Genomics for cryo-collections

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CRB-Anim

Paris 2017

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IMAGE
Innovative Management of Animal Genetic Resources

Genetic diversity worth to conserve

- Different breeds harbour unique genetic variation
- May be useful, not only within old/low input breeds
- Conservation in gene banks

Genetic diversity within breeds

- Changes constantly
- Rare breeds (e.g. low input, some companion animals)
    - Small (effective) population size
    - High levels of genetic drift
    - Depletes genetic variation
- Large breeds (e.g. global production breeds)
    - Selection
        - Changes specific traits
        - Can reduce genetic variation on specific regions of the genome
        - Can reduce effective population size

Gene banks

- Long term storage
- Genetic variation in collections is fixed to level at time of sampling
- Use for
    - Backup
    - Support life population
    - Research
- DNA typing provides detailed information

Genomics and gene banks

- Provides more detailed inventory
- Back up
  - What genetic diversity in the life population is in the gene bank and what not?
  - Which animals to add?
- Support life population
  - What genetic diversity is in the gene bank and absent in the life population? And how useful is it?
  - Source for introgression
- Research
  - Identify changes in genetic diversity over time

Two initiatives

- Dutch gene bank
  - All cattle in gene bank (to be) typed with 50K SNP chip
  - 7 breeds
  - 1985 till 2017

- Image
  - EU Horizon 2020 project
  - Considers all aspects of animal genetic resources
  - WP4 Genomic characterization
    - DNA typing: SNPs and sequencing
  - WP6 use of genetic collections
    - Use in life population

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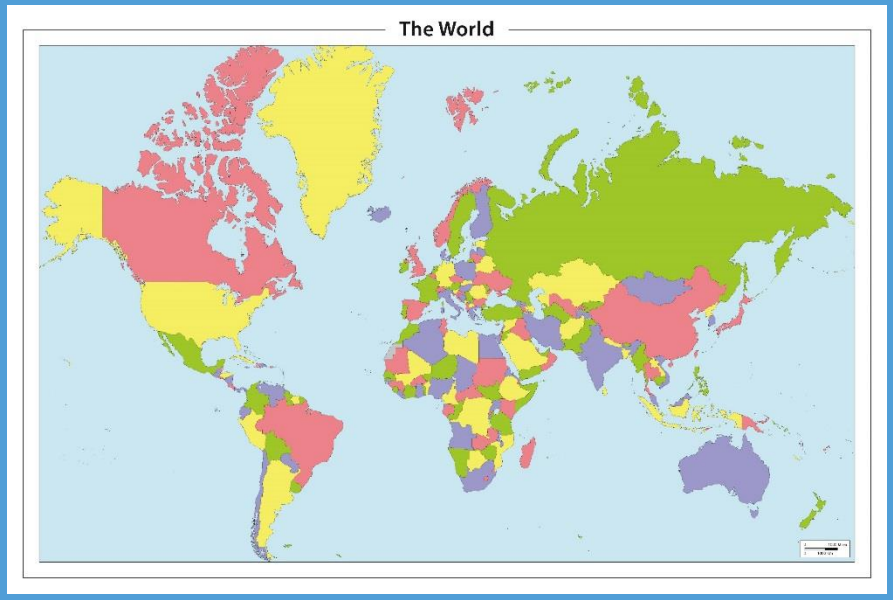
Back up

Which animals to store in gene bank, to maximise diversity conserved?

Holstein Friesian



- The main dairy cattle breed
- Used and bred globally
- Superior production, fertility less well
- Diversity under threat due to limited number of sires being used

Maximise diversity in gene bank

- Method of choice: Optimal contributions
- Find combination of parents/animals with minimum average kinship
  - Mathematical solution
  - Selection from all animals with varying contribution
  - Or selection of fixed number of animals with equal contribution
- Two variants:
  - Gene bank: n animals with lowest average kinship
  - Breeding programme: maximise genetic merit (EBV) while constraining average kinship to fixed value

Pedigree vs. SNP chips

PhD Krista Engelsma 2011

- Data: 566 Holstein cows 50K SNP chip
- Selection: 10 animals equal contribution

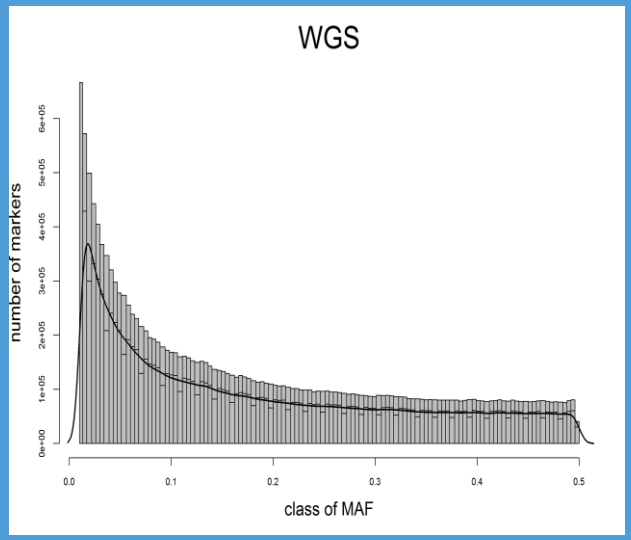
Diversity	before selection	random	Gencont pedigree	Gencont Markers
f (pedigree)	0.081	0.176	0.103	0.129
f (SNP)	0.163	0.254	0.212	0.174
% fixed	6.5%	16.3%	14.1%	13.6%

- Optimal contributions work
- SNP-chips slightly better than pedigree
  - Includes kinship from before founders

SNP vs. Sequence (WGS)

PhD Sonia Eynard (2016)

- 1000 Bull genome, 277 Holstein bulls
  - 50K SNP
    - 44 367 segregating loci
    - 7.5% rare (MAF <5%)
  - WGS
    - 15 864 157 loci
    - 27.8% rare



Extra gain with sequence?

- Selection: 10 animals equal contribution
- % Fixed alleles in selection relative to total population

Kinship based on	SNP (prev.)	total	common	rare
Pedigree	14.1%	21.6%	8.7%	55.1%
SNP	13.6%	20.0%	6.7%	54.4%
WGS		19.4%	6.5%	52.8%

- More than 50% of rare alleles are lost
- Use of sequence information conserves slightly more
    - Especially rare alleles

Need to type everything?

- For identifying candidates to be stored in the gene bank benefit of typing over pedigree is limited
    - But if no reliable pedigree available...
- Benefit of sequencing over SNP chips is even more limited, but provides information on rare alleles
- When the interest is in genetic diversity on specific regions animals need to be typed
- Strategy
    - Sequence limited number of animals
    - Type some animals with HD SNP chip
    - Type rest with LD SNP chip
    - Missing DNA information of relatives can be imputed

Use of gene bank material in life population

Is genetic diversity in gene bank useful for the life population?

Maas-Rijn-IJssel vee (MRIJ)

PhD Sonia Eynard (2018)

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Source picture: http://szh.nl/runderen/mrij/
The map is kindly provided by CRV BV.

Maas-Rijn-IJssel (MRIJ) cattle

- Red-and-white cattle
- 2nd breed in numbers in NL (1st = Holstein)
- Dual purpose (milk & meat)
- High milk protein percentage
- Robust, strong & self-reliant
    - Good fertility & longevity

- About 7500 purebred animals left (3% of population size in 1970s)
- Still an active breeding program
- Bulls from 1986 onwards in gene bank

Use gene bank bulls in life population?

Population:

- Conserved: 294 bulls born before 2000
- Current: 119 bulls born in or after 2000

- 50k SNP genotypes on all bulls

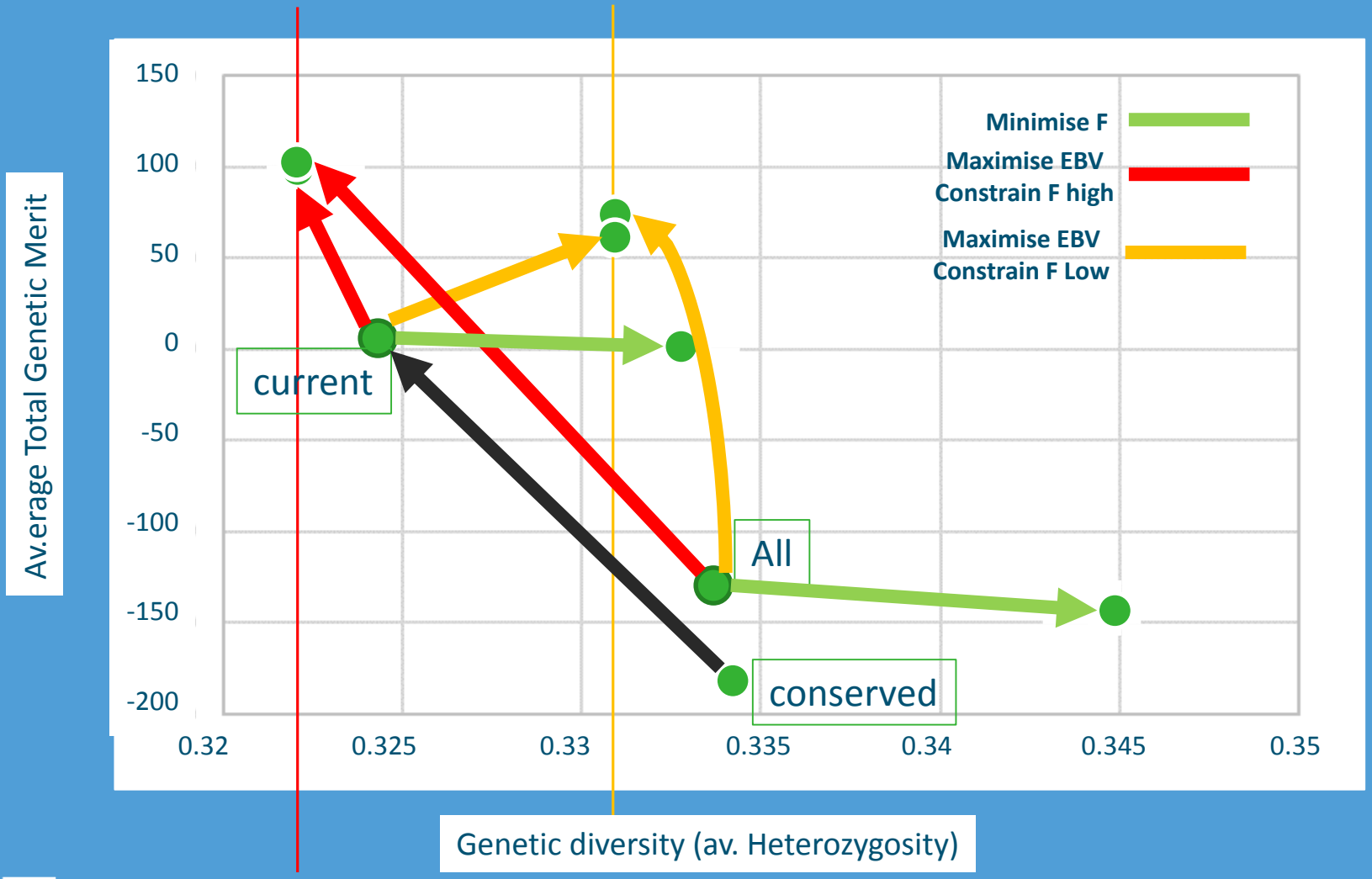
=> Is there any added benefit of considering MRIJ bulls from the gene bank in the current (breeding) population?

Two scenarios

Compute optimal contributions from perspective of:

- Breeding program
  - Maximize genetic gain while restricting inbreeding
- Gene bank
  - Minimize inbreeding rate
- Using:
  - Current bulls
  - Current + conserved bulls
- Evaluation:
  - Genetic diversity and Total Genetic Merit (includes production, health and fertility)

MRIJ: impact of using conserved animals



MRIJ Results

Using conserved in addition to current bulls

Breeding program perspective:

- At same genetic diversity
- Slightly increased realized genetic merit
- The higher the genetic diversity constraint the stronger the increase in genetic merit because of using conserved bulls

Gene bank perspective:

- Considerably higher genetic diversity

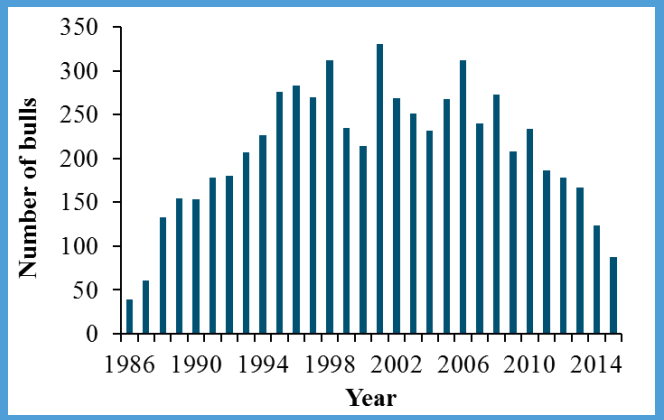
Research on diversity stored in gene bank

Identify changes in genetic diversity over time

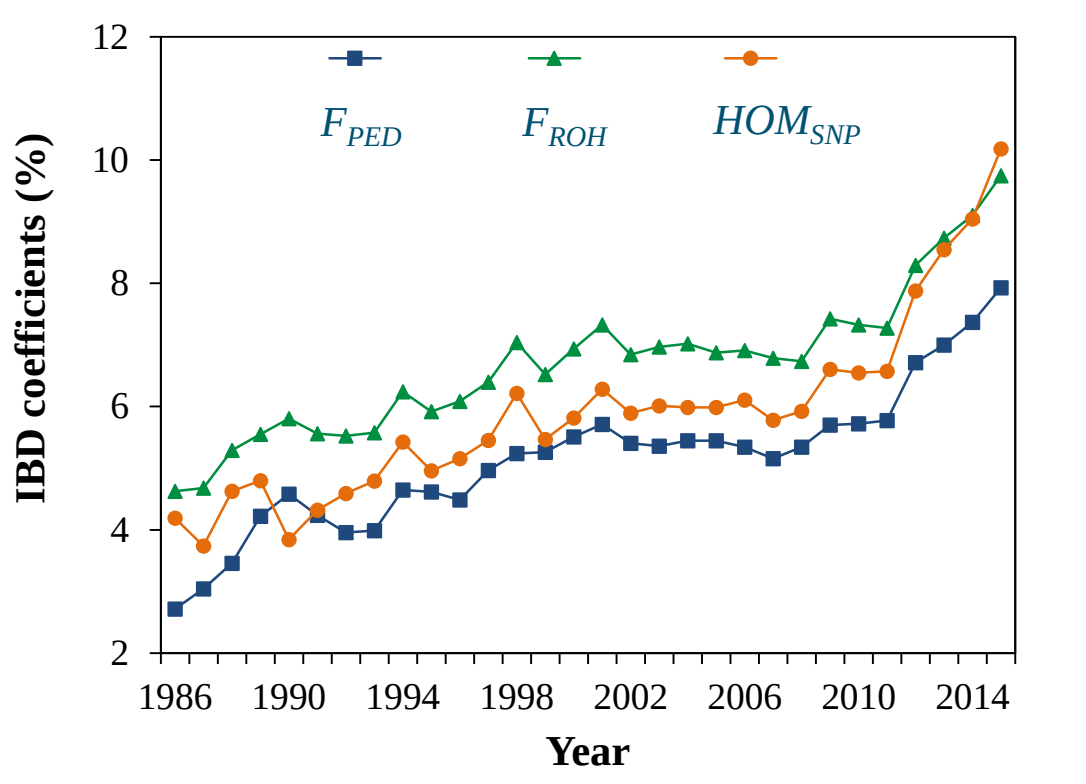
Holstein bulls in gene bank

PhD Harmen Doekes(2018)

- Data
  - Genotypes (50K SNP) of all bulls used in Dutch breeding program between 1986 and 2015
- Measurement Genetic diversity
  - Pedigree inbreeding (Fped) = since founders
  - Marker homozygosity (HOMsnp) = since mutation
  - Rows of homozygosity (Froh) = recent generations
- Over whole genome
- Region specific



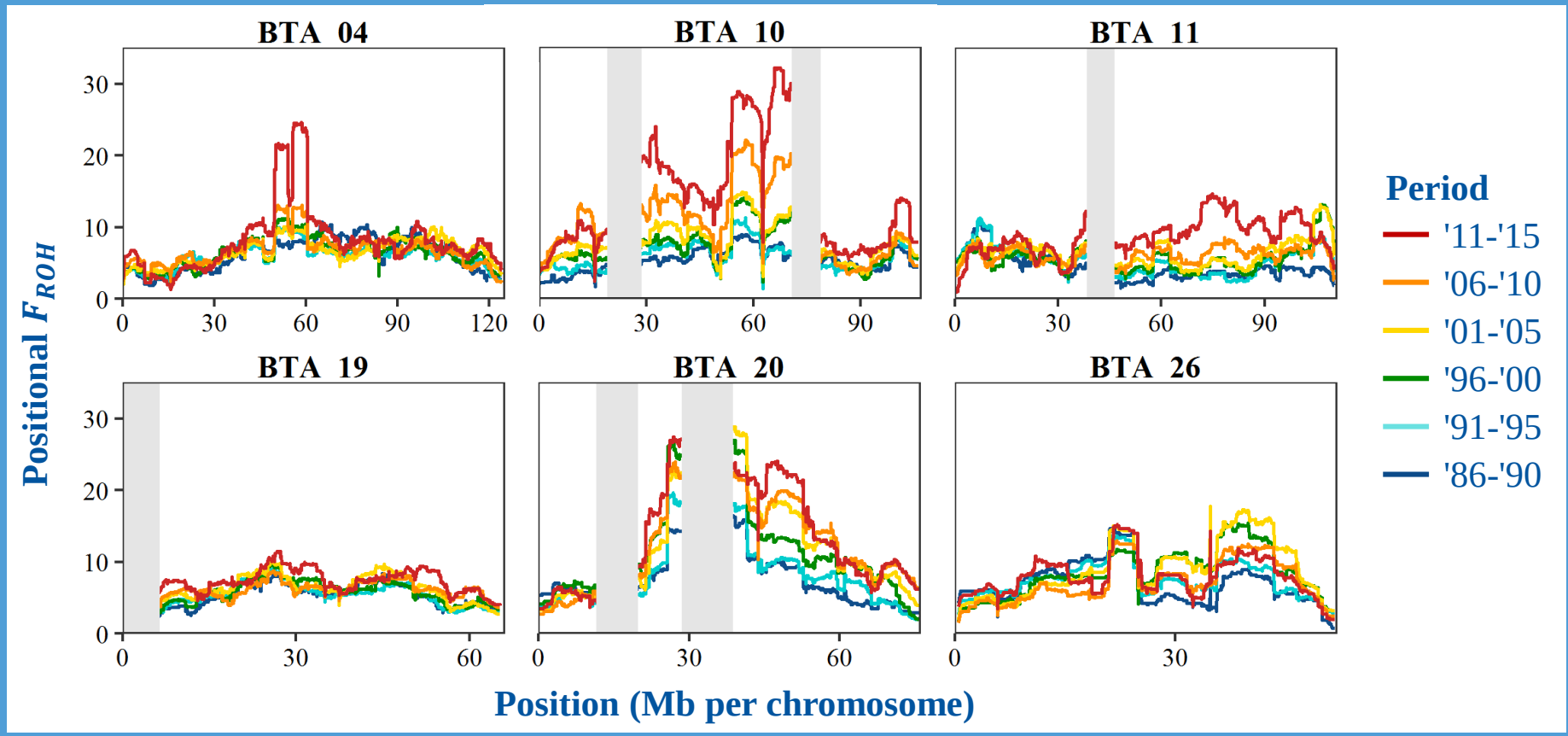
Genome wide inbreeding



- 1986 – 2000 Steady increase
- 2000 – 2009 Rather constant
- Since 2009 Sharp increase especially for homozygosity

- 2000: fertility, health and longevity were included in the breeding goal + use of optimal contributions
- 2009: start of genomic selection

Positional inbreeding (F_{ROH})



- Substantial heterogeneity across genome over time
- Peaks emphasized in 2011-2015

Results: correlation allele frequency changes

Correlations between Δp in 5-year periods					
Period	86-90	91-95	96-00	01-05	06-10
91-95	0.09				
96-00	0.09	0.08			
01-05	-0.06	-0.13	-0.09		
06-10	-0.03	-0.11	-0.09	0.09	
11-15	0.04	-0.04	0.00	-0.07	0.26

- Δp in consecutive periods generally same direction
- Negative after shift selection goal (2000)
- Strong positive after introduction GS (2010)

Conclusions

- Changes in breeding program have affected diversity trends

2000

Introduction OCS

Shift breeding goal

- Decrease ΔF
- Shift direction Δp

2009

Introduction GS

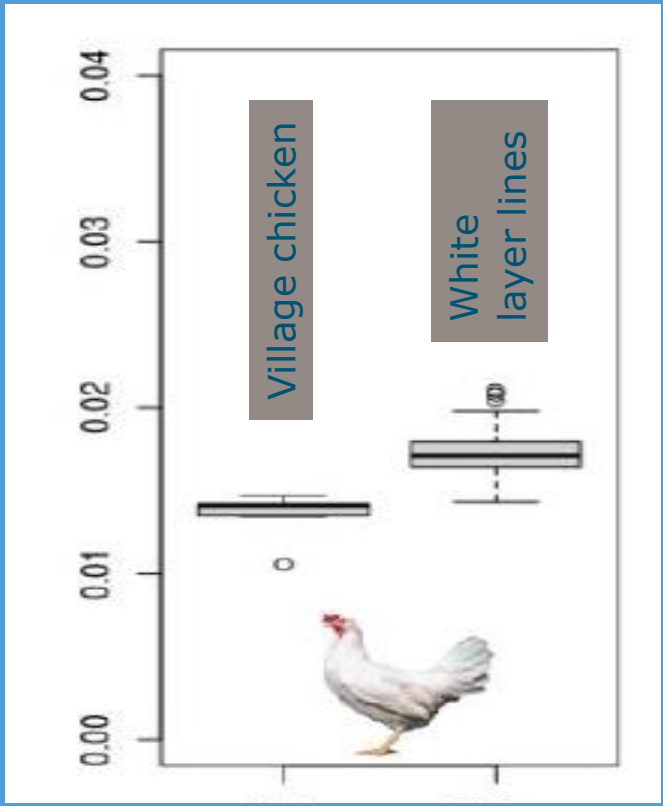
- Acceleration!
- Increase ΔF
- Especially old diversity
- Increase Δp
- Same direction Δp

- Substantial differences across the genome
- Gene banks can provide valuable information on evolution of genetic diversity in life stock populations

Sequence information

Mirte Bosse (2018)

- Provides detailed picture of all diversity present
- Loci can be characterized
  - Within regions coding for genes
  - Silent mutations
  - With effect predicted
  - Etc.
- Ratio of heterozygous sites with a predicted effect over heterozygous silent mutations
- In highly selected populations more deleterious mutations



Conclusions

- Genomics offers additional opportunities for conservation
- Gene banks fix genetic diversity to level at time of sampling
- This diversity can be used in life population
- DNA typing provides insight in the evolution of genetic diversity in livestock