

Why has dengue resurged, why does malaria persist, and can these diseases be controlled by CRISPR-based gene drive and other novel tools?

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Step 1



Step 2



Talk outline

Mathematical models of malaria & dengue:

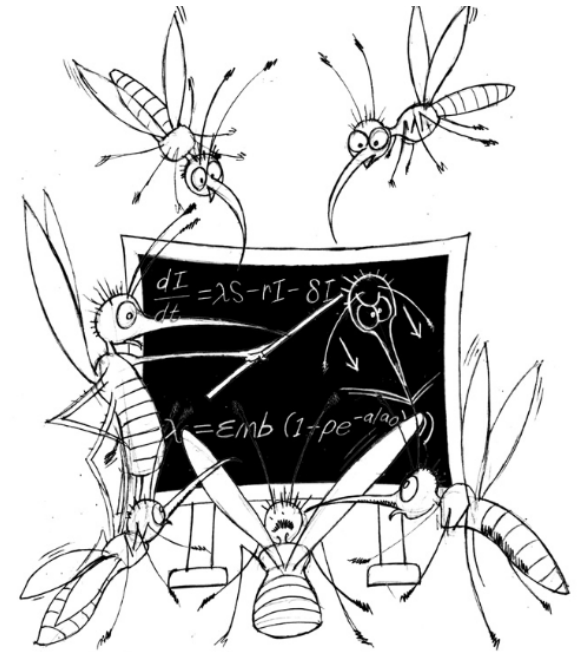
1. Ross-Macdonald model of malaria transmission
2. Persistence of malaria in sub-Saharan Africa
3. Resurgence of dengue & the 2014 outbreak in Guangzhou

Gene drive systems:

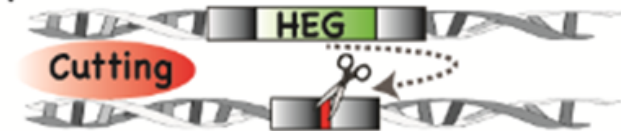
4. CRISPR/Cas9 and homing-based systems
5. Potential for confined field trials using threshold-dependent systems
6. Circumventing resistance to gene drive

An expanded vector control toolbox:

7. Attacking the mosquito on multiple fronts (VCOM modeling framework)



Step 1



Step 2

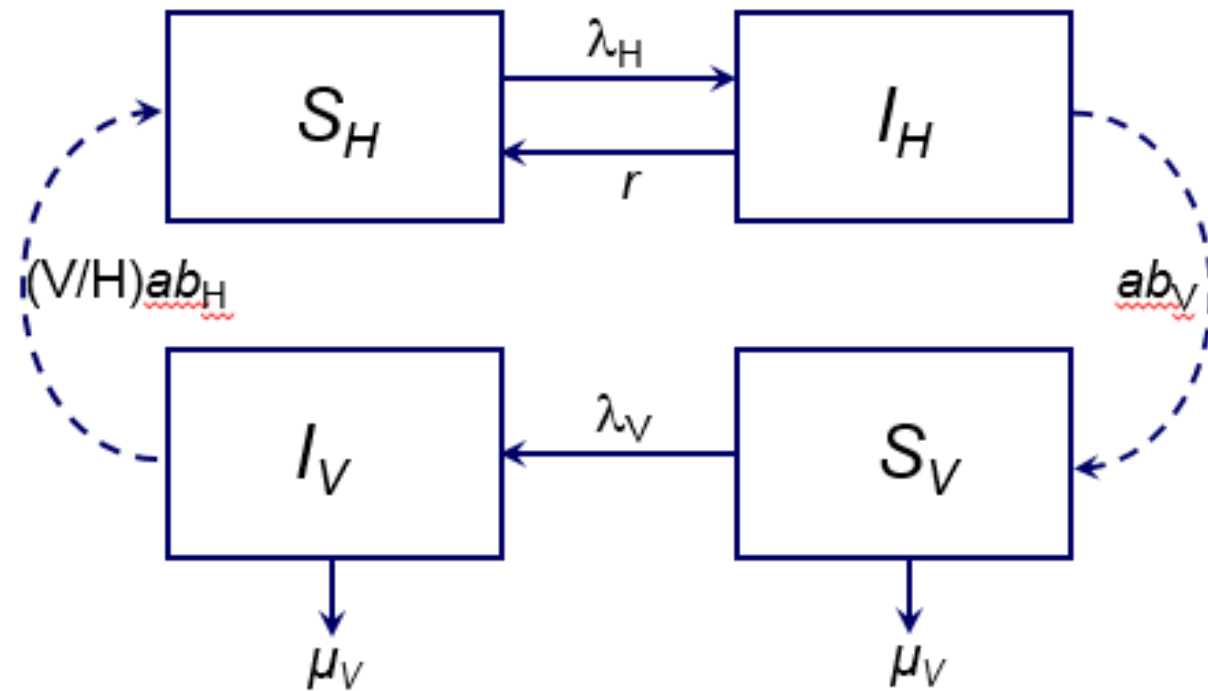


Ross-Macdonald model

*An Application of the Theory of Probabilities to the Study of
a priori Pathometry.—Part I.*

By Lieut.-Colonel Sir RONALD ROSS, K.C.B., F.R.S., R.A.M.C.T.F.

(Received July 14, 1915.)

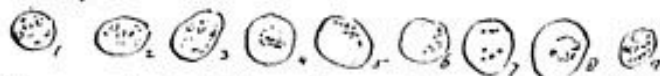


20th August 1947

36) Larva 1stst (4th day) dead. Brown with white wings etc.
As usual from cells with adhesion, but granules? (3) (3)
No pseudo. No filariae.

37) Larva 1stst (4th day) dead. Small, wrinkled, black
Pseudomonas

38) Larva 1stst (4th day) living. Brown with white wings etc.
The stomach just under the outer surface contained
some large cells with pigment (2) 7 numerous granules



The pigment sometimes vacillates, is quite black like that of haemocytes
numbers; 7 - not found outside these cells. 2 & 8 are arranged in
a circle. The vacuoles do not change position & the cells do not change
shape. The outer part of the cell is generally thick, but in 10 smaller some
rather short. About 12-15 μ in diameter.

This specimen irrigated with 1% formalin & stained with Mallory's stain.

21st August

Just the usual specimen. Pigmented bodies still present, but not more
visible.



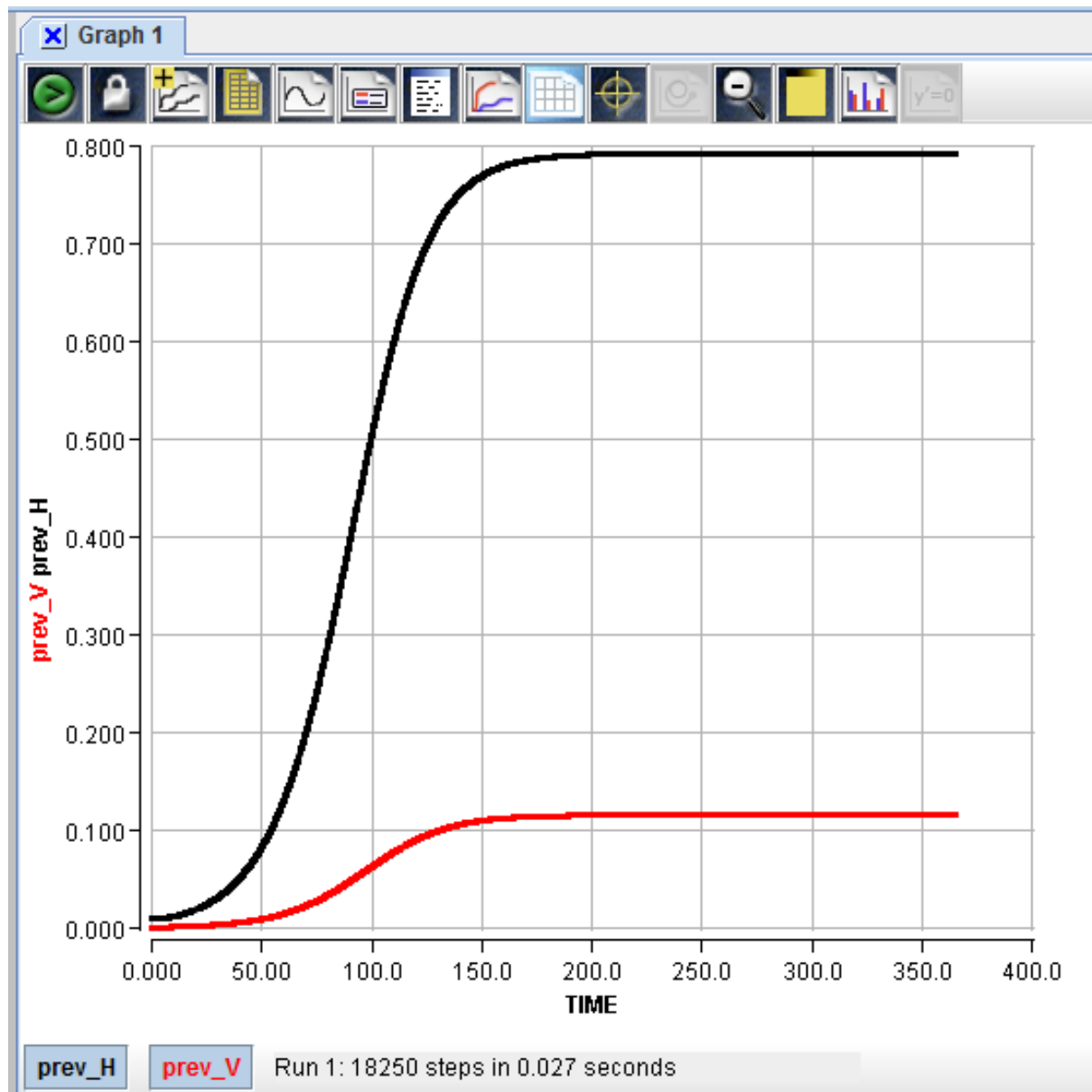
No 1 shows signs of a nucleus & nos 5 & 6 are distinctly more fleshy &
bright than the rest.

39) Larva 1stst (5th day) alive. Large, brown, white wings etc.
The same cells in stomach under superficial layer - 2 of a
cell layer & better defined

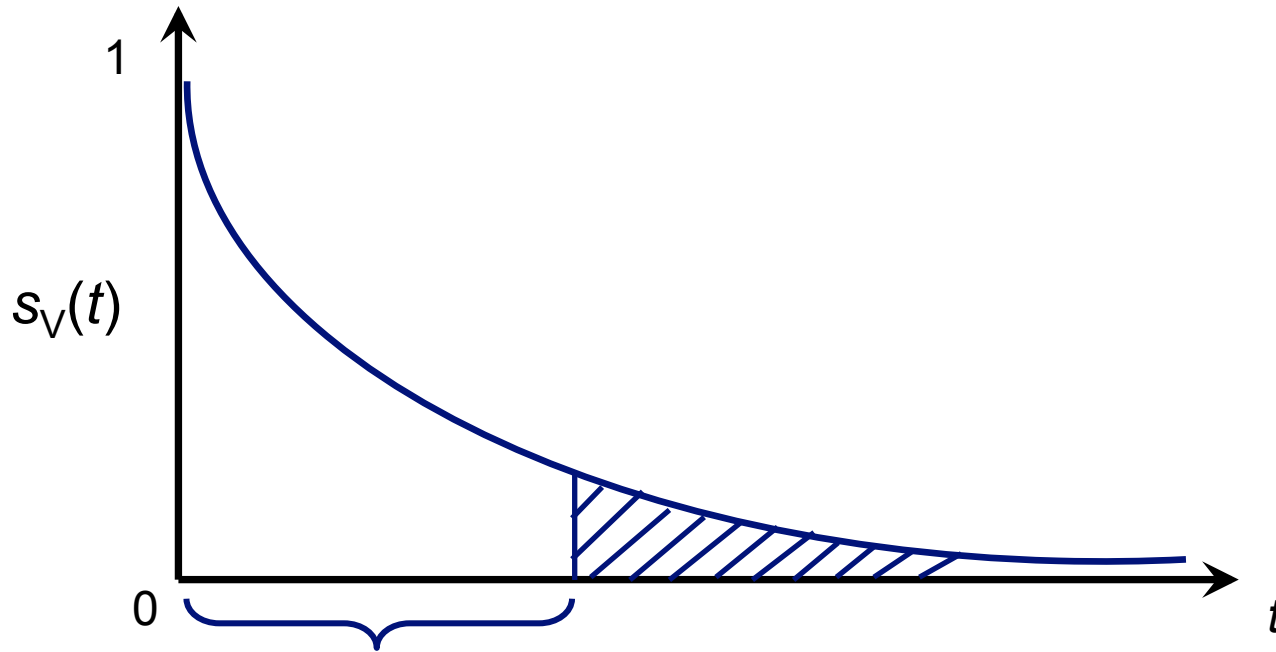


Pigment vacillates in some. Largest about 20 μ in diam. Outer ones much thicker.
2/3 of them in stomach, chiefly toward upper end.

Question: Why is human and mosquito malaria prevalence so high for this model?



The motivation for decades of adult vector control



**Extrinsic incubation period
(EIP)**

**Mosquitoes that could
potentially transmit must
be older than the EIP**

**Therefore, prioritize mosquito
killing for malaria control**

The Kermack-McKendrick model



B. Constant Rates.

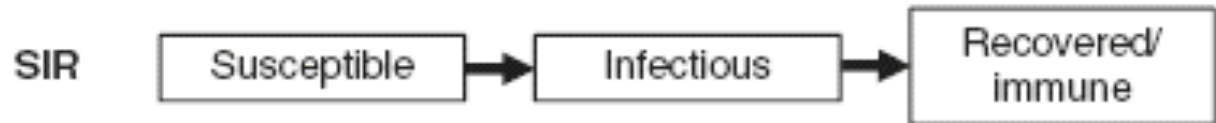
(10) Much insight can be obtained as to the process by which epidemics in limited populations run their peculiar courses, and end in final extinction,

from the consideration of the special case in which ϕ and ψ are constants κ and l respectively.

In this case the equations are

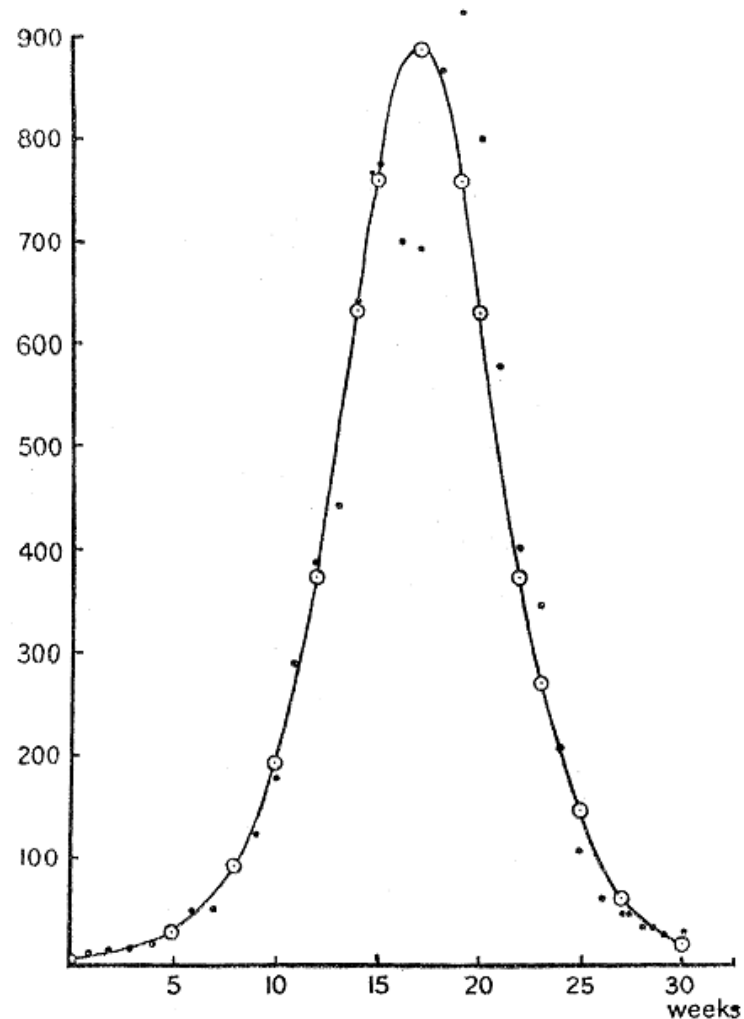
$$\left. \begin{aligned} \frac{dx}{dt} &= -\kappa xy \\ \frac{dy}{dt} &= \kappa xy - ly \\ \frac{dz}{dt} &= ly \end{aligned} \right\} \quad (29)$$

and as before $x + y + z = N$.



Kermack & McKendrick (1927), A mathematical contribution to the theory of epidemics, Proc Roy Soc A

Fit to plague deaths (Mumbai, Dec 1905 - July 1906)



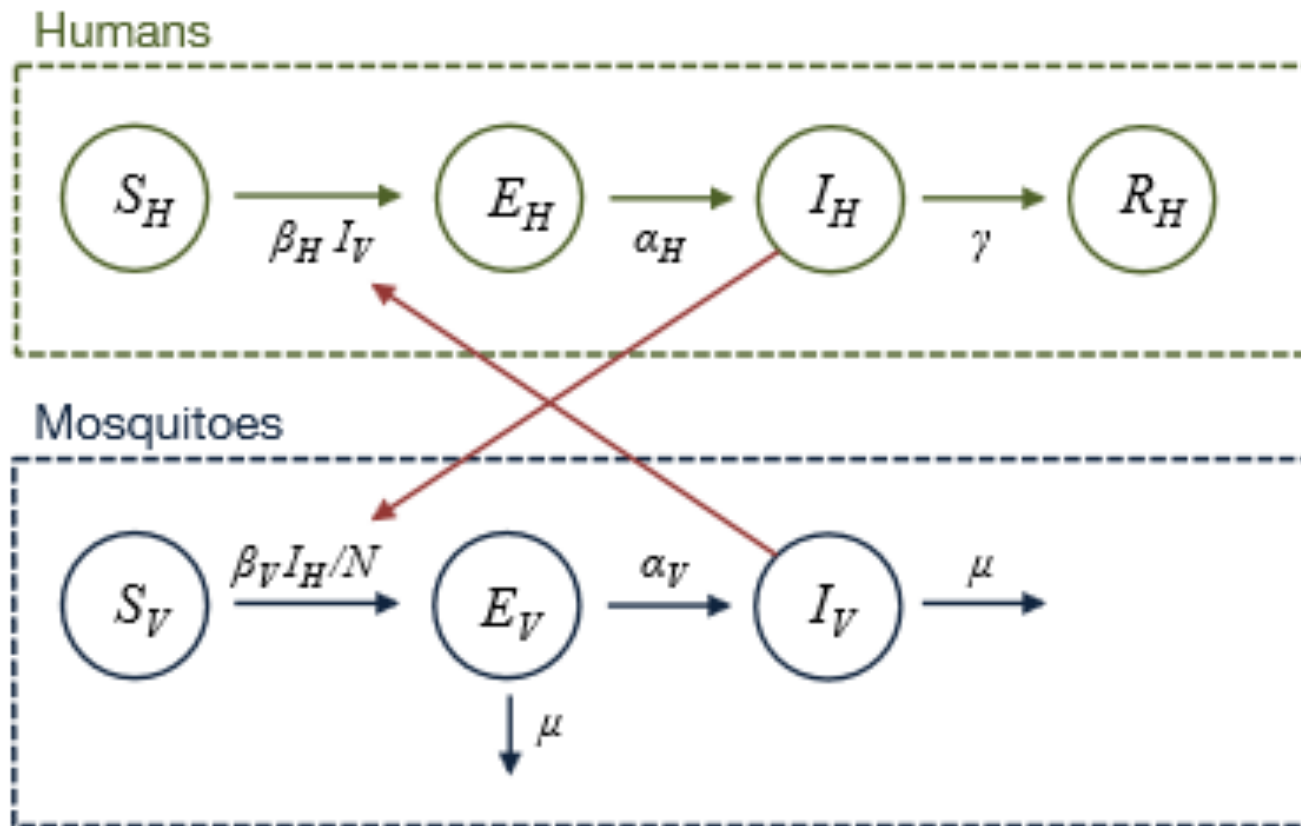
The accompanying chart is based upon figures of deaths from plague in the island of Bombay over the period December 17, 1905, to July 21, 1906. The ordinate represents the number of deaths per week, and the abscissa denotes the time in weeks. As at least 80 to 90 per cent. of the cases reported terminate fatally, the ordinate may be taken as approximately representing dz/dt as a function of t . The calculated curve is drawn from the formula

$$\frac{dz}{dt} = 890 \operatorname{sech}^2(0.2t - 3.4).$$

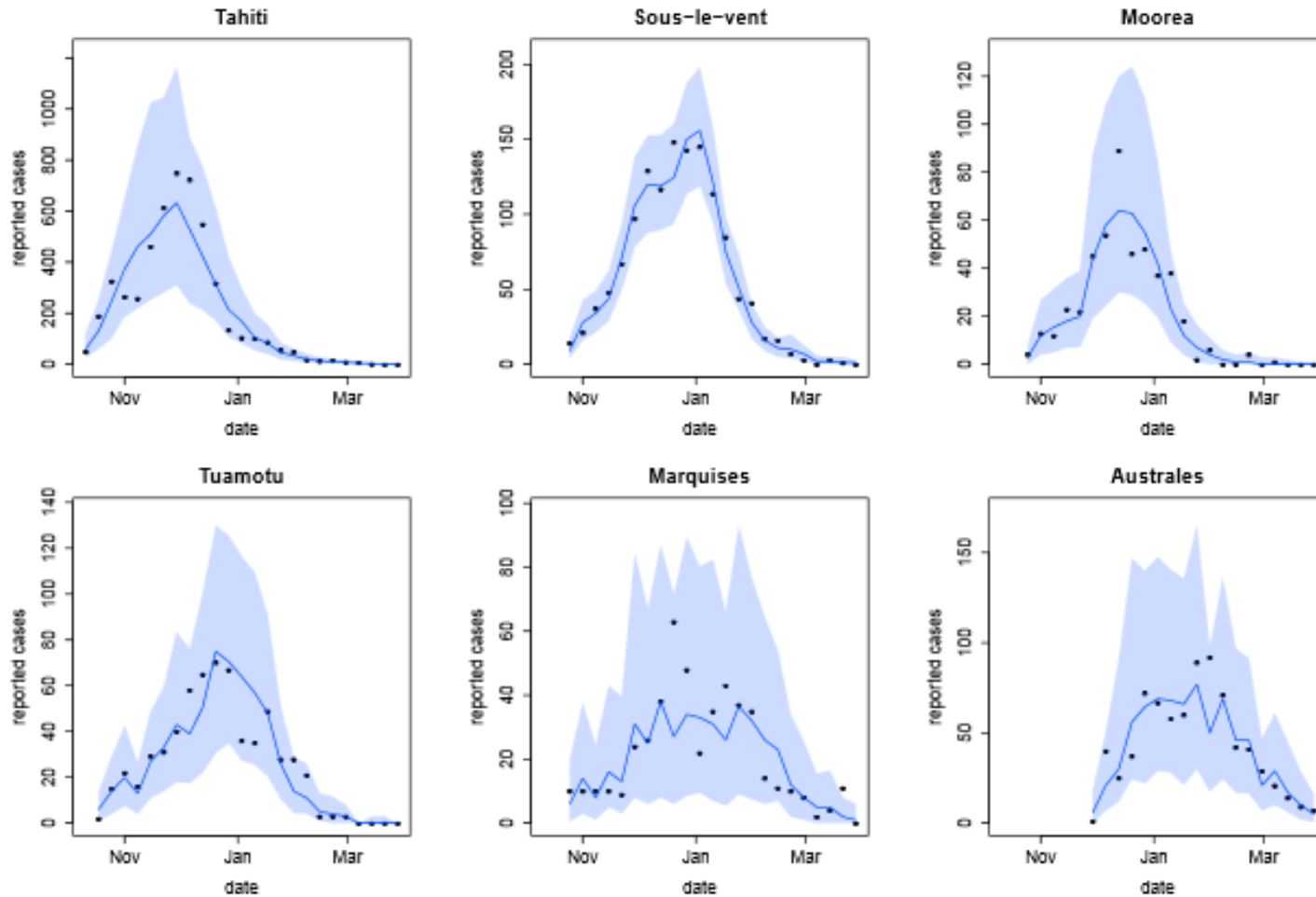
Compartmental model of Zika virus

Transmission dynamics of Zika virus in island populations: a modelling analysis of the 2013–14 French Polynesia outbreak

Adam J. Kucharski^{1,*}, Sebastian Funk¹, Rosalind M. Eggo¹, Henri-Pierre Mallet²,
W. John Edmunds¹, Eric J. Nilles³



Fitting compartmental models to incidence data using Bayesian MCMC



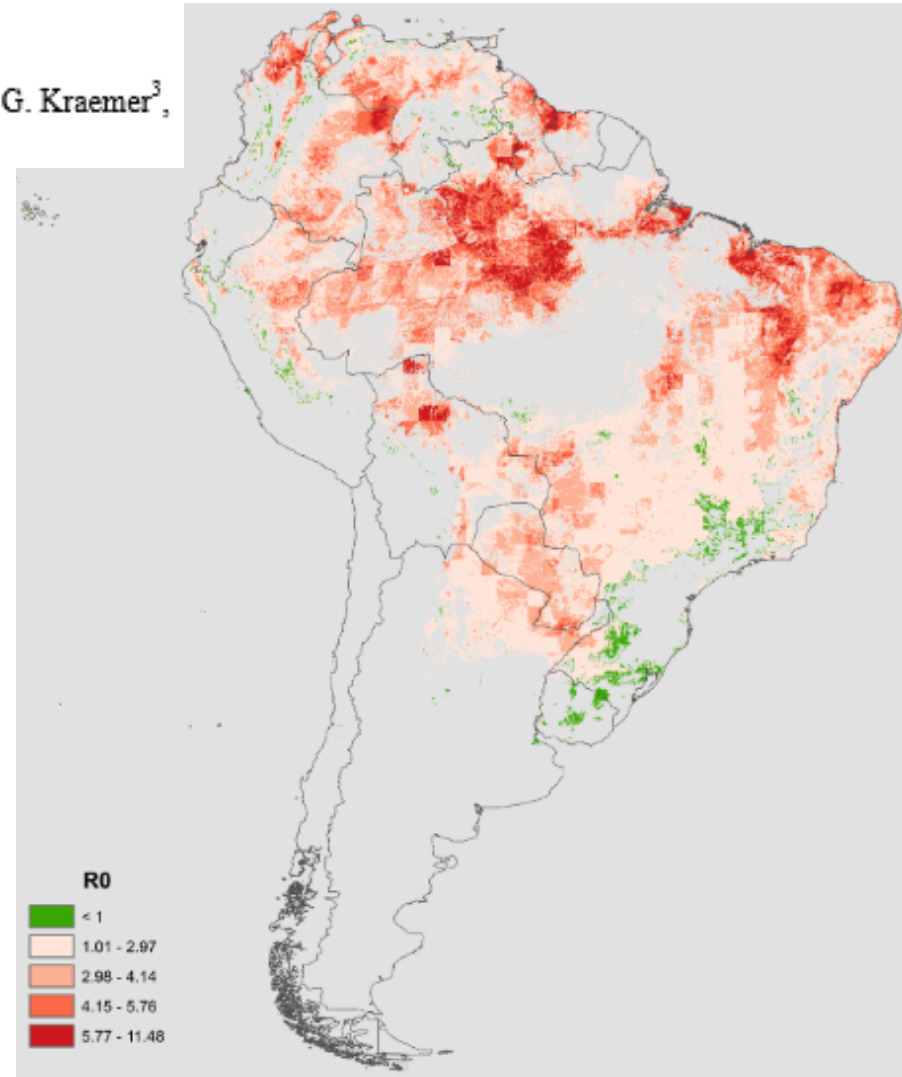
Implications for Latin America

Model-based projections of Zika virus infections in childbearing women in the Americas

T. Alex Perkins^{1*}, Amir S. Siraj¹, Corrine Warren Ruktanonchai², Moritz U.G. Kraemer³,
Andrew J. Tatem^{2,4}

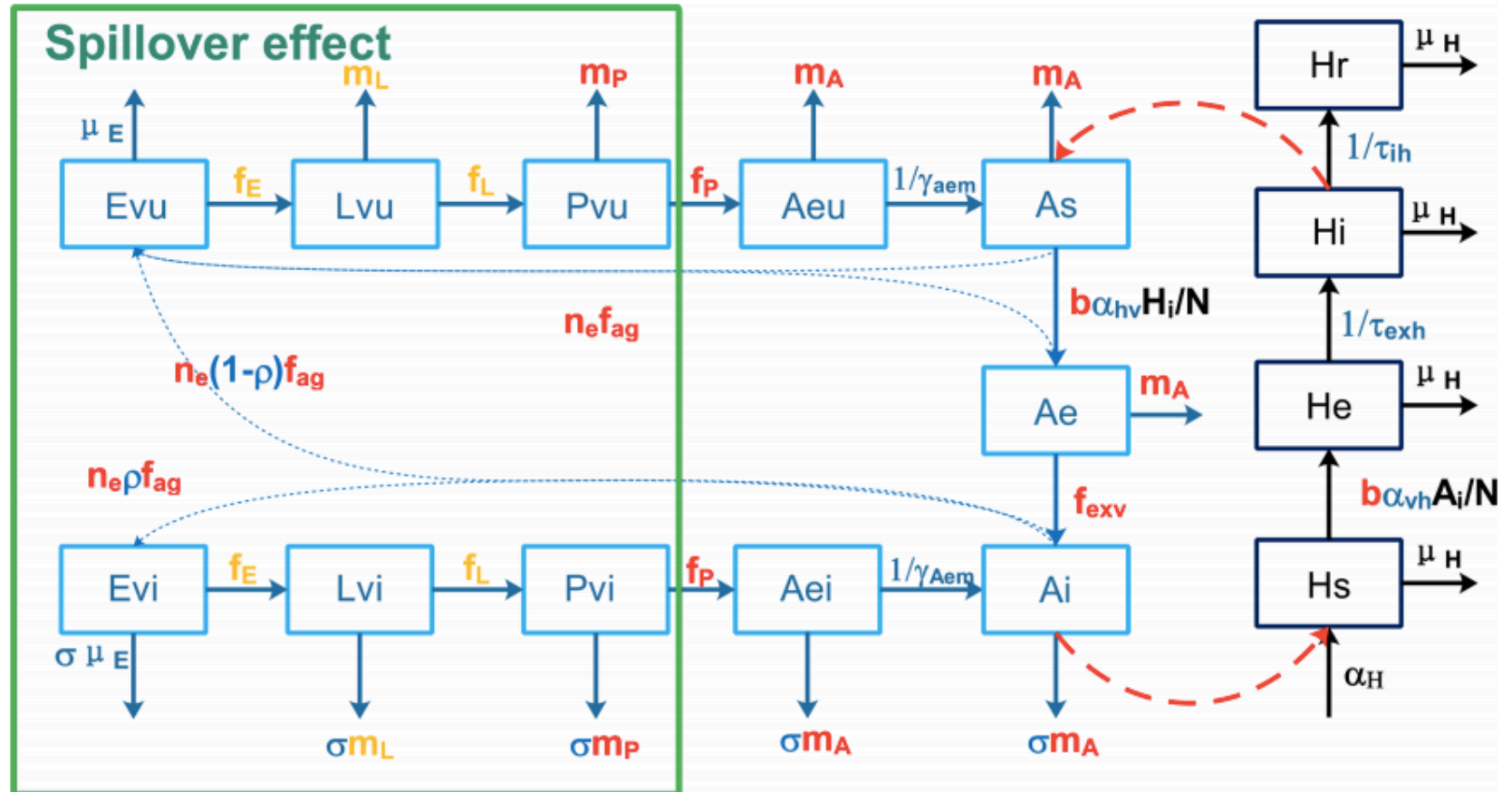
$$R_0(T) = \frac{mbca^2 e^{-\mu(T)n(T)}}{\mu(T)r}$$

- m = Number of mosquitoes per person (derived from species mapping with correction factor from economic index)
- $\mu(T)$ = Mosquito death rate (function of temperature)
- $n(T)$ = Virus incubation period in mosquito (function of temperature)

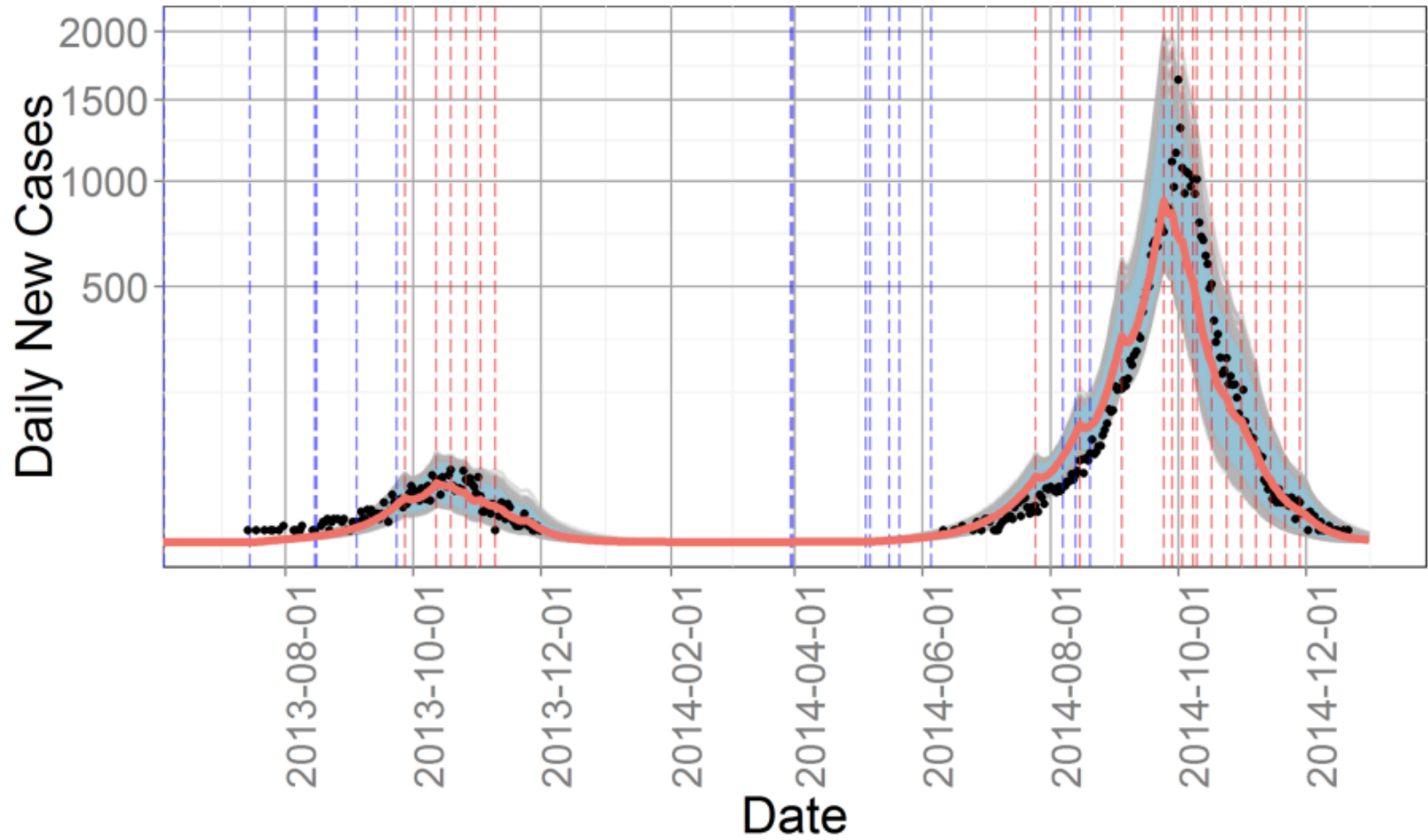


Climate and the Timing of Imported Cases as Determinants of the Dengue Outbreak in Guangzhou, 2014: Evidence from a Mathematical Model

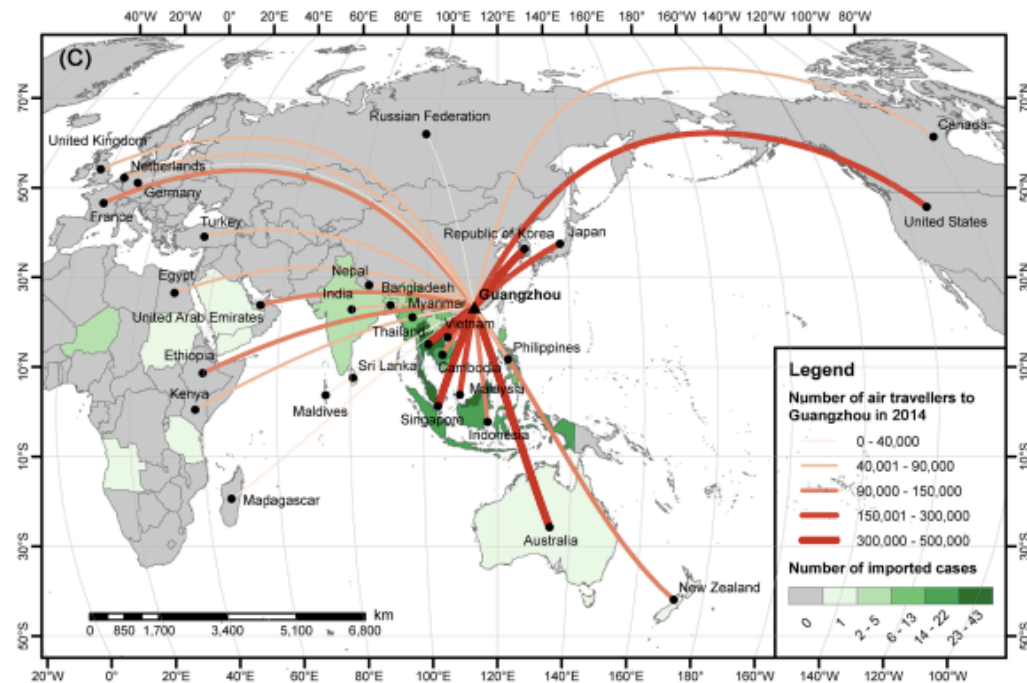
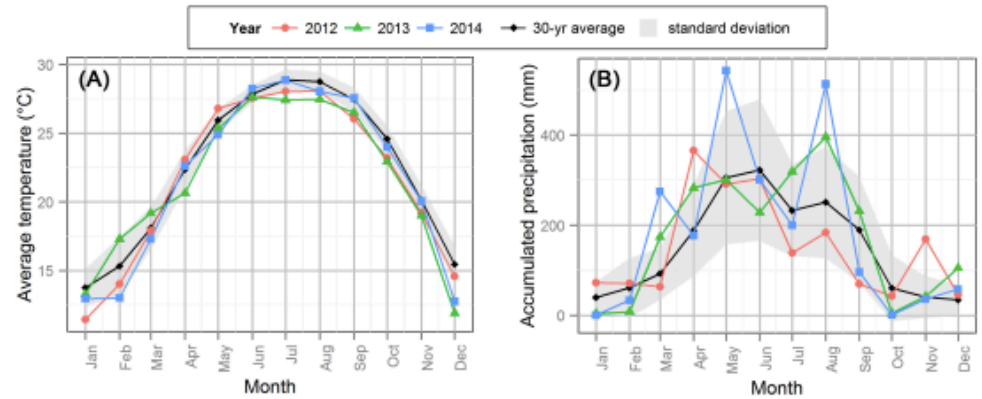
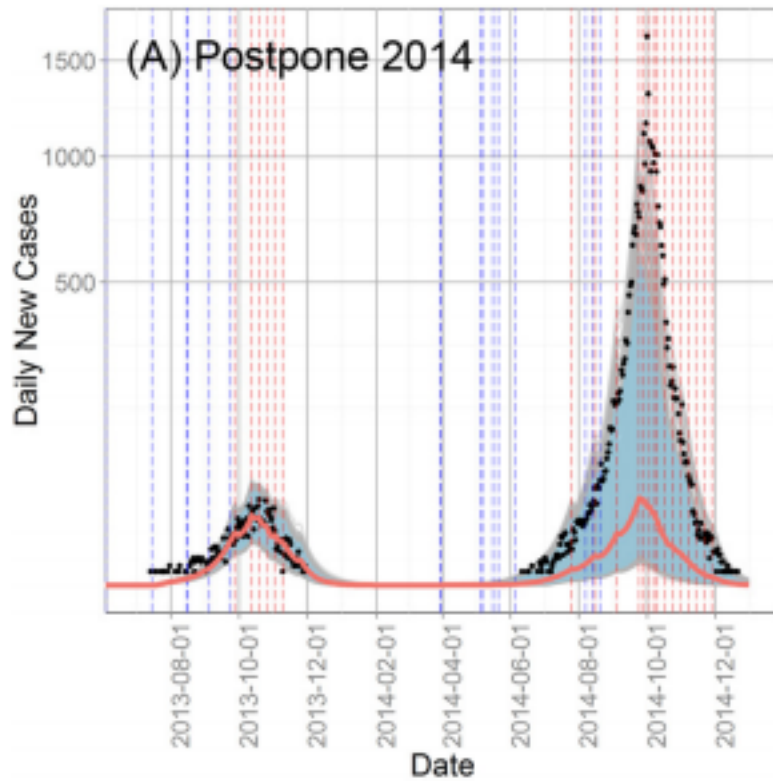
Qu Cheng , Qinlong Jing , Robert C. Spear, John M. Marshall, Zhicong Yang , Peng Gong 



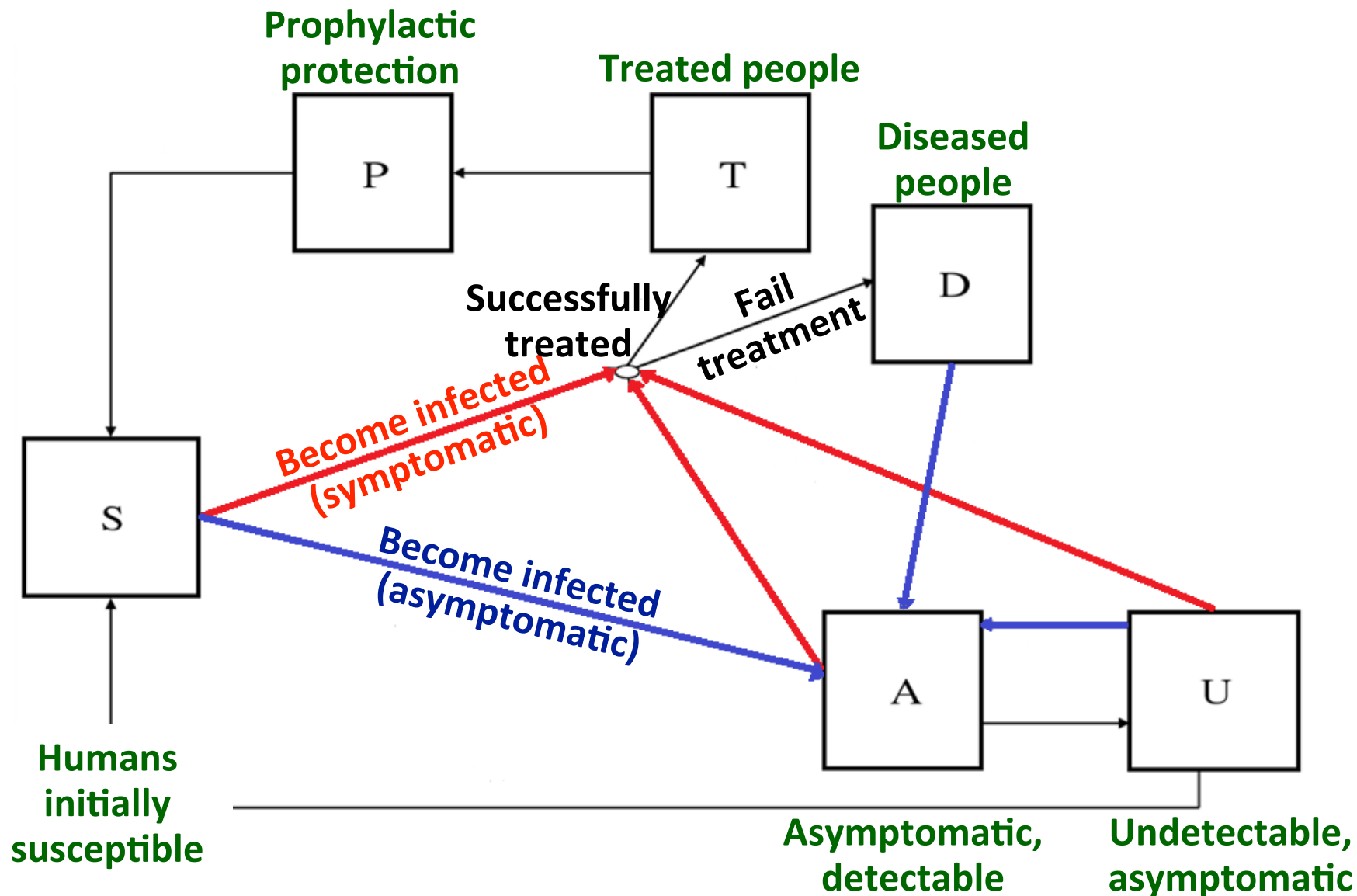
2014 dengue outbreak in Guangzhou



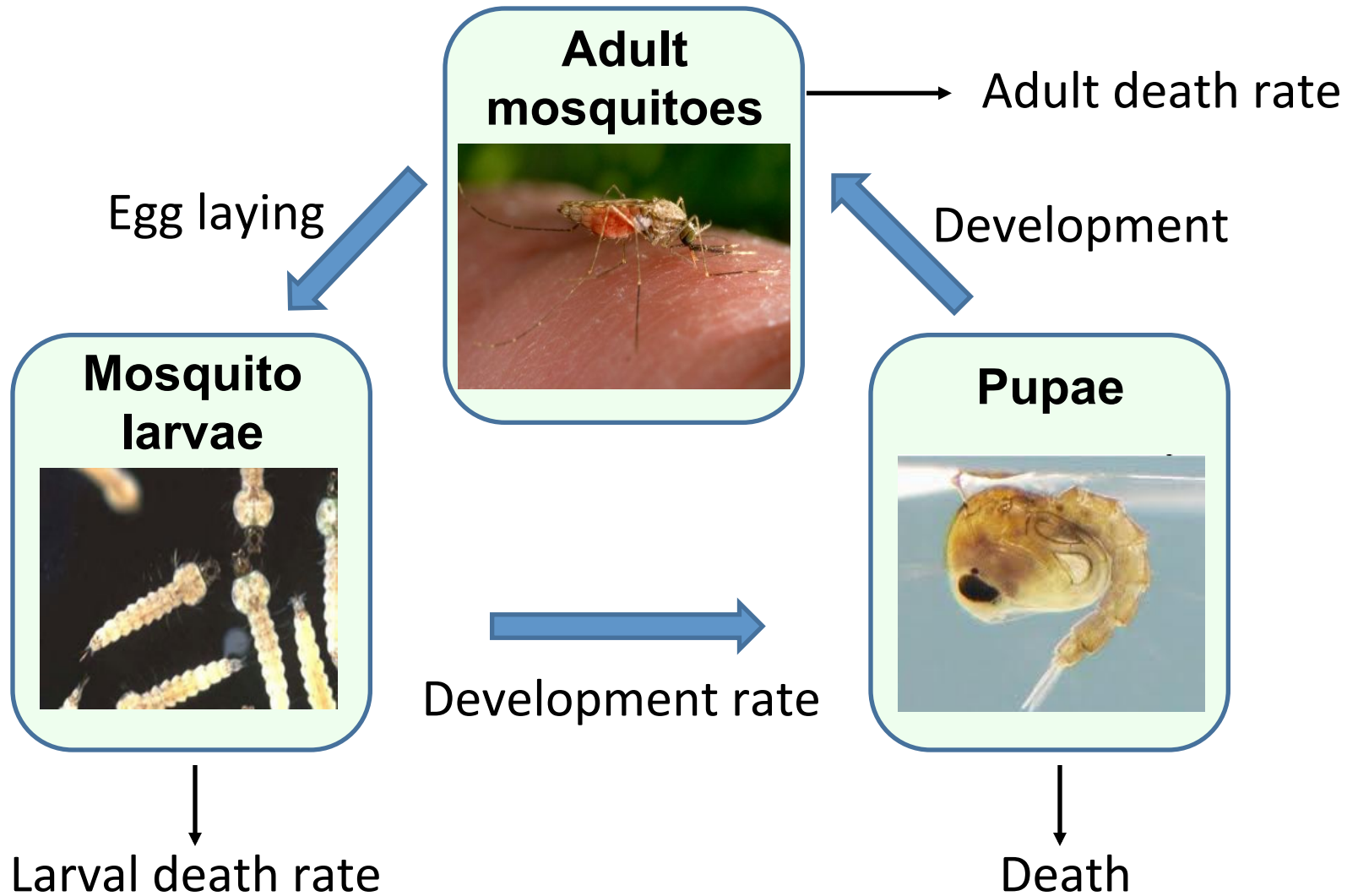
Role of human movement and climate in outbreak



Human malaria transmission model (with ACTs)



Mosquito ecology model



Function of carrying capacity, K

Environmental variables influencing K

- K is a linear function of satellite-derived, high-resolution environmental variables:

- **Climate**

- Day & night temperature

- Rainfall

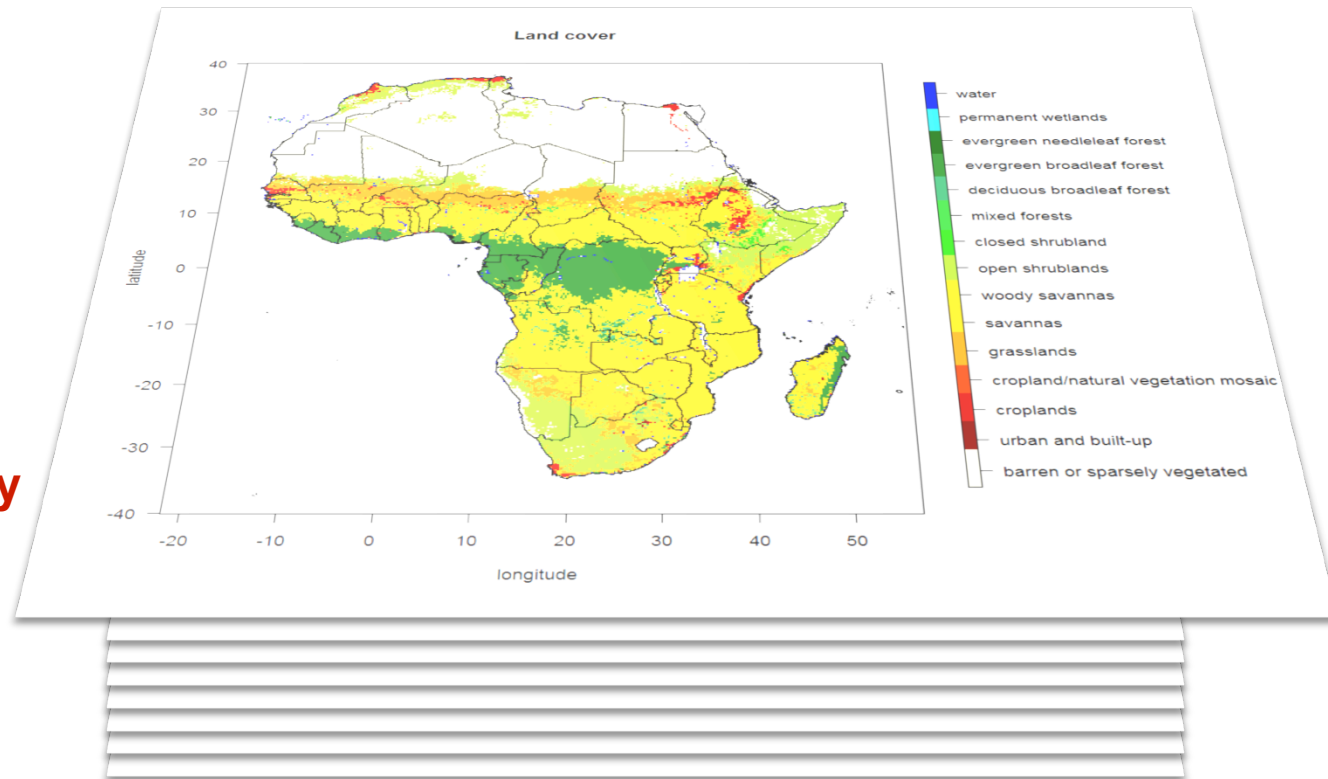
- **MIR**

- **EVI**

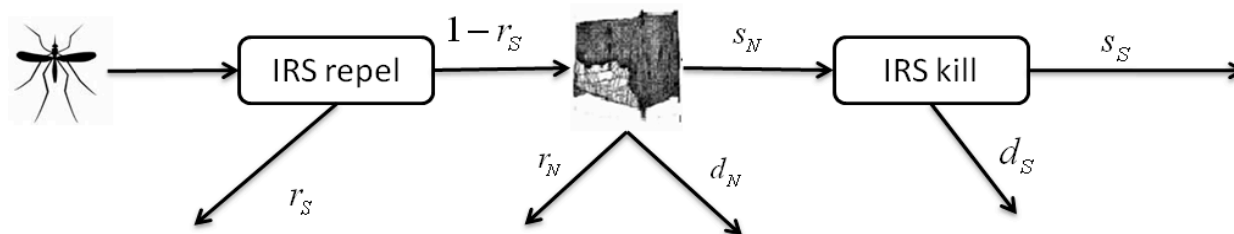
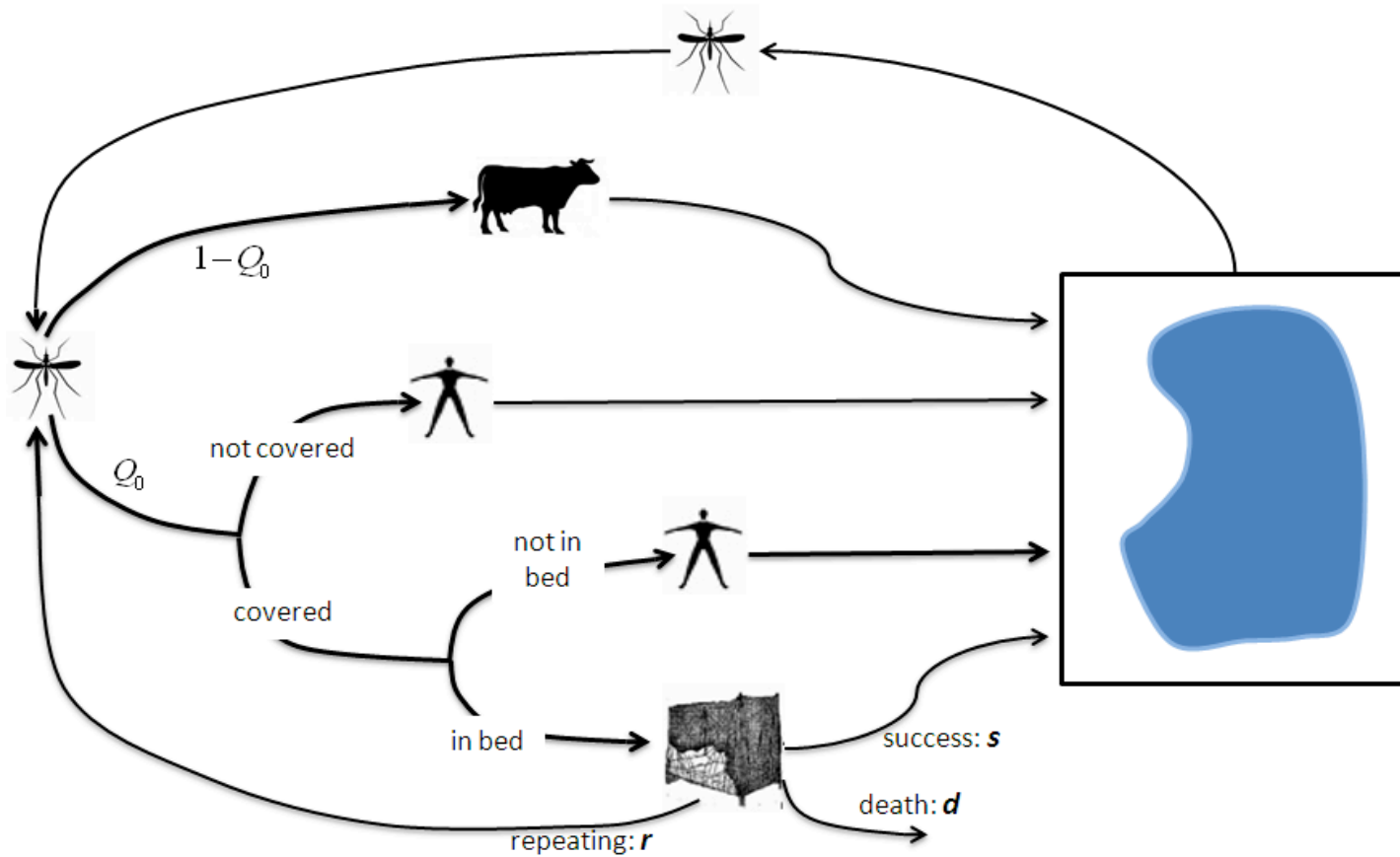
- **Altitude**

- **Population density**

- **Land-use**

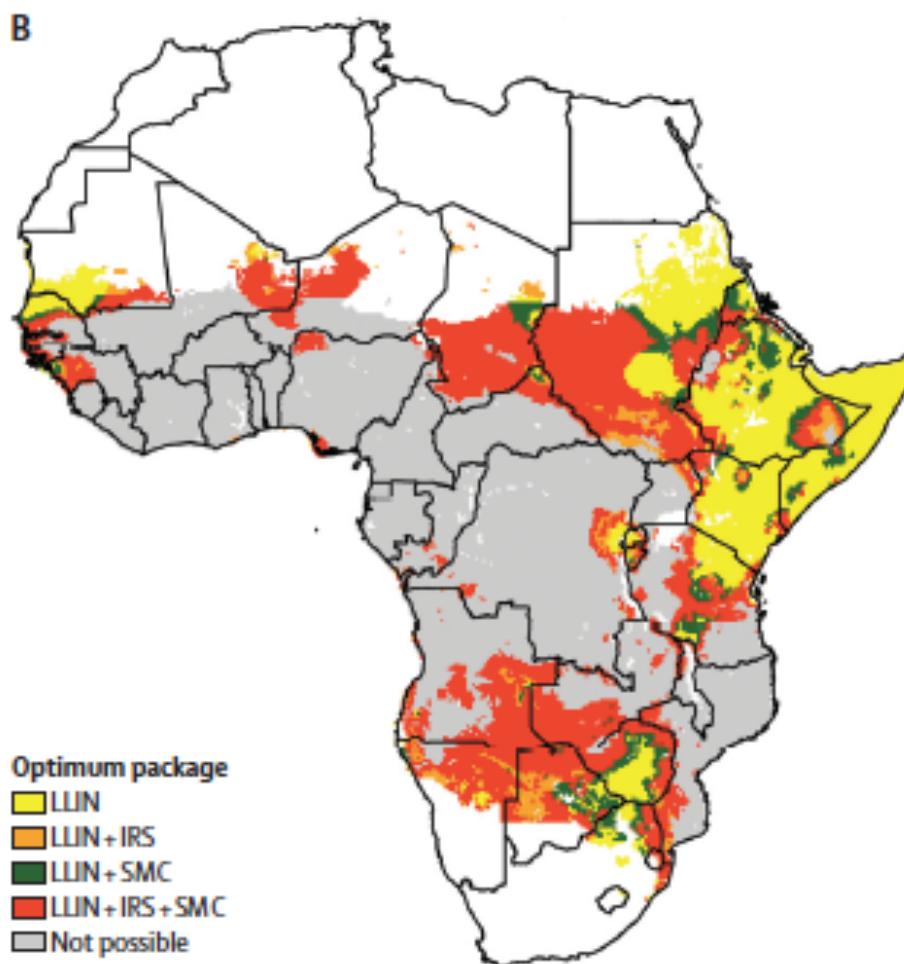


Vector intervention model

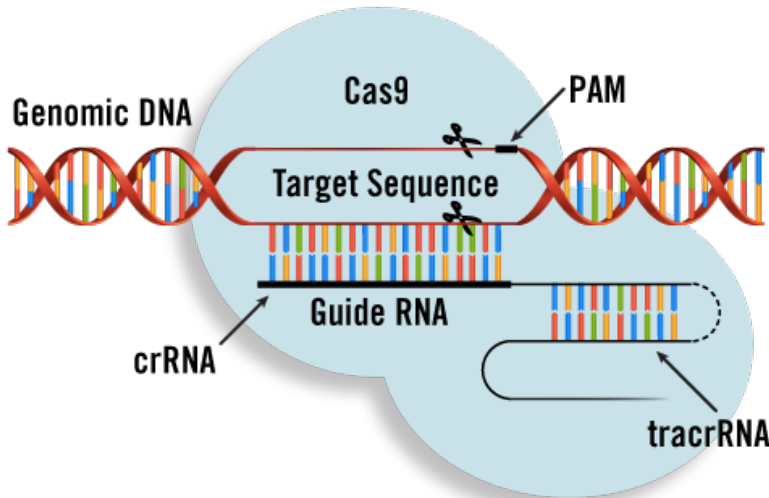
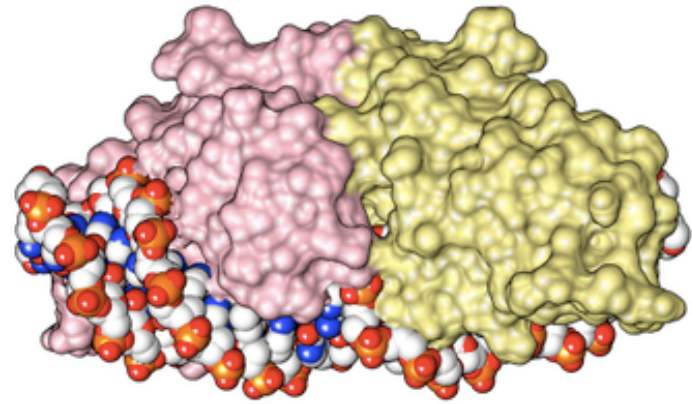
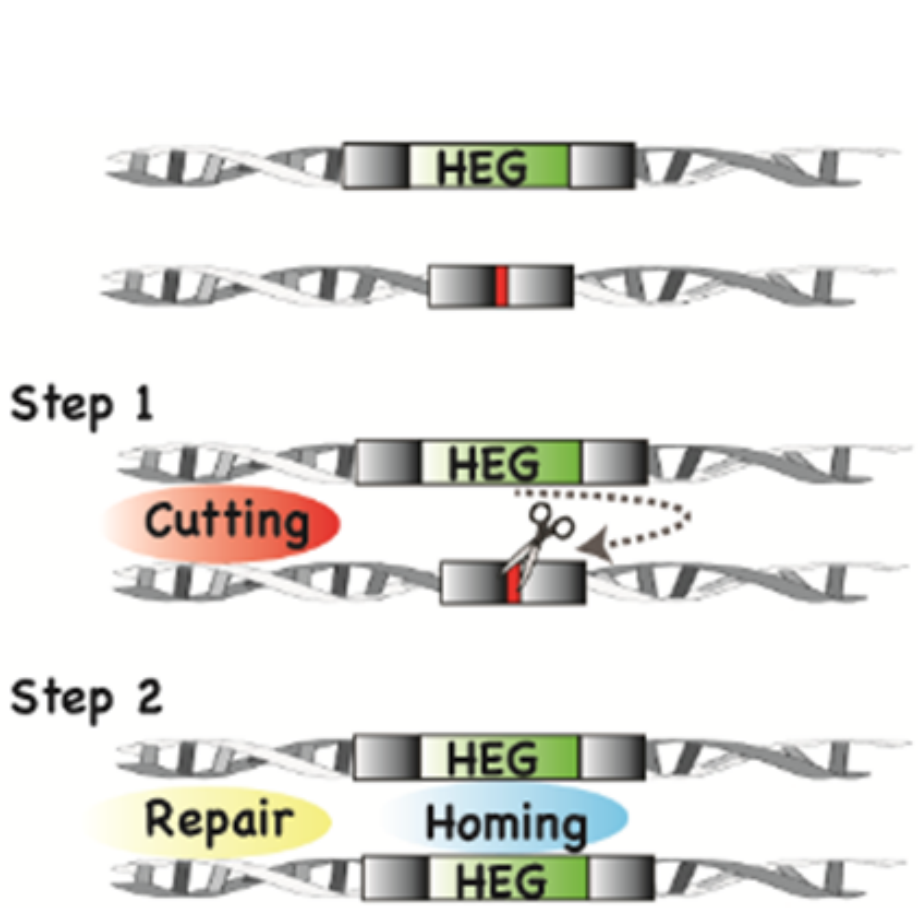


Estimating the most efficient allocation of interventions to achieve reductions in *Plasmodium falciparum* malaria burden and transmission in Africa: a modelling study

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



CRISPR/Cas9 & homing-based gene drive systems



Recent progress in engineering CRISPR/Cas9-based homing gene drive systems

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

Valentino M. Gantz* and Ethan Bier*

The logo for Scienceexpress, featuring the word "Science" in a bold, sans-serif font and "express" in a lighter, italicized sans-serif font, both in white against a black background.The logo for PNAS (Proceedings of the National Academy of Sciences), consisting of the letters "PNAS" in white, stacked vertically on a blue rectangular background.

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

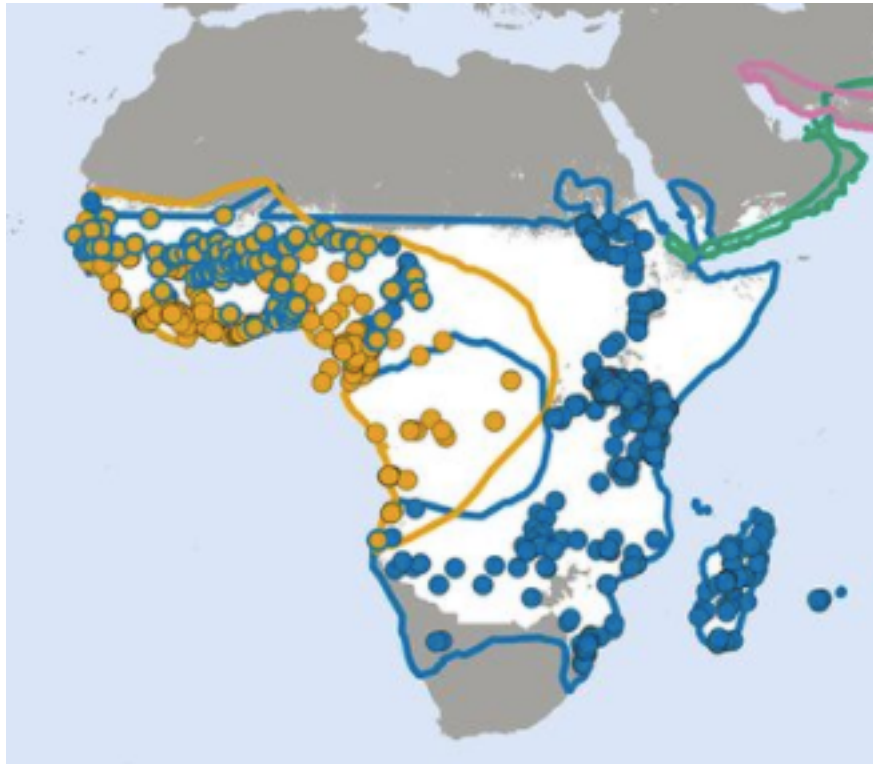
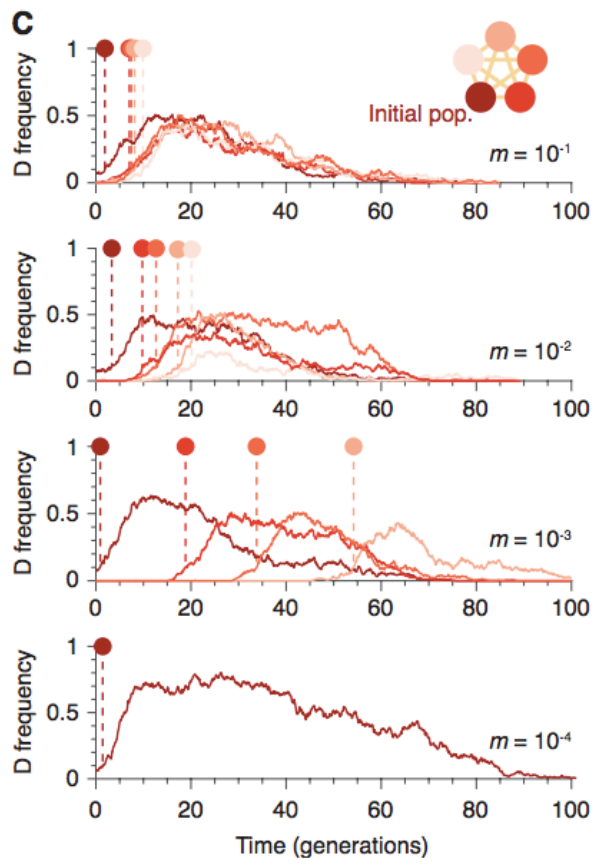
nature
biotechnology

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

'Gene Drives' Are Too Risky for Field Trials, Scientists Say



Carl Zimmer
MATTER NOV. 16, 2017



- Killeen GF, Kiware SS, Okumu FO, Sinka ME *et al.* (2017) *BMJ Global Health* 2: e000198.
- Noble C, Adlam B, Church GM, Esvelt KM *et al.* (2017) *bioRxiv* <https://doi.org/10.1101/219022>

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

John M Marshall*¹, Mahamoudou B Touré², Mohamed M Traore², 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

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

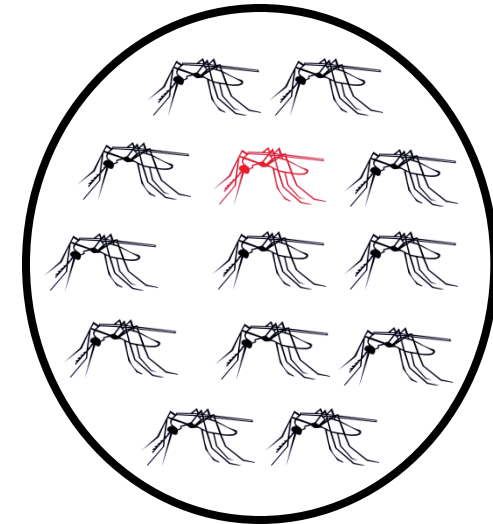
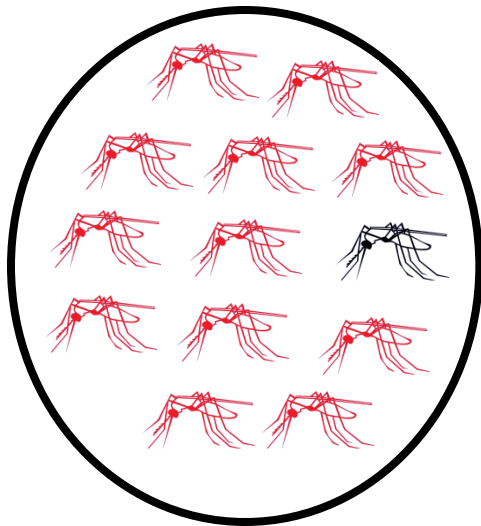


Banambani, Mali

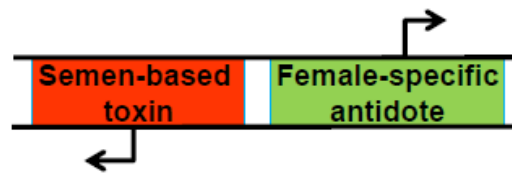
7 km
~1% / gen



Doneguebougou, Mali



Semele



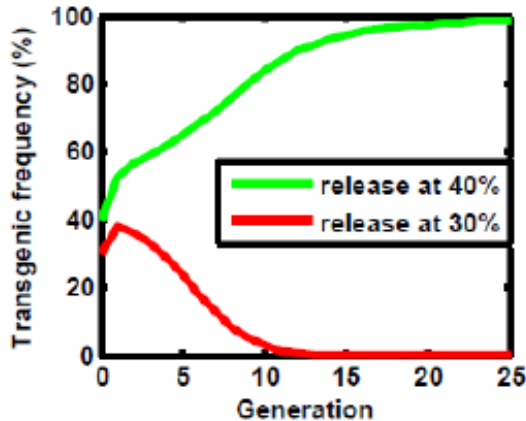
Transgenic males produce **toxic semen**

		Male			
		TT	Tt	tt	
Female	TT	TT ₁	TT ₂	Tt ₆	Tt ₅
	Tt	TT ₃	TT ₄	Tt ₈	Tt ₇
		Tt ₁₁	Tt ₈	tt ₁₄	tt ₁₃
	tt	Tt ₉	Tt ₁₀	tt ₁₂	tt

Transgenic females produce **antidote**

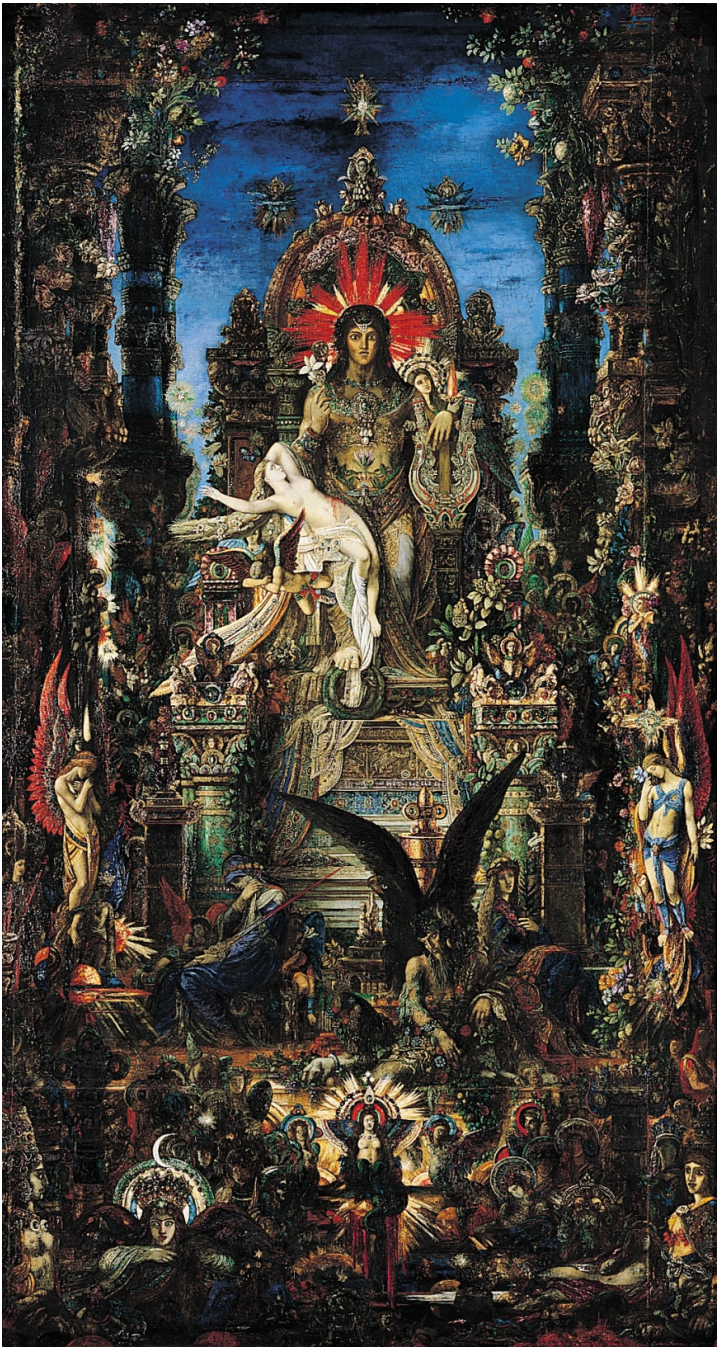
		Male			
		TT	Tt	tt	
Female	TT	TT ₁	TT ₂	Tt ₆	Tt ₅
	Tt	TT ₃	TT ₄	Tt ₈	Tt ₇
		Tt ₁₁	Tt ₈	tt ₁₄	tt ₁₃
	tt	Tt ₉	Tt ₁₀	tt ₁₂	tt

		Male			
		TT	Tt	tt	
Female	TT	TT ₁	TT ₂	Tt ₆	Tt ₅
	Tt	TT ₃	TT ₄	Tt ₈	Tt ₇
		Tt ₁₁	Tt ₈	tt ₁₄	tt ₁₃
	tt	Tt₉	Tt₁₀	tt₁₂	tt

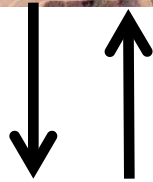


- A **release including females** results in **gene drive** (GM females are favored at high population frequencies).

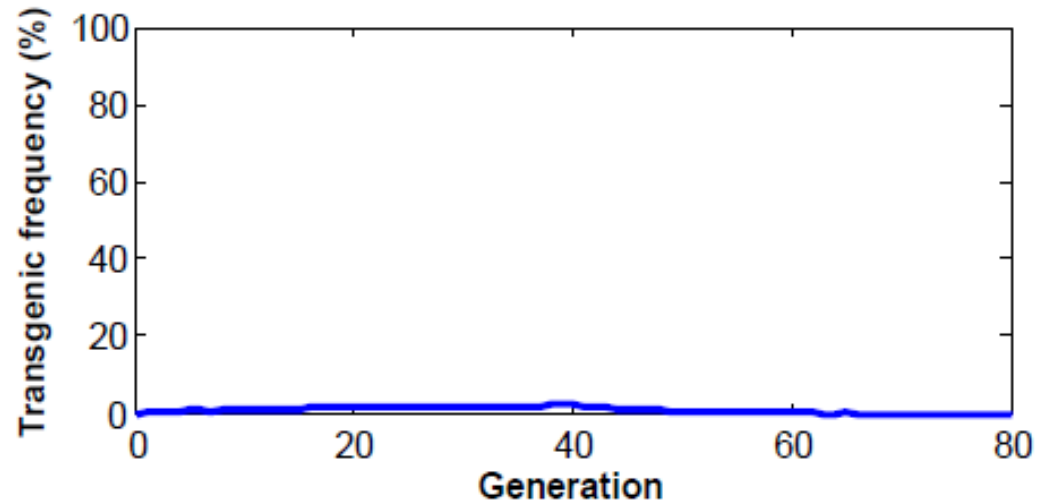
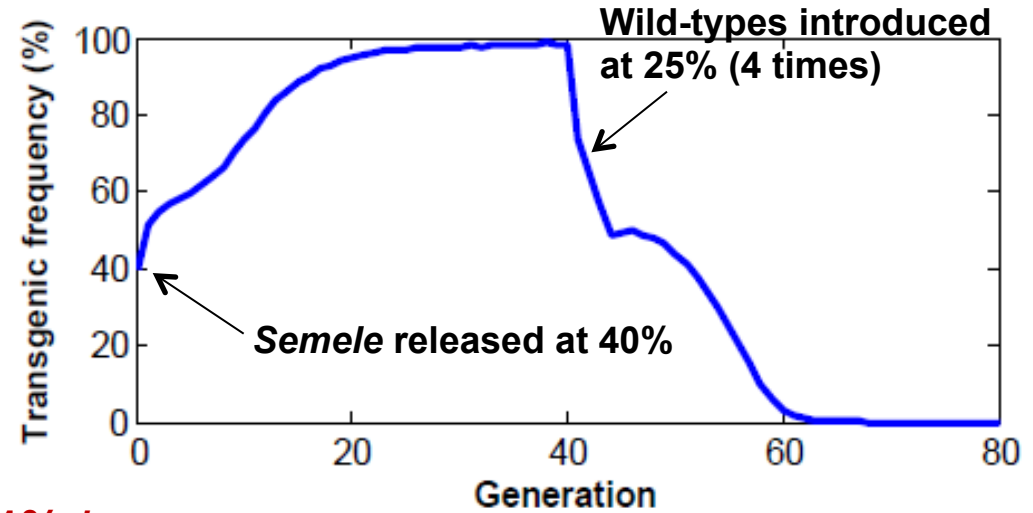
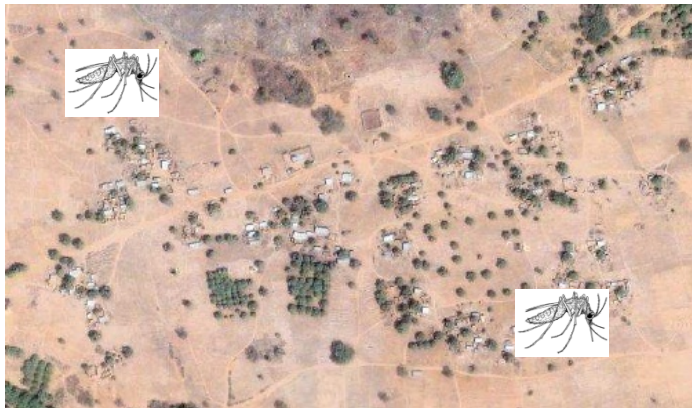
- **Release threshold = 36.4%:**



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

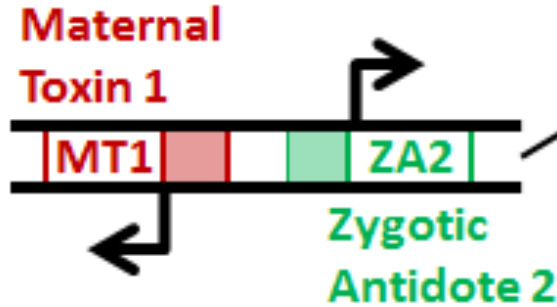


Migration rate = 1% /gen

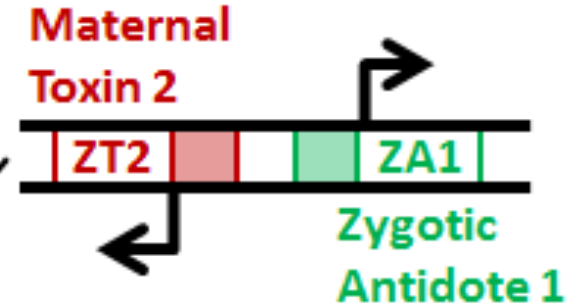


- Marshall JM, Pittman GW, Buchman A, Hay BA (2011) Genetics 187: 535-551.

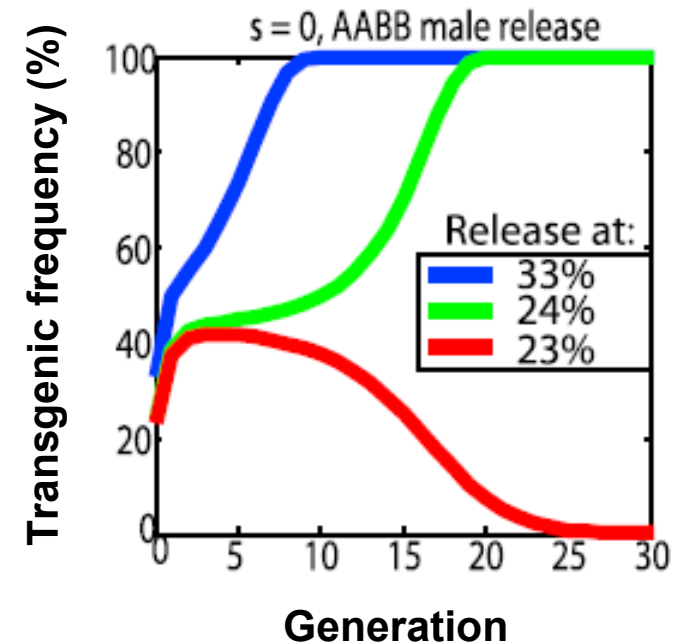
Construct A:



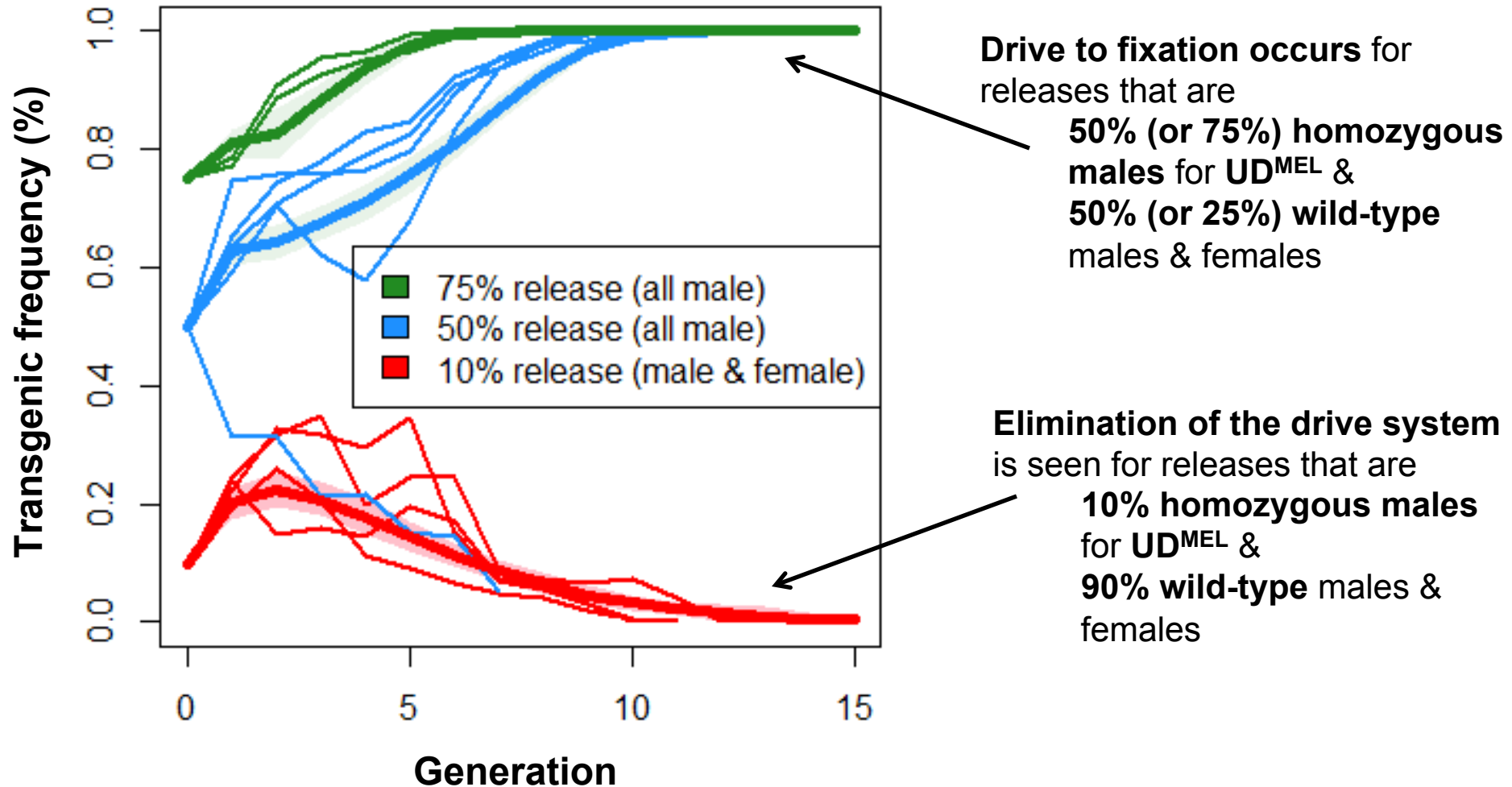
Construct B:



- 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.



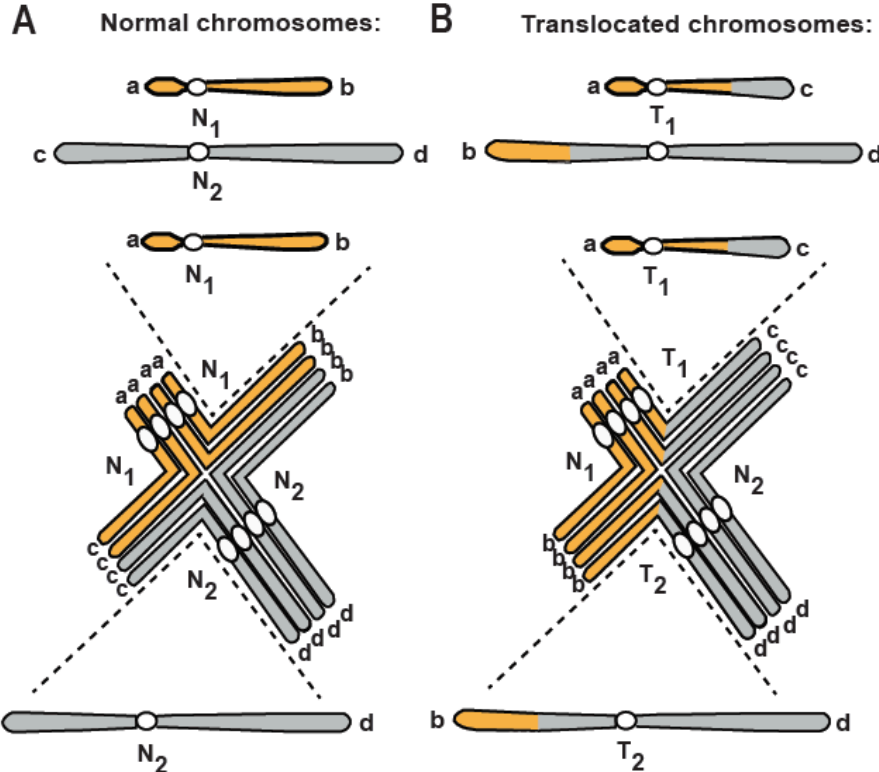
UD^{MEL} drive experiments agree with mathematical predictions & display threshold behavior



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

Translocations also display threshold dynamics

Figure 1

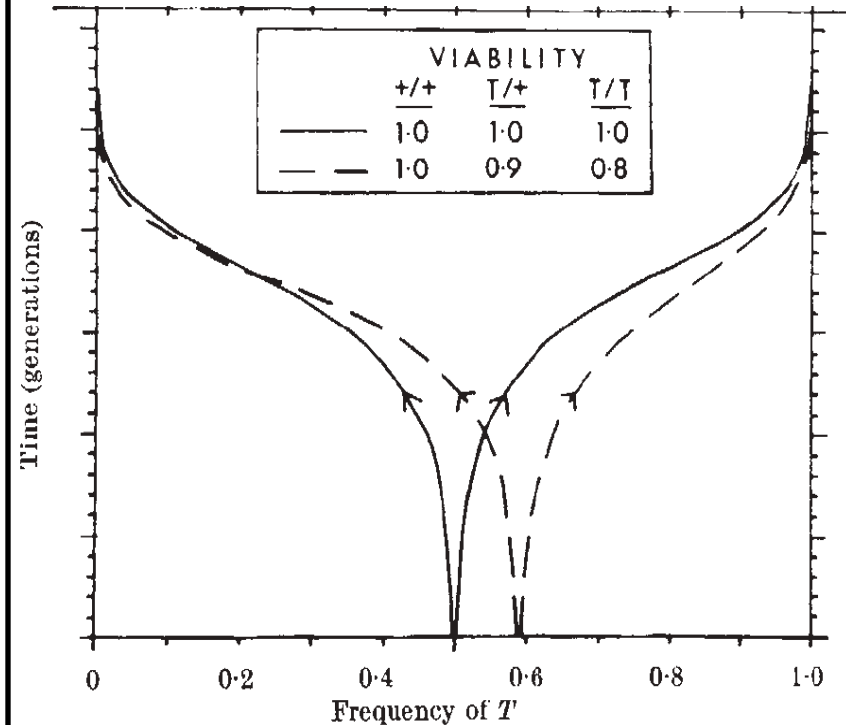


C

	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

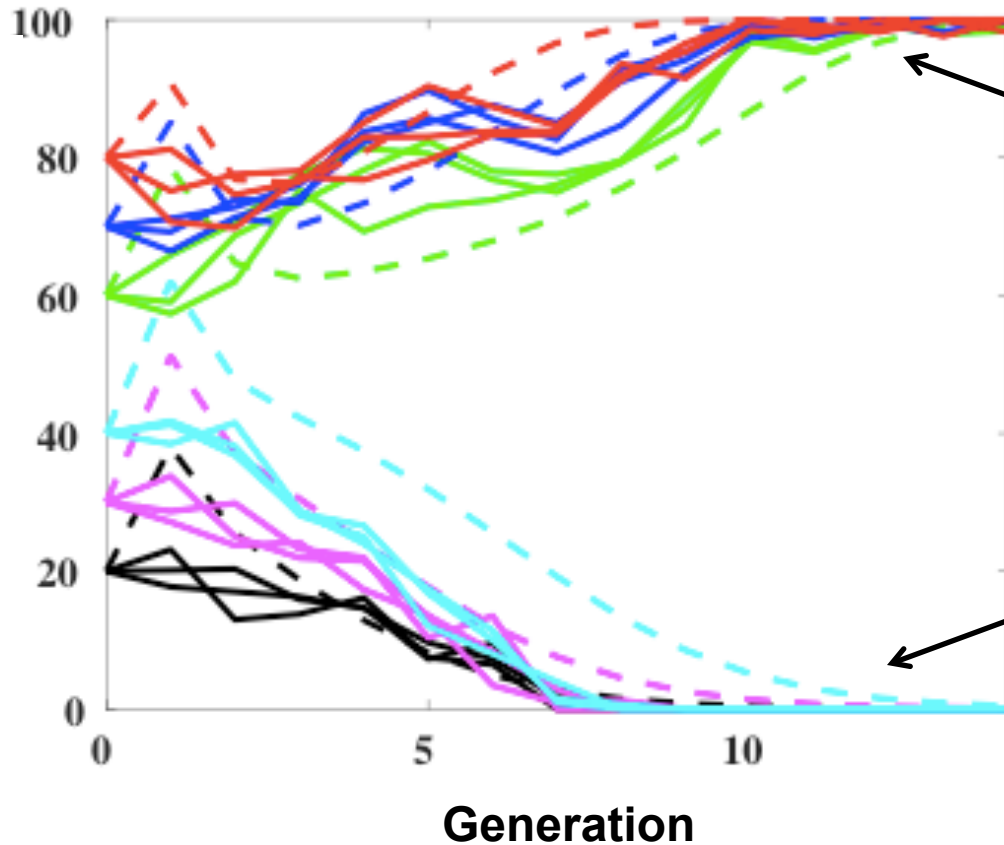
Possible Use of Translocations to fix Desirable Genes in Insect Pest Populations



- 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

Frequency translocation bearing (%)



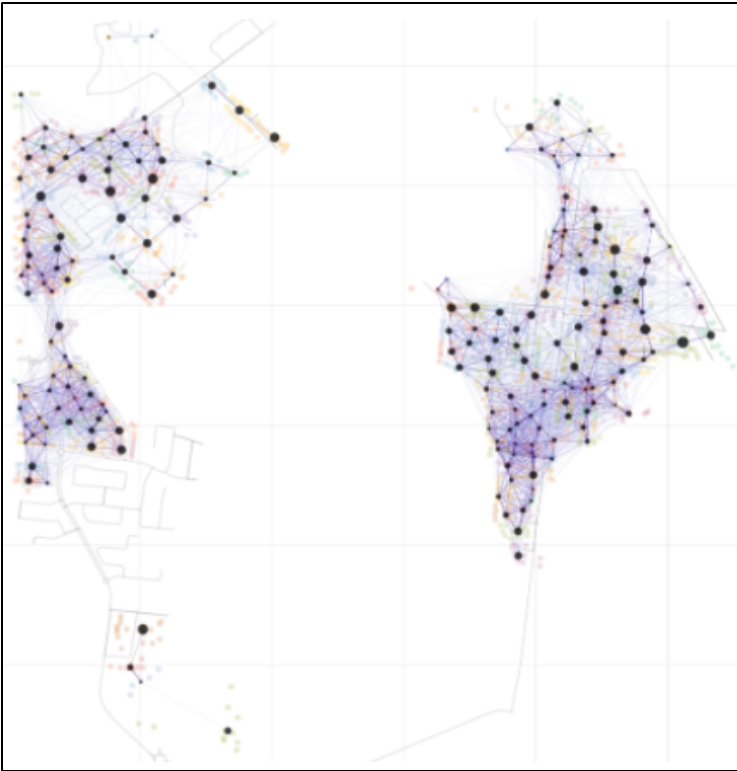
Drive to fixation occurs for releases that are **60-80% homozygous males & females** for the translocation

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>

MGDrivE modeling framework (Mosquito Gene Drive Explorer)

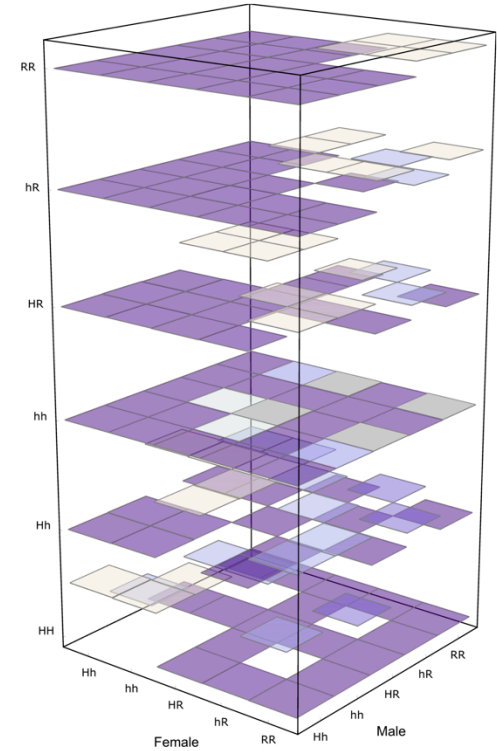


Spatial Setting

+

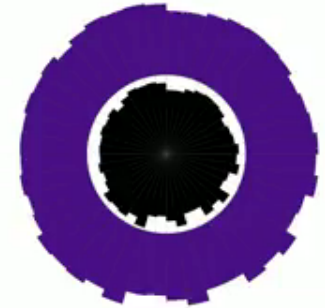
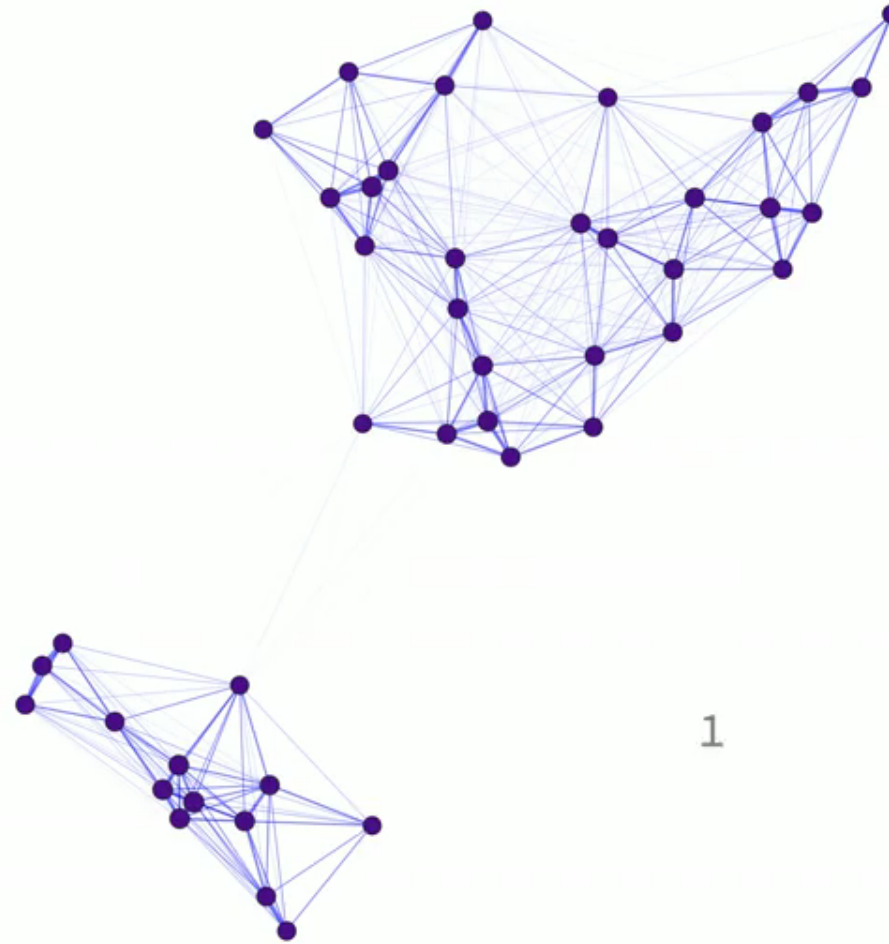
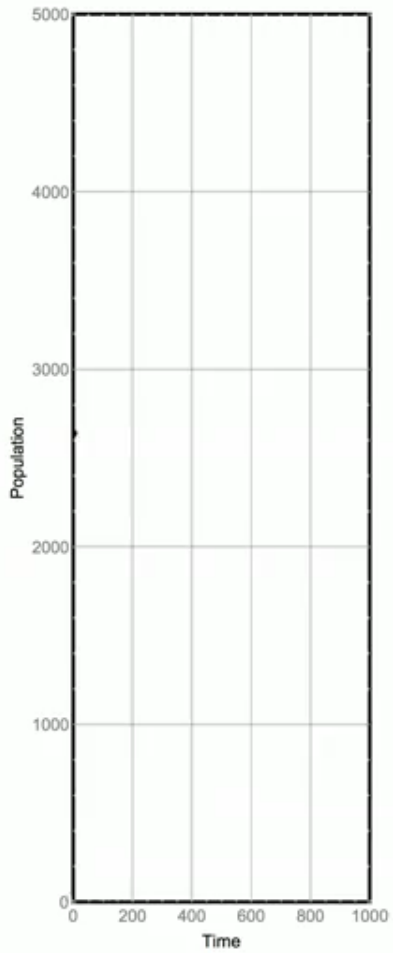


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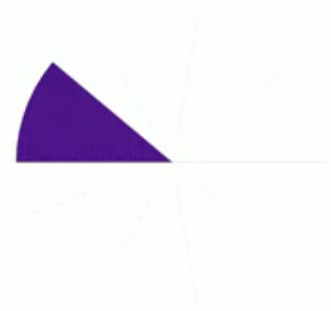


Genetic Inheritance

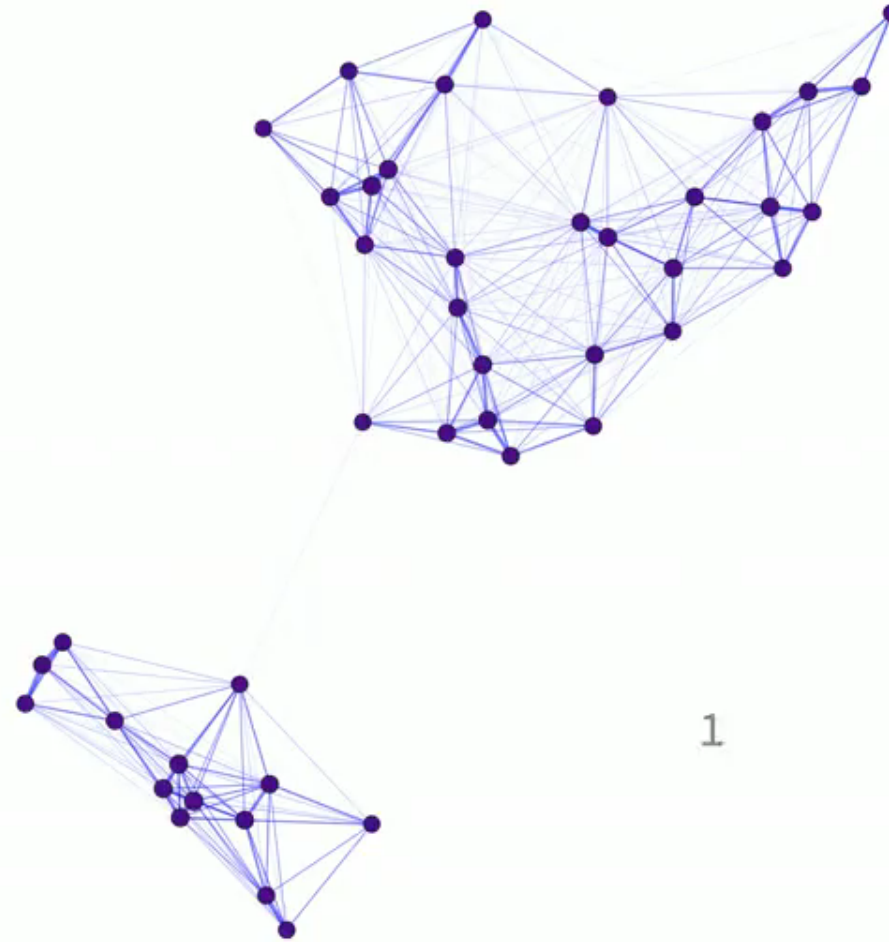
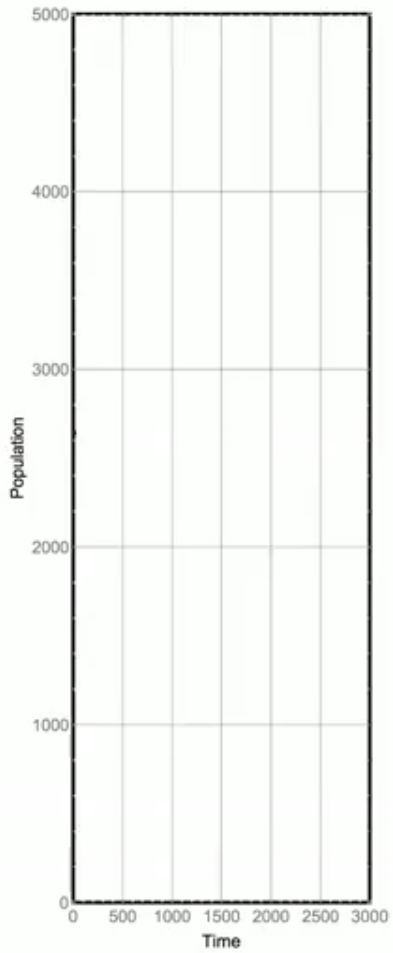
MGDrivE: Translocations with remediation



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



MGDrivE: UD^{MEL} without remediation



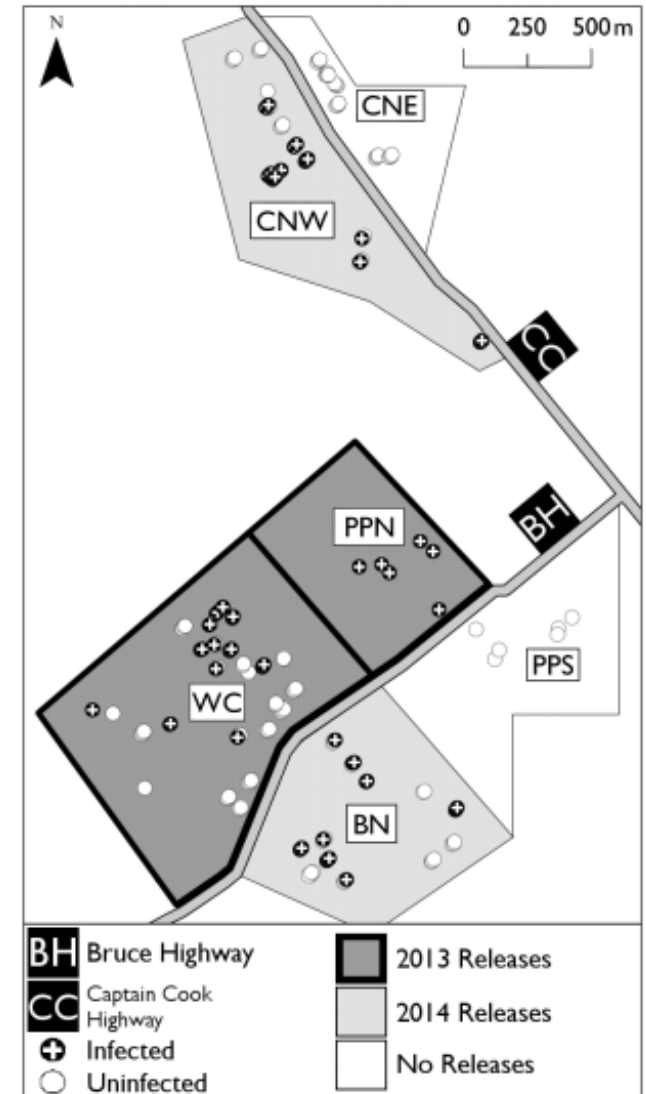
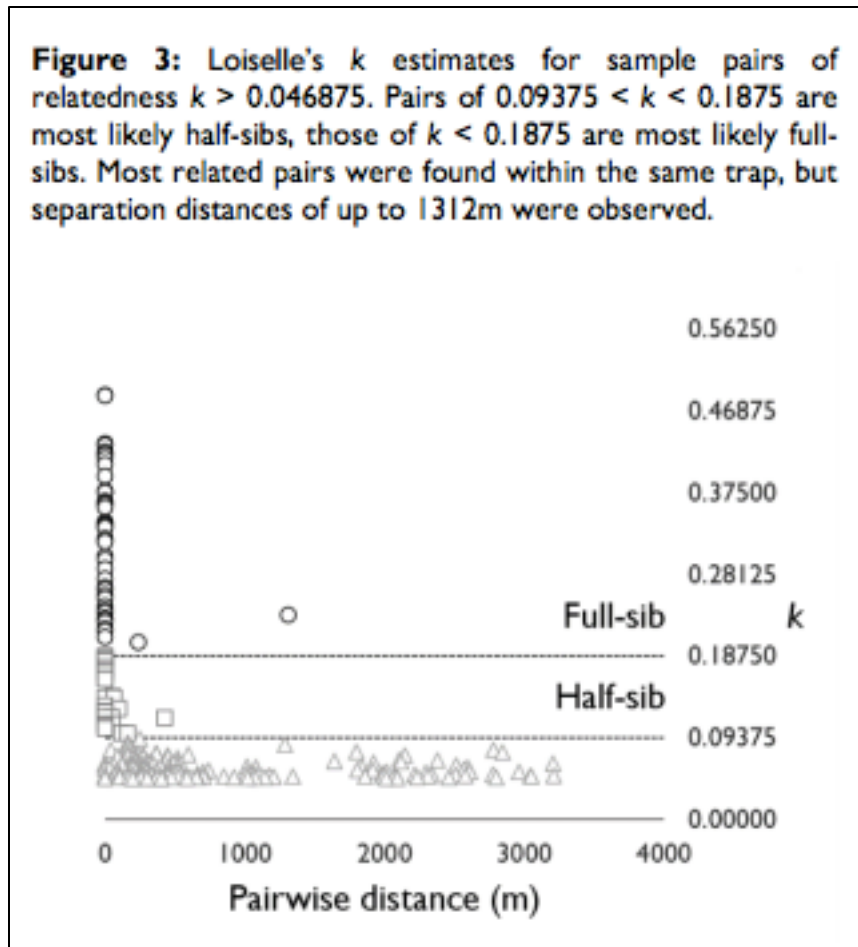
AABB	0
AABb	0
AAbb	0
AaBB	0
AaBb	0
Aabb	0
aaBB	0
aaBb	0
aabb	2640
Total	2640



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

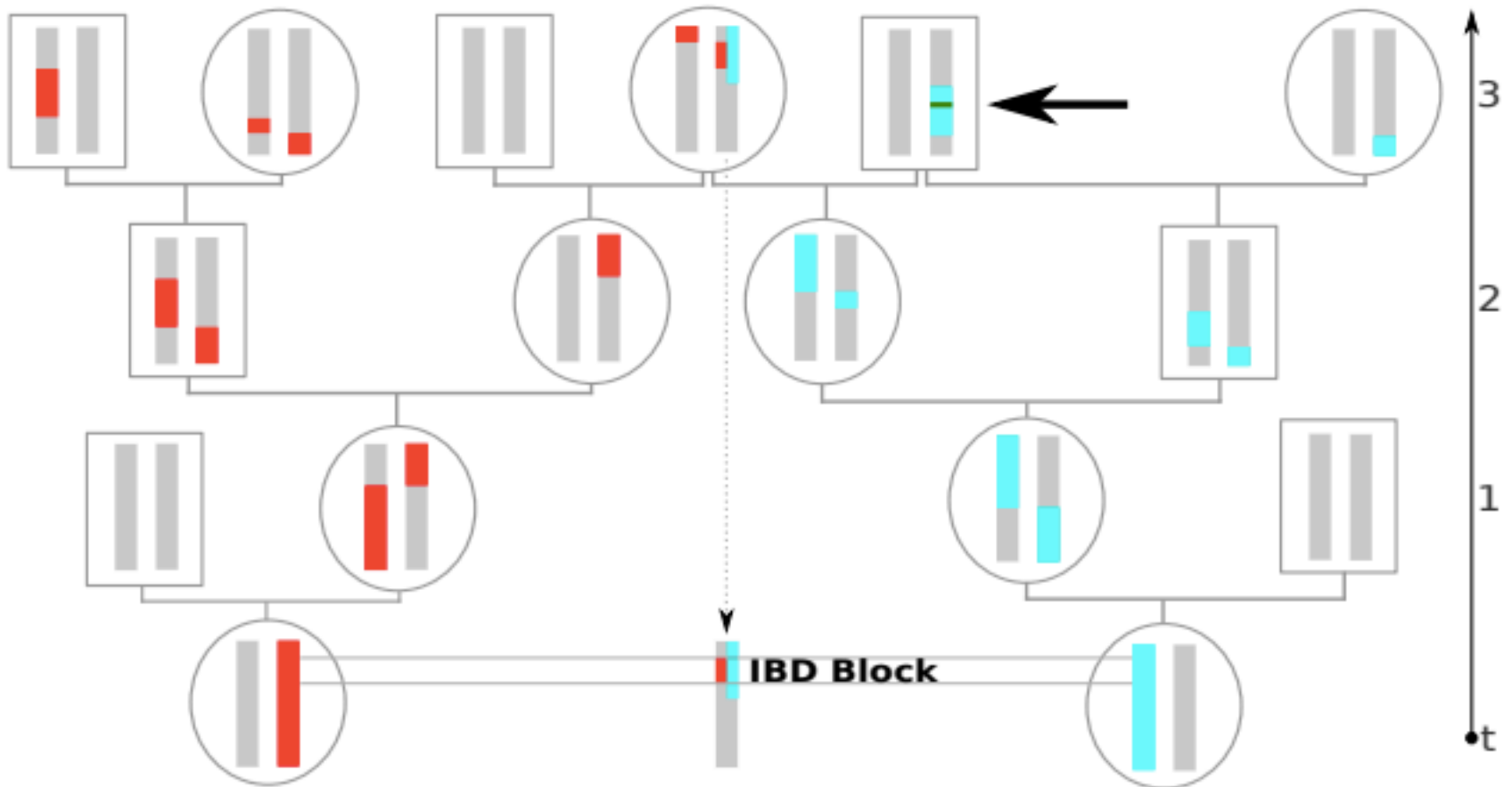
Figure 3: Loiselle's k estimates for sample pairs of relatedness $k > 0.046875$. Pairs of $0.09375 < k < 0.1875$ are most likely half-sibs, those of $k < 0.1875$ are most likely full-sibs. Most related pairs were found within the same trap, but separation distances of up to 1312m were observed.



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

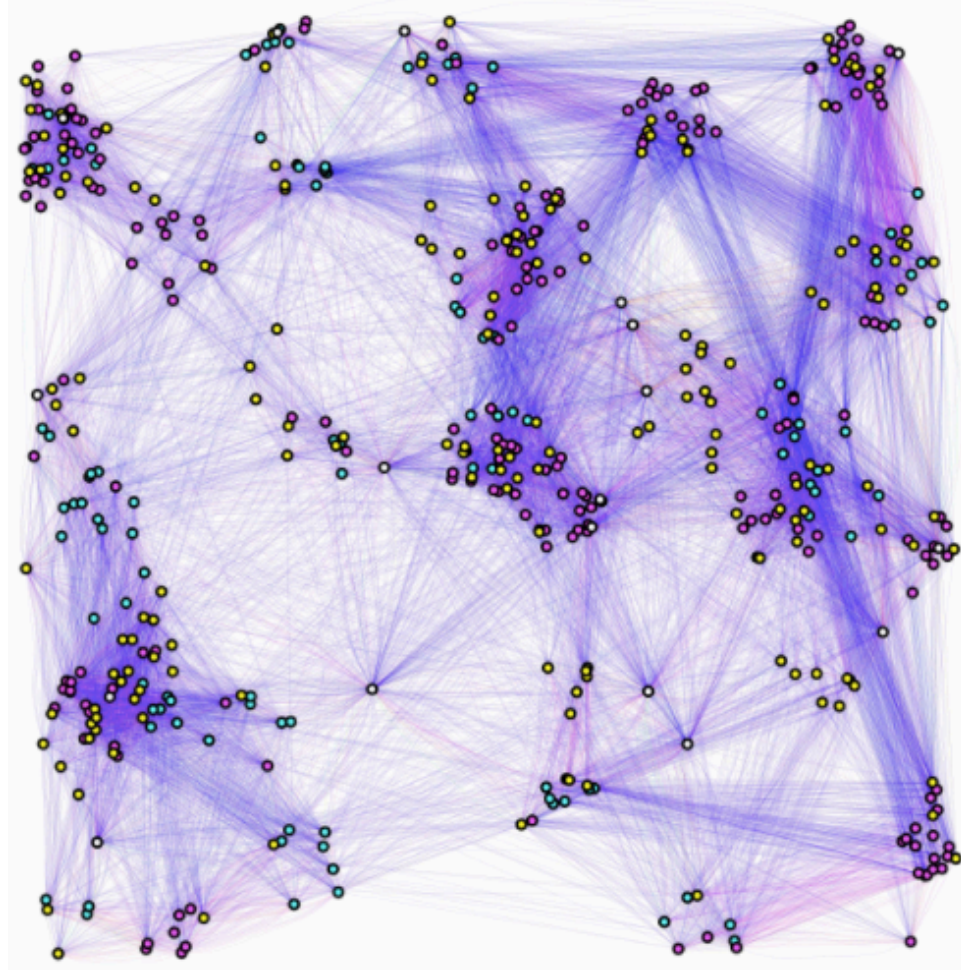
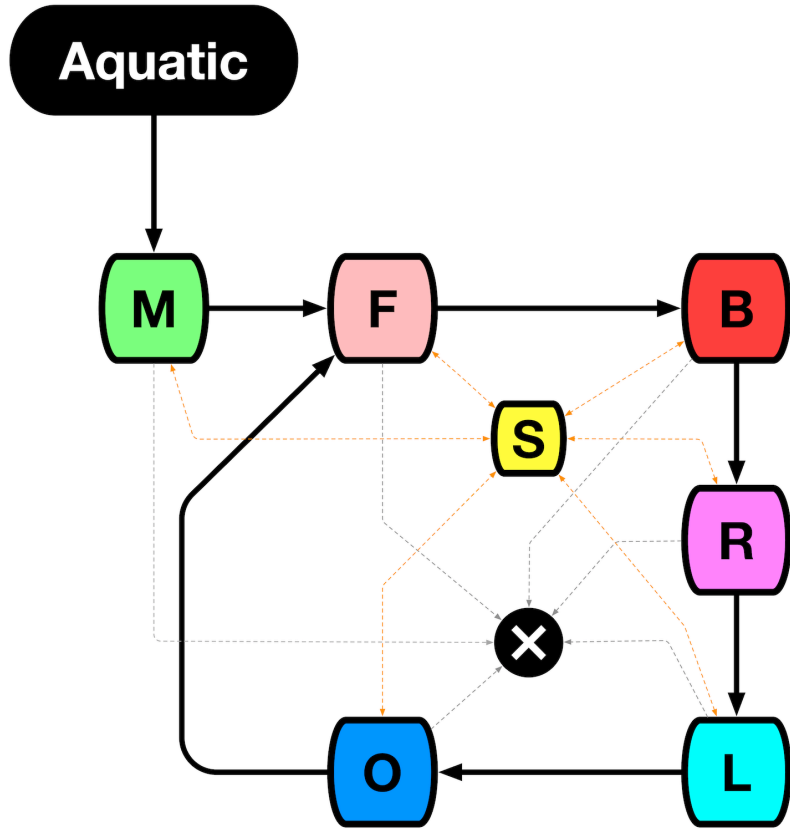
Inferring recent demography from isolation by distance of long shared sequence blocks

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

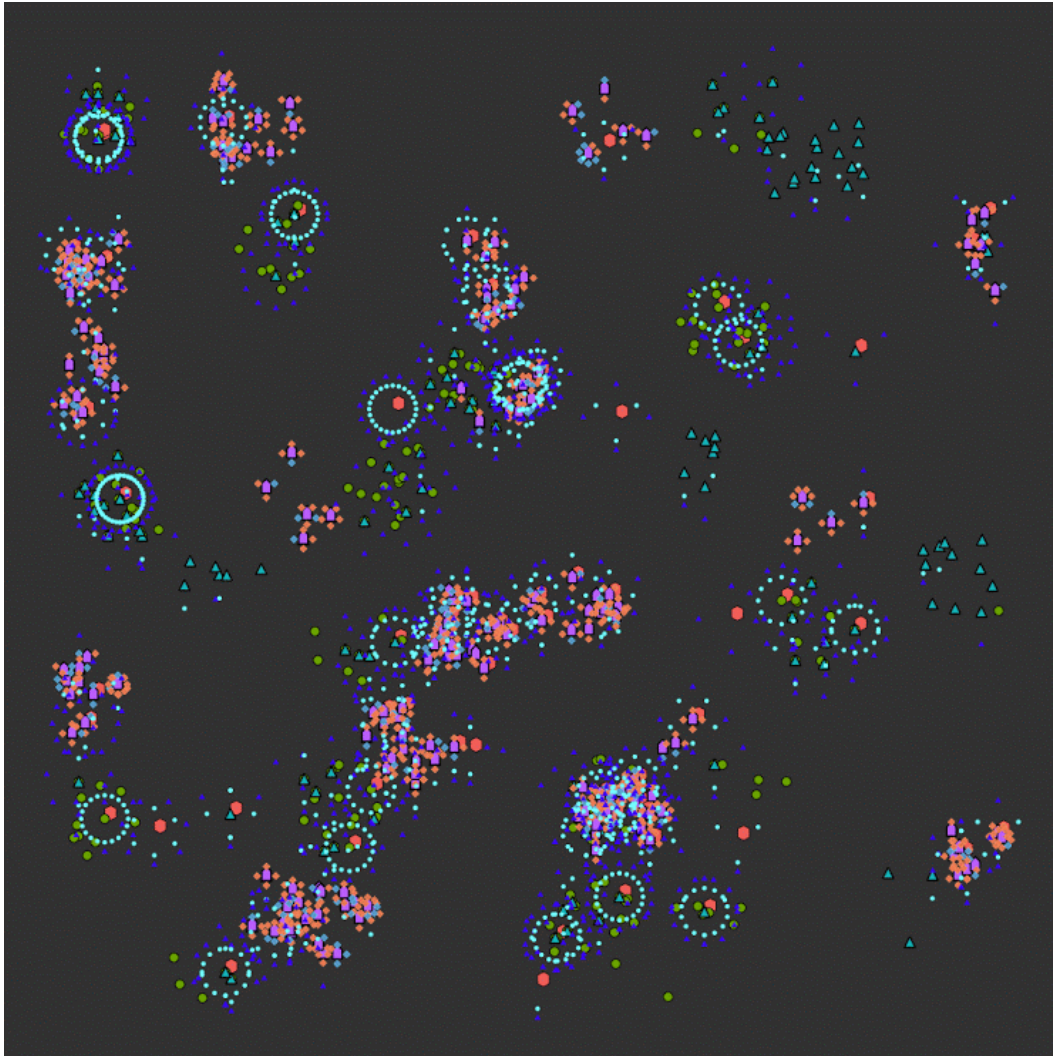


- Ringbauer H, Coop G, Barton NH (2017) Genetics doi: 10.1534/genetics.116.196220.

MASH modeling framework (Modular Analysis & Simulation for human Health)



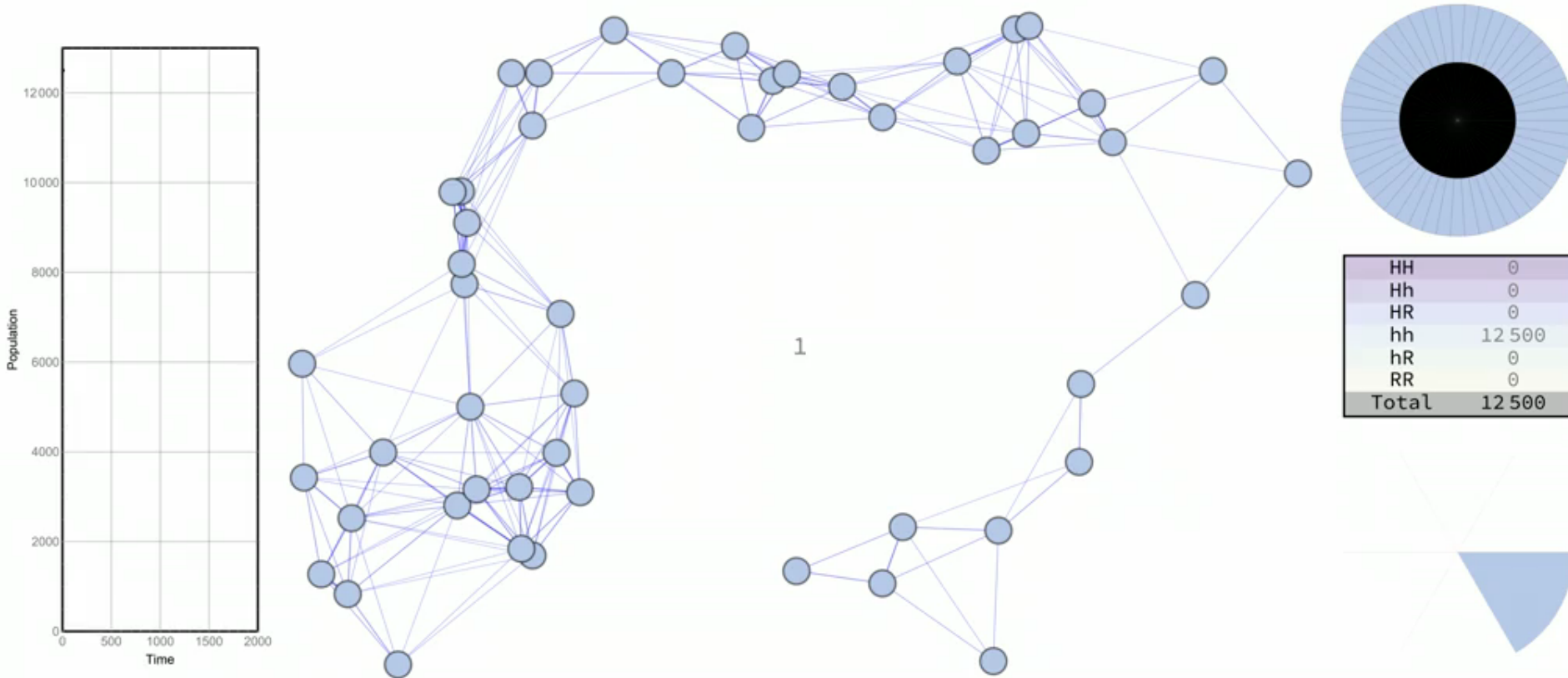
MASH: Mosquito movement patterns



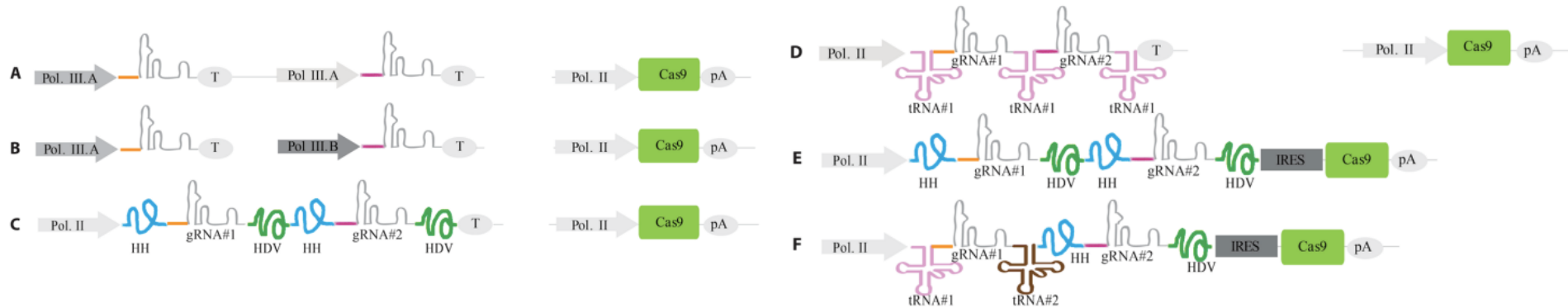
- Moving pink triangles are female mosquitoes
- Moving blue triangles are male mosquitoes
- Lines represent the trace of their movement
- Purple pentagons are blood-feeding sites
- Green circles are sugar-feeding sites
- Blue triangles are breeding sites/aquatic habitats
- Salmon hexagons are swarming/mating sites
- Blue/salmon diamonds around houses are susceptible and infectious humans

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

MGDrive



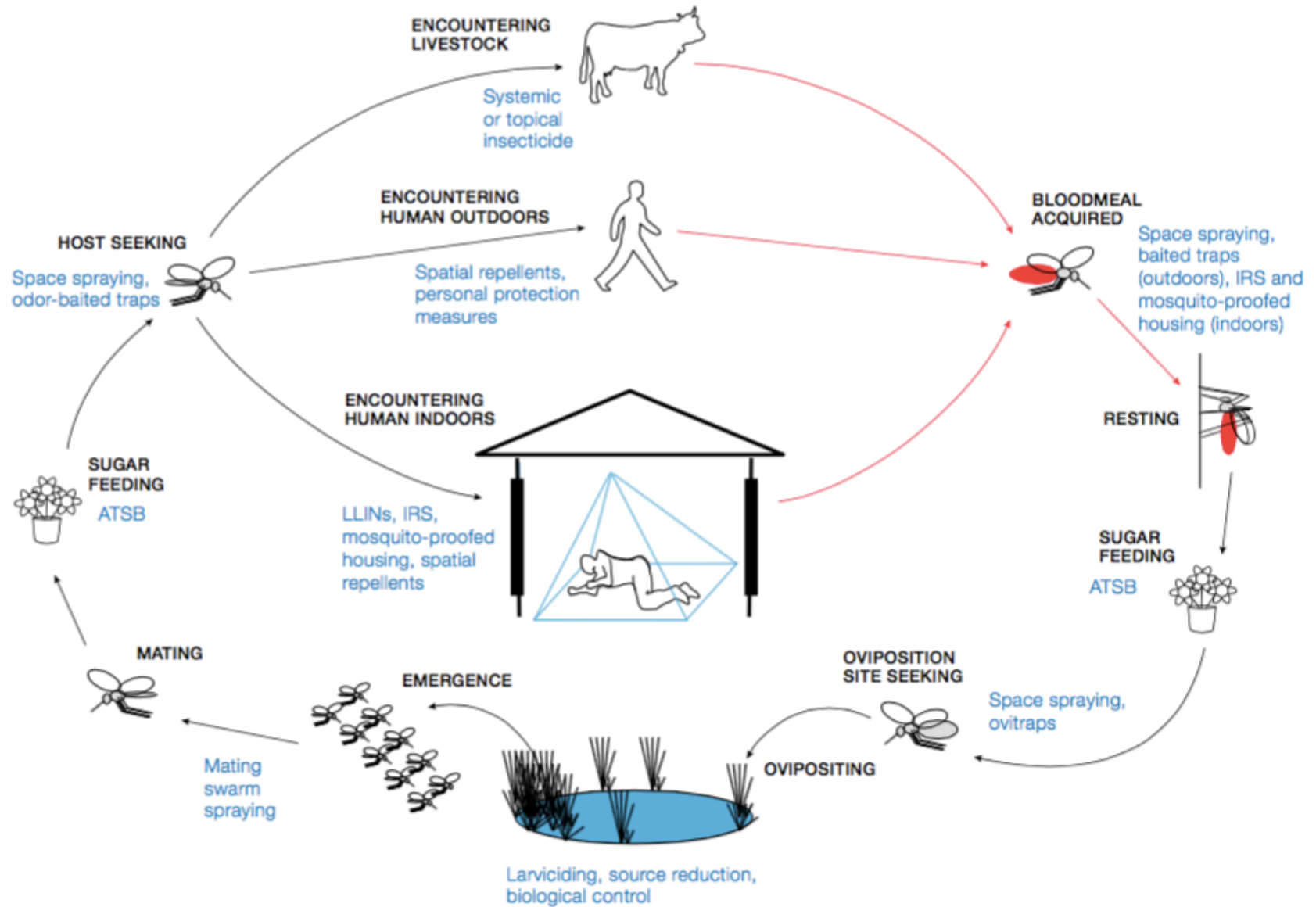
Multiplexing gRNAs may provide part of the solution to enable elimination of large populations



Multiplex number:	Resistance allele generation rate:	Population size capable of eliminating:
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

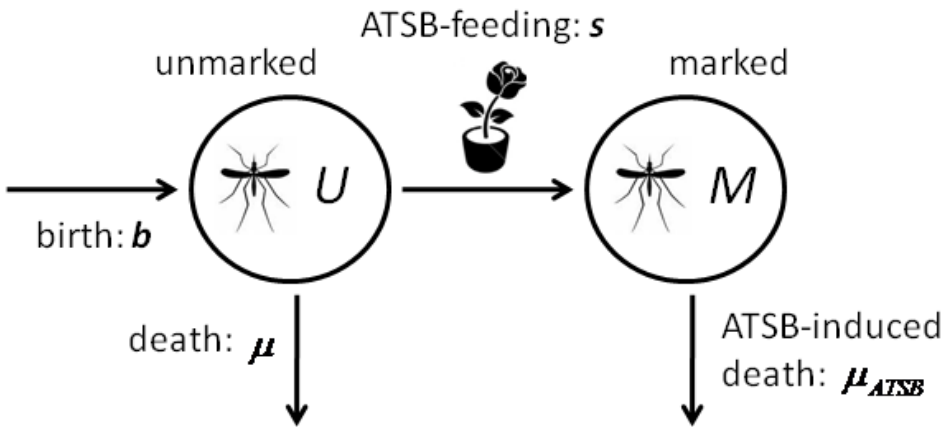
- Marshall JM, Buchman A, Sanchez HM *et al.* (2017) Nature Sci Rep 7: 3776

Vector Control Optimization Model (VCOM)



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

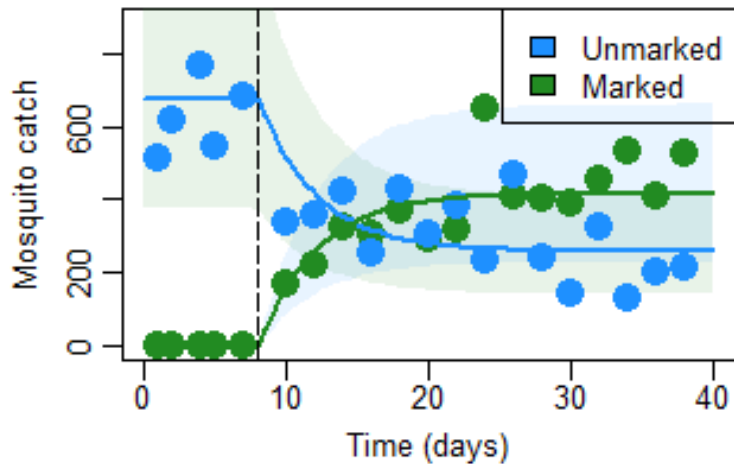
Inferring parameter values from experimental data



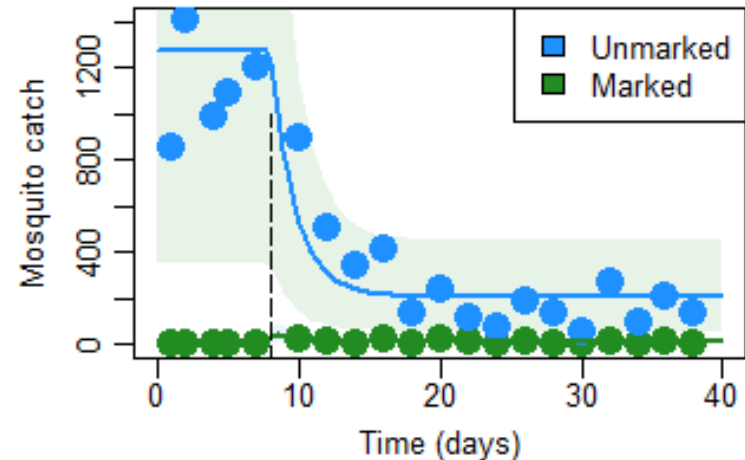
Rate of feeding on ATSB-sprayed plants: 0.5 / day
(CrI: 0.27-0.97)

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, Beier JC (2013) Malaria J 12: 291

Vector Control Optimization Model (VCOM) GUI

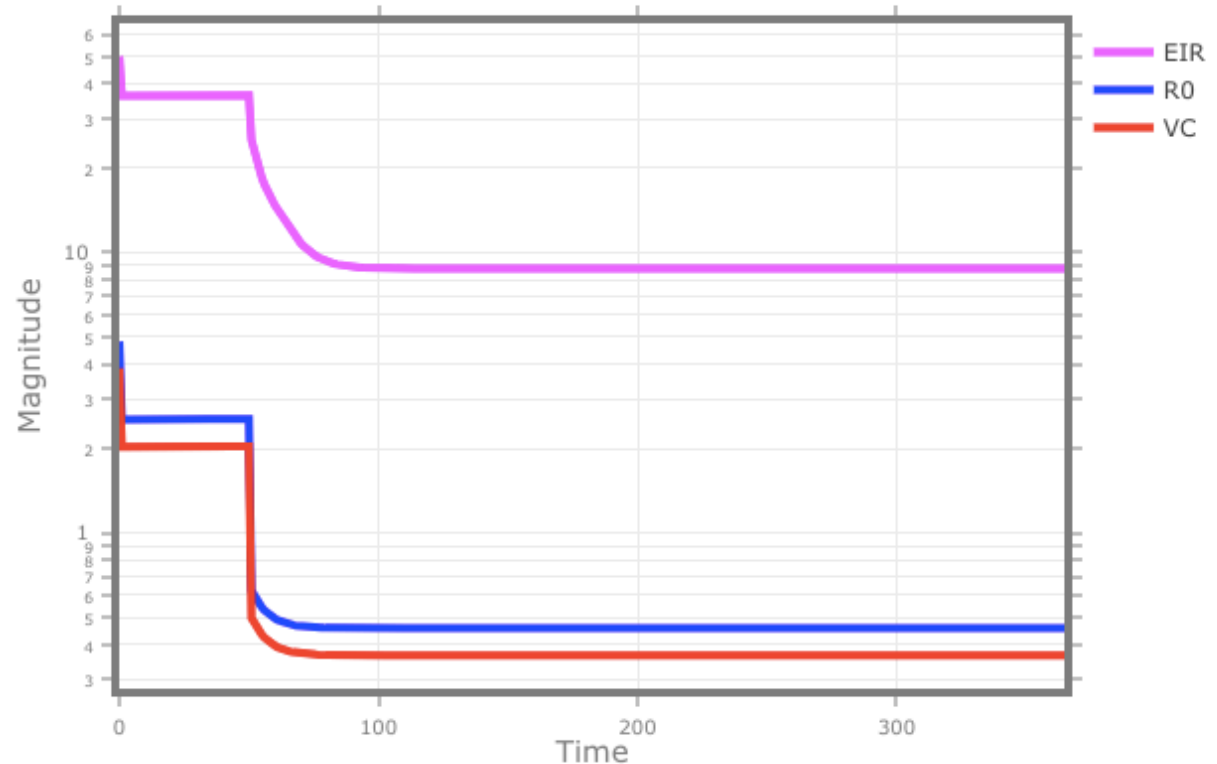
VCOM: Simple

Vector Control Optimization Model

Home

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 optional) Download a PDF report of the plots.
- (6) Setup the desired interventions and repeat step 4 as required.
- (7) Eliminate malaria!

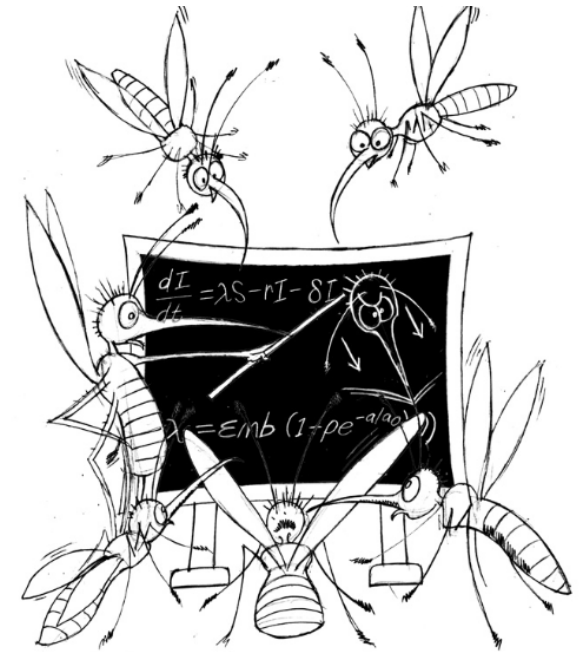


- Kiware SS, Chitnis C, Tatarsky A, Wu SL, Sanchez HM *et al.* (2017) PLoS ONE In press

Conclusion

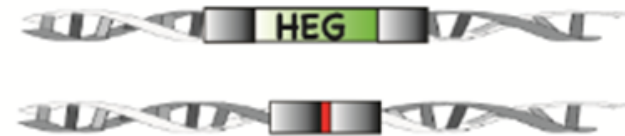
Mathematical models of malaria & dengue:

- The Ross-Macdonald model highlights the importance of mosquito control.
- Dengue outbreaks are likely to be more severe due to frequent importation leading to earlier outbreaks.
- Malaria is very difficult to eliminate with currently-available tools due to hotspots of transmission.



Gene drive & other novel tools:

- Homing-based systems hold promise, but are highly invasive.
- Threshold-dependent systems may allow confined field trials to be conducted.
- Multiplexing may provide part of the solution to achieving population suppression on a wide scale.
- A wide range of novel tools are now becoming available to control mosquito-borne diseases.



Step 1



Step 2



Acknowledgements

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- James Lab @ UC Irvine
- Bier Lab @ UCSD
- Hay Lab @ Caltech
- Lanzaro Lab @ UC Davis
- Malaria Elimination Initiative @ UCSF
- Prof David Smith @ IHME, UW
- School of Public Health @ UC Berkeley

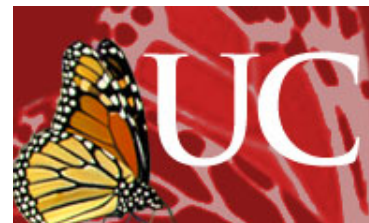
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