Coalescent Theory
Beyond the Standard Neutral Model

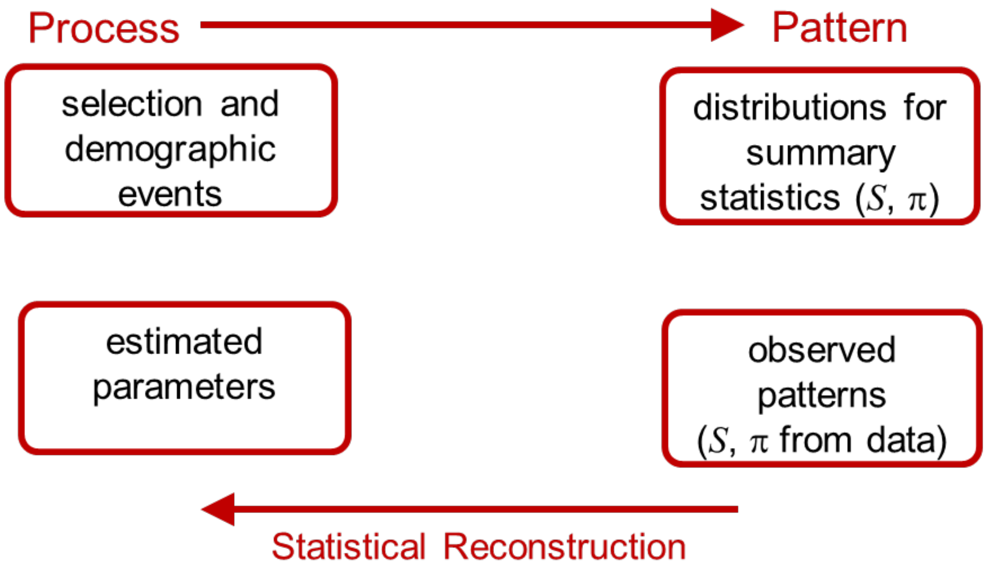
- Genetic differences have no consequences on fitness
- No population subdivision

Exchangable offspring distribution, independent of any *state label* (genotype, location, age, …)

⇩

- Constant population size

➢ Wright-Fisher: multinomial sampling



Process → Pattern

selection and demographic events

distributions for summary statistics (S, π)

estimated parameters

observed patterns (S, π from data)

Statistical Reconstruction

Coalescent Theory
Beyond the Standard Neutral Model

- Genetic differences have no consequences on fitness
- No population subdivision

Exchangable offspring distribution, independent of any *state label* (genotype, location, age, …)

⇩

- Constant population size

➢ Wright-Fisher: ~~multinomial sampling~~

What happens for a different offspring distribution (variance σ^2)?

Coaleasence probability per sequence pair:

$$p_{c,1} = E\left[\sum_{i=1}^{2N} \frac{k_i(k_i-1)}{2N(2N-1)}\right] = \frac{E[k_1^2 - k_1]}{2N-1} = \frac{\sigma^2}{2N-1}$$

Coalescent Theory
Beyond the Standard Neutral Model

Concept of the effective population size N_e :

Coaleasence probability per sequence pair:

$$p_{c,1} = \frac{\sigma^2}{2N-1} \equiv \frac{1}{2N_e} \quad ; \quad N_e = \frac{N-1/2}{\sigma^2} \approx \frac{N}{\sigma^2}$$

N_e : *“coalescence effective population size“*

population size of a standard Wright-Fisher model with the
same coalescence rate = same amount of drift
as the original (non-standard) model

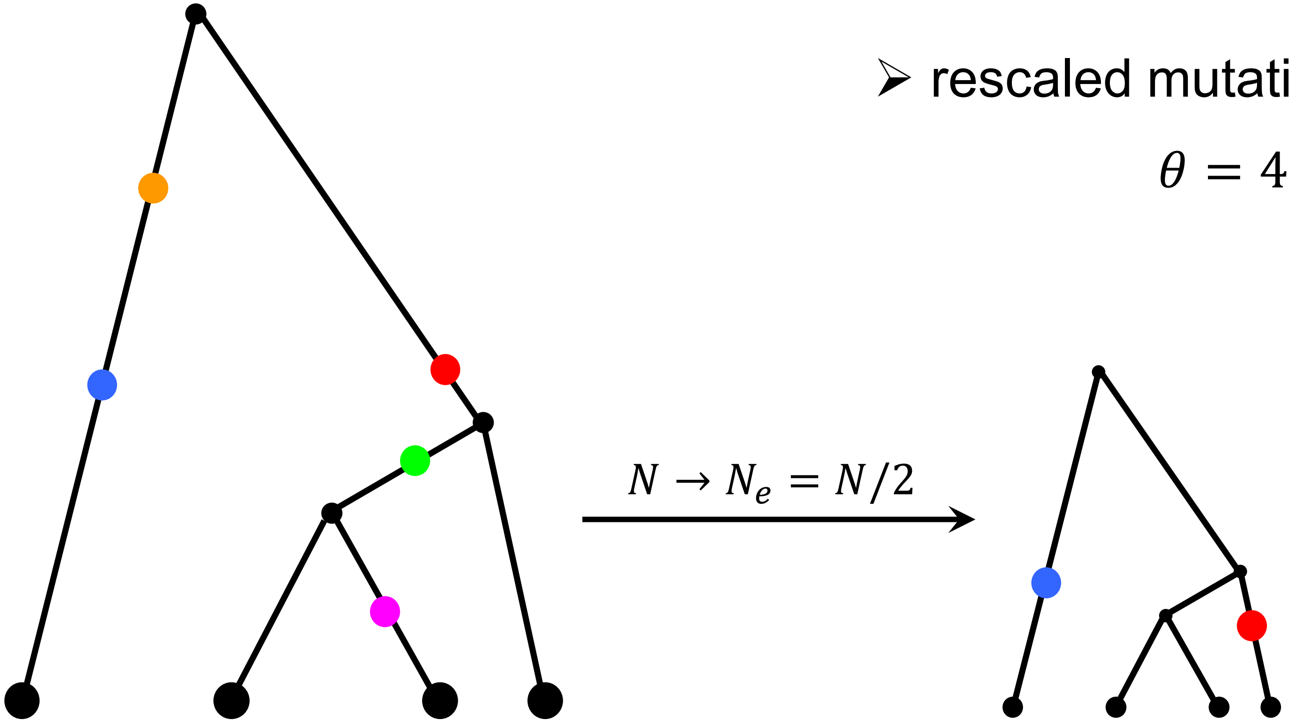
Coalescent Theory
Beyond the Standard Neutral Model

Concept of the effective population size N_e:

Corresponds to a rescaling of
coalescent times and tree sizes:

- rescaled mutation parameter:

$$\theta = 4N_e \cdot u$$



Coalescent Theory
Beyond the Standard Neutral Model

Sex dependance of offspring variance:

Consider: apes in zoo, 20♀, 20♂, but only one ♂ breeds $N_e = ?$

In general: breeding females and males: N_f, N_m

$$p_c = \underbrace{\frac{1}{4}}_{\text{both from ♀}}\underbrace{\frac{1}{2N_f}}_{\text{both from same gene in ♀}} + \frac{1}{4}\frac{1}{2N_m} = \frac{1}{8}\left(\frac{1}{N_f} + \frac{1}{N_m}\right) \overset{\text{def}}{=} \frac{1}{2N_e}$$

$$\boxed{\Longrightarrow \; N_e = \frac{4N_f N_m}{N_f + N_m} \le N_f + N_m}$$

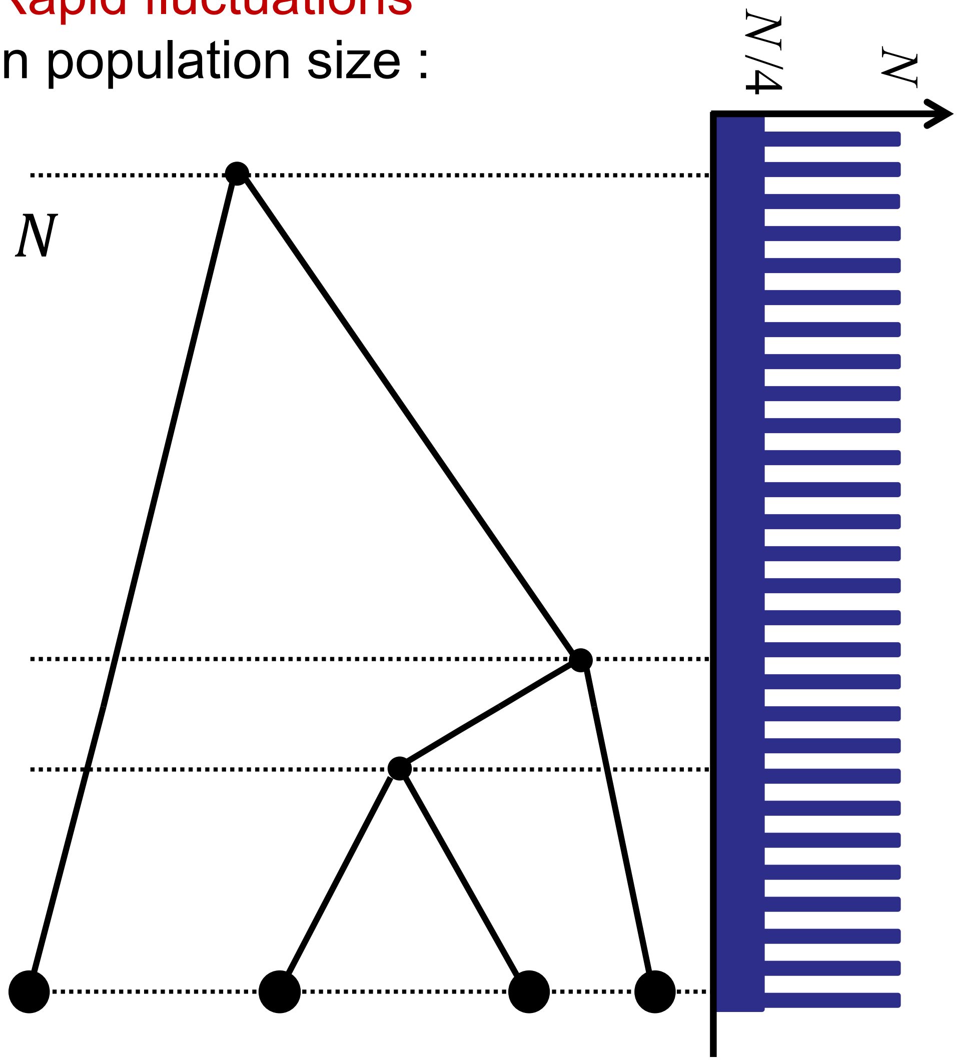
E.g., apes in zoo:

$$N_e = \frac{4 \cdot 20 \cdot 1}{20 + 1} \approx 3.8$$

Coalescent Theory

Beyond the Standard Neutral Model

Rapid fluctuations
in population size :



$$\bar{p}_{c,1} \approx \frac{1}{2}\left(\frac{1}{2N} + \frac{1}{2N/4}\right)$$

$$\Rightarrow N_e = \frac{1}{2\bar{p}_{c,1}} = \frac{2}{5}N$$

in general for period T :

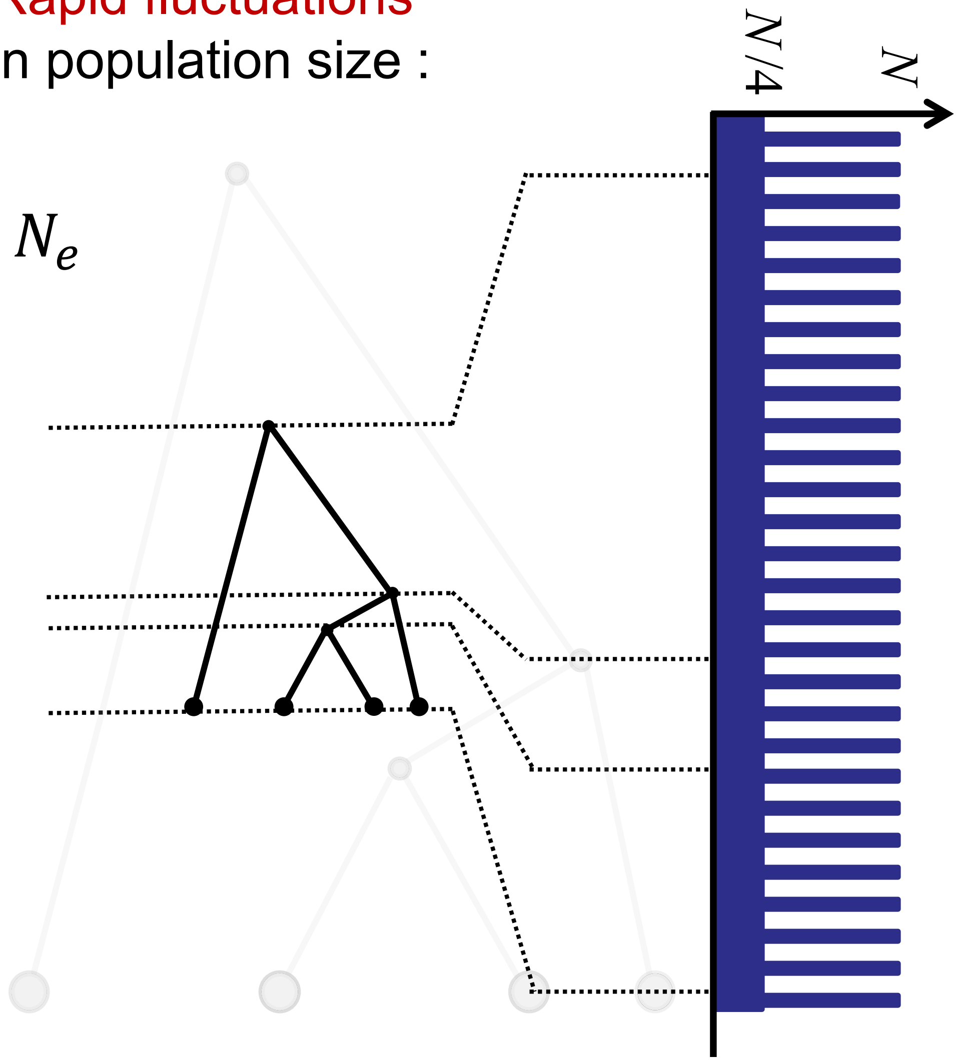
$$N_e = \left(\frac{1}{T}\sum_{i=1}^{T}\frac{1}{N_i}\right)^{-1}$$

harmonic mean population size

Coalescent Theory

Beyond the Standard Neutral Model

Rapid fluctuations
in population size :



$$\bar{p}_{c,1} \approx \frac{1}{2}\left(\frac{1}{2N}+\frac{1}{2N/4}\right)$$

$$\Rightarrow N_e = \frac{1}{2\bar{p}_{c,1}} = \frac{2}{5}N$$

in general for period T :

$$N_e = \left(\frac{1}{T}\sum_{i=1}^{T}\frac{1}{N_i}\right)^{-1}$$

harmonic mean population size

Coalescent Theory
Beyond the Standard Neutral Model

- Genetic differences have no consequences on fitness
- No population subdivision

Exchangable offspring distribution, independent of any *state label* (genotype, location, age, …)

- ~~Constant population size~~ → Variable population size $N_e(t)$

➢ Time-dependent rescaling of coalescent branch-lengths

➢ distribution of topologies remains unchanged
(due to exchangable offspring distribution)

Coalescent Theory

Beyond the Standard Neutral Model

$$N_e = N_e(t)$$

- time-dependent coalescence rates

$$p_{c,1}(t) = \frac{1}{2N_e(t)}$$

- can be accounted for by time-dependent rescaling of coalescent times and branch lengths

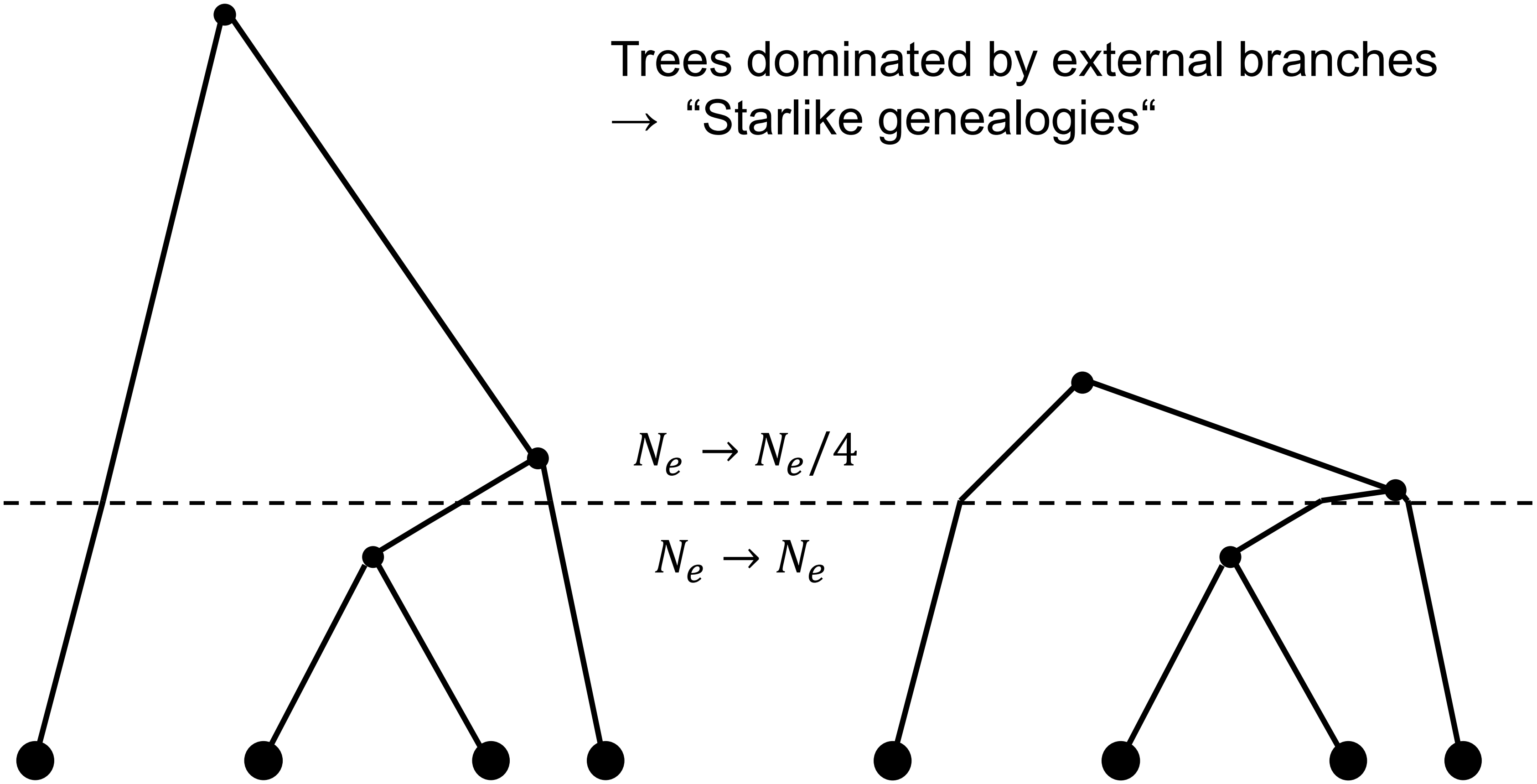
  … while the distribution of topologies remains unchanged (due to exchangable offspring distribution)

Coalescent Theory

Beyond the Standard Neutral Model

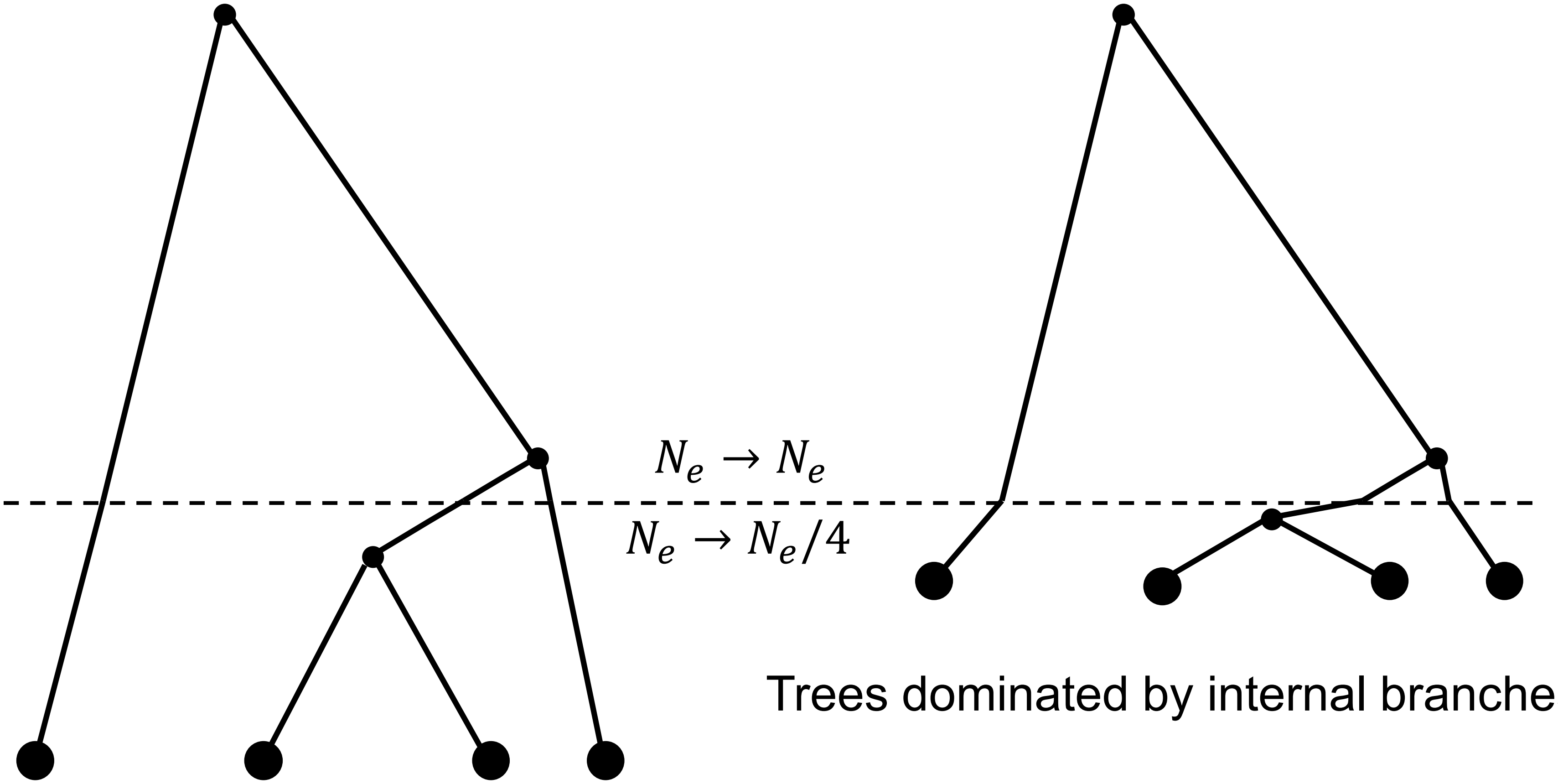
Growing populations (shrinking backward in time) :

Trees dominated by external branches
→ “Starlike genealogies“



Coalescent Theory
Beyond the Standard Neutral Model

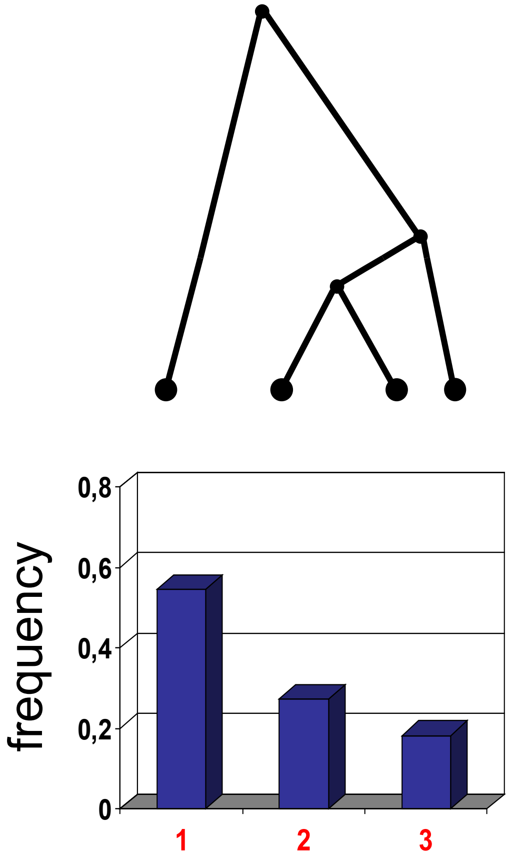
Shrinking populations (growing backward in time) :



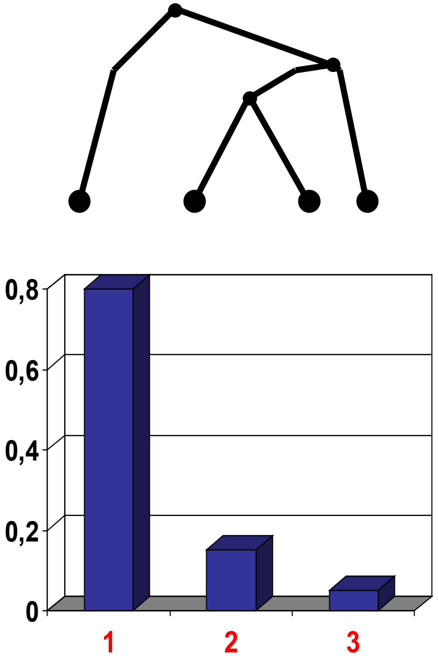
Trees dominated by internal branches

Coalescent Theory
Beyond the Standard Neutral Model

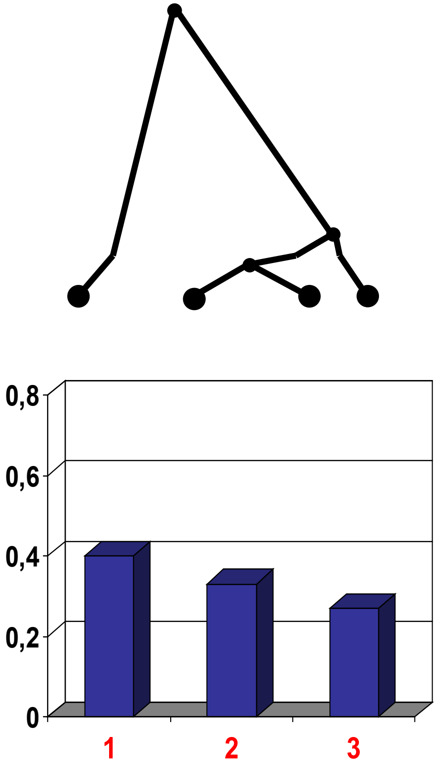
Expected frequency spectrum for growing/shrinking populations :



standard neutral



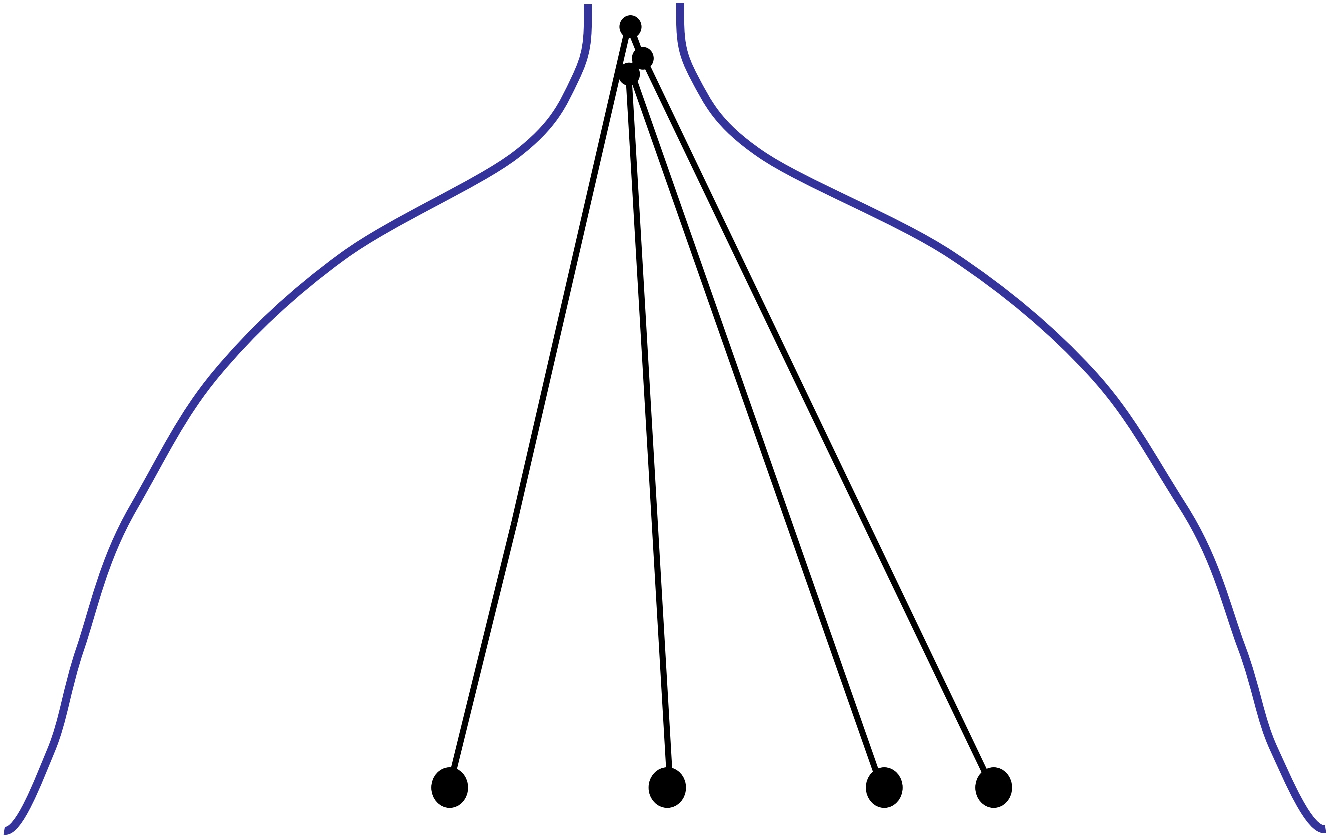
growth: excess of low frequency polymorphism



decrease: reduced low frequency polymorphism

Coalescent Theory
Beyond the Standard Neutral Model

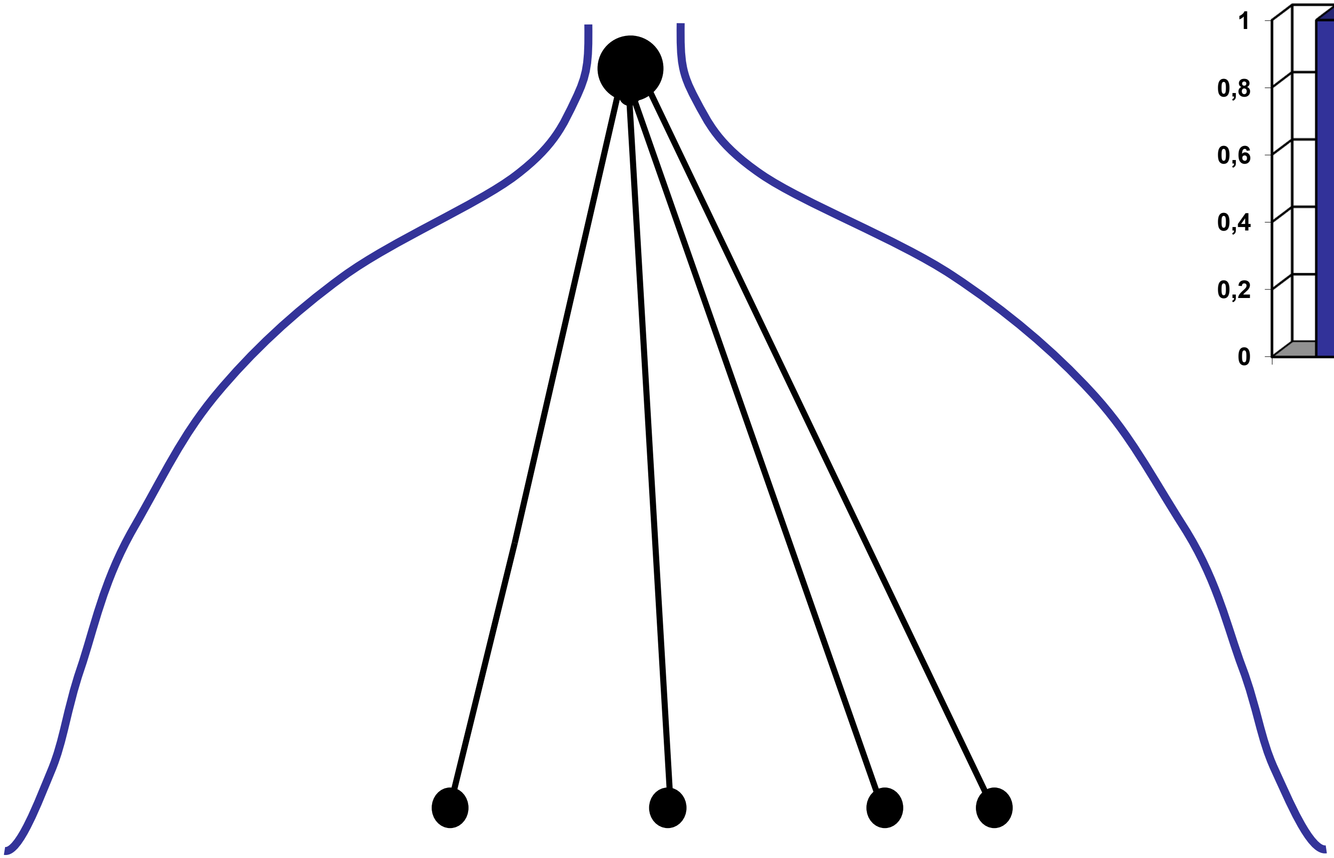
(Very) strong population growth: Starlike genealogy

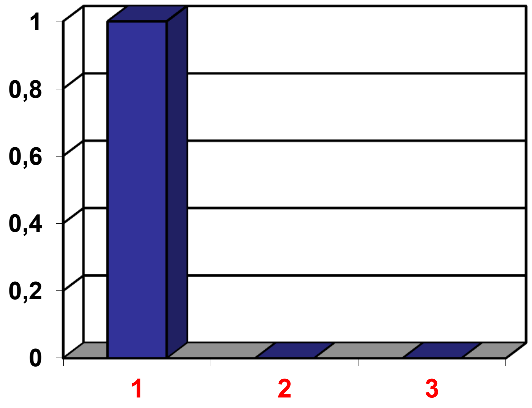


Coalescent Theory

Beyond the Standard Neutral Model

(Very) strong population growth: Starlike genealogy

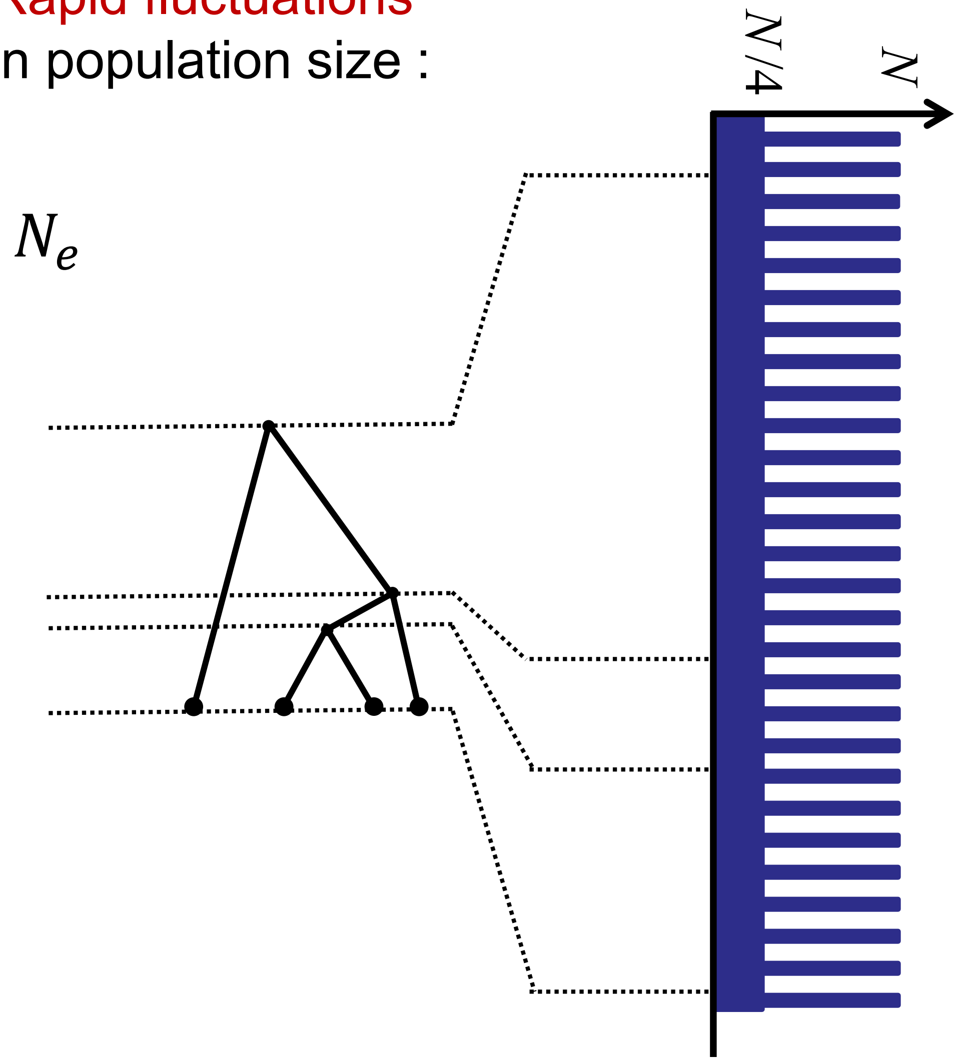




Coalescent Theory

Beyond the Standard Neutral Model

Rapid fluctuations
in population size :



$$\bar{p}_{c,1} \approx \frac{1}{2}\left(\frac{1}{2N}+\frac{1}{2N/4}\right)$$

$$\Rightarrow N_e = \frac{1}{2\bar{p}_{c,1}} = \frac{2}{5}N$$

in general for period T :

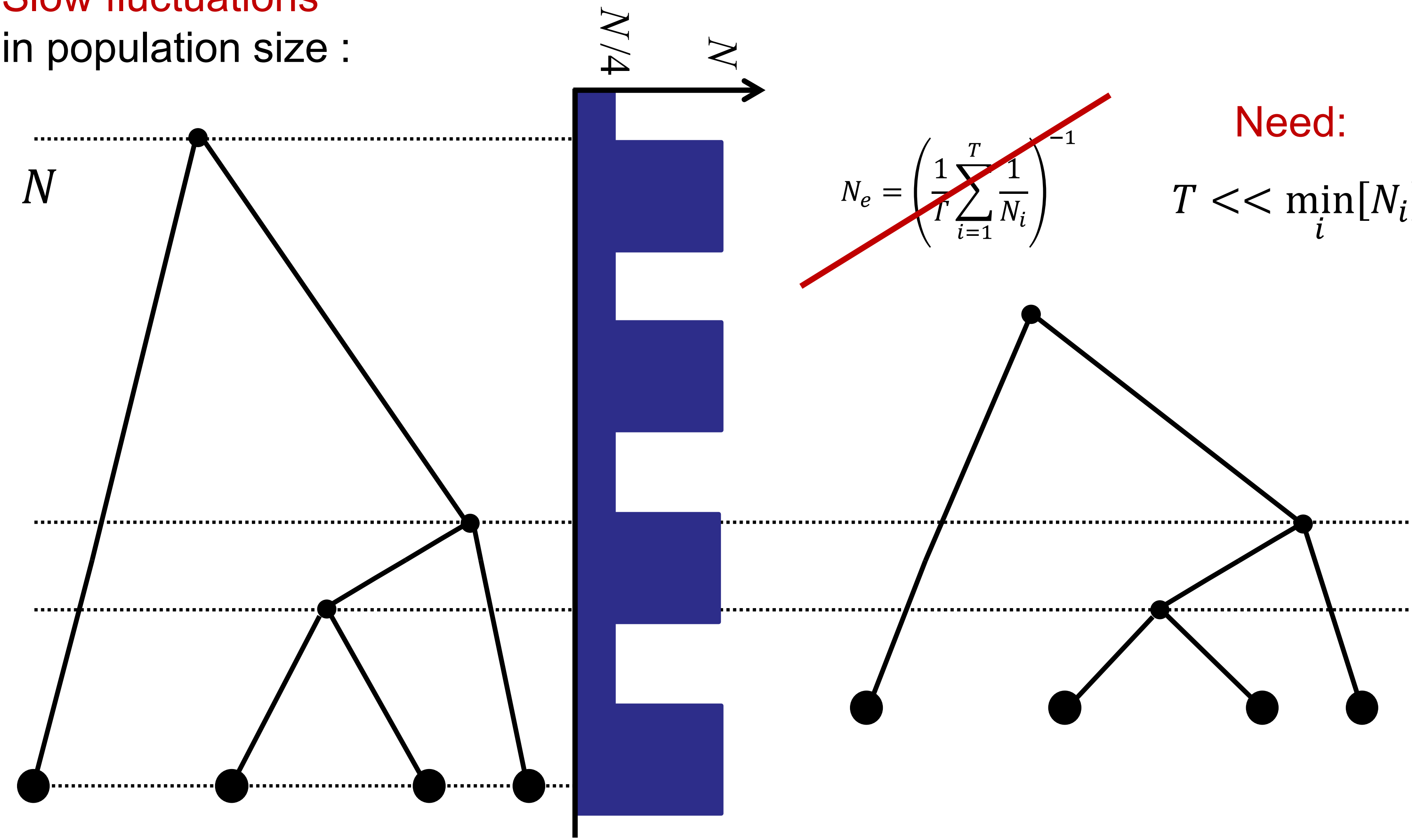
$$N_e = \left(\frac{1}{T}\sum_{i=1}^{T}\frac{1}{N_i}\right)^{-1}$$

harmonic mean population size

Coalescent Theory

Beyond the Standard Neutral Model

Slow fluctuations
in population size :



$$\cancel{N_e = \left(\frac{1}{T}\sum_{i=1}^{T}\frac{1}{N_i}\right)^{-1}}$$

Need:

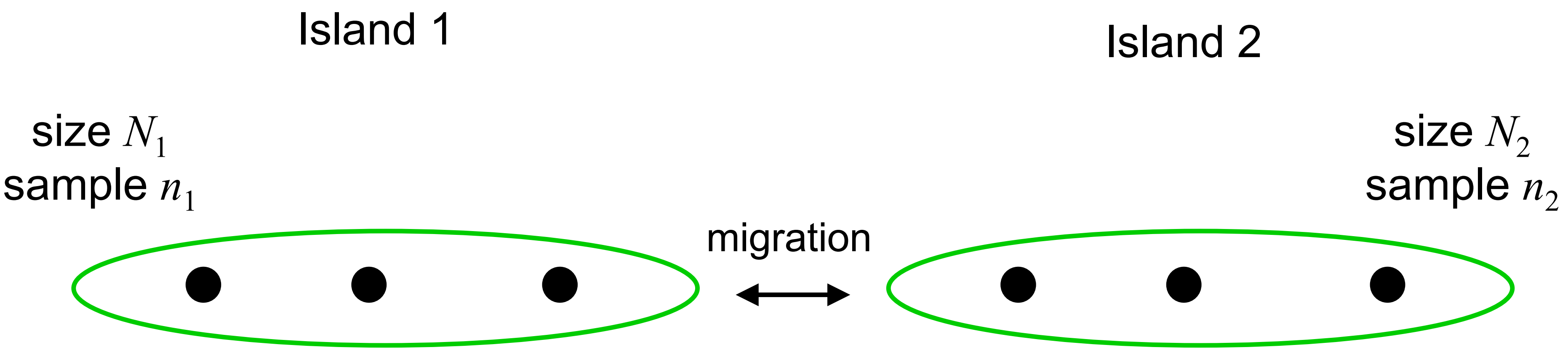
$$T << \min_i [N_i]$$

Coalescent Theory
Beyond the Standard Neutral Model

- Genetic differences have no consequences on fitness
- ~~No population subdivision~~

~~Exchangable offspring distribution, independent of any *state label* (genotype, location, age, …)~~

Structured population: e.g. two islands



Island 1

size N_1
sample n_1

migration

Island 2

size N_2
sample n_2

Coalescent Theory

Beyond the Standard Neutral Model

The structured coalescent: *two types of events*

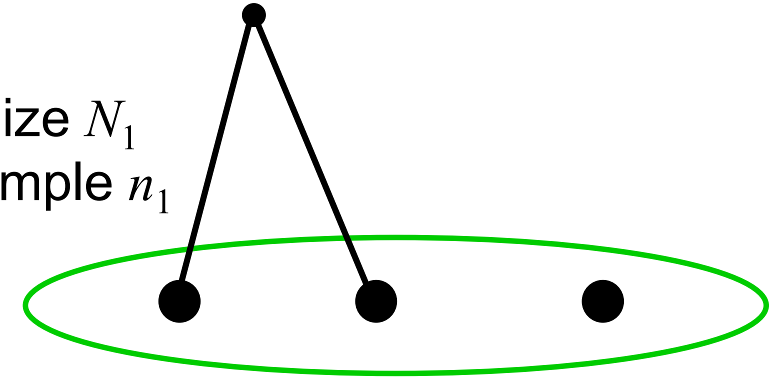
coalescence on
island 1

$$p_{c,1}^{(1)} = \binom{n_1}{2}\frac{1}{2N_1}$$

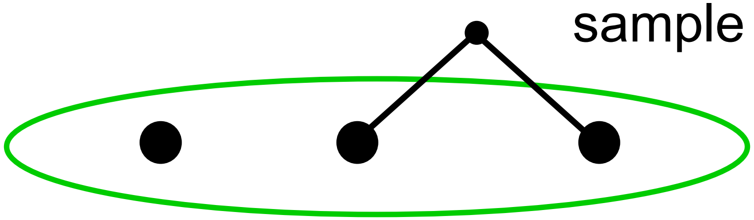
coalescence on
island 2

$$p_{c,1}^{(2)} = \binom{n_2}{2}\frac{1}{2N_2}$$

size N_1
sample n_1



size N_2
sample n_2



Coalescent Theory
Beyond the Standard Neutral Model

The structured coalescent: *two types of events*

forward migration

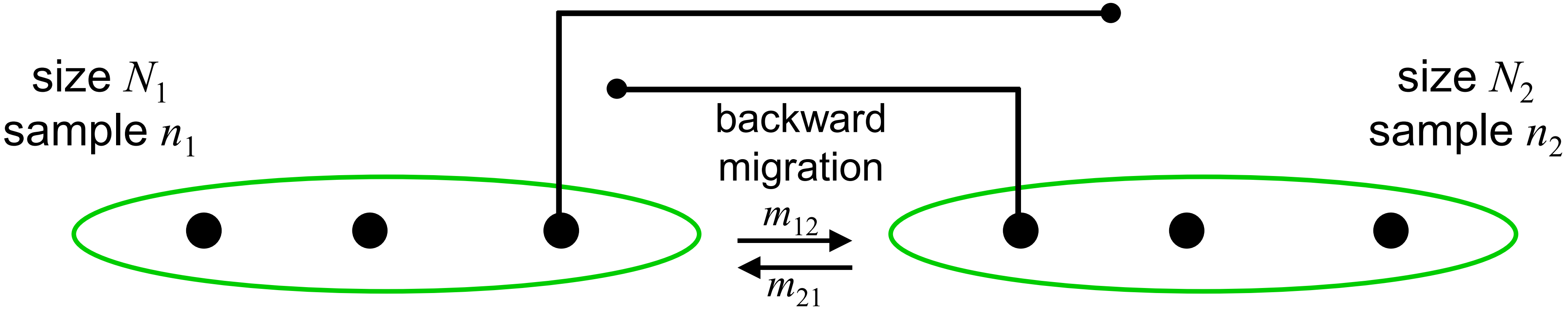
$$\overset{\mu_{12}}{\underset{\mu_{21}}{\rightleftarrows}}$$

backward migration

m_{ij}: *proportion of indiv. in deme i that are new migrants from deme j*

$$m_{12} = \frac{N_2\mu_{21}}{N_2\mu_{21} + N_1(1-\mu_{12})}$$

$$m_{21} = \frac{N_1\mu_{12}}{N_1\mu_{12} + N_2(1-\mu_{21})}$$



size N_1
sample n_1

backward migration

$$\overset{m_{12}}{\underset{m_{21}}{\rightleftarrows}}$$

size N_2
sample n_2

Coalescent Theory

Beyond the Standard Neutral Model

The structured coalescent: *two types of events*

coalescence on
island 1

$$p_{c,1}^{(1)} = \binom{n_1}{2}\frac{1}{2N_1}$$

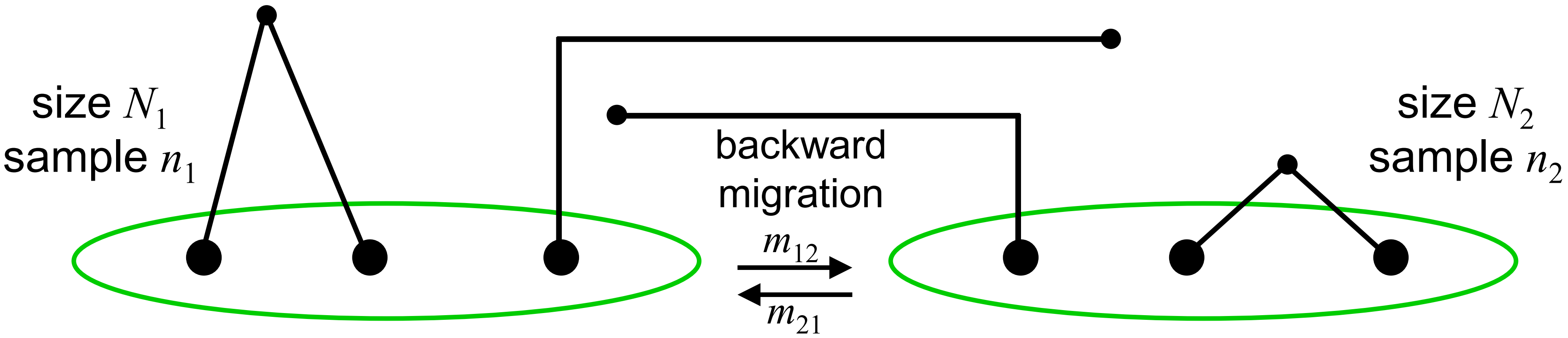
migration
island 1 ↔ island 2

$$p_{m,1}^{(1\rightarrow 2)} = n_1 \cdot m_{12}$$

$$p_{m,1}^{(2\rightarrow 1)} = n_2 \cdot m_{21}$$

coalescence on
island 2

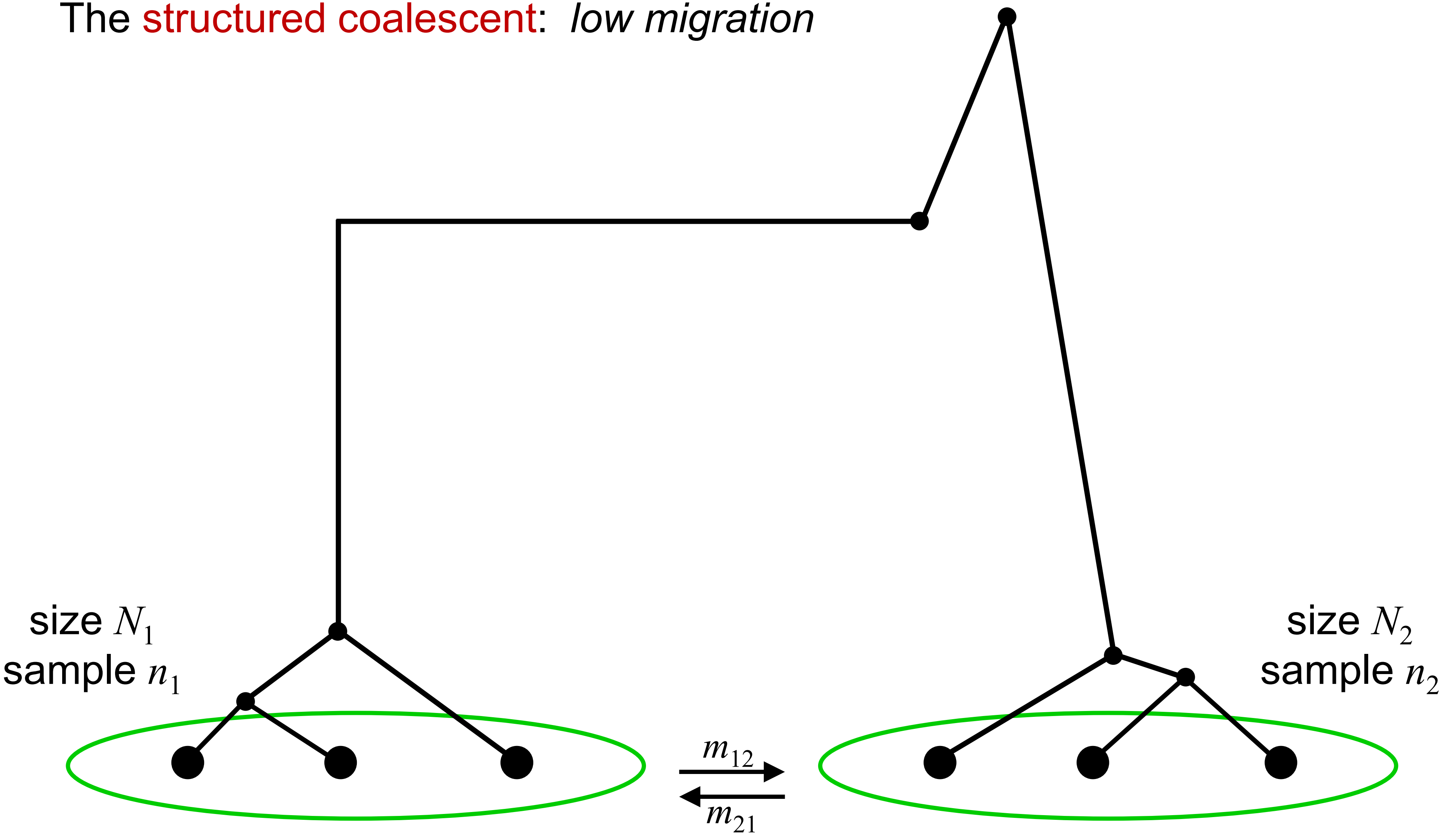
$$p_{c,1}^{(2)} = \binom{n_2}{2}\frac{1}{2N_2}$$



Coalescent Theory

Beyond the Standard Neutral Model

The structured coalescent: *low migration*

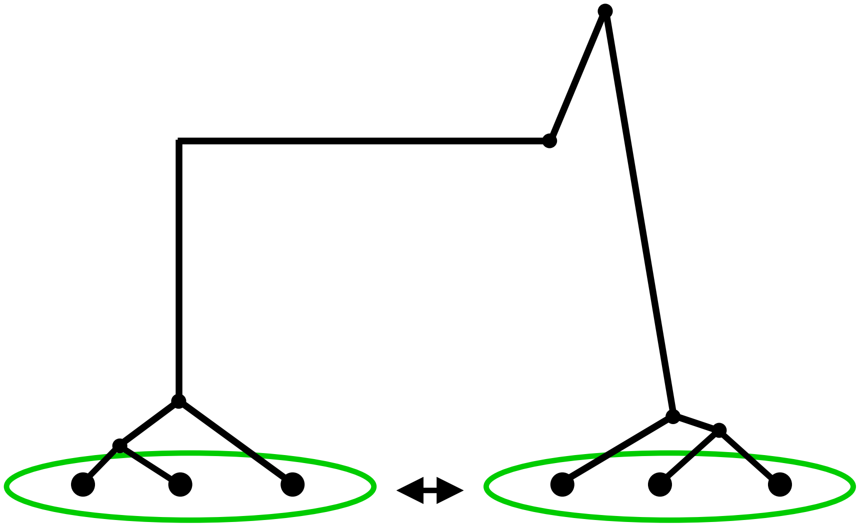


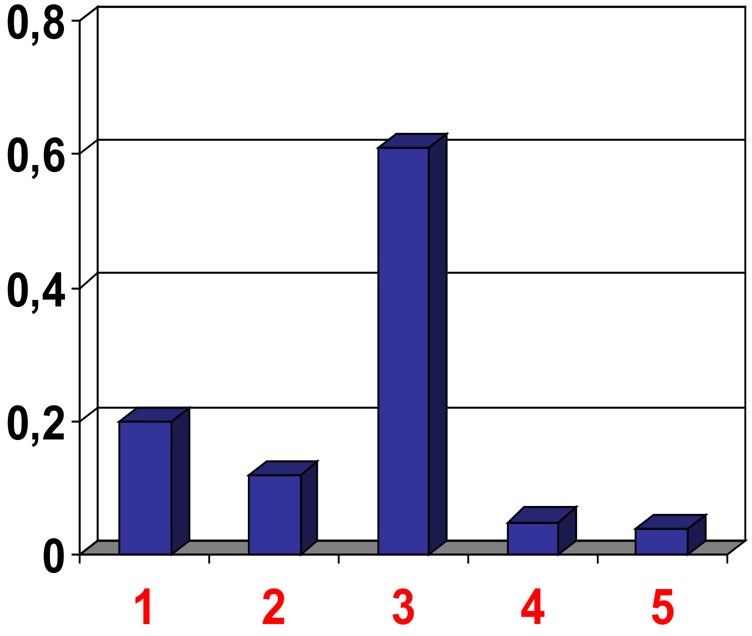
Coalescent Theory

Beyond the Standard Neutral Model

The structured coalescent: *low migration*

- the expected frequency spectrum



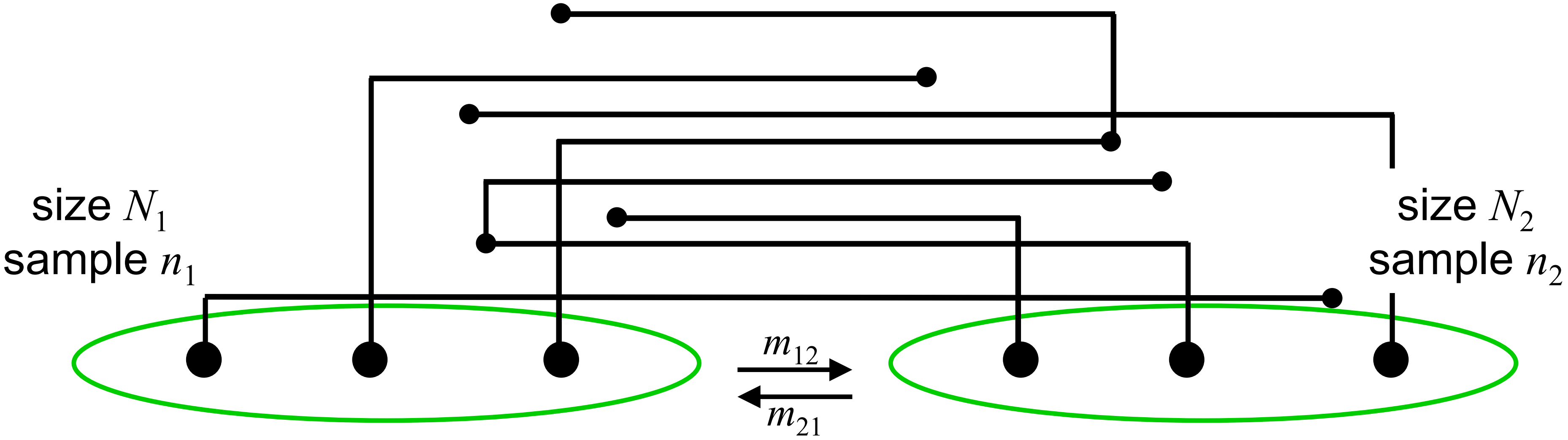


Coalescent Theory
Beyond the Standard Neutral Model

The structured coalescent: *strong migration* $m_{ij}N_i >> 1$

- First step: coalescent reaches migration equilibrium

$$p_1 = \frac{m_{21}}{m_{12} + m_{21}} \qquad p_2 = \frac{m_{12}}{m_{12} + m_{21}}$$

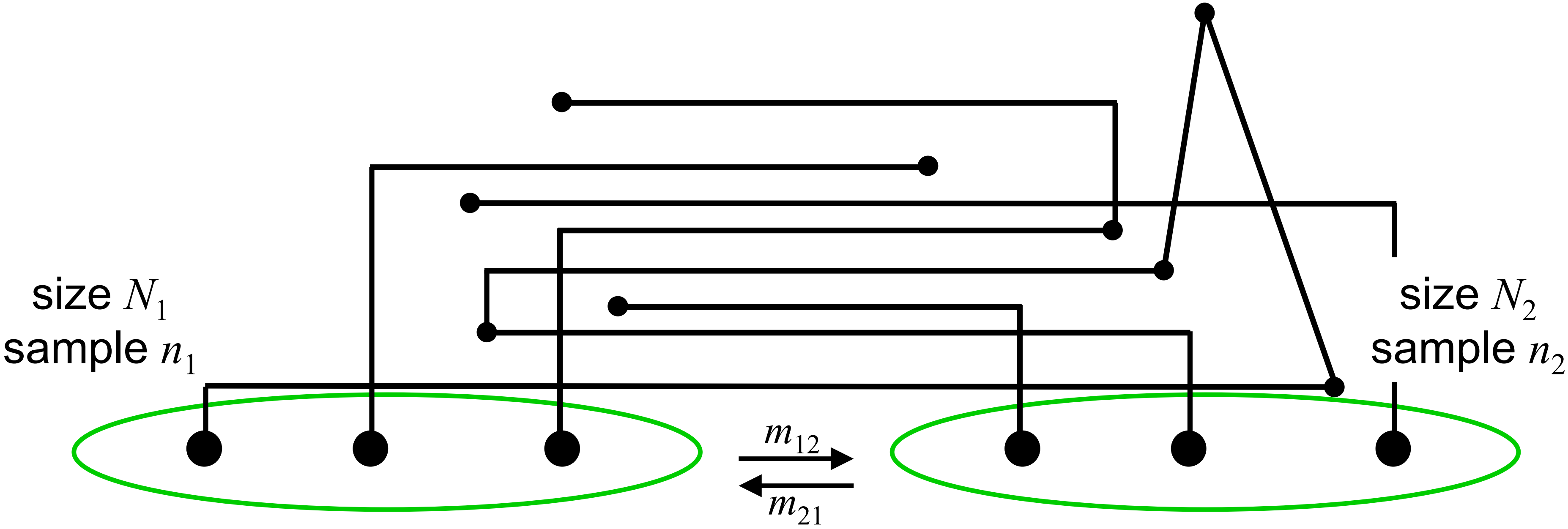


Coalescent Theory
Beyond the Standard Neutral Model

The structured coalescent: *strong migration* $m_{ij} N_i >> 1$

- Second step: coalescence probability in equilibrium

$$p_{c,1} = \binom{n}{2} \left(\frac{p_1^2}{2N_1} + \frac{p_2^2}{2N_2} \right)$$



Coalescent Theory
Beyond the Standard Neutral Model

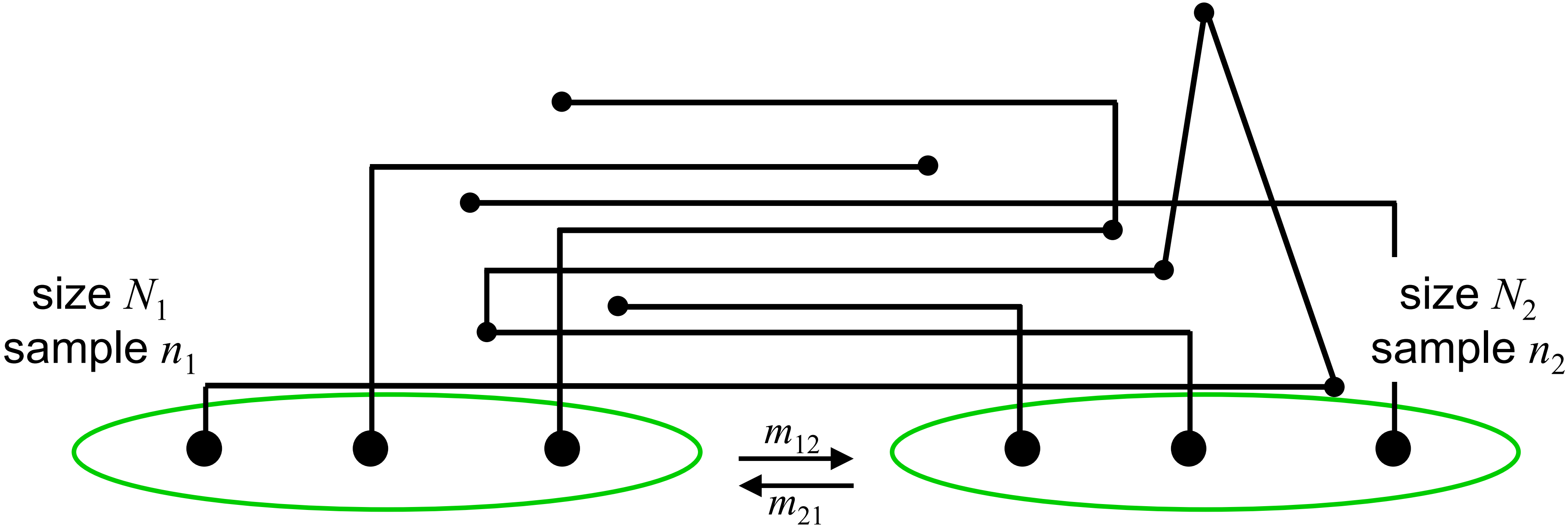
The structured coalescent: *strong migration* $m_{ij} N_i >> 1$

- In general: effective population size

$$p_{c,1} = \binom{n}{2} \cdot \sum_i \frac{p_i^2}{2N_i} \equiv \binom{n}{2} \cdot \frac{1}{2N_e}$$

(for $p_i = N_i / N$:

$$N_e = \sum_i N_i = N \text{)}$$

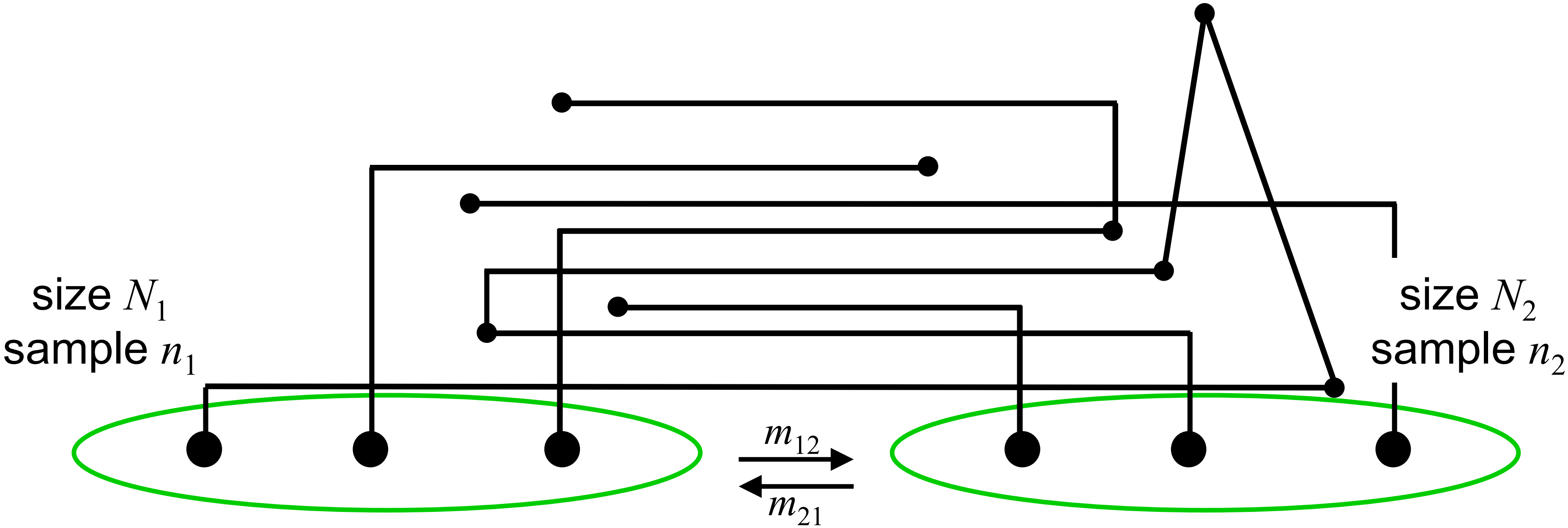


Coalescent Theory

Beyond the Standard Neutral Model

The structured coalescent: *strong migration* $m_{ij}N_i >> 1$

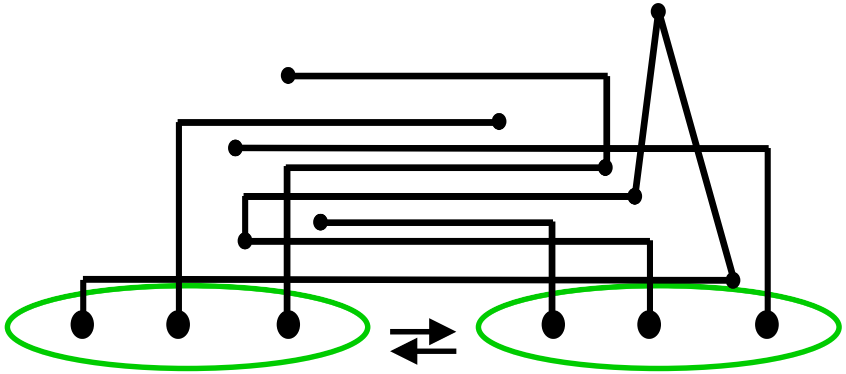
- Other kinds of structure:
  - diploid individuals (individuals = islands)
  - separate sexes (male and female "island")
  - age structure, etc.

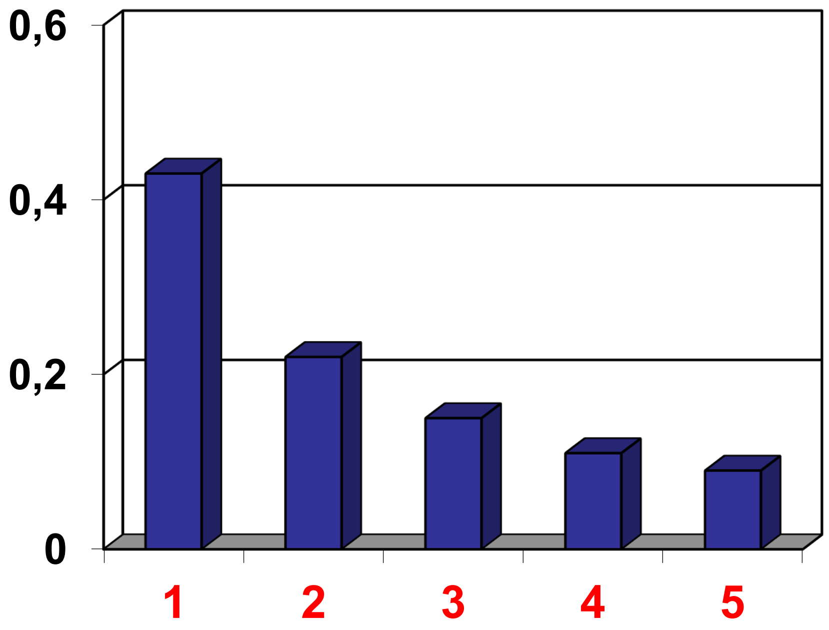


Coalescent Theory
Beyond the Standard Neutral Model

The structured coalescent: *strong migration* $m_{ij}N_i >> 1$

- The expected frequency spectrum





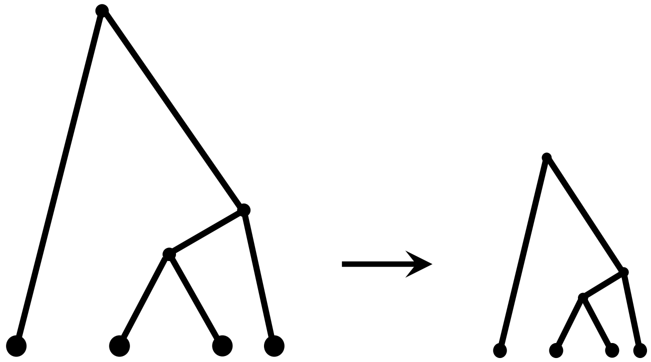
➢ Standard neutral spectrum (with effective population size)

Coalescent Theory

Robustness of the Coalescent

Many biological details only lead to a rescaling of coalescence trees (changed effective population size):

- non Poisson variance in offspring number
- diploids and separate sexes
- weak structure with rapid migration
- short-term fluctuations in population size



All these processes occur on much shorter time scales than coalescence and can therefore be averaged out. We say the coalescent is robust with respect to these details. In contrast, coalescence trees are affected by:

- “large“ demographic changes
- strong population structure
- selection

Consequence:
Only these phenomena can be detected from polymorphism data !

Coalescent Theory
Estimators

Unbiased estimators of the mutation parameter $\theta = 4Nu$:

Watterson‘s estimator:

$$\hat{\theta}_W = \frac{S}{a_n} = \sum_{k=1}^{n-1} \xi_i \Big/ \sum_{k=1}^{n-1} \frac{1}{k}$$

(equal weights)

π-based estimator:

$$\hat{\theta}_\pi = \pi = \binom{n}{2}^{-1} \sum_{k=1}^{n-1} k(n-k)\ \xi_k$$

(intermediate frequencies)

Fay and Wu‘s estimator:

$$\hat{\theta}_H = \binom{n}{2}^{-1} \sum_{k=1}^{n-1} k^2\, \xi_k$$

(high frequencies)

singleton estimator:

$$\hat{\theta}_s = \frac{n-1}{n} \underbrace{(\xi_1 + \xi_{n-1})}_{\text{singletons of the folded spectrum}}$$

(extreme frequencies)

Coalescent Theory
Test statistics

Test statistics for the deviation from neutrality:

Tajima‘s D:

$$D_T = \frac{\hat{\theta}_\pi - \hat{\theta}_W}{\sqrt{\mathrm{Var}[\hat{\theta}_\pi - \hat{\theta}_W]}}$$

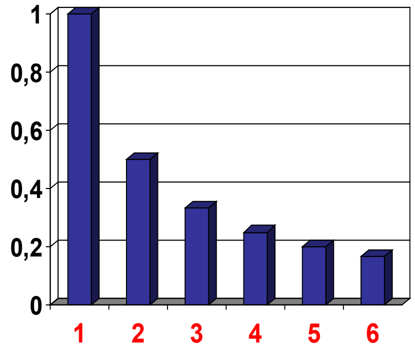
Fu and Li‘s D:

$$D_{FL} = \frac{\hat{\theta}_W - \hat{\theta}_S}{\sqrt{\mathrm{Var}[\hat{\theta}_W - \hat{\theta}_S]}}$$

Fay and Wu‘s H:

$$H_{FW} = \frac{\hat{\theta}_\pi - \hat{\theta}_H}{\sqrt{\mathrm{Var}[\hat{\theta}_\pi - \hat{\theta}_H]}}$$

standard neutral evolution:



$$D_T = D_{FL} = H_{FW} = 0$$

Coalescent Theory
Test statistics

Test statistics for the deviation from neutrality:

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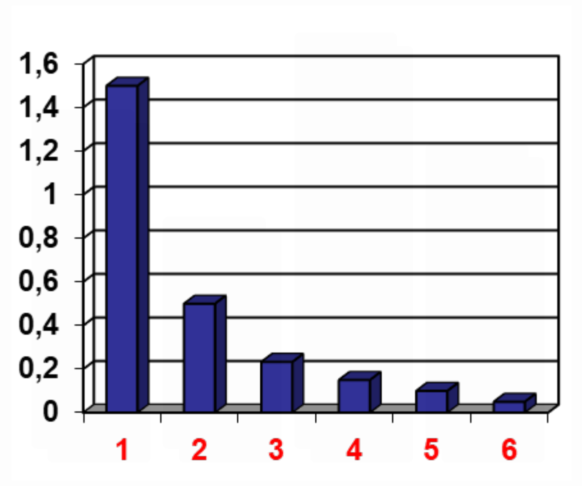
Fay and Wu‘s H:

$$H_{FW} = \frac{\hat{\theta}_\pi - \hat{\theta}_H}{\sqrt{\mathrm{Var}[\hat{\theta}_\pi - \hat{\theta}_H]}}$$

population growth:



$$D_T;\ D_{FL} < 0\ ;$$
$$H_{FW} > 0$$

Coalescent Theory
Test statistics

Test statistics for the deviation from neutrality:

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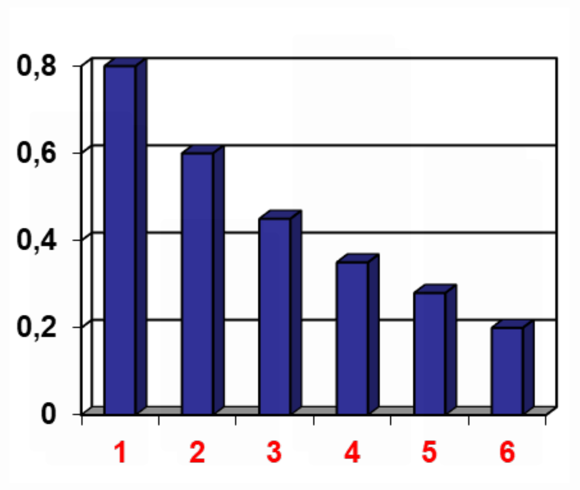
population decline:



$$D_T;\ D_{FL} > 0\ ;$$
$$H_{FW} < 0$$

Coalescent Theory
Test statistics

Test statistics for the deviation from neutrality:

Tajima‘s D:

$$D_T = \frac{\hat{\theta}_\pi - \hat{\theta}_W}{\sqrt{\mathrm{Var}[\hat{\theta}_\pi - \hat{\theta}_W]}}$$

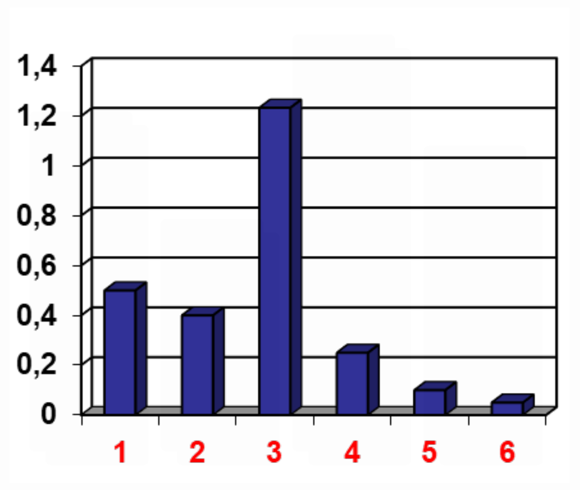
Fu and Li‘s D:

$$D_{FL} = \frac{\hat{\theta}_W - \hat{\theta}_S}{\sqrt{\mathrm{Var}[\hat{\theta}_W - \hat{\theta}_S]}}$$

Fay and Wu‘s H:

$$H_{FW} = \frac{\hat{\theta}_\pi - \hat{\theta}_H}{\sqrt{\mathrm{Var}[\hat{\theta}_\pi - \hat{\theta}_H]}}$$

population structure:



$$D_T;\ D_{FL} > 0\ ;$$
$$H_{FW} = \ ?$$