Bayesian phylogenetics:

an introduction

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Who is this man?

How sure are you?

The one 'true' tree?

- Methods we've learned so far try to find a single tree that best describes the data
- However, they do not search everywhere, and it is difficult to find the "best" tree
- Many (gazillions of) trees may be almost as good

Bayesian phylogenetics: general principle

- Using Bayesian principles, we will search for and average over sets of plausible trees (weighted by their probability) instead a single "best" tree
- In this method, the "space" that you search is limited by **prior** information and the **data**

- The **posterior** distribution of trees naturally translates into probability statements (and uncertainty) on aspects of direct scientific interest
  - When did an evolutionary event happen?
  - Are a subset of sequences more closely related?
- The cost: we must formalize our prior beliefs

Conditional probability: intuition

Linda is 31 years old, single, outspoken, and very bright. She majored in philosophy. As a student, she was deeply concerned with issues of discrimination and social justice, and also participated in antinuclear demonstrations.

1. Linda is a bank teller.
2. Linda is a bank teller and is active in the feminist movement.

Which is more probable?

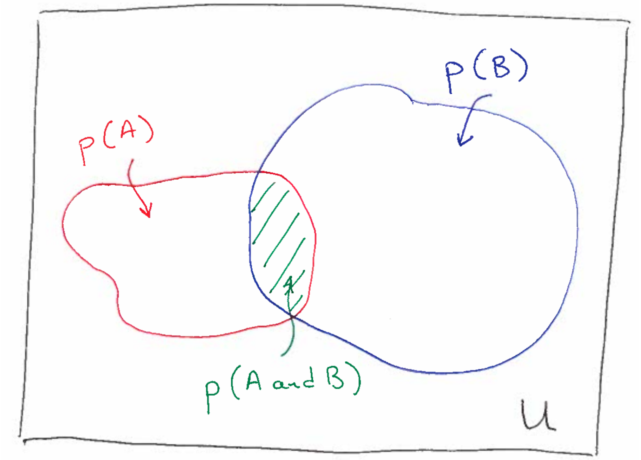
Conditional probability: intuition

Conjunction (joint probably) fallacy:

- Tversky and Kahneman (1982)
- 85% of undergraduates chose the joint

> *I am particularly fond of this example [the Linda problem] because I know that the [conjoint] statement is least probable, yet a little homunculus in my head continues to jump up and down,shouting at me – "but she can't just be a bank teller; read the description."*
>
> \- Stephen J. Gould

Conditional probability: intuition



- Arbitrary events A (teller) and B (activist) from sample space U

Bayes theorem

Definition of conditional probability in words:

$$\text{probability}(A \text{ and } B) = \text{probability}(A \text{ given } B) \times \text{probability}(B)$$

In usual mathematical symbols:

$$p(A|B)p(B) = p(A, B) = p(B|A)p(A)$$

With a slight re-arrangement:

$$p(A|B) = \frac{p(B|A)p(A)}{p(B)}$$

- “Just" a restatement of conditional probability

Bayes theorem

Integration (averaging) yields a marginal probability:

$$p(A) = \int p(A, B)\mathrm{d}B = \underbrace{\int p(A|B)p(B)\mathrm{d}B}_{\text{over all possible values of } B}$$

- probability(teller) = probability(teller and activist) + probability(teller and not activist)

Conditional probability: pop quiz

What do you know about Thomas Bayes?
Bayes theorem?

Some discussion points:

- Favorite game? Best buddies?

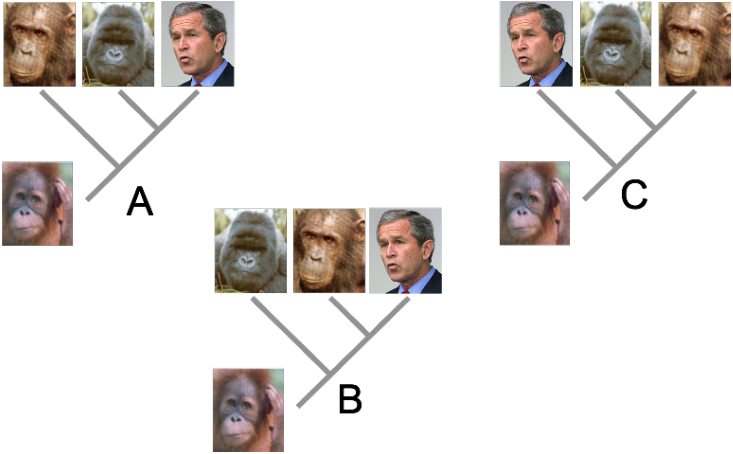
Bayes theorem for statistical inference

- Unknown quantity θ (model parameters, scientific hypotheses)
- Prior $p(\theta)$ beliefs before observed data Y become available
- Conditional probability $p(Y|\theta)$ of the data given fixed θ – also called the likelihood of Y
- Posterior $p(\theta|Y)$ beliefs:

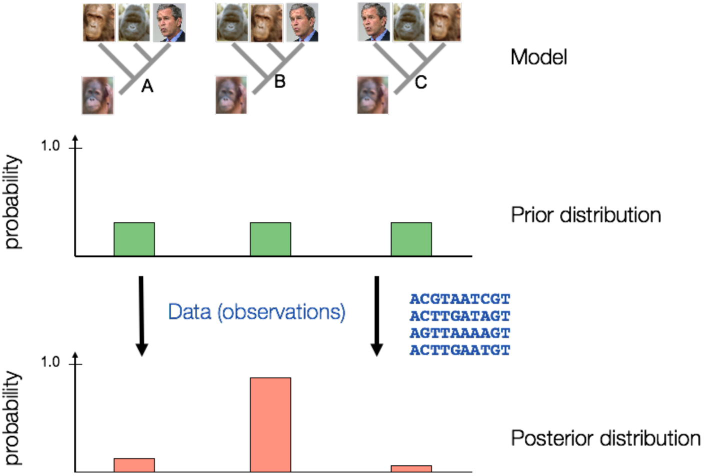
$$p(\theta|Y) = \frac{p(Y|\theta)p(\theta)}{p(Y)}$$

- $p(\theta)$ and $p(Y|\theta)$ – easy
- $p(Y) = \int p(Y|\theta)p(\theta)\mathrm{d}\theta$ – hard

Bayesian phylogenetic inference



Bayesian phylogenetic inference



Model

Prior distribution

Data (observations)

ACGTAATCGT
ACTTGATAGT
AGTTAAAAGT
ACTTGAATGT

Posterior distribution

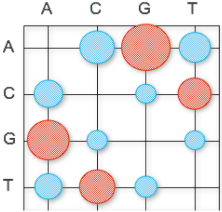
Bayesian phylogenetic inference

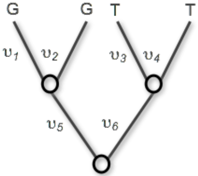
- Posterior:

$$p(\theta|Y) = \frac{p(Y|\theta)p(\theta)}{p(Y)}$$

- Trouble: $p(Y)$ is not computable – sum over all possible trees
- For N taxa: there are $G(N) = (2N-3) \times (2N-5) \times \cdots \times 1$

- $\theta = (\text{tree}, \text{substitution process})$
- $p(Y|\theta)$ - continuous-time Markov chain process that gives rise to sequences at tips of tree

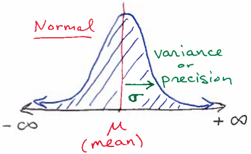


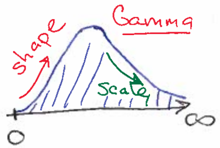


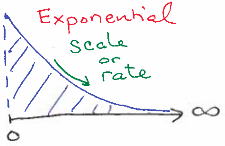
E.g., $G(21) > 3 \times 10^{23}$

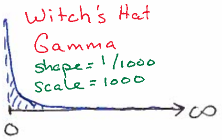
Priors

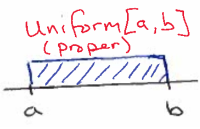
- Strongest assumption: most parameters are separable, e.g. the tree is independent of the substitution process
- Weaker assumption: tree $\sim$ Coalescent process
- Weaker assumption: functional form on substitution parameters







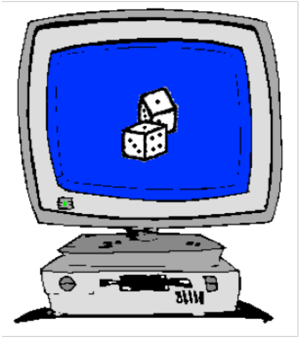


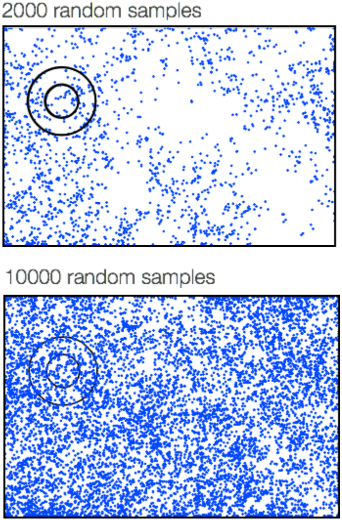


- Specialized priors as well
- If worried: check sensitivity

Posterior inference

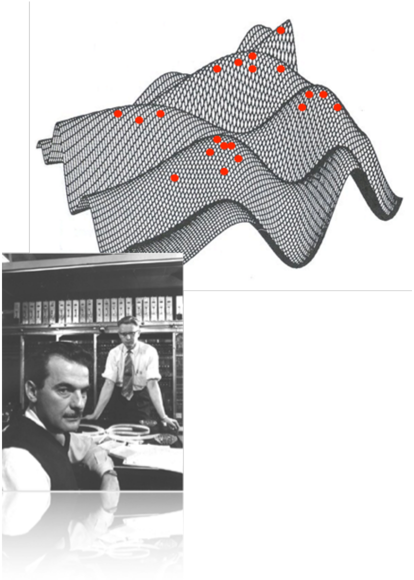
Numerical (Monte Carlo) integration as a solution:





Markov chain Monte Carlo

- Metropolis et al (1953) and Hastings (1970) proposed a stochastic integration algorithm that can explore vast parameter spaces
- Algorithm generates a Markov chain that visits parameter values (e.g., a specific tree) with frequency equal to their posterior density / probability.
- Markov chain: random walk where the next step only depends on the current parameter state



Metropolis-Hastings Algorithm

- Each step in the Markov chain starts at its current state θ and proposes a new state $\theta^\star$ from an **arbitrary** proposal distribution $q(\cdot|\theta)$ (transition kernel)
- $\theta^\star$ becomes the new state of the chain with probability:

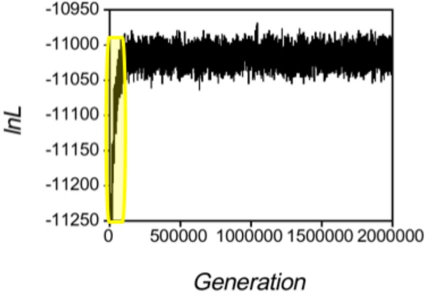
$$
\begin{aligned}
R &= \min\left(1, \frac{p(\theta^\star|Y)}{p(\theta|Y)} \times \frac{q(\theta|\theta^\star)}{q(\theta^\star|\theta)}\right) \\
&= \min\left(1, \frac{p(Y|\theta^\star)p(\theta^\star) \,/\, p(Y)}{p(Y|\theta)p(\theta) \,/\, p(Y)} \times \frac{q(\theta|\theta^\star)}{q(\theta^\star|\theta)}\right) \\
&= \min\left(1, \frac{p(Y|\theta^\star)p(\theta^\star)}{p(Y|\theta)p(\theta)} \times \frac{q(\theta|\theta^\star)}{q(\theta^\star|\theta)}\right)
\end{aligned}
$$

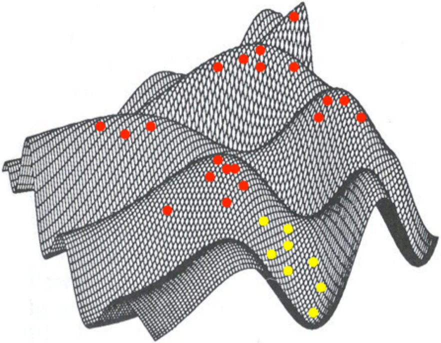
- Otherwise, θ remains the state of the chain

Posterior sampling

We repeat the process of proposing a new state, calculating the acceptance probability and either accepting or rejecting the proposed move millions of times

Although correlated, the Markov chain samples are valid draws from the posterior; however …

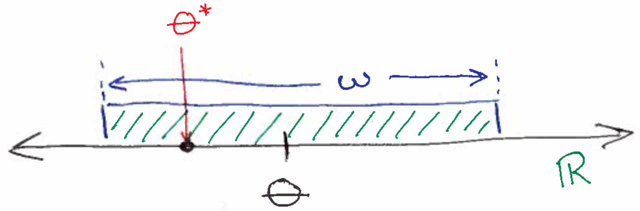




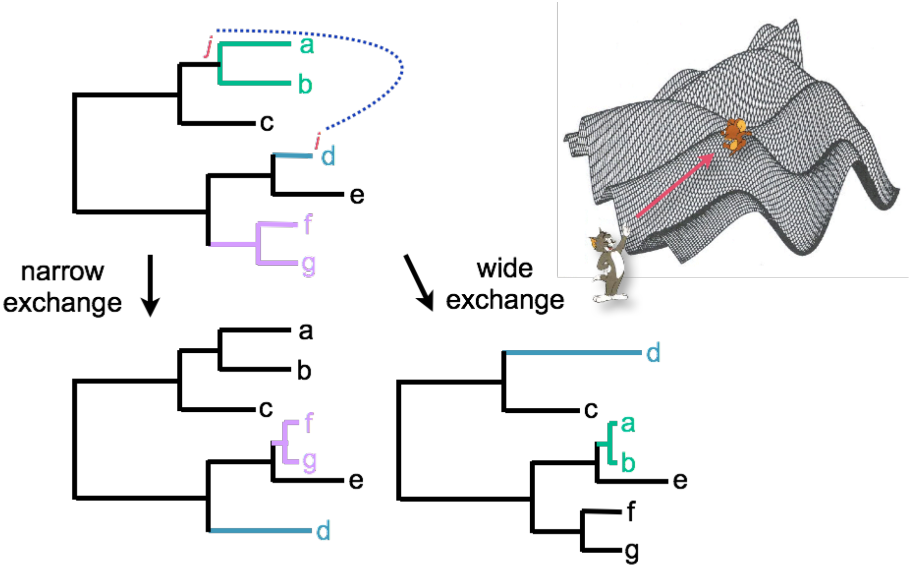
Initial sampling (burn-in) is often discarded due to correlation with chain's starting point ($\neq$ posterior)

Transition Kernels

- Often we propose changes to only a small # of dimensions in θ at a time (Metropolis-within-Gibbs)
- In phylogenetics, mixing (correlation) in continuous dimensions is much better (smaller) than for the tree
- So, dominant approach has been keep-it-simple-stupid – alternatives exist and may become necessary:
  - Gibbs sampler; slice sampler; Hamiltonian MC



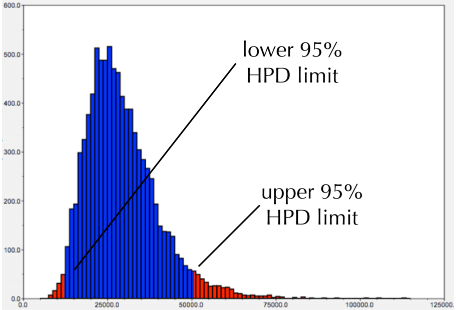
Tree Transition Kernels



Posterior Summaries

For continuous θ, consider:

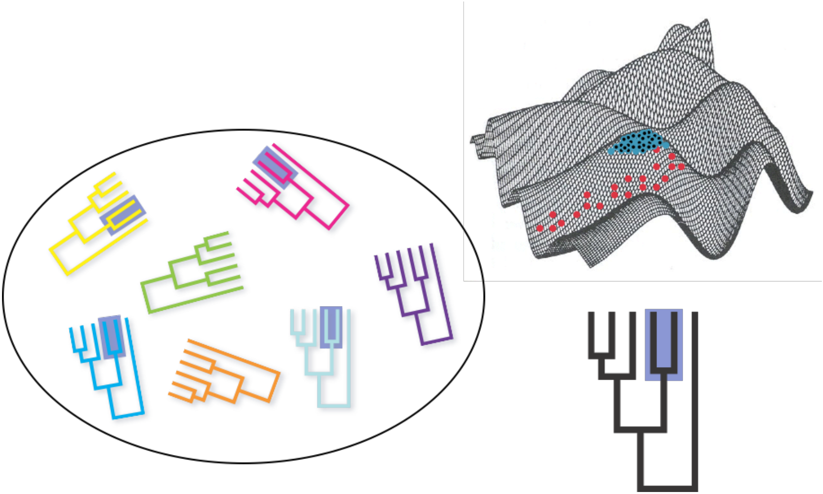
- posterior mean or median $\approx$ MCMC sample average or median
- quantitative measures of uncertainty, e.g. high posterior density interval



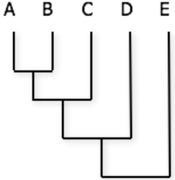
For trees, consider:

- scientifically interesting posterior probability statement, e.g. the probability of monophyly $\approx$ MCMC sample proportion under which hypothesis is true

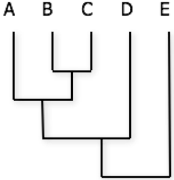
Posterior Probabilities



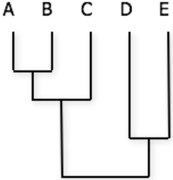
Summarizing Trees



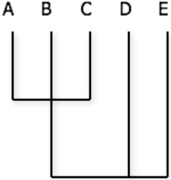
Tree 1



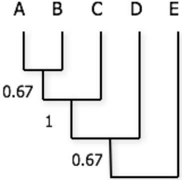
Tree 2



Tree 3



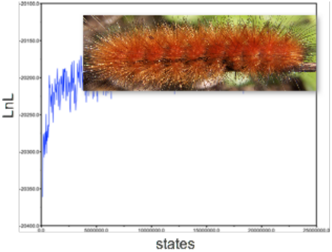
Strict
consensus tree



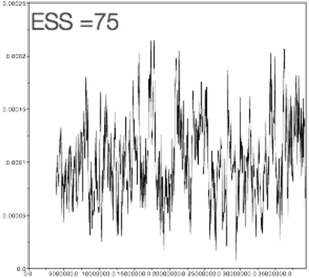
Majority-rule
consensus tree

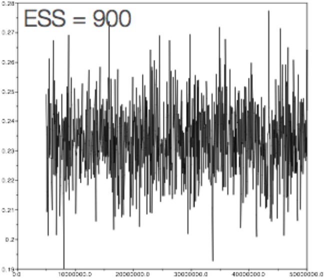
MCMC Diagnostics: within a single chain

- Visually inspect MCMC output traces



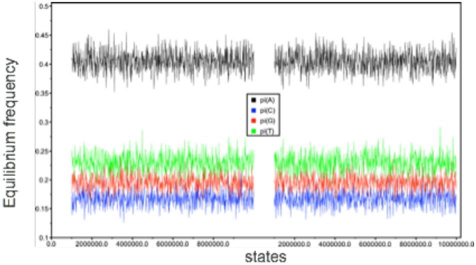
- Measure autocorrelation within a chain: the effective sample size (ESS)





MCMC Diagnostics: across multiple chains

- Visually inspect MCMC output traces

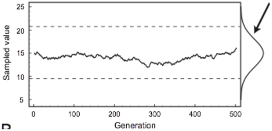


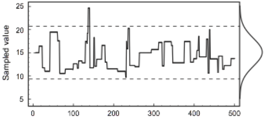
Comparing different chains → variance among and between chains

Improving Mixing

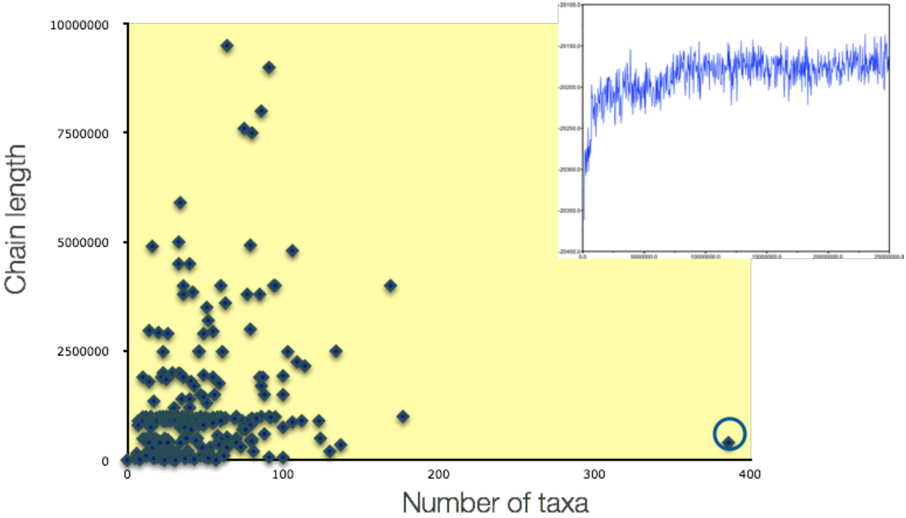
(Only if convergence diagnostics suggest a problem)

- **Run the chain longer**
- Use a more parsimonious model (uninformative data)
- Change tuning parameters of transition kernels to bring acceptance rates to 10% to 70%
- Use different transition kernels (consult an expert)





Improving Mixing



Why Bother being Bayesian?

In practice, we have almost no prior knowledge for the model parameters. So, why bother with Bayesian inference?

- Analysis provides directly interpretable probability statements given the observed data
- MCMC is a stochastic algorithm that (in theory) avoids getting trapped in local sub-optimal solutions
- Search space under Coalescent prior is astronomically “smaller”
- By numerically integrating over all possible trees, we obtain marginal probability statements on hypotheses of scientific interest, e.g. specific branching events or population dynamics, avoiding bias