Modeling Molecular Evolution: Hypothesis testing

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Many substitution models exist.
Which model to use? The best!

But what does this mean?
Need a criterion

Sir R. A. FIsher

Likelihood

The likelihood of model M, parameters θ,
Given data D is:

L(M; θ I D) = Pr(D I M; θ)

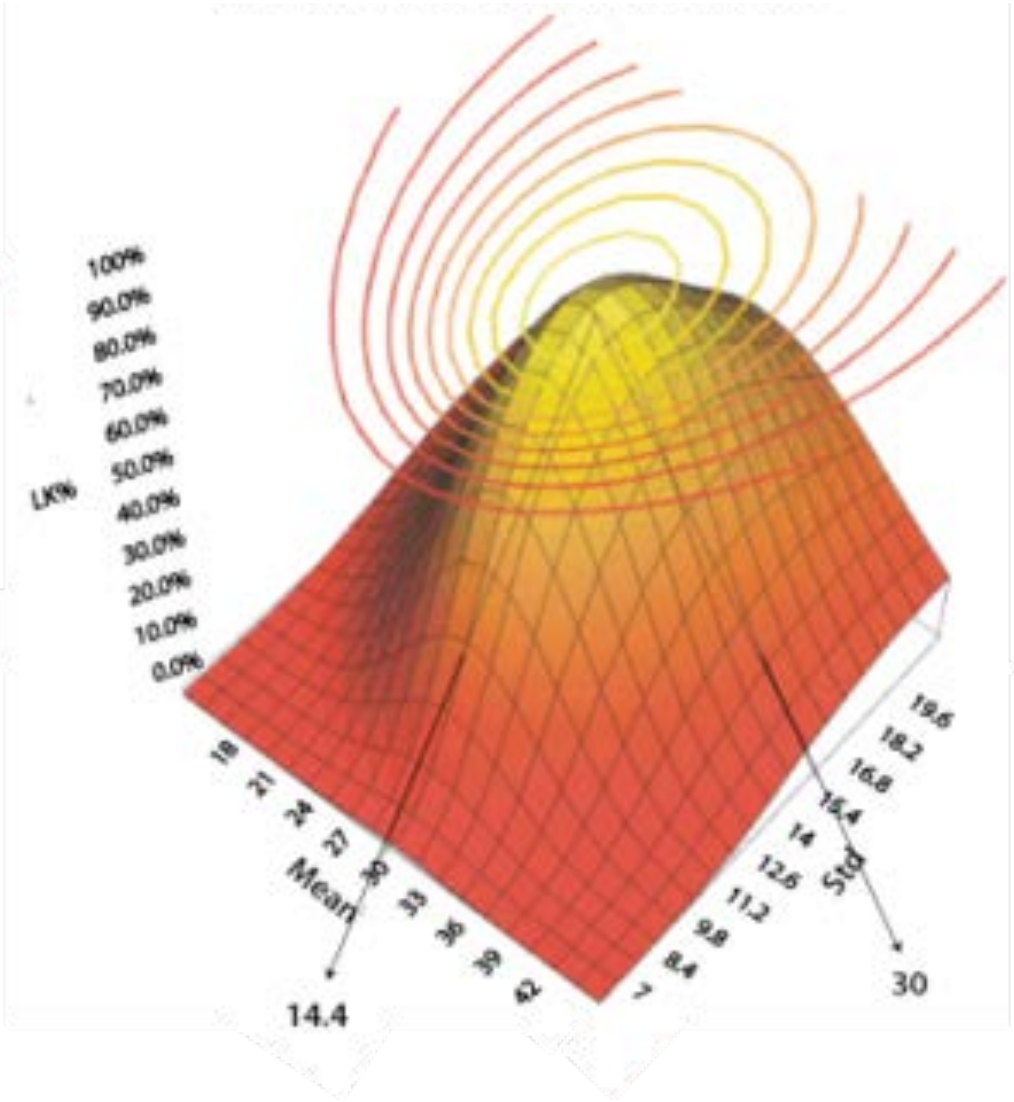
Maximum likelihood (ML) inference finds $\hat{\theta}$, the best-supported value of parameters θ:

such that L(M; $\hat{\theta}$ I D) ≥ L(M; $\hat{\theta}$ I D) for all other θ

M with parameters θ describes your hypothesis.

The ML method was pioneered by Sir R.A. Fisher in 1921-22
Lindgren (1968), Edwards (1984)

Likelihood



Hypothesis tests

A hypothesis is a statement about the state of nature. It may need substantiation, verification or rejection.

A test of a hypothesis assigns one of the inferences:

- 'accept' the hypothesis or
- 'reject' the hypothesis for some result of an experiment

Example: Fair coin

Toss coin 100 times, observe 65 heads and 35 tails.

Null hypothesis H_0: "The coin is fair"
(i.e. probability 0.5 for Heads)

Calculate the likelihood:

$$L(H_0|D) = \binom{100}{65} \times 0.5^{65} \times 0.5^{35} = 0.000864$$

$$\log(L(H_0|D)) = \log(0.000864) = -7.0541$$

Example: Biased coin

Alternative hypothesis H_1:
"The coin is biased with probability p of heads"
The ML estimate of p is 65/100 = 0.65
Optimized the likelihood:

$$L(H_1|D) = \binom{100}{65} \times p^{65} \times (1-p)^{35}$$

$$= \binom{100}{65} \times 0.65^{65} \times 0.35^{35} = 0.08340$$

$$\log(L(H_1|D)) = \log(0.08340) = -2.484$$

H_1 is more likely, but is the result significant?

Hypothesis testing

Test the null hypothesis H_0 against the alternative H_1

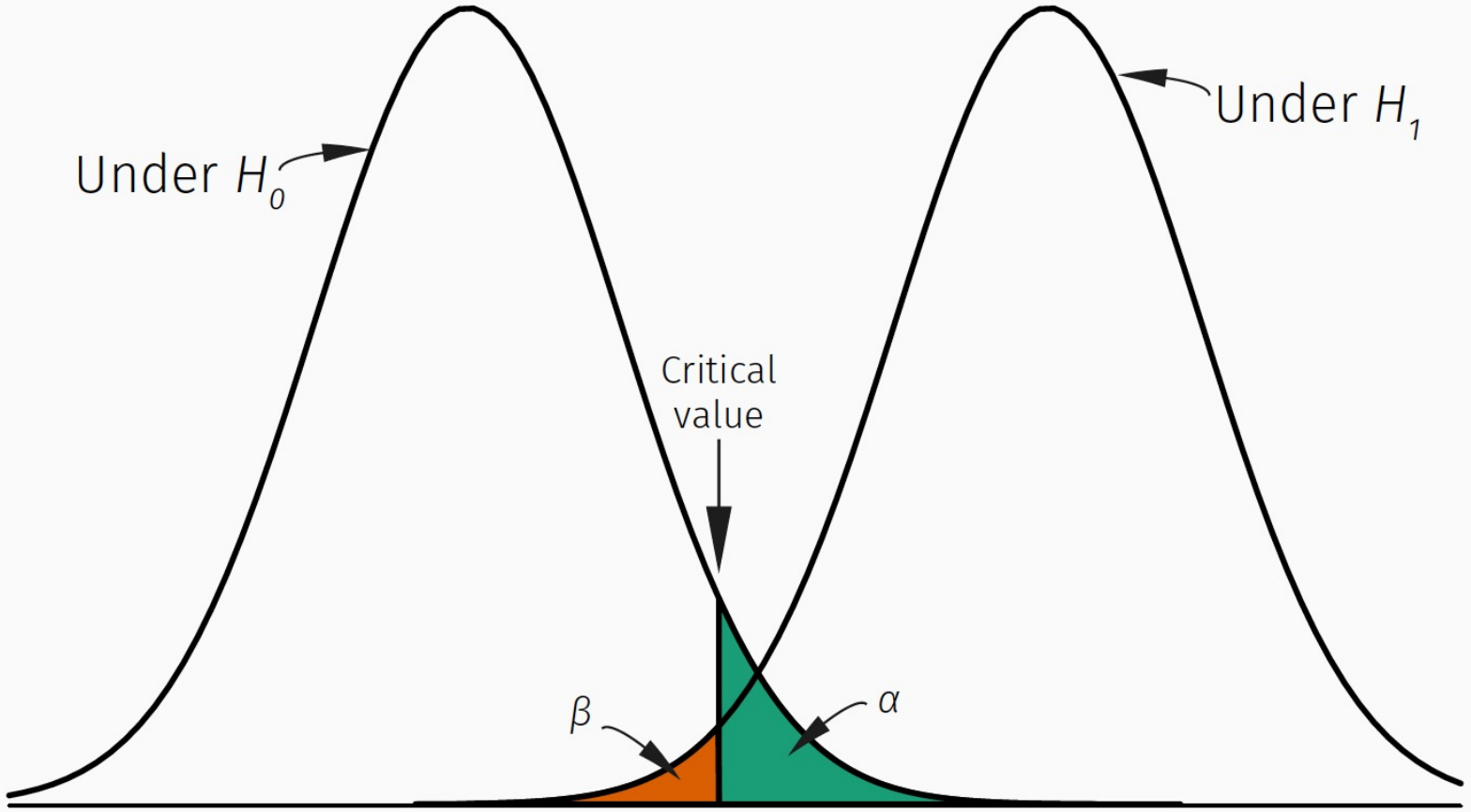
- A *test statistic T* is used as a reduction of the data
- The range of values for rejecting H_0 being
- tested is called the *critical region*
- There are good and bad tests, leading to the wrong inference or statistical errors:

  Type I error: Rejecting H_0 when H_0 is true.

  Type II error: Accepting H_0 when H_0 is false

Type I and II errors

- α = "size of type I error" = P_{H_0}(reject H_0)
- β = "size of type II error" = P_{H_1}(accept H_0)



Nested hypotheses

Two models are *nested* if one model can be reduced to another model by constraining some of its parameters.

In our example: forcing p = 0.5 in H_1 reduces it to H_0

H_1 has one more parameter than H_0

$$P(H_1, p) = \binom{100}{65} \times p^{65} \times (1-p)^{35}$$

Fix p to 0.5

$$P(H_1, p = 0.5) = \binom{100}{65} \times 0.5^{65} \times 0.5^{35} = P(H_0)$$

Likelihood ratio test (LRT)

Test H_0 against H_1, given they are nested

Use likelihood ratio statistic:

$$\ell_0 = \log\{L(H_0)\}$$
$$\ell_1 = \log\{L(H_1)\}$$
$$T = 2\delta = 2\log\left(\frac{L(H_1)}{L(H_0)}\right) = 2(\ell_1 - \ell_0)$$

When H_0 is correct, the LRT statistic is asymptotically distributed as χ^2 distribution with *k* degrees of freedom (equal to the difference in the number of parameters in H_0 and H_1)

Significance level and *p*-value

Choose the rejection region given null is true:

$P(T \geq t \mid H_0) = \alpha$

T is the calculated test statistic from data

t is the chosen cut-off for the critical region

α is the desired significance level

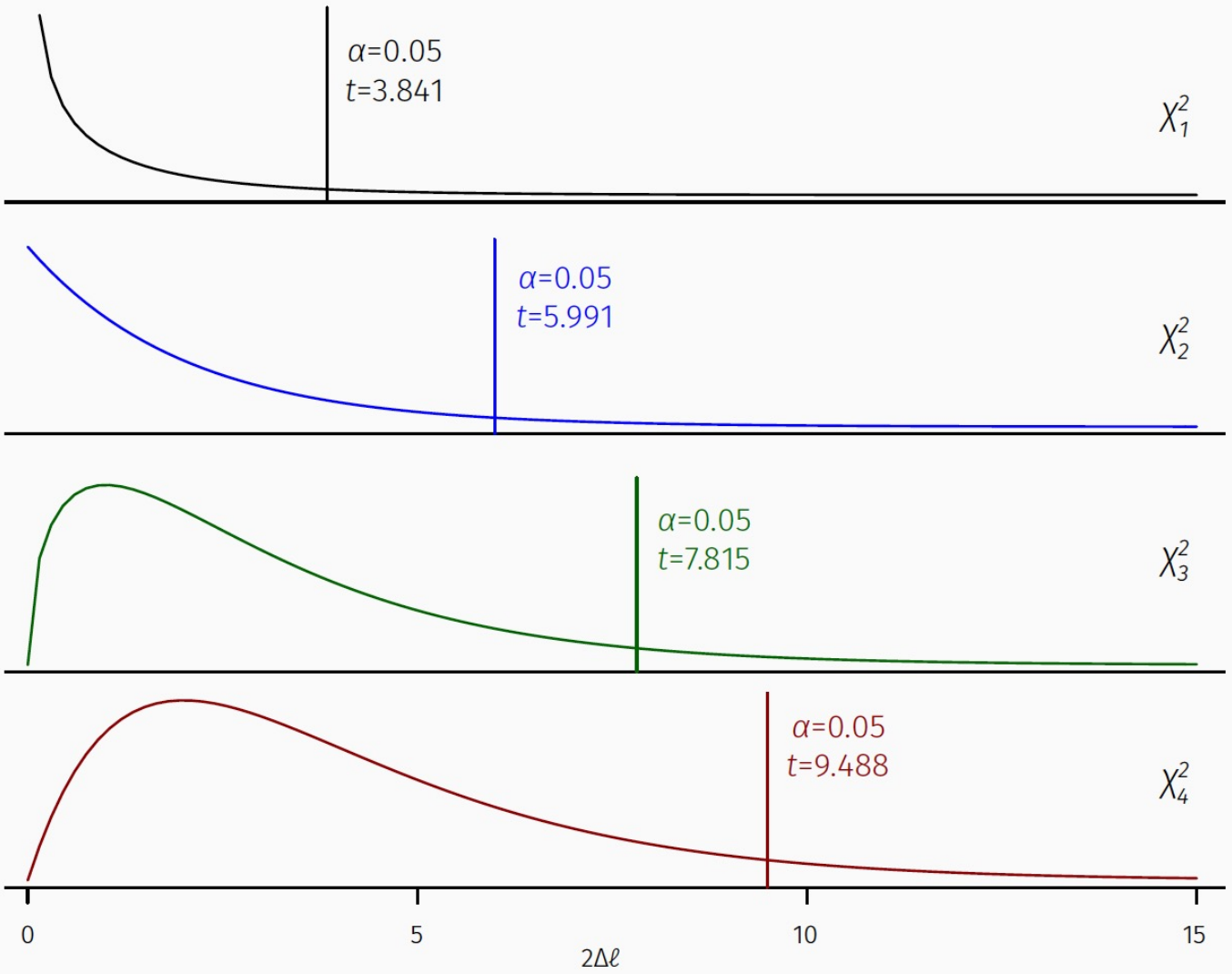
Choose a small value of α (e.g. 0.05 or 0.01)

For example, for χ^2 with d.f. = 1:

$P(T \geq 3.841) = 0.05$ and $P(T \geq 6.634) = 0.01$

p-value is probability of a result at least as extreme as that observed if H_0 were true

X^2 distributions



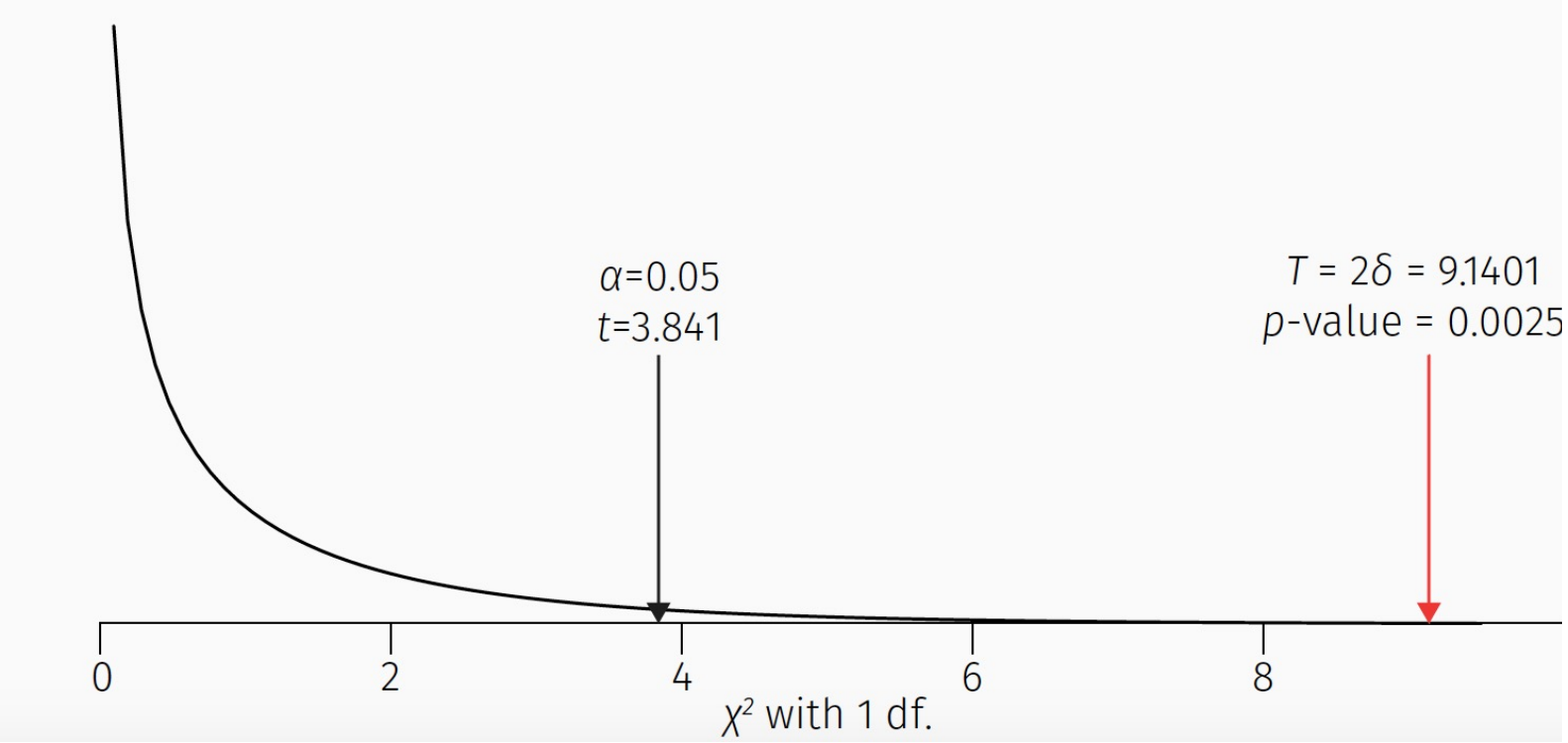
Exampl LRT: Fair vs biased coin

$2\delta = 2(\ell_1 - \ell_0) = 2(-2.484 - -7.0541) = 9.1401$

1 more parameter (p) in H_1, so use χ^2 with 1 d.f.

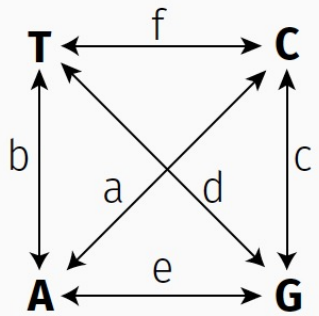
p-value = 0.0025 < 0.05

Reject the null H_0 in favour of the alternative H_1



Nested models

Model	Base frequencies	Substitution rates	Free parameters
JC	$\pi_T = \pi_C = \pi_A = \pi_G$	a = b = c = d = e = f	0
K80	$\pi_T = \pi_C = \pi_A = \pi_G$	a = b = c = d ≠ e = f	1
F81	$\pi_T \neq \pi_C \neq \pi_A \neq \pi_G$	a = b = c = d = e = f	3
HKY	$\pi_T \neq \pi_C \neq \pi_A \neq \pi_G$	a = b = c = d ≠ e = f	4
GTR	$\pi_T \neq \pi_C \neq \pi_A \neq \pi_G$	a ≠ b ≠ c ≠ d ≠ e ≠ f	8



Adapted from Posada & Crandall (2001).

LRT: JC vs K80

H_0: JC model
H_1: K80 model (with κ or ts/tv rate ratio)

- Both hypotheses use the same tree topology and have
- same number of branch length parameters.
- JC is nested within the K80 model.
- Fixing κ = 1 in K80 gives the JC model.
- The difference in number of parameters is 1 (κ).
- Perform the LRT by comparing 2δ with χ^2 d.f. = 1

LRT: GTR vs GTR+Γ

H_0: GTR model

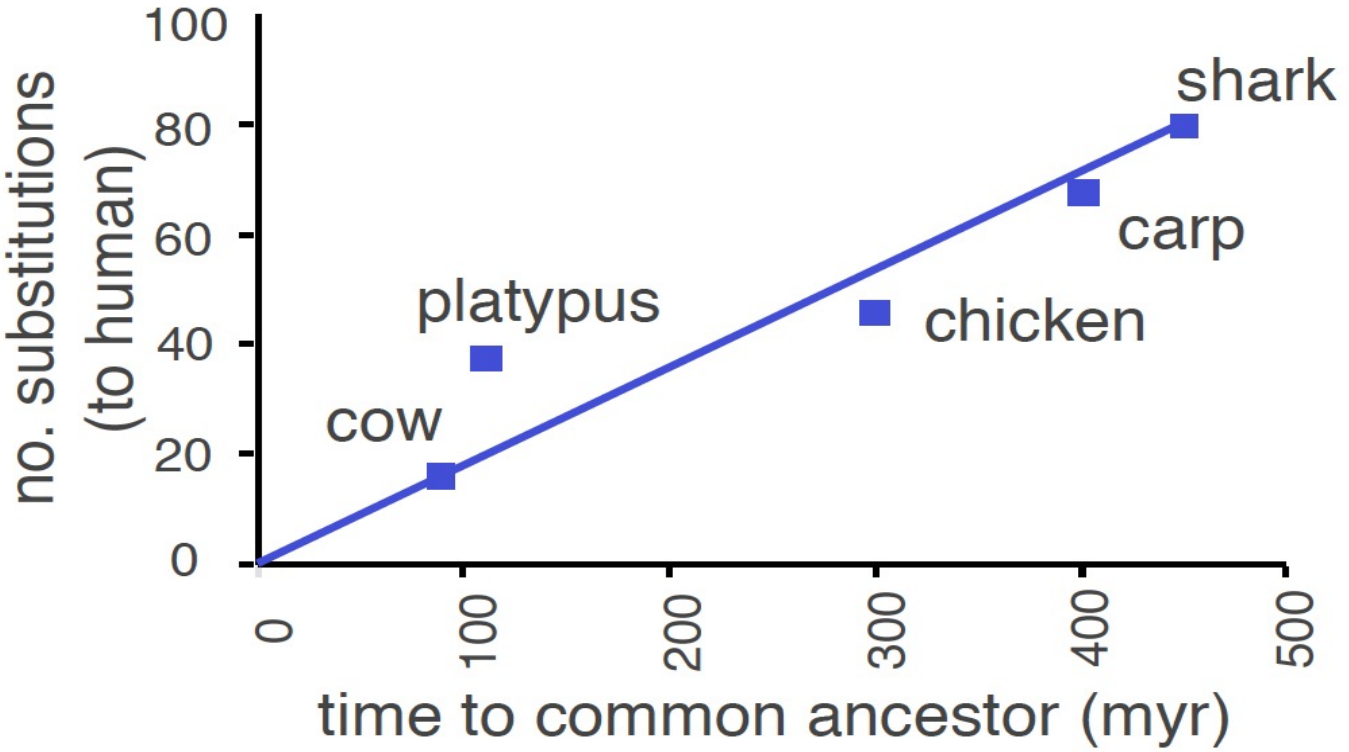
H_1: GTR+Γ (GTR parameters + α parameter)

GTR is nested within GTR+Γ, as $\alpha \to \infty$ recovers GTR

But, this value is on the boundary of the parameter space, so:

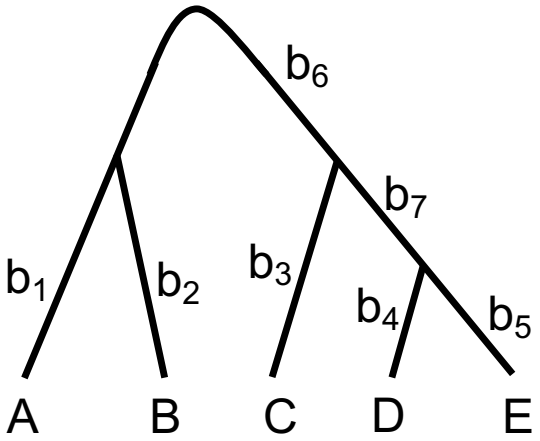
- Test 2δ with 50:50 mixture of point mass 0 and χ^2 with d.f. = 1
- Critical values are 2.71 at 5% and 5.41 at 1%
- See Goldman & Whelan (2000) for further details and table of critical values.

LRT: constant rate over time?



LRT: constant rate over time?

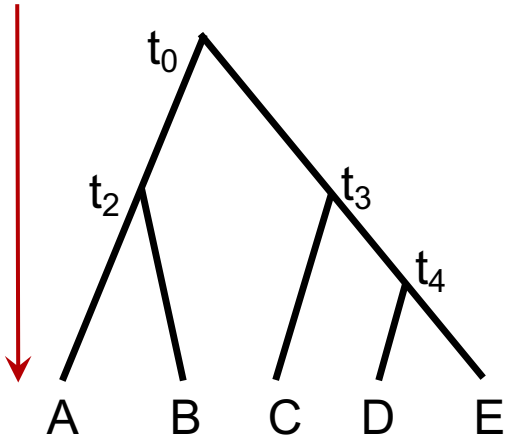
H_1: no clock
Parameters:
$2T - 3 = 7$ for T taxa



$$b_1 = b_2$$
$$b_4 = b_5$$
$$b_3 = b_4 + b_7$$

$T - 2 = 3$
constraints

H_0: clock
Parameters:
$T - 1 = 4$



Akaike Information Criterion

$$AIC = 2k - 2\log(L)$$

k is number of free model parameters
L is the maximum likelihood

- More parameters lead to a larger penalty
- We choose the model with the lowest AIC value
- Can be used with non-nested models
- Can rank models

AICc and BIC

For small sample size *n* compared to the number of parameters *k* (e.g. *n* / *k* < 40) use corrected AIC:

$$AIC_c = 2k - 2\log(L) + \frac{2k(k+2)}{n-k-1}$$

Bayesian information criterion is related to AIC.
BIC has a larger penalty for parameters than AIC,
so is more conservative and prefers simpler models.

$$BIC = k\log(n) - 2\log(L)$$