Genomic selection

1- Linkage disequilibrium

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Linkage disequilibrium

- « Gametic phase disequilibrium »

Statistical association between alleles at two loci in the same chromosome

  - Loci : places
  - Alleles: alternative forms of a gene (A,B,0)
  - Phase: notion of being in the same chromosome (of a pair) or coming from same origin (sire or dam)

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Biallelic case

- Assume we genotype 5 individuals, thus 10 chromosomes (and that we know the phase)
- Now we compute allelic frequencies

AB
AB
ab
aB
ab
ab
Ab
AB
Ab
AB

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Biallelic case

p(A)=0.6
p(B)=0.5
if independent, p(AB)=0.3,p(ab)=0.2
The expected proportions are:

	A	a
B	0.3	0.2
b	0.3	0.2

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Biallelic case

p(A)=0.6
p(B)=0.5
in reality:

	A	a
B	0.4	0.2
b	0.1	0.3

vs. **expected**

	A	a
B	0.3	0.2
b	0.3	0.2

More AB & ab than expected !!
This is **linkage disequilibrium**

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Linkage disequilibrium

- Is a *statistical* concept
- Describes not-random association of two loci
  - Nothing more, so, why is it useful?
- Two loci in LD *most often* are (very) close
  - This is because LD breaks down with recombination
- Linkage disequilibrium of two loci decays *on average* with the distance
- Hence it serves to map genes

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Where does it come from?

- Because chromosomes are transmitted together
  - Within known families (« linkage analysis »)
  - Within the history of a population (« populational linkage disequilibrium » or « linkage disequilibrium » in short)
- <u>This distinction is rather artificial</u>
  - Remember: a population *is* a very old, large family

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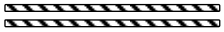
Populational linkage disequilibrium

- Assume we mix two populations (say Churra and Merino)
- Or, that Adam was 
  - and Eve 
  - The first generation is an F1
  - Then animals are mixed at random
- What do we get after many generations?

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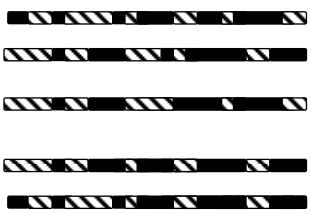
Populational linkage disequilibrium

- The chromosomes become a fine-grained mosaic of grey and black



- However, complete mixture is difficult to attain

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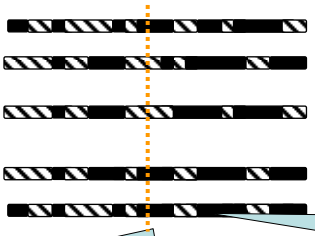
Populational linkage disequilibrium



•Some people distinguish LD and pedigree relationships
•It's pretty much the same thing

An stretch (=chromosomal segment) is conserved because it comes from the same ancestor (co-ancestry).

The « existence » of only a few conserved stretches at the same place creates LD.

LD is therefore:
an <u>over-representation</u> of segments from a few gametes that existed in the population some time ago.

•The value of LD (e.g. r^2) observed at <u>large</u> distances is a function of <u>recent</u> relationships
•… at <u>short</u> distances is a function of <u>distant</u> relationships

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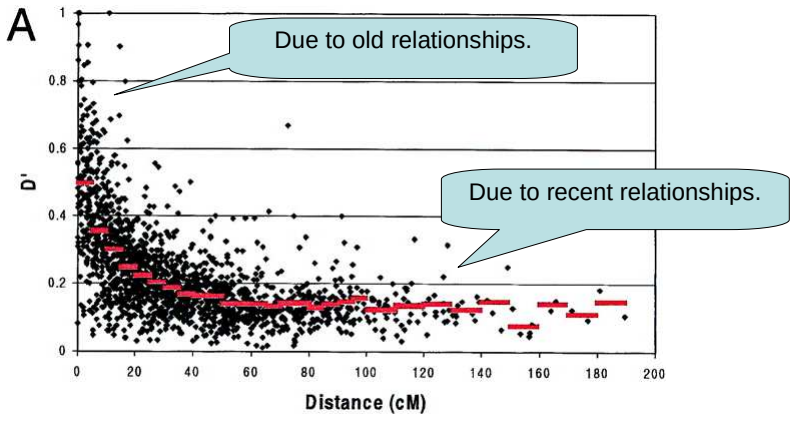

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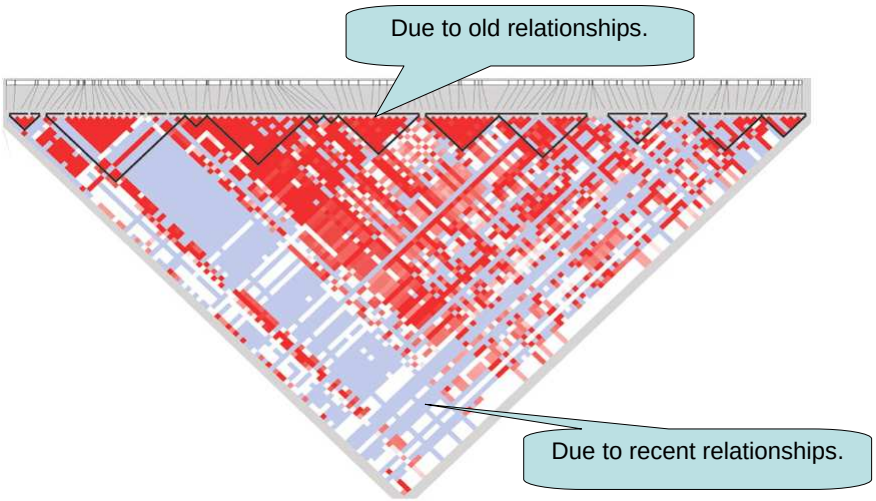

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Populational linkage disequilibrium

- Mechanisms generating linkage disequilibrium of this kind are:
  - Drift
  - Selection
  - Migration
    - These three because at some point the chromosome of one animal is overrepresented
  - Mutation
    - considered by coalescence theory
    - less important in animal breeding

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Genomic selection

2- Models for Genomic selection

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Models for Genomic selection

- Single marker
- Whole-genome (multiple marker) genomic selection

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Single marker

- Assume there is a marker in complete LD with a QTL
- For example, the polymorphism in the halothane gene (HAL) which is a predictor of bad meat quality in swine

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Single marker

- Estimate breeding values including the marker is a piece of cake
- $\mathbf{y}_i$= marker effect in animal *i* + *e*
  - We substitute the true, possibly unknown gene by a proxy observed marker and estimate effects of the latter using a linear model
  - We can include an additional polygenic genetic value of animal *i*

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Base model

- **y= …+ Za + e**
  - **Z**= incidence matrix of marker effects
  - **a**= marker effect
  - **e**=residuals

3 individuals, 1 marker with 4 alleles

$$\mathbf{Za} = \begin{bmatrix} 0 & 1 & 1 & 0 \\ 2 & 0 & 0 & 0 \\ 0 & 1 & 0 & 1 \end{bmatrix} \begin{bmatrix} a_1 \\ a_2 \\ a_3 \\ a_4 \end{bmatrix}$$

- This can be solved, for example, by least squares

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Single marker

- This is fine if we know what markers are good predictor of what genes
- But this is rarely the case
  - It can be shown that you miss a lot of information by trying to locate the QTLs
  - And those that you find are certainly exaggerated

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Genomic selection

- So this is why we need genomic selection
- Although the idea is old, Meuwissen et al (2001) showed that high accuracies can be obtained with high density markers (under quite ideal scenarios)

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Meuwissen's points

1. QTL mapping is a lot of work
   1. lots of people
   2. lots of time
   3. Not-automatic procedure
2. QTL detection is biased: estimated effect of « accepted » QTLs is exaggerated.
   1. Beavis effect
3. Very serious problem if many QTL positions are tested

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Beavis effect

- We are mapping QTLs
- To declare a QTL in a position, we perform a test (for example a t-test)
- This test depends on the estimated effect of the QTL
  - estimated effect = real effect + « estimation noise »
  - by keeping selected QTLs, we often keep large and positive noises
    - this is negligible if there were few QTLs with large effects but this is not the case
    - large noises will occur in analysis with *many* markers
  - this biases the estimated QTL effect

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Whole genome

- If we don't select QTL regions we skip the problem of bias
- Therefore :
  - Genetic value = sum of effects of all regions
    - We effectively treat all regions as being carriers of a QTL
  - How do we estimate the effects of all regions?

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Whole genome

- The simpler is to do an extension of single marker analysis
- Do multiple marker regression
- Works well only with dense markers!

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Multiple marker additive model

- **y**= **Za** + **e**
  - **Z**= incidence matrix of marker effects
  - **a**= marker effect
  - **e**=residuals

4 individuals, 2 markers each

2 alleles in 1st marker

$$\mathbf{Za} = \left[\begin{array}{cc|cccc} 1 & 1 & 0 & 1 & 1 & 0 \\ 2 & 0 & 2 & 0 & 0 & 0 \\ 0 & 2 & 1 & 0 & 0 & 1 \\ 0 & 2 & 1 & 1 & 0 & 0 \end{array}\right] \left[\begin{array}{c} a_{1,1} \\ a_{1,2} \\ \hline a_{2,1} \\ a_{2,2} \\ a_{2,3} \\ a_{2,4} \end{array}\right]$$

4 alleles in 2nd marker

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Estimating SNP effects

- The simultaneous estimates of many markers by least squares are very poor,
  - if we have much more SNPs than individuals
  - They are thus terribly bad for genomic predictions as well
- Even if we had many individuals, there is a missing piece of information:
  - we think that most SNPs do *not* have an effect or at least a big one
  - this is a « prior » information
- Can we do something?

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Integration

- Need to postulate p(**a**) : this means SNP are <u>random</u> effects
- Best Predictor is optimal for selection (Goffinet and Elsen 1984 GSE; Gianola and Fernando 1986 JAS)
- The Best Predictor comes from the conditional mean of SNP effects after observing the data

$$\hat{\mathbf{a}} = E(\mathbf{a} \mid \mathbf{y}) = \frac{\int \mathbf{a}\, p(\mathbf{y} \mid \mathbf{a})\, p(\mathbf{a})\, d\mathbf{a}}{\int p(\mathbf{y} \mid \mathbf{a})\, p(\mathbf{a})\, d\mathbf{a}}$$

- Remember: classical BLUP is an example of BP if
  - $p(\mathbf{g}) \sim N(0, \mathbf{A}\sigma^2_u)$

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A priori Distributions for marker effects

- *Unknown*
- *Still we don't have a good theory*
- Agreement on
  - Small effects more frequent than big ones
  - marker effects are assumed *a priori* independent

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A priori Distributions for marker effects

- Several distributions for SNP effects have been proposed
  - Normal (Meuwissen et al., Genetics 2001; Van Raden JDS 2008) -> BLUP_SNP or GBLUP or RR-BLUP
  - BayesA, BayesB, (Meuwissen et al. 2001; Habier et al., 2011)
  - Mixture of normal , BayesC(Pi) (Van Raden JDS 2008, Habier et al., 2011)
  - (Bayesian) Lasso (Usai et al., 2009; De los Campos, et al., 2009)

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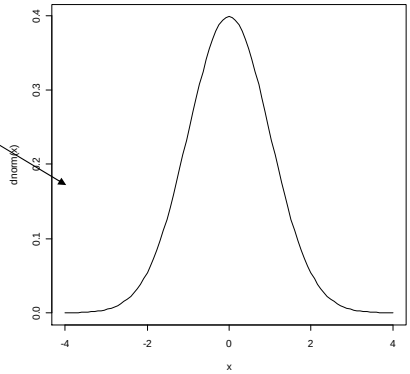
Normal distribution

$$a_i \sim N\left(0, \sigma_a^2\right)$$

Few « big » effects



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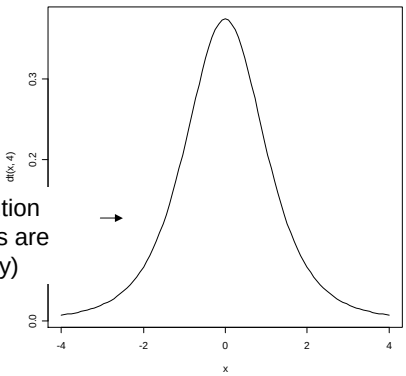
BayesA (*t* distribution)

a *t* distribution (big effects are not unlikely)



representation as « t »

$$a_i \sim t\left(0, \nu, \sigma_a^2\right)$$

$$\equiv$$

$$a_i \sim N\left(0, \sigma_{a,i}^2\right)\chi_\nu^{-2}\sigma_a^{-2}$$

Meuwissen et al. representation

Gianola et al. (2009) proved that fitting a variance by locus is equivalent to postulating t distribution for all locus

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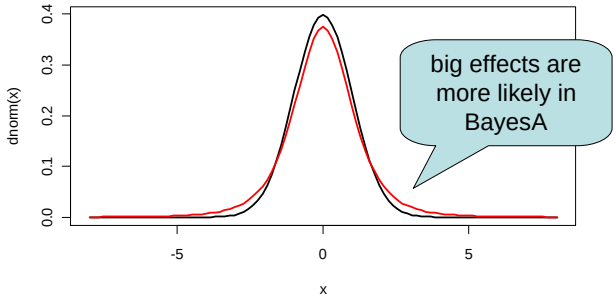
Normal vs. BayesA



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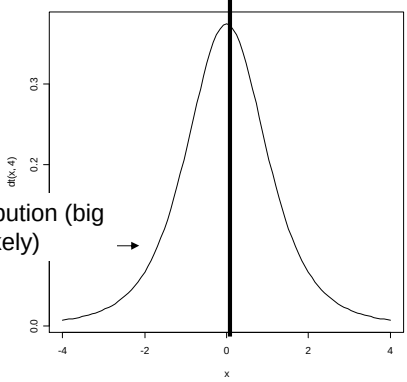
BayesB (mixture with *t* distribution)

$$a_i \sim \pi(0) + (1-\pi)\, t\left(0, \nu, \sigma_a^2\right)$$

A fraction π of markers has null effects.



Otherwise a *t* distribution (big effects are not unlikely)

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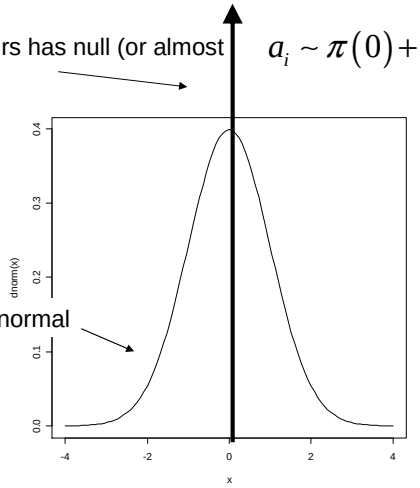
Mixture distribution or BayesC(Pi)

A fraction π of markers has null (or almost null) effects.

$$a_i \sim \pi(0) + (1-\pi)\, N\left(0, \sigma_a^2\right)$$



Otherwise they are normal

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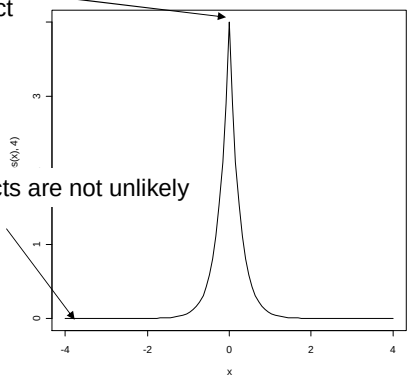
Lasso (double exponential)

$$a_i \sim \frac{\lambda}{2}\exp\left(-\lambda\left|a_i\right|\right)$$

Often marker has *almost* null effect



Otherwise big effects are not unlikely

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What is the best distribution?

- Depends on what truth is ☺
- Not a good quantitative genetics theory to choose one
- Funny distributions (mixtures, BayesB, double exponential) have tricky parameters (e.g. π).
- Optimal methods are not the same for different data (traits)
- Normal distribution quite good

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Recipe for genomic selection

- Genotype all your animals
- Get records (e.g. weight)
- Pick a model for **a**, say normal distribution
- **y=Xb + Za + e**
  - **b**: fixed effects (herd, year)
  - **a**: SNP effects
- Solve for **â** using some method

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Recipe for genomic selection

- What do you do with a candidate for selection – say a young bull – with no data or daughters?
  - Genotype it
  - build its incidence matrix for SNPs $\mathbf{z}_i$
  - take the estimates for SNP effects $\hat{\mathbf{a}}$
  - The estimated breeding value is EBV=$\mathbf{z}_i\hat{\mathbf{a}}$

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