# Introduction to population genetics:

# Basic terms and concepts

**Copenhagen PopGen Course, 2024**

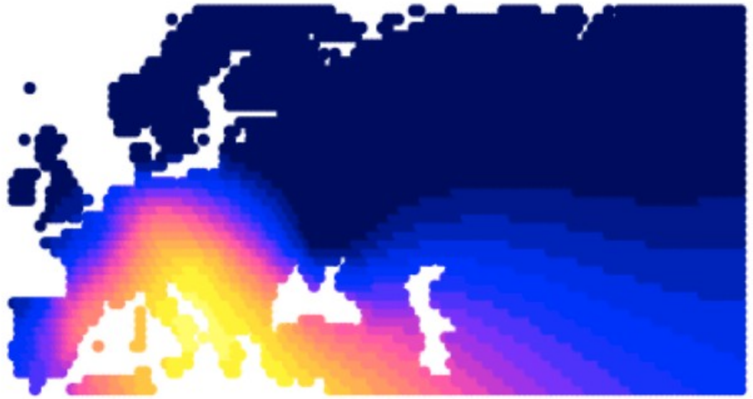
**Fernando Racimo**

# A bit about me and my research group

GLOBE Institute

## Paleogenomics and paleoproteomics

## Spatiotemporal modelling and paleoecology



## Academic activism

## Degrowth and socio-ecological transformation

# Beyond doing research and teaching, I am also a **scientist-activist**


If you’re interested in talking more about

**evolutionary genomics**

or **degrowth**

or **activism**

...feel free to come talk with me after lecture, or send an email to:
fracimo@sund.ku.dk

Always happy to chat about these topics!

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**Copenhagen PopGen Course, 2024**

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# Today

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- Terminology

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- Wright-Fisher Model and Genetic Drift

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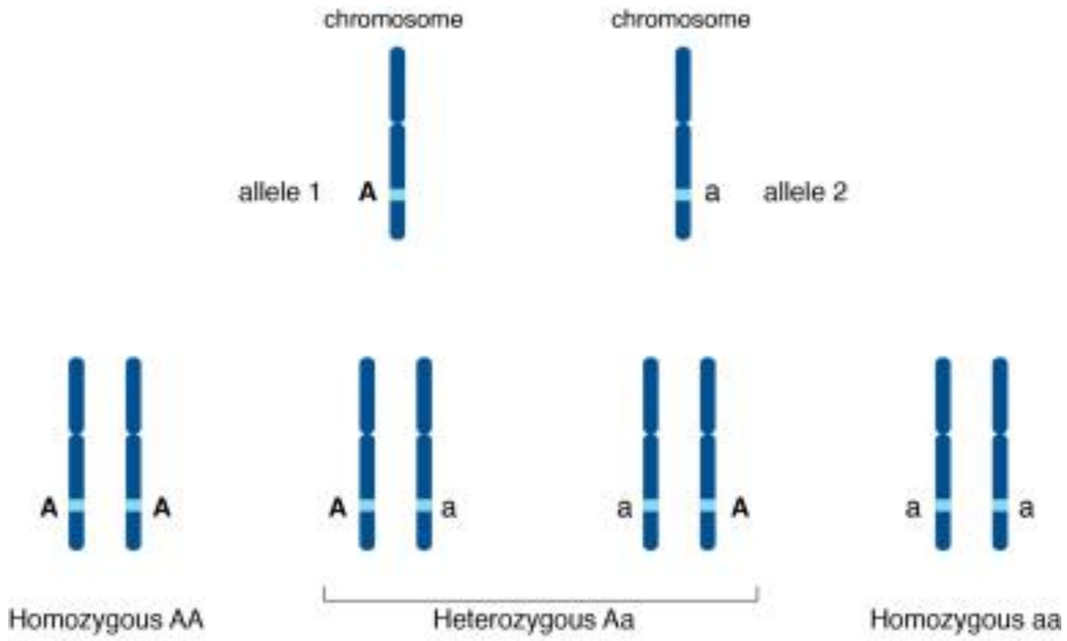
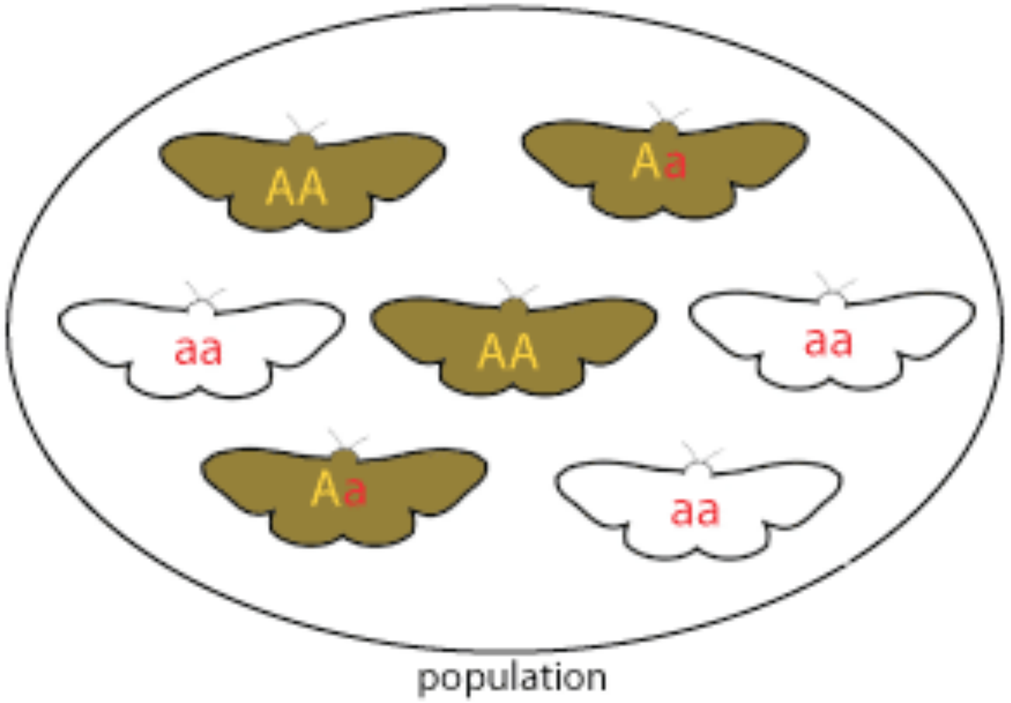
- **Genotype**: the set of alleles present at a locus in a particular organism ( set size = 2 if the organism is diploid)



# Terminology



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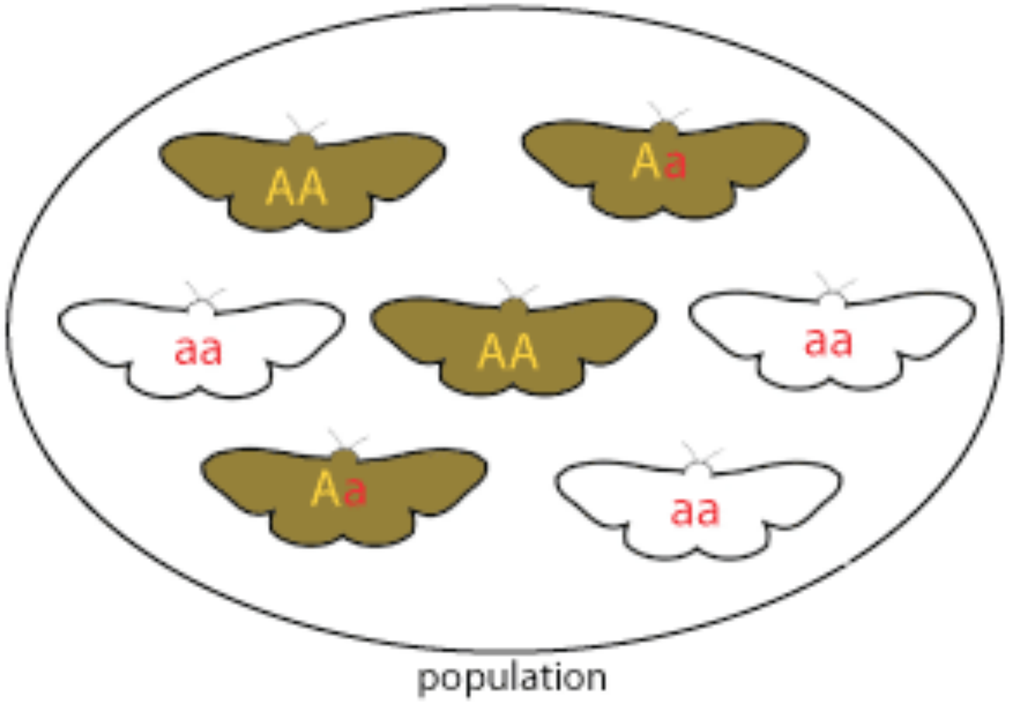


## Allele frequencies

- f(A) = 6/14
- f(a) = 8/14

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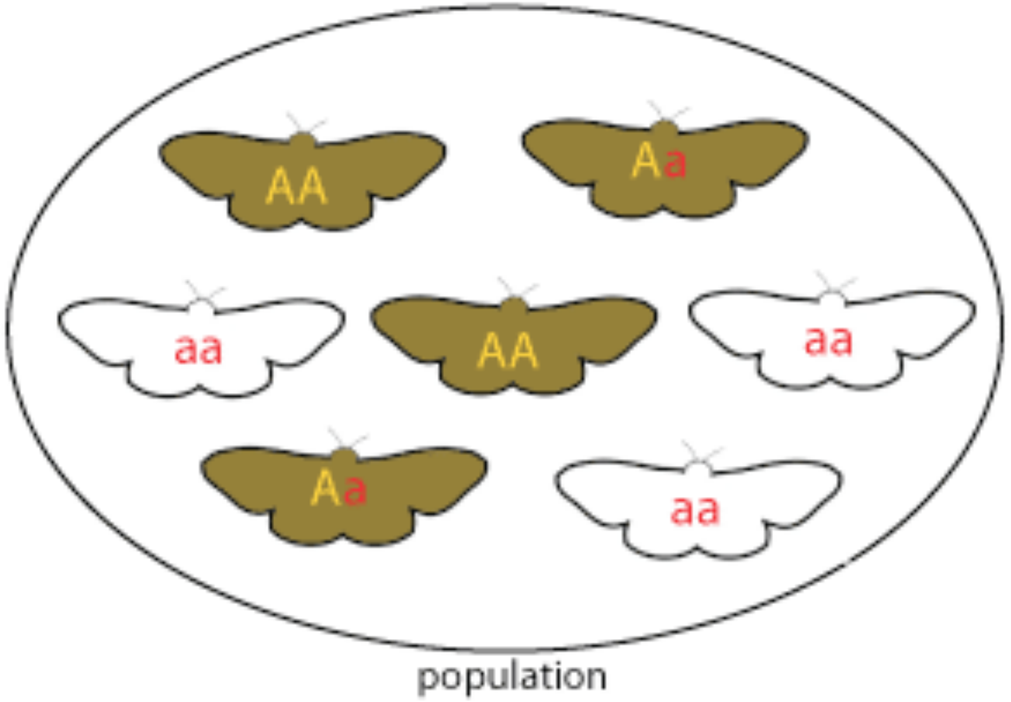


## Allele frequencies

- f(A) = 6/14
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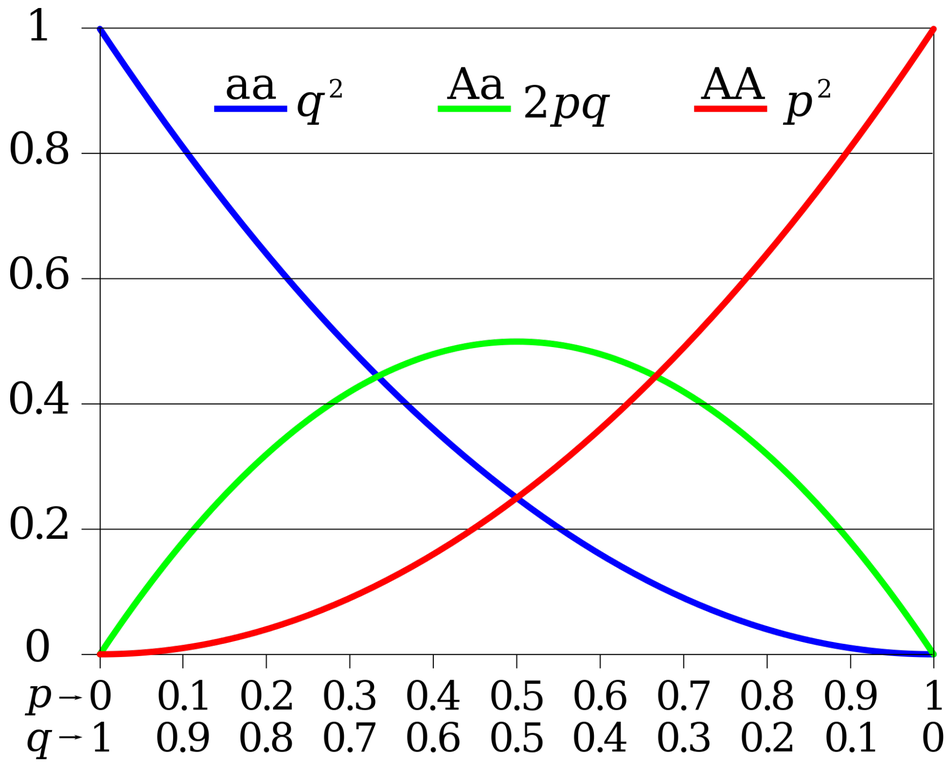
## Genotype frequencies

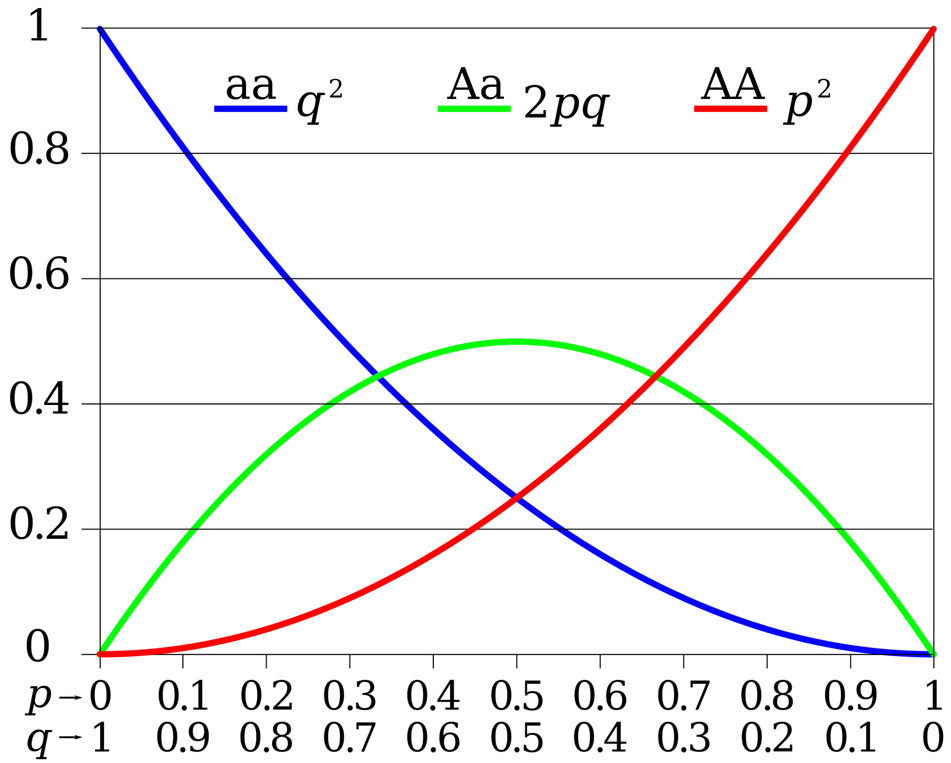
- f(AA) = 2/7
- f(Aa) = 2/7
- f(aa) = 3/7

# Hardy-Weinberg Equilibrium




**Allele frequencies** → **Genotype frequencies**

# Hardy-Weinberg Equilibrium




**Assuming:**

- Infinite population size
- No migration
- No mutation
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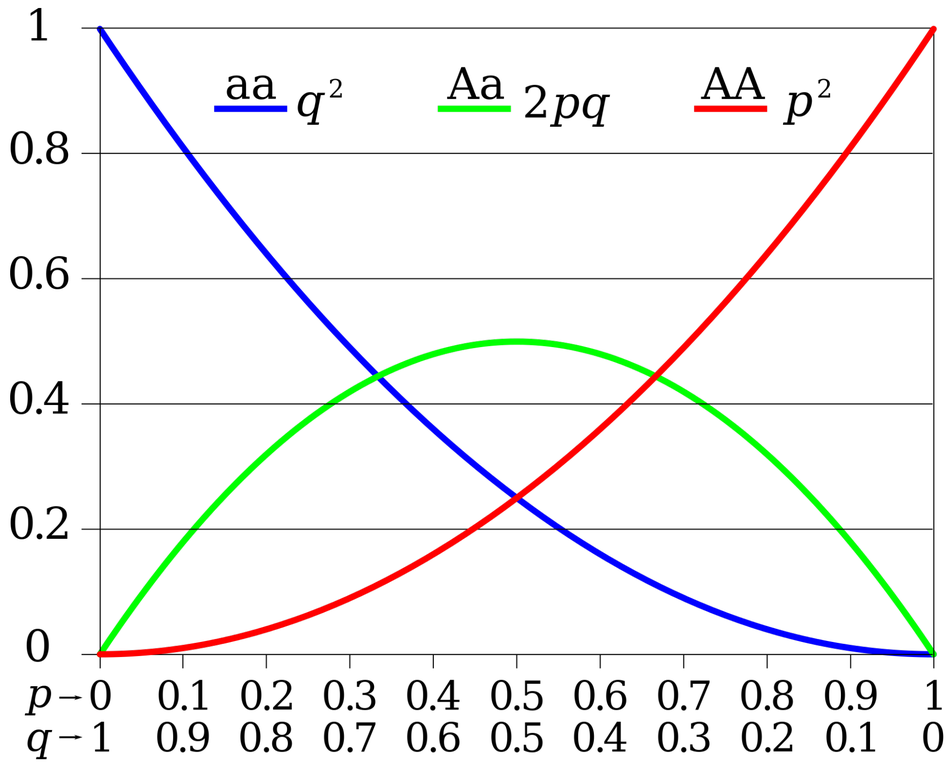
- Random mating
- Non-overlapping generations

**Allele frequencies** → **Genotype frequencies**

# Hardy-Weinberg Equilibrium

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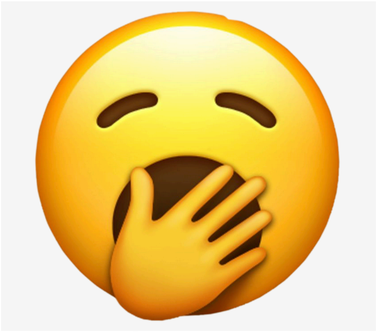
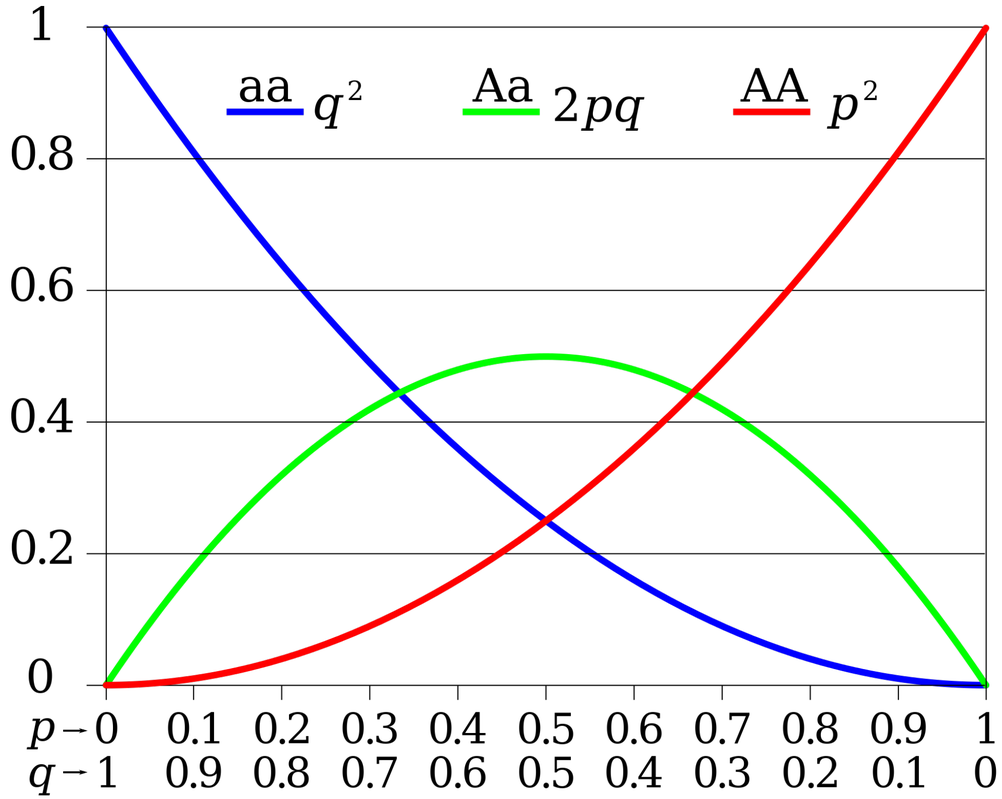


**Allele frequencies** → **Genotype frequencies**

# That being said…




https://cooplab.github.io/popgen-notes/

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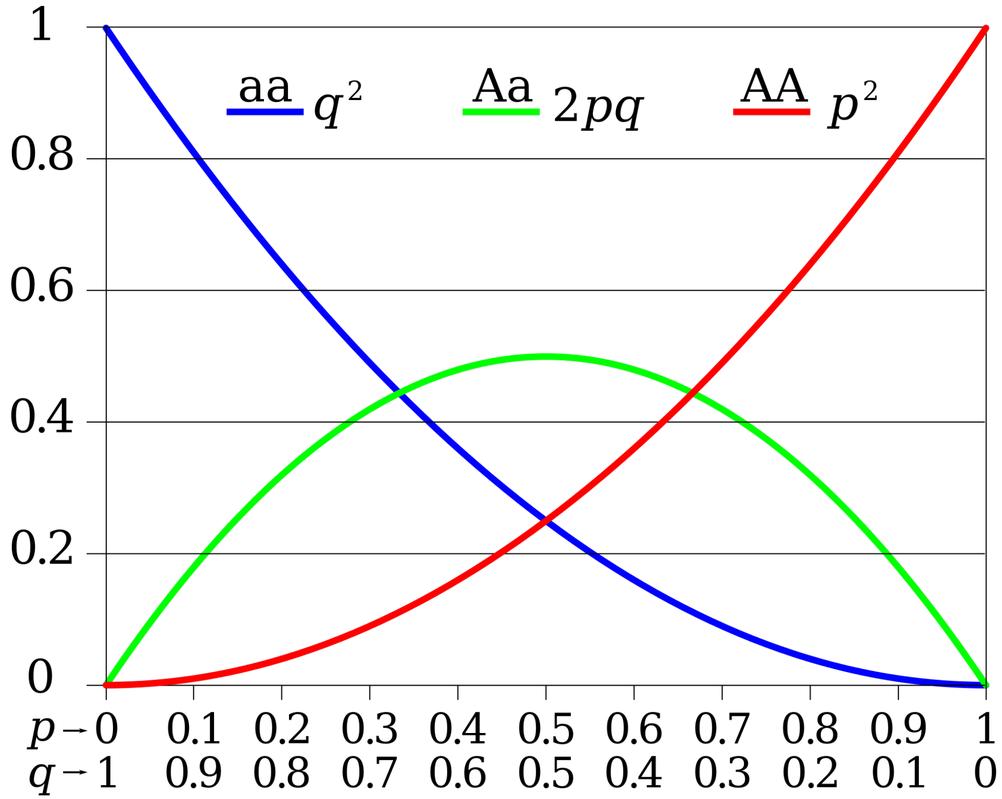


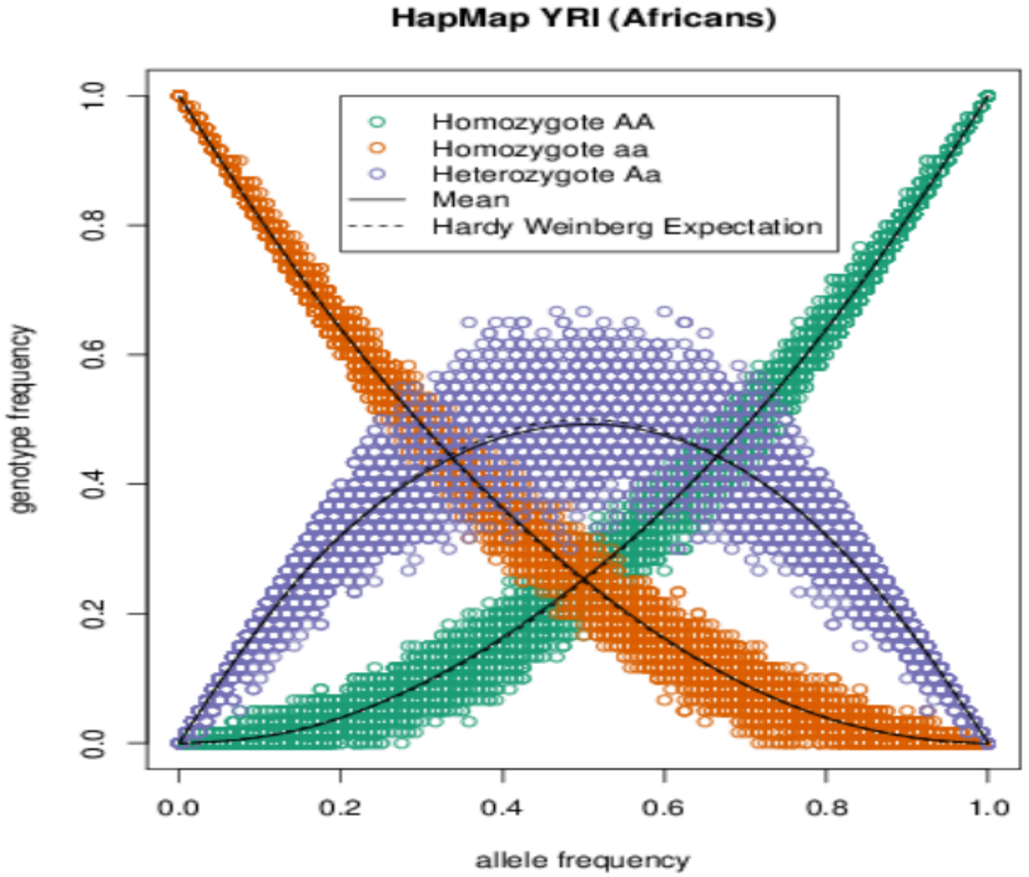


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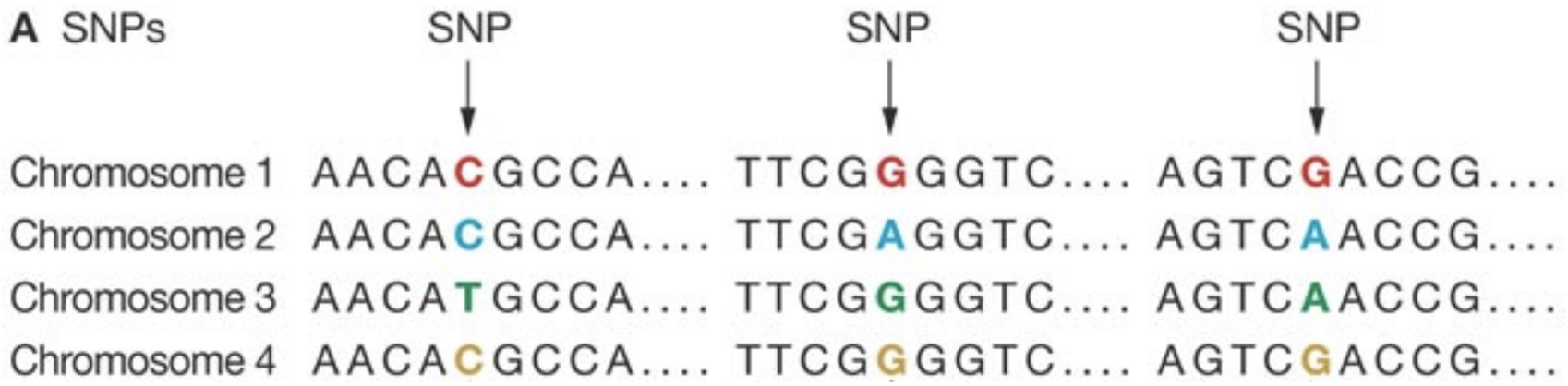

# Linkage


Haplotype 1
A A G T A C G G T T C A G G C A
Haplotype 2
T T G C G C A A C A G T A A T A
Haplotype 3
A T C T G T G A T A ? T G G T G
Haplotype 4
T T C C G C G G T T ? A G A C A

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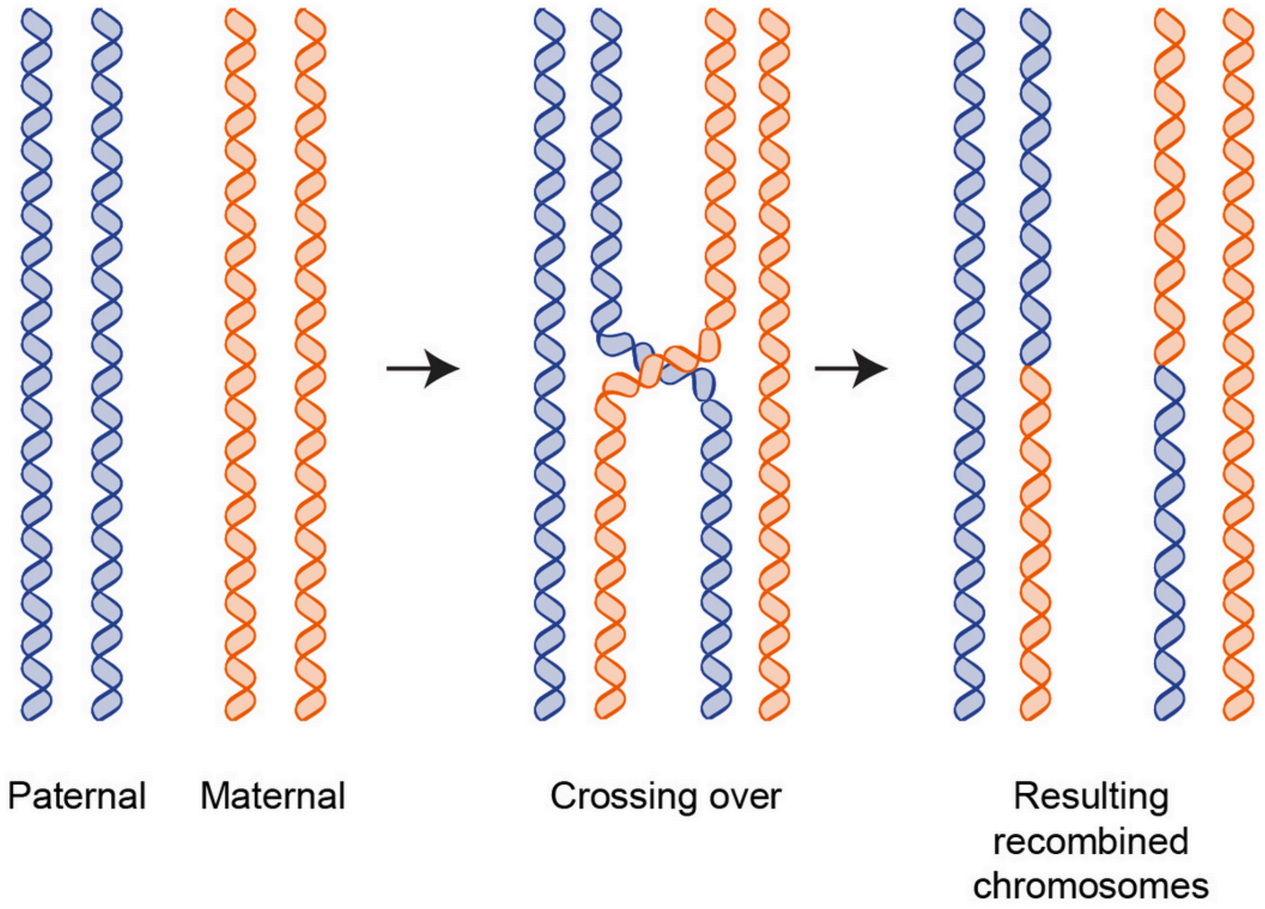
# Recombination breaks apart correlations between SNPs




https://www.genome.gov/genetics-glossary/homologous-recombination

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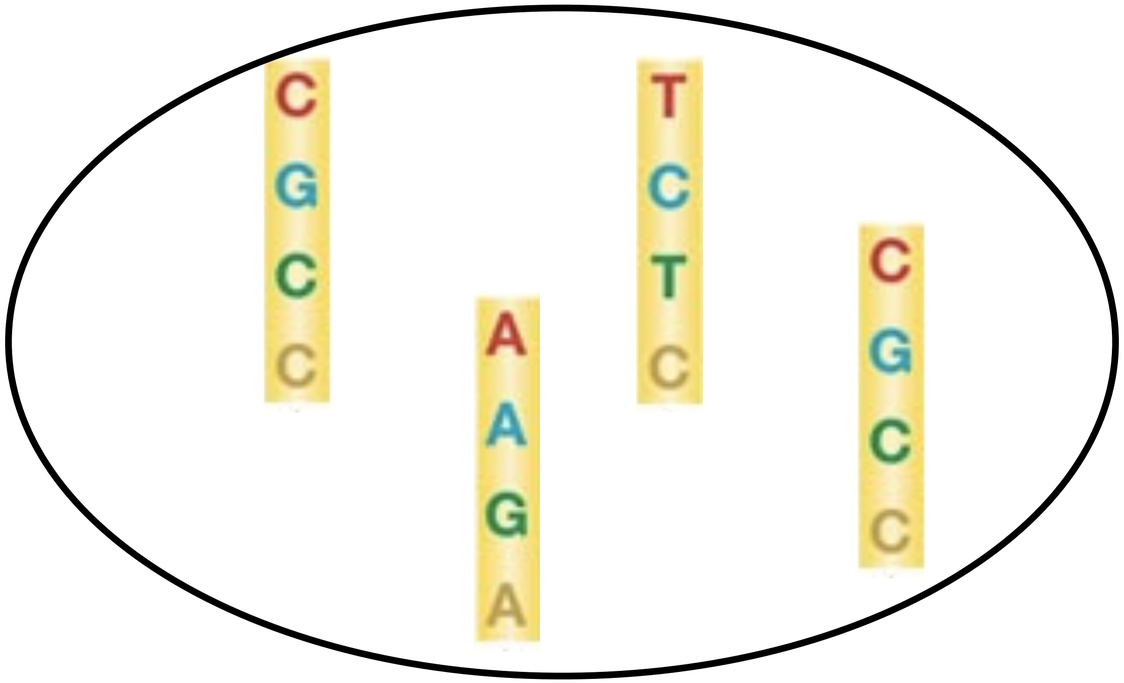

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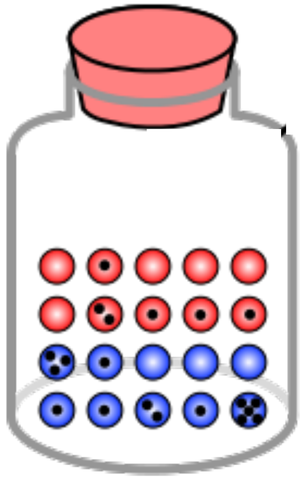
# Wright-Fisher Model

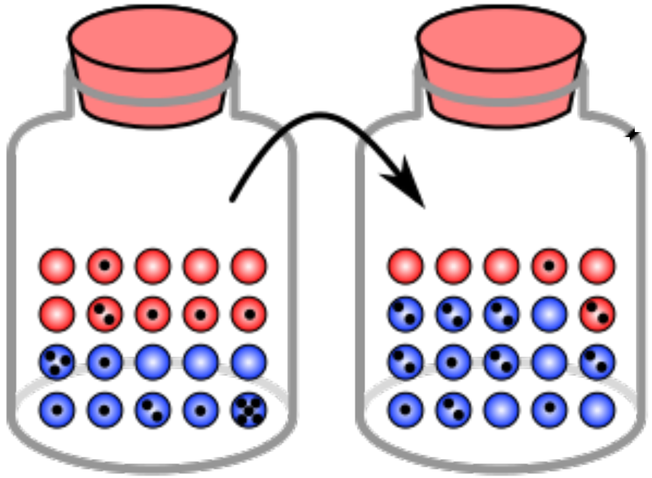
10 red

10 blue



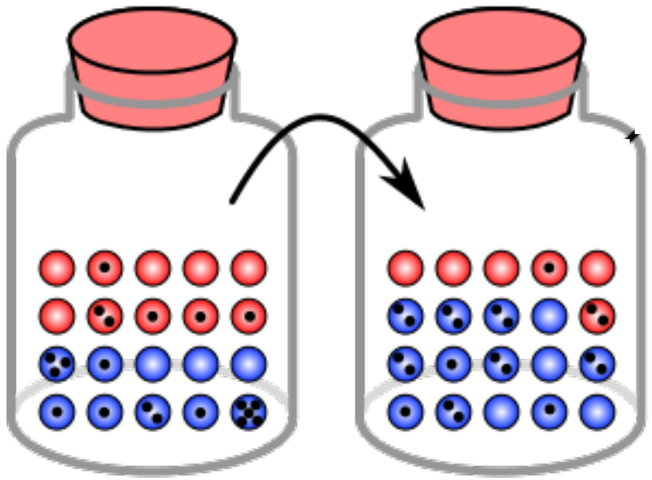
20 marbles

# Wright-Fisher Model



20 marbles  20 marbles

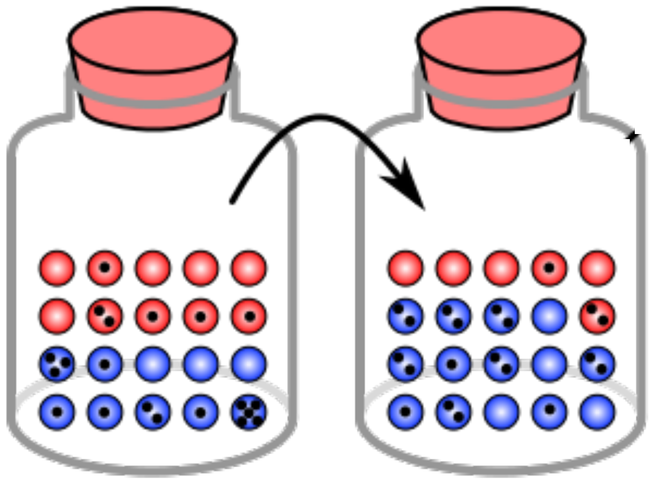
# Wright-Fisher Model



20 marbles  20 marbles

- Sample **with replacement** to fill the next jar

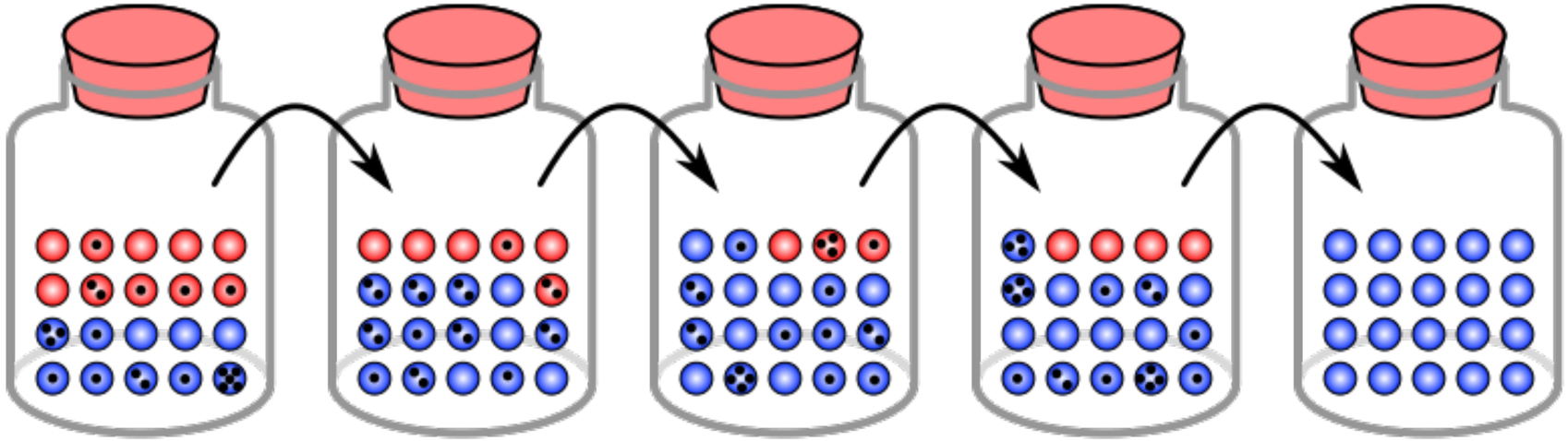
# Wright-Fisher Model



20 marbles  20 marbles

- Sample **with replacement** to fill the next jar
- The total number of marbles in each jar is the same (N = 20)

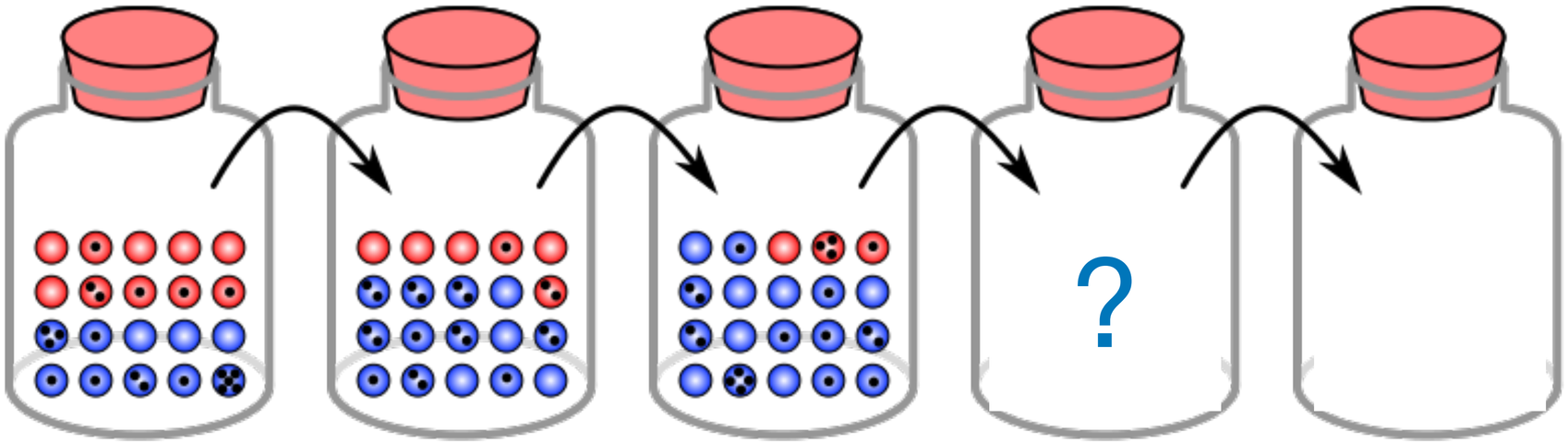
# Wright-Fisher Model



https://en.wikipedia.org/wiki/Genetic_drift#/media/File:Random_sampling_genetic_drift.svg

# Wright-Fisher Model

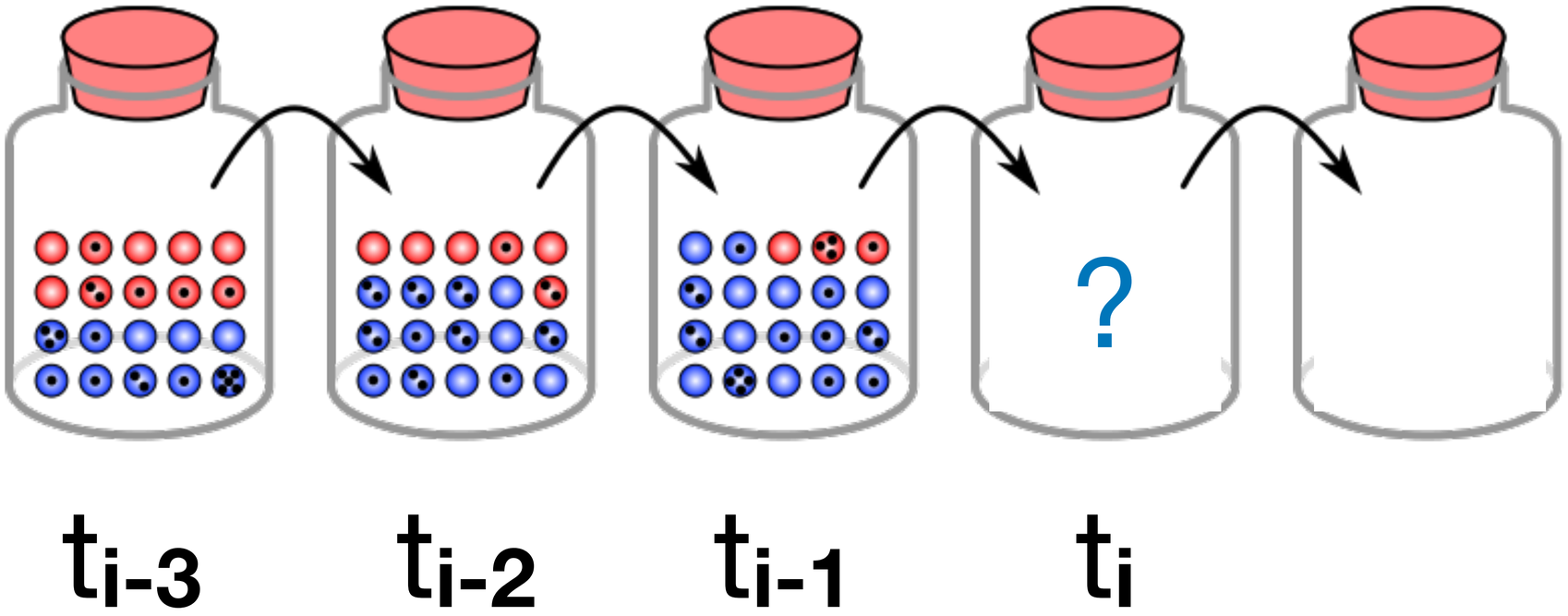
- Let's say we're interested in predicting the number of blue marbles at **time $t_i$**




$t_{i-3}$ $t_{i-2}$ $t_{i-1}$ $t_i$

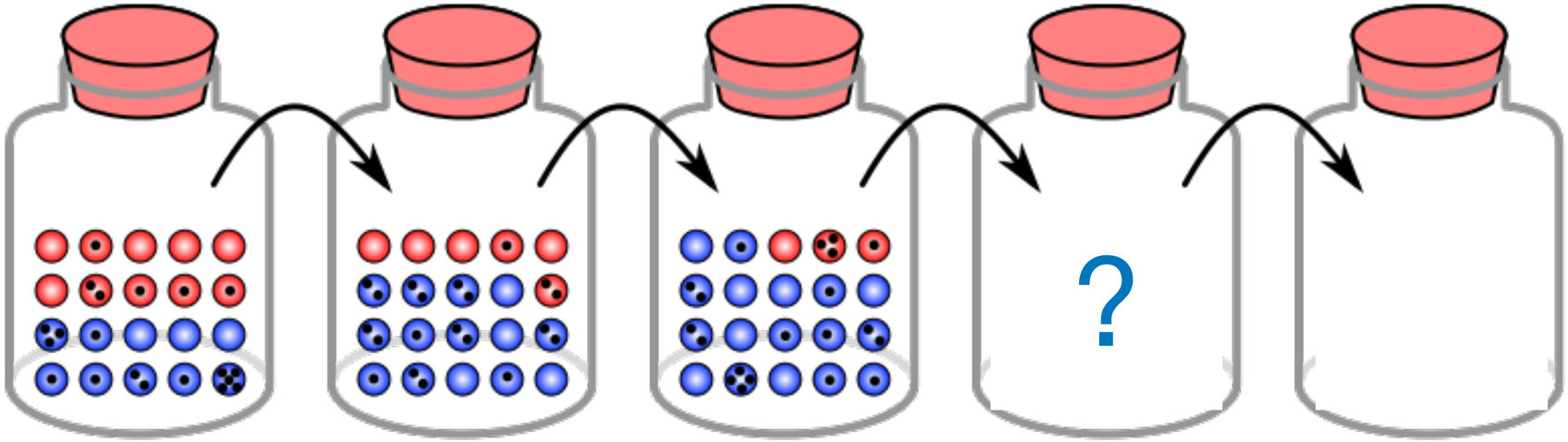
# Wright-Fisher Model

- Let $f(t_i)$ be the frequency of blue marbles at time $t_i$



# Wright-Fisher Model

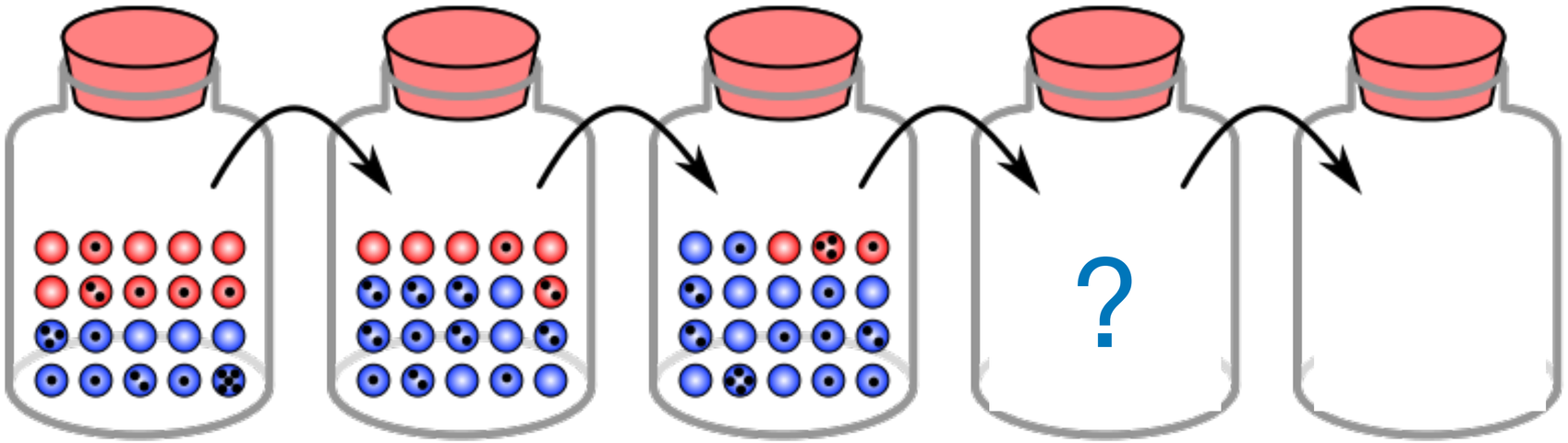
- Let $f(t_i)$ be the frequency of blue marbles at time $t_i$
- P[ # blue marbles = k | $f(t_{i-1})$, $f(t_{i-2})$, $f(t_{i-3})$, …] = P[ # blue marbles = k | $f(t_{i-1})$]




$t_{i-3}$ $t_{i-2}$ $t_{i-1}$ $t_i$

# Wright-Fisher Model

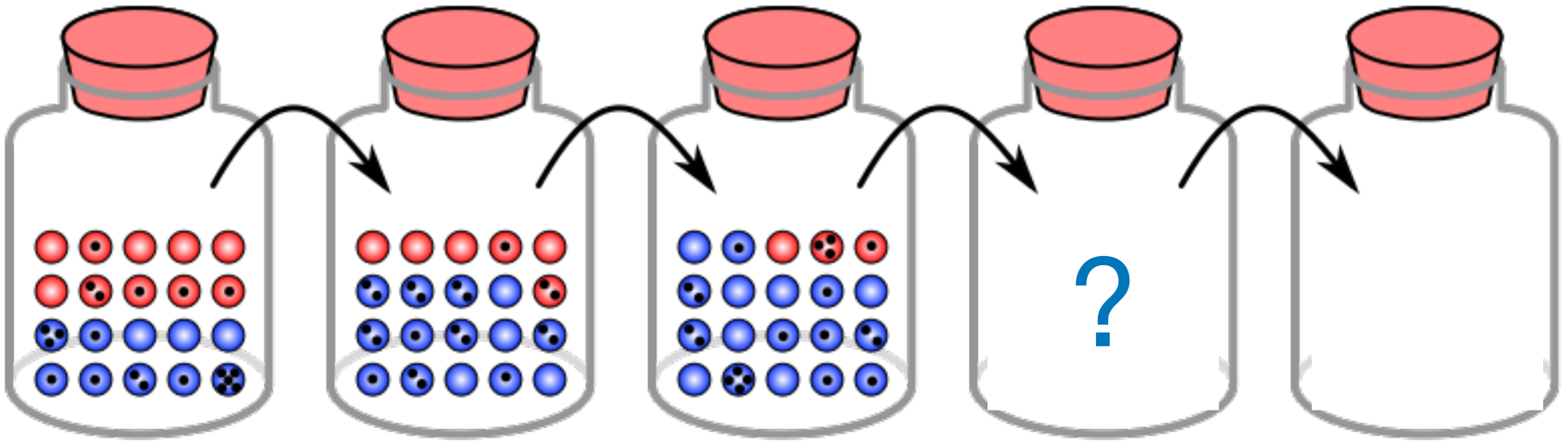
- P[ # blue marbles = k | $f(t_{i-1})$ ] = $\binom{N}{k} f(t_{i-1})^k (1 - f(t_{i-1}))^{N-k}$



# Wright-Fisher Model

Binomial distribution

- P[ # blue marbles = k | $f(t_{i-1})$ ] = $\binom{N}{k} f(t_{i-1})^k (1 - f(t_{i-1}))^{N-k}$

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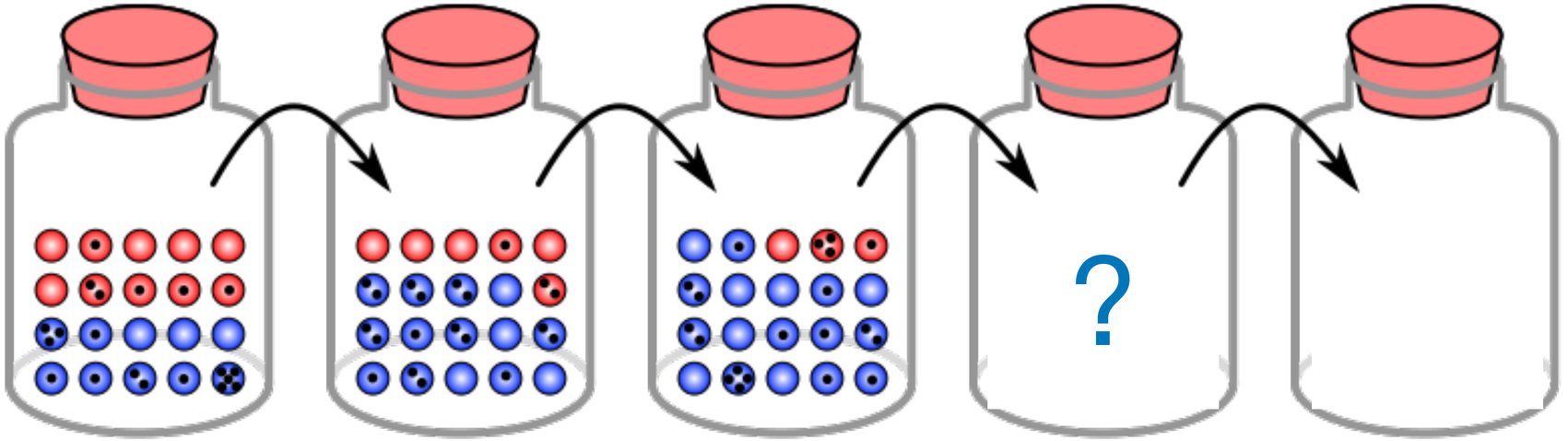
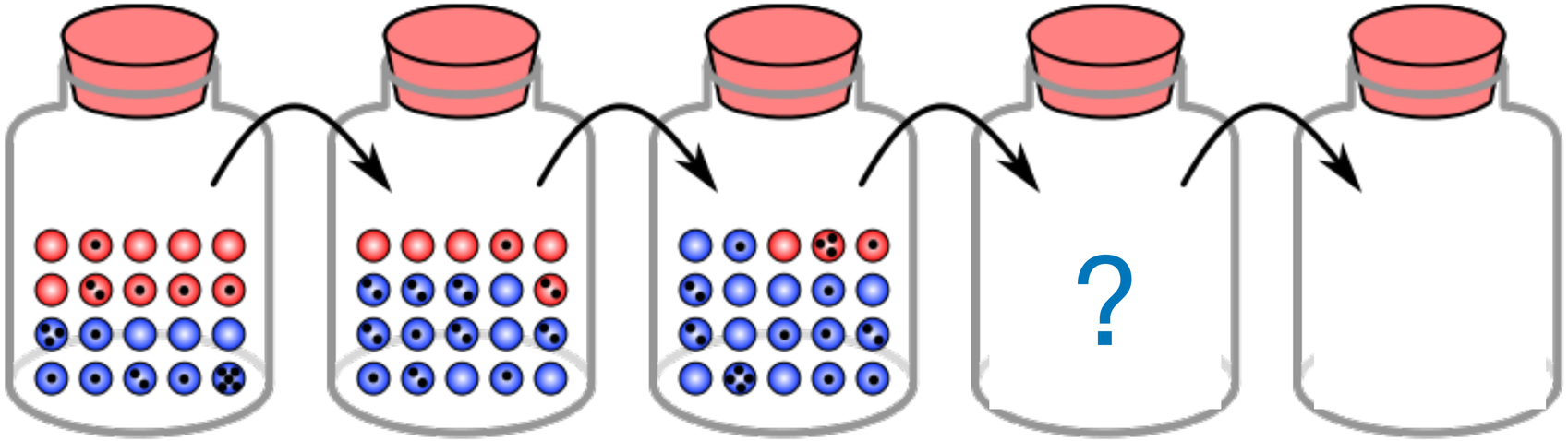


# Wright-Fisher Model

We draw a blue marble
k times

- P[ # blue marbles = k | $f(t_{i-1})$ ] = $\binom{N}{k} f(t_{i-1})^k (1 - f(t_{i-1}))^{N-k}$

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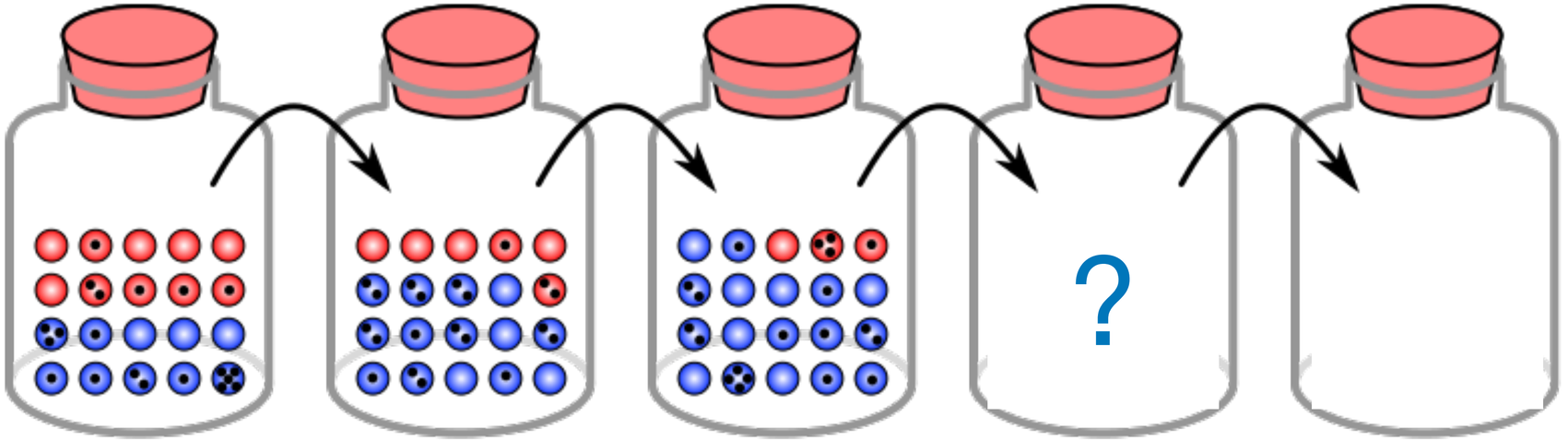


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# Wright-Fisher Model

There are these many ways to order **k** blue marbles in a set of **n marbles**

We draw a blue marble k times

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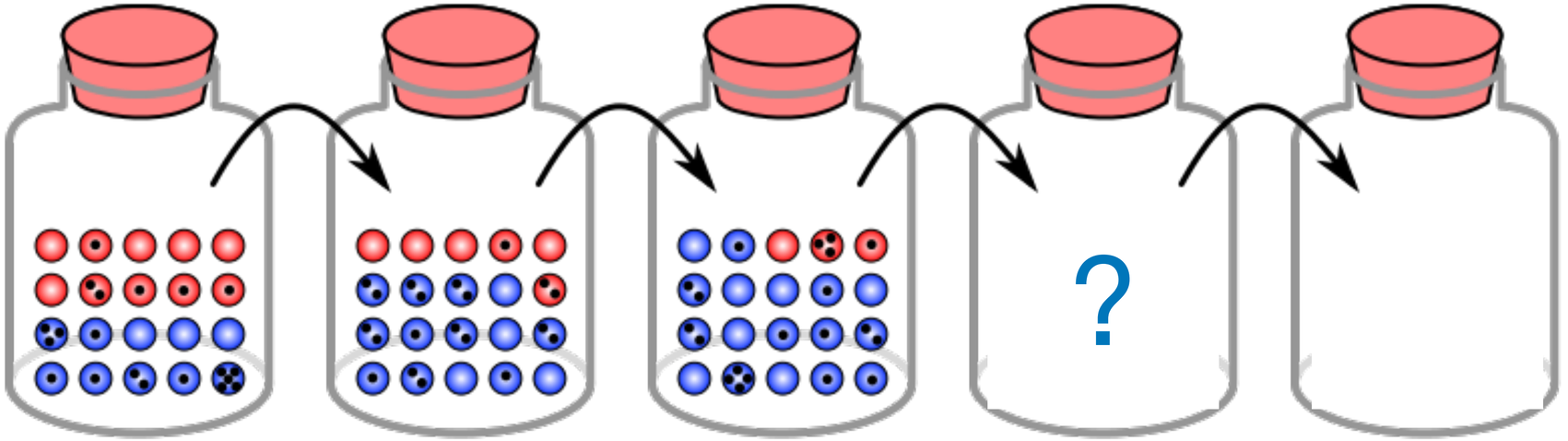
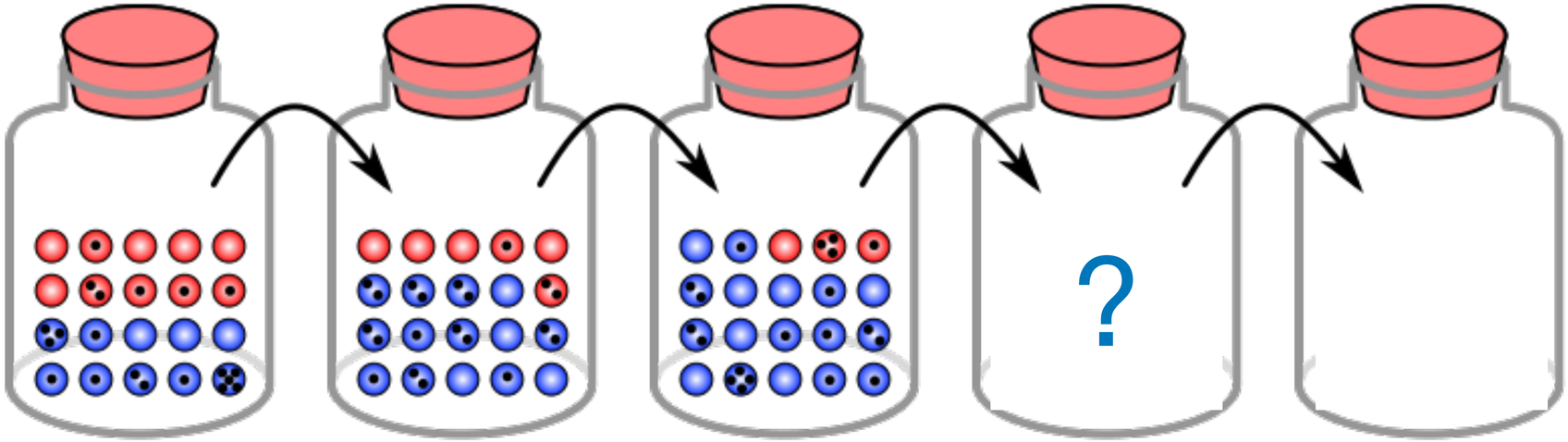
- P[ # blue marbles = k | $f(t_{i-1})$ ] = $\binom{N}{k} f(t_{i-1})^k (1 - f(t_{i-1}))^{N-k}$




$t_{i-3}$ $t_{i-2}$ $t_{i-1}$ $t_i$

# Wright-Fisher Model

- In statistics lingo, $\#\ blue\ marbles \mid f(t_{i-1}) \sim Bin(N, f(t_{i-1}))$



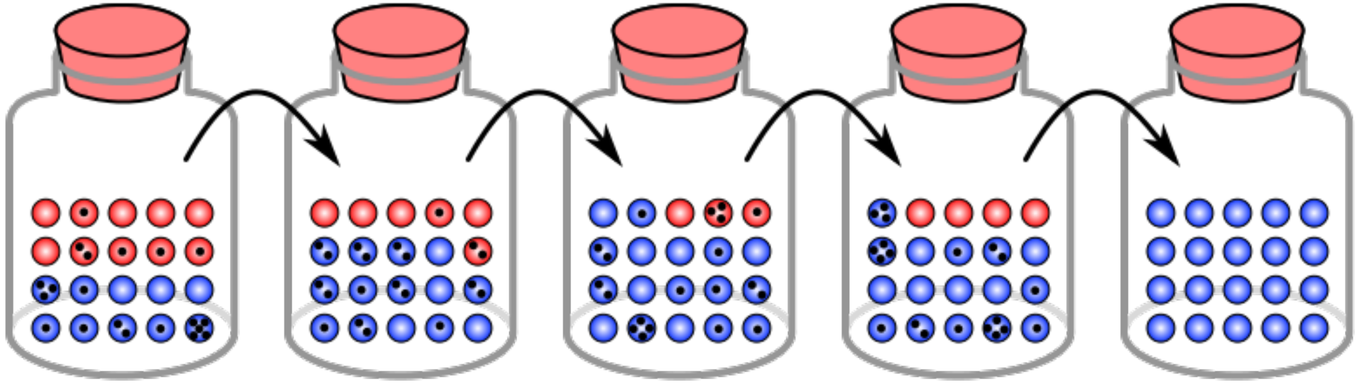
# Wright-Fisher Model

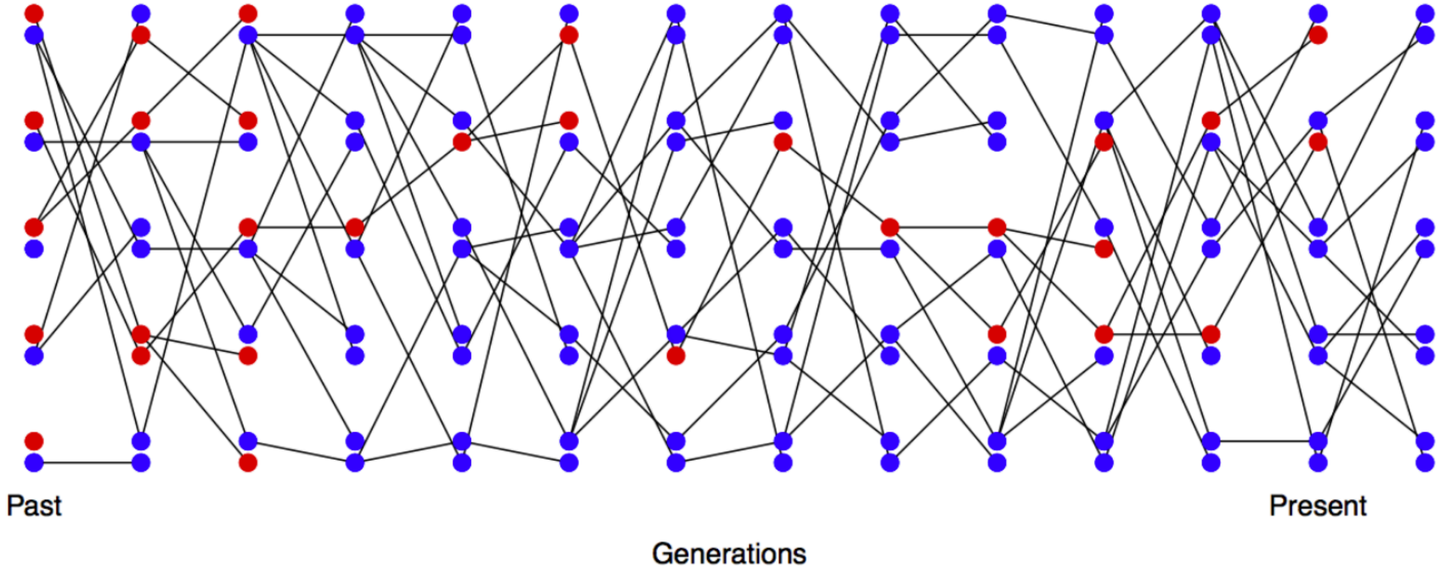
blue marbles =
blue alleles

red marbles =
red alleles

**N** total marbles =
population size **N**

Jar $\mathbf{t_i}$ =
Generation $\mathbf{t_i}$



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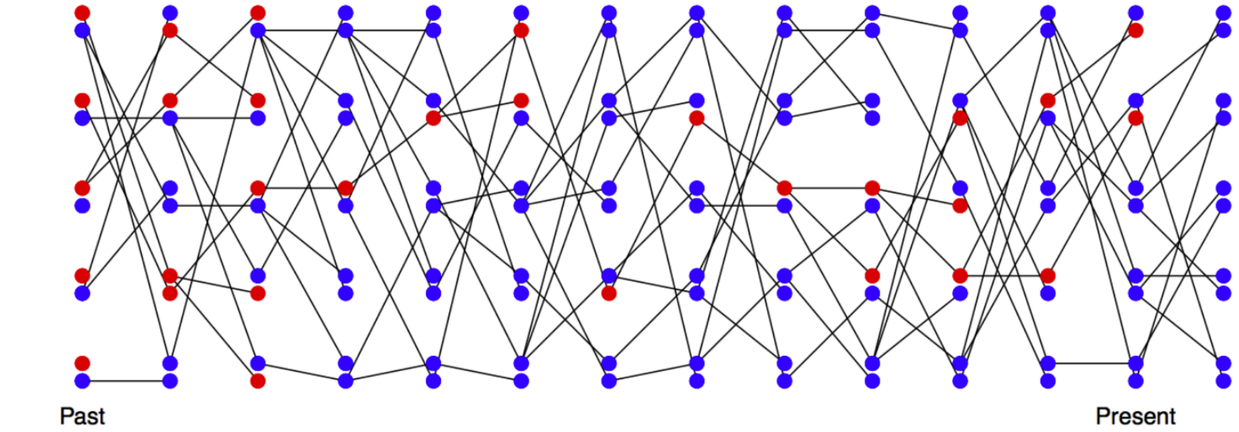


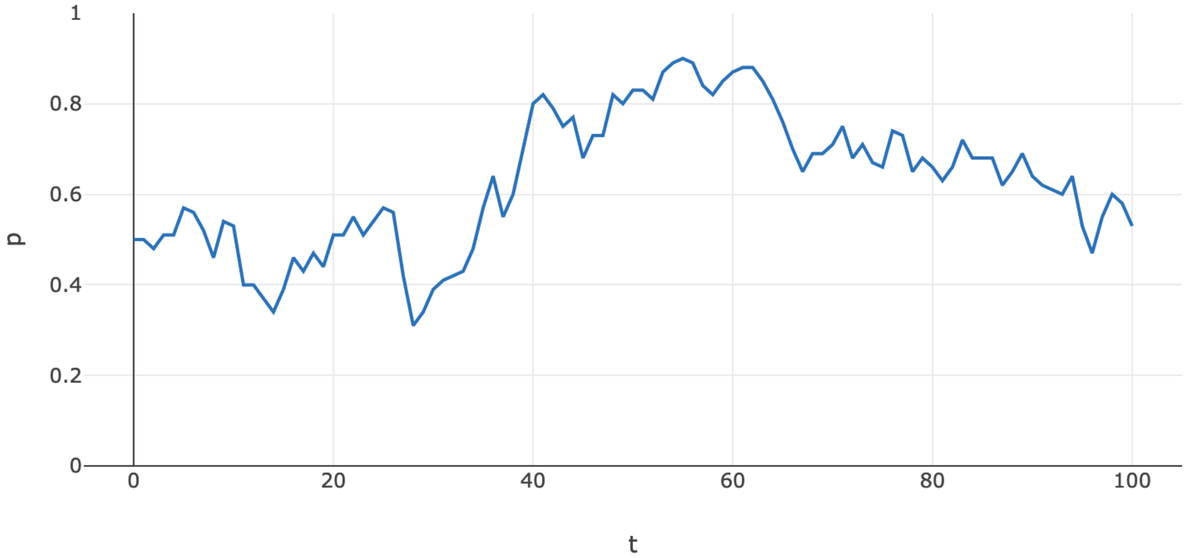


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- Constant population size
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- **N** if we are studying a population of N haploid organisms.
- **2N** if we are studying a population of N diploid organisms (which we treat as if they were equivalent to a haploid population twice its size)

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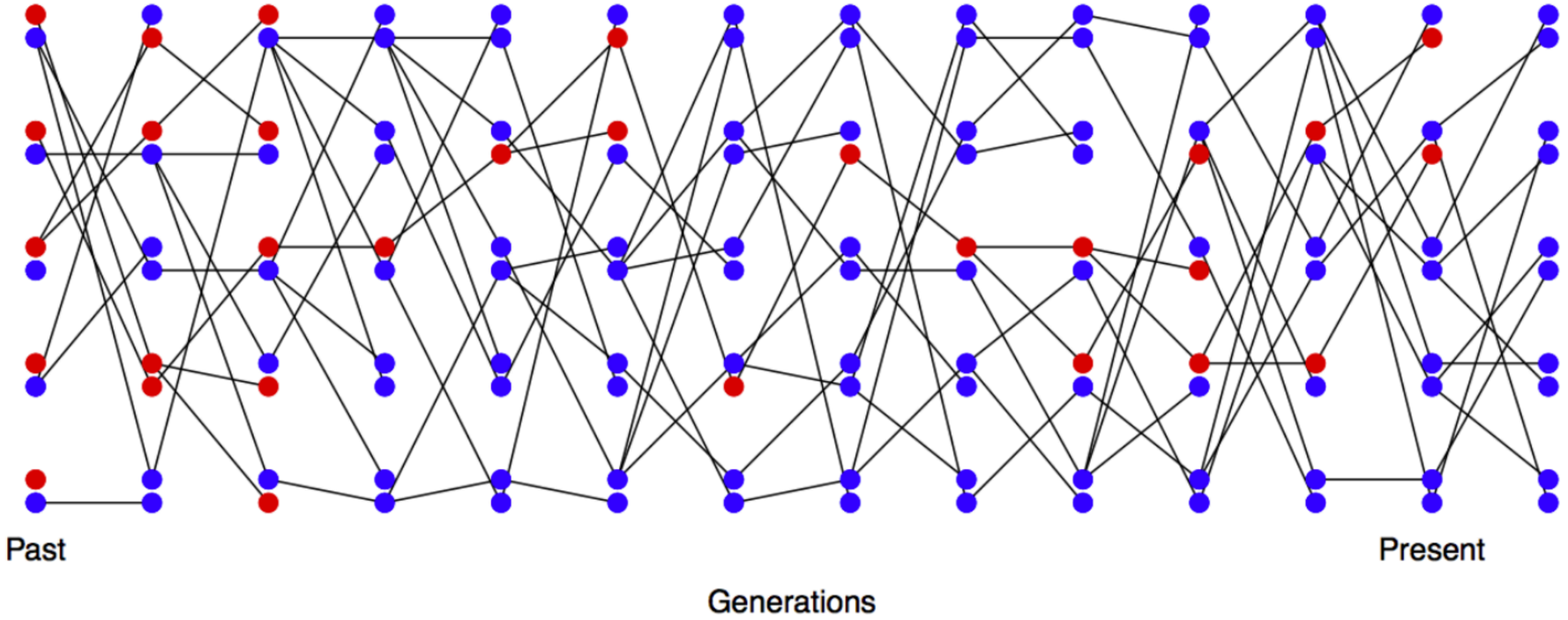
What assumption of the Hardy-Weinberg model are we now relaxing?

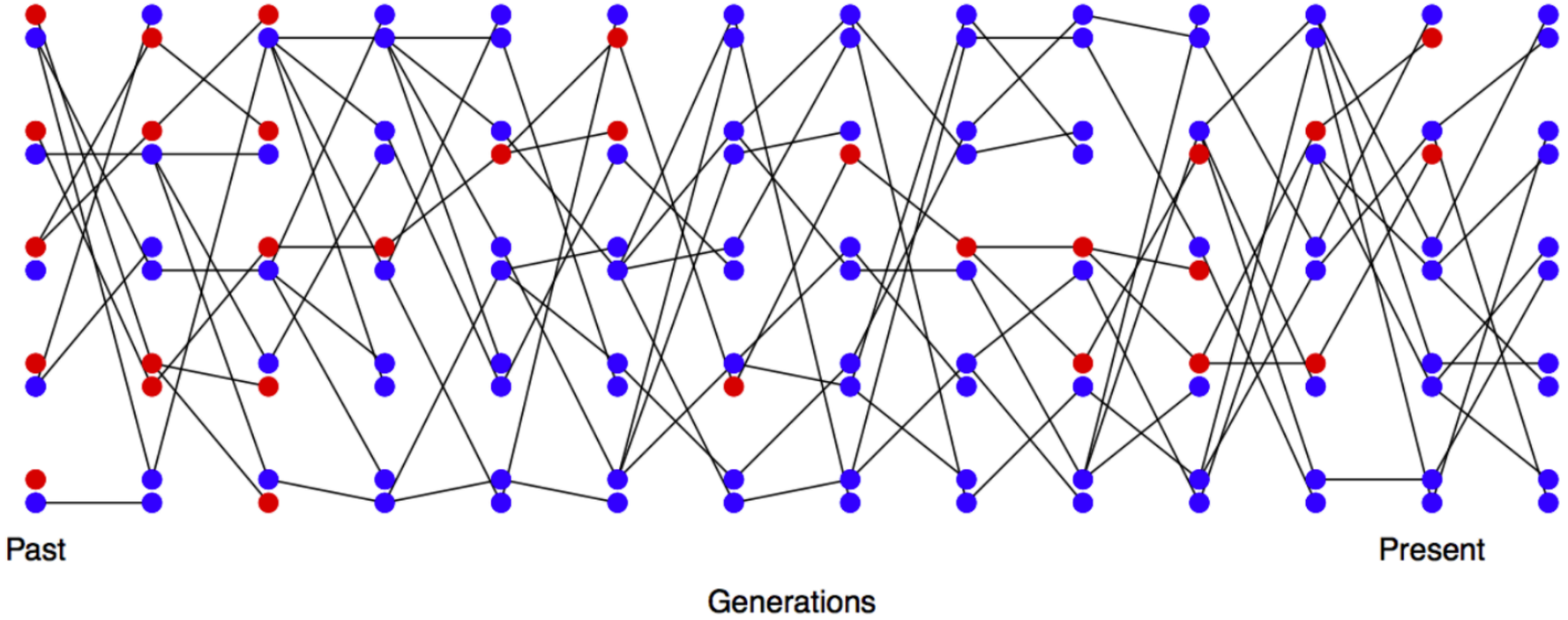
# Wright-Fisher Model




https://cooplab.github.io/popgen-notes/

# Wright-Fisher Model

5 diploid organisms in each generation, so **2N = 10**

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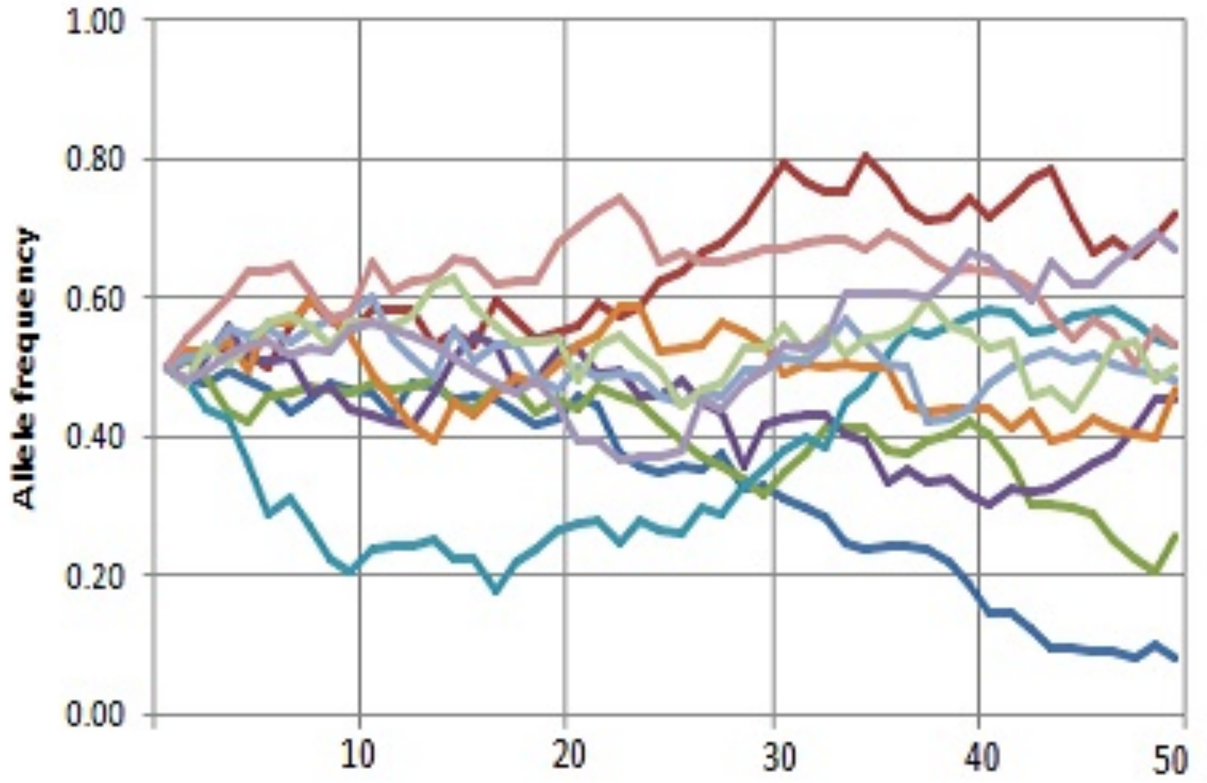
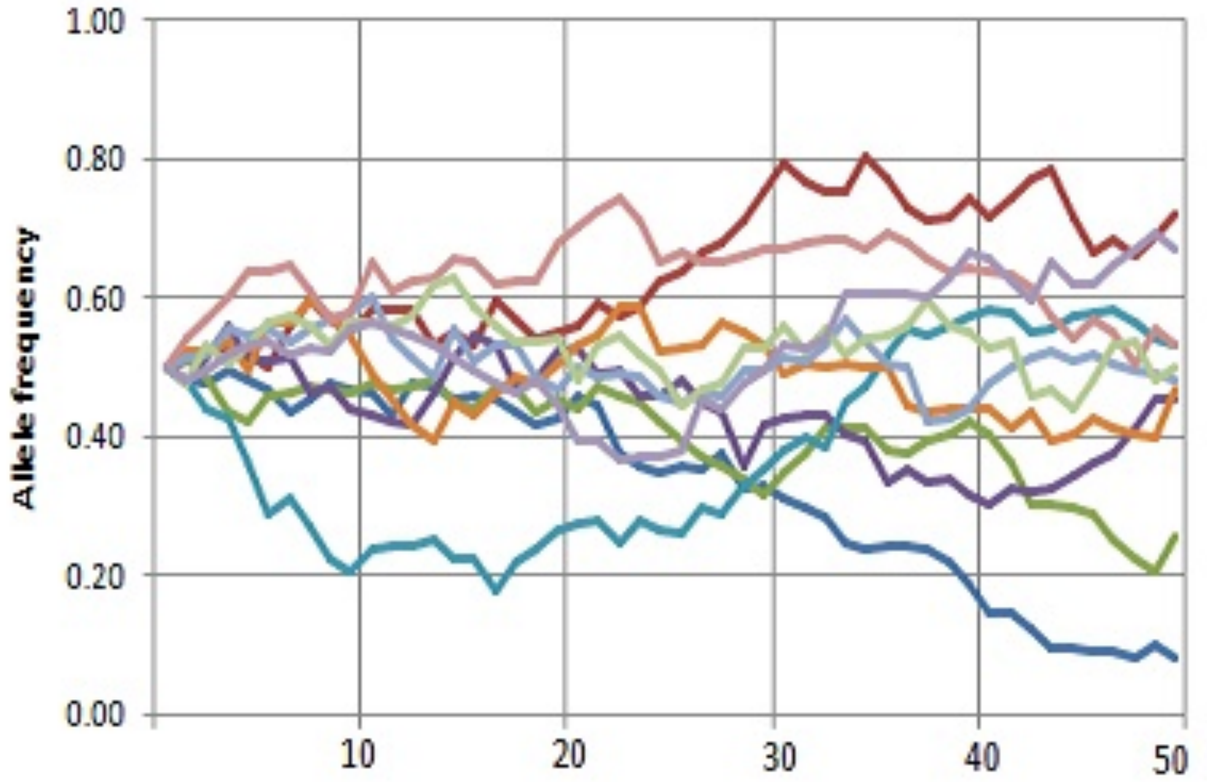


# Wright-Fisher Model

- The Wright-Fisher model is a stochastic process



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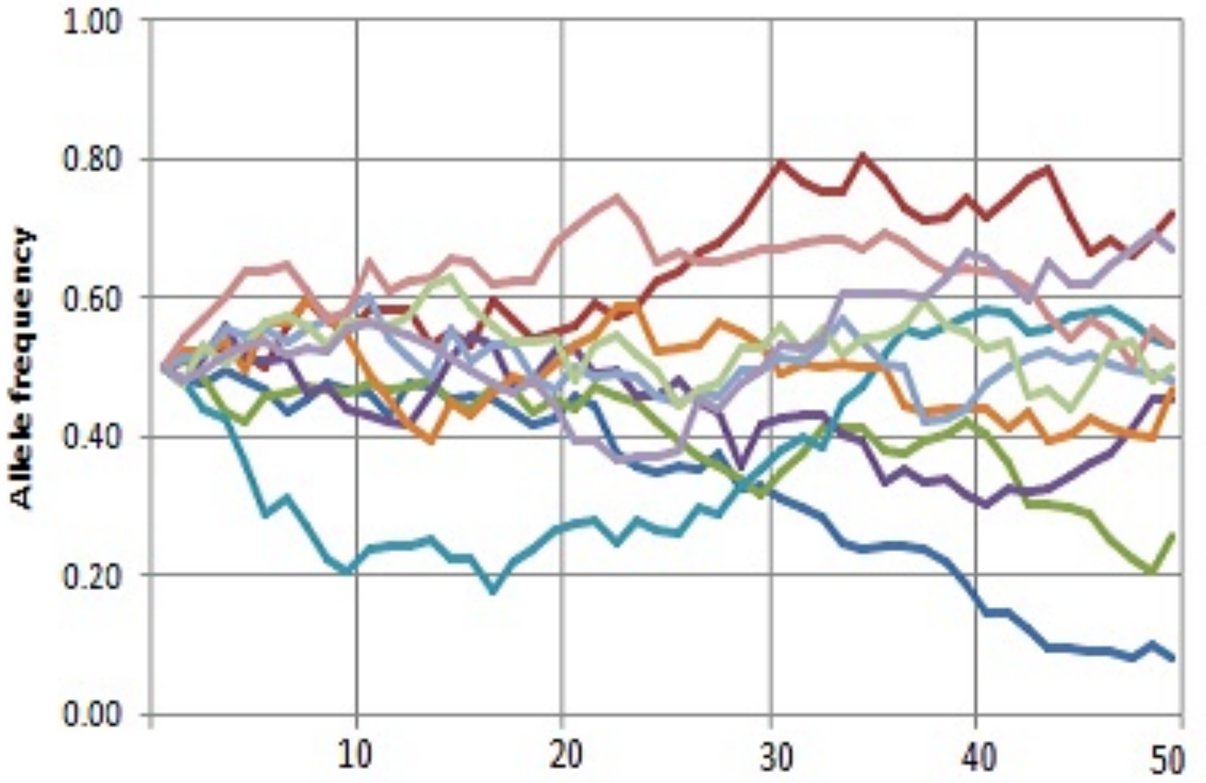
- If you start from the same allele frequency, you might end up at a different frequency **purely by chance**.



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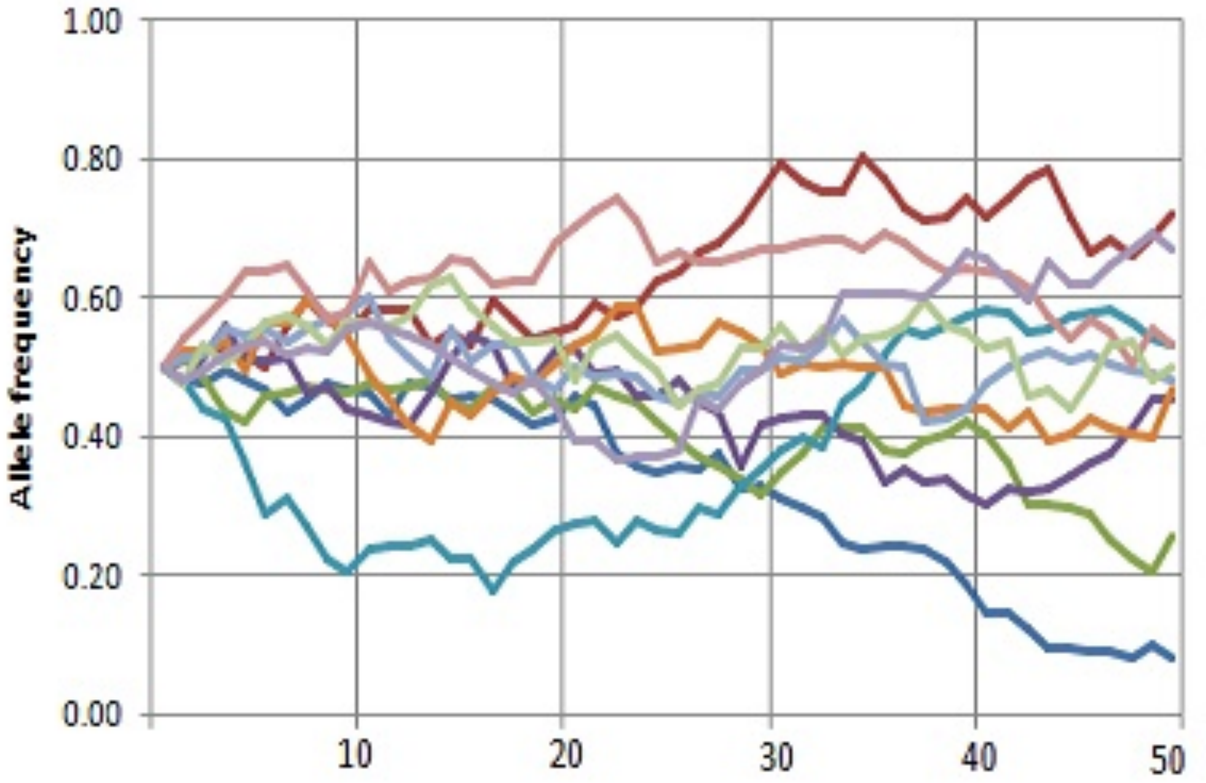

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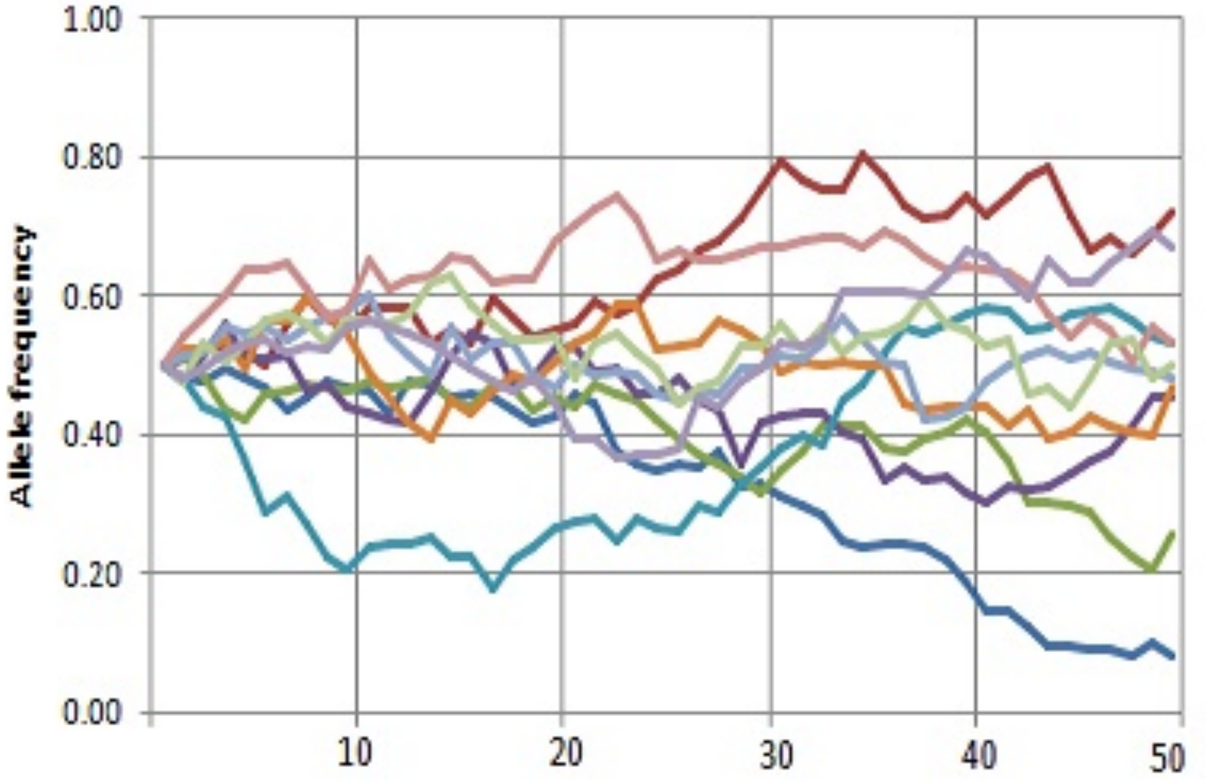
- No allele has any special advantage over the others.



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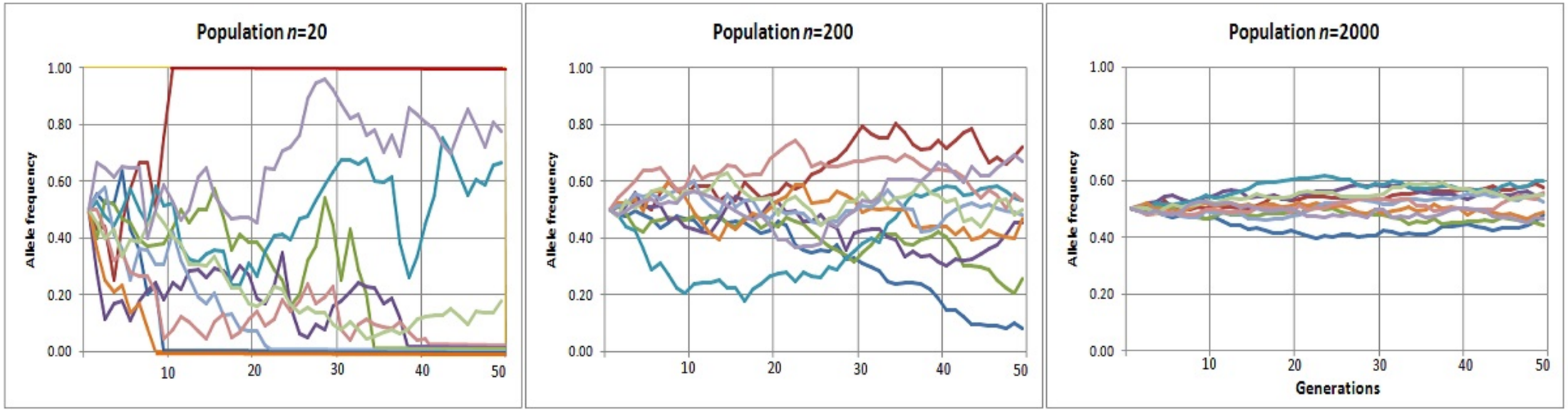
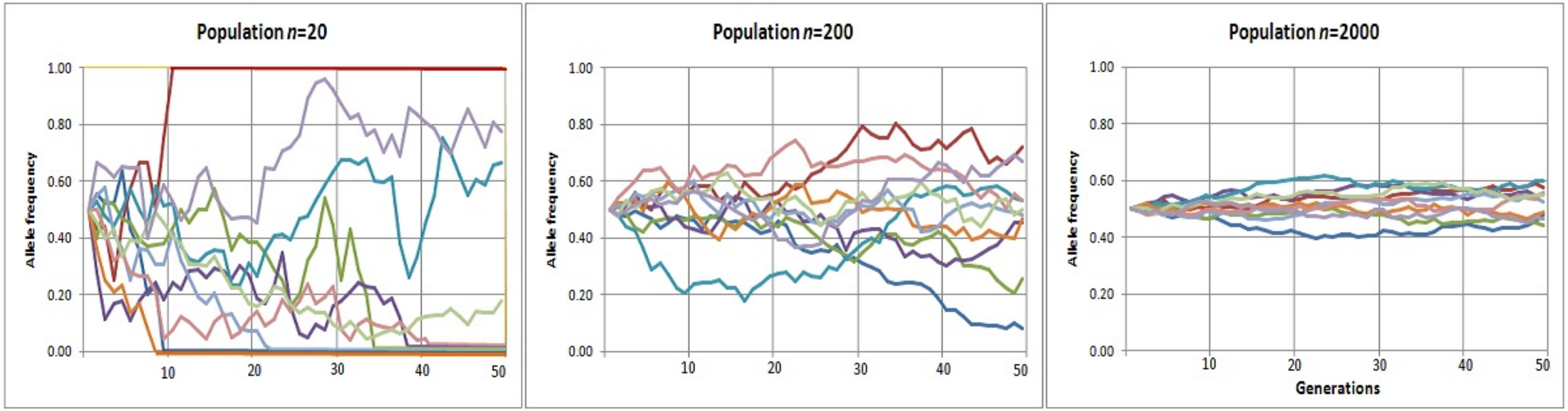


# Wright-Fisher Model

- Drift is stronger in small than in large populations



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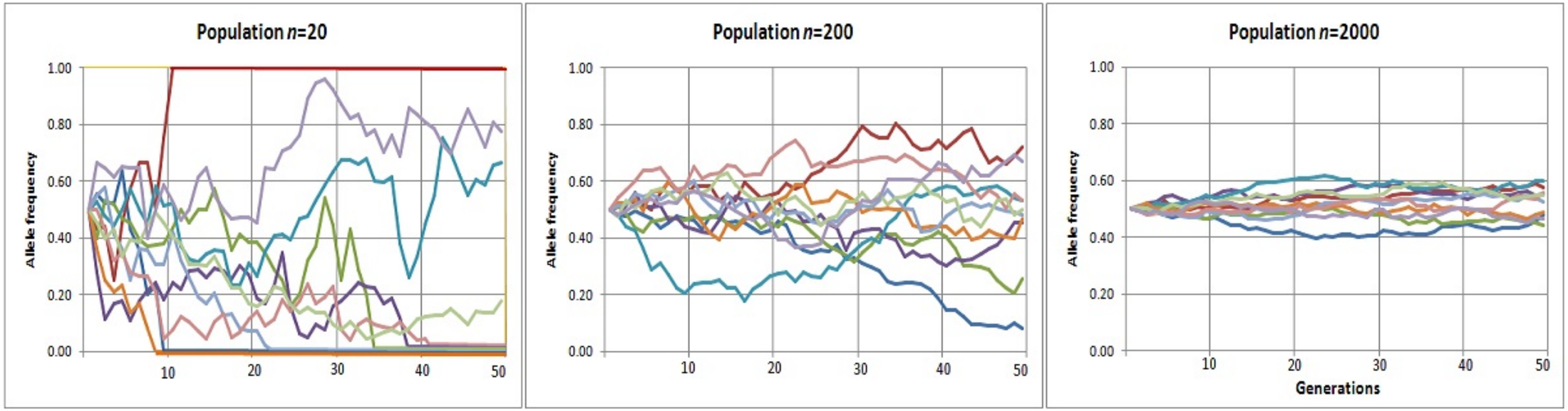

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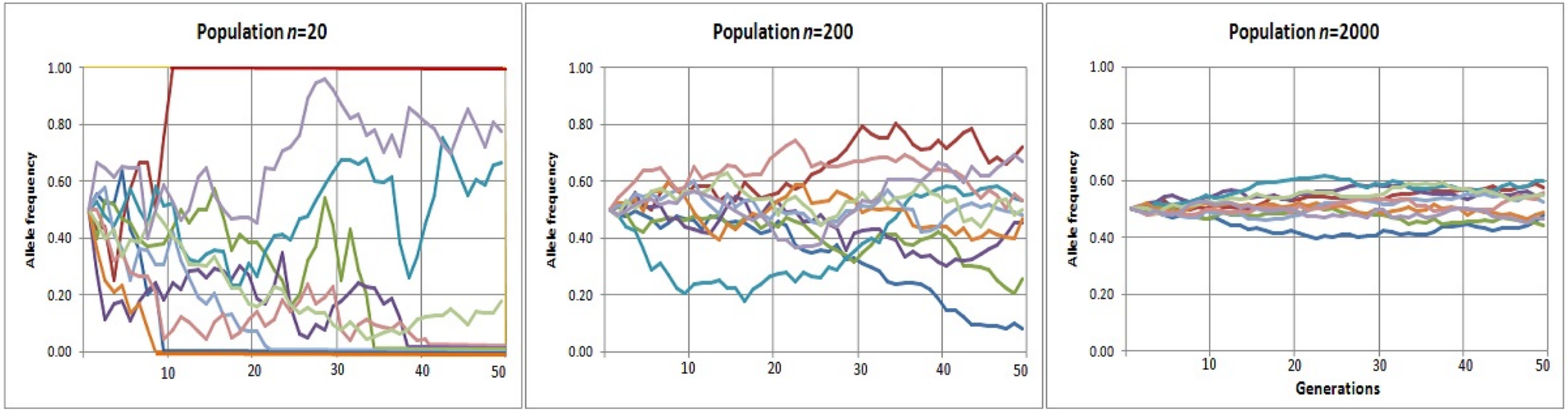
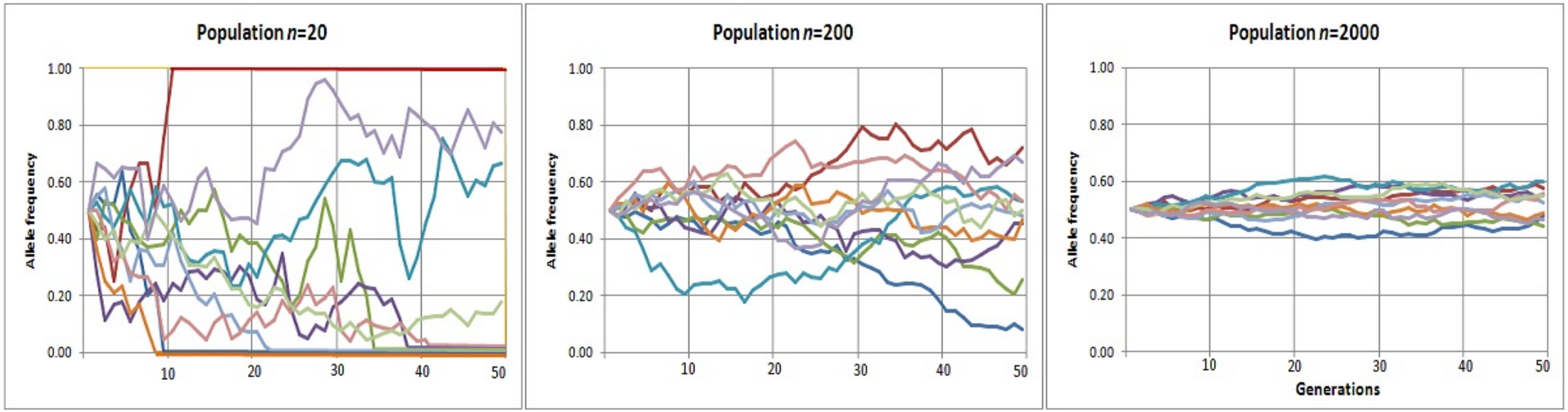


# Wright-Fisher Model

- The expected allele frequency is the same at each generation, and equal to the starting frequency p.



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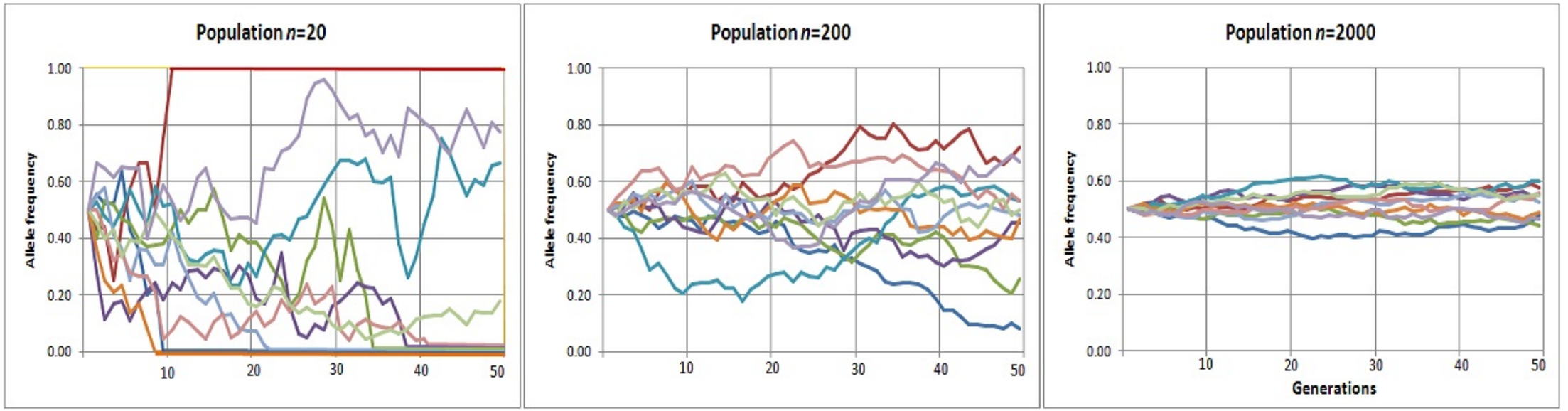

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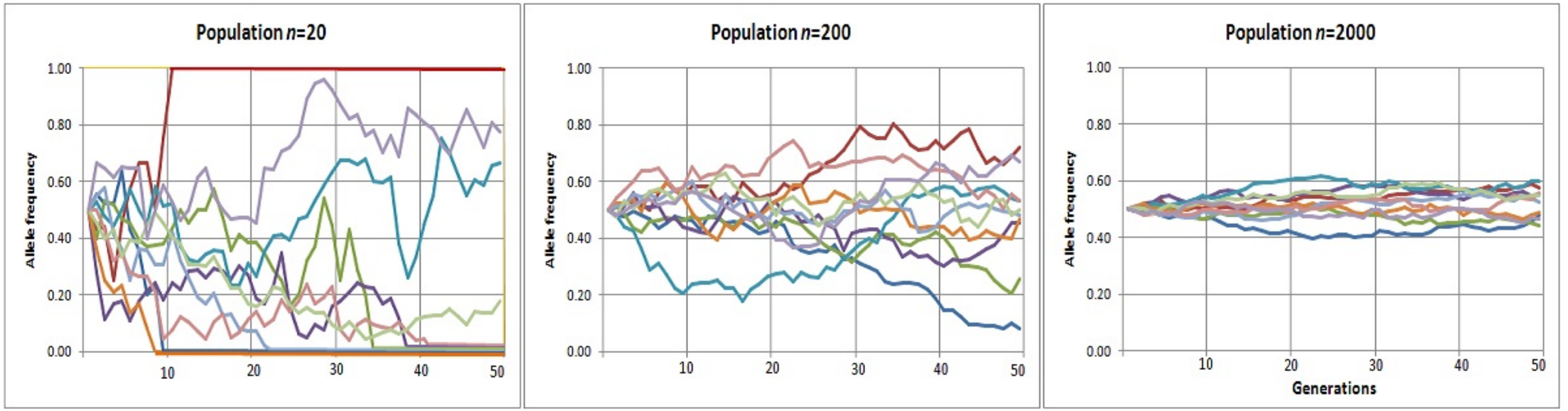

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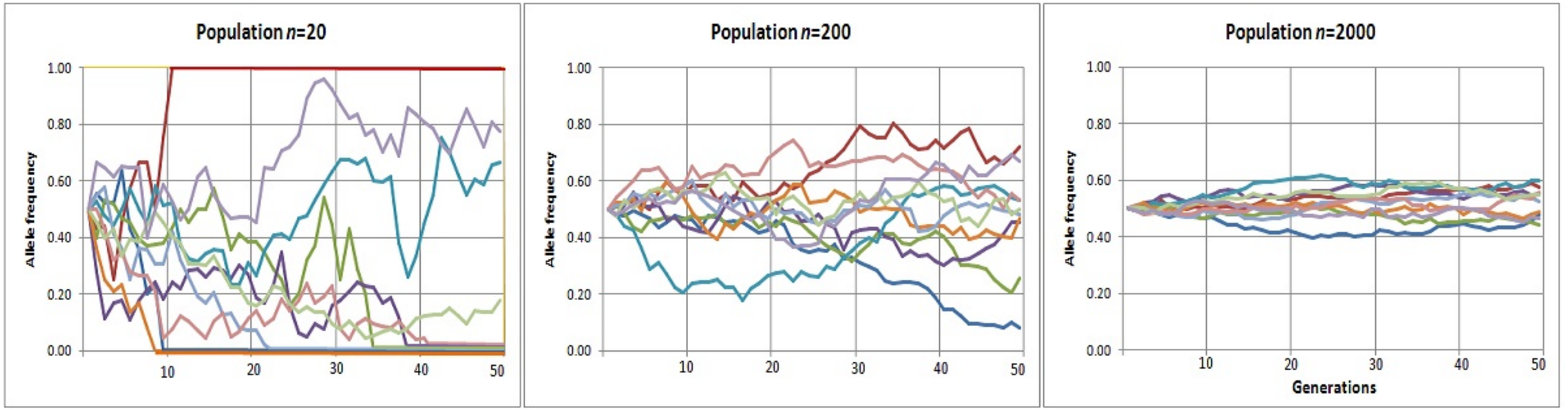
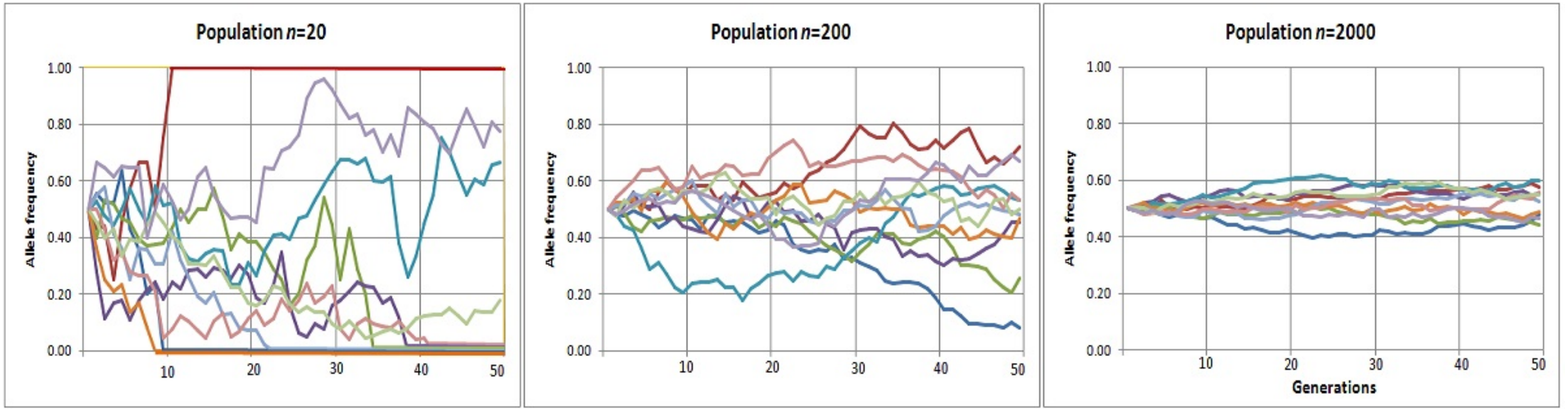


# Wright-Fisher Model

- When an allele reaches a frequency of 1, we say it has **fixed.**



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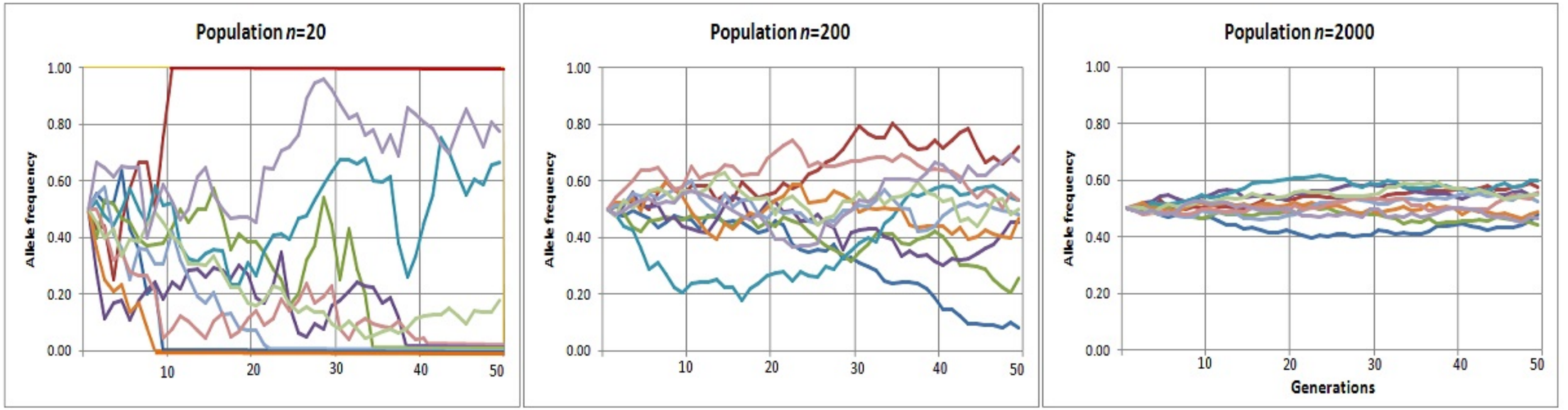
- When an allele reaches a frequency of 1, we say it has **fixed**.
- When an allele reaches a frequency of 0, we say it has **gone extinct**.



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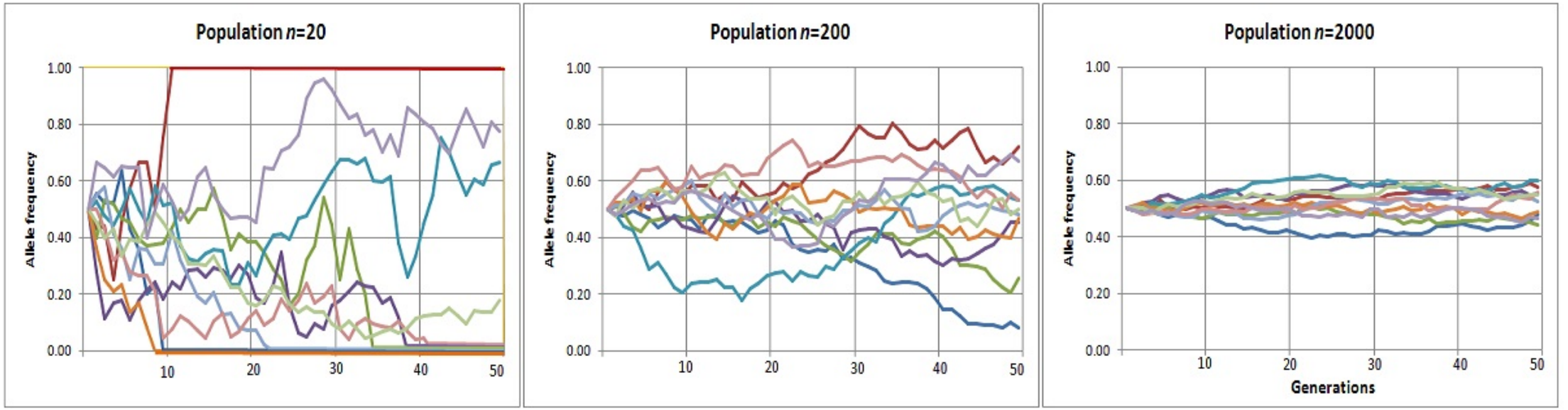
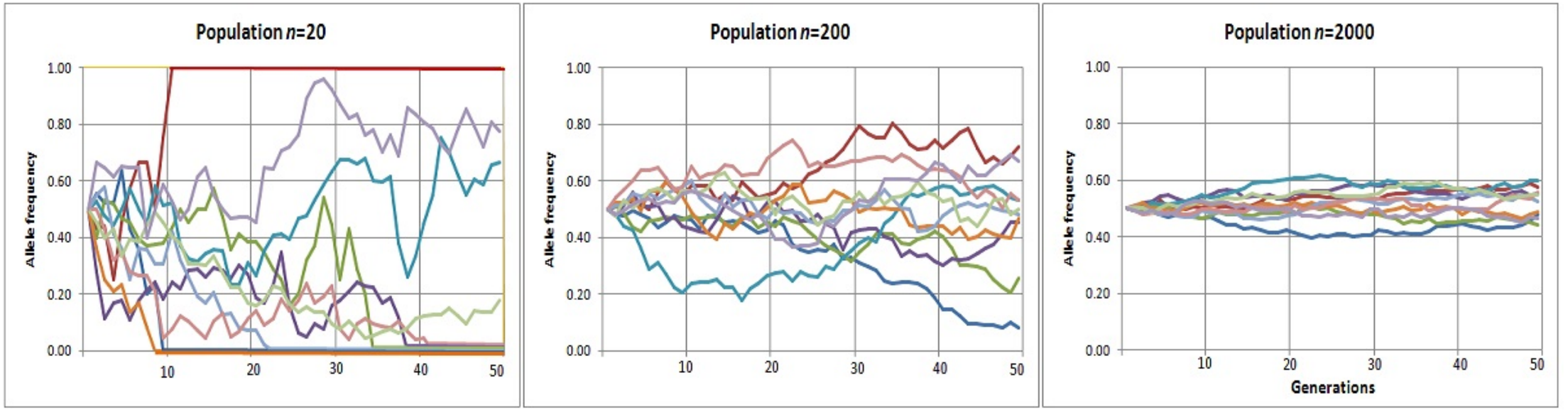


# Wright-Fisher Model

- When an allele reaches a frequency of 1, we say it has **fixed**.
- When an allele reaches a frequency of 0, we say it has **gone extinct**.
- **Assuming no recurrent mutation**, alleles that fix or go extinct remain so forever
- All alleles must eventually fix or go extinct, given enough time.



# Thinking forwards in time in time

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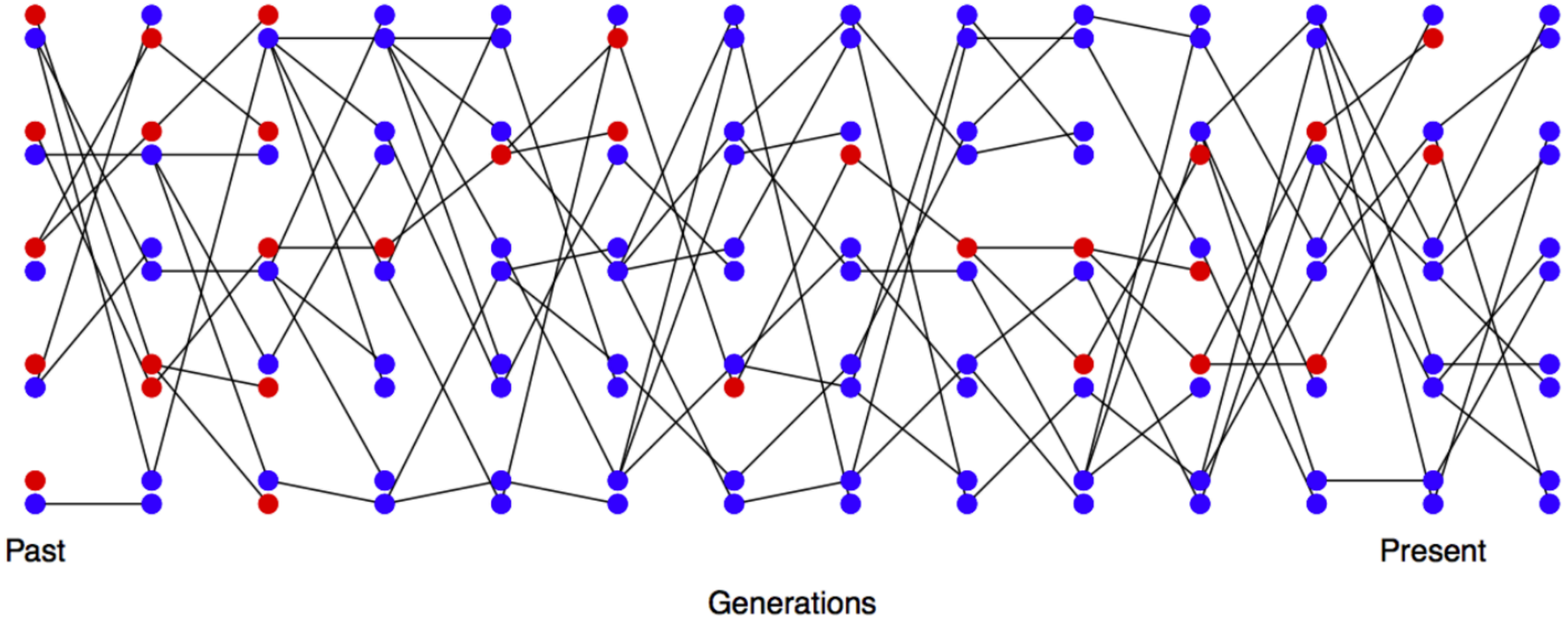
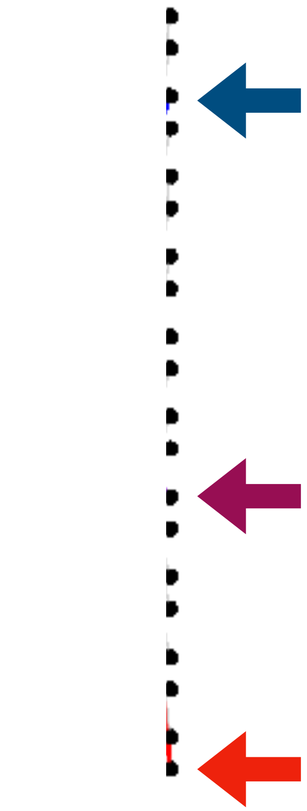


# Thinking backwards in time



Present-day population

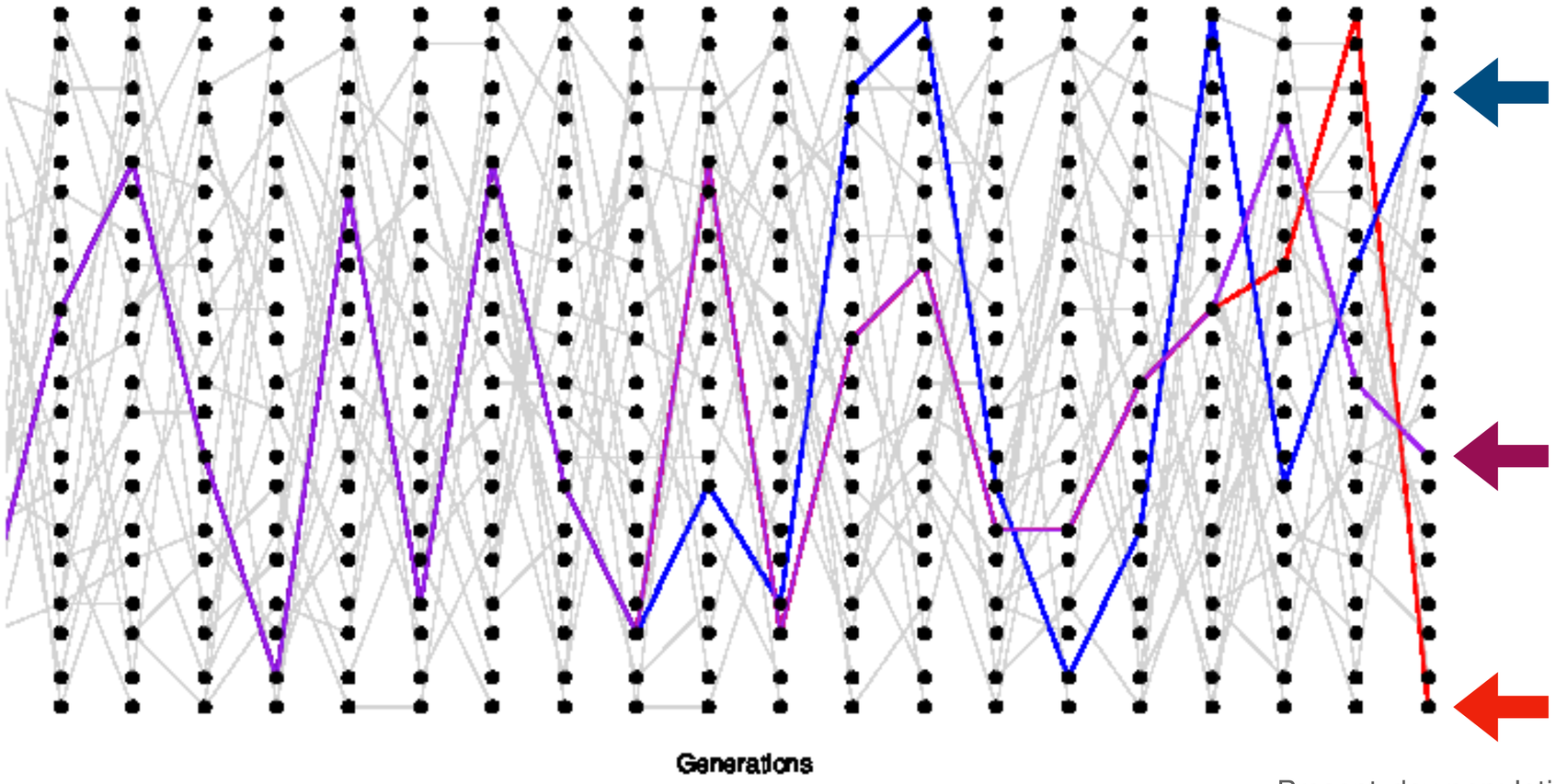
# Thinking backwards in time



We sample n=3 alleles in a population of size 2N=20

Present-day population

# Thinking backwards in time

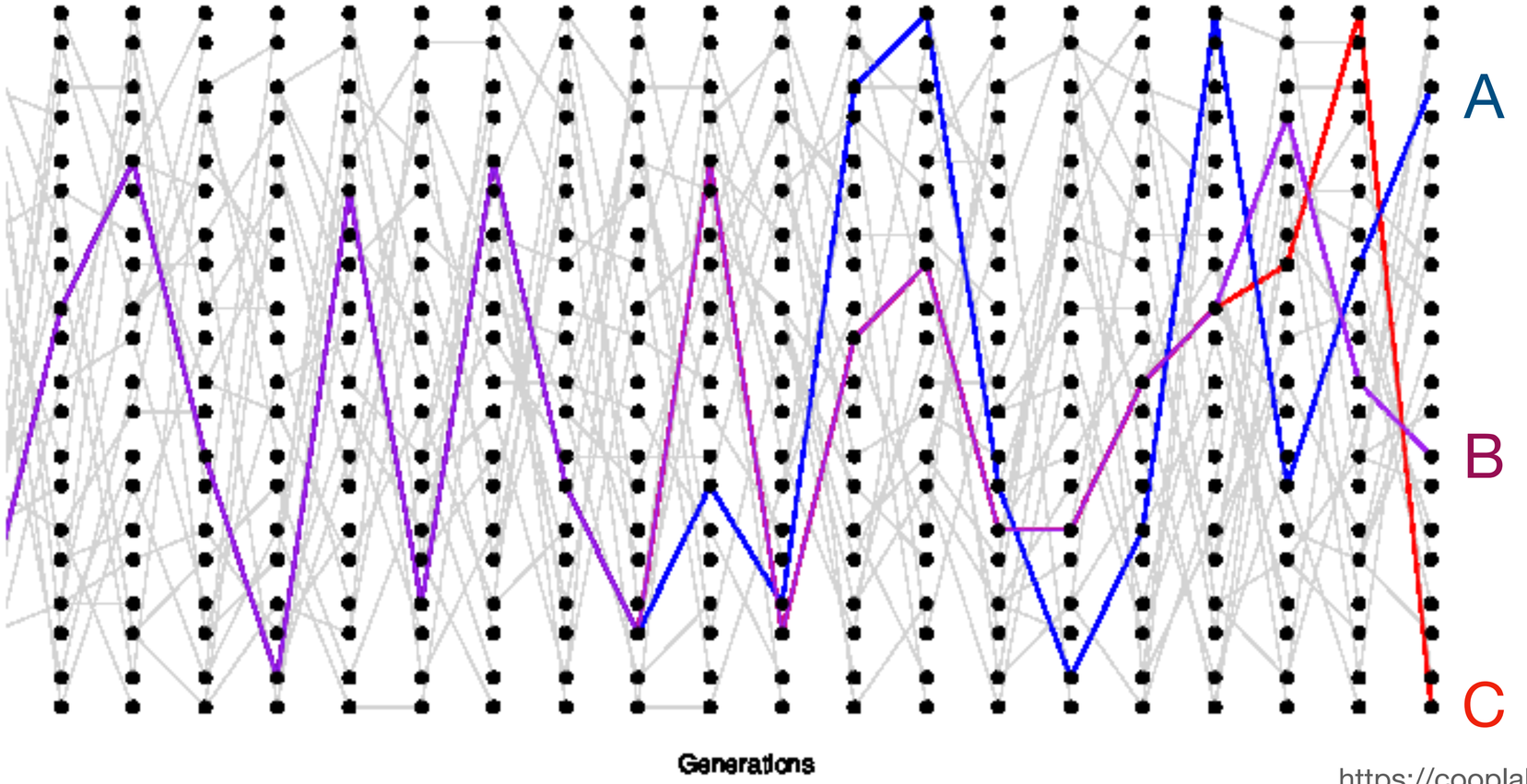



We sample n=3 alleles in a population of size 2N=20

Present-day population

We trace their lineages into the past

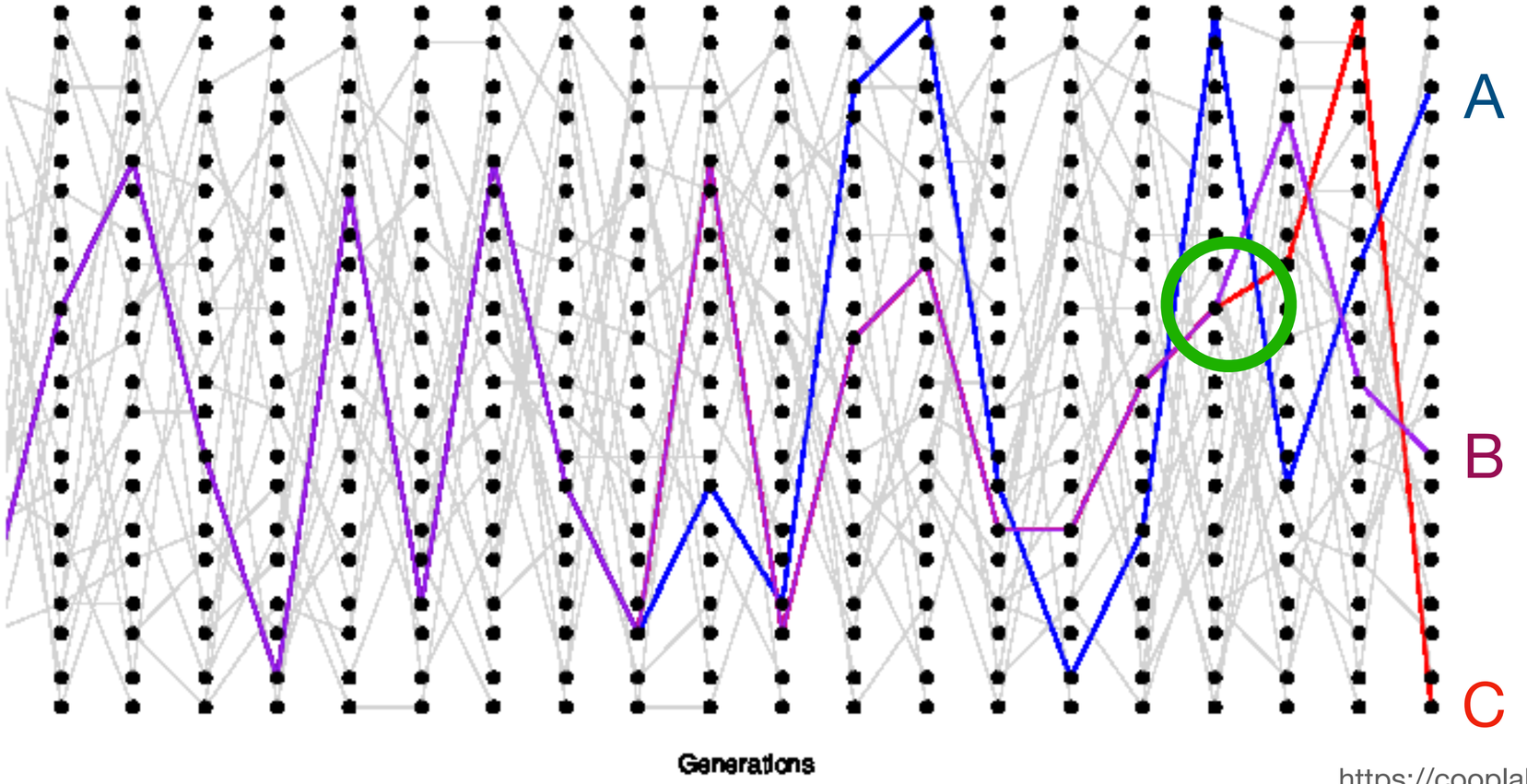
# Thinking backwards in time




https://cooplab.github.io/popgen-notes/

# Thinking backwards in time

Coalescence between lineages
B and C -> new lineage “D”

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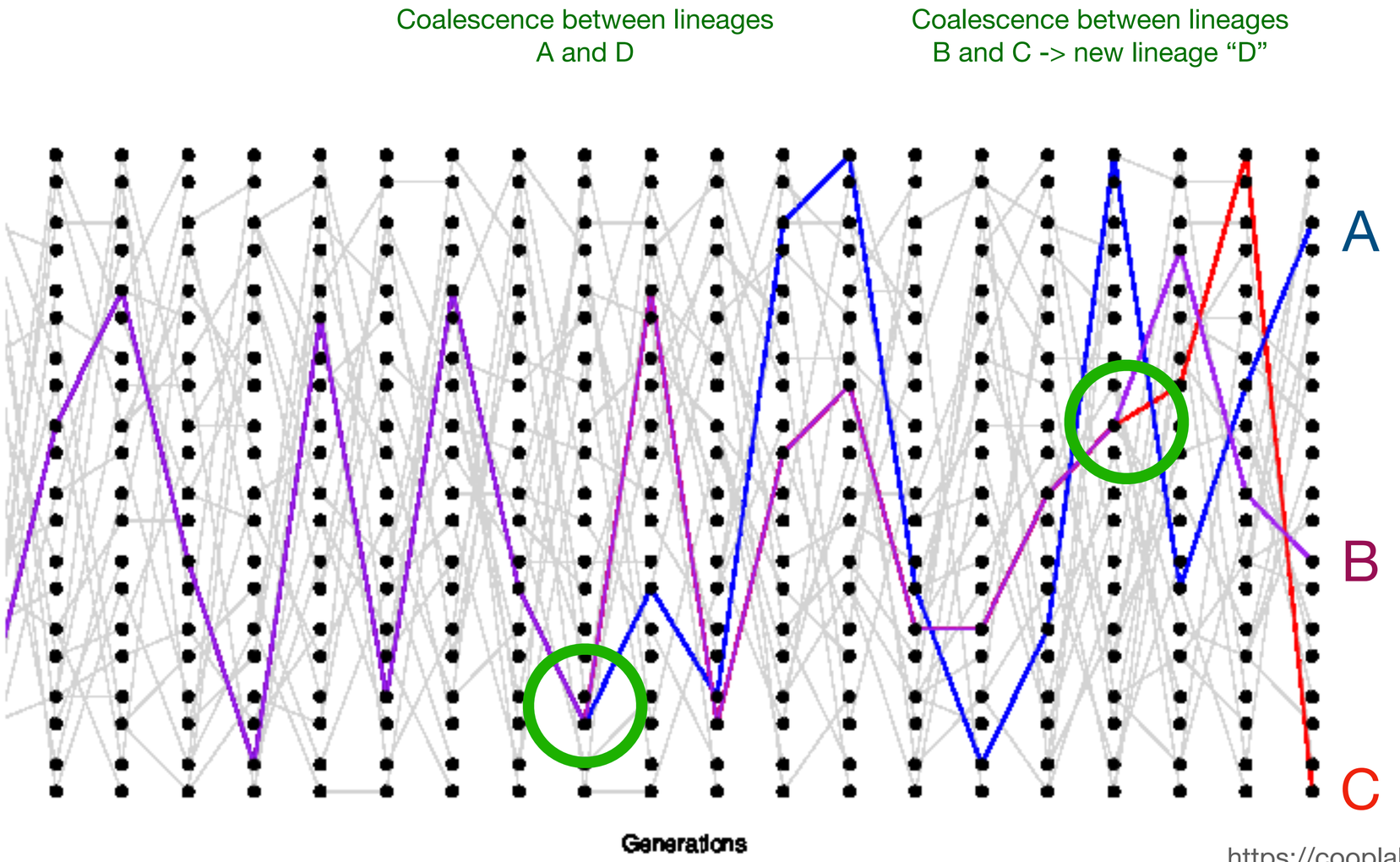


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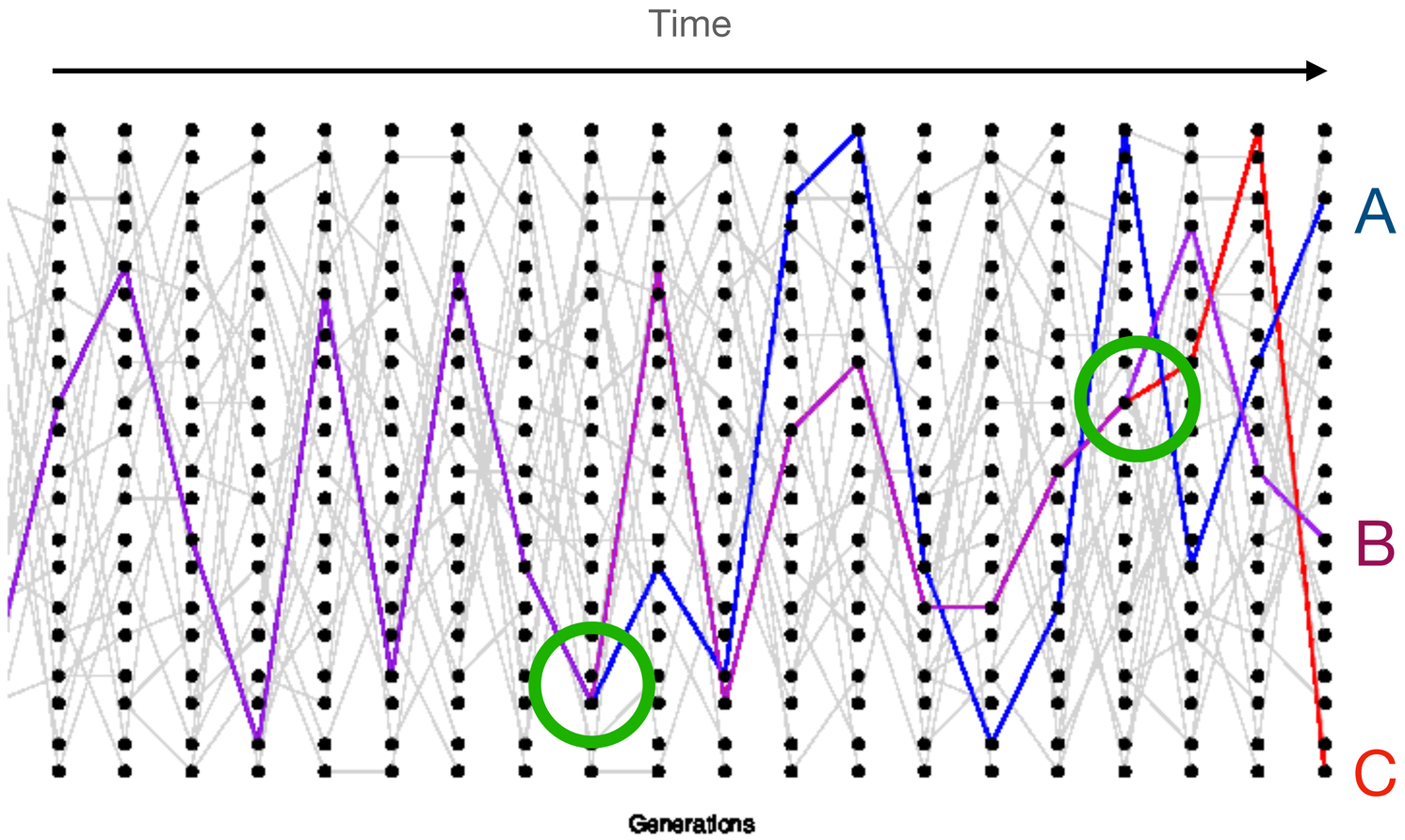


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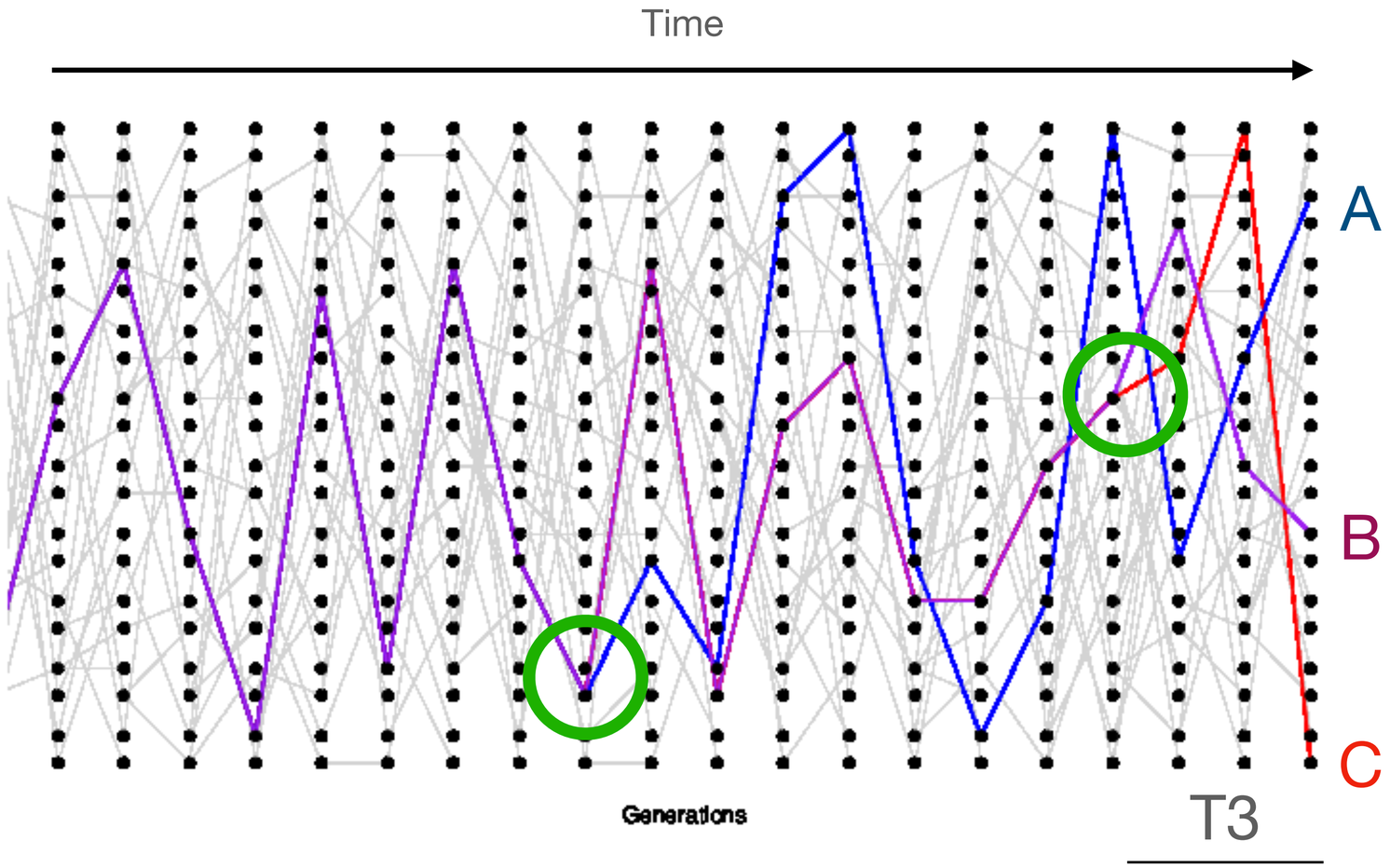


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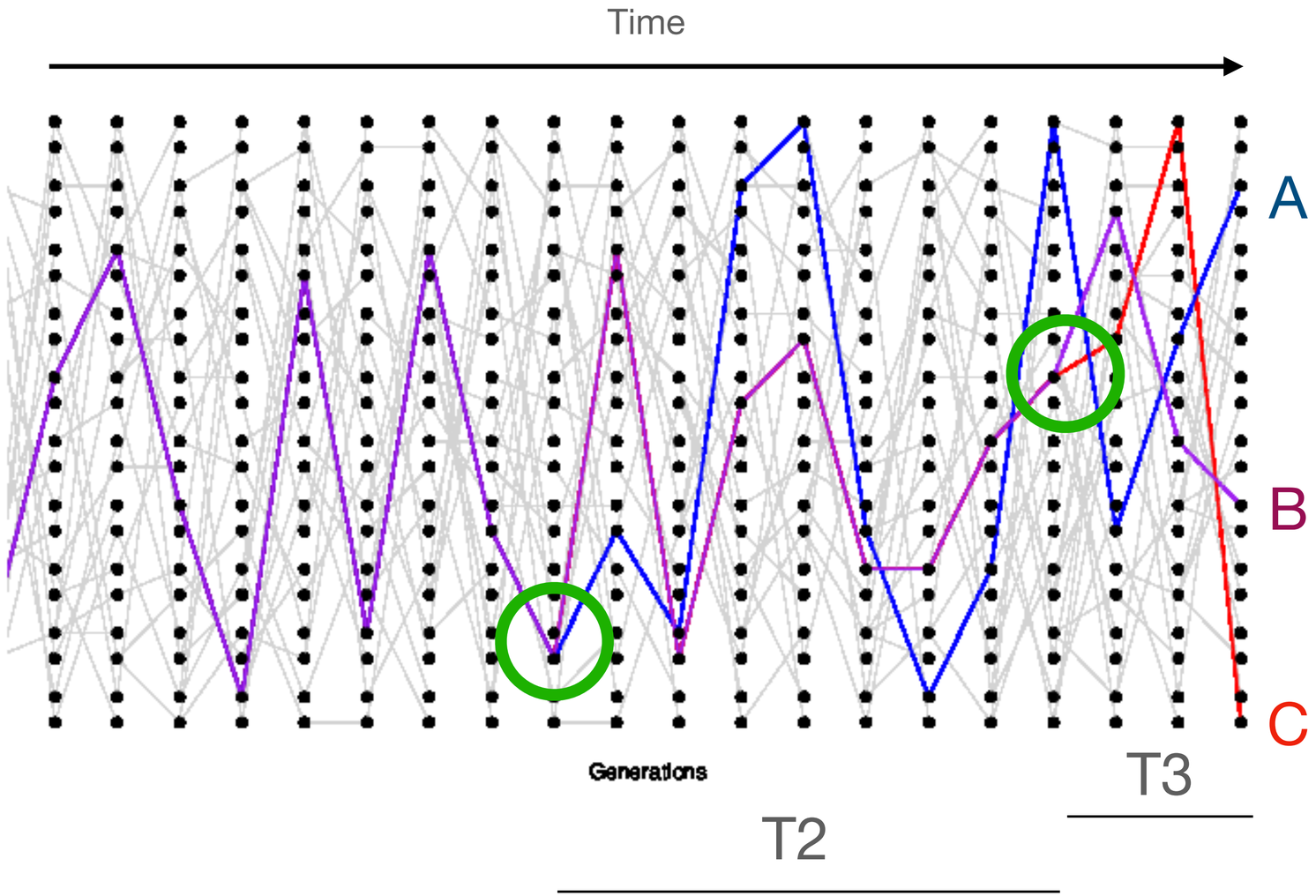


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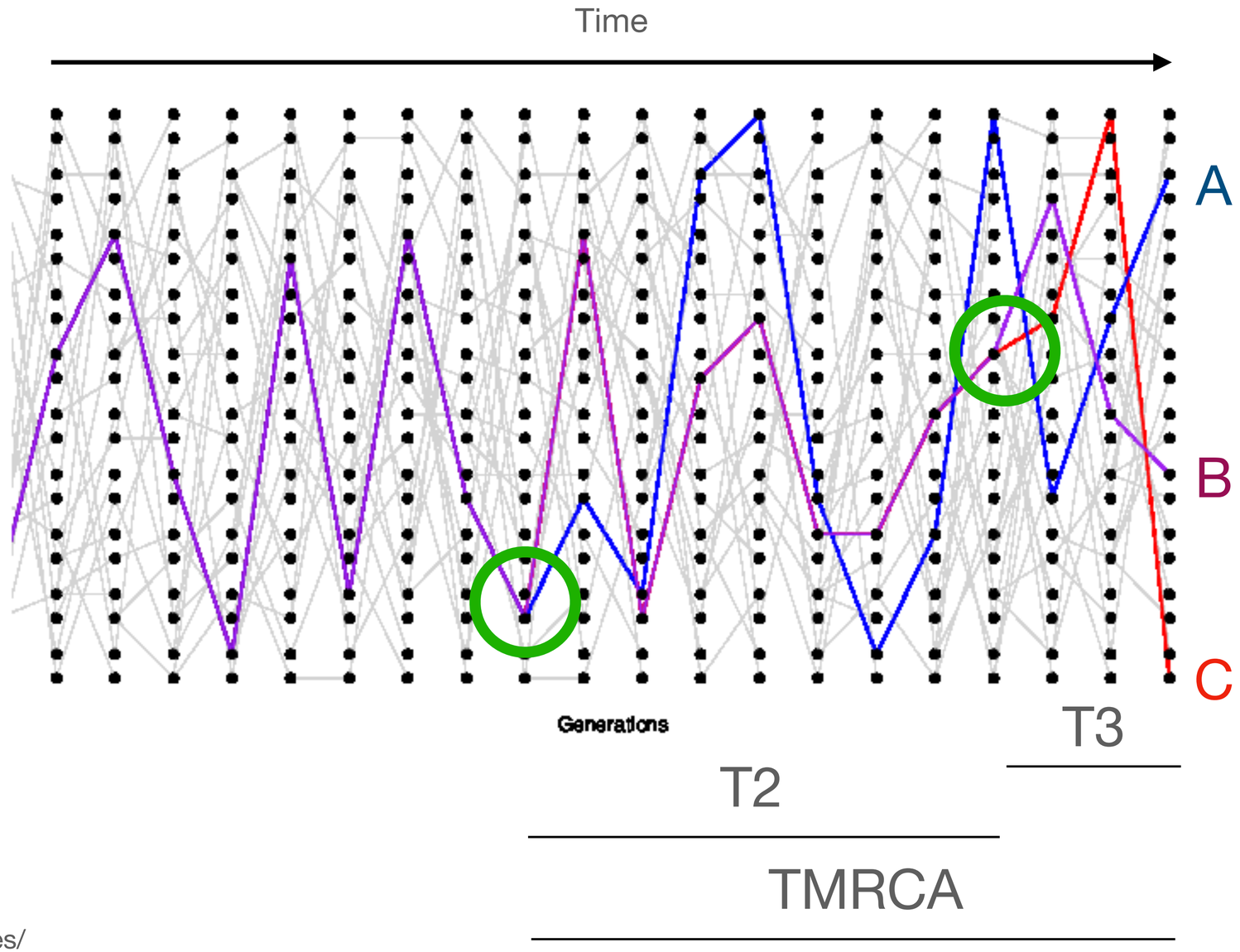


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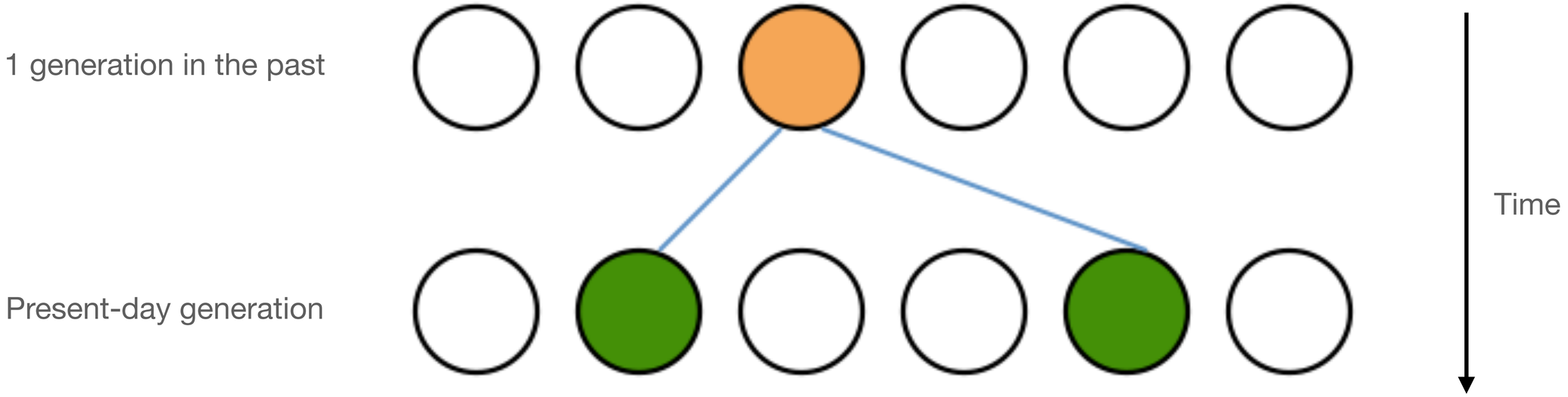
# Coalescence in a sample of two sequences

P[ 2 samples have the same parent in the previous generation ] =



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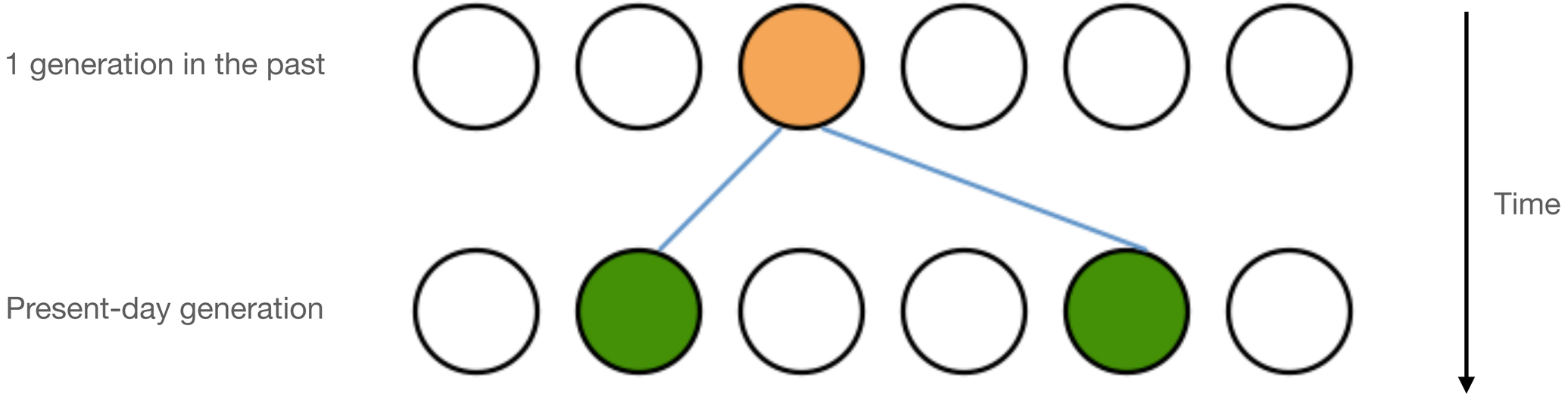
$$2N\frac{1}{2N}\frac{1}{2N} = \frac{1}{2N}$$



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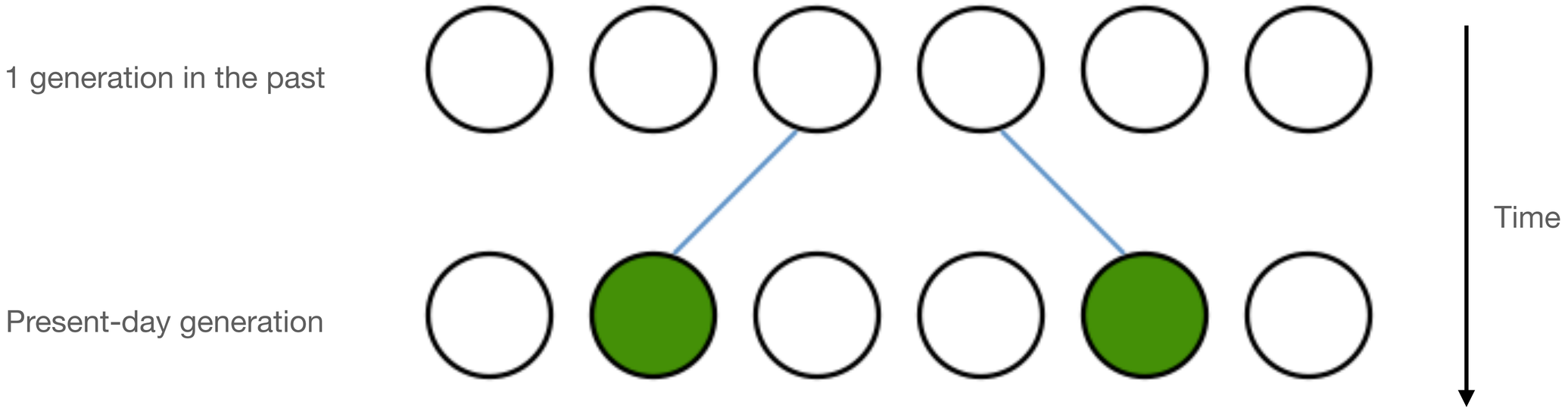

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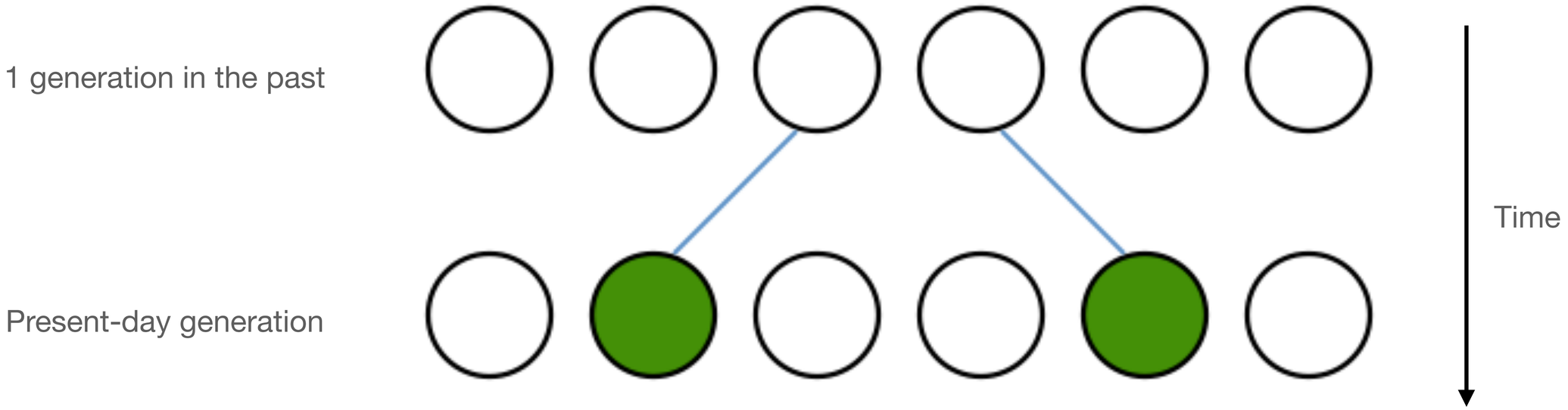
P[ 2 samples do not have the same parent in the previous generation ] =

$$1 - \frac{1}{2N}$$



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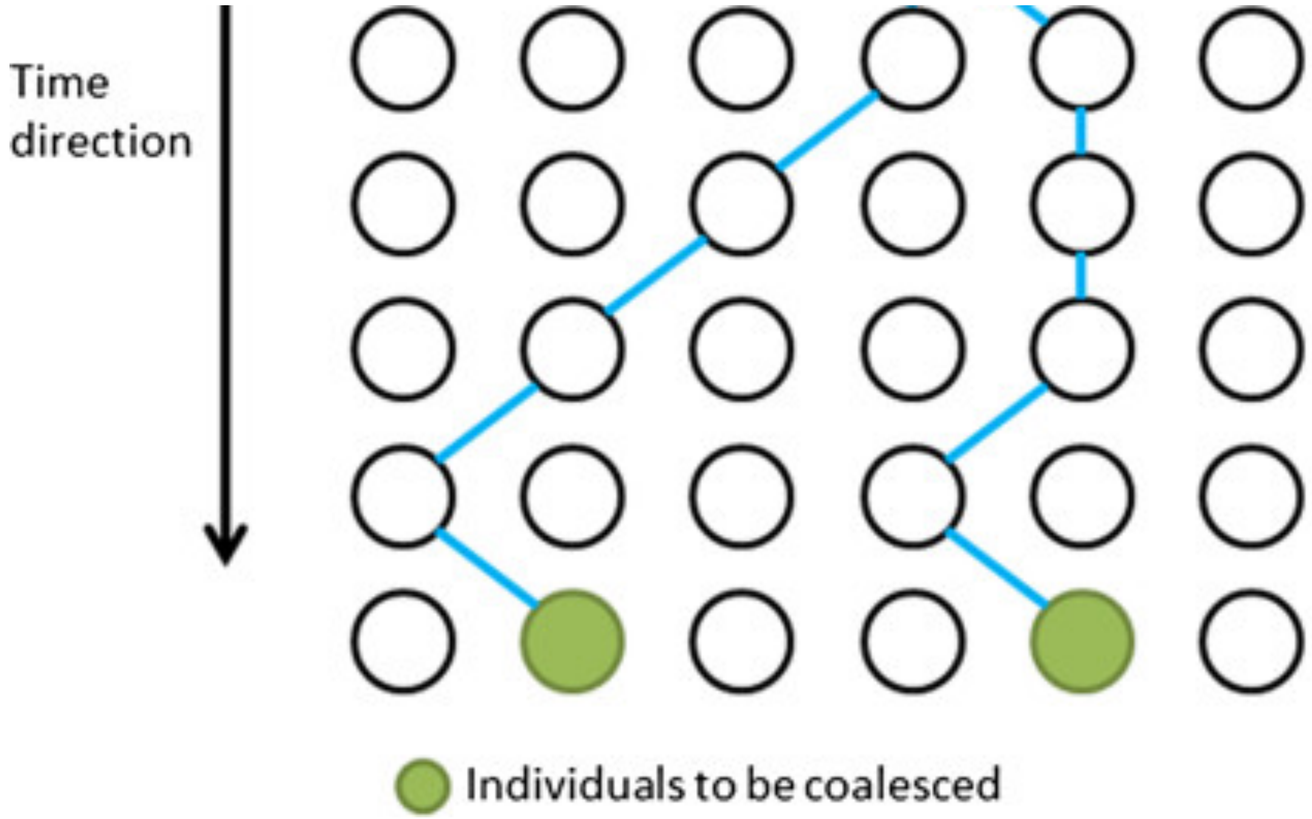
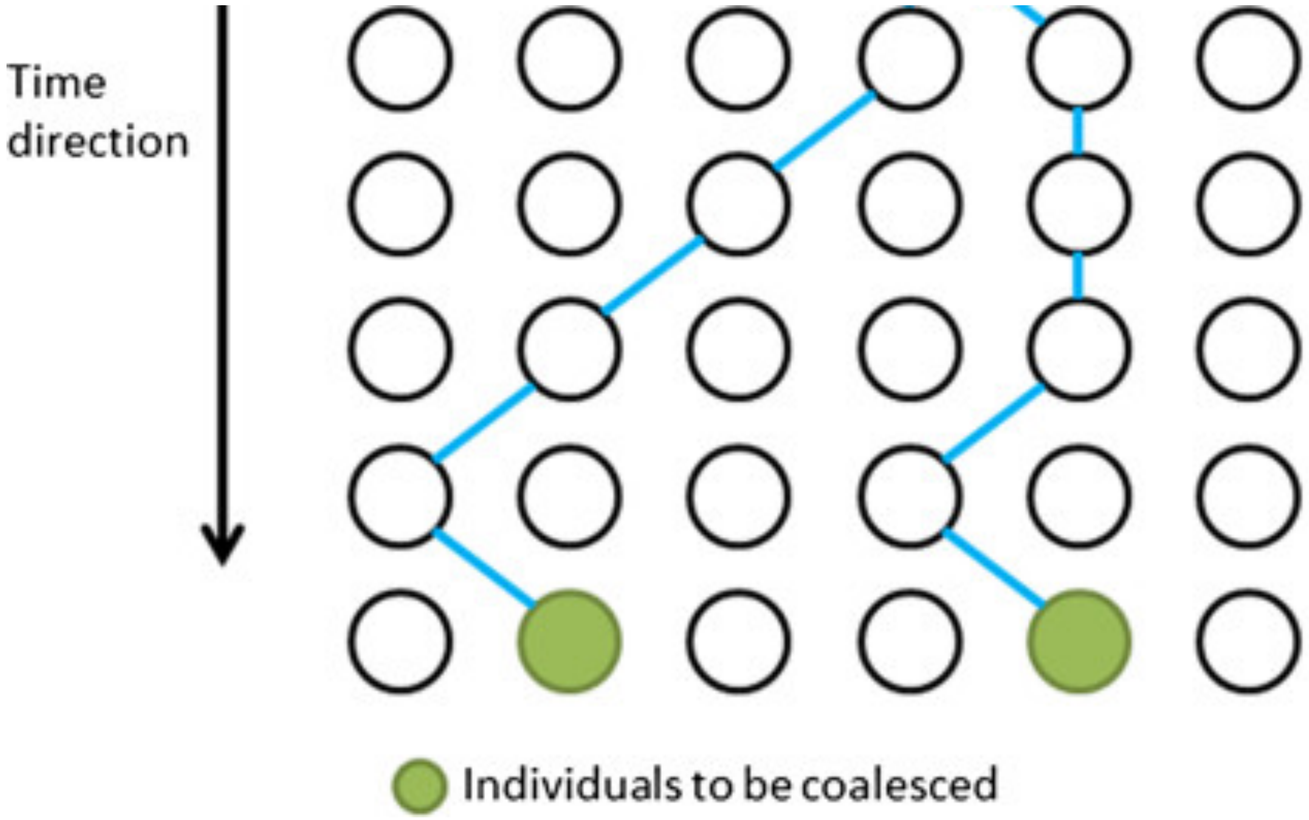
P[ 2 samples do not find a common ancestor in **r** generations ] =



# Coalescence in a sample of two sequences

P[ 2 samples do not find a common ancestor in **r** generations ] =

$$\left(1 - \frac{1}{2N}\right)^r$$



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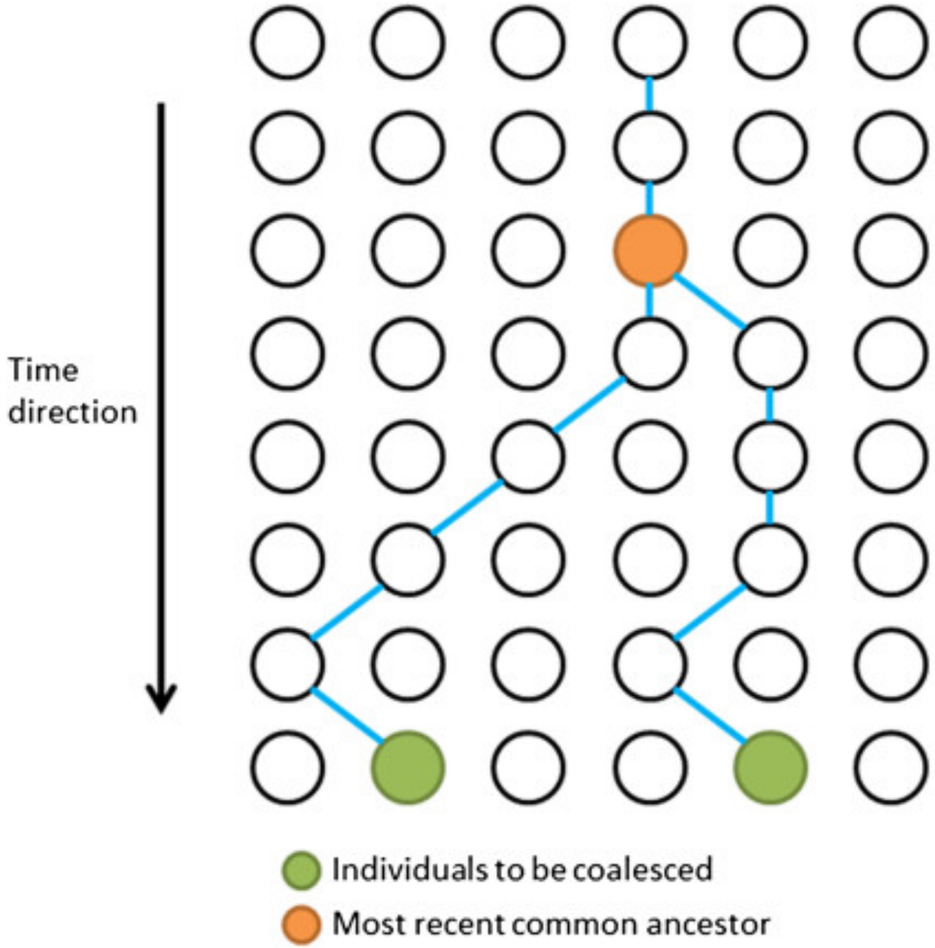

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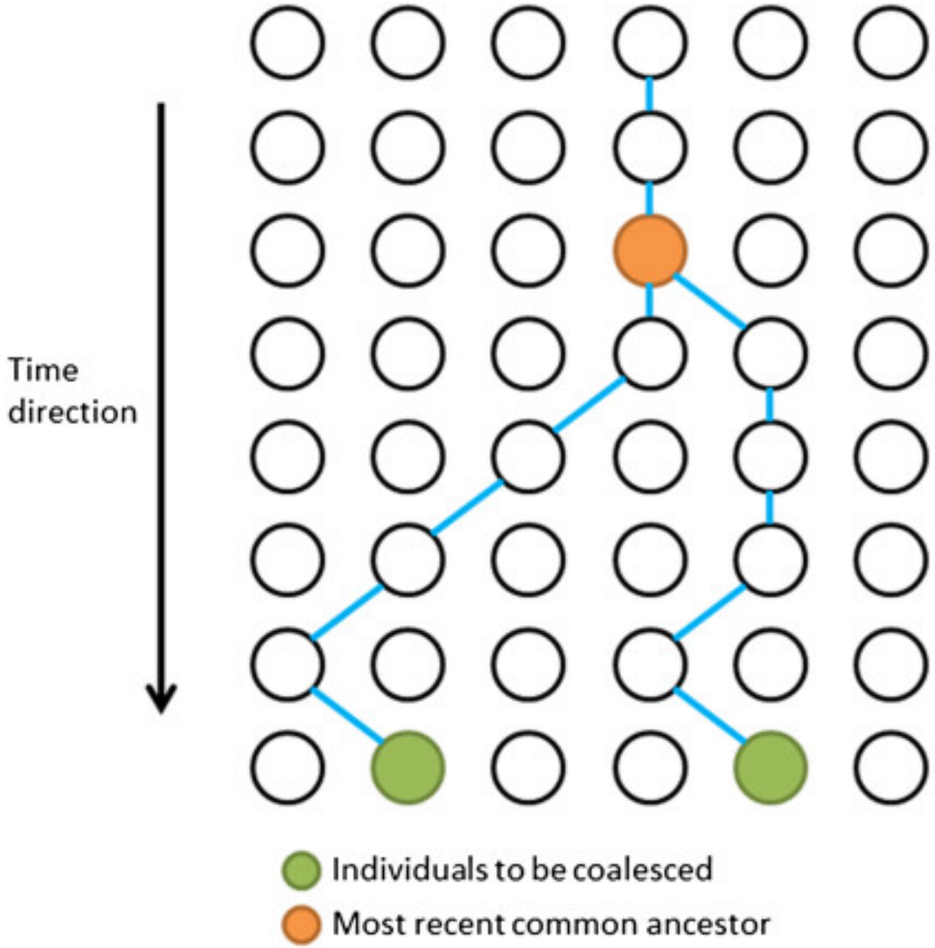
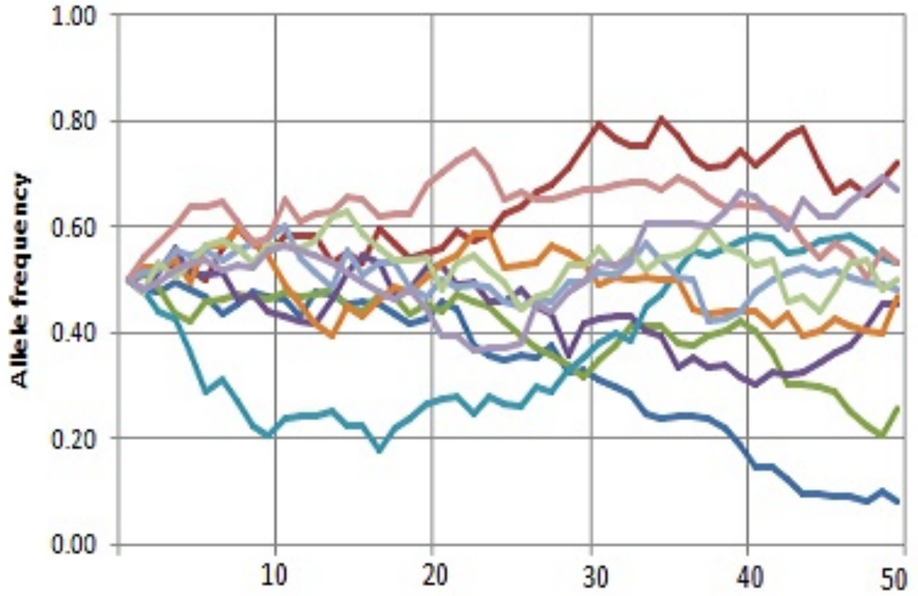



$$\left(1-\frac{1}{2N}\right)^{r-1}\frac{1}{2N}$$

# Wright-Fisher exercises

Follow the instructions in the Wright-Fisher exercise prompt:

https://github.com/FerRacimo/CopenhagenTutorial/blob/master/WrightFisherTutorial.md



# Today

- Terminology
- Wright-Fisher Model and Genetic Drift
- Intro to coalescent theory
- Mutations and the coalescent

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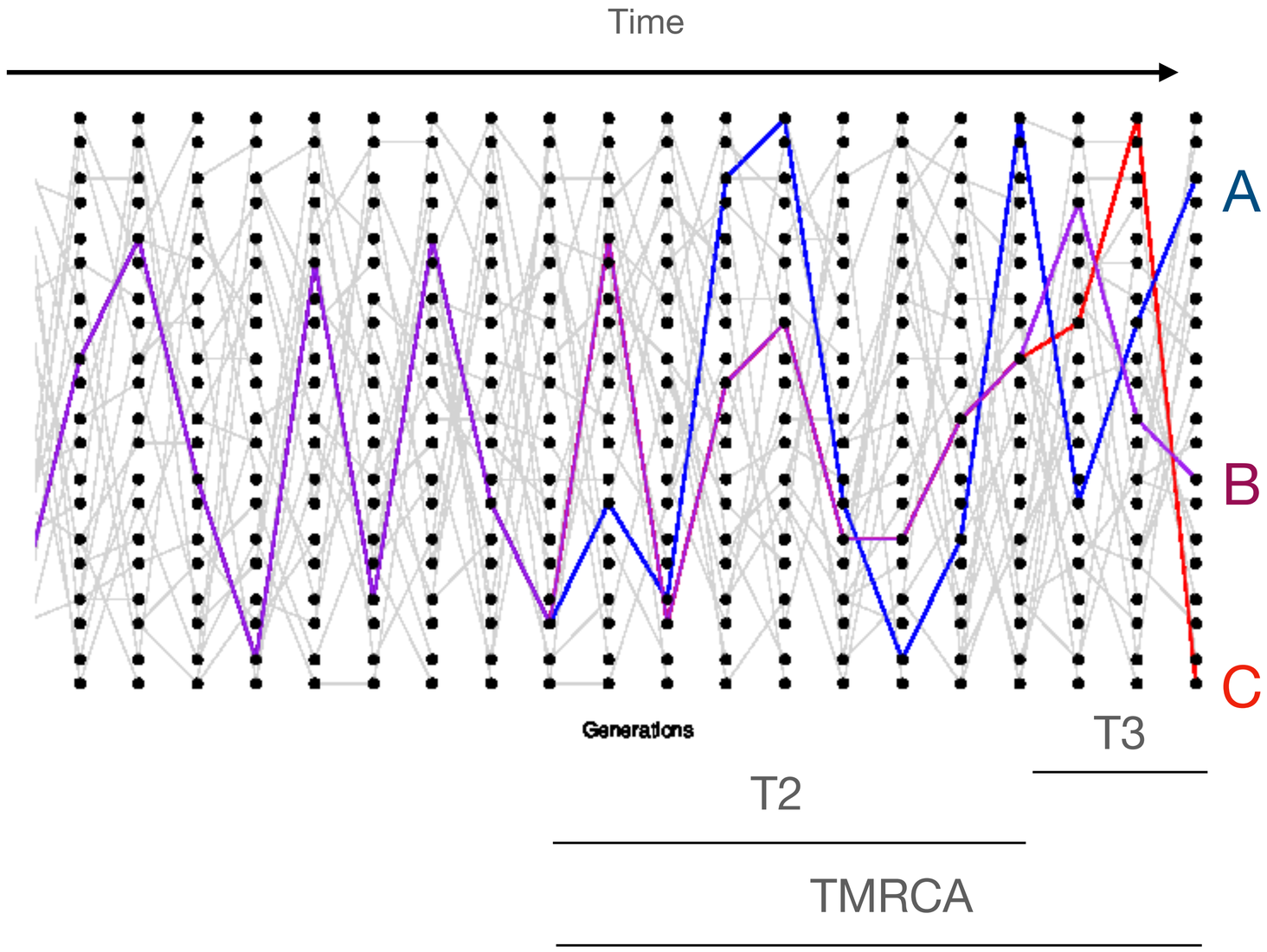


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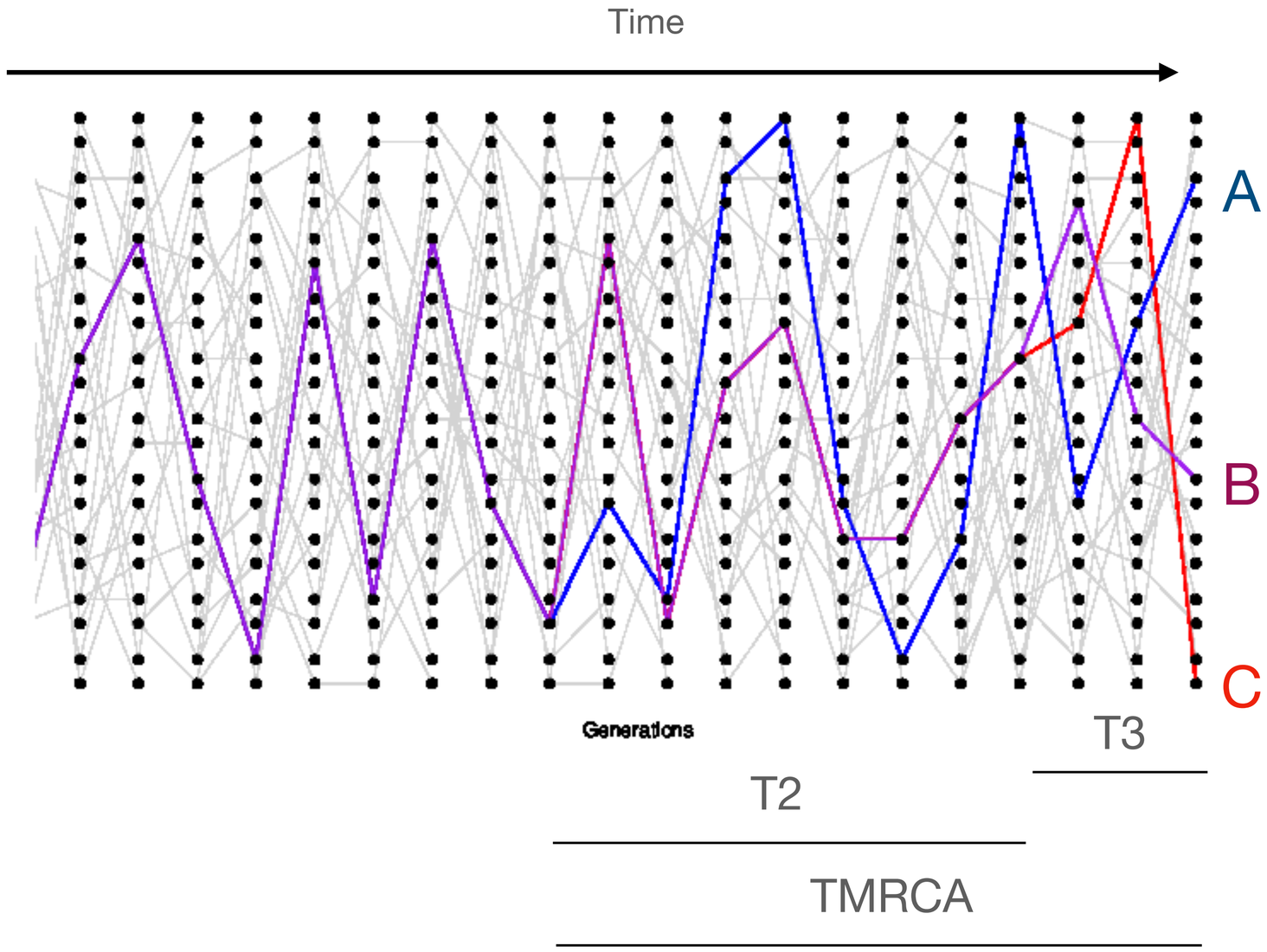
# Motivation: tractability

- Hard to **keep track of all alleles at each time step**

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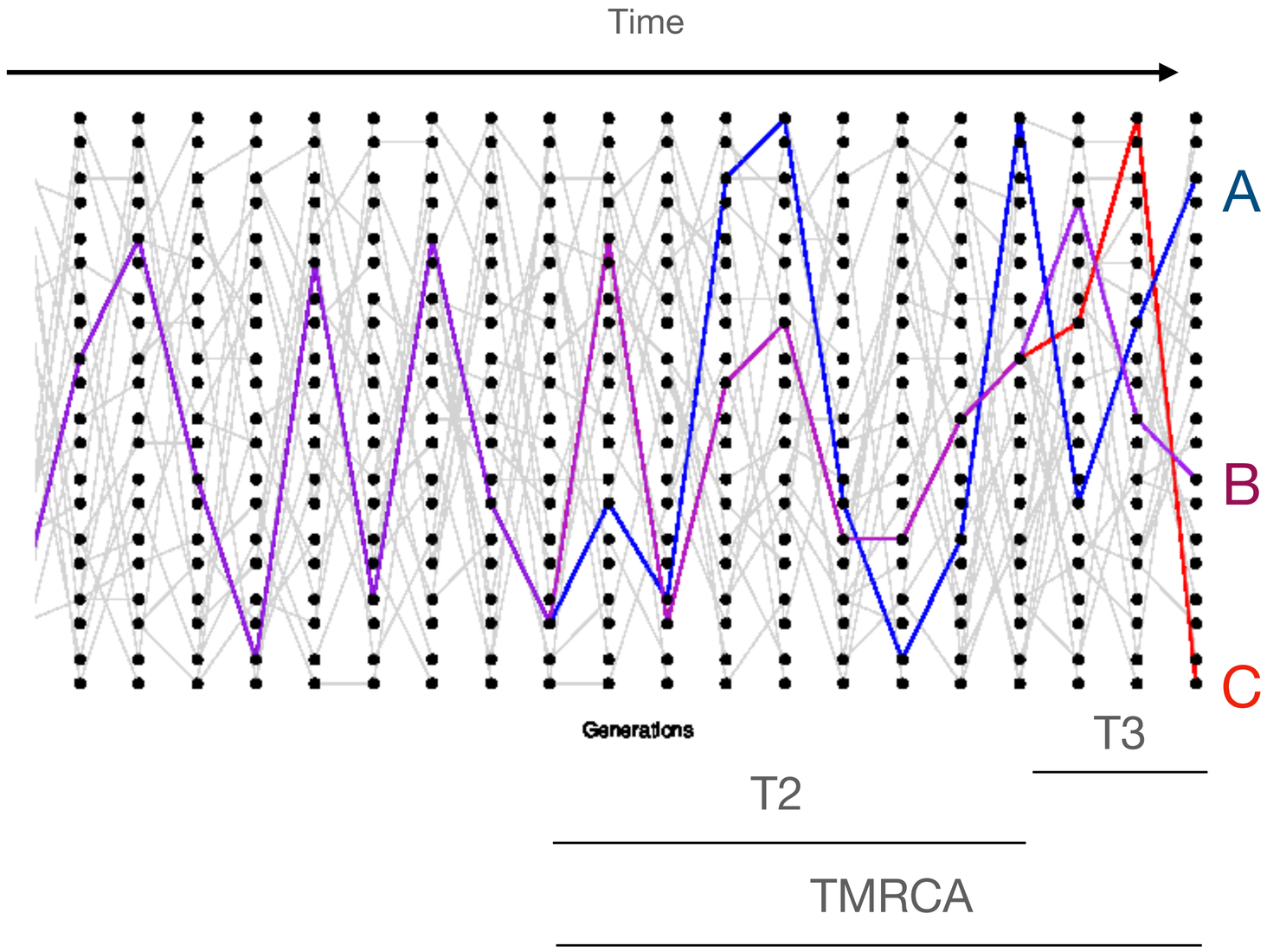
# Motivation: tractability

- Hard to **keep track of all alleles at each time step**
- Example: given that we sample 3 individuals in a population of size 2N=20, what is the **expected time till all 3 individuals find a common ancestor**?

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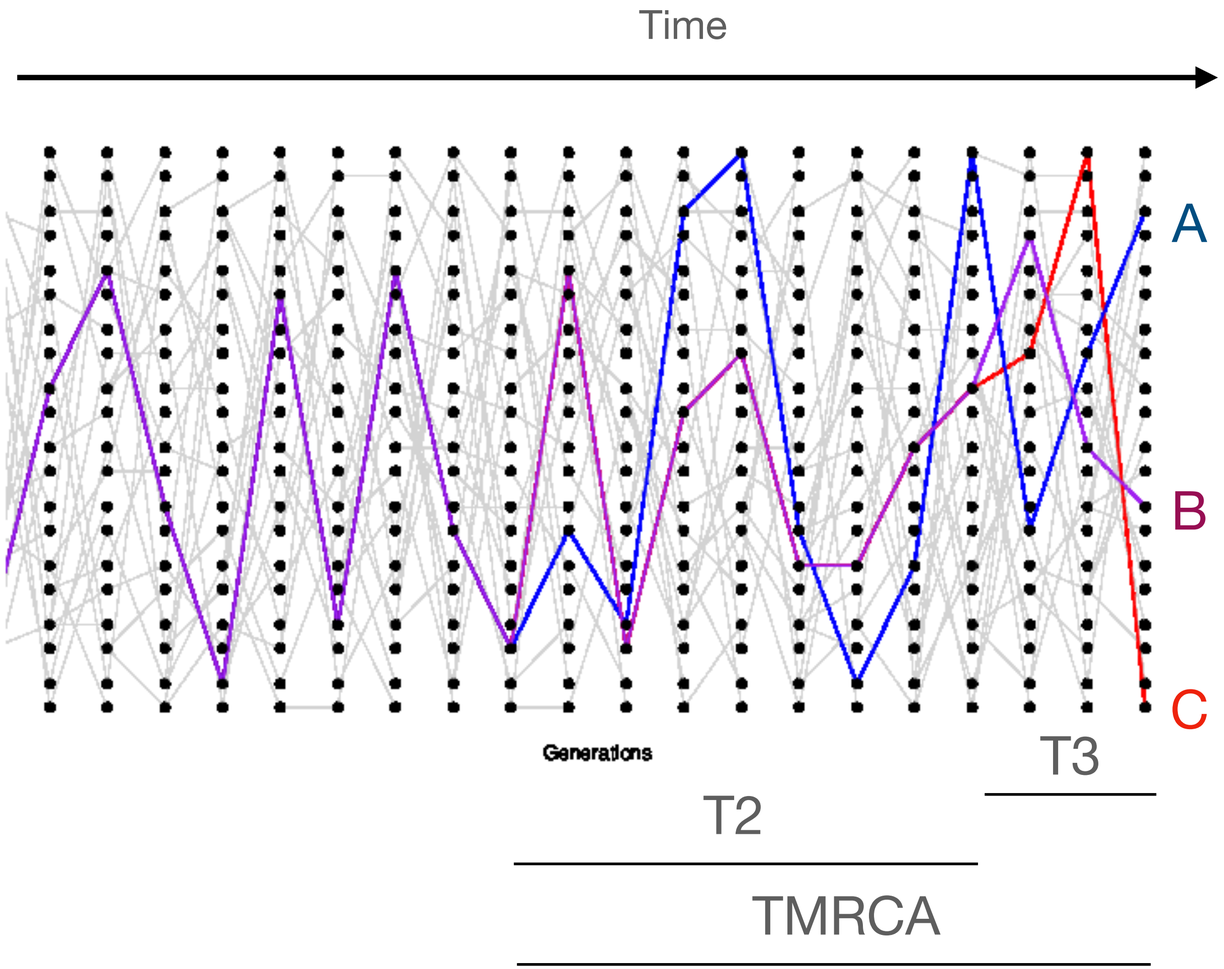
# Solution: keep track of sampled lineages only

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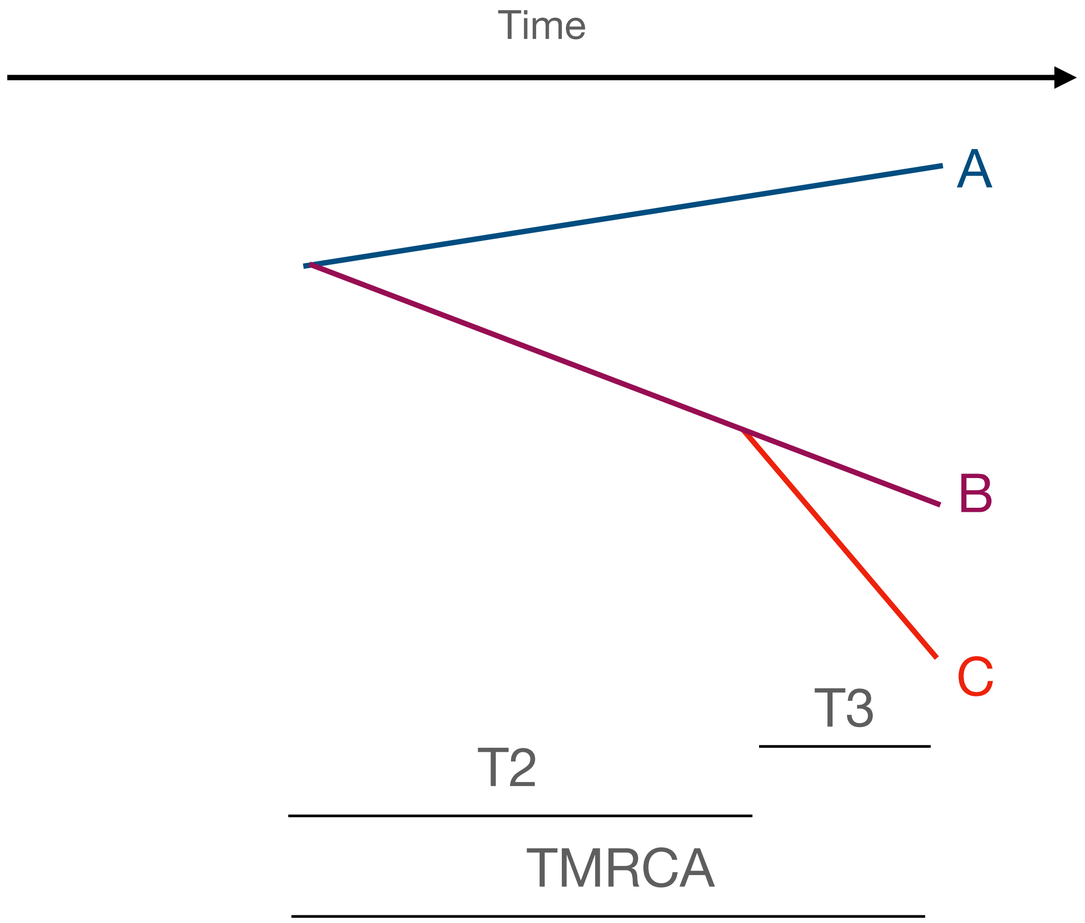
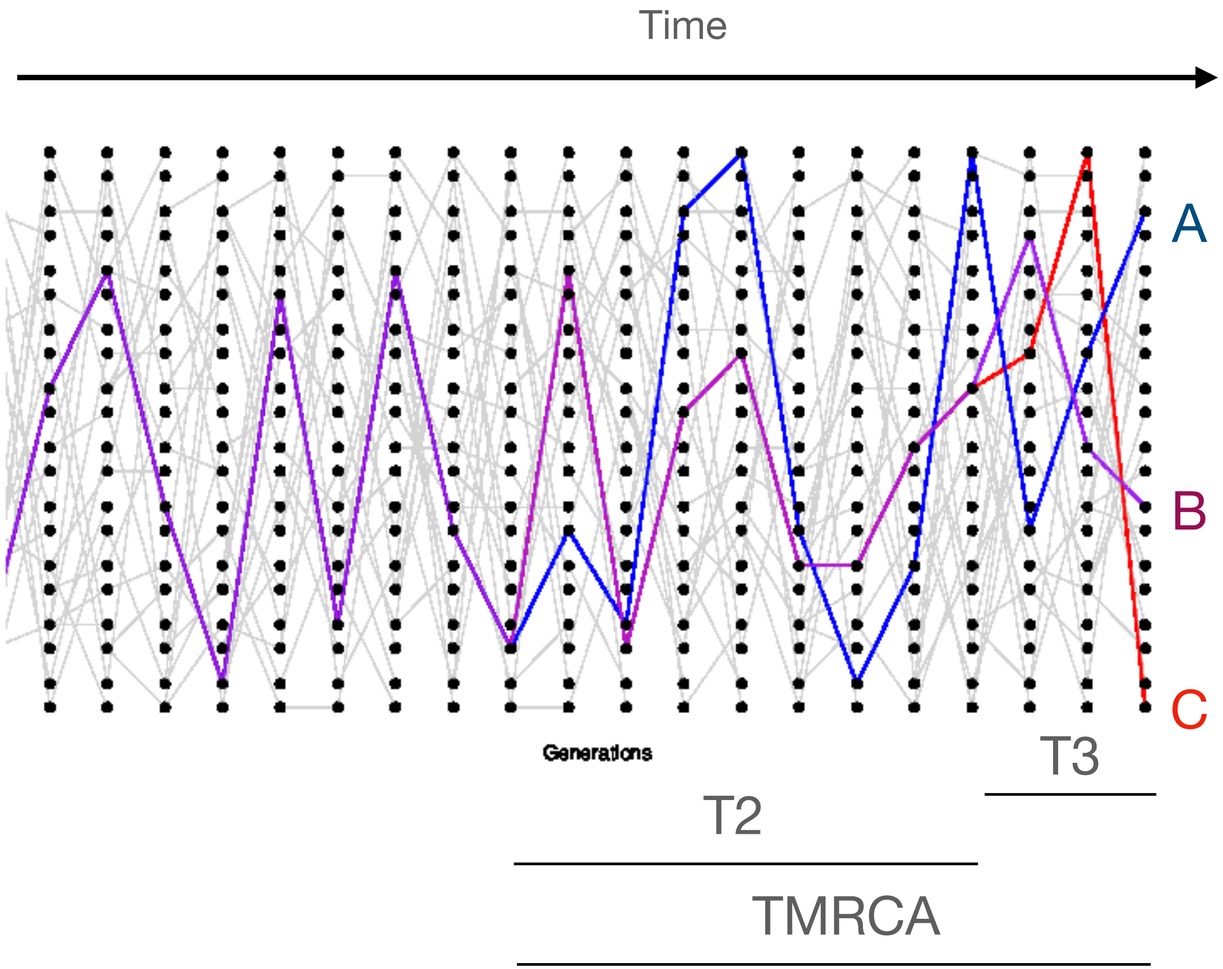
# Solution: keep track of sampled lineages only




https://cooplab.github.io/popgen-notes/

# Coalescent theory

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- A way to model how the genealogies of a sample behave over long time periods.

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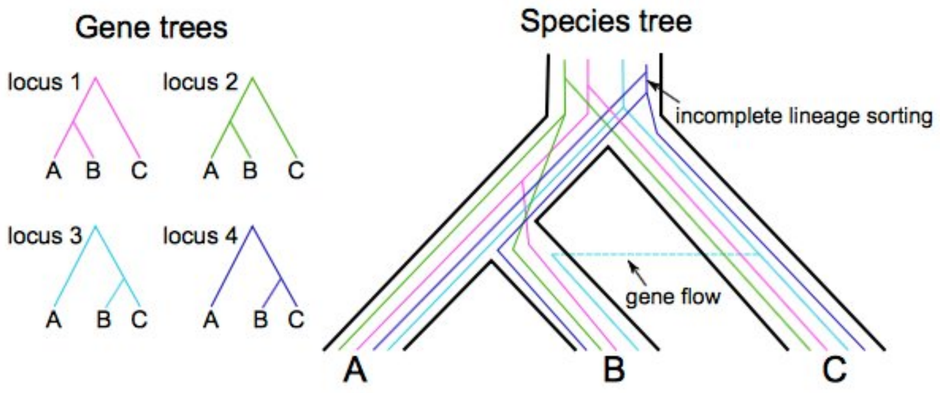

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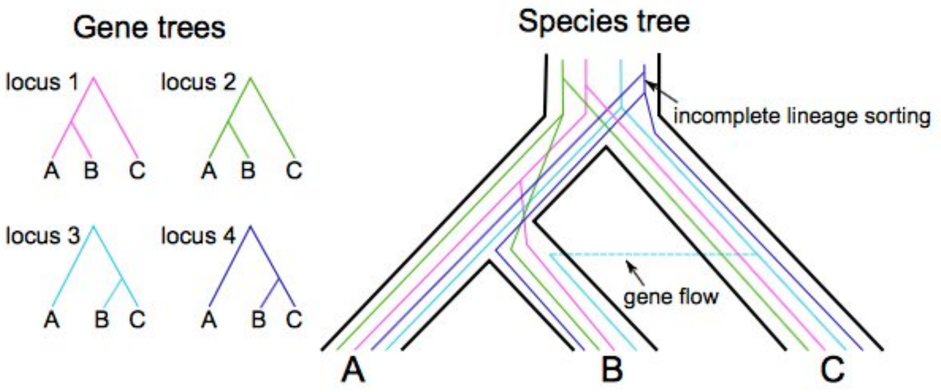


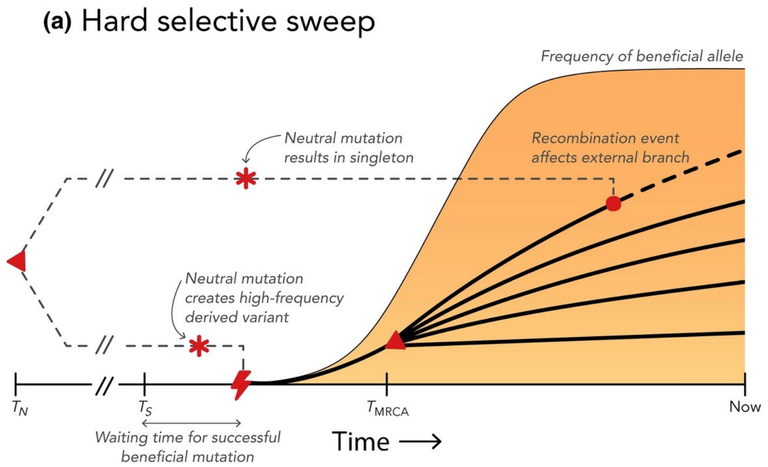


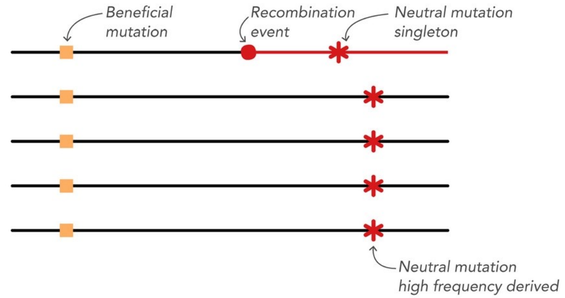

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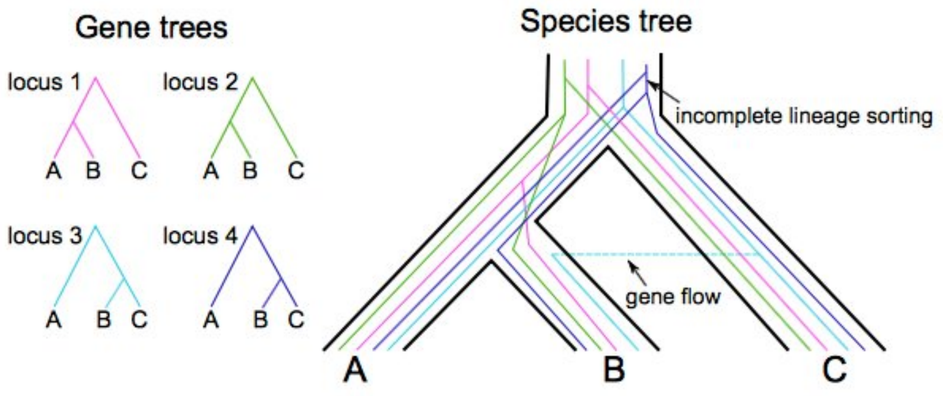
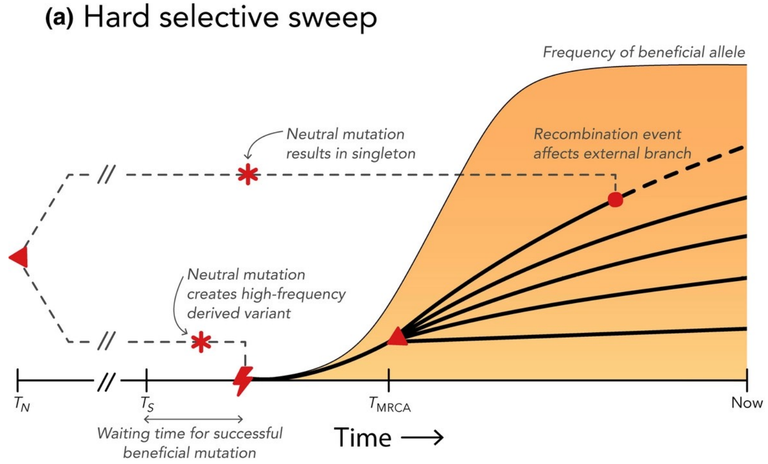
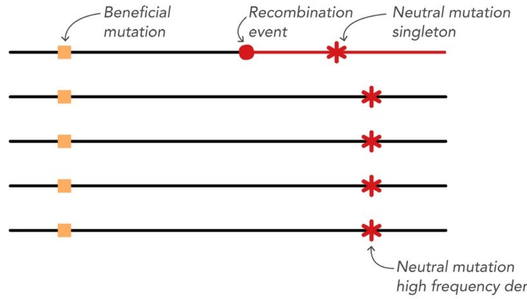
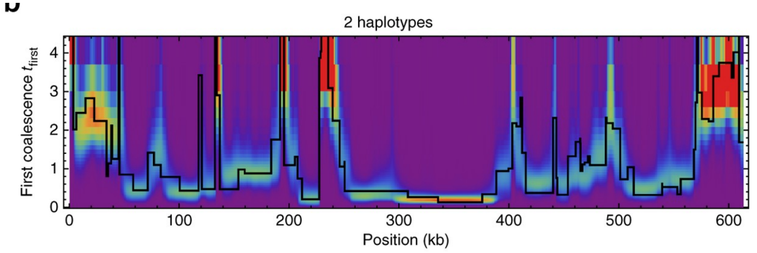
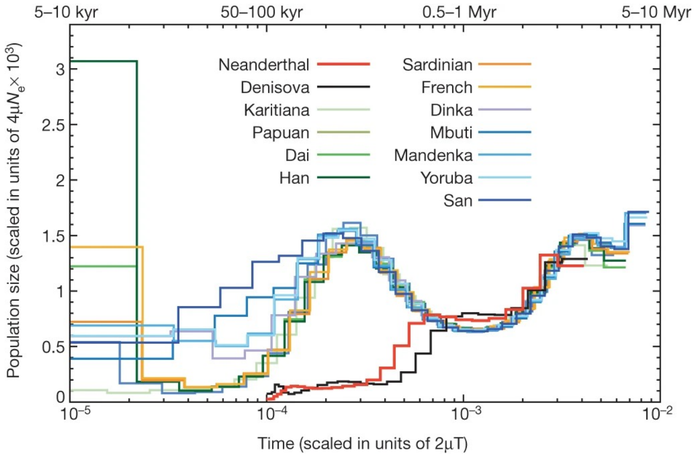
ms prime



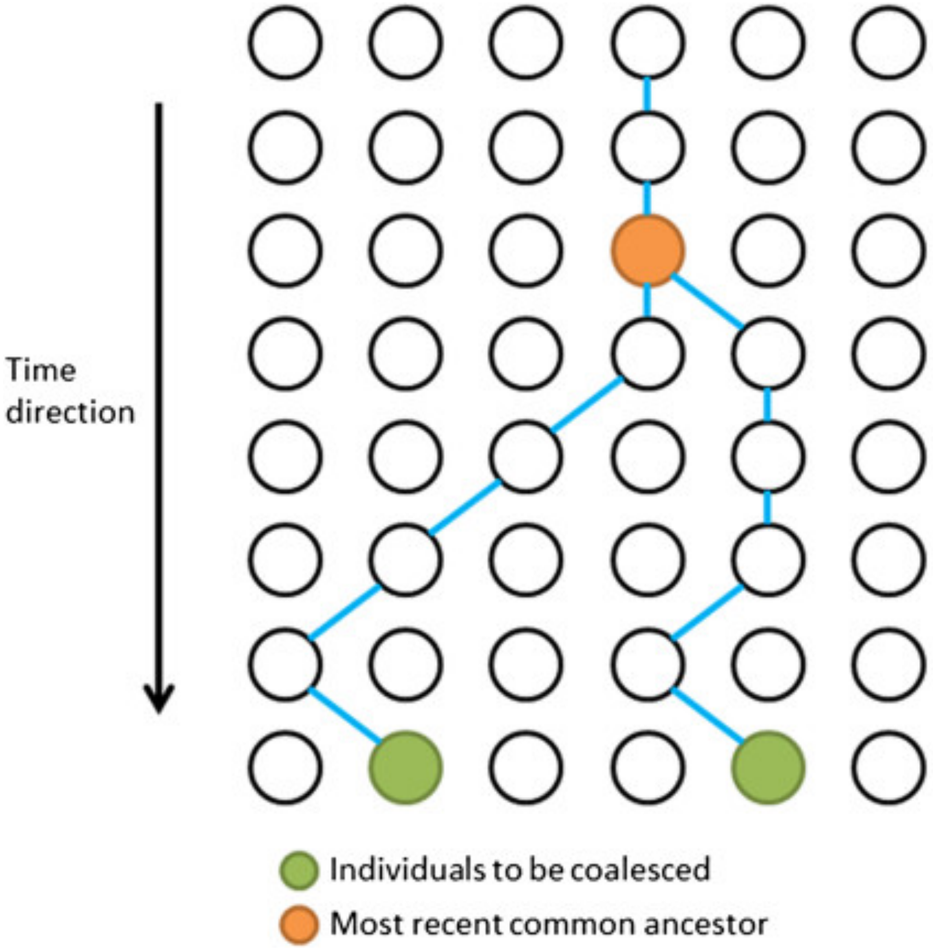



# Coalescence in a sample of two sequences

P[ 2 samples find a common ancestor in **exactly r** generations ] =



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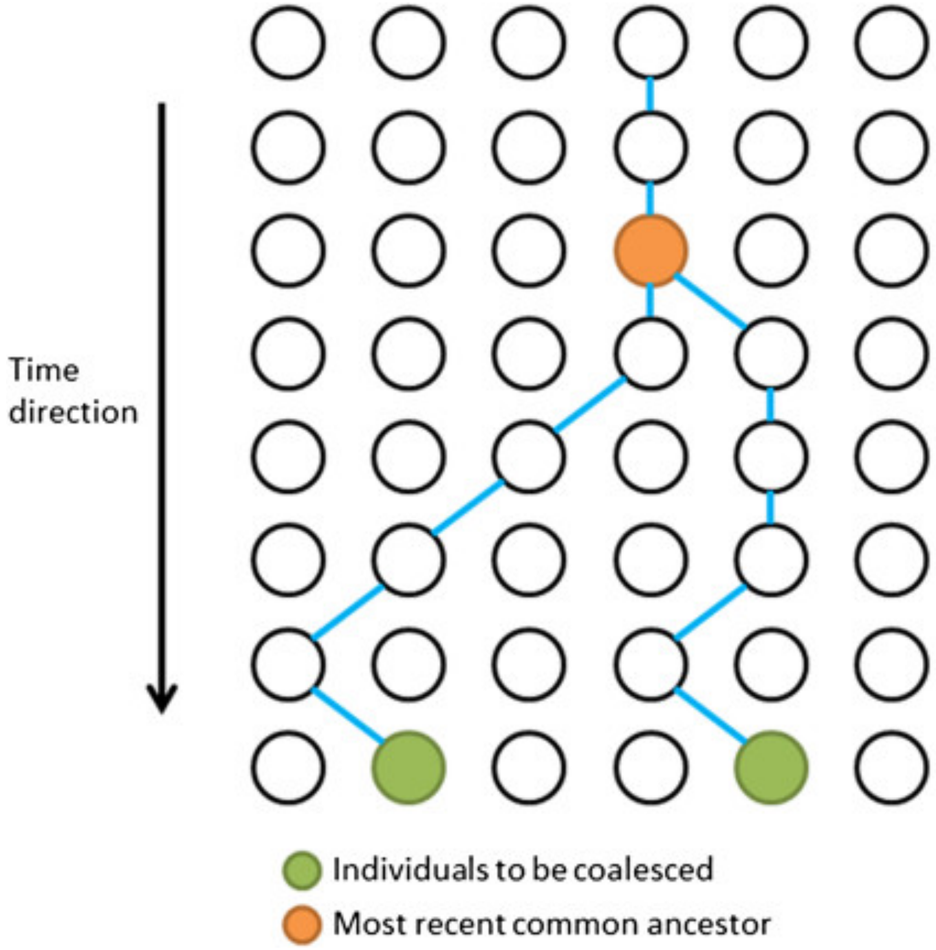


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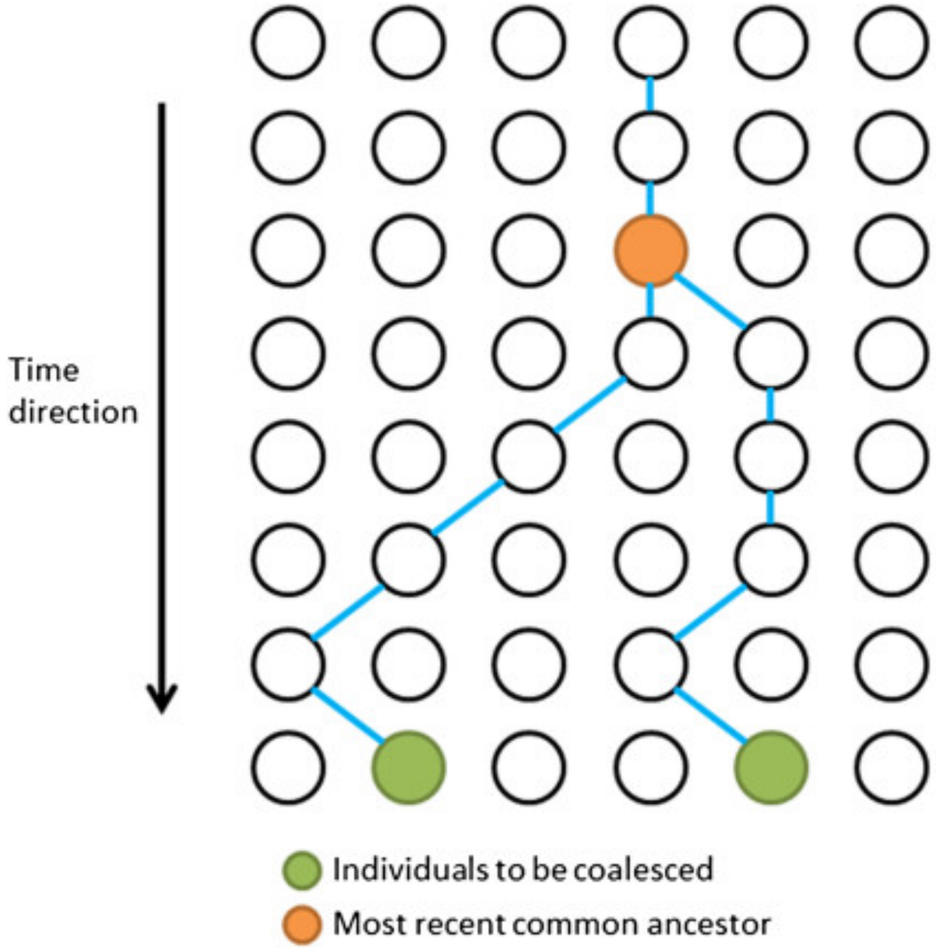


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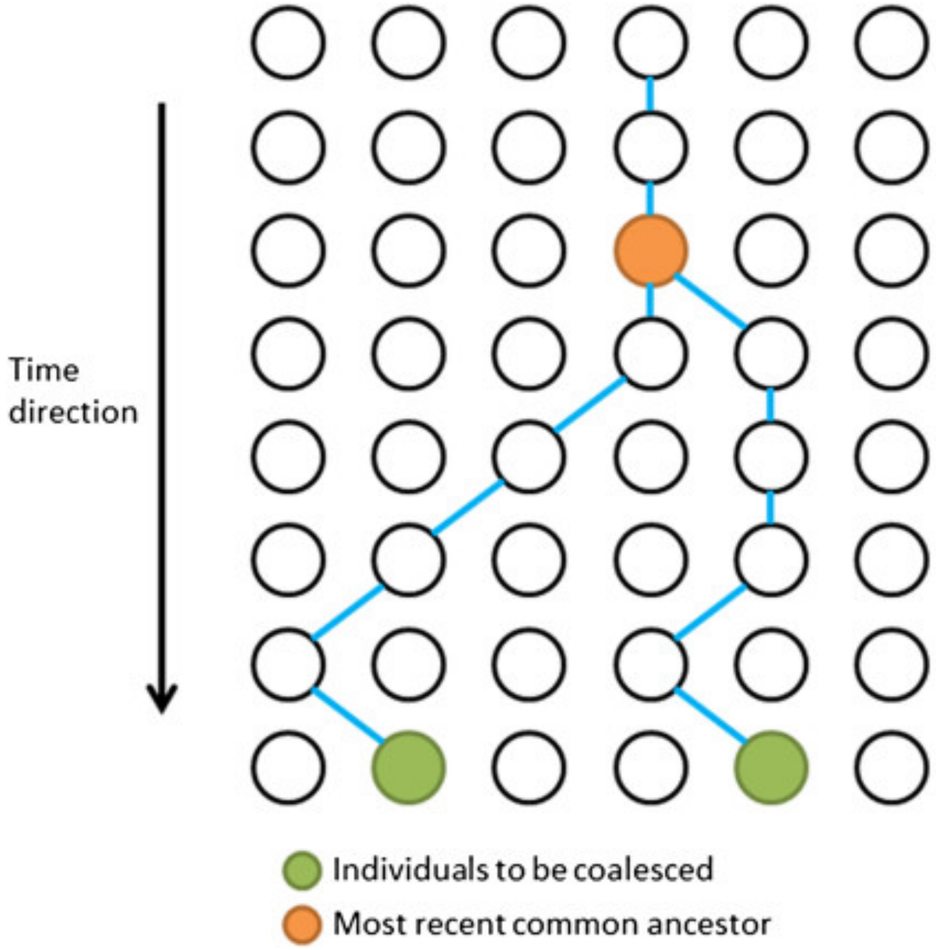


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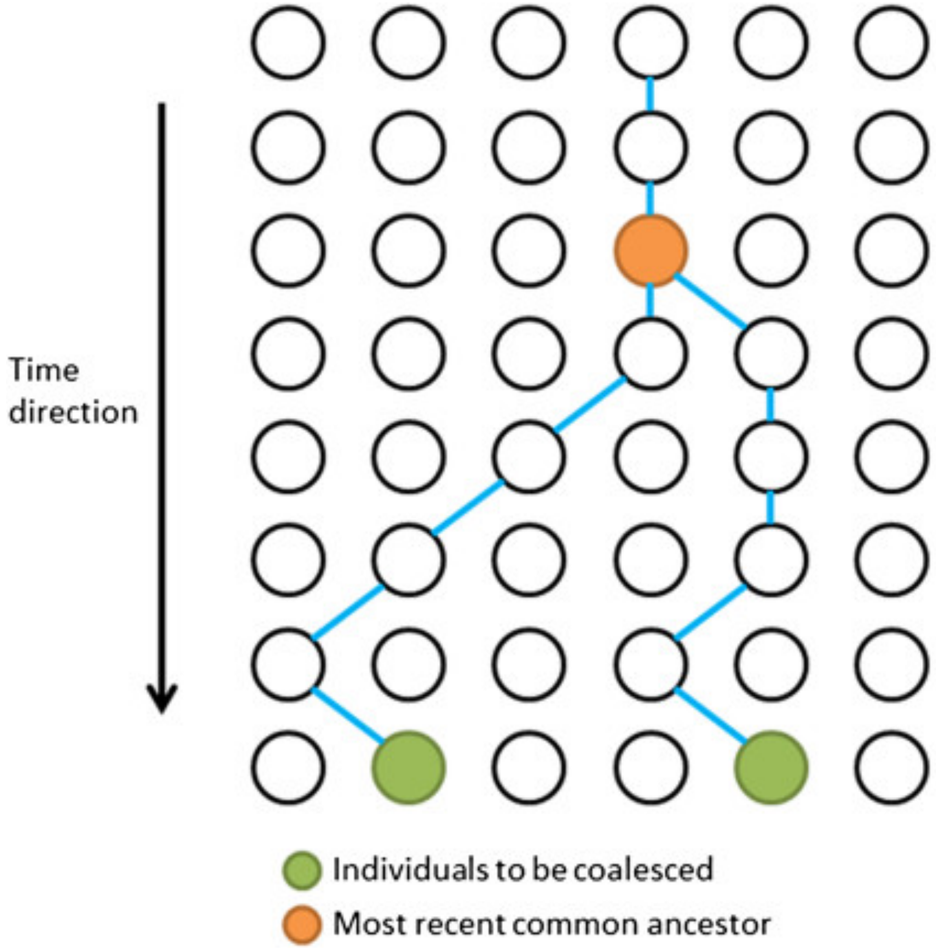


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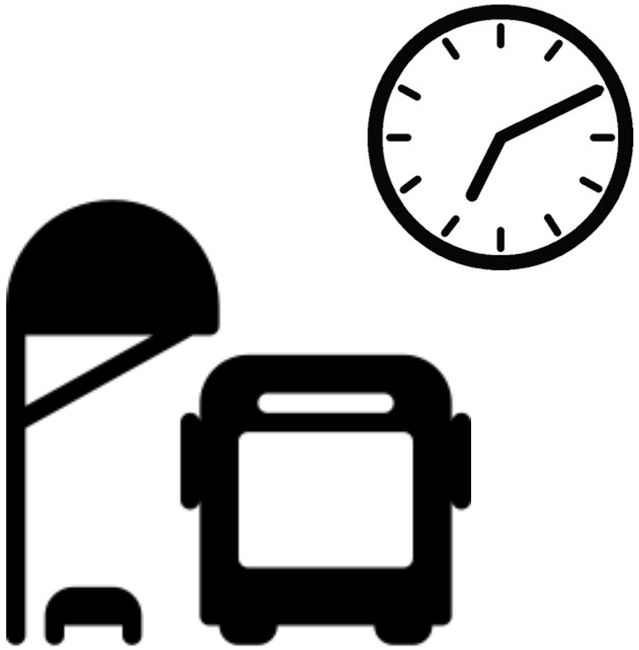
This is an **exponential distribution** with rate 1

# The Exponential Distribution

- Used to model **waiting times**
  - “What is the probability that I have to wait less than 30 minutes till the next bus arrives?”



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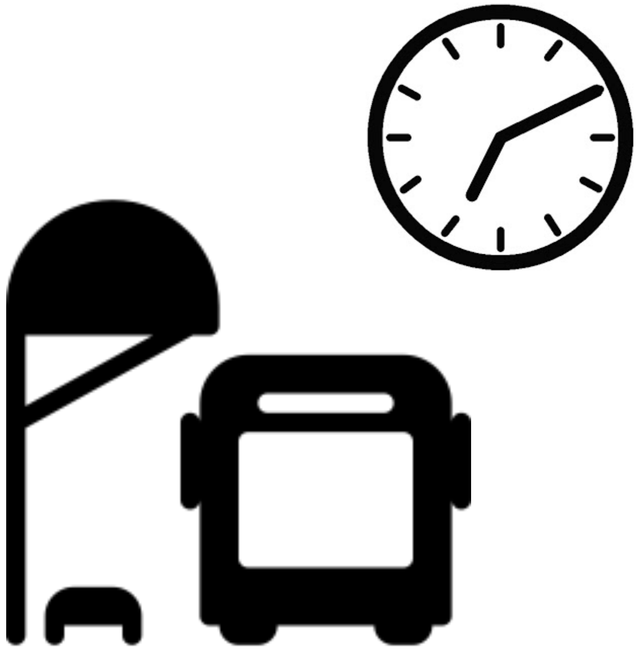

- One parameter: rate ($\lambda$)
  - The higher the rate, the less I will have to wait

# The Exponential Distribution

One parameter: $\lambda$

$$E[T] = \frac{1}{\lambda}$$

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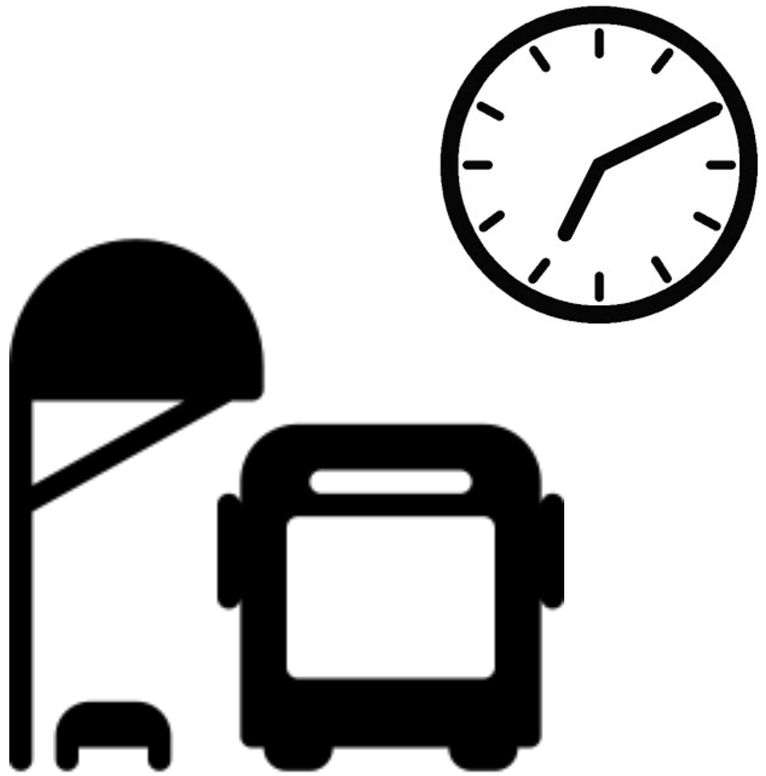
The expected waiting time is the inverse of the rate

If buses arrive at an average rate of $\lambda$=4 per hour,
I expect to wait 1/4 of an hour for the next bus, on average

# The Expected Waiting Time

"Buses arrive at a rate of $\lambda$ per hour"

$$f(t) = \lambda e^{-\lambda t}$$



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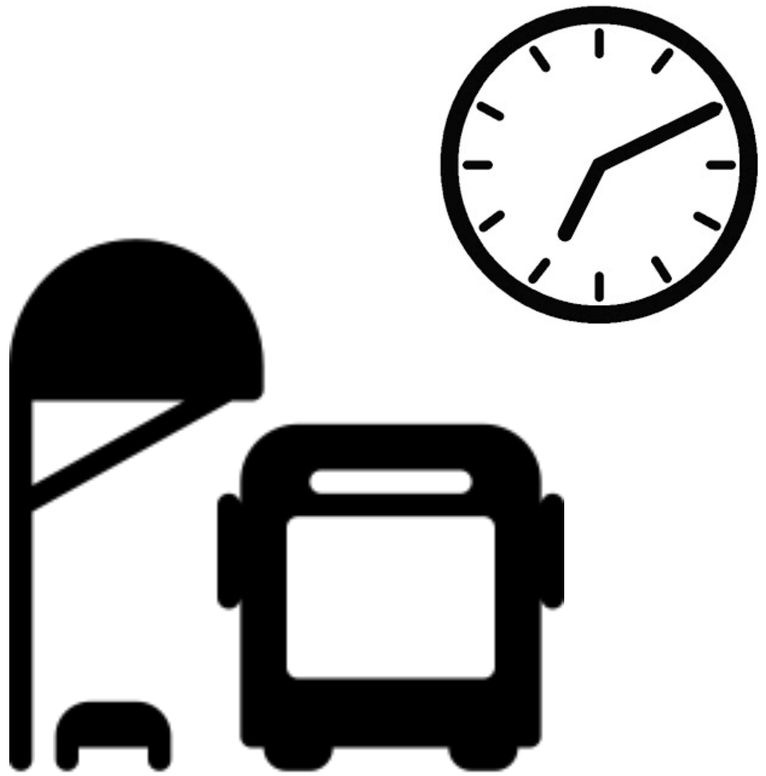
"Buses arrive at a rate of $\lambda$ per hour"

$$f(t) = \lambda e^{-\lambda t}$$

"The expected waiting time for the next bus is $1/\lambda$ hours"

$$E[T] = \frac{1}{\lambda}$$



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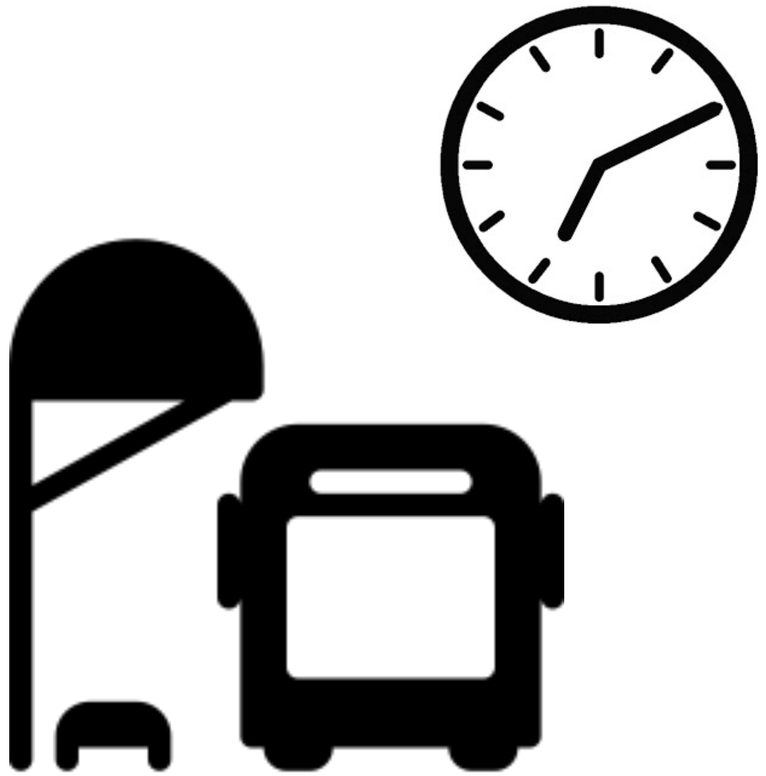
"Buses arrive at a rate of $\lambda$=4 per hour"

$$f(t) = 4e^{-4t}$$



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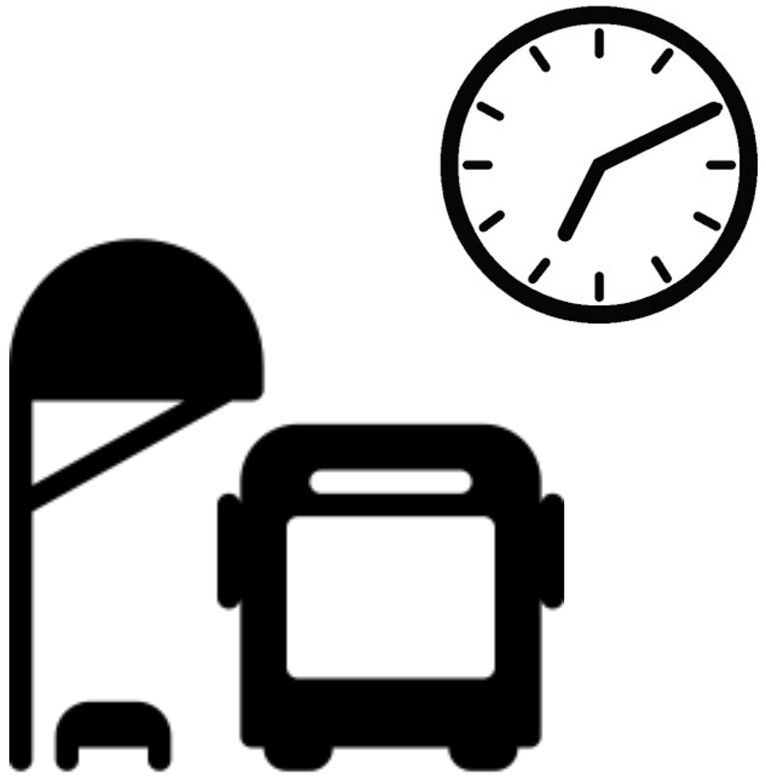


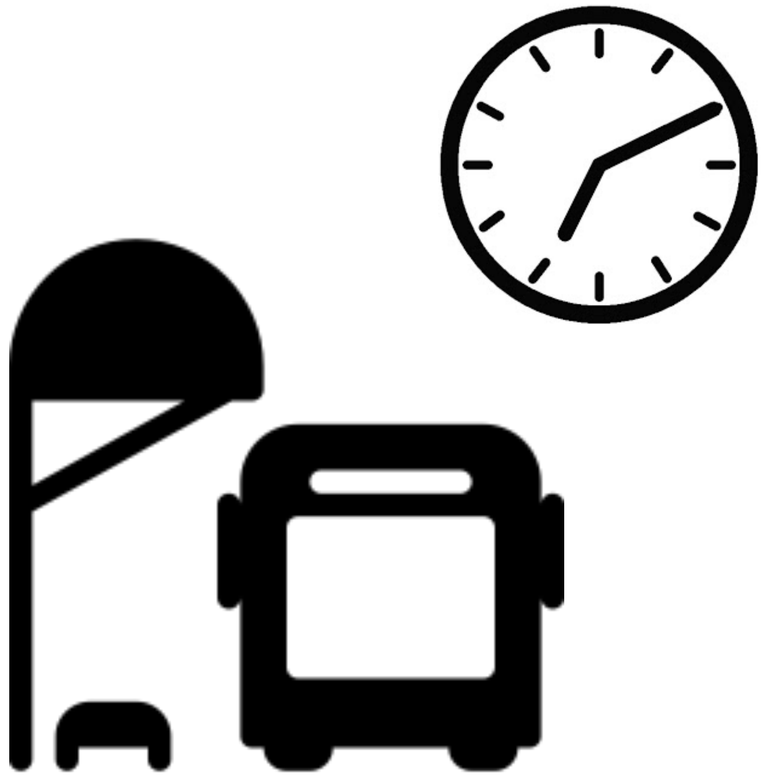
"The expected waiting time for the next bus is 1/4 hours"

$$E[T] = \frac{1}{4}$$

# The Expected Waiting Time

"Buses arrive at a rate of $\lambda$ =4/60=0.0666… per minute"

$$f(t) = \frac{4}{60} e^{-\frac{4}{60}t}$$



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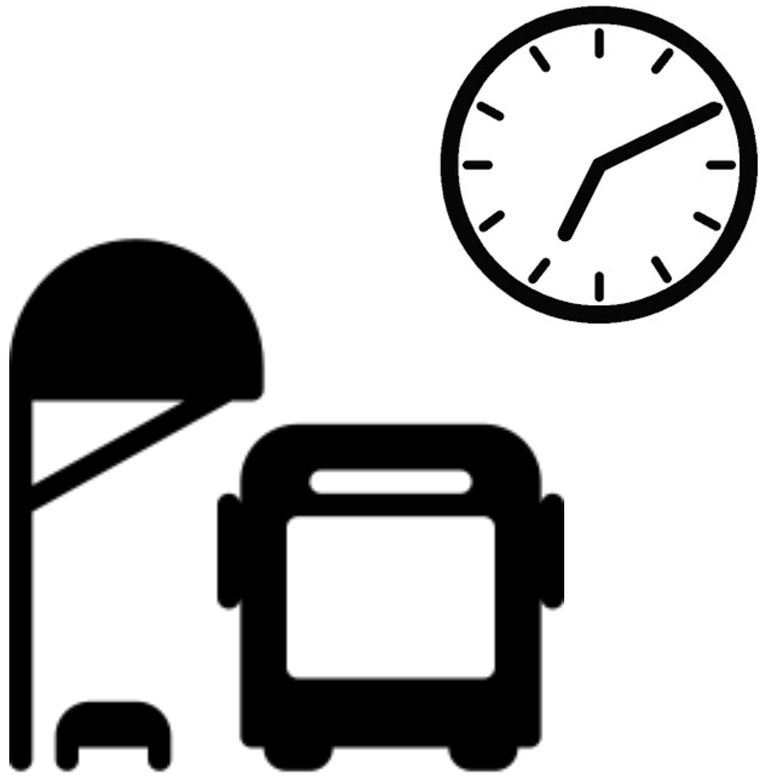
$$f(t) = \frac{4}{60} e^{-\frac{4}{60}t}$$

"The expected waiting time for the next bus is 1/0.0666… = 15 minutes"

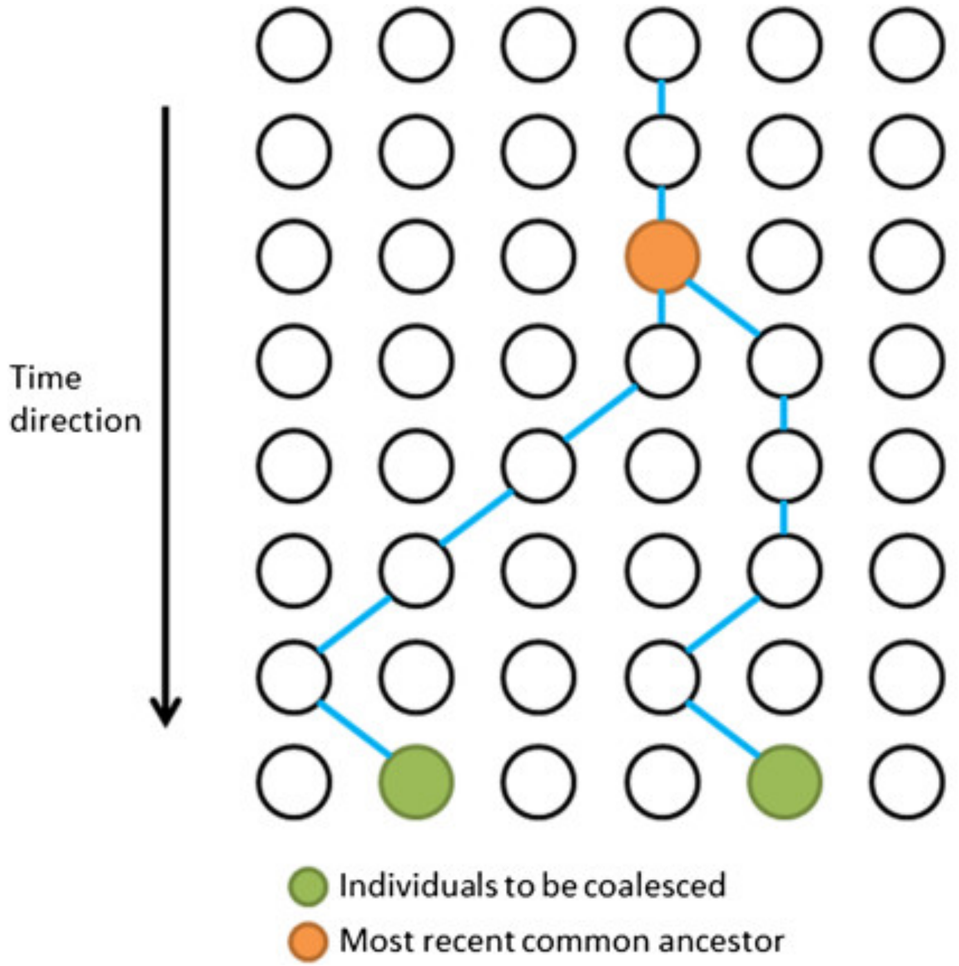
$$E[T] = 15$$



# The Expected Waiting Time

"A coalescent event between 2 lineages occurs at a rate of 1/2N per generation"

$$f(t) = \frac{1}{2N} e^{-t/(2N)}$$



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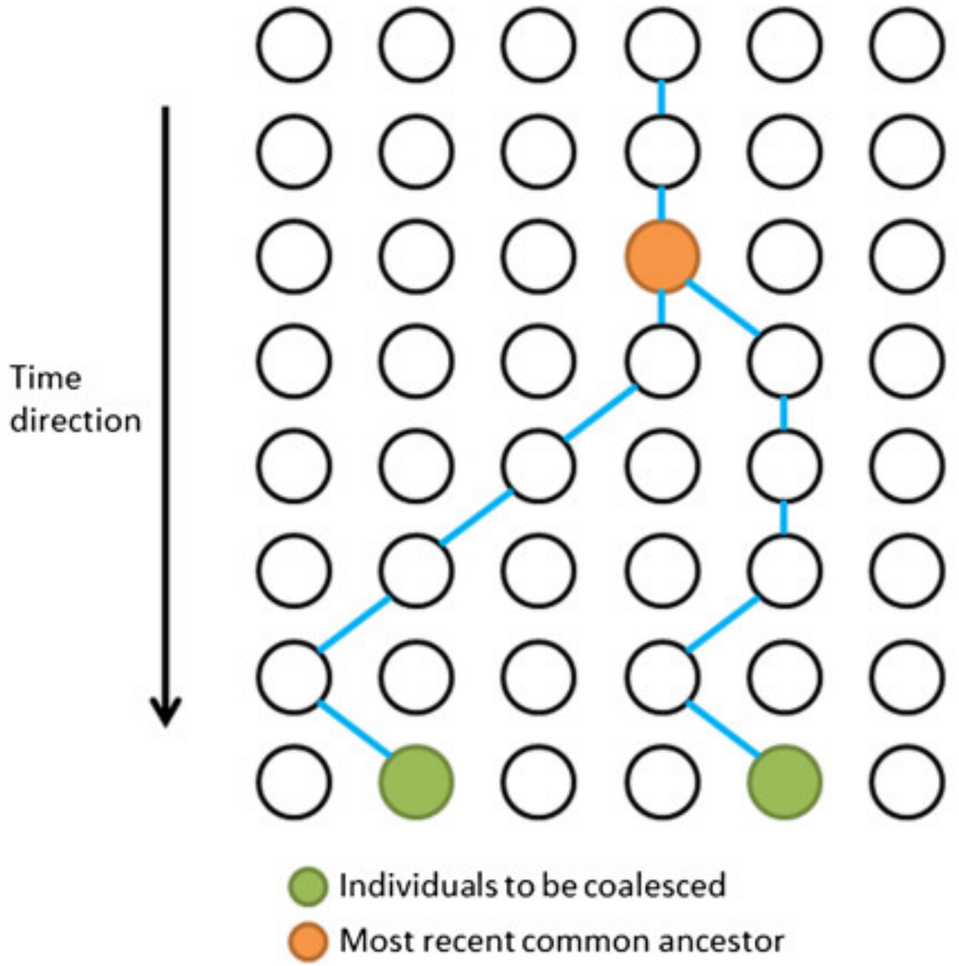
"A coalescent event between 2 lineages occurs at a rate of 1/2N per generation"

$$f(t) = \frac{1}{2N} e^{-t/(2N)}$$

"The expected waiting time for a coalescent event is 2N generations"

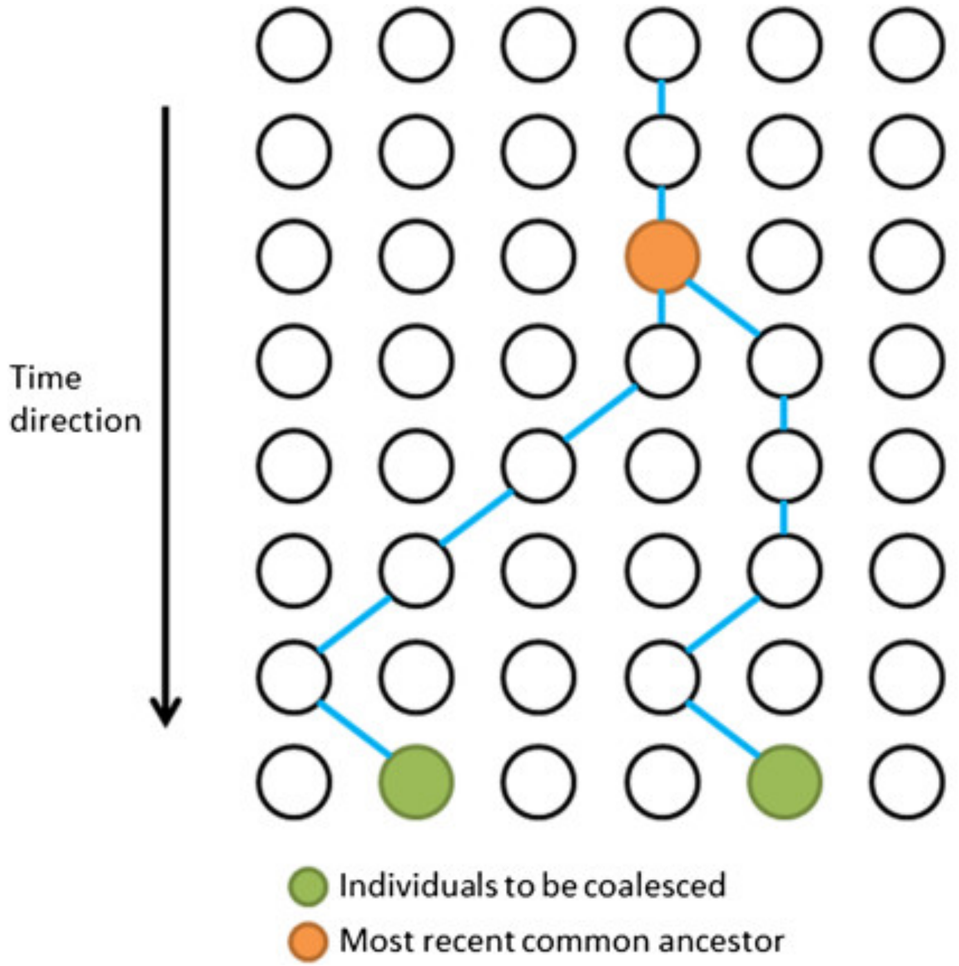
$$E[T] = 2N$$



# The Expected Waiting Time

"A coalescent event between 2 lineages occurs at a rate of 1 per coalescent unit (1 unit = 2N generations)."

$$f(t) = e^{-t}$$



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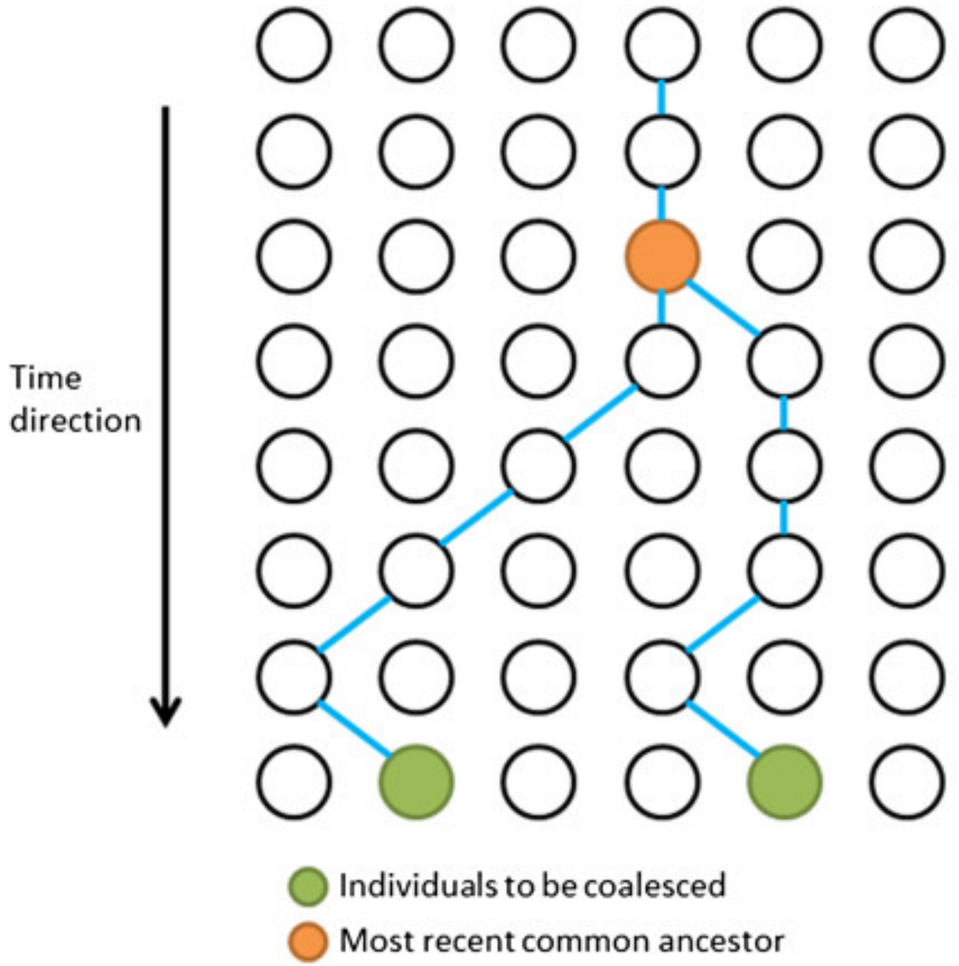
"The expected waiting time for a coalescent event is 1 coalescent unit"

$$E[T] = 1$$



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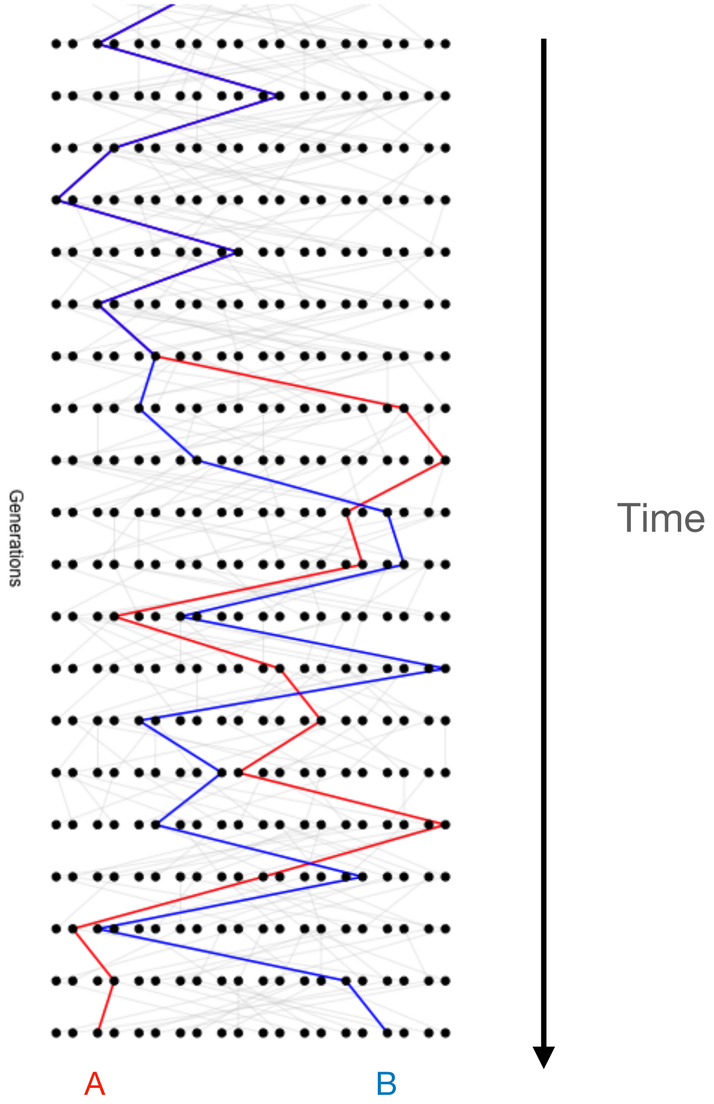

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**Rate:**

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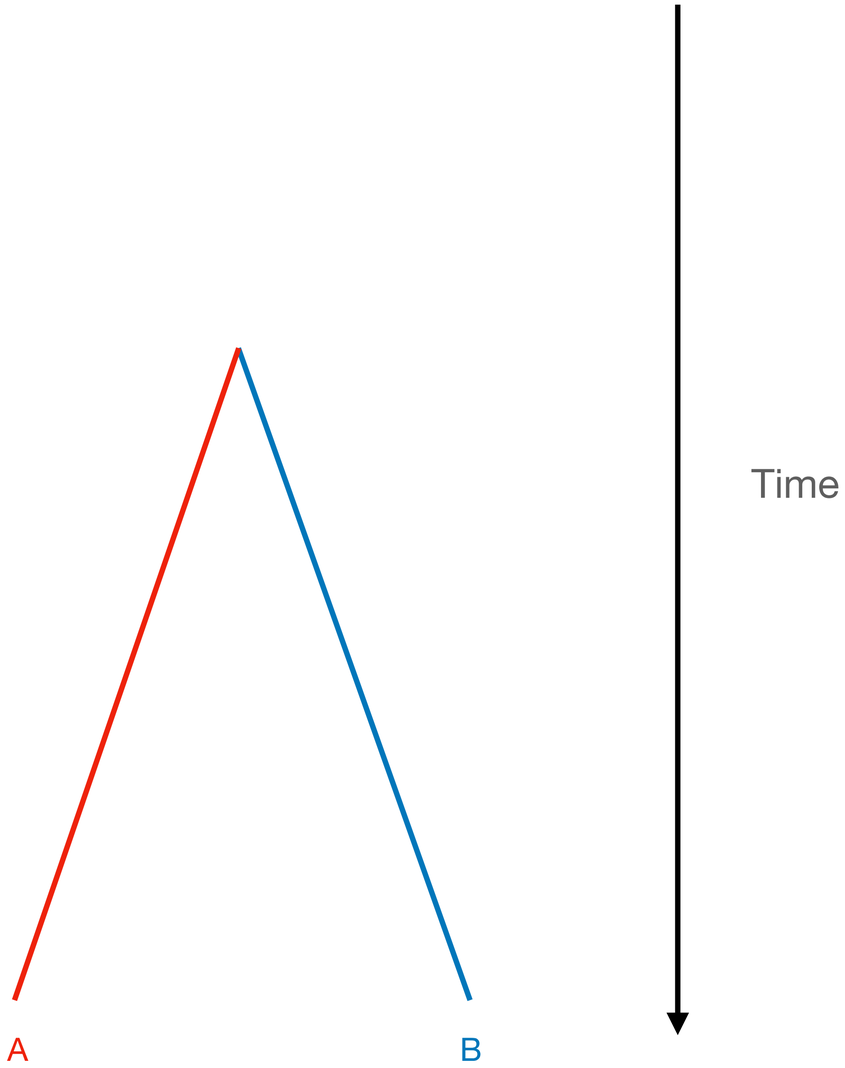

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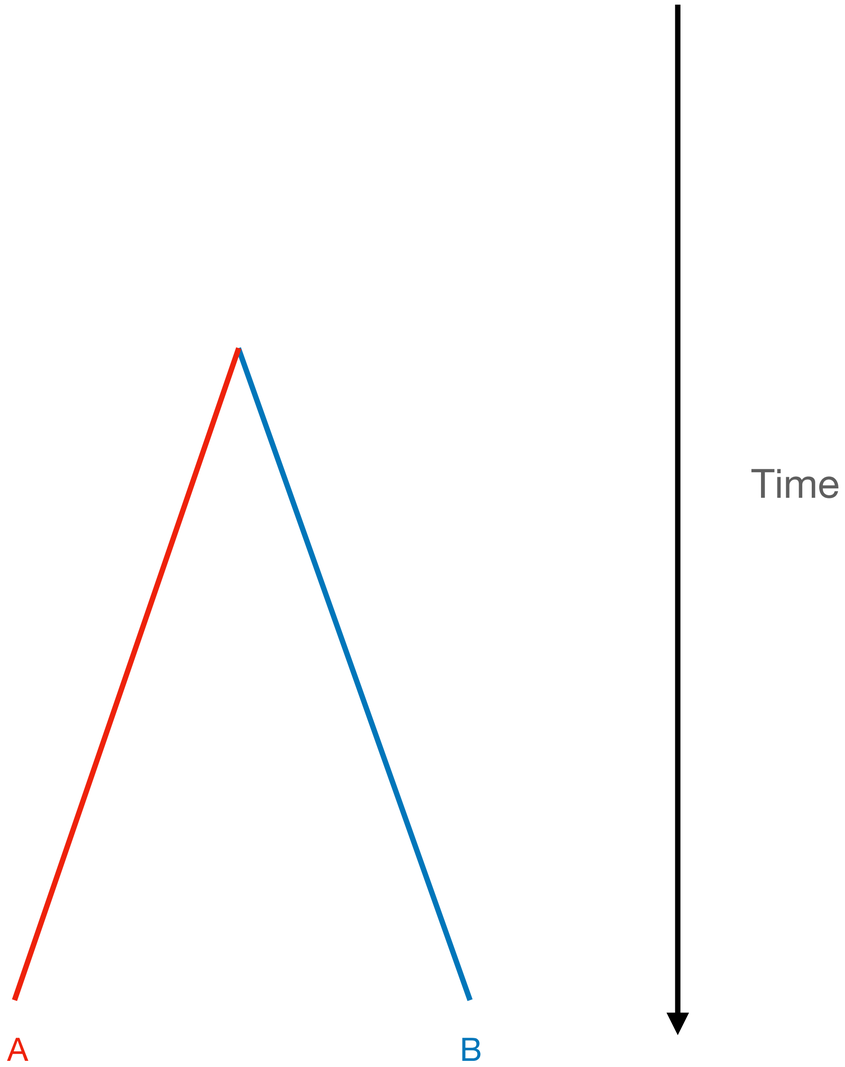

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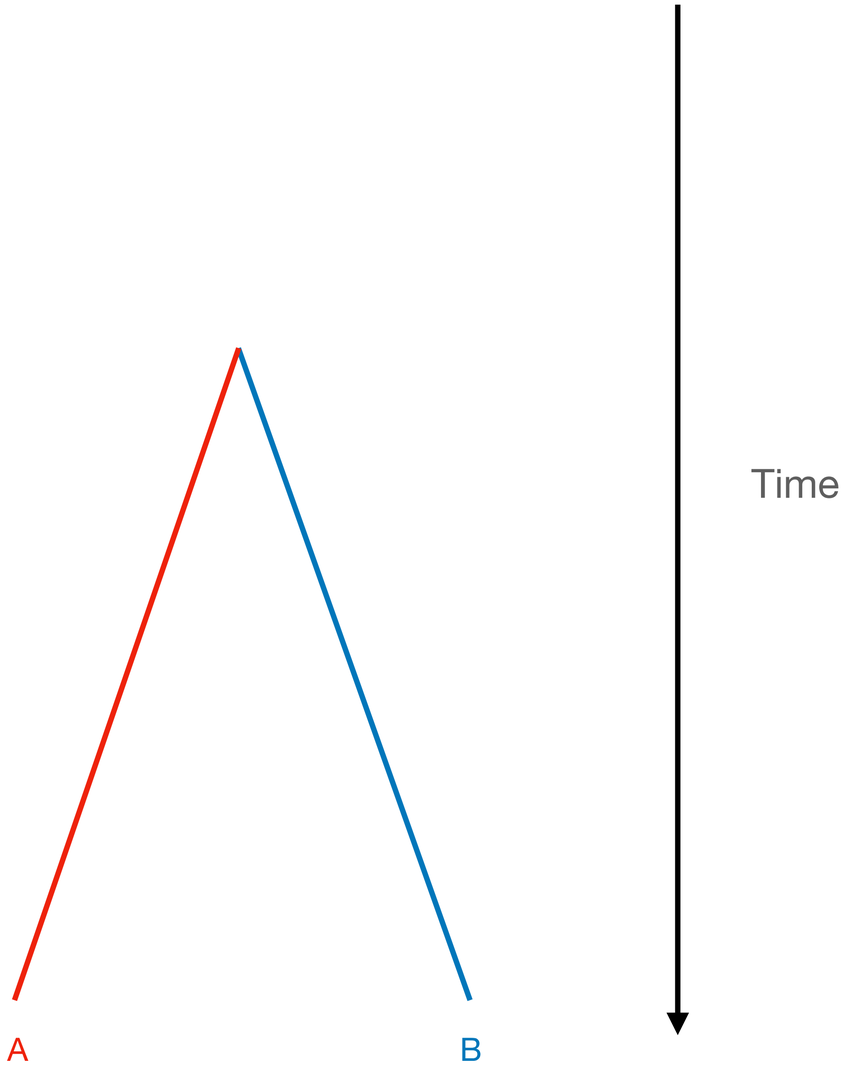

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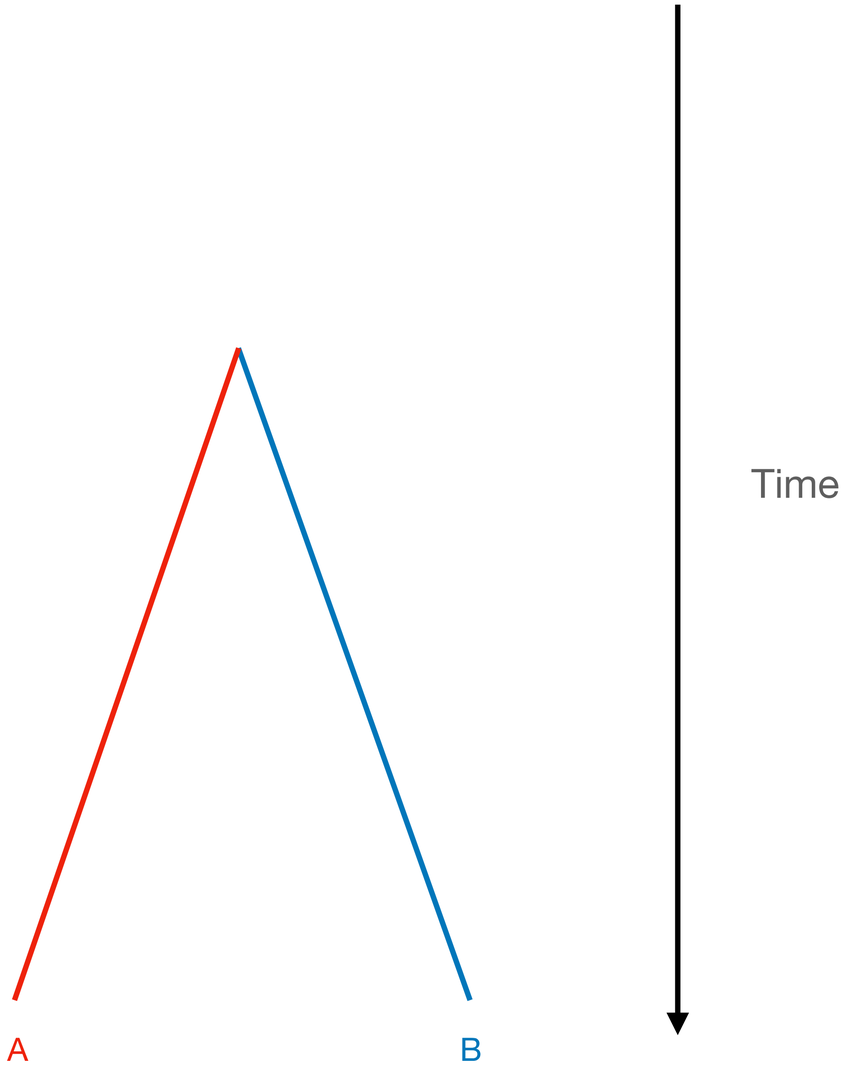

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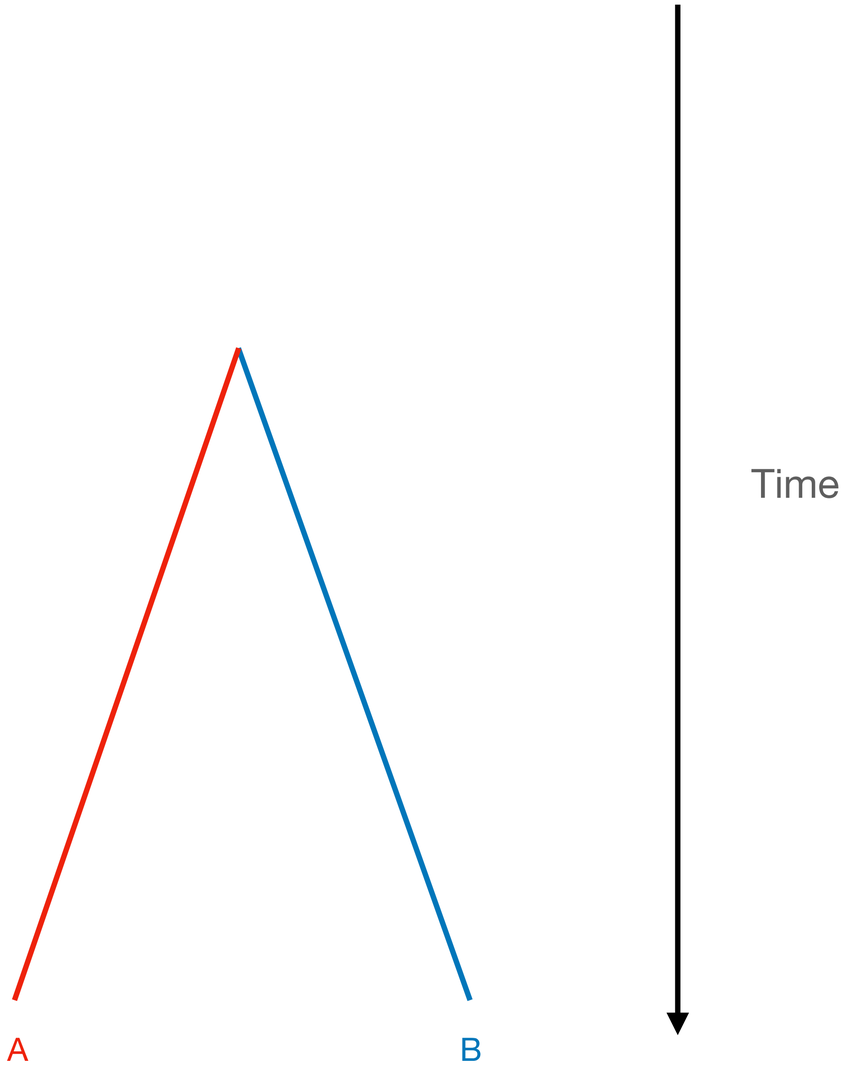
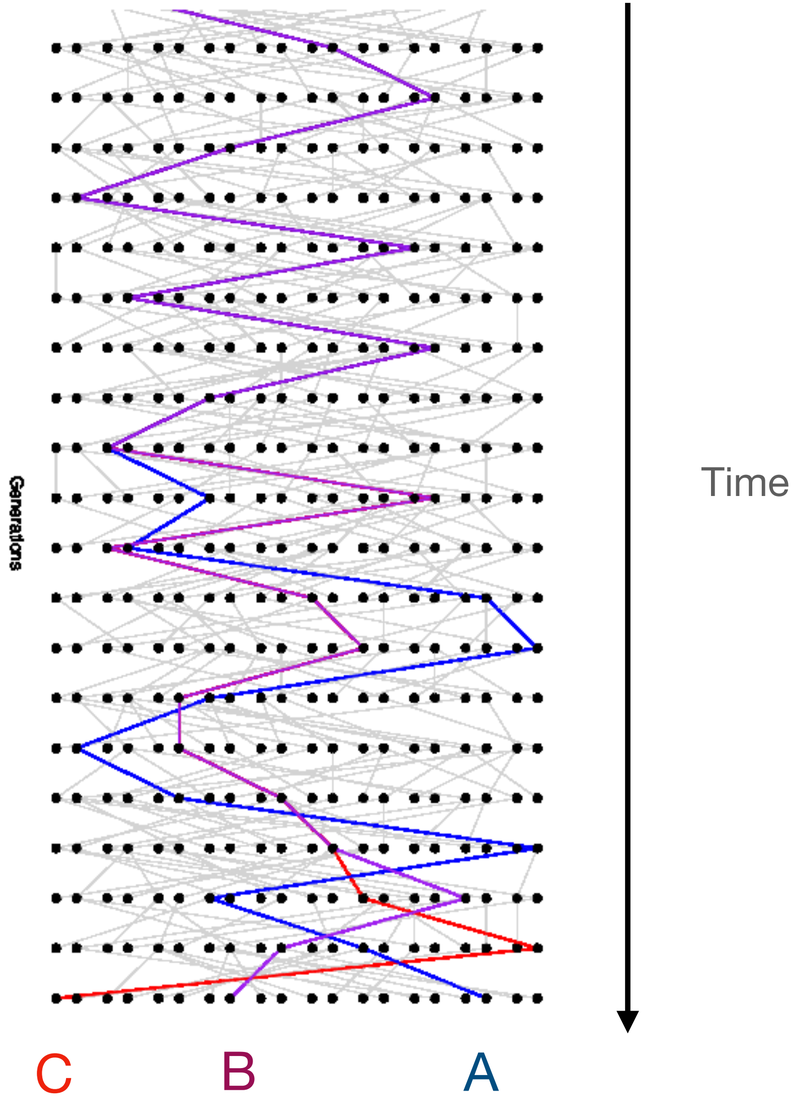


# Tree with 3 samples



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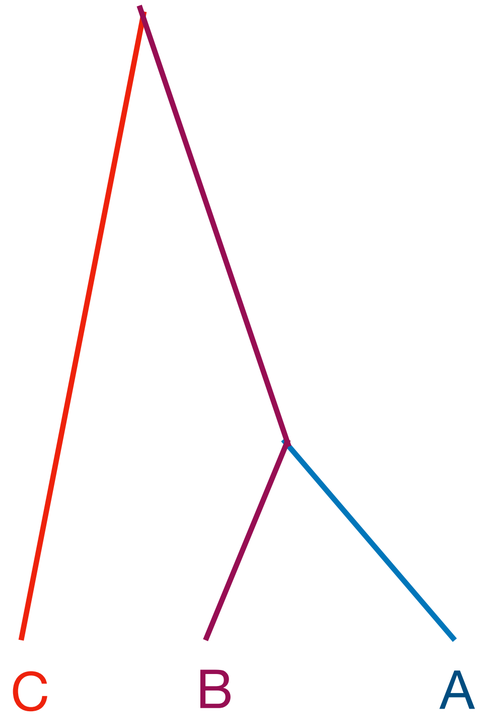

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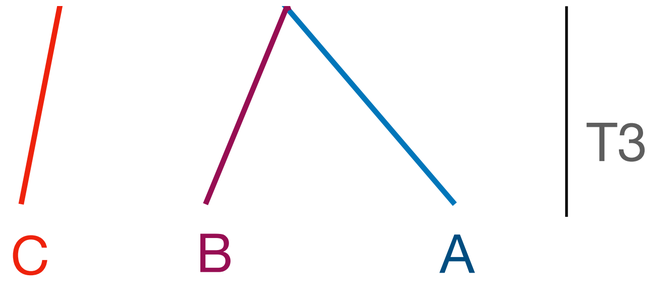

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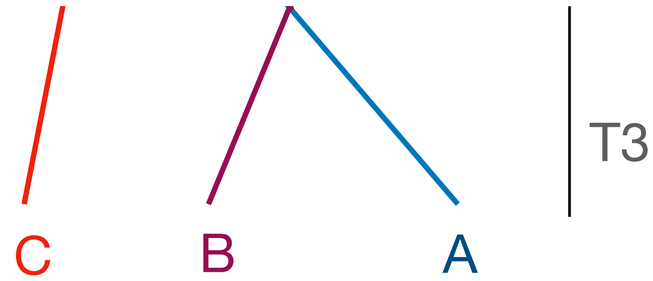
**T3 = time while there are 3 lineages**

**Rate:** $\lambda_{T3} = 1 * \binom{3}{2} = 3$



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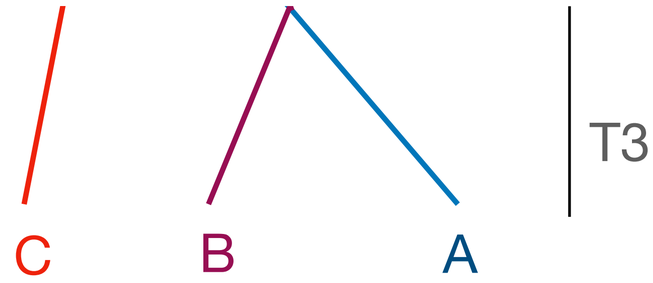
…because there are 3 “competing pairs” of lineages fighting for the opportunity to coalesce (each at rate 1): A+B, B+C, A+C



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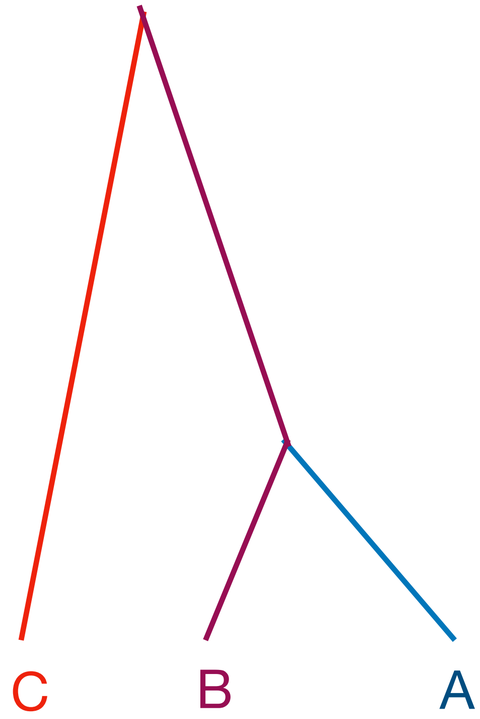

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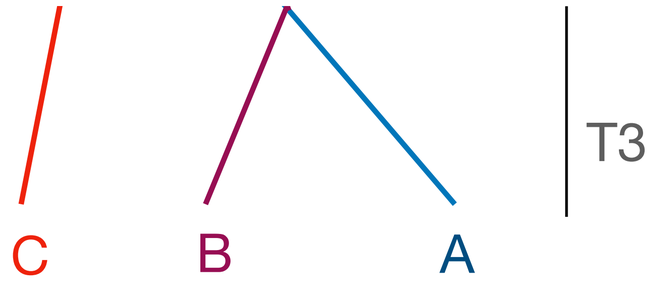

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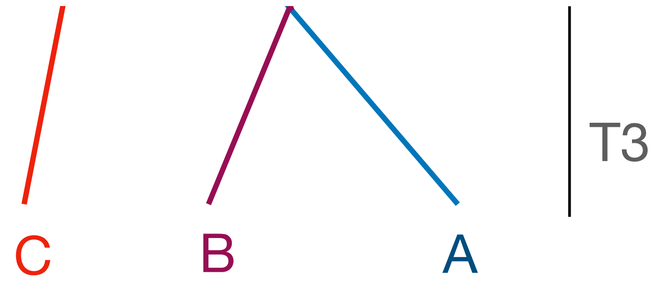
Rate: $\lambda_{T3} = 1 * \binom{3}{2} = 3$

…because there are 3 “competing pairs” of lineages fighting for the opportunity to coalesce (each at rate 1): A+B, B+C, A+C

Expected time: $E[T3] = \frac{1}{\binom{3}{2}} = \frac{1}{3}$



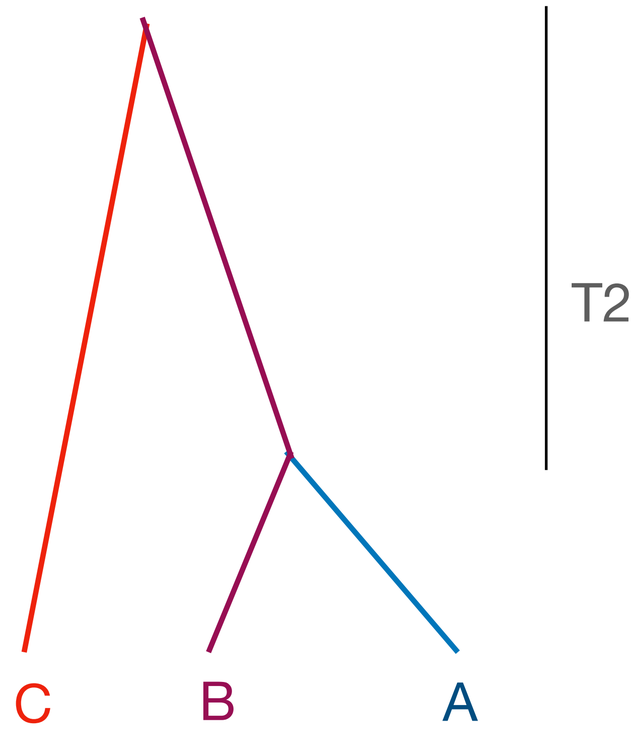
# Tree with 3 samples

**T2 = time while there are 2 lineages**

**Rate:** $\lambda_{T2} = \frac{1}{\binom{2}{2}} = 1$

…because there is just one possible pair
that can coalesce (at rate 1)

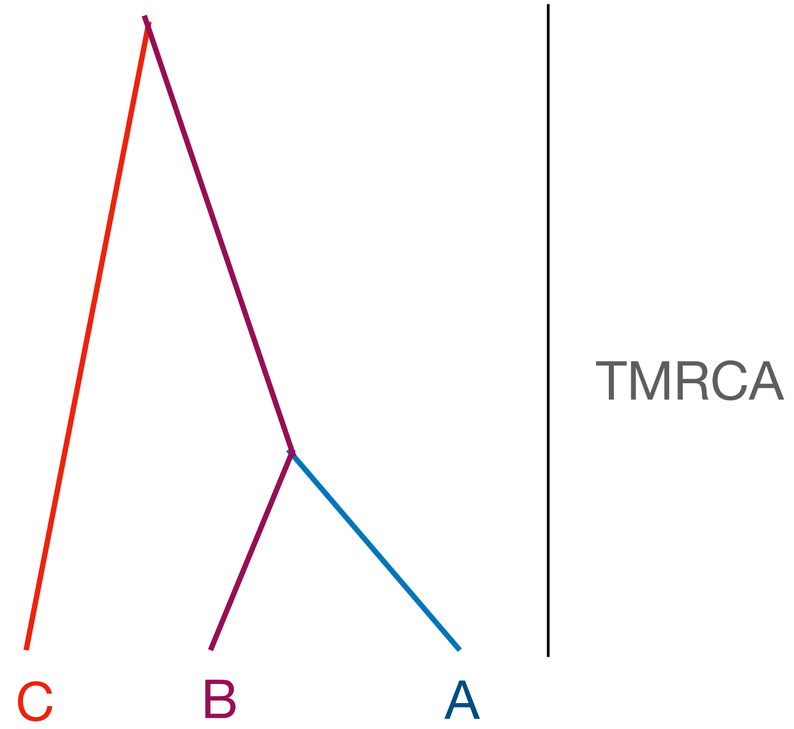
Expected time: $E[T2] = 1$



# Tree with 3 samples

$E[T_{MRCA}] = T_2 + T_3 = 1 + 1/3$ coalescent units

$E[T_{MRCA}] = (1 + 1/3) * 2N$ generations

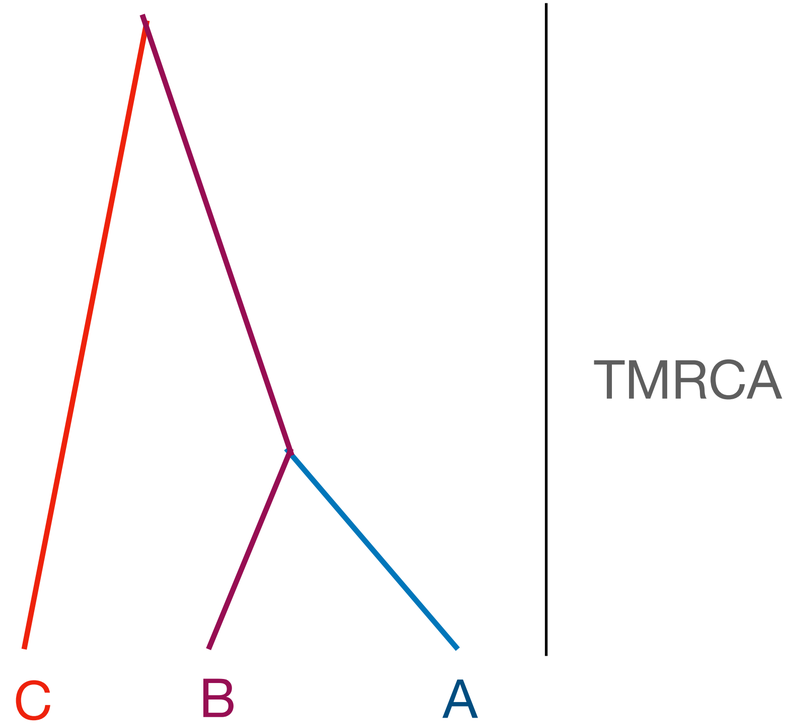


# Tree with 3 samples

$E[T_{MRCA}] = T_2 + T_3 = 1 + 1/3$ coalescent units

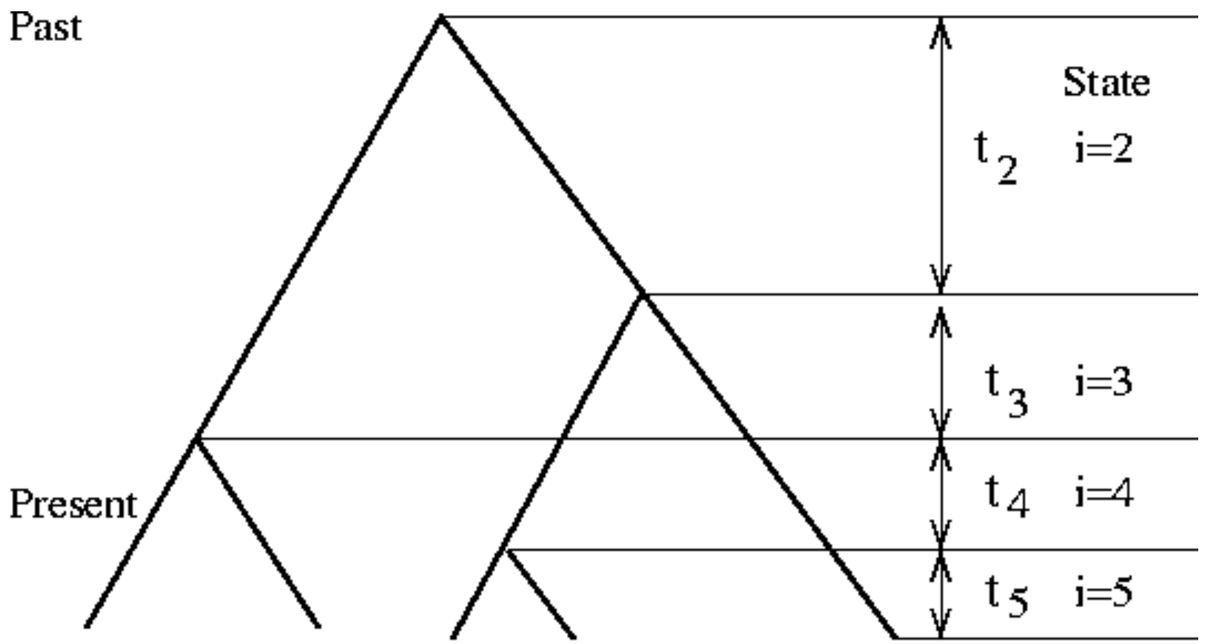
$E[T_{MRCA}] = (1 + 1/3) * 2N$ generations

Example: if 2N = 10,000, then:
$E[T_{MRCA}] \approx$ 13,333 generations



# TMRCA

$$E[T_{MRCA}] = T_2 + T_3 + \ldots + T_n$$

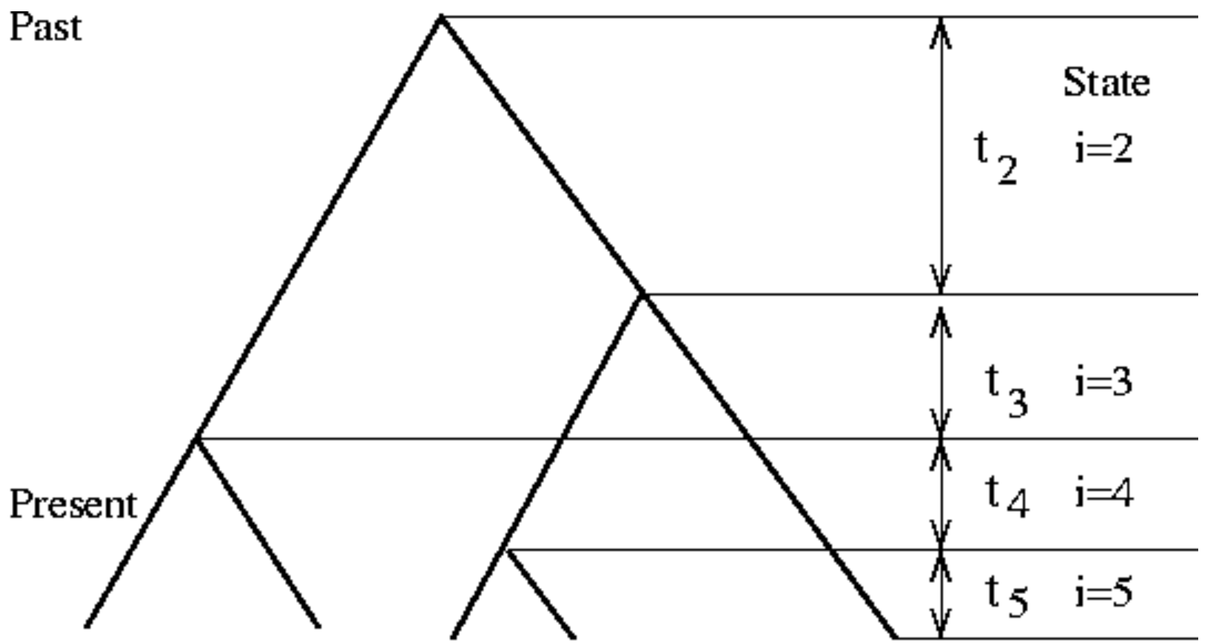


# TMRCA

$$E[T_{MRCA}] = T_2 + T_3 + \ldots + T_n$$

$$E[T_{MRCA}] = \sum_{i=2}^{n} \frac{1}{\binom{i}{2}} = 2\left(1 - \frac{1}{n}\right)$$

where n is our sample size



# Variance of an exponential distribution

One parameter: $\lambda$

$$E[T] = \frac{1}{\lambda}$$

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One parameter: $\lambda$

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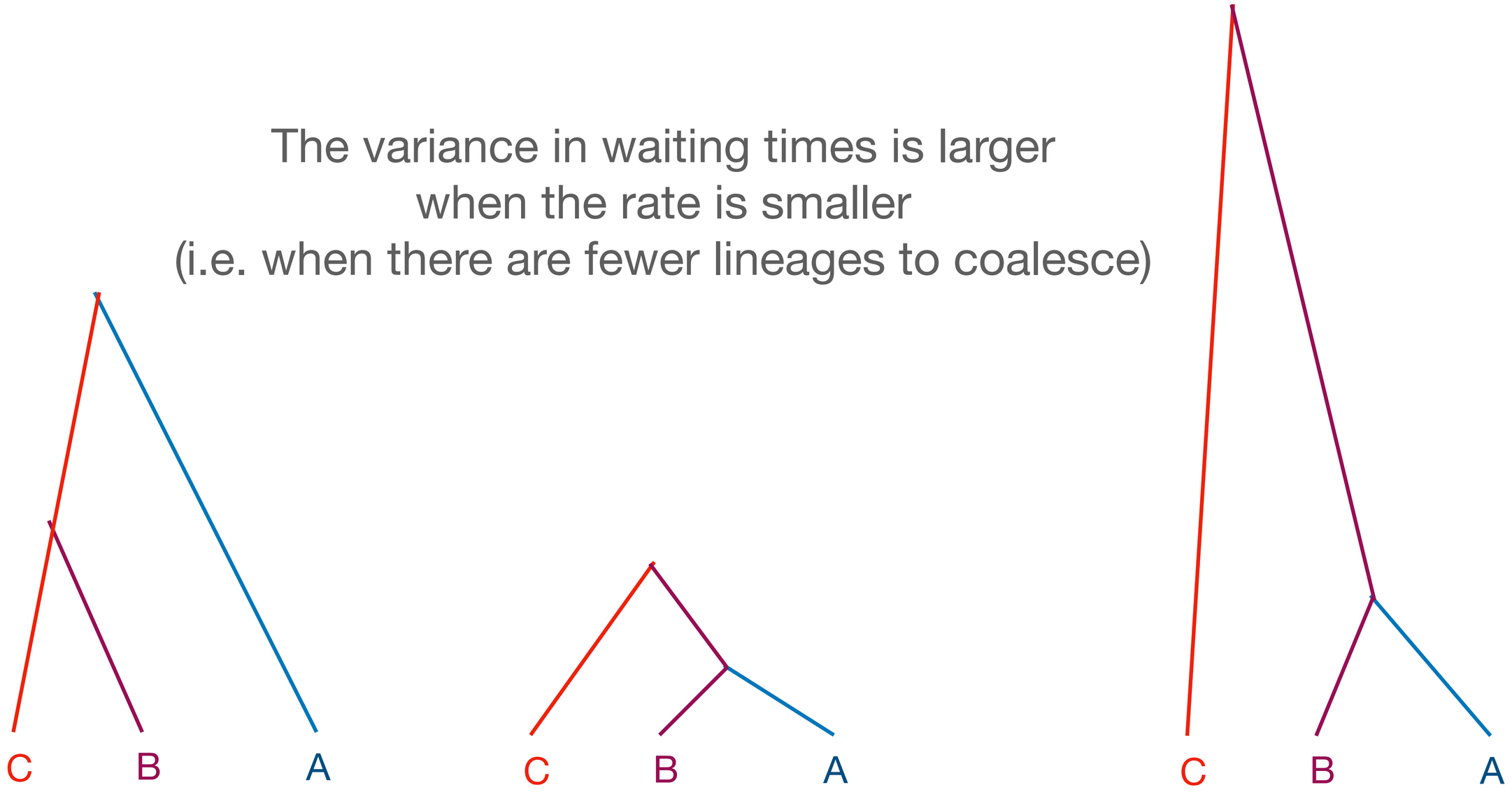
$$Var[T] = \frac{1}{\lambda^2} \longrightarrow$$ The variance in waiting times is larger when the rate is smaller

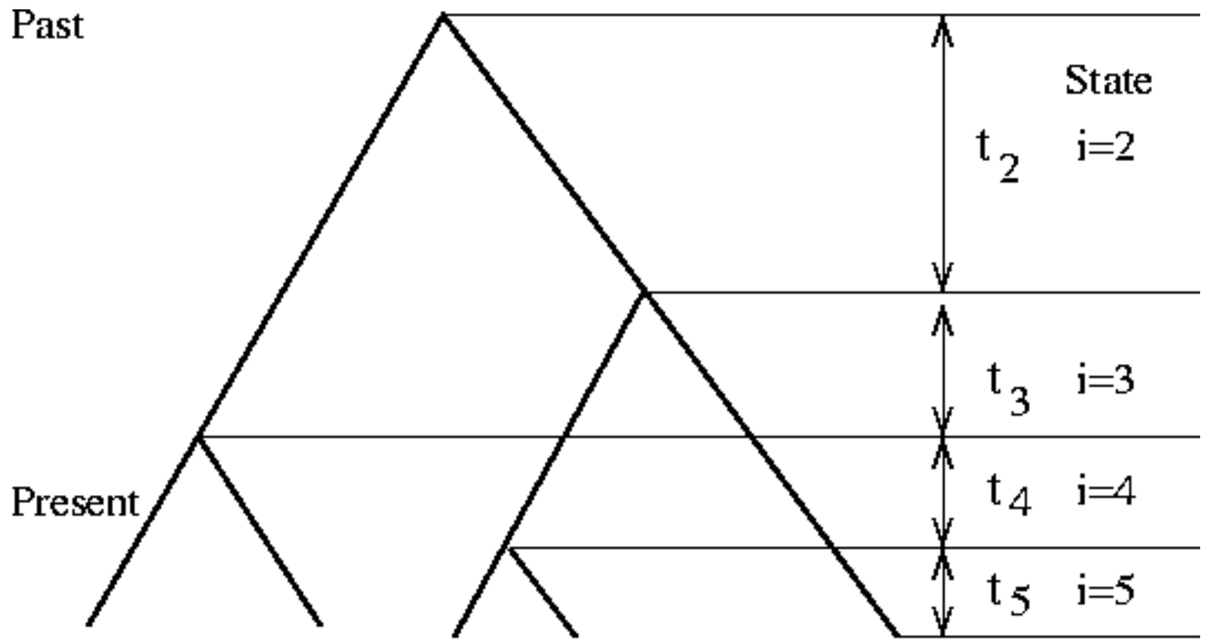
# Variance in coalescence times

The variance in waiting times is larger
when the rate is smaller
(i.e. when there are fewer lineages to coalesce)



# Take-home message

The Kingman coalescent allows us to model the **genealogy of our sample** without worrying about details of the entire unsampled population.



# Today

- Terminology
- Wright-Fisher Model and Genetic Drift
- Intro to coalescent theory
- Mutations and the coalescent

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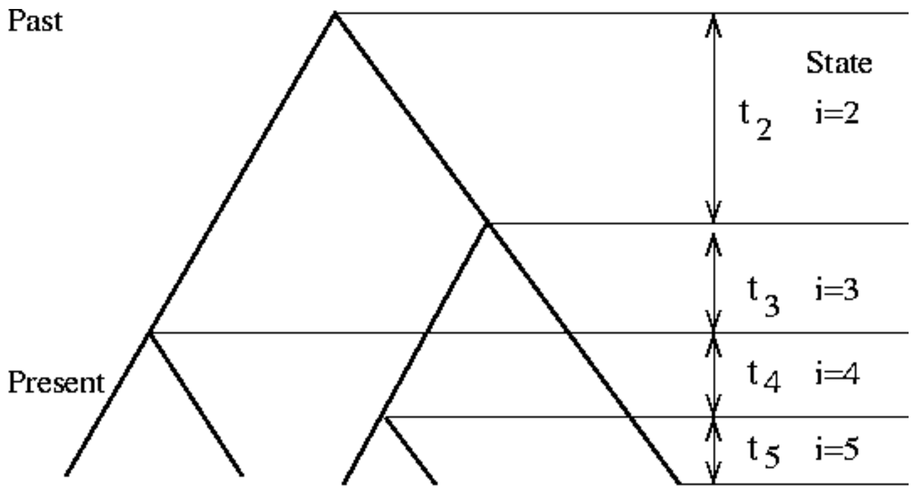
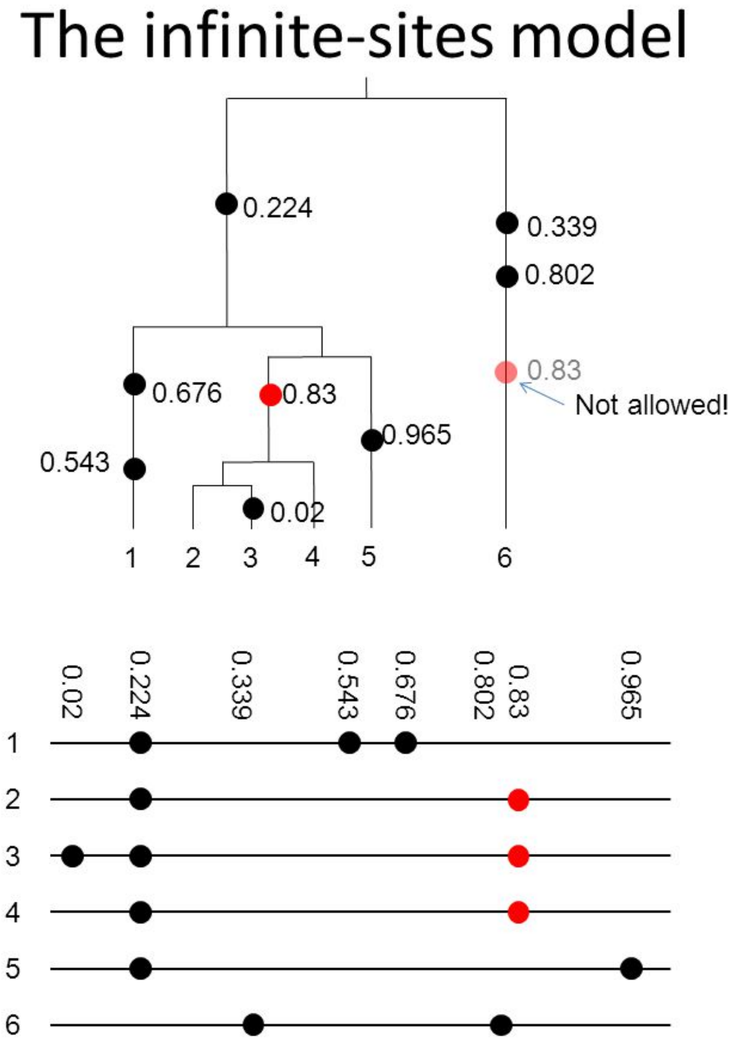
# Relating expectations about trees with data




?

# Introducing mutations into trees

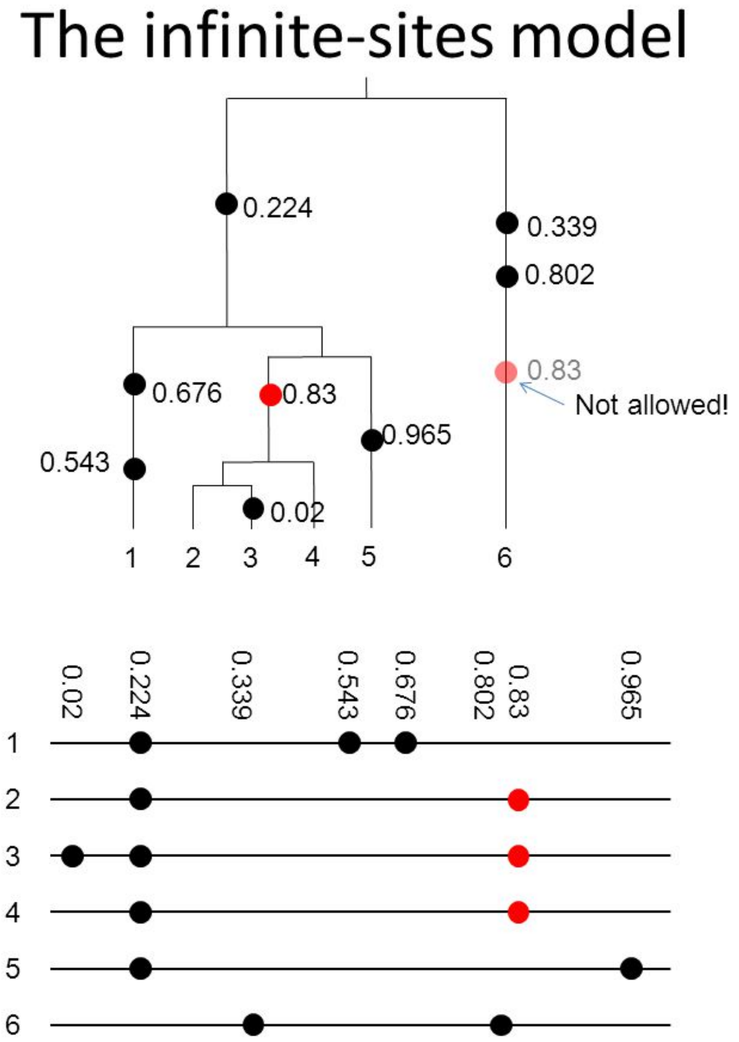
- One way of introducing mutations in a genealogy is the **infinite sites model**.
- Assume we have a sequence with infinite number of sites (for example, a real line).
- This means no two mutations can occur in the same position of our sequence.
- In other words, each mutation creates a new segregating site.




Song, Y. 2021

# Introducing mutations into trees

- Allows us to assume that each segregating site is **due to a single mutation** in the past
- Ignores double-substitutions and back-mutations
- Valid as long as the **sequence we are studying is long** and the **mutation rate is low**
- Good for short time-scales (population genetics) but not long time-scales (phylogenetics)

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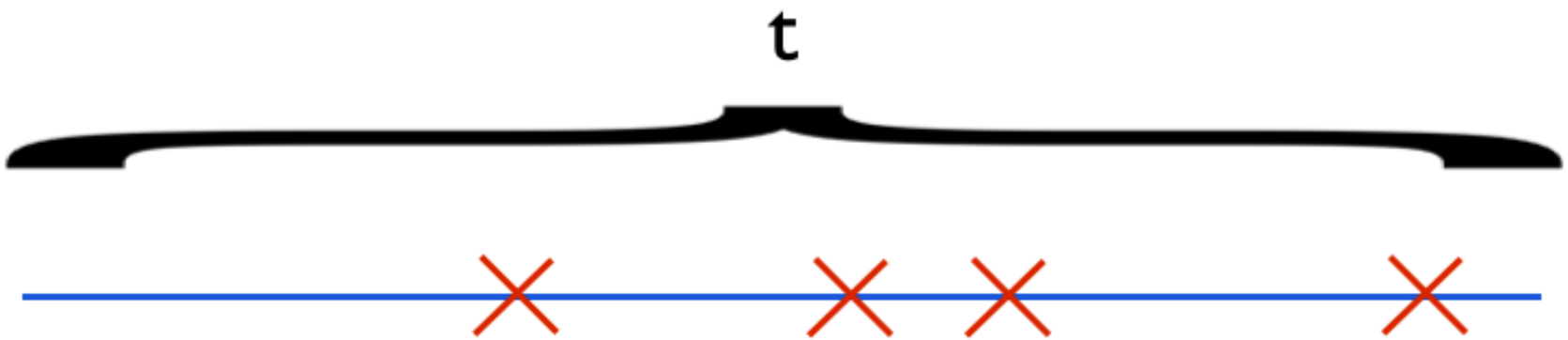
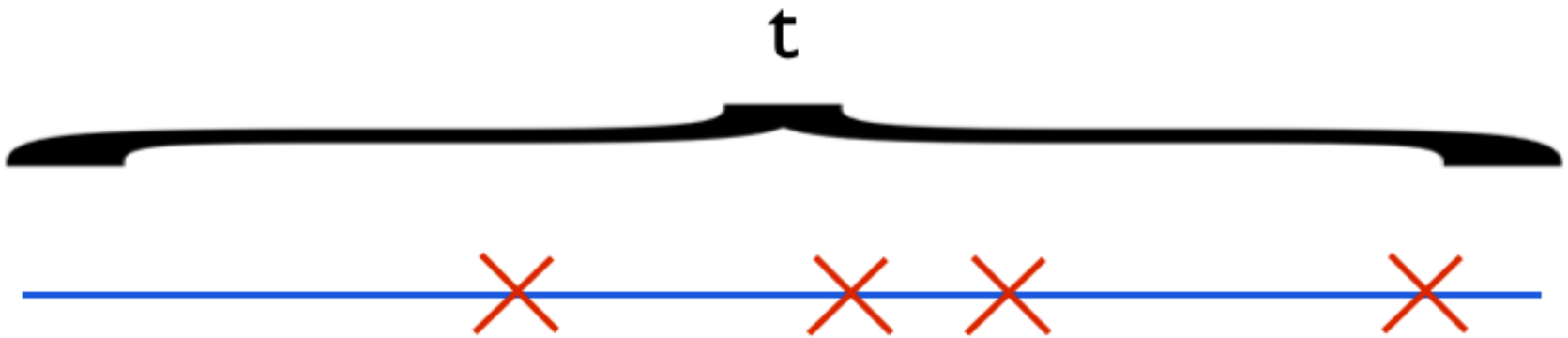
# Introducing mutations into a lineage



# Introducing mutations into a lineage

- Mutations occur at rate **u per generation**



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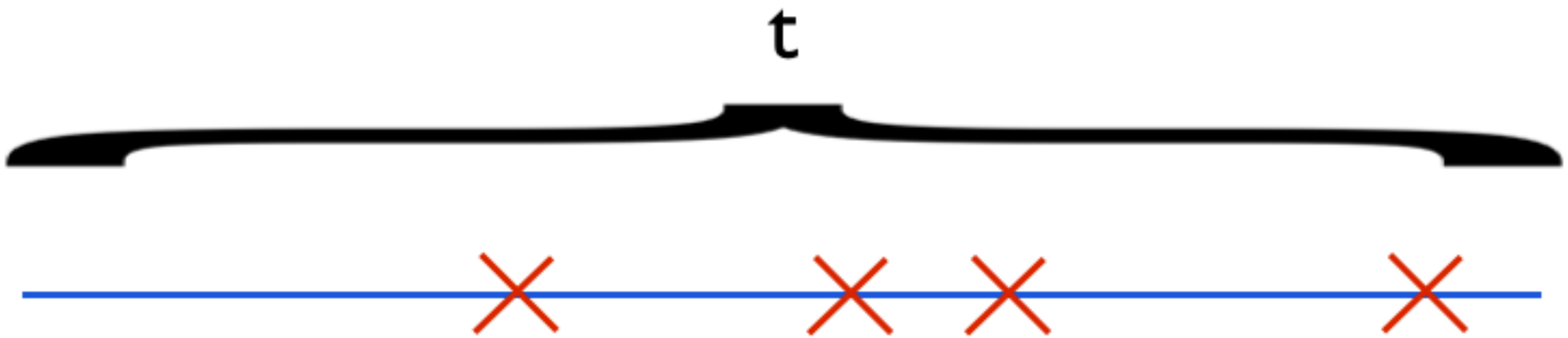

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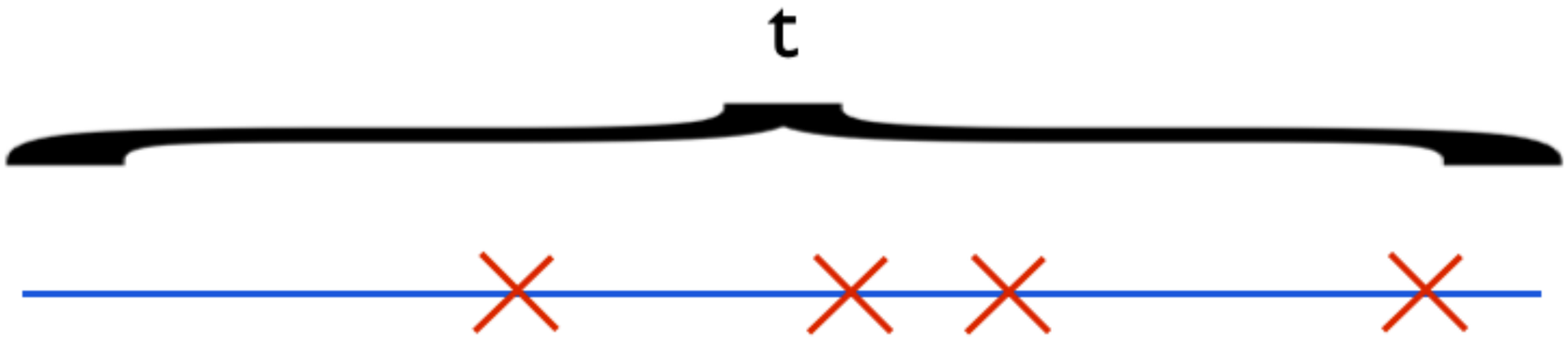
- In other words, we expect u*r mutations in r generations



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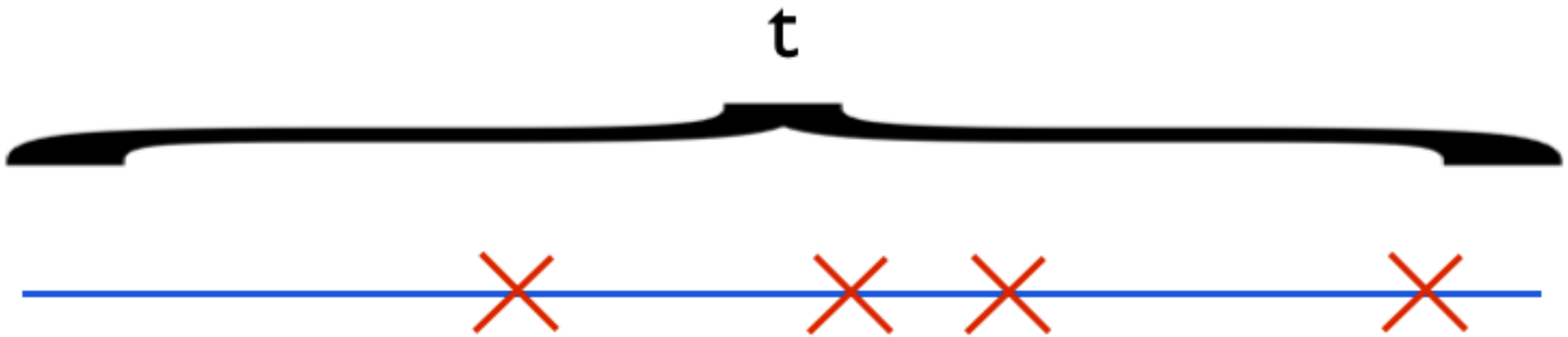

# Introducing mutations into a lineage

- Mutations occur at rate **u per generation**
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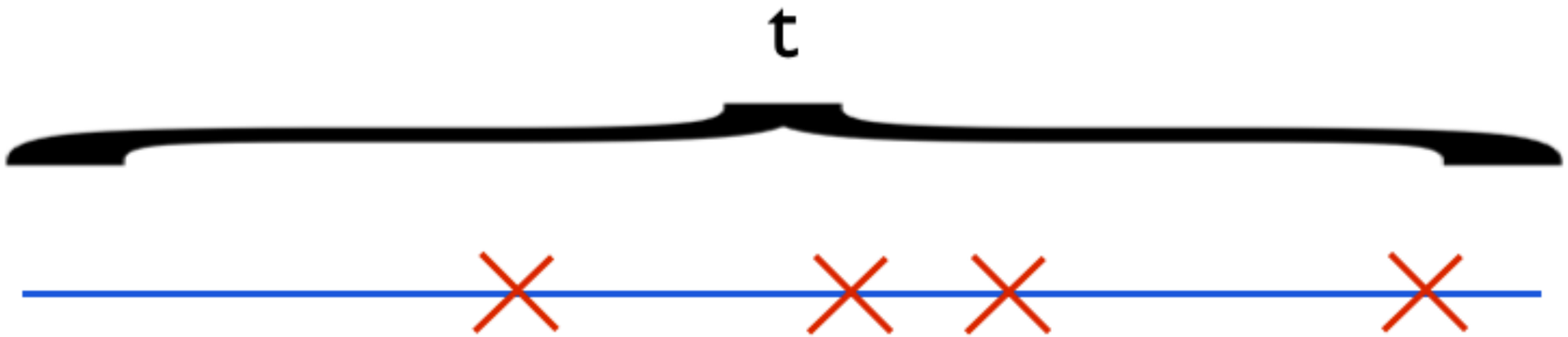
- If we measure time in units t of 2N generations, **we expect 2N*t*u mutations in t units of time**



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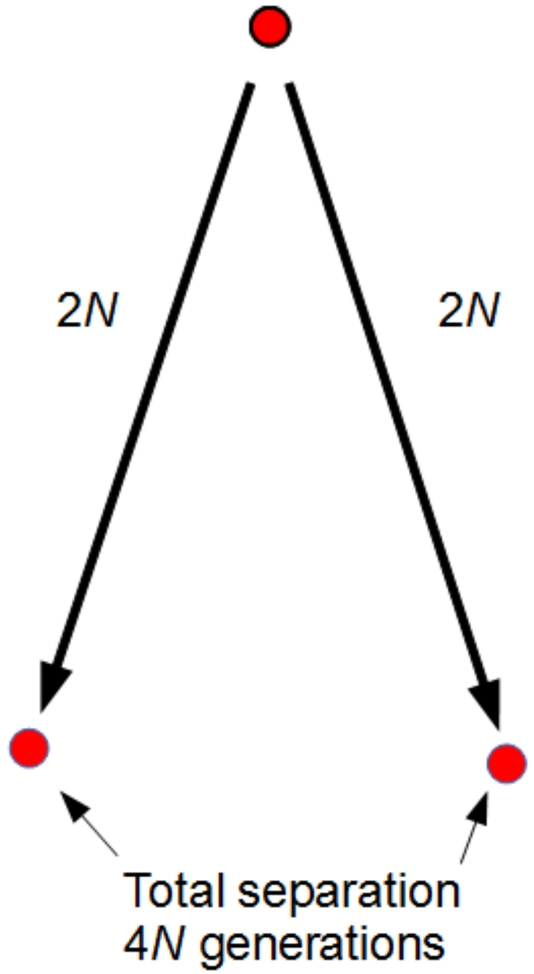
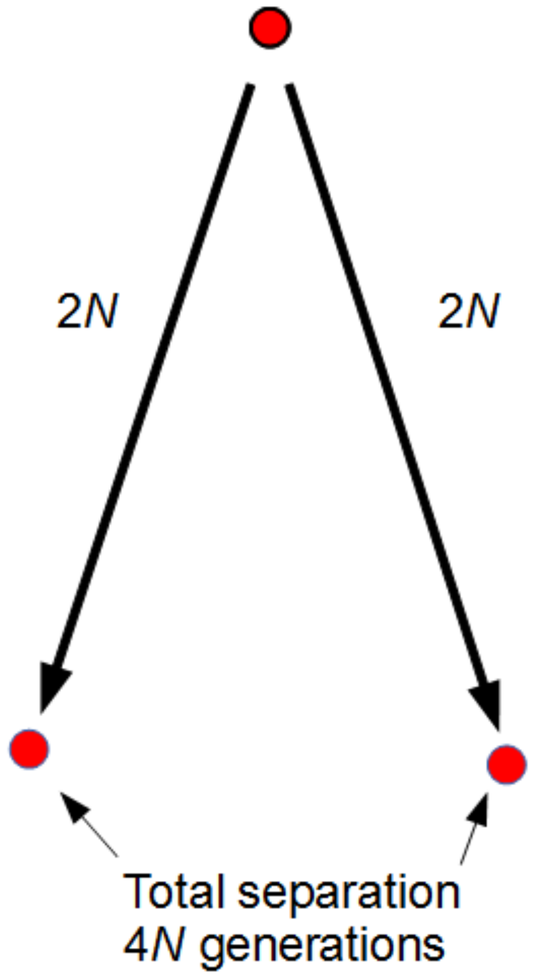


# Introducing mutations into a lineage

- Total expected length = 4N generations = **2 units of coalescent time**



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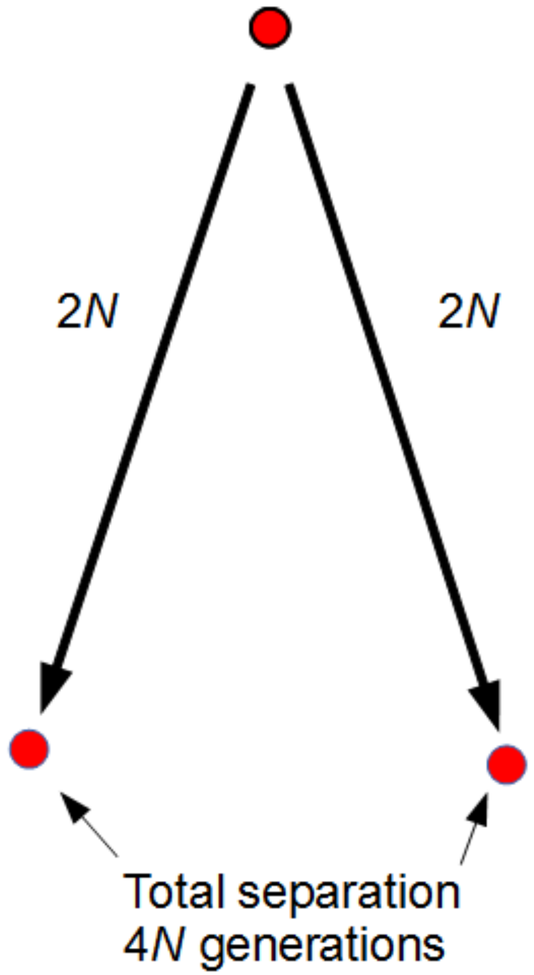

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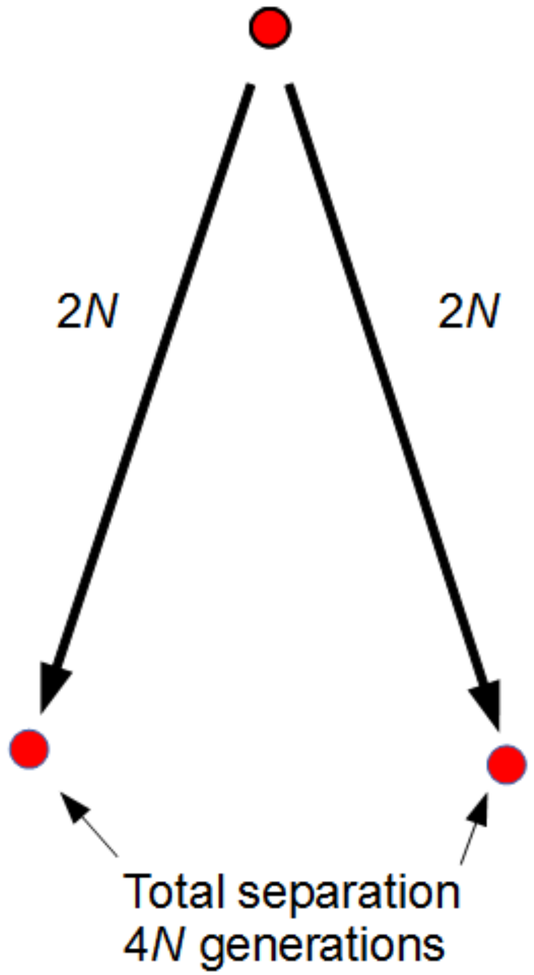
- Therefore, the total expected number of mutations is 2N*t*u = 4Nu, which is also conveniently labeled as θ



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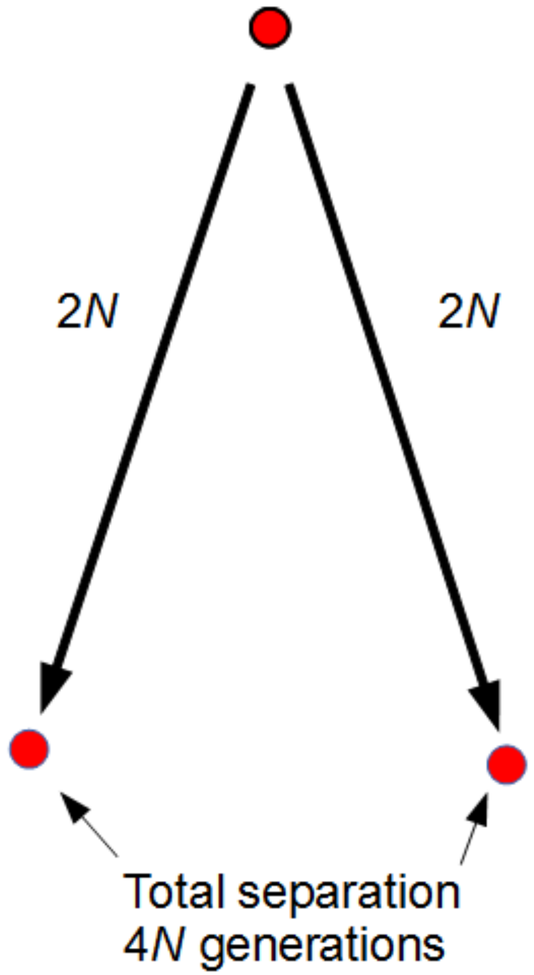

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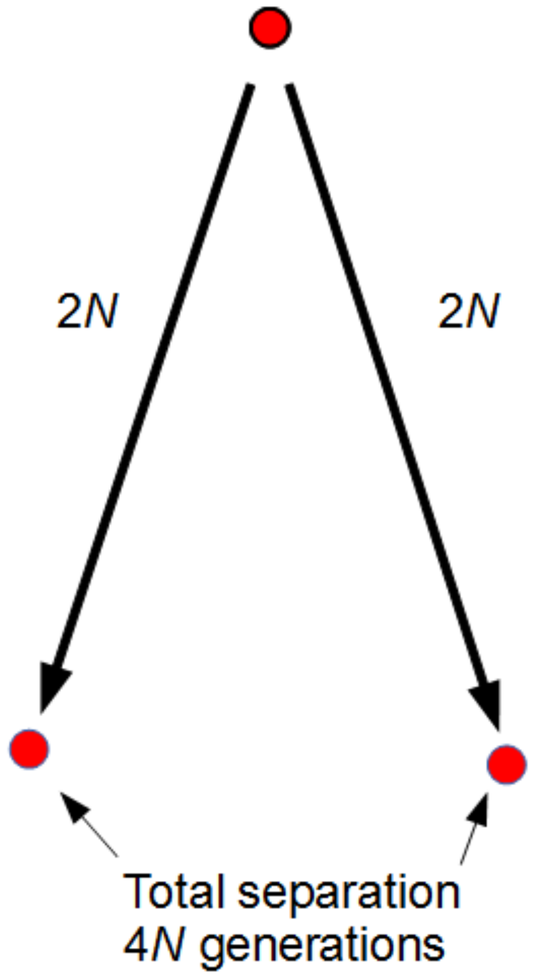
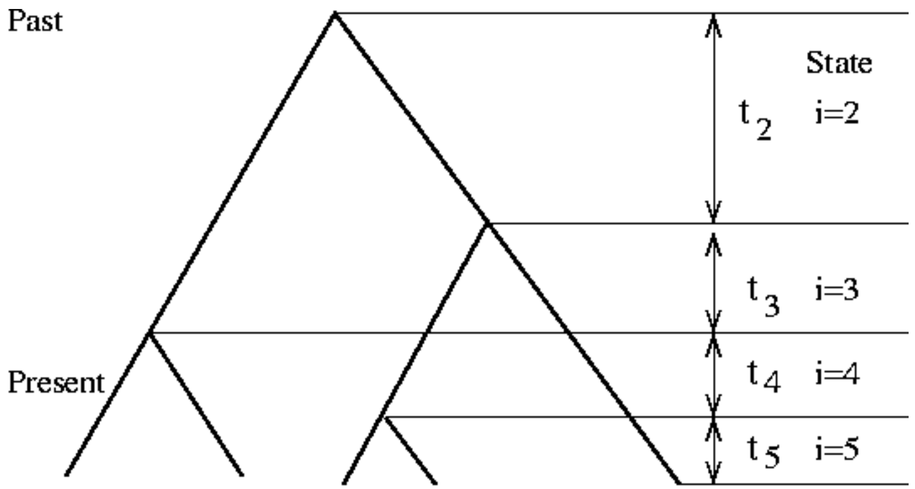
- In other words, **mutations occur at rate θ/2 per unit of coalescent time**



# Relating expectations about trees to data




infinite sites model


coalescent model

data

# Relating expectations about trees to data

Hidden properties of populations

infinite sites model


data

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Hidden properties of populations


Example: population size 2N

data

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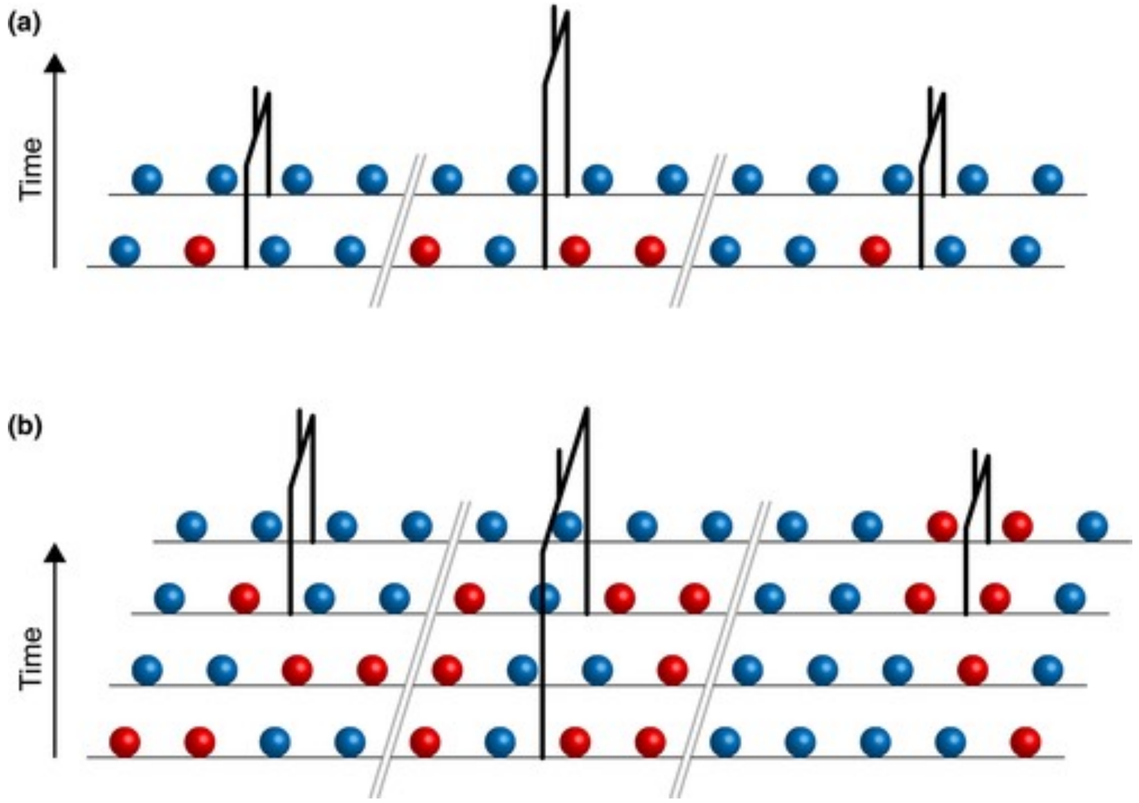
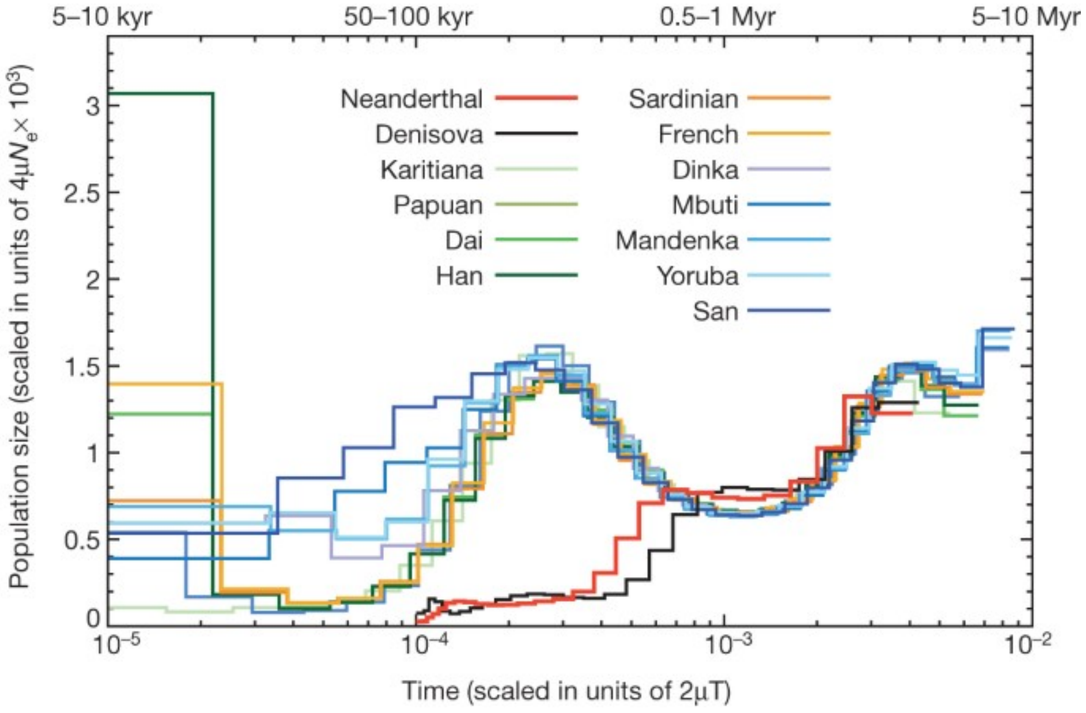



**PSMC, MSMC, SMC++, etc.**

Mather et al. (2019)




Prüfer et al. (2014)

# Relating expectations about trees to data

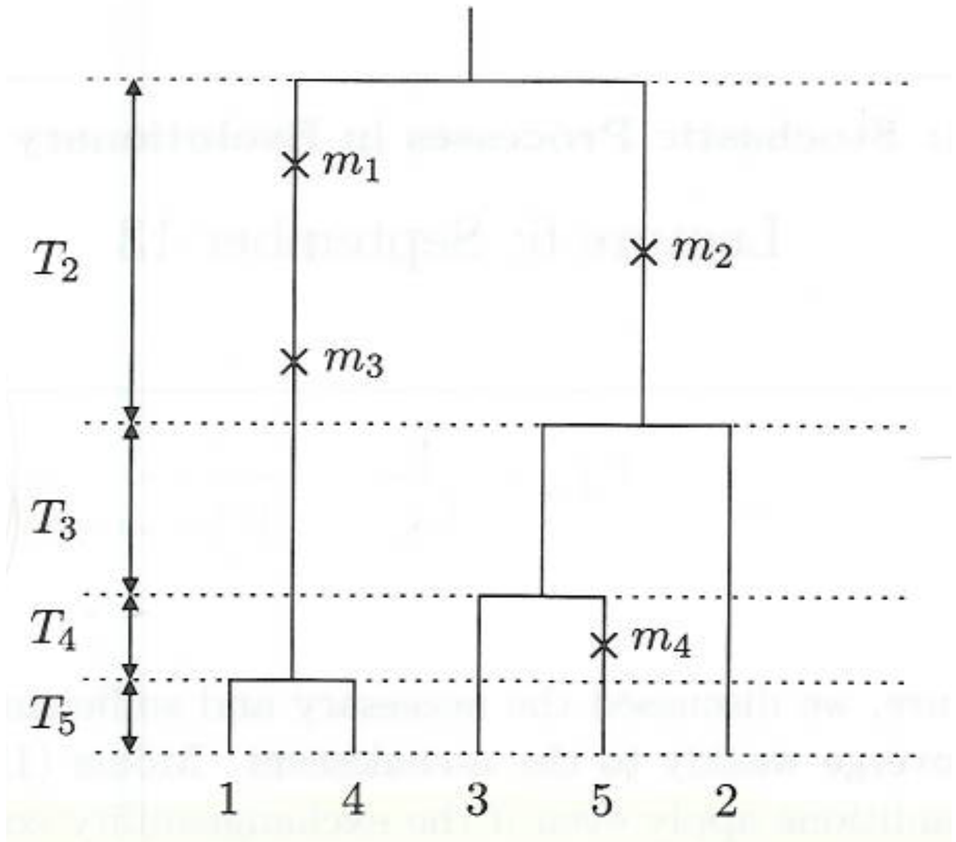
infinite sites model

Hidden properties of populations


data

Example: population size 2N, **assuming it has stayed constant over time**

# Relating expectations about trees to data

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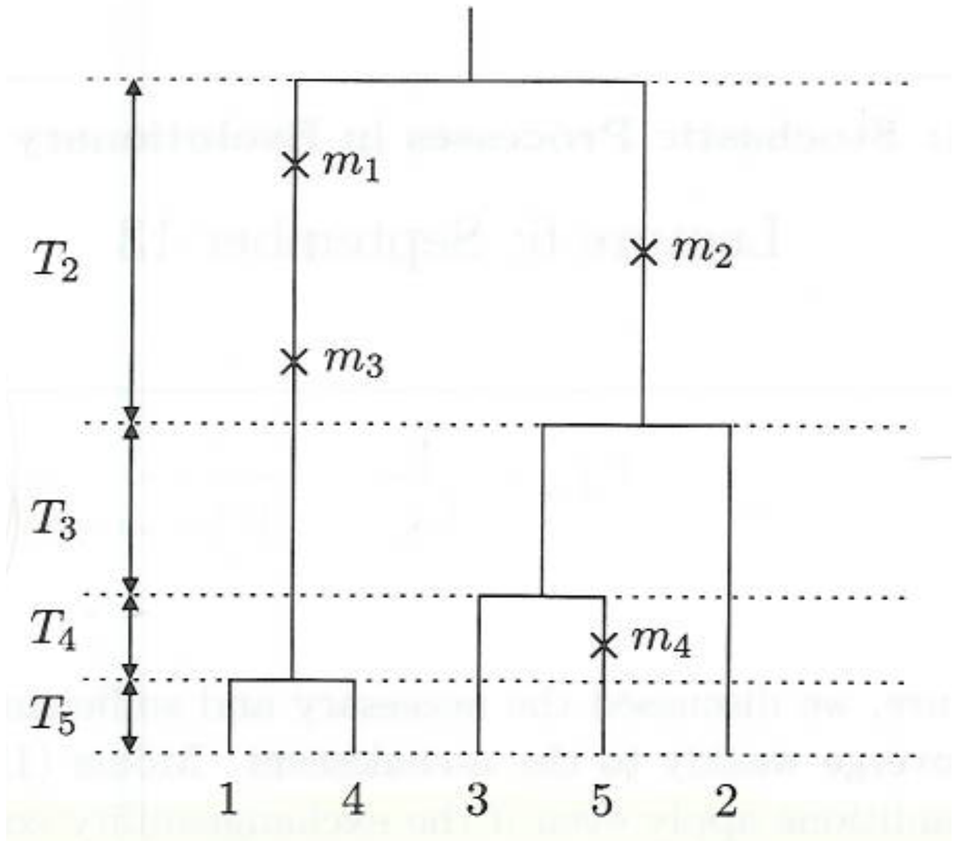
- We can use statistics computed on data to estimate hidden parameters, e.g. θ = 4Nu

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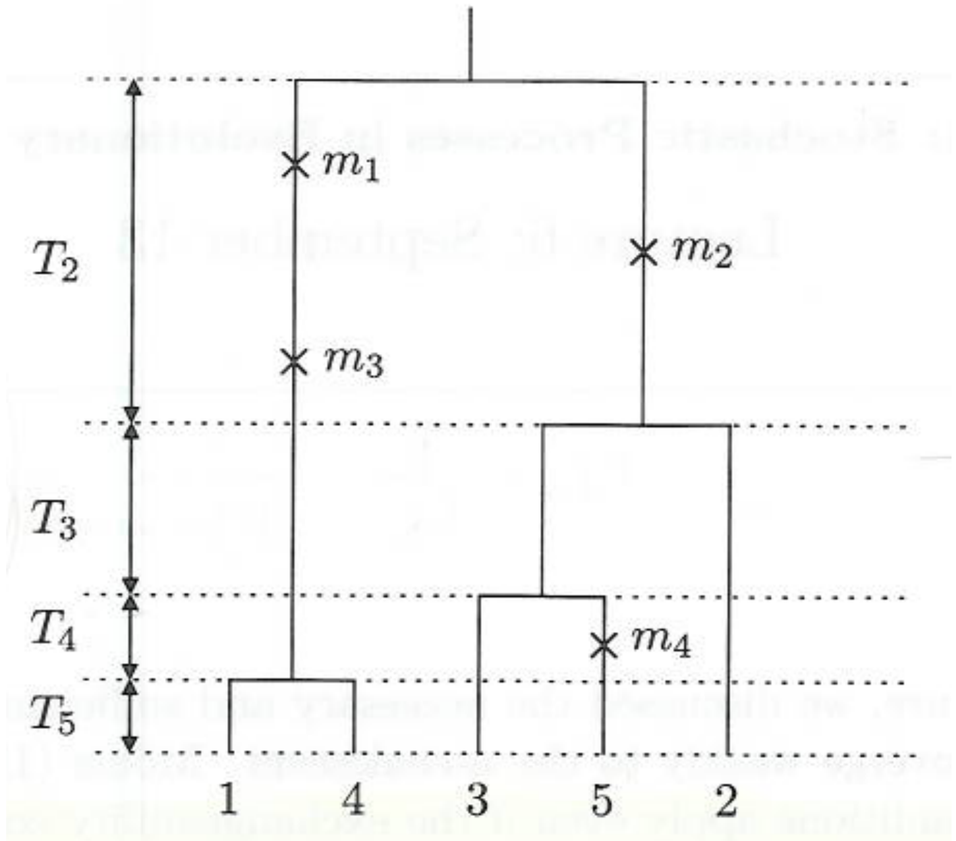


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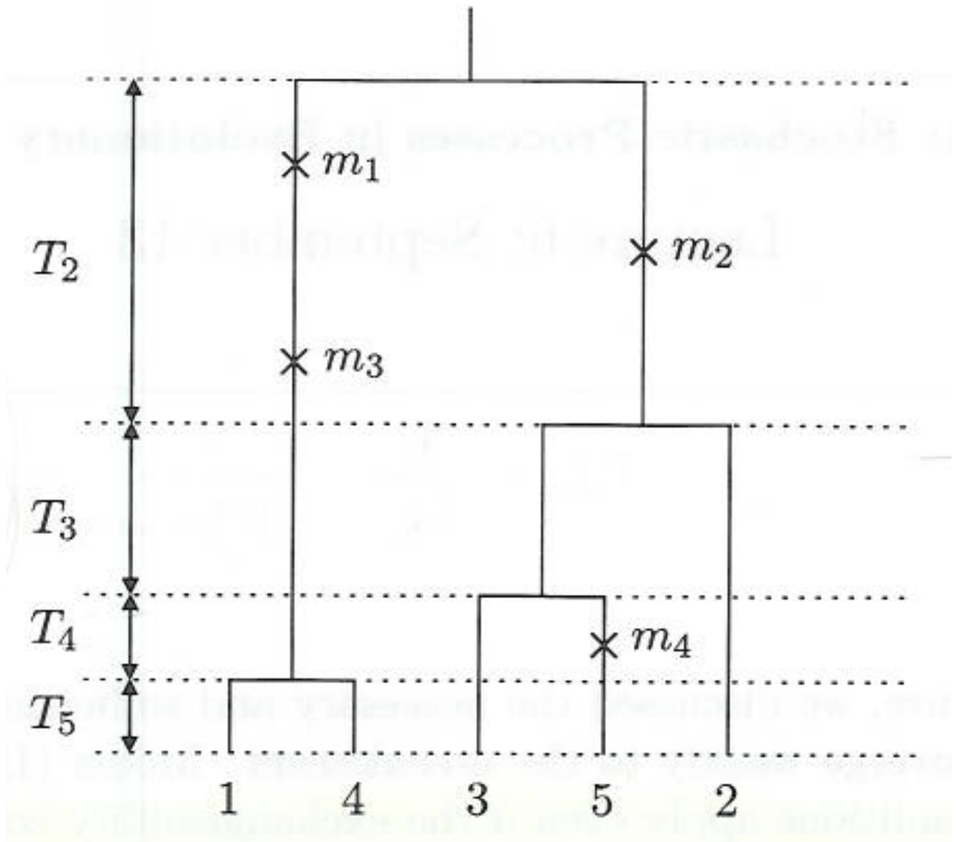


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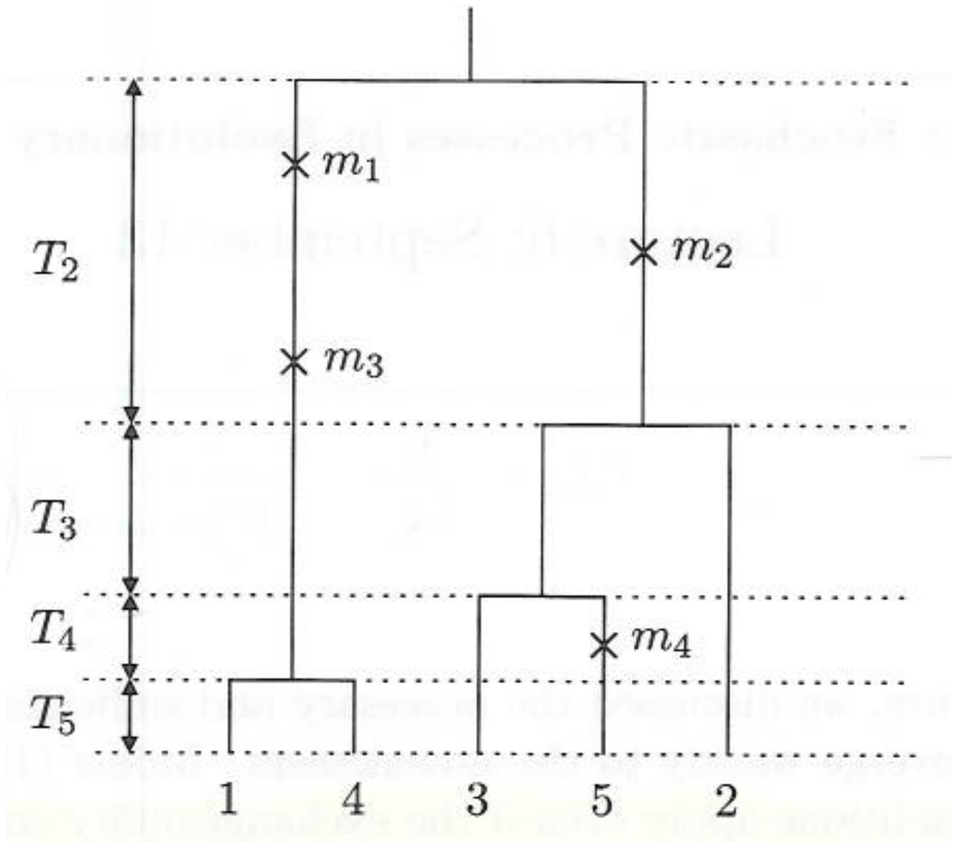


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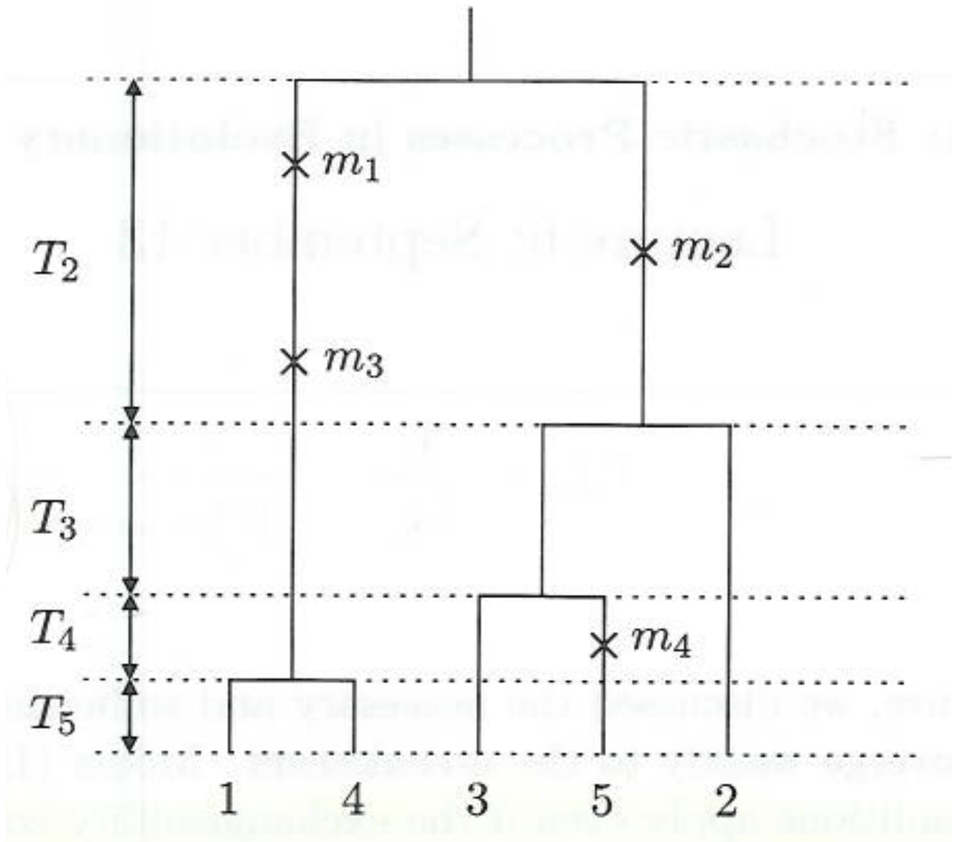
- One statistic that is informative of θ is the **number of segregating sites in a sample**

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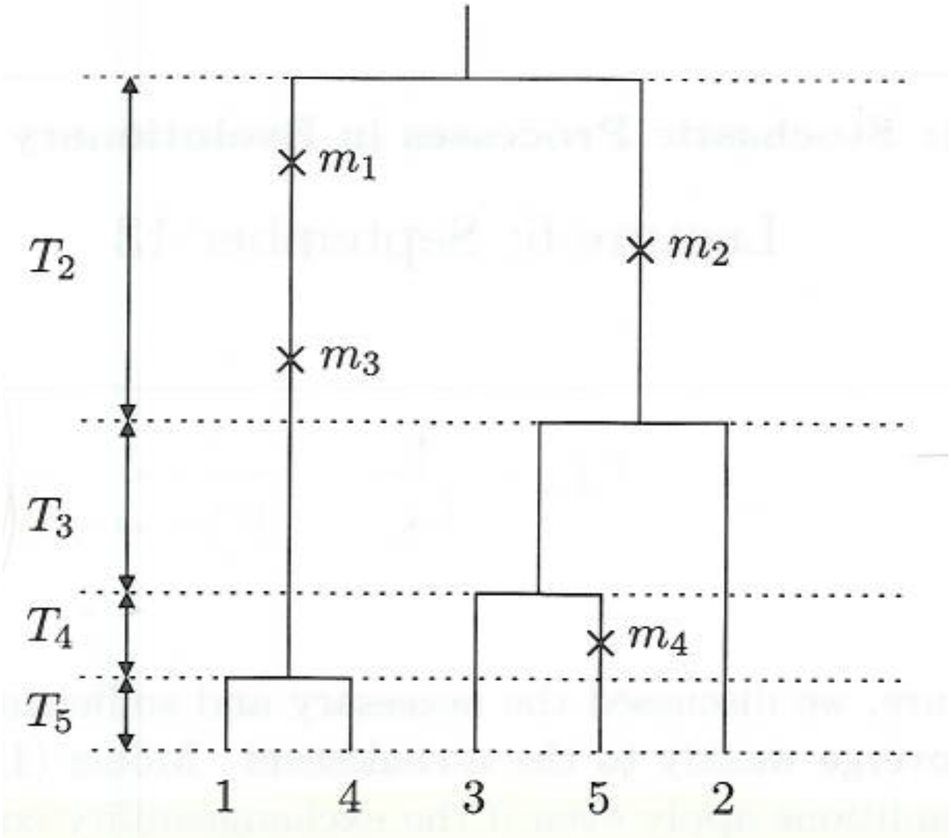


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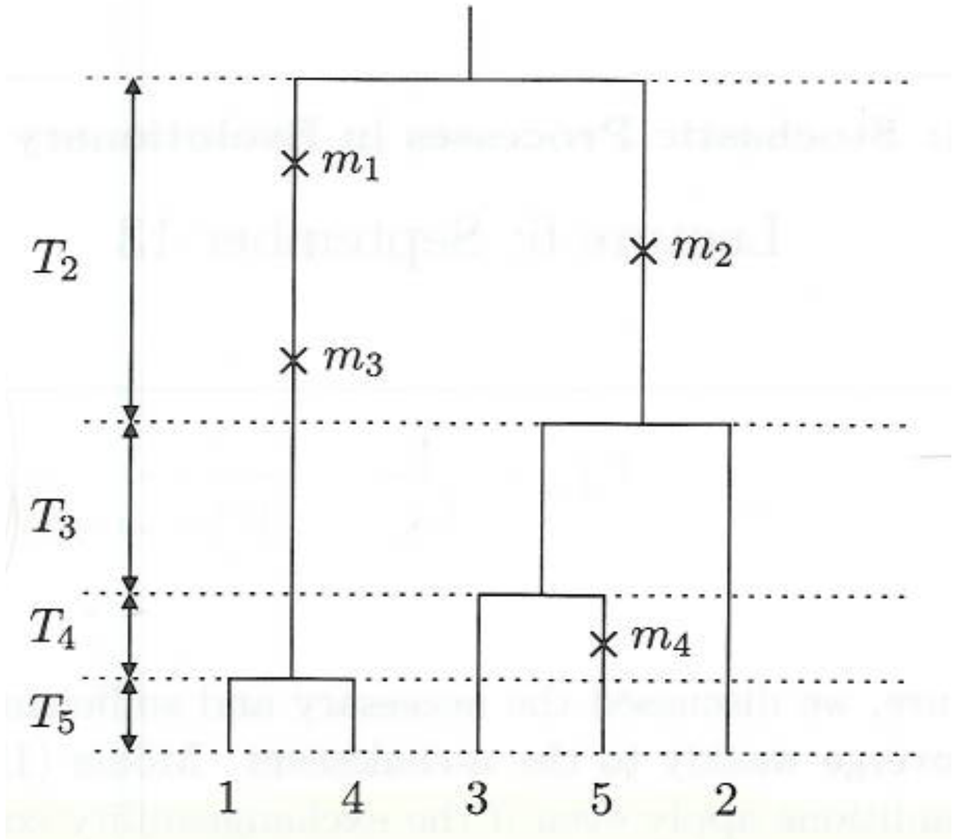
# Relating expectations about trees to data

- Let S = number of segregating sites at a locus

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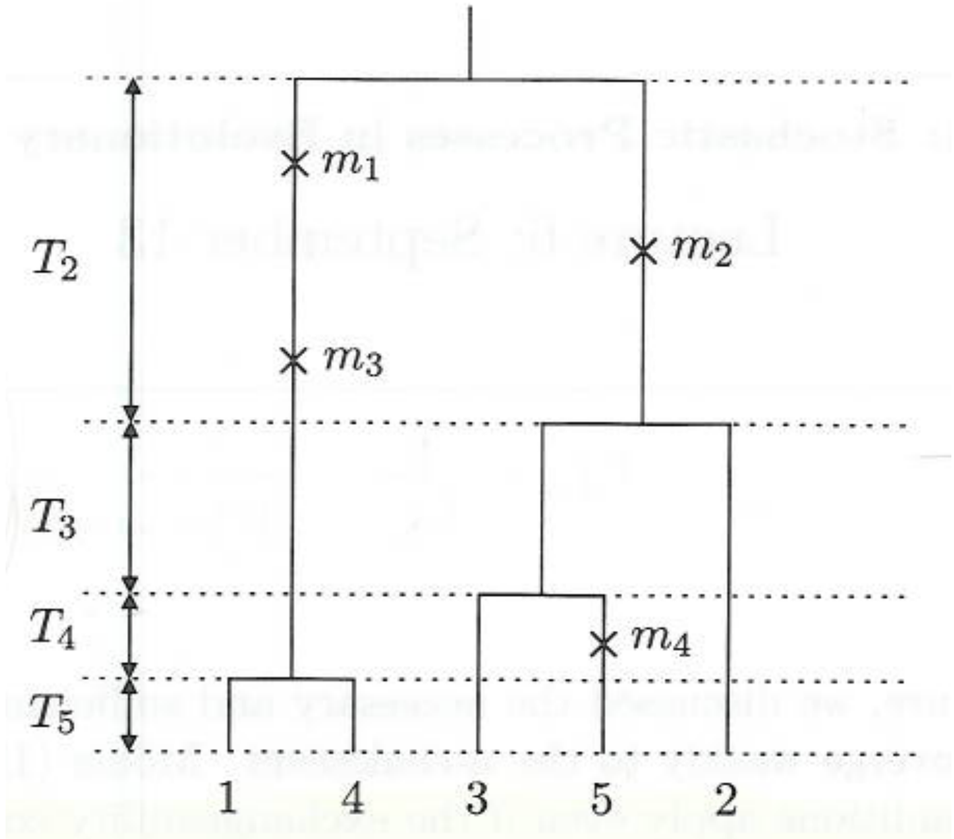


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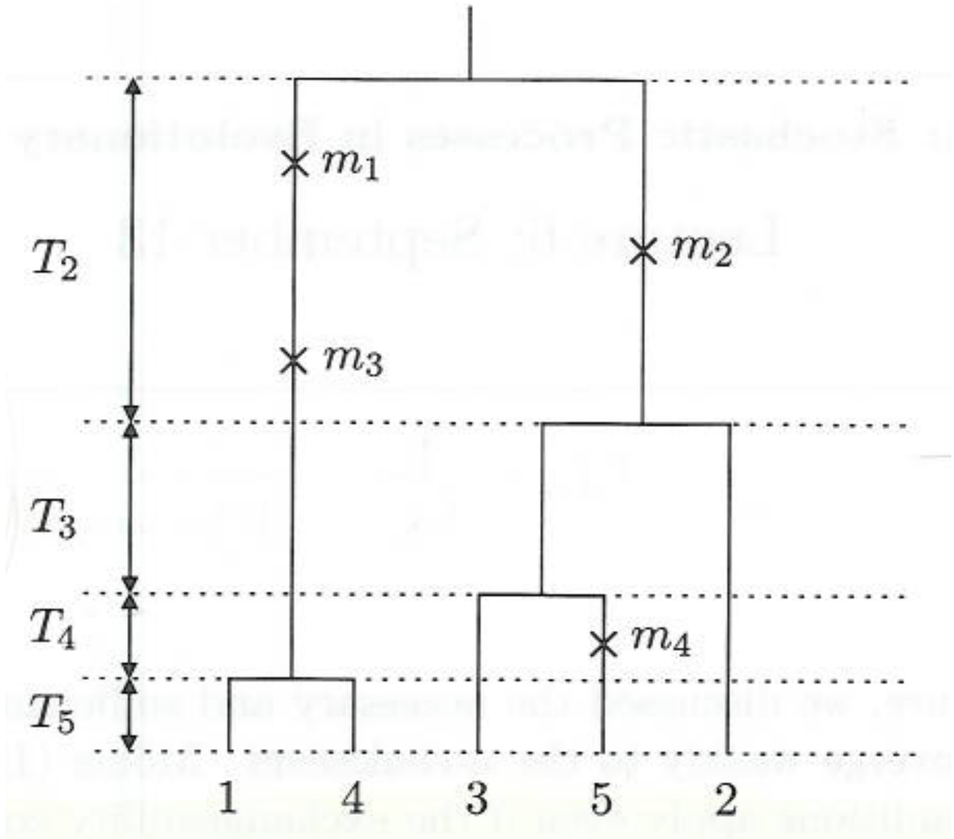
- Let S = number of segregating sites at a locus
- Under the infinite sites model, S = number of mutations in the tree at a locus = M

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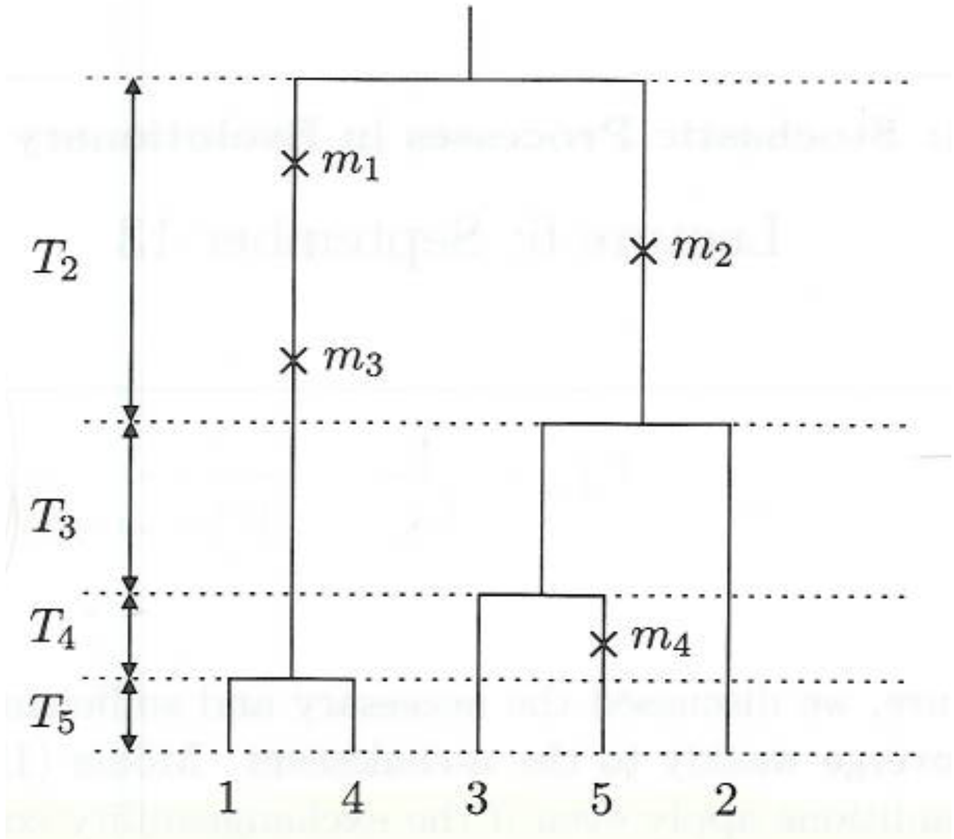


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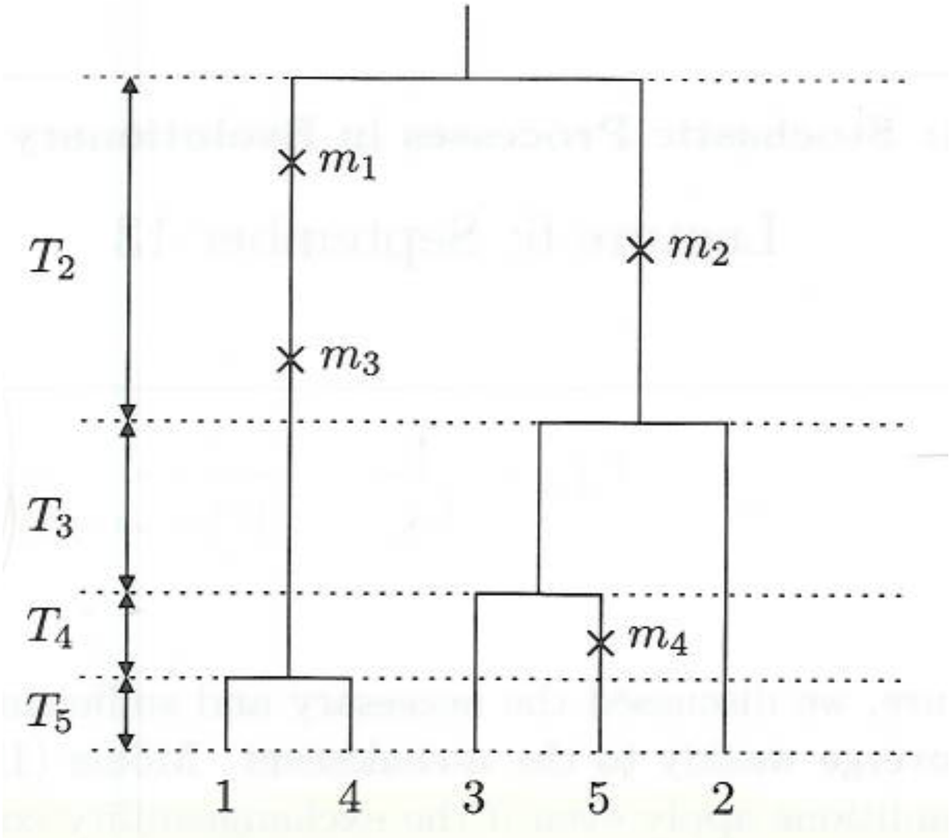


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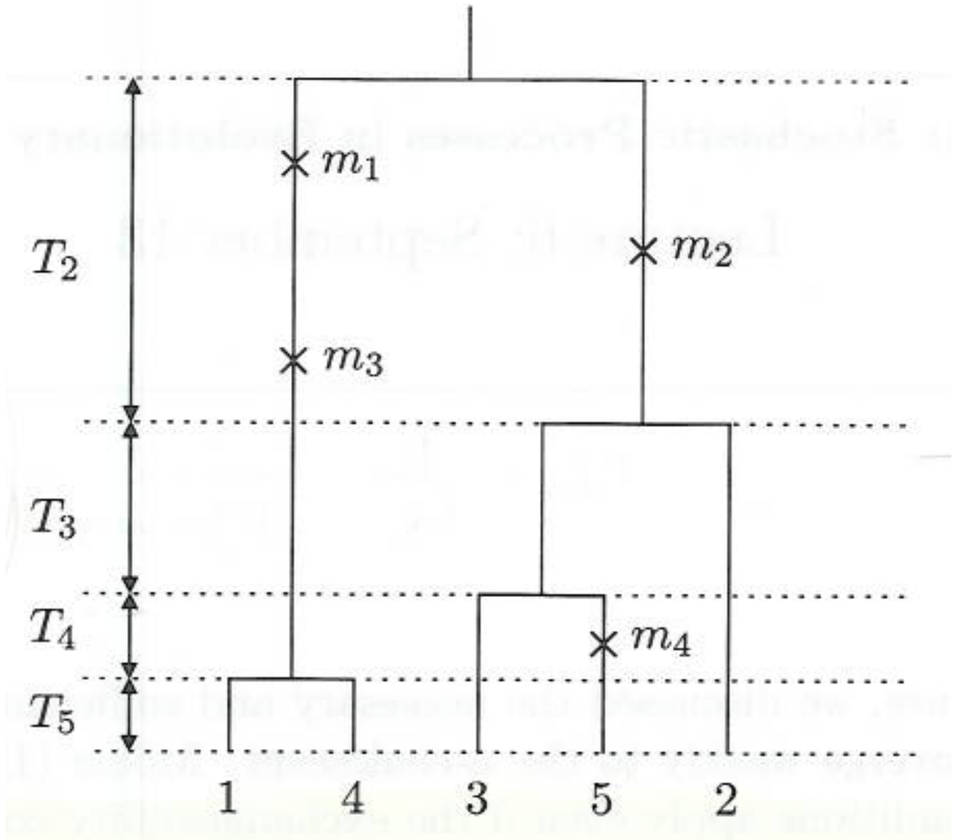
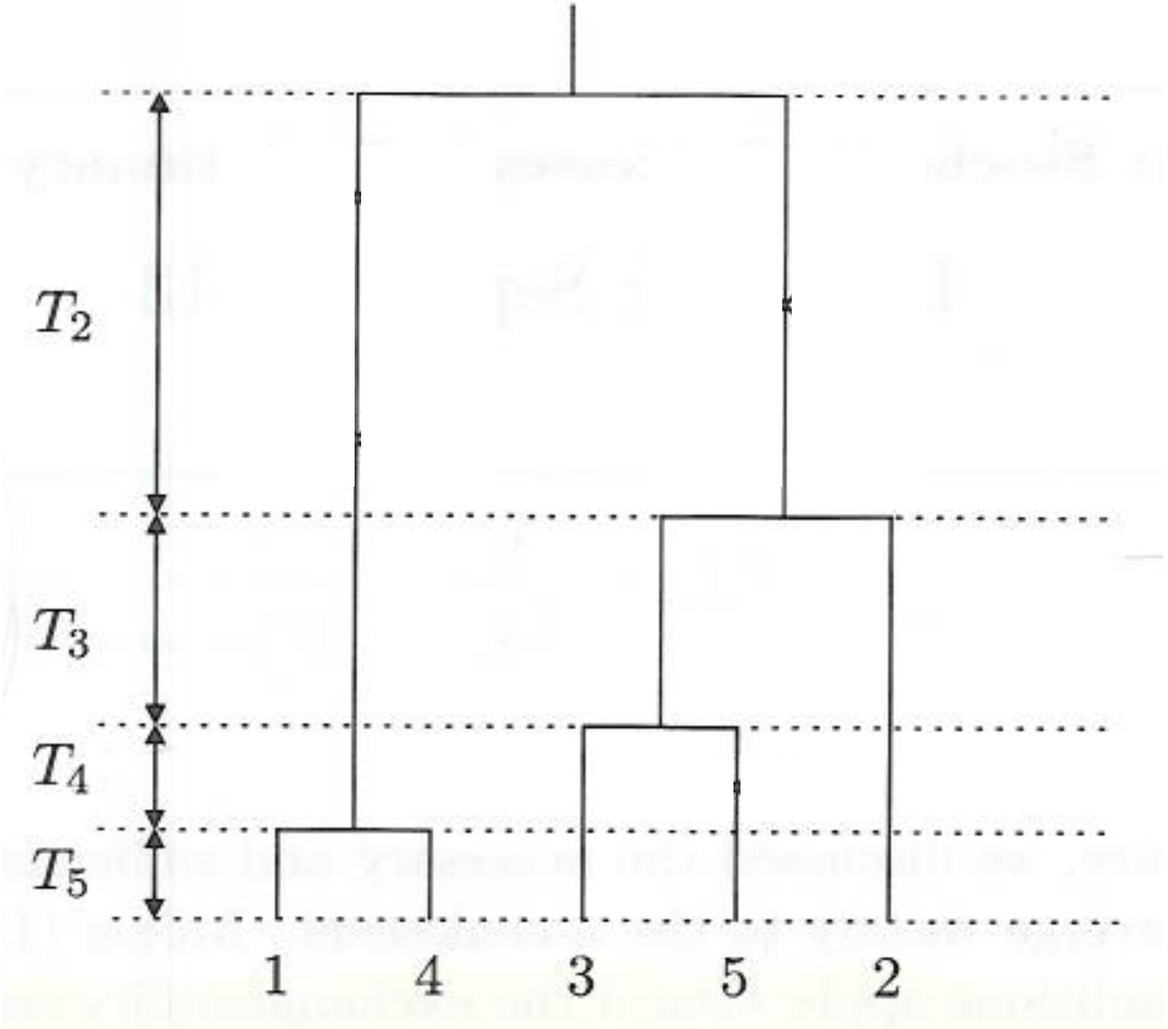
Rate at which mutations happen




Song, Y. 2021

# Total length of tree




Song, Y. 2021

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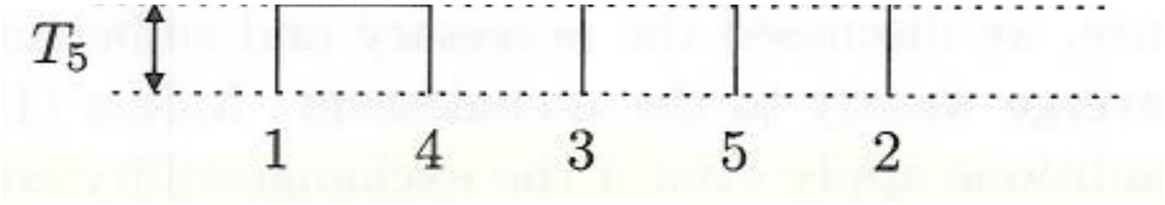
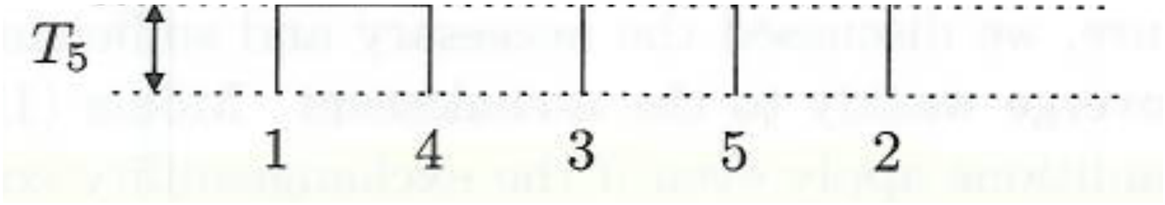



Song, Y. 2021

# Total length of tree

5 lineages

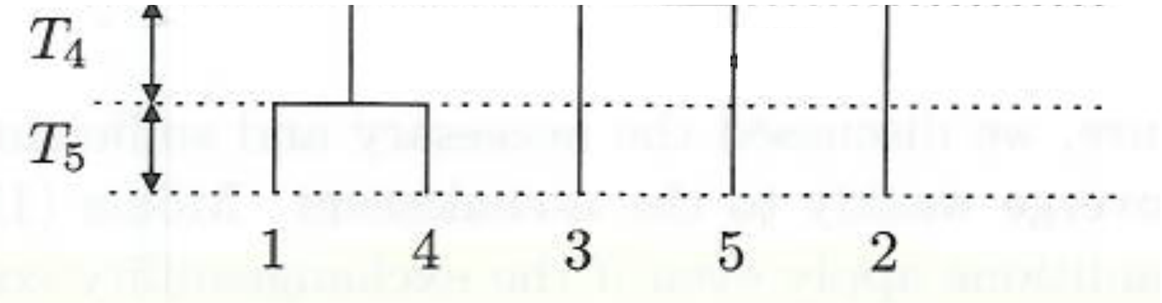



Song, Y. 2021

# Total length of tree

4 lineages

5 lineages



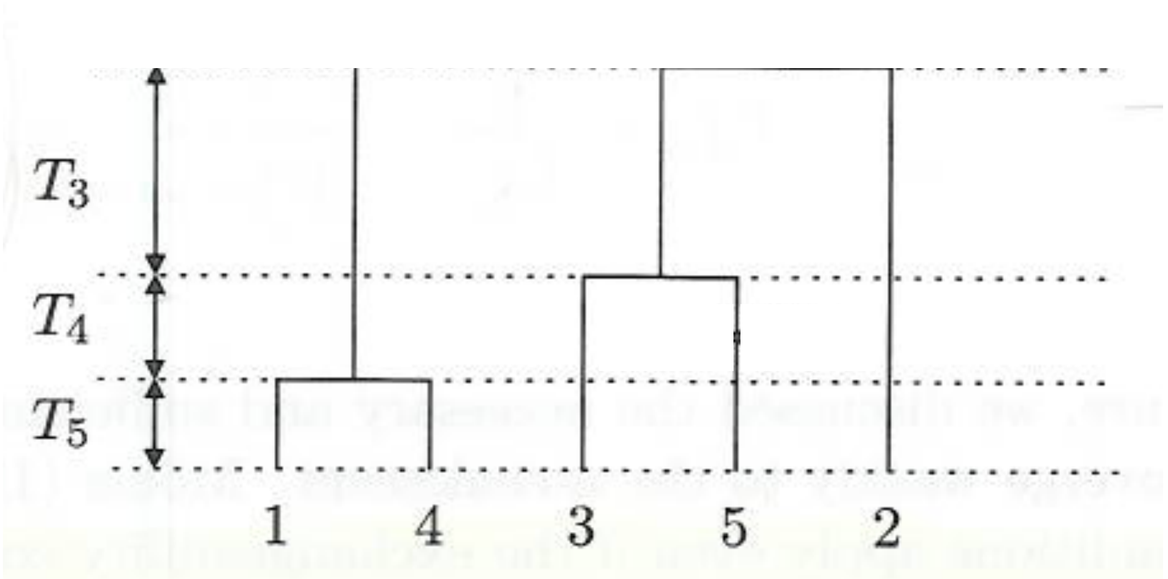

Song, Y. 2021

# Total length of tree

3 lineages

4 lineages

5 lineages




Song, Y. 2021

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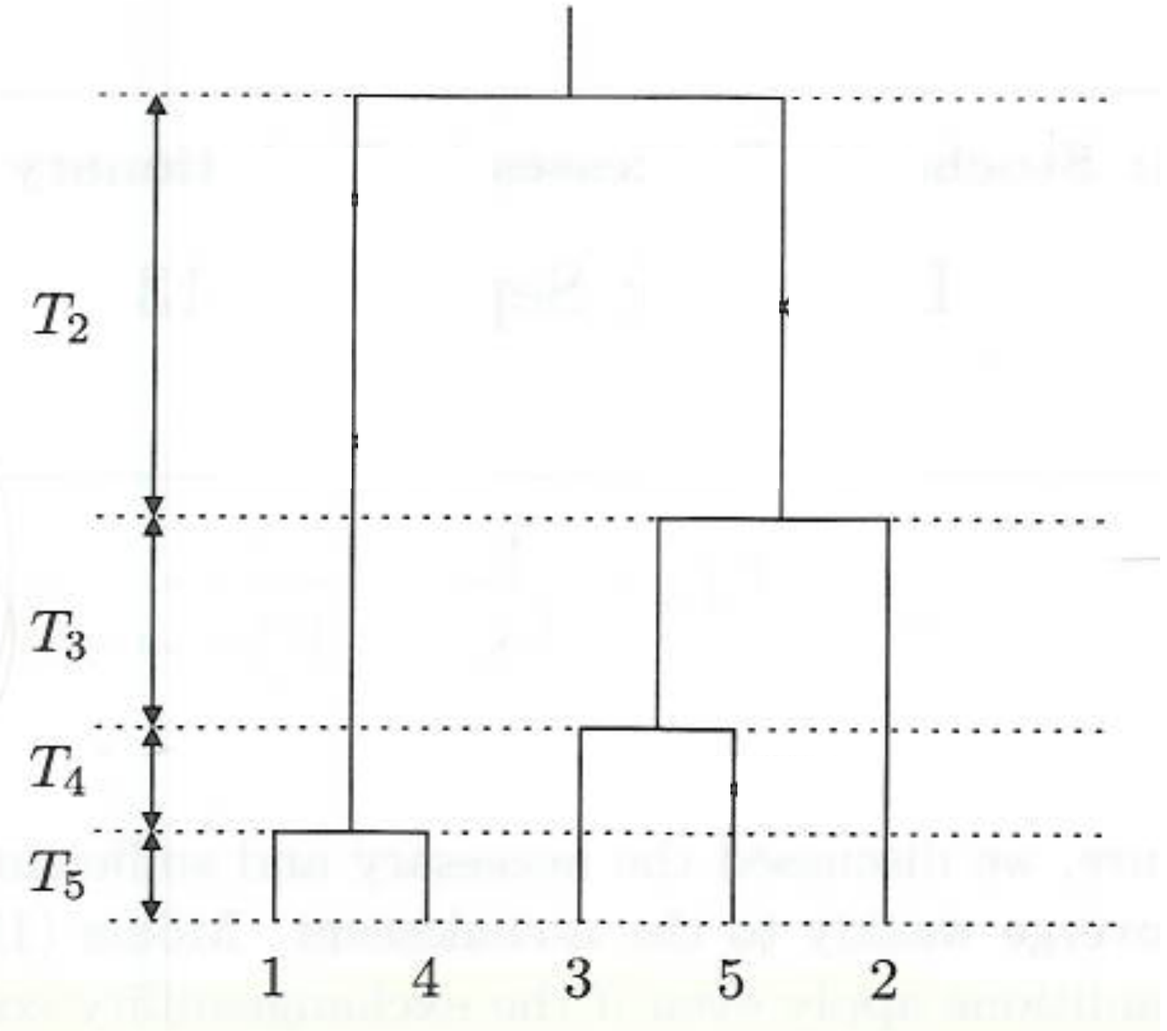


Song, Y. 2021

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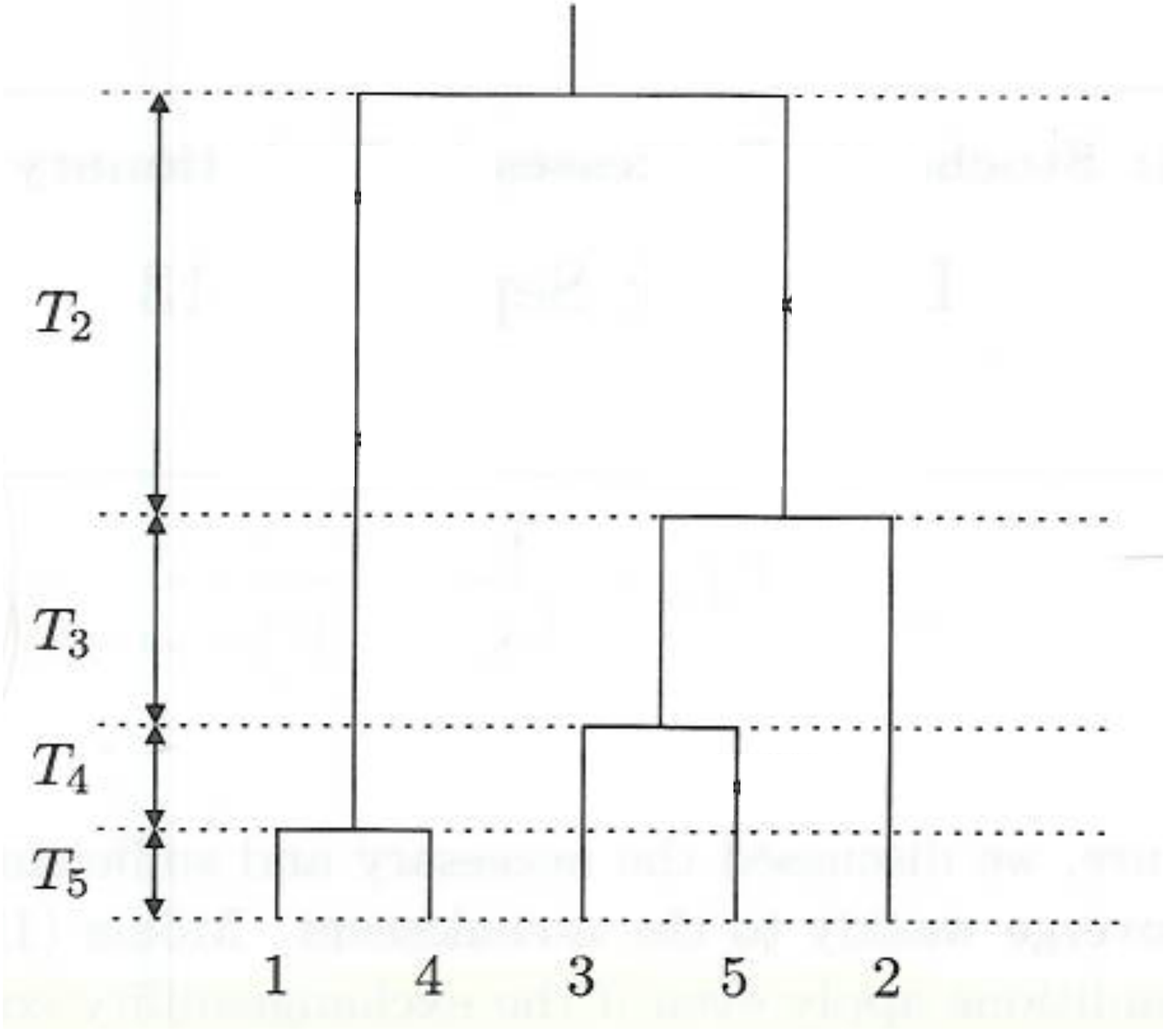


Song, Y. 2021

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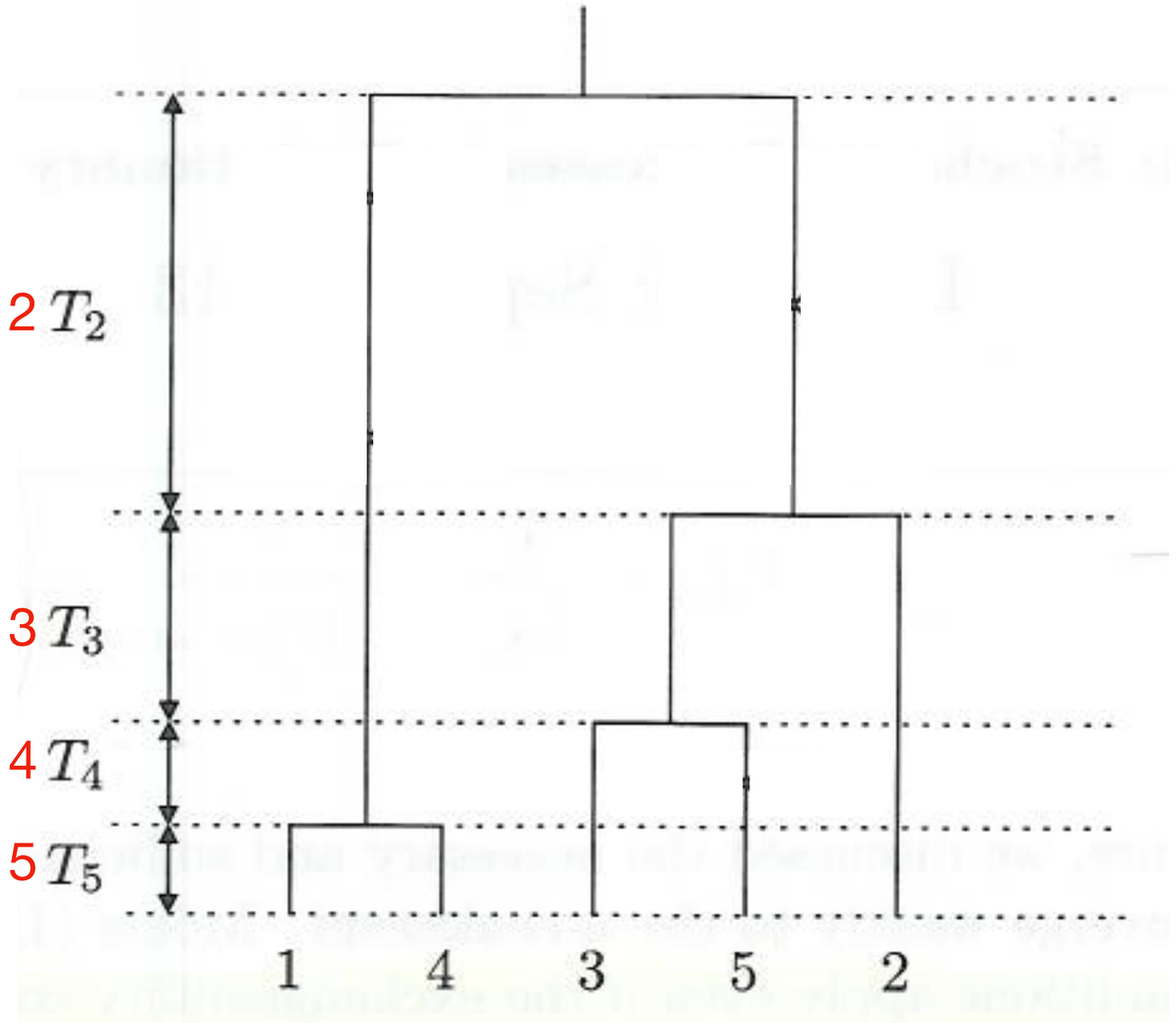
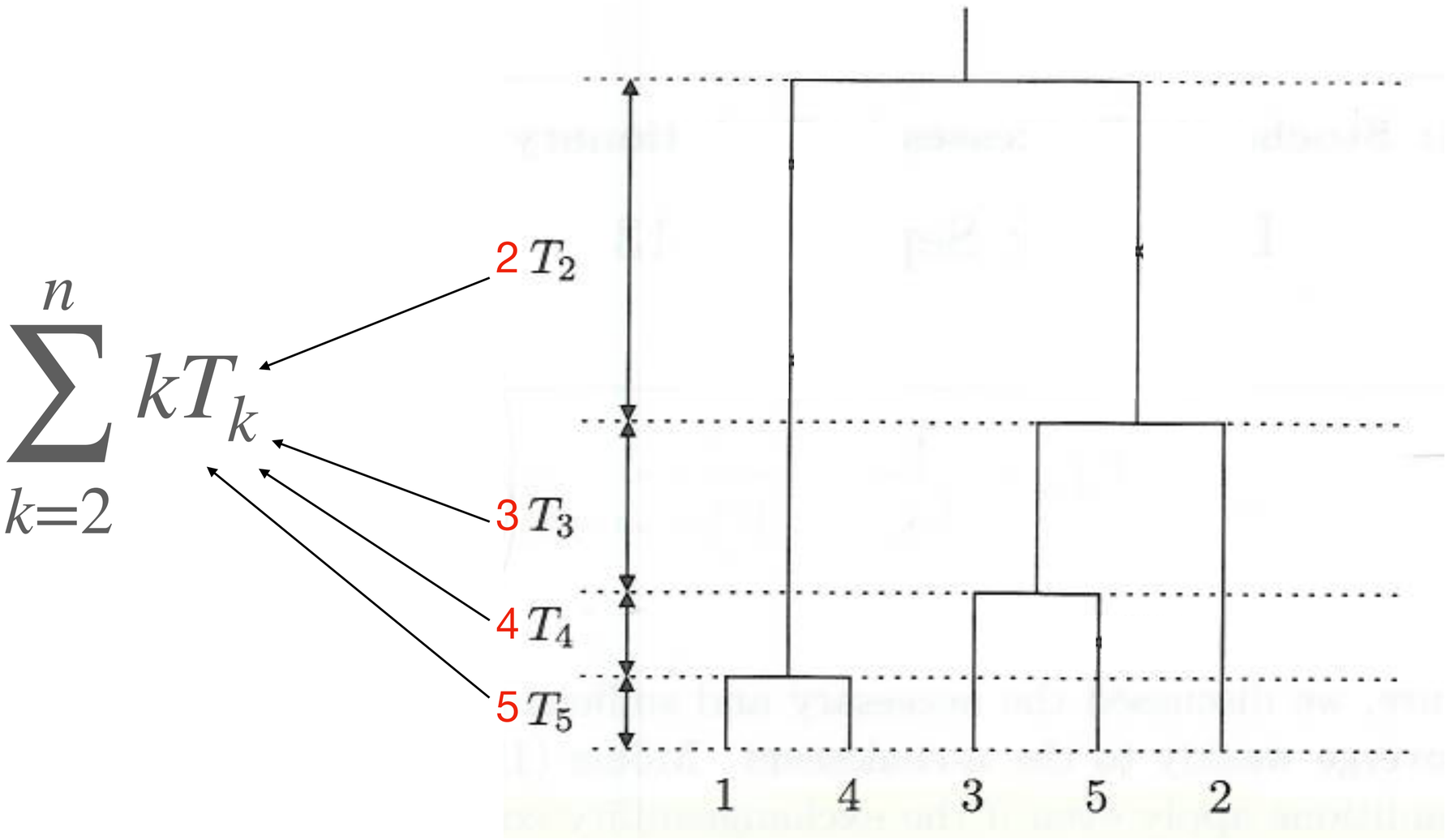



Song, Y. 2021

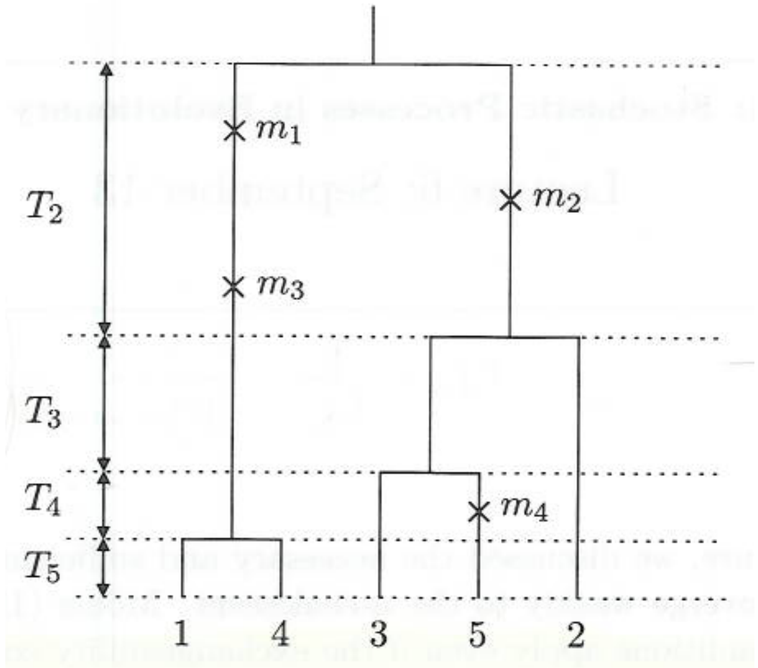
# Total length of tree

$$\sum_{k=2}^{n} kT_k$$




Song, Y. 2021

# Relating expectations about trees to data




Song, Y. 2021

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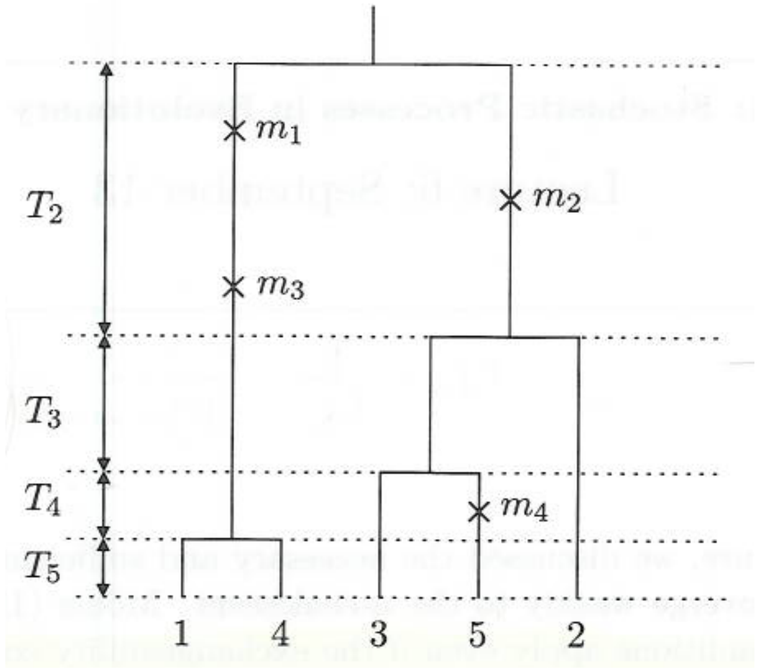
- $E[S] = E[M] = \frac{\theta}{2} E[Total\ length\ of\ tree]$

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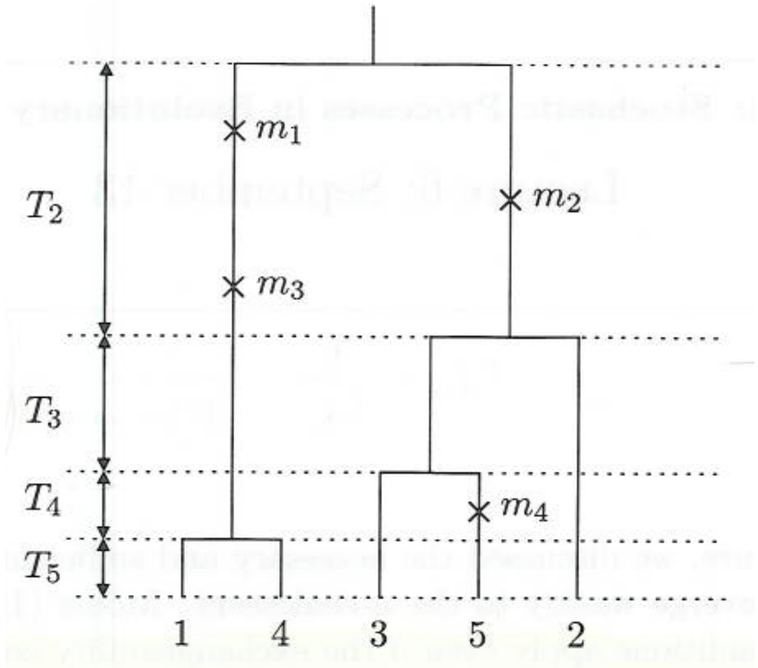


Song, Y. 2021

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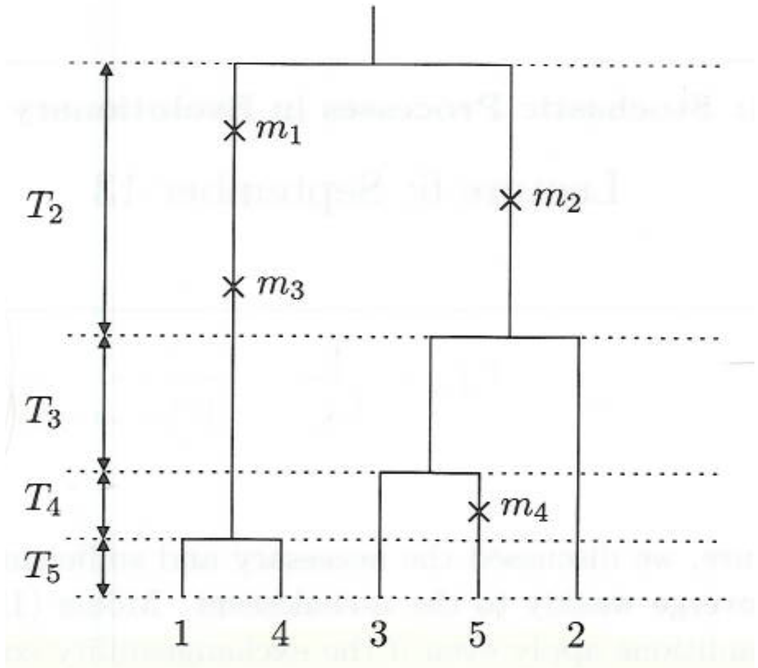


Song, Y. 2021

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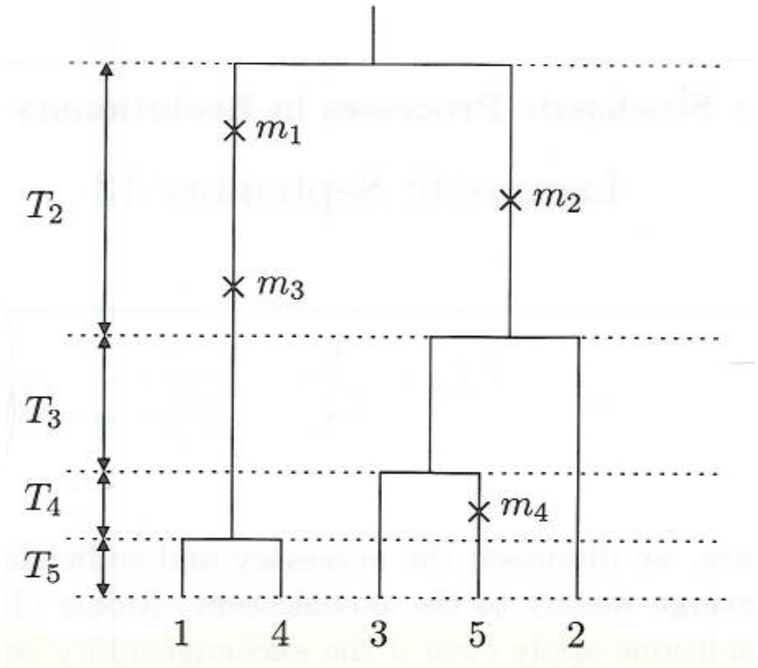


Song, Y. 2021

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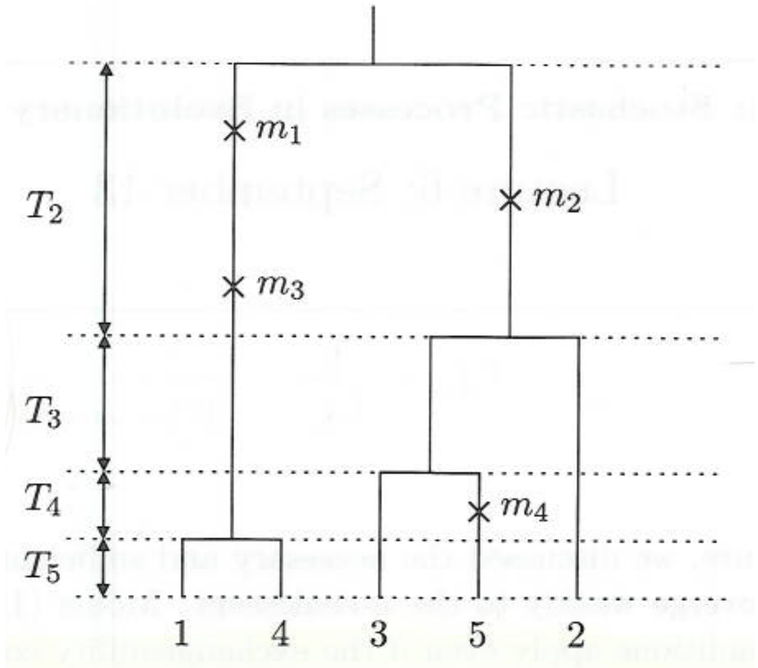


Song, Y. 2021

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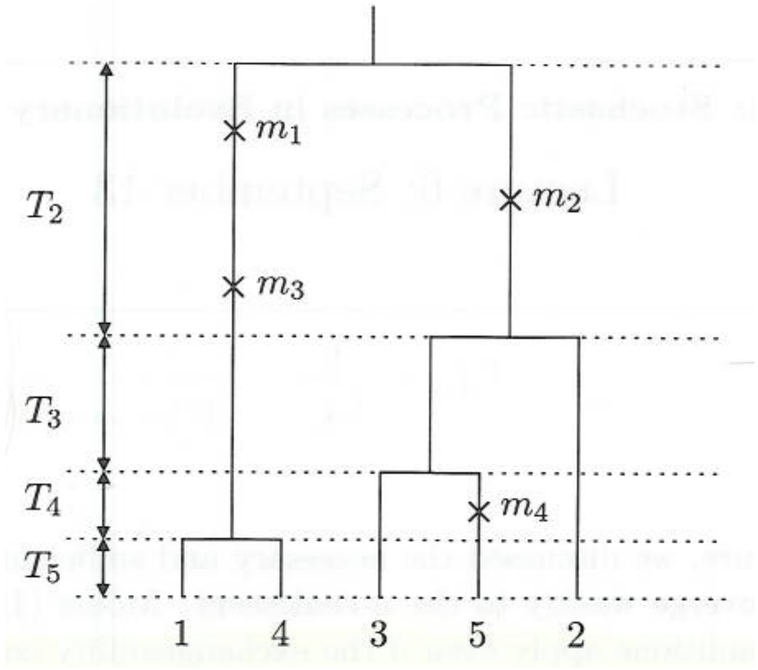


Song, Y. 2021

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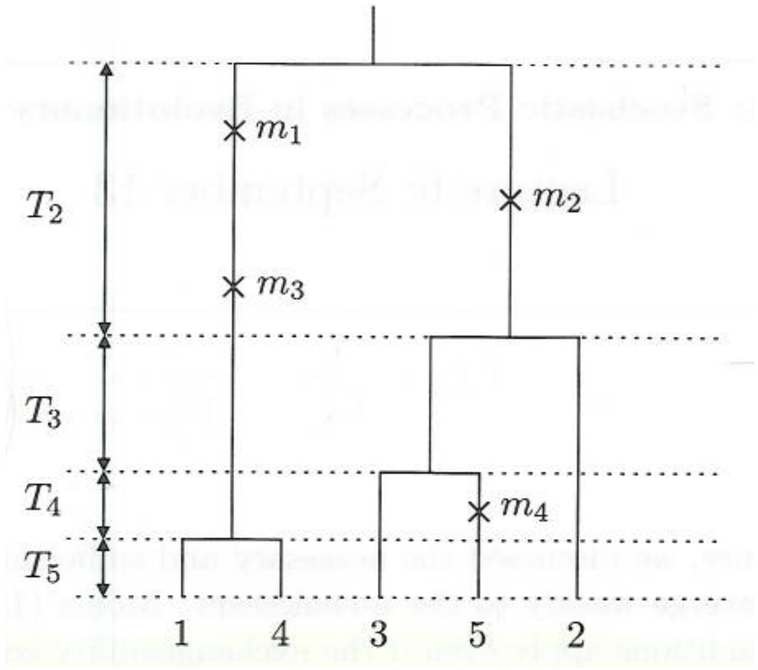
- $E\left[\sum_{k=2}^{n} kT_k\right] = \sum_{k=2}^{n} kE[T_k] = \sum_{k=2}^{n} k\frac{1}{\binom{k}{2}} = \sum_{k=2}^{n} \frac{2}{k-1}$




Song, Y. 2021

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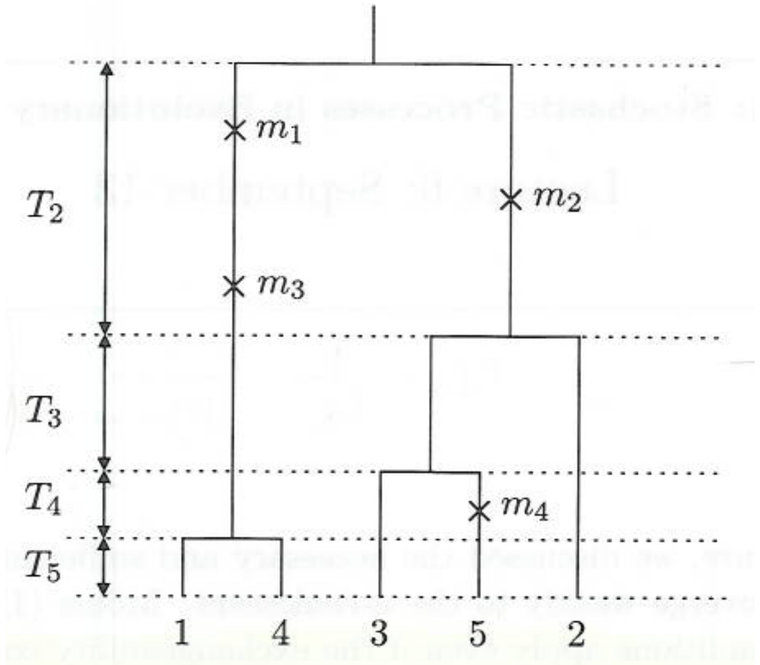
$$E[S] = \frac{\theta}{2} \sum_{k=2}^{n} \frac{2}{k-1} = \theta \sum_{k=2}^{n} \frac{1}{k-1}$$




Song, Y. 2021

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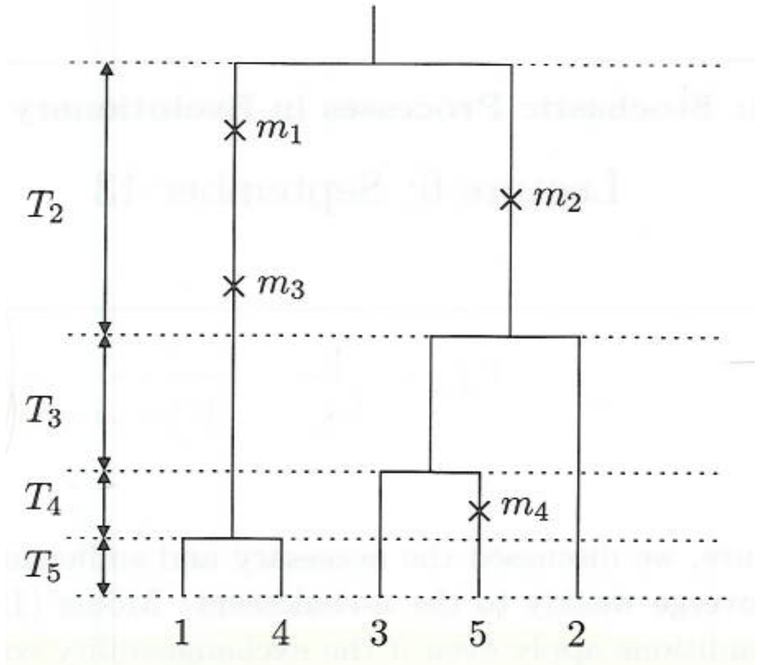


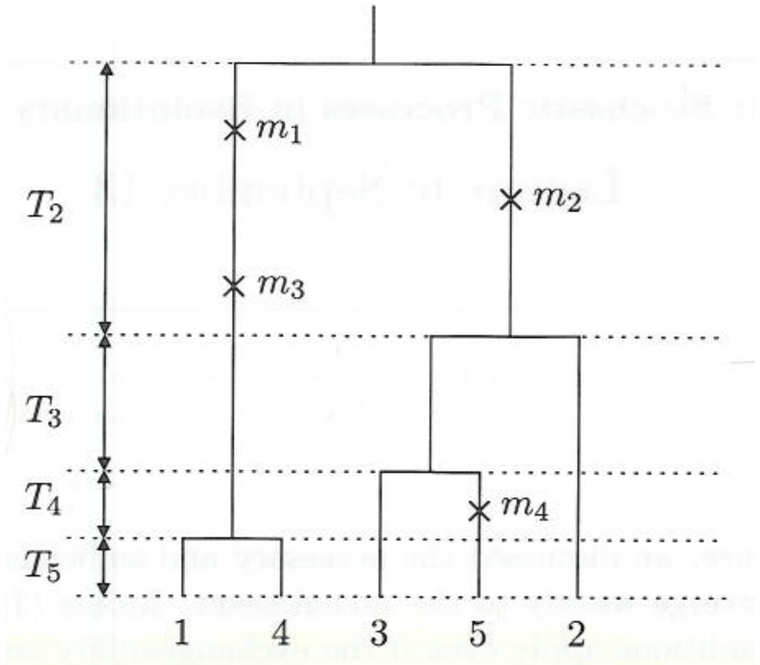

Song, Y. 2021

# Relating expectations about trees to data

$$E[S] = \frac{\theta}{2}\sum_{k=2}^{n}\frac{2}{k-1} = \theta\sum_{k=2}^{n}\frac{1}{k-1}$$

Observed

Unknown




Song, Y. 2021

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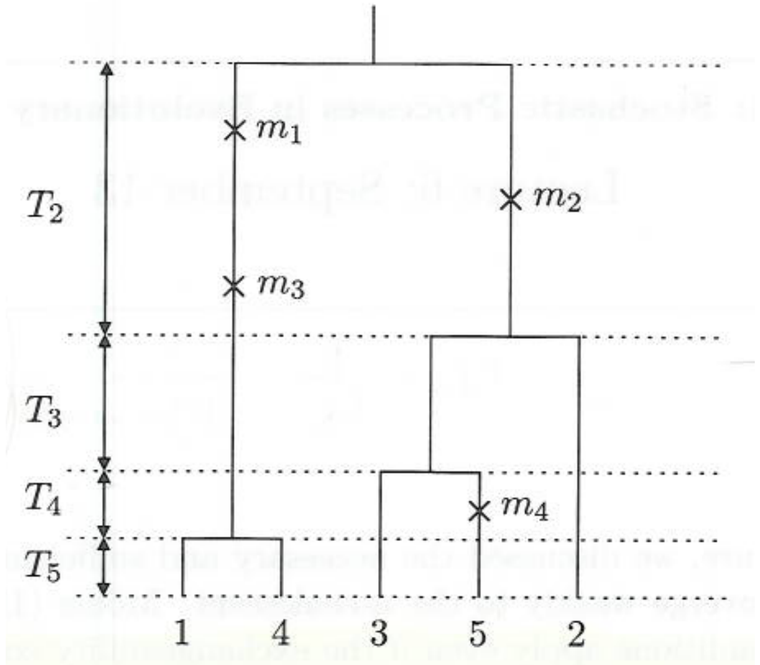



$$\hat{\theta} = \frac{S}{\sum_{k=2}^{n}\frac{1}{k-1}}$$

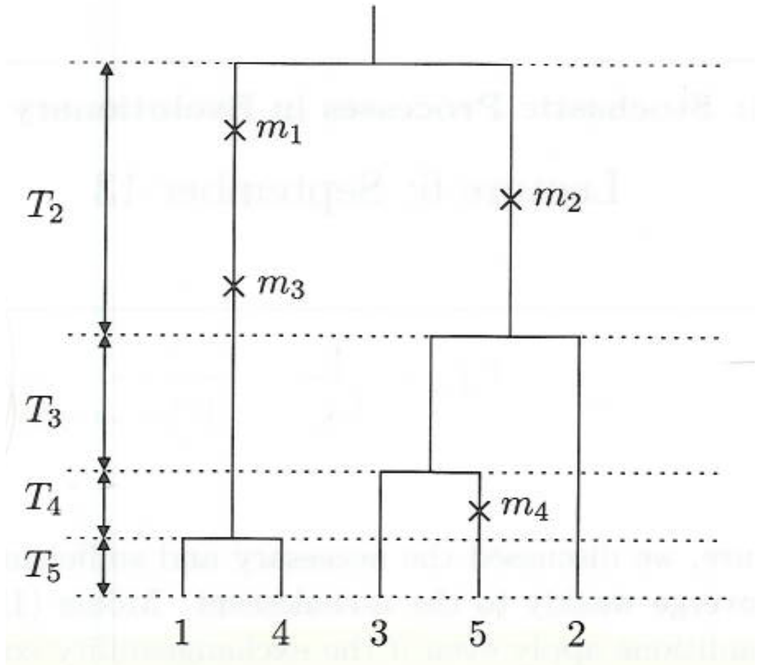
Song, Y. 2021

# Relating expectations about trees to data

$$E[S] = \frac{\theta}{2}\sum_{k=2}^{n}\frac{2}{k-1} = \theta\sum_{k=2}^{n}\frac{1}{k-1}$$

Observed

Unknown




Observed

$$\hat{\theta} = \frac{S}{\sum_{k=2}^{n}\frac{1}{k-1}}$$

"Watterson's estimate" for θ

Song, Y. 2021

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Observed

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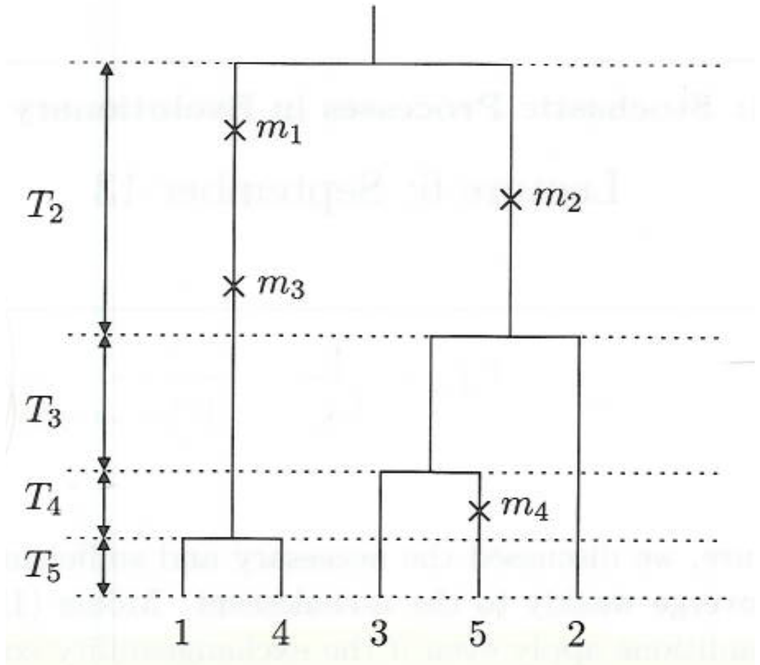



$$\hat{\theta} = \frac{S}{\sum_{k=2}^{n}\frac{1}{k-1}}$$

Observed

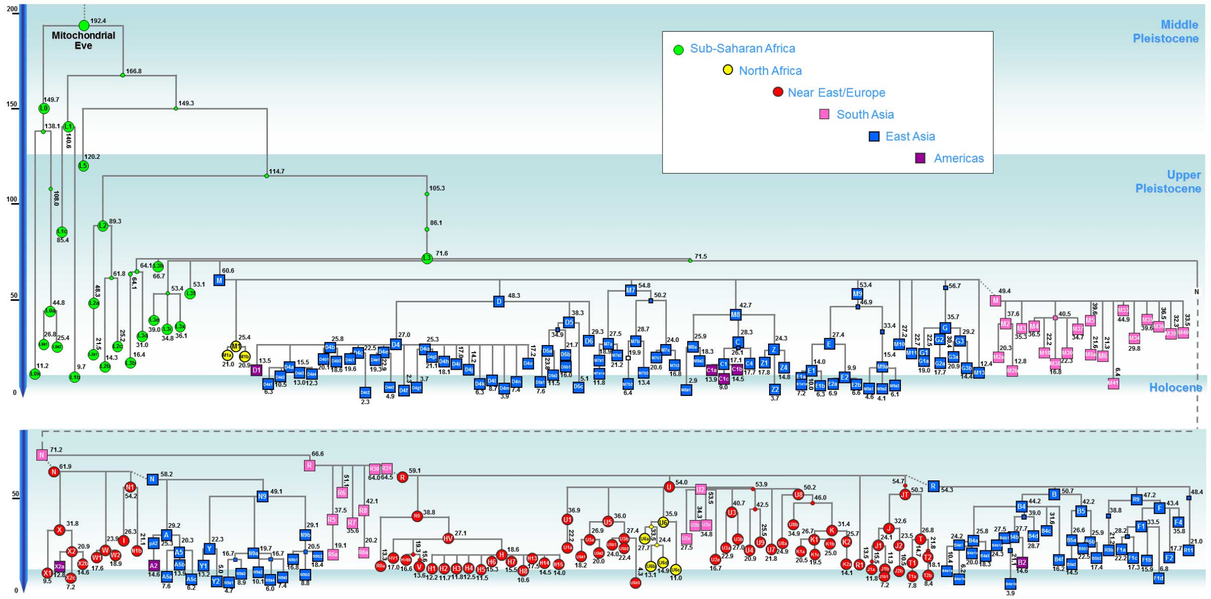
"Watterson's estimate" for θ

If we know u a priori, we can solve for N, and get an estimate of the population size:

$$2\hat{N} = \frac{\hat{\theta}}{2u}$$

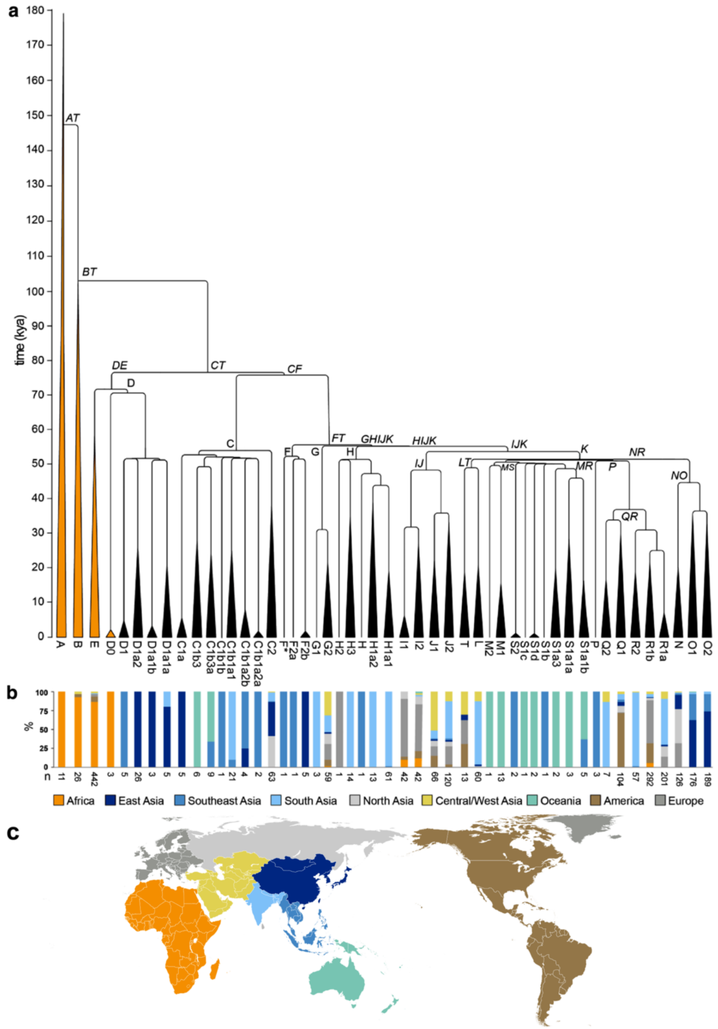
Song, Y. 2021

# Trees in non-recombining loci




mtDNA

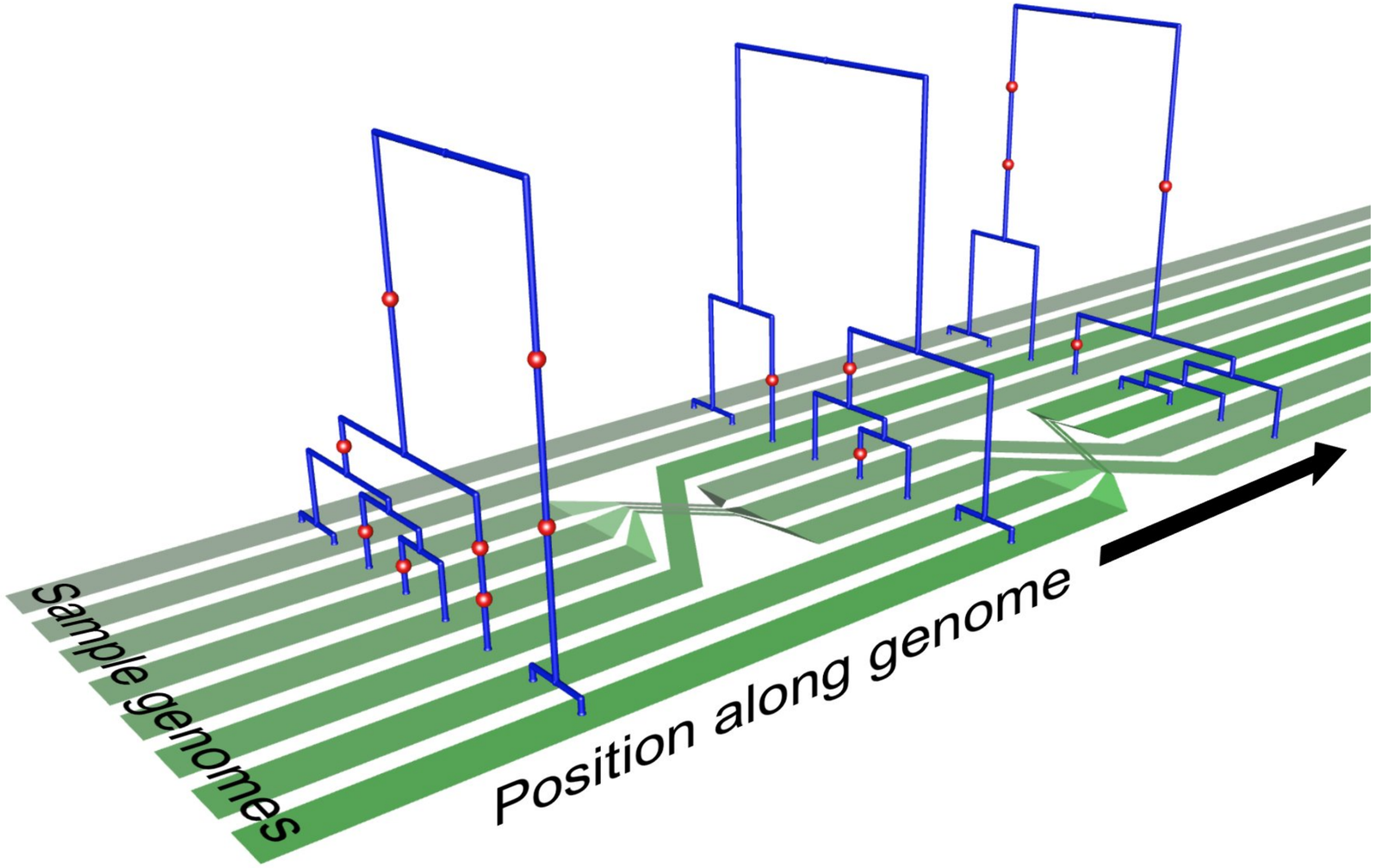
Soares et al. 2009




chrY

Agdzhoyan et al. 2020

# Trees in the rest of the genome




Yan Wong, 2020

# Trees contain information about population history

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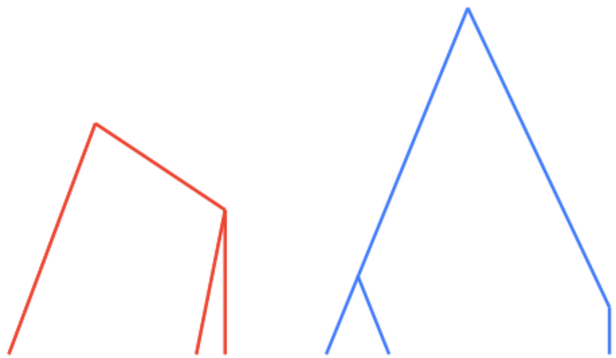
- The shape of trees is random (but follows some rules)



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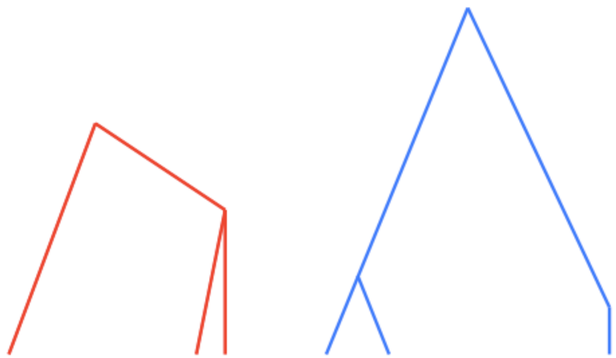

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- The shape of trees is random (but follows some rules)
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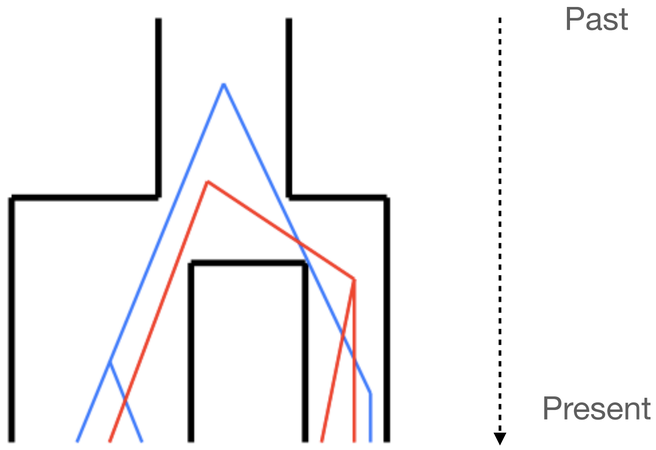

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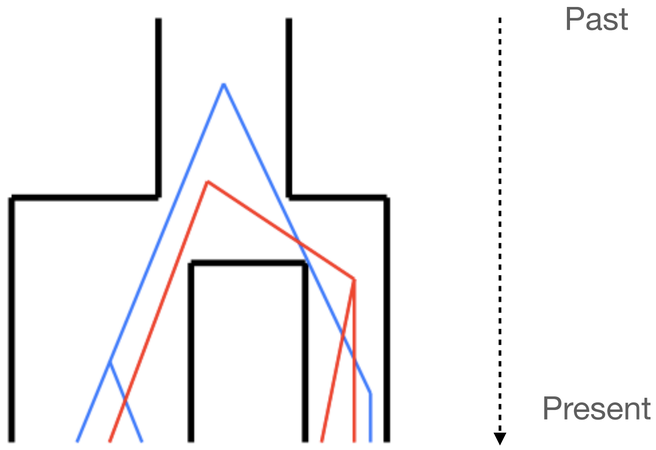
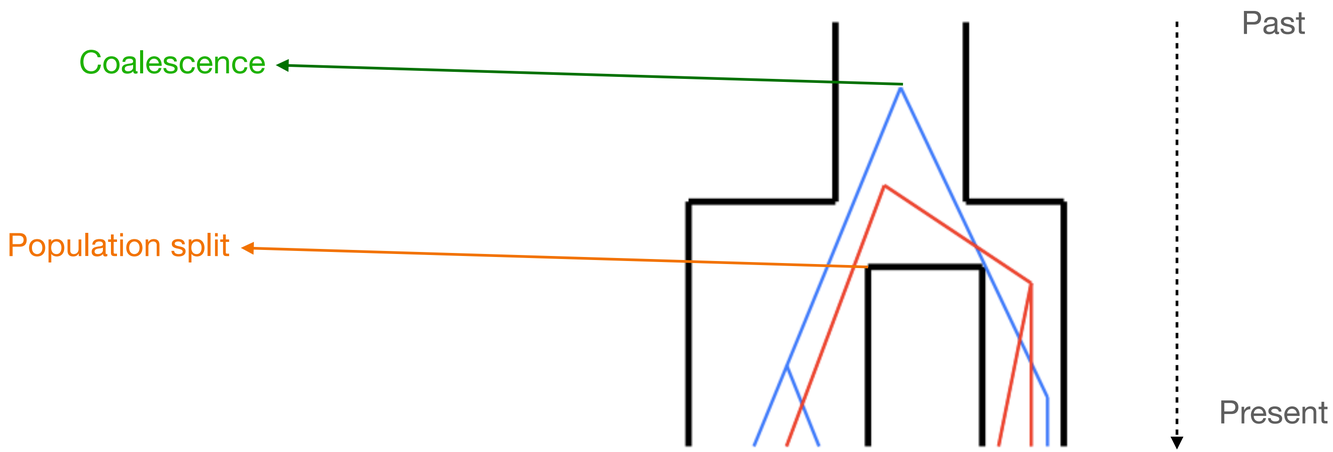


# Trees contain information about population history

- The shape of trees is random (but follows some rules)
- Two lineages can only coalesce if they exist in the same population
- Coalescent events do not represent population splits! (but they contain information about them)



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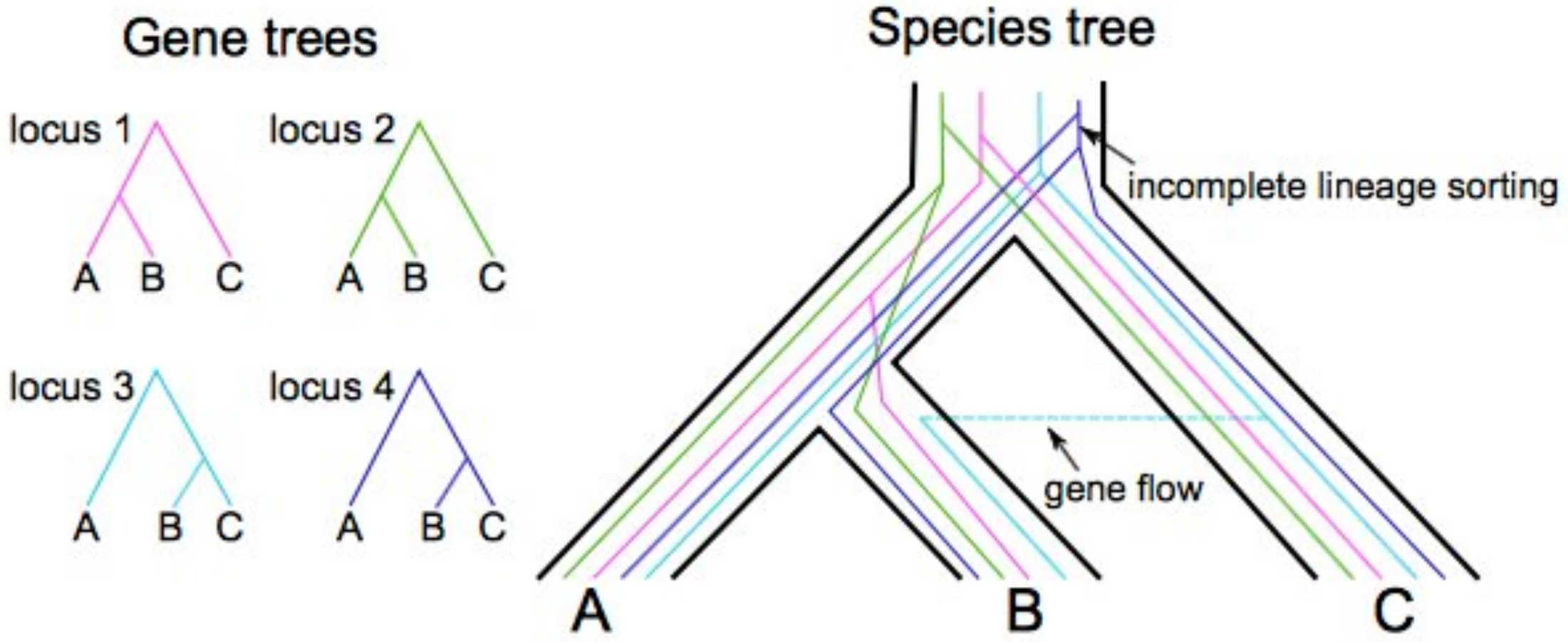

# Exercises

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- Follow the instructions in this prompt: https://github.com/FerRacimo/CopenhagenTutorial/blob/master/CoalTutorial.md