Lecture Handout 22, Linkage disequilibrium and recombination: Multilocus selection

Only under certain circumstances does multilocus selection play a role in linkage disequilibrium.

“**supergenes**:” genes that show linkage disequilibrium. So closely linked that there is little recombination between them; eg MHC

Genetic background of a neutral allele may result in apparent fitness difference at a neutral locus, due to association with an allele at a different gene subject to selection.

Genetic hitchhiking: a neutral allele associated with an allele at a different locus is “carried along” because of the selective advantage of the associated allele.

Selective sweep: reduction of heterozygosity and molecular variation in the region around a selected allele, due to genetic hitchhiking; eg selective sweep with s = 0.01 can reduce variation 10 kb away from selected locus.

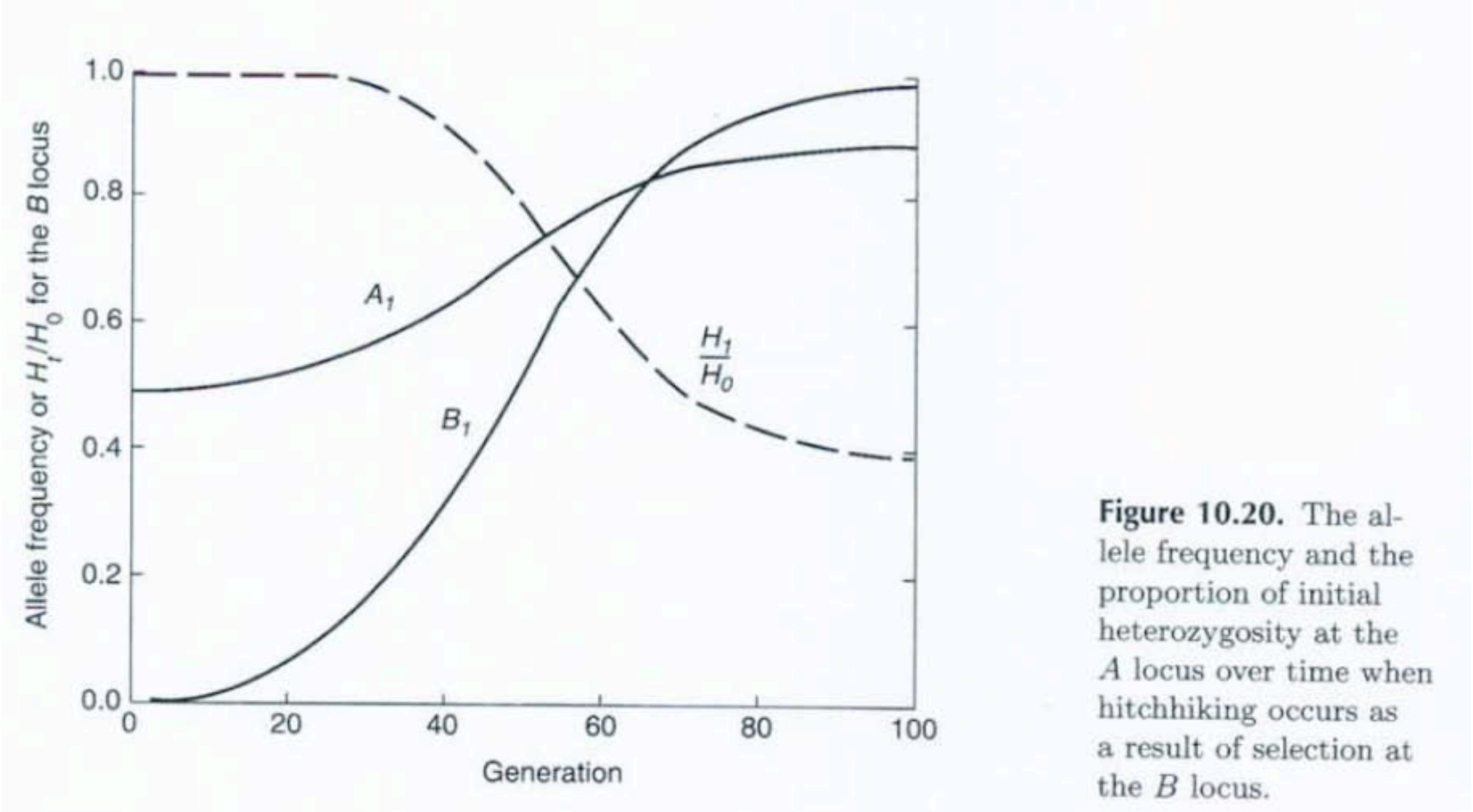
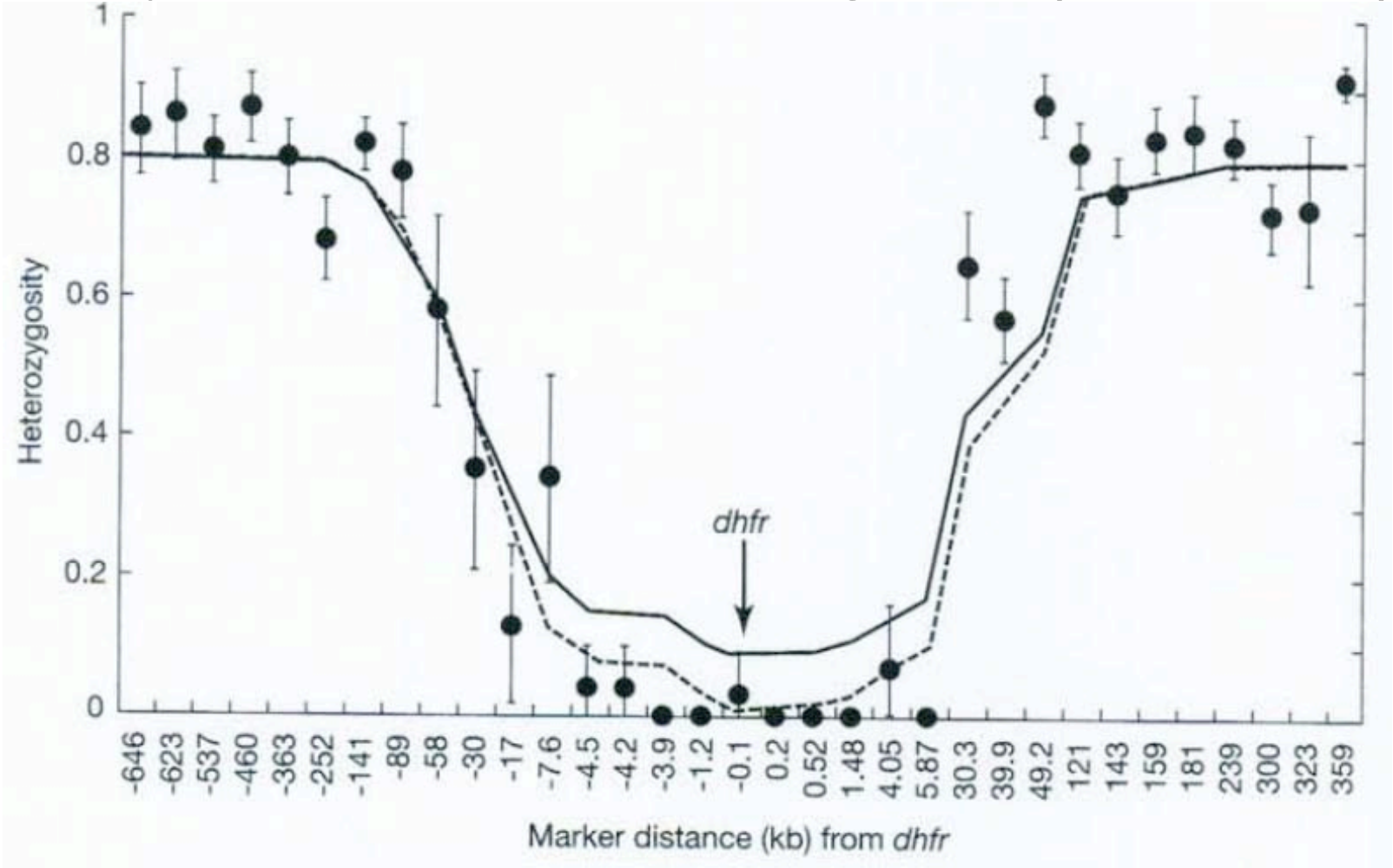


Figure 10.20. The allele frequency and the proportion of initial heterozygosity at the *A* locus over time when hitchhiking occurs as a result of selection at the *B* locus.

Selective sweep: example. Resistance of *Plasmodium falciparum* to pyrimethamine (substitute for chloroquine), due to mutations in dihydrofolate reductase gene. (STR hets)



Background selection: the chromosome on which a new detrimental mutant allele occurs will be lost due to selection, as will neutral alleles surrounding the mutation unless there is recombination. The effect of many such events can have a significant cumulative effect on nucleotide diversity.

The time since appearance of a favorable mutation: can be estimated by examining the breakdown of linkage disequilibrium between the mutant allele and the haplotype in which it appeared, and by examining the number of new additional mutations on the haplotype on which the mutant allele of interest appeared.

$$t = \frac{\ln(P_t)}{\ln(1 - c' - u)}$$

The time since appearance of a favorable mutation: example, CCR5 gene codes for receptor used by HIV to enter cells. CCR5-Δ32 is a mutant that prevents viral entry.

TABLE 10.15 The frequencies of *CCR5* haplotypes observed in a sample of 46 haplotypes with the deletion Δ32 and 146 haplotypes with the + allele (Stephens *et al.*, 1998). The putative origin of the five Δ32 haplotypes is given.

CCR5	*GAAT*	*AFMB*	*Frequency*	*Type of haplotype*
Δ32	197	215	0.848	ancestral
Δ32	197	217	0.065	recombination
Δ32	193	215	0.043	recombination
Δ32	197	219	0.022	recombination or mutation
Δ32	197	213	0.022	mutation
+	197	215	0.363	
+	197	217	0.308	
+	193	215	0.137	
+	197	219	0.014	
+	193	217	0.144	
+	191	217	0.014	
+	191	215	0.021	

Advantages and disadvantages of recombination (sexual reproduction vs asexual reproduction):

Disadvantages of sexual reproduction:

-offspring only receive one half of genes from each parent

-favorable gene combinations may be broken up

Advantages and disadvantages of recombination (sexual reproduction vs asexual reproduction):

Advantages of sexual reproduction:

-potential for allele combinations with higher fitness states

-avoidance of **Muller's ratchet**: without sexual reproduction (recombination), detrimental mutations can accumulate and fitness will decline over time.

Advantage of sexual reproduction is due to recombination of favorable mutants in different lineages.

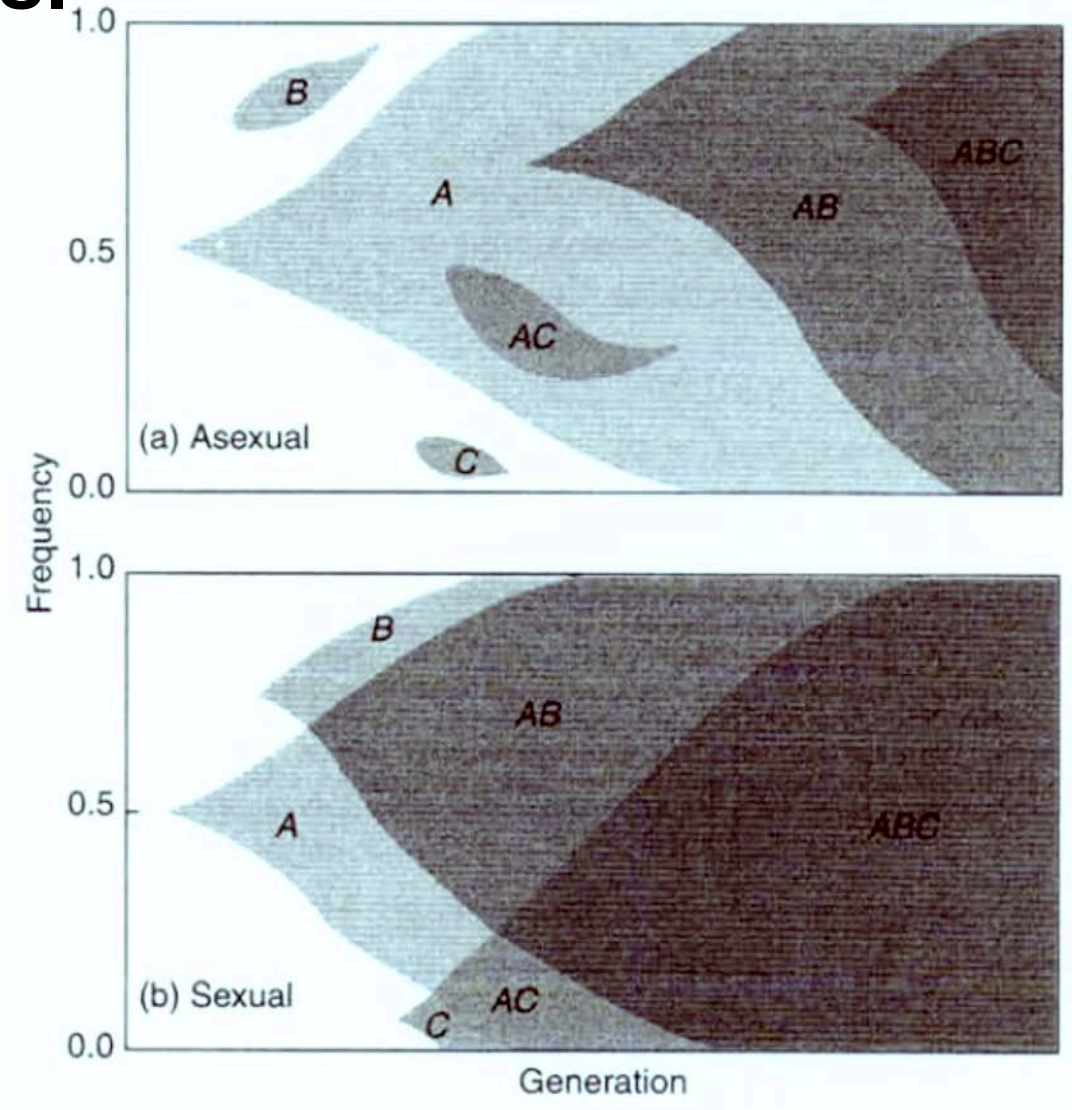


Figure 10.23. The frequency of different genotypes over time when there is (a) asexual or (b) sexual reproduction (Crow and Kimura, 1965).

Linkage disequilibrium plot: sites with significant LD are darkened; dots indicate no statistical power; white squares indicate lack of LD

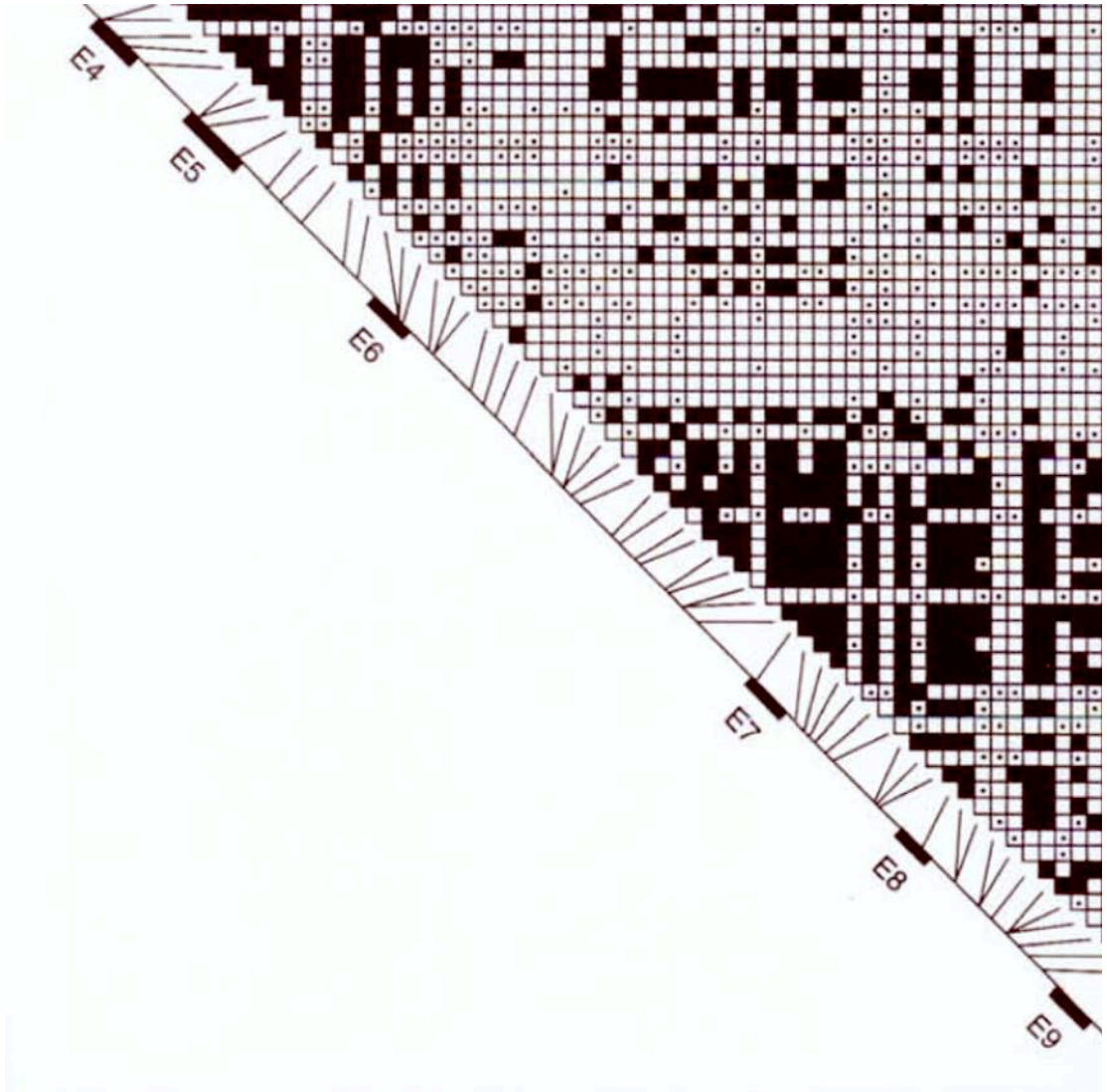


Figure 10.24. Significant linkage disequilibrium between the 88 polymorphic sites at the human lipoprotein lipase gene (solid squares). The diagonal line indicates the location of the site and the position of exons 4 to 9. The squares with a dot in the center are ones that lack the power to test for a significant association (Clark *et al.*, 1998).