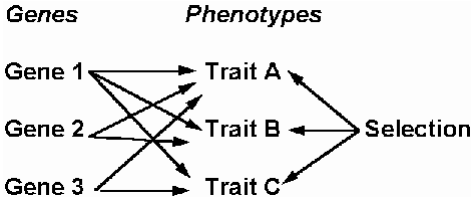
BIOL2007
EVOLUTION AT MORE THAN ONE GENE

GENE INTERACTIONS : *PLEIOTROPY AND EPISTASIS*



Gametic "associations": linkage disequilibrium. Expected gametic frequencies

allele		A	a
	allele freq.	p_A	$1-p_A$
B	p_B	p_Ap_B	$(1-p_A)p_B$
b	$1-p_B$	$p_A(1-p_B)$	$(1-p_A)(1-p_B)$

Sum of frequencies = 1

Deviation from two locus equilibrium: ***D*** is the disequilibrium coefficent:

Gametic = random +/- deviation frequencies

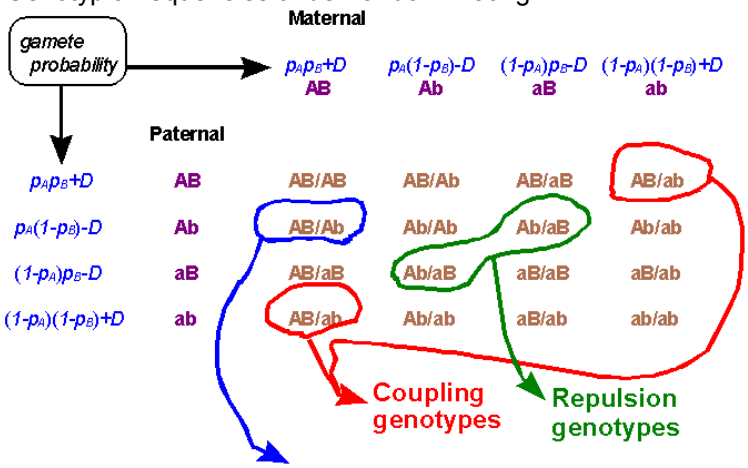
p_{AB}	=	p_Ap_B	**+ *D***
p_{Ab}	=	$p_A(1-p_B)$	**- *D***
p_{aB}	=	$(1-p_A)p_B$	**- *D***
p_{ab}	=	$(1-p_A)(1-p_B)$	**+ *D***

Obviously, the sum $p_{AB} + p_{Ab} + p_{aB} + p_{ab} = 1$

You will often find gametic disequilibrium referred to as linkage disequilibrium.

GENOTYPIC FREQUENCIES IF THERE IS DISEQUILIBRIUM

Genotypic frequencies under random mating:



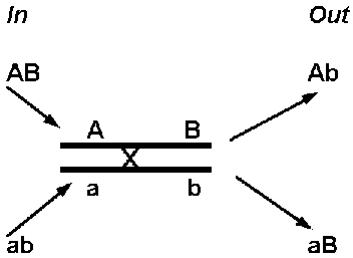
The **AB/Ab** genotype has probability $[p_A(1-p_B)-D][p_Ap_B+D]$, and there is another way you can get this genotype, with the same probability. Thus, total probability of the **AB/Ab** (i.e. **AABb**) genotype assuming random mating is : $2[p_A(1-p_B)-D][p_Ap_B+D]$.

(For information only –not covered this year).

There are two types of **AaBb** "genotype": **AB/ab**, or "coupling" double heterozygotes, and **Ab/aB** or "repulsion" double heterozygote.

FACTORS THAT CAN DECREASE *D*

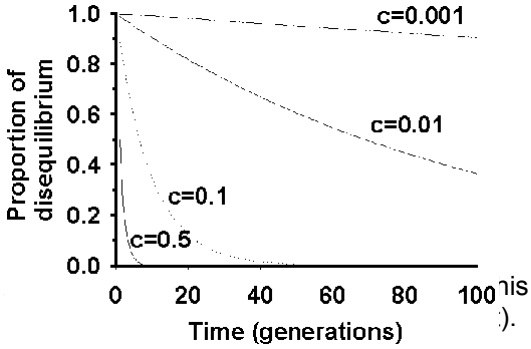
Recombination reduces disequilibrium



Disequilibrium actually declines by a factor ***c*** every generation, where ***c*** = recombination fraction:

$D_t = D_{t-1}(1-c)$

After many generations (***t***), $D_t = D_0(1-c)^t$. Here is this function plotted (left):



FACTORS THAT CAN INCREASE *D*

A: *Drift* - random sampling of gametic frequencies, approx. proportional to $1/2N_e$

e.g. Closely linked markers in humans and *Drosophila*? Here the rate of loss of disequilibrium is so slow that random factors such as drift, even in very large populations have an effect.

B: *Selection* - epistatic selection (for gene combinations)

Mimetic butterflies:

- Much of the pattern of the polymorphic swallowtail butterfly *Papilio memnon*, is switched at one major locus, which turns out to be a "supergene", or tightly linked complex of separate mutatable sites which have different effects on the phenotype, on the tail length and on different components of the colour pattern.
- Batesian mimicry selects for only certain combinations of pattern and morphology, those which look like the unpalatable model species. In this case, the polymorphism is only possible because there are few recombinant, non-adaptive, patterns produced, because of the tight linkage. The genes for pattern and morphology are in tight linkage disequilibrium.

Heterostyly in primroses (*Primula*)

- "Pin" and "thrum" morphs of the primrose are a good example of "heterostyly" in plants
- This is the other classical example of a "supergene", this time in a plant. The supergene has effects on anther position, style position, pollen size, incompatibility, and even the microscopic papilla size on the stigma surface.

Human Leucocyte Antigens (HLA):

- Part of Major Histocompatibility Complex (**MHC**), a large complex of loci involved in the immune system.
- Involved in antibody/antigen reactions - present antigen, involved in recognition - lysis
- Highly polymorphic, involved in immunity to disease; probable frequency-dependent selection for rare forms
- Disequilibria over 10s-100s of millions of bp apart, suggesting selection for combinations of loci.

C: *Migration* - mixing of populations with different frequencies

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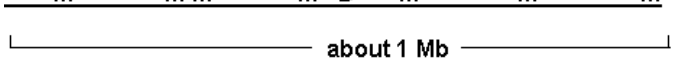
USES

1) Studying **migration** or **dispersal** between populations with different gene frequencies, or between species. Because gene frequencies differ, there will be different frequencies of gene combinations in the two populations, so that mixing will produce disequilibrium. This disequilibrium will persist for some generations (see above).

2) **Linkage mapping** of Human loci when ***c*** = 0.01 or less

For example, disease locus **D** and marker loci **m**



In humans 1 million bp is approximately equal to ***c***=0.01, or 1 map unit (centimorgan). Empirically, disequilibria show up between marker loci like microsatellites, and between marker loci and genetic disease loci at about this distance and less. This is presumably caused by preservation of drift-induced disequilibria due to the very low levels of recombination in a finite population size. Linkage disequilibria can be very useful for fine-scale gene mapping , because it is almost impossible to get enough human pedigree and recombination data on a rare disease when the loci are less than about 5 map units (***c***=0.05) apart. The detection of linkage disequilibria (i.e. differences in marker loci between affected and unaffected individuals) can quickly narrow down the search for the "candidate loci". This approach has been used successfully in a variety of recent studies.

In *Drosophila* we find the same appearance of disequilibria in natural populations. At one locus, the ***Adh*** locus, the disequilibria seem to show up only in regions less than a few hundred or so base pairs apart. This suggests greater recombination and also a much higher population size, so that recombination is more effective at homogenizing chromosomes.

READINGS

Chapter 9: 205-207, Chapter 13: 303-304
Freeman & Herron Chapter 7.