One-minute responses

- Q: How does an organism know to produce fewer homozygotes when they are disfavored in an overdominant situation?

- A: It doesn't know. Offspring are at H-W at conception, but the homozygotes don't survive as well, so by breeding time there are fewer.

- Q: How do you know which term goes where in $t/(s+t)$?

- A: If you are calculating pA, the one on top is the badness of the other allele a

Linkage of Genes on Chromosomes

1. Finishing up sex linkage
2. Linkage and natural selection
3. Effects of recombination
4. Pros and cons of recombination
5. Linkage disequilibrium

X linked traits

Suppose that among X chromosomes, $p(X^H) = 0.8$ and $p(X^h) = 0.2$ in both sexes.

Genotype	X^HX^H	X^HX^h	X^hX^h	X^HY	X^hY
Fitness	1.0	1.0	0.1	1.0	0.1
HW	0.32	0.16	0.02	0.40	0.10

We can see immediately that a rare recessive sex-linked disease shows up mostly in males.

Sex linked traits

Genotype	$X^H X^H$	$X^H X^h$	$X^h X^h$	$X^H Y$	$X^h Y$
Fitness	1.0	1.0	0.0	1.0	0.0
HW	0.32	0.16	0.02	0.40	0.10
Post-Selection	0.36	0.19	0.0	0.45	0.0

The new allele frequencies are:
Females: $p(X^H) = 0.91$, $p(X^h) = 0.09$
Males: $p(X^H) = 1.0$, $p(X^h) = 0.0$

Sex linked traits are weird

- Even if selection stops, system won't go straight to HW:
  - Mating is non-random with respect to sex
  - Males and females have different allele frequencies

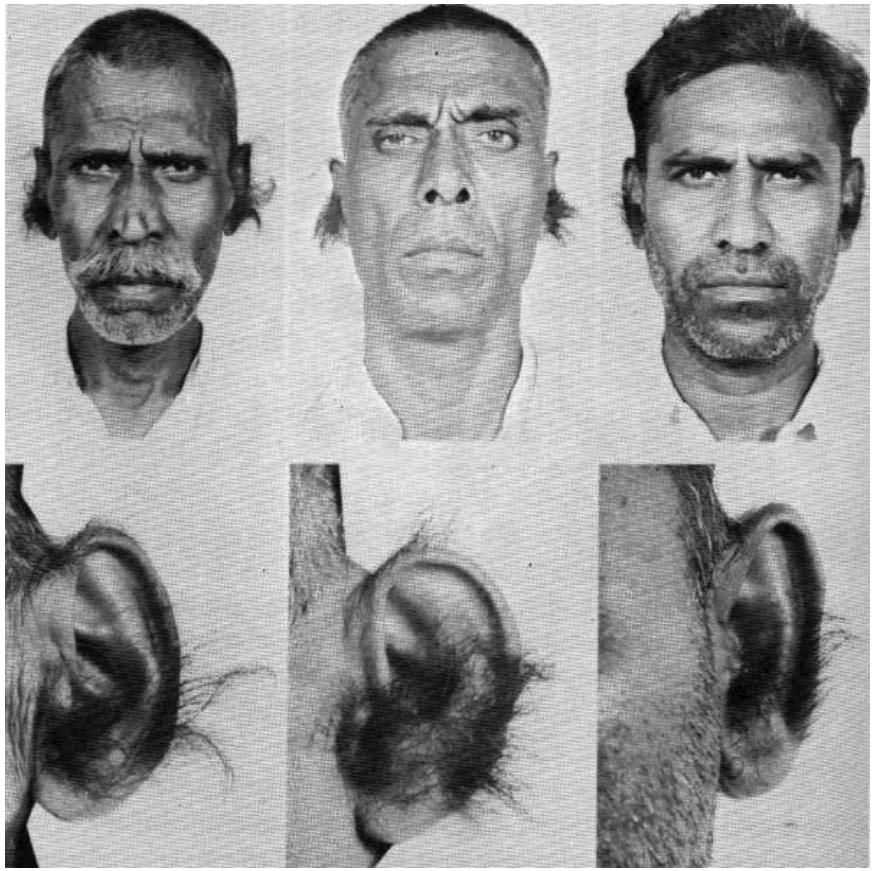
X linked traits

- X-linked recessive decreases faster than an autosomal recessive
- Exposed to selection when in males
- Sex-linked traits don't go to Hardy-Weinberg in one generation
  - Without selection, they go to Hardy-Weinberg slowly over many generations
  - With selection, they may never get there

Sex linked traits

- A point to bear in mind:
  - Most sex-specific traits are not sex-linked (on X or Y)
  - Most sex-linked traits (on X) are unrelated to sex
  - Examples: hemophilia, color vision
  - The Y chromosome contains a few "switch" genes which control sex in humans
  - Almost all of the genes controlled by these switches are autosomal
- Why?

The only Y-linked non-sex gene I know of



Sex linked traits

- Why aren't sex-related traits sex-linked?
- Both males and females have X
- Why aren't male traits on the Y?
  - If sex-related traits evolved from other traits, they would start off on the autosomes
  - The Y is haploid and mostly non-recombining, which can cause its genes to deteriorate
  - Having one master switch rather than many independent sex-related trait genes may be less fragile

Selection at multiple loci, no linkage

- IF loci are unlinked (e.g. different chromosomes, or far apart)
- AND phenotypes don't interact
- THEN each locus experiences selection independently

Example with unlinked loci

Two unlinked loci A and B with non-interacting phenotypes:

Genotype	AA	Aa	aa
Fitness	1.0	1.0	0.2
Genotype	BB	Bb	bb
Fitness	0.8	1.0	0.8

Assume that an organism's fitness is the product of its fitness at each locus

- What will happen at locus A?
- What will happen at locus B?

Linkage in Organisms Without Recombination

In an organism without recombination, if two mutations occur on different copies of a chromosome, they cannot be brought together.

```
-------A-------b--------

-------a-------B--------
```

- If they occured on the same copy, they can't be separated either
- The only way to break up combinations is repeated mutation

Linkage in Organisms Without Recombination

```
-------A-------b--------

-------a-------B--------
```

If both A and B are advantageous alleles, this linkage blocks the population from reaching maximum fitness.

- May remain polymorphic (both alleles present)
- One may eliminate the other
- In either case, maximum fitness cannot be reached

Practical examples

Genotype	AA	Aa	aa
Fitness	1.0	1.0	0.7

Genotype	BB	Bb	bb
Fitness	1.0	1.0	0.7

If the population contains only Ab and aB gametes, and there is no recombination, what will selection do?

Assume allele frequencies of p(A)=0.6, p(B)=0.4, and that an organism's fitness is the product of its fitness at the two loci.

What will happen in the short term? In the long term?

Practical examples

The population really behaves like this:

Genotype	Ab/Ab	Ab/aB	aB/aB
Fitness	0.7	1.0	0.7
Frequency	0.36	0.48	0.16

This will move to an equilibrium p(A)=p(B)=0.5 and stay there. Even though it contains two loci with clear-cut bad recessives, it behaves like one overdominant locus.

Practical examples

Now add recombination of 10% between the two loci.

p(Ab)=0.6, p(aB)=0.4

Gametes after 1 generation:

90% are non-recombinant, producing 0.54 Ab and 0.36 aB.

10% are recombinant, and will therefore be assorted at random: 0.024 AB, 0.036 Ab, 0.016 aB, 0.024 ab.

Totals: 0.024 AB, 0.576 Ab, 0.376 aB, 0.024 ab

A Punnett Square is the easiest way to proceed from here.

Practical examples

	AB 0.024	Ab 0.576	aB 0.376	ab 0.024
AB 0.024	0.0006	0.0138	0.0090	0.0006
Ab 0.576	0.0138	0.3318	0.2166	0.0138
aB 0.376	0.0090	0.2166	0.1414	0.0090
ab 0.024	0.0006	0.0138	0.0090	0.0006

Practical examples

Genotype	AABB	AABb	AAbb	AaBB	AaBb
Freq	0.0006	0.0276	0.3318	0.0180	0.4344
Fitness	1.0	1.0	0.7	1.0	1.0

Genotype	Aabb	aaBB	aaBb	aabb
Freq	0.0276	0.1414	0.0180	0.0006
Fitness	0.7	0.7	0.7	0.49

Now selection has something to work on, and p(a) and p(b) will go down. Recombination has converted one "overdominant locus" to two dominant/recessive loci.

Evolutionary consequences of recombination

- Good:
  - Avoid "Muller's Ratchet"
  - Avoid hitchhiking
  - Rapidly combine favorable mutations
  - Increase offspring diversity
  - Repair damaged DNA
- Bad:
  - Break up favorable combinations
  - Illegitimate recombination can damage chromosomes
  - Costs energy

Apparently recombination is not essential

Bdelloid rotifer. The entire class is believed to have gone without sex for at least 40 million years (maybe as long as 100 million years). They are common and widespread with at least 360 different species.

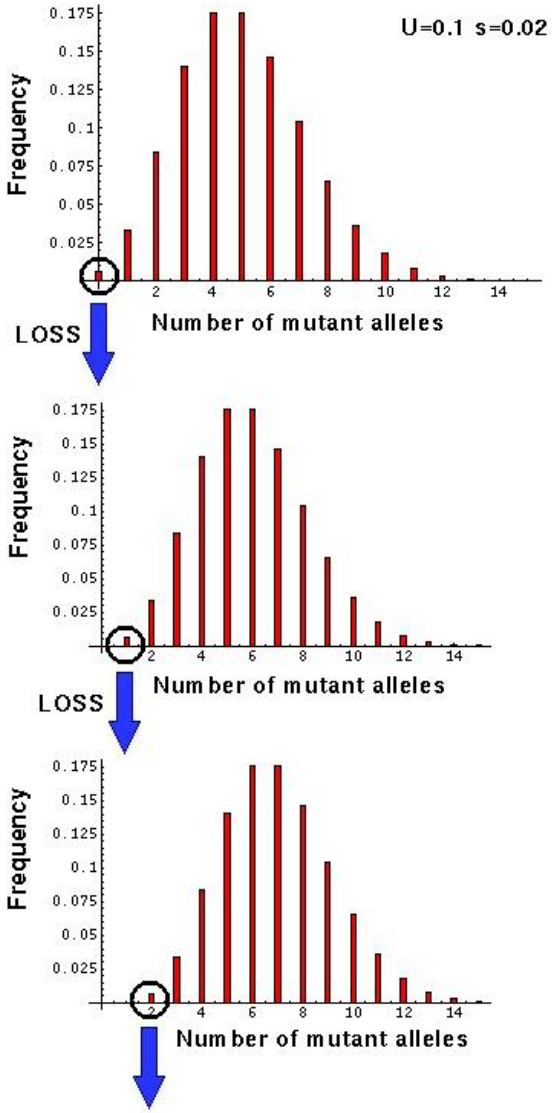
Evidence for Asexuality of Bdelloids

- Chromosomes do not match up in pairs
- No males; no meiosis; eggs produced by mitosis
- Relationships between individuals form a simple tree
- Very few active transposable elements

What's risky about this lifestyle?

Muller's Ratchet

- Without recombination:
  - All mutation-free copies of a chromosome might be lost
  - Once lost, they are hard to get back
- (A "ratchet" is a gear that turns only one way)
- Muller thus predicts that an asexual genome will deteriorate over time



Muller's Ratchet

What can counteract the ratchet?

- Back mutation
- New favorable mutations
- Strong selection
- Recombination–two bad chromosomes can recombine into a better one

Bdelloids and their lack of transposons

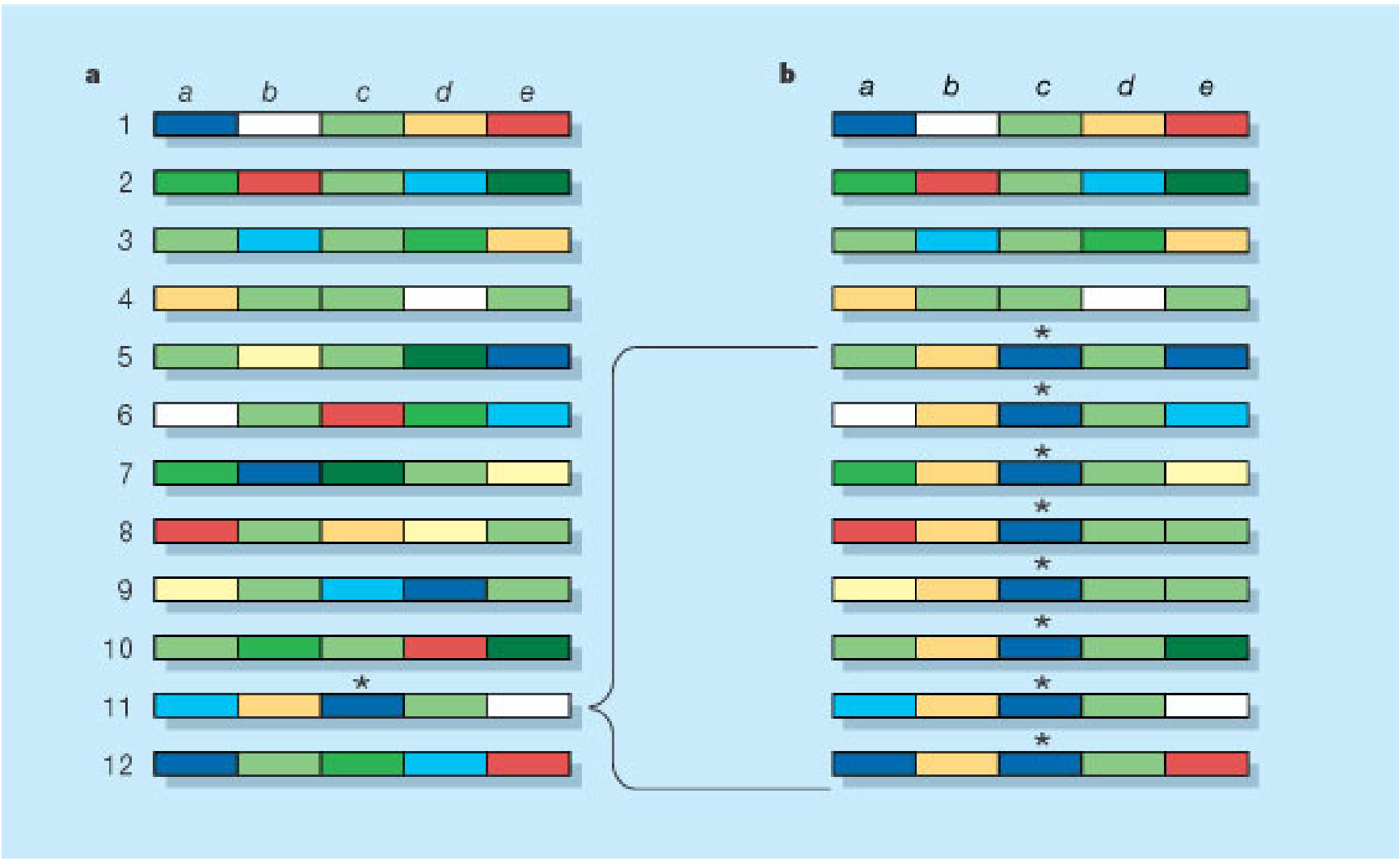
- Transposons can be costly:
  - Slower DNA replication
  - Production of useless transposase
  - Genomic damage due to transposition
- Transposons tend to increase
- A sexual organism can recombine two transposon-ridden chromosomes and perhaps produce a transposon-free one
- So transposons might be too dangerous for bdelloids to tolerate

How do bdelloids survive without sex?

- Bdelloid lifestyle is prone to desiccation
  - They are highly mutation-resistant (to survive this)
  - They pick up DNA from the environment when dried out
- This may pre-adapt them to living without sex
  - Low mutation rate slows the ratchet
  - Pick-up of foreign DNA allows occasional recombination

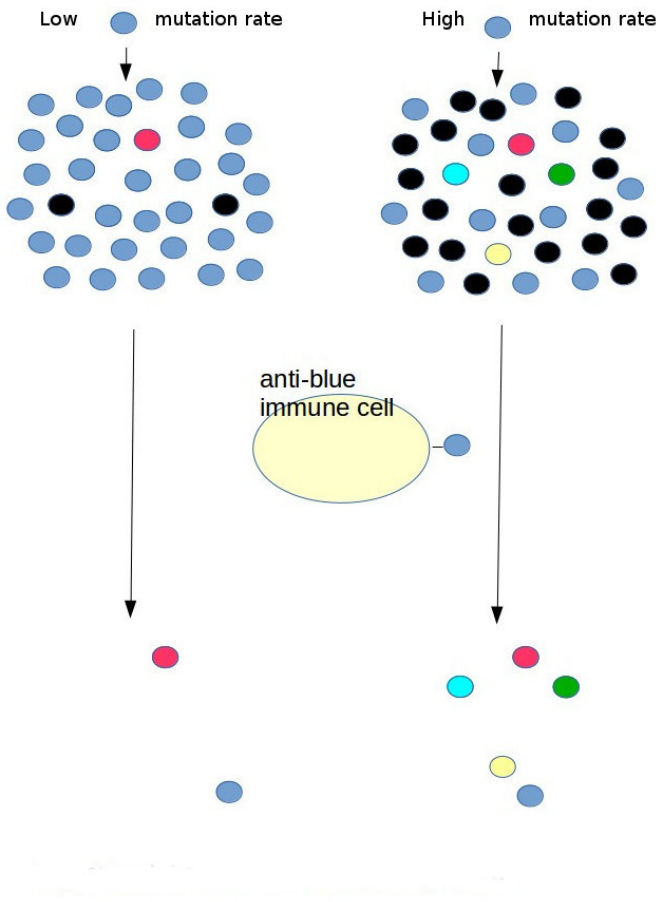
Hitchhiking

- A good mutation arises and will sweep the population
- If there were any mildly bad mutations on that chromosome, they will sweep too ("hitchhiking")
- Recombination allows hitchhikers to be removed


a
a
b
c
d
e
1
2
3
4
5
6
7
8
9
10
11
12
b
a
b
c
d
e

Diverse offspring

- Recombination creates novel gene combinations
- If offspring diversity is favorable, recombination helps
- Many organisms use sexual reproduction to produce:
  - Dispersal forms
  - Over-wintering forms



Disequilibrium

- Linkage disequilibrium (LD) is association between alleles at different loci
- Examples:
  - Only AB and ab are present
  - All four combos are present but some are disproportionately common
- Linkage equilibrium is lack of association:
  - You can predict pAB as $(pA)(pB)$
- With recombination, population moves towards equilibrium

Disequilibrium

An example:

If we know the allele frequencies:

$pA = 0.7$
$pa = 0.3$
$pB = 0.2$
$pb = 0.8$

then if we have linkage equilibrium, we can immediately predict the proportion of gametes:

$pAB = 0.7 \times 0.2 = 0.14$
$pAb = 0.7 \times 0.8 = 0.56$
$paB = 0.3 \times 0.2 = 0.06$
$pab = 0.3 \times 0.8 = 0.24$

Disequilibrium

The disequilibrium coefficient D is defined as:

D=(pAB*pab) - (pAb*paB)

pA = 0.7
pa = 0.3
pB = 0.2
pb = 0.8

It can be interpreted as the excess of AB and ab over the other two. If we have D=0.01:

pAB = 0.7 x 0.2 + 0.01 = 0.15
pAb = 0.7 x 0.8 - 0.01 = 0.55
paB = 0.3 x 0.2 - 0.01 = 0.05
pab = 0.3 x 0.8 + 0.01 = 0.25

Practice problem

pA = 0.7
pa = 0.3
pB = 0.2
pb = 0.8
(just like before)

If D=-0.01, what are the genotype frequencies?

Practice problem

pA = 0.7

pa = 0.3

pB = 0.2

pb = 0.8

If D=-0.01, what are the genotype frequencies?

pAB = 0.7 x 0.2 - 0.01 = 0.13

pAb = 0.7 x 0.8 + 0.01 = 0.57

paB = 0.3 x 0.2 + 0.01 = 0.07

pab = 0.3 x 0.8 - 0.01 = 0.23

Disequilibrium

The disequilibrium coefficient D can range between -0.25 and +0.25. Zero is linkage equilibrium.

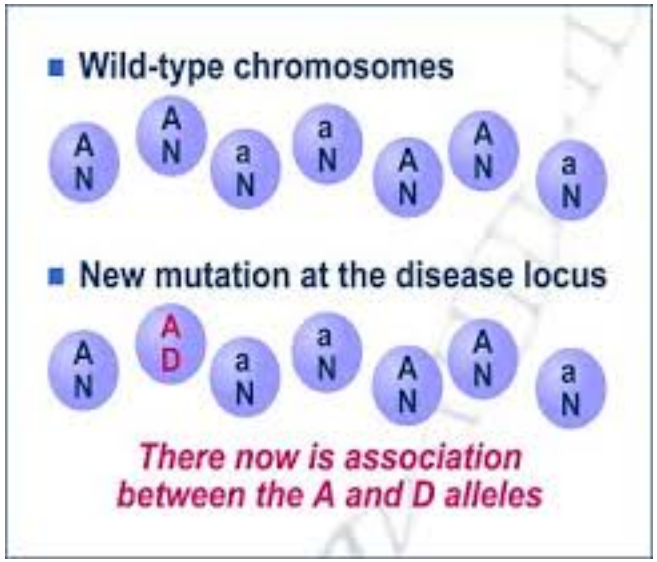
Only two loci with the same allele frequencies can reach -0.25 or +0.25.

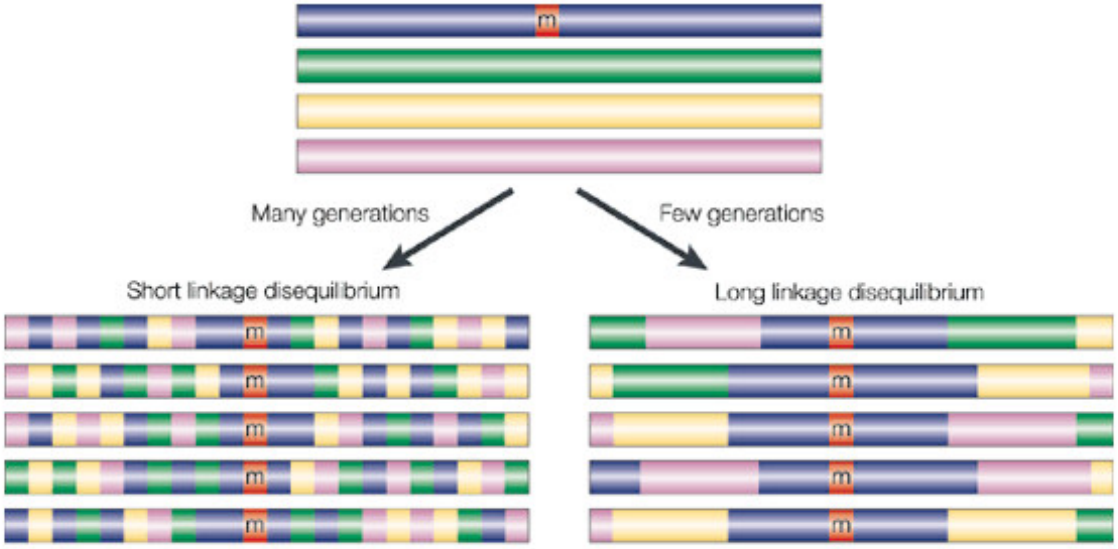
Many papers use a normalized coefficient D' which divides by the maximum disequilibrium possible for those allele frequencies. This is easier to compare among loci.

Disequilibrium

Where does disequilibrium come from?

- Newly arisen mutation
- Mixing of population with different alleles
- Selection for specific combinations
- Drift (usually won't produce very much)


Wild-type chromosomes
A N
A N
a N
a N
A N
A N
a N
New mutation at the disease locus
A N
A D
a N
a N
A N
A N
a N
There now is association between the A and D alleles


m
Many generations
Few generations
Short linkage disequilibrium
Long linkage disequilibrium

Disequilibrium

- Joe Felsenstein showed in 1988 that a key effect of sexual reproduction and recombination is to reduce linkage disequilibrium
- In asexuals, only back mutation and repeated occurance of the same mutation can break down disequilibrium
- In sexuals, chromosome segregation and recombination also break down disequilibrium

A human example

Remember the DuffyO allele from HW1?

- Probably (almost) all current DuffyO descends from 1 copy of chr. 1 3000-5000 years ago
- Without recombination every African would have THAT WHOLE CHROMOSOME
- If anything bad was on it, every African would have that too (or it would have stopped DuffyO from fixing)
- With recombination, Africans share only a few kb on either side of Duffy

Effects of Recombination

- Recombination might break up cooperative groups of alleles
- Bacterial genomes often have related genes close together:
  - To reduce the impact of recombination?
  - To make coordinated regulation easier?
- Eukaryotes have less clustering, but sometimes related genes are still found together.

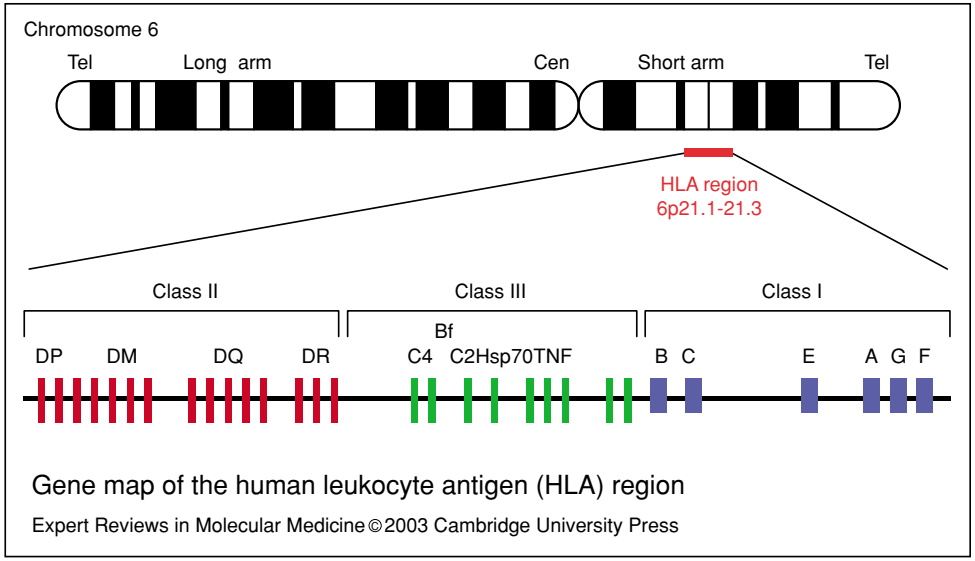
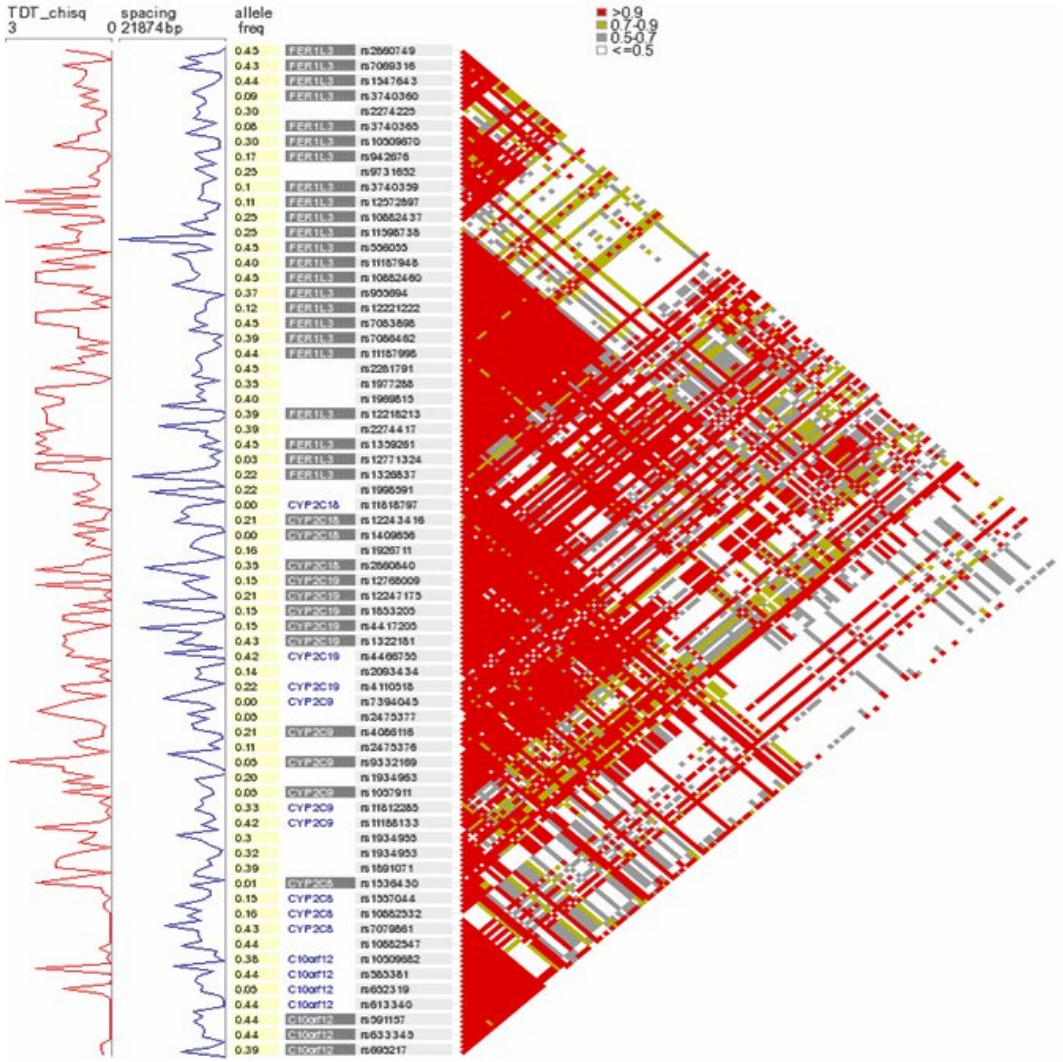


Figure 1. Gene map of the human leukocyte antigen (HLA) region. The HLA region spans 4×10^6 nucleotides on chromosome 6p21.1 to p21.3, with class II, class III and class I genes located from the centromeric (Cen) to the telomeric (Tel) end. HLA class I molecules restrict $CD8^+$ cytotoxic T lymphocyte function and mediate immune responses against 'endogenous' antigens and virally infected targets, whereas HLA class II molecules are involved in the presentation of 'exogenous' antigens to T helper cells. The HLA class III region contains many genes encoding proteins that are unrelated to cell-mediated immunity but that nevertheless modulate or regulate immune responses in some way, including tumour necrosis factor (TNF), heat shock proteins (Hsps) and complement proteins (C2, C4) **(fig001nmn)**.

Gene map of the human leukocyte antigen (HLA) region

Effects of Recombination

- MHC genes tightly linked in many vertebrates
- MHC linkage disequilibrium high in mice and humans, probably elsewhere too
- Is the linkage important or a historical accident?
- Is the LD important or a historical accident?
- (I don't know the answer)



Blocks of LD around cytochrome P450 genes. Walton et al. Nature Genetics 2005.

LD graphs

- Graphs like this plot D' (or the similar statistic r^2) between sites
- In humans, conspicuous blocks of LD are usually seen
- Different ideas about their origin:
  - Recombination hotspots (at edges of blocks)
  - Population admixture followed by a few recombinations
  - Random chance
- I wish we could apply more statistics to this graph!

One-minute responses

- Tear off a half-sheet of paper
- Write one line about the lecture:
  - Was anything unclear?
  - Did anything work particularly well?
  - What could be better?
- Leave in front on your way out