



Gene drives across engineered fitness valleys

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Engineered gene drive: potential

Invade population with a **payload**



Public health
Drive genes that
reduce disease



Conservation
Drive genes that
protect species at risk

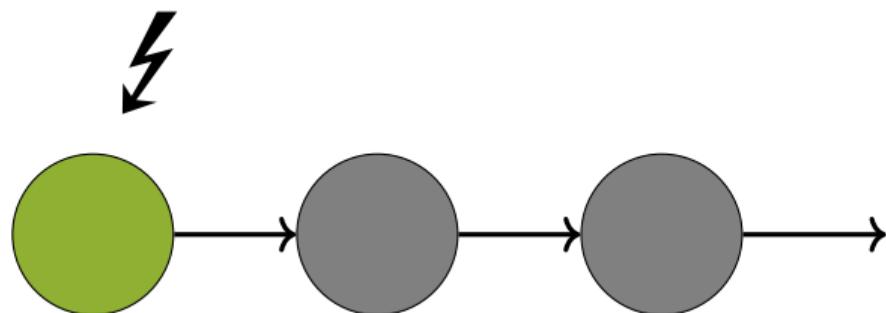


Agriculture
Drive genes that
reduce pest damage

Engineered gene drive: risks

Risks of gene drive following release are also great, including

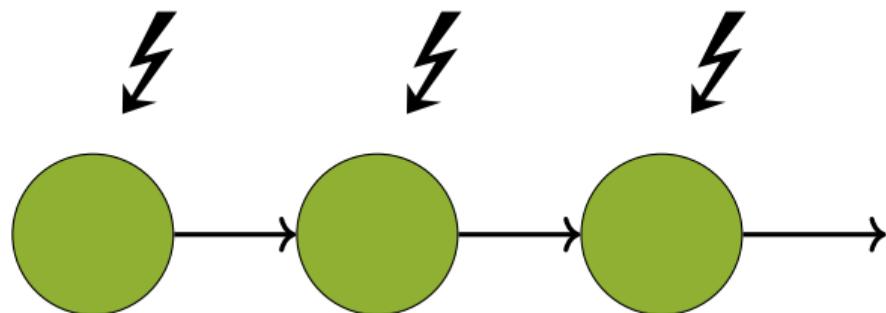
- Spread **payload** beyond the area of interest
- Spread **payload** beyond the target species



Engineered gene drive: risks

Risks of gene drive following release are also great, including

- Spread **payload** beyond the area of interest
- Spread **payload** beyond the target species



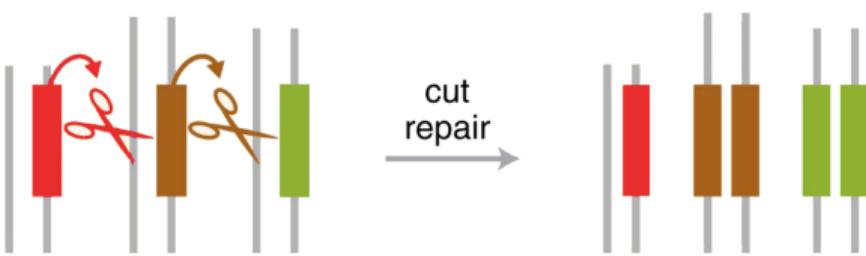
Engineered gene drive: risks

Risks of gene drive following release are also great, including

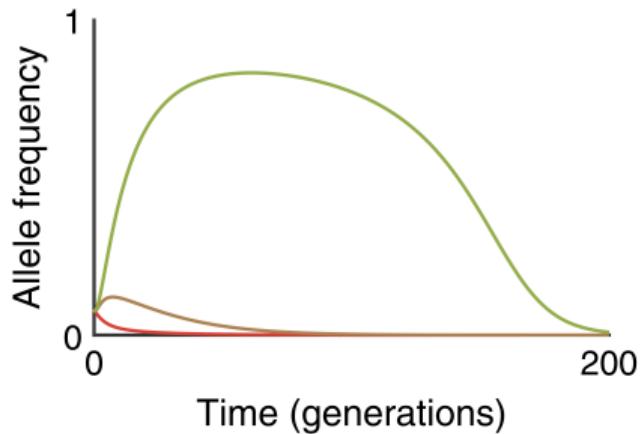
- Spread **payload** beyond the area of interest
- Spread **payload** beyond the target species

Need: develop spatially controlled drives

Homing based gene drive: Daisy Chain

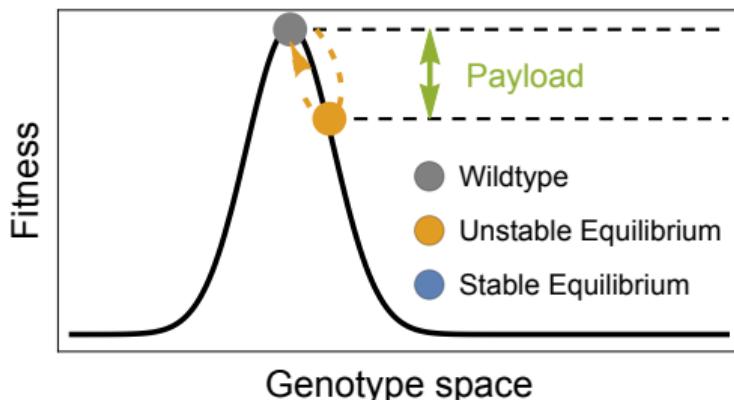


- Low threshold method
- Temporal



Comparing drives

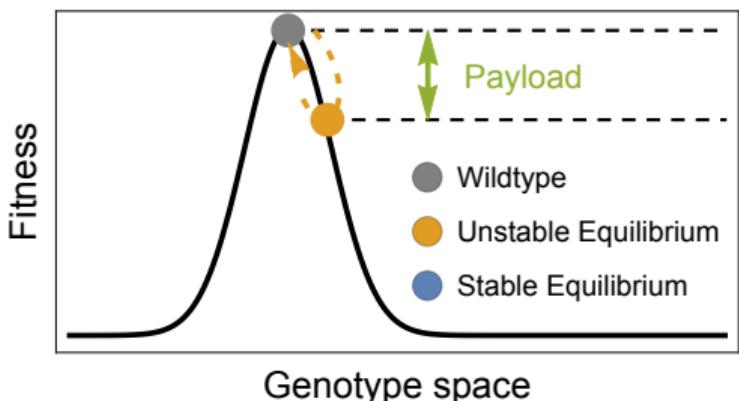
Daisy chain based gene drive



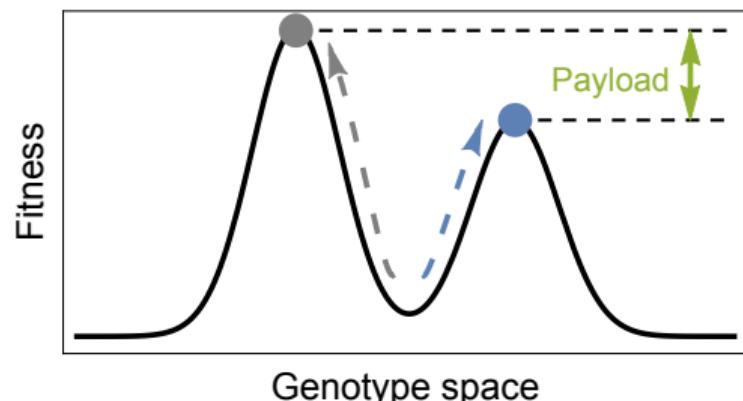
- + Low threshold method
- Payload does not fix

Comparing drives

Daisy chain based gene drive

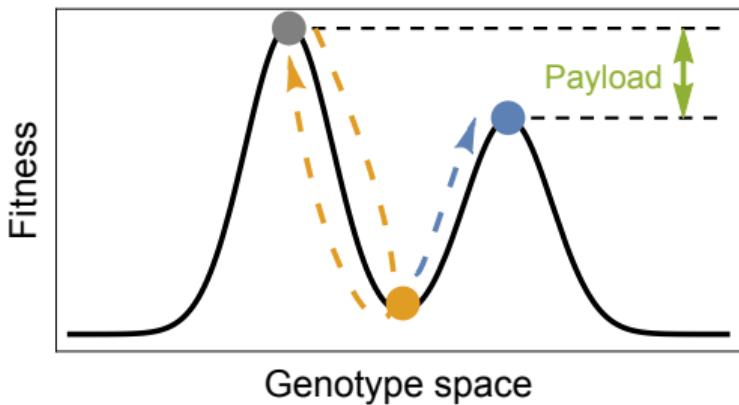


Pushing across a fitness valley



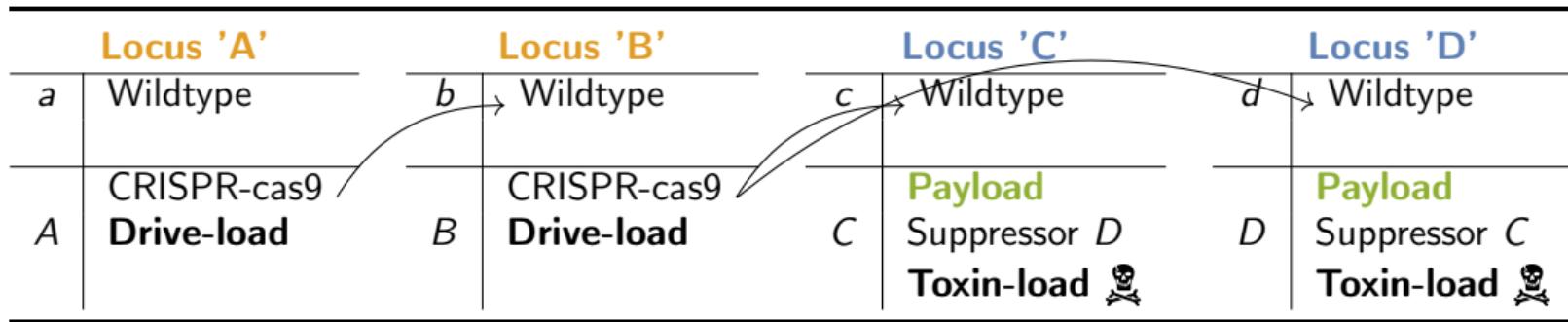
- + Low threshold method
- Payload does not fix
- High threshold method
- + Payload fixes

Combining drives



- + Low to high threshold system
- + Payload fixes
- + Locally stable equilibrium

Overview drive construct



Engineered fitness valley

- 'C' or 'D'
express the 

	cd	cD	Cd	CD
cd	1			
cD				
Cd				
CD				

Locus 'C'		Locus 'D'	
c	Wildtype	d	Wildtype
C	Payload Suppressor D Toxin-load 	D	Payload Suppressor C Toxin-load 

Engineered fitness valley

- 'C' or 'D'
express the 

	cd	cD	Cd	CD
cd	1			
cD				
Cd				
CD				

Locus 'C'		Locus 'D'	
c	Wildtype	d	Wildtype
C	Payload Suppressor D Toxin-load 	D	Payload Suppressor C Toxin-load 

Engineered fitness valley

- ' C ' or ' D ' express the 
- ' C ' and ' D ' do not express the  but carry the **payload**

	cd	cD	Cd	CD
cd	1			
cD				
Cd			$1 - s$	
CD				

Locus 'C'		Locus 'D'	
c	Wildtype	d	Wildtype
C	Payload Suppressor D Toxin-load 	D	Payload Suppressor C Toxin-load 

Engineered fitness valley

- ' C ' or ' D ' express the 
- ' C ' and ' D ' do not express the  but carry the **payload**

	cd	cD	Cd	CD
cd	1			
cD				
Cd		$1 - s$		
CD	$1 - s$	$1 - s$	$1 - s$	$1 - s$

Locus 'C'		Locus 'D'	
c	Wildtype	d	Wildtype
C	Payload Suppressor D Toxin-load 	D	Payload Suppressor C Toxin-load 

Engineered fitness valley

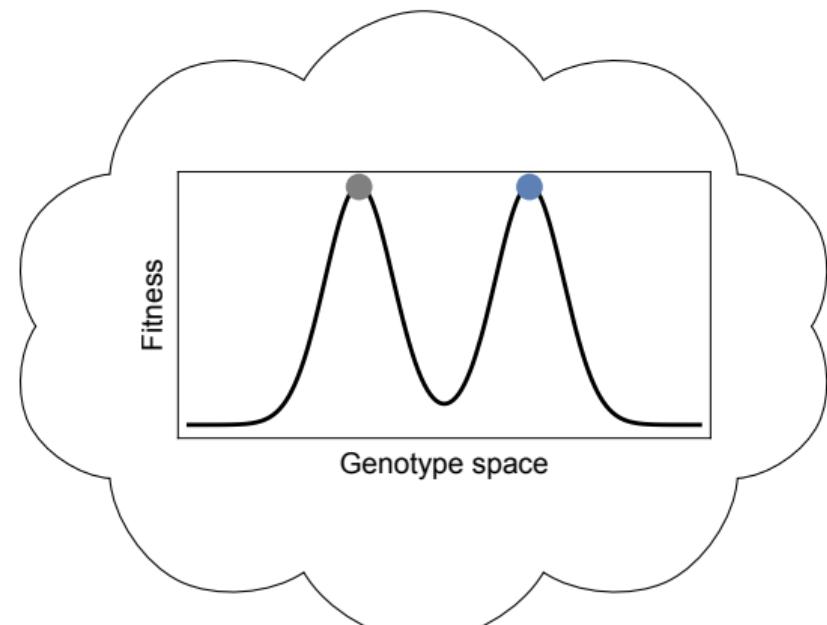
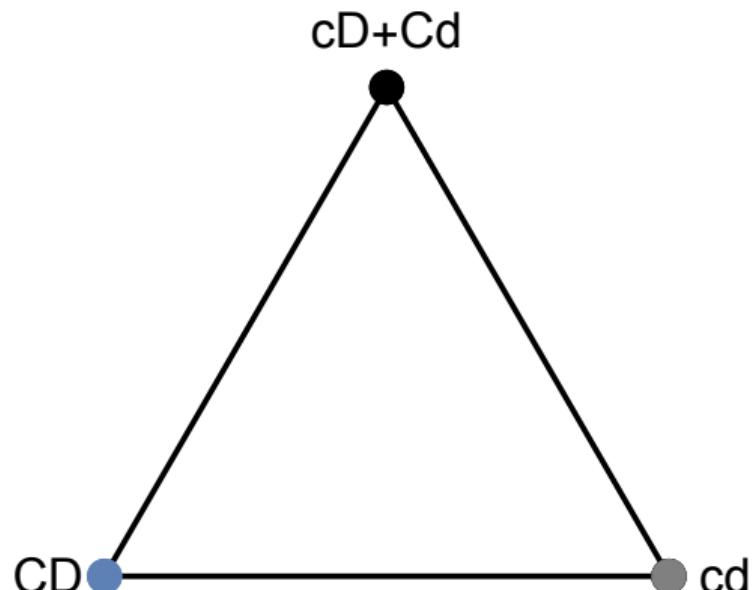
- ' C ' or ' D ' express the 
- ' C ' and ' D ' do not express the  but carry the **payload**
- Recombination helps by creating genotypes with one ' C ' or one ' D '.

	cd	cD	Cd	CD
cd	1			
cD				
Cd		$1 - s$		
CD	$1 - s$	$1 - s$	$1 - s$	$1 - s$

Locus 'C'		Locus 'D'	
c	Wildtype	d	Wildtype
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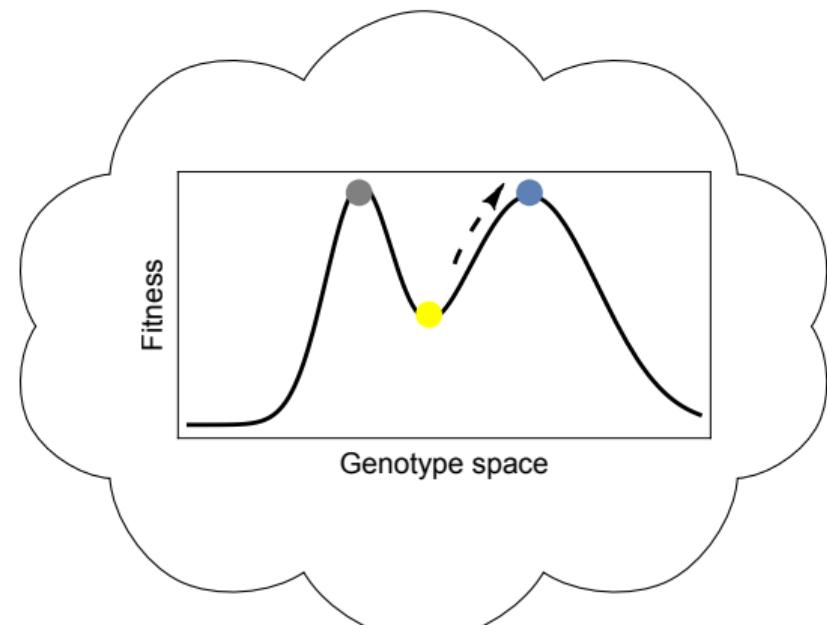
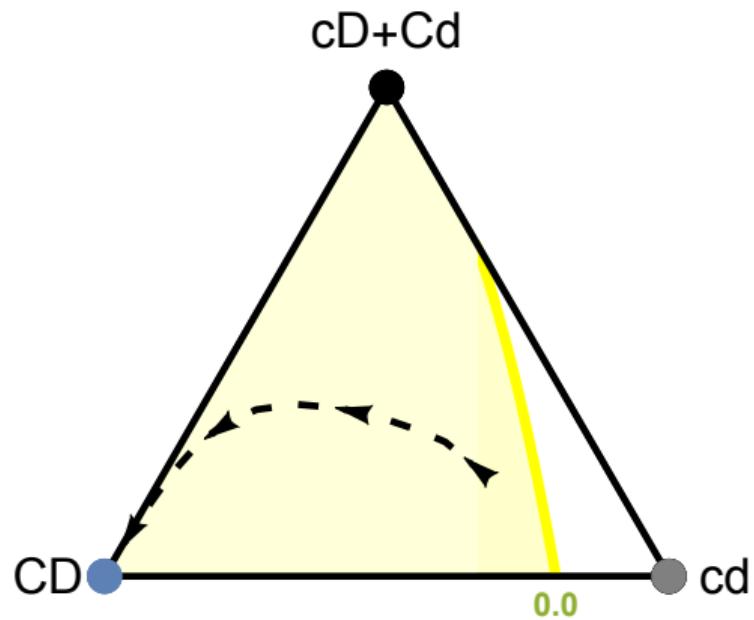
Engineered fitness valley

Toxin kills 100%



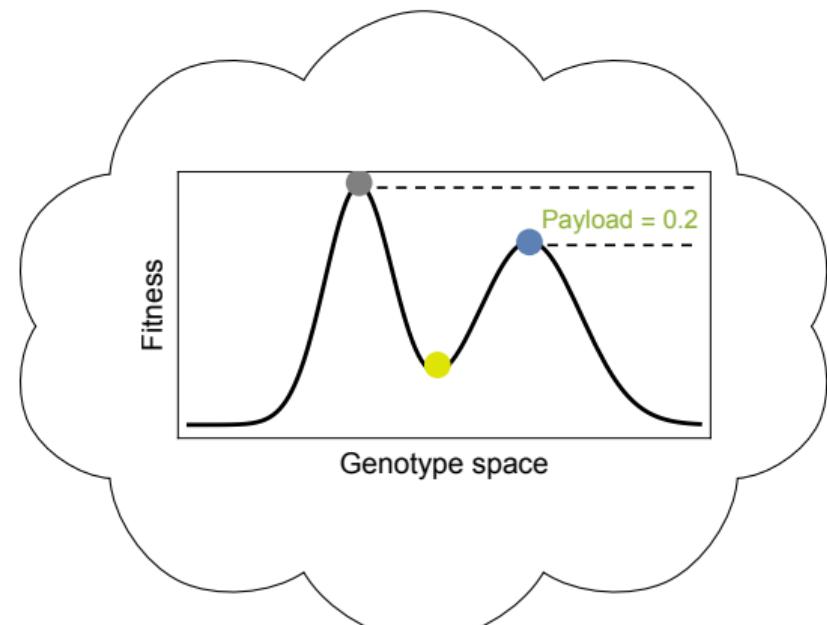
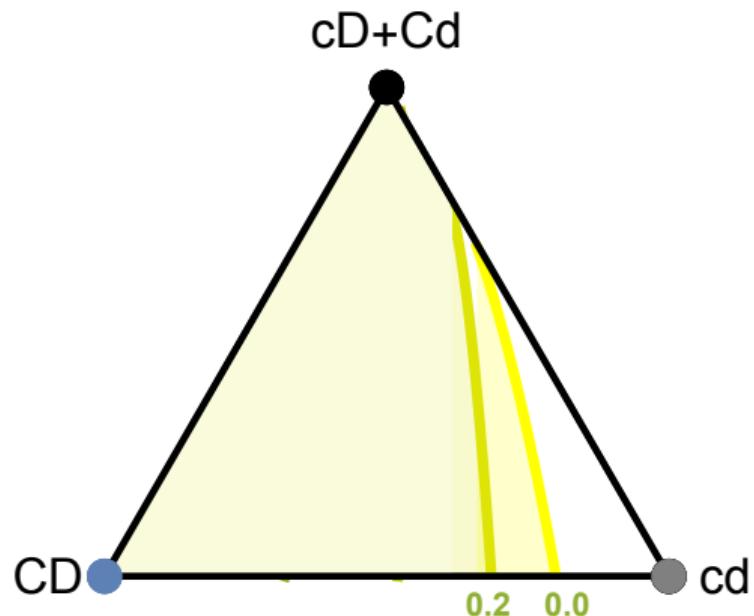
Engineered fitness valley

Toxin kills 100%



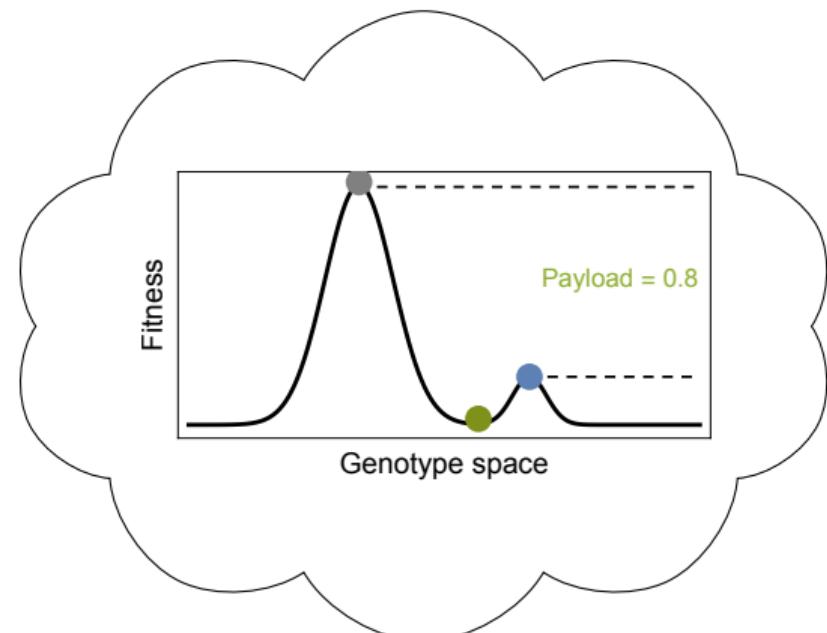
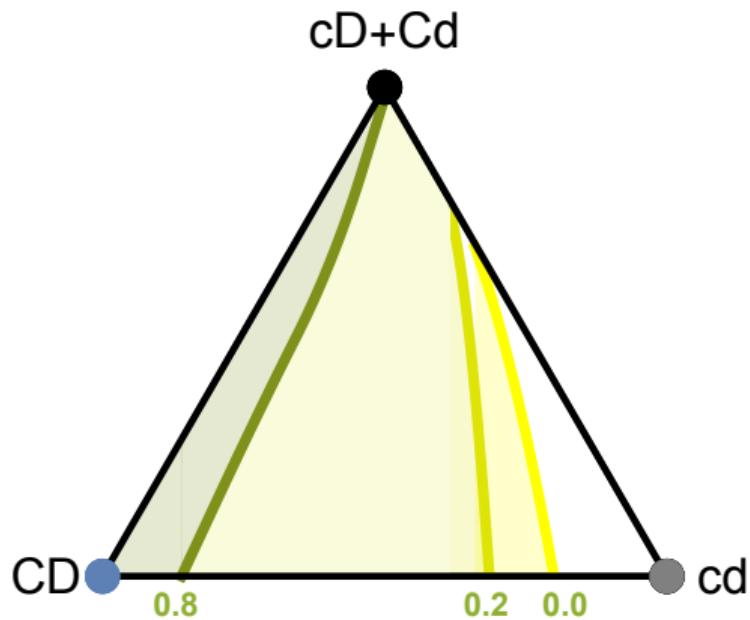
Engineered fitness valley

Toxin kills 100%



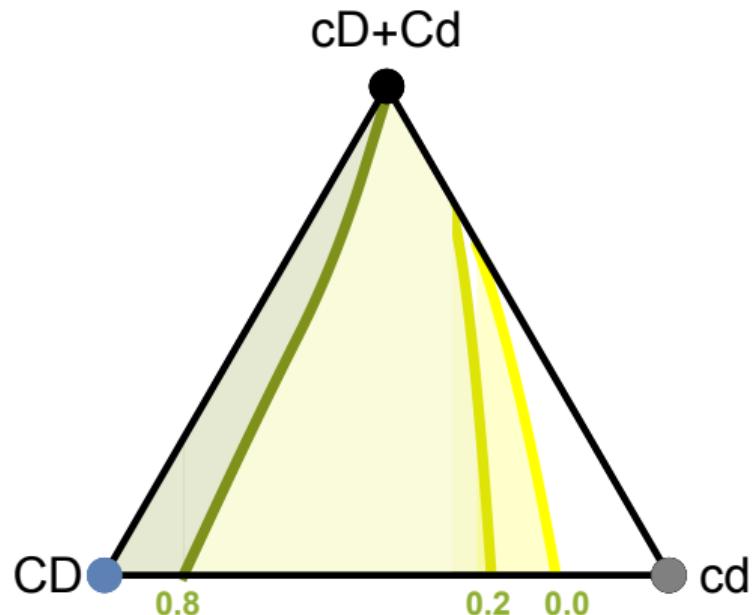
Engineered fitness valley

Toxin kills 100%

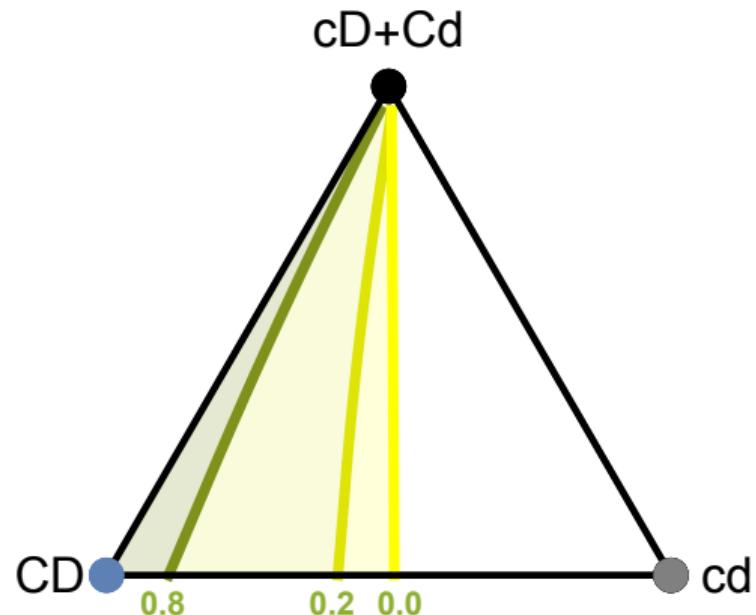


Engineered fitness valley

Toxin kills 100%

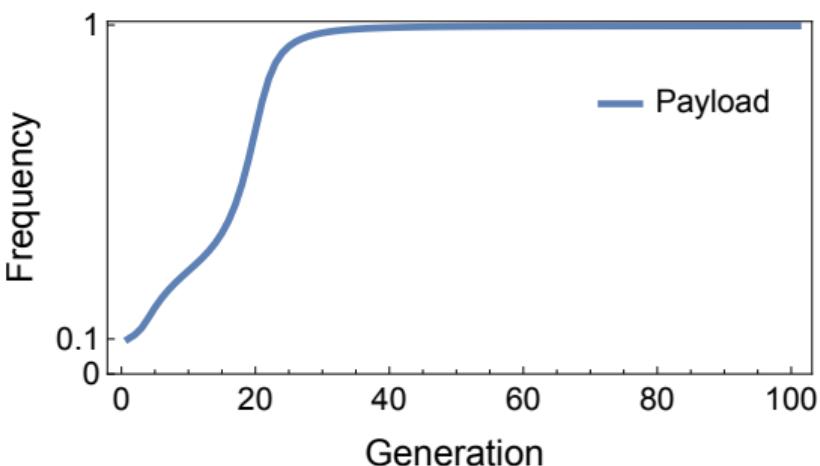


Toxin kills 1%

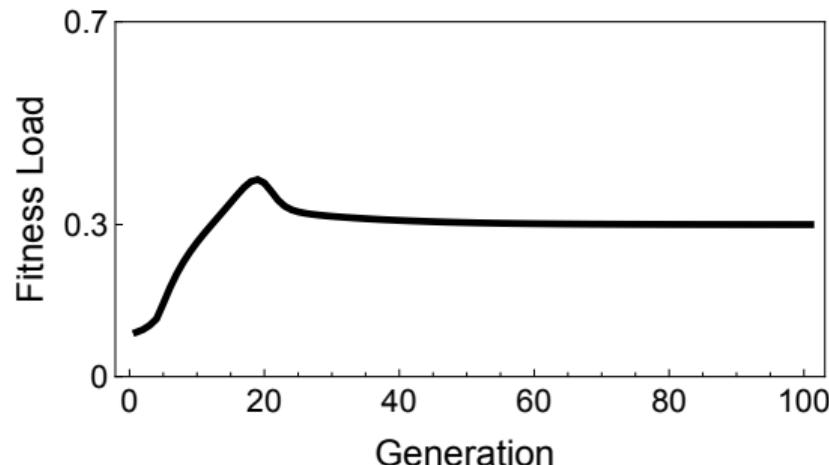


Proof of concept

Dynamics



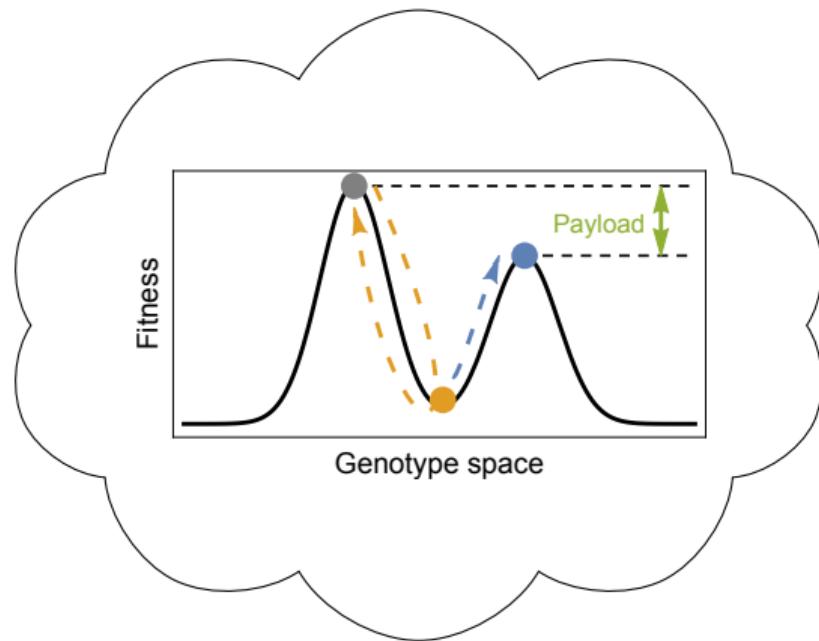
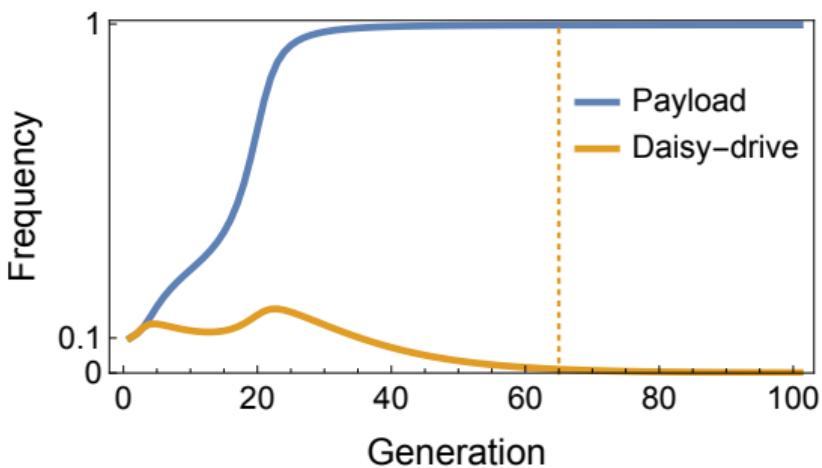
Fitness Load



- Idealized scenario: drive and toxin-load are 100% effective

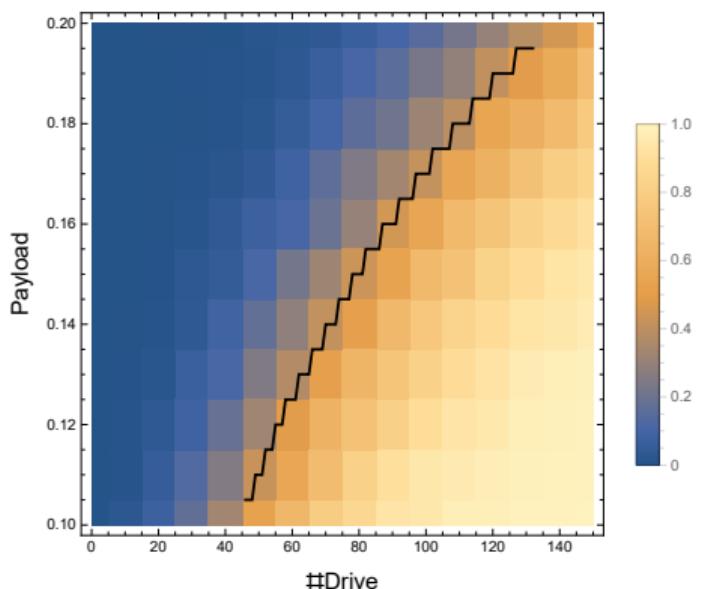
Proof of concept

Dynamics



Simulations

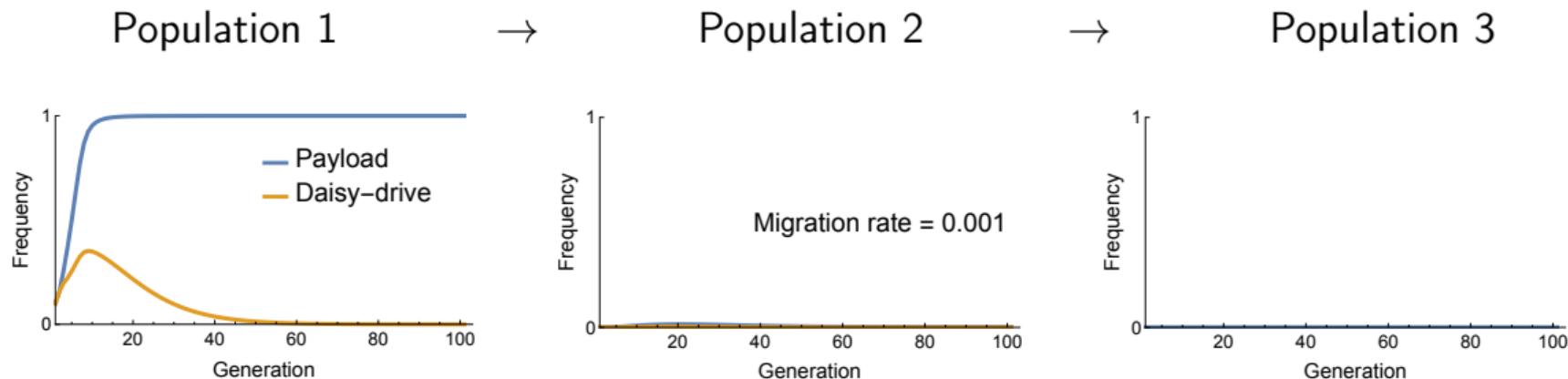
Probability of extinction



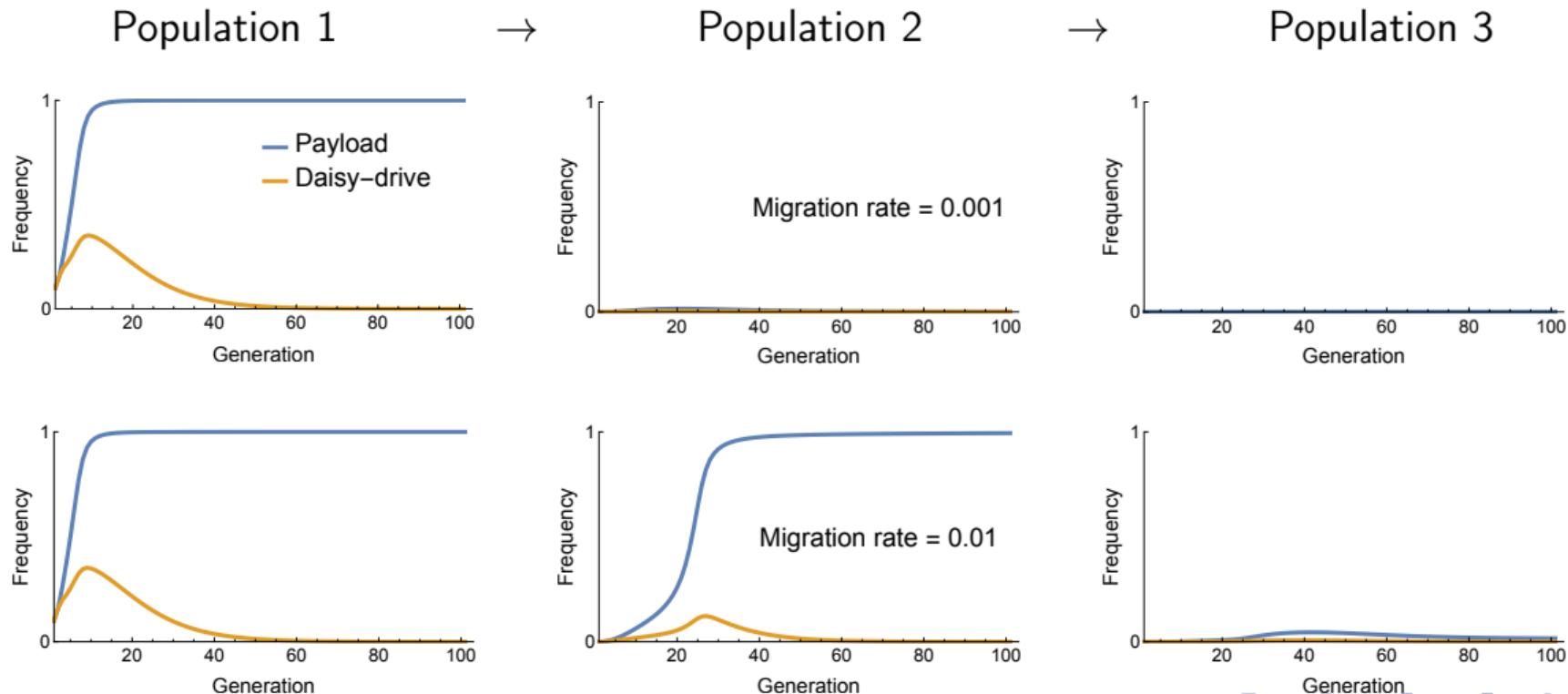
Individual based simulations

- Carrying Capacity = 1000
- Fertility = 1.1

Migration threshold



Migration threshold



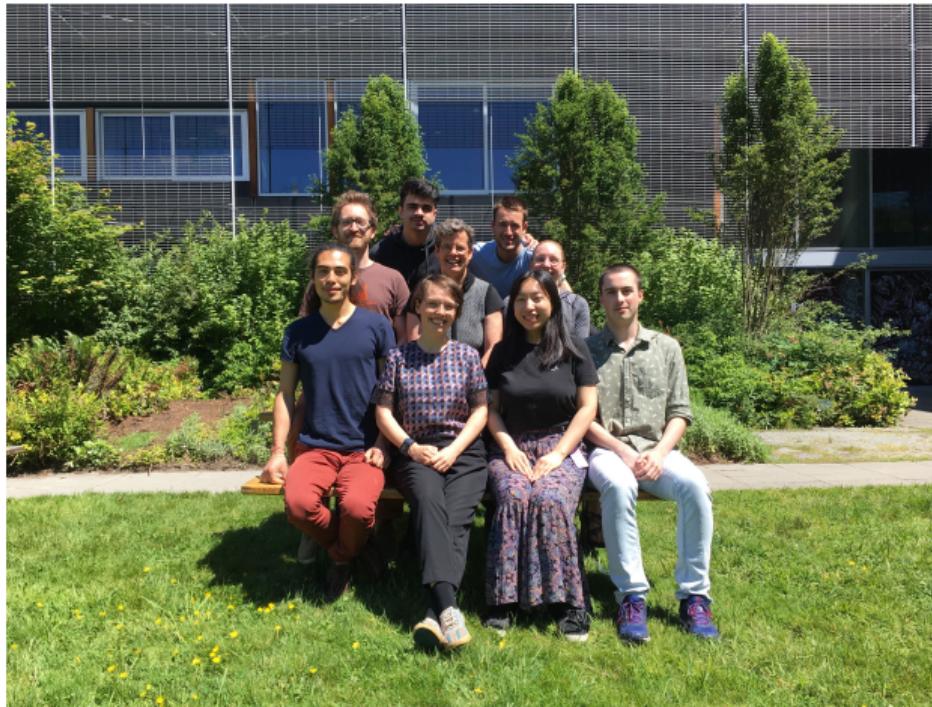
Take home message:

Risks of gene drive following release are also great, including

- Spread beyond the area of interest
- Spread beyond the target species
- Resistance might evolve, leaving the potential for gene drive

Need: develop drives with fewer risks

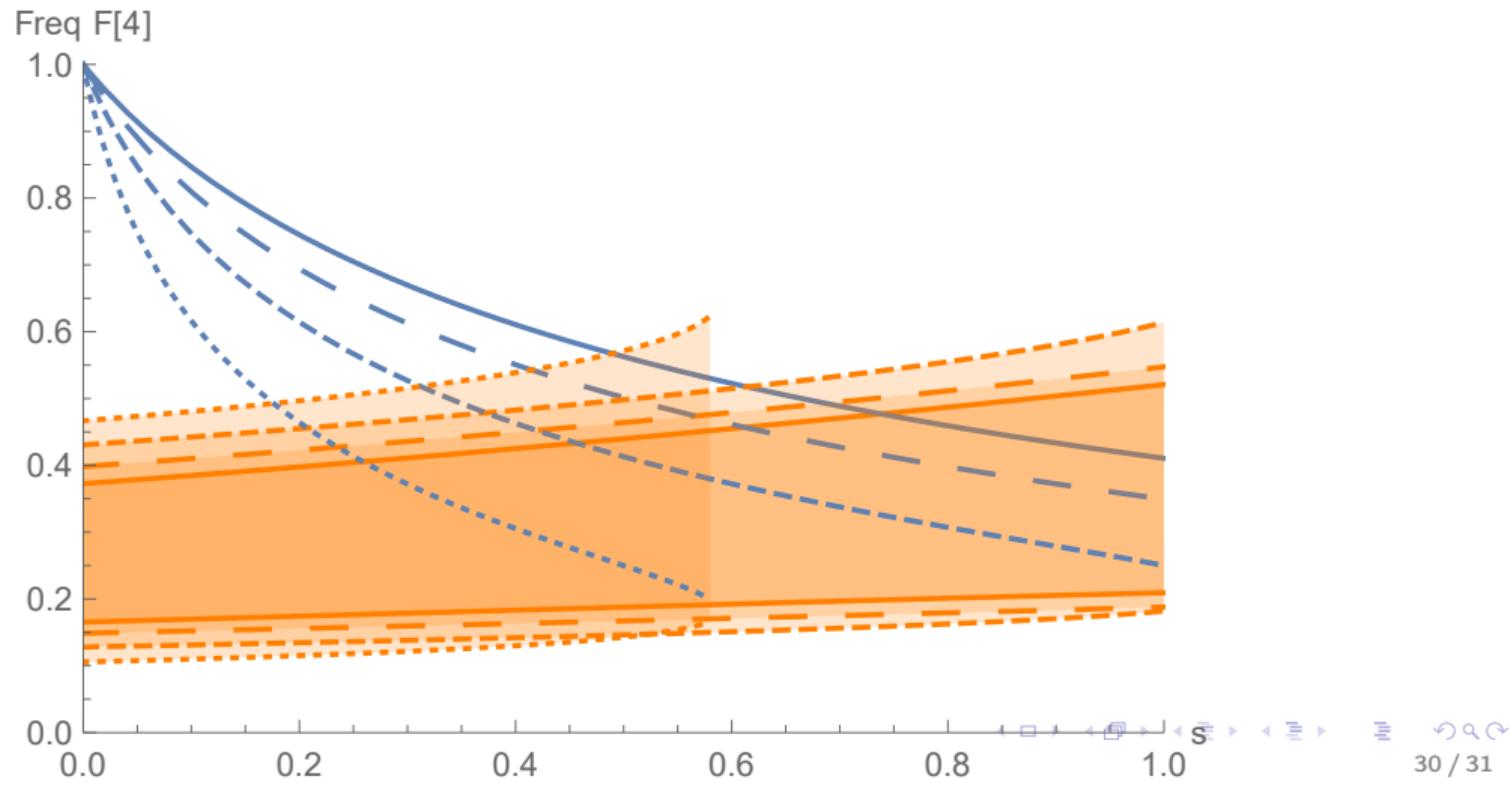
Acknowledgements



Thanks

Extra slides

Recessive fitness payload



Multiplicative fitness payload

