A brief introduction to gene drives

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Natural gene drive mechanisms

Gene drives

- Mechanisms that cause genetic elements to be inherited at super-Mendelian rates

Natural mechanisms

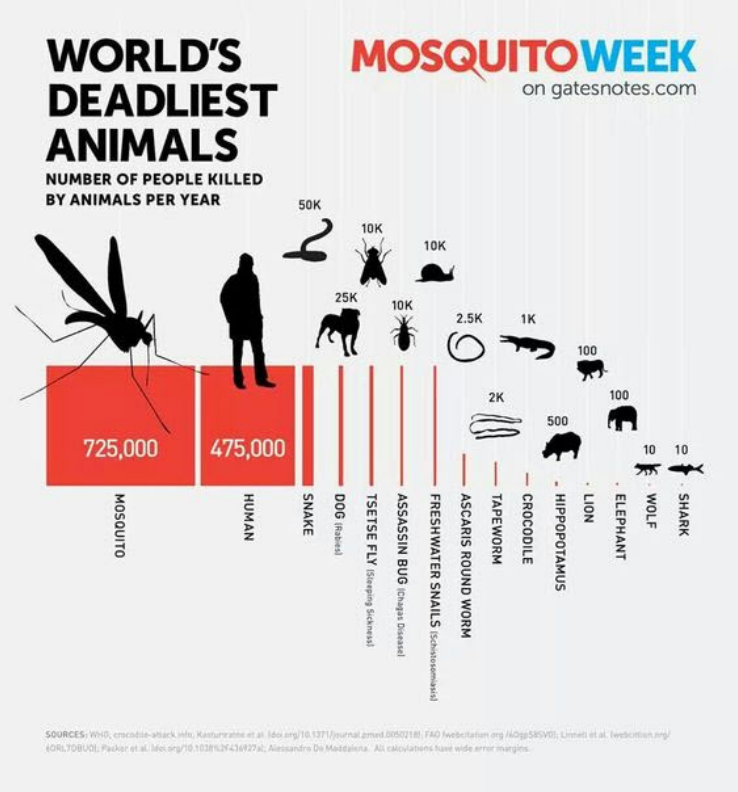
- Transposable elements
- Maternal Effect Dominant Embryonic Arrest (MEDEA)
- Homing Endonuclease genes
- Cytoplasmic incompatibility
- Cytoplasmic male sterility
- Meiotic drive
- Underdominance

Characteristics of gene drives (Sinkins and Gould, 2006)

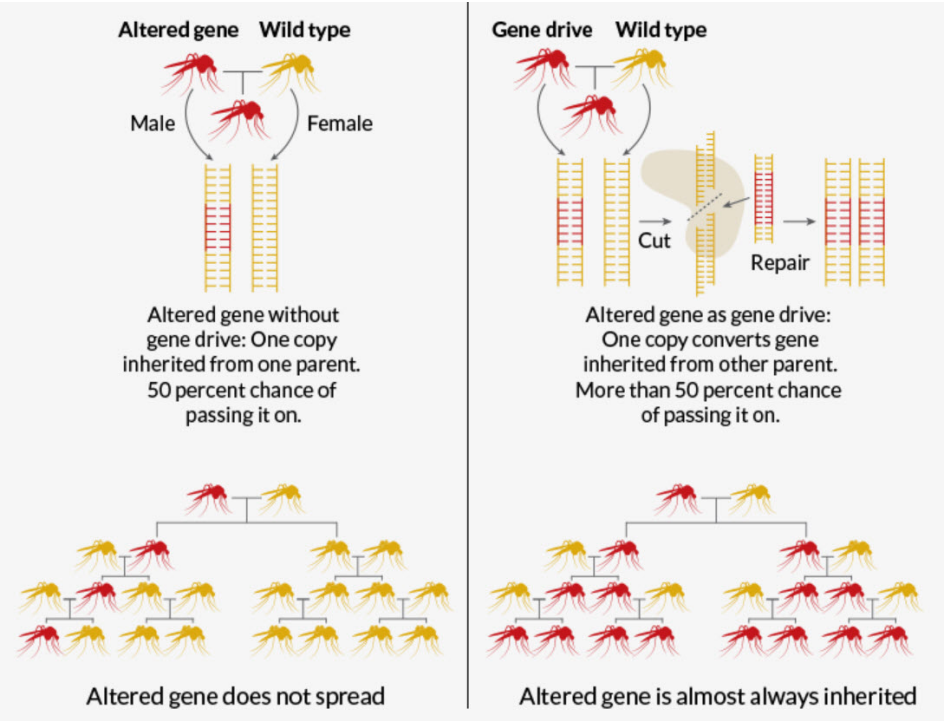
Characteristic	Classes of potential drive systems				
	Transposable elements	Natural meiotic drive	Engineered meiotic drive or HEG	Engineered underdominance	*Wolbachia*
Is a release threshold required before population spread begins?	No	No	No	Comparatively high	Usually low
Is efficiency of drive dependent on insert size?	Yes	No	No; unknown for HEGs	No	No
Is there a mechanism for repeated spread?	Different transposable elements might be required	No	Redesign of target sequence	Different promoters and suppressors	Incompatible strains
Can insect tissue-specific promoters be used?	Yes	Yes	Yes	Yes	No
Is there a mechanism for transgene removal from the population?	No	No	Redesign of target sequence	Large-scale release of wild-type insects	Incompatible strains
Is there a risk of spread to non-target species?	Low	Close to zero	Close to zero	Close to zero	Low
Is the system known to function in important pest species?	Yes	Yes, but insensitivity alleles occur	No	No	Yes
Is there a potential use for the same system in secondary vectors?	Yes	Unlikely	Yes	Yes	Yes

CRISPR game changer

Why would we deploy this technology?



Population suppression or alteration with CRISPR-Cas9



Source: Saey (2015)

Gene drive in randomly mating population (Unckless et al., 2015)

Frequency of transgenic allele q depends on conversion rate c, fitness cost s, and fitness cost dominance in heterozygotes ($h = 1$ dominant, $h = 0$ recessive) :

$$q' = \Big[\underbrace{q^2(1-s)}_{\text{Homozygotes}} + \underbrace{q(1-q)(1-c)(1-hs)}_{\text{Unconverted heterozygotes,}} + \underbrace{q(1-q)2c(1-s)}_{\text{Converted heterozygotes}}\Big]\bar{w}^{-1}$$

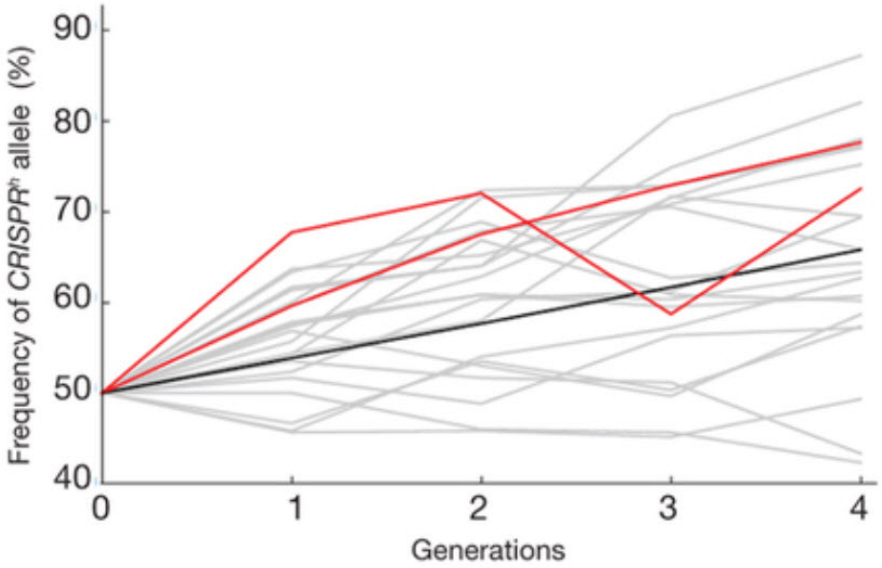
When allele is rare $q^2 \simeq 0$ and $\bar{w} \simeq 1$ so

$$q' = q^2(1 - s_e)$$
$$s_e = hs(c-1) + (1-2s)c$$

Which means that deleterious allele can spread so long as

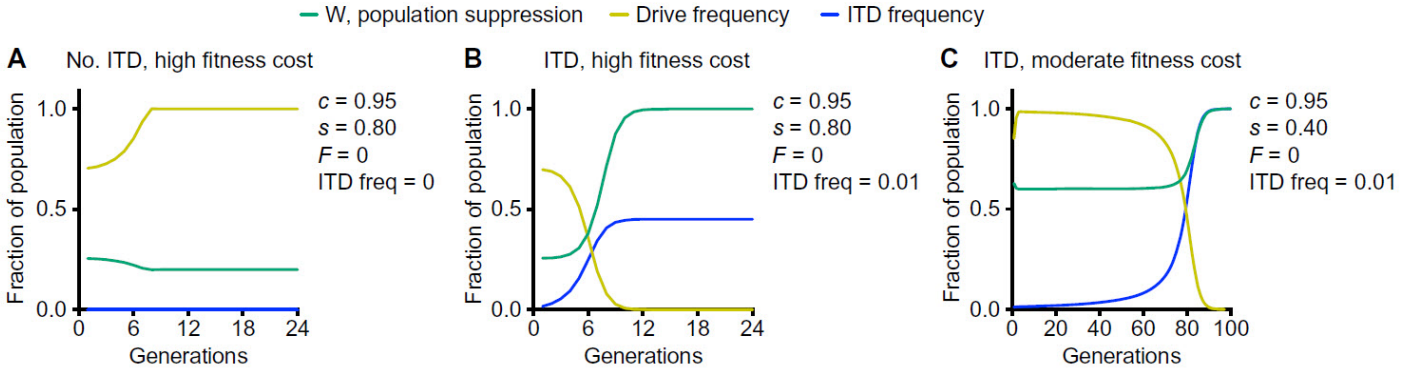
$$c > hs/(1 - 2s + hs)$$

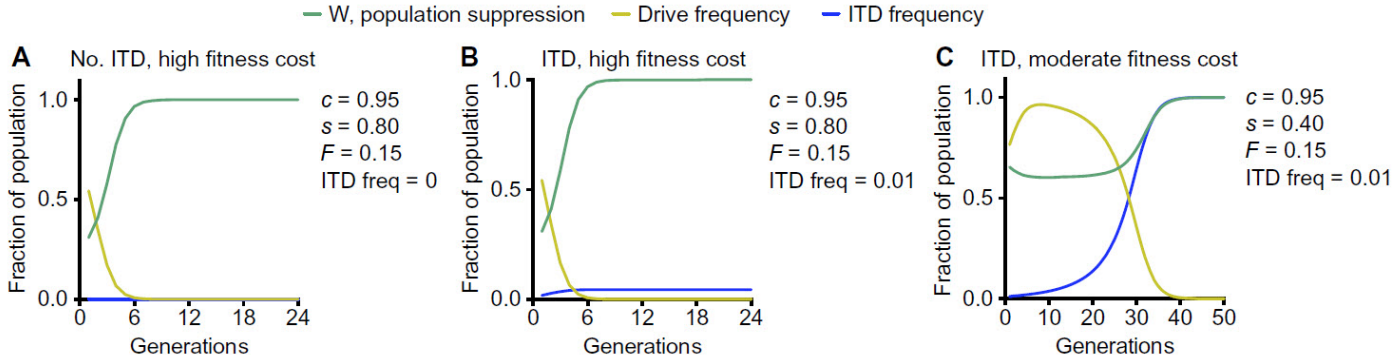
Recessive female-sterile gene drive in *An. gambiae*



Source: Hammond et al. (2016)

Immunity To Drive in Flour Beetles (Drury et al., 2017)





CRISPR-Offcuts (Schaefer et al., 2017)

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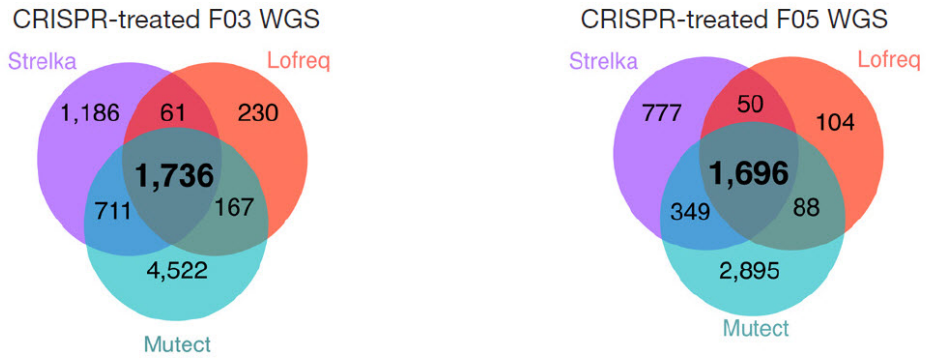

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Variant type	CRISPR-treated F03 mouse	CRISPR-treated F05 mouse	Identical variants in CRISPR-treated mice
WGS SNVs	1,736	1,696	1,397
WGS indels	164	128	117
Exon SNVs	60	51	39
Exon indels	6	3	2
Nonsynonymous protein coding	26	18	15
Top 50 predicted sites	0	0	0

References

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Thank You

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