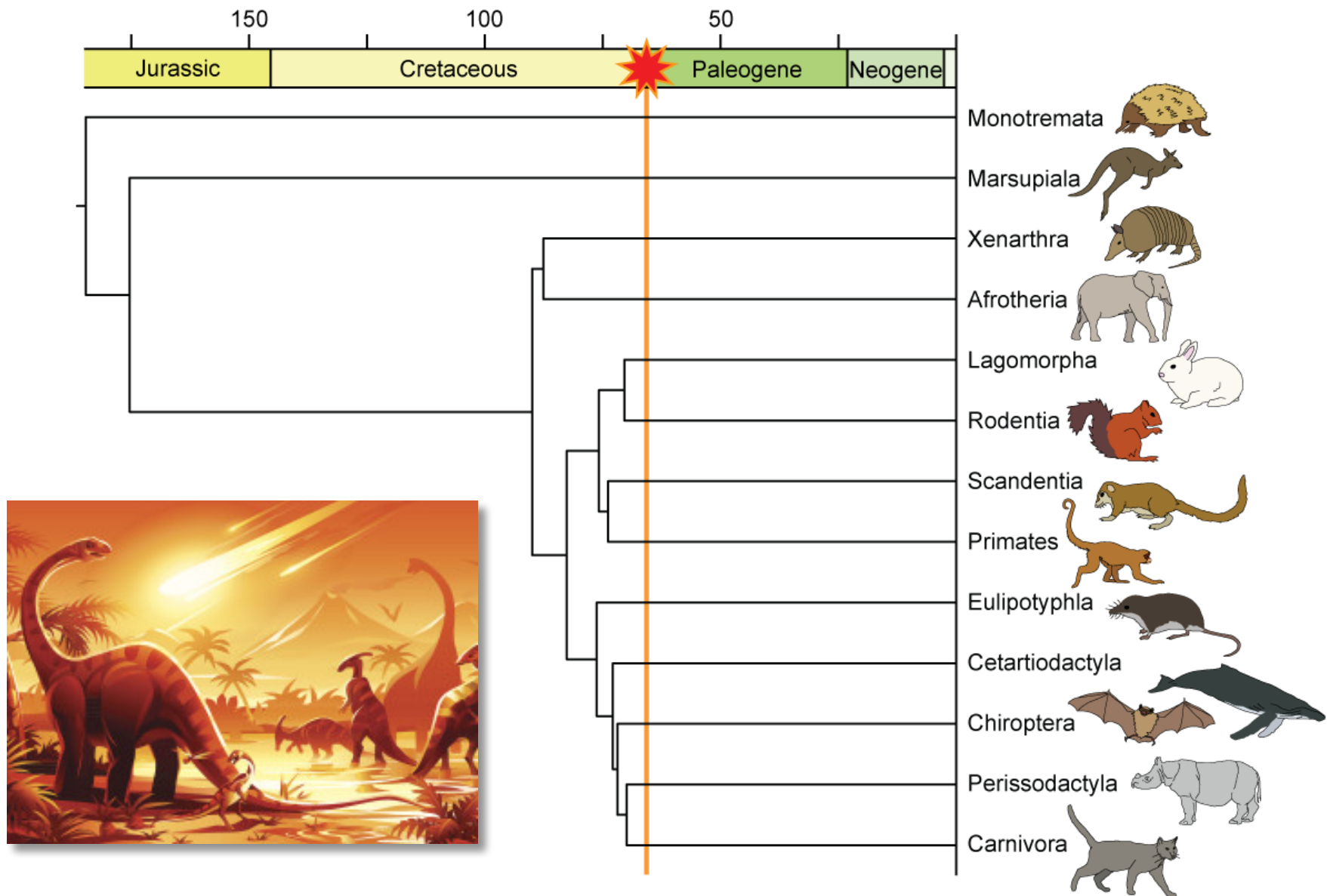


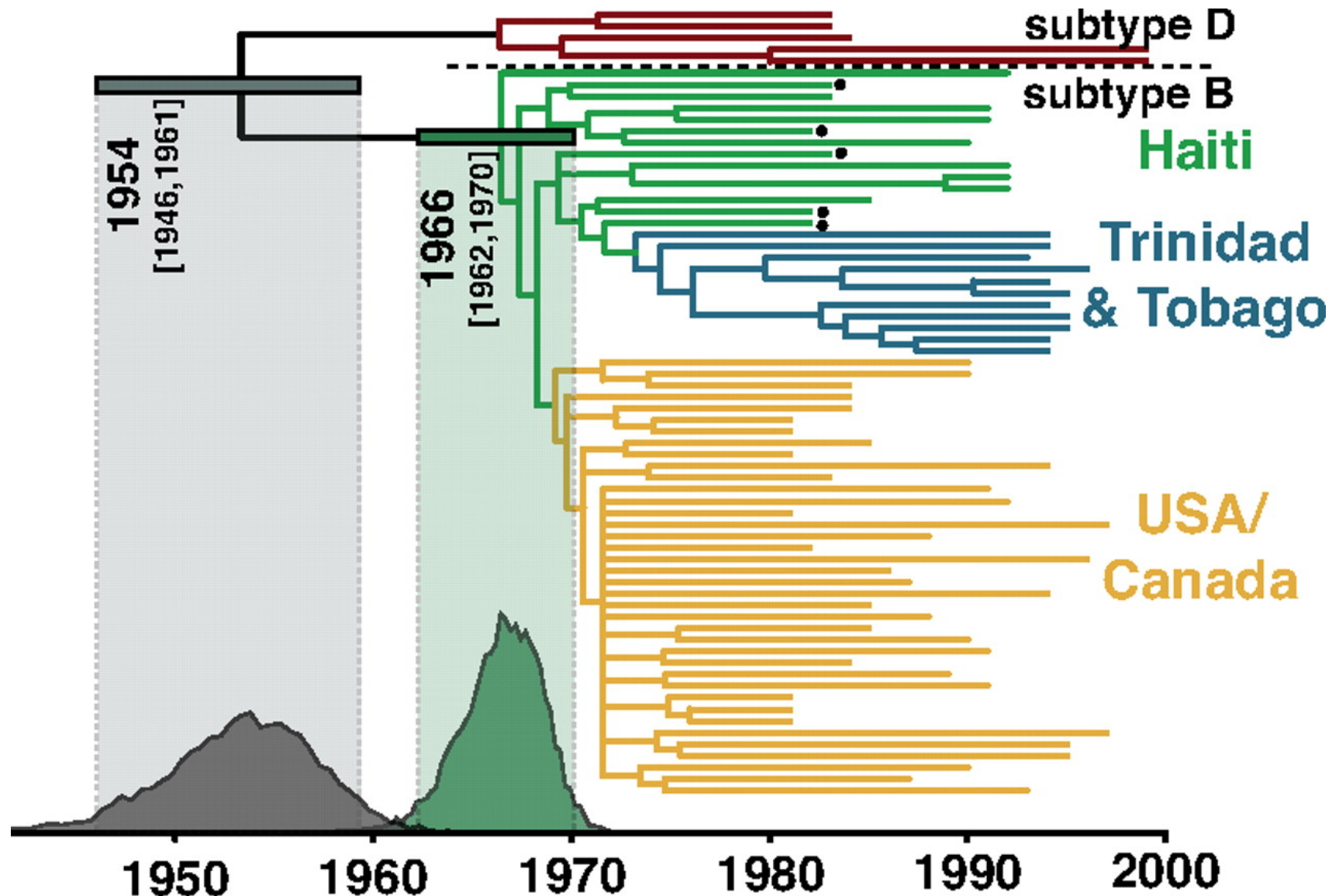
Lecture 1.4:

The Molecular Clock

Diversification of mammals

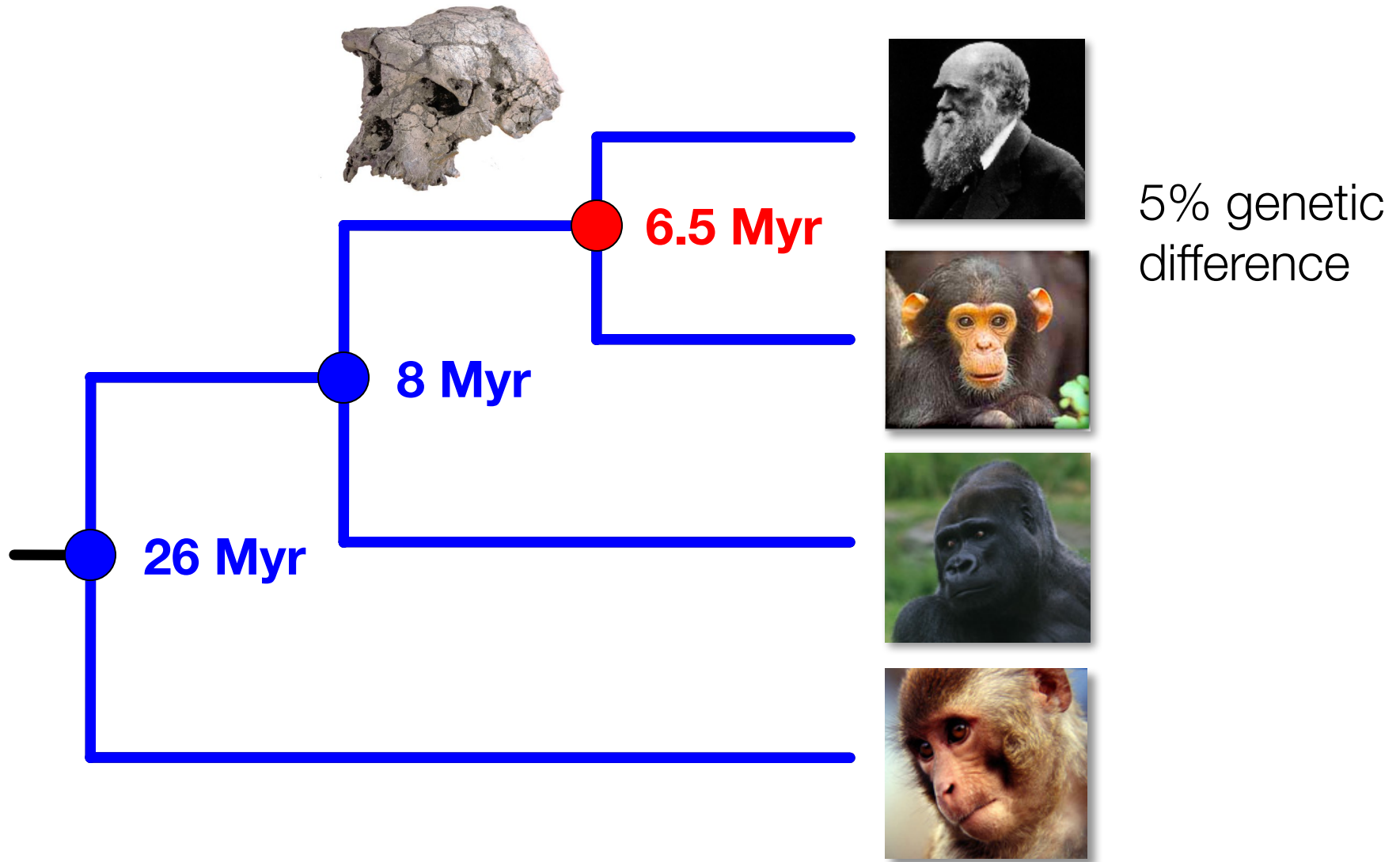


Emergence of HIV/AIDS in the Americas



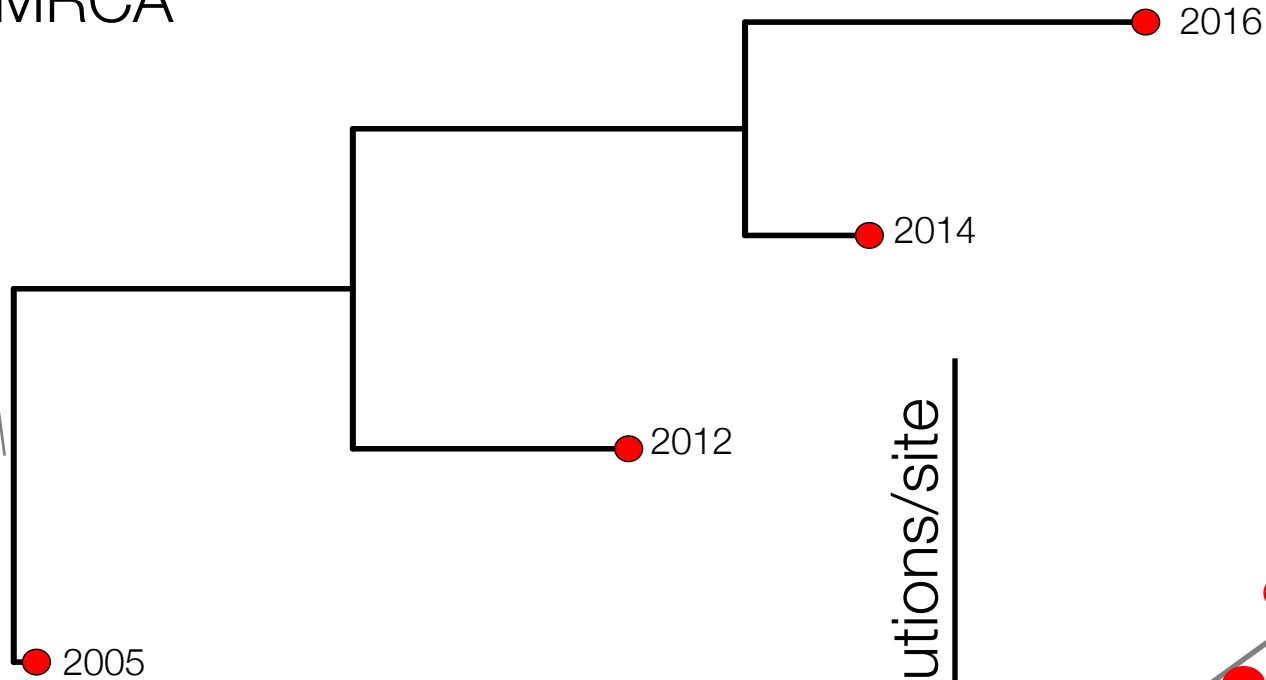
The Molecular Clock

The molecular clock

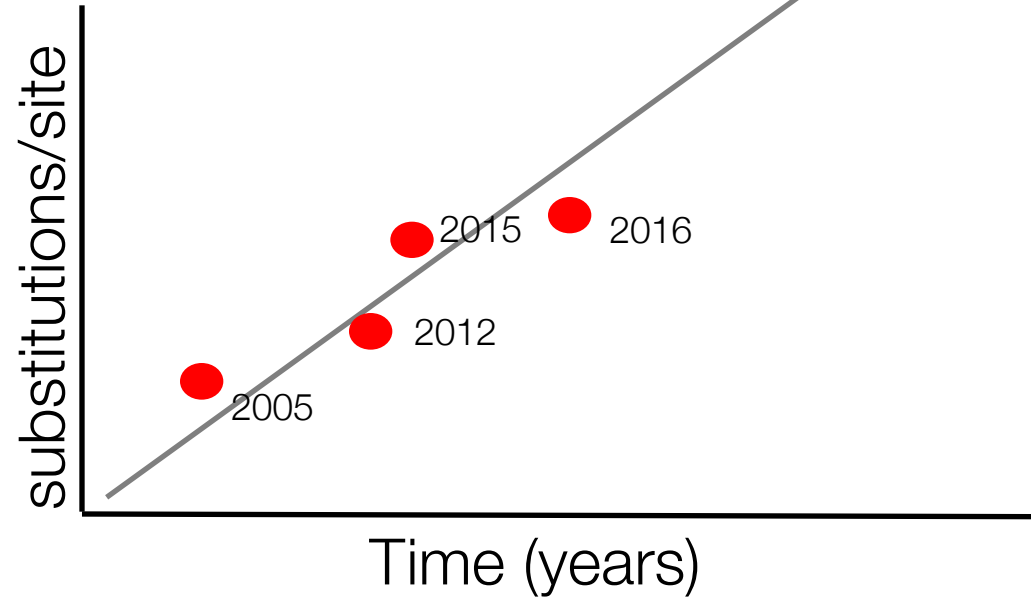


The molecular clock

TMRCA



substitutions/site



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

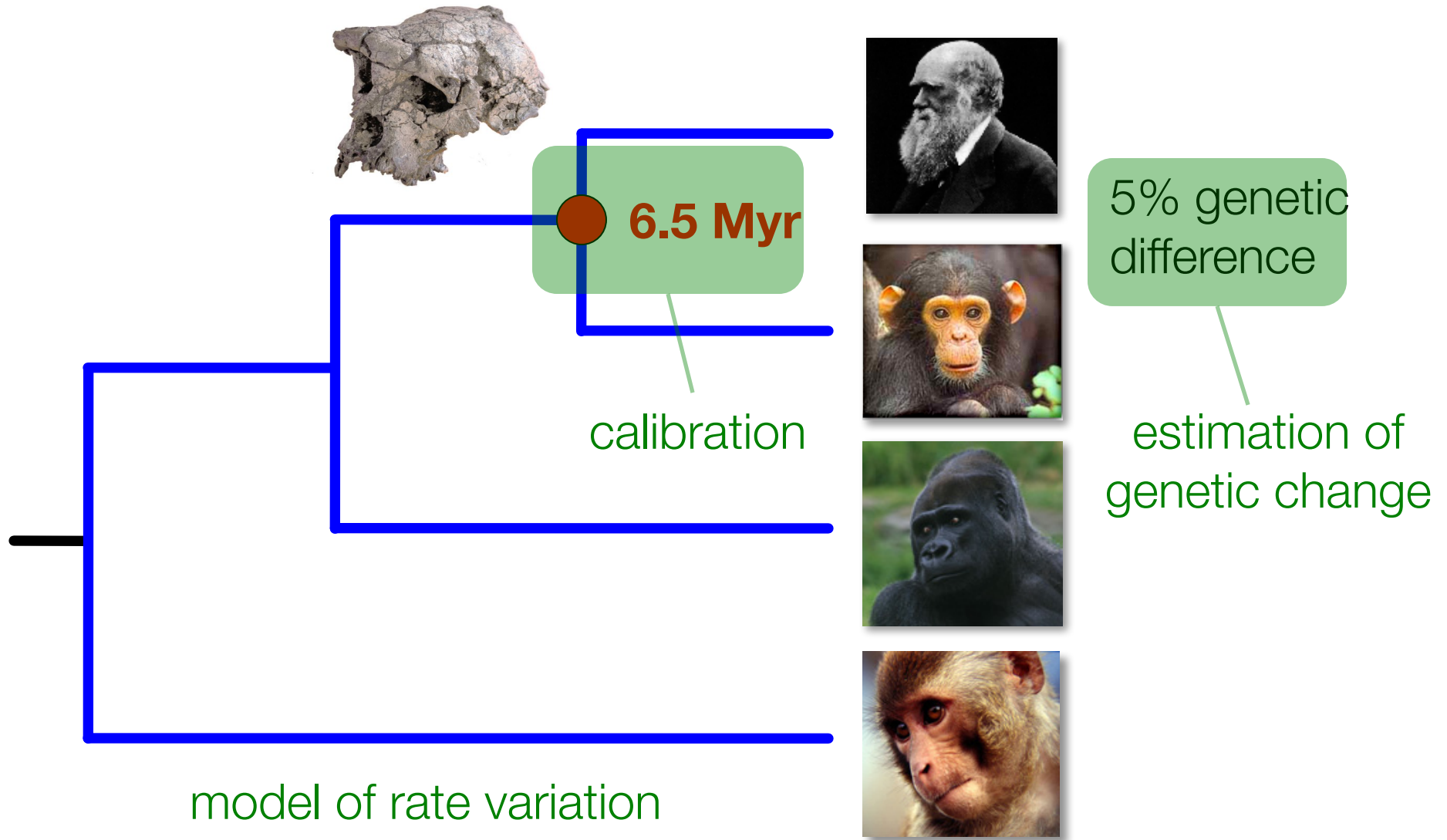
Proportional relationship between genetic distance and time since divergence



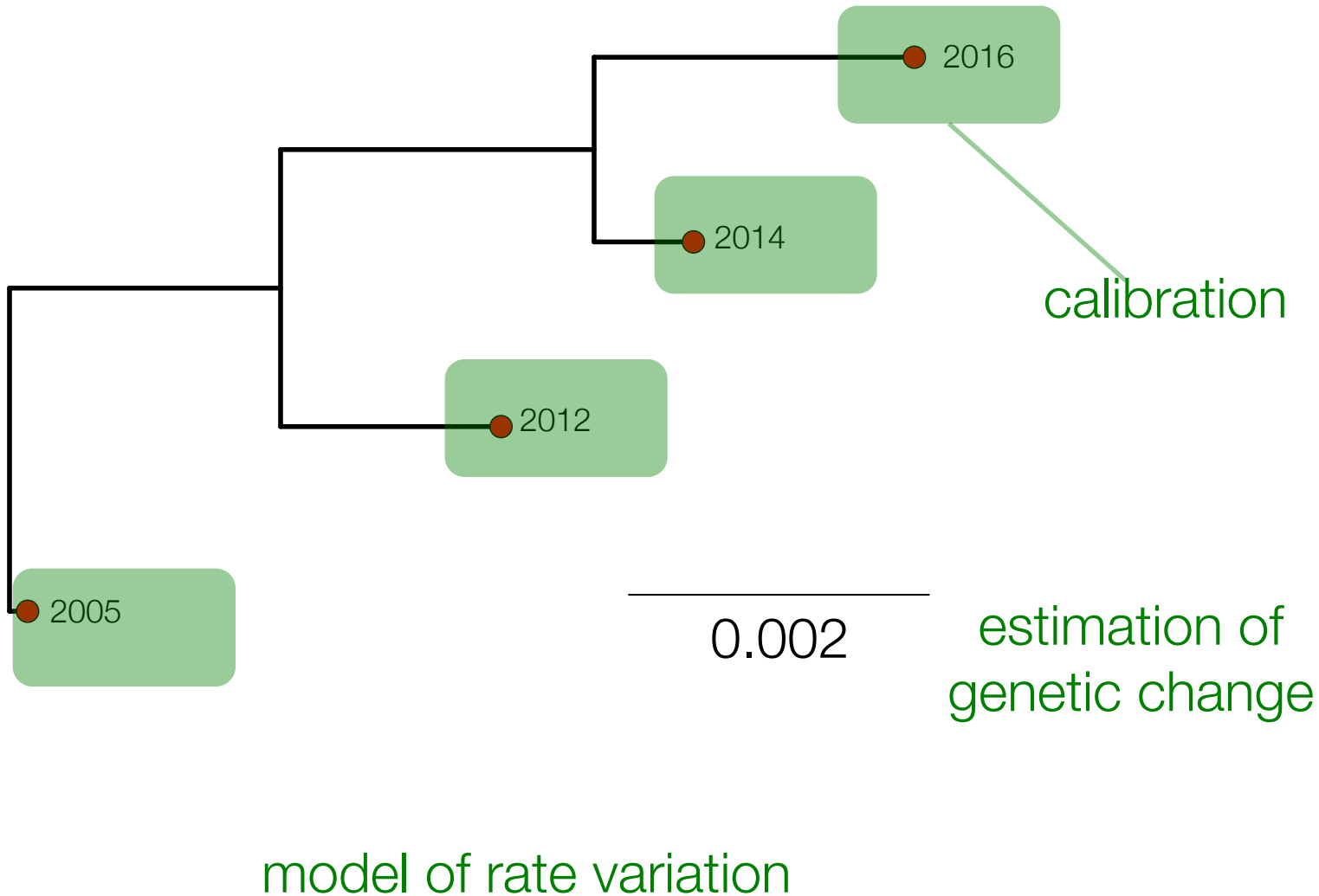
Examined correlation between time and genetic divergence in mammalian fibrinopeptides

Introduced the term ‘molecular evolutionary clock’

Sources of error



Sources of error



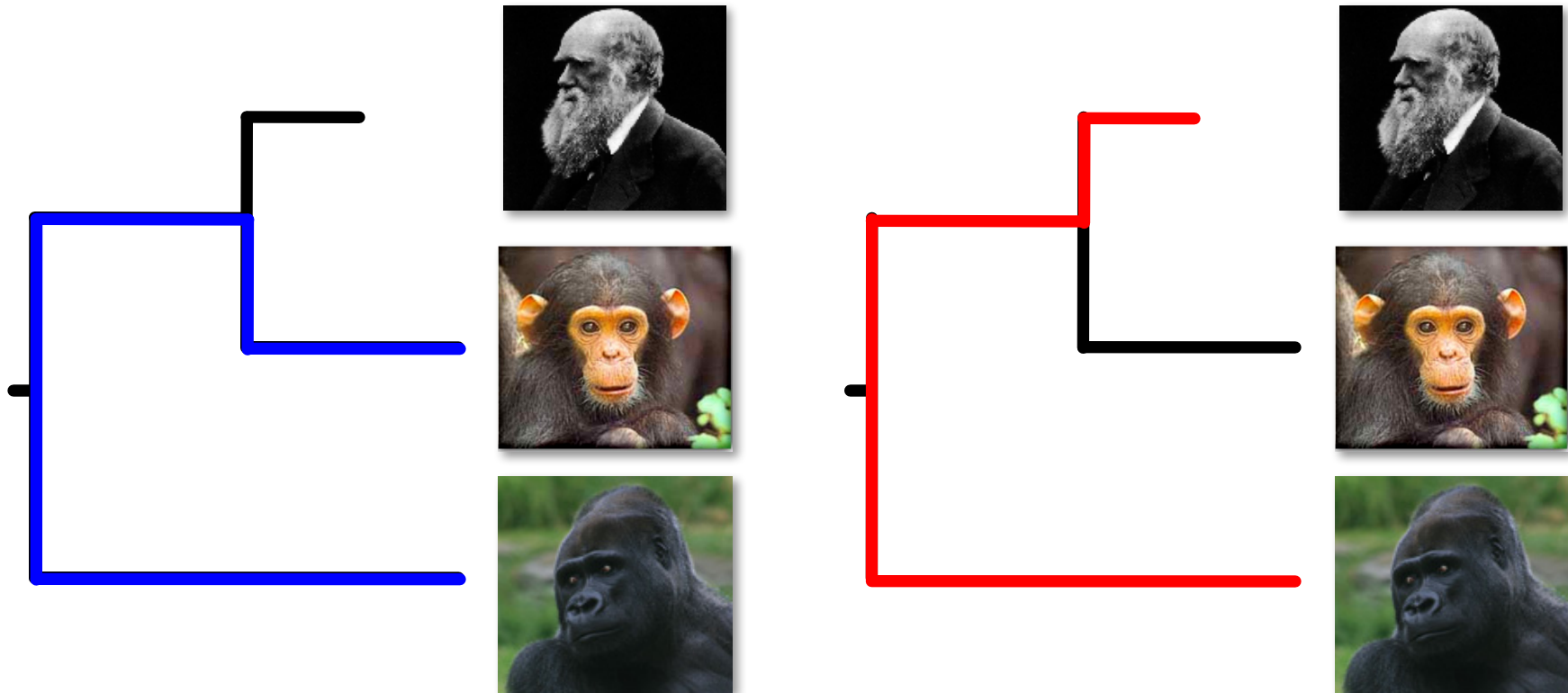
Departures from the clock

- 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

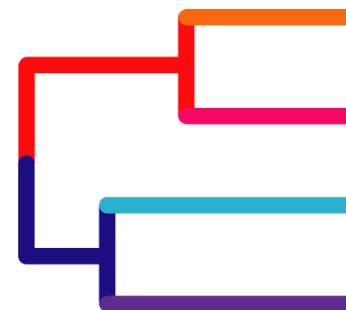
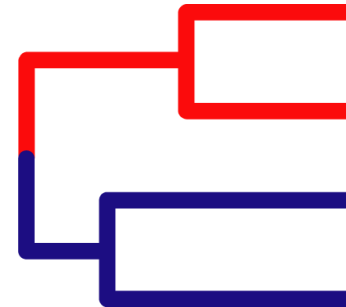
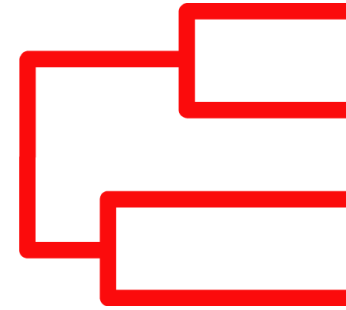
Bromham & Penny (2003):

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

Relaxed Molecular Clocks

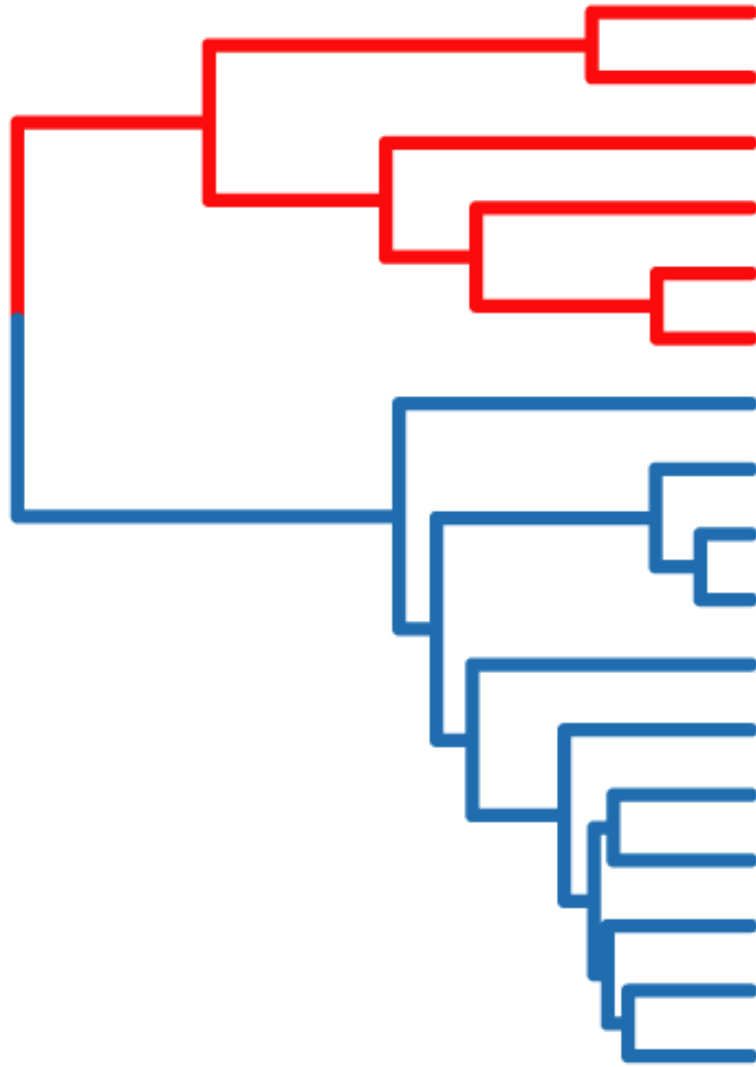
Molecular-clock models

- Strict or ‘global’ molecular clock
- Local molecular clock
- Relaxed molecular clock

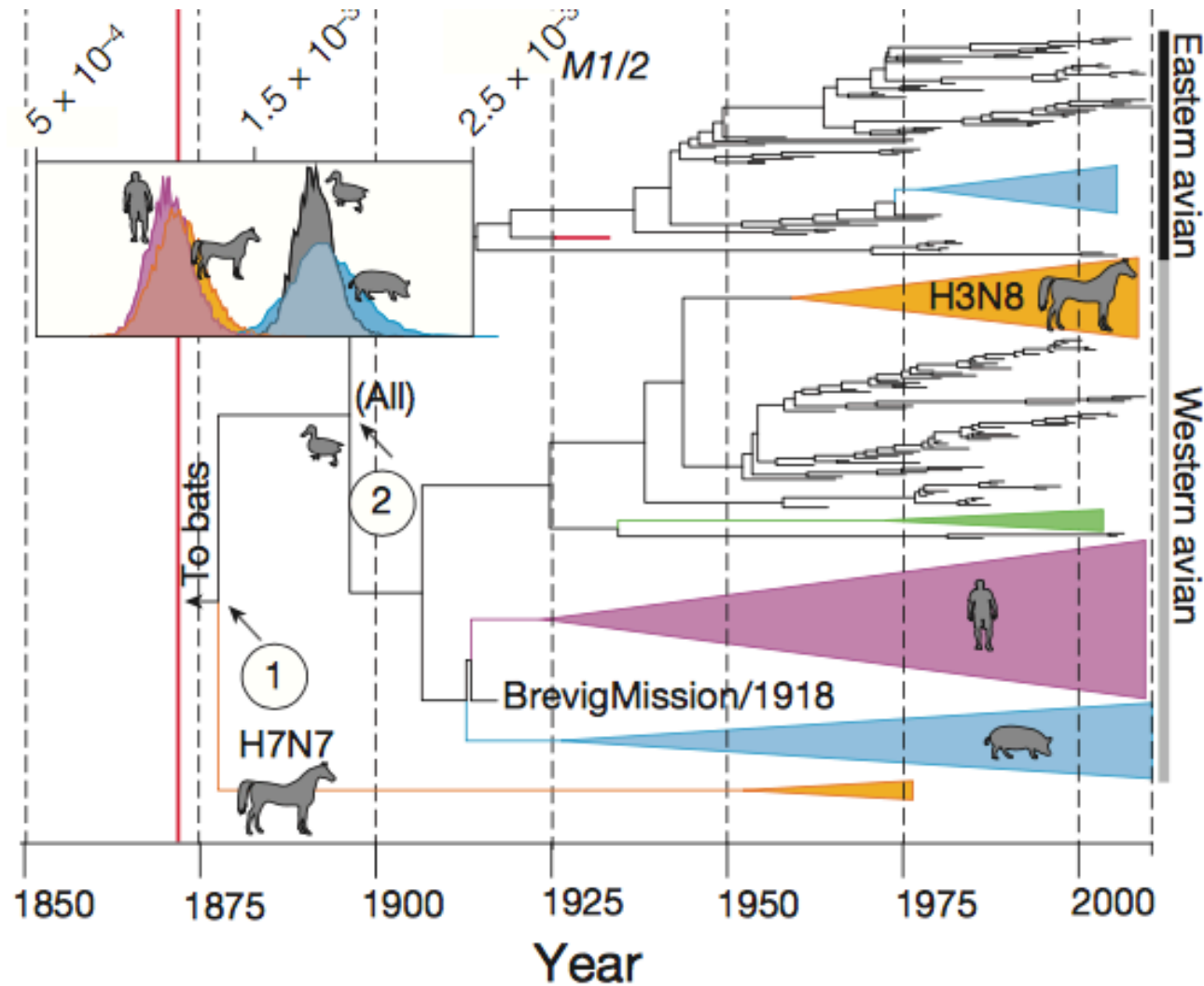


From: Ho and Duchene 2014 *Mol Ecol*

Local molecular clock



Host-specific clock



From: Worobey et al. 2014 *Nature*

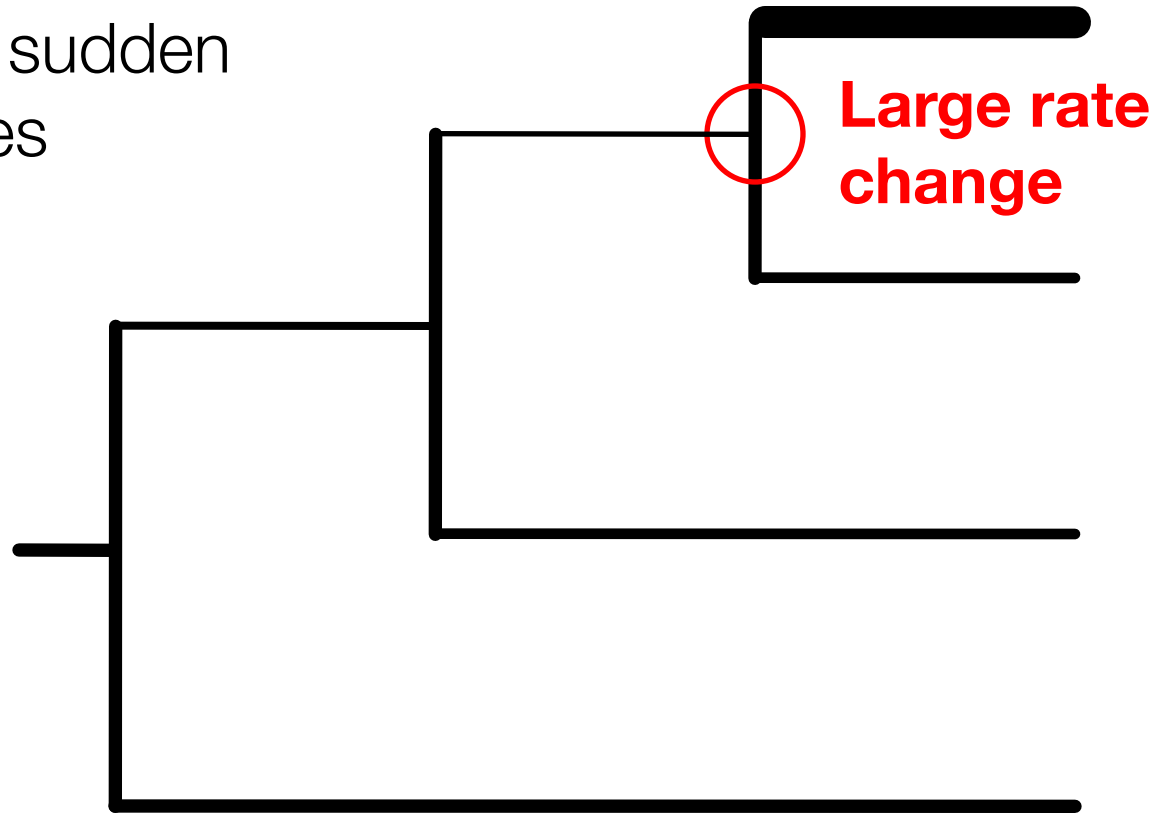
Relaxed clocks

- 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



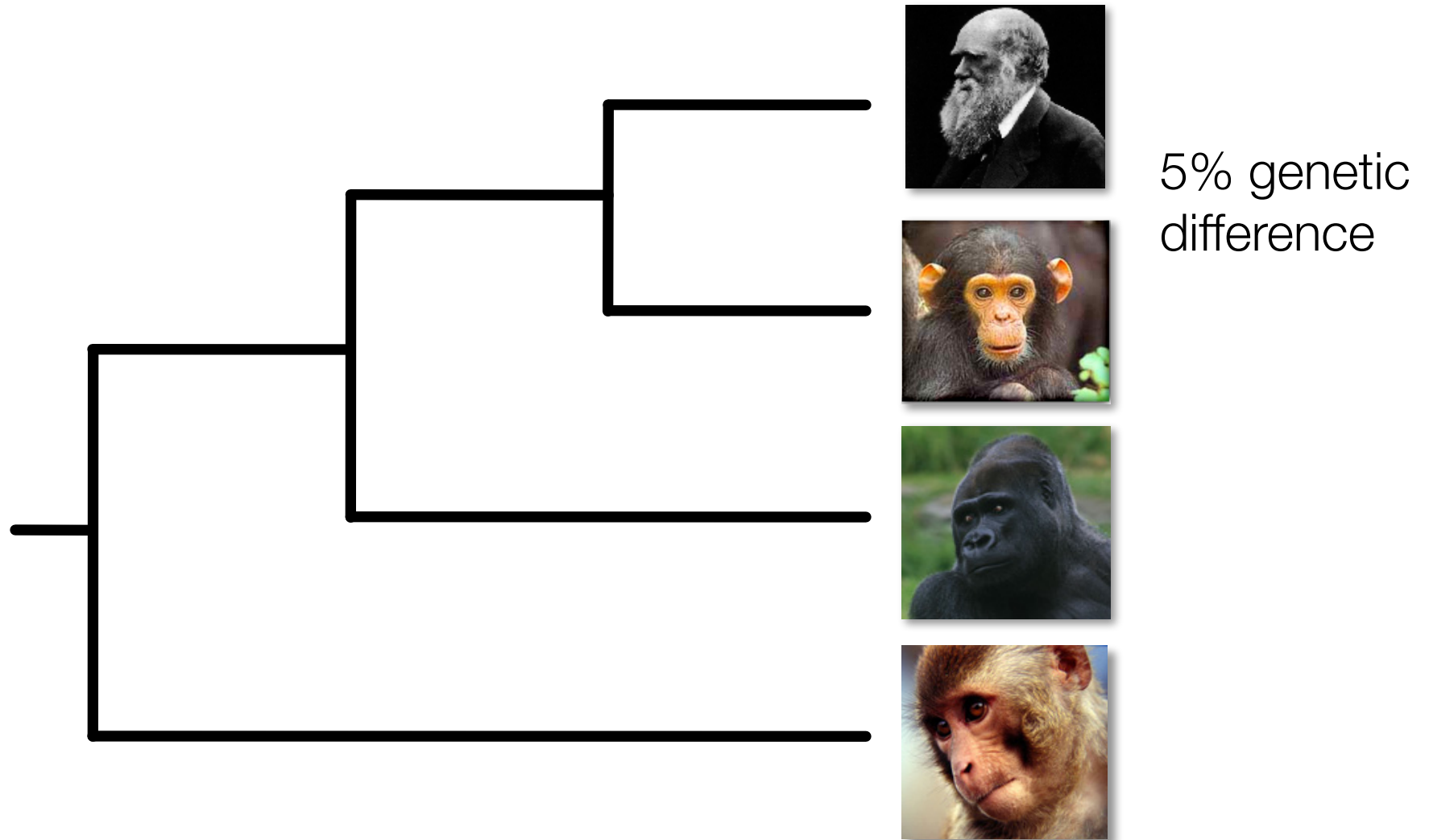
Likelihood-based relaxed clocks

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

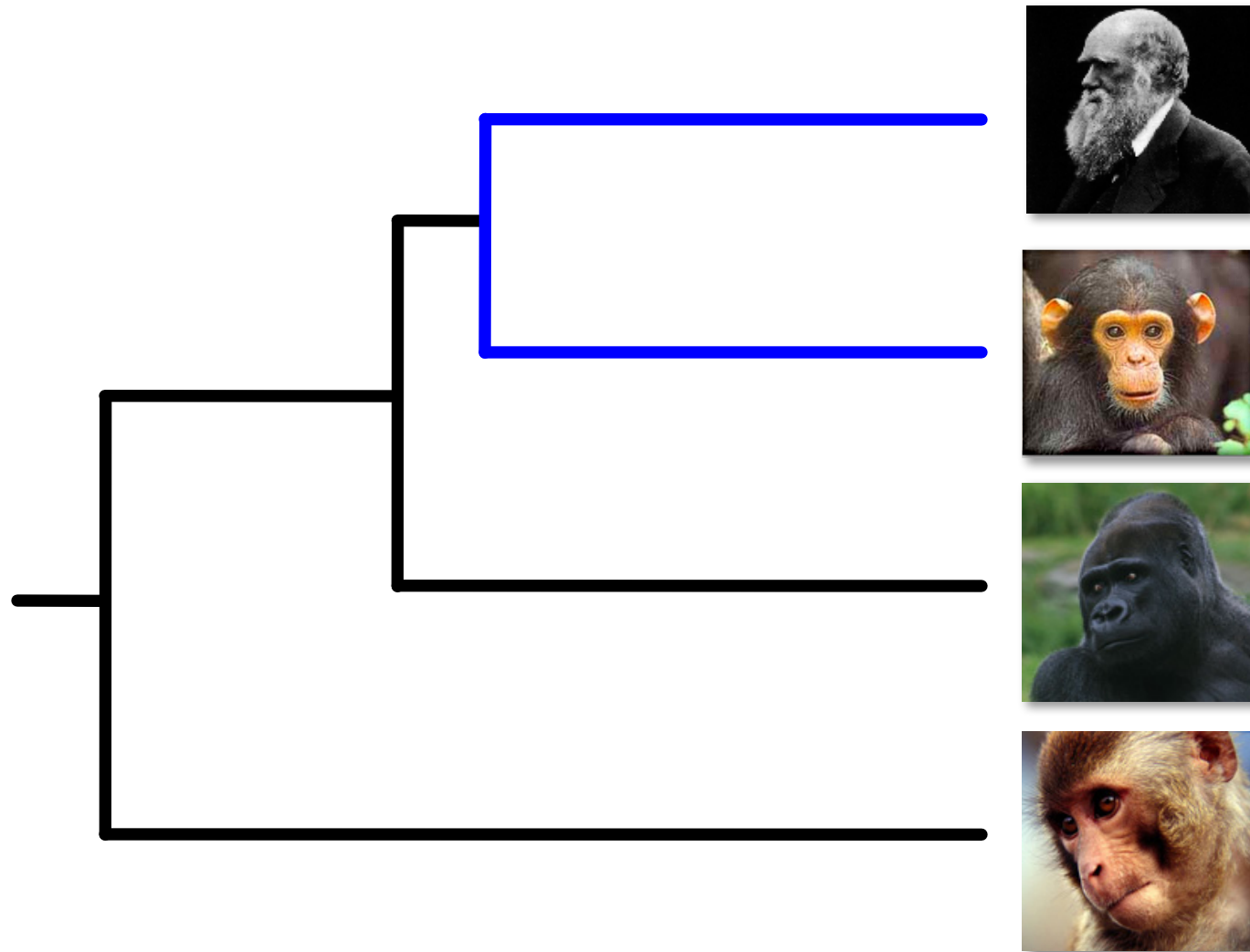


Calibrating the Molecular Clock

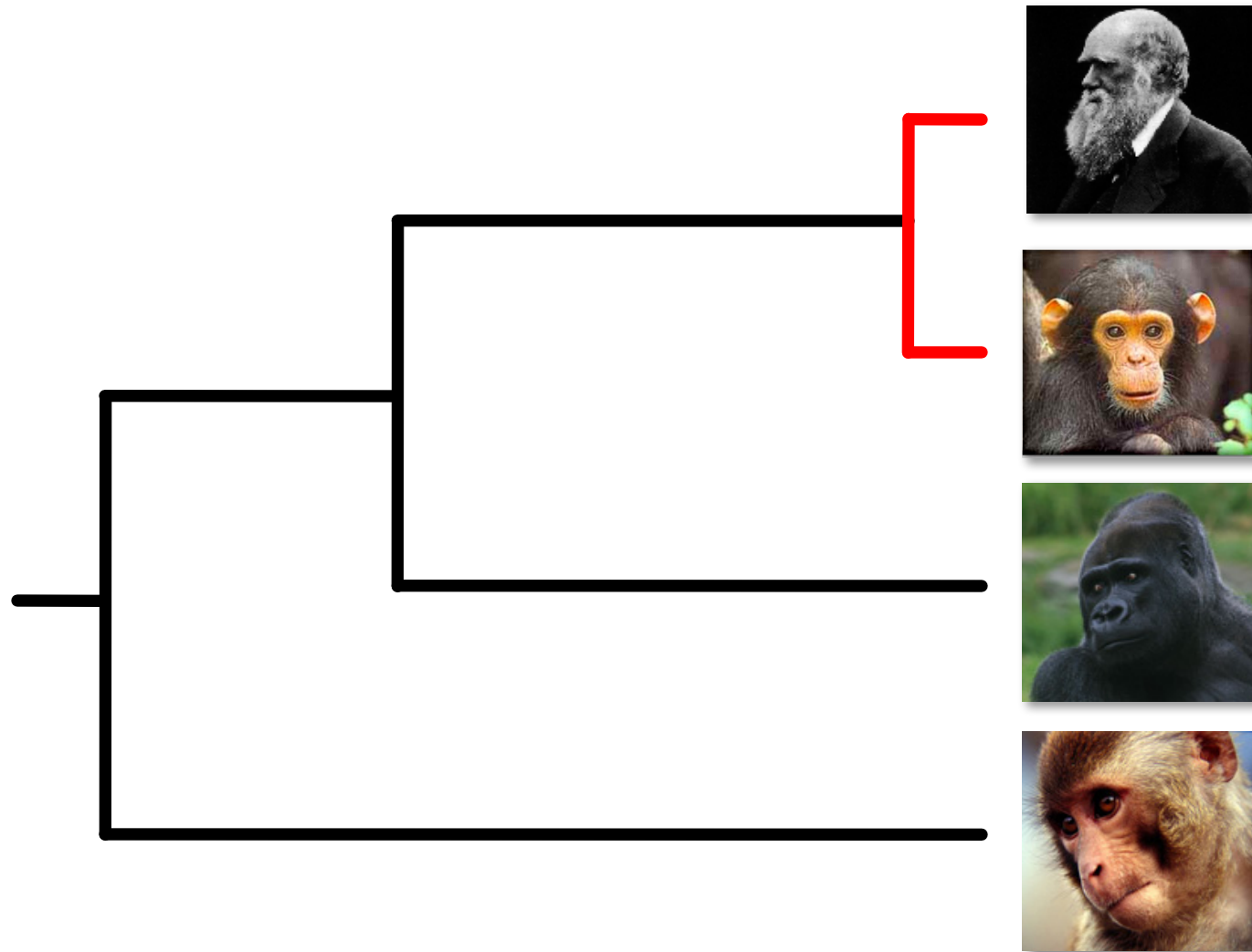
Calibrating the molecular clock



Calibrating the molecular clock



Calibrating the molecular clock



Calibrating information

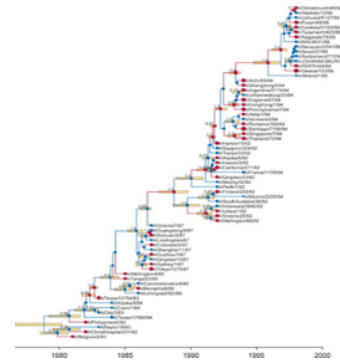
- Information about the rate
 - Substitution rate obtained from an independent study
- Information about time



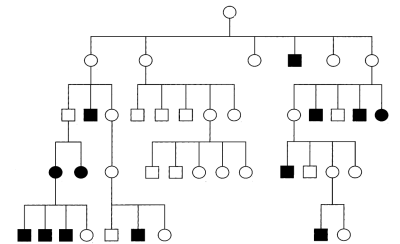
Fossil record



Biogeography



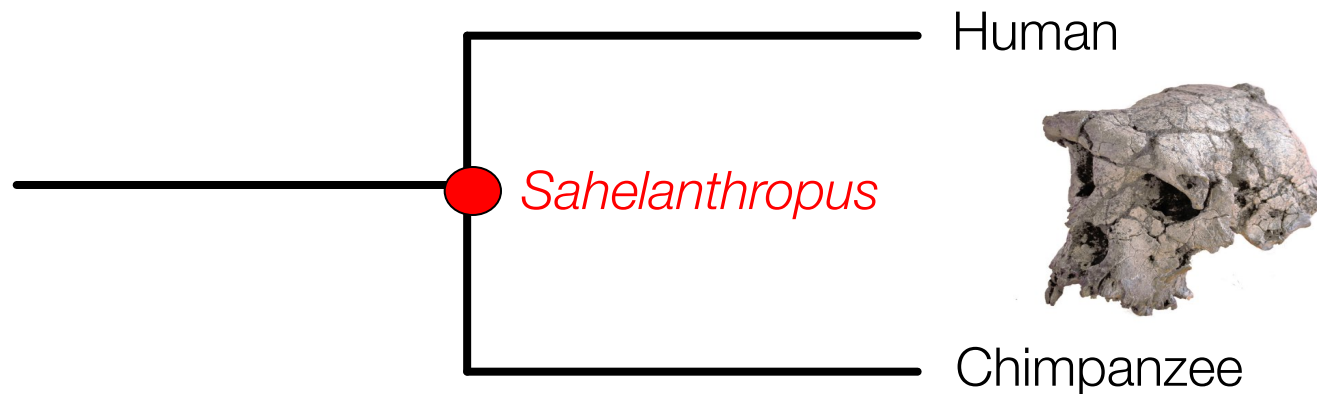
Sampling times



Pedigrees

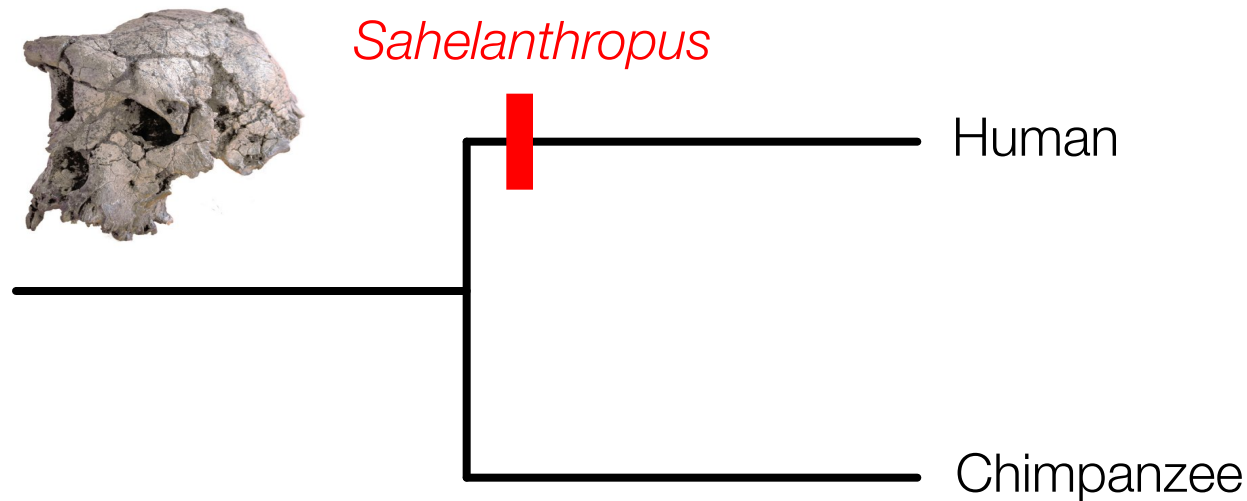
Point calibrations

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



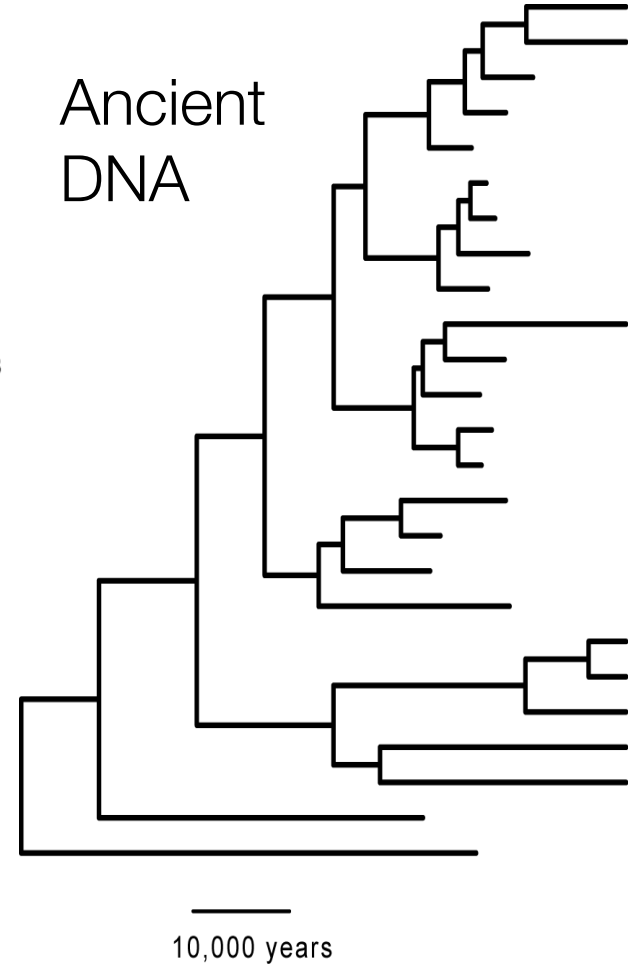
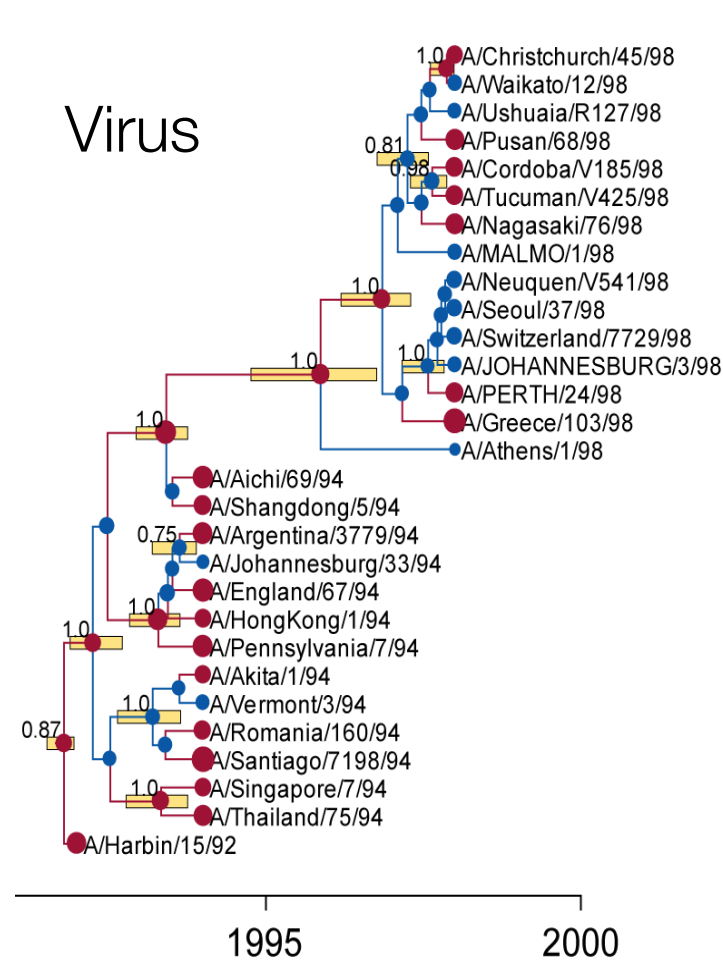
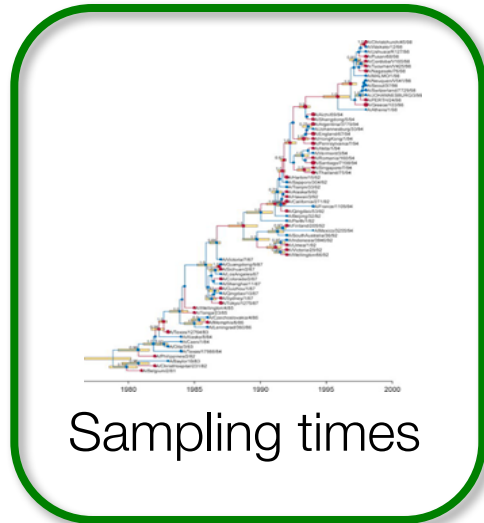
Hard calibration bounds

- Minimum or maximum age constraints

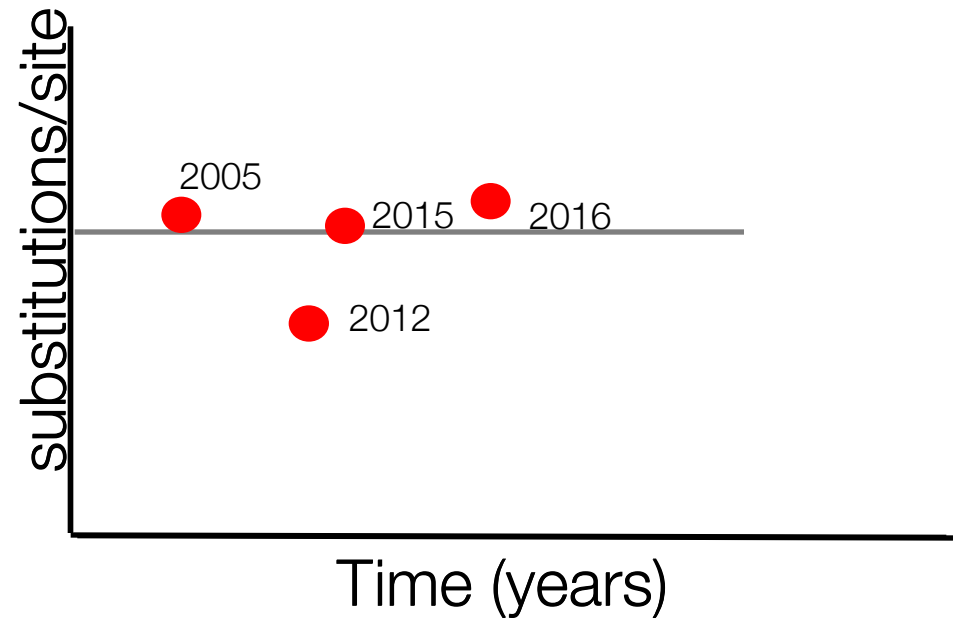
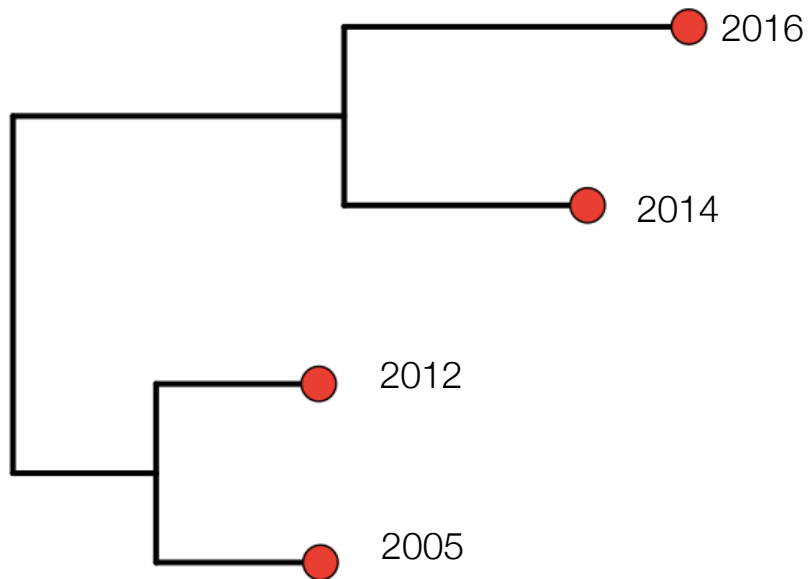


- Discards potentially useful information
- Inadequate information for estimating divergence times

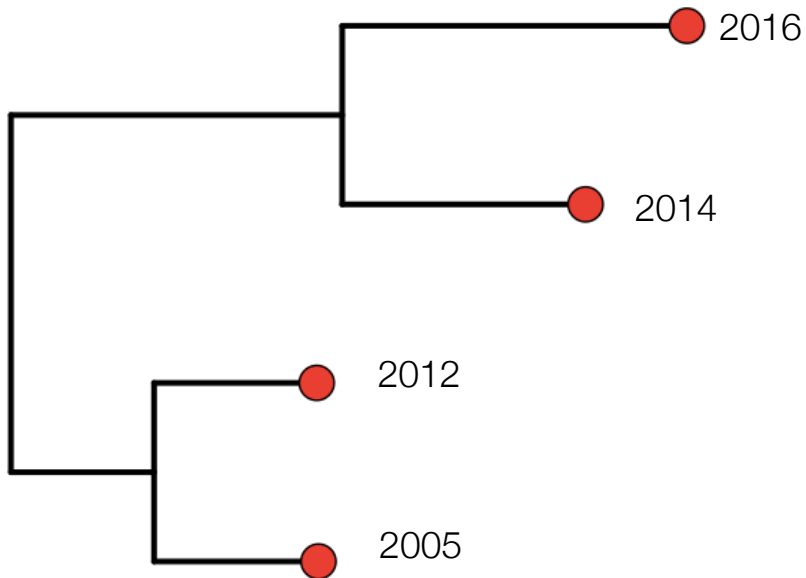
Calibration: Sampling times



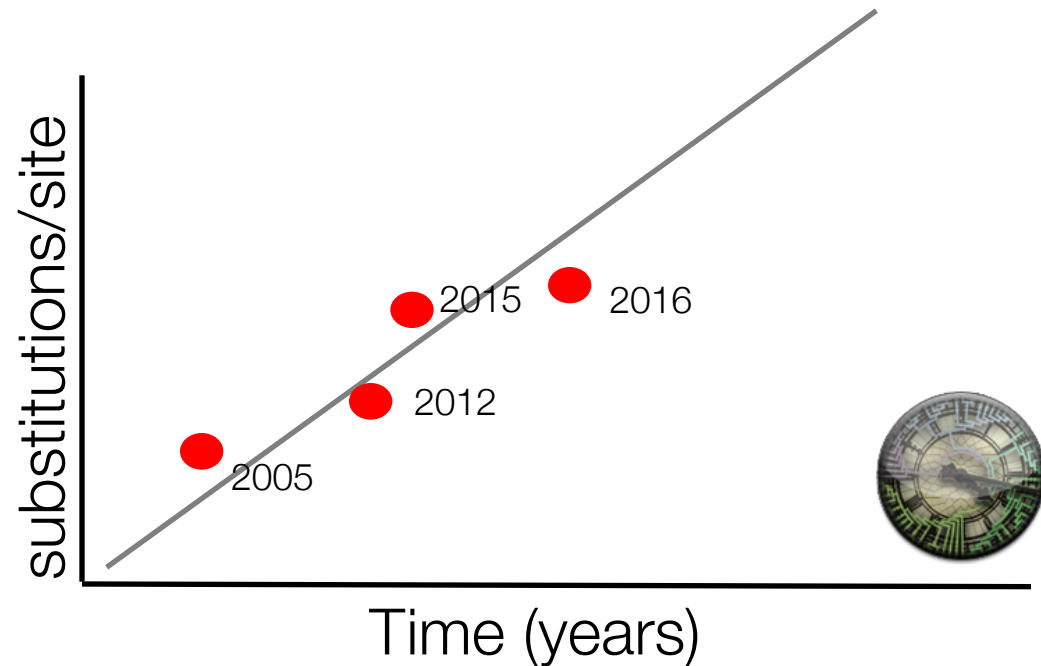
Validating estimates: Root-to-tip regression



Validating estimates: Root-to-tip regression



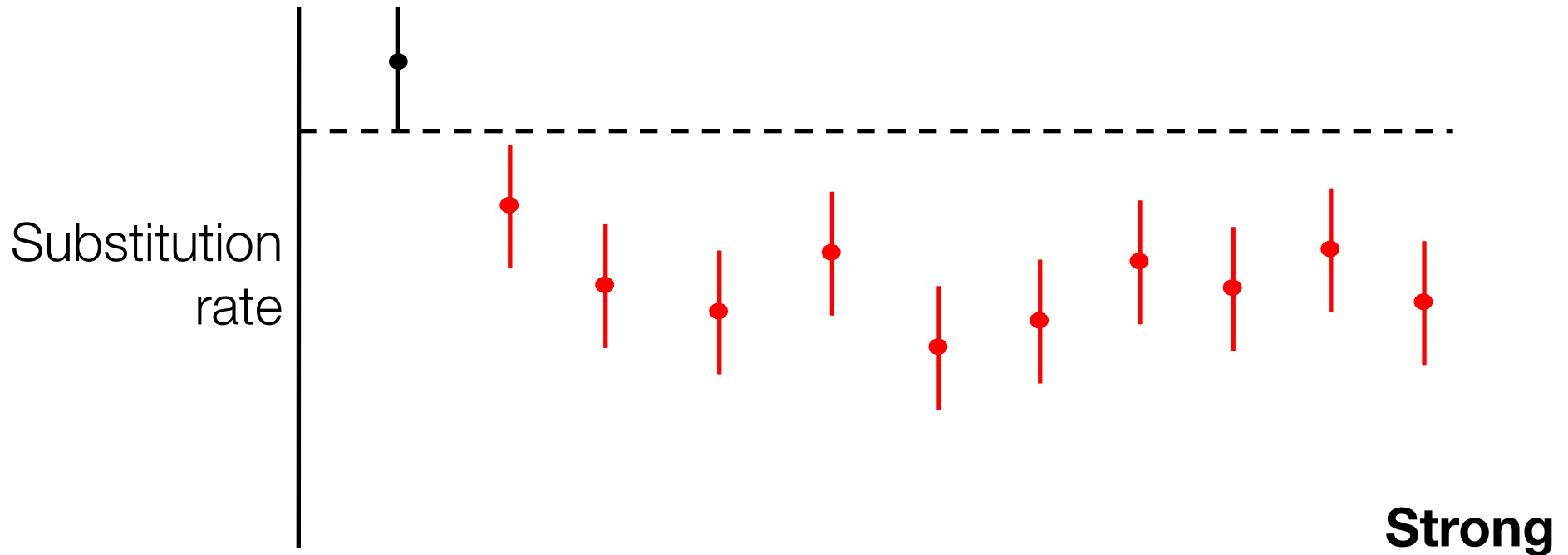
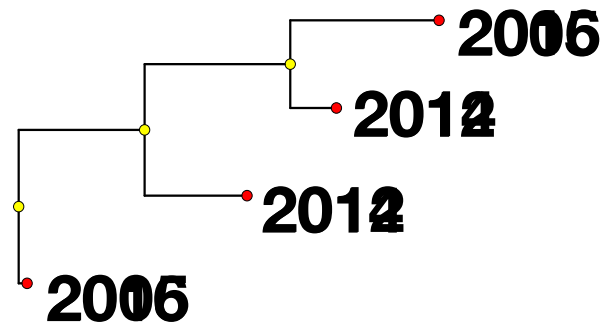
The rate estimate is phylogenetically non-independent



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

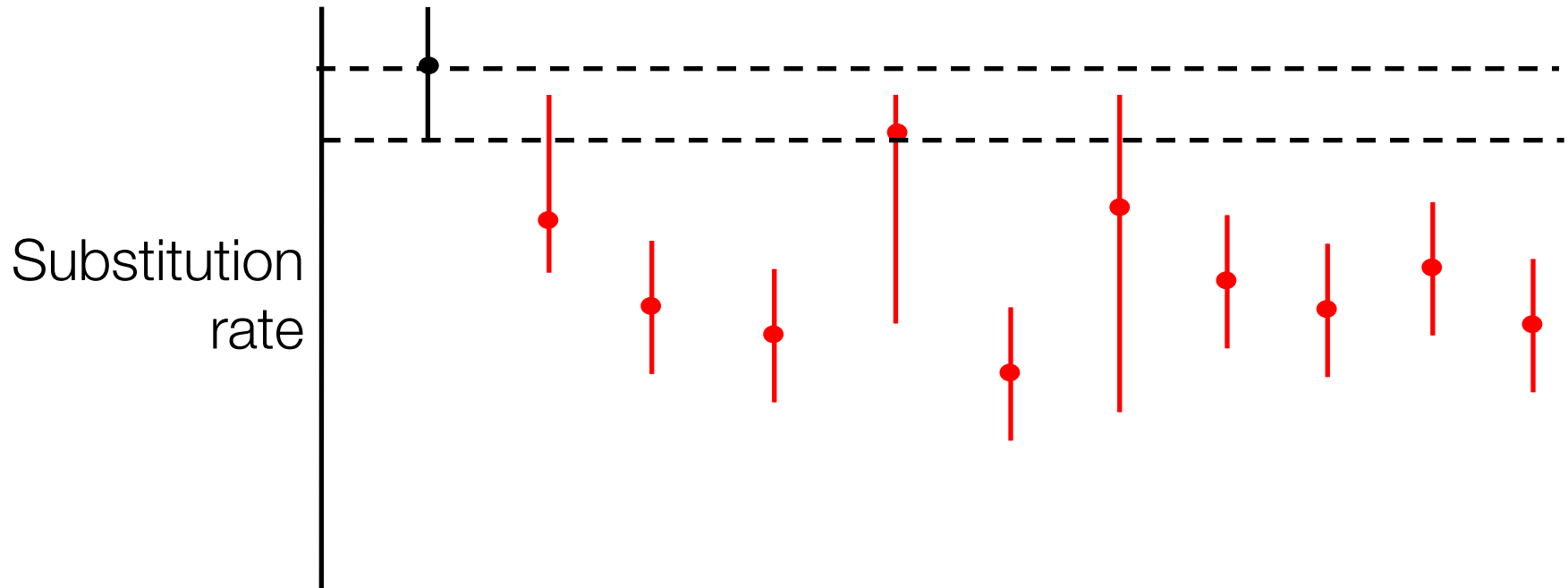
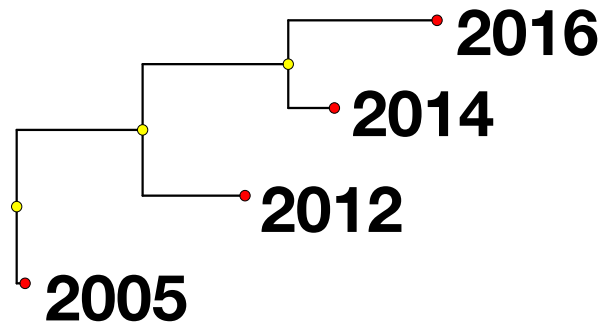


The date-randomisation test



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

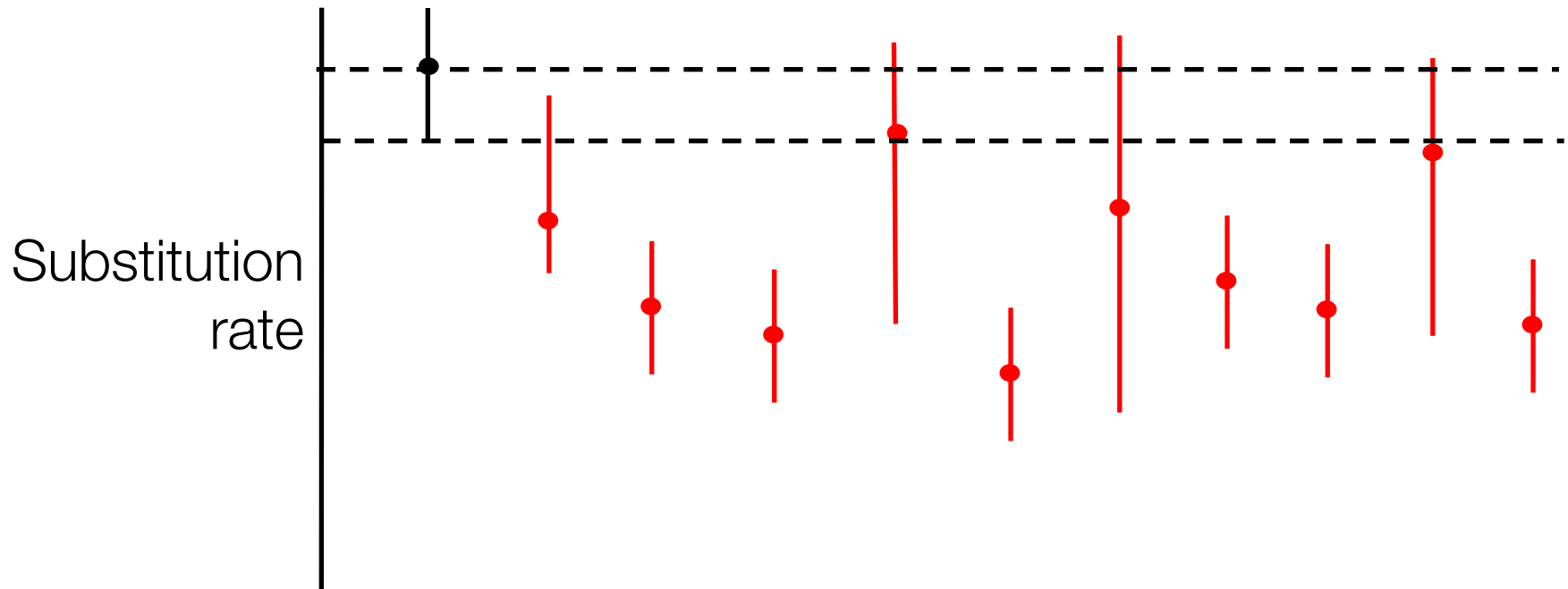
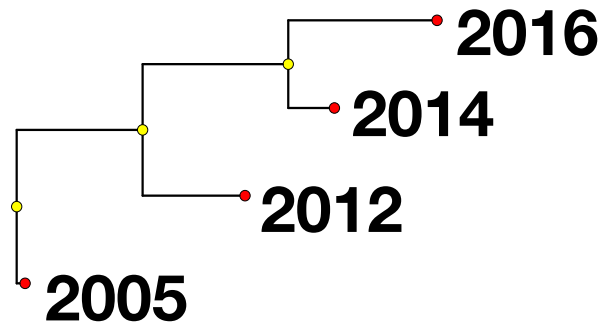
The date-randomisation test



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***

Note: TempEst for mac sometimes doeworking. Please download the Linux version, and run the .jar file.