Computational Biology

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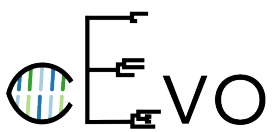
Computational Evolution
Department of Biosystems Science and Engineering

HS 2019



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- Suppose you had a tree inferred using present-day samples from a population that experienced a severe bottleneck in its recent past. How and why would this bottleneck likely affect our ability to infer ancestral population dynamics?
- Imagine spreading a Wright-Fisher population across islands in an archipelago, so that movement between the islands is restricted but within each island the population is "well-mixed". Qualitatively, how would you expect this population structure to influence estimates of the effective population size?

One of us has a birthday tomorrow. . . who?





	Jérémie	Jūlija	Tanja	Tim	Carsten
Prior					
Posterior					

We assign a probability to each column such that the row adds up to 1!

Lessons learned from the birthday guessing

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- You obtained data from me.
- You had an implicit "model" in your head. Using this model and the data you updated your starting assumptions to obtain your final belief.
- Everyone received the same facts about each of us, i.e. gets the same data. However your initial assumptions and the models may differ, thus your final beliefs differ.

How would we apply this to phylogenetics?

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- We would then obtain and analyze sequencing data leading to a posterior distribution of trees & model parameters.
- If we received more data, we could use the knowledge obtained from the first analysis as the starting point for the analysis of the new data.

How can we make this kind of procedure quantitative?

What do we mean by "probability"?

Frequency Interpretation

For this interpretation, probabilities are **relative frequencies of outcomes of repeatable random experiments**.

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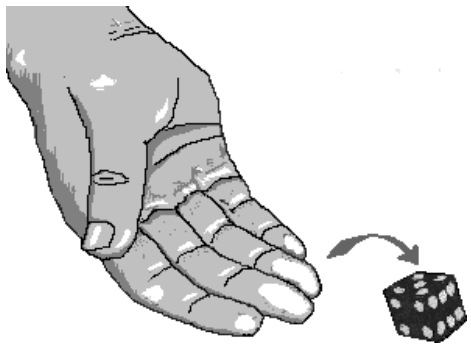

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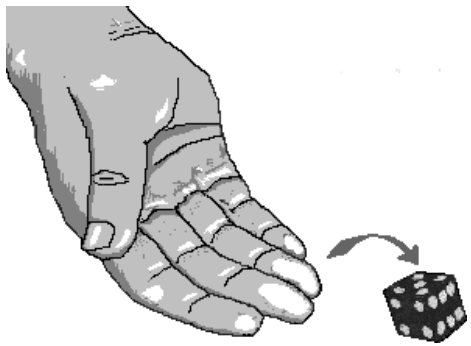

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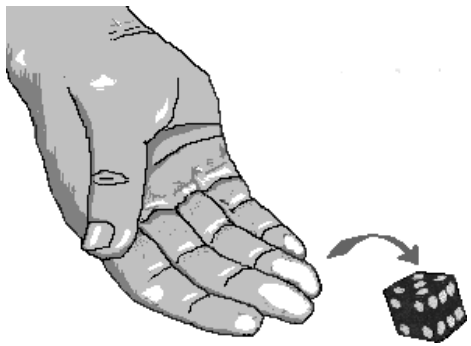

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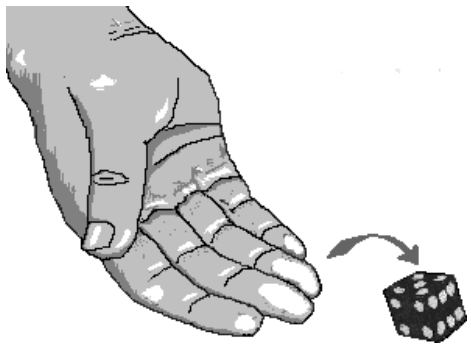

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- Probabilities treated as an intrinsic property of the system.
- Inference of model parameters is treated as a fundamentally distinct problem to the prediction of outcomes.

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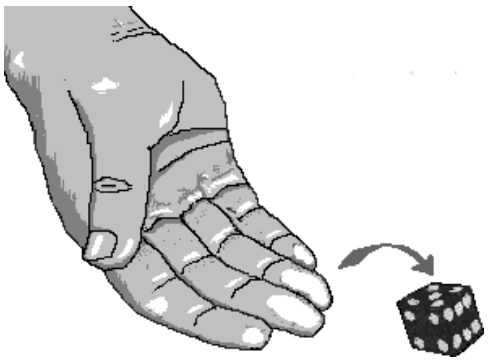

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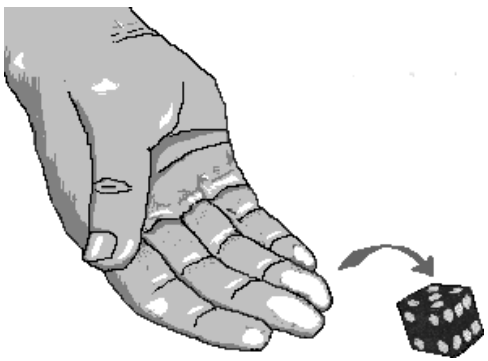

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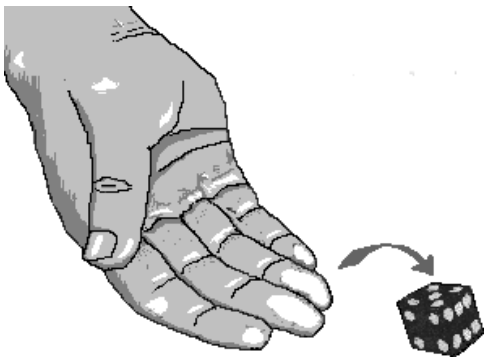

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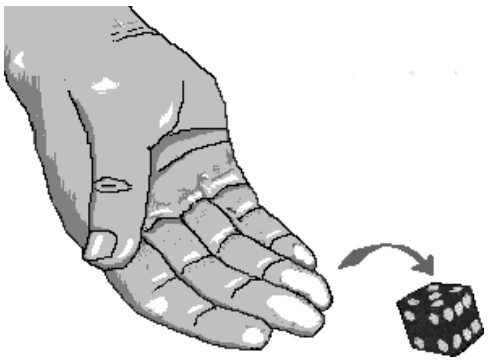

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Example confusing statement: $\mathrm{P}(\mathrm{N}|\mathrm{N} > 0.5)$. How could this be written more carefully?

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However, note that $f(x)$ may exceed 1!

Example: Inference of genetic distance

These two sequences are separated by an unknown genetic distance, $\mathbf{d}$:

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The Jukes-Cantor transition probabilities for each site are a function of the random variable $\mathbf{d}$:

$$\mathbf{p}_{ij}(\mathbf{d}) = \begin{cases} \frac{1}{4} + \frac{3}{4}\exp\left(-\frac{4}{3}\mathbf{d}\right) & \text{if } \mathbf{i} = \mathbf{j} \\ \frac{1}{4} - \frac{1}{4}\exp\left(-\frac{4}{3}\mathbf{d}\right) & \text{if } \mathbf{i} \neq \mathbf{j} \end{cases},$$

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$$\mathrm{P}[\mathrm{S}|\mathrm{d}, \mathrm{L}] = \left[\frac{1}{4} + \frac{3}{4}\exp\left(-\frac{4}{3}\mathrm{d}\right)\right]^{\mathrm{L}-S} \times \left[\frac{1}{4} - \frac{1}{4}\exp\left(-\frac{4}{3}\mathrm{d}\right)\right]^{S}$$

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This is precisely what we want to know!

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$\mathrm{P}(\mathbf{d}|\mathrm{L}, \mathrm{M}) = \mathrm{P}(\mathbf{d}|\mathrm{M})$ quantifies knowledge of $\mathbf{d}$ in the absence of the observation, while $\mathrm{P}(S|\mathrm{L}, \mathrm{M})$ is the distribution over possible numbers of segregating sites given the JC69 model and any independent knowledge of $\mathbf{d}$.

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Here we assume that our prior information is only that $0 \leqslant \mathrm{d} \leqslant 3$, so we take

$$\mathrm{P}(\mathrm{d}|\mathrm{M}) = \begin{cases} \frac{1}{3} & \text{for } 0 \leqslant \mathrm{d} \leqslant 3 \\ 0 & \text{otherwise} \end{cases} \tag{1}$$

(i.e. a uniform distribution between 0 and 3).

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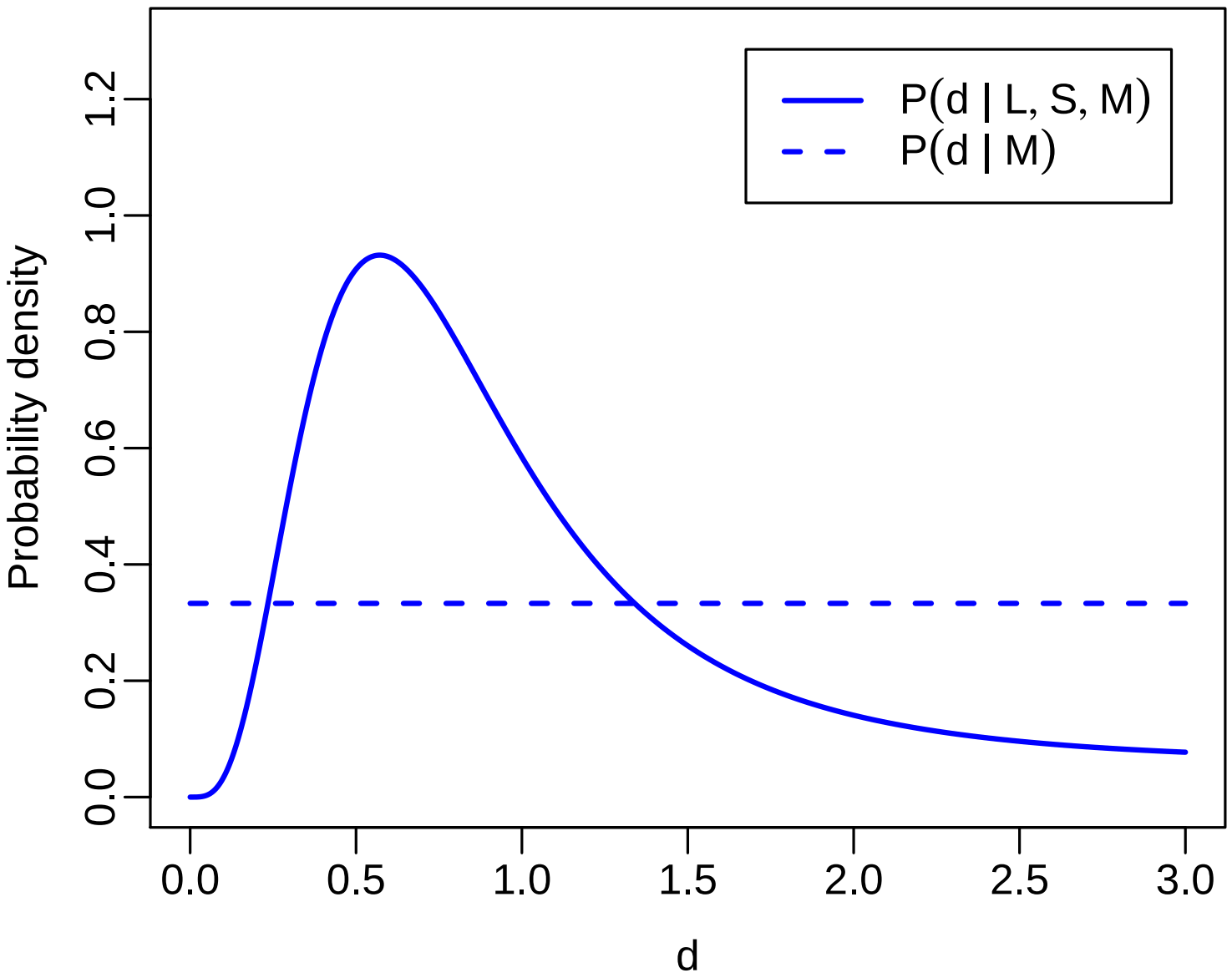

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- $P(\theta_M|D, M)$ is the posterior of the model parameters given the model and the data.

Rev. Thomas Bayes (1701–1761)

- 18th century Presbyterian minister.
- Derived special case of what we now know as Bayes theorem.
- Published in "An Essay towards solving a Problem in the Doctrine of Chances (1763)".

Bayesian updating: including more data

Suppose we acquired sequence data for an additional 90 sites from the same pair of genomes as the original 10 sites. This new alignment has length $\mathrm{L}' = 90$ and differs at $S' = 48$ sites.

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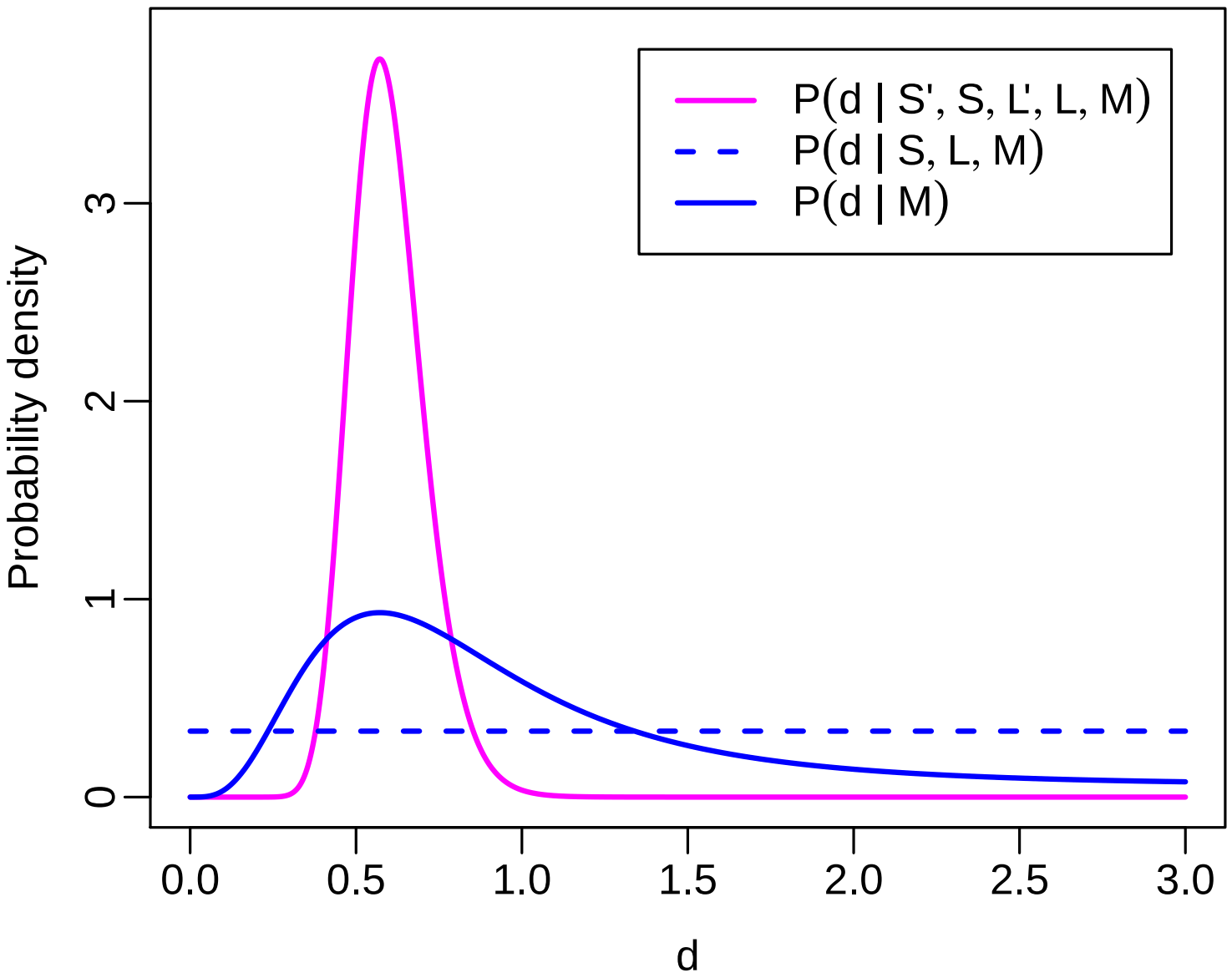
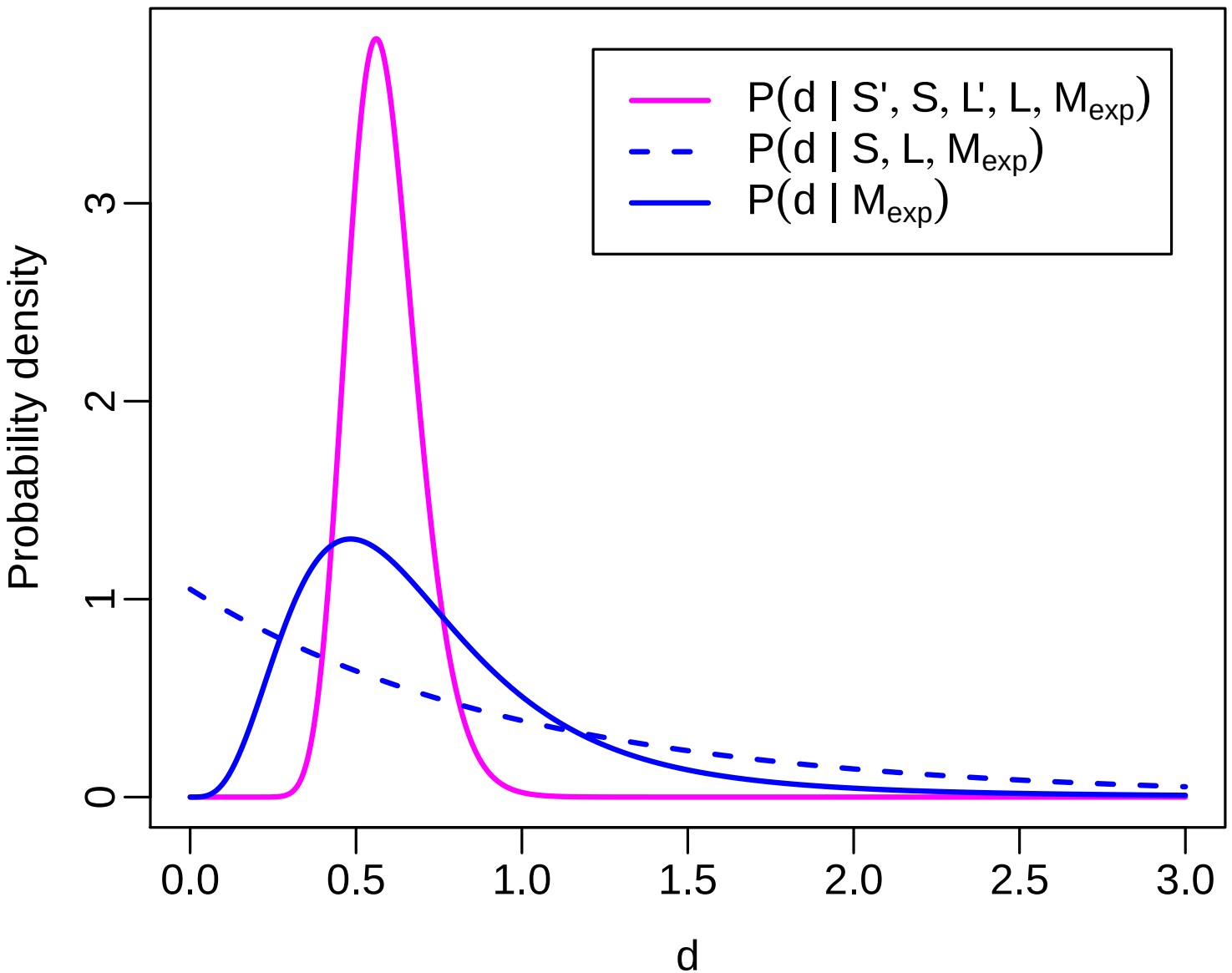
\end{aligned}$$

Equivalent to inferring d *from both data sets simultaneously!*

Bayesian updating: including more data



Using different prior info.: $P(d|M_{exp}) = e^{-d}$



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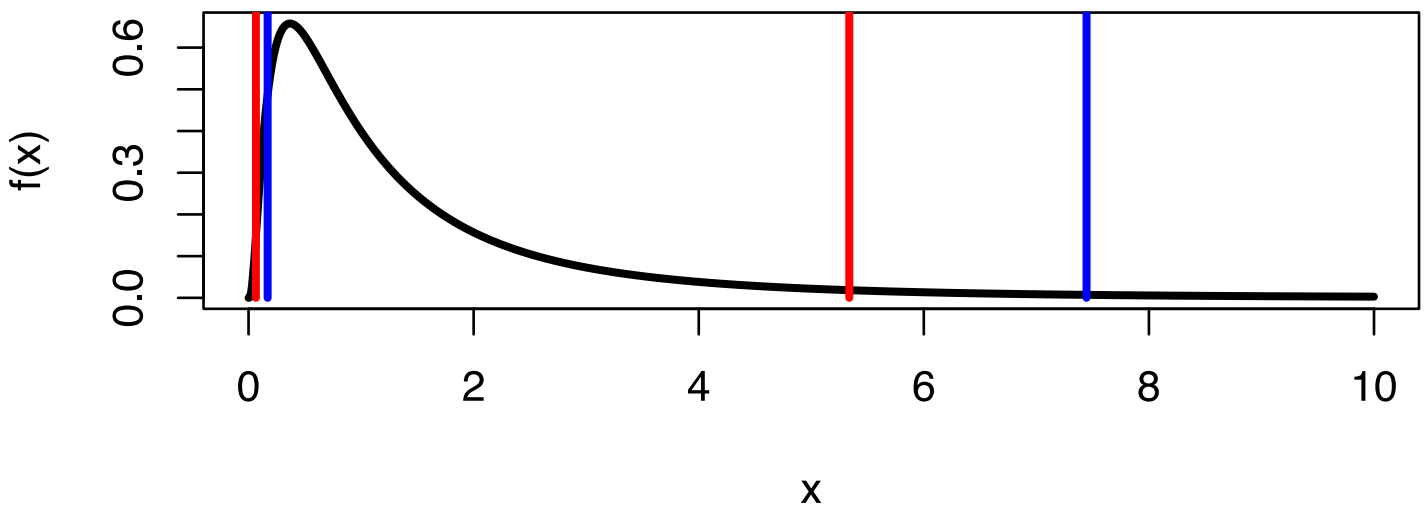
In practice, truly objective prior selection is difficult to achieve.

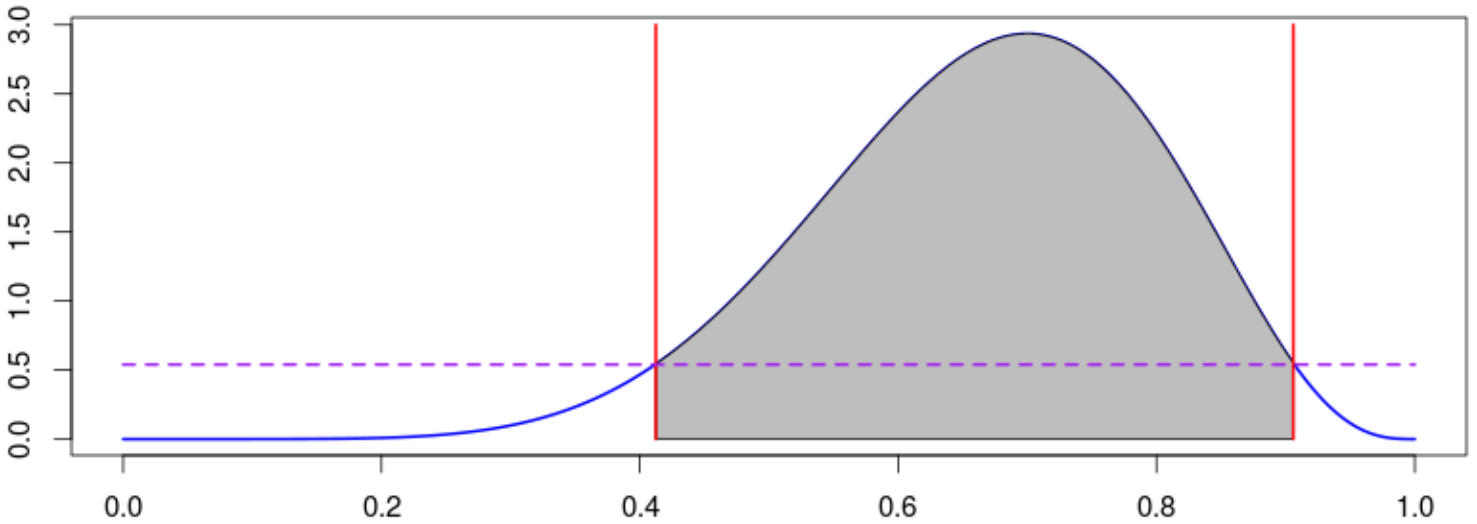
Credible Intervals

The 95 % credible interval is an interval of the posterior distribution containing 95 % of the probability.

- One can neglect 2.5 % of the samples on both ends of the posterior distribution (blue below).
- Often, the smallest interval spanned by 95 % of the samples is chosen (also called highest posterior density (HPD), red below).



Highest posterior density (HPD intervals



- The 95% HPD interval can also be found by lowering a threshold density until the area under the curve where the density exceeds the threshold is 0.95.

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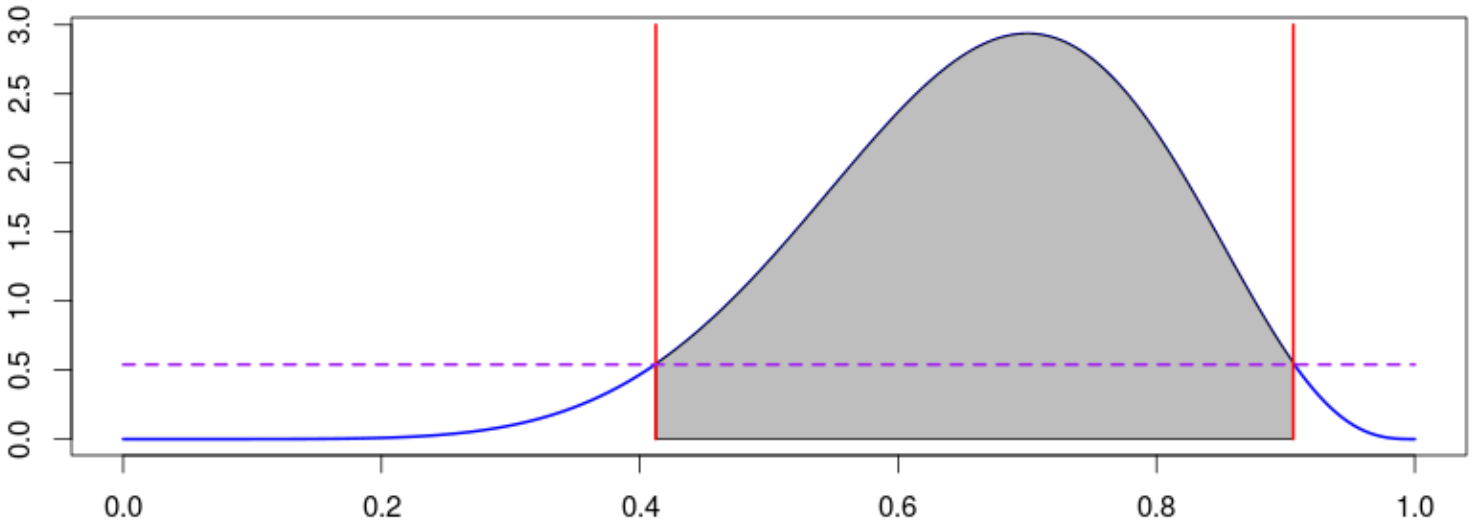

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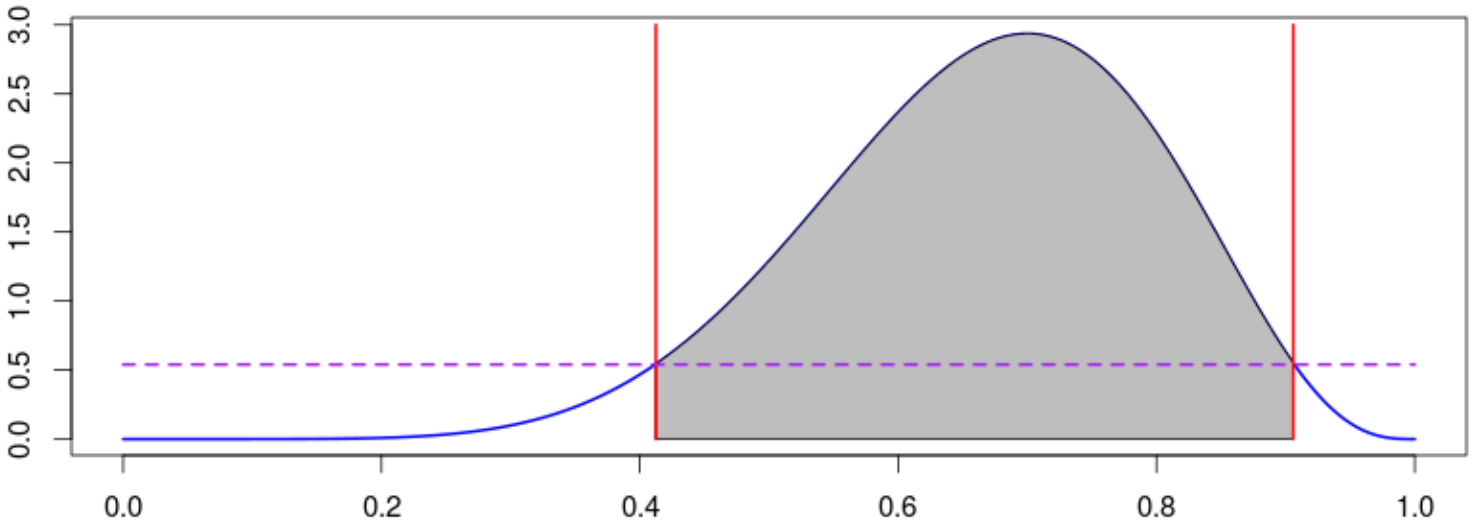

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- The meaning of this interval is simply: the probability of the unknown value falling in this region is 95% **given the observed data**.
- This is different to a 95% *confidence* interval, which is instead an interval produced by a method which generates truth-containing intervals 95% of the time when averaging over **all possible data sets**.

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This is true for most phylogenetic and phylodynamic problems.

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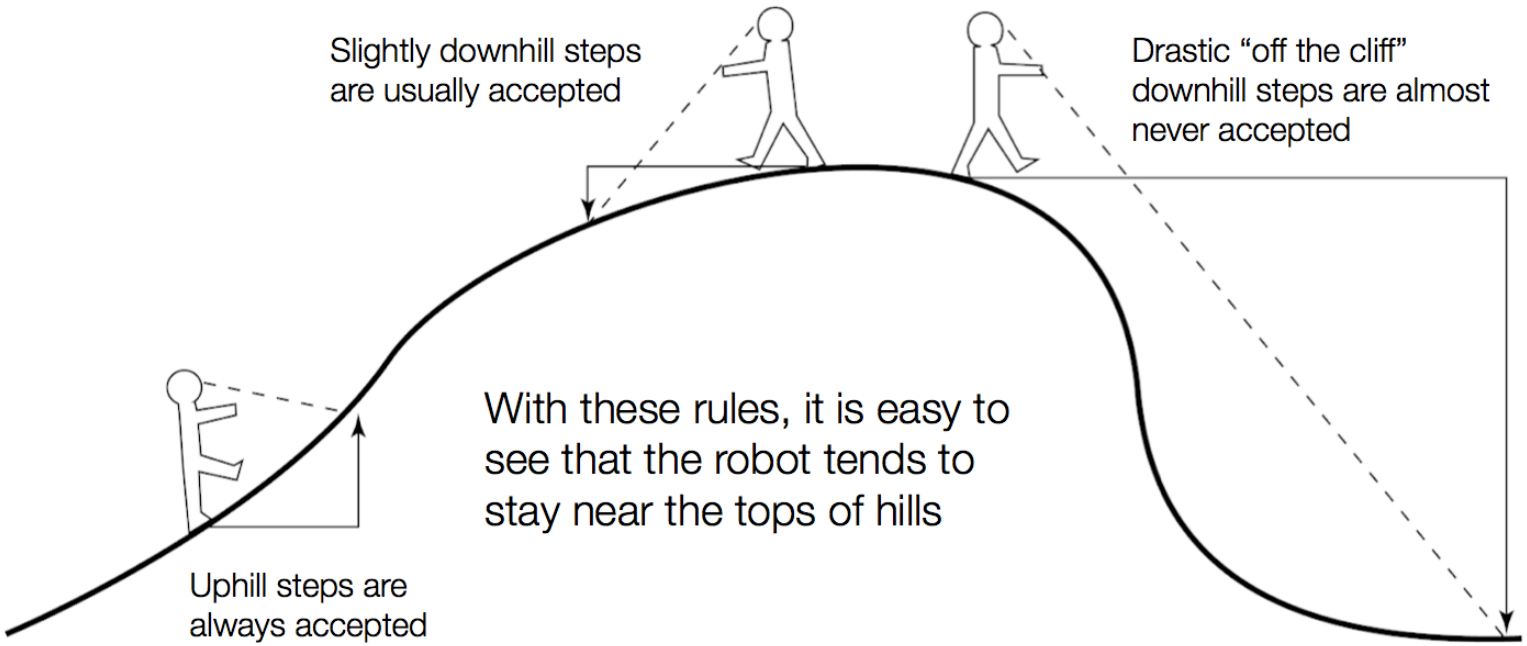
- Usually, the algorithms we deal with seek to produce an arbitrary number of independent samples of possible parameter values θ_M drawn from the posterior distribution $P(\theta_M|D, M)$.
- Markov Chain Monte Carlo is an example of such an algorithm which is extremely popular in Bayesian phylogenetics and phylodynamics.

Markov chain Monte Carlo (MCMC) robot

[courtesy of Paul O Lewis]



The MCMC robot produces a carefully constructed random walk on the domain of the target distribution.

In Bayesian MCMC the target distribution is the posterior distribution $\mathrm{P}(\theta_{\mathrm{M}}|\mathrm{D},\mathrm{M})$.

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Let $\theta_{\mathcal{M}}$ be the current state. Let $\theta'_{\mathcal{M}}$ be a proposed parameter set for the new state.

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- For the proposed parameter set, we calculate

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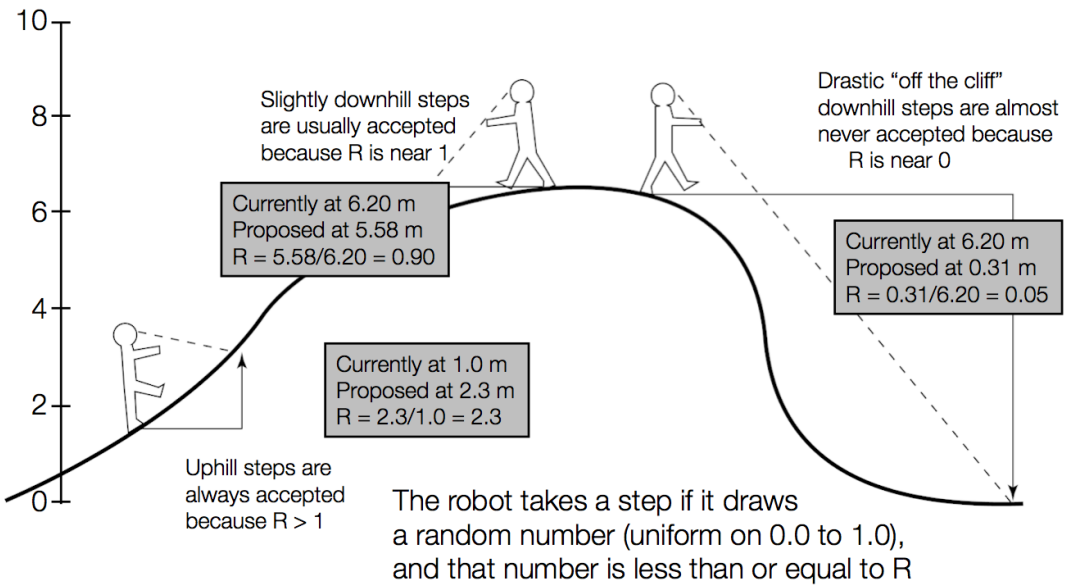

Figure adapted from PO Lewis.

Metropolis-Hastings algorithm

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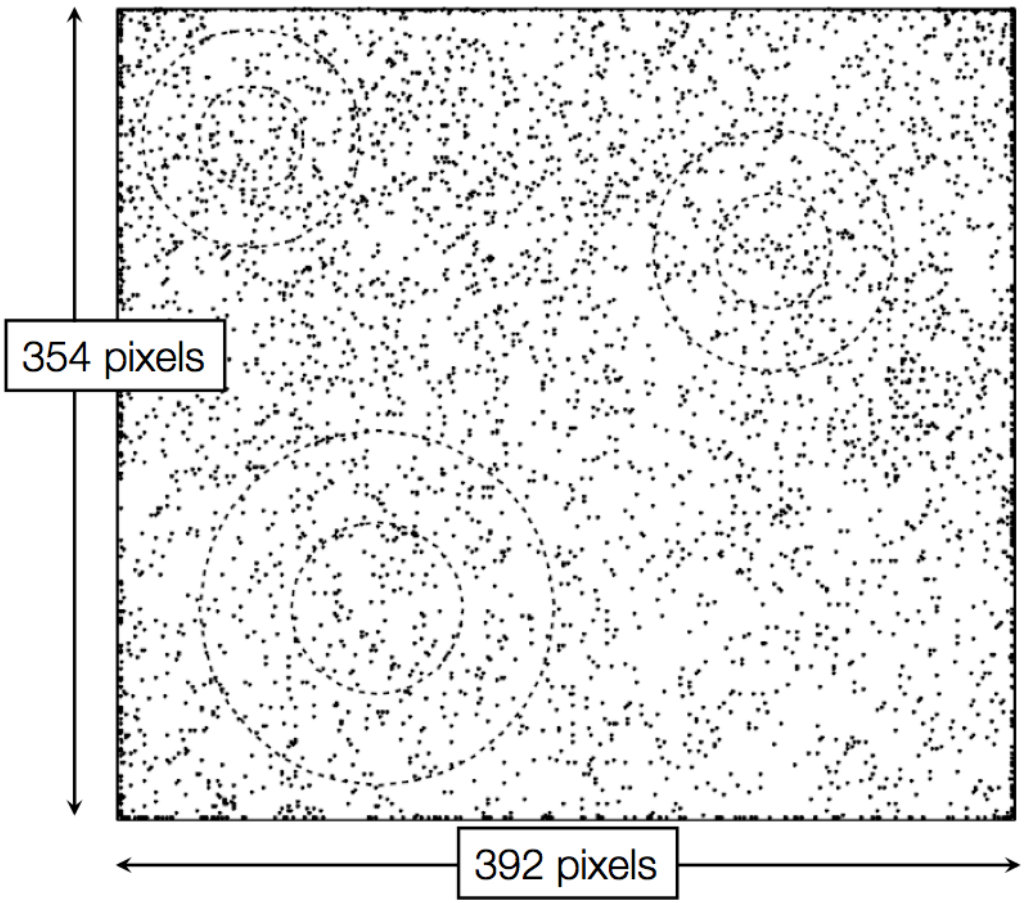
- The Metropolis-Hastings algorithm allows for non-symmetric proposals by using

$$R = \frac{P(\theta'_M|D, M)q(\theta_M|\theta'_M)}{P(\theta_M|D, M)q(\theta'_M|\theta_M)}.$$

Pure Random Walk

[courtesy of Paul O Lewis]



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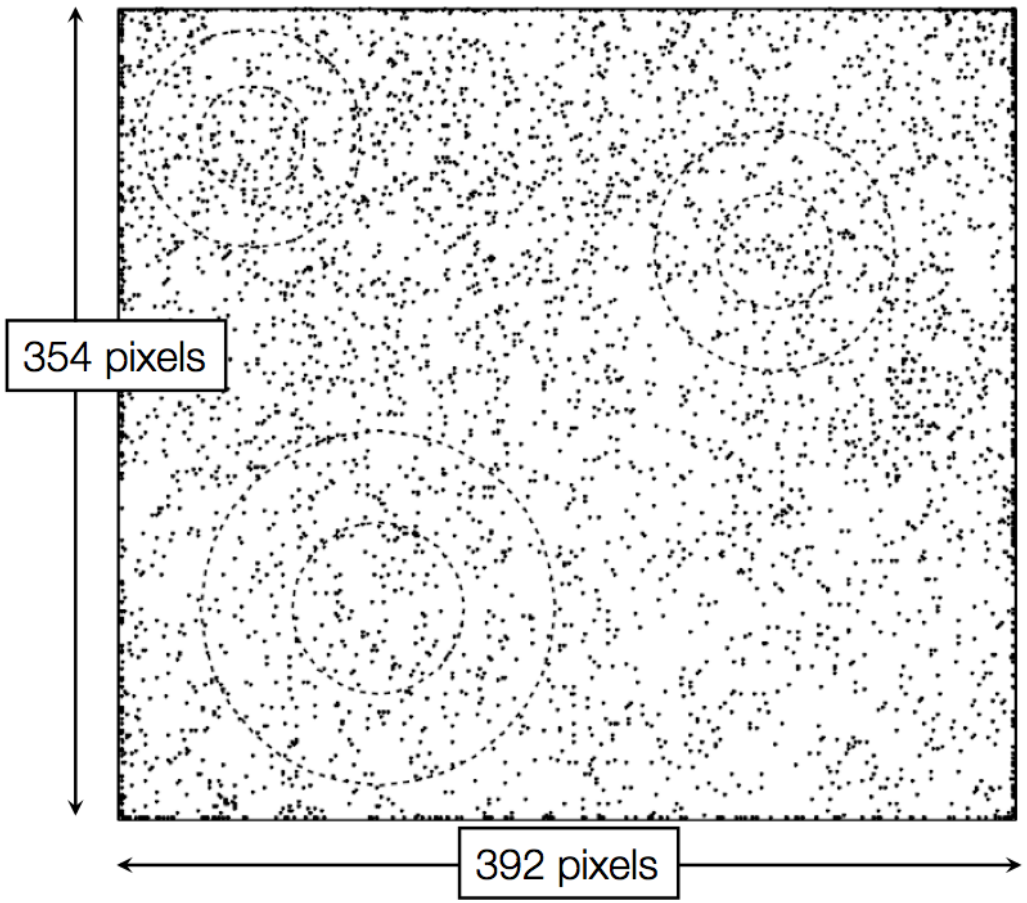

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- reflection at edges

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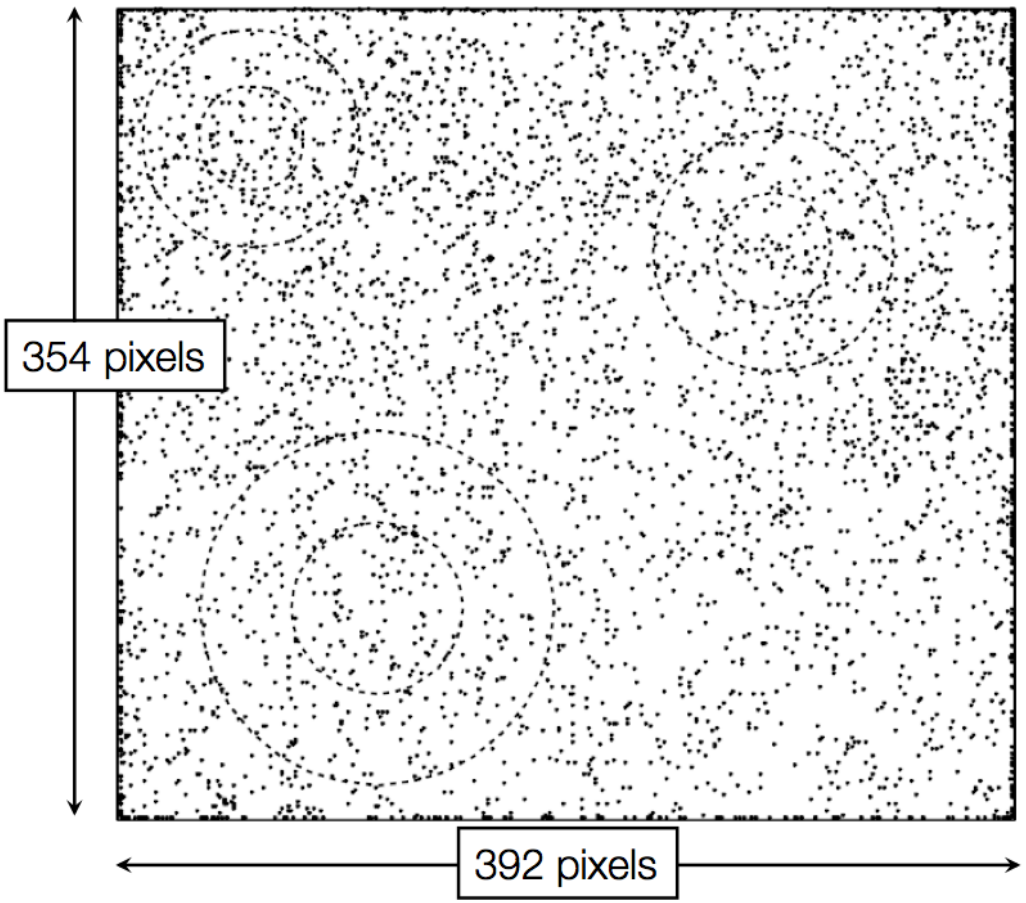

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- reflection at edges

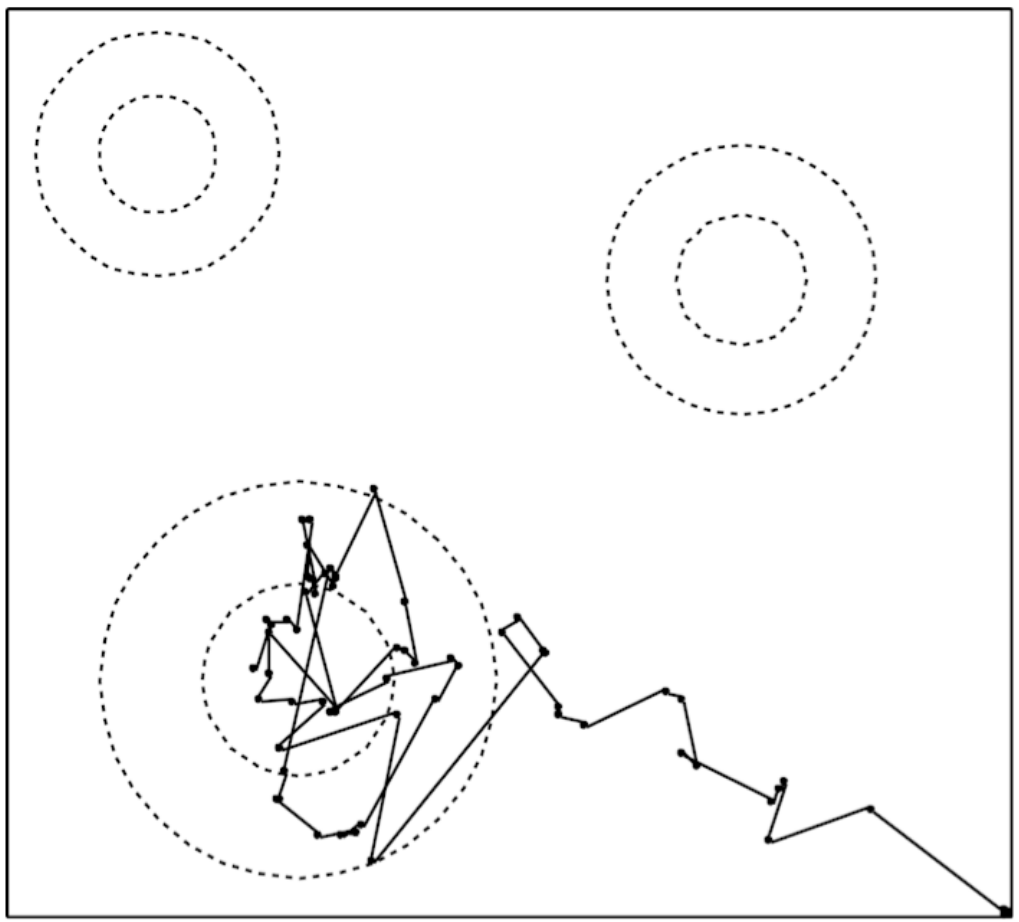
Target distribution:

- equal mixture of 3 bivariate normal "hills"
- inner contours: 50%
- outer contours: 95%

In this case the robot is accepting every step and 5000 steps are shown.

Burn In

[courtesy of Paul O Lewis]



Robot is now following the Metropolis rules and thus quickly finds one of the three hills.

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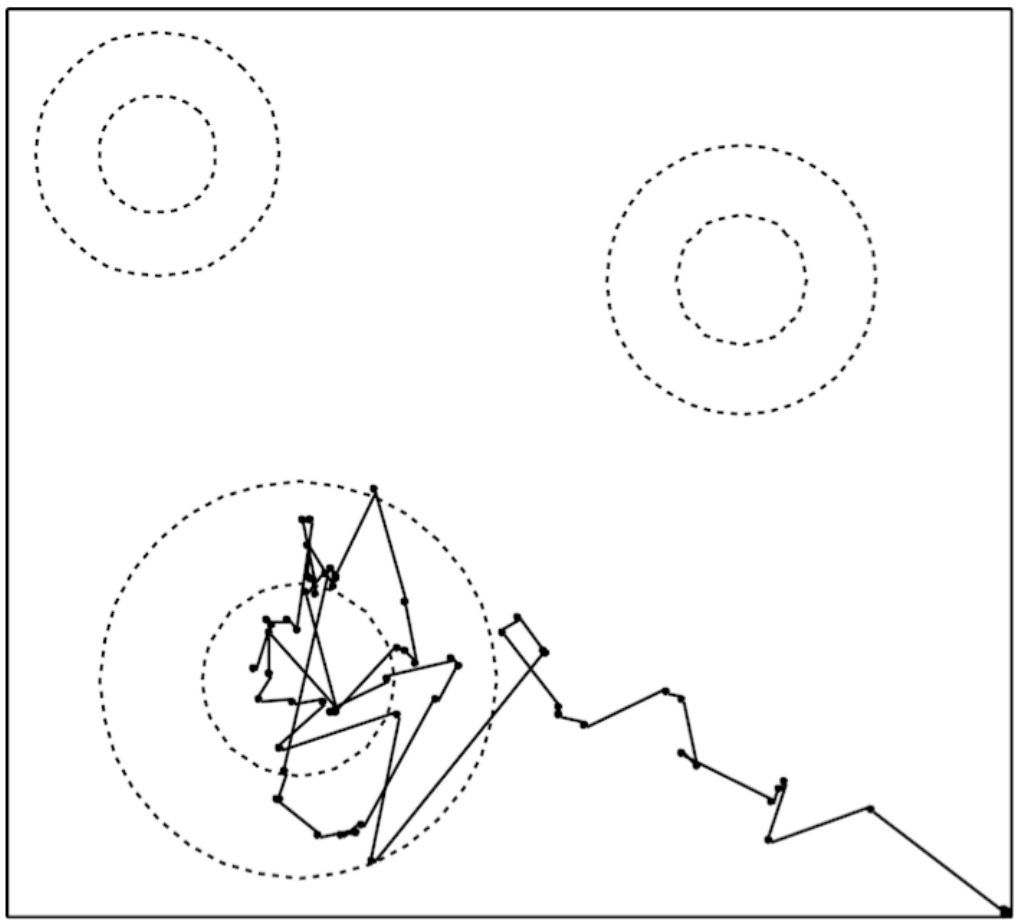

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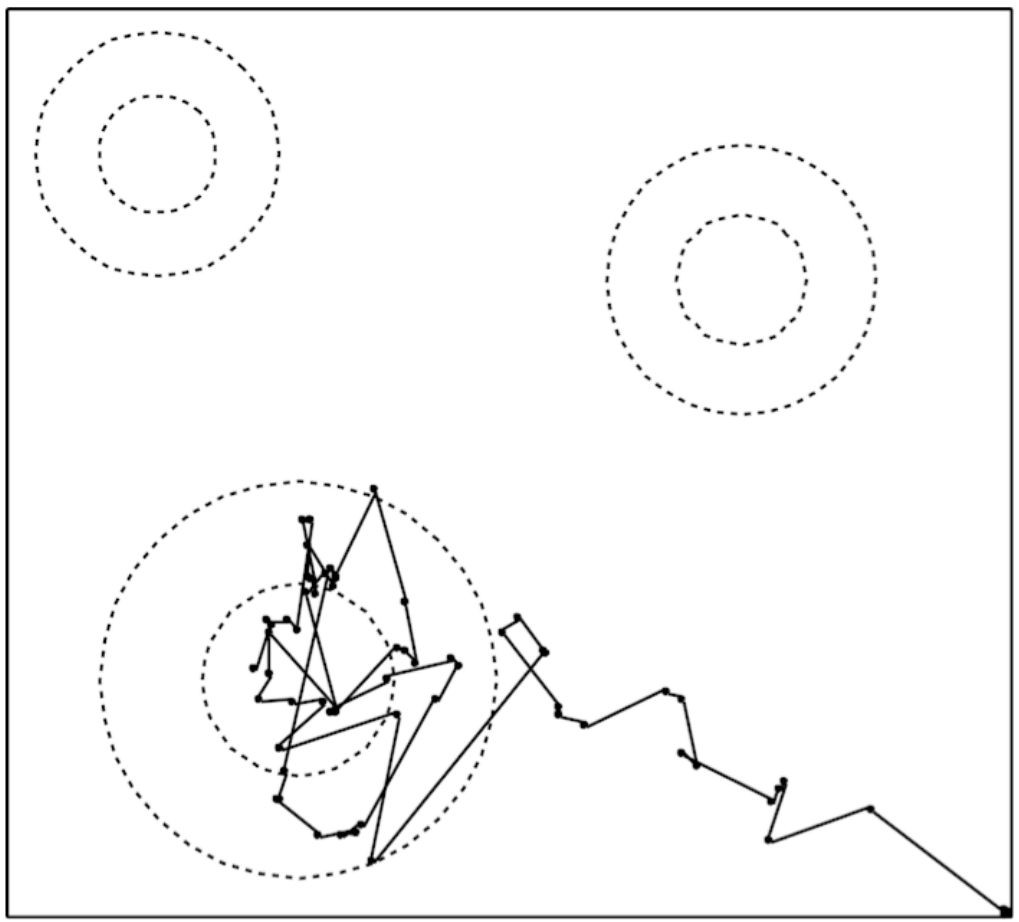

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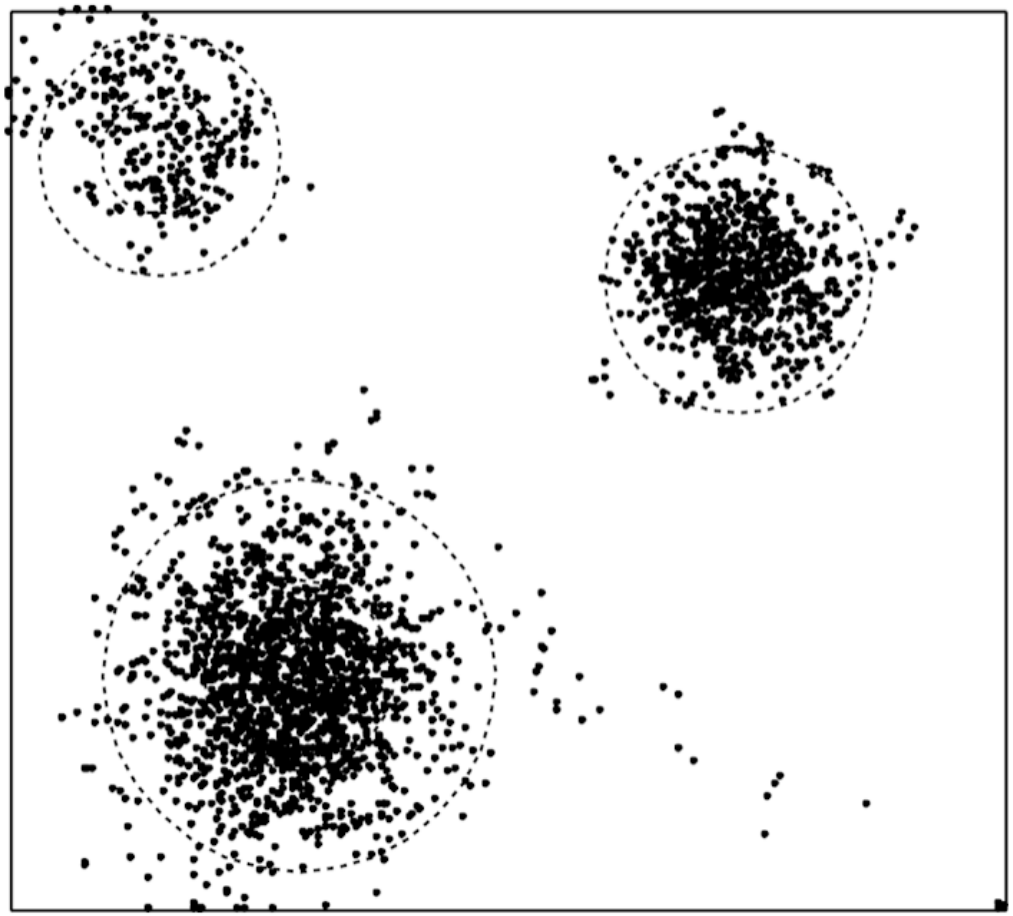
100 steps have been taken since the starting point.

Posterior Distribution Approximation

[courtesy of Paul O Lewis]



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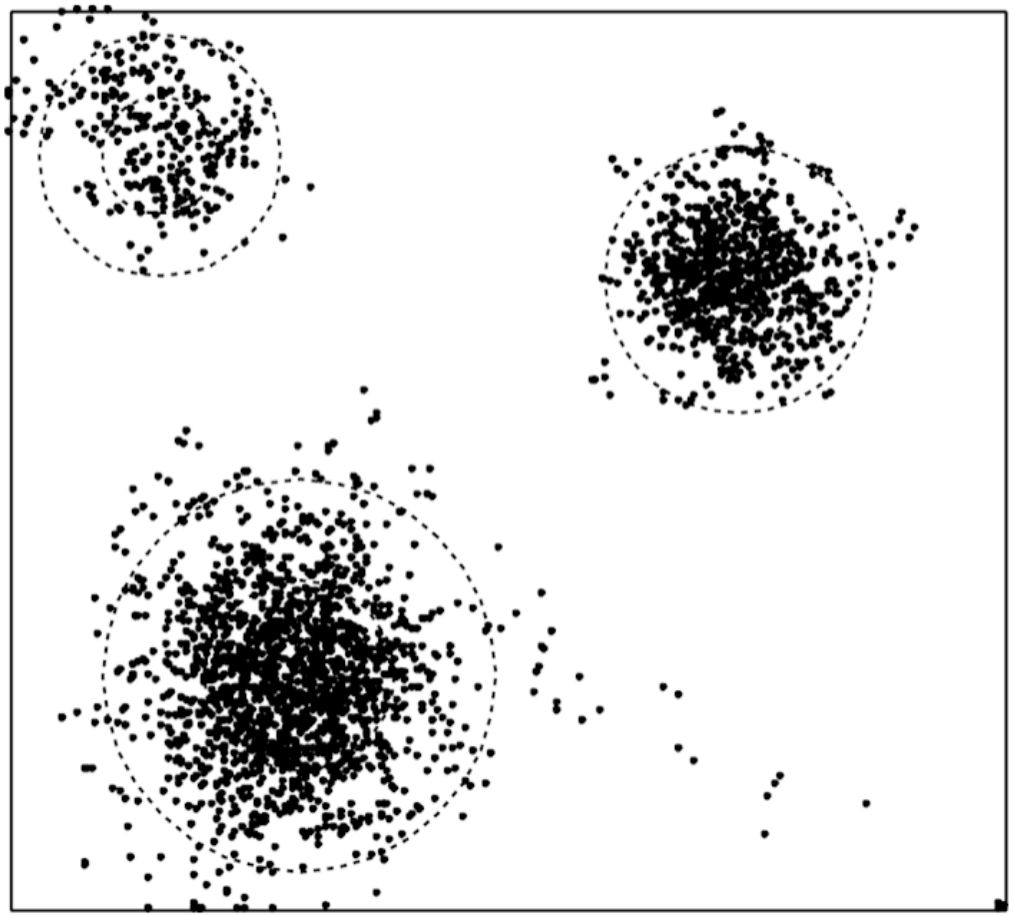

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- 51.2% of points are inside inner contours (cf. 50% actual).
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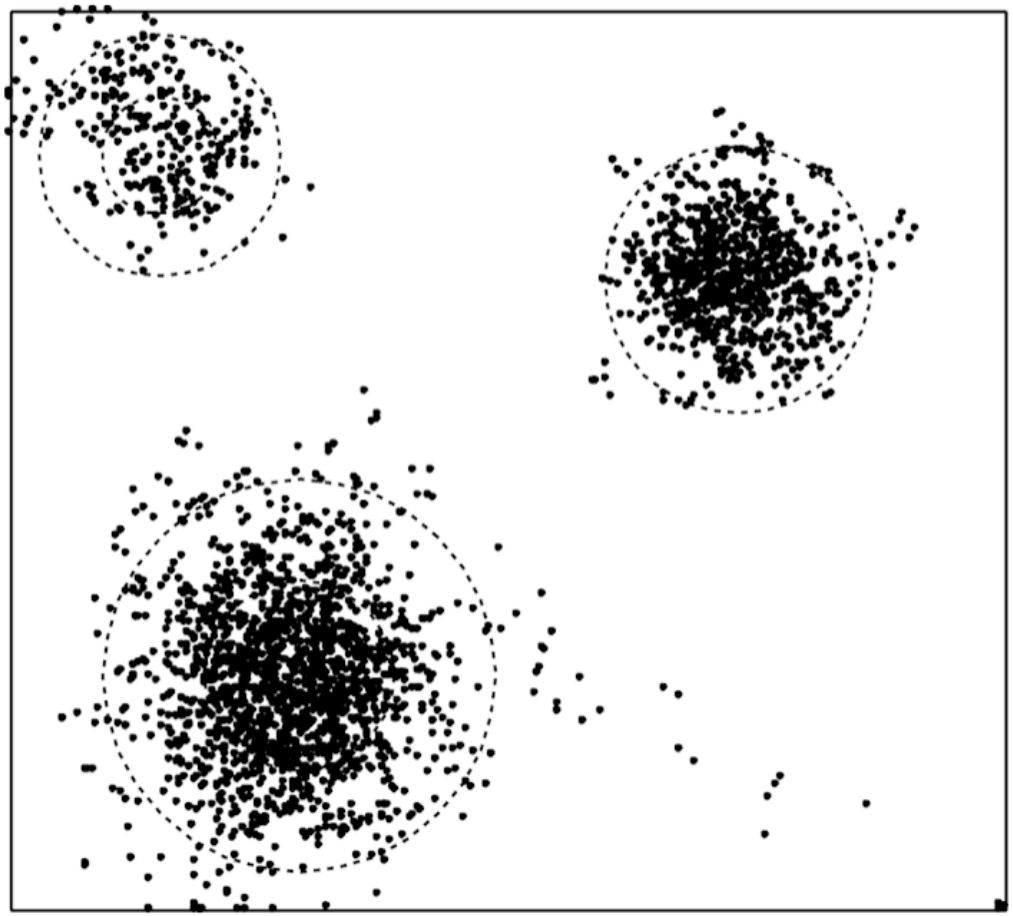

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Approximation gets better the longer the chain is allowed to run.

(here 5000 steps have been taken).

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$$P(A|\tau, Q)$$

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We are doing Bayesian inference though: we need a probability distribution for τ!

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- Resulting posterior distributions naturally include the uncertainty in the inference results.

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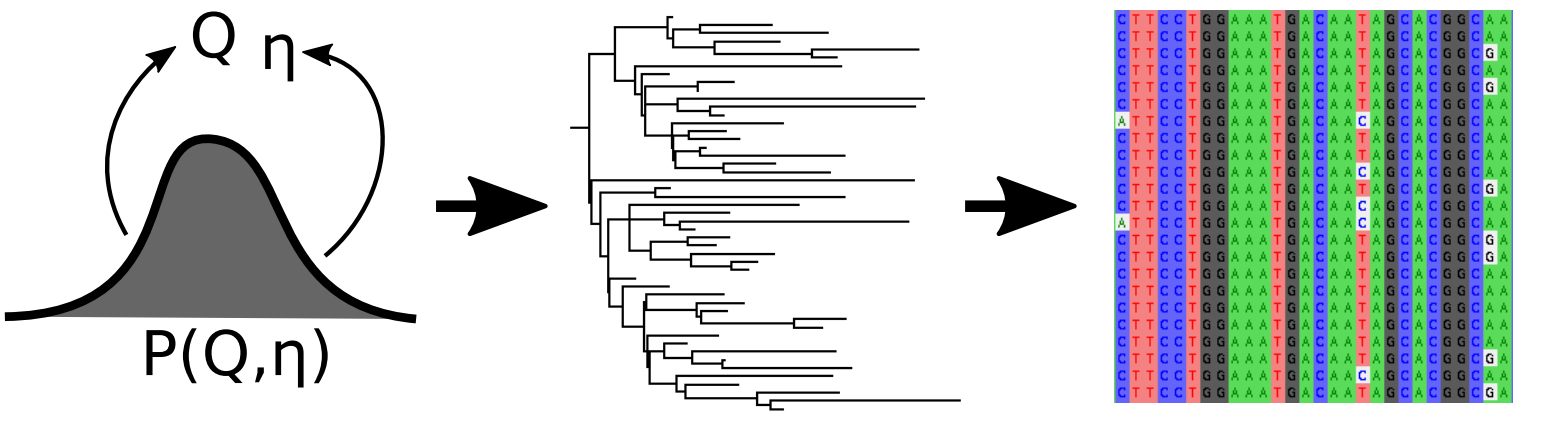

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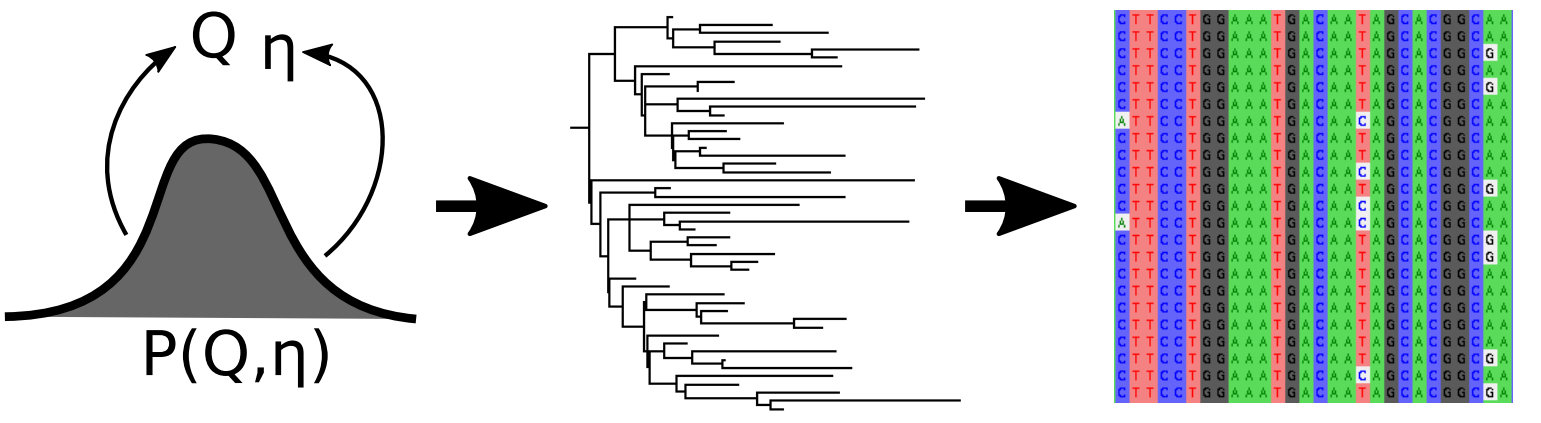

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Separating the process of tree generation from that of sequence evolution implies the sequence evolution is effectively neutral.

MCMC with Metropolis-Hastings algorithm

$$P(\tau, Q, \eta|A) = \frac{1}{P(A)} P(A|\tau, Q) P(\tau|\eta) P(Q, \eta)$$

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- Acceptance/rejection of the new state leads eventually to a set of accepted states which is a sample from the posterior distribution $P(\tau, Q, \eta|D)$.

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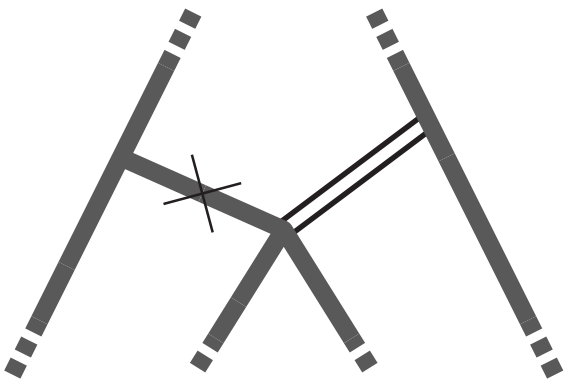
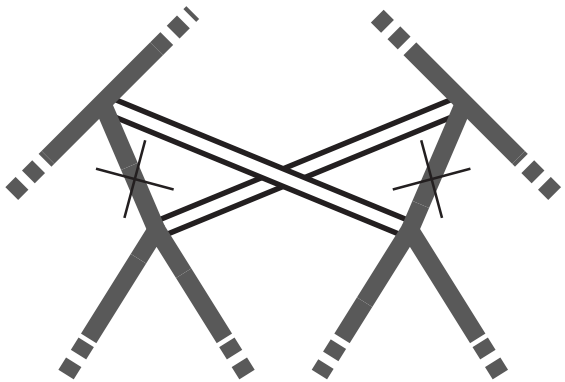
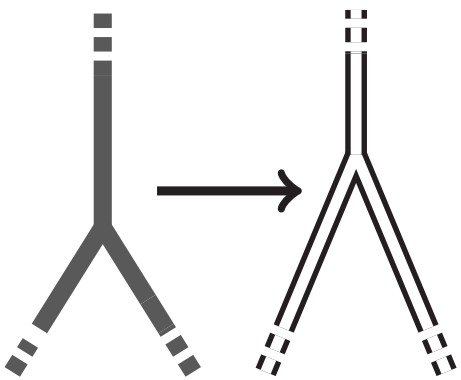
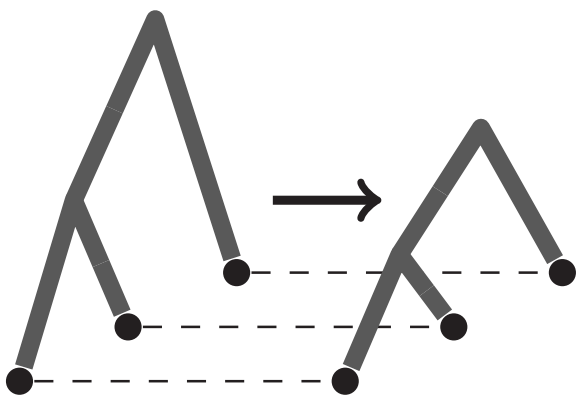


Subtree Exchange





Uniform node height



Tree Scaling

Bayesian phylogenetic inference software

Popular Bayesian phylogenetic inference software:

MrBayes [Huelsenbeck et al., 2001]
Early command-line program for phylogenetic inference.

RevBayes [Höhna et al., 2015]
R-like syntax for specifying phylogenetic models.

BEAST/BEAST2 [Drummond and Rambaut, 2007, Bouckaert et al., 2014, Bouckaert et al., 2019]
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Some software implementing special models:

MIGRATE [Beerli and Felsenstein, 2001]
Performs inference under the Structured Coalescent (accounts for population structure).

ClonalFrame/ClonalOrigin
[Didelot and Falush, 2007, Didelot et al., 2010]
Infers bacterial Ancestral Recombination Graphs (generalization of phylogenetic trees when recombination is present).

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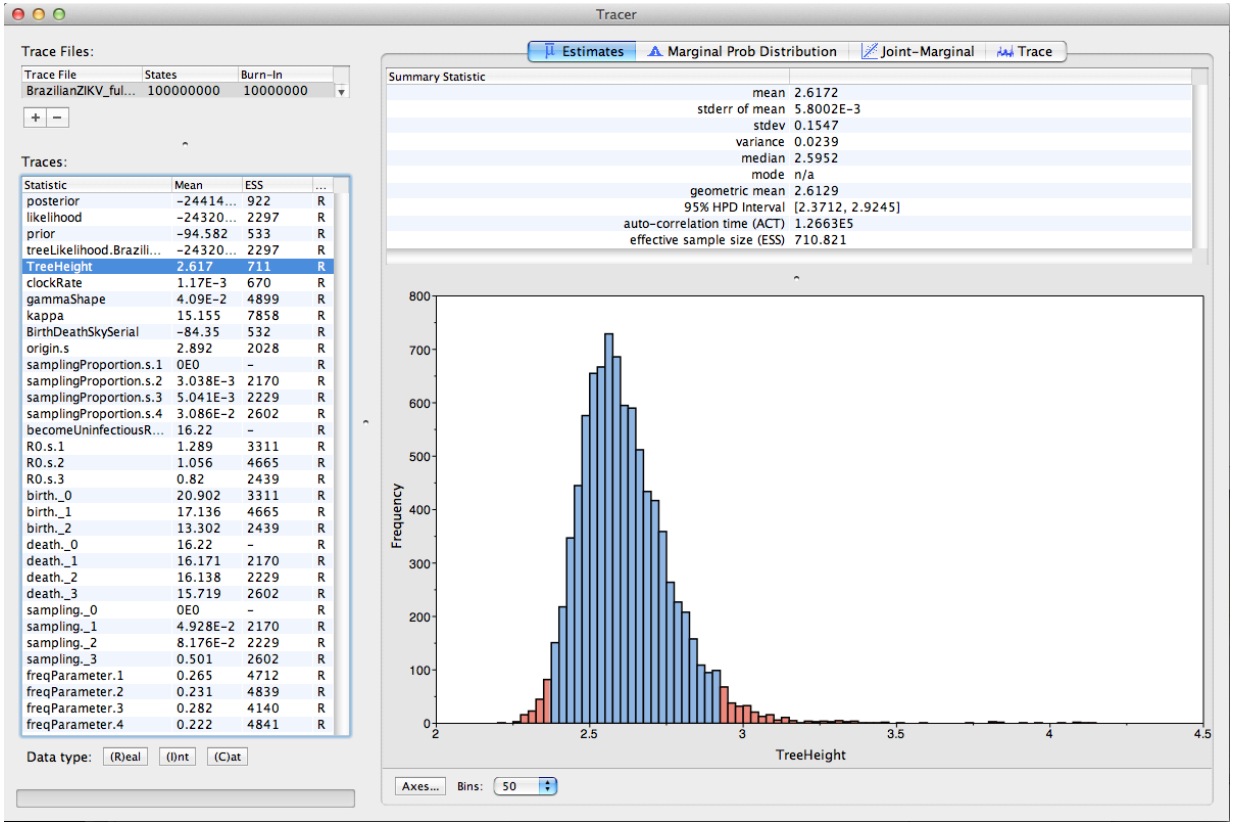
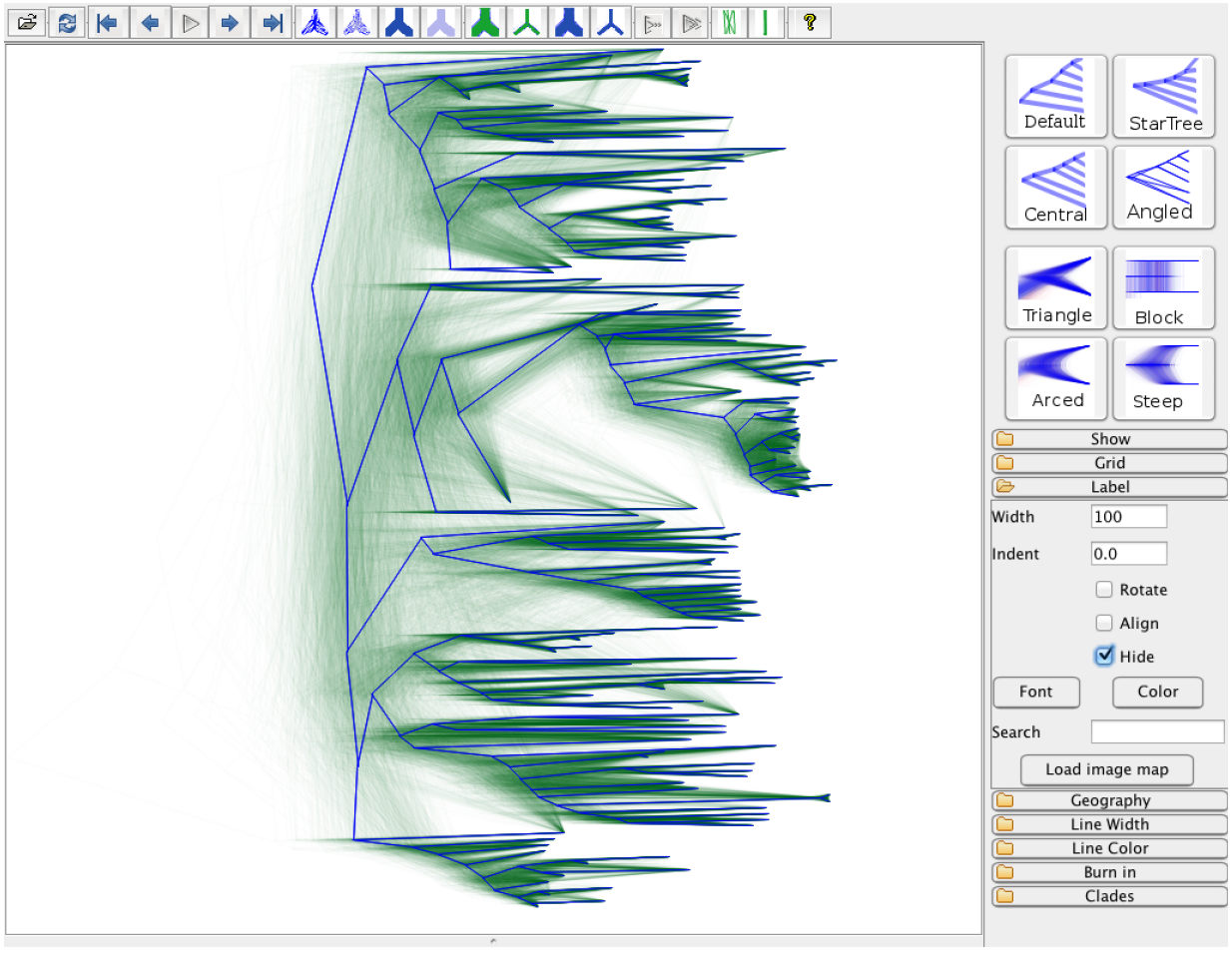
  - A chain of length N will result in N trees and N values for each parameter.

Summarizing the tree height marginal posterior



Posterior distribution of the tree height based on the Zika samples in South America, visualized in Tracer; tree height is the time between the first branching event and the most recent sample.

Summarizing the phylogenetic tree posterior



Posterior distribution of a Zika virus phylogeny , visualized in DensiTree.

Application: quantifying the spread of Ebola

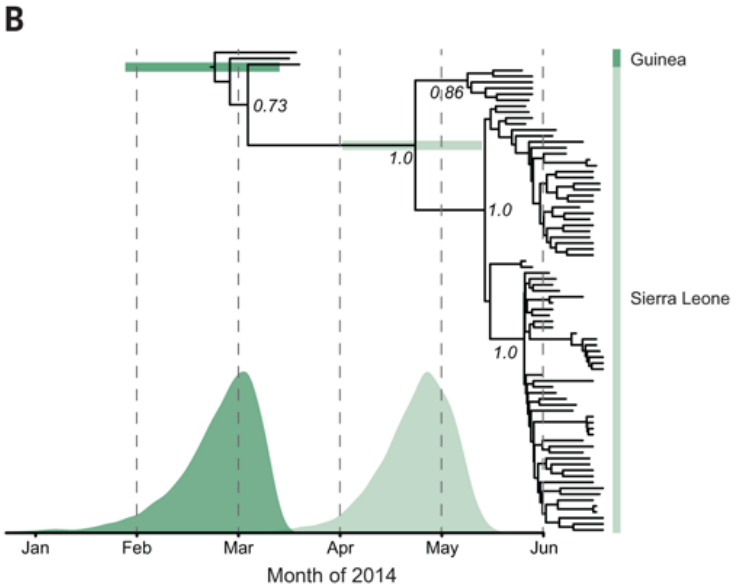


Figure adapted from [Gire et al., 2014]

Phylogenetic tree of Ebola in West Africa.

- [Stadler et al., 2014] obtained the maximum likelihood estimates $\hat{\beta}$ and $\hat{\delta}$ using the phylodynamic likelihood, and estimated $R_0 = \hat{\beta}/\hat{\delta}$ (1.34 (1.12 - 1.55)).

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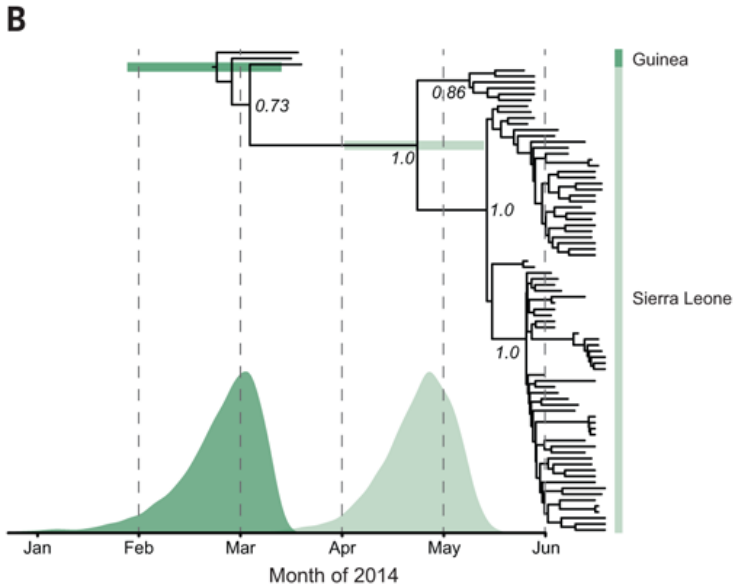

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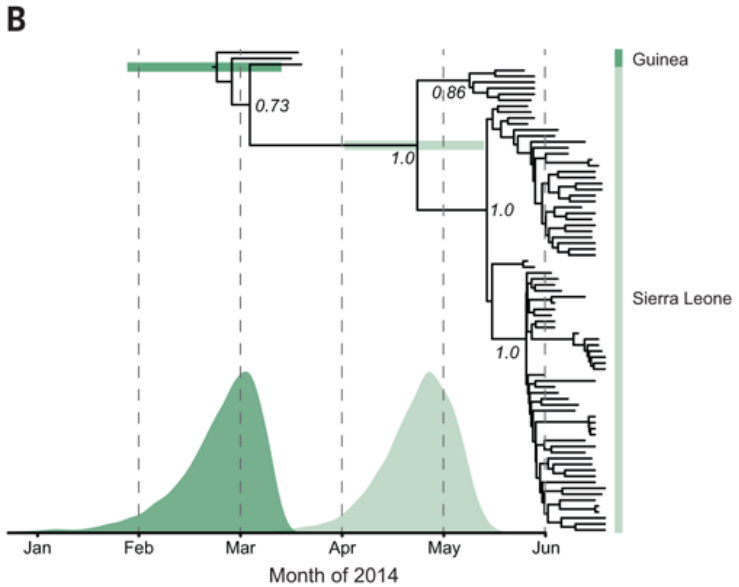

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- Also, ML result does not incorporate prior knowledge of these parameters.

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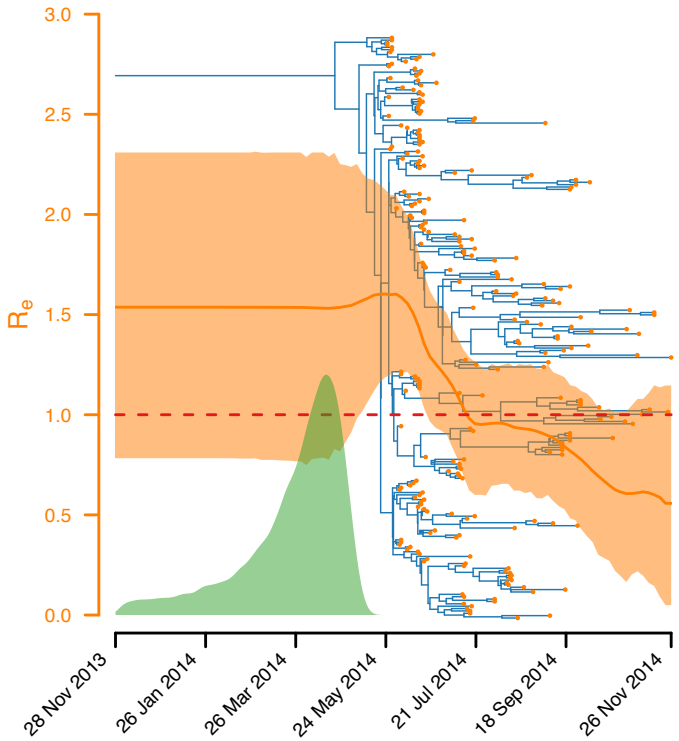

Sierra Leone was first affected by Ebola in the South-East. Here we plot one tree, the posterior distribution of the start of the epidemic, and the median with 95% HPDs for the reproductive number, all obtained from a Bayesian analysis in BEAST2. Analysis performed by Louis du Plessis.

Application: dating the penguin phylogeny

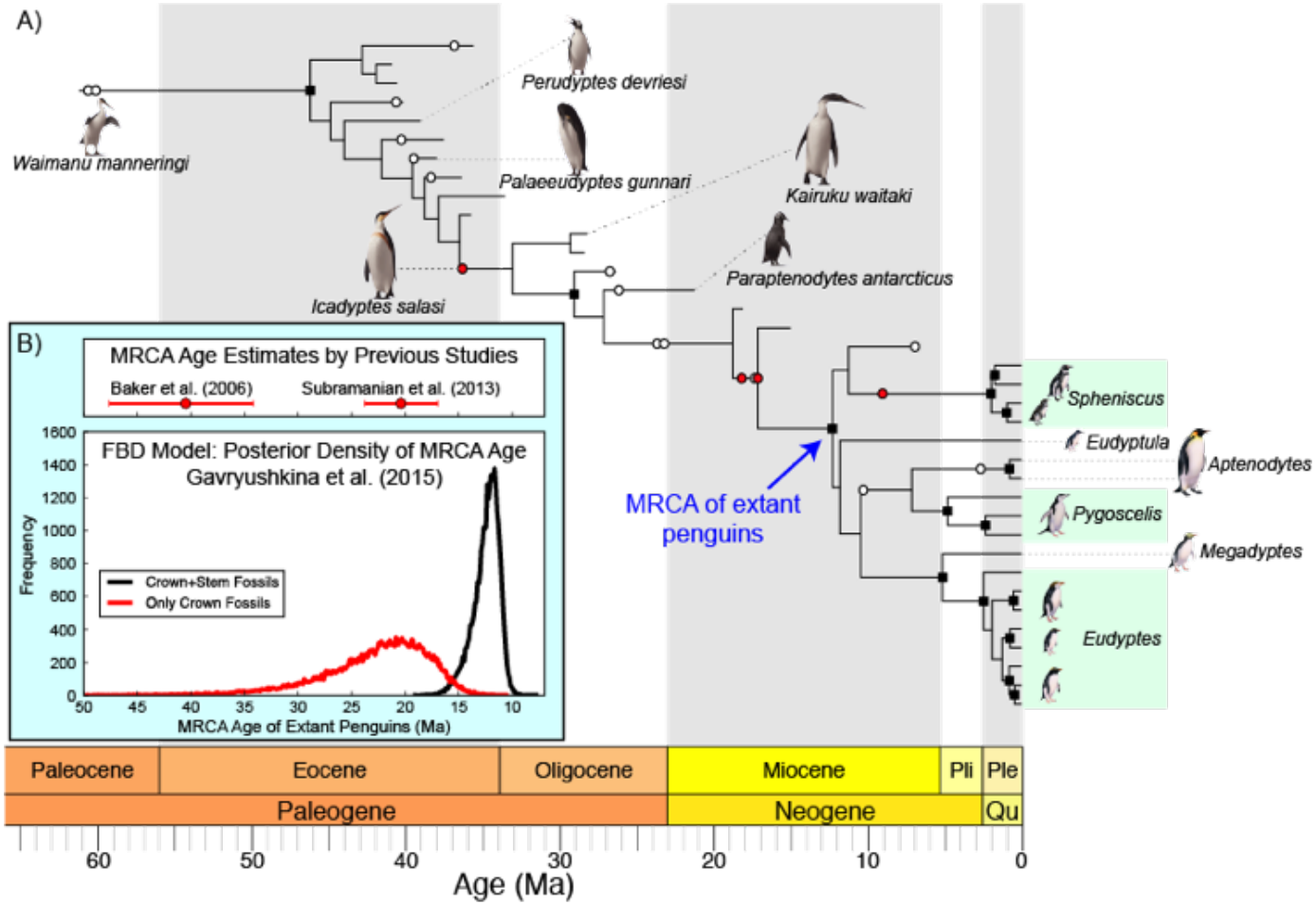

Figure adapted from [Gavryushkina et al., 2017]

Penguin phylogeny obtained from fossil dates, morphology, and extant species sequencing data, again using BEAST2.

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- If priors do not exclude the truth, then two practitioners with the same likelihood functions will converge on the same inference with increasing amounts of data.
- Markov chain Monte Carlo is a simple algorithm that can be employed to study large problems.

Bayesian Inference: Questions

- Does a Bayesian phylogenetic analysis of the kind described here allow one to directly infer ancestral sequences? Why/Why not?
- How might we test to see whether a Bayesian MCMC analysis has explored the full state space supported by the posterior?
- Suppose you have conducted a Bayesian phylodynamic analysis and recovered a 95% HPD interval for the birth rate parameter. If you take this result and use it to construct a new prior for this parameter and use this prior to analyze the *same data*, would the resulting second posterior be valid?

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