Demographic inference based on Site frequency spectrum (SFS) – Part I

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Outline

Part I

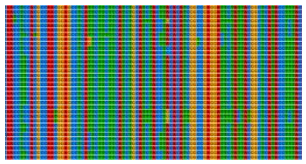
- Modeling demographic history: Population trees vs gene trees
- The SFS and coalescent trees
- Fastsimcoal2 principles – composite likelihood
- Approximate Bayesian Computation

Part II

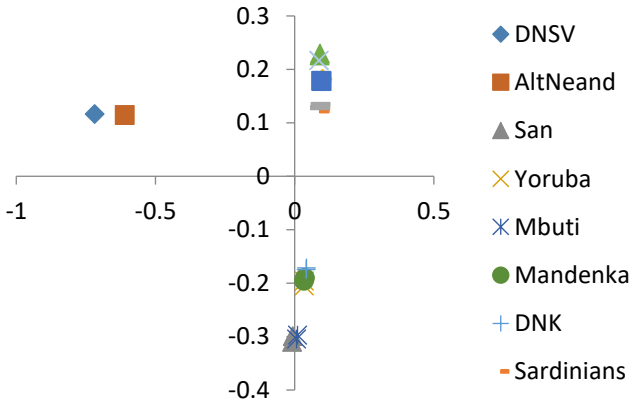
- Example of applications to different problems and types of data

What can we learn from population genomic data?

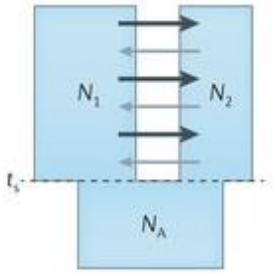
Genomic data



«Model-free» methods e.g. PCA



Model-based methods



Summary statistics:

- Characterize **genetic diversity** within and among populations

- Characterize **genetic differentiation** among populations

Evolutionary Processes:

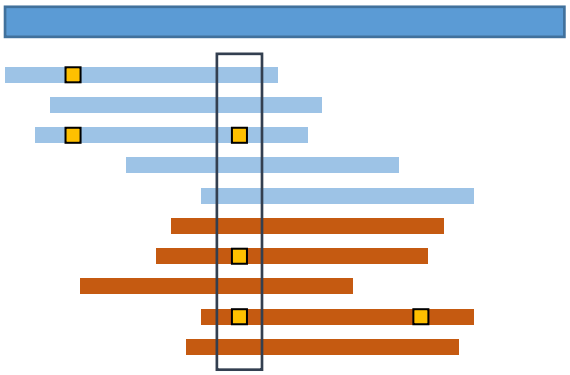
- Demography
- Selection
- Mutation
- Recombination

Patterns

Processes

Genomic data with Next Generation Sequencing

Mapping



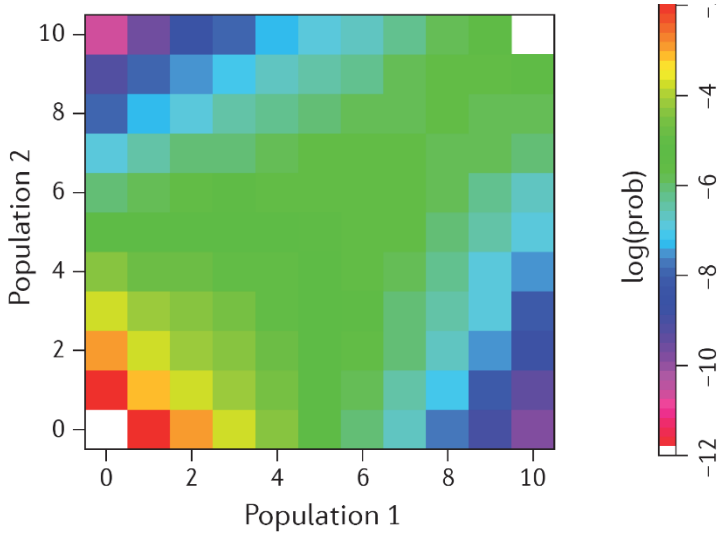
Genotypes

	SNP1	SNP2	SNP3	...	SNP *L*
Ind. 1	0	2	0	...	1
Ind. 2	0	0	1	...	2
Ind. 3	1	0	0	...	2
...	...	...	...	...	...
Ind. *n*	0	0	1	...	0

Information about:

- frequencies of variants
- linkage disequilibrium

Site-frequency spectrum (SFS)



Evolutionary forces affecting the history of populations

Demography

- Past effective population sizes
- Past migration rates

Genomic processes

- Mutation rate
- Recombination rate

Selection

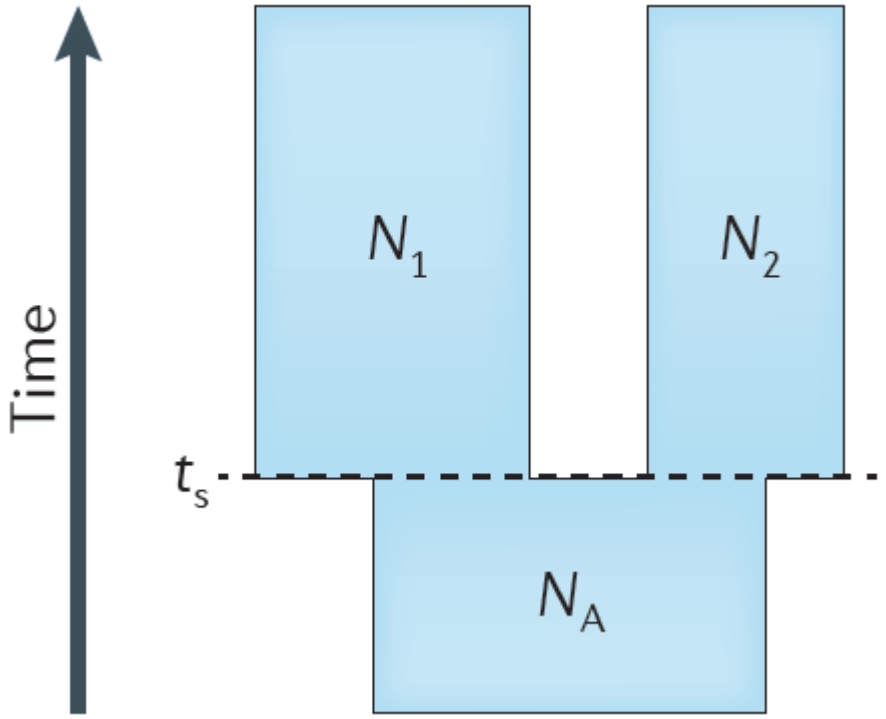
- Natural selection
  - Beneficial mutations involved in adaptation
  - Deleterious mutations with negative effect

Demographic history of populations

Past demographic events:

- Population split
- Migration events
- Changes in effective population sizes (expansions or bottlenecks)
- Temporal changes in migration rates and effective sizes

Population tree



Why do we care about demographic history?

Demography affects the efficiency of natural selection

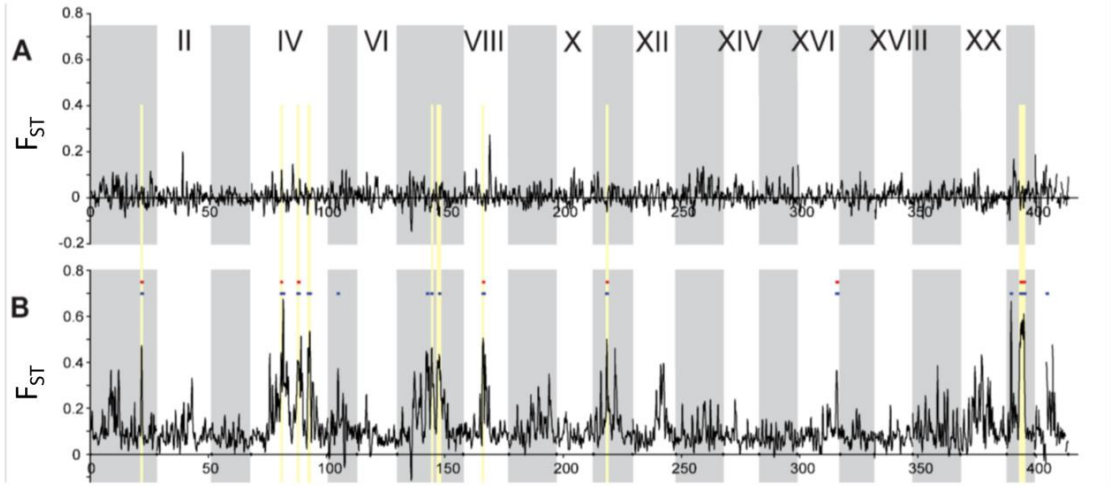
- Response to selection is different in small *vs* large populations, with *vs* without gene flow, etc.

Demographic history affects the genome-wide patterns

- It can be seen as a "null" model. Regions under selection are detected as outliers.

Between a pair of marine populations

Between marine and freshwater populations



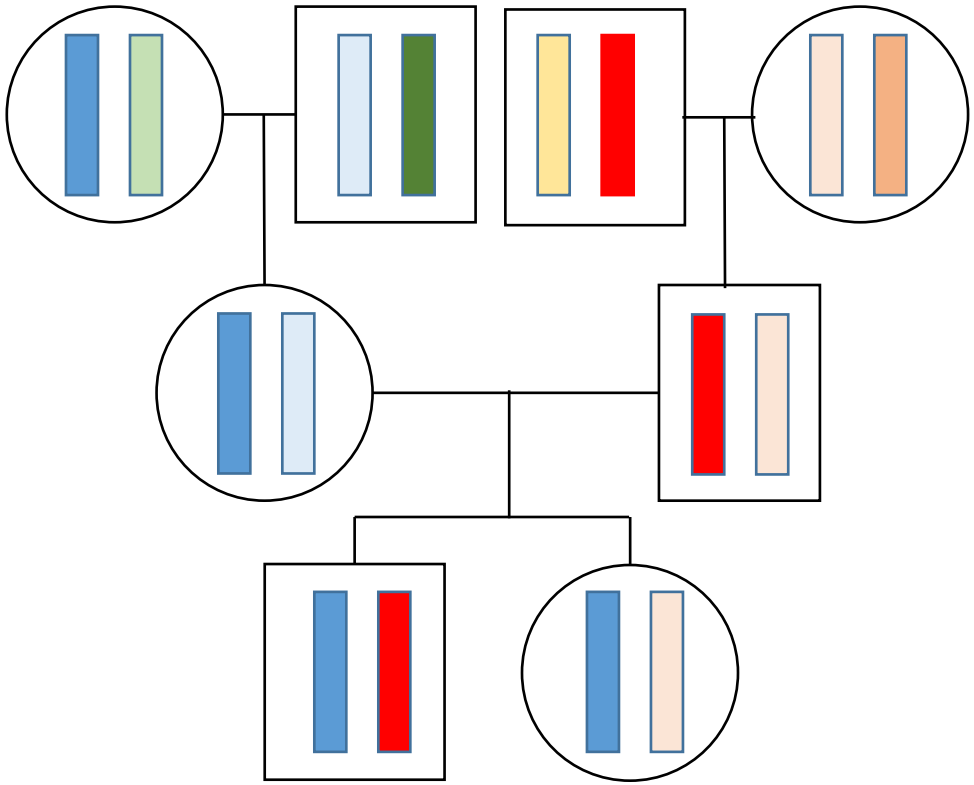
Chromosome position

Alternating white and grey indicate linkage groups (chromosomes)

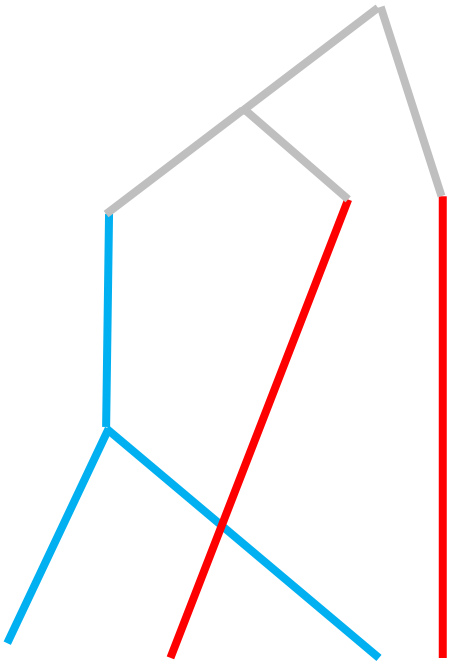
Hohenlohe et al (2010) Plos Genetics

Gene trees within pedigrees

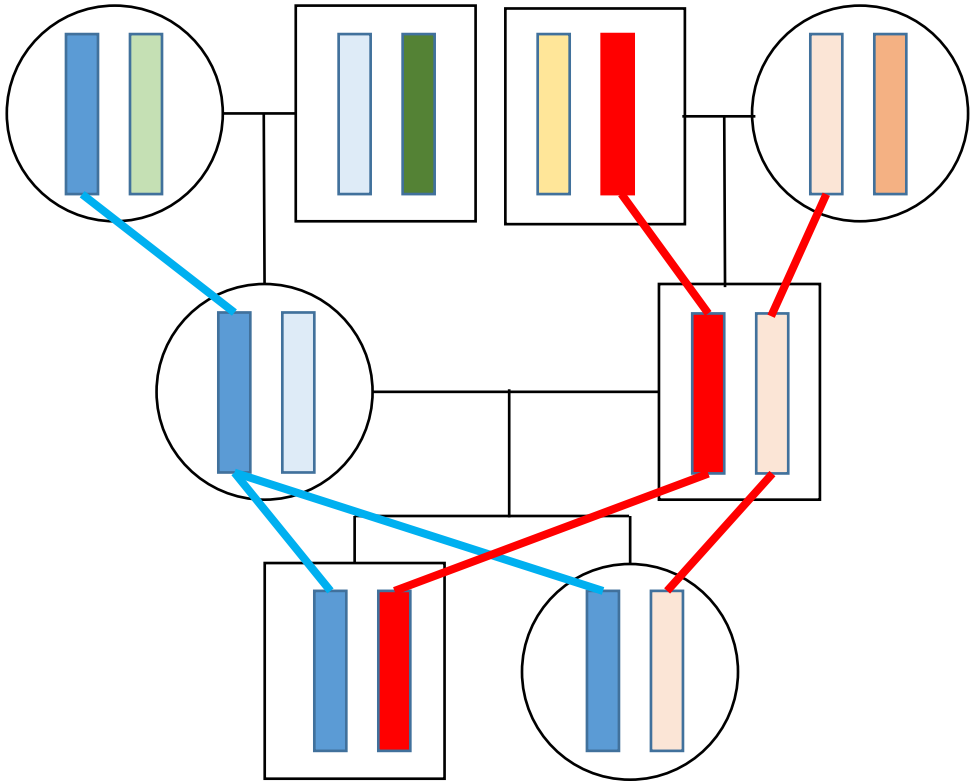
- **Gene trees** reflect the ancestral relationship of sampled gene copies
- For now, lets assume there is no mutations (**branch lengths do not reflect mutations in coalescent gene trees**!).
- Because of transmission of genes at each generation, at each position of the genome there is always a gene tree describing the relationship of gene copies in our sample.
- **All individuals share the same pedigree, but gene trees can vary due to independent segregation and recombination**



The same pedigree can lead to different gene trees across the genome

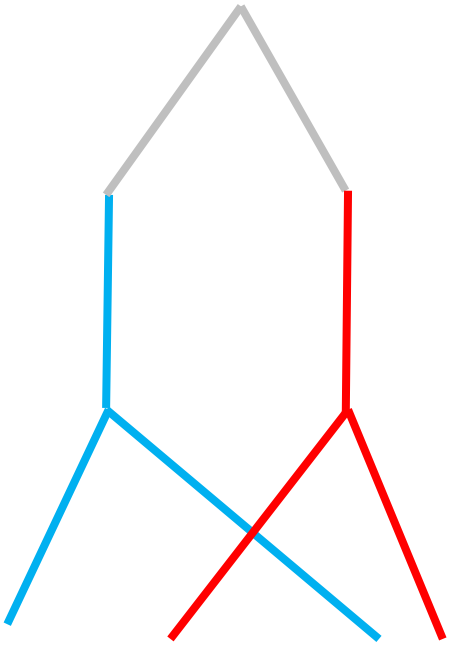


Gene tree of a sample of size n=4
(2 diploid individuals)



Chromosome 1

The same pedigree can lead to different gene trees across the genome



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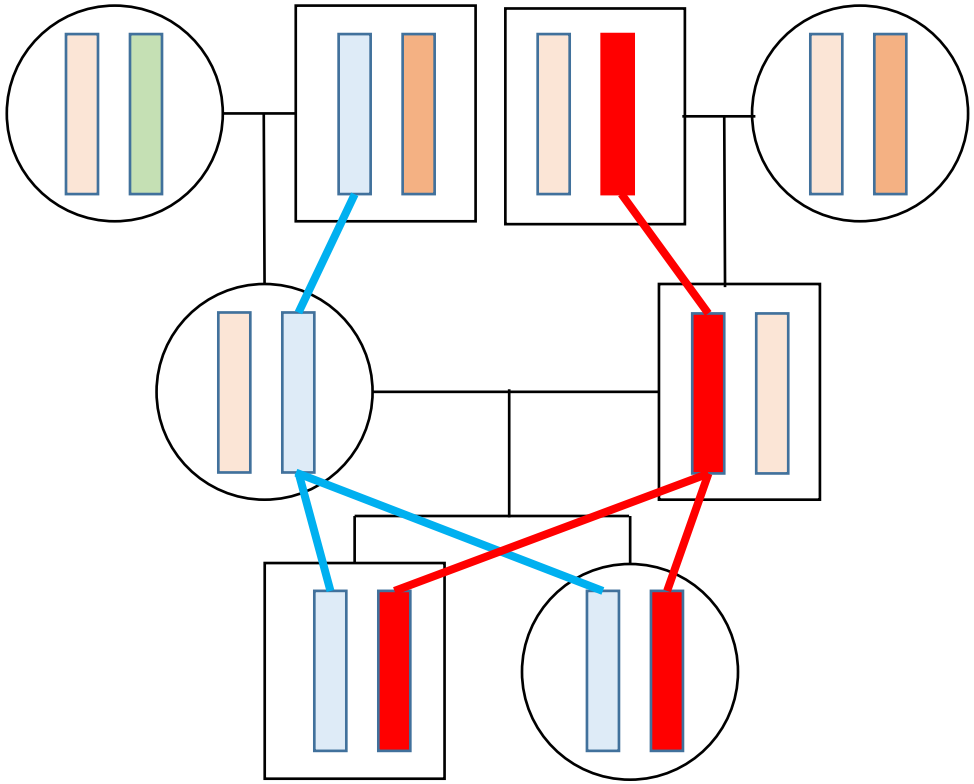
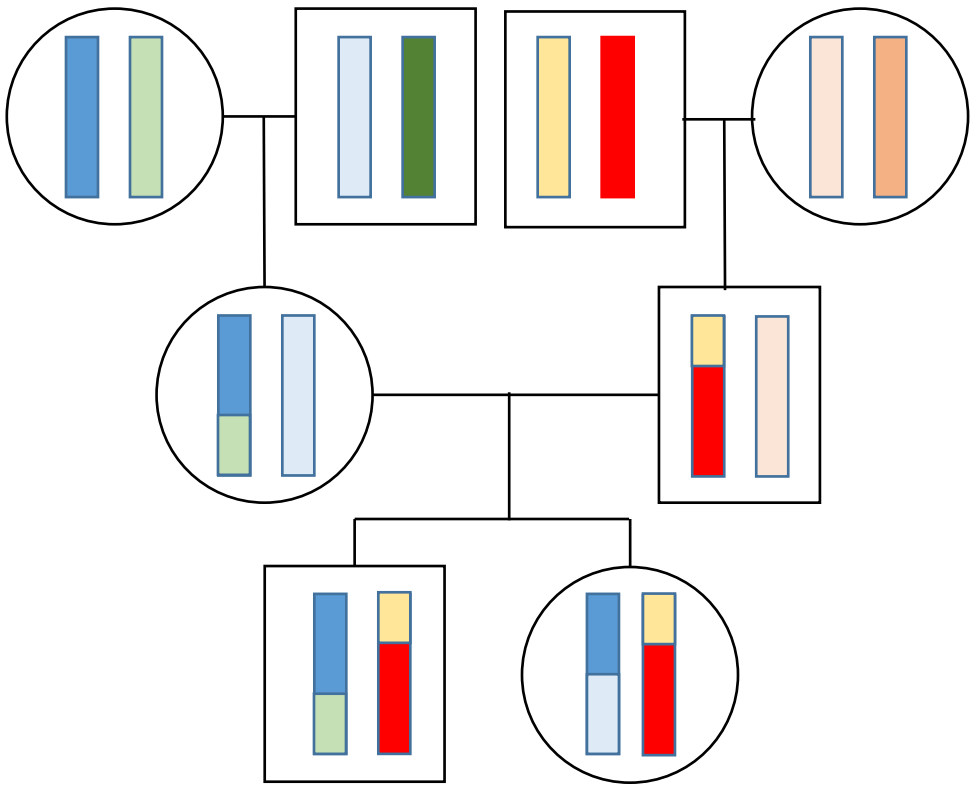


Chromosome 2

Gene trees and pedigrees

- Although we have the same pedigree, the gene trees at different loci will be different
- Ancestral chromosomes that did not contribute to our sample can be ignored
- With recombination, different regions of the chromosome will have different (correlated) gene trees



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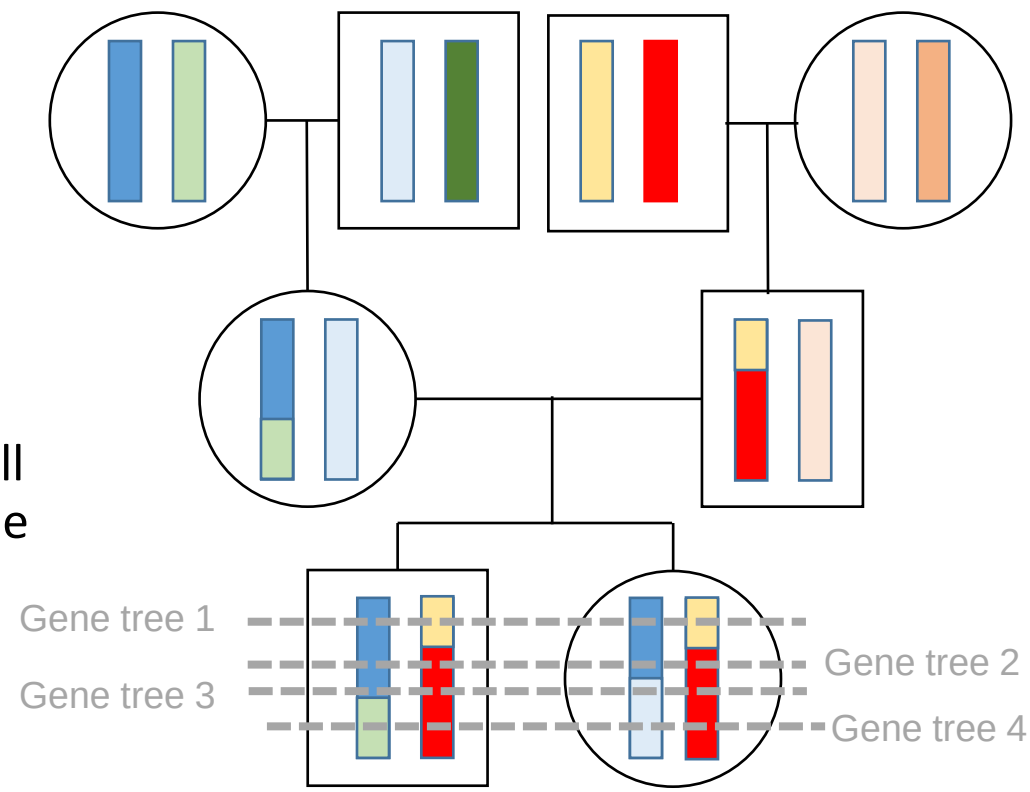


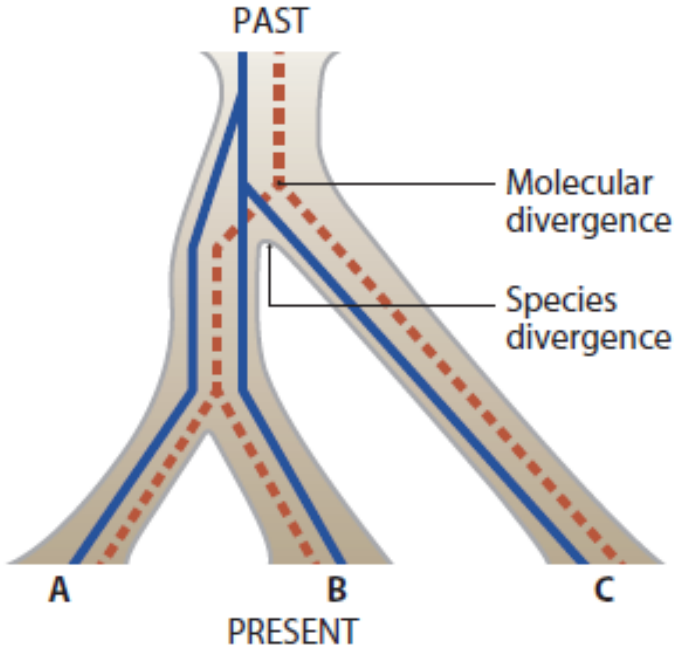
Gene trees vs. Population trees

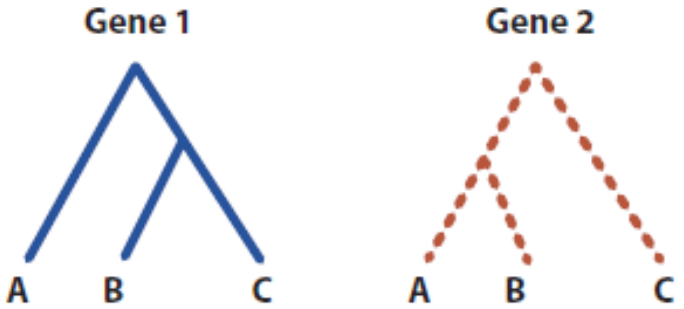
Gene trees reflect the ancestral relationship of sampled gene copies.

The relationship between populations is given by the **population tree**. As with pedigrees, the population tree reflects the relationship between populations that is shared by all individuals.

In phylogenetics it is usually assumed that the gene tree reflects the population/species tree.

However, in the time scale of population genetics, gene trees at a particular region of the genome (locus) can be very different from the population tree.



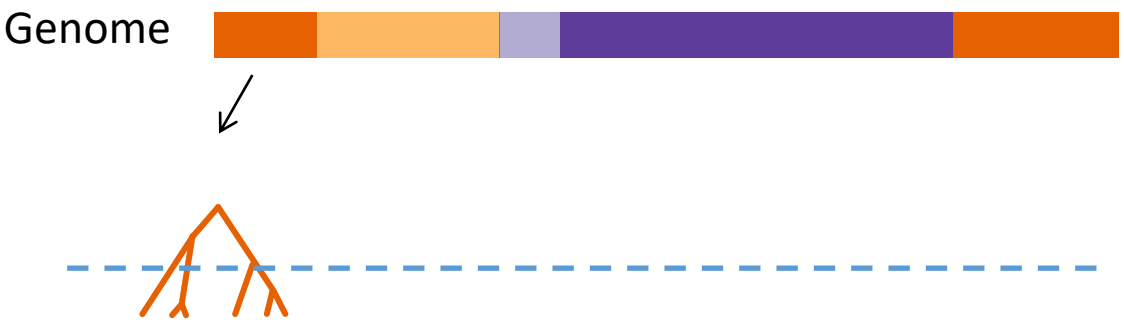


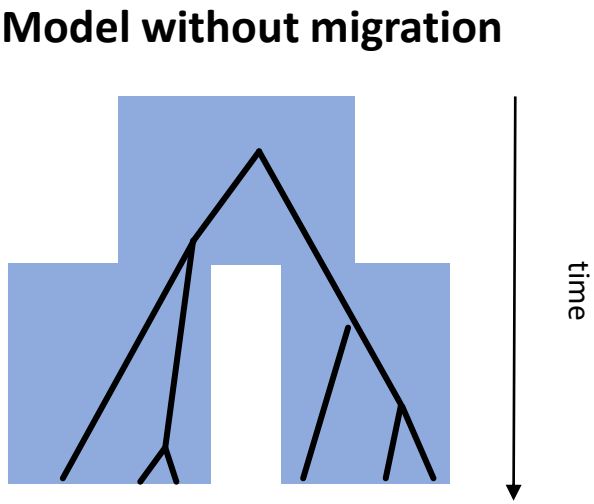
Nichols (2001) TREE

Jobling et al (2014) Human Evolutionary Genetics,2nd edition

Reconstructing the demographic history from genomic data

Because of recombination, different regions of the genome can have different gene trees





- Demography is expected to affect the entire genome
- Natural selection acts on specific functional regions

All gene trees are consistent with the population tree. Independent gene trees can be seen as independent replicates of the same population tree.

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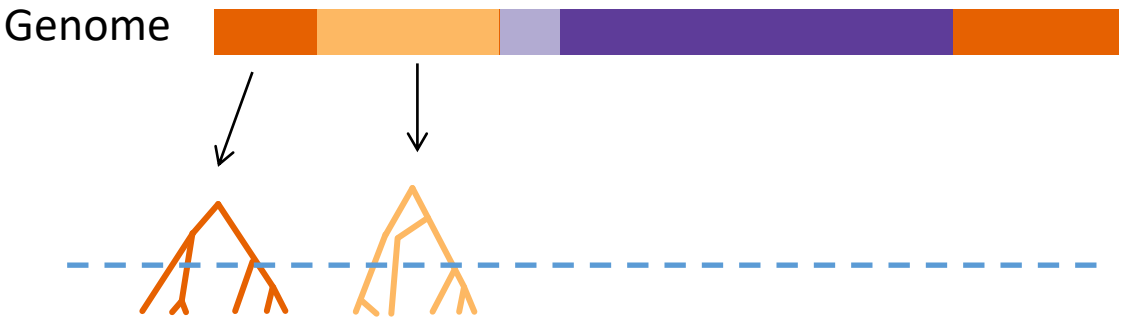

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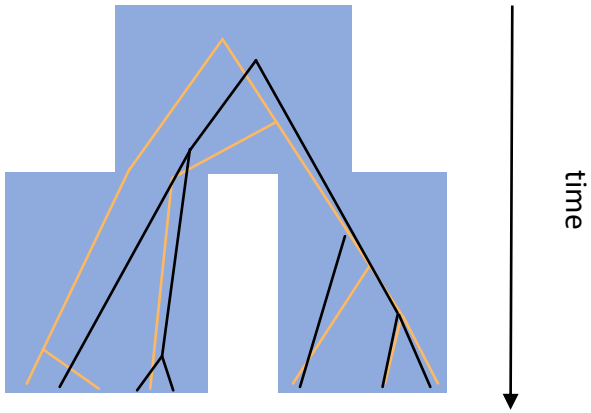
Model without migration



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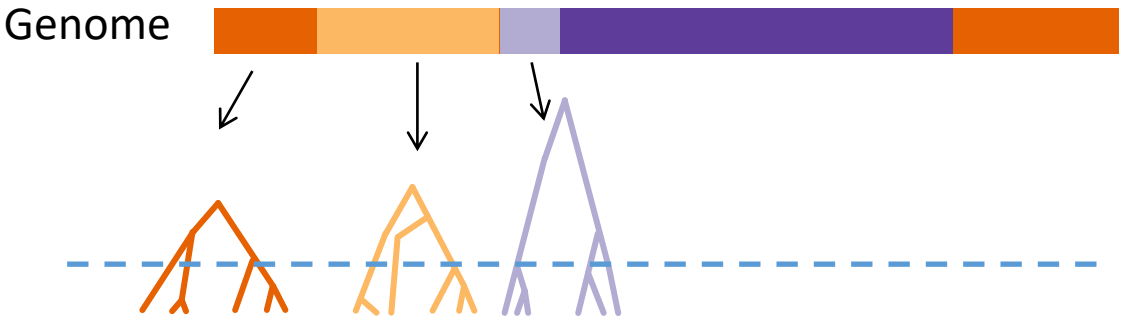

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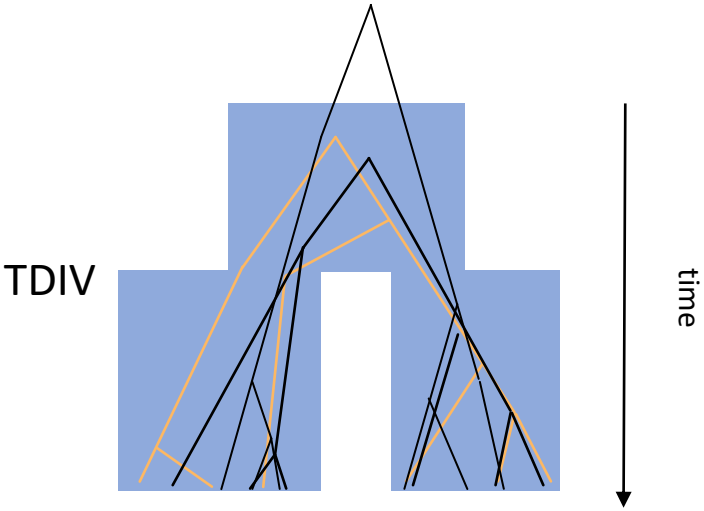

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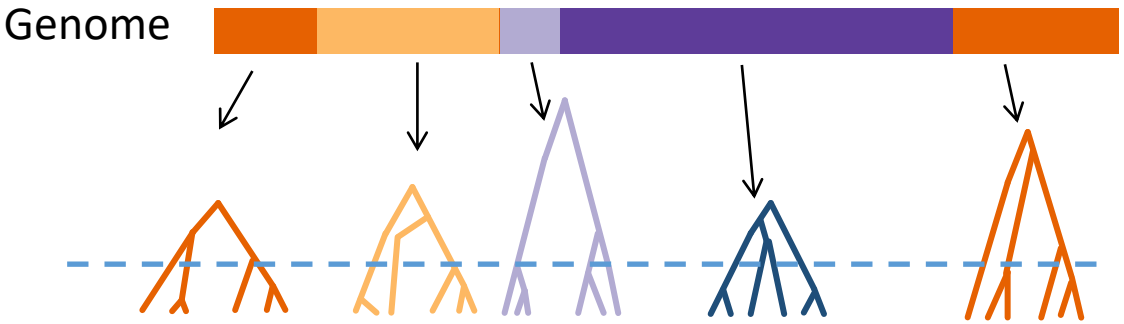

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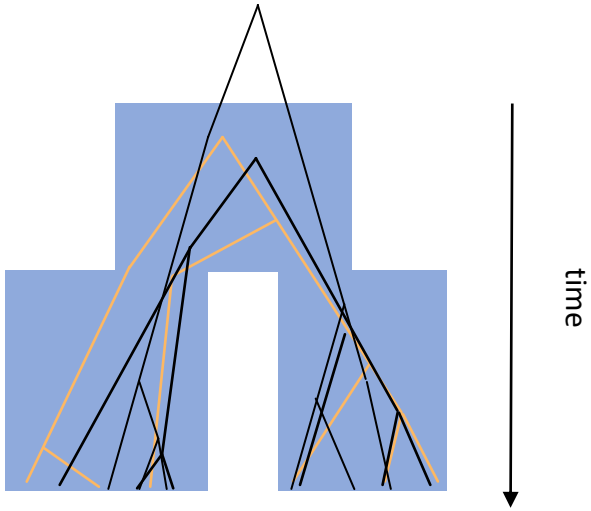

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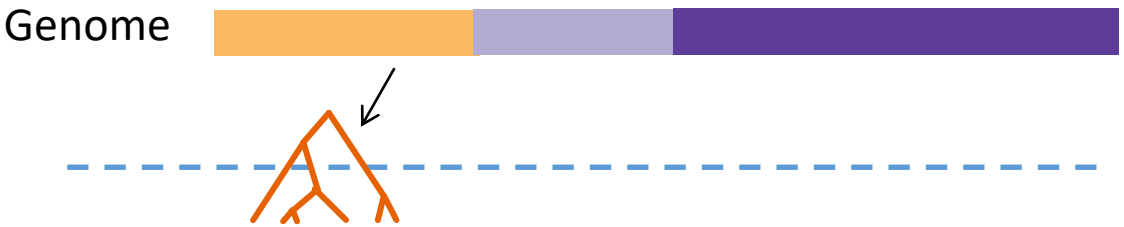
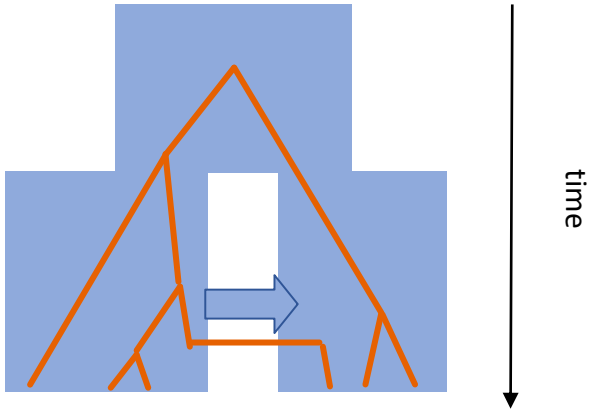


Model with migration



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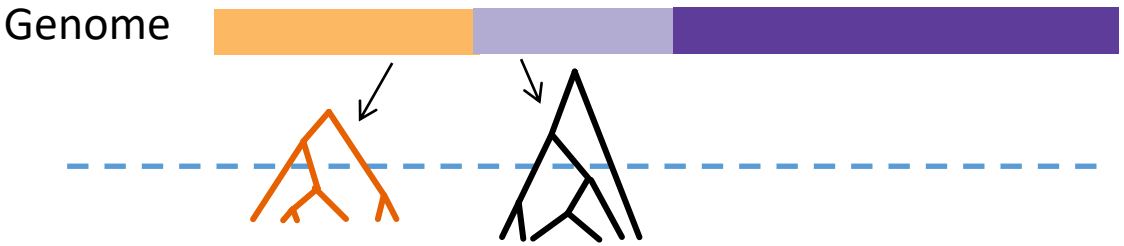

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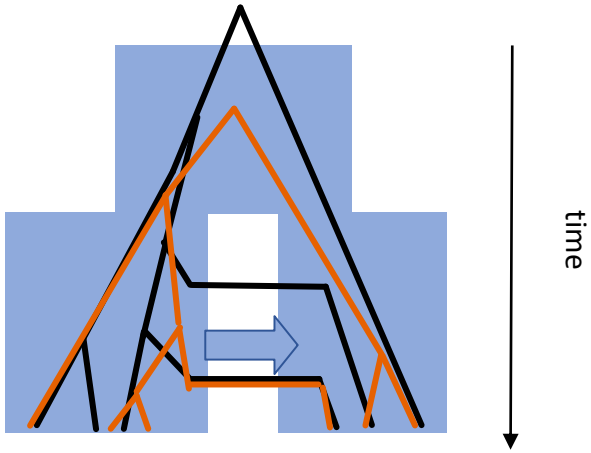

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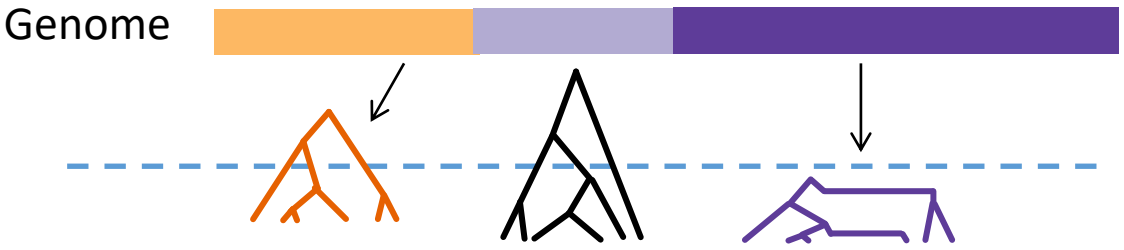

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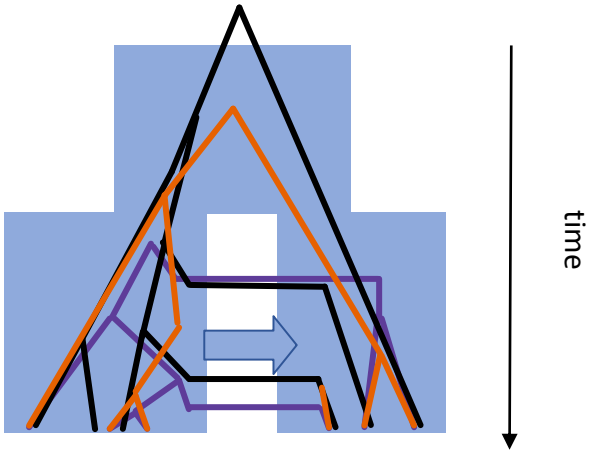

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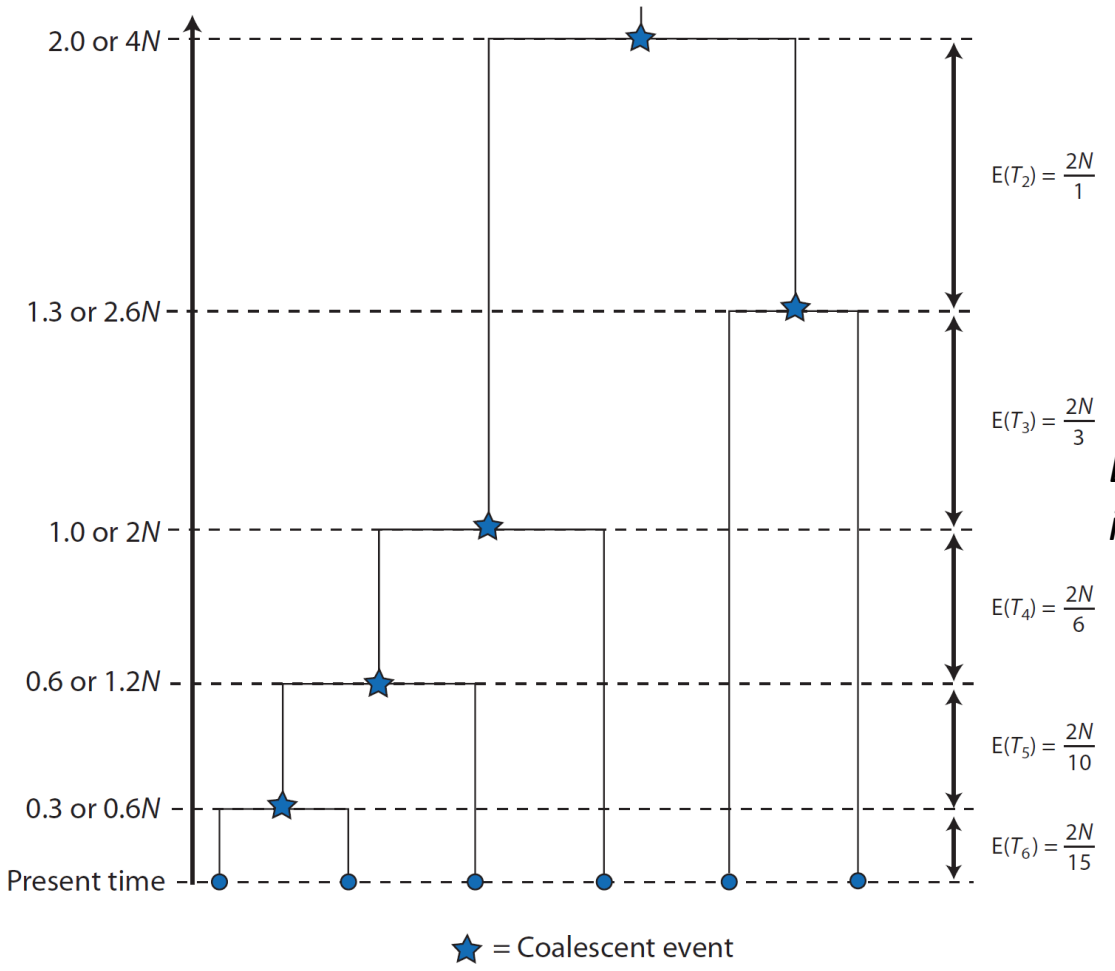
Expected coalescent times in a constant size population

For a sample of *n* lineages the expected TMRCA is approximately $4N_e$



Continuous time (in 2N units)

Discrete time in generations

- What are the longest branches we expect in a stationary population?
- Do we expect the relative branch length to differ in large and small populations?

The expected time is $4N_e$, but there is a large variance

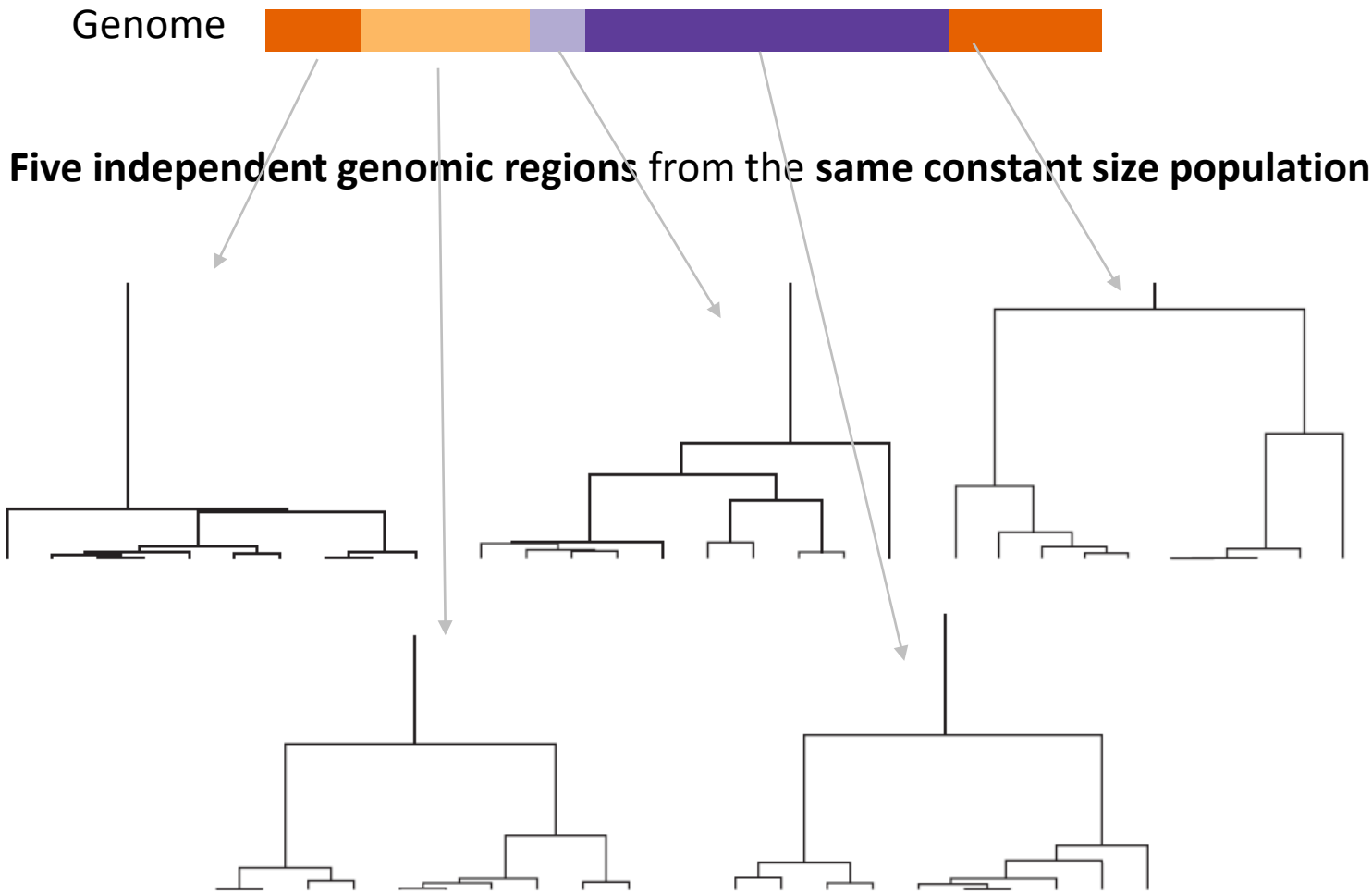
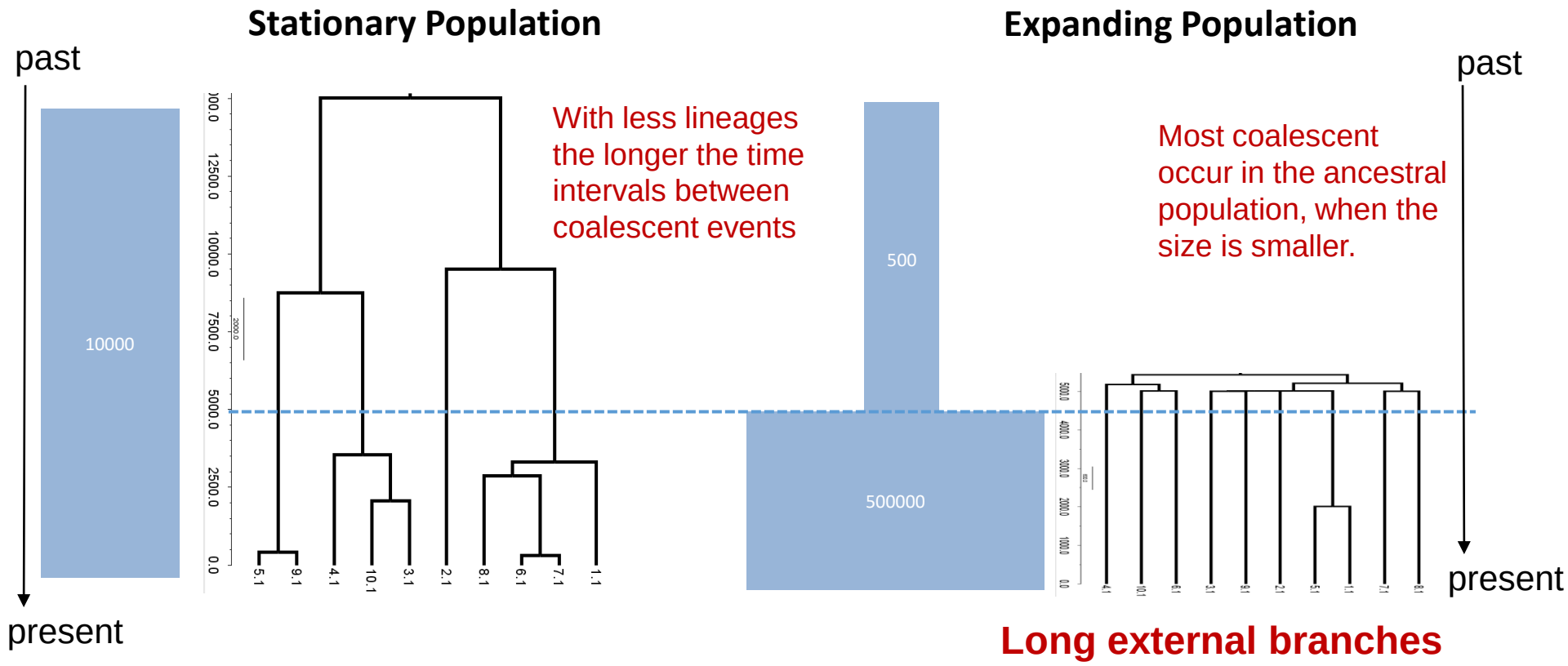


Figure 4.2 Five replicates of the coalescent process with constant population size for a sample of ten genes. Note the large variance in the time of the MRCA among replicates.

Hein et al (2004) Gene Genealogies, Variation and evolution

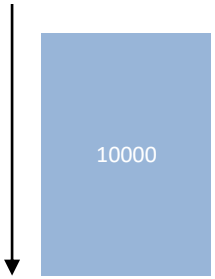
Gene trees in expanding populations

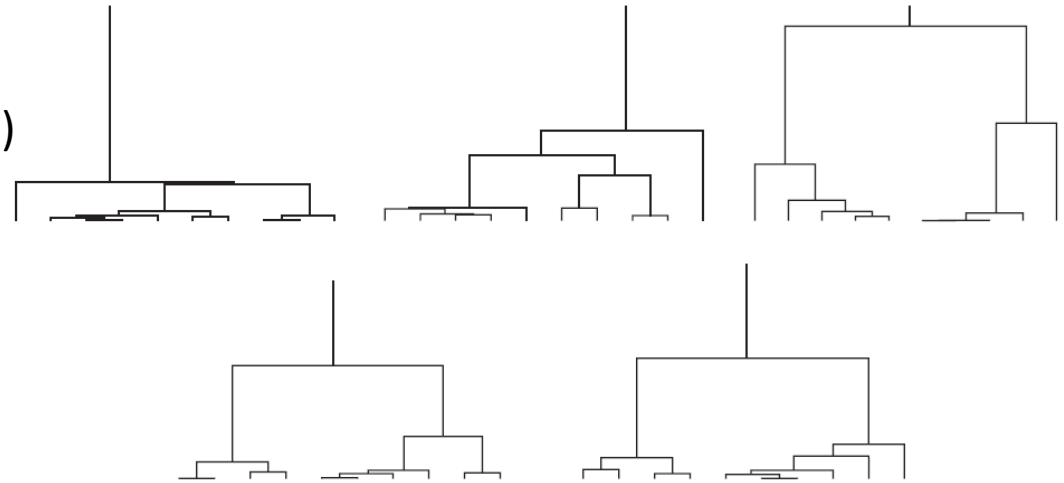


- Coalescent rate is larger in smaller populations, and so we expect smaller intervals between coalescent events in smaller populations
- Coalescent rate is lower with a lower number of lineages, and so we expected larger intervals between coalescent events as the number of lineages decrease

Stationary population

gene trees at five genome regions
(all share same population history!)





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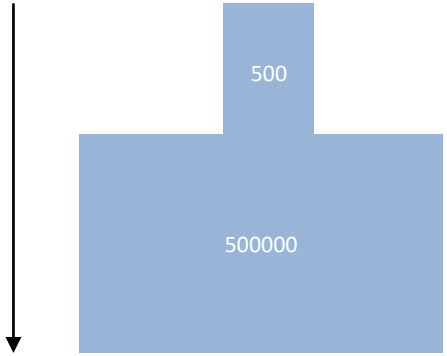


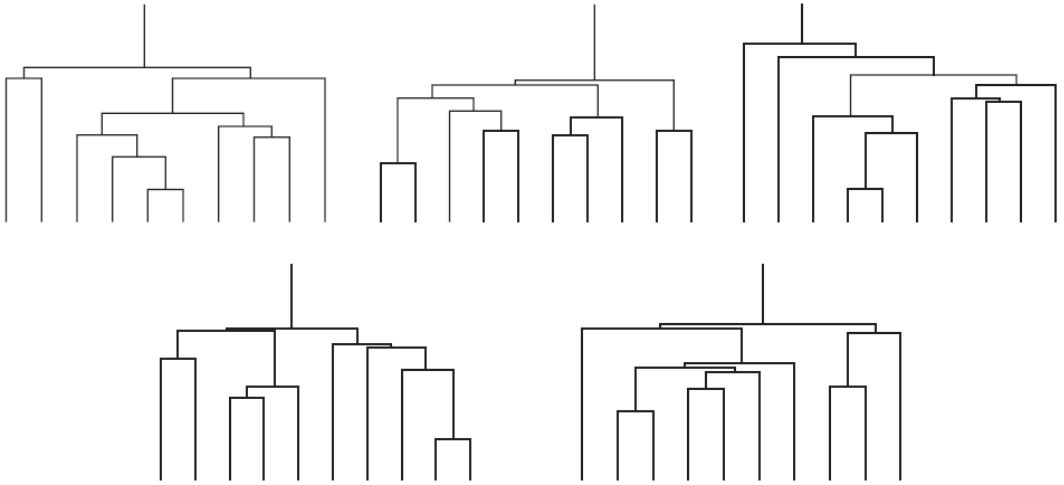
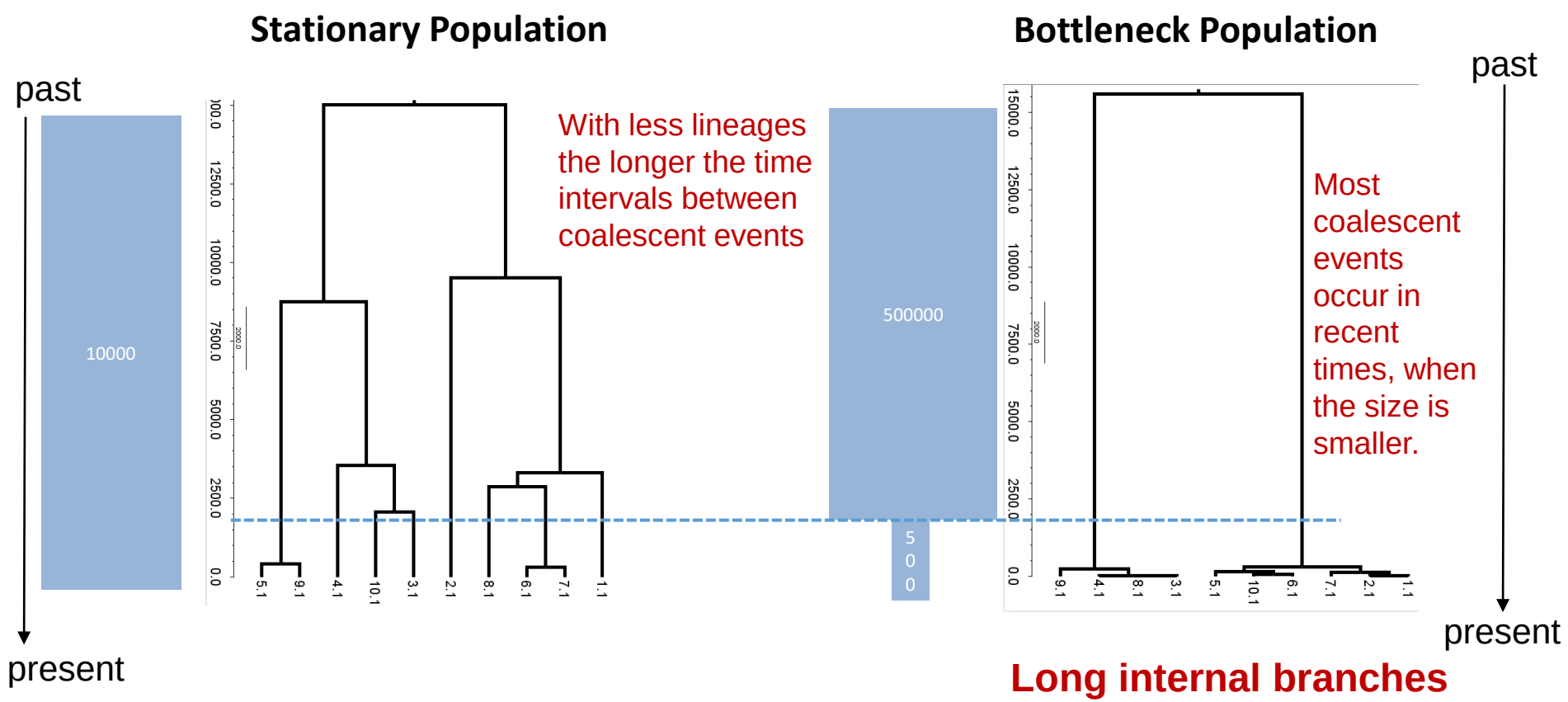


Figure 4.3 Five replicates of the coalescent with exponential growth, $\beta = 1000$, for a sample of $n = 10$ genes. Note the smaller variance in the time until the MRCA compared to the same quantity in Figure 4.2.

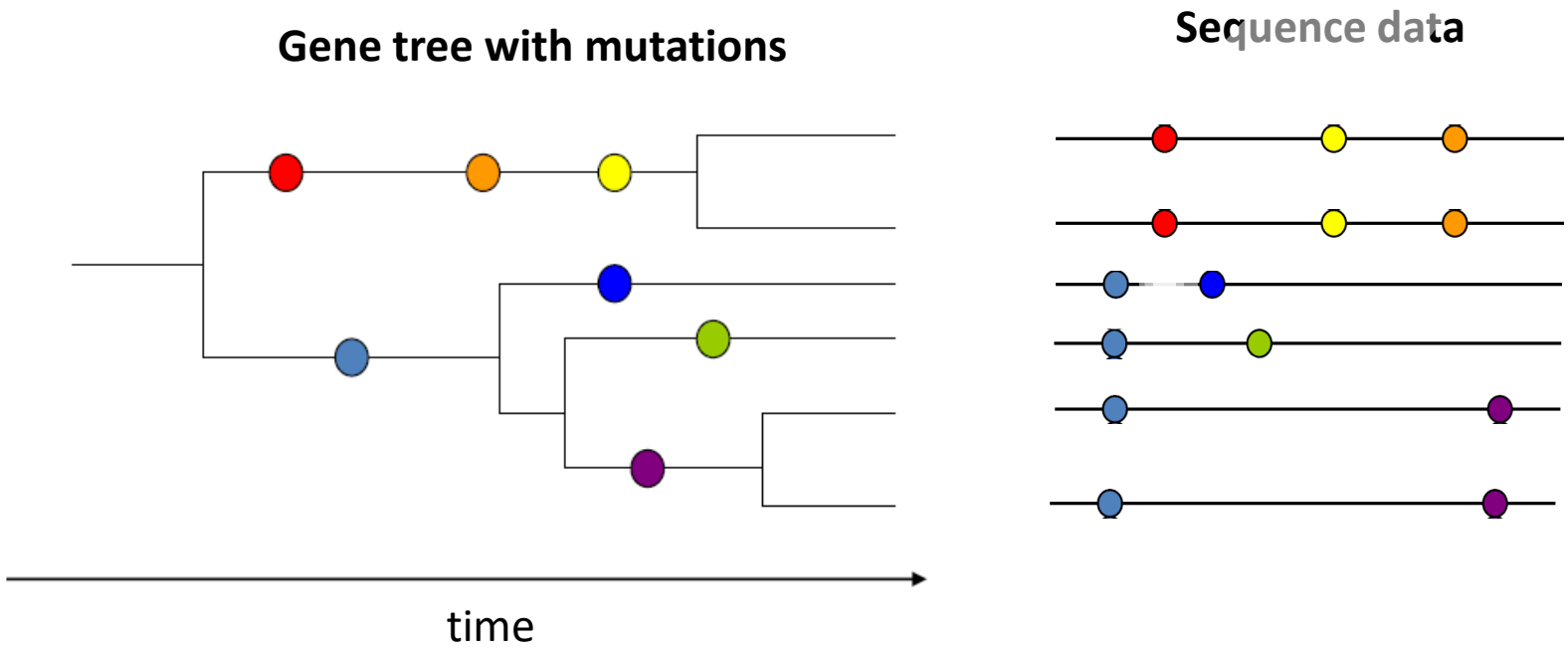
Hein et al (2004) Gene Genealogies, Variation and evolution

Gene trees for decreasing populations



- If we could observe directly the gene trees, we could easily reconstruct the population tree and the demographic history.
- But we do not observe gene trees…
- We can still learn about gene trees from the observed mutations and the allele frequencies in samples

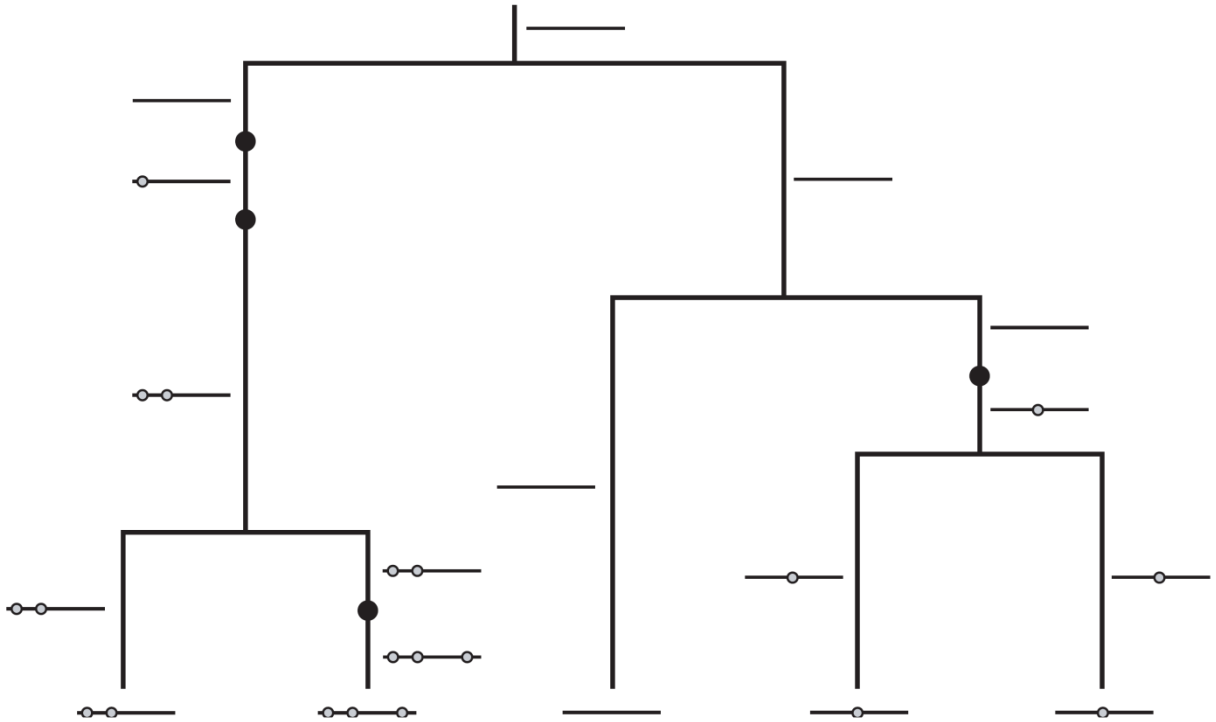
Adding neutral mutations to gene trees under the Infinite sites model



No back mutations, no multiple mutations on the same site.

Adding neutral mutations

The shape of neutral coalescent trees only depend on the population demography, and not on the mutational process. Assuming that all alleles have the same fitness, the mutational process can be modeled as an independent process superimposed on a realized coalescent tree.

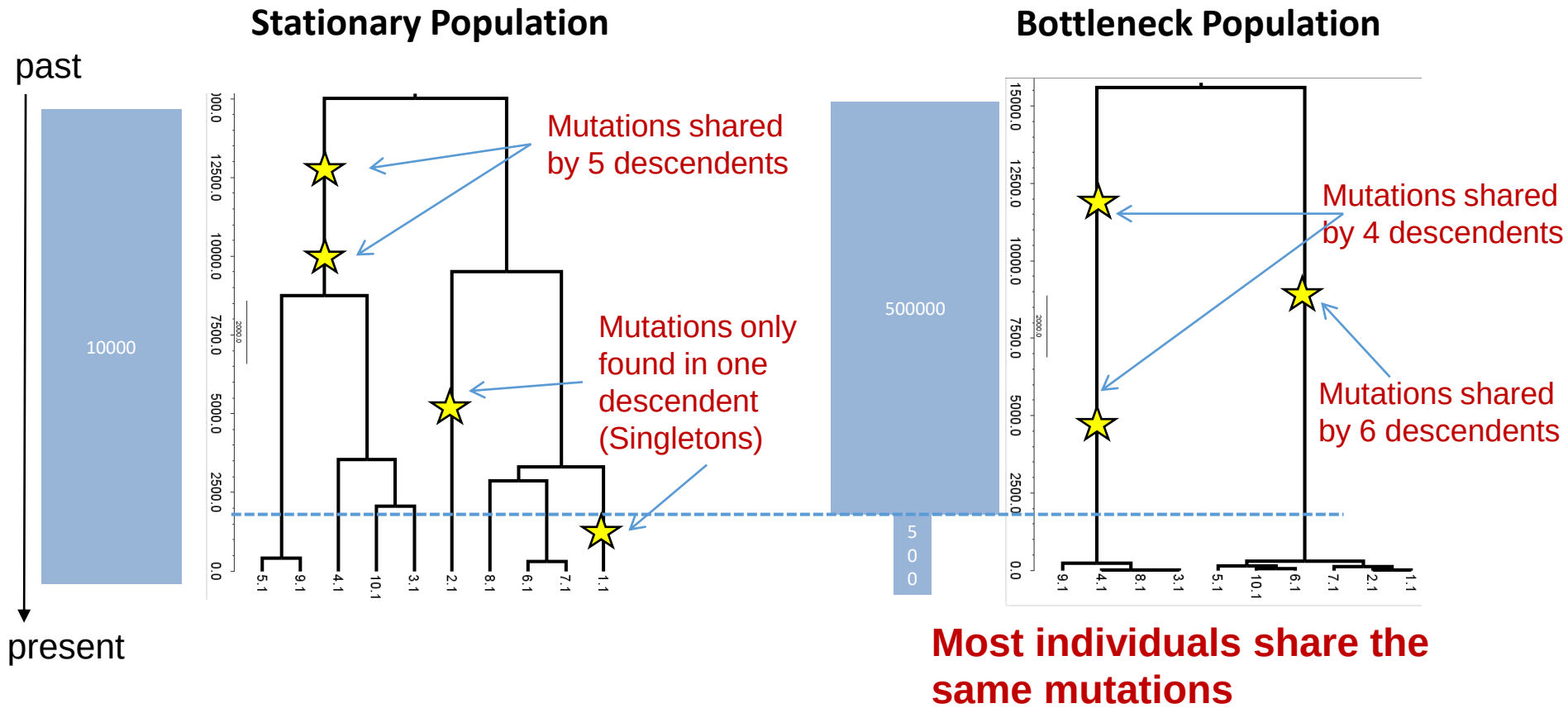


Mutations just accumulate along the branches of the tree according to a **Poisson process** with rate $\lambda_i = \mu t_i$ for the *i*-th branch of length t_i. The Poisson process is stochastic but it should be immediately **obvious that long branches will carry more mutations than short branches**

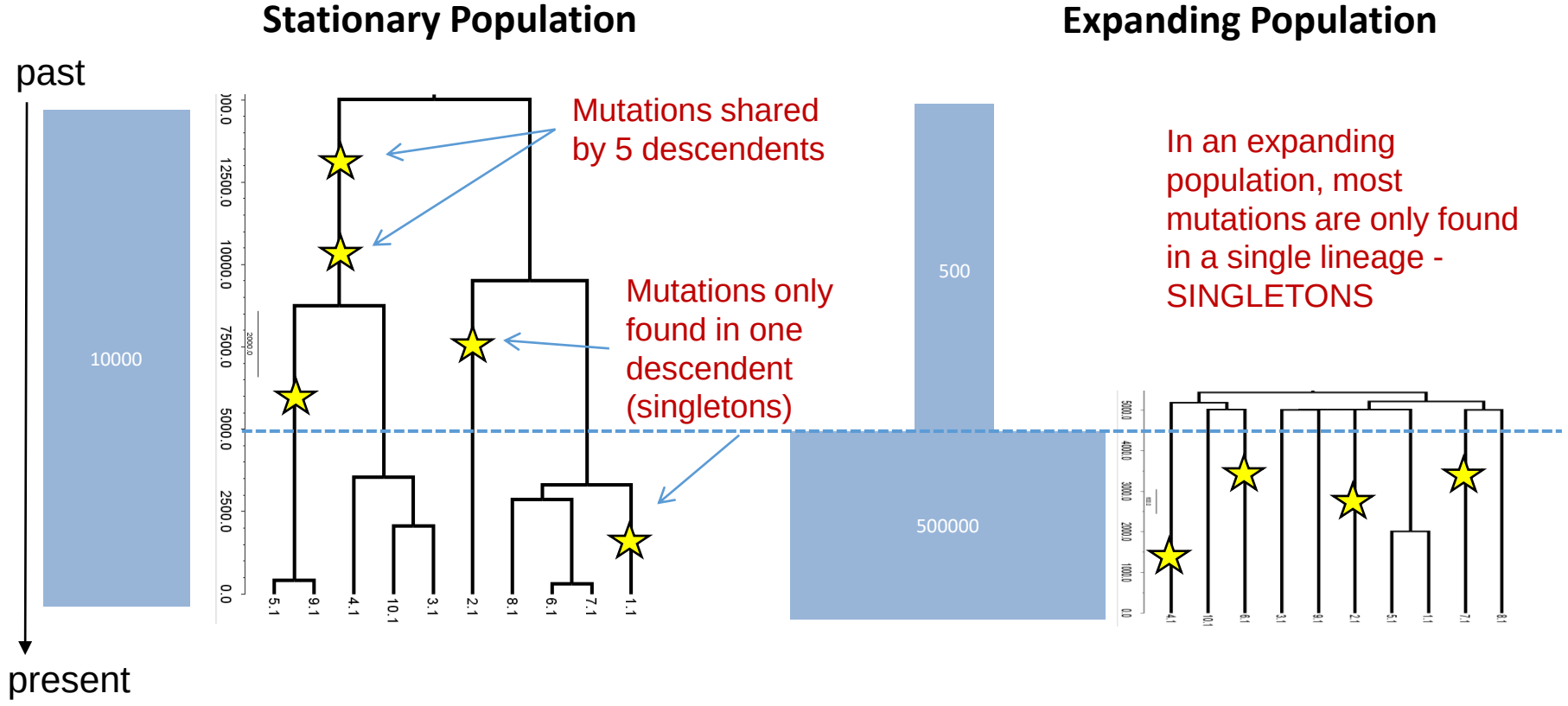
Hein et al (2004) Gene Genealogies, Variation and evolution

We expect less rare variants in populations that went through a bottleneck

- Mutations accumulate along the branches.
- The longer a given branch the more likely it becomes that a mutation have happened on it.

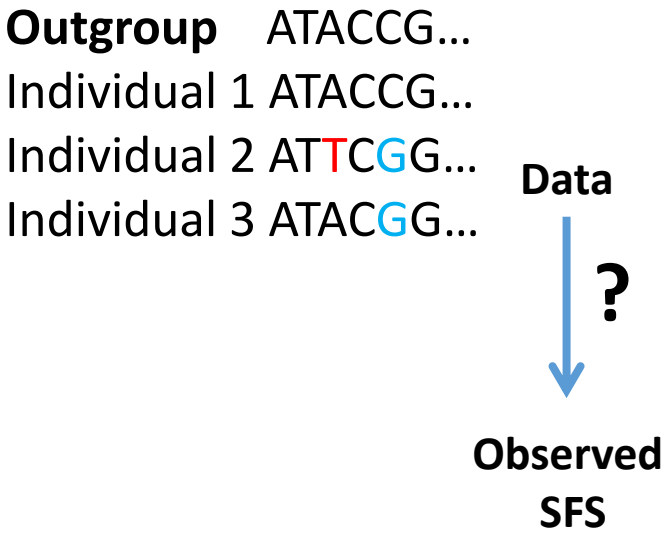


We expect more rare variants in expanding populations than in populations with a constant size



Site frequency spectrum (SFS)

- The SFS summarizes efficiently genome-wide data
- Assuming a single population – 1Dimensional SFS



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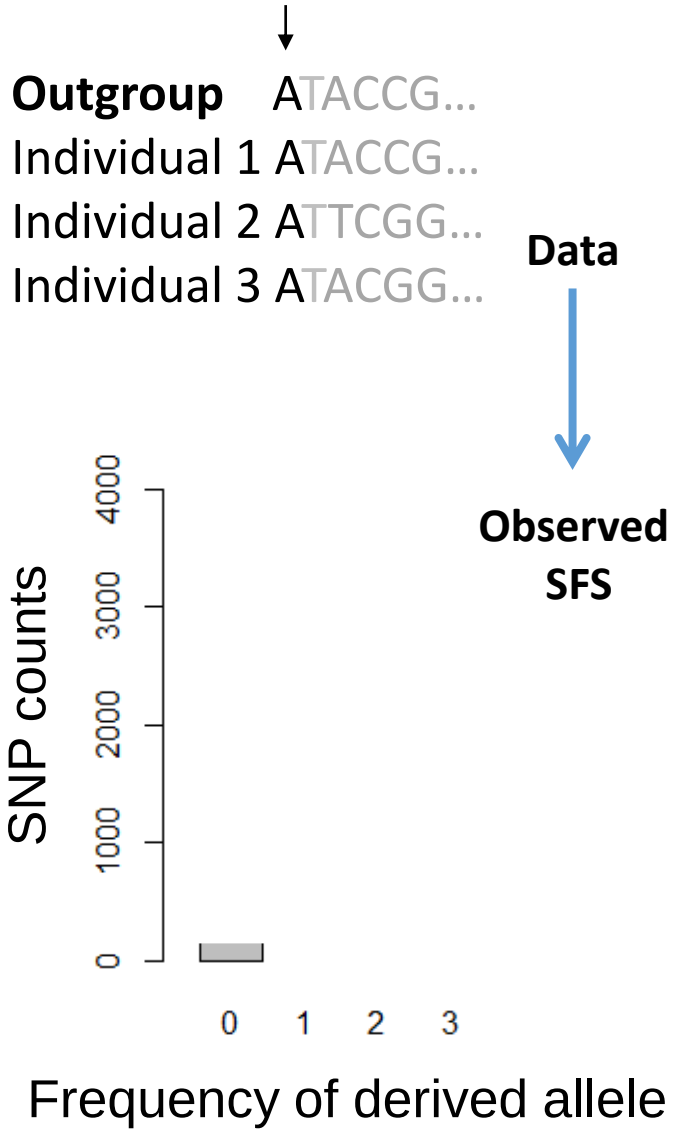
- Assuming a single population – 1Dimensional SFS



Site frequency spectrum (SFS)

- The SFS summarizes efficiently genome-wide data
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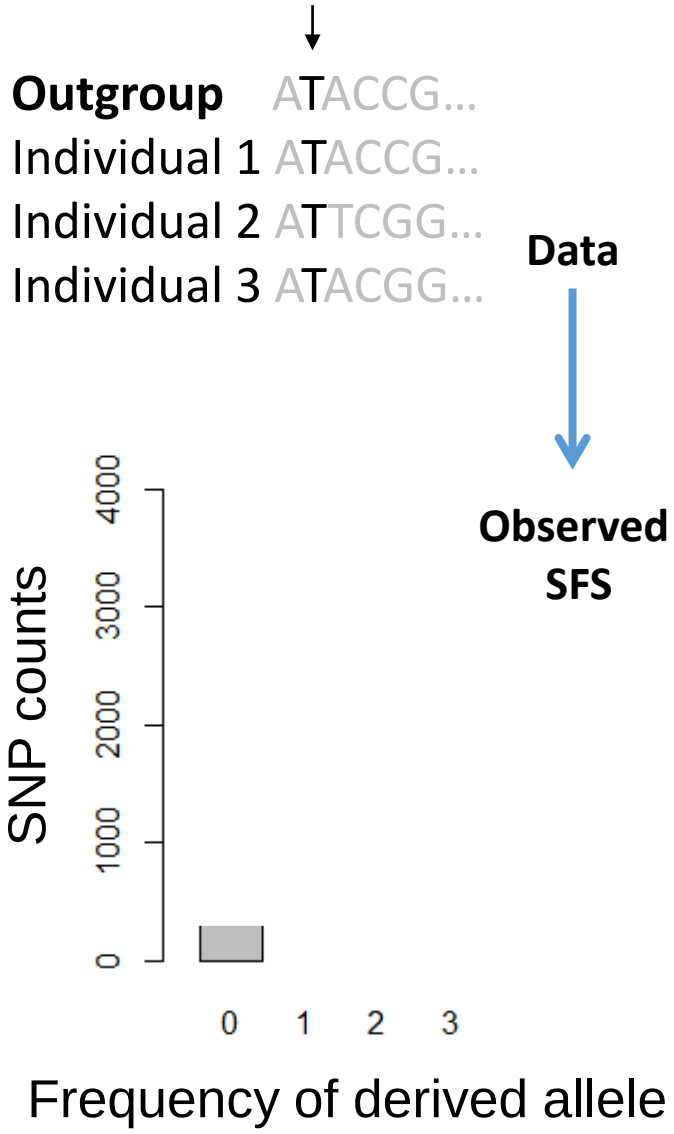
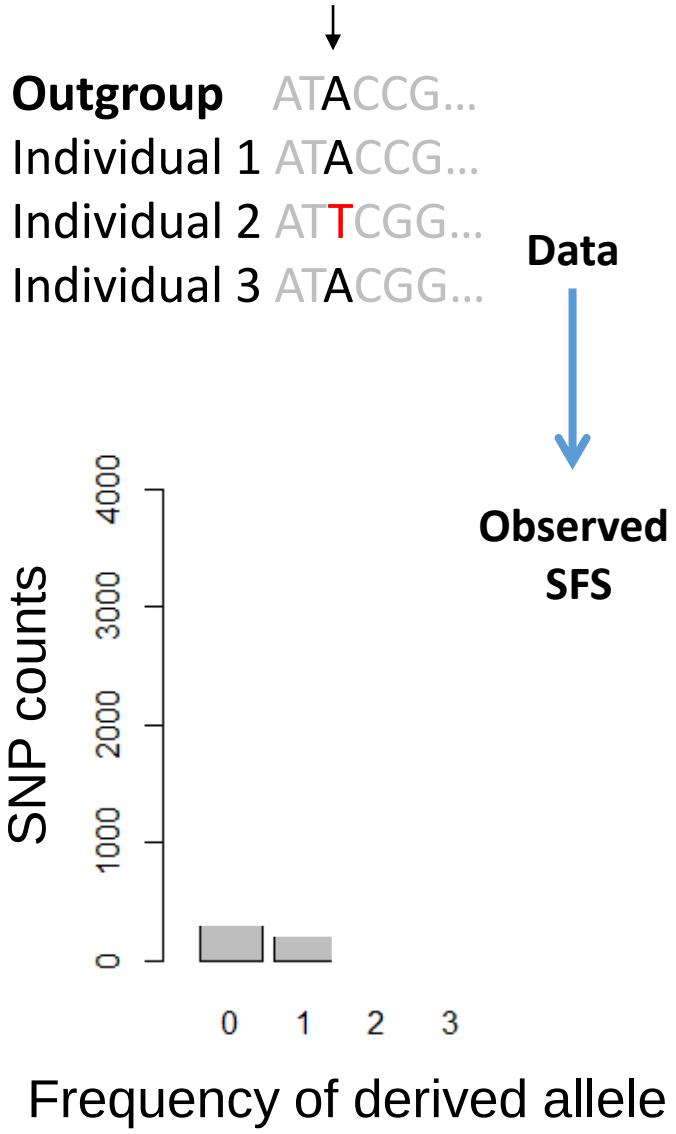


Site frequency spectrum (SFS)

- The SFS summarizes efficiently genome-wide data
- Assuming a single population – 1Dimensional SFS



Site frequency spectrum (SFS)

- The SFS summarizes efficiently genome-wide data

- Assuming a single population – 1Dimensional SFS

The SFS ignores information about linkage. It is best suited for the study of many unlinked (or recombining) DNA sequences.

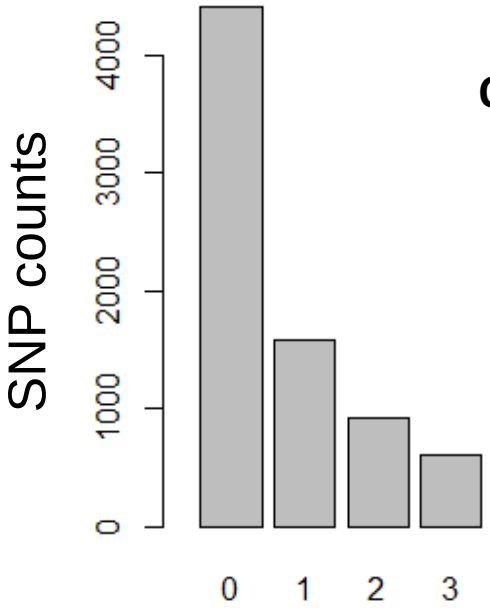
In a stationary population, the expected SFS relative frequencies are given by:

$$E(\xi_i) = \frac{\theta}{i}$$

Fu and Li, 1993

Outgroup ATACCG…
Individual 1 ATACCG…
Individual 2 ATTCGG…
Individual 3 ATACGG…

Data



Observed SFS

VCF (variant call format) files

CHROM	POS	ID	REF	ALT	QUAL	FILTER	FORMAT	BL2009P4_us23
"Supercontig_1.50"	"2"	NA	"T"	"A"	"44.44"	NA	"GT:AD:DP:GQ:PL"	"0|0:62,0:62:99:0,190,2835"
"Supercontig_1.50"	"246"	NA	"C"	"G"	"144.21"	NA	"GT:AD:DP:GQ:PL"	"1|0:5,5:10:99:111,0,114"
"Supercontig_1.50"	"549"	NA	"A"	"C"	"68.49"	NA	"GT:AD:DP:GQ:PL"	NA
"Supercontig_1.50"	"668"	NA	"G"	"C"	"108.07"	NA	"GT:AD:DP:GQ:PL"	"0|0:1,0:1:3:0,3,44"
"Supercontig_1.50"	"765"	NA	"A"	"C"	"92.78"	NA	"GT:AD:DP:GQ:PL"	"0|0:2,0:2:6:0,6,49"
"Supercontig_1.50"	"780"	NA	"G"	"T"	"58.38"	NA	"GT:AD:DP:GQ:PL"	"0|0:2,0:2:6:0,6,49"

https://grunwaldlab.github.io/Population_Genetics_in_R/reading_vcf.html

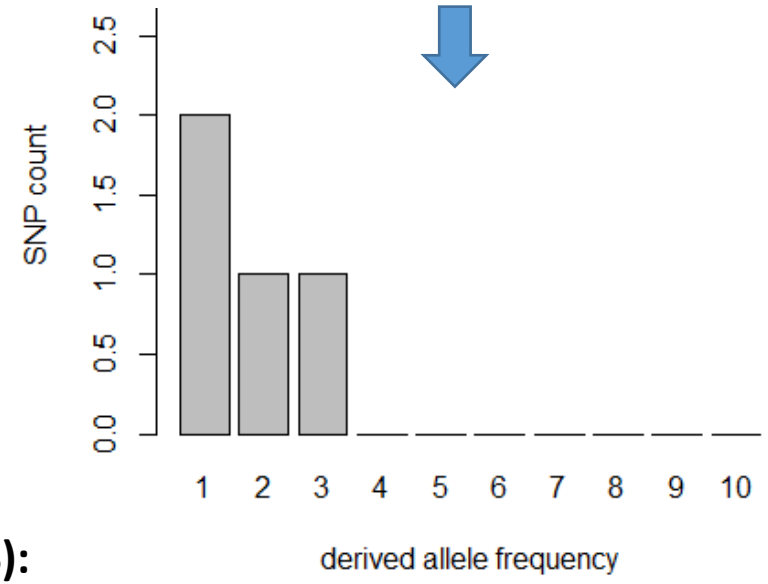
We can obtain the SFS from genotype call data

Genotypes:

- 0 homozygote for reference allele
- 1 heterozygote
- 2 homozygote for alternative allele

This can be done if we have enough depth of coverage (>10x)

	SNP1	SNP2	SNP3	SNP4
Individual 1	0	2	0	1
Individual 2	0	0	1	0
Individual 3	1	0	0	0
Individual 4	0	1	0	0
Individual 5	0	0	1	0



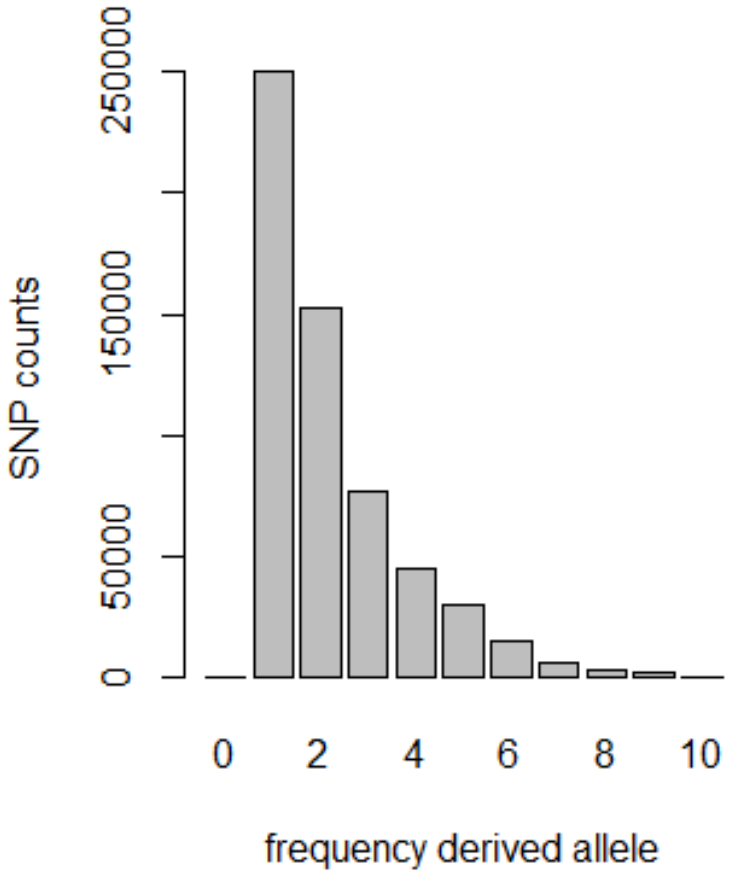
Observed SFS is a vector (1 dimensional SFS):

Frequency	0	1	2	3	4	5	6	7	8	9	10
SNP count	0	2	1	1	0	0	0	0	0	0	0

SFS from genotype call data

Even if we have millions of SNPs we can summarize the genomic data to 10 numbers with the SFS!

The size of the SFS depends on the number of sampled individuals.



Observed SFS is a vector (1 dimensional SFS):

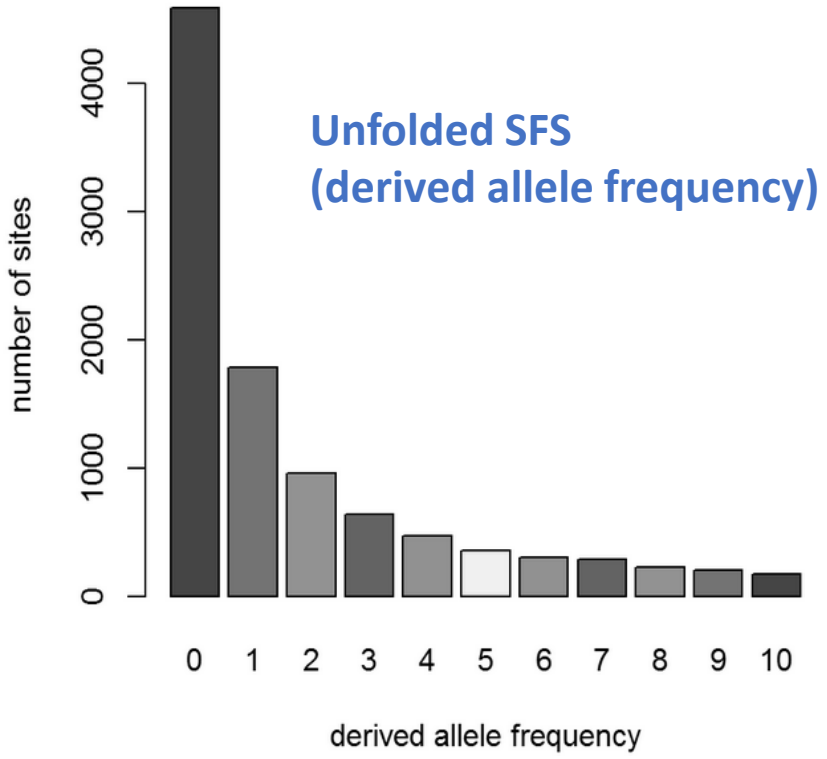
Frequency	0	1	2	3	4	5	6	7	8	9	10
SNP count	0	250,032	152,300	76,504	45,362	30,210	15,329	5,642	3,524	2,123	0

Derived vs Minor allele frequency spectrum

- So far, we have assumed that the allele frequency is the number of sequences with the derived allele frequency (unfolded SFS). We need information (outgroup) to determine the ancestral/derived state.
- If we do not have that information, we can work with the minor allele frequency (folded SFS). In this case, the allele with a lower frequency is treated as the reference.

Folded SFS (minor allele frequency spectrum)

If you cannot determine the ancestral or derived state of mutations (e.g., no outgroup reference genome available), you can assume that the allele with the lower frequency is the “derived”.



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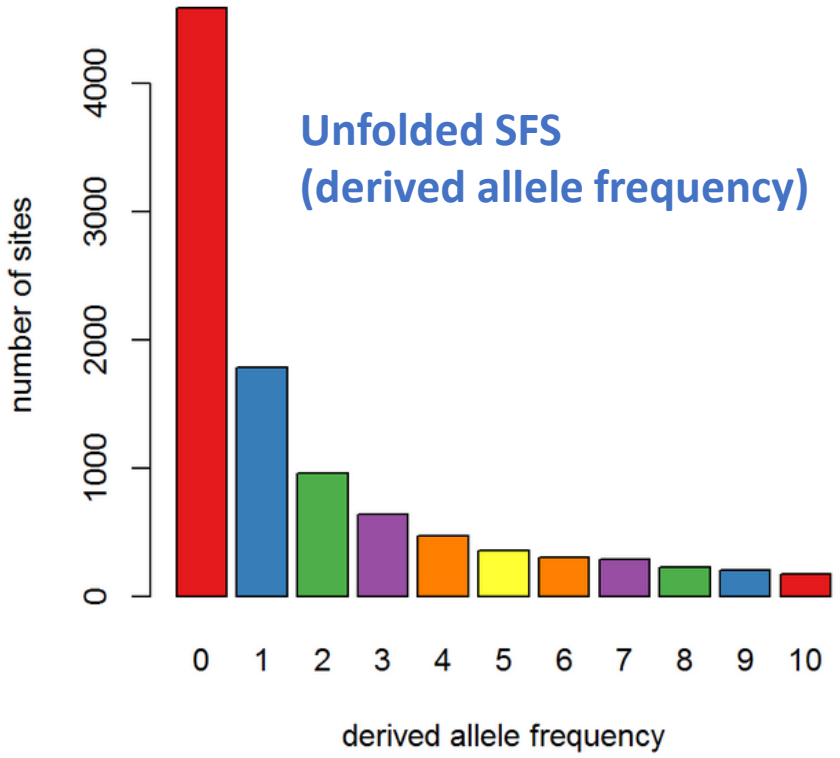
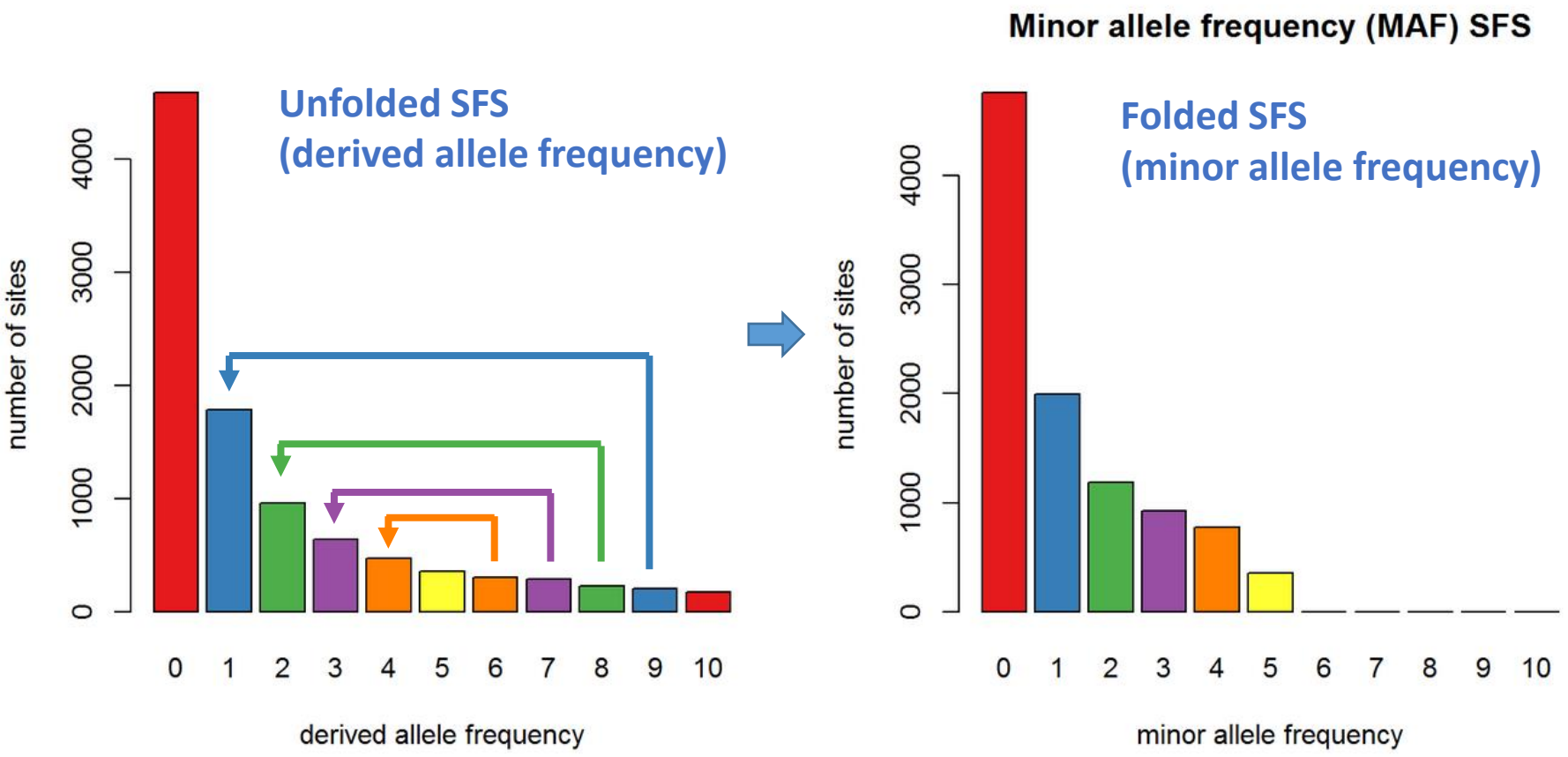
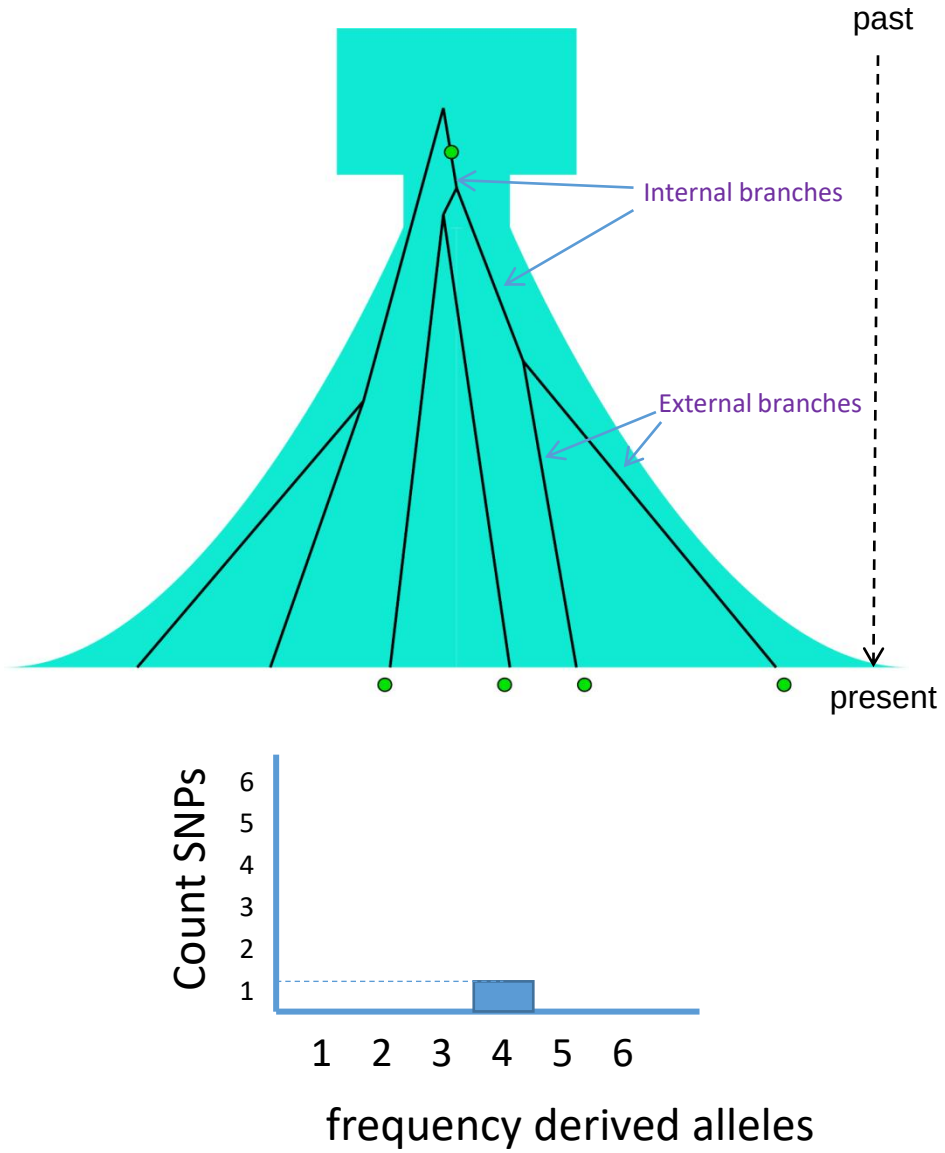


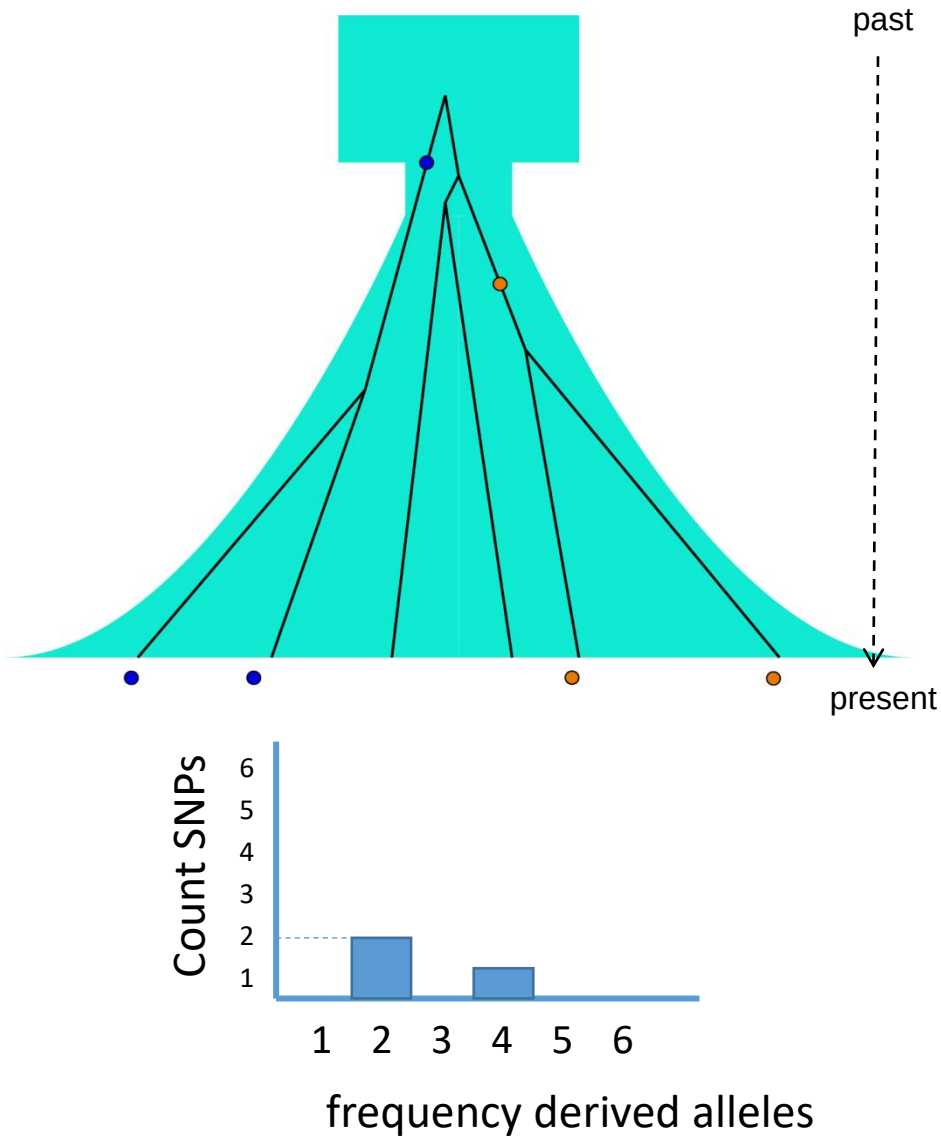
Folded SFS (minor allele frequency spectrum)



Coalescent and the SFS

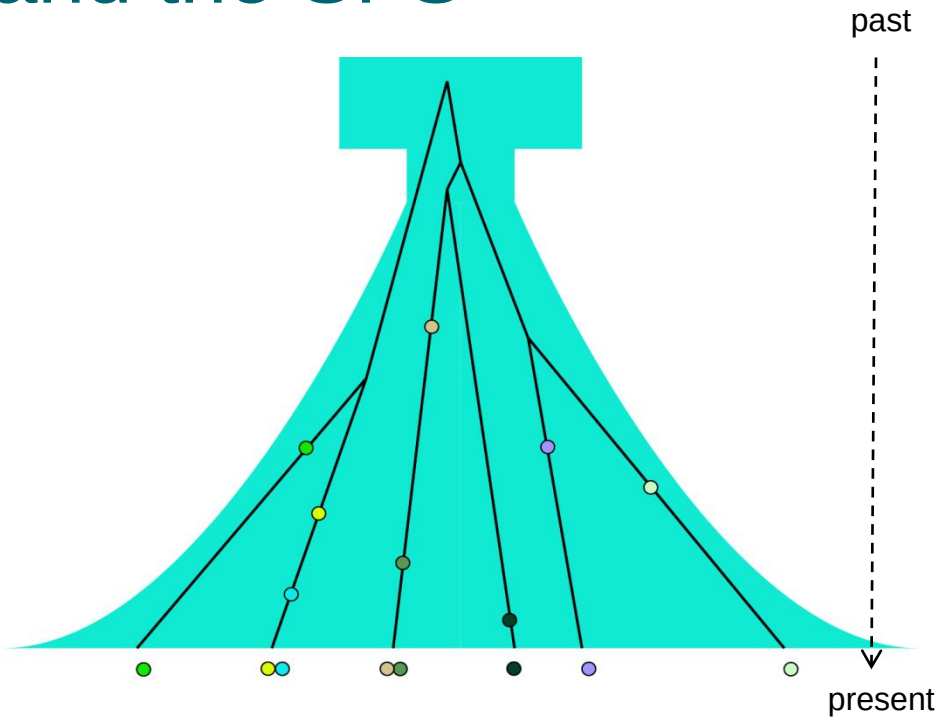


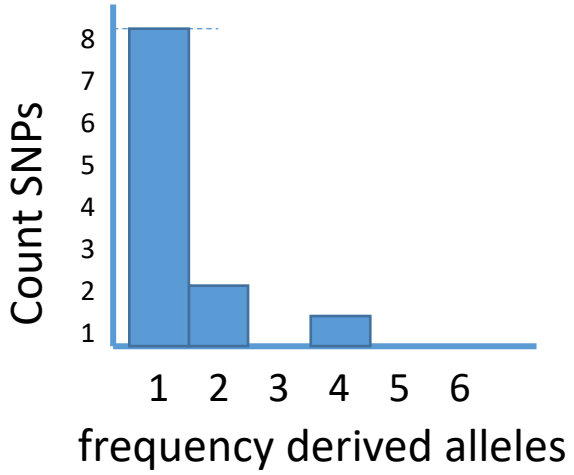
Coalescent and the SFS



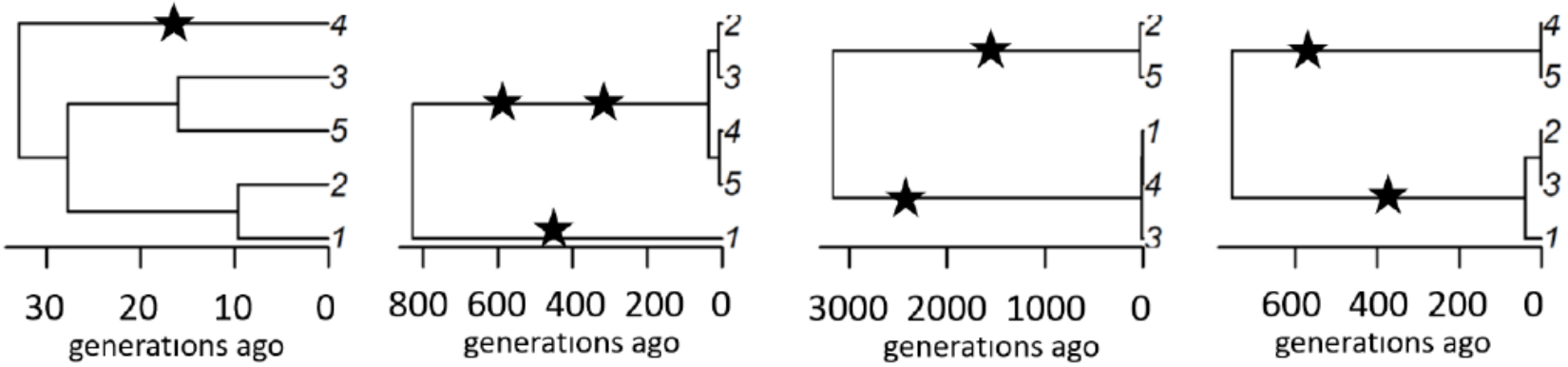
Coalescent and the SFS

- A recent population growth following a bottleneck leads to gene trees with long external branches
- Very few mutations in the internal branches
- Most mutations in long external branches are only found in one lineage, resulting in an excess of singletons

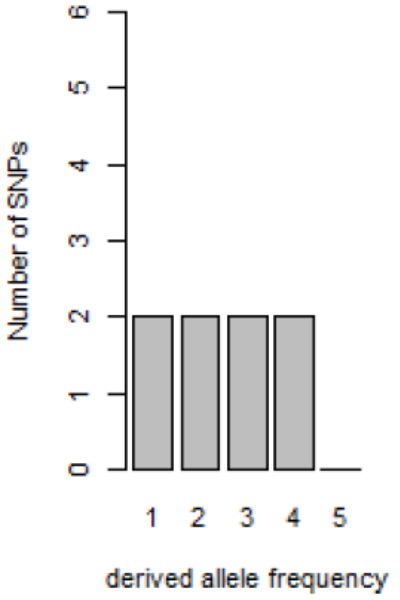




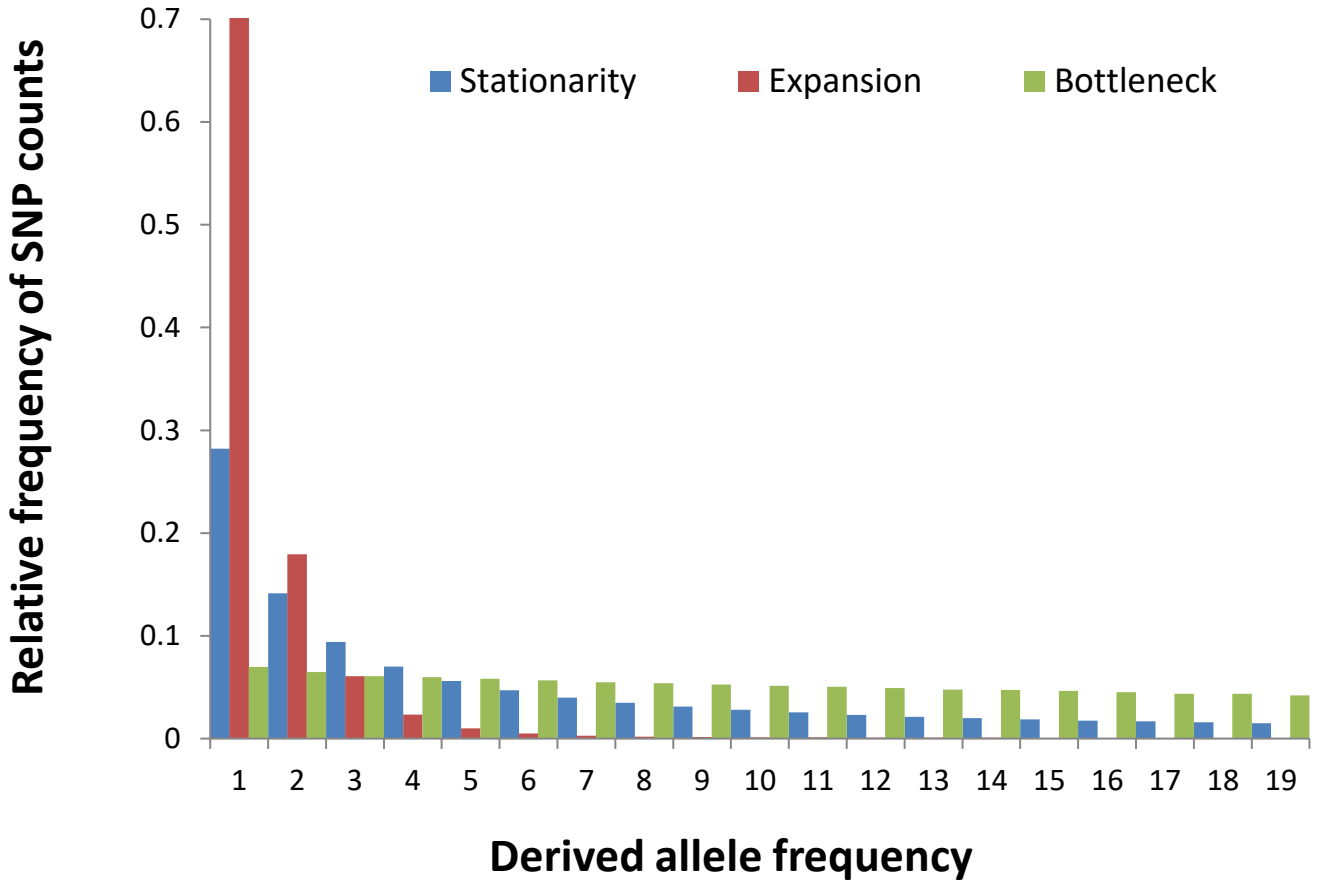
Coalescent gene trees at multiple independent sites and the SFS



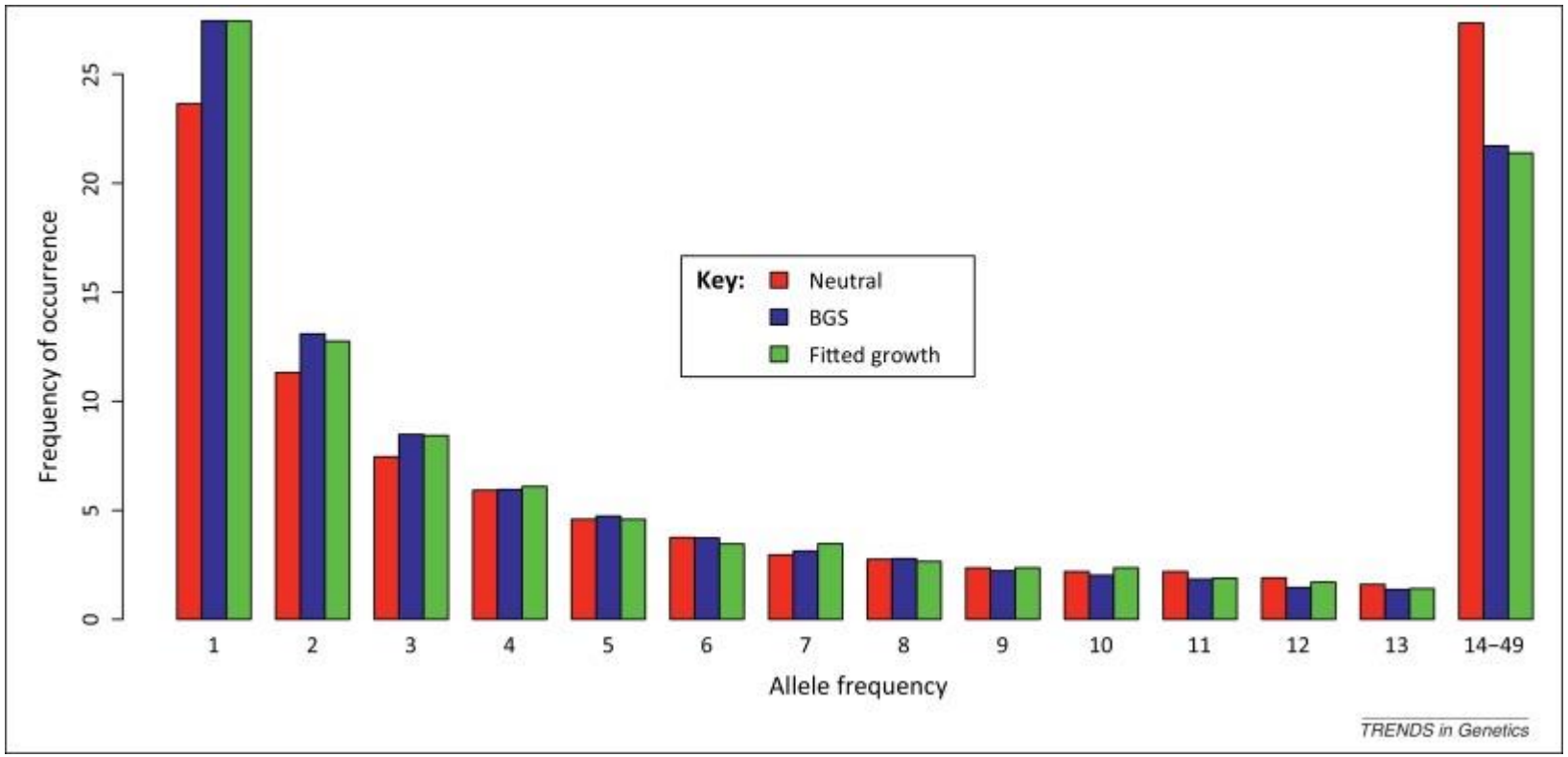
- The SFS is summed across loci
- Independent loci can have different gene trees, and different mutations and allele frequencies
- But, assuming neutrality, all sites in the genome reflect the population tree and the demographic history
- What can we say about the demographic events that lead to this SFS?
  - Bottleneck, expansion, constant size population?
  - Time of event?



SFS depends on past demography



Natural selection also affects the SFS



Background selection (BGS) leads to patterns similar to population expansion.

Bank et al (2014) Trends in Genetics

Population structure

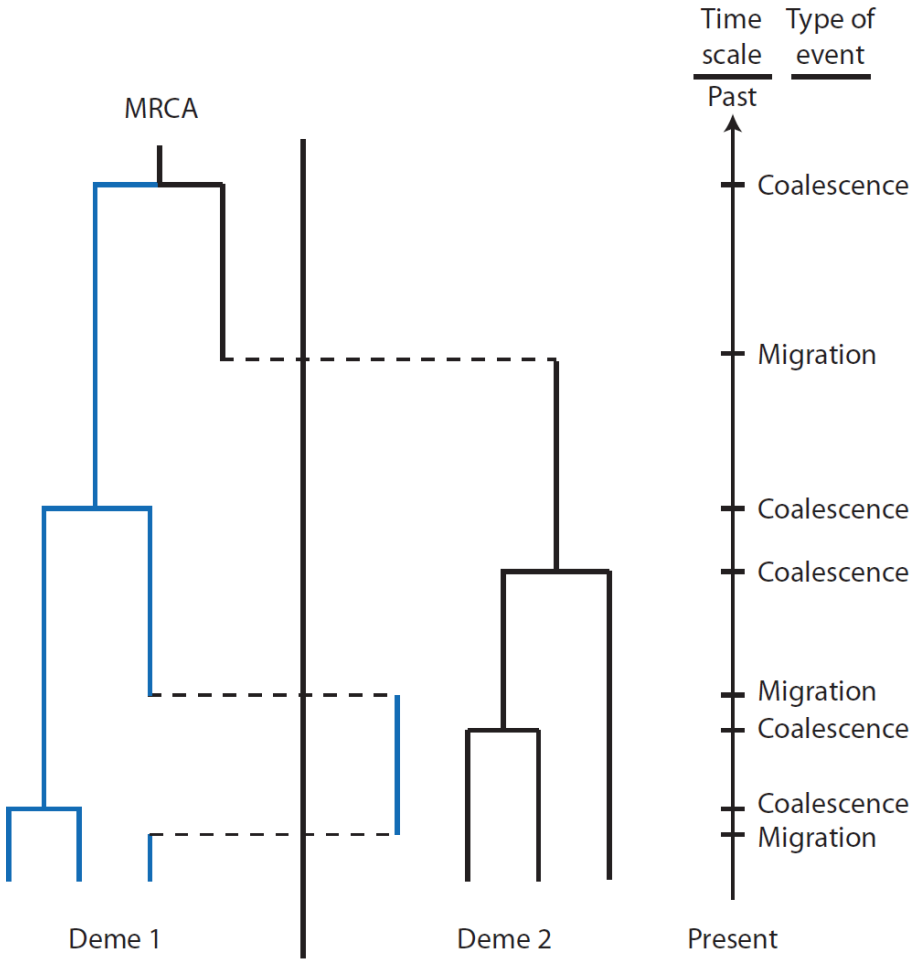
Migration events can be incorporated into gene trees.

Migration from Pop 2 to Pop 1, leads to lineages moving from Pop 1 to pop 2 backward in time.

At each generation, the probability of immigration into population 1 from population 2 is given by:

Pr(migrate) = $n_1 * m$

Where n_1 is the number of lineages in population 1, and m is the immigration rate.



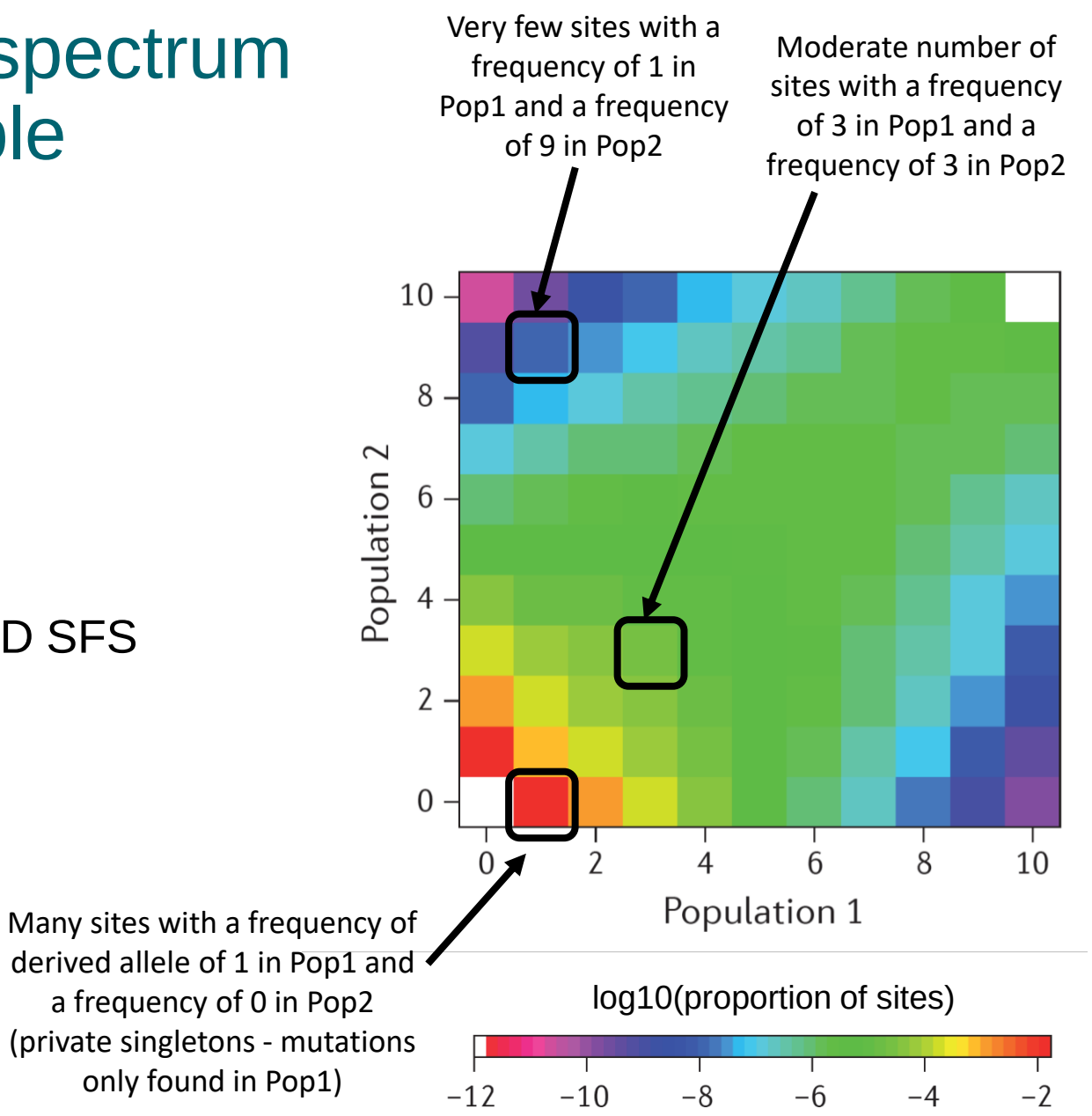
Site frequency spectrum (SFS) for multiple populations

- Single population:

  1D SFS

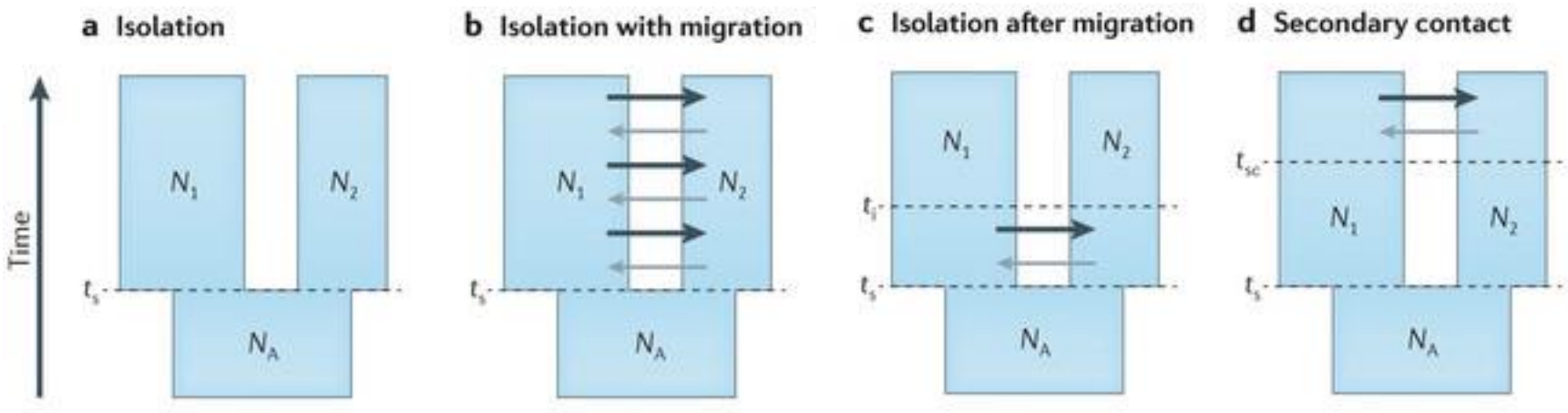
- Multiple populations:

  2D, 3D, …, n_{pop}D SFS



Model based inference

- What is the model that best fits the data?
- What are the most likely parameters of each model?



Sousa and Hey (2013) Nat. Rev. Gen.

A model is represented by a population tree that reflects the past evolutionary history

Parameters:

Demography

- Population split times
- Migration rates
- Effective population sizes
- Temporal changes in migration rates and effective sizes

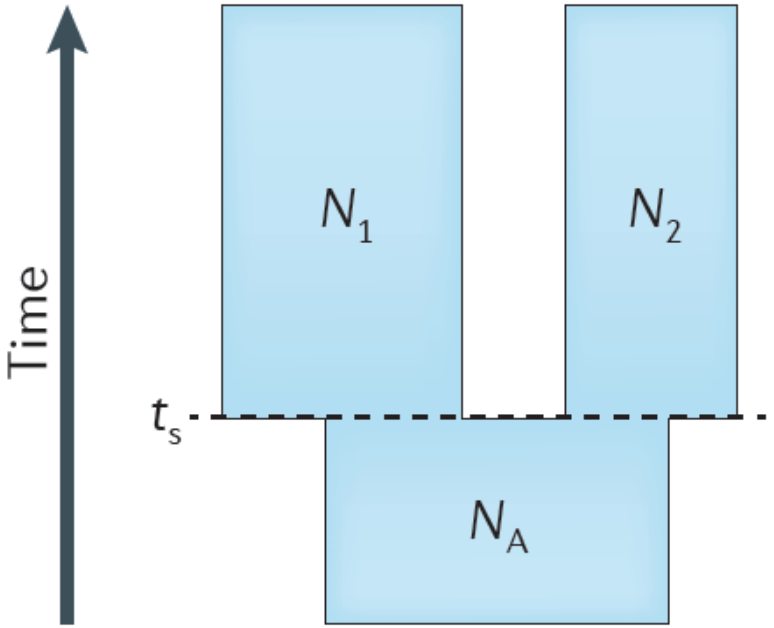
Selection

- Selective coefficients, type of selection (positive or negative)

Genomic processes

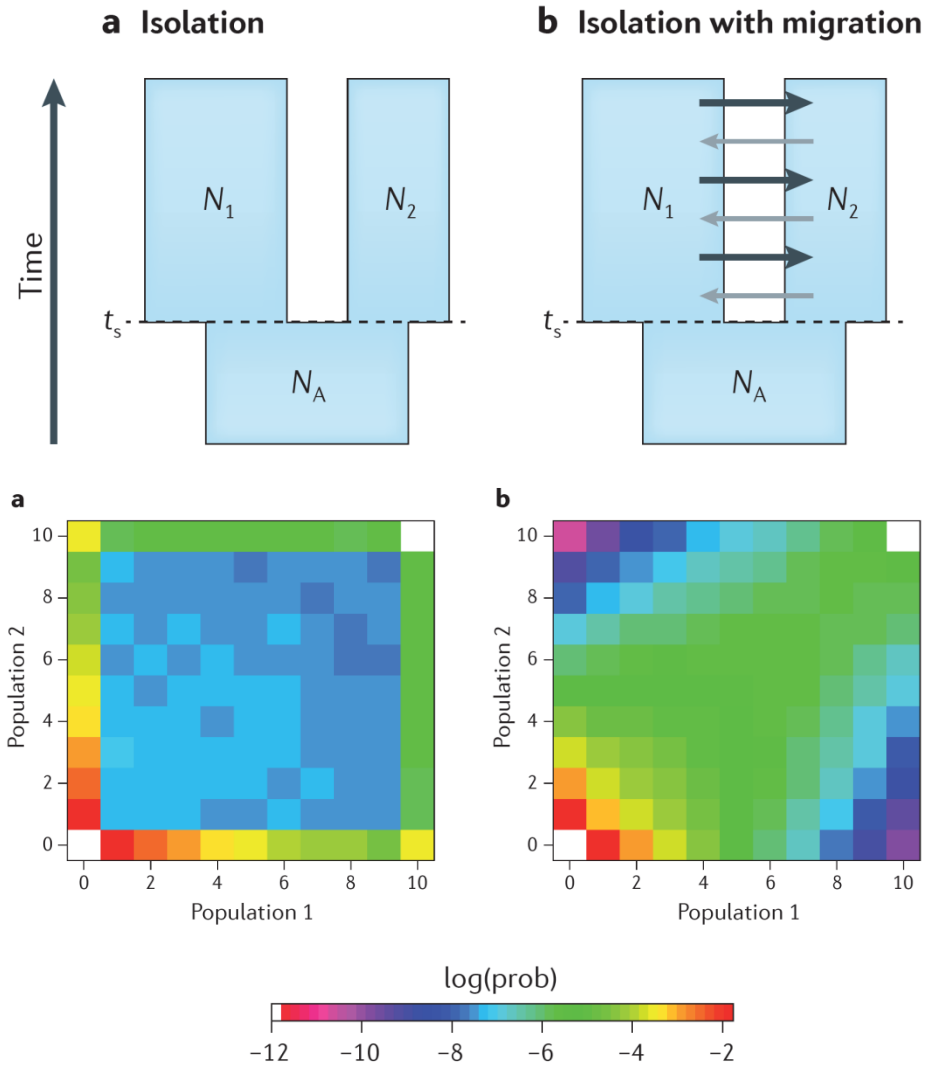
- Mutation rate
- Recombination rate

Population tree



Site frequency spectrum (SFS)

The SFS contains information about the demographic history of populations

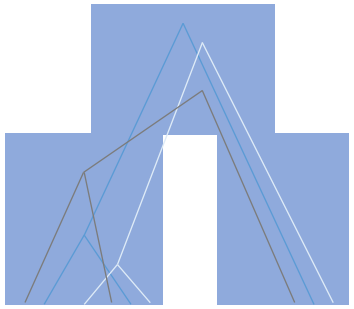


Sousa and Hey (2013) Nat. Rev. Genet.

Inferring the demographic history from the SFS

Genomic Data

Model



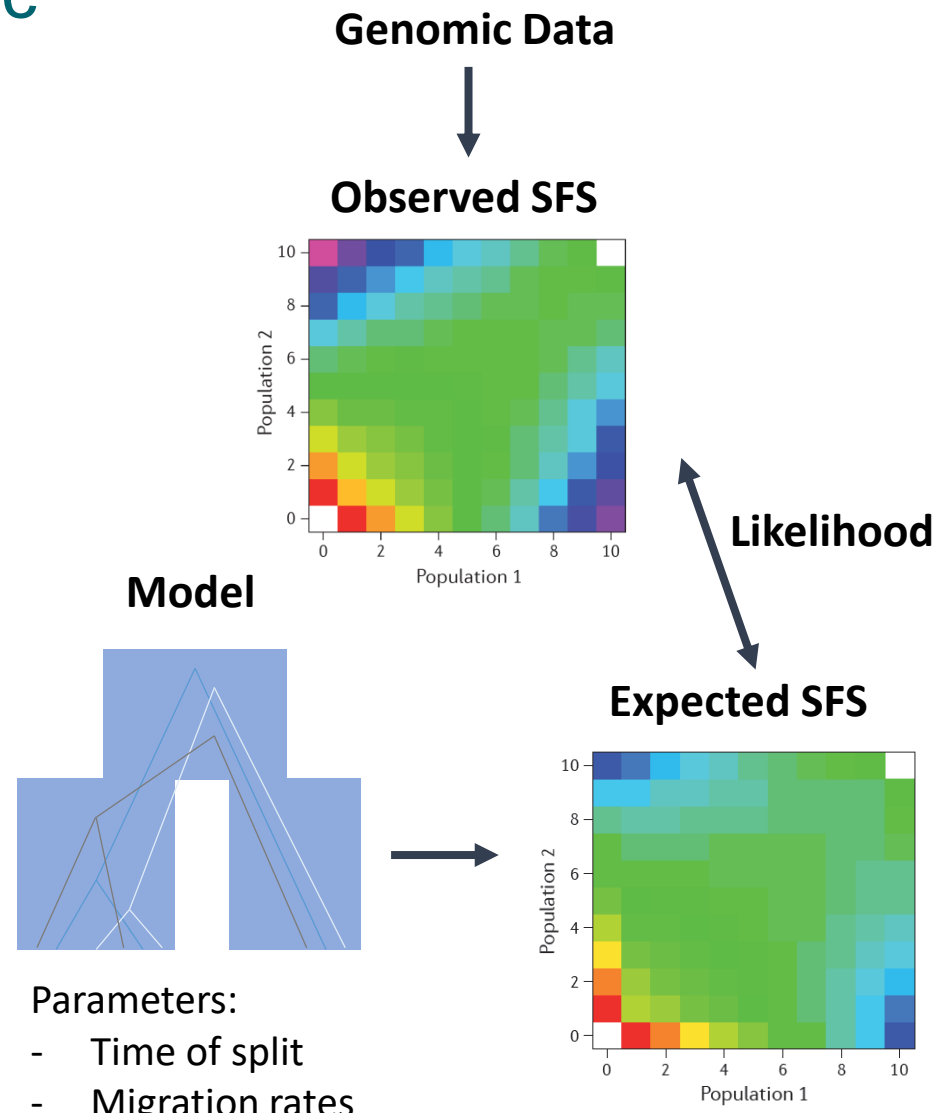
Parameters:

- Time of split
- Migration rates
- Effective sizes

Inferring the demographic history from the SFS

- The likelihood is easily computed based on the expected SFS under a given model

- There are different ways to obtain the expected SFS
  - Diffusion (forward in time)
  - Coalescent (backward in time)



Excoffier et al. (2013) *PloS Genetics*

Estimating the expected SFS under a given model using coalescent

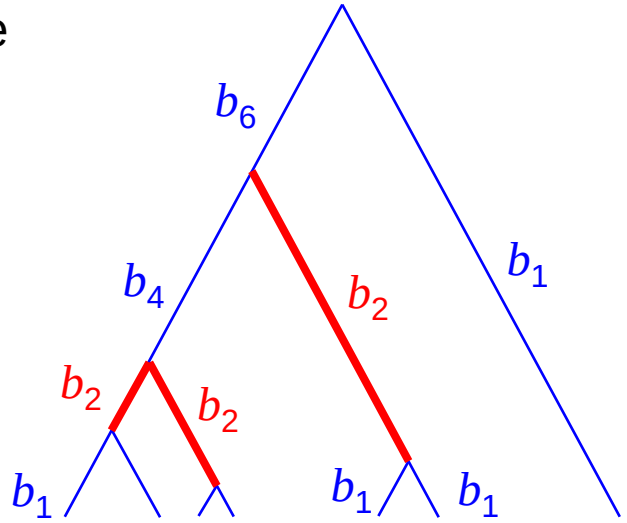
The probability of a SFS entry *i* can be estimated under a specific model *θ* from its expected coalescent tree as (Nielsen 2000)

$$p_i = \frac{E(t_i \mid \theta)}{E(T \mid \theta)}$$

Where t_i is the total length of all branches directly leading to i terminal nodes, and T is the total tree length.

It gives the relative probability that if a mutation occurs on one of these b_i branches, it will be observed *i* times in the sample

This is true under the infinite sites model. No more than 1 mutation per site, back mutations not allowed!



Composite likelihood

Even though we can have linked sites, we assume that all sites are independent. Given *S* polymorphic sites (SNPs) out of *L* sites (Adams and Hudson, 2004) the composite likelihood is:

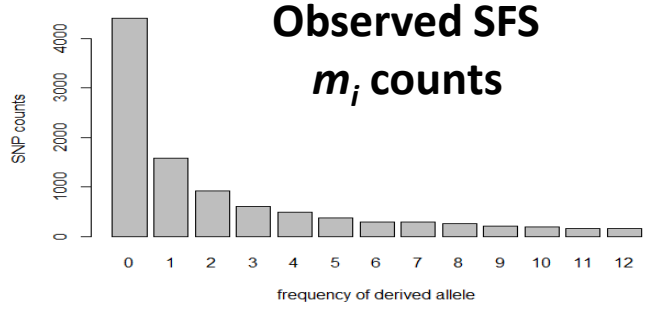
$$CL = \Pr(X \mid \theta) \propto P_0^{L-S} (1-P_0)^S \prod_{i=1}^{n-1} \hat{p}_i^{\,m_i}$$

probability of no mutation on the tree

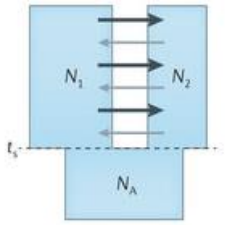
probability of at least one mutation in the tree

3 ingredientes for likelihood

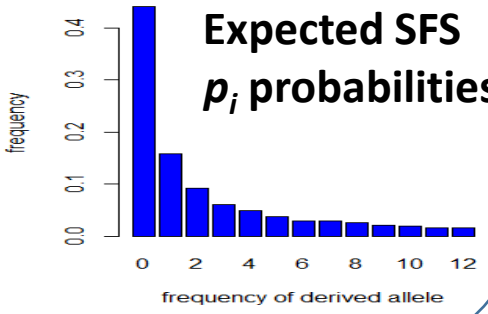
Observed SFS
m_i counts



Model



Expected SFS
p_i probabilities

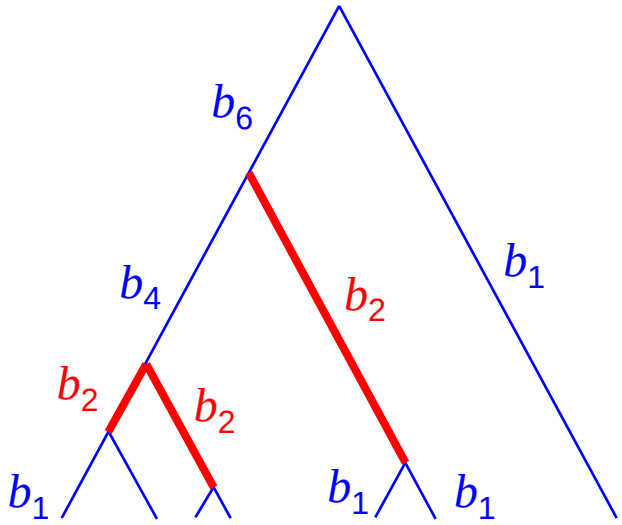


Composite likehood

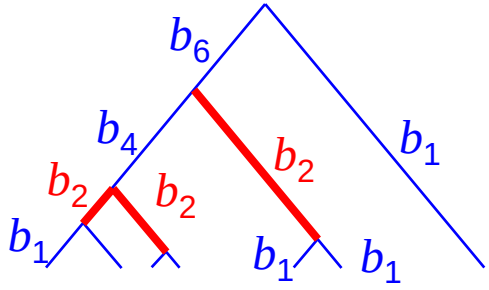
These probabilities depend:
- Number of monomorphic sites
- A fixed and mutation rate

Excoffier et al. (2013) *PloS Genetics*

Everything is relative



T_L = total branch length



Frequency	0	1	2	3	4	5	6	7
SNP probability p_i	0	Sum(b_1)/ T_L	Sum(b_2)/ T_L	Sum(b_3)/ T_L	Sum(b_4)/ T_L	Sum(b_5)/ T_L	Sum(b_6)/ T_L	0

- The same expected SFS can be obtained in a large or small tree
- We need a mutation rate and the number of monomorphic sites to distinguish among the two!

Methods based on the SFS

Different ways to obtain the expected SFS p_i under different demographic models

- Coalescent-based
  - Multiple populations
    - Fastsimcoal2 (Excoffier et al 2013 PLoS Genetics)
    - Momi (Kamm et al 2015) and Momi 2
    - Rarecoal (Schiffels et al 2016 Nat Genetics)
  - Single population
    - Stairway plot (Liu and Fu, 2015 Nat Genetics)
- Diffusion-based
    - Dadi (Gutenkunst et al 2009 PLoS Genetics)
    - Multipop (Lukic and Hey 2012 Genetics)
    - Jouganous et al (2017) Genetics

Inferring demographic history with fastsimcoal2 based on the SFS

- Fastsimcoal2 can estimate parameters from the SFS using coalescent simulations
- Maximum (composite) likelihood method
- Uses a conditional expectation (CEM) maximization algorithm to find parameter combinations that maximize the likelihood
- **It approximate the expected SFS** by performing coalescent simulations (>100,000)

Estimating the SFS and likelihoods with coalescent simulations

The expected SFS probability $\boldsymbol{p_i}$ under a given model can then be estimated on the basis of Z coalescent simulations as

$$\hat{p}_i = \frac{\sum_j^Z \sum_{k \in \Phi_i} b_{kj}}{\sum_j^Z T_j}$$

where b_{kj} is the length of the k-th compatible branch in simulation j.

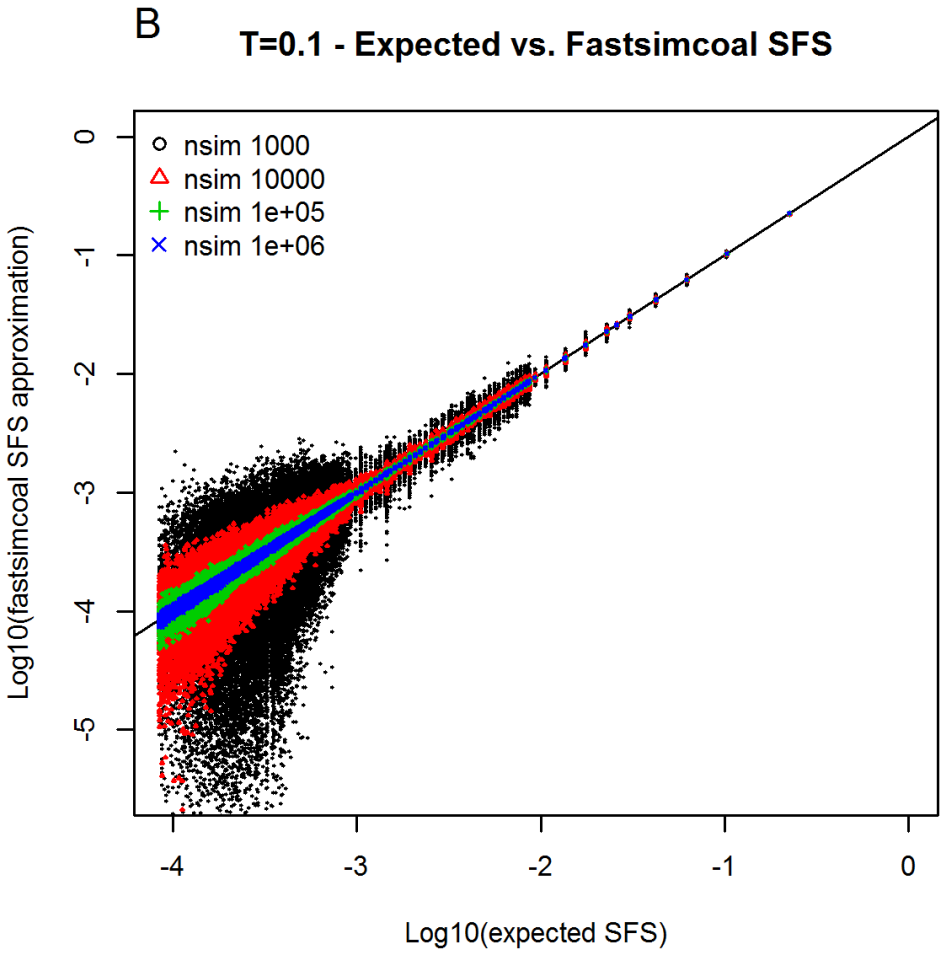
These probabilities can then be used to compute the **composite likelihood** (CL) of a given model as (Adams and Hudson, 2004)

$$CL = \Pr(X \mid \theta) \propto P_0^{L-S} (1 - P_0)^S \prod_{i=1}^{n-1} \hat{p}_i^{\,m_i}$$

where X is the SFS in a population sample of size n, S is the number of polymorphic sites, L is the length of the studied sequence, P_0 is the probability of no mutation on the tree (e^{-uT}), and m_i is the observed counts at SFS entry i.

Approximating the expected SFS with coalescent simulations

Increasing the number of simulations improves the approximation of the expected SFS

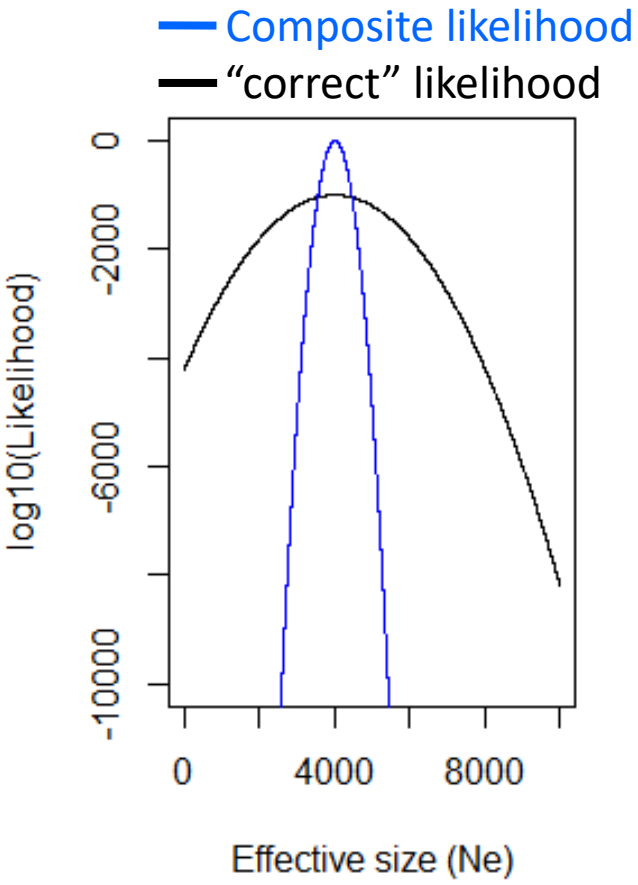


Excoffier et al. (2013) PloS Genetics; Chen (2012) TPB

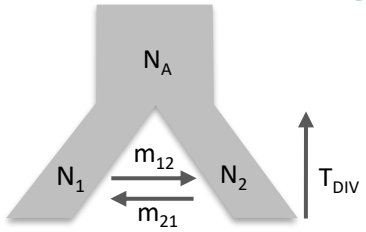
Properties of composite likelihoods

This composite likelihood (CL) is not a proper likelihood due to the non-independence of allele frequencies at linked sites.

- CL is maximized for the same parameters as full likelihood
- Can be used for parameter estimation
- Confidence intervals cannot be estimated from likelihood profile, need to bootstrap
- CL surface might be more complex than likelihood surface, and thus more difficult to explore and get the global maximum
- CL ignores information on linkage disequilibrium (recombination) between sites

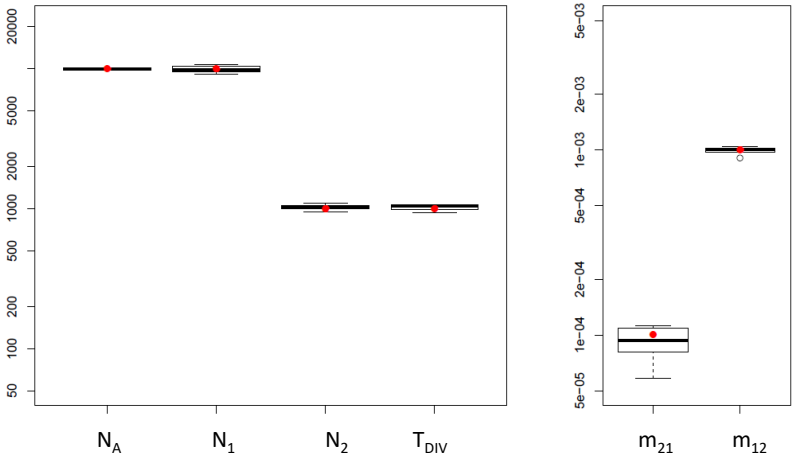


Comparisons of approaches



Simulation of 20 Mb data

fastsimcoal2



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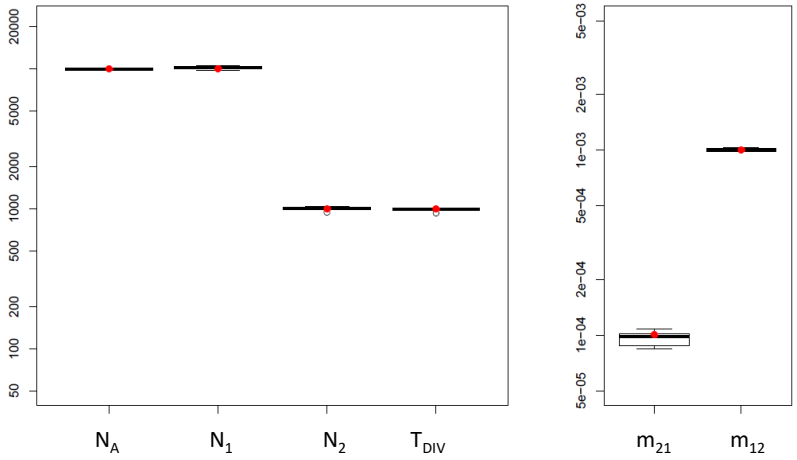

Protocol for parameter estimation

1. **Get the observed SFS**:
   - derived SFS (DAF or unfolded SFS), when the ancestral state is known;
   - minor allele frequency SFS (MAF or folded SFS) when the ancestral state is unknown
2. Define the **demographic model**
3. **Estimate the parameters** – repeat 50-100 runs, and selecting the run with maximum likelihood
4. **Bootstrap** to obtain confidence intervals for each parameter – bootstrap 10-100 datasets, by repeating a few runs for each dataset
   - For datasets with linked sites use block-bootstrap, diving the genome into blocks

Potential problems

- Maximization of the CL is not trivial (precision of the approximation and convergence problems)
- Need to repeat estimations to find maximum CL
- Needs genomic data (several Mb), difficult to have gene-specific estimates
- Next-generation sequencing data must have high coverage (>10x) to correctly estimate SFS

Limitations of estimating demographic parameters from SFS

Can one learn history from the allelic spectrum?

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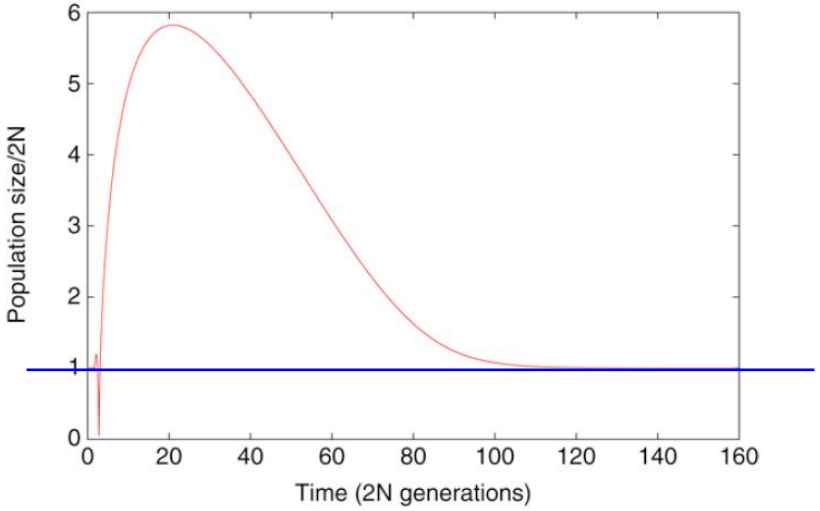
Available online 30 January 2008

A demographic history with the same spectrum as a constant size population



ELSEVIER

Theoretical Population Biology
Volume 120, March 2018, Pages 42-51

On the decidability of population size histories from finite allele frequency spectra

Soheil Baharian, Simon Gravel

Geometry of the Sample Frequency Spectrum and the Perils of Demographic Inference

Zvi Rosen, Anand Bhaskar, Sebastien Roch and Yun S. Song

GENETICS *October 1, 2018 vol. 210 no. 2 665-682;*
https://doi.org/10.1534/genetics.118.300733

Fundamental limits on the accuracy of demographic inference based on the sample frequency spectrum

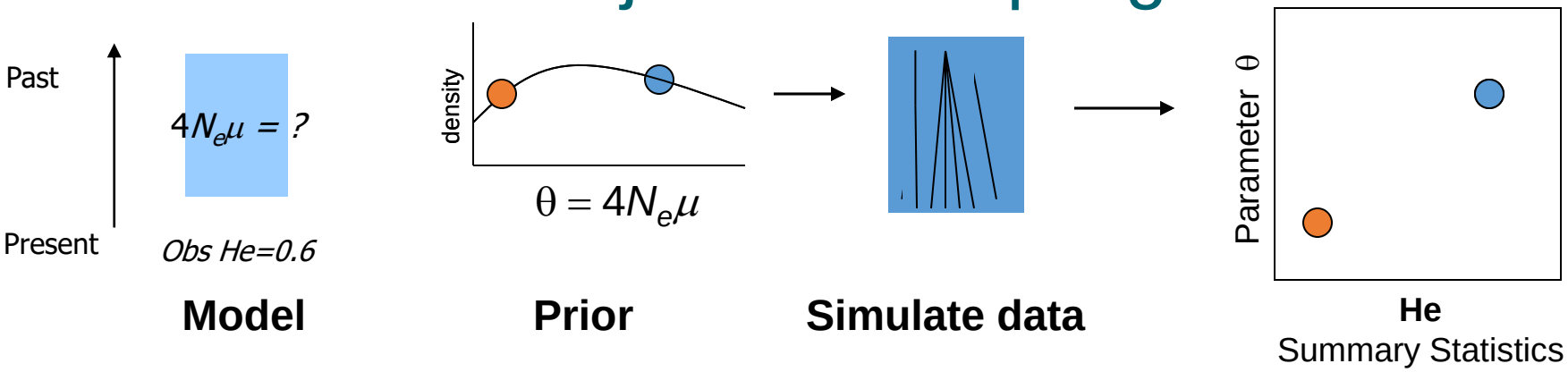
Jonathan Terhorst and Yun S. Song

PNAS June 23, 2015 112 (25) 7677-7682; first published June 8, 2015 https://doi.org/10.1073/pnas.1503717112

Approximate Bayesian Computation

- Replace the likelihood function by simulations to obtain an approximation of the posterior probability when a likelihood function is not available
- Replace data by **summary statistics**
- **Disadvantadge:** Uses less information than full-likelihood methods
- **Advantages:** Applicable to complex models, easy to perform validations and assess the quality of the estimates

Approximate Bayesian Computation
Rejection sampling

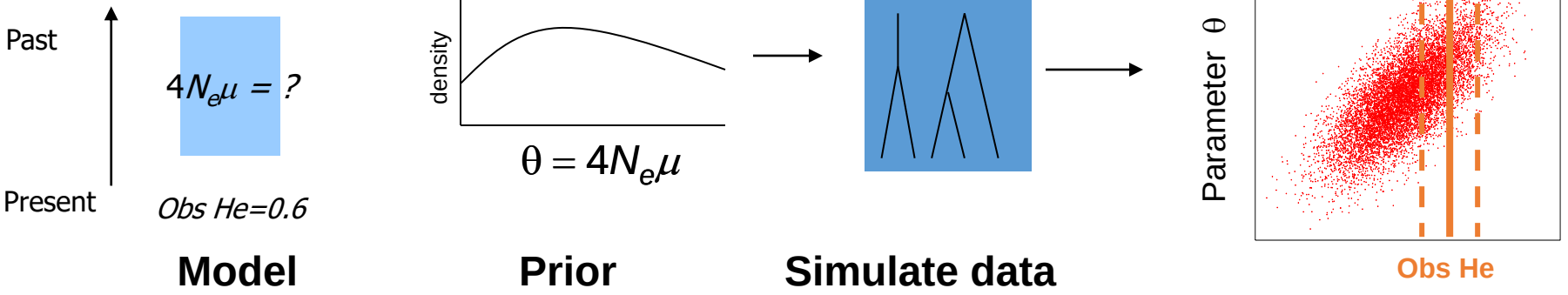


Model **Prior** **Simulate data**

- Sample θ^* from the **prior**
- Simulate data with parameter θ^*
- Compute the summary statistics of simulated data S_{sim}
- Compute a distance between $\mathbf{d} = d(S_{sim}, S_{obs})$
- Accept the parameter values if $\mathbf{d} < \delta$

Beaumont et al. (2002) Genetics, Marjoram et al. (2003) PNAS

Approximate Bayesian Computation
Rejection sampling



Model **Prior** **Simulate data**

He
Summary Statistics

- Sample θ^* from the **prior**
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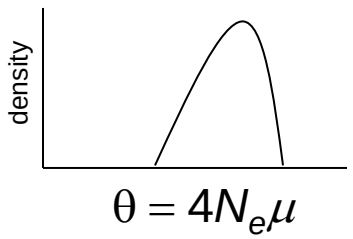
- Compute the summary statistics of simulated data S_{sim}
- Compute a distance between $\mathbf{d} = d(S_{sim}, S_{obs})$
- Accept the parameter values if $\mathbf{d} < \delta$

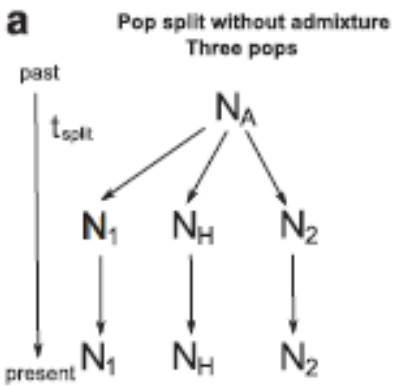


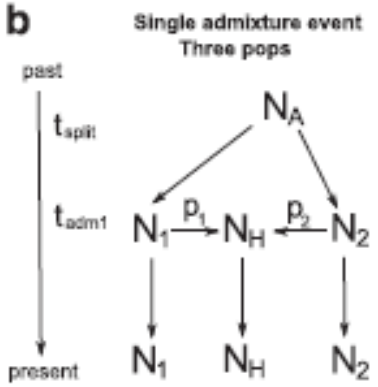
Posterior
$\mathbf{P(\theta|d(S_{obs},S_{sim})<\delta)}$

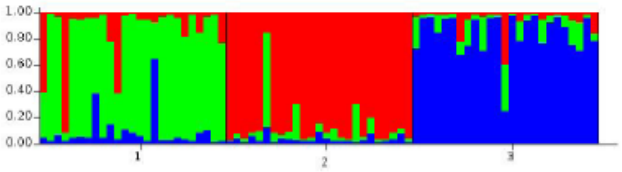
Beaumont et al. (2002) Genetics, Marjoram et al. (2003) PNAS

Model choice using ABC

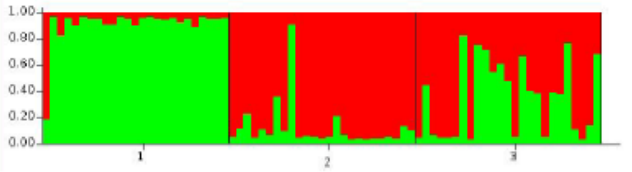
Example with 10 loci of microsatellites





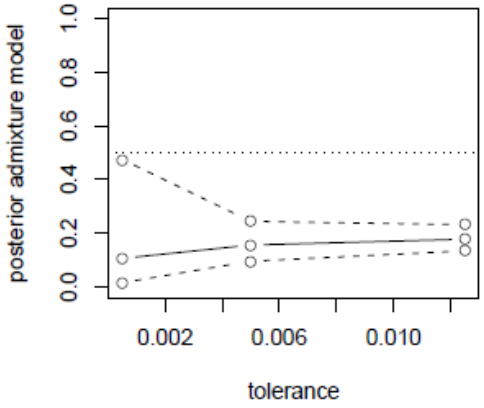


(a) No Admixture - Structure

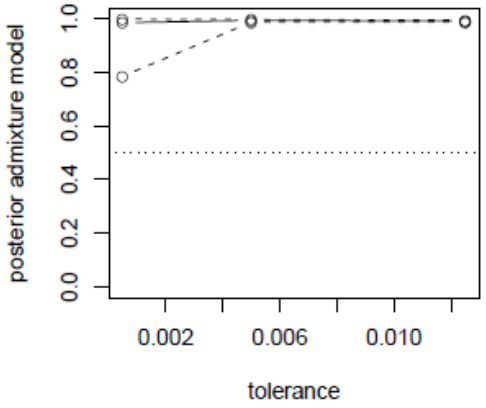


(b) Admixture - Structure

Posterior probability for the admixture model



(c) No Admixture - ABC



(d) Admixture - ABC

Sousa *et al.* (2011) Heredity

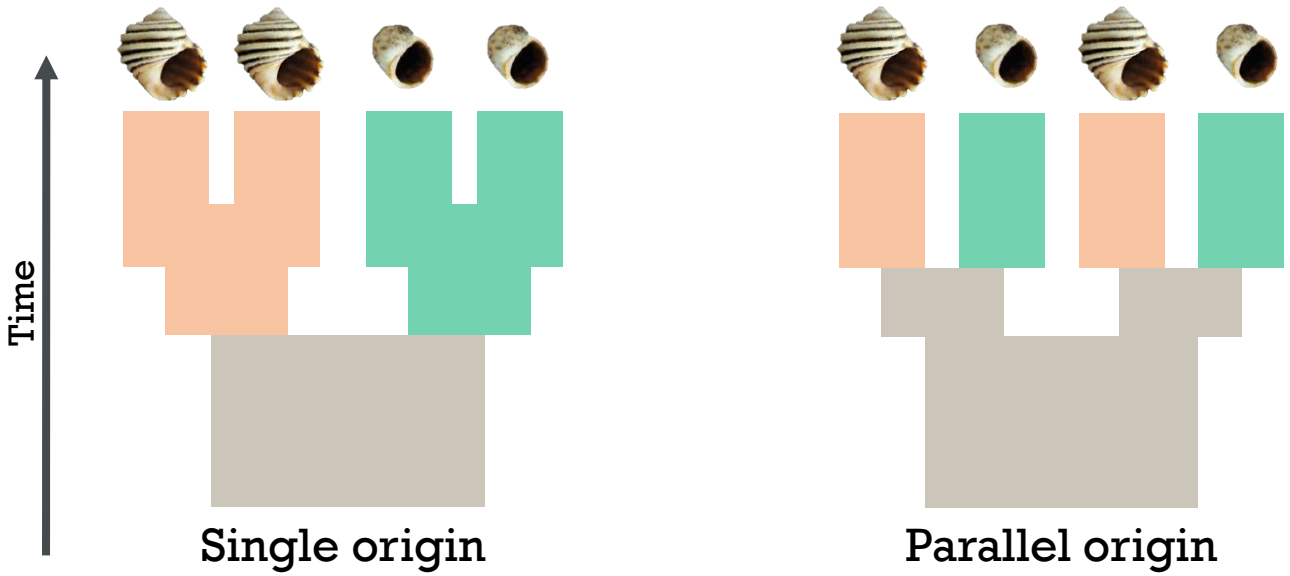
Example: ABC for Poolseq data

ABC is useful to model complex datasets, e.g., poolSeq data by explicitly modelling differential individual contribution into the pool.

João Carvalho
(EG, cE3c)

Roger Butlin
(Sheffield Univ., UK)

Evolutionary history of parallel ecotype divergence in *Littorina* snails



Risks and remedies in ABC

Table 2. Potential risks and remedies in ABC-based statistical inference.

Error Source	Potential Issue	Solution	Subsection
Nonzero tolerance ε	The inexactness introduces a bias in the computed posterior distribution.	Theoretical/practical studies of the sensitivity of the posterior distribution to the tolerance. Noisy ABC.	Approximation of the posterior
Nonsufficient summary statistics	The information loss causes inflated credible intervals.	Automatic selection/semi-automatic identification of sufficient statistics. Model validation checks (e.g., Templeton 2009 [19]).	Choice and sufficiency of summary statistics
Small number of models/mis-specified models	The investigated models are not representative/lack predictive power.	Careful selection of models. Evaluation of the predictive power.	Small number of models
Priors and parameter ranges	Conclusions may be sensitive to the choice of priors. Model choice may be meaningless.	Check sensitivity of Bayes factors to the choice of priors. Some theoretical results regarding choice of priors are available. Use alternative methods for model validation.	Prior distribution and parameter ranges
Curse-of-dimensionality	Low parameter acceptance rates. Model errors cannot be distinguished from an insufficient exploration of the parameter space. Risk of overfitting.	Methods for model reduction if applicable. Methods to speed up the parameter exploration. Quality controls to detect overfitting.	Curse-of-dimensionality
Model ranking with summary statistics	The computation of Bayes factors on summary statistics may not be related to the Bayes factors on the original data, which may therefore render the results meaningless.	Only use summary statistics that fulfill the necessary and sufficient conditions to produce a consistent Bayesian model choice. Use alternative methods for model validation.	Bayes factor with ABC and summary statistics
Implementation	Low protection to common assumptions in the simulation and the inference process.	Sanity checks of results. Standardization of software.	Indispensable quality controls

doi:10.1371/journal.pcbi.1002803.t002

Sunnaker et al. (2013) PLoS Comp. Biol.

ABC programs

Table 3. Software incorporating ABC.

Software	Keywords and Features
DIY-ABC	Software for fit of genetic data to complex situations. Comparison of competing models. Parameter estimation. Computation of bias and precision measures for a given model and known parameters values.
ABC R package	Several ABC algorithms for performing parameter estimation and model selection. Nonlinear heteroscedastic regression methods for ABC. Cross-validation tool.
ABC-SysBio	Python package. Parameter inference and model selection for dynamical systems. Combines ABC rejection sampler, ABC SMC for parameter inference, and ABC SMC for model selection. Compatible with models written in Systems Biology Markup Language (SBML). Deterministic and stochastic models.
ABCtoolbox	Open source programs for various ABC algorithms including rejection sampling, MCMC without likelihood, a particle-based sampler, and ABC-GLM. Compatibility with most simulation and summary statistics computation programs.
msBayes	Open source software package consisting of several C and R programs that are run with a Perl "front-end." Hierarchical coalescent models. Population genetic data from multiple co-distributed species.
PopABC	Software package for inference of the pattern of demographic divergence. Coalescent simulation. Bayesian model choice.
ONeSAMP	Web-based program to estimate the effective population size from a sample of microsatellite genotypes. Estimates of effective population size, together with 95% credible limits.
ABC4F	Software for estimation of F-statistics for dominant data.
2BAD	Two-event Bayesian ADmixture. Software allowing up to two independent admixture events with up to three parental populations. Estimation of several parameters (admixture, effective sizes, etc.). Comparison of pairs of admixture models.

doi:10.1371/journal.pcbi.1002803.t003

ABC_GWH http://www.abcgwh.sitew.ch/#Background.A

Sunnaker et al. (2013) PLoS Comp. Biol.

Demography and linked selection

Research article

Background selection as null hypothesis in population genomics: insights and challenges from *Drosophila* studies

Josep M. Comeron

Published: 06 November 2017 https://doi.org/10.1098/rstb.2016.0471

The Impact of Purifying and Background Selection on the Inference of Population History: Problems and Prospects

Parul Johri, Kellen Riall, Hannes Becher, Laurent Excoffier, Brian Charlesworth, Jeffrey D. Jensen

Molecular Biology and Evolution, Volume 38, Issue 7, July 2021, Pages 2986–3003, https://doi.org/10.1093/molbev/msab050

Published: 16 February 2021

Research Article

Genetics and Genomics

Background selection and biased gene conversion affect more than 95% of the human genome and bias demographic inferences

Fanny Pouyet, Simon Aeschbacher, Alexandre Thiéry, Laurent Excoffier

University of Bern, Switzerland; Swiss Institute of Bioinformatics, Switzerland; University of Zurich, Switzerland

Aug 20, 2018 · https://doi.org/10.7554/eLife.36317

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CONSENSUS VIEW

Recommendations for improving statistical inference in population genomics

Parul Johri, Charles F. Aquadro, Mark Beaumont, Brian Charlesworth, Laurent Excoffier, Adam Eyre-Walker, Peter D. Keightley, Michael Lynch, Gil McVean, Bret A. Payseur, Susanne P. Pfeifer, Wolfgang Stephan, Jeffrey D. Jensen

Published: May 31, 2022 • https://doi.org/10.1371/journal.pbio.3001669

Demographic inference based on Site frequency spectrum (SFS) – Part II

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2022 WSPG Cesky Krumlov
09 Jun 2022

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Outline part II

Example of Applications:

- Human dispersal out of Africa (high quality whole-genome) – lessons on model comparison with linked SNPs
- Human colonization of Siberia and America (ancient whole-genome data) - lessons on dealing with sequencing errors
- Deer mice colonization of Nebraska Sand Hills (targeted re-capture data) – lessons on effects of filtering
- Divergence times and gene flow in sawflies (ddRAD-seq data) – lessons from model comparison with ddRAD
- Hybridization in freshwater fish (GBS data) - lessons from inferring relative parameters

Nourlangie, Kakadu National Park, NT, Australia

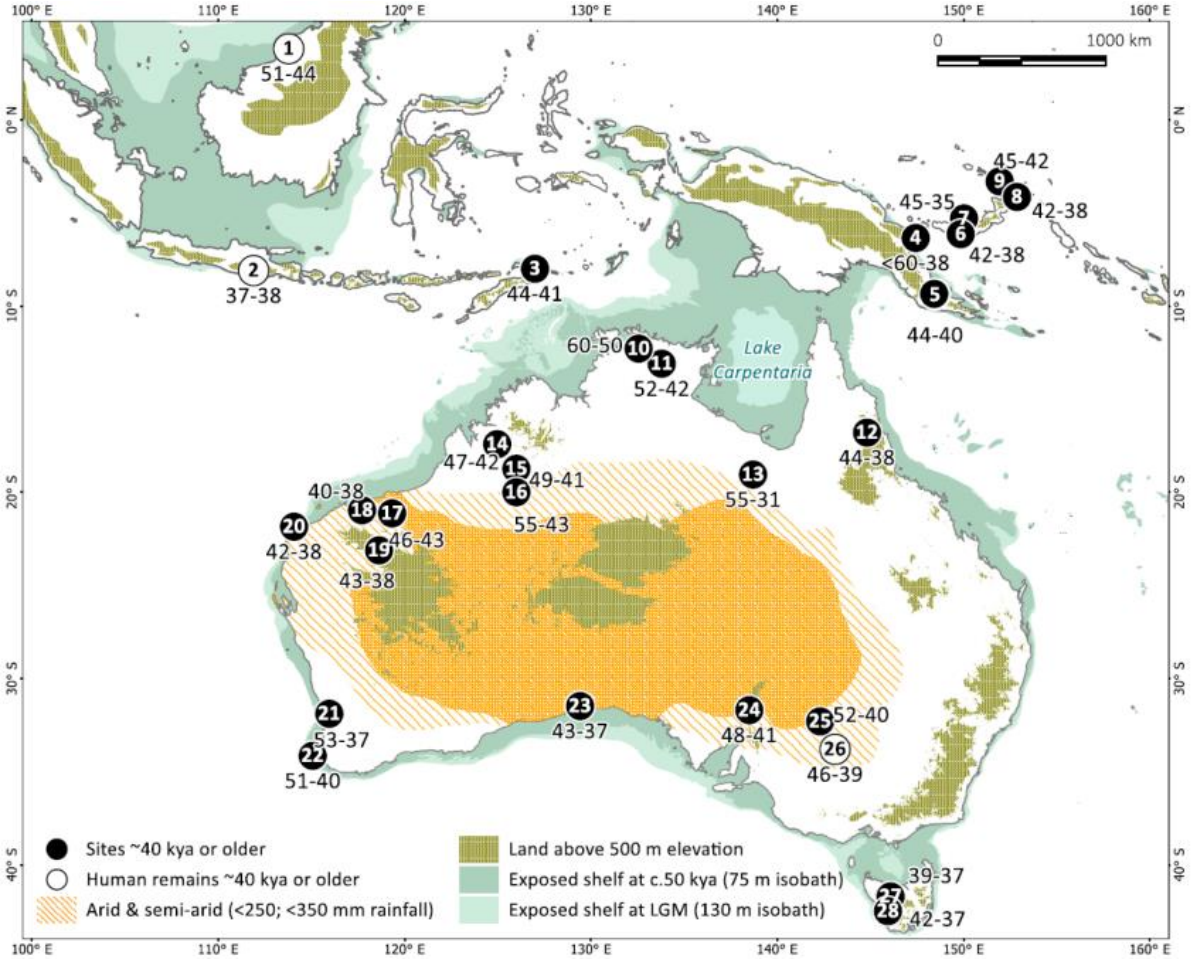
A genomic history of Aboriginal Australia

Anna-Sapfo Malaspinas[1,2,3]*, Michael C. Westaway[4]*, Craig Muller[1]*, Vitor C. Sousa[2,3]*, Oscar Lao[5,6]*, Isabel Alves[2,3,7]*, Anders Bergström[8]*, Georgios Athanasiadis[9], Jade Y. Cheng[9,10], Jacob E. Crawford[10,11], Tim H. Heupink[4], Enrico Macholdt[12], Stephan Peischl[3,13], Simon Rasmussen[14], Stephan Schiffels[15], Sankar Subramanian[4], Joanne L. Wright[4], Anders Albrechtsen[16], Chiara Barbieri[12,17], Isabelle Dupanloup[2,3], Anders Eriksson[18,19], Ashot Margaryan[1], Ida Moltke[16], Irina Pugach[12], Thorfinn S. Korneliussen[1], Ivan P. Levkivskyi[20], J. Víctor Moreno-Mayar[1], Shengyu Ni[12], Fernando Racimo[10], Martin Sikora[1], Yali Xue[8], Farhang A. Aghakhanian[21], Nicolas Brucato[22], Søren Brunak[23], Paula F. Campos[1,24], Warren Clark[25], Sturla Ellingvåg[26], Gudjugudju Fourmile[27], Pascale Gerbault[28,29], Darren Injie[30], George Koki[31], Matthew Leavesley[32], Betty Logan[33], Aubrey Lynch[34], Elizabeth A. Matisoo-Smith[35], Peter J. McAllister[36], Alexander J. Mentzer[37], Mait Metspalu[38], Andrea B. Migliano[29], Les Murgha[39], Maude E. Phipps[21], William Pomat[31], Doc Reynolds[40], Francois-Xavier Ricaut[22], Peter Siba[31], Mark G. Thomas[28], Thomas Wales[41], Colleen Ma'run Wall[42], Stephen J. Oppenheimer[43], Chris Tyler-Smith[8], Richard Durbin[8], Joe Dortch[44], Andrea Manica[18], Mikkel H. Schierup[9], Robert A. Foley[1,45], Marta Mirazón Lahr[1,45], Claire Bowern[46], Jeffrey D. Wall[47], Thomas Mailund[9], Mark Stoneking[12], Rasmus Nielsen[1,48], Manjinder S. Sandhu[8], Laurent Excoffier[2,3], David M. Lambert[4] & Eske Willerslev[1,8,18]

Nature(2016)

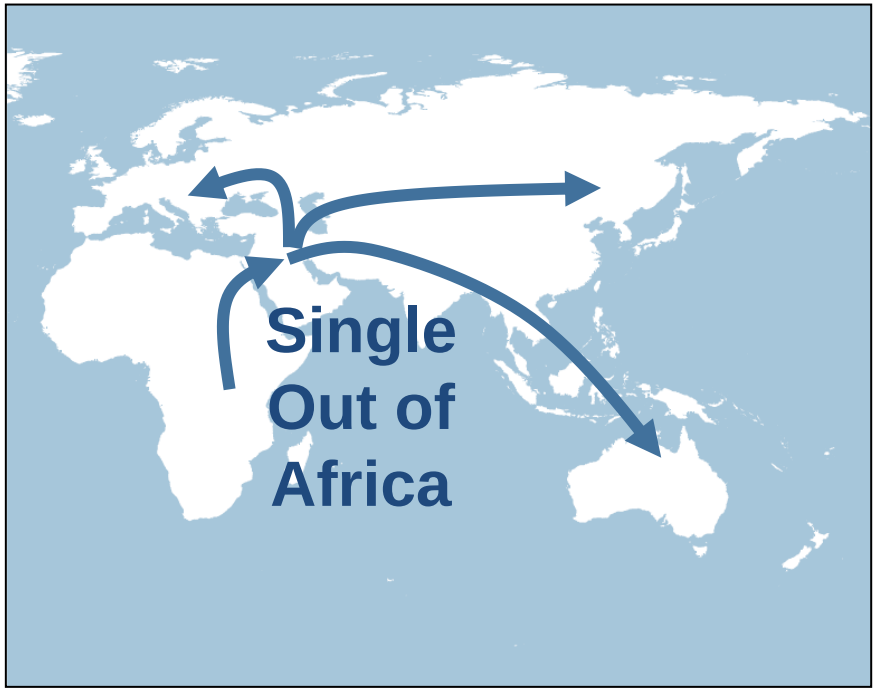
Ewaninga Rock Carvings Conservation Reserve, NT, Australia

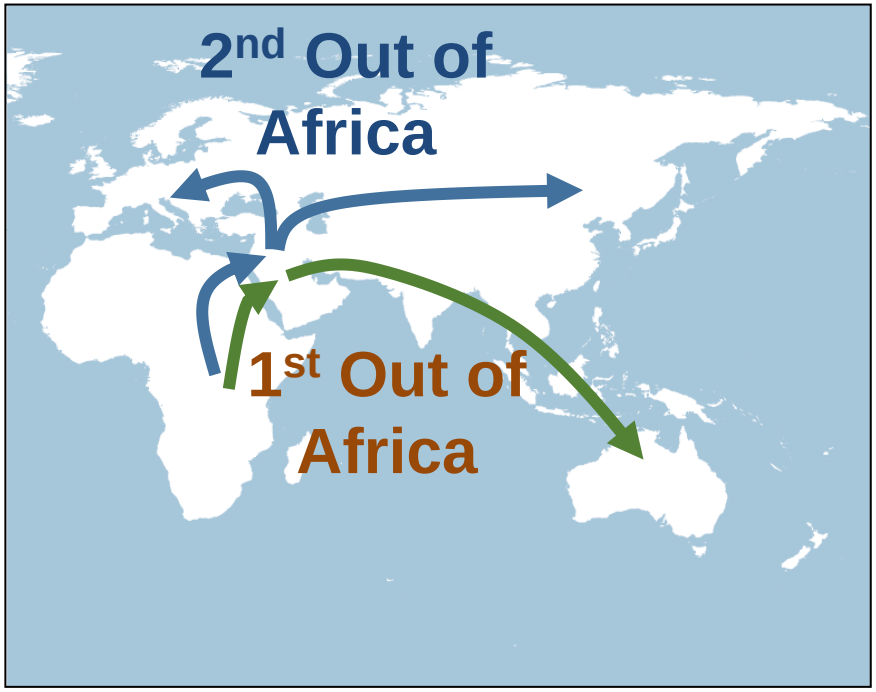
Australia harbors some of the oldest modern human remains outside Africa



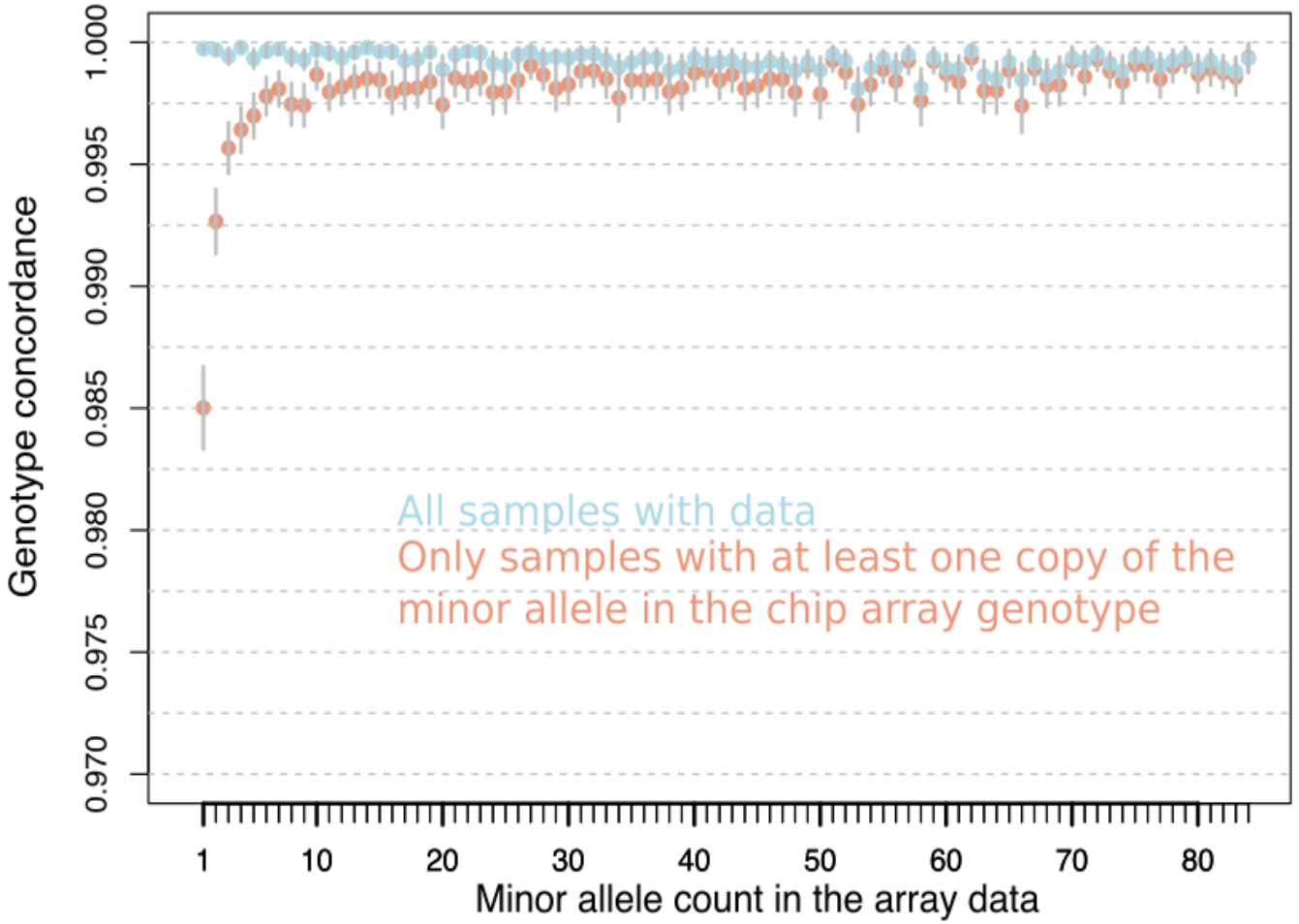
Many sites and remains dated to be older than 40 kya, suggesting a human settlement 47.5-55 kya

One wave out of Africa *vs* Two waves out of Africa





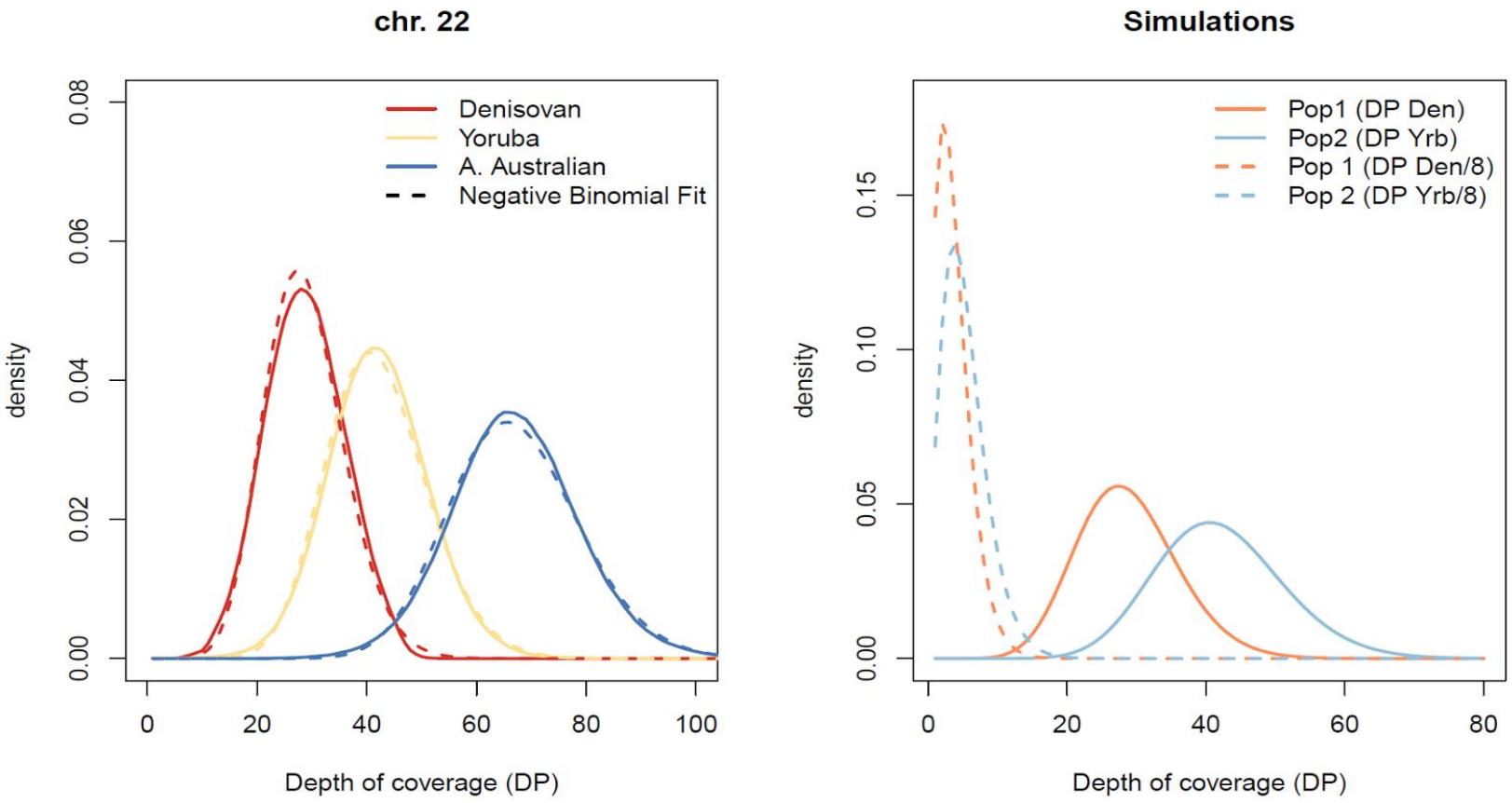
83 high-coverage Aboriginal Australians genomes



Average depth of coverage: 65x

Very good quality of genotype calls

Effect of depth of coverage on SFS

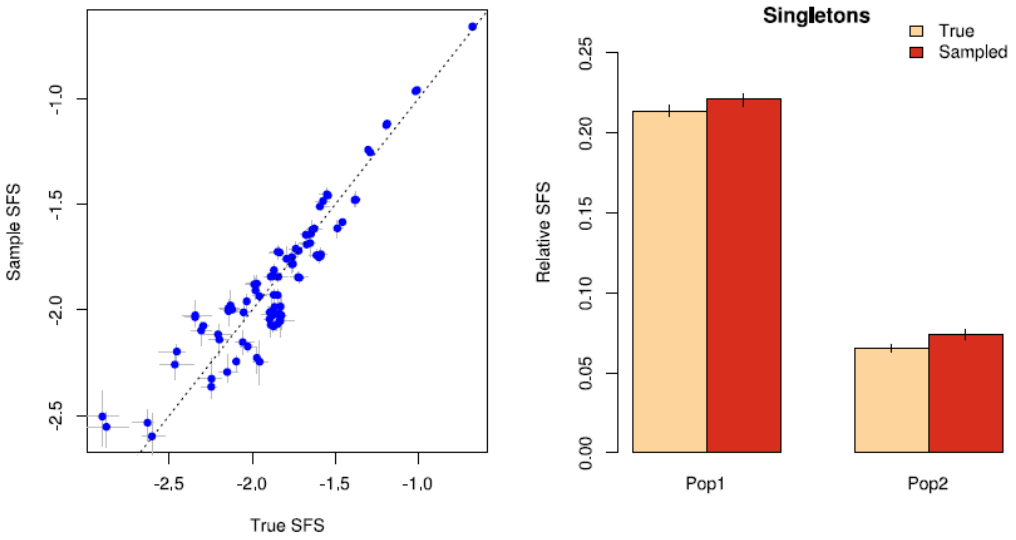


- Compared 2D SFS based on depth of coverage of observed data (mean larger than >20x), with a distribution 8 times smaller.

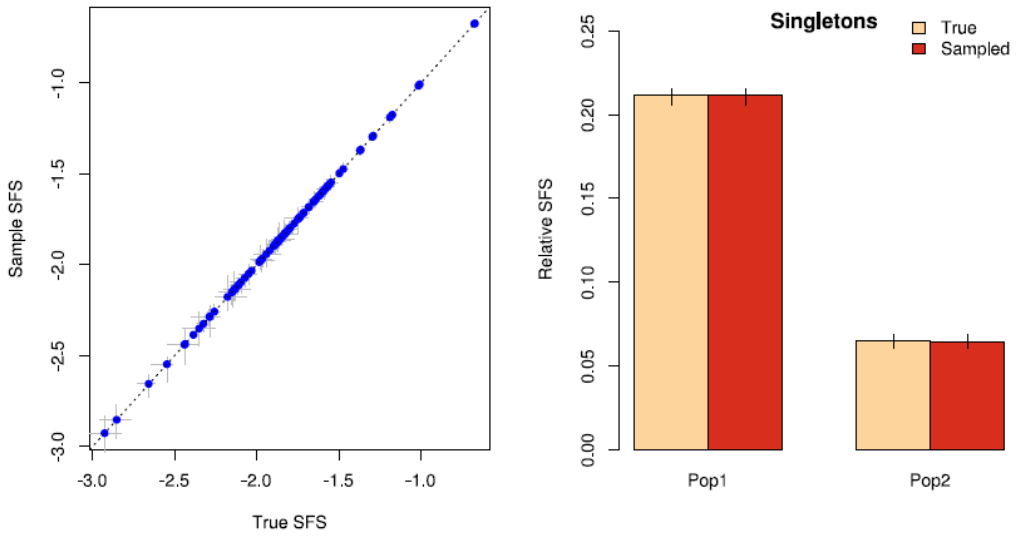
A note on recovering the SFS from genomic data

- Simulation study
- Low depth of coverage and missing data lead to biased SFS towards rare variants

a) Low depth of coverage, no GQ filter, allowing missing data



b) Depth of coverage similar to observed data, GQ>30 filter, no missing dat



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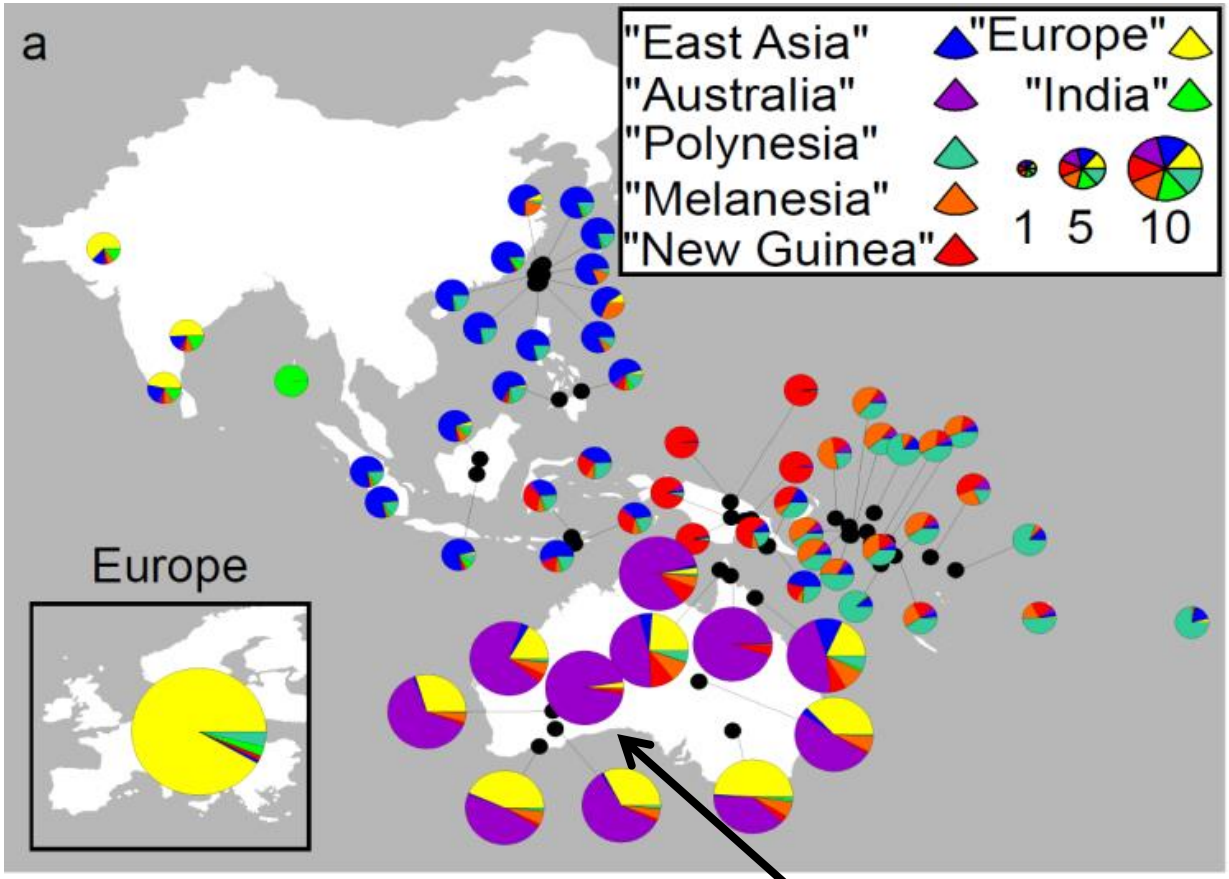


Average depth of coverage: 65x

★ Archaic human genomes:
- 1 Neanderthal (~66 kya)
- 1 Denisovan (~52 kya)

Mutation rate assumed
1.25×10^{-8} /site/gen
Scally and Durbin (2012) *Nat. Rev. Genet.*

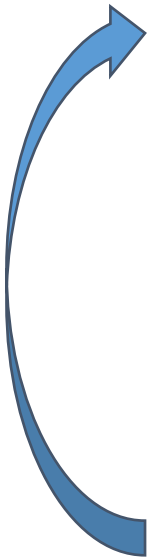
Generation time
29 years/gen
Fenner (2005) *Am. J. Phys. Anthropol.*

Since we want to infer demography we tried to minimize the number of sites affected by selection:

- 985 1Mb blocks outside genic regions and CpG islands (~4.3 Million SNPs)
- 5 dimensional SFS (16,875 entries)
- Confidence intervals obtained using block-bootstrap

Towards a model to test the hypotheses: One *vs* Two waves Out of Africa

- Data (SFS)
- (Re-)Define model (hypotheses to test)
- Run fastsimcoal2
- Estimates!
  - Assess the fit to the data



Do you have an outgroup?

- **Yes** – use the derived (unfolded) SFS
- **No** – use the minor allele frequency spectrum (folded)

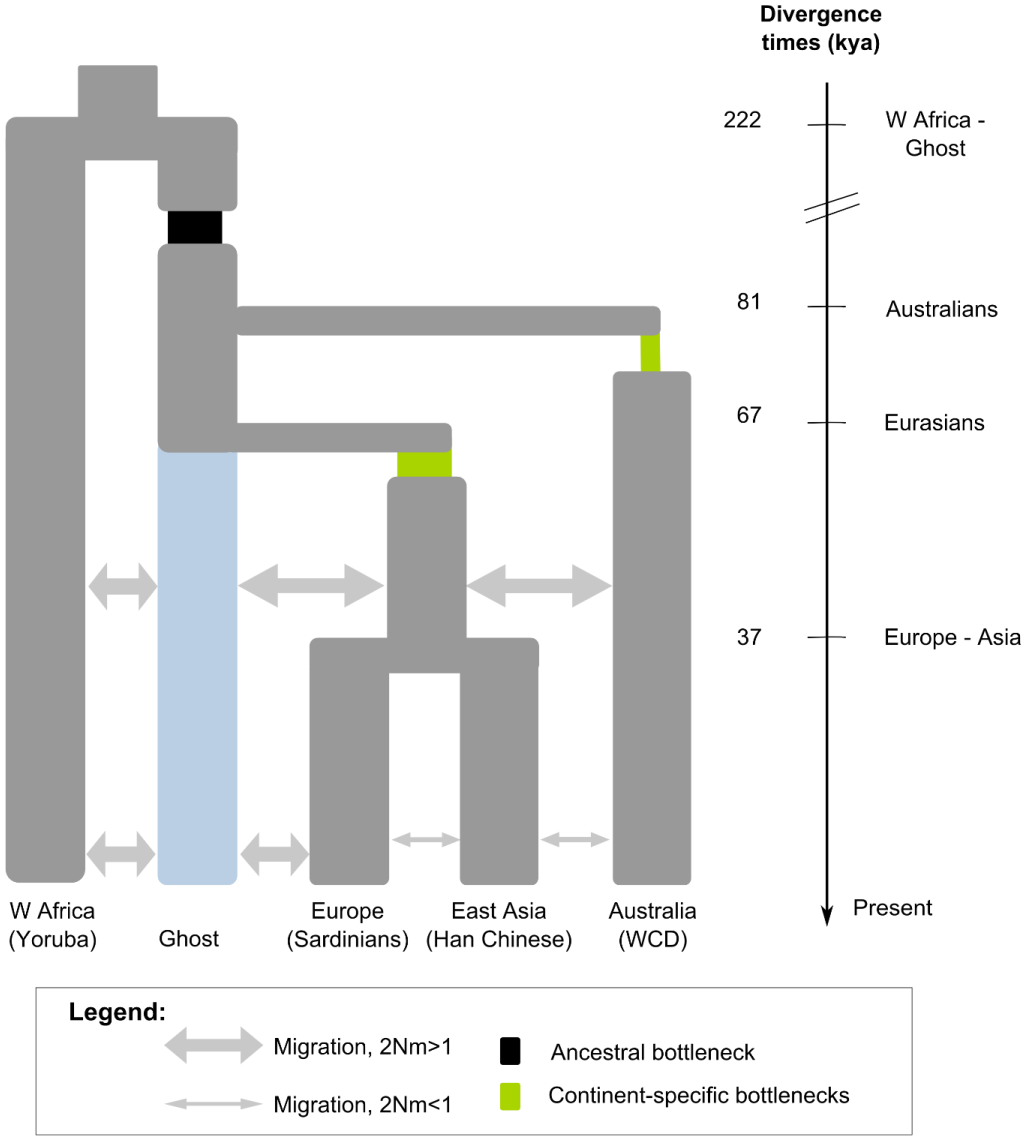
Do you have monomorphic sites?

- **Yes** - then, given a mutation rate you can infer the absolute times and effective sizes
- **No** – then all your estimates need to be relative to a fixed parameter (fixed Ne or fixed time)

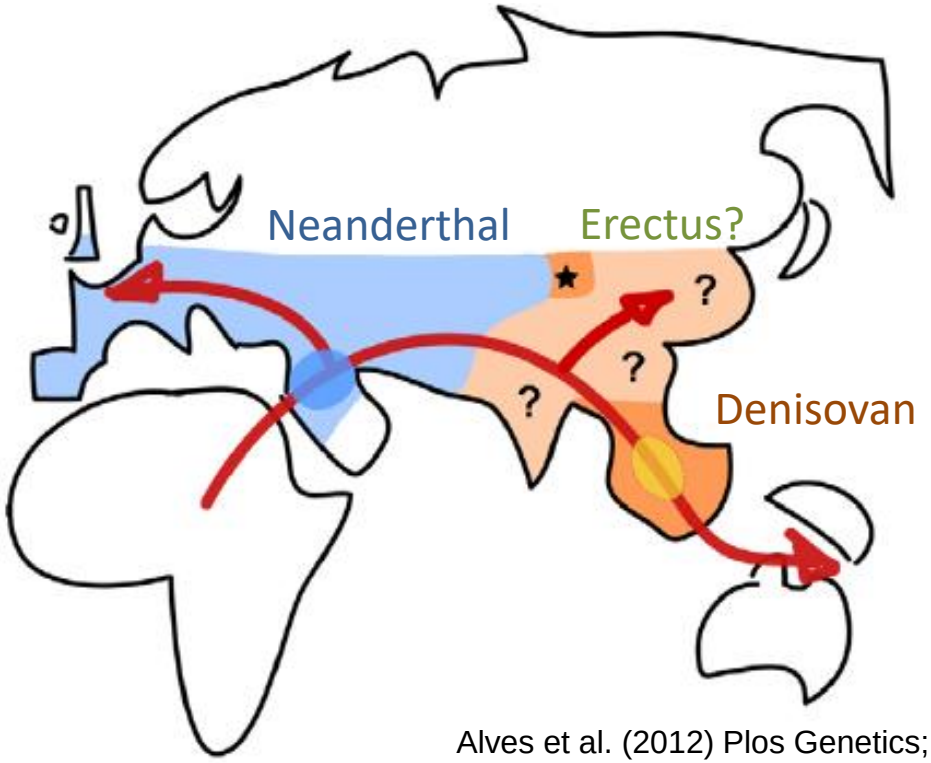
We always get results…

Evidence of two waves Out of Africa:

- Old split leading to colonization of Australia (81kya)
- More recent split leading to colonization of Eurasia (67 kya)



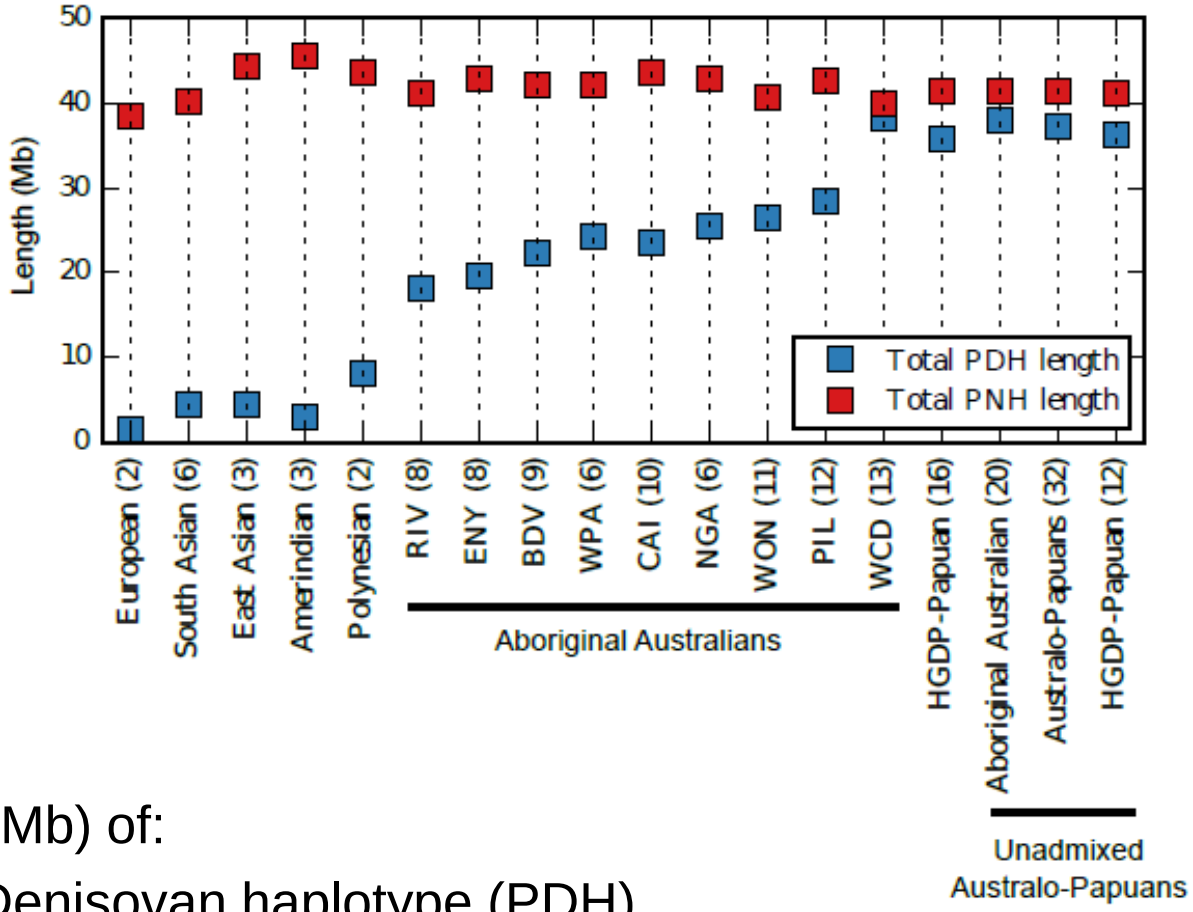
Towards a model incorporating Neanderthal and Denisovan admixture



Alves et al. (2012) Plos Genetics;

- Non-African populations: 1-4% estimated Neanderthal admixture
- Aboriginal Australians and New Guineans: 3-6% estimated Denisovan admixture
- Archaic admixture can affect times of split estimates

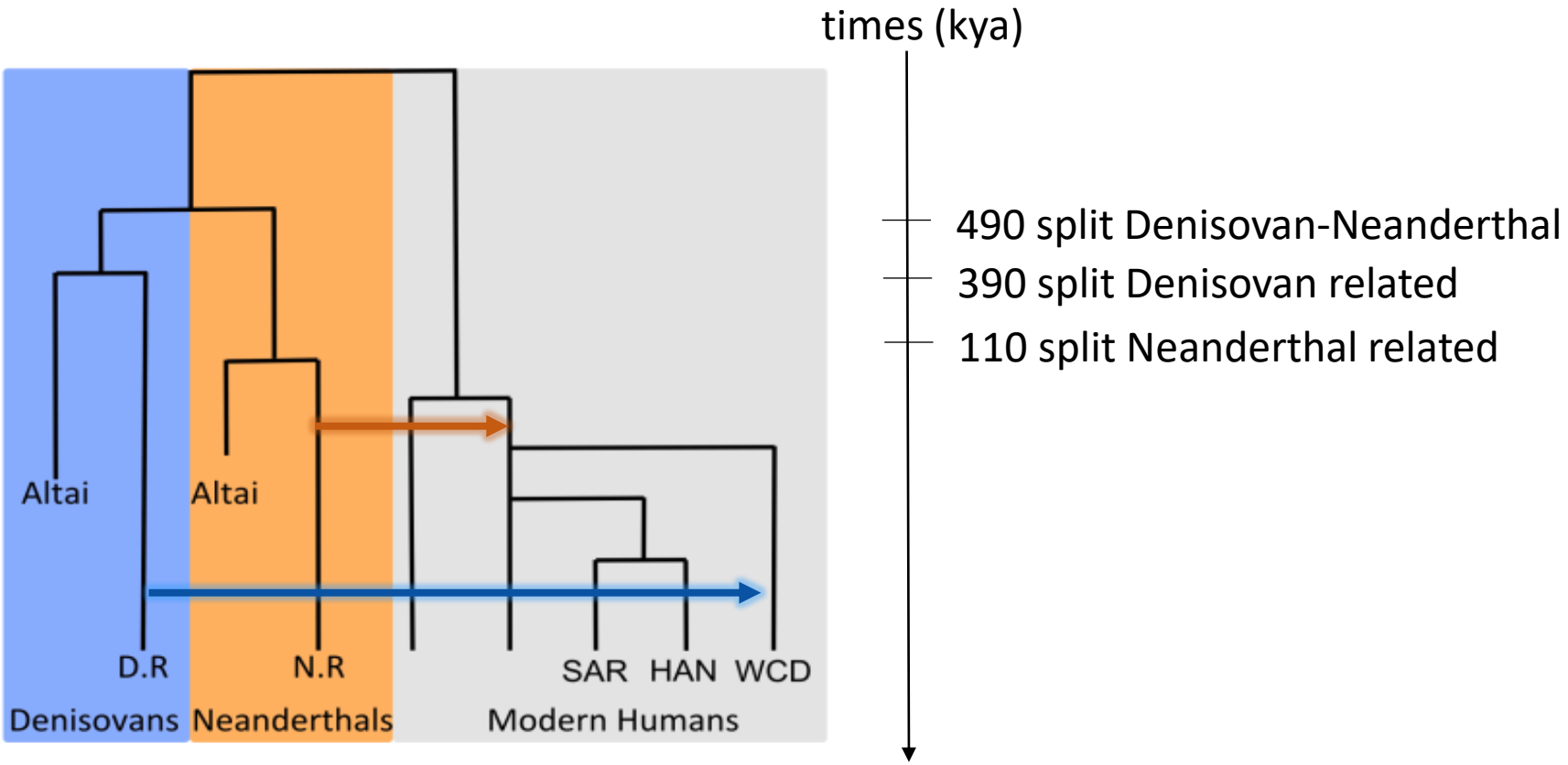
Evidence of archaic introgression



Total length (Mb) of:

- Putative Denisovan haplotype (PDH)
- Putative Neanderthal haplotypes (PNH)

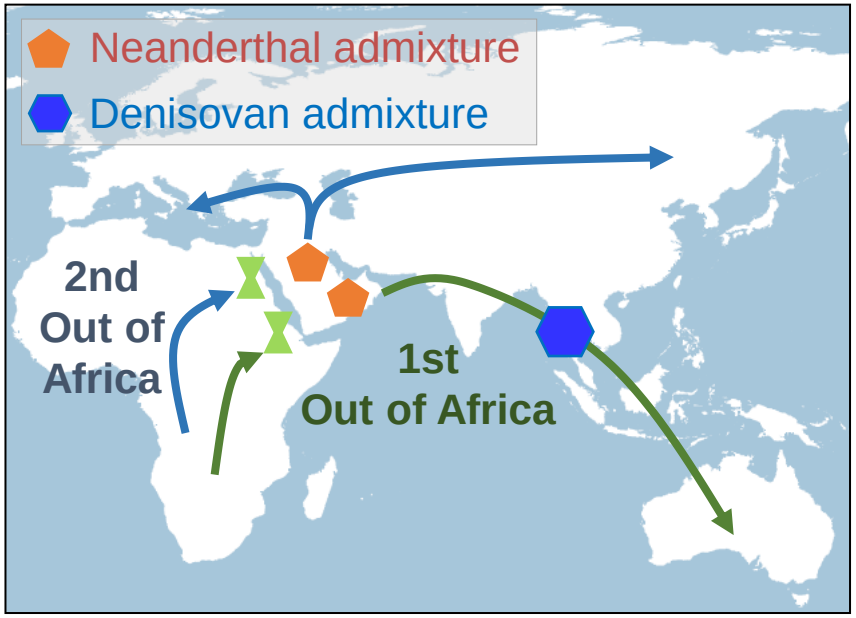
Accounting for shared ancestry of Neanderthal and Denisovan

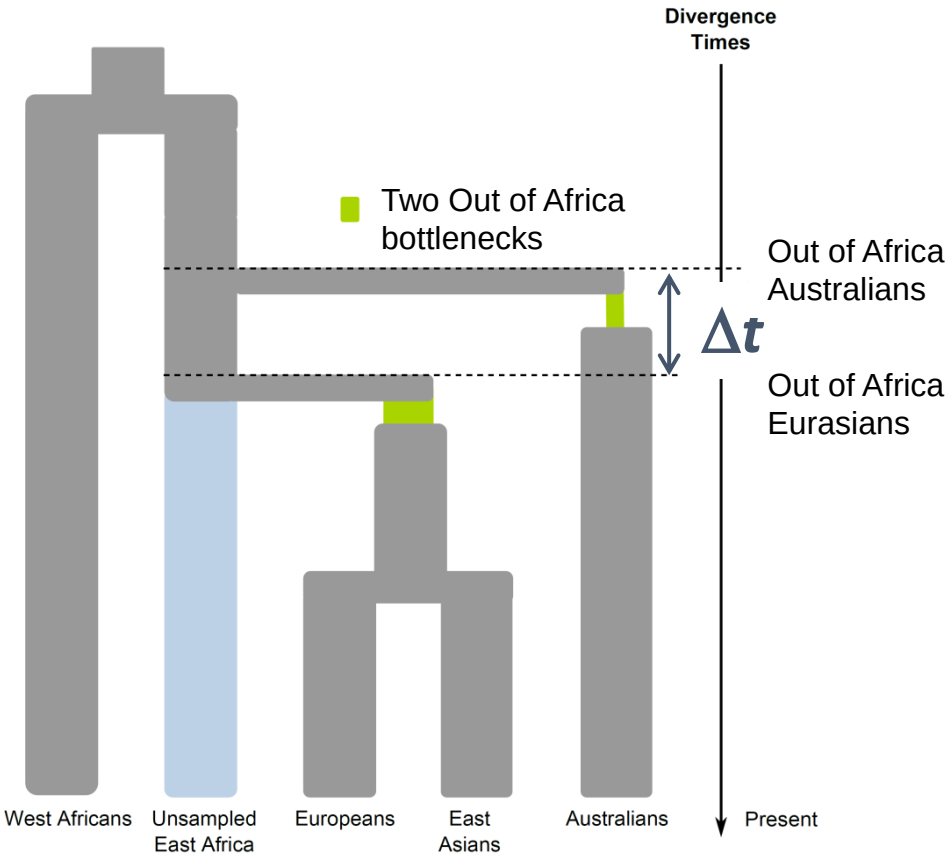


Admixture occurs between modern humans and:

- Denisovan-related (D.R.) population
- Neanderthal-related (N.R.) population

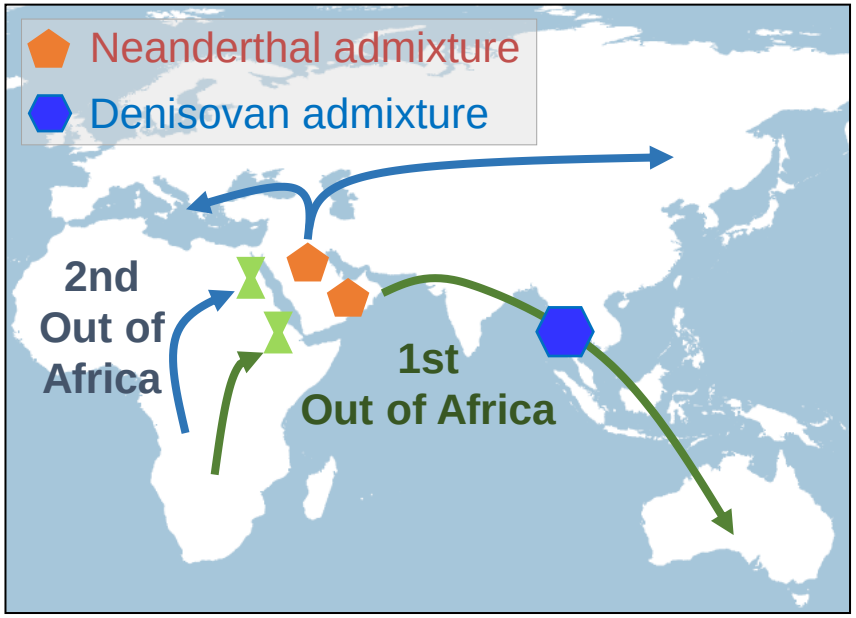
Two-waves out of Africa

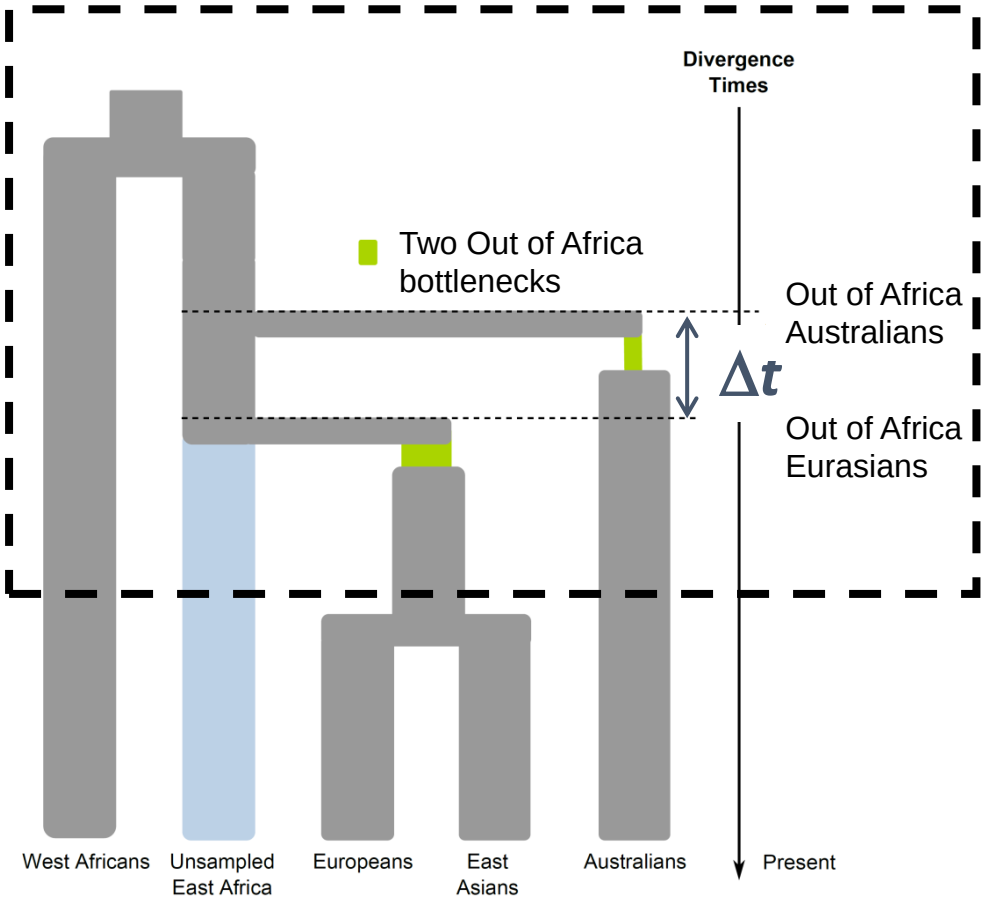




- Two different divergence times ($\Delta t >> 0$)
- Two independent bottlenecks associated with the two Out of Africa events

Two-waves out of Africa





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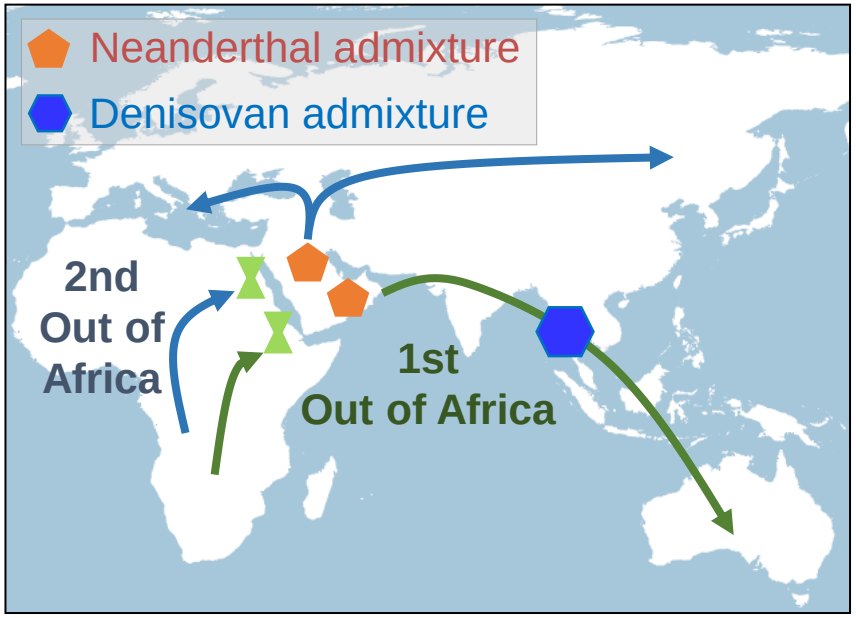
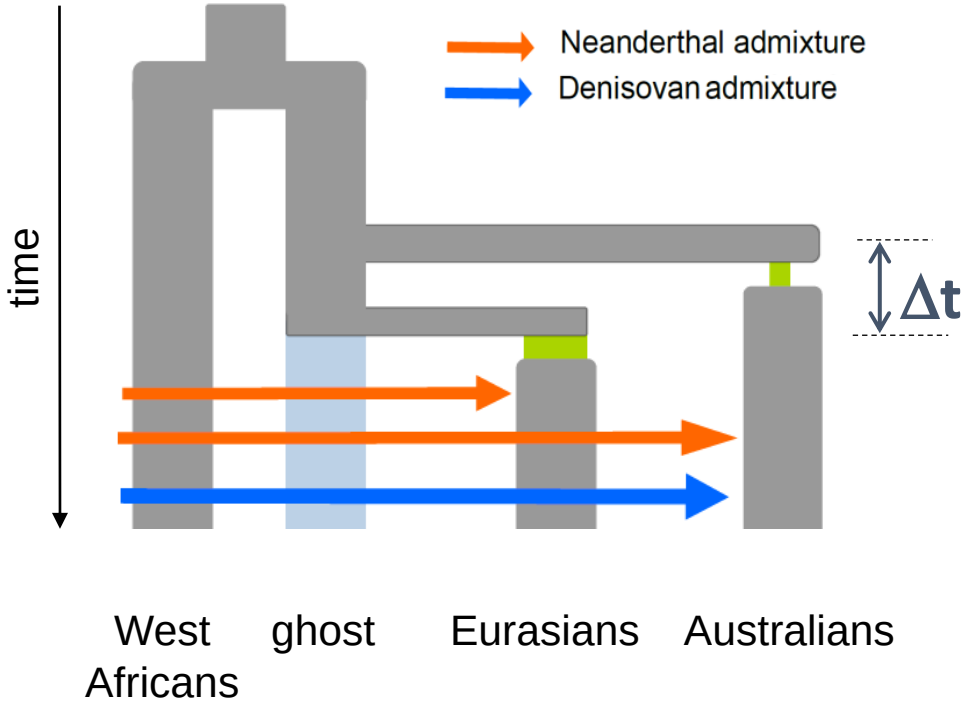
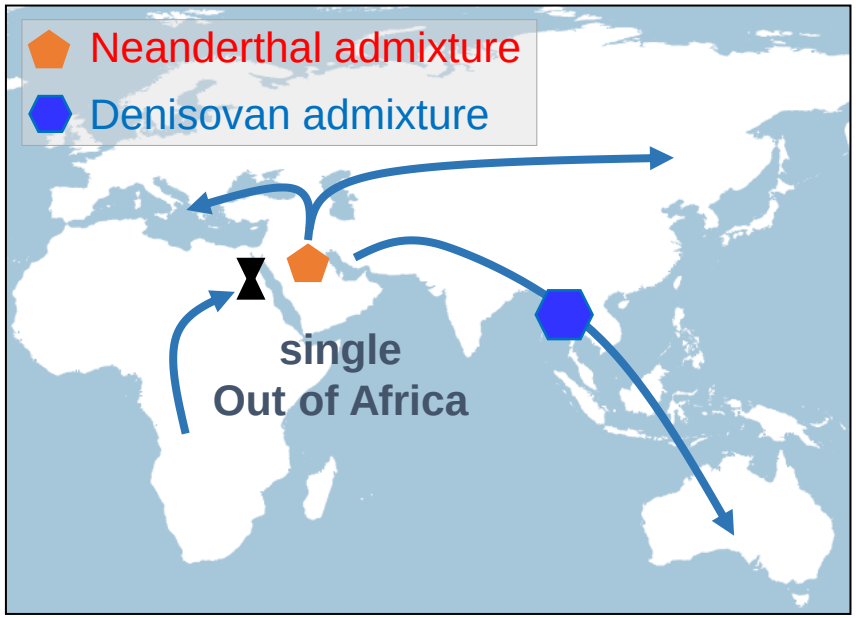
Two-waves out of Africa

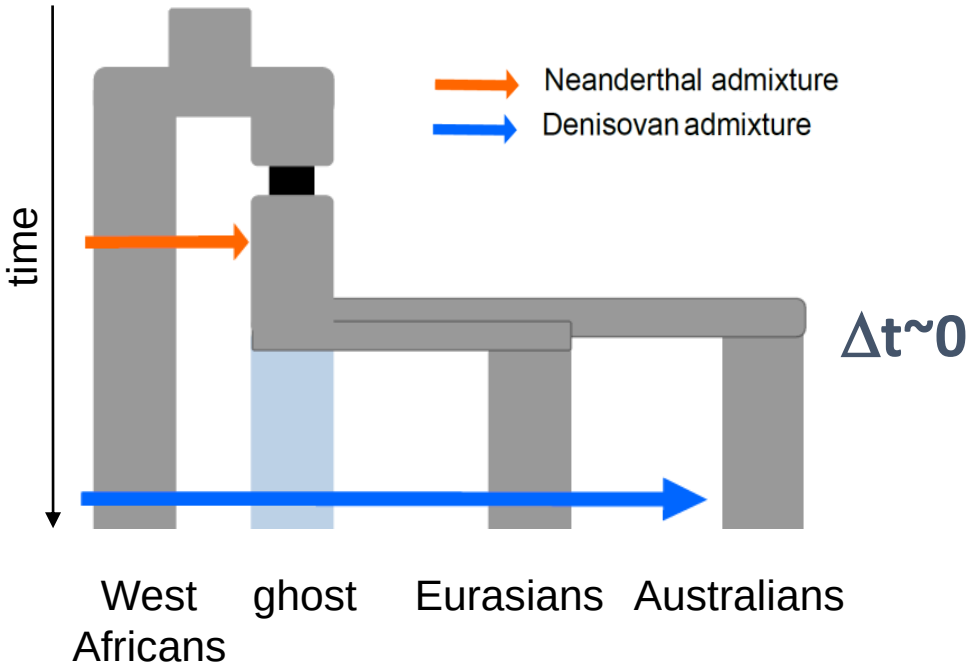




- Two different divergence times ($\Delta t >> 0$)
- Two independent bottlenecks associated with the two Out of Africa events

One wave out of Africa

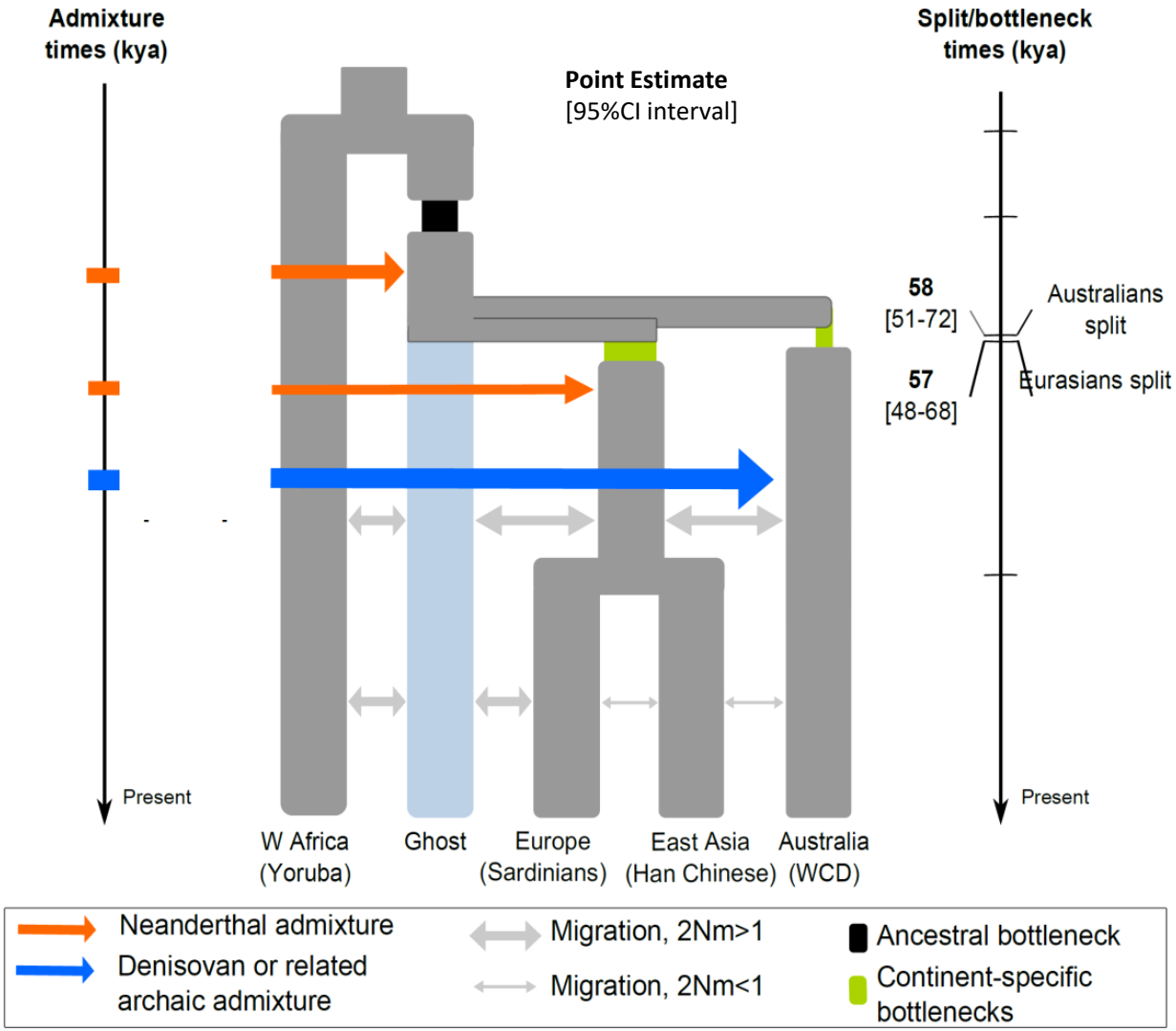




- Similar divergence times (Δt close to zero)
- One single bottlenecks associated with the Out of Africa events
- A major admixture pulse with Neanderthal

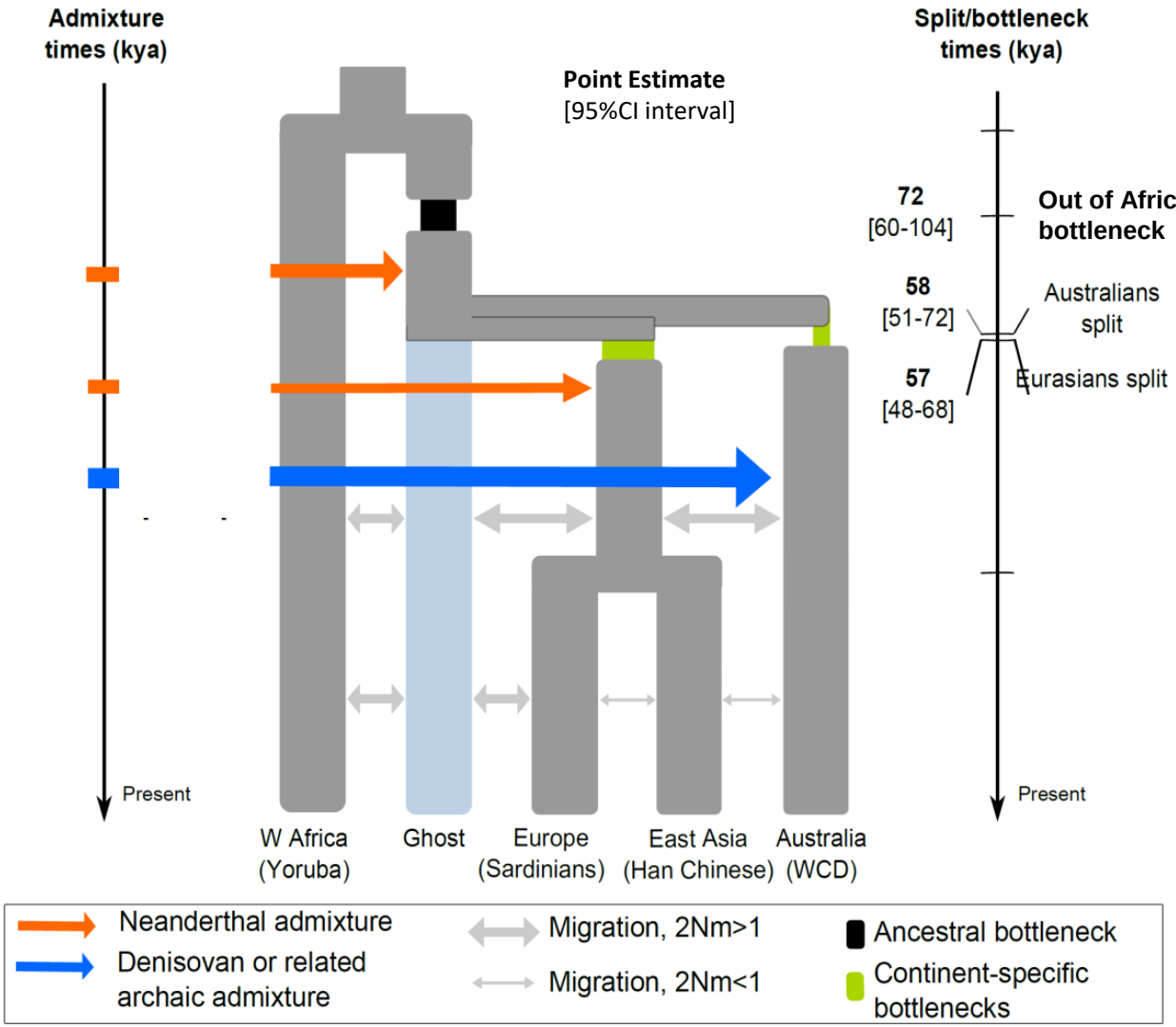
A single wave Out of Africa is consistent with our estimates when accounting for archaic admixture

- Similar divergence time (Δt close to zero)



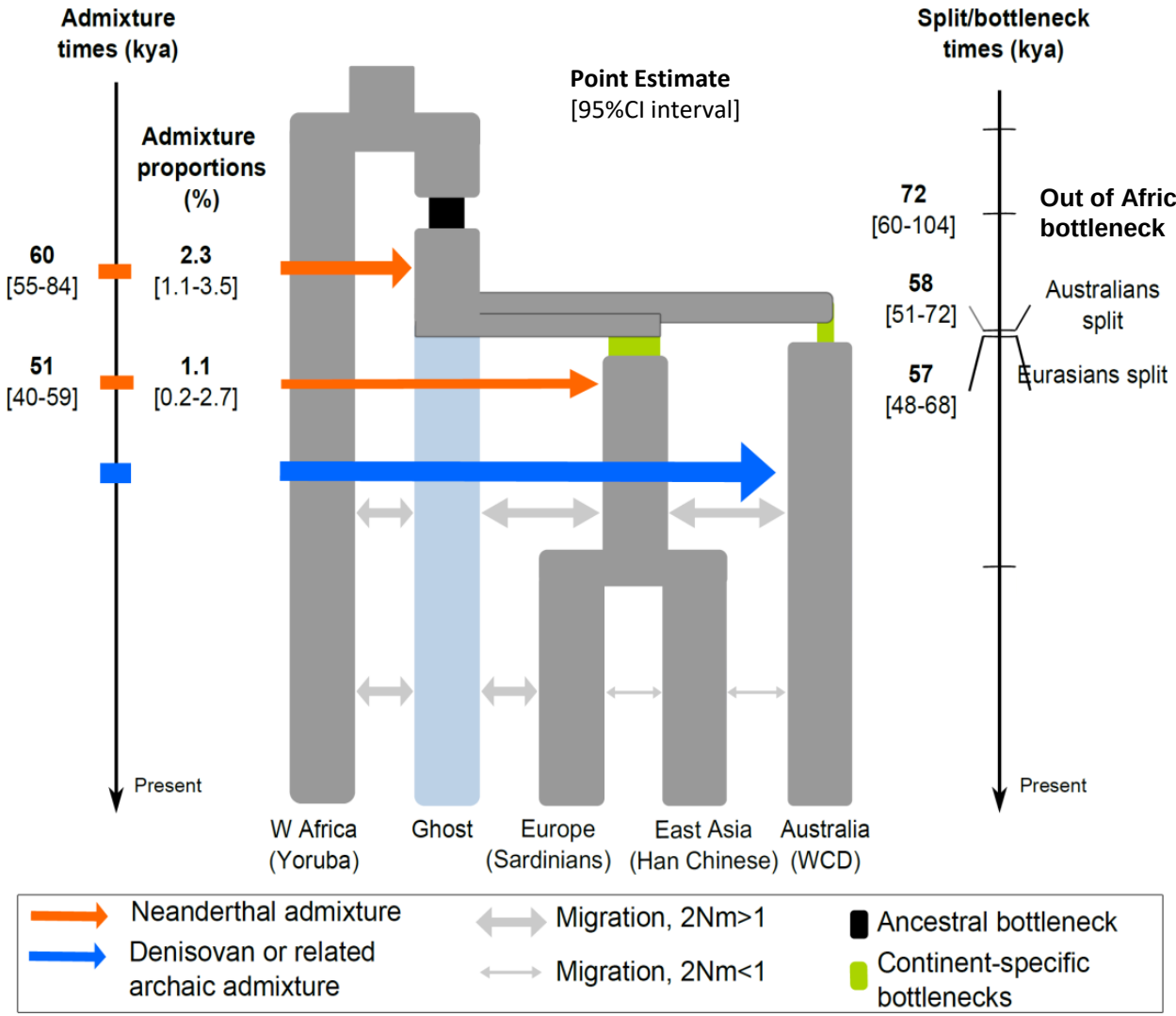
A single wave Out of Africa is consistent with our estimates when accounting for archaic admixture

- Similar divergence time (Δt close to zero)
- Bottleneck associated with the Out of Africa event



A single wave Out of Africa is consistent with our estimates when accounting for archaic admixture

- Similar divergence time (Δt close to zero)
- Bottleneck associated with the Out of Africa event
- A major admixture pulse with Neanderthal in ancestors of all non-Africans



A single wave Out of Africa is consistent with our estimates when accounting for archaic admixture

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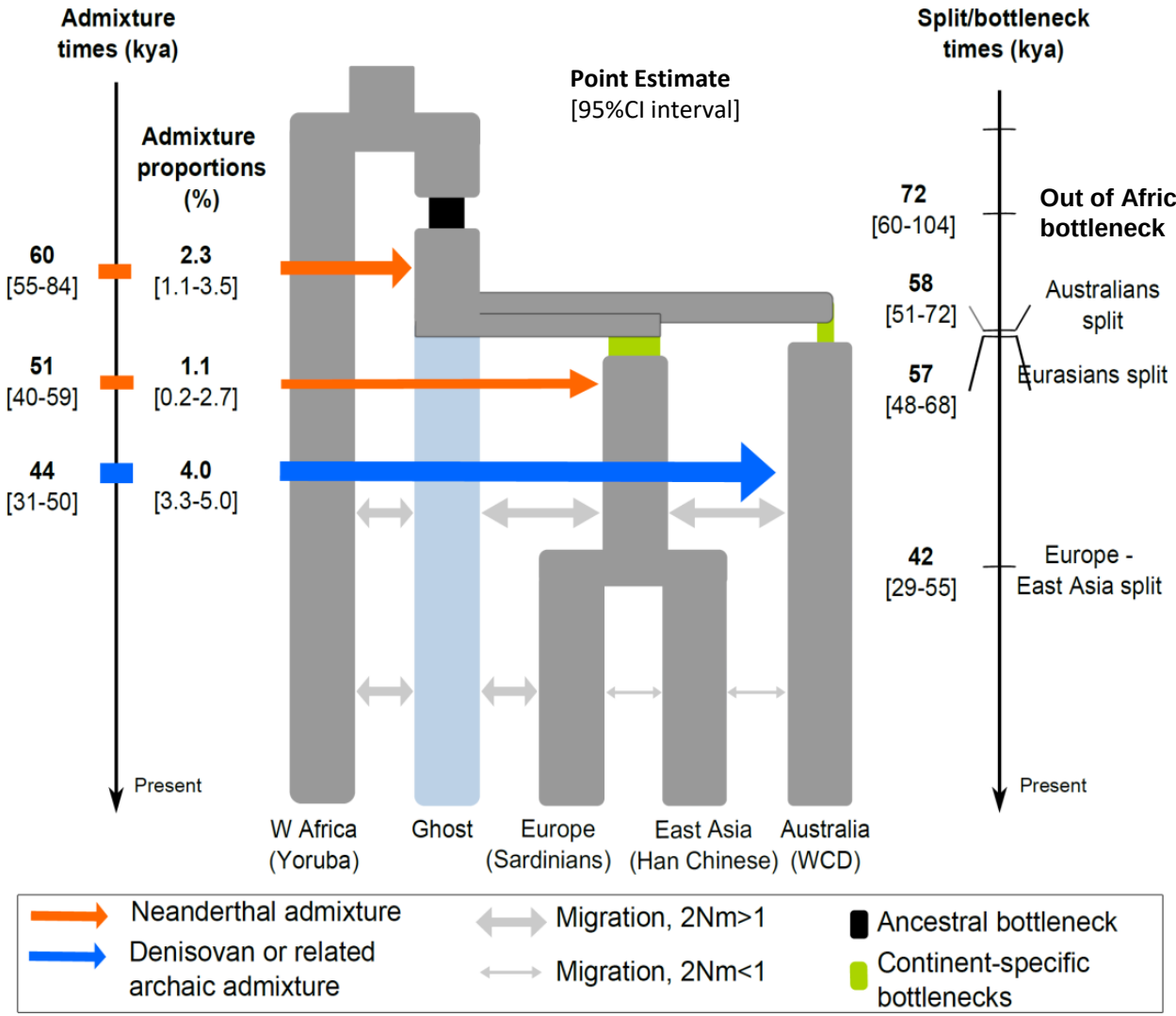
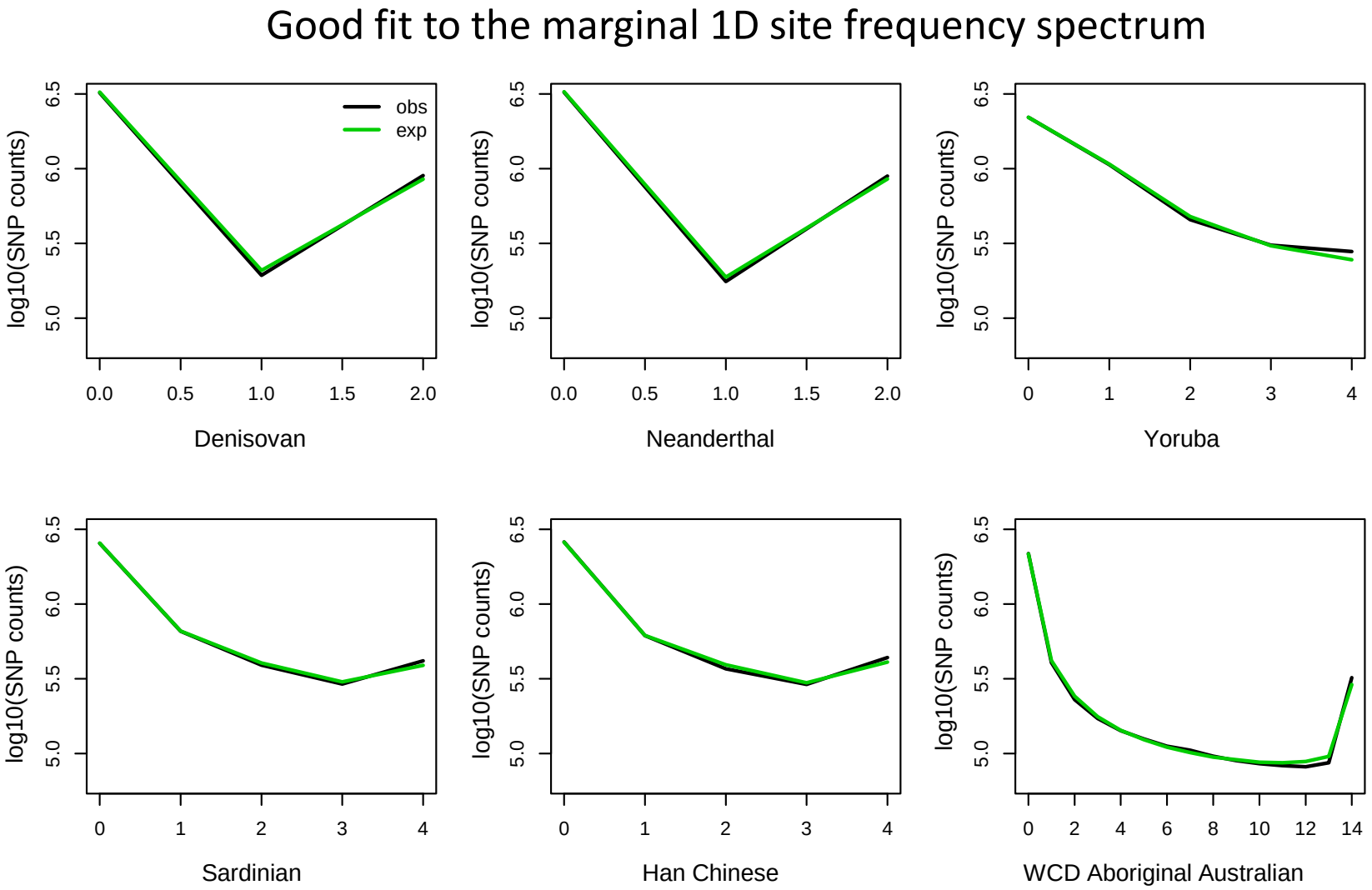
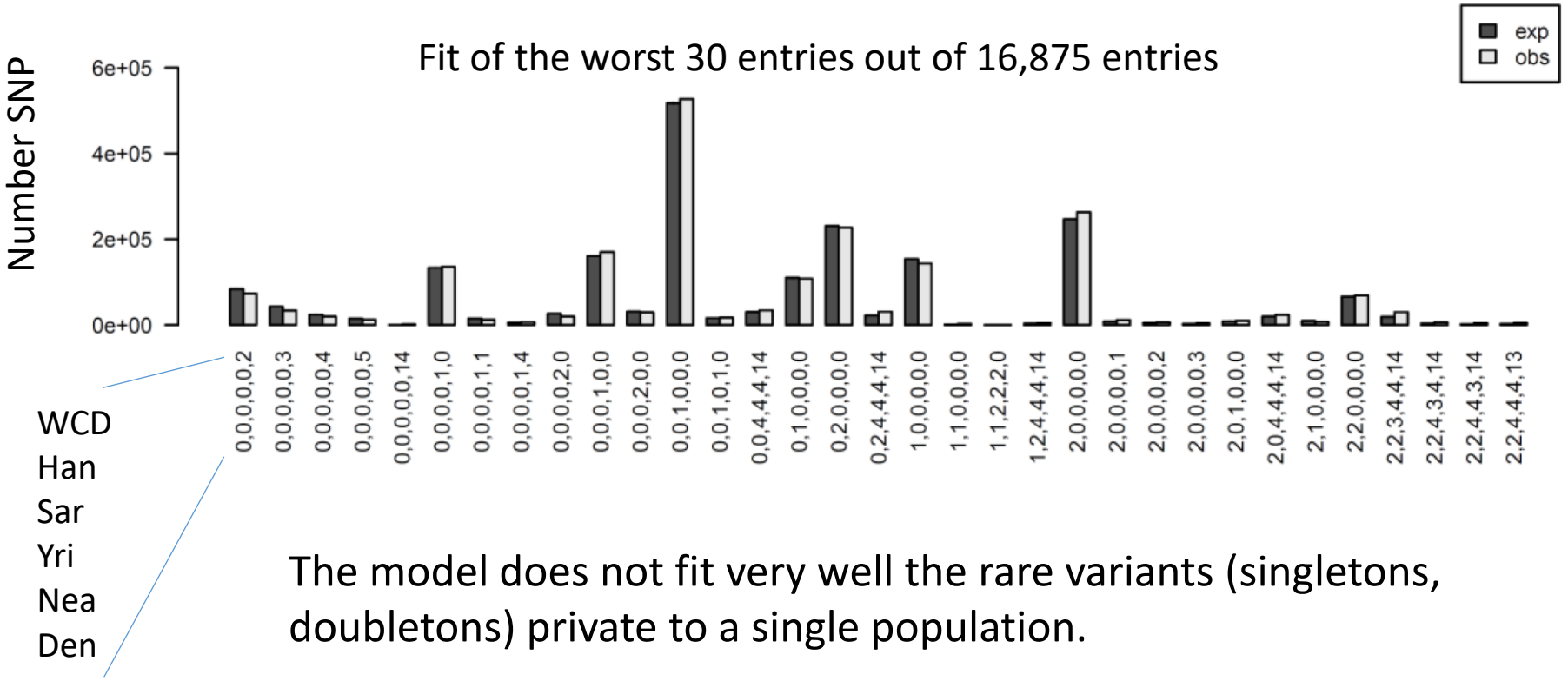


Model captures aspects about the observed data



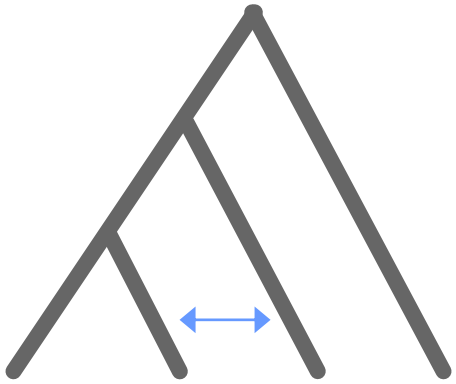
What entries are not well fitted?



The model does not fit very well the rare variants (singletons, doubletons) private to a single population.

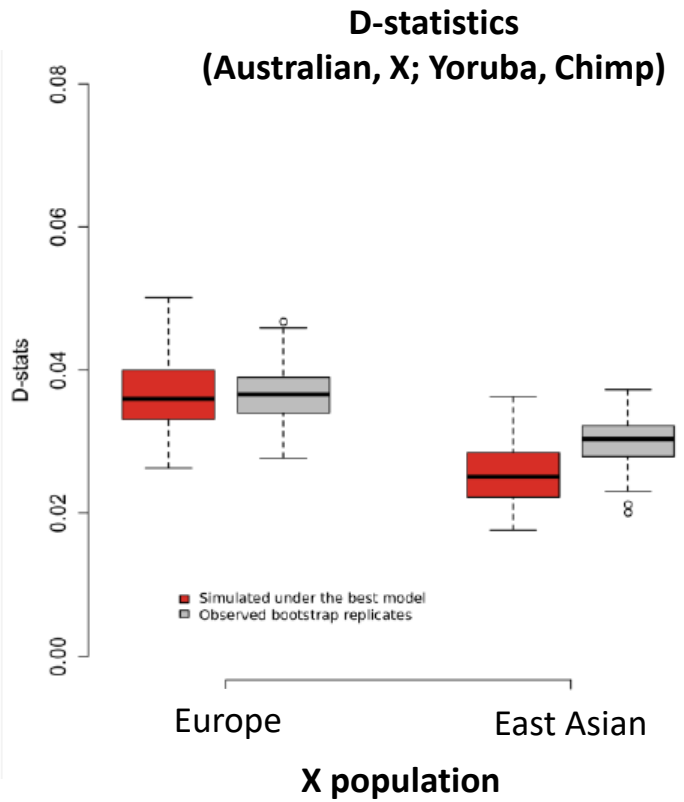
Pagani et al (2016) suggests two waves: Papuan genomes with signature of admixture with humans from first wave (at least 2% of their genome).

Model captures the higher derived allele sharing between Eurasians and Yoruba



Australia Europe or East Asian Yoruba Chimp

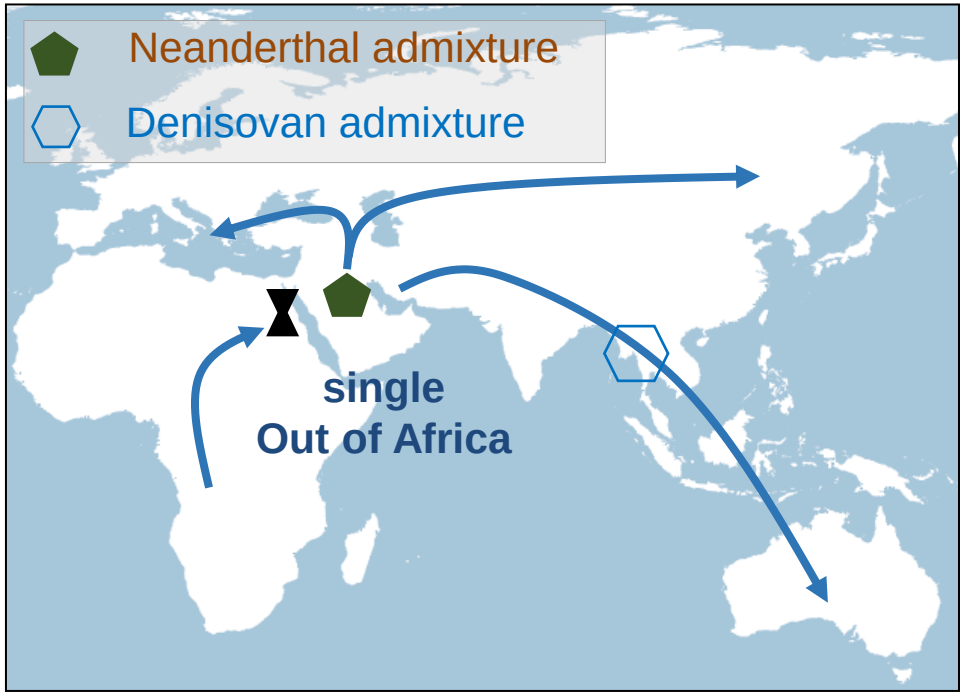
D-statistics suggest that Yoruba and Eurasians share more derived alleles than Yoruba and Australians



Summary

Aboriginal Australians genomes support a single major wave out of Africa

- Accounting for archaic admixture with Neanderthal and Denisovan was crucial to understand population divergence
- Genomic data consistent with a single major dispersal event out of Africa (60-104 kya)
- Two major dispersal waves into Asia: Aboriginal Australians diverged 51-72 kya from Eurasians



ARTICLE

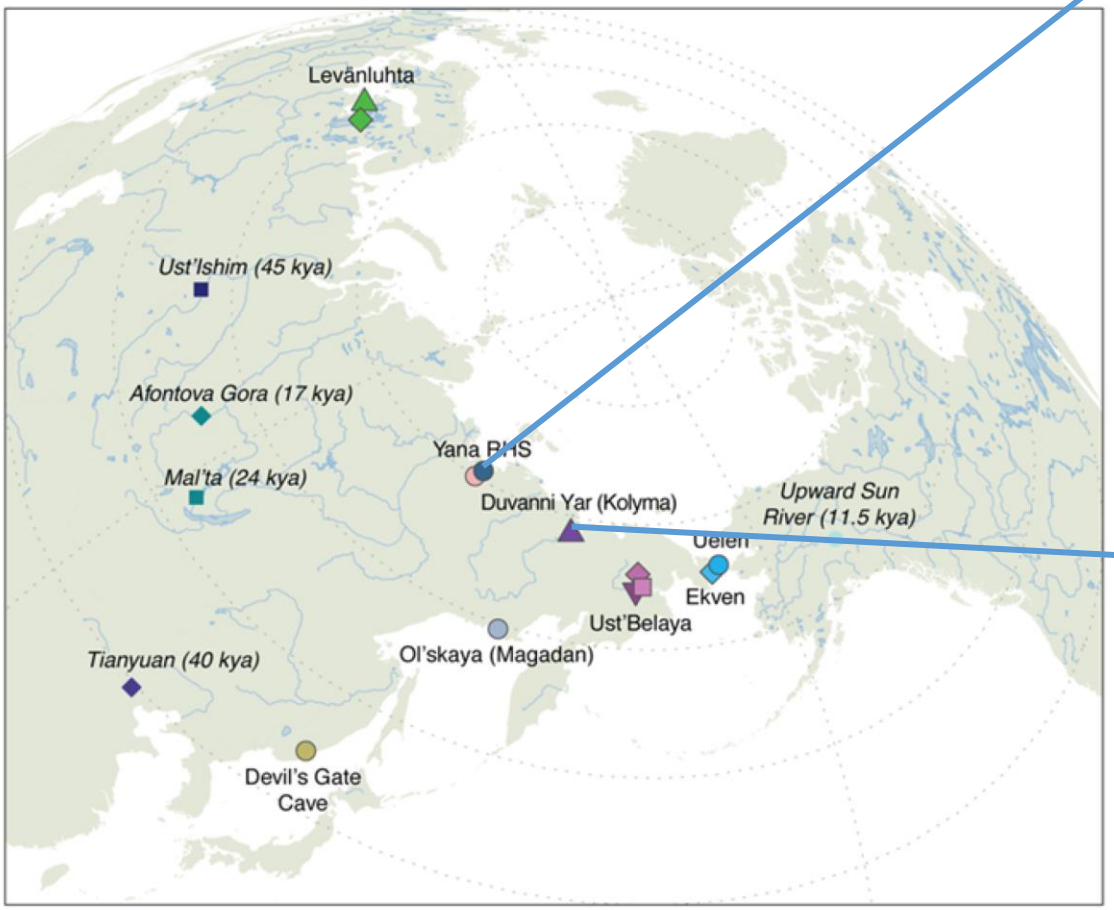
https://doi.org/10.1038/s41586-019-1279-z

The population history of northeastern Siberia since the Pleistocene

Martin Sikora[1,43]*, Vladimir V. Pitulko[2,43]*, Vitor C. Sousa[3,4,5,43], Morten E. Allentoft[1,43], Lasse Vinner[1], Simon Rasmussen[6,41], Ashot Margaryan[1], Peter de Barros Damgaard[1], Constanza de la Fuente[1,42], Gabriel Renaud[1], Melinda A. Yang[7], Qiaomei Fu[7], Isabelle Dupanloup[8], Konstantinos Giampoudakis[9], David Nogués-Bravo[9], Carsten Rahbek[9], Guus Kroonen[10,11], Michaël Peyrot[11], Hugh McColl[1], Sergey V. Vasilyev[12], Elizaveta Veselovskaya[12,13], Margarita Gerasimova[12], Elena Y. Pavlova[2,14], Vyacheslav G. Chasnyk[15], Pavel A. Nikolskiy[2,16], Andrei V. Gromov[17], Valeriy I. Khartanovich[17], Vyacheslav Moiseyev[17], Pavel S. Grebenyuk[18,19], Alexander Yu. Fedorchenko[20], Alexander I. Lebedintsev[18], Sergey B. Slobodin[18], Boris A. Malyarchuk[21], Rui Martiniano[22], Morten Meldgaard[1,23], Laura Arppe[24], Jukka U. Palo[25,26], Tarja Sundell[27,28], Kristiina Mannermaa[27], Mikko Putkonen[25], Verner Alexandersen[29], Charlotte Primeau[29], Nurbol Baimukhanov[30], Ripan S. Malhi[31,32], Karl-Göran Sjögren[33], Kristian Kristiansen[33], Anna Wessman[27,34], Antti Sajantila[25], Marta Mirazon Lahr[1,35], Richard Durbin[22,36], Rasmus Nielsen[1,37], David J. Meltzer[1,38], Laurent Excoffier[4,5]* & Eske Willerslev[1,36,39,40]*

Nature (2019)

Colonization of Siberia



Yana RHS (31,600 years ago)

Whole-genome depth of coverage 25x

Kolyma (9,800 years ago)

Whole-genome depth of coverage 14x

Hypothesis: Continuity vs Replacement of populations

Data: Ancient and present-day samples; 625 blocks of 1Mb (~1.5 Million SNP), far from genic regions and CpG islands

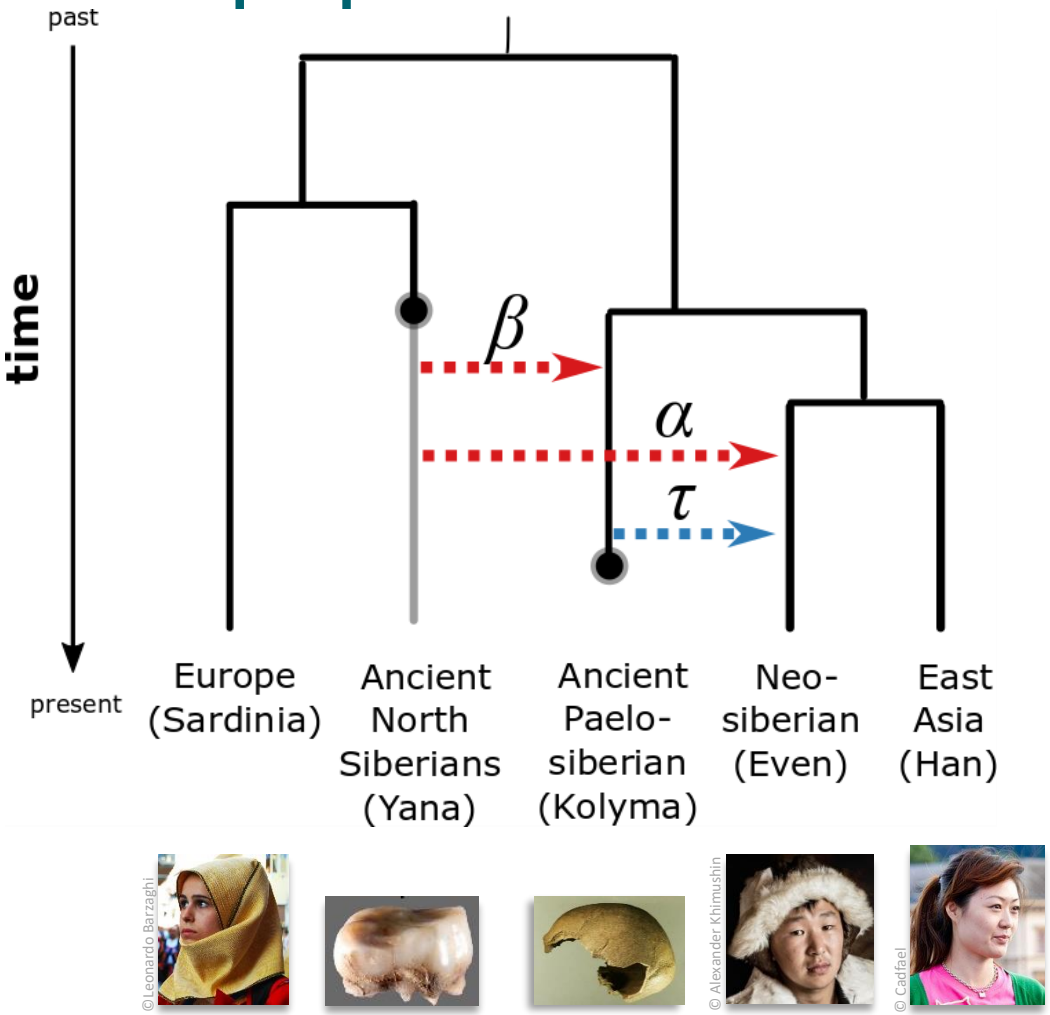
Method: Composite likelihood - *fastsimcoal2*
(Excoffier et al, 2013 Plos Genetics)

Hypothesis: Continuity vs Replacement of populations

For instance:

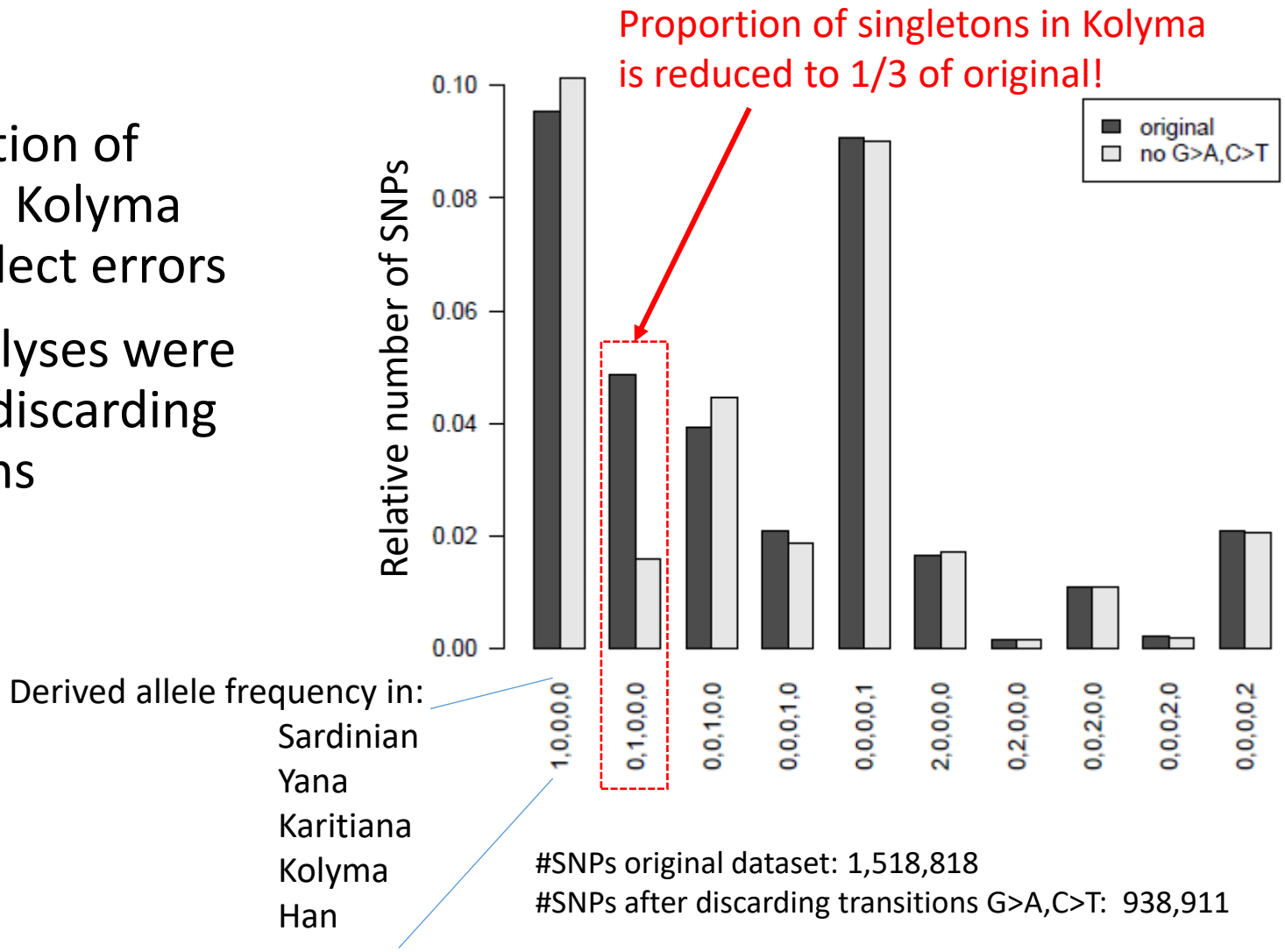
β = 1 indicates continuity: Kolyma descends from Yana

β = 0 indicates replacement of Yana by Kolyma

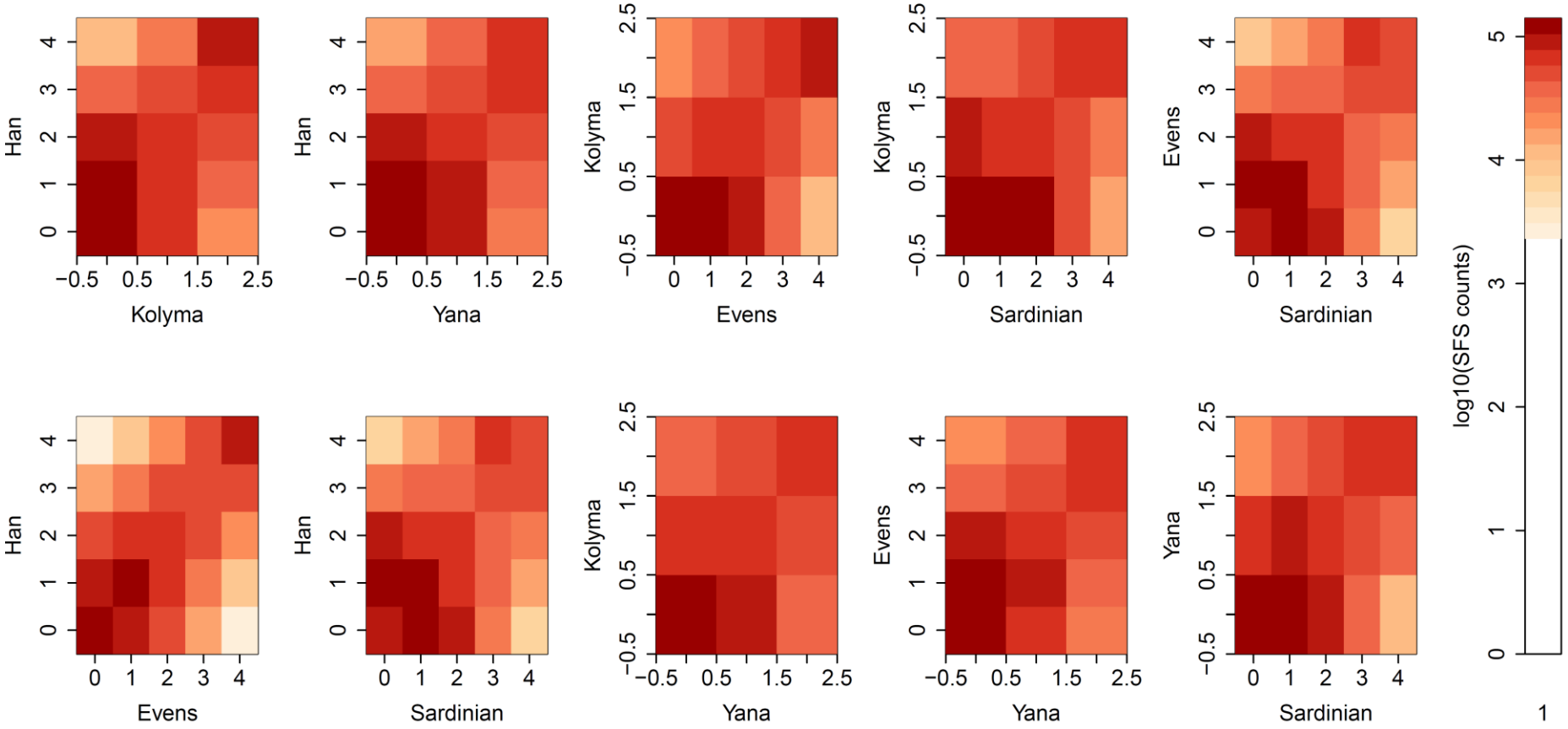


Site frequency spectrum is affected by damage patterns in ancient DNA

- High proportion of singletons in Kolyma probably reflect errors
- Thus, all analyses were performed discarding the singletons

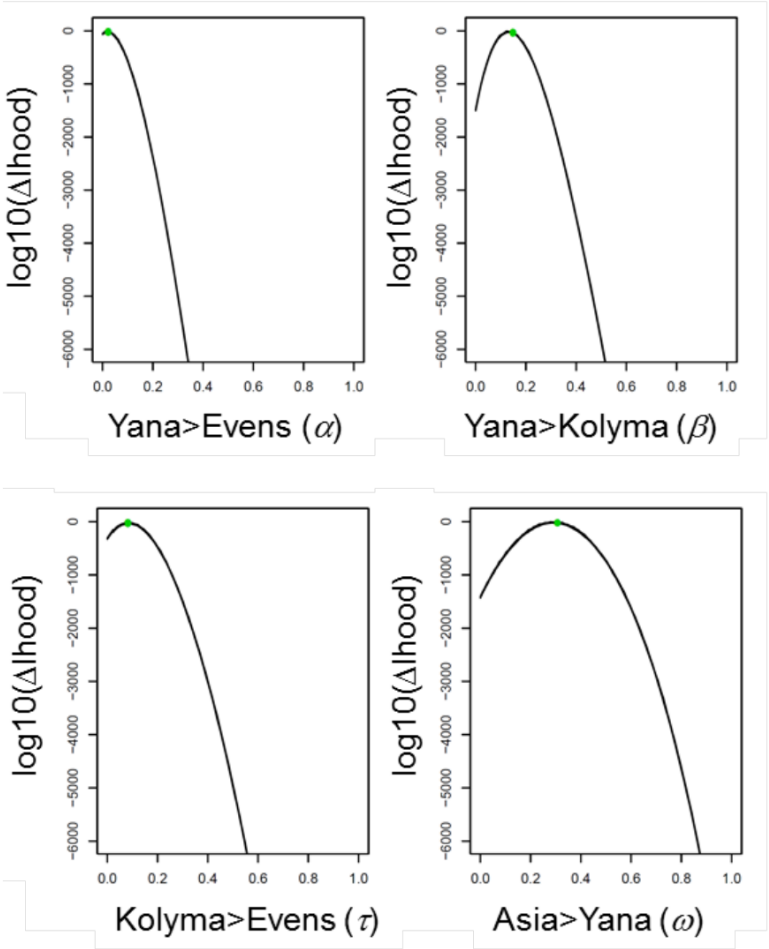


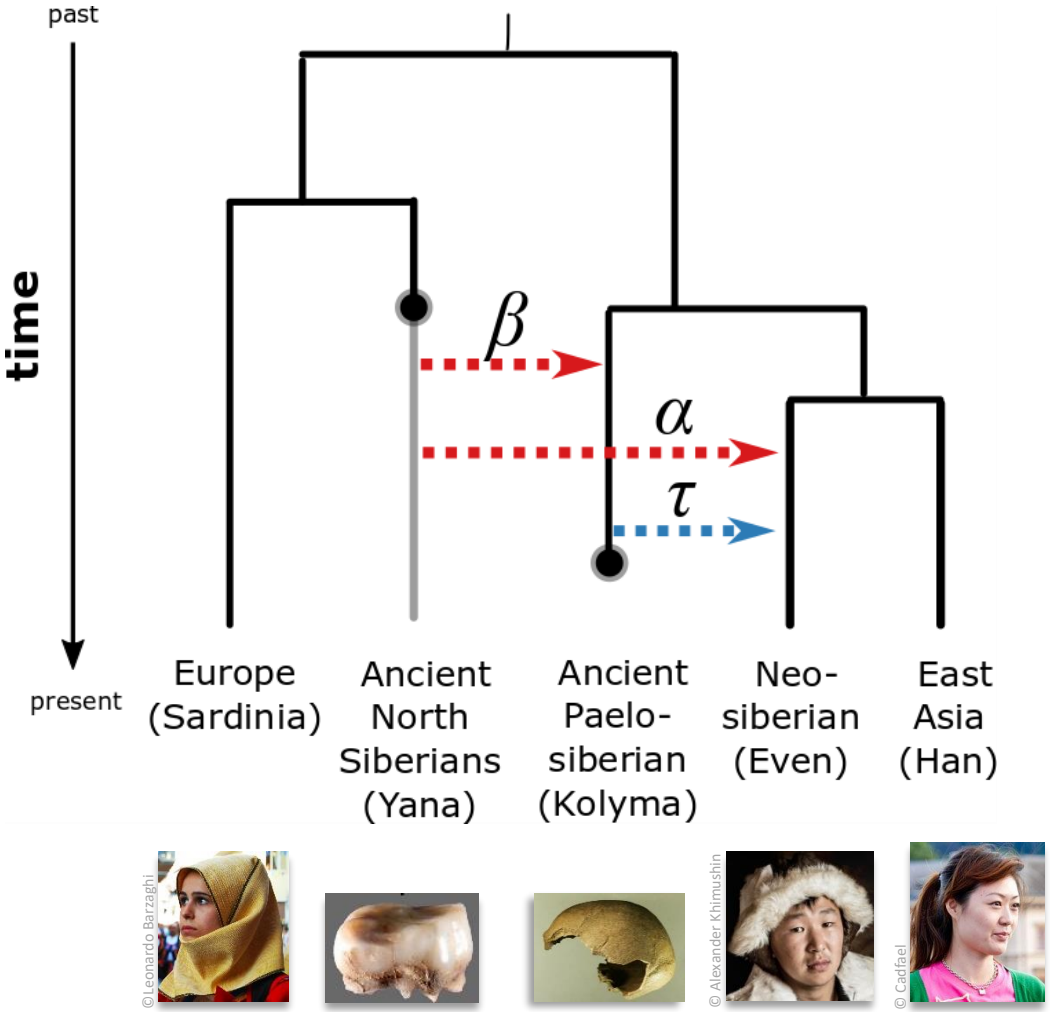
Data: Marginal 2D-SFS



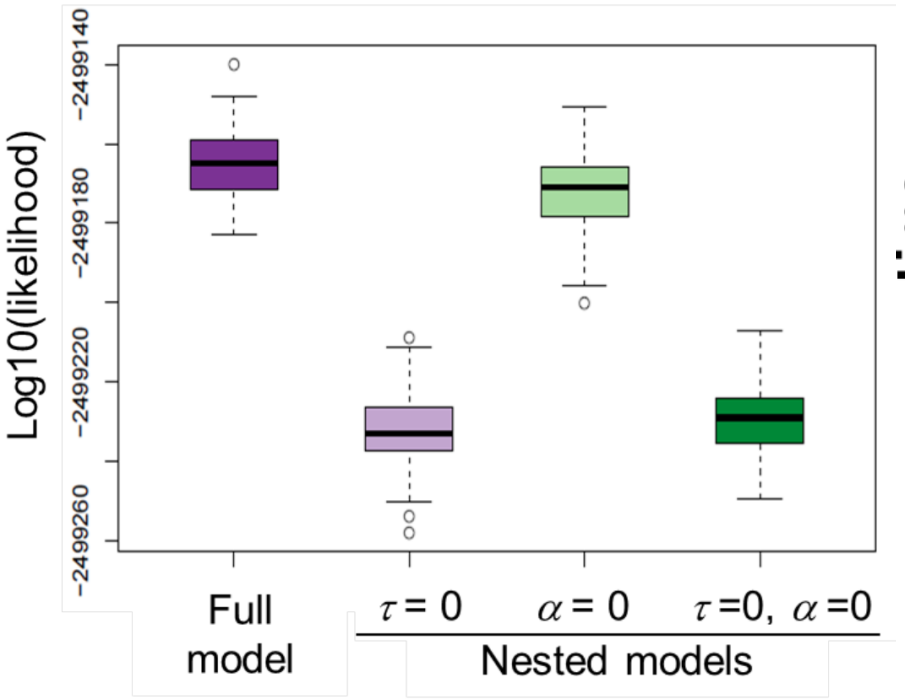
Observed Data: Joint 5 population site-frequency spectrum (1125 entries) obtained from 625 blocks of 1Mb (~1.5 Million SNP)

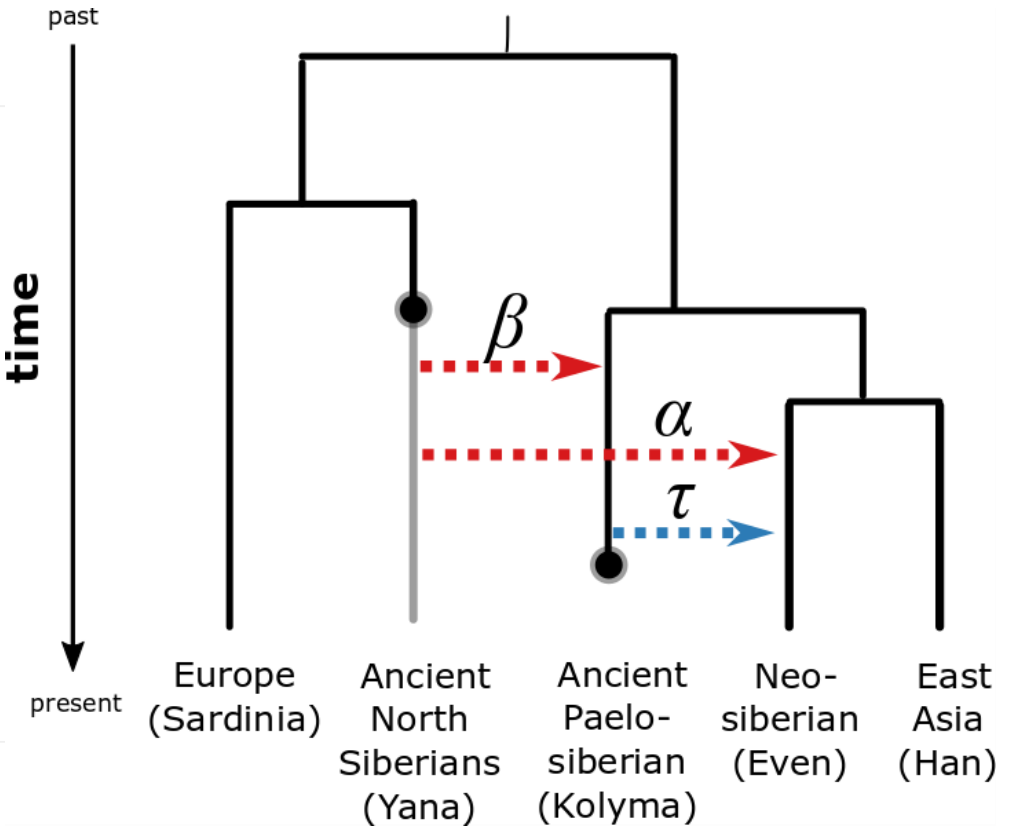
Model comparison and likelihood profiles consistent with replacement with gene flow



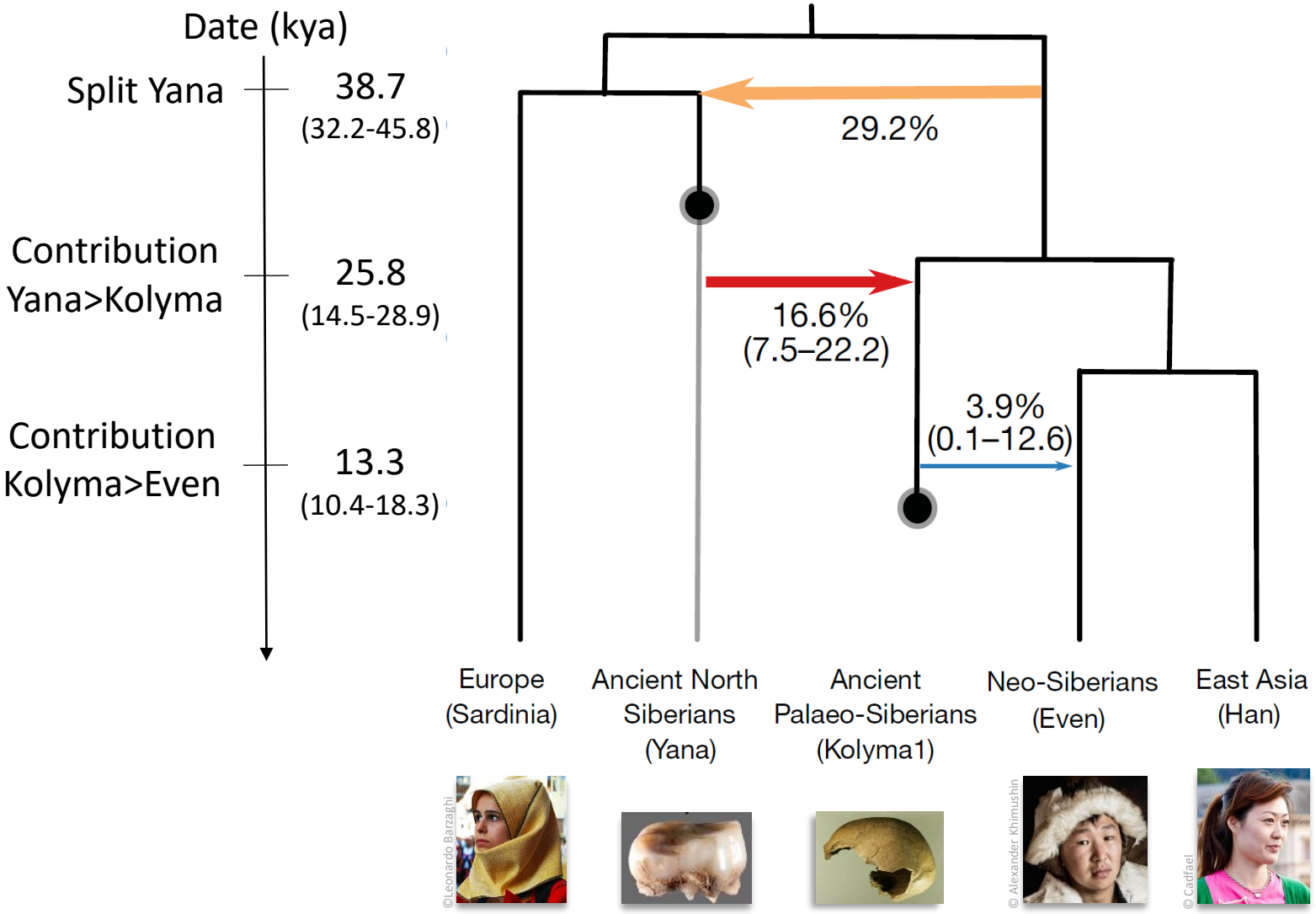


Model comparison and likelihood profiles consistent with replacement with gene flow

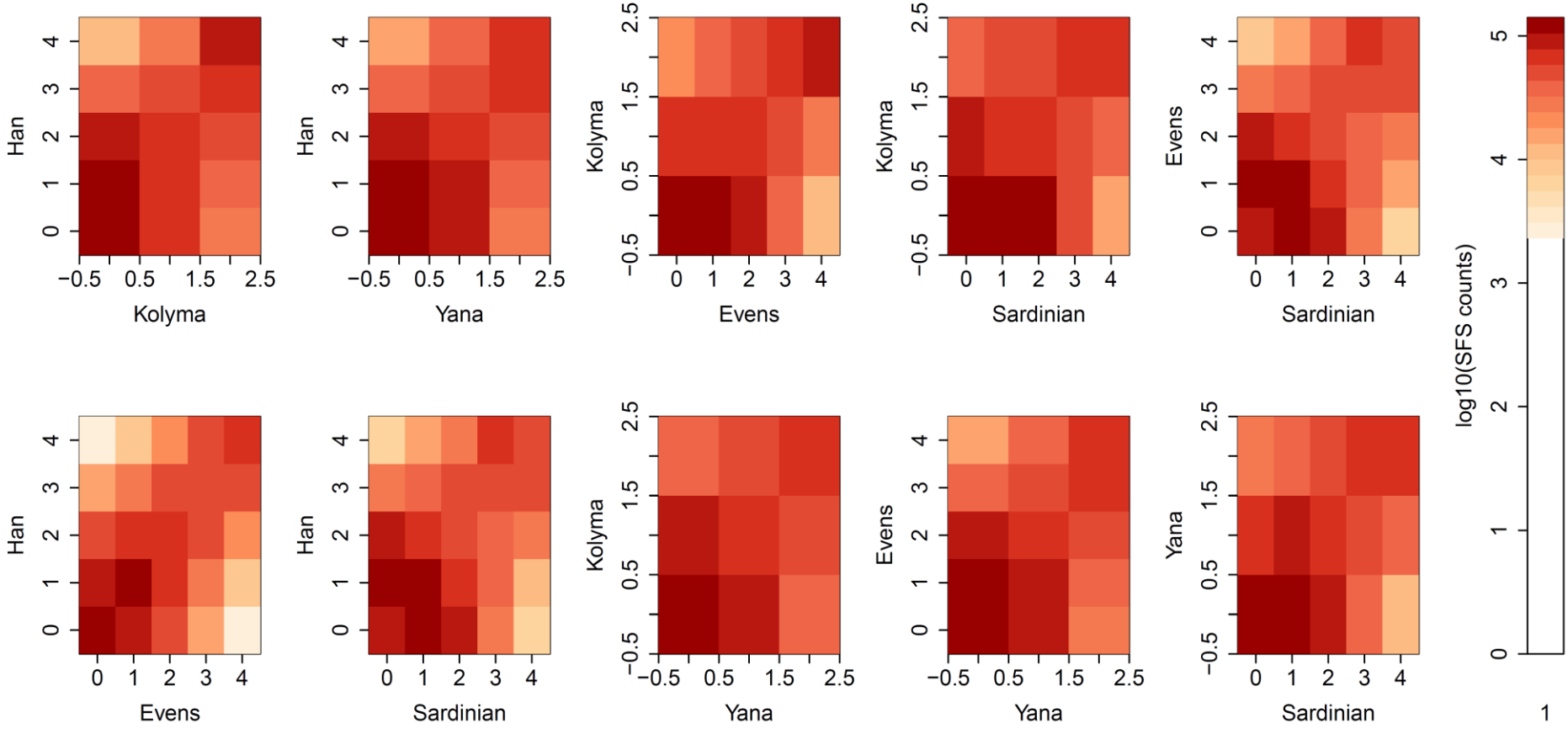




Estimates of best nested model indicate replacement with gene flow

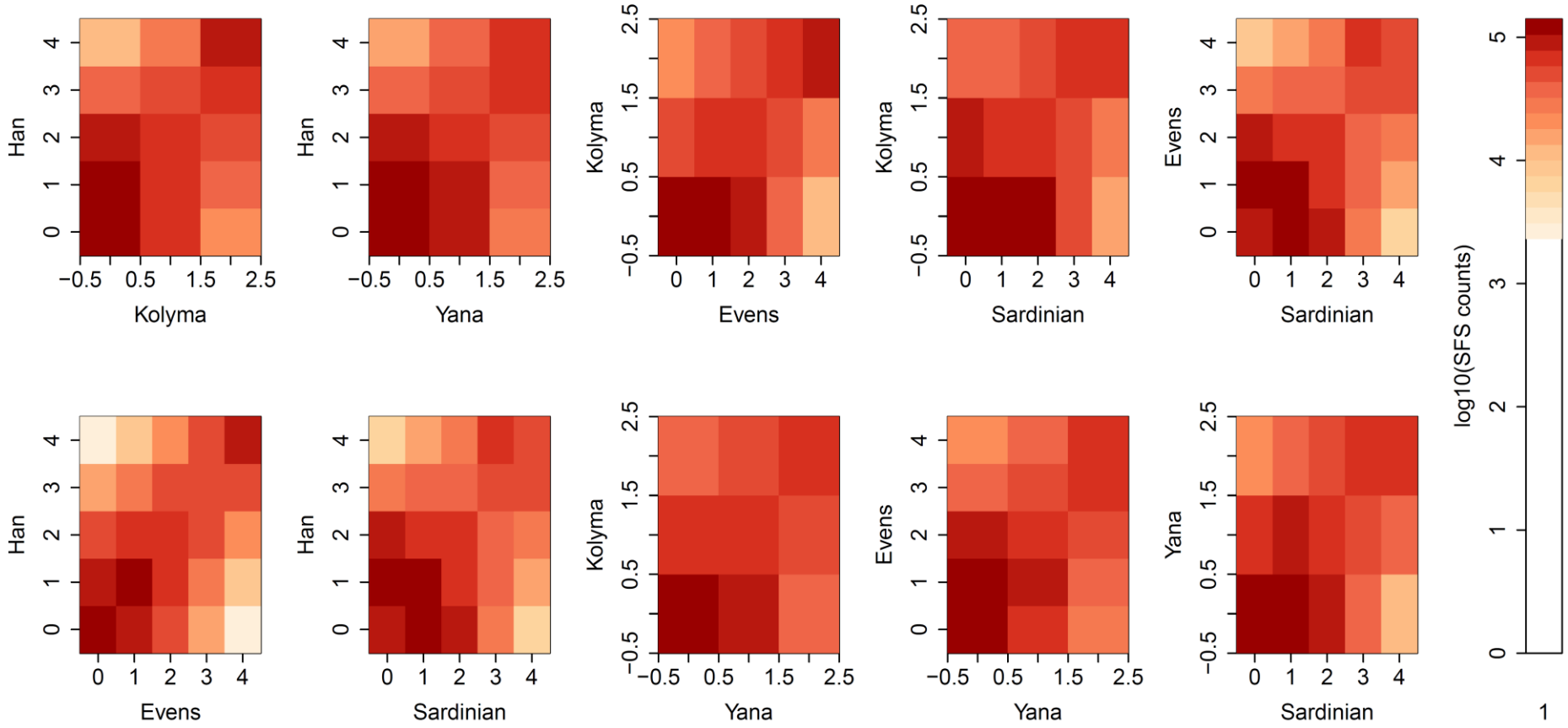


Fit of expected SFS to observed data



Expected SFS according to the parameters that maximize the likelihood

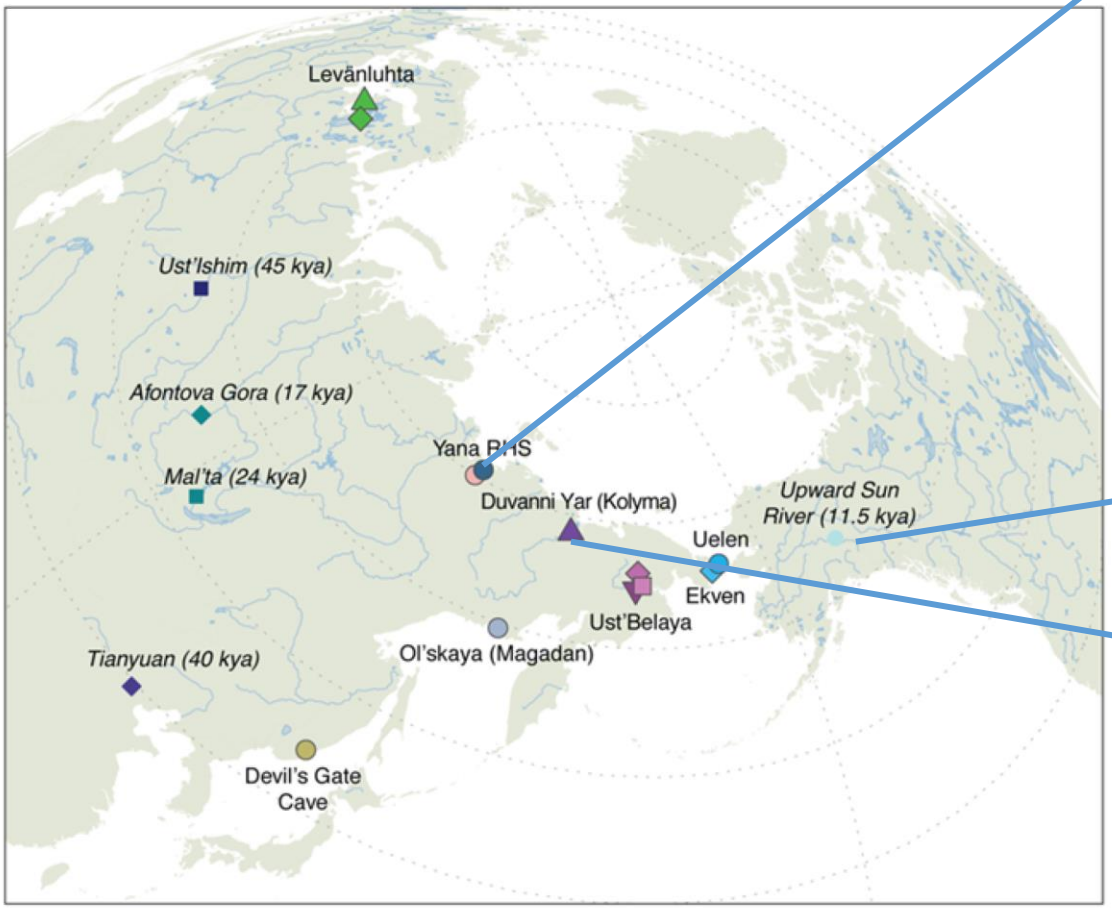
Fit of expected SFS to observed data



Observed SFS

Siberia and colonization of the Americas

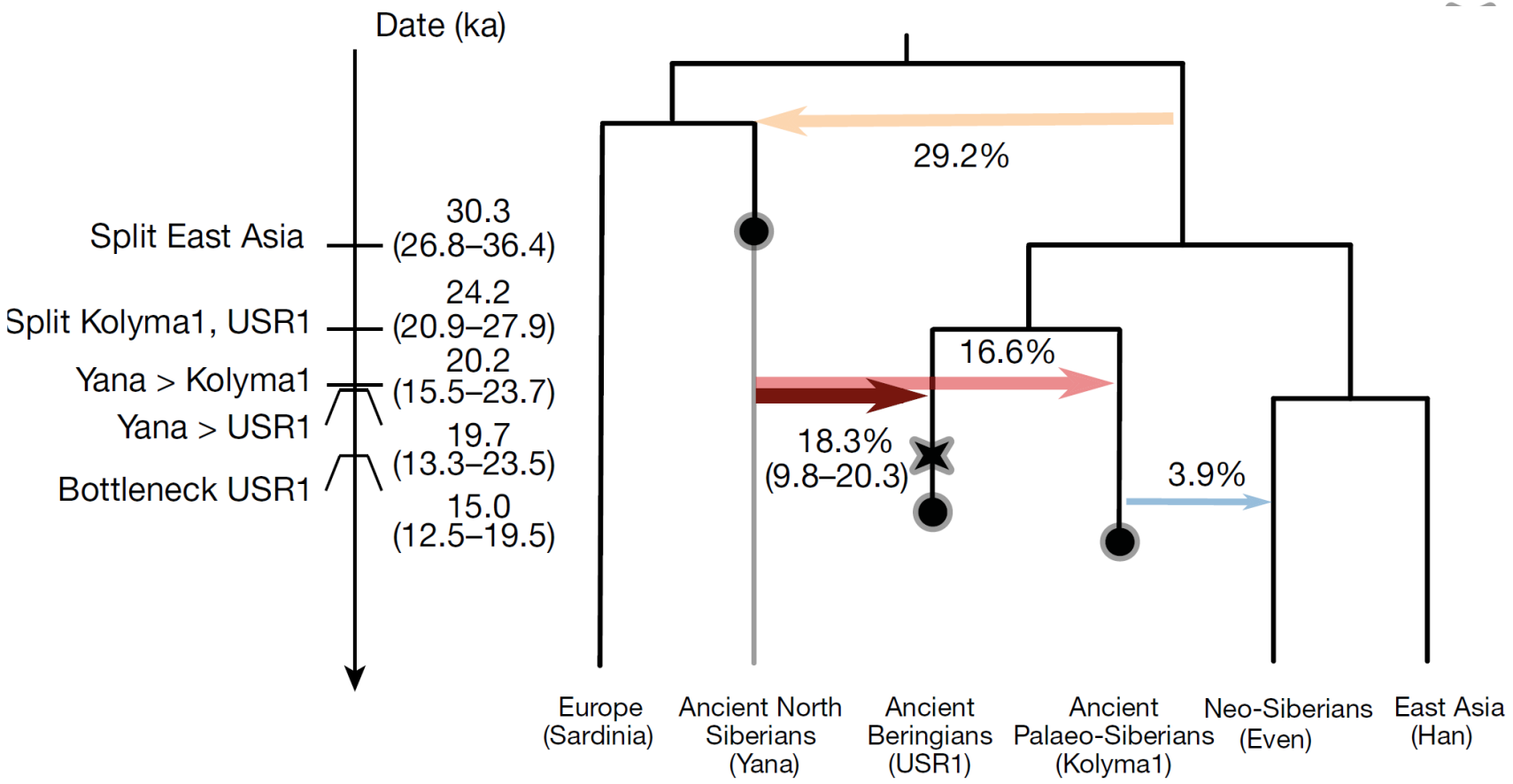
Yana RHS (31,600 years ago)
Whole-genome depth of coverage 25x



USR1 (11,500 years ago) Alaska

Kolyma (9,800 years ago)
Whole-genome depth of coverage 14x

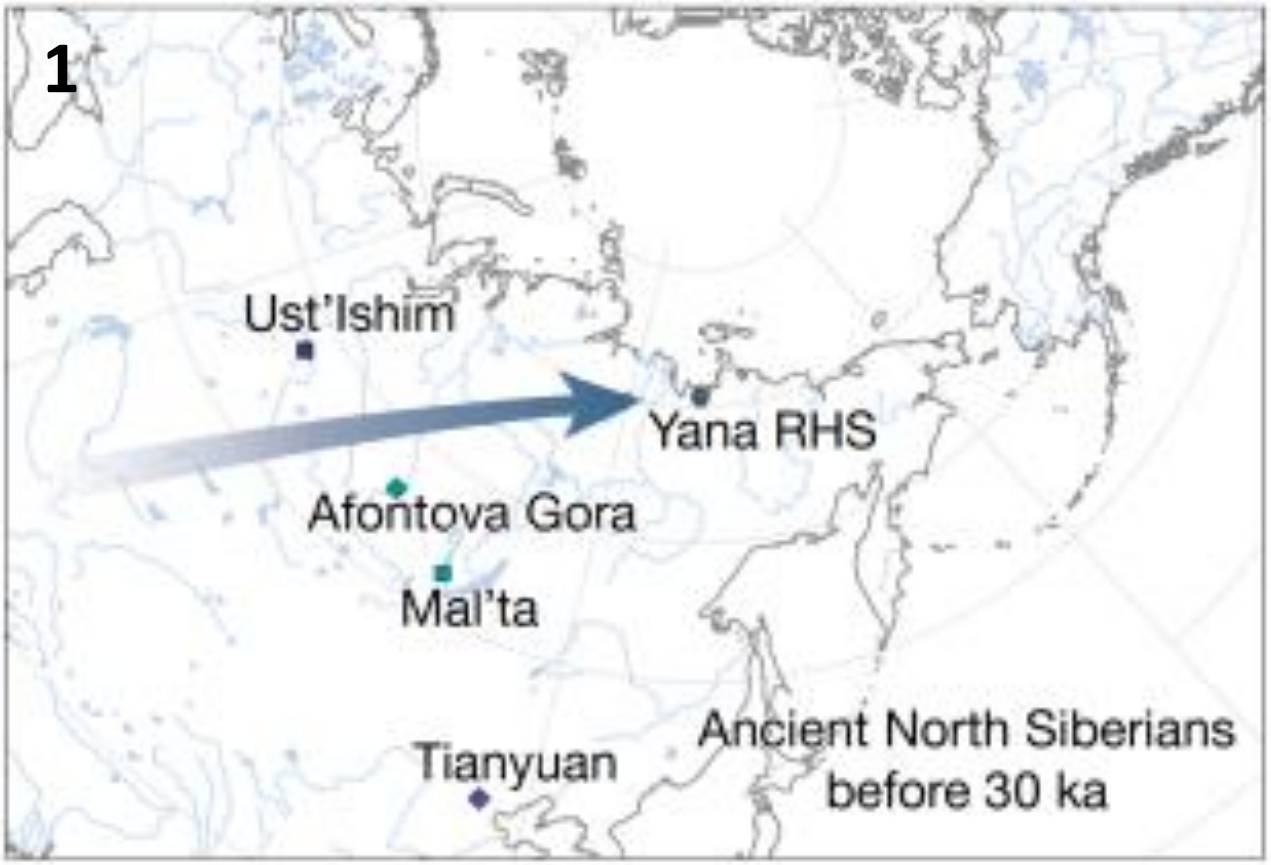
Estimates consistent with replacement with gene flow



- Kolyma is the closest population to Native Americans (USR1 and Karitiana)
- Native Americans with a contribution of up to 20% from Yana

Summary: 3 migration waves

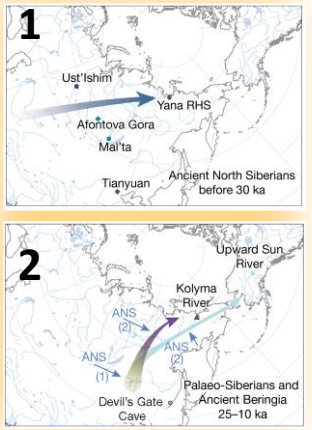
- Ancient North Siberians (Yana) reached Siberia before 30 ka (thousand-years ago)

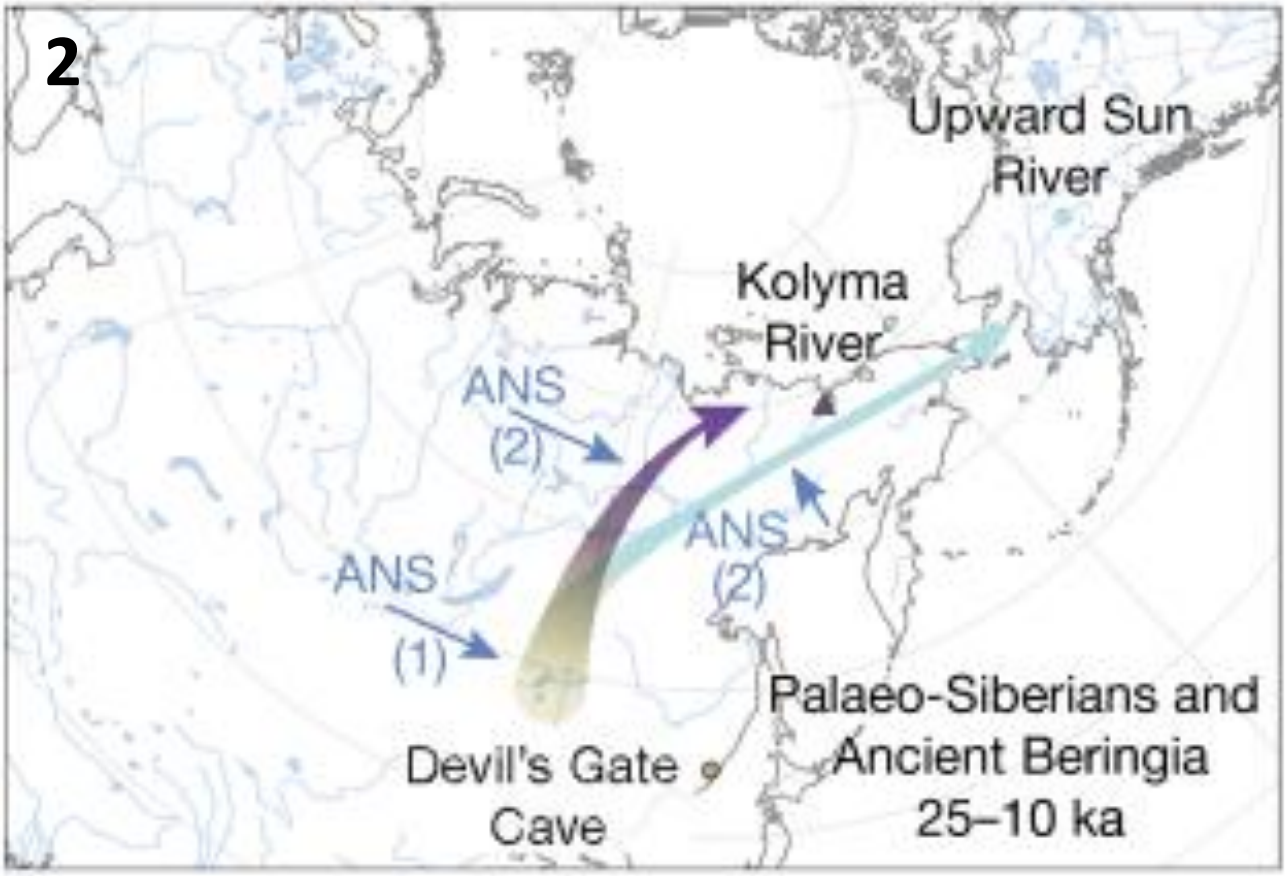


1st migration wave

Summary: 3 migration waves

- Ancient North Siberians (Yana) reached Siberia before 30 kya
- Paleo-Siberians (Kolyma) migrated after Last Glacial Maximum (26.5 ka)
- Native-Americans are closer to Kolyma, with 20% of Yana contribution

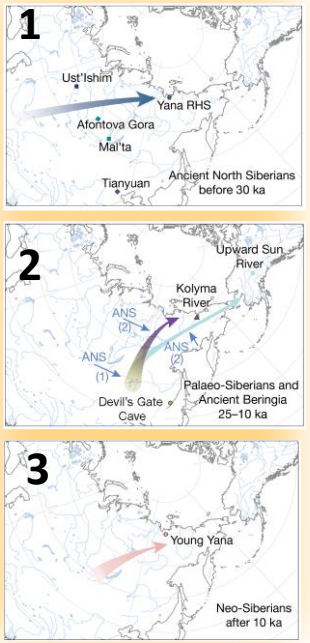


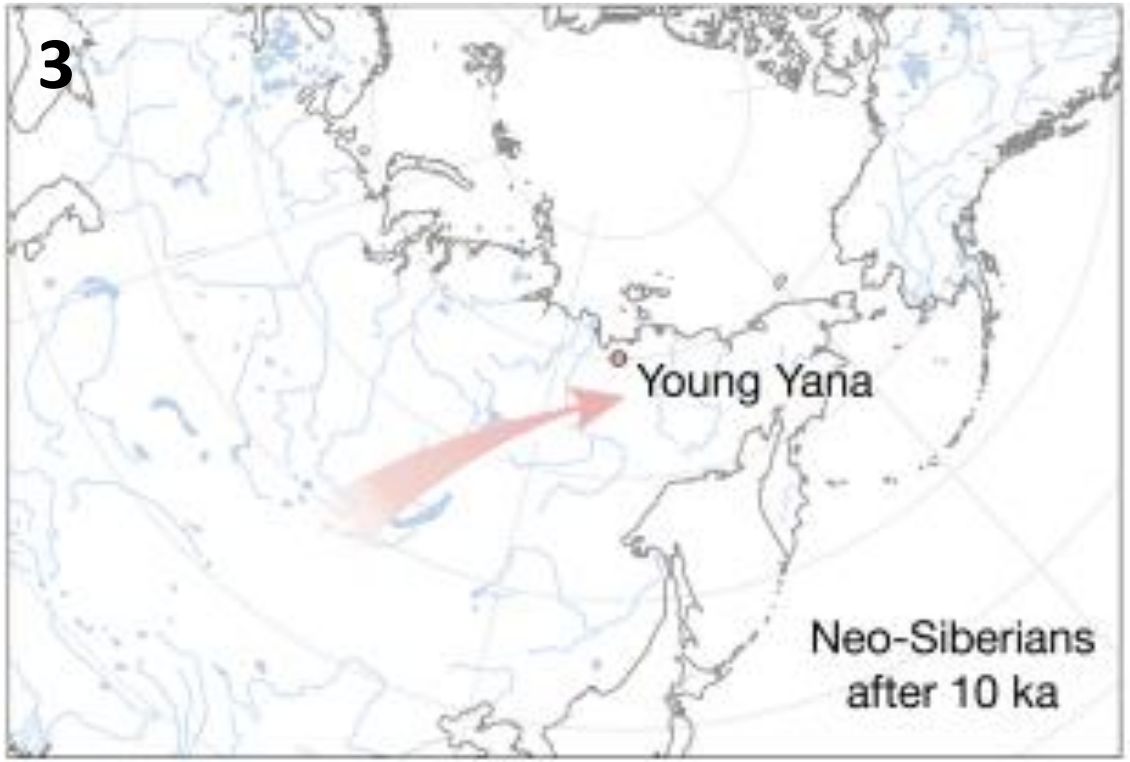


2nd migration wave

Summary: 3 migration waves

- Ancient North Siberians (Yana) reached Siberia before 30 ka
- Paleo-Siberians (Kolyma) likely migrated after Last Glacial Maxima
- Native-Americans are closer to Kolyma, with 20% of Yana contribution
- Paleo-Siberians (Kolyma) were replaced by Neo-Siberians, likely associated with the cooler period “Younger Dryas” (12.8-11.5 ka)





3rd migration wave

Deer mice from Nebraska Sand Hills

S. Pfeifer, S. Laurent, V. Sousa, C. Linnen, H. Hoekstra, L. Excoffier, J. Jensen

Coat color adaptation in deer mice *Peromyscus maniculatus*

- Habitat (soil color) correlated with coat phenotype
- Field experiments suggest that light color confers selective advantage against visually hunting predators
- Nebraska Sand Hills were formed 8000 to 15,000 years ago

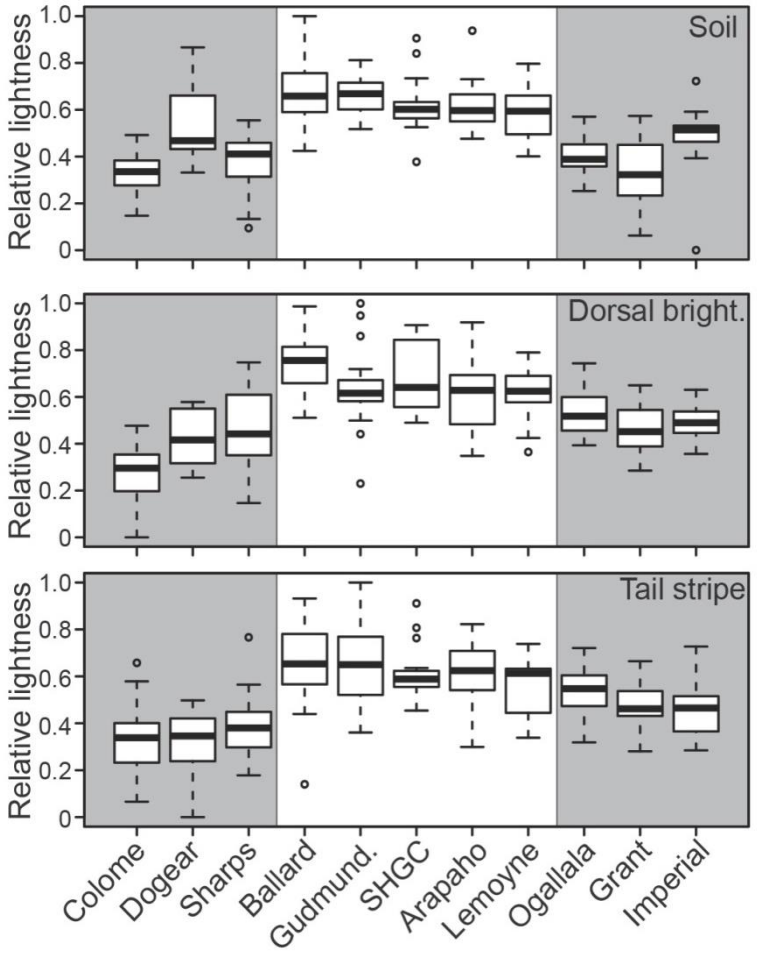
Linnen et al (2013) Science

Pfeifer*, Laurent*, Sousa* et al (2018) MBE

A transect across the Sand Hills (ON and OFF)

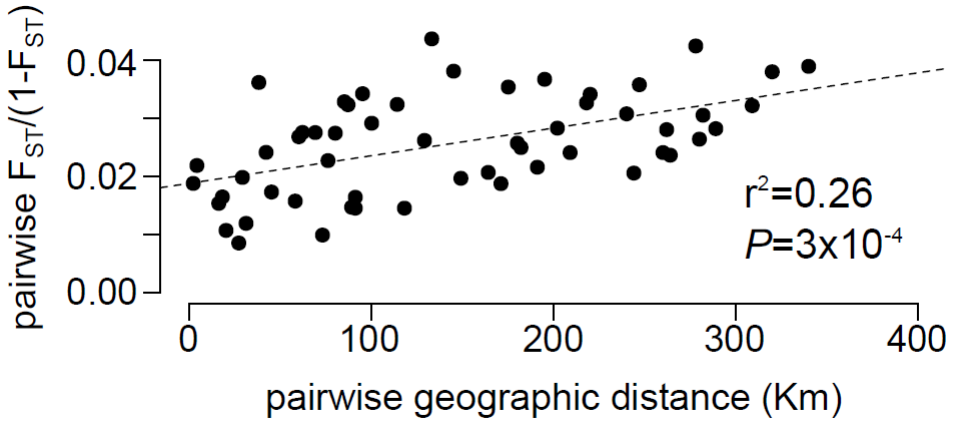
Sample locations “off” and “on” the Sand Hills

- 11 populations
- 330 individuals

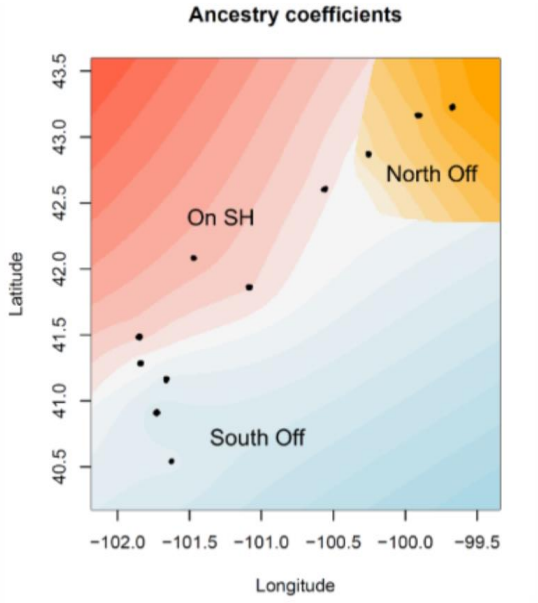


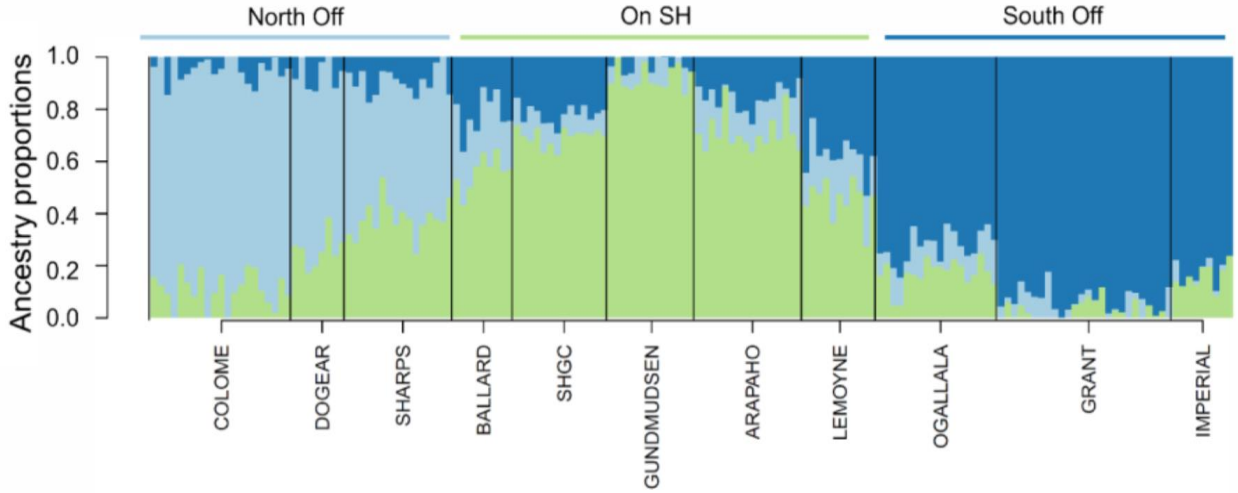
- Genomic data (NGS) data
  - Target 10,000 random 1.5kb regions
  - 185kbp region comprising the *Agouti* gene
- Phenotypic data for each individual

Evidence for isolation by distance but three groups



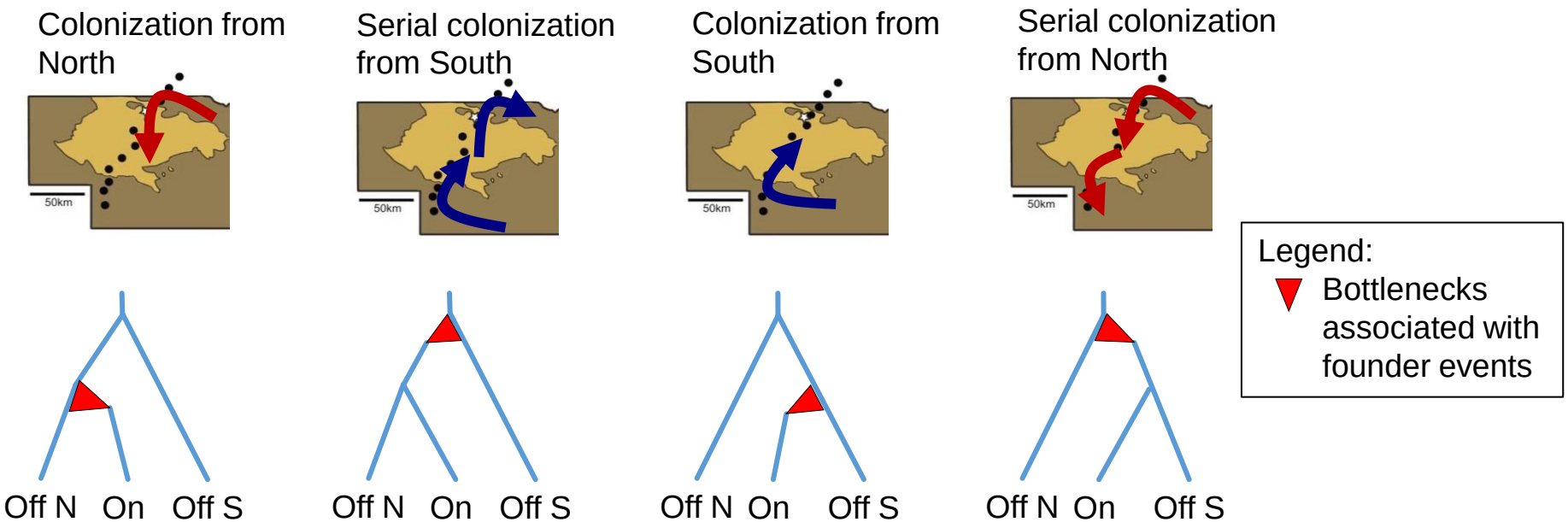
Geographically closer samples are genetically more similar





Model-based inference

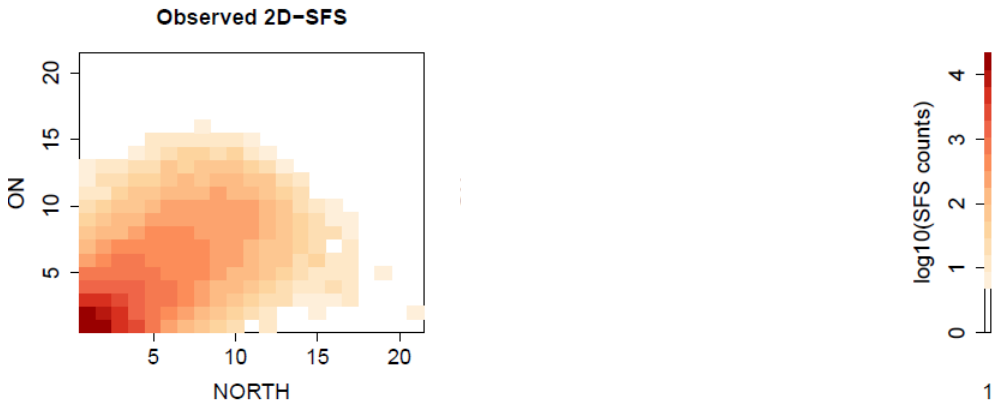
Is there evidence of gene flow between Off and On the Sand Hills?

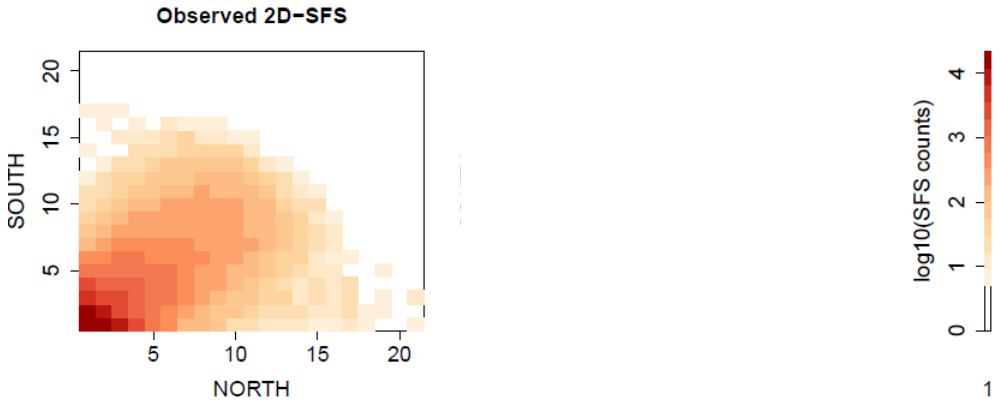


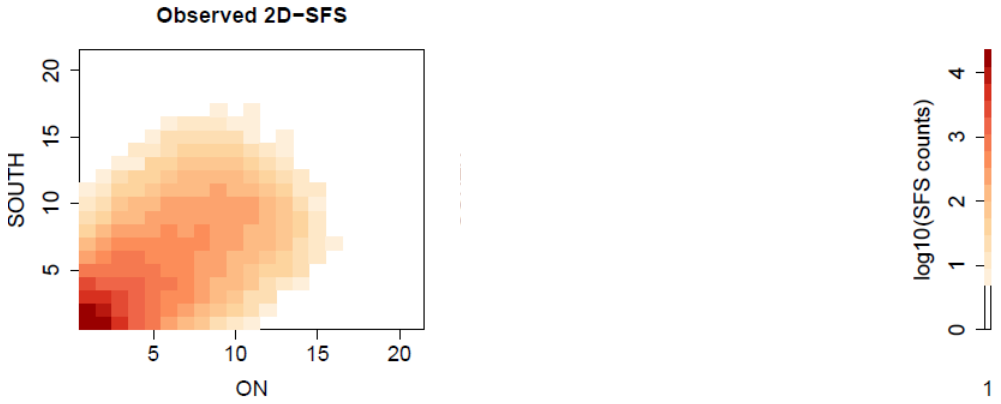
Estimates based on the joint **3D site frequency spectrum** (SFS):

- folded SFS with 140,358 SNPs

Deer mice: Pairwise marginal 2D SFS
Since we did not have an outgroup we used the folded SFS



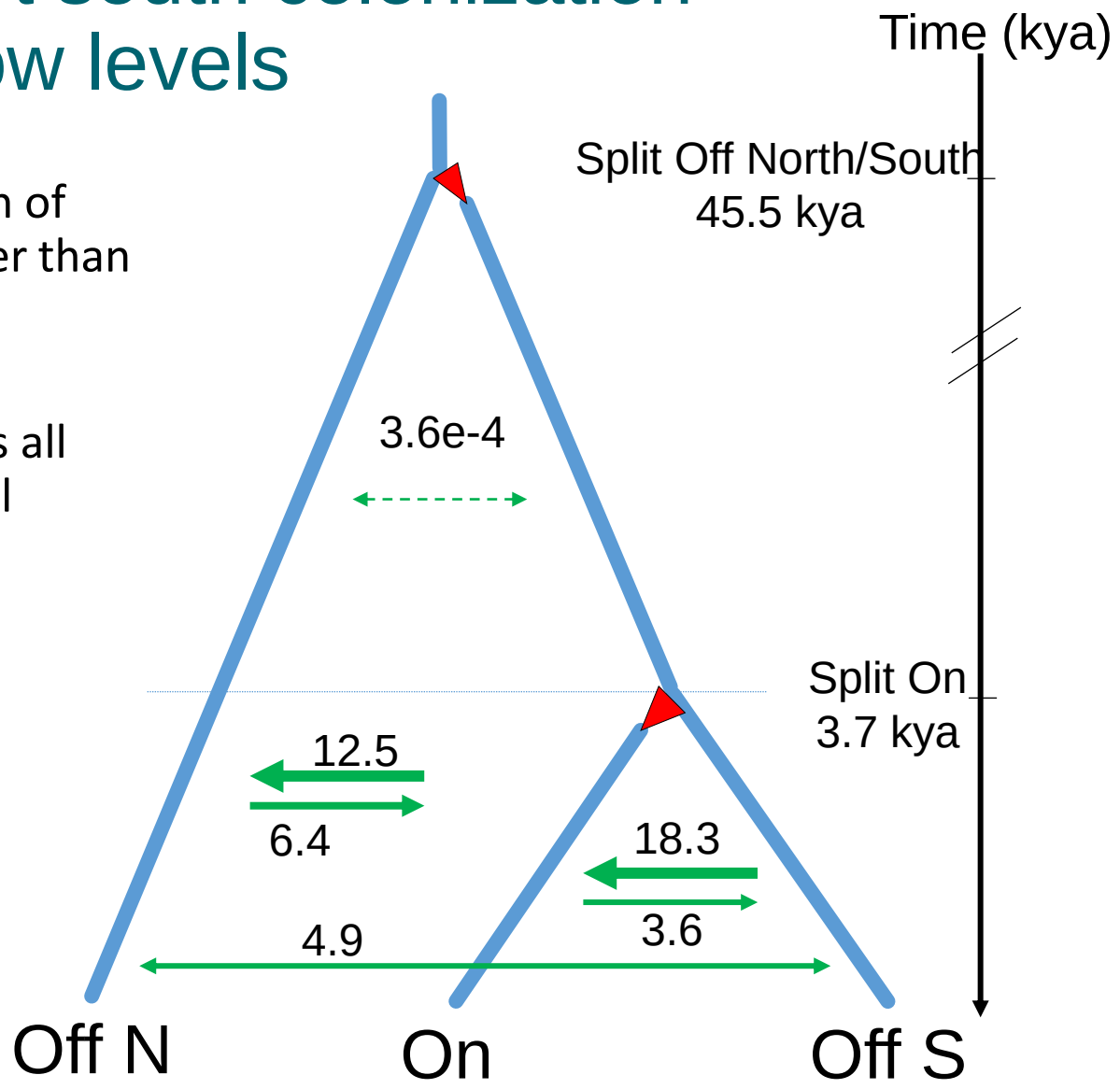




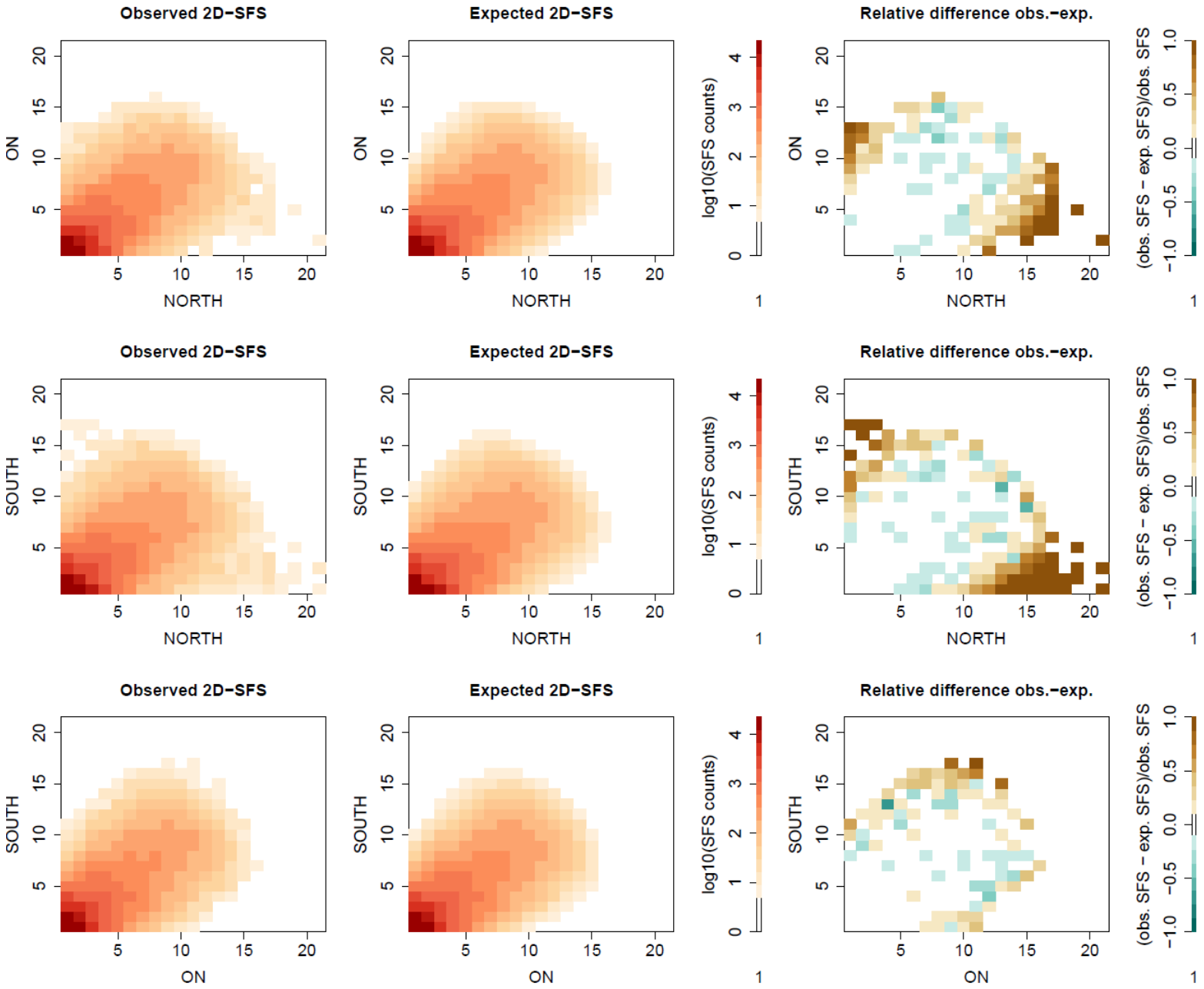
Estimates support south colonization and high gene flow levels

- Recent time of colonization of Sand Hills ~3-5 kya, younger than formation of Sand Hills 8-15 kya
- High migration rates across all populations, inferred for all models

Migration rates above/below arrows in units of 2Nm, i.e. average number of immigrants per generation.



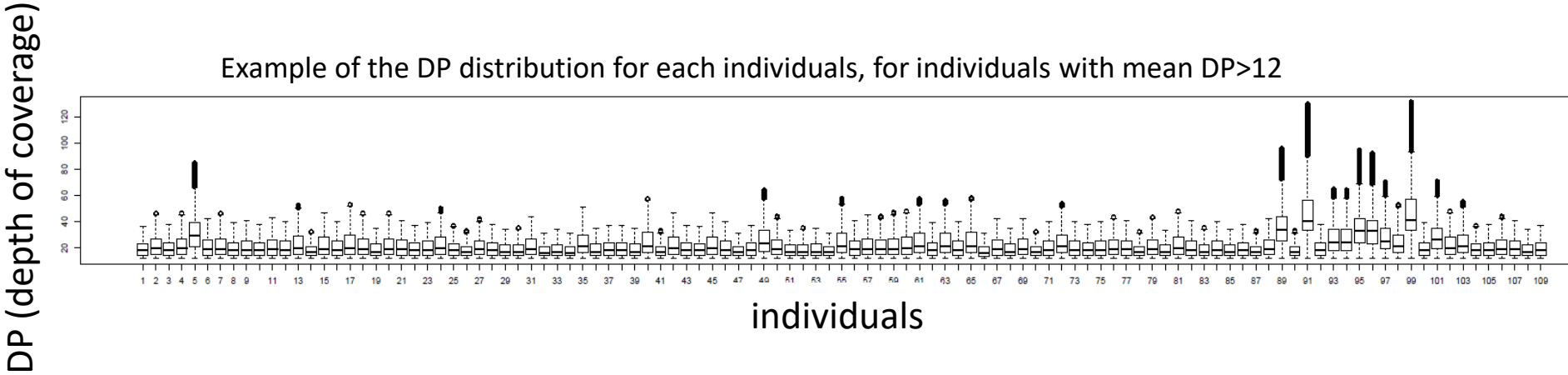
Deer mice: Model fit to marginal SFS



Some lessons I learned working with the deer mice data

- Be carefull when applying Hardy-Weinberg filters to your data
- Be carefull when filtering on depth of coverage applying the same thresholds for all individuals

The depth of coverage varied considerably across individuals



- Applying the same threshold for all individuals can lead to biases
- Apply a filter on DP for each individual

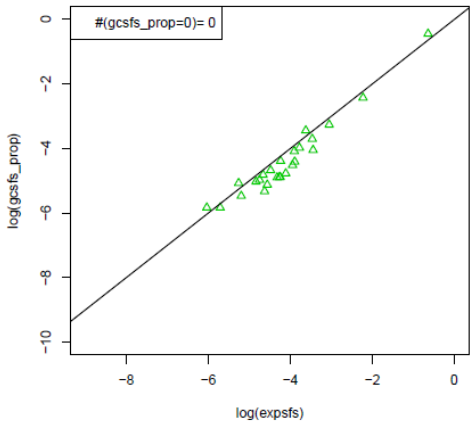
Effect of DP filters on the SFS
Simulation study

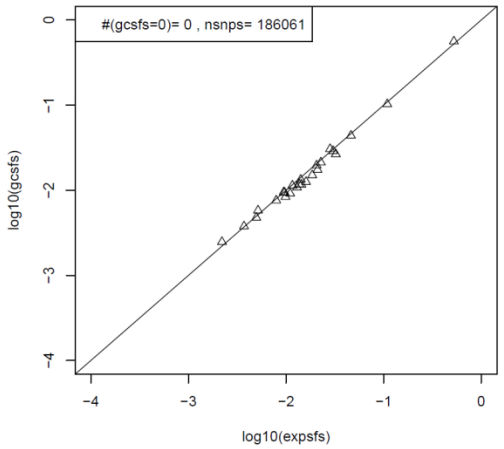
DP > 10

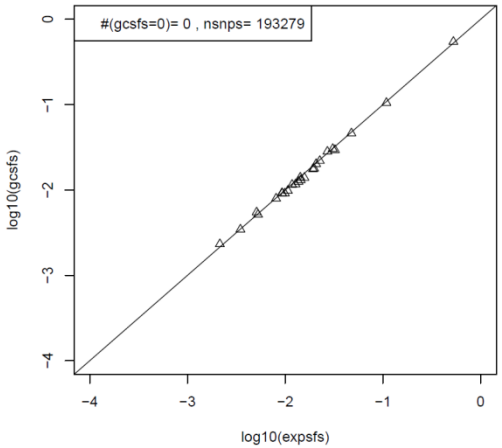
DP > 15

DP > 20

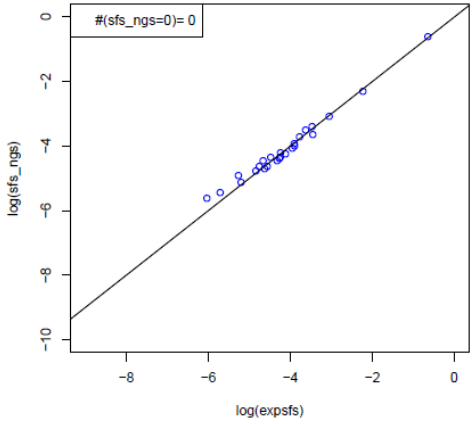
SFS based on called genotypes







SFS accounting for genotype uncertainty (ANGSD)

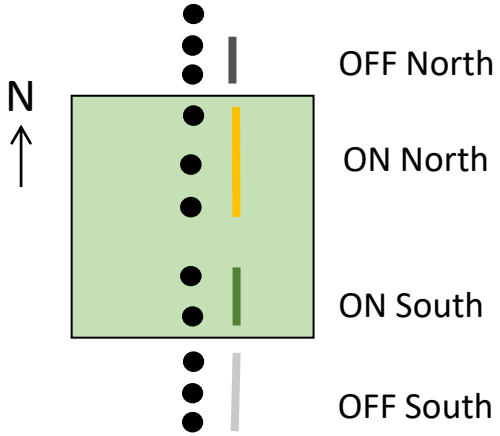


Simulated 2 pops SFS sampling 4 diploids from each pop, 200000 SNPs, mean coverage=**10x**, error rate=0.01. Simulated with correlated allele frequencies model (F_{ST}=(0.275, 0.01))

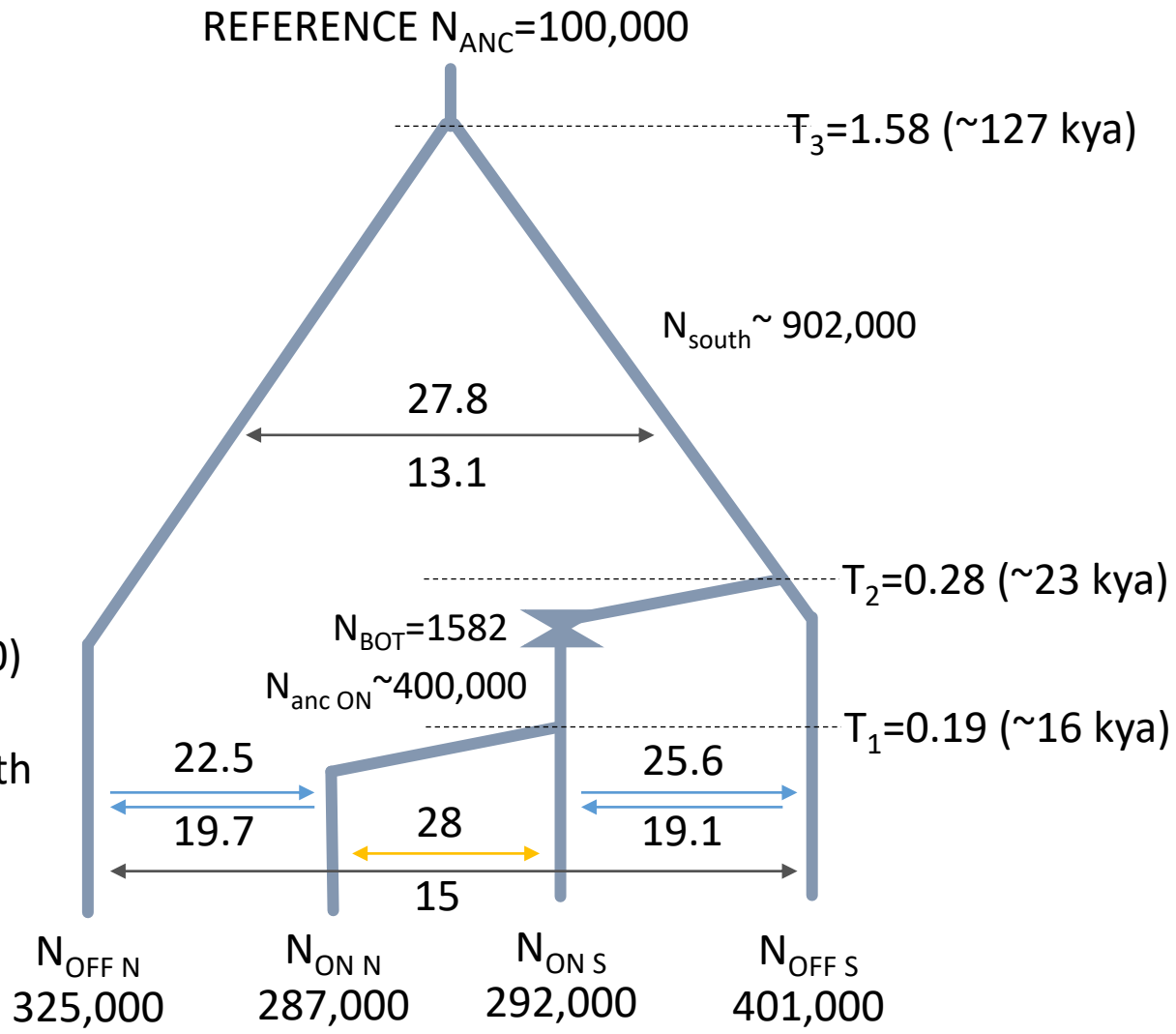
With DP>15 we have a very good approximation to the correct SFS, even when using the called genotypes

Effect of HW filtering on demographic estimates

Removing sites with HWE excess and deficit leads to different estimates



- High migration between all groups of populations (2Nm~20)
- No evidence of a strong bottleneck signal associated with colonization of SH



Sawflies and RAD data

MOLECULAR ECOLOGY

Molecular Ecology (2016) doi: 10.1111/mec.13972

History, geography and host use shape genomewide patterns of genetic variation in the redheaded pine sawfly (*Neodiprion lecontei*)

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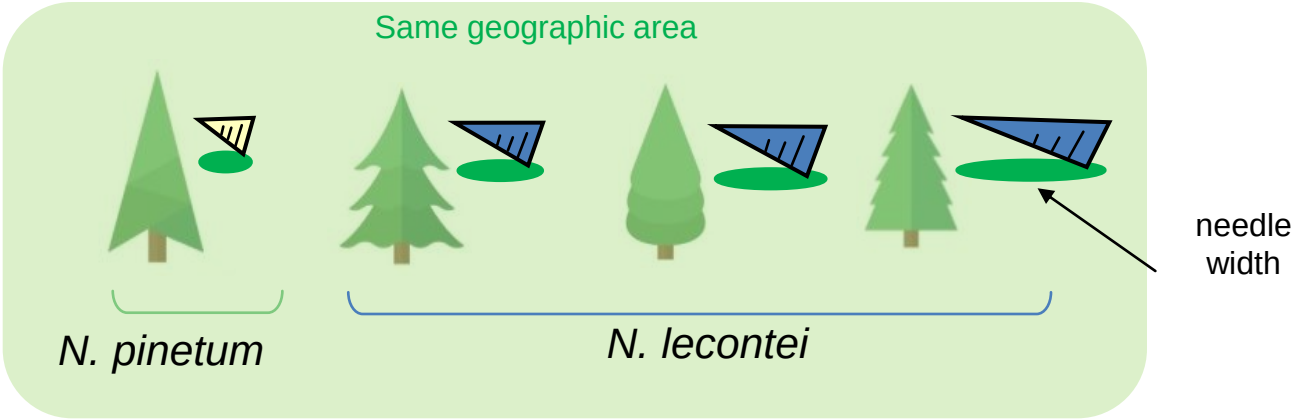
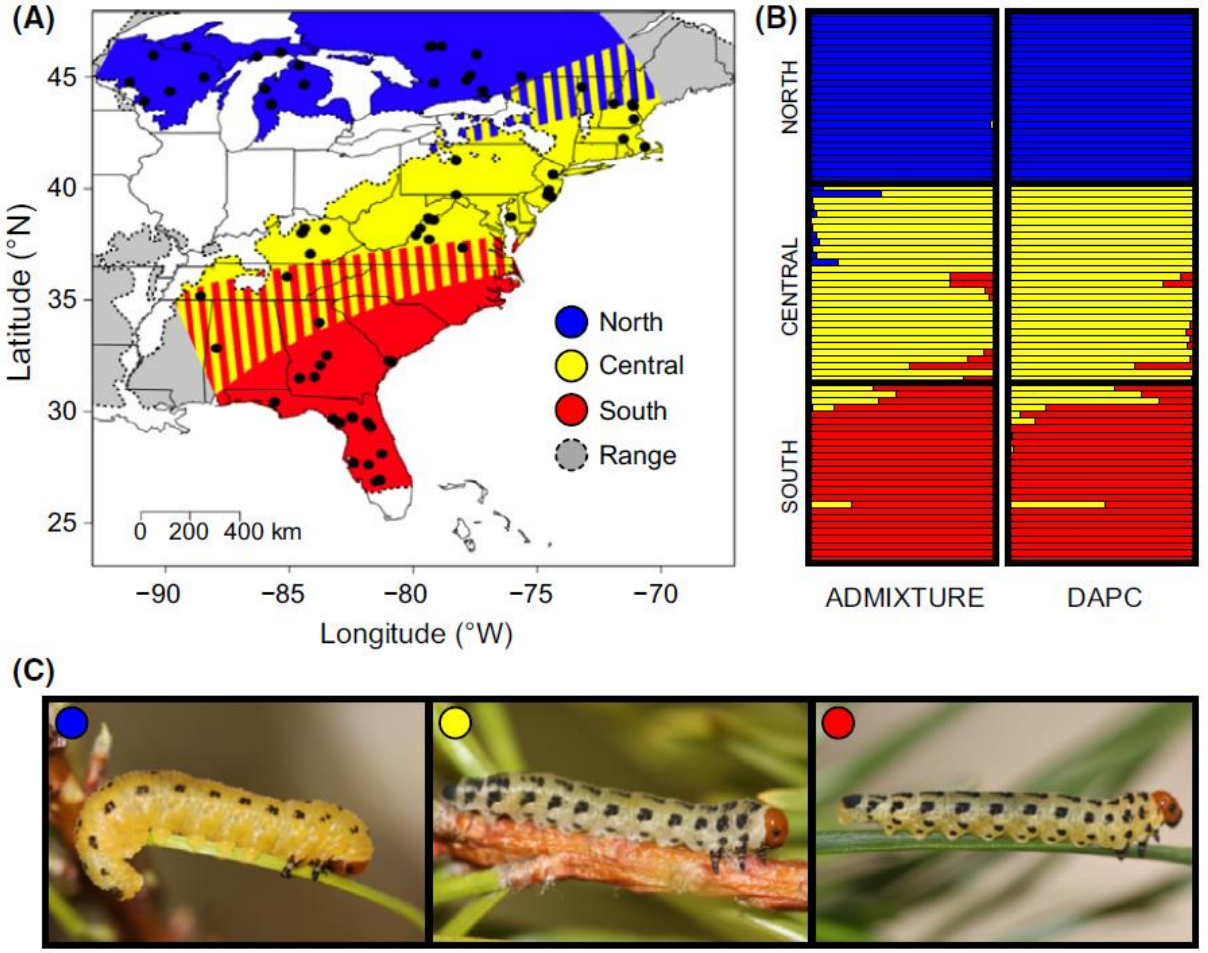
Sawflies *Neodiprion lecontei*

- Hymenoptera
- Plant-feeding insects
- Pine tree specialists



ddRAD seq data

- 80 individuals from 77 localities and 13 host species
- 100 bp paired-end reads, mapped to reference genome of *N. lencontei*
- Depth of coverage filter DP>10

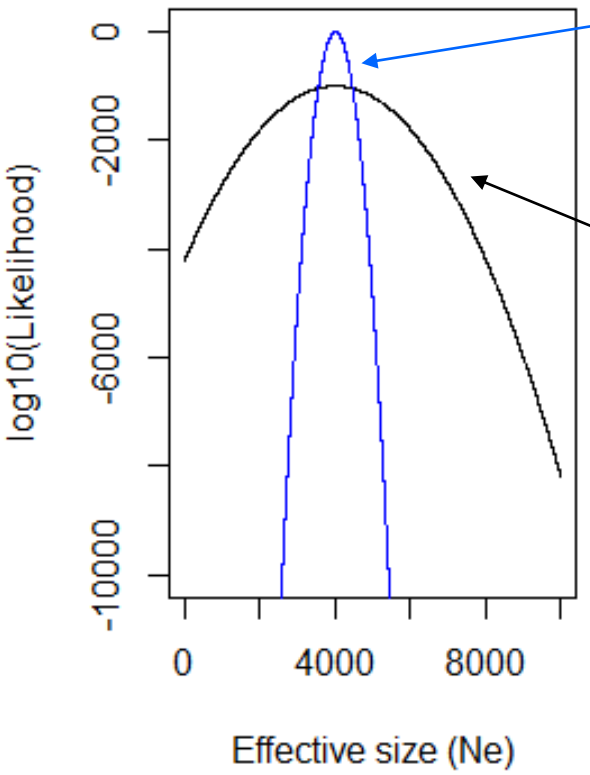


Given the detected three groups (North, Central, South):

- What is the the population tree topology?
- What are the split times?
- What are the migration levels among groups?

Comparing models with composite likelihoods

- Fastsimcoal2 likelihood is “correct” if all SNPs are independent
- We can then compare the model likelihoods using Akaike Information Criterion (AIC)



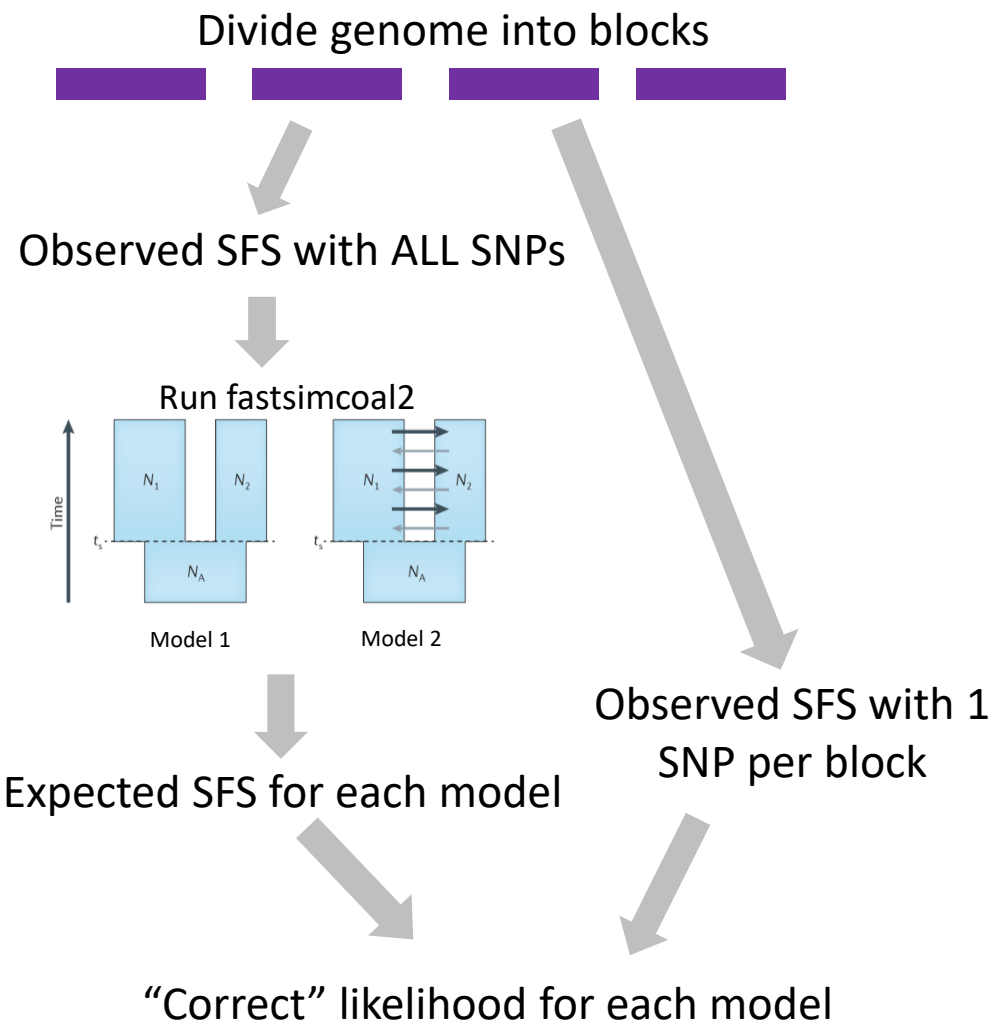
Composite likelihood (assuming linked sites are independent)

“correct” likelihood (all sites are actually independent)

Composite likelihood provide unbiased maximum likelihood parameter estimates, but the likelihoods are inflated

A strategy to compare models

1. Divide the dataset into LD blocks.
2. Create a dataset with all SNPs (including linked SNPs)
3. For each model, obtain the parameters that maximize the likelihood (this is ok even with linked sites!) and the corresponding expected SFS
4. Create a dataset with "independent" SNPs (1 SNP per RAD tag)
5. Given the expected SFS of each model, compute the "correct" likelihood for each model with the dataset with independent SNPs
6. Compare models with AIC

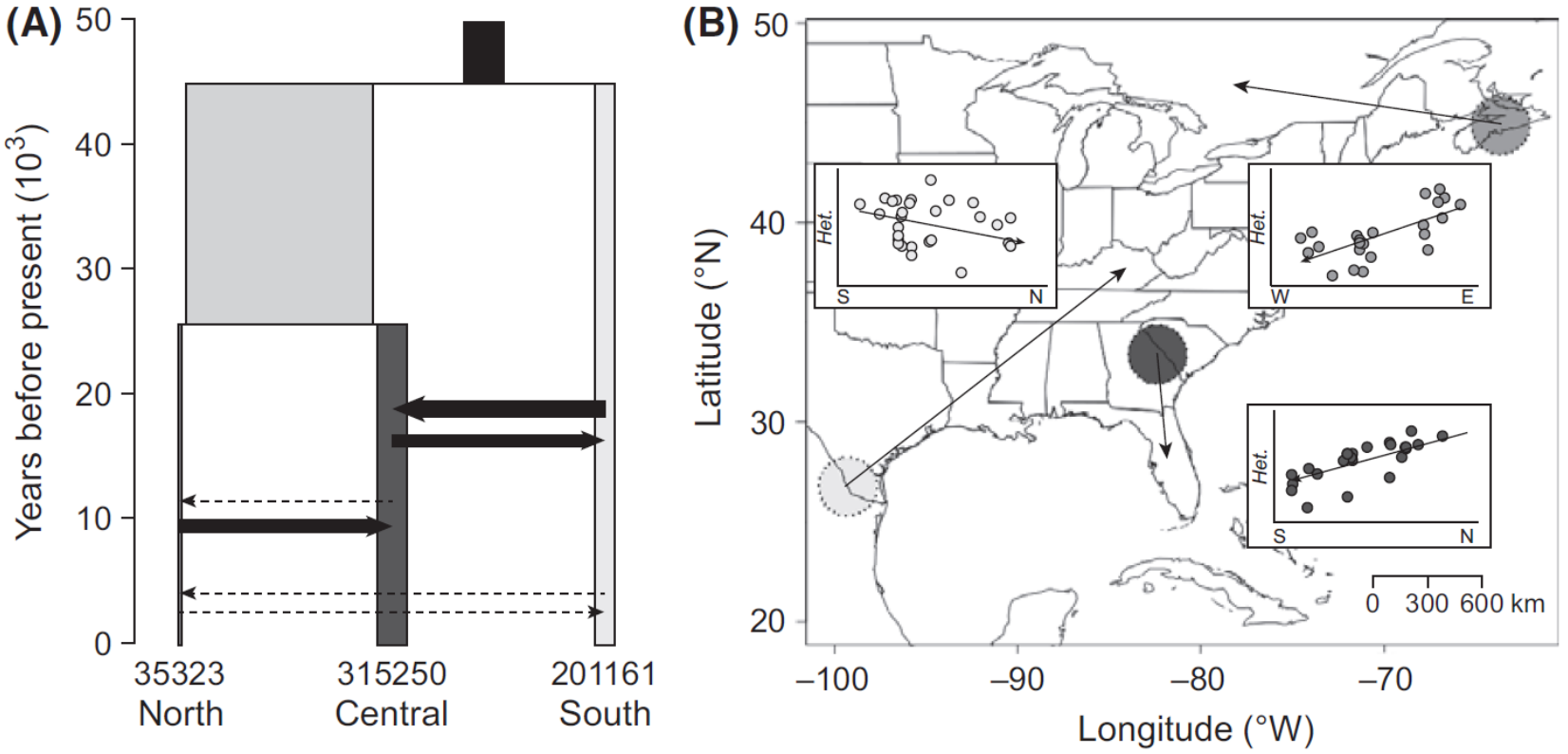


Comparing alternative models

Table 2 Summary of the likelihoods for the sixteen demographic models tested. Lhood (ALL SNPs) and Lhood (1 SNP) correspond to the mean likelihood computed with the data sets containing 'all SNPs' (including monomorphic sites) and a 'single SNP' (without monomorphic sites) per RAD locus, respectively. Mean likelihoods were computed based on 100 expected site frequency spectra simulated according to the parameters that maximized the likelihood of each model. Topology names for each model are as indicated in Fig. S1 (Supporting information). AIC scores and relative likelihoods (Akaike's weight of evidence) were calculated based on the 'single SNP' data set following Excoffier *et al.* 2013.

Topology	Migration allowed?	Exponential growth?	North bottleneck?	$\log_{10}$(Lhood) ALL SNPs	$\log_{10}$(Lhood) 1 SNP	# Parameters	AIC	ΔAIC	Relative likelihood
North–South	No	No	No	−46502.02	−7381.4	7	34006.70	75.69	0.000
North–Central	No	No	No	−46475.82	−7369.0	7	33949.44	18.43	0.000
South–Central	No	No	No	−46502.18	−7381.6	7	34007.60	76.59	0.000
Trifurcation	No	No	No	−46501.54	−7380.4	5	33998.07	67.06	0.000
North–South	Yes	No	No	−46470.49	−7365.0	15	33947.25	16.24	~0.000
North–Central	Yes	No	No	−46462.24	−7361.5	15	33931.01	0.00	0.851
South–Central	Yes	No	No	−46467.69	−7363.8	15	33941.57	10.56	0.004
Trifurcation	Yes	No	No	−46470.28	−7364.7	11	33937.93	6.91	0.027
North–South	Yes	Yes	No	−46469.48	−7362.8	18	33942.91	11.90	0.002
North–Central	Yes	Yes	No	−46461.17	−7361.7	18	33937.82	6.80	0.028
South–Central	Yes	Yes	No	−46463.73	−7363.9	18	33948.15	17.13	~0.000
Trifurcation	Yes	Yes	No	−46467.72	−7363.3	14	33937.39	6.37	0.035
North–South	Yes	Yes	Yes	−46467.45	−7361.5	20	33940.86	9.85	0.006
North–Central	Yes	Yes	Yes	−46461.25	−7362.1	20	33943.82	12.81	0.001
South–Central	Yes	Yes	Yes	−46463.58	−7364.1	20	33953.08	22.07	0.000
Trifurcation	Yes	Yes	Yes	−46466.06	−7362.4	16	33936.93	5.92	0.044

Estimates favors a scenario where North and Central diverged more recently with asymmetric gene flow



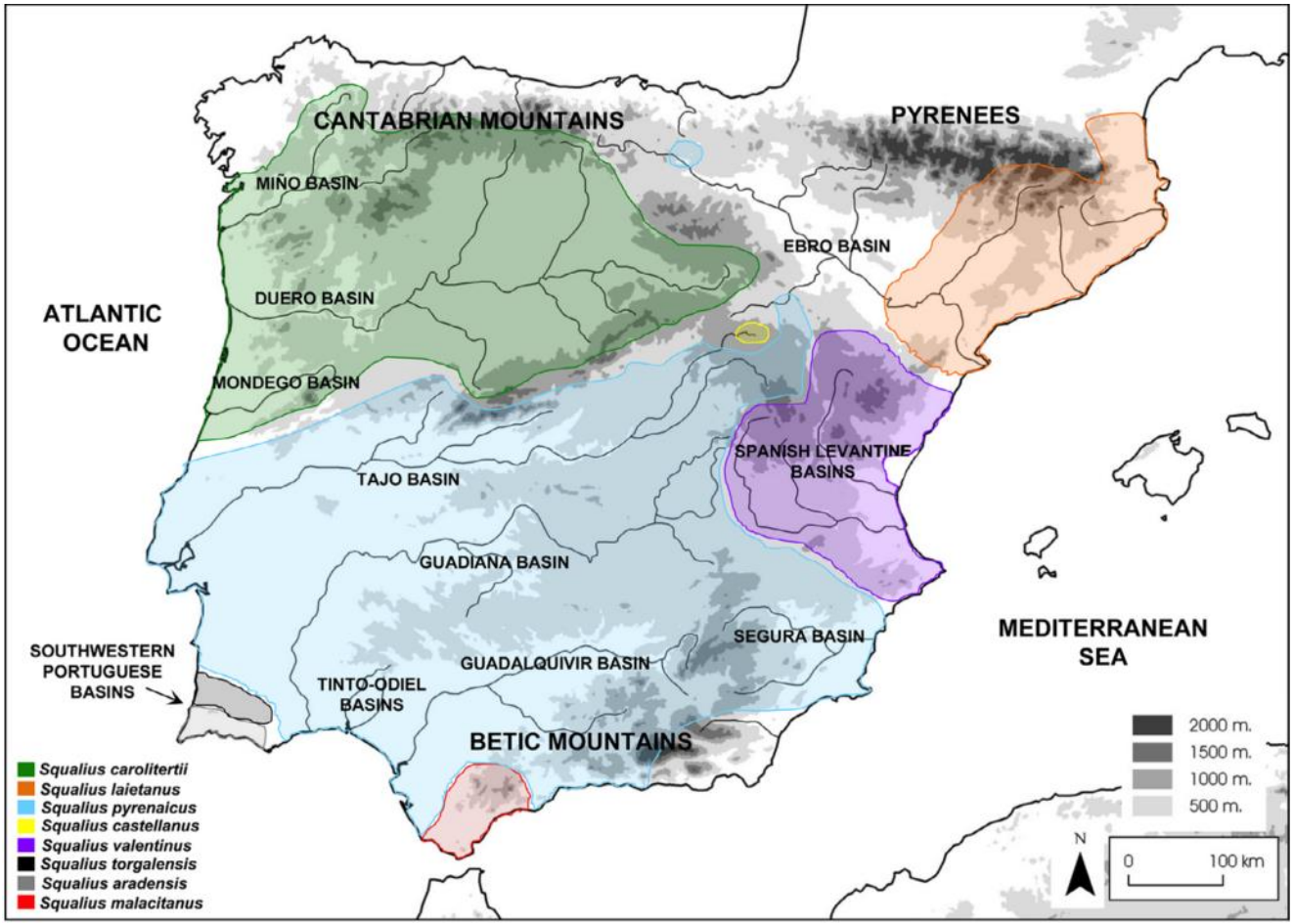
The inferred population tree topology and divergence times are consistent with divergence and range expansion from different refugia after LGM

Summary

- Fastsimcoal2 can be applied to RAD seq data
- We used a strategy to obtain (as close as possible) the “correct” likelihood by dividing the data into blocks, inferring the expected SFS for each model with ALL SNPs, and then re-computing the “true” likelihood with independent SNPs (1 SNP per block)
- Despite the reduced number of SNPs we were able to discriminate models based on their likelihoods

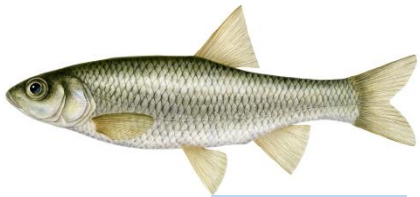
Inferring admixture in freshwater fish species

Sofia Mendes (EG, cE3c)



GBS data (48 individuals, 23,562 SNPs with ~37% missing data)

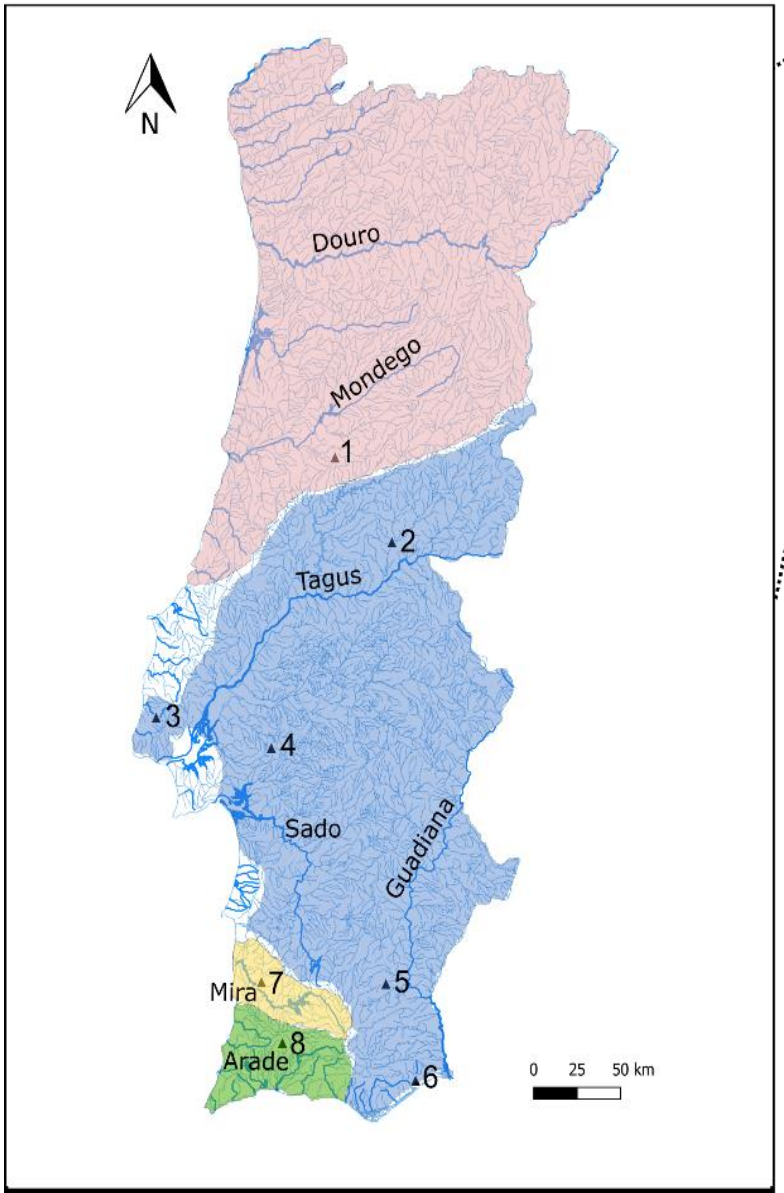
S. carolitertii



S. pyrenaicus

S. torgalensis

S. aradensis



Sampling locations:

1. Mondego — *S. carolitertii*
2. Ocreza
3. Lizandro — *S. pyrenaicus North*
4. Canha
5. Guadiana — *S. pyrenaicus South*
6. Almargem
7. Mira — *S. torgalensis*
8. Arade — *S. aradensis*

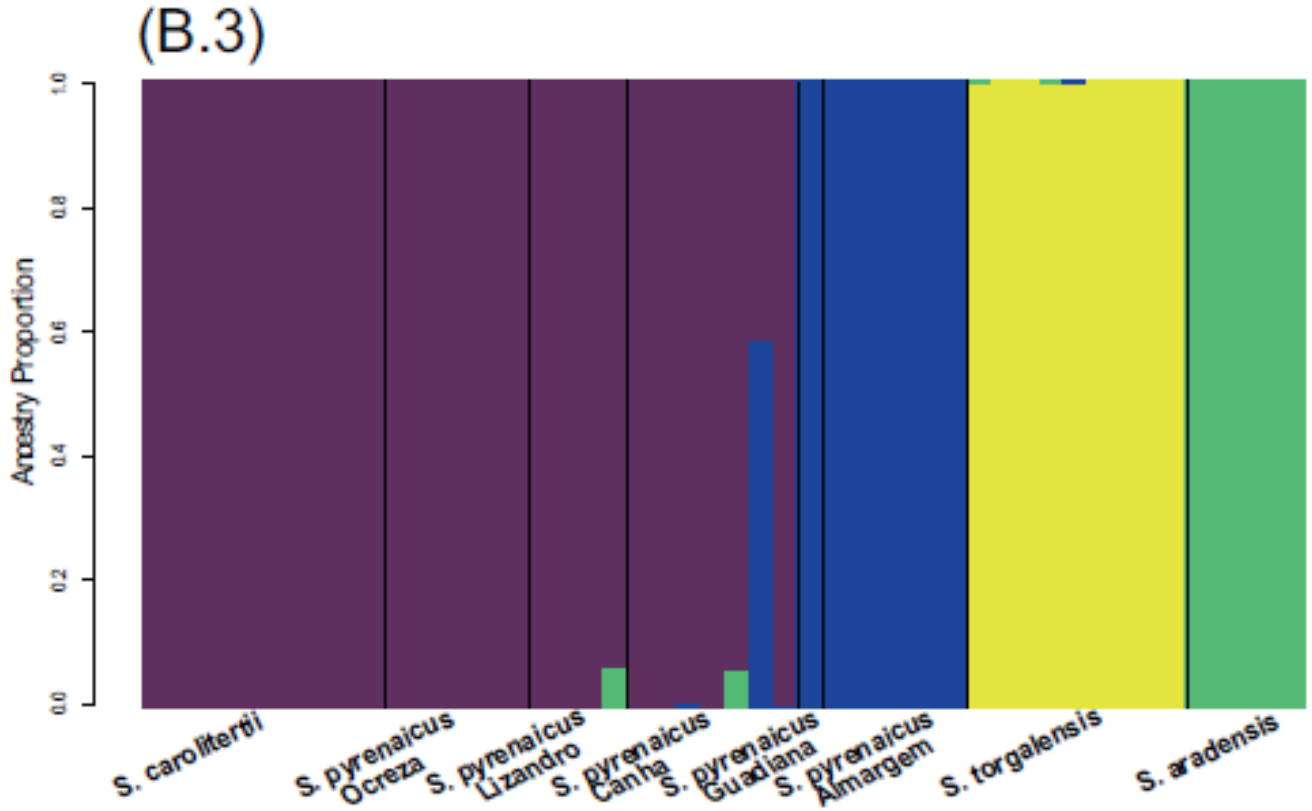
S. carolitertii

S. pyrenaicus

S. torgalensis

S. aradensis

Admixture results (*K*=4)



Mendes et al. (2021) Heredity

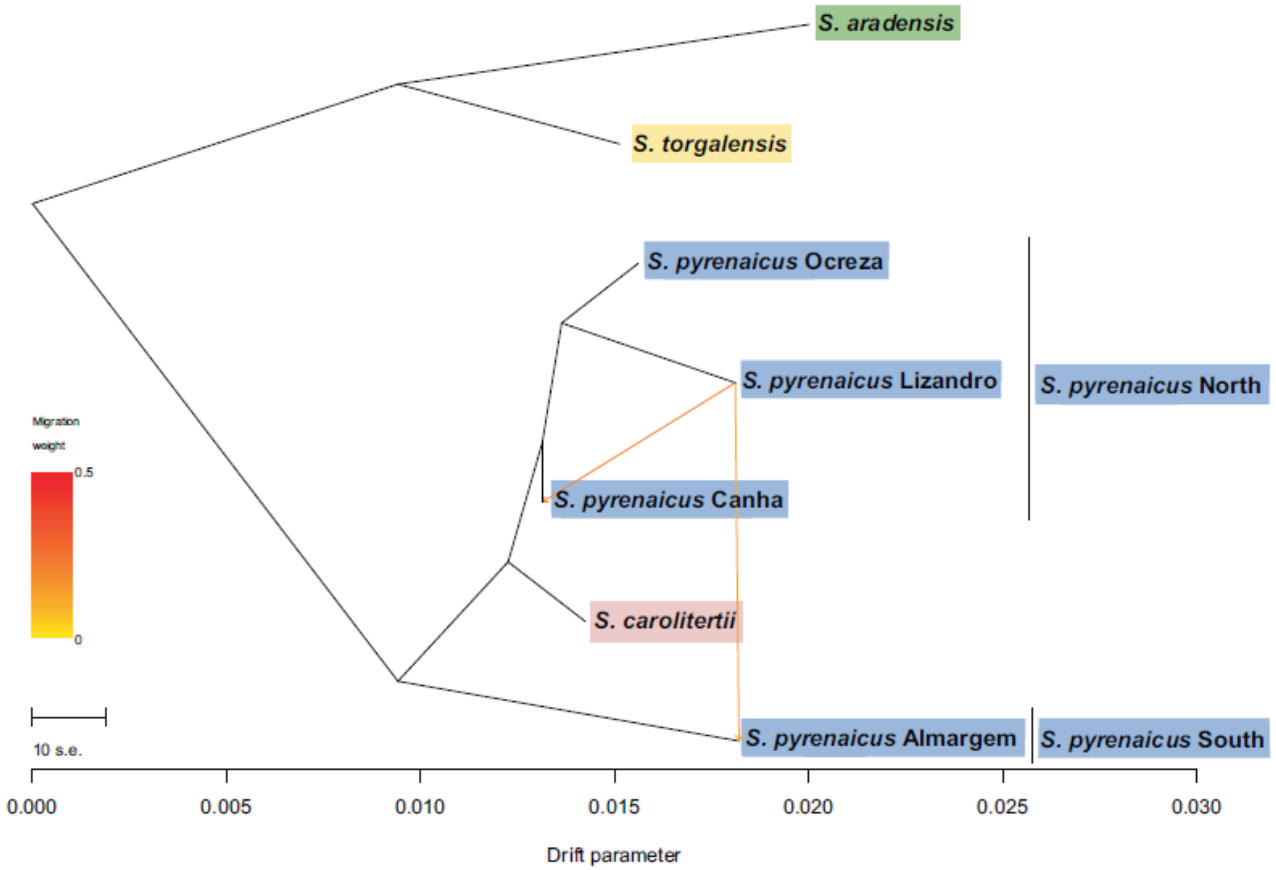
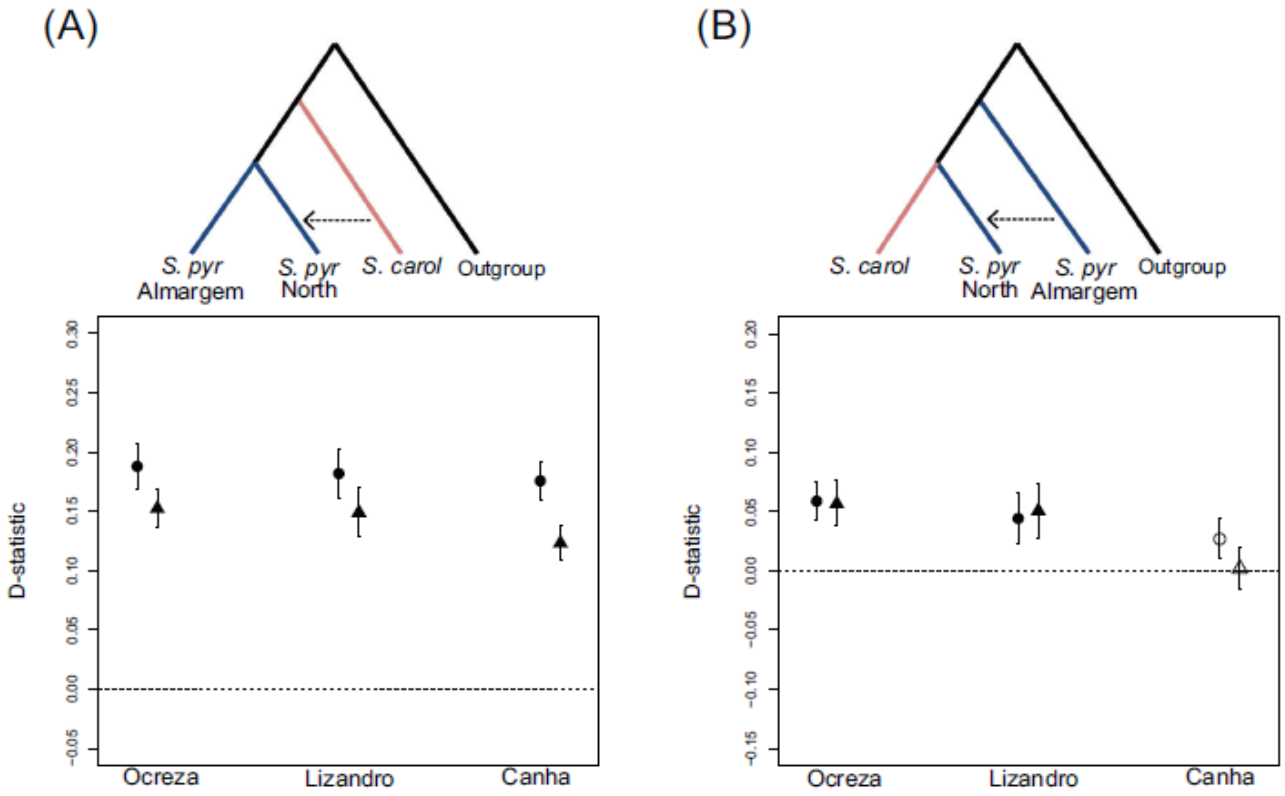


Fig. 3 Unrooted species tree graph obtained with TreeMix. Branch lengths are represented in units of genetic drift, i.e. the longer a given branch the stronger the genetic drift experienced in that lineage. Higher genetic drift can be due to older divergence times or smaller effective population sizes of a given lineage. Arrows represent migration events.

Mendes et al. (2021) Heredity

D-statistic (ABBA-BABA)



D-statistic indicates that the relationship cannot be described by a bifurcating tree

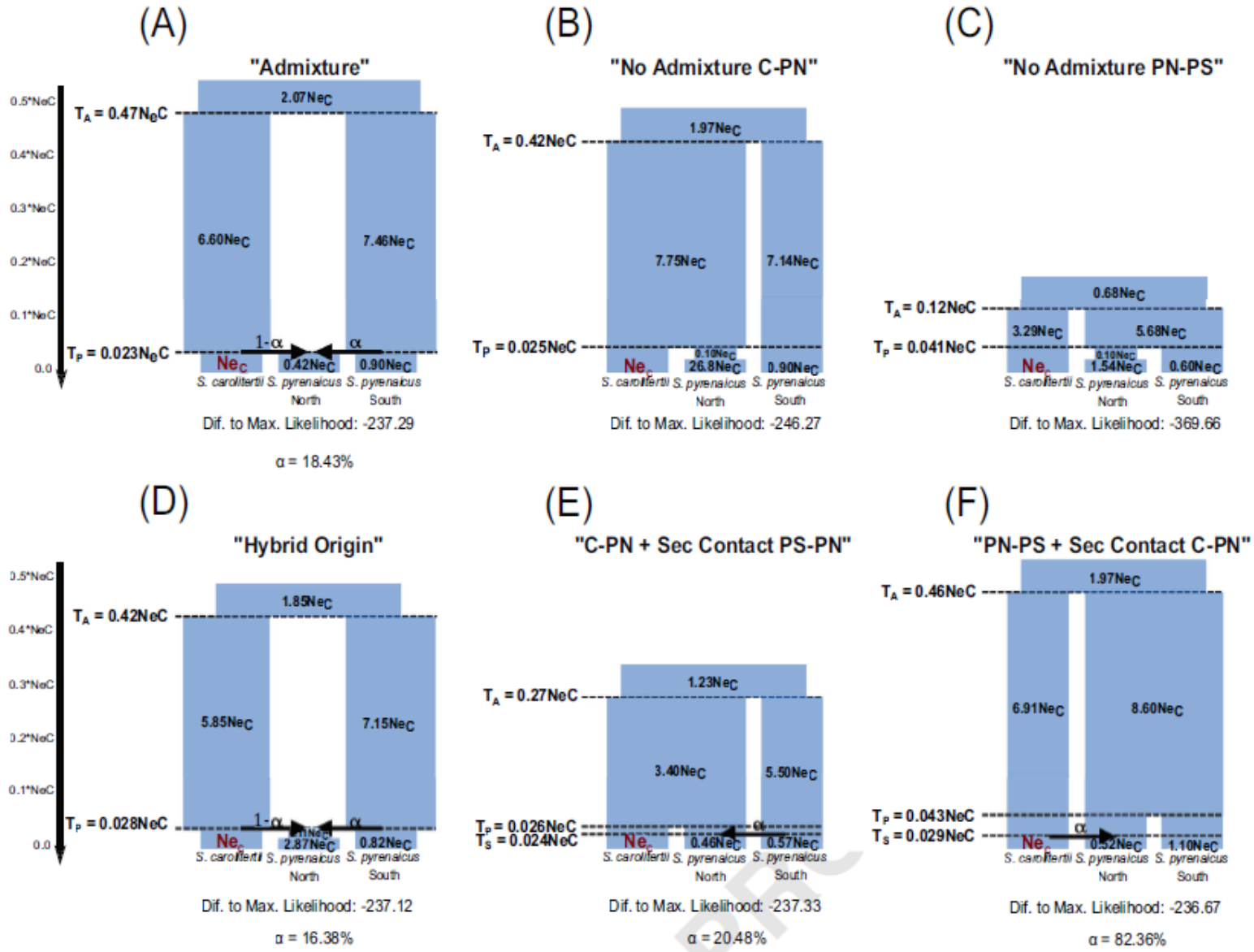
Mendes et al. (2021) Heredity

Pairwise 2D-folded SFS without monomorphic sites – inference based on relative parameters

- DP>10x
- Dowsampling 3 individuals from P1 (*S. carolitertii*), 4 individuals from H (*S. pyrenaicus North*), 3 individuals from P2 (*S. pyrenaicus* South)
- 8,758 SNPs
- Folded SFS according to minor allele across the 3 populations
- Size of the three pairwise 2D-SFS: 175 entries

Mendes et al. (2021) Heredity

Relative parameter estimates



Mendes et al. (2021) Heredity

3D-SFS including linked sites

3D-SFS 1SNP per GBS locus

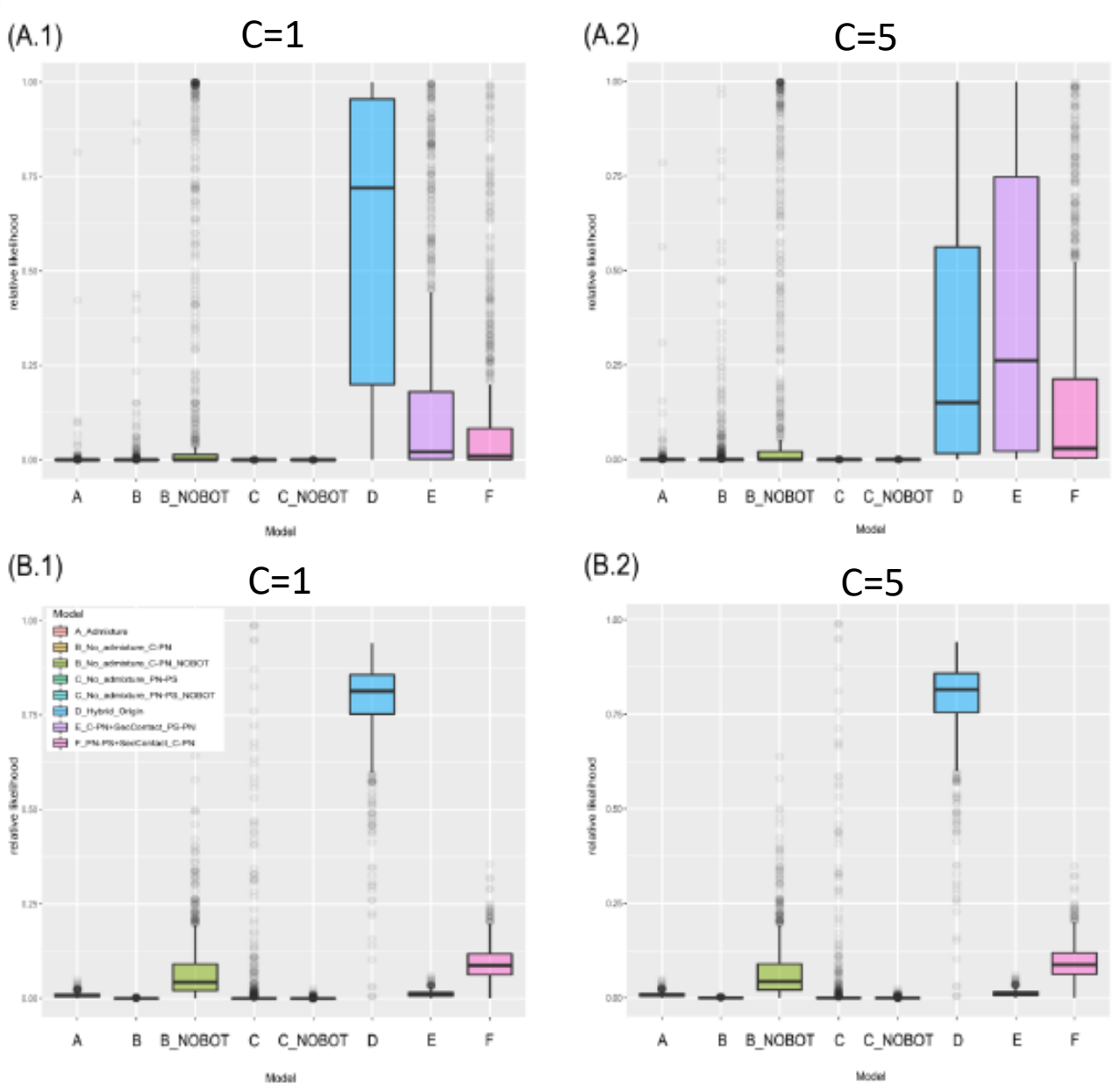


Figure S11– Relative likelihoods of demographic models based on AIC. Comparison of 8 models, including models B and C without bottlenecks, with 1000 bootstrap replicates. (A) Boxplots of relative likelihoods based on 3D-SFS with all SNPs per block with n=3 *S. carolitertii*, n=4 *S. pyrenaicus* North and n=3 *S. pyrenaicus* South individuals. Size of the joint 3D-SFS is SFSsize=441.

Protocol for model comparison based on AIC when we have independent SNPs

- Get the observed SFS
- Define the alternative models
- Perform 50-100 runs under each model
- Select the runs with maximum likelihood under each model
- Compute the AIC (Akaike information critera) for each model based on dataset with unlinked SNPs
- Select the model with minimum AIC

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b
UNIVERSITÄT
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SIB
Swiss Institute of
Bioinformatics

Thank you!

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centre for ecology, evolution
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