# SISMID
# Module 16: Evolutionary Dynamics and Molecular Epidemiology of Viruses

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TAs: Nídia Trovão and Joëlle Barido-Sottani

# Logistics

- Zoom sessions are recorded and will be available after the session.
- Other instructors will be available in slack for questions and discussions during zoom sessions.
- For this lecture, Nicola is available in slack for questions.

https://juliapalacios.github.io/SISMID_EvolutionaryDynamics/

# Evolutionary dynamics and molecular epidemiology of viruses

The goal is to:

- Understand patterns of transmission and spread (effective population size)
- Estimate the rate of evolution / mutation rate
- Compare evolution across pathogens
- Understand the sources of molecular variation (mutation, selection, recombination)
- Surveillance

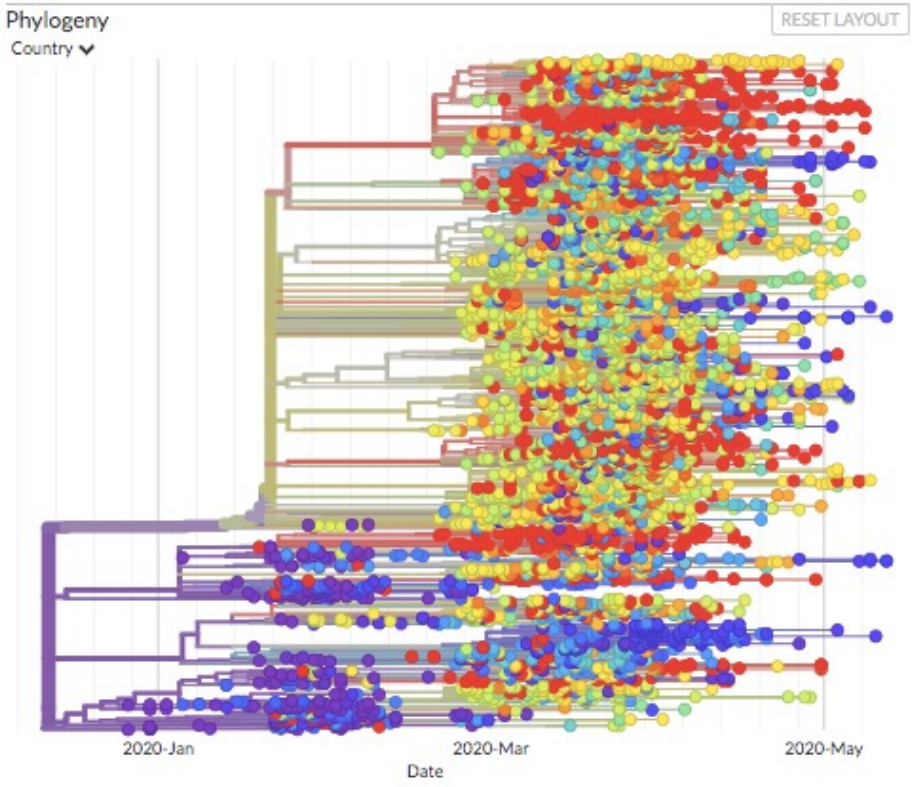
**Molecular epidemiology** and **phylodynamics** of infectious diseases aim to study infectious disease behavior through a combination of evolutionary, epidemiological and immunological processes from molecular variation [Holmes and Grenfell, 2009].

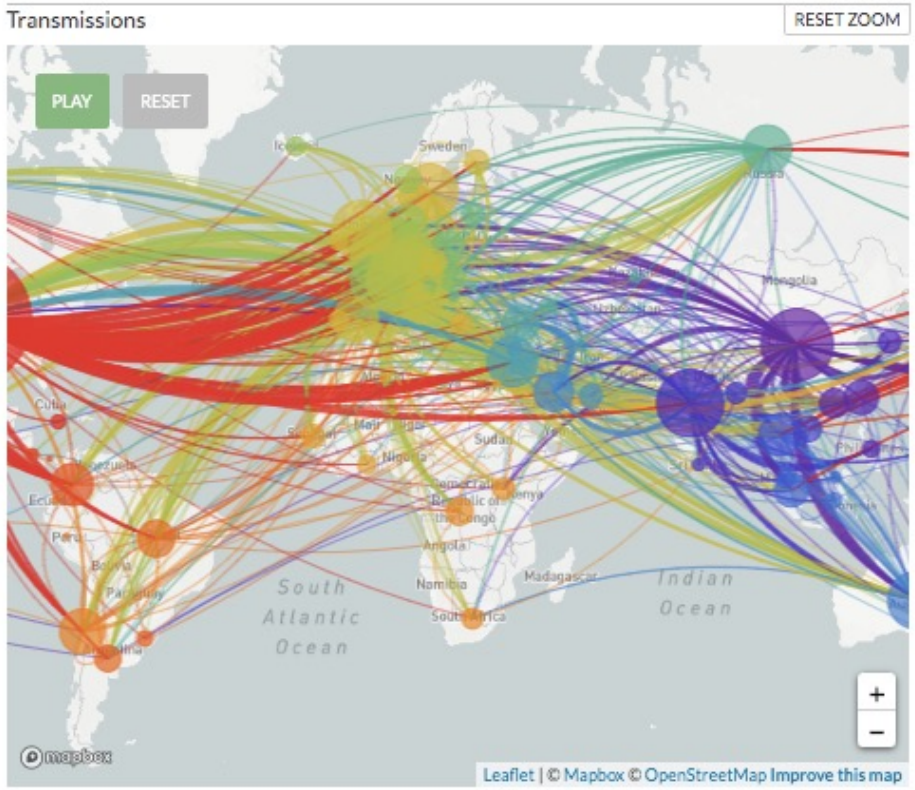
# Global spread of SARS-CoV-2

## Genomic epidemiology of novel coronavirus - Global subsampling

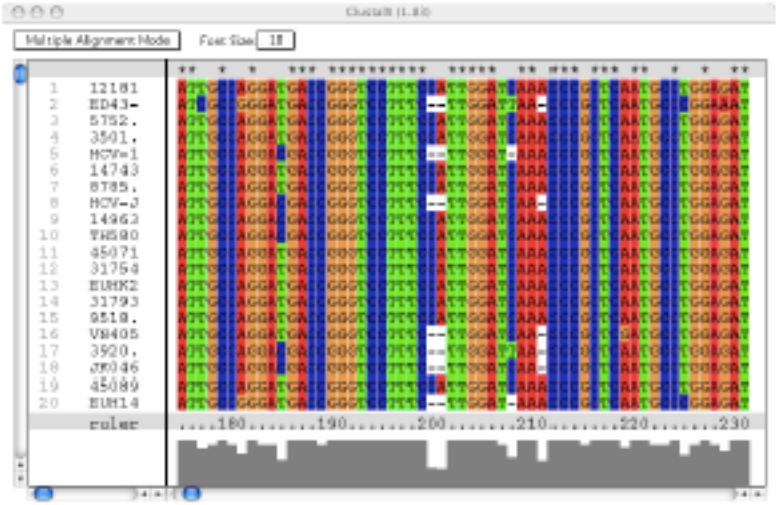
Maintained by the Nextstrain team. Enabled by data from GISAID

Showing 4256 of 4256 genomes sampled between Dec 2019 and May 2020.



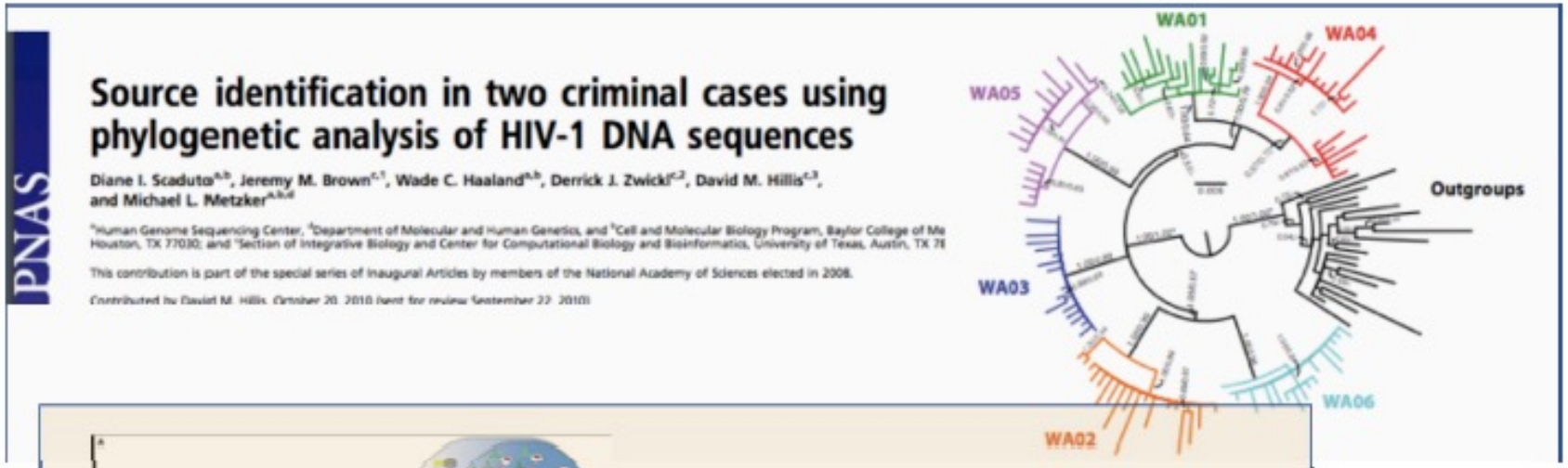



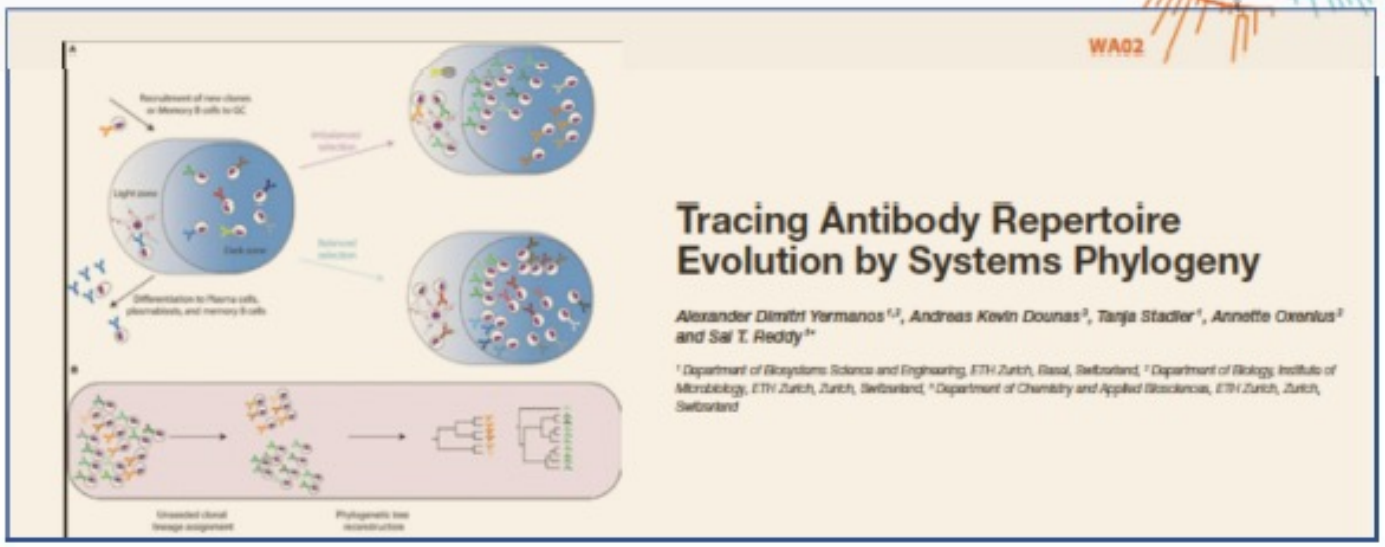
# Observed data

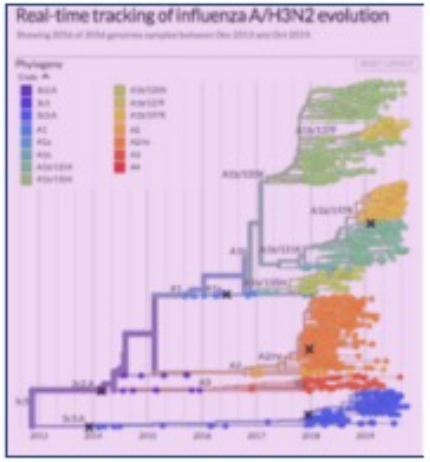



- **Biological sequences** (DNA, RNA, protein) contain information about their underlying evolutionary processes.
- Molecular sequences from different organisms are **not independent** because they share evolutionary history.
- The central concept is a **genealogy**: a bifurcating tree that depicts the **ancestral relationships** of the samples.

# Estimation of genealogies and phylogenies has allowed …

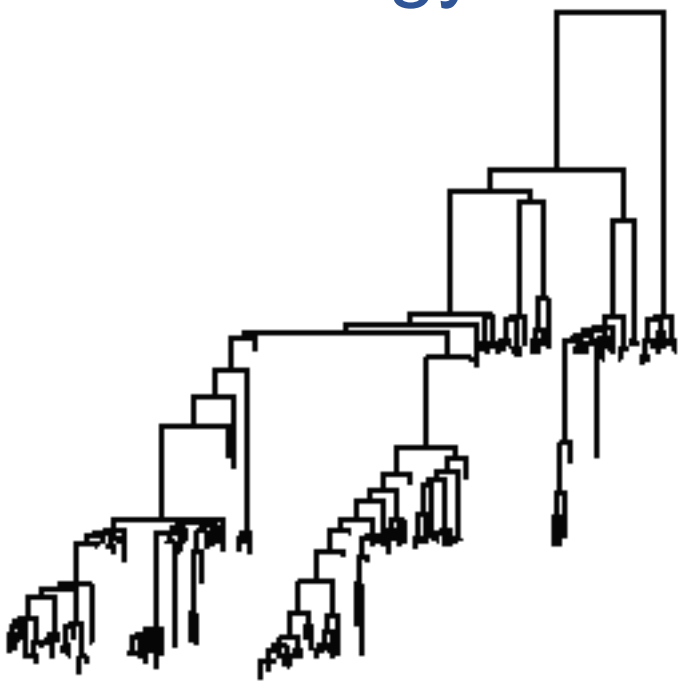


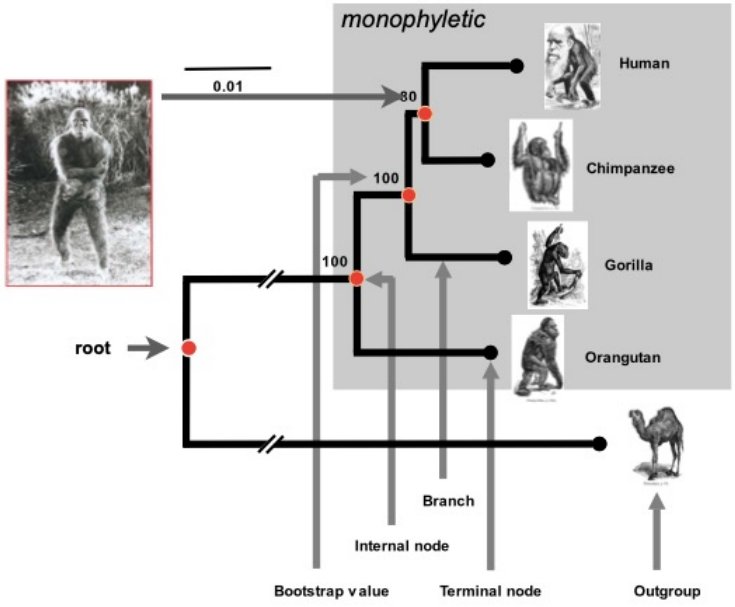
# What is a genealogy?

## Genealogy



Time

## Phylogeny

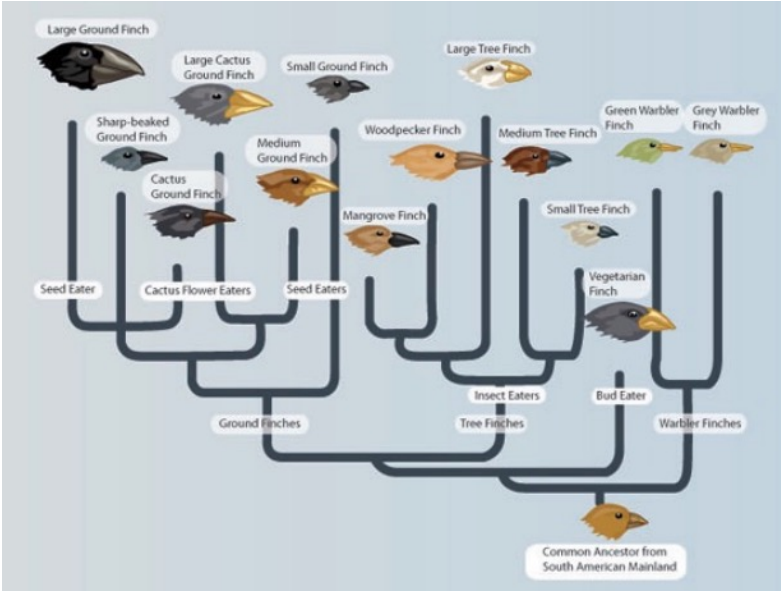



- Tips correspond to individuals
- Internal nodes are ranked
- Branch lengths are in the same scale
- Samples are time stamped (tips)

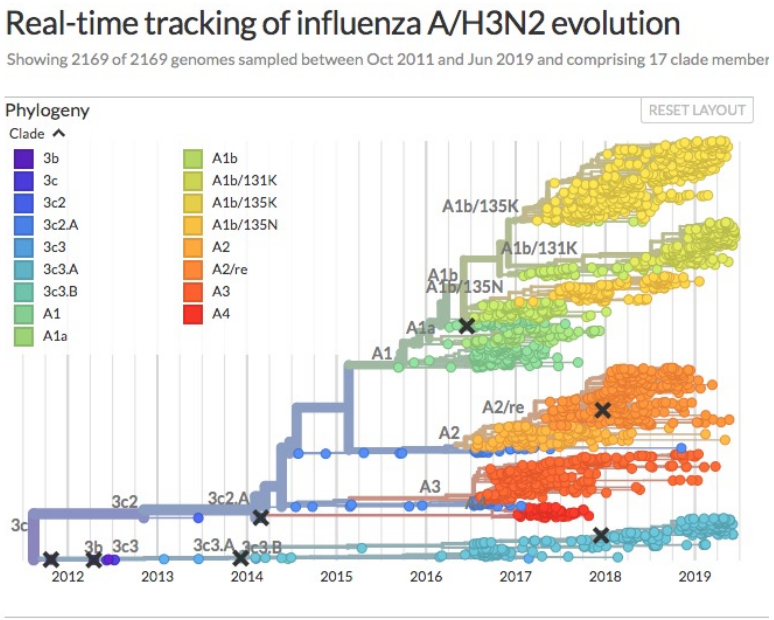
- Tips correspond to species
- Usually internal nodes are not ranked
- Branch lengths are in different scales
- Unrooted trees are commonly analyzed

# Phylogenetics, phylodynamics and population genetics

- **Phylogenetics** is the study of the evolutionary history of species. It seeks to determine the “family tree”.
  - Understanding selection
  - Evidence for coevolution
  - Pathways of trait evolution

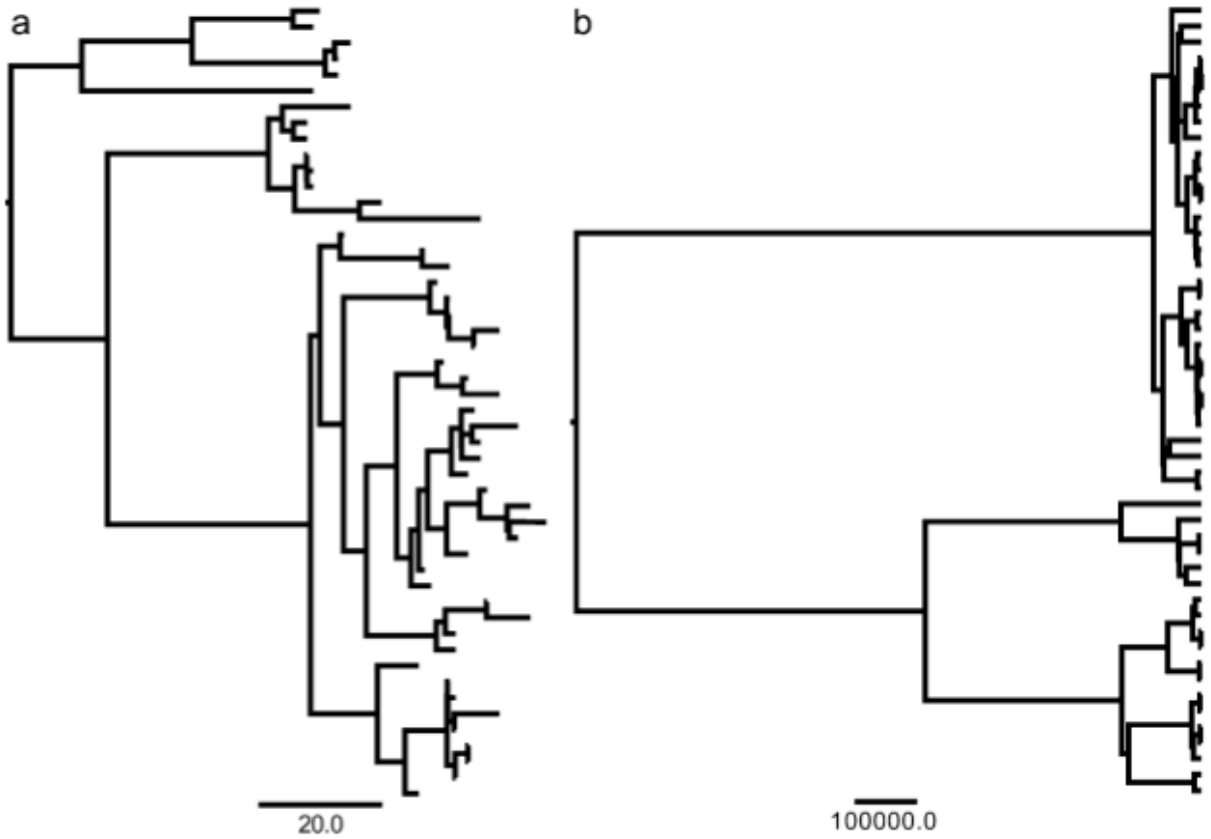



- **Phylodynamics**
  - Attempts to enhance understanding of infectious disease dynamics using pathogen phylogenies



# Phylodynamics and population genetics

- **For rapidly evolving organisms**
- **For slowly evolving organisms**



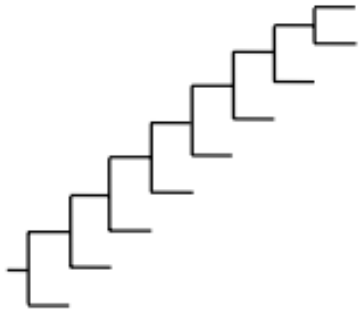
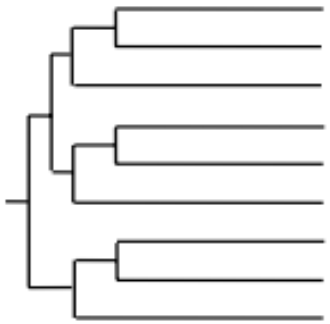
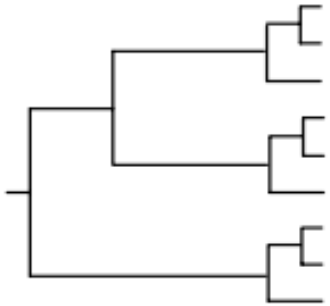
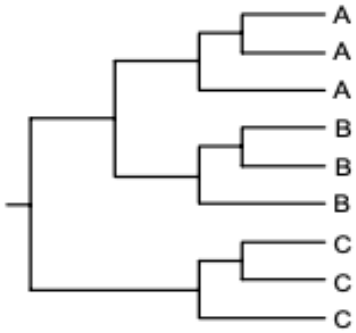
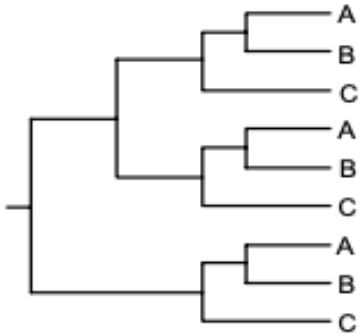

$10^{-4}$ subs/site/year

$10^{-8}$ subs/site/year

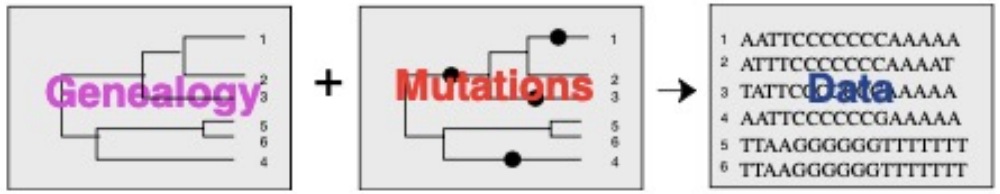
# Statistical Phylogenetics seeks to infer genealogies/phylogenies from molecular data

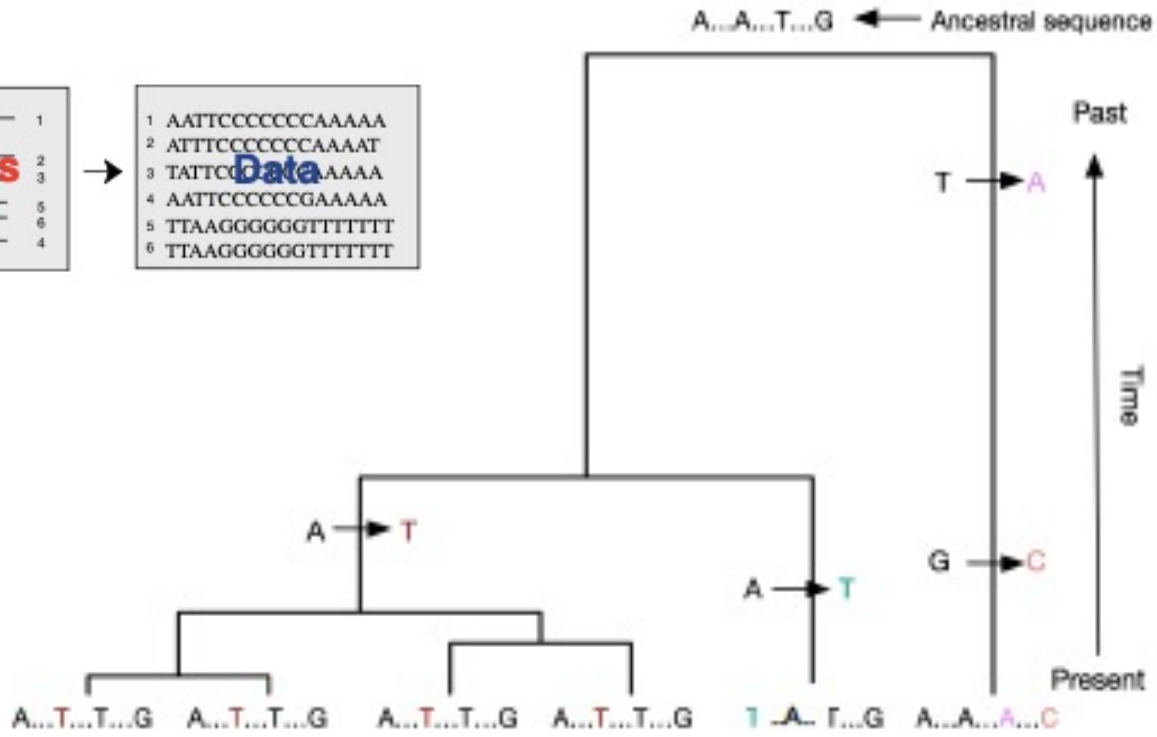

- Genealogies inform about past evolutionary history.
  - Ancestry
  - Signatures of selection
  - Population structure
  - Population history

# Phylodynamic Patterns

| | Continual Immune Selection | Weak/No Immune Selection | |
|---|---|---|---|
| | | Population dynamics | Spatial dynamics |
| **Idealised Phylogeny Shapes** |  | *Population growth*  *Population decline*  | *Strong spatial structure*   *Weak spatial structure*   |
| **Examples** | Human influenza A<br>within-host HIV | among-host HIV<br>among-host HCV | Measles<br>Rabies, Dengue |

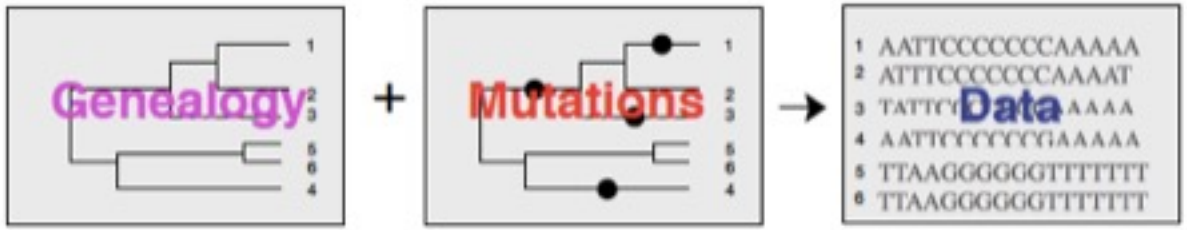
# A process of substitutions superimposed on the genealogy **generates** observed sequences at the tips of the genealogy



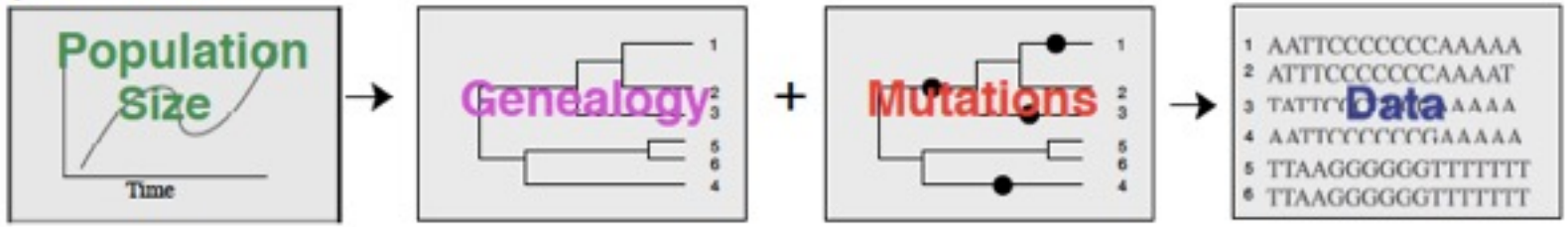
# Statistical Phylogenetics

Goal: Estimate genealogy/phylogeny



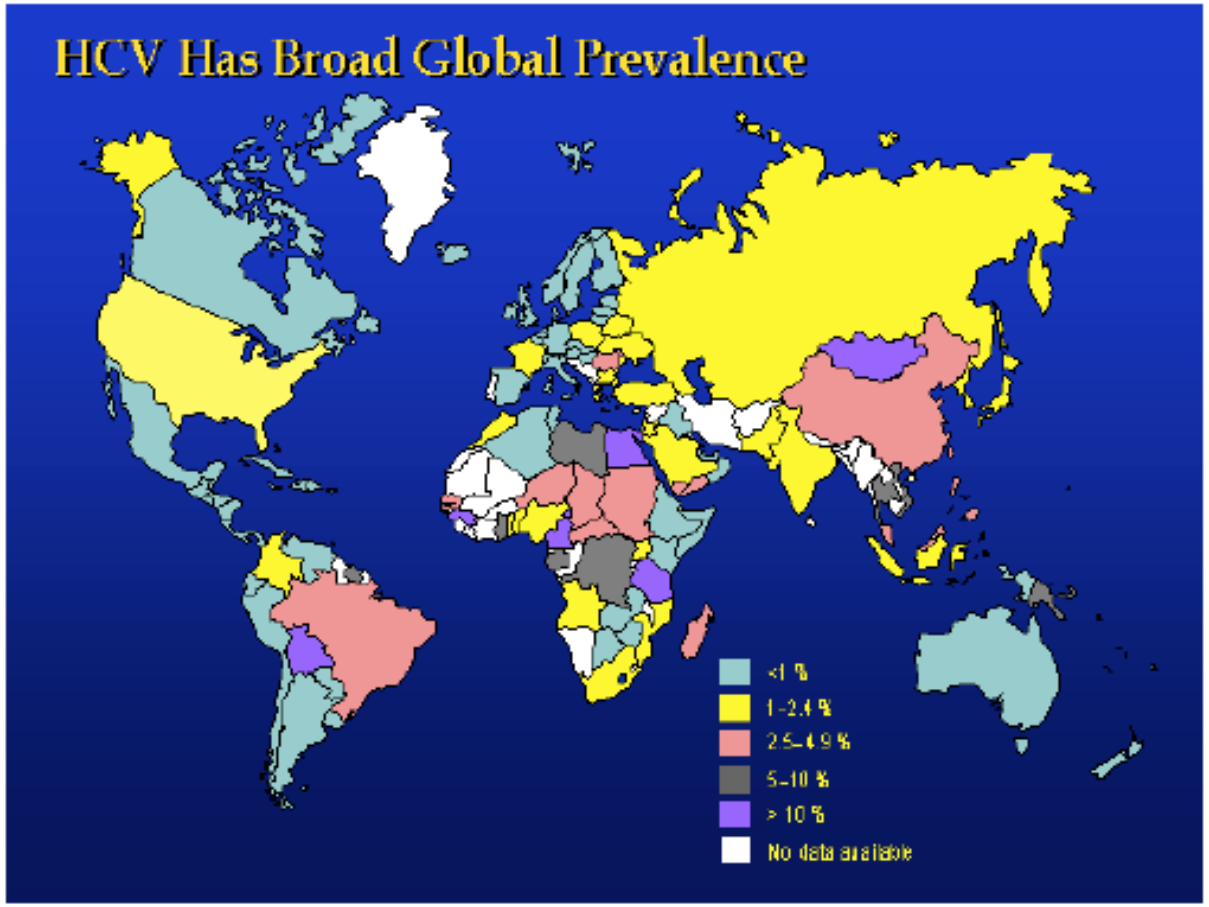

# Phylodynamics

Goal: Estimate effective population size $N_e(t)$ from DNA sequences




Coalescent Process

# Example 1: Hepatitis C in Egypt



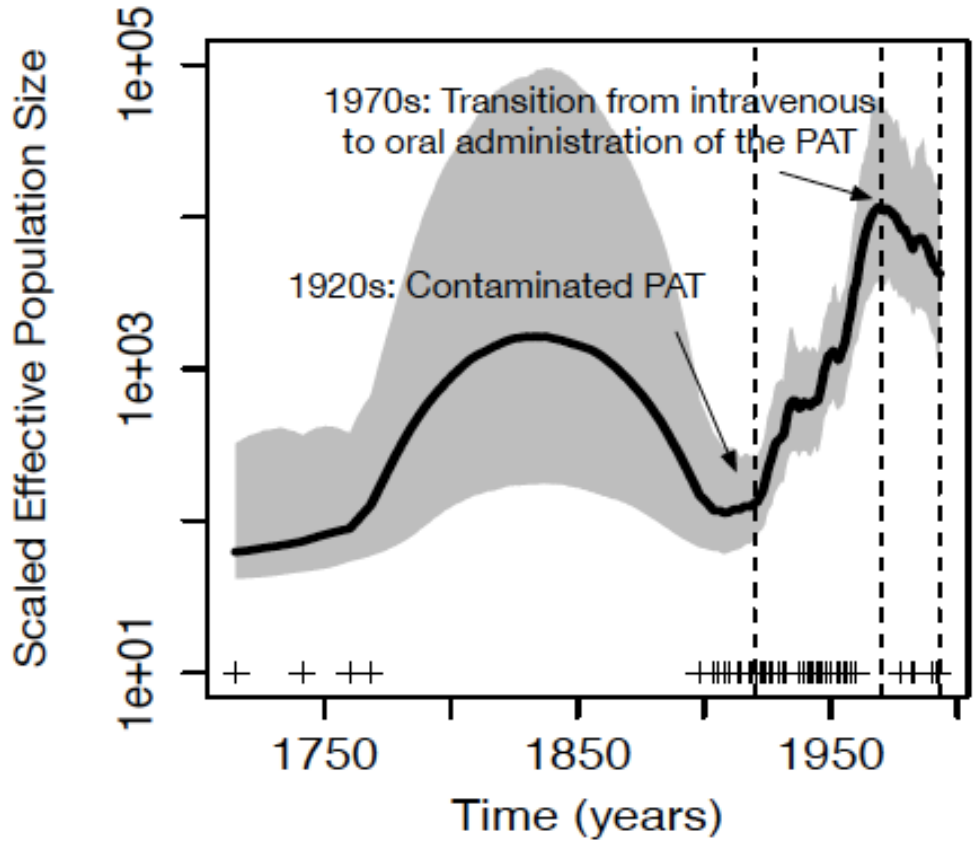

*Prevalence of HCV - WHO 1999*

- Identified in 1989
- Spread by blood to blood contact
- ≈3% of infected population worldwide
- 8,000 - 10,000 deaths per year in the USA
- Egypt has the highest prevalence

# Example 1: Hepatitis C in Egypt

- 62 samples in 1993 from the E1 gene (411bp)
- Parenteral antischistosomal therapy (PAT) was practiced from 1920s to 1980s
- In the 1970s started a transition from the intravenous to the oral administration of the PAT

# Example 1: Hepatitis C in Egypt




[Palacios and Minin, Biometrics 2013]

- 62 samples in 1993 from the E1 gene (411bp)
- Parenteral antischistosomal therapy (PAT) was practiced from 1920s to 1980s
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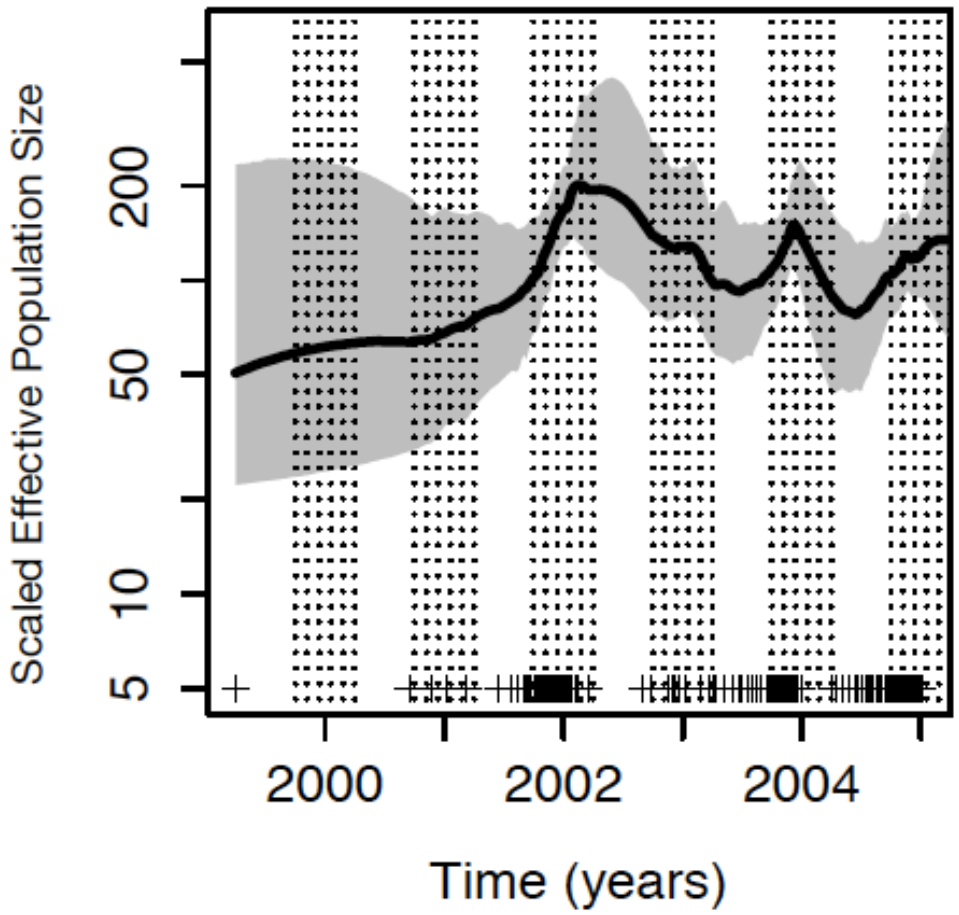
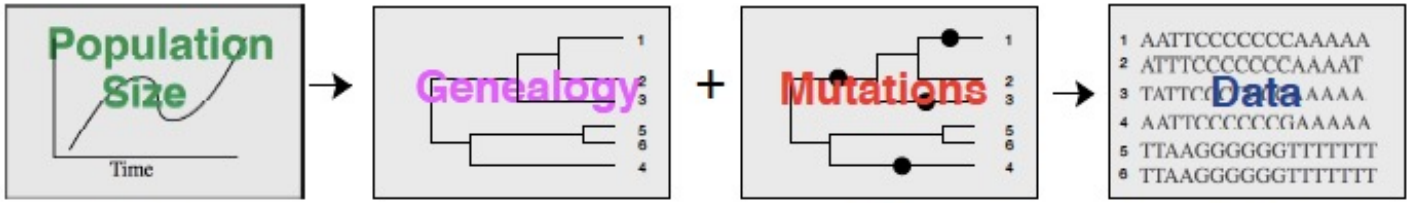
# Example 2: Influenza in NY




[Palacios and Minin, Biometrics 2013]

- Human Influenza A in N.Y.
- 288 sequences from 2001-2005 from HA gene

# Bayesian Evolutionary Analysis by Sampling Trees




$N_e(t)$ $\quad$ $\mathbf{G}$ $\quad$ $\mathbf{Q}$ $\quad$ $\mathbf{Y}$

$$P(N_e(t), \mathbf{G}, \mathbf{Q}, \tau \mid \mathbf{Y}) \propto \underbrace{P(\mathbf{Y} \mid \mathbf{G}, \mathbf{Q})}_{\text{Likelihood}} \underbrace{P(\mathbf{G} \mid N_e(t))}_{\text{Coalescent prior}} P(\mathbf{Q}) \underbrace{P(N_e(t) \mid \tau)}_{\log \mathrm{GP}(0, \mathbf{C}(\tau))} P(\tau)$$

Posterior

Birth-death prior

Piece-wise constant (deterministic)
Parametric prior

# Frequentist vs Bayesian Inference

- Frequentist
  - Probability is interpreted as long run frequency.
  - The goal is to create procedures with long run guarantees.
  - Procedures are random while parameters are fixed and unknown
- Bayesian
  - Probability is interpreted as a measure of subjective degree of belief
  - Everything is regarded as random
  - Goal is to quantify and analyze degrees of belief

Larry Wasserman –All of Statistics

# Bayesian Inference

- We begin with a *prior* belief about the values of the parameters $\theta \in \Theta$ of the model.

$$\pi(\theta) \tag{1}$$

  This express your belief about $\theta$ before you have seen the data.
- The sampling distribution (or likelihood) has a known functional form: $L(X_1 \ldots, X_n \mid \theta)$.
- Applying Bayes' rule, we get the following posterior distribution

$$P(\theta \mid X_1, \ldots, X_n) = \frac{L(X_1, \ldots, X_n \mid \theta)\pi(\theta)}{\int_{\theta \in \Theta} L(X_1, \ldots, X_n \mid \theta)\pi(\theta)d\theta} \tag{2}$$

# Bayesian Inference

$$\pi(\theta) \tag{3}$$

$$L(X_1, \ldots, X_n \mid \theta) \tag{4}$$

If one is **philosophically Bayesian**, then the interpretation is the following: “Given my prior beliefs about the unknown parameters, my assumptions about the sampling model, and the data I have observed, my beliefs about the unknown parameters are now expressed by the posterior, the conditional distribution of parameters given data"

$$P(\theta \mid X_1, \ldots, X_n) \tag{5}$$

# Example: Poisson-Gamma

- Suppose your observations are a realization from a Poisson distribution with parameter $\lambda$ =1
- You don't know that $\lambda$ =1
- You have a prior belief that $\lambda$ may behave as a Gamma(.1,1)

$$\mathrm{P}(\theta \mid x_1, \ldots, x_n) = \frac{\mathrm{P}(x_1,\ldots,x_n|\theta)\mathrm{P}(\theta)}{\mathrm{P}(x_1,\ldots,x_n)}$$

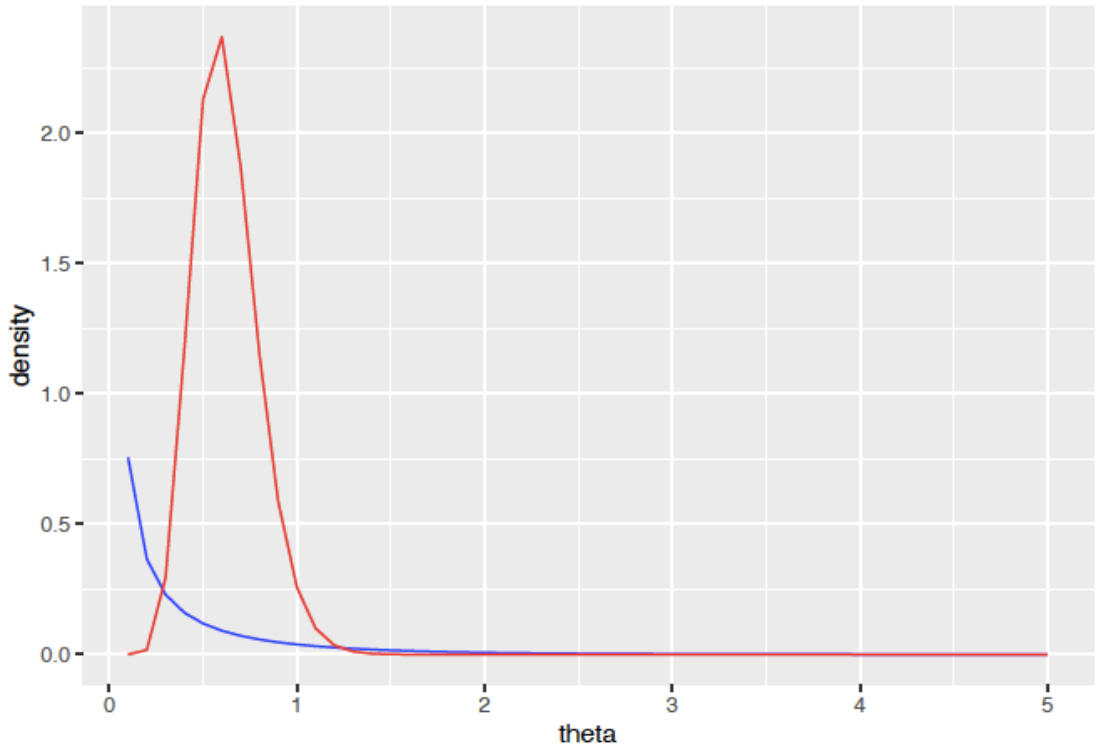
$$\mathrm{P}(\theta \mid x_1, \ldots, x_n) = \frac{\theta^{\sum_i^n x_i} e^{-\theta} (\prod_{i=1}^n x_i!)^{-1} \theta^{\alpha-1} e^{-\theta/\beta} (\Gamma(\alpha)\beta^\alpha)^{-1}}{\mathrm{P}(x_1,\ldots,x_n)}$$

$$\mathrm{Gamma}(\textstyle\sum_{i=1}^n x_i + \alpha, (n + 1/\beta)^{-1})$$

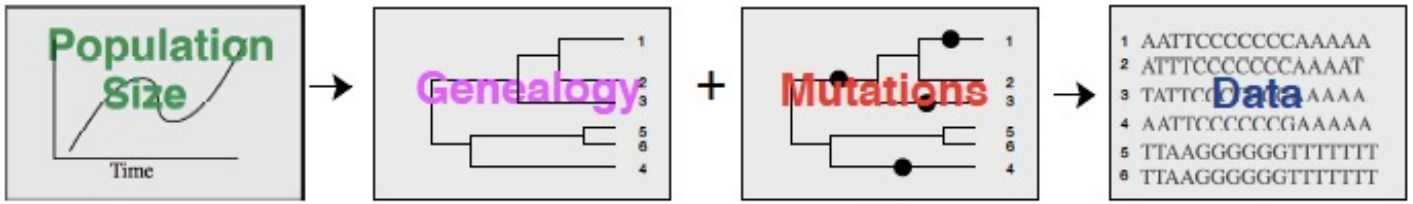
# Example: Poisson-Gamma

```
n<-20
y<-rpois(n,1) #true theta=1
```

```
library("ggplot2")
x<-seq(0.1,5,by=.1)
prior<-dgamma(x,.1,1)
posterior<-dgamma(x,sum(y)+.1,1+n)
df<-data.frame(x=x,prior=prior,posterior=posterior)
ggplot() +
  geom_line(data = df, aes(x = x, y = prior), color = "blue") +
  geom_line(data = df, aes(x = x, y = posterior), color = "red")+ xlab('theta') +
  ylab('density')
```



# Bayesian Evolutionary Analysis by Sampling Trees

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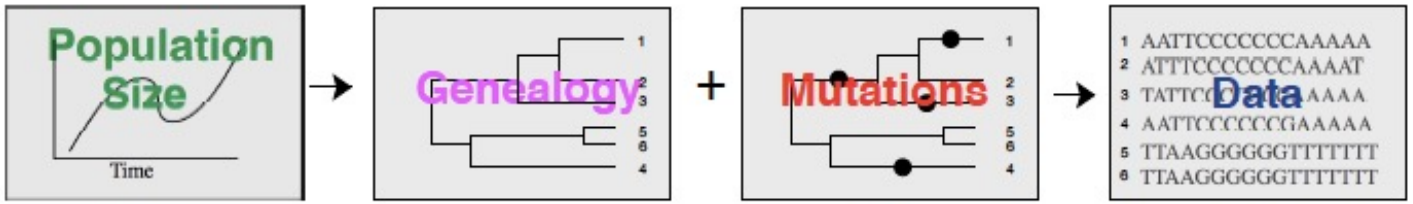
Posterior

Likelihood

Coalescent prior
Birth-death prior

log GP$(0, \mathbf{C}(\tau))$
Piece-wise constant (deterministic)
Parametric prior

# Bayesian Evolutionary Analysis by Sampling Trees

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Posterior

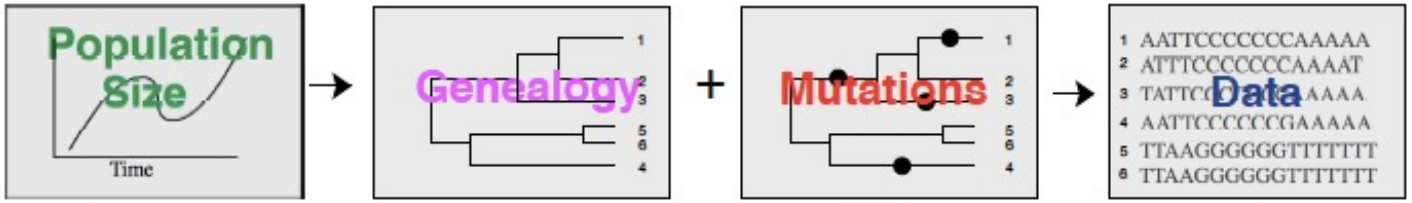
Birth-death prior

Piece-wise constant (deterministic)
Parametric prior

Target of interest: $$p(\theta|Y) = \frac{p(Y|\theta)p(\theta)}{p(Y)}$$

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

# Bayesian Evolutionary Analysis by Sampling Trees




$N_e(t)$ $\quad$ $\mathbf{G}$ $\quad$ $\mathbf{Q}$ $\quad$ $\mathbf{Y}$

- Goal: $P\left(N_e(t), \mathbf{G}, \mathbf{Q}, \tau \mid \mathbf{Y}\right)$
- The likelihood $P\left(\mathbf{Y} \mid \mathbf{G}, \mathbf{Q}\right)$ is tractable.

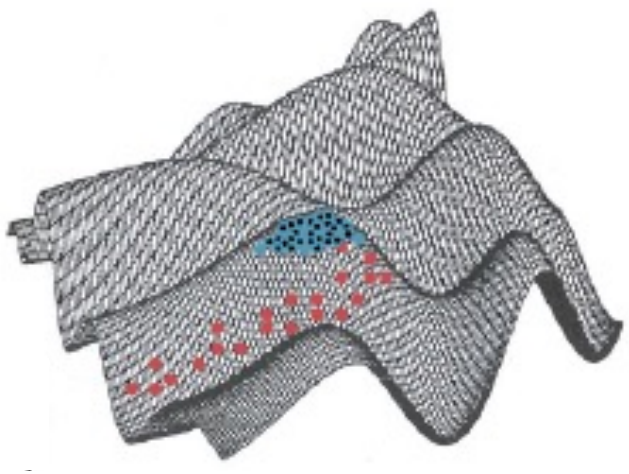
The state space of genealogies $\mathcal{G}$

- $\mathcal{G} = \mathcal{T}_n \times \mathbb{R}_+^{n-1}$
- $|\mathcal{T}_n| = n!(n-1)!/2^{n-1}$
- $|\mathcal{T}_{100}| \approx 10^{284}$

Trouble: $p(Y)$ is not computable – sum over all possible trees

# Markov Chain Monte Carlo

- 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



Marc Suchard – Past SISMID

# Metropolis-Hastings Algorithm

- Each step in the Markov chain starts at its current state $\theta$ 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, $\theta$ remains the state of the chain

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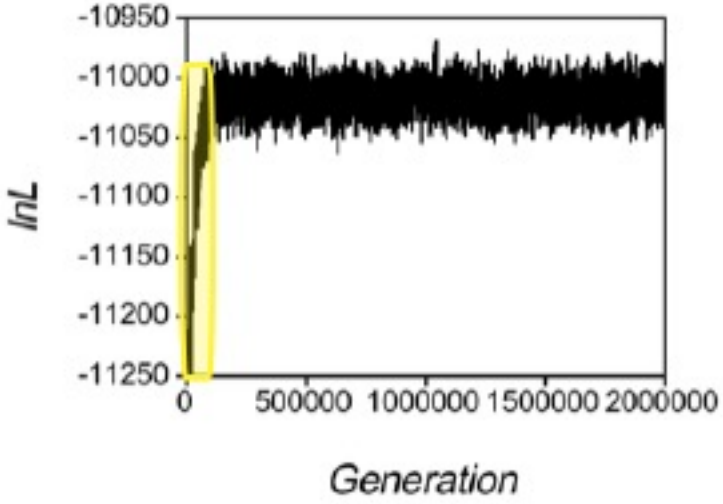
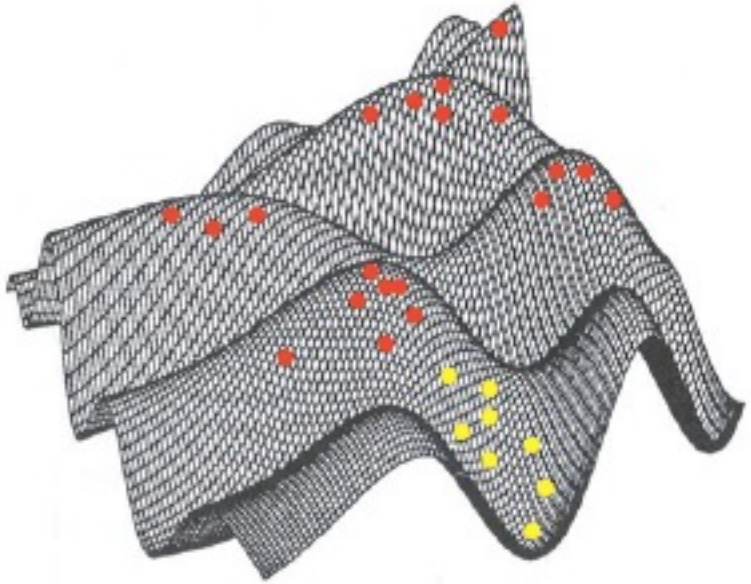
# Metropolis-Hastings Algorithm

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)

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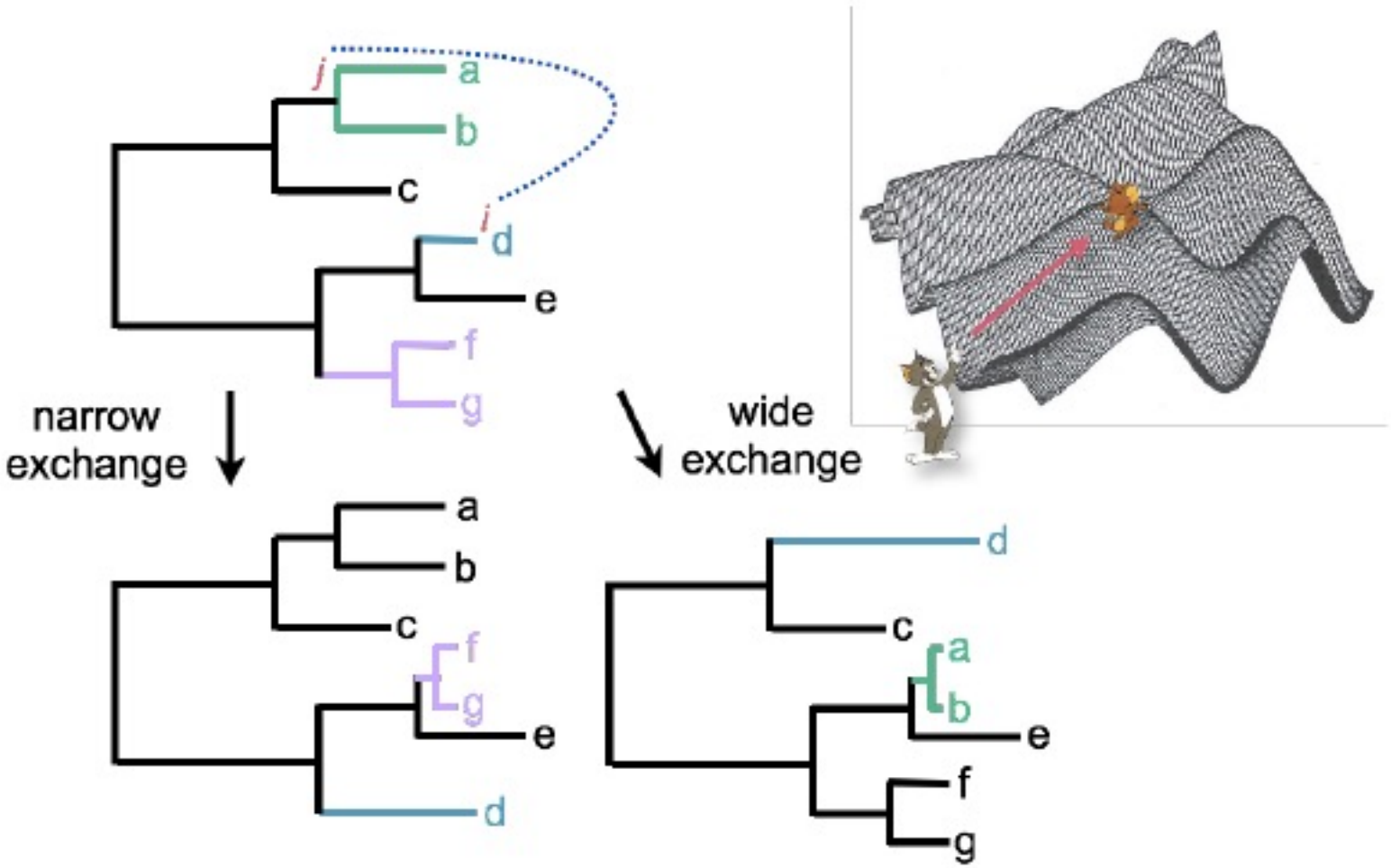
# Transition kernels

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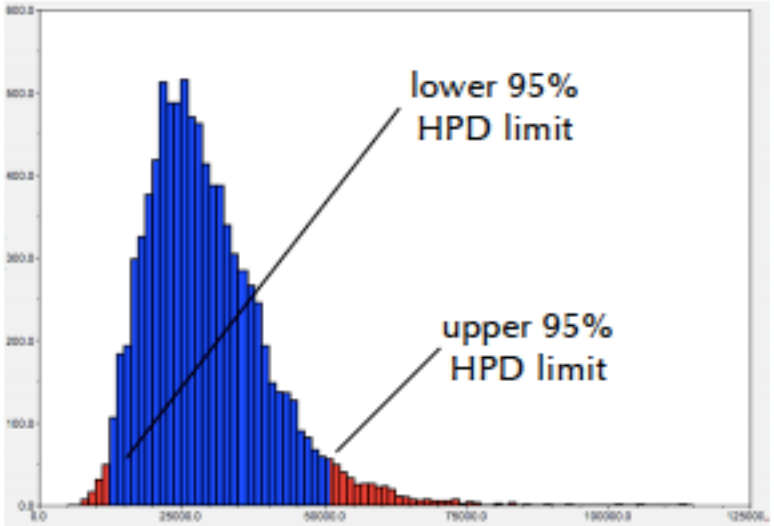
# Posterior summaries

For continuous $\theta$, consider:

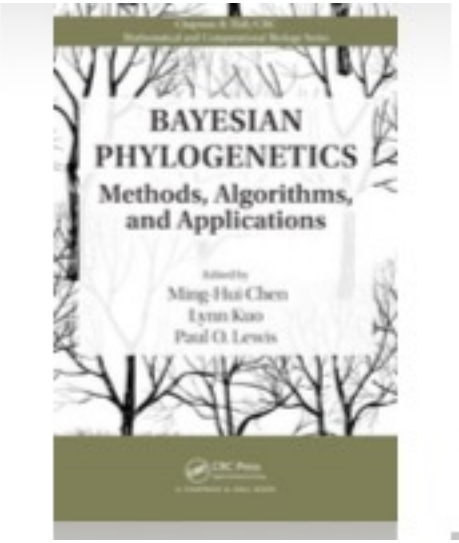
- posterior mean or median $\approx$ MCMC sample average or median
- quantitative measures of uncertainty, e.g. high posterior density interval

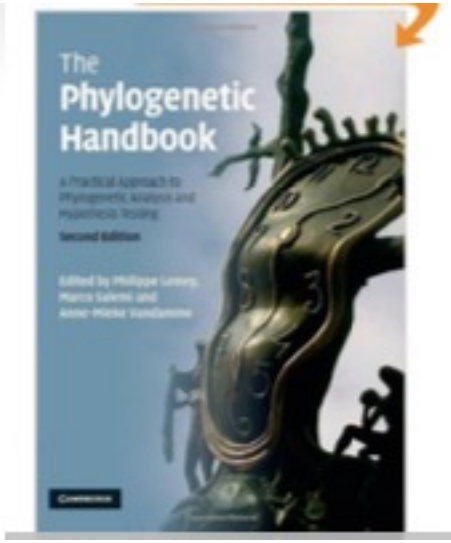


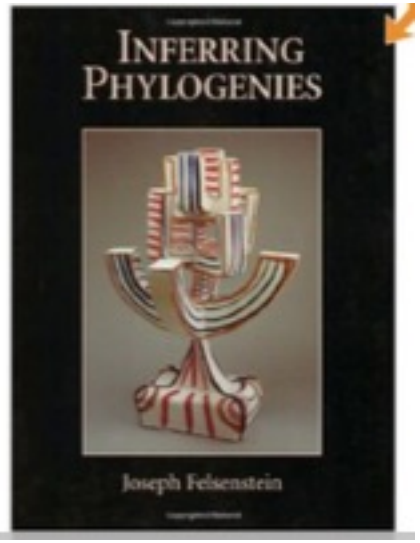

For trees, consider:

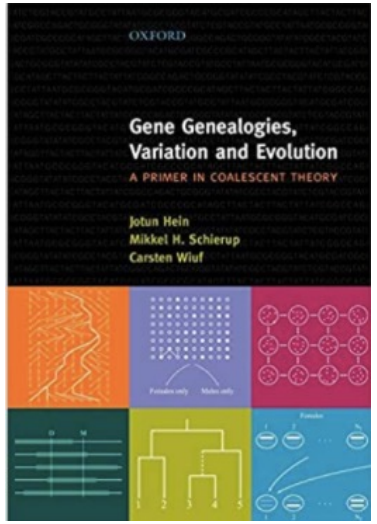
- scientifically interesting posterior probability statement, e.g. the probability of monophyly $\approx$ MCMC sample proportion under which hypothesis is true

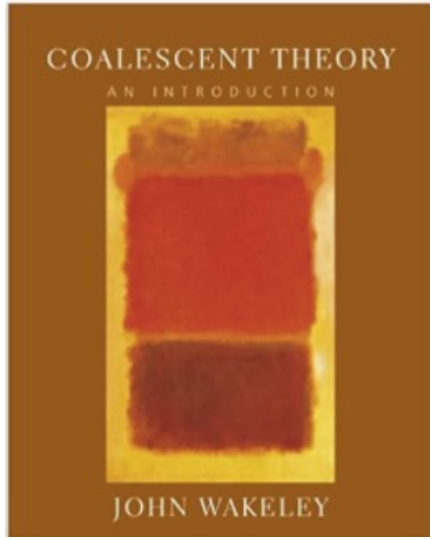
# Book references

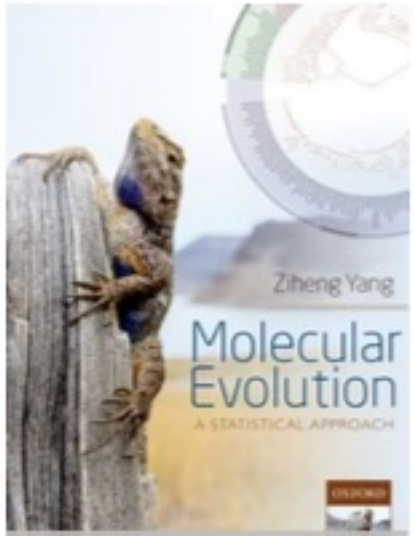


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VIRUS EVOLUTION

*Virus Evolution*, 2022, **8(1)**, 1–12
DOI: https://doi.org/10.1093/ve/veac045
Advance access publication date: 2 June 2022
**Review Article**

## Epidemiological inference from pathogen genomes: A review of phylodynamic models and applications

Leo A. Featherstone,[1,*,†] Joshua M. Zhang,[1] Timothy G. Vaughan,[2,3,‡] and Sebastian Duchene[1]

## Statistical Challenges in Tracking the Evolution of SARS-CoV-2

Lorenzo Cappello, Jaehee Kim, Sifan Liu, Julia A. Palacios

Author Affiliations +

Statist. Sci. 37(2): 162-182 (May 2022). DOI: 10.1214/22-STS853