

Lose to conserve: Predicting deleterious genomic variants for conservation

séminaire "Taille efficace et dépression de consanguinité «

Mirte Bosse, Paris 13-05

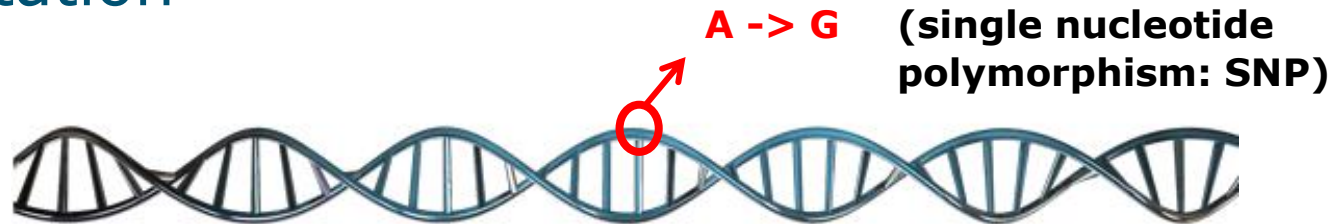


(Genetic) management of populations

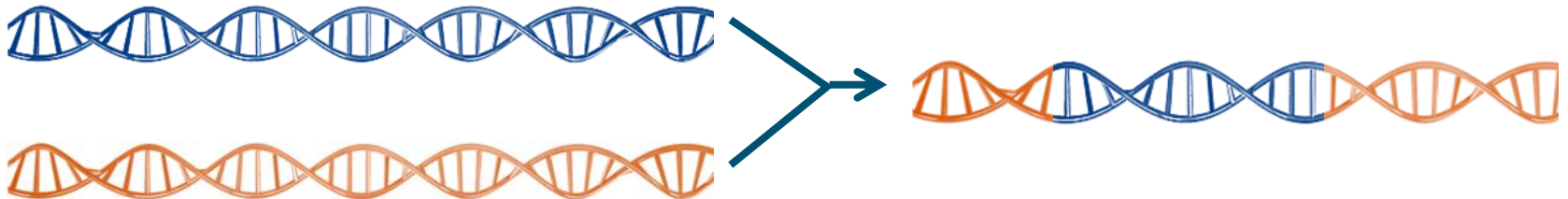
- Select for beneficial traits
 - Local adaptation
 - Specific characteristics (commercial?)
- Maintaining genetic diversity
 - Keep adaptive potential of population
 - Avoid inbreeding depression

Genetic diversity of populations

1). Mutation



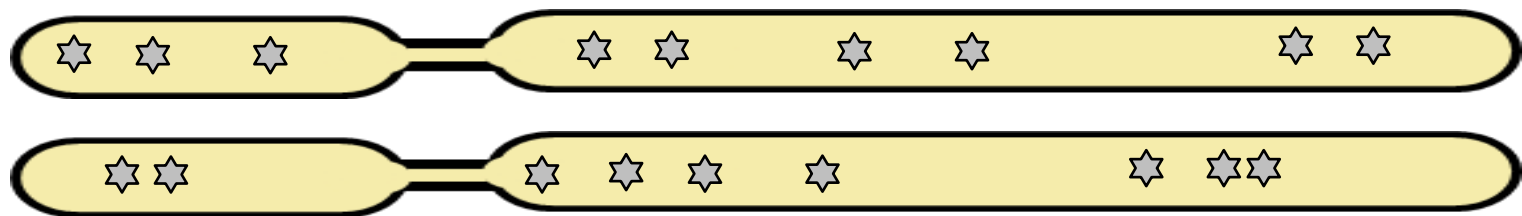
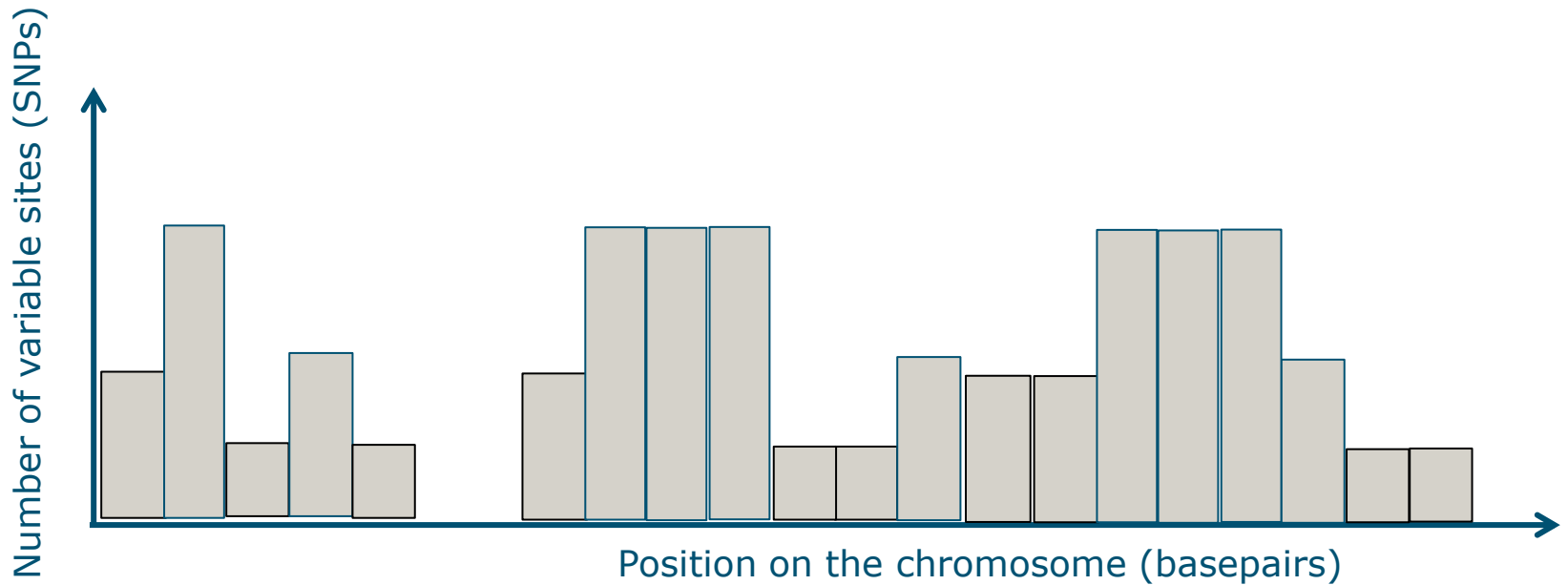
2). Recombination



Driving forces of genetic diversity

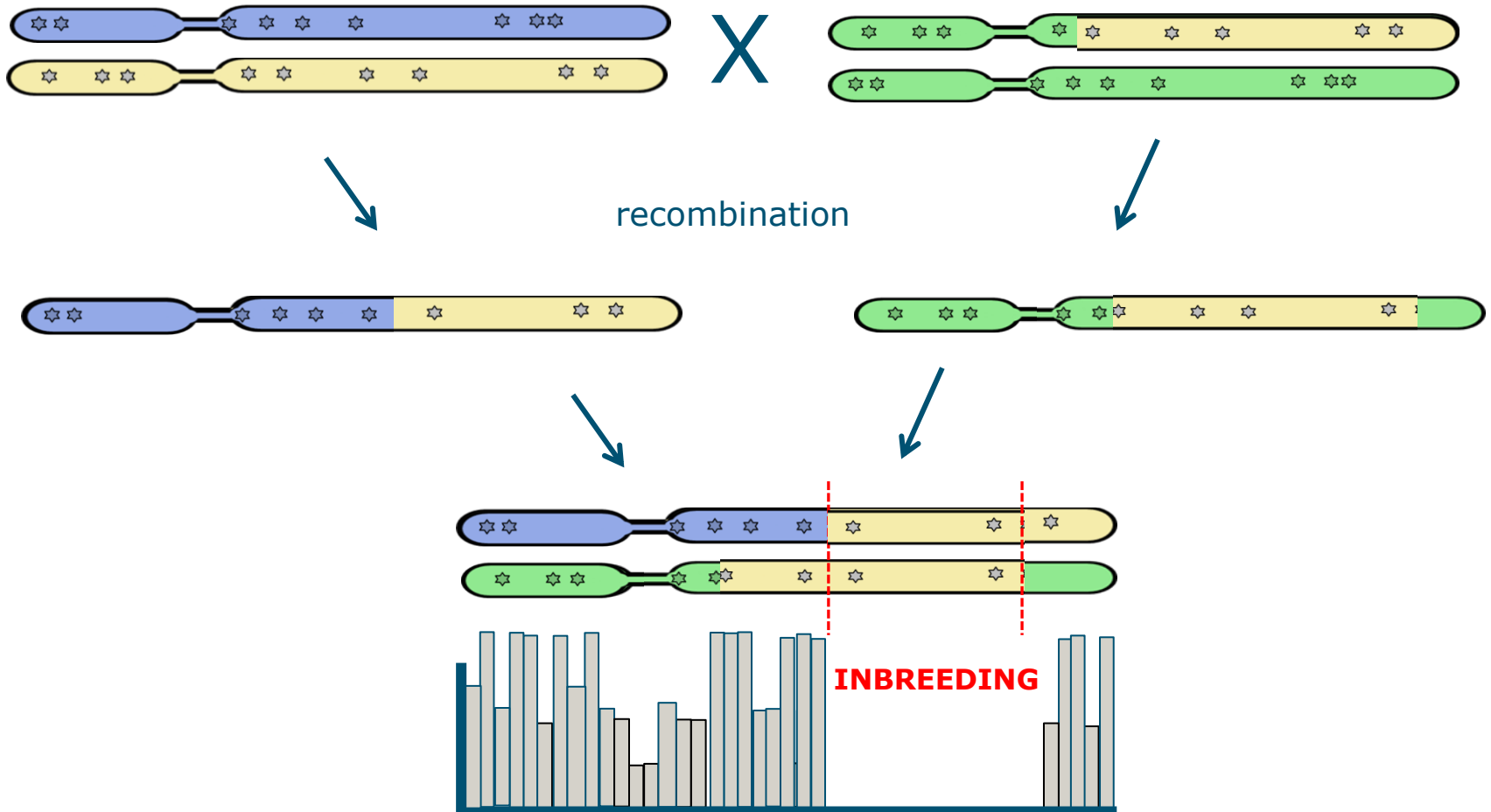
Genetic diversity of populations

How to measure genetic diversity along the genome?



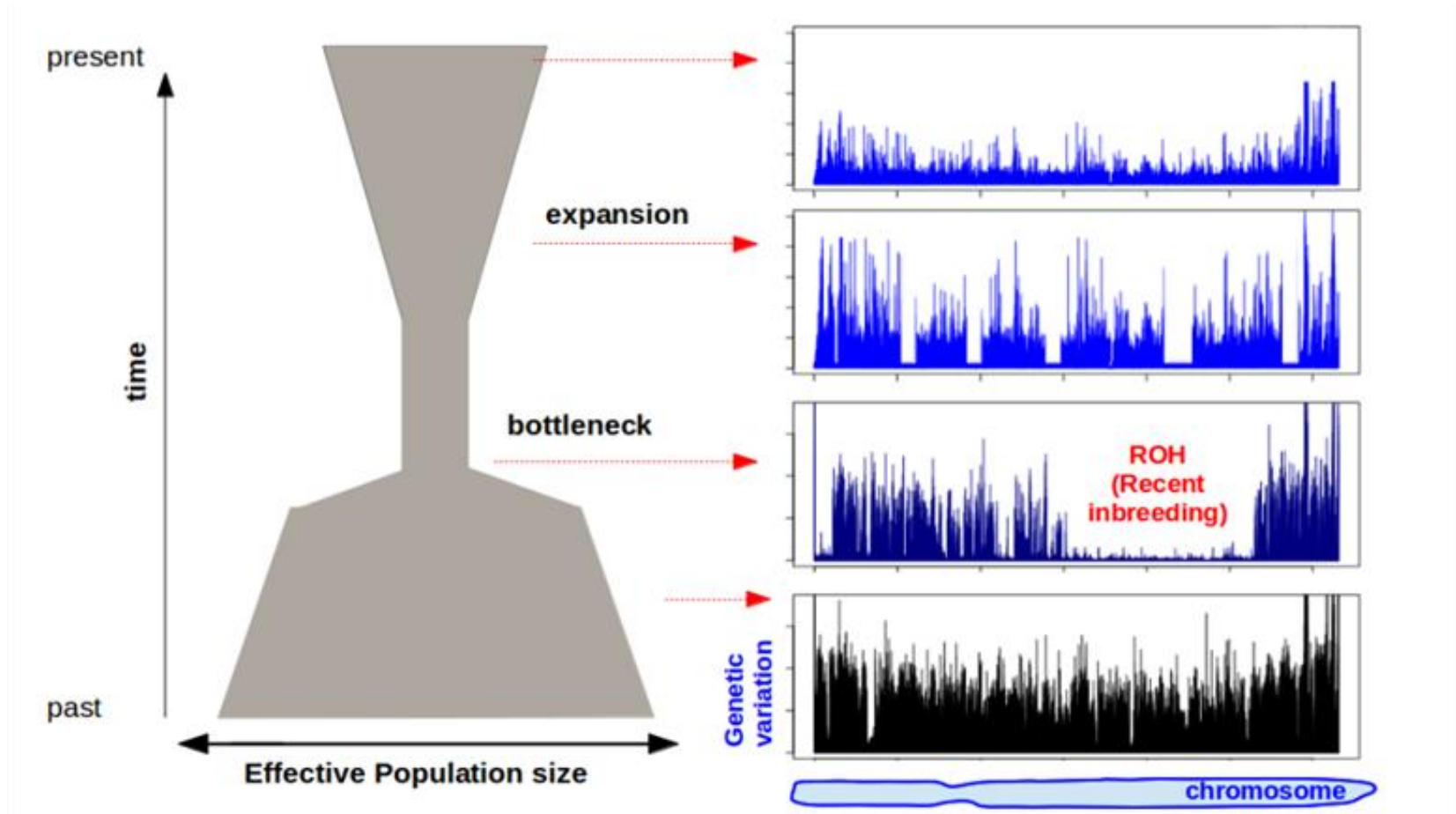
Genetic diversity of populations

How does population size affect genetic diversity?



Genetic diversity of populations

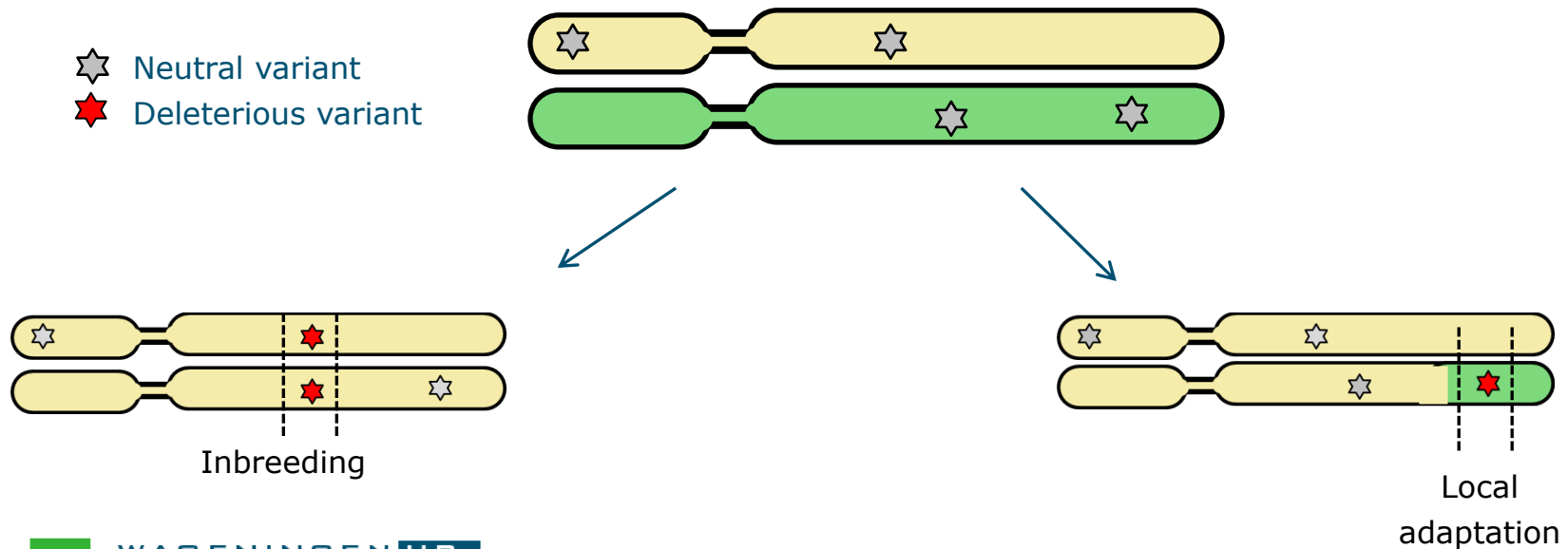
How does population size affect genetic diversity?



Deleterious genetic variation

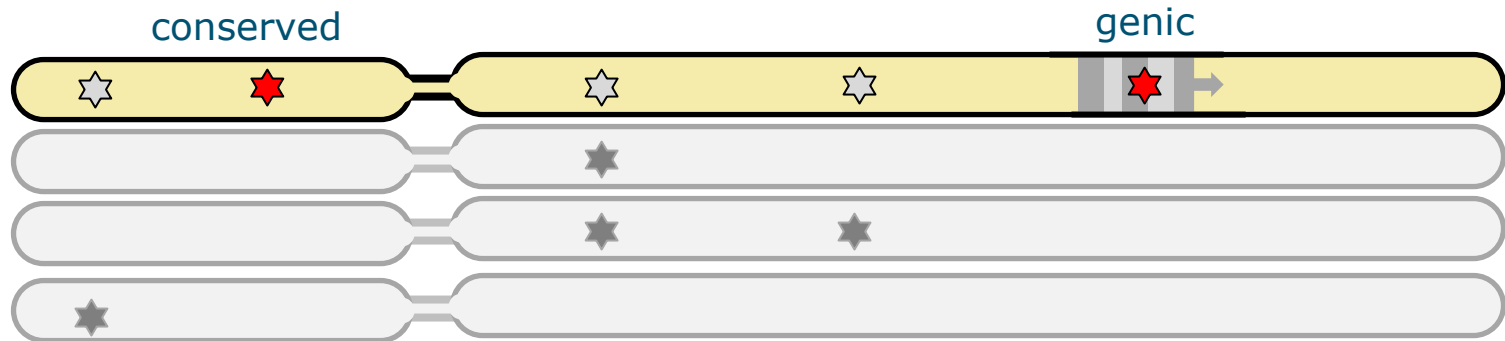
■ Genetic load

- Each genome contains deleterious variants
- Plays a role in inbreeding depression
- Deleteriousness can be context dependent



Predicting deleterious variants – how?

- **Effect of non-synonymous mutations:**
 - 'Sorting Intolerant From Tolerant' (SIFT)
 - 'Polymorphism Phenotyping' (PolyPhen-2)



- **Towards genome-wide predictions:**
 - 'Combined Annotation Dependent Depletion' (CADD)

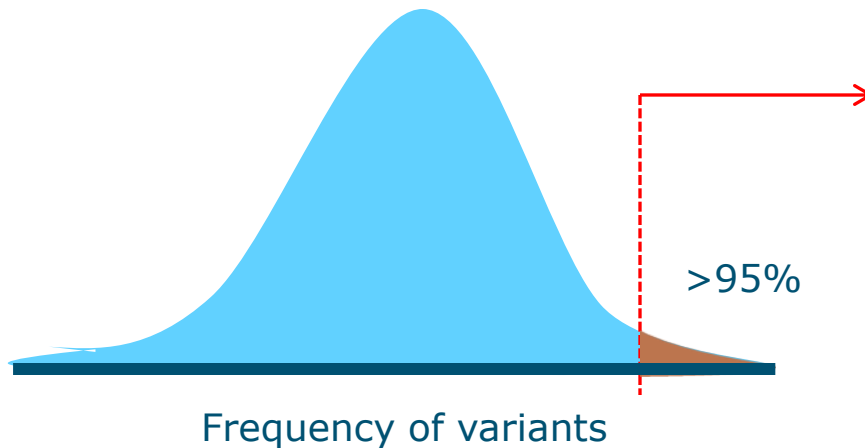
A general framework for estimating the relative pathogenicity of human genetic variants

nature
genetics

Martin Kircher^{1,5}, Daniela M Witten^{2,5}, Preti Jain^{3,4}, Brian J O'Roak^{1,4}, Gregory M Cooper³ & Jay Shendure¹

Predicting deleterious variants – how?

- CADD score for livestock species
 - Similar approaches as for human:



Machine learning approach:

- Simulate variants
- Compare simulation with high-frequency **derived** alleles:
 - Sequence features
 - ENCODE info
 - 60+ annotations total
- Screen for absence in real data

- Some variants are always harmful, regardless species and/or environment

Predicting deleterious variants – how?

- CADD score for livestock species
 - Similar approach

Possible in the (near) future for many species!

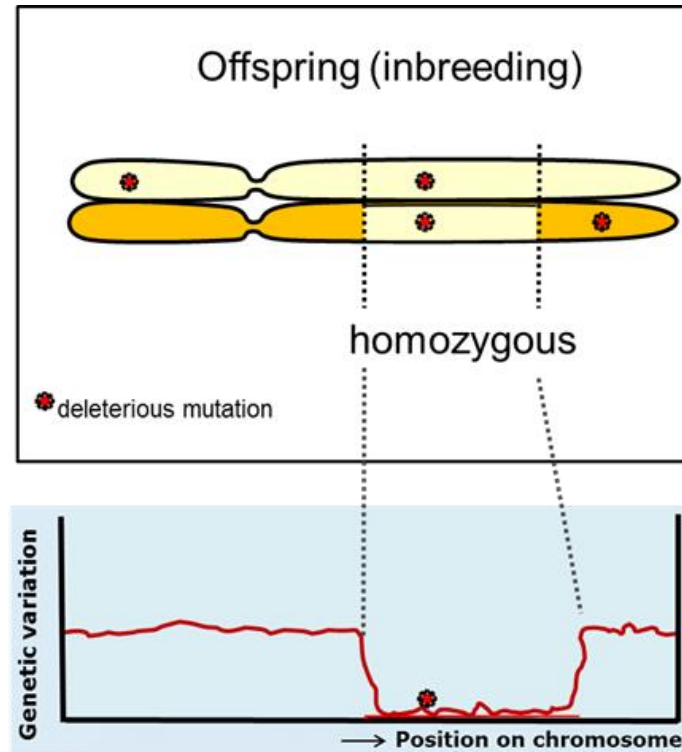
- S
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total
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, regardless species and/or

Managing genetic diversity in populations

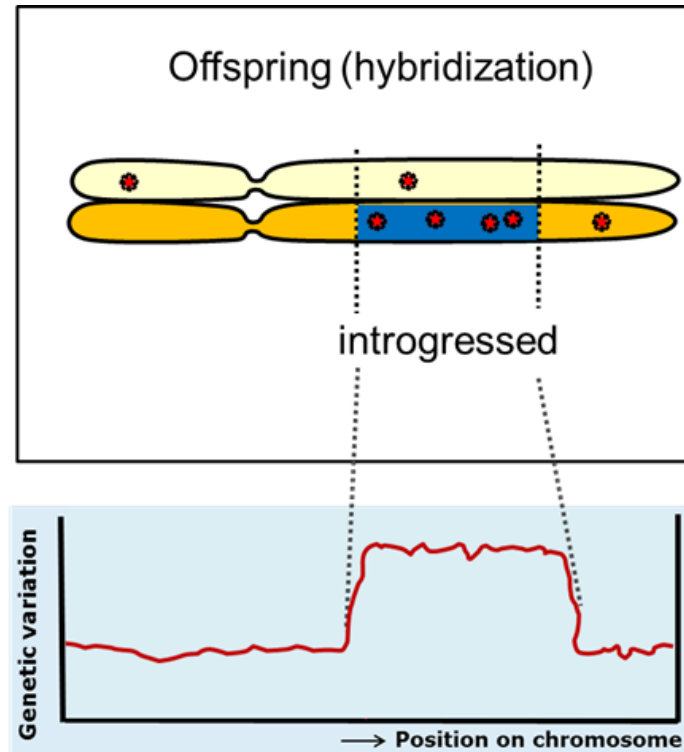
Where do deleterious variants occur?



Runs Of Homozygosity are enriched for deleterious variation!

Managing genetic diversity in populations

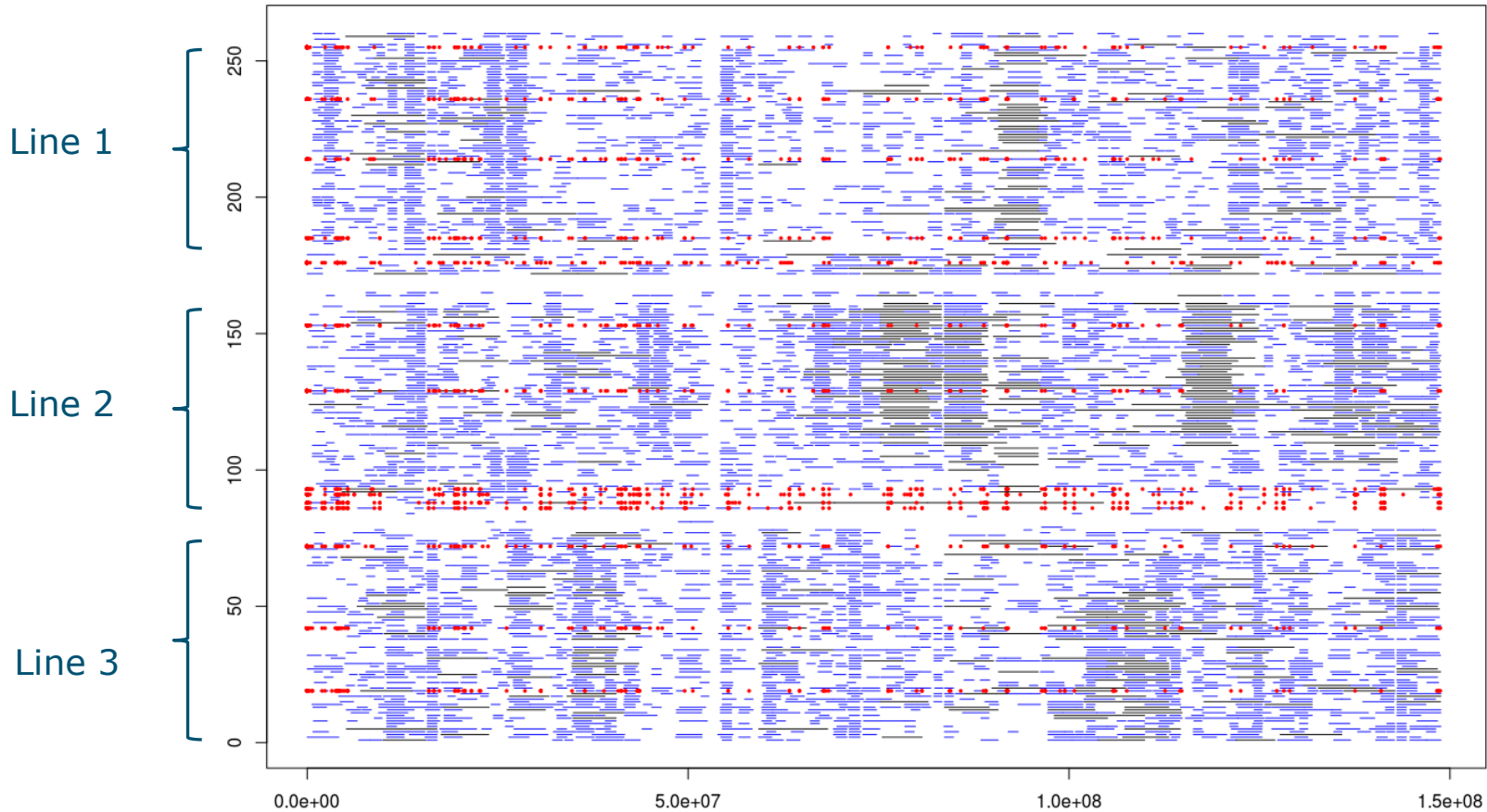
Where do deleterious variants occur?



Hybridization can lead to outbreeding depression!

Occurrence of deleterious variants

What is the genomic distribution of deleterious variants?



Managing genetic diversity in populations

How to manage for genetic diversity AND fitness?

→ Minimize coancestry in offspring

3 Methods to measure coancestry:

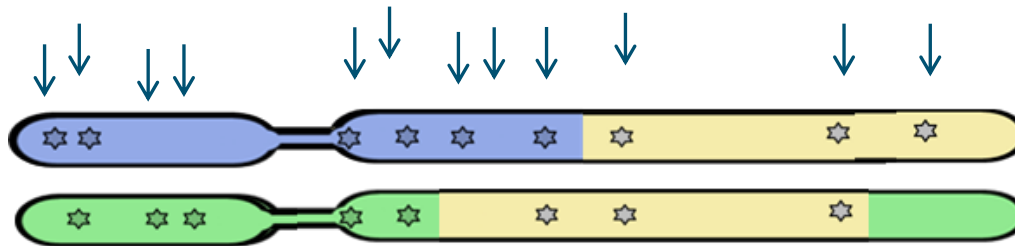
- Molecular
- Pedigree-based
- Runs of Homozygosity

Managing genetic diversity in populations

How to manage for genetic diversity AND fitness?

3 Methods to measure coancestry:

- Molecular
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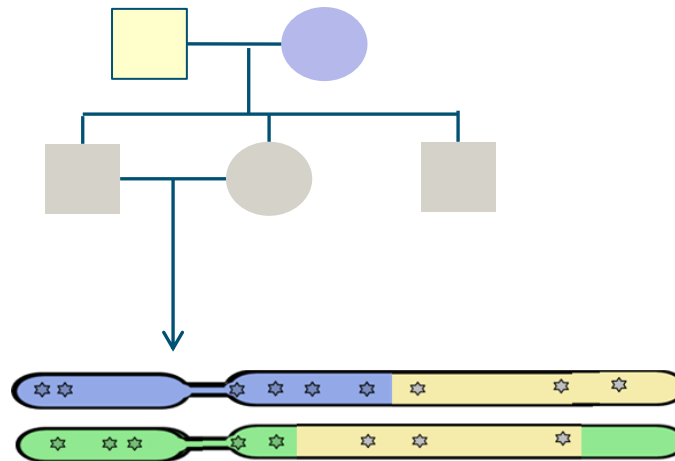
Use all information from genetic markers to minimize IBS

Managing genetic diversity in populations

How to manage for genetic diversity AND fitness?

3 Methods to measure coancestry:

- Molecular
- Pedigree-based
- Runs of Homozygosity



Use all information from family relationships

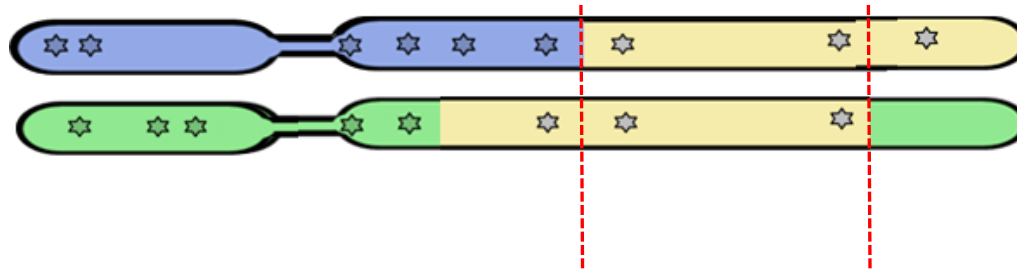


Managing genetic diversity in populations

How to manage for genetic diversity AND fitness?

3 Methods to measure coancestry:

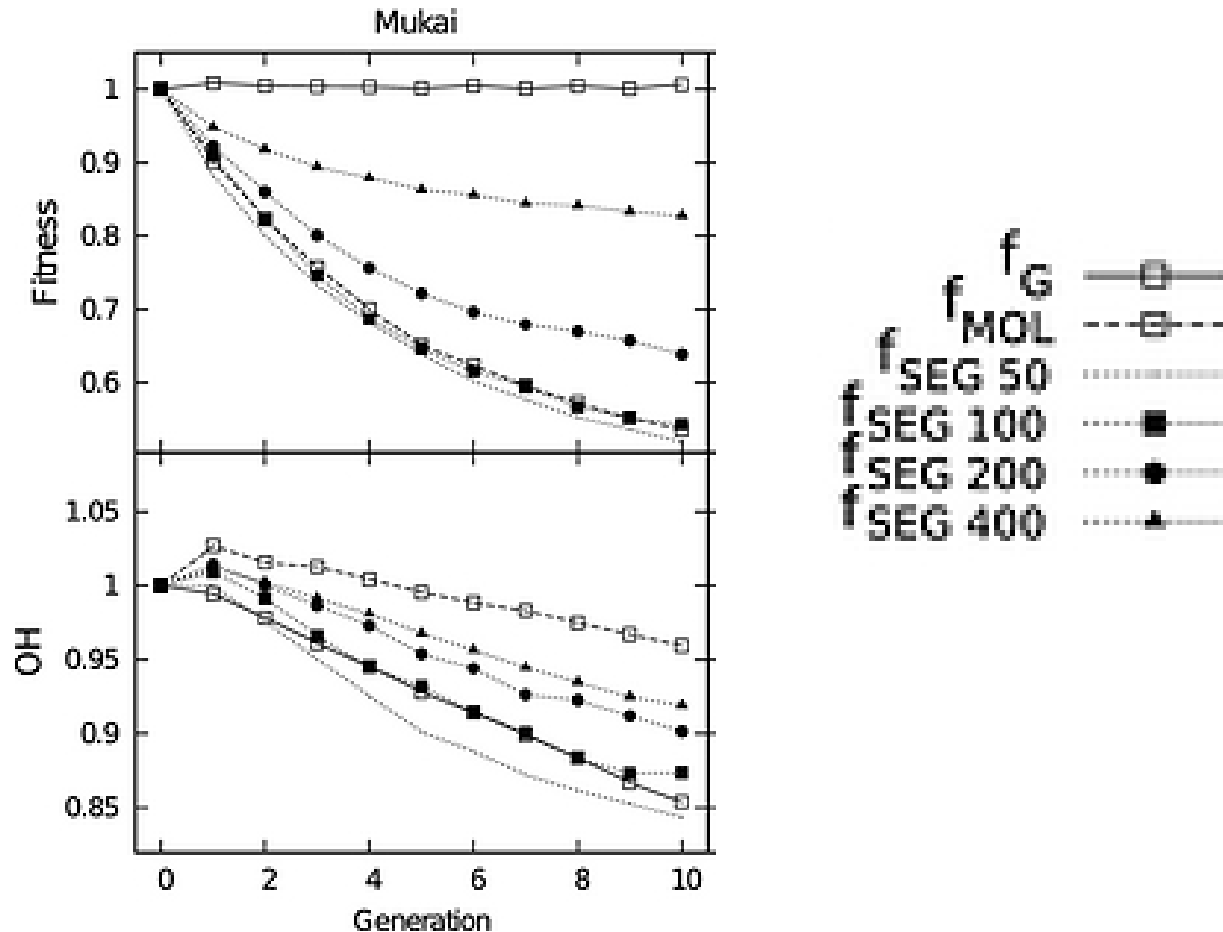
- Molecular
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Use ROH information from genetic markers to minimize IBD

Managing genetic diversity in populations

How to manage for genetic diversity AND fitness?



Using deleterious variants in management

- Case study: Managing two pig populations



Pietrain
(commercial)

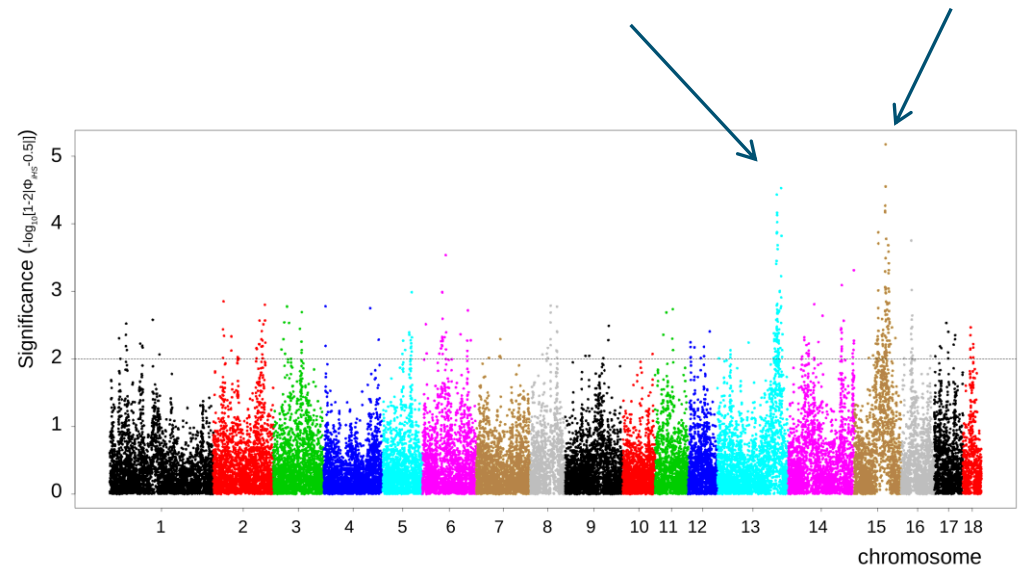
Visayan warty pig
(endangered)



Using deleterious variants in management

The commercial Pietrain breed

- Used for commercial breeding
- Effective population size of ~ 50
- Selected for specific traits:
 - 'selective sweeps' in genome



Using deleterious variants

the endangered warty pig *Sus cebifrons*



- Panay: founders brought to San Diego Zoo
- Negros: founders brought to Rotterdam Zoo

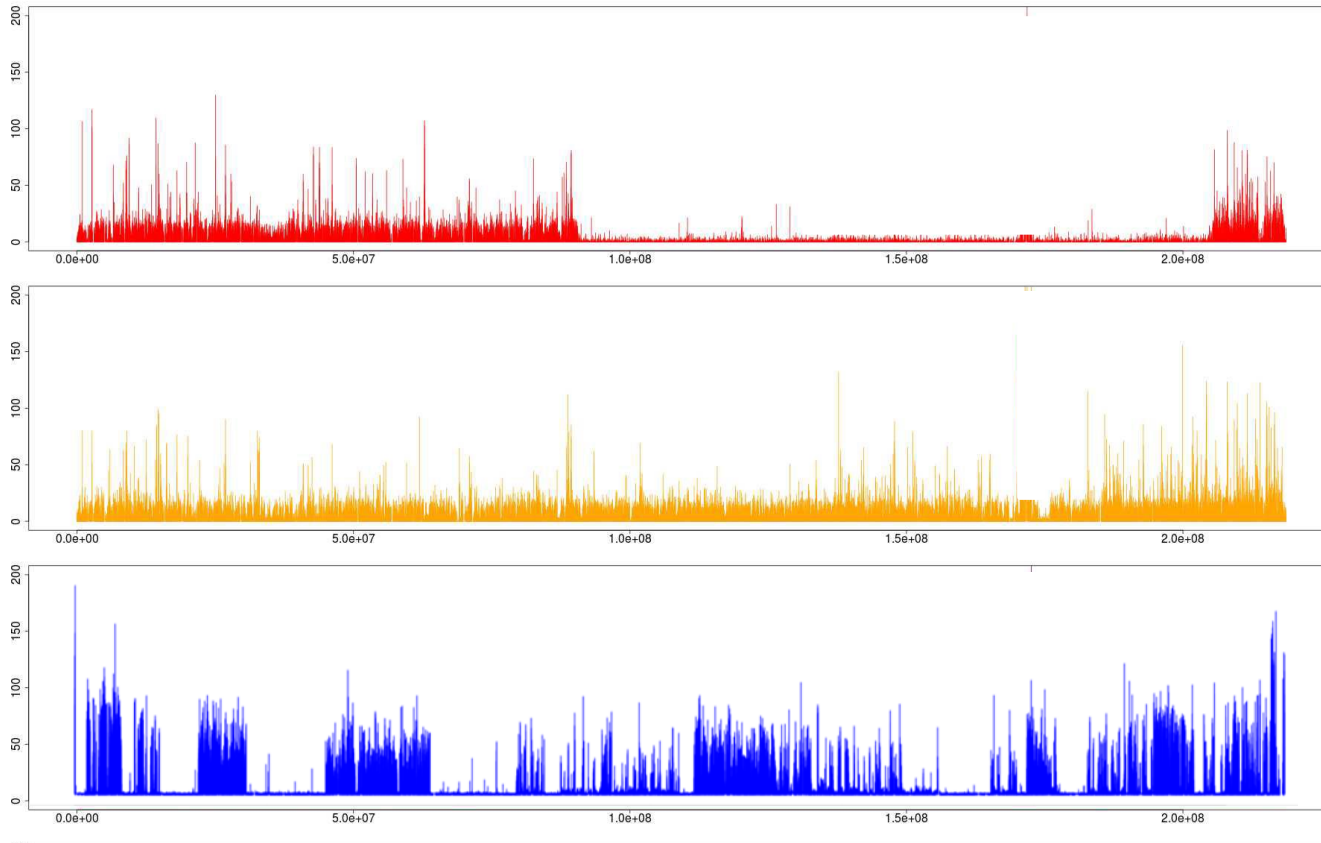




Using deleterious variants: case study



- Long runs of homozygosity in younger generations

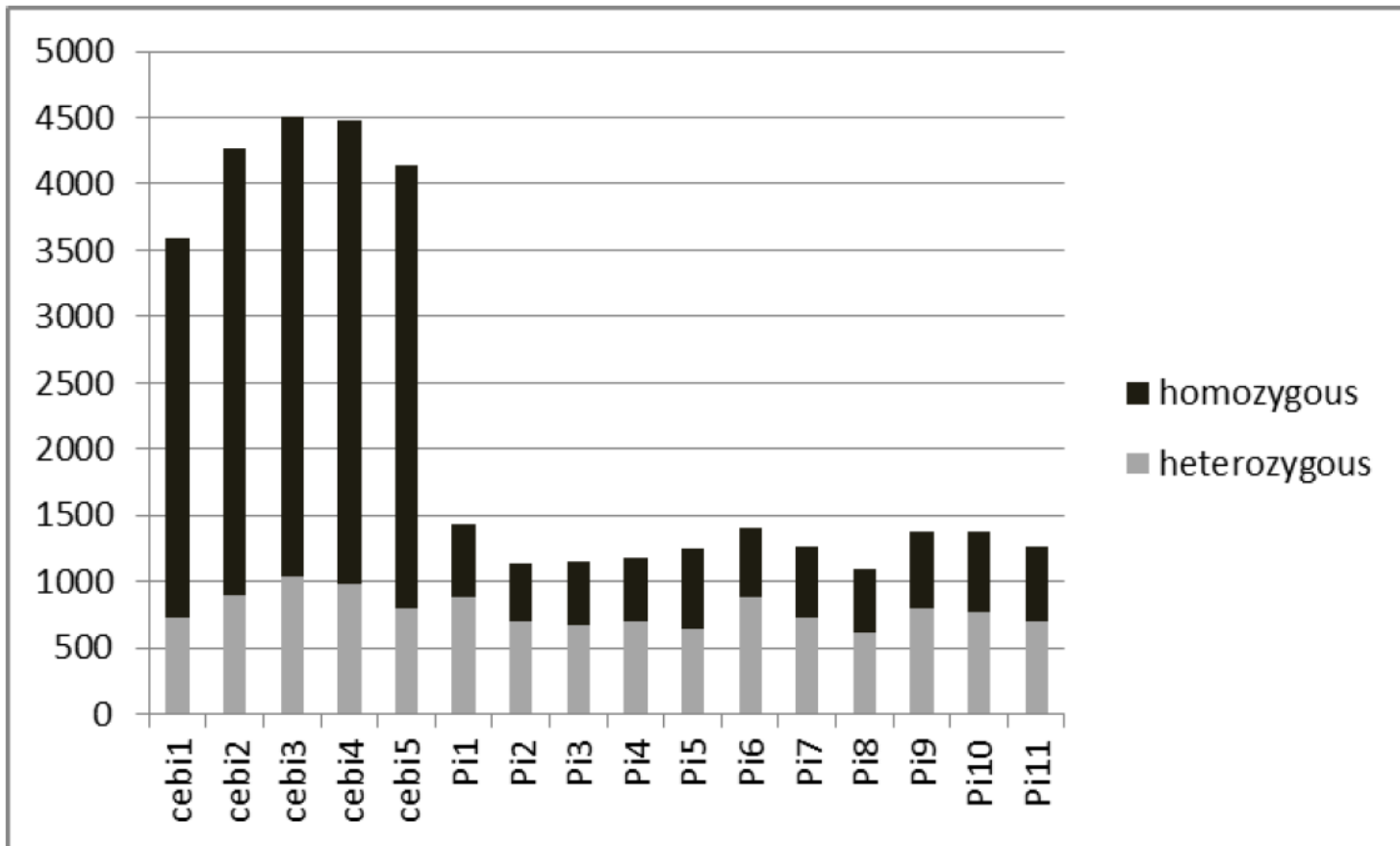




Using deleterious variants: case study



More deleterious variants in Cebifrons



Using deleterious variants: case study



■ In silico management

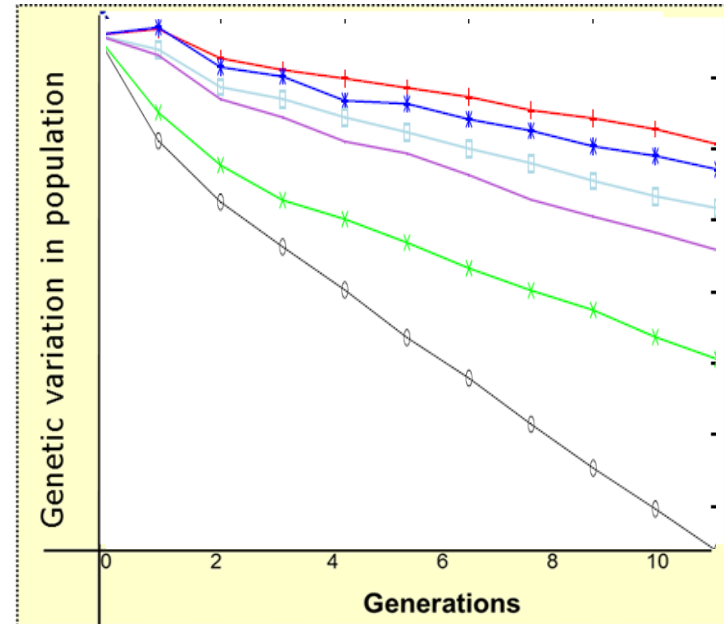
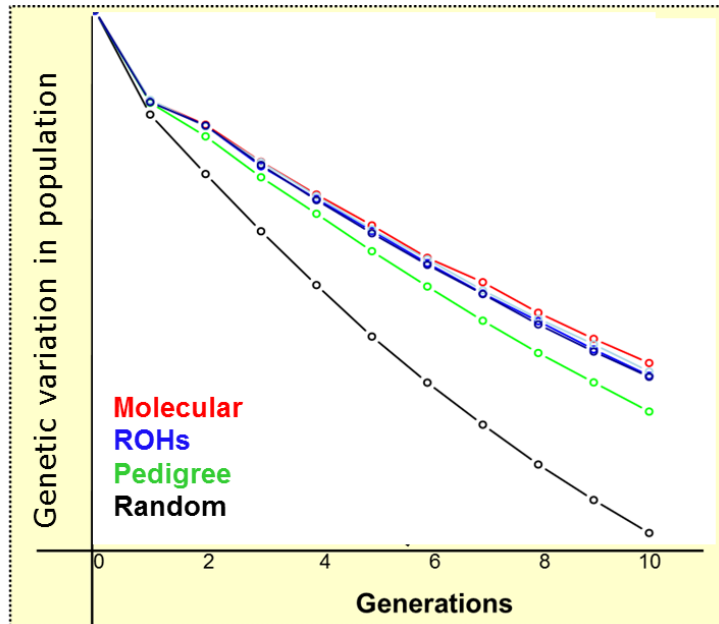
- Managed for 10 generations
- Optimization of variation and fitness
 - *Molecular*
 - *Runs Of Homozygosity*
 - *Pedigree*
 - *Random mating*



Using deleterious variants: case study



- Managed for 10 generations with optimal contributions:



Kept most genetic diversity with molecular coancestry

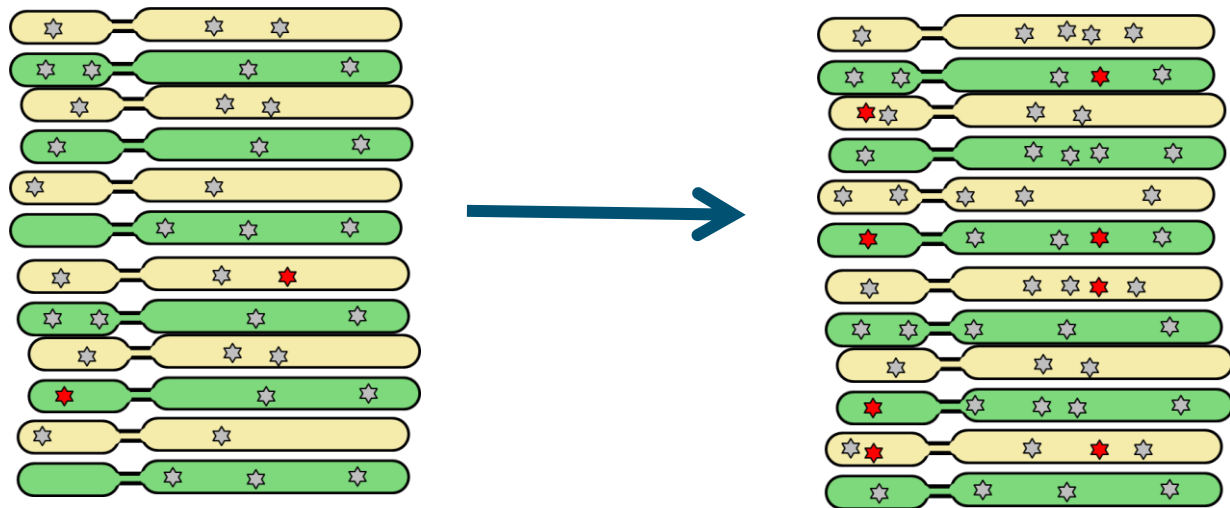
Using deleterious variants: case study



- Managed for 10 generations with optimal contributions:

If genetic diversity is optimized....

★ Neutral variant
★ Deleterious variant

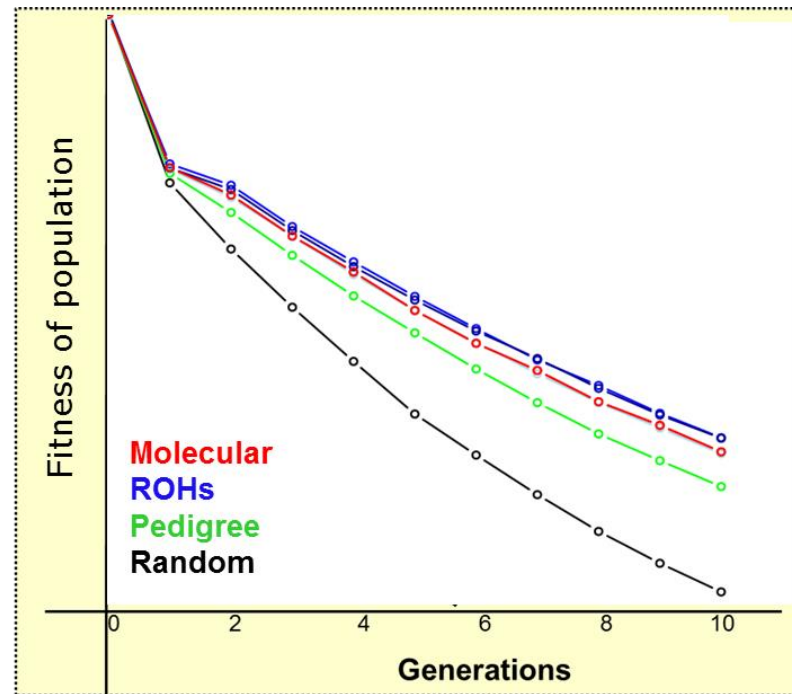


....deleterious variants will rise in frequency!

Using deleterious variants: case study



- Managed for 10 generations with optimal contributions:

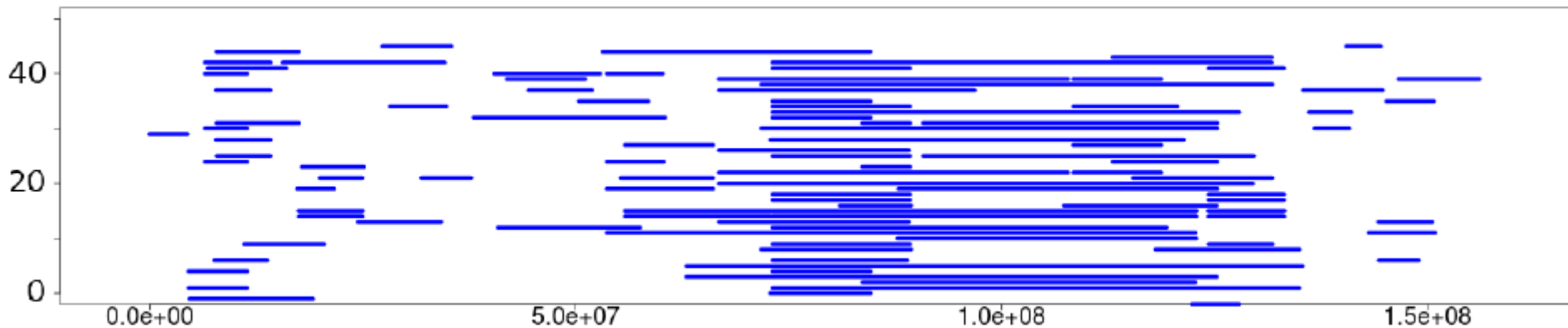
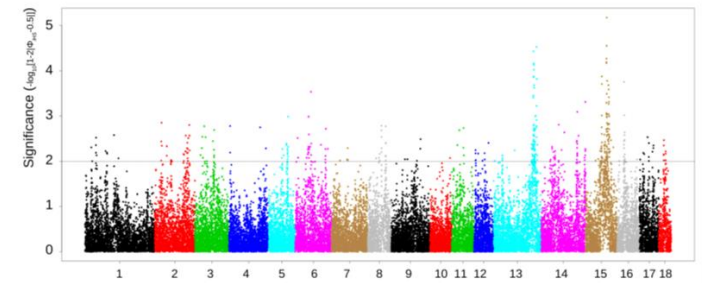


Highest fitness with ROH-based measures

Using deleterious variants: case study



- Managed for 10 generations with optimal contributions:

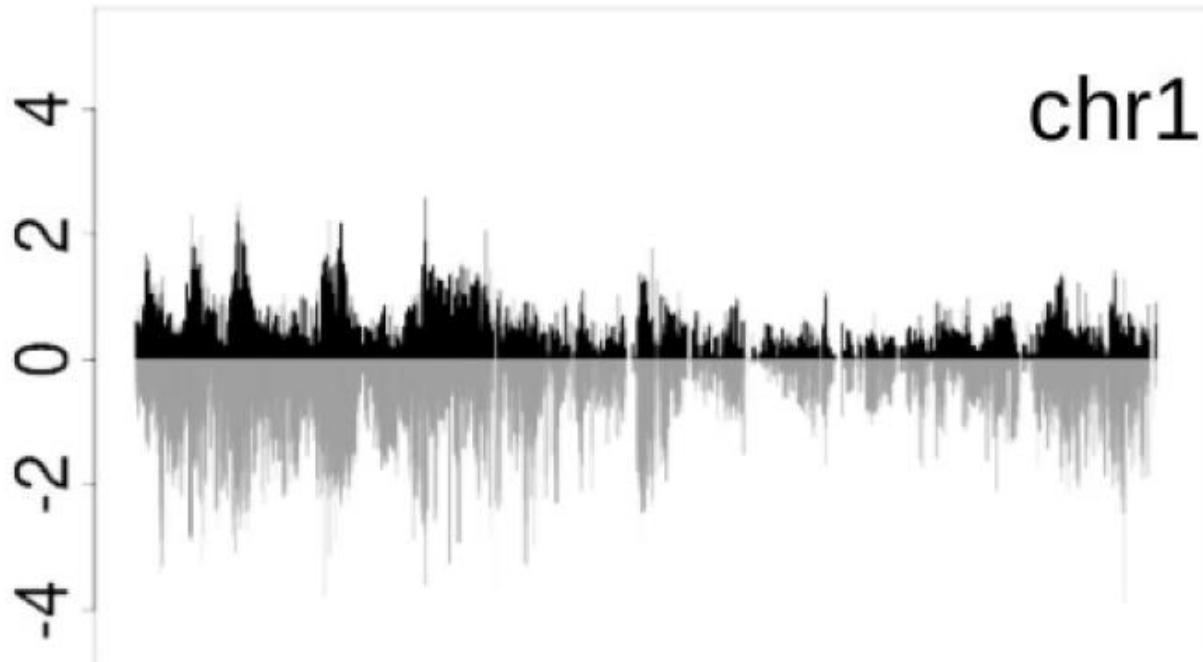


If genetic diversity is optimized....

Using deleterious variants: case study



- Managed for 10 generations with optimal contributions:



...selective sweeps are counteracted!

Implications for management?

- Distinguish quantity and quality of genetic variation
- Prioritize breeding strategy
 - Balance between fitness and diversity
 - *Context dependent!*
- Avoid counteracting selection
- Predict success of genetic rescue
- Targeted purging

Acknowledgements

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