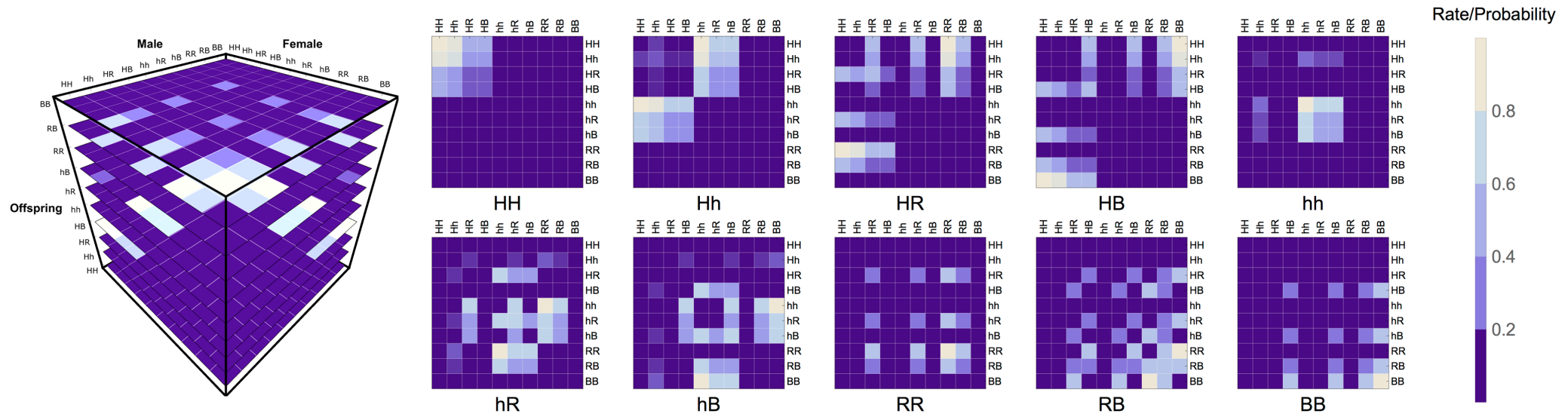
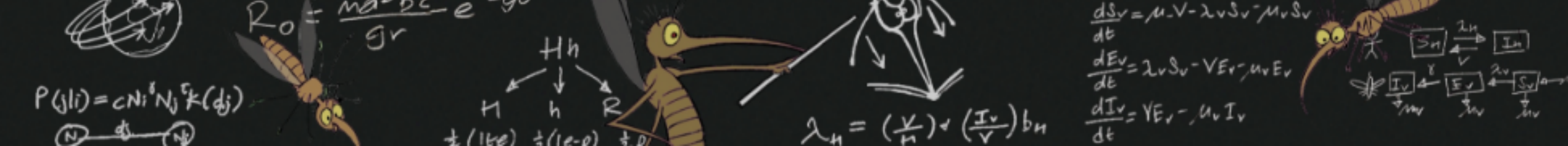


MGDrivE: A simulation framework for gene drive in spatially-explicit mosquito populations and its application to threshold-dependent systems



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Sean Wu



Jared Bennett



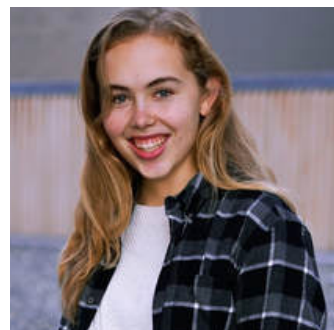
Partow Imani



Francois Rerolle



Tomas Leon



Sarafina Smith



Biyonka Liang

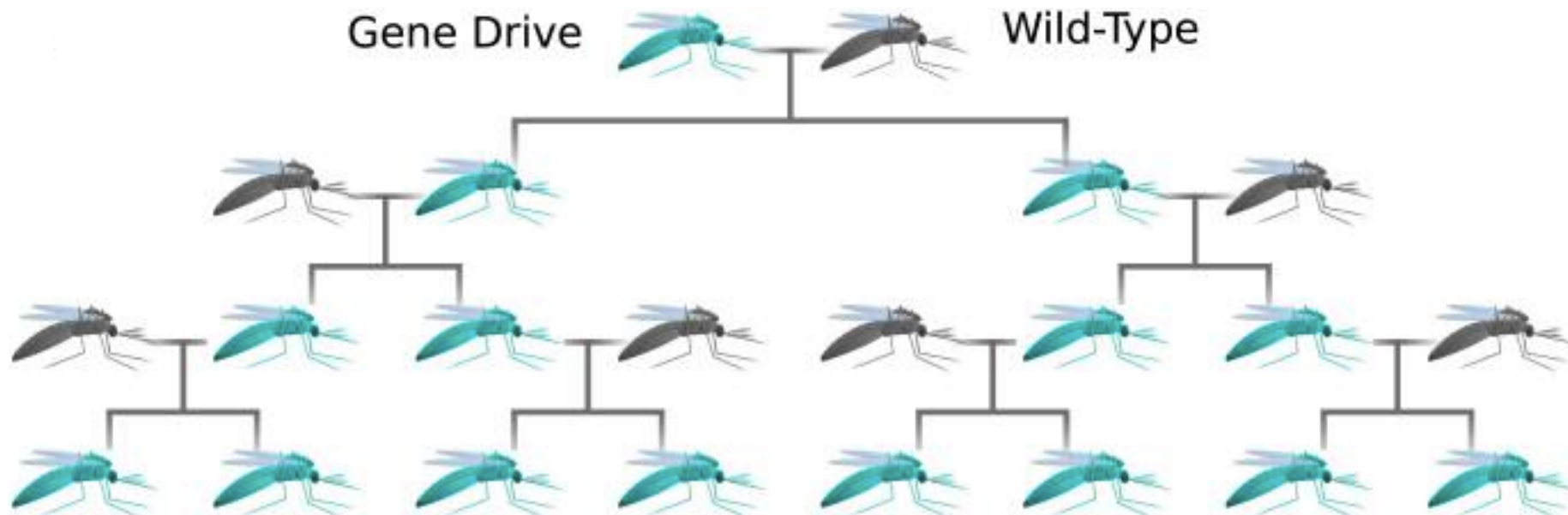


Yi Li

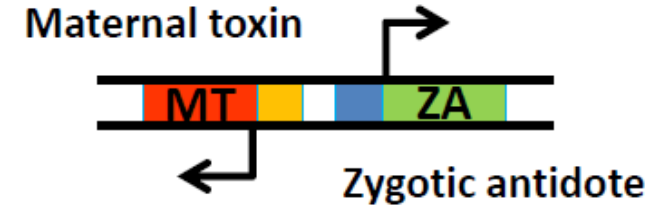
Homing-based CRISPR-mediated gene drive



Construct cuts recognition site and serves as template for repair



Medea & toxin-antidote based gene drive



Transgenic mothers produce toxin

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

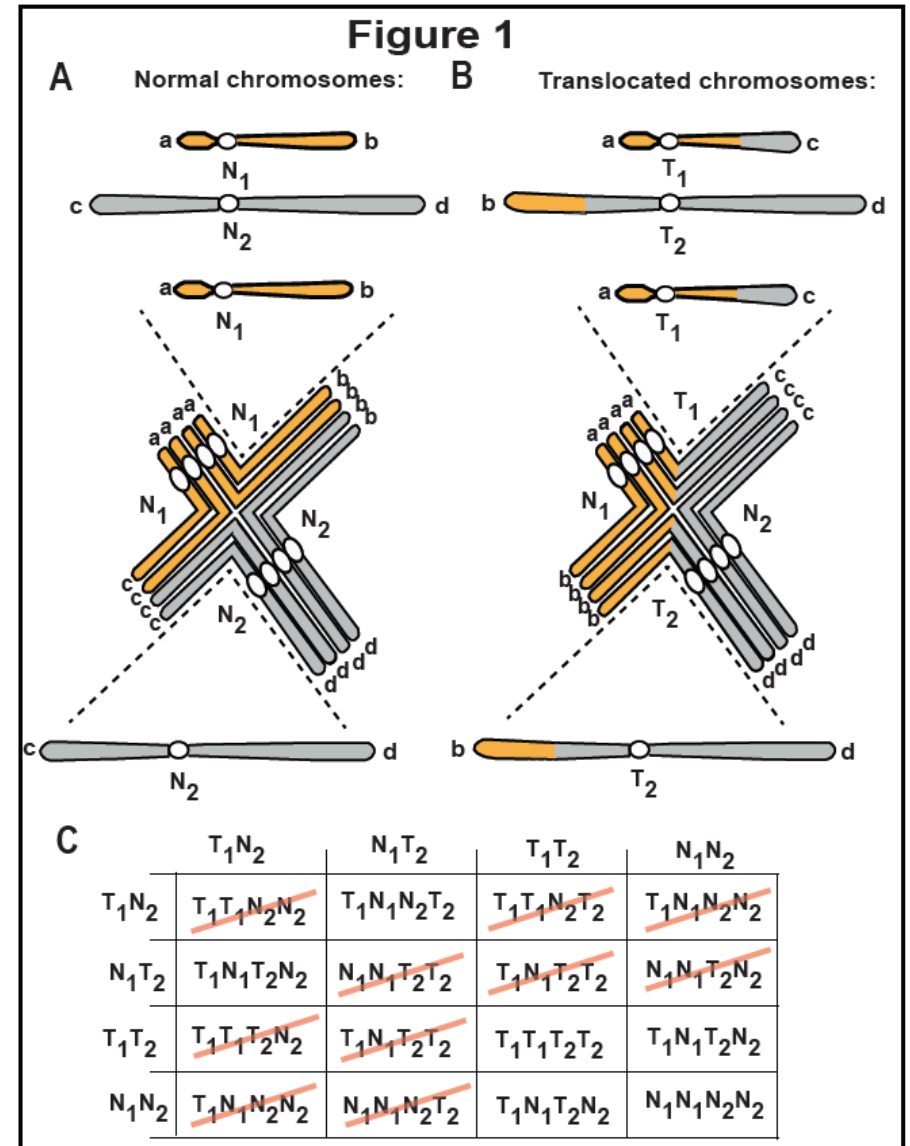
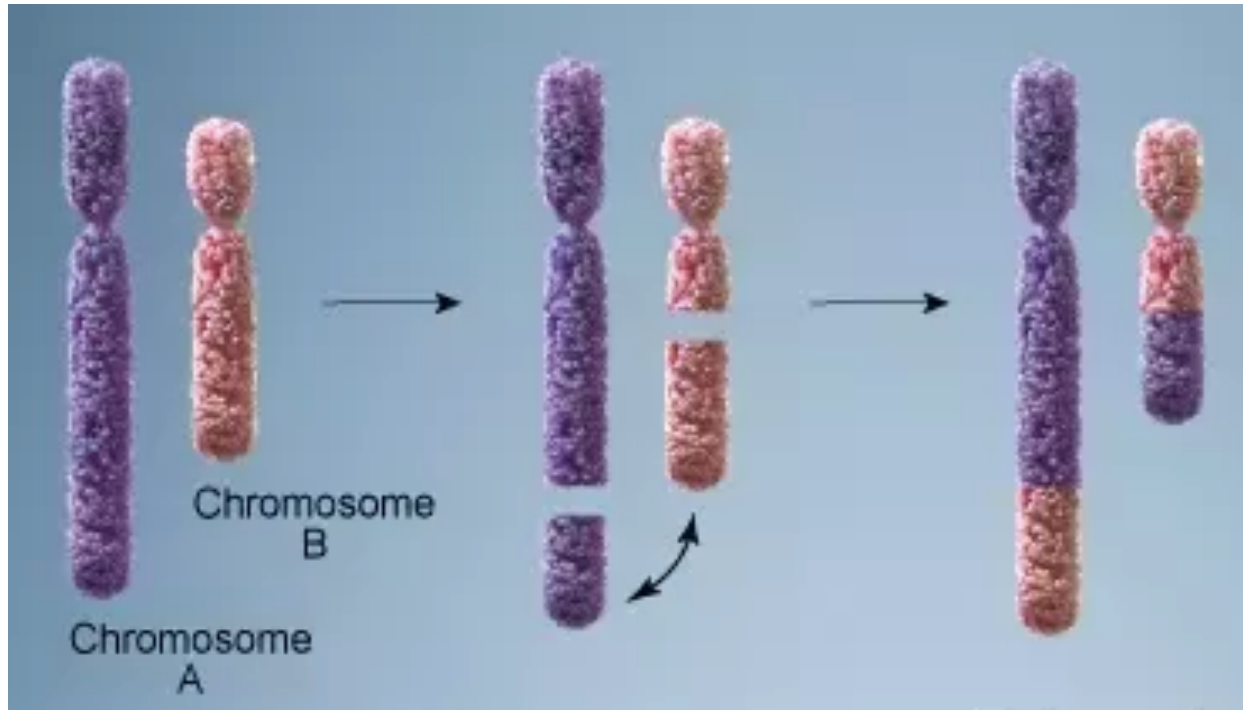
Transgenic offspring produce antidote

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

		Male				
		TT	Tt	Tt	tt	
Female	TT	TT ₁	TT ₂	Tt ₆	Tt ₅	
	Tt	TT ₃	TT ₄	Tt ₈	Tt ₇	
	tt	Tt ₁₁	Tt ₈	tt₁₄	tt₁₃	
		tt	Tt ₉	Tt ₁₀	tt ₁₂	tt

This causes the death of all offspring of heterozygous mothers that do not inherit the Medea allele (*tt*).

Reciprocal chromosomal translocations



Mosquito vector species of interest



Aedes aegypti



Anopheles gambiae



Anopheles stephensi

Insect agricultural pests species of interest



Drosophila suzukii



Ceratitis capitata

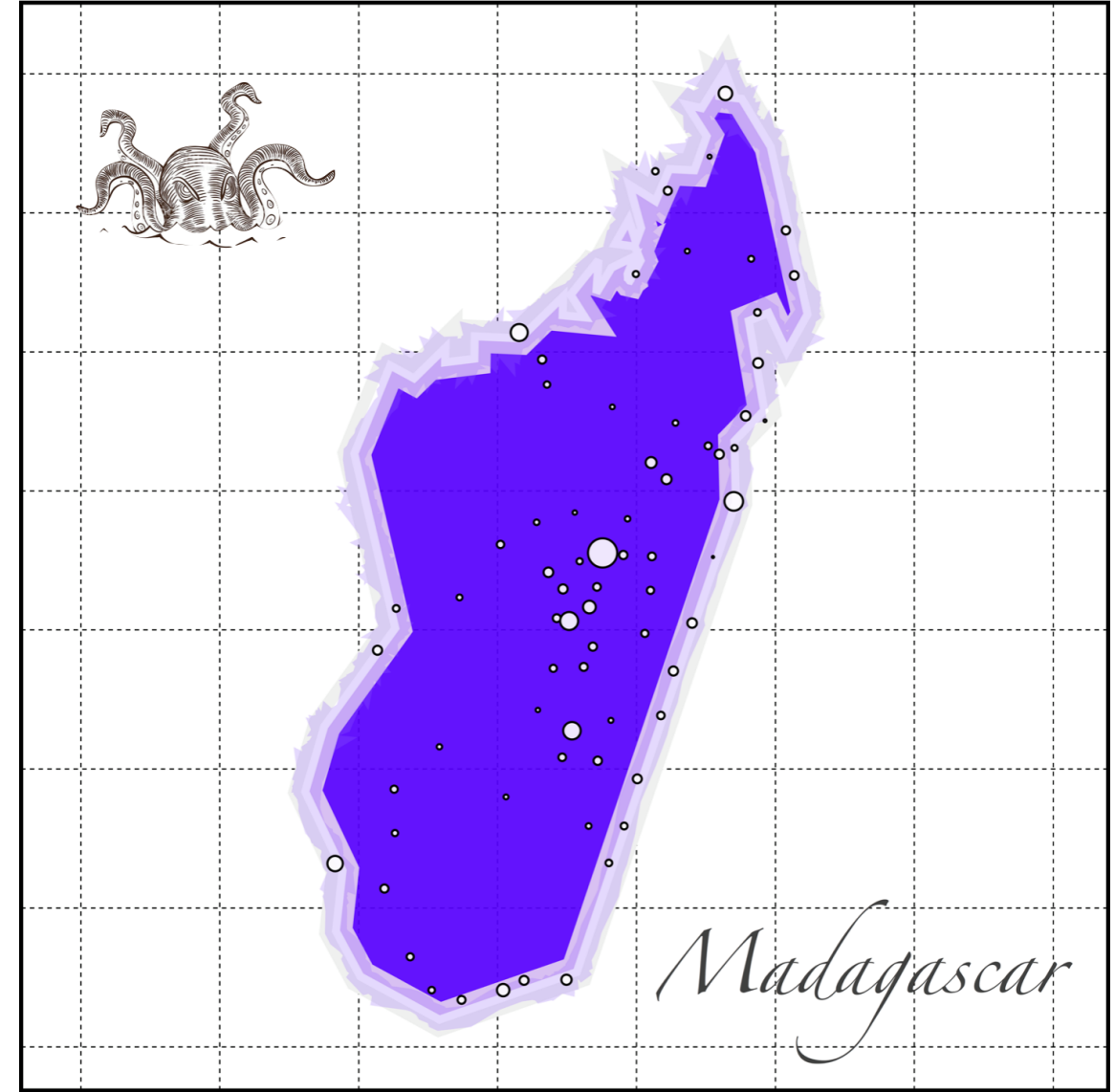
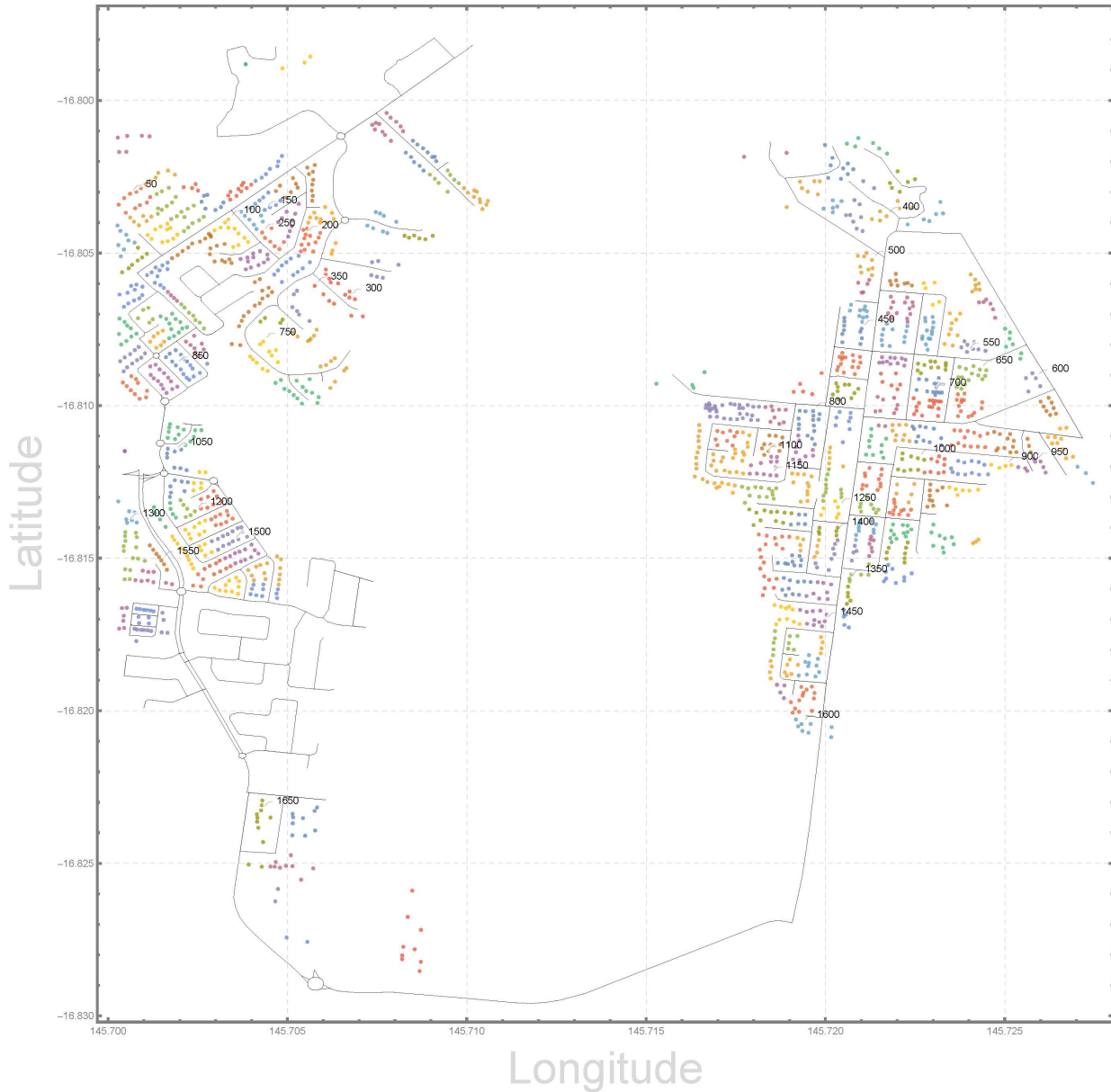


Asian citrus psyllid

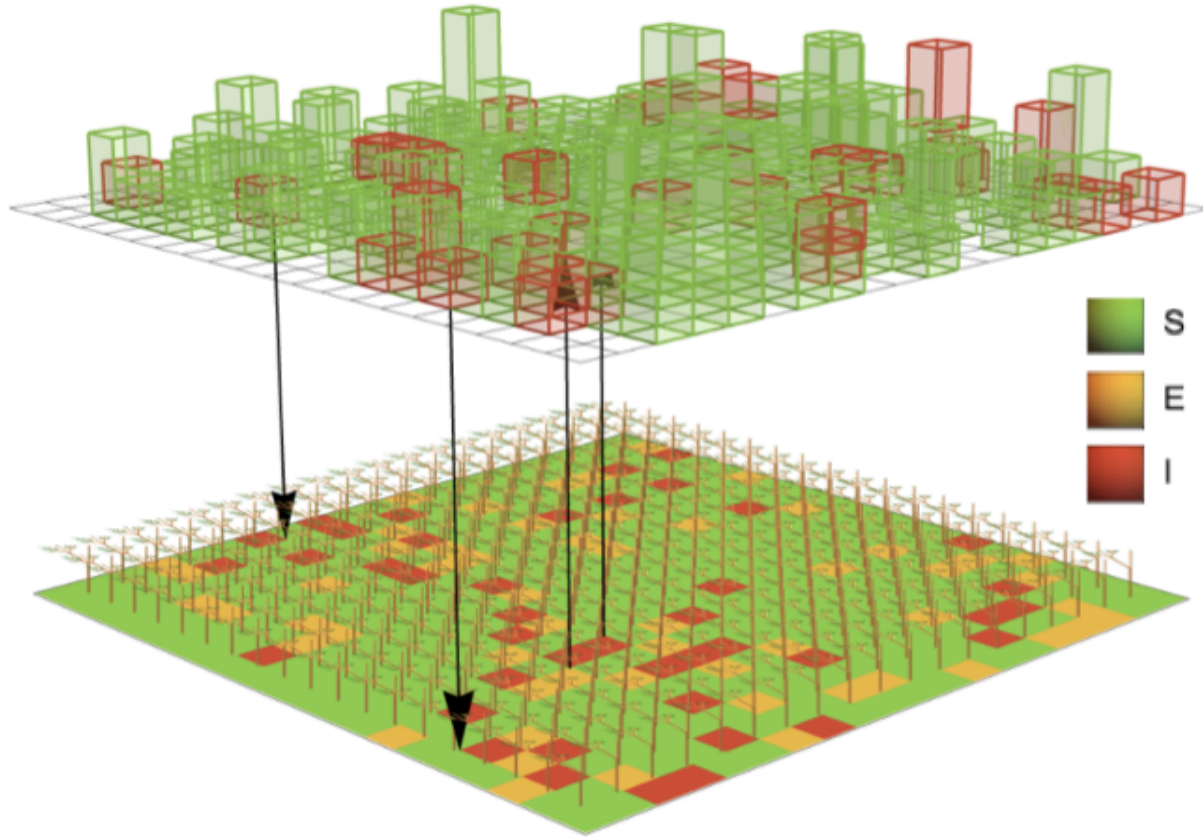


Pink bollworm

Landscapes of interest for mosquito vectors

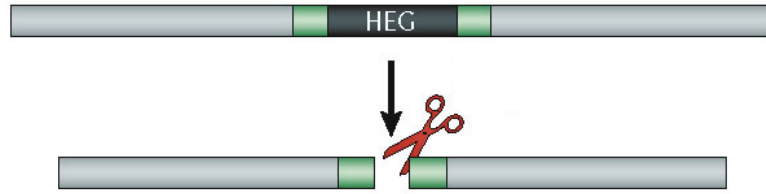


Landscapes of interest for agricultural pests

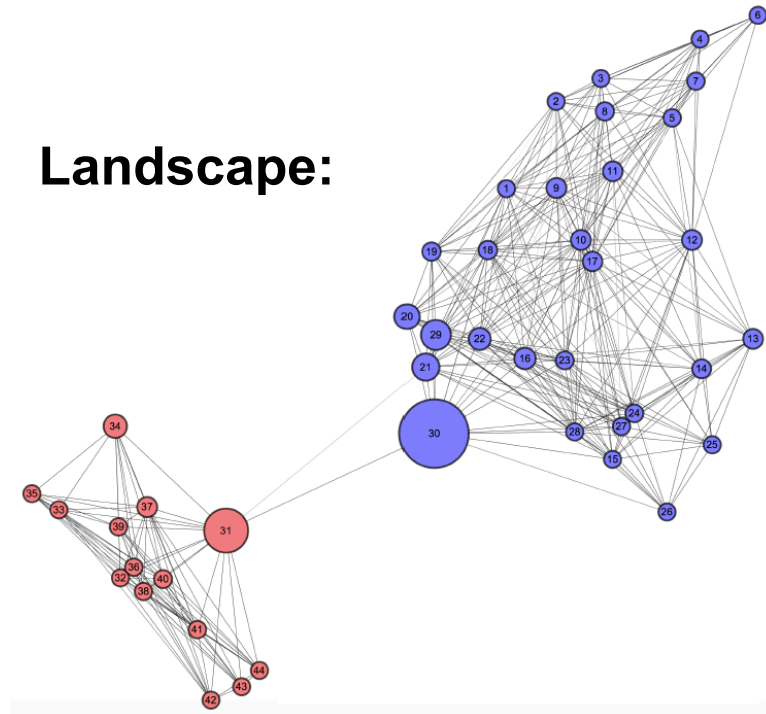


Integrating these in a model to address specific questions

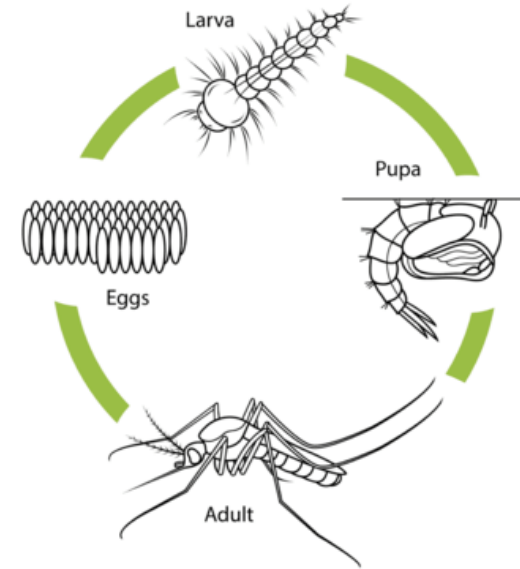
Inheritance pattern:



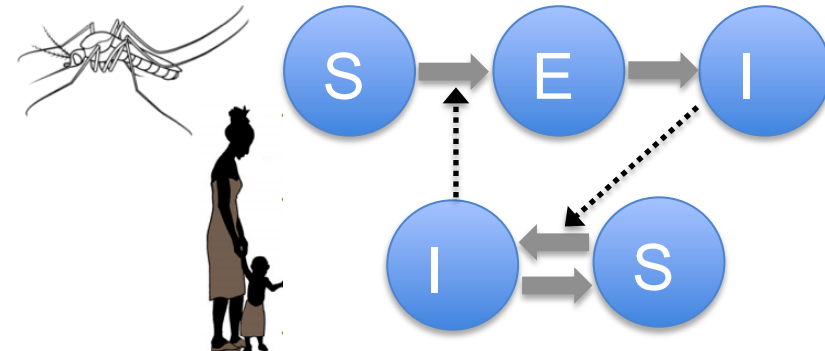
Landscape:



Mosquito life cycle:



Disease epidemiology:



Mosquito Gene Drive Explorer (MGDrivE)

MGDrivE

Mosquitos + Tensors +
Genetics + CS + Networks +
Math + Coffee

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TAR Ball](#)

Developed in [John Marshall's Lab](#) by:

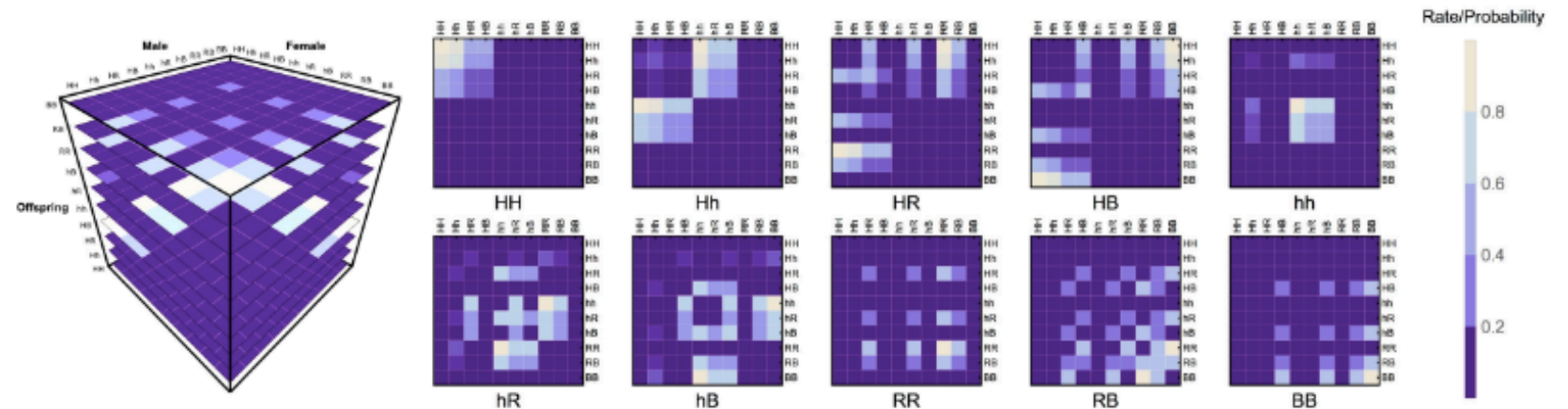
- Lead: [Héctor M. Sánchez C.](#)
- Core Dev: [Sean L. Wu](#), [Jared Bennett](#)
- Spatial Analysis: [Biyonka Liang](#), [Sarafina Smith](#), [Sabrina Wong](#)
- Movement Kernels: [Partow Imani](#)

...and, of course, our PI: [John M. Marshall](#)!

Mosquito Gene Drive Explorer

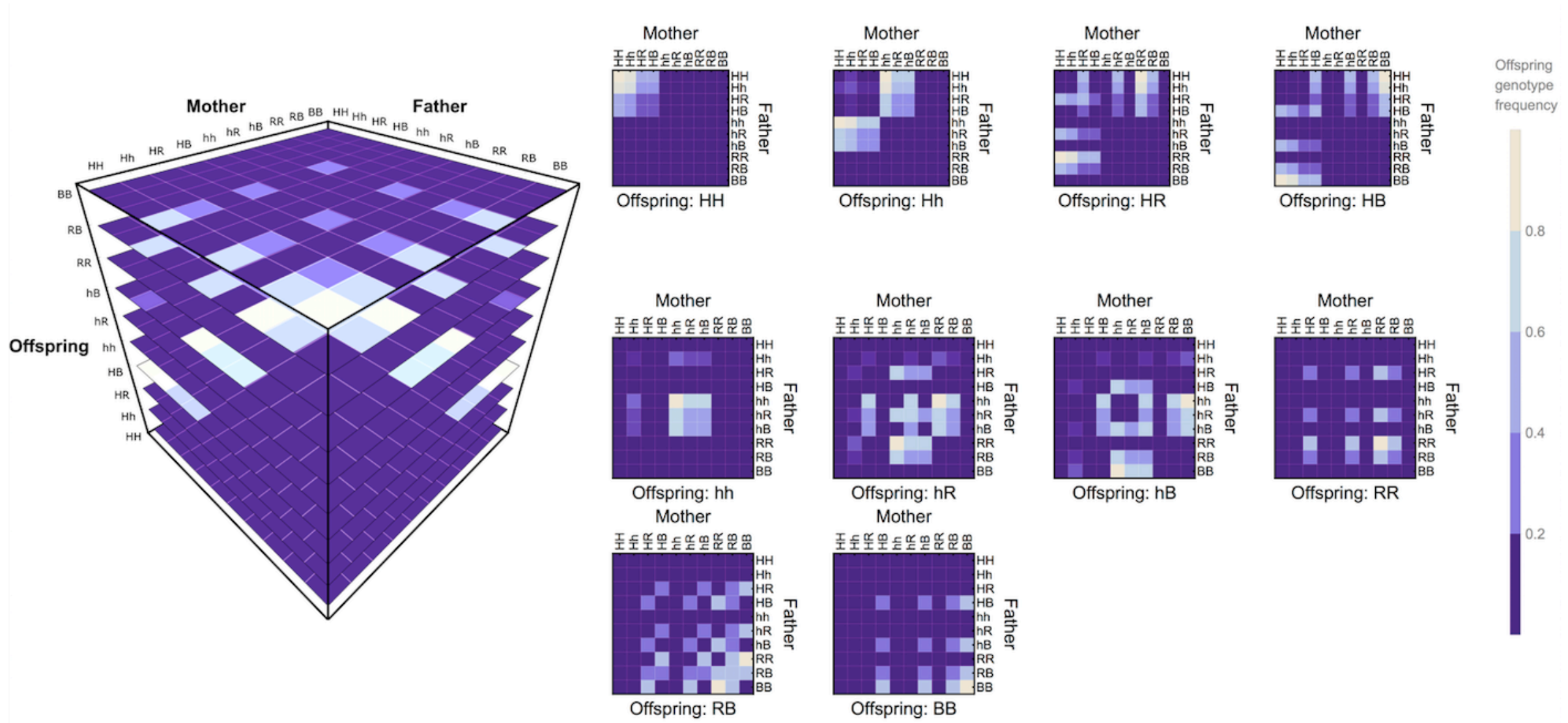
Brief Description

MGDrivE is a framework designed to serve as a testbed in which gene-drive releases for mosquito-borne diseases control can be tested. It is being developed to accommodate various mosquito-specific gene drive systems within a population dynamics model that allows migration of individuals between nodes in a spatial landscape.

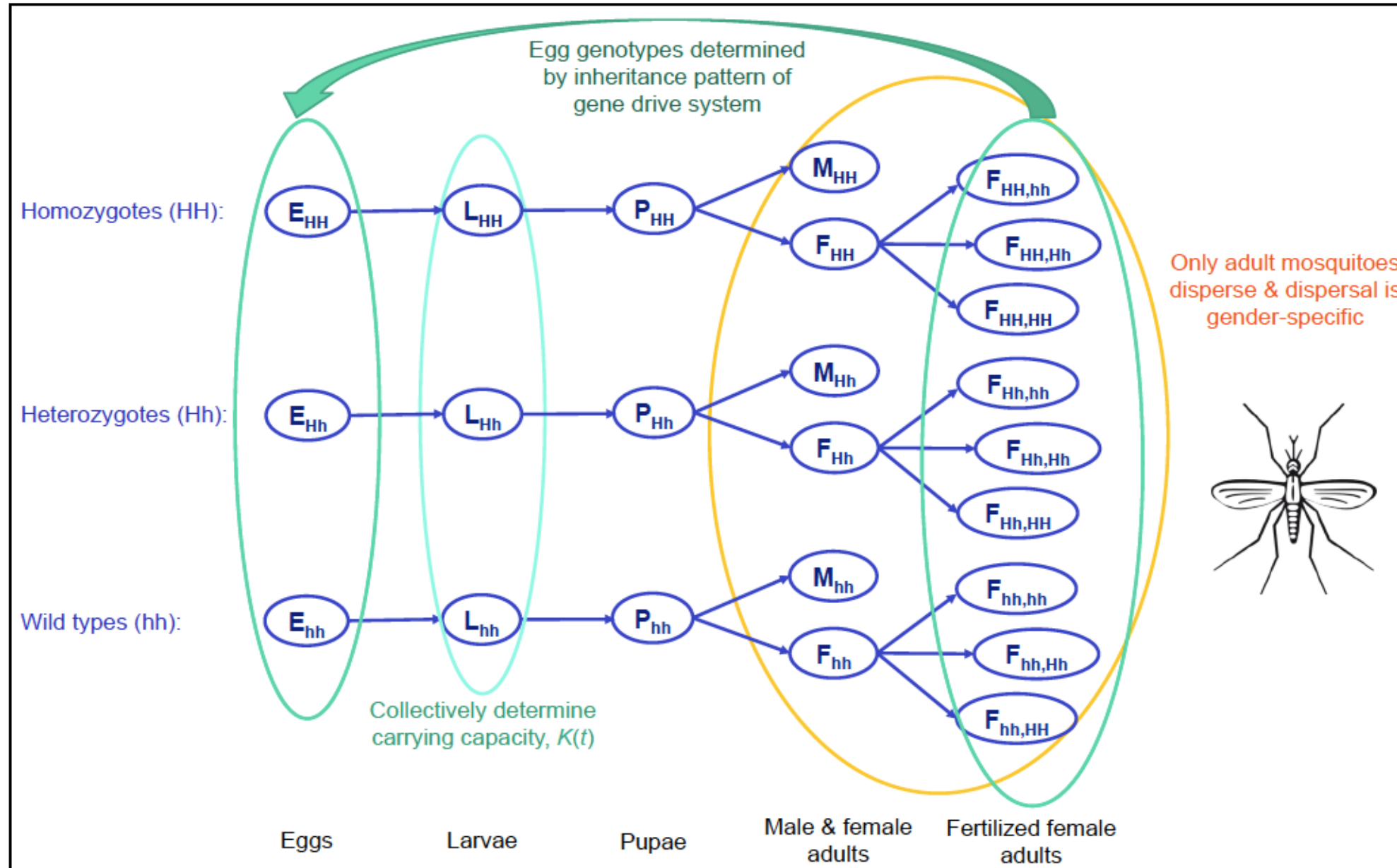


Demonstration

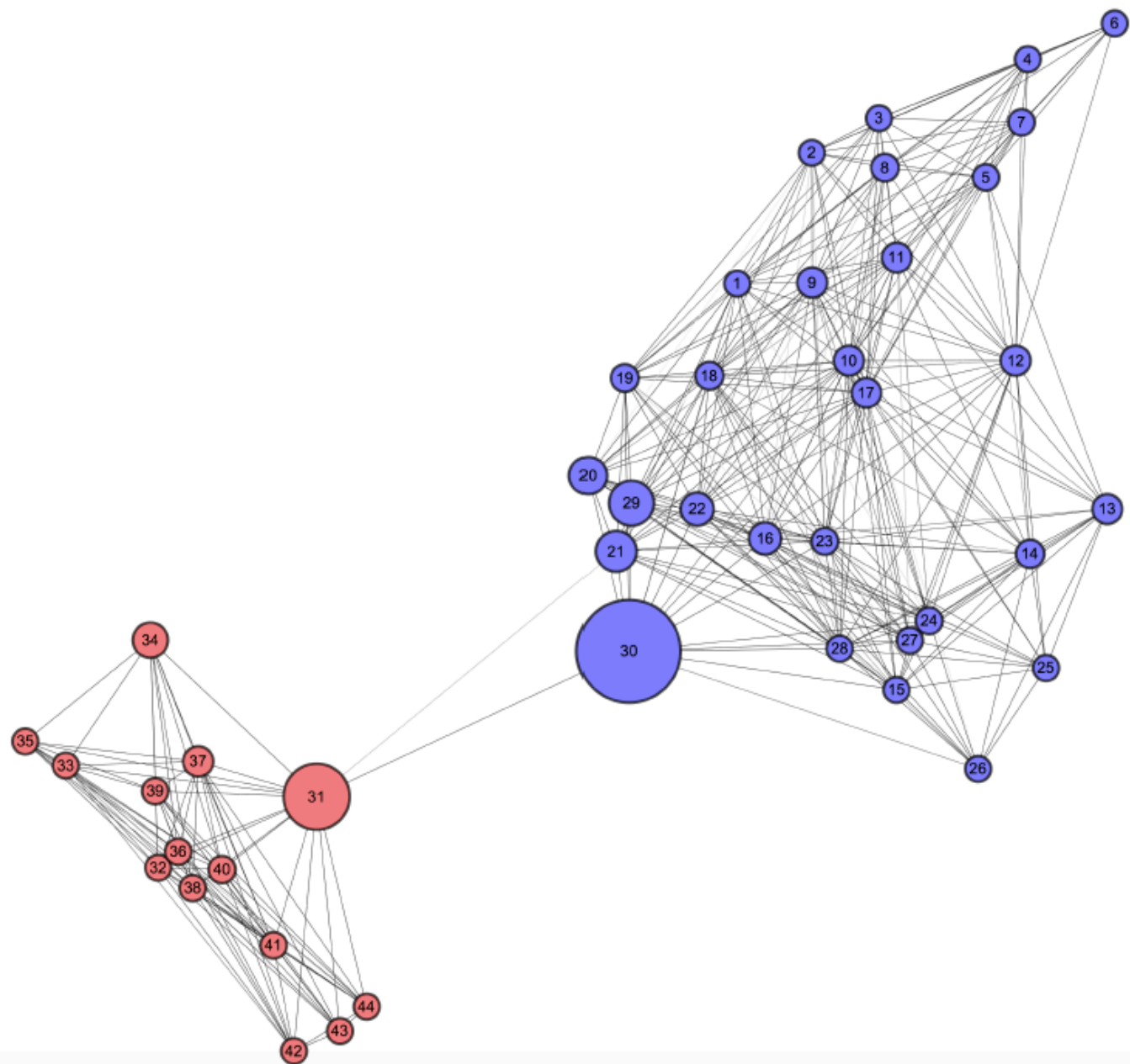
MGDrivE: Inheritance module



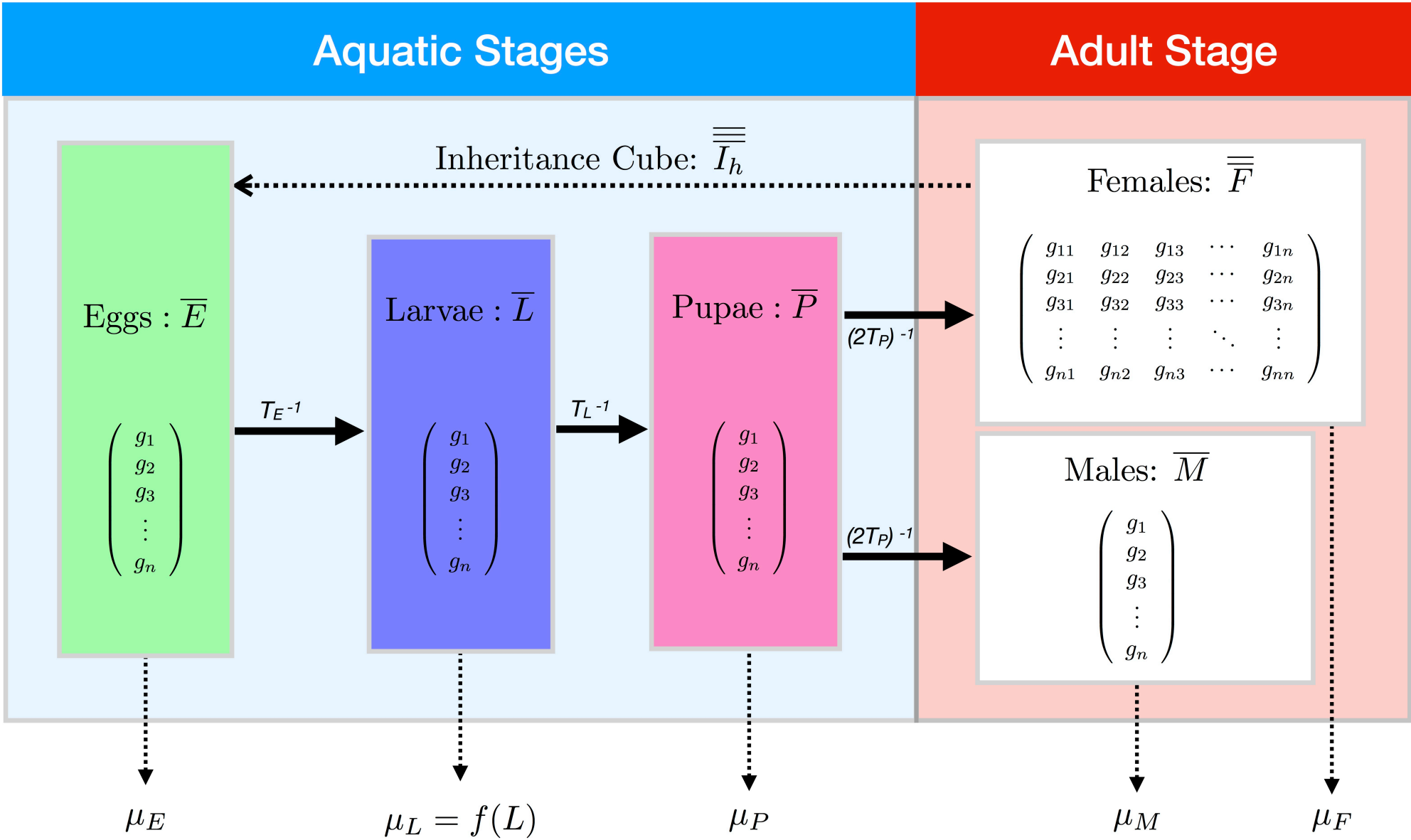
MGDrivE: Ecology module



MGDrivE: Landscape module



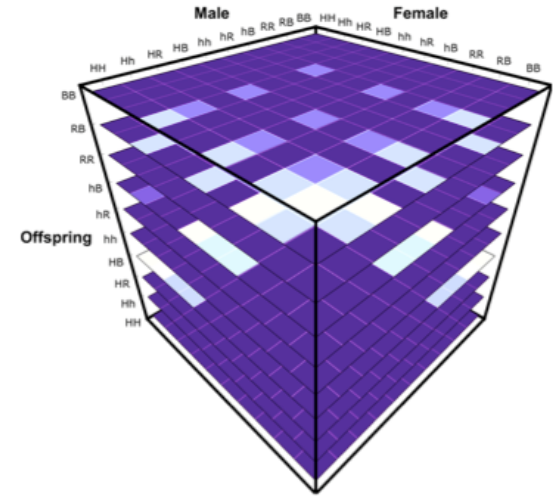
Tensor modeling framework



Tensor modeling framework

Inheritance & oviposition:

$$\overline{O(T_x)} = \sum_{j=1}^n \left(\left((\beta * \bar{s} * \overline{Af[t-T_x]}) * \overline{Ih} \right) * \Lambda \right)_{ij}^T$$

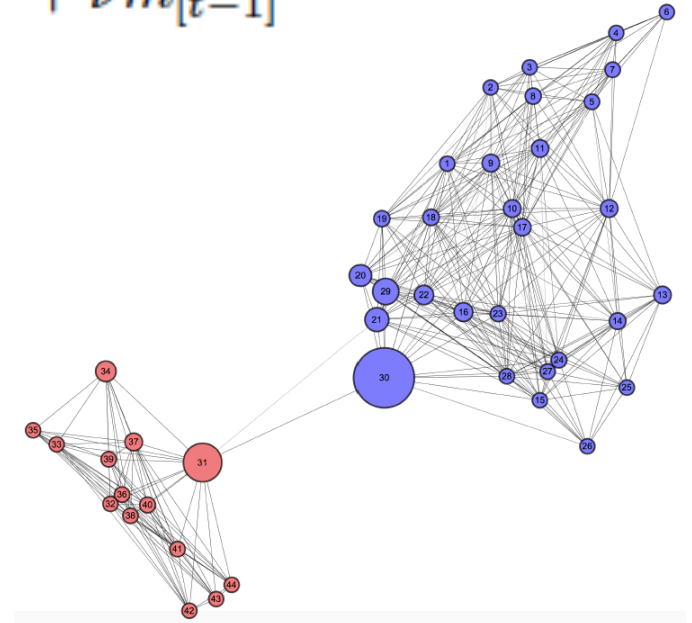


Adult male survival & development:

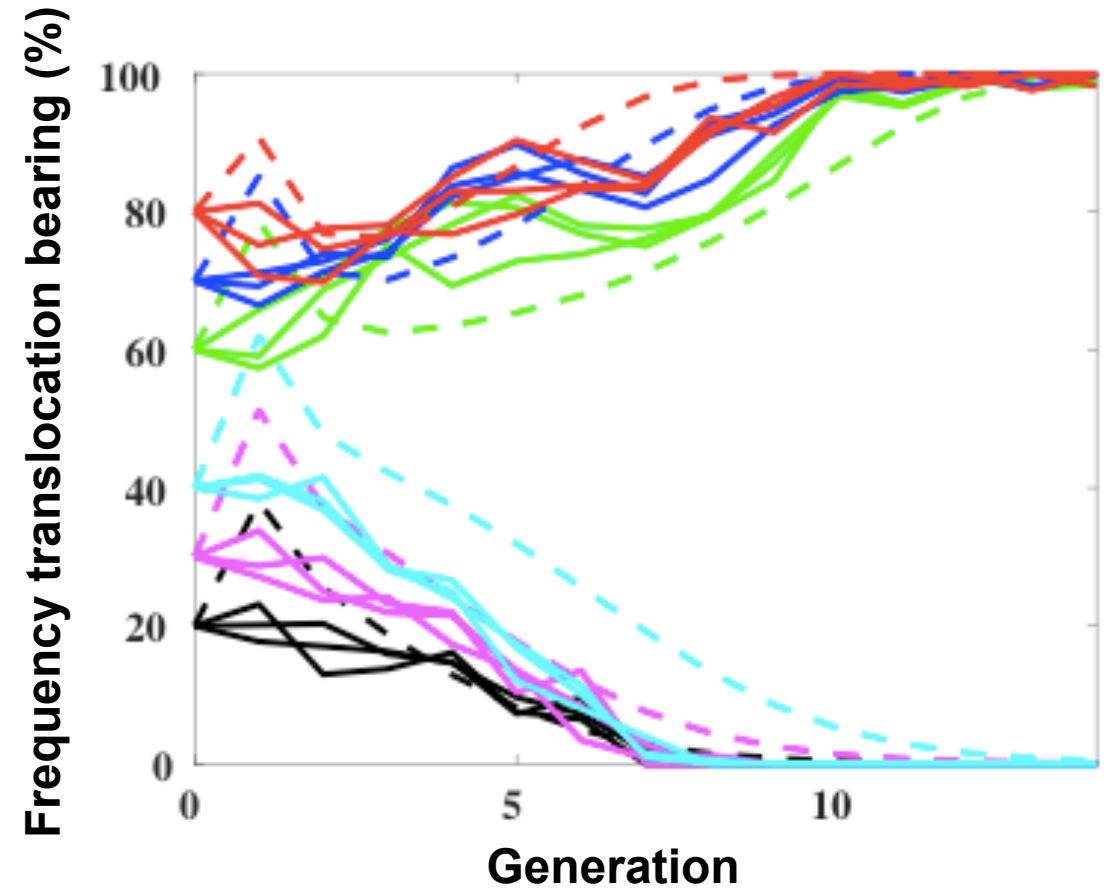
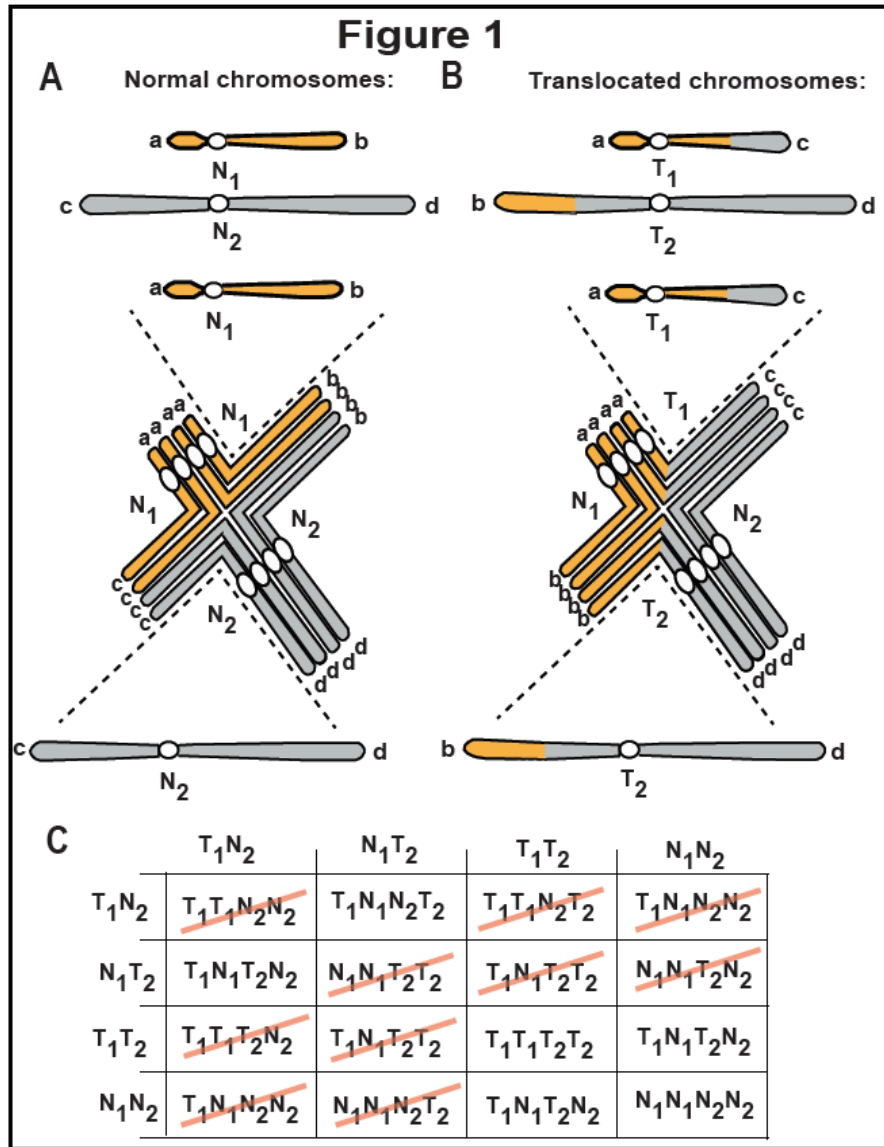
$$\overline{Am[t]} = \overline{Am[t-1]} * (1 - \mu_{ad}) * \overline{\omega_m} + (1 - \overline{\phi}) * \overline{E'} + \overline{\nu m[t-1]}$$

Adult male migration:

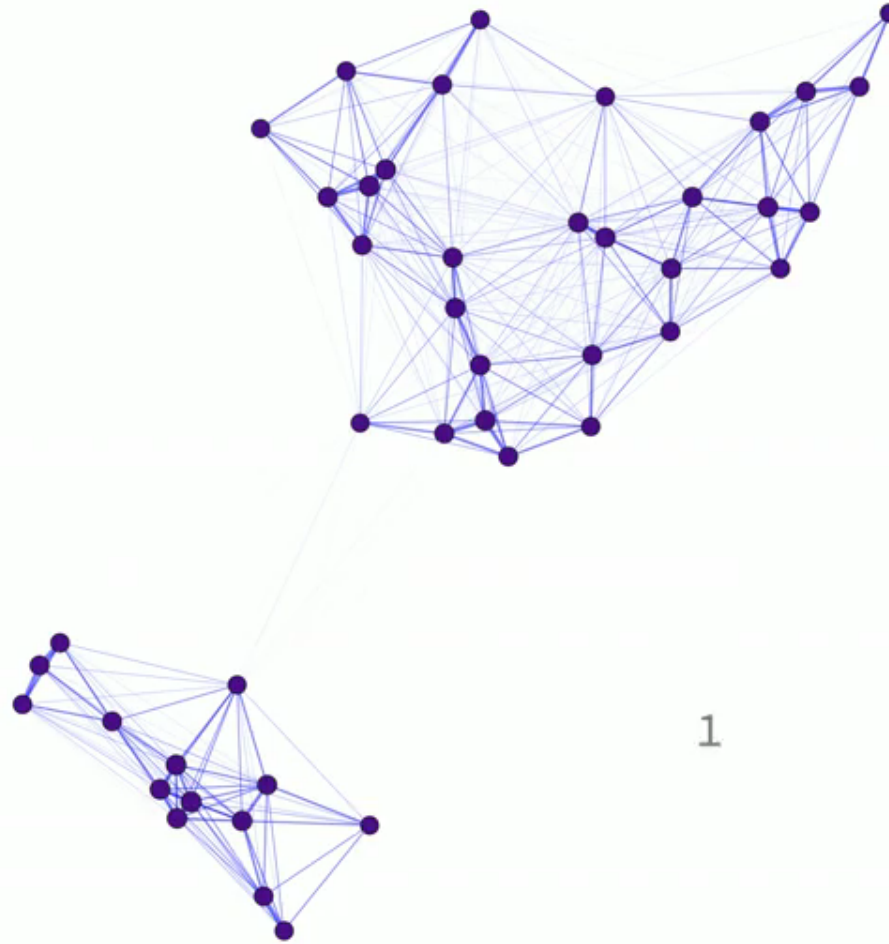
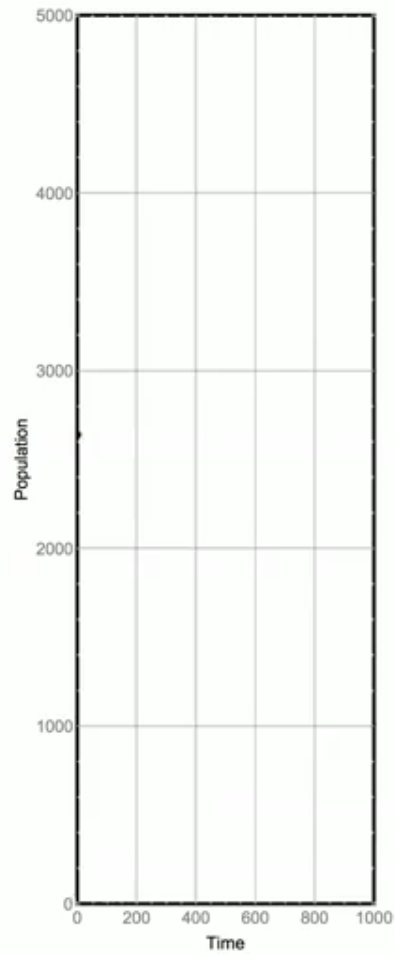
$$\overline{Am^i(t)} = \sum A_m^j \otimes \overline{\tau m[t-1]}$$



Application to chromosomal translocations



MGDrivE: Translocations with remediation



Public attitudes to gene editing for malaria control in Mali



“You have to start somewhere. From this, people will know whether it’s good or bad... I would like you to conduct a trial in my village because I would like to be an example for another community.”

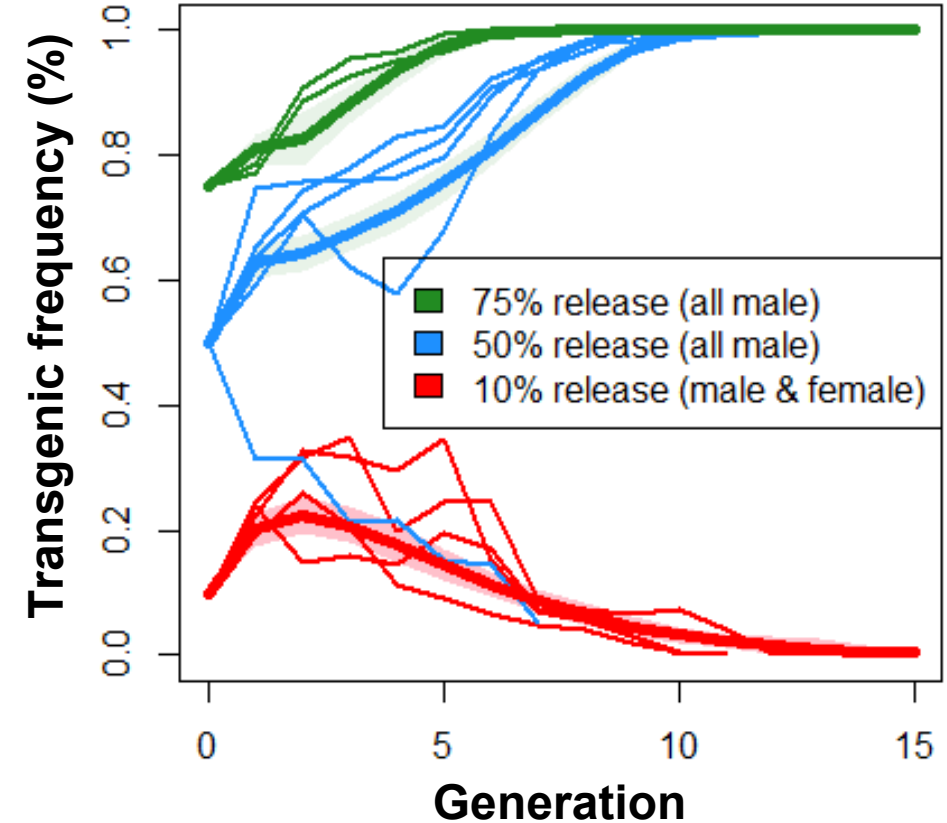
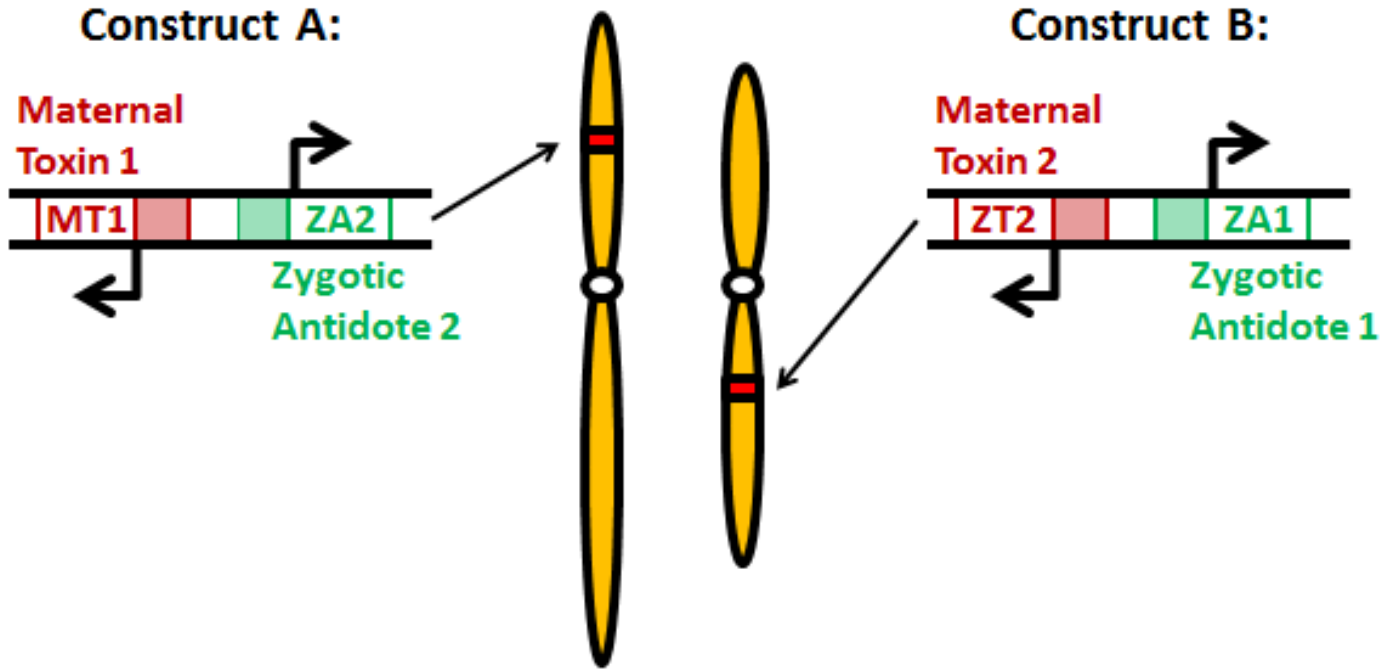
Elder, Koporo-na, Mali

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

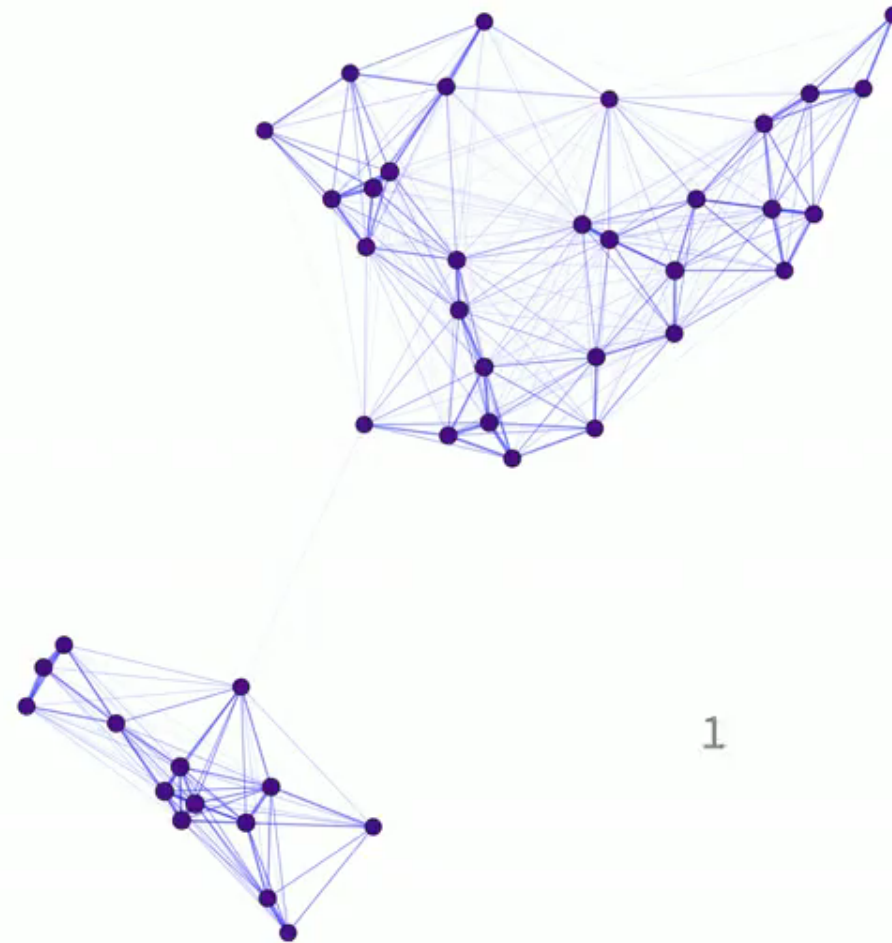
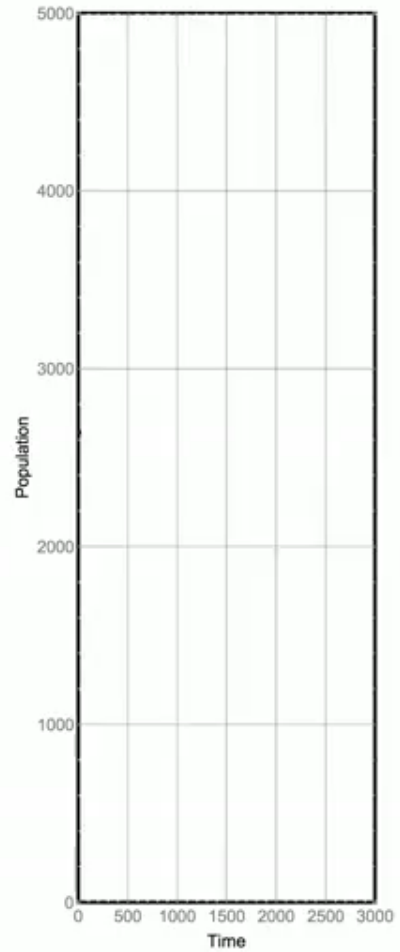
Elder, Tienfala, Mali

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

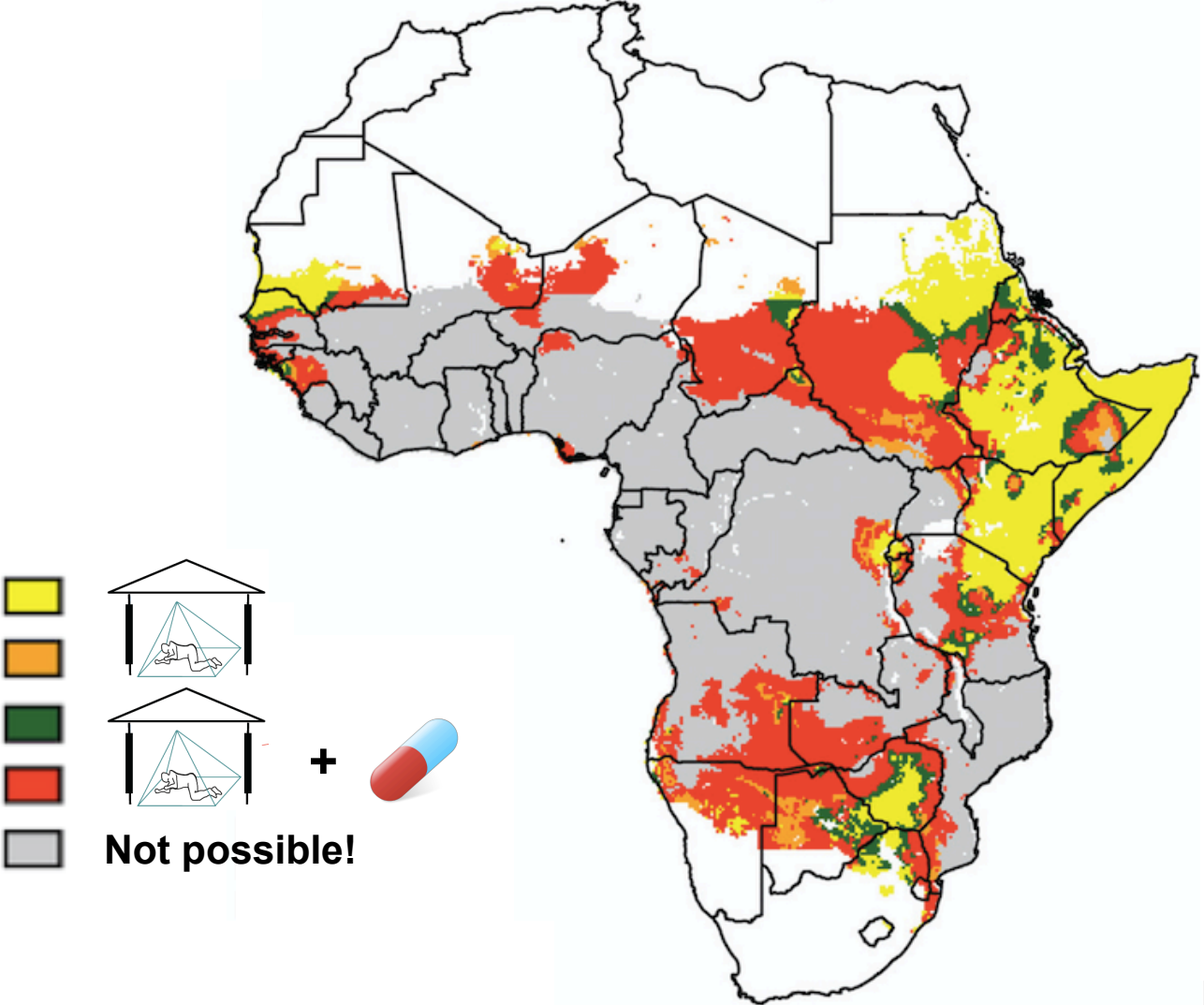
Application to toxin-antidote-based underdominance



MGDrivE: Toxin-antidote-based underdominance

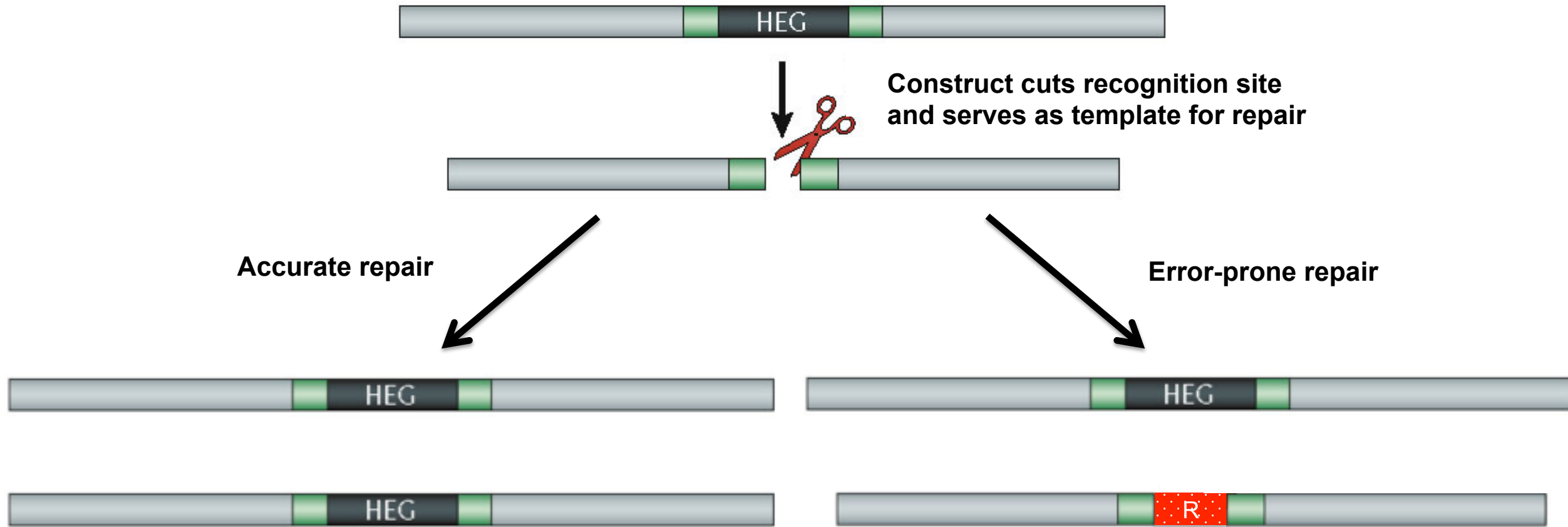


Optimal interventions to eliminate malaria

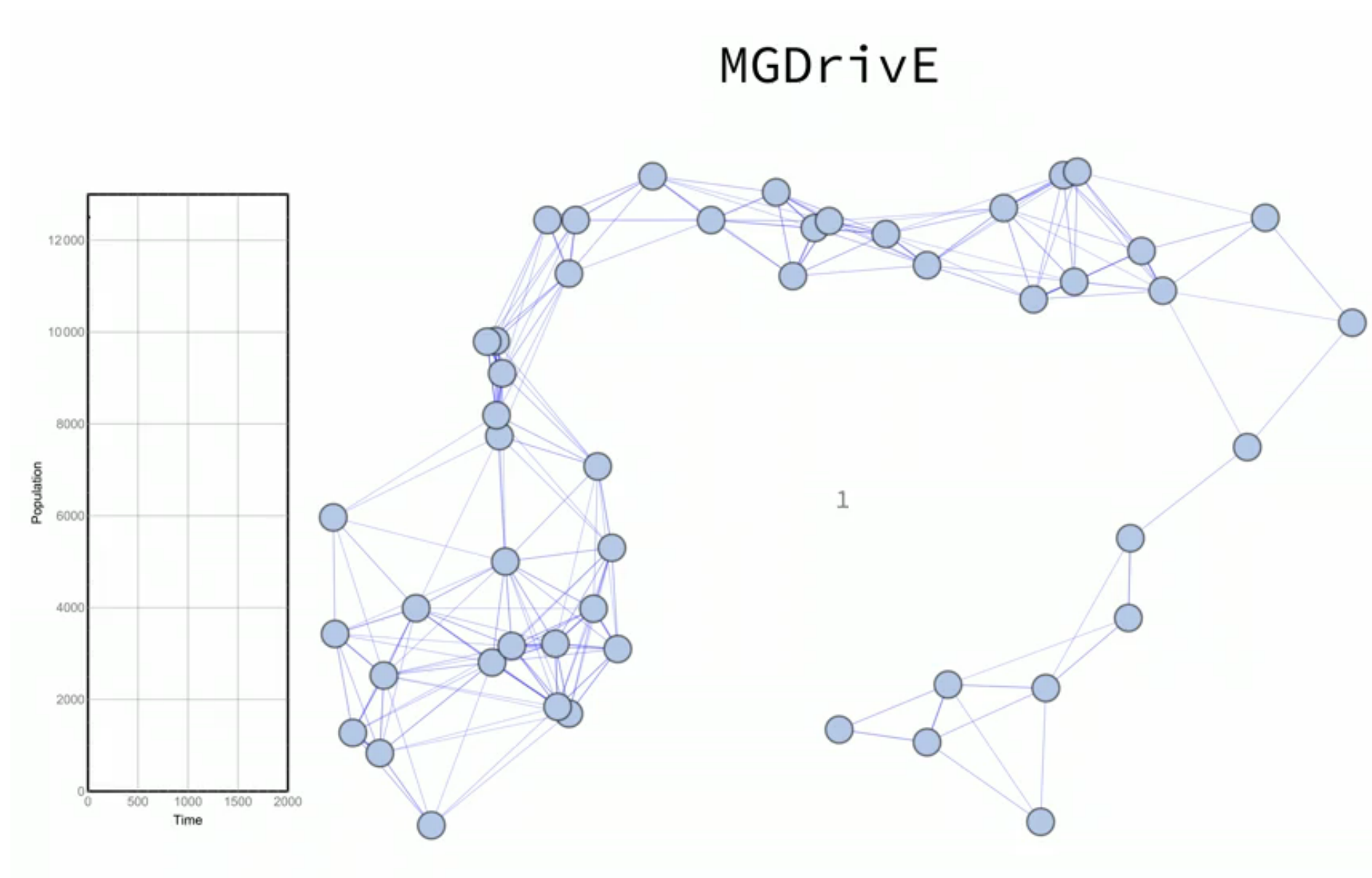


• Walker PGT, Griffin JT, Ferguson NM, Ghani AC (2016) Lancet Global Health

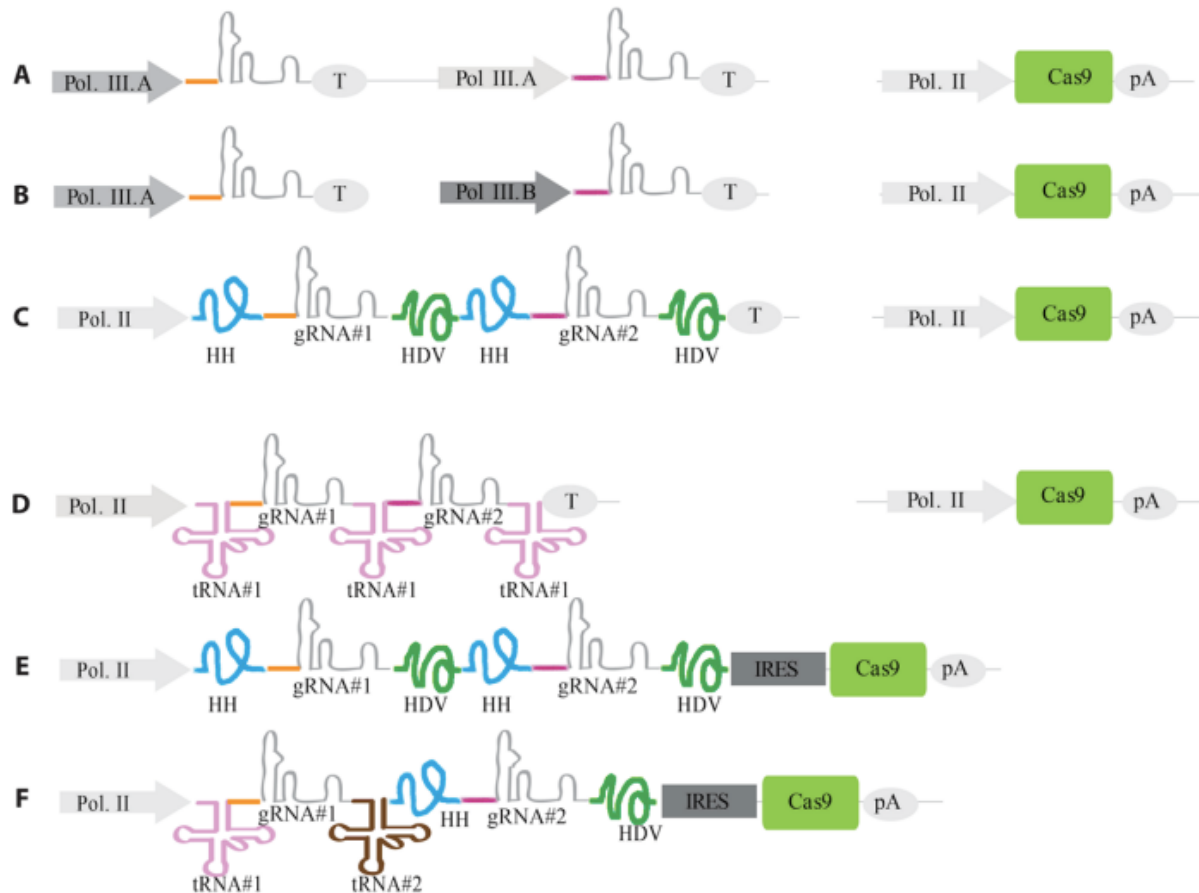
Homing-based gene drive with resistant alleles



MGDrive: Homing-based gene drive with resistance



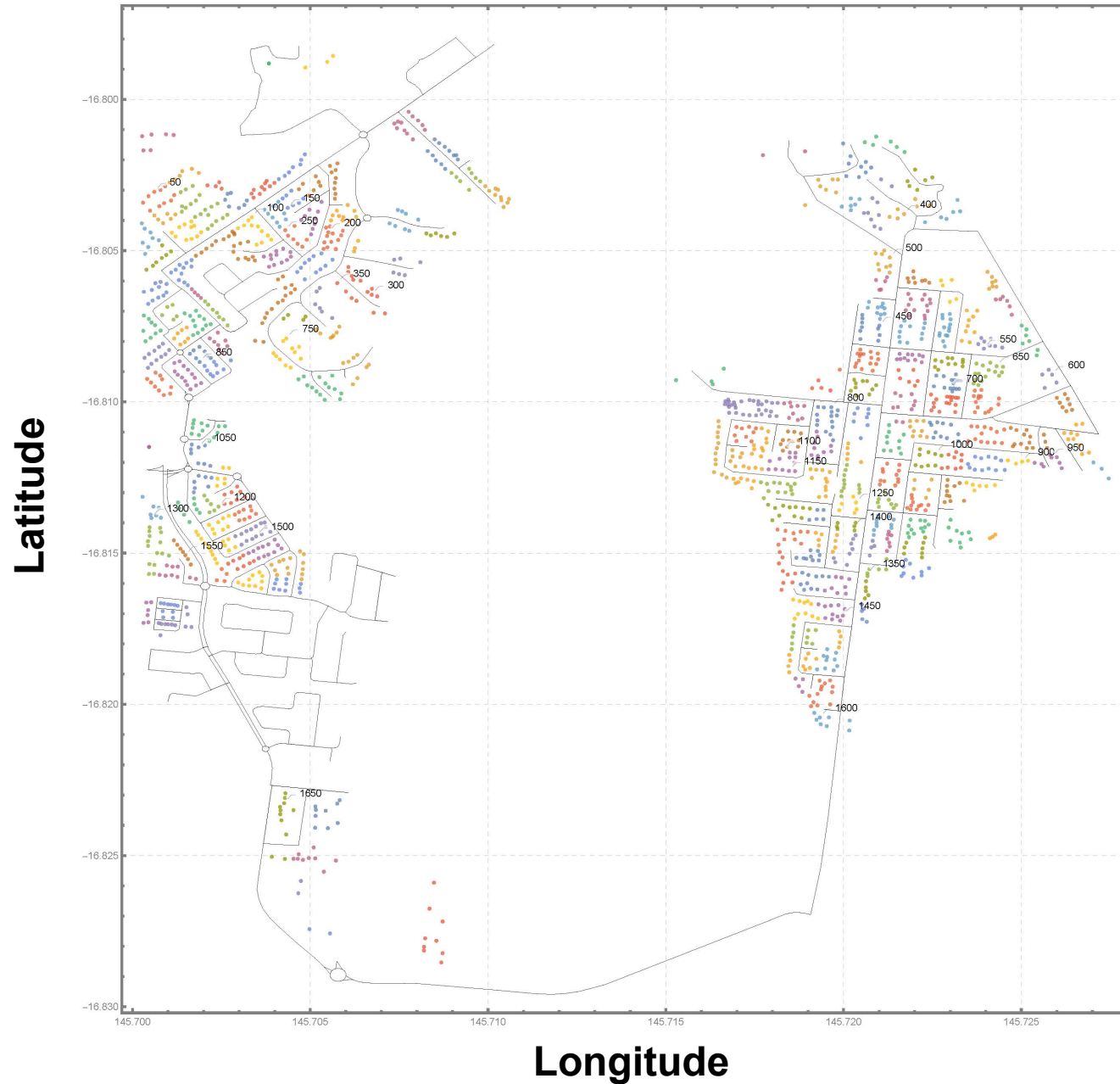
Multiplexing gRNAs as a solution to resistant alleles



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: Extensions & future directions



Molecular biology:

- Modeling guide RNA multiplexing for homing-based gene drive. How does this impact the homing and resistant allele generation?
- Individual-based model for when number of possible genotypes exceeds number of individuals.

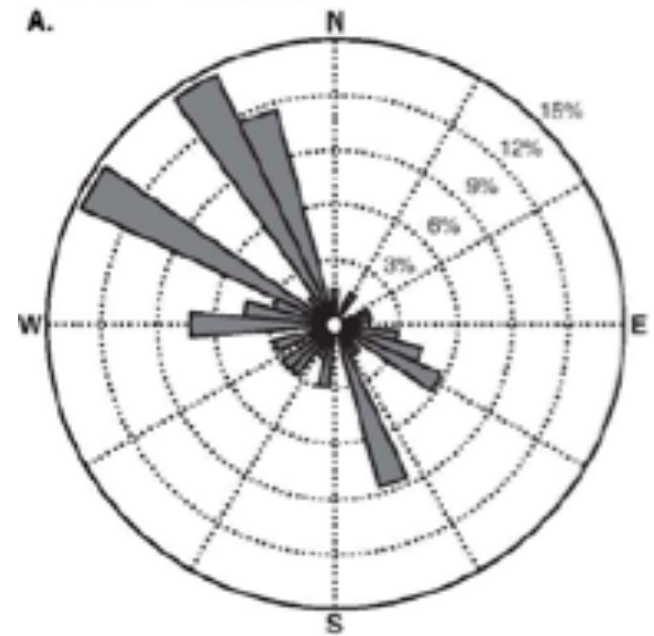
Ecology:

- Quantifying dispersal at multiple scales – inter-household, intermediate & large-scale movement mediated by humans, etc.
- Impact of environmental covariates and other barriers on mosquito movement.
- Impact of environmental covariates on mosquito population size.
- Implications for seasonality in population size.
- Alternative models for density-dependent competition at the larval stage.

Close-kin capture methods to infer dispersal patterns



Plectropomus maculatus



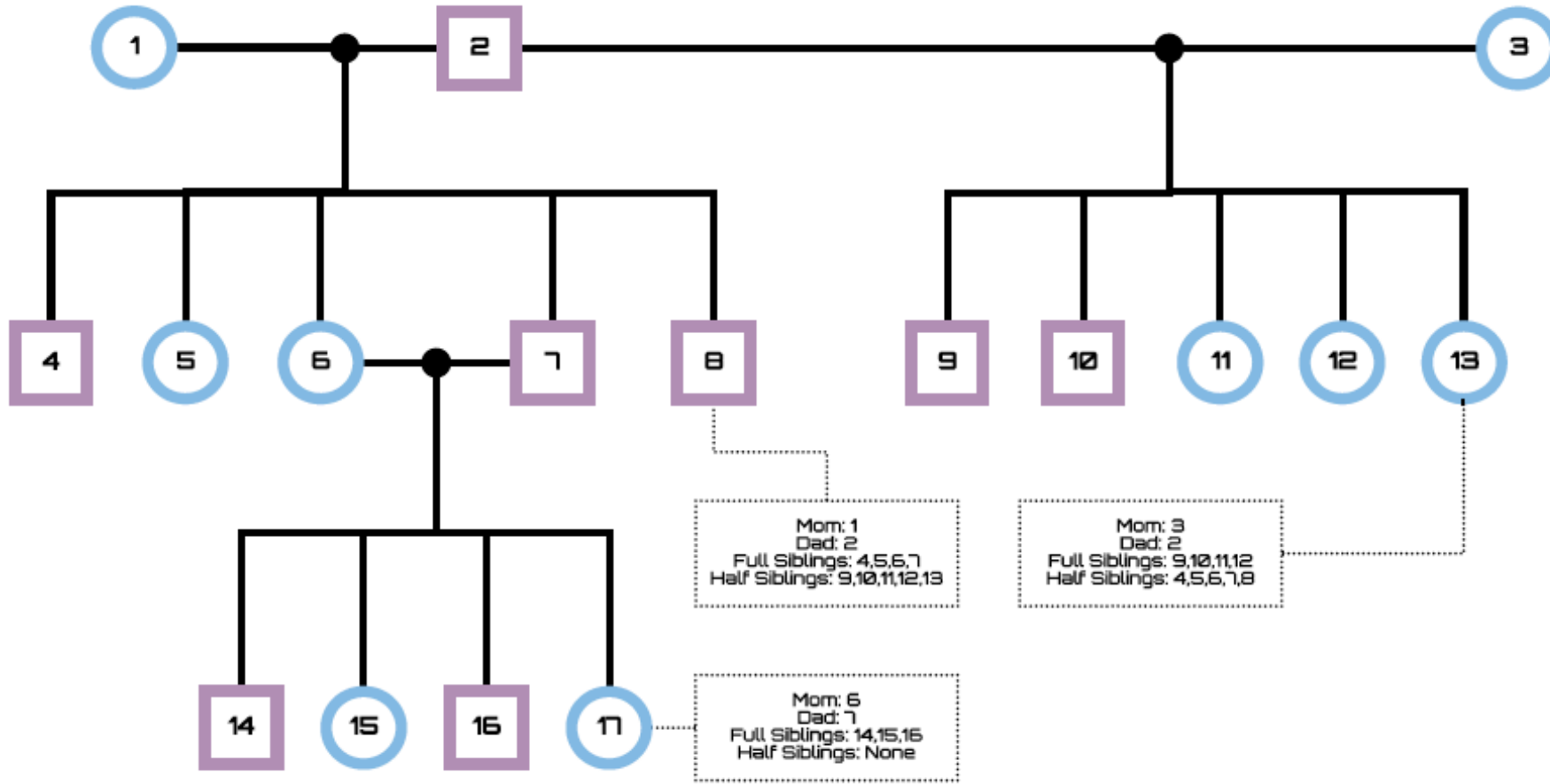
Close-Kin Pair	Event Histories by which distances accumulate		
Mother-Offspring (larval)		Mother disperses	
Father-Offspring (larval)		Mother disperses	
		Father disperses	
Mother-Offspring (adult)		Adult offspring disperses	
		Father disperses	
Full-Sibling (adult)		Adult offspring disperses	
		Mother disperses	
		Adult offspring disperses	

$$(3.1) \quad \mathbb{P}[K_{ij} = \text{MO} | z_i, z_j] = \mathbb{E}_{Y_j, X_j | z_j} \left[\frac{\mathbb{E}[R_i(X_j, Y_j) | z_i]}{\mathbb{E}[R_+(X_j, Y_j)]} \right]$$

$$(4.1) \quad l_P(\theta) = \sum_{1 \leq i < j \leq n} \log \mathbb{P}(K_{ij} = k_{ij} | z_i, z_j; \theta)$$

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

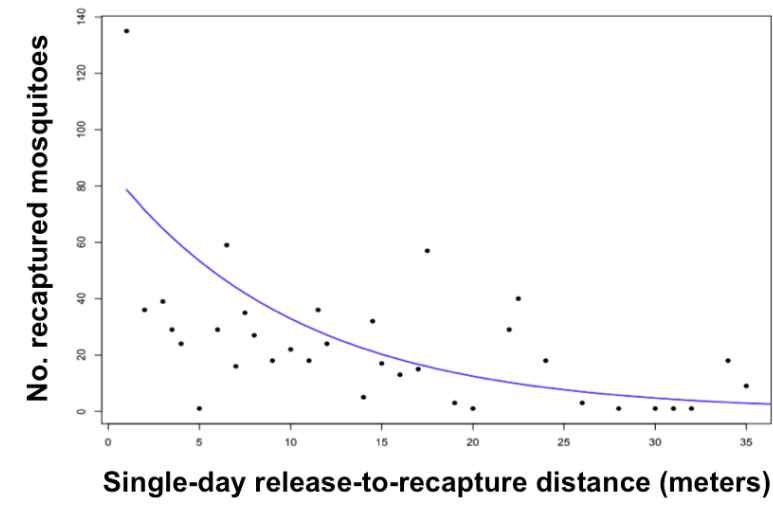
Incorporating parental IDs into MGDriveE



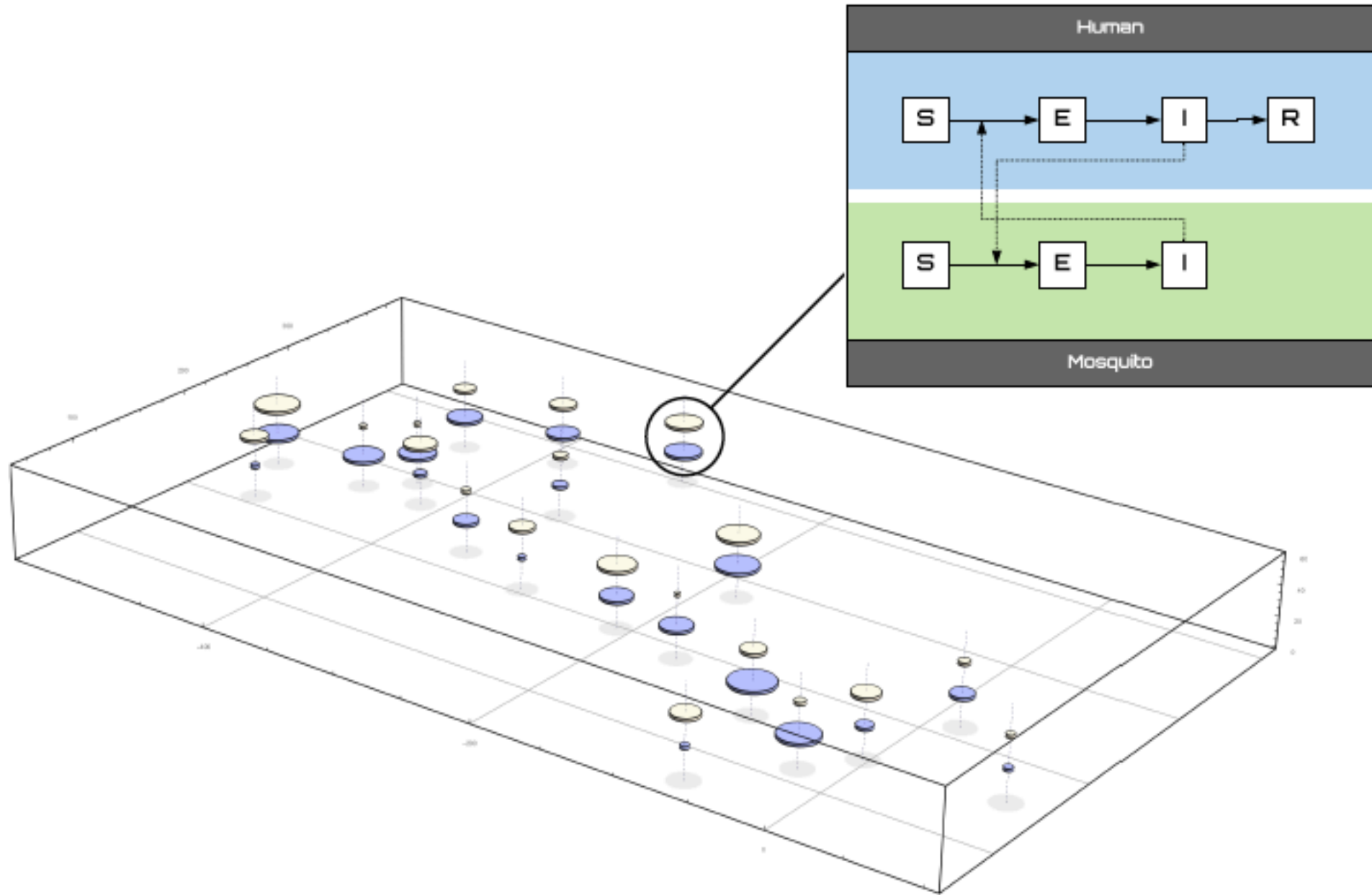
Mom: 1
Dad: 2
Full Siblings: 4,5,6,7
Half Siblings: 9,10,11,12,13

Mom: 3
Dad: 2
Full Siblings: 9,10,11,12
Half Siblings: 4,5,6,7,8

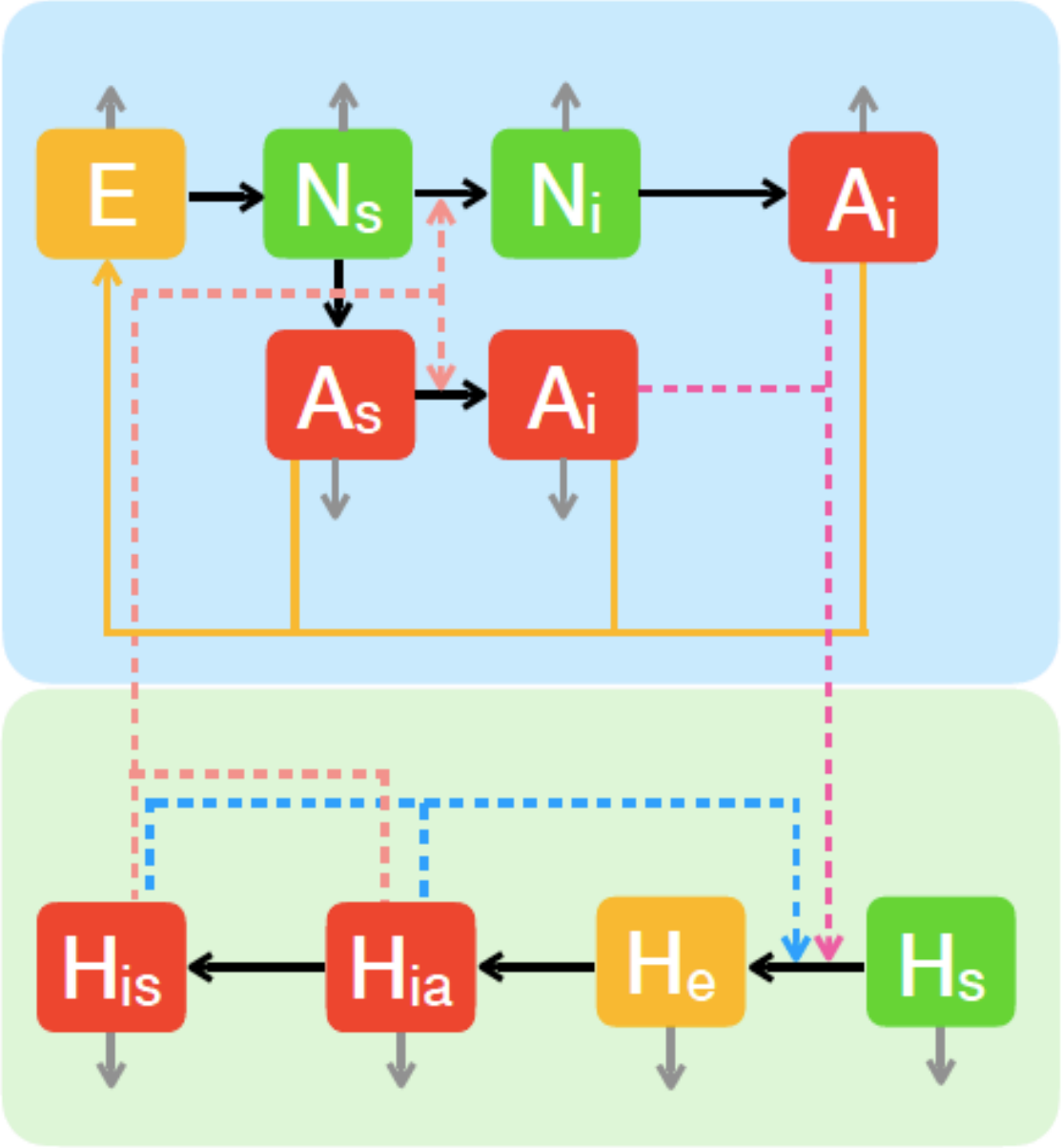
Mom: 6
Dad: 7
Full Siblings: 14,15,16
Half Siblings: None



Epidemiological extension for mosquito-borne diseases



Epidemiological extension for insect agricultural pests



Acknowledgements

COLLABORATORS:

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