GEroNIMO and RUMIGEN Joint Final Event

Breeding the Future

Genomics, Epigenomics & Societal Acceptability for Sustainability in Livestock

The management of rare alleles, including GE, in breeding schemes

RUMIGEN WP4
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What did we address?

- Genomic selection breeding scheme
  - High rate of genetic improvement
  - But also, high rate of inbreeding (especially in Holsteins)
    - Loss of genetic diversity / variance
    - Genetic drift:
      - (rare) allele frequencies changes
      - Random trait changes
- Does genomic selection increase inbreeding and why?
- How to manage inbreeding / genetic diversity ?
  - New possibilities with genomics
- Emphasis on rare alleles and gene-editing

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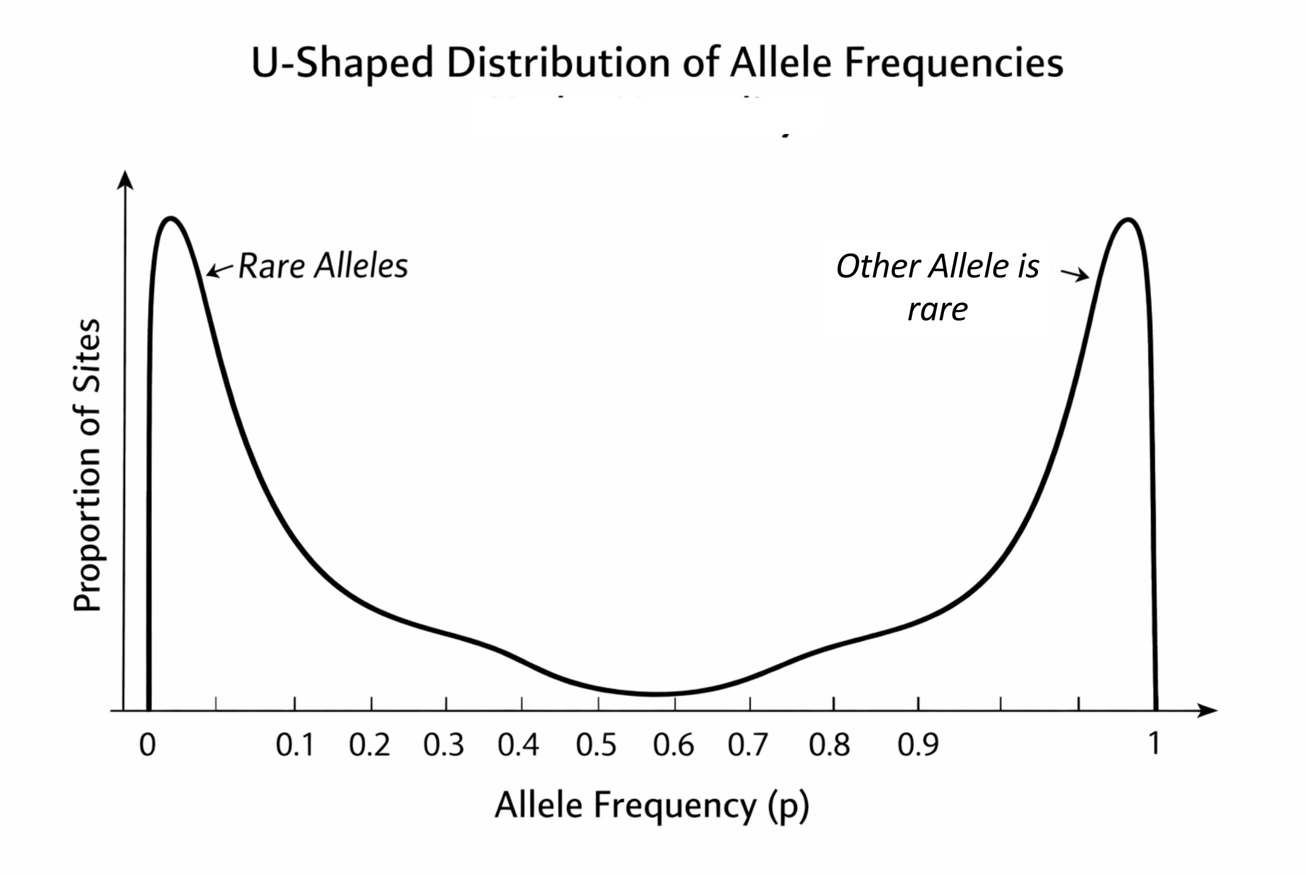
Most alleles are rare:



U-Shaped Distribution of Allele Frequencies

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Rare alleles

- Often recent mutations
  - Increased to frequency ~0.05 but may still get lost
- Mutations are:
  - Often (near) neutral
  - Some are detrimental (few are lethal)
  - Very few are beneficial

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What WP4 Delivered

- A philosophy for animal breeding:
  - Livestock populations have many desirable traits, some we want to improve
  - Desirable traits: breeding should maintain these incl. diversity
  - Traits with room for improvement: select for in breeding goal
- Practical breeding schemes should consist of:
  - Selection part
  - Maintaining genetic diversity and genetic levels part
- W.r.t. rare alleles:
  - Some we know & want to select up/down
    - Also: weighted SNPs depending on effect and frequency
  - Others we leave up to artificial/natural selection
    - Management of diversity part should be neutral w.r.t. allele freqs

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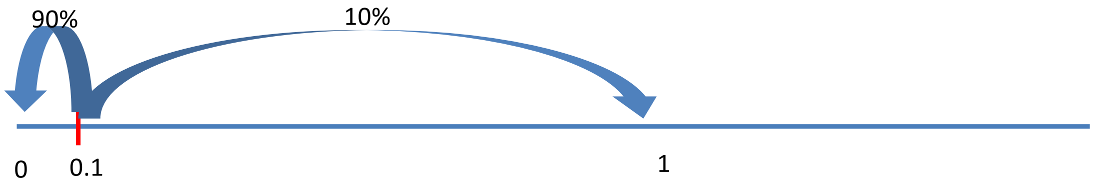
Neutral rare allele in small population



- Initial freq is 0.1
- Random allele freq changes
- On average no change in frequency
- Long term: allele is either lost or fixed
- 90% of loci : rare allele is eventually lost
- 10% of loci: rare allele is eventually fixed
- Alleles drift increasingly away from 0.1
- On average homozygosity increases

- This process is related to inbreeding (F)/ Identity-by-descent (IBD) of alleles:
  - If frequency increases some ancestral alleles leave more than 1 copy in the current generation
  - Pedigree-F: probability that copy of same ancestral allele was inherited from mum & dad

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(Genomic) measures of inbreeding

- Rate of increase of homozygosity: Fhom
- Rate of change of allele frequencies: Fdrift
- Rate of increase of IBD:
  - Fped: based on pedigree (50/50 inheritance from parent to offspring)
  - FIBD: based on pedigree & DNA (use DNA data to see which allele is inherited)
- FROH: detect Runs-of-Homozygosity
  - Longer stretches of homozygous markers are unikely by chance ➔IBD
- For neutral loci: all these F's are expected to be the same
  - But neutral loci no longer exist when selecting for genome-wide dense DNA data (GS)

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Optimal contribution selection (OCS)

- Selection method that maximises genetic improvement at fixed rate of F
  - Which method to use to measure F
  - Fped not good enough: GS can select full sibs that are more than expected related
  - Fhom and Fdrift hold under neutrality but not under selection
    - When using Fhom in OCS, keeps Fhom low at the expensive of execessive Fdrift
      - Rare alleles move generally up in frequency
    - When using Fdrift in OCS (GRM), keeps Fdrift low a the expense of Fhom
      - Increased loss of rare alleles
  - Fibd is not manipulated by selection
    - Preferred F-measure

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What WP4 Delivered (2)

- An algorithm to calculate FIBD genome-wide in large practical data
    - (github.com/theomeuwissen/Fgla)
- FIBD is the preferred choice in OCS (not affected by selection)
- Investigated effect of GS on Fhom and Fdrift:
    - More Fdrift than Fhom ➔rare alleles move generally to higher freqs
    - Fdrift-based OCS: more Fhom than Fdrift (and *vice-versa*)

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What WP4 delivered (3)

- Investigated effect of genomic selection on 5 small cattle breeds
    - Abondance (Fr), Tarentaise (Fr), Vosgienne (Fr), MRY (NL), NRC (No)
    - No clear trend that GS increased inbreeding
    - Concluded that management can counteract effect of GS on F

- Allele-reweighted selection strategies in computer simulations:
    - Reduced loss of variation and increased long term genetic gain
    - Reduced loss of favourable de novo mutations

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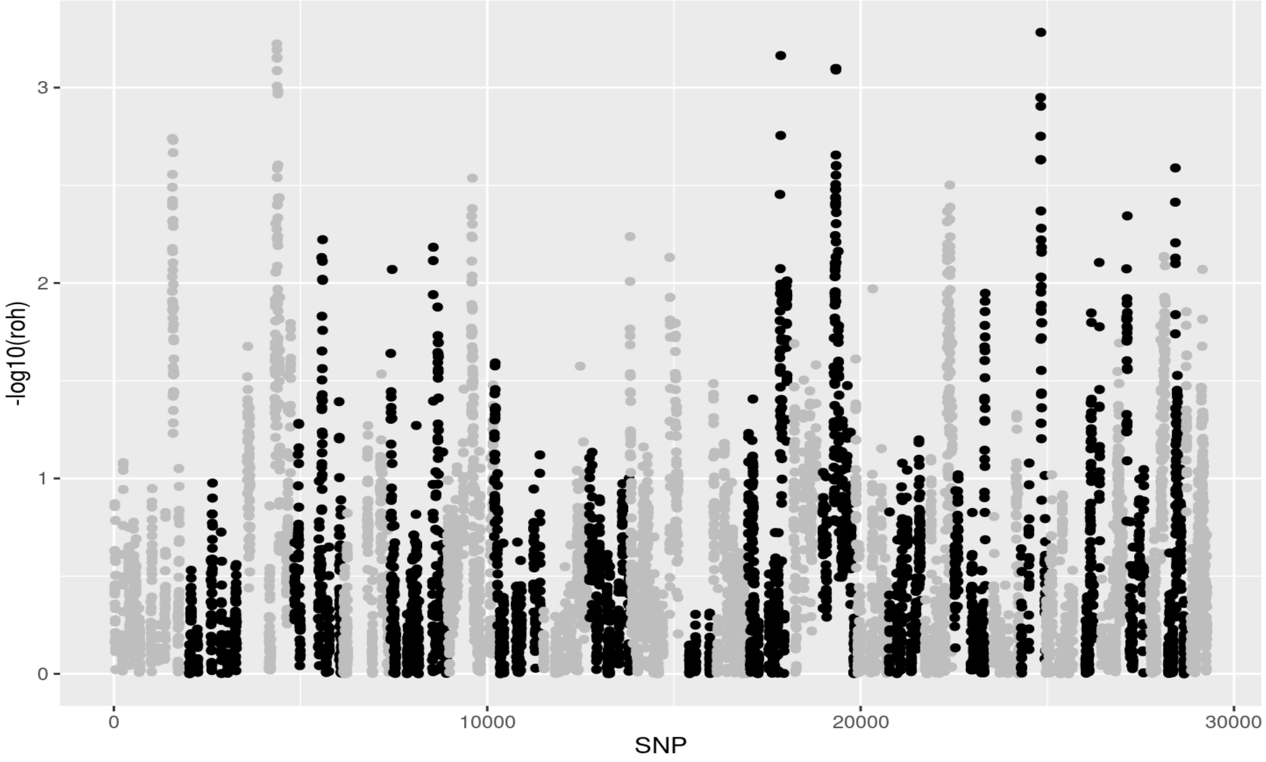
Localising inbreeding depression

- Vosgienne breed



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Gene-editing and known rare alleles

- Editing known rare genetic defects:
  - Traditionally: avoiding animals with defects reduces selection differential
  - Very desirable homozygous sire: use and edit offspring for defect
  - Very desirable carrier sire: use and and edit offspring for defect
    - Can also generate more offspring and weed-out carrier offspring
- Editing rare desirable single genes (introgression):
  - Selection of carriers reduces selection differential too much
    - Mate carriers with very good sires, select carrier offspring, loses 1-2 generations of progress
  - Edit desirable single gene into embryos from elite matings

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Final messages:

- Rare alleles may be neutral, detrimental or beneficial
  - Diversity management should not directly affect their freqs
    - FIBD based OCS is needed
    - Fhom/Fdrift based OCS manages the symptoms of inbreeding but not the cause
  - Leave allele freq changes to selection part of breeding scheme
- Genomic selection may increase inbreeding
  - Can be fixed by management of the population
  - Genomic selection increases Fdrift more than Fhom
    - Rare alleles move generally towards intermediate frequencies
      - May increase frequency of genetic defects
- Genomic tools measure homozygosity, drift or IBD
  - which are not the same in genomic selection / conservation schemes
- Gene-editing may help using famous bulls with defects & introgression

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THANK YOU

Rumigen
TOWARDS IMPROVEMENT OF **RUMI**NANT BREEDING
THROUGH **GEN**OMIC AND EPIGENOMIC APPROACHES

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GENOME AND EPIGENOME ENABLED BREEDING IN MONOGASTRICS

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