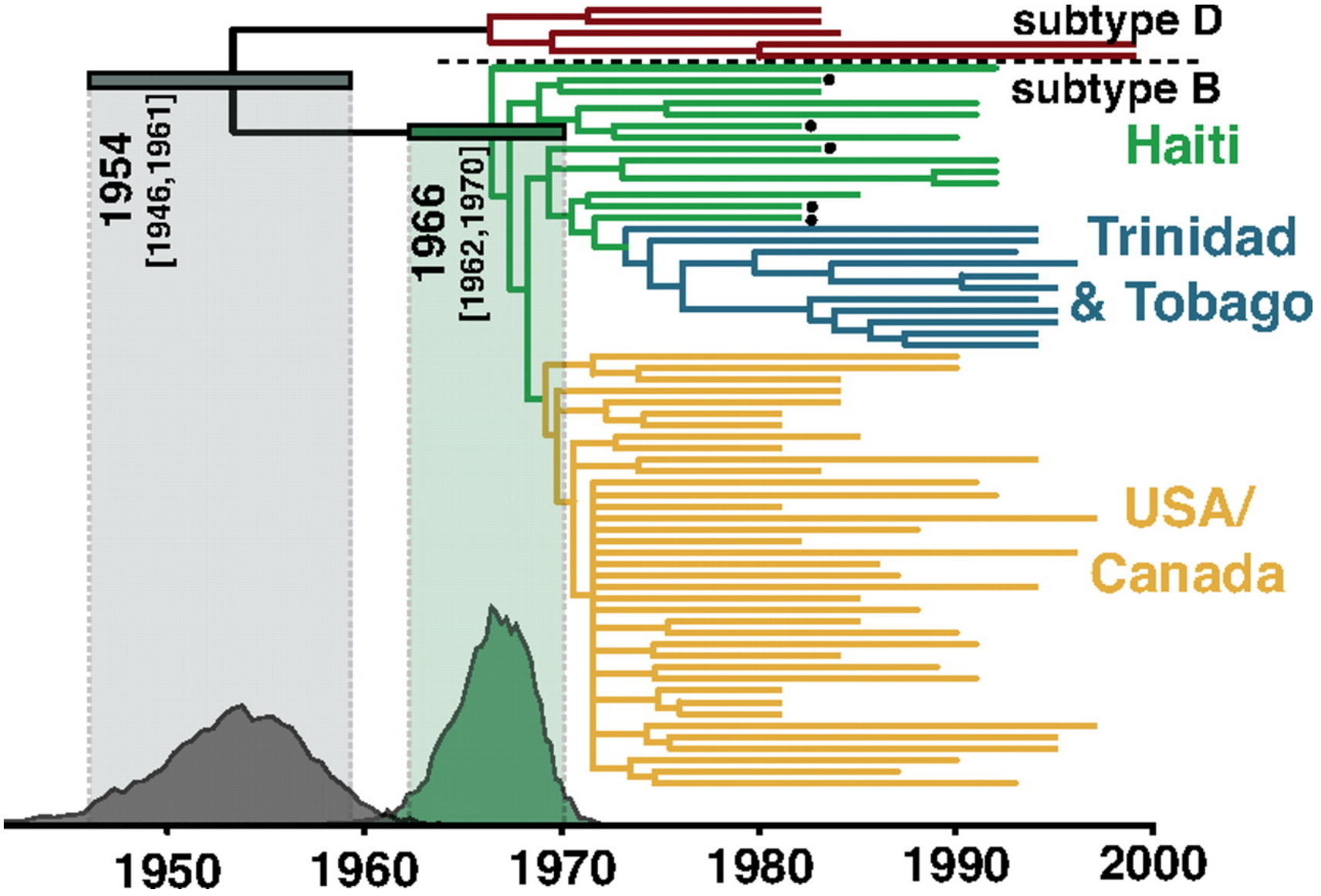
Lecture 1.4:
The Molecular Clock

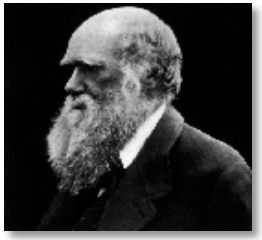
Diversification of mammals

Emergence of HIV/AIDS in the Americas



The Molecular Clock

The molecular clock



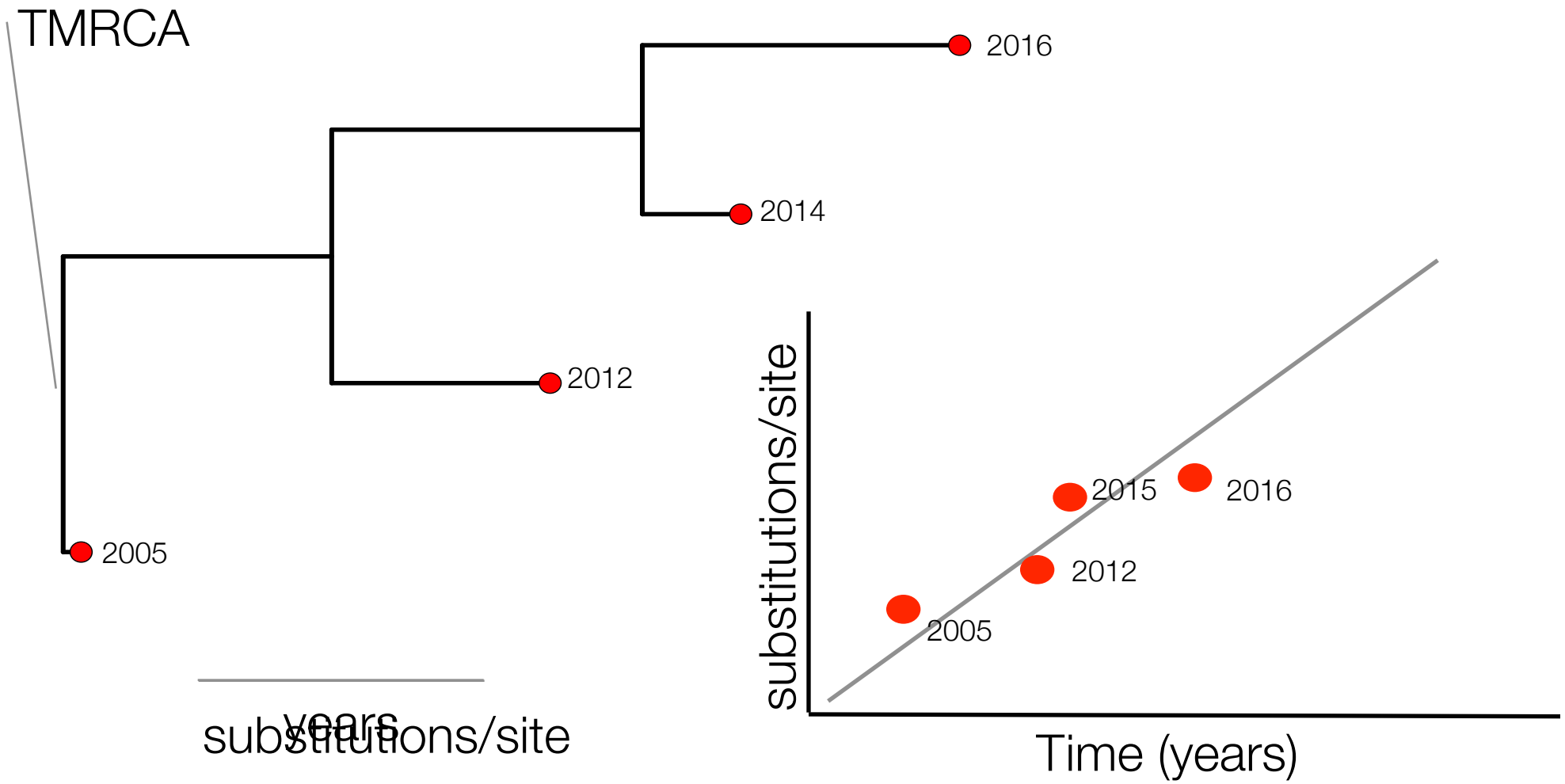
6.5 Myr

8 Myr

26 Myr

5% genetic difference

The molecular clock



The molecular clock

- Zuckerkandl & Pauling (1962)
- Margoliash (1963)
- Doolittle & Blomback (1964)
- **Zuckerkandl & Pauling (1965)**

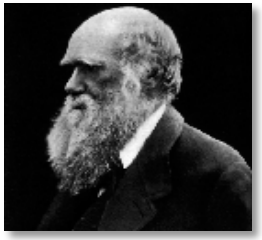
Assumed constant rate among species to estimate timing of globin gene duplications

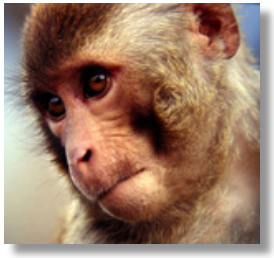
Proportional relationship between genetic distance and time since divergence

Examined correlation between time and genetic divergence in mammalian fibrinopeptides

Introduced the term ‘molecular evolutionary clock’

Sources of error





6.5 Myr

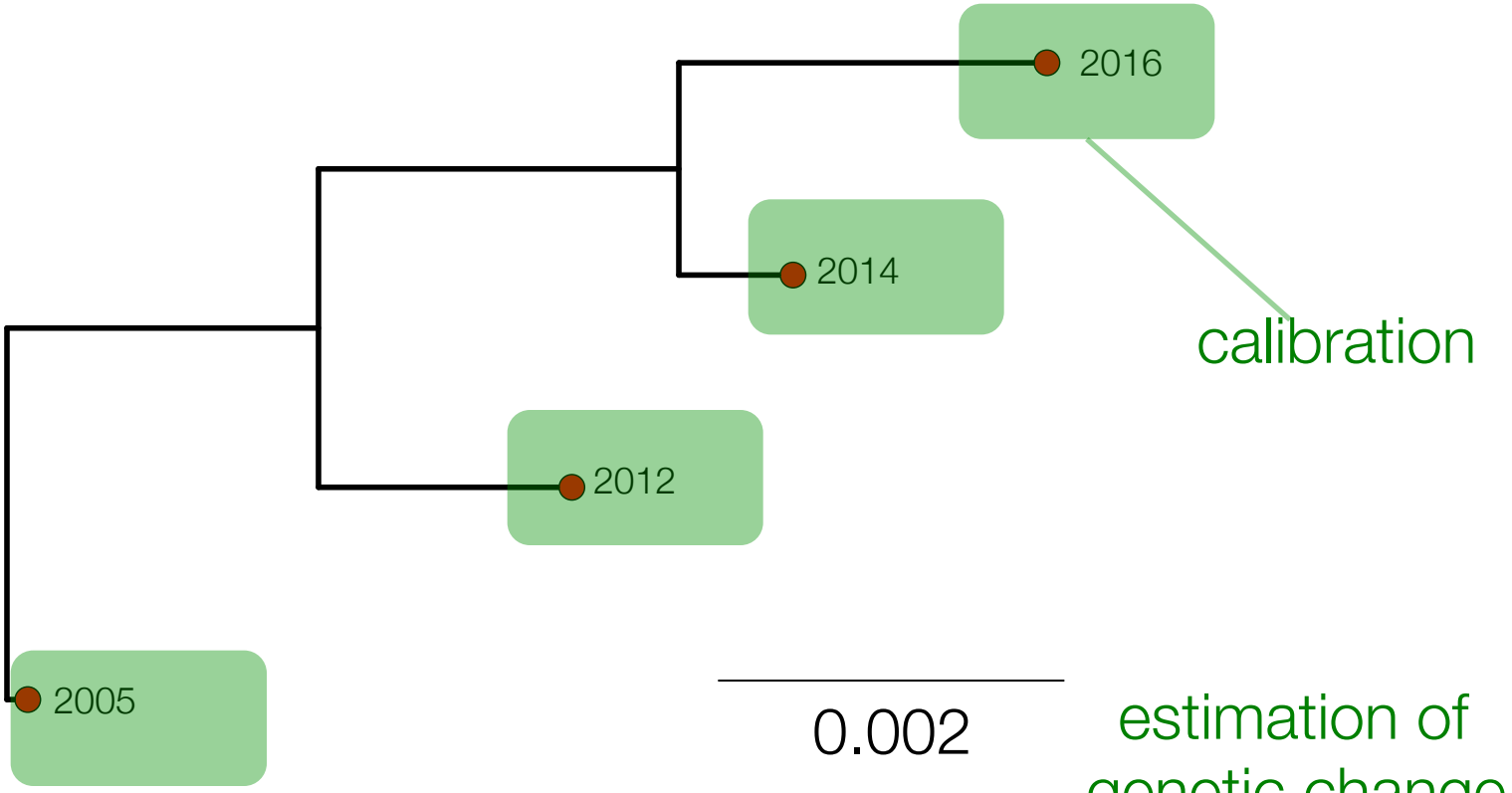
calibration

5% genetic difference

estimation of genetic change

model of rate variation

Sources of error



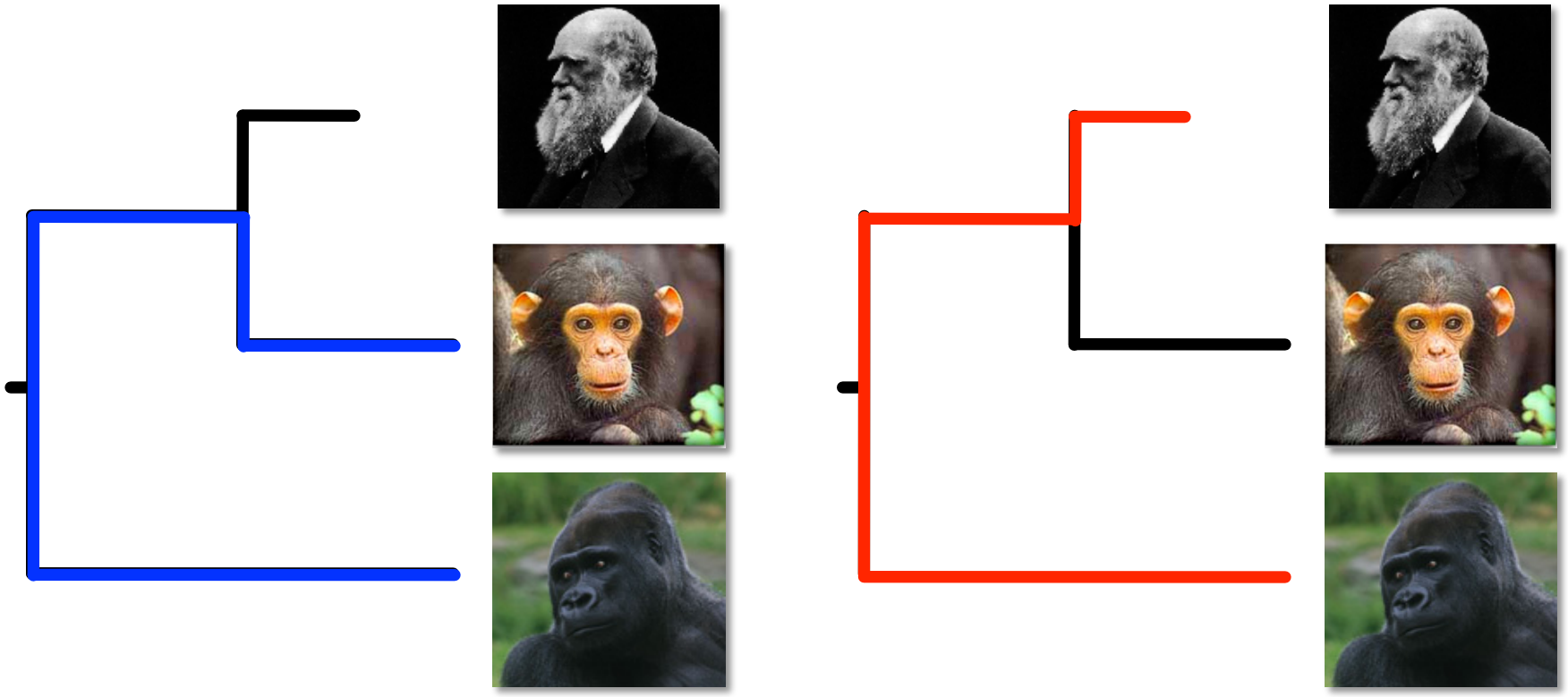
model of rate variation

Departures from the clock

- Rates vary among lineages
  - Differences in mutation rates
  - Differences in strength and direction of selection
  - Differences in population size

Testing for clocklike evolution

- Relative-rates test (Fitch, 1976)



Why keep the molecular clock?

- The behaviour of most real sequences does not satisfy the assumption of a strict molecular clock

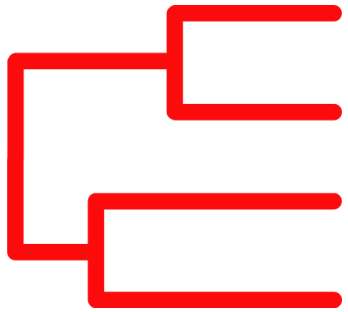
Bromham & Penny (2003):

> *The molecular clock is an irreplaceable source of information in evolutionary biology and it would be foolish to abandon it altogether*

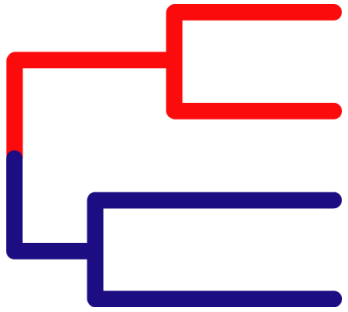
Relaxed Molecular Clocks

Molecular-clock models

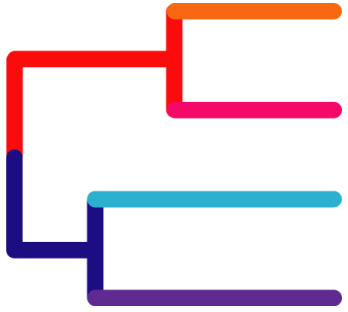
- Strict or ‘global’ molecular clock



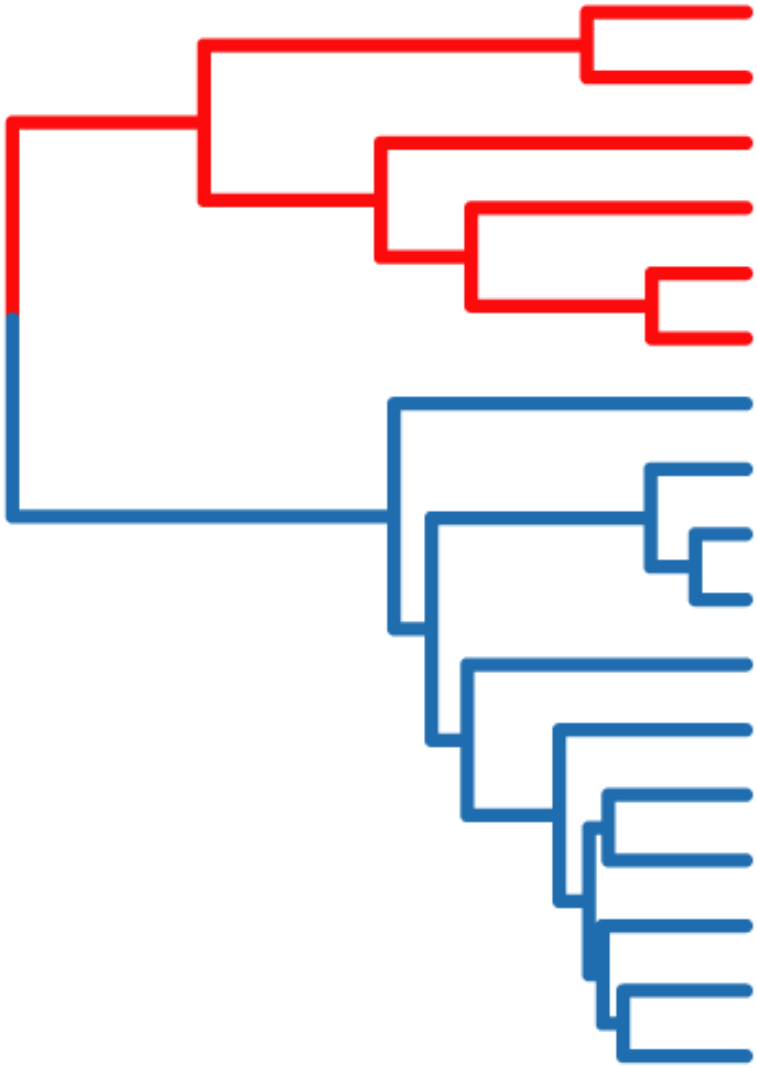
- Local molecular clock



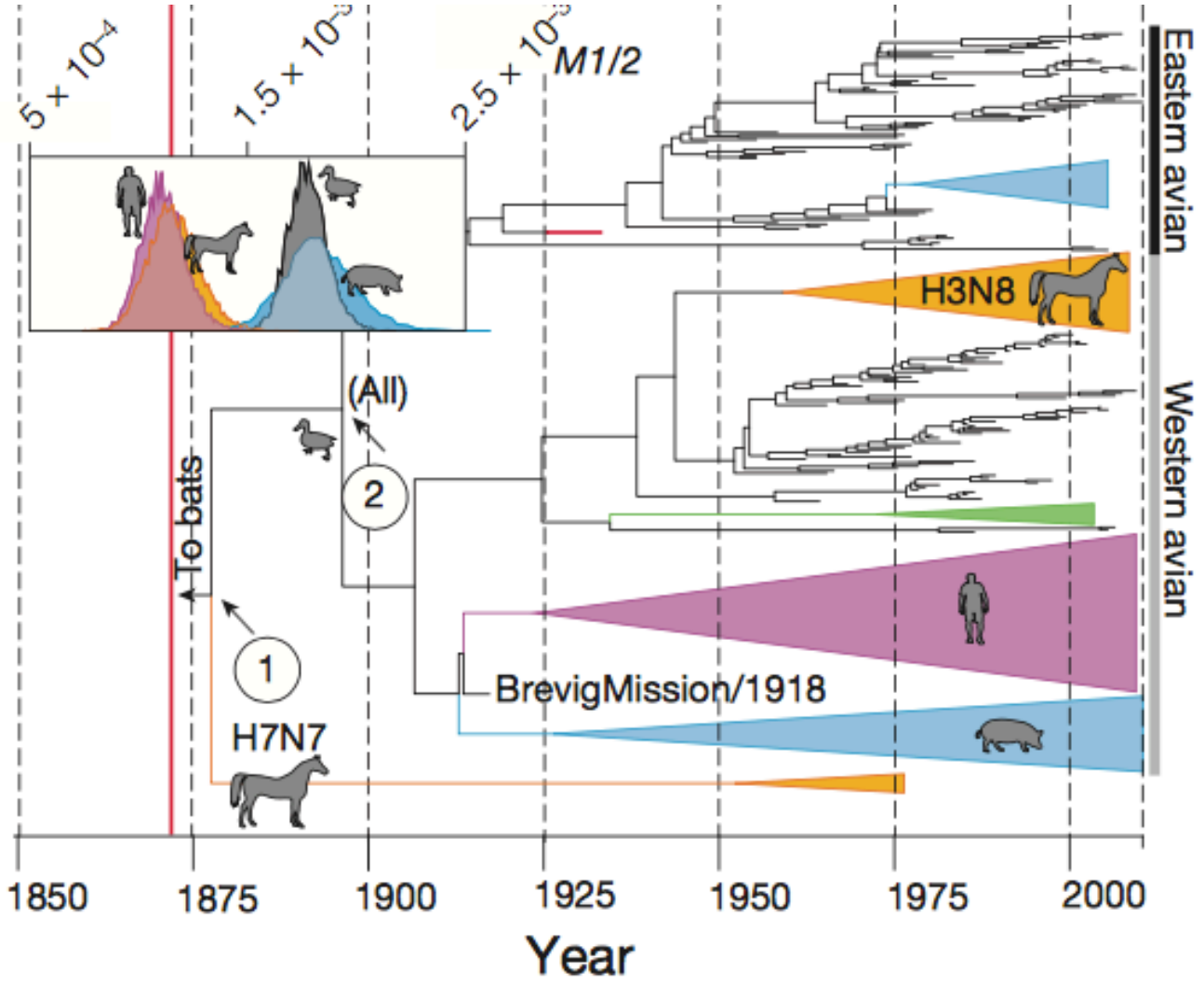
- Relaxed molecular clock



Local molecular clock



Host-specific clock



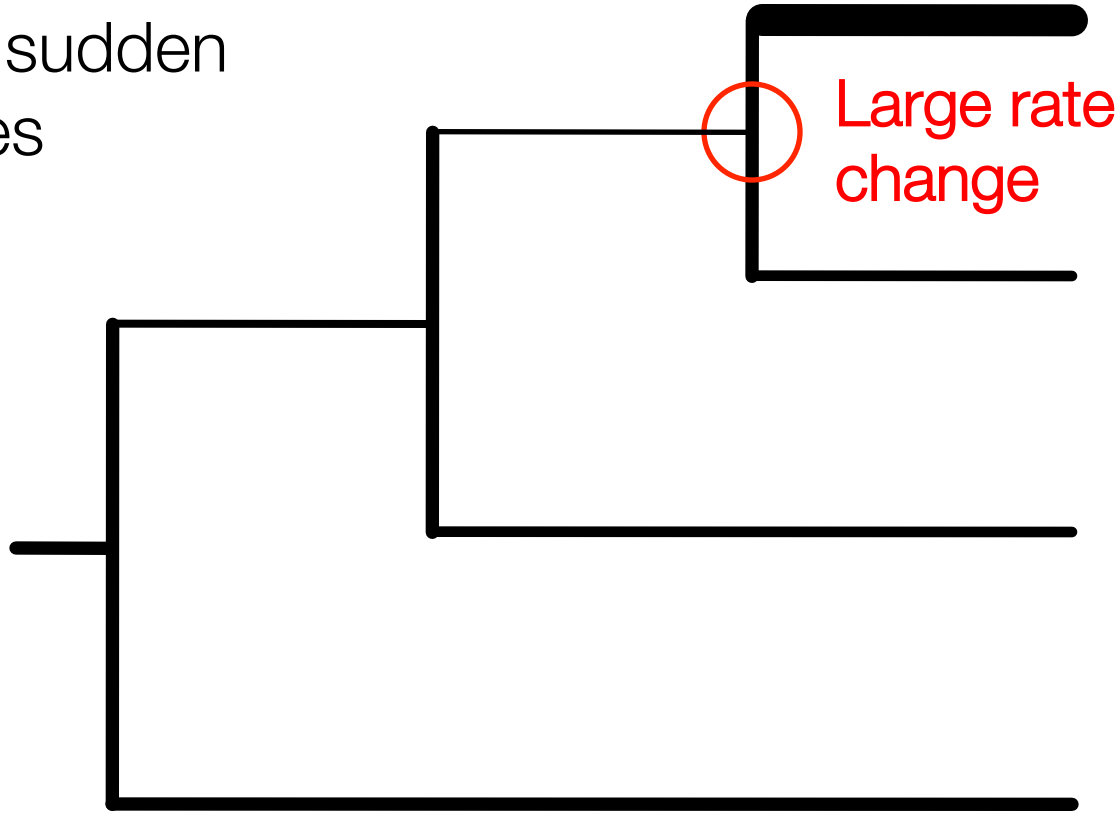
From: Worobey et al. 2014 *Nature*

Relaxed clocks

- We know that life-history characteristics:
  - Have effects on rates of molecular evolution
  - Are usually heritable to some degree
- Treat molecular rate as a heritable trait
- Relaxed clocks generally assume that closely related species share similar rates

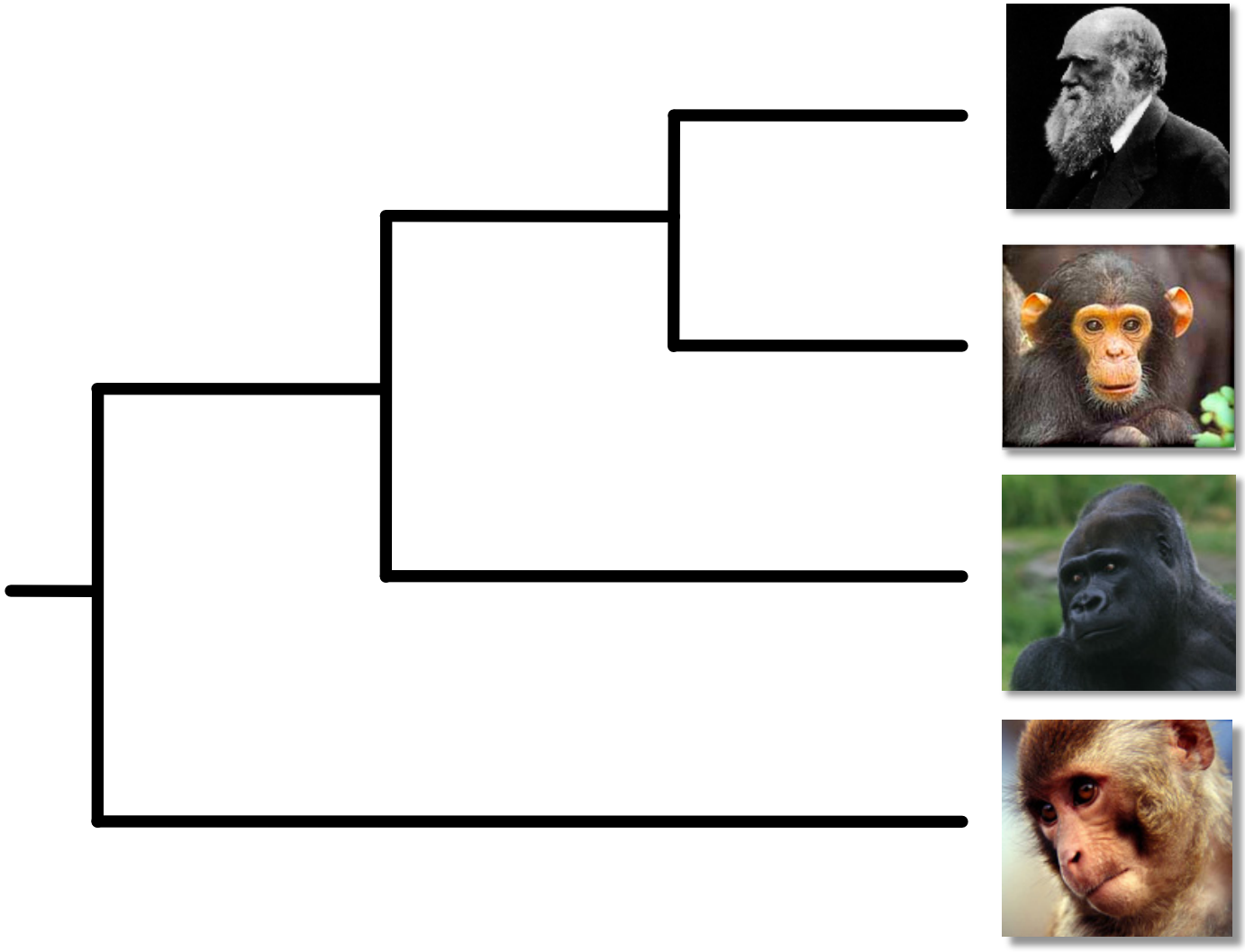
Likelihood-based relaxed clocks

- Allow a different rate in each branch
- Penalise large, sudden changes in rates



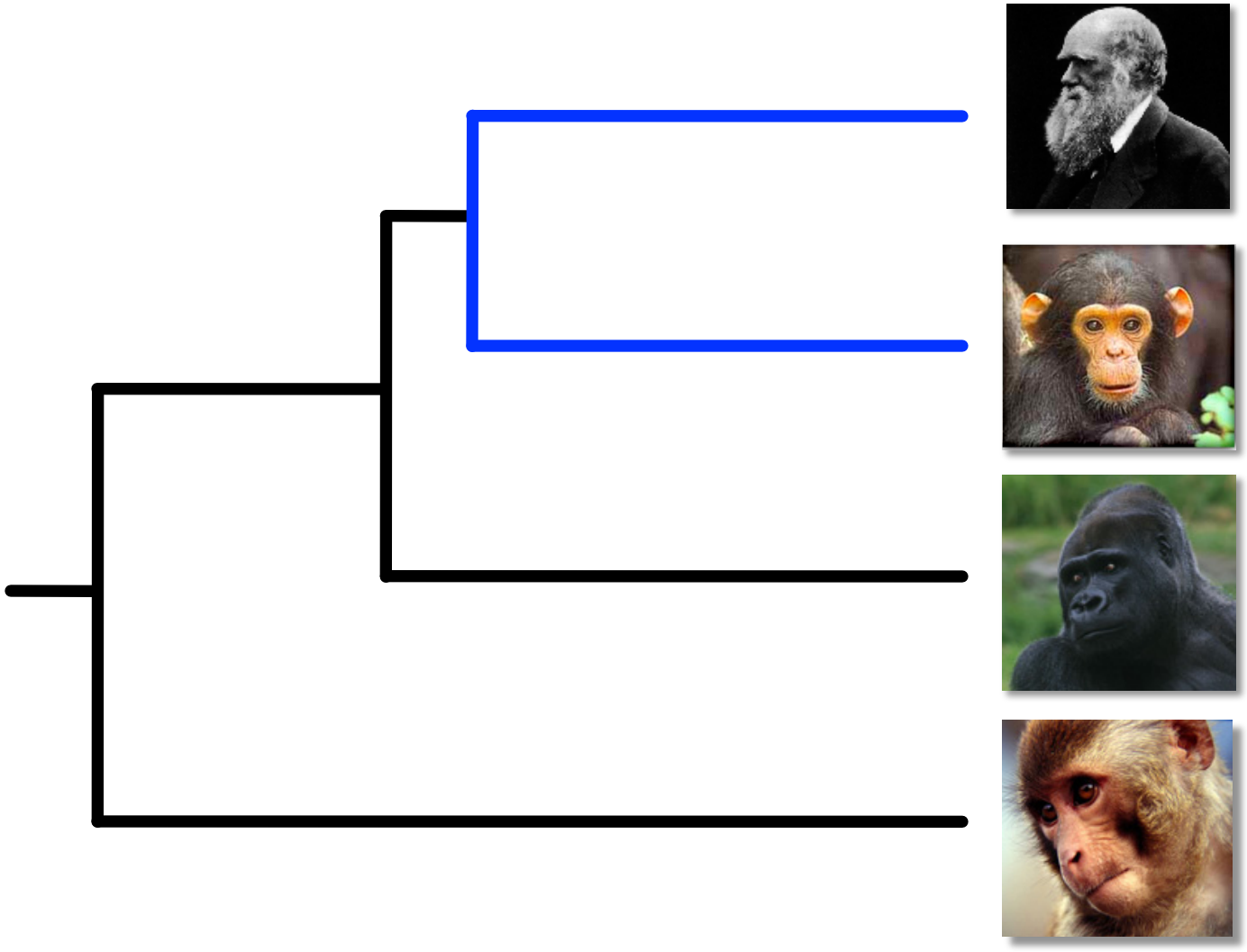
Calibrating the Molecular Clock

Calibrating the molecular clock

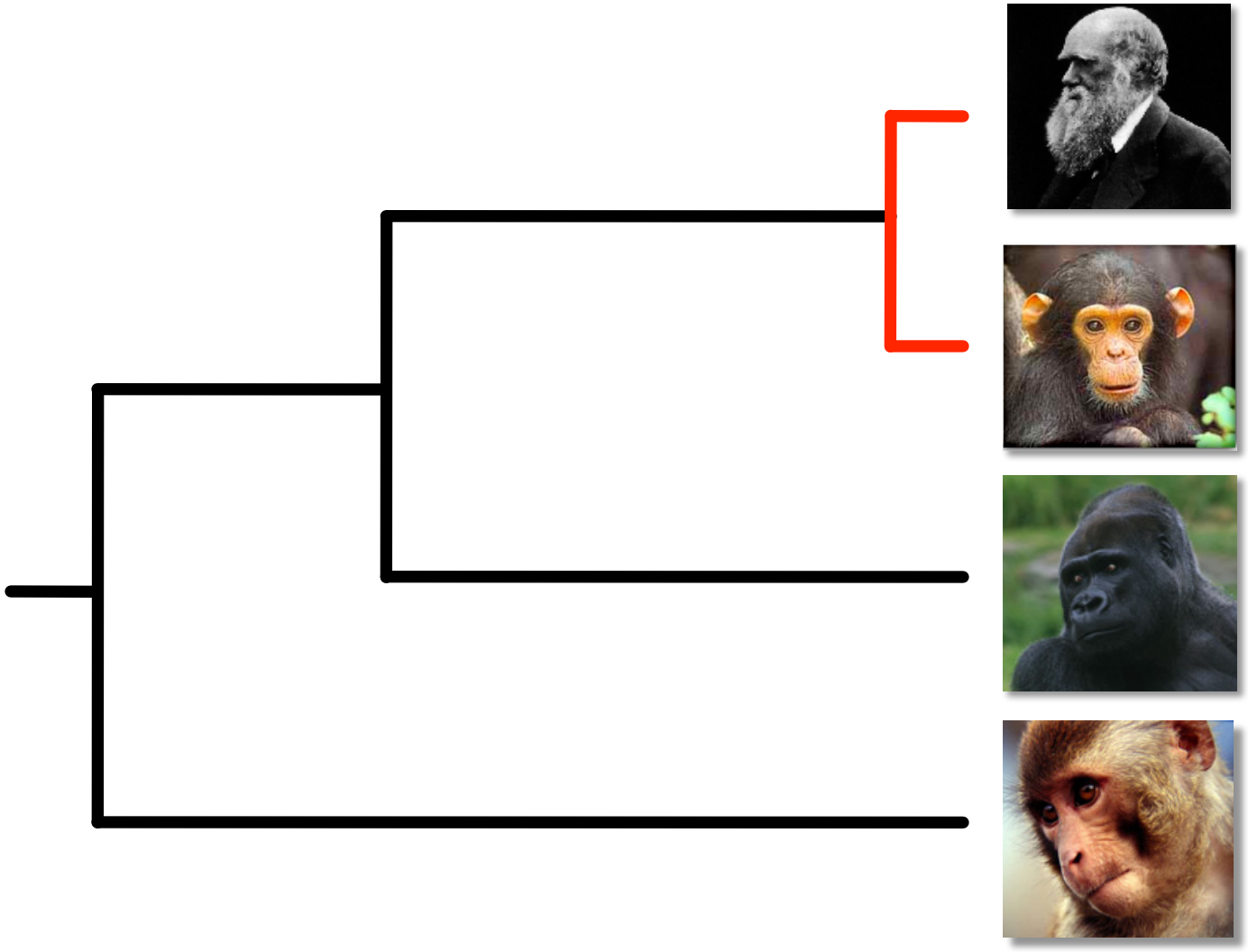


5% genetic difference

Calibrating the molecular clock



Calibrating the molecular clock

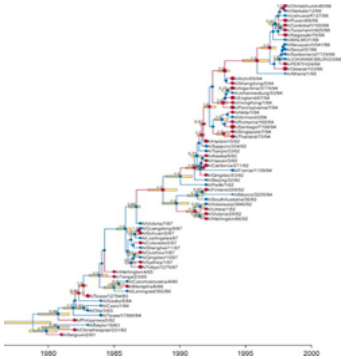


Calibrating information

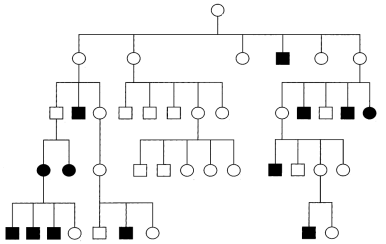
- Information about the rate
  - Substitution rate obtained from an independent study
- Information about time

Fossil record

Biogeography



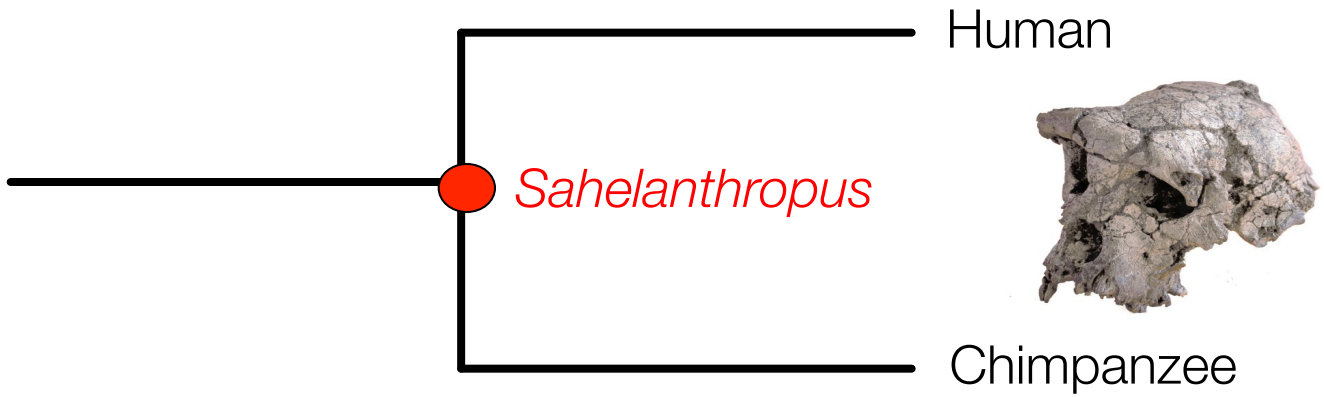
Sampling times



Pedigrees

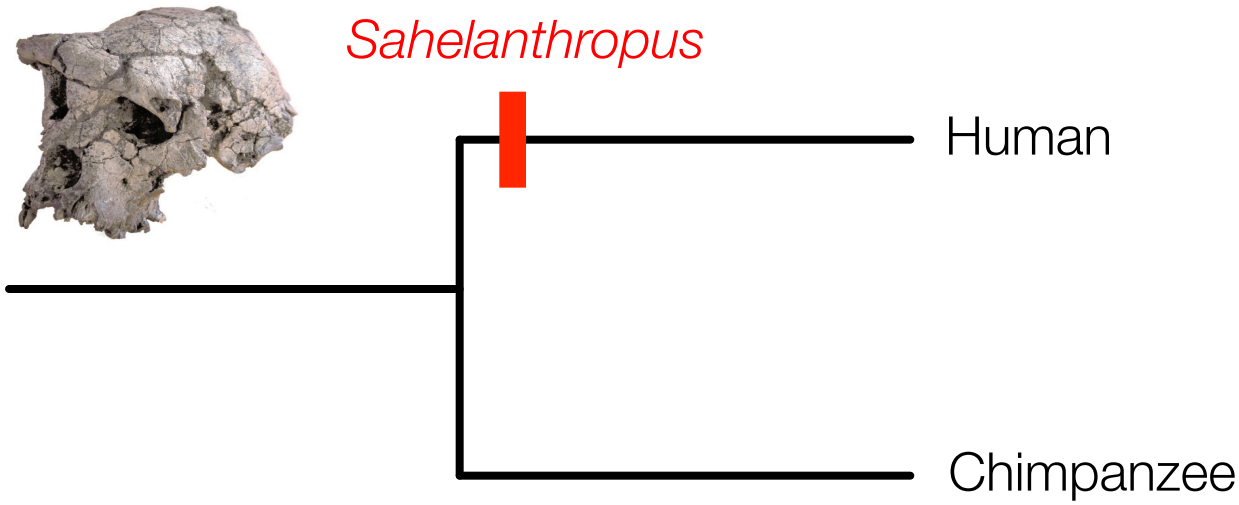
Point calibrations

- Traditional approach
- Artificial precision: ignores the uncertainty arising from preservational biases, isotopic dating errors, *etc.*



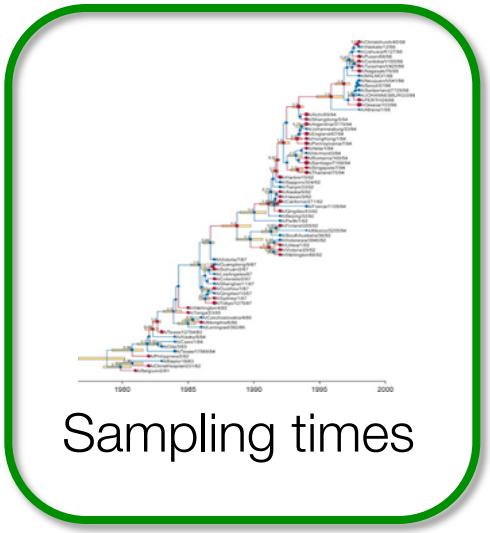
Hard calibration bounds

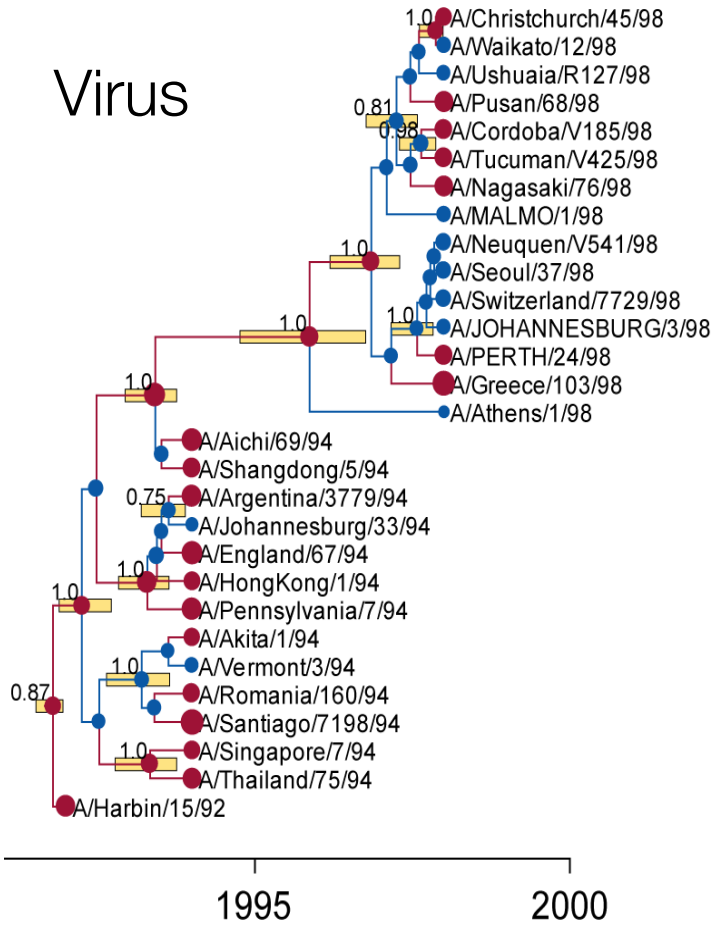
- Minimum or maximum age constraints

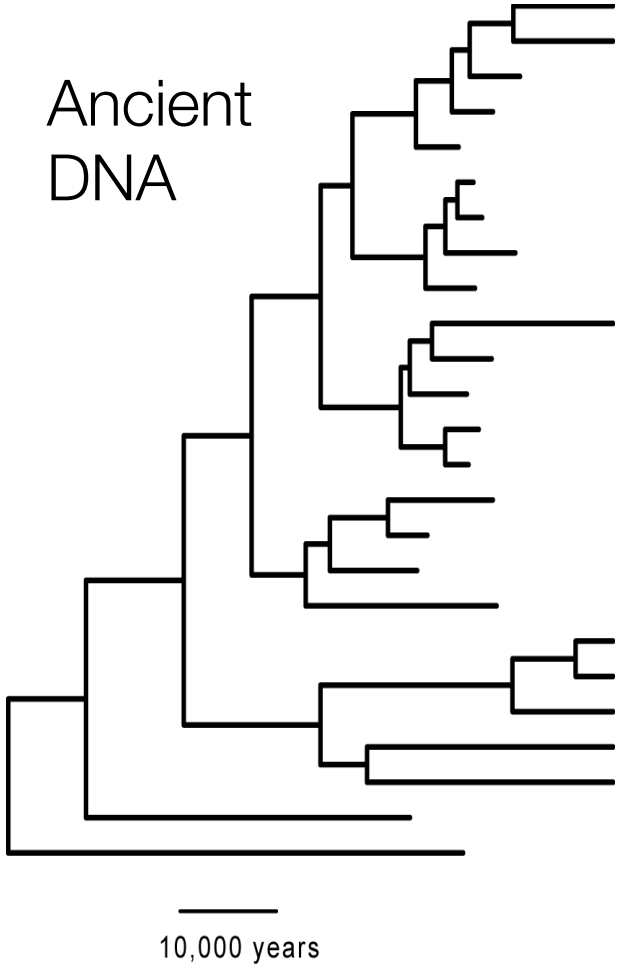


- Discards potentially useful information
- Inadequate information for estimating divergence times

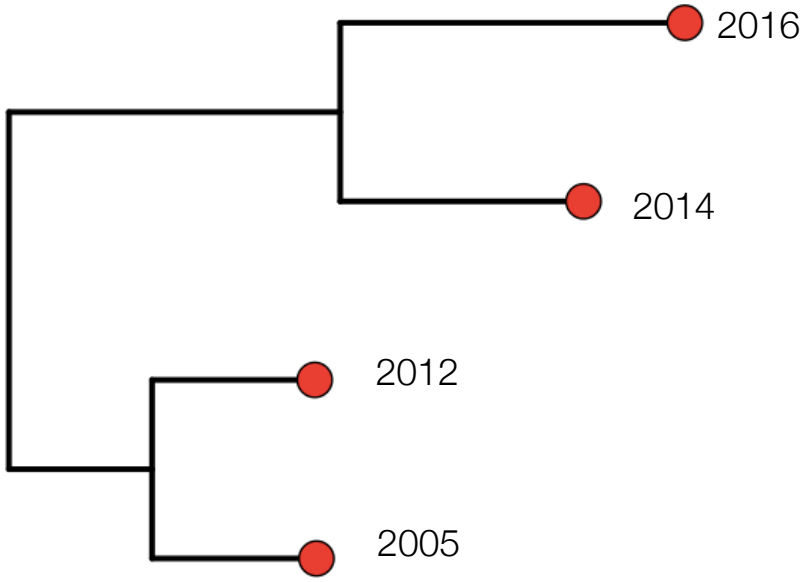
Calibration: Sampling times

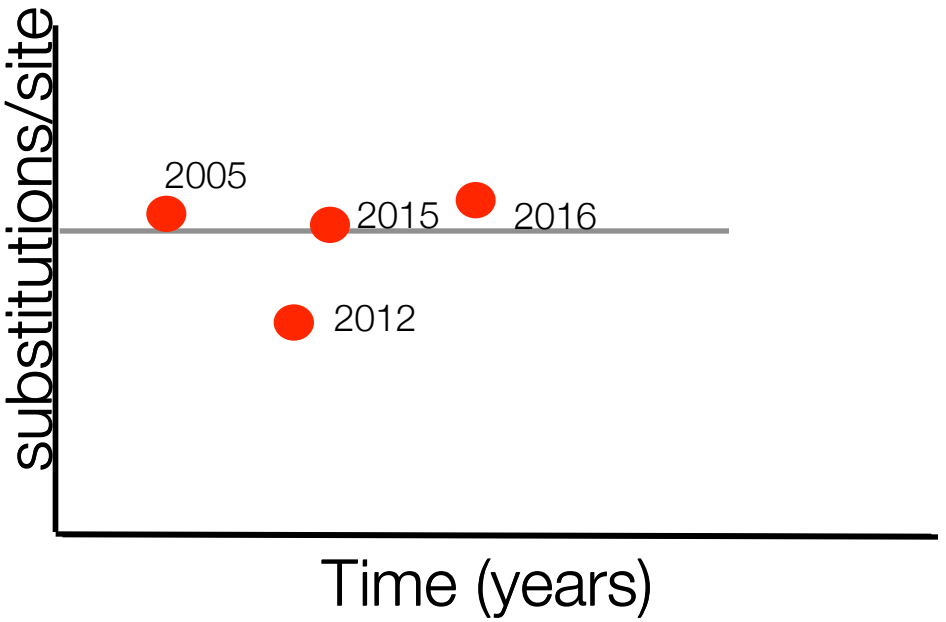






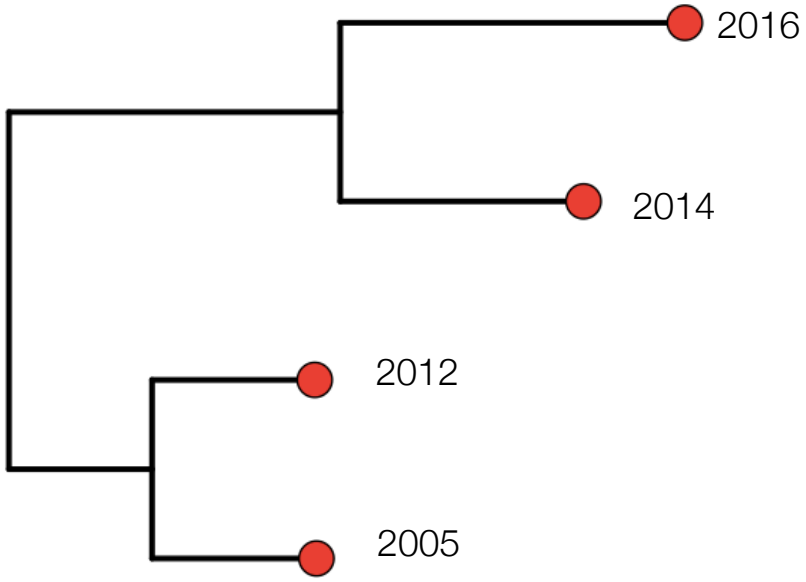
Validating estimates: Root-to-tip regression





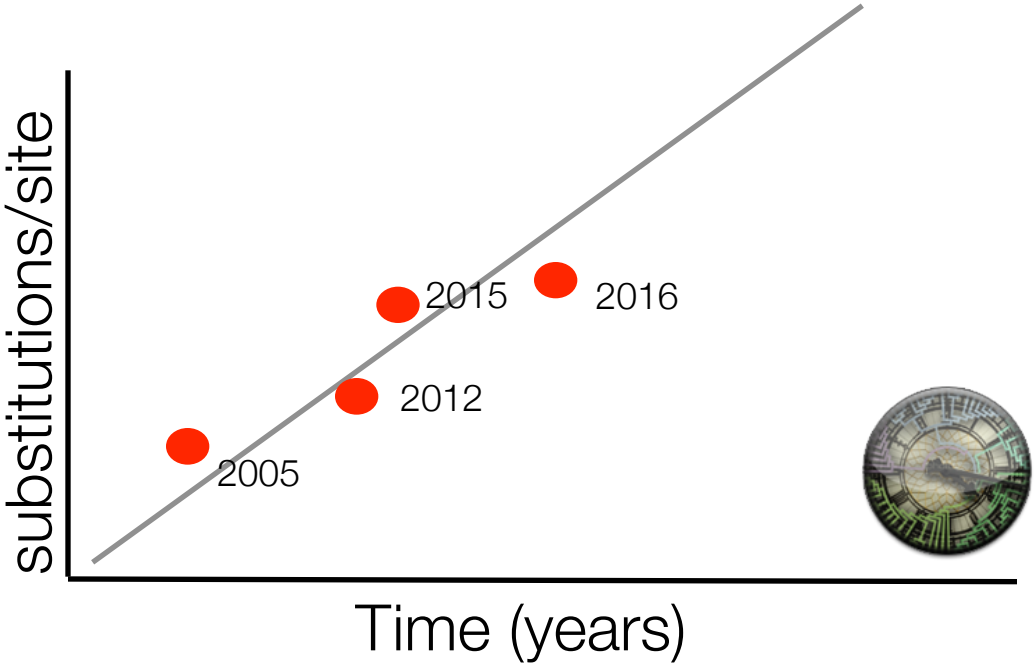
- High R^2
- Positive rate
- P-value (controversial)

Validating estimates: Root-to-tip regression

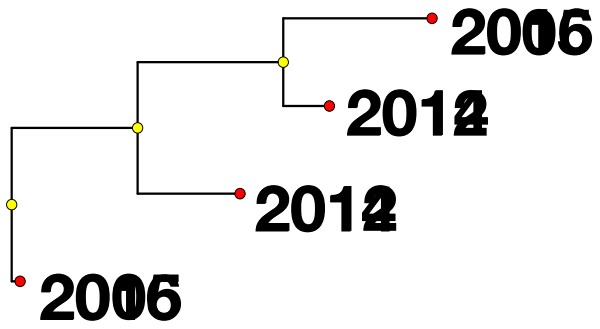


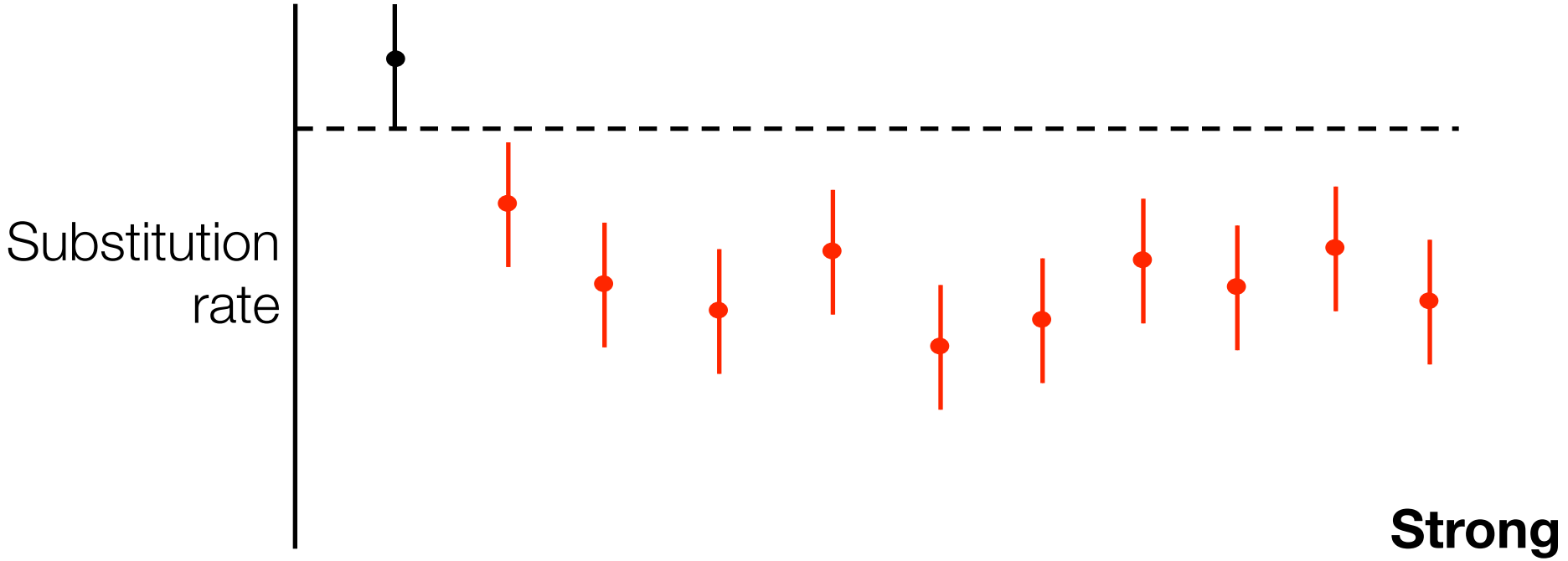
- High R^2
- Positive rate
- P-value (controversial)

The rate estimate is phylogenetically non-independent



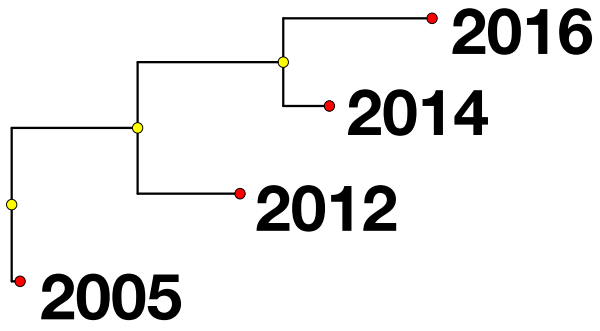
The date-randomisation test

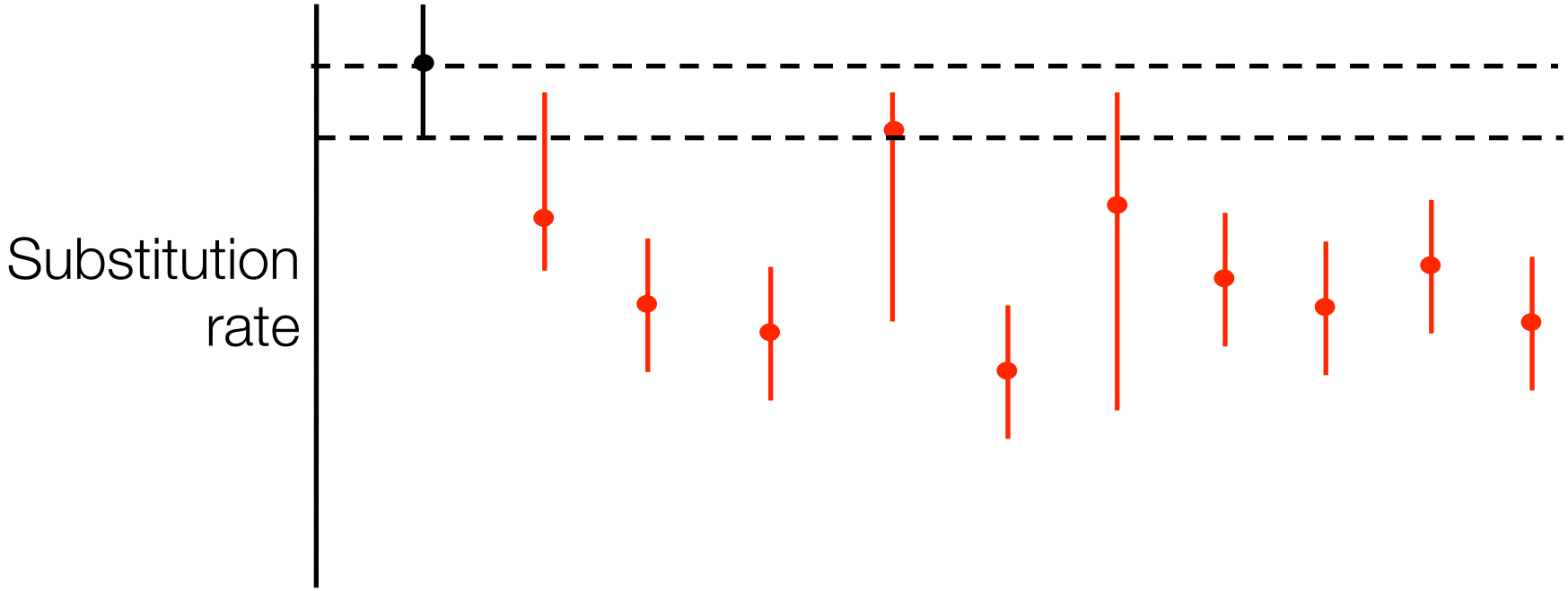




From: Duchene et al. 2015 *Mol Biol Evo*

The date-randomisation test

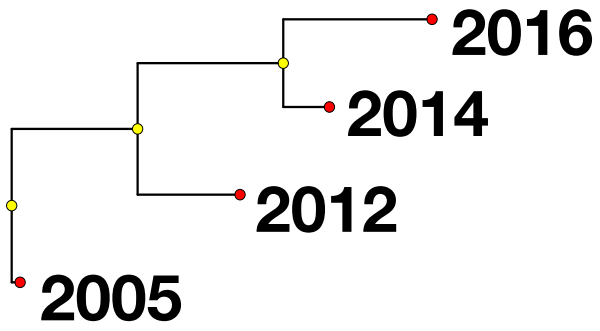


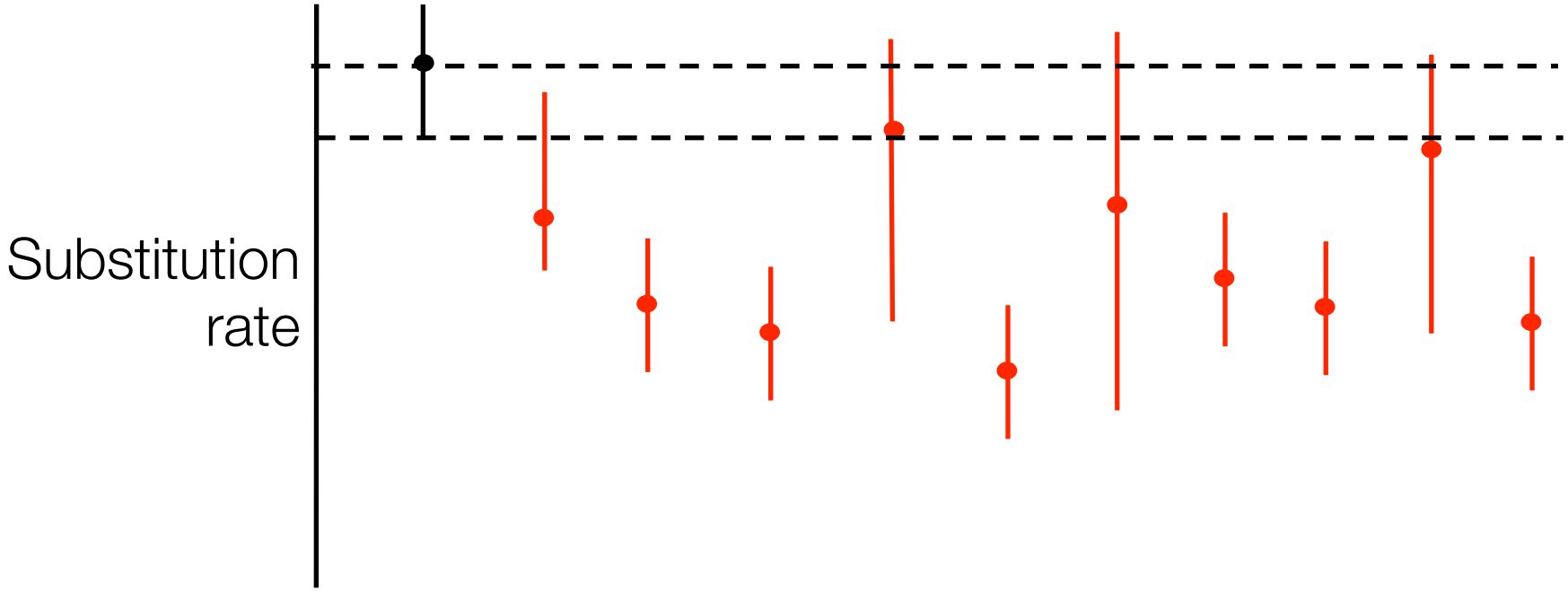


From: Duchene et al. 2015 *Mol Biol Evo*

Medium

The date-randomisation test





From: Duchene et al. 2015 *Mol Biol Evo*

Weak

Some useful references

- Ho, Simon YW, and Sebastián Duchêne. "Molecular-clock methods for estimating evolutionary rates and timescales." *Molecular Ecology* 23.24 (2014): 5947-5965.
- Rieux, Adrien, and François Balloux. "Inferences from tip-calibrated phylogenies: a review and a practical guide." *Molecular ecology* 25.9 (2016): 1911-1924.
- Duchêne, Sebastián, et al. "The performance of the date-randomisation test in phylogenetic analyses of time-structured virus data." *Molecular biology and evolution* (2015).

Go to Practical 1d: Assessing temporal structure in *TempEst*