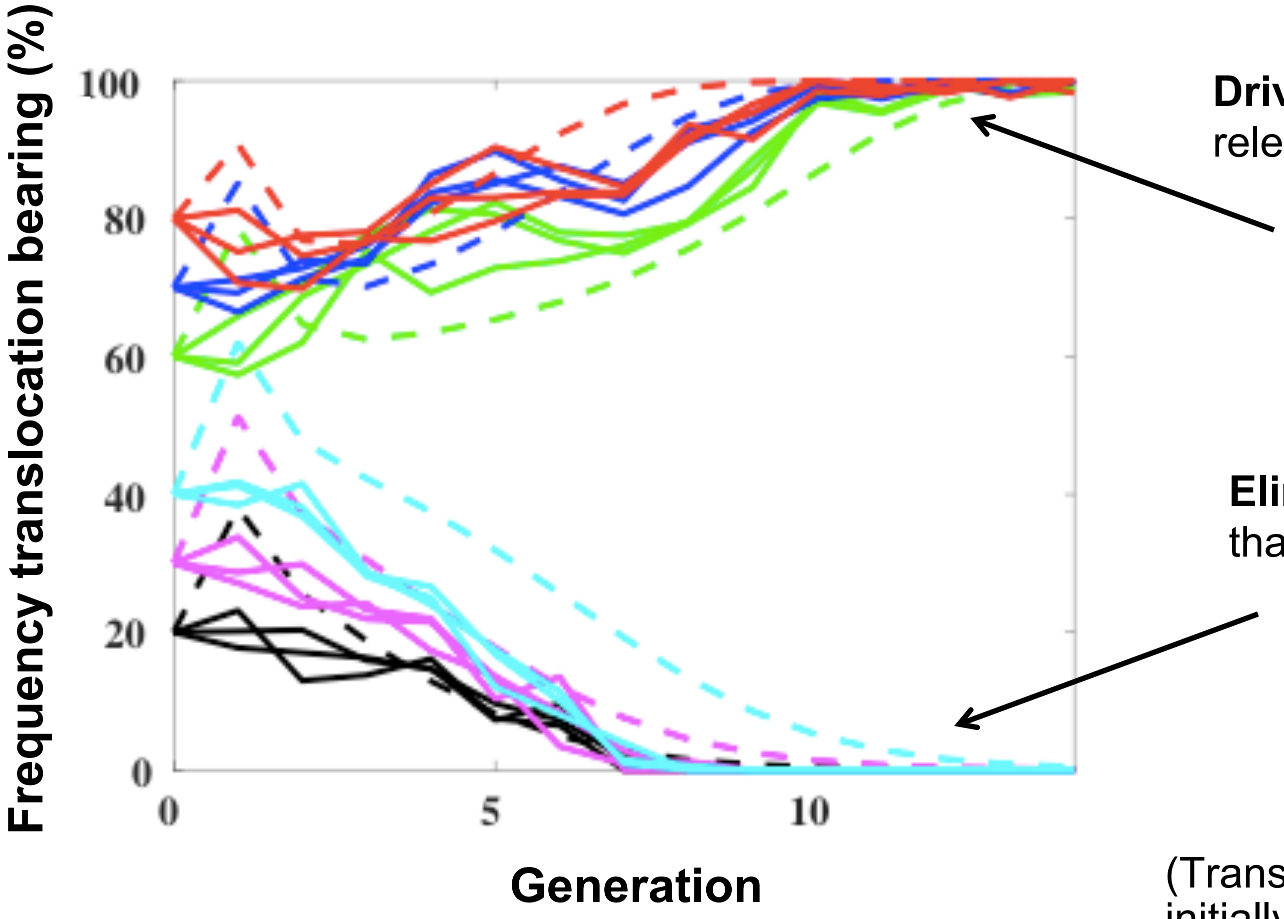


NATURE, VOL. 218, APRIL 27, 1968

Possible Use of Translocations to fix Desirable Genes in Insect Pest Populations

- Curtis CF (1968) Nature 218: 368-369
- Buchman A, Ivy T, Marshall JM, Akbari OS, Hay BA (2016) http://dx.doi.org/10.1101/088393

Translocation drive experiments agree with model predictions & display threshold behavior



Drive to fixation occurs for releases that are

60-80% homozygous males & females for the translocation

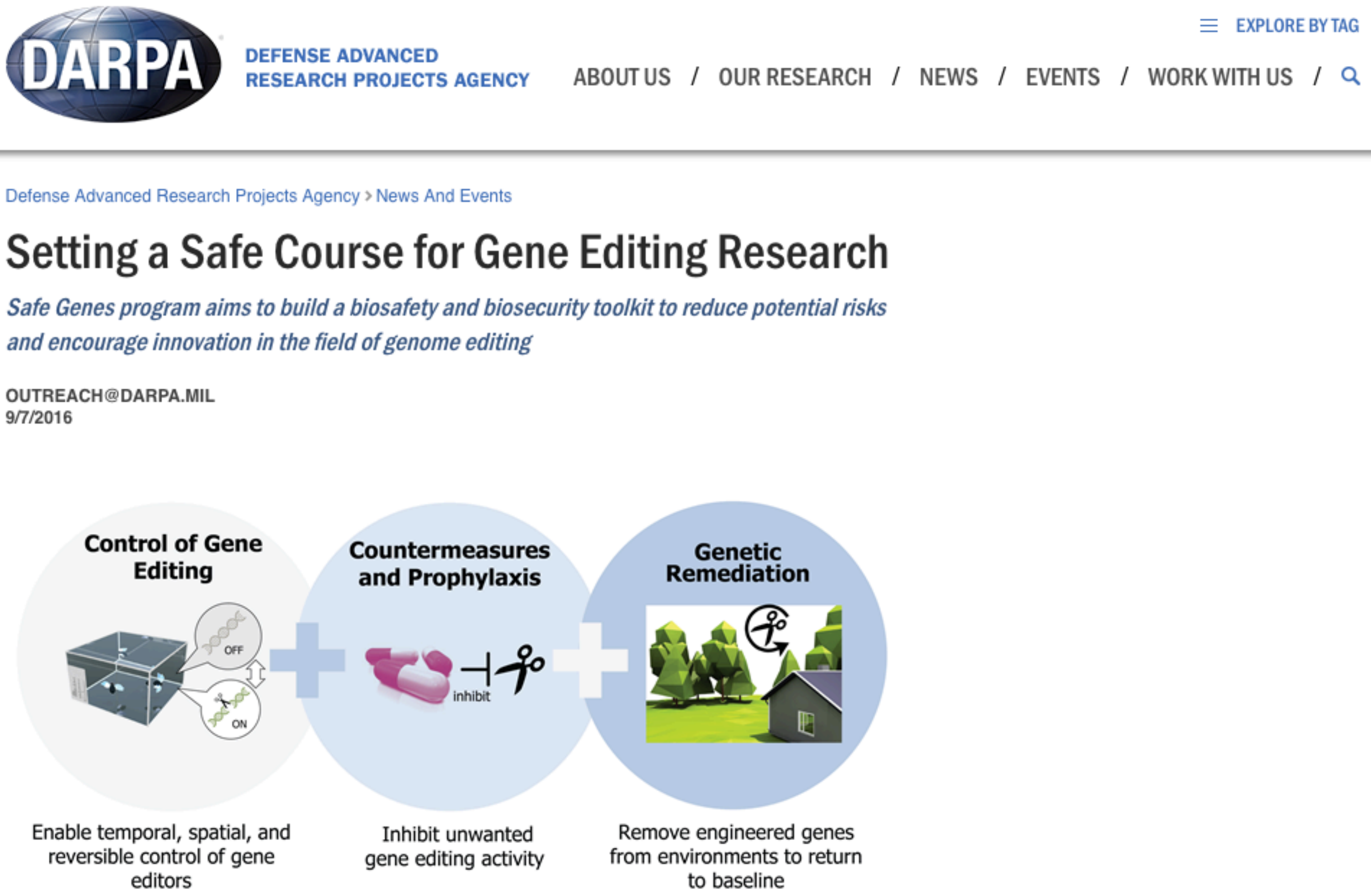
Elimination is seen for releases that are

20-40% homozygous males & females for the translocation

(Translocation homozygotes are initially very unfit; but rapidly increase in fitness in a couple of generations)

- Buchman A, Ivy T, Marshall JM, Akbari OS, Hay BA (2016) http://dx.doi.org/10.1101/088393

DARPA & “safe” gene drives



Defense Advanced Research Projects Agency > News And Events

Setting a Safe Course for Gene Editing Research

Safe Genes program aims to build a biosafety and biosecurity toolkit to reduce potential risks and encourage innovation in the field of genome editing

OUTREACH@DARPA.MIL
9/7/2016

Control of Gene Editing

Enable temporal, spatial, and reversible control of gene editors

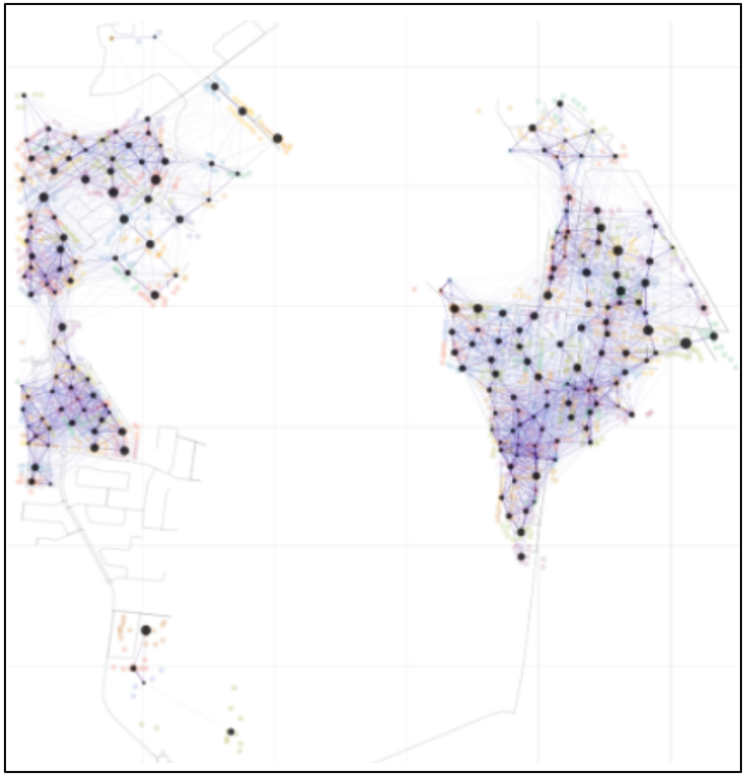
Countermeasures and Prophylaxis

Inhibit unwanted gene editing activity

Genetic Remediation

Remove engineered genes from environments to return to baseline

MGDrivE modeling framework
(Mosquito Gene Drive Explorer)



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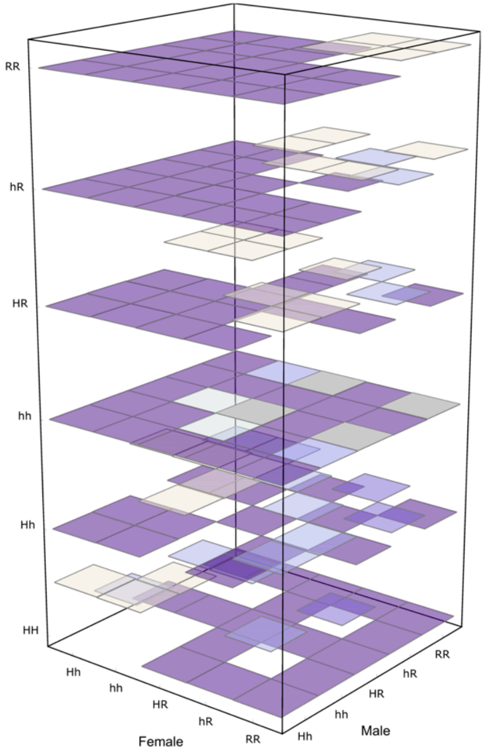
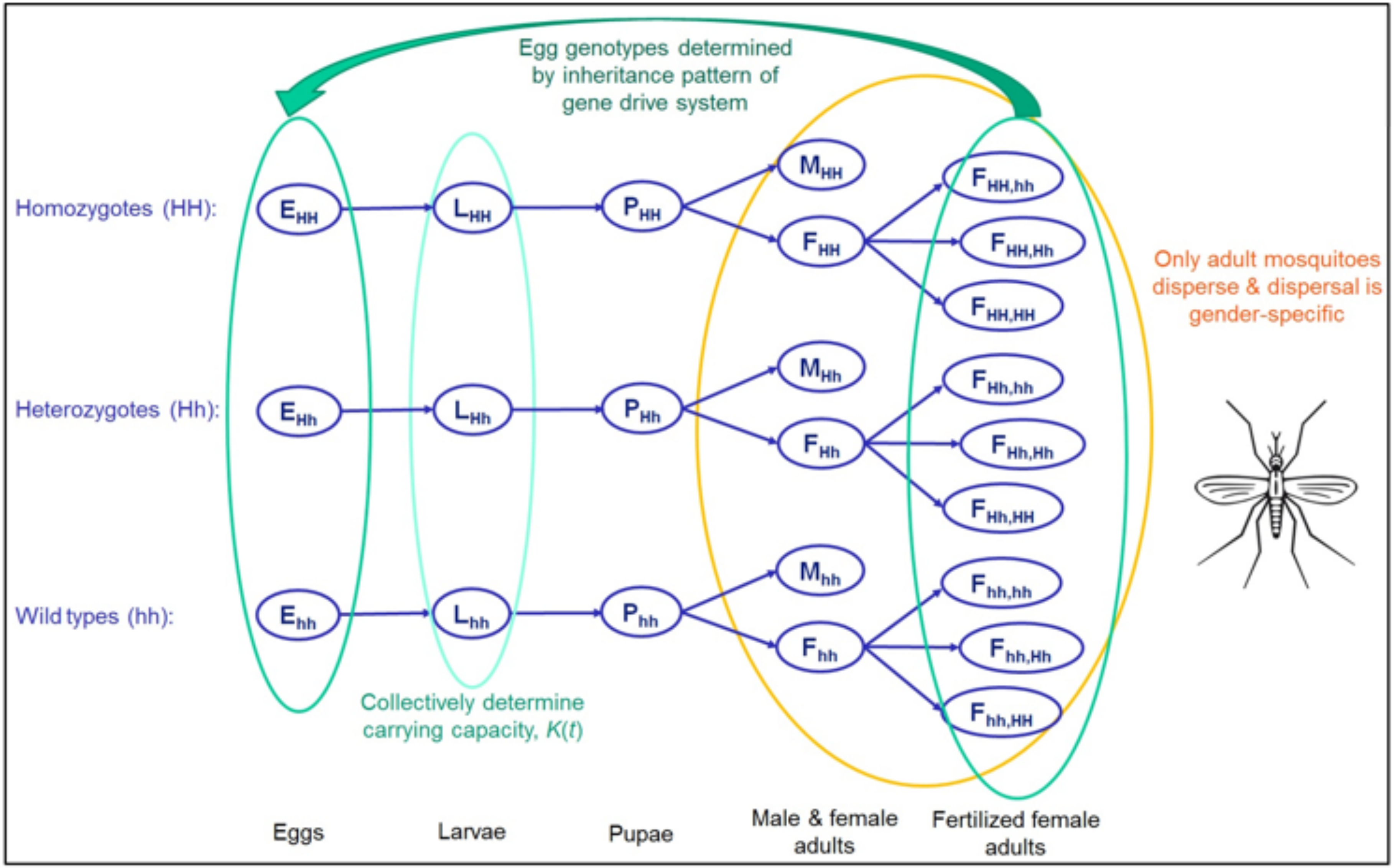


Spatial Setting **Mosquitoes** **Genetic Inheritance**

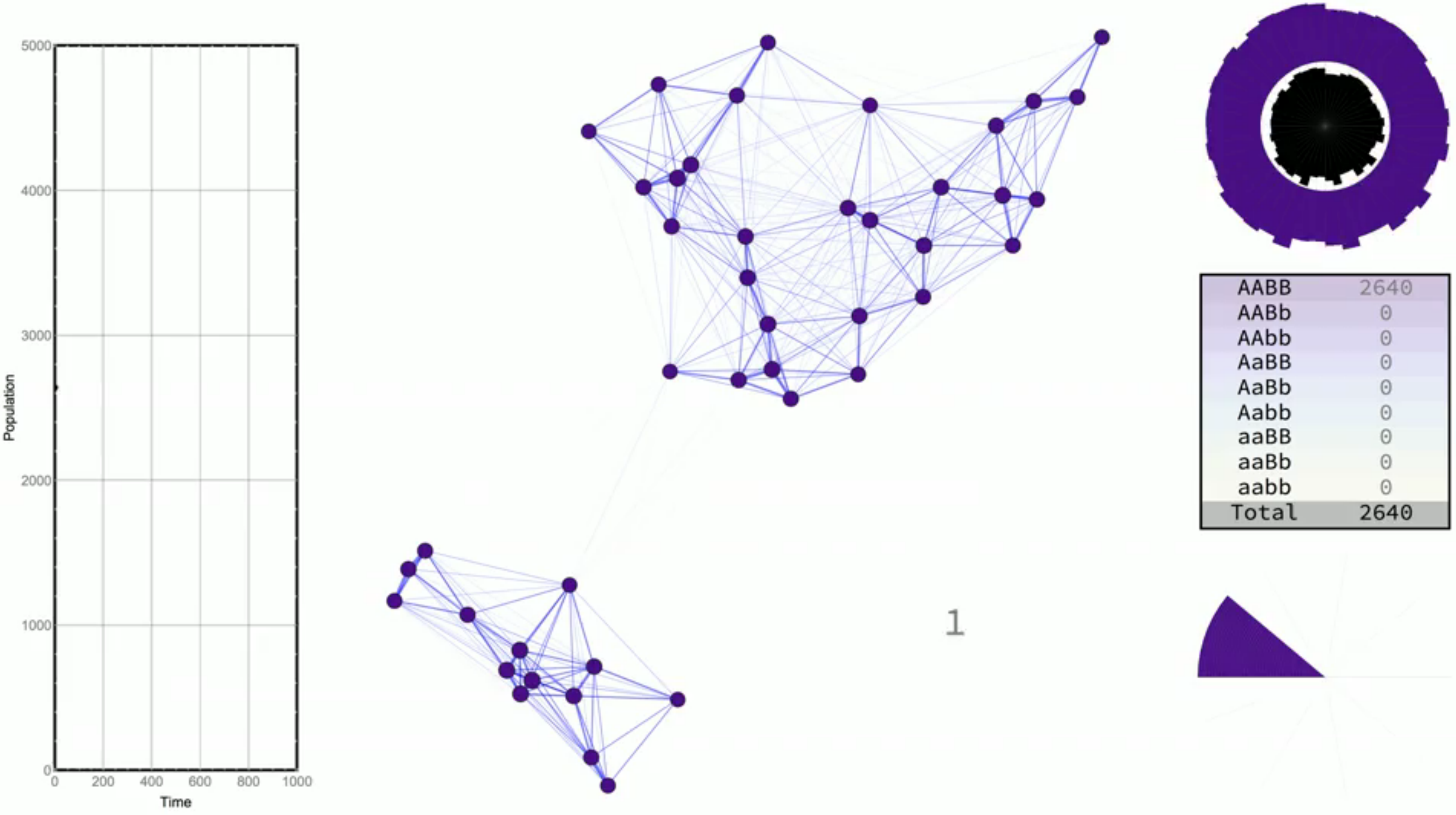
- Sanchez HM, Wu SL, Bennett J, Marshall JM (In preparation)

MGDrivE: Mosquito ecology module



- Sanchez HM, Wu SL, Bennett J, Marshall JM (In preparation)

MGDrivE: Translocations with remediation



AABB	2640
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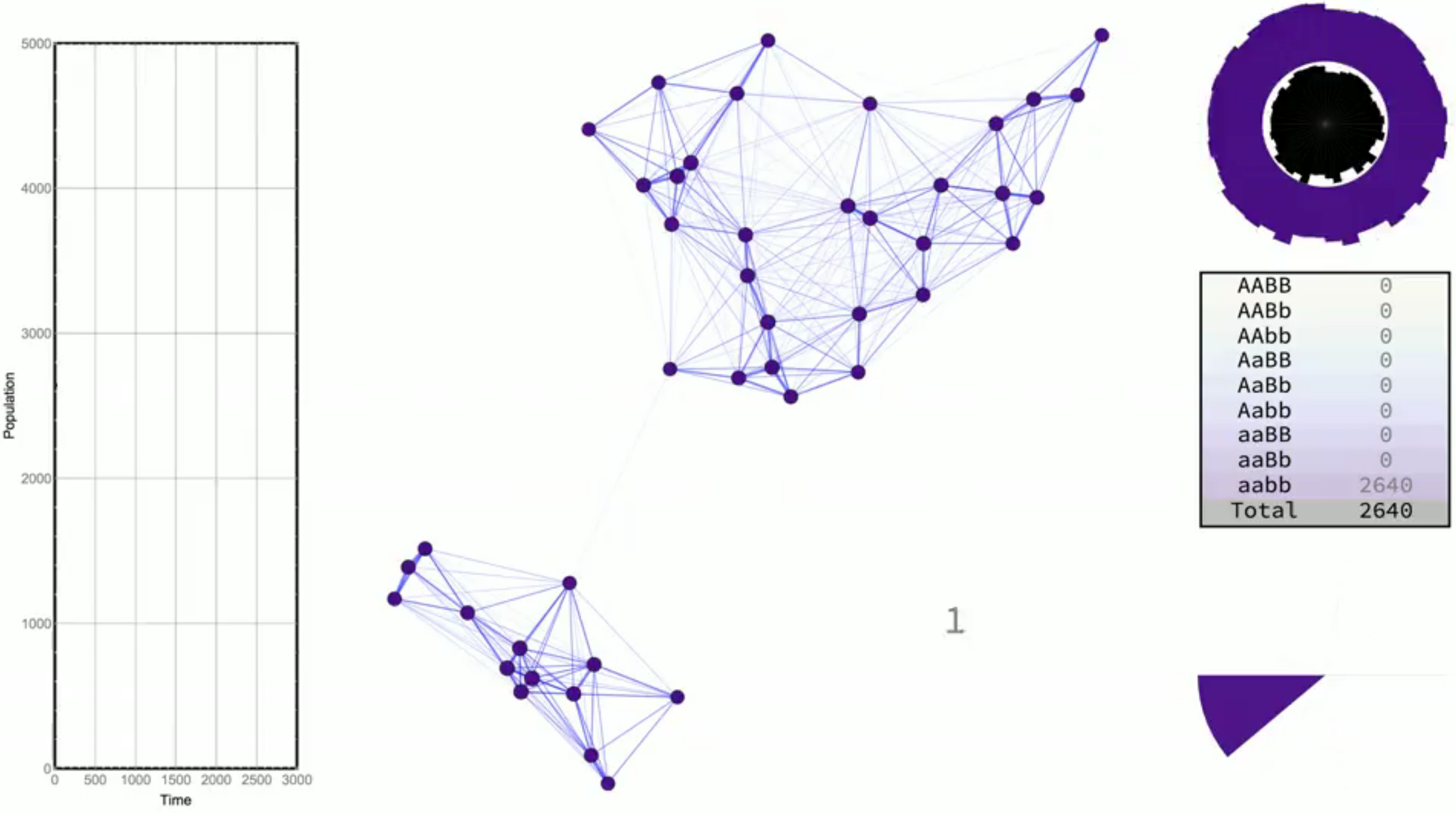
AAbb	0
AaBB	0
AaBb	0
Aabb	0
aaBB	0
aaBb	0
aabb	0
Total	2640

- Sanchez HM, Wu SL, Bennett J, Marshall JM (In preparation)

MGDrivE: UD^{MEL} without remediation



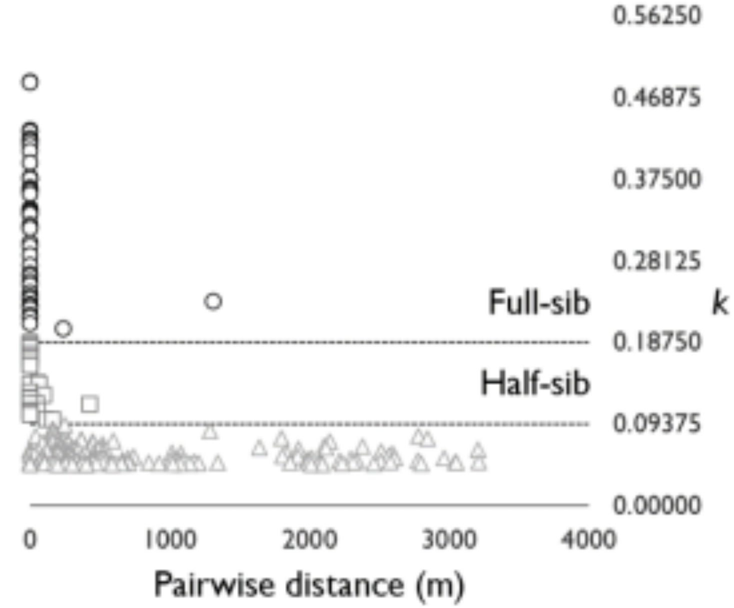
AABB	0
AABb	0
AAbb	0
AaBB	0
AaBb	0
Aabb	0
aaBB	0
aaBb	0
aabb	2640
Total	2640

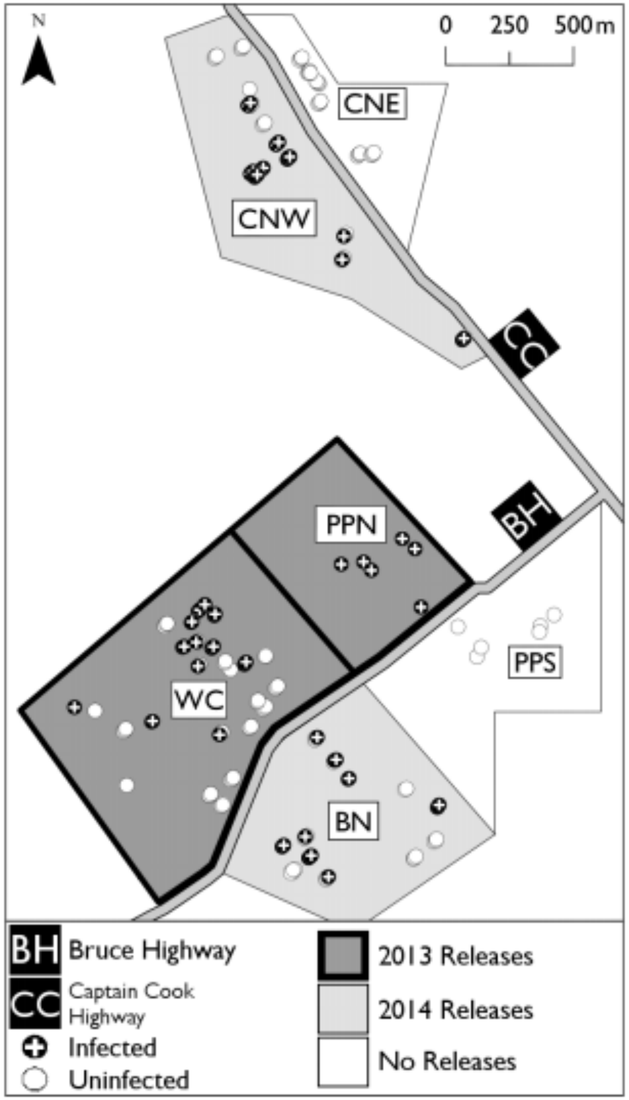
- Sanchez HM, Wu SL, Bennett J, Marshall JM (In preparation)

Fine-scale landscape genomics helps explain the slow spread of *Wolbachia* through the *Aedes aegypti* population in Cairns, Australia

Thomas L Schmidt, Igor Filipovic, Ary A Hoffmann, Gordana Rasic

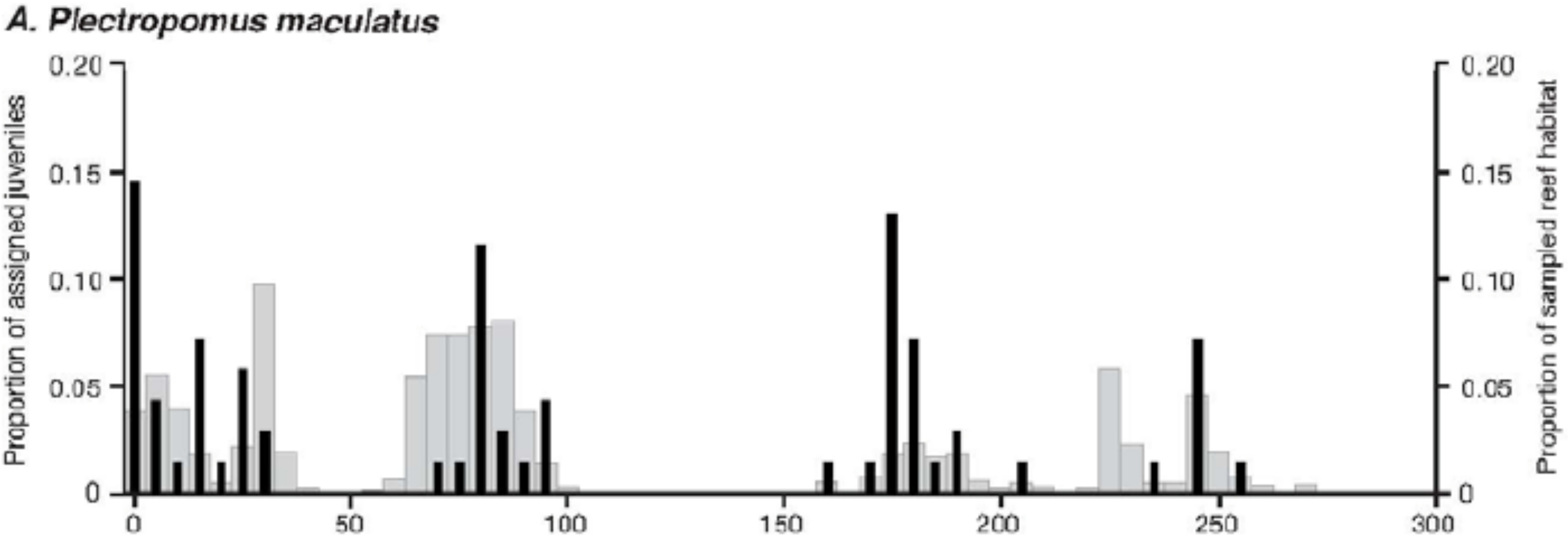
Figure 3: Loiselle's k estimates for sample pairs of relatedness $k > 0.046875$. Pairs of $0.09375 < k < 0.1875$ are most likely half-sibs, those of $k < 0.1875$ are most likely full-sibs. Most related pairs were found within the same trap, but separation distances of up to 1312m were observed.

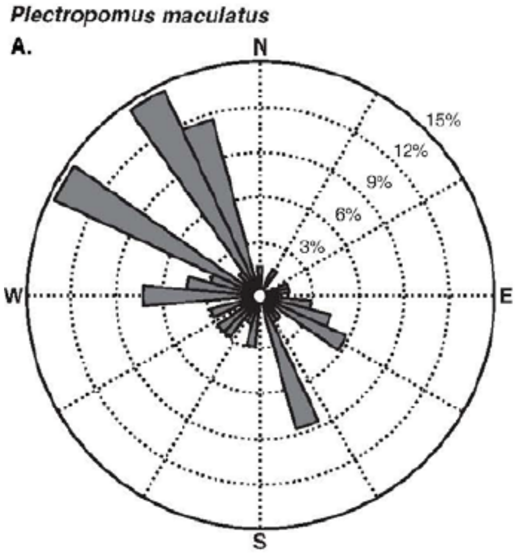


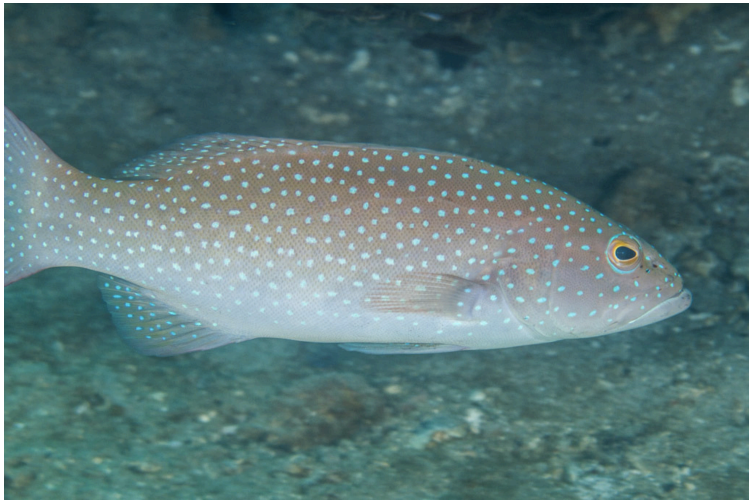


- Schmidt TL, Filipovic I, Hoffmann AA, Rasic G (2017) http://dx.doi.org/10.1101/103598

Dispersal inferred from genetic parentage analyses



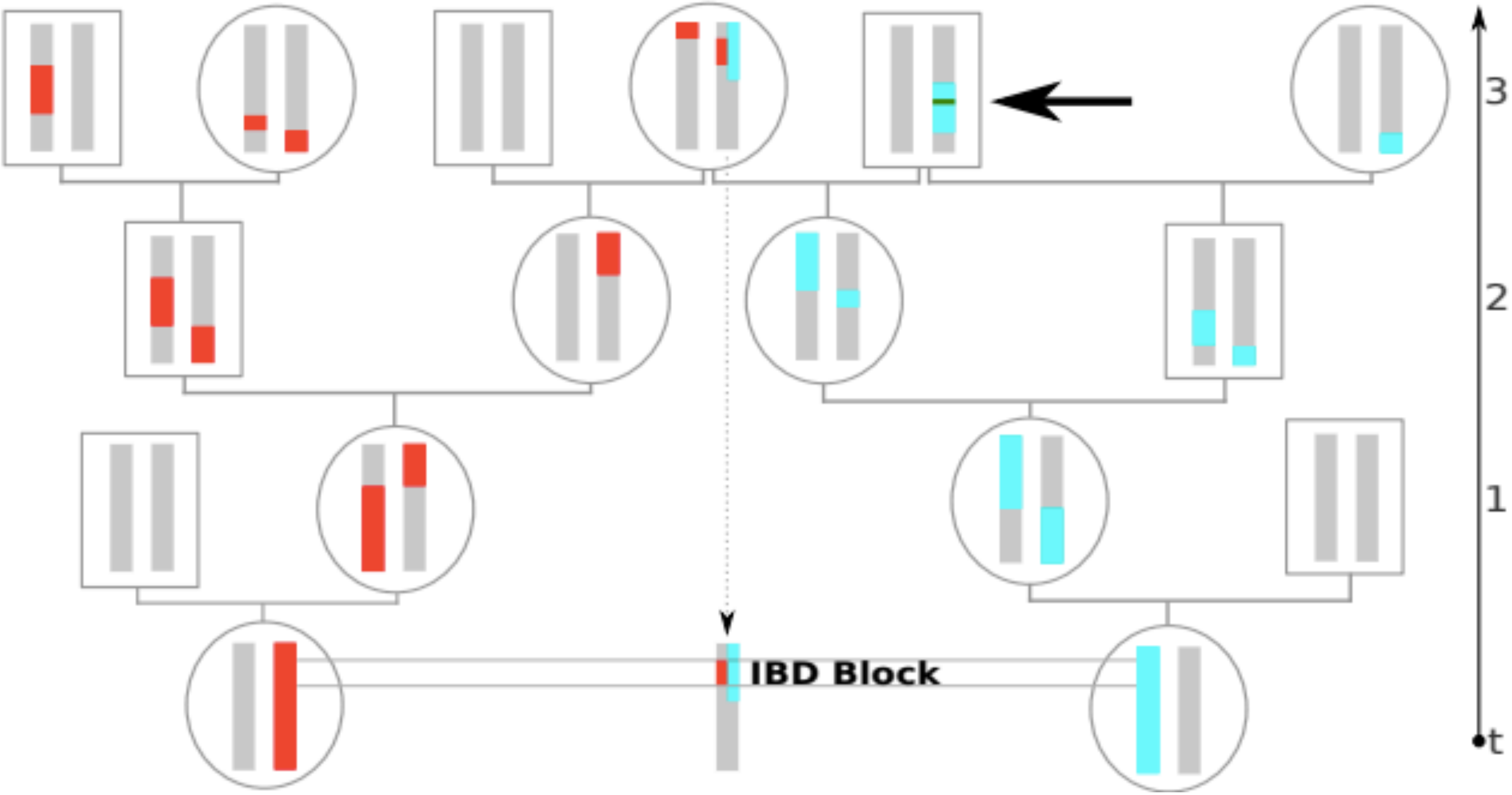




- Williamson DH, Harrison HB, Almany GR, Berumen ML *et al.* (2016) Mol. Ecol. 25L 6039-6054

Inferring recent demography from isolation by distance of long shared sequence blocks

Harald Ringbauer*[,1], Graham Coop[†] and Nicholas H. Barton*[,1]



- Ringbauer H, Coop G, Barton NH (2017) Genetics doi: 10.1534/genetics.116.196220.

UCI establishes Malaria Initiative to fight deadly disease in Africa

Acclaimed vector biologist Anthony James will lead multi-campus effort

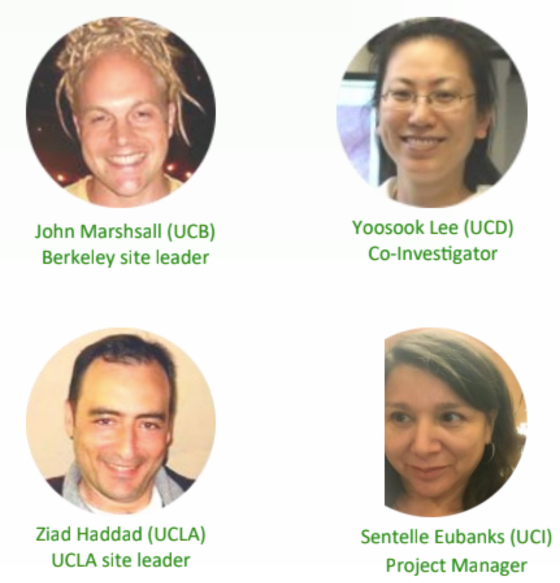
Team members

Ethan Bier (UCSD)
UCSD site leader

Valentino Gantz (UCSD)
Co-Investigator

Gregory Lanzaro (UCD)
UCD site leader

Anthony Cornel (UCD)
Co-Investigator



John Marshsall (UCB)
Berkeley site leader

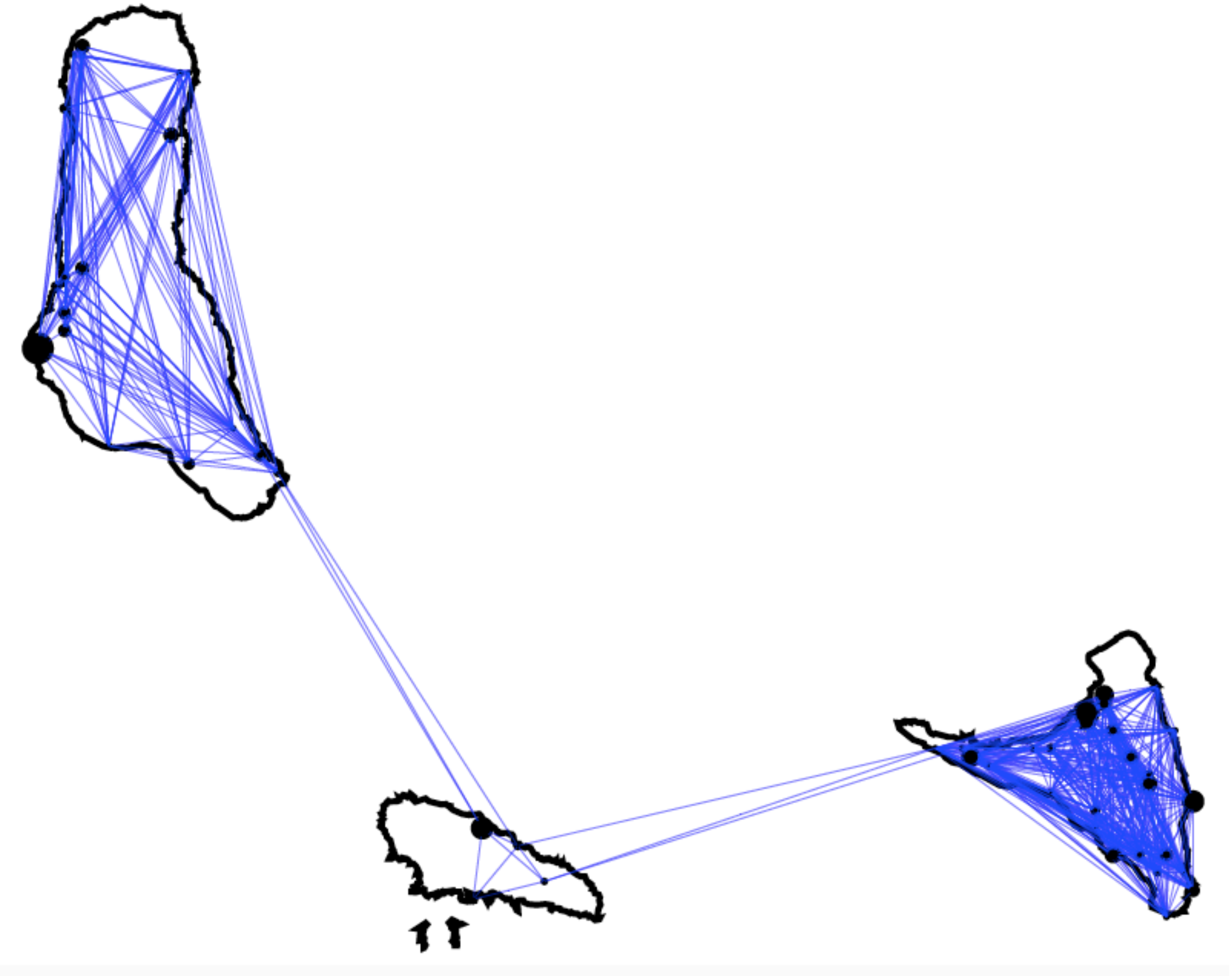
Yoosook Lee (UCD)
Co-Investigator

Ziad Haddad (UCLA)
UCLA site leader

Sentelle Eubanks (UCI)
Project Manager

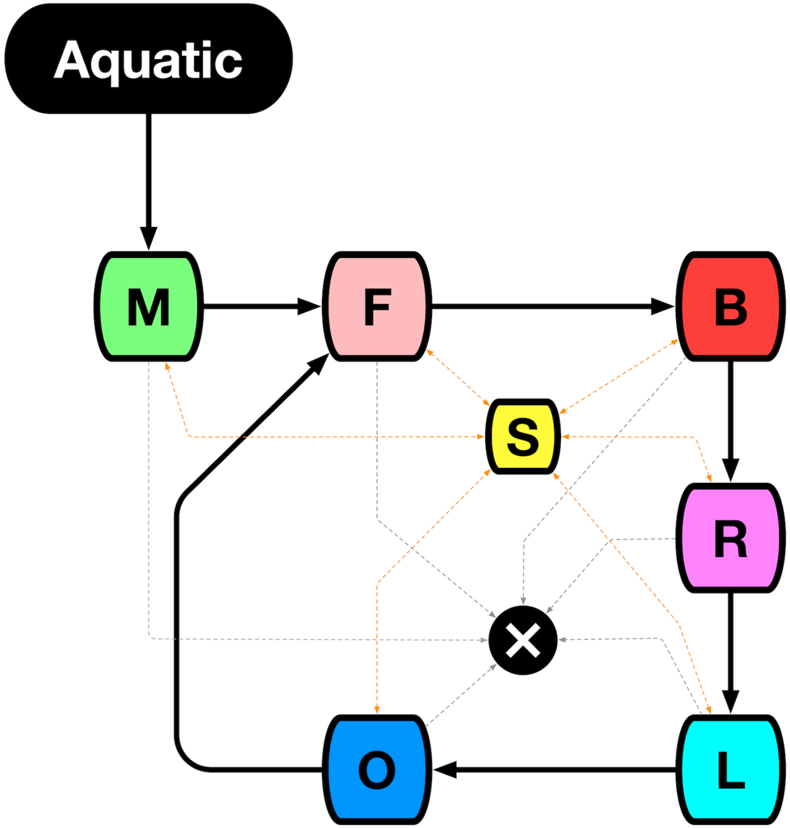
Population replacement strategy using homing-based gene drive.

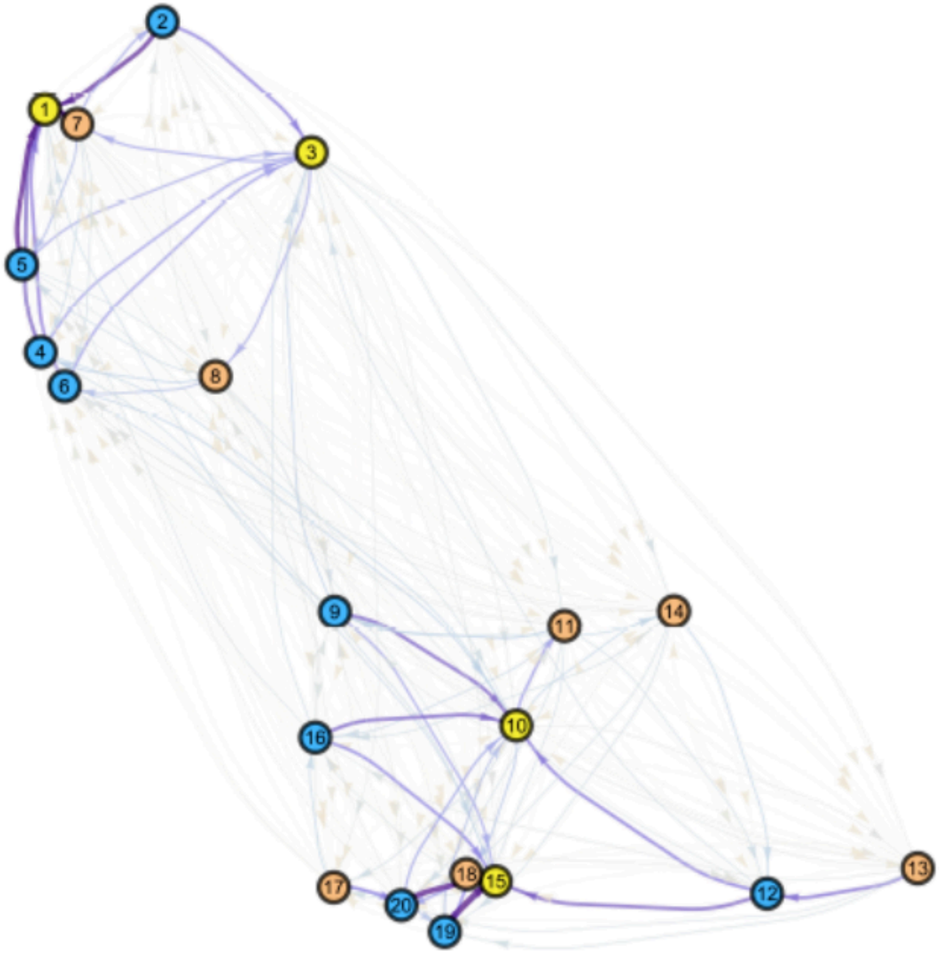
Application of MGDrivE to the Comoros Islands



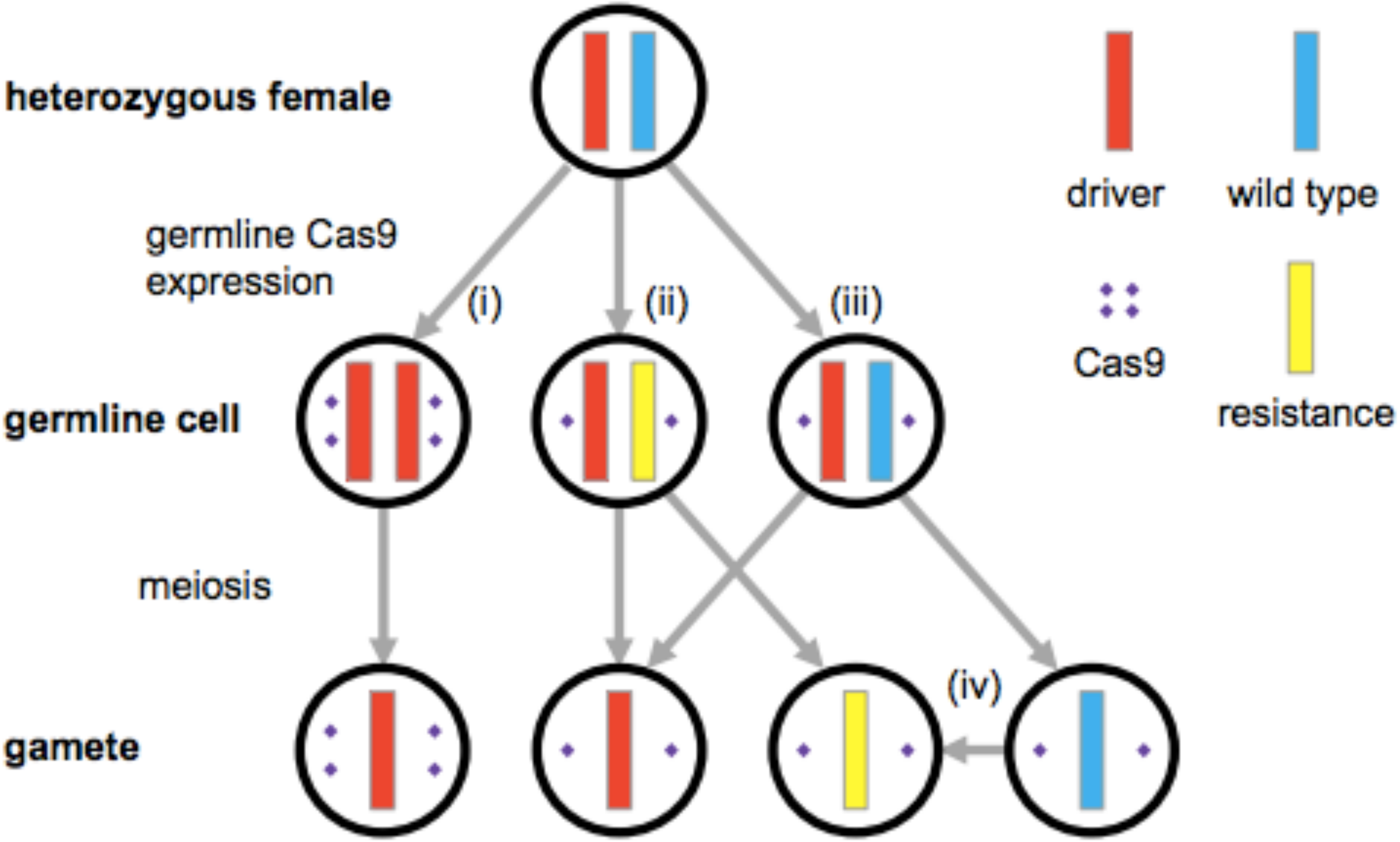
- Sanchez HM, Wu SL, Bennett J, Marshall JM (In preparation)

Understanding potential fine-scale population structure using MASH modeling framework

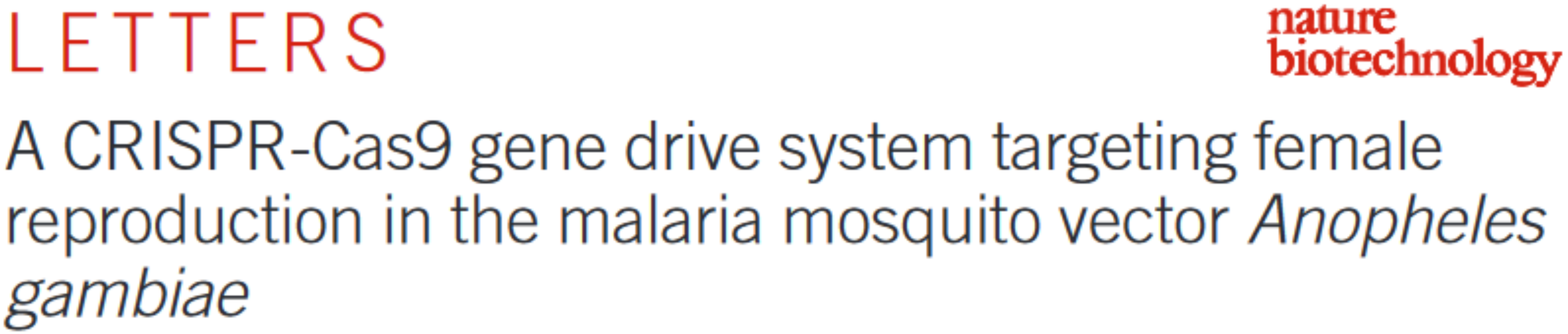




Q2. Can CRISPR-based gene drive be effective at disease control on a wide scale?



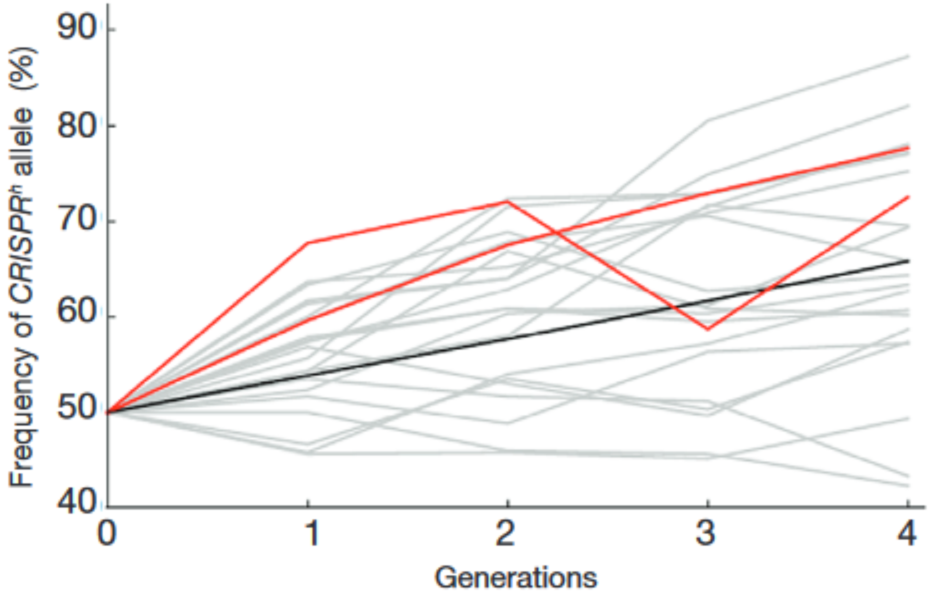
- Champer J, Reeves R, Oh SY, Liu C, Liu J *et al.* (2017) PLoS Genetics 13: e1006796



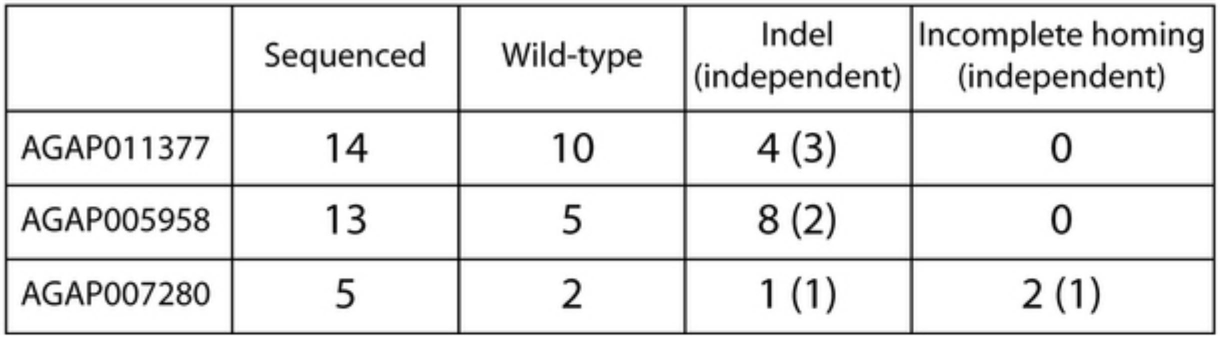
LETTERS

nature biotechnology

A CRISPR-Cas9 gene drive system targeting female reproduction in the malaria mosquito vector *Anopheles gambiae*



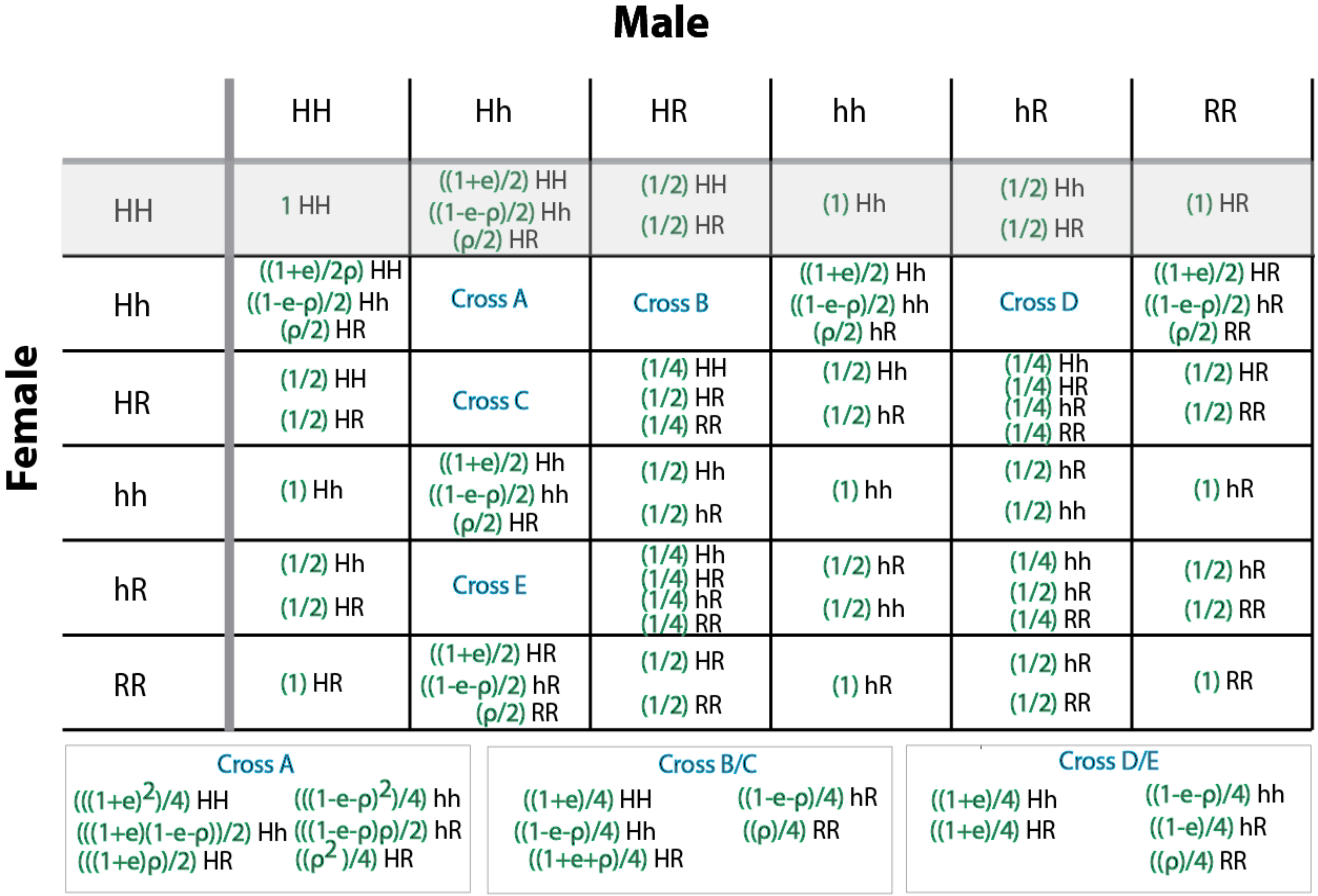
- Homing rate = 98%
- Non-cleavage rate = 1%
- Resistant allele generation rate = 0.13% (in-frame indels)
- Fertility of heterozygous females reduced by 90.7%



	Sequenced	Wild-type	Indel (independent)	Incomplete homing (independent)
AGAP011377	14	10	4 (3)	0
AGAP005958	13	5	8 (2)	0
AGAP007280	5	2	1 (1)	2 (1)

- Champer J, Reeves R, Oh SY, Liu C, Liu J *et al.* (2017) PLoS Genetics 13: e1006796

Modeling error-prone homing-based gene drive



Male

Female

	HH	Hh	HR	hh	hR	RR
HH	1 HH	((1+e)/2) HH ((1-e-ρ)/2) Hh (ρ/2) HR	(1/2) HH (1/2) HR	(1) Hh	(1/2) Hh (1/2) HR	(1) HR
Hh	((1+e)/2ρ) HH ((1-e-ρ)/2) Hh (ρ/2) HR	Cross A	Cross B	((1+e)/2) Hh ((1-e-ρ)/2) hh (ρ/2) hR	Cross D	((1+e)/2) HR ((1-e-ρ)/2) hR (ρ/2) RR
HR	(1/2) HH (1/2) HR	Cross C	(1/4) HH (1/2) HR (1/4) RR	(1/2) Hh (1/2) hR	(1/4) Hh (1/4) HR (1/4) hR (1/4) RR	(1/2) HR (1/2) RR
hh	(1) Hh	((1+e)/2) Hh ((1-e-ρ)/2) hh (ρ/2) HR	(1/2) Hh (1/2) hR	(1) hh	(1/2) hR (1/2) hh	(1) hR
hR	(1/2) Hh (1/2) HR	Cross E	(1/4) Hh (1/4) HR (1/4) hR (1/4) RR	(1/2) hR (1/2) hh	(1/4) hh (1/2) hR (1/4) RR	(1/2) hR (1/2) RR
RR	(1) HR	((1+e)/2) HR ((1-e-ρ)/2) hR (ρ/2) RR	(1/2) HR (1/2) RR	(1) hR	(1/2) hR (1/2) RR	(1) RR

Cross A

$(((1+e)^2)/4)$ HH
$(((1+e)(1-e-\rho))/2)$ Hh
$(((1+e)\rho)/2)$ HR
$(((1-e-\rho)^2)/4)$ hh
$(((1-e-\rho)\rho)/2)$ hR
$((\rho^2)/4)$ HR

Cross B/C

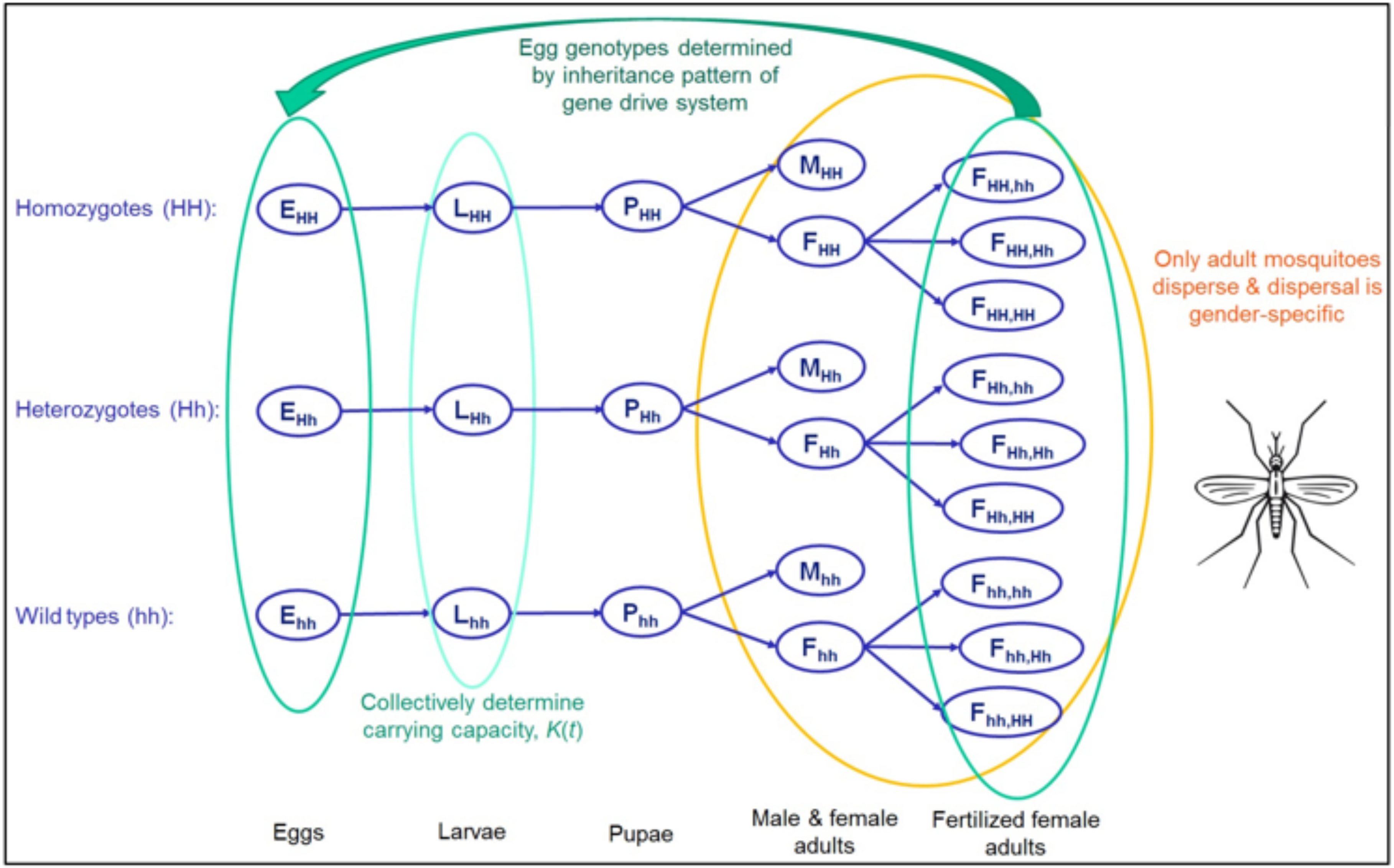
((1+e)/4) HH
((1-e-ρ)/4) Hh
((1+e+ρ)/4) HR
((1-e-ρ)/4) hR
((ρ)/4) RR

Cross D/E

((1+e)/4) Hh
((1+e)/4) HR
((1-e-ρ)/4) hh
((1-e)/4) hR
((ρ)/4) RR

- Marshall JM, Buchman A, Sanchez HM *et al.* (2017) Nature Sci Rep 7: 3776

MGDrivE: Mosquito ecology module

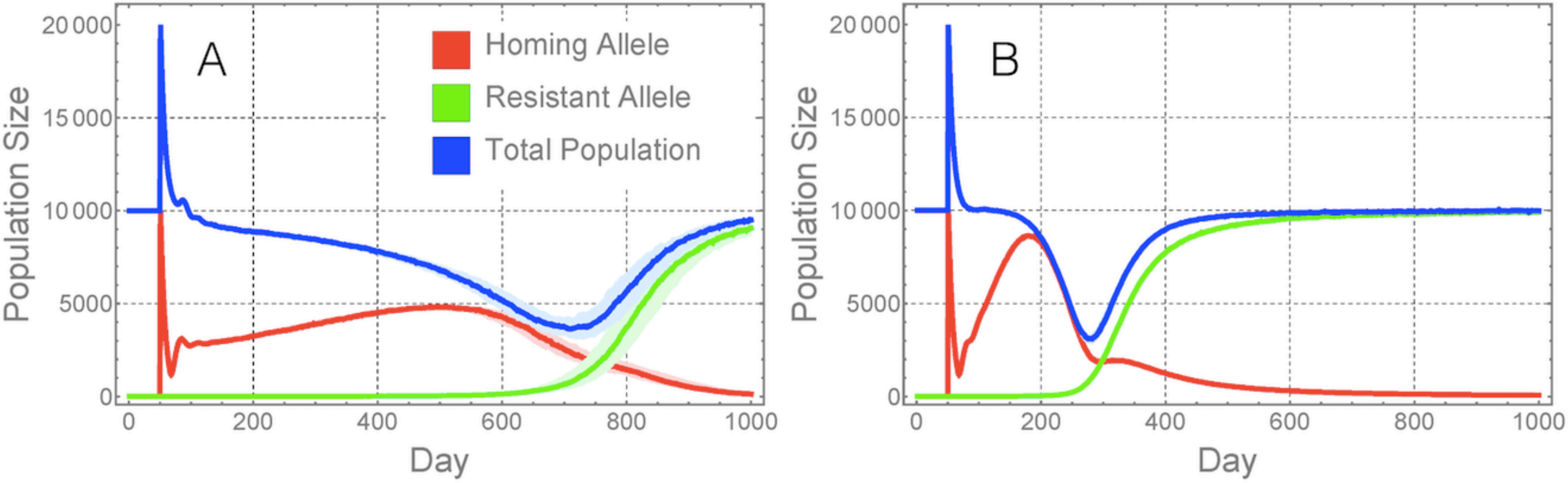


- Marshall JM, Buchman A, Sanchez HM *et al.* (2017) Nature Sci Rep 7: 3776

Dynamics of current constructs

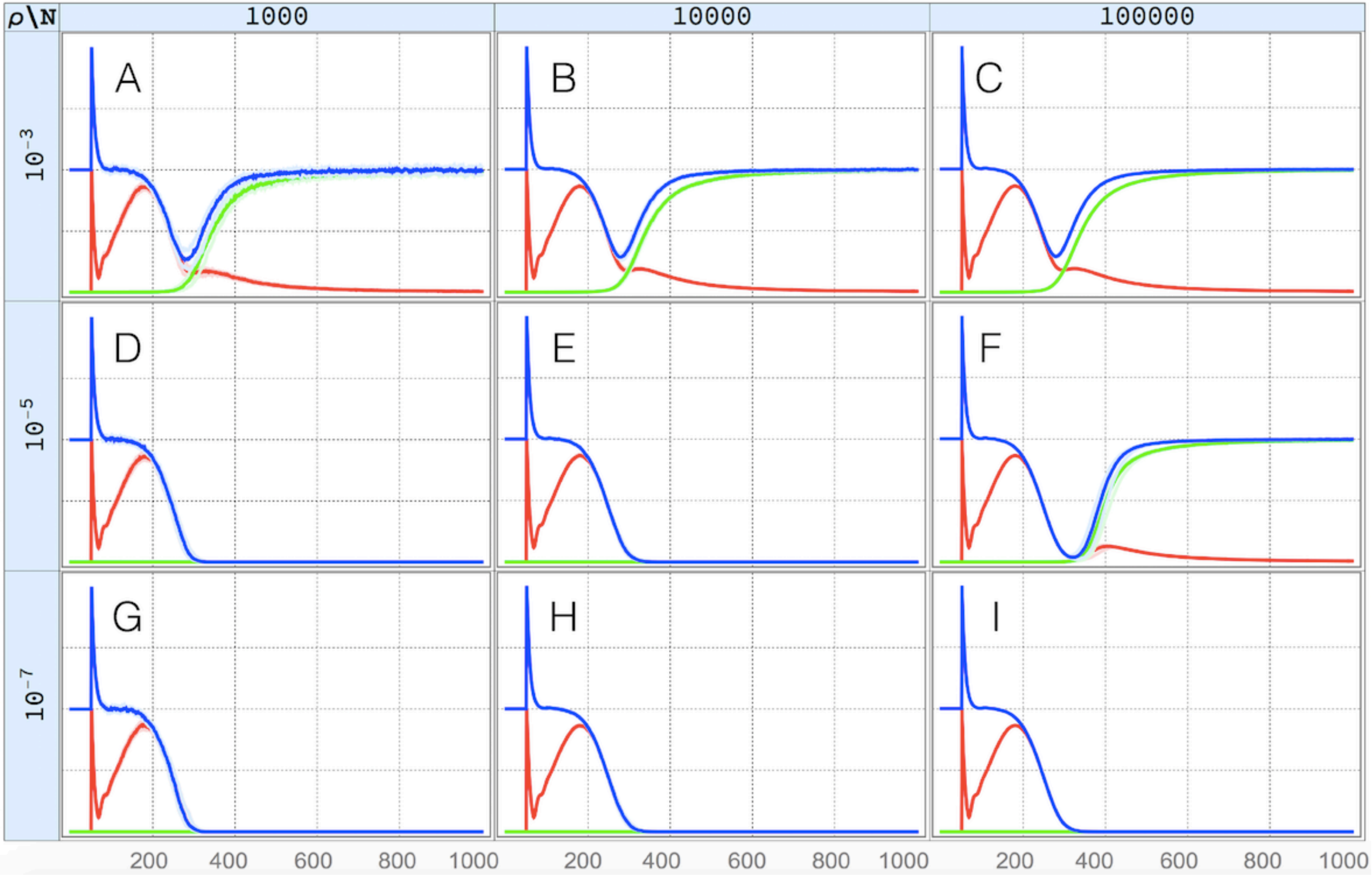
a) Hammond *et al.* (2016) construct:
- Homing rate = 98%
- NHEJ rate = 0.13%
- Fertility of heterozygotes reduced by 90.7%

b) Hammond *et al.* (2016) construct:
- Homing rate = 98%
- NHEJ rate = 0.13%
- **Fertility of heterozygotes same as wild-type**



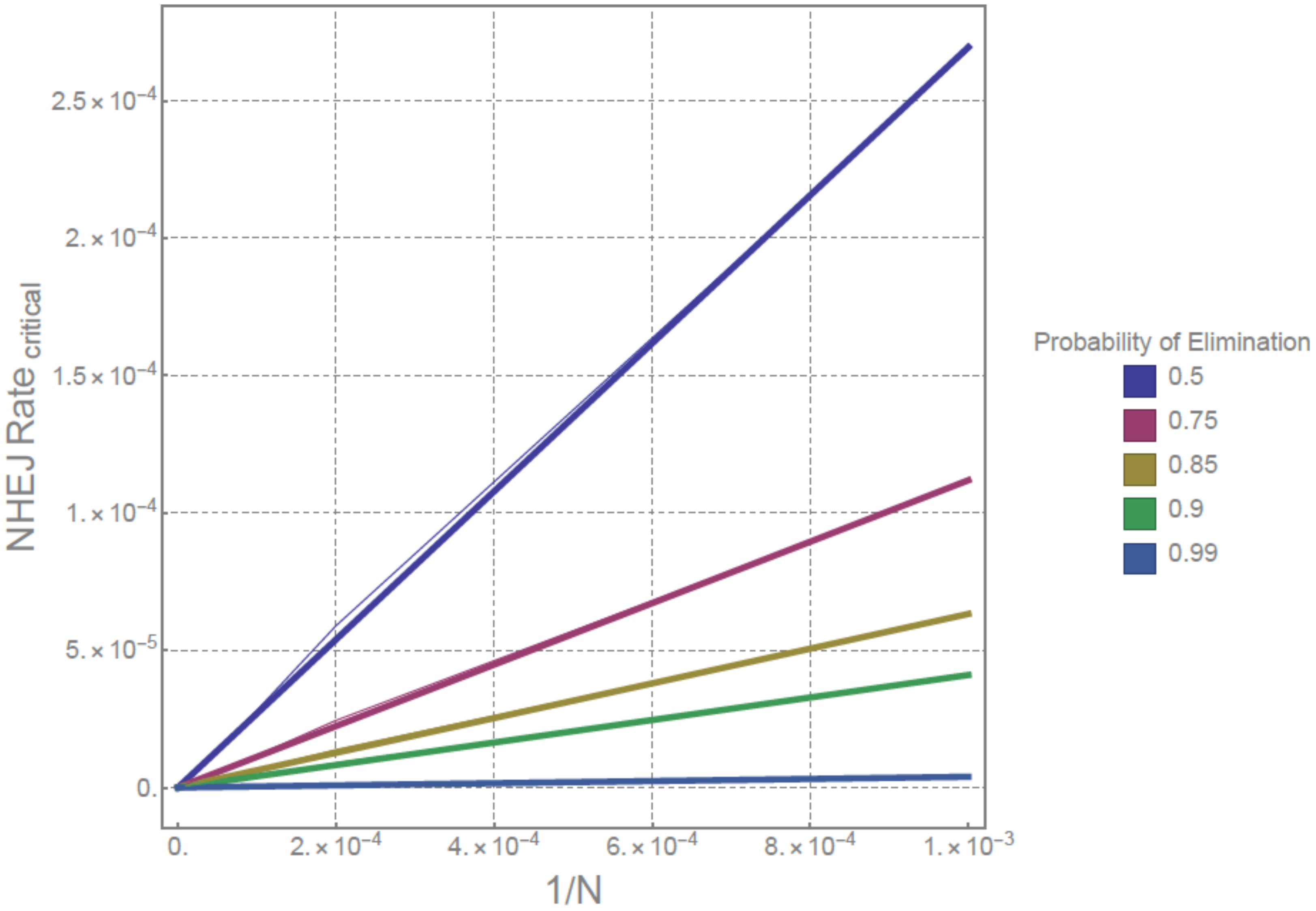
- Marshall JM, Buchman A, Sanchez HM *et al.* (2017) Nature Sci Rep 7: 3776

As the resistance allele generation rate declines, the population size you can eliminate increases



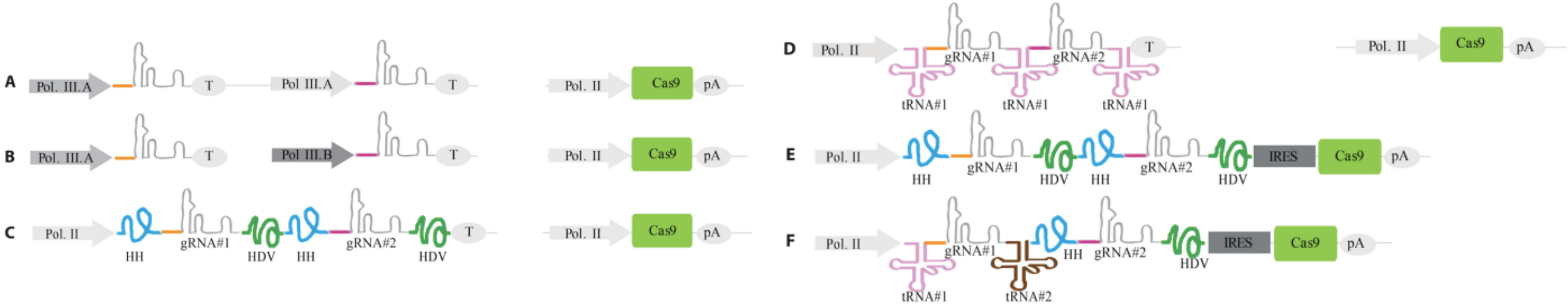
- Marshall JM, Buchman A, Sanchez HM *et al.* (2017) Nature Sci Rep 7: 3776

Tolerable rates of resistant allele generation are inversely proportional to the population size



- Marshall JM, Buchman A, Sanchez HM *et al.* (2017) Nature Sci Rep 7: 3776

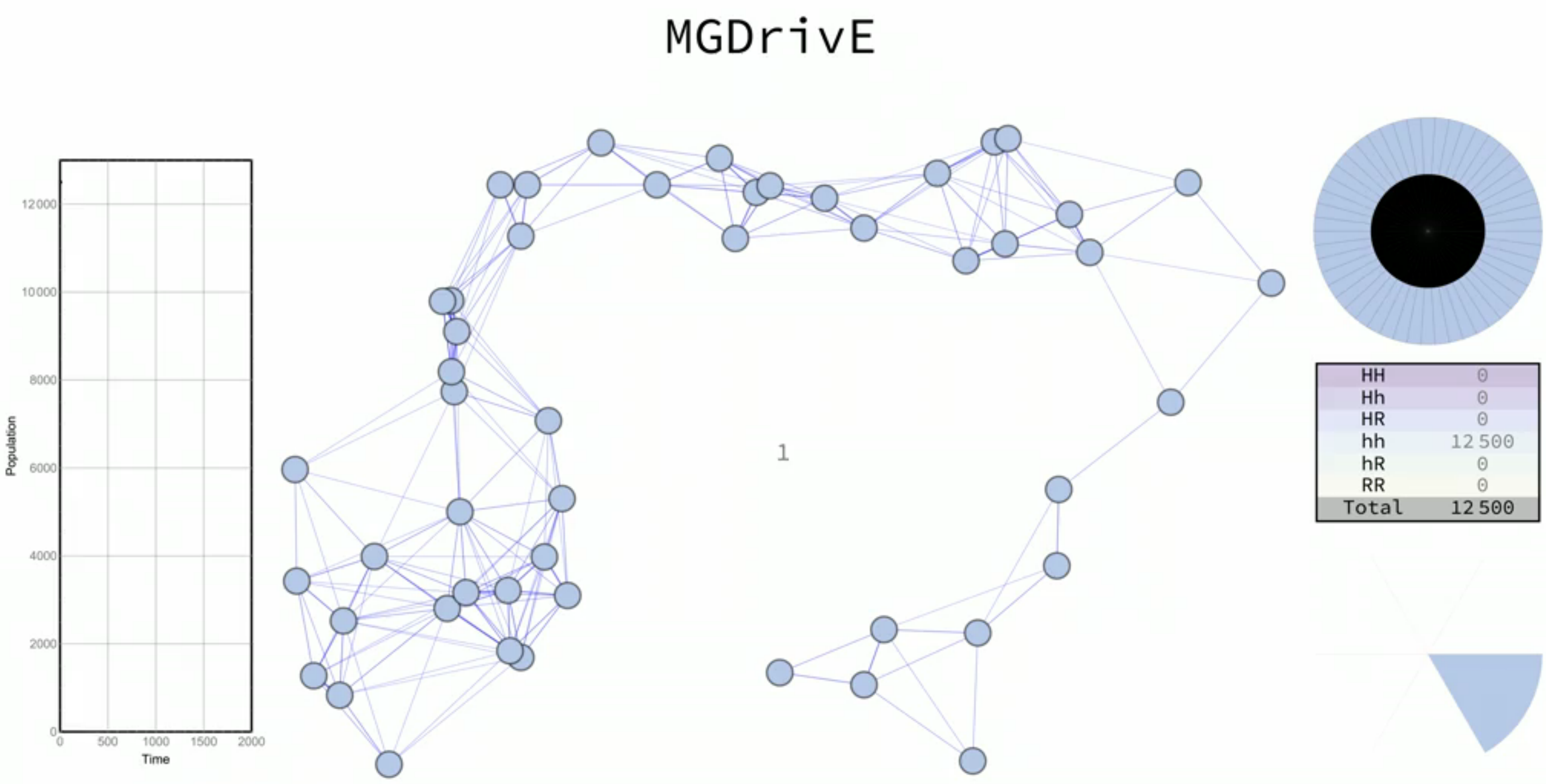
Multiplexing gRNAs may provide part of the solution to enable elimination of large populations



Multiplex number:	**Resistance allele generation rate:**	**Population size capable of eliminating (90% of sims):**
1	1.3×10^{-3}	32
2	1.7×10^{-6}	24 thousand
3	2.2×10^{-9}	19 million
4	2.9×10^{-12}	14 billion

- Marshall JM, Buchman A, Sanchez HM *et al.* (2017) Nature Sci Rep 7: 3776

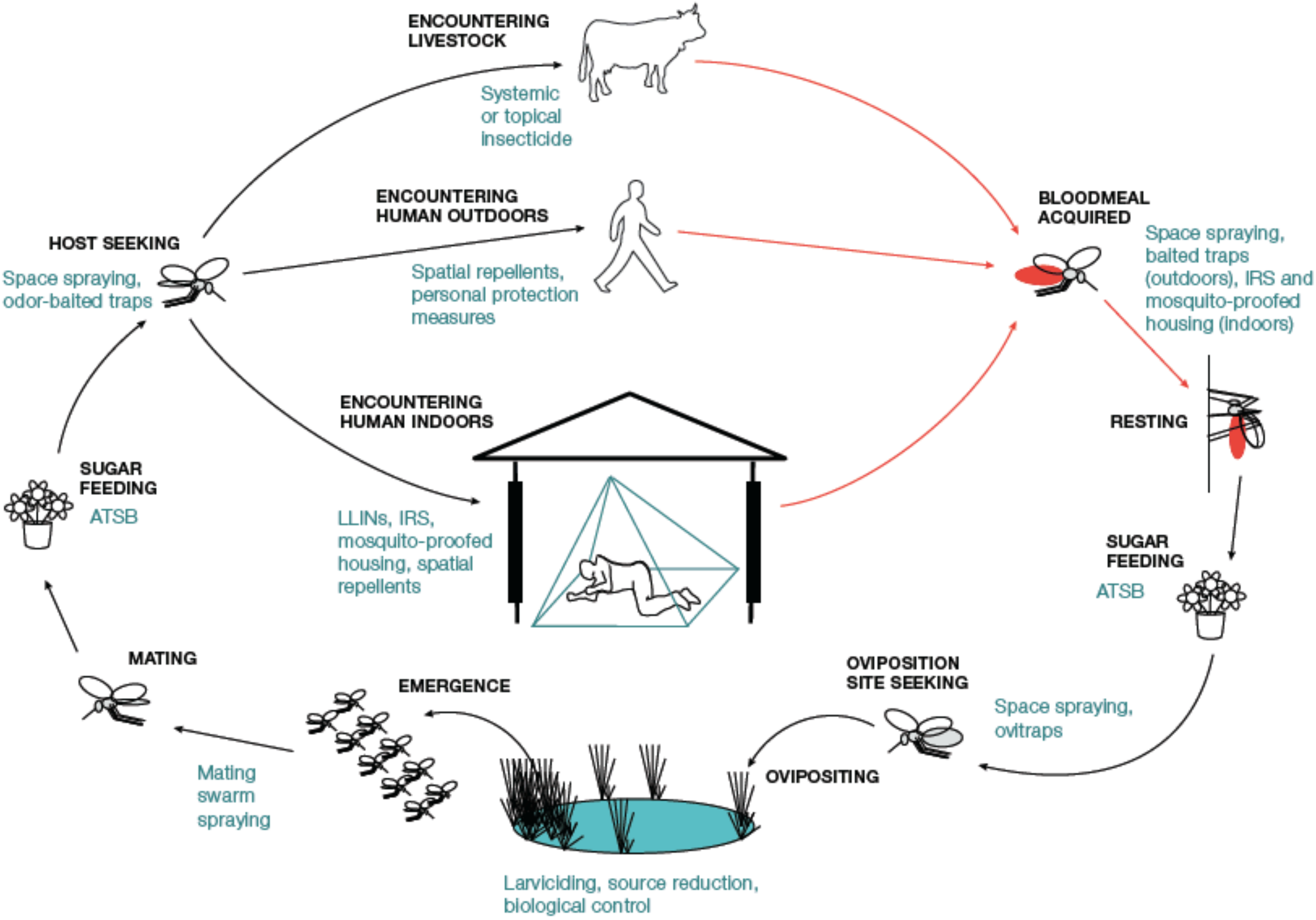
MGDrivE: Homing-based drive targeting a female fertility gene with resistance allele generation



HH	0
Hh	0
HR	0
hh	12 500
hR	0
RR	0
Total	12 500

- Sanchez HM, Wu SL, Bennett J, Marshall JM (In preparation)

Q3. Which other novel vector control tools should we be prioritizing?



- Kiware SS, Chitnis C, Tatarsky A, Wu SL, Sanchez HM *et al.* (2017) PLoS ONE 12: e0187680

Attractive toxic sugar baits (ATSB)

- **Attract with**:
  - **Fruity** or **flowery** scent (**bait**)

- **Tested extensively** in **Israel** on:
  - ***Anopheles sergentii***
  - ***Culex pipiens***

- Then **kill with**:
  - **Sugar** (**feeding stimulant**)
  - **Boric acid** (**oral toxin**)

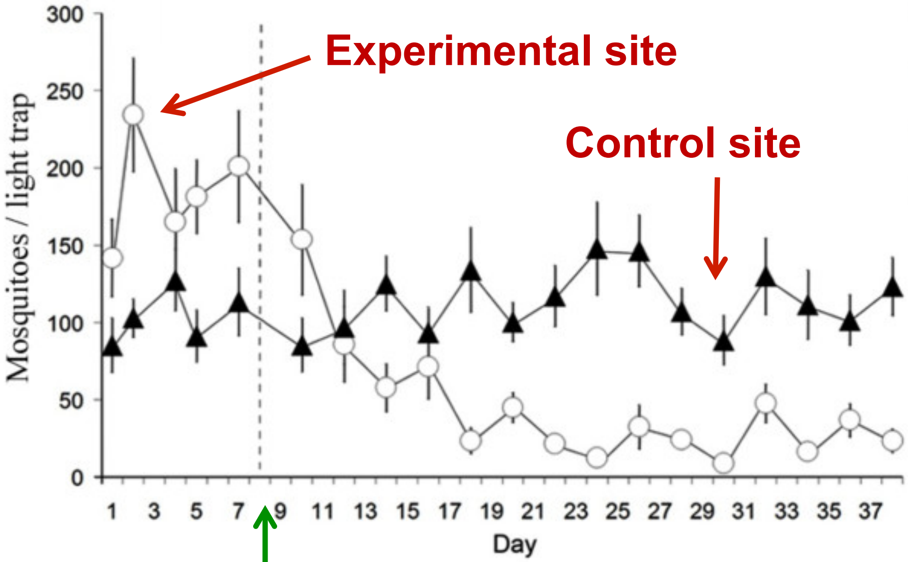
- **Recently tested** in **Mali** on:
  - ***Anopheles gambiae***
- **+ more field trials being planned…**

RESEARCH **Open Access**

Successful field trial of attractive toxic sugar bait (ATSB) plant-spraying methods against malaria vectors in the *Anopheles gambiae* complex in Mali, West Africa

Günter C Müller*[1], John C Beier[2], Sekou F Traore[3], Mahamoudou B Toure[3], Mohamed M Traore[3], Sekou Bah[4], Seydou Doumbia[3] and Yosef Schlein[1]

Females

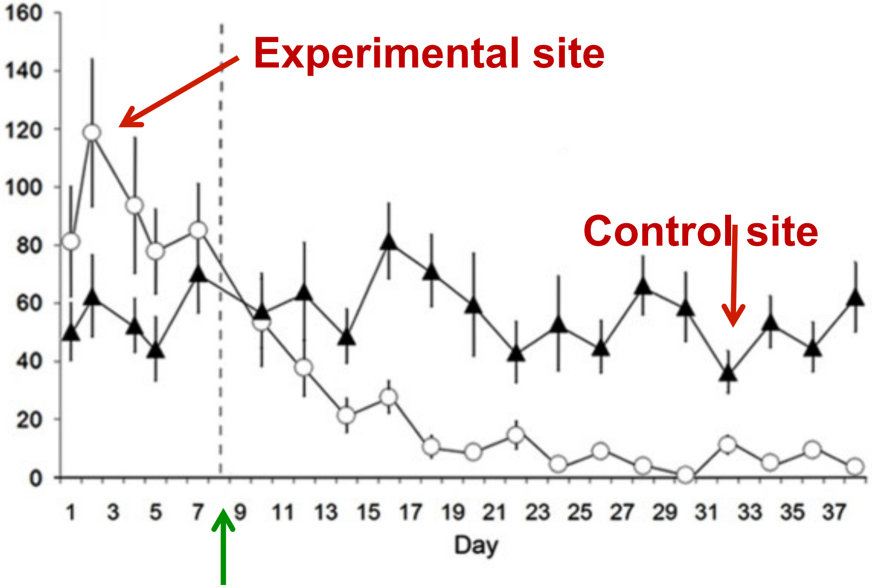


Experimental site

Control site

Intervention
(ATSB sprayed near breeding sites)

Males



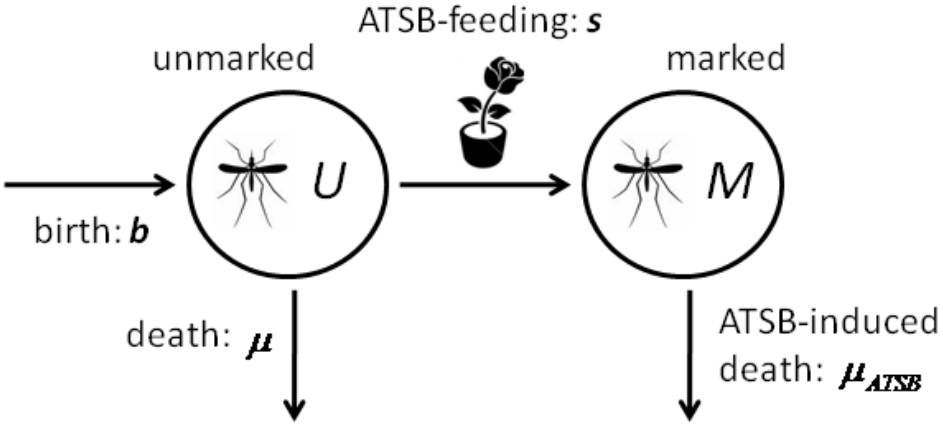
Experimental site

Control site

Intervention

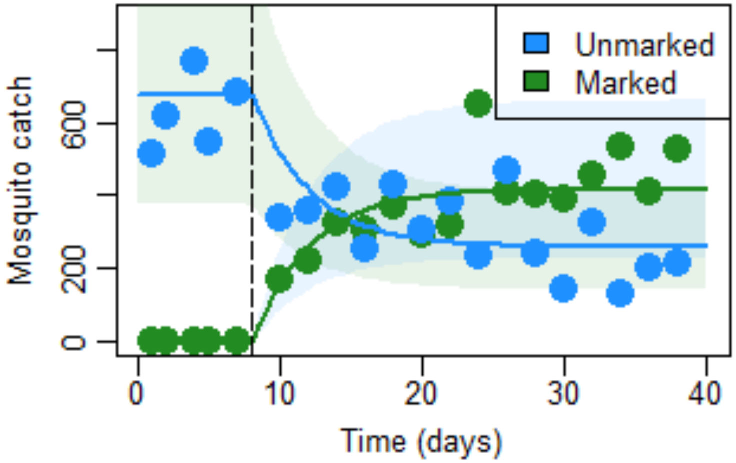
- Muller GC, Beier JC, Traore SF, Toure MB, Traore MM, Bah S *et al.* (2010) Malaria J 9: 210

ATSB data & model fitting

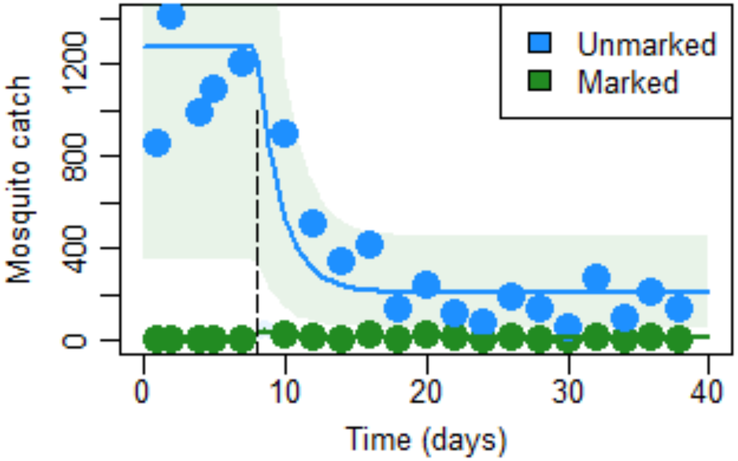


Rate of feeding on ATSB-sprayed plants: 0.5 / day (CrI: 0.27-0.97)

Mean lifetime after ingesting of ATSB: 2.1 hours (CrI: 1.1-3.8)



Female control

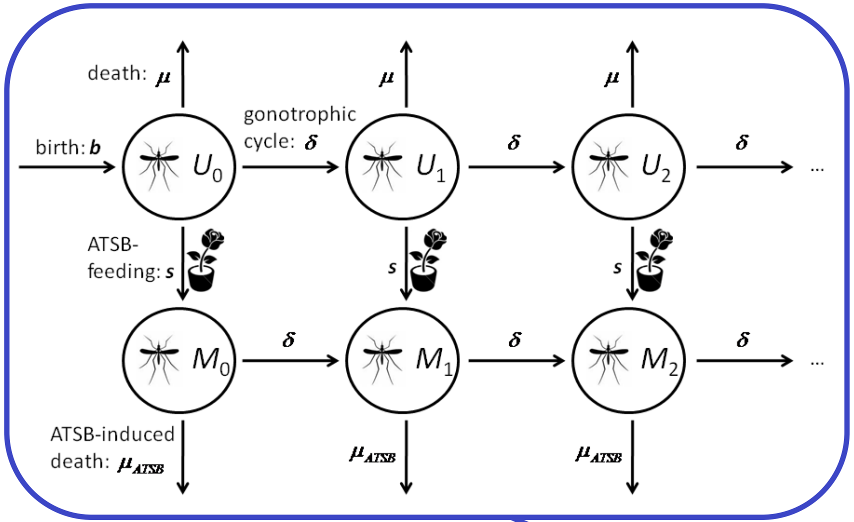


Female experiment

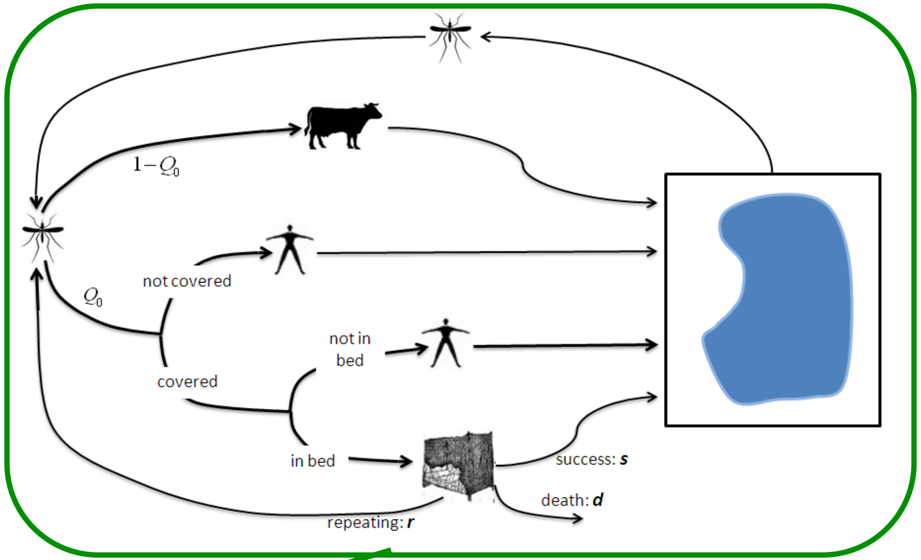
- Marshall JM, White MT, Ghani AC, Schlein Y, Muller GC *et al.* (2013) Malaria J 12: 291

Combine ATSB model with models of mosquito ecology, gonotrophic cycle & vector control

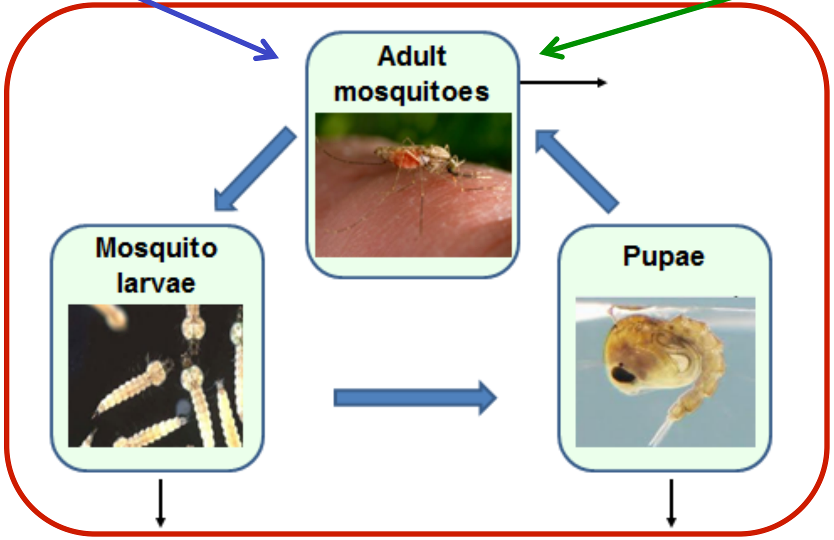
ATSB model:



Bed net & insecticide model:



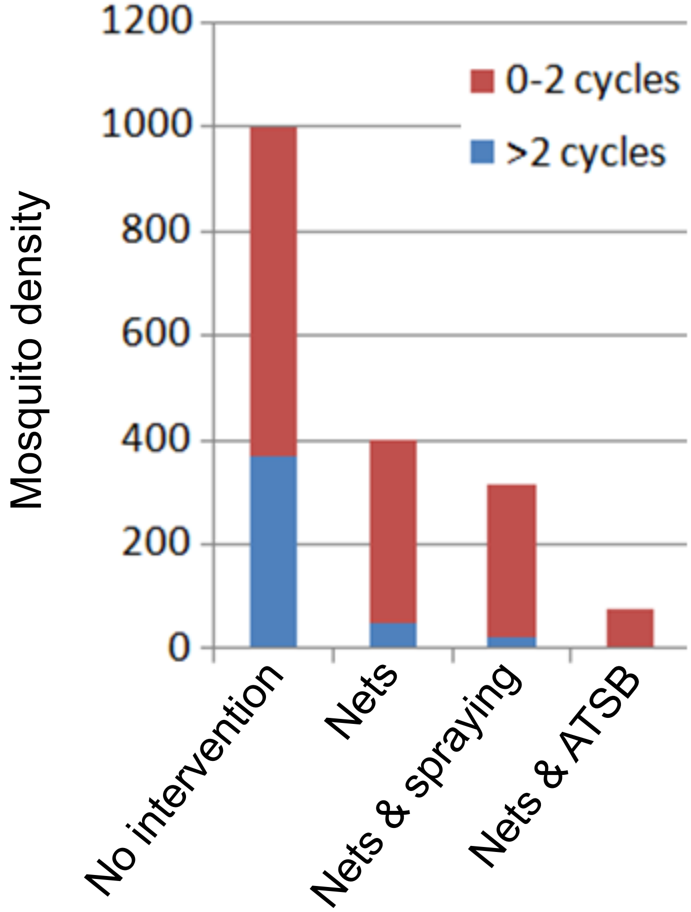
Mosquito ecology model:



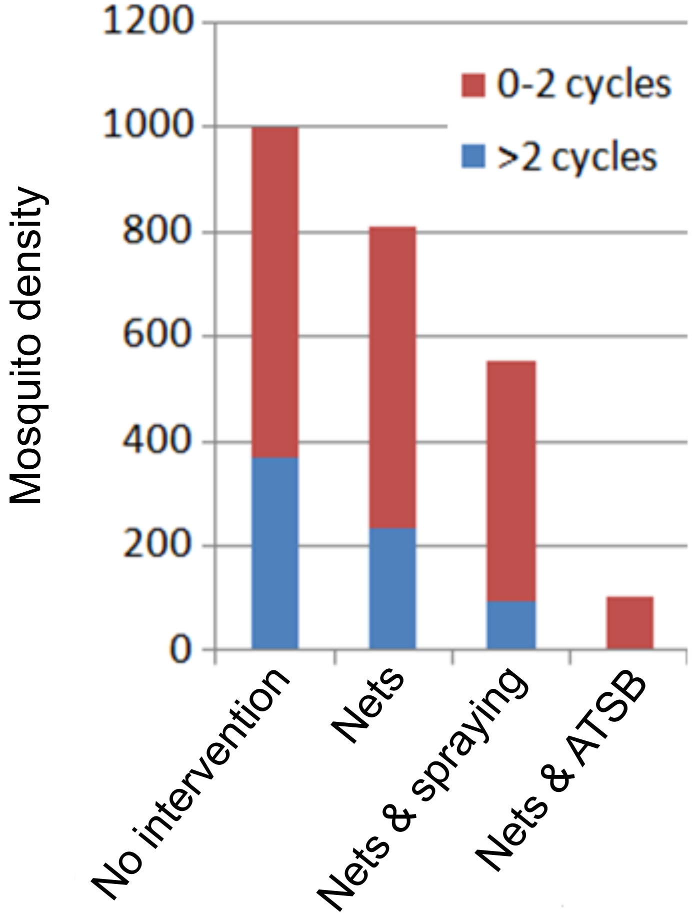
- Marshall JM, White MT, Ghani AC, Schlein Y, Muller GC *et al.* (2013) Malaria J 12: 291

Predicted combined impact on vector density

***Anopheles gambiae*:**



***Anopheles arabiensis*:**

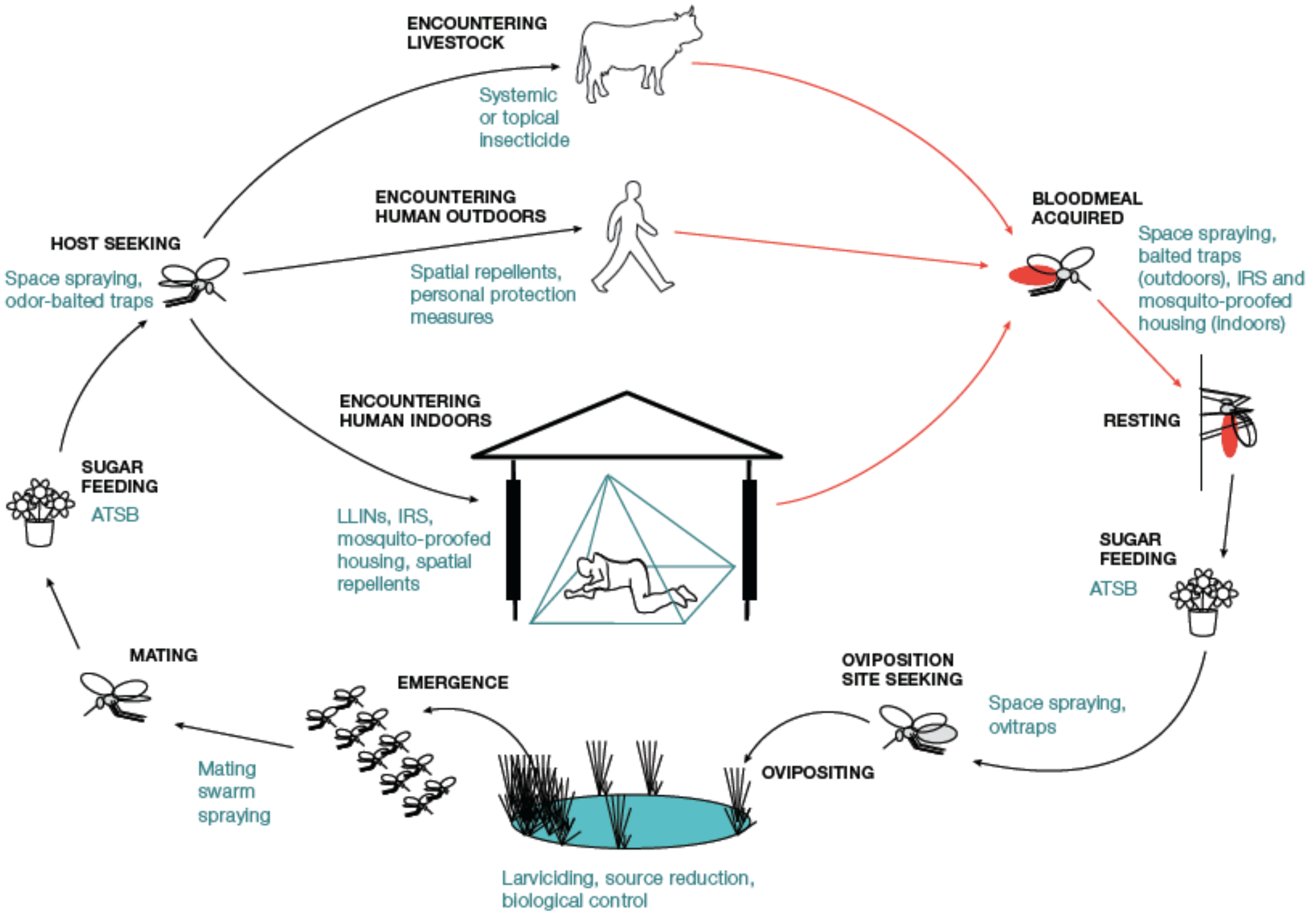


- **Nets & spraying significantly reduce *An. gambiae* vector density**
- However, **ATSB complements nets** better than insecticide spraying

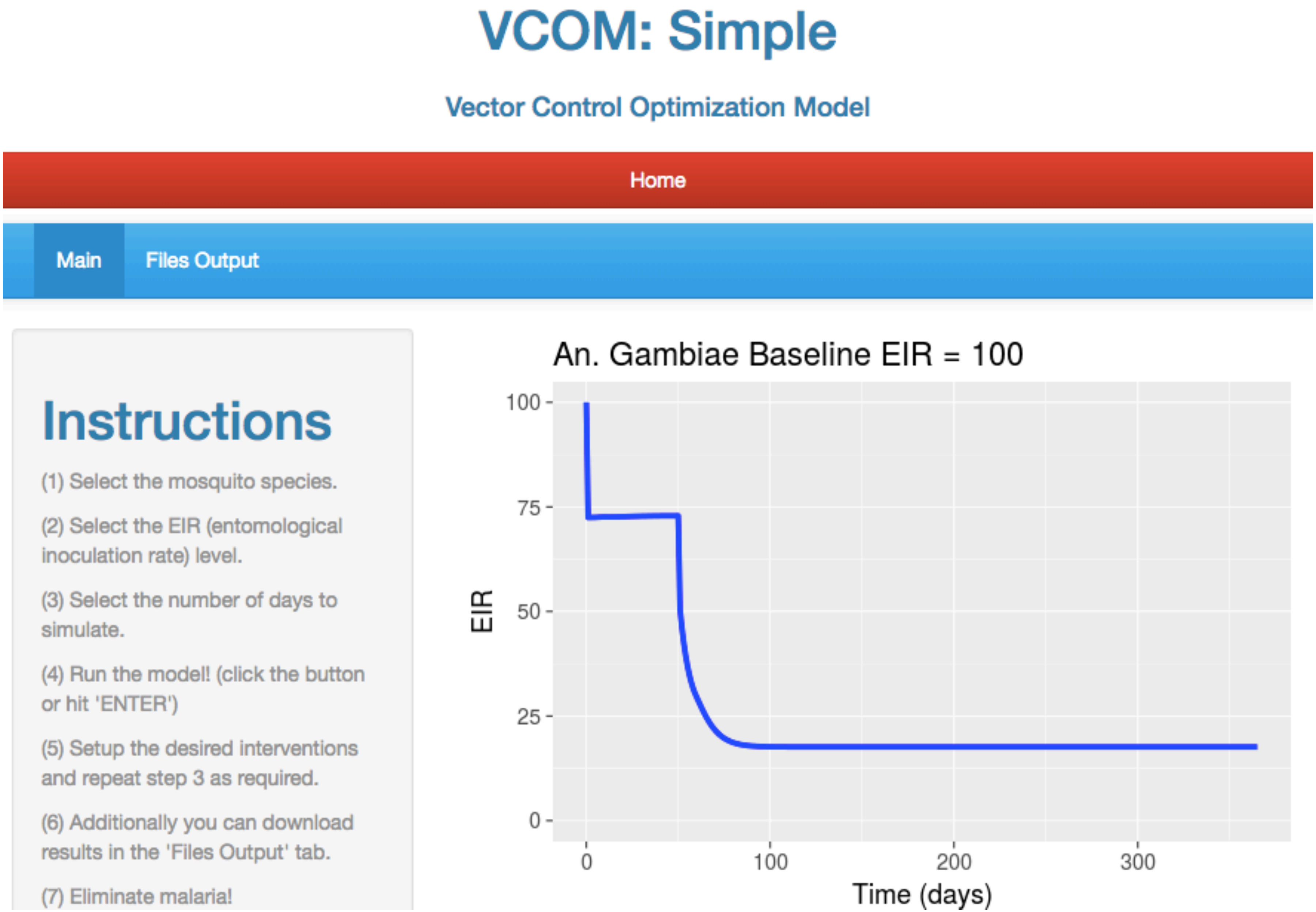
- **Nets & spraying** are **less effective** against the **exophilic *An. arabiensis***

- Marshall JM, White MT, Ghani AC, Schlein Y, Muller GC *et al.* (2013) Malaria J 12: 291

Vector Control Optimization Model (VCOM)



- Kiware SS, Chitnis C, Tatarsky A, Wu SL, Sanchez HM *et al.* (2017) PLoS ONE 12: e0187680



VCOM: Simple

Vector Control Optimization Model

Instructions

(1) Select the mosquito species.

(2) Select the EIR (entomological inoculation rate) level.

(3) Select the number of days to simulate.

(4) Run the model! (click the button or hit 'ENTER')

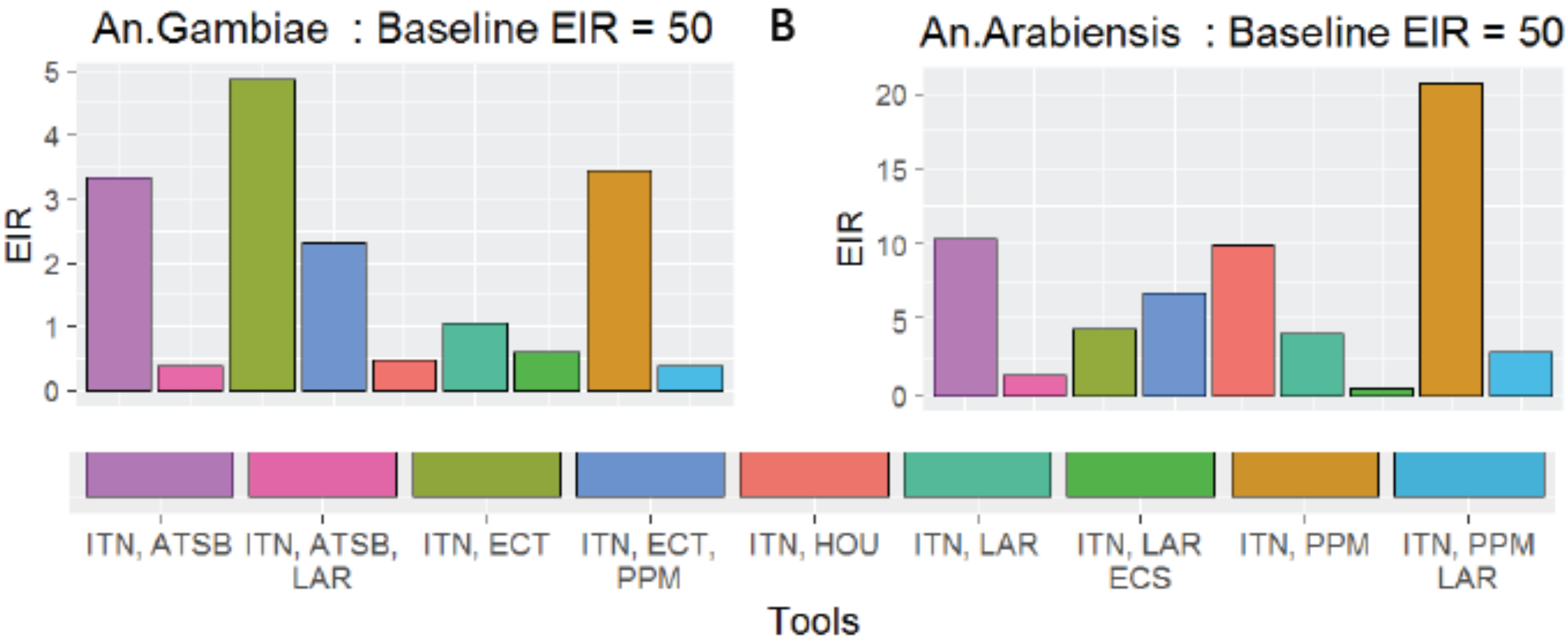
(5) Setup the desired interventions and repeat step 3 as required.

(6) Additionally you can download results in the 'Files Output' tab.

(7) Eliminate malaria!

- Kiware SS, Chitnis C, Tatarsky A, Wu SL, Sanchez HM *et al.* (2017) PLoS ONE 12: e0187680

VCOM predictions for combined vector control

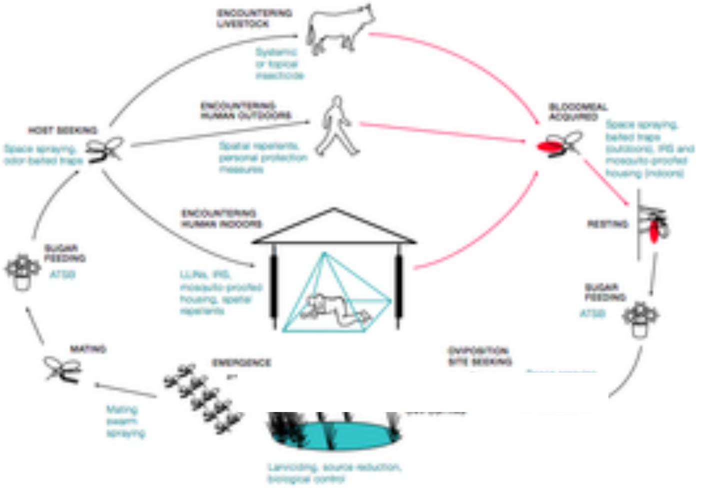


- **Nets, ATSB & larvaciding significantly reduce densities of** both ***An. gambiae*** & ***An. arabiensis***
- Other effective combinations for ***An. gambiae*** are: i) **nets & housing modification**, and ii) **nets, personal protection measures & larvaciding**

- Other effective combinations for ***An. arabiensis*** are: i) **nets, larvaciding & cattle treated with endectocide systemically**
- **Elimination is very difficult**, even under **unrealistically optimistic conditions**

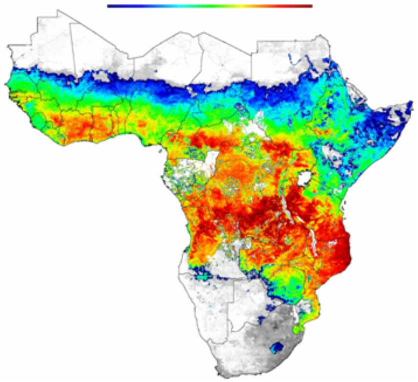
- Kiware SS, Chitnis C, Tatarsky A, Wu SL, Sanchez HM *et al.* (2017) PLoS ONE 12: e0187680

Conclusions



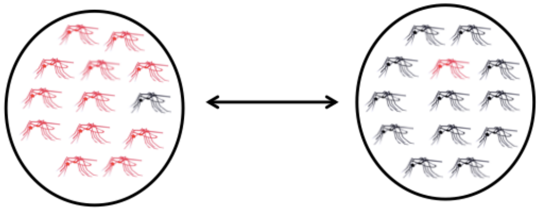
Q3. Which novel vector control tools should we be prioritizing?

- Attractive toxic sugar baits offer synergies to insecticide-based vector control
- But existing tools are not expected to eliminate malaria in high-prevalence settings



Q2. Can CRISPR-based gene drive be effective at disease control on a wide scale?

- Multiplexing guide RNAs could sufficiently reduce resistant allele generation rates
- More study is needed of guide RNA multiplexing



Q1. Is it possible to perform a confined trial of a gene drive system?

- Threshold-dependent systems may be confineable to partially isolated populations
- More study is needed of mosquito population structure

Acknowledgements

COLLABORATORS:

MARSHALL LAB @ UC BERKELEY

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- **Akbari & Bier Labs** @ UCSD
- **James Lab** @ UC Irvine
- **Hay Lab** @ Caltech
- **Lanzaro Lab** @ UC Davis
- **Malaria Elimination Initiative** @ UCSF
- **Prof David Smith** @ IHME, UW
- **School of Public Health** @ UC Berkeley
- **Malaria Modeling Group** @ Imperial

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