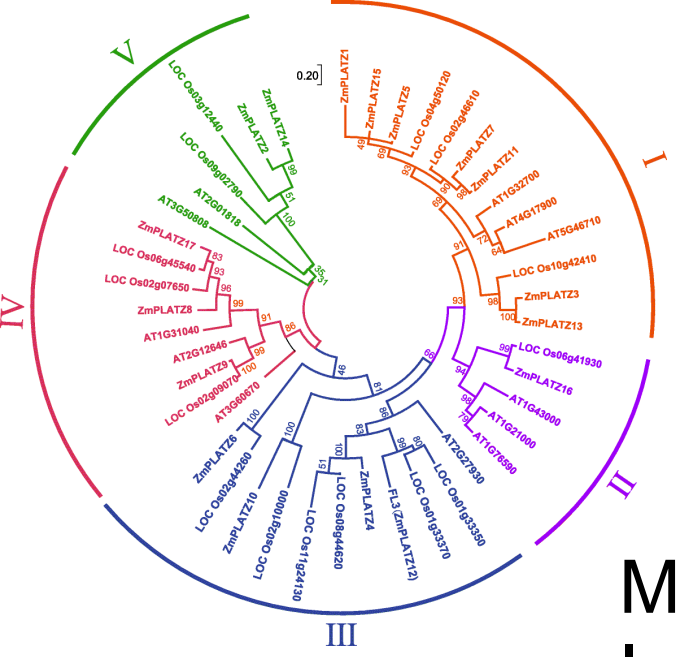
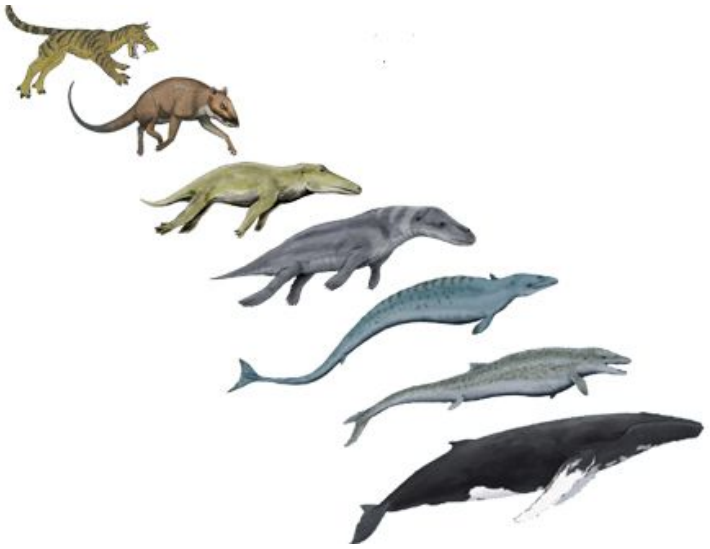
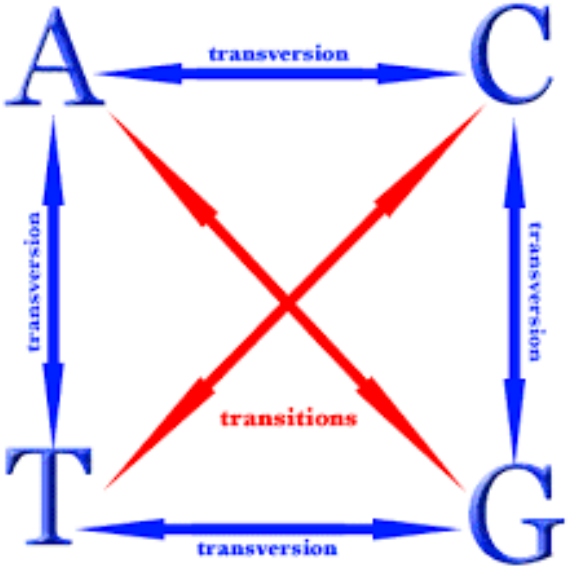
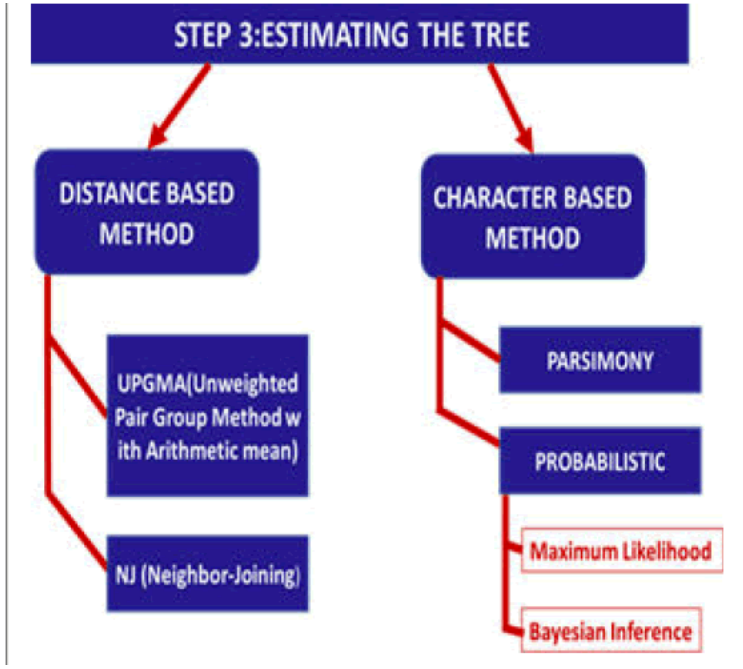




Maximum-Likelihood and Bayesian Inference

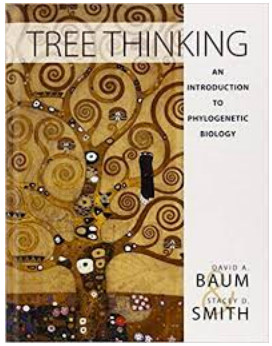
22 Oct 2020



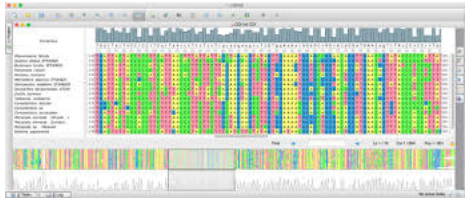


Covered on Tuesday

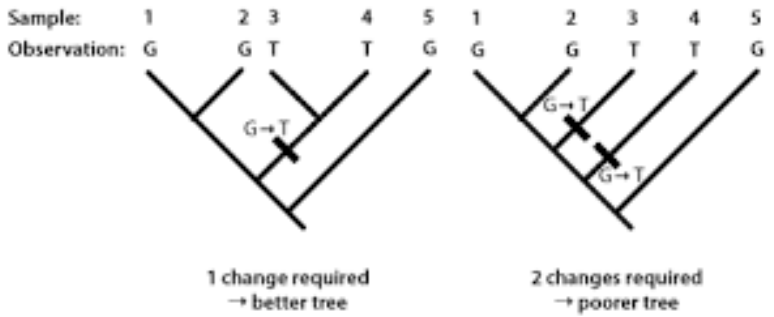
- Tree thinking



- Sequence alignment



- Parsimony for tree inference



Topics to cover today

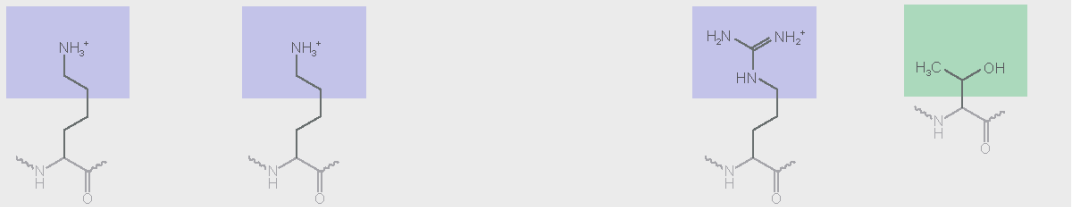
Maximum Likelihood
- Specifying models of molecular evolution
- Maximum-likelihood inference
- Bootstrap support

Bayesian Inference
- Bayes theorem
- Bayesian phylogenetics and MCMC

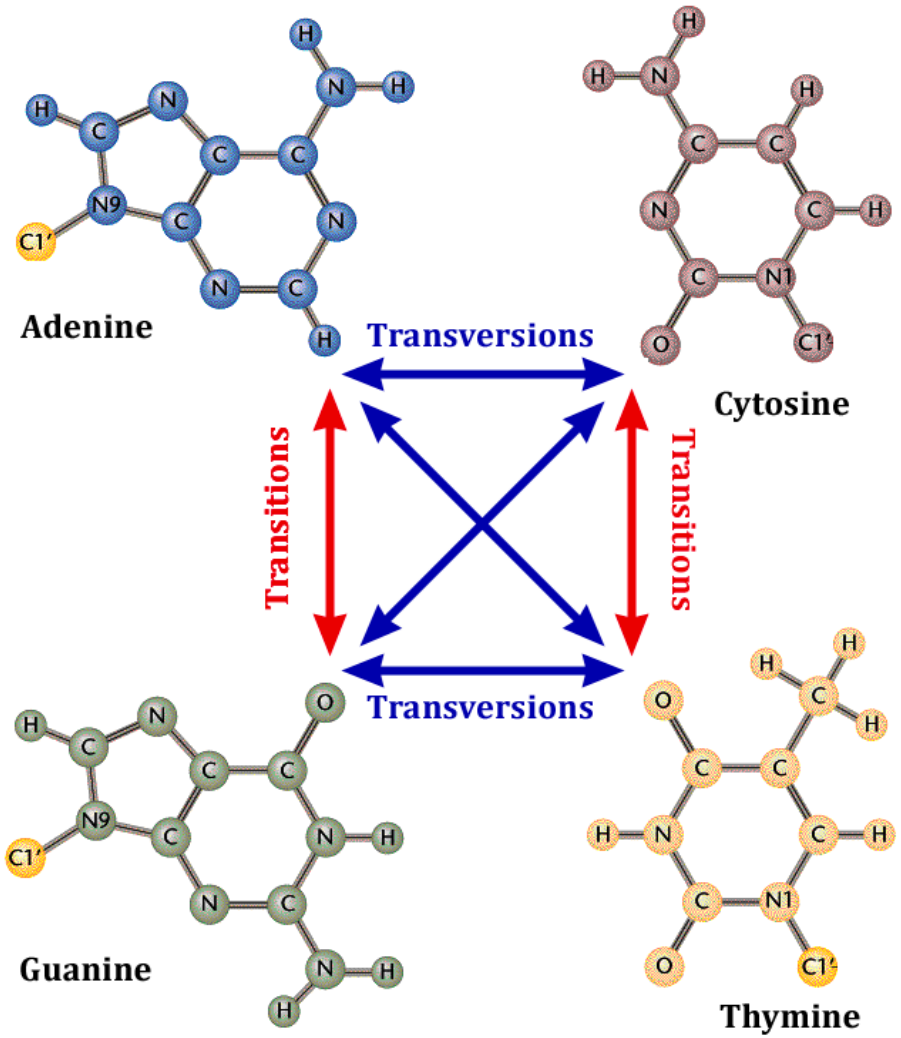
How do nucleotides change?

- Change at any given site is independent of the base in its prior iteration

	No mutation	Point mutations			
		Silent	Nonsense	Missense	
				conservative	non-conservative
DNA level	TTC	TTT	ATC	TCC	TGC
mRNA level	AAG	AAA	UAG	AGG	ACG
protein level	Lys	Lys	STOP	Arg	Thr

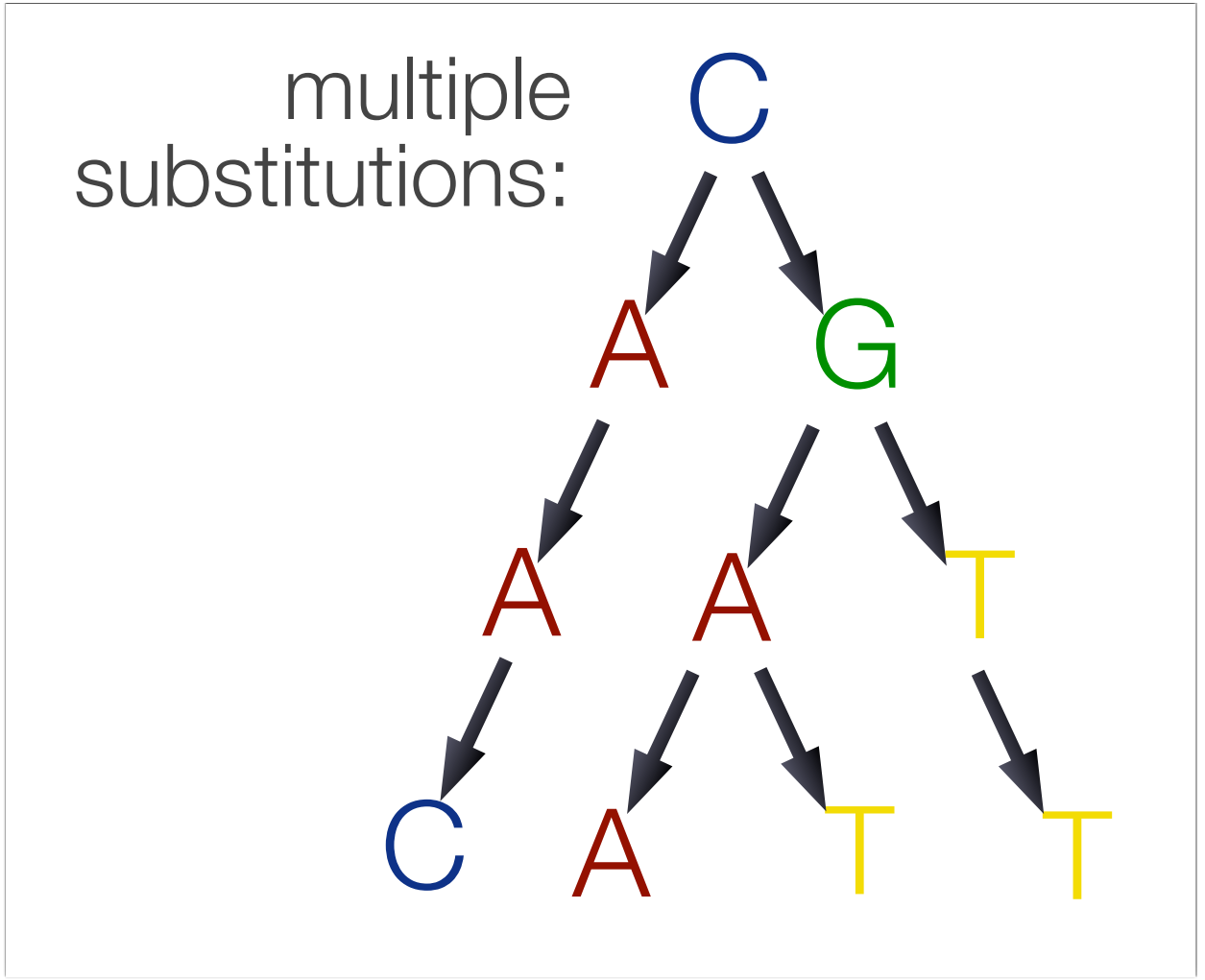


basic
polar

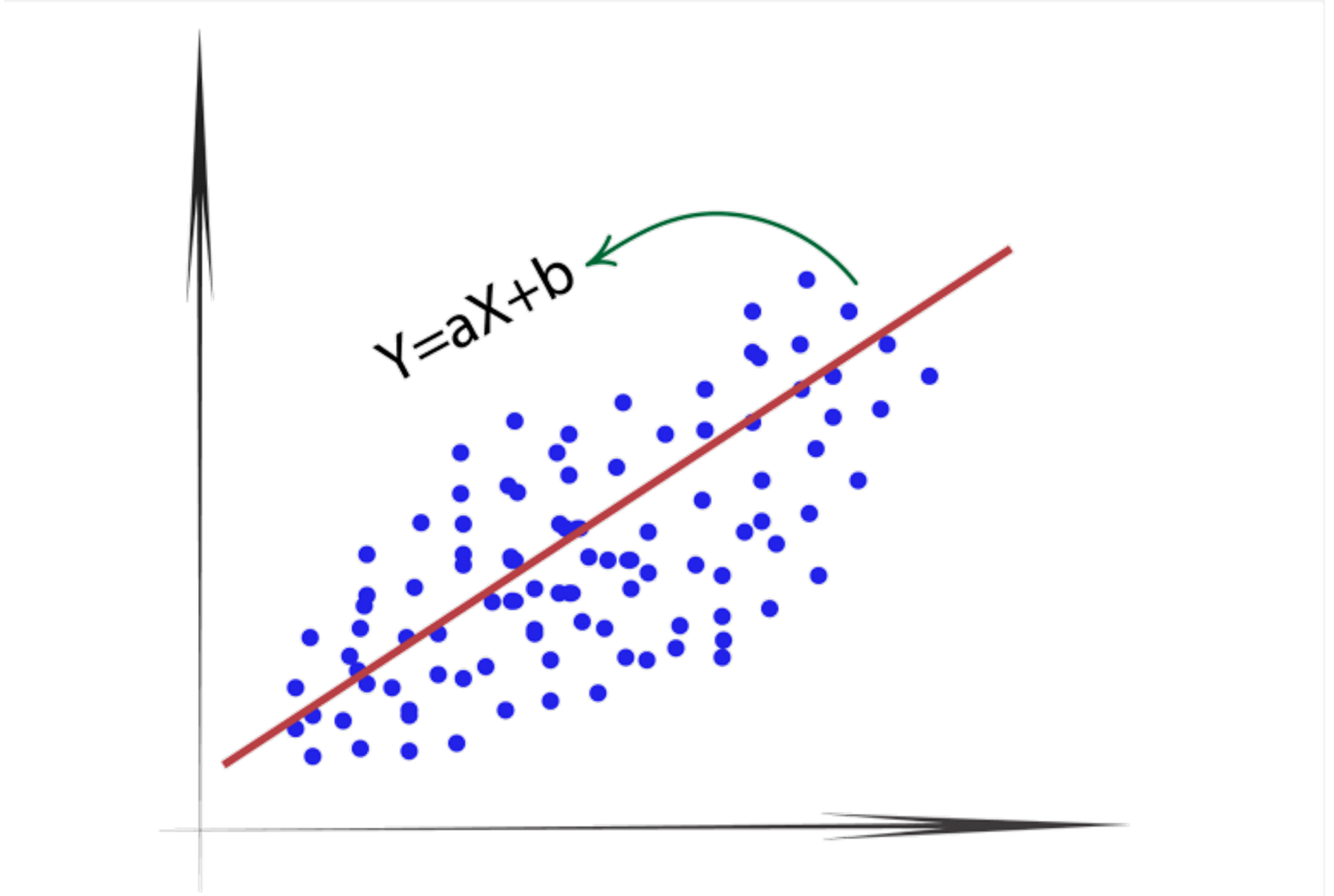


Multiple substitutions

- Given enough time, may be multiple changes
- 25% of nucleotide sites are expected to be identical by chance
- Models vary in complexity from very simple to extremely complex
- Model choice is important
- Model must suit the data

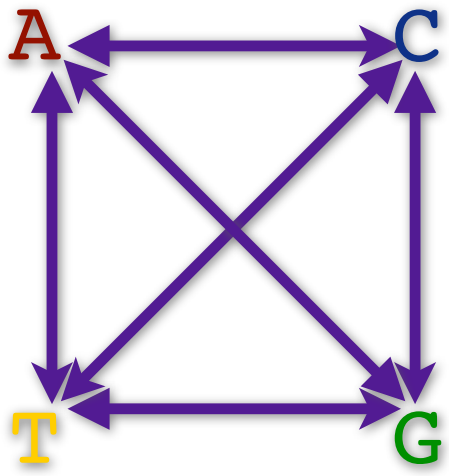


A model?



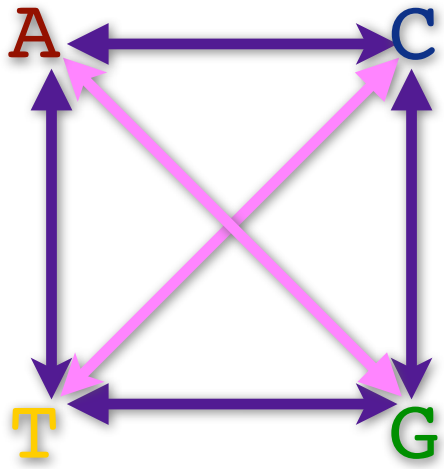
Underlying models

Jukes Cantor



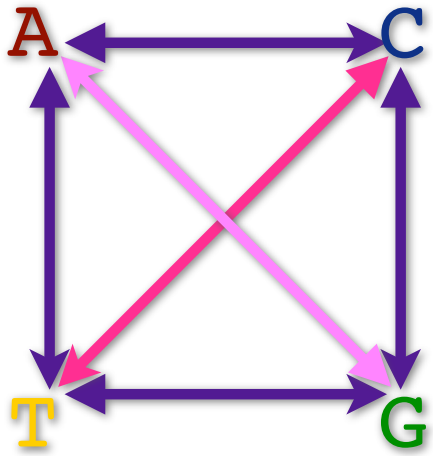
- All bases evolve independently
- All bases are equal frequency
- Each base can change with equal probability

Kimura



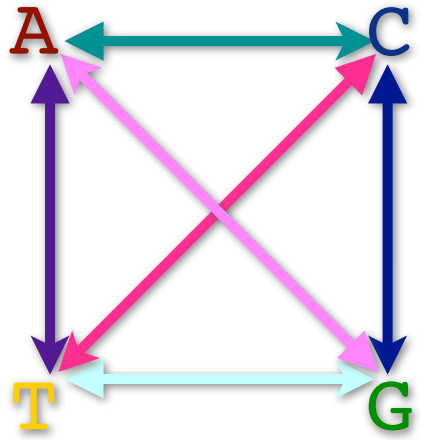
- All bases evolve independently
- All bases are equal frequency
- Transitions and transversions evolve at different rates

TrN



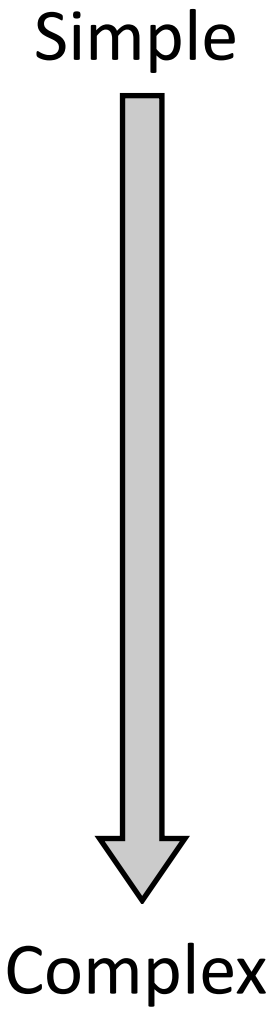
- All bases evolve independently
- All bases at unequal frequency
- Transitions and transversions evolve at two different rates

GTR



- All bases evolve independently
- All bases at unequal frequency
- All changes occur at different rates

Model hierarchy



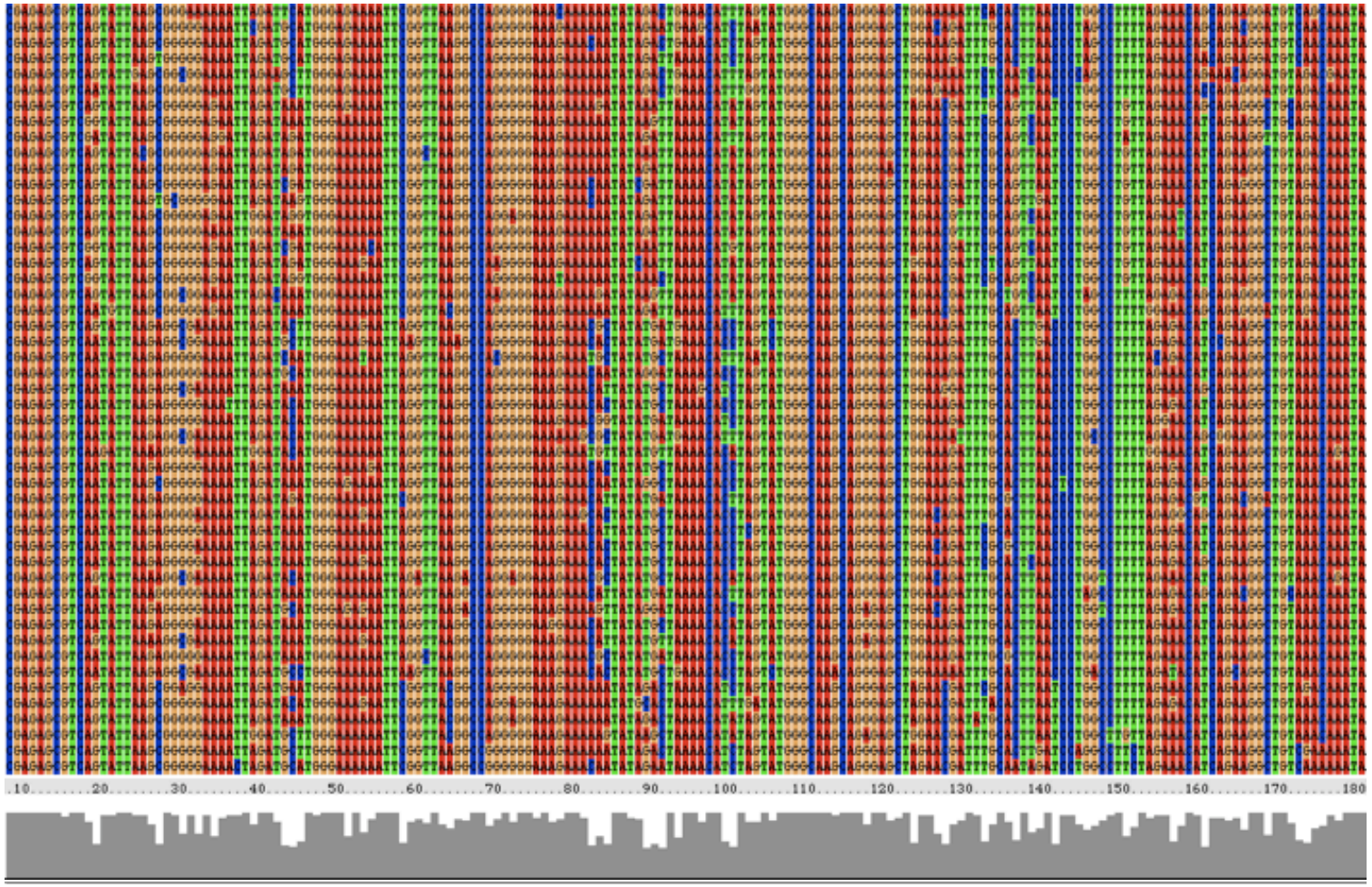
base frequencies are equal and
all substitutions are equally likely
(Jukes-Cantor)

base frequencies are equal but transitions and
transversions occur at different rates
(Kimura 2 parameter)

unequal base frequencies and transitions and
transversions occur at different rates
(Hasegawa-Kishino-Yano)

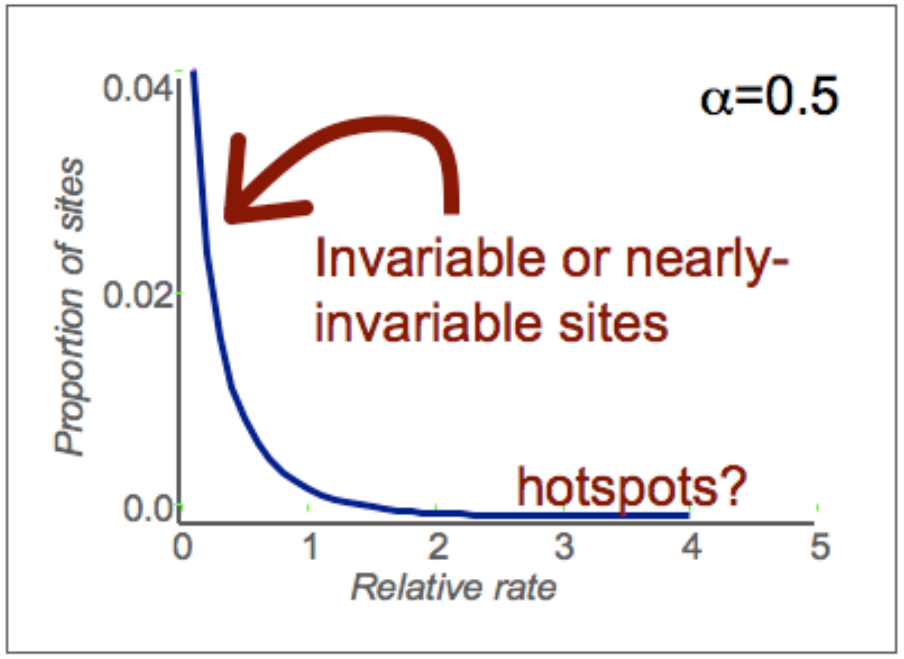
unequal base frequencies and all
substitution types occur at different rates
(General Reversible Model)

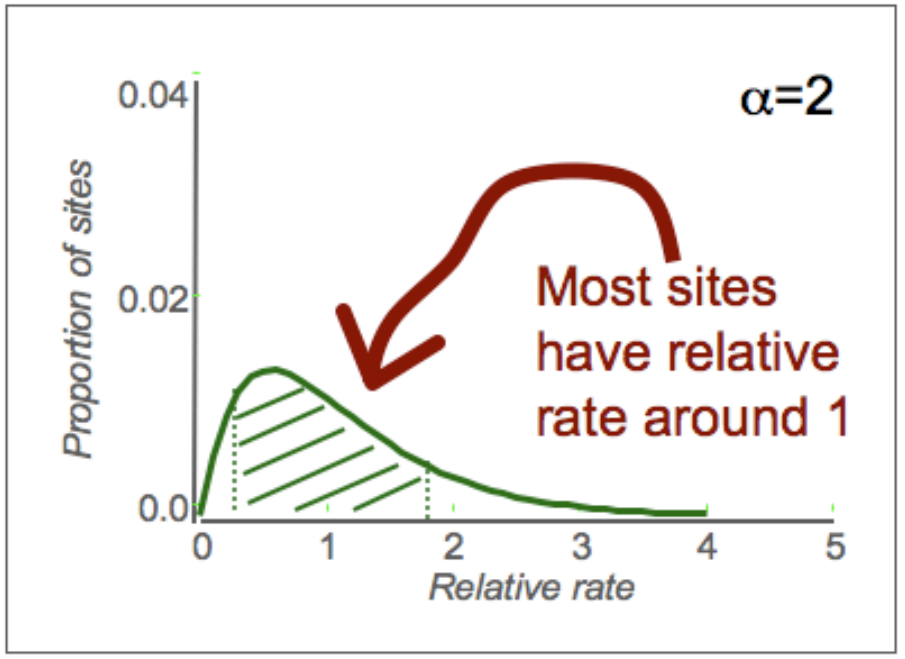
Rate Heterogeneity between sites



- Most models assume rate heterogeneity
  - 3rd position wobble
  - Hypervariable vs invariant sites
- Use a gamma distribution to model heterogeneity
  - Usually 4-8 discrete categories of rates

Rate heterogeneity



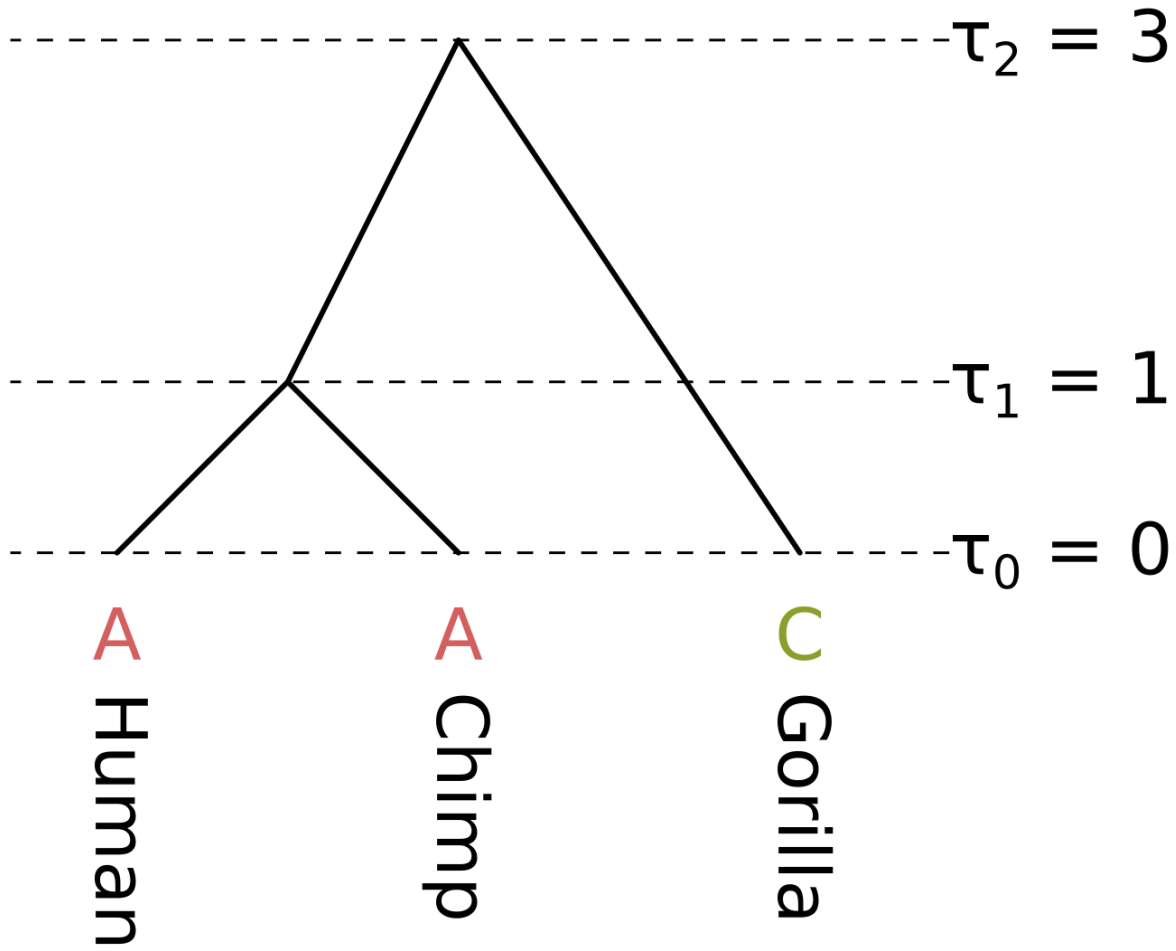


- Strong rate heterogeneity alpha < 1
- Weak rate heterogeneity alpha > 1

Maximum likelihood

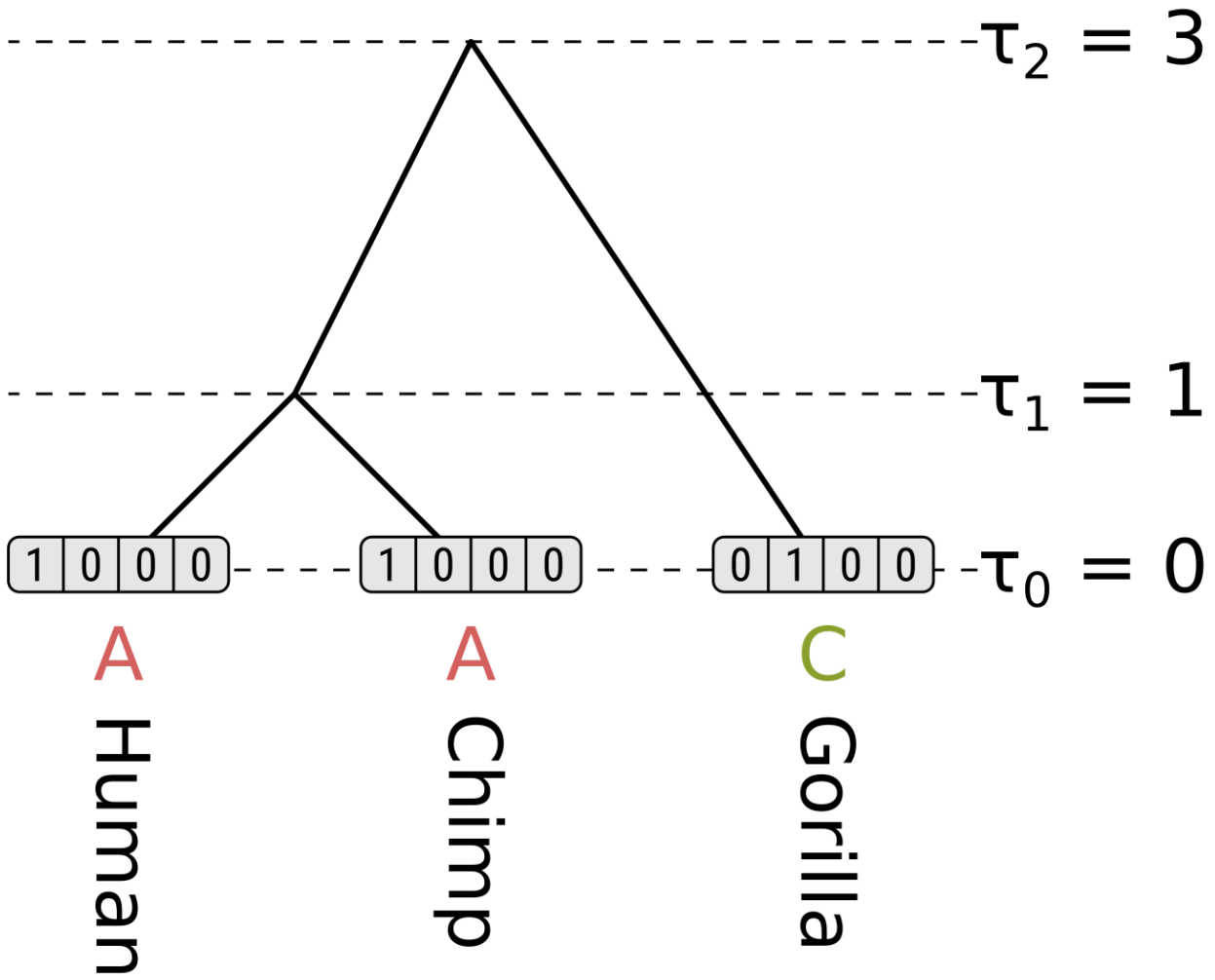
- Closely related to the more common concept of probability
- Considered the most statistically valid approach for molecular phylogenetics
  - Along with Bayesian
- Incorporates detailed models of molecular evolution

Parsimony v. Likelihood



•Huw A. Ogilvie https://www.cs.rice.edu/~ogilvie/comp571/2019/12/04/ultrametric-likelihood-example.html

Parsimony v. Likelihood



•Huw A. Ogilvie https://www.cs.rice.edu/~ogilvie/comp571/2019/12/04/ultrametric-likelihood-example.html

Parsimony v. Likelihood

For the human and chimp branches, these will be (to four decimal places):

$$P_{xx}(0.1) = \frac{1}{4}\left(1 + 3e^{-\frac{4}{3}0.1}\right) = 0.9064$$

$$P_{xy}(0.1) = \frac{1}{4}\left(1 - e^{-\frac{4}{3}0.1}\right) = 0.0312$$

For the HC branch, these will be:

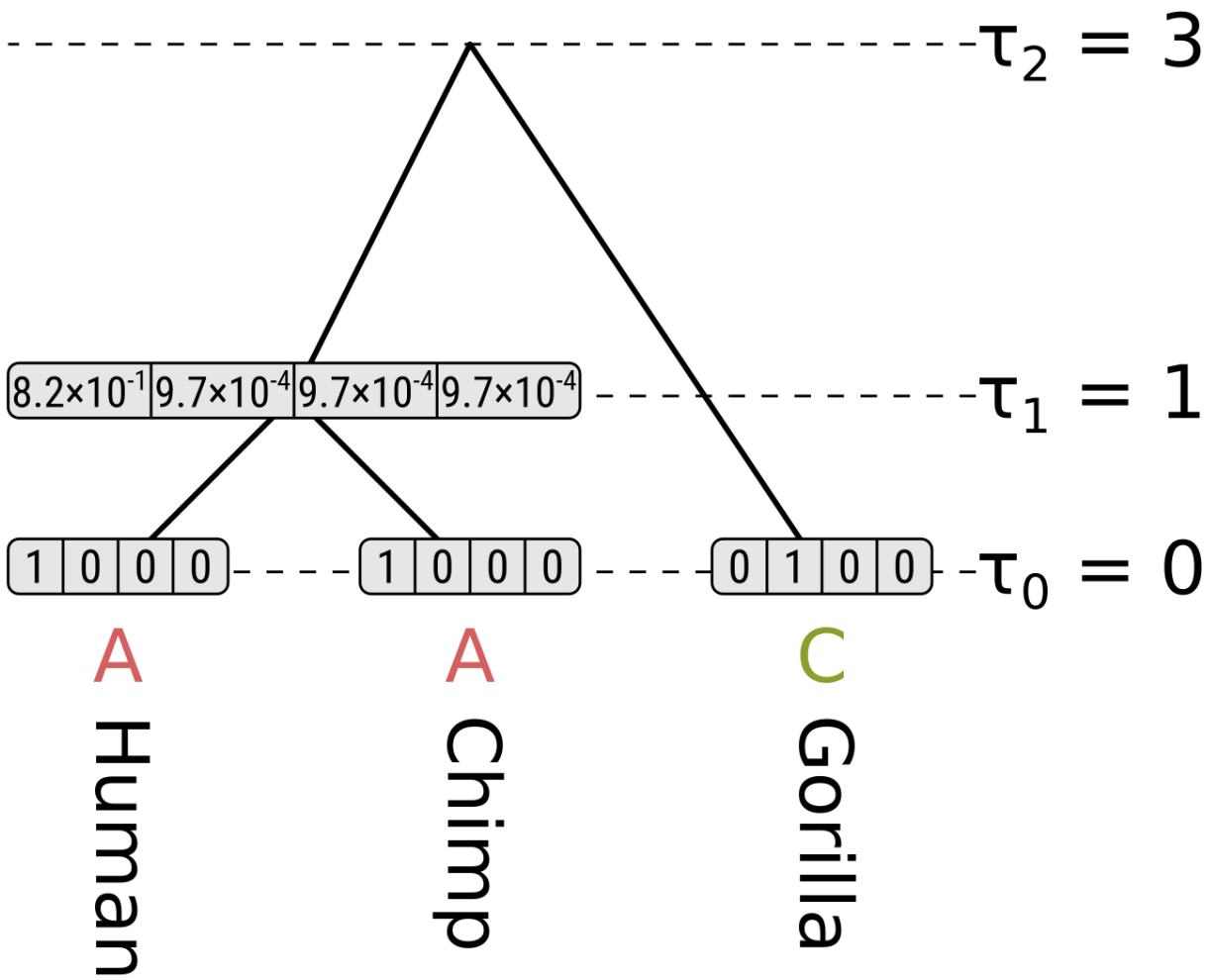
$$P_{xx}(0.2) = \frac{1}{4}\left(1 + 3e^{-\frac{4}{3}0.2}\right) = 0.8245$$

$$P_{xy}(0.2) = \frac{1}{4}\left(1 - e^{-\frac{4}{3}0.2}\right) = 0.0585$$

For the gorilla branch, these will be:

$$P_{xx}(0.3) = \frac{1}{4}\left(1 + 3e^{-\frac{4}{3}0.3}\right) = 0.7528$$

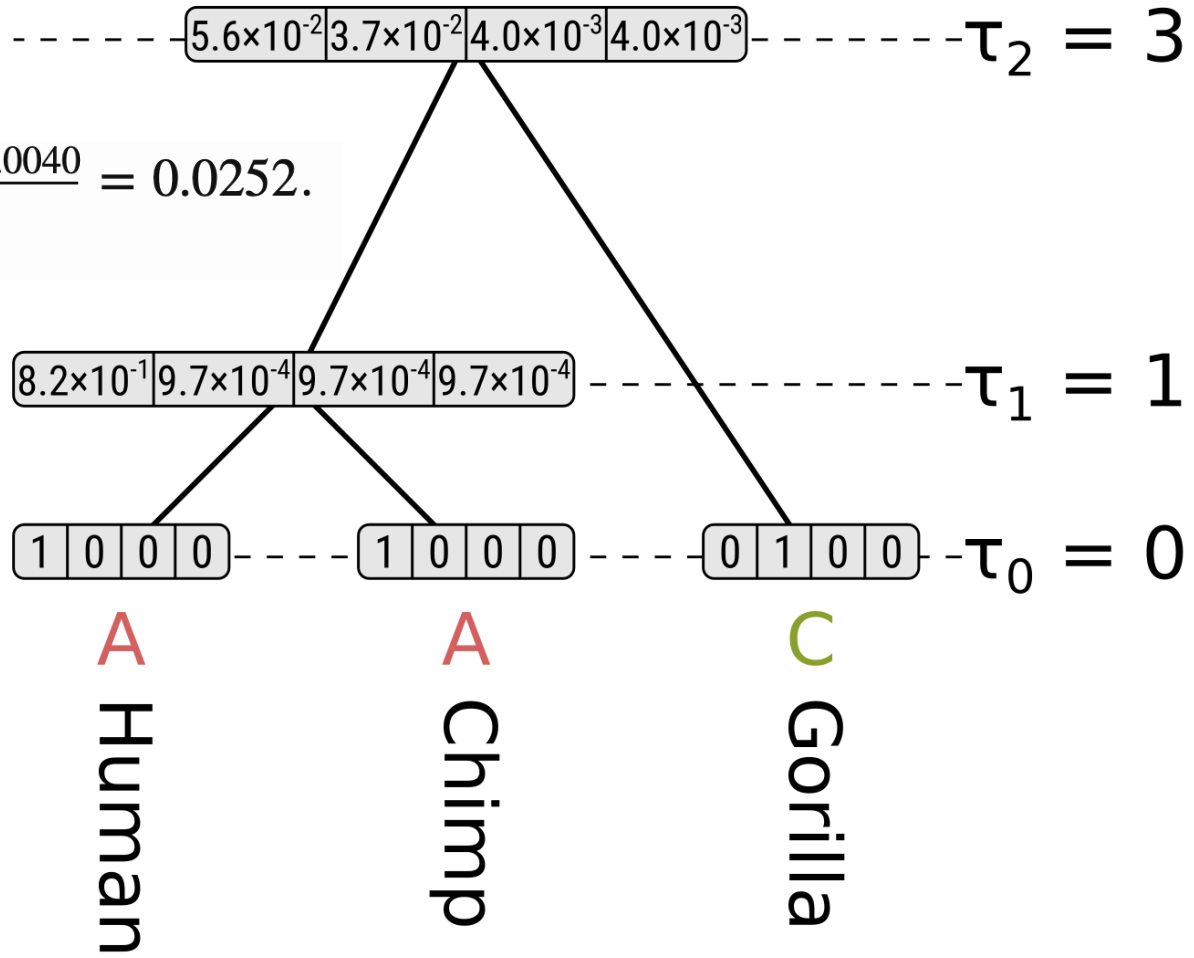
$$P_{xy}(0.3) = \frac{1}{4}\left(1 - e^{-\frac{4}{3}0.3}\right) = 0.0824$$



•Huw A. Ogilvie https://www.cs.rice.edu/~ogilvie/comp571/2019/12/04/ultrametric-likelihood-example.html

Parsimony v. Likelihood

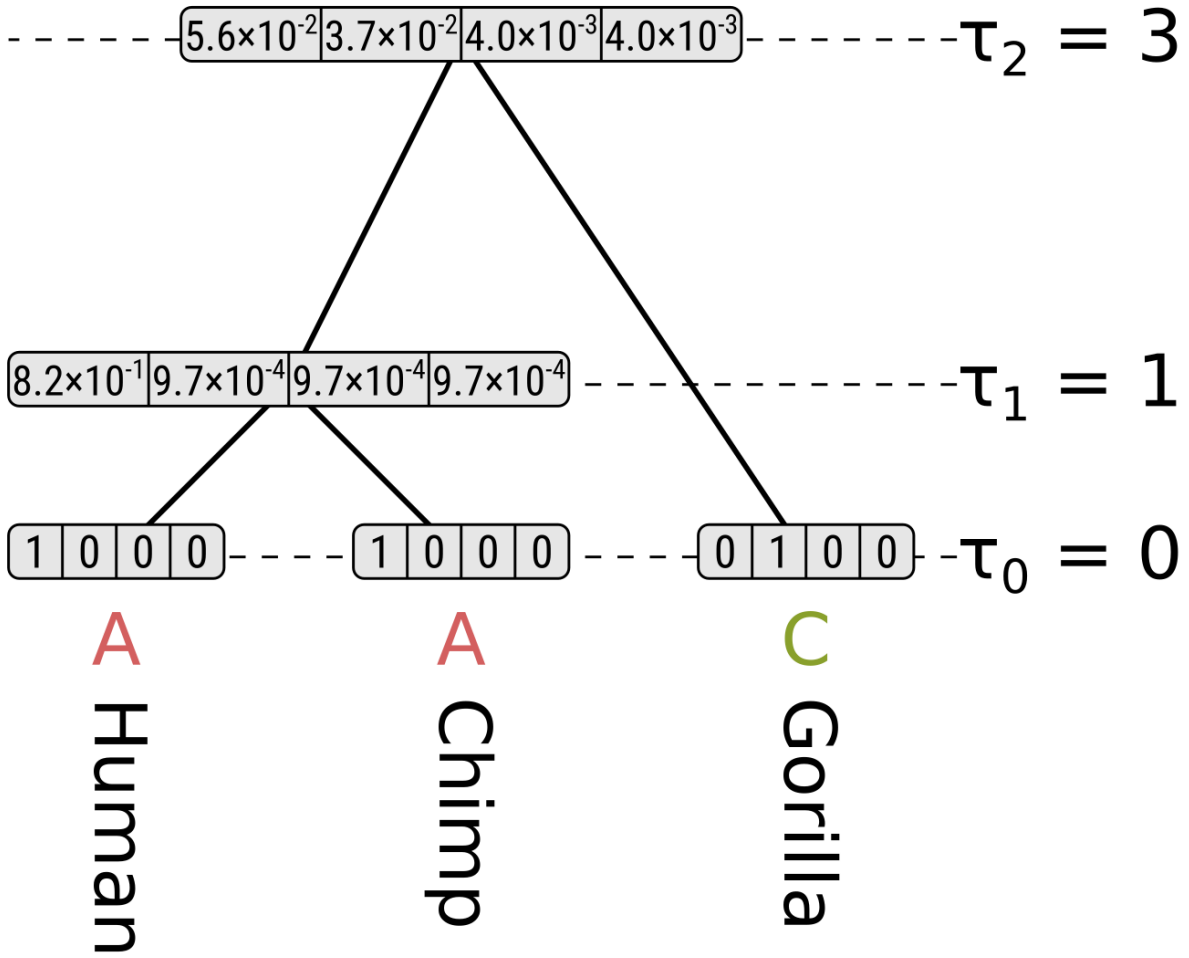
$$P(D|T,h) = \frac{0.0588+0.0369+2\times0.0040}{4} = 0.0252.$$



•Huw A. Ogilvie https://www.cs.rice.edu/~ogilvie/comp571/2019/12/04/ultrametric-likelihood-example.html

Parsimony v. Likelihood

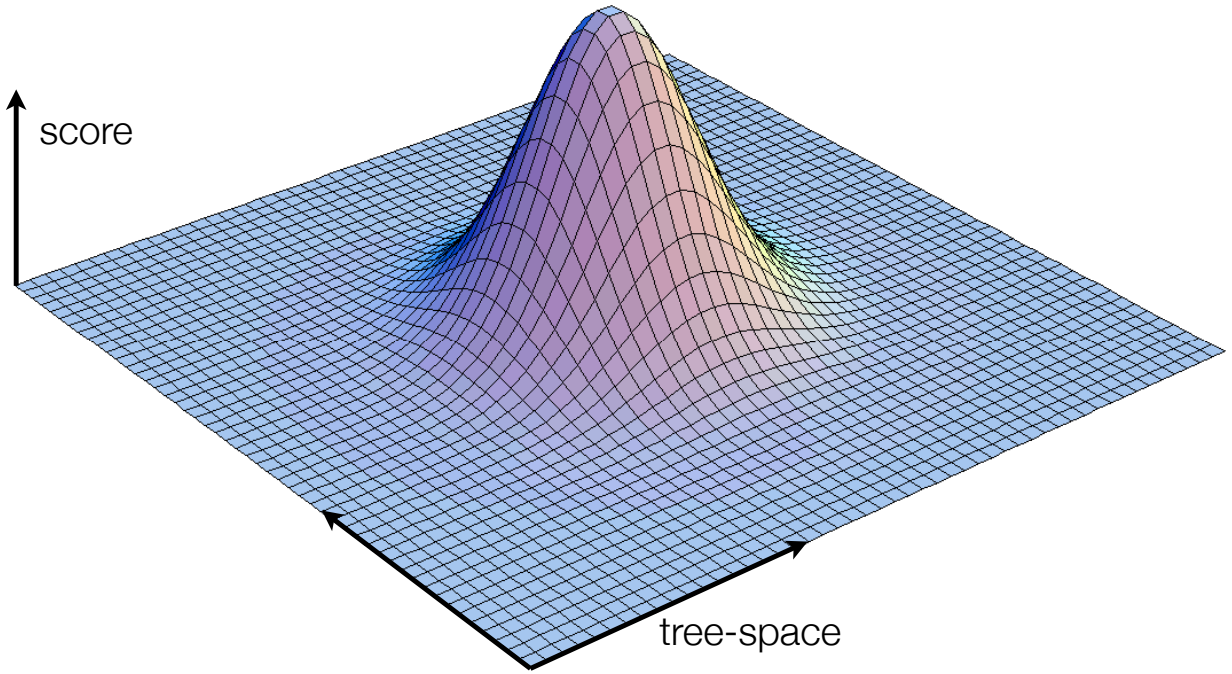
Parsimony score would be?



•Huw A. Ogilvie https://www.cs.rice.edu/~ogilvie/comp571/2019/12/04/ultrametric-likelihood-example.html

Tree space

hill-climbing method

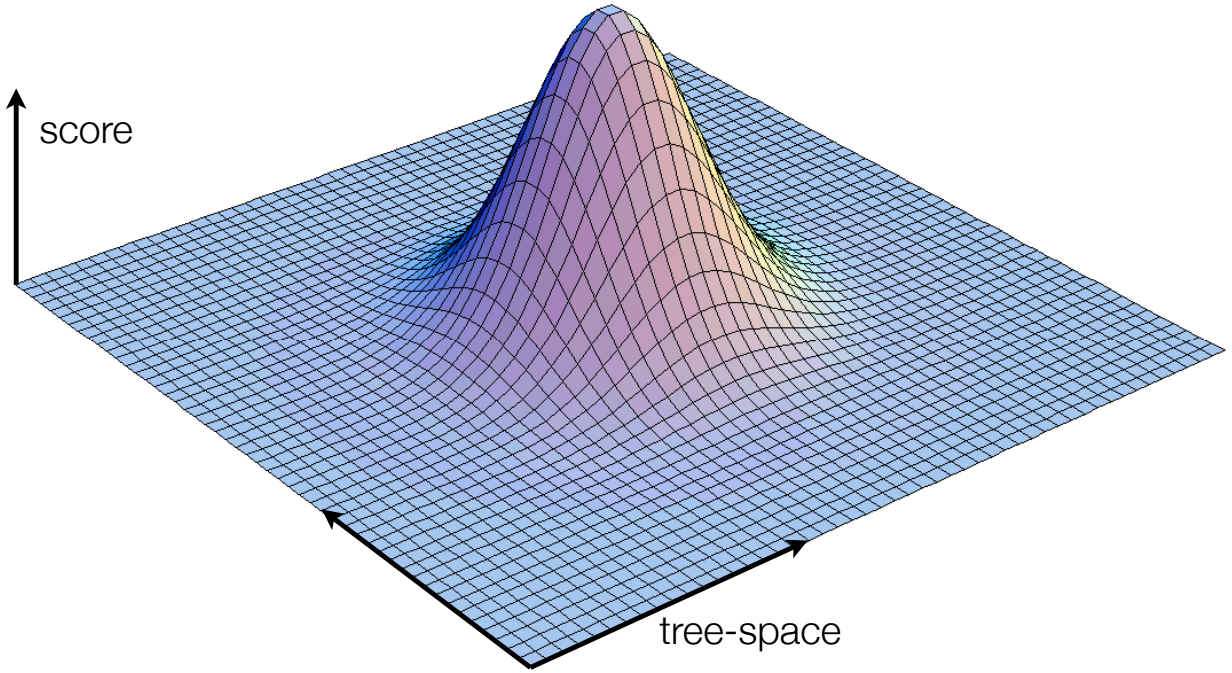


ML search

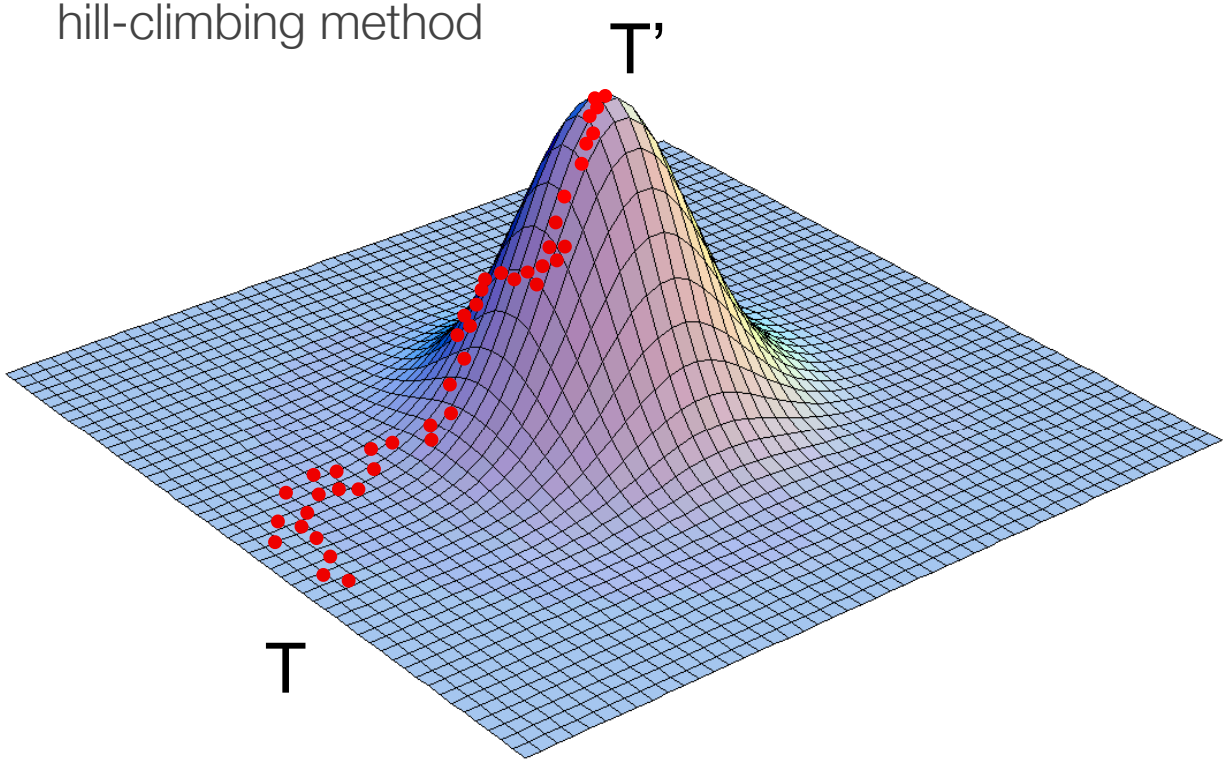
- Start with a tree (T)
- Perturb with branch-swapping (T’)
- Calculate likelihood of tree
- If T’ has better score than T, continue walk; if not, try different perturbations
- For each tree, need to optimize parameters of the model

Tree space

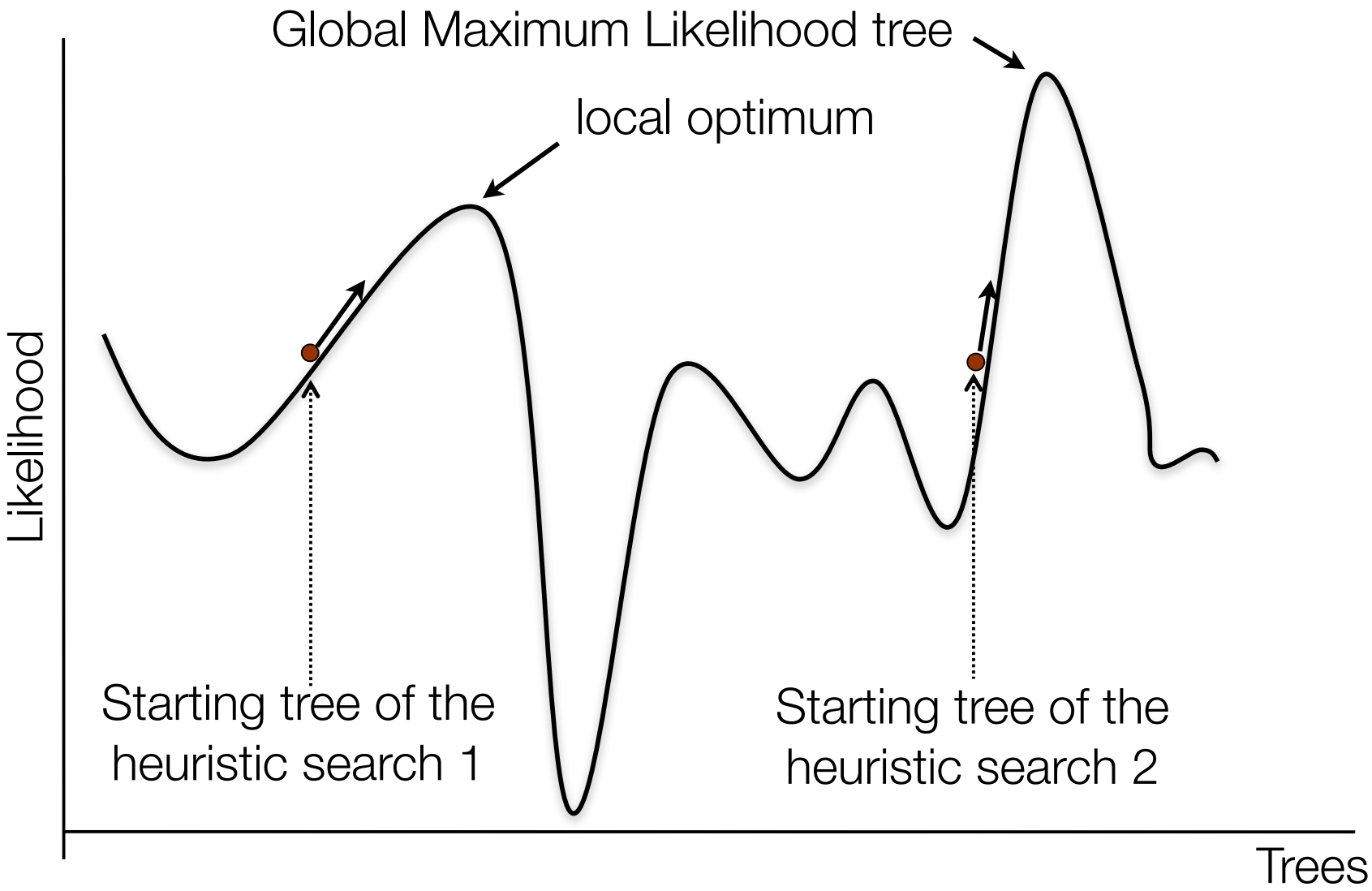
hill-climbing method



hill-climbing method



Tree space


Global Maximum Likelihood tree
local optimum
Likelihood
Starting tree of the heuristic search 1
Starting tree of the heuristic search 2
Trees

Programs for inferring trees

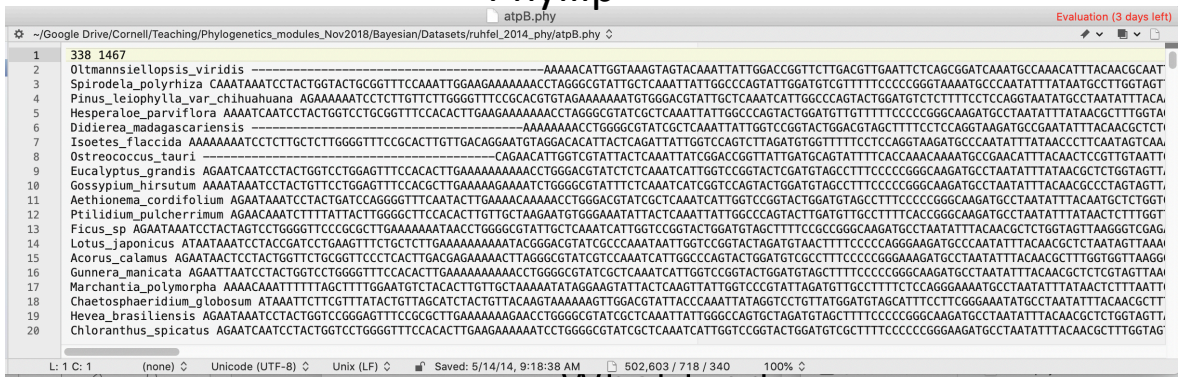
- Garli
  - Limited GUI but full functioning command line
  - Complete control of model selection
  - Great for small data sets <300 tips and one gene, but slow for many genes and tons of taxa
- RAxML
  - Great for large data sets; also have a RAXML NG for NGS data
  - Limitation in the number of models of molecular evolution
  - Command line, but there is a RAxML BlackBox
- Mega
  - GUI version, easy to learn
  - However not widely accepted in publications (not all reasons are supported)
  - May not work very well for large data sets, but fast on small data sets

What kind of data do we need?

- Alignment files in either fasta or phyllip format

Fasta

Phyllip

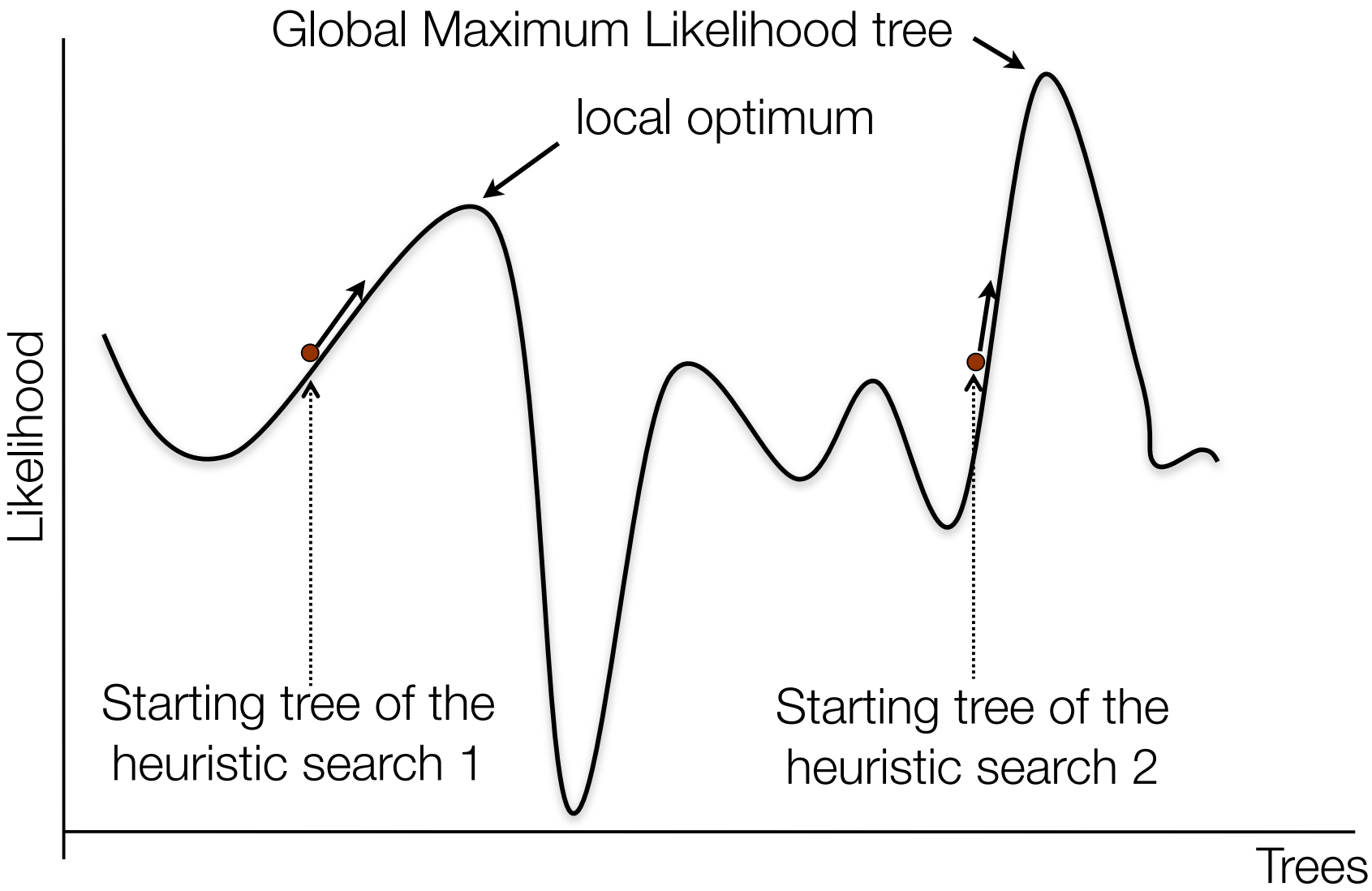


- Either nucleotide or amino acids; specify the appropriate model
- Missing data/gaps are treated as N's
- Should specify an outgroup, but will run without it
  - If you specify multiple, but they are not monophyletic, the first will be used

Once you hit go, what happens?

- RAxML generates starting trees using stepwise addition order parsimony
  - Taxa are inserted into the tree one at a time
- After all taxa added, subtree pruning re-grafting (SPR)
  - Similar to TBR as done in TNT
- Other programs us a Neighbor Joining distance tree as the starting tree
  - Parsimony subtrees seen as an advantage because each start is a distinct and different starting point, which helps search tree space
  - Why is this good?

Tree space

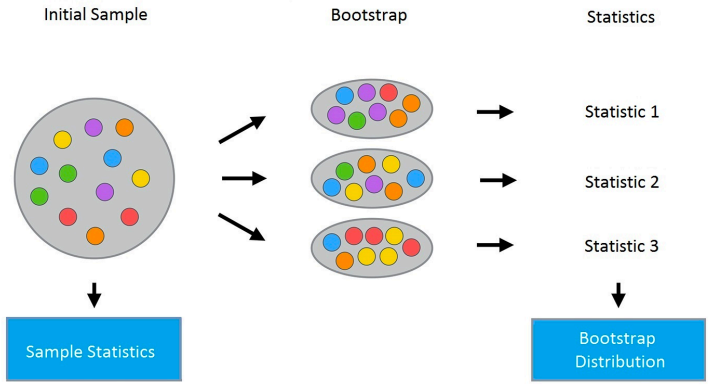

Global Maximum Likelihood tree
local optimum
Likelihood
Starting tree of the heuristic search 1
Starting tree of the heuristic search 2
Trees

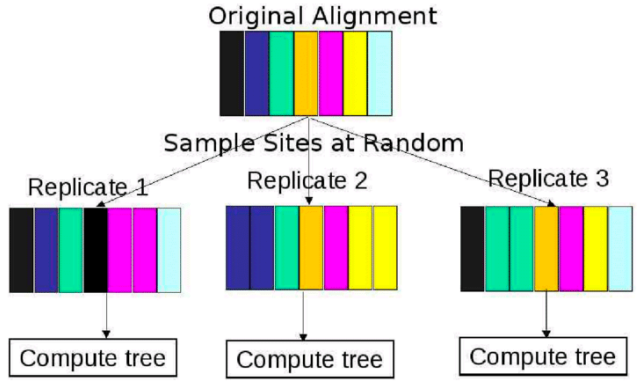
Scope of the question and data

- RAxML was designed for large data sets
  - Reason the models of molecular evolution are constrained to GTR
- For broad taxonomic questions
  - chloroplast genes (slower evolving the nuclear)
  - Amino acid/protein alignments – avoid the third position wobble
- Questions below the species level
  - Can use SNP data from RAD-Seq or Genome Resequencing
  - Models of molecular evolution are different, no invariant sites

How do we tell support for a topology?

- Most analyses use bootstrap support

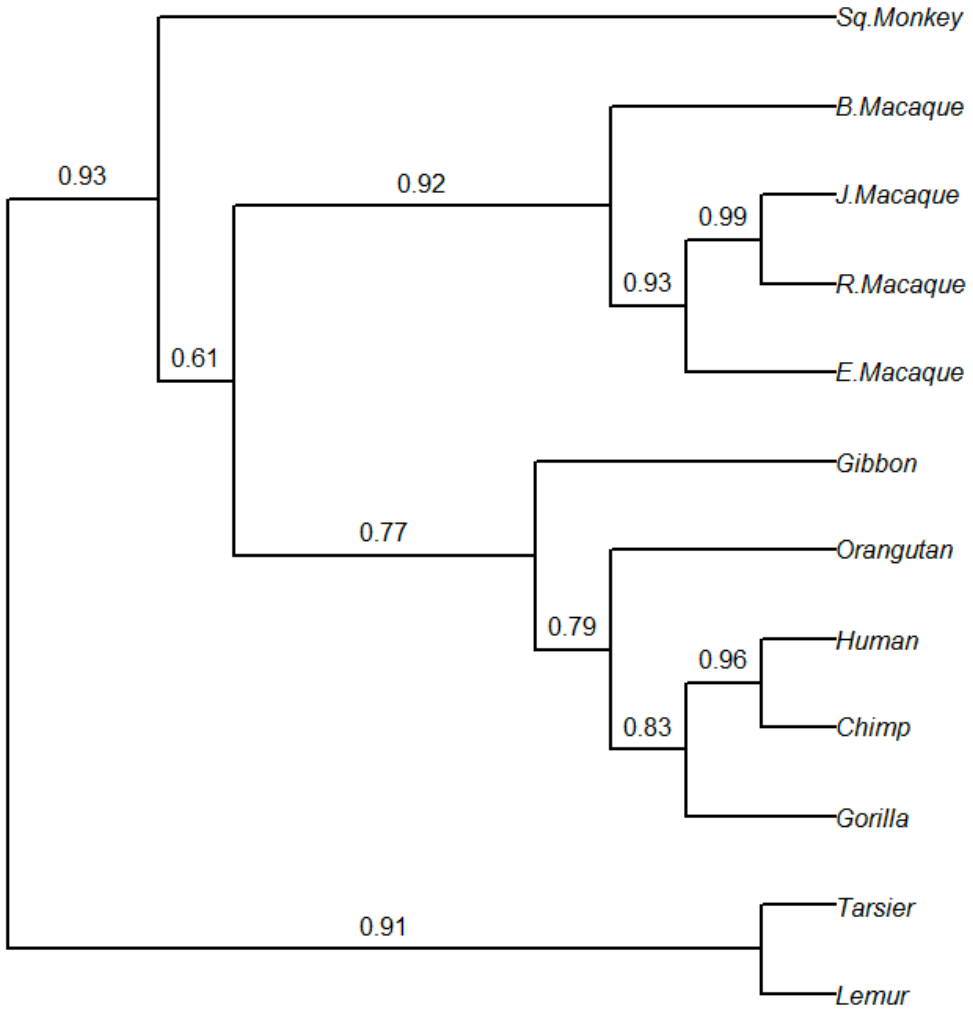




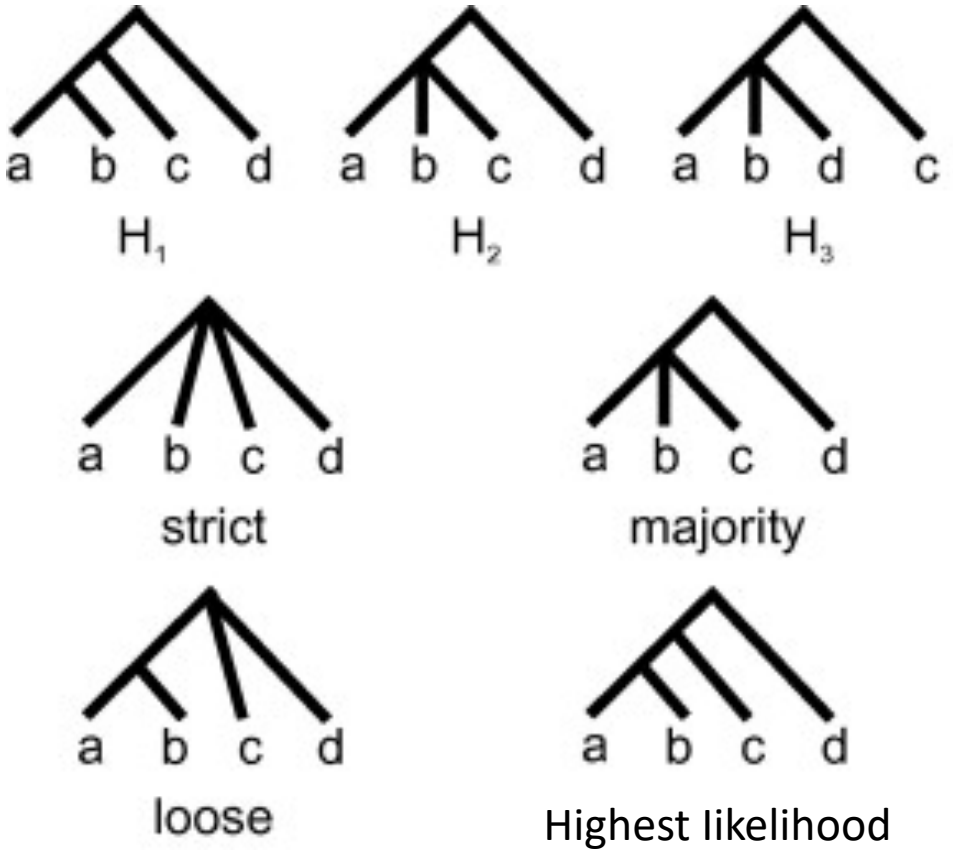
- In our case, we will sample with replacement the original alignment to generate 1000 alignments of the same length
- How often are the same taxa related to each other out of the 1000 replicates
- Usually a value of BS > 70 or more is considered strong support

What do we consider good support?

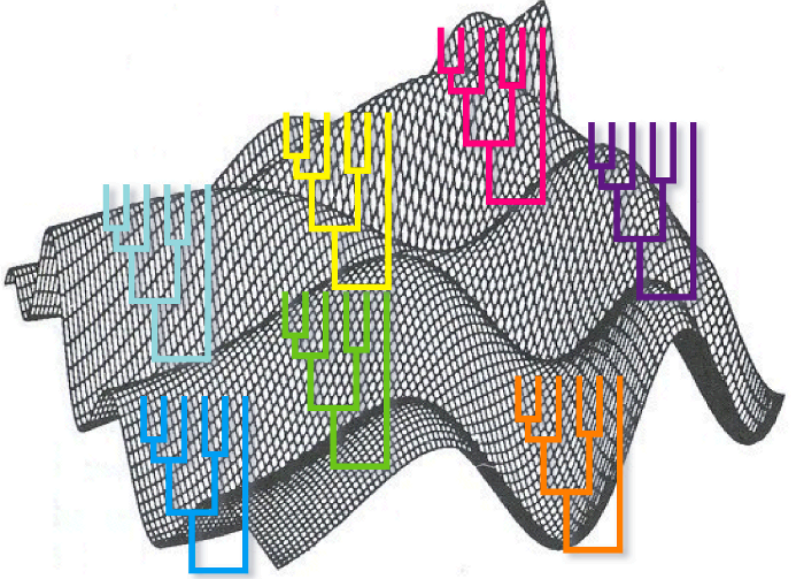
- If there is strong support for relationships in the original data, it will come through in the bootstrap support



Support for topology



- If topology is different between analyses, need to look at how well-supported relationships are
- The ”best” tree may not be well-supported at
- Polytomies?



Bayesian approaches

Can we apply prior knowledge to inform our analyses?

ML vs Bayesian

- Maximum likelihood
  - Search for the tree that maximizes the chance of seeing the data
    (P (Data | Tree))
  - Data are random variables but parameters are fixed

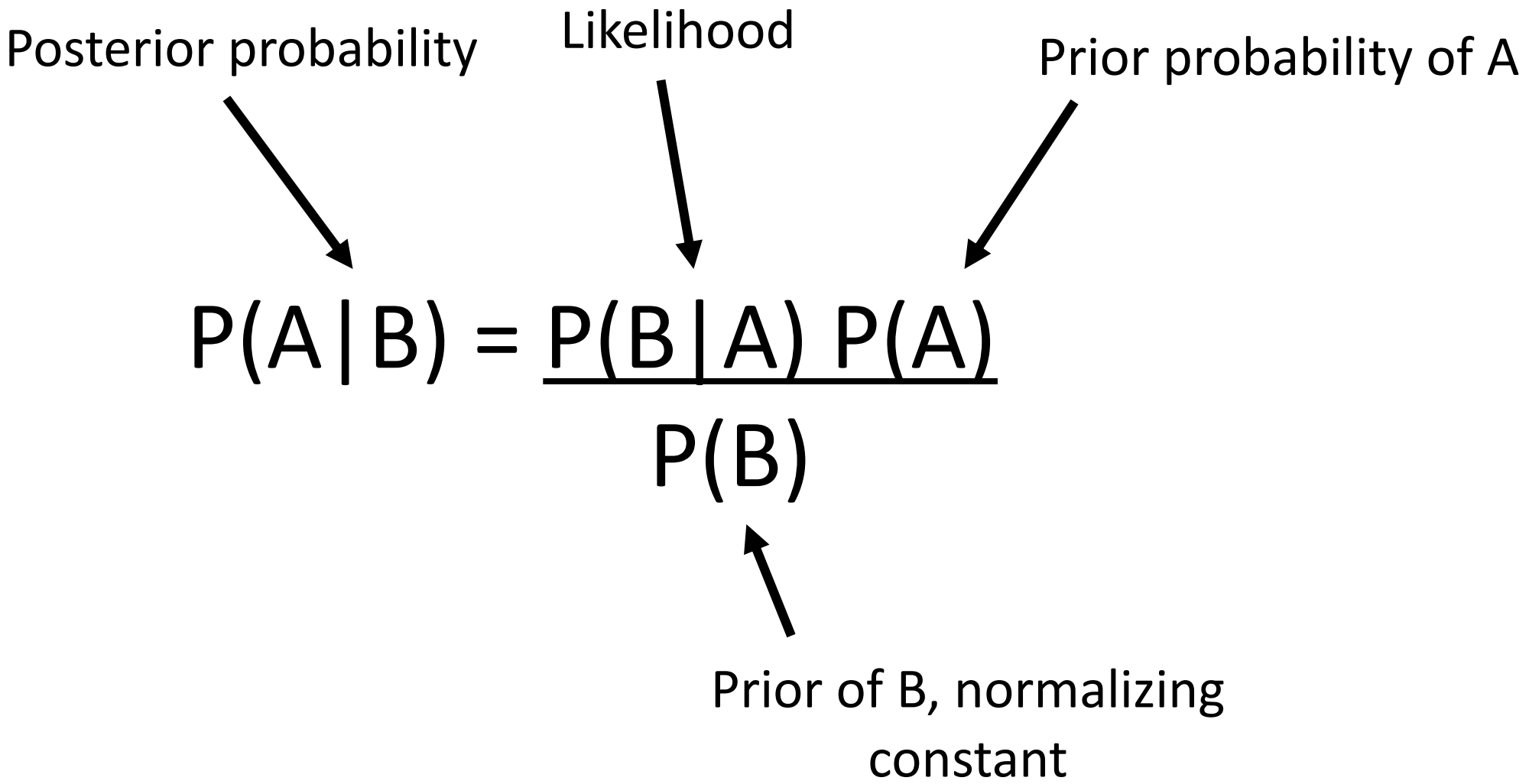
- Bayesian
  - Search for the tree that maximizes the chance of seeing the tree given the data (P (Tree | Data))
  - Data are random variables and so are the model parameters

- If priors are well-behaved, then both ML and Bayesian inference converge on the same value (i.e. tree topology)

Expected outcomes

- For any ML analysis, we can expect a tree with the highest likelihood score
- For Bayesian any given run (sampler) may work well in most cases, all runs will fail in some cases, and not guaranteed to work for any particular case
- When do we know the run provides an accurate approximation for a given analysis?
  - We Never do

Bayes Theorem



Bayes theorem rewritten

$$P(\text{tree}|\text{data}) = \frac{P(\text{data}|\text{tree})\ P(\text{tree})}{P(\text{data})}$$

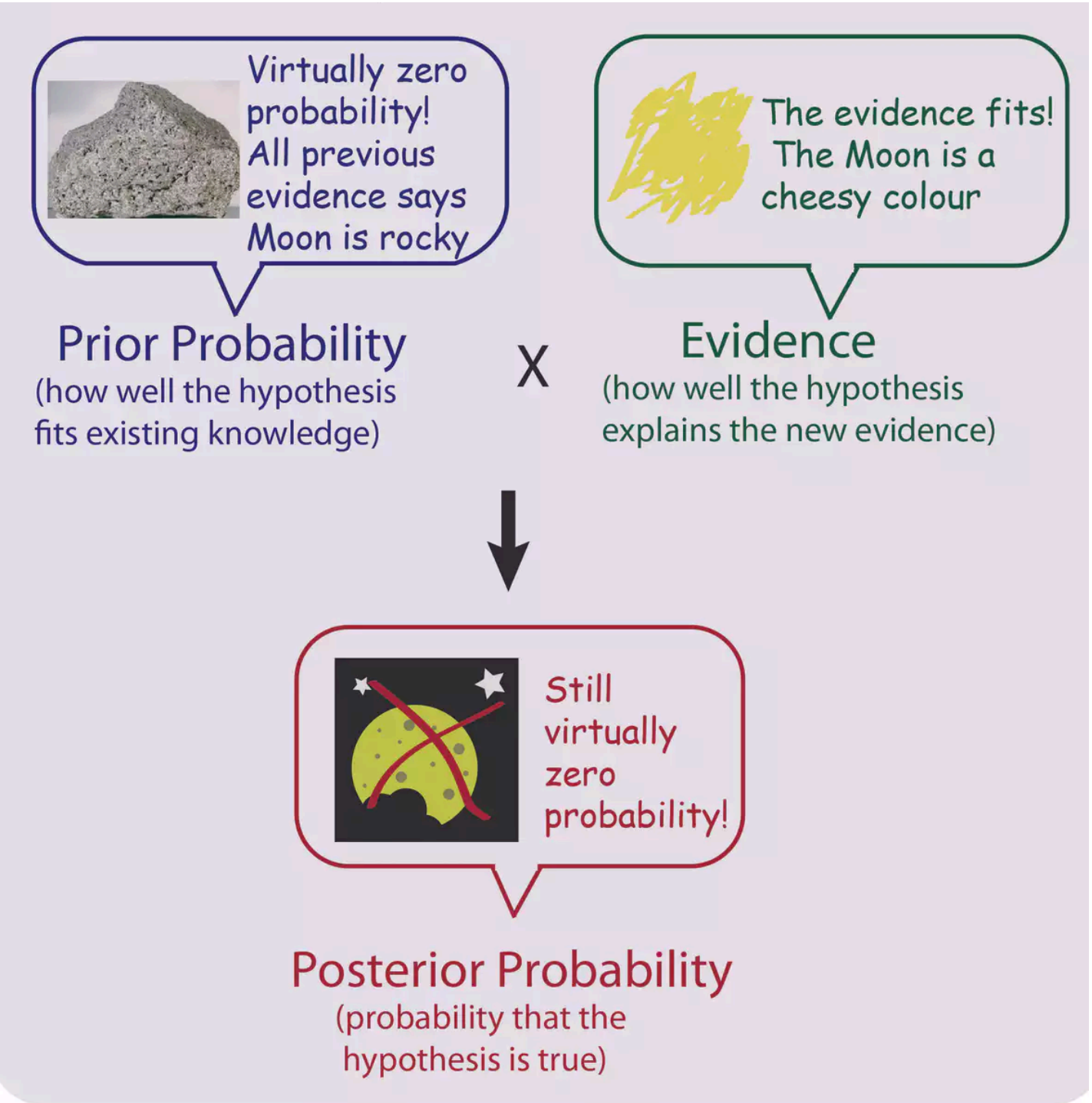
- P(Data) generally not computable
- Parameter space includes
  - Tree topology
  - Branch lengths
  - Substitution model parameters

Example

Hypothesis: The moon is made of cheese

New Evidence: I see the moon is yellow

http://theconversation.com/bayes-theorem-the-maths-tool-we-probably-use-every-day-but-what-is-it-76140



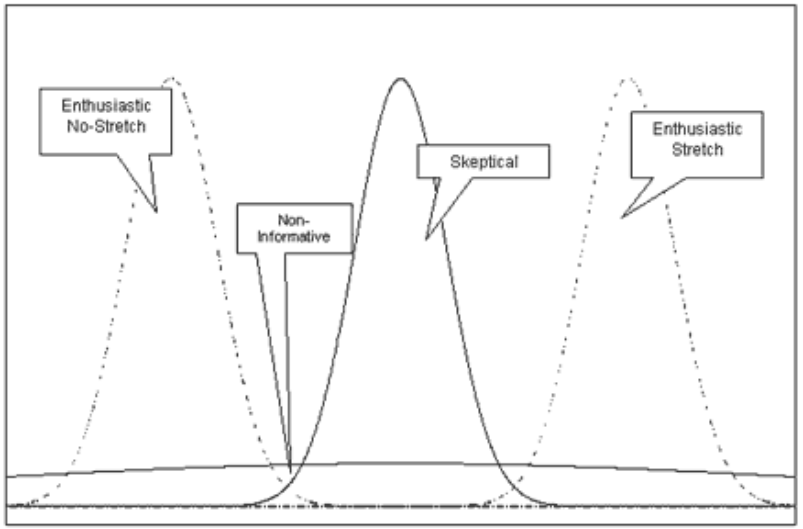
Bayesian inference

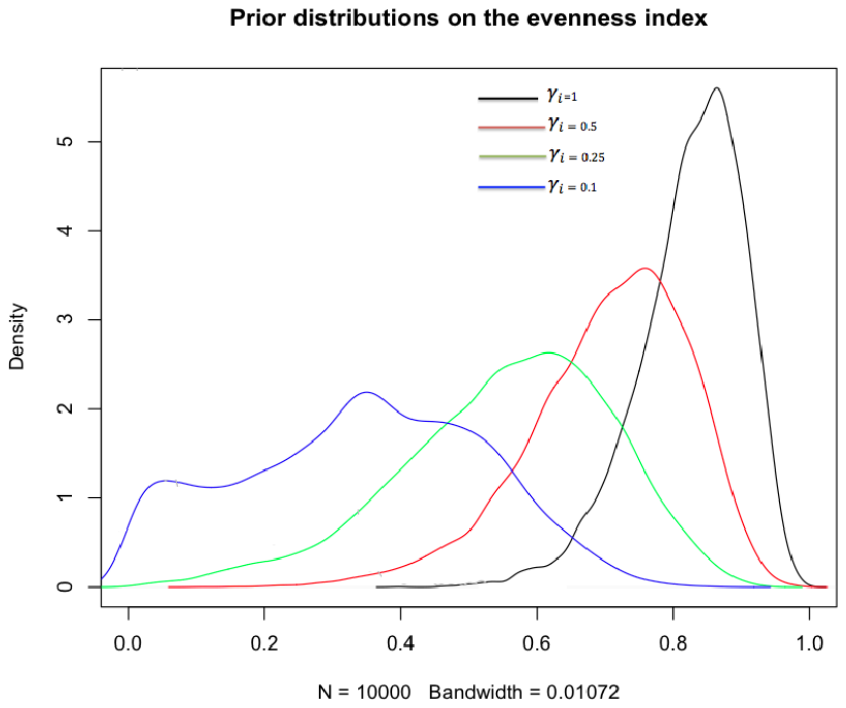
http://theconversation.com/bayes-theorem-the-maths-tool-we-probably-use-every-day-but-what-is-it-76140

Priors

- Priors can benefit the analysis
  - Incorporate previous information
  - Make the analysis more conservative
- Priors can be detrimental if the data is not very informative
- Probability distributions of parameters
  - Reflect the action of random forces or reflect your uncertainty
  - What are the likely values?

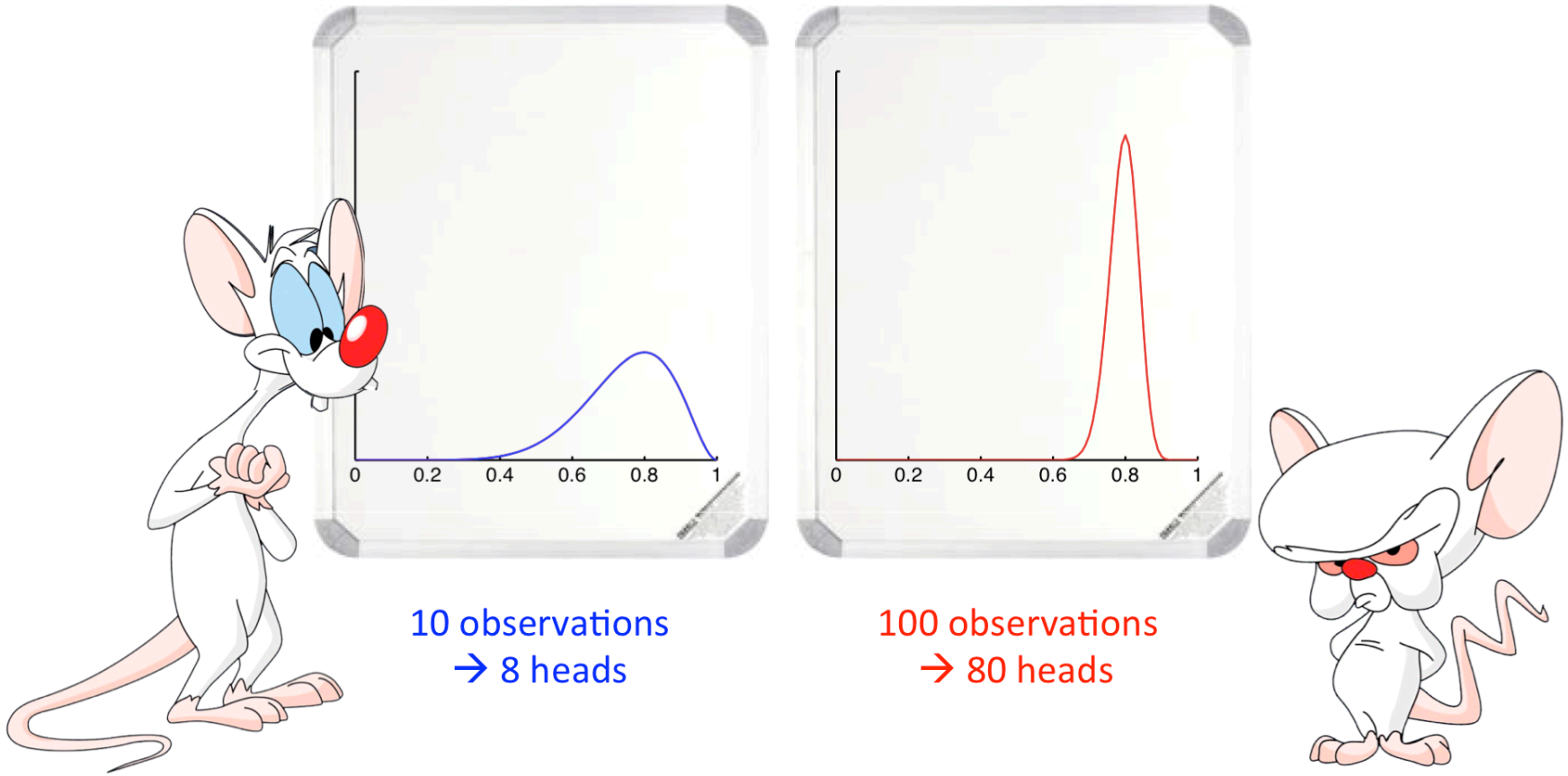
Benefits of stretching before exercise?





How much “faith” do we put in our priors?

Precision-weighting: who are you going to believe more?

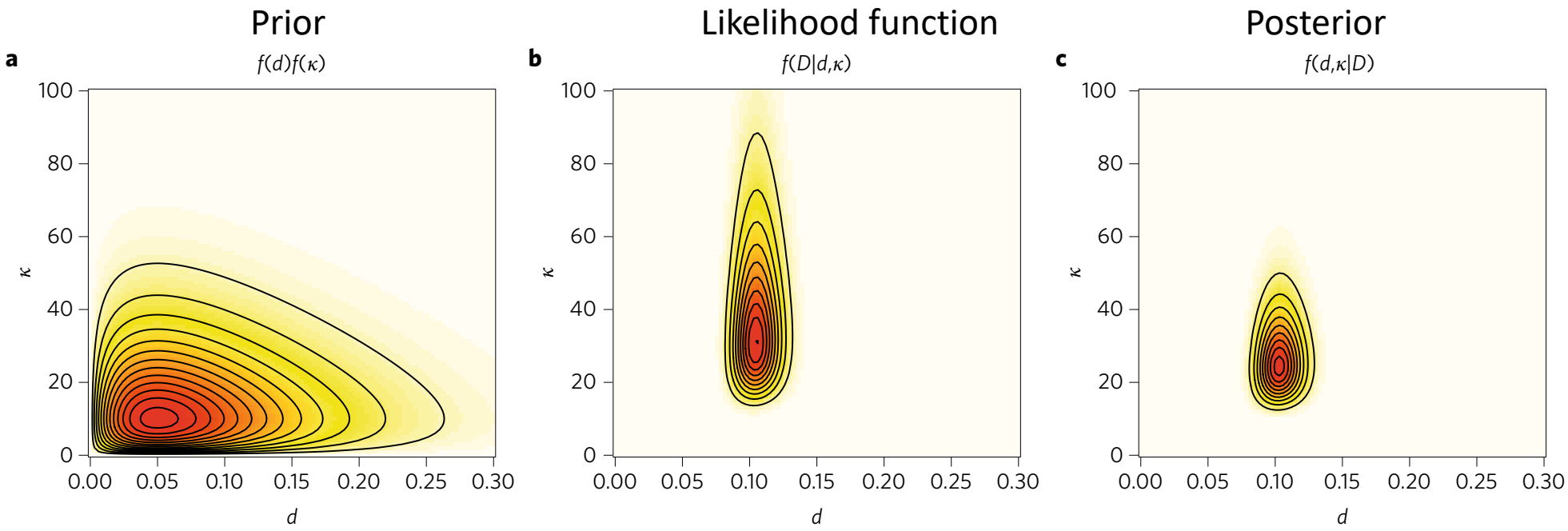


10 observations
→ 8 heads

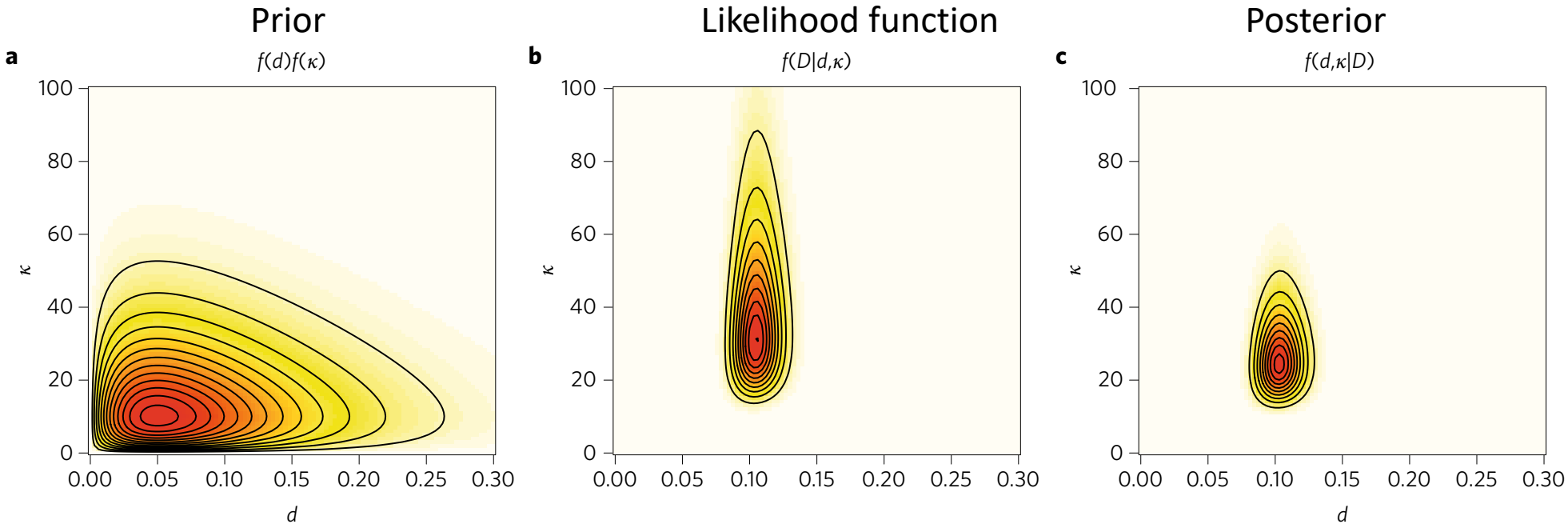
100 observations
→ 80 heads

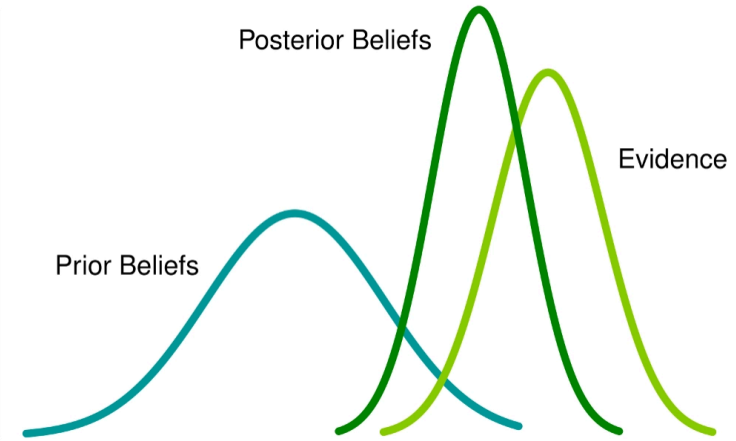
https://hannekedenouden.ruhosting.nl/RLtutorial/html/BayesPart1Review.html

Impact of prior on posterior



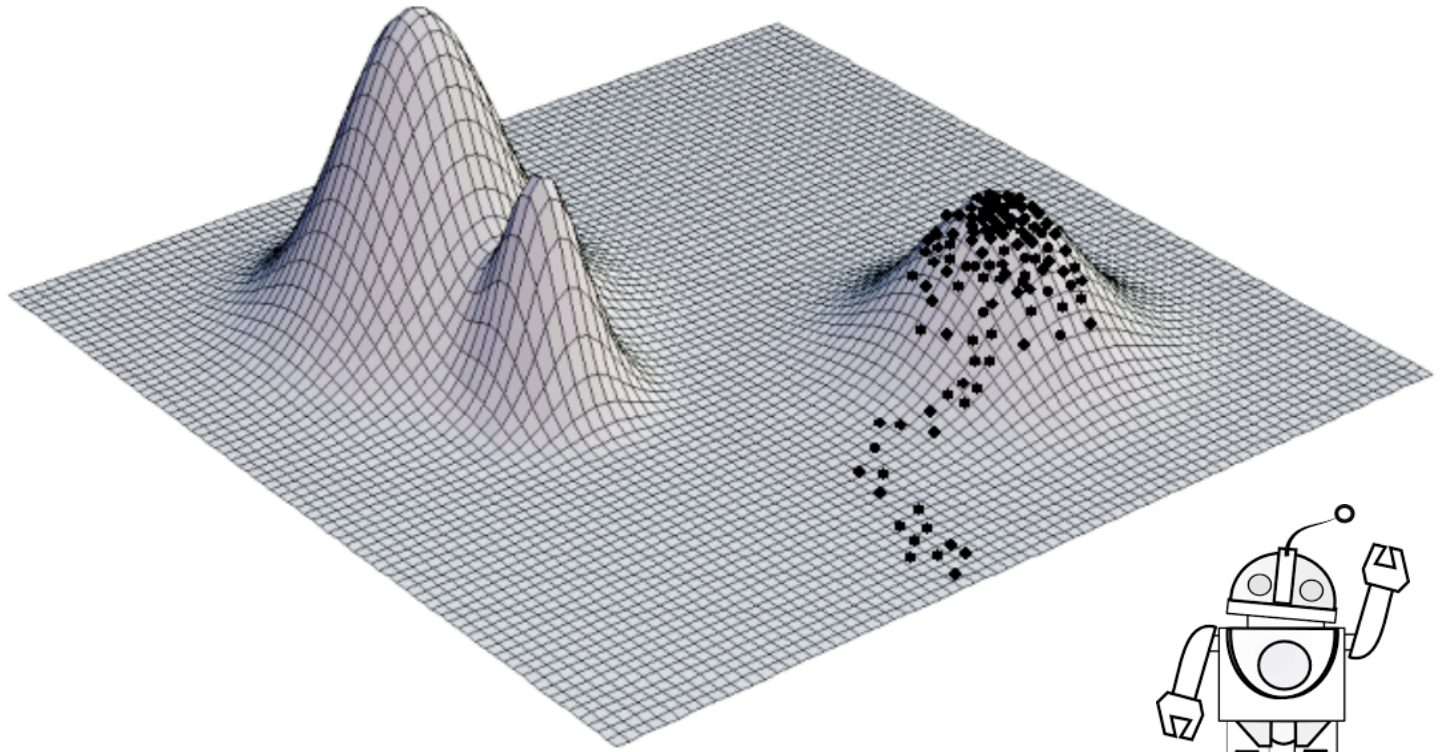
Impact of prior on posterior

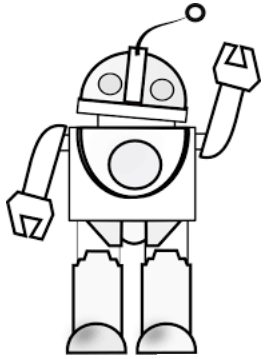




Tree space may be complex

Stuck at a local optimum





Markov Chain Monte Carlo (MCMC)

Proposal 1: 2 steps uphill → Accepted

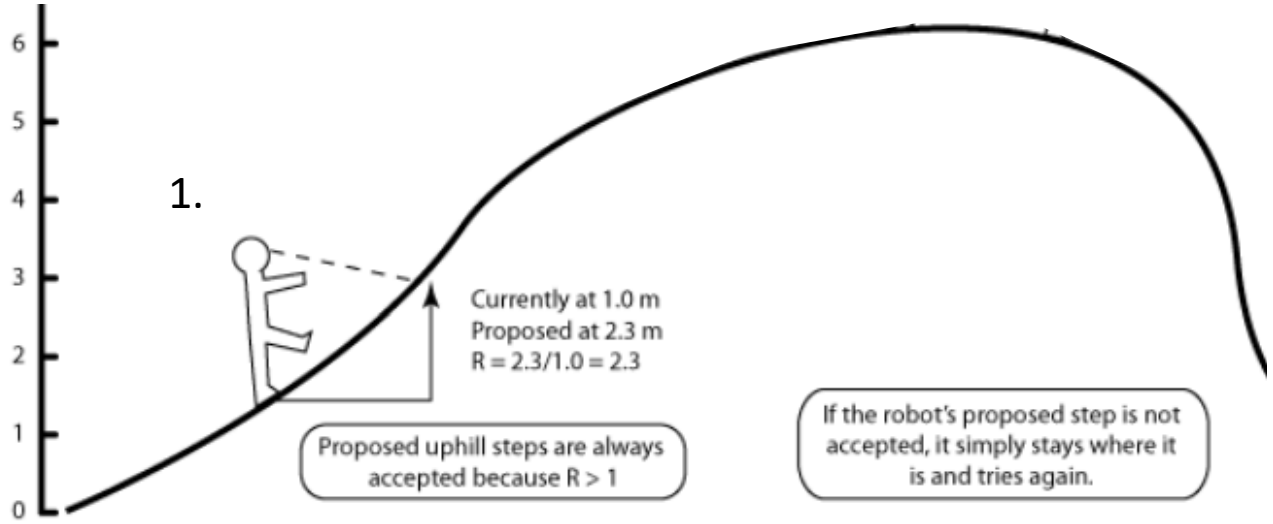
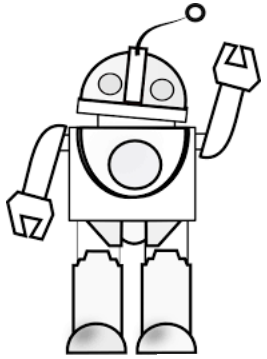


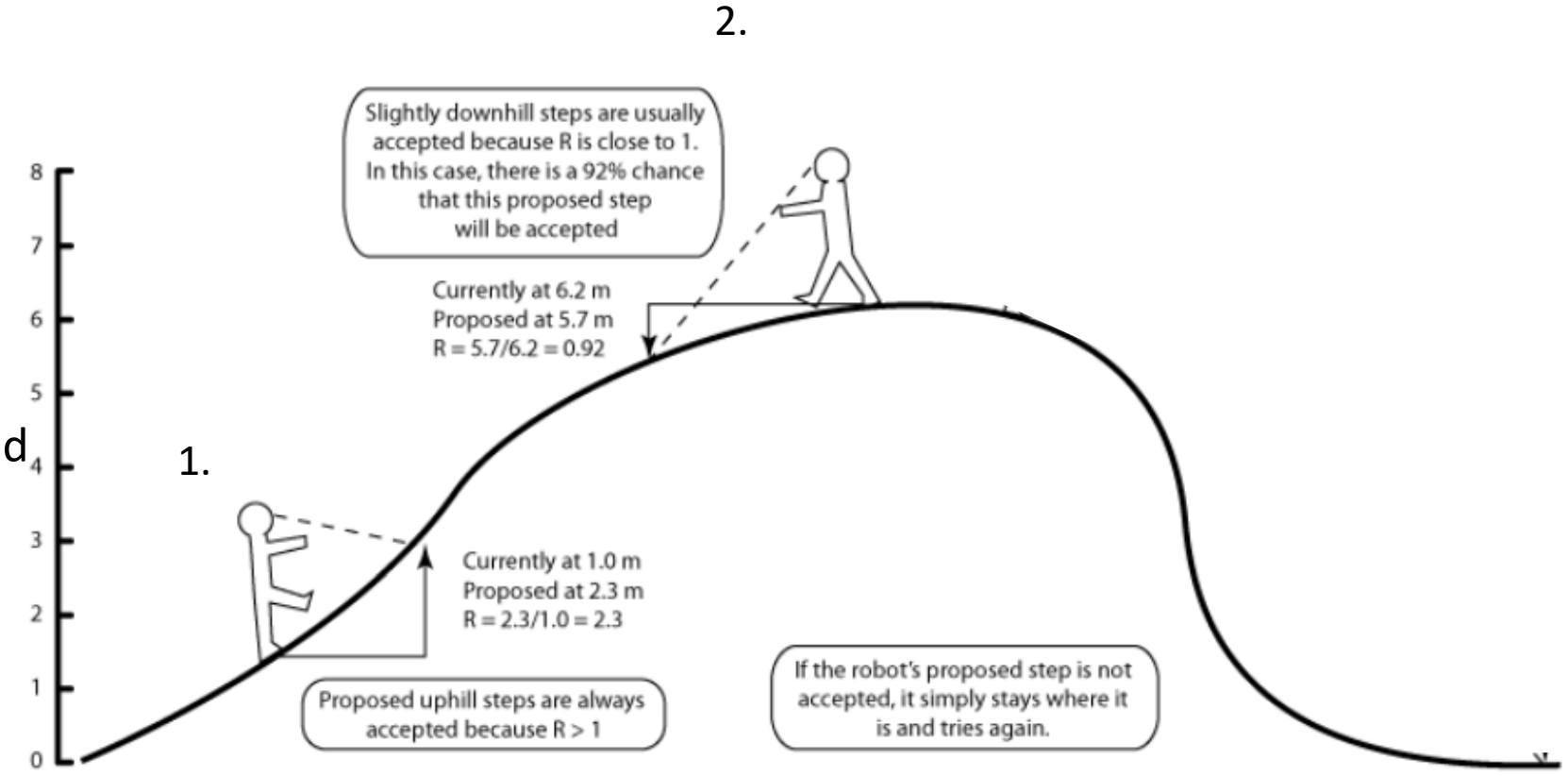
Illustration of MCMC method process (Lewis, 2011)



Markov Chain Monte Carlo (MCMC)

Proposal 1: 2 steps uphill → Accepted

Proposal 2: 1 step downhill → Accepted



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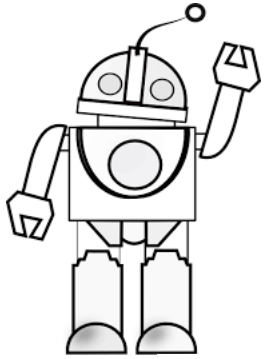
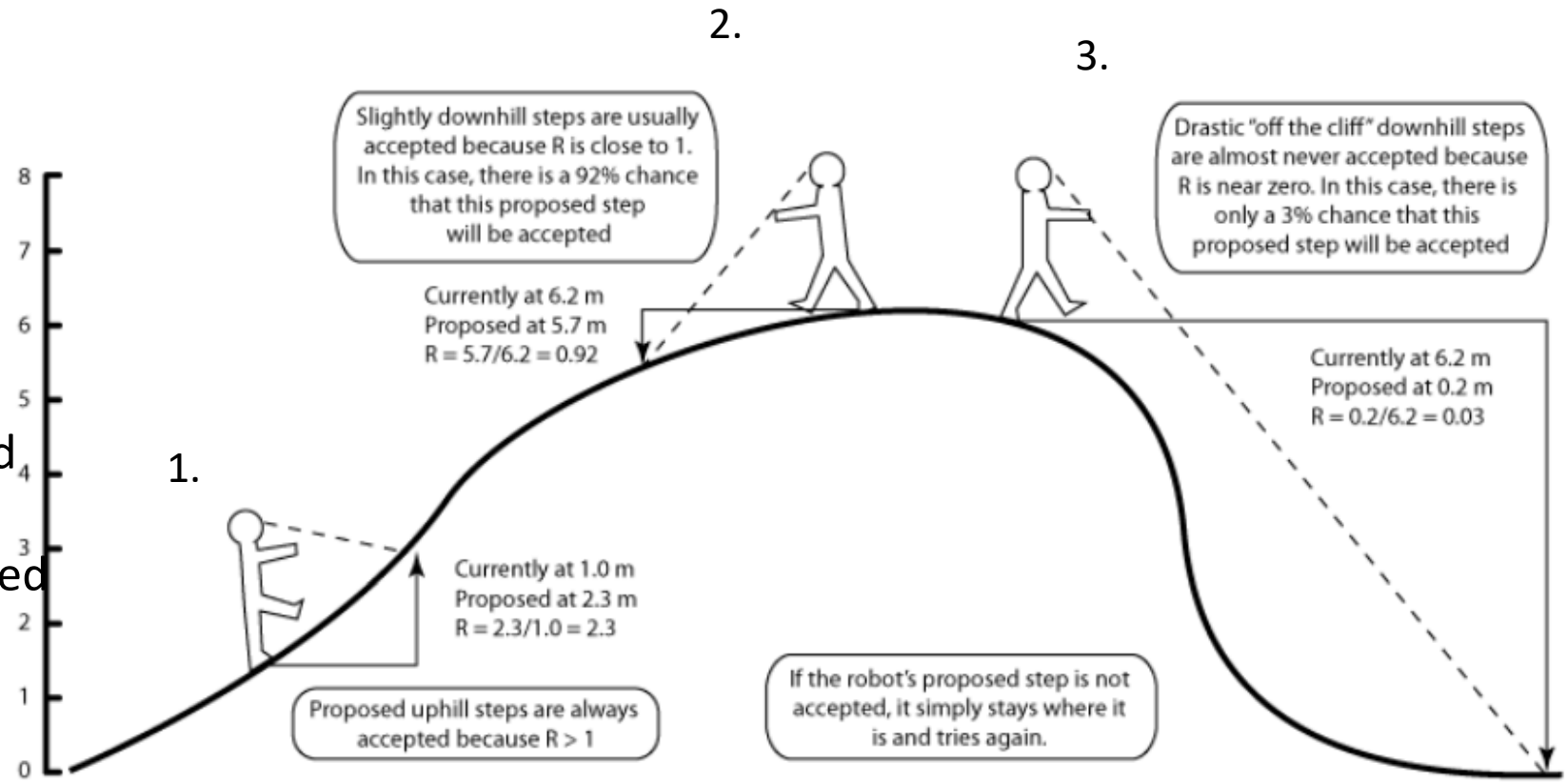


Markov Chain Monte Carlo (MCMC)

Proposal 1: 2 steps uphill → Accepted

Proposal 2: 1 step downhill → Accepted

Proposal 3: 10 steps downhill → Rejected



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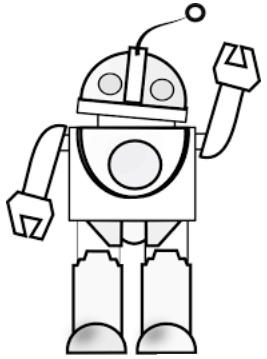

Markov Chain Monte Carlo (MCMC)

Proposal 1: 2 steps uphill → Accepted

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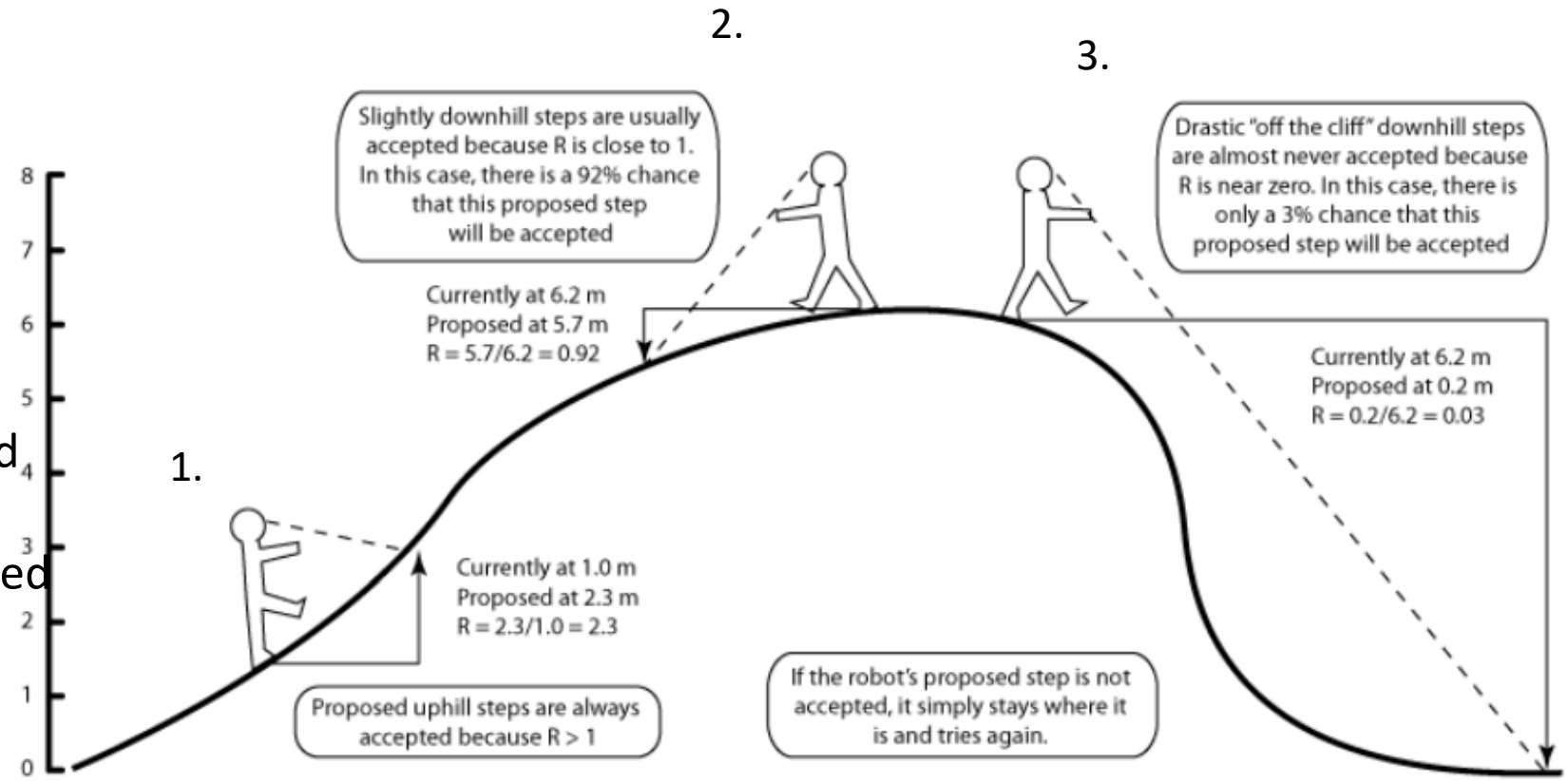
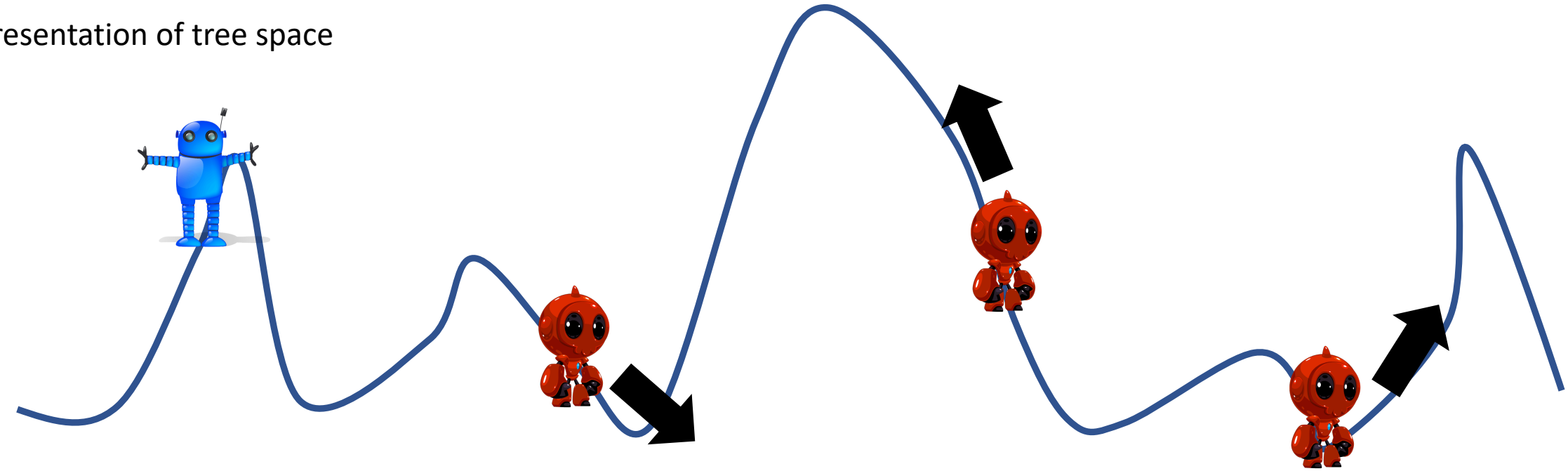


Illustration of MCMC method process (Lewis, 2011)

Markov Chain Monte Carlo (MCMC)

- Four chains (robots) exploring tree space
- 1 cold chain never takes a step with a worse score, 3 heated chains vary in chance of taking a worse step

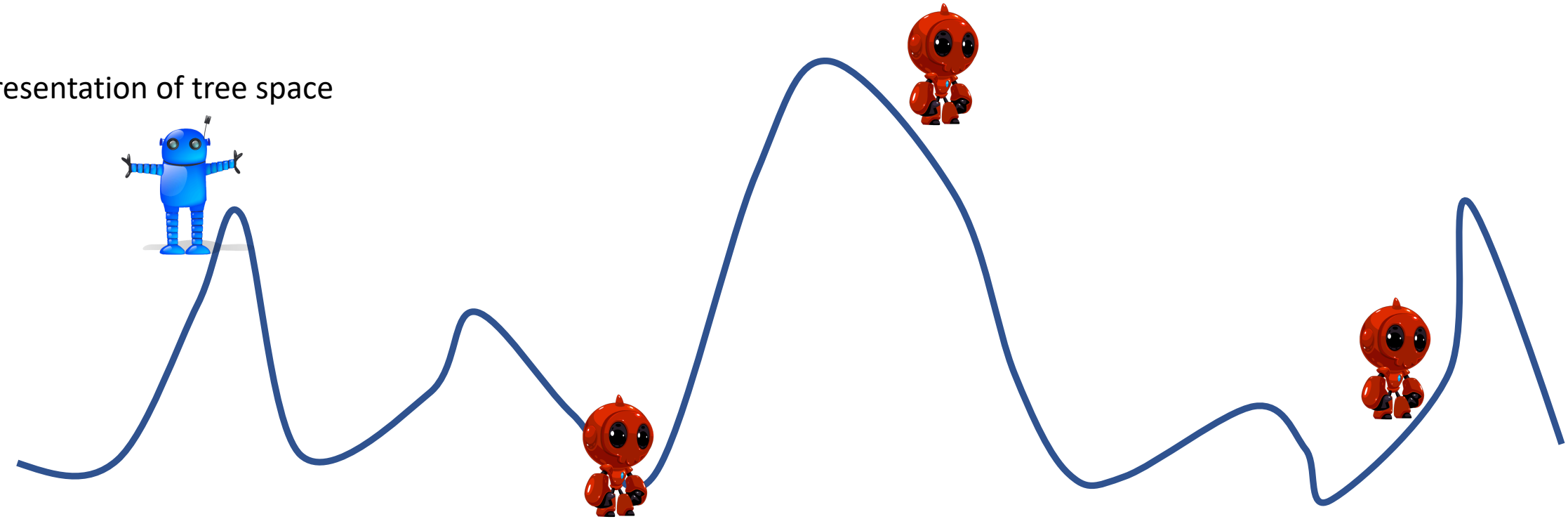
Representation of tree space



Markov Chain Monte Carlo (MCMC)

- Four chains (robots) exploring tree space
- The cold chain is the recorder, and if one of the hot chains finds a higher scoring place, they will switch positions

Representation of tree space



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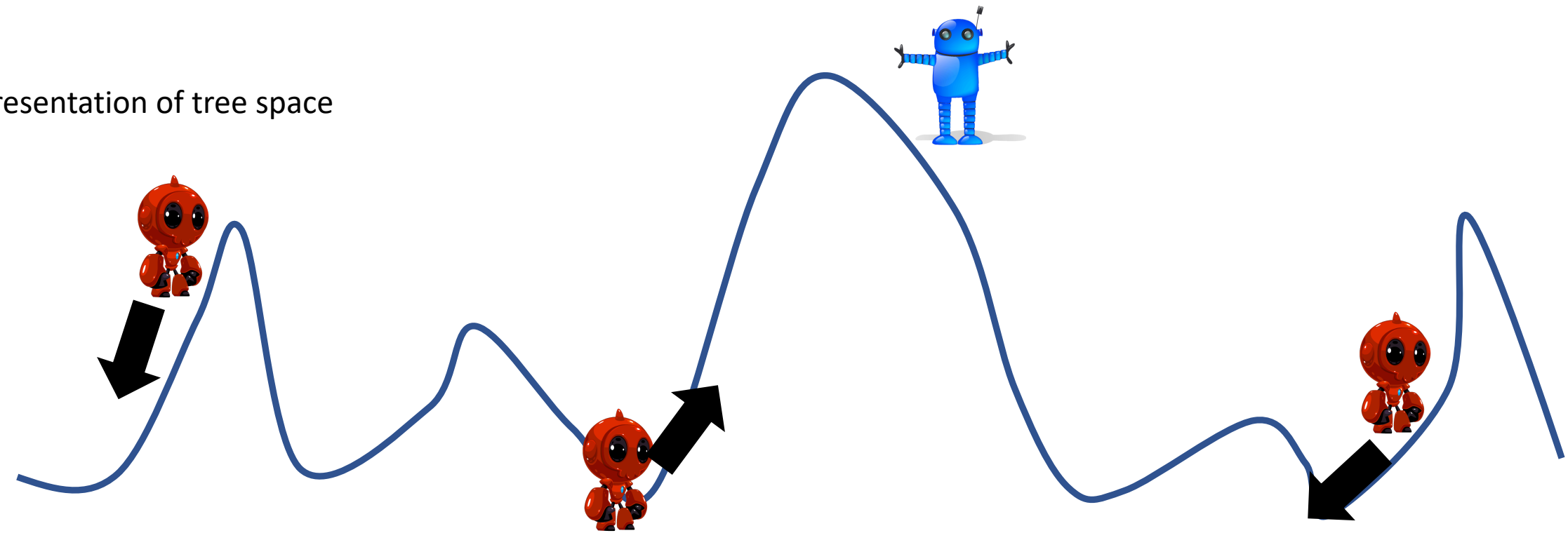
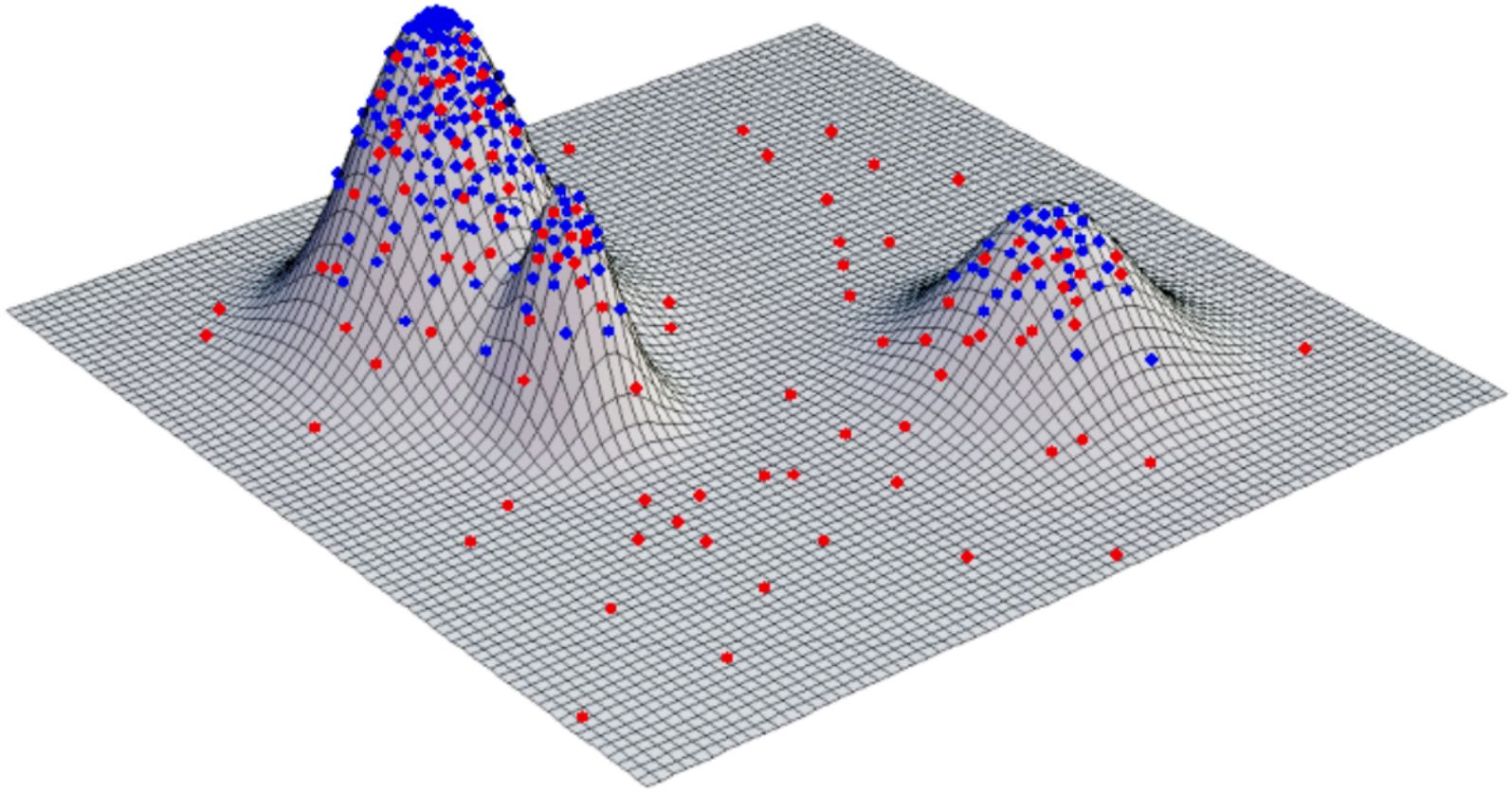
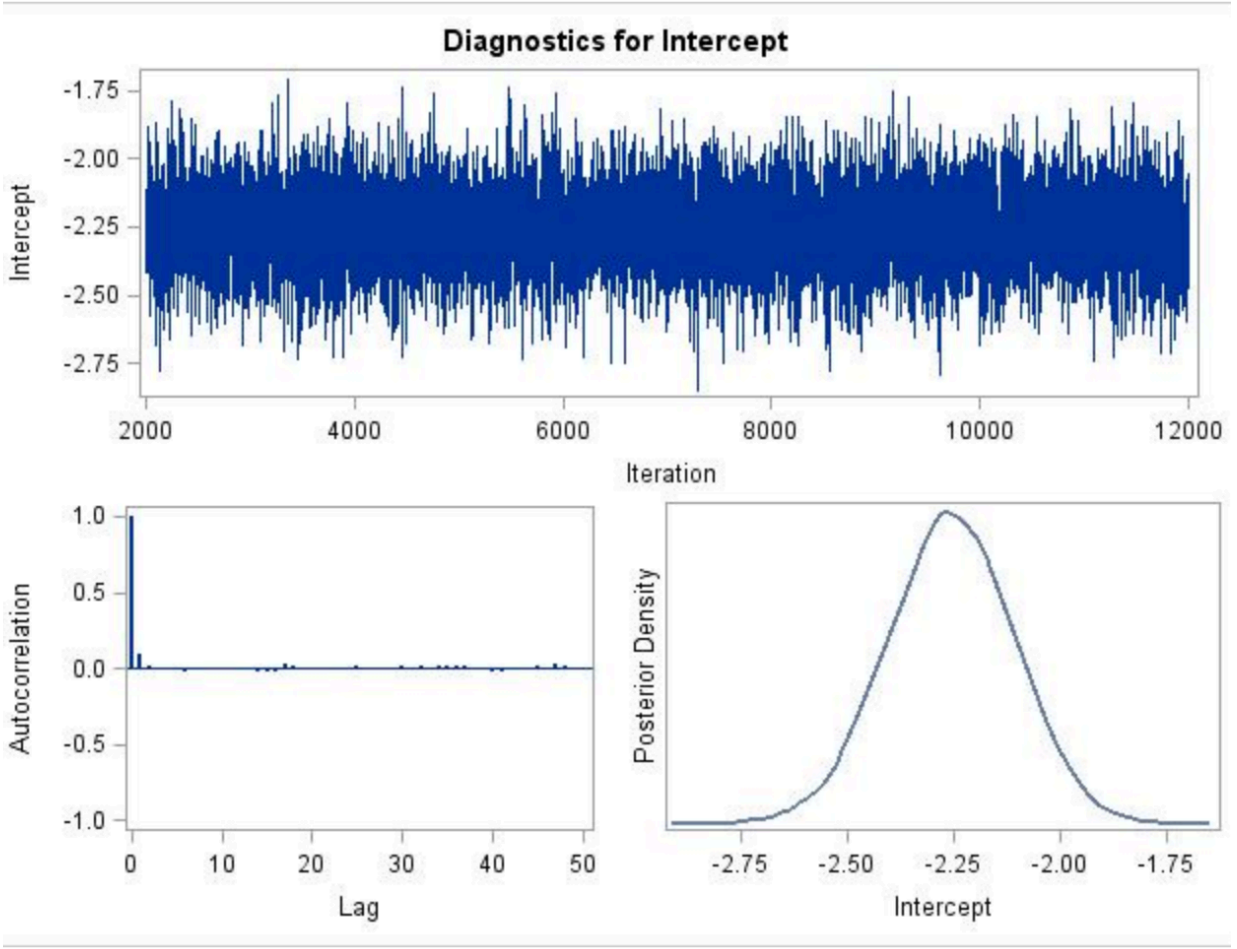


Exploration of tree space



MCMC

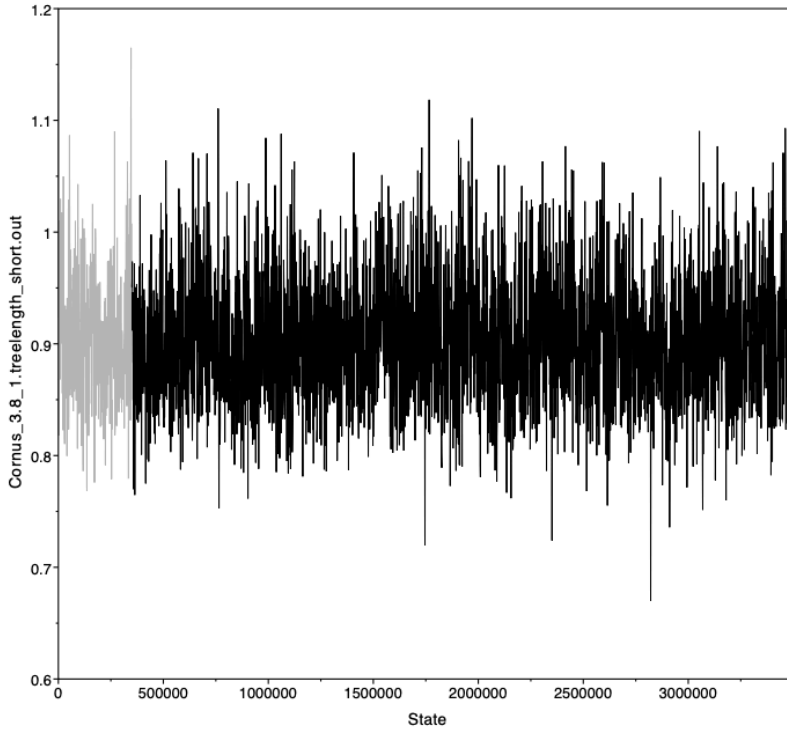
- Yields much larger sample of trees than ML because it produces one tree for every generation versus one tree per tree search
- Trees produced are highly auto-correlated
  - Sample relatively infrequently and discard trees early in the process
  - Millions of generations required compared to 1,000 bootstrap replicates to explore tree space



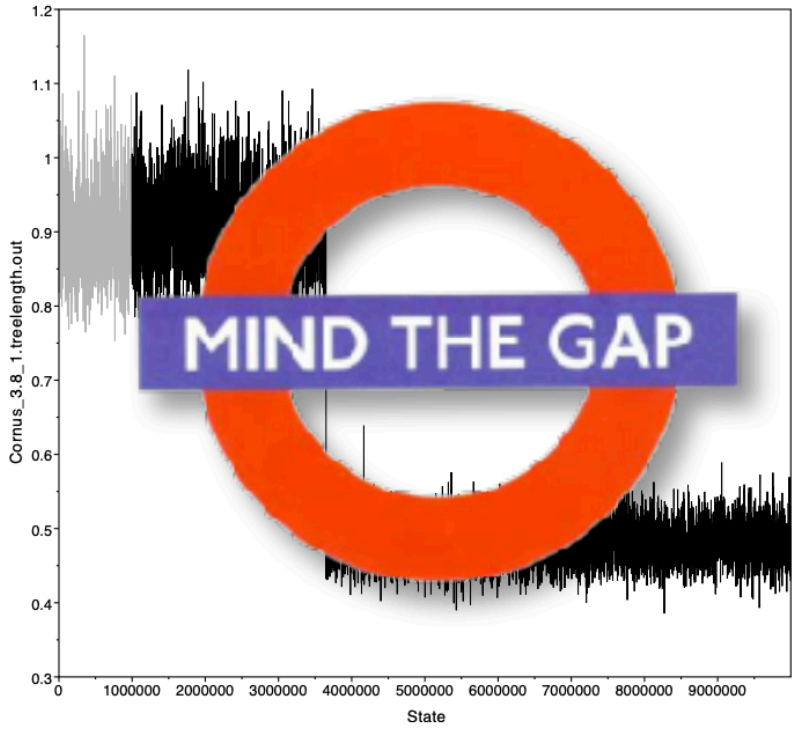
How the run may look

Tracer run after a Bayesian run

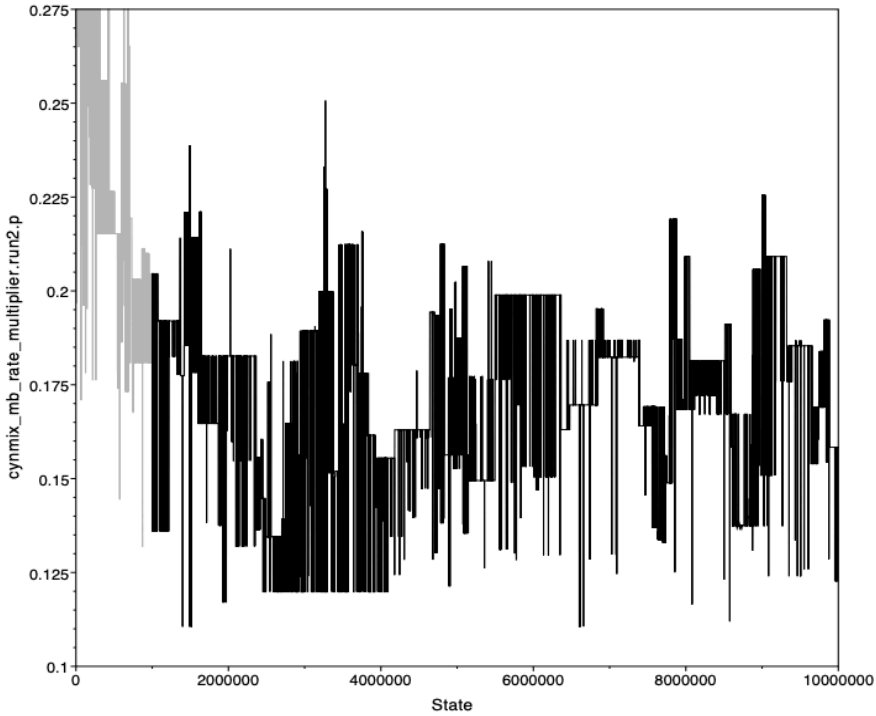
all looks good...



until it doesn't



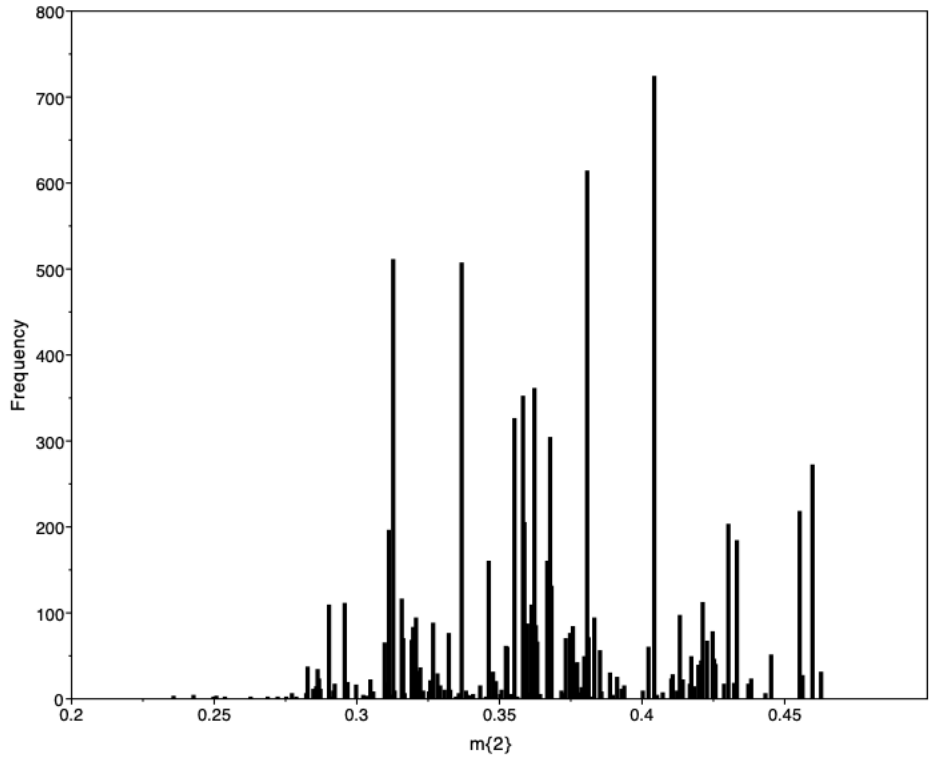
bad mixing



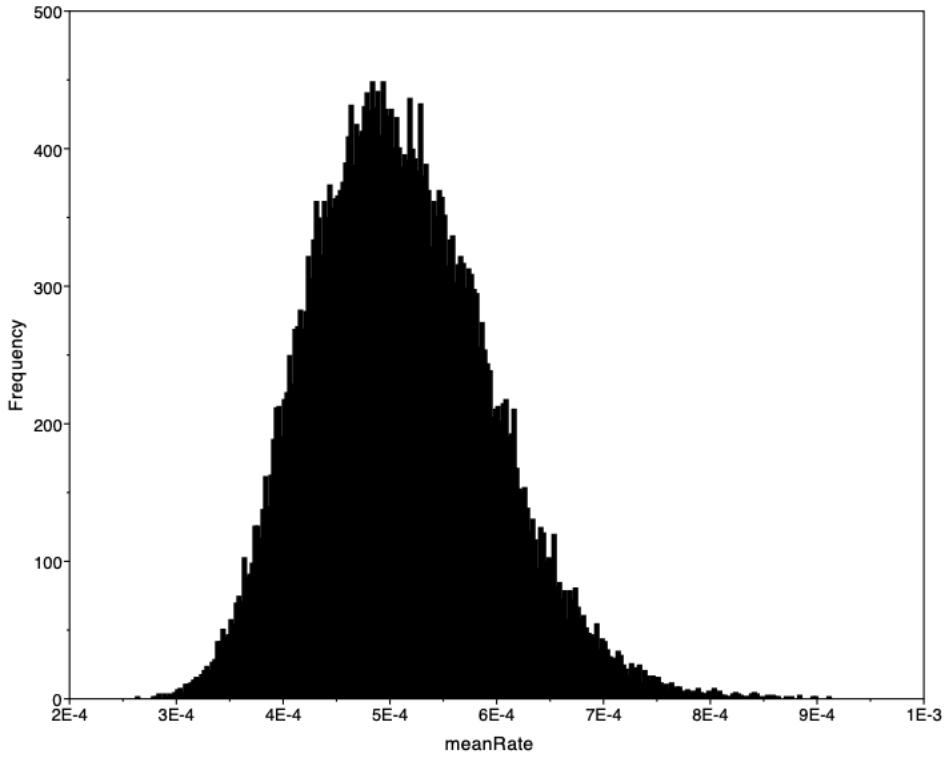
How the run may look

Posterior estimates of parameters

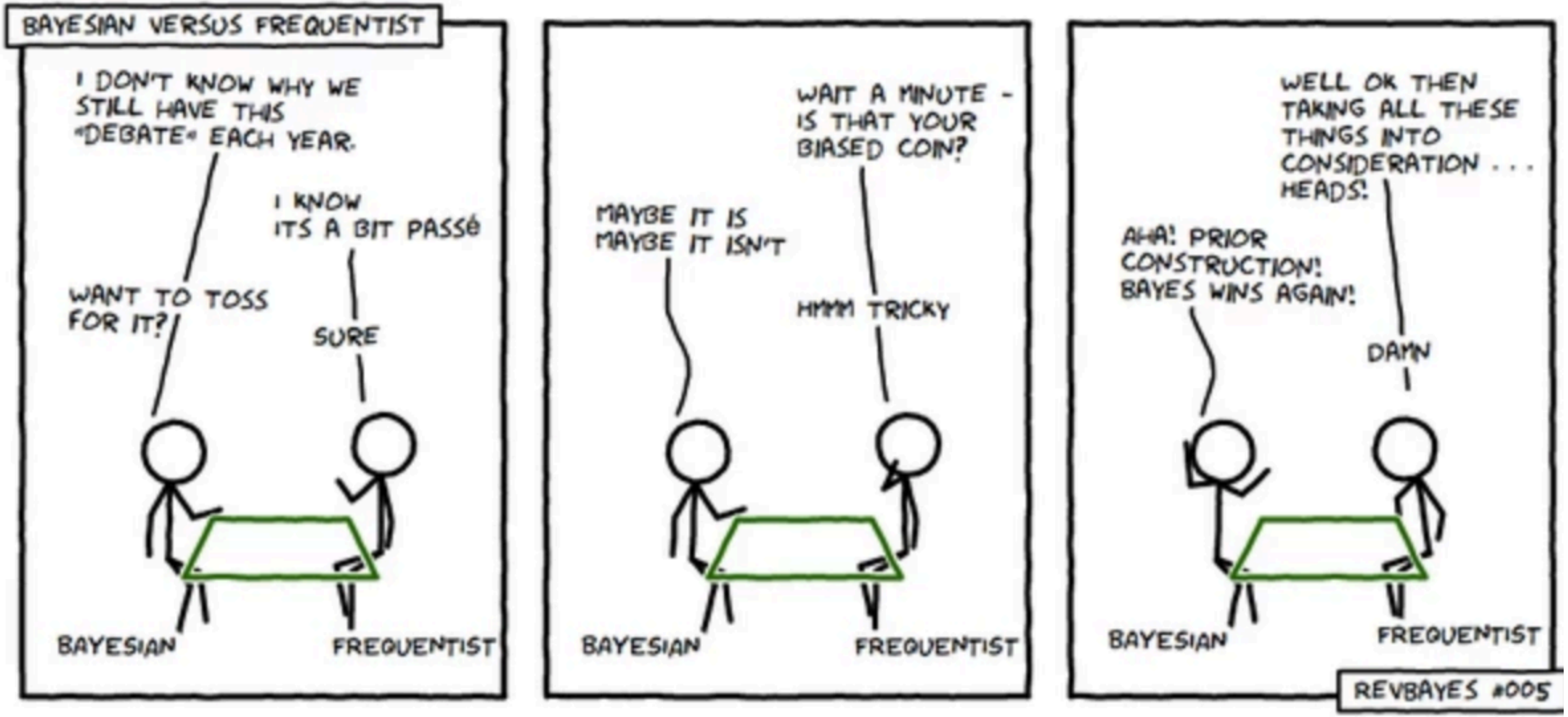
bad mixing



better mixing



Bayesian humor



slides adapted from Jacob B. Landis