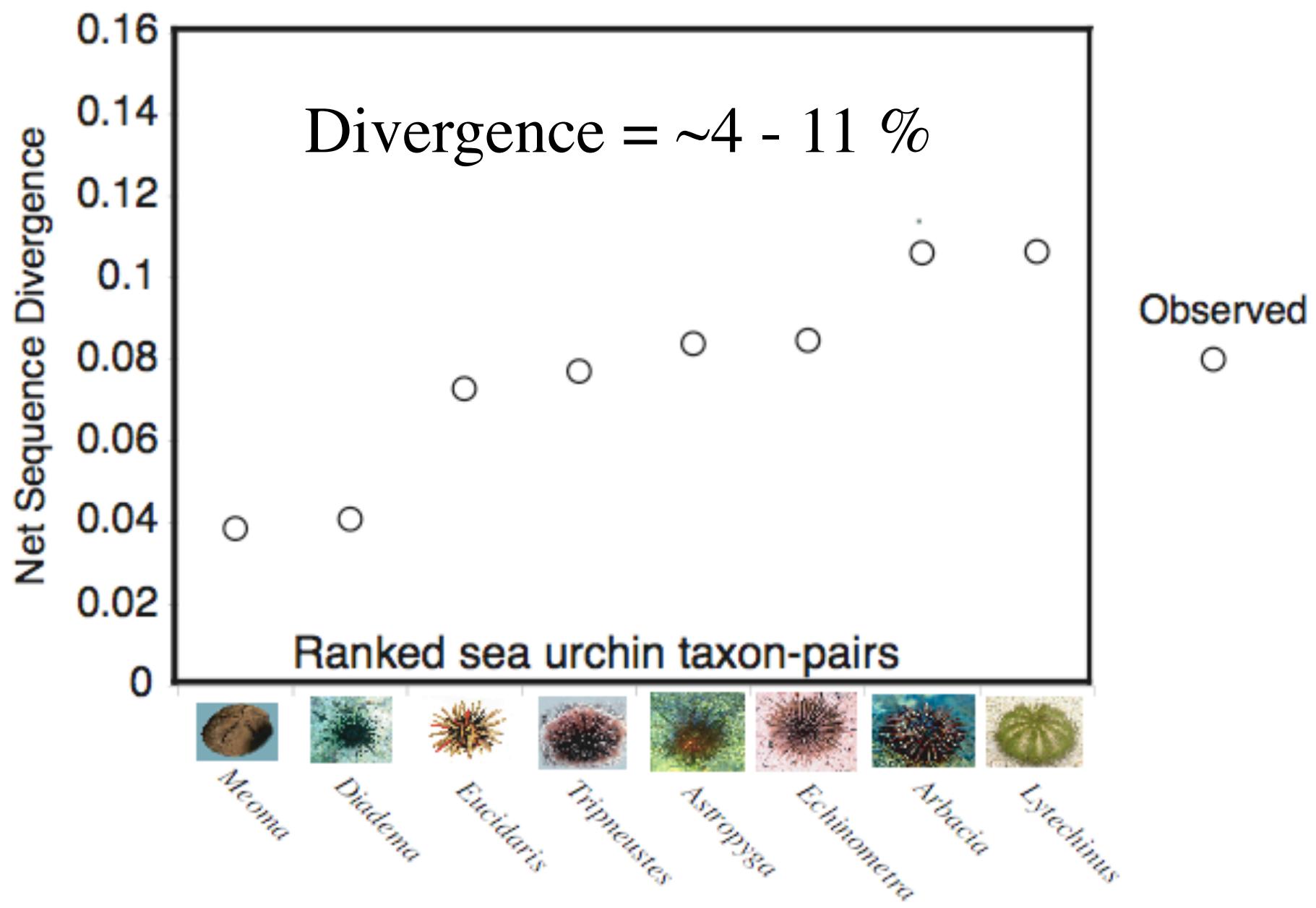
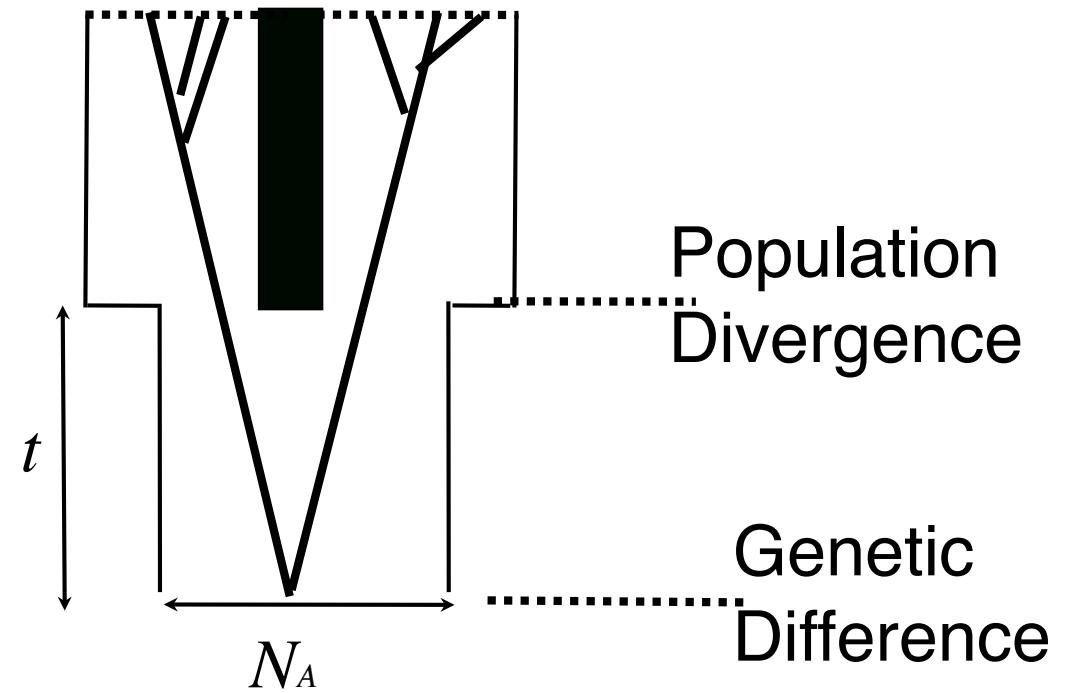
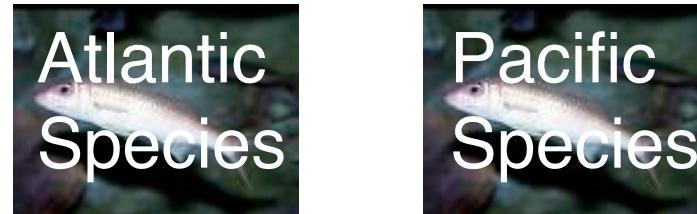
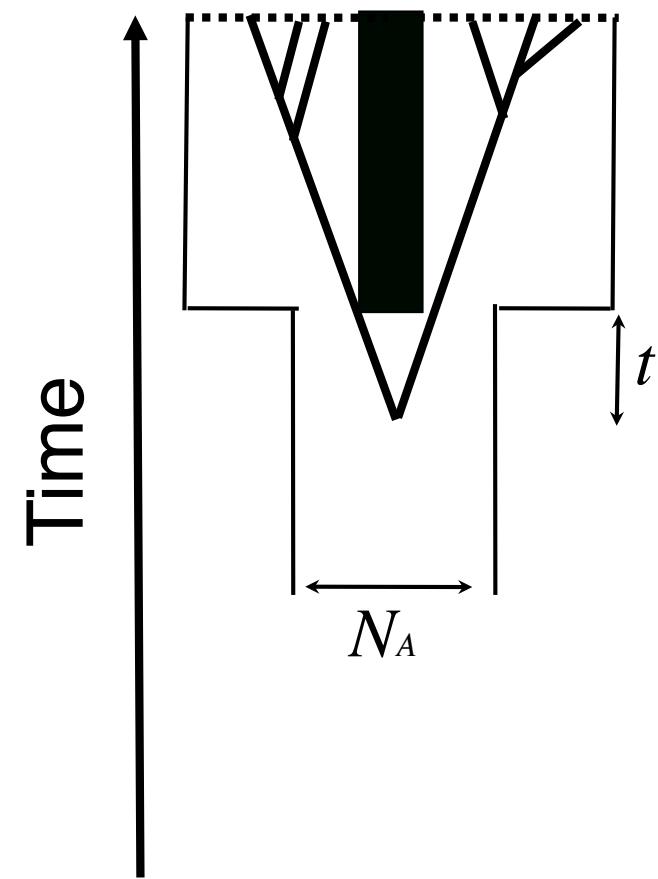


# **Population Gen Simulation and Inference**

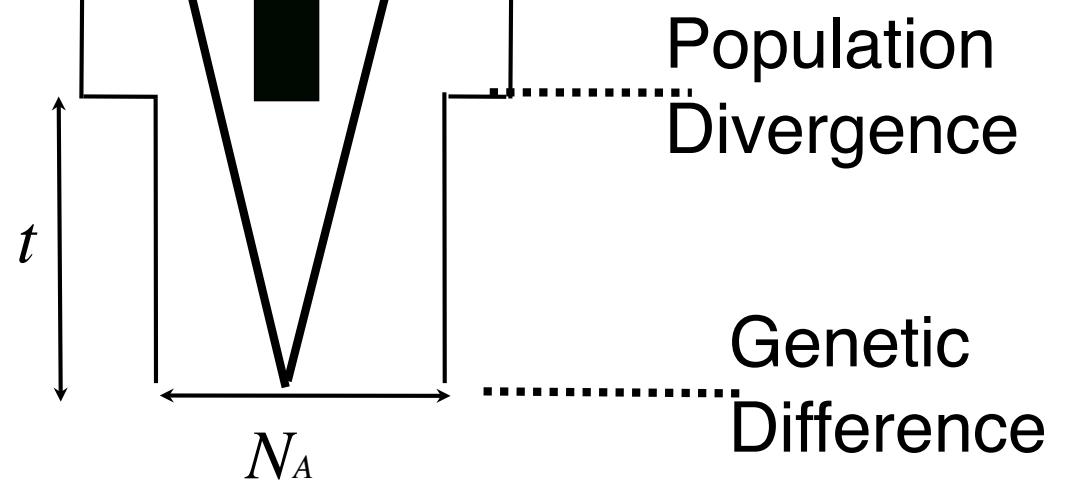
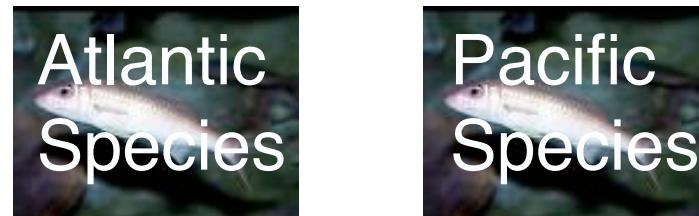
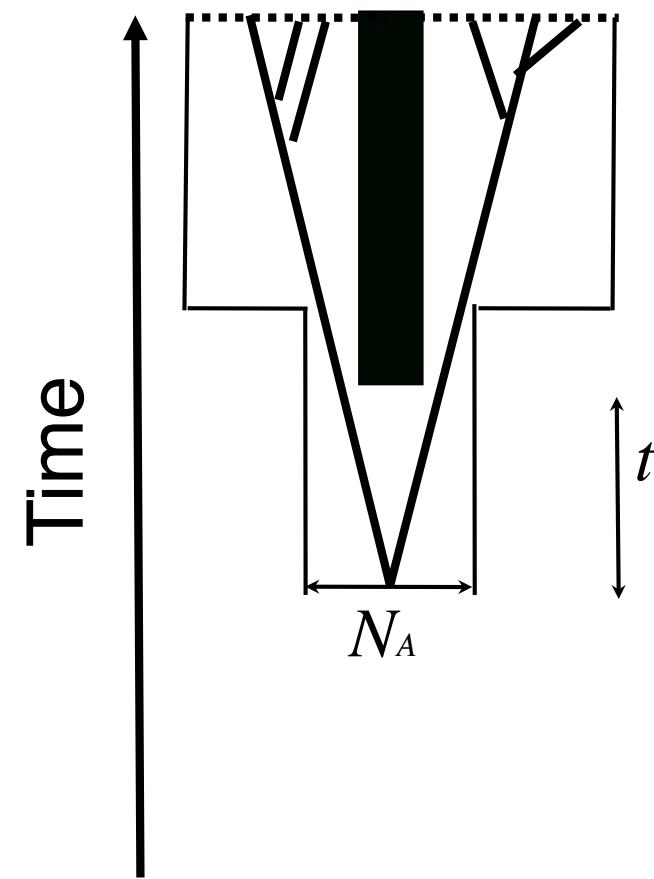
## ***Lecture 3:*** **The Coalescent**



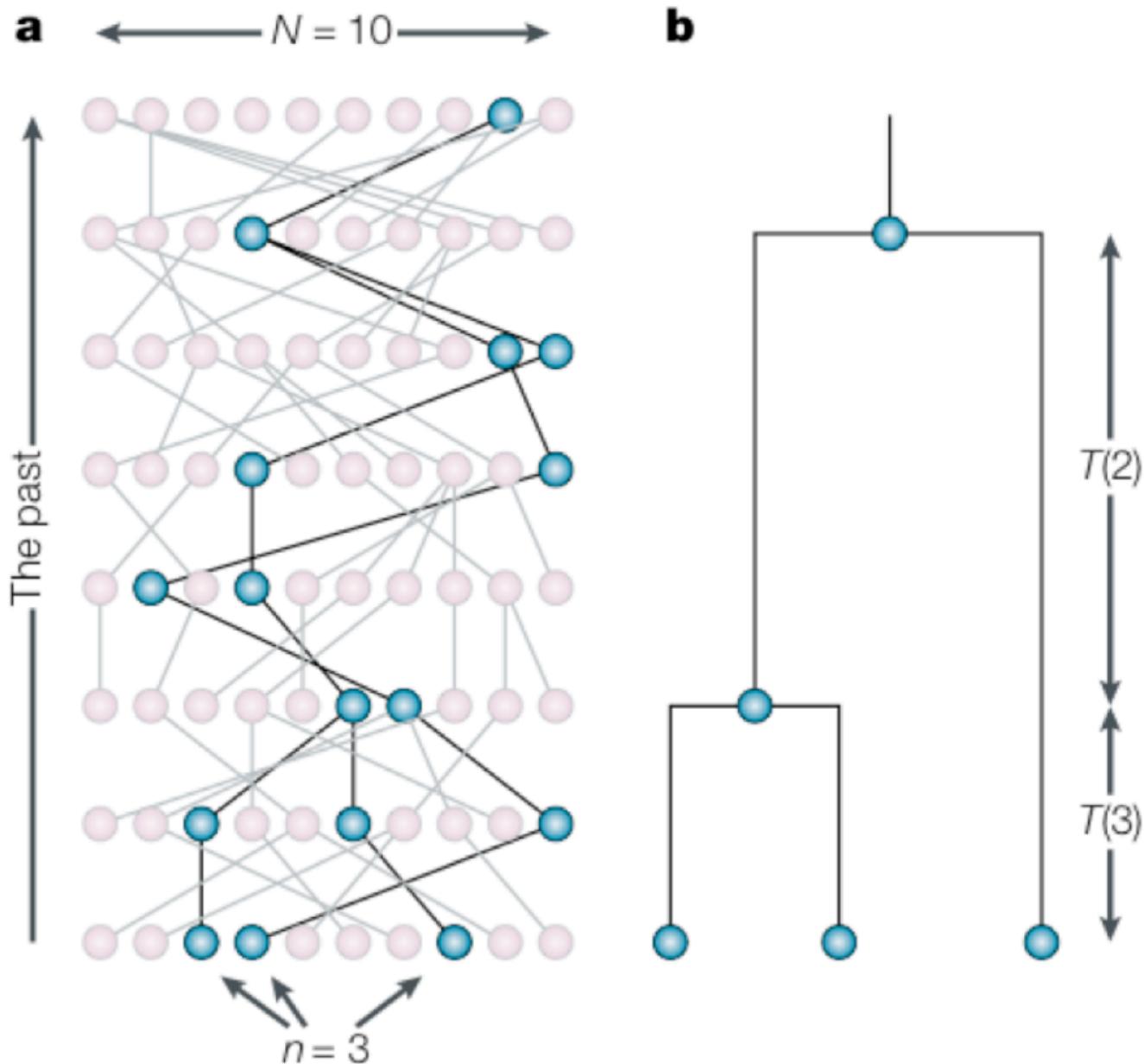
# coalescent theory predicts noise



# genetic data are noisy



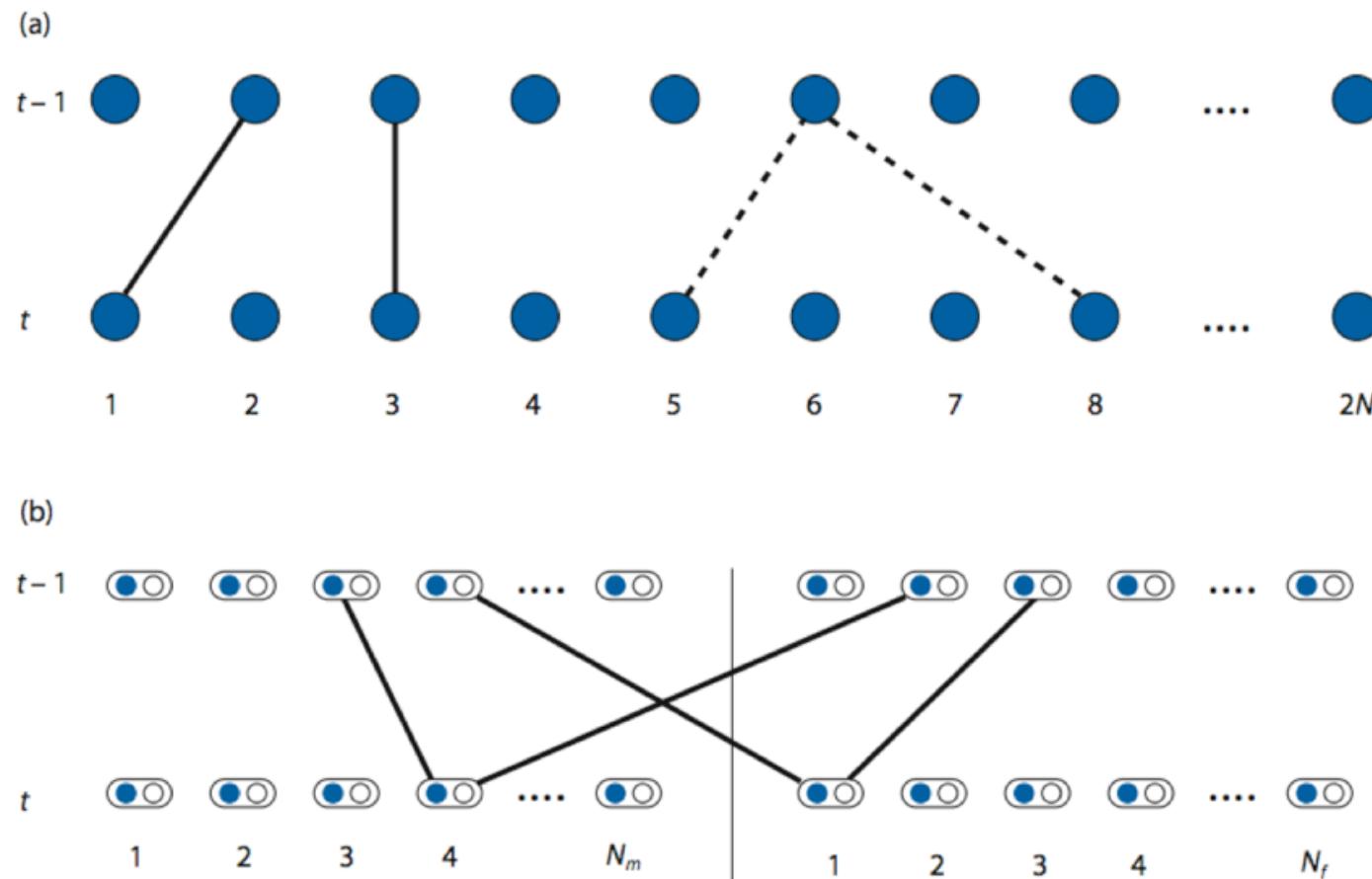
# Example of a gene genealogy



## Define

- ① Gene genealogy
- ② Coalescent event
- ③ Most Recent Common Ancestor (MRCA)
- ④ Time to MRCA (or TMRCA)

# haploid vs Diploid models



**Figure 3.23** Haploid (a) and diploid (b) reproduction in the context of coalescent events. In a haploid population, the probability

NOTE: The haploid model is often used as an approximation for the diploid model. To do so, the number of haplotypes is set equal to the number of chromosomes in the diploid model.

# coalescent probabilities per generation

## Question

What is the probability that 2 sampled haplotypes have the same parent in the previous generation?

# coalescent probabilities per generation

## Question

What is the probability that 2 sampled haplotypes have the same parent in the previous generation?

Related question: What is the probability you and I have the same birthday?

# coalescent probabilities per generation

## Question

What is the probability that 2 sampled haplotypes have the same parent in the previous generation?

$$Pr(2 \text{ coalesce to one}) = \frac{1}{\# \text{ of haplotypes}}$$

so for diploids:

$$Pr(2 \text{ coalesce to one}) = \frac{1}{2N}$$

# coalescent probabilities per generation

## Question

What is the probability that 2 sampled haplotypes have the same parent in the previous generation?

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What is the probability 3 sampled genes coalesce in the same generation?

# coalescent probabilities per generation

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so for diploids:

$$Pr(2 \text{ coalesce to one}) = \frac{1}{2N}$$

## Question

What is the probability 3 sampled genes coalesce in the same generation?

$$Pr(3 \text{ coalesce to one}) = \frac{1}{2N} \frac{1}{2N} = \frac{1}{4N^2}$$

# coalescent probabilities

## Implications

- If  $N$  is large and the number of lineages under consideration is small, the probability of 2 coalescent events per generation is very small relative to single coalescent events per generation.
- Suggests the approximation that we only consider *pairwise* (i.e. 2-way) coalescent as being possible.
- Thus, if there are  $k$  lineages to consider, there are  $\binom{k}{2}$  possible lineages we can join, the total probability of a coalescent event in a generation is:

$$\binom{k}{2} \times \frac{1}{2N}$$

and the mean waiting time is then the reciprocal

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

$$\binom{k}{2} = \frac{k!}{2!(k-2)!} * \frac{1}{2N}$$

number of lineages

$$\binom{k}{2} = \frac{k!}{2!(k-2)!} * \frac{1}{2N}$$

$$\binom{2}{2} = \frac{2!}{2!(2-2)!} * \frac{1}{2N} = \frac{1}{2N}$$



number of lineages

$$\text{mean waiting time} = \frac{2N}{1}$$

$$\binom{k}{2} = \frac{k!}{2!(k-2)!} * \frac{1}{2N}$$

$$\binom{2}{2} = \frac{2!}{2!(2-2)!} * \frac{1}{2N} = \frac{1}{2N}$$

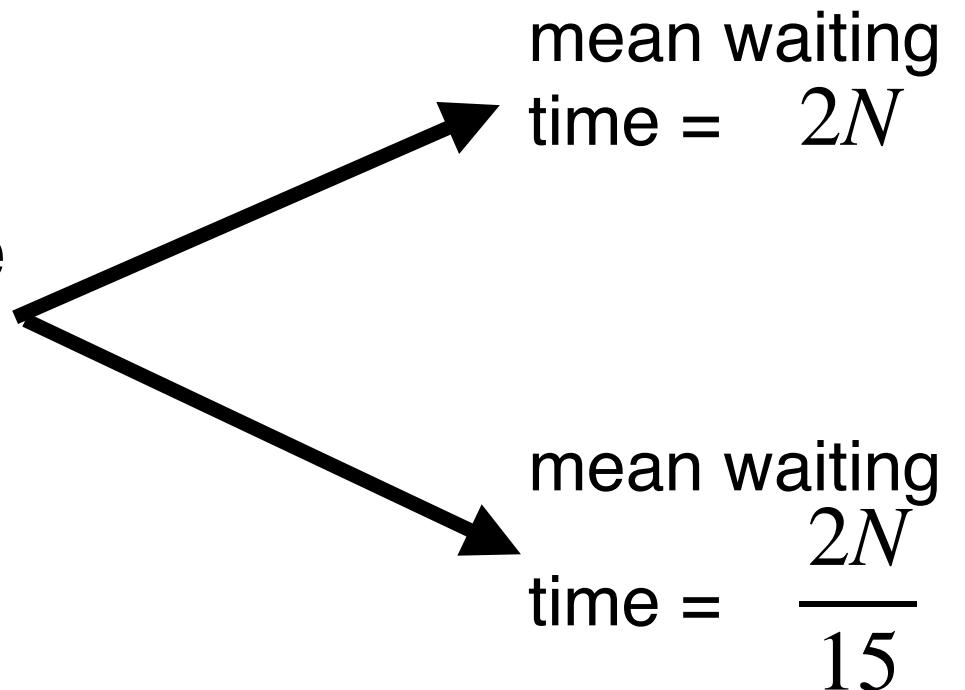
mean waiting  
time =  $\frac{2N}{2N}$

$$\binom{6}{2} = \frac{6!}{2!(6-2)!} * \frac{1}{2N} = \frac{15}{2N}$$

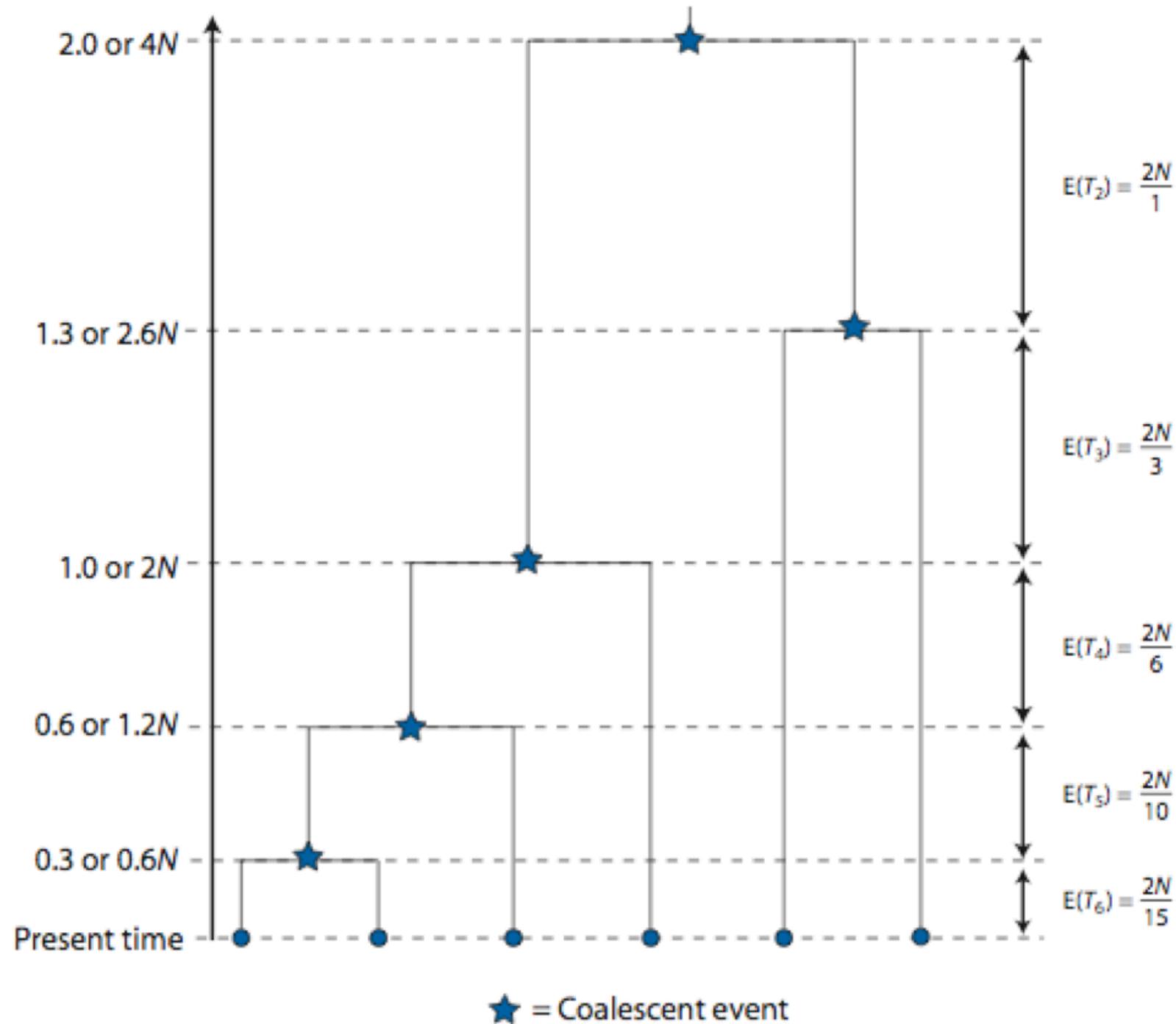
mean waiting  
time =  $\frac{2N}{15}$

$$\binom{k}{2} = \frac{k!}{2!(k-2)!} * \frac{1}{2N}$$

can be approximated by the exponential distribution



# The expected rate of coalescent events



times between coalescent events are smaller when there are fewer lineages (for instance, toward the tips of the tree) until only the last two lineages remain. Using the exponential distribution, now write down five easy steps for generating genealogies of size  $n$ :

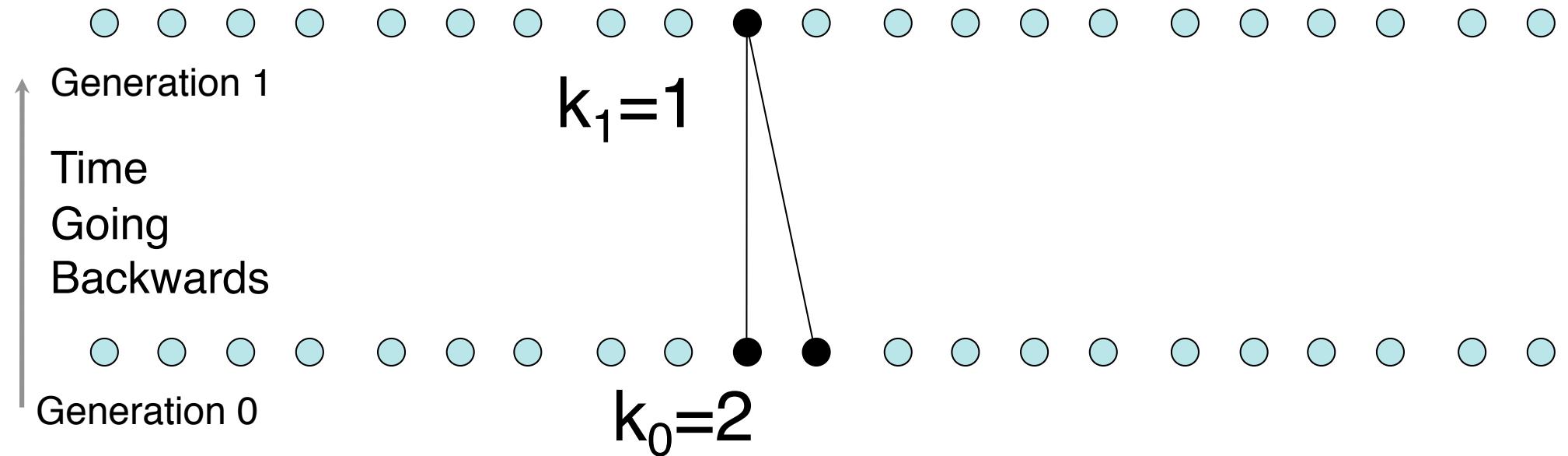
## the basic coalescent algorithm

1. Start with  $i = n$  chromosomes.
2. Choose a time until the next coalescence from an exponential distribution with parameter  $\lambda = i(i - 1)/2$ .
3. Choose two chromosomes at random to coalesce.
4. Merge the two lineages that were chosen and set  $i \rightarrow i - 1$ .
5. If  $i > 1$ , go to step 2; if not, stop.

As an example, **FIGURE 6.2** shows one possible genealogy generated by following the above steps for  $n = 5$ . Starting with  $i = n = 5$ , the process

probability of 2 gene copies descending from  
a single copy ...

$$\Pr(k_1=1 \mid k_0=2) = 1/2N$$

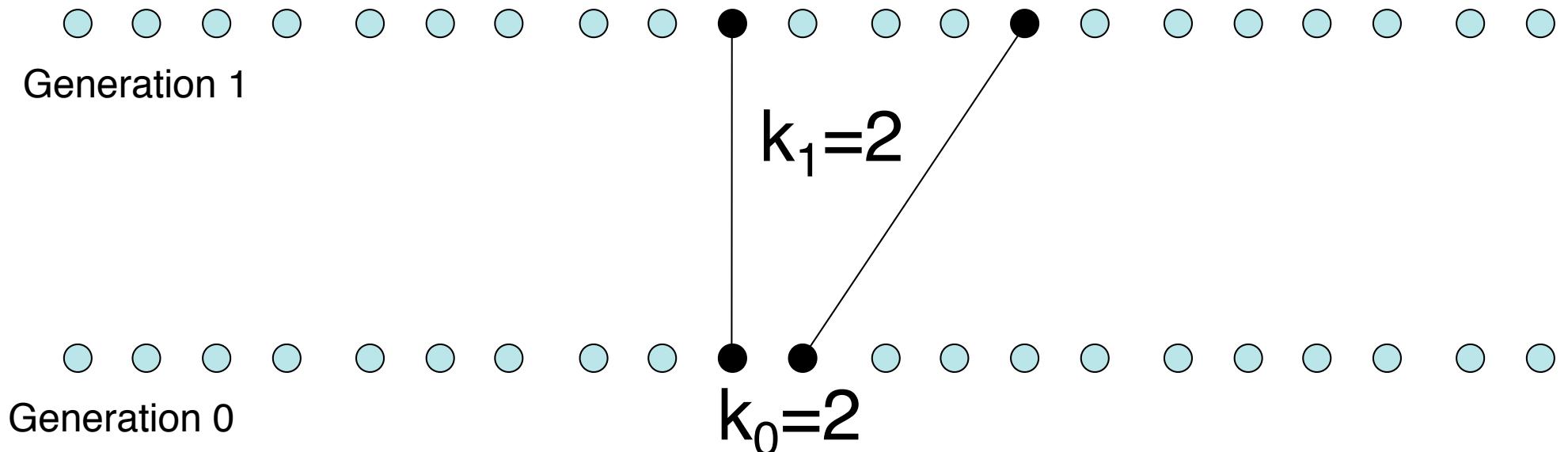


Pop size = N (2 gene copies per individual)

Therefore, probability of 2 gene copies descending from different copies

$$\Pr(k_1=2 | k_0=2) = 1 - 1/2N$$

(law of probability)

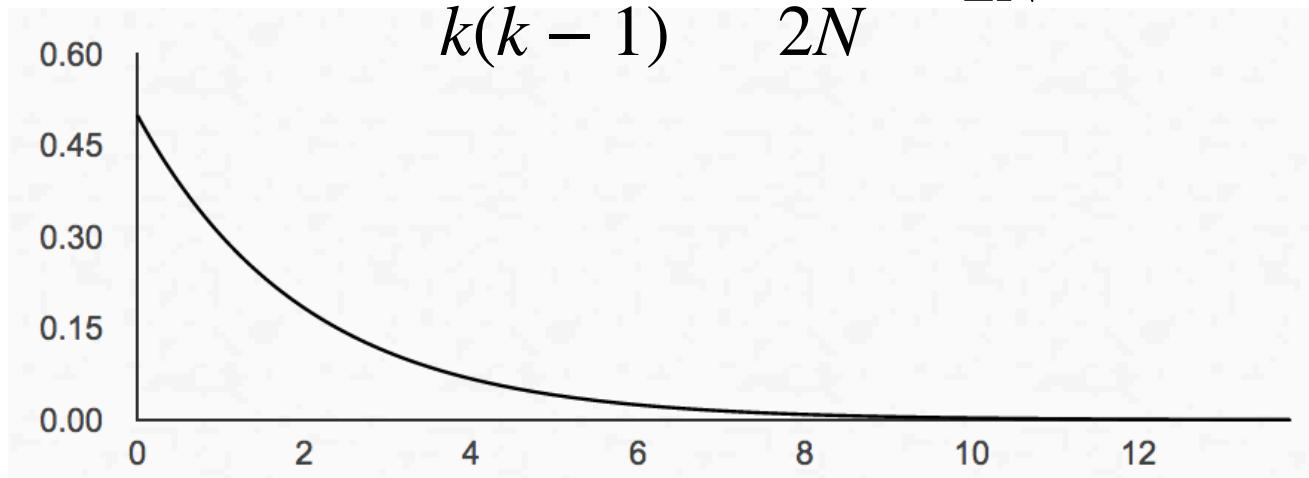


Pop size = N (2 gene copies per individual)

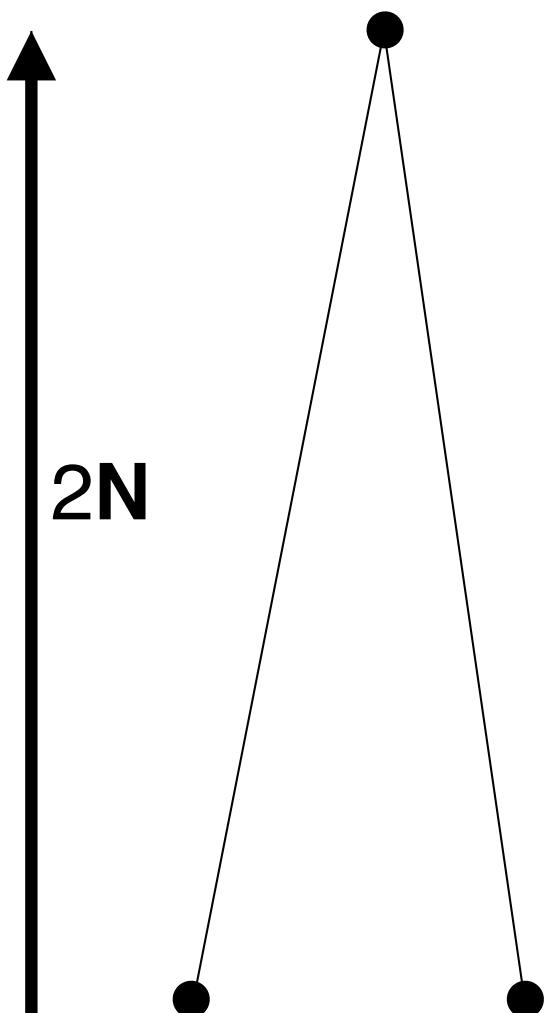
Number of generations since 2 randomly picked gene copies have common ancestor approximates an exponential distribution with a mean of  $2N$  (run of the mill Poisson process)

$$\frac{4N}{k(k - 1)} = \frac{4N}{2N} = 2N$$

Pr

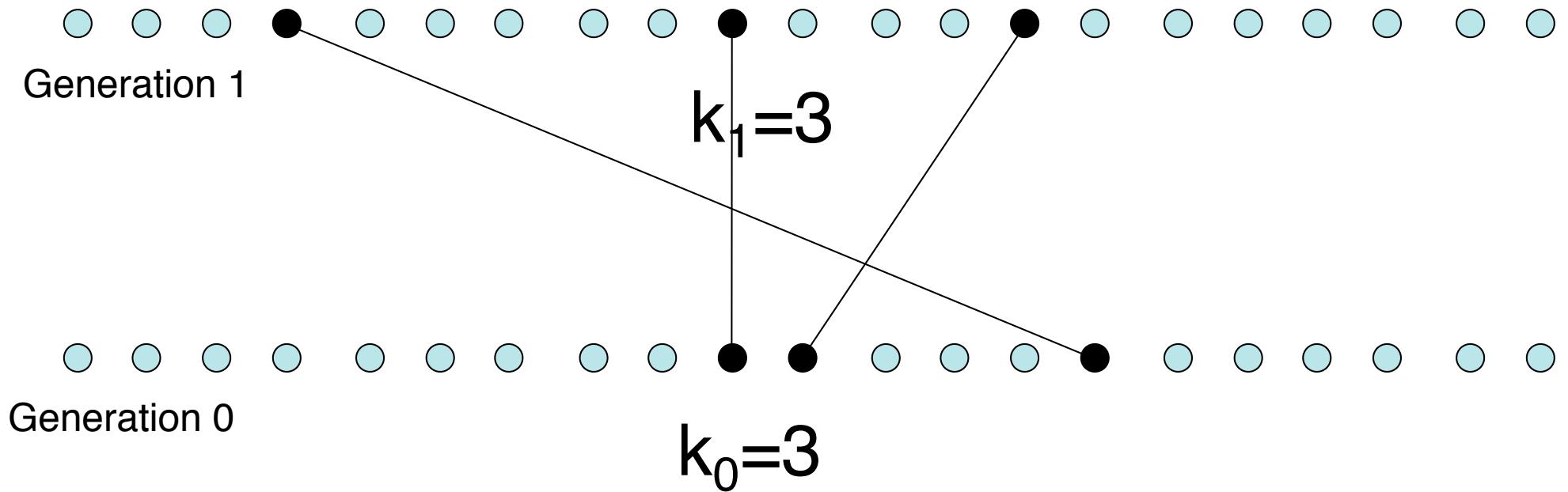


t



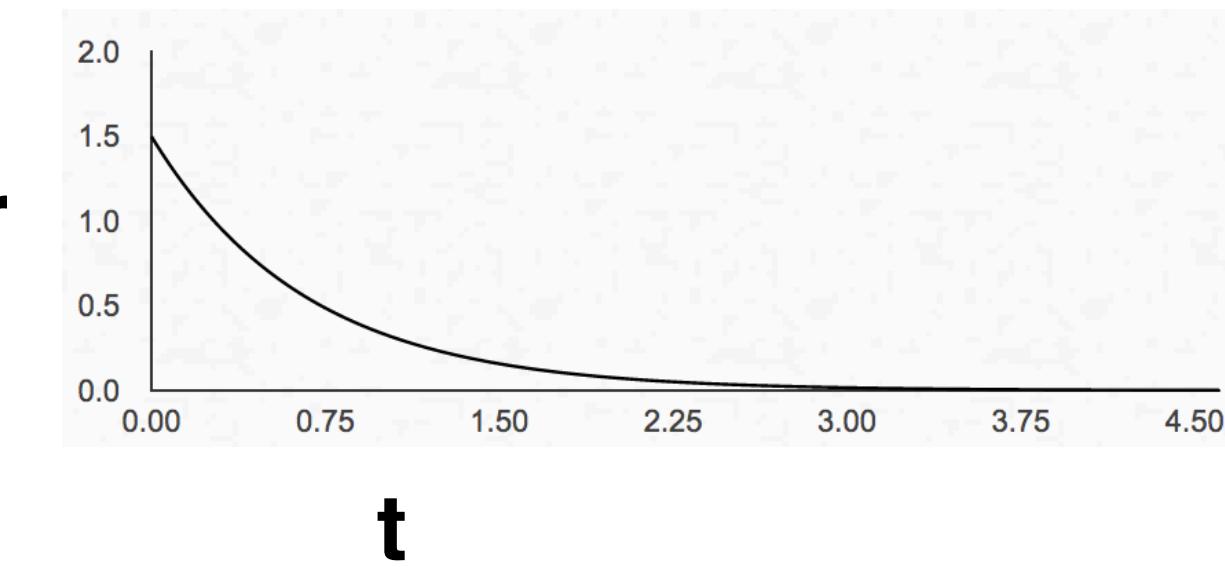
$\Pr(k_1=3|k_0=3)$  is  
probability of 2 copies having different parents  
( $1-1/2N$ ), multiplied by probability of the 3rd  
having different parents than the other two ( $1-2/2N$ )

$$\begin{aligned}\Pr(k_1=3|k_0=3) &= (1-1/2N) \times (1-2/2N) \\ &= 1 - 3/2N + 2/2N^2 \text{ (can ignore 2nd b/c N is large)}\end{aligned}$$

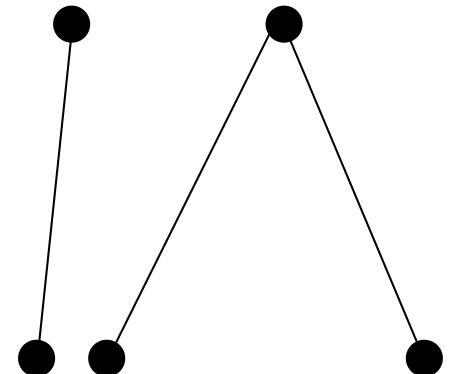


Waiting time ( $t$ ) for  $k_0 = 3$  copies having  $k_t = 2$  ancestors has an exponential distribution with a mean of  $2N/3$  generations

$$\frac{4N}{k(k - 1)} = \frac{4N}{3(3 - 1)} = \frac{2N}{3}$$



$N/3$



# Simulating The Coalescent

$k$  = sample size;

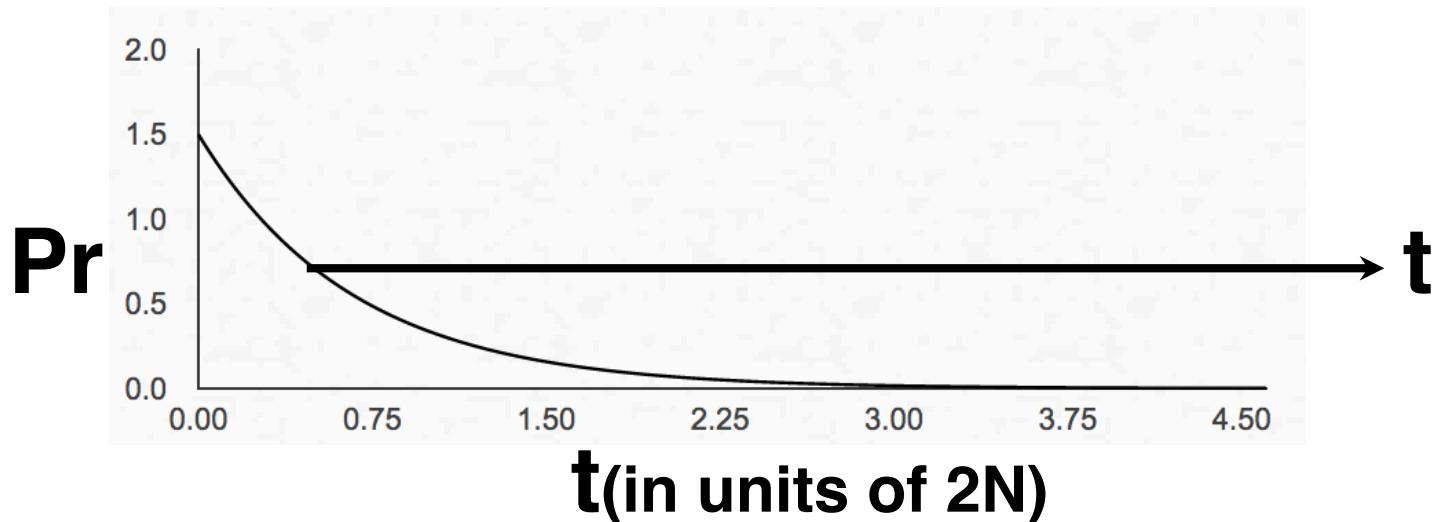
$N$  = population size

$t$  (time) = 0; go backwards;

1. randomly draw  $t$  from exponential

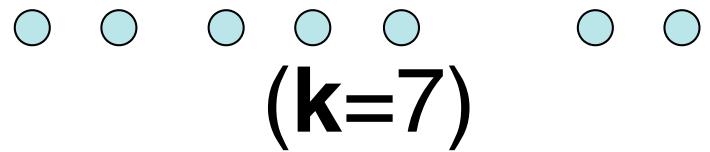
$$4N$$

with mean =  $\frac{4N}{k(k - 1)}$



# Simulating The Coalescent

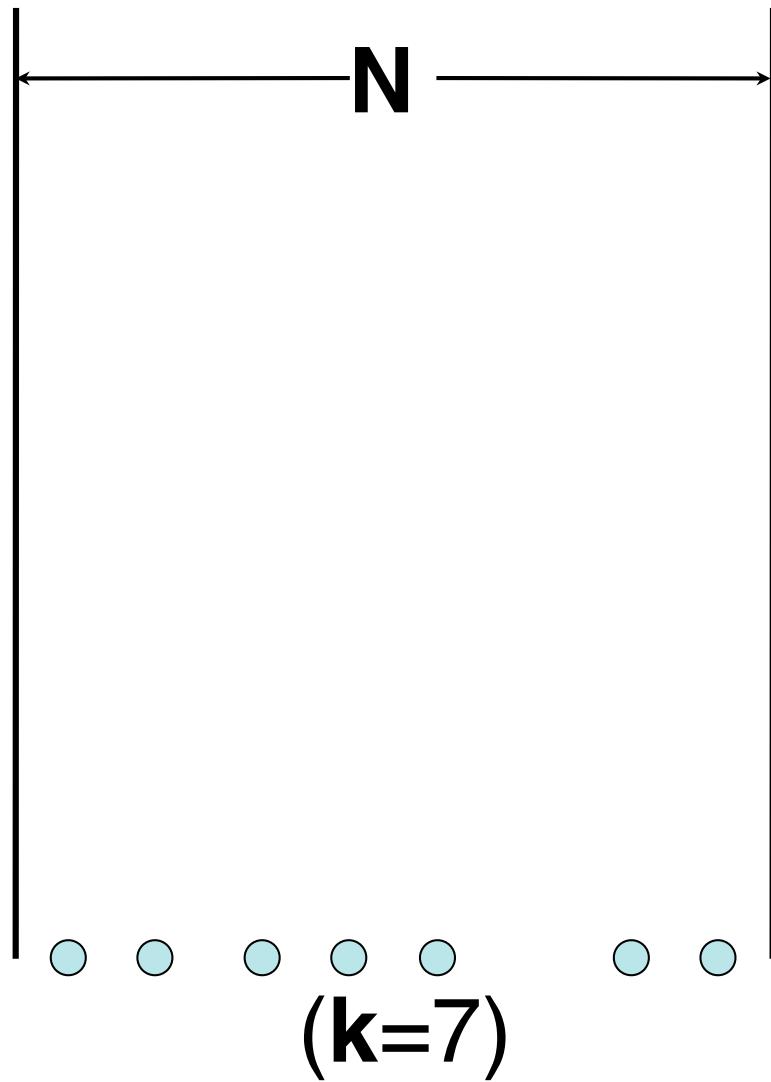
**k** = sample size



# Simulating The Coalescent

$N$  = population size

$k$  = sample size



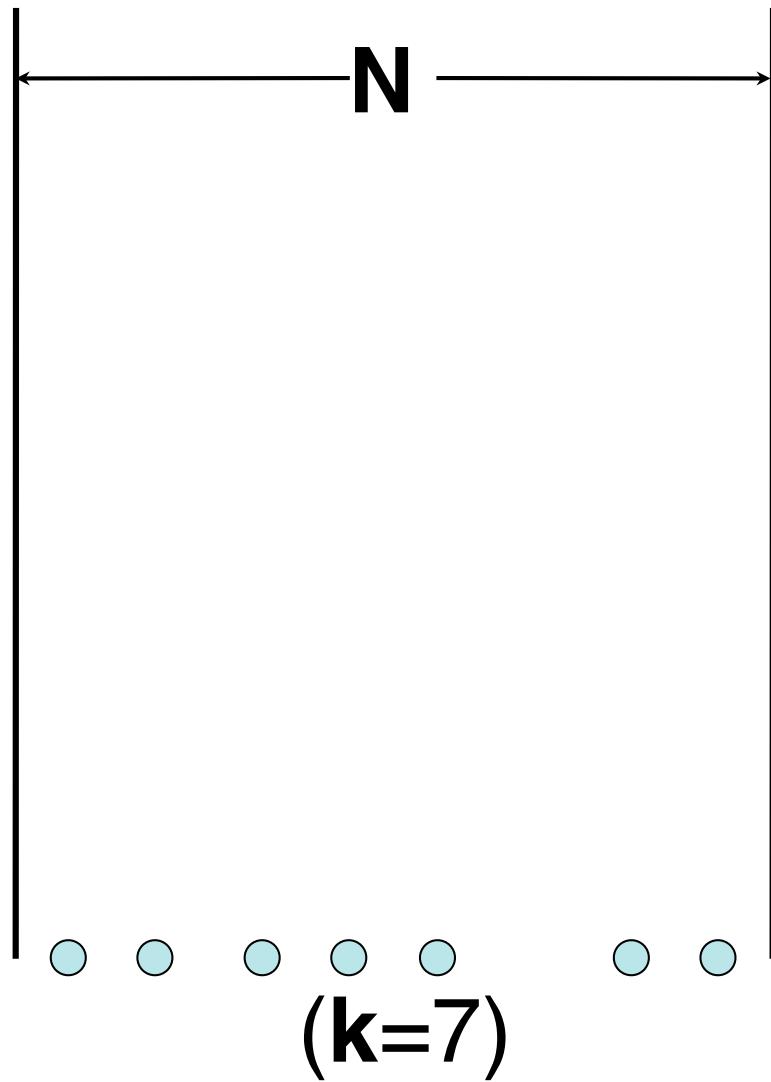
# Simulating The Coalescent

$T$  = time (go backwards)

$N$  = population size

$k$  = sample size

$T=0$

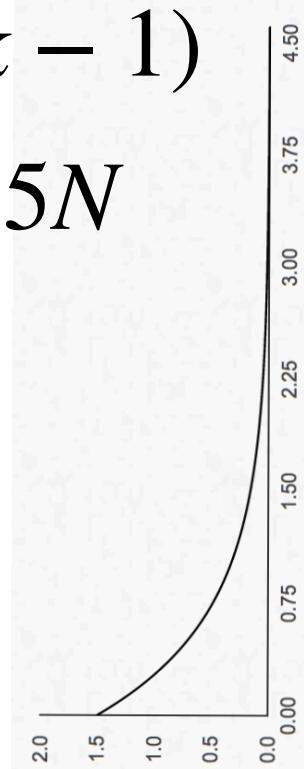


# Simulating The Coalescent

randomly draw  $t$  from exponential with

$$\text{mean} = \frac{4N}{k(k - 1)}$$

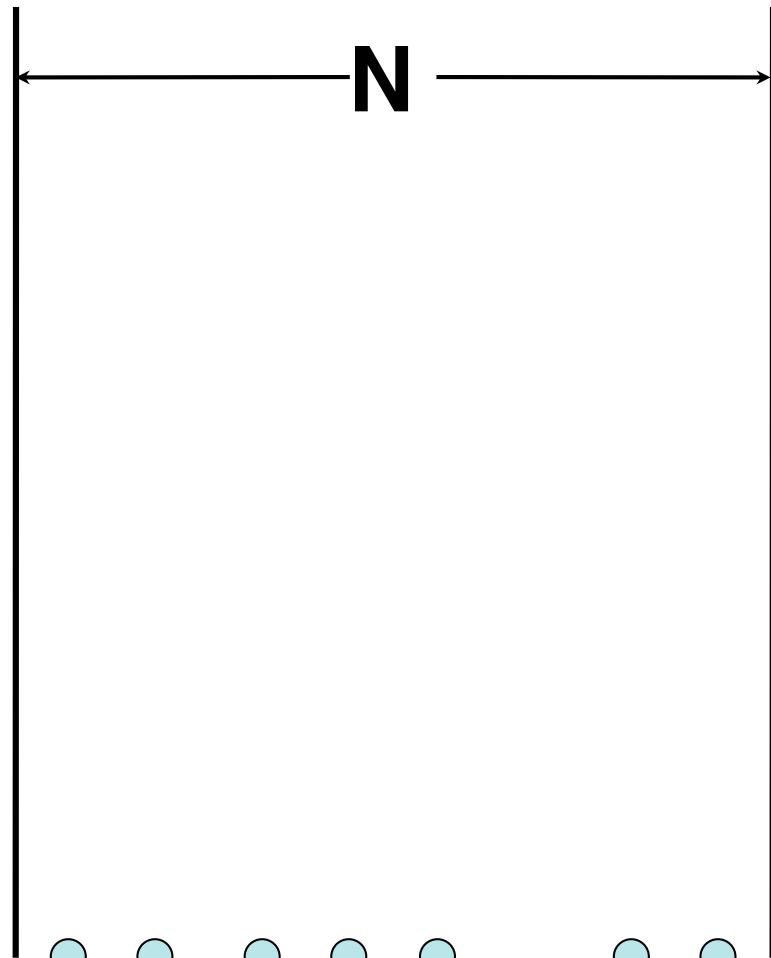
$$\frac{4N}{42} = 0.095N$$



**Pr**

**T=0**

**(k=7)**

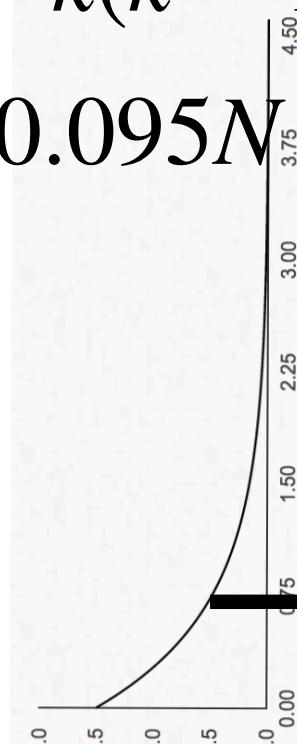


# Simulating The Coalescent

randomly draw  $t$  from exponential with

$$\text{mean} = \frac{4N}{k(k - 1)}$$

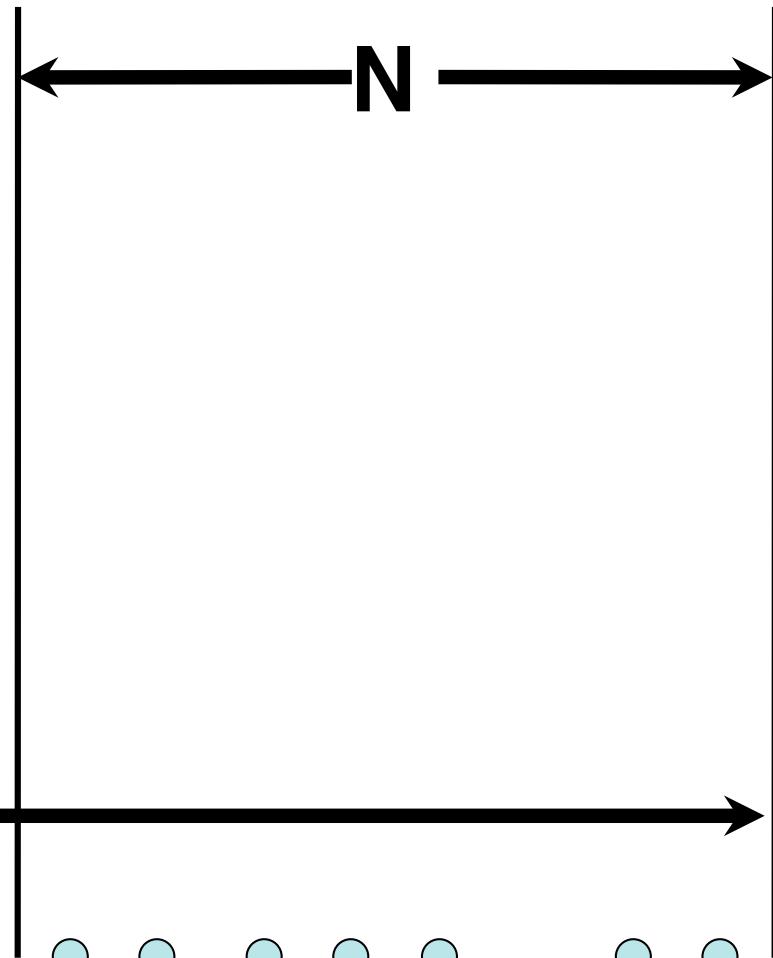
$$\frac{4N}{42} = 0.095N$$



**Pr**

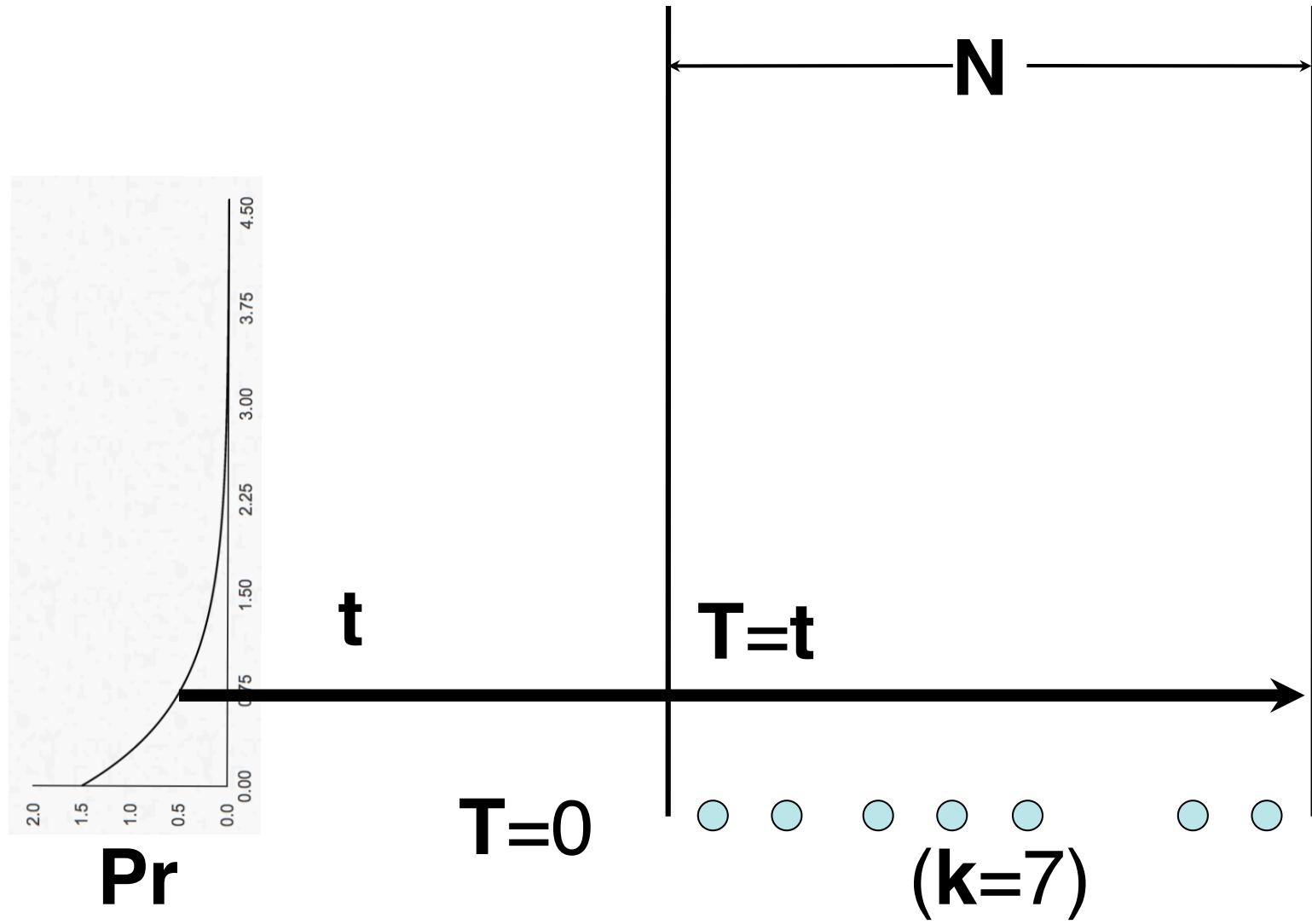
**T=0**

**(k=7)**



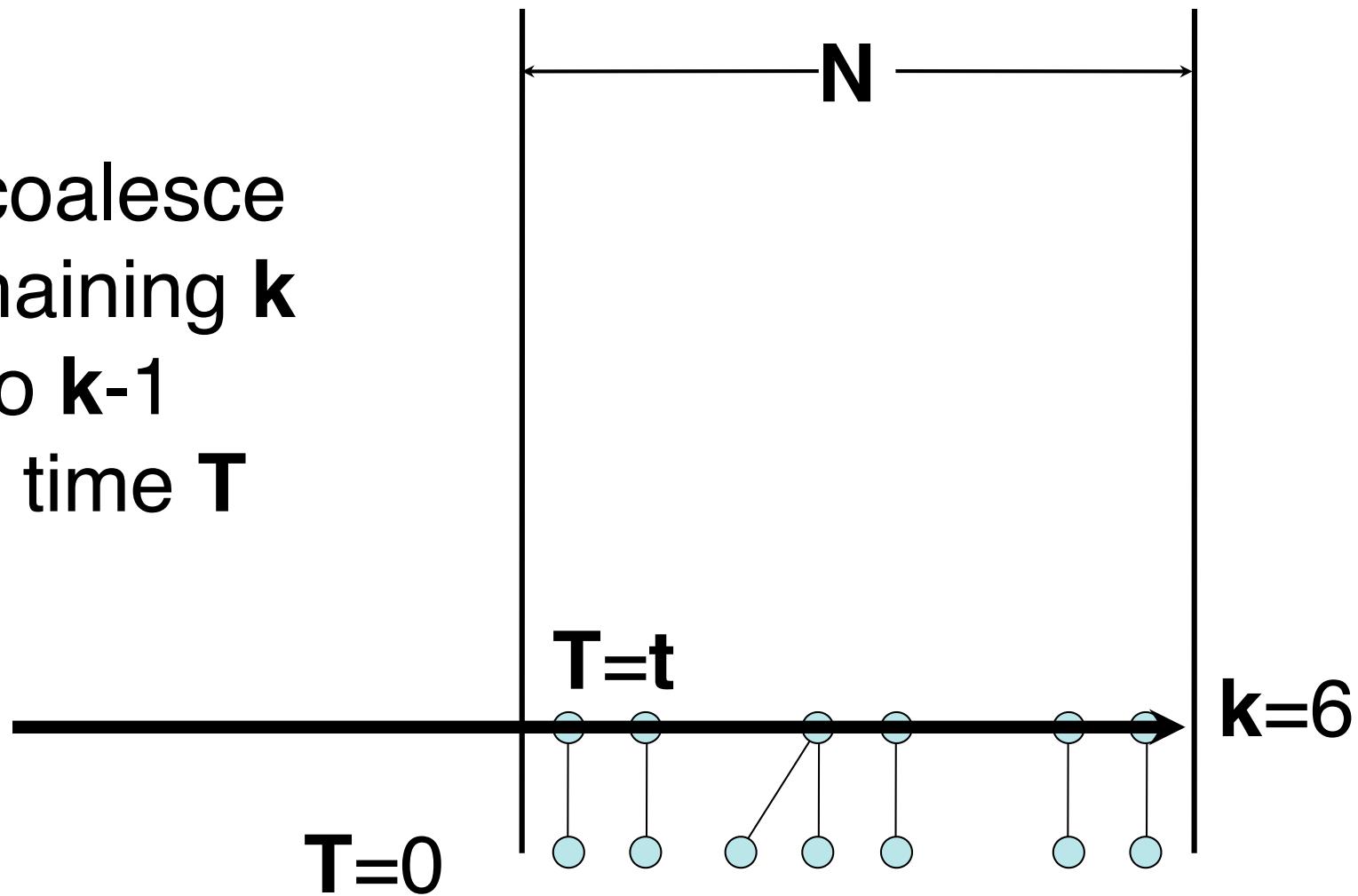
# Simulating The Coalescent

set  $T = T + t$



# Simulating The Coalescent

Randomly coalesce  
2 of the remaining  $k$   
lineages into  $k-1$   
Lineages at time  $T$

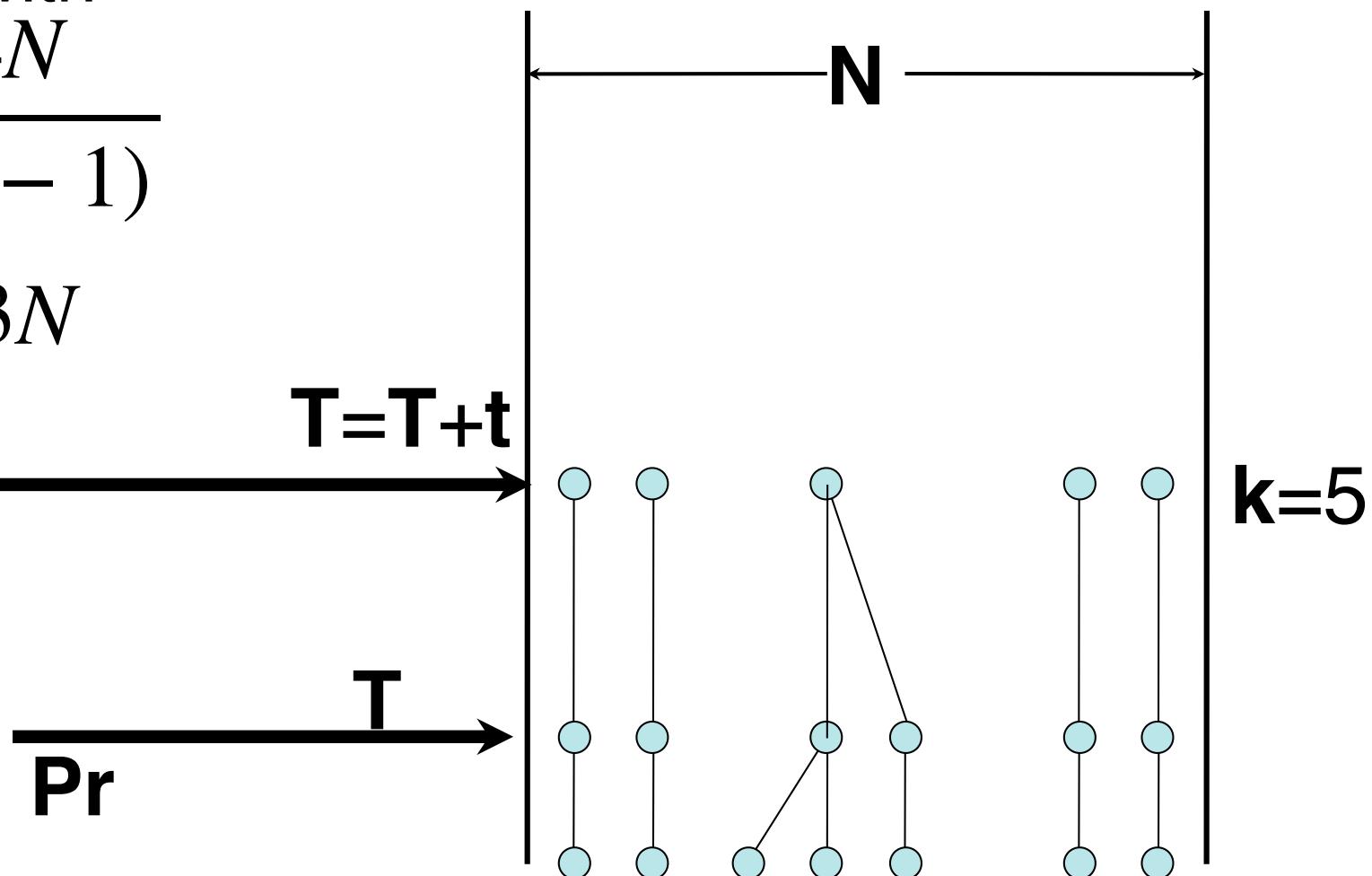
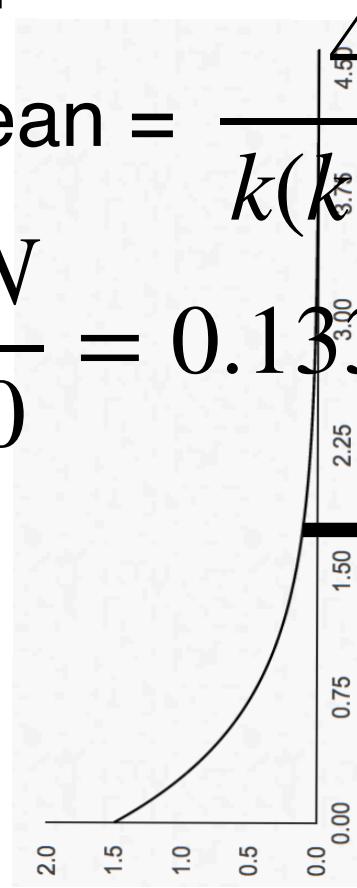


# Simulating The Coalescent

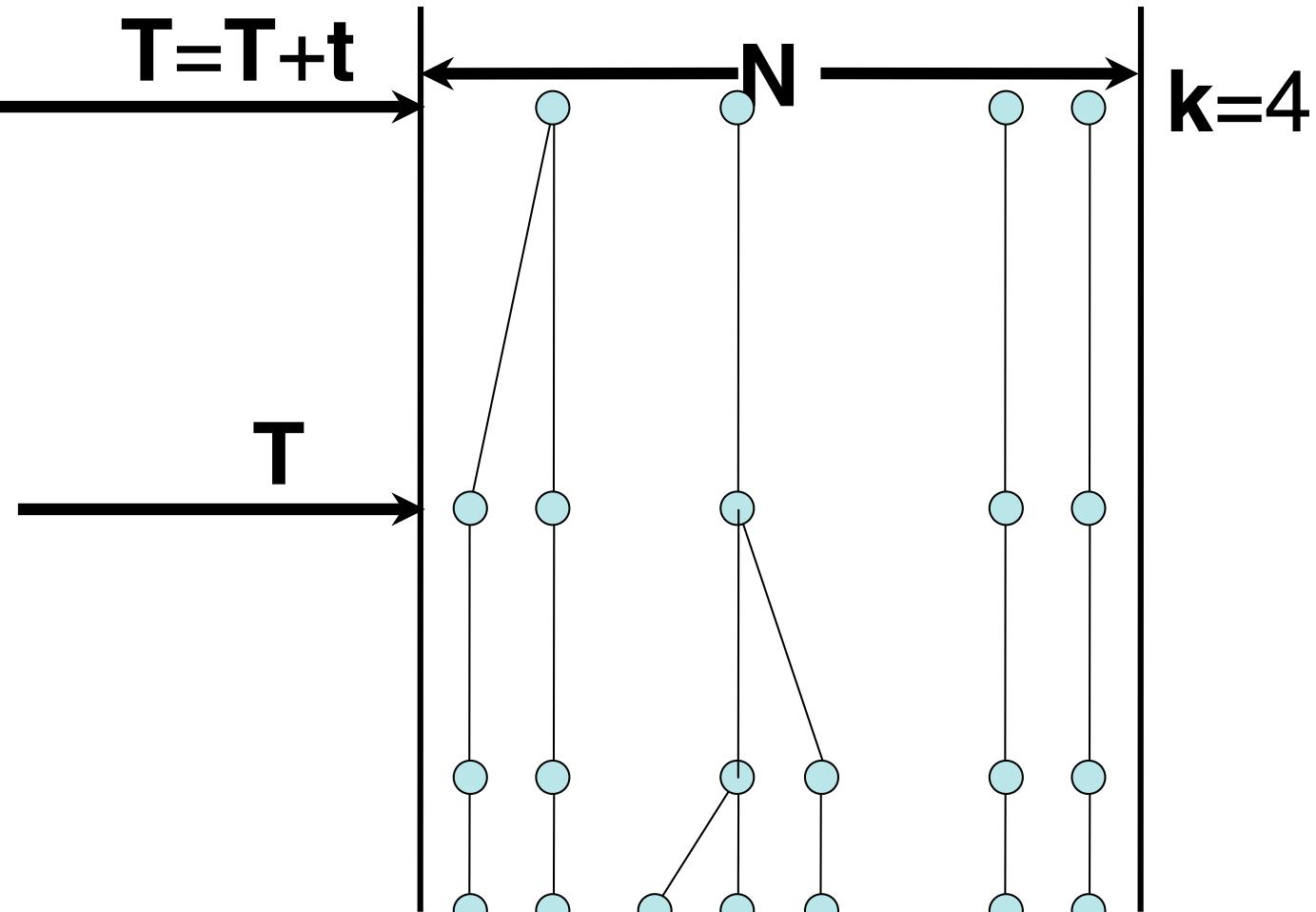
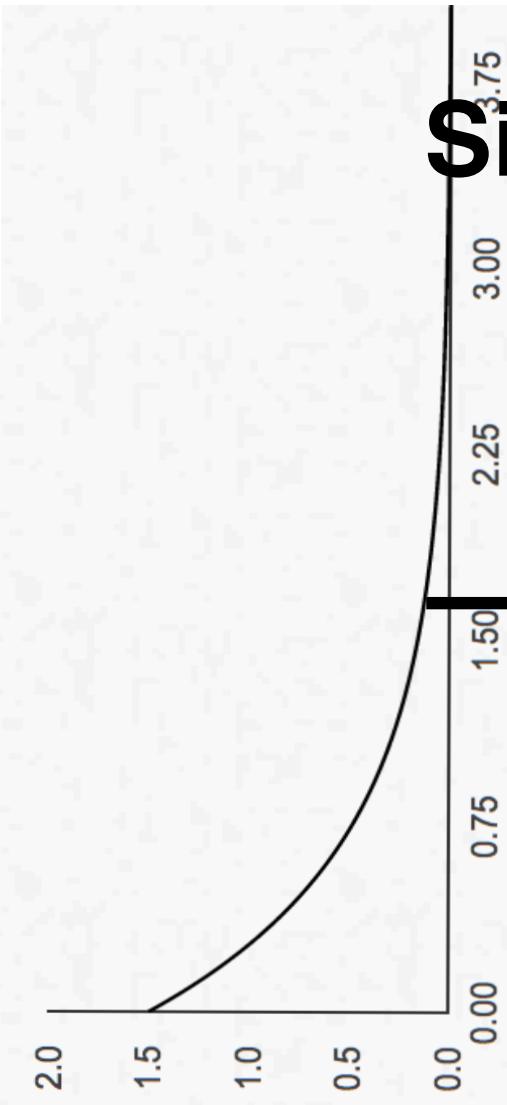
randomly draw  $t$  from exponential with

$$\text{mean} = \frac{4N}{k(k - 1)}$$

$$\frac{4N}{30} = 0.133N$$



# Simulating The Coalescent



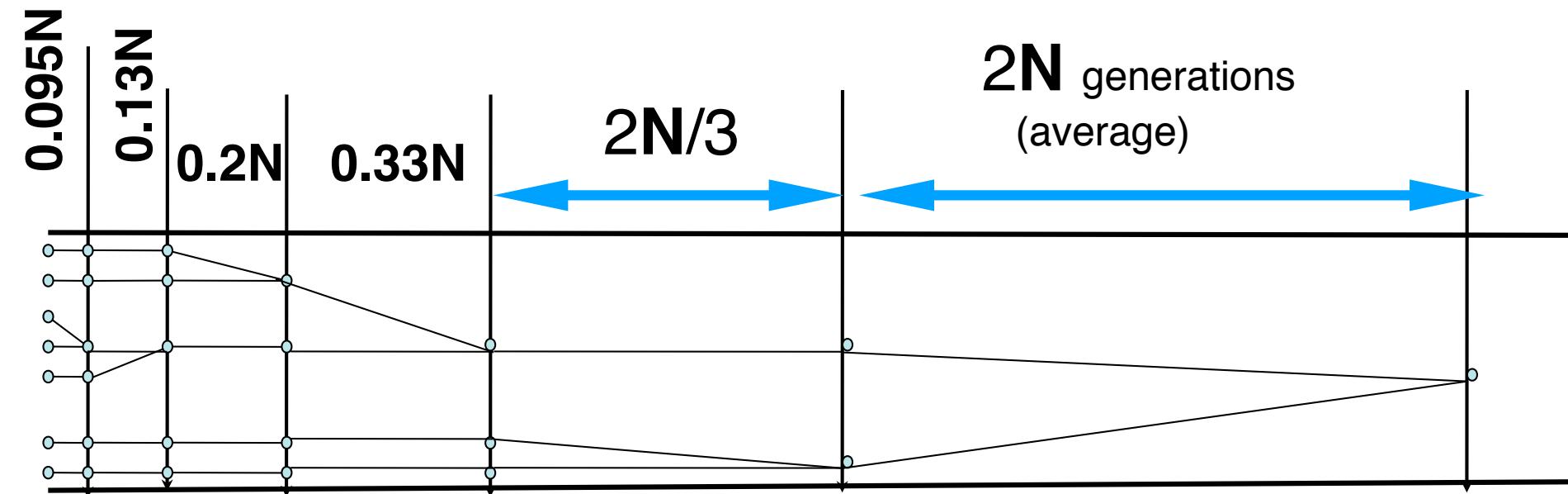
randomly draw  $t$  from exponential with

$$4N$$

$$\text{mean} = \frac{4N}{k(k - 1)}$$

$$\frac{4N}{20} = 0.2N$$

# Simulating The Coalescent



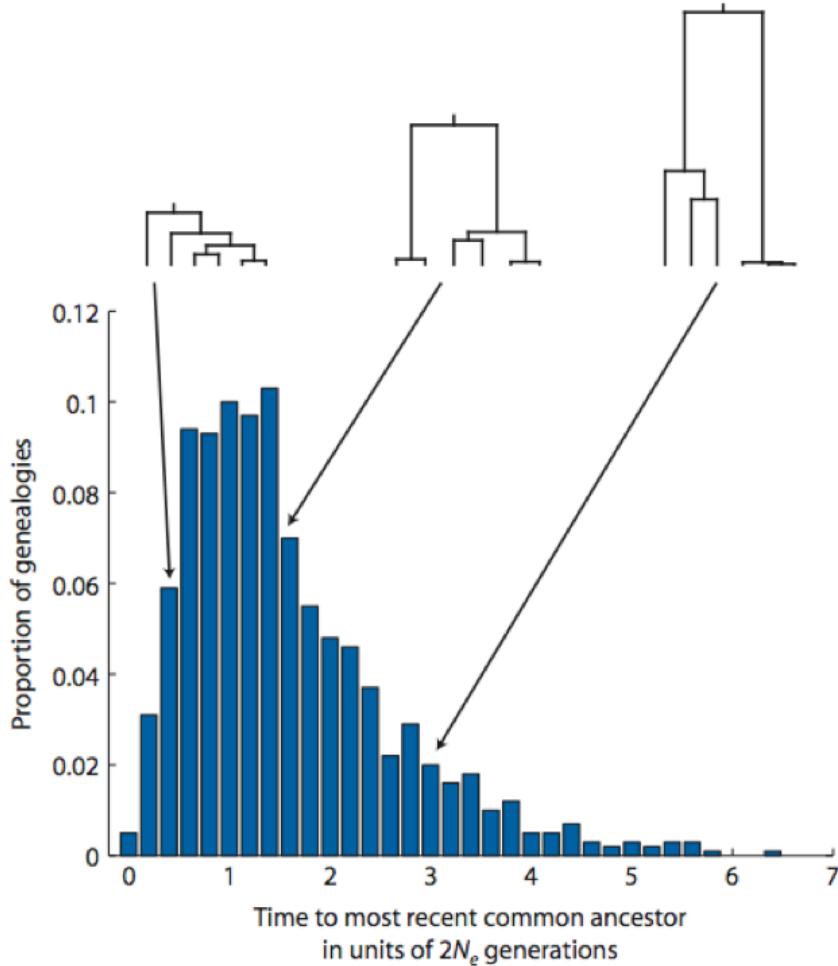
# properties of the coalescent

## Large Variance



9 randomly generated realizations of gene trees from the coalescent process, all with 20 tips & drawn to same scale  
(Figure 26.5 from Felsenstein book)

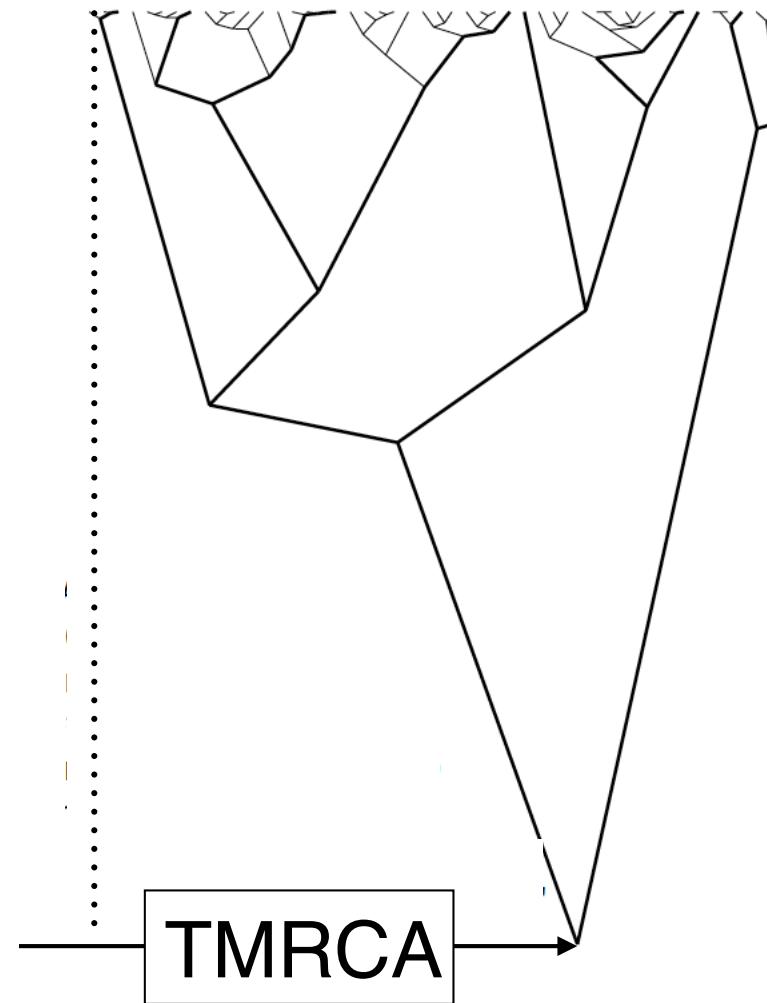
# coalescent process leads to highly variable gene genealogies



**Figure 3.27** The distribution of times to a MRCA (or genealogy heights) for 1000 replicate genealogies starting with six lineages ( $k = 6$ ). The distribution of total coalescence

# properties of the coalescent

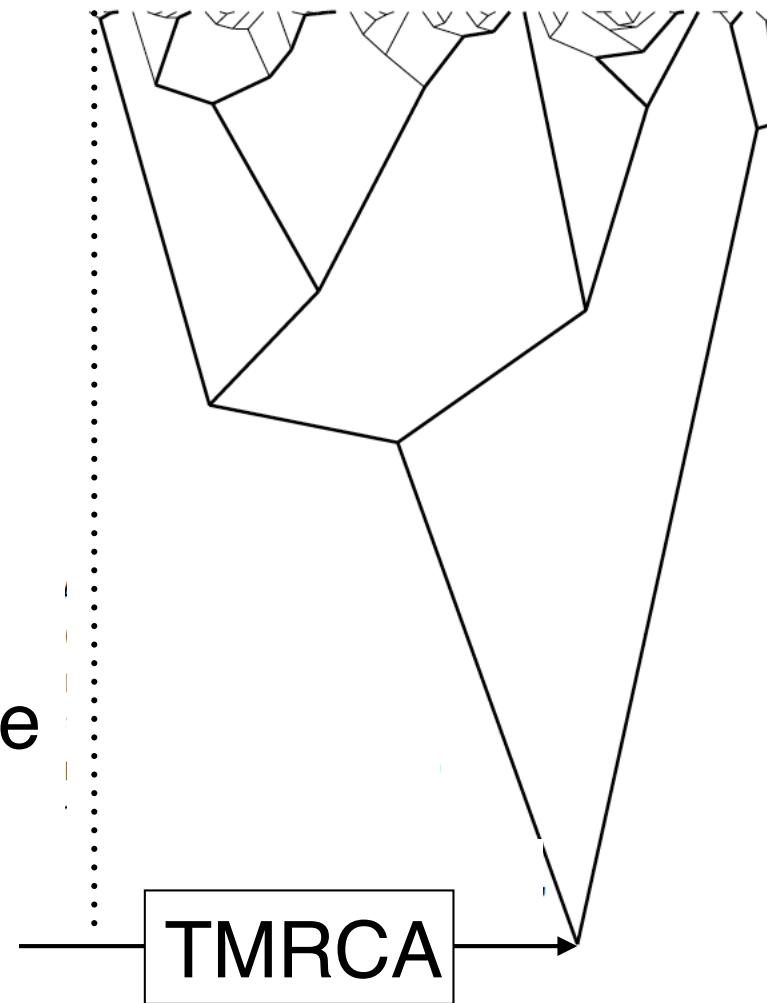
For any  $k$  samples,  
TMRCA sample =  $4N(1 - 1/k)$



# properties of the coalescent

For any  $k$  samples,  
TMRCA sample =  $4N(1 - 1/k)$

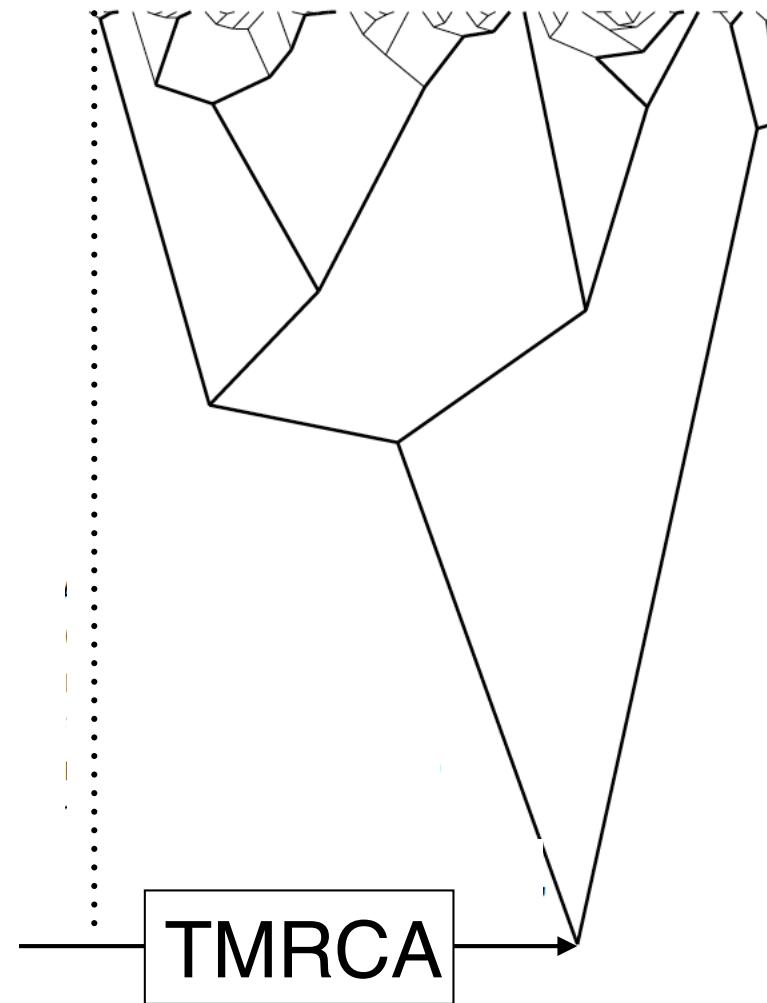
Half this time ( $\sim 2N$ ) is waiting for the  
last 2 coalescent events



# properties of the coalescent

For any  $k$  samples,  
TMRCA sample =  $4N(1 - 1/k)$

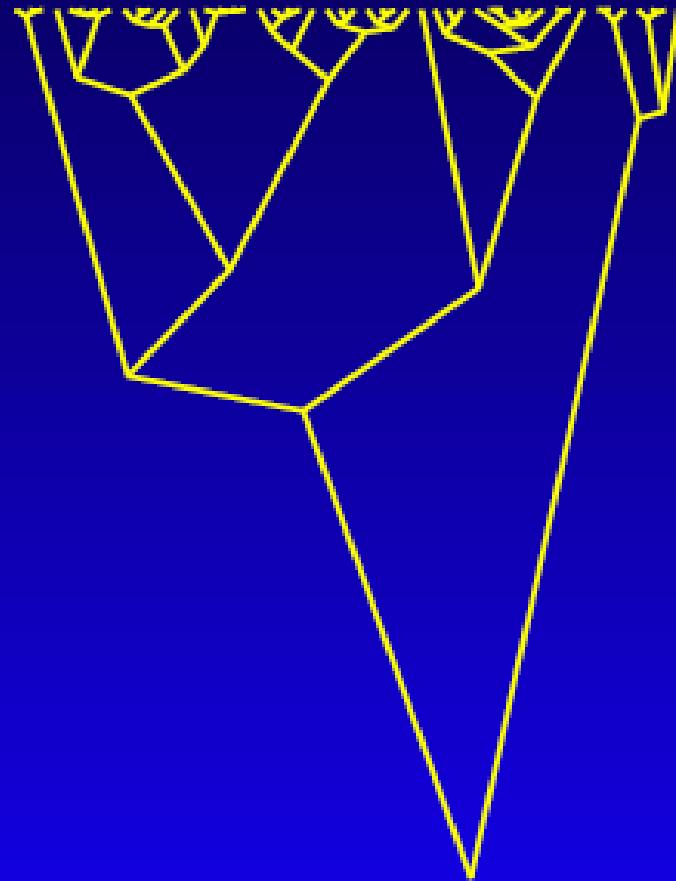
$$Var = 16N^2(1 - 1/k)^2$$



**MOST** of the variance/noise comes from  
the last coalescent event

# properties of the coalescent

50-gene sample in a coalescent tree



Samples of  
 $k = 10$  has most of the information

# properties of the coalescent

10 genes sampled randomly out of a  
10–gene sample in a coalescent tree



Samples of  
 $k = 10$  has most of the information

# properties of the coalescent

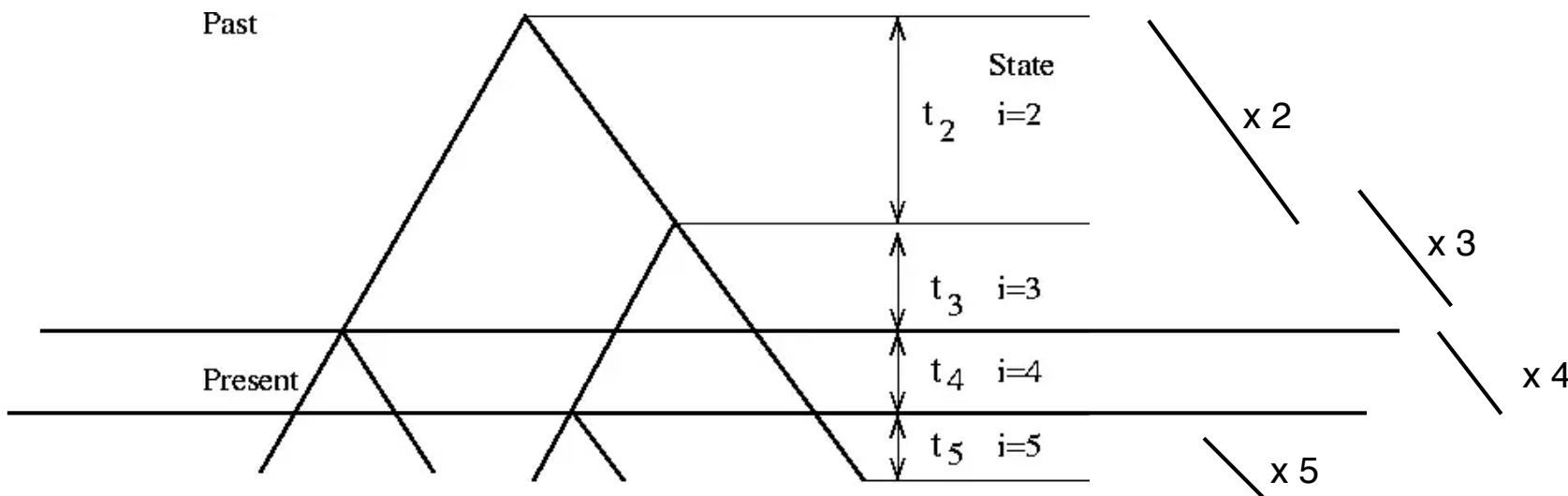
10 genes sampled randomly out of a  
50-gene sample in a coalescent tree



Samples of  
 $k = 10$  has most of the information

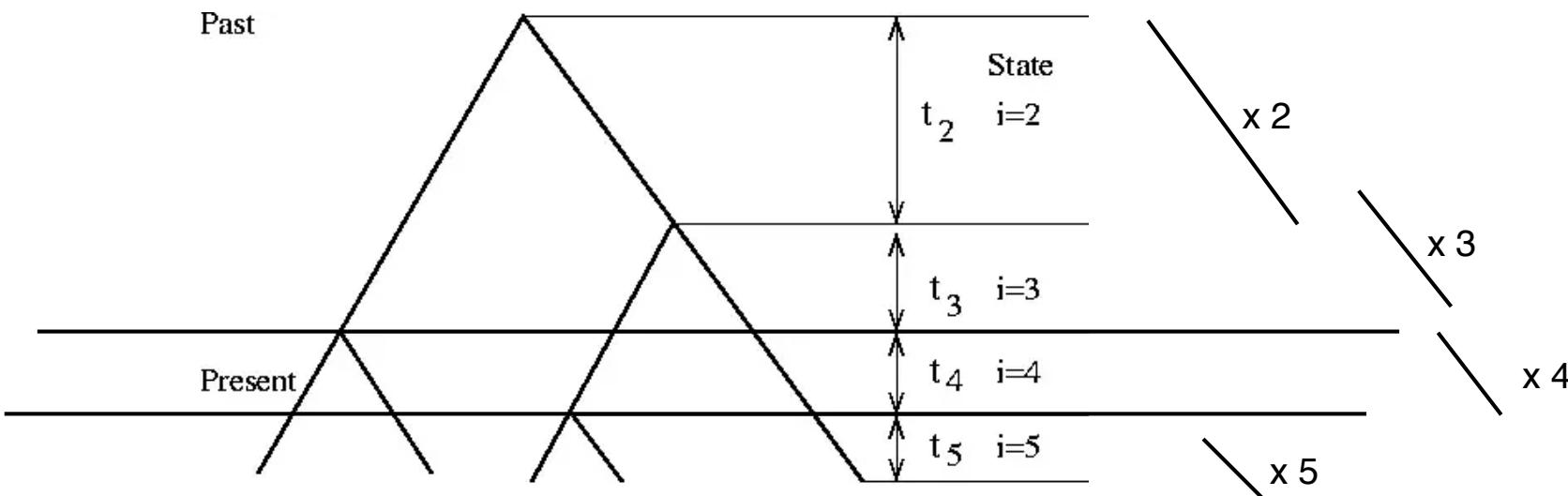
For any  $k$  samples,  
the total tree length is

$$E(T_{total}) = \sum_{k=2}^n k \frac{4N}{k(k - 1)}$$



For any  $k$  samples,  
the total tree length is

$$E(T_{total}) = \sum_{k=2}^n k \frac{4N}{k(k - 1)}$$

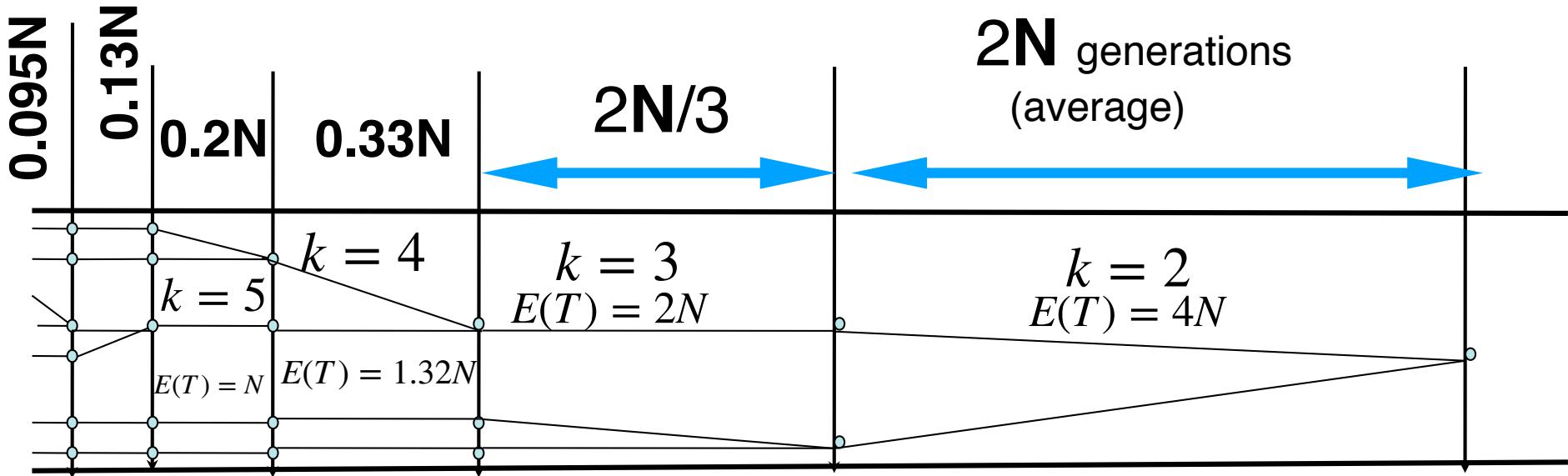


given that the time that there is  $k$  lineages before  $k-1$

lineages =  $\frac{4N}{k(k - 1)}$ , we can sequentially multiple these times by  $k$ .

For any  $k$  samples,  
the total tree length

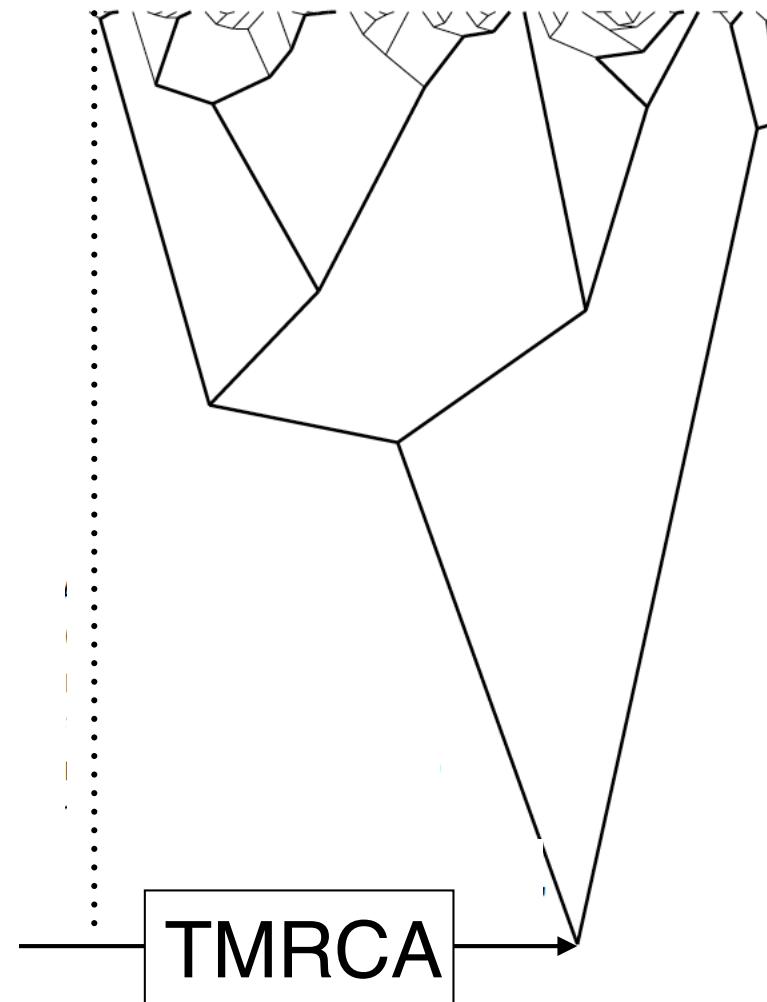
$$E(T_{total}) = \sum_{k=2}^n k \frac{4N}{k(k-1)}$$



if we “sprinkle” mutations, then  $E(T_{total})$  gives you  $E(\# \text{ polymorphic sites})$

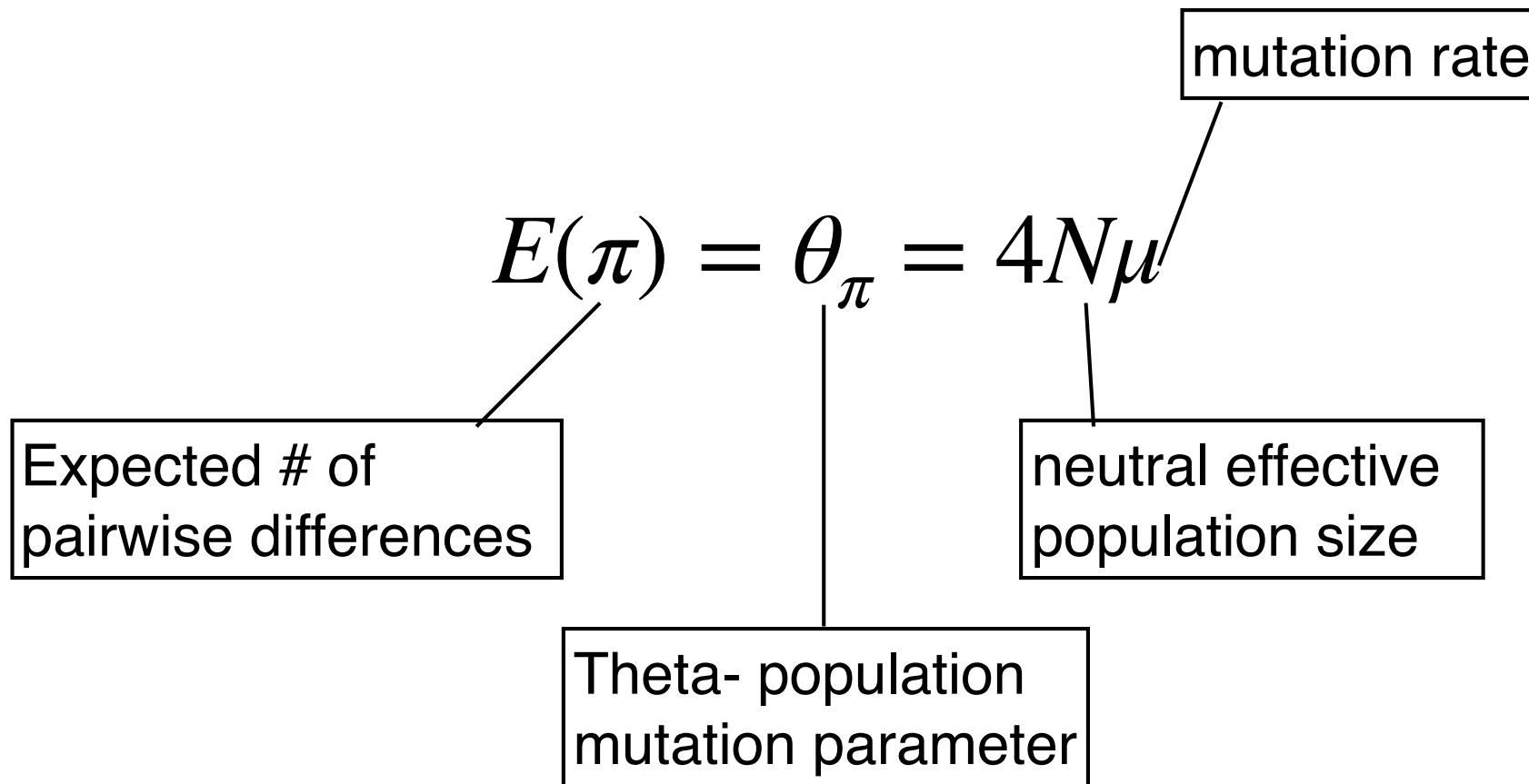
recall

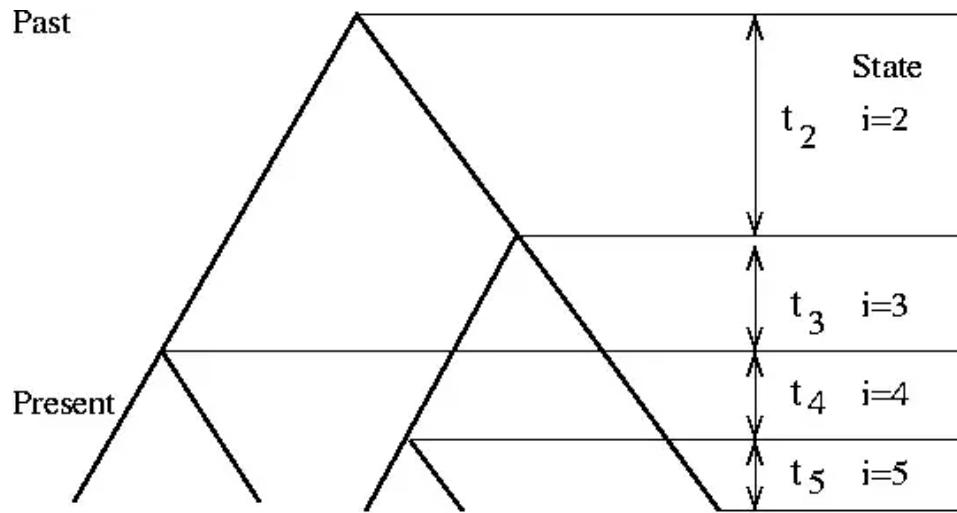
For any  $k$  samples,  
TMRCA sample =  $4N(1 - 1/k)$



if we “sprinkle” mutations, then TMRCA for any two samples becomes  $4N\mu$

now back to the classic sumstat, average pairwise differences





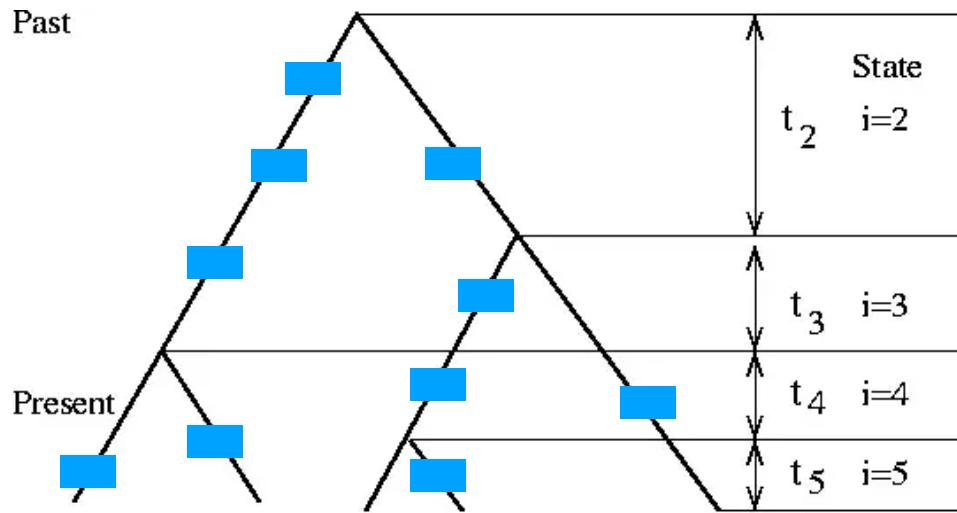
think about the case of 2 lineages ( $k = 2$ )

$$\text{TMRCA sample} = 4N(1 - 1/k) = 4N(1 - 1/2) = 2N$$

$2^*$ TMRCA between any 2 samples

$$= 4N$$

sprinkling mutations  $\longrightarrow E(\pi) = \theta_\pi = 4N\mu$

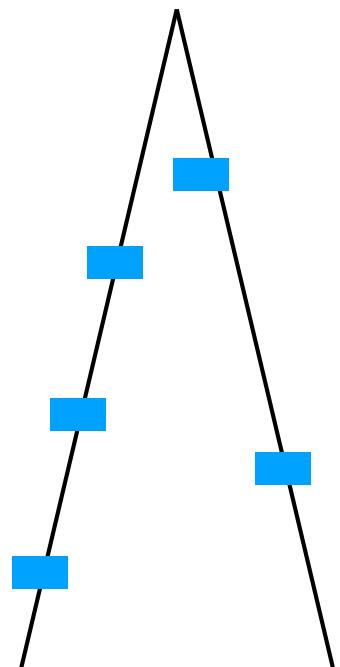


think about the case of 2 lineages ( $k = 2$ )

$$\text{TMRCA sample} = 4N(1 - 1/k) = 4N(1 - 1/2) = 2N$$

$$\begin{aligned} & 2^*\text{TMRCA between any 2 samples} \\ & = 4N \end{aligned}$$

sprinkling mutations  $\longrightarrow E(\pi) = \theta_\pi = 4N\mu$



$$\theta = 4\Lambda \mu$$

S (# of polymorphic sites) estimator of  $\theta$

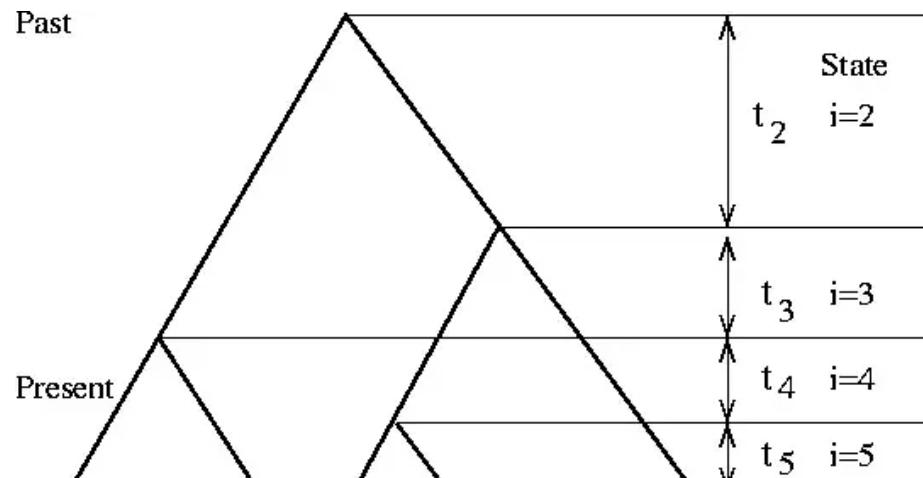
$$\theta_W = S / \sum_{k=1}^{n-1} \frac{1}{k}$$

looks like total tree length!

$$E(T_{total}) = \sum_{k=2}^n k \frac{4N}{k(k-1)} = 4N \sum_{k=1}^{n-1} \frac{1}{k}$$

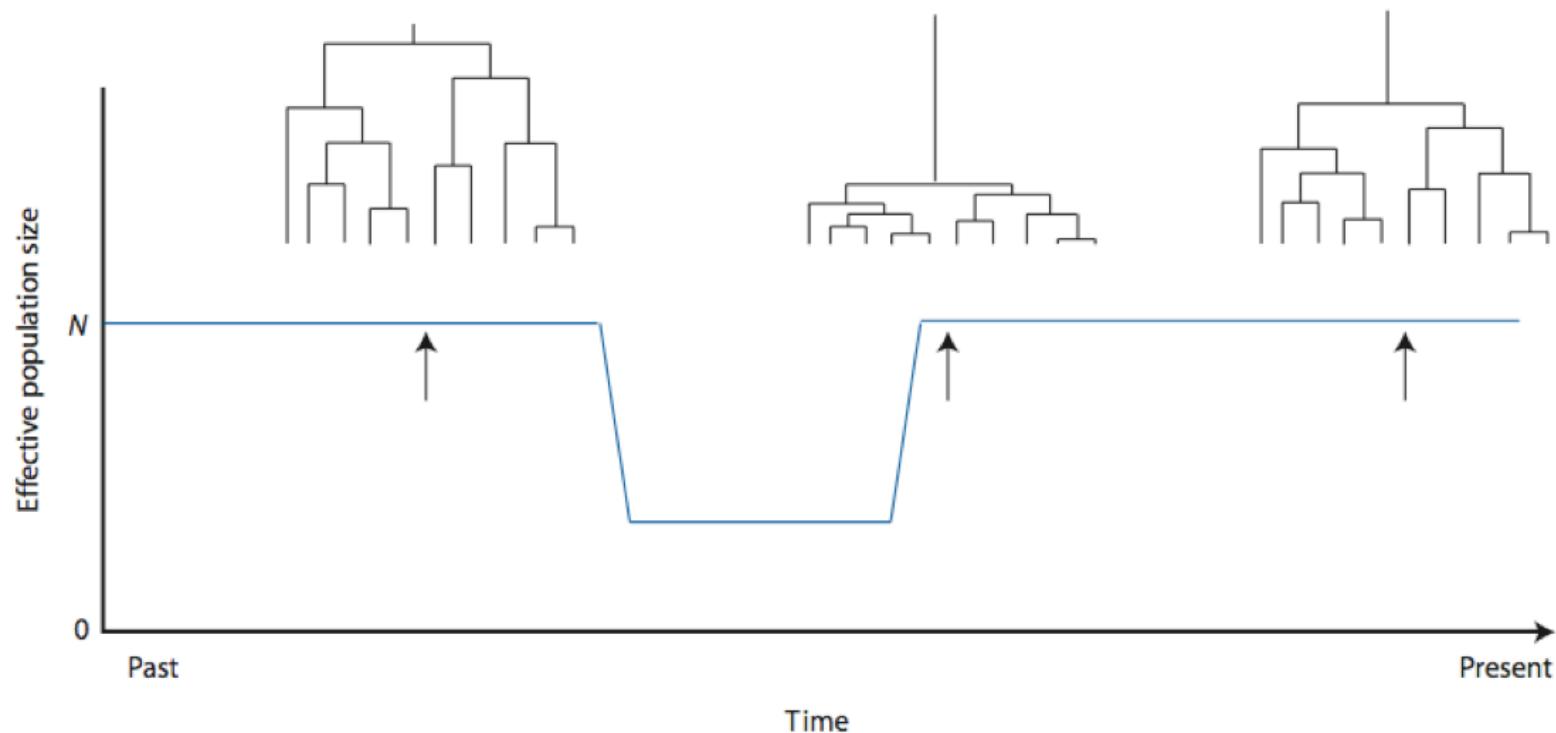
if we “sprinkle” mutations, then  $E(T_{total})$  becomes  $E(S)$  (# polymorphic sites)

$$E(T_{total}) = \mu * 4N \sum_{k=1}^{n-1} \frac{1}{k}$$



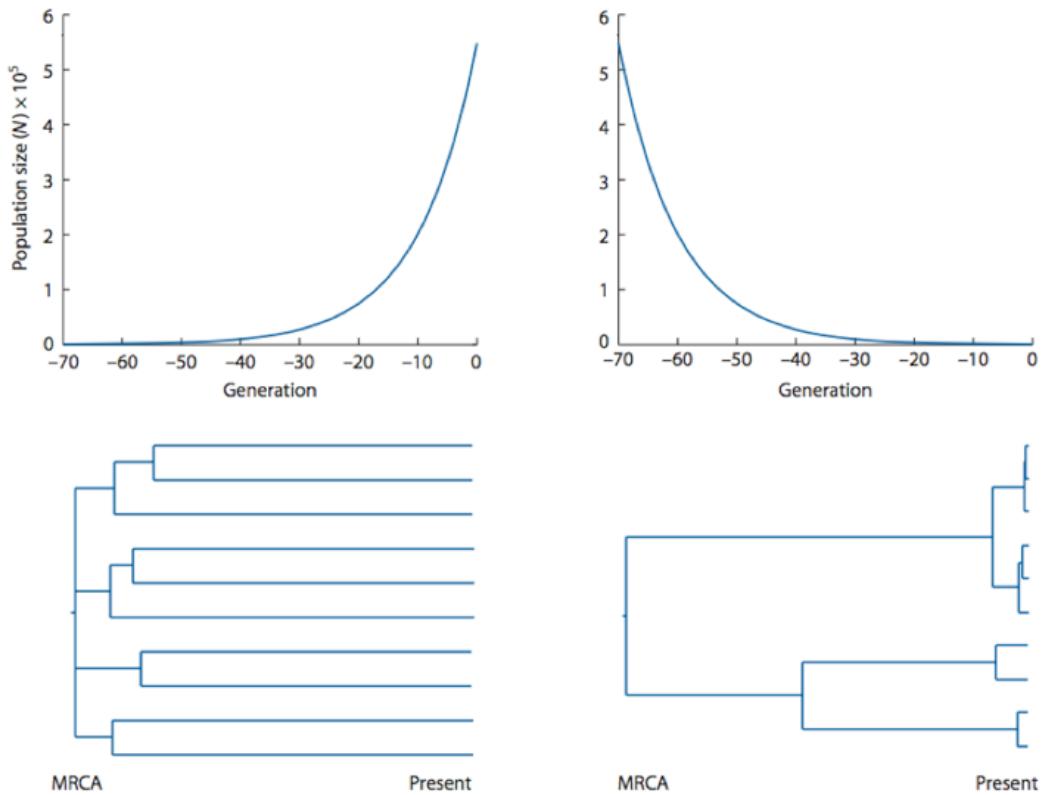
adding more lineages increases  $S$ , but less and less to the total length

# demographic events can change the shape of the tree



**Figure 3.28** The effects of a population bottleneck on gene genealogies. During the bottleneck the chance that two randomly sampled gene copies are derived from one copy in the previous generation  $\left(\frac{1}{2N_e}\right)$  increases. This can also be thought of as a

# demographic events can change the shape of the tree



NOTE: Tree-shape determines pattern of variation in the population.

Population growth (left) will create many alleles that are carried by one individual. Population declines (right) will create many loci carried by 1 or more individuals.

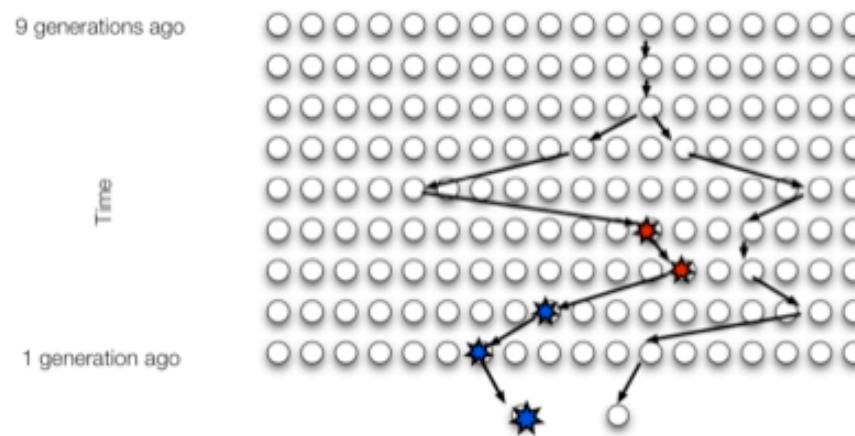
# review

Why do we find:

- The coalescent to be faster in small populations than large ones?
- The coalescent to be much faster when  $k$  is large then when small?

# review: expected number of differences between a random pair of sequences

Differences must arise due to mutation before the coalescent event.



NOTE: We'll assume every mutation gives rise to an observable difference (i.e. infinite sites model)

## Example

Sequence 1: TG

Sequence 2: AA

# review: expected number of differences between a random pair of sequences

- Differences must arise due to mutation.
- What is the average amount of time before the coalescent event?

# review: expected number of differences between a random pair of sequences

- Differences must arise due to mutation.
- What is the average amount of time before the coalescent event?
  - Answer:  $2N$  generations

# review: expected number of differences between a random pair of sequences

- Differences must arise due to mutation.
- What is the average amount of time before the coalescent event?
  - Answer:  $2N$  generations
- What is the rate of mutation while there are two lineages?

# review: expected number of differences between a random pair of sequences

- Differences must arise due to mutation.
- What is the average amount of time before the coalescent event?
  - Answer:  $2N$  generations
- What is the rate of mutation while there are two lineages?
  - Answer:  $2\mu$  mutations per generation.

# review: expected number of differences between a random pair of sequences

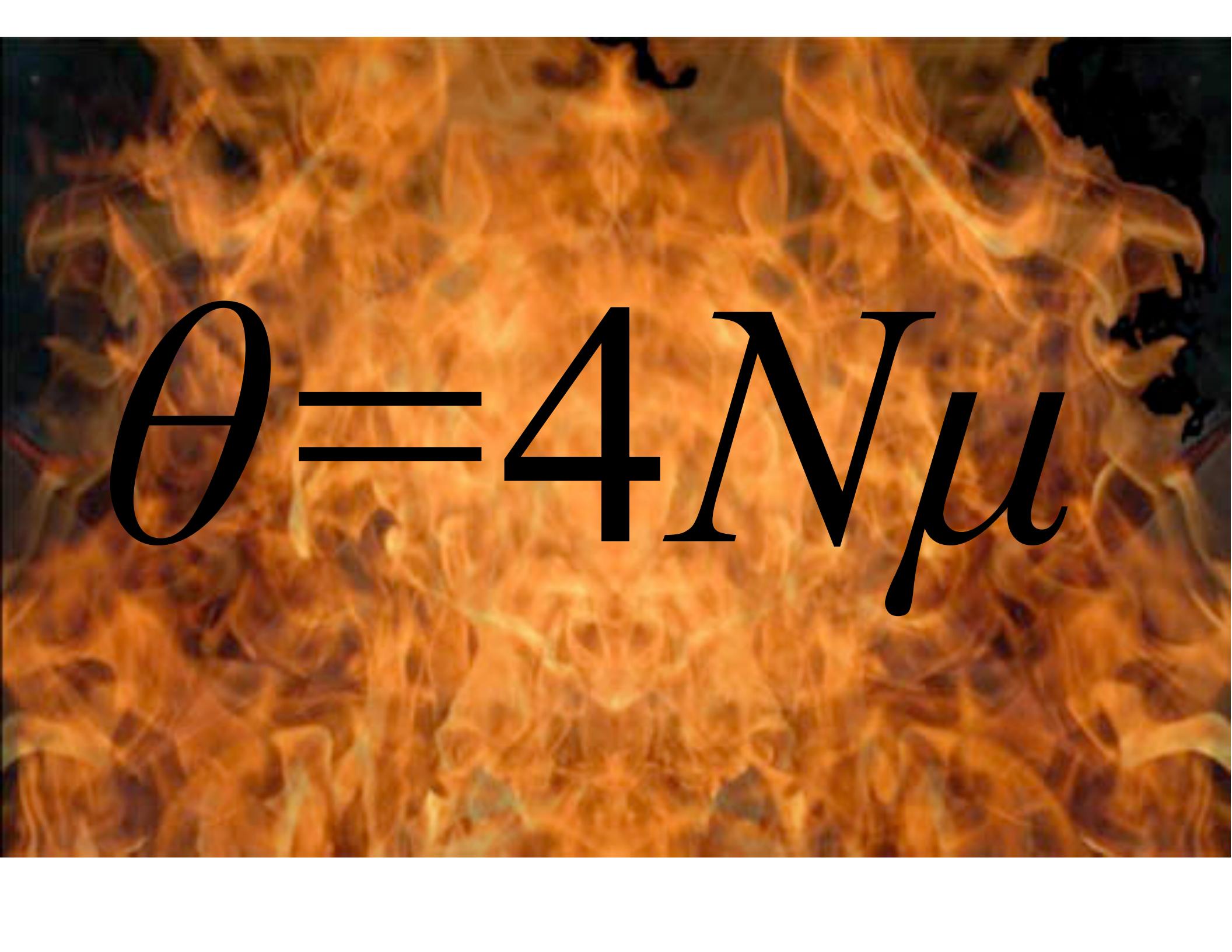
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## Definition

$\theta = 4N\mu$ : sometimes called the “fundamental population genetic parameter”

The background of the image is a close-up photograph of intense orange and yellow flames, suggesting a fire or a furnace. The flames are highly textured and dynamic, filling most of the frame.
$$\theta = 4\lambda\mu$$

# review: expected # of SNPs

Seq1 ACTAAAGGCG

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Seq3 ACGAAATGCG

Seq4 ACTAAAGGCG

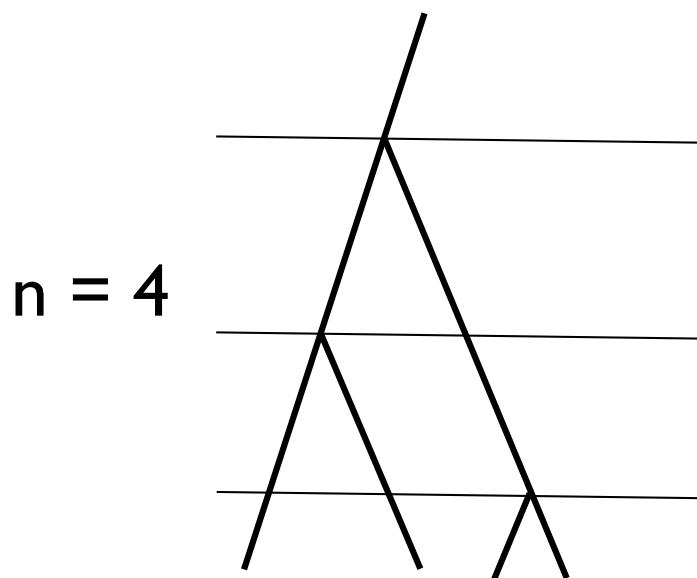
---\*----\*

2 segregating sites out of 10.

## Question

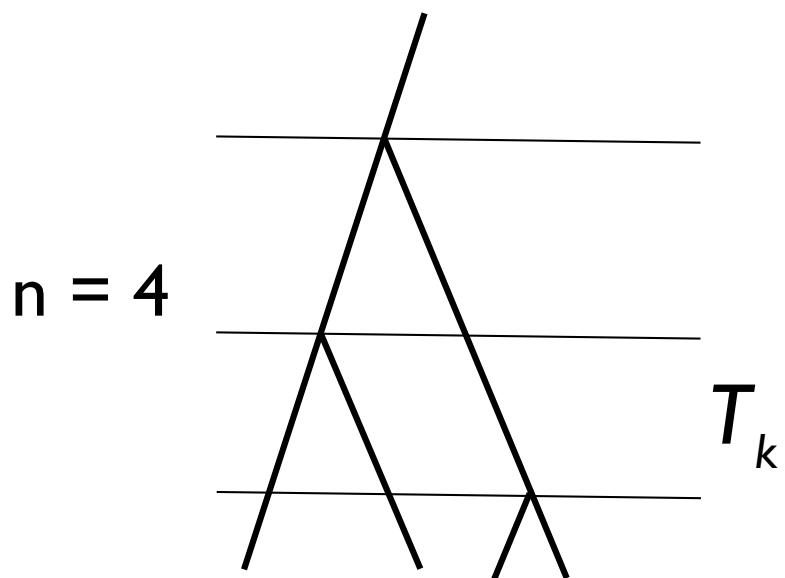
What is the expected number of segregating sites in the sample?

- We can divide the tree up into  $n - 1$  segments.

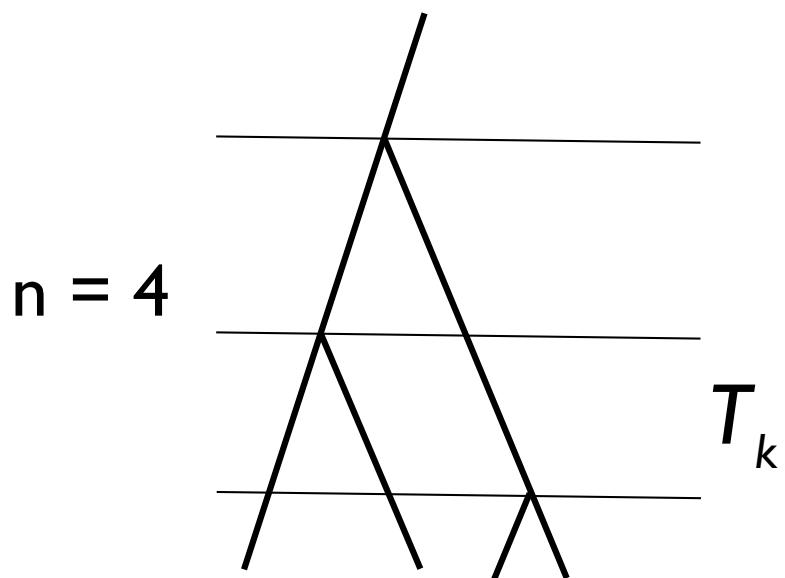


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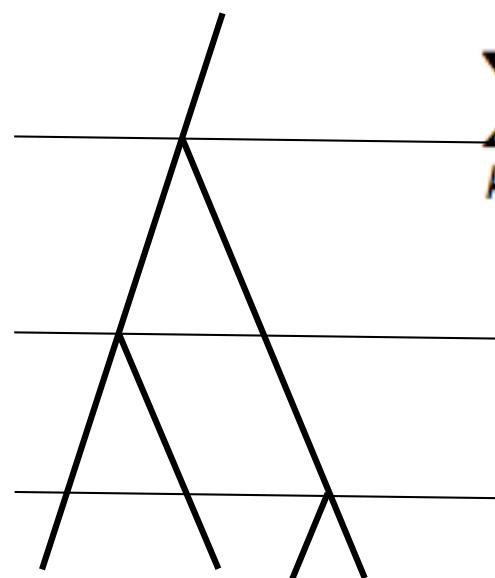
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$$E[T_k] = \mu k \text{ (ie } \mu^* 3)$$

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$$= \mu \sum_{k=2}^n k \frac{4N}{k(k-1)} \tag{1}$$

$$= 4N\mu \sum_{k=2}^n \frac{1}{k-1} \tag{2}$$

$$= 4N\mu \sum_{k=1}^{n-1} \frac{1}{k} \tag{3}$$

# Summary of our coalescent-derived results

- Mean number of differences between a pair of sequences =  $\theta$
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If  $N = 10000$  and  $\mu = 2.5 \times 10^{-8}$  per site and we consider a sequence of length 1000 bp, then  $\theta = 4 \times 10^4 \times 2.5 \times 10^{-8} \times 10^3 = 1$ .

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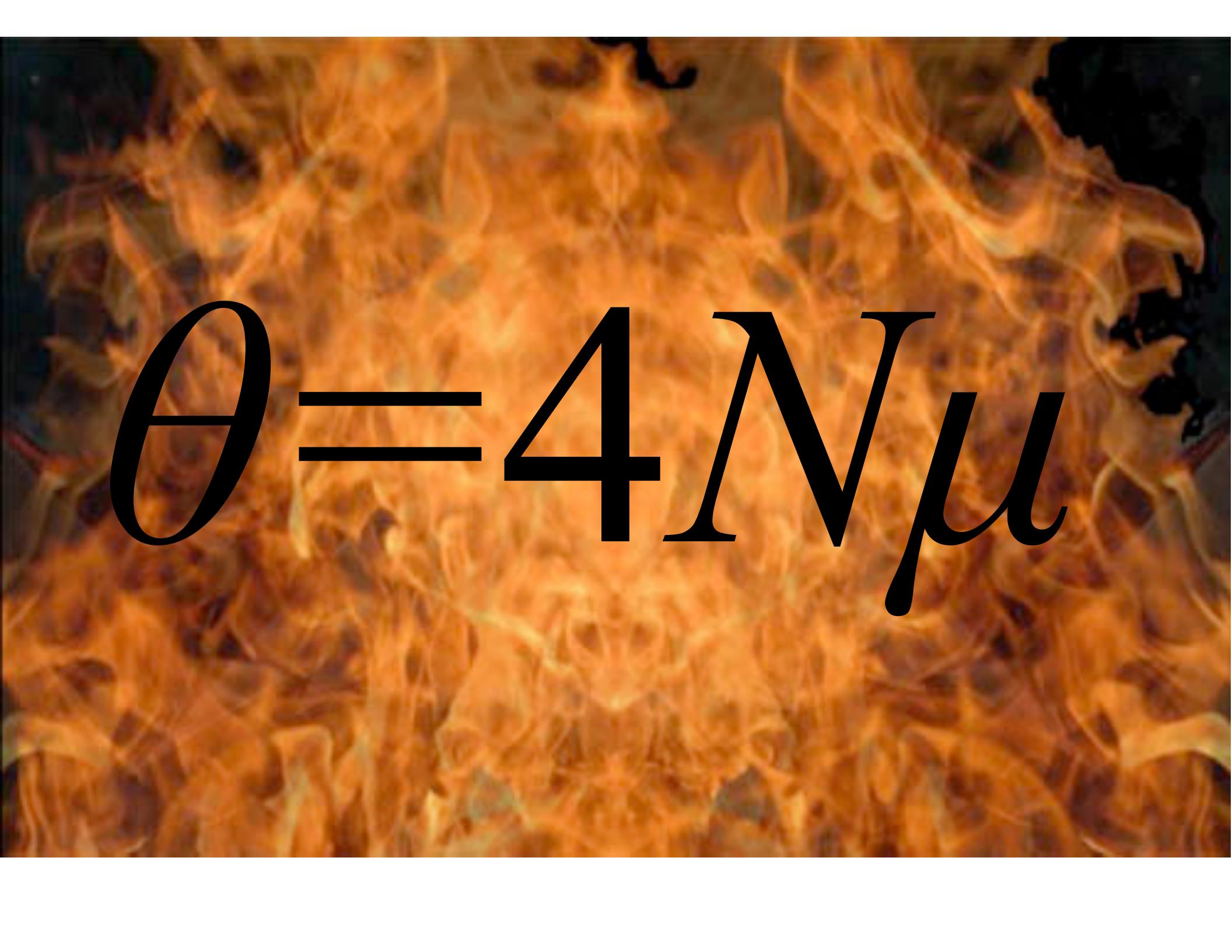
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## NOTE

The parameter  $\theta = 4N\mu$  came up in each of our three results.

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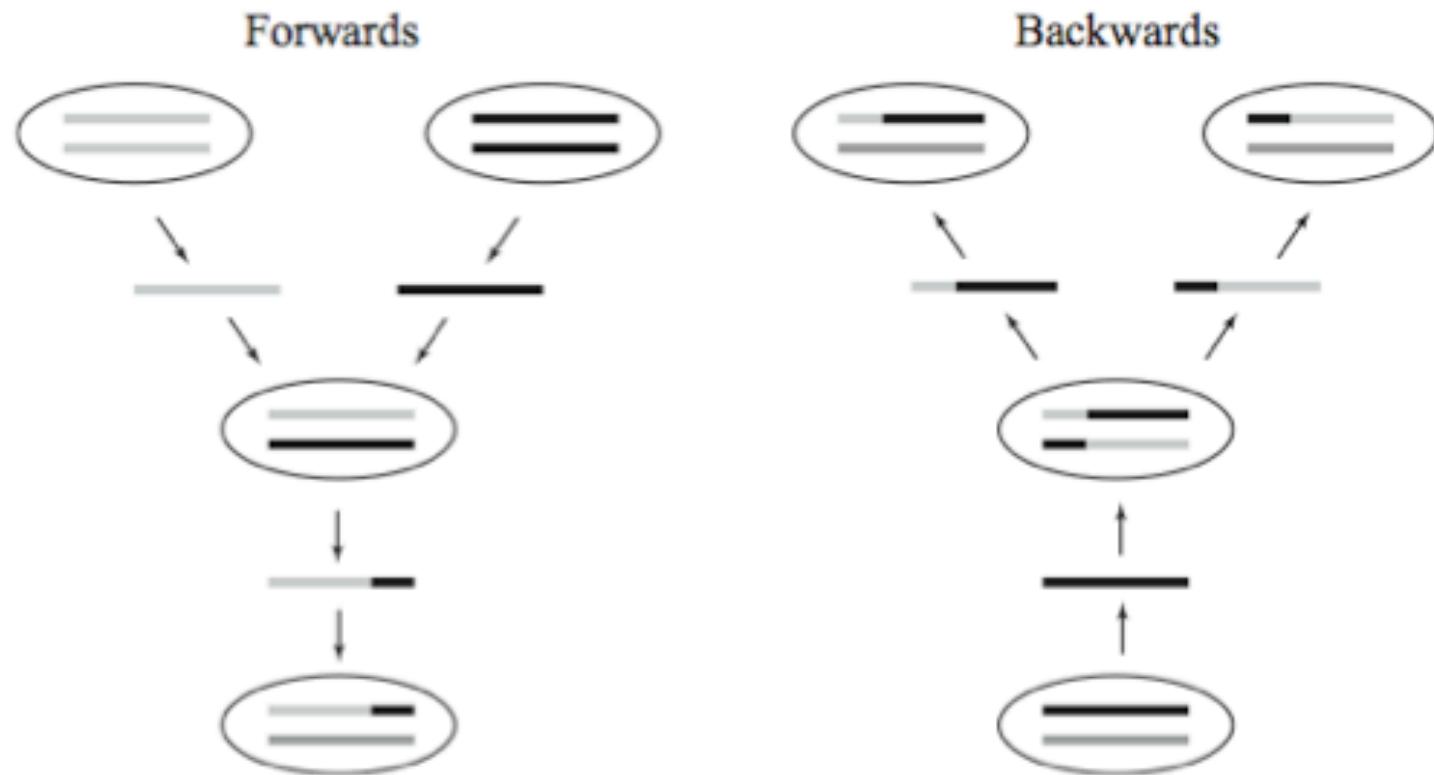
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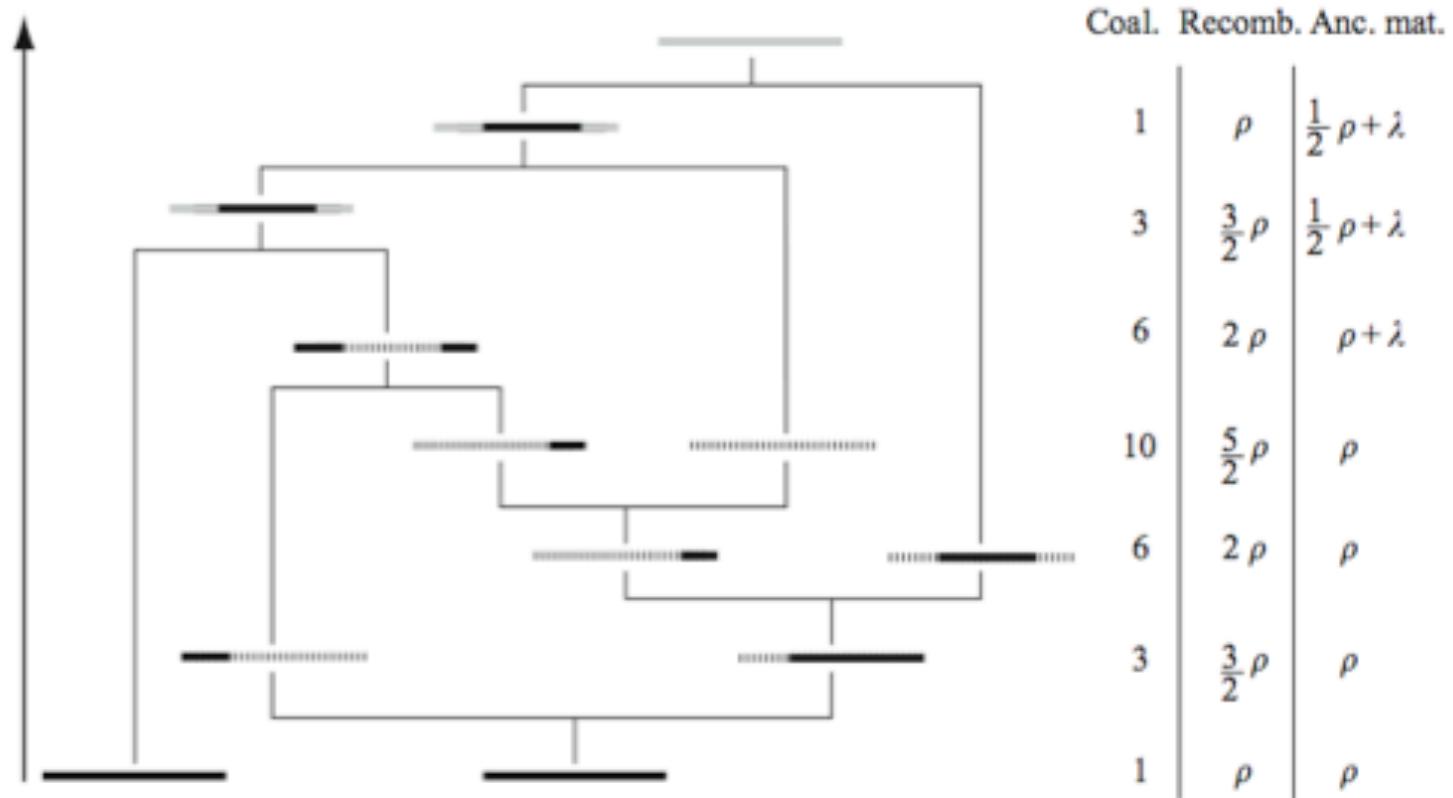
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- **Recombination:** Adds a complication - genes break apart at a rate of  $kr$  where  $r$  is the recombination rate.



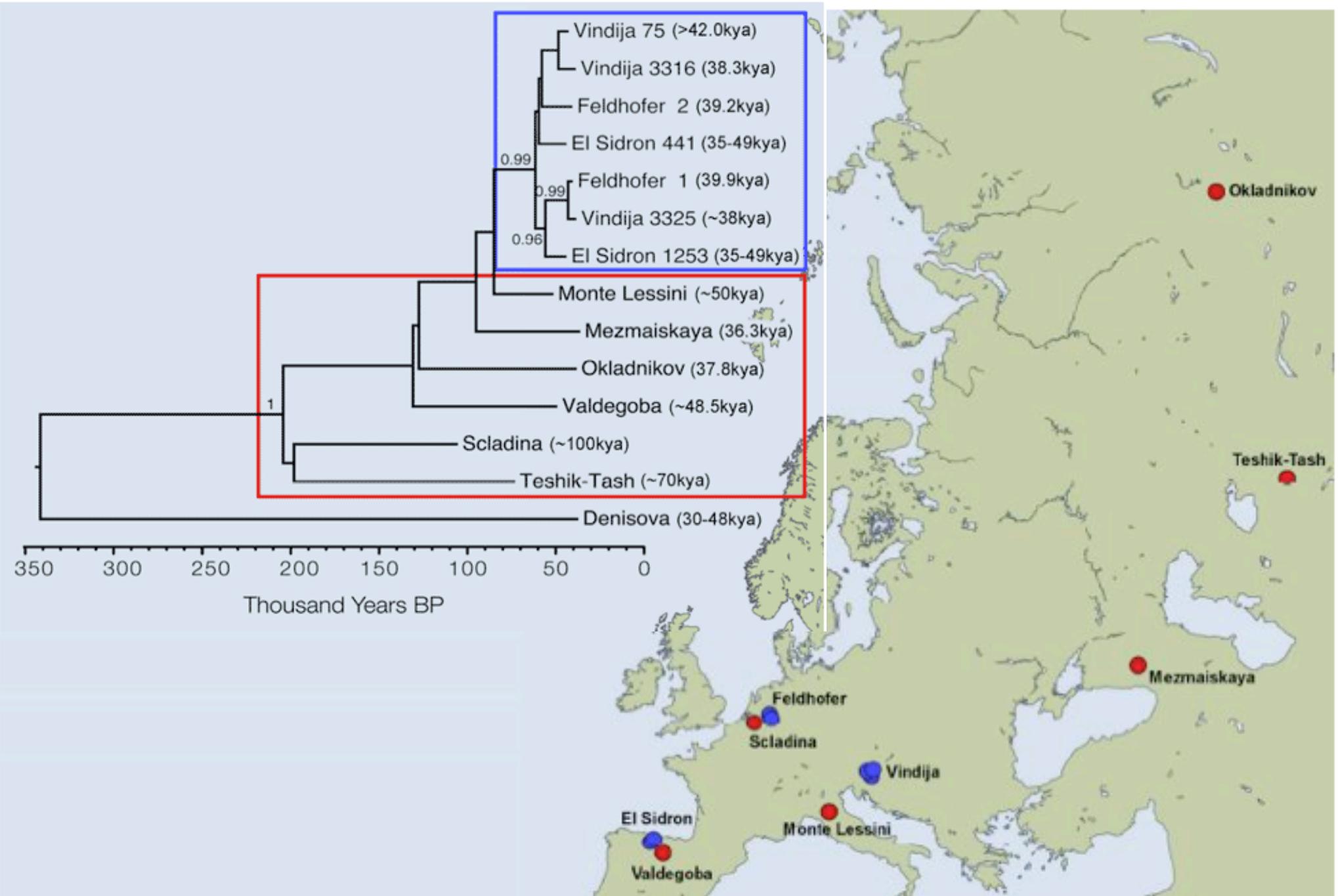
Recombination induces splits in an ancestral line as we look backwards in time.



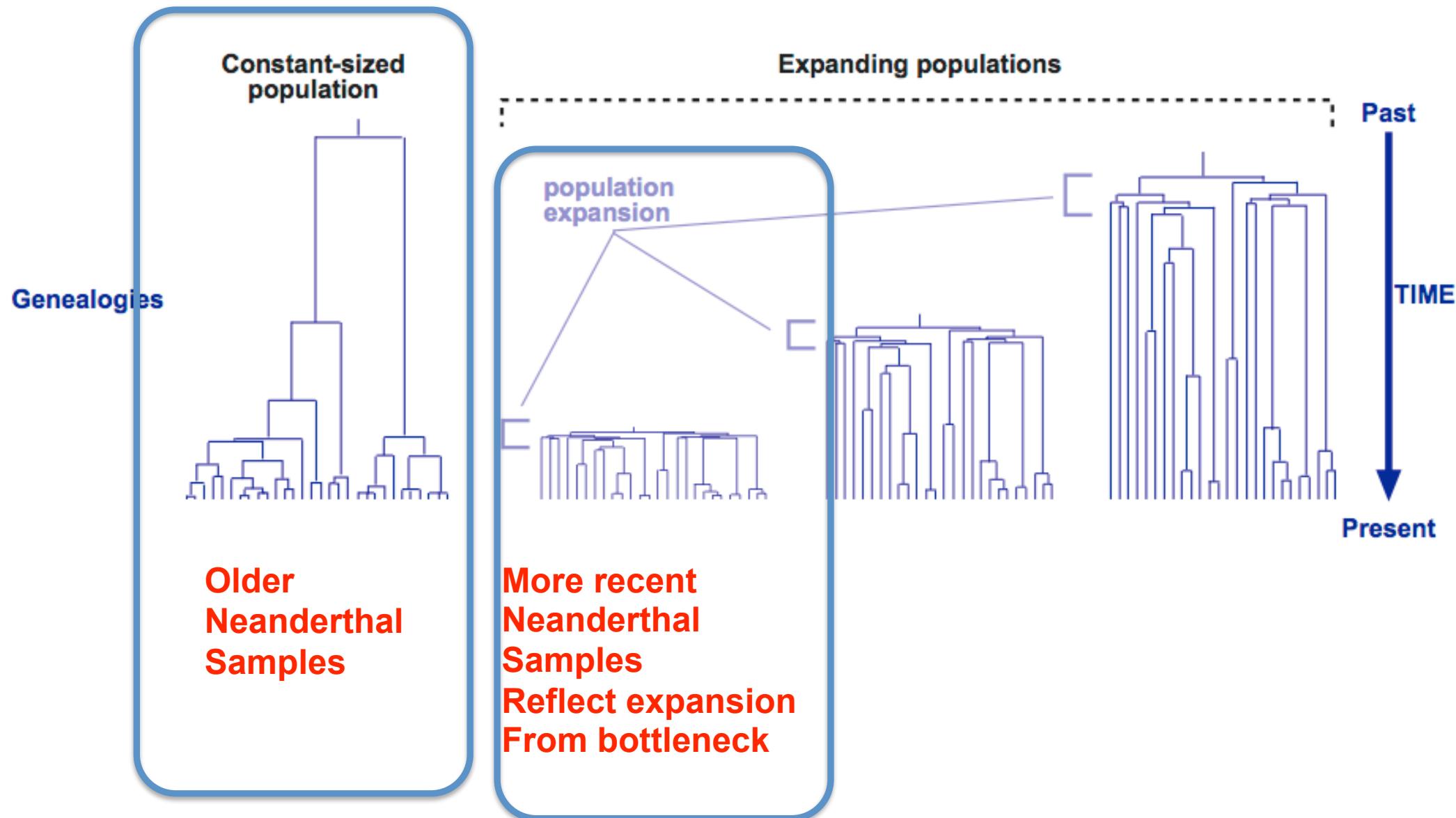
An example of a coalescent tree with recombination.

Note: We can also view this as a series of trees arrayed along the chromosome.

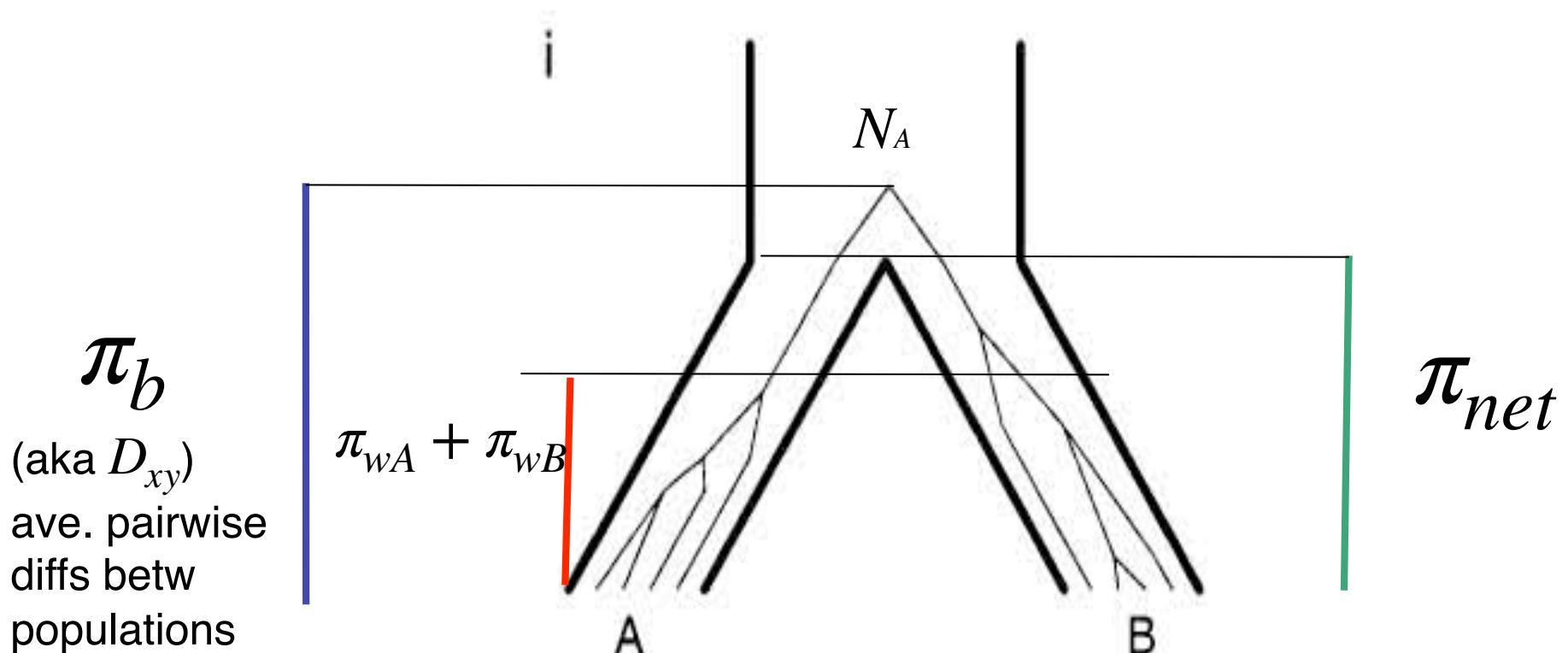
# Neandertal population structure



# Shape of gene tree reflects different histories



# Estimating Divergence time with Nei and Li's $\pi$ -net



$$\pi_{net} = \pi_b - (\pi_{wA} + \pi_{wB})/2$$

# Simulation Assignment

Moving away from the forward time SliM (for now), here we'll focus again on msPrime, a state of the art backwards coalescent simulator

go to <https://github.com/DRL/SMBE-SGE-2019>

go back to “Session1”

2.Introduction\_to\_msprime.ipynb

# Simulation Exercises

go to <https://github.com/DRL/SMBE-SGE-2019>

go back to “Session1”

2.Introduction to msprime.ipynb

go through the steps up through ***2.4 Mutation***

Heavily Recommended:

1. instead of running the msprime tutorial on Binder-launched notebook (which was great/easy yet unstable), run it on your own local jupyter notebook.

a. instructions for windows

- 1) Download and install conda for windows from here (probably want the python3.7 64bit version).
- 2) From the Start menu, open the Anaconda Prompt
- 3) `conda install jupyter -y`
- 4) `jupyter notebook`

b. instructions for mac:

<https://github.com/geohackweek/ghw2017/wiki/Running-Jupyter-Notebooks-Locally>

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go through the steps up through **2.4 Mutation**

turn can mutation off by “recombination\_rate = 0”

simulate with different sample sizes n=2, n=5, n=10, n=15.  
10 iterations each sample size (by changing the seed each time)  
for a total of 40 simulations

For each of the 4 sample sizes, calculate

1.  $\pi$  (average pairwise differences)

use the “ts.diversity()” command after simulating data

2. Watterson’s corrected number of polymorphic sites ( $S$ )

$$\theta_W = S / \sum_{k=1}^{n-1} \frac{1}{k}$$

if you want to shortcut  $\theta_W$  calculations in R window, you can use

$$S/(1/15+1/14+1/13+1/12+1/11+1/10+1/9+1/8+1/7+1/6+1/5+1/4+1/3+1/2)$$

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3. Plot these 8 histograms out (4 sample sizes & 2 sumstats)

4. turn recombination back on ("recombination\_rate = 10e-4"), repeat 40 simulations and re-plot. Anything change? Any reason why?

## Next Week Marcelo and PipeMaster

preview PipeMaster tutorial

[https://github.com/compphylo/compphylo.github.io/blob/master/Oslo2019/PM\\_files/Dermatonotus\\_example.md](https://github.com/compphylo/compphylo.github.io/blob/master/Oslo2019/PM_files/Dermatonotus_example.md)



