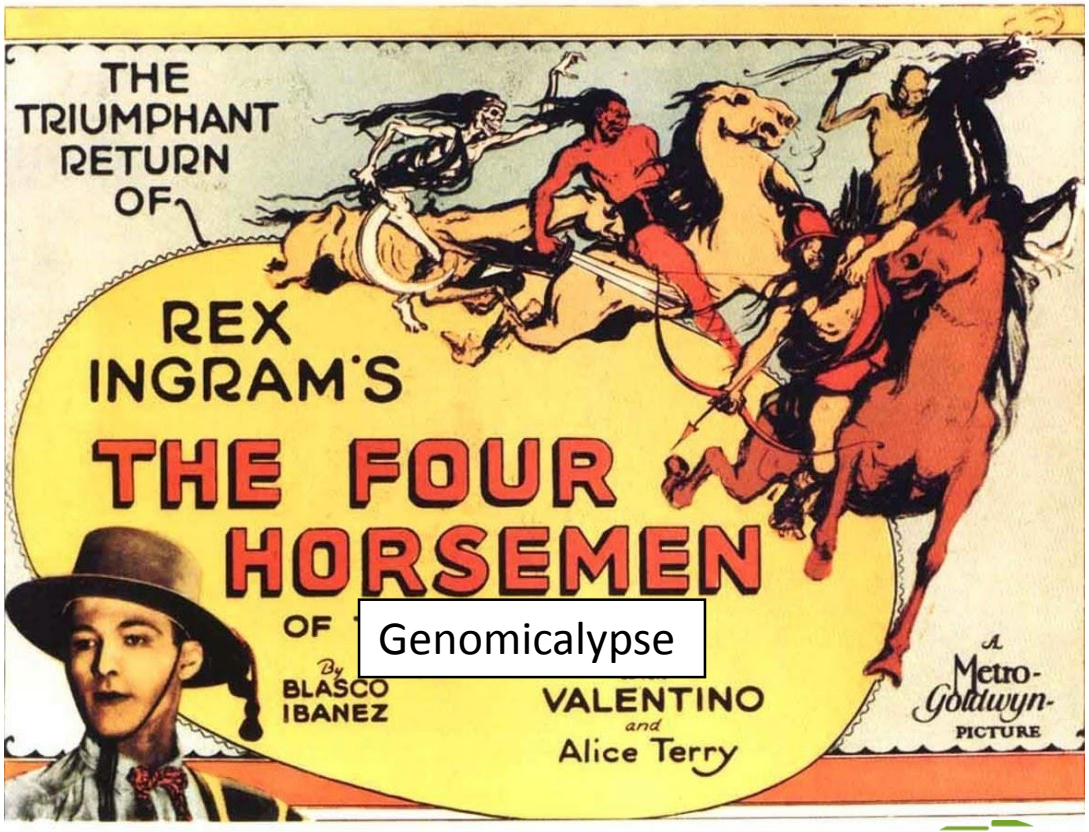

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INRA
SCIENCE & IMPACT

Genomic accuracy depends on… *what*?

- Starting points for the discussion diverge among people
  - Simulations, Ne, Me, LD, relationships, n, h^2, …
- Historically:
  - Forefathers of animal breeding assumed large populations and infinitesimal genomes:
    - Selection index on “unrelated” candidates to selection
    - Relationship matrix
    - BLUP
  - This leads to meaningful estimates of accuracy from a few parameters.
- Can we reach a similar consensus?

What you can achieve with theory

Selection index

TABLE 8.1. WEIGHTS AND ACCURACY VALUES FOR PREDICTING ADDITIVE GENETIC VALUE FROM RECORDS OF VARIOUS RELATIVES. (h^2 IS HERITABILITY; r IS REPEATABILITY).

Records		Selection Index Weights	Accuracy = r_{TI}
Individual	(1)	h^2	$\sqrt{h^2}$
	(n)	$nh^2/[1 + (n-1)r]$	$\sqrt{nh^2/[1 + (n-1)r]}$
Dam or sire or progeny	(1)	$h^2/2$	$.50\sqrt{h^2}$
	(n)	$nh^2/[1 + (n-1)r](2)$	$.50\sqrt{nh^2/[1 + (n-1)r]}$
Sire and dam	(1)	$h^2/2$; $h^2/2$	$.71\sqrt{h^2}$
	(n)	$.5nh^2/[1 + (n-1)r]$; $.5nh^2/[1 + (n-1)r]$	$.71\sqrt{nh^2/[1 + (n-1)r]}$
One grandparent		$h^2/4$	$.25\sqrt{h^2}$
Four grandparents		All $h^2/4$	$.50\sqrt{h^2}$
One great-grandparent		$h^2/8$	$.125\sqrt{h^2}$
Eight great-grandparents		All $h^2/8$	$.35\sqrt{h^2}$

BLUP

$$\begin{pmatrix} u \\ e \end{pmatrix} \quad \begin{pmatrix} 0 \\ 0 \end{pmatrix} \qquad \begin{pmatrix} e \end{pmatrix}$$

$$\begin{pmatrix} \mathbf{Z'X} & \mathbf{Z'Z}+\sigma^2\mathbf{G}^{-1} \end{pmatrix} \begin{pmatrix} \hat{\boldsymbol{u}} \end{pmatrix} = \begin{pmatrix} \mathbf{Z'}\boldsymbol{y} \end{pmatrix}.$$

The solutions are:

$$\begin{pmatrix} \hat{\boldsymbol{\beta}} \\ \hat{\boldsymbol{u}} \end{pmatrix} = \begin{pmatrix} \mathbf{C}^{xx} & \mathbf{C}^{xz} \\ \mathbf{C}^{zx} & \mathbf{C}^{zz+} \end{pmatrix} \begin{pmatrix} \mathbf{X'}\boldsymbol{y} \\ \mathbf{Z'}\boldsymbol{y} \end{pmatrix} \quad \text{where}$$

$$\begin{pmatrix} \mathbf{C}^{xx} & \mathbf{C}^{xz} \\ \mathbf{C}^{zx} & \mathbf{C}^{zz+} \end{pmatrix} = \begin{pmatrix} \mathbf{X'X} & \mathbf{X'Z} \\ \mathbf{Z'X} & \mathbf{Z'Z}+\sigma^2\mathbf{G}^{-1} \end{pmatrix}^{-1}.$$

The inverse of a non-full rank coefficient ma
generalized inverse without affecting the PEV.

Pseudo-BLUP

the current generation. Such an index is called a pseudo-BLUP index. Thus the information sources are:

1. phenotypic own performance (P_i)
2. phenotypic information of full sibs (P_{FS})
3. phenotypic information of half sibs (P_{hs})
4. phenotypic information of progeny testing (P_{prog})
5. estimated breeding value of the sire (EBV_s)
6. estimated breeding value of the dam (EBV_d)
7. average estimated breeding values of the dams of the half sibs ($EBV_{hs\text{-}dams}$)

Four “horsemen” that “ride” genomic selection

- Simulations

- Linkage disequilibrium

- Relationships

- Effective number of segments

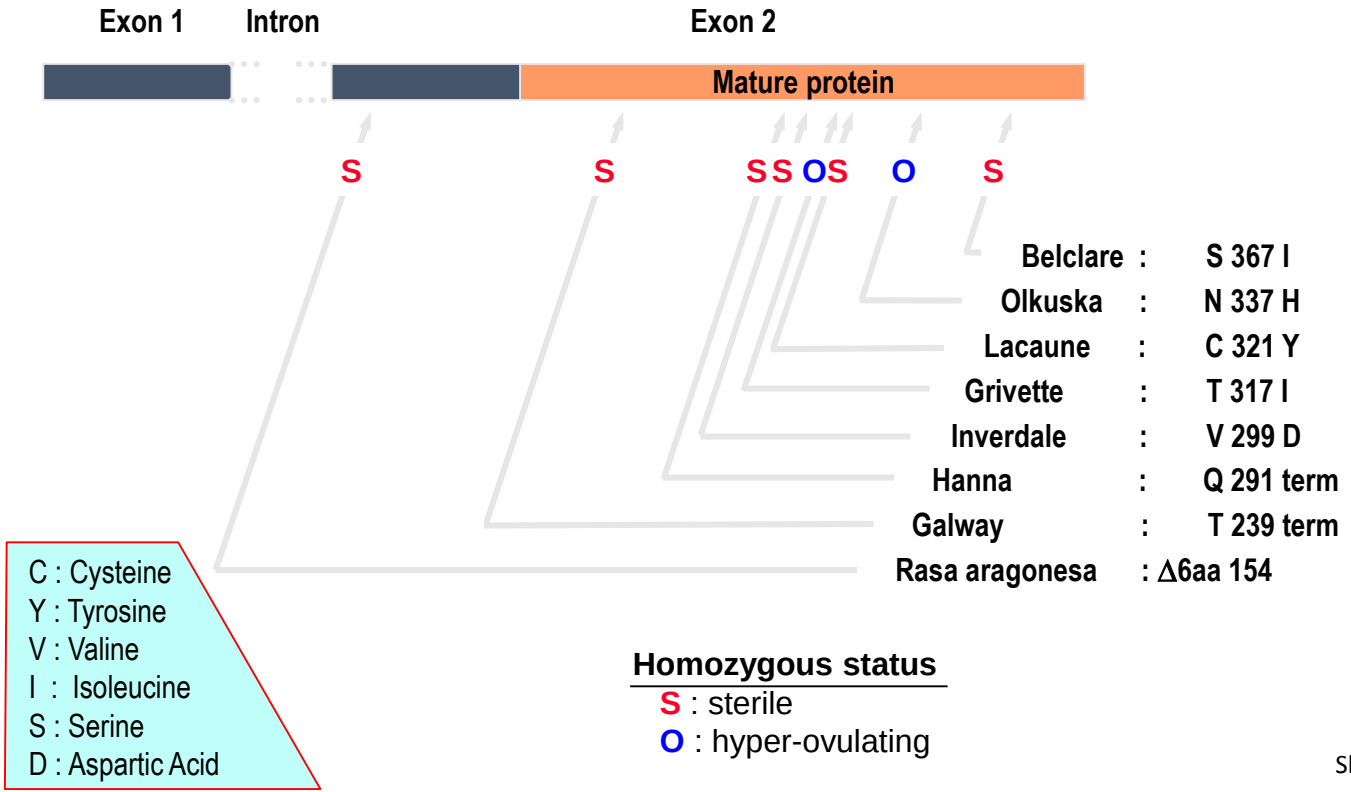
Everyone agrees that these are important notions

Simulations (1/2)

We rely too much on simulations as substitute for theory …and we do very poor simulations

- Genes are not QTN: biallelic, single nucleotide polymorphisms
- Genes have coding parts, deletions, enhancers, promoters
- Genes are multiallelic with “fuzzy” locations (PRNP, α_{s1} casein…)
- Mutations are not the same across breeds
- Genes interact !!!!
- Genes mute

Eight known mutations of the BMP15 gene



Slide by Loys Bodin

Molecular characterization of the goat *CSN1S1*^{01} allele

Gianfranco Cosenza[1], Rosa Illario[1], Andrea Rando[2], Paola di Gregorio[2], Piero Masina[2] and Luigi Ramunno[1*]

Mahè & Grosclaude, 1993). Such alleles are characterized by different mutations: single point mutations, responsible for premature stop codons, characterize null alleles of the *CSN2* (Rando et al. 1996; Persuy et al. 2000) and *CSN1S2* (Ramunno et al. 2001) *loci*; large DNA rearrangement (deletion/insertion) events of unknown origin and location characterize the two null alleles (*CSN1S1*^{01} and *CSN1S1*^{02}) of the *CSN1S1 locus* (Martin et al. 1999).

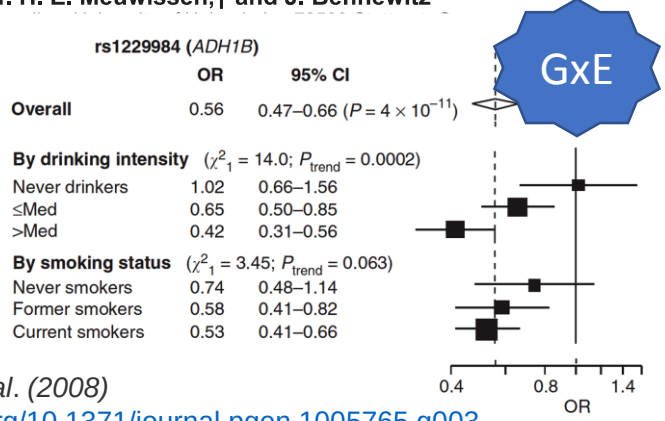
More than QTN

Short communication: Evidence for a major gene by polygene interaction for milk production traits in German Holstein dairy cattle

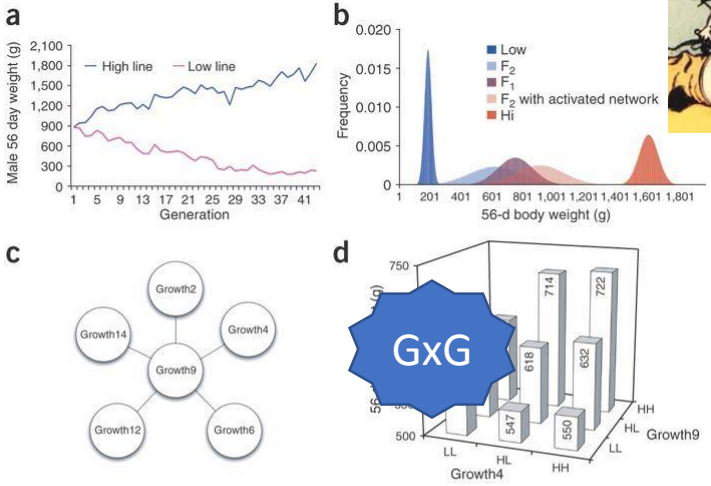
M. Streit,* N. Neugebauer,* T. H. E. Meuwissen,† and J. Bennewitz*[1]

GxG

GxE



Hashibe et al. (2008)
https://doi.org/10.1371/journal.pgen.1005765.g003



Carlborg, Örjan, et al. "Epistasis and the release of genetic variation during long-term selection." *Nature genetics* 38.4 (2006): 418.

Simulations (2/2)

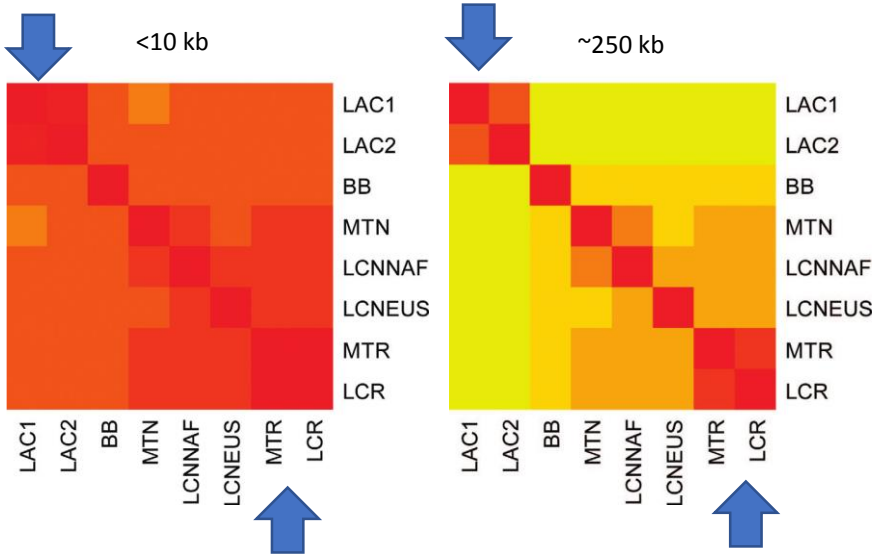
From simulations, we had the following “fake news”

- Additive variance diminishes quickly (but mutation, dominance, epistasis refill)
- Across-breed predictions are possible (but gene substitution effects depend on background, environment)
- Sequence is more accurate than SNP chips (but it has high redundancy and genes are not QTN)
- Bayesian regressions are better than GBLUP (most often they’re not)

Linkage disequilibrium (1/2)

- We don’t have consensual global statistics to describe
  - the relationship between LD and accuracy in a population
  - Reduction of genetic variance due to LD (i.e. Bulmer effect)
- All that we have is those pairwise r^2
- Do we need n-loci statistics or higher moments?
- Can we correlate LD measures with genomic accuracy?
  - Maybe not

Legarra et al. 2014



- High LD phase agreement…
- But it does not result in higher accuracy

Linkage disequilibrium (2/2)

- Mental model of Bayesian regression: there will be at least one SNP in complete LD with the QTL
  - Maybe, but then there will be *many* SNP in almost-complete LD
- Mental model of GBLUP: does $\boldsymbol{ZZ'} \approx \boldsymbol{QQ'}$?
- Is any of these models correct? To what extent?

Relationships (1/2)

Several definitions not easy to conciliate

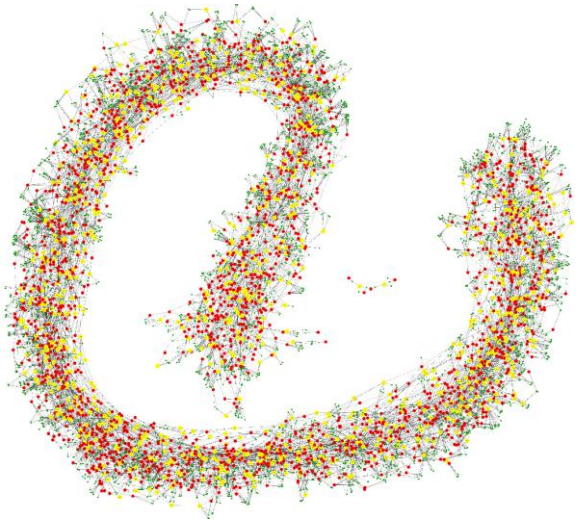
Probabilistic: assuming an unrelated base population (which one ?)

- Expected IBD relationships *conditional* on the pedigree (**A**)
- Real unobserved IBD relationships ($\widetilde{\boldsymbol{R}}$)

Statistical: using cross-products

- VanRaden's $\boldsymbol{G}$ (base population is whatever we use in p)

Pedigrees go back in time “forever”



A closed rabbit line of 45 discrete generations: 934 sires (yellow) with 1,950 dams (green) and 3,492 progeny (red).

Universidad Politécnica de Valencia, Spain

All G-matrices are equal

Allele coding in genomic evaluation

Ismo Strandén[1*] and Ole F Christensen[2]

On curious properties of genomic relationship matrices in mixed models

Bruce Tier and Karin Meyer
Animal Genetics and Breeding Unit, University of New England, Armidale, NSW 2351, Australia

Which GRM?

- GRM that look very different . . .
  - ⟶ different allele coding, centering, scaling, etc.
  - . . . give ‘equivalent’ predictions → shifted breeding values
  - . . . but not necessarily the same prediction error variances

Strandén, I., Christensen, O. F. 2011. Allele coding in genomic evaluation. Genet. Sel. Evol. 43:25.

- IMPLICATIONS?

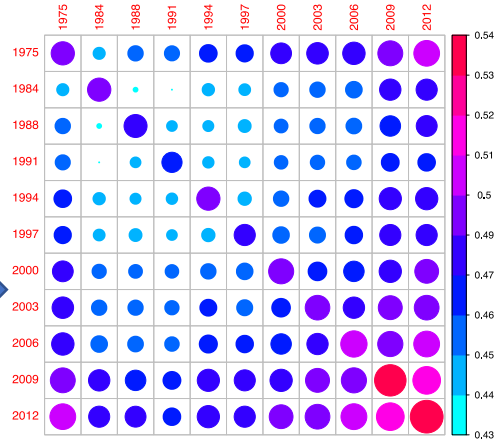
Relationships (2/2)

We advertise the <u>unified</u> theory of relationships based on metafounders

- $\boldsymbol{G}$ = crossproduct of $Z = \{-1,0,1\}$ is the absolute reference (Christensen, 2012)
- As a byproduct, pedigree base populations are related

- Other options?

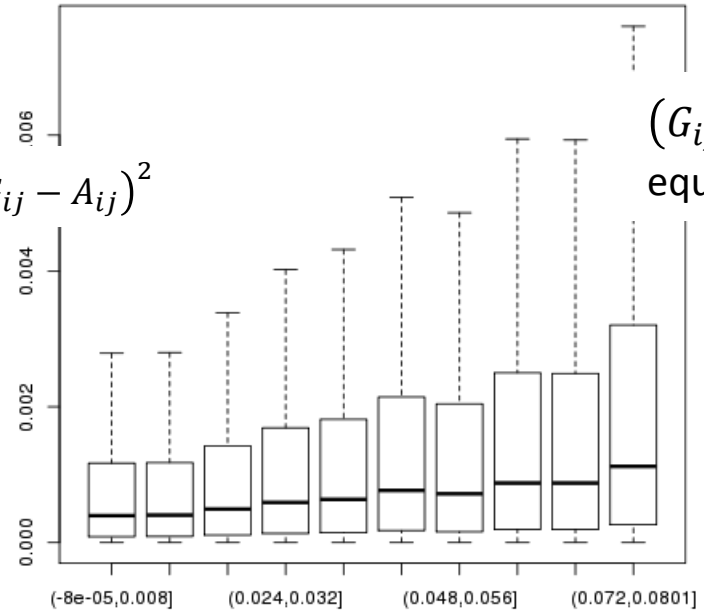
Relationships within/across Genetic Groups , Manech Tete Rousse



Effective number of segments (Me) (1/3)

- Me describes the "non infinitesimallity" of the genome
  - If $Me = \infty$ (infinitesimal) then $\tilde{R}_{ij} = A_{ij}$ and $Var\left(\tilde{R}_{ij} - A_{ij}\right) = 0$
  - If $Me = 1$ (single locus) then $Var\left(\tilde{R}_{ij} - A_{ij}\right) = 4\left(\phi_{ij,ij} - \phi_{ij}\phi_{ij}\right)$
- To me, Me is a parameter of the population like h^2
- To other people (Lee, Wientjes) this is data specific: an empirical quantity $\frac{1}{var\left(G_{ij} - A_{ij}\right)}$ or $\frac{1}{r^2}$

y-axis: observed $\left(G_{ij} - A_{ij}\right)^2$



x-axis: expected $Var\left(\tilde{R}_{ij} - A_{ij}\right)$ for 1 locus

$\left(G_{ij} - A_{ij}\right)^2$ increases according to theoretical equation $4\left(\phi_{ij,ij} - \phi_{ij}\phi_{ij}\right)$ based on pedigree

Differences between genomic-based and pedigree-based relationships in a chicken population, as a function of quality control and pedigree links among individuals

H. Wang[1], I. Misztal[2] & A. Legarra[3]

Effective number of segments (Me) (2/3)

Paradoxes of data specific Me; for 2 generations (Hill and Weir 2011) :

- $Me = \infty$ between father and offspring
- $Me = 636$ for fullsibs,
- $Me = 318$ for halfsibs and
- $Me = 503$ for cousins

I'd rather prefer a population parameter from which to deduce these values…

Effective number of segments (Me) (3/3)

Can it be a population parameter?

- The distribution of segments from an ideal infinite base population is described by the theory of junctions, too complicated ☹
- Segments should be created by meiosis and disappear by drift
- Is there an equilibrium?

An attempt to conclude

- Simulations are misleading
- LD is not well quantified
- What do we mean by relationship?
- Can we better define Me?

- We animal breeders should make an effort to clearly define concepts
- Lack of formalization leads to improvisation and misunderstanding
- Lack of agreement leads to disparate conclusions

Acknowledgments

- Poctefa funding project “ARDI”
- INRA SelGen metaprogram, project EpiSel