Predicting genetic inbreeding load in dairy sheep

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Summary

- Introduction
- Material and Methods :
    - Example with 7 animals
    - Real data in dairy sheep breeds
- Results
- Conclusions

Inbreeding load

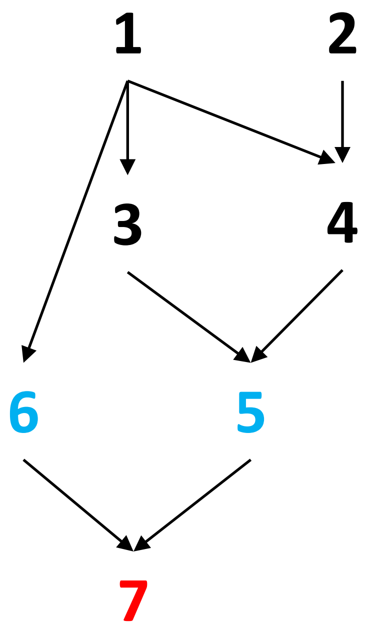
- **Inbreeding load** is the fraction of the mutation load that is due to recessive variants which can be hidden in heterozygous condition
- The **inbreeding load** of individuals is a heritable additive trait that is only expressed when inbreeding occurs in their offspring and has an effect on the studied trait (e.g. milk yield)
- The magnitude of inbreeding depression in the offspring depends on the hidden (recessive) **inbreeding load** among ancestors

Objective

This work contributes

To estimate the genetic parameters for the **inbreeding load**, and predict the additive genetic value for the **inbreeding load** for milk yield in three dairy sheep breeds

Example of 7 individuals



Pedigree of 7 animals

Inbreeding load

$$y = X\beta + Zu + ZKi + e$$

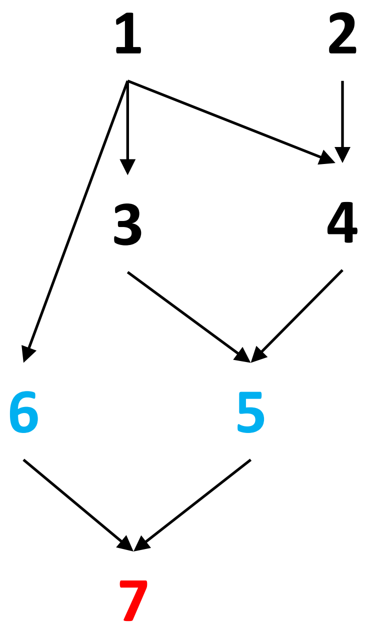
Partial inbreeding coefficients of each individual and the ancestors in cause

Individuals	Ancestors	Partial inbreeding
5	1	0.12500
6	1	0.25000
7	1	0.18750
7	2	0.03125
7	4	0.06250

Example of 7 individuals

Inbreeding load

$$\boldsymbol{y} = \boldsymbol{X\beta} + \boldsymbol{Zu} + \boldsymbol{ZKi} + \boldsymbol{e}$$



Pedigree of 7 animals

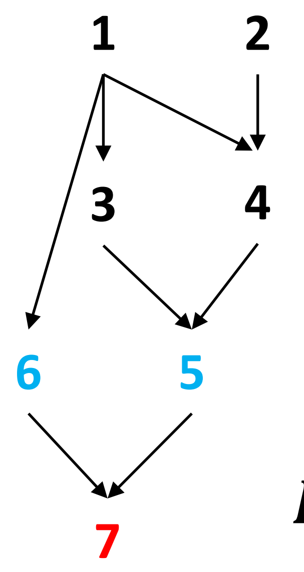
Partial inbreeding coefficients of each individual and the ancestors in cause

Individuals	Ancestors	Partial inbreeding
5	1	0.12500
6	1	0.25000
7	1	0.18750
7	2	0.03125
7	4	0.06250

= 0.28125

Inbreeding coefficient can be partitioned into coefficients attributed to specific ancestors, known as **partial inbreeding coefficients**

Inbreeding load



Pedigree of 7 animals

$$y = X\beta + Zu + ZKi + e$$

$\boldsymbol{K}$: Lower triangular matrix

$$\boldsymbol{K} = \boldsymbol{T}(\boldsymbol{I} - \boldsymbol{P})$$

$\boldsymbol{T}$: matrix, contains the partial inbreeding coefficients from the Mendelian decomposition

$\boldsymbol{P}$: matrix with a diagonal of 0 and 0.5 in the elements that link an individual with its sire and dam

$$\boldsymbol{K} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0.1250 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0.2500 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0.15625 & 0.28125 & 0 & 0.0625 & 0 & 0 & 0 \end{bmatrix}$$

$$\boldsymbol{T} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0.1250 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0.2500 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0.1875 & 0.3125 & 0 & 0.0625 & 0 & 0 & 0 \end{bmatrix}$$

$$\boldsymbol{P} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0.5 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0.5 & 0.5 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0.5 & 0.5 & 0 & 0 & 0 \\ 0.5 & 0 & 0 & 0.5 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0.5 & 0.5 & 0 \end{bmatrix}$$

Real data

Breed	Nb of animals in the pedigree	Nb of equivalent complete generations	Average milk yield (liters)
BB	190,276	7.04	193.00 ± 76.25
MTN	166,029	6.18	144.31 ± 60.25
MTR	633,655	7.82	197.52 ± 83.66

French dairy sheep breeds:

- Basco-Béarnaise (BB),
- Manech Tête Noire (MTN),
- Manech Tête Rousse (MTR)

Which have been selected for milk yield since ~1985

AI+Progeny testing until 2016, genomic selection since 2016

Material and Methods

Our full model for real data on **milk yield**

$$\boldsymbol{y} = \boldsymbol{X\beta} + \boldsymbol{F}b + \boldsymbol{Z}_u\boldsymbol{u} + \boldsymbol{Z}_u\boldsymbol{K}\boldsymbol{i} + \boldsymbol{Z}_p\boldsymbol{p} + \boldsymbol{e}$$

Flock-year-parity
Age at lambing*
Period of lambing*
Lambing-first test-day interval*

$\boldsymbol{X}, \boldsymbol{Z}_u, \boldsymbol{Z}_p$ and $\boldsymbol{K}$: incidence matrices
$\boldsymbol{\beta}$: fixed effects effect
$\boldsymbol{F}$: inbreeding coefficients
b : inbreeding depression parameter
$\boldsymbol{u}$: additive genetic effects
$\boldsymbol{i}$: **inbreeding load**
$\boldsymbol{p}$: permanent environmental effect
$\boldsymbol{e}$: residual effect

*within year and parity

Material and Methods

- $\boldsymbol{F}$ is the pedigree-based inbreeding (inbupgf90)

- **Partial inbreeding coefficients** partition total inbreeding into the different ancestors. Matrix $\mathbf{K}$ contains regression coefficients based on this partition. Programs available at https://github.com/alegarra/getPartialInbreeding

- Programs of the BLUPF90+ family were used to estimate variance components http://nce.ads.uga.edu/wiki/doku.php

Comparison of models

- A likelihood ratio test (LRT) was performed from the REML results to assess goodness-of-fit and to compare both models:

Reduced Model (RM): $\boldsymbol{y} = \boldsymbol{X\beta} + \boldsymbol{F}b + \boldsymbol{Z}_u\boldsymbol{u} + \boldsymbol{Z}_p\boldsymbol{p} + \boldsymbol{e}$

Full Model (FM): $\boldsymbol{y} = \boldsymbol{X\beta} + \boldsymbol{F}b + \boldsymbol{Z}_u\boldsymbol{u} + \boldsymbol{Z}_u\boldsymbol{Ki} + \boldsymbol{Z}_p\boldsymbol{p} + \boldsymbol{e}$

- We calculated : $\boldsymbol{LRT = -2logL_{RM}} - (\boldsymbol{-2logL_{FM}})$

Breed	-2 log Likelihood		LRT	
	FM	RM	χ^2	P-value
BB	6,759,011.664	6,759,143.696	132.032	7.4×10^{-31}
MTN	5,379,562.702	5,379,715.675	152.973	1.9×10^{-35}
MTR	22,626,973.729	22,627,357.574	383.845	9.1×10^{-86}

Model with inbreeding load fitted the data better than without inbreeding load in all the breeds

Parameter estimates

The **inbreeding load** variance in:

- BB: was not different from zero
- MTN and MTR: was different from zero

	σ_i^2	$r_{(u,i)}$
BB	11,804.0 $\pm$ 7,356.2	-0.09 $\pm$ 0.3
MTN	9434.7 $\pm$ 4,089.5	-0.08 $\pm$ 0.2
MTR	12,923.0 $\pm$ 3,627.1	-0.12 $\pm$ 0.1

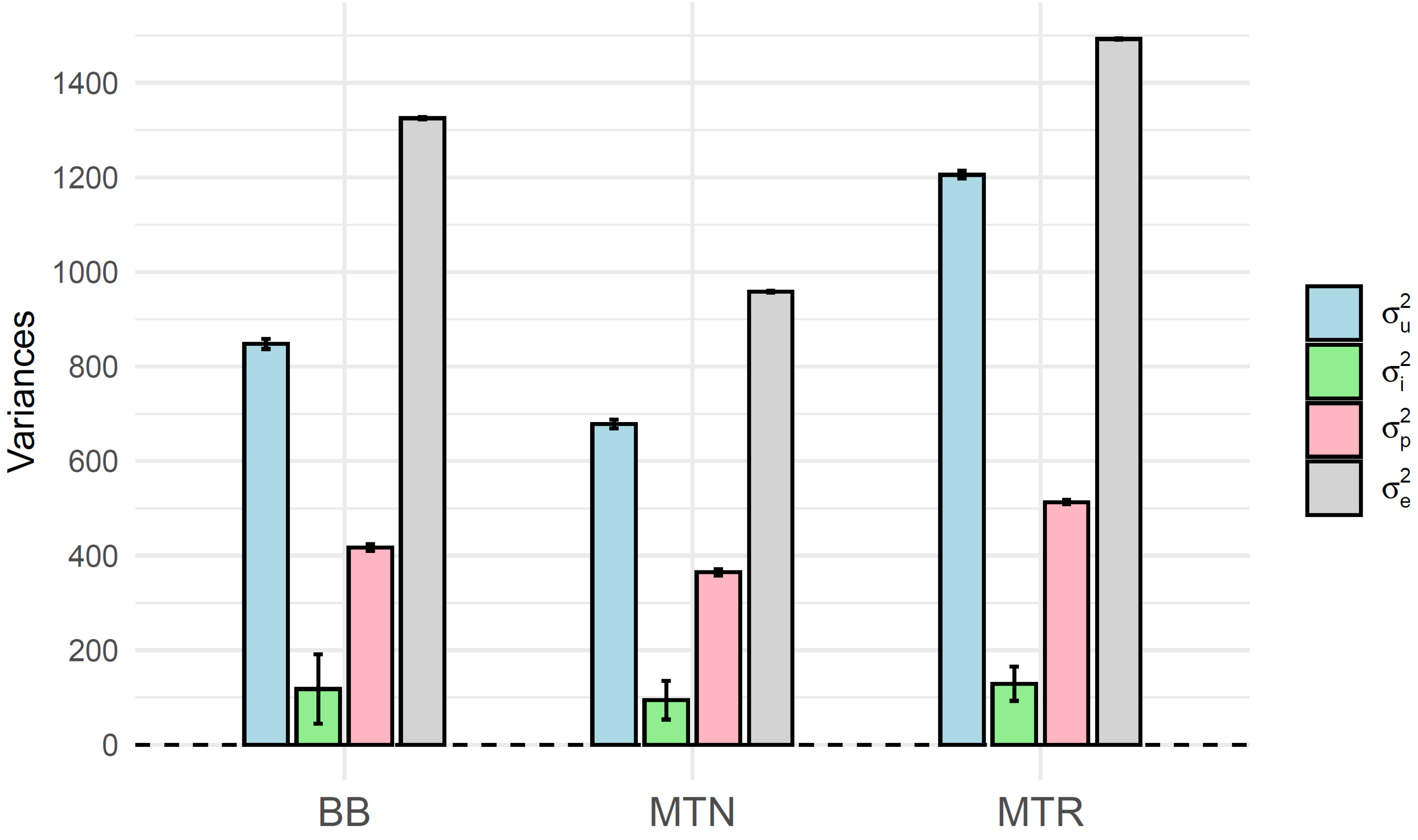
$r_{(u,i)} \approx -0.1$ negative (as expected), small and with large standard errors in all cases

Versus $r_{(u,i)} \approx -0.4$ in Varona et al. (2019):

- Inbreeding load effect is not genetically correlated with the additive genetic effect of milk yield
- Animals with high breeding values will not cause worse inbreeding depression if their descendants are inbred

Parameter estimates

The **inbreeding load** variance (green) corresponds around 4% of the phenotypic variance in BB, MTN and MTR



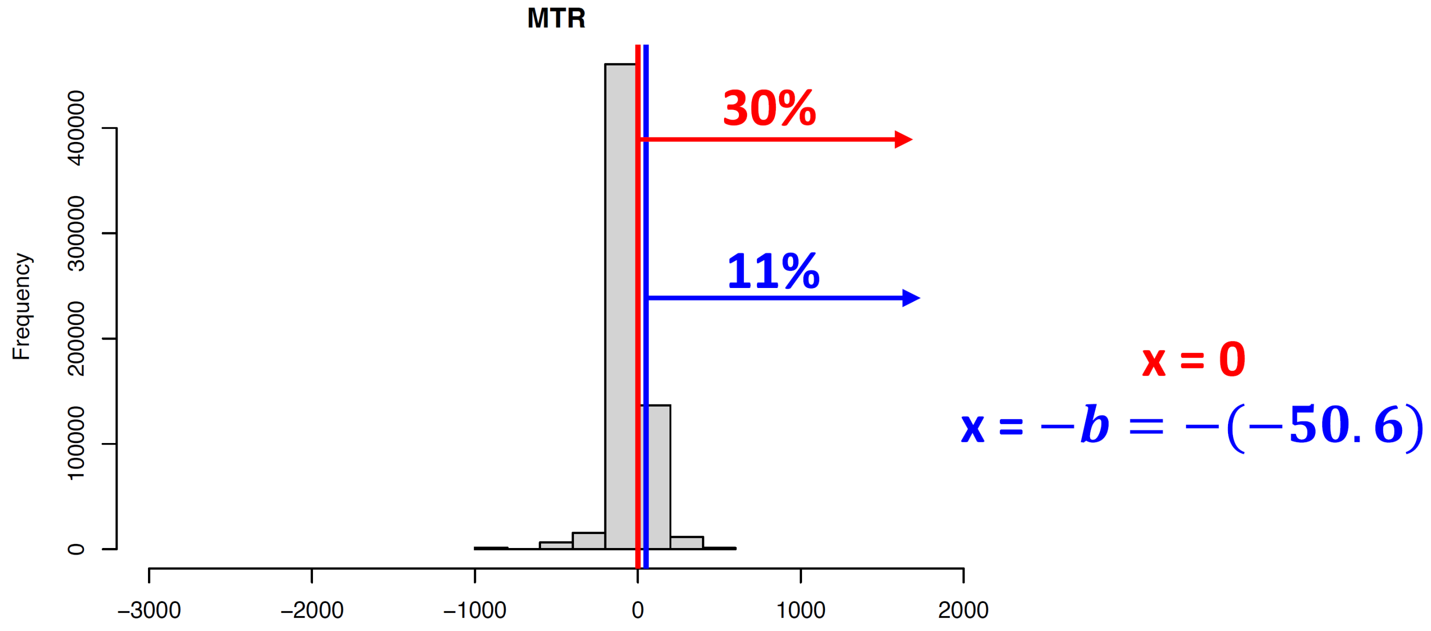
Parameter estimates for milk yield (liters) obtained using the full model

Distribution of the predicted inbreeding load genetic effects

Individuals with predicted **inbreeding loads** $> -b$:

- Would basically remove recessive alleles reducing milk yield in homozygote carriers
- Would compensate **inbreeding load** and produce a positive inbreeding effect

Which cause an improving in milk yield of their inbred descendants



Distribution of the predicted inbreeding load genetic effects in MTR breed (all animals)

Conclusions

- A genetic variance exists for **inbreeding load** in MTN and MTR breeds
- Low values of genetic correlation between **inbreeding load** and breeding value effects imply that selection for milk yield will not cause increase inbreeding depression in milk yield in inbred animals
- The small magnitude of **inbreeding load** does not warrant selection based on this criterion

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Consolidating Research, Development and Innovation in sheep

Thank you for your attention!