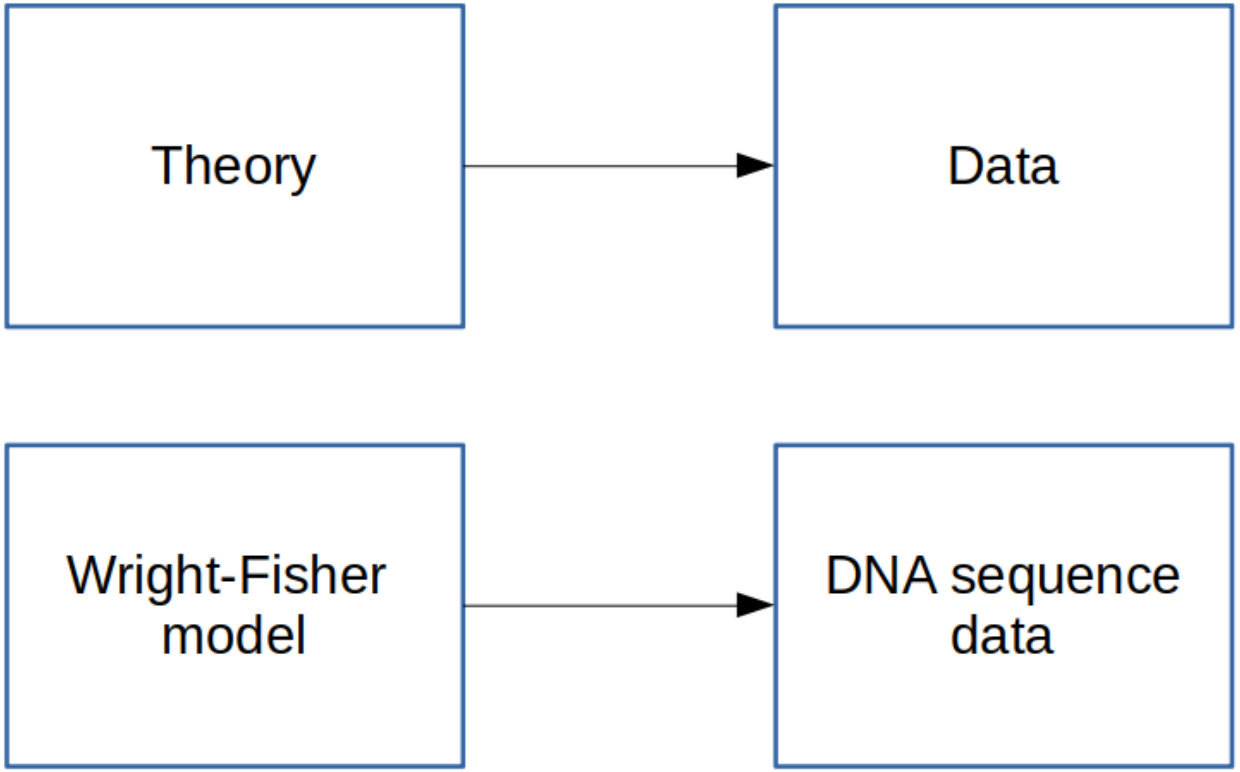
# Intended Learning Outcomes

Coalescence theory

In this lecture you will learn to

- describe principles and assumptions of the coalescence theory
- discuss the infinite sites model
- provide estimators of $\theta$ and effective population size
- measure genetic variability with summary statistics and the site frequency spectrum with `R`

# Motivation



# Motivation

e.g. on the X chromosomes, two Europeans differ, on average, in 0.08% of sites, while individuals from African populations differ in 0.12% of sites.

What do these numbers tell us *about* the two populations?

# Motivation

e.g. on the X chromosomes, two Europeans differ, on average, in 0.08% of sites, while individuals from African populations differ in 0.12% of sites.

What do these numbers tell us *about* the two populations?

We use **coalescence theory**, which is based on Wright-Fisher model, to consider the genealogy history of a sample and make inferences about populations instead of modelling changes of allele frequencies forward in time.

# Coalescence

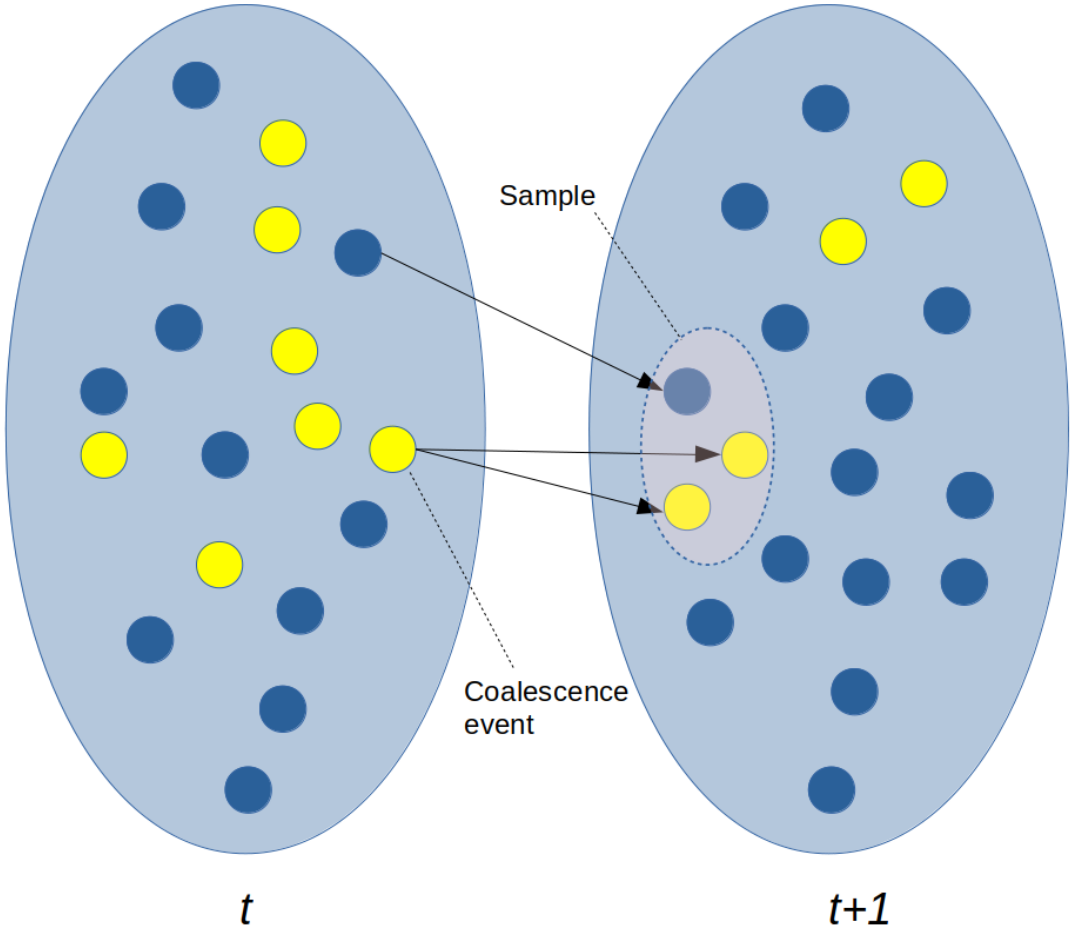



Figure 15: Tracking the ancestry of a sample between two generations.

# Coalescence

If two individual gene copies have the same parent in the previous generation, we say that the **ancestral lineage** representing these two individuals have **coalesced**.

They have a **common ancestor** and a **coalescent event** has occured.

# Coalescence tree

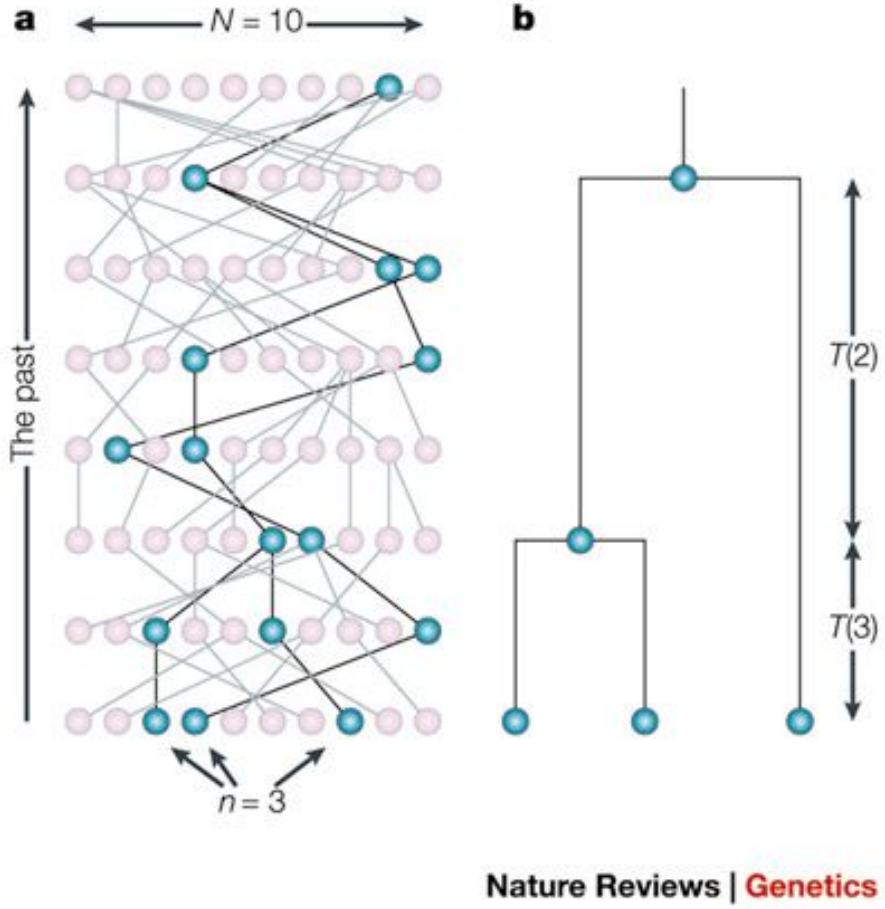



Figure 16: Ancestry of three samples.

# Coalescence tree

The ancestry of an individual gene copy is represented by a line (or edge).

The time until two lineages find a **most recent common ancestor (MRCA)** is called **coalescence time**.

How can we find the coalescence time?

# Coalescence in a sample of two gene copies

As there are $2N$ potential parents "chosen" with equal probability, the probability of two individuals having the same parent in the previous generation is

# Coalescence in a sample of two gene copies

As there are $2N$ potential parents "chosen" with equal probability, the probability of two individuals having the same parent in the previous generation is $1/(2N)$.

The probability that two gene copies did NOT have the same parent in the previous generation is

# Coalescence in a sample of two gene copies

As there are $2N$ potential parents "chosen" with equal probability, the probability of two individuals having the same parent in the previous generation is $1/(2N)$.

The probability that two gene copies did NOT have the same parent in the previous generation is $1 - 1/(2N)$.

The probability that two gene copies did not have the same parent in the past $r$ generations is

# Coalescence in a sample of two gene copies

As there are $2N$ potential parents "chosen" with equal probability, the probability of two individuals having the same parent in the previous generation is $1/(2N)$.

The probability that two gene copies did NOT have the same parent in the previous generation is $1 - 1/(2N)$.

The probability that two gene copies did not have the same parent in the past $r$ generations is $[1 - 1/(2N)]^r$.

# Coalescence in a sample of two gene copies

The probability of not finding any common ancestor in generation $r-1$ but then finding the first common ancestor in generation $r$ is

# Coalescence in a sample of two gene copies

The probability of not finding any common ancestor in generation $r-1$ but then finding the first common ancestor in generation $r$ is

$$Pr(\ldots) = [1 - 1/(2N)]^{r-1}[1/(2N)] \tag{13}$$

This equation gives us the probability distribution of the time to the MRCA in a sample of size $n = 2$. This is a geometric random variable: the probability distribution of the number of Bernoulli trials needed to get one success.

jupyter-notebook: coalescence

# Coalescence in large populations

- If we consider the limit of an infinitely large population, calculations simplify but we can still consider the effect of genetic drift.
- It is convenient to measure time in $2N$ generations, by setting $r = 2Nt$ with $t$ measuring time in $2N$ generations.

# Coalescence in large populations

- If we consider the limit of an infinitely large population, calculations simplify but we can still consider the effect of genetic drift.
- It is convenient to measure time in $2N$ generations, by setting $r = 2Nt$ with $t$ measuring time in $2N$ generations.

The probability that two gene copies do not find a common ancestor in $2Nt$ generations becomes

$$[1 - 1/(2N)]^{2Nt} \to e^{-t} \text{ as } N \to \infty$$

# Coalescence in large populations

As $N$ becomes large, the distribution of the coalescence times follows an **exponential distribution** with mean 1.

As time is measured in $2N$ generations, the mean (expected) time to coalescence is actually $2N$ generations. In other words, there is a constant rate of coalescence of 1 per $2N$ generations.

jupyter-notebook: coalescence

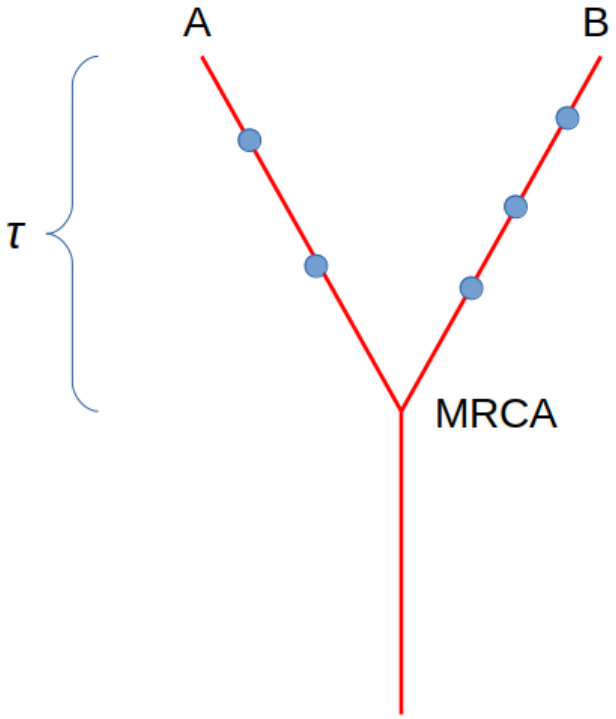
# Coalescence in large population

- The random process of following the lineages backward in time until a most recent common ancestor has been found is called a **coalescence process**.
- If the coalescence rate is 1 per $2N$ generations, it is intuitive to understand that the expected coalescence time (the time until the coalescent event occurs) is $2N$ generations (although there is considerable variability in the coalescence times).

# Coalescence in large population

- The coalescence process in a large randomly mating diploid population with two sexes is the same as that in the simple haploid model.
- Once we have a convenient description of the geneaology, then it is easy to derive various properties of our sample.

# Genetic variability and population size



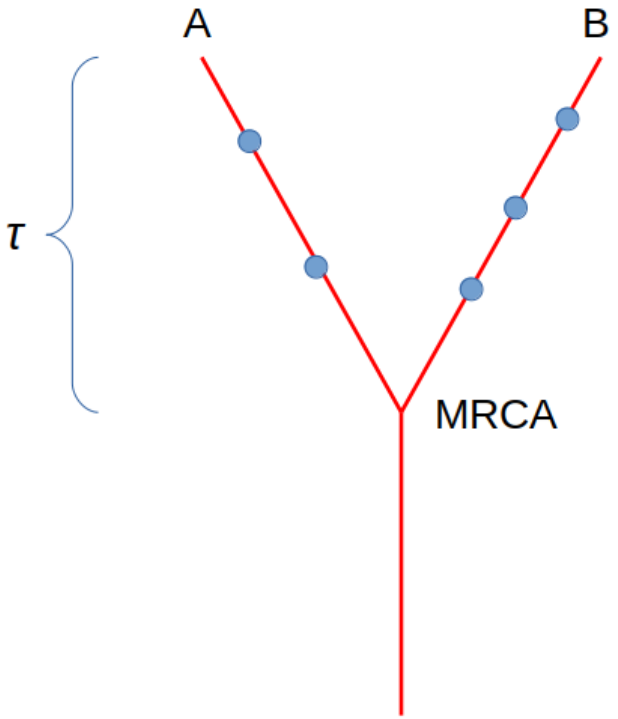

We expect $\mu r$ mutations in $r$ generations. If we measure time by $2N$ generations, that is $t = r/(2N)$, we expect $2N\mu t$ mutations on a lineage of length $t$.

Since $E[t] = 1$ and there are two lineages, the expected number of mutations separating two gene copies is

$$\theta = 4N\mu \tag{14}$$

which is a simple relationship between the amount of genetic variability and population sizes.

# Genetic variability and population size




The expected number of mutations occuring in a lineage during any time interval of length $\tau$ is $2N\mu\tau = \tau\theta/2$.

As such, we can think of the data generated by a coalescence process producing a coalescence tree and a subsequent process in which mutations are distributed across the lineage of the tree at rate $\theta/2$.

# Infinite Sites Model

Each new mutation creates a new variable site, i.e. that each new mutation hits a new site in the sequence, such that no site experiences more than one mutation.

Figure 17: The sequence is infinitely long so that the chance of two mutations hit the same site is essentially zero.

# Infinite Sites Model

The sites in which some of the individuals differ are called **segregating sites** or **single nucleotide polymorphisms** (SNPs).

| | | |
|---|---|---|
| Sequence | 1 | agga**a** ggac**c** **a**agac gatag |
| Sequence | 2 | agga**a** ggaa**c** **g**agac gatag |
| Sequence | 3 | agga**a** ggaa**c** **g**agac gatag |
| Sequence | 4 | agga**g** ggac**c** **g**agac gatag |
| Sequence | 5 | agga**g** ggac**c** **g**agac gatag |

Under the infinite sites model, we can deduce which mutations occurred in the ancestry of a sample of sequences.

# Infinite Sites Model

The model does not distinguish between different nucleotides and does not care about invariable sites.

| | | |
|---|---|---|
| Sequence | 1 | agga**a** gga**c**c **a**agac gatag |
| Sequence | 2 | agga**a** gga**a**c **g**agac gatag |
| Sequence | 3 | agga**a** gga**a**c **g**agac gatag |
| Sequence | 4 | agga**g** gga**c**c **g**agac gatag |
| Sequence | 5 | agga**g** gga**c**c **g**agac gatag |

| | | | | |
|---|---|---|---|---|
| Sequence | 1 | 0 | 0 | 0 |
| Sequence | 2 | 0 | 1 | 1 |
| Sequence | 3 | 0 | 1 | 1 |
| Sequence | 4 | 1 | 0 | 1 |
| Sequence | 5 | 1 | 0 | 1 |

Figure 18: Data as a binary matrix of the variable sites.

# Infinite Sites Model

- Labelling with zeros and ones is arbitrary.
- Good approximation if the rate of mutation is low.
- DNA sequences with different mutations are different **haplotypes**.

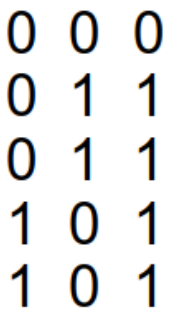



Figure 19: How many DNA sequences? How many haplotypes?

# Tajima's estimator

We want an estimate of $\theta = 4N\mu$ under the infinite sites model from the expected number of mutations separating two individuals based on the DNA sequences obtained from data.

# Tajima's estimator

We want an estimate of $\theta = 4N\mu$ under the infinite sites model from the expected number of mutations separating two individuals based on the DNA sequences obtained from data.

Data can be summarised as the **average number of pairwise differences**, or $\pi$.

$$\pi = \frac{\sum_{i<j} d_{i,j}}{n(n-1)/2} \tag{15}$$

with $n$ sequences, $d_{i,j}$ number of differences between sequence $i$ and $j$.

# Tajima's estimator

| | | |
|---|---|---|
| 0 | 0 | 0 |
| 0 | 1 | 1 |
| 0 | 1 | 1 |
| 1 | 0 | 1 |
| 1 | 0 | 1 |

Figure 20: What is the value of $\pi$?

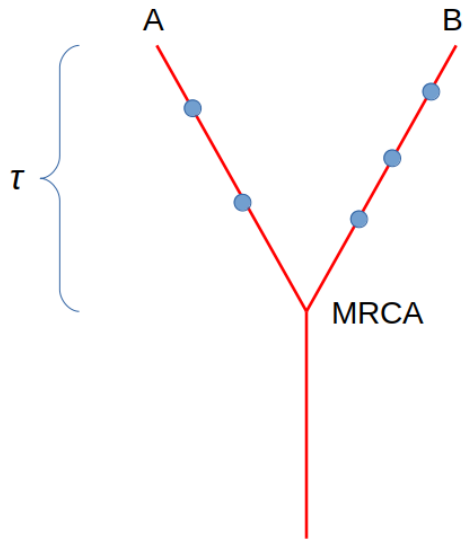
# Tajima's estimator

| | | |
|---|---|---|
| 0 | 0 | 0 |
| 0 | 1 | 1 |
| 0 | 1 | 1 |
| 1 | 0 | 1 |
| 1 | 0 | 1 |

Figure 20: What is the value of $\pi$?

$$\pi = (2+2+2+2+0+2+2+2+2+0)/(5 \times 4/2) = 1.6$$

# Tajima's estimator




The expected number of nucleotide differences between two sequences is the expected number of mutations, $\theta = 4N\mu$.

$$E[d_{i,j}] = \theta \tag{16}$$

$$E[\pi] = \theta \tag{17}$$

$\hat{\theta}_T = \pi$ is called **Tajima's** estimator of $\theta$.

# Effective population size

The number of individuals in a Wright-Fisher model that would produce the same amount of genetic drift as in the real population.

The amount of genetic drift can be measured as

- the expected heterozygosity
- expected number of pairwise differences
- rate of coalescence
- ...

# Effective population size ($N_e$)

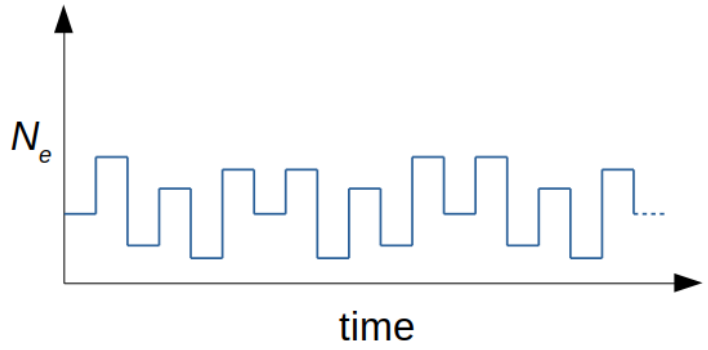
*e.g. "A population with an effective size of 200 with respect to heterozygosity harbours the same amount of heterozygosity as a Wright-Fisher population of 200 individuals."*

The true number of individuals in the population can be very different from its effective population size!

# Effective population size

Figure 21: The effective population size of the Chinook salmon (*Oncorhynchus tshawytscha*) has been estimated to be very low, possibly because the population size fluctuates between years and high variance offspring.

# Effective population size ($N_e$)




If a population fluctuates between sizes $N_1$, $N_2$, ..., $N_k$ at a proportion $p_1$, $p_2$, ..., $p_k$ of the time, the coalescent effective population size is the harmonic mean:

$$N_e = \frac{1}{p_1/N_1 + p_2/N_2 + ...p_k/N_k} \tag{18}$$

which is smaller that the arithmetic mean and gives more weight to smaller sizes.

# Effective population size ($N_e$)

The effective population size with unequal sex ratio is

$$N_e = \frac{4N_m N_f}{N_m + N_f} \tag{19}$$

which is smaller than $N_m + N_f$.

# Interpreting estimates of $\theta$

| $\pi$ on autosomes | |
|---|---|
| Mandenka | 0.00120 |
| Biaka | 0.00121 |
| San | 0.00126 |
| Han | 0.00081 |
| Basque | 0.00087 |
| Melanesians | 0.00078 |

# Interpreting estimates of $\theta$

| $\pi$ on X chromosomes | |
|---|---|
| Mandenka | 0.00099 |
| Biaka | 0.00095 |
| San | 0.00085 |
| Han | 0.00058 |
| Basque | 0.00071 |
| Melanesians | 0.00066 |

# Watterson's estimator

$$\hat{\theta}_W = \frac{S}{\sum_{k=1}^{n-1} \frac{1}{k}} \tag{20}$$

with $S$ segregating sites and $n$ samples.

$$E[\hat{\theta}_W] = \theta \tag{21}$$

# Watterson's estimator

| | | |
|---|---|---|
| 0 | 0 | 0 |
| 0 | 1 | 1 |
| 0 | 1 | 1 |
| 1 | 0 | 1 |
| 1 | 0 | 1 |

Figure 22: What is the value of $\hat{\theta}_W$?

# Watterson's estimator

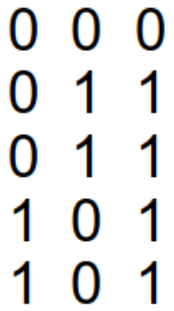



Figure 22: What is the value of $\hat{\theta}_W$?

$\hat{\theta}_W = 3/(1 + 1/2 + 1/3 + 1/4) = 1.4$
but before we obtained $\hat{\theta}_T = 1.6$.
Why?

# Summary statistics

Possible summaries of DNA sequence data are:

- the number of segregating sites ($S$)
- the average number of pairwise differences ($\pi$)

but they don't provide much information regarding **allele frequencies**.

# The Site Frequency Spectrum (SFS)

## SFS

The SFS is obtained by tabulating the sample allele frequencies of all mutations.

0 0 0
0 1 1
0 1 1
1 0 1
1 0 1

# The Site Frequency Spectrum (SFS)

## SFS

The SFS is obtained by tabulating the sample allele frequencies of all mutations.

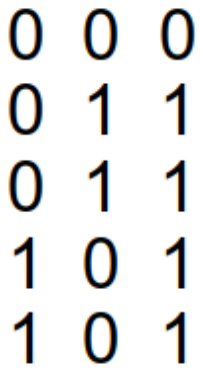
| | | |
|---|---|---|
| 0 | 0 | 0 |
| 0 | 1 | 1 |
| 0 | 1 | 1 |
| 1 | 0 | 1 |
| 1 | 0 | 1 |

The "1" alleles have frequencies 2/5, 2/5 and 4/5. The proportions of "1" alleles with a frequency of 1/5, 2/5, 3/5 and 4/5 in the sample are

# The Site Frequency Spectrum (SFS)

## SFS

The SFS is obtained by tabulating the sample allele frequencies of all mutations.




The "1" alleles have frequencies 2/5, 2/5 and 4/5. The proportions of "1" alleles with a frequency of 1/5, 2/5, 3/5 and 4/5 in the sample are $f_1 = 0$, $f_2 = 2/3$, $f_3 = 0$ and $f_4 = 1/3$.

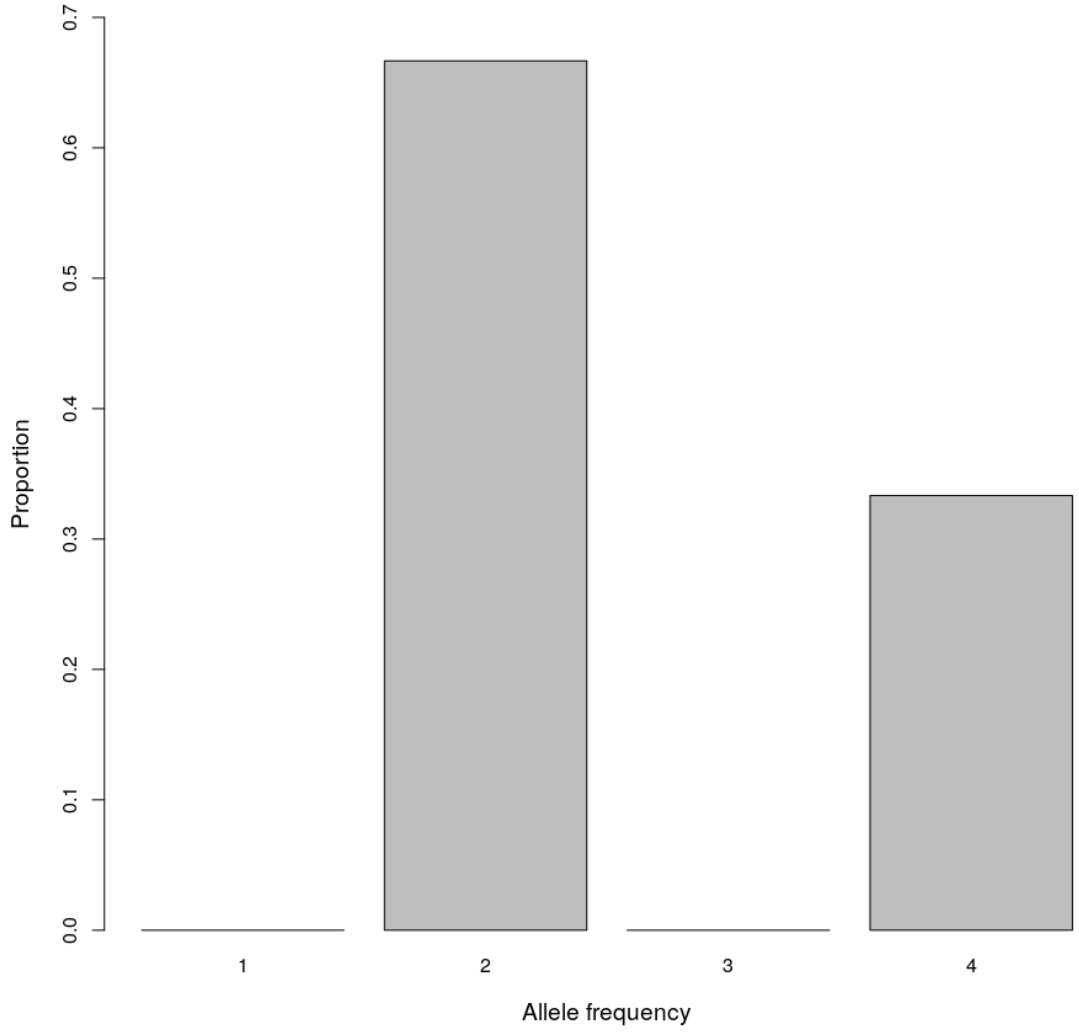
$$\vec{f} = (f_1, f_2, ..., f_{n-1})$$

for a sample of $n$ haploid individuals.

Imperial College London

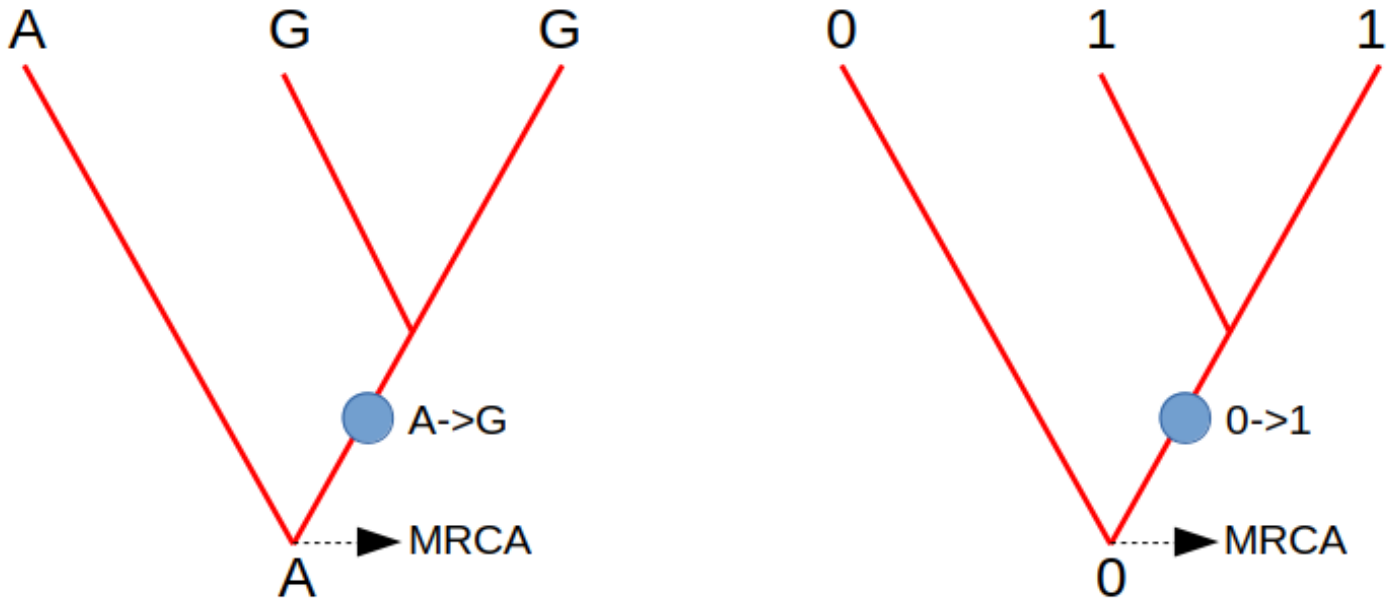
# The Site Frequency Spectrum (SFS)

0 0 0
0 1 1
0 1 1
1 0 1
1 0 1



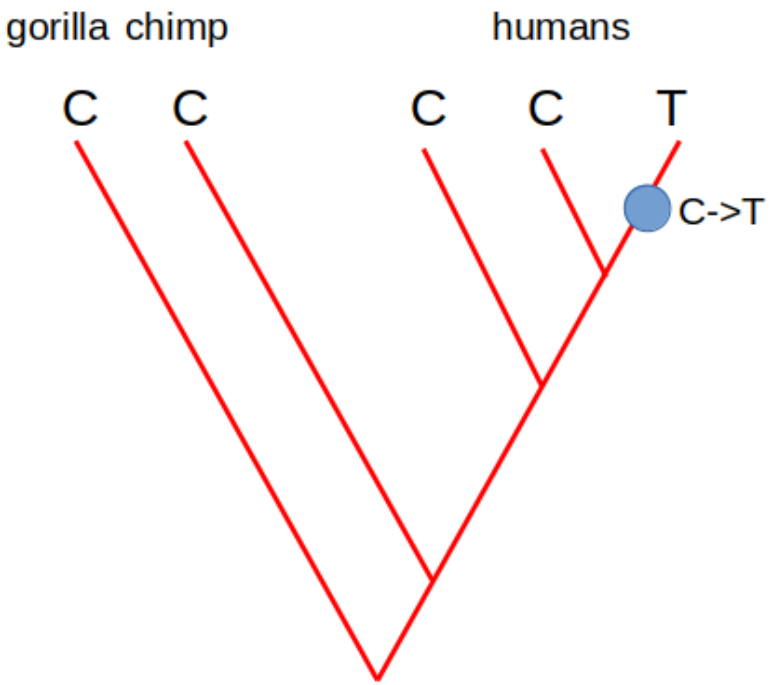
# Alleles

- **ancestral** allele is the allele found in the MRCA of the sample.
- **derived** allele (or mutated) is an allele that is not ancestral.



# Alleles

The ancestral allele is often inferred using **outgroups**.
e.g. if $C/T$ polymorphism in humans and primate have $C$, then $C$ is likely to be the ancestral allele.



# Alleles

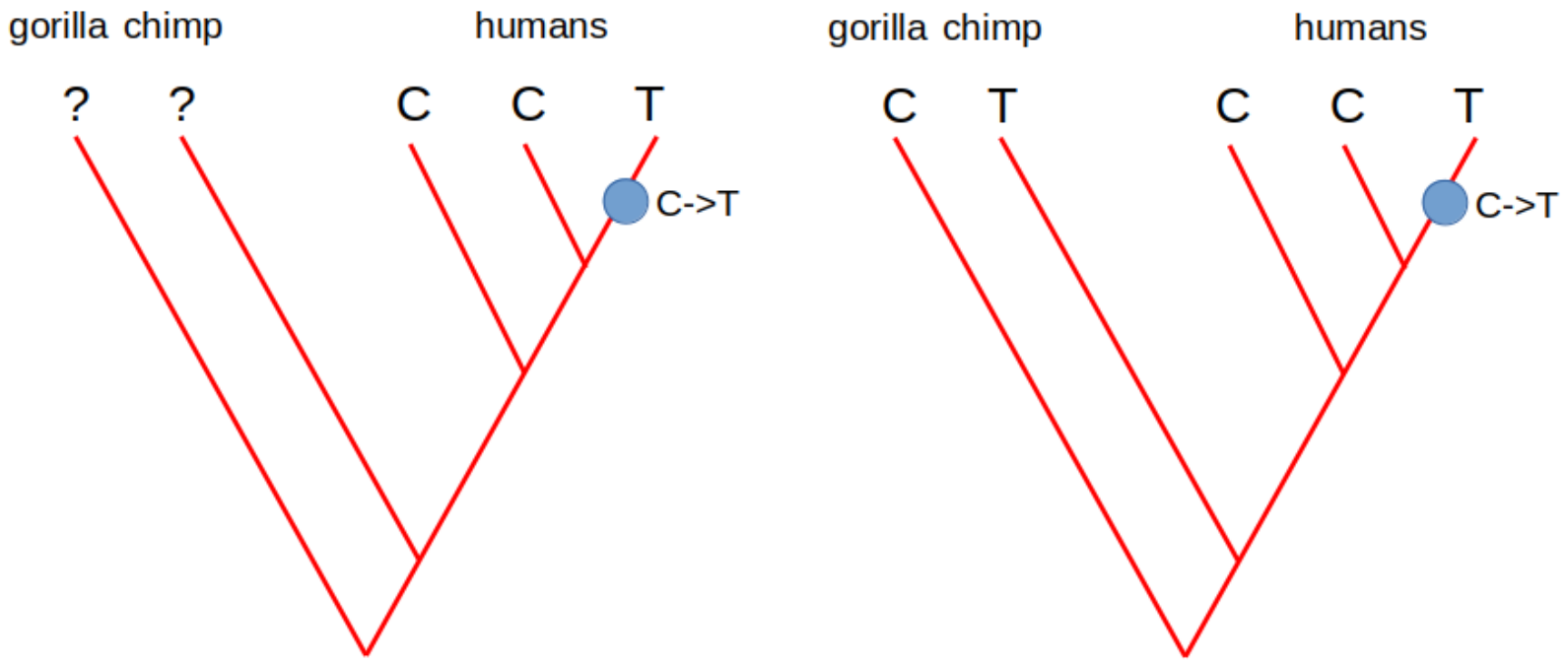



Figure 23: Uncertain ancestral allele.

# The Site Frequency Spectrum (SFS)

If no information on the ancestral allele is available, we can *fold* the frequency spectrum.

The **folded frequency spectrum** $f^*$ is obtained by adding together the frequencies of the derived and ancestral alleles.

$f^* = f_i + f_{n-j}$ for $j < n/2$ and
$f^* = f_j$ for $j = n/2$
only defined for values of $f^* \leq n/2$.

Imperial College London

# The folded SFS

| | | |
|---|---|---|
| 0 | 0 | 0 |
| 0 | 1 | 1 |
| 0 | 1 | 1 |
| 1 | 0 | 1 |
| 1 | 0 | 1 |

$$\vec{f}^* =$$

# The folded SFS

| | | |
|---|---|---|
| 0 | 0 | 0 |
| 0 | 1 | 1 |
| 0 | 1 | 1 |
| 1 | 0 | 1 |
| 1 | 0 | 1 |

$$\vec{f^*} = (f_1^* = 1/3, f_2^* = 2/3)$$

# The Site Frequency Spectrum

- $S$ and $\pi$ can be calculated directly from $\vec{f}$ but the opposite is not true.
- Alleles segregating at frequency of $1/n$ are called **singletons**.
- The expected SFS under the standard coalescence model with infinite sites mutations is

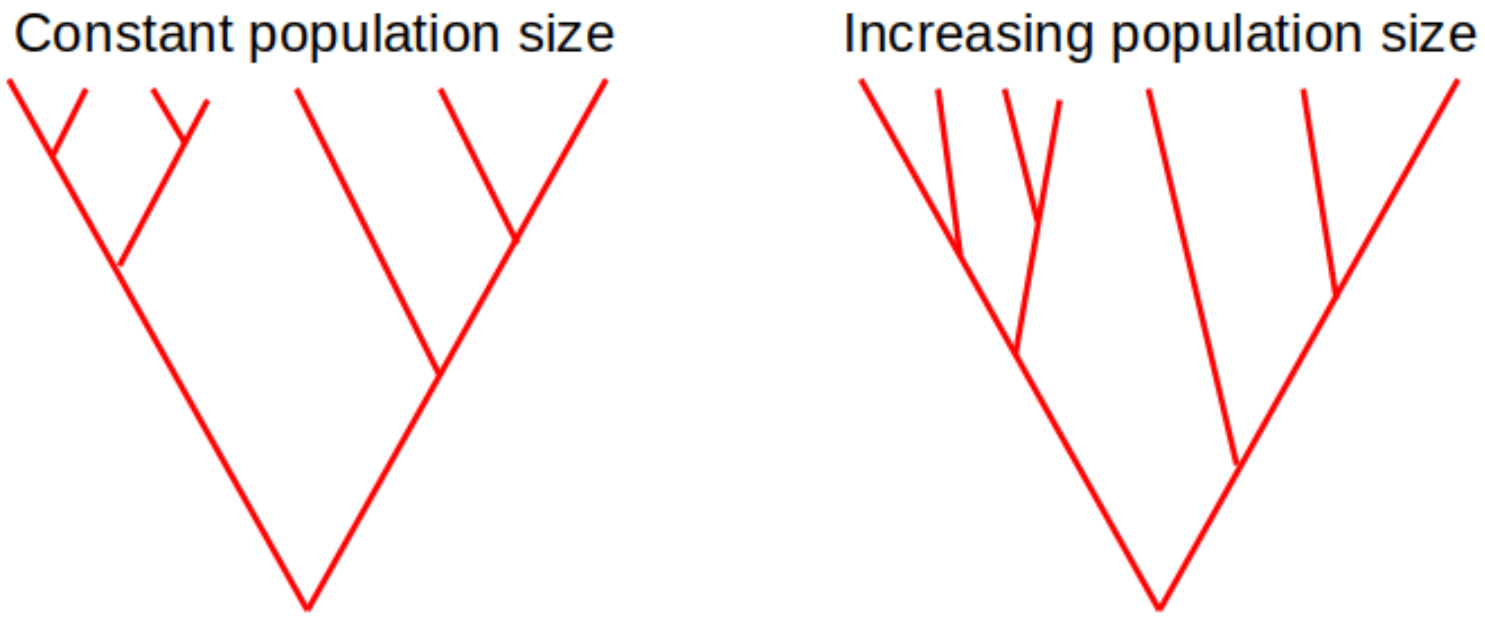
$$E[f_i] = \frac{1/j}{\sum_{k=1}^{n-1} \frac{1}{k}} \tag{22}$$

with $j = 1, 2, ..., n-1$

jupyter-notebook: coalescence

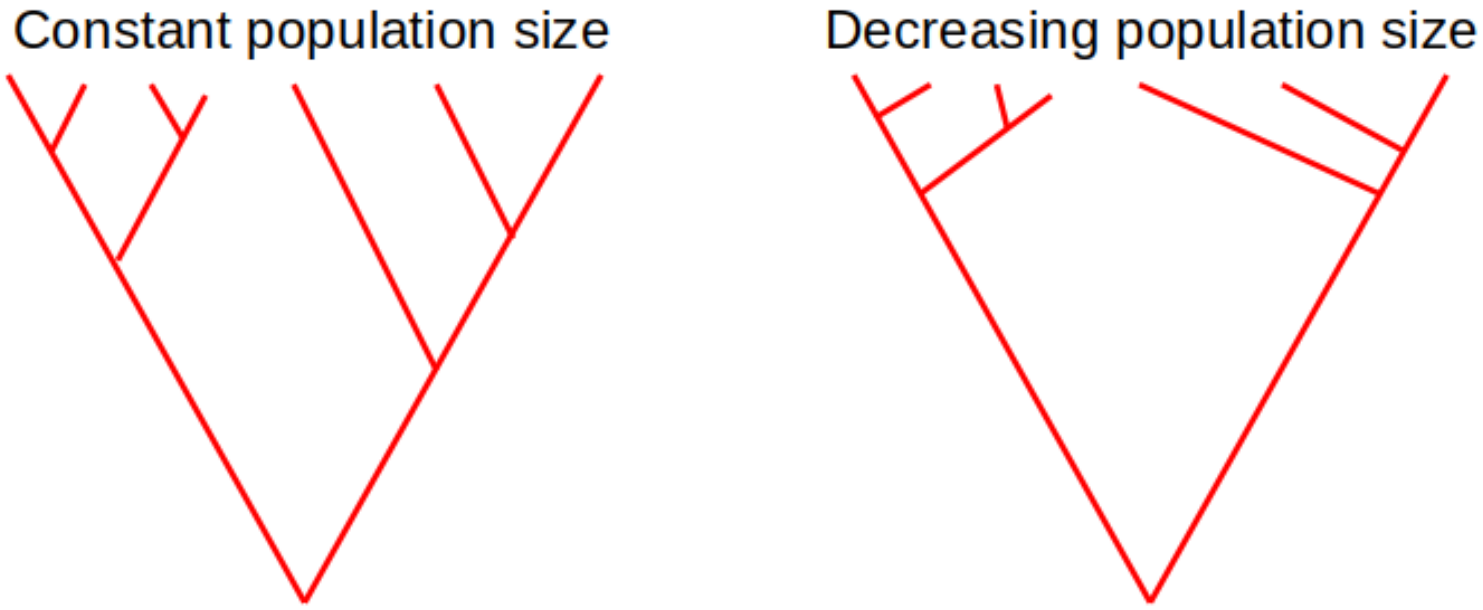
# Tree shape and population size

Measured in number of generations, the expected coalescence time for $k$ lineages is $2N/[k(k-1)]$.



# Tree shape and population size

Measured in number of generations, the expected coalescence time for $k$ lineages is $2N/[k(k-1)]$.



# Intended Learning Outcomes

Coalescence theory

In this lecture you have learnt to

- describe principles and assumptions of the coalescence theory
- discuss the infinite sites model
- provide estimators of $\theta$ and effective population sizes
- measure genetic variability with summary statistics and the site frequency spectrum with `R`

# Intended Learning Outcomes

## Population subdivision

In this lecture you will learn to

- quantify the effect of population subdivision on allele frequencies and heterozygosity
- calculate measures of population genetic differentiation
- discuss divergence models

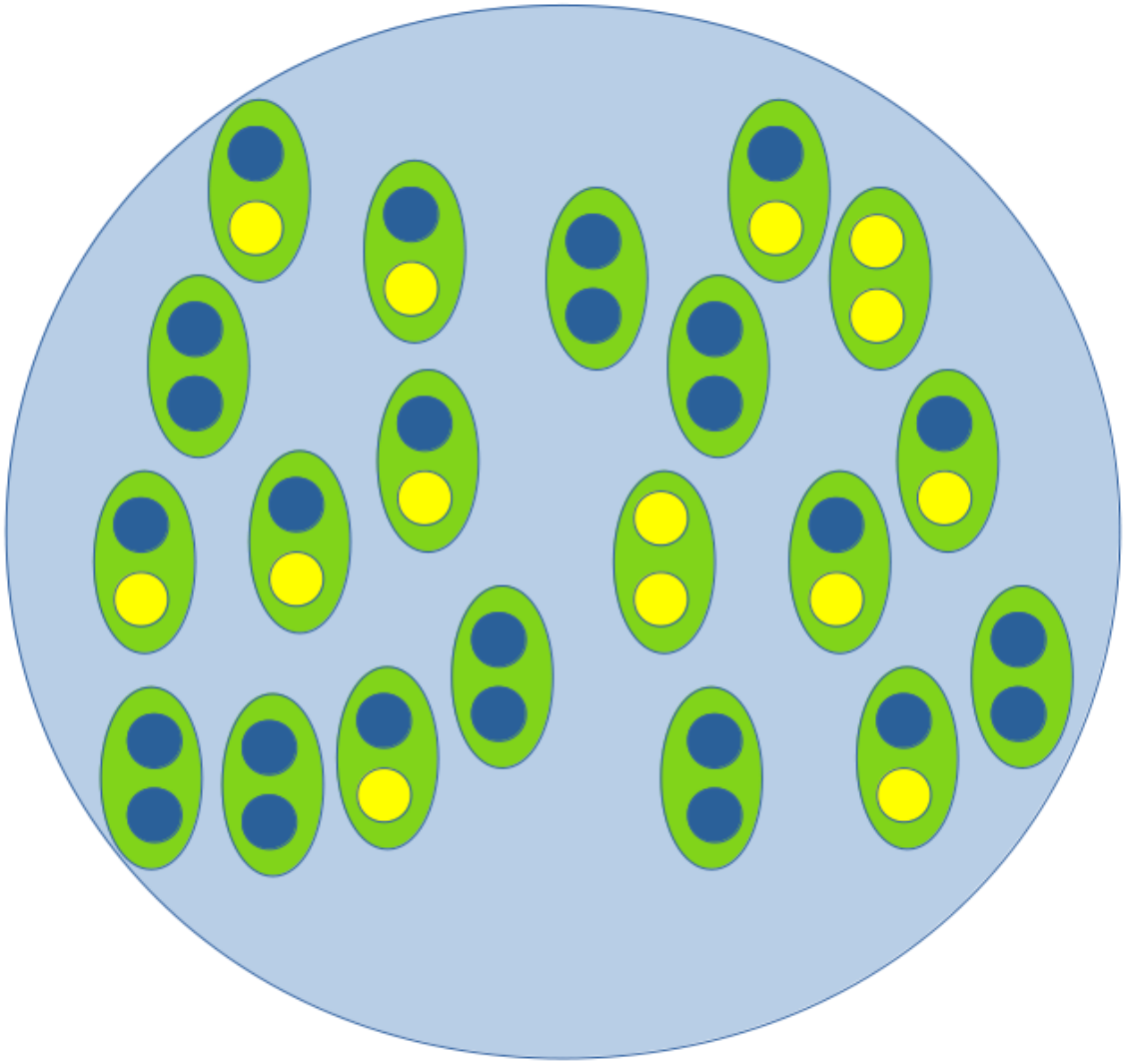
# Population subdivision

There is population subdivision, or **structure**, when the population is not randomly mating because of geographic or social structure.

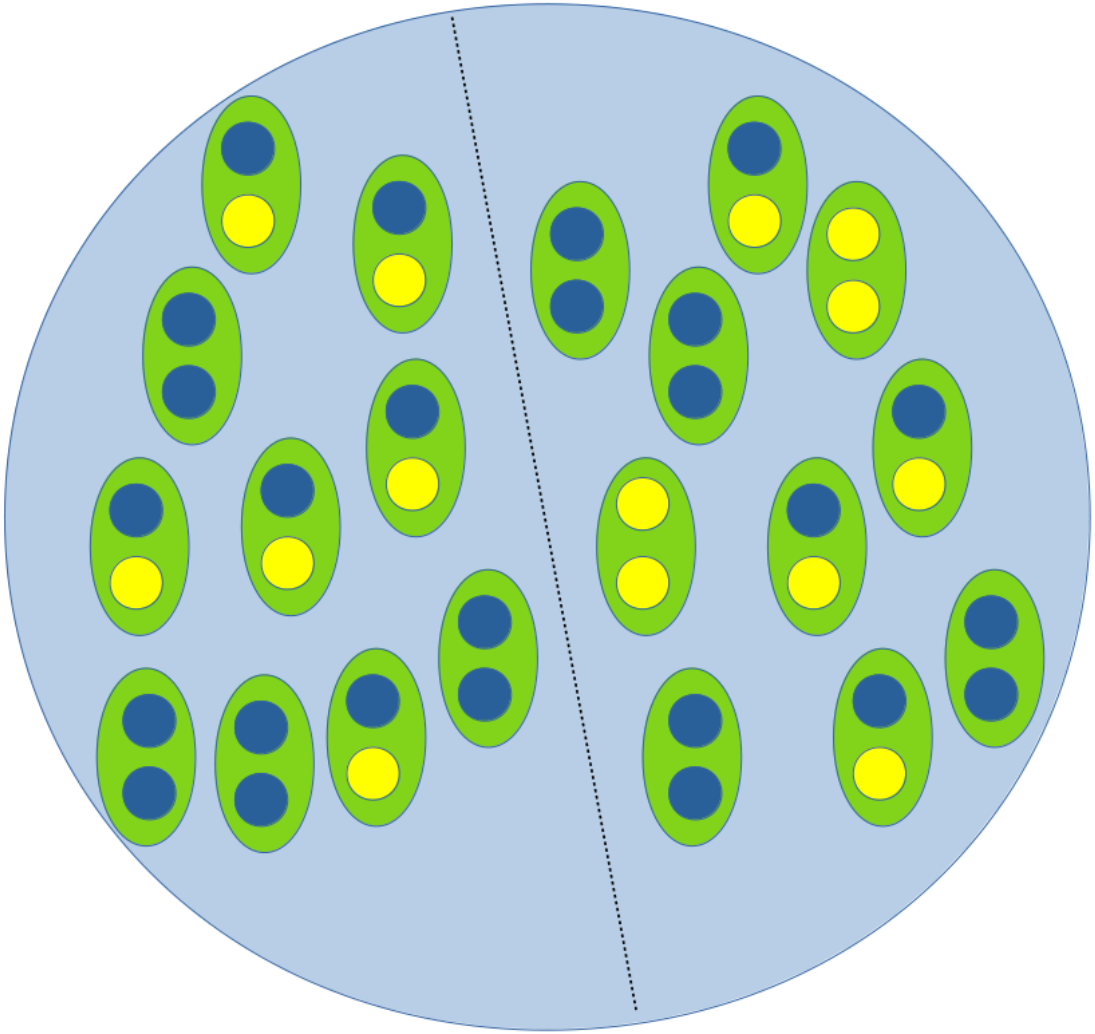
Population subdivision is important to

- understand the effects of drift and natural selection
- plan conservation strategies for rare or endangered species

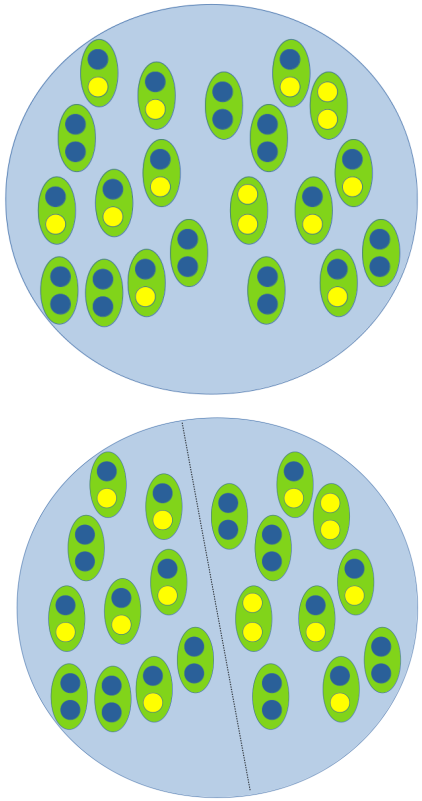
# Population subdivision



# Population subdivision



# Allele frequencies in a subdivided population



Assume two subpopulations, each one in HW equilibrium with $N_1$ and $N_2$ individuals, respectively.

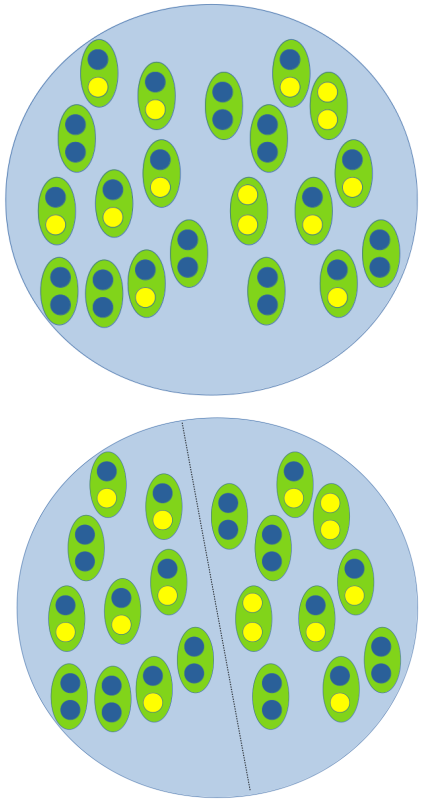
The average frequency of allele $A$ when pooling the two subpopulations is

$$f_A = \frac{2N_1 f_{A1} + 2N_2 f_{A2}}{2N_1 + 2N_2} \tag{23}$$

If $N_1 = N_2$

$$f_A = \frac{f_{A1} + f_{A2}}{2} \tag{24}$$

# Heterozygosity in a subdivided population



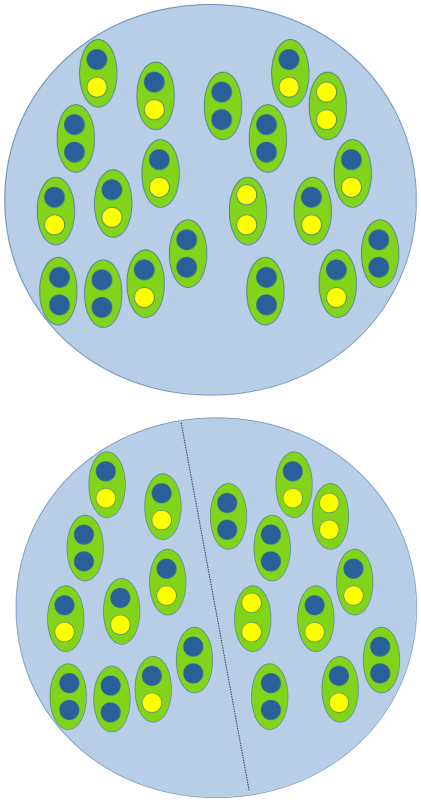
The proportion of heterozygous individuals is

$$H_S = \frac{2f_{A1}(1-f_{A1}) + 2f_{A2}(1-f_{A2})}{2} \qquad (25)$$

which is the expected heterozygosity when both populations are sampled.

$S$ in $H_S$ stands for "in the subdivided population"

# Heterozygosity in a subdivided population



However, the expected proportion of heterozygous individuals in a population with frequency $f_A$ is

$$H_T = 2\frac{f_{A1} + f_{A2}}{2}(1 - \frac{f_{A1} + f_{A2}}{2}) \qquad (26)$$

$T$ in $H_T$ stands for "in the total (pooled) population"

# Heterozygosity in a subdivided population

After some rearrangements we have

$$H_S = f_{A1}(1 - f_{A1}) + f_{A2}(1 - f_{A2}) \tag{27}$$

and

$$H_T = f_{A1}(1 - f_{A1}) + f_{A2}(1 - f_{A2}) + \delta^2/2 \tag{28}$$

with $\delta = |f_{A1} - f_{A2}|$.

# Heterozygosity in a subdivided population

$H_T = H_S + \delta^2/2$

- If $\delta = 0$ then

# Heterozygosity in a subdivided population

$H_T = H_S + \delta^2/2$

- If $\delta = 0$ then $H_T = H_S$ and the total (pooled) population is also in HWE.
- If $\delta >> 0$ then

# Heterozygosity in a subdivided population

$H_T = H_S + \delta^2/2$

- If $\delta = 0$ then $H_T = H_S$ and the total (pooled) population is also in HWE.
- If $\delta >> 0$ then $H_T > H_S$ and

# Heterozygosity in a subdivided population

$H_T = H_S + \delta^2/2$

- If $\delta = 0$ then $H_T = H_S$ and the total (pooled) population is also in HWE.
- If $\delta >> 0$ then $H_T > H_S$ and the total (pooled) population contains fewer heterozygous individuals than expected given the pooled allele frequency.

**Wahlund effect**

The decrease of heterozygosity in a subdivided population compared to a randomly mating one with the same (total) allele frequency.

# Quantifying population subdivision

$$F_{ST} = \frac{H_T - H_S}{H_T} \tag{29}$$

# Quantifying population subdivision

$$F_{ST} = \frac{H_T - H_S}{H_T} \tag{29}$$

$F_{ST}$ has a range defined as

- if $\delta = 0$ then $H_T = H_S$ and $F_{ST} = 0$
- if $\delta >> 0$ then $F_{ST} \approx 1$

$F_{ST}$ can be calculated for more than two subpopulations.

# $F_{ST}$: population genetic differentiation

Figure 24: Humpback whales in the Pacific and Atlantic have strong genetic differentiation ($F_{ST} > 0.4$) while populations in the North Atlantic have low differentation ($F_{ST} \approx 0.04$).

# Wright-Fisher model with migration

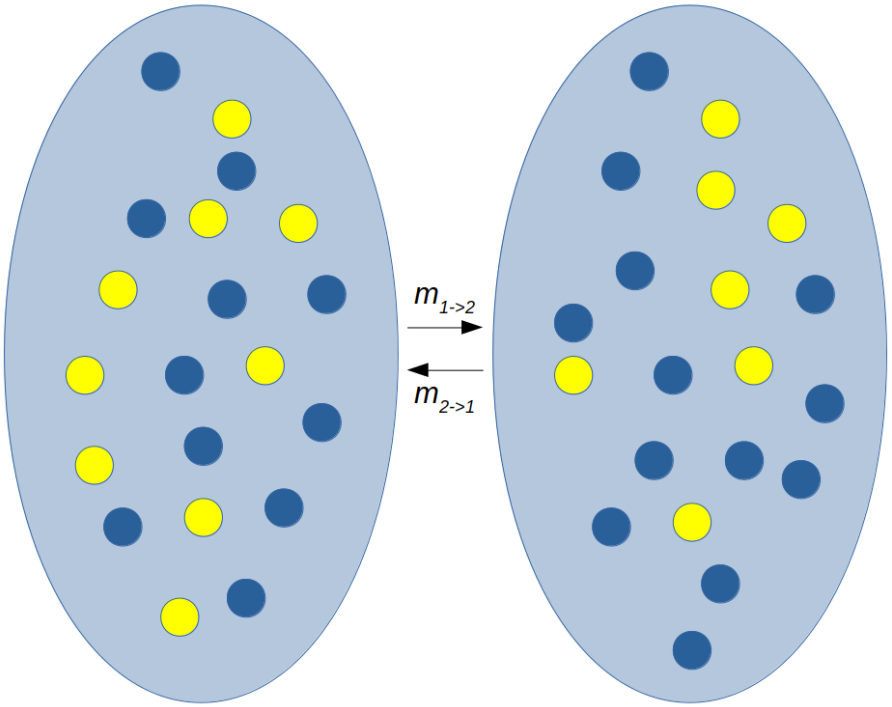



Figure 25: An individual from one population is replaced with an individual from the other with probability $m$ (migration rate).

# $F_{ST}$ and migration rates

Using the coalescence theory assuming an infinite sites model, we can derive that

$$F_{ST} = \frac{1}{1 + 4Nm_T} \tag{30}$$

with $m_T$ being the total number of migrants.

jupyter-notebook: subdivision

# "Island" model

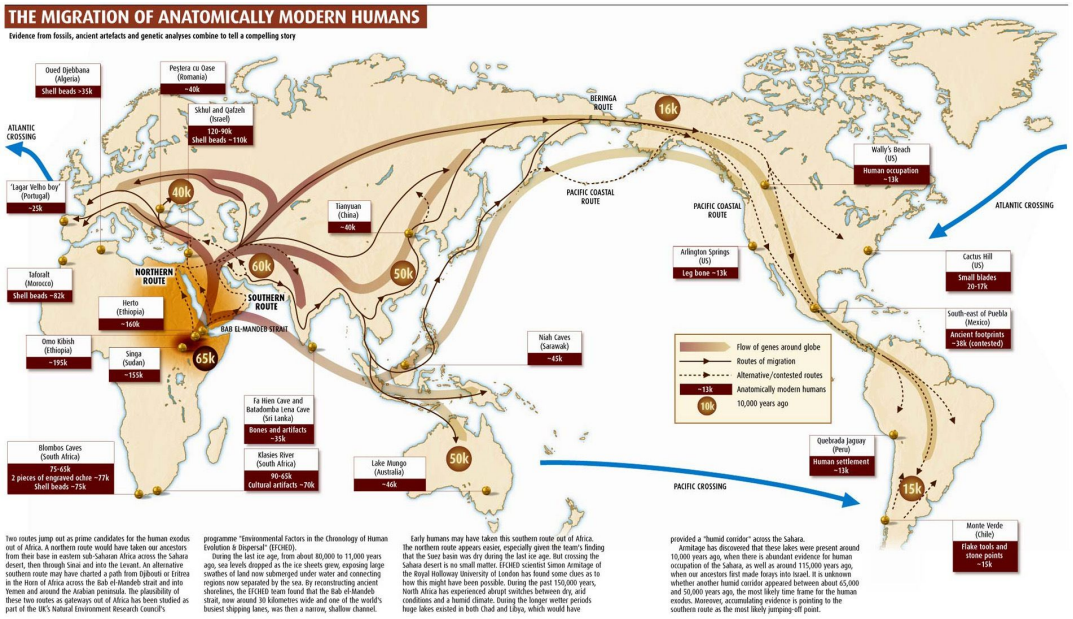
It assumes that populations have been subdivided for a very long time so that an equilibrium has been established and that then there is ongoing **gene-flow**.

It is not a realistic model for some species.

# "Island" model

It assumes that populations have been subdivided for a very long time so that an equilibrium has been established and that then there is ongoing **gene-flow**.

It is not a realistic model for some species.



# Divergence model

It describes populations diverging from common ancestral populations without subsequent gene-flow.

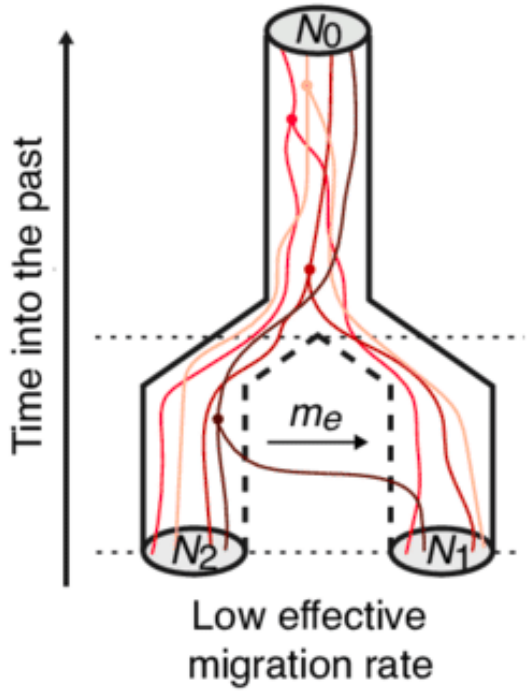



Figure 26: TMRCA overestimates the divergence time.

# Isolation by distance

The degree of population subdivision increases with geographical distance.

- migration rate is a linear function of geographical distance
- migration occurs only between adjacent populations (stepping-stone models)
- series of divergence events (sequential colonisation)

# Isolation by distance

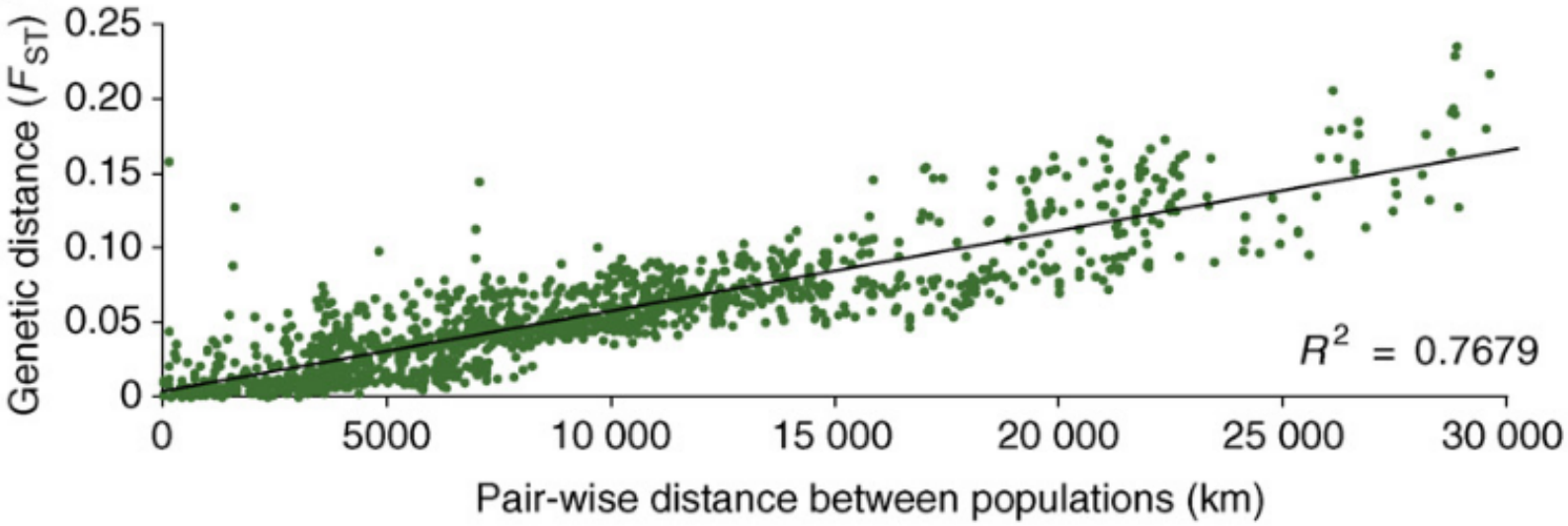



Figure 27: Isolation by distance in human populations.

# Intended Learning Outcomes

## Population subdivision

In this lecture you have learned to

- quantify the effect of population subdivision on allele frequencies and heterozygosity
- calculate measures of population genetic differentiation
- discuss divergence models