Ask your questions here!

Theory & background 1

This is for general discussion about theory (e.g., population genetics), history of genetics and behavioral genetics, and programming (e.g., UNIX, R).

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International Statistical Genetics Workshop • Boulder, Colorado • IBG

Population Genetics Theory is concerned with characterizing and quantifying **genetic variation** within and between **populations**.

What is a Population?

“All inhabitants of particular place” – Oxford dictionary

[BIOLOGY] – “A community of animals, plants, or humans among whose members interbreeding occurs” – Oxford dictionary

“Any complete group with at least one characteristic in common” – Australian Bureau of Statistics

“All the inhabitants of a country, territory, or geographic area, total or for a given sex and/or age group, at a specific point of time. In demographic terms it is the total number of inhabitants of a given sex and/or age group that actually live within the border limits of the country, territory, or geographic area at a specific point of time, usually mid-year. The mid-year population refers to the actual population at July 1st.” – World Health Organization

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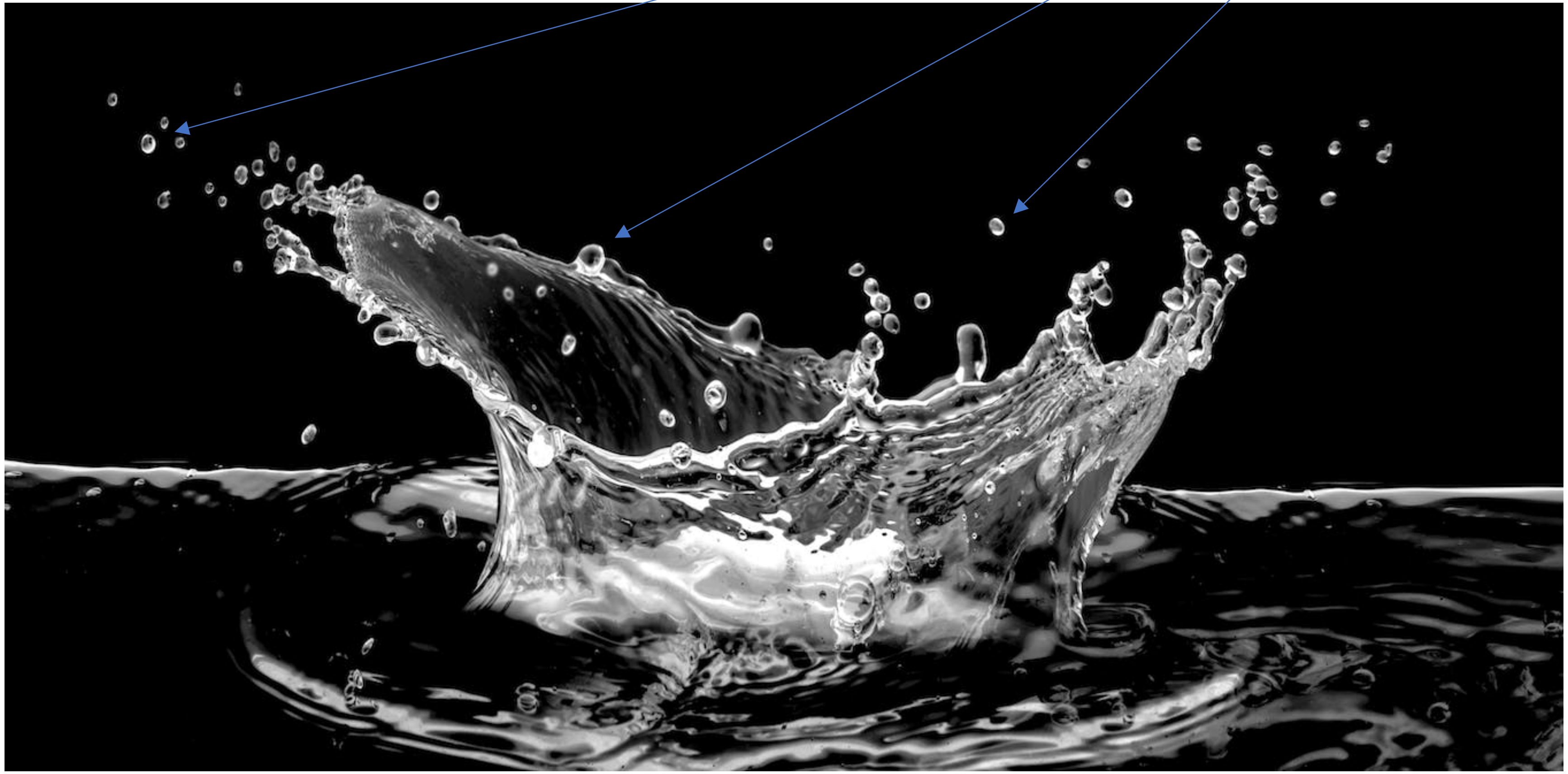
Source: https://www.shutterstock.com/image-photo/water-splashwater-splash-isolated-on-backgroundwater-573666874?src=sv-vkrkfiyUnpA-vYq4Oog-1-16

A population is a concrete abstraction…

1. Population = Group of individuals
2. Who is *inside* or *outside* is arbitrary, i.e., depends on your research question

Are these drops from the same population?



Time

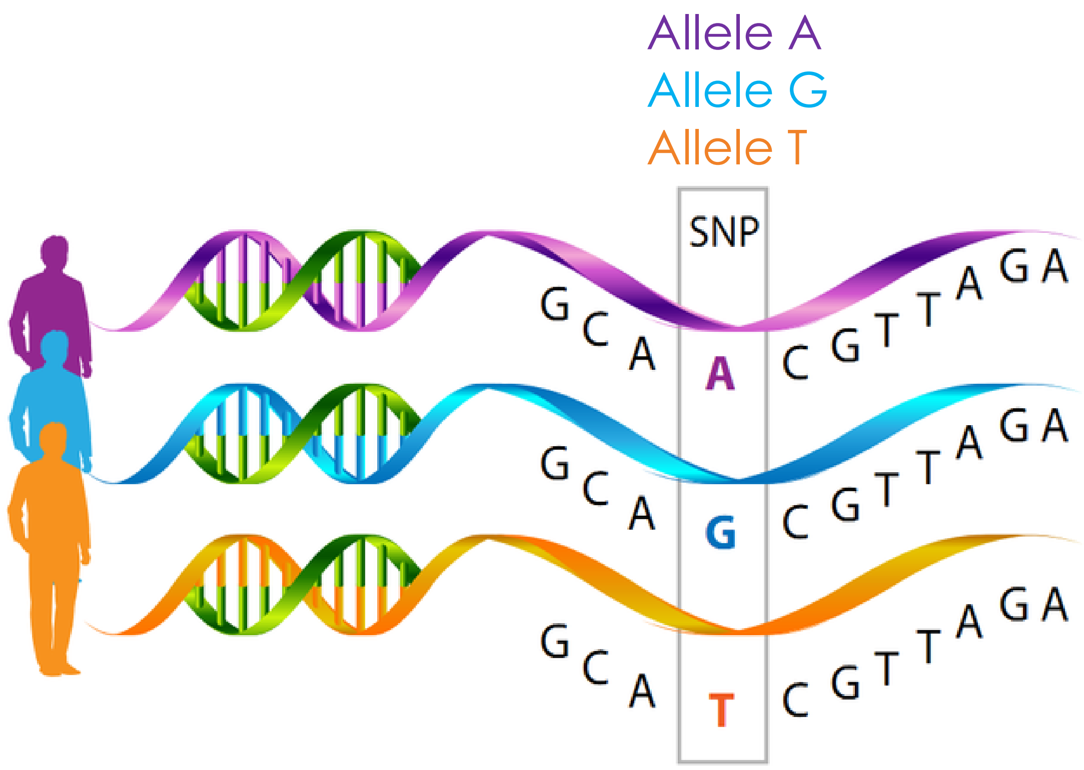
Space

What is Genetic Variation?

Genetic variation…

There is a near infinite number of ways to measure a distance between DNA sequences of two individuals

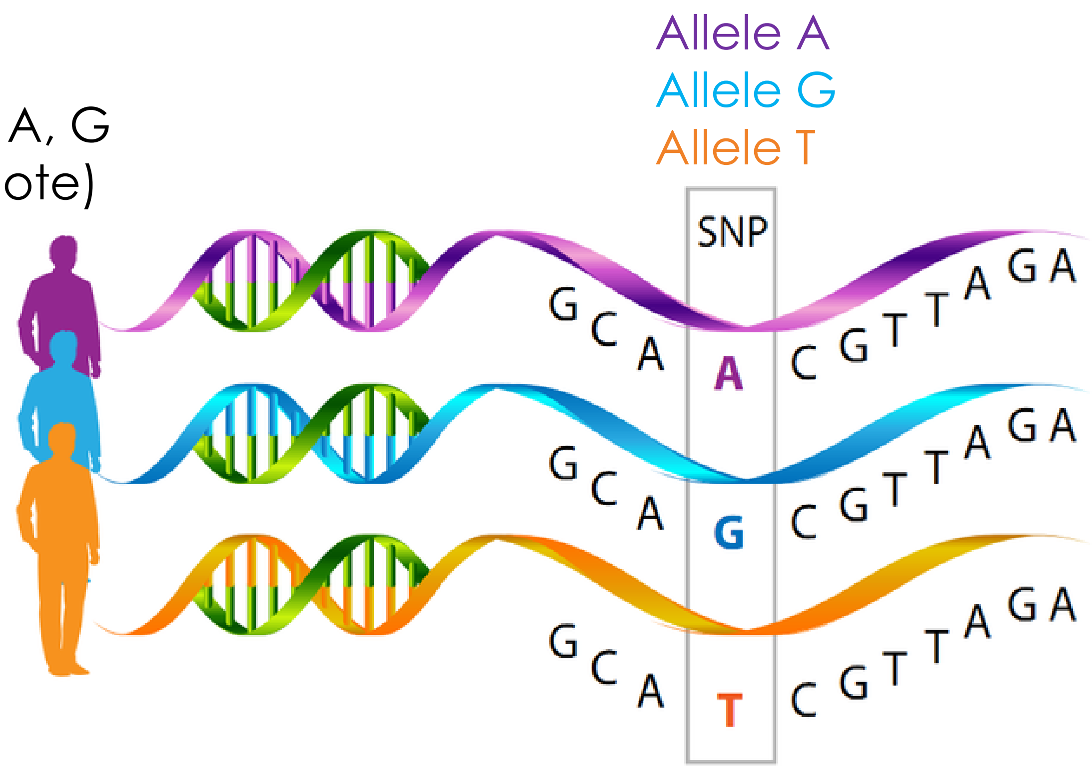
(1) Number of repeats
(2) Inversions
(3) Deletions
(4) Single letter (nucleotide) changes
(5) …



Single Nucleotide Polymorphisms

Definitions
Allele = possible state of the DNA sequence at a given locus.
Genotype = defined by the states of all alleles at the locus.

<u>Examples</u>: In a diploid individual. If there are three alleles A, G and T, then possible genotypes are AA, GG, TT (homozygote) and AG, AT, GT (heterozygote)



Single Nucleotide Polymorphisms

Population Genetics Theory is the theory of **alleles and genotypes frequencies** within and between **groups of individuals**.

Outline

- Hardy-Weinberg Equilibrium
- What drives changes in allele/genotype frequencies?
- How can you measure genetic distance between populations?
- Linkage Disequilibrium

Learn more: **https://www.colorado.edu/ibg/isg-workshop/isgw-online-resources/2-introduction-population-genetics**

Hardy-Weinberg Equilibrium

G. H. Hardy (1877 – 1947)
W. Weinberg (1862 - 1937)

Relationship between alleles and genotypes frequencies

Let's consider a population of N diploid individuals at a particular locus with two alleles 0 and 1.

We denote n_{00}, n_{01} and n_{11} the genotypes counts and n_0 and n_1 the allele counts in the population. So, $n_{00} + n_{01} + n_{11} = N$.

We have the following relationships:

=> $n_0 = 2n_{00} + n_{01}$ and $n_1 = 2n_{11} + n_{01}$.

=> $p_0 = n_0 /(2N) = (n_{00} /N) + 0.5(n_{01} /N)$ and $p_1 = 1- p_0$.

$\Rightarrow$ $p_0 = p_{00} + 0.5p_{01}$ and $p_1 = 1- p_0$.

In general, we can not predict the genotype frequencies from the allele frequencies (under-determined).

If genotypes and alleles frequencies are **constant from one generation to the next**, then the population is said to be under Hardy-Weinberg Equilibrium.

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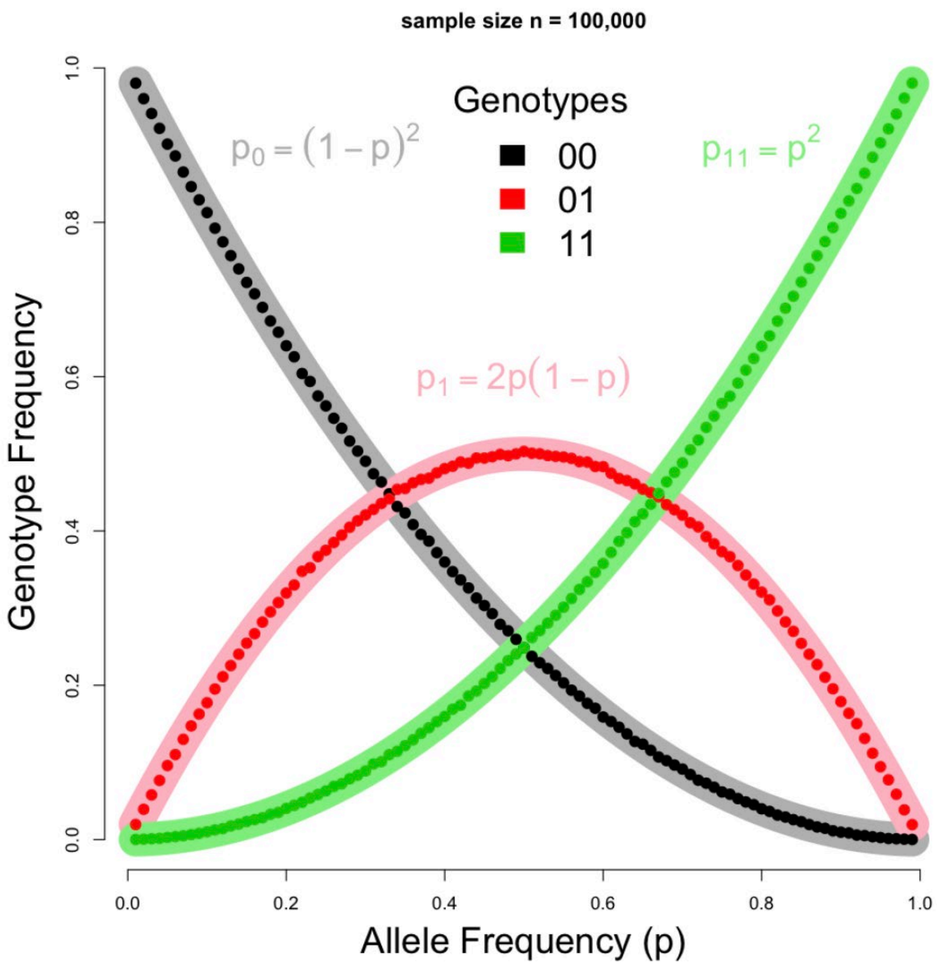


*This is the diploid / autosomal version of the HWE.

Under which assumption(s) does HWE holds?

Constant allele frequency:

- no migration,
- no mutation,
- no natural selection

Random mating (diploid individuals, sexual reproduction, allele frequencies are the same between sexes)

Large population size

Testing HWE (1/3)

Deviation from HWE can be detected using a χ^2 test with 1 degree of freedom.

Example: Diploid population with the following genotypes counts

Observed			
AA	AB	BB	N_{total}
125	225	150	500

$p_A = (2 \times 125 + 225)/(2 \times 500) = 0.475 \implies p_B = 0.525.$

$p_{AA} = 125/500 = 0.25$, $p_{AB} = 225/500 = 0.45$ and $p_{BB} = 150/500 = 0.3$.

Expectation under HWE: $E[n_{AA}] = p_A^2 \times N_{total} = 112.8125.$

Testing HWE (2/3)

Observed AA	AB	BB	N_{total}	Expected E[AA]	E[AB]	E[BB]
125	225	150	500	112.8	249.4	137.8

Test Statistic

$$\chi^2 = \frac{(125 - 112.8)^2}{112.8} + \frac{(225 - 249.4)^2}{249.4} + \frac{(150 - 137.8)^2}{137.8}$$
$$= 4.78 > 3.84.$$

This example illustrates a **significant** deviation from HWE.

Testing HWE (3/3)

General form of the test statistic

$$\chi^2 = \frac{(n_{AA} - E[n_{AA}])^2}{E[n_{AA}]} + \frac{(n_{AB} - E[n_{AB}])^2}{E[n_{AB}]} + \frac{(n_{BB} - E[n_{BB}])^2}{E[n_{BB}]} \tag{1}$$

$$\begin{aligned} E[n_{AA}] &= N_{total} \times p_A^2 \\ E[n_{AB}] &= N_{total} \times 2p_A p_B \\ E[n_{BB}] &= N_{total} \times p_B^2. \end{aligned}$$

with

$p_A = (2n_{AA} + n_{AB})/(2N_{total})$ and $p_B = 1 - p_A$.

Summary

- Population can be characterized by the frequency distribution of alleles and genotypes
- Under certain assumptions, genotype frequencies can be predicted from allele frequencies (Hardy-Weinberg Equilibrium)
- HWE can be extended to sex-linked loci and polyploid individuals
- Deviation from HWE can be used to inform non-random mating (e.g., inbreeding), population history or quality of genetic data (see GWAS lectures)

Changes of Allele and Genotype Frequencies

Main evolutionary forces

1. Mutation / Migration: new alleles in the population

2. Natural selection (fitness)

3. Genetic drift (Wright-Fisher’s model of neutral evolution)

4. Demography: bottleneck / expansion

Main evolutionary forces affecting allele frequencies

1. Mutation / Migration: new alleles in the population

2. Natural selection (fitness)

3. Genetic drift (Wright-Fisher's model of neutral evolution)

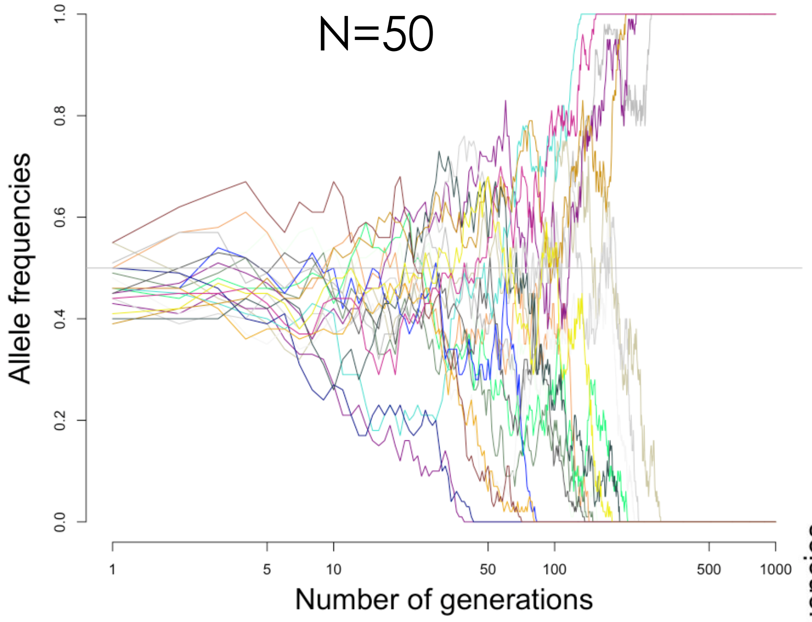
4. Demography: bottleneck / expansion

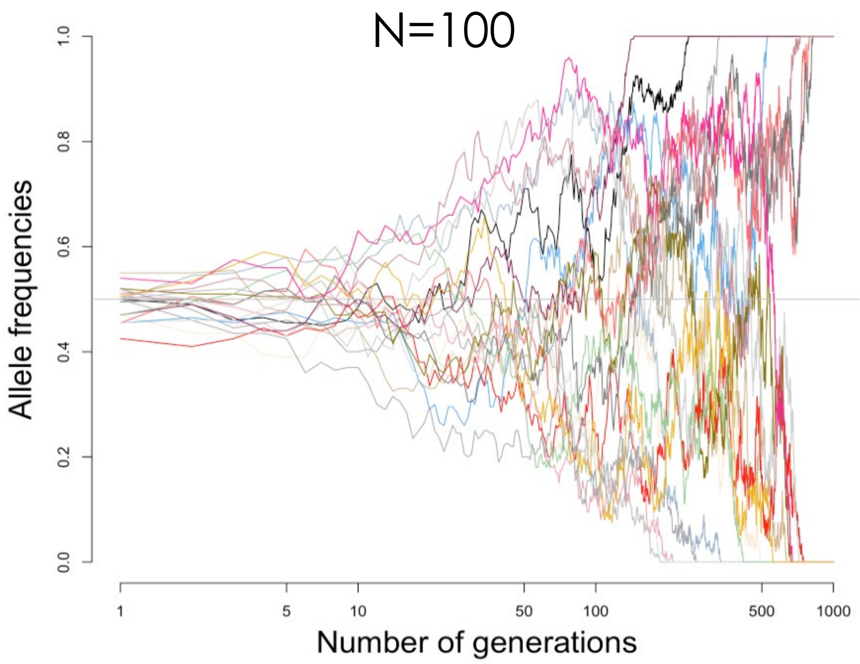
Wright-Fisher's model

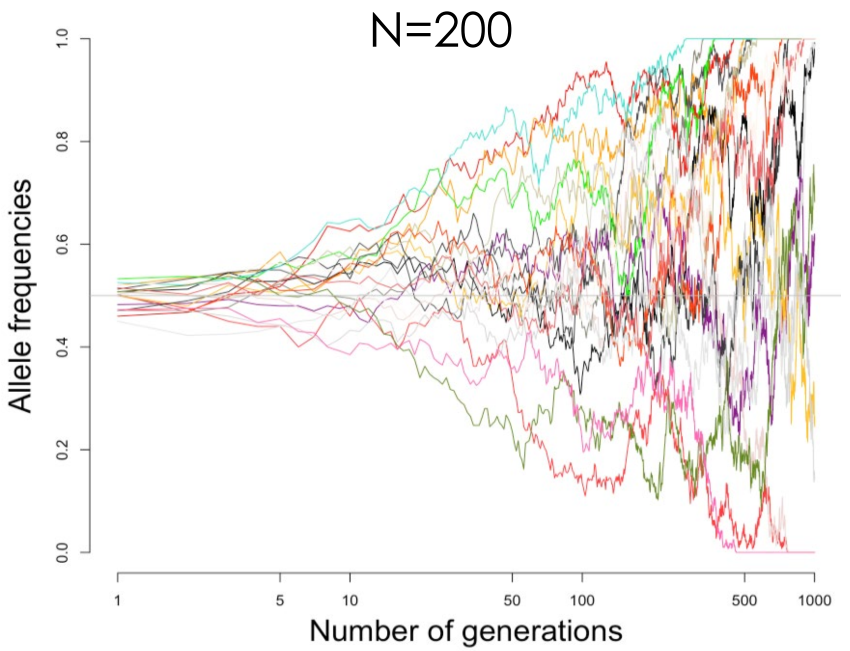
Let us consider a population of 2N individuals (N males and N females). At each generation we randomly form N pairs of mates. Each pair to generate 2 progenies.

How do allele frequencies change over time in that population?

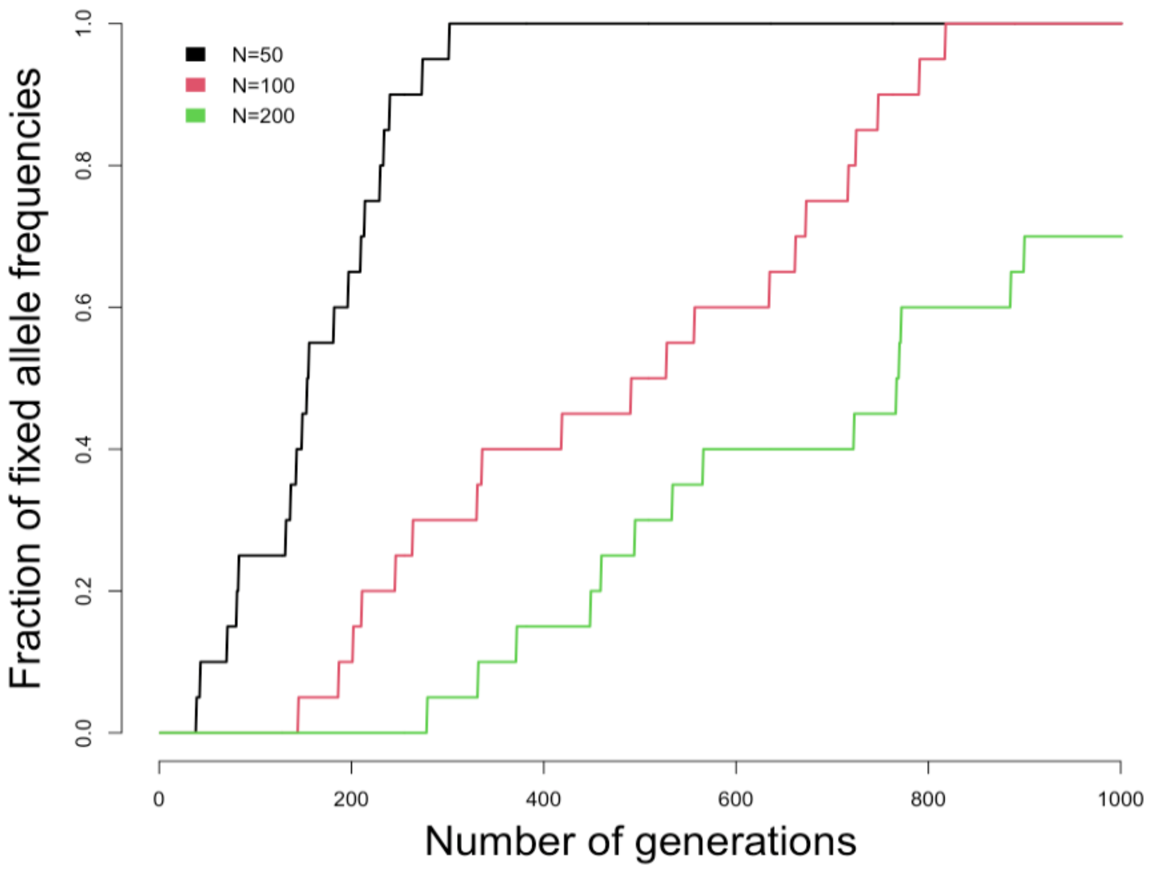
Let's run some simulations…


N=50
Allele frequencies
0.0
0.2
0.4
0.6
0.8
1.0
1
5
10
50
100
500
1000
Number of generations


N=100
Allele frequencies
0.0
0.2
0.4
0.6
0.8
1.0
1
5
10
50
100
500
1000
Number of generations


N=200
Allele frequencies
0.0
0.2
0.4
0.6
0.8
1.0
1
5
10
50
100
500
1000
Number of generations

Time to fixation or fixation rate depends on
(1) Effective population size
(2) Allele frequency

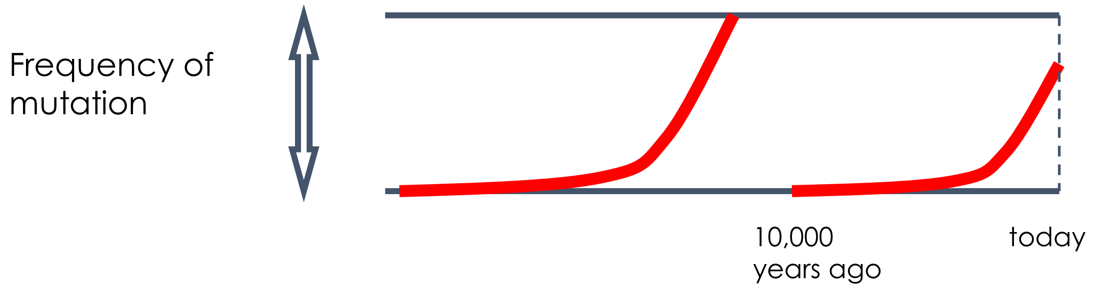


Formulas available in textbooks (e.g., Crow & Kimura (1970))

50 shades of natural selection…

Negative (purifying) selection: deleterious alleles are maintained at low frequencies

Positive selection: advantage allele rises at high frequencies (adaptation to high altitude)



Balancing/Stabilizing selection tries to maintain an optimum value in the population (e.g., birthweight)

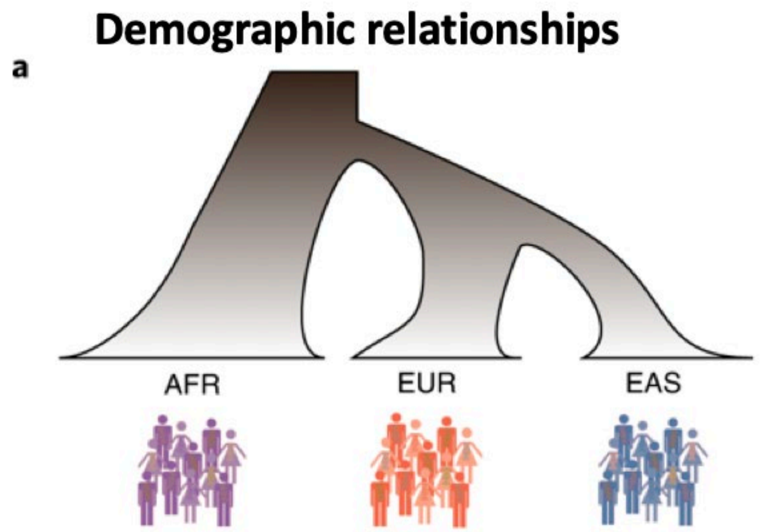
Recommended: Walsh & Lynch, 2018

Summary and other considerations

- Genetic drift, selection, migration, mutation can change allele (and genotype) frequencies
- Non-random mating (e.g., inbreeding) can increase homozygosity and change genotype frequencies.
- Strength of selection and degree of dominance is required to predict how selection will change genotype frequencies
- Drift can dominate selection sometimes: $s<1/(2Ne)$

Wright's Fixation Index (F_{ST})

Population structure = frequency differences between populations



Martin et. al., *Nature Genetics*, 2019

Ancestral population

p_0

p_1

Derived population 1

p_2

Derived population 2

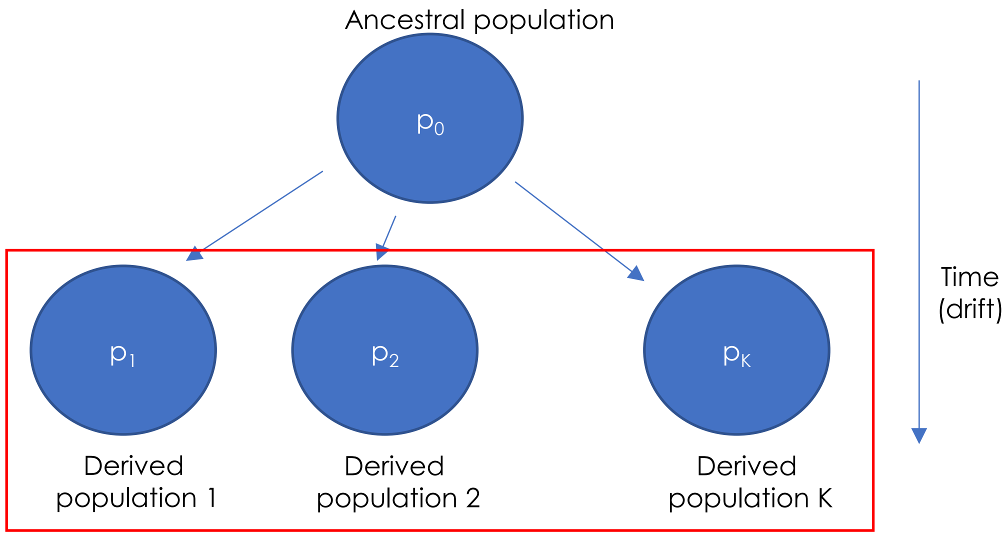
p_K

Derived population K

Time (drift)

Many definitions and many estimators

- F_{ST} as a ratio of variance (Wright):
  $F_{ST}=var_B(X)/[var_B(X)+var_W(X)]$; $X=0,1$ (allelic state)
  $F_{ST}=0$: no frequency differences between populations
  $F_{ST}=> 1$: allele is fixed in one population (fixation index)



Estimators
Weir & Cochram (1984)
Nei (1973)
Hudson (1992)

Weir & Hill (2002) definition
$$\mathbf{var(p_i|p_0) = F_{ST}\, p_0\, (1-p_0)}$$

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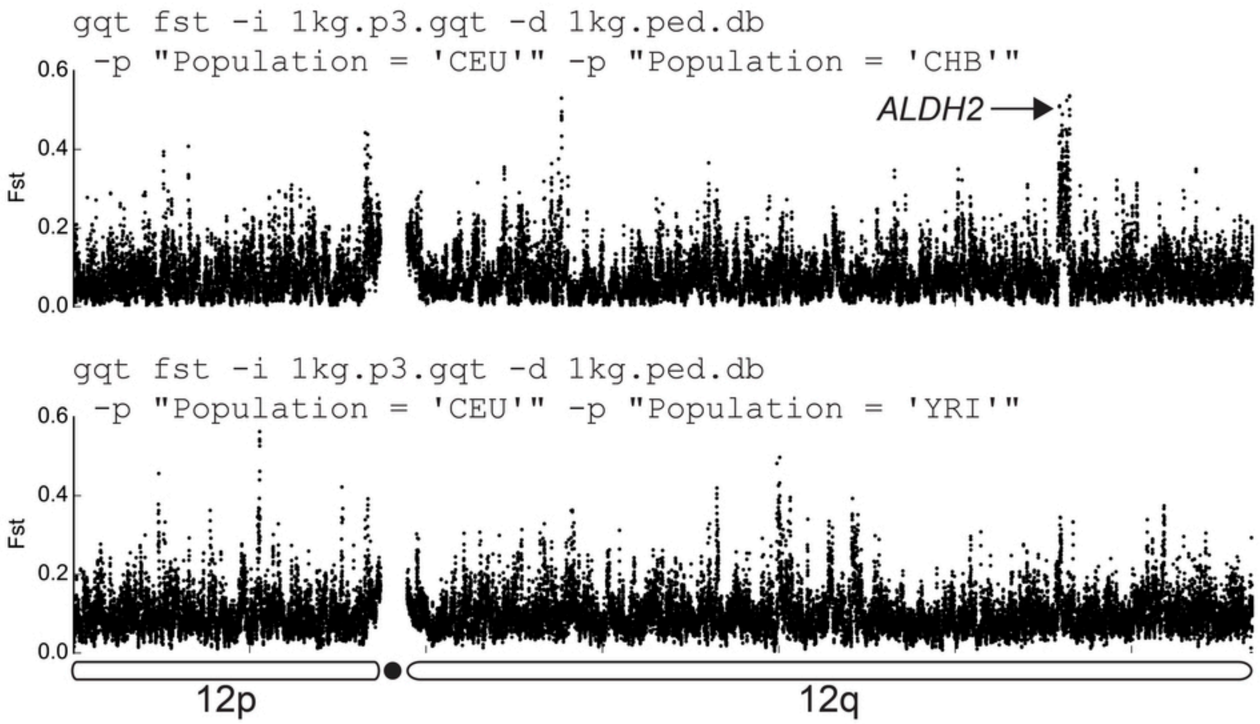
Genome Res. 2013 Sep; 23(9): 1514–1521.
doi: 10.1101/gr.154831.113
PMCID: PMC3759727
PMID: 23861382

Estimating and interpreting F_{ST}: The impact of rare variants

Gaurav Bhatia,[1,2,6,7] Nick Patterson,[2,6,7] Sriram Sankararaman,[2,3] and Alkes L. Price[2,4,5,7]

F_{ST} varies across the genome => *not just drift at play here!*



Layer R.M. et al. Efficient genotype compression and analysis of large genetic-variation data sets. *Nature Methods* (2016).

Typical F_{ST} ranges

F_{ST} is ~0.1- 0.2 between continental groups

F_{ST} is ~0.01- 0.05 within continental groups

F_{ST} is <0.01within countries

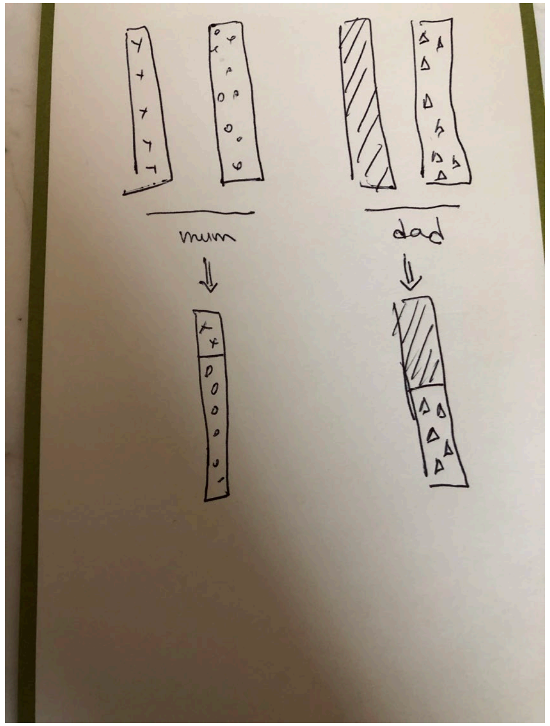
Let's play again…

Practical Part 2

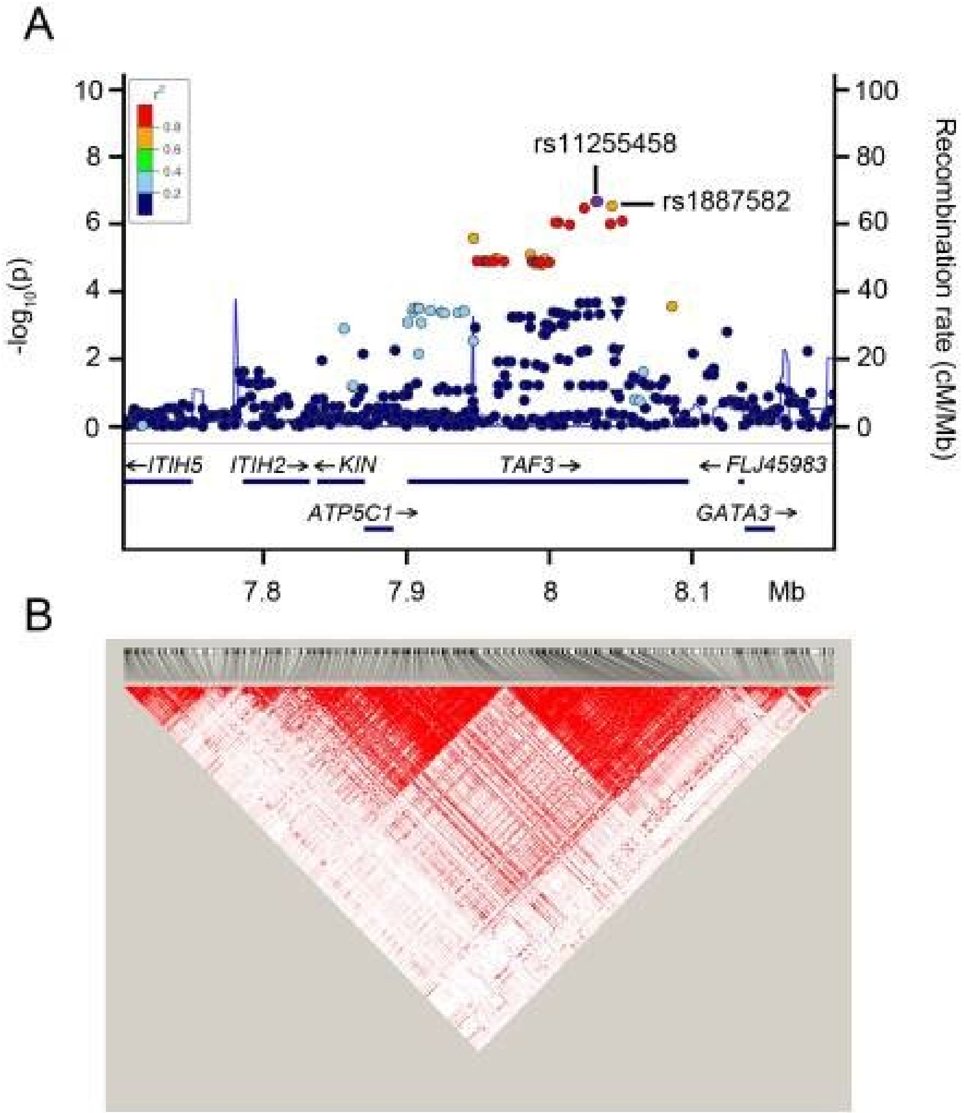
Linkage Disequilibrium

Meoisis and genetic linkage

- In sexual reproduction gametes are produced during specialized cell division called meiosis.
- Meiosis involves multiple phases prophase, meiosis I and II) in which genetic information is exchanged between homologous chromosomes: recombination.
- Recombinant chromosomes are then transmitted to the offspring.
- => Close DNA sequences on a chromosome will tend to be transmitted together: linkage disequilibrium (LD).

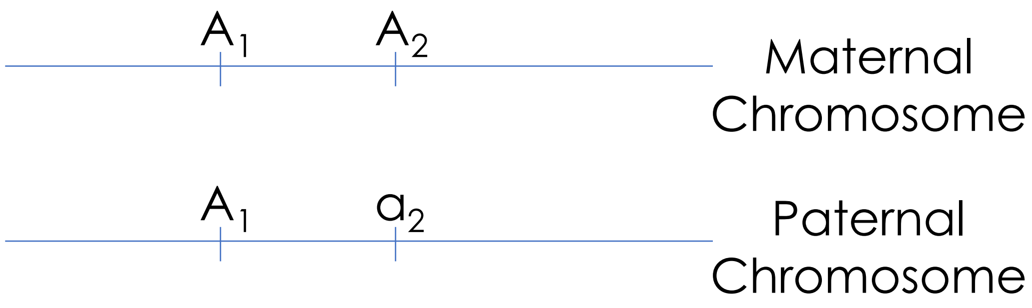


Haplotype



Pistis et al. (2013) Plos One

Haplotype = Group of variants within a chromosome (e.g., within a LD block)



Statistical measures of linkage disequilibrium (1/3)

Let us consider two loci j and k with alleles $a_j\,/\,A_j$ and $a_k\,/\,A_k$.

Linkage disequilibrium between alleles a_j and A_k (for example) is often measured as using the coefficient $D(a_j, A_k)$

$$D(a_j, A_k) = p(a_j A_k) - p(a_j)p(A_k)$$

where $p(a_j A_k)$ is the proportion of individuals in the population with both alleles a_j and A_k; and $p(a_j)$ and $p(A_k)$ the proportion of individuals with allele a_j and A_k respectively.

Statistical measures of linkage disequilibrium (2/3)

	a_j	A_j	
a_k	$p_j p_k + D_{jk}$	$(1 - p_j)p_k - D_{jk}$	p_k
A_k	$(1 - p_k)p_j - D_{jk}$	$(1 - p_j)(1 - p_k) + D_{jk}$	$(1 - p_k)$
	p_j	$(1 - p_j)$	1

Table: Joint distribution of allele frequencies, as a function of the linkage disequilibrium parameter D_{jk}. a_j and a_k are the minor alleles at locus j and k, and A_j and A_k the corresponding major alleles respectively.

$D_{jk} > 0$ (positive LD) $\Longrightarrow$ alleles a_j and a_k or A_j and A_k are often "transmitted" (observed) together.

Statistical measures of linkage disequilibrium (3/3)

Common measures of linkage disequilibrium (LD) are D'_{jk}

$$D'_{jk} = D_{jk} \,/\, D_{max} \tag{2}$$

and the squared correlation r_{jk} between allele counts

$$r^2_{jk} = \frac{D^2_{jk}}{p_j(1 - p_j)p_k(1 - p_k)} \tag{3}$$

where

$$D_{max} = \begin{cases} min\left(p_j p_k, (1 - p_j)(1 - p_k)\right) & \text{when } D_{jk} < 0 \\ min\left(p_j(1 - p_k), (1 - p_j)p_k\right) & \text{when } D_{jk} > 0 \end{cases}$$

D' takes values between -1 and 1 and r^2 between 0 and 1.
LD depends on alleles frequencies and population size.

LD calculations (1/2)

Allele counts	a_j	A_j	Total
a_k	1000	1500	2500
A_k	1500	1000	2500
	2500	2500	5000

$p(a_j) = 0.5$, $p(a_k) = 0.5$, $p(a_j a_k) = 1000/5000 = 0.2$.

$D(a_j, a_k) = p(a_j a_k) - p(a_j)p(a_k) = 0.2 - 0.25 = -0.05$.

$D(a_j, A_k) = D(a_k, A_j) = 0.3 - 0.25 = +0.05$ and
$D(A_j, A_k) = -0.05$.

$$\Longrightarrow r^2(a_j, a_k) = r^2(A_j, A_k) = r^2(a_j, A_k) = r^2(A_j, a_k) = \frac{0.05^2}{0.5^4} = 0.04.$$

LD calculations (2/2)

Allele frequency	a_j	A_j	
a_k	$p(a_j a_k)$	$p(A_j a_k)$	$p(a_k)$
A_k	$p(a_j A_k)$	$p(A_j A_k)$	$p(A_k)$
	$p(a_j)$	$p(A_j)$	1

$$D(a_j, a_k) = p(a_j a_k)p(A_j A_k) - p(A_j a_k)p(a_j A_k) \tag{4}$$

$D(a_j, a_k)$ is the determinant of the matrix of allele frequencies.

LD decay over time

Let us consider two loci with alleles A_1 and A_2. We denote r_n the frequency of A_1A_2 in the current generation and c the probability of recombination between locus 1 and locus 2.

Under random mating the frequency of A_1A_2 in the next generation can be written

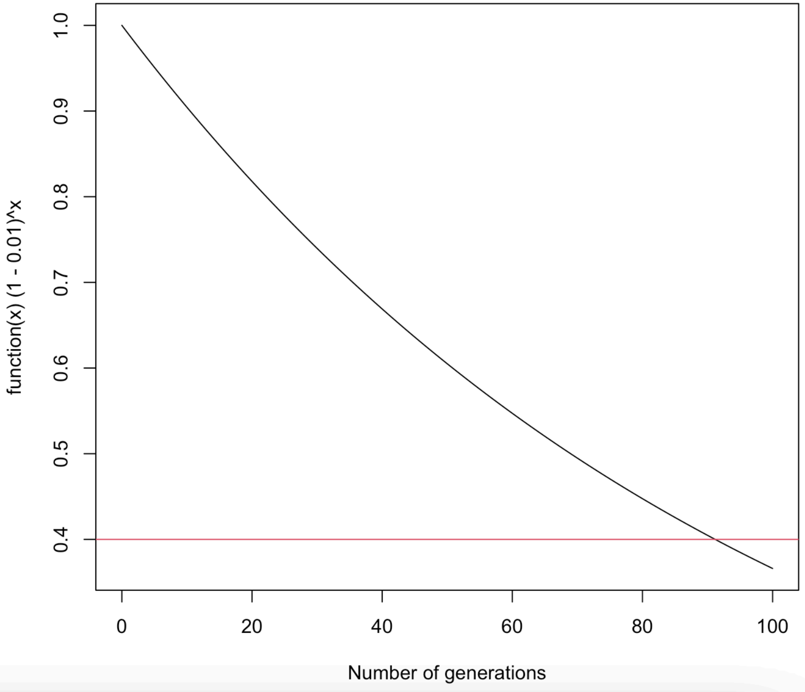
$$r_{t+1} = r_t\,(1 - c) + c\,p(A_1)p(A_2)$$

In terms of of disequilibrium can be expressed as

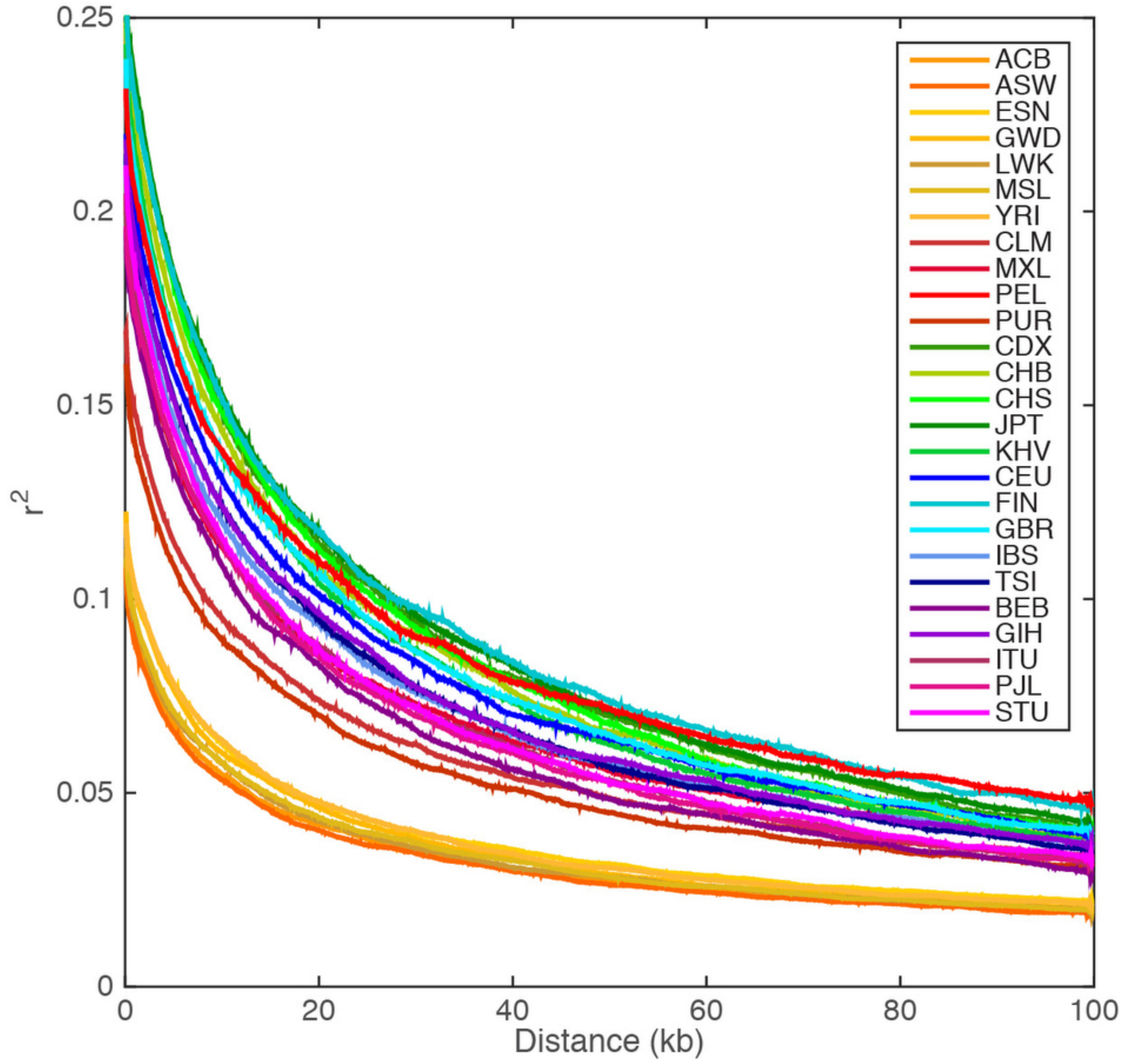
$$\begin{aligned} D_{t+1}(A_1,A_2) &= r_{t+1} - p(A_1)p(A_2) \\ &= [r_t\,(1 - c) + c\,p(A_1)p(A_2)] - p(A_1)p(A_2) \\ &= D_t(A_1,A_2)(1 - c) \end{aligned}$$

This can be generalized as

$$D_t(A_1,A_2) / D_0(A_1,A_2) = (1 - c)^t$$



LD decay with physical distance



A. Auton et al. (1000 Genomes Consortium) A Global Reference for Human Genetic Variation. *Nature* (2015).

A reasons why LD might differ between populations…

(1) Demographic history [Effective population size: Large N_e => small LD]

(2) Selection [positive selection increases LD]

Summary

Summary – outline (again)

- Hardy-Weinberg Equilibrium
- What drives changes in allele/genotype frequencies?
- How can you measure genetic distance between populations?
- Linkage Disequilibrium

In this lecture…

Key parameters to describe the genetic constitution of a population are

- Alleles and genotypes frequencies (Hardy-Weinberg Equilibrium)
- Correlations between alleles: linkage disequilibrium (LD)

Key parameter to compare frequency differences between populations:
$F_{ST} = var(p_i)/[p_0(1-p_0)]$

Frequencies and LD are affected by drift, demography (Ne), selection, etc.