

Selection at Two Loci

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Model with random mating, no selection

x_1	=	frequency of AB -gametes
p_A	=	frequency of A -gametes
p_B	=	frequency of B -gametes
c	=	probability of recombination

Change in frequency of AB -gametes during one generation:

$$x'_1 = x_1 - cD$$

All four gametes, still no selection

Gamete	<i>Recurrence</i>
AB	$x'_1 = x_1 - cD$
Ab	$x'_2 = x_2 + cD$
aB	$x'_3 = x_3 + cD$
ab	$x'_4 = x_4 - cD$

Selection affecting gametes

Gamete		<i>Recurrence</i>
AB	x'_1	$= w_1(x_1 - cD)/\bar{w}$
Ab	x'_2	$= w_2(x_2 + cD)/\bar{w}$
aB	x'_3	$= w_3(x_3 + cD)/\bar{w}$
ab	x'_4	$= w_4(x_4 - cD)/\bar{w}$

where $\bar{w} = \sum x_i w_i$ is mean fitness.

What if selection acts on adults?

The effect of recombination

What gametes are produced by the following genotypes?

Genotype	loci	Heterozygous				Gametes produced			
		AB	Ab	aB	ab				
AB/AB	0		1						
AB/Ab	1		$1/2$	$1/2$					
AB/ab	2	$\frac{1-c}{2}$	$\frac{c}{2}$	$\frac{c}{2}$	$\frac{1-c}{2}$				
Ab/aB	2	$\frac{c}{2}$	$\frac{1-c}{2}$	$\frac{1-c}{2}$	$\frac{c}{2}$				

Only double heterozygotes make recombinant gametes. If these genotypes have low fitness, few recombinants appear.

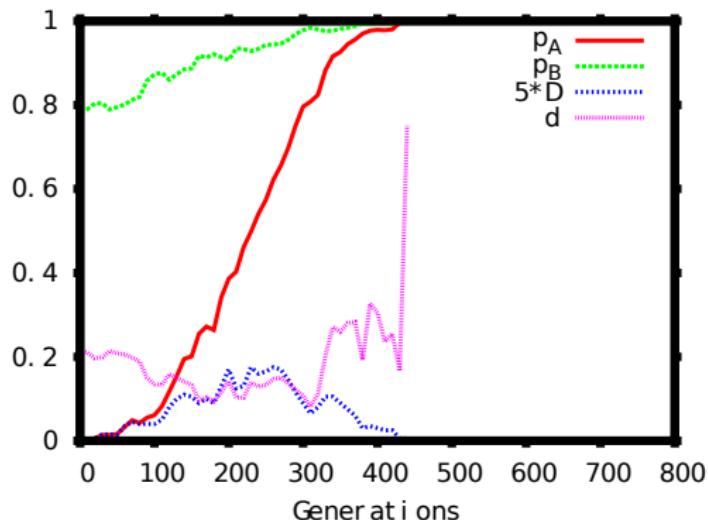
Selection affecting diploid adults

Gamete		Recurrence
AB	x'_1	$\bar{w}_1(x_1 - cw_h D)/\bar{w}$
Ab	x'_2	$\bar{w}_2(x_2 + cw_h D)/\bar{w}$
aB	x'_3	$\bar{w}_3(x_3 + cw_h D)/\bar{w}$
ab	x'_4	$\bar{w}_4(x_4 - cw_h D)/\bar{w}$

- ▶ Fitnesses become \bar{w}_i : weighted mean over genotypes in which gamete i appears.
- ▶ Recombination limited by the fitness (w_h) of double heterozygotes: only these contribute recombinant gametes.
- ▶ Useful as a recipe for calculation.

A sweeps; *B* hitch-hikes

Parameters: $s = 0.02$, $c = 0.001$, $N = 5000$



Selective sweep of allele *A*.

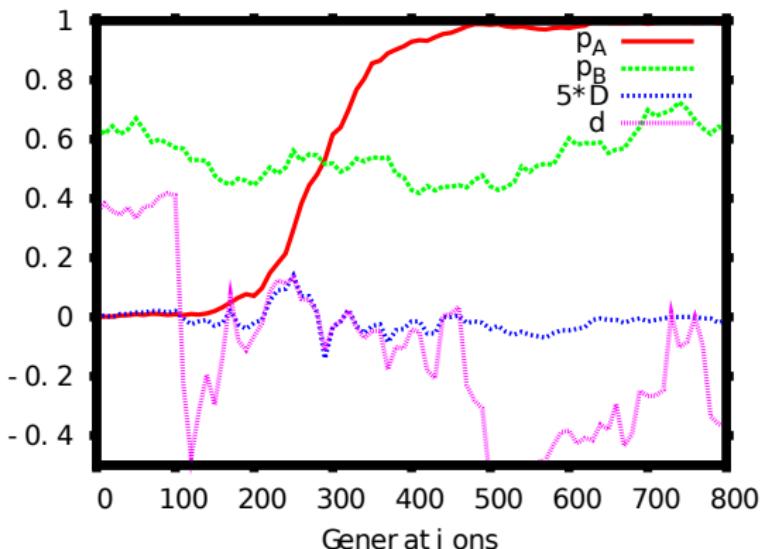
Allele *B* hitch-hikes to fixation.

D high when p_A has high heterozygosity.

d high throughout

Linked allele may fail to increase

Parameters: $s = 0.02$, $c = 0.001$, $N = 5000$

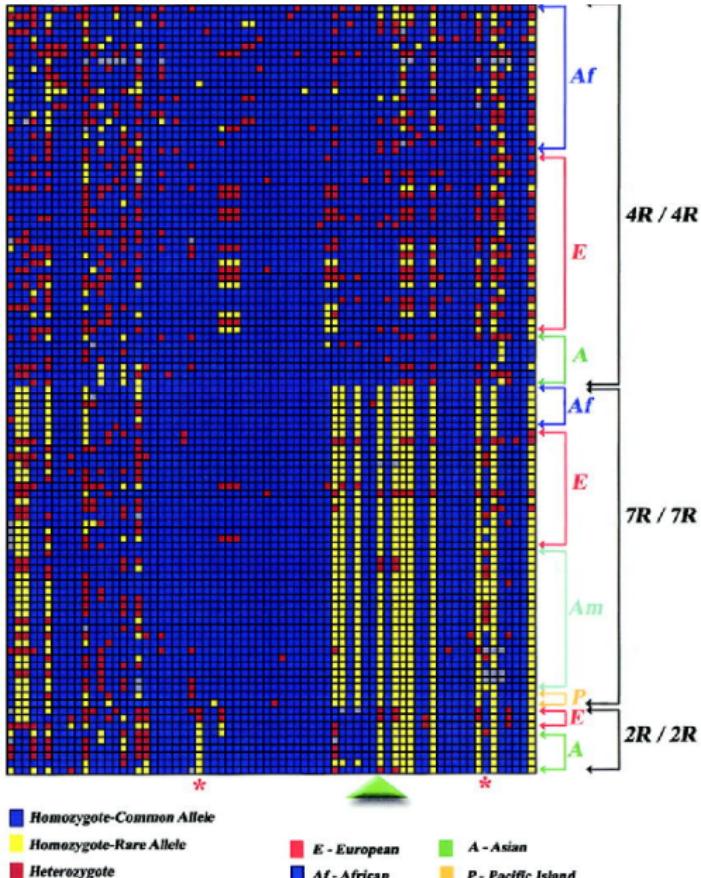


Allele A sweeps to fixation.

Little change in linked allele. Why?

LD lost early on this run, so D near 0.

Loss of LD shows as big drop in d .



- ▶ LD at D4 dopamine receptor
- ▶ Rows are diploid genotypes
- ▶ Blue: common homozygote
- ▶ Yellow: rare homozygote
- ▶ Red: heterozygote
- ▶ Note LD w/i 7R genotypes

█ Homozygote-Common Allele
█ Homozygote-Rare Allele
█ Heterozygote
█ Undetermined

█ E - European █ A - Asian
█ Af - African █ P - Pacific Island
█ Am - North and South American

DNA sequences from region of human lactase gene

cgcttcaggcatttatctaaacagaccaacgtAgggtacaatgcctaaccagacgttcaactct
20
21
22
23
24
25
26
27t.....
28t.....
29c.....
37G..a.gt.....t.....gac.c.tgtct.
38 ...ccgga....gat..at..gg..c.....tc.gGaaa.g..ccttt..tg.....c..t.t...
39 ...ccgga....gat..at..gg..c.....tc.gGaaa.g..ccttt..tg.....c..t.t...
40 ..tcc...agtag.t.cat..g.....t..ttccgG..a.gt.....t.....gac.c.tgtct.
41 ..tcc...agtag.t.cat..g.....t.gttccgG..a.gt.....t.....gac.c.tgtct.
42 ..tcc...agtag.t.cat..g.....t.gttccgG..a.gt.....t.....gac.c.tgtct.
43 ..tcc...agtag.t.cat..g.....t.g.tc.gG..a.gt.....t.....gac.c.tgtct.
44 ..tcc...agtag.t.cat..g.....t.ttc.gG..acgt.....t.....gac.c.tgtct.
45 ..tcc...agtag.t.cat..g.....t.gtcc.gG..a.gt.....t.....gac.c.tgtct.
46 ...ccgga....gat..at..gg..c.....tc.gGaaa.g..ccttt..tg.....cg.gt.t..c
47 ..tcc...agtag.t.cat..g.....t.gttccgG..a.gt.....t.....gac.c.tgtct.
48 ..tcc...agtag.t.cat..g.....t.gttccgG..a.gt.....t.....gac.c.tgtct.
49 ..tcc...agtag.t.cat..g.....t.gtccgG..a.gt.....t.....gac.c.tgtct.
50 tatccgga....g.tc.atcgg.tc.g.tg.tc.gG..a.g.g....tg....ggt....cg.gt.t..c
51 ta.ccggta....g.t..atcgg.tc.g.tg.tc.gG..a.g.g....tg....ggt....cg.gt.t..c
52 ta.ccggta....g.t..atc.g.tc.g.tg.tc.gG..a.g.g....tg....ggt....cg.gt.t..c
53 ta.ccggta....g.t..atcgg.tc.g.tg.tc.gG..a.g.g....tg....ggt....cg.gt.t..c

Why LD Helps Us Find Selective Sweeps

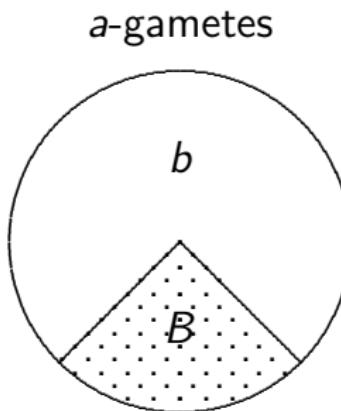
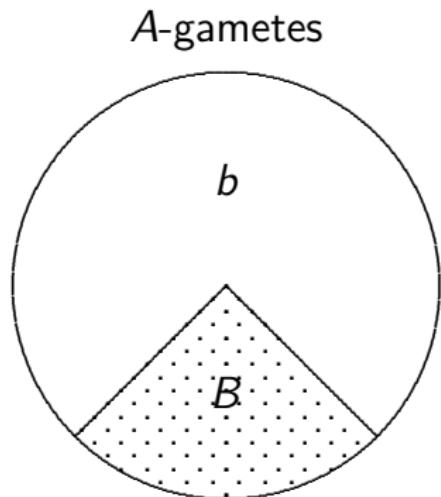
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LD helps us detect ongoing selective sweeps

This is curious, because we have known for over 50 years that selection at a single locus does not cause LD (Felsenstein 1965).

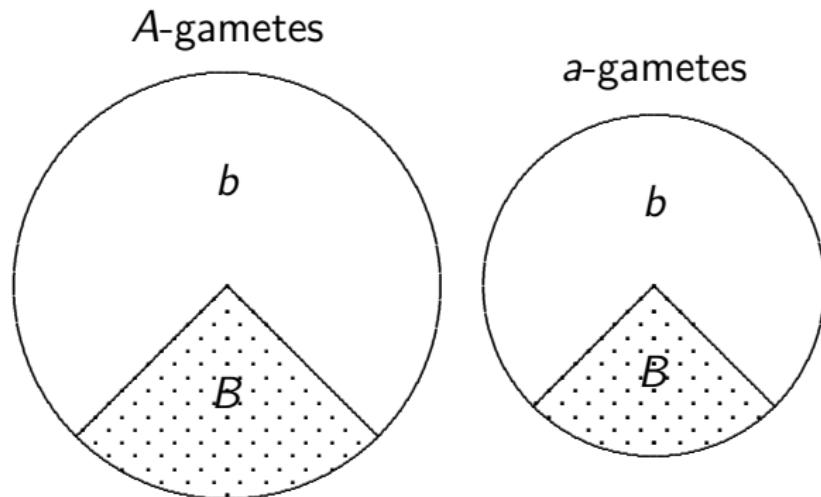
Linkage equilibrium \iff shaded fractions equal



LE: Neither locus predicts other

Here, B is equally common among a -gametes and A -gametes.

Suppose allele A is favored; B/b are neutral



Selection inflates left circle.

Shrinks right one.

Shaded wedges unchanged.

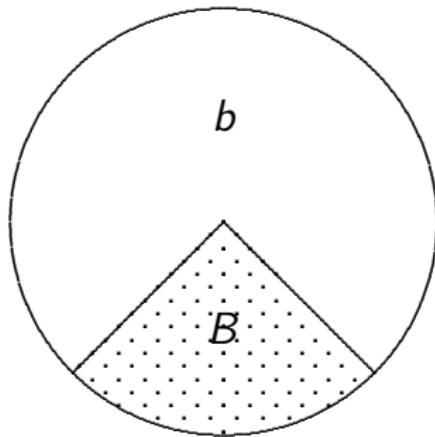
System remains in LE.

Notation for gamete frequencies

Gamete type	AB	Ab	aB	ab
Frequency	x_1	x_2	x_3	x_4

Conditional allele frequencies

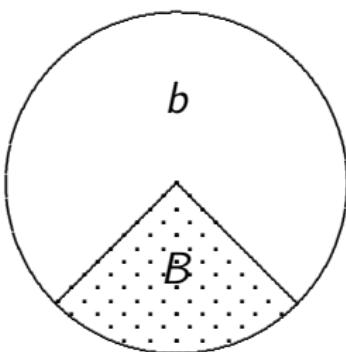
A-gametes



Freq of *B* among *A*-gametes

$$p_{B|A} = \frac{x_1}{x_1 + x_2}$$

a-gametes



Freq of *B* among *a*-gametes

$$p_{B|a} = \frac{x_3}{x_3 + x_4}$$

Selection on *A/a* affects neither.

The Nei-Li measure of linkage disequilibrium, d

$$d = p_{B|A} - p_{B|a}$$

Difference in frequency of B between A - and a -gametes.

Selection on A/a affects neither $p_{B|A}$, $p_{B|a}$, nor d .

(Nei & Li, 1980)

Linkage disequilibrium: calculating D and d

Gamete	Locus	
	1	2
1	A	B
2	A	B
3	A	B
4	A	B
5	A	B
6	A	b
7	a	B
8	a	B
9	a	b
10	a	b

B	A	a	
	5	2	7
b	1	2	3
	6	4	10

$$D = \frac{5}{10} \cdot \frac{2}{10} - \frac{1}{10} \cdot \frac{2}{10} = \frac{2}{25}$$

$$d = p_{B|A} - p_{B|a} = \frac{5}{6} - \frac{1}{2} = \frac{1}{3}$$

D depends on heterozygosity at locus A .

$$\begin{aligned}d &= \frac{x_1}{x_1 + x_2} - \frac{x_3}{x_3 + x_4} \\&= \frac{D}{p_A(1 - p_A)}\end{aligned}$$

$$D = dp_A(1 - p_A)$$

Selection at locus A affects $p_A(1 - p_A)$ and therefore D .

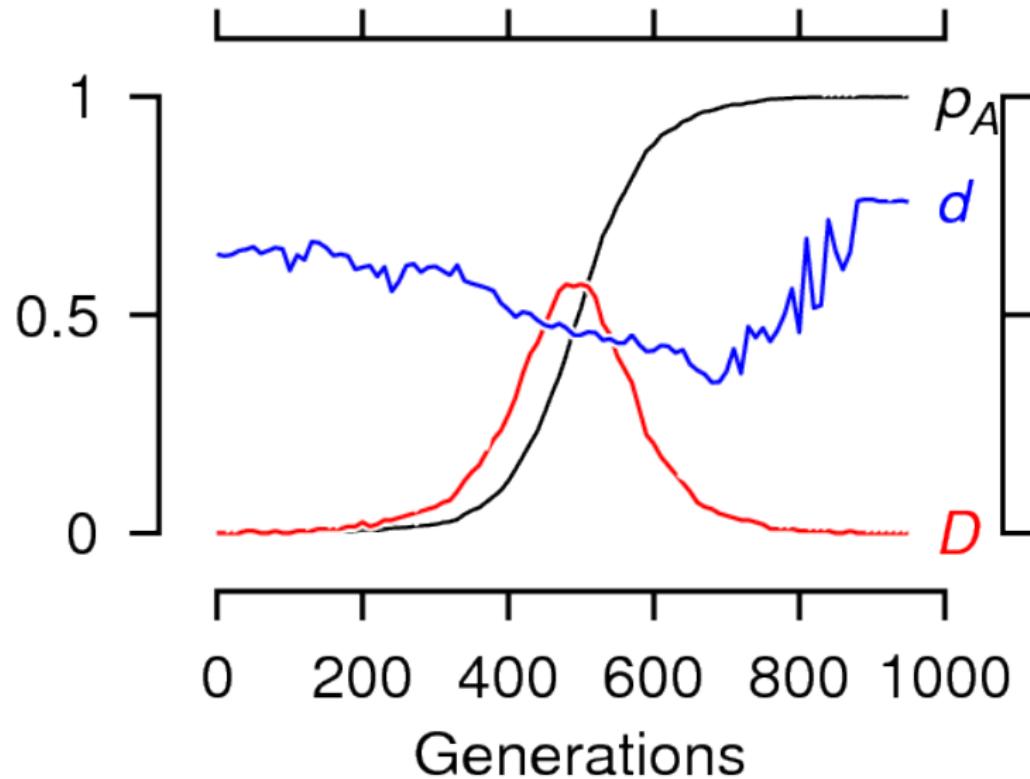
LD of a new mutant

When allele A first arises by mutation, it will be rare, so $p_A(1 - p_A) \approx 0$ and $D \approx 0$.

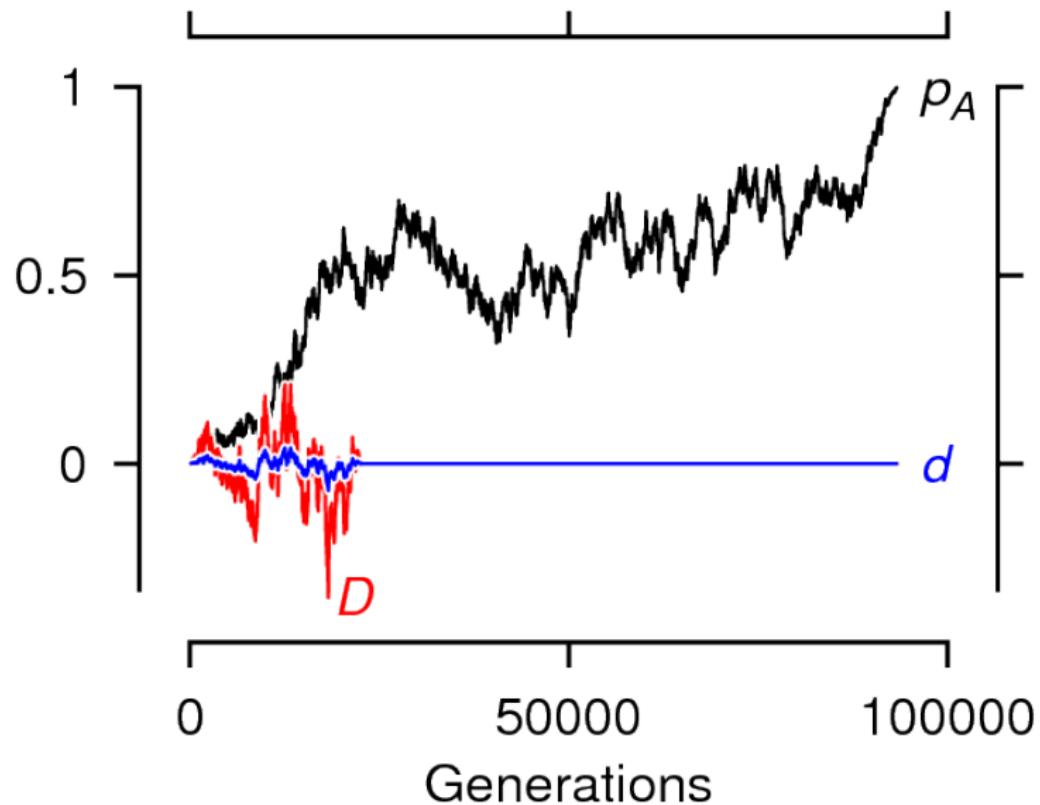
But d may be large: it is either $1 - p_B$ or $-p_B$, depending on whether the mutant gamete is AB or Ab .

The value of d stays large if selection outruns recombination and drift.

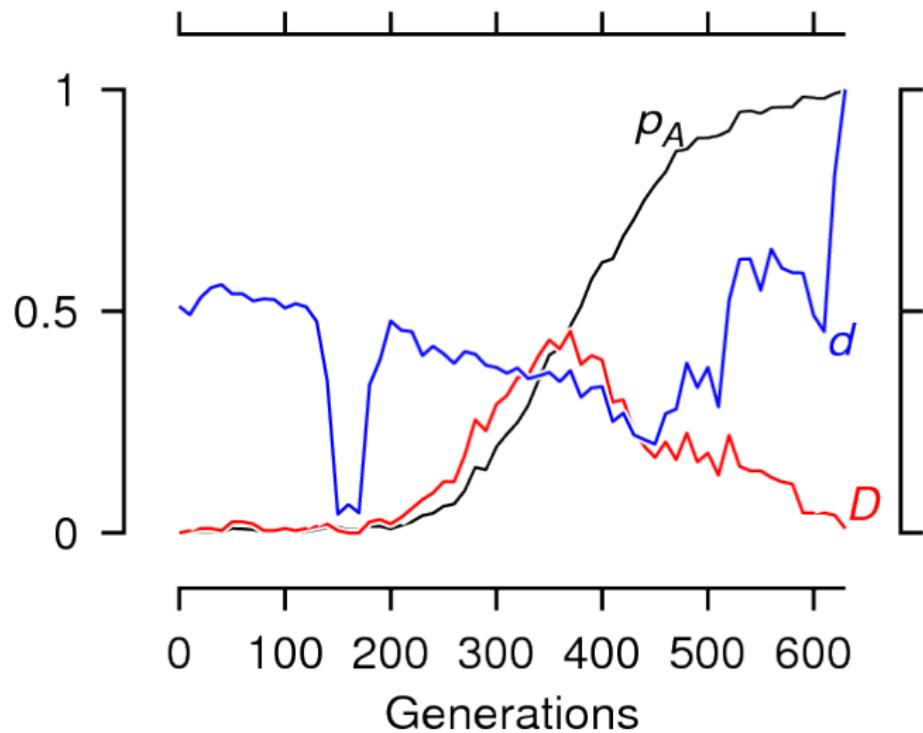
Selective sweep of A , with $s = 0.02$, $c = 0.001$, and
 $2N = 50,000$



Neutral drift to fixation, $c = 0.001$, and $2N = 50,000$



Selective sweep in small population ($s = 0.02$, $c = 0.001$, $2N = 5,000$)



Summary

- ▶ LD decays gradually in response to recombination.
- ▶ This is more obvious for d than for D , because d is insensitive to p_A .
- ▶ Advantageous alleles increase rapidly: there is little time for LD to decay.
- ▶ Neutral alleles increase slowly; plenty of time for LD to decay.