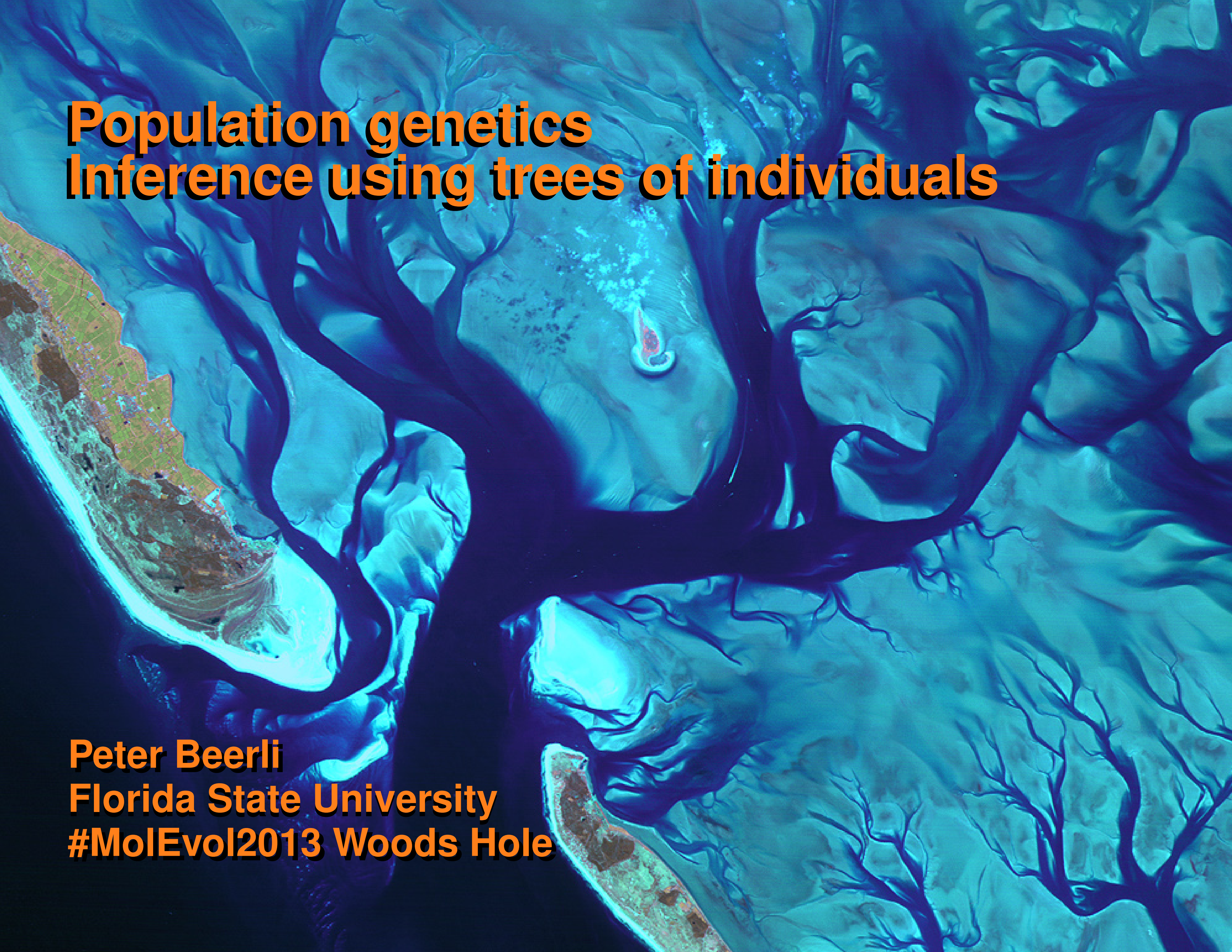

Population genetics
Inference using trees of individuals

Peter Beerli
Florida State University
#MolEvol2013 Woods Hole

Problems that need to be solved

Problems that need to be solved

- What is the rate of emergence of new diseases?
  How many strains of influenza could there be?
  How fast do new strains adapt to humans (other species)?

- How do diseases spread?
  Are there recurrent patterns of emergence (old strains maintenance) ?
  What are the most common routes of distributions of diseases?

Problems that need to be solved

Problems that need to be solved

- How can we maintain the genetic variability within a population?
- How are populations connected?
  What was the connectivity among populations in the past? In the future?

How do we approach problems like these?

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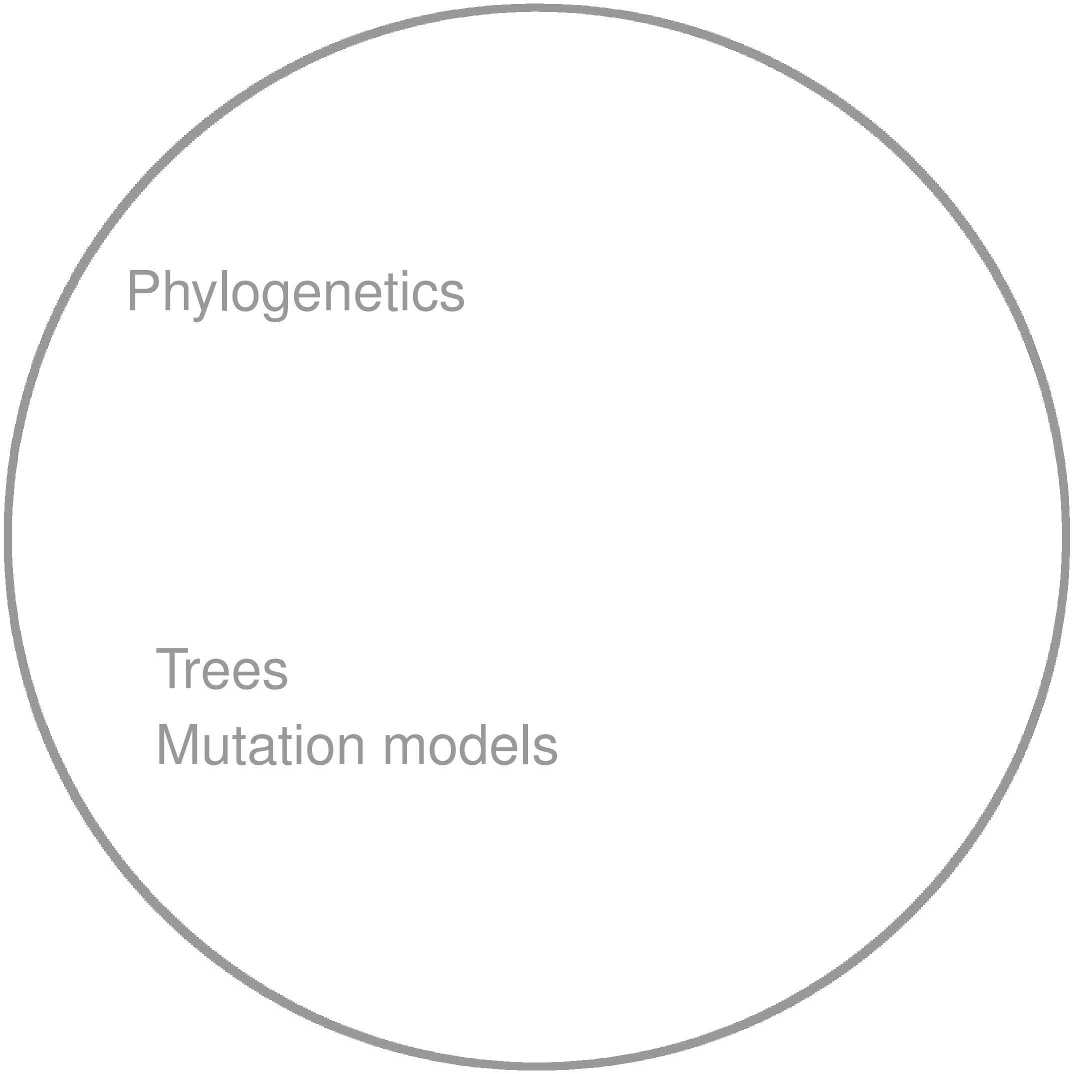
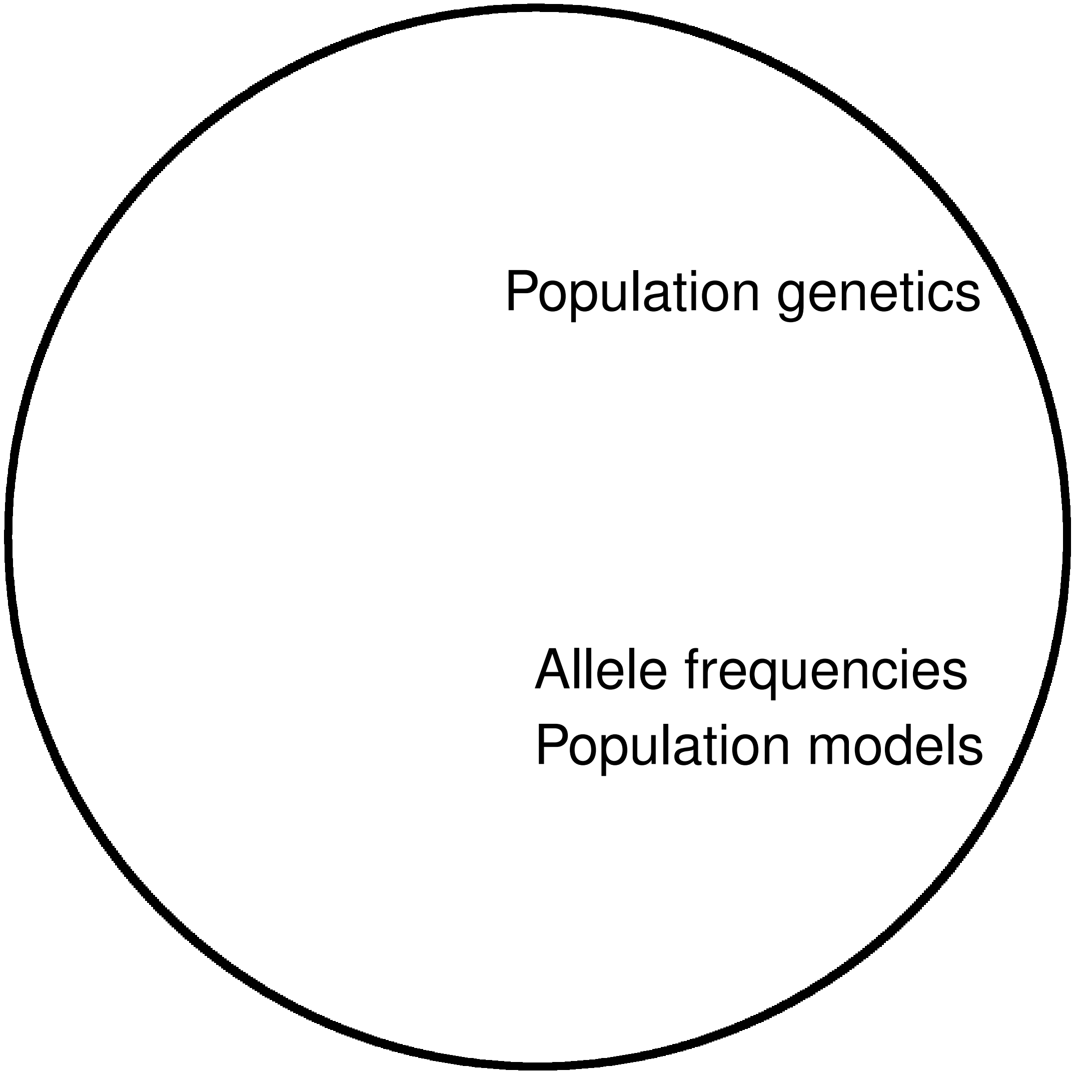


Phylogenetics

Trees

Mutation models

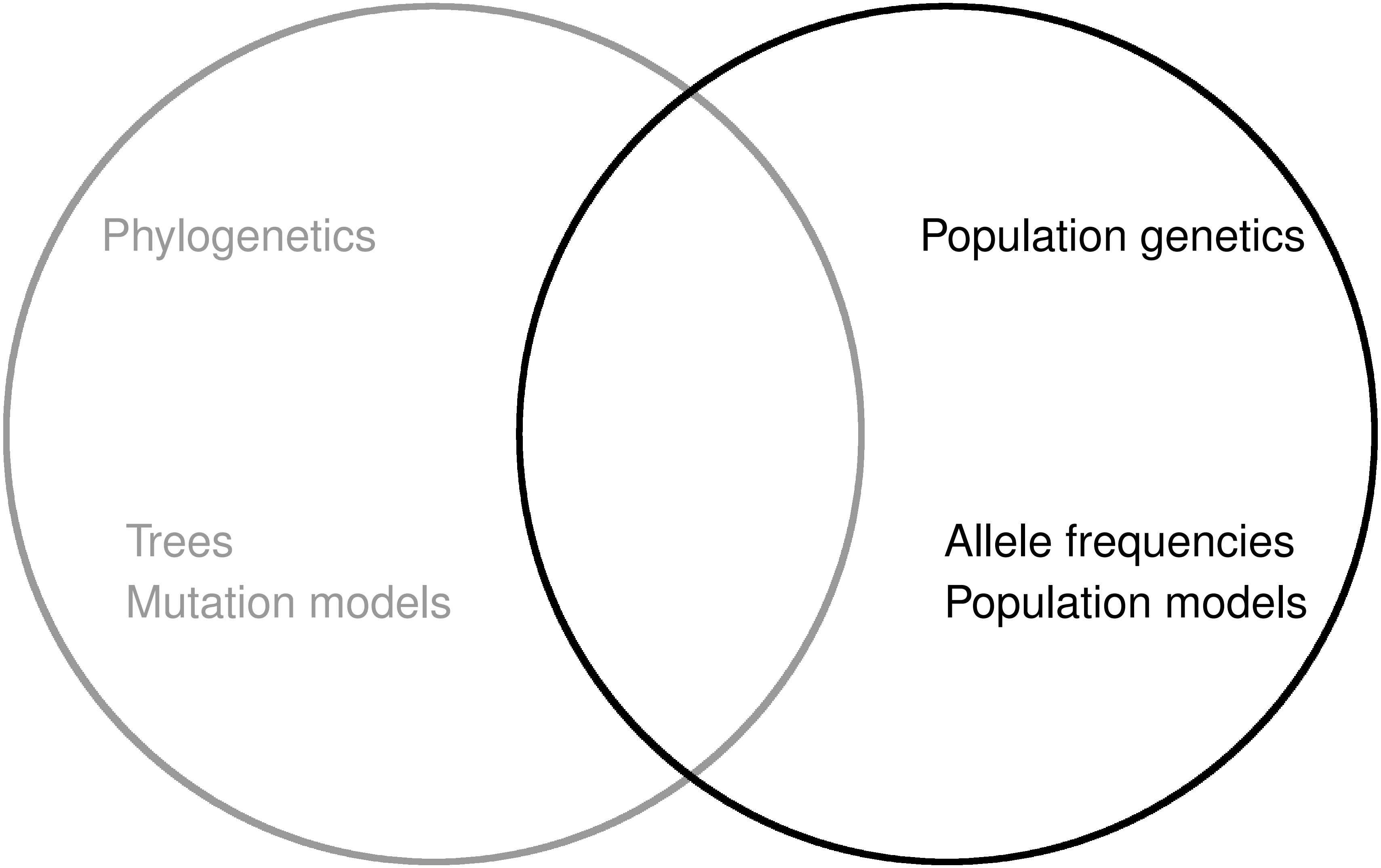
How do we approach problems like these?



Population genetics

Allele frequencies
Population models

How do we approach problems like these?



Phylogenetics

Trees
Mutation models

Population genetics

Allele frequencies
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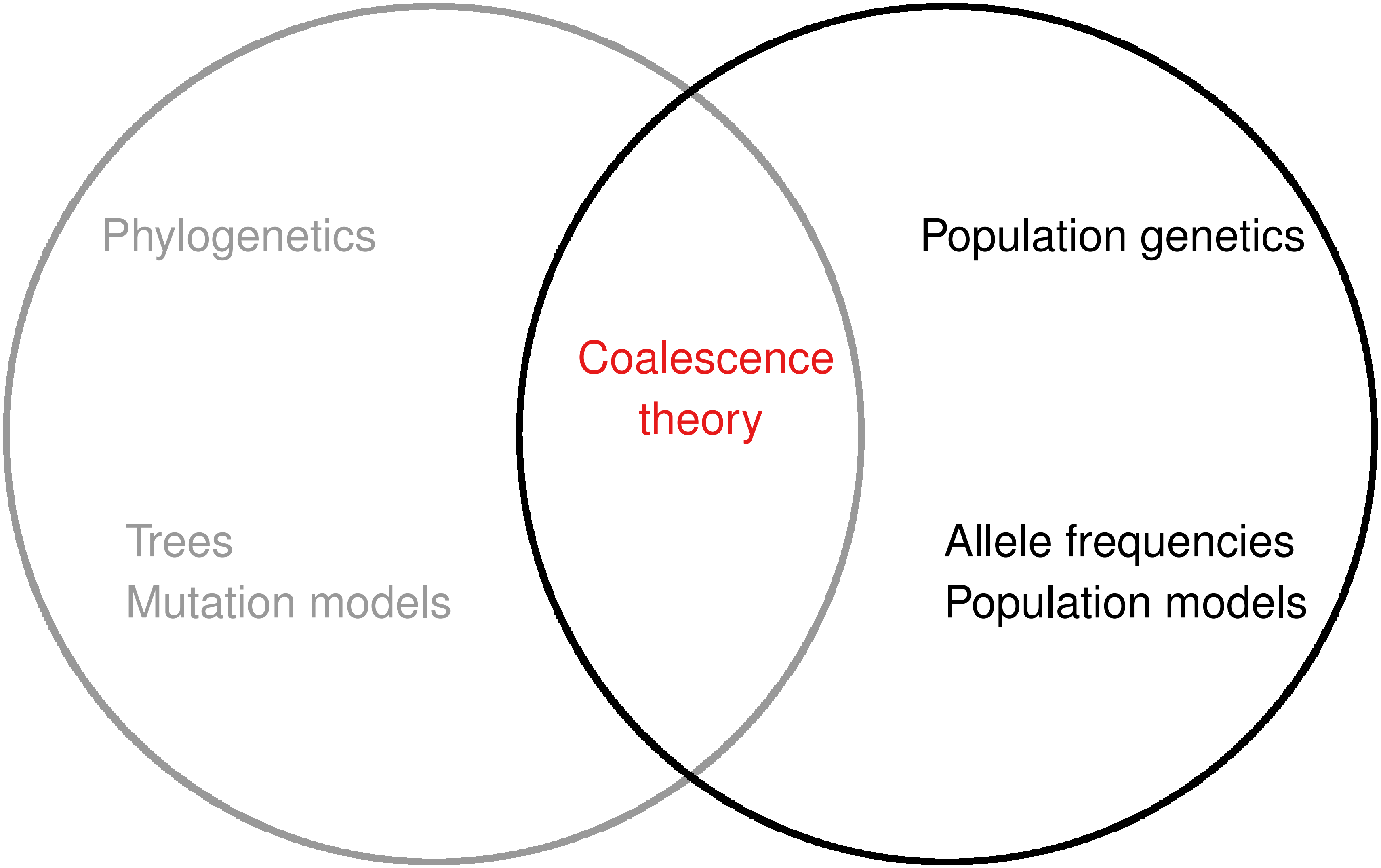
How do we approach problems like these?



Phylogenetics

Trees
Mutation models

Coalescence theory

Population genetics

Allele frequencies
Population models

Coalescence theory as a tool for population genetics

co•a•lesce |ˌkōəˈles|

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.*

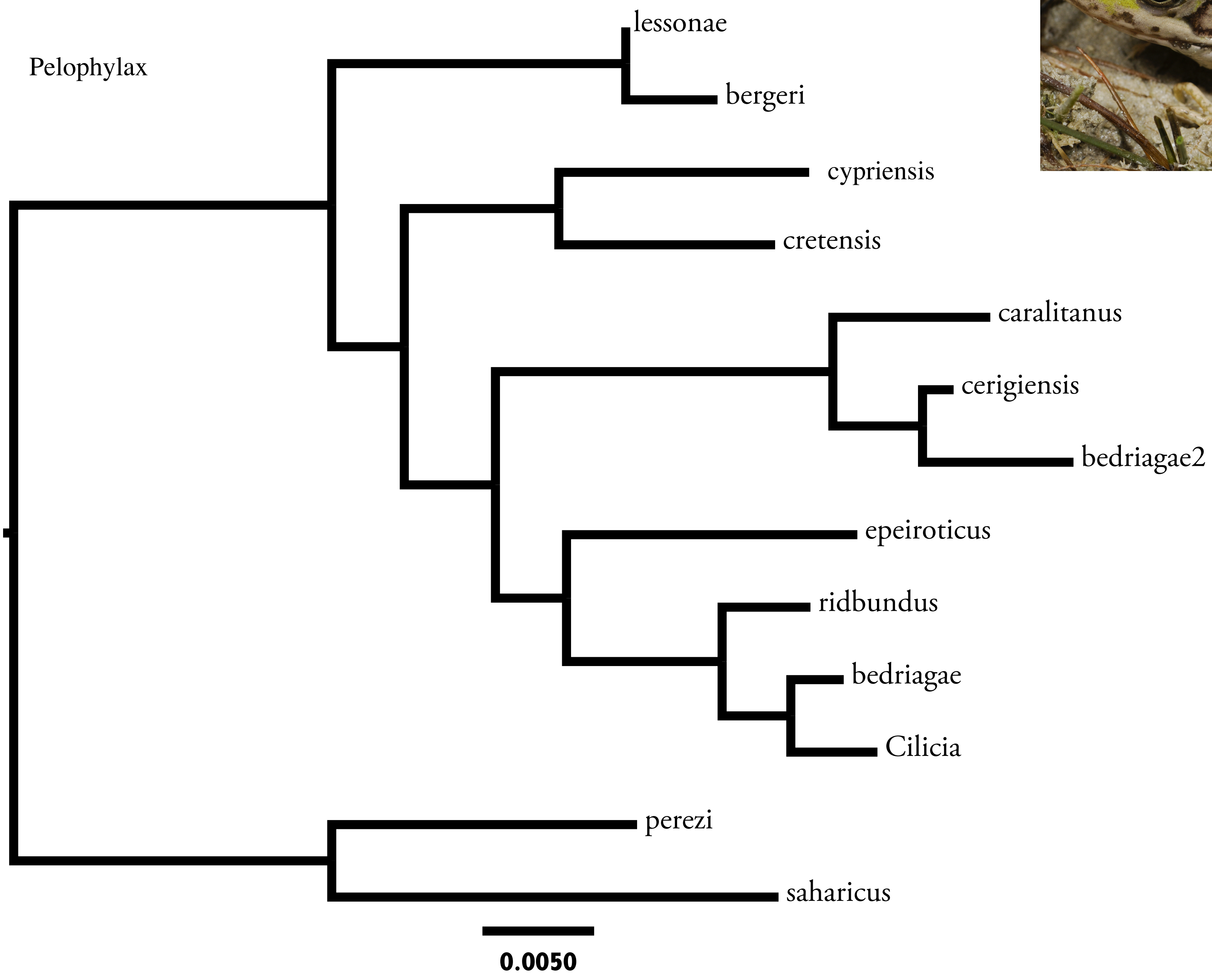
DERIVATIVES

co•a•les•cence |-ˈlesəns| noun

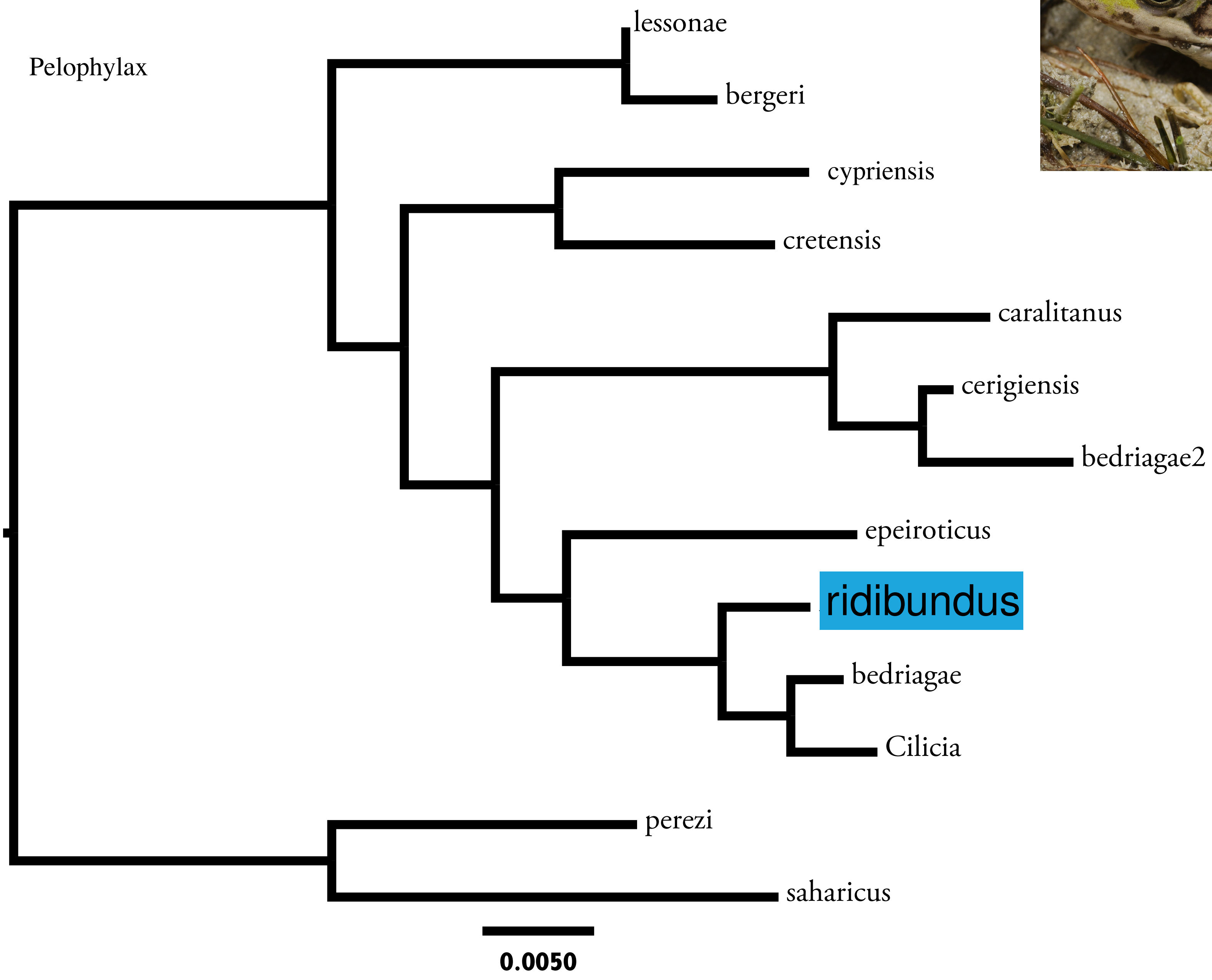
co•a•les•cent |-ˈlesənt| adjective

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

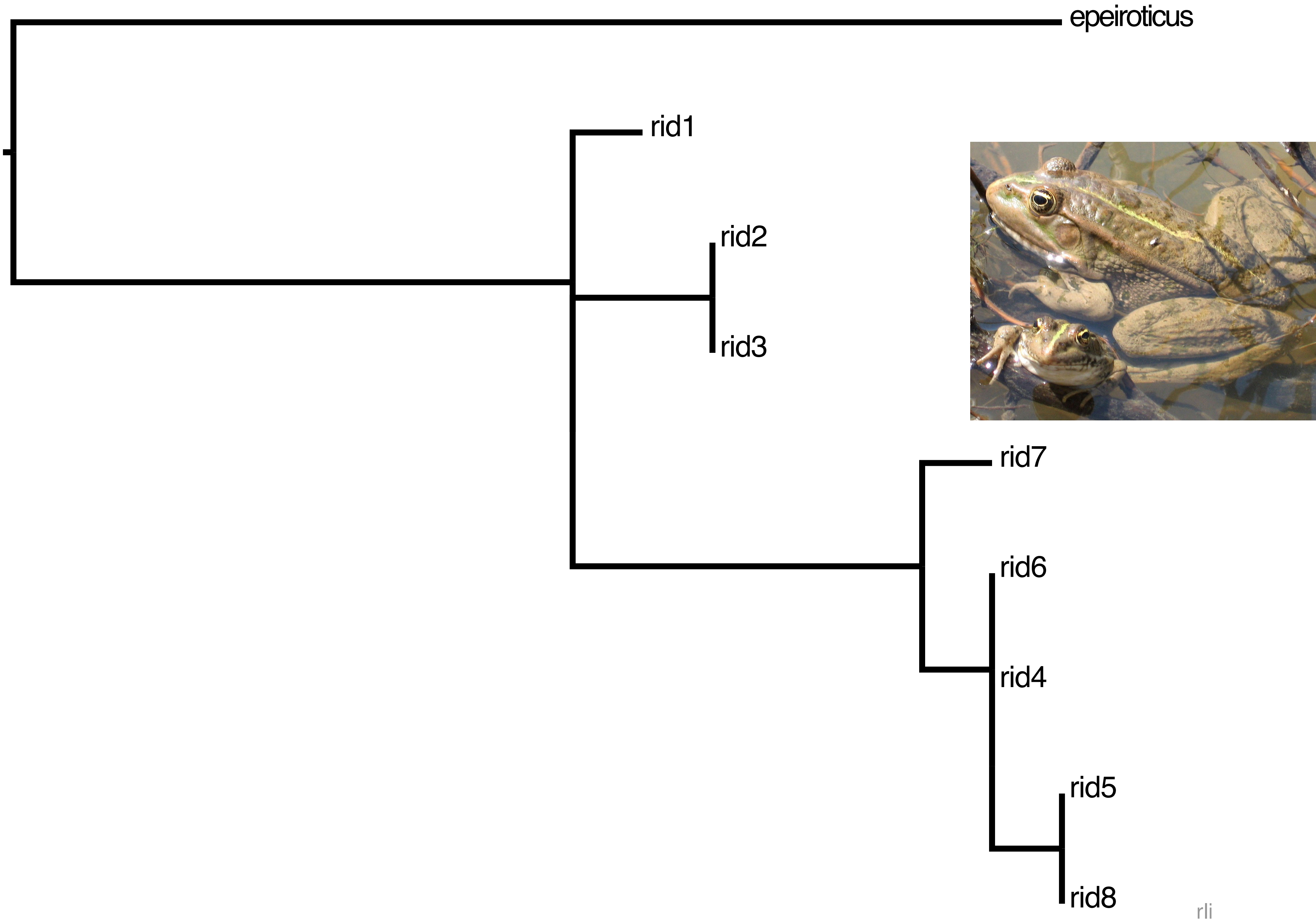
Species trees



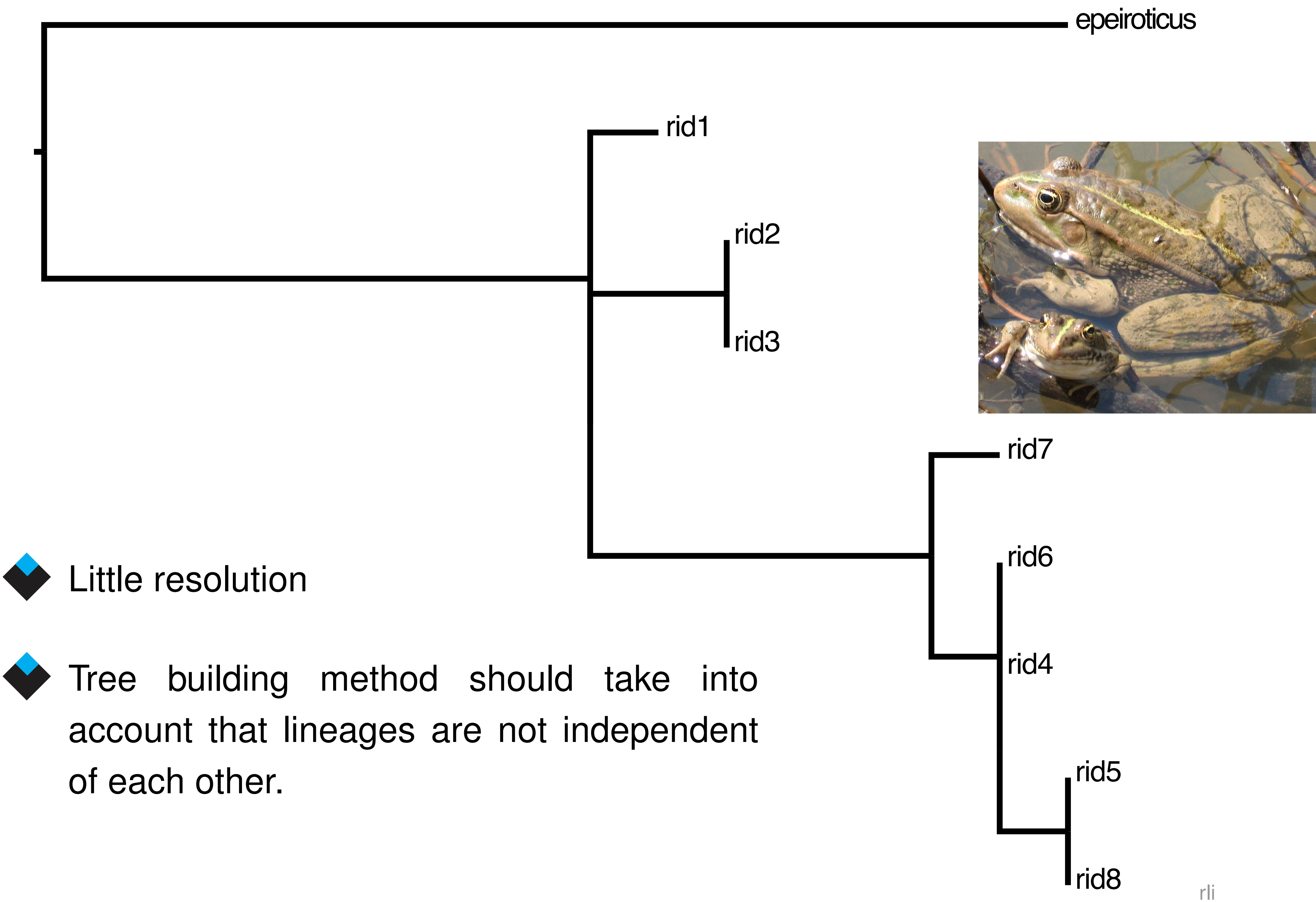
Species trees



Tree of individuals of same species

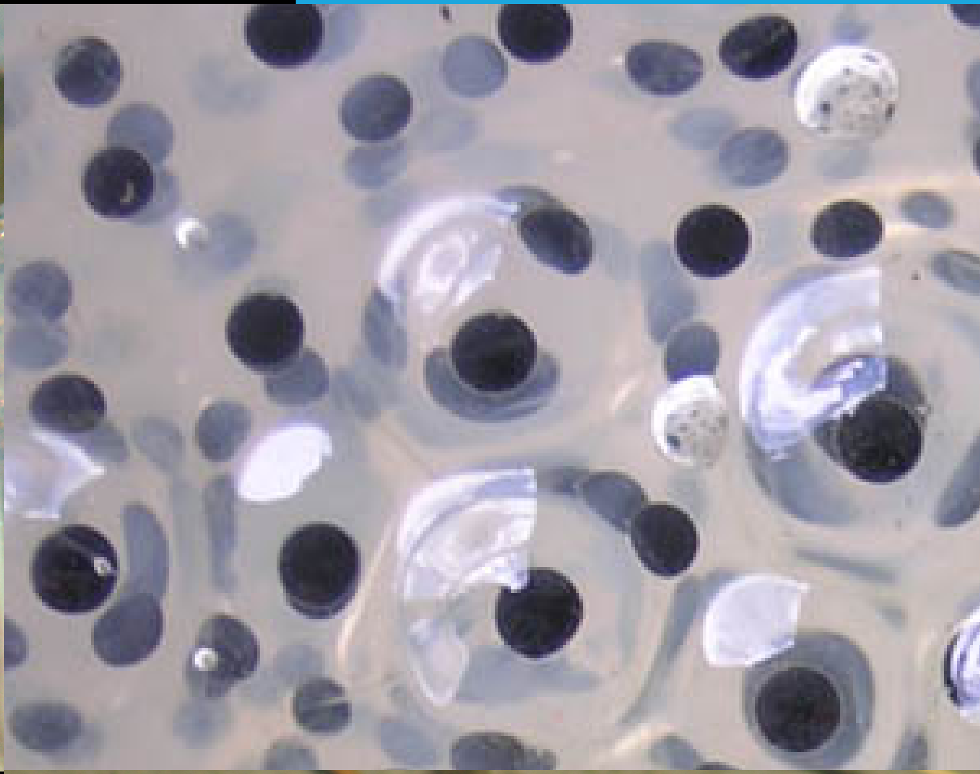


Tree of individuals of same species

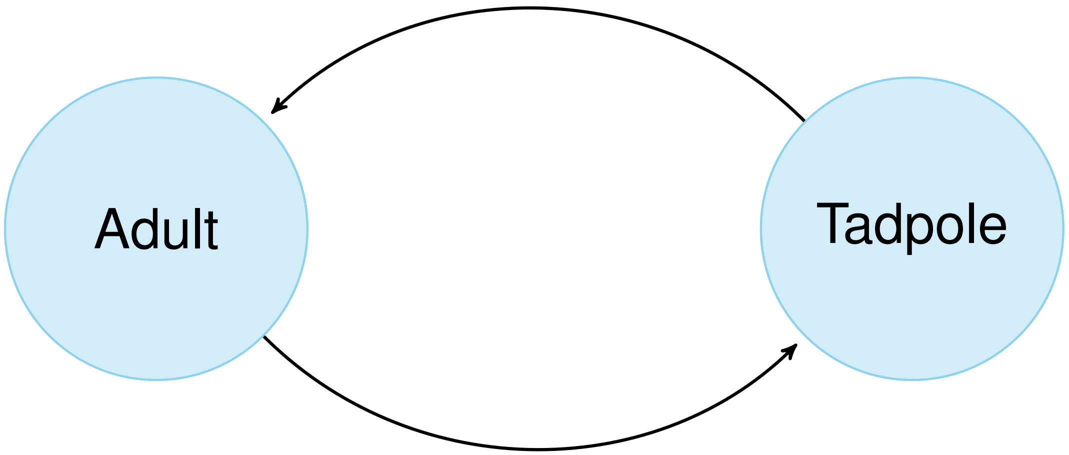


- Little resolution
- Tree building method should take into account that lineages are not independent of each other.

Interaction among individuals



Interaction among individuals



Wright-Fisher population model

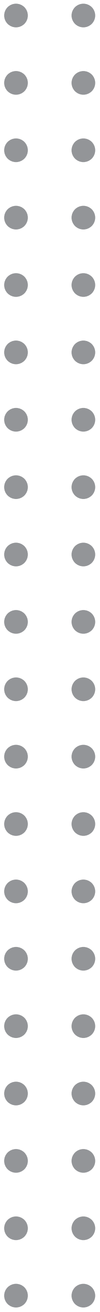
- All individuals live one generation and get replaced by their offspring
- All have same chance to reproduce, all are equally fit
- The number of individuals in the population is constant

Population model

Past
Present

Population model

Wright-Fisher

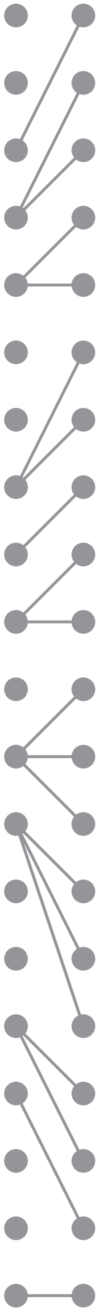


Past

Present

Population model

Wright-Fisher

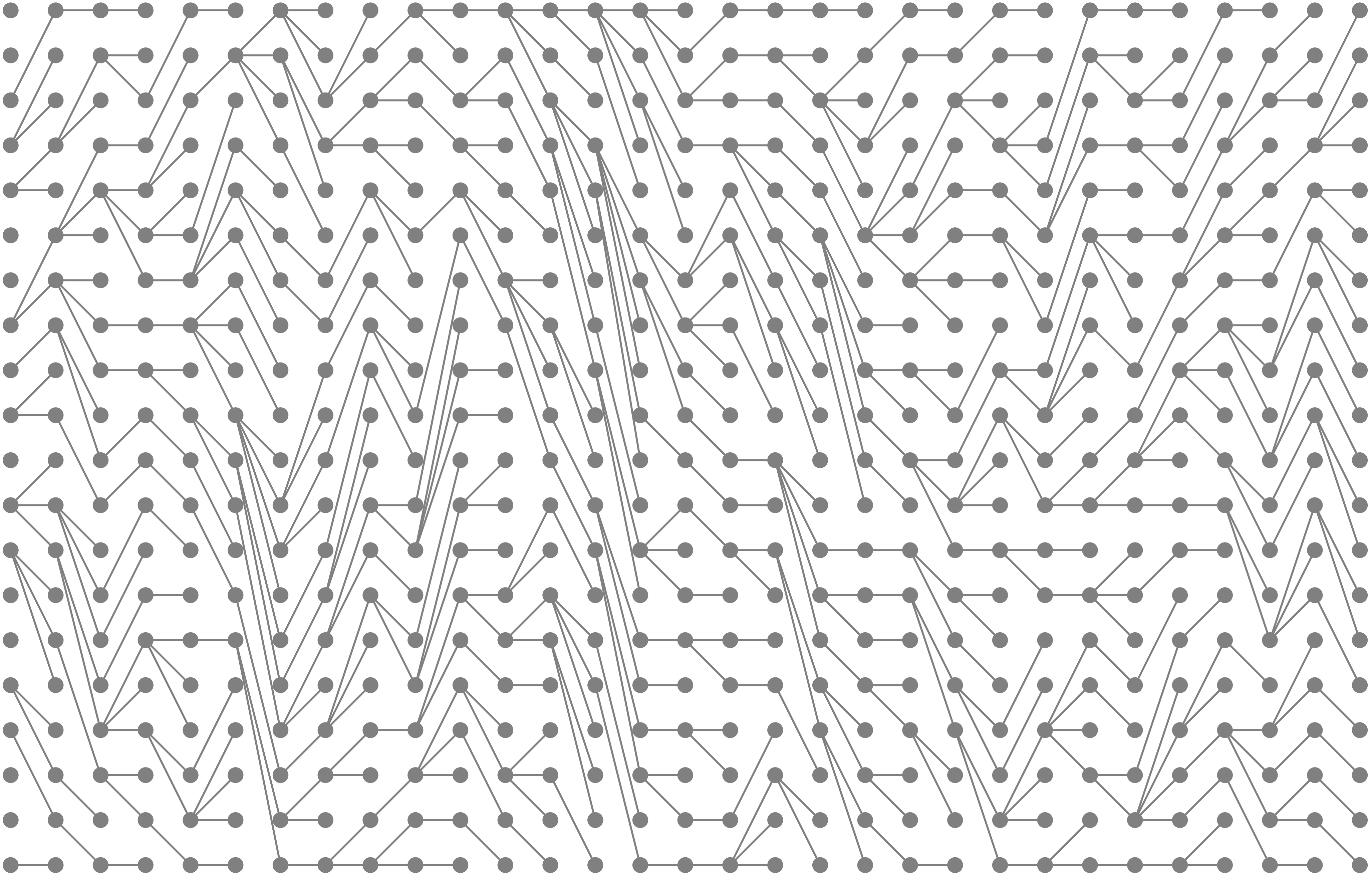


Past

Present

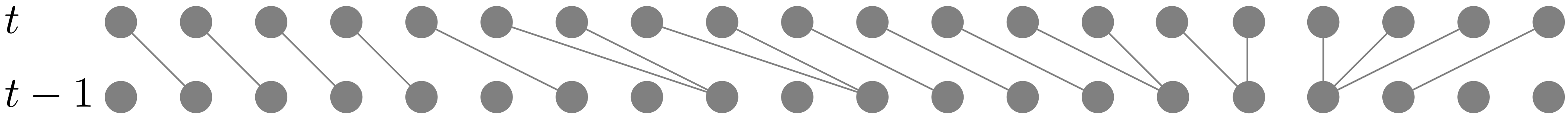
Population model

Wright-Fisher



Population model

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

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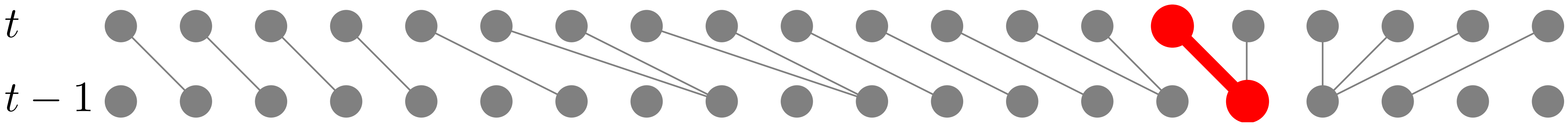
$$1.0$$

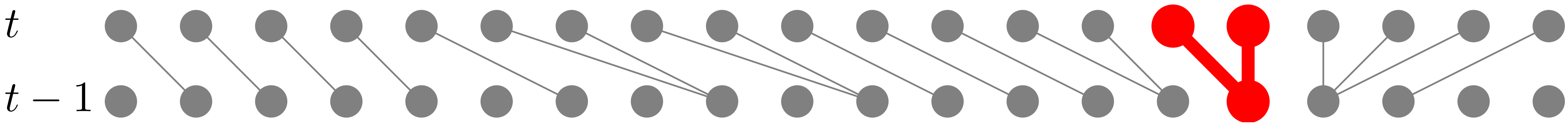


Population model

Wright

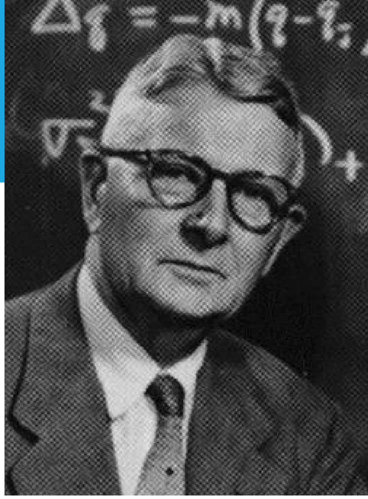
Sewall Wright evaluated the probability that two randomly chosen individuals in generation t have a common ancestor in generation $t-1$. If we assume that there are $2N$ chromosomes then the probability of sharing a common ancestor in the last generation is

$$1.0 \times \frac{1}{2N}$$



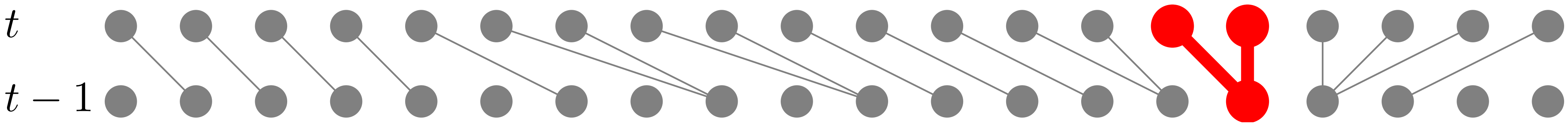
Population model

Wright



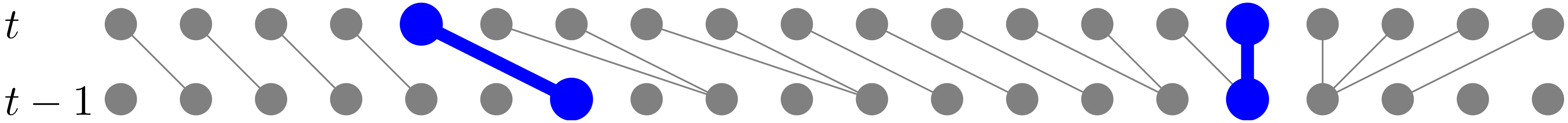
Sewall Wright evaluated the probability that two randomly chosen individuals in generation t have a common ancestor in generation $t-1$. If we assume that there are $2N$ chromosomes then the probability of sharing a common ancestor in last generation is

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



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

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



Population model

Wright

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

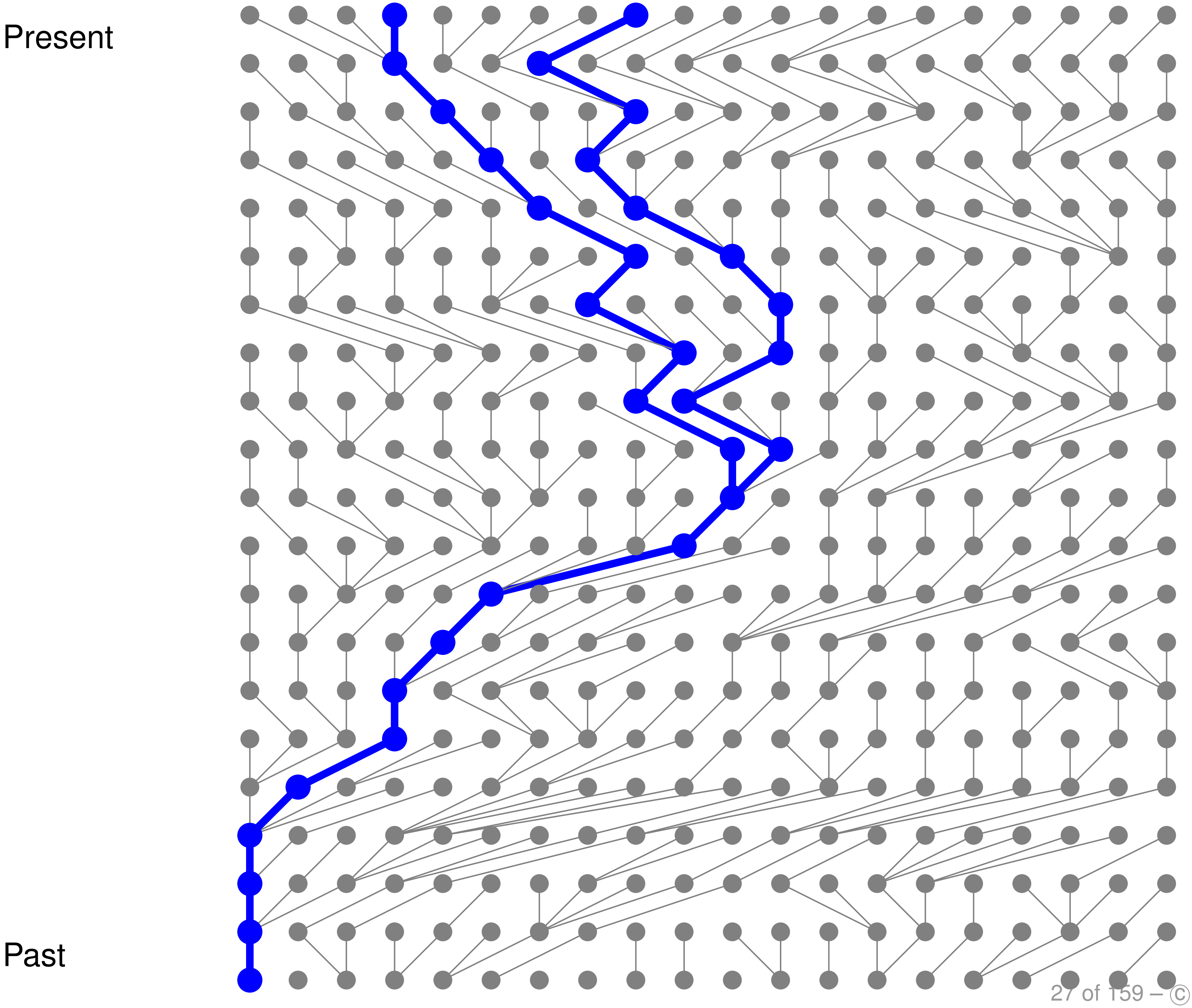
$$\mathrm{P}(\tau|N) = \left(1 - \frac{1}{2N}\right)^{\tau} \left(\frac{1}{2N}\right)$$

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:

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

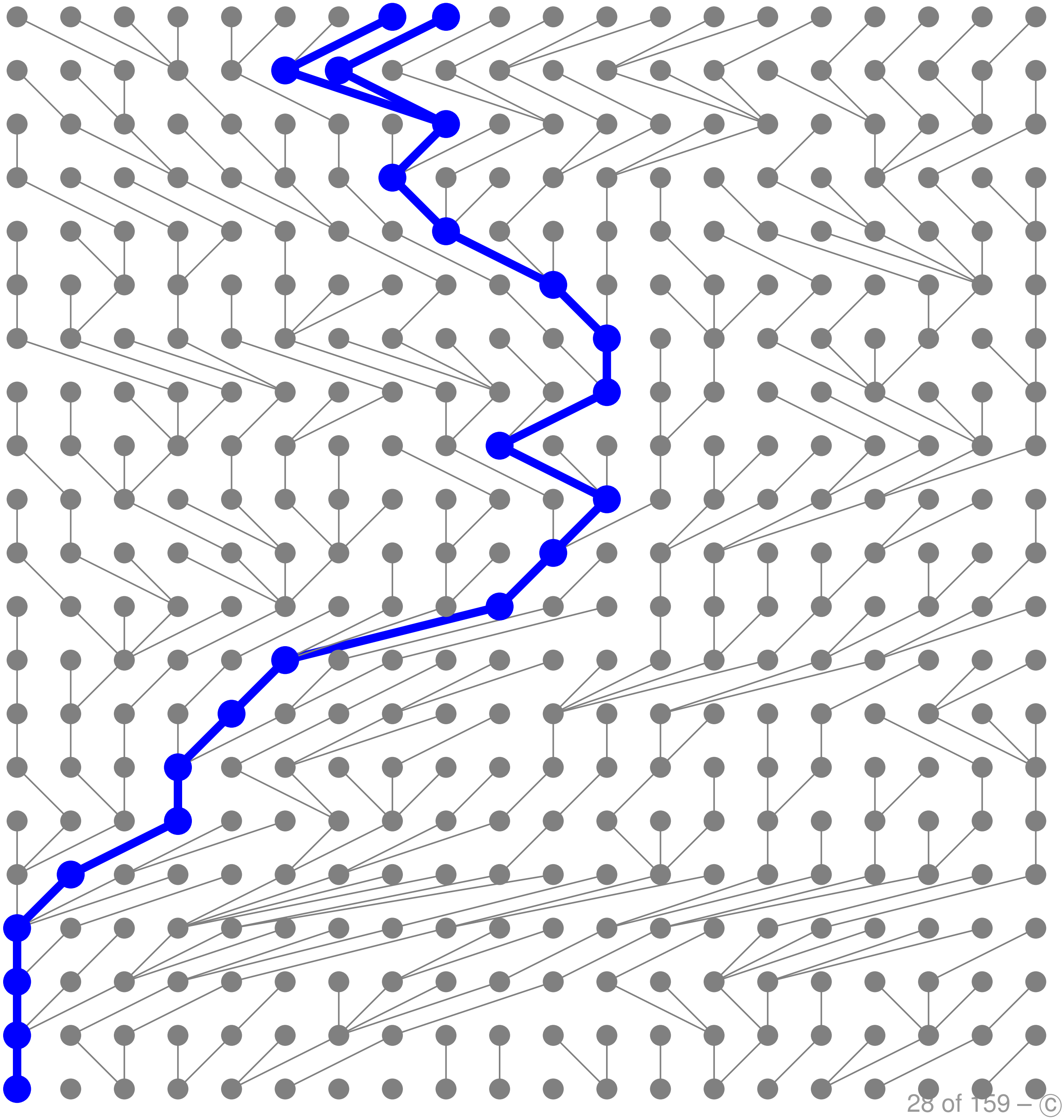
Population model

Wright-Fisher



Population model

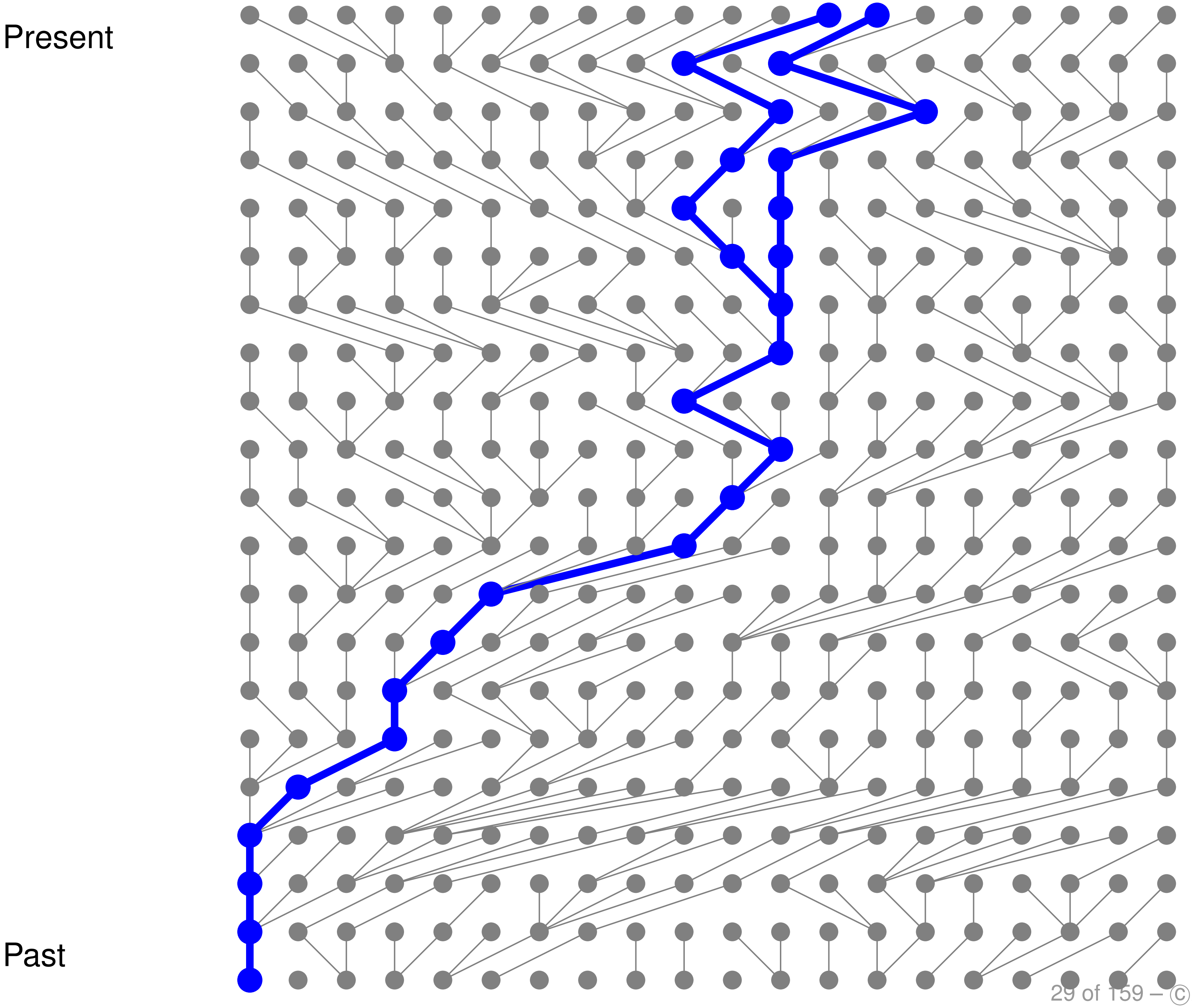
Present



Past

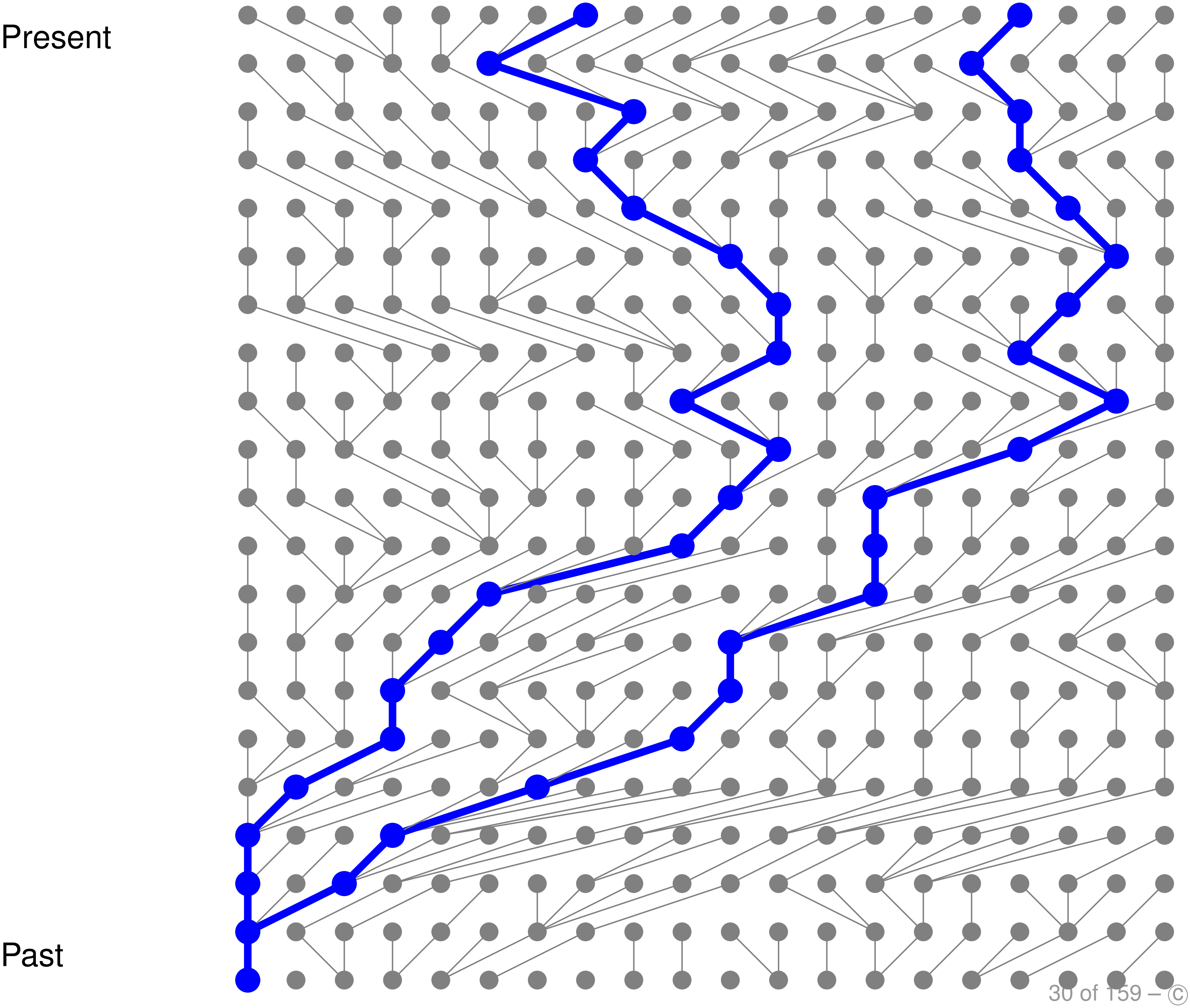
Population model

Wright-Fisher



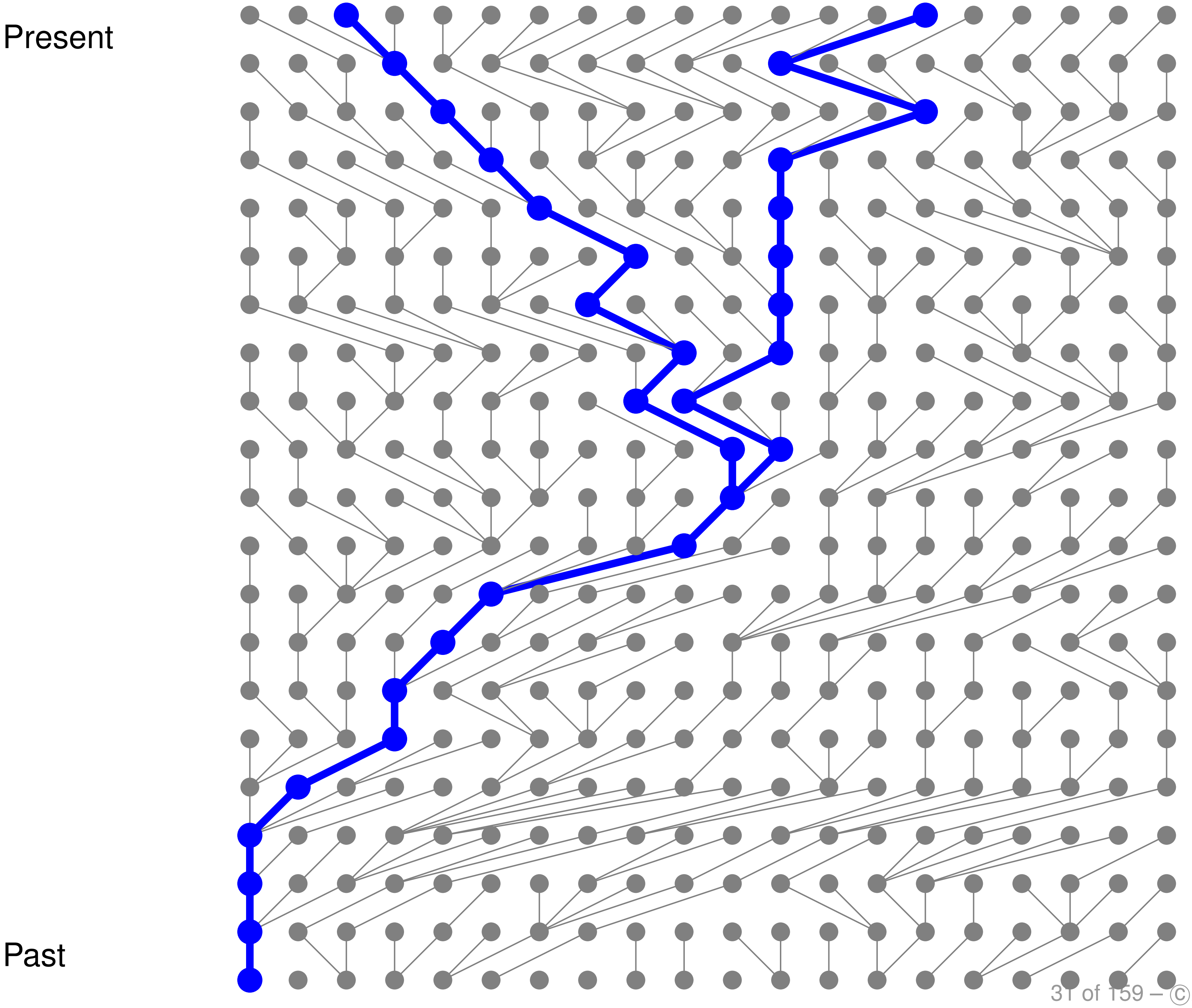
Population model

Wright-Fisher



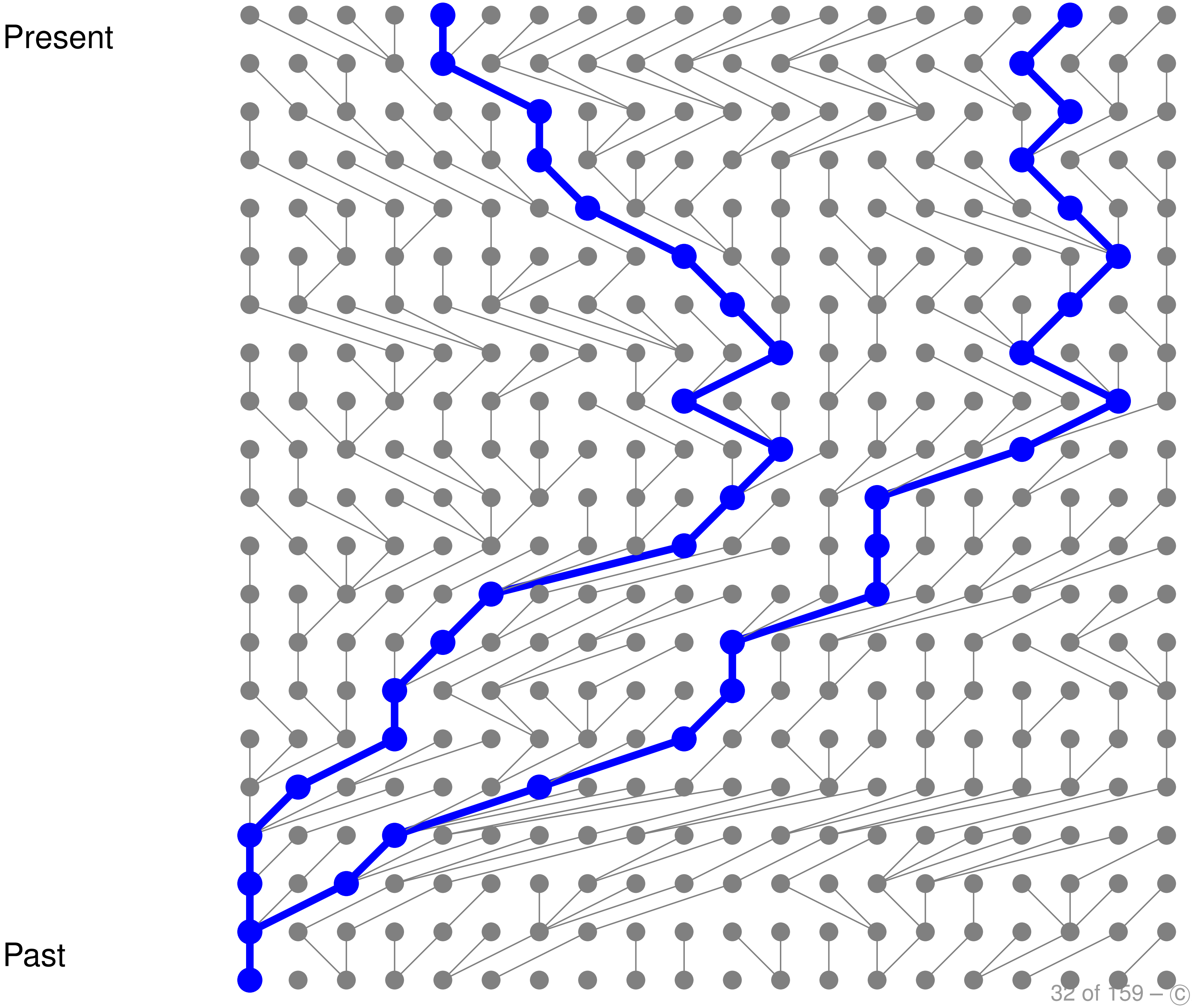
Population model

Wright-Fisher

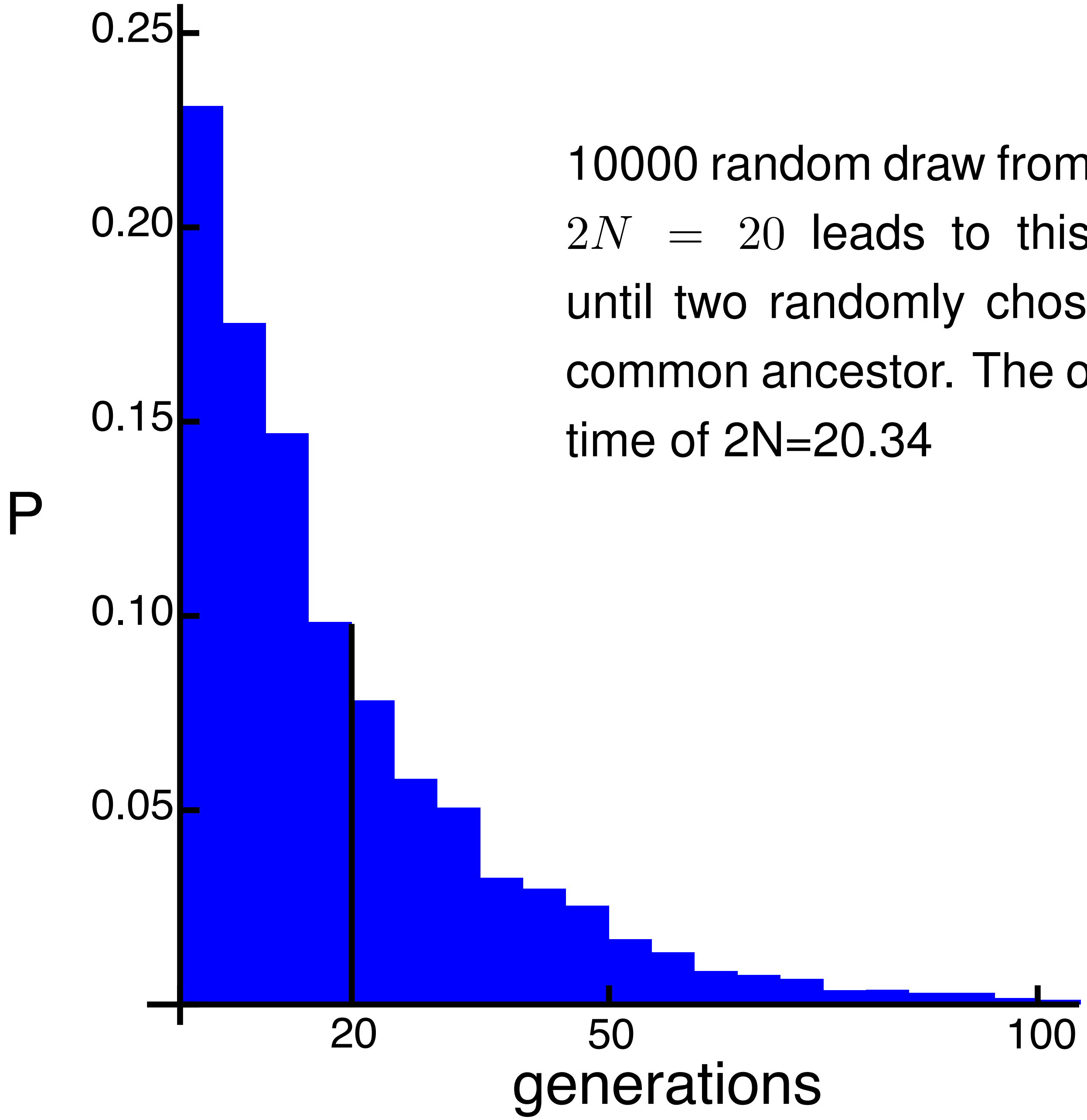


Population model

Wright-Fisher



Probability Distribution



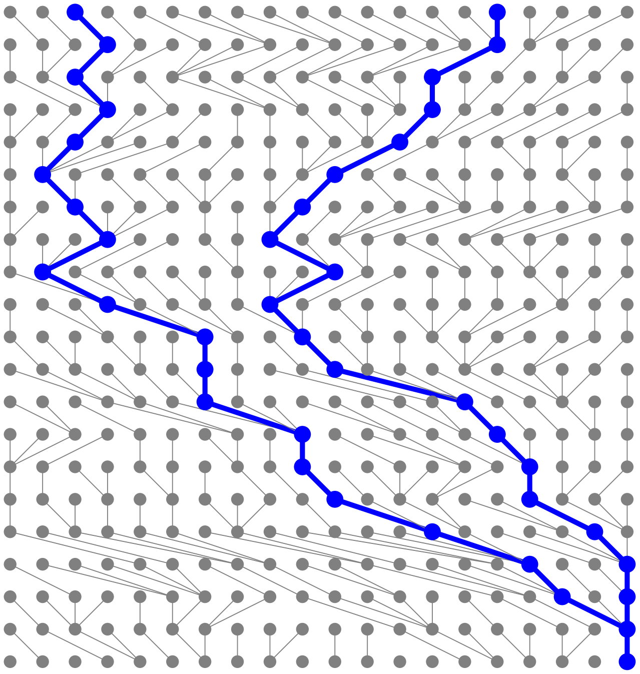
10000 random draw from a population with size $2N = 20$ leads to this distribution of times until two randomly chosen individuals have a common ancestor. The observed mean waiting time of 2N=20.34

Observations

- 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

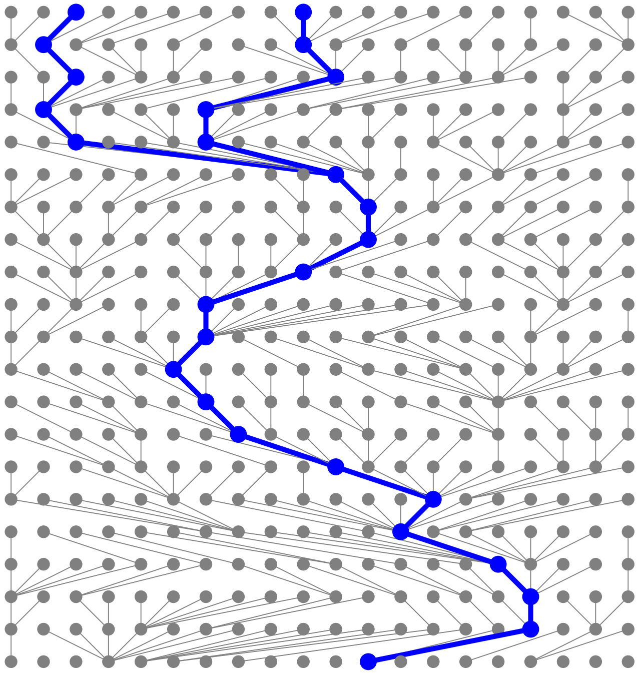


$\sigma^2_{\text{offspring}} \simeq 1$

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

generation time $g = 1$

Canning

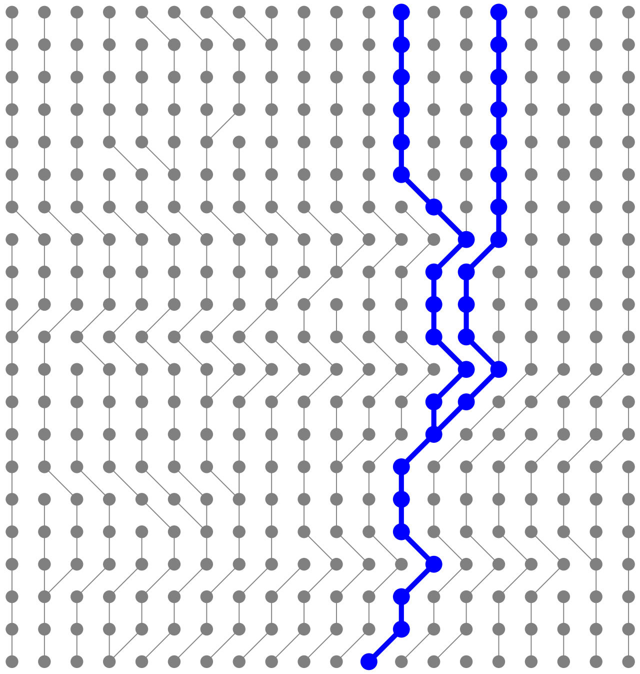


$\sigma^2_{\text{offspring}} = x$

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

$g = 1$

Moran

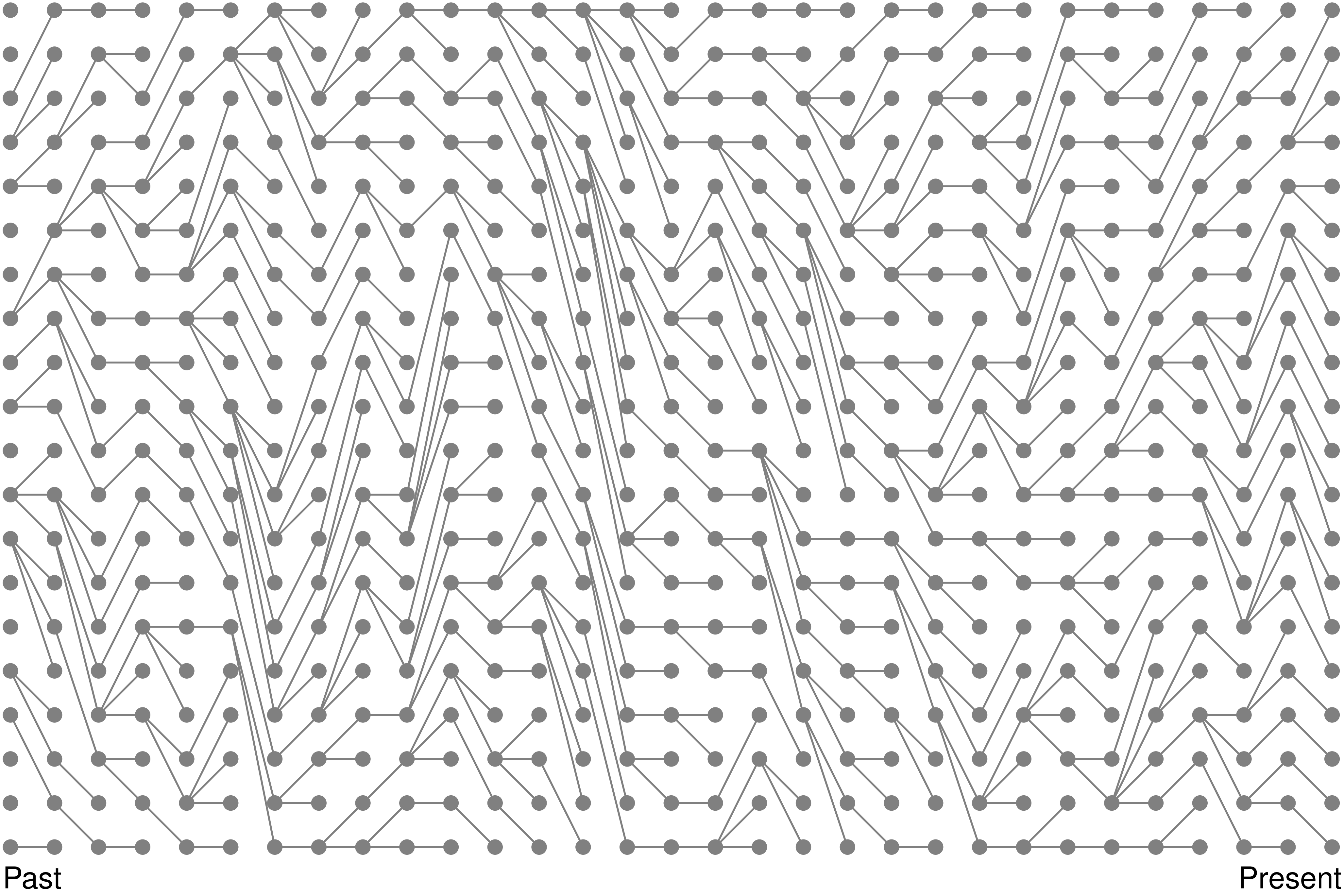


$\sigma^2_{\text{offspring}} = \frac{2}{2N}$

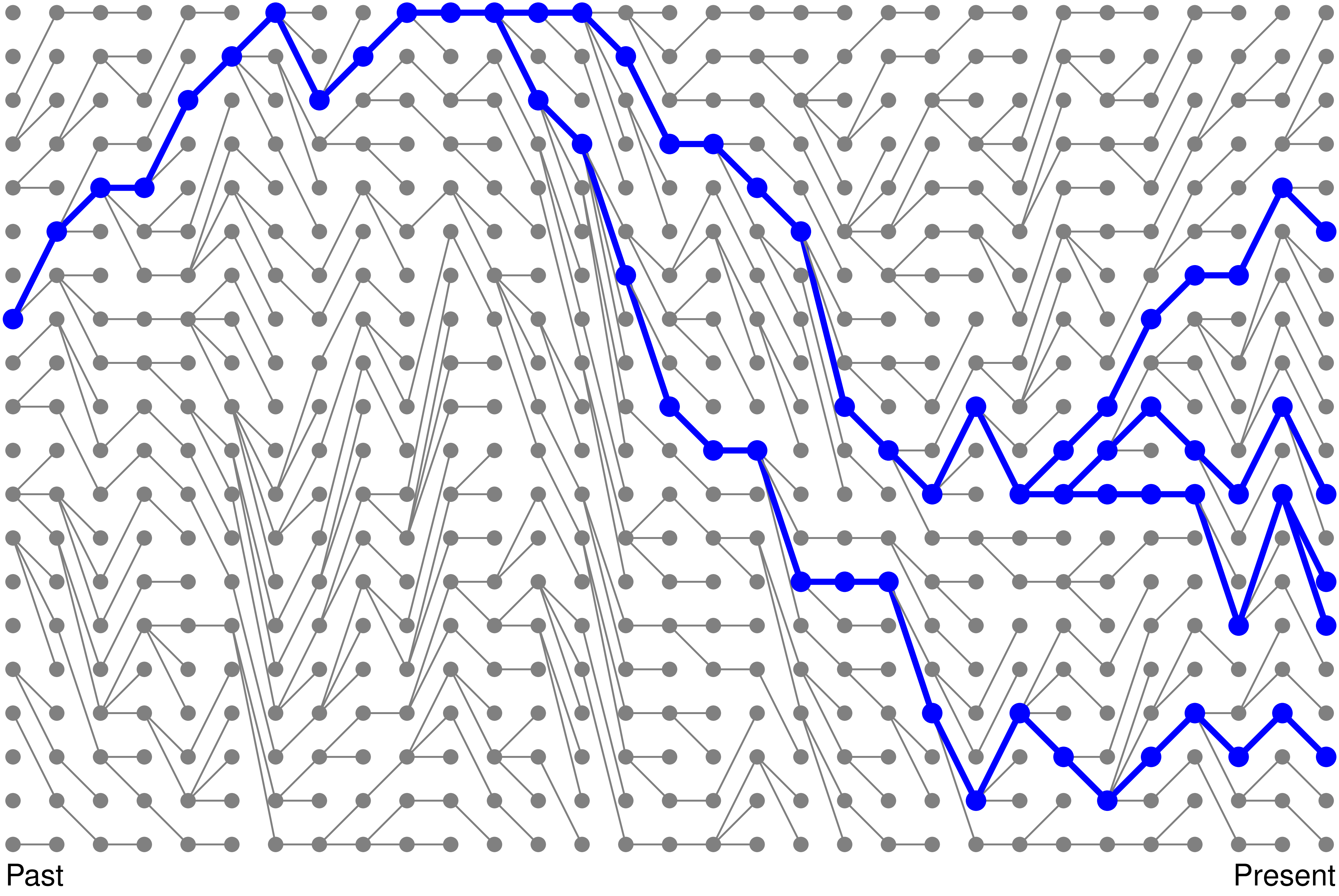
$\mathbb{E}(\tau) = \frac{1}{2}(2N)^2$

$g = 2N$

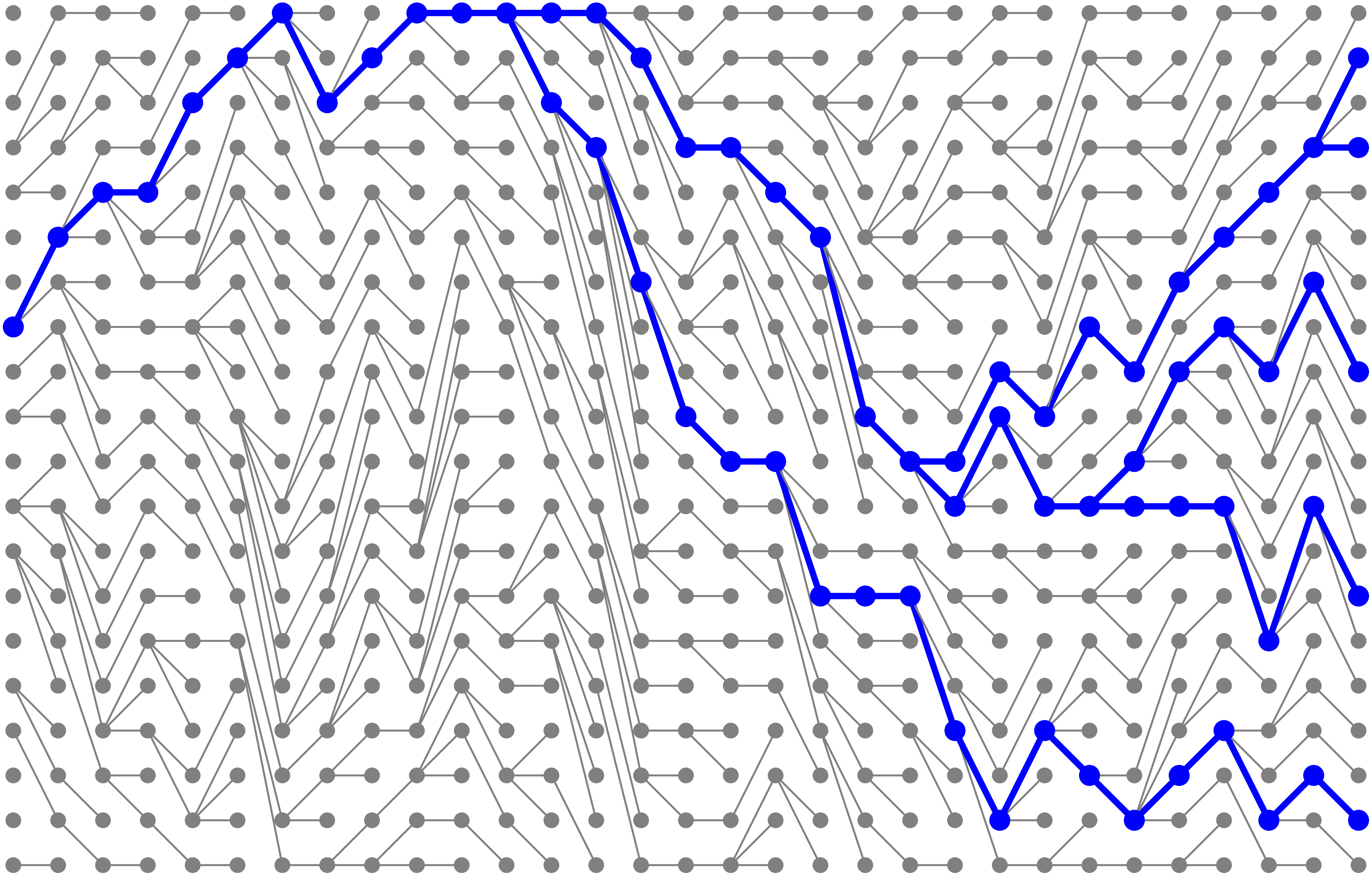
Sample larger than TWO



Sample larger than TWO



Sample larger than TWO

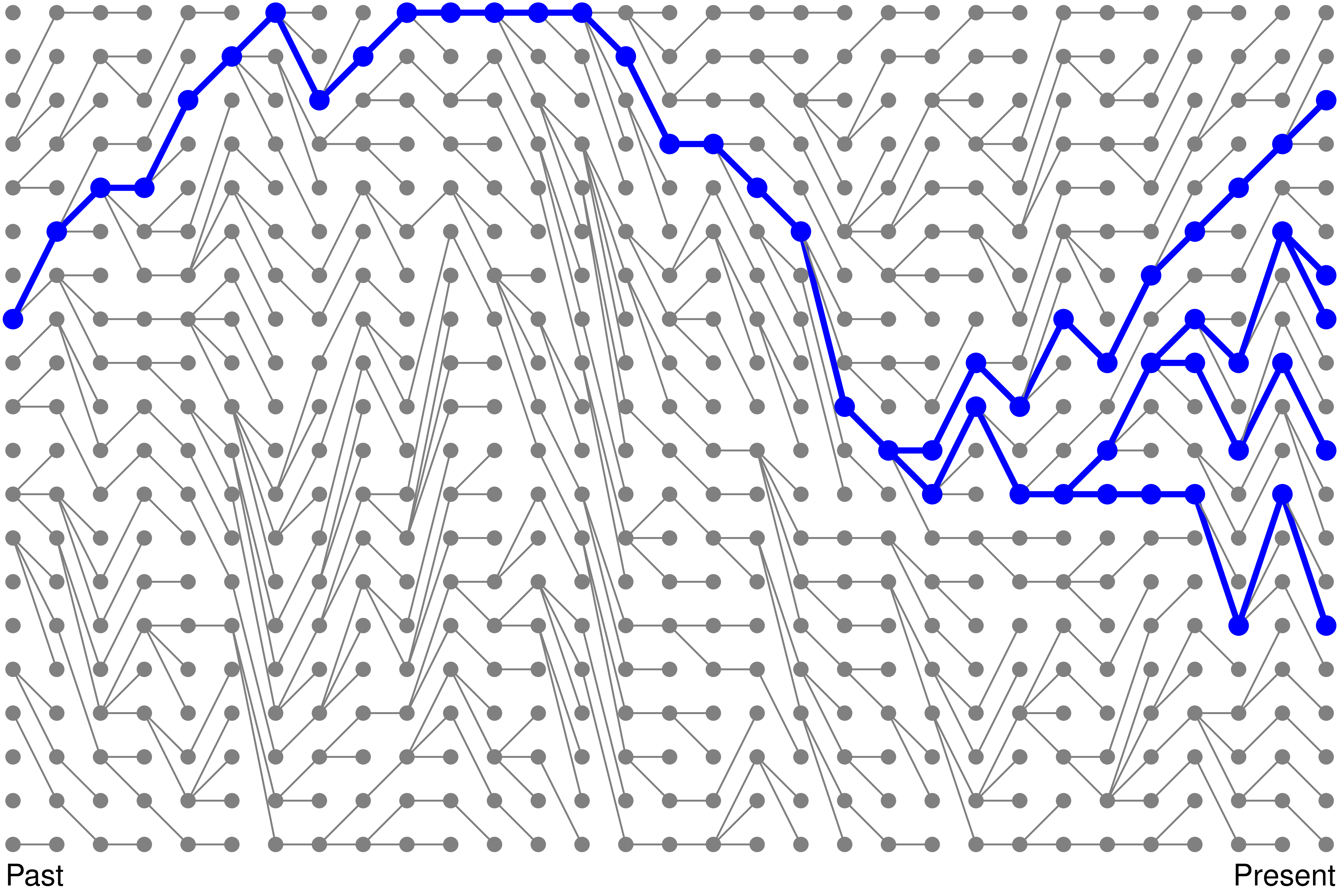


Past

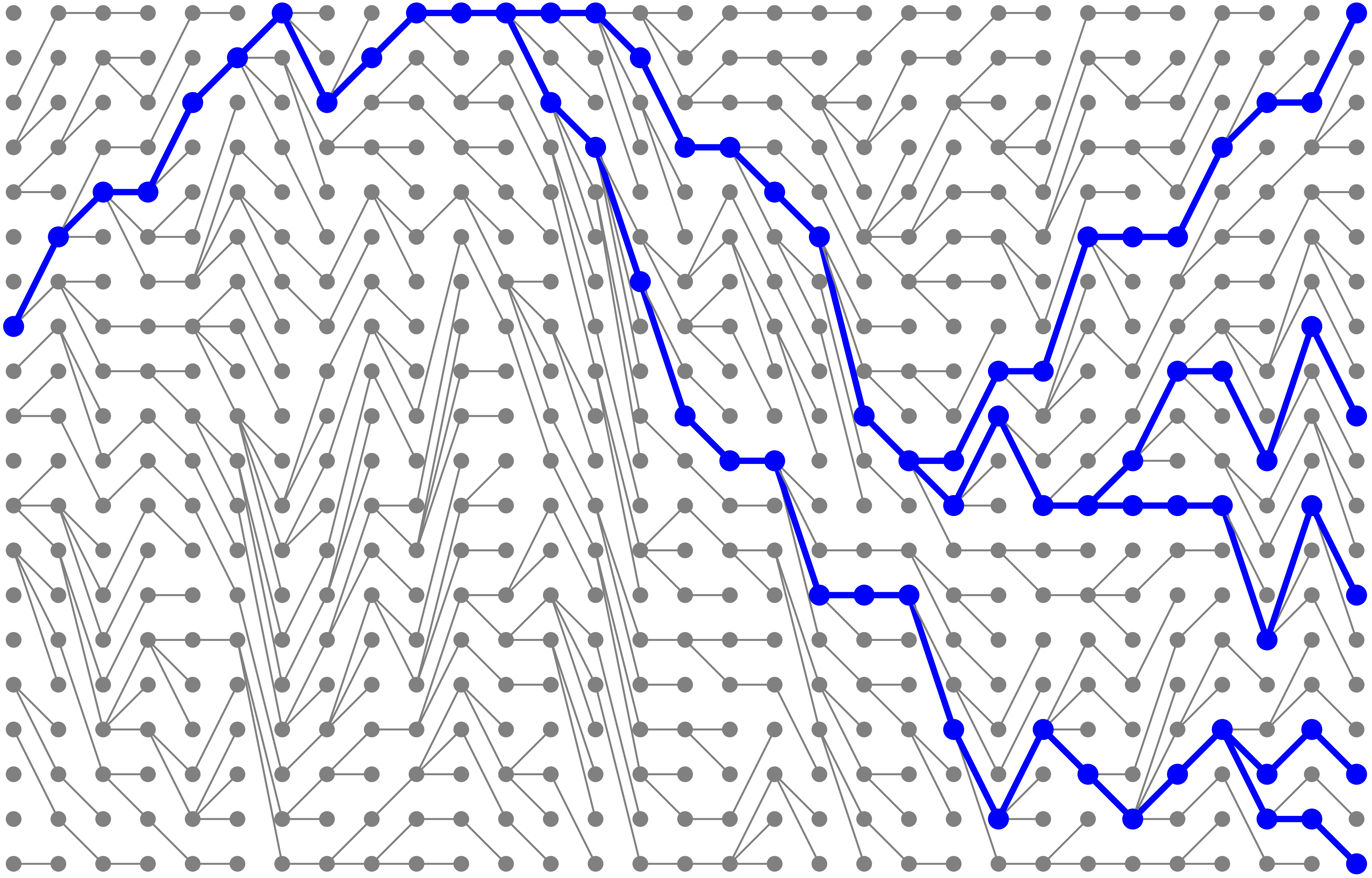
Present

Sample larger than TWO

Wright-Fisher



Sample larger than TWO



Past

Present

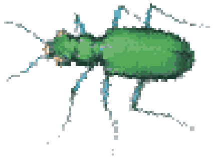
Samples larger than two

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

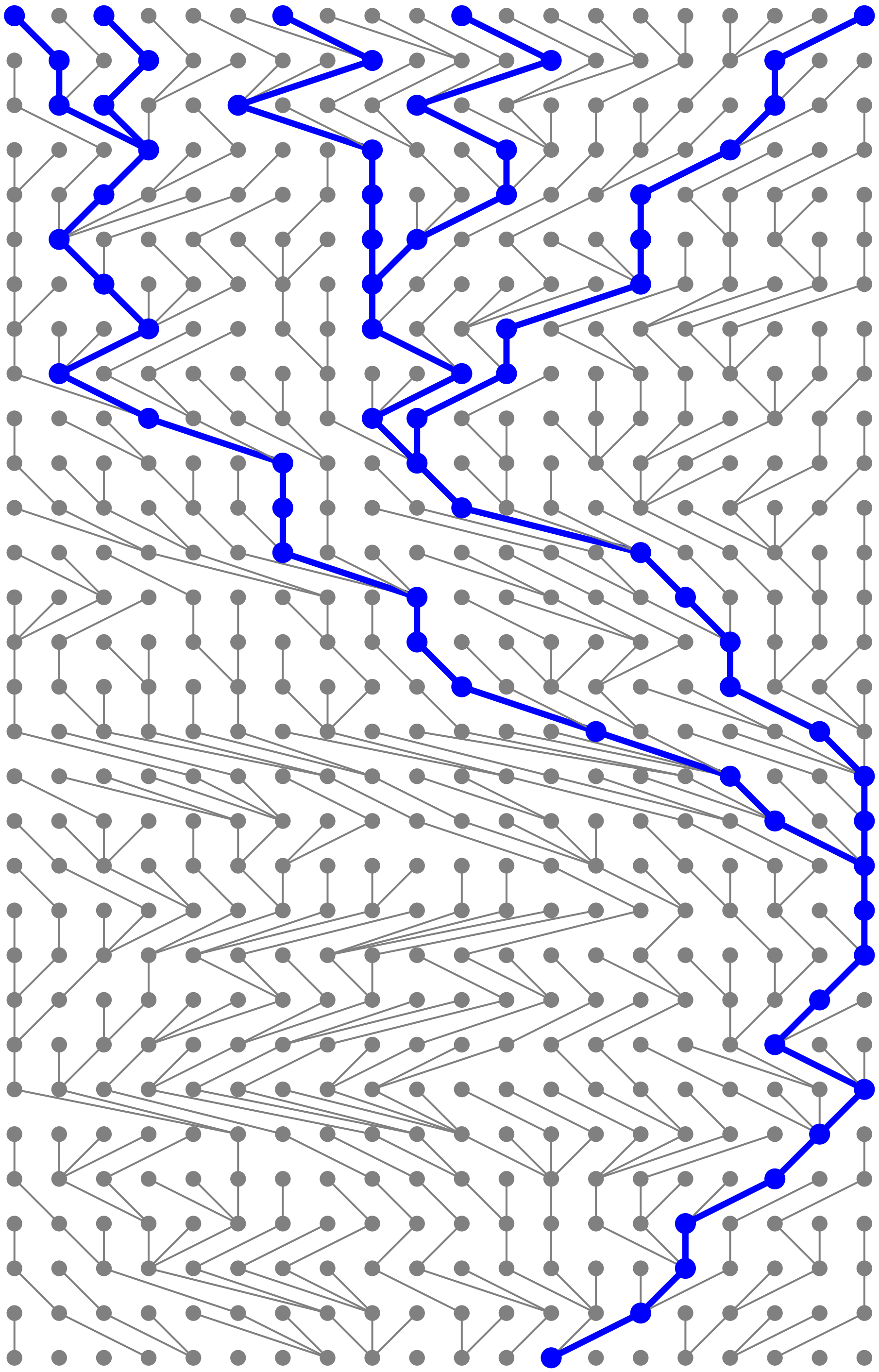
General findings:

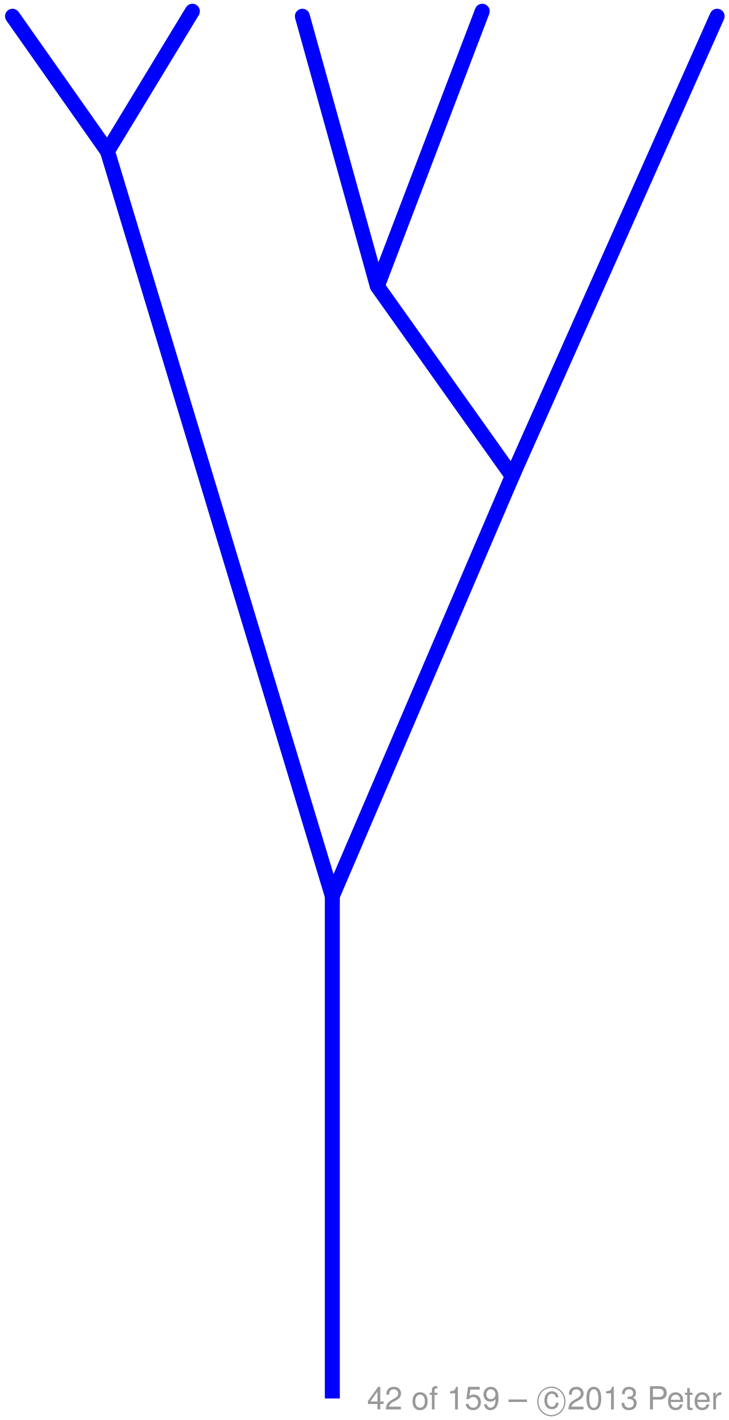
$$\text{coalescence rate} = \binom{n}{2} = \frac{n(n-1)}{2}$$

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

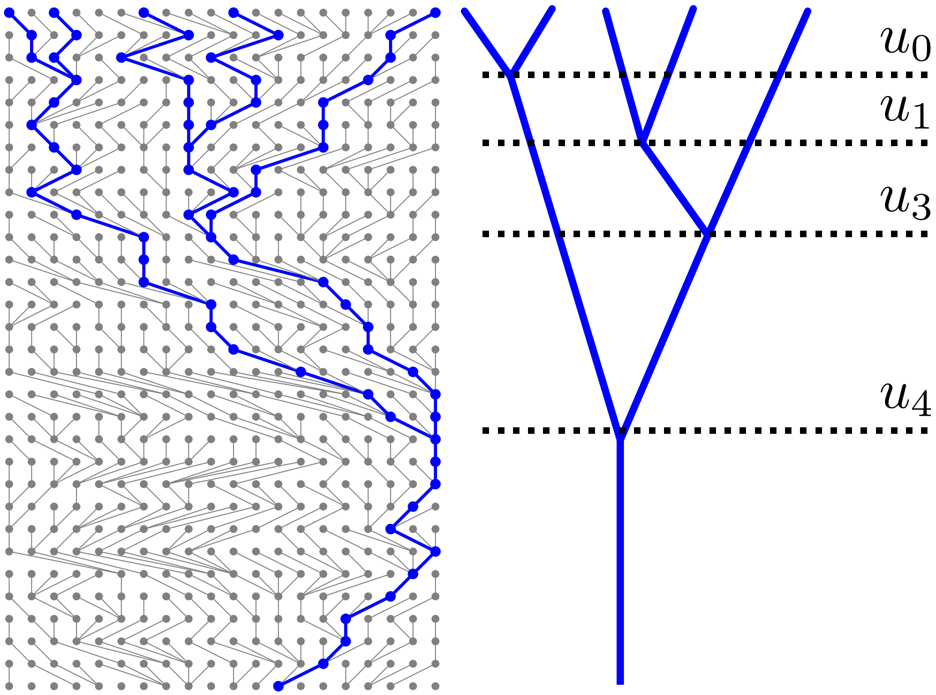


Samples larger than two



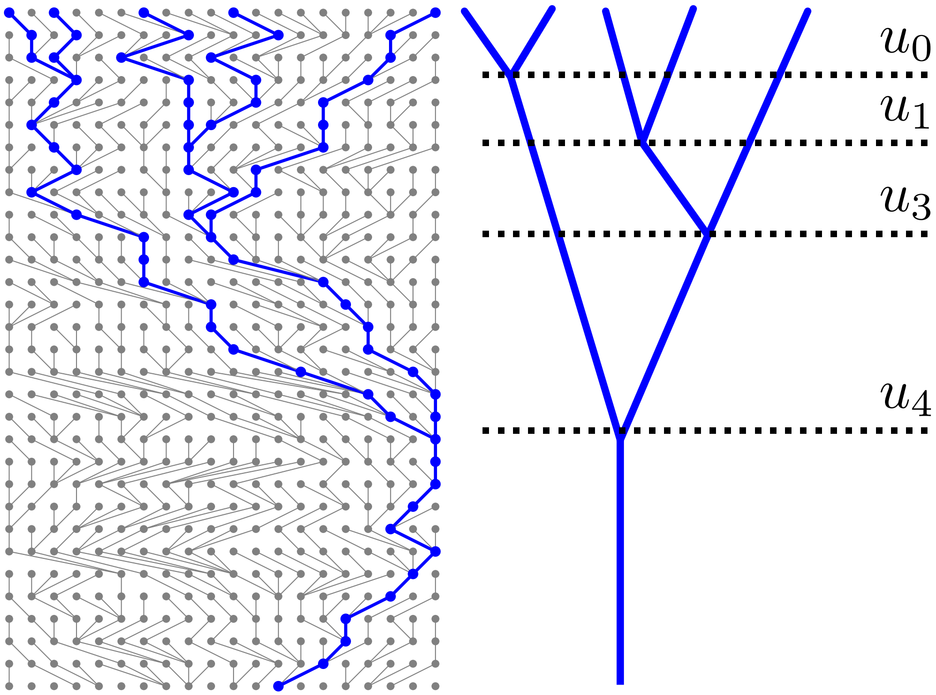


Samples larger than two



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.

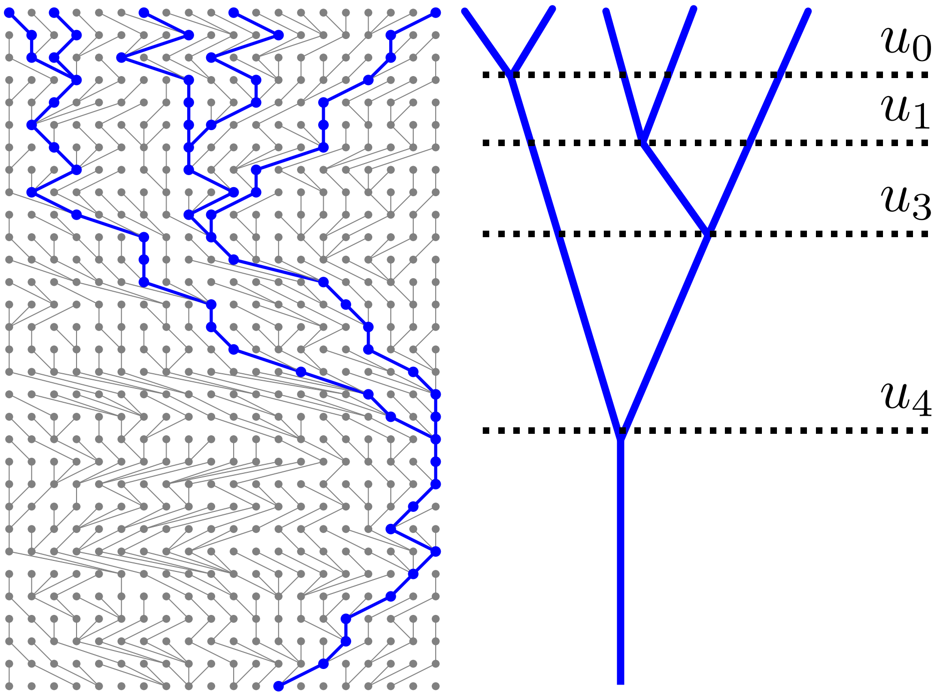
Samples larger than two



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 a exponential distribution:

Samples larger than two



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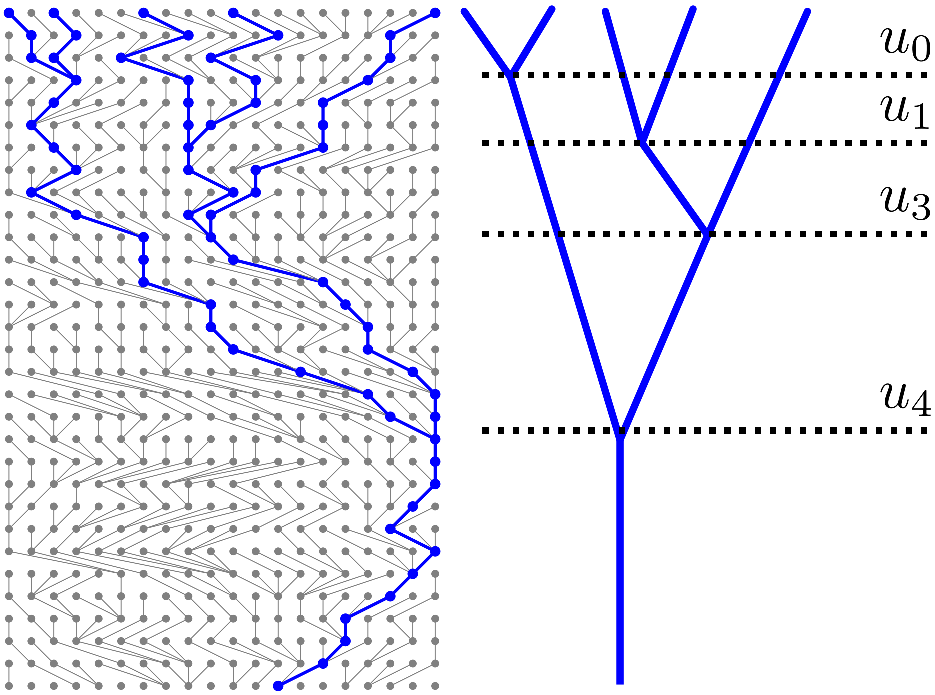
Using Kingman's coalescence rate and imposing a time scale we can approximate the process with an exponential distribution:

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

with the scaled coalescence rate

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

Samples larger than two



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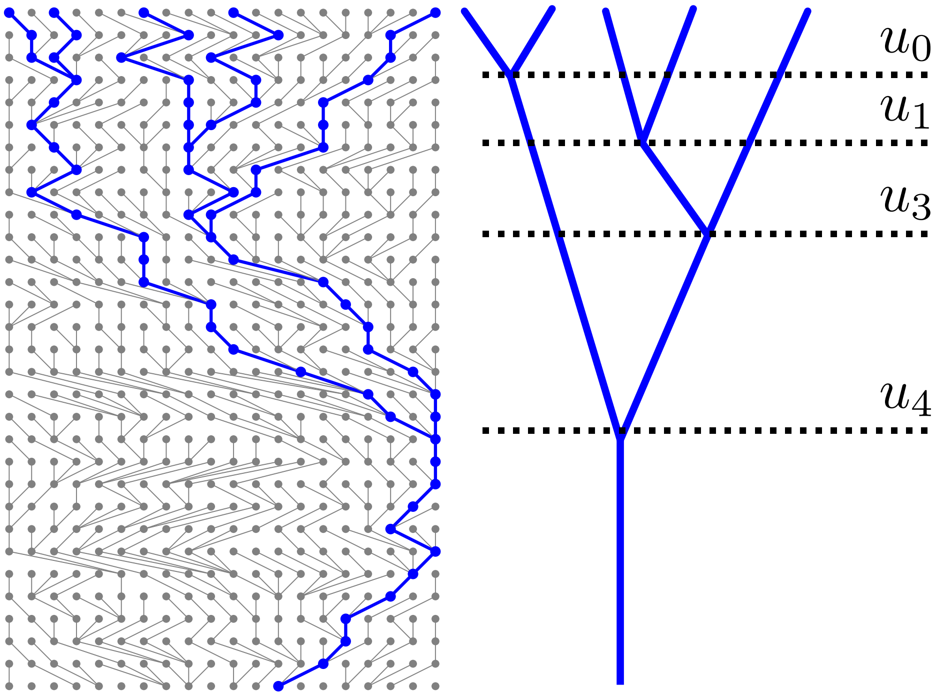
$$\lambda = \binom{k}{2}\frac{1}{2N} \times (1-\frac{1}{2N}) \times (1-\frac{2}{2N}) \times .... \times (1-\frac{k-2}{2N})$$

Samples larger than two



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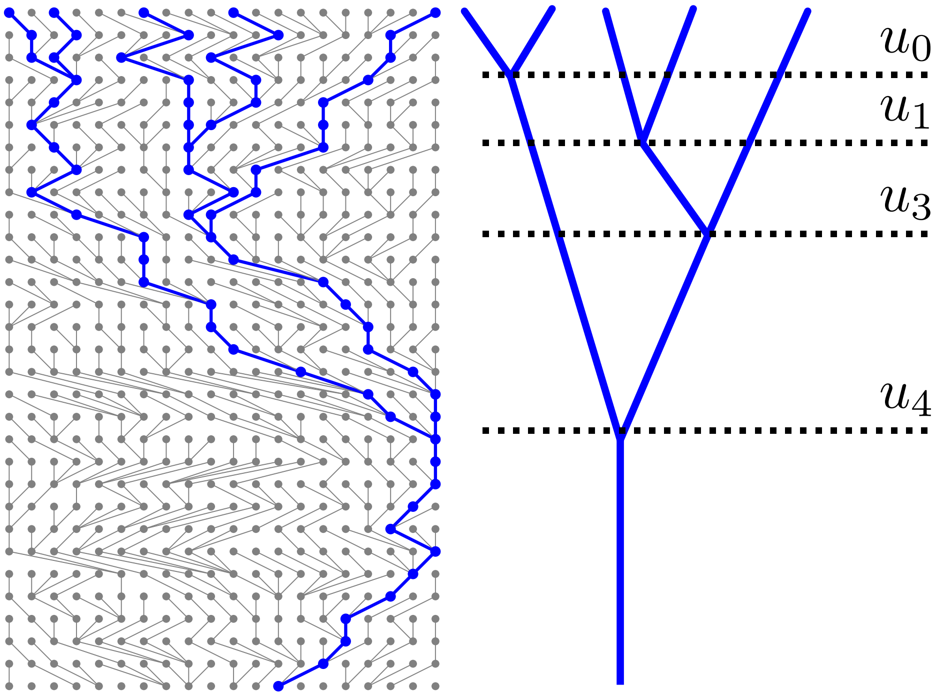
$$\lambda = \binom{k}{2}\frac{1}{2N} + O(\frac{1}{N^2})$$

Samples larger than two



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

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

with the scaled coalescence rate

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

Chance of coalescence in a particular generation

Our approximation is

$$\lambda = \binom{k}{2}\frac{1}{2N} + O(\frac{1}{N^2})$$

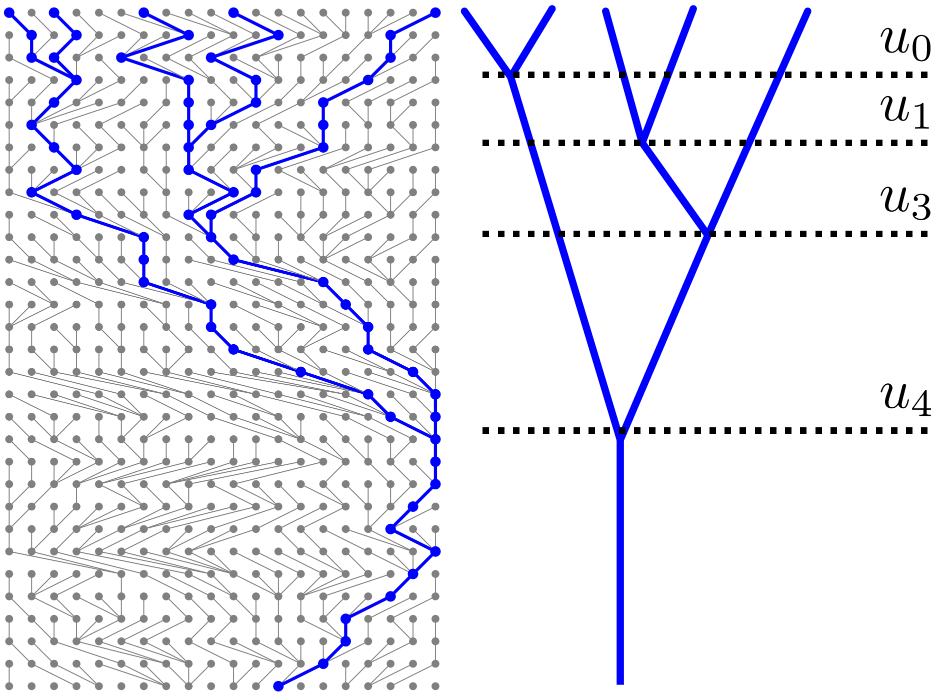
This approximation ignores multiple coalescences in one generation. We may want to worry about that because the approximation ignores those. Here are the exact probabilities of 0, 1, or more coalescences with 10 lineages in populations of different sizes:

N	0	1	>1
100	0.79560747	0.18744678	0.01694575
1000	0.97771632	0.02209806	0.00018562
10000	0.99775217	0.00224595	0.00000187

Note that increasing the population size by a factor of 10 reduces the coalescent rate for pairs by about 10-fold, but reduces the rate for triples (or more) by about 100-fold.

Courtesy of Joe Felsenstein

Samples larger than two



If we know the relationships among all individuals we can calculate the probability for each of the particular coalescence event.

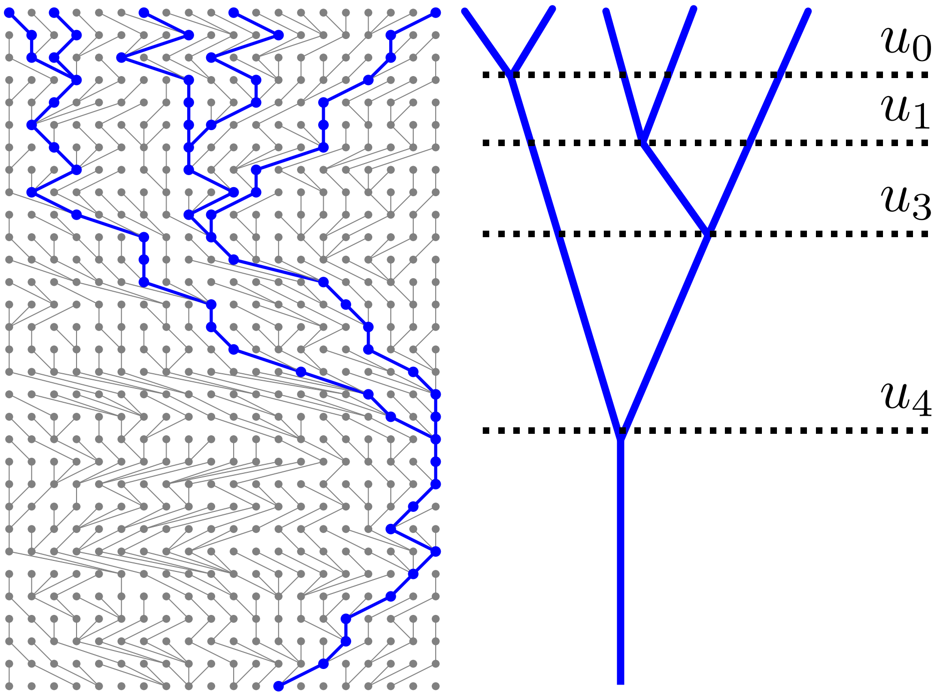
With probability $\mathrm{P}(u_j|N)$ a coalescent event happens, but we still do not know which pair of individuals is involved, we pick a random pair with probability

$$\frac{1}{\binom{k}{2}},$$

therefore

$$\mathrm{P}(u_j|N, i_1, i_2) = \left[e^{-u_j\frac{k(k-1)}{4N}}\frac{k(k-1)}{4N}\right]\frac{2}{k(k-1)}$$

Samples larger than two



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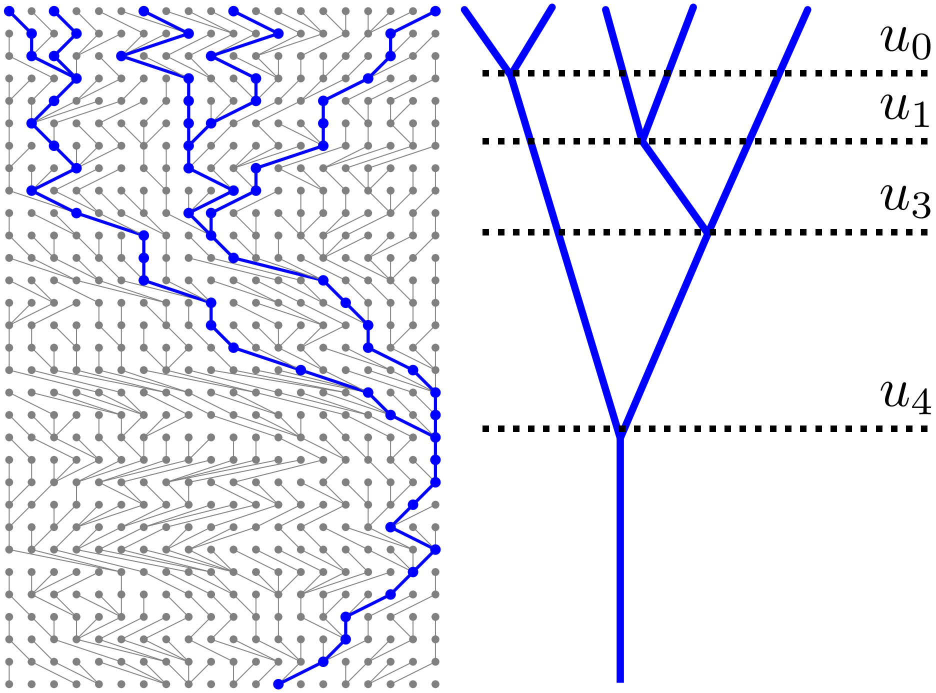
$$\mathrm{P}(u_j|N,i_1,i_2) = e^{-u_j\frac{k(k-1)}{4N}}\frac{2}{4N}$$

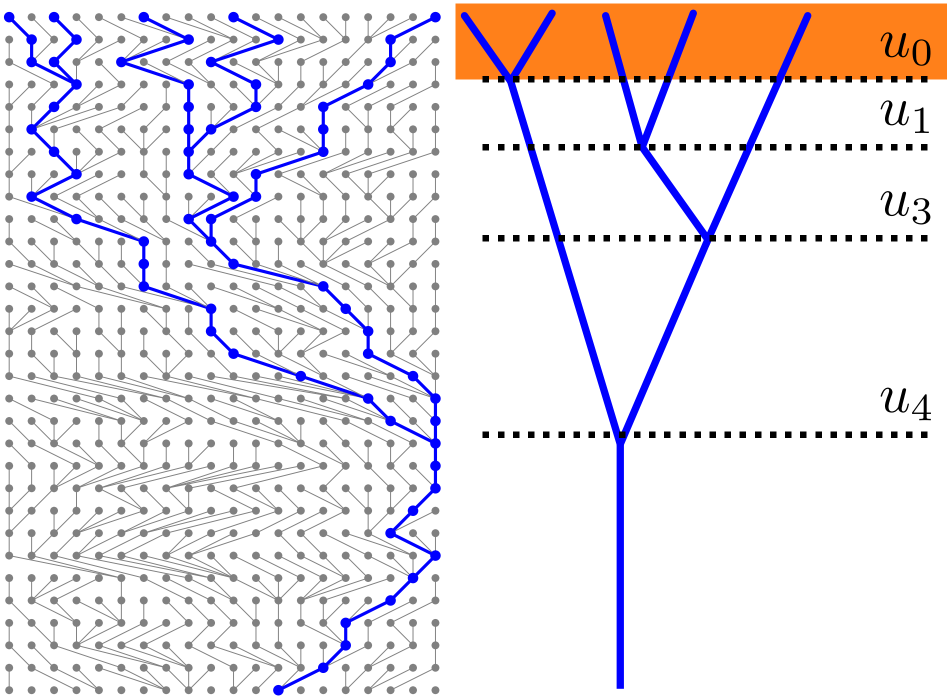
Samples larger than two



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:

$$\mathrm{P}(G|N)$$

Samples larger than two



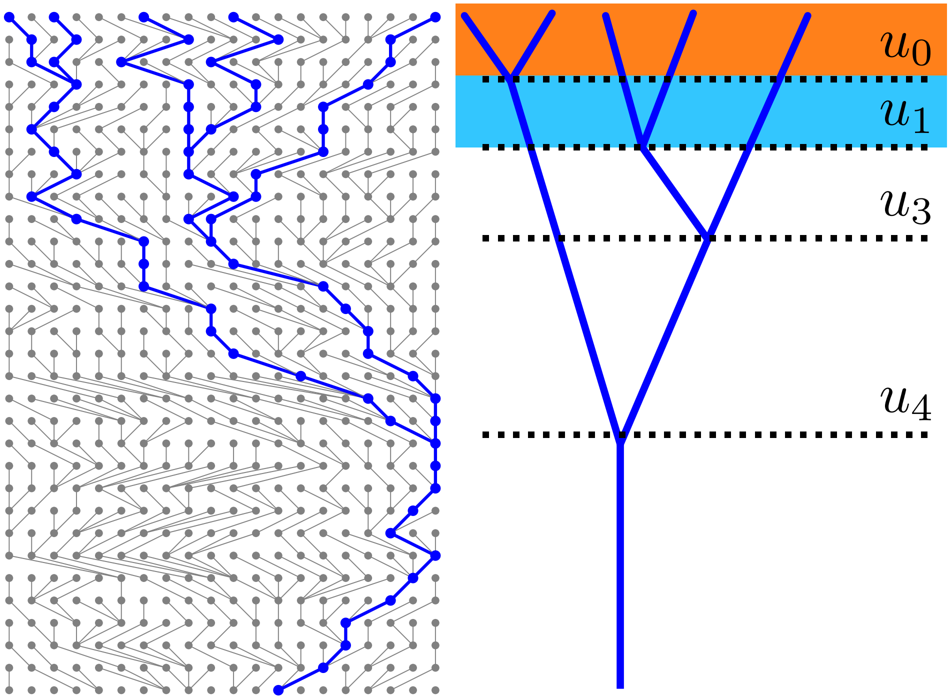
We are now able to calculate the probability of a whole relationship tree (Genealogy G). We assume that each coalescence is independent from any other:

$$\mathrm{P}(G|N) = \quad \mathrm{P}(u_0|N, i_1, i_2)$$

$$\times$$

$$)$$

Samples larger than two



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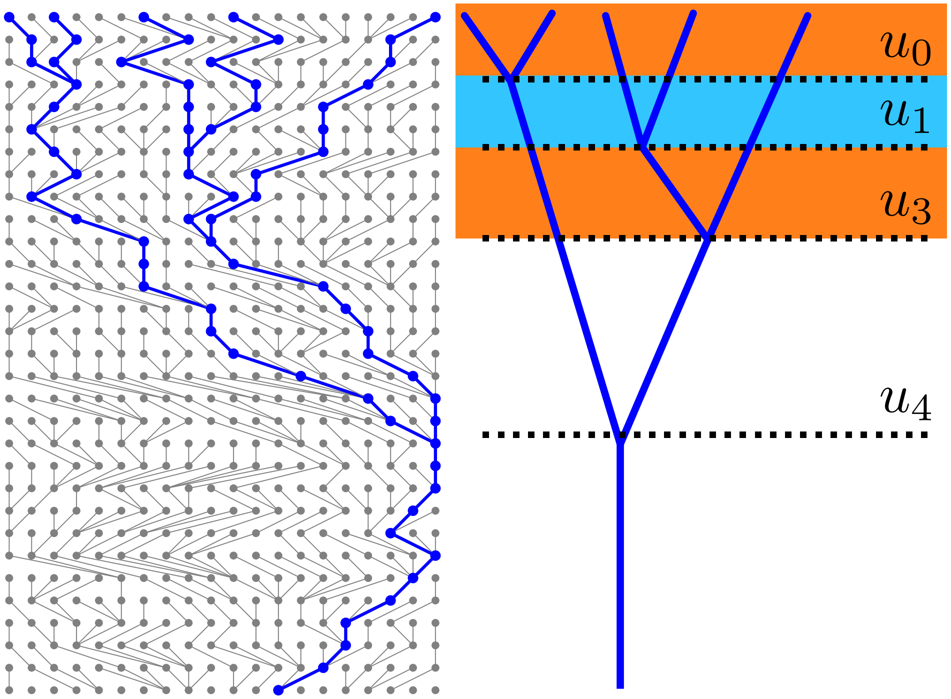
$$\mathrm{P}(G|N) = \mathrm{P}(u_0|N, i_1, i_2) \times \mathrm{P}(u_1|N, i_3, i_4)$$

Samples larger than two



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:

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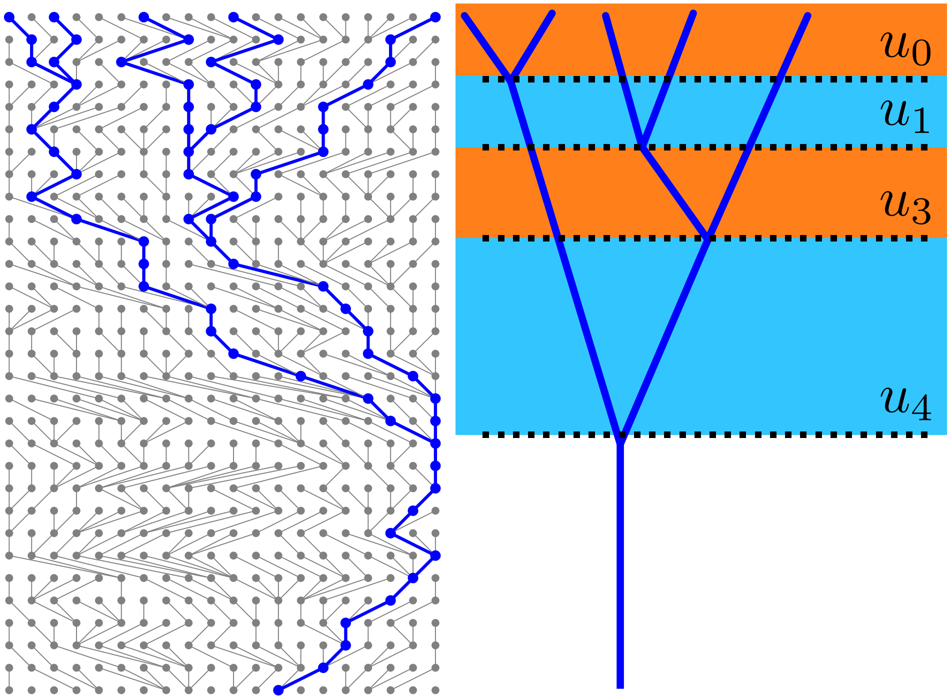
Samples larger than two



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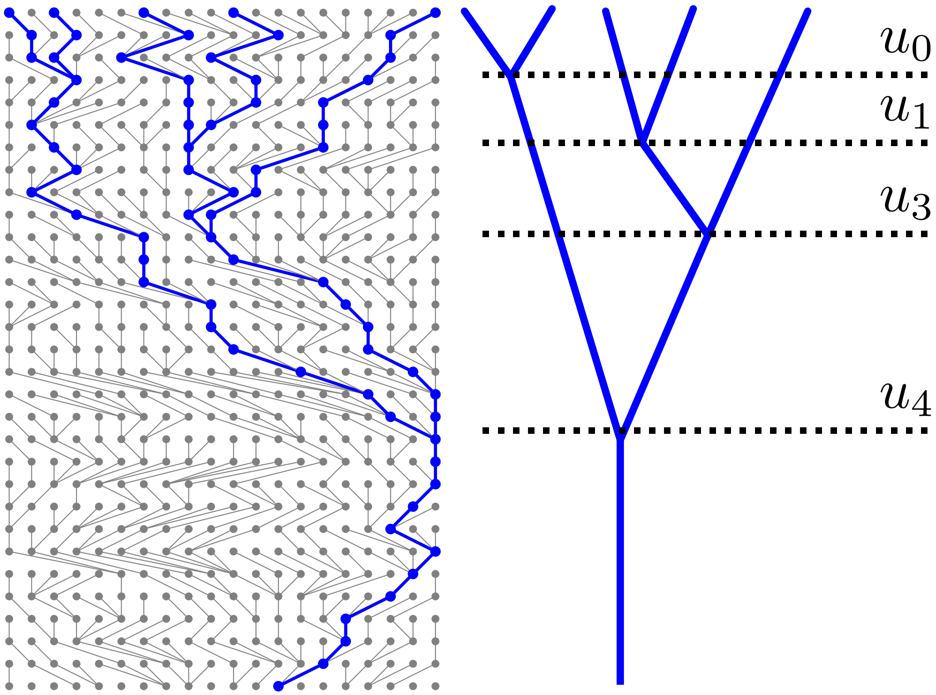
Samples larger than two



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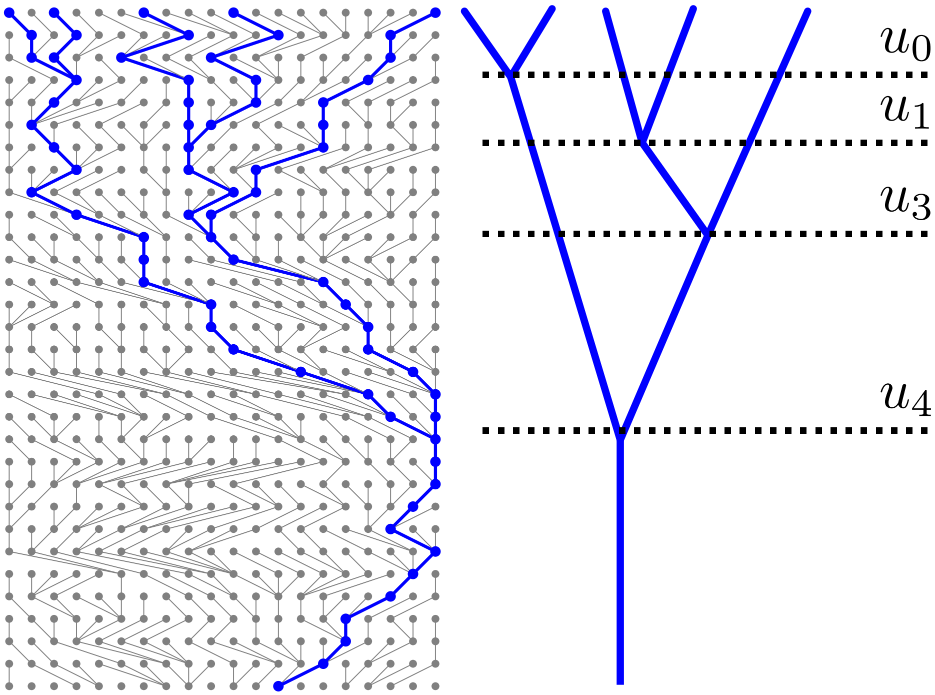
$$\mathrm{P}(G|N) = \prod_{j=0}^{T} e^{-u_j \frac{k_j(k_j-1)}{4N}} \frac{2}{4N}$$

Samples larger than two



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

The expectations of the total time to coalescence is the sum of the expectations for each interval. Each interval has expectation

$$\mathbb{E}(u) = \frac{4N}{k(k-1)}$$

this leads to the expectation for the time of the most recent common ancestor

$$\mathbb{E}(\tau_{\text{MRCA}}) = \sum_{j=0}^{J} \frac{4N}{k_j(k_j-1)}$$

where J is the number of time intervals u_j. In the limit this is

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

What is it good for?

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

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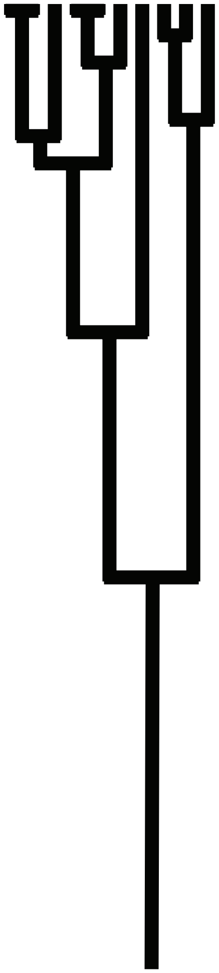
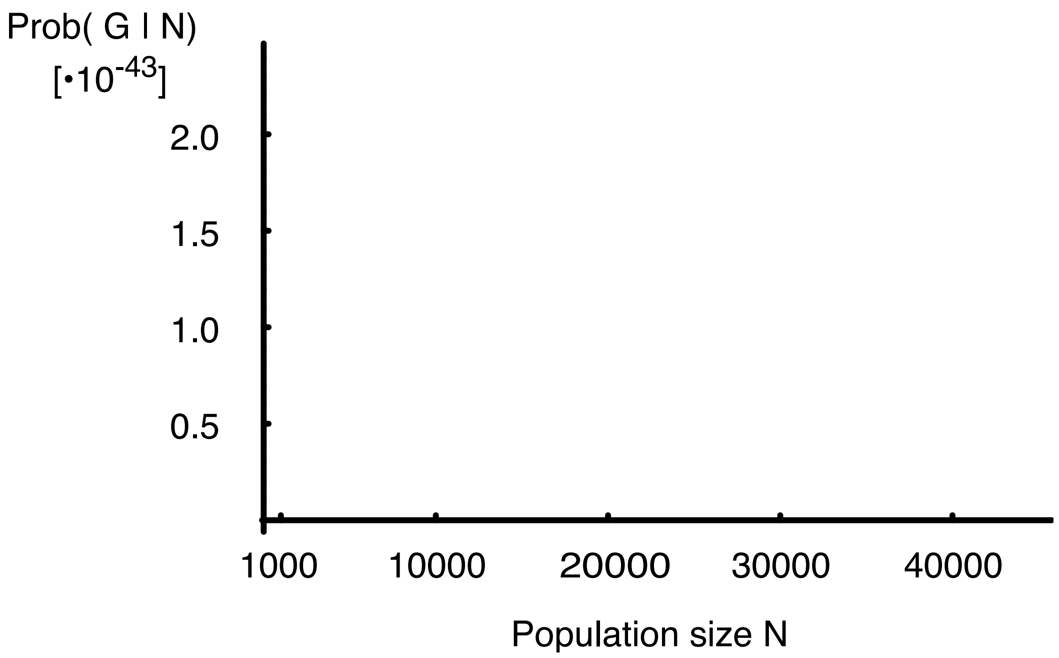


Population size estimation

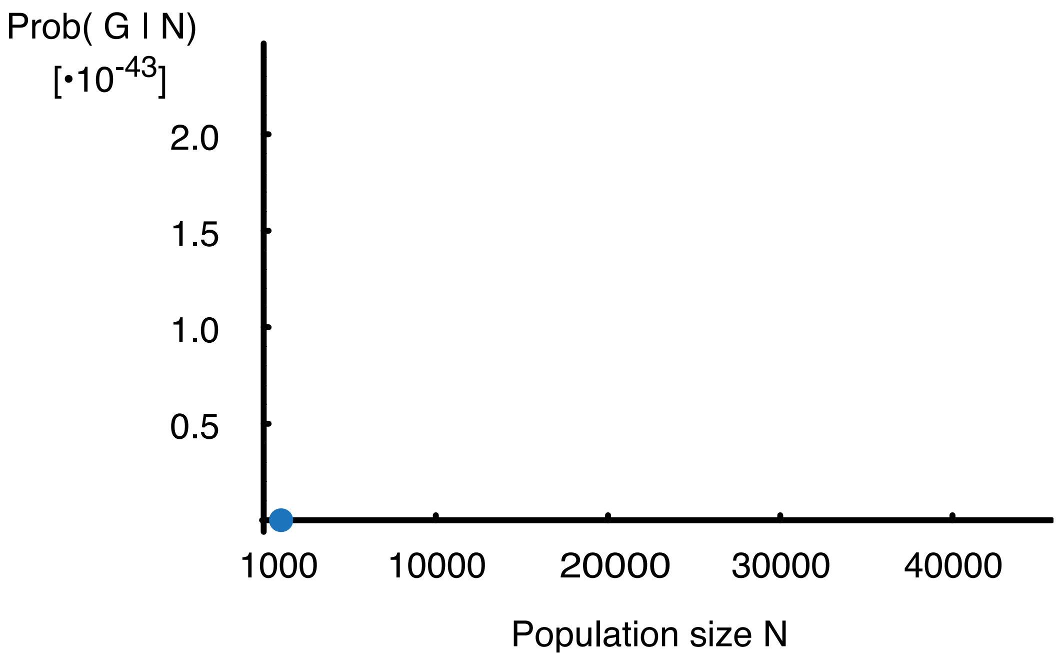
using an oracle



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



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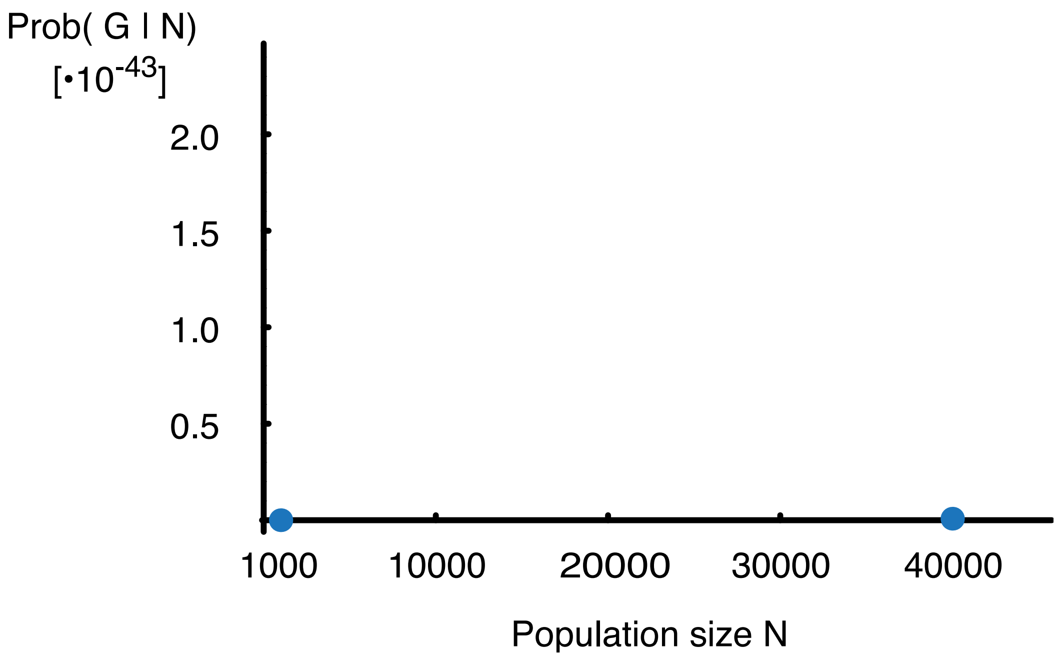

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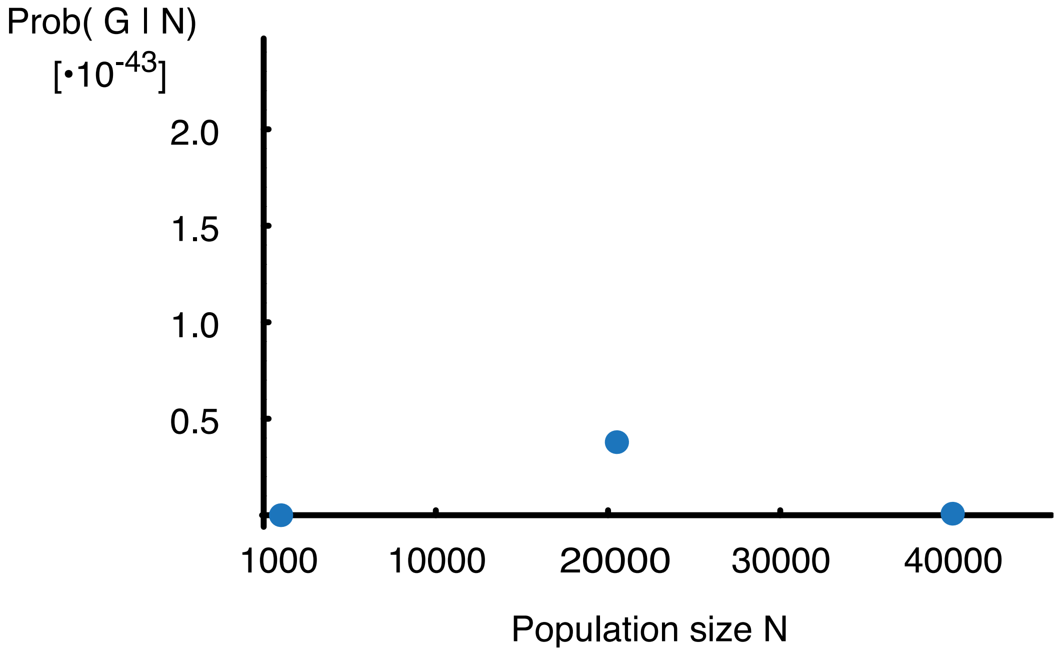

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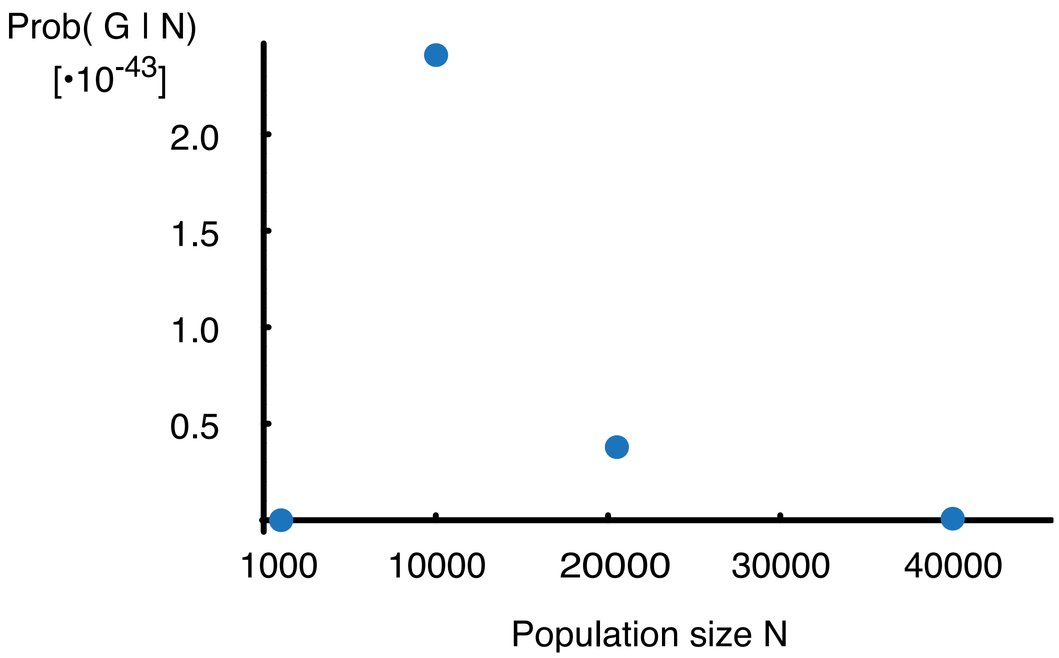

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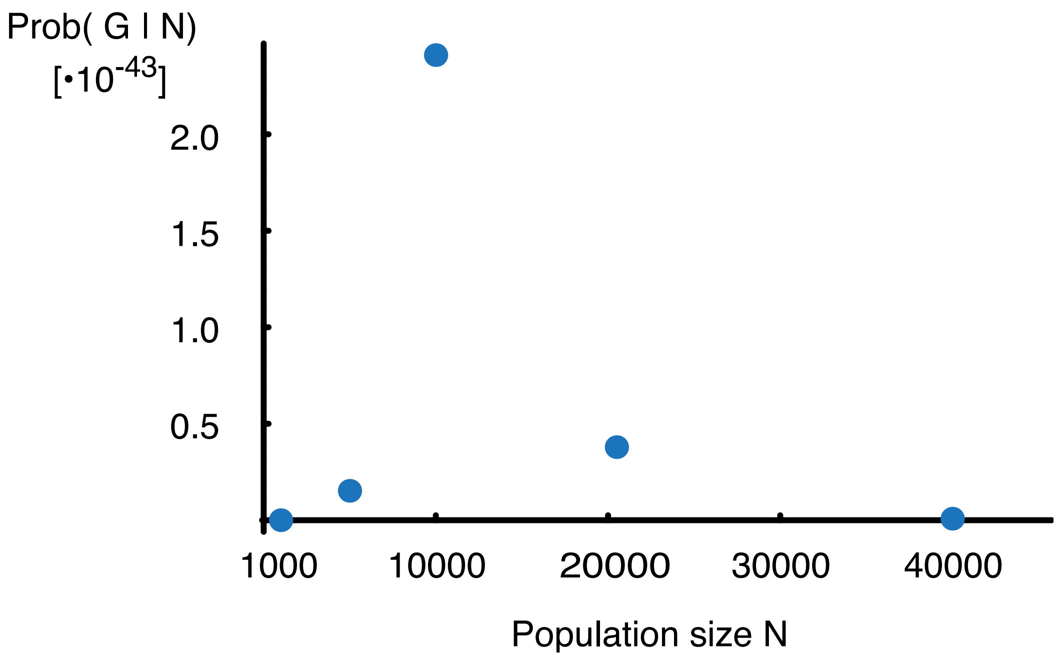

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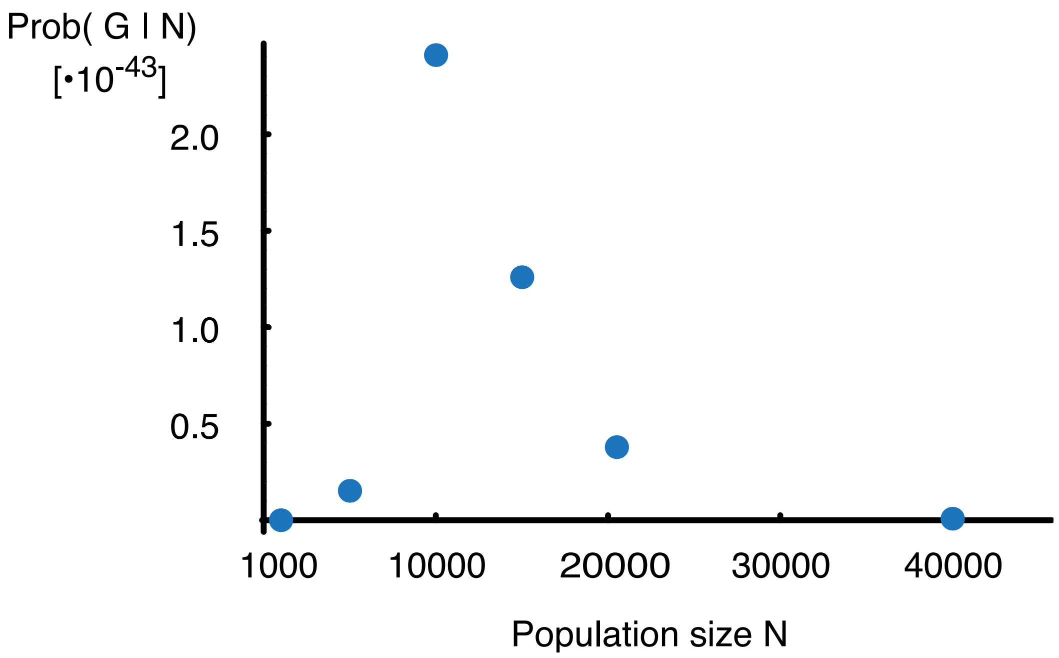

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Population size estimation

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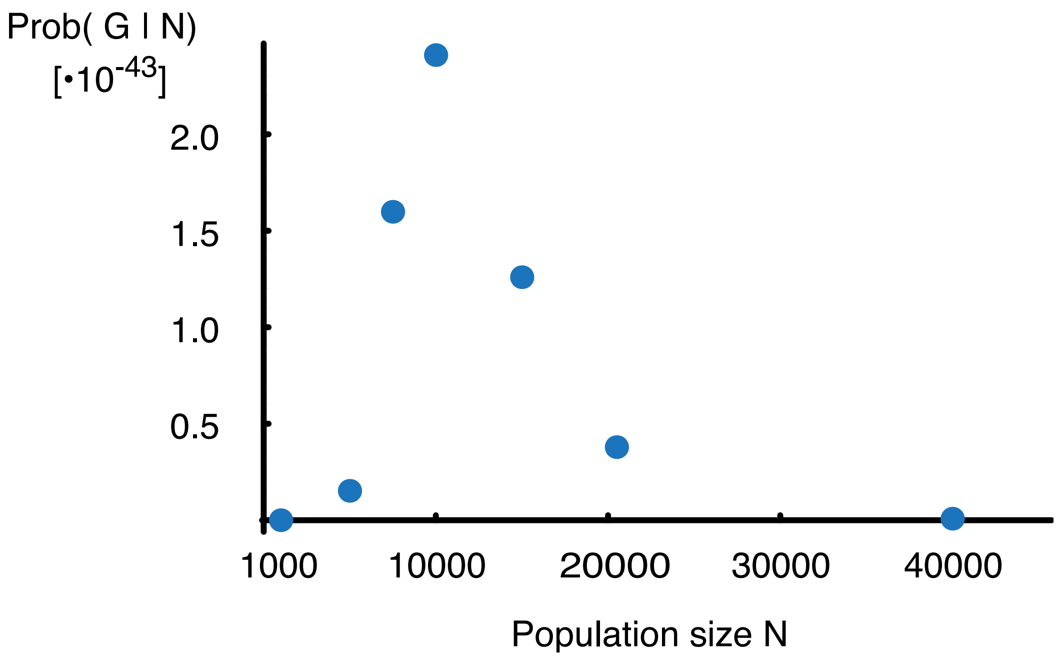

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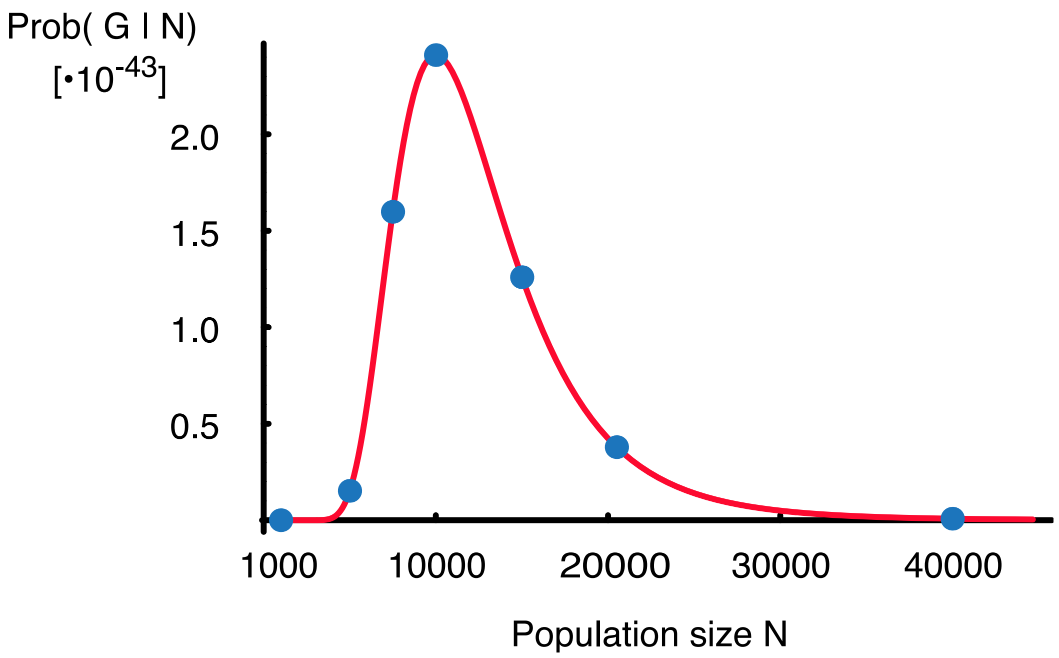

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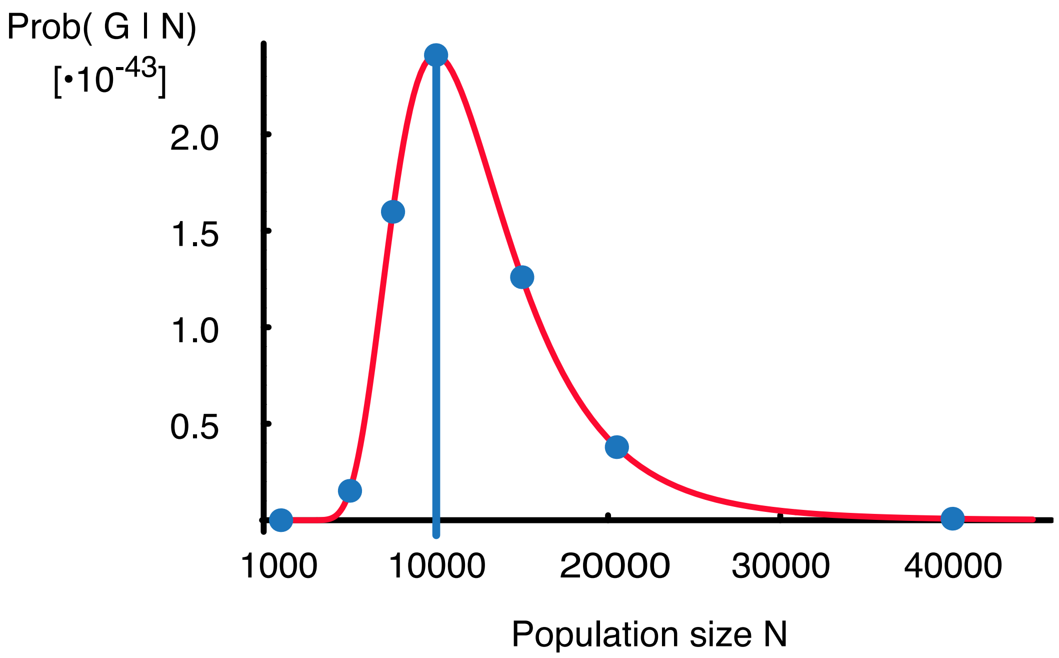

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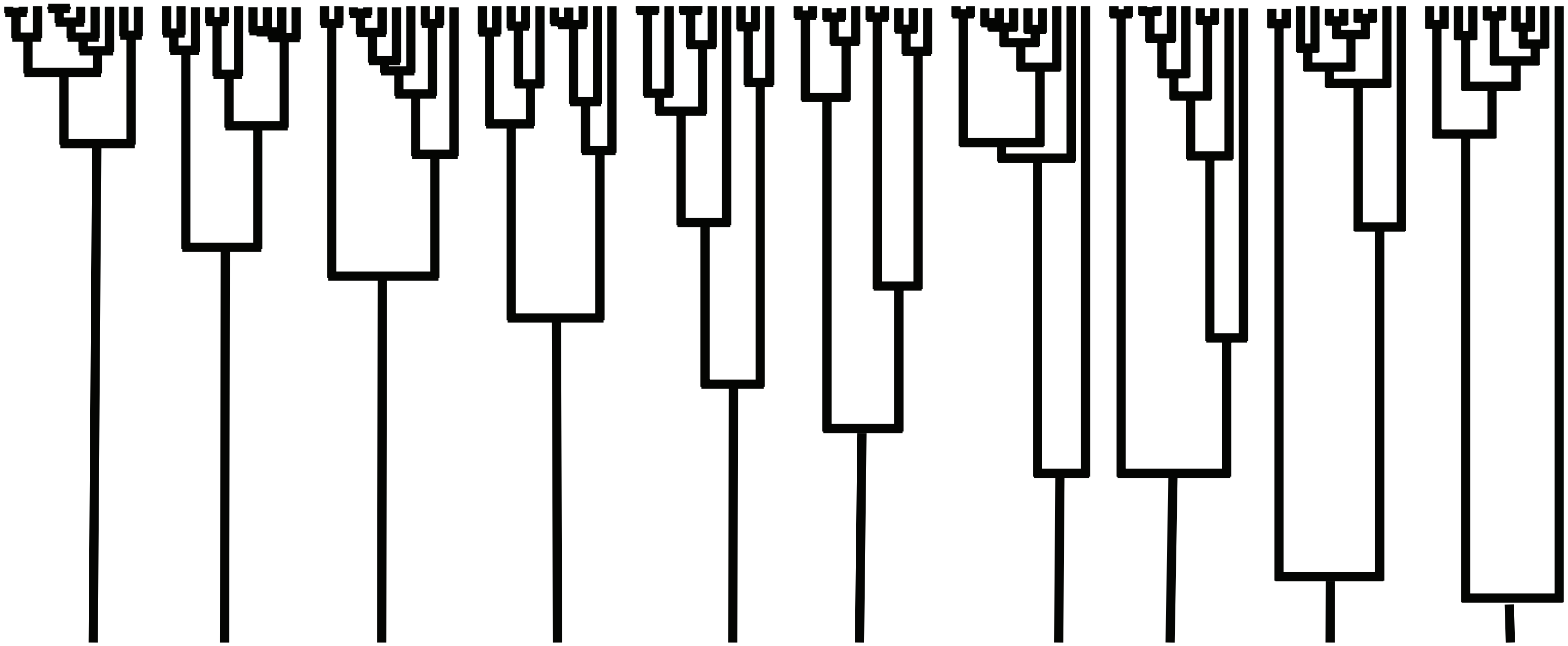
Population size estimation

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

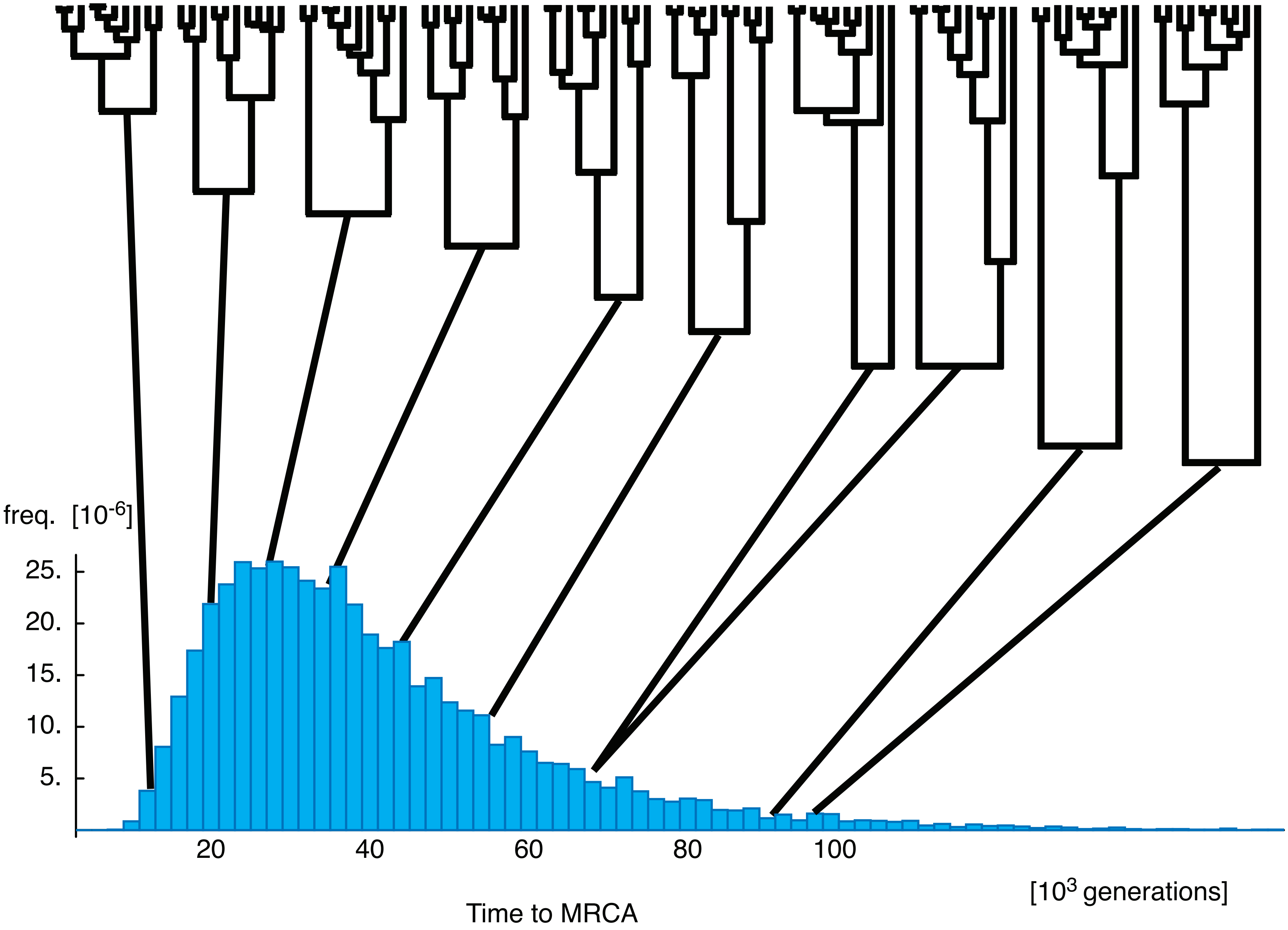
- There is no oracle to gives us clear information!
- We do not record genealogies, our data are sequences, microsatellite loci!
- What about the variability of the coalescence process?

Variability of the coalescent process



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

Variability of the coalescent process



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

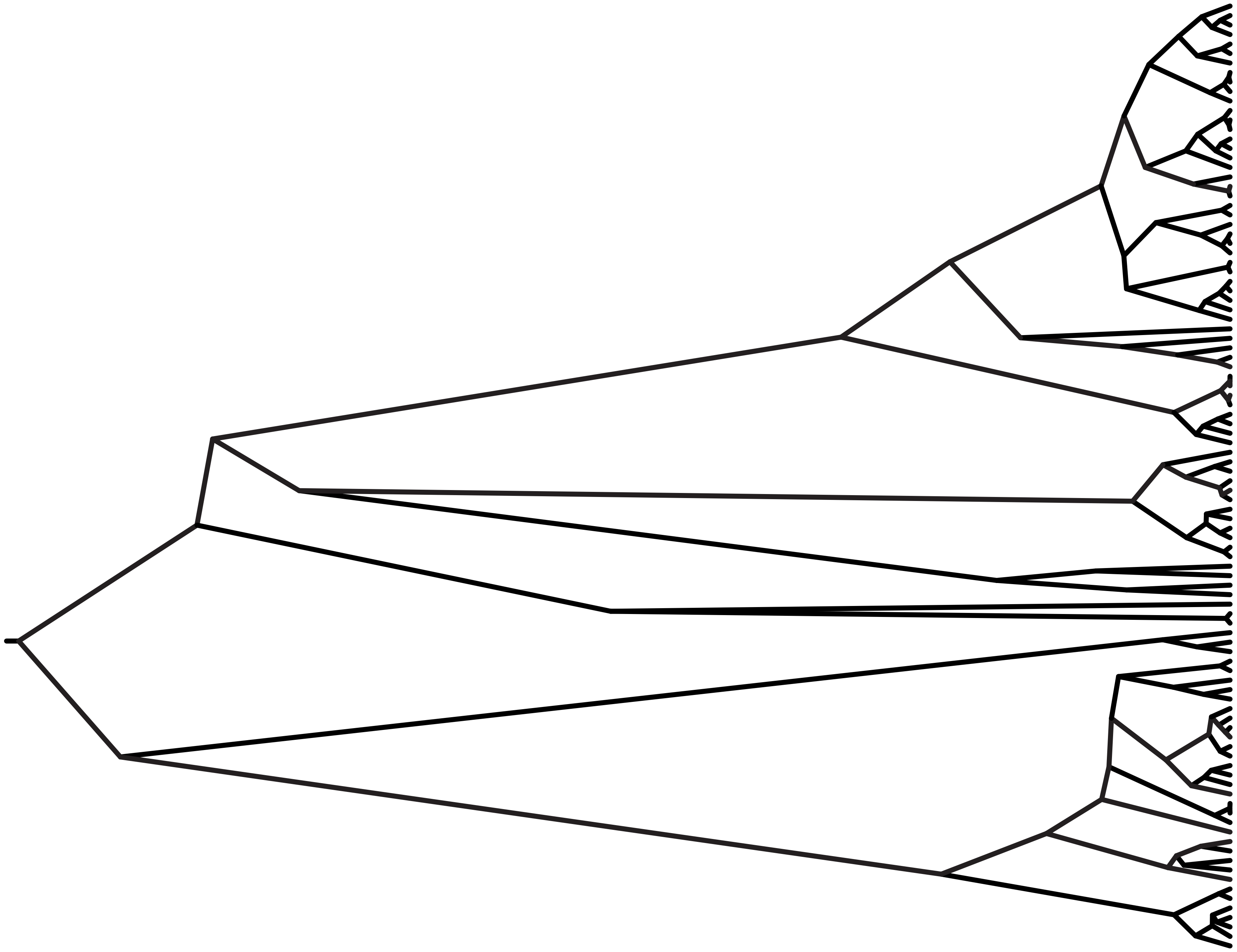
Kingman's n-coalescent is an approximation

- 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.

$$n << N$$

- 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



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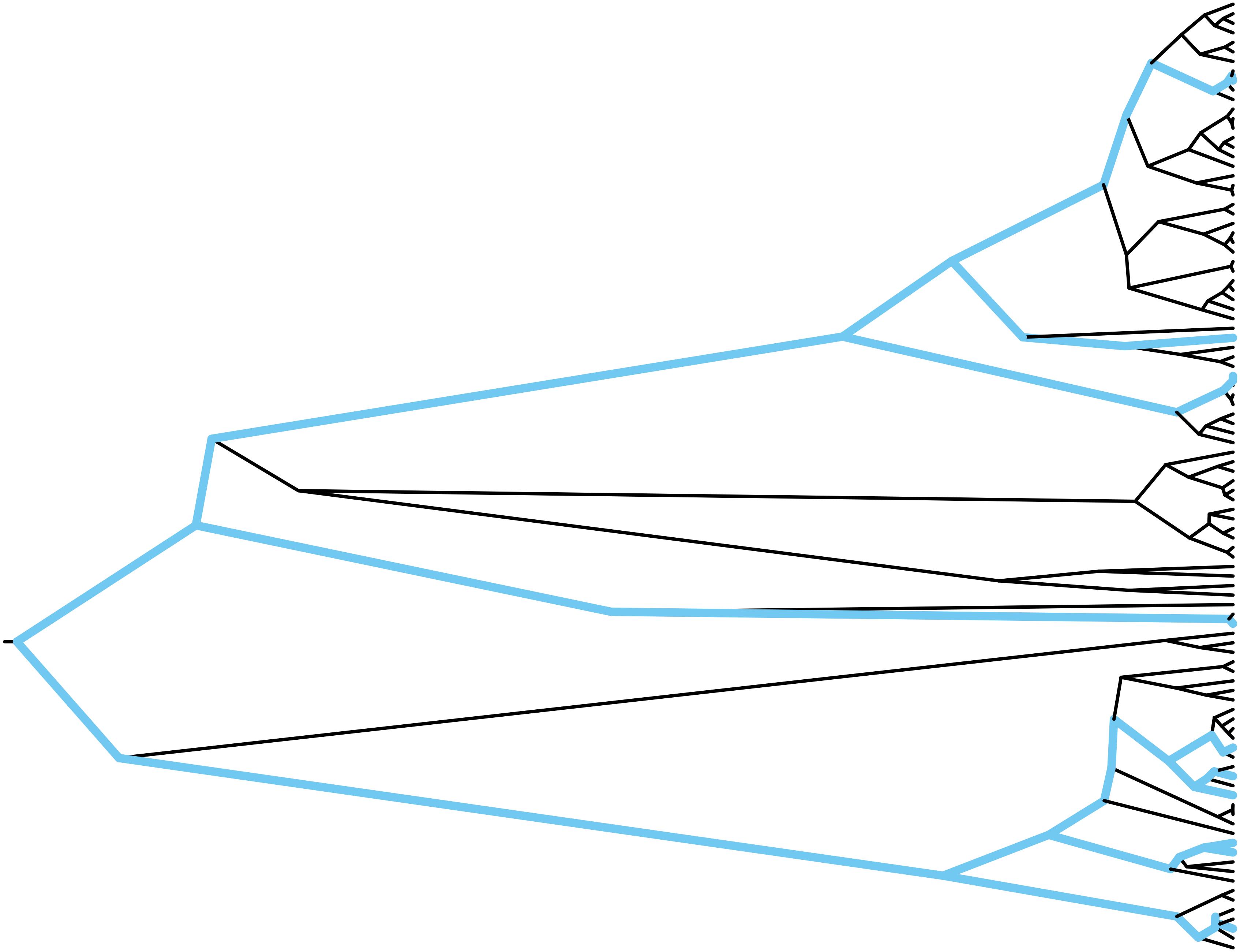
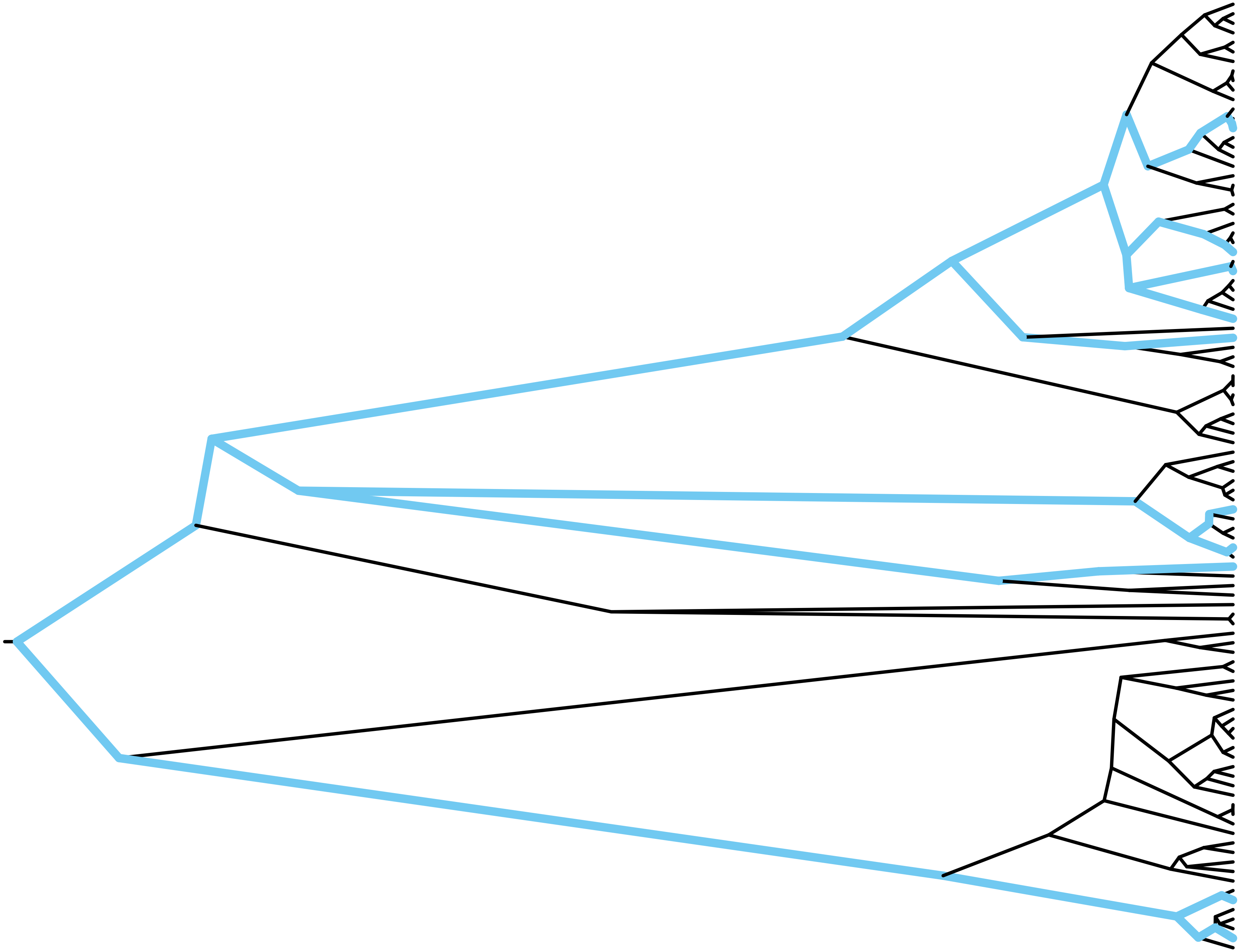


Kingman's n-coalescent is an approximation

Sample size



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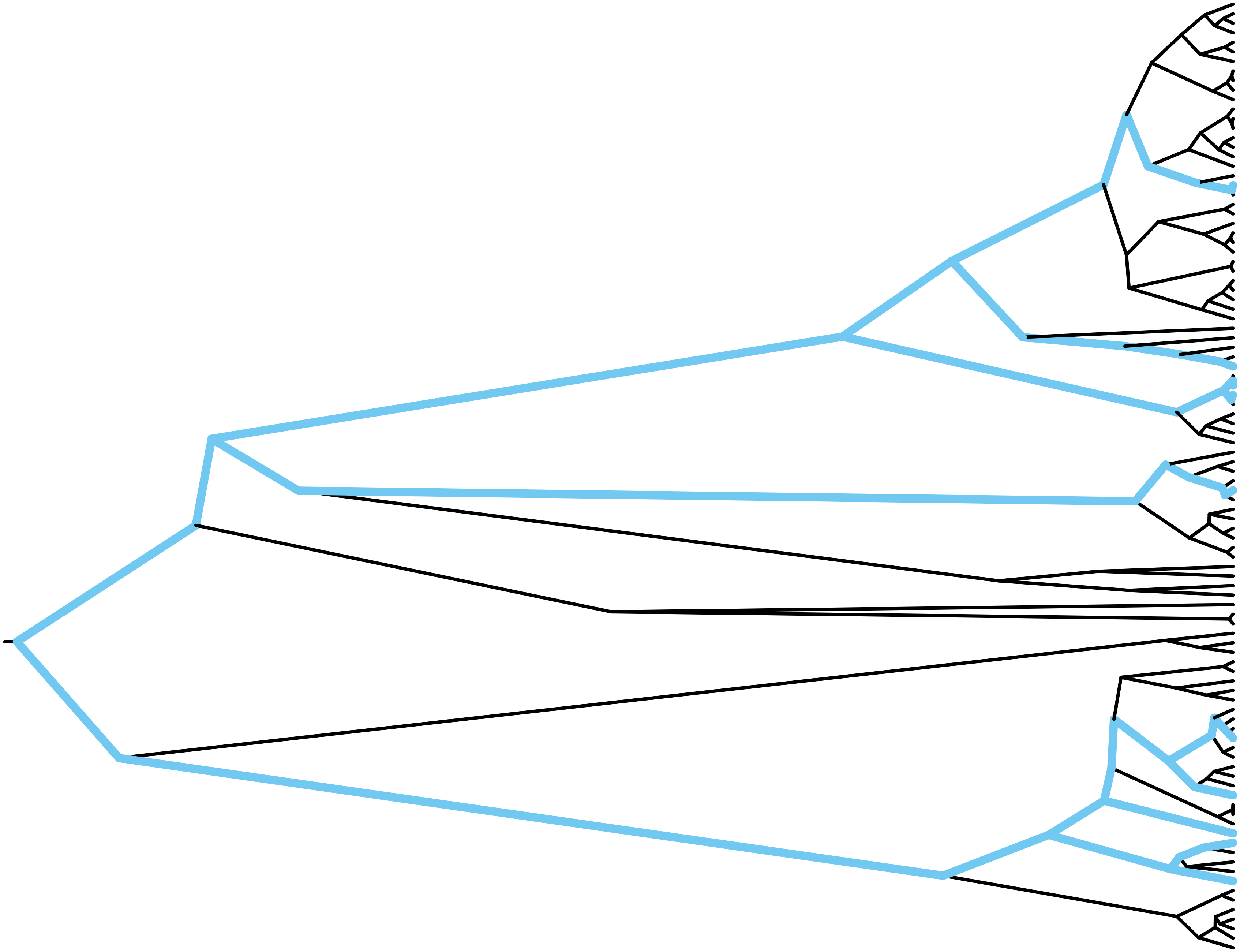
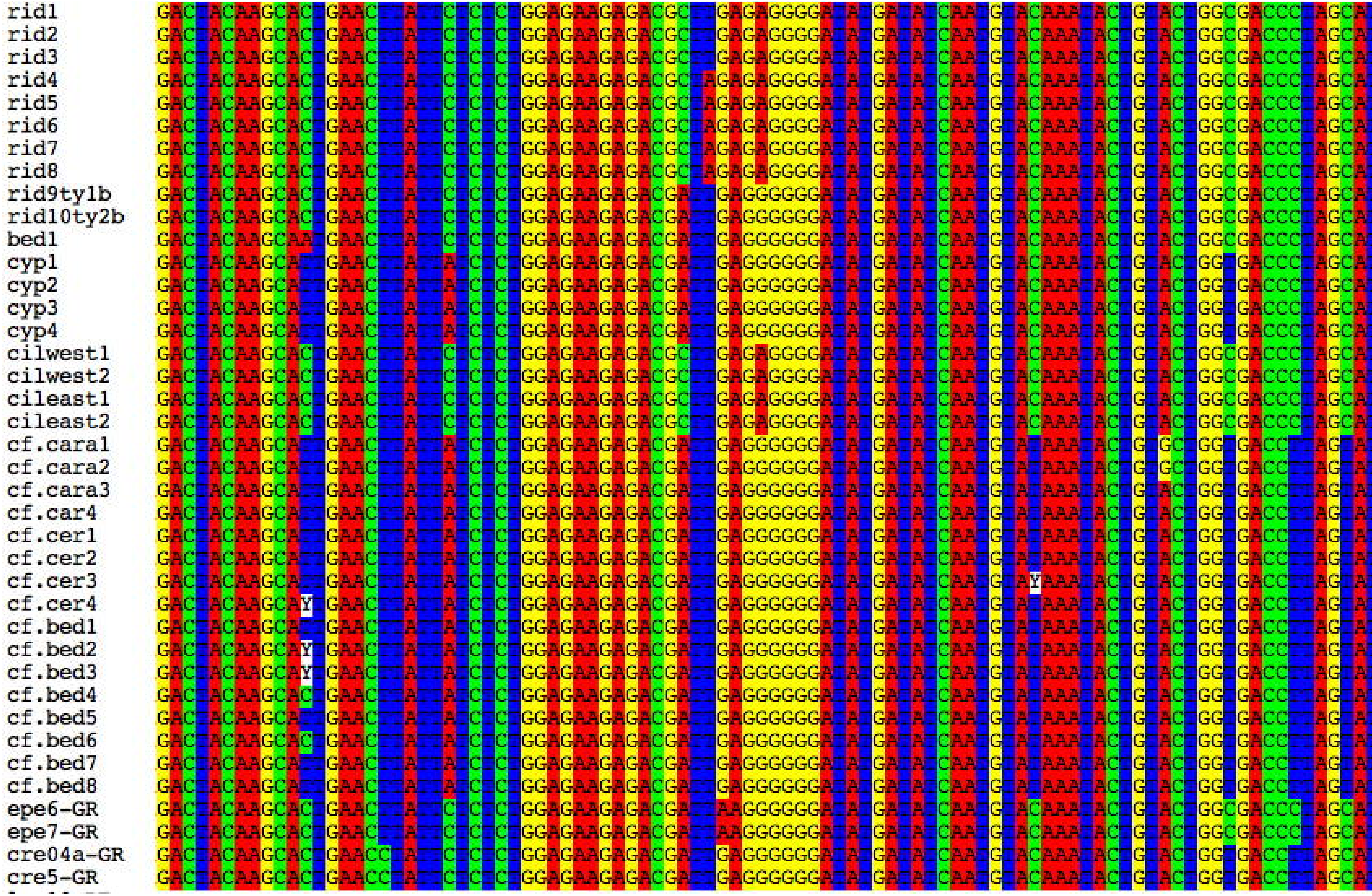


Observations

- 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:



Genealogy and data

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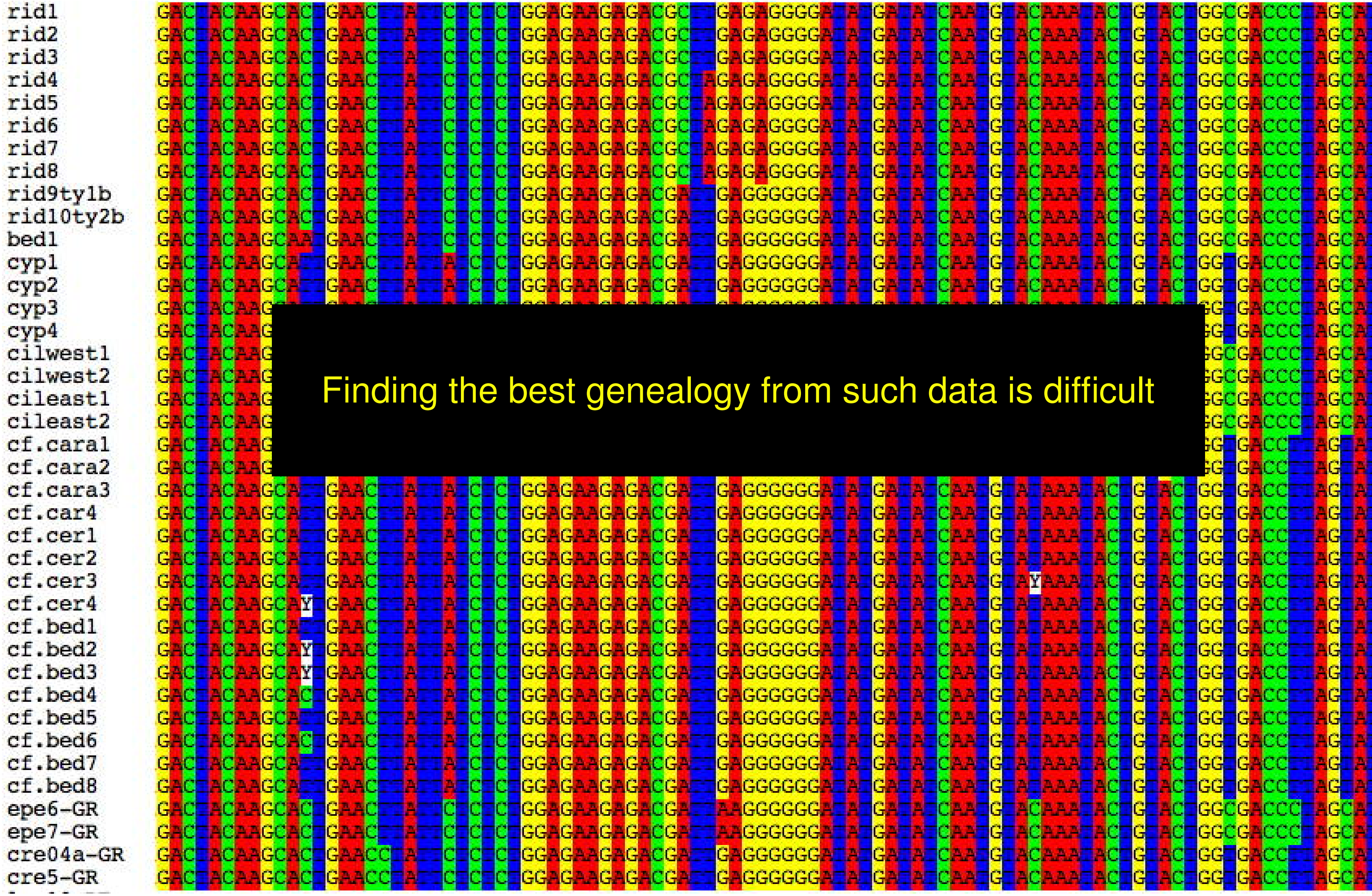


Finding the best genealogy from such data is difficult

Genetic data and the coalescent

- Finite populations loose 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 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^2_S
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.

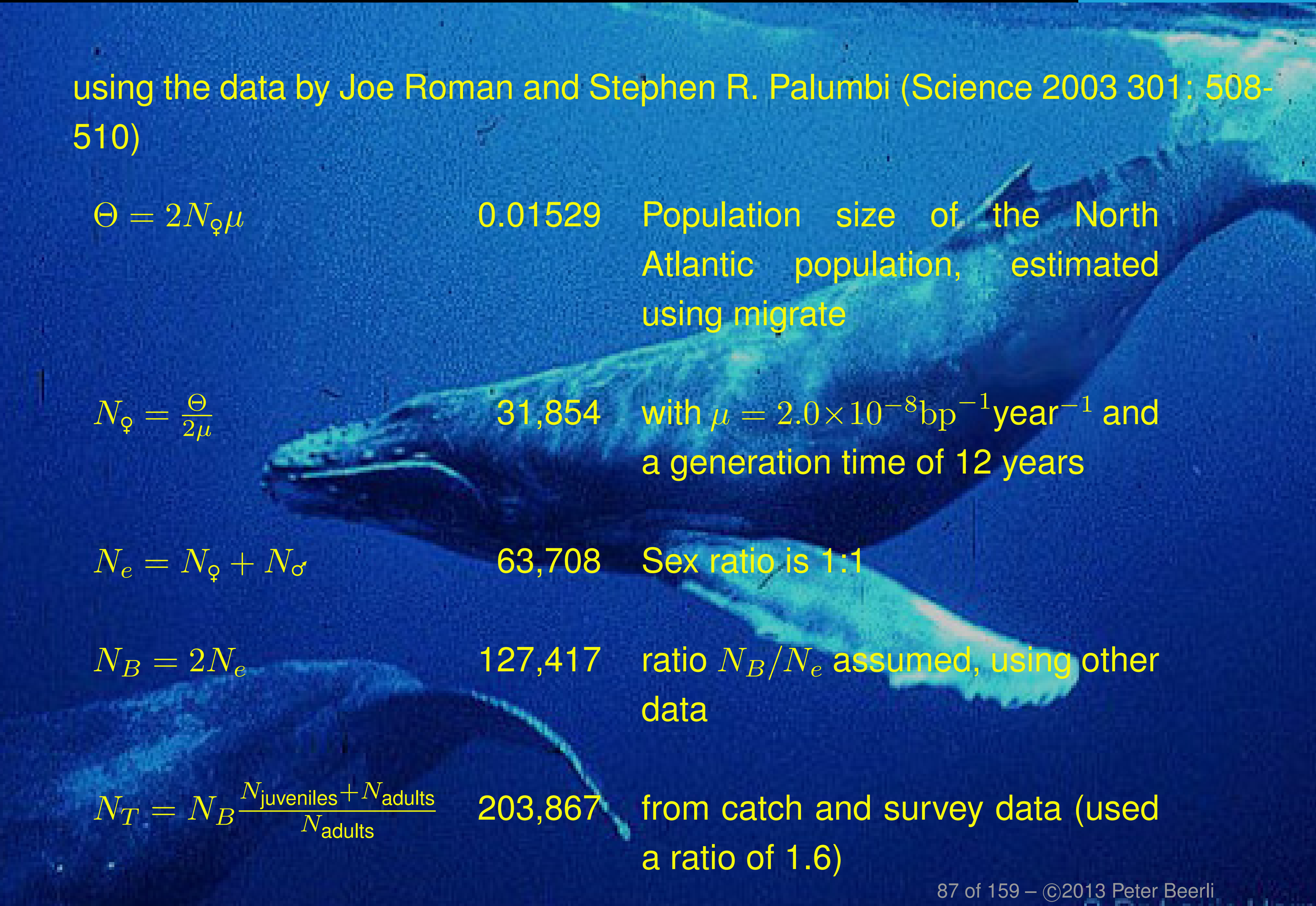
- for diploids: $\Theta = 4N\mu$.
- for haploids: $\Theta = 2N\mu$.
- For mtDNA in diploids with strictly maternal inheritance this leads to $\Theta = 2N_f\mu$, and if the sex ratio is $1:1$ then $\Theta = N\mu$

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.

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)

$\Theta = 2N_{♀}\mu$	0.01529	Population size of the North Atlantic population, estimated using migrate
$N_{♀} = \frac{\Theta}{2\mu}$	31,854	with $\mu = 2.0\times10^{-8}\mathrm{bp}^{-1}$year^{-1} and a generation time of 12 years
$N_e = N_{♀} + N_{♂}$	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)

Genetic data and the coalescent

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.

Construction of a versatile estimator

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

Coalescent to describe the population genetic processes.

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

Construction of a versatile estimator

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

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

where $\mathrm{p}(\mathrm{D}|\Theta)$ is the likelihood of the parameters.

(almost) Felsenstein equation

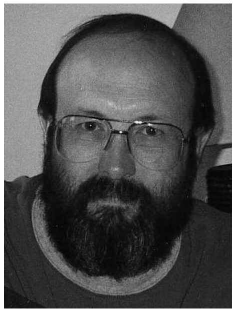
aka Likelihood calculation

$$p(D|\boldsymbol{\Theta}, G) = \mathrm{p(G}|\boldsymbol{\Theta}\mathrm{)p(D|G)}$$

$p(G|\boldsymbol{\Theta})$

The probability of a genealogy given parameters.

$\mathrm{p(D|G)}$



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

Felsenstein equation

aka Likelihood calculation

$$p(D|\mathbf{\Theta}) = \int_G \mathrm{p(G|\mathbf{\Theta})p(D|G)dG}$$

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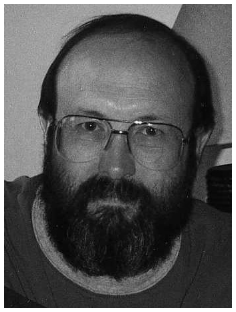
$\mathrm{p(D|G)}$



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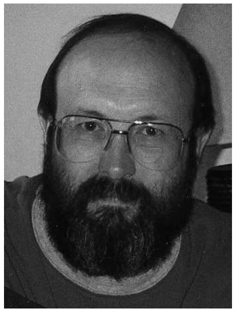

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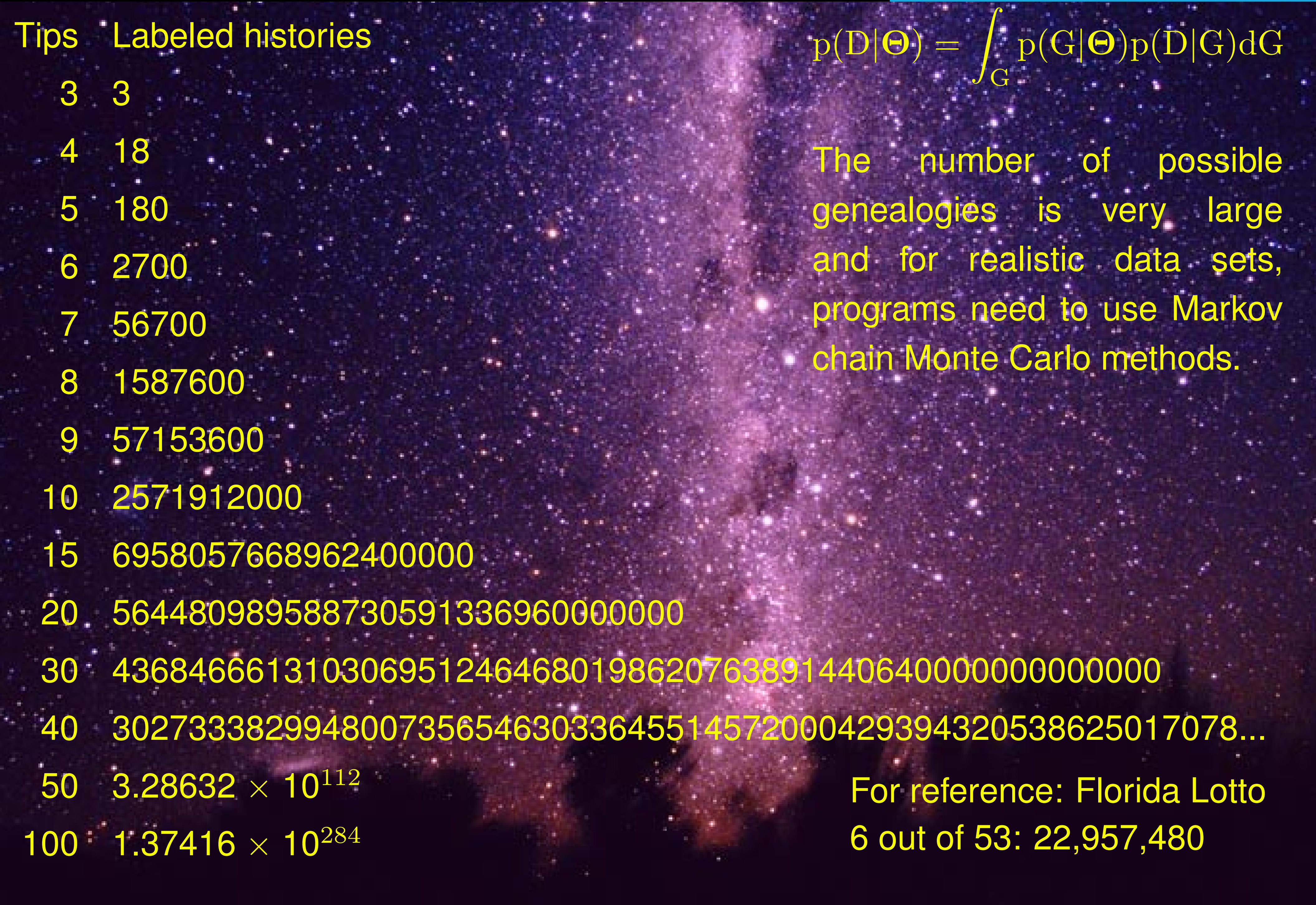
Problem with integration formula



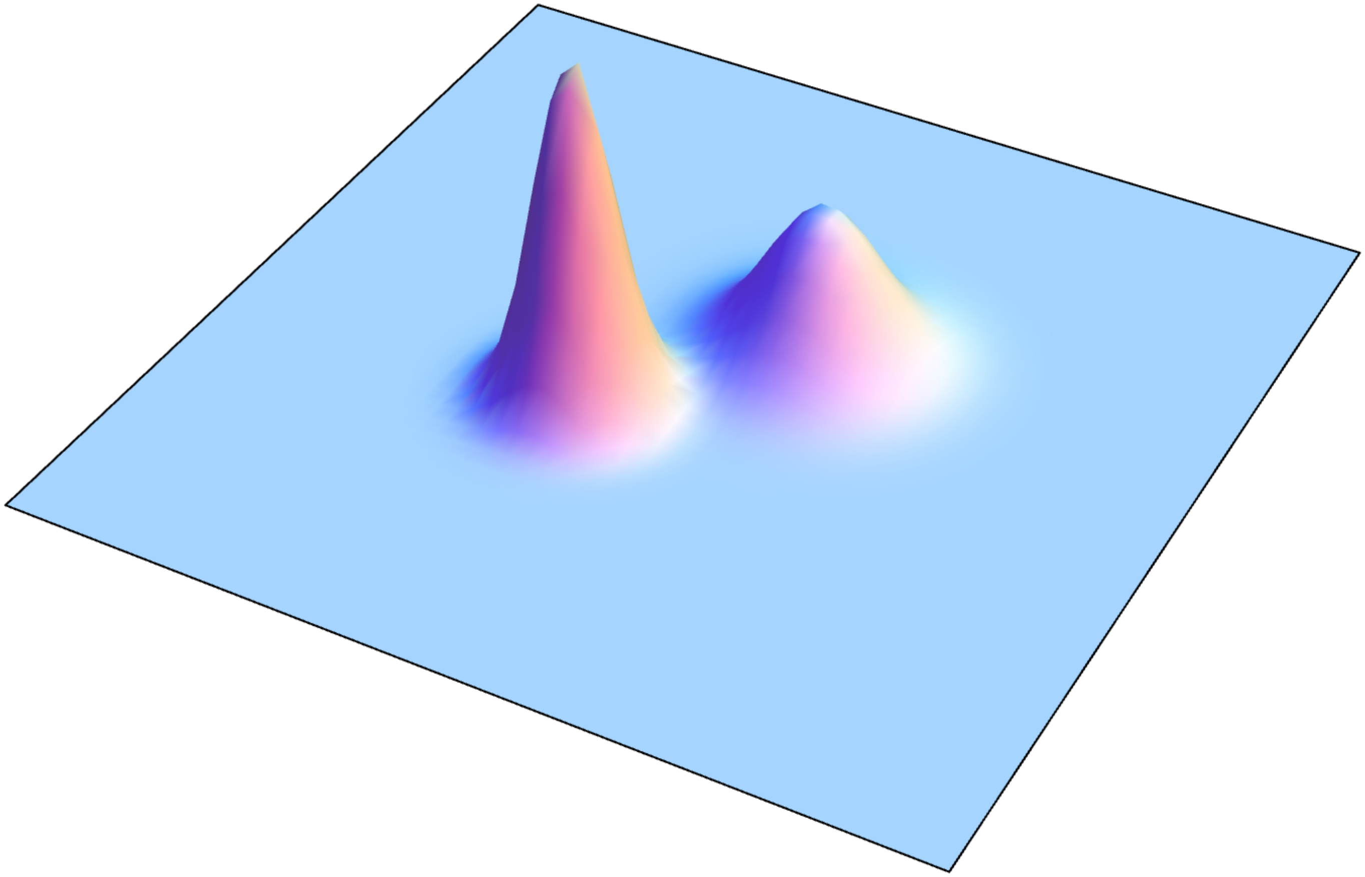
Tips	Labeled histories
3	3
4	18
5	180
6	2700
7	56700
8	1587600
9	57153600
10	2571912000
15	6958057668962400000
20	5644809895887305913369600000000
30	4368466613103069512464680198620763891440640000000000000
40	3027333829948007356546303364551457200042939432053862501 7078...
50	3.28632×10^{112}
100	1.37416×10^{284}

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

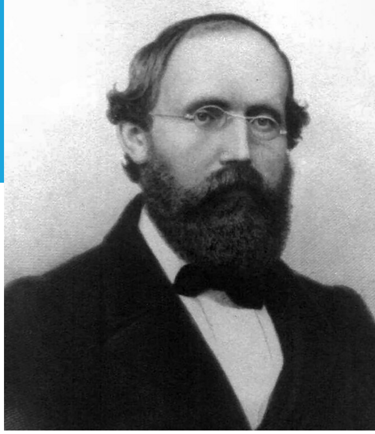
The number of possible genealogies is very large and for realistic data sets, programs need to use Markov chain Monte Carlo methods.

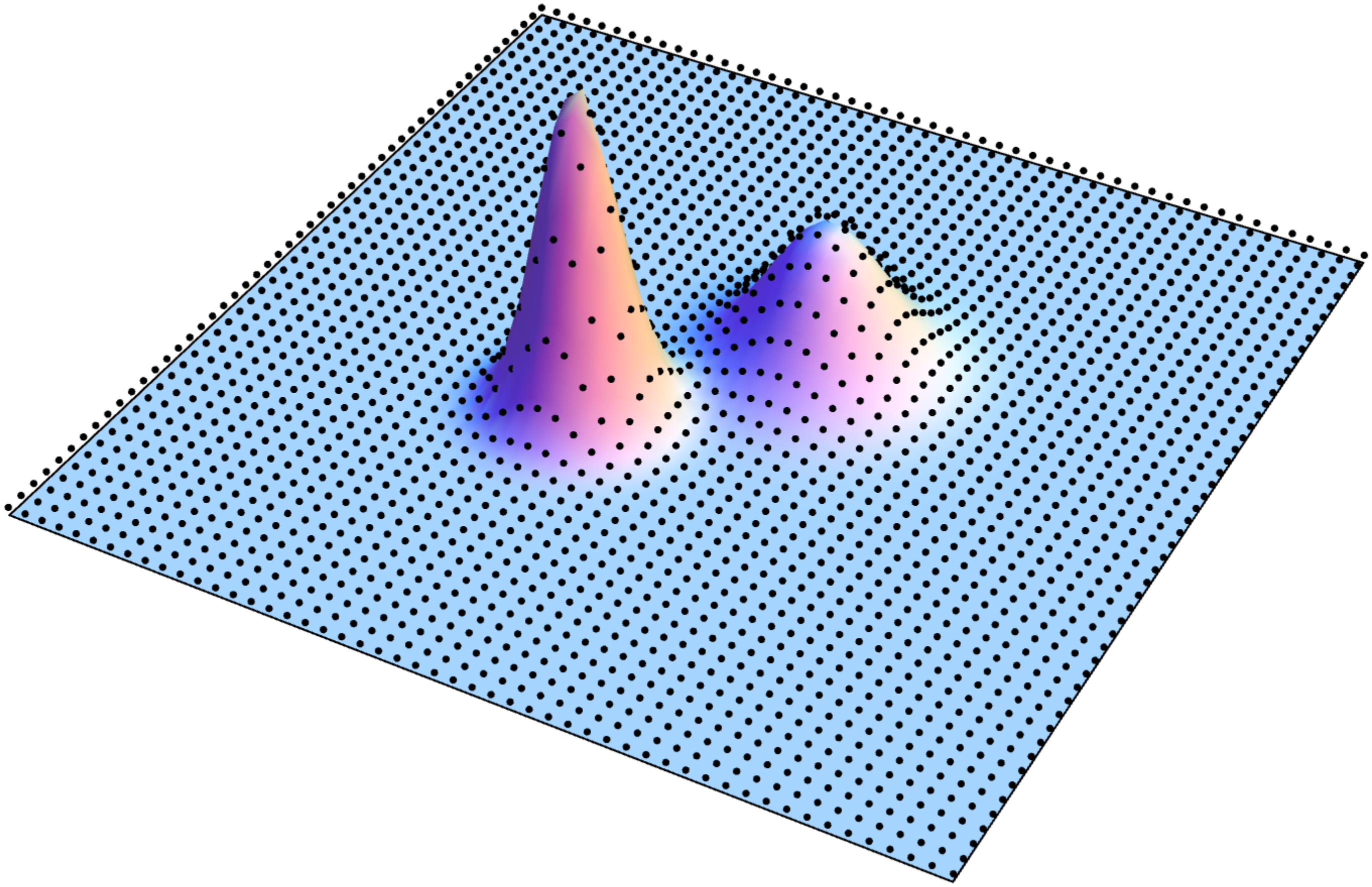
For reference: Florida Lotto
6 out of 53: 22,957,480

Naive integration approach



Naive integration approach

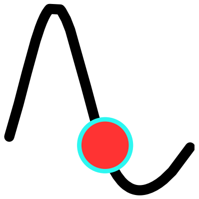




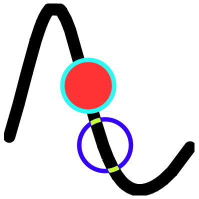
Markov chain Monte Carlo

Metropolis recipe

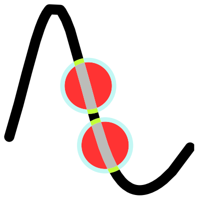
0. first state



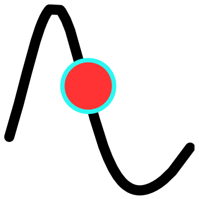
1. perturb old state and calculate probability of new state



2. test if new state is better than old state: accept if ratio of new and old is larger than a random number between 0 and 1.

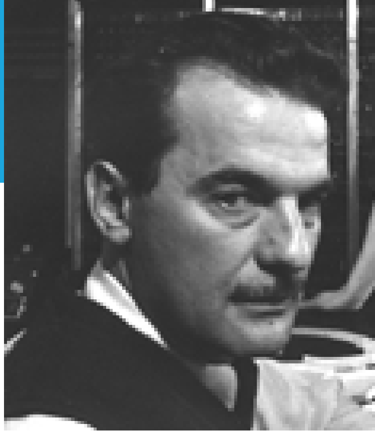


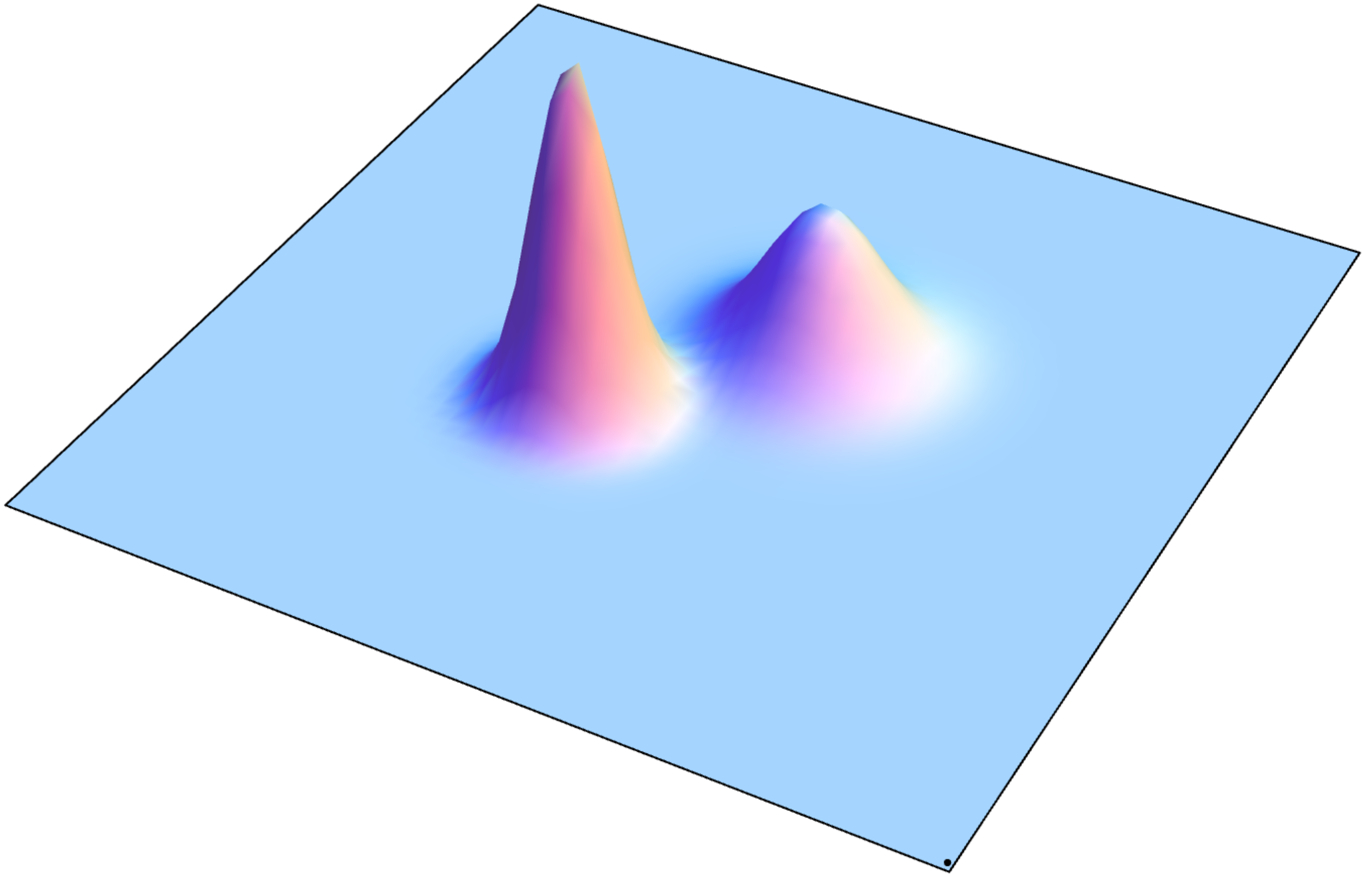
3. move to new state if accepted otherwise stay at old state



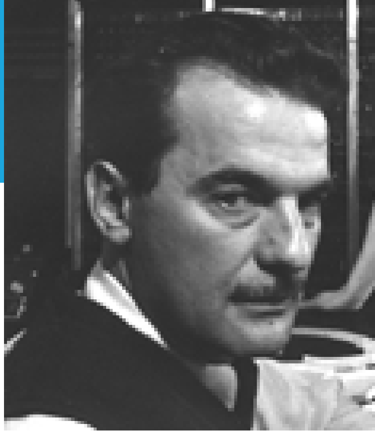
4. go to 1

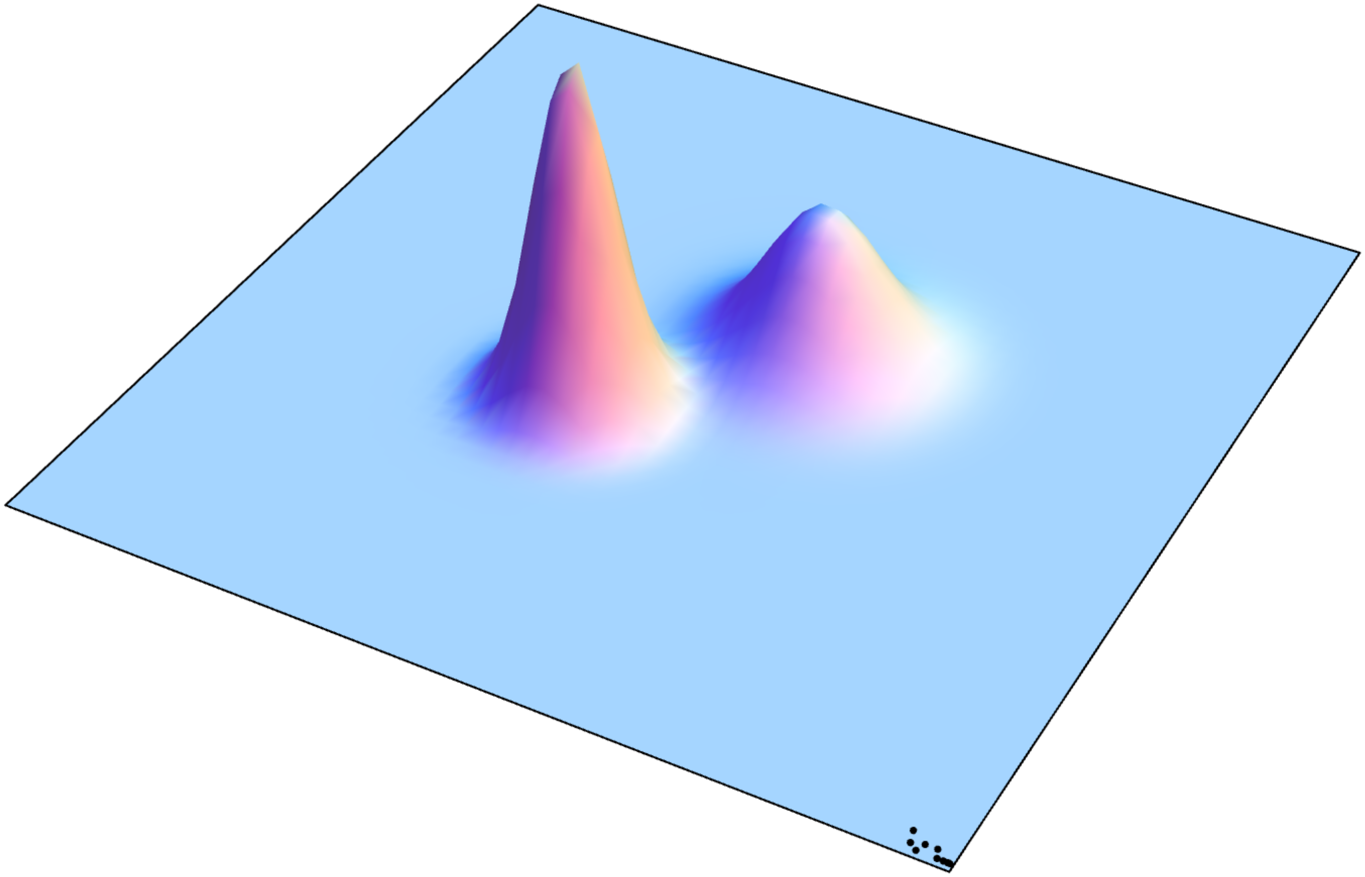
Metropolis-Hastings algorithm



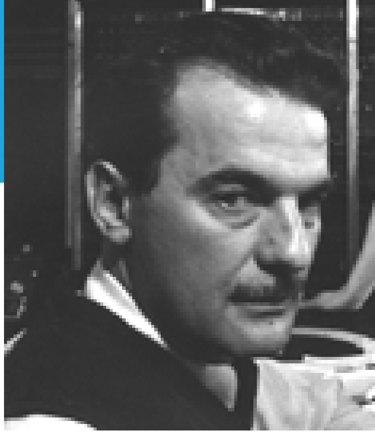


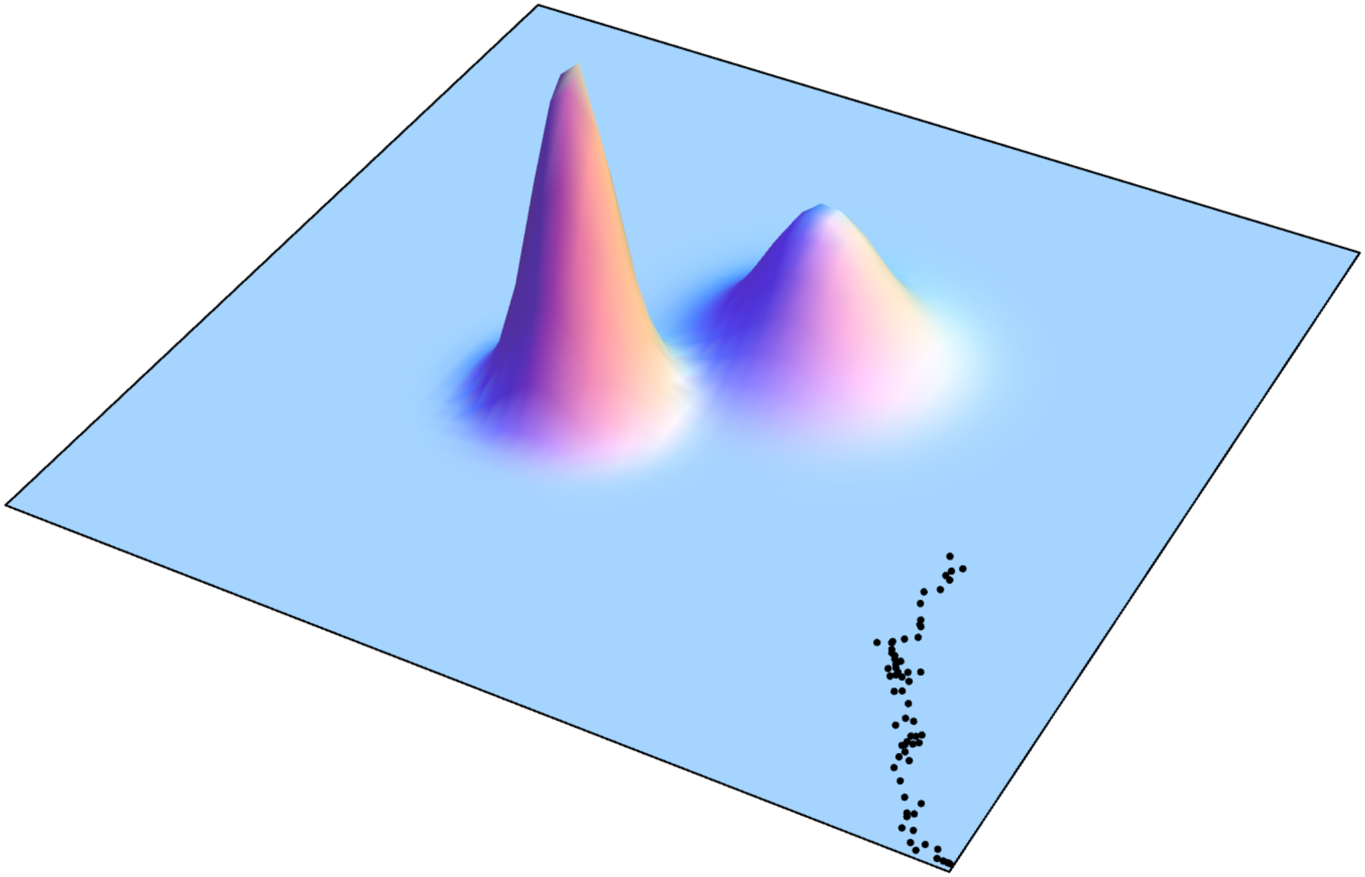
Metropolis-Hastings algorithm



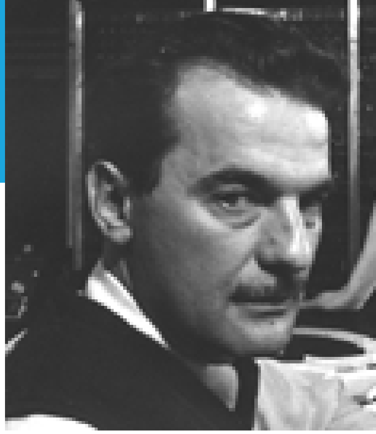


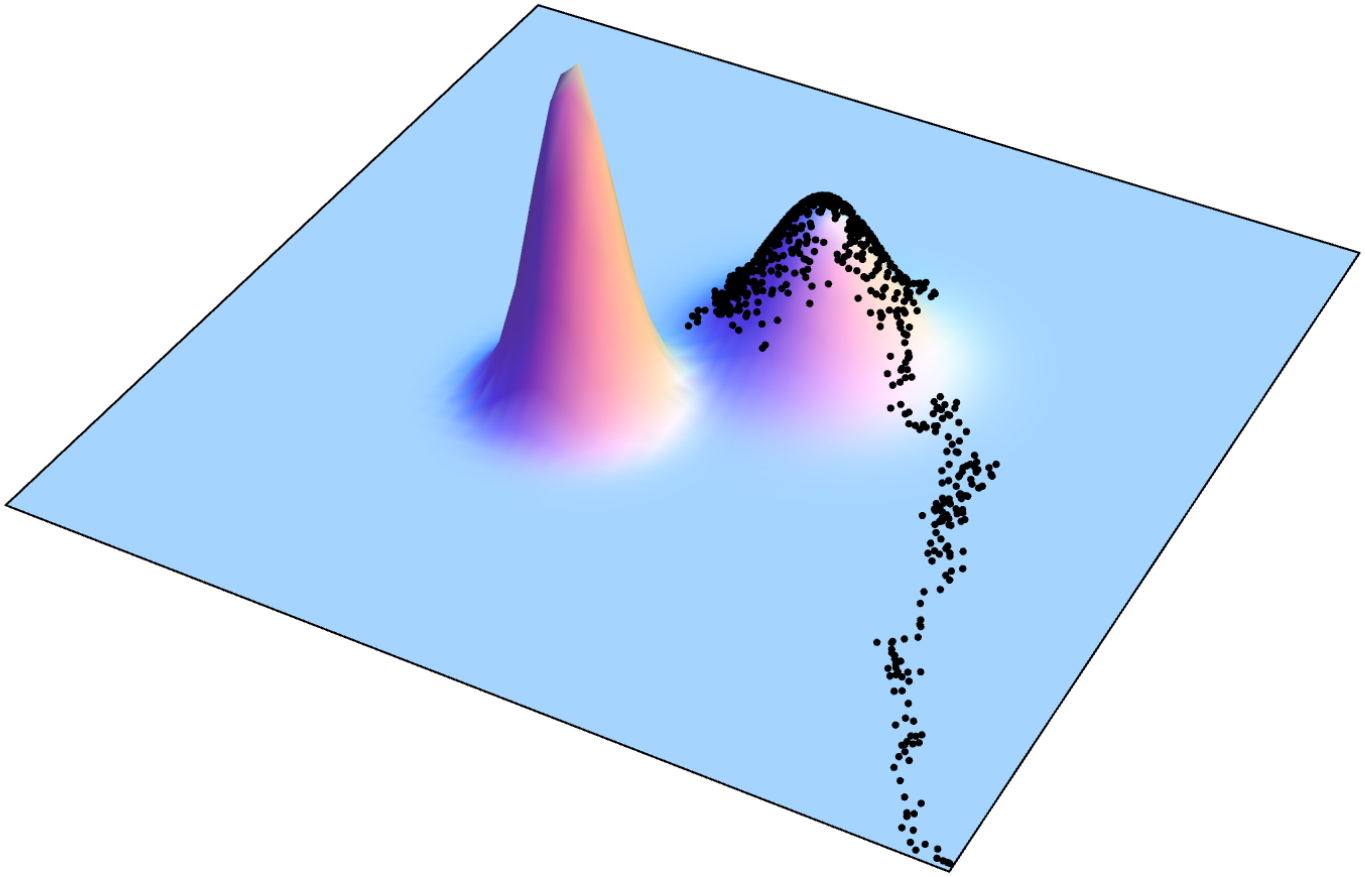
Metropolis-Hastings algorithm



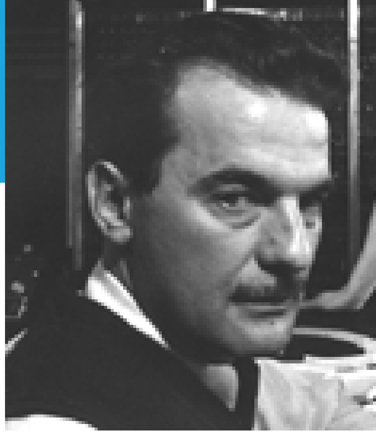


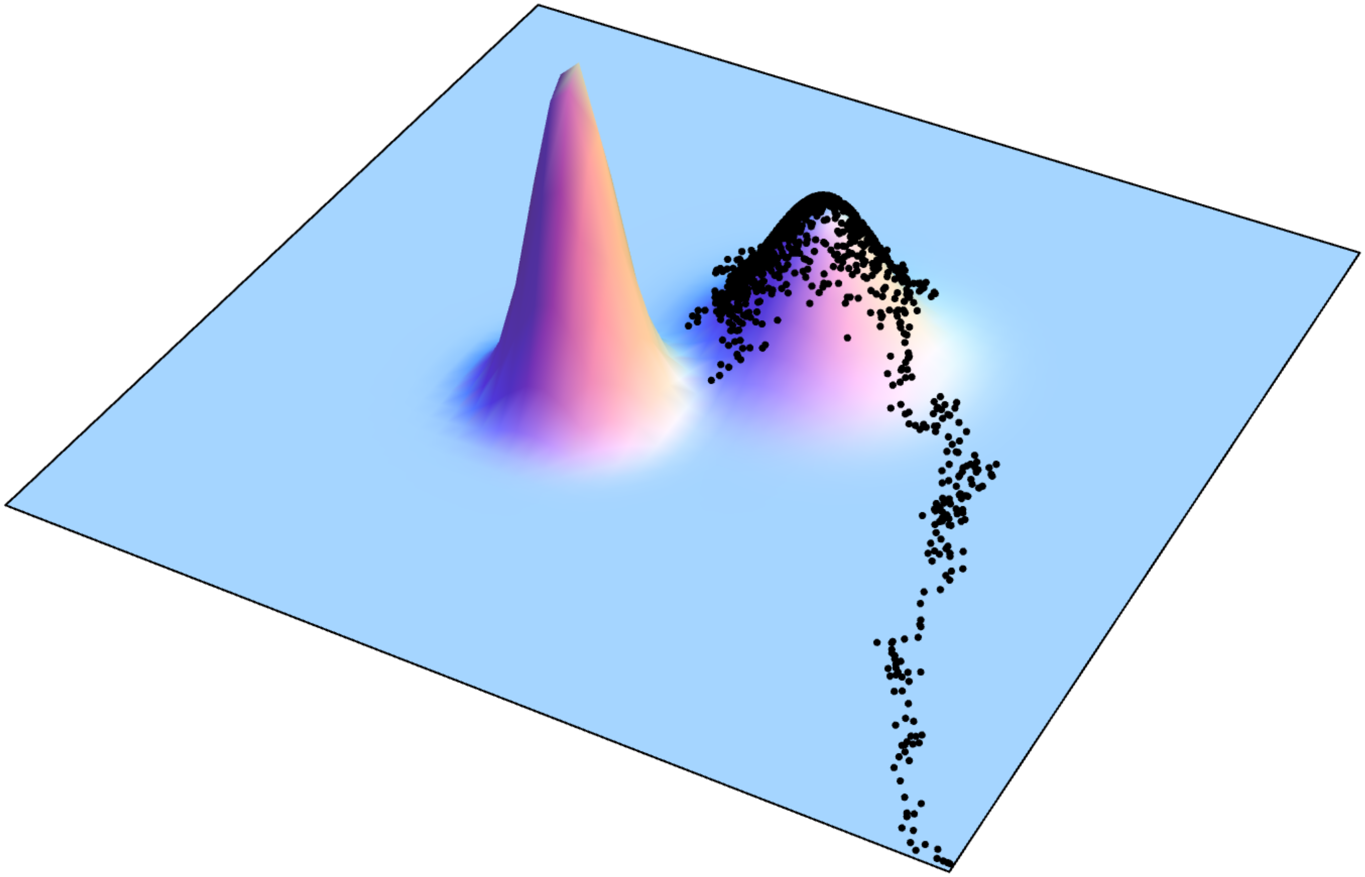
Metropolis-Hastings algorithm



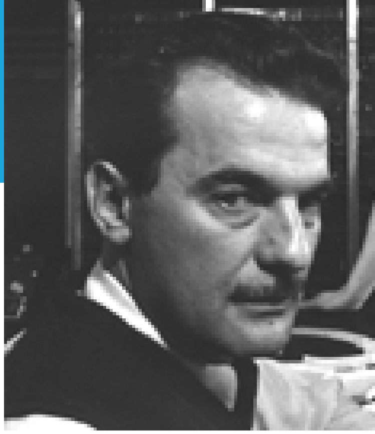


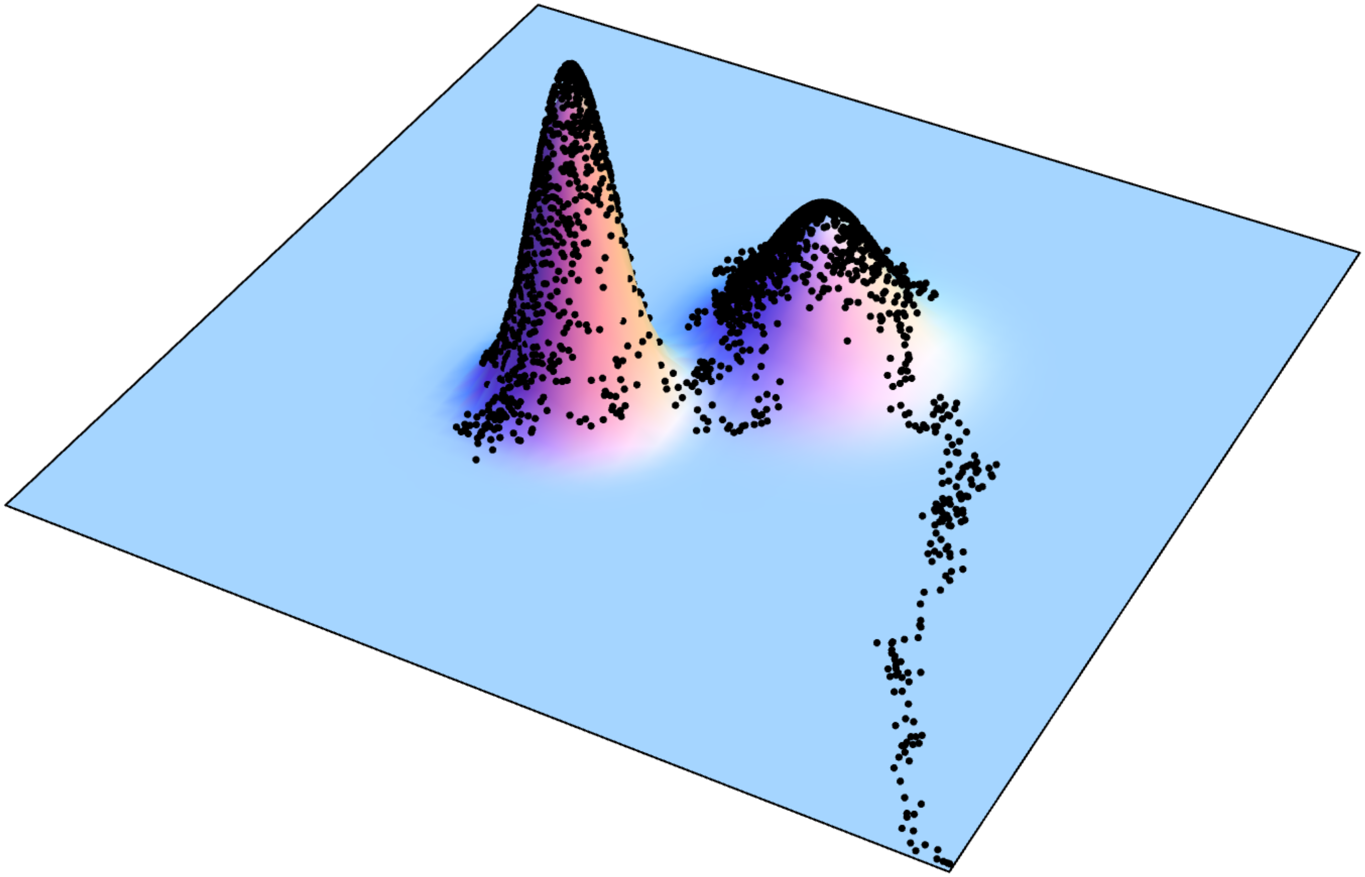
Metropolis-Hastings algorithm



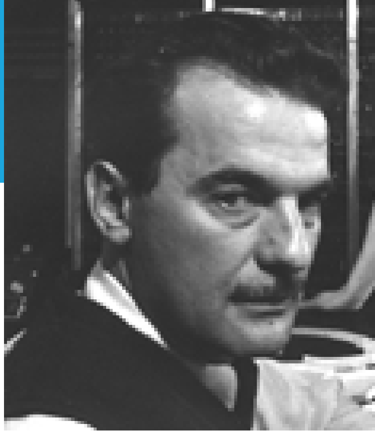


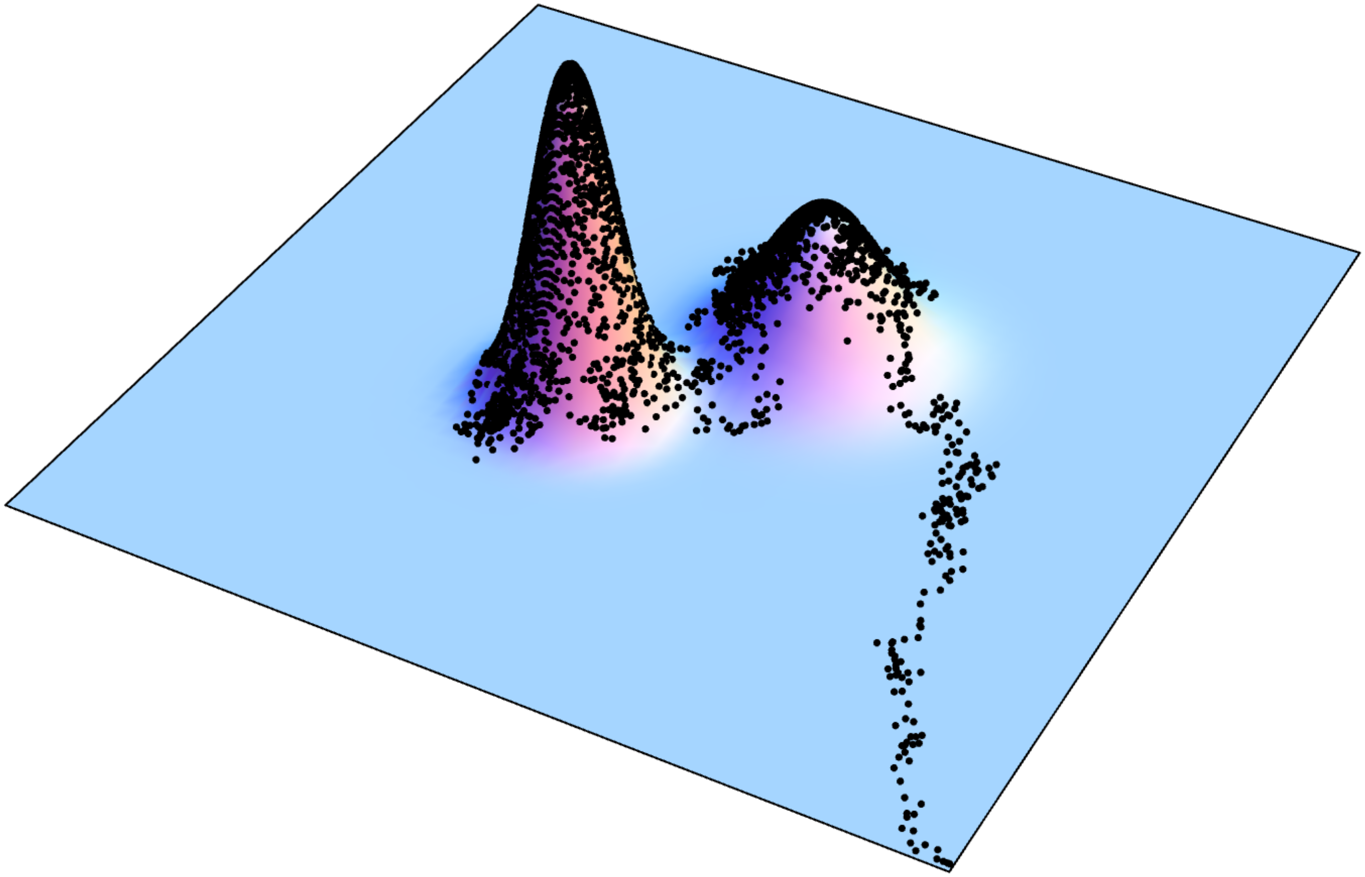
Metropolis-Hastings algorithm



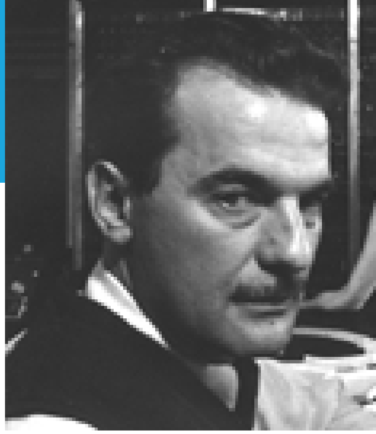


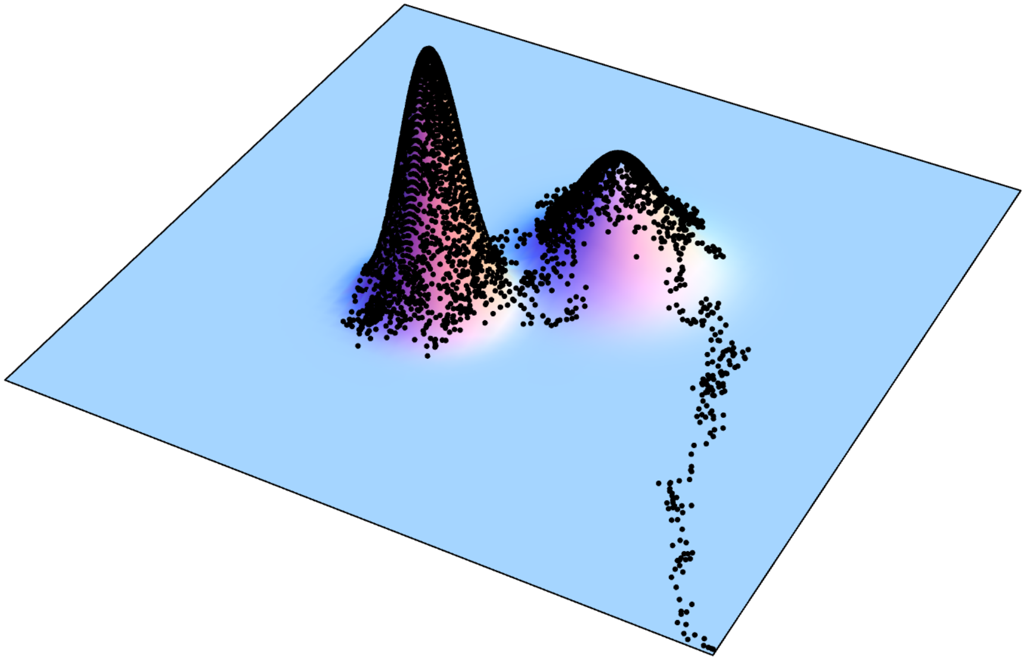
Metropolis-Hastings algorithm





Metropolis-Hastings algorithm





- *Irreducibility*: the Markov chain must be able to reach all interesting parts of the distribution.

- *Recurrence*: all interesting parts must be reached (in principle) infinitely often if the chain is run infinitely long.

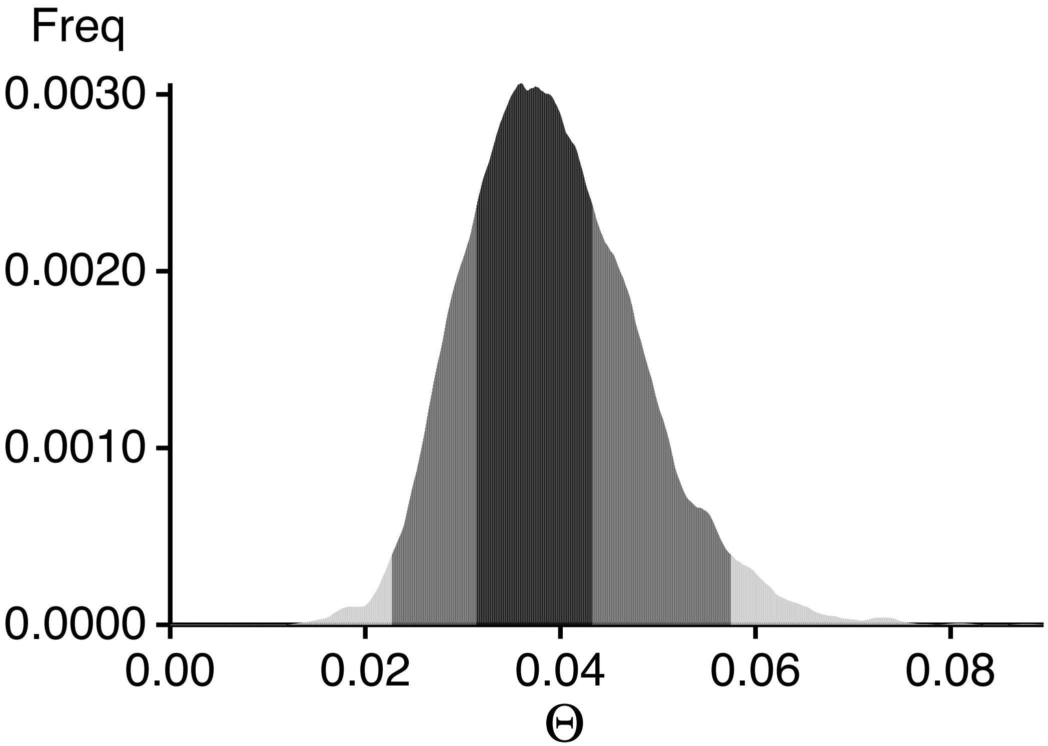
- *Convergence*: the sample mean must converge to the expectation.

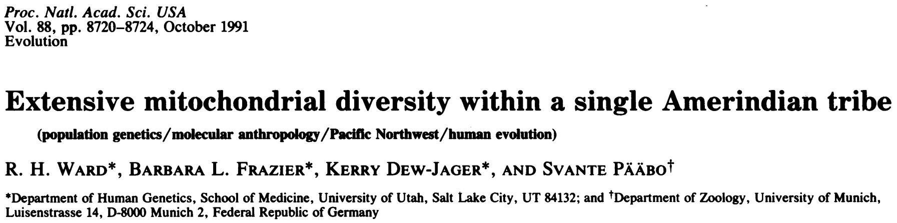
Inference of population size

Nuu-Chah-Nulth

Around 1930 – Friendly Cove, Vancouver Island

Inference of population size





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)]

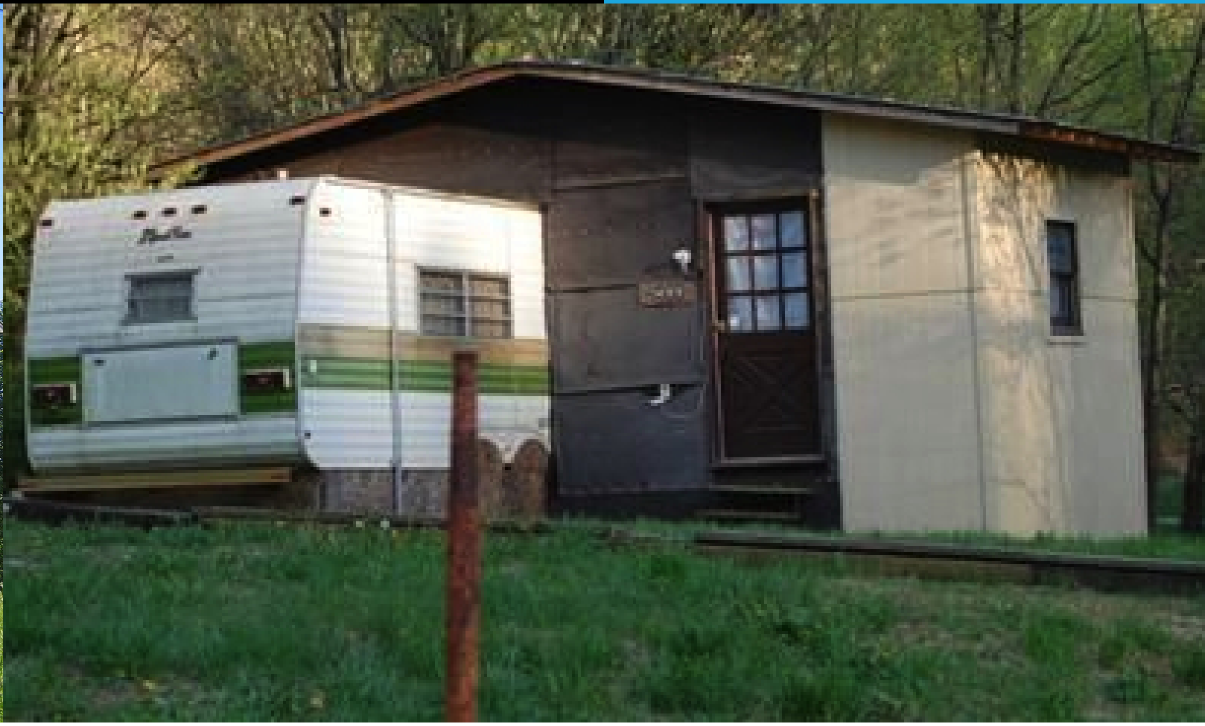
Bayesian inference: $\Theta = 0.036$

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 $N_{\text{females}} = 2082$. Assuming same numbers of men and women and on average 2 children we get $N = 8328$.

Extensions of the basic coalescence

Extensions of the basic coalescence



Extensions of the basic coalescence

Extensions of the basic coalescence

Extensions of the basic coalescence

- Population growth (2 parameters) or fluctuations
- Migration among populations (2 to many, potentially thousands, parameters)
- Population splitting (2 to many parameters)
- Recombination (2 parameters)

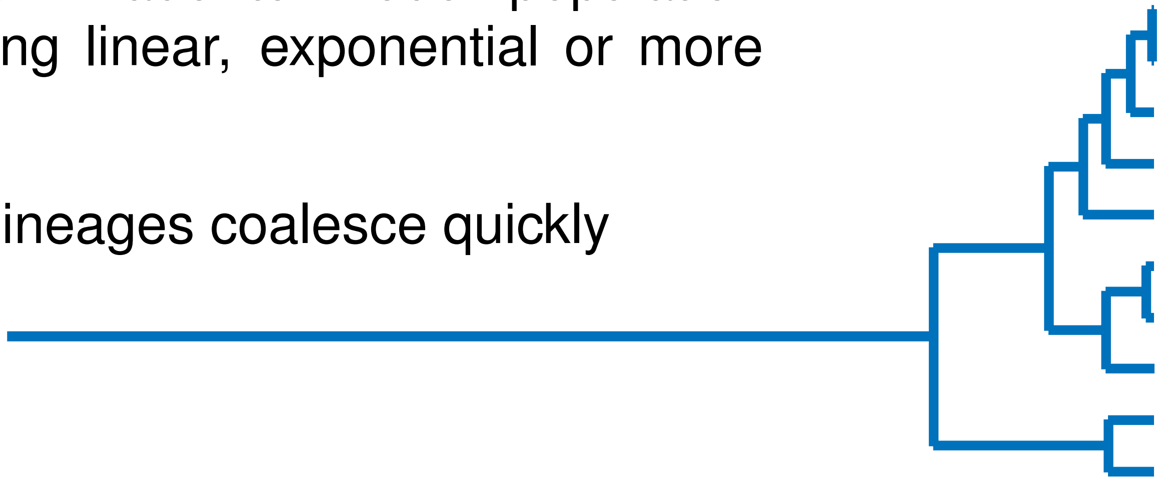
Extensions of the basic coalescent

Populations are rarely completely stable through time, and attempts have been made to model population growth or shrinkage using linear, exponential or more general approaches.

Extensions of the basic coalescent

Populations are rarely completely stable through time, and attempts have been made to model population growth or shrinkage using linear, exponential or more general approaches.

- In a small population lineages coalesce quickly

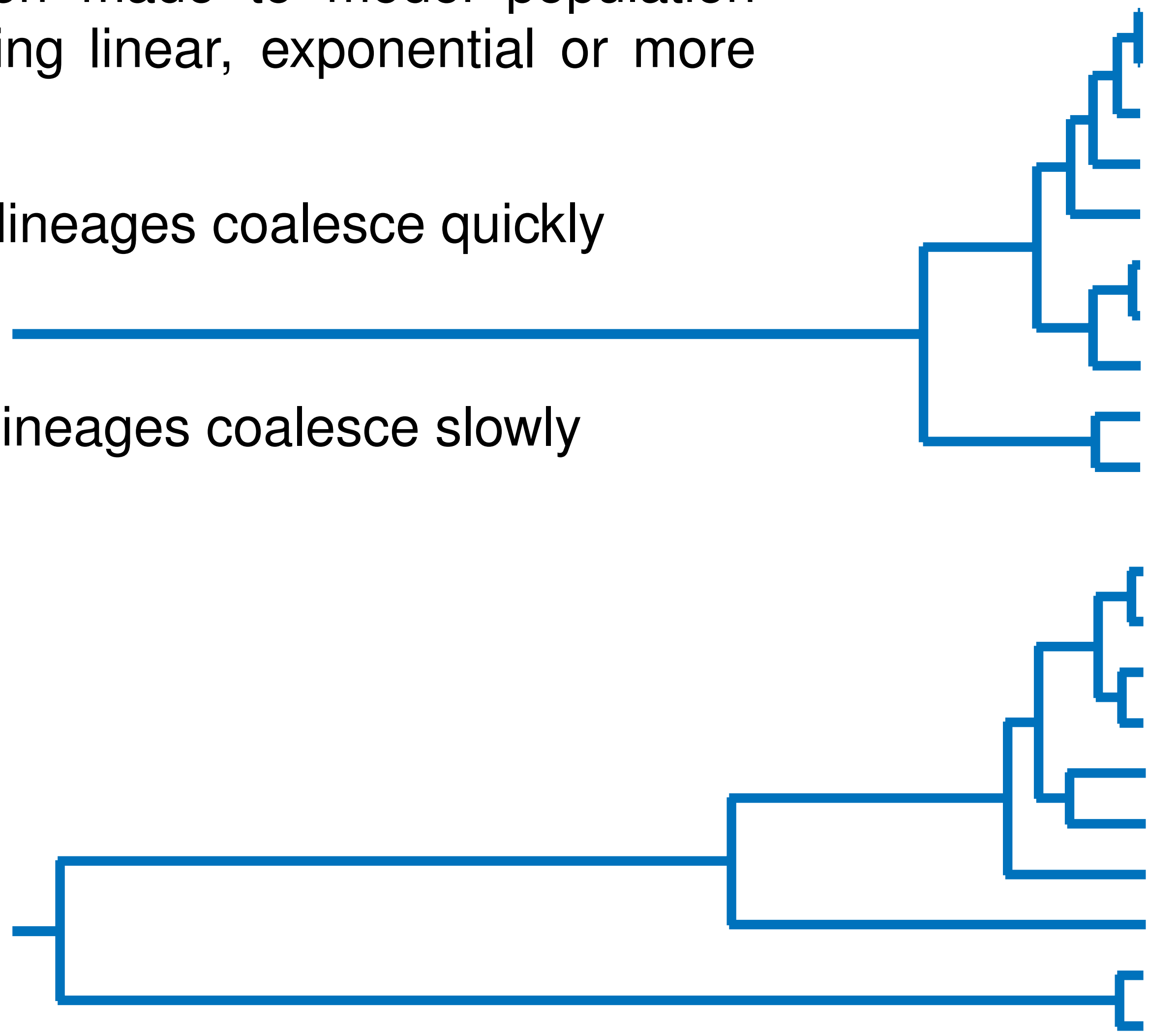


This leaves a signature in the data. We can exploit this and estimate the population growth rate g jointly with the current population size Θ.

Extensions of the basic coalescent

Populations are rarely completely stable through time, and attempts have been made to model population growth or shrinkage using linear, exponential or more general approaches.

- In a small population lineages coalesce quickly
- In a large population lineages coalesce slowly



This leaves a signature in the data. We can exploit this and estimate the population growth rate g jointly with the current population size Θ.

Extensions of the basic coalescent

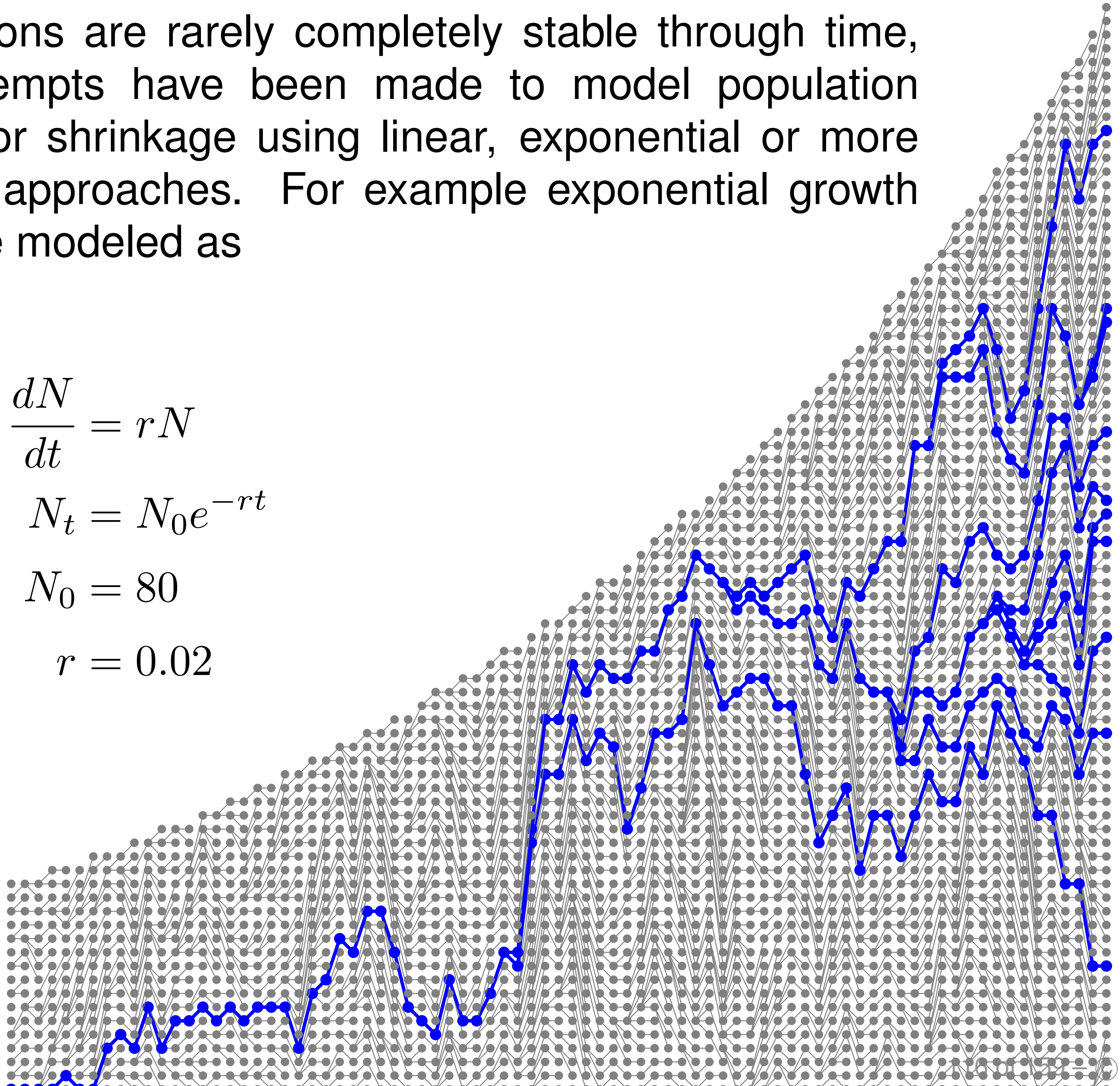
Populations are rarely completely stable through time, and attempts have been made to model population growth or shrinkage using linear, exponential or more general approaches. For example exponential growth could be modeled as

$$\frac{dN}{dt} = rN$$

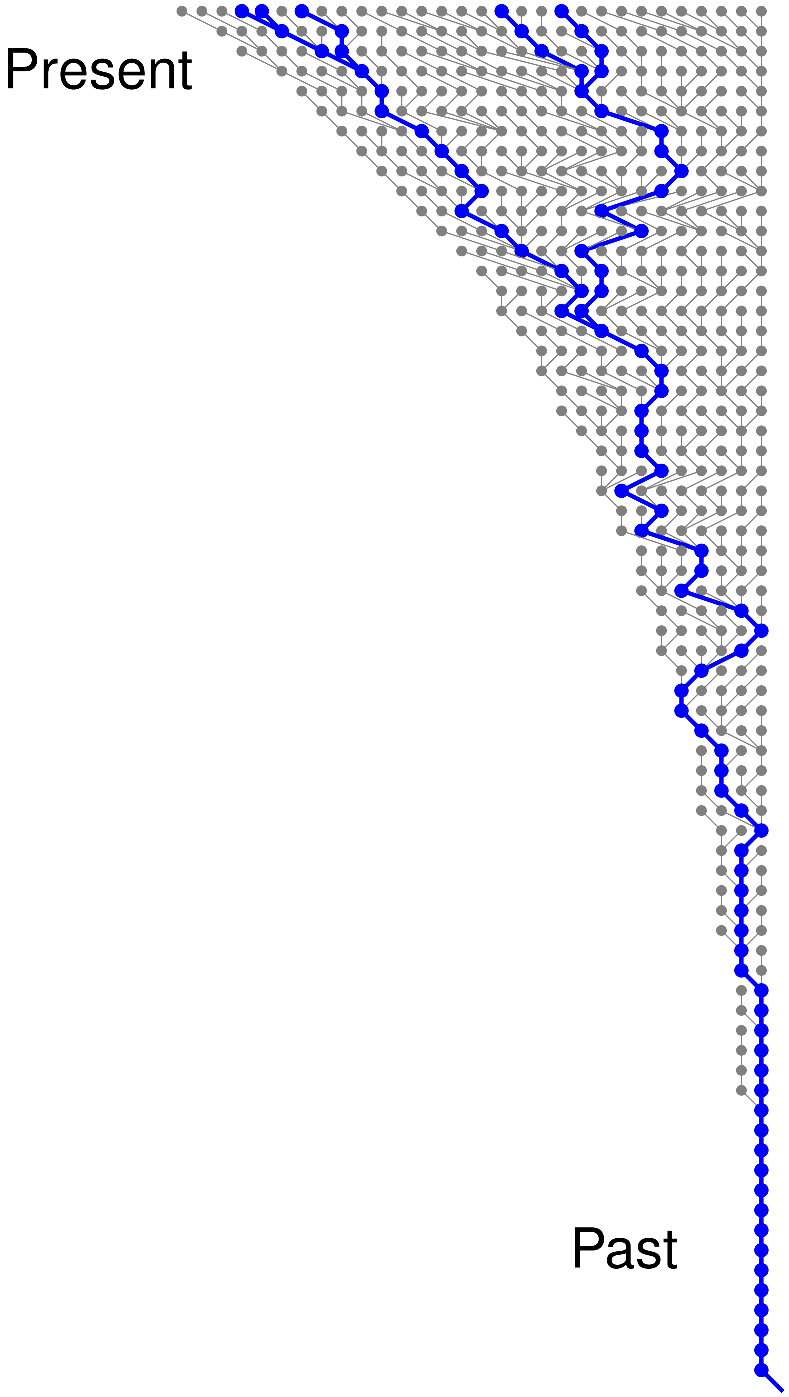
$$N_t = N_0 e^{-rt}$$

$$N_0 = 80$$

$$r = 0.02$$



Extensions of the basic coalescent



For constant population size we found

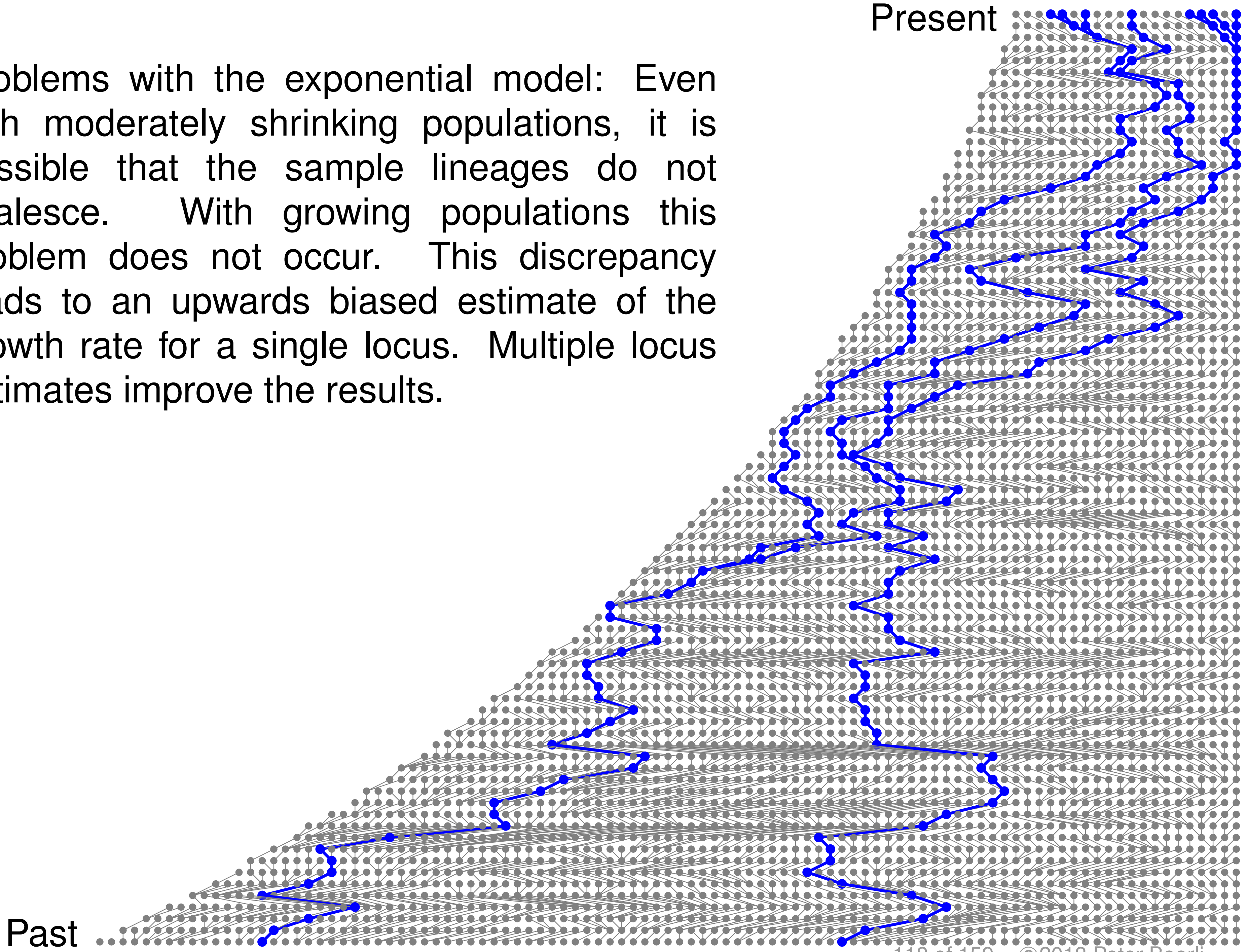
$$p(G|\Theta) = \prod_j e^{-u_j \frac{k(k-1)}{\Theta}} \frac{2}{\Theta}$$

Relaxing the constant size to exponential growth and using $g = r/\mu$ leads to

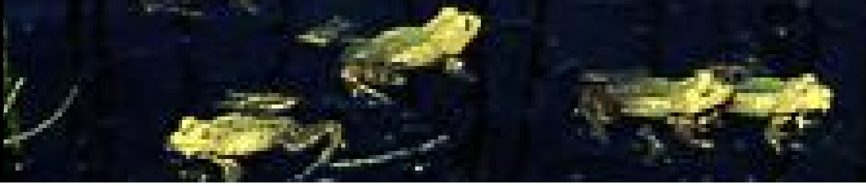
$$p(G|\Theta_0, g) = \prod_j e^{-(t_j - t_{j-1}) \frac{k(k-1)}{\Theta_0 e^{-gt}}} \frac{2}{\Theta_0 e^{-gt}}$$

Extensions of the basic coalescent

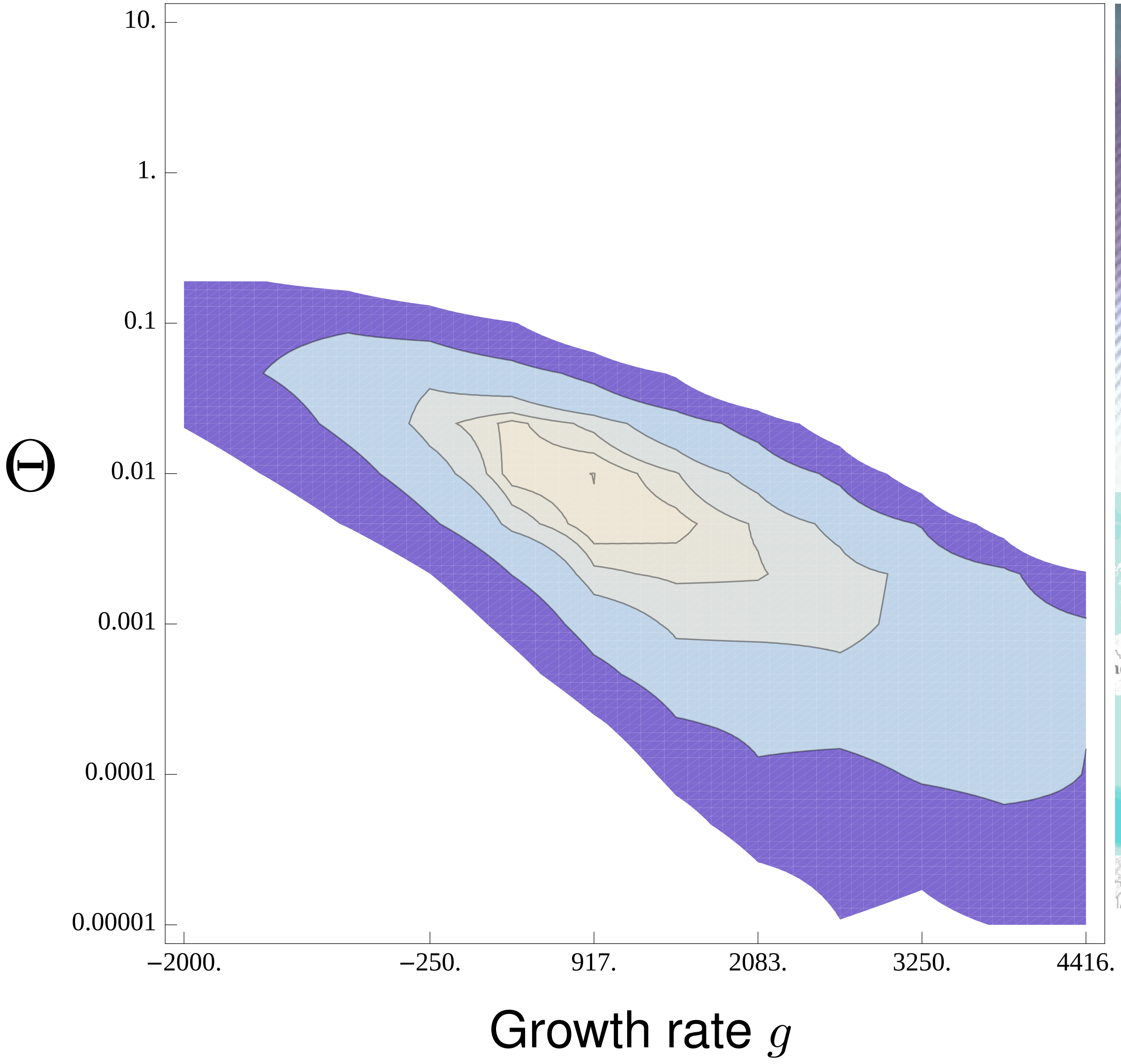
Problems with the exponential model: Even with moderately shrinking populations, it is possible that the sample lineages do not coalesce. With growing populations this problem does not occur. This discrepancy leads to an upwards biased estimate of the growth rate for a single locus. Multiple locus estimates improve the results.

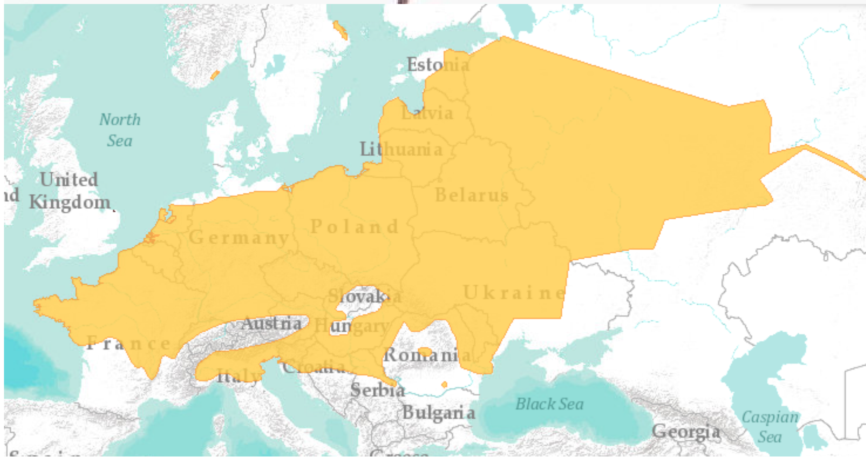


Grow-A-Frog



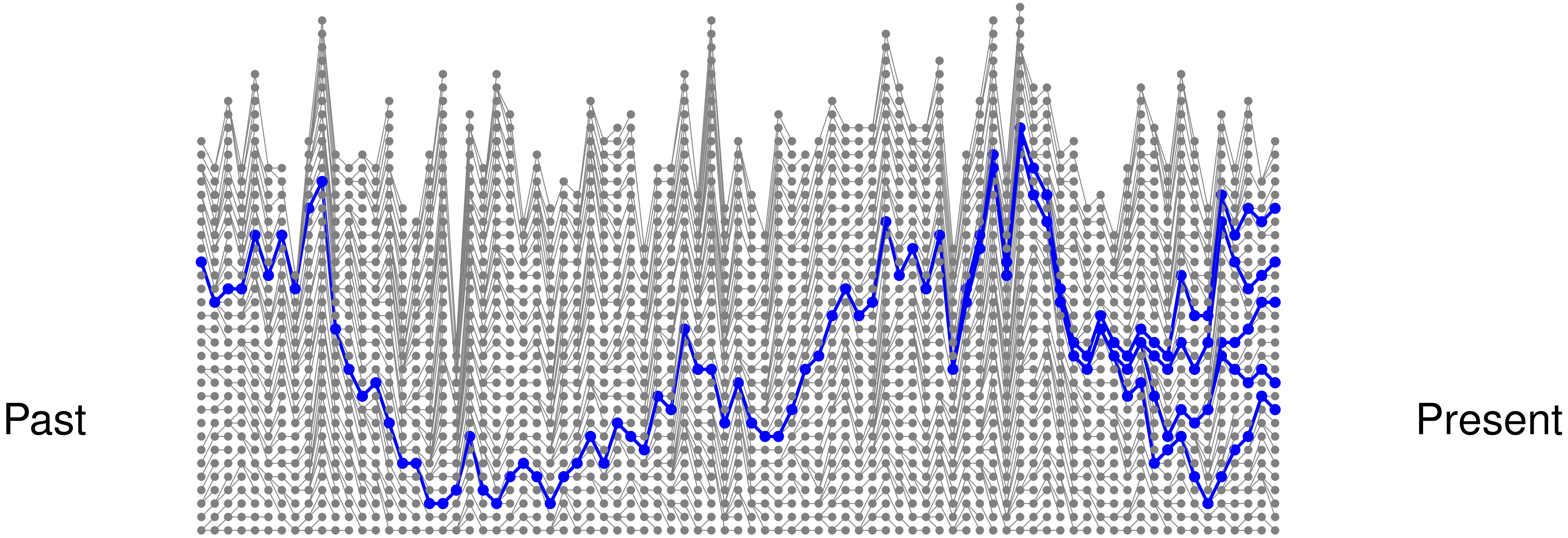
Expansion of *Pelophylax lessonae* in Europe



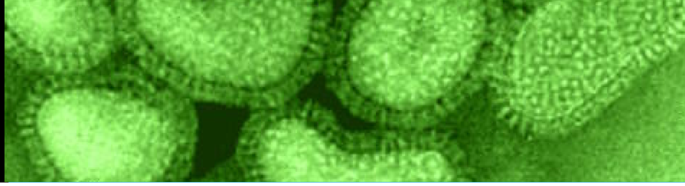


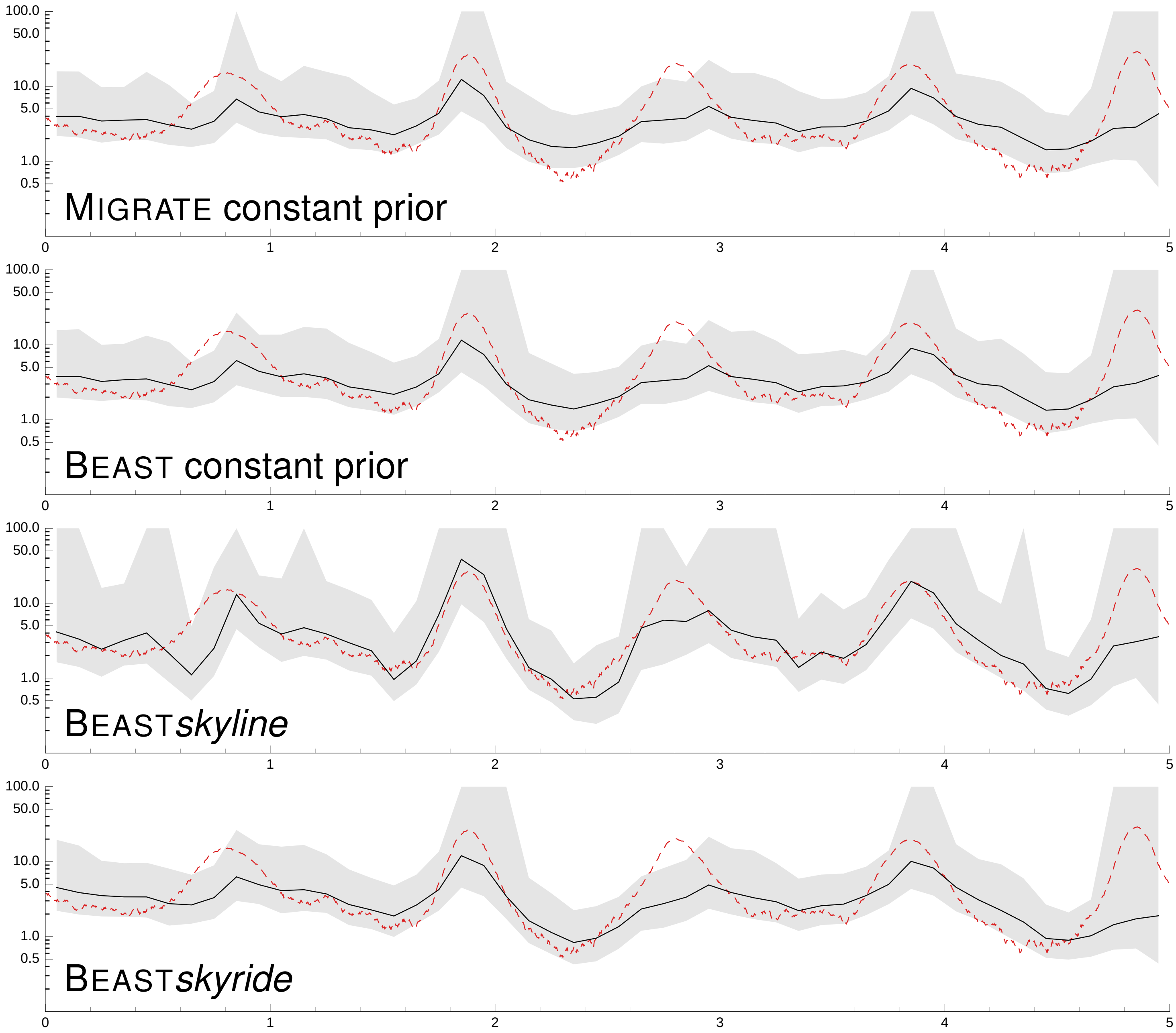
Extensions of the basic coalescent

Random fluctuations of the population size are most often ignored. BEAST (and to some extent MIGRATE) can handle such scenarios. BEAST is using a full parametric approach (skyride, skyline) whereas MIGRATE uses a non-parametric approach for its skyline plots that has the tendency to smooth the fluctuations too much, compared to beast.



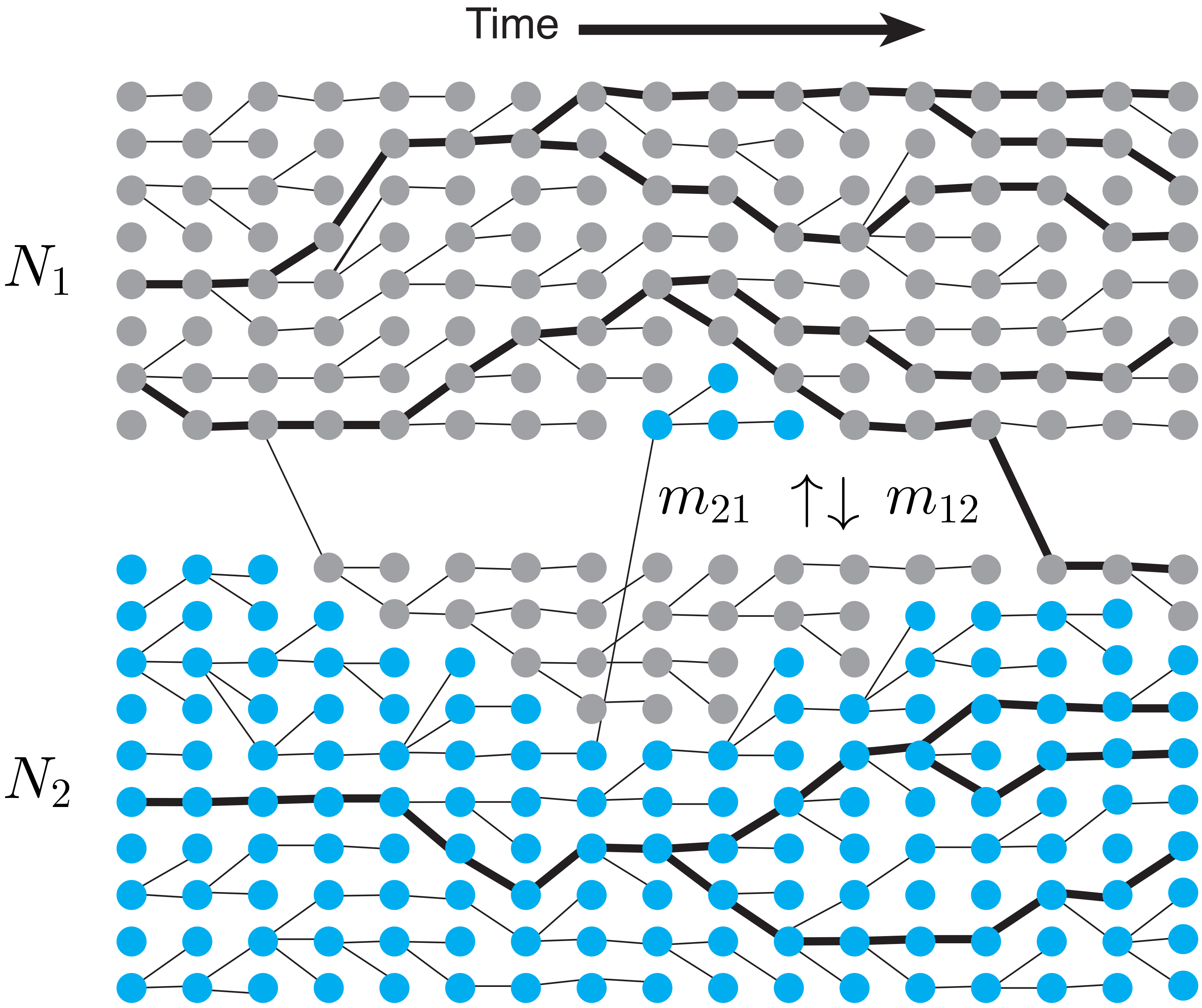
Extensions of the basic coalescent



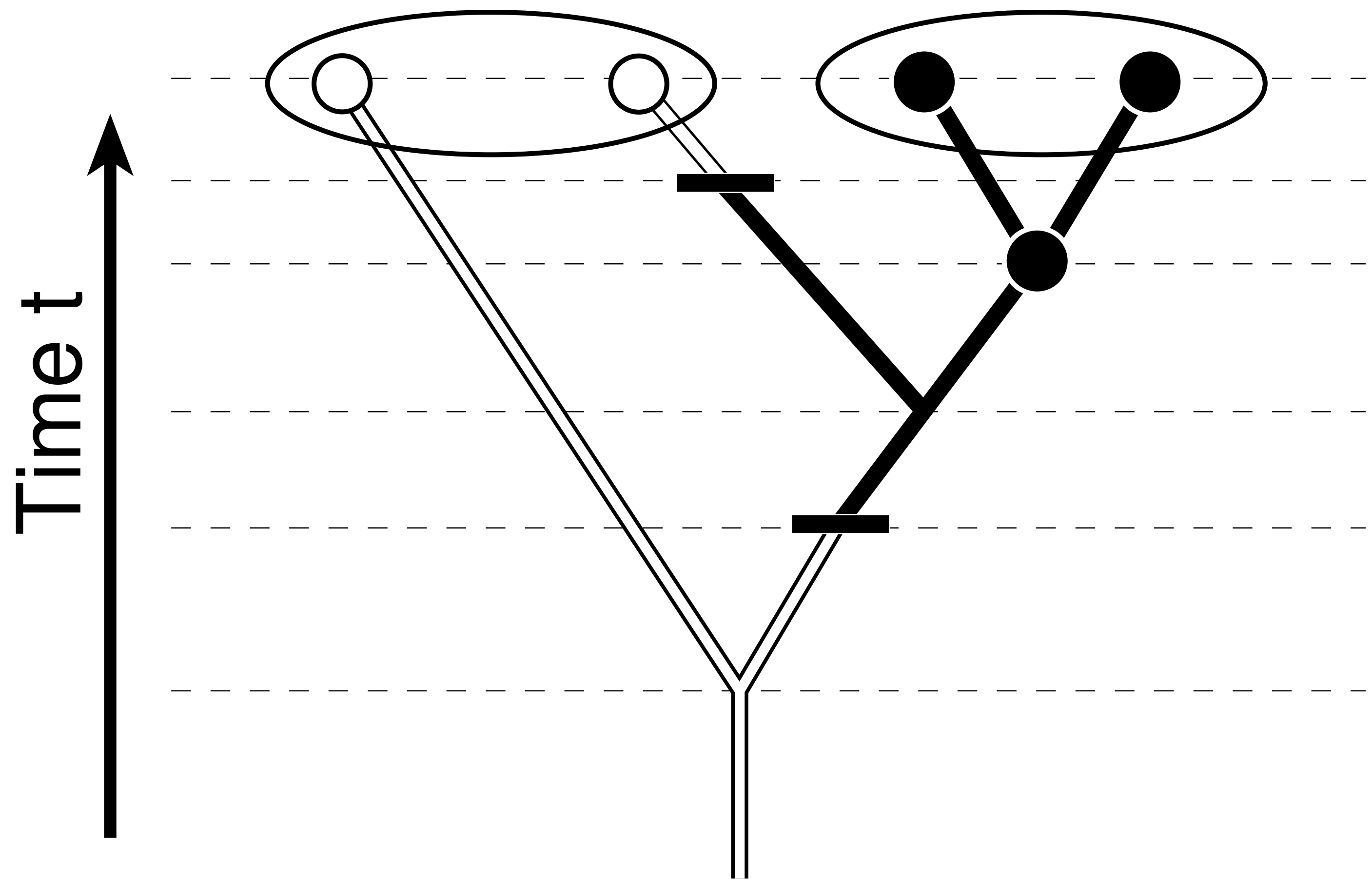


Comparison of the skyline plots of simulated influenza dynamics analyzed by MIGRATE and BEAST. The x-axis is the time in years and the y-axis is effective population size. The data are sequences from 250 individuals sampled at regular intervals over 5 years. The dashed curve is the actual population size deduced from the true genealogy; black lines are the mean results of MIGRATE or BEAST; gray area is the 95% credibility interval. BEAST *skyline* matches the actual population size better than all other methods. Simulation and graphs courtesy of Trevor Bedford.

Extensions of the basic coalescent



Extensions of the basic coalescent



Δt	k_1	k_2
u_1	2	2
u_2	1	3
u_3	1	2
u_4	1	3
u_5	2	0

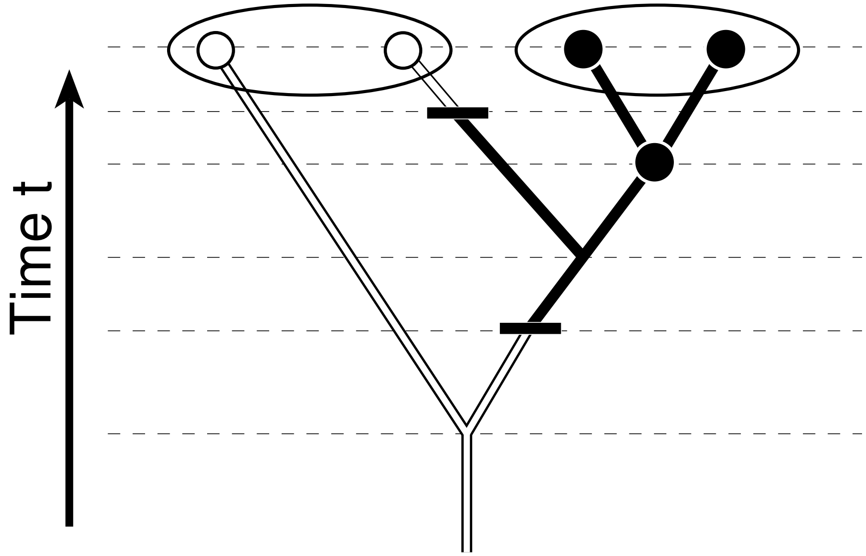
Extensions of the basic coalescent

The single population coalescence rate is

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

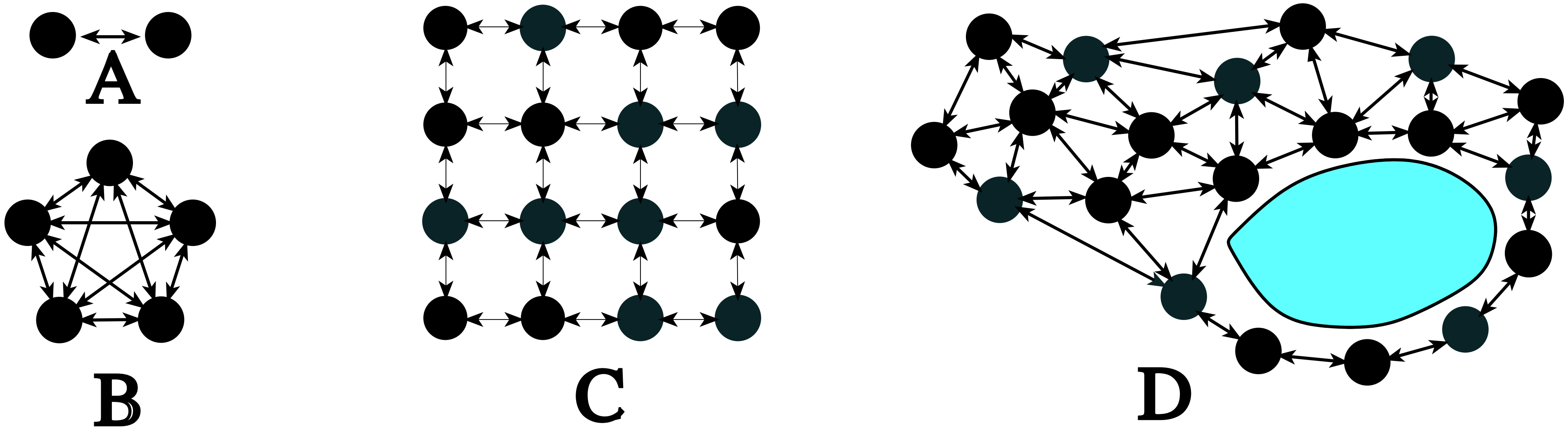
Changes for two populations to

$$\frac{k_1(k_1-1)}{\Theta_1}+\frac{k_2(k_2-1)}{\Theta_2}+k_1M_{2,1}+k_2M_{1,2}$$



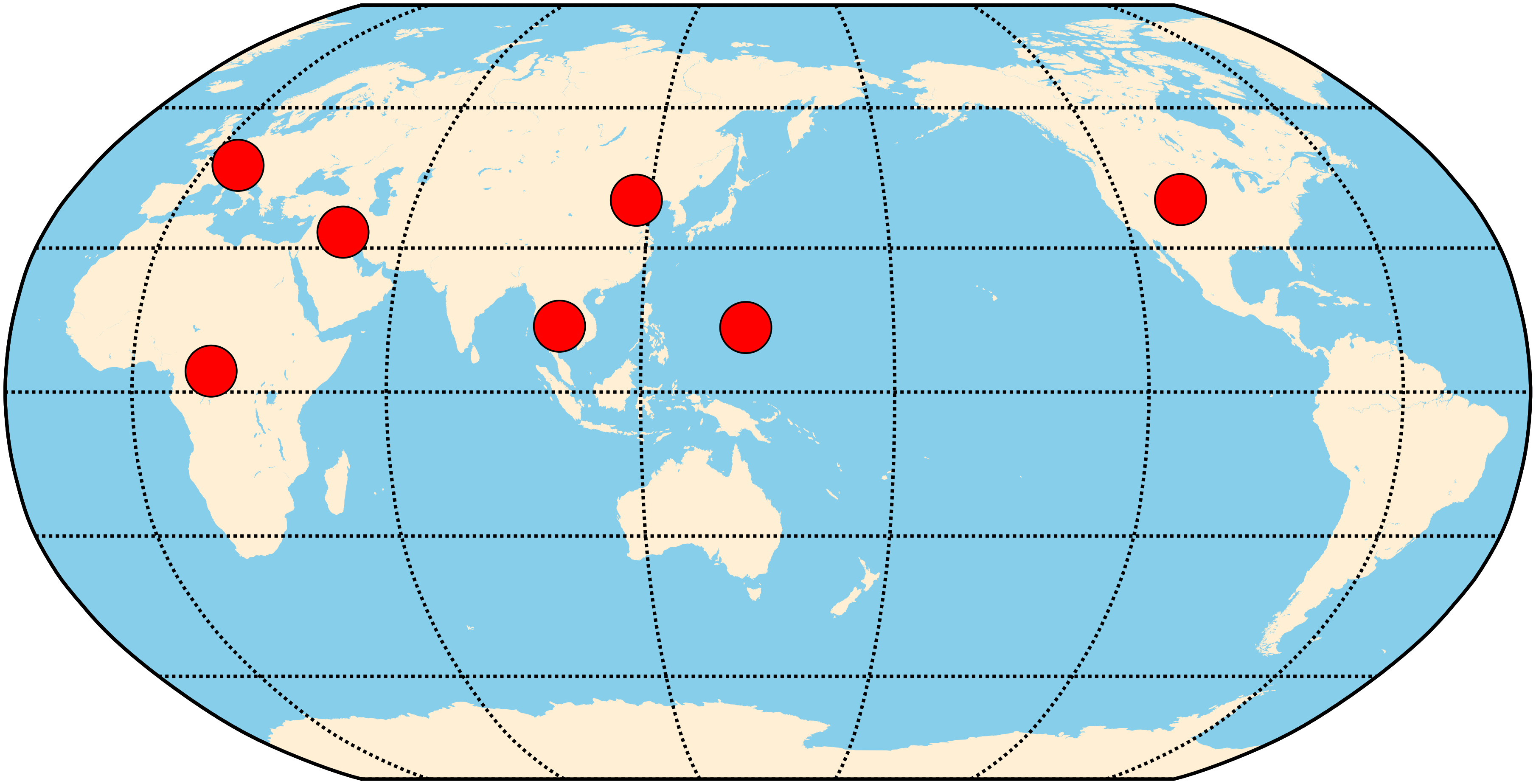
Δt	k_1	k_2
u_1	2	2
u_2	1	3
u_3	1	2
u_4	1	3
u_5	2	0

Structured populations



Structured populations

Locations of samples [377 microsatellites]

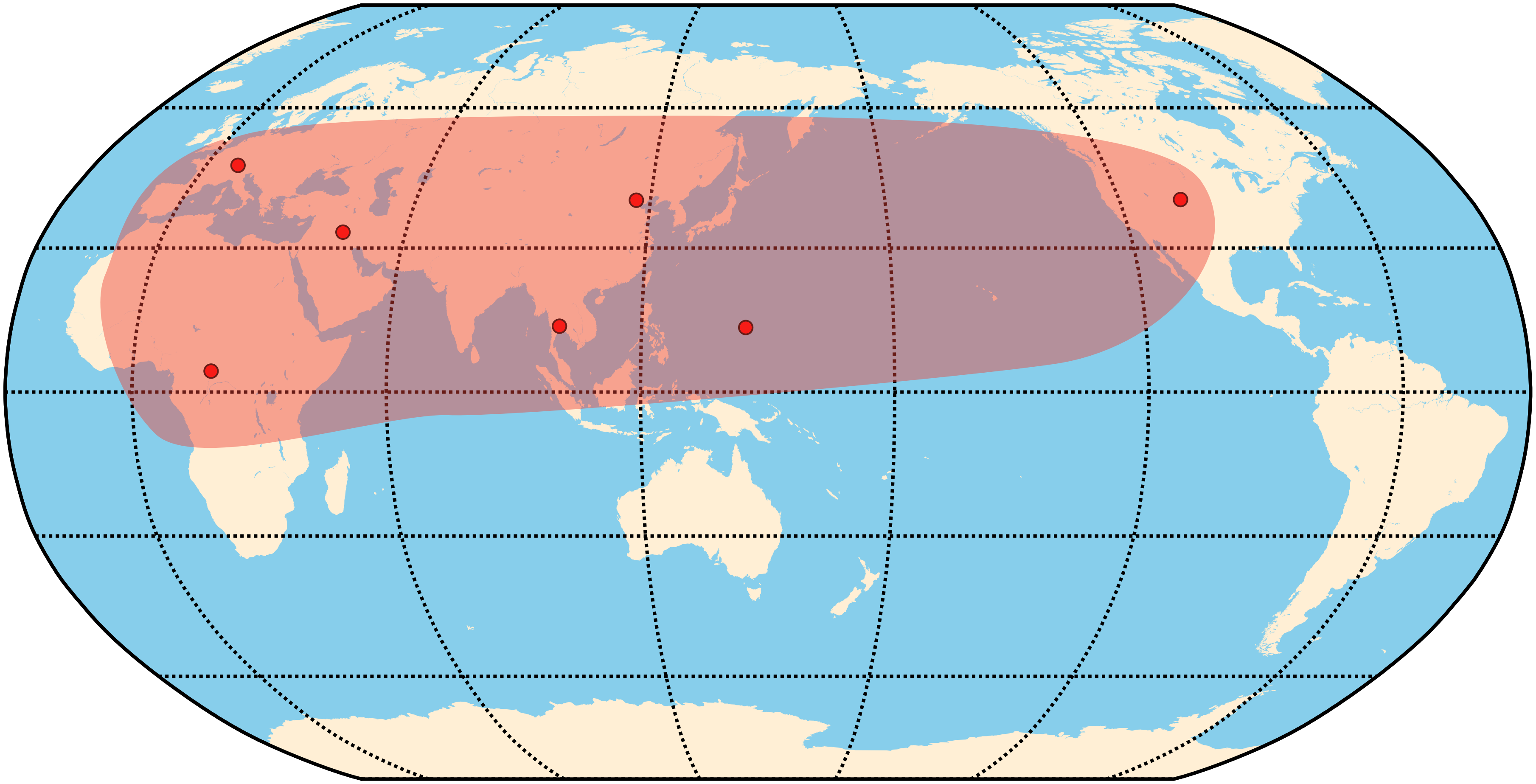


A total of 70 individuals from 7 populations analyzed for 377 microsatellite loci: Mutation model is Brownian motion approximation to the single-step mutation model

Reanalysis of data from Rosenberg et al. Science 2001

Structured populations

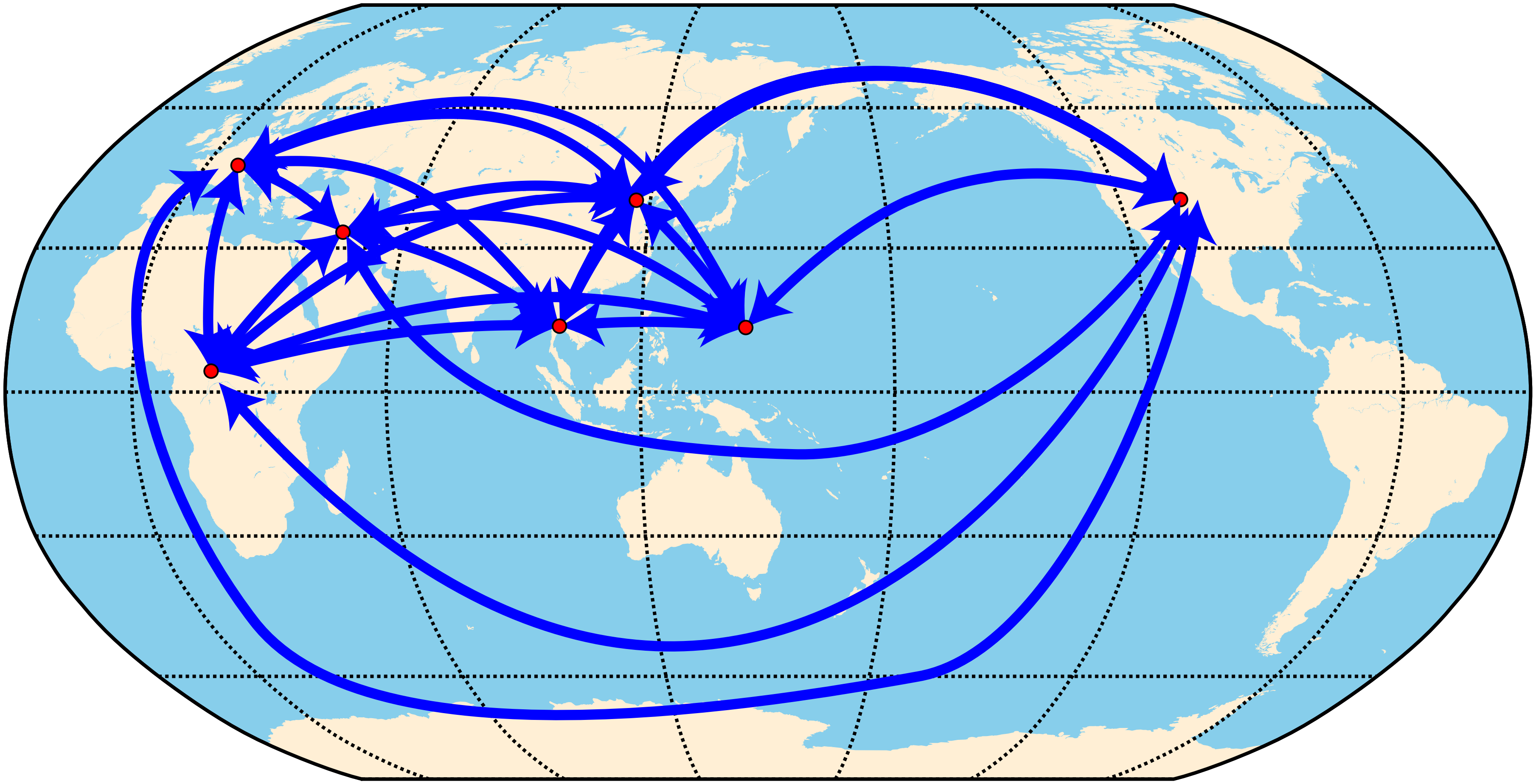
H_3: One panmictic population



Reanalysis of data from Rosenberg et al. Science 2001

Structured populations

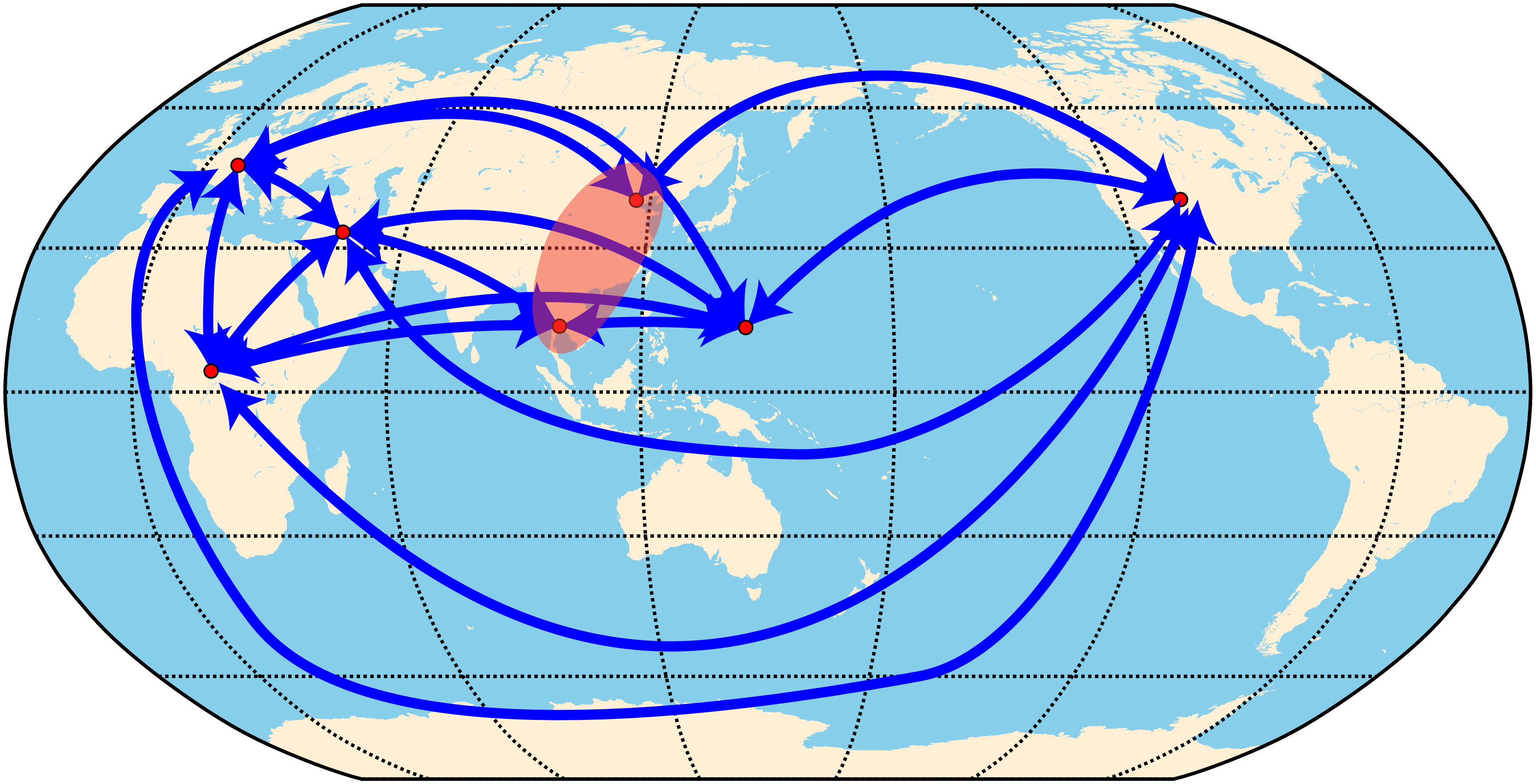
H_2: Tangled mess



Reanalysis of data from Rosenberg et al. Science 2001

Structured populations

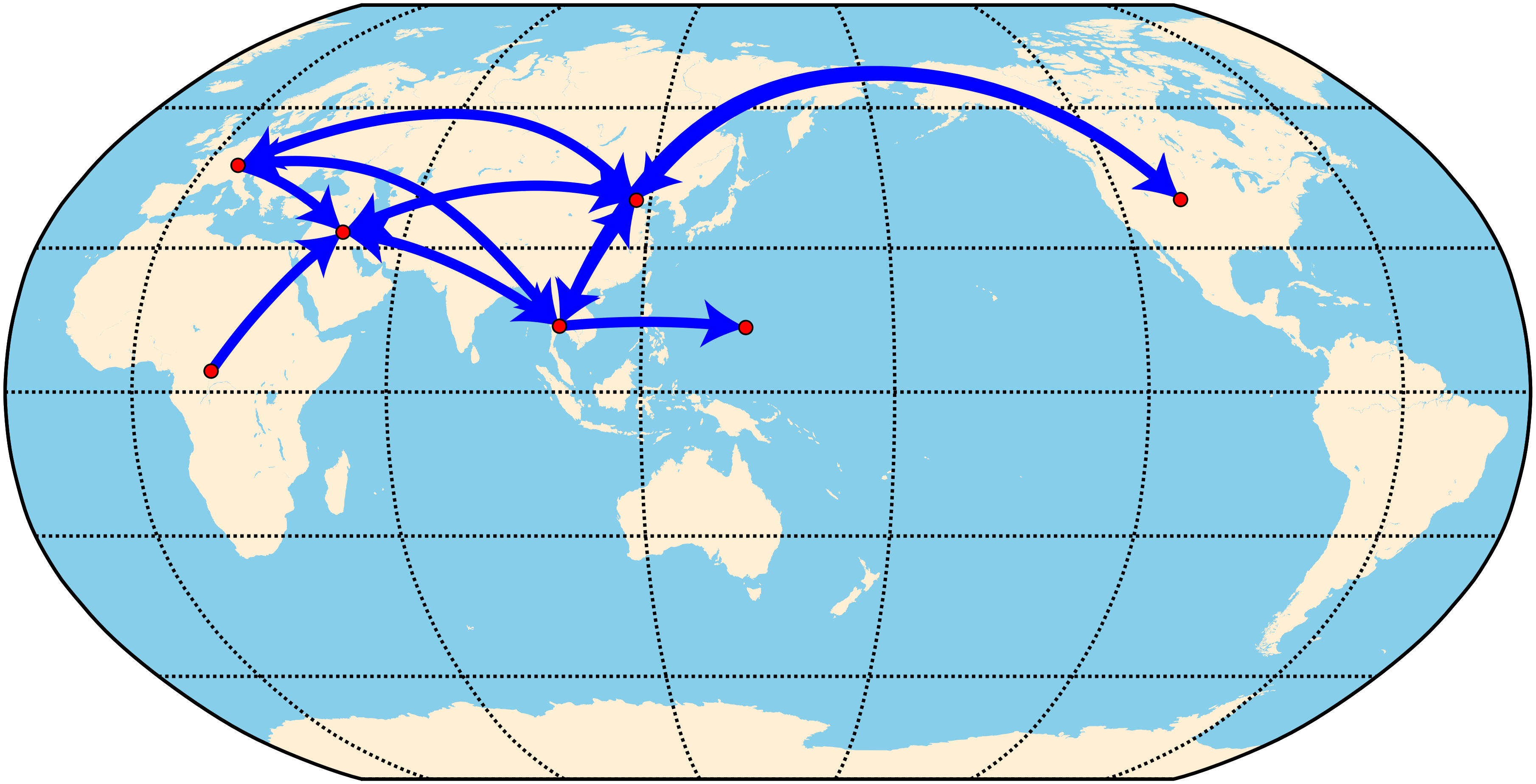
H_4 : Somewhat less Tangled mess



Reanalysis of data from Rosenberg et al. Science 2001

Structured populations

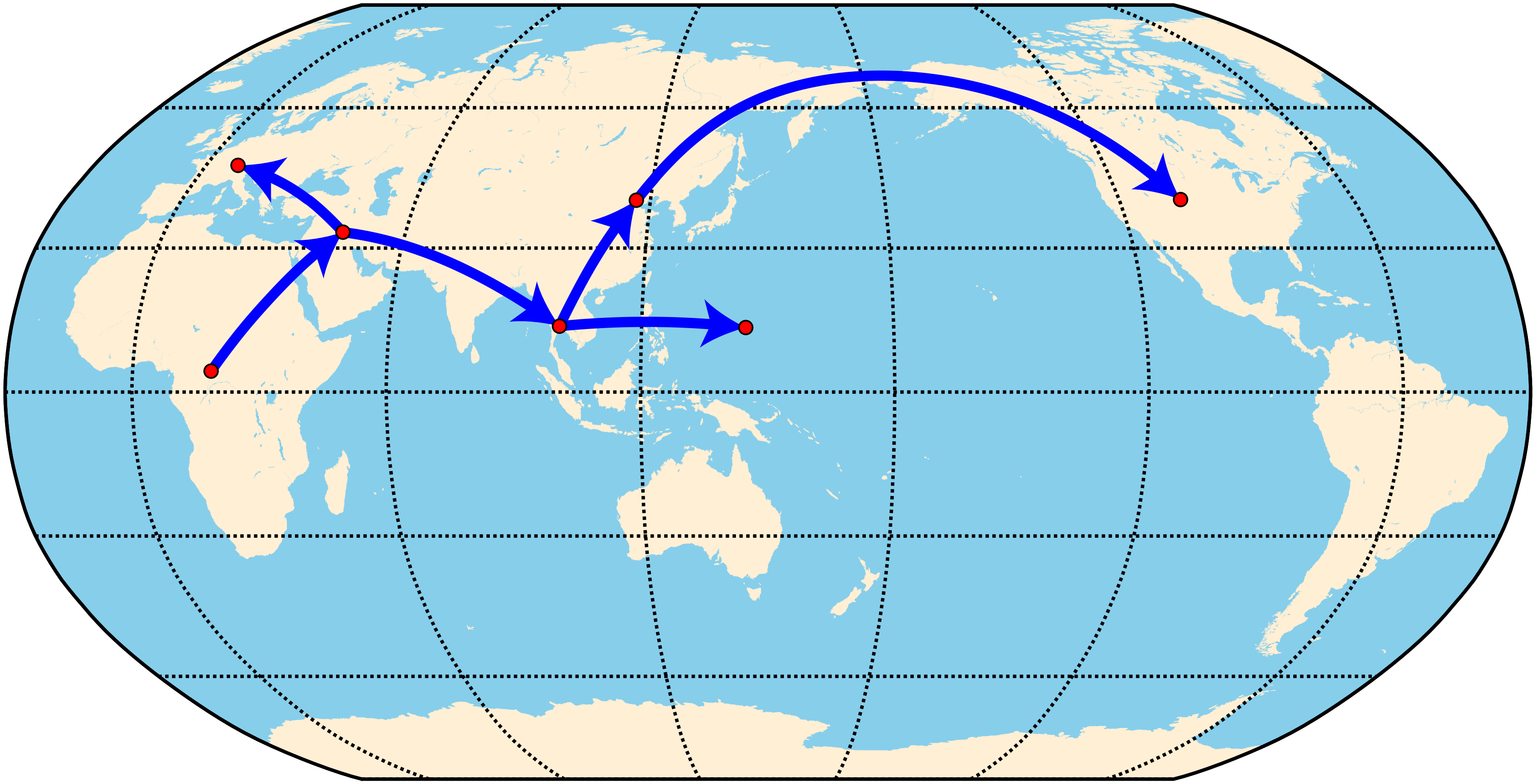
H_1: Out of Africa, indecision anywhere else



Reanalysis of data from Rosenberg et al. Science 2001

Structured populations

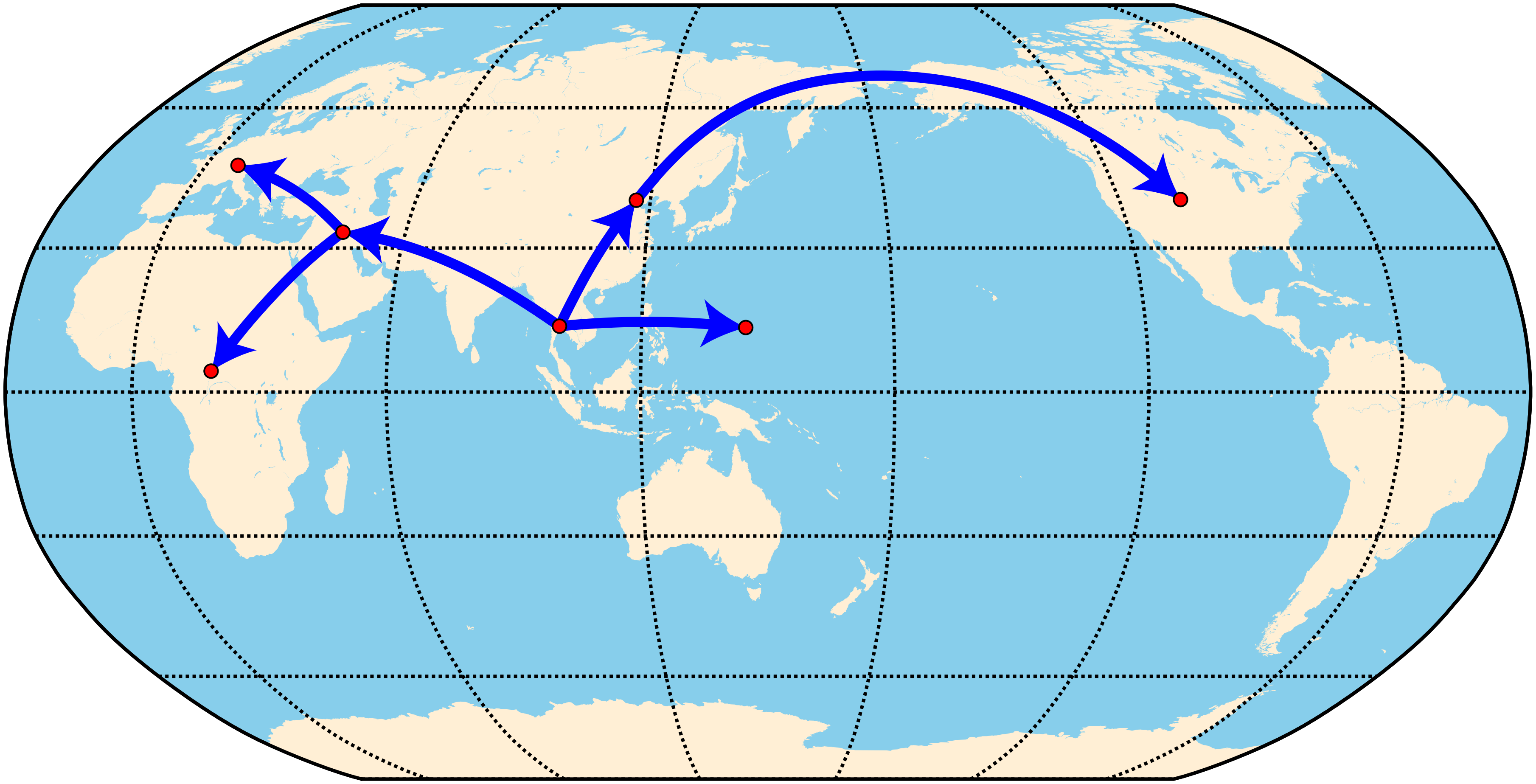
H_5: Minimal model



Reanalysis of data from Rosenberg et al. Science 2001

Structured populations

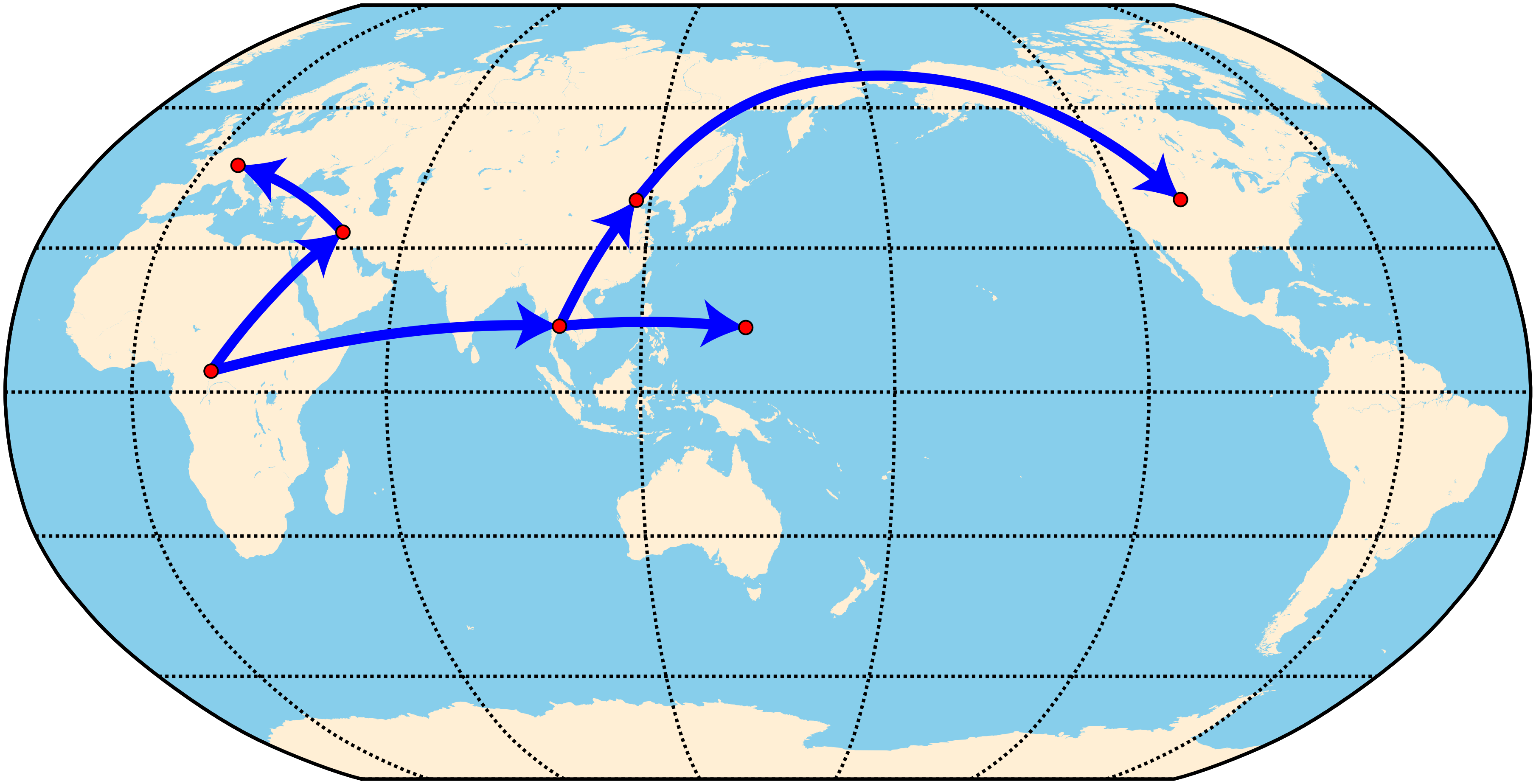
H_6 : South-Asia is cradle of humans



Reanalysis of data from Rosenberg et al. Science 2001

Structured populations

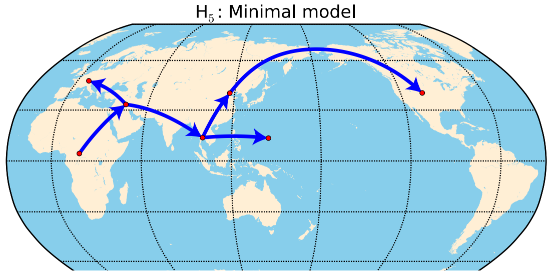
H_7: Direct train to Asia



Reanalysis of data from Rosenberg et al. Science 2001

Structured populations

1.



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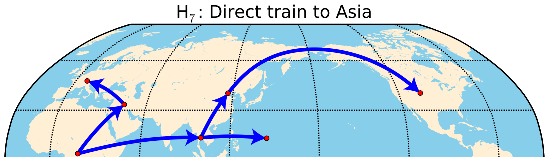

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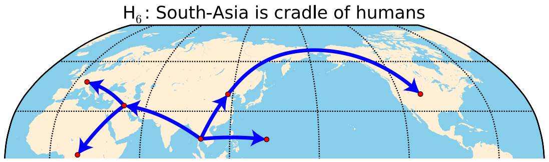

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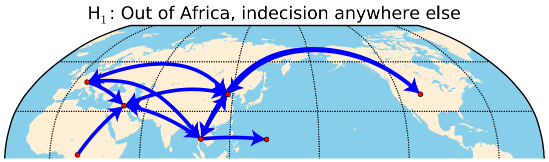

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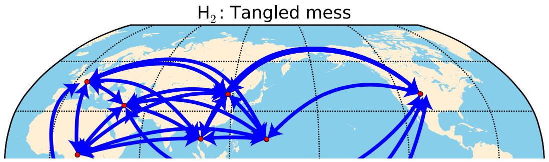

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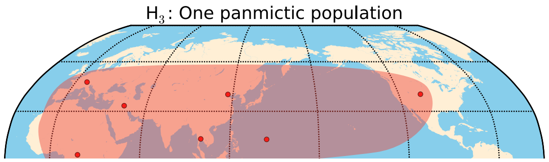
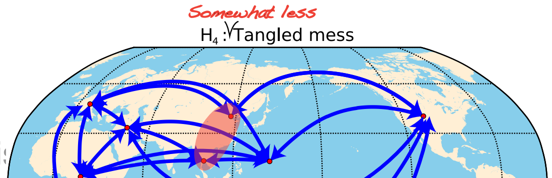
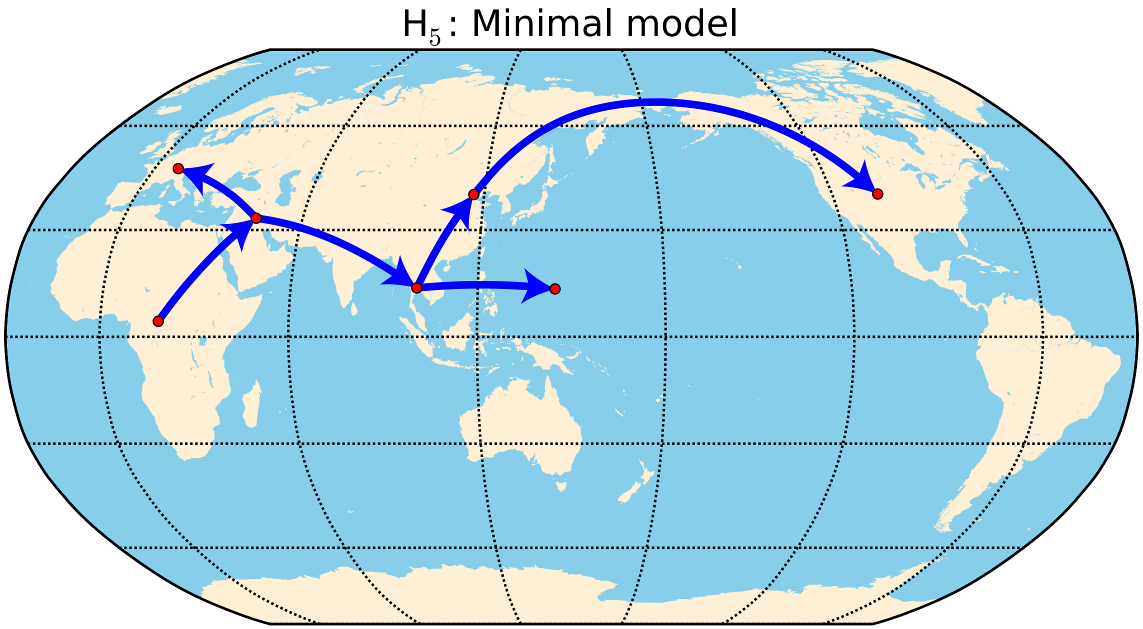


7.



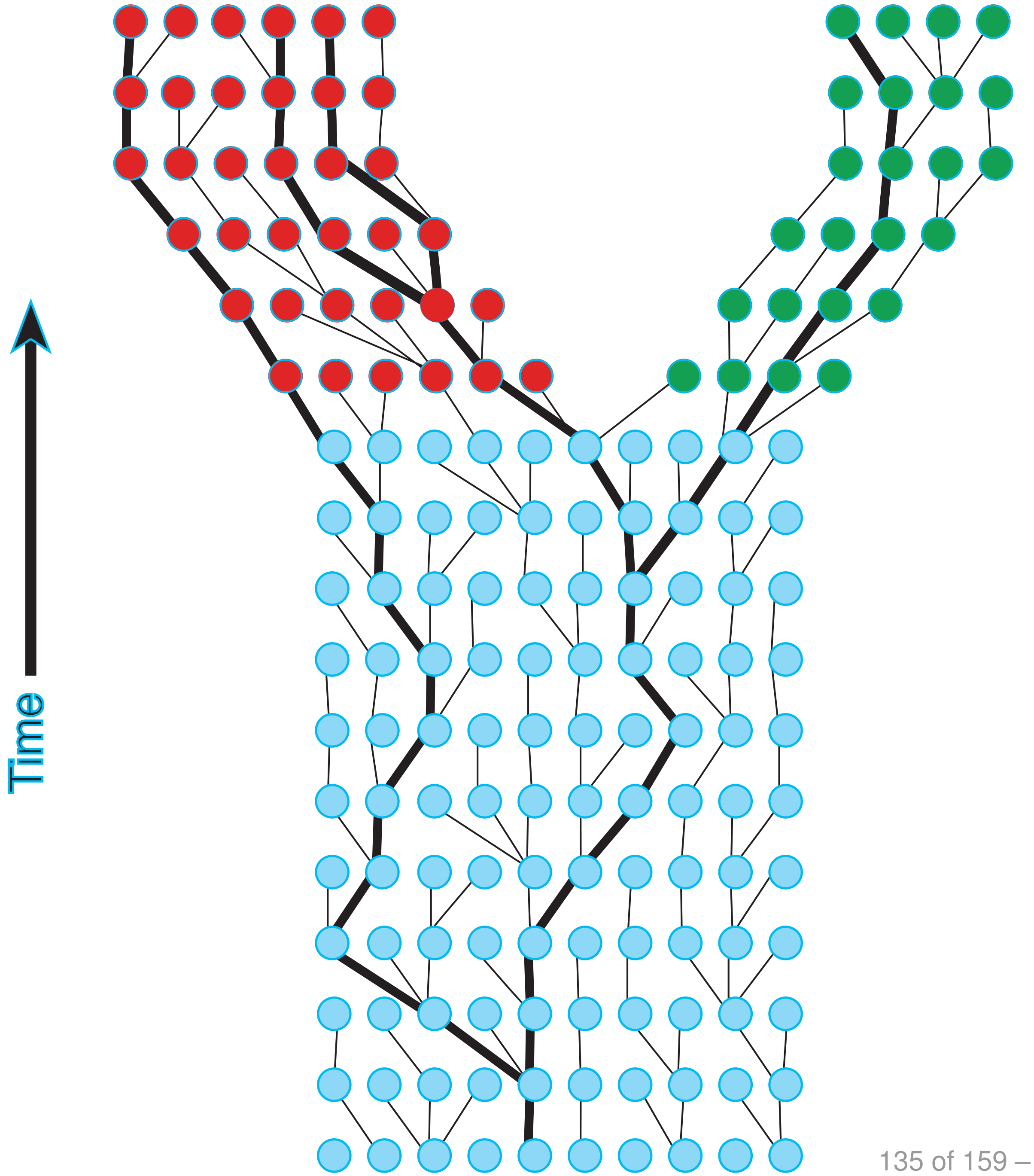
Model order and probability using Bayes factors

all other models: 0.0
Minimal model 1.0

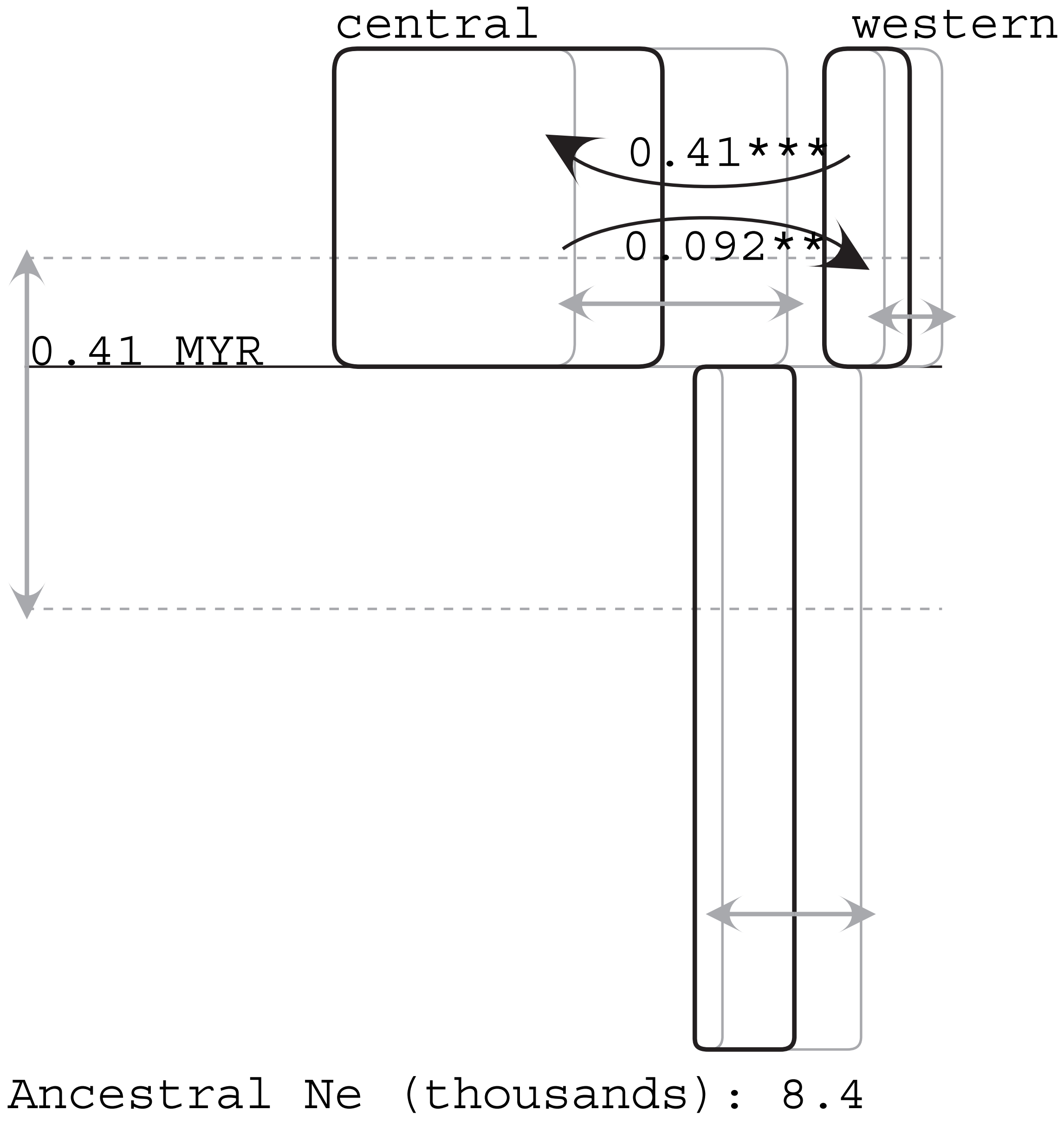


Extensions of the basic coalescent

Population splitting



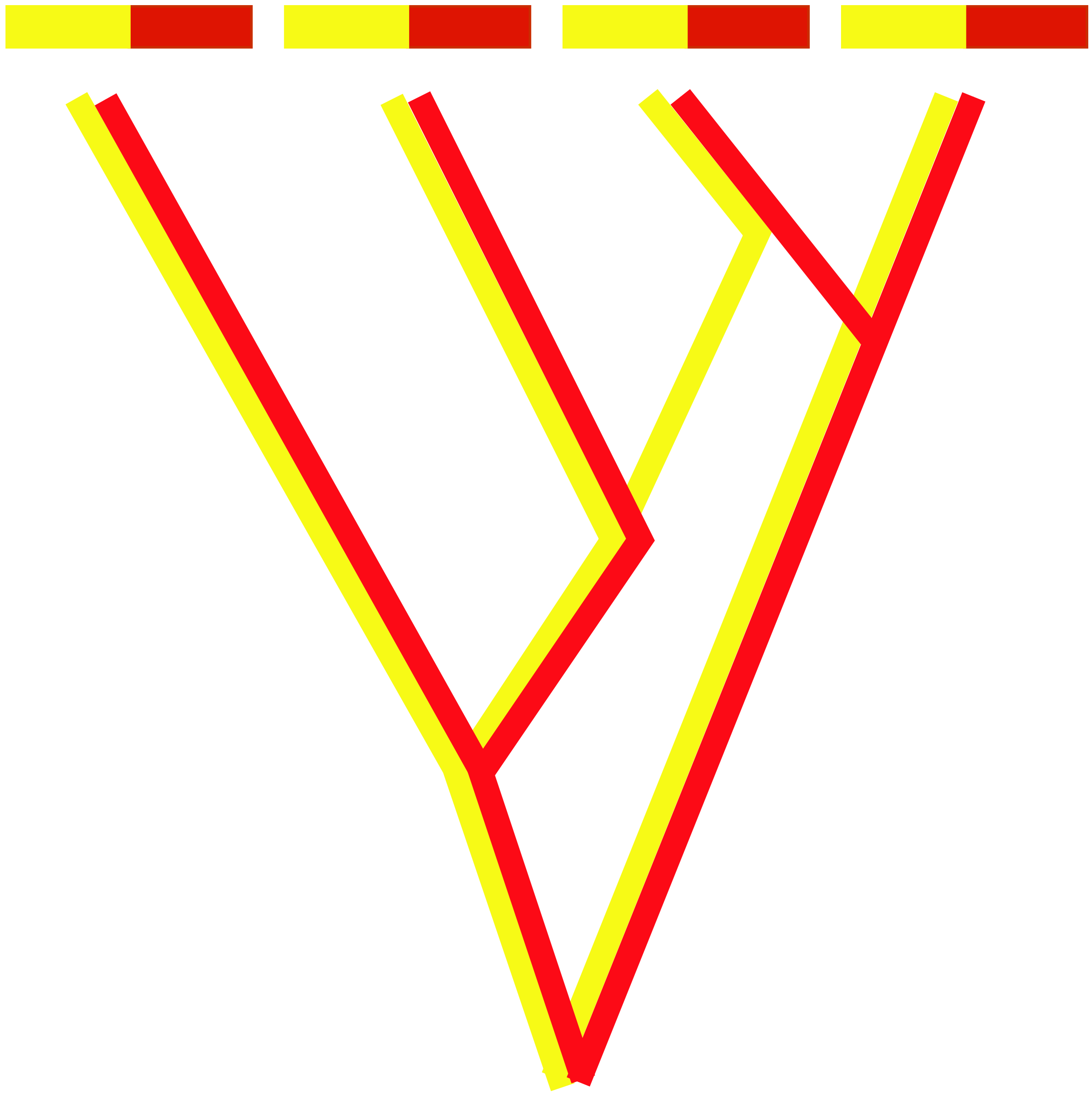
Population splitting



IM: isolation with migration; co-estimation of divergence parameters, population sizes and migration rates. Not all datasets can separate migration from divergence, and multiple loci are helpful.

Hey 2010

Extensions of the basic coalescent



Age of mutations

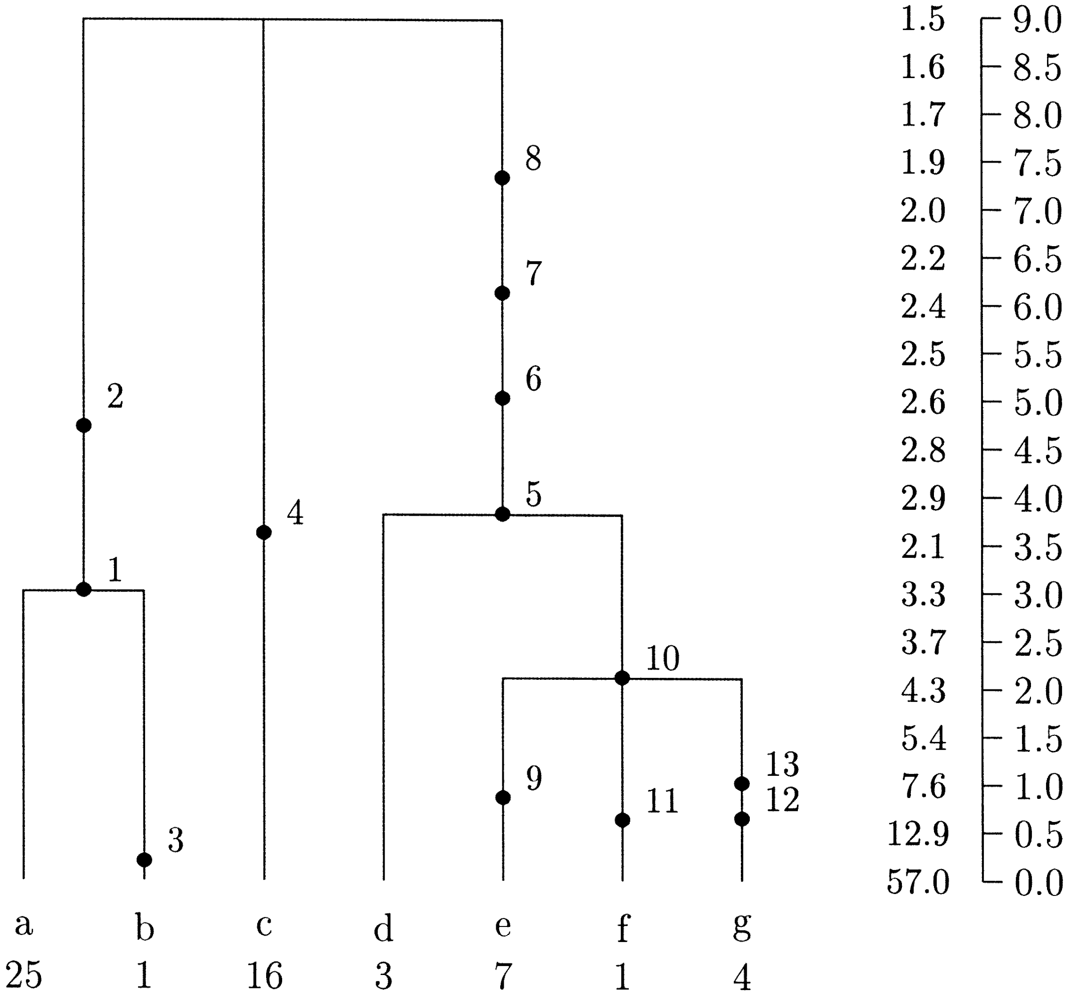
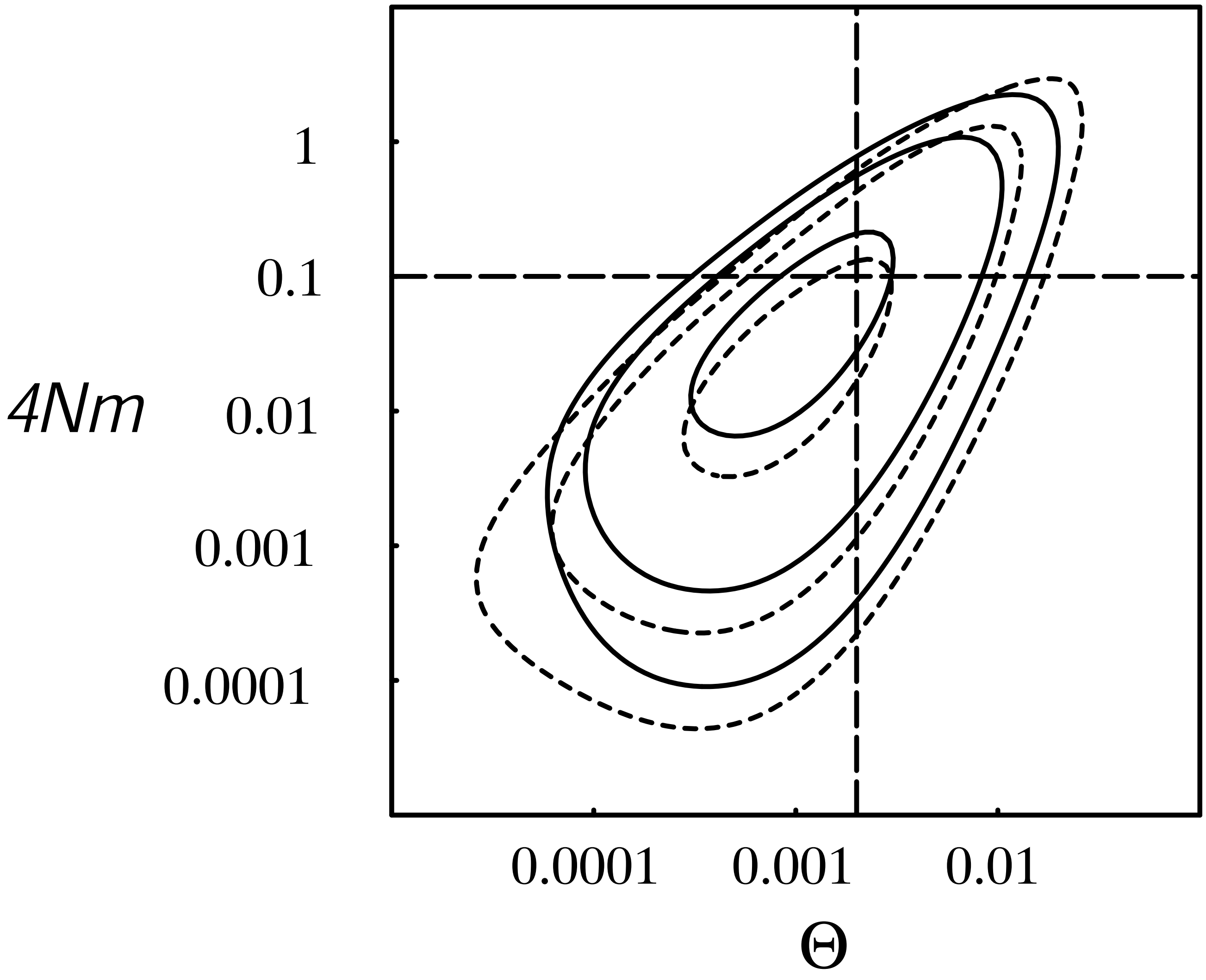


FIG. 3. *Melanesian β-globin tree. Time in units of* 100,000 *years.*

MIGRATE versus GENETREE



Robustness of the coalescence

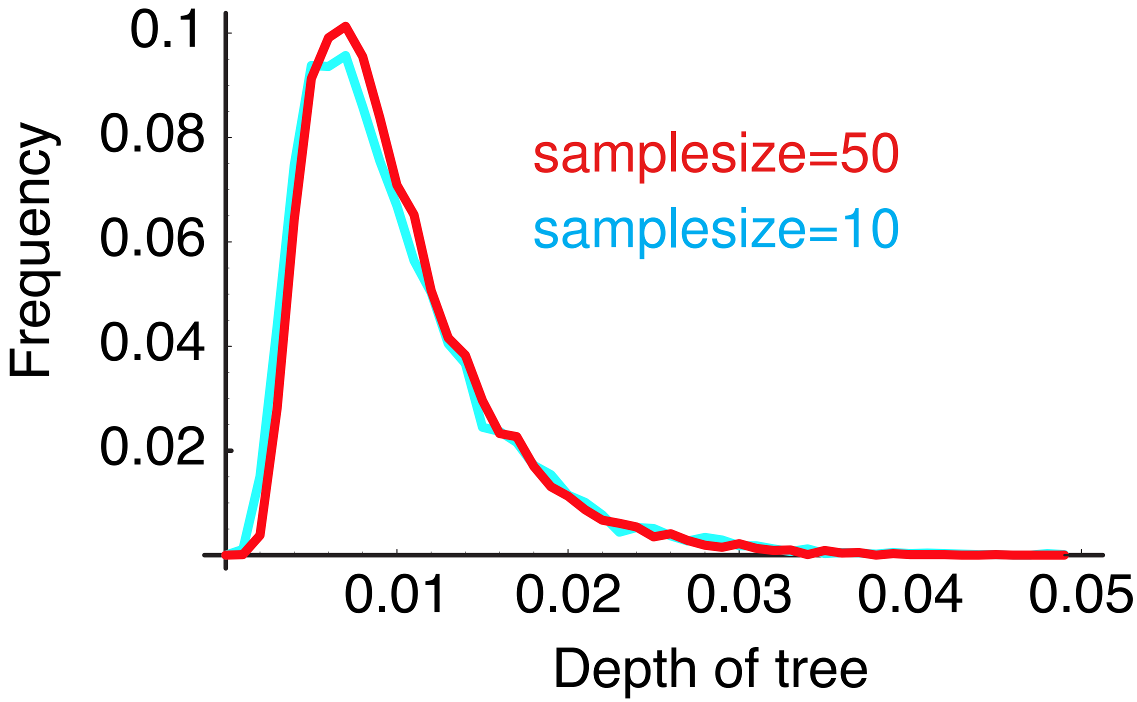
Violating assumptions

The evil reviewer says: *“You shall not use method/program X because your data does not fit the assumptions for...”*

- Required samples
- Recombination
- Population size fluctuation
- Divergence

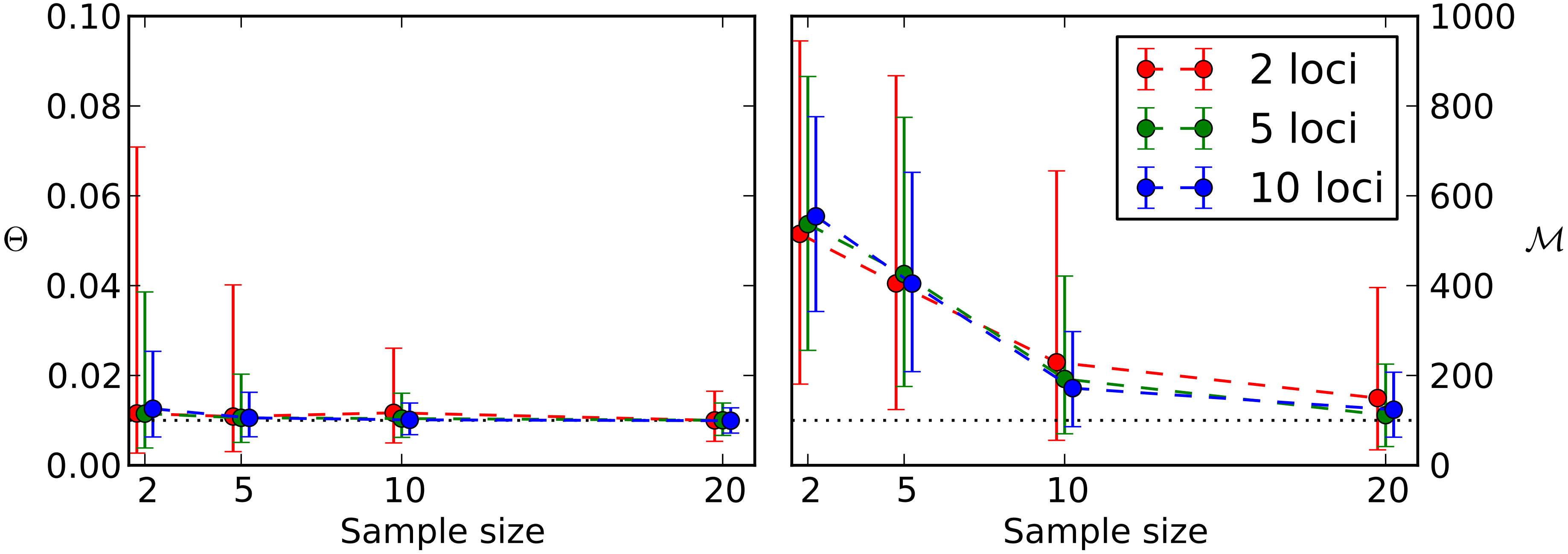
Required samples is small

- The time to the most recent common ancestor is robust to different sample sizes.
- Simulated sequence data from a single population have shown that after 8 individuals you should better add another locus than more individuals.



Felsenstein (2005)
Pluzhnikov and Donnelly (1996)

Required samples is small

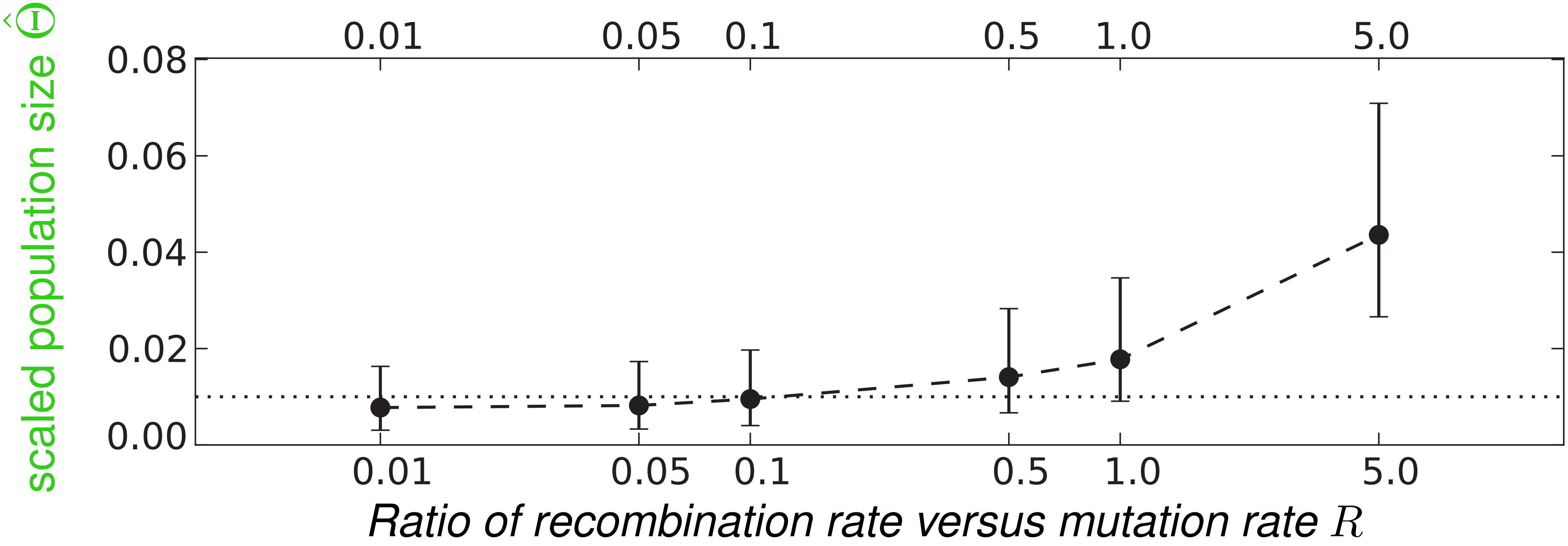


Medium variability DNA dataset: Mutation-scaled population size Θ and mutation-scaled migration rate M versus sample size for 2, 5, and 10 loci. The true $\Theta_T = 0.01$ is marked with the dotted gray line; $M = 100$

Ignoring recombination

0.0

~500 simulated datasets

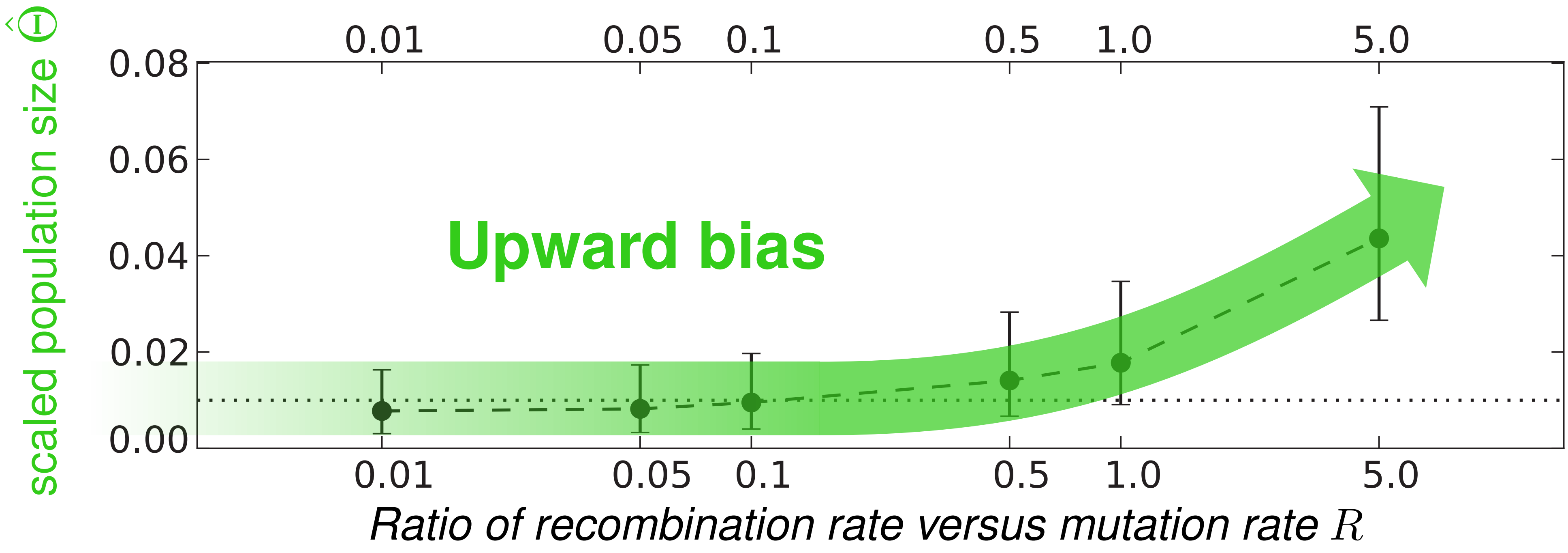


Averages with 95% credibility intervals of runs with different mutation-scaled recombination rates $R = C/\mu$. The dotted lines mark the 'true' values.

Ignoring recombination

0.0

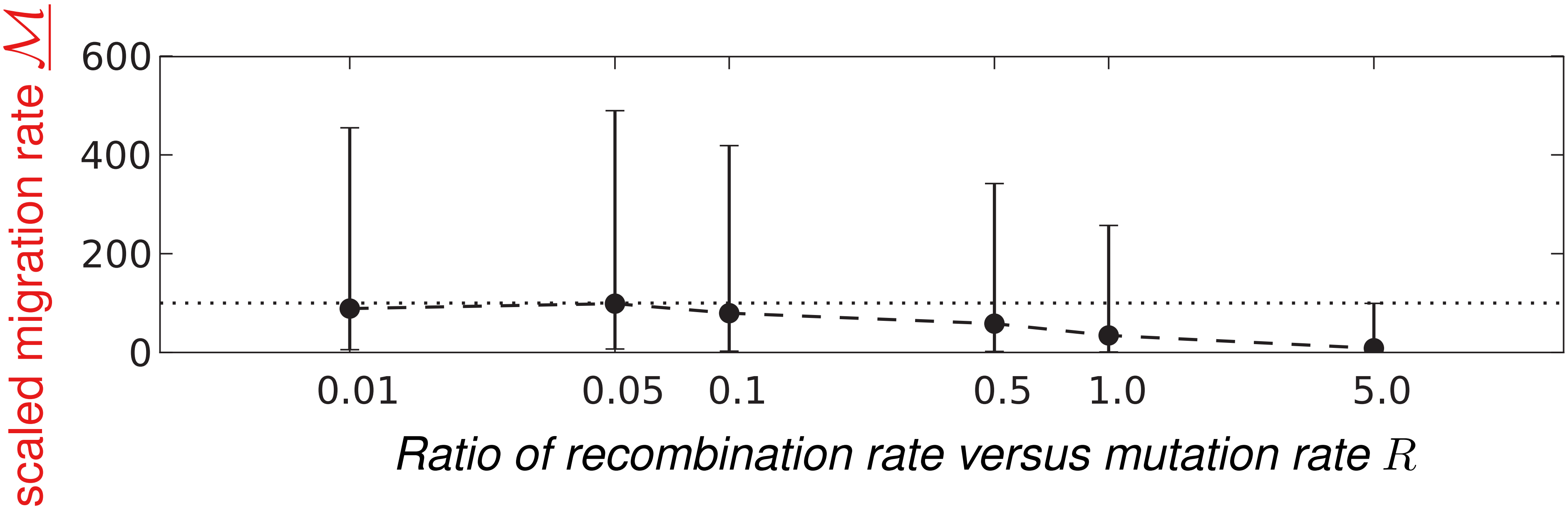
~500 simulated datasets



Averages with 95% credibility intervals of runs with different mutation-scaled recombination rates $R = C/\mu$. The dotted lines mark the 'true' values.

Ignoring recombination

∼500 simulated datasets



Averages with 95% credibility intervals of runs with different mutation-scaled recombination rates $R = C/\mu$. The dotted lines mark the 'true' values.

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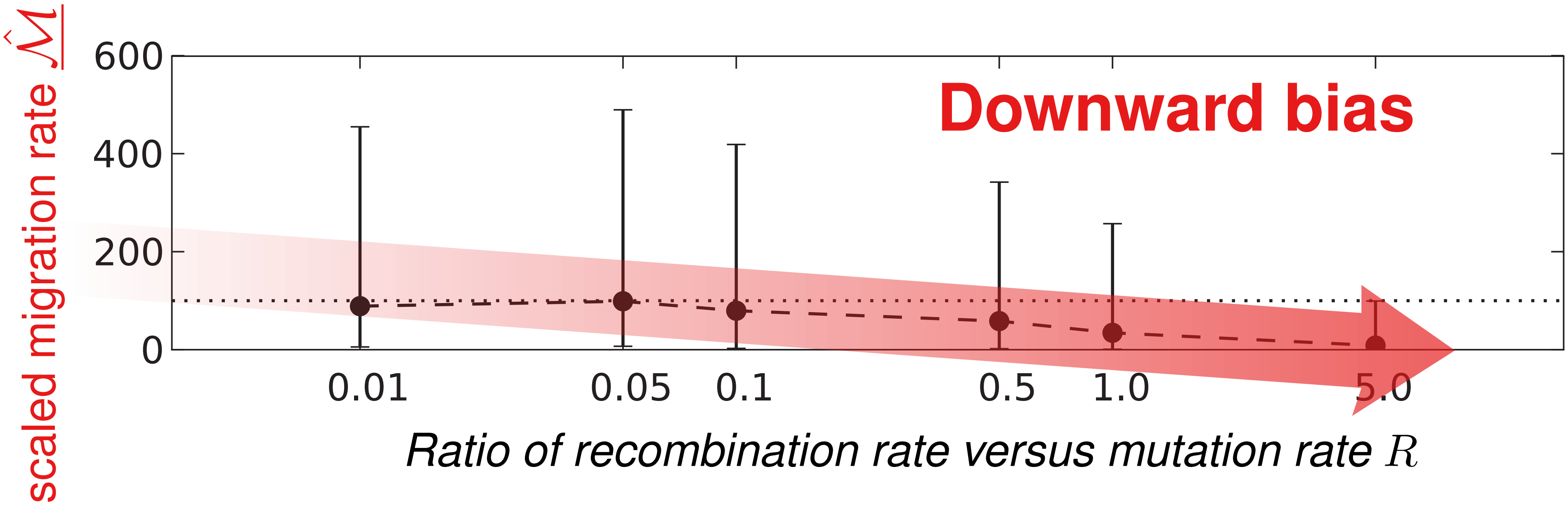


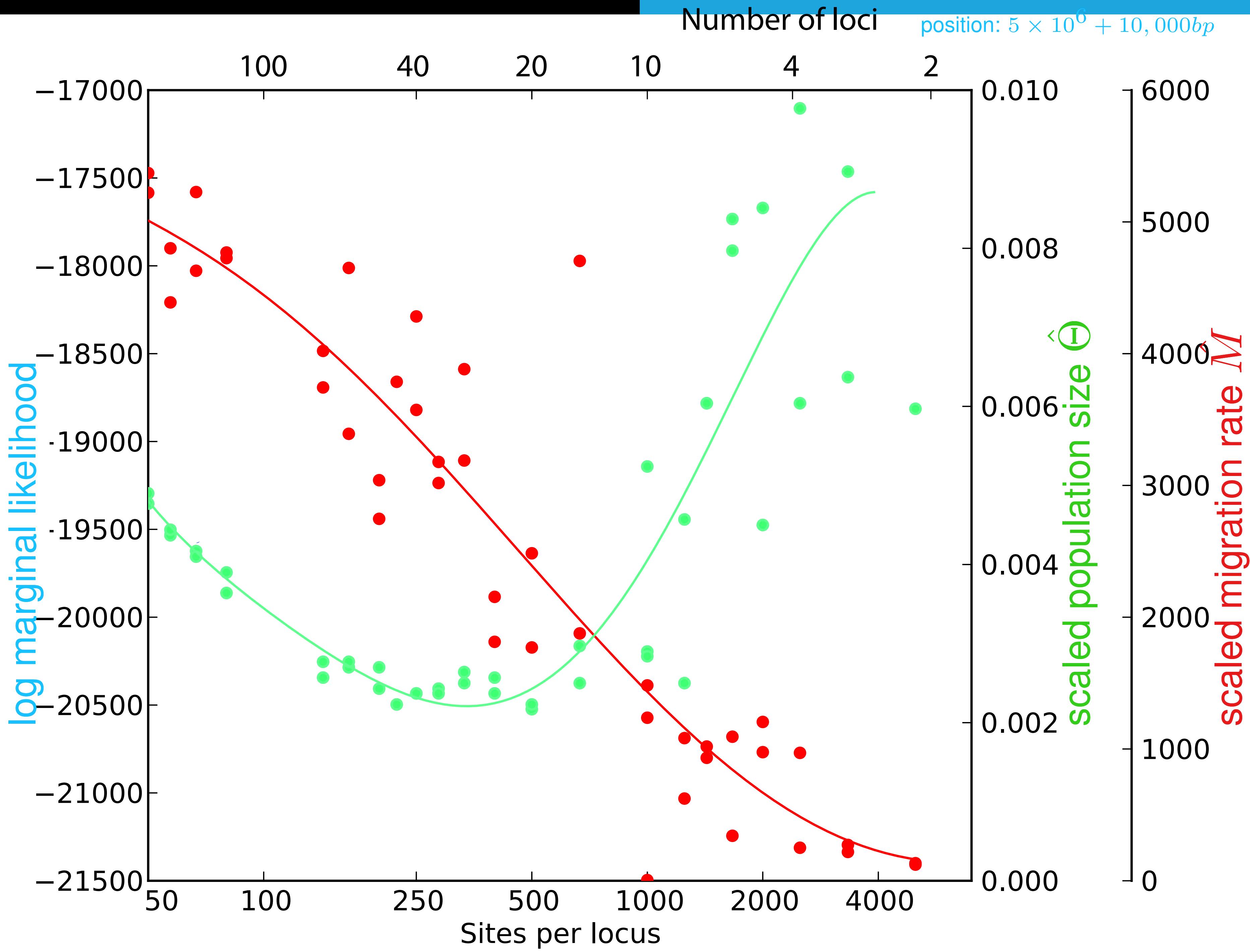
Averages with 95% credibility intervals of runs with different mutation-scaled recombination rates $R = C/\mu$. The dotted lines mark the 'true' values.

Chopping a real dataset

0.0

D. melanogaster Chr2L

position: $5 \times 10^6 + 10,000bp$



Chopping a real dataset

D. melanogaster Chr2L

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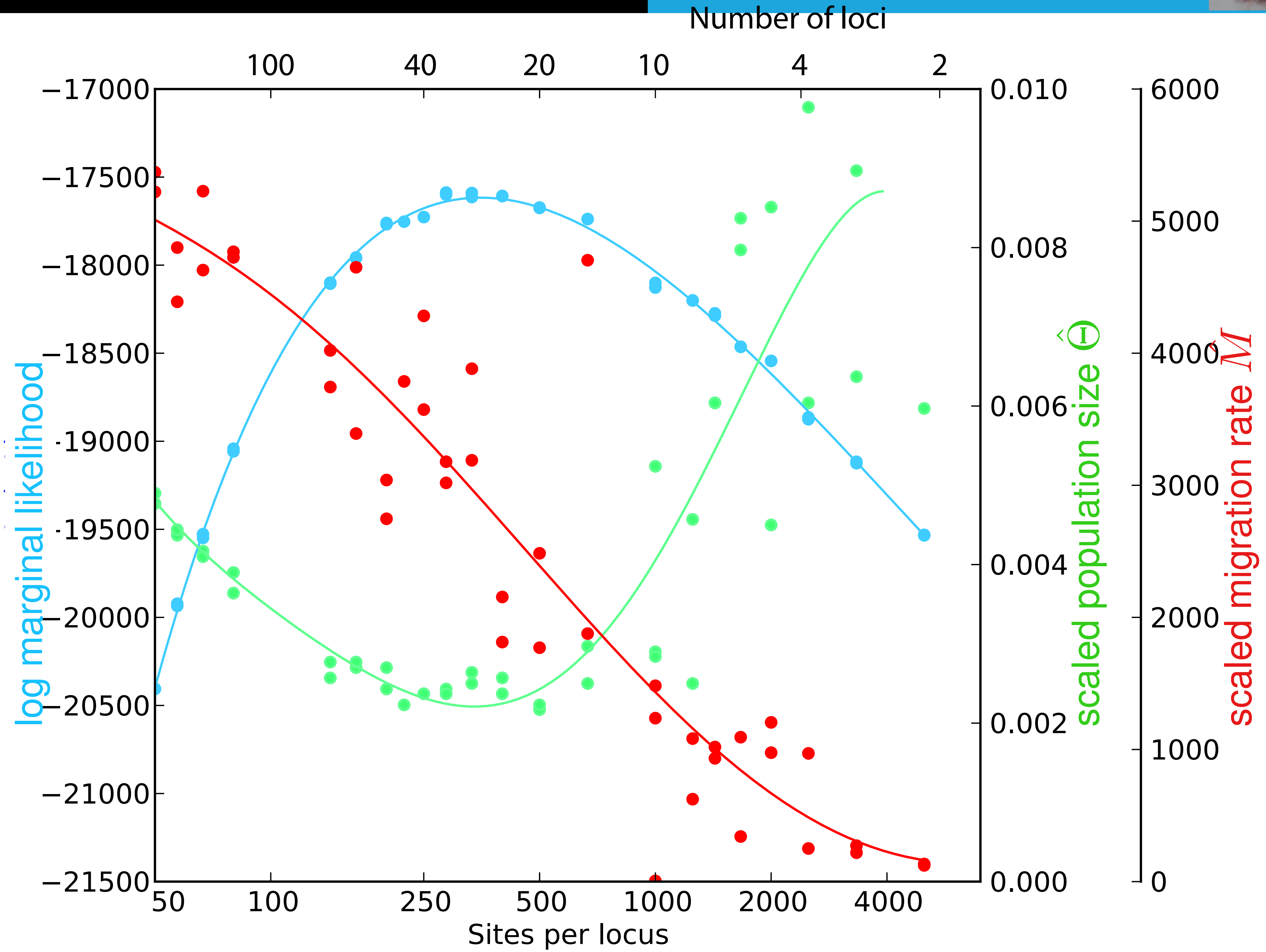
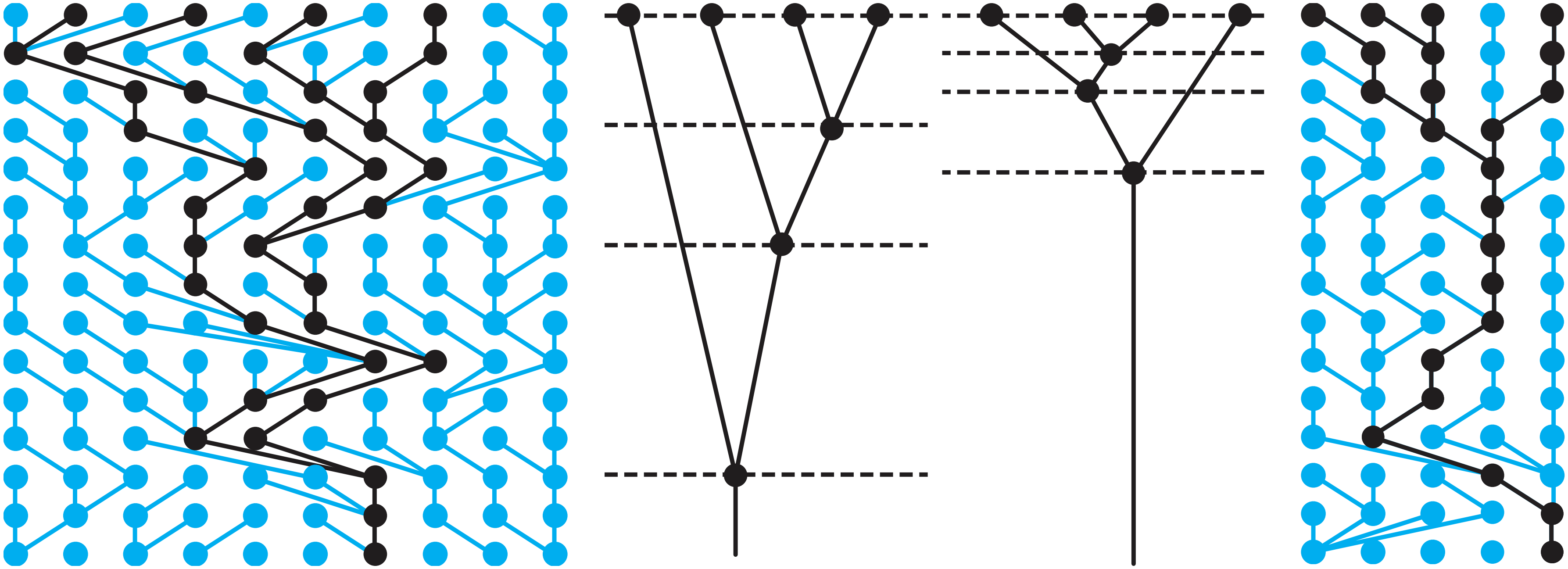


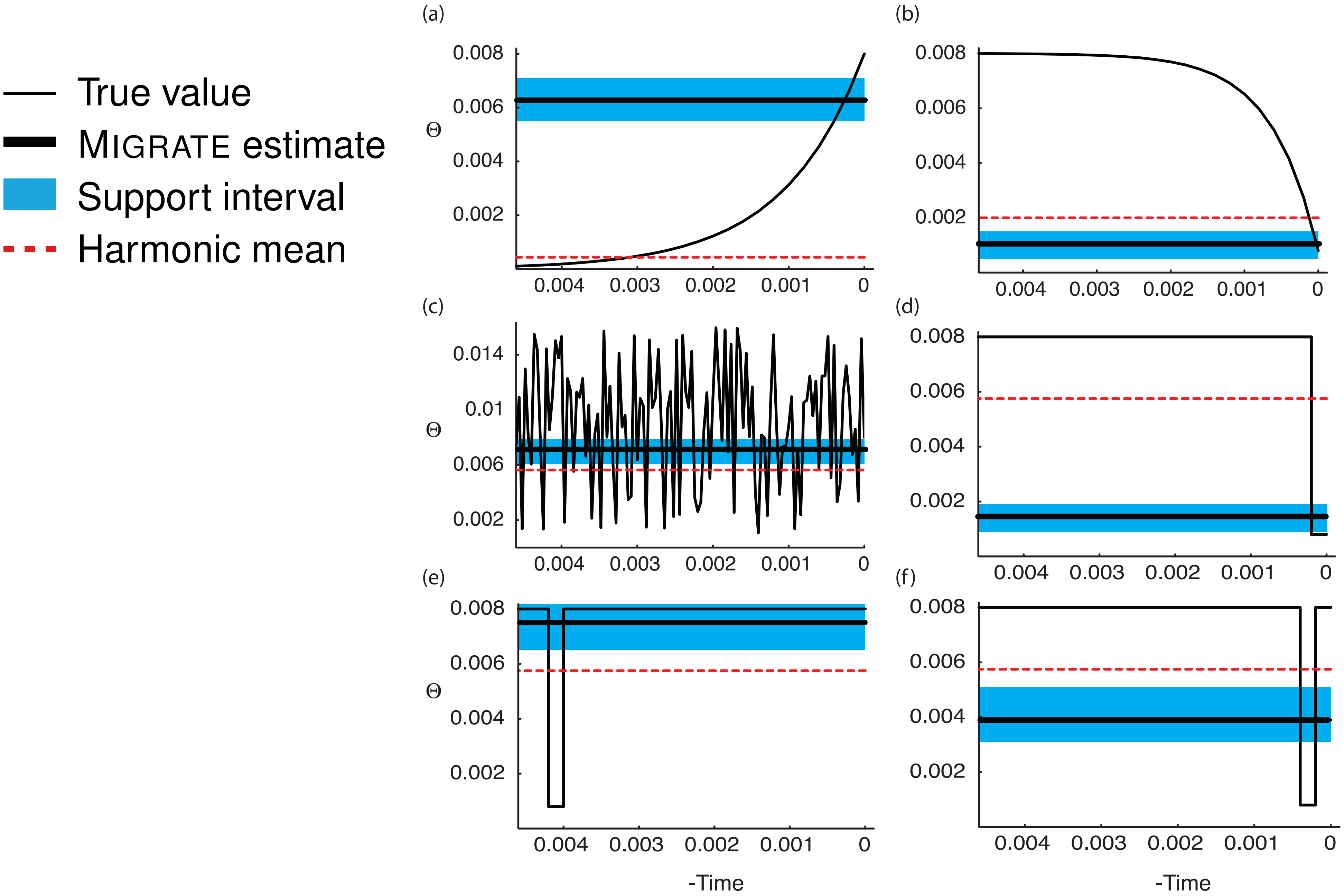
Average of parameters over long time

Researchers from the frequency-based camp claim that the coalescence-based methods are working on an evolutionary time-scale and therefore are not really usable in a conservation genetics or management context.

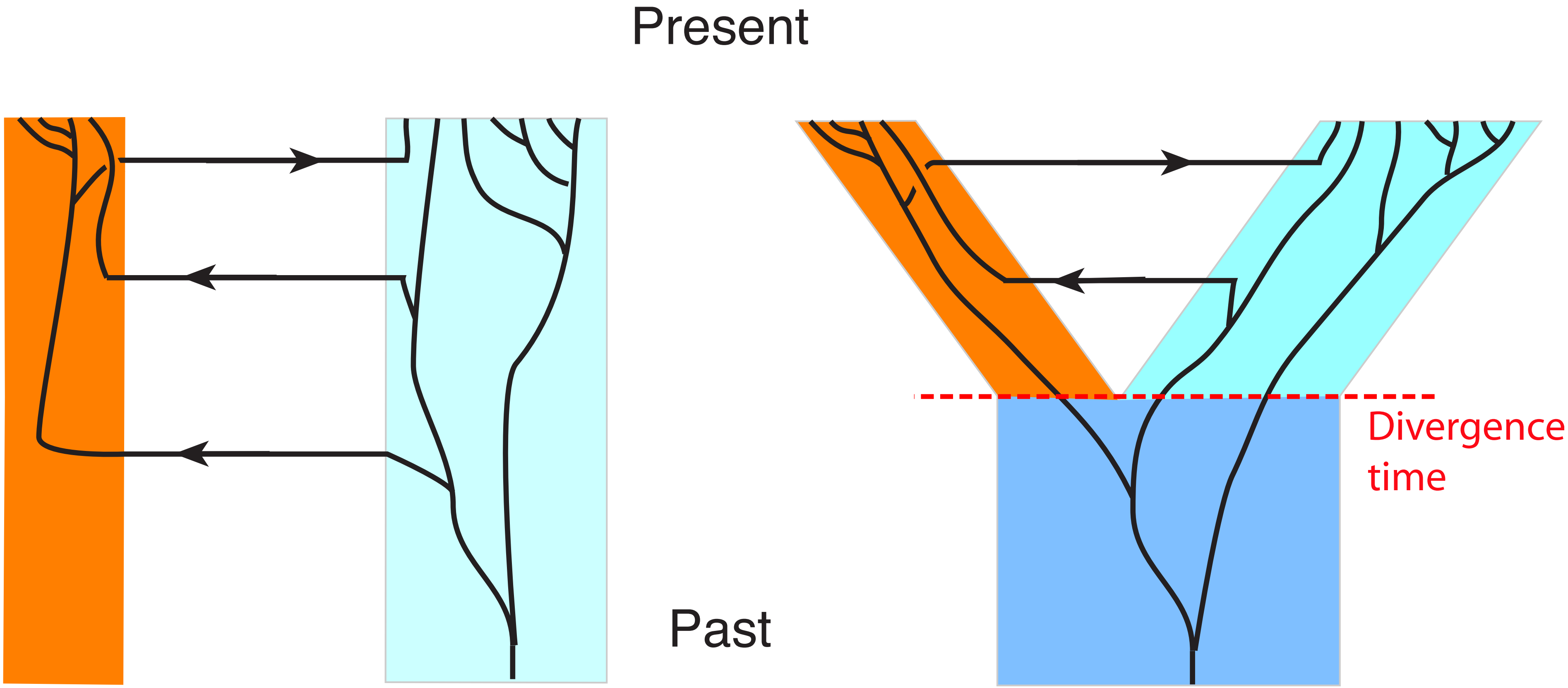
There is some truth to this claim because the time scale for the genealogies is in generations and with large populations such genealogies are deep, but ...



Average of parameters over long time



Ignored divergence

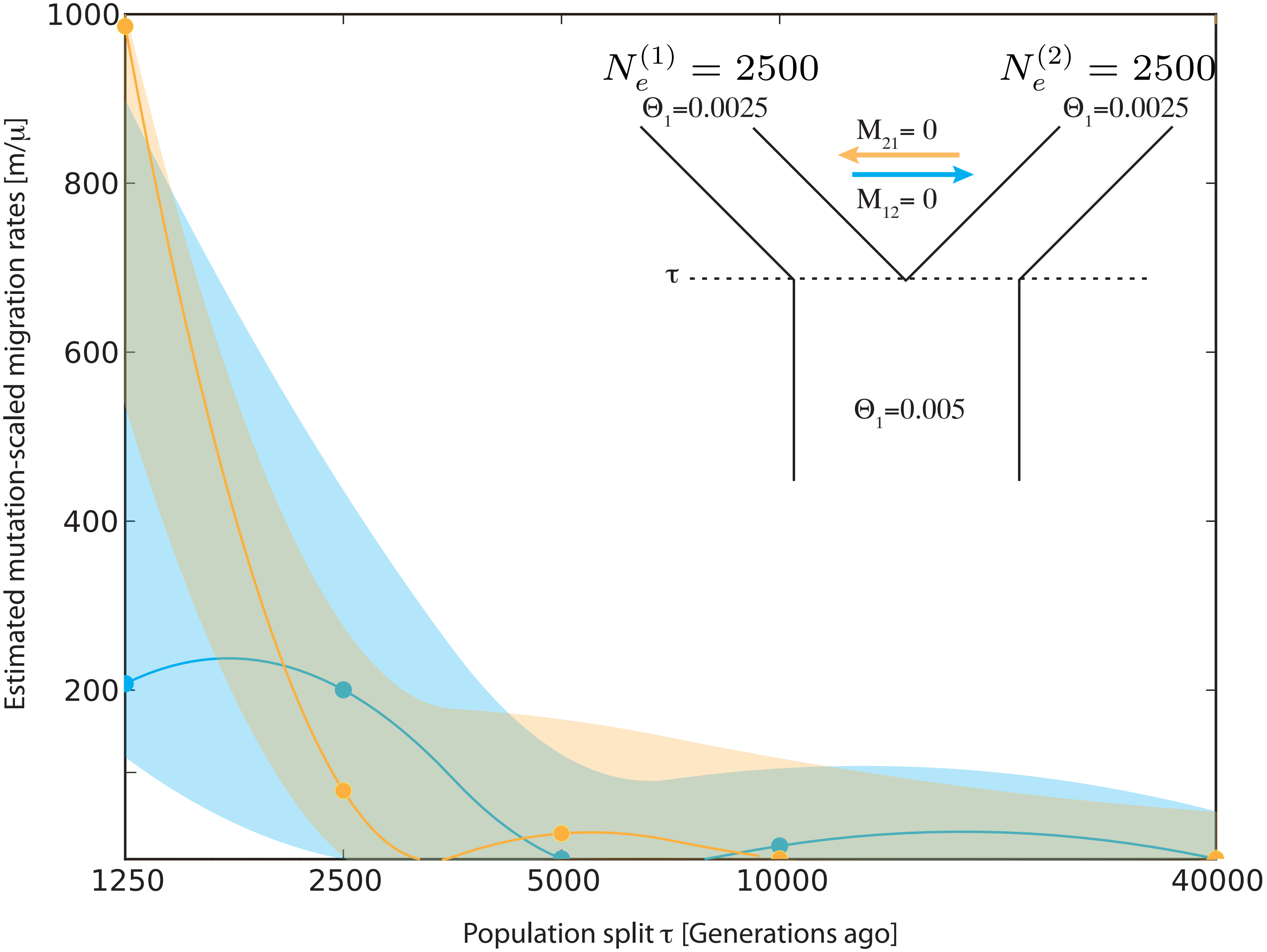


Present

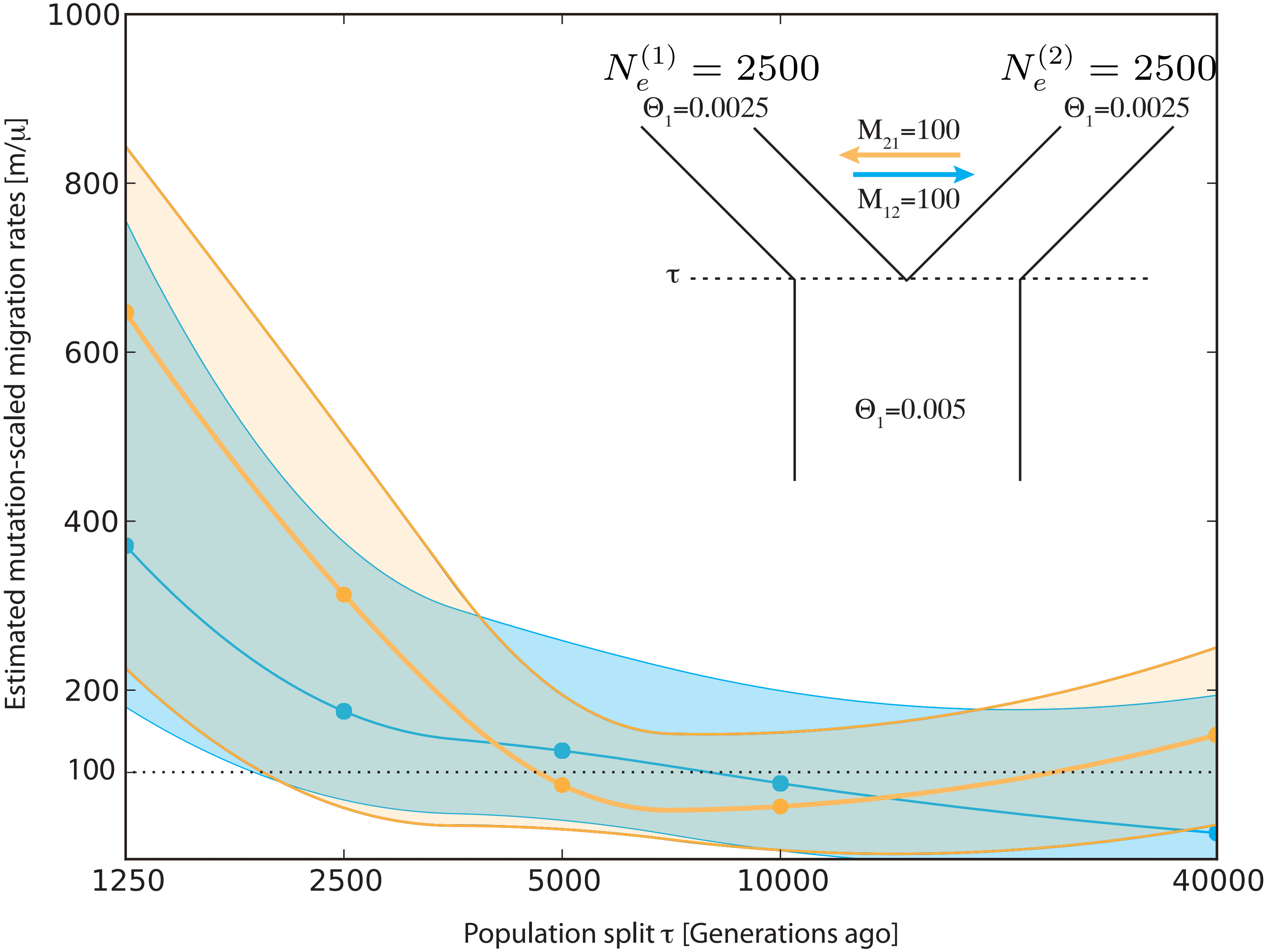
Past

Divergence time

Ignored divergence



Ignored divergence



Ignored selection

The standard coalescent assumes neutral mutations and also exchangeable number of offspring, loci under selection will violate both tenets.

- A new mutation that has a positive effect will replace some of the variability present in the population. All linked sites will suffer a drop in effective population size.

- A new mutation that has a negative effect and will be most likely removed , also resulting in a reduction of variability (and population size)

This is used in genome-wide selection scans, but influence of population growth, population structure on such estimates are not studied.

Software

Program	Maximal # populations	Population sizes	Change through time	Migration rates ,	Divergence	Recombination rate	Serial Sampling
MIGRATE	>20	🔴	🔵	🔴	-	-	🔴
LAMARC	>20	🔴	🔴	🔴	🔵	🔴	-
IM	<10	🔴	🔵	🔴	🔴	-	-
BEAST	2?	🔴	🔴	🔵	🔵	🔵	🔴
GENETREE	>10	🔴	🔴	🔴	-	?	-

Outlook

- Evening: MIGRATE; use to compare different migration hypotheses using Bayes factors. We will also run a few basic LAMARC runs.

- (On the #molevol2013 website, check out “Bayes factors” and“Parallel migrate”)

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; Sigurğardóttir 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.
Inference:

Learn a computer scripting language today to be ready for tomorrow, the parallel genome sequencing revolution has begun.