



UH Systematics fall 2021:

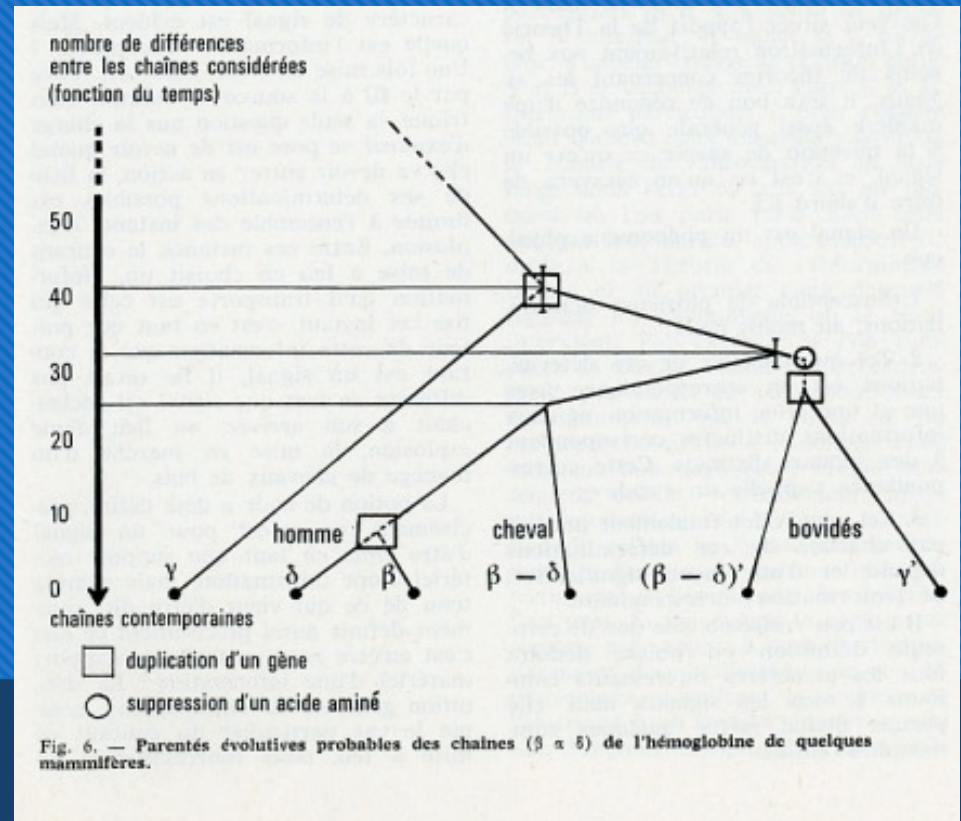
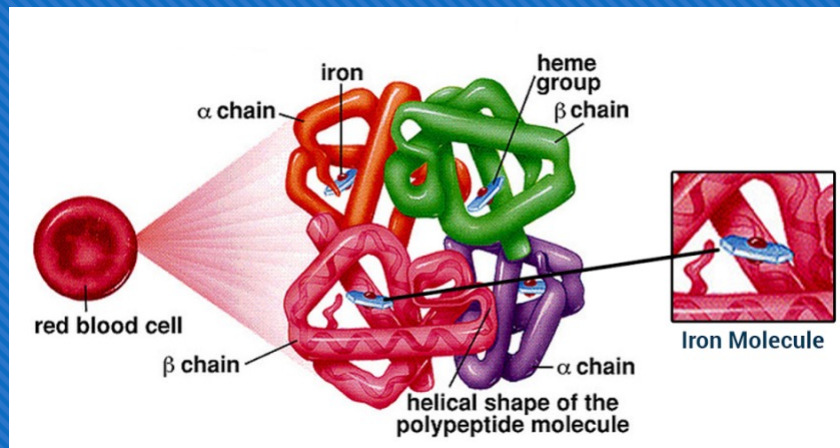
Molecular clocks



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20210901

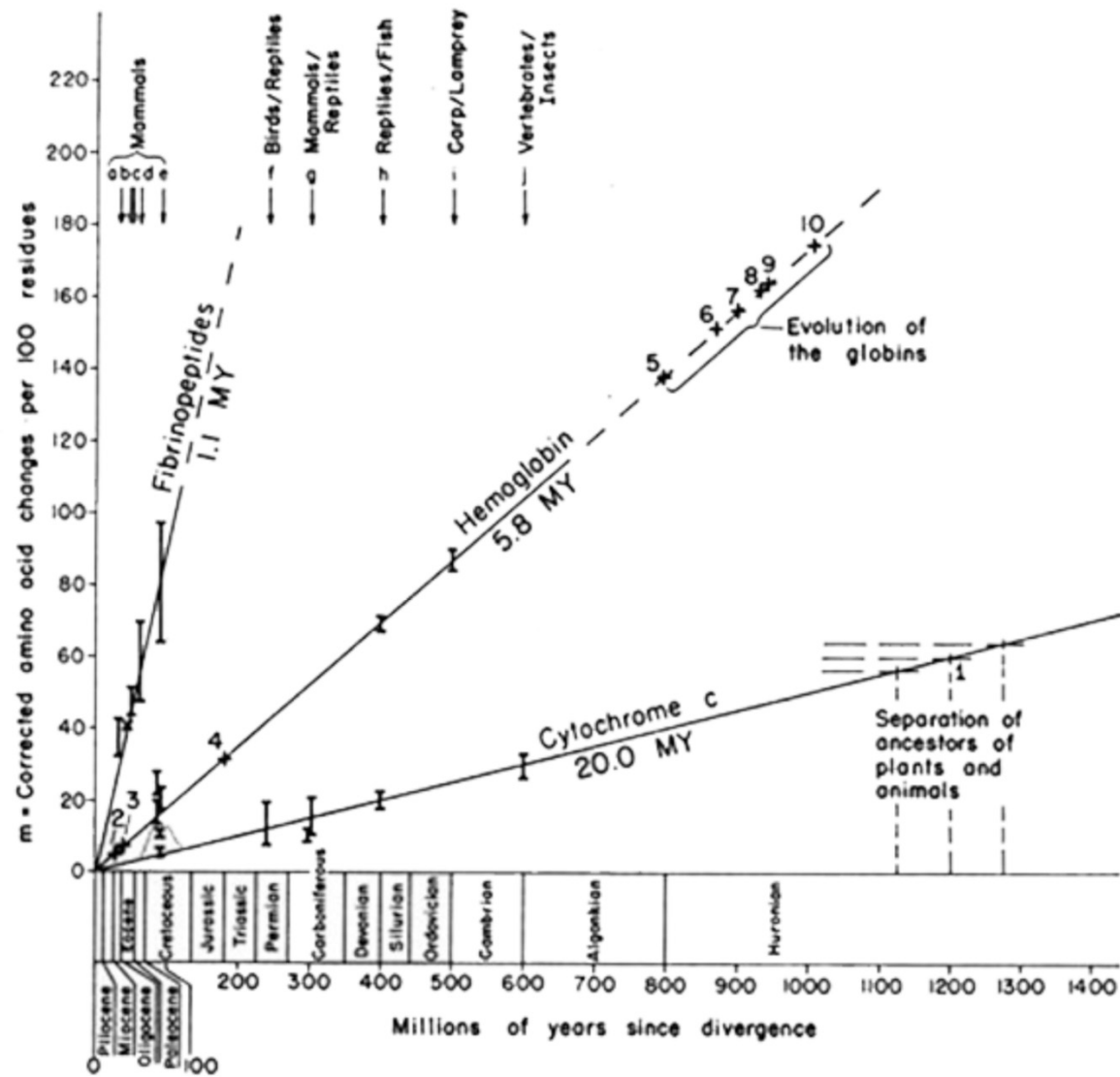
1965 Zuckerkandl & Pauling

“Molecules as documents of Evolutionary history”

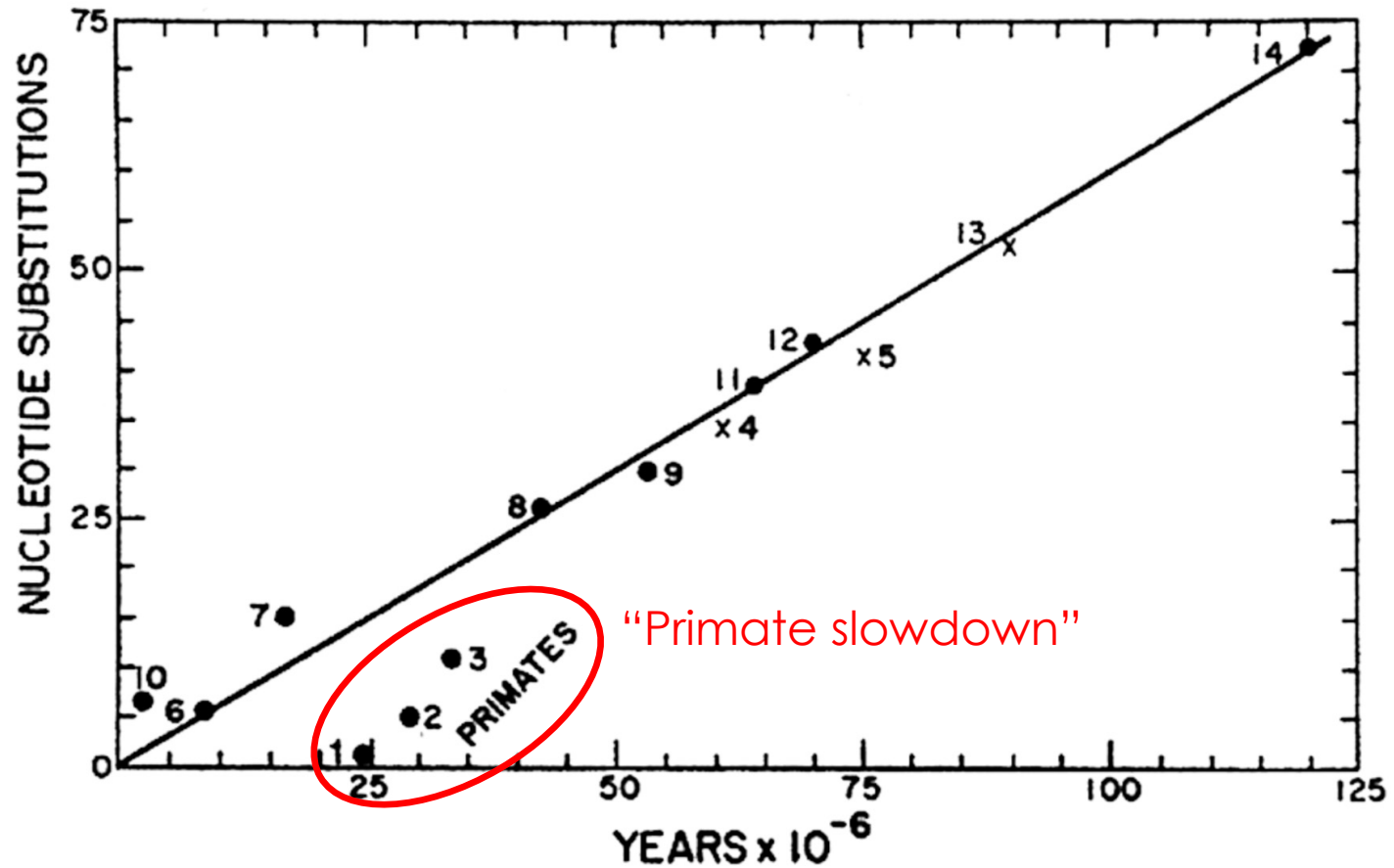


Substitutions accumulate as a function of time

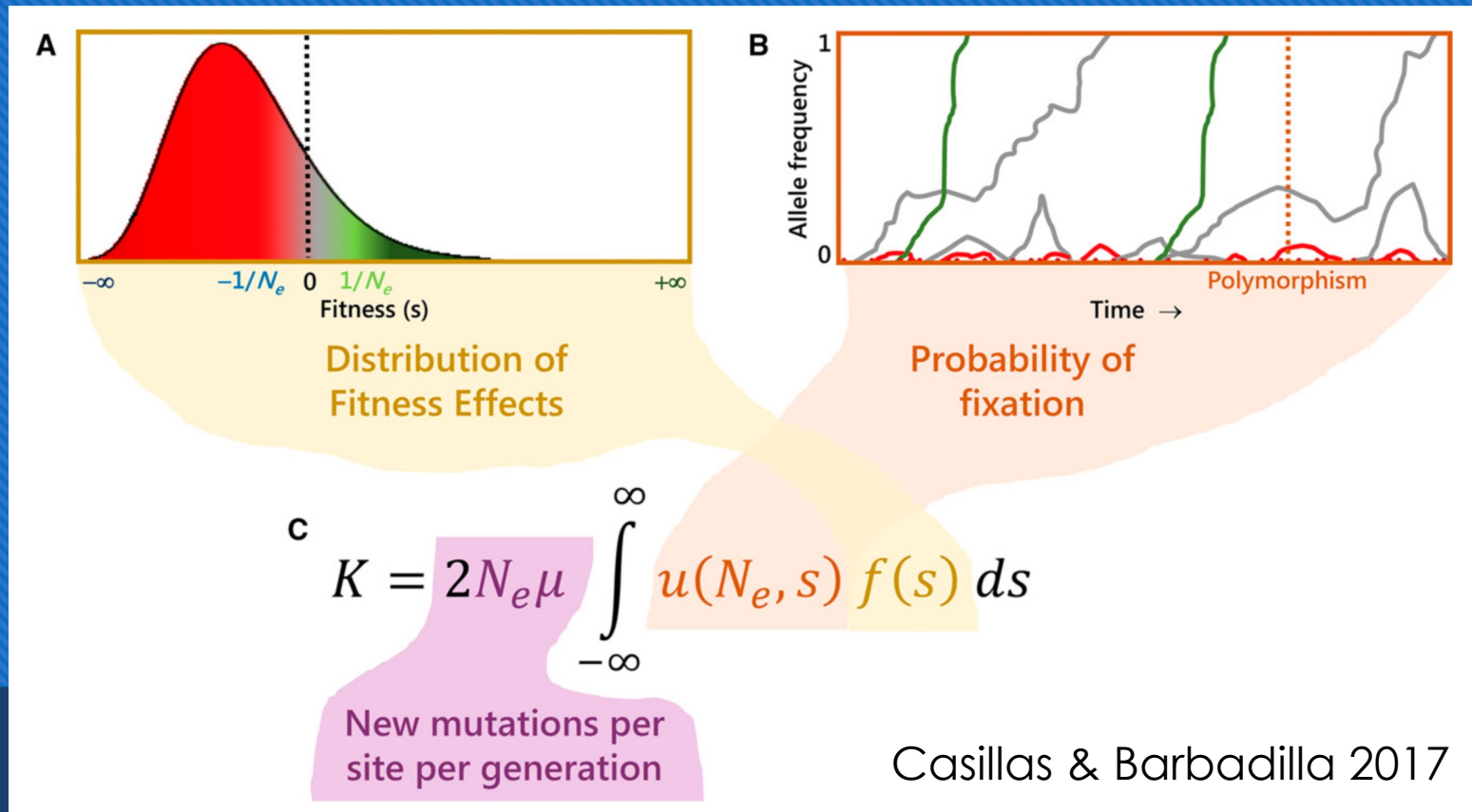
Dickerson 1971: a linear representation



Langley and Fitch 1974



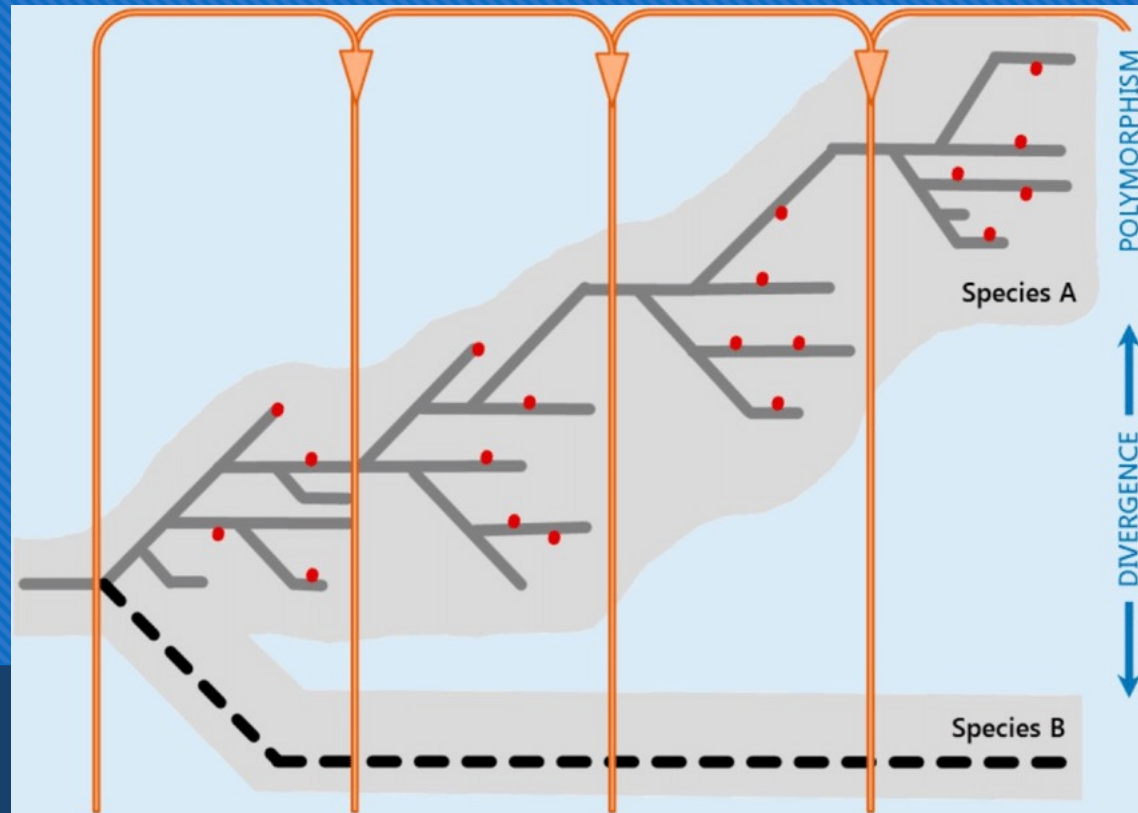
Kimura 1983: Neutral Theory of Molecular Evolution



The molecular evolutionary rate (K) is a function of the the rate of new mutations and the probability of fixation of mutations

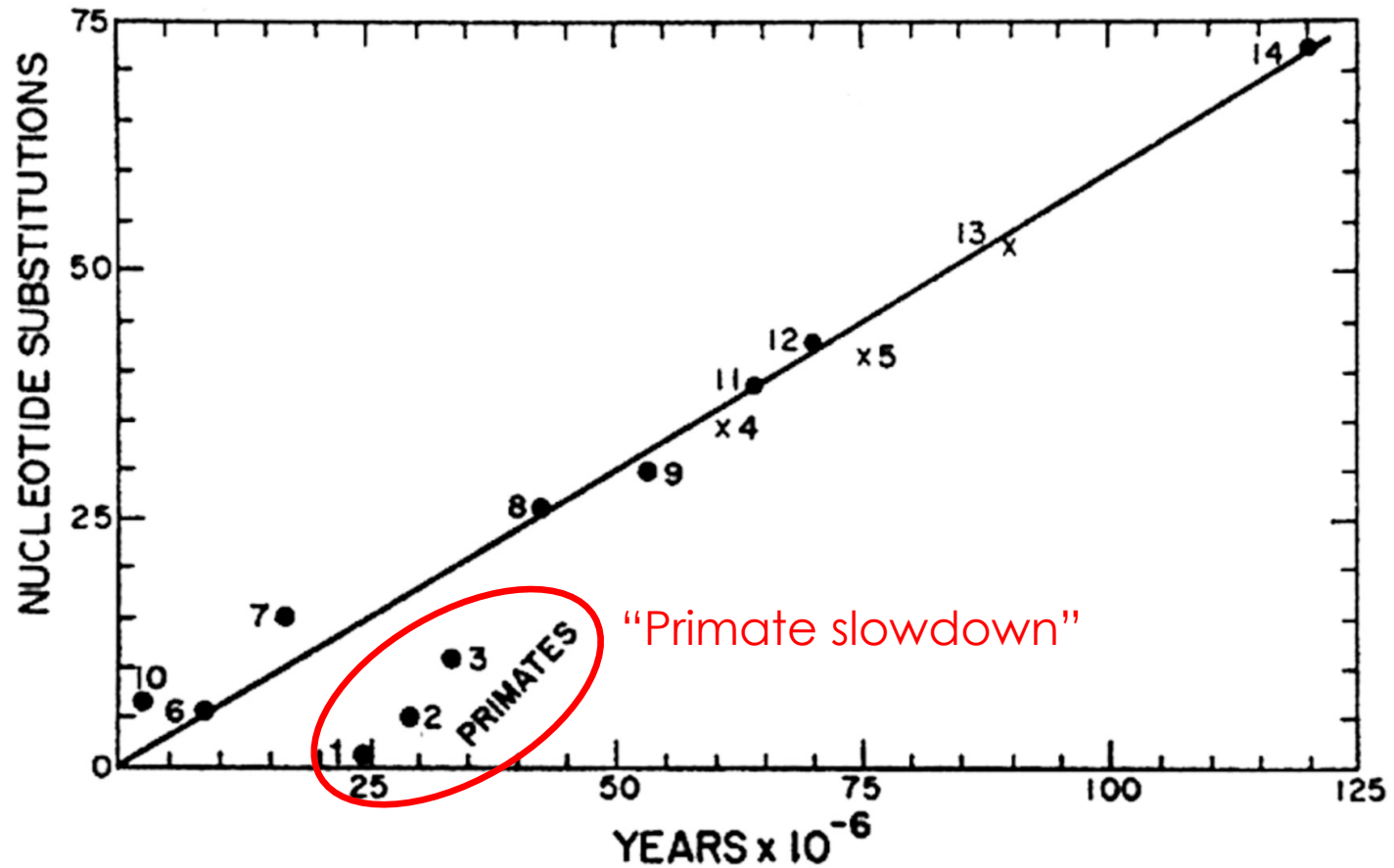
Kimura 1983: Neutral Theory of Molecular Evolution

1. Strongly deleterious mutations are rapidly removed from the population and adaptive mutations are rapidly fixed; therefore, most variation within species is the result of neutral mutations
2. Polymorphisms are transient (on their way to loss or fixation) rather than balanced by selection
3. The level of polymorphism in a population (θ) is a function of the neutral mutation rate (μ_0) and the effective population size: $\theta = 2Ne\mu_0$
4. A steady-state rate at which neutral mutations are fixed in a population (K) equals the neutral mutation rate: $K = \mu_0$. Therefore, the average time between consecutive neutral substitutions is independent of population size or generation time.



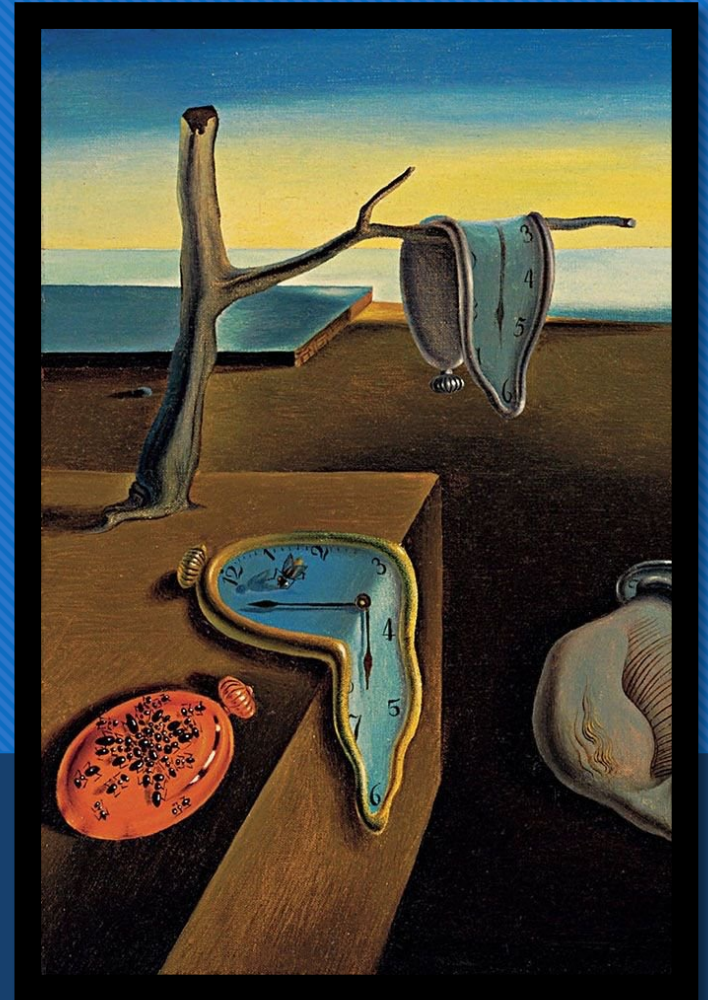
Casillas & Barbadilla 2017

Langley and Fitch 1974



Strict clocks and relaxed clocks

- **Strict molecular clock model:** constant substitution rate across all branches
- **Uncorrelated relaxed clock model:** branch substitution rate is drawn independently from a common underlying distribution
- **Correlated (or autocorrelated) relaxed clock:** branch substitution rates depend on the rate of neighboring branches



Ultrametric trees

Example with tip dating: virus genomes on nextstrain.org

Nextstrain: real-time tracking of pathogen evolution

James Hadfield , Colin Megill, Sidney M Bell, John Huddleston, Barney Potter, Charlton Callender, Pavel Sagulenko, Trevor Bedford, Richard A Neher [Author Notes](#)

Bioinformatics, Volume 34, Issue 23, 01 December 2018, Pages 4121–4123,
<https://doi.org/10.1093/bioinformatics/bty407>

Published: 22 May 2018 **Article history** ▼

Not every dated tree has to be ultrametric

Substitution rates versus calibration points



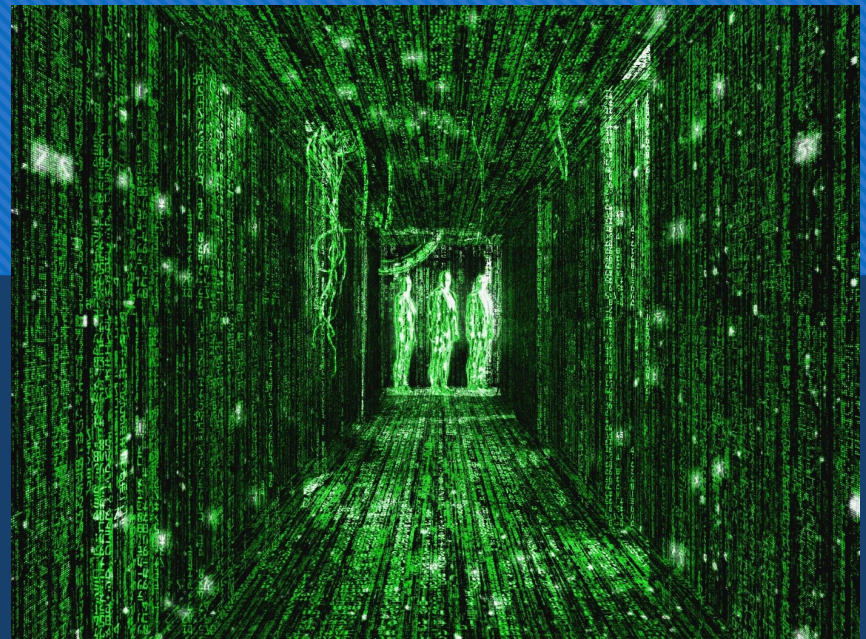
Setting calibration points:

- Crown or stem?
- Strict, normal or log-normal distribution?

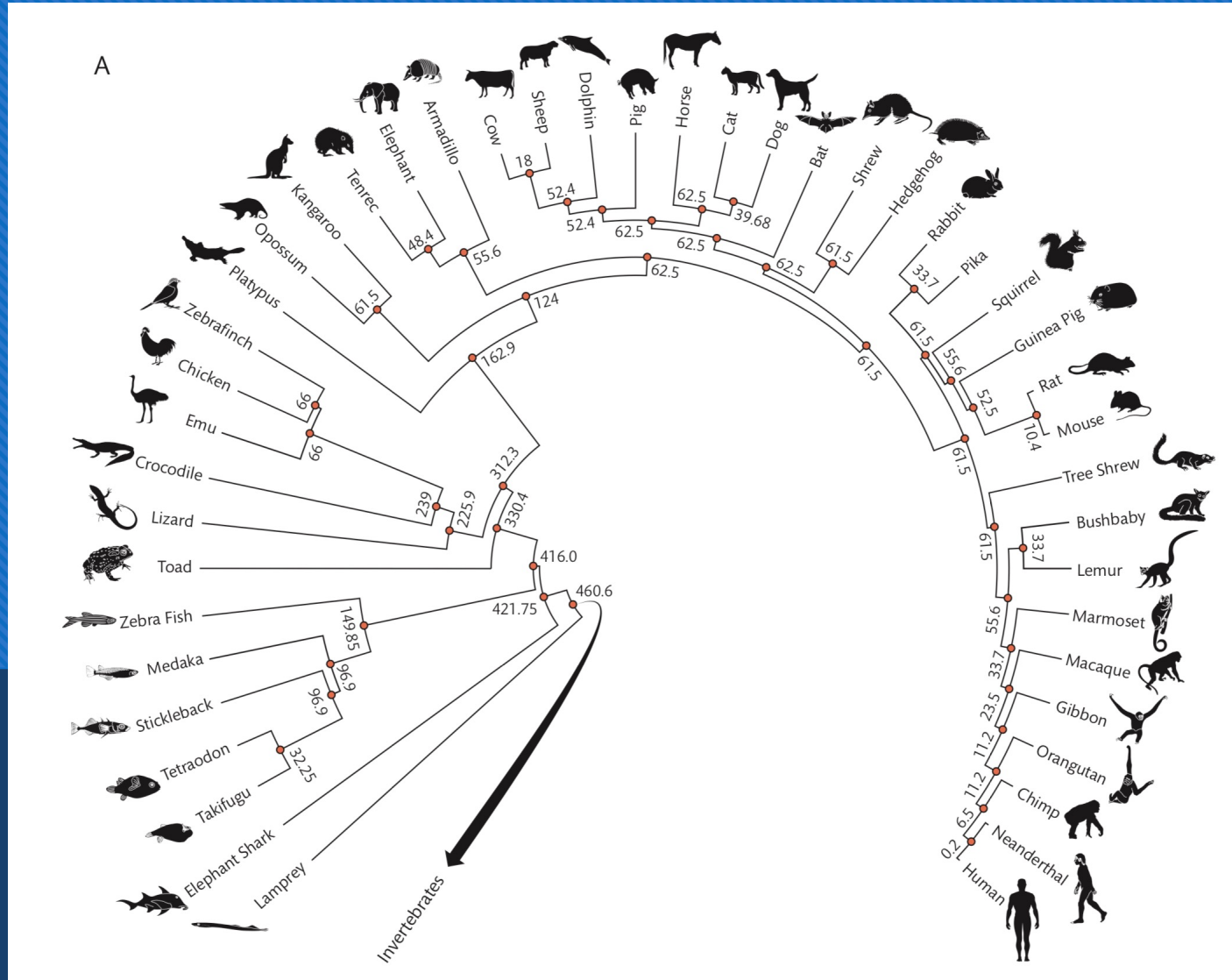


Software driven innovation

- 2021: IQ-Tree [Least-Square Dating] [C++]
- 2018: RevBayes
- 2017: BEAST 2 (& Beauti) [Java]
- 2016: TreeTime [python] used for nextstrain.org
- 2016: treedater [R] Gamma-Poisson mixture model
- 2016: Least-Square Dating (LSD) [C++]
- 2015: (beta): PhyTime. [C] Part of PhyML package
- 2003: r8s [C] [Poisson distribution of substitutions]



A supertree approach: Timetree.org



References

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<https://doi.org/10.1534/genetics.116.196493>

Hadfield J, Megill C, Bell SM, Huddleston J, Potter B, Callender C, Sagulenko P, Bedford T, Neher RA (2018) NextStrain: Real-time tracking of pathogen evolution. *Bioinformatics* 34: 4121–4123.
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