Introduction to BEAST 2

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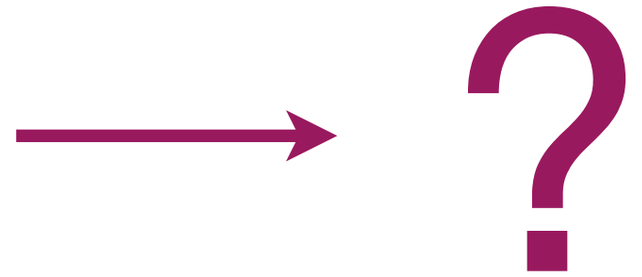
1. What goes into a BEAST model?
2. BEAST2 workflow
3. Introduction to BEAST2 tutorial
4. BEAST best practice

We all have one thing in common…

ACACACCTACAGACTTACAGACCC
TCACACCTACACACCCACAGACTT
TCAGACTTTCACACCTTCAGACCT
ACAGACTTTCAGACTTTCAGACCC
TCACACCTACACACCCACAGACTT
TCAGACTTTCACACCTTCAGACCTT



BEAST2

We all use **BEAST** to answer questions about our data

Bayesian **phylogenetic** and **phylodynamic** inference

Likelihood

$$P(\text{model} \mid \text{data}) = \frac{P(\text{data} \mid \text{model}) \times P(\text{model})}{P(\text{data})}$$

Posterior

Marginal likelihood of the data

Prior

Bayesian inference
(Data and model parameters are both described by probabilities)

Prior → P(model)

- Have some degree of belief in our hypothesis
- All model parameters have priors, whether you specify them or not

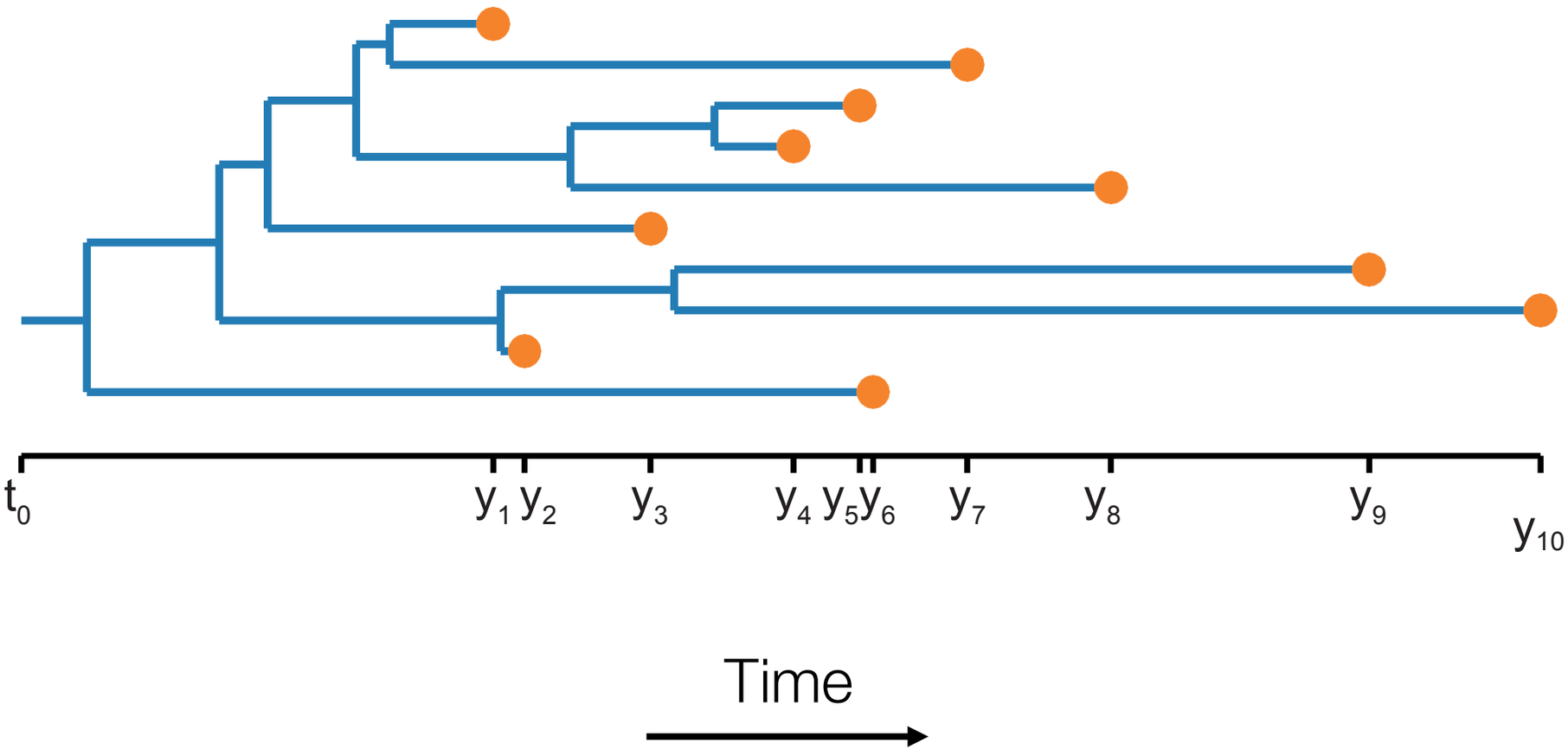
Likelihood → P(data | model)

- Likelihood is proportional to the probability of observing the data given a hypothesis

Posterior → P(model | data)

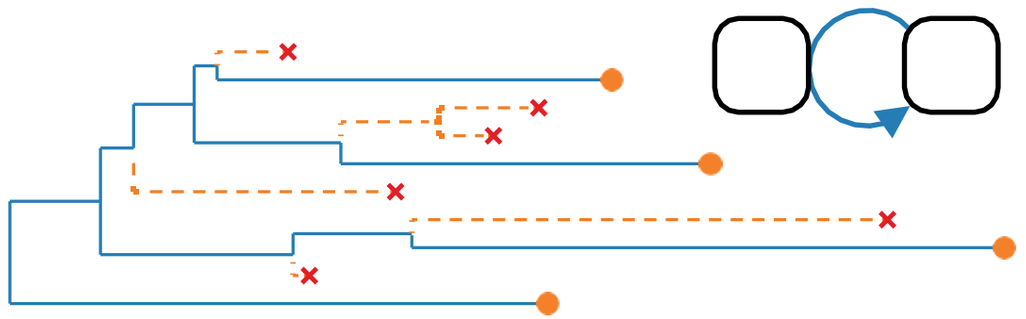
- Combines information from the data (likelihood) and previous knowledge (prior)

Rooted time-trees

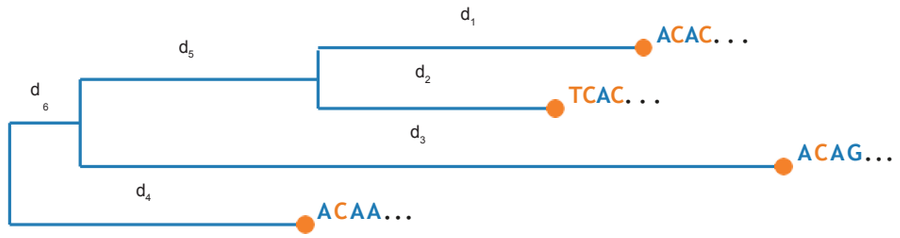


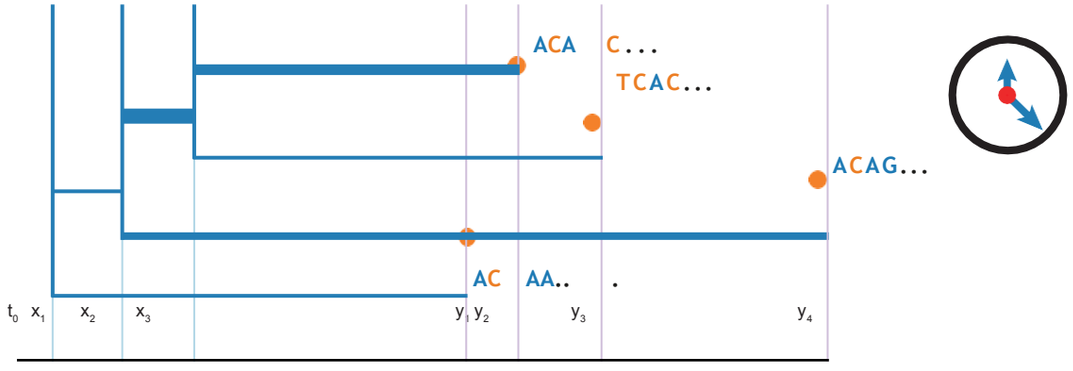
Fundamental data structure in **BEAST** is a **rooted time-tree**

What goes into a BEAST model?



TCAG





ACAC...
TCAC...
ACAG...
Genetic sequences

Genealogy

Demographic model

Site model

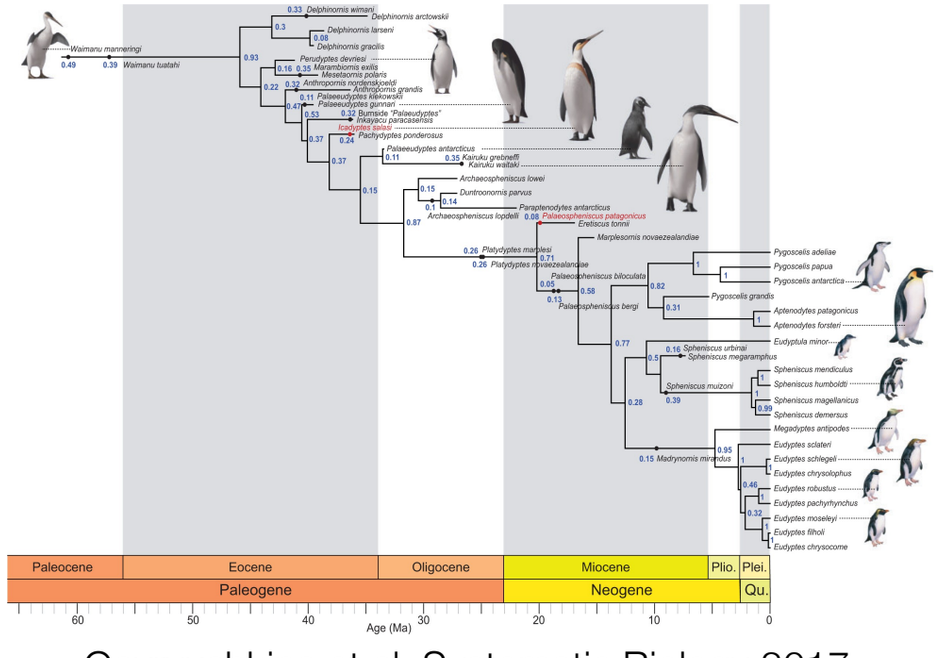
Molecular clock model

The Data!

- Typically an alignment of DNA or RNA sequences
- Can also be amino acids or codons
- Often split data into multiple partitions
  - Multiple genes
  - 1st, 2nd and 3rd codon positions
- Does **not** have to be genetic sequences!

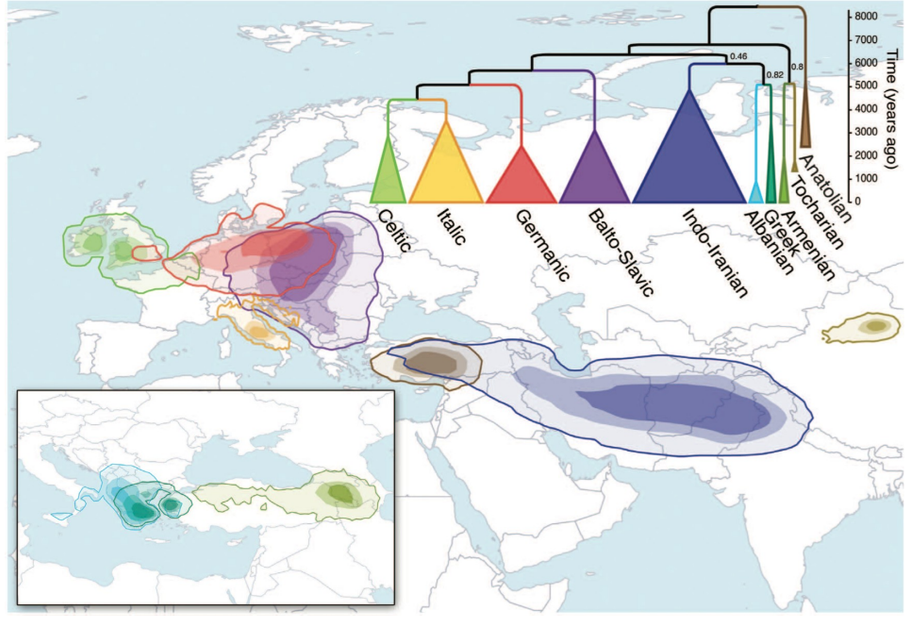
ACAC…
TCAC…
ACAG…
ACAC…
TCAC…
ACAG…
ACAC…
TCAC…
ACAG…

Morphological traits



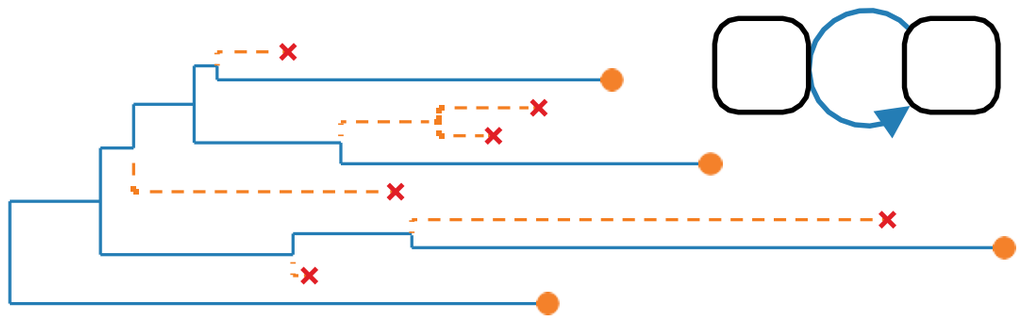
Gavryushkina et al. Systematic Biology 2017

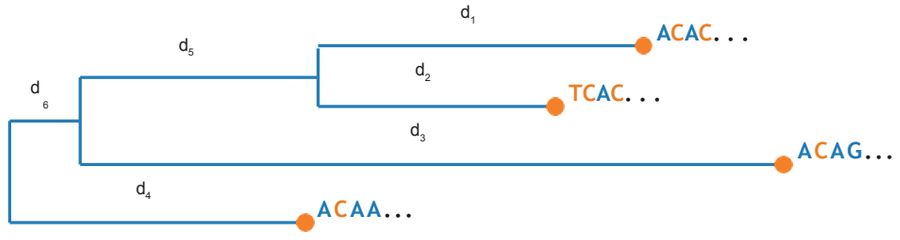
Roots of words

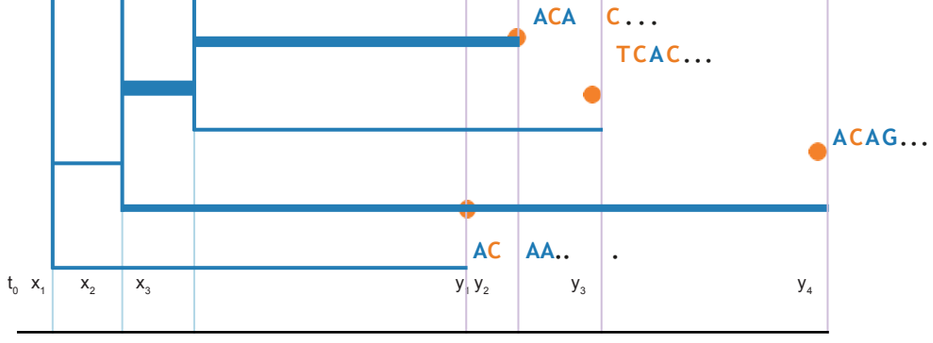


Bouckaert et al. Science 2012

What goes into a BEAST model?







ACAC...
TCAC...
ACAG...

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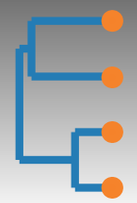
Genealogy

Demographic model

Site model

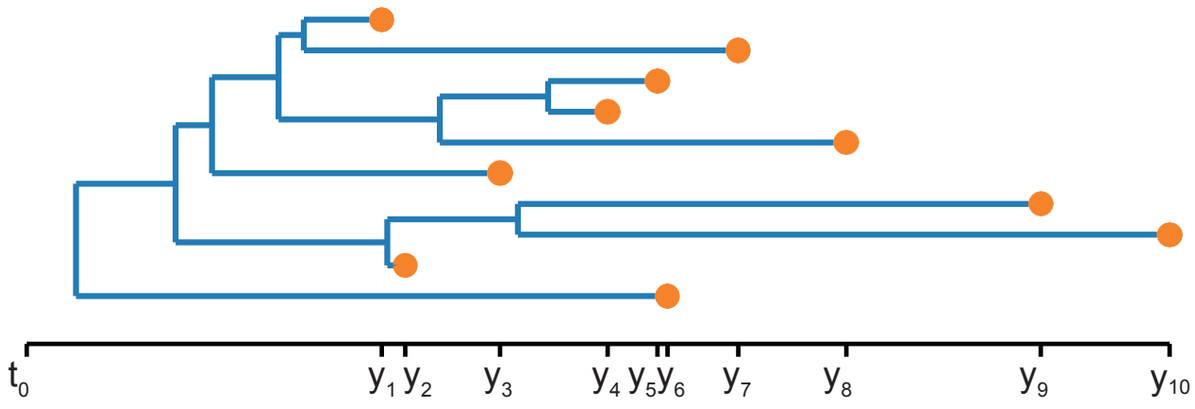
Molecular clock model

The genealogy (phylogenetic tree)

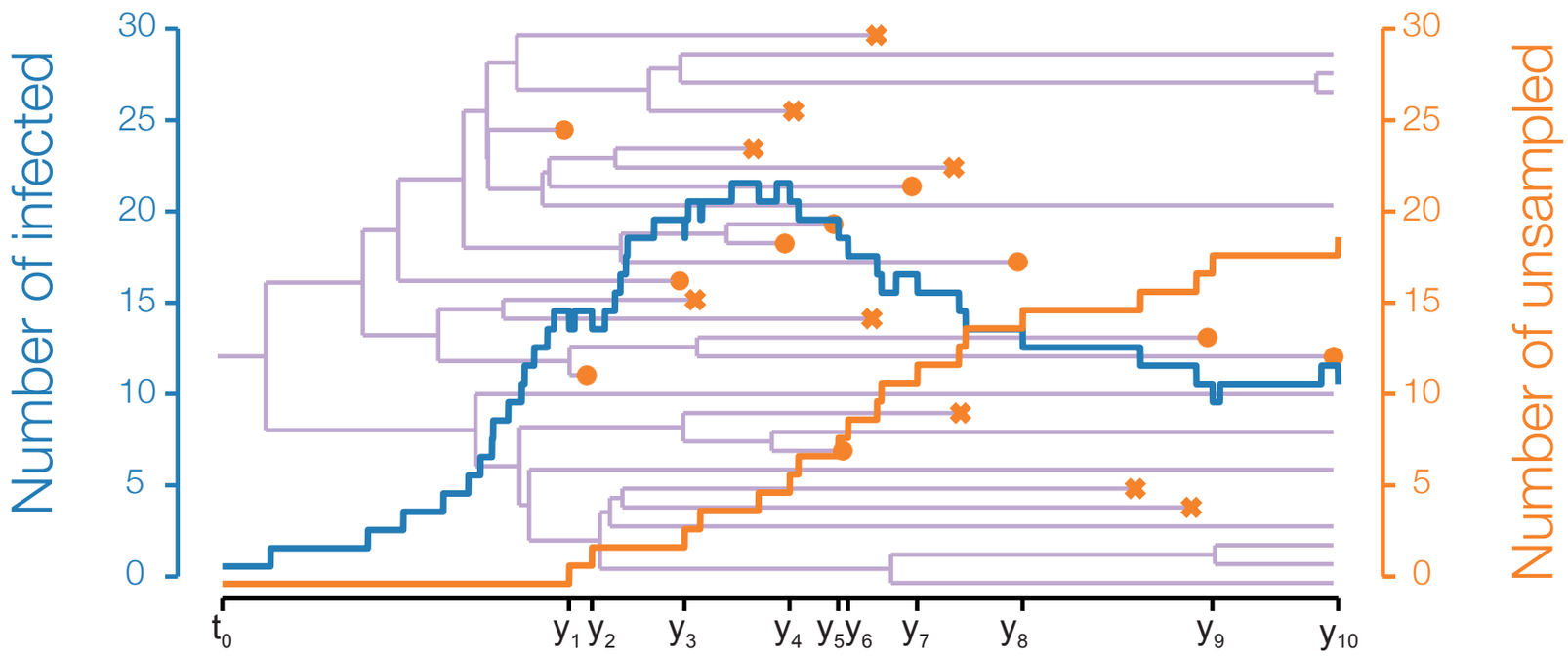


- What are the ancestral relationships between the sequences in our dataset?

Sampled tree

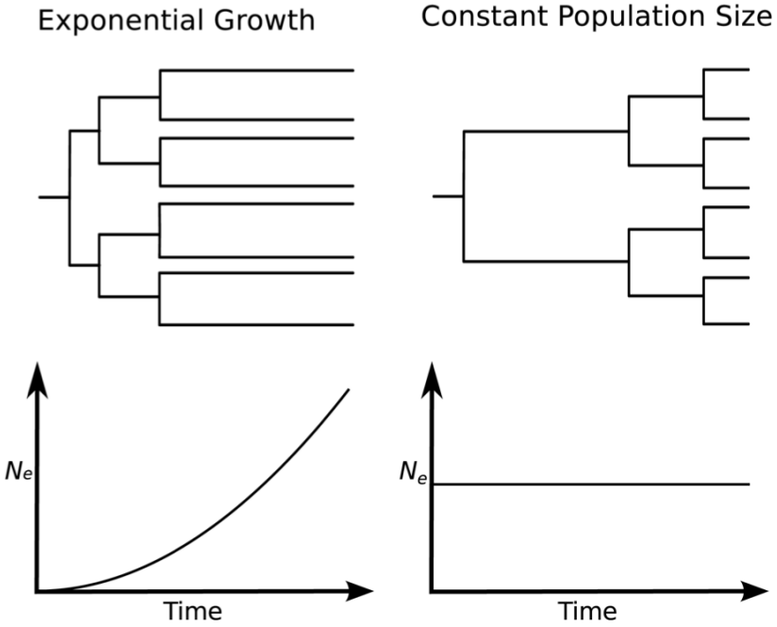


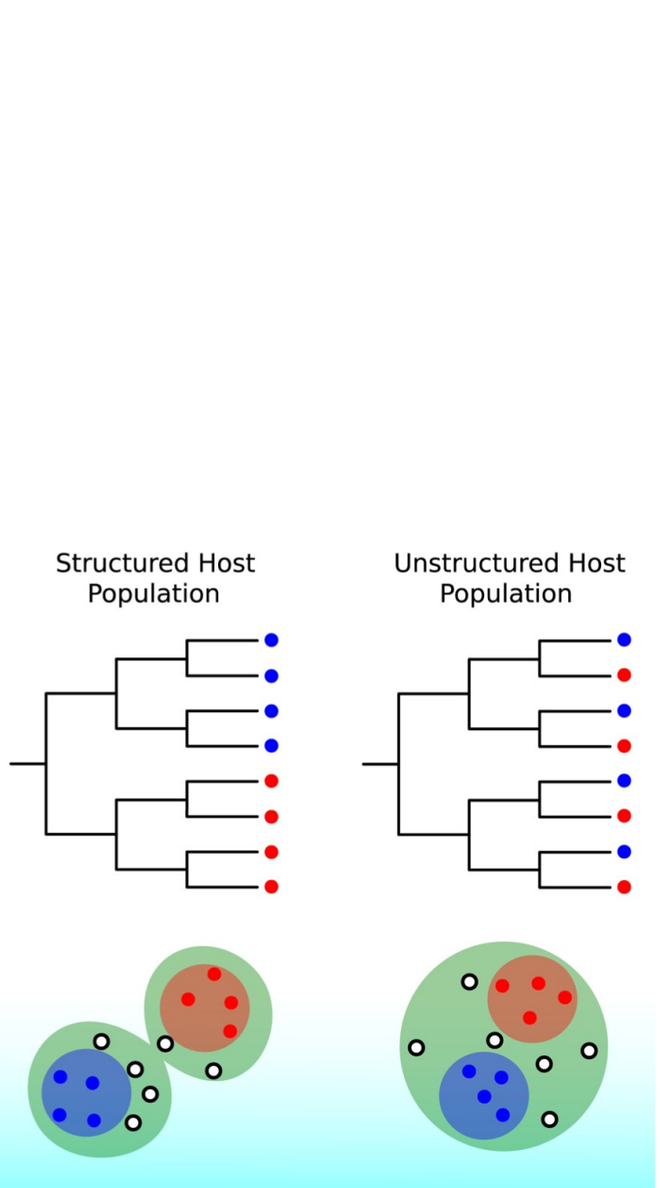
Full tree

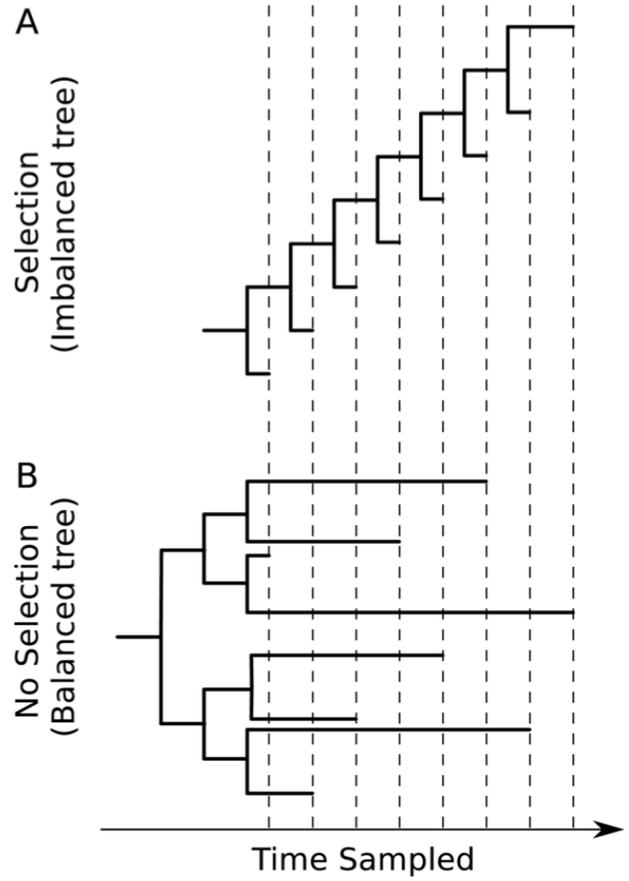


- Only the relationships between the **sampled** sequences!

Different population dynamics generate different trees



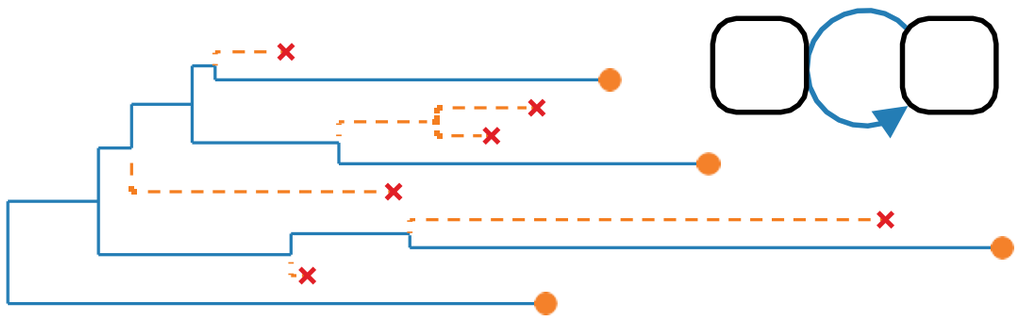




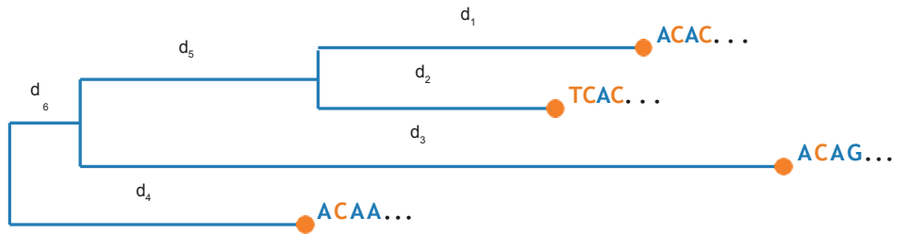
Volz et al. PLoS Comput Biol 2013.

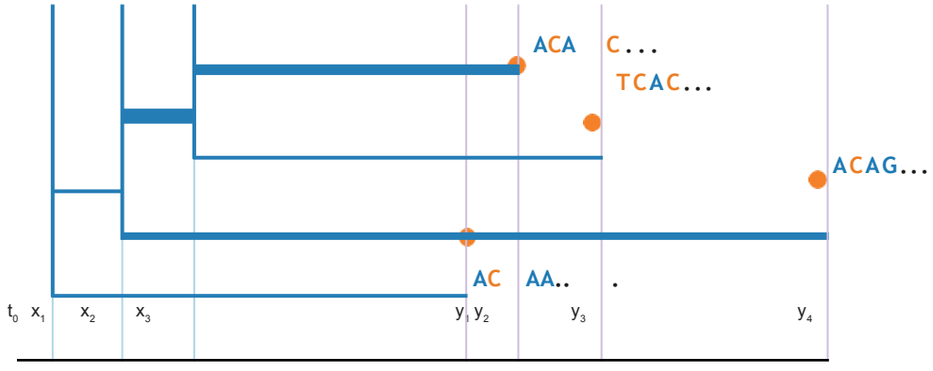
Grenfell et al. Science 2004

What goes into a BEAST model?



TCAG





ACAC...
TCAC...
ACAG...
Genetic sequences

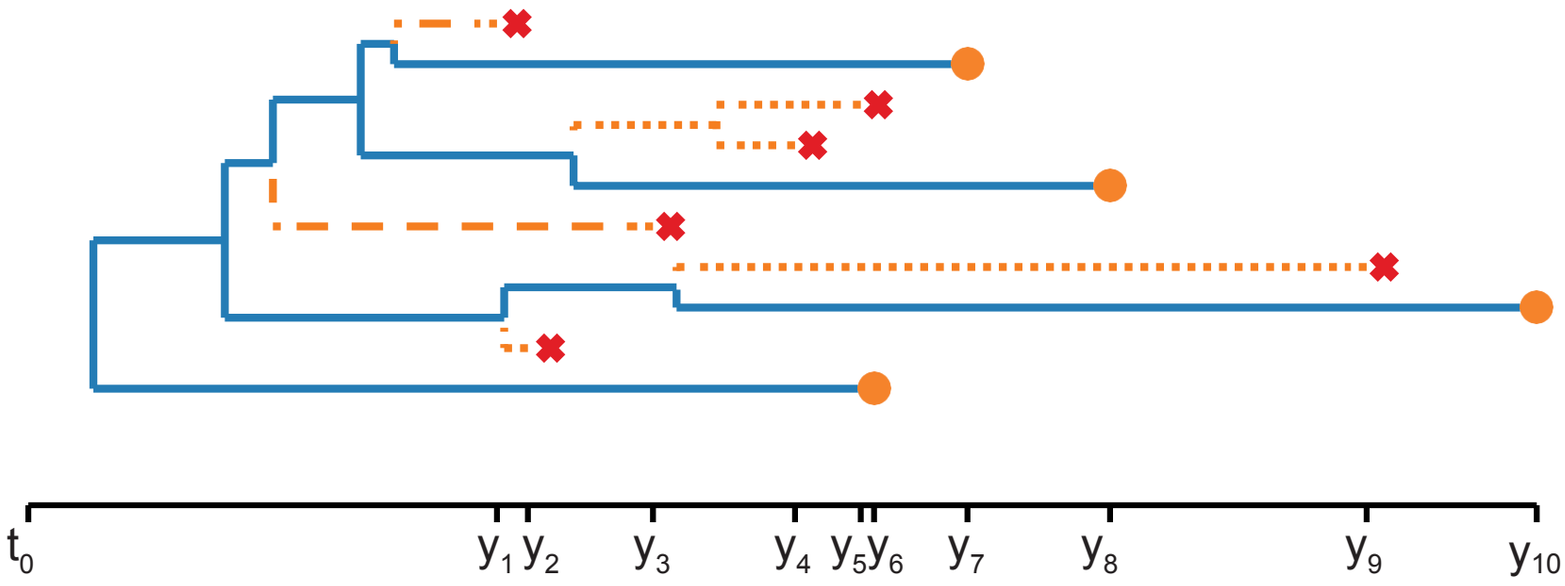
Genealogy

Demographic model

Site model

Molecular clock model

Demographic model

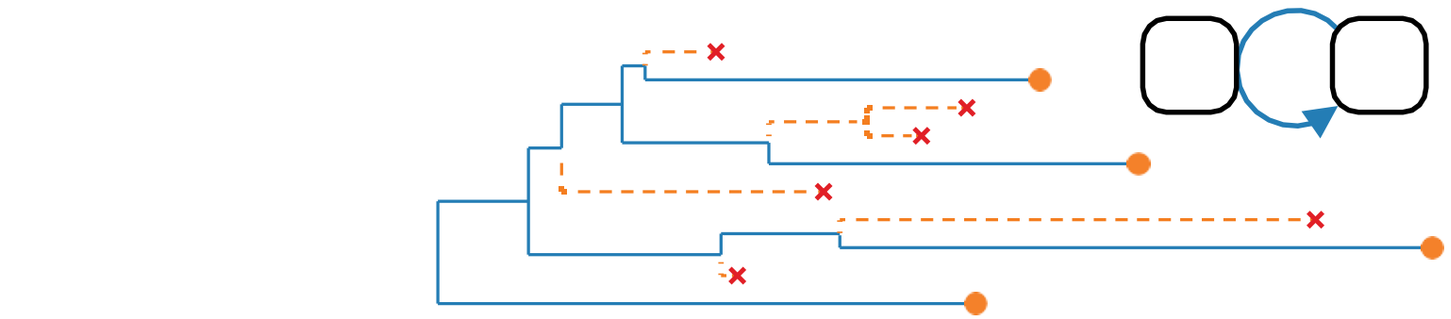


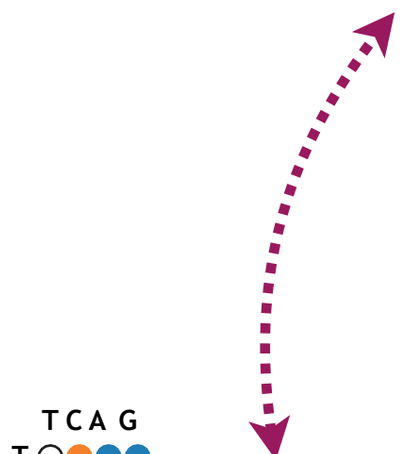
- Describes the population/speciation dynamics
- How does the population grow over time?
- How does the species diversity change over time?

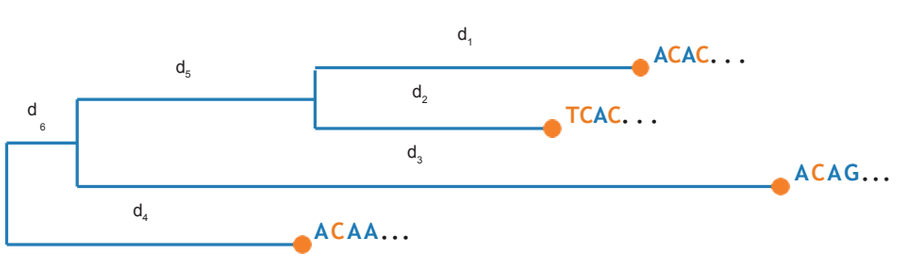
$P(\text{tree} \mid \text{demography})$ ◀····· Tree-Prior

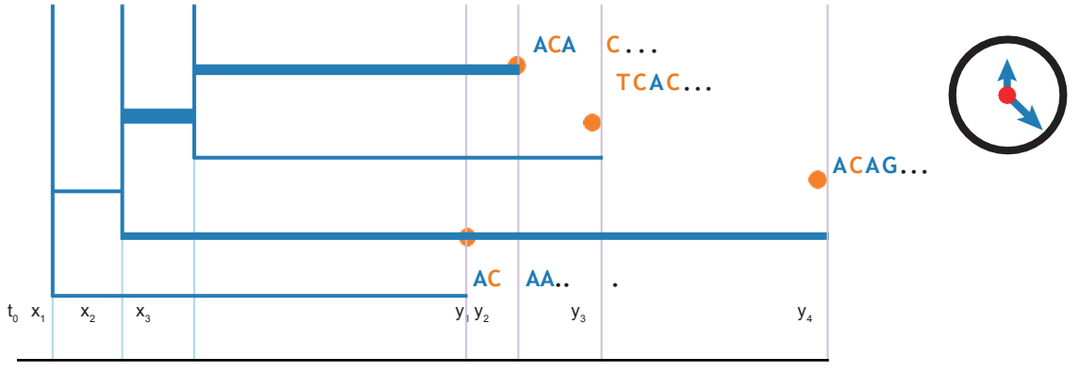
- How likely is the genealogy given a demographic model?
- Usually a birth-death or a coalescent model

What goes into a BEAST model?









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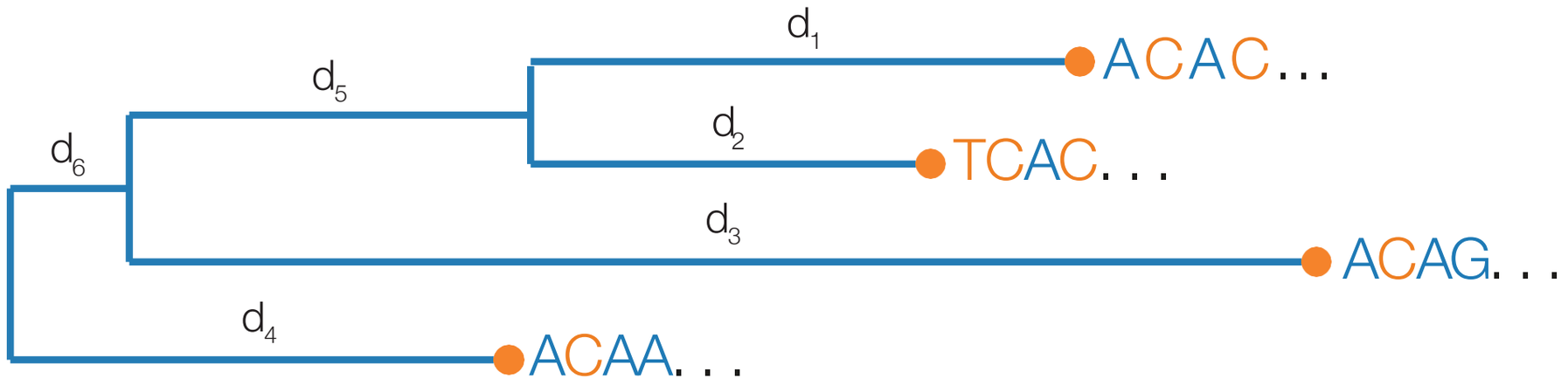


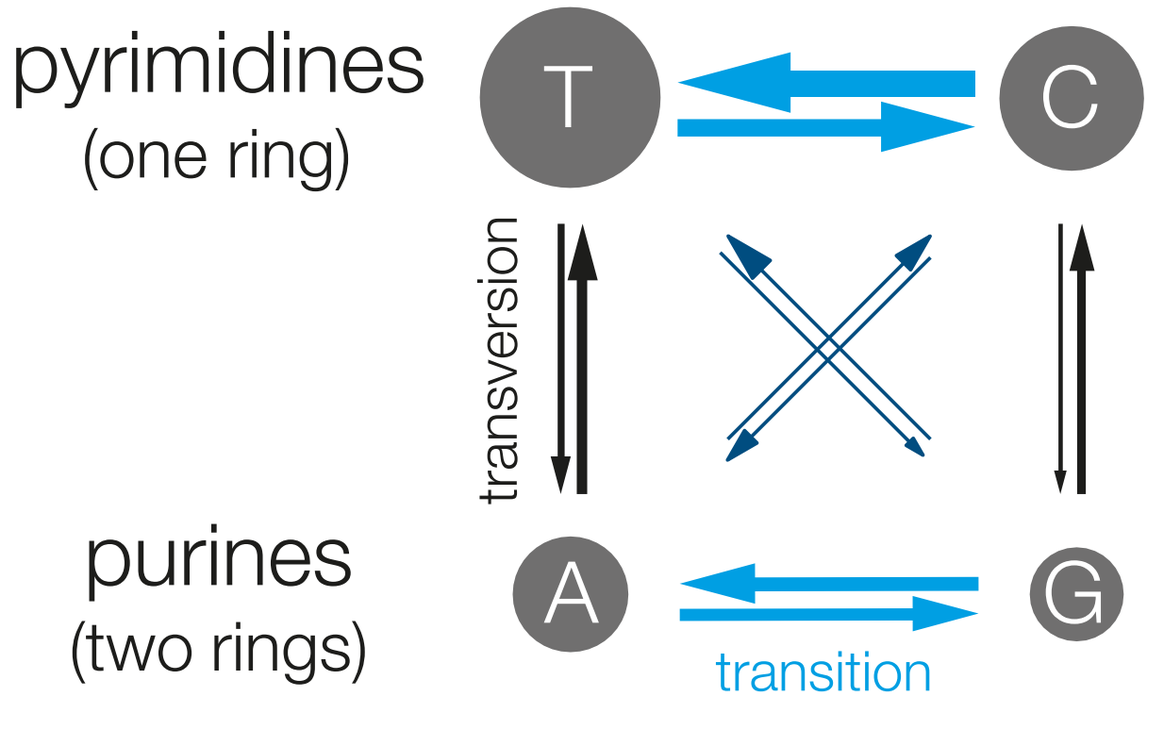
+

$(\pi_T, \pi_C, \pi_A, \pi_G)$

d: Genetic distance from common ancestor

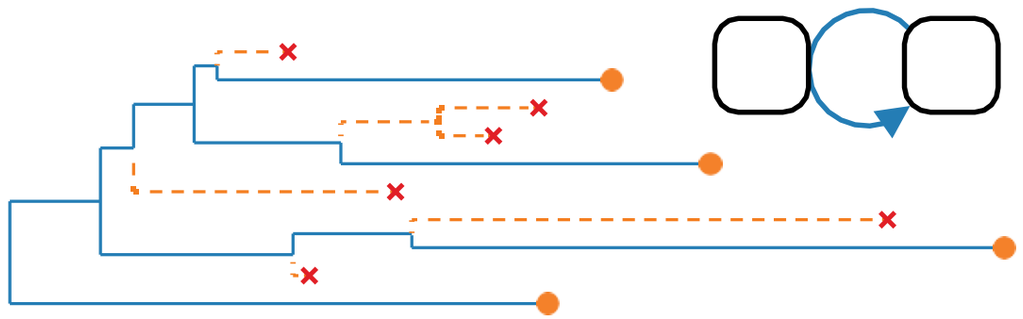
- Links the genome sequences to the genealogy
- We observe sequences at the tips, not their histories
- Multiple substitutions at the same site means not all substitutions are observed
- To infer the evolutionary history we need to take **all possible evolutionary trajectories** into account!

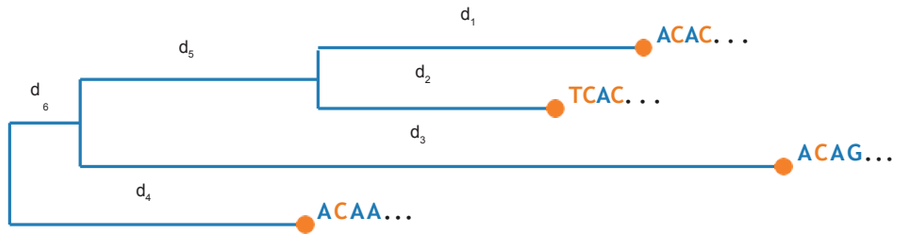
Substitutions as a Markov process

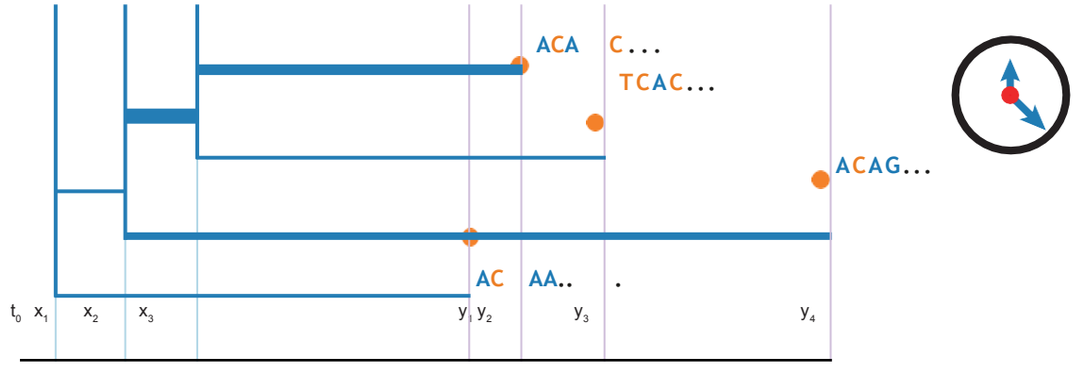


- Assume every site is evolving independently
- Assume nucleotide substitutions at each site is governed by a Markov process
- Account for rate heterogeneity between sites:
  - Proportion of invariant sites
  - Discrete Γ model
  - Multiple partitions with different rates

What goes into a BEAST model?







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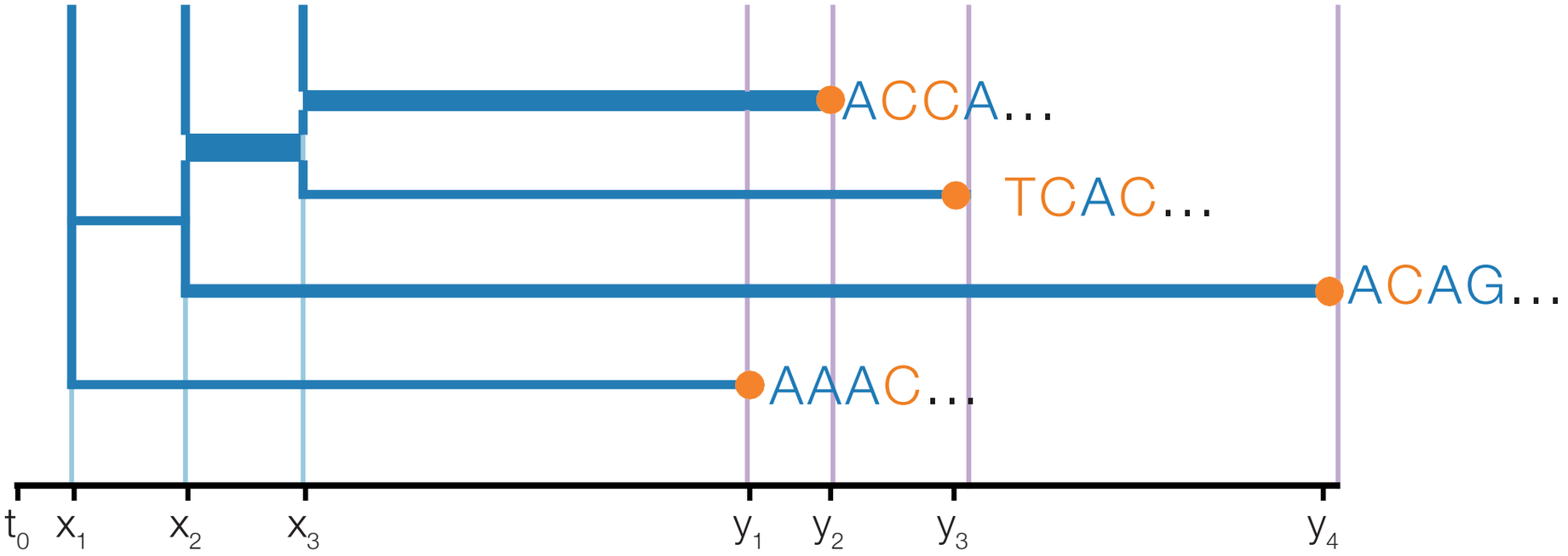
Site model

Molecular clock model

Molecular clock model



- Scales branch lengths to calendar time
- How long does it take for substitutions to appear?
- Different branches may have different clock rates
- Priors on internal nodes can help to calibrate the clock

Putting it all together…

Genetic sequences


Genealogy


Demographic model


Site model

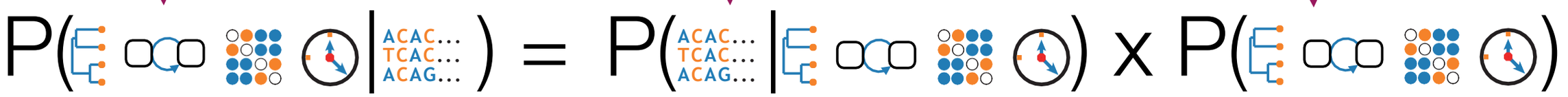

Molecular clock model

$$P(\text{model} \mid \text{data}) = \frac{P(\text{data} \mid \text{model}) \times P(\text{model})}{P(\text{data})}$$

Posterior

Likelihood

Prior



Marginal likelihood of the data

Putting it all together…

ACAC…
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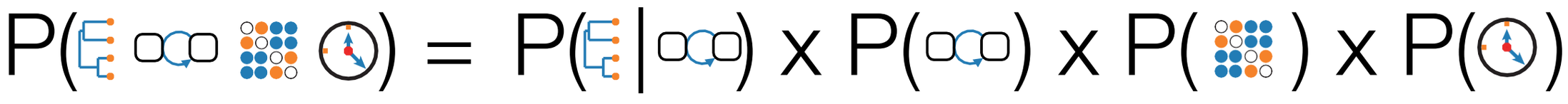
Marginal likelihood of the data

Assume independence



Posterior distribution in BEAST2

Genetic sequences

Genealogy

Demographic model

Site model

Molecular clock model

Posterior

Likelihood

Prior

$$P(\text{tree}, \text{demo}, \text{site}, \text{clock} \mid \text{ACAC...}\ \text{TCAC...}\ \text{ACAG...}) = \frac{P(\text{ACAC...}\ \text{TCAC...}\ \text{ACAG...} \mid \text{tree}, \text{site}, \text{clock})\ P(\text{tree} \mid \text{demo})\ P(\text{demo})\ P(\text{site})\ P(\text{clock})}{P(\text{ACAC...}\ \text{TCAC...}\ \text{ACAG...})}$$

Marginal likelihood of the data

How can we find the posterior?

We want to calculate the posterior distribution

But we cannot easily calculate the marginal likelihood

→ use **MCMC**! (Markov-chain Monte Carlo)

MCMC is a stochastic algorithm that performs a random walk on the posterior, preferentially sampling high-density areas

MCMC (Markov-chain Monte Carlo)

- MCMC draws samples from the posterior
  → output is a list of values that can approximate the posterior

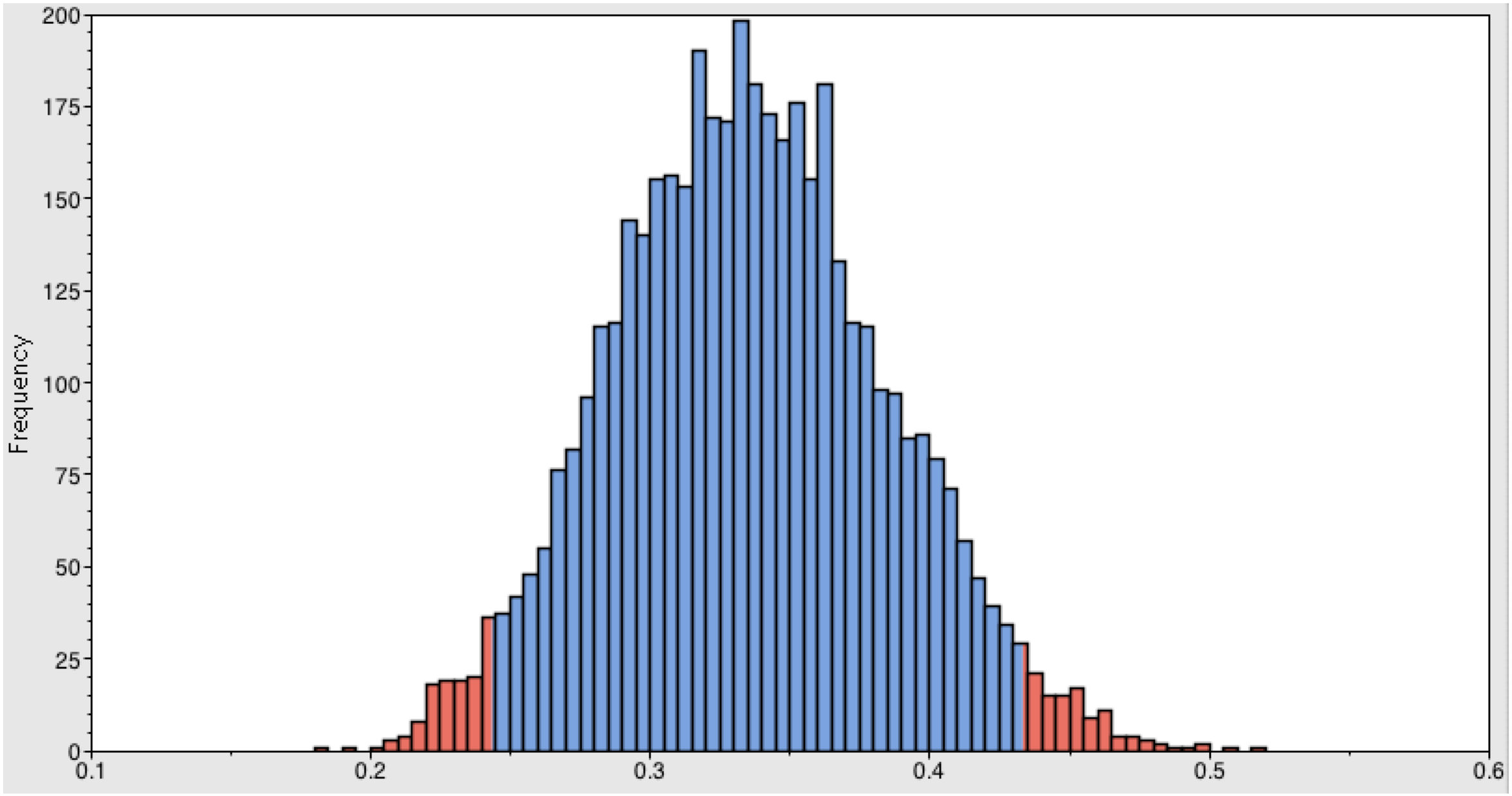
- Only need to compare which posterior density is higher
  → So we only need the ratio of posteriors
  (marginal likelihoods cancel out!)

$$\frac{P(\text{model}_1 \mid \text{data})}{P(\text{model}_2 \mid \text{data})} = \frac{\dfrac{P(\text{data} \mid \text{model}_1)P(\text{model}_1)}{\cancel{P(\text{data})}}}{\dfrac{P(\text{data} \mid \text{model}_2)P(\text{model}_2)}{\cancel{P(\text{data})}}}$$

Marginal distributions

- We only have the joint posterior: $P(\text{tree}, \text{topology}, \text{clock}, \text{rates}, \text{ages} \mid \text{ACAC...}, \text{TCAC...}, \text{ACAG...})$

- But we want distributions for each of the parameters we are interested in → marginalize



Operators

Target distribution

- This is the posterior in BEAST2: $P($  $)$
- MCMC steps through the state space and samples the target distribution

Proposal distribution

- Used to decide where to step to next
- The choice only affects the efficiency of the algorithm
- In BEAST1 and BEAST2 operators are used to propose the next step
- A parameter (or multiple parameters) are selected and perturbed to propose a step

Operators are a part of the MCMC **algorithm**, **not the model**!
Tuning operators can help to improve efficiency, but should not change the results.

MCMC in practice

Before

- Decide on the length of the chain (total number of steps to take)
- Decide on the sampling frequency (how often to record samples so that they are uncorrelated)

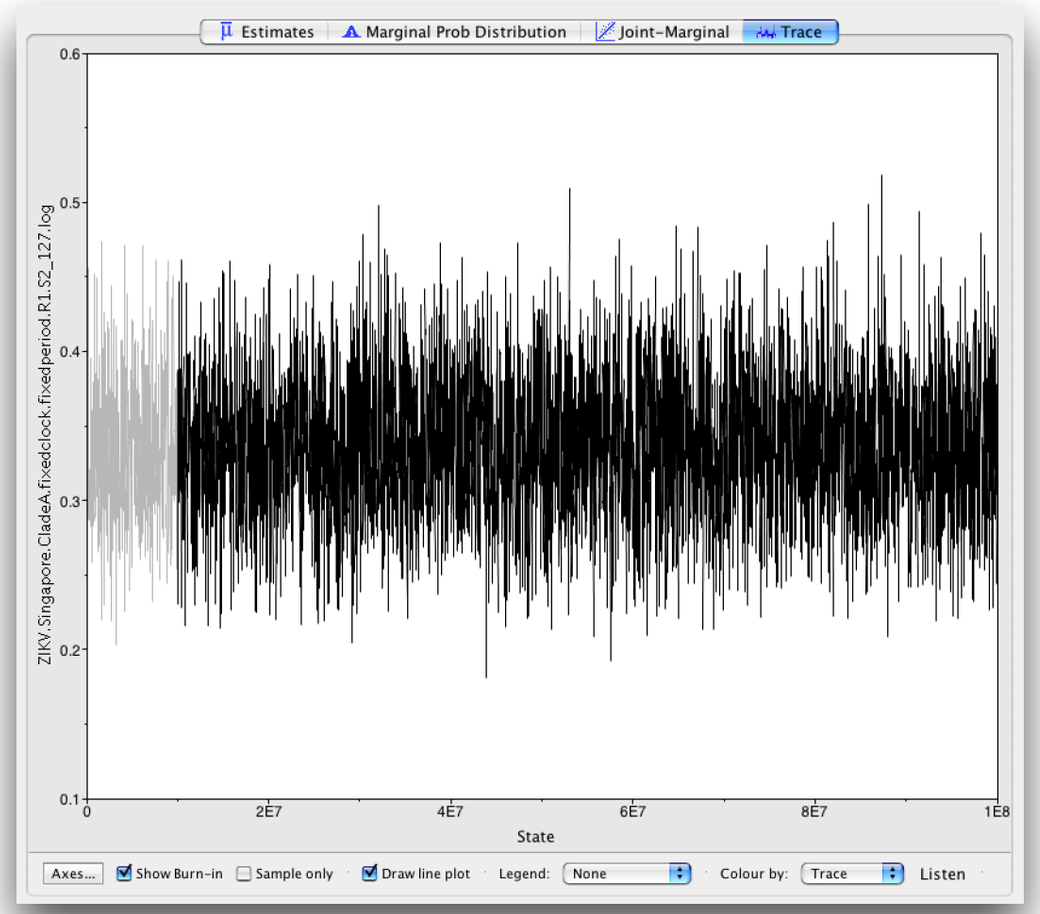
After

- Discard burn-in (until stationary state is reached)
- Assess convergence and mixing

More than 10 000 samples is a waste of space
But need to sample at the right frequency

What we hope will happen

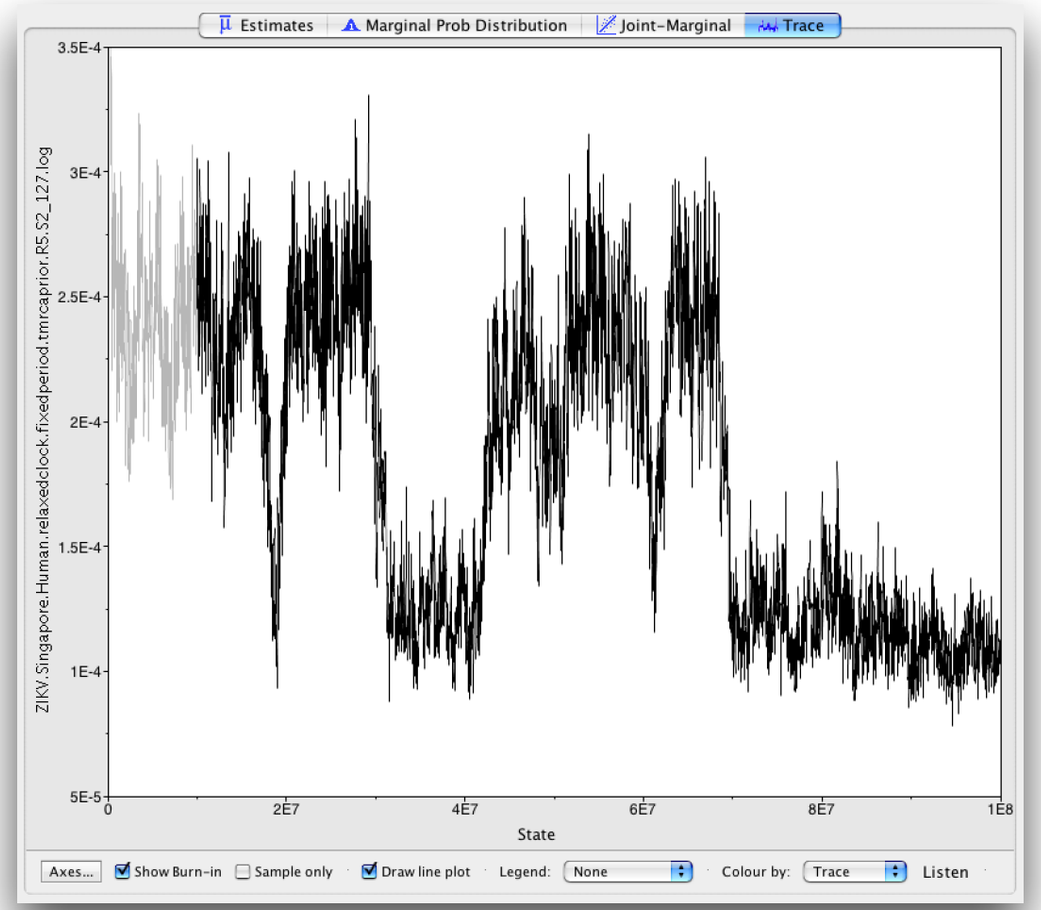
- The MCMC algorithm samples efficiently from high density areas of the posterior distribution
- We end up with a good approximation of the posterior distribution in finite time
- Appearance of white noise
- Everything is awesome!



Mixing well! 😄

Questions to ask…

- Is the chain mixing well?
- Are samples uniformly drawn from all over the stationary distribution?
- “Sticky chain”



Not mixing! 😨

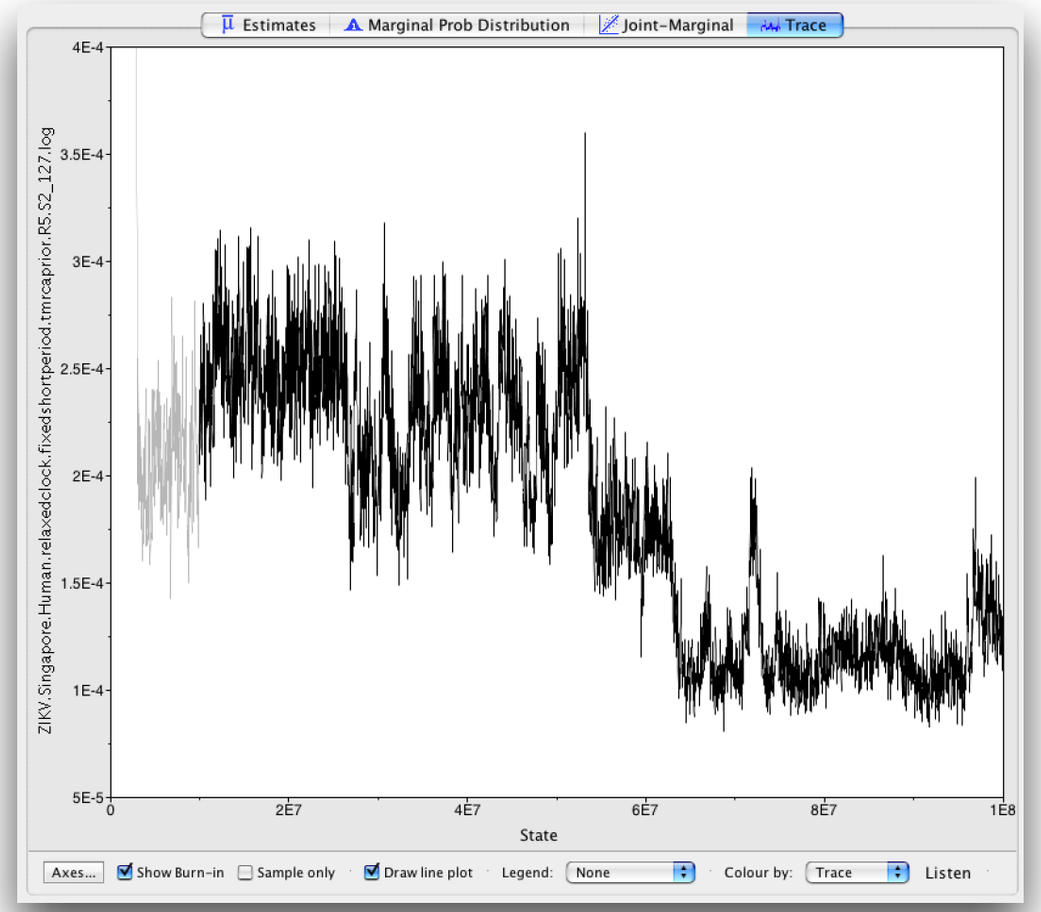
Solutions

- MCMC gets stuck in some states for long times
- Tune operators to make better proposals

Questions to ask…

- Has the chain converged to the stationary distribution?
- Did we pass the burn-in?

Solution: Run for longer



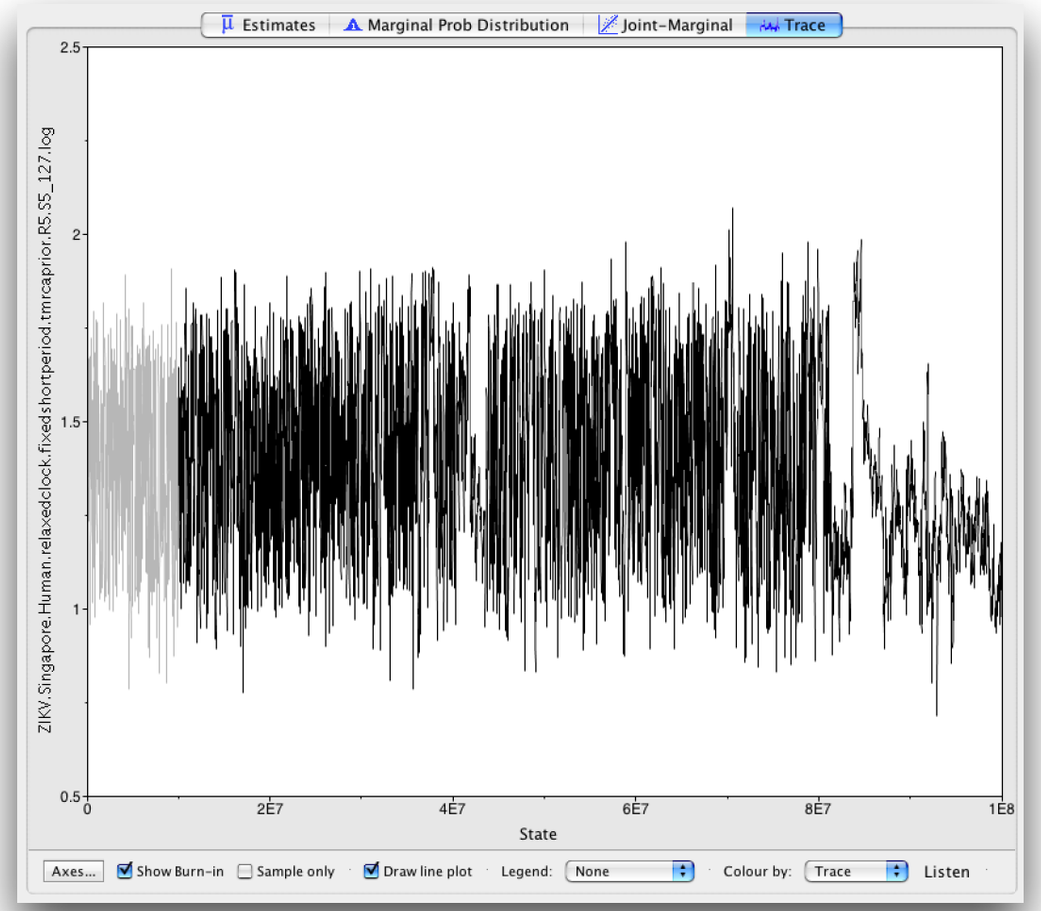
Not converged! 😓

Questions to ask…

- Are we there yet?
- How do we know if the chain is long enough?

Solution

- Run multiple chains
- Combine chains
- Check that all chains give the same result

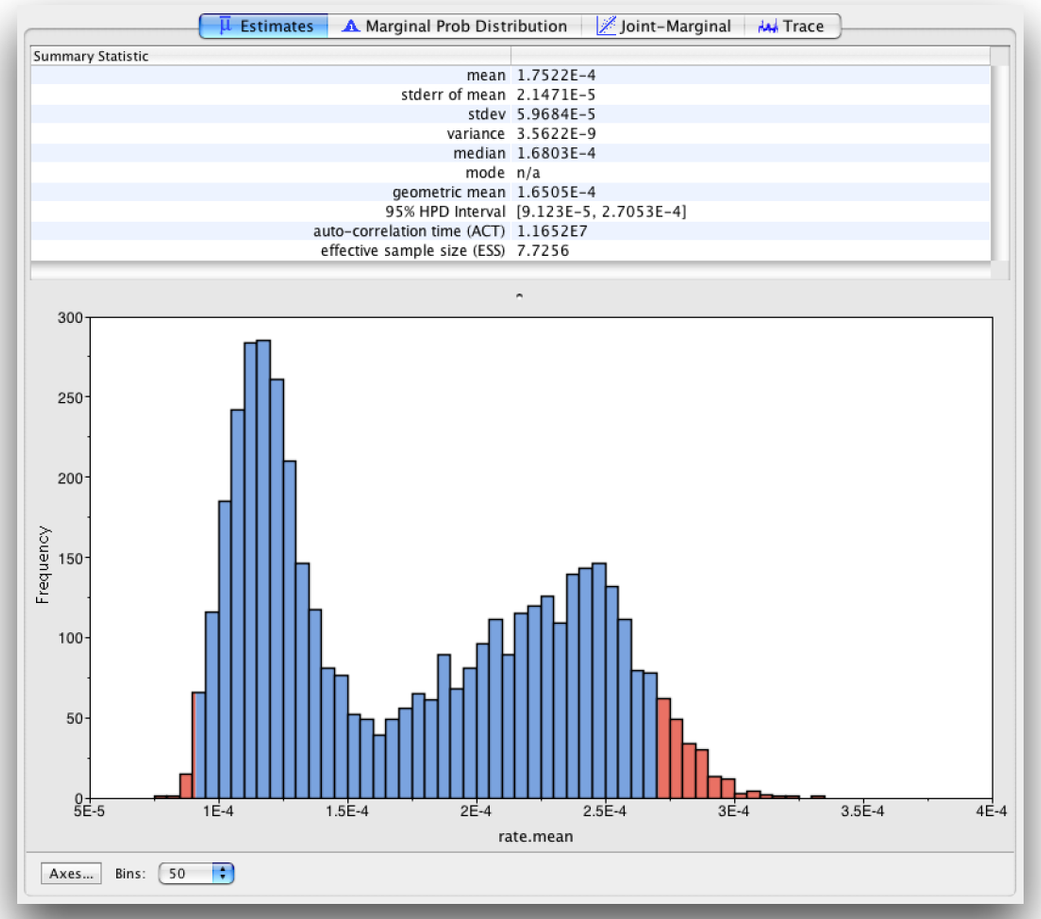


Still not converged! 😵

What if the answer is not what we wanted?

What is happening here?

- If the chain converged and mixed well then this is due to the data and model choice
  The model supports a bimodal posterior distribution
  May not be the answer we wanted but it may be the truth
  Should we change the model or parameterization?
- How would we know if another model fits better?



Is this a problem? 🤔

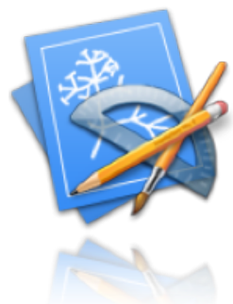
Solution: Be more open-minded

FANTASTIC BEASTS AND WHERE TO FIND THEM

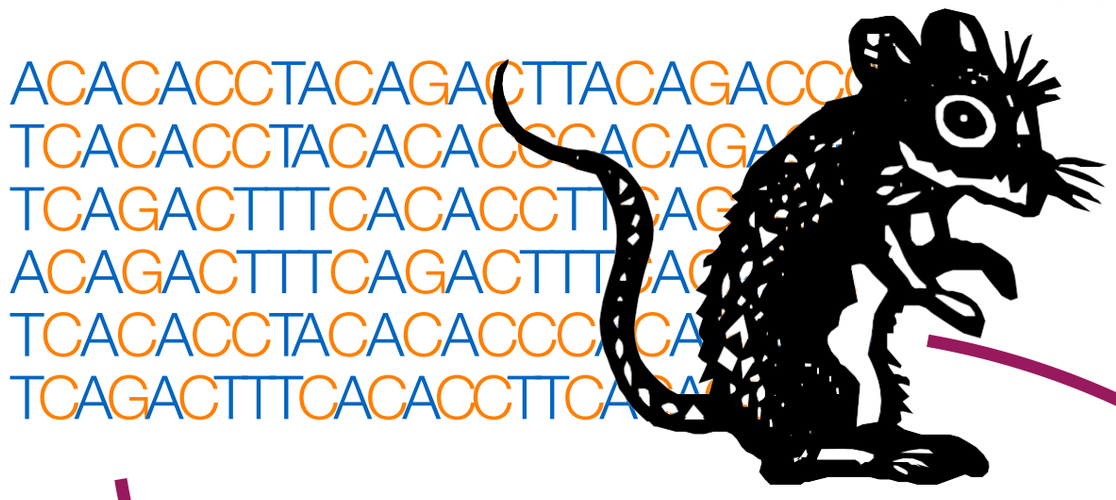
BEAST2 workflow

Tracer

TreeAnnotator



FigTree



IcyTree

log file

trees file

BEAUti2

xml file

BEAST2

ggtree

BEAUti2 (http://beast2.org)

BEAUti 2: Standard /Users/louis/Documents/Taming_the_BEAST/Tutorials-Git/Introduction-to-BEAST2/xml/Primates.xml

Partitions | Tip Dates | Site Model | Clock Model | Priors | MCMC

Link Site Models | Unlink Site Models | Link Clock Models | Unlink Clock Models | Link Trees | Unlink Trees

Name	File	Taxa	Sites	Data Type	Site Model	Clock Model	Tree	...
noncoding	primate-mtDNA	12	205	nucleotide	noncoding	clock	tree	
1stpos	primate-mtDNA	12	231	nucleotide	1stpos	clock	tree	
2ndpos	primate-mtDNA	12	231	nucleotide	2ndpos	clock	tree	
3rdpos	primate-mtDNA	12	231	nucleotide	3rdpos	clock	tree	

+ | – | r | Split

BEAUti2 (http://beast2.org)

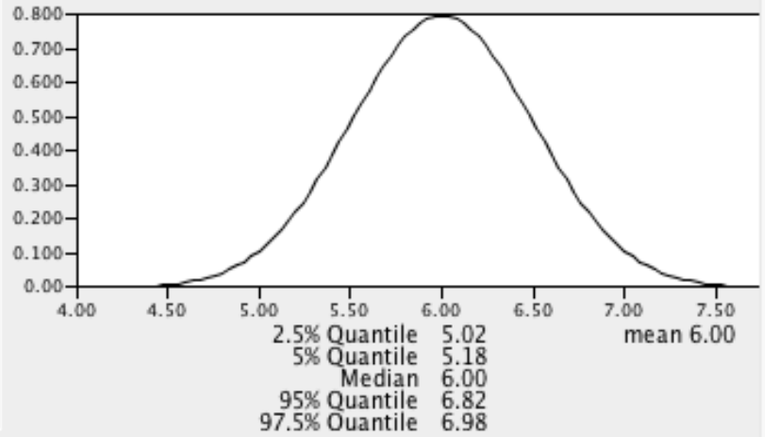
BEAUti 2: Standard /Users/louis/Documents/Taming_the_BEAST/Tutorials-Git/Introduction-to-BEAST2/xml/Primates.xml

Partitions | Tip Dates | Site Model | Clock Model | Priors | MCMC

Tree.t:tree	Calibrated Yule Model		
birthRateY.t:tree	Gamma	initial = [1.0] [−∞,∞]	Calibrated Yule speciation process birth rate for t:3rdpos
clockRate.c:clock	Uniform	initial = [1.0] [−∞,∞]	substitution rate of partition c:3rdpos
gammaShape.s:1stpos	Exponential	initial = [1.0] [−∞,∞]	Prior on gamma shape for partition s:1stpos
gammaShape.s:2ndpos	Exponential	initial = [1.0] [−∞,∞]	Prior on gamma shape for partition s:2ndpos
gammaShape.s:3rdpos	Exponential	initial = [1.0] [−∞,∞]	Prior on gamma shape for partition s:3rdpos
gammaShape.s:noncoding	Exponential	initial = [1.0] [−∞,∞]	Prior on gamma shape for partition s:noncoding
kappa.s:1stpos	Log Normal	initial = [2.0] [0.0,∞]	HKY transition-transversion parameter of partition s:1stpos
kappa.s:2ndpos	Log Normal	initial = [2.0] [0.0,∞]	HKY transition-transversion parameter of partition s:2ndpo
kappa.s:3rdpos	Log Normal	initial = [2.0] [0.0,∞]	HKY transition-transversion parameter of partition s:3rdpos
kappa.s:noncoding	Log Normal	initial = [2.0] [0.0,∞]	HKY transition-transversion parameter of partition s:nonco

human-chimp.prior — Normal — monophyletic

Mean	6.0	estimate
Sigma	0.5	estimate
Offset	0.0	



Tipsonly

Use Originate

BEAUti2 (http://beast2.org)

Primates_long.xml

Primates_long.xml

```
39
40  <run id="mcmc" spec="MCMC" chainLength="2500000">
41      <state id="state" storeEvery="5000">
42          <tree id="Tree.t:tree" name="stateNode">
43              <taxonset id="TaxonSet.noncoding" spec="TaxonSet">
44                  <alignment id="noncoding" spec="FilteredAlignment" filter="1,458-659,897-898">
45                      <data idref="primate-mtDNA"/>
46                  </alignment>
47              </taxonset>
48          </tree>
49          <parameter id="mutationRate.s:noncoding" name="stateNode">1.0</parameter>
50          <parameter id="gammaShape.s:noncoding" name="stateNode">1.0</parameter>
51          <parameter id="kappa.s:noncoding" lower="0.0" name="stateNode">2.0</parameter>
52          <parameter id="kappa.s:1stpos" lower="0.0" name="stateNode">2.0</parameter>
53          <parameter id="gammaShape.s:1stpos" name="stateNode">1.0</parameter>
54          <parameter id="mutationRate.s:1stpos" name="stateNode">1.0</parameter>
55          <parameter id="kappa.s:2ndpos" lower="0.0" name="stateNode">2.0</parameter>
56          <parameter id="gammaShape.s:2ndpos" name="stateNode">1.0</parameter>
57          <parameter id="mutationRate.s:2ndpos" name="stateNode">1.0</parameter>
58          <parameter id="kappa.s:3rdpos" lower="0.0" name="stateNode">2.0</parameter>
59          <parameter id="gammaShape.s:3rdpos" name="stateNode">1.0</parameter>
60          <parameter id="mutationRate.s:3rdpos" name="stateNode">1.0</parameter>
61          <parameter id="birthRateY.t:tree" name="stateNode">1.0</parameter>
62          <parameter id="clockRate.c:clock" name="stateNode">1.0</parameter>
63      </state>
64
65      <init id="RandomTree.t:tree" spec="beast.evolution.tree.RandomTree" estimate="false" initial="@Tree.t:tree" taxa="
        @noncoding">
66          <populationModel id="ConstantPopulation0.t:tree" spec="ConstantPopulation">
67              <parameter id="randomPopSize.t:tree" name="popSize">1.0</parameter>
68          </populationModel>
69      </init>
70
71      <distribution id="posterior" spec="util.CompoundDistribution">
72          <distribution id="prior" spec="util.CompoundDistribution">
73              <distribution id="CalibratedYuleModel.t:tree" spec="beast.evolution.speciation.CalibratedYuleModel"
                birthRate="@birthRateY.t:tree" tree="@Tree.t:tree"/>
74              <prior id="CalibratedYuleBirthRatePrior.t:tree" name="distribution" x="@birthRateY.t:tree">
75                  <Gamma id="Gamma.0" name="distr">
76                      <parameter id="RealParameter.0" estimate="false" name="alpha">0.001</parameter>
77                      <parameter id="RealParameter.01" estimate="false" name="beta">1000.0</parameter>
78                  </Gamma>
79              </prior>
80              <prior id="ClockPrior.c:clock" name="distribution" x="@clockRate.c:clock">
81                  <Uniform id="Uniform.0" name="distr" upper="Infinity"/>
82              </prior>
```

Line 1, Column 3 | 0 misspelled words | Spaces: 4 | XML

BEAST2 (http://beast2.org)

Bayesian **e**

Performs M cted
sequence iation)
model

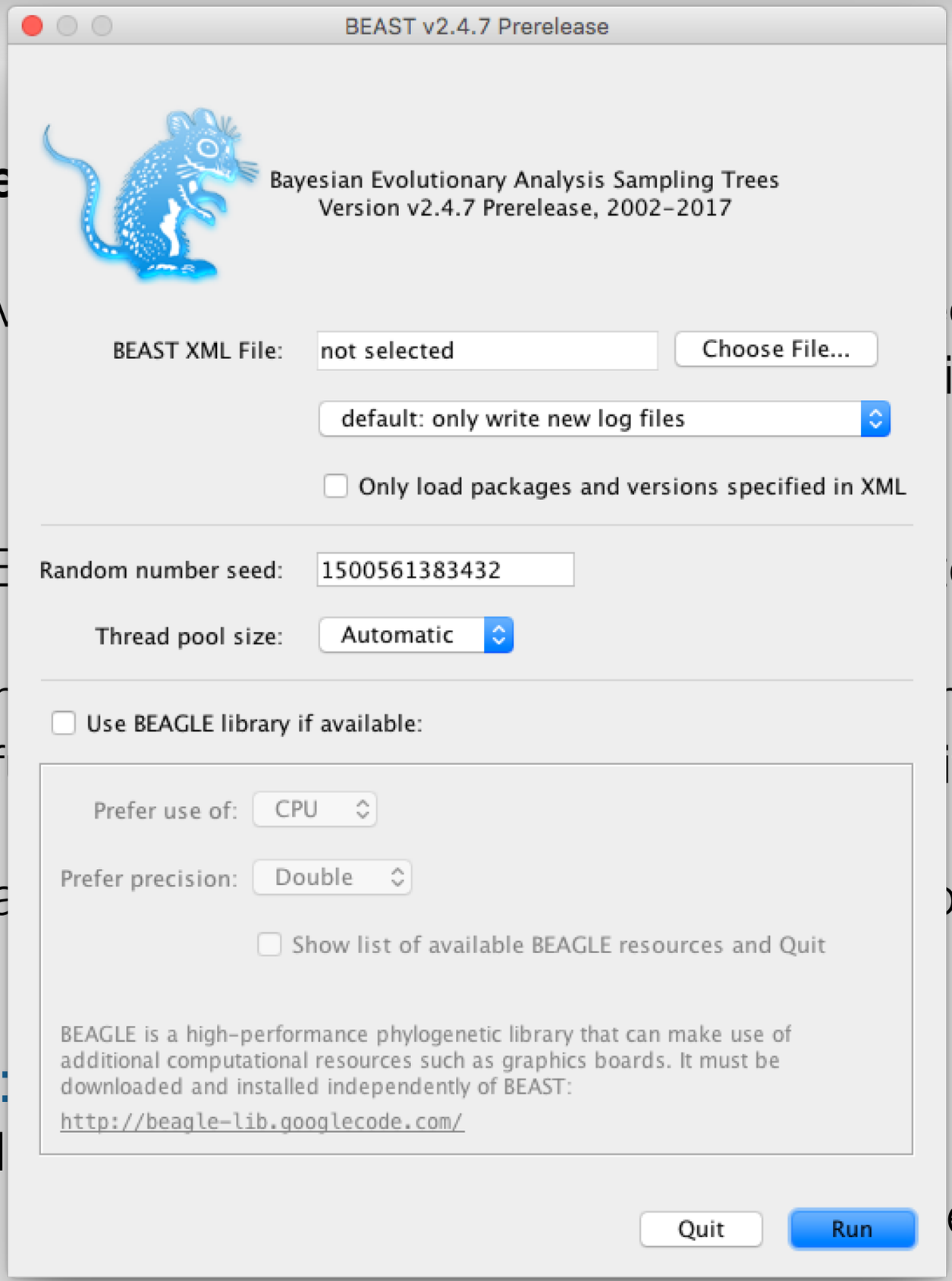
Similar to E e

BEAST2 ar much of
the same f ific niche

BEAST2 ha extend

Input:

- xml



BEAST2 packages

Ind es

Pac

BE

Pac

Phy
mo

Inst

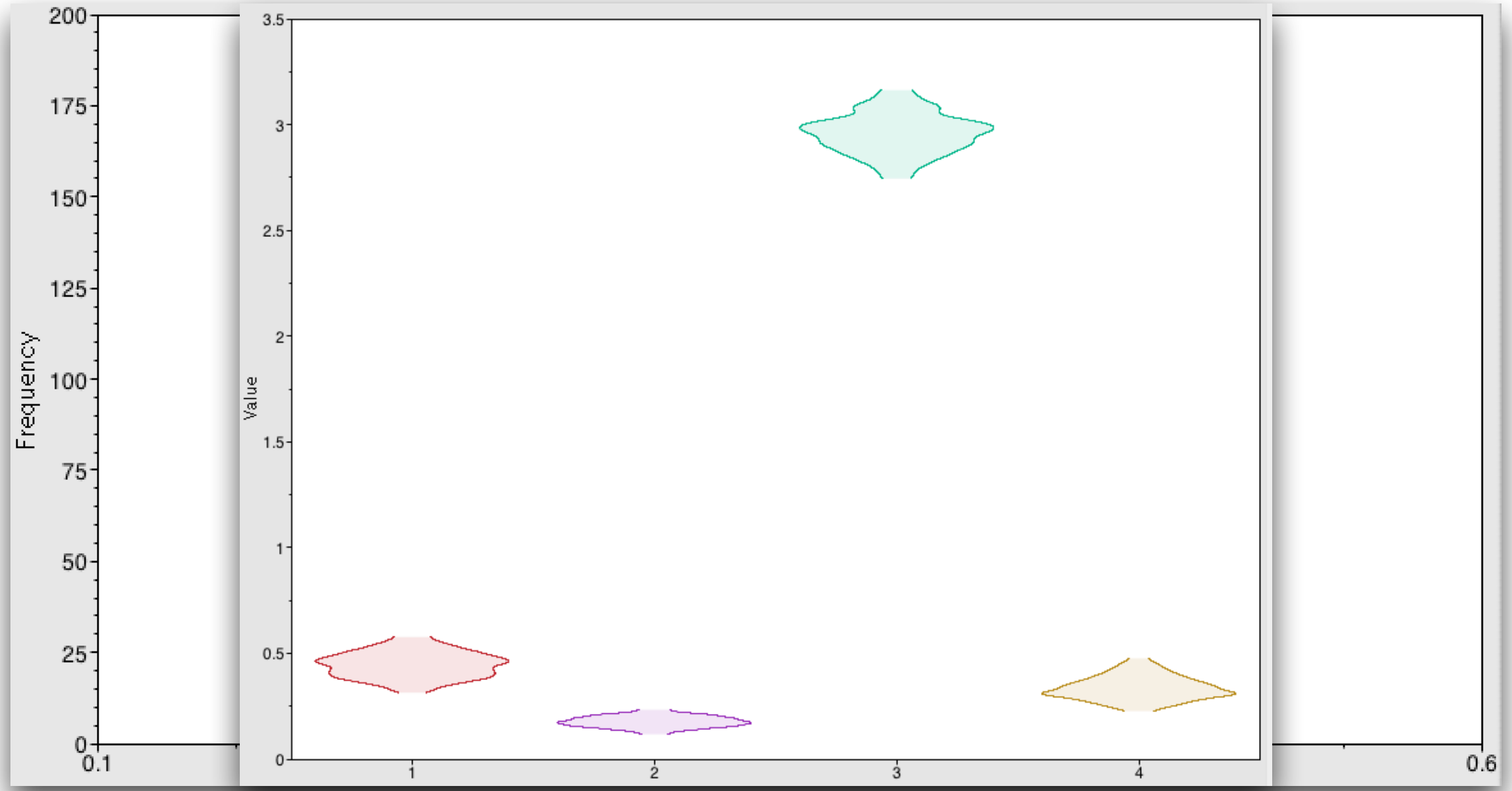
BEAST 2 Package Manager

List of available packages for BEAST v2.4.*

Name	Installed	Latest	Dependencies	Link	Detail
BEAST	2.4.7	2.4.7			BEAST core
bacter	1.2.1	1.2.1			Bacterial ARG inference.
BASTA		2.3.1			Bayesian structured coalescent approximation
bdmm	0.2.0	0.2.0	MultiTypeTree		pre-release of multitype birth-death model (aka birth-...
BDSKY	1.3.3	1.3.3			birth death skyline - handles serially sampled tips, piec...
BEAST_CLASSIC	1.3.0	1.3.0	BEASTLabs		BEAST classes ported from BEAST 1 in wrappers
BEASTLabs	***1.7.0***	***1.7.1***			***BEAST utilities, such as Script, multi monophyletic c...***
BEASTShell		1.3.0			BEAST Shell - BeanShell scripting for BEAST
BEASTvntr		0.1.1			Variable Number of Tandem Repeat data, such as micr...
bModelTest	1.0.4	1.0.4	BEASTLabs		Bayesian model test for nucleotide subst models, gamm...
CA		1.2.1			CladeAge aPackage for fossil calibrations
DENIM		0.3.0			Divergence Estimation Notwithstanding ILS and Migration
EpiInf		5.0.1	SA		Inference of epidemic trajectories
GEO_SPHERE		1.1.2	BEASTLabs		Whole world phylogeography
Mascot		0.0.2			Marginal approximation of the structured coalescent
MASTER		5.1.1			Stochastic population dynamics simulation
MGSM		0.2.1			Multi-gamma and relaxed gamma site models
MM		1.0.5			Enables models of morphological chatacter evolution
MODEL_SELECTION		1.3.4	BEASTLabs		Select models through path sampling/stepping stone an...

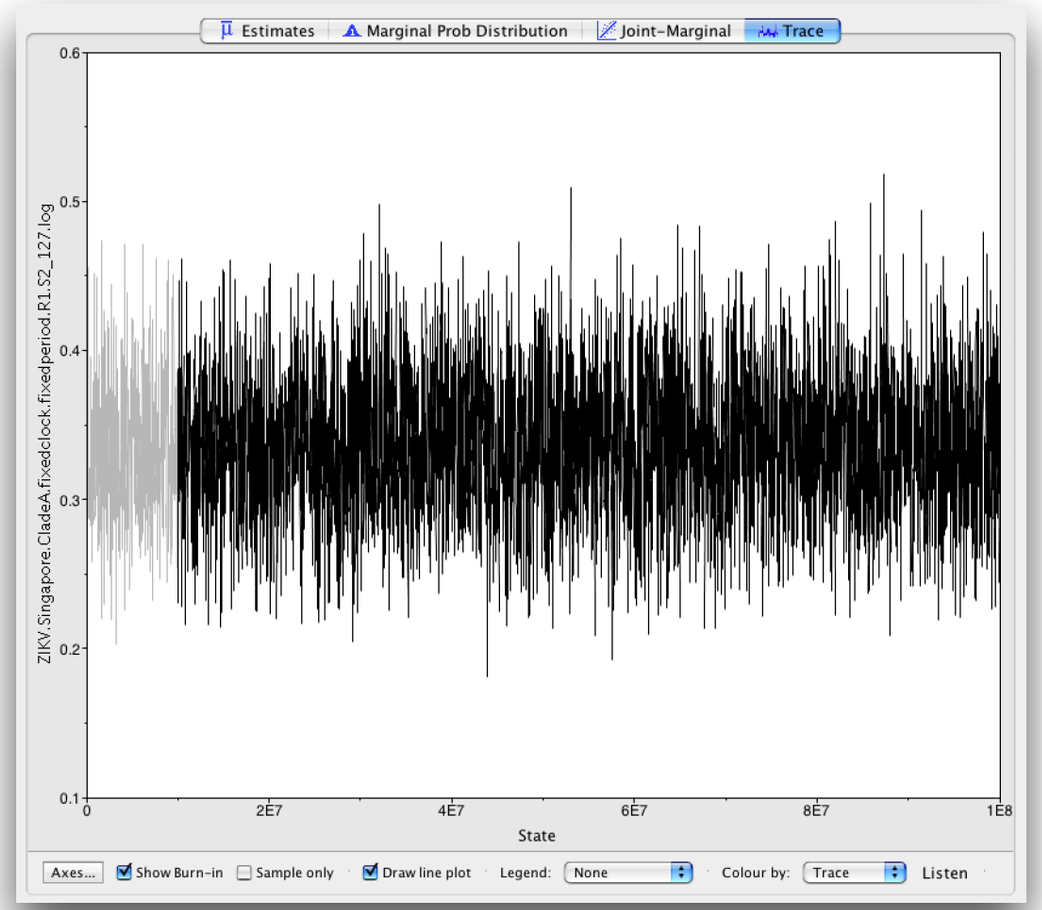
Latest | Install/Upgrade | Uninstall | Package repositories | Close | ?

Tracer (http://beast.community)

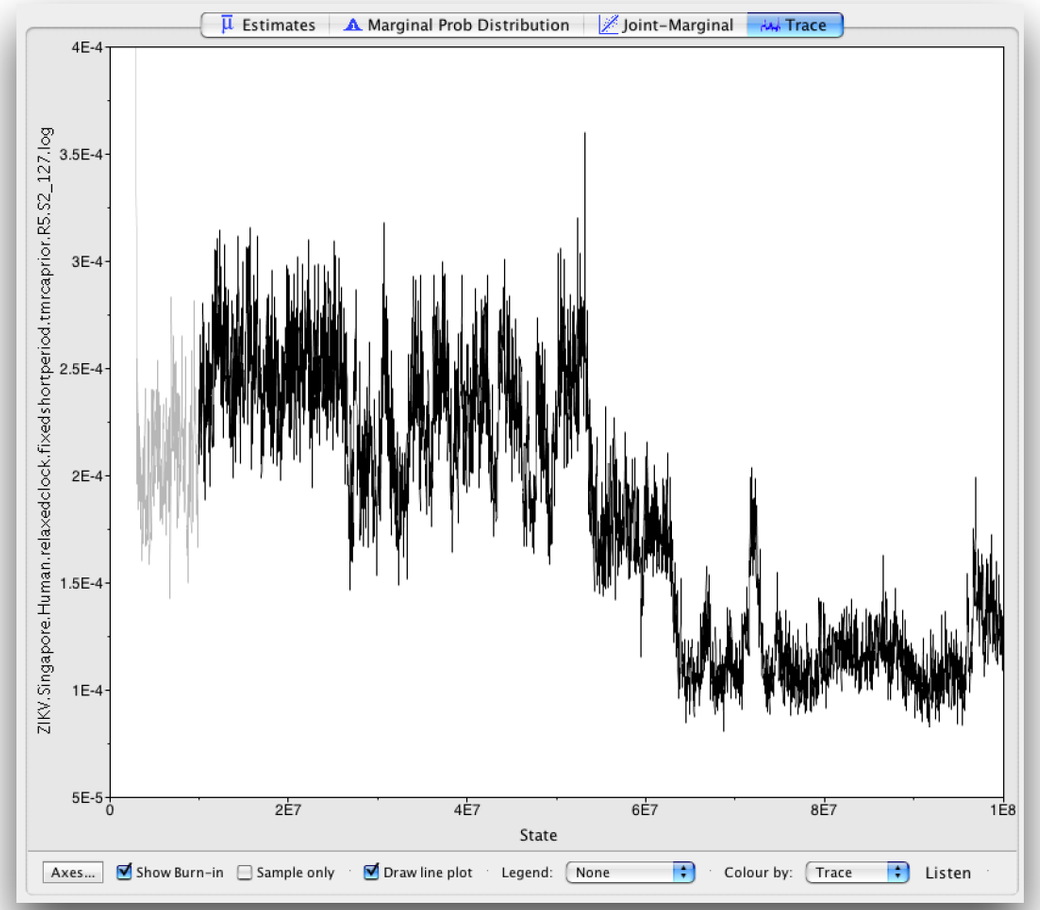


Tracer (http://beast.community)

Look at the chains first!

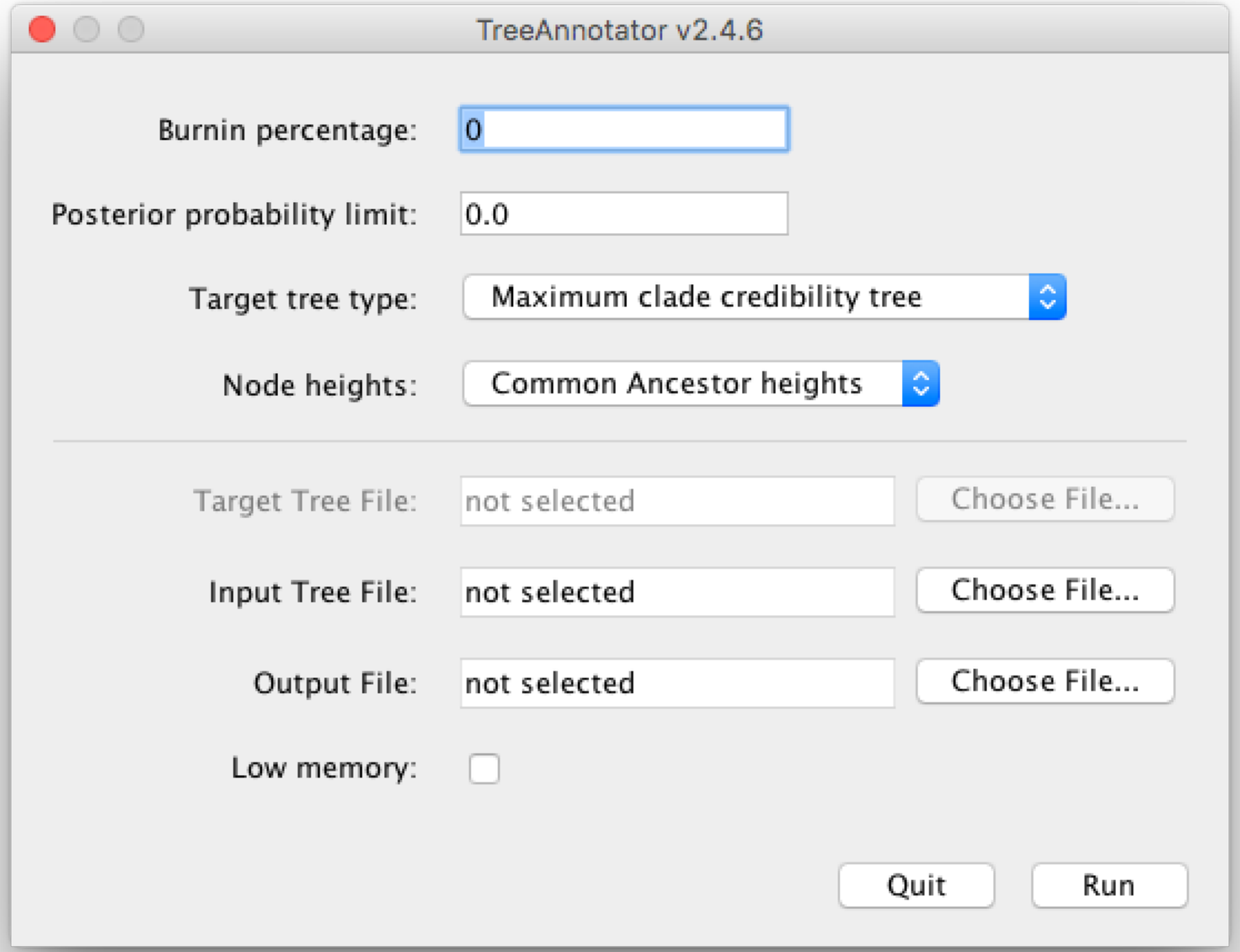


Mixing well! 😄

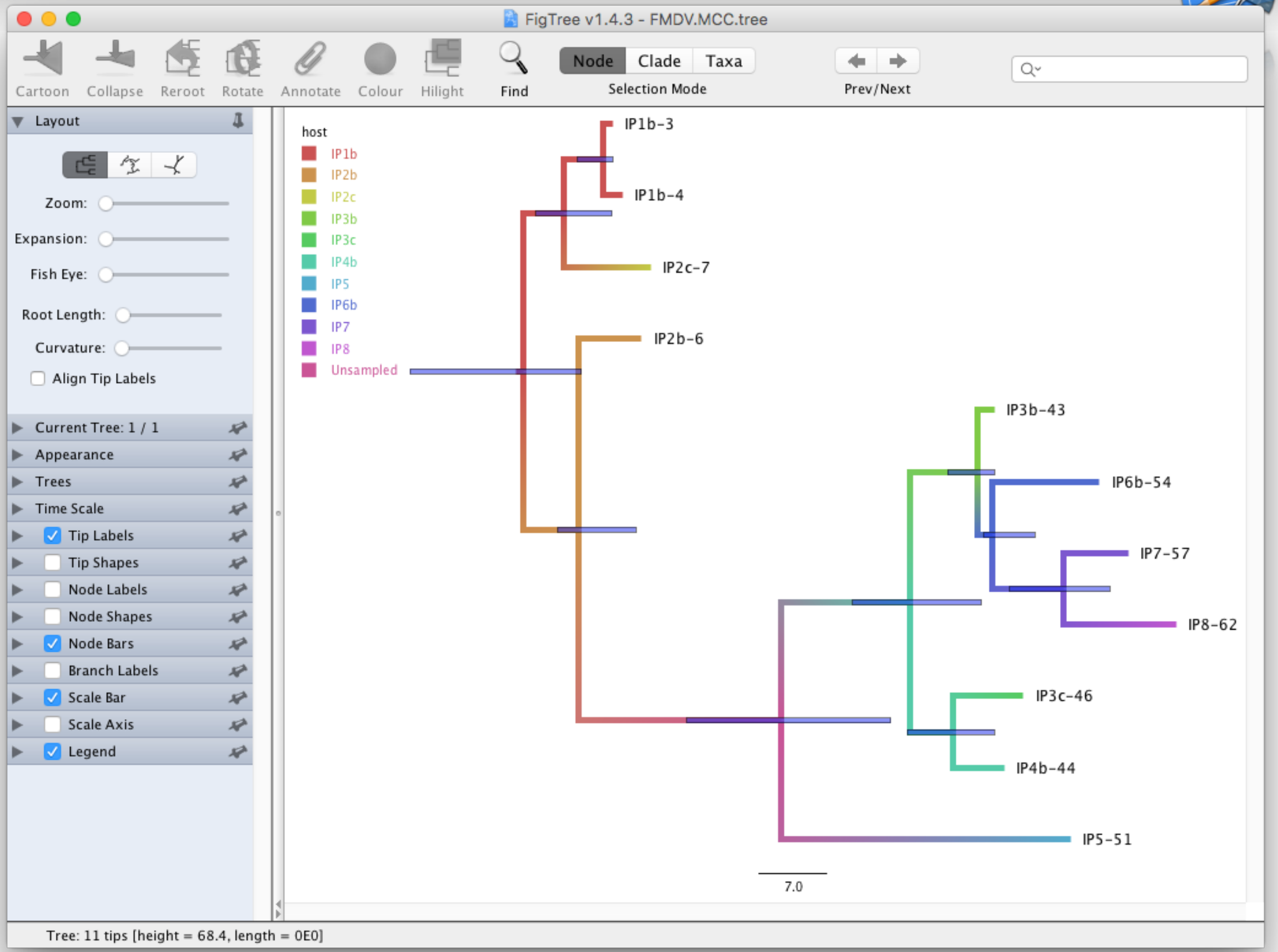


Not mixing! 😭

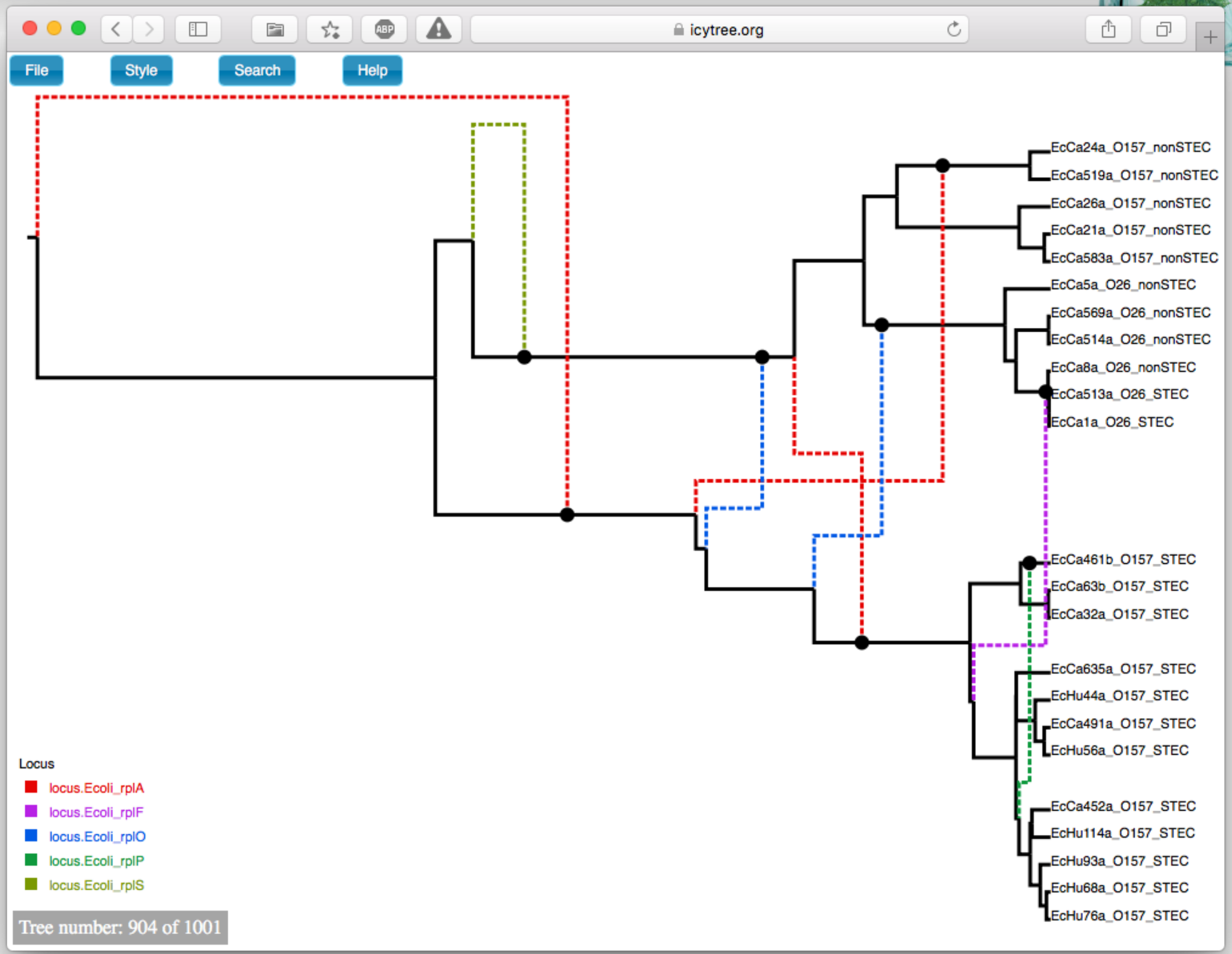
TreeAnnotator (Included with BEAST2)



FigTree (http://tree.bio.ed.ac.uk/software/figtree/)

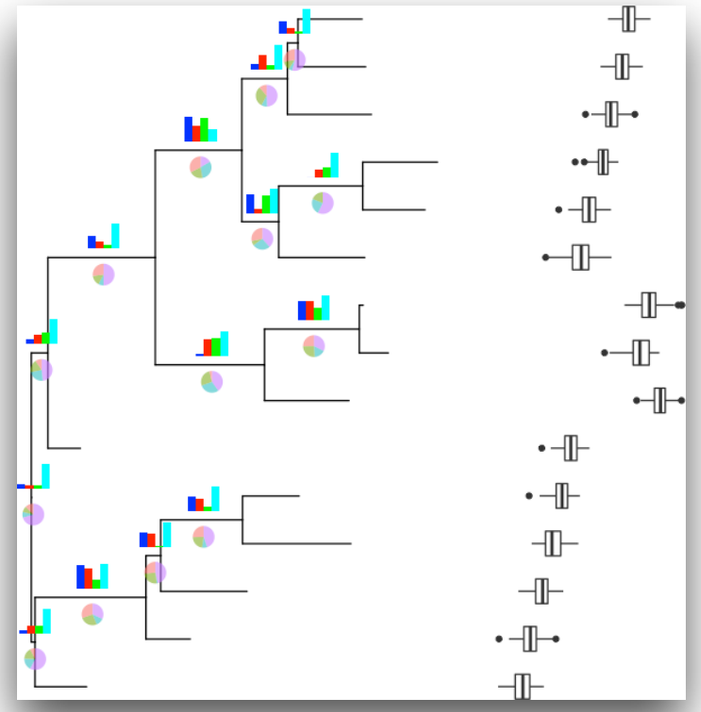


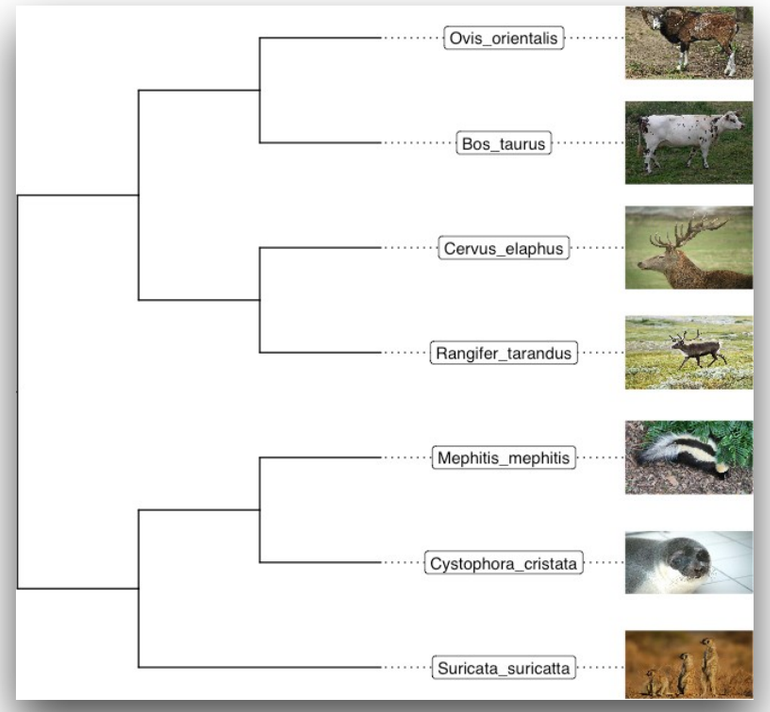
IcyTree (https://icytree.org)

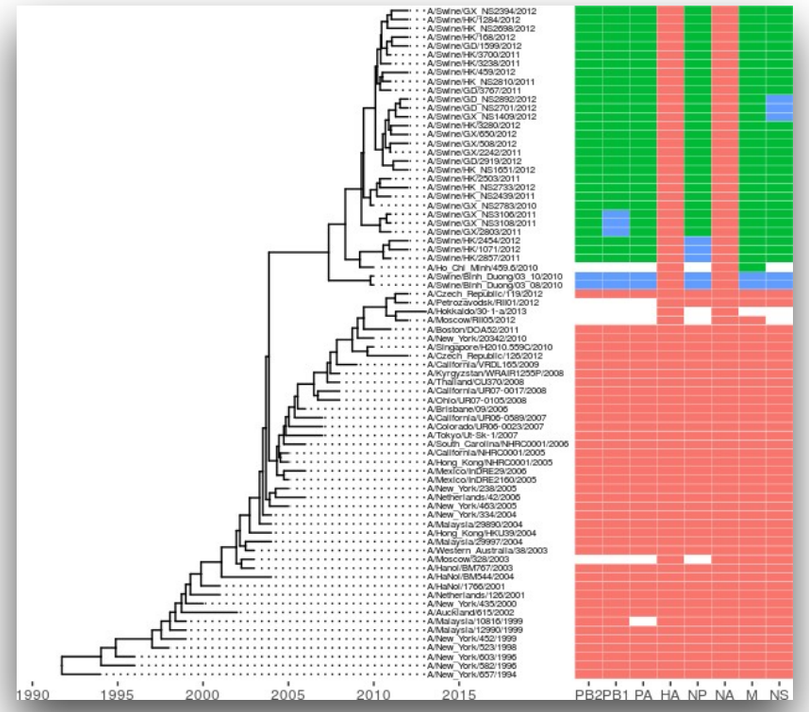


ggtree (https://guangchuangyu.github.io/software/ggtree/)

- R-package to visualize trees using ggplot grammar
- Works with BEAST2 tree files (and many other packages)
- Can be easily annotate trees with other analyses in R







BEAST best practice

(This is just a guideline and each analysis is unique)

Before you begin

1) Know your data
2) Plan your analysis carefully

Before you run the analysis

3) Ask someone else to look at your XML file
4) Sample from the prior (run without data)

Actually running the analysis

5) Run analysis with multiple chains

After the analysis

6) Combine chains
7) Assess convergence and mixing
8) Ask someone else to look at your log files