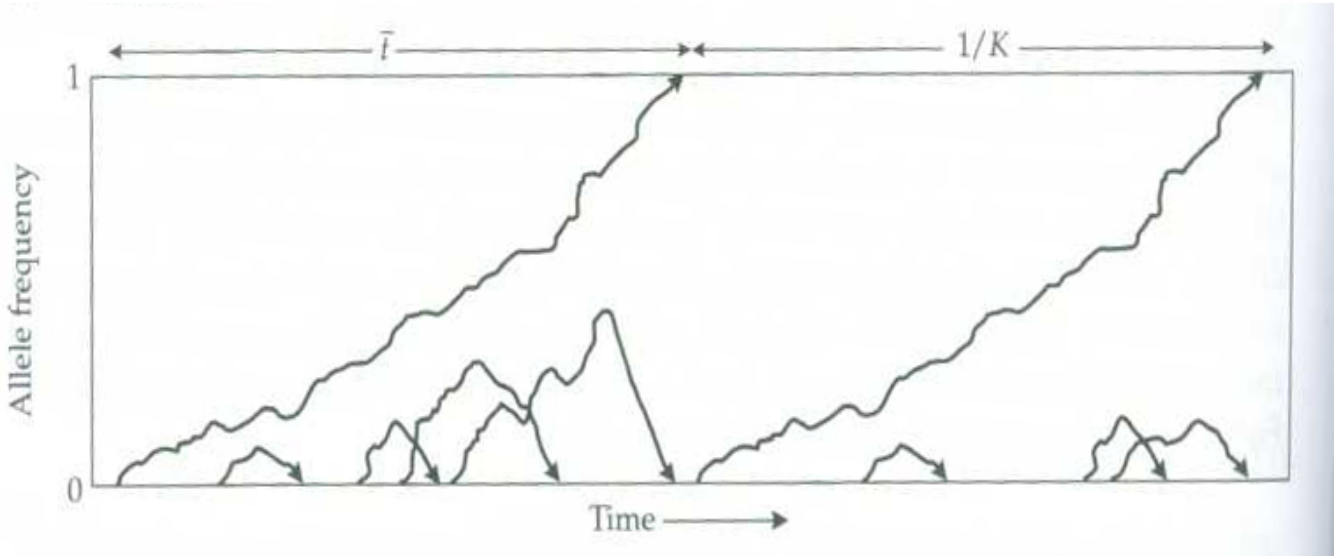
Theory of neutral evolution

Theory of neutral evolution

- Describes the rate of molecular evolution and levels of genetic variation if mutations are neutral and their frequency is affected only by genetic drift.

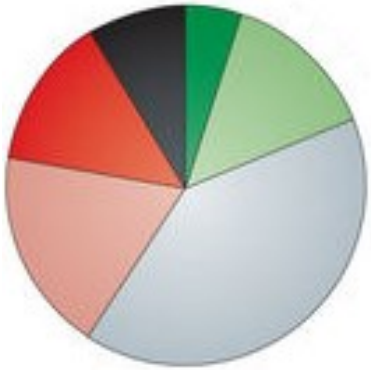
Mottoo Kimura

Mutation vs. substitution rate



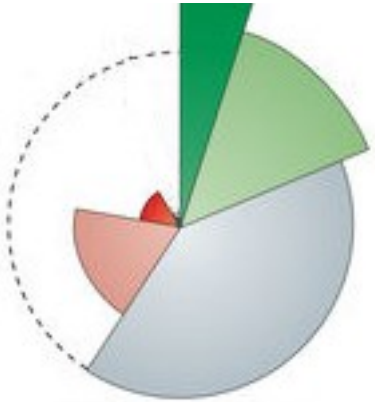
Mutation rate

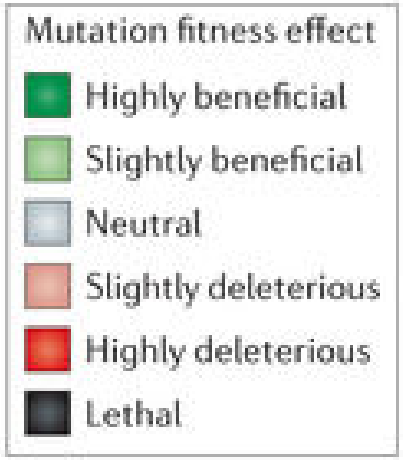
Rate of origin of new mutations.



Substitution rate

Rate of fixation of new mutations.





Substitution rate

= number of new mutations x probability of their fixation

$$k = 2N_e\mu \frac{1}{2N_e} = \mu$$

N_e … effective population size
μ … mutation rate

Probability of their fixation

Number of new mutations

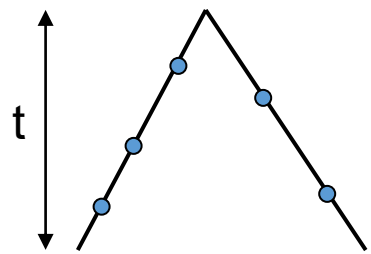
Substitution rate of neutral mutations is given only by mutation rate. If mutation rate is constant over time, subtitution rate is also constant. **Molecular clocks.**

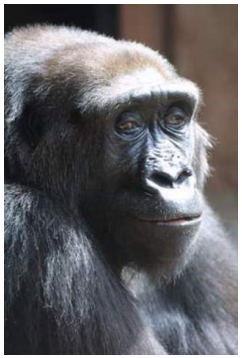
Genetic divergence

= substitution rate x time

$$D = 2\mu t$$

- Number of substitutions between species.
- For neutral substitutions increases lineary with time





Estimation of genetic divergence

sequence 1 AGTGAGTCGTCAGTACTGCT
sequence 2 ACTTAGCCGTGAGTACAGCT

$$D = \frac{5}{20} = 0.25\ (25\%)$$

Proportion of nucleotides differing between two sequences (p-distance).

sequences of species 1

AGTGAGTCGTCAGTACTGCT
ACTGAGTCGACAGTACTGCT
AGTGACTCGTCAGTACTGCT

sequences of species 2

ACTTAGCCGTGAGTACAGCT
ACTTAGCGGTGAGTACAGCT
ACTTAGCCGTGAGTACAGCA

Dxy, avergage pairwise divergence

Genetic saturation

- The result of multiple substitutions at the same site in a sequence.

AGTGAGTCGTCAGTACTGCTG

4 substitutions

ACTAAGTCGACAGTACTGCTA

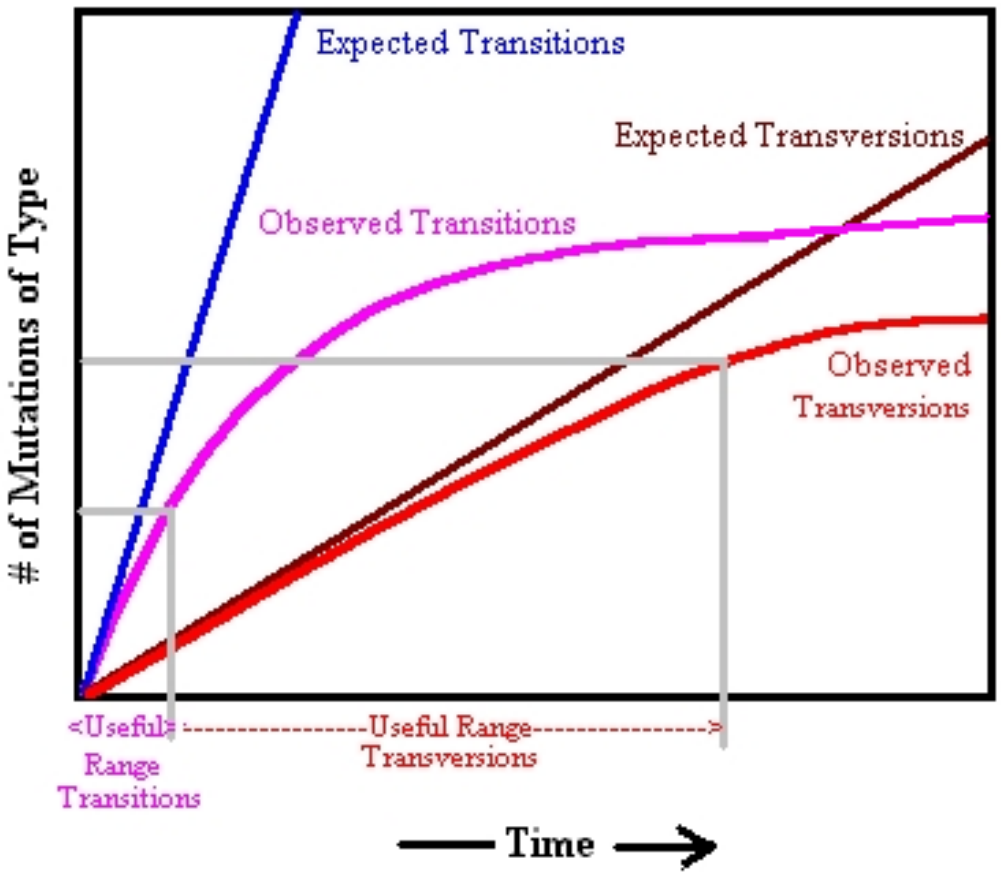
4 substitutions

ACTTAGCCGTCAGTACAGCTA

5 substitutions

Genetic saturation

- Observed number of substitutions is underestimated at higher divergences.



Nucleotide substitution models

Correction for multiple substitutions and estimates of the true genetic divergences.

Jukes & Cantor (1 parameter) model
-all substitutions the same probability (α) and all nucleotides the same frequency

Kimura (2 parameter) model
-probability of transitions higher than probability of transversions

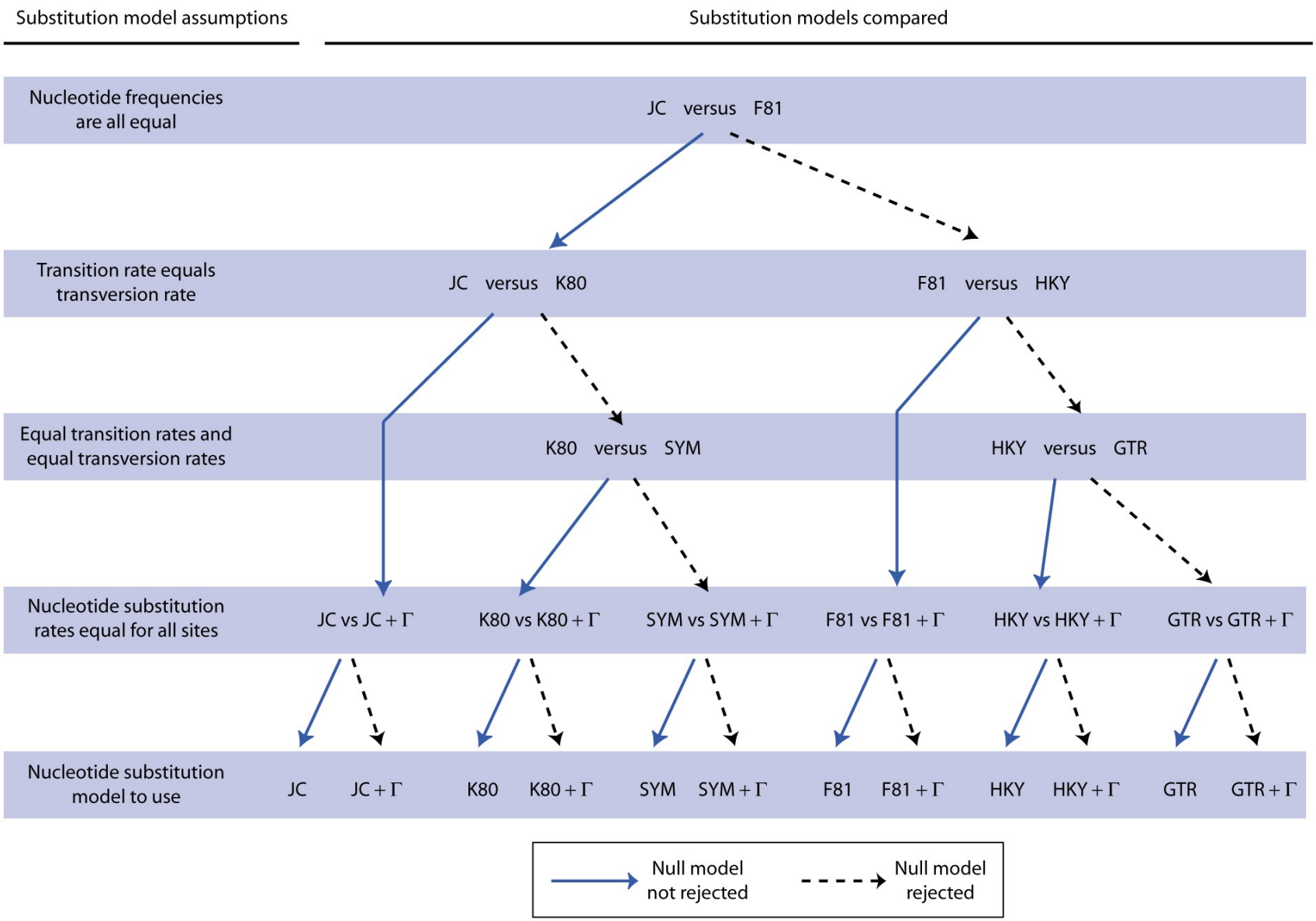
Felsenstein 81 (4 parameter) model
-Different frequencies of nucleotides

HKY-Hasegawa,Kishino,Yano (5 parameter) model
-Different probabilities of transitions and transversions and different nucleotide frequencies

HKY + Γ
-Gama parametr can model different substitution rate at different sites

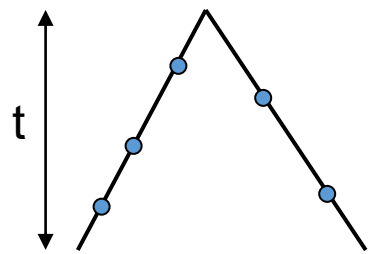
Program ModelTest

Nucleotide substitution models

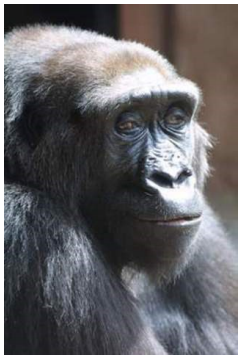


Molecular clocks
dating the divergence time

- Divergence time (t) can be calculated if we know the genetic distance (D) and substitution rate (μ)

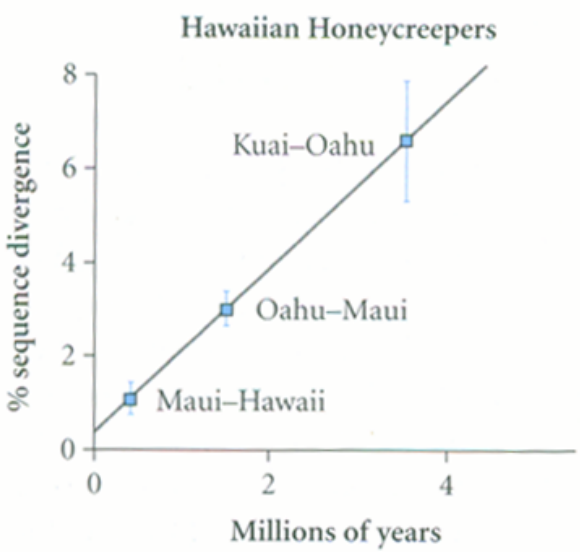


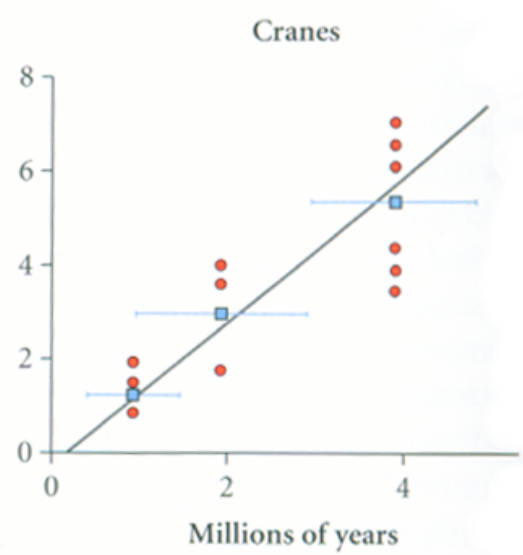
$$D = 2\mu t$$



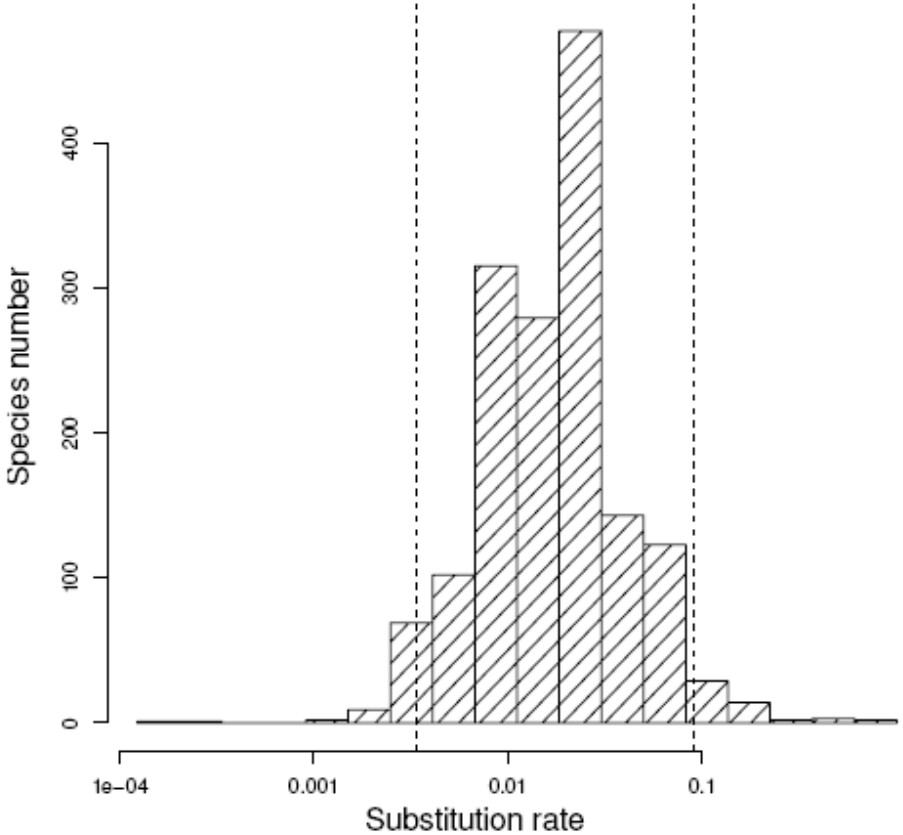
Molecular clocks
dating the divergence time

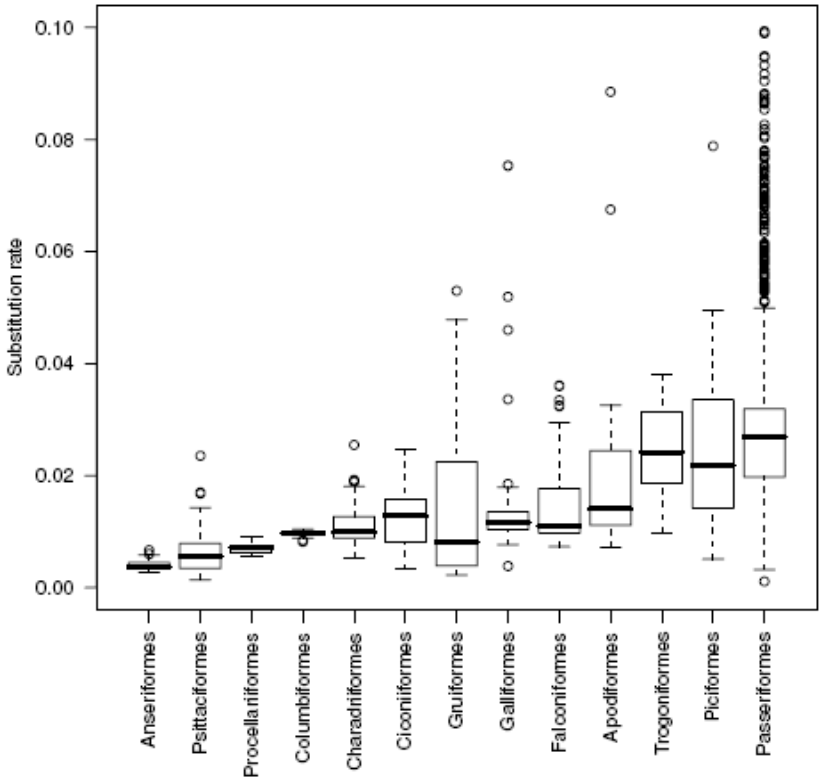
- Estimation of substitution rate (**calibration of molecular clocks**).
- Fossil records, known geological events
- cytochromu b sequence (mt DNA), substitution rate in mammals and birds cca 0,01. **2% divergence ~ 1 mil let.**





Substitution rate varies among species



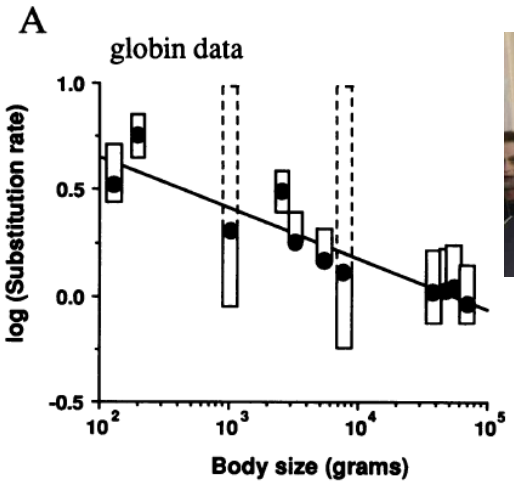


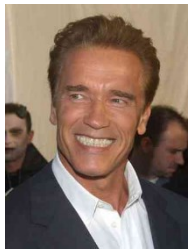
Substitution rate for cytochrome b in birds

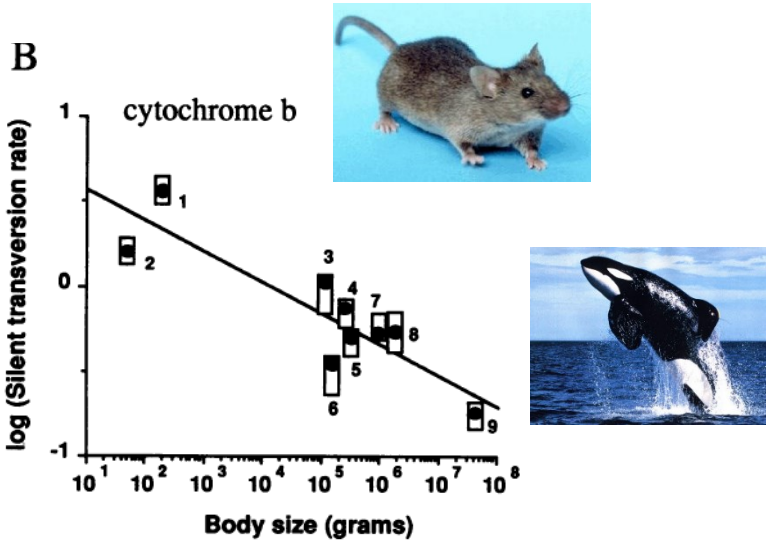
Causes of variation in substitution rate

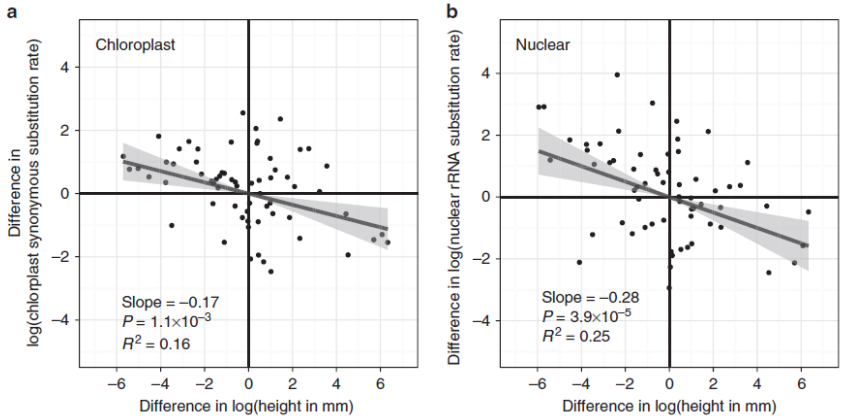
Body size

Organisms with smaller body size have higher substitution rate.



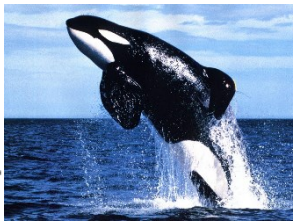


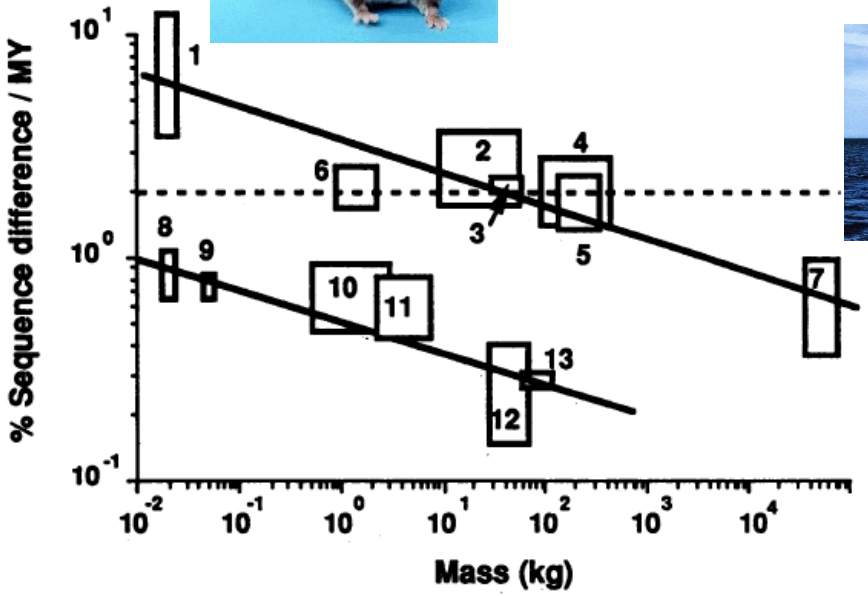




Metabolic rate

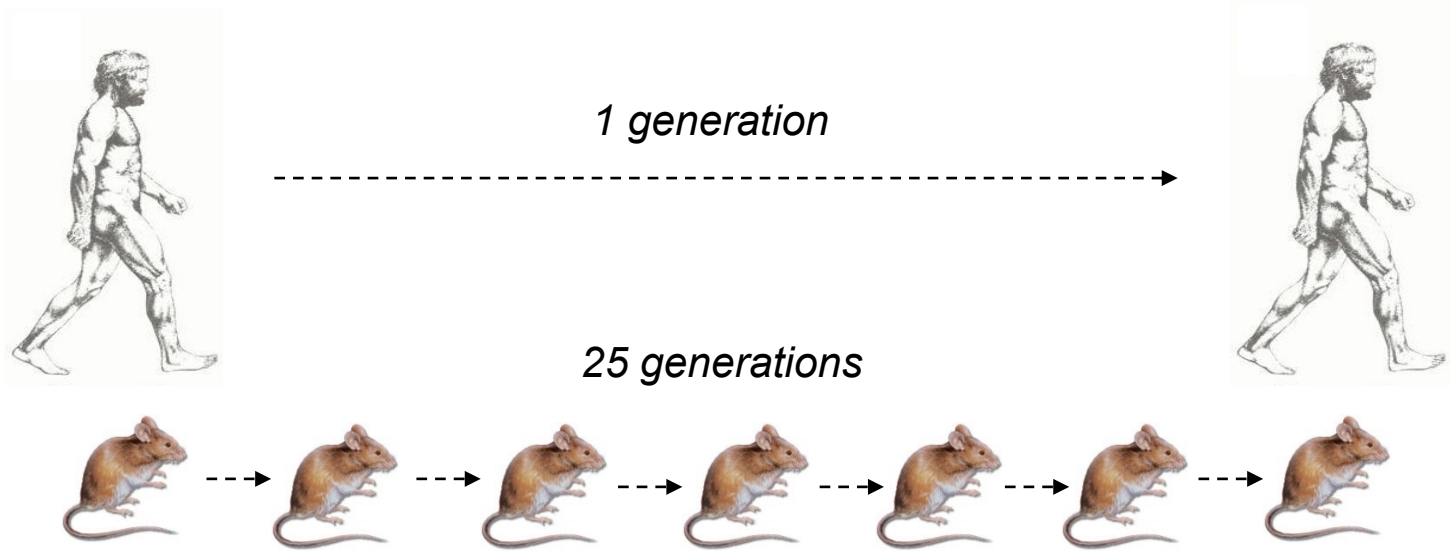
- Species with higher metabolic rate (i.e. smaller body size) have higher substitution rate.
- Homoiothermic vertebrates have higher substitution rate than poikilotermic vertebrates.





Generation time

- Species with shorter generation time (usually smaller body size) have higher substitution rate (per year). More cell divisions in the germline per year -> higher mutation rate per year.
- Species with longer generation time, however, have higher substitution rate per generation. They produce gametes longer time -> higher mutation rate per generation.

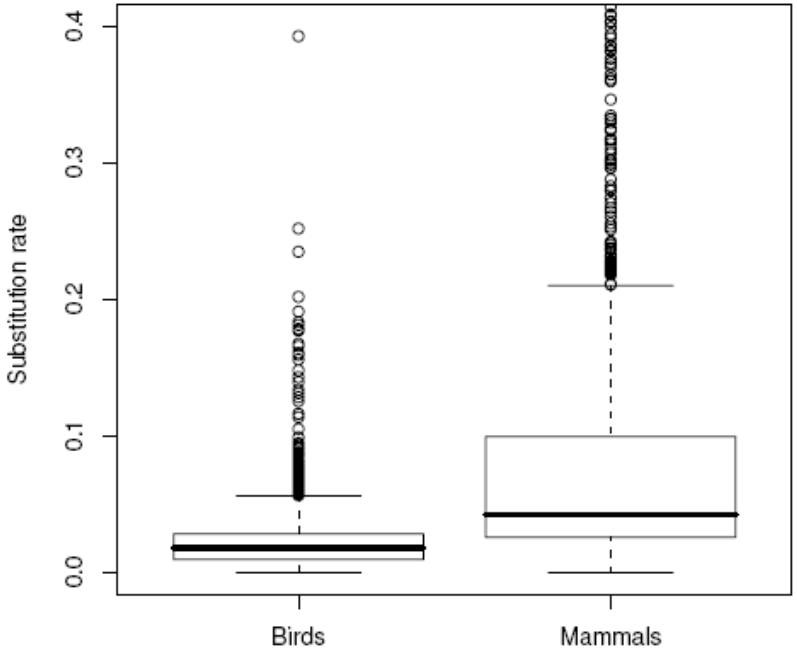


Longevity

- Long-lived species have more efficient DNA repair mechanisms -> lower mutation rate.

Gerbillus nanus
0.741 substitution/site/Myr

Balaenoptera borealis
0.007 substitution/site/Myr



Temperature

EVOLUTION
INTERNATIONAL JOURNAL OF ORGANIC EVOLUTION
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BRIEF COMMUNICATION | Full Access

Temperature predicts the rate of molecular evolution in Australian Eugongylinae skinks

Jeremias Ivan, Craig Moritz, Sally Potter, Jason Bragg, Rust Turakulov, Xia Hua,

First published: 05 September 2021 | https://doi.org/10.1111/evo.14342

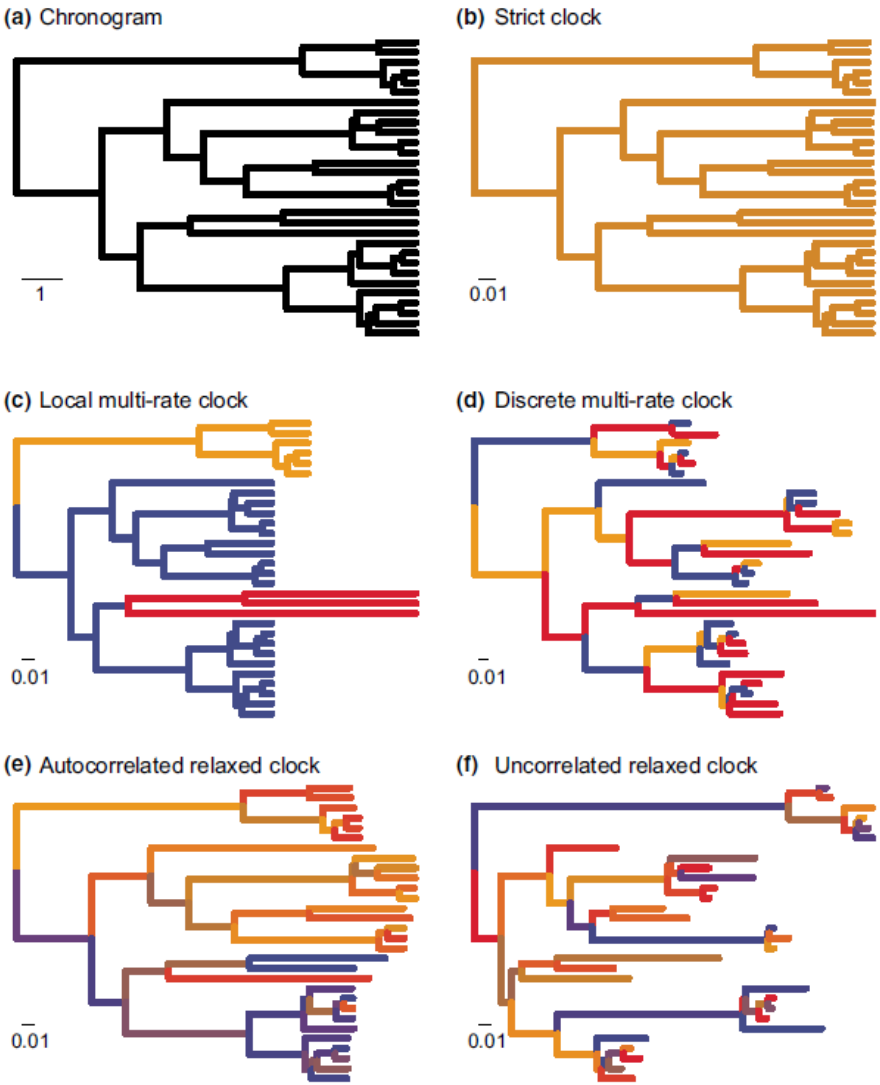
Molecular clocks

Strict clocks

- Substitution rate is homogenous across the phylogeny.

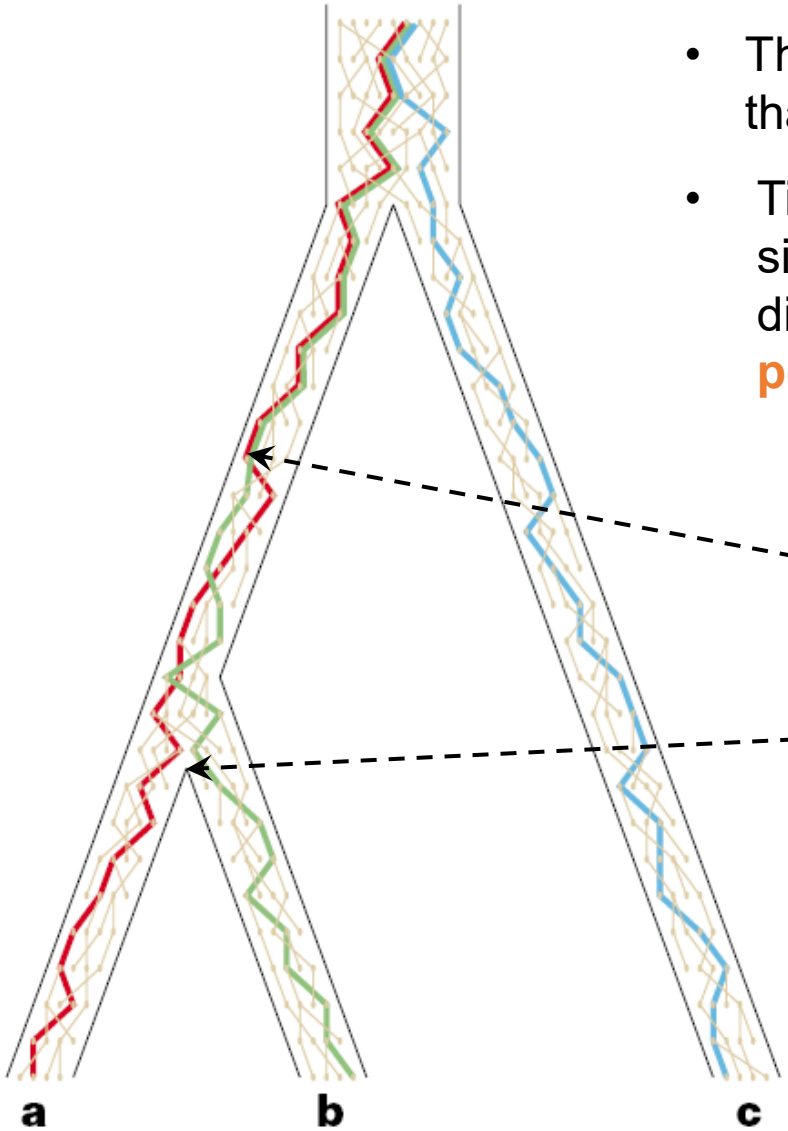
Relaxed clocks

- Variability in substitution rate among lineages.



Ho and Duchene, 2014

Other problems of molecular clocks



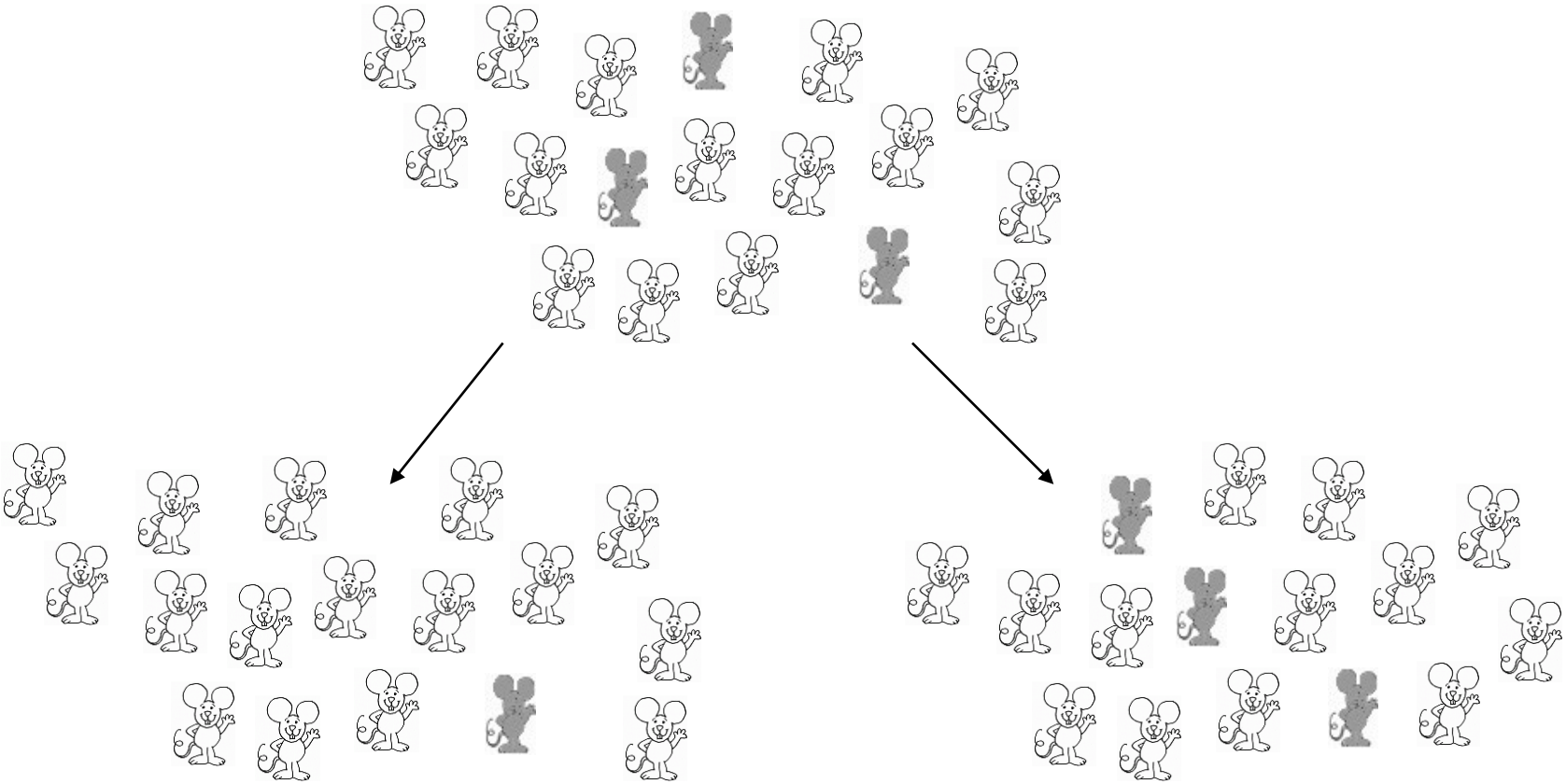
- They estimate sequence divergence time rather than species divergence time.
- Time to sequence divergence can be significantly higher compared to time to species divergence if there is still **ancestral polymorfism**.

sequence divergence

species divergence

Ancestral polymorfism

- Shared polymorphism inherited from common ancestor
- Time to fixation for neutral alleles: $t = 4N_e$ generations
- Species with high Ne have more ancestral polymorphism.



The nearly neutral theory of evolution

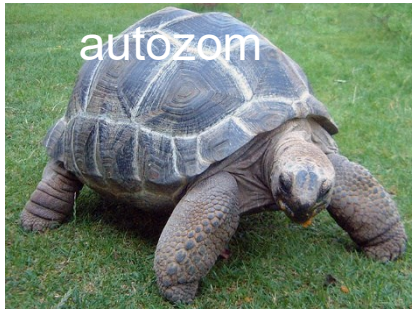
The nearly neutral mutations: $|2s| < \frac{1}{2N_e}$

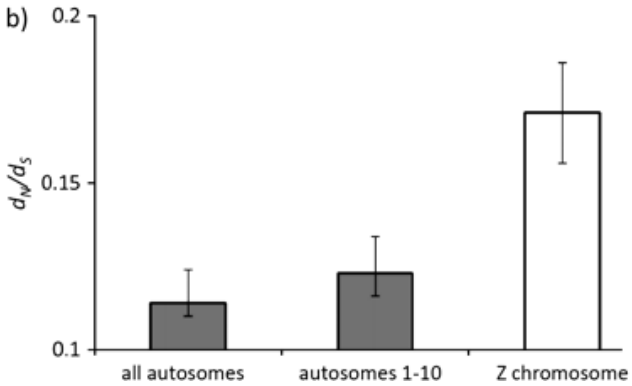
In small populations they behave as neutral (genetic drift), while in large populations as beneficial or disadvantageous (selection).

Tomoko Ohta

- Given that most mutations are disadvantageous, more mutations will be fixed in small populations than in large populations.
- Species with small populations will have higher substitution rate compared to species with large populations.

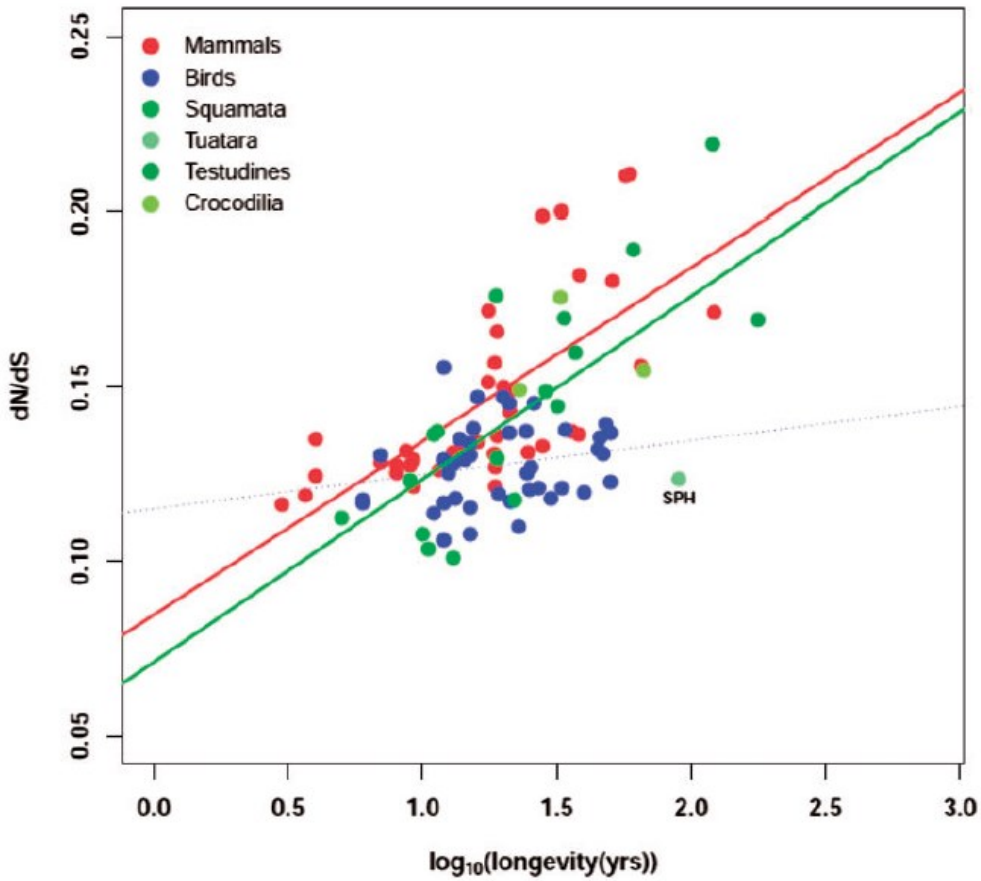
Faster X evolution





Mank et al. 2010

Species with smaller populations (higher longevity) show relatively more non-synonymous substitutions (dN) compared to synonymous substitutions (dS).



Figuet et al. 2016

Molecular clocks

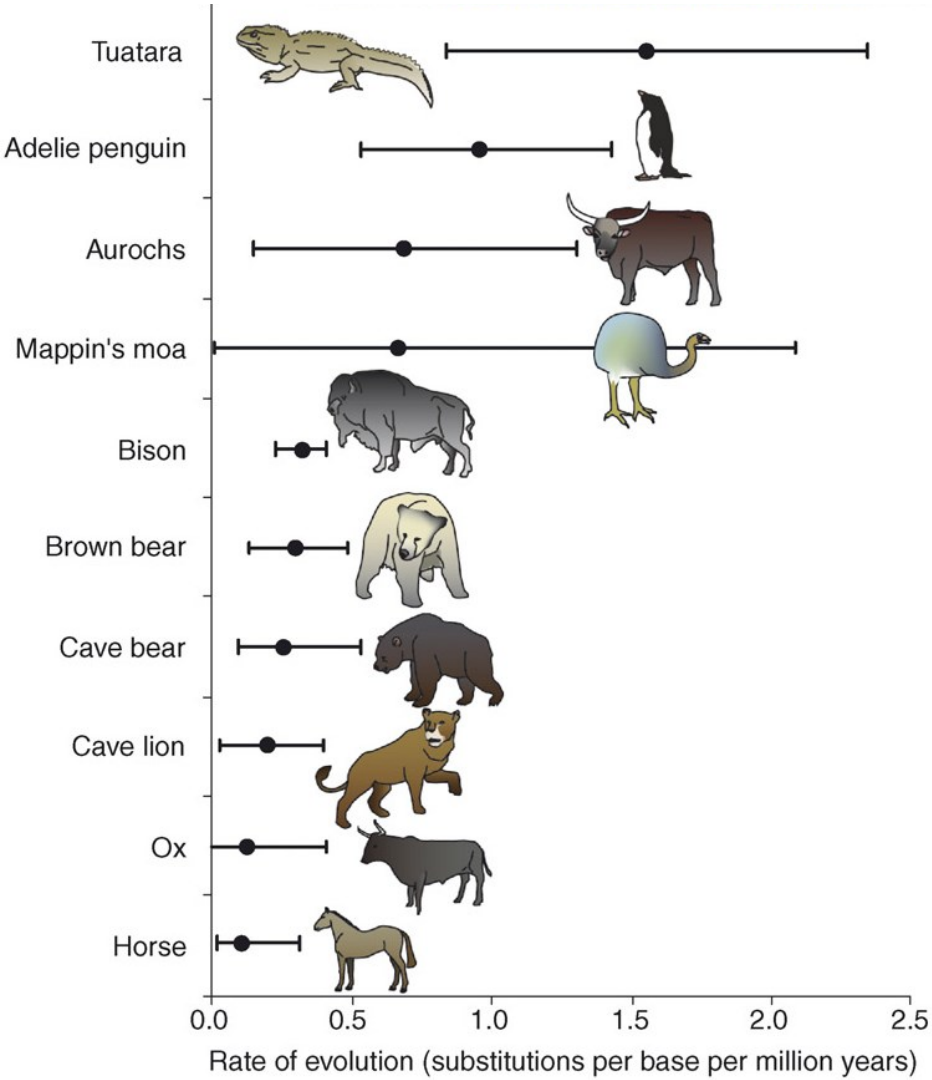
1. Mutation rate is not constant.
2. Substitution rate depends on the effective population size.
3. Time to sequence divergence does not need to correspond to time to species divergence.

Is there correlation between substitution rate and the rate of phenotypic evolution?

Tuatara
(Sphenodon punctatus)

Slow metabolism
Long generation time
Slow phenotypic evolution

But relatively high substitution rate in mtDNA.

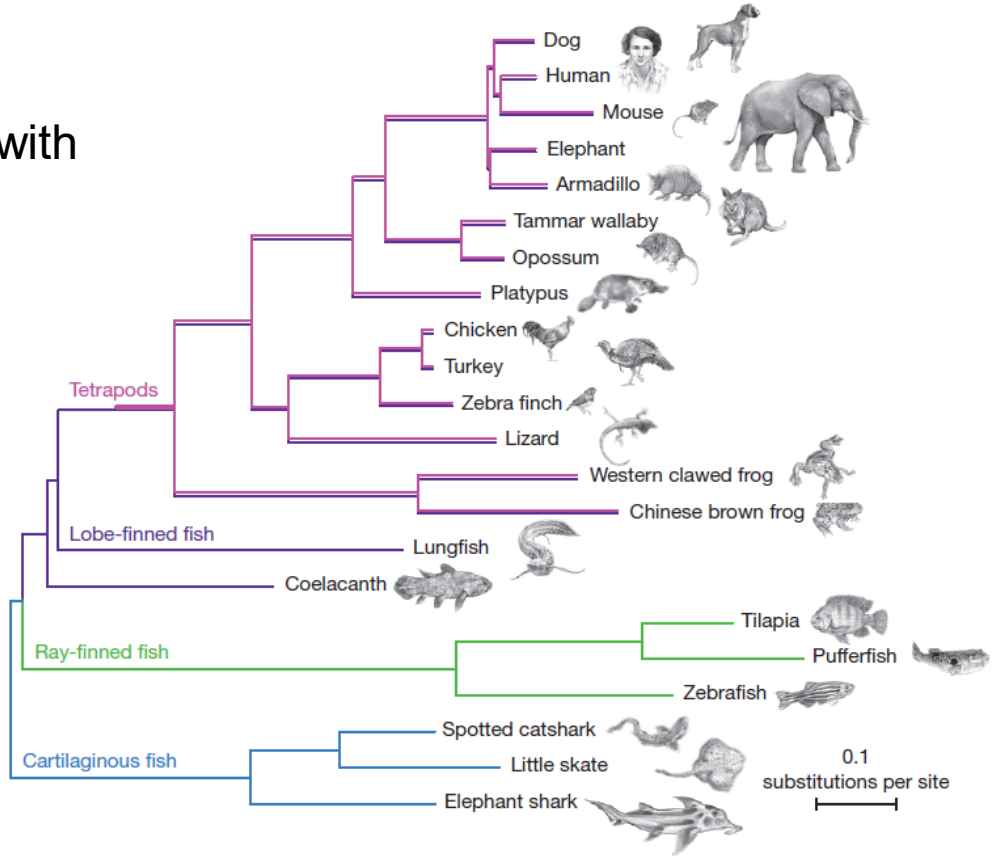


TRENDS in Genetics

Is there correlation between substitution rate and the rate of phenotypic evolution?

The West Indian Ocean coelacanth (***Latimeria chalumnae***)

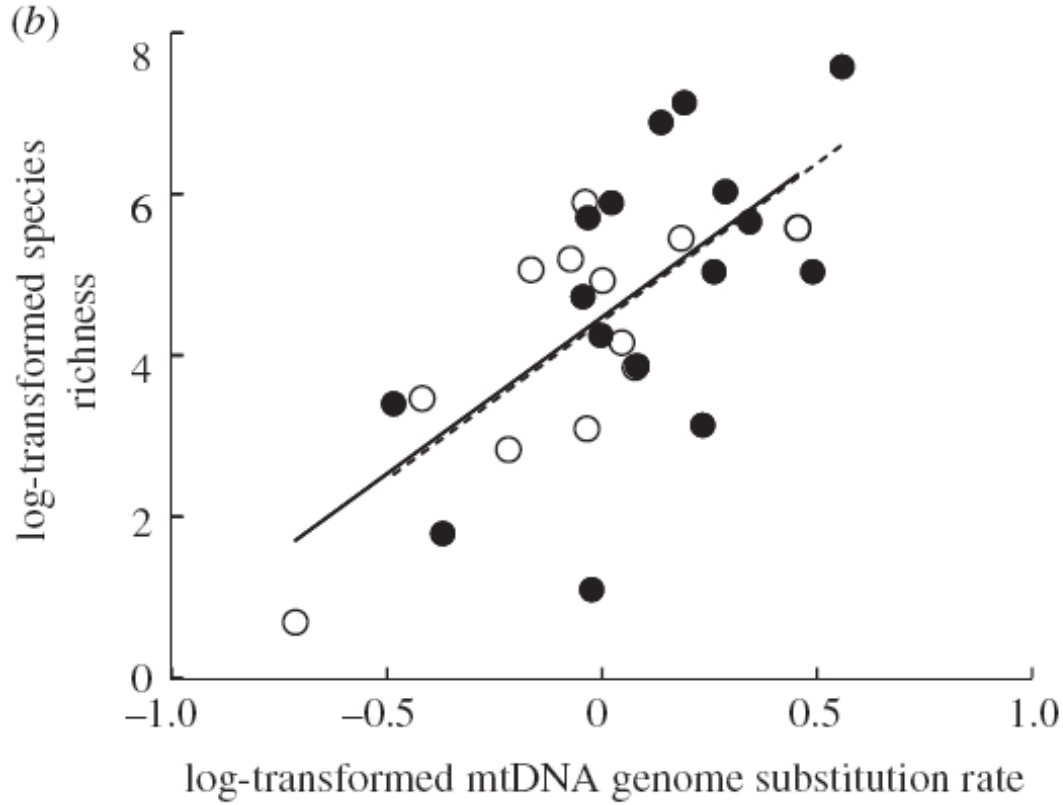
Two times slower substitution rate at protein coding genes in comparison with tetrapods.



Substitution rate and speciation rate

Taxons with higher number of species have higher substitution rate.

Higher substitution rate could fasten the speciation rate.



○ birds ● reptiles

Or higher speciation rate leads to faster substitution rate?

ACCEPTED MANUSCRIPT

Nucleotide substitutions during speciation may explain substitution rate variation

Thijs Janzen, Folmer Bokma, Rampal S Etienne

Systematic Biology, syab085, https://doi.org/10.1093/sysbio/syab085

Published: 21 October 2021 **Article history** ▾

Abstract

Although molecular mechanisms associated with the generation of mutations are highly conserved across taxa, there is widespread variation in mutation rates between evolutionary lineages. When phylogenies are reconstructed based on nucleotide sequences, such variation is typically accounted for by the assumption of a relaxed molecular clock, which is a statistical distribution of mutation rates without much underlying biological mechanism. Here, we propose that variation in accumulated mutations may be partly explained by an elevated mutation rate during speciation. Using simulations, we show how shifting mutations from branches to speciation events impacts inference of branching times in phylogenetic reconstruction. Furthermore, the resulting nucleotide alignments are better described by a relaxed than by a strict molecular clock. Thus, elevated mutation rates during speciation potentially explain part of the variation in substitution rates that is observed across the tree of life.