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?

Number of variable sites (SNPs) vs. Position on the chromosome (basepairs)
Genetic diversity of populations

How does population size affect genetic diversity?

![Diagram showing recombination and inbreeding process](image-url)
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)
  - ‘Polyorphism Phenotyping’ (PolyPhen-2)

• **Towards genome-wide predictions:**
  - ‘Combined Annotation Dependent Depletion’ (CADD)
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 approaches as for human

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

- 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
    >95% frequency of variants

Possible in the (near) future for many species!
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:

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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
- Pedigree-based
- Runs of Homozygosity

*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!

Bosse et al. Genome Res 2015
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....

Bosse et al. Genome Res 2015
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
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