Technology characterisation of Gene Drives and potential applications - an introduction -

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Remote control of populations via a „genomic interface“?

„Gene Drives“

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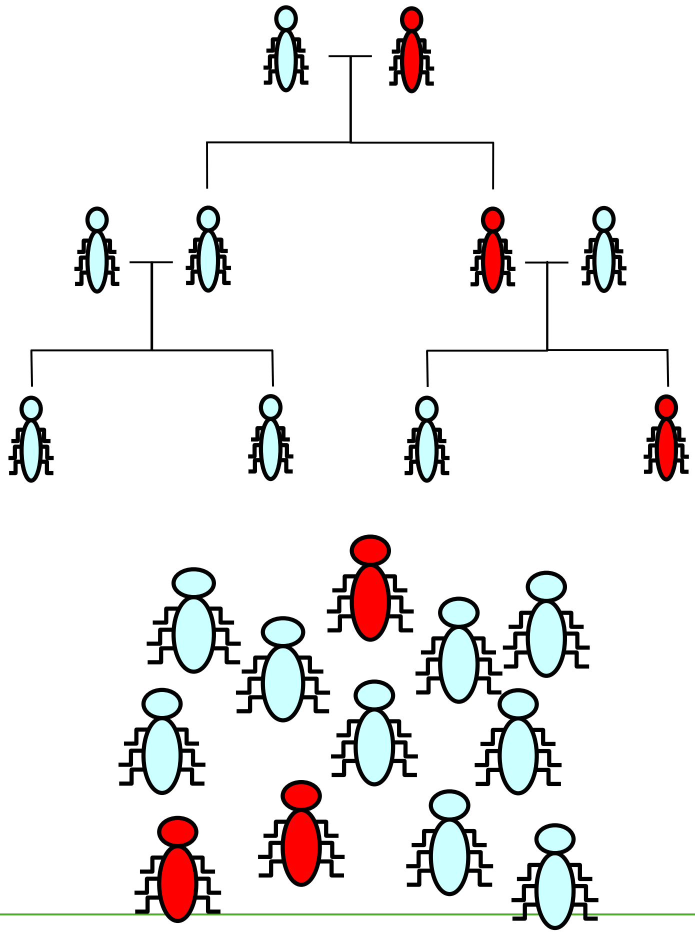
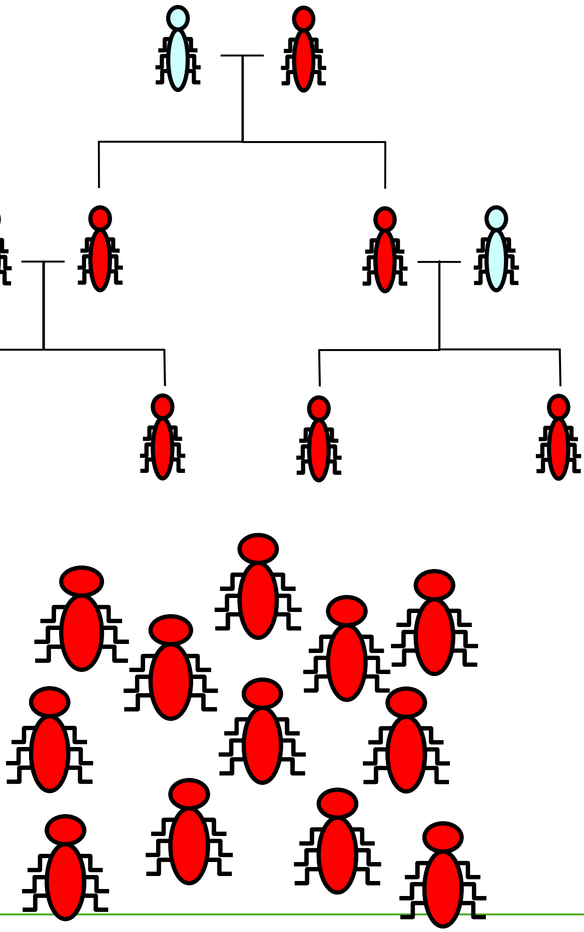
(Mendelian) inheritance of a **Gene**



Gene Drive biased inheritance



Gene Drives as Conversion Drives

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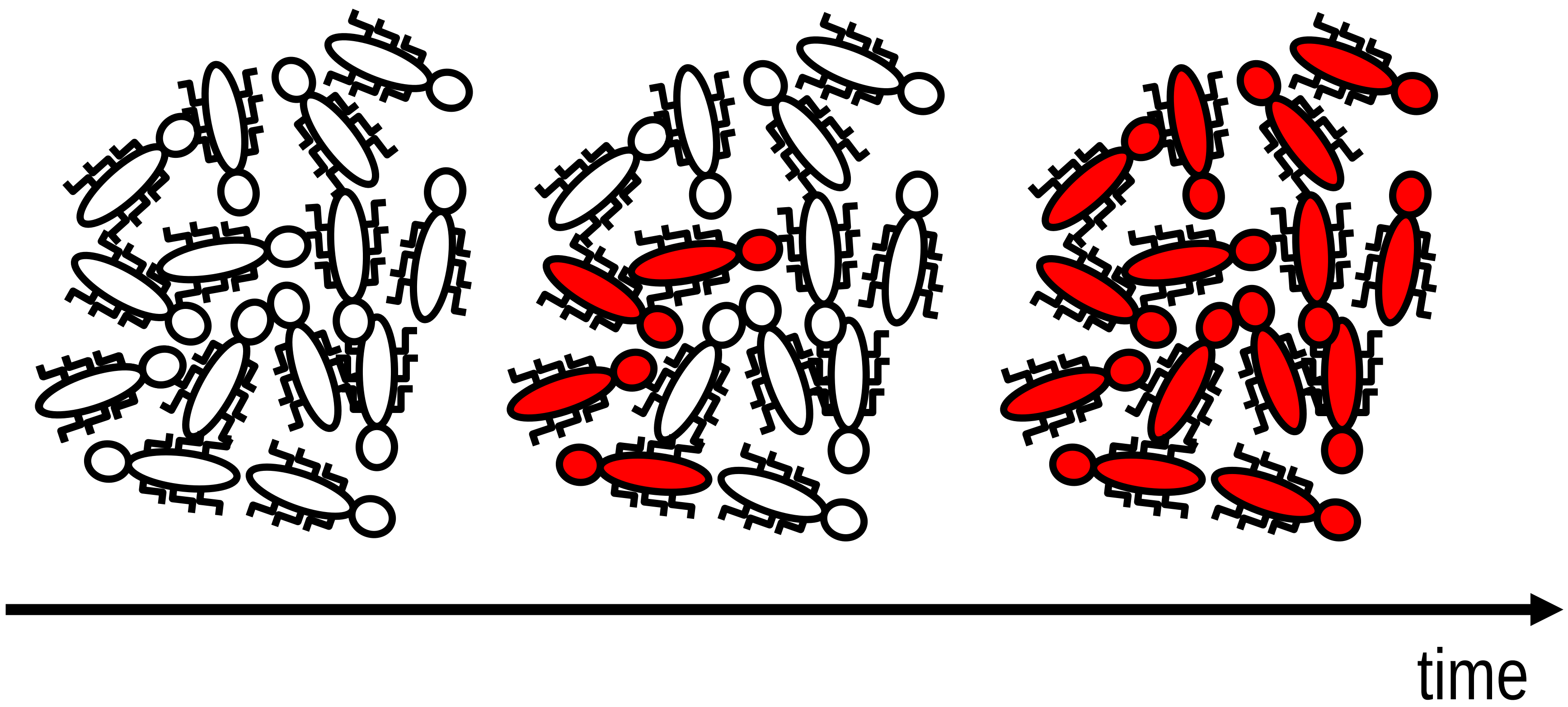
→ Control by spread (of new traits)



Gene Drives as Suppression Drives

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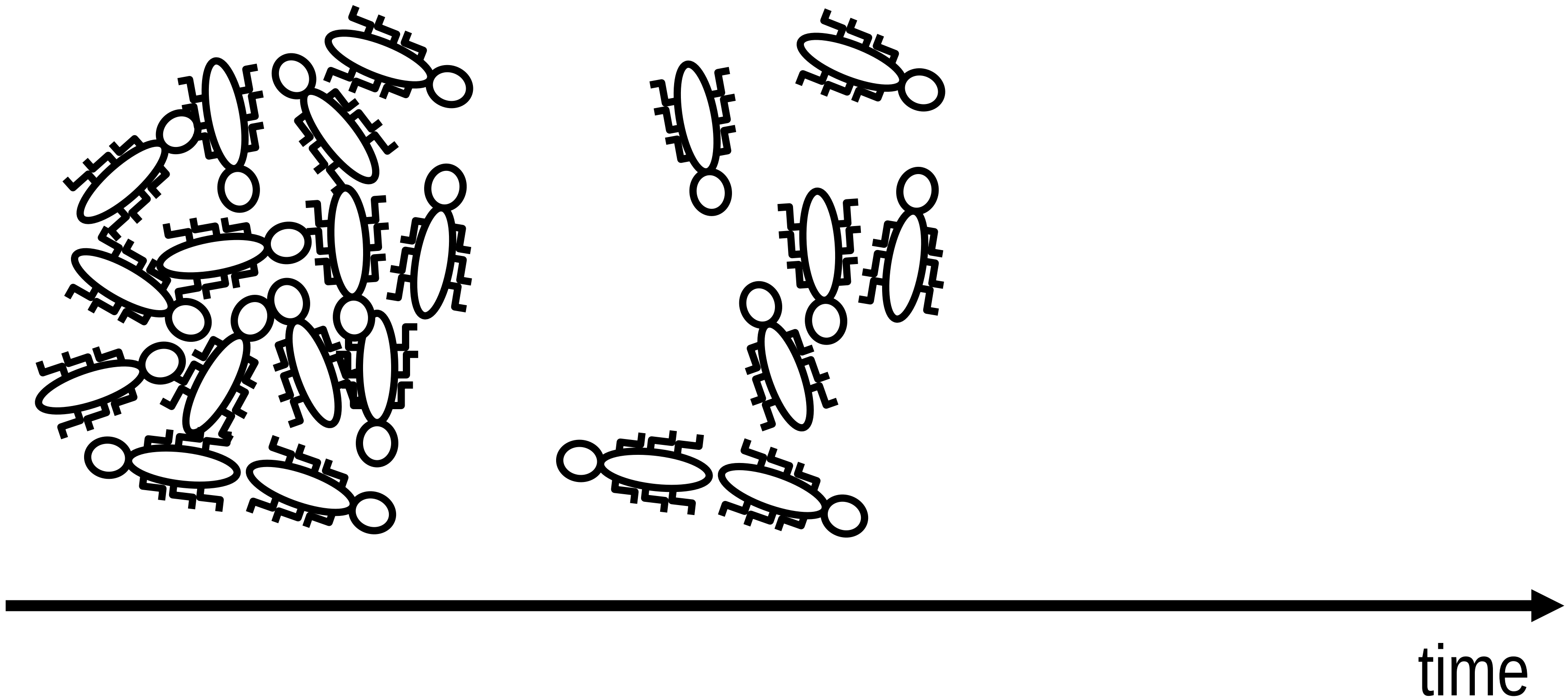
→ Suppression or even eradication of populations



SPAGE-Technologies and Gene Drives

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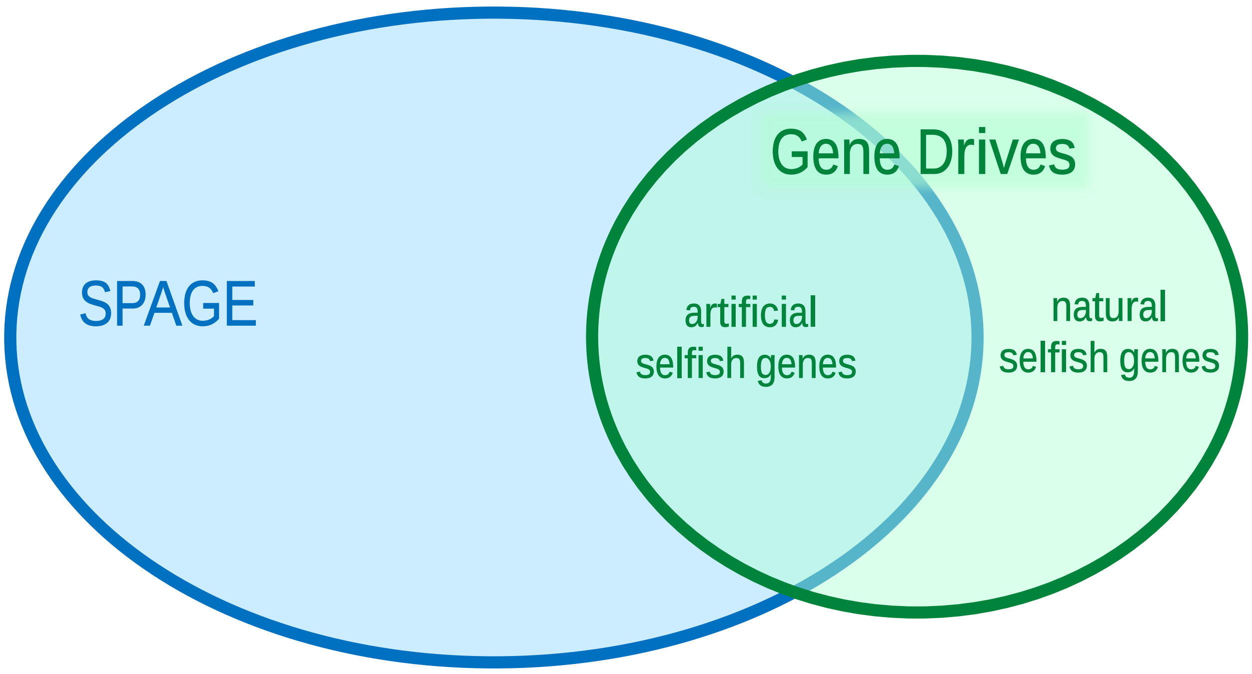
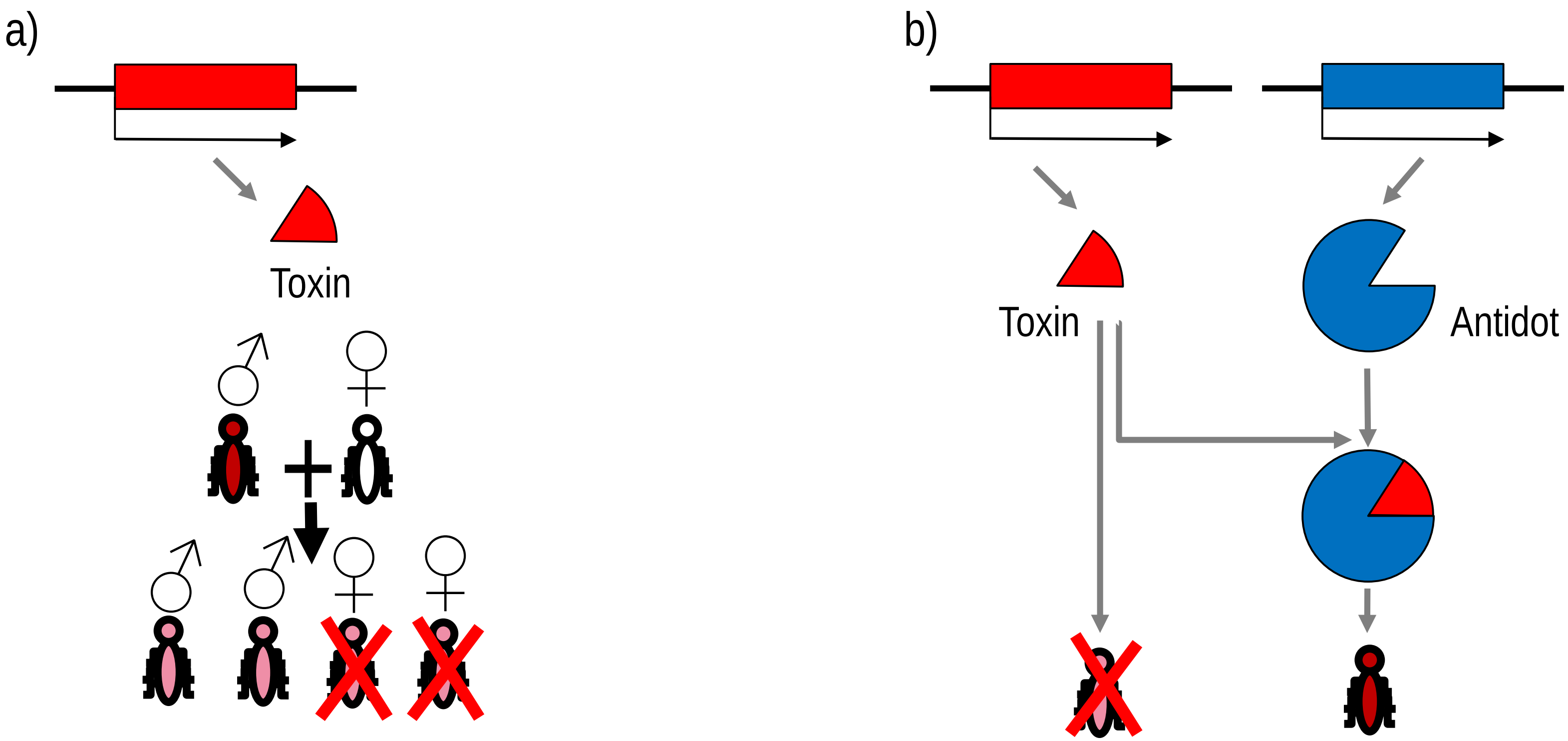
SPAGE= self-propagating artificial genetic element



Types of SPAGE/Gene Drives

Passive:

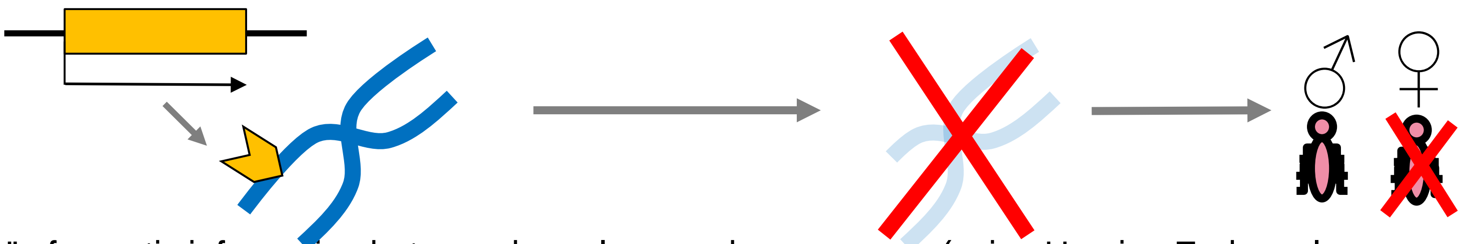
- Only offspring not targeted by a toxin or
  carrying a particular combination of genetic elements (toxin + antidot) survives



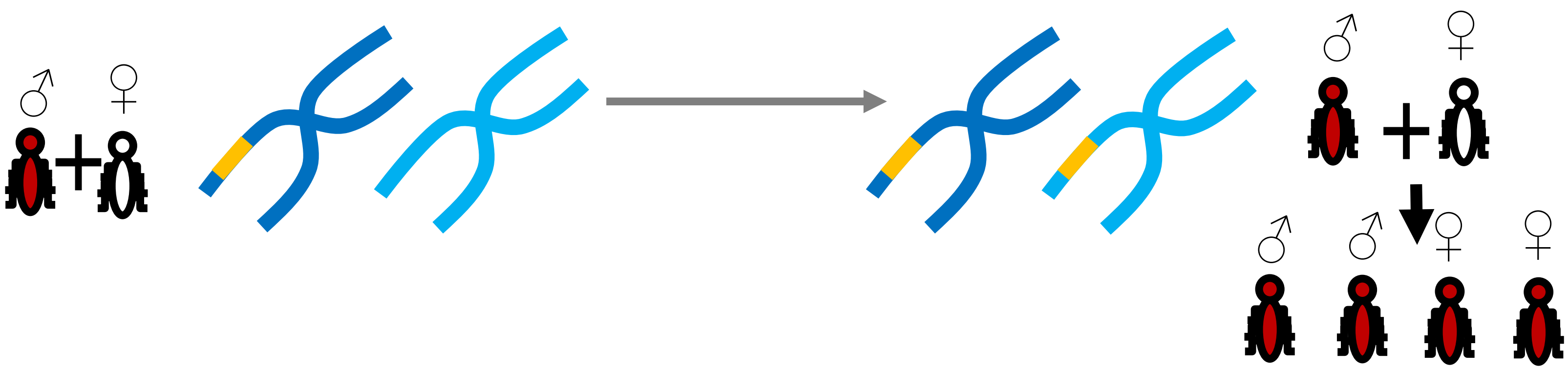
Types of SPAGE/Gene Drives

Active (by genome modifications):

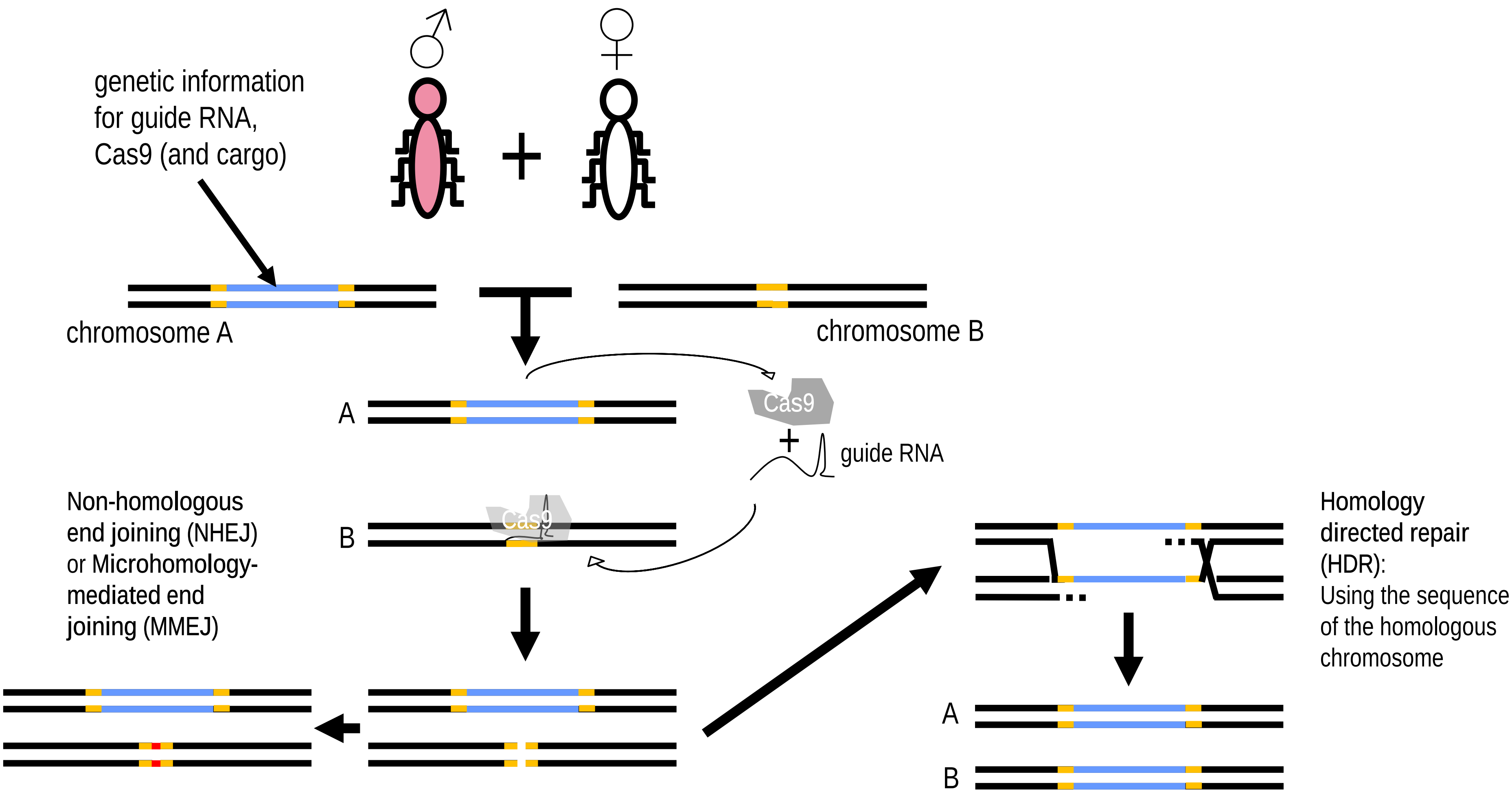
- Bias of sex ratio by (enzymatic) mechanisms influencing meiotic segregation (inhibition of sperm development) /„shredding“ of the X-chromosome



- “Copying” of genetic information between homologous chromosomes (using Homing Endonuclease Genes (HEG))



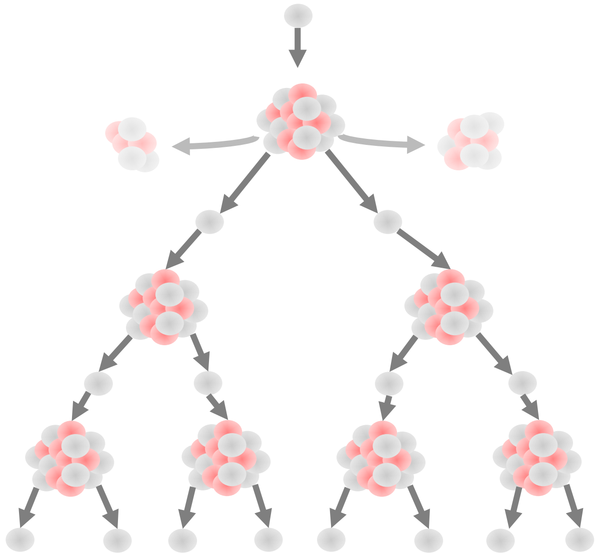
Mechanism of CRISPR/Cas9 – based Gene Drives



High power by Homing Endonuclease based drives

- for CRISPR/Cas9-based gene drives copying efficiencies of 91–99% can be achieved

(Gantz and Bier 2015; Gantz et al. 2015; Hammond et al. 2015 cited in Lin and Potter 2016)



A “mutagenic chain reaction”?

Cp. Gantz & Bier, Science, 24 APRIL 2015 • VOL 348 ISSUE 6233

Deficiencies of CRISPR/Cas-Gene drives

Potential unintended effects and/or reduced power by:

- Non-homologous end joining (NHEJ) and Microhomology-mediated end joining (MMEJ) instead of Homology-directed repair (HDR) reduces the conversion rate and may cause resistance due to mutations, deletions etc.
- Resistance due to genomic variations (sequence polymorphisms), homing resistant alleles
- Maternal effects due to Cas9 deposit may cause resistance
- On-target misinsertions
- Off target-effects (unspecific binding of gRNA causes unintended insertions at different locations)
- Intragenomic interactions

No claim to be complete …

Intervening in organisms

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- Gene Drives in general represent a **high depth of intervention** due to
  - the directed modification of the genome
  - the ability to bias the genotype of populations
  - Accordingly, it holds the potential for a
    - high **technological power** by its toxic / enzymatic mode of action and the option of cargo genes
      (→ **hazard potential**)
    - high **range** due to its influence on the pattern of heredity or even the capability of self-replication
      (→ **exposure potential/potential of contamination**)

Depth of Intervention, Power and Range of generations of breeding technologies

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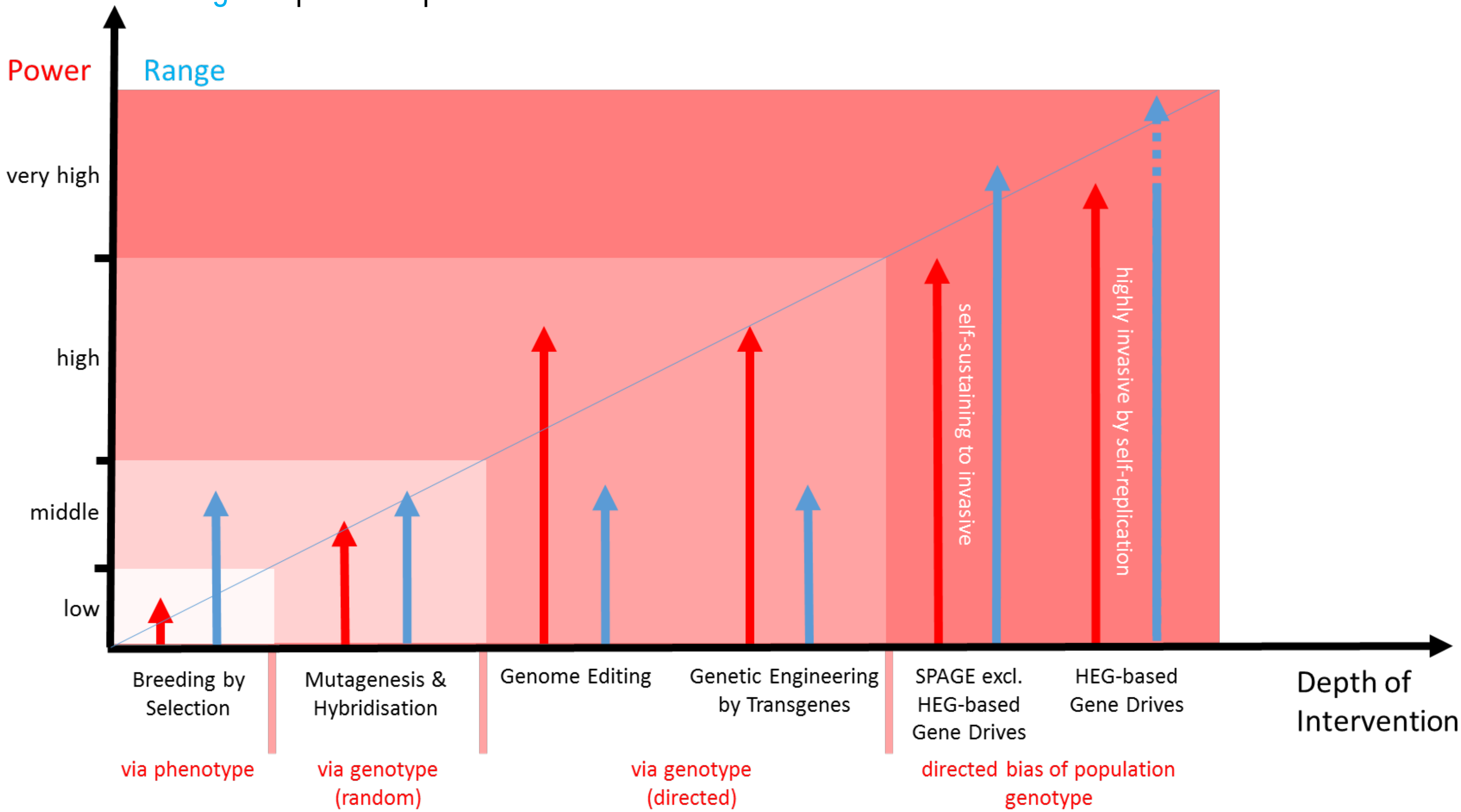
Power = directedness and character of the implemented trait
Range = spatio-temporal radius



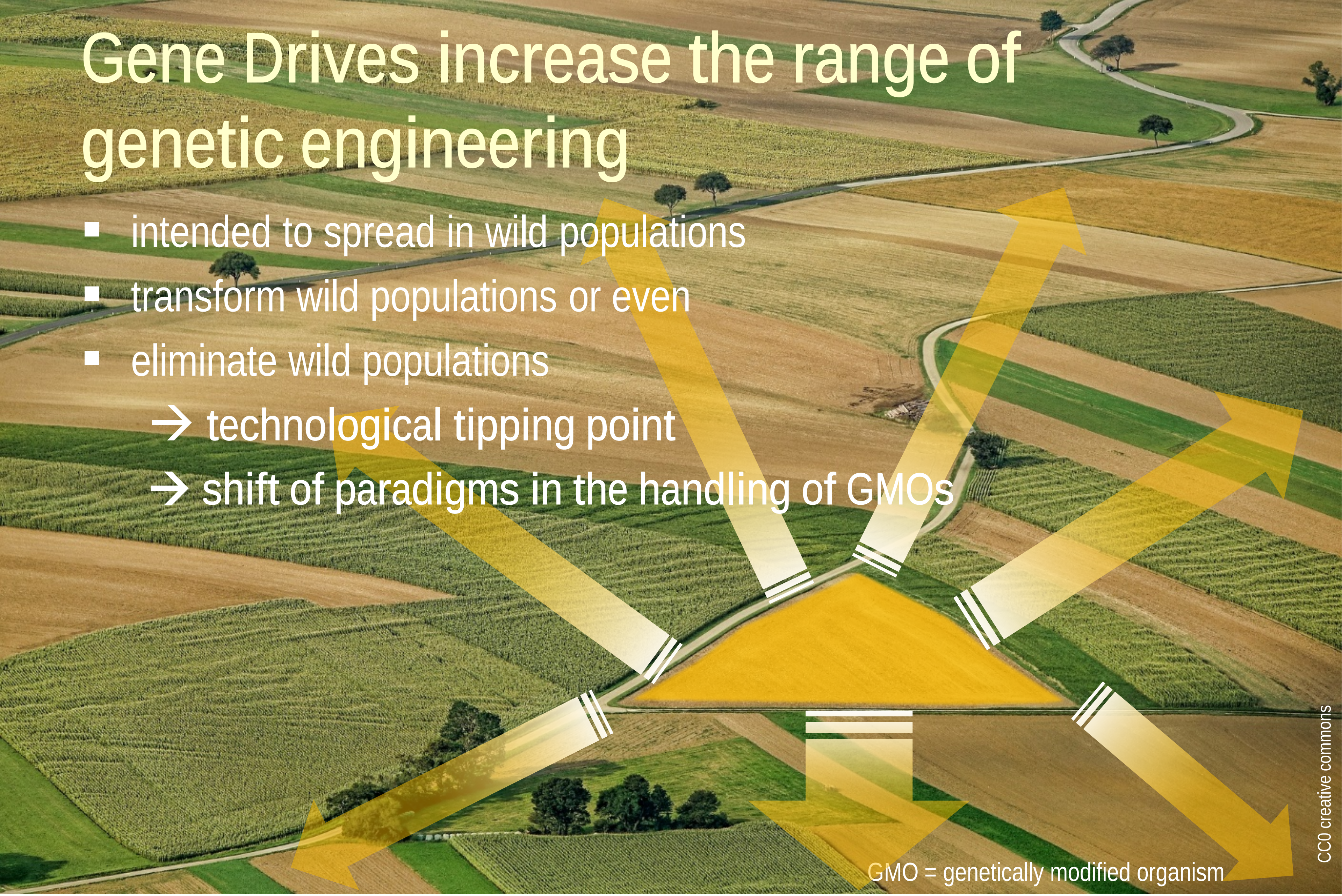
SPAGE = self-propagating artificial genetic elements

Gene Drives increase the range of genetic engineering

- intended to spread in wild populations
- transform wild populations or even
- eliminate wild populations

  → technological tipping point

  → shift of paradigms in the handling of GMOs



GMO = genetically modified organism

Applications of Gene Drives

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- Medical:
  - Immunization or elimination of disease vectors

- Agricultural:
  - Elimination of plant and animal pests
  - Control of pesticide-resistant weeds

- Ecosystem ‚engineering':
  - Invasive species (e.g. in New Zealand)
  - Immunization of endangered species

Malaria and Dengue

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By James D. Gathany - The Public Health Image Library

By James Gathany, CDC - This media comes from the Centers for Disease Control and Prevention's Public Health Image Library (PHIL)

Malaria

- pathogen: 5 *Plasmodium* species
- vector: mainly 3 *Anopheles* mosquito species
- endemic in 91 countries
- 216 million new cases in 2016
- 445,000 deaths
- insecticide and drug resistances evolve

Dengue

- pathogen: Dengue Virus (4 serotypes)
- vector: *Aedes* mosquito genus
- endemic in ~100 countries
- ~93 million clinical cases/year
- ~22,000 deaths
- mostly preventive vector control

Invasive Species

New Zealand:

- initiative Predator Free 2050
- especially rats, stoats and possums
- gene drive application considered
- problem of confinement (global diffusion)

By Martin Cooper from Ipswich, UK - Spotted-wing Drosophila (Drosophila suzukii) male, CC BY 2.0

Spotted-Wing Fruit Fly in California:

- deposits eggs in cherries with an ovipositor
- Medea Gene Drive is considered to eradicate the fly / alter its ovipositor

„Weed“- Control

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- e.g., Palmer Amaranth
- infested agricultural fields (cotton etc.) in the Southern United States
- related species are cultivated crops in Mexico and South America (in China and India as well)

NAS-Report (2016): *„What mechanisms are in place for dialogue with the Mexican national government? How will any concerns raised by the Mexican government be incorporated into US decision-making processes?”*

Potential ecological effects

- Evolutionary effects:
  - gene flow
    - intraspecific (may influence fitness of GE- and wild population)
    - interspecific (interspecific mating may influence fitness of other species)
  - mutations of genetic information
  - evolution of resistance (→ blockade of gene drive spread)
- **Ecological interactions:**

→ How many ecosystem processes are dependent upon the target species?

  - role of the species
    - resource/consumer (predator/prey), symbiont/parasite, disease vector, competitor,
    - Loss of ecosystem services? e.g., as pollinators
  - Cascading effects?
  - Loss of diversity?
  - Niche filling by alternative species?

Source: David et al., Ecology and Evolution 2013; 3(11): 4000–4015, doi: 10.1002/ece3.737
Fang 2010, NATURE, Vol 466, 22 July 2010

Potential ecological effects depend

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… on the structure and vulnerability of the affected (eco-)system

Important aspects to consider:

- Critical elements in affected system?
- Structural instabilities?
- Potential tipping points?
- Adaptive capacity?
- Potential for self-repair?

→ structural analysis of vulnerability

… on the character of the drive

Important aspects to consider:

- Exposure potential?
- Hazard potential?

→ effect-related analysis of vulnerability

Source: David et al., Ecology and Evolution 2013; 3(11): 4000–4015
doi: 10.1002/ece3.737

Summary

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- gene drives represent a „tipping point“ of genetic engineering, because
  - power and range potentially exceed capabilities of previous stages in genetic enegineering („active genetics“*)
  - gene drives are designed to
    - actively shape the genotype of wild populations and
    - engineer ecosystems by the conversion or suppression/elimination of wild populations
- in particular actively replicating drives based on homing endonuclease genes (e.g., CRISPR/Cas9) are probably highly invasive
- with potentially extreme power and range many open questions arise regarding effects, control and reversibility

→ urgent demand for prospective analysis of impact, side effects, countermeasures and the feasibility of low-risk approaches

*Gantz and Bier, Bioessays 38:50–63, 2015