GEroNIMO and RUMIGEN Joint Final Event

Breeding the Future

Genomics, Epigenomics & Societal Acceptability for Sustainability in Livestock

Selection, genetic load and genetic diversity

Gwendal RESTOUX, Thierry TRIBOUT, Renzo BONIFAZI, Theo MEUWISSEN, Jack WINDIG, Anne BARBAT, Stéphanie MINERY, Jeremie VANDENPLAS & Pascal CROISEAU

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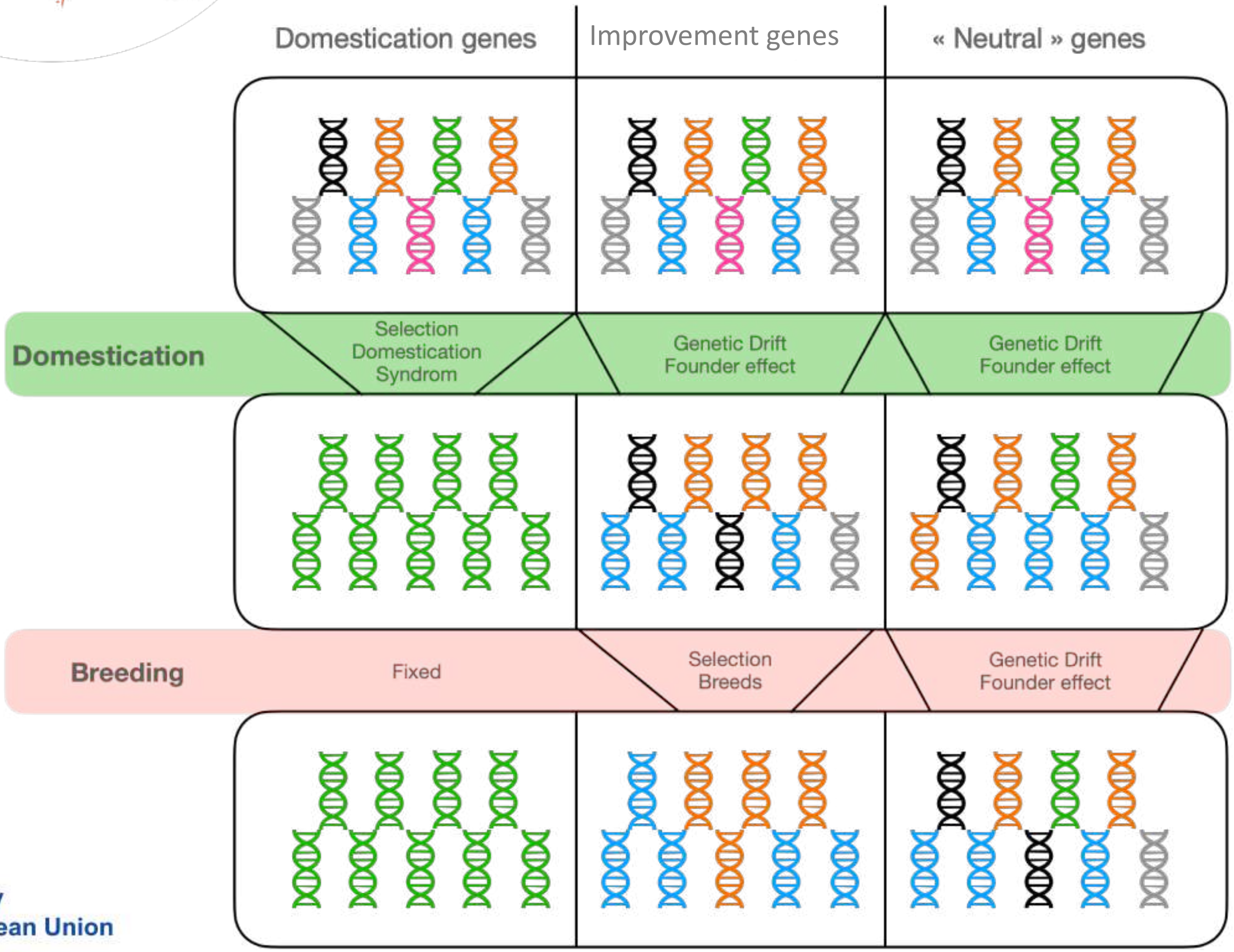
Breeding: a source of genetic diversity?



Restoux, 2023

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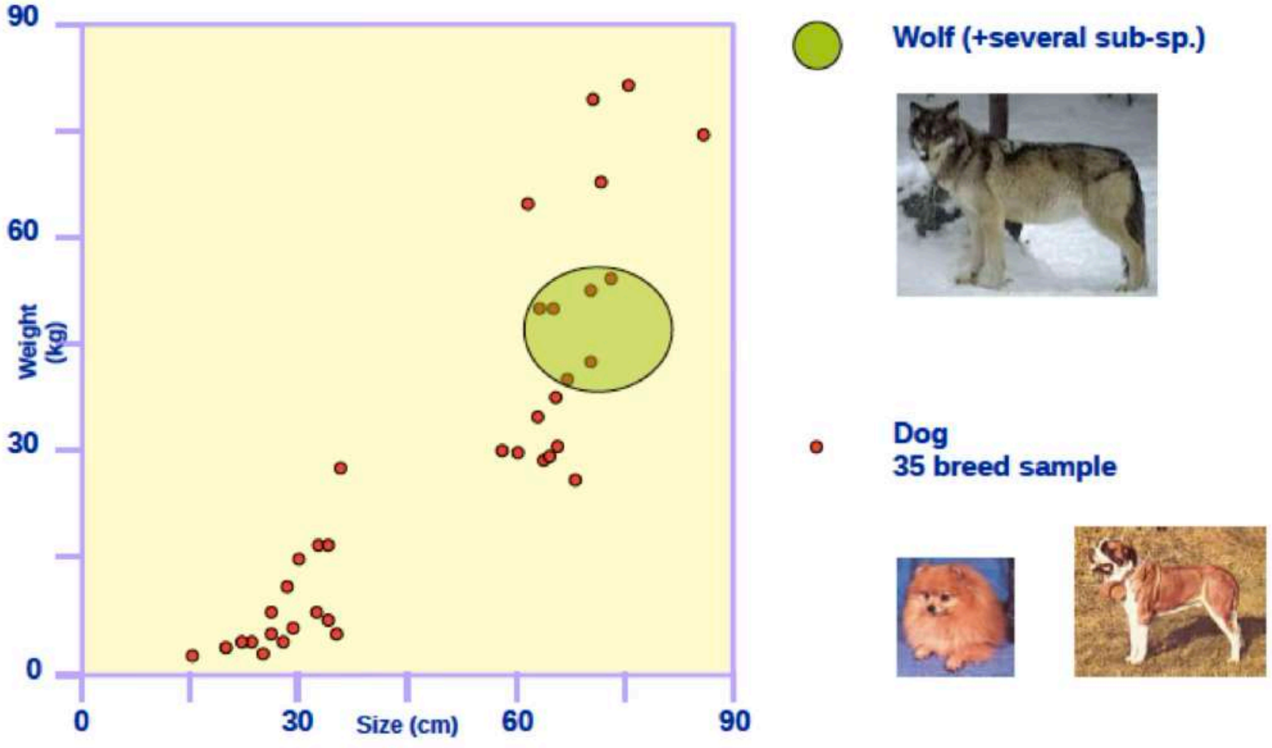
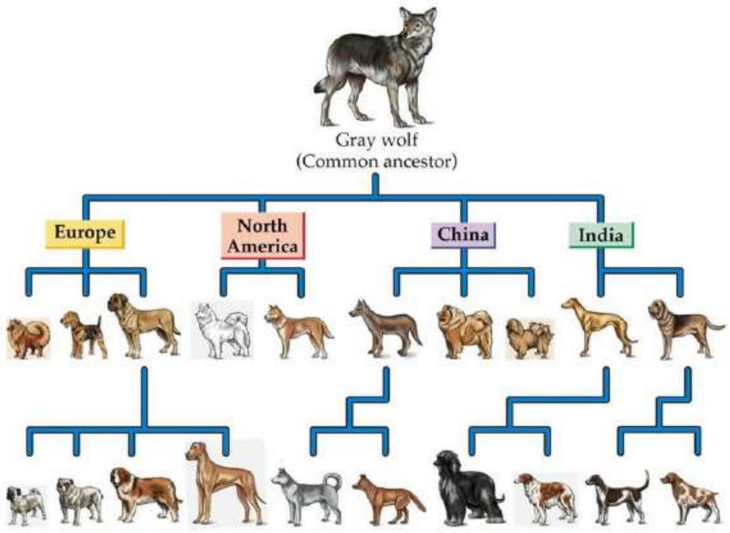
Breeding redistributes diversity



Leroy



Sled dog society of Wales ©

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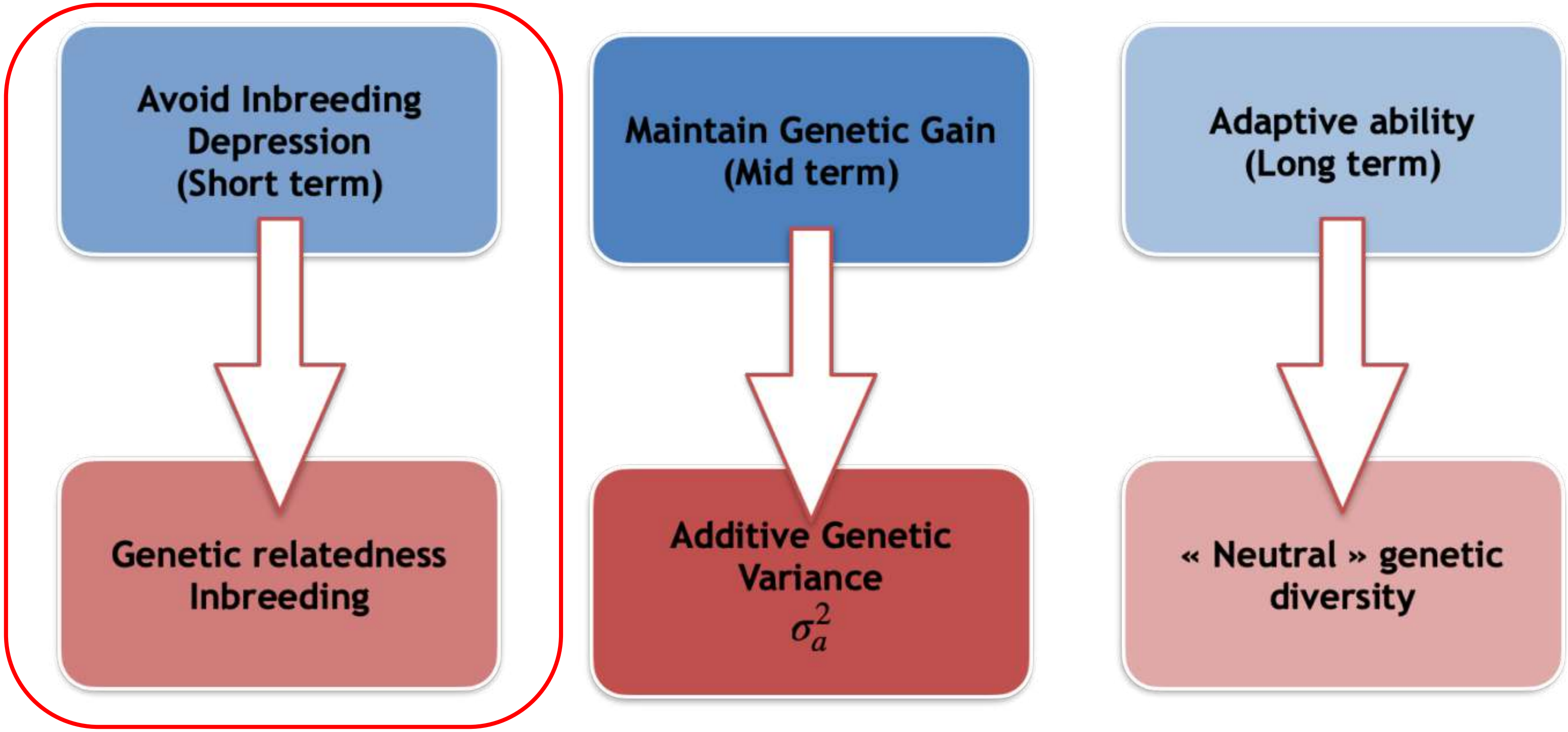
Genetic diversity management : Why and How



Avoid Inbreeding Depression (Short term)

Genetic relatedness Inbreeding

Maintain Genetic Gain (Mid term)

Additive Genetic Variance σ_a^2

Adaptive ability (Long term)

« Neutral » genetic diversity

$\sigma_a^2 = 2\overline{pq}a^2$ with $2\overline{pq} = 2p_0q_0(1-F)$ and so $\sigma_a^2 = 2p_0q_0a^2(1-F)$

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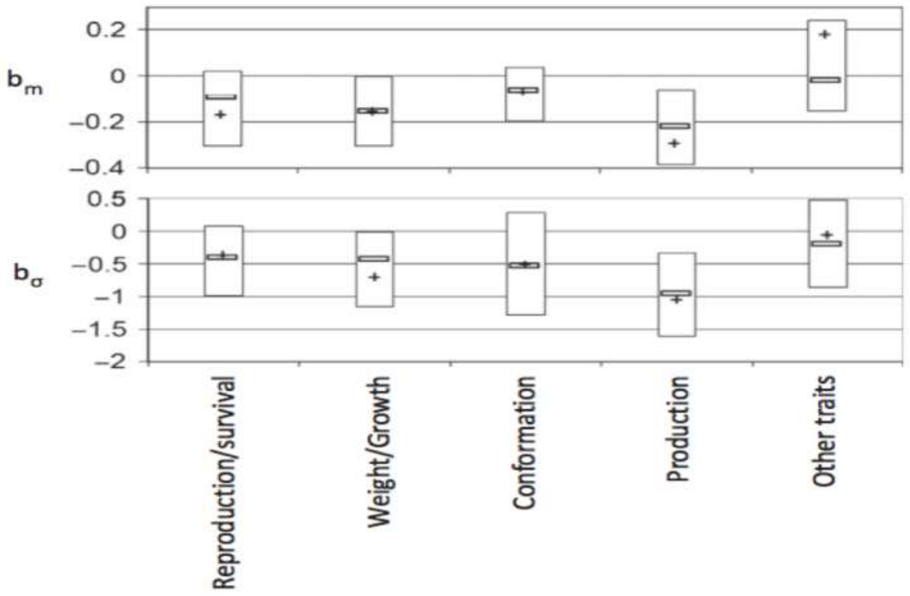
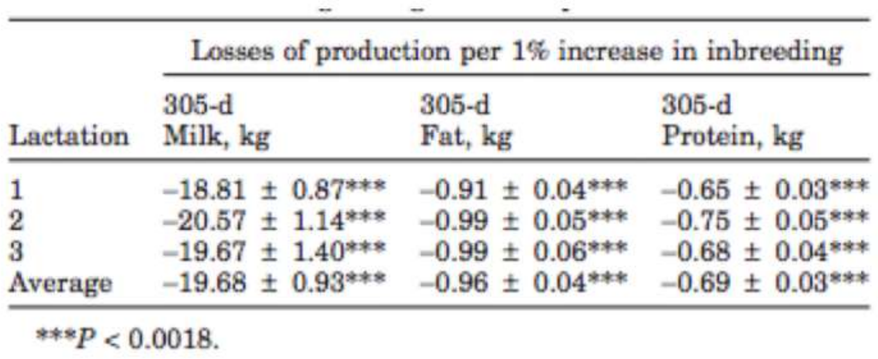
Genetic diversity, Inbreeding and its consequences



Leroy, 2014



	Losses of production per 1% increase in inbreeding		
Lactation	305-d Milk, kg	305-d Fat, kg	305-d Protein, kg
1	−18.81 ± 0.87***	−0.91 ± 0.04***	−0.65 ± 0.03***
2	−20.57 ± 1.14***	−0.99 ± 0.05***	−0.75 ± 0.05***
3	−19.67 ± 1.40***	−0.99 ± 0.06***	−0.68 ± 0.04***
Average	−19.68 ± 0.93***	−0.96 ± 0.04***	−0.69 ± 0.03***

***$P < 0.0018$.

Croquet et al., 2006

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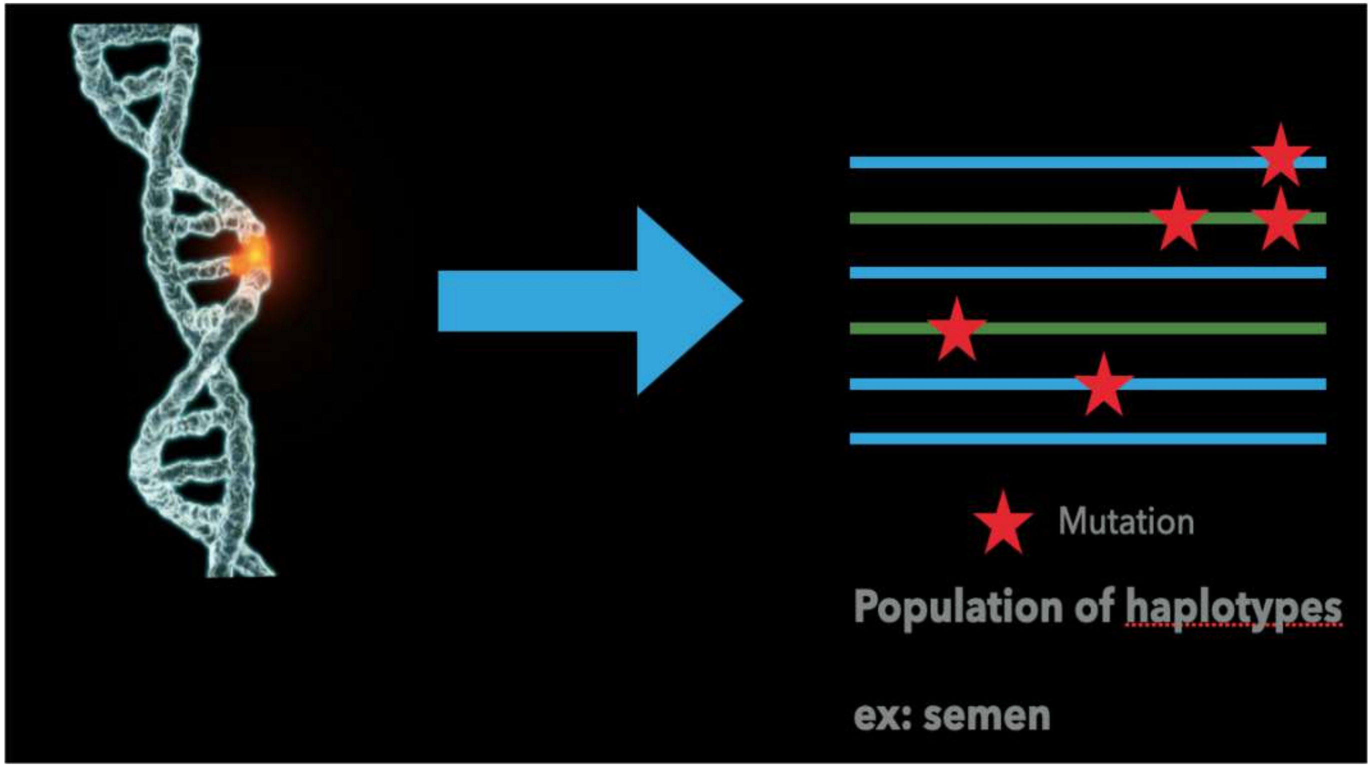
The genetic load



- Continuous accumulation of mutations
- **Deleterious**
- **Recessive**
- **Low frequencies** in the population (~mu)
- **Segregate** and hardly eliminated in absence of inbreeding
- Fixed and segregating mutations -> **genetic load (heterosis vs ID)**

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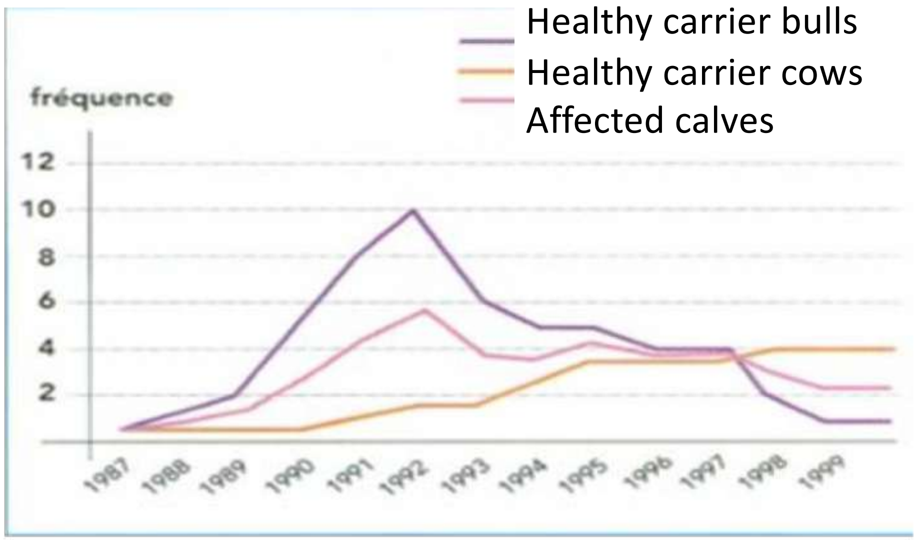
Bovine Leucocyte Adhesion Deficiency (BLAD)



One male responsible: Ivanohe (born in 1952)

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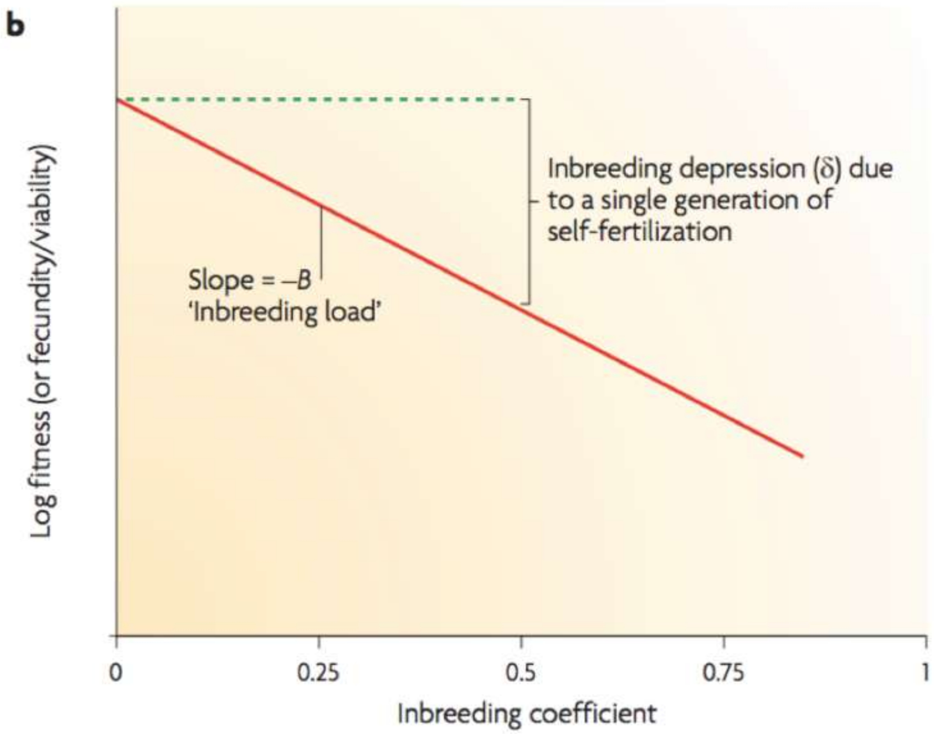
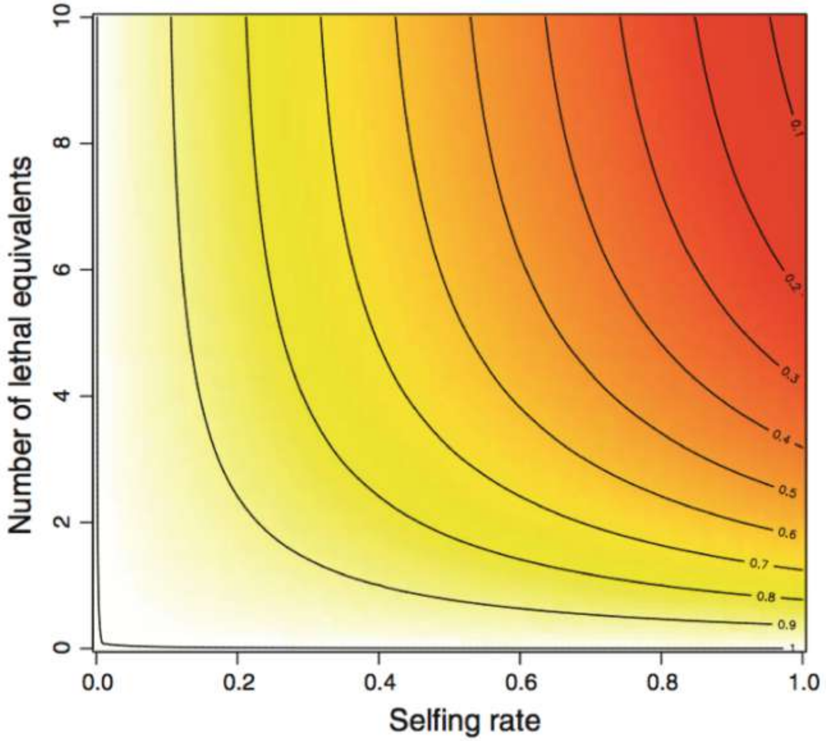
Combination of genetic load and inbreeding



Charlesworth & Willis, 2009



Restoux et al., 2009

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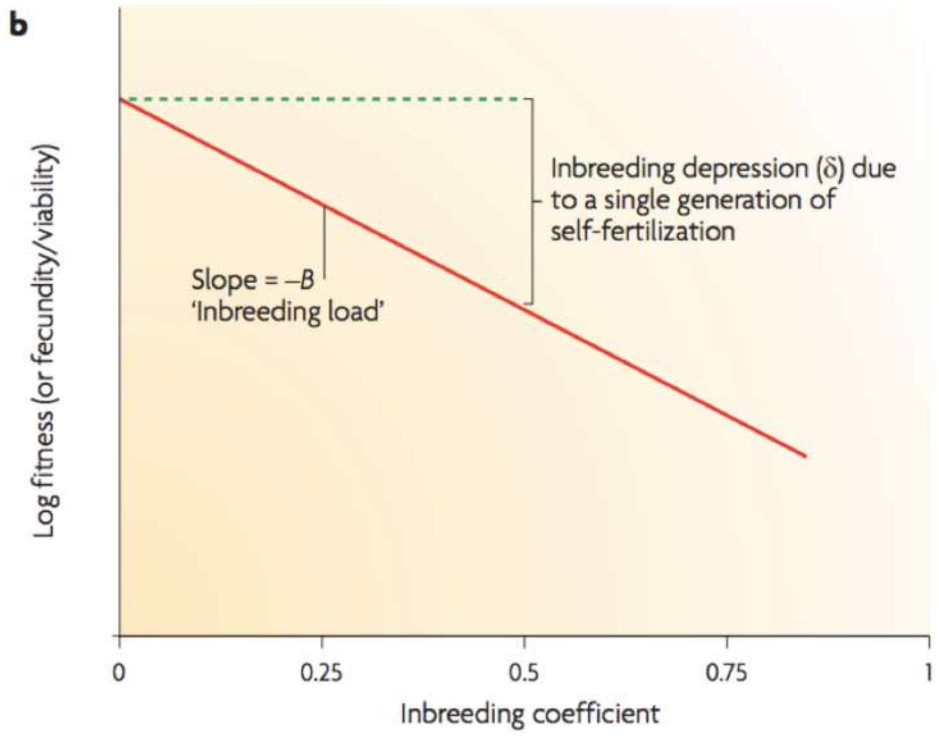
Management of inbreeding depression

Inbreeding depression is the expression of **genetic load** through **inbreeding**.

Thus, two options are possible :

1. Avoid inbreeding
   a. Estimate inbreeding
   b. Set a breeding scheme to limit it

2. Reduce / control inbreeding load
   a. Evaluate inbreeding load
   b. Set a breeding scheme to reduce it



Charlesworth & Willis, 2009

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European local dairy cattle breeds

Abondance

46 810 females

Tarentaise

17 269 females

Vosgienne

5 363 females

Norwegian Red

175 975 females

MRY

8 068 females

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the European Union

The impact of genomic selection

J. Dairy Sci. TBC
https://doi.org/10.3168/jds.2025-27562

Impact of genomic selection on genetic diversity in 5 local European cattle breeds

R. Bonifazi,[1*] T. H. E. Meuwissen,[2] P. Croiseau,[3] G. Restoux,[3] S. Minéry,[4] J. Vandenplas,[1] and J. J. Windig[1]

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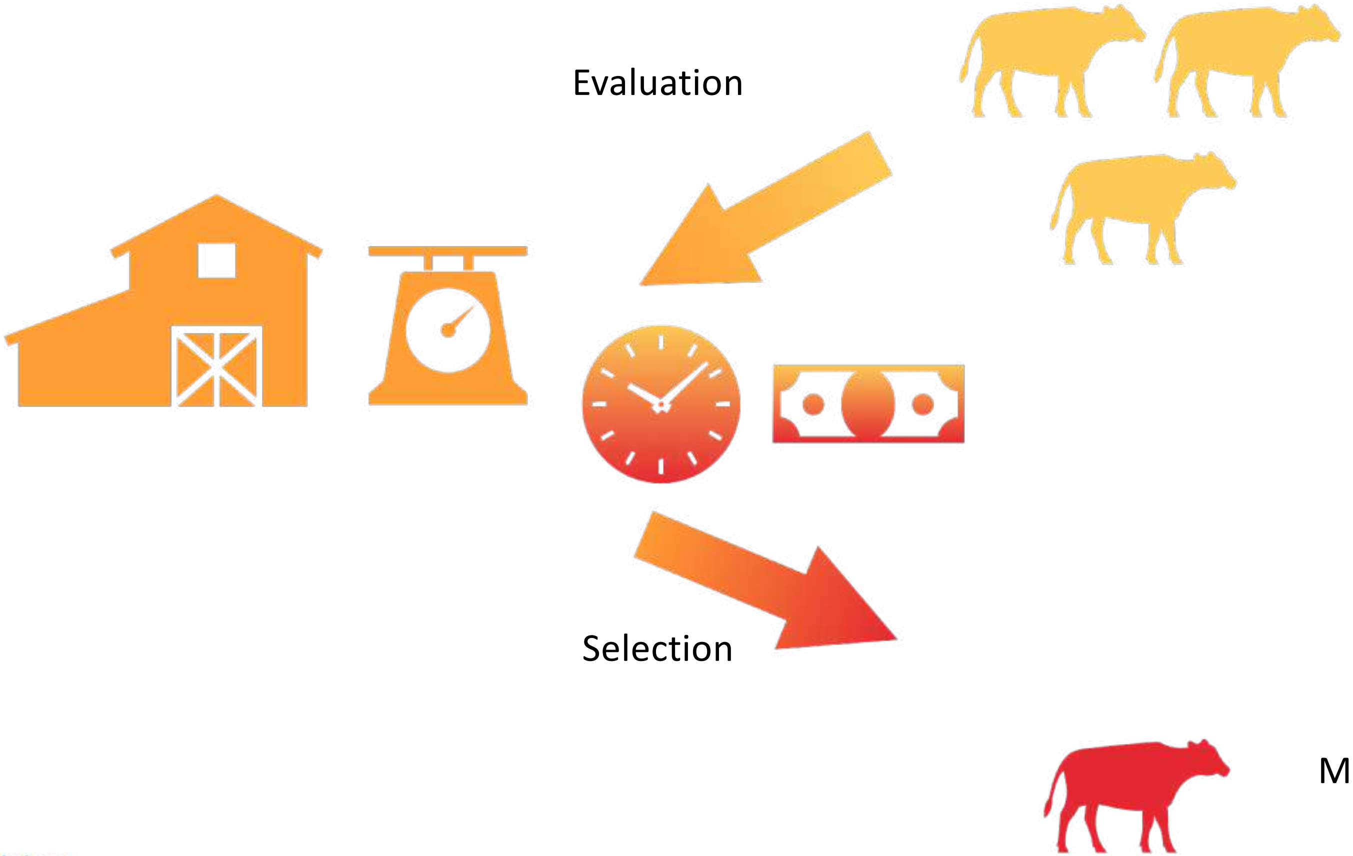
Context: Progeny testing (pre GS)



Evaluation

Candidate sires for selection

Testing station

EBV

Selection

Marketed bulls

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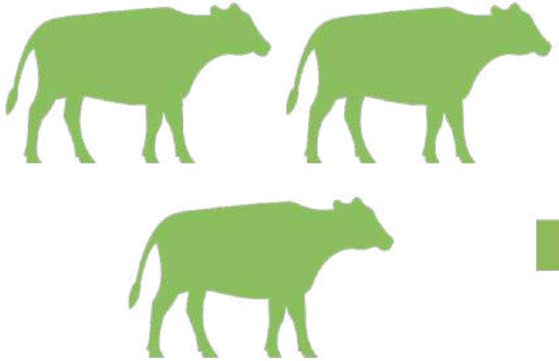
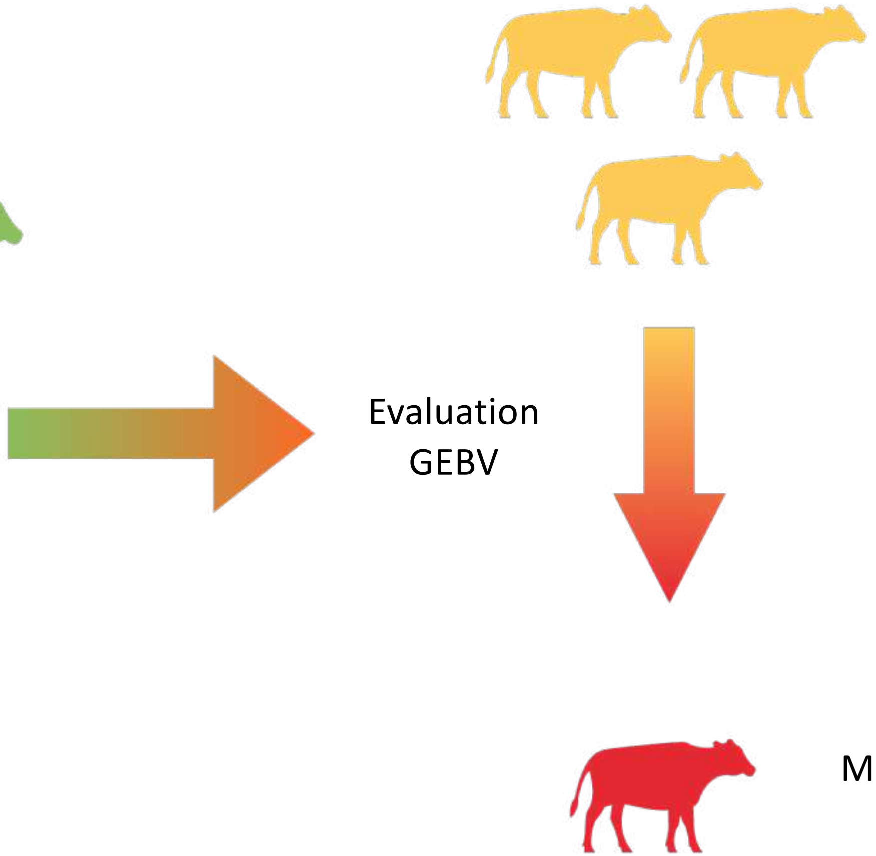
Context: Genomic selection rationale

Reference population
(genotypes + performances)



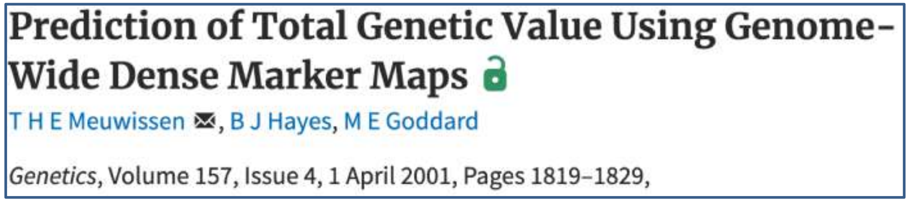


Genotyped
candidates

Evaluation
GEBV

Evaluation
Selection

Marketed bulls



Prediction of Total Genetic Value Using Genome-Wide Dense Marker Maps

T H E Meuwissen ✉, B J Hayes, M E Goddard

Genetics, Volume 157, Issue 4, 1 April 2001, Pages 1819–1829,

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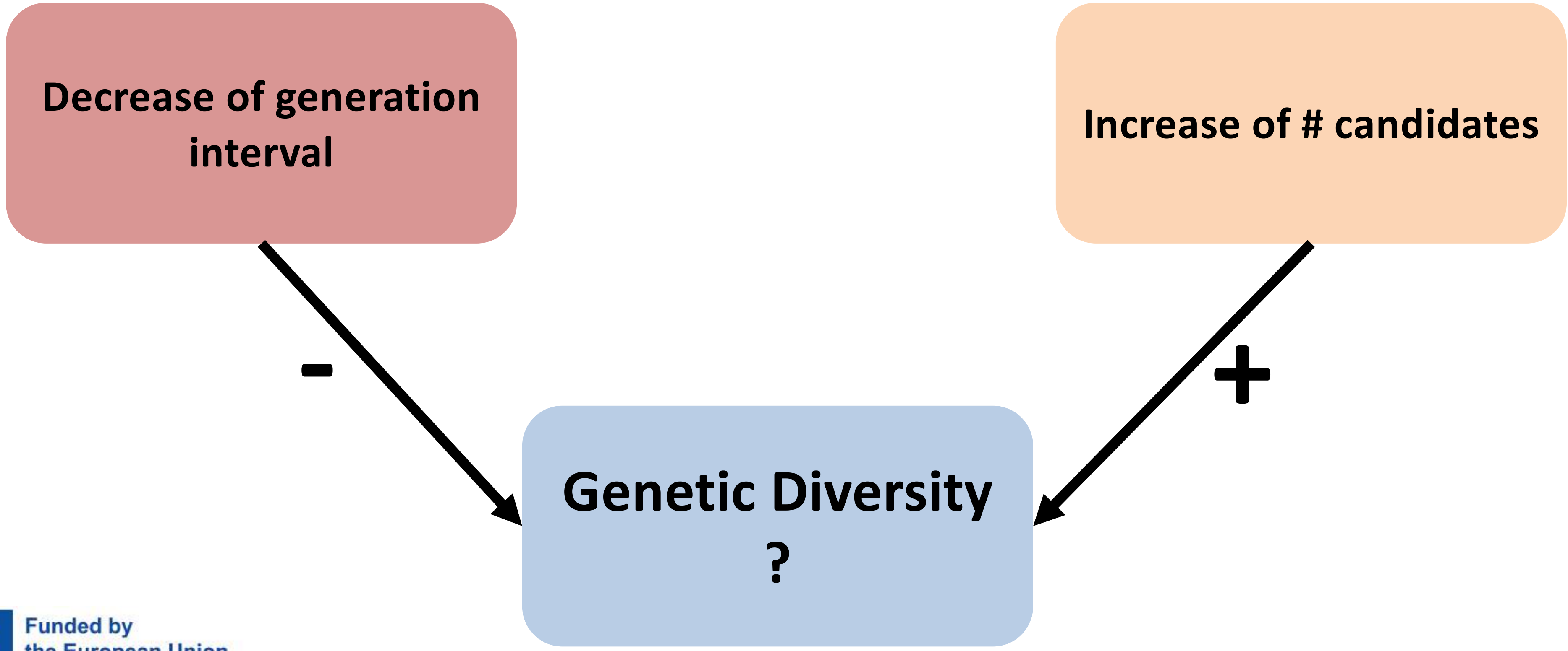
Potential impact of GS



Decrease of generation interval

Increase of # candidates

-

+

Genetic Diversity
?

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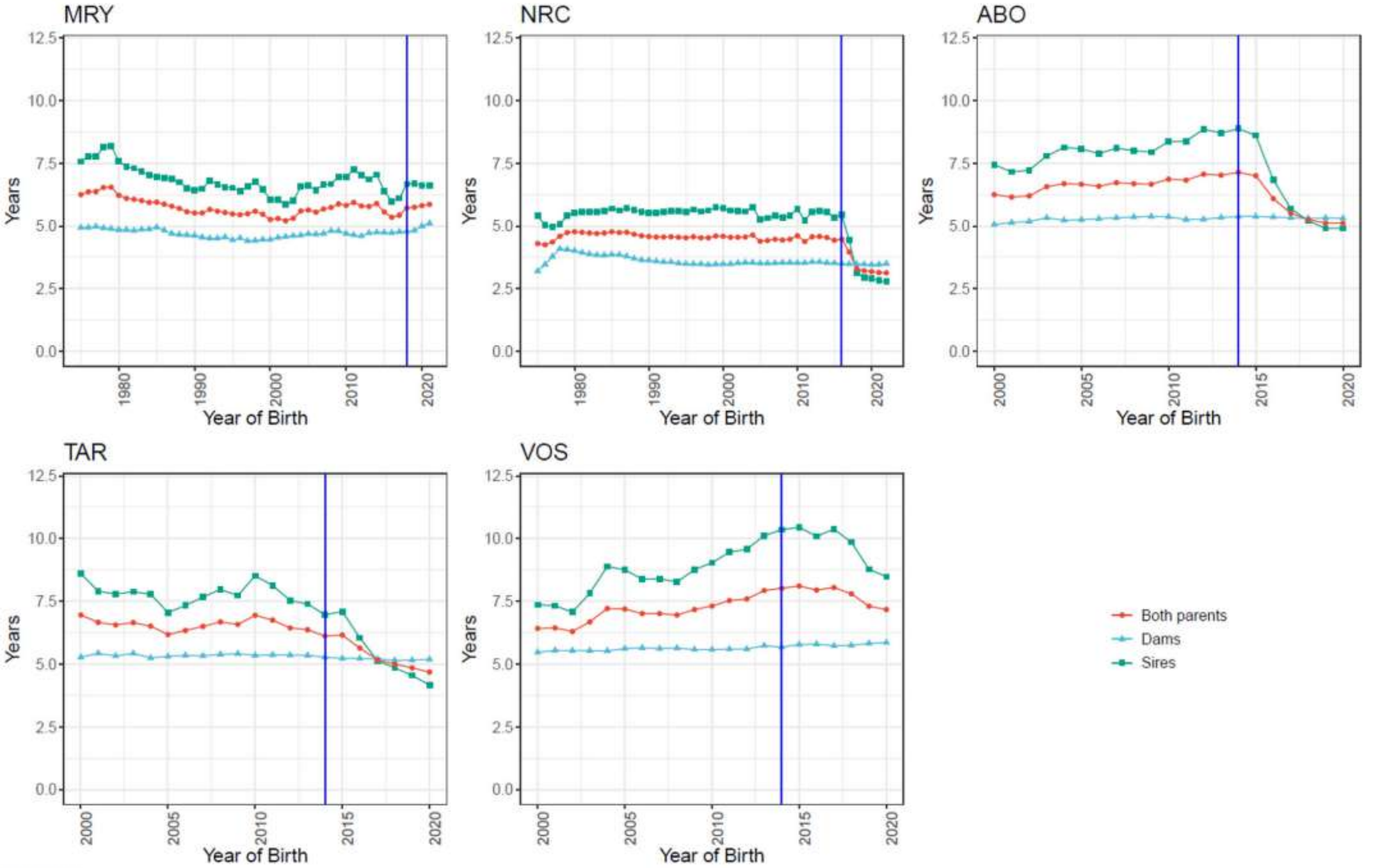
Decrease of generation interval



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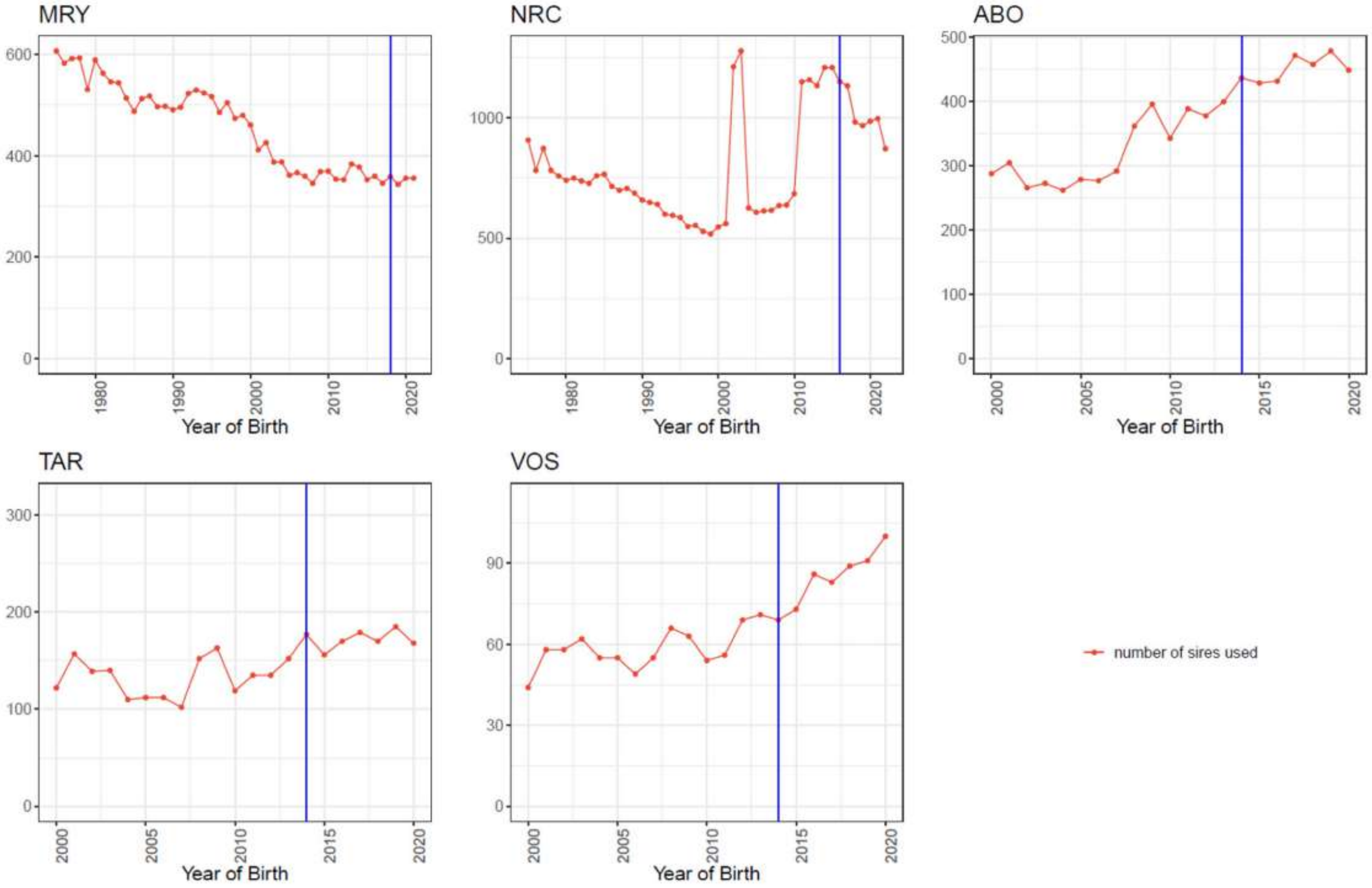
Changes in the use of sires



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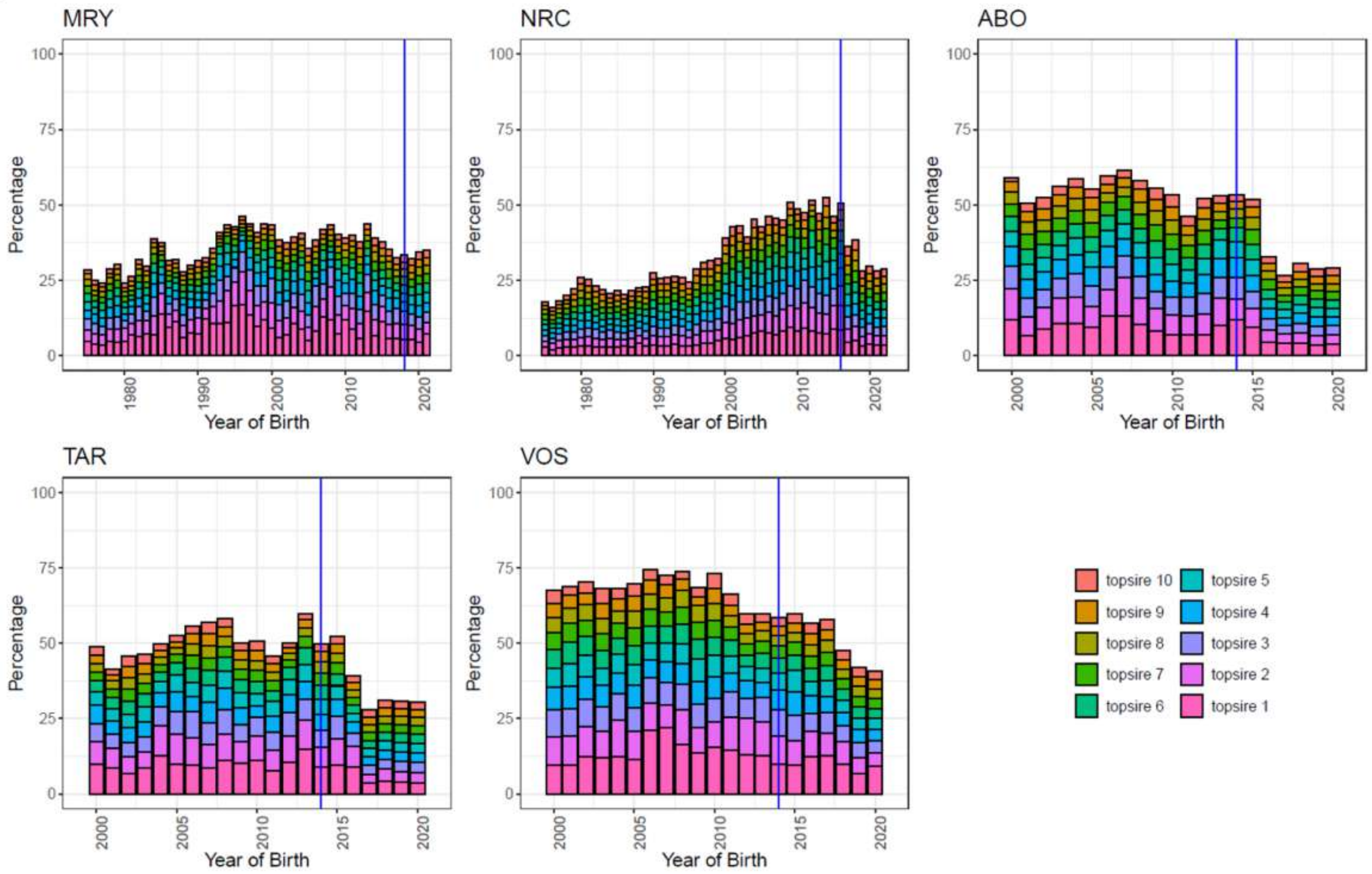
More balanced use of sires



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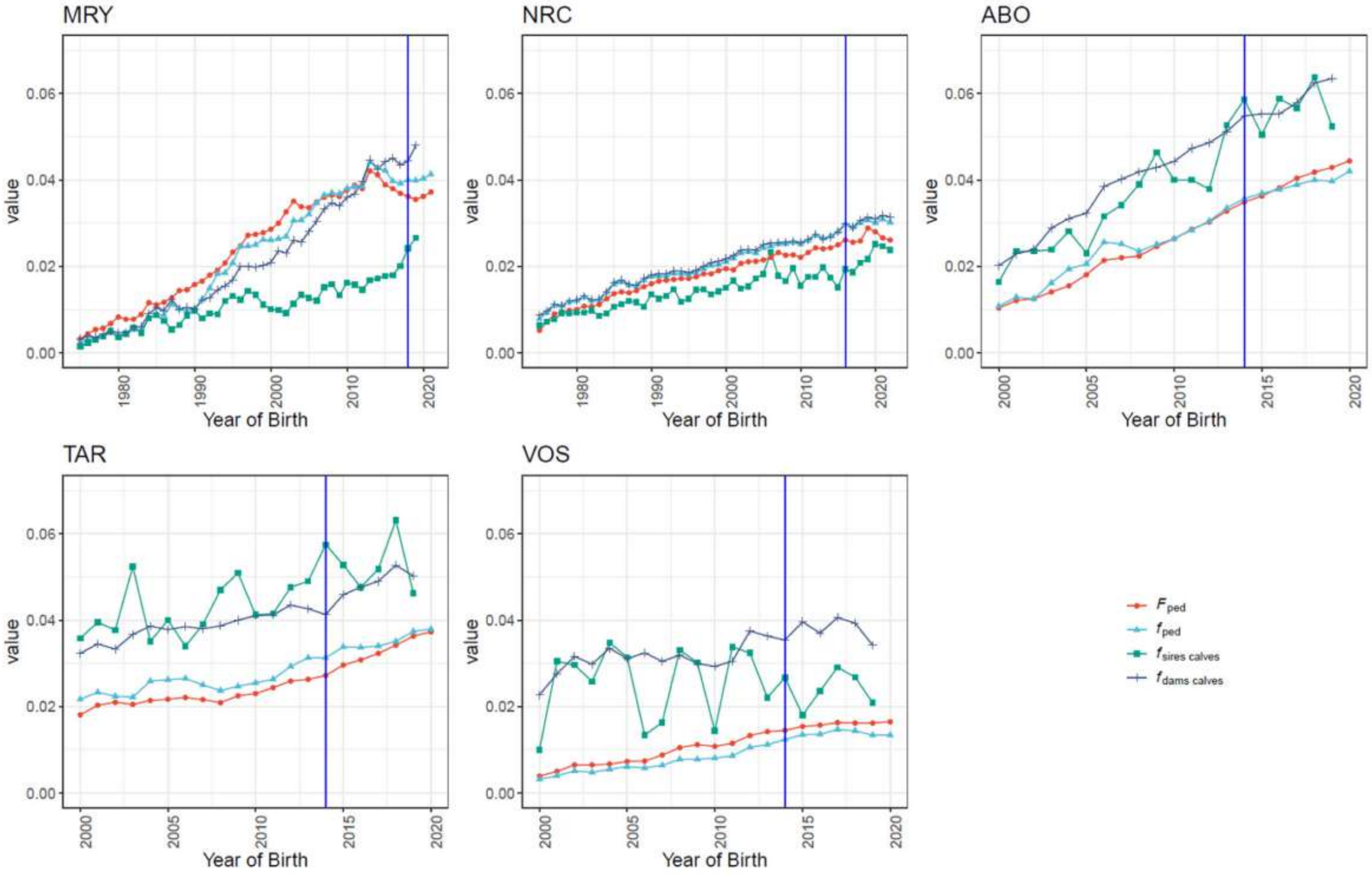
Pedigree-based kinship/inbreeding evolution



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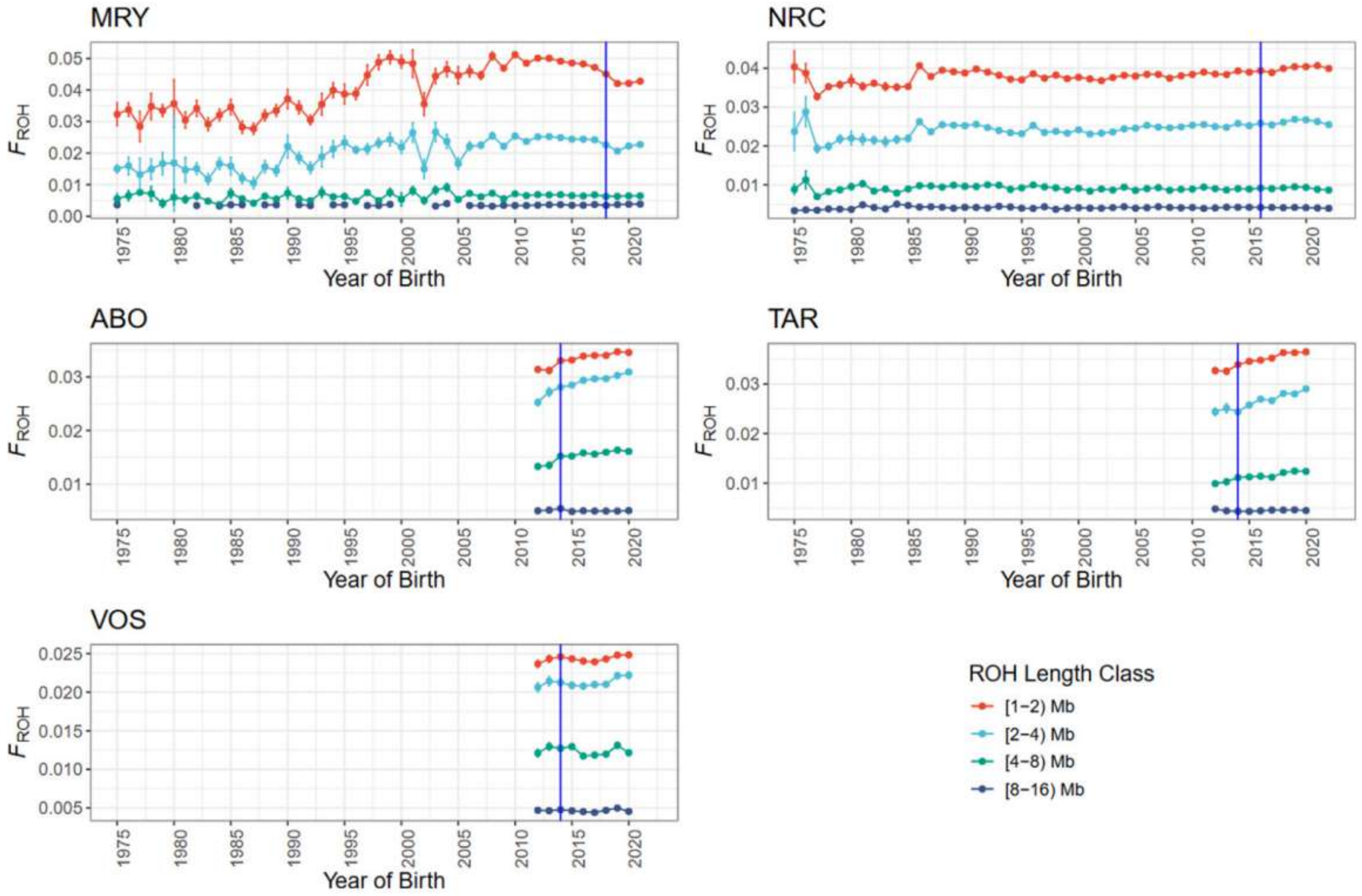
Molecular-based kinship/inbreeding evolution



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Main results

- Massive decrease in generation interval
- Inconsistent impact on the number of sires used
  - But more balanced contributions of each of them
- No major change in inbreeding rates
  - Mainly due to old inbreeding (probably less deleterious)

- Genomic selection itself is not the main driver of diversity evolution
  - Management associated to it and its implementation is the key

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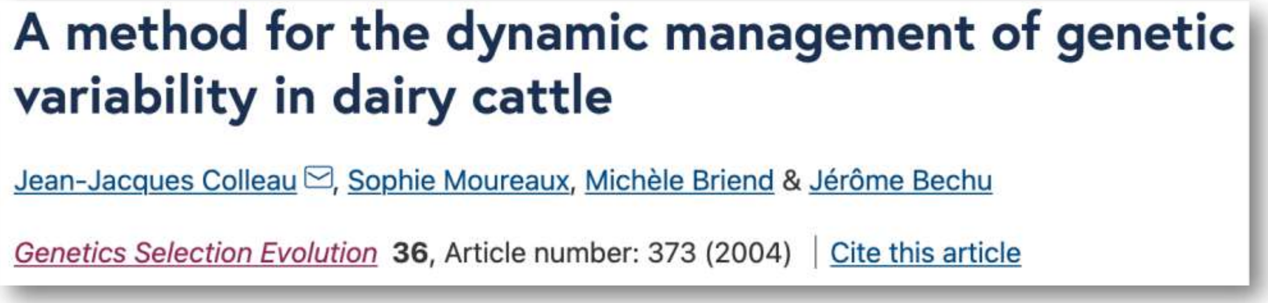
Managing inbreeding

Maximizing the response of selection with a predefined rate of inbreeding

T.H.E. Meuwissen

Journal of Animal Science, Volume 75, Issue 4, April 1997, Pages 934–940,

Max $\Delta G \mid \Delta F$



A method for the dynamic management of genetic variability in dairy cattle

Jean-Jacques Colleau, Sophie Moureaux, Michèle Briend & Jérôme Bechu

Genetics Selection Evolution **36**, Article number: 373 (2004) | Cite this article

Min $\Delta F \mid \Delta G$

(cf Geronimo WP3 / RUMIGEN WP4)

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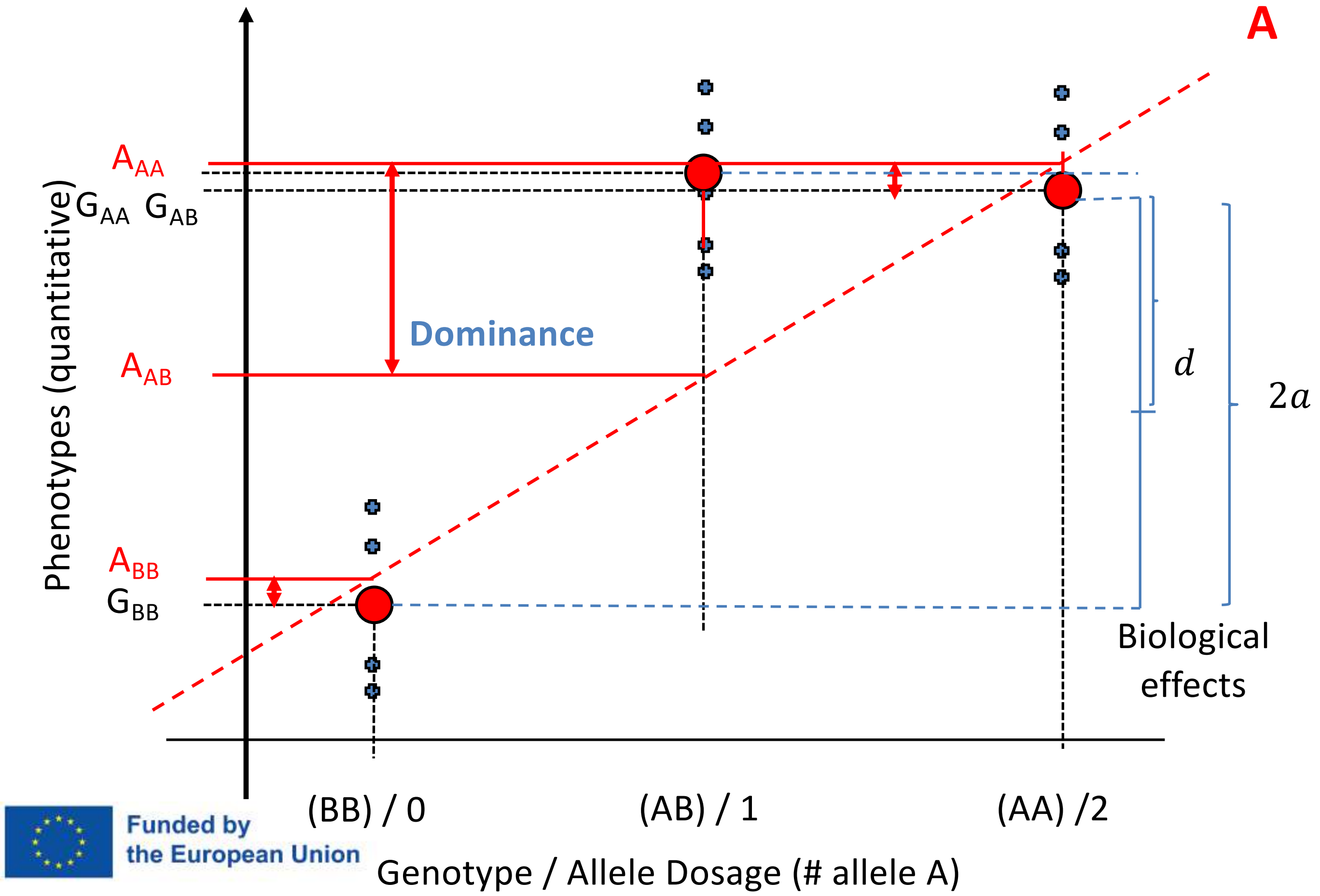
Genetic modeling



- **Deleterious** (negative effect)
- **Recessive** (dominance effect)
- **Low frequencies** in the population (~mutation rate, μ)
- **Segregate** and hardly eliminated in absence of inbreeding

Only (BB) are counter-selected

$$P(BB) = (1-F)\mu^2 + F\mu$$

but $\mu^2 \ll \mu$

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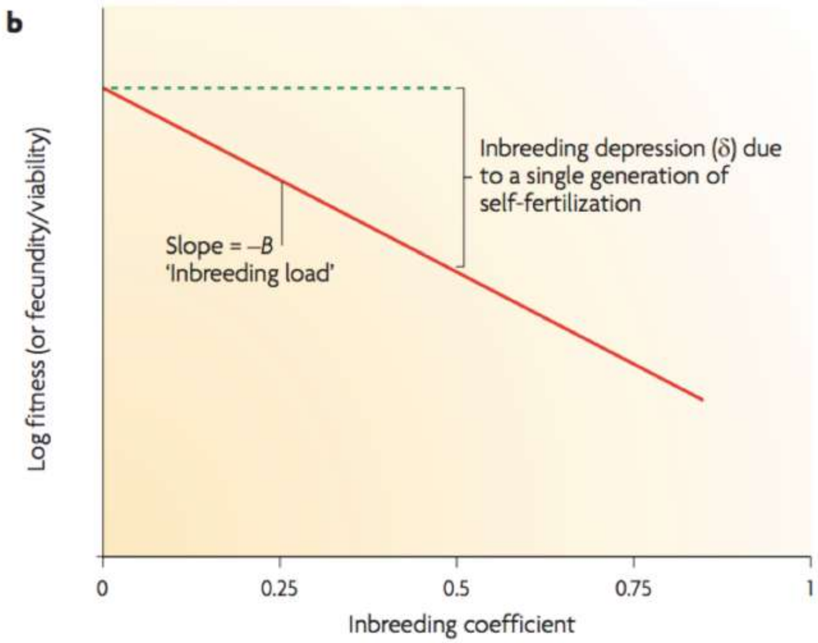
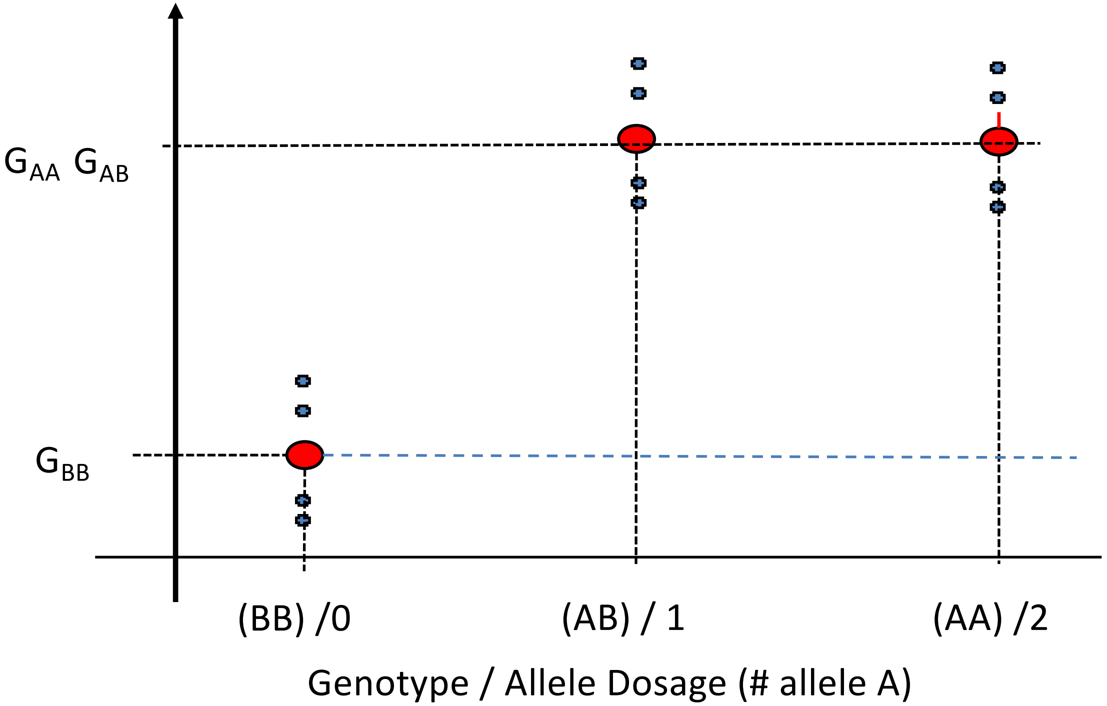
Main rationale

Restoux et al., in prep



Charlesworth & Willis, 2009



Inbreeding load:

1. Deleterious
2. Recessive
3. Rare

Context:

No access to whole genome
LD between causal and neutral SNPs

To consider:

Avoid confounding effects between SNP under scrutiny and individual level in:

- Breeding value level
- Inbreeding

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Global inbreeding depression

$$y_i = \mu + F_i I_0 + u_i + e_i \qquad \text{(M0)}$$

Global effect of (pedigree) inbreeding on the phenotype

	Milk yield Quté Lait	Fat yield MG	Protein yield MP	Fat percent. TB	Protein percent. TP	SCS
R12 Abondance	Favour, NS	Unfavour. NS	Favour. NS	Unfavour. Signif	Favour, NS	Favour, NS
R31 Tarentaise	Unfavour. Signif	Unfavour. trend	Unfavour. trend	Favour, NS	Favour, NS	Favour, NS
R57 Vosgienne	Unfavour. Signif	Unfavour. Signif	Unfavour. Signif	Unfavour. Signif	Unfavour. NS	Unfavour. NS

Significant effect trend effect Non significant effect

Favourable effect

Unfavourable effect

Unfavourable effect of global inbreeding on phenotype observed for some traits

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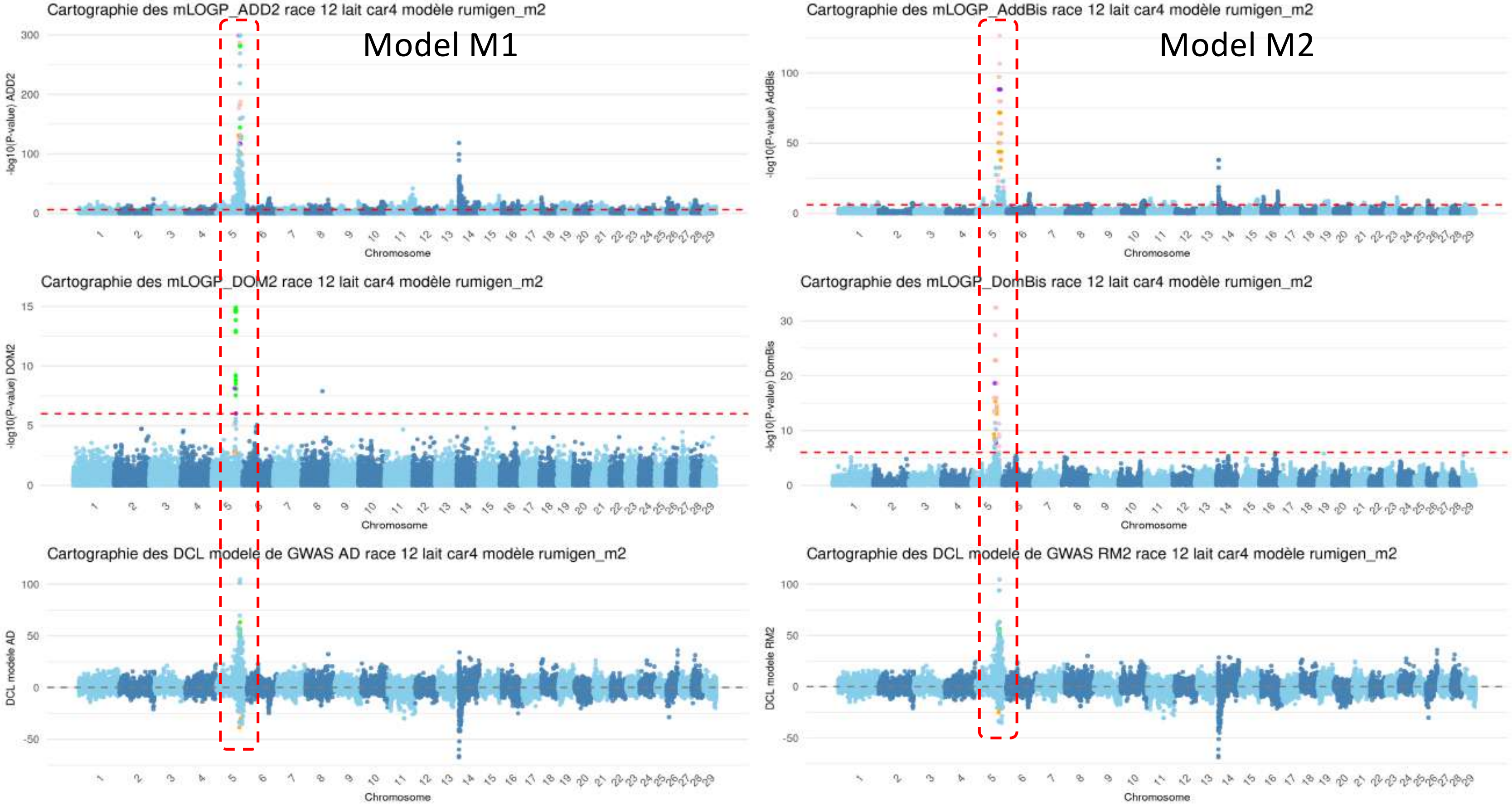
Detection of genetic load regions

Without IBD consideration **With IBD consideration**

Additive Effects

Dominance Effects

Impact on global inbreeding depression



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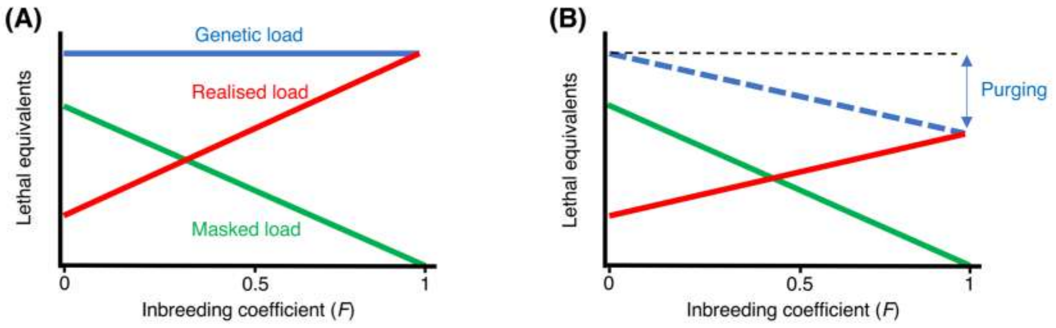
Remove these mutations?



Dussex et al., 2023

Novel strategies to minimize progeny inbreeding while maximizing genetic gain using genomic information

J.E. Pryce [*,†] · B.J. Hayes [*,†,‡] · M.E. Goddard [*,†,§]

Controlling Coancestry and Thereby Future Inbreeding by Optimum-Contribution Selection Using Alternative Genomic-Relationship Matrices

G. T. Gebregiwergis[1*] Anders C. Sørensen[2] Mark Henryon[3,4] Theo Meuwissen[1]

Purging ?

Too costly -> Needs large population
Welfare impact

Weighting ?

Mating plan level
If too numerous could affect selection efficiency

Considering other relationship matrices ?

Which ones ?
Addverse effects

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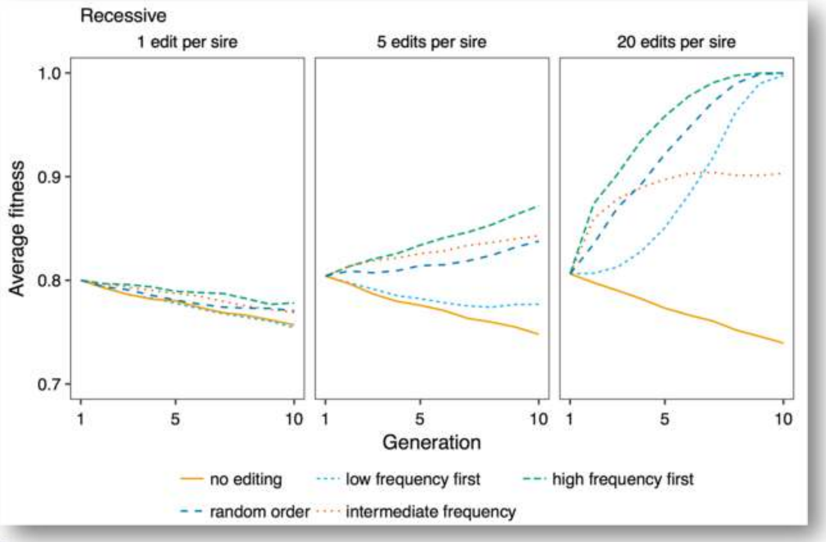
What about genome editing?

Removal of alleles by genome editing (RAGE) against deleterious load

Martin Johnsson[1,2], R. Chris Gaynor[1], Janez Jenko[1], Gregor Gorjanc[1], Dirk-Jan de Koning[2] and John M. Hickey[1*]



- Need to edit many positions to be efficient

- Need to edit many individuals

  - Promotion of few edited sires
  - Same problem than with ‘star system’

- Edited animals should not become the gold standard at the expense of non-edited ones
  -> Same issue than with local breeds

- We need to include the diversity question into our room of acceptance for this biotechnology too (cf Rasmus talk).

- **A new technology is not good or bad per se, it depends on how we use and implement it into the field**

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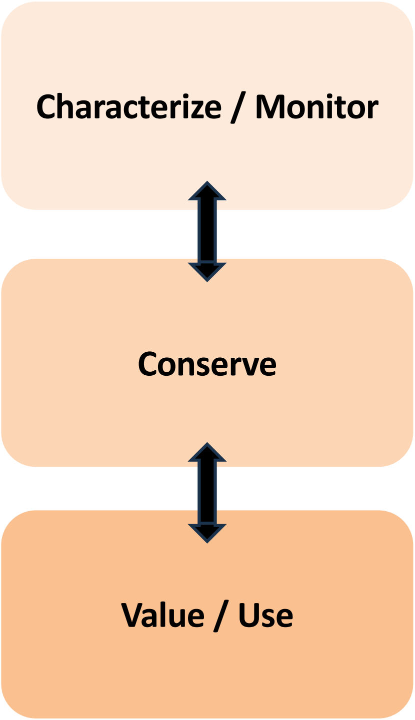
Recommendation



Characterize / Monitor

Conserve

Value / Use

Levels of genetic diversity

- Which kind of genetic diversity?
  e.g. Improvement, neutral, rare, commons, deleterious…
- What about phenotypic variability ?
  cf GxE, Landscape genomics, resistance genes…

Conservation programs

- Avoiding inbreeding
- Maintaining genetic diversity (adapted OCS, cf Theo’s talk)
- Remove deleterious alleles (weighting SNP, cf WP8 RUMIGEN)
- Reintroduce genetic diversity (cryobanking)

Breeding programs

- Balance genetic gain and conservation of genetic diversity on both short and long term
- …

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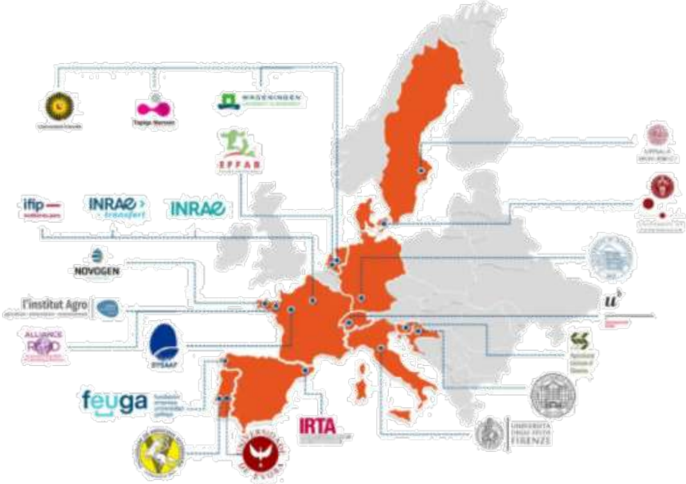
Genomics, Epigenomics & Societal Acceptability for Sustainability in Livestock

THANK YOU

TOWARDS IMPROVEMENT OF RUMINANT BREEDING THROUGH GENOMIC AND EPIGENOMIC APPROACHES

GENOME AND EPIGENOME ENABLED BREEDING IN MONOGASTRICS



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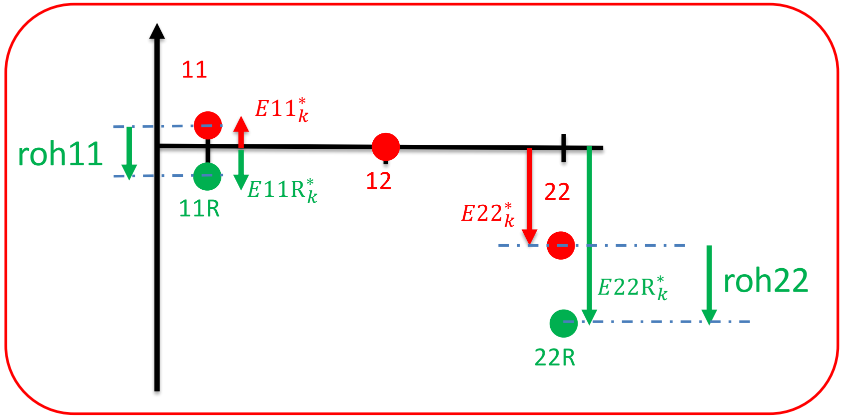
Genetic load : « unfavourable effect of being homozygous on a local segment » → model #2 : use ROH information

$$y_i = \mu + F_i I_p + u_i + [c1_{ik} \quad c2_{ik} \quad c4_{ik} \quad c5_{ik}] \begin{bmatrix} E11_k^* \\ E11R_k^* \\ E22_k^* \\ E22R_k^* \end{bmatrix} + e_{ik} \qquad u_i \sim N(0, \sigma_g^2)$$

$E12_k$ = reference = 0

$E11_k^* = E11_k - E12_k$
$E11R_k^* = E11R_k - E12_k$
$E22_k^* = E22_k - E12_k$
$E22R_k^* = E22R_k - E12_k$

$[c1_{ik} \quad c2_{ik} \quad c4_{ik} \quad c5_{ik}]$ = $[1 \quad 0 \quad 0 \quad 0]$ for genotype 11 not in ROH segment at variant k
= $[0 \quad 1 \quad 0 \quad 0]$ for genotype 11 in ROH segment at variant k
= $[0 \quad 0 \quad 1 \quad 0]$ for genotype 22 not in ROH segment at variant k
= $[0 \quad 0 \quad 0 \quad 1]$ for genotype 22 in ROH segment at variant k
= $[0 \quad 0 \quad 0 \quad 0]$ for genotype 12 at variant k



First idea :

→ search for variants with significant unfavourable $\widehat{roh11}_k$ or $\widehat{roh22}_k$ effects ?

i.e. unfavourable effect of being locally homogeneous ?

Genetic load : « unfavourable allele hidden by recessive determinsm »

→ model #1 = additive + dominance

$$y_i = \mu + F_i I_p + u_i + [g_{ik} add_k + d_{ik} dom_k] + e_{ik}$$

where $u_i \sim N(0, \sigma_g^2)$

add_k = additive effect of variant k

dom_k = dominance effect of variant k

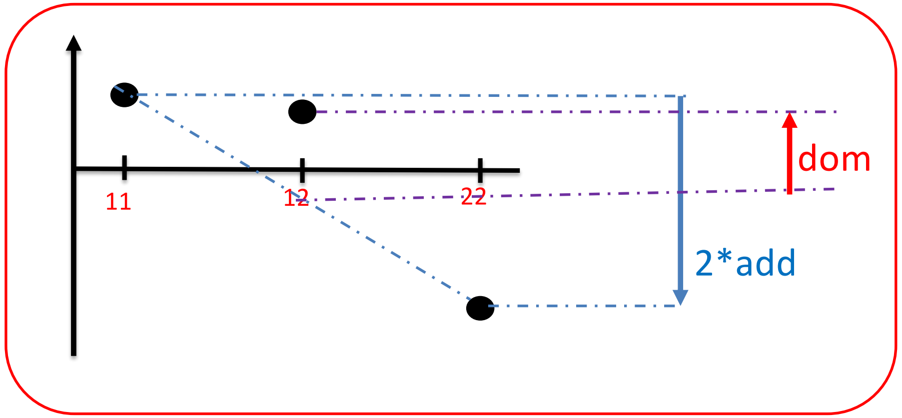
I_p = global inbreeding effect on phenotype

g_{ik} = genotype (nb of alleles 2) carried by animal i at variant k

d_{ik} = covariable for dominance for animal i at variant k

F_i = pedigree inbreeding coefficient of animal i

Genotype at variant k	g_{ik}	d_{ik}
11	0	0
12	1	1
22	2	0



add effect < 0

Unfavourable additive effect of allele 2 on the phenotype

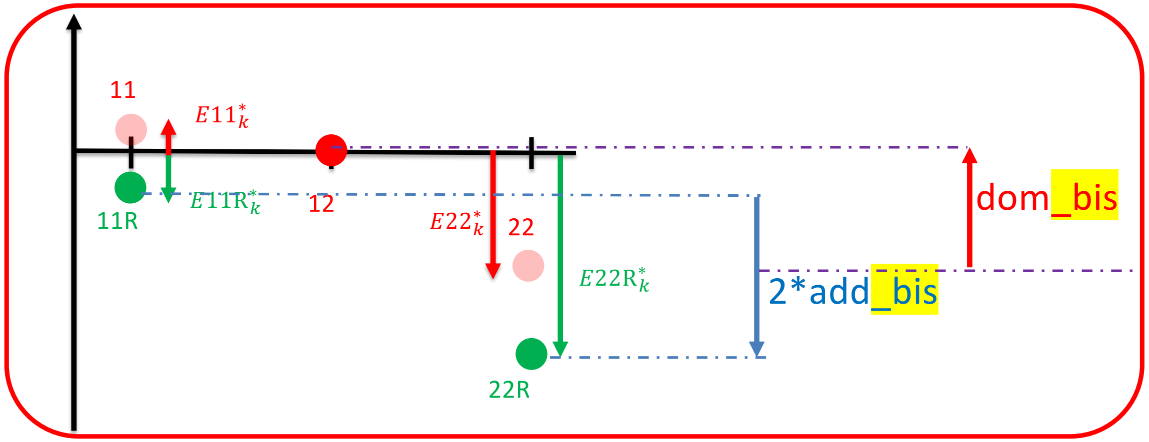
dom effect > 0

The unfavourable allele 2 carried by heterogeneous individuals is « hidden »

→ model #2 : better estimation of additive and dominance effect ?

→ Introducing ‘add_bis’ and ‘dom_bis’ effects from contrasts between estimated effects

→ Take advantage of the (likely) better LD between markers and CM in ROH segments (no recombination)



May be larger if higher LD with CM ?

$$\text{NB : } test\_statistic_k = \frac{|\widehat{effect_k}|}{std\_err_k}$$

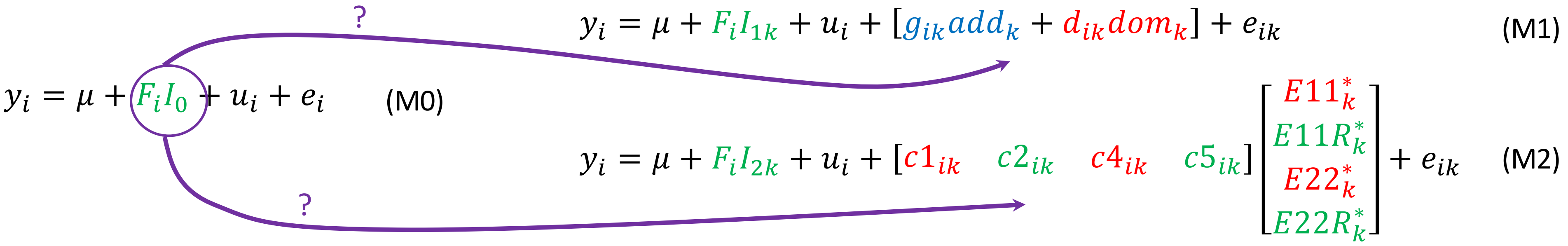
Larger because less observations

$$add\_bis_k = \begin{bmatrix} 0 & -0,5 & 0 & 0,5 \end{bmatrix} \begin{bmatrix} E11_k^* \\ E11R_k^* \\ E22_k^* \\ E22R_k^* \end{bmatrix} \qquad dom\_bis_k = \begin{bmatrix} 0 & -0,5 & 0 & -0,5 \end{bmatrix} \begin{bmatrix} E11_k^* \\ E11R_k^* \\ E22_k^* \\ E22R_k^* \end{bmatrix}$$

→ Search for variant with significant $\widehat{add\_bis}$ and $\widehat{dom\_bis}$ effects & favourable $\widehat{dom\_bis}$ effect

= variant with unfavourable recessive determinism

Evaluate the contribution of SNP to total inbreeding depression



$$y_i = \mu + F_i I_{1k} + u_i + [g_{ik} add_k + d_{ik} dom_k] + e_{ik} \qquad \text{(M1)}$$

$$y_i = \mu + F_i I_0 + u_i + e_i \qquad \text{(M0)}$$

$$y_i = \mu + F_i I_{2k} + u_i + [c1_{ik} \quad c2_{ik} \quad c4_{ik} \quad c5_{ik}] \begin{bmatrix} E11^*_k \\ E11R^*_k \\ E22^*_k \\ E22R^*_k \end{bmatrix} + e_{ik} \qquad \text{(M2)}$$

Assuming that global Inbreeding effect I $\approx \sum_{\text{all genomic segments}}$ (local inbreeding effect of a genomic segment)

→ shouldn't a variant associated with a local genetic load effect « absorb » a portion of global Inbreeding effect I ?

→ run M0 model (i.e. without any variant) → $\hat{I}_0$ (and PEV($\hat{I}_0$))

run GWAS with M1 and M2 models → for each variant k, get $\hat{I}_{1k}$ and $\hat{I}_{2k}$ (and PEV($\hat{I}_{1k}$) & PEV($\hat{I}_{2k}$))

For m = 1 and 2 :

$$\begin{cases} \text{If } \hat{I}_0 < 0 : \ DCL\_Var_{mk} = \dfrac{\hat{I}_0 - \hat{I}_{mk}}{\hat{I}_0} * 100 \\ \text{If } \hat{I}_0 > 0 : \ DCL\_Var_{mk} = \dfrac{-1 * (\hat{I}_0 - \hat{I}_{mk})}{\hat{I}_0} * 100 \end{cases} \Longrightarrow$$

$DCL\_Var_{mk} > 0$ ↔ variant k explains a portion of global unfavourable inbreeding effect

→ *sign of local inbreeding depression ?*

$DCL\_Var_{mk} < 0$ ↔ sign of local inbreeding favourable effect ?