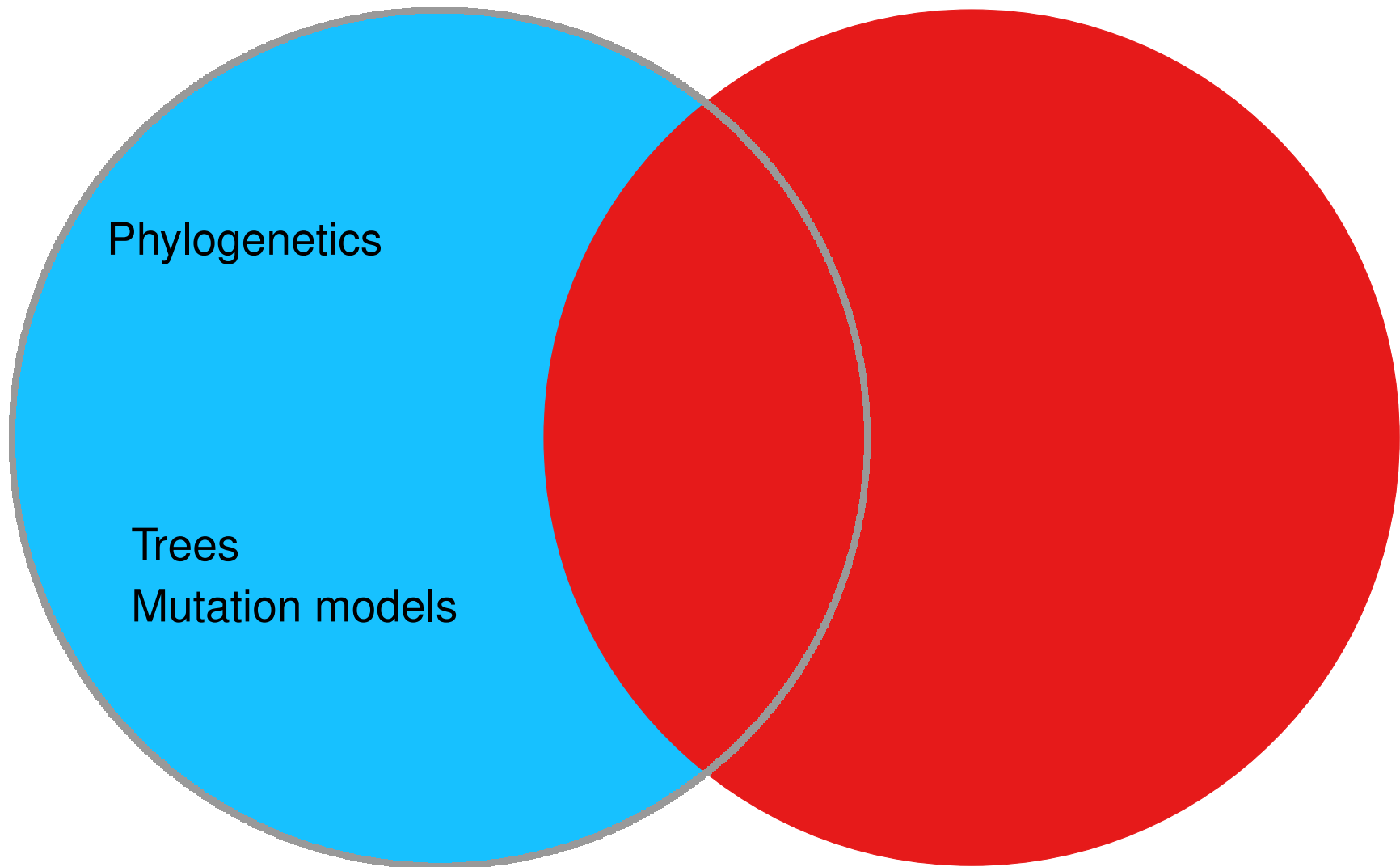


A photograph of a red cardinal perched on a tree branch. The tree has a thick, textured trunk and several bare, thin branches extending outwards. The background is a pale, overcast sky. The cardinal is facing right, with its characteristic red plumage and crest clearly visible.

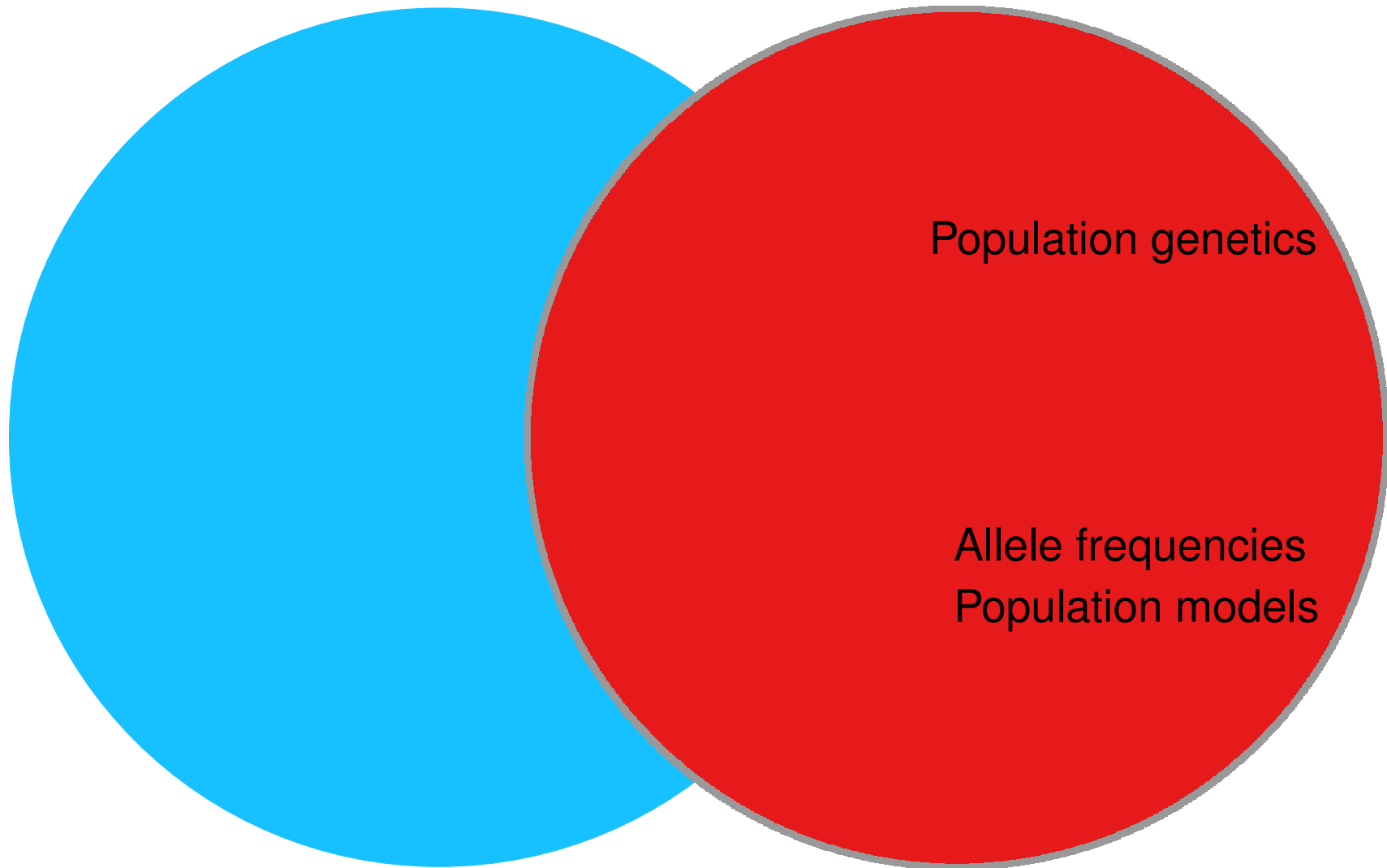
Population genetics Inference using trees of individuals

**Peter Beerli
Florida State University
#MolEvol2016 MBL Woods Hole**

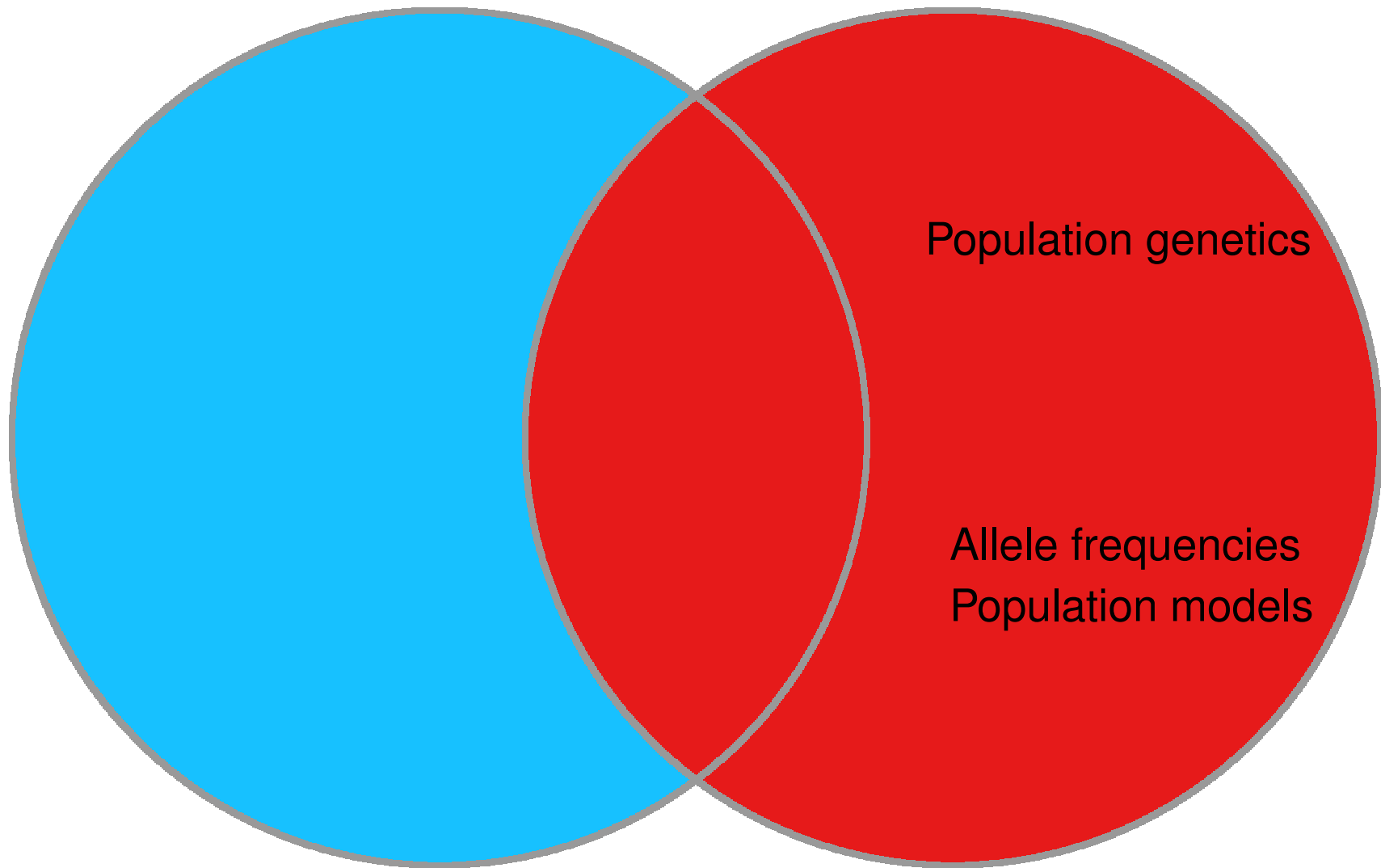
The big overview



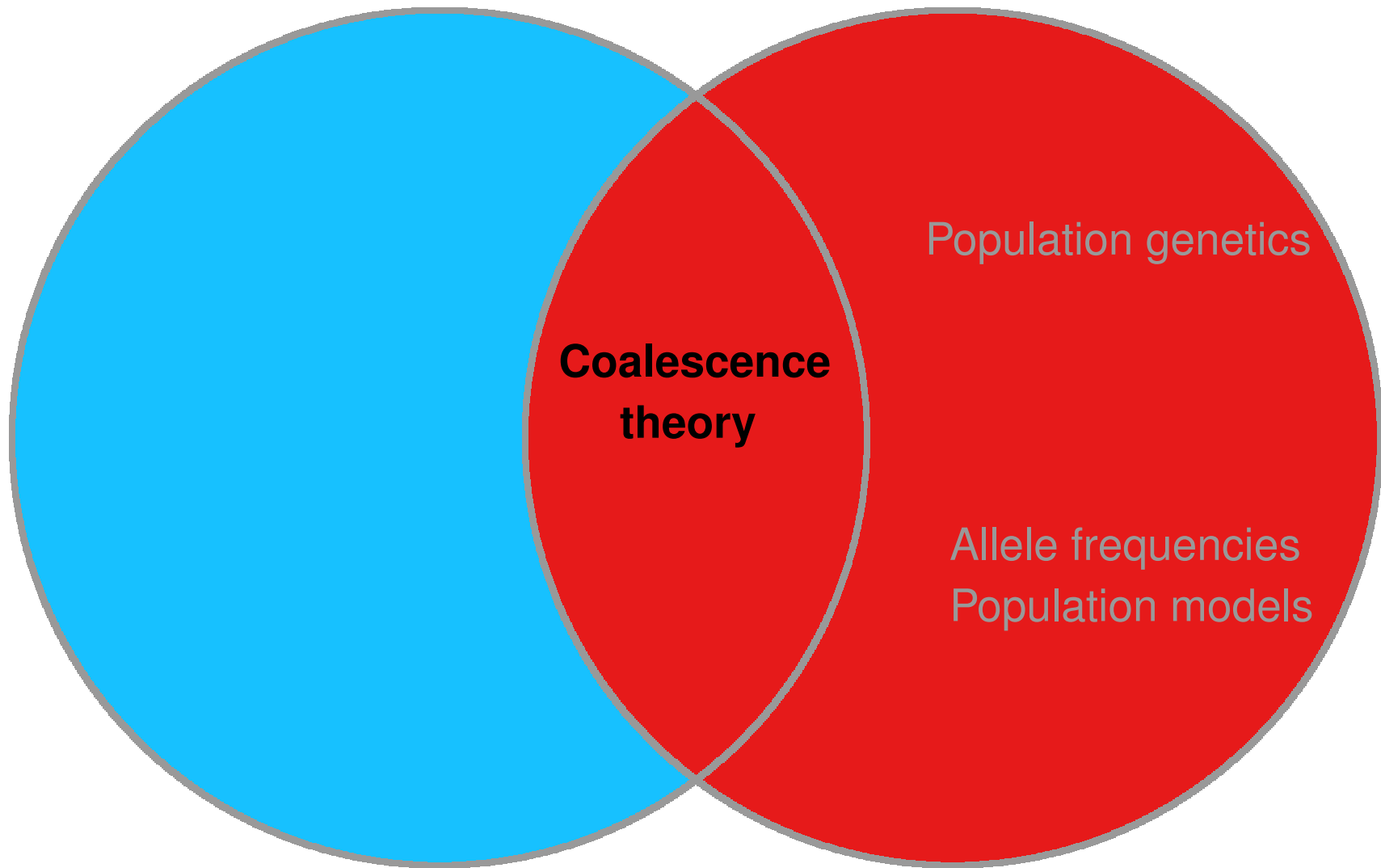
The big overview



The big overview



The big overview



Coalescence theory as a tool for population genetics

co•a•lesce |,kōə'les|

verb [intrans.]

come together and form one mass or whole : *the puddles had **coalesced into** shallow streams | the separate details coalesce to form a single body of scientific thought.*

- [trans.] combine (elements) in a mass or whole : *to help coalesce the community, they established an office.*

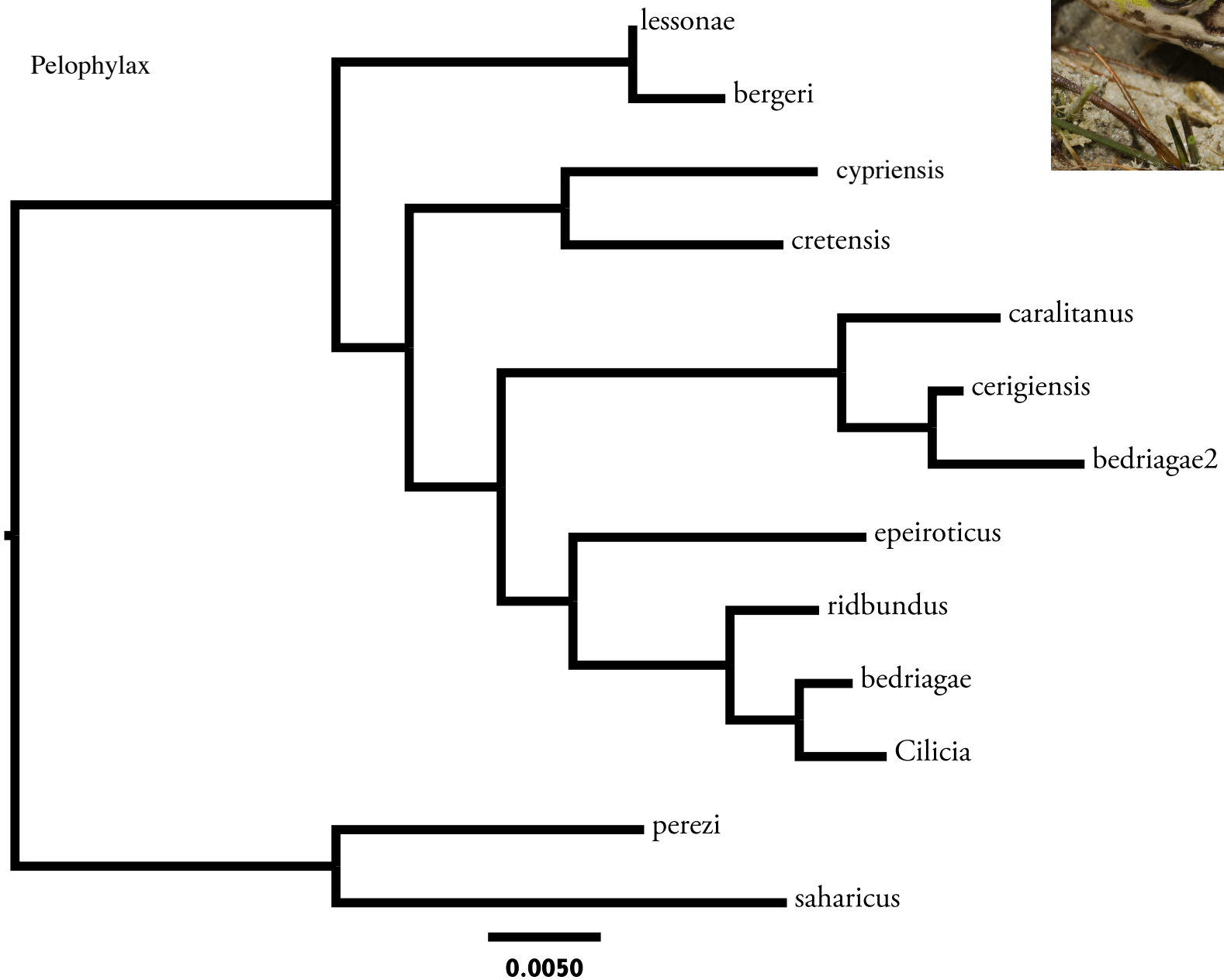
DERIVATIVES

co•a•les•cence |-'lesəns| noun

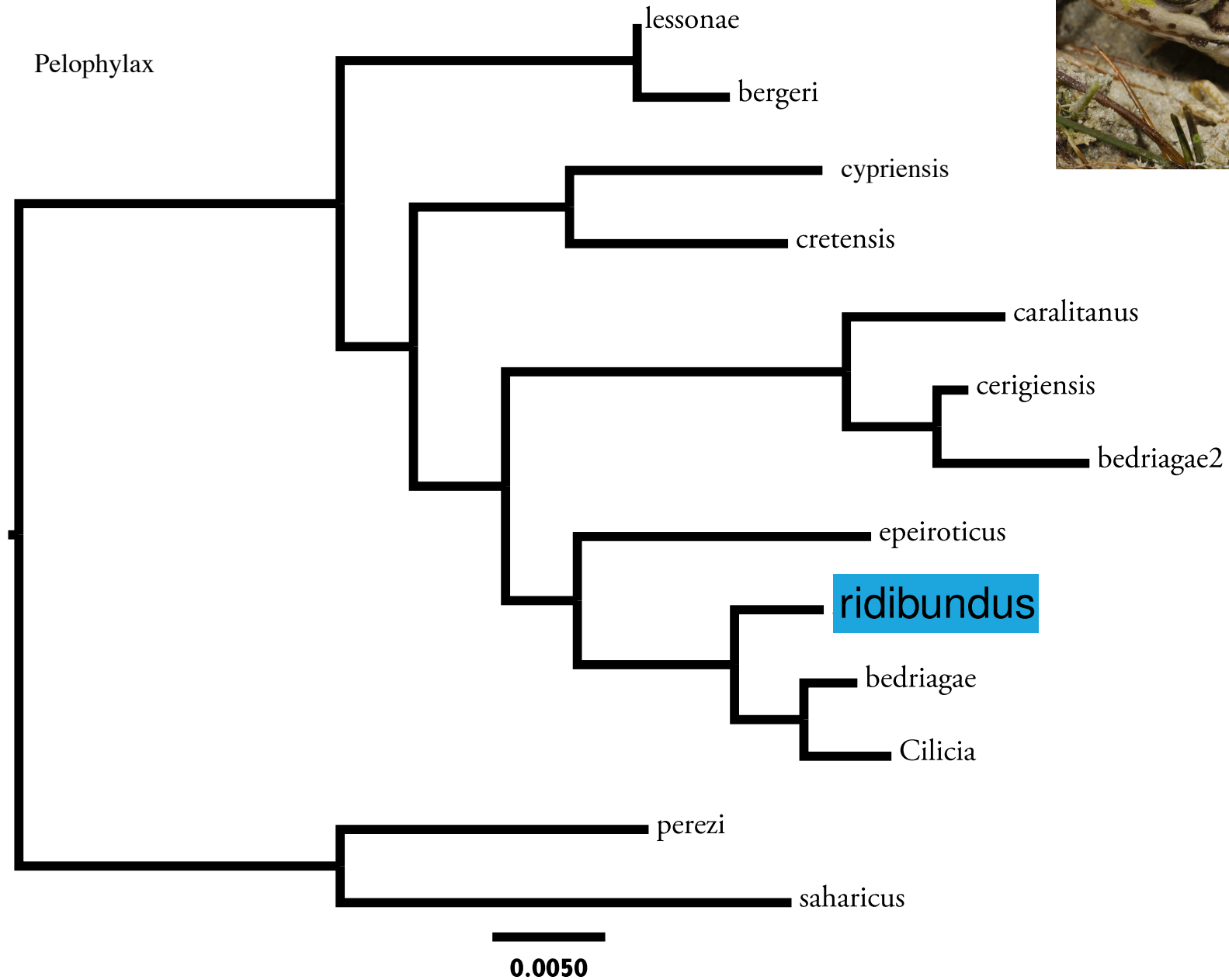
co•a•les•cent |-'lesənt| adjective

ORIGIN mid 16th cent. (in the sense [bring together, unite]): from Latin *coalescere*, from *co-* (from *cum* 'with') + *alescere* 'grow up' (from *alere* 'nourish').

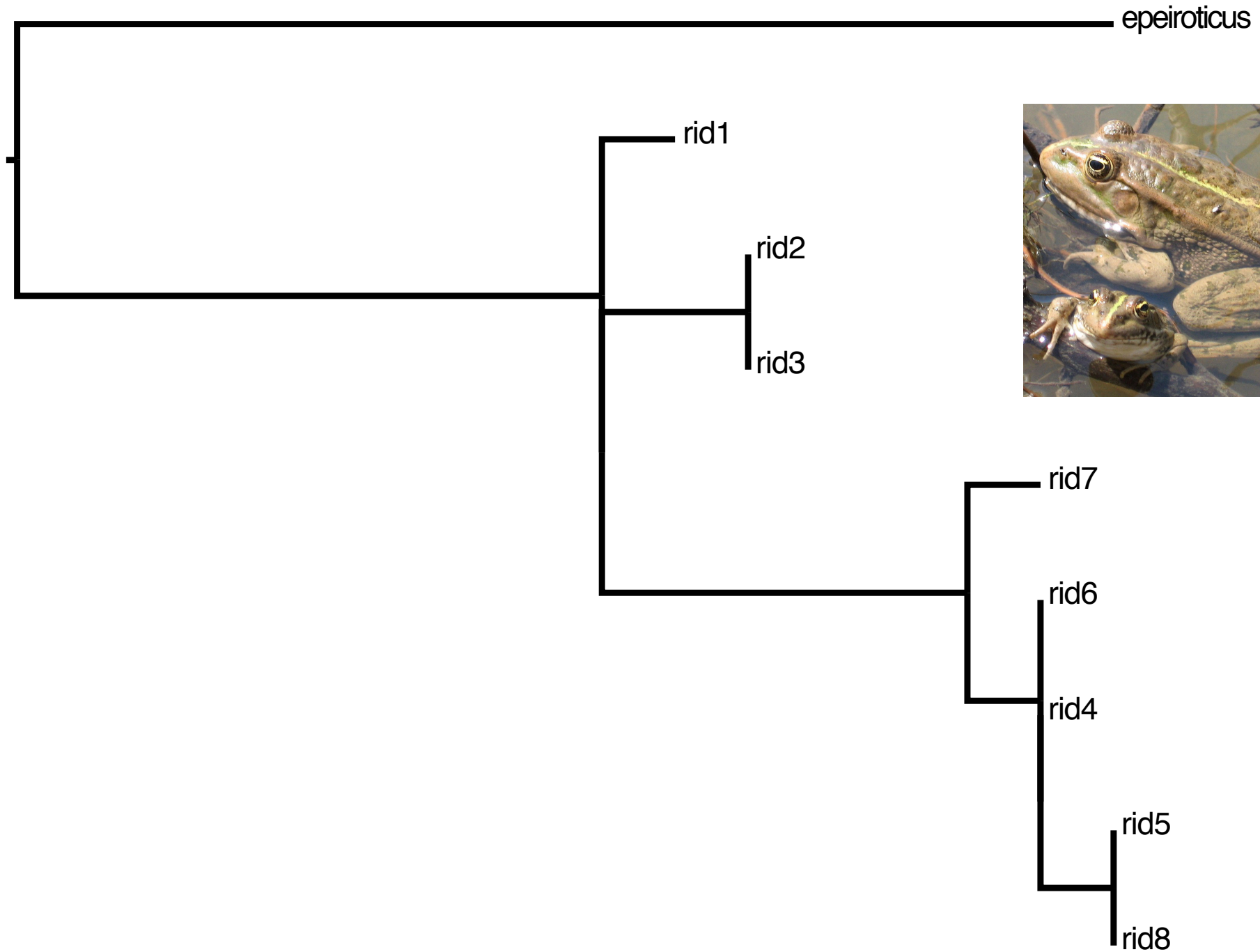
Species trees



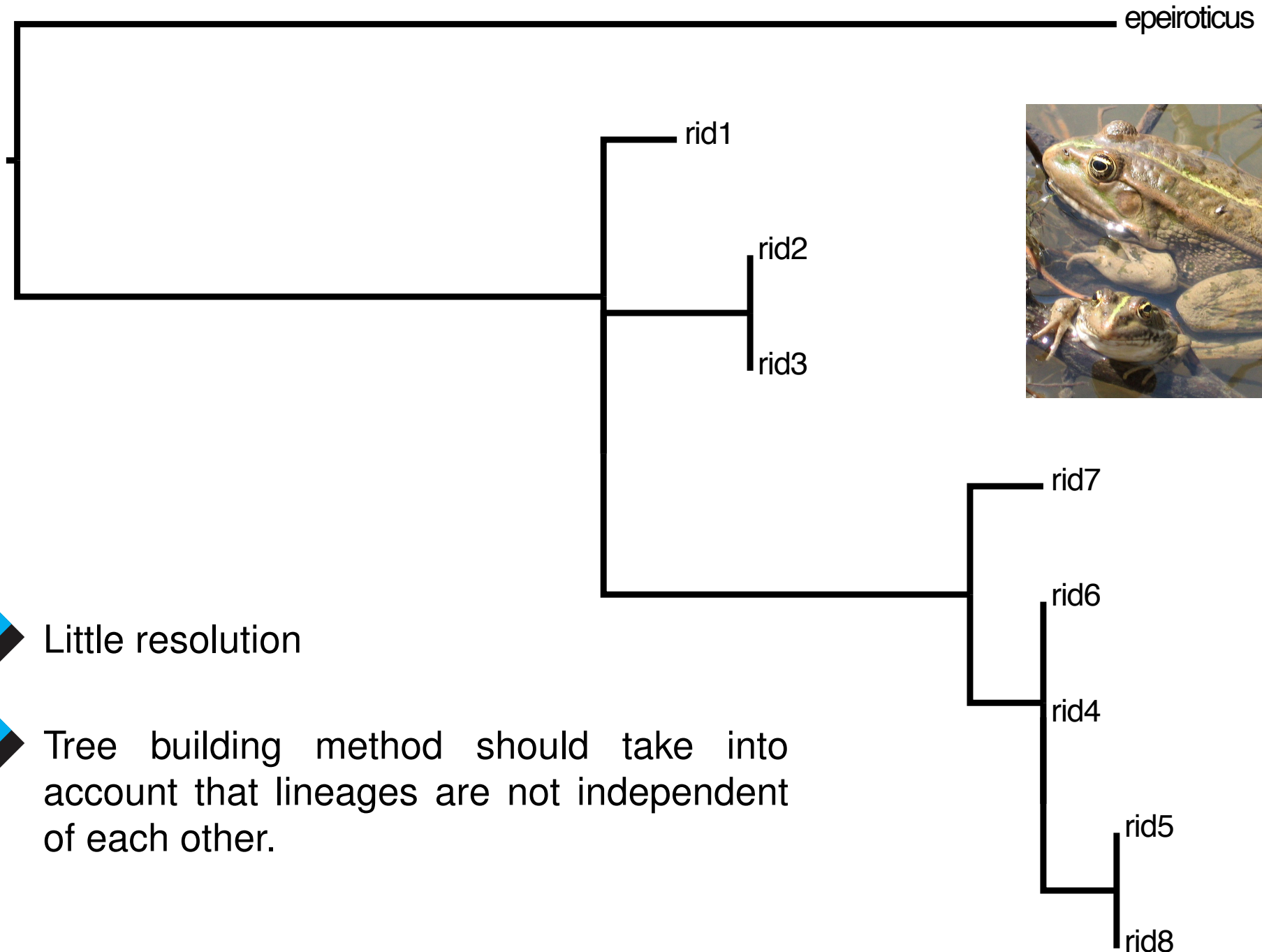
Species trees



Tree of individuals of same species

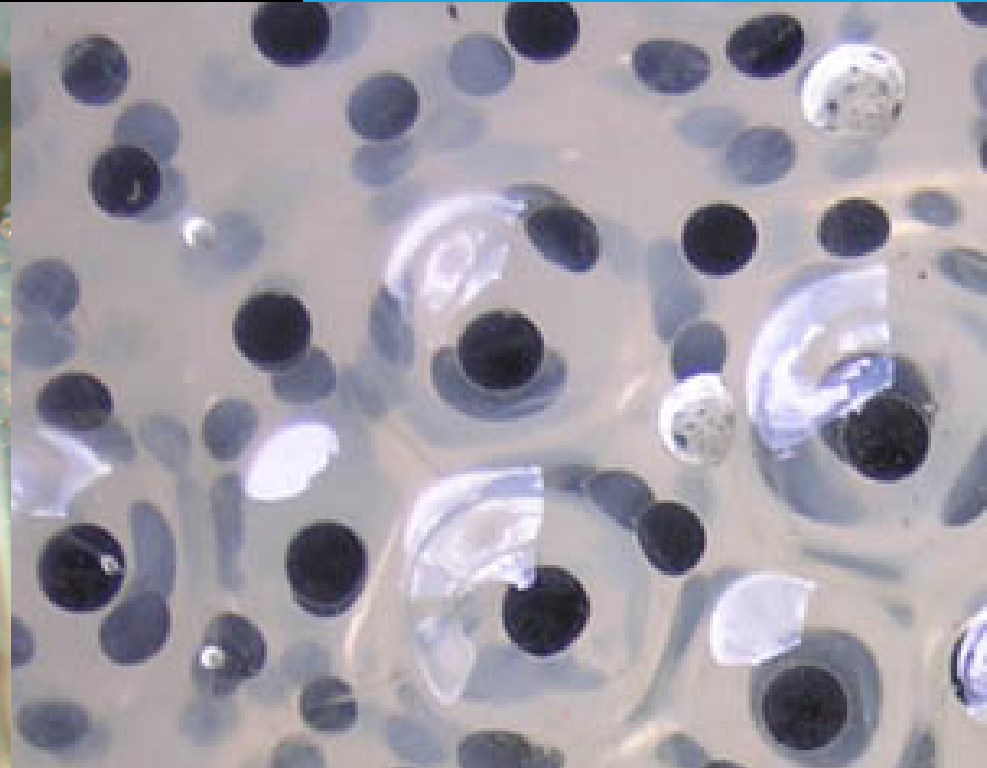


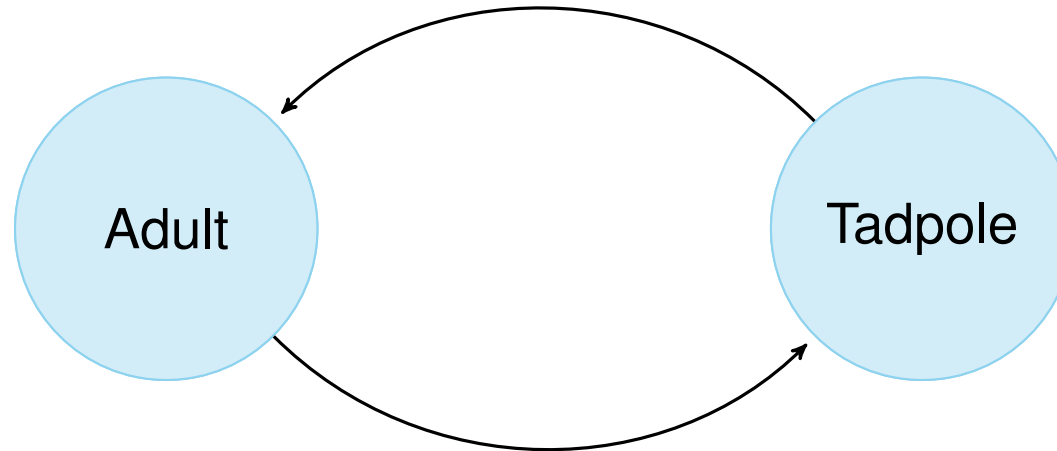
Tree of individuals of same species



◆ Little resolution

◆ Tree building method should take into account that lineages are not independent of each other.





Wright-Fisher population model

- ◆ All individuals live one generation and get replaced by their offspring
- ◆ All have same chance to reproduce, all are equally fit
- ◆ The number of individuals in the population is constant



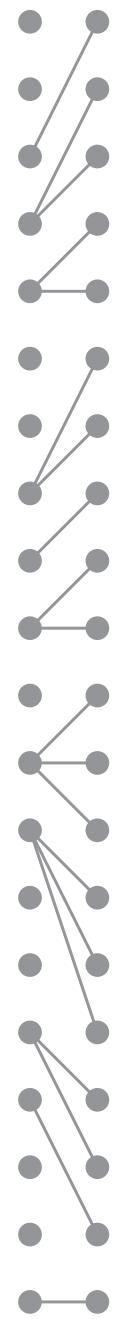
Past

Present



Past

Present

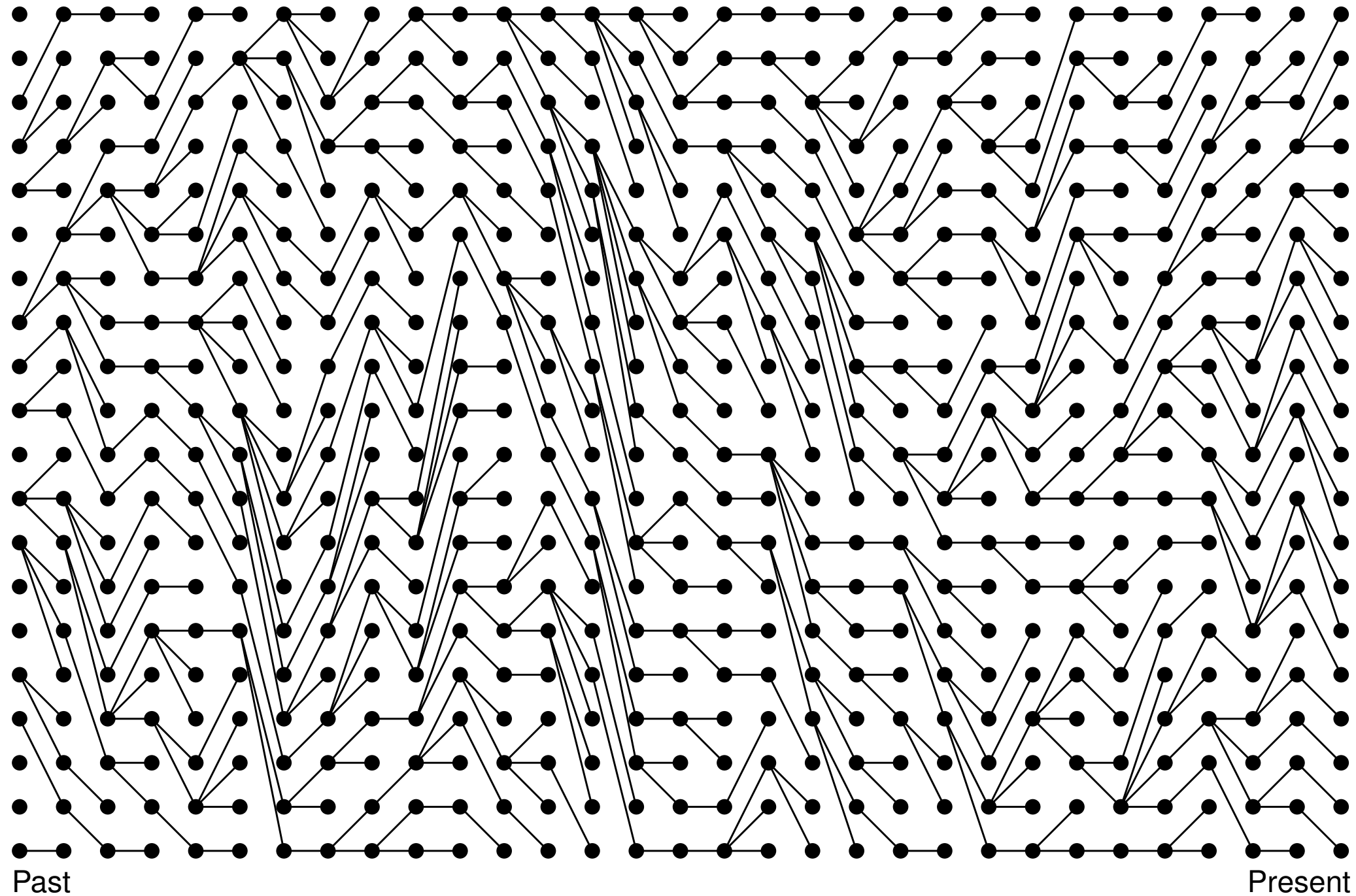


Past

Present

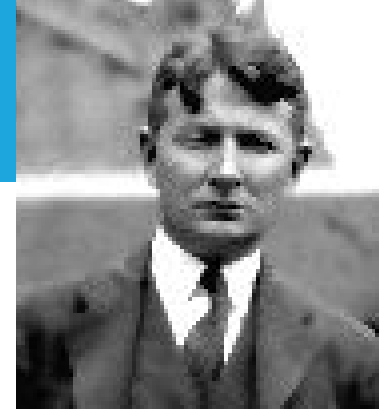
Population model

Wright-Fisher

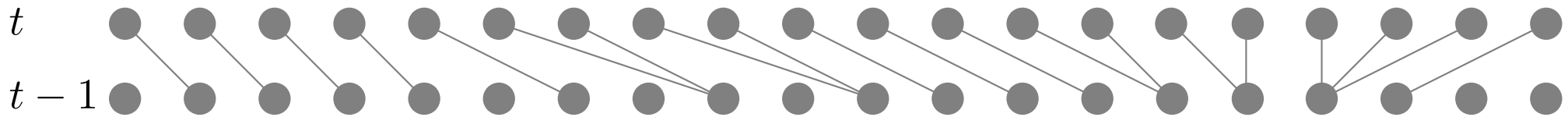


Population model

Wright

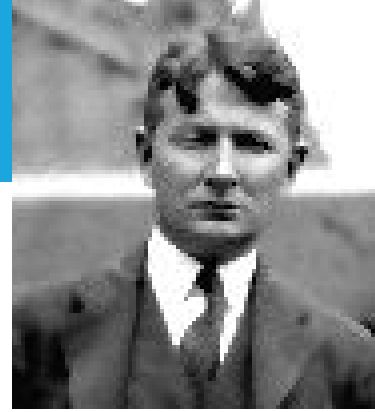


Sewall Wright evaluated the probability that two randomly chosen individuals in generation t have a common ancestor in generation $t - 1$. If we assume that there are $2N$ chromosomes then the probability of sharing a common ancestor in the last generation is

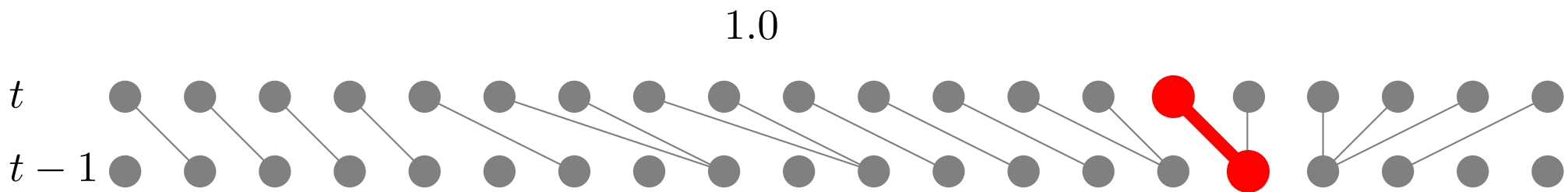


Population model

Wright

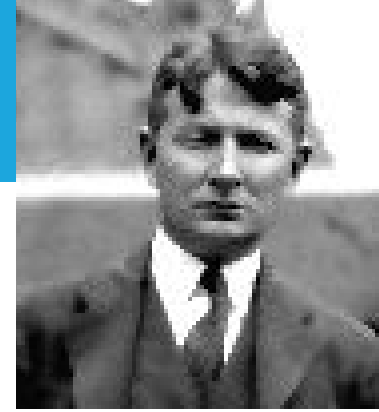


Sewall Wright evaluated the probability that two randomly chosen individuals in generation t have a common ancestor in generation $t - 1$. If we assume that there are $2N$ chromosomes then the probability of sharing a common ancestor in the last generation is

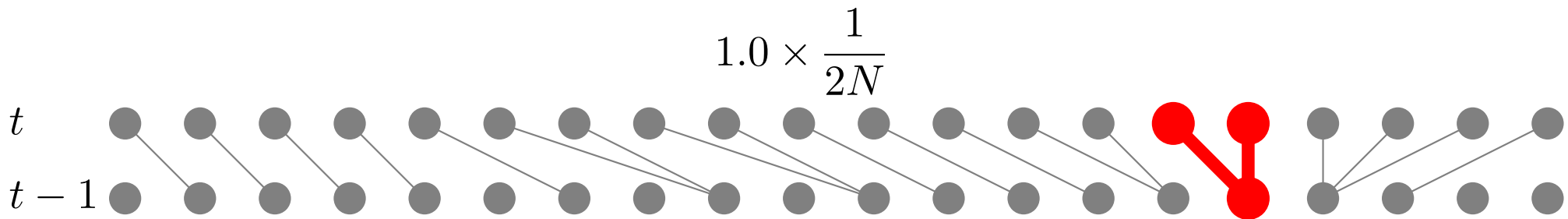


Population model

Wright

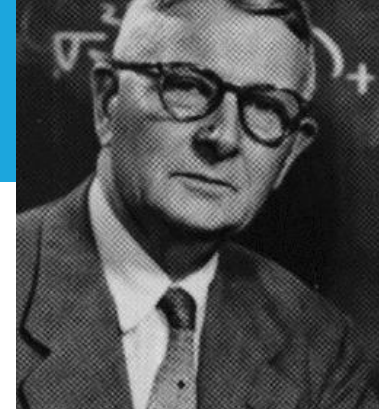


Sewall Wright evaluated the probability that two randomly chosen individuals in generation t have a common ancestor in generation $t - 1$. If we assume that there are $2N$ chromosomes then the probability of sharing a common ancestor in the last generation is

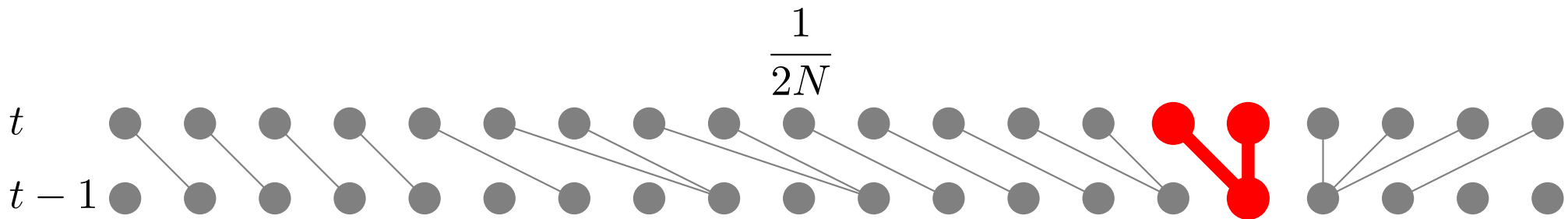


Population model

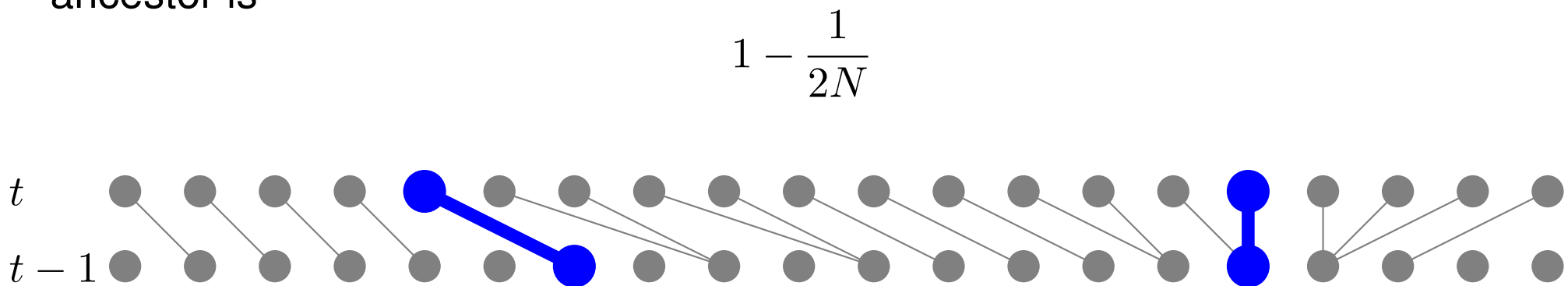
Wright



Sewall Wright evaluated the probability that two randomly chosen individuals in generation t have a common ancestor in generation $t - 1$. If we assume that there are $2N$ chromosomes then the probability of sharing a common ancestor in last generation is



The probability that two randomly picked chromosome do not have a common ancestor is





If we know the genealogy of the two individuals then we can calculate the probability as

$$P(\tau|N) = \left(1 - \frac{1}{2N}\right)^\tau \left(\frac{1}{2N}\right)$$

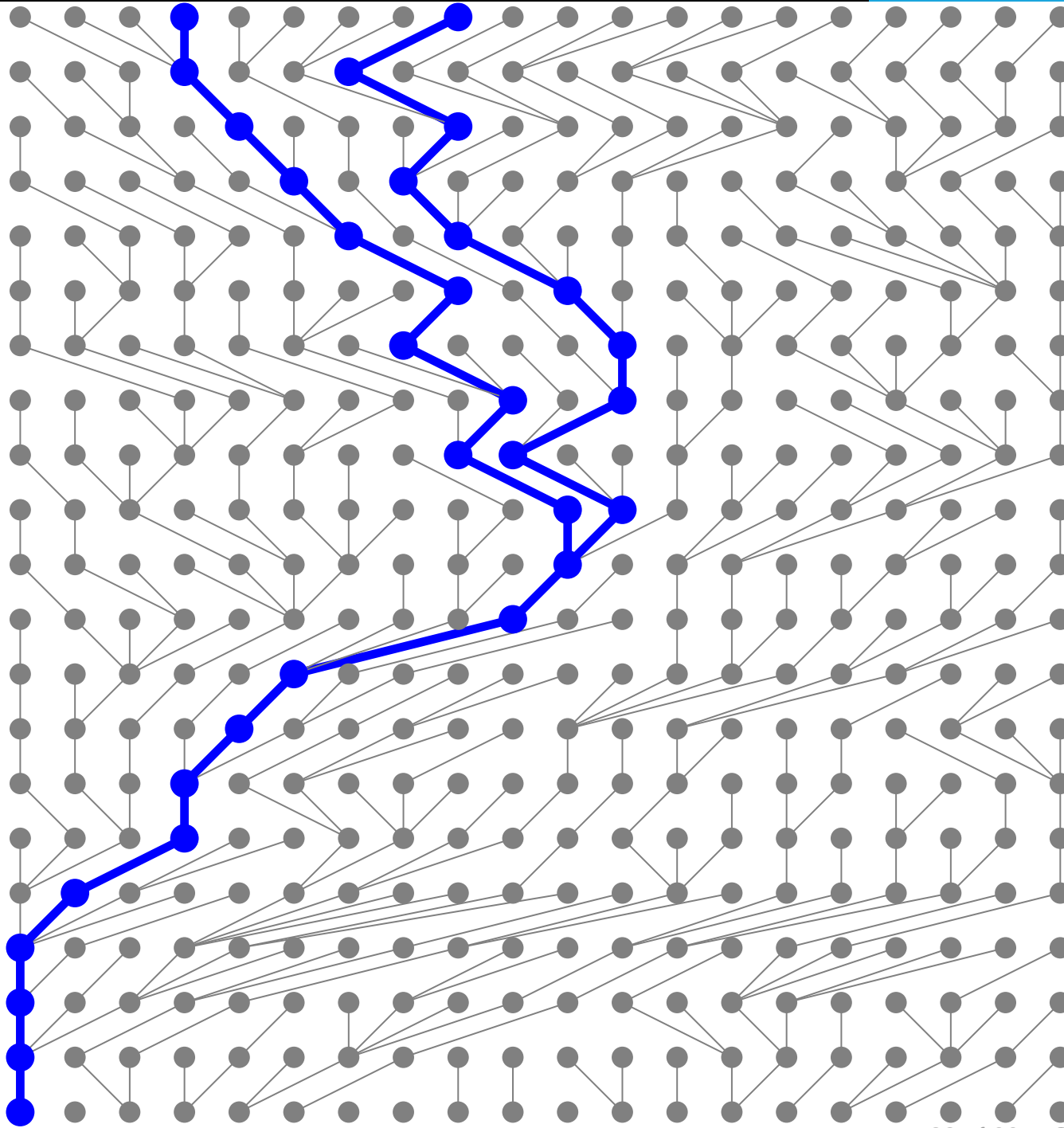
where τ is the number of generations with no coalescence. This formula is the Geometric Distribution and we can calculate the expectation of the waiting time until two random individuals coalesce:

$$\mathbb{E}(\tau) = 2N$$

Population model

Wright-Fisher

Present

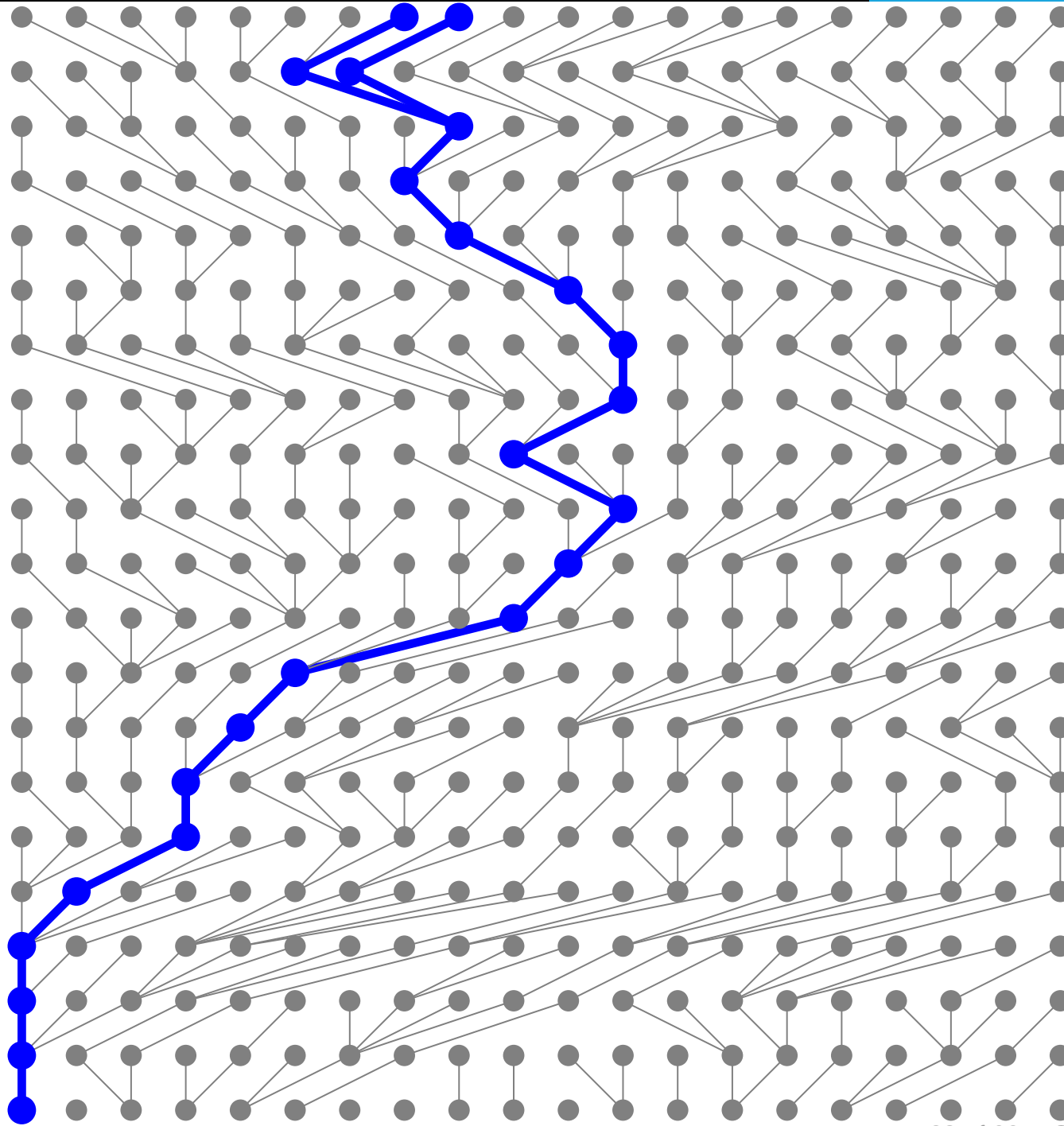


Past

Population model

Wright-Fisher

Present

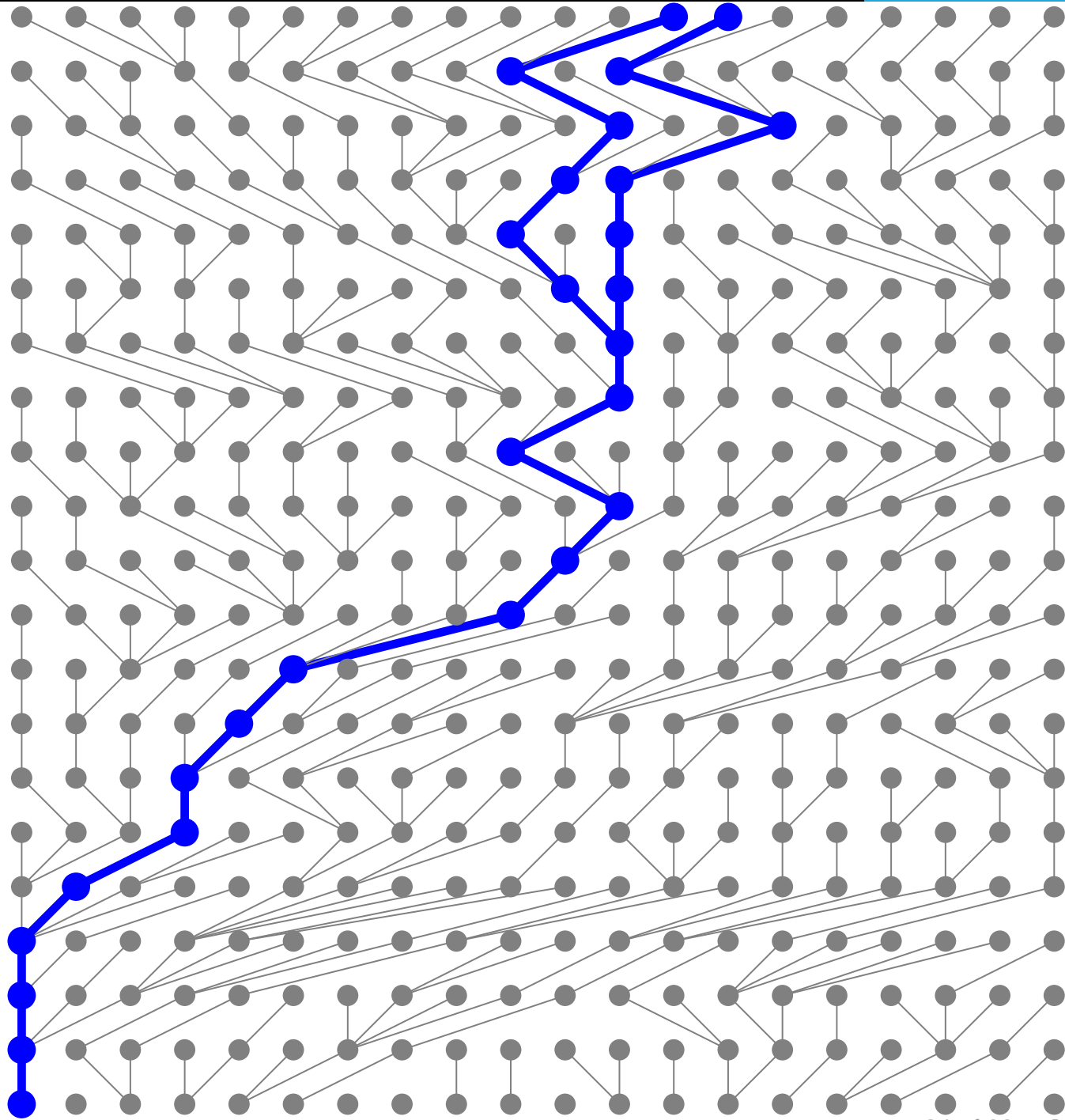


Past

Population model

Wright-Fisher

Present

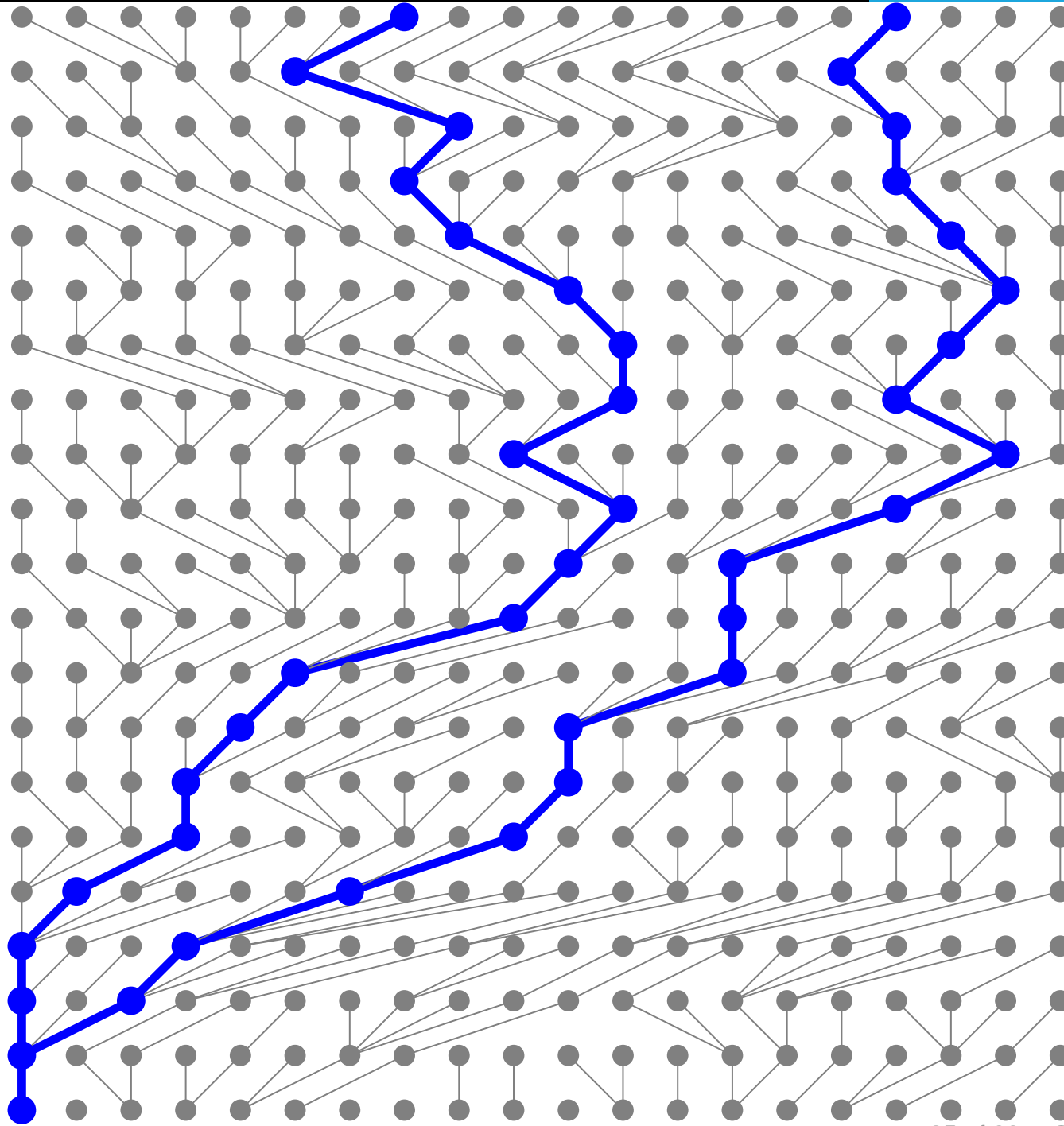


Past

Population model

Wright-Fisher

Present

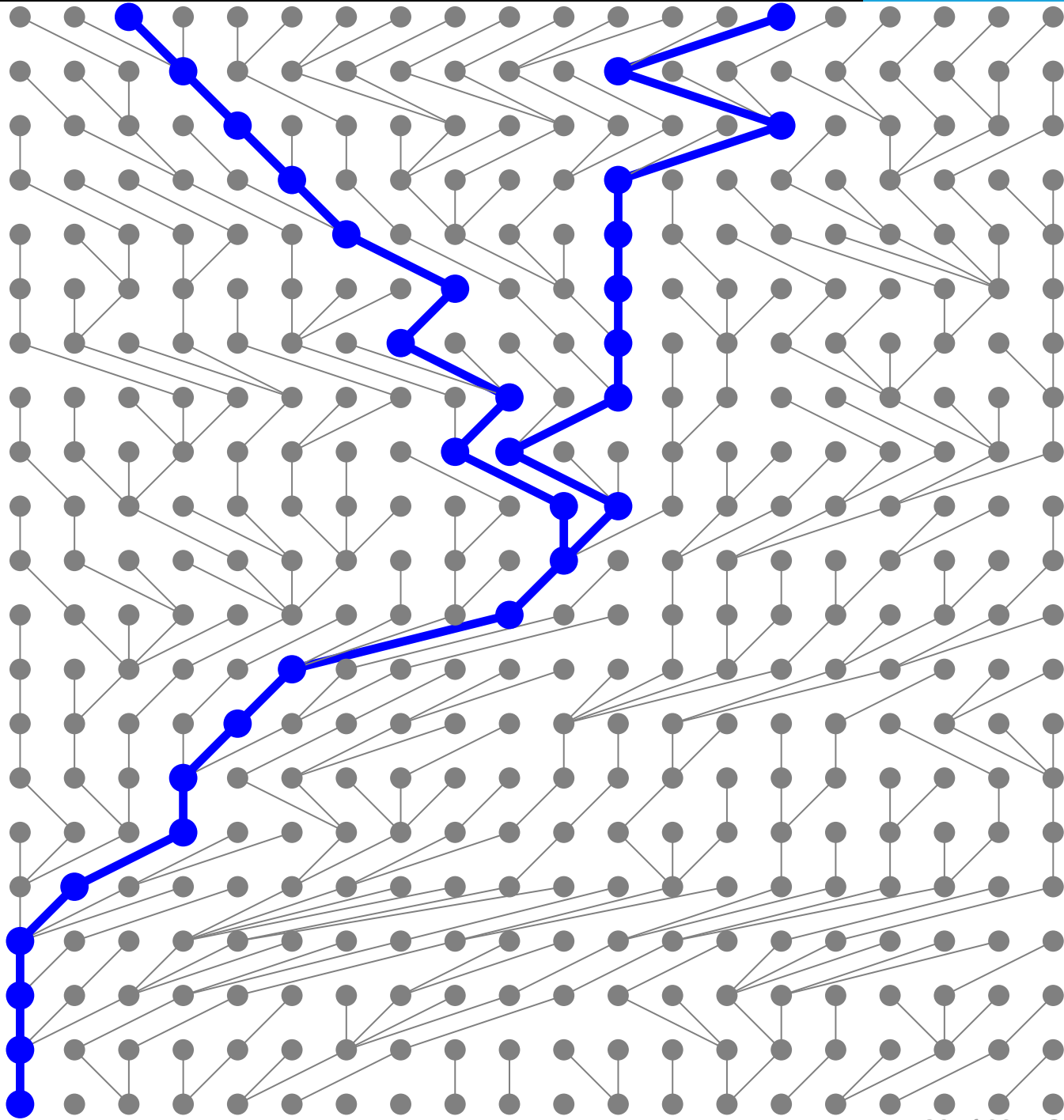


Past

Population model

Wright-Fisher

Present

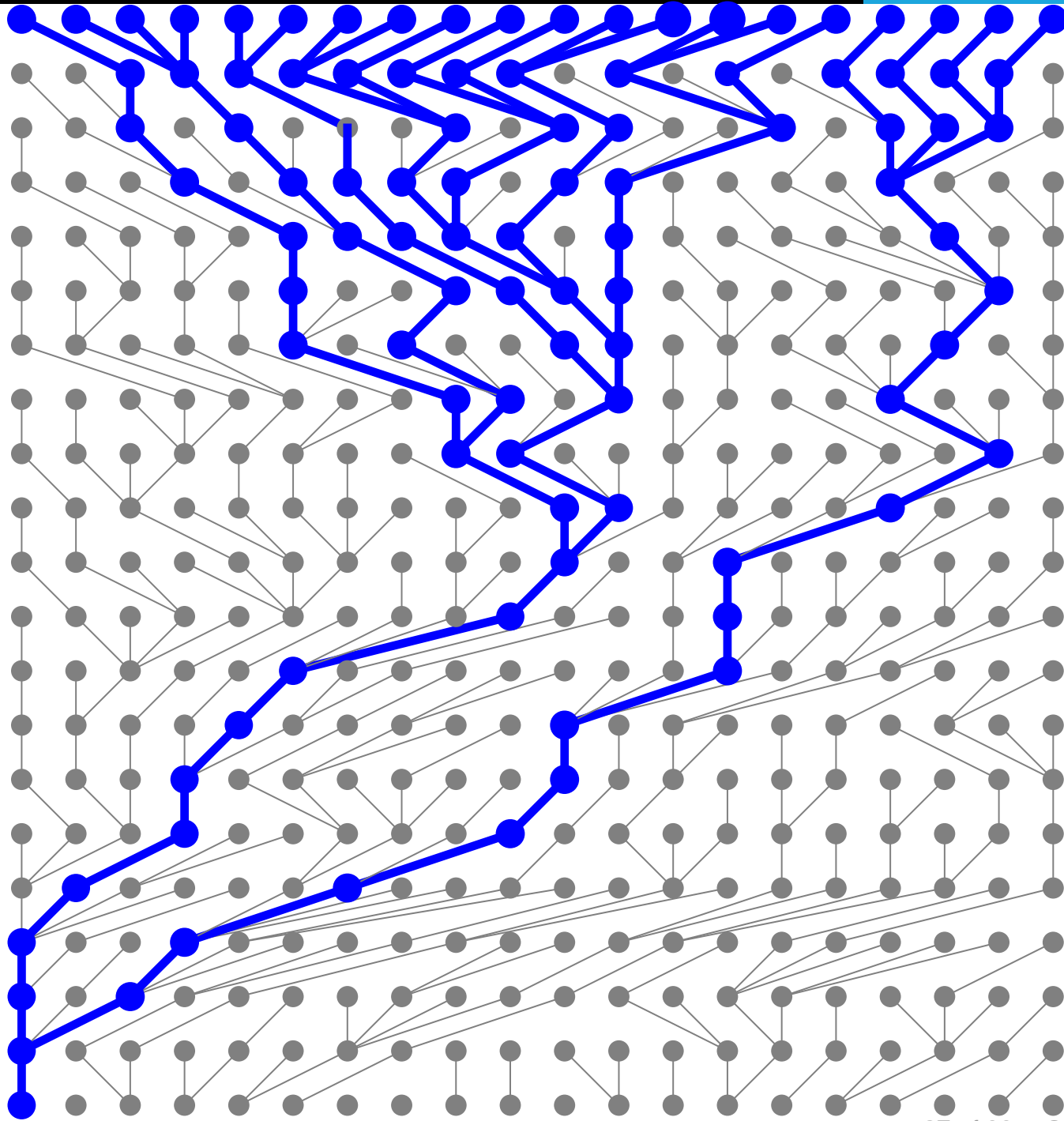


Past

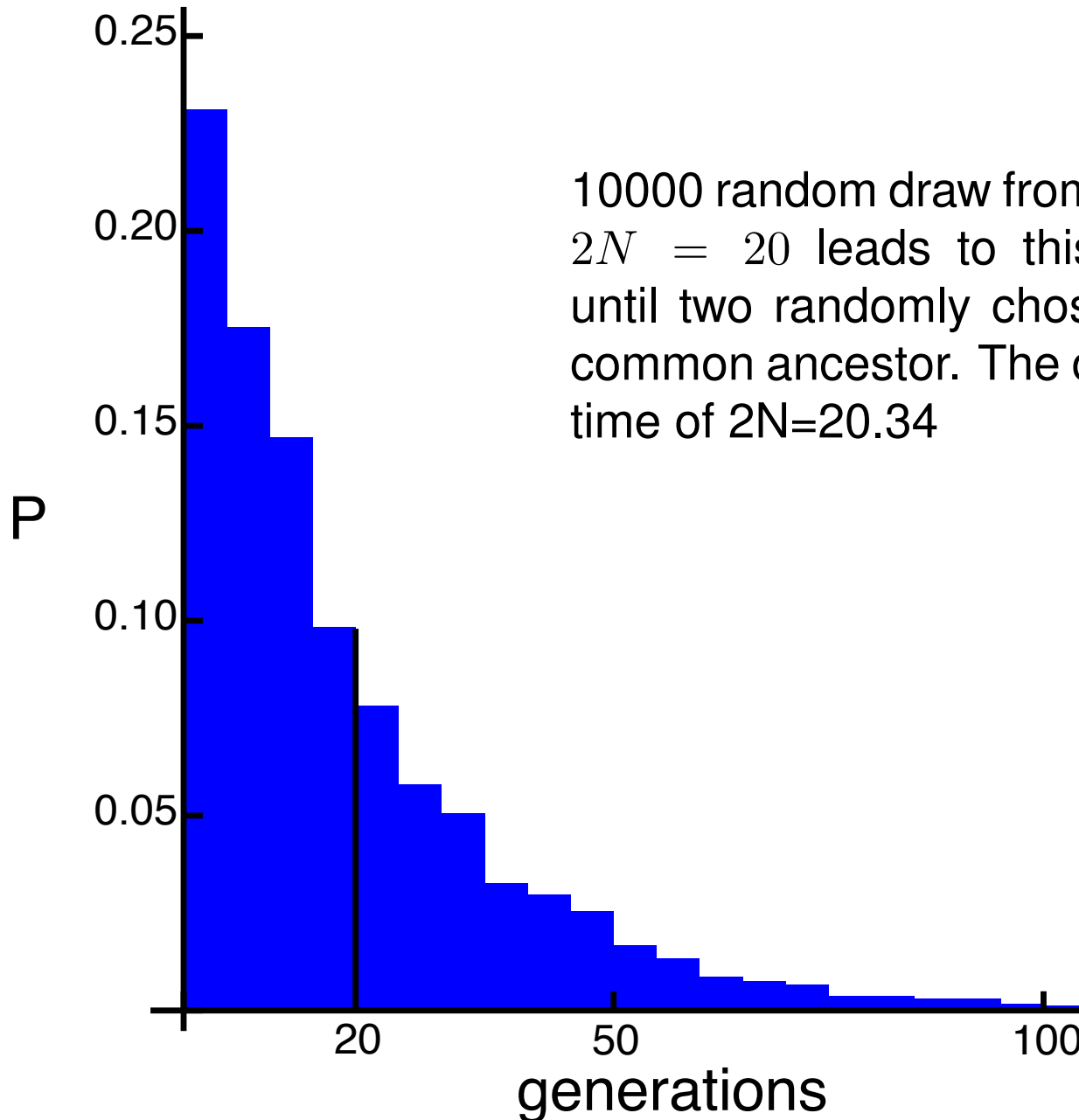
Population model

Wright-Fisher

Present



Past

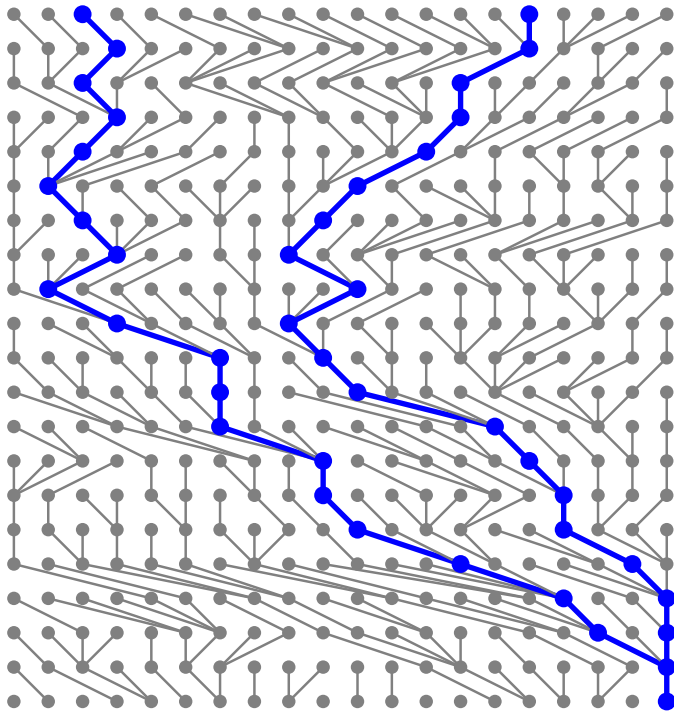


10000 random draw from a population with size $2N = 20$ leads to this distribution of times until two randomly chosen individuals have a common ancestor. The observed mean waiting time of $2N=20.34$

- ◆ For the time of coalescence in a sample of **TWO** , we will wait on average $2N$ generations assuming it is a Wright-Fisher population
- ◆ The model assumes that the generations are discrete and non-overlapping
- ◆ Real populations do not necessarily behave like a Wright-Fisher (the *'ideal' population*)
- ◆ *We assume that calculation using Wright-Fisher populations can be extrapolated to real populations.*

Other population models

Wright-Fisher

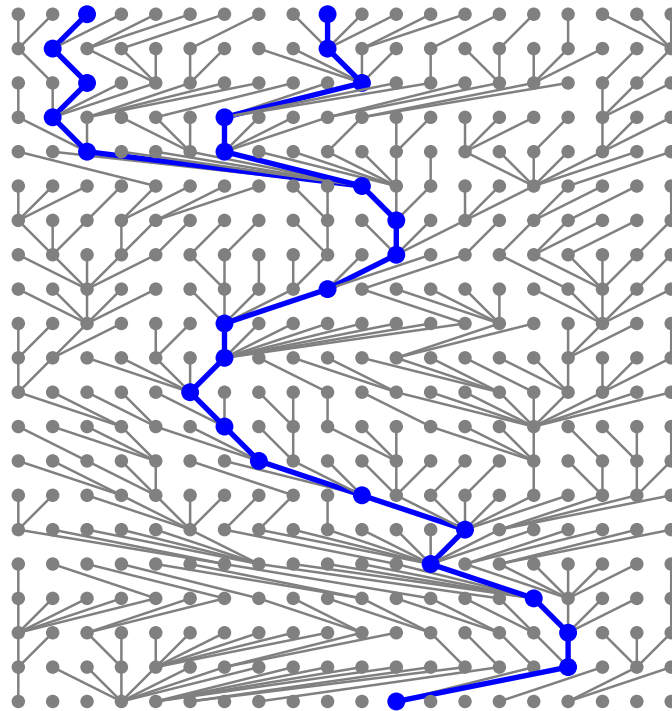


$$\sigma_{\text{offspring}}^2 \simeq 1$$

$$\mathbb{E}(\tau) = 2N$$

generation time $g = 1$

Canning

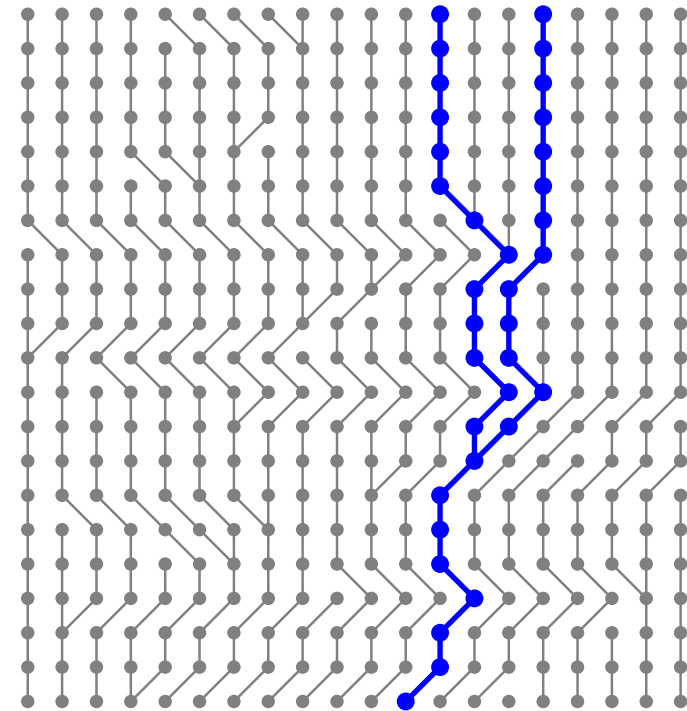


$$\sigma_{\text{offspring}}^2 = x$$

$$\mathbb{E}(\tau) = 2N/x$$

$g = 1$

Moran



$$\sigma_{\text{offspring}}^2 = \frac{2}{2N}$$

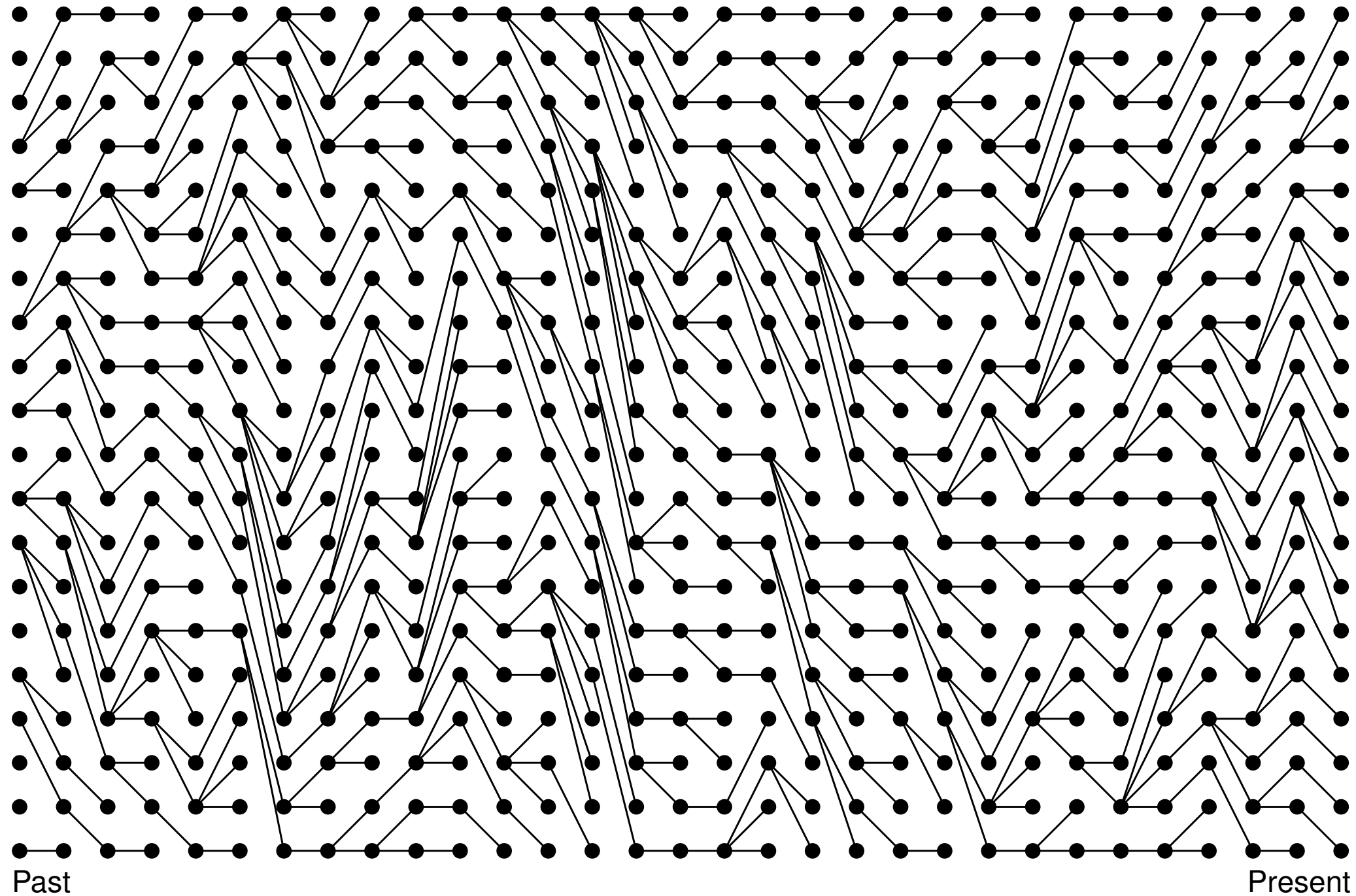
$$\mathbb{E}(\tau) = \frac{1}{2}(2N)^2$$

$g = 2N$

You can generate graphs like this using the python program *popsim* (check out my faculty page for the link)

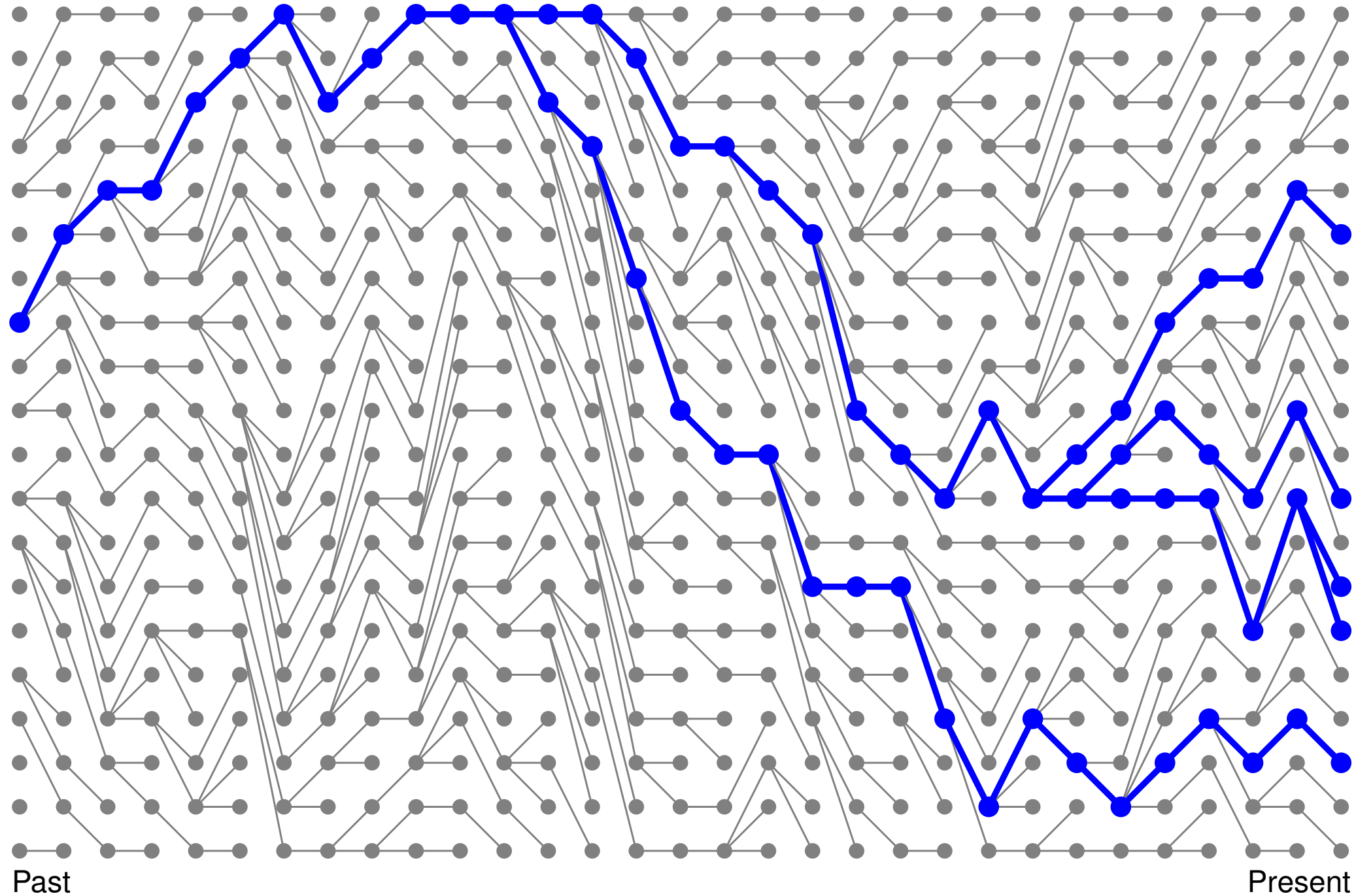
Sample larger than TWO

Wright-Fisher



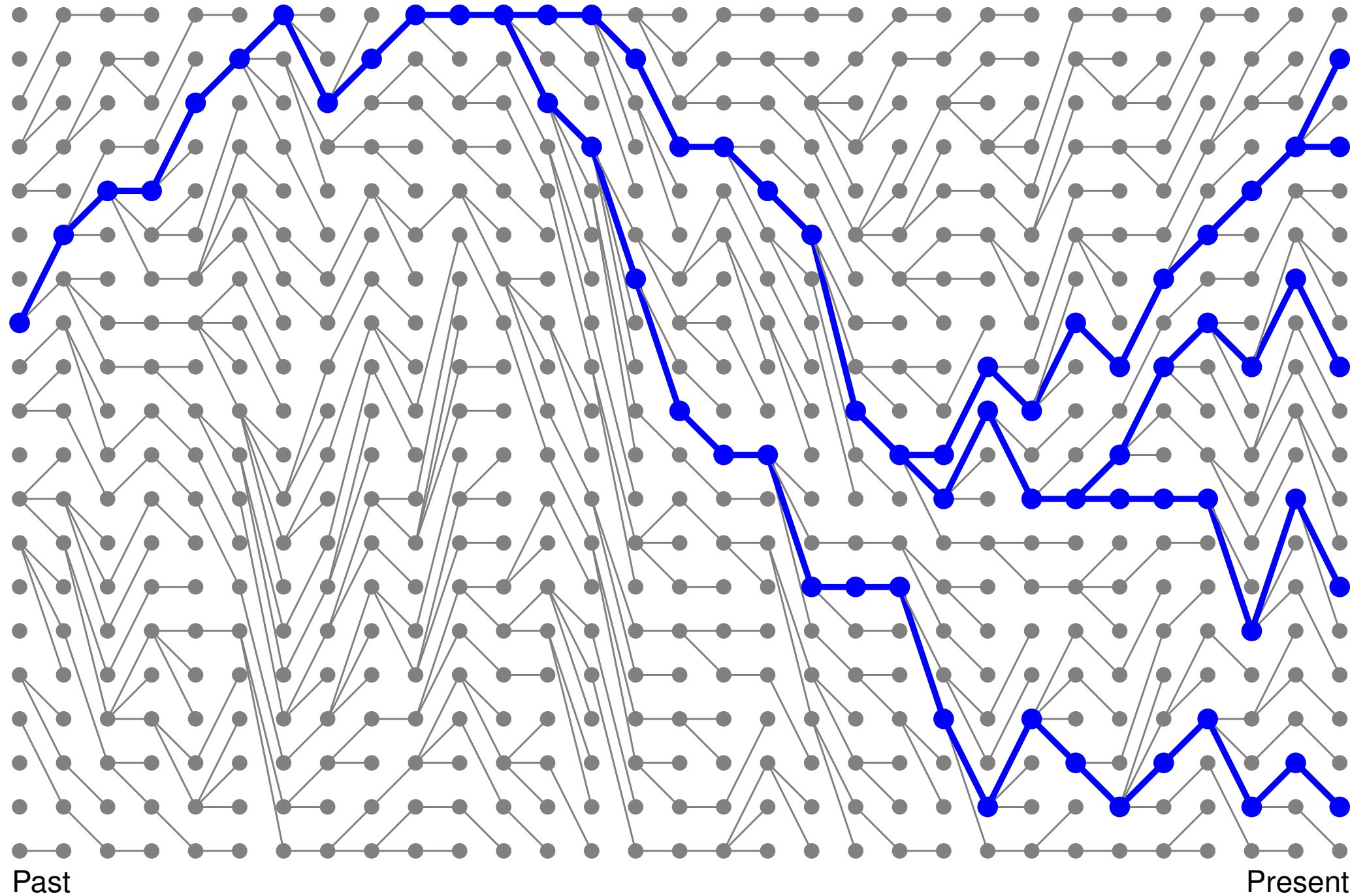
Sample larger than TWO

Wright-Fisher



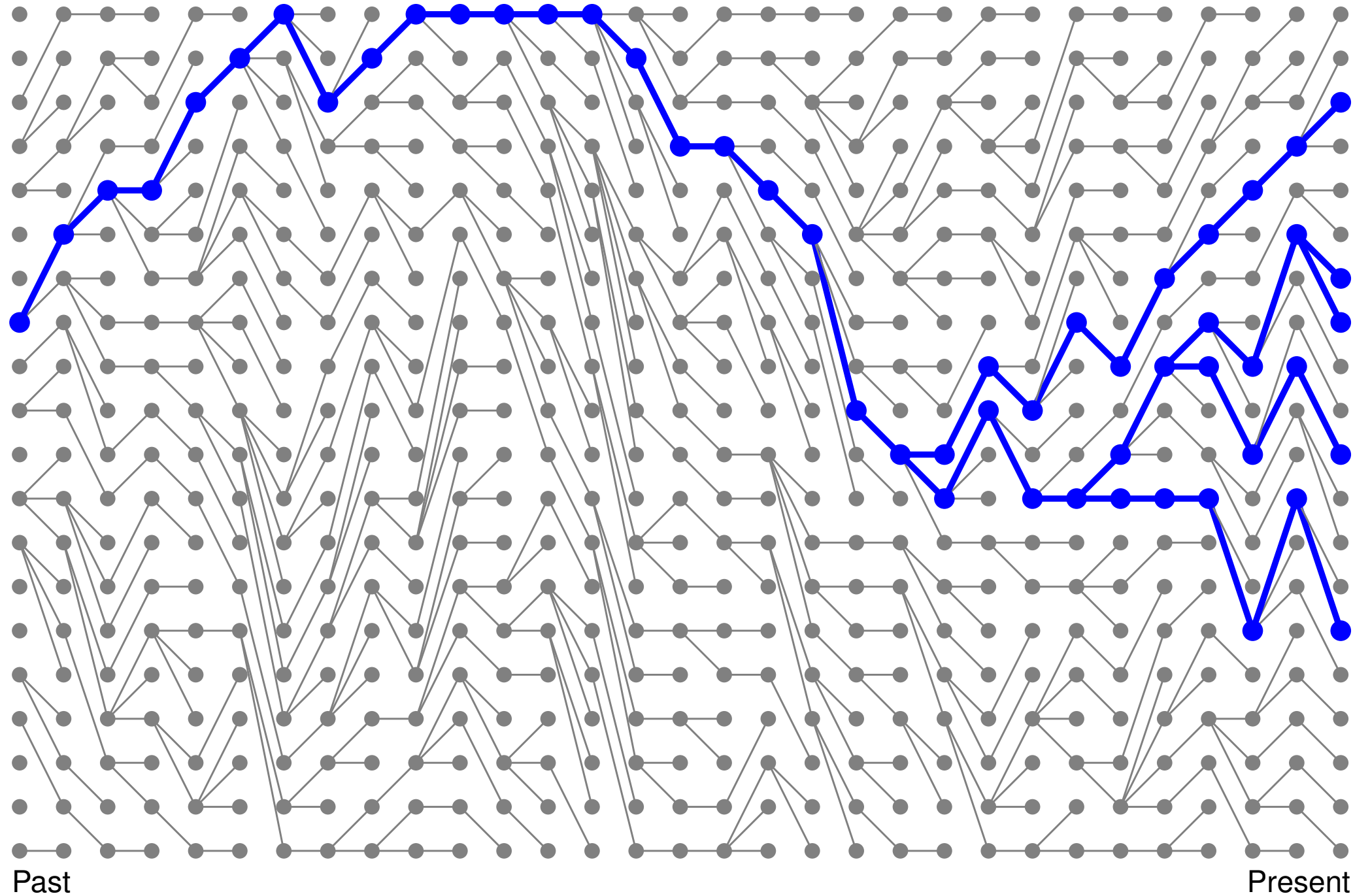
Sample larger than TWO

Wright-Fisher



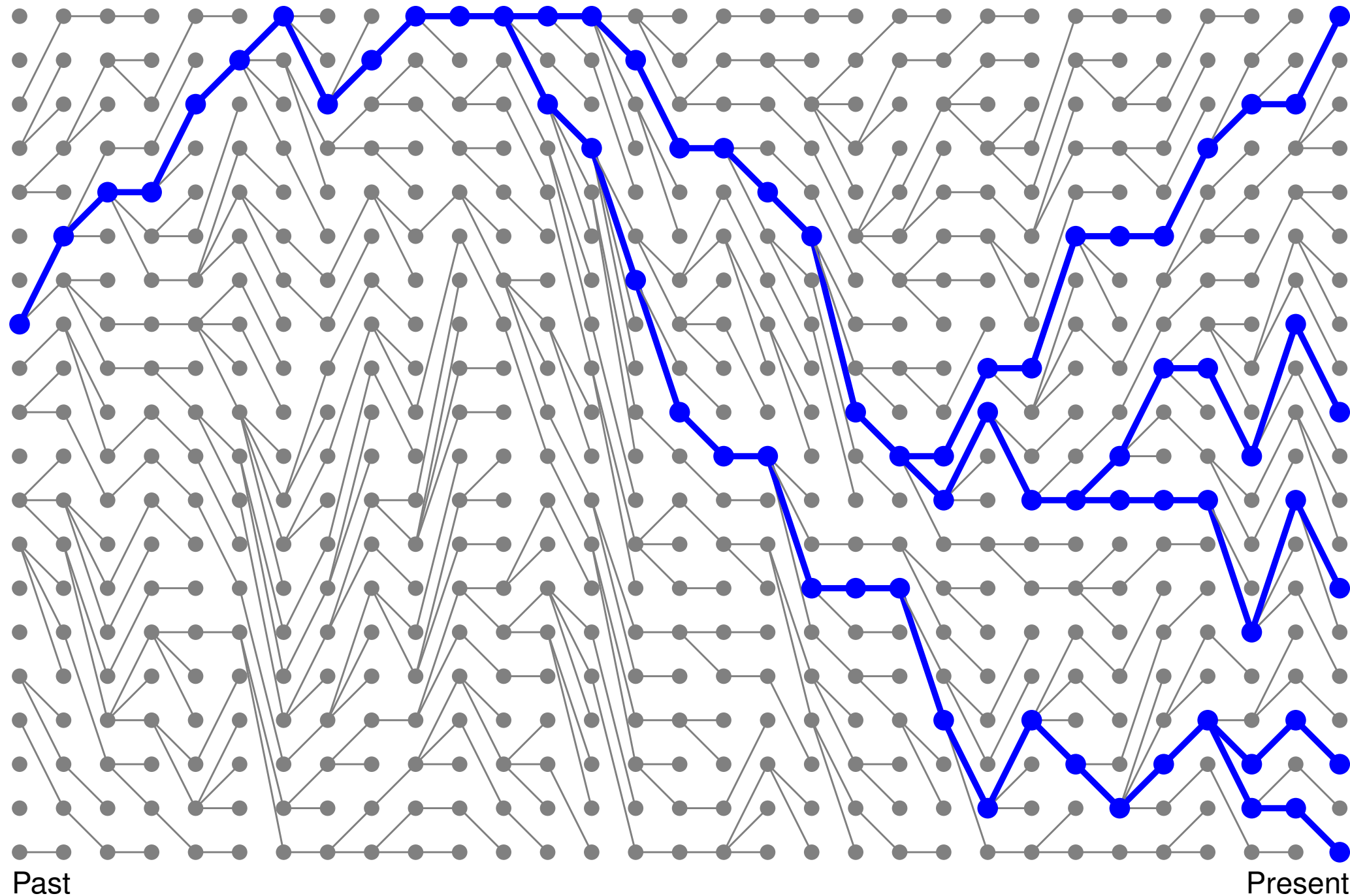
Sample larger than TWO

Wright-Fisher



Sample larger than TWO

Wright-Fisher



Samples larger than two

Sir J. F. C. Kingman described in 1982 the n -coalescent. He showed the behavior of a sample of size n , and its probability structure looking backwards in time.

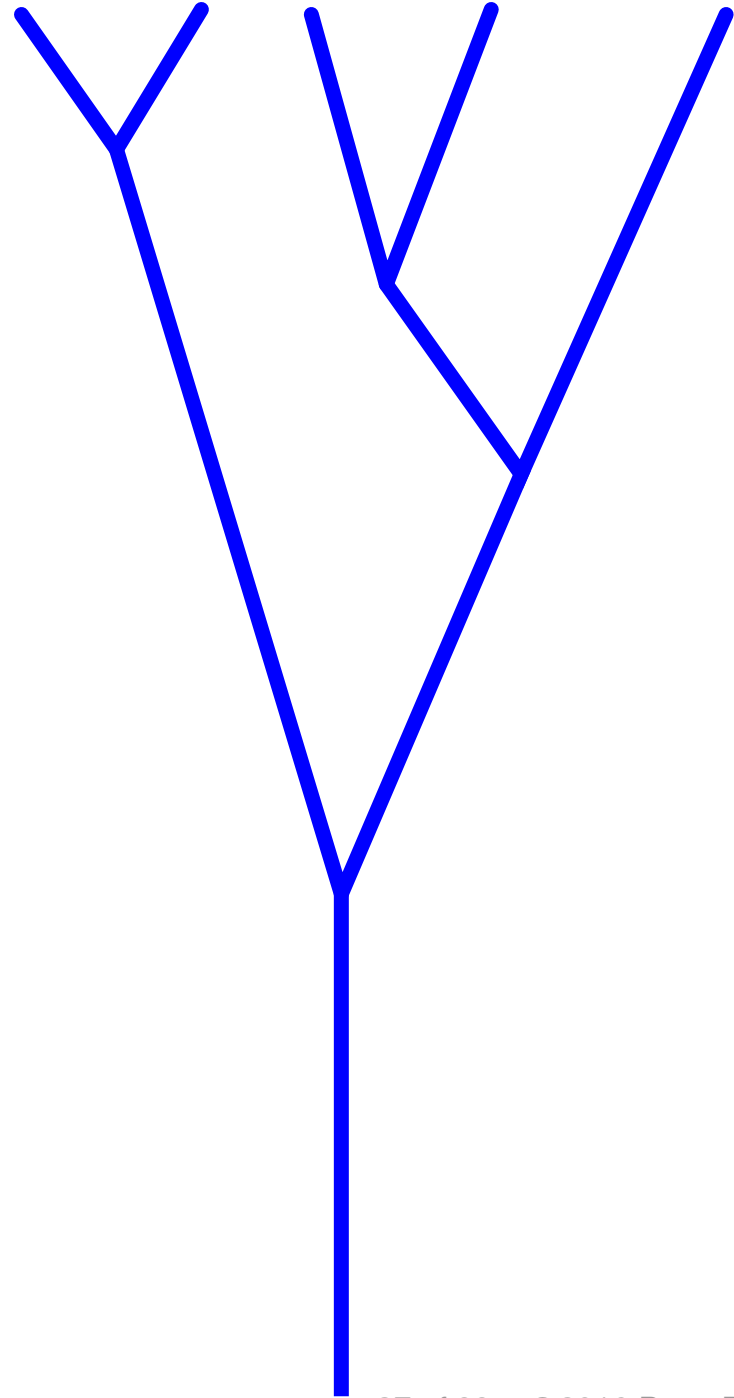
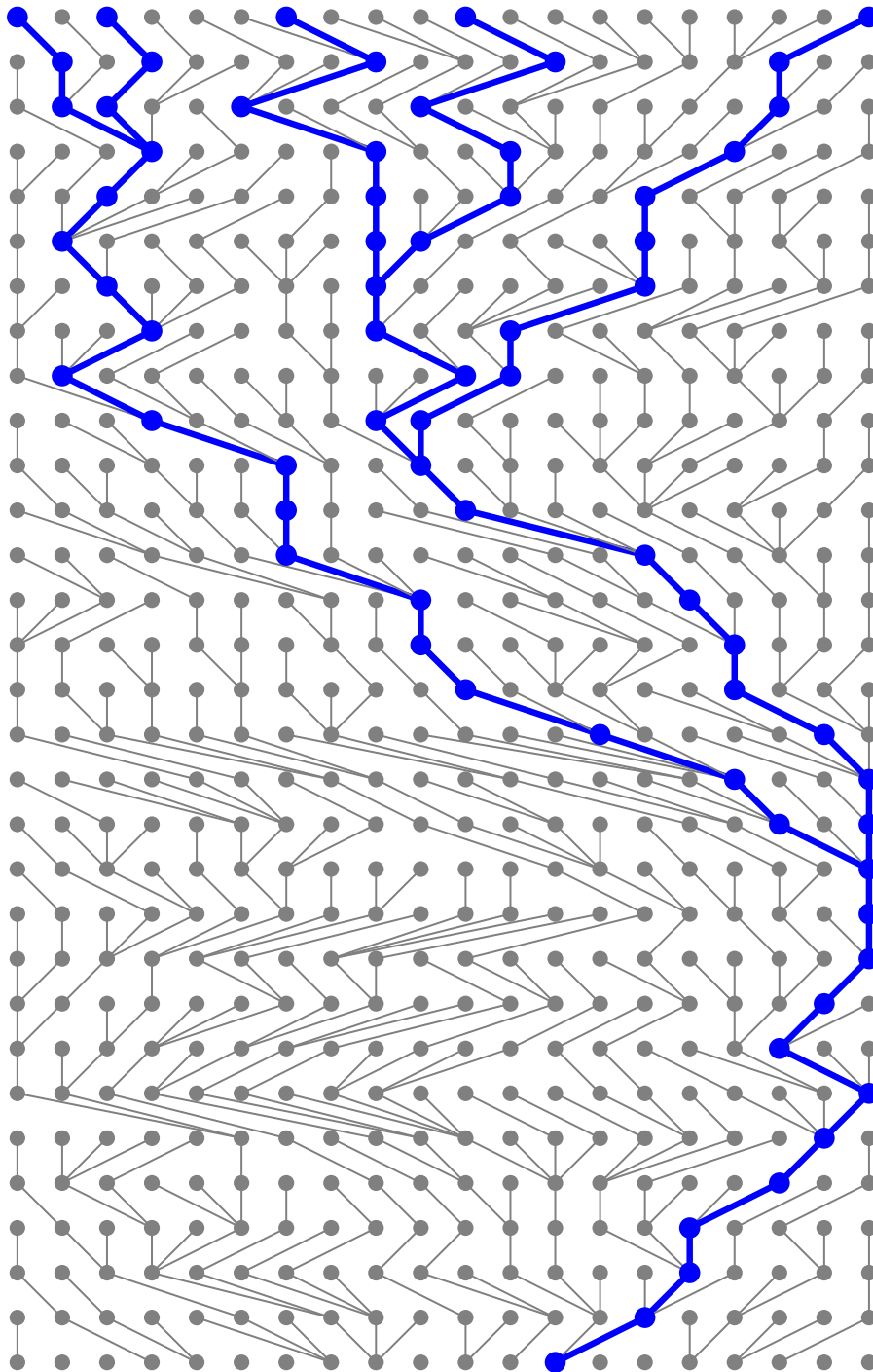
General findings:

$$\text{coalescence rate} = \binom{n}{2} = \frac{n(n-1)}{2}$$

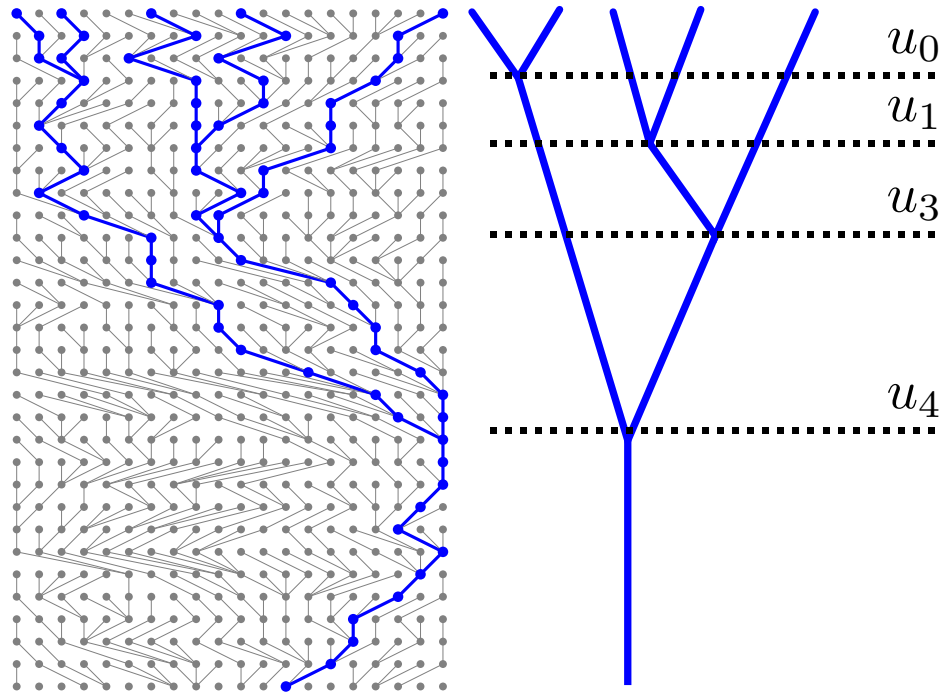
Once a coalescence happened n is reduced to $n - 1$ because two lineages merged into one. He then imposed a continuous approximation of the Canning's exchangeable model to get results.



Samples larger than two

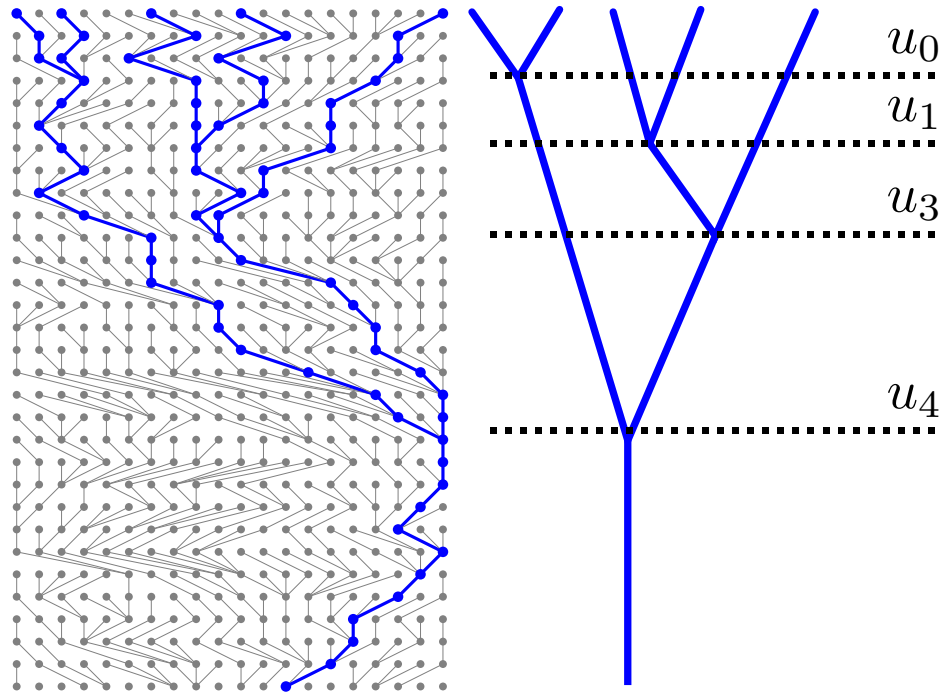


Samples larger than two



Looking backward in time, the first coalescence between two random individuals is the result of a waiting process that depends on the sample n and the total population size N .

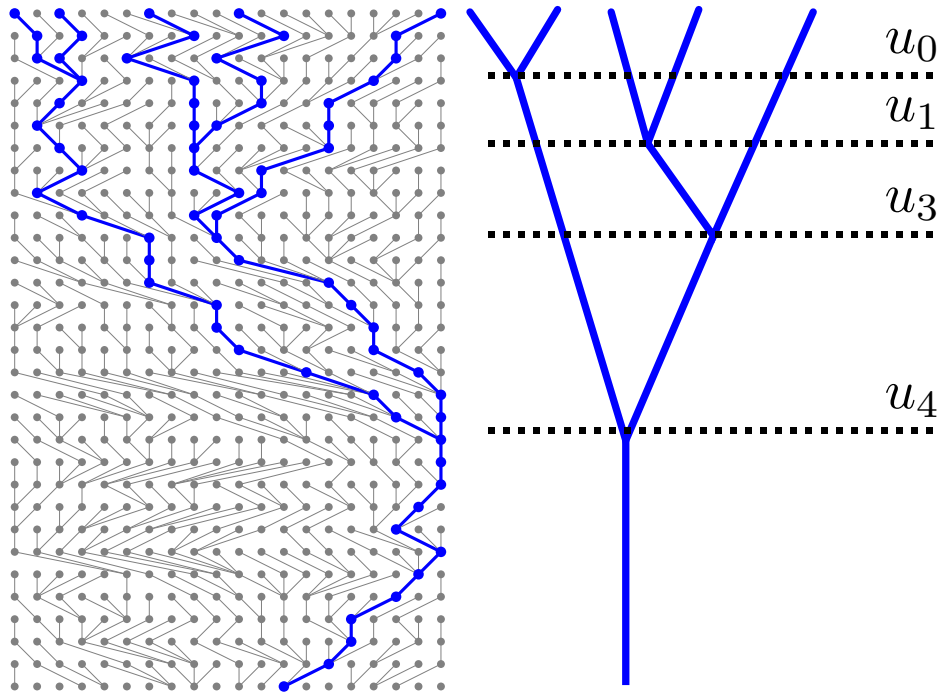
Samples larger than two



Looking backward in time, the first coalescence between two random individuals is the result of a waiting process that depends on the sample n and the total population size N .

Using Kingman's coalescence rate and imposing a time scale we can approximate the process with an exponential distribution:

Samples larger than two



Looking backward in time, the first coalescence between two random individuals is the result of a waiting process that depends on the sample n and the total population size N .

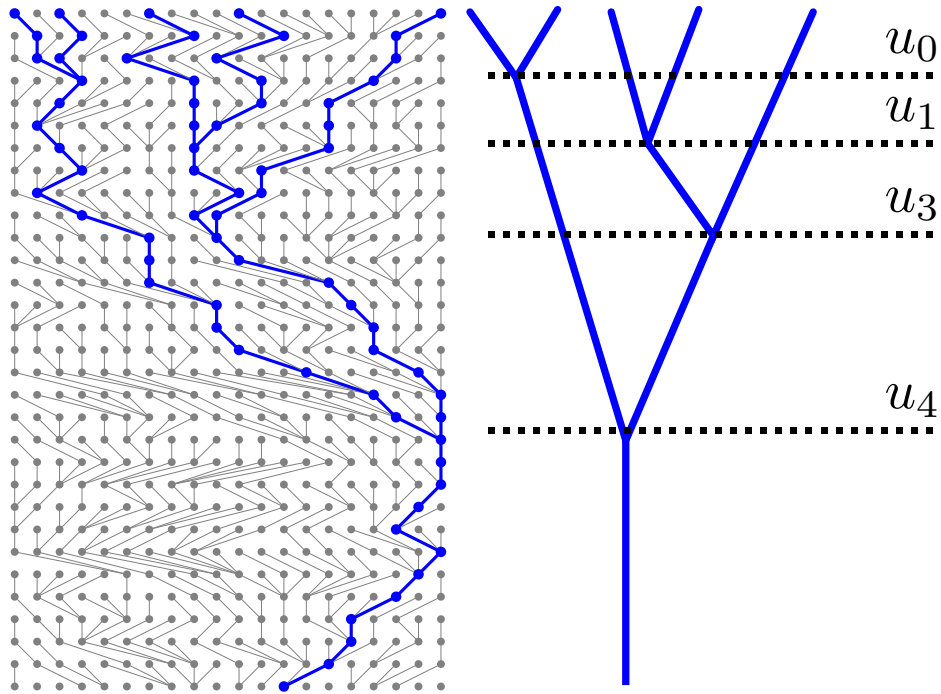
Using Kingman's coalescence rate and imposing a time scale we can approximate the process with an exponential distribution:

$$P(u_j|N) = e^{-u_j\lambda}\lambda$$

with the scaled coalescence rate

$$\lambda = \binom{k}{2} \frac{1}{2N} \times \text{Prob}(\text{others do not coalesce})$$

Samples larger than two



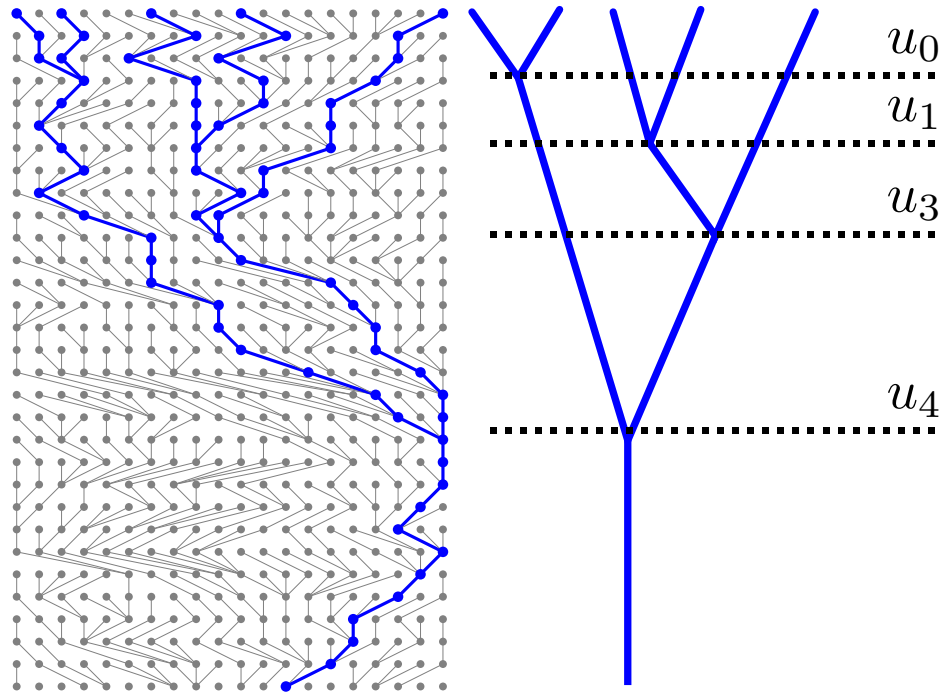
Looking backward in time, the first coalescence between two random individuals is the result of a waiting process that depends on the sample n and the total population size N .

Using Kingman's coalescence rate and imposing a time scale we can approximate the process with an exponential distribution:

$$P(u_j|N) = e^{-u_j\lambda}\lambda$$

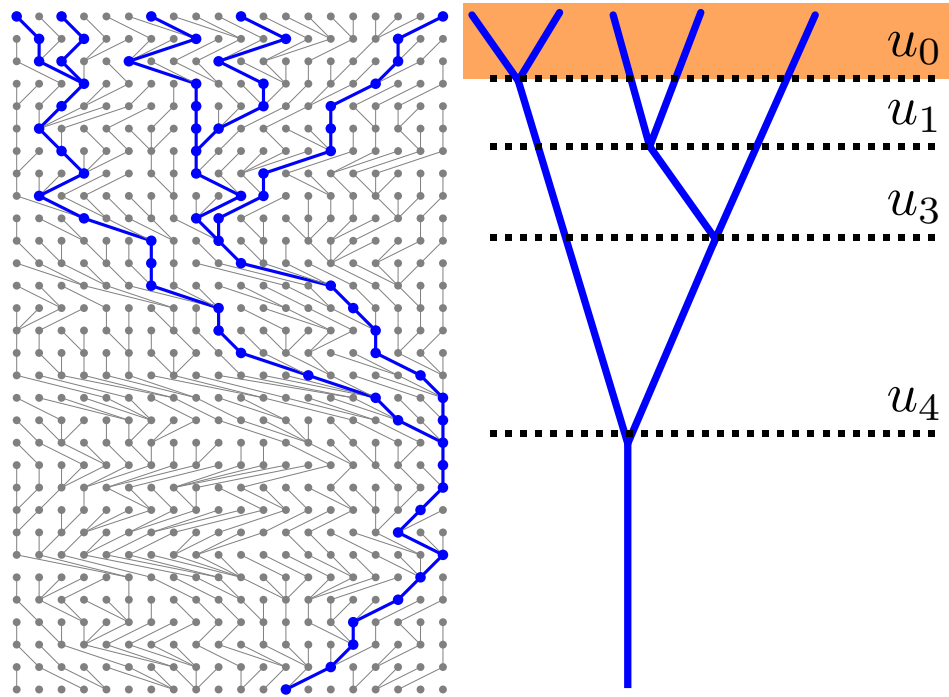
with the scaled coalescence rate

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



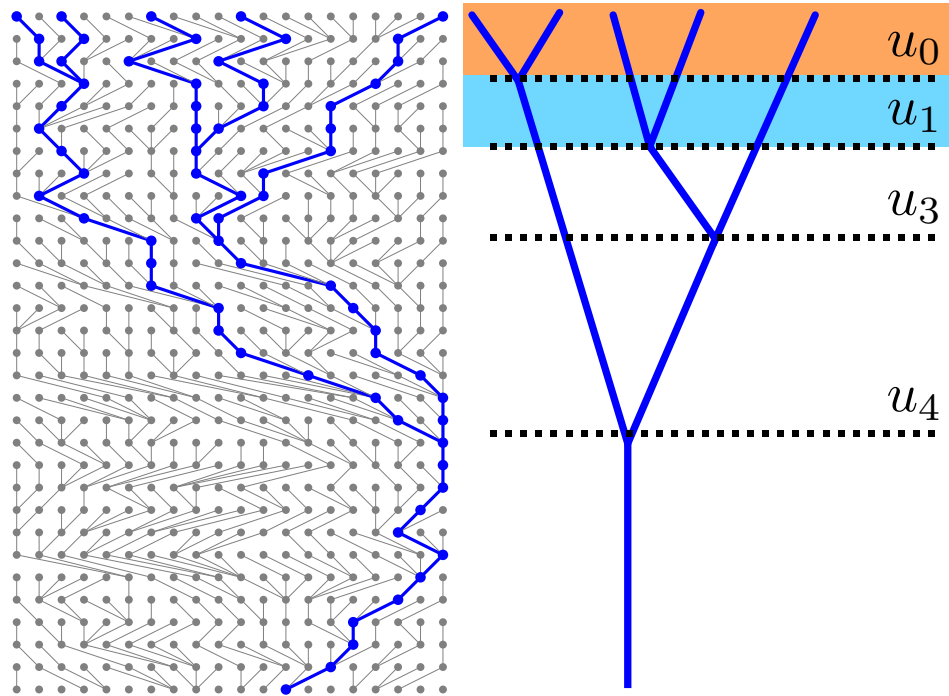
We are now able to calculate the probability of a whole relationship tree (Genealogy G). We assume that each coalescence is independent from any other:

$$P(G|N)$$



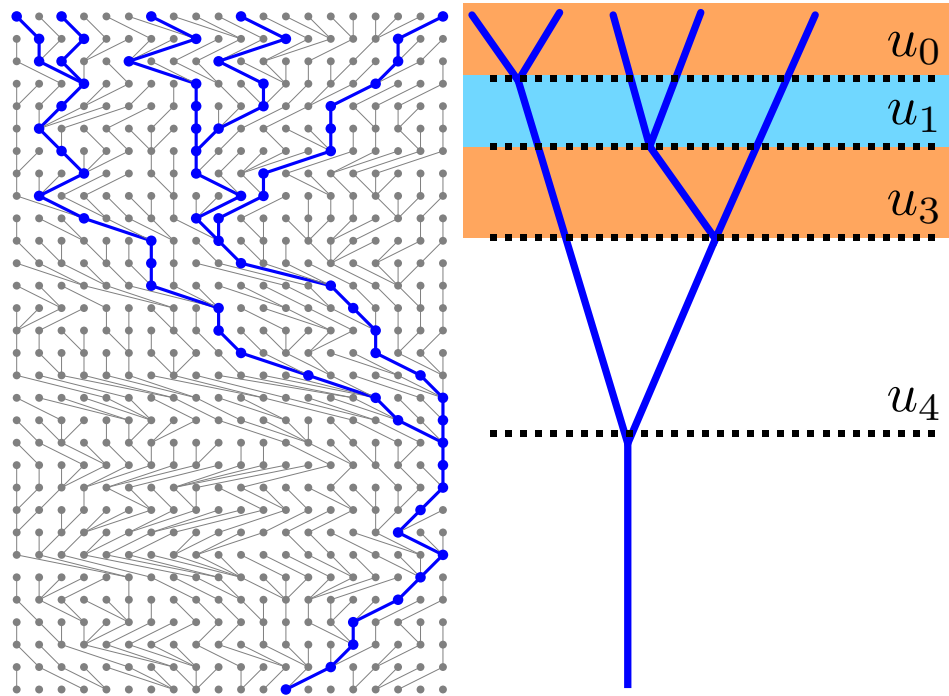
We are now able to calculate the probability of a whole relationship tree (Genealogy G). We assume that each coalescence is independent from any other:

$$P(G|N) = P(u_0|N, i_1, i_2) \times$$



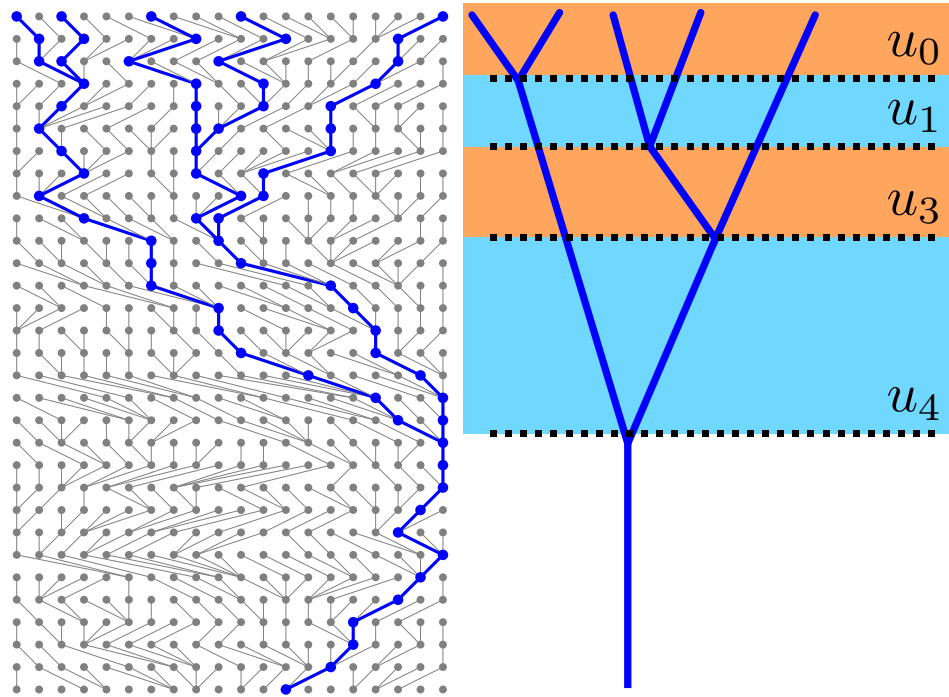
We are now able to calculate the probability of a whole relationship tree (Genealogy G). We assume that each coalescence is independent from any other:

$$P(G|N) = P(u_0|N, i_1, i_2) \times P(u_1|N, i_3, i_4)$$



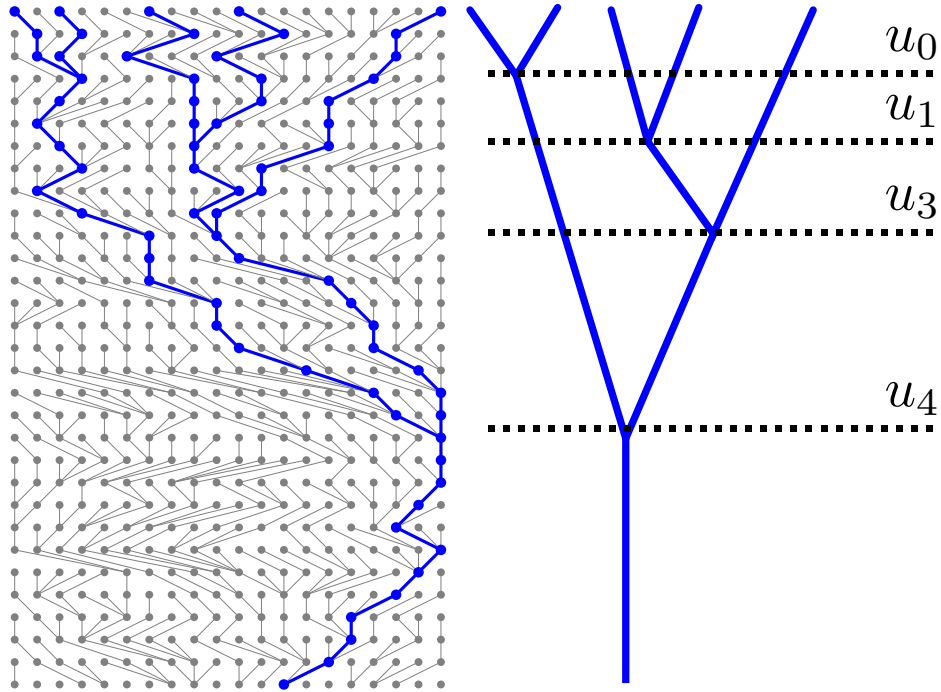
We are now able to calculate the probability of a whole relationship tree (Genealogy G). We assume that each coalescence is independent from any other:

$$\begin{aligned} P(G|N) = & P(u_0|N, i_1, i_2) \\ & \times P(u_1|N, i_3, i_4) \\ & \times P(u_3|N, i_{3,4}, i_5) \end{aligned}$$



We are now able to calculate the probability of a whole relationship tree (Genealogy G). We assume that each coalescence is independent from any other:

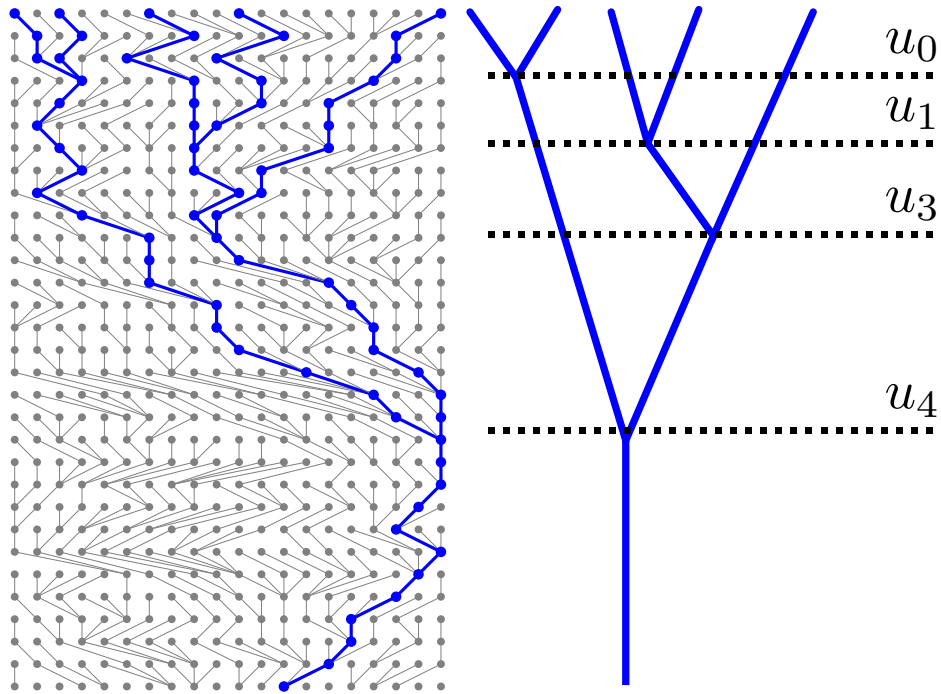
$$\begin{aligned} P(G|N) = & P(u_0|N, i_1, i_2) \\ & \times P(u_1|N, i_3, i_4) \\ & \times P(u_3|N, i_{3,4}, i_5) \\ & \times P(u_4|N, i_{1,2}, i_{3,4,5}) \end{aligned}$$



We are now able to calculate the probability of a whole relationship tree (Genealogy G). We assume that each coalescence is independent from any other:

$$\begin{aligned}
 P(G|N) = & P(u_0|N, i_1, i_2) \\
 & \times P(u_1|N, i_3, i_4) \\
 & \times P(u_3|N, i_{3,4}, i_5) \\
 & \times P(u_4|N, i_{1,2}, i_{3,4,5})
 \end{aligned}$$

$$P(G|N) = \prod_{j=0}^T e^{-u_j \frac{k_j(k_j-1)}{4N}} \frac{2}{4N}$$



Each interval u_j is independent of the others, the expected length of the interval is the inverse of the coalescent rate. Thus we can sum these expectations to get to expectation of the depth of the genealogy.

$$\mathbb{E}(\tau_{\text{MRCA}}) = \text{Sum of the expectation of each time interval} = \sum_{j=0}^J \frac{4N}{k_j(k_j - 1)}$$

$$\lim_{k \rightarrow \infty} \mathbb{E}(\tau_{\text{MRCA}}) = 2N + \frac{2}{3}N + \frac{1}{3}N + \frac{1}{5}N + \frac{2}{15}N + \dots = 4N$$

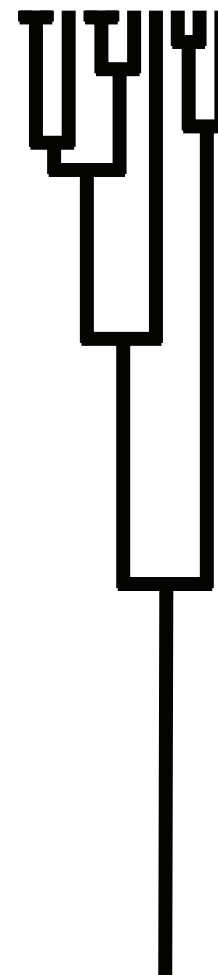
$$\lim_{k \rightarrow \infty} \sigma(\tau_{\text{MRCA}}) = 4N$$

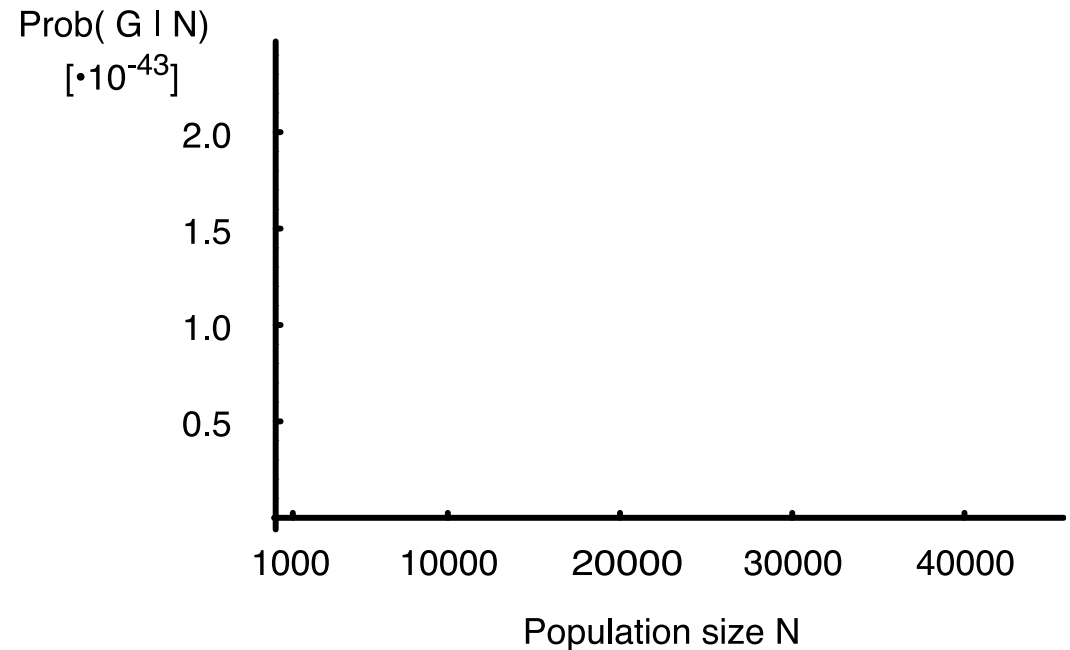
If we know the genealogy G with certainty then we can calculate the population size N . Finding the maximum probability $P(G|N, k)$ is simple, we evaluate all possible values for N and pick the value with the highest probability.

If we know the genealogy G with certainty then we can calculate the population size N . Finding the maximum probability $P(G|N, k)$ is simple, we evaluate all possible values for N and pick the value with the highest probability.



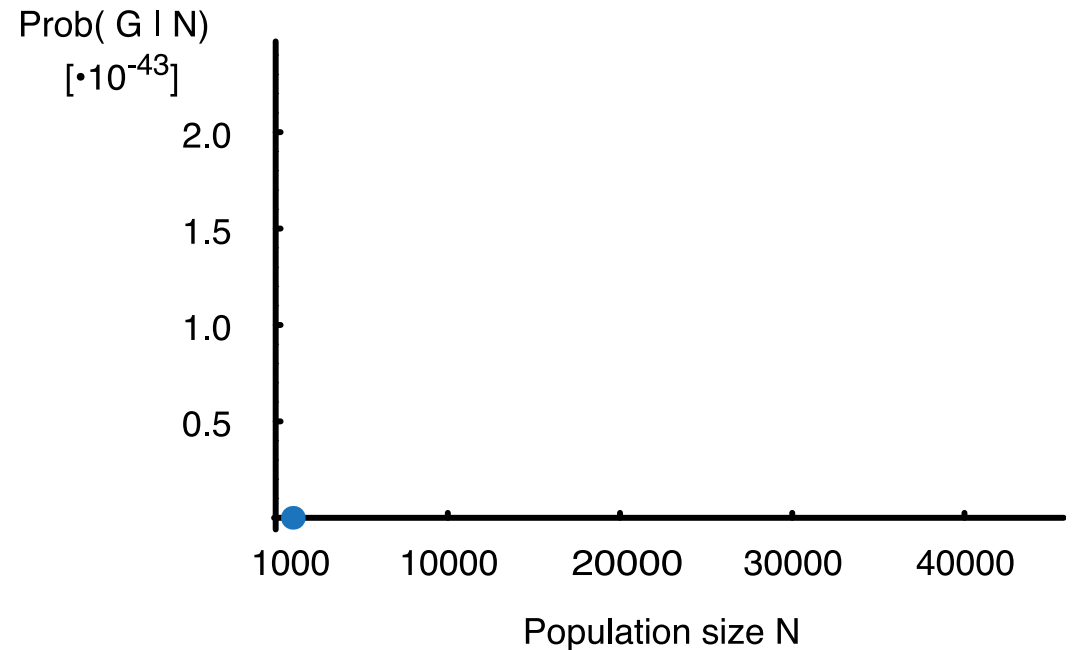
If we know the genealogy G with certainty then we can calculate the population size N . Finding the maximum probability $P(G|N, k)$ is simple, we evaluate all possible values for N and pick the value with the highest probability.





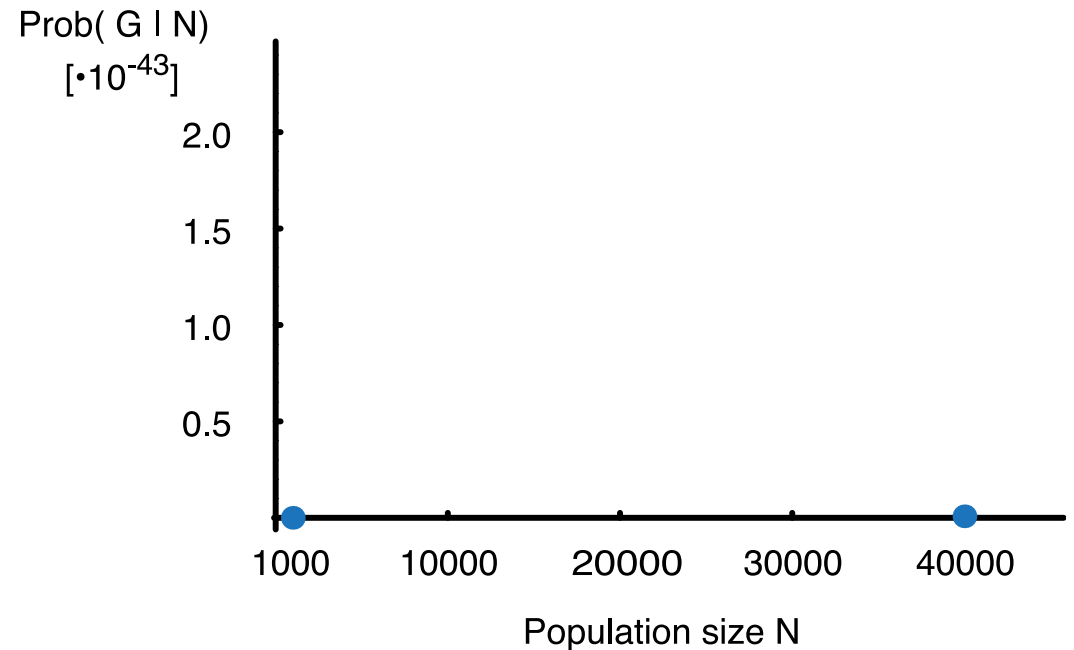
If an oracle gives us the true relationship tree G then we can calculate the population size N .

$$p(G|N, n) = \prod_{k=2}^n \exp\left(-u_k \frac{k(k-1)}{4N}\right) \frac{2}{4N}$$



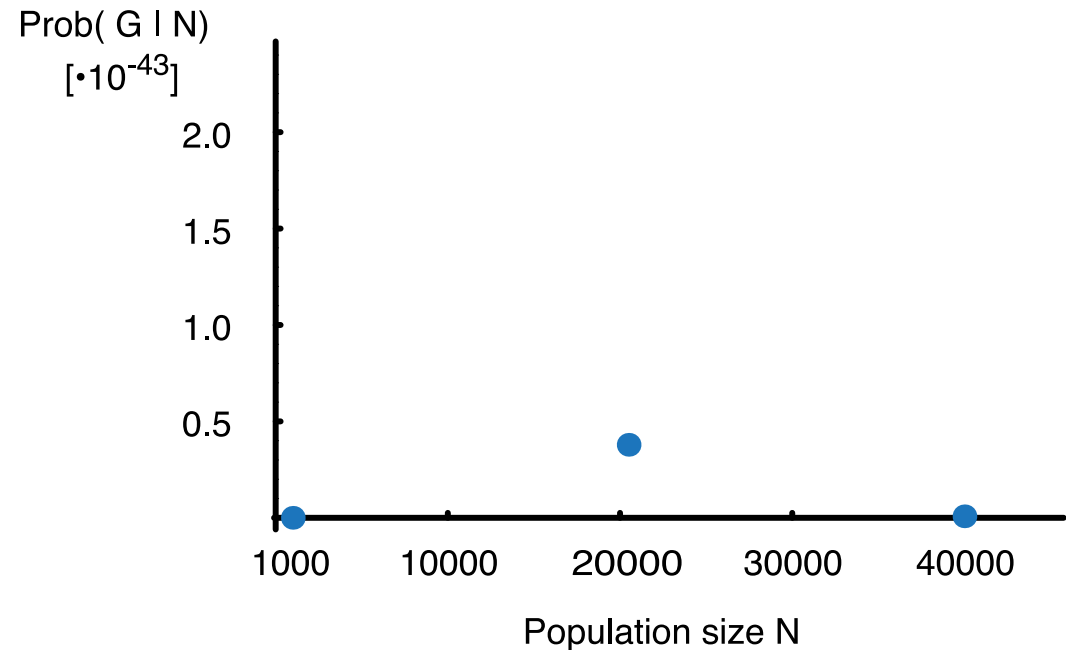
If an oracle gives us the true relationship tree G then we can calculate the population size N .

$$p(G|N, n) = \prod_{k=2}^n \exp\left(-u_k \frac{k(k-1)}{4N}\right) \frac{2}{4N}$$



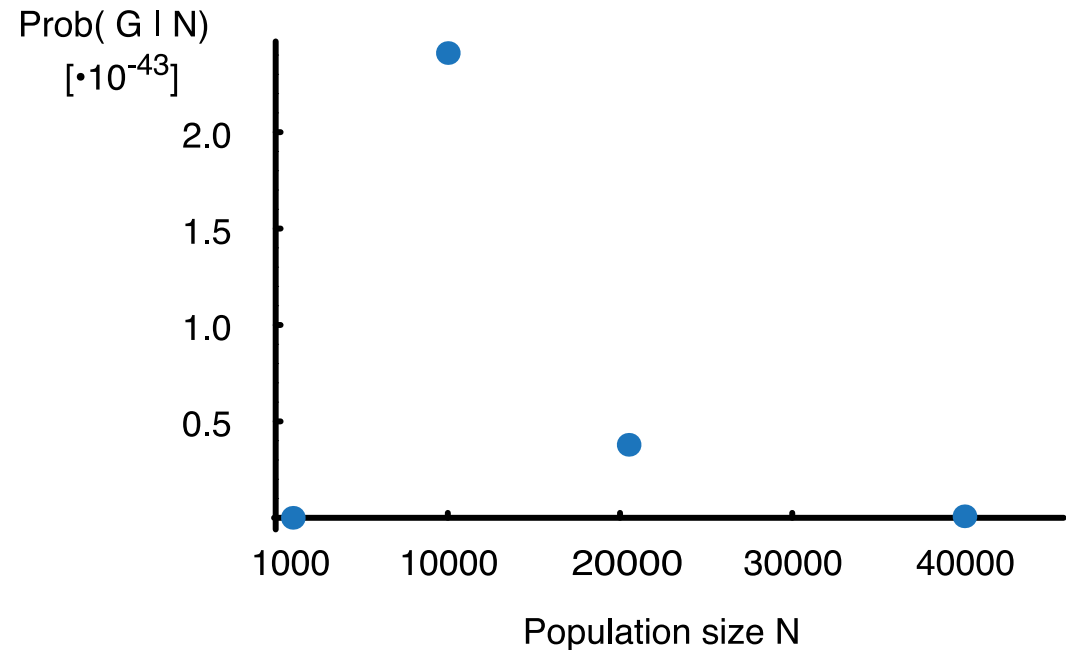
If an oracle gives us the true relationship tree G then we can calculate the population size N .

$$p(G|N, n) = \prod_{k=2}^n \exp\left(-u_k \frac{k(k-1)}{4N}\right) \frac{2}{4N}$$



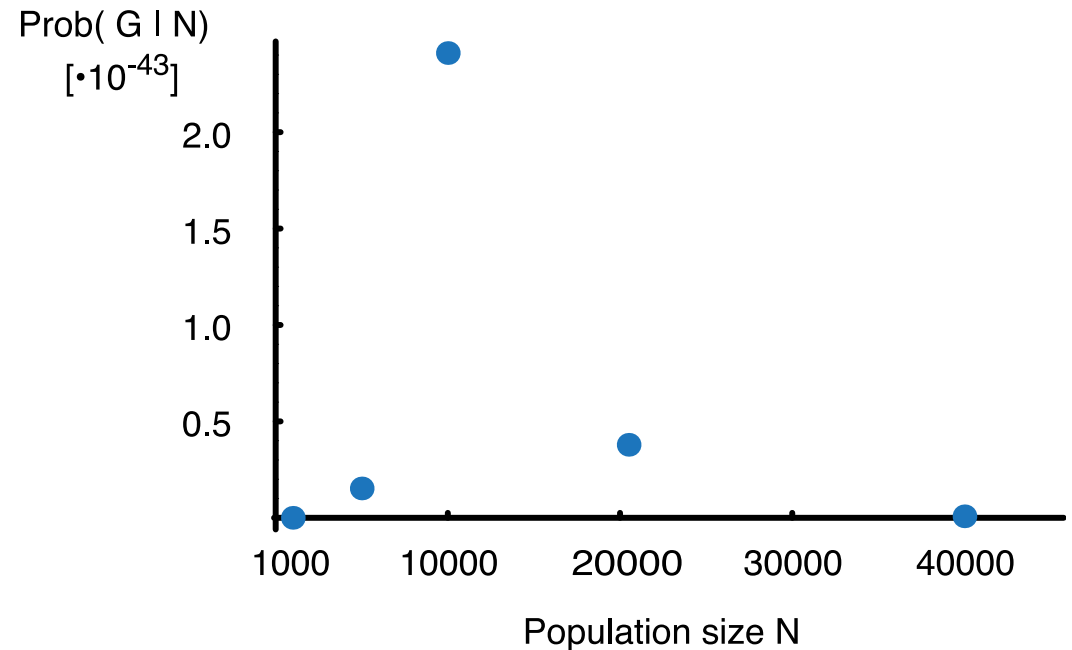
If an oracle gives us the true relationship tree G then we can calculate the population size N .

$$p(G|N, n) = \prod_{k=2}^n \exp\left(-u_k \frac{k(k-1)}{4N}\right) \frac{2}{4N}$$



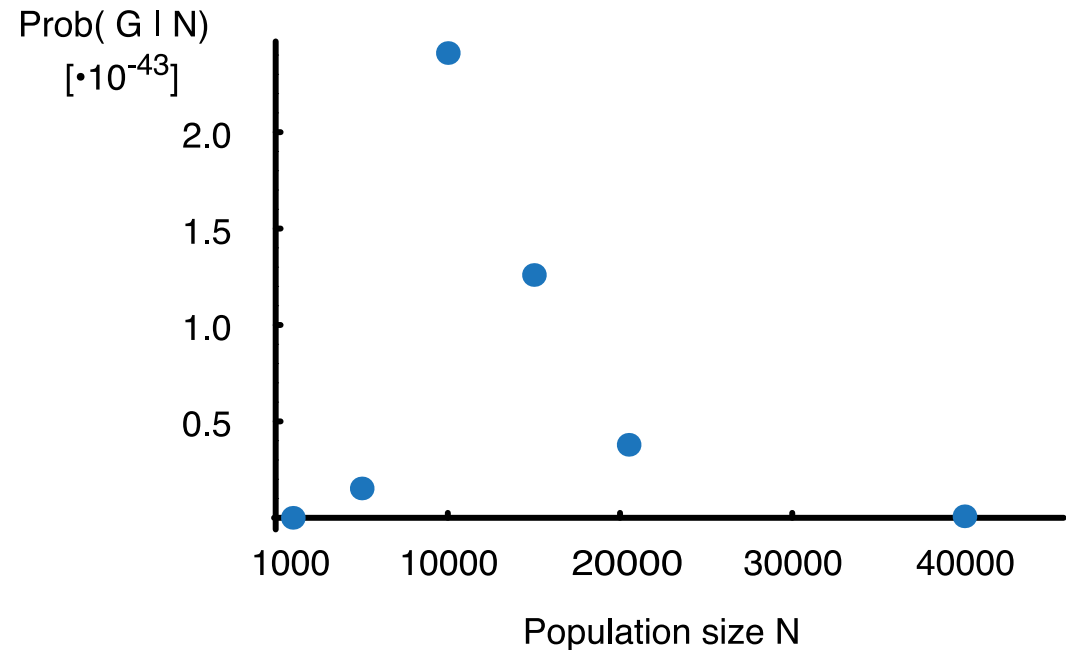
If an oracle gives us the true relationship tree G then we can calculate the population size N .

$$p(G|N, n) = \prod_{k=2}^n \exp\left(-u_k \frac{k(k-1)}{4N}\right) \frac{2}{4N}$$



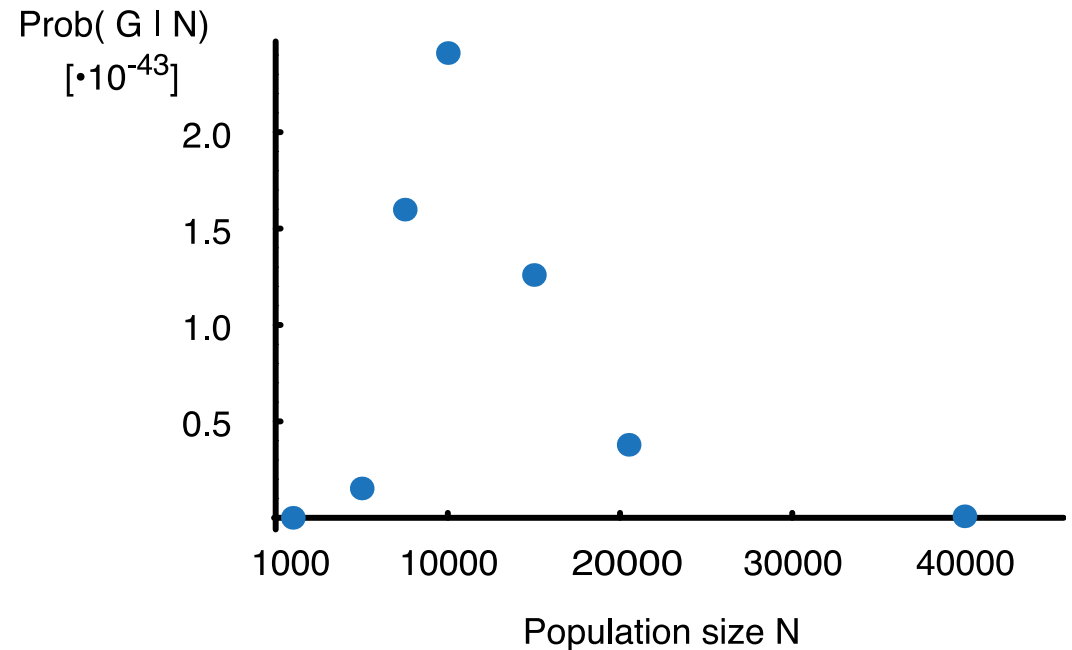
If an oracle gives us the true relationship tree G then we can calculate the population size N .

$$p(G|N, n) = \prod_{k=2}^n \exp\left(-u_k \frac{k(k-1)}{4N}\right) \frac{2}{4N}$$



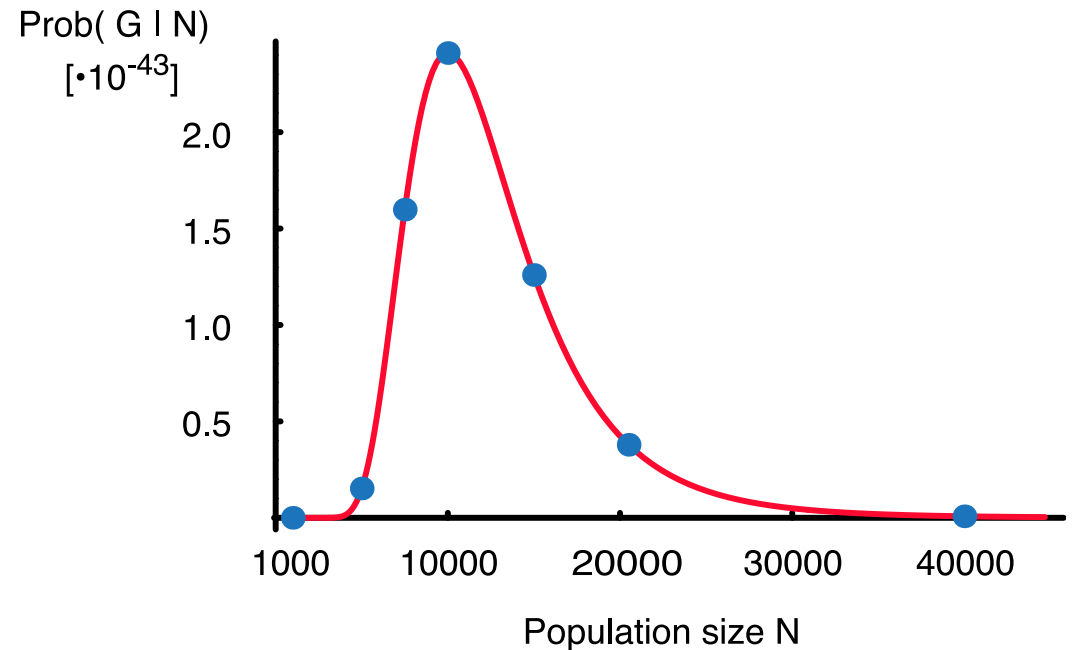
If an oracle gives us the true relationship tree G then we can calculate the population size N .

$$p(G|N, n) = \prod_{k=2}^n \exp\left(-u_k \frac{k(k-1)}{4N}\right) \frac{2}{4N}$$



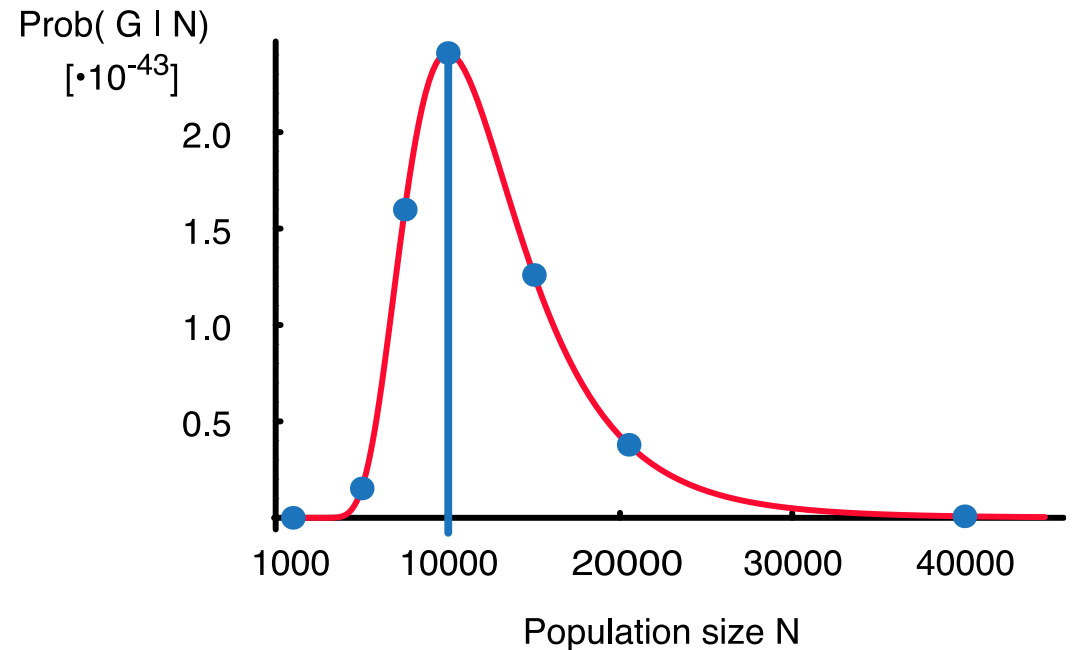
If an oracle gives us the true relationship tree G then we can calculate the population size N .

$$p(G|N, n) = \prod_{k=2}^n \exp\left(-u_k \frac{k(k-1)}{4N}\right) \frac{2}{4N}$$



If an oracle gives us the true relationship tree G then we can calculate the population size N .

$$p(G|N, n) = \prod_{k=2}^n \exp\left(-u_k \frac{k(k-1)}{4N}\right) \frac{2}{4N}$$



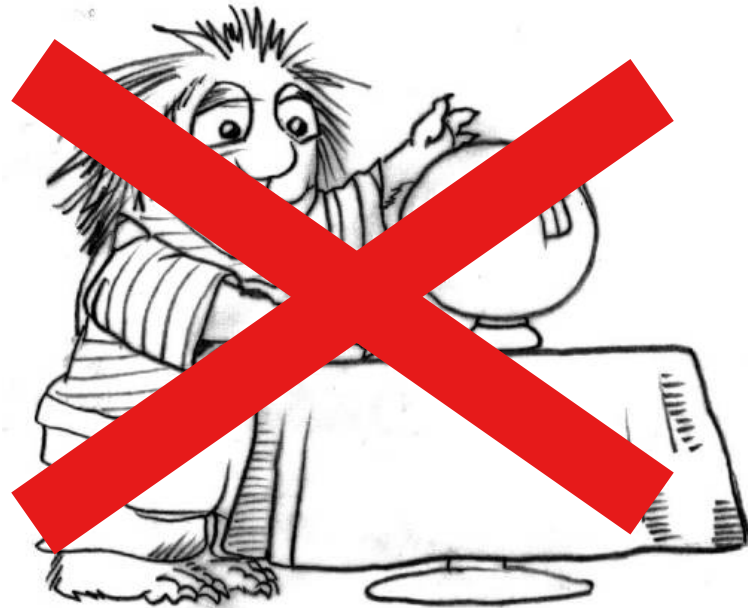
If an oracle gives us the true relationship tree G then we can calculate the population size N .

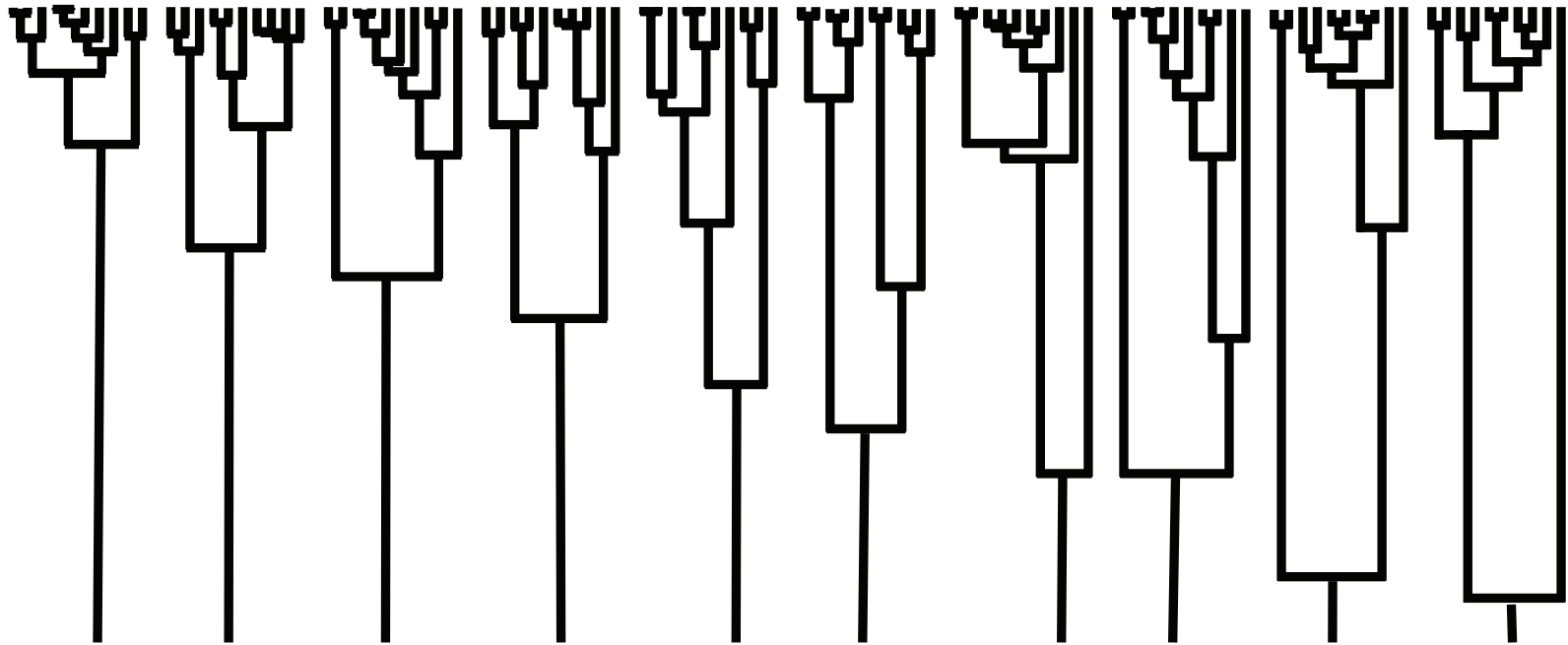
$$p(G|N, n) = \prod_{k=2}^n \exp\left(-u_k \frac{k(k-1)}{4N}\right) \frac{2}{4N}$$

Population size estimation

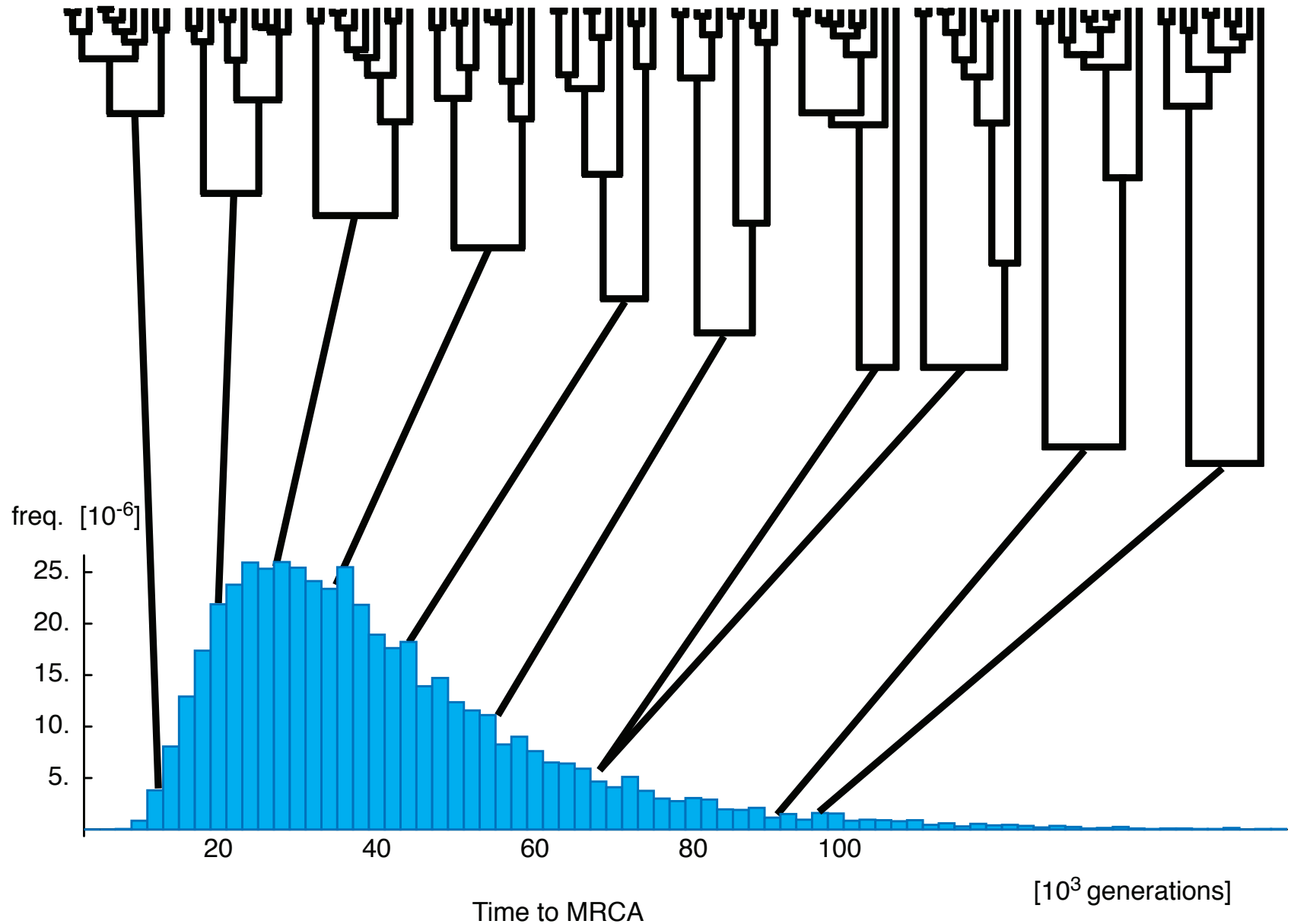
There are at least two problems with the oracle-approach:

- ❖ There is no oracle to gives us clear information!
- ❖ We do not record genealogies, our data are sequences, microsatellite loci!
- ❖ What about the variability of the coalescence process?





All genealogies were simulated with the same population size $N_e = 10,000$



MRCA = most recent common ancestor (last node in the genealogy)

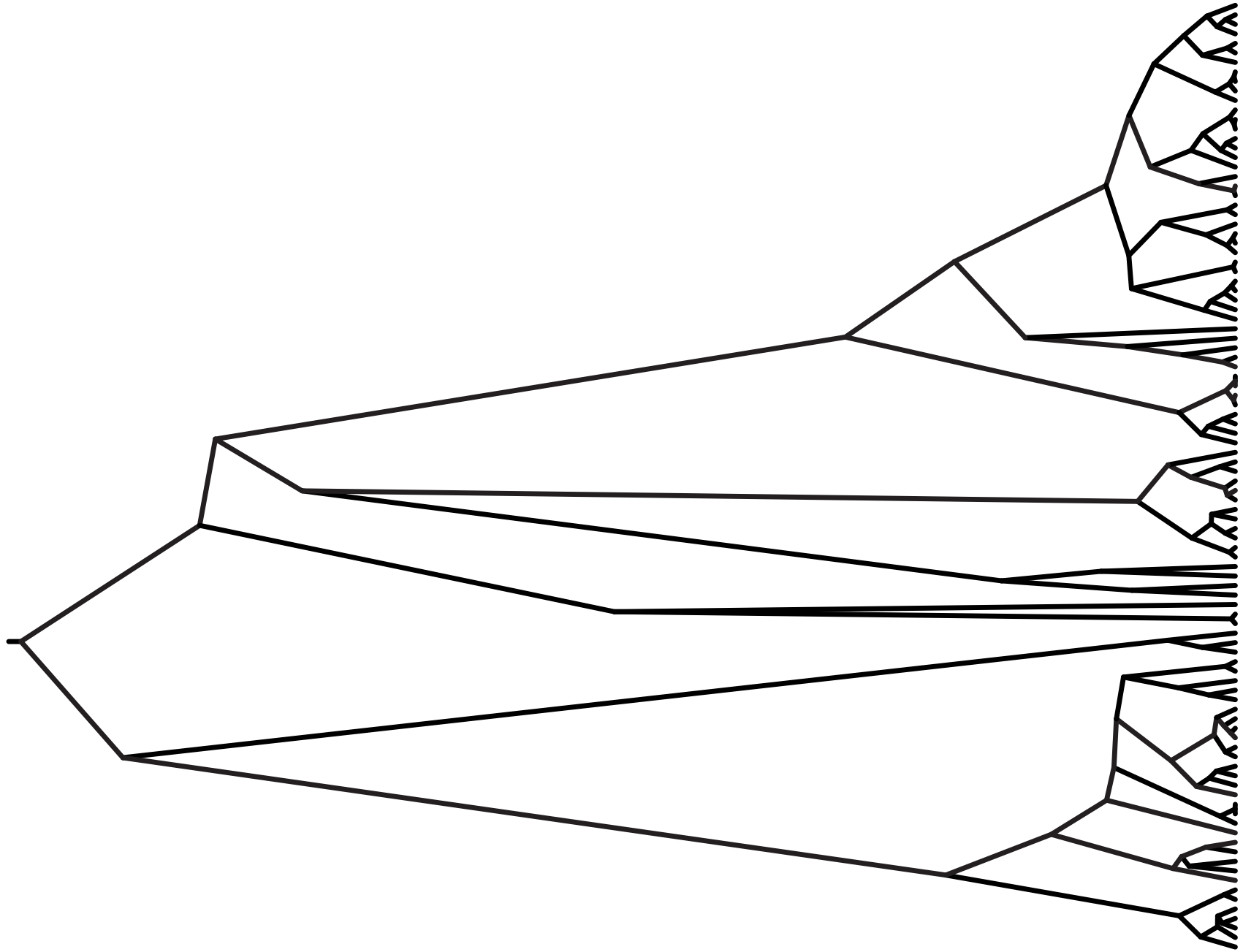
- ◆ All individuals have the same fitness (no selection).
- ◆ All individuals have the same chance to be in the sample (random sampling).
- ◆ The coalescent allows only merging two lineages per generation. This restricts us to to have a much smaller sample size than the population size.

$$n \ll N$$

- ◆ Yun-Xin Fu (2005) described the exact coalescent for the Wright-Fisher model and derived a maximal sample size $n < \sqrt{4N}$ for a diploid population. Although this may look like a severe restriction for the use of the coalescence in small populations, it turned out that the coalescence is rather robust and that even sample sizes close to the effective population size are not biasing immensely.

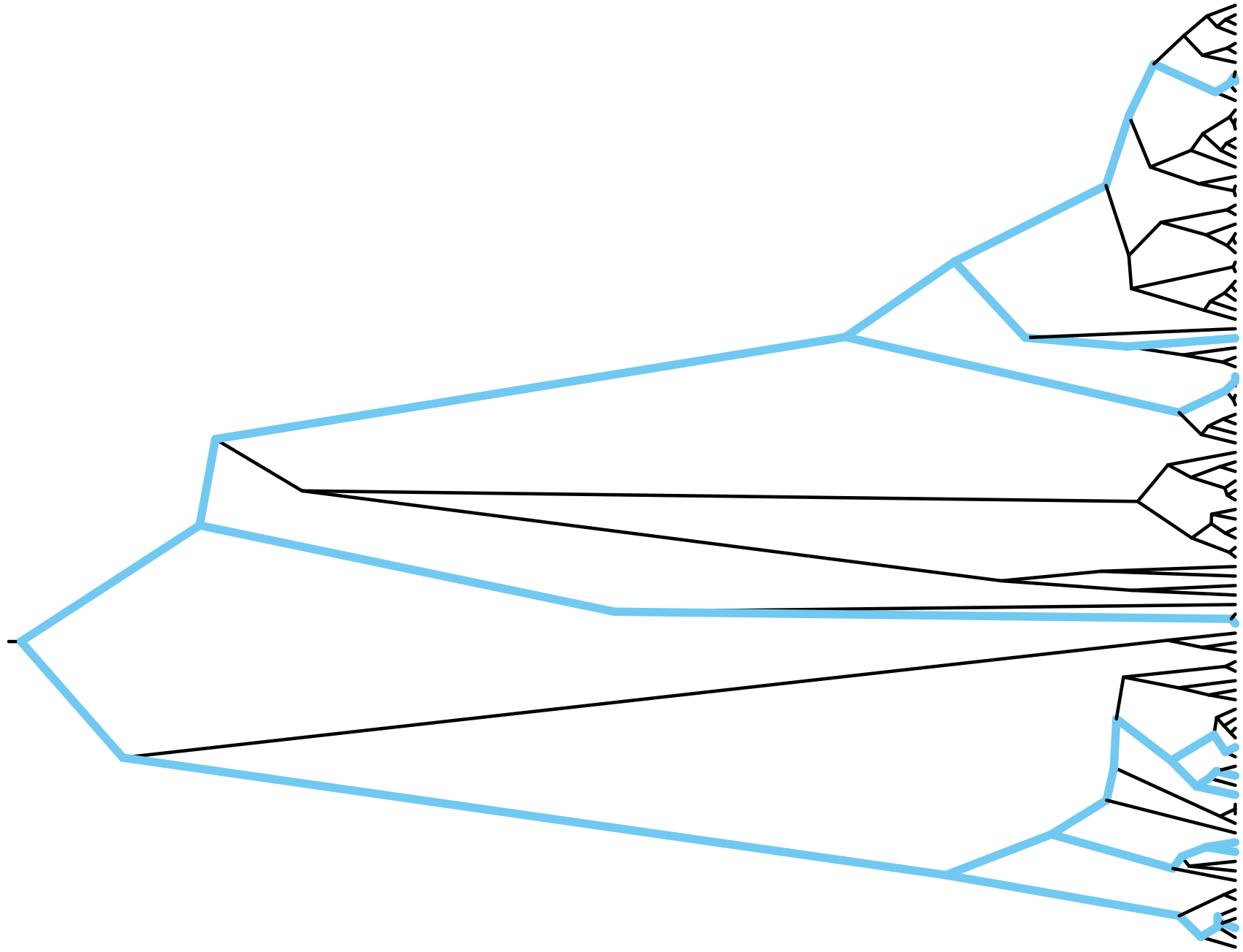
Kingman's n -coalescent is an approximation

Sample size



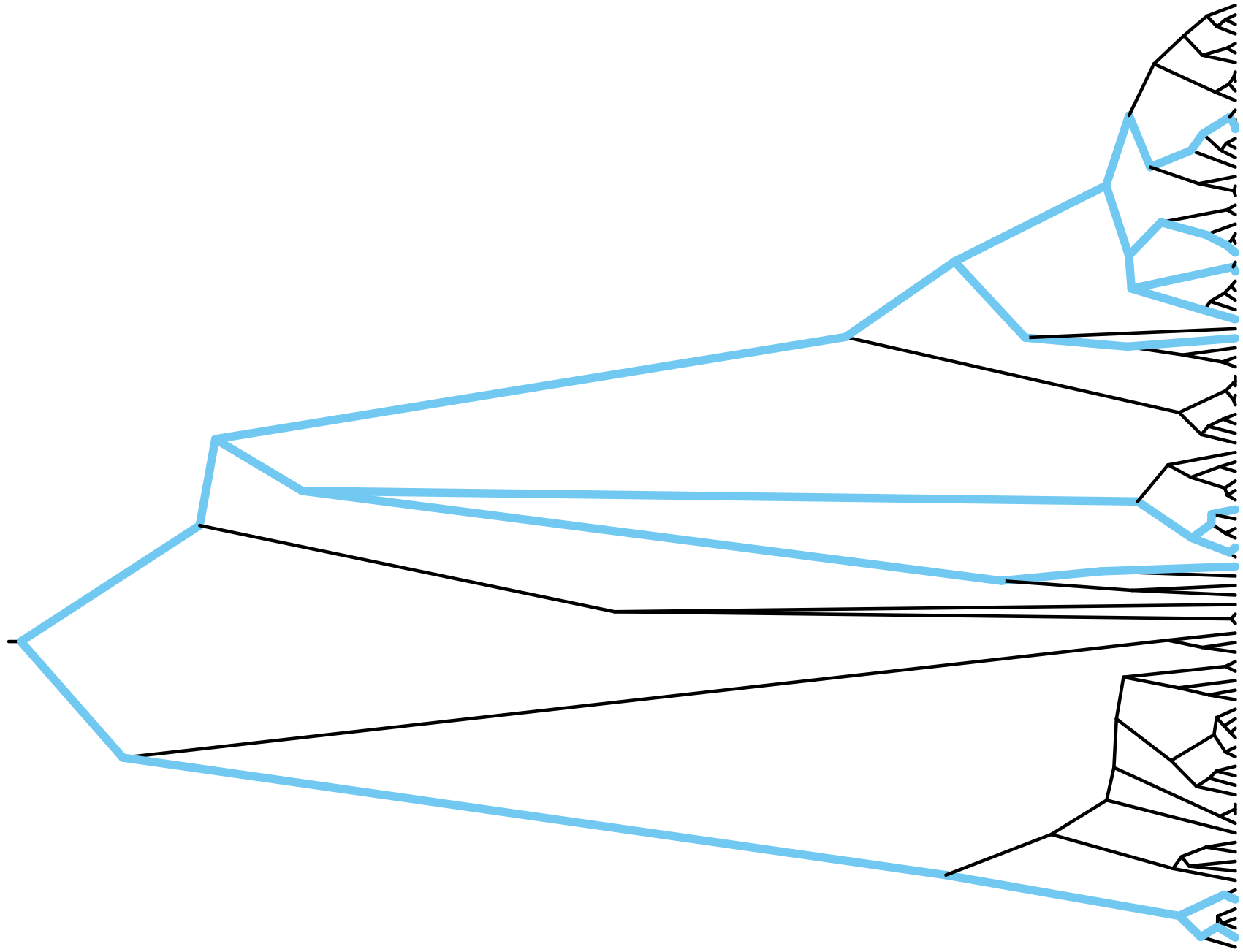
Kingman's n -coalescent is an approximation

Sample size



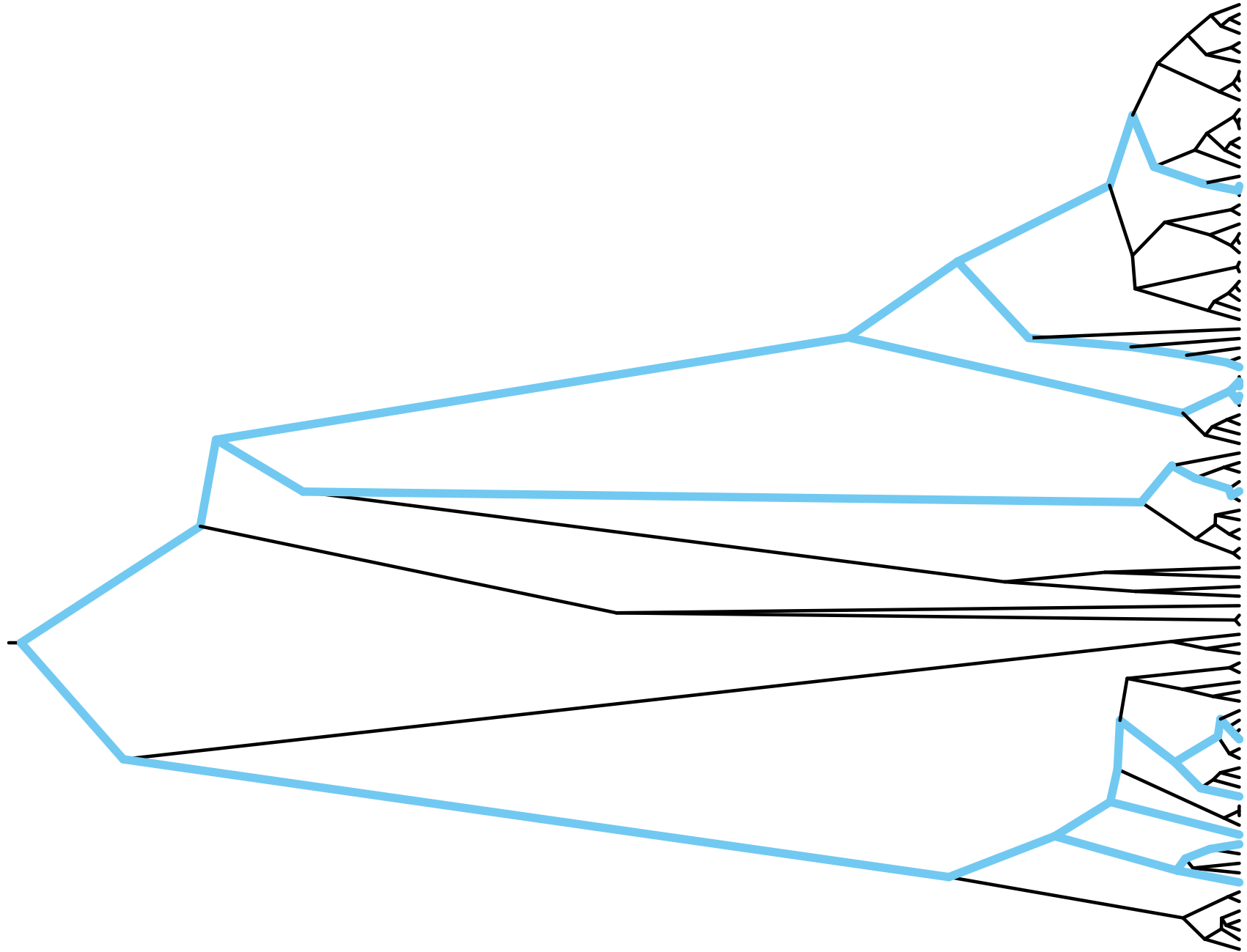
Kingman's n -coalescent is an approximation

Sample size



Kingman's n -coalescent is an approximation

Sample size



- ❖ Large samples coalesce on average in $4N$ generations.
- ❖ The time to the most recent common ancestor (TMRCA) has a large variance
- ❖ Even a sample with few individuals can most often recover the same TMRCA as a large sample.
- ❖ The sample size should be much smaller than the population size, although severe problems appear only with sample sizes of the same magnitude as the population size, or with non-random samples because Kingman's coalescence process assumes that maximally two sample lineages coalesce in any generation.
- ❖ With a known genealogy we can estimate the population size. Unfortunately, the true genealogy of a sample is rarely known.

Genealogy and data

our data looks like this:

```
rid1 GAC ACAAGCAC GAAC TAA C C C GGAGAAGAGACGC TAGAGAGGGGA A GATA CAA G AC AAA AC G AC GGCGACCC AGCA
rid2 GAC ACAAGCAC GAAC TAA C C C GGAGAAGAGACGC TAGAGAGGGGA A GATA CAA G AC AAA AC G AC GGCGACCC AGCA
rid3 GAC ACAAGCAC GAAC TAA C C C GGAGAAGAGACGC TAGAGAGGGGA A GATA CAA G AC AAA AC G AC GGCGACCC AGCA
rid4 GAC ACAAGCAC GAAC TAA C C C GGAGAAGAGACGC TAGAGAGGGGA A GATA CAA G AC AAA AC G AC GGCGACCC AGCA
rid5 GAC ACAAGCAC GAAC TAA C C C GGAGAAGAGACGC TAGAGAGGGGA A GATA CAA G AC AAA AC G AC GGCGACCC AGCA
rid6 GAC ACAAGCAC GAAC TAA C C C GGAGAAGAGACGC TAGAGAGGGGA A GATA CAA G AC AAA AC G AC GGCGACCC AGCA
rid7 GAC ACAAGCAC GAAC TAA C C C GGAGAAGAGACGC TAGAGAGGGGA A GATA CAA G AC AAA AC G AC GGCGACCC AGCA
rid8 GAC ACAAGCAC GAAC TAA C C C GGAGAAGAGACGC TAGAGAGGGGA A GATA CAA G AC AAA AC G AC GGCGACCC AGCA
rid9ty1b GAC ACAAGCAC GAAC TAA C C C GGAGAAGAGACGA TAGGGGGGA A GATA CAA G AC AAA AC G AC GGCGACCC AGCA
rid10ty2b GAC ACAAGCAC GAAC TAA C C C GGAGAAGAGACGA TAGGGGGGA A GATA CAA G AC AAA AC G AC GGCGACCC AGCA
bed1 GAC ACAAGCAA GAAC TAA C C C GGAGAAGAGACGA TAGGGGGGA A GATA CAA G AC AAA AC G AC GGCGACCC AGCA
cyp1 GAC ACAAGCA GAAC TAA A C C GGAGAAGAGACGA TAGGGGGGA A GATA CAA G AC AAA AC G AC GG GACCC AGCA
cyp2 GAC ACAAGCA GAAC TAA A C C GGAGAAGAGACGA TAGGGGGGA A GATA CAA G AC AAA AC G AC GG GACCC AGCA
cyp3 GAC ACAAG GAAC TAA A C C GGAGAAGAGACGA TAGGGGGGA A GATA CAA G AC AAA AC G AC GG GACCC AGCA
cyp4 GAC ACAAG GAAC TAA A C C GGAGAAGAGACGA TAGGGGGGA A GATA CAA G AC AAA AC G AC GG GACCC AGCA
cilwest1 GAC ACAAG GAAC TAA A C C GGAGAAGAGACGA TAGGGGGGA A GATA CAA G AC AAA AC G AC GGCGACCC AGCA
cilwest2 GAC ACAAG GAAC TAA A C C GGAGAAGAGACGA TAGGGGGGA A GATA CAA G AC AAA AC G AC GGCGACCC AGCA
cileast1 GAC ACAAG GAAC TAA A C C GGAGAAGAGACGA TAGGGGGGA A GATA CAA G AC AAA AC G AC GGCGACCC AGCA
cileast2 GAC ACAAG GAAC TAA A C C GGAGAAGAGACGA TAGGGGGGA A GATA CAA G AC AAA AC G AC GGCGACCC AGCA
cf.caral GAC ACAAG GAAC TAA A C C GGAGAAGAGACGA TAGGGGGGA A GATA CAA G AC AAA AC G AC GG GACCC AGCA
cf.cara2 GAC ACAAG GAAC TAA A C C GGAGAAGAGACGA TAGGGGGGA A GATA CAA G AC AAA AC G AC GG GACCC AGCA
cf.cara3 GAC ACAAGCAA GAAC TAA A C C GGAGAAGAGACGA TAGGGGGGA A GATA CAA G AC AAA AC G AC GG GACCC AGCA
cf.car4 GAC ACAAGCAA GAAC TAA A C C GGAGAAGAGACGA TAGGGGGGA A GATA CAA G AC AAA AC G AC GG GACCC AGCA
cf.cer1 GAC ACAAGCAA GAAC TAA A C C GGAGAAGAGACGA TAGGGGGGA A GATA CAA G AC AAA AC G AC GG GACCC AGCA
cf.cer2 GAC ACAAGCAA GAAC TAA A C C GGAGAAGAGACGA TAGGGGGGA A GATA CAA G AC AAA AC G AC GG GACCC AGCA
cf.cer3 GAC ACAAGCAA GAAC TAA A C C GGAGAAGAGACGA TAGGGGGGA A GATA CAA G AYAAA AC G AC GG GACCC AGCA
cf.cer4 GAC ACAAGCAAY GAAC TAA A C C GGAGAAGAGACGA TAGGGGGGA A GATA CAA G AC AAA AC G AC GG GACCC AGCA
cf.bed1 GAC ACAAGCA GAAC TAA A C C GGAGAAGAGACGA TAGGGGGGA A GATA CAA G AC AAA AC G AC GG GACCC AGCA
cf.bed2 GAC ACAAGCAAY GAAC TAA A C C GGAGAAGAGACGA TAGGGGGGA A GATA CAA G AC AAA AC G AC GG GACCC AGCA
cf.bed3 GAC ACAAGCAAY GAAC TAA A C C GGAGAAGAGACGA TAGGGGGGA A GATA CAA G AC AAA AC G AC GG GACCC AGCA
cf.bed4 GAC ACAAGCAC GAAC TAA A C C GGAGAAGAGACGA TAGGGGGGA A GATA CAA G AC AAA AC G AC GG GACCC AGCA
cf.bed5 GAC ACAAGCA GAAC TAA A C C GGAGAAGAGACGA TAGGGGGGA A GATA CAA G AC AAA AC G AC GG GACCC AGCA
cf.bed6 GAC ACAAGCAC GAAC TAA A C C GGAGAAGAGACGA TAGGGGGGA A GATA CAA G AC AAA AC G AC GG GACCC AGCA
cf.bed7 GAC ACAAGCA GAAC TAA A C C GGAGAAGAGACGA TAGGGGGGA A GATA CAA G AC AAA AC G AC GG GACCC AGCA
cf.bed8 GAC ACAAGCA GAAC TAA A C C GGAGAAGAGACGA TAGGGGGGA A GATA CAA G AC AAA AC G AC GG GACCC AGCA
epe6-GR GAC ACAAGCAC GAAC TAA C C C GGAGAAGAGACGA TAGGGGGGA A GATA CAA G AC AAA AC G AC GGCGACCC AGCA
epe7-GR GAC ACAAGCAC GAAC TAA C C C GGAGAAGAGACGA TAGGGGGGA A GATA CAA G AC AAA AC G AC GGCGACCC AGCA
cre04a-GR GAC ACAAGCAC GAACC TAA C C C GGAGAAGAGACGA TAGGGGGGA A GATA CAA G AC AAA AC G AC GG GACCC AGCA
cre5-GR GAC ACAAGCAC GAACC TAA C C C GGAGAAGAGACGA TAGGGGGGA A GATA CAA G AC AAA AC G AC GG GACCC AGCA
```

Finding the best genealogy from such data is difficult

Genetic data and the coalescent

- ◆ Finite populations lose alleles due to genetic drift
- ◆ Mutation introduces new alleles into a population at rate μ
- ◆ With $2N$ chromosomes we can expect to see every generation $2N\mu$ new mutations. The population size N is positively correlated with the mutation rate μ .
- ◆ With genetic data sampled from several individuals we can use the mutational variability to estimate the population size.

Population size

The observed genetic variability

$$\mathcal{S} = f(N, \mu, n).$$

Different N and appropriate μ can give the same number of mutations. For example, for 100 loci sampled from 20 individuals with 1000bp each, we get :

N	μ	$4N\mu$	\hat{S}	σ_S^2
1250	10^{-5}	0.05	153.95	16.25
12500	10^{-6}	0.05	152.89	16.05

Using genetic variability alone therefore **does not allow** to disentangle N and μ .

With **multiple dated samples** and known generation time we **can** estimate N and μ independently.

Mutation-scaled population size

By convention we express most results as the compound $N\mu$ and an inheritance scalar x , for simplicity we call this the **mutation-scaled population size**

$$\Theta = xN\mu,$$

where μ is the mutation rate per generation and per site. With a mutation rate per locus we use θ .

◆ for diploids: $\Theta = 4N\mu$.

◆ for haploids: $\Theta = 2N\mu$.

◆ For mtDNA in diploids with strictly maternal inheritance this leads to $\Theta = 2N_f\mu$, and if the sex ratio is 1 : 1 then $\Theta = N\mu$

Most real populations do not behave exactly like Wright-Fisher populations, therefore we subscript N and call it the **effective** population size N_e , and consider Θ the **mutation-scaled EFFECTIVE population size**.

Mutation-scaled population size

By convention we express most results as the compound $N\mu$ and an inheritance scalar x , for simplicity we call this the **mutation-scaled population size**

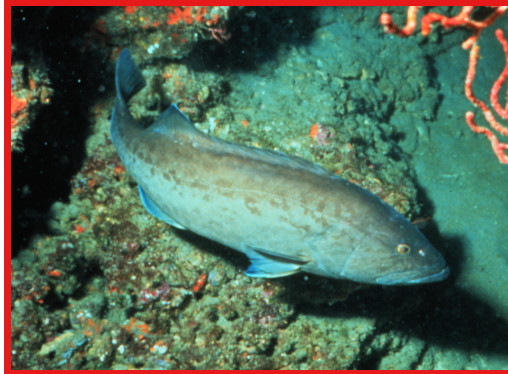
$$\Theta = xN\mu,$$

where μ is the mutation rate per generation and per site. With a mutation rate per locus we use θ .

◆ for diploids: $\Theta = 4N\mu$.

◆ for haploids: $\Theta = 2N\mu$.

◆ For mtDNA in diploids with strictly maternal inheritance this leads to $\Theta = 2N_f\mu$, and if the sex ratio is 1 : 1 then $\Theta = N\mu$



Gag Grouper starts out as a female and later in life becomes male.

Most real populations do not behave exactly like Wright-Fisher populations, therefore we subscript N and call it the **effective** population size N_e , and consider Θ the **mutation-scaled EFFECTIVE population size**.

Historical humpback whale population size

Humpback whales in the North Atlantic: Census population size around 12,000.



Historical humpback whale population size

using the data by Joe Roman and Stephen R. Palumbi (Science 2003 301: 508-510)

$\Theta = 2N_{\text{♀}}\mu$ 0.01529 Population size of the North Atlantic population, estimated using migrate

$N_{\text{♀}} = \frac{\Theta}{2\mu}$ 31,854 with $\mu = 2.0 \times 10^{-8} \text{bp}^{-1} \text{year}^{-1}$ and a generation time of 12 years

$N_e = N_{\text{♀}} + N_{\text{♂}}$ 63,708 Sex ratio is 1:1

$N_B = 2N_e$ 127,417 ratio N_B/N_e assumed, using other data

$N_T = N_B \frac{N_{\text{juveniles}} + N_{\text{adults}}}{N_{\text{adults}}}$ 203,867 from catch and survey data (used a ratio of 1.6)

More modern estimates for mtDNA: 150,000 [improved estimation of mutation rate]; for nucDNA: 112,000(45,000 – 235,000) [Conservation Genetics (2013) 14:103114]

Using the infinite sites model we use the number of variable sites S per locus to calculate the mutation-scaled population size:

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

from a sample of n individuals. For a single population the Watterson's estimator works marvelously well, but it is vulnerable to population structure.

Watterson's θ_W uses a mutation rate per locus! To compare with other work use mutation rate per site.

[in the second part of the coalescence talk I will discuss estimates based on site frequency spectra]

For Bayesian inference we want to calculate the probability of the model parameters given the data $p(\text{model}|D)$.

Coalescent to describe the population genetic processes.

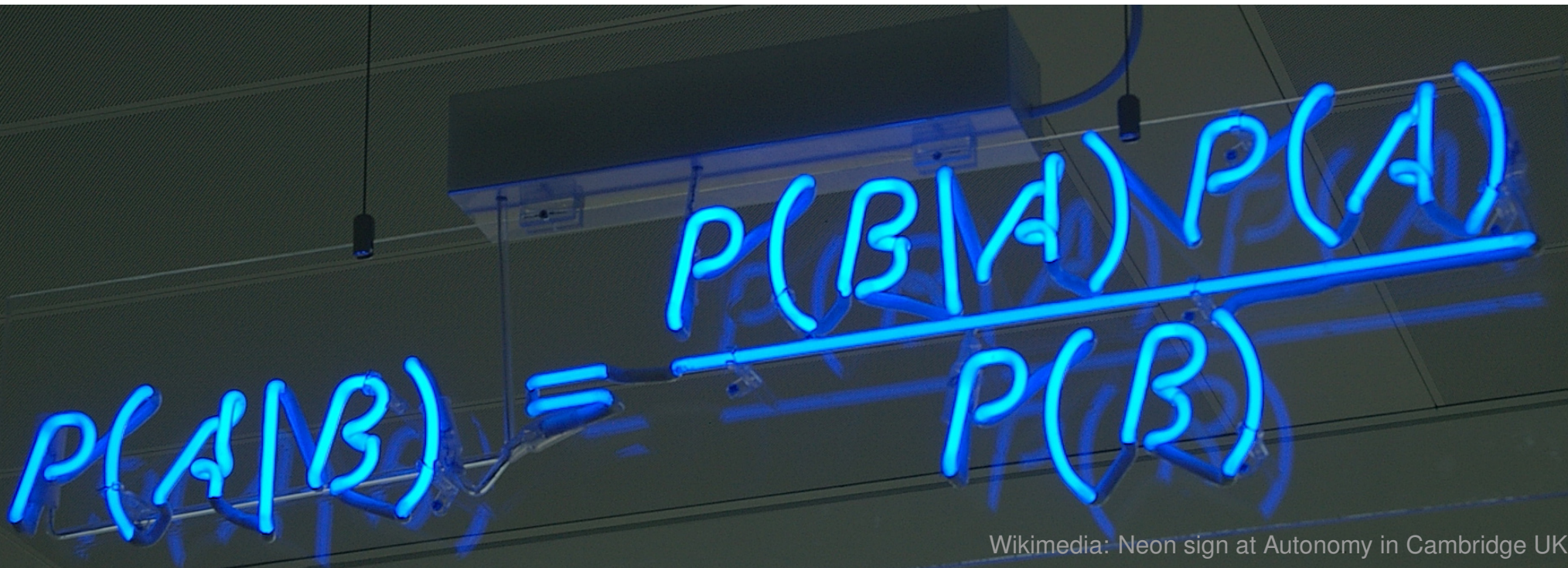
Mutation model to describe the change of genetic material over time.



We calculate the **Posterior distribution** $p(\Theta|D)$ using Bayes' rule

$$p(\Theta|D) = \frac{p(\Theta)p(D|\Theta)}{p(D)}$$

where $p(D|\Theta)$ is the **likelihood** of the parameters.



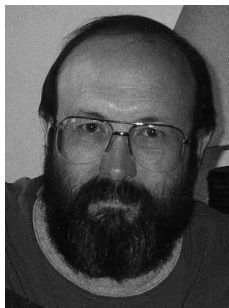
$$p(D|\Theta, G) = p(G|\Theta)p(D|G)$$

$$p(G|\Theta)$$



The probability density of a genealogy given parameters.

$$p(D|G)$$



The probability density of the data for a given genealogy. Phylogeneticists know this as the tree-likelihood.

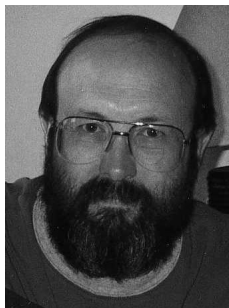
$$p(D|\Theta) = \int_G p(G|\Theta)p(D|G)dG$$

$p(G|\Theta)$



The probability density of a genealogy given parameters.

$p(D|G)$



The probability density of the data for a given genealogy. Phylogeneticists know this as the tree-likelihood.

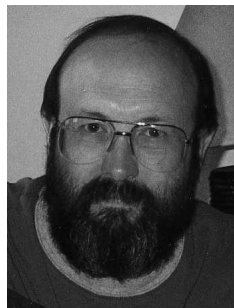
$$p(D|\Theta) = \sum_G p(G|\Theta)p(D|G)$$

$p(G|\Theta)$



The probability of a genealogy given parameters.

$p(D|G)$

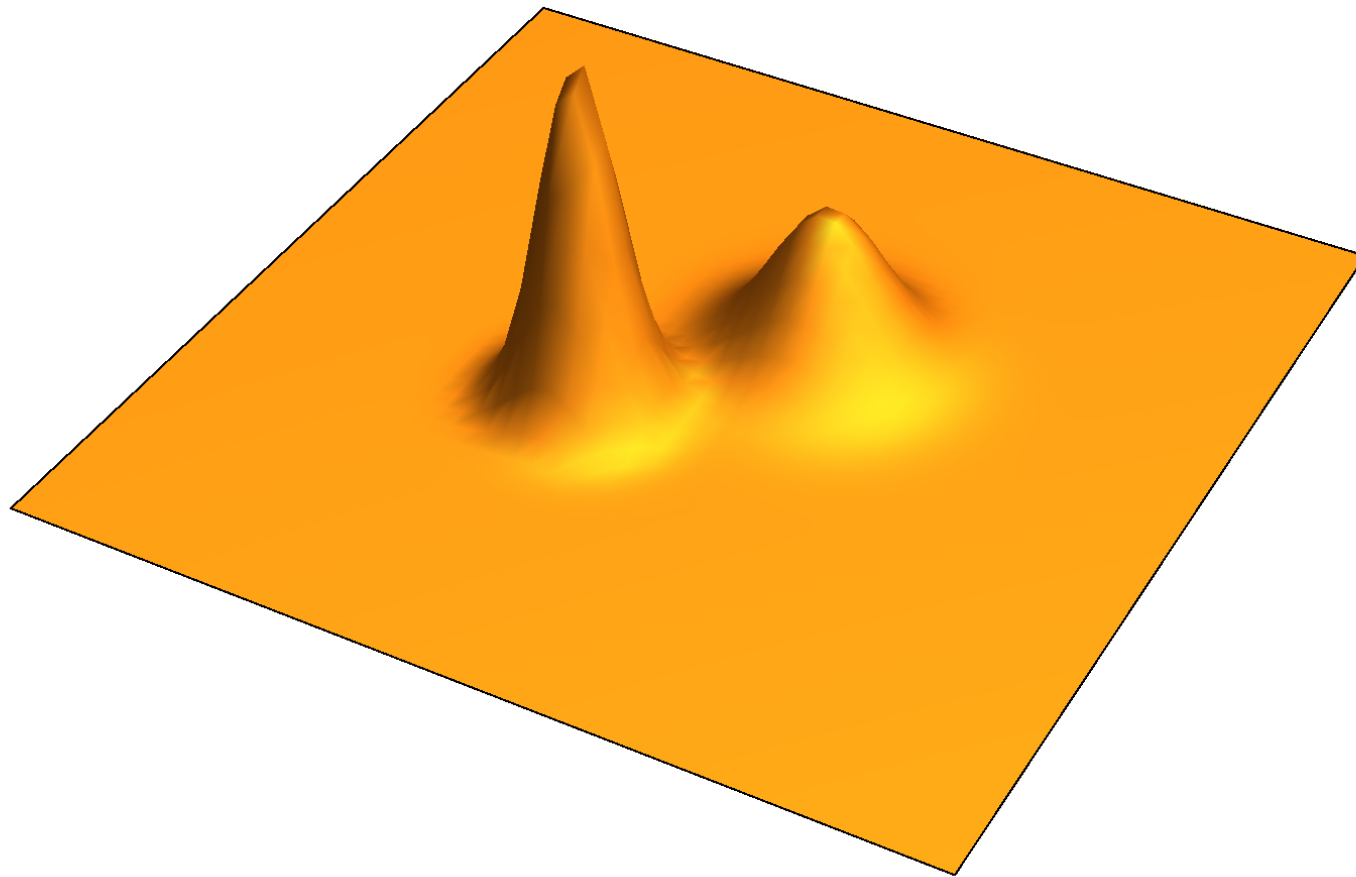


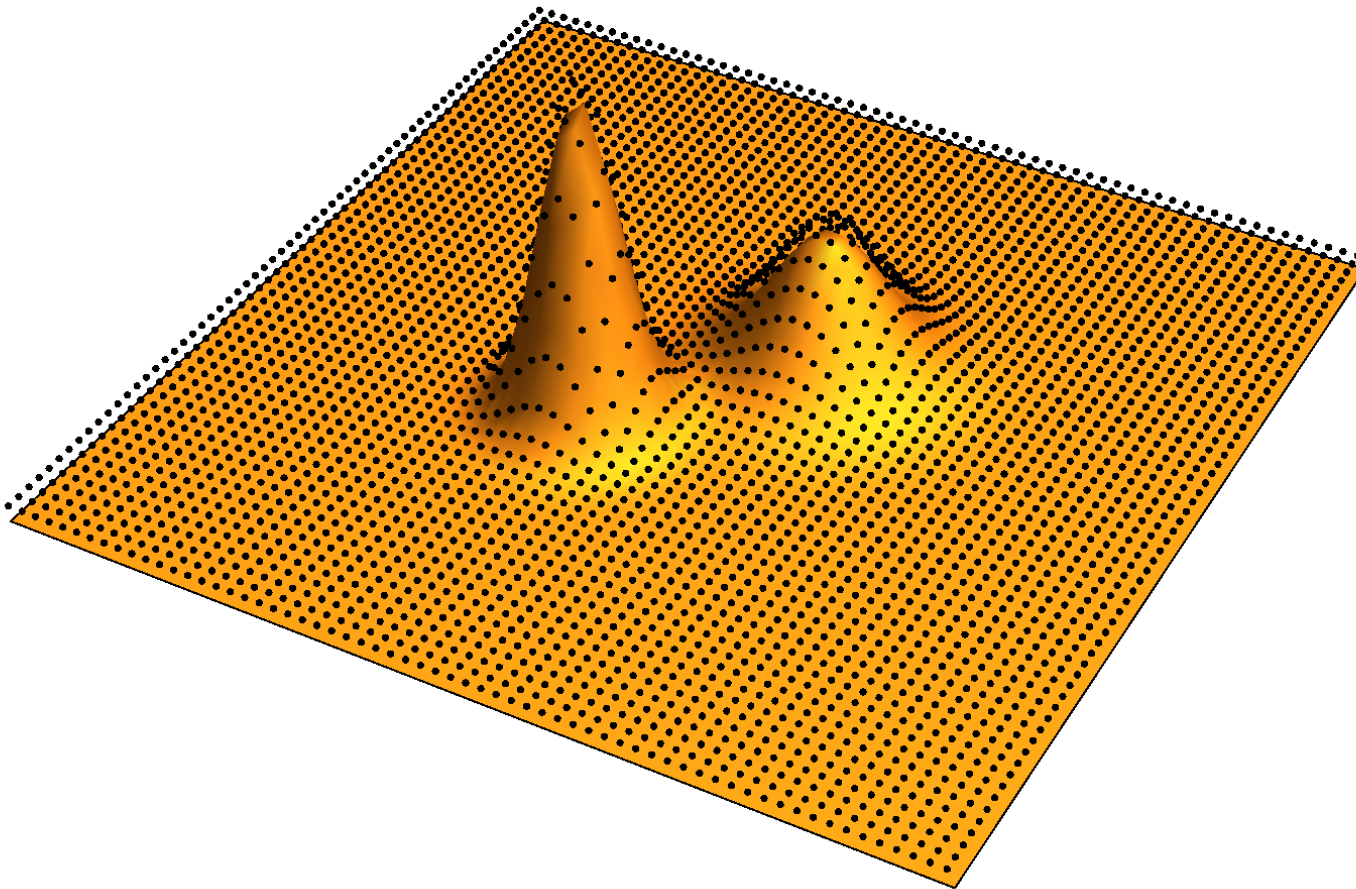
The probability of the data for a given genealogy. Phylogeneticists know this as the tree-likelihood.

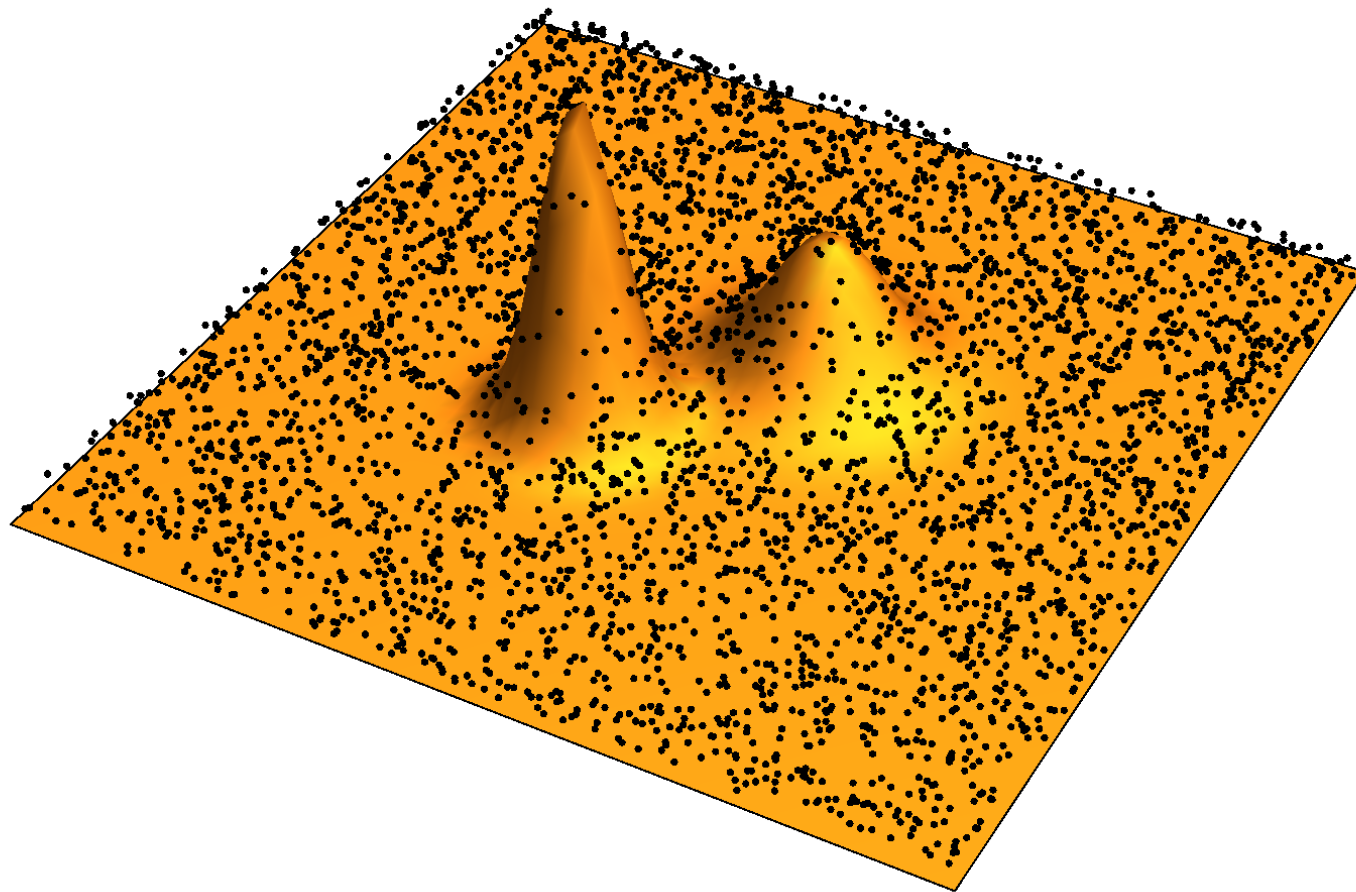
Problem with integration formula

$$p(D|\Theta) = \int_G p(G|\Theta)p(D|G)dG$$

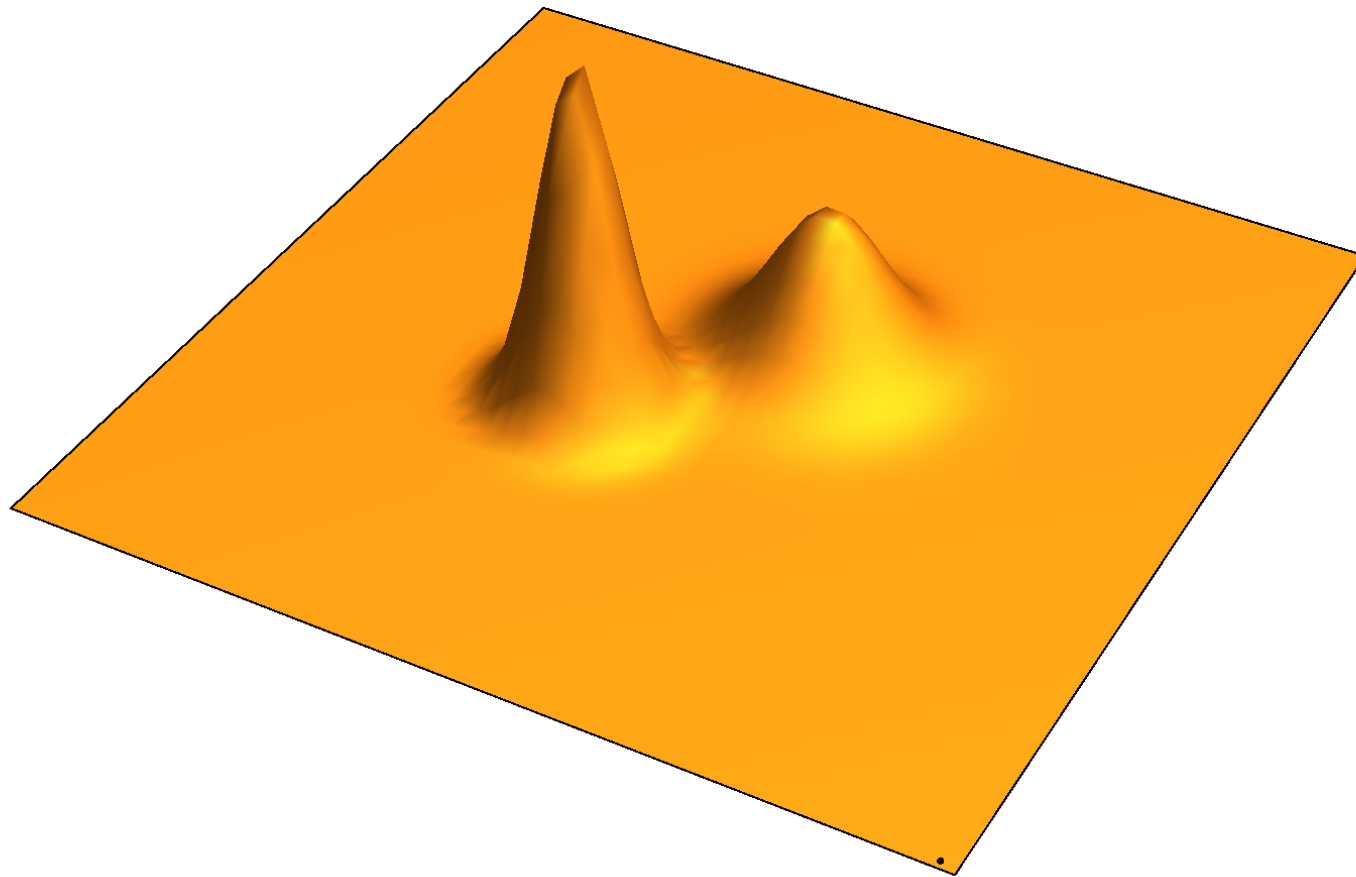
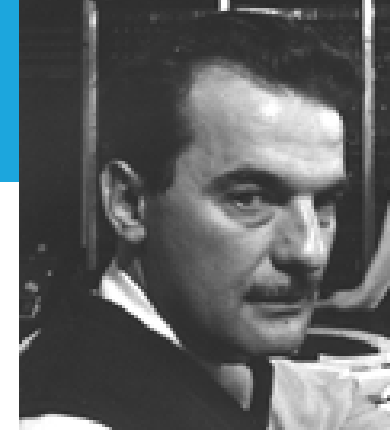
The number of possible genealogies is very large and for realistic data sets, programs need to use Markov chain Monte Carlo methods.



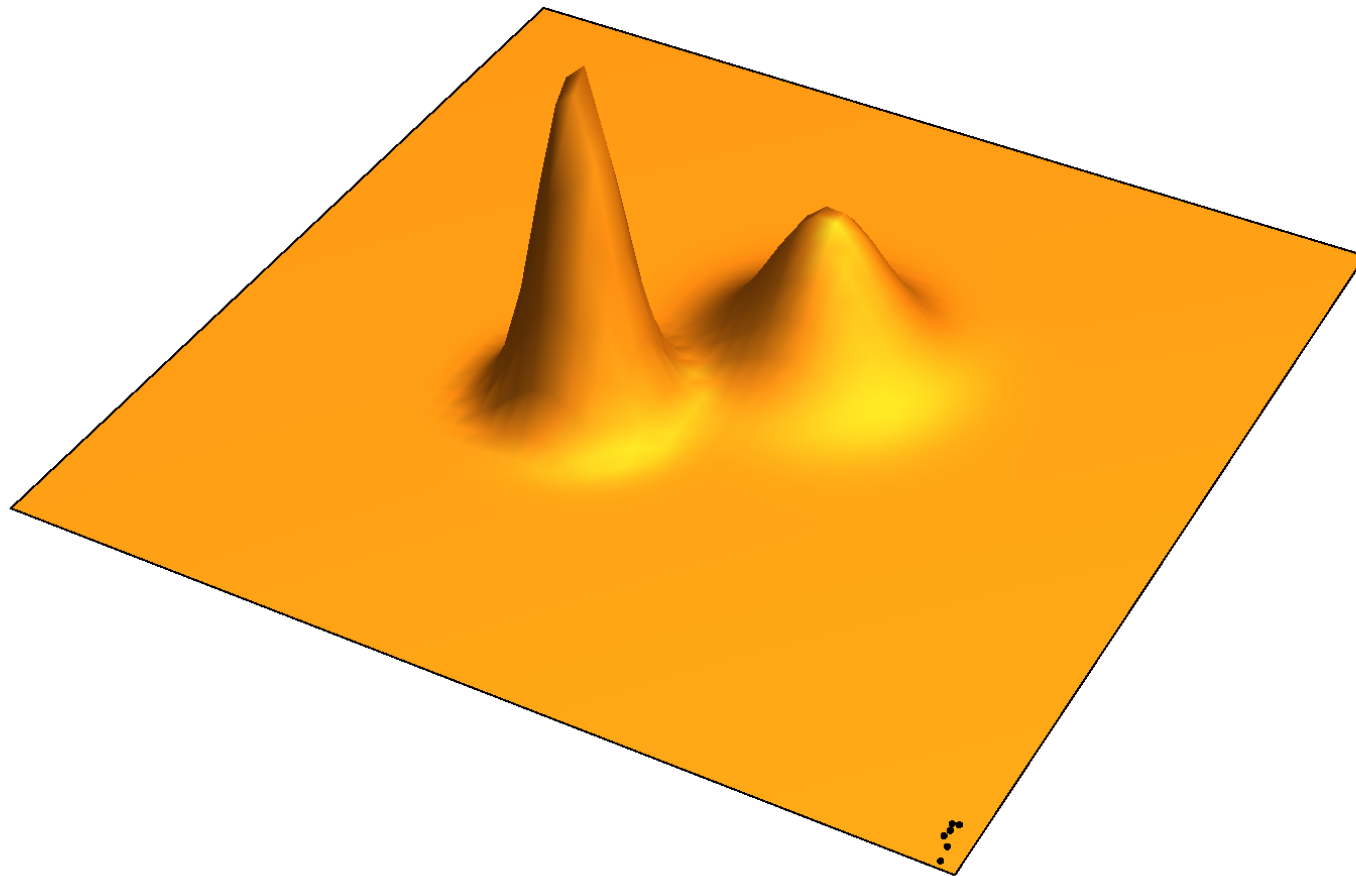
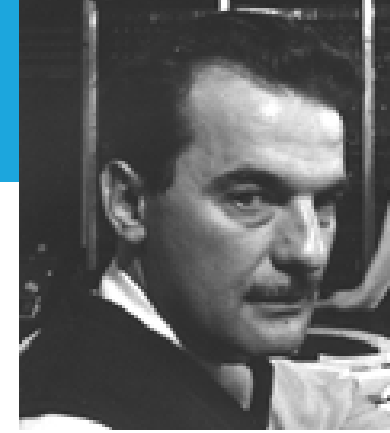




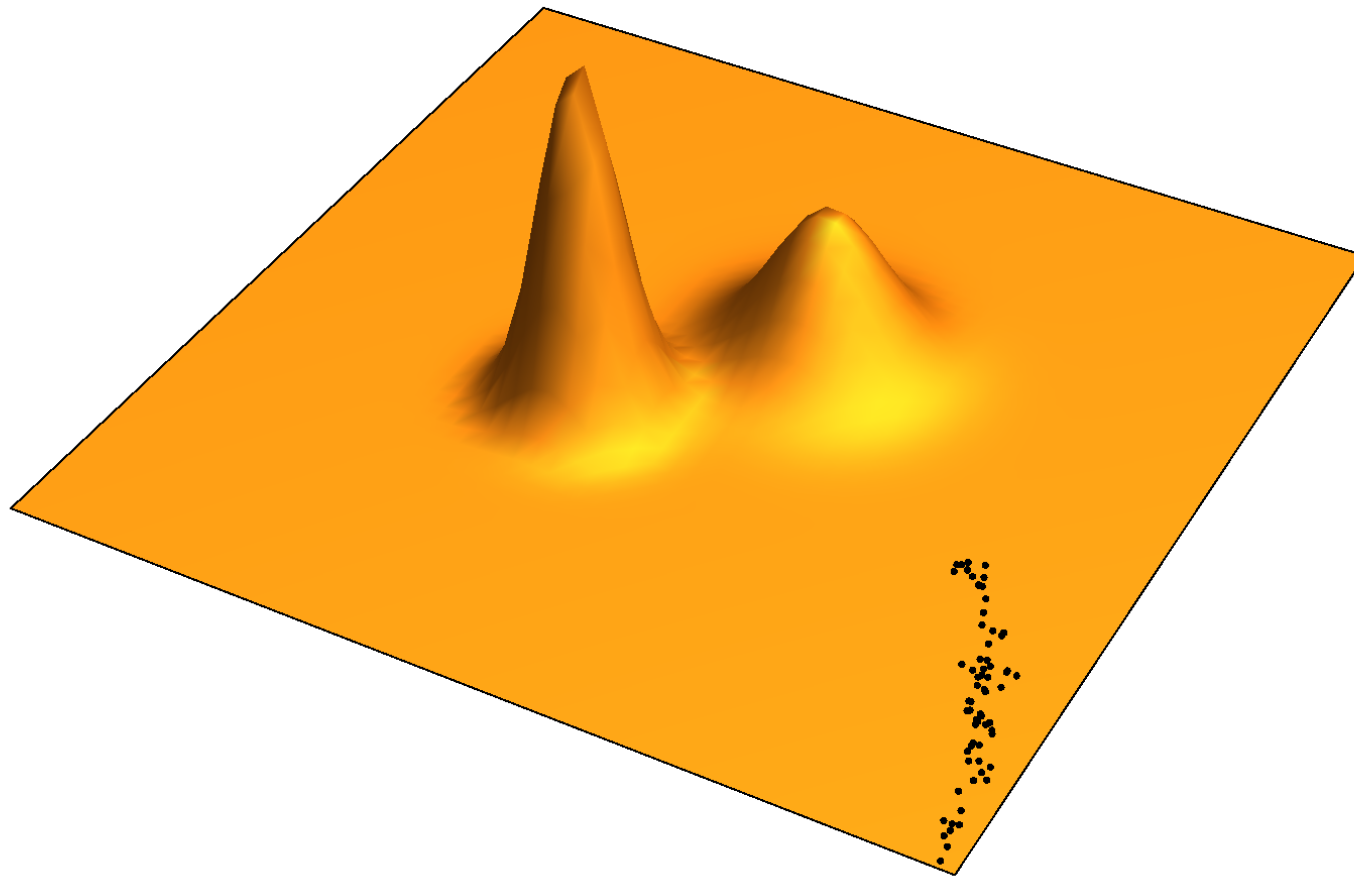
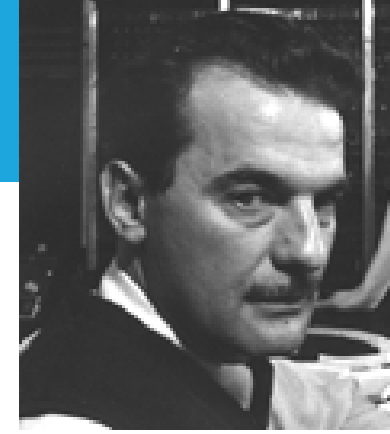
Metropolis-Hastings algorithm



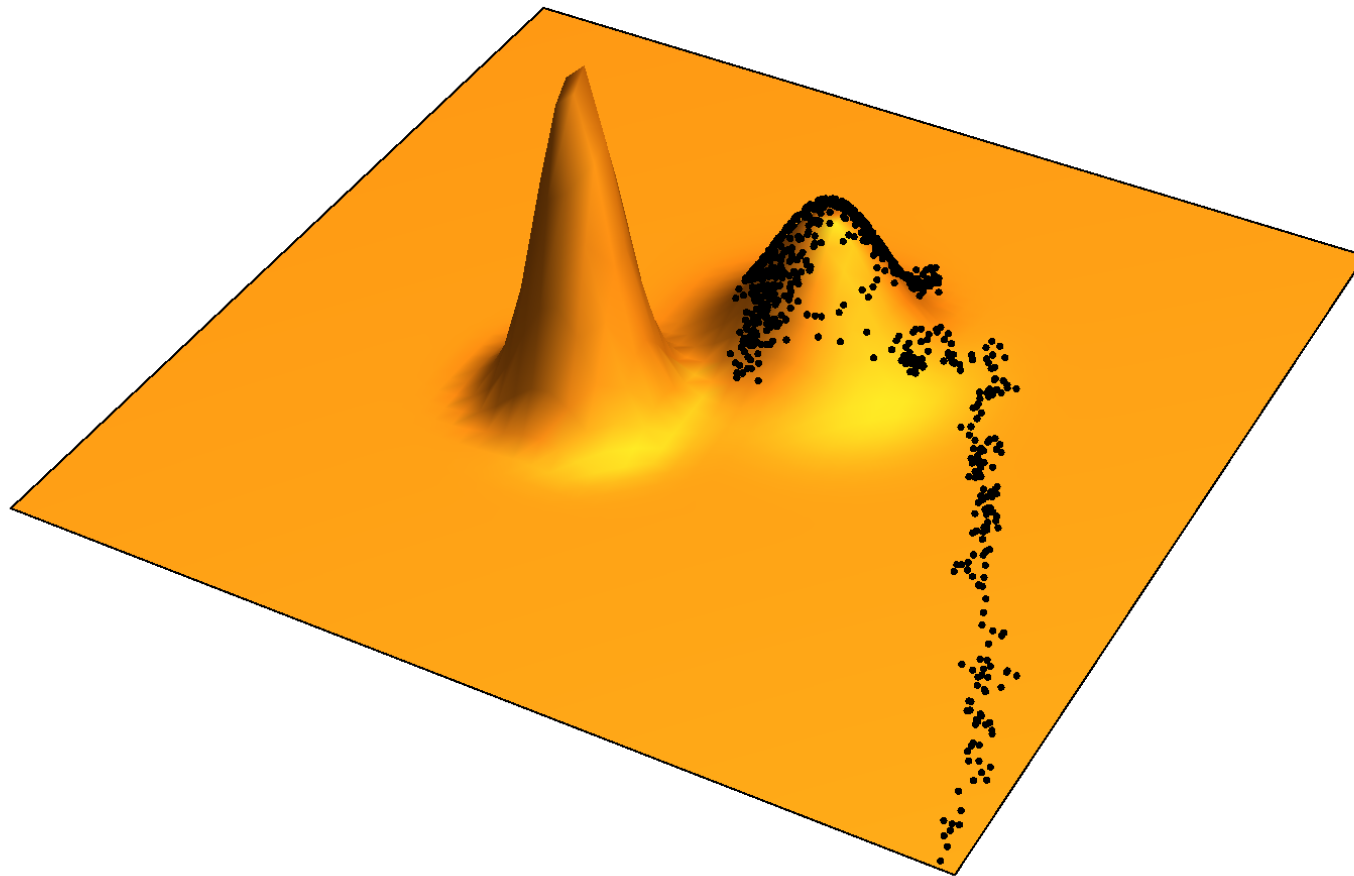
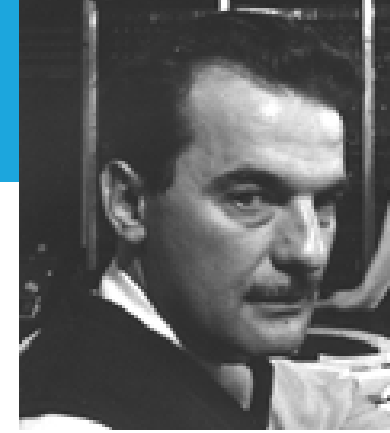
Metropolis-Hastings algorithm



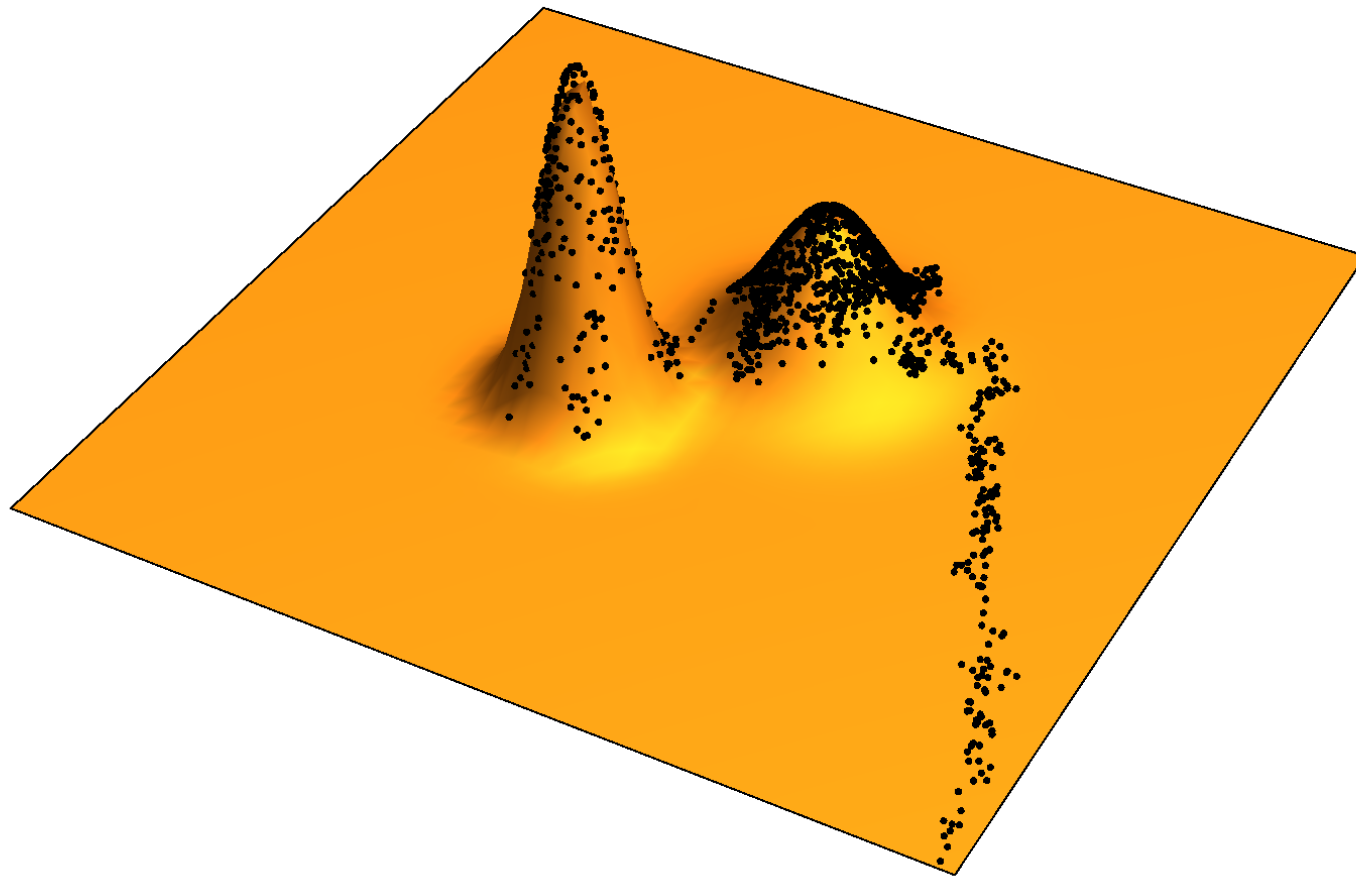
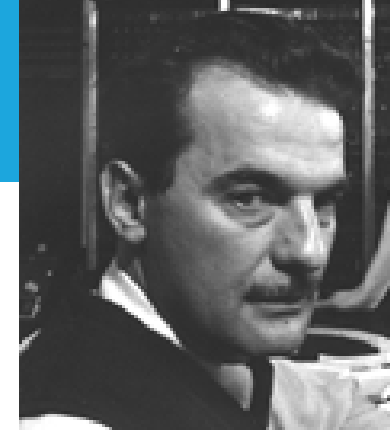
Metropolis-Hastings algorithm



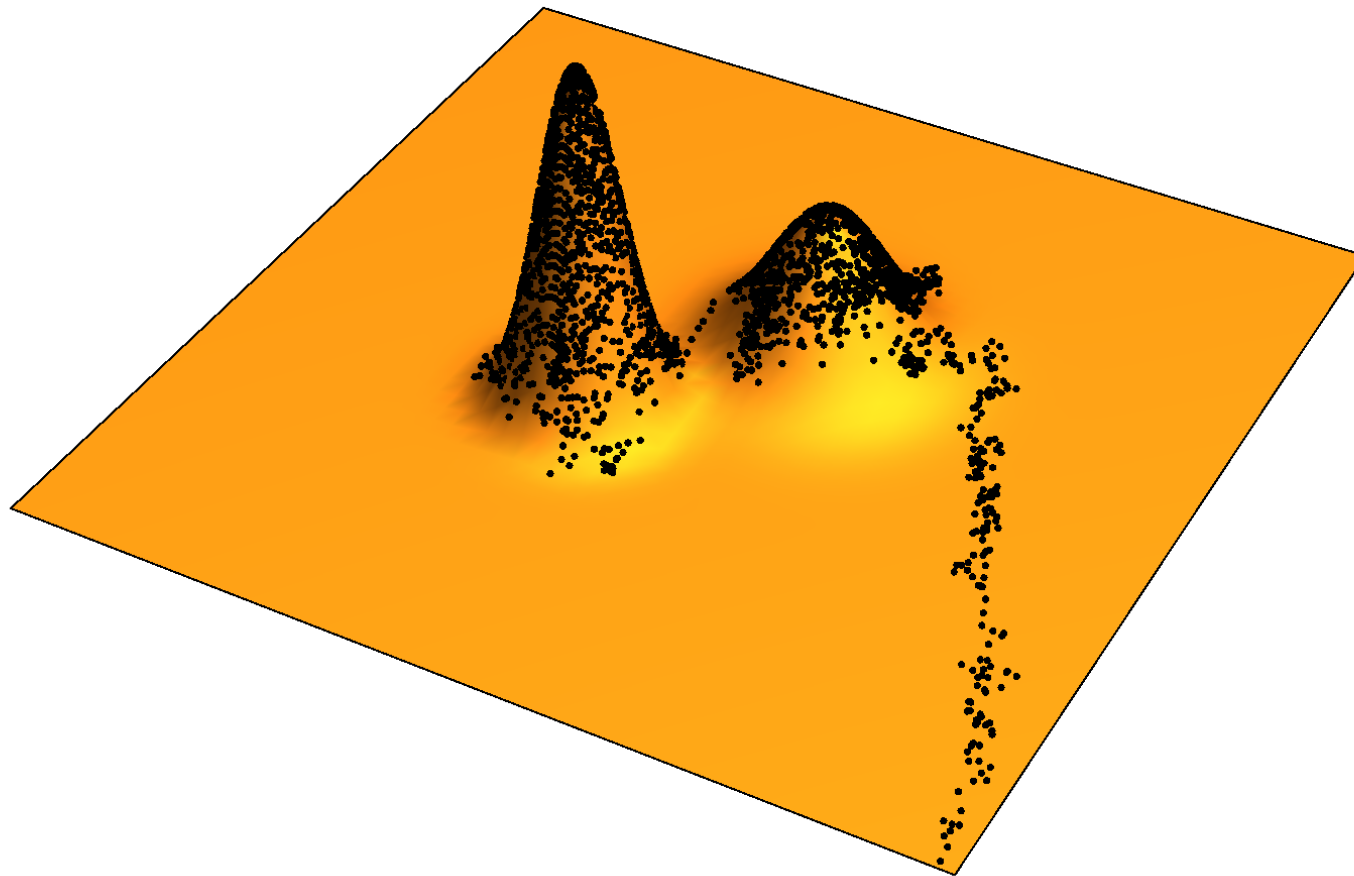
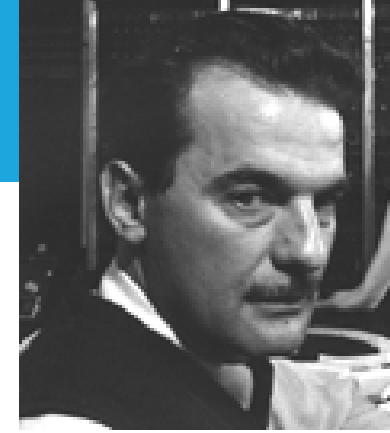
Metropolis-Hastings algorithm



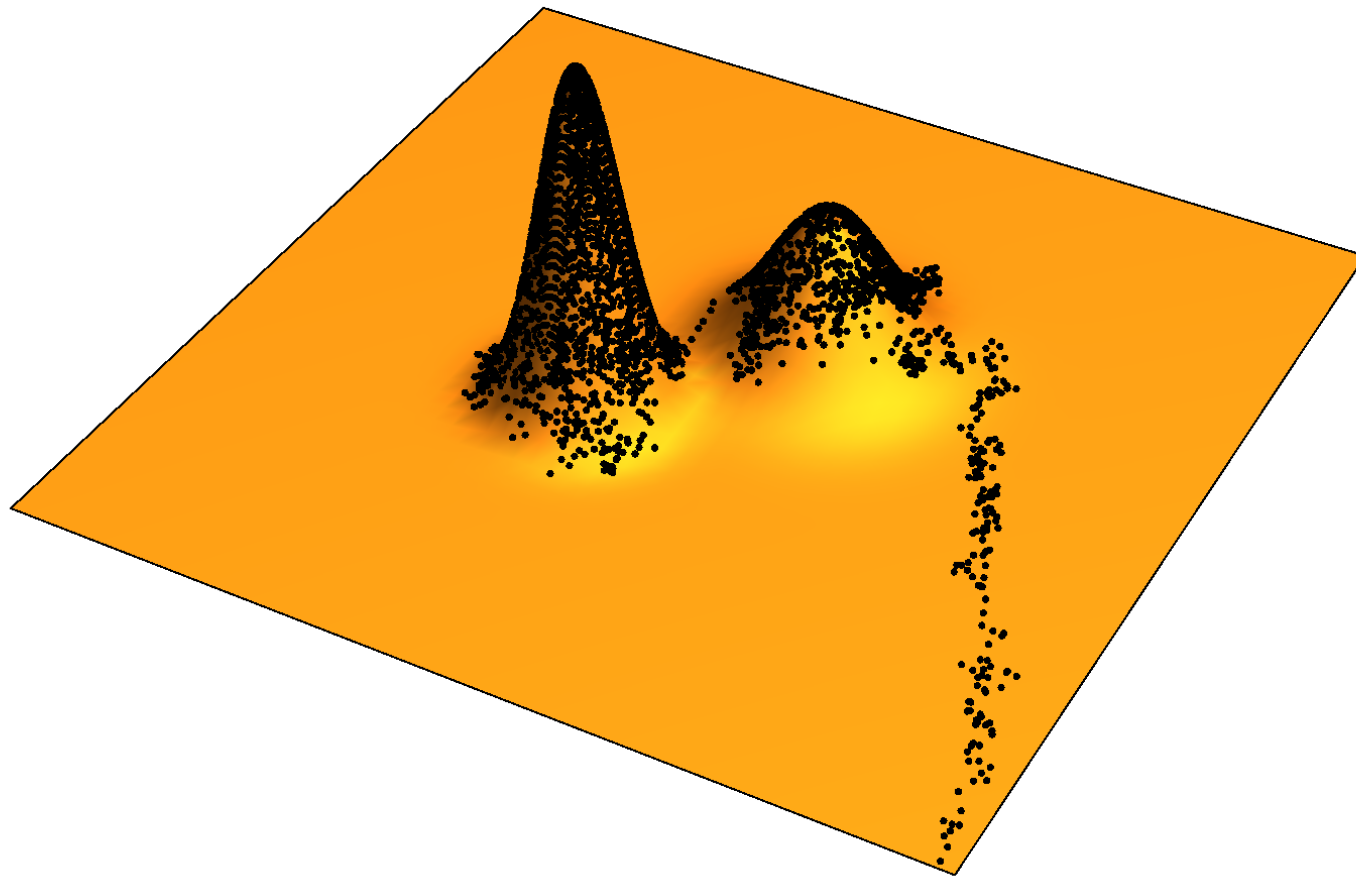
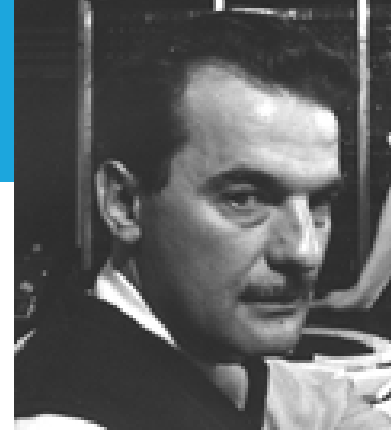
Metropolis-Hastings algorithm



Metropolis-Hastings algorithm



Metropolis-Hastings algorithm

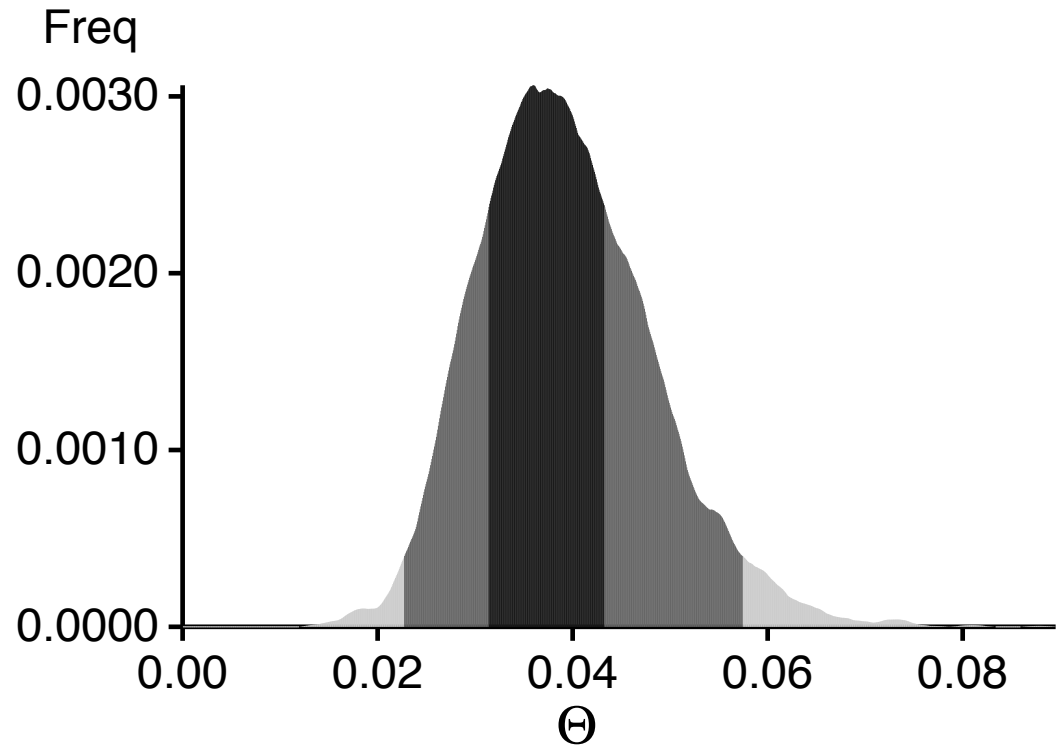


Inference of population size

Nuu-Chah-Nulth



Around 1930 – Friendly Cove, Vancouver Island



Proc. Natl. Acad. Sci. USA
Vol. 88, pp. 8720–8724, October 1991
Evolution

Extensive mitochondrial diversity within a single Amerindian tribe

(population genetics/molecular anthropology/Pacific Northwest/human evolution)

R. H. WARD*, BARBARA L. FRAZIER*, KERRY DEW-JAGER*, AND SVANTE PÄÄBO†

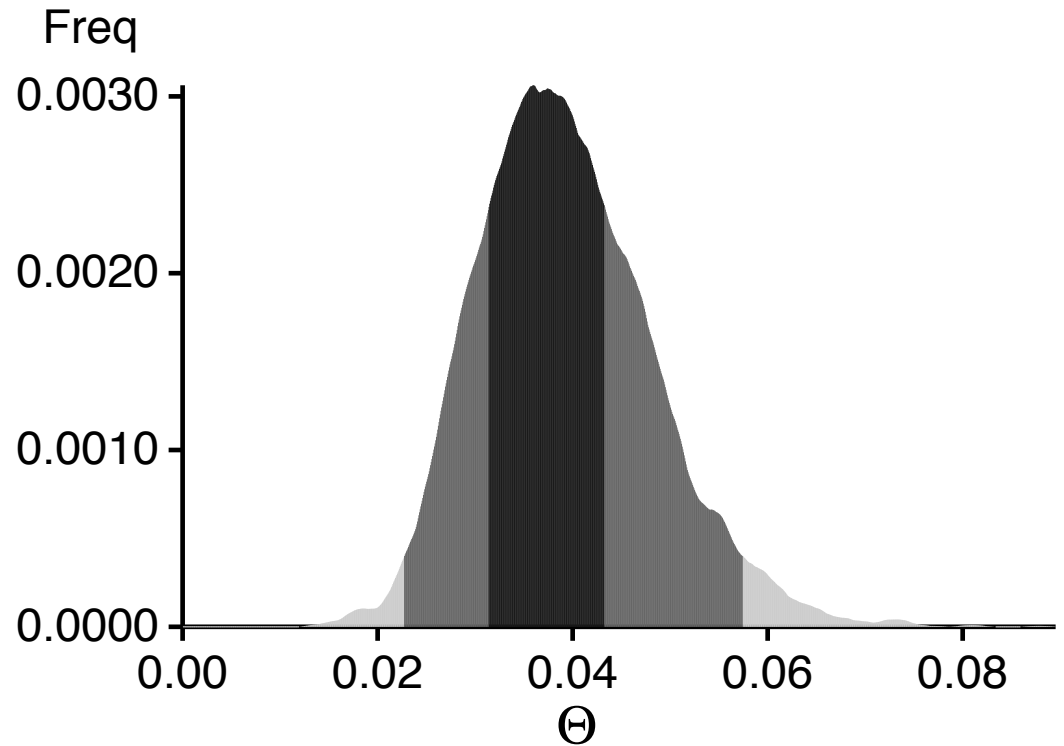
*Department of Human Genetics, School of Medicine, University of Utah, Salt Lake City, UT 84132; and †Department of Zoology, University of Munich, Luisenstrasse 14, D-8000 Munich 2, Federal Republic of Germany

[The Nuu-Cha-Nulth are organized in 14 nations totaling 8147 (Nuuchahnulth tribal council Indian registry from February 2006)]

Bayesian inference: $\Theta = 0.036$

Ward *et al* calculated $\Theta_{Ewens} = 0.043$

With a mutation rate of 0.32/site/million year and a generation time of 27 years we get $N_{\text{women}} = 2082$. Assuming same numbers of men and women and on average 2 children we get $N = 8328$.



Proc. Natl. Acad. Sci. USA
Vol. 88, pp. 8720–8724, October 1991
Evolution

Extensive mitochondrial diversity within a single Amerindian tribe

(population genetics/molecular anthropology/Pacific Northwest/human evolution)

R. H. WARD*, BARBARA L. FRAZIER*, KERRY DEW-JAGER*, AND SVANTE PÄÄBO†

*Department of Human Genetics, School of Medicine, University of Utah, Salt Lake City, UT 84132; and †Department of Zoology, University of Munich, Luisenstrasse 14, D-8000 Munich 2, Federal Republic of Germany

[The Nuu-Cha-Nulth are organized in 14 nations totaling 8147 (Nuuchahnulth tribal council Indian registry from February 2006)]

Bayesian inference: $\Theta = 0.036$

Ward *et al* calculated $\Theta_{Ewens} = 0.043$

With a mutation rate of 0.32/site/million year and a generation time of 27 years we get $N_{\text{women}} = 2082$. Assuming same numbers of men and women and on average 2 children we get $N = 8328$.

This sounds very good, but the 95%credibility interval is 5000 – 13500

References

Coalescent:

- Nuu-Cha-Nulth population size: J. Felsenstein. 1971. Inbreeding and variance effective numbers in populations with overlapping generations. *Genetics* 68:581-597;
- R. H. Ward, B. L. Frazier, Kerry Dew-Jager, and S. Pääbo. 1991. Extensive mitochondrial diversity within a single Amerindian tribe. *PNAS* 88:8780-8724;
- Sigurđardóttir S, Helgason A, Gulcher JR, Stefansson K, Donnelly P. 2000. The mutation rate in the human mtDNA control region. *Am J Hum Genet.* 66:1599-609;
- S. Matsumura and P. Forster. 2008. Generation time and effective population size in Polar Eskimos. *Proc. R. Soc. B* 275:1501-1508.

Sample size:

- Felsenstein, J. 2005. Accuracy of coalescent likelihood estimates: Do we need more sites, more sequences, or more loci? *MBE* 23: 691-700.
- Pluzhnikov A, Donnelly P. 1996. Optimal sequencing strategies for surveying molecular genetic diversity. *Genetics* 144: 1247-1262.