1.5.1 ESTIMATION OF HAPLOTYPE FREQUENCIES:

• For 2 SNPs, alleles A_j,B_j at locus j there are 4 haplotypes: A_1A_2, A_1B_2, B_1A_2 and B_1B_2 frequencies q_1, q_2, q_3, q_4. Assume HWE at haplotype level.

• Only the double heterozygote A_1B_1, A_2B_2 cannot be phased,

Loc-2	Locus 1 A_1A_1	 A_1B_1	 B_1B_1	
A_2A_2	q_1^2	$2q_1q_3$	q_3^2	$(q_1+q_3)^2$
A_2B_2	$2q_1q_2$	$2(q_1q_4 + q_2q_3)$	$2q_3q_4$	$2(q_1+q_3)(q_2+q_4)$
B_2B_2	q_2^2	$2q_2q_4$	q_4^2	$(q_2+q_4)^2$
	$(q_1+q_2)^2$	$2(q_1+q_2)(q_3+q_4)$	$(q_3+q_4)^2$	1

• There are 10 two-locus genotypes, but only 9 phenotypes.

• Haplotype frequencies can be estimated from phenotype frequencies via the EM algorithm:

$$\Pr(A_1A_2/B_1B_2|A_1B_1, A_2B_2) = q_1q_4/(q_1q_4 + q_2q_3)$$

Given a set of current haplotype frequency estimates q_i, $i = 1, \ldots, 4$ and the phenotypic counts, the conditional expected genotypic counts are easily obtained. New haplotype estimates then are the expected multinomial proportions of each haplotype.

• For consistency with PHASE and other software we will temporarily label the two alleles at each SNP 0 and 1.

• At two loci there are 4 haplotypes: 00, 01, 10, 11, freqs q_{00},q_{10}....
There are 10 phased two-locus genotypes: eg; 10/00, 11/00, 10/01
There are 9 observable two-locus genotypes: (00,00), (10, 11), ...

• Only the double-heterozygotes (10,10) is ambiguous: 11/00 or 10/01.
For other genotype pairs we just count.

• Suppose there are H double-heterozygotes.
Then $\mathbf{E}(\#(11/00) \mid H) \;=\; Hq_{11}q_{00}/(q_{11}q_{00} + q_{10}q_{01})$

• So EM is easily implemented.
For two (or a very few) loci it works well.

1.5.2 ESTIMATING PHASE AND HAPLOTYPE FREQUENCIES:

• Consider diallelic loci (e.g. SNPs): Label alleles 0 and 1.

• Then the genotypes are a set of pairs e.g. 00, 10, 11, 10, 10, and haplotypes a string such as 01010. Determining phase is determining which of the 4 possibilities 01111 and 00100, 01110 and 00101, 01101 and 00110, 01100 and 00111 holds.

• For convenience we may write an unphased genotype as (01111,00100) and the phased version as (01111/00100).

• For large samples and/or small numbers of SNPs we may use EM algorithm to estimate haplotype frequencies, and this also provides probabilities of phasings, given the estimated frequencies.

• However, for large numbers of SNPs this does not work well: many sample haplotype freqs are 0, and likelihood surface is high-dimensional and multimodal.

1.5.3 HAPLOTYPING: TWO (OTHER) ALGORITHMS:

• Clark (1990)’s algorithm: note where individuals are homozygous, haplotyping is trivial. Also trivial if heterozygous at just 1 locus.

• Use individuals heterozygous at at most 1 locus to identify haplotypes that must be present. Assuming these, see which other individuals can be explained by one of these haplotypes, plus a new one – add these new ones to the collection, and continue for as long as possible.

• Problems: May not be able to start. May not be able to finish. Final guess may depend on order one adds haplotypes to the pool.

• Stephens’ algorithm (PHASE): use a model that summarizes similarities of haplotypes in a population – the idea is that haplotypes should look like each other ”in chunks”. Use Monte Carlo to simulate alternative phasings under the model. Produces ”probable phasings” with estimates probabilities. (Now also fastPHASE. Scheet and Stephens (2006).

1.6.1 ALLELIC ASSOCIATION; LINKAGE DISEQULIBRIUM:

- A measure of allelic association between the two loci is

$$\begin{aligned}\Delta &= \Pr(A_1A_2) \ - \ \Pr(A_1)\Pr(A_2) \\ &= q_1 \ - \ (q_1+q_2)\,(q_1+q_3) \\ &= (q_1q_4 \ - \ q_2q_3)\end{aligned}$$

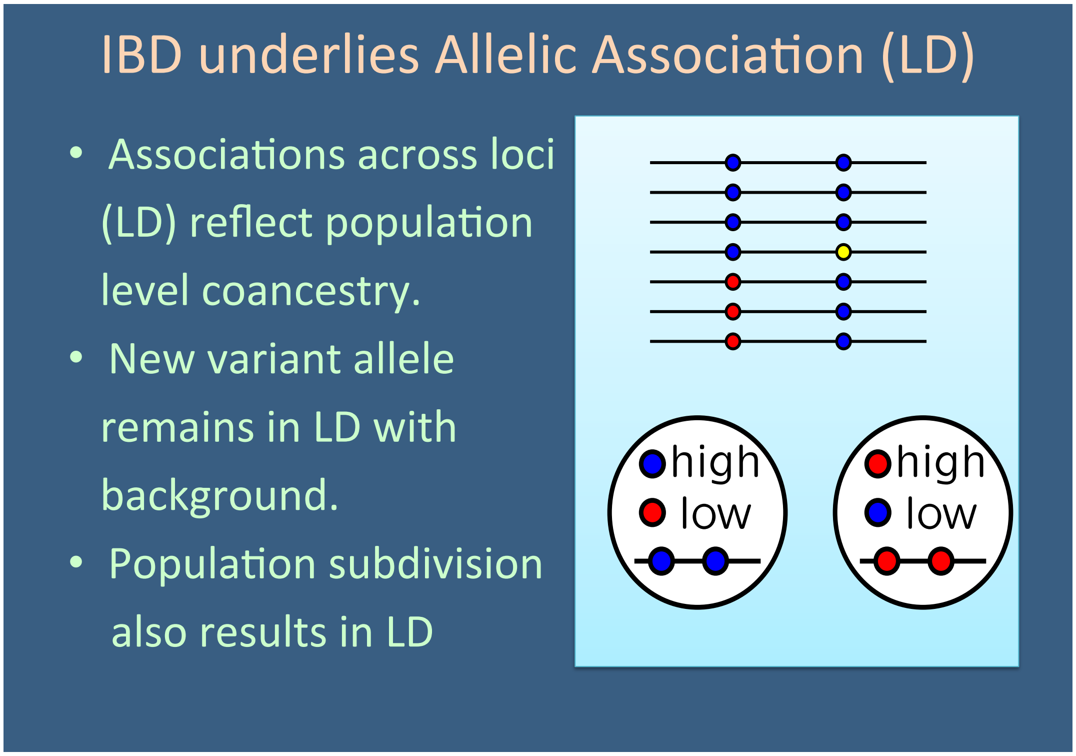
since $q_1+q_2+q_3+q_4 = 1$. This measure is known as the coefficient of *linkage disequilibrium*.

- Allelic associations between loci arise from population structure, admixture and history, or from selection.(See 1.6.2 and 1.6.3). Example of mixture/subdivision— the “nuisance” case. Vs. case of interest— original mutation on some genetic background.

- Associations are, however, maintained by tight linkage ($\rho \approx 0$). LD blocks are the remnants of recombination; they are not caused by linkage, but they survive because of linkage. (See 1.6.5).

- Contrast with HWE: Even for unlinked loci equilibrium ($\Delta = 0$) is not achieved in one generation.

1.6.2 LD ARISES BY MUTATION OR STRUCTURE:



IBD underlies Allelic Association (LD)

- Associations across loci (LD) reflect population level coancestry.
- New variant allele remains in LD with background.
- Population subdivision also results in LD

1.6.3 LD and POPULATION STRUCTURE:

• Population stratification creates LD, even if there is no LD within subpopulations. If allele frequencies differ so will the frequency of haplotypes.

• Consider populations i in proportions α_i and allele A alleles frequencies p_{1i}, p_{2i} at two loci.
As before $\Pr(A_1) = p_1 = \sum_i \alpha_i p_{1i}$, and $\Pr(A_2) = p_2 = \sum_i \alpha_i p_{2i}$.

• Assume there is NO LD within each subpopulation, so the overall frequency of the A_1A_2 haplotype is $\Pr(A_1A_2) = \sum_i \alpha_i p_{1i} p_{2i}$

• Then

$$\begin{aligned} \triangle &= \Pr(A_1A_2) \ - \ \Pr(A_1)\Pr(A_2) \\ &= \sum_i \alpha_i p_{1i} p_{2i} - (\sum_i \alpha_i p_{1i})(\sum_j \alpha_j p_{2j}) \\ &= \sum_i \alpha_i (p_{1i} - p_1)(p_{2i} - p_2). \end{aligned}$$

1.6.4 SEGREGATION OF HAPLOTYPES:

• Homozygous individuals (both loci): for example an A_1A_1, B_2B_2 individual segregates only A_1B_2 haplotypes.

• Homozygote/Heterozygote: for example, an A_1A_1, A_2B_2 individual passes on A_1A_2 or A_1B_2 each with probability $1/2$ regardless of recombinaton probability ρ.

• A double-heterozygote individual passes each of the four haplotypes A_1A_2, A_1B_2, B_1A_2 and B_1B_2, with probabilities:
$(1-\rho)/2$, $\rho/2$, $\rho/2$ and $(1-\rho)/2$ if his genotype is A_1A_2/B_1B_2,
$\rho/2$, $(1-\rho)/2$, $(1-\rho)/2$, and $\rho/2$ if his genotype is A_1B_2/B_1A_2.

Case: A_1A_2/B_1B_2.

	A_2	B_2	
A_1	$(1-\rho)/2$	$\rho/2$	$\frac{1}{2}$
B_1	$\rho/2$	$(1-\rho)/2$	$\frac{1}{2}$
	$\frac{1}{2}$	$\frac{1}{2}$	1

• Recombination breaks up chromosomes, but we only see this directly if genotypes are heterozygous at both loci.

1.6.5 DECAY OF LD:

• Suppose current haplotype freqs of A_1A_2, A_1B_2, B_1A_2 and B_1B_2 are q_1, q_2, q_3 and q_4, and at next generation are q_1^*, q_2^*, q_3^* and q_4^*.

• Now, for example, an offspring A_1A_2 haplotype arises
from a A_1A_1, A_2A_2 parent with prob 1.
from a A_1A_1, A_2B_2 or A_1B_1, A_2A_2, with prob $1/2$,
from a $A_1B_1,\ A_2B_2$ who is A_1A_2/B_1B_2 with prob $(1-\rho)/2$
from a $A_1B_1,\ A_2B_2$ who is A_1B_2/B_1A_2 with prob $\rho/2$. Thus

$$\begin{aligned} q_1^* &= q_1^2 + 2q_1(q_2+q_3)/2 \ + \ 2q_1q_4(1-\rho)/2 + 2q_2q_3\rho/2 \\ &= q_1(q_1+q_2+q_3+q_4) \ - \ \rho(q_1q_4 - q_2q_3) \ = \ q_1 \ - \ \rho\Delta. \end{aligned}$$

Analogously, $q_2^* = q_2+\rho\Delta$, $q_3^* = q_3+\rho\Delta$ and $q_4^* = q_4-\rho\Delta$. Thus, in expectation, allele frequencies are unchanged ($q_1^*+q_2^* = q_1+q_2$):

$$\begin{aligned} \Delta^* &= q_1^*q_4^* - q_2^*q_3^* \\ &= (q_1-\rho\Delta)(q_4-\rho\Delta) \ - \ (q_2+\rho\Delta)(q_3+\rho\Delta) \\ &= \Delta - \rho\Delta(q_1+q_2+q_3+q_4) + \rho^2(\Delta^2 - \Delta^2) \\ &= (1-\rho)\Delta. \end{aligned}$$

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