

Day 4 IDENTITY BY DESCENT AND GENETIC RELATIONSHIPS

Objective

Develop methods to quantify/model genetic relationships between individuals

- based on pedigree ↔ based on markers
- average across the genome ↔ at individual loci

Genetic relationships are important to quantify covariances between individuals for a quantitative trait in order to:

- Estimate genetic parameters (heritability) from phenotypes on relatives
- Use phenotypes on relatives to estimate breeding values using BLUP

Genetic relationships at individual loci are important to quantify covariances between individuals for effects of a QTL at that locus in order to:

- Detect and map QTL using phenotypes and marker data on relatives
 - variance component linkage analysis
- Incorporate marker data in to genetic evaluation by Marker-assisted BLUP

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Concept of the use of genetic relationships for quantitative genetic analyses – 2 components

1. OBSERVATIONAL /statistical model to estimate resemblance between relatives from data

e.g. Covariance/correlation between phenotypes on relatives

Is the phenotype of relatives more similar than non-relatives

if it is then this suggests that the trait is heritable

Covariance between phenotype of individuals that have the same marker genotype or that inherited the same marker allele from a parent

Is the phenotype of individuals that have the same genotype at a marker more similar than the phenotype of individuals that have a different genotype at that marker?

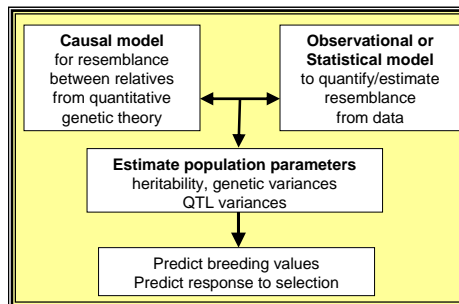
If yes, then that suggests that this marker is in LD with a QTL affecting the trait

2. CAUSAL model for the degree that relatives are expected to resemble each other, i.e.

a. The proportion of alleles that individuals share / have in common / are identical by descent

- across the genome for resemblance between relatives
- at the QTL/marker for resemblance at a QTL

b. the amount of genetic / QTL variance



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Day 4
IDENTITY BY DESCENT AND GENETIC RELATIONSHIPS

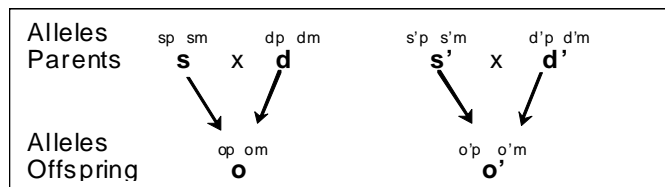
1. **A causal model for genetic resemblance between relatives**
 - a. **Covariance between relatives based on pedigree**
 - b. **Identity By State vs. Identity By Descent based on pedigree**
 - c. **The pedigree relationship matrix A**
2. **Genetic relationships derived from marker genotypes**
3. **A causal model for genetic resemblance of relatives at QTL**
 - a. **IBD at QTL based on a linked marker**
 - b. **IBD at QTL based on dense marker haplotypes**
4. **IBD at QTL based on linkage disequilibrium**
 - a. **Accounting for genetic relationships – fit polygenic effect**
 - b. **Overestimation of significant SNPs – fit random SNP effect**
5. **Genetic resemblance at QTL based on combined linkage disequilibrium and linkage / cosegregation**

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1. CAUSAL MODEL FOR GENETIC RESEMBLANCE BETWEEN RELATIVES
 based on pedigree

Consider two individuals, **o** and **o'** with parents **s, d** and **s', d'** and alleles at a locus denoted as:

i_p = paternal allele for individual i = allele received from sire



If **o** and **o'** are related and the trait has a genetic basis, **o** and **o'** will share alleles and have similar phenotype, i.e. a non-zero covariance: $cov(P_o, P_{o'}) > 0$.

We want to derive a causal model for $cov(P_o, P_{o'})$

Phenotypes of individuals can resemble each other because:

- they share **genetics** – they are genetically related - and/or because
- they share **environment** (e.g. pigs raised by the same dam or in the same pen):

$$Cov(P_o, P_{o'}) = Cov(G_o + E_o, G_{o'} + E_{o'}) = Cov(G_o, G_{o'}) + Cov(E_o, E_{o'})$$

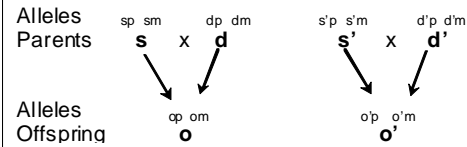
We will here only consider resemblance through genetics

For simplicity, we will also only consider the additive effects of loci

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Model for GENETIC resemblance

First developed using single locus theory but results also apply to multi-locus quantitative traits



o carries alleles o_p and o_m
o' carries alleles o'_p and o'_m

α_{ip} = average (additive) effect of the paternal allele of individual i
 α_{im} = average (additive) effect of the maternal allele of individual i

The model for breeding values is:
 $A_o = \alpha_{op} + \alpha_{om}$
 $A_{o'} = \alpha_{o'p} + \alpha_{o'm}$

Then: $Cov(A_o, A_{o'}) = Cov(\alpha_{op}, \alpha_{o'p}) + Cov(\alpha_{op}, \alpha_{o'm}) + Cov(\alpha_{om}, \alpha_{o'p}) + Cov(\alpha_{om}, \alpha_{o'm})$

Note that $Cov(\alpha_{op}, \alpha_{o'p}) \neq 0$ only if there is a possibility that alleles o_p and o'_p are the same, because then α_{op} and $\alpha_{o'p}$ are the same (the same holds for other pairs of alleles)

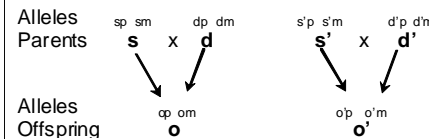
Are two alleles the same? Identity By State (IBS) versus Identity By Descent (IBD)

- **IBS**: if we can genotype individuals o and o' for this locus (QTL), then we can directly determine whether the alleles the two individuals carry are indeed the same – if they are the same, this is referred to as the alleles being **IBS**.
- **IBD**: if we cannot genotype the locus (ie. the usual case), then we cannot determine IBS directly but, if **o** and **o'** have a **common ancestor**, then we can determine the **probability** that the two alleles are identical because they may have originated from a common ancestor

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IBD probabilities from pedigree

$Prob(o_p \text{ is IBD to } o'_p) = P(o_p \equiv o'_p)$
 = **probability that alleles o_p and o'_p originated from the same allele of the common ancestor**



Example IBD probabilities, coefficients of coancestry and additive and dominance coefficients

	IBD probabilities for pairs of alleles				Coancestry coefficient	Additive relationship coefficient	Dominance relationship coefficient
	$op-o'p$	$om-o'm$	$op-o'm$	$om-o'p$			
Individual o – o'					$f_{oo'}$	$r_{oo'}$	$u_{oo'}$
Sire(o) – Offspring(o')	$\frac{1}{2}$	0	0	$\frac{1}{2}$	$\frac{1}{4}$	$\frac{1}{2}$	0
Dam – Offspring	0	$\frac{1}{2}$	$\frac{1}{2}$	0	$\frac{1}{4}$	$\frac{1}{2}$	0
Paternal half-sibs	$\frac{1}{2}$	0	0	0	$\frac{1}{8}$	$\frac{1}{4}$	0
Full sibs	$\frac{1}{2}$	$\frac{1}{2}$	0	0	$\frac{1}{4}$	$\frac{1}{2}$	$\frac{1}{4}$
Identical twins	1	1	0	0	$\frac{1}{2}$	1	1

Some side notes:

Coefficient of coancestry (also coeff. of kinship or consanguinity) between **o** and **o'**

$= f_{oo'}$ = probability that an allele drawn at random from **o** is IBD to an allele drawn random from **o'**
 = average of the 4 possible IBD probabilities between alleles at **o** and **o'**

$r_{oo'} = 2f_{oo'}$ = **coefficient of relationship** = **additive genetic relationship coefficient**

NOTE: $f_{oo'}$ is also equal to the **coefficient of inbreeding** of a progeny produced by **o** and **o'**
 = probability that an individual's alleles are IBD

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From IBD probabilities to covariances between relatives

Covariance between the average effect of allele p from o and the average effect of allele p from o' :

$$= \text{Cov}(\alpha_{op}, \alpha_{o'p}) = E(\alpha_{op} \alpha_{o'p}) - E(\alpha_{op})E(\alpha_{o'p})$$

Note: $E(\alpha_{op}) = E(\alpha_{o'p}) = 0$

2 possibilities:
 op and $o'p$ are IBD
 or they are not IBD

$$= E(\alpha_{op} \alpha_{o'p} | op \equiv o'p) \Pr(op \equiv o'p) + E(\alpha_{op} \alpha_{o'p} | op \not\equiv o'p) \Pr(op \not\equiv o'p)$$

$$= E(\alpha_{op} \alpha_{op}) \Pr(op \equiv o'p) = E(\alpha_{op}^2) \Pr(op \equiv o'p)$$

$$= \Pr(op \equiv o'p) \text{Var}(\alpha_p)$$

Note: $\text{Var}(\alpha_p) = E(\alpha_p^2) - E(\alpha_p)^2$ but $E(\alpha_p) = 0$

$$= \Pr(op \equiv o'p) \frac{1}{2} \sigma_a^2$$

Note that $\text{Var}(\alpha_p) = \frac{1}{2} \sigma_a^2 = \frac{1}{2} \text{QTL variance}$

The same holds for the other pairs of alleles:

$$\text{Cov}(\alpha_{om}, \alpha_{o'm}) = \Pr(om \equiv o'm) \frac{1}{2} \sigma_a^2$$

$$\text{Cov}(\alpha_{op}, \alpha_{o'm}) = \Pr(op \equiv o'm) \frac{1}{2} \sigma_a^2$$

$$\text{Cov}(\alpha_{om}, \alpha_{o'p}) = \Pr(om \equiv o'p) \frac{1}{2} \sigma_a^2$$

Using this in each of the covariance terms between average allele effects in the following gives:

$$\text{Cov}(\mathbf{A}_o, \mathbf{A}_{o'}) = \text{Cov}(\alpha_{op}, \alpha_{o'p}) + \text{Cov}(\alpha_{op}, \alpha_{o'm}) + \text{Cov}(\alpha_{om}, \alpha_{o'p}) + \text{Cov}(\alpha_{om}, \alpha_{o'm})$$

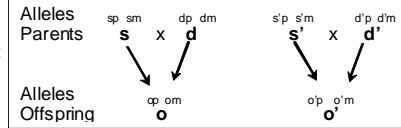
$$= \{ \Pr(op \equiv o'p) + \Pr(op \equiv o'm) + \Pr(om \equiv o'p) + \Pr(om \equiv o'm) \} \frac{1}{2} \sigma_a^2 = r_{oo'} \sigma_a^2$$

This applies to each QTL (without marker data) but also to total genetic value because $\sum \sigma_a^2 = \sigma_a^2$

$$\Rightarrow \text{Cov}(\mathbf{A}_o, \mathbf{A}_{o'}) = r_{oo'} \sigma_a^2$$

Thus, the genetic covariance (resemblance) between relatives is equal to their genetic relationship x genetic variance - - they 'share' a portion $r_{oo'}$ of the genetic variance.

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The pedigree A matrix

Elements = additive genetic relationship

= the proportion of genes shared based on IBD from pedigree

	Animal 1	Animal 2	Animal 3	Animal 4	Animal 5	Animal 6
Animal 1	1					
Animal 2	0	1				
Animal 3	0	0	1			
Animal 4	0.5	0.5	0	1		
Animal 5	0.5	0.5	0	0.5	1	
Animal 6	0.5	0	0.5	0.25	0.25	1

Use in Animal Model

Breeding Value Estimation:

$$\mathbf{y} = \mathbf{X}\mathbf{b} + \mathbf{Z}\mathbf{u} + \mathbf{e}$$

Fixed effects

$$\mathbf{u} = \begin{pmatrix} u_1 \\ u_2 \\ u_3 \\ u_4 \\ u_5 \\ u_6 \end{pmatrix}$$

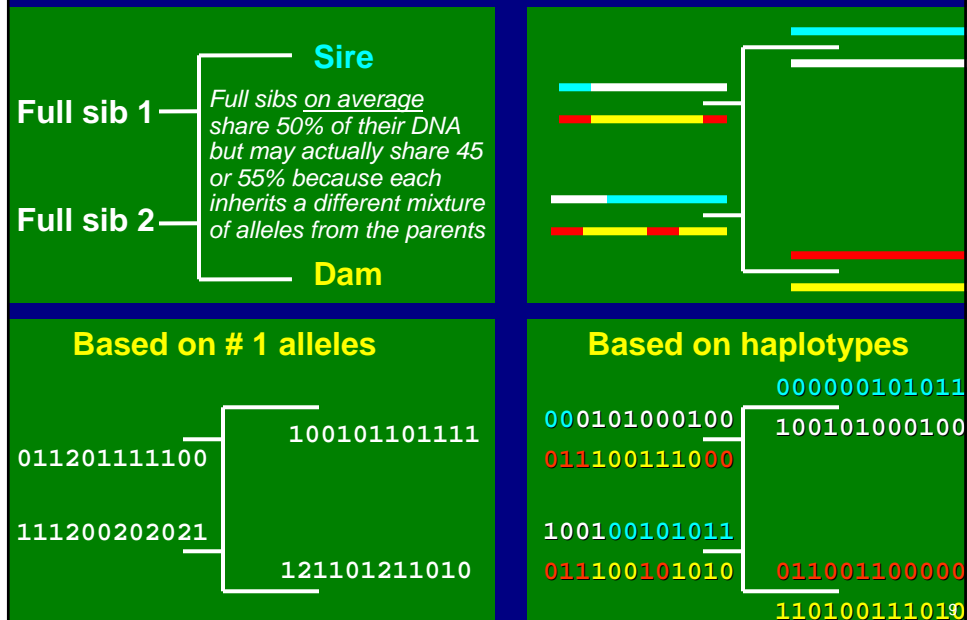
$$\text{Var}(\mathbf{u}) = \mathbf{A} \sigma_a^2$$

= covariances between breeding values of individuals based on pedigree relationships

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2. Genetic relationships derived from marker genotypes

How much are relatives really related?



Computing Relationships from marker genotypes

Observed genotypes at a marker allow IBS calculations

Note that we actually want IBD because we need covariances at unobserved QTL
 (Jacquard '83 Biometrics; Lynch '88 Mol. Biol. Evol.; Eding&Meuwissen '01 J.Anim.Breed.Genet.)

$S_{xy,k}$ = similarity index between individuals x and y at locus k

$$= \frac{1}{4} (I_{11} + I_{12} + I_{21} + I_{22})$$

IBS indicators

= IBS equivalent of coeff.coancestry

$I_{ij} = 1$ if allele i of x = allele j of y
 = 0 otherwise

Animal		IBS indicators				S_{xy}
x	y	I_{11}	I_{12}	I_{21}	I_{22}	
00	00	1	1	1	1	1
00	01	1	0	1	0	1/2
00	11	0	0	0	0	0
01	00	1	1	0	0	1/2
01	01	1	0	0	1	1/2
01	11	0	0	1	1	1/2

To compute genetic relationship

(x,y): average $S_{xy,k}$ across n loci:

$$S_{xy} = \sum S_{xy,k} / n$$

This would be the IBD-based relationship if IBS=IBD = ok of all founder alleles are unique = unlikely

Correct S_{xy} for non-IBD IBS by adjusting for the minimum of S_{xy} across all pairs:

$$\rightarrow r_{xy} = (S_{xy} - S_{min}) / (1 - S_{min})$$

For other methods to adjust for IBS see Eding&Meuwissen '01

(Hayes&Goddard '09 JAS) 10

Computing Relationships from marker genotypes

Matrix method to compute Similarity Index

M_{0k} = nx1 vector with # 0 alleles for each of n individuals for locus k

M_{1k} = nx1 vector with # 1 alleles for each of n individuals for locus k

Geno- type	M_0	M_1
00	0	2
10	1	1
11	2	0

Matrix of relationships based on similarity

index at locus k = $G_k = \frac{1}{4} (M_{0k} M_{0k}' + M_{1k} M_{1k}')$

$$G_k = \frac{1}{4} \left\{ \begin{bmatrix} 0 \\ 1 \\ 2 \end{bmatrix} \begin{bmatrix} 0 & 1 & 2 \end{bmatrix} + \begin{bmatrix} 2 \\ 1 \\ 0 \end{bmatrix} \begin{bmatrix} 2 & 1 & 0 \end{bmatrix} \right\} =$$

$$= \frac{1}{4} \begin{bmatrix} 4 & 2 & 0 \\ 2 & 2 & 2 \\ 0 & 2 & 4 \end{bmatrix} = \begin{bmatrix} 1 & \frac{1}{2} & 0 \\ \frac{1}{2} & \frac{1}{2} & \frac{1}{2} \\ 0 & \frac{1}{2} & 1 \end{bmatrix}$$

To average similarity indexes
across m loci:

M_0 = nxp matrix with # 0 alleles for each individual for each of m loci

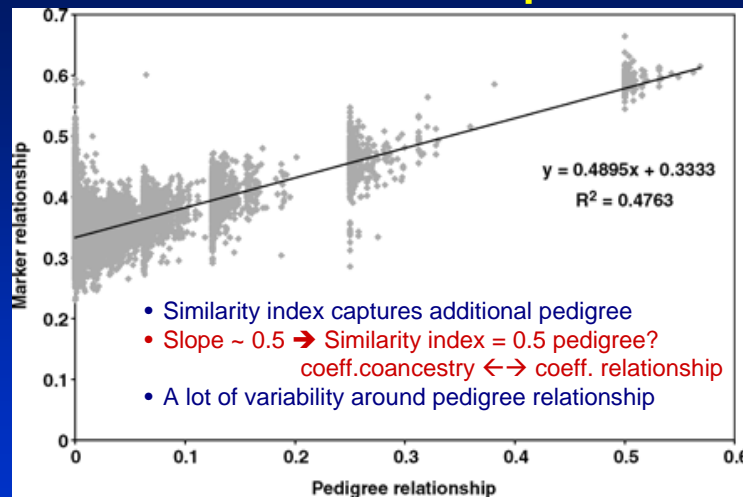
M_1 = nxp vector with # 1 alleles for each individual for each of m loci

Matrix of genetic relationships based on similarity index at across all loci

$$= G = \frac{1}{4m} (M_0 M_0 + M_1 M_1)$$

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Comparison of Marker-based to Pedigree-based relationships



Trangie Experimental Angus herd. Hayes&Goddard '09 JAS

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Distribution of the proportion of alleles shared by Sibs

Based on Van Raden 2007, Interbull

Proportion of alleles shared by fullsib pair	Probability					
1 locus						
0/2 = 0	1/4	Unlinked loci	Percentage of alleles shared			
1/2 = 0.25	1/2		Full sibs			
2/2 = 1	1/4		Mean	SD	Mean	SD
Average	0.5		50	35.4	25	17.7
St.Dev.	0.35		50	15.8	25	7.9
			50	11.2	25	5.6
2 loci						
0/4 = 0	1/8	50	5.0	25	2.5	
1/4 = 0.25	1/4	50	3.5	25	1.8	
2/4 = 0.50	3/8	50	0.0	25	0.0	
3/4 = 0.75	1/4	Linked loci				
4/4 = 1	1/8	50	≥3.5	25	≥1.8	
Average	0.5					
St.Dev.	0.25					

Marker-based relationships capture some of the Mendelian sampling terms

Note that a parent and offspring always share exactly 50% of their alleles

3. Causal model for resemblance of relatives at QTL

Recap – why do we need models for genetic resemblance?

Models for genetic resemblance are used to estimate genetic parameters:

Genetic relationships among individuals to quantify covariances to:

- Estimate genetic parameters (heritability) from phenotypes on relatives
- Use phenotypes on relatives to estimate breeding values using BLUP

$$\mathbf{Y} = \mathbf{X}\mathbf{b} + \mathbf{Z}\mathbf{u} + \mathbf{e} \quad \text{Var}(\mathbf{u}) = \mathbf{A}\sigma_a^2$$

We can also quantify genetic relationships at individual loci, as will be derived next. These can be used to quantify covariances between individuals or alleles for effects of a QTL in order to:

- Detect and map QTL using phenotypes and marker data on relatives
- Variance component linkage analysis, LD analysis, and combined LD-LA analysis

$$\mathbf{Y} = \mathbf{X}\mathbf{b} + \mathbf{Z}\mathbf{u} + \mathbf{W}\mathbf{v} + \mathbf{e} \quad \text{Var}(\mathbf{v}) = \mathbf{G}_v\sigma_v^2$$

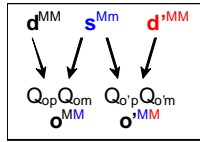
\mathbf{v} = vector with effects of QTL alleles (paternal and maternal) carried by each individual

\mathbf{G}_v = IBD matrix for QTL alleles

σ_v^2 = variance from 1 QTL allele = $\frac{1}{2}\sigma_Q^2$

Model for individual i : $y_i = X_i b + u_i + v_i^p + v_i^m + e_i$

Effects of the individual's Paternal and Maternal QTL alleles



a. IBD AT QTL BASED ON A LINKED MARKER

Derive the probability that QTL alleles o and o' received from s are IBD:

$$\Pr(Q_{op} \equiv Q_{o'p} \mid \text{marker alleles received from } s \text{ by } o \text{ and } o' \text{ are IBD}) = (1-c)^2 + c^2$$

Both o and o' received non-recombinant recombinant marker-QTL segments from s

$\Pr(Q_{om} \equiv Q_{o'm} \mid o \text{ and } o' \text{ both received } M \text{ from their dam}) = 0$ if d and d' are unrelated and marker-QTL LE across population

$$\rightarrow \text{Cov} \left[\begin{array}{l} A_{Qo}, A_{Qo'} \\ \text{maternal marker alleles not IBD} \end{array} \mid \text{paternal marker alleles are IBD} \right] = [(1-c)^2 + c^2] \cdot \sigma_v^2 + 0 \cdot \sigma_v^2 = [(1-c)^2 + c^2] \sigma_v^2$$

for paternal alleles maternal

Note that if $c=1/2$ (i.e. marker and QTL unlinked), then this covariance reduces to the covariance based on average relationships ($1/4$ for halfsibs and $1/2$ for fullsibs)

If o and o' received paternal marker alleles that are NOT IBD, then one of the paternal gametes must be a marker-QTL recombinant for the paternal QTL alleles to be IBD:

$$\Pr(Q_{op} \equiv Q_{o'p} \mid \text{marker alleles received from } s \text{ by } o \text{ and } o' \text{ not IBD}) = 2c(1-c)$$

$$\rightarrow \text{Cov} \left[\begin{array}{l} A_{Qo}, A_{Qo'} \\ \text{maternal marker alleles not IBD} \end{array} \mid \text{paternal marker alleles not IBD} \right] = [2c(1-c)] \cdot \sigma_v^2 + 0 \cdot \sigma_v^2 = 2[c(1-c)] \sigma_v^2$$

for paternal alleles maternal

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a. IBD AT QTL BASED ON A LINKED MARKER

Measures of genetic resemblance derived above are based on average relationships. E.g. paternal halfsibs share half of the alleles that they received from their sire.

But for a given locus, two halfsibs either have received the same or a different allele from their sire.

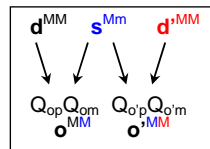
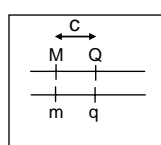
From before, based on pedigree only:

$$\text{Cov}(A_o, A_{o'}) = \{ \Pr(op \equiv o'p) + \Pr(op \equiv o'm) + \Pr(om \equiv o'p) + \Pr(om \equiv o'm) \} \cdot \frac{1}{2} \sigma_Q^2 = r_{oo'} \sigma_Q^2$$

For halfsibs, when using average relationships: $\Pr(op \equiv o'p) = 1/4$ and all other IBD probs are 0 and the covariance between additive genetic values at a QTL (A_Q) between o and o' is:

$$\text{Cov}(A_{Qo}, A_{Qo'} \mid \text{halfsibs}) = \frac{1}{4} V_Q \quad \text{with } V_Q = \text{variance explained by the QTL} = 2pq\alpha_Q^2$$

When marker data is available, genetic resemblance at a linked QTL can be estimated more precisely by using information on whether the marker alleles inherited by o and o' are IBD:

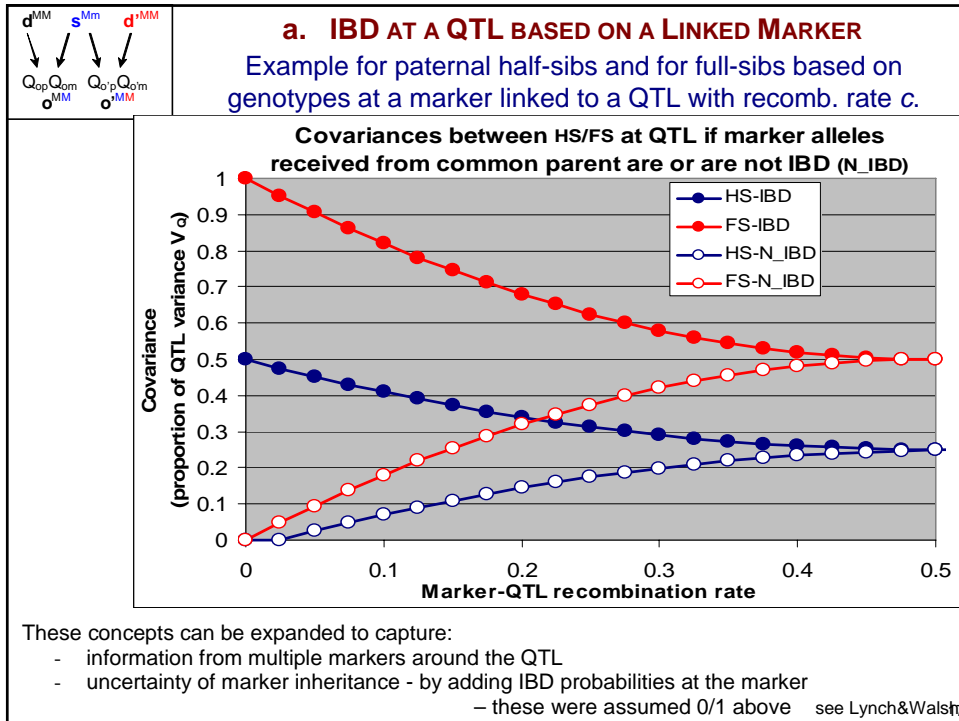


Q_{ip} = QTL allele received by i from its sire (paternal)

Q_{im} = QTL allele received by i from its dam (maternal)

In this example, marker alleles received by o and o' from s are IBD (both M).

Based on this we can derive the probability that the QTL alleles o and o' received from s are IBD:



b. IBD at a QTL based on dense marker haplotypes

With dense marker haplotypes, we can ignore recombination and directly evaluate IBD between haplotypes of relatives (and of QTL captured by these haplotypes) by evaluating IBS

E.g. consider the following 4-SNP haplotypes of a progeny and his sire and dam:

(paternal / maternal)
 Sire 0100 / 0101
 Dam 0111 / 0100
 Progeny 0100 / 0111 Hayes'07

Ignoring recombination, we can assume that:
 progeny's 0100 segment is IBD to the sire's 0100
 progeny's 0111 segment is IBD to the dam's 0111

We can then set up the following IBD matrix for any QTL in the segment.
 Here we distinguish paternal and maternal segments.

		Sire		Dam		Progeny	
		Pat	Mat	Pat	Mat	Pat	Mat
Sire	Pat	1					
	Mat	0	1				
Dam	Pat	0	0	1			
	Mat	0	0	0	1		
Progeny	Pat	1	0	0	0	1	
	Mat	0	0	1	0	0	1

Note that assignment of paternal and maternal haplotypes for the sire and dam is arbitrary.
 Also, the sire and dam segments are assumed unrelated.

Thus, the covariance between the sire's paternal and the progeny's paternal allele at a putative QTL in the segment = $1 * \sigma_v^2 = \sigma_v^2$ ($\sigma_v^2 = \text{variance of one allele at the QTL} = \frac{1}{2} \sigma_a^2$)

This is a linkage-based IBD matrix for computing the covariance at QTL
 It models covariances based on marker-QTL co-segregation from parents to progeny.
 It does not model LD because founder segments (sire and dam) are assumed non-IBD.

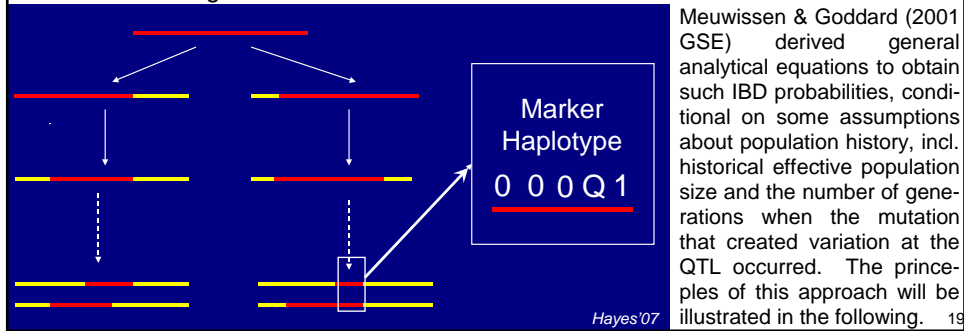
4. IBD at a QTL based on Linkage Disequilibrium

The previous assumed **Linkage Equilibrium** between the marker and QTL across the population, and only used linkage information or LD **within** a family

When markers and QTL are closely linked, they can be in LD across the population. This allows non-zero IBD probabilities to be quantified even between seemingly unrelated (based on pedigree) individuals, by utilizing observed IBS at markers.

The main principle is that existence of LD implies small segments of chromosomes in the population with are descended from a common ancestor.

This makes these segments IBD, not only at marker loci but also at any QTL that is located in the segment.



IBD from LD based on haplotypes

- If we find two identical haplotypes in the population, what is the probability they carry the same QTL allele?
- Haplotypes are identical either because chromosome segments from same common ancestor – are IBD
- Or because of chance recombination.....
- With more markers in haplotype, the chance of creating the same haplotype by recombination becomes small



Consider 3 haplotypes drawn from population (P is putative QTL position)

A 001P001

B 101P001 $P(\text{IBD at QTL A,B}) > P(\text{IBD at QTL B,C})$

C 111P111 because A and B have longer identical haplotype

Parameters determining IBD probs are: - extent of LD
- length of identical haplotype
- # markers in haplotype

Hayes'07

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Building LD-IBD matrix from marker haplotypes

Algorithm of Meuwissen and Goddard (2001) deterministically predicts IBD probs at putative QTL from marker haplotypes based on the number of markers that are **IBS to the left** and **IBS to the right** of the putative QTL

	SNP haplotypes around ●	# markers IBS to	
		left of ●	right of ●
Haplotype 1:	01111●11001		
Haplotype 2:	01111●11011	5	3
Haplotype 3:	00101●11011	1	3

Pr(1 and 2 are IBD at ●)
is greater than
Pr(1 and 3 are IBD at ●)

- An example with $N_e = 100$
- 6 markers in 10 cM, putative QTL position in centre: M_M_M_Q_M_M_M
- Sample 4 haplotypes from population: 001001, 001001, 011001, 111011
- IBD matrix is:

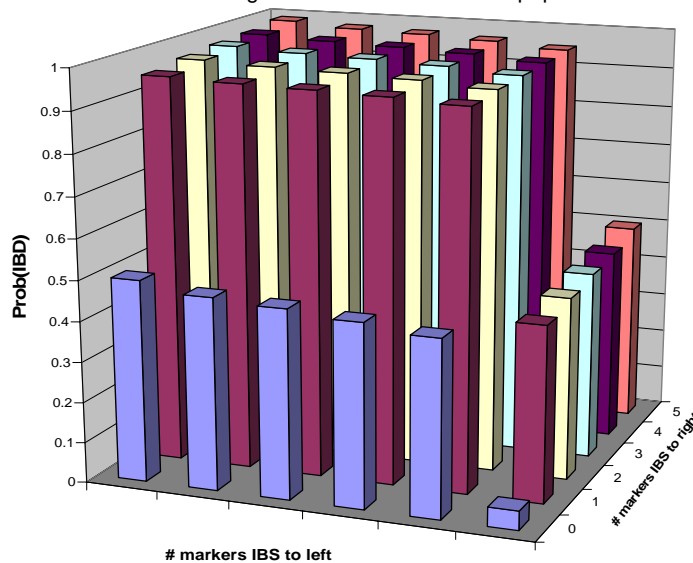
This is an LD-based IBD matrix

	001001	001001	011001	111011
001001	1			
001001	0.82	1		
011001	0.63	0.63	1	
111011	0.49	0.49	0.56	1

Thus, the covariance between a individual with haplotype 112112 and an individual with haplotype 122112 = $0.63 * \sigma_v^2$ if this segment contains a QTL with variance $2\sigma_v^2$ Hayes07 21

Marker-based IBD Covariances based on LD

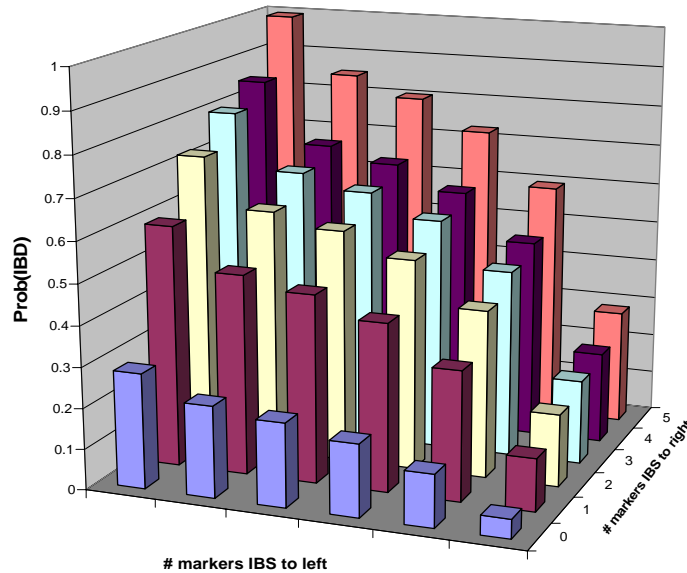
The predicted IBD probabilities of haplotype pairs at locus A. The haplotypes consist of 10 markers that had founder alleles in the base population, are evenly spaced and 1 cM apart. Locus A is at the middle of this haplotype. The effective population size and number of generations since the base population are both 100.



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IBD probabilities based on haplotypes

The IBD probabilities of haplotype pairs at locus A. The haplotypes consist of 10 bi-allelic markers that had allele frequencies equal to 0.5 in the base population, are evenly spaced and 1 cM apart. Locus A is at the middle of this haplotype.



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5. Genetic resemblance at QTL based on combined linkage disequilibrium and linkage / cosegregation

- Linkage IBD matrices assume QTL alleles in founders are not IBD
 - LD IBD matrices capture IBD between founder QTL alleles
- combine these two approaches → LD-LA analysis

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E.g. consider again the dense marker haplotypes:

Sire 0100 / 0101

Dam 0111 / 0100

Progeny 0100 / 0111

LA

The linkage-based IBD matrix was:

		Sire		Dam		Progeny	
		Pat	Mat	Pat	Mat	Pat	Mat
Sire	Pat	1					
	Mat	0	1				
Dam	Pat	0	0	1			
	Mat	0	0	0	1		
Progeny	Pat	1	0	0	0	1	
	Mat	0	0	1	0	0	1

LD

The LD-based IBD matrix of founder haplotypes is, eg:

		Sire		Dam	
		Pat	Mat	Pat	Mat
Sire	Pat	1			
	Mat	0.8	1		
Dam	Pat	0.5	0.5	1	
	Mat	0.9	0.5	0.5	1

LD-LA

Combining these gives:

		Sire		Dam		Progeny	
		Pat	Mat	Pat	Mat	Pat	Mat
Sire	Pat	1					
	Mat	0.8	1				
Dam	Pat	0.5	0.5	1			
	Mat	0.9	0.5	0.5	1		
Progeny	Pat	1	0.8	0.5	0.9	1	
	Mat	0.5	0.5	1	0.5	0.8	1

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Day 4

IDENTITY BY DESCENT AND GENETIC RELATIONSHIPS

1. A causal model for genetic resemblance between relatives
 - a. Covariance between relatives based on pedigree
 - b. Identity By State vs. Identity By Descent based on pedigree
 - c. The pedigree relationship matrix A
2. Genetic relationships derived from marker genotypes
3. A causal model for genetic resemblance of relatives at QTL
 - a. IBD at QTL based on a linked marker
 - b. IBD at QTL based on dense marker haplotypes
4. IBD at QTL based on linkage disequilibrium
 - a. Accounting for genetic relationships – fit polygenic effect
 - b. Overestimation of significant SNPs – fit random SNP effect
5. Genetic resemblance at QTL based on combined linkage disequilibrium and linkage / cosegregation

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