Phylogenetic inference and likelihood

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(With thanks to Mark Holder and Paul Lewis for slides)

This pattern is surprising.

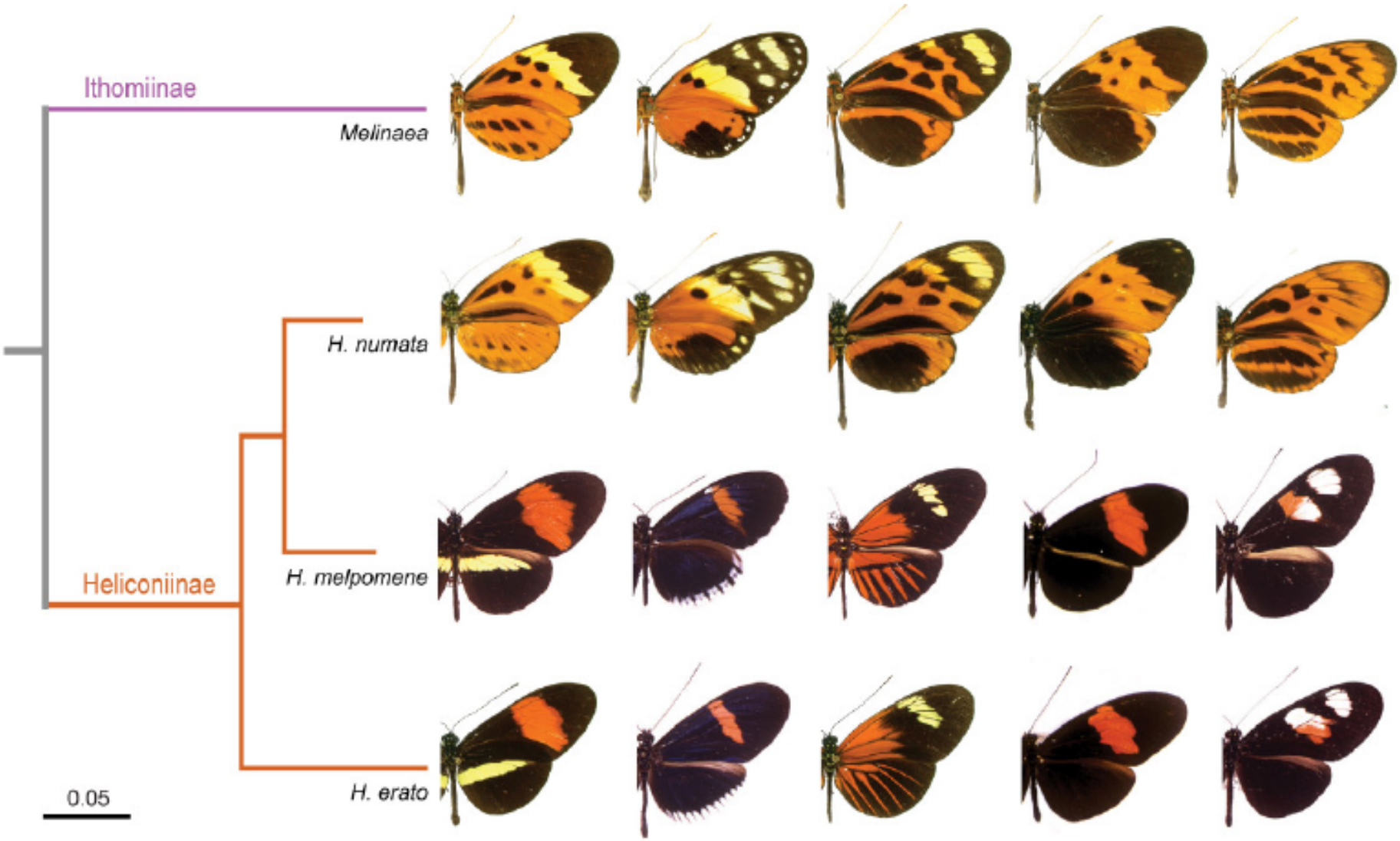


Figure by Mathieu Joron: http://xyala.cap.ed.ac.uk/joron/

(?)

Should we expect character conflict?

- Data type?
- Evolutionary history?

How can we deal with character conflict?

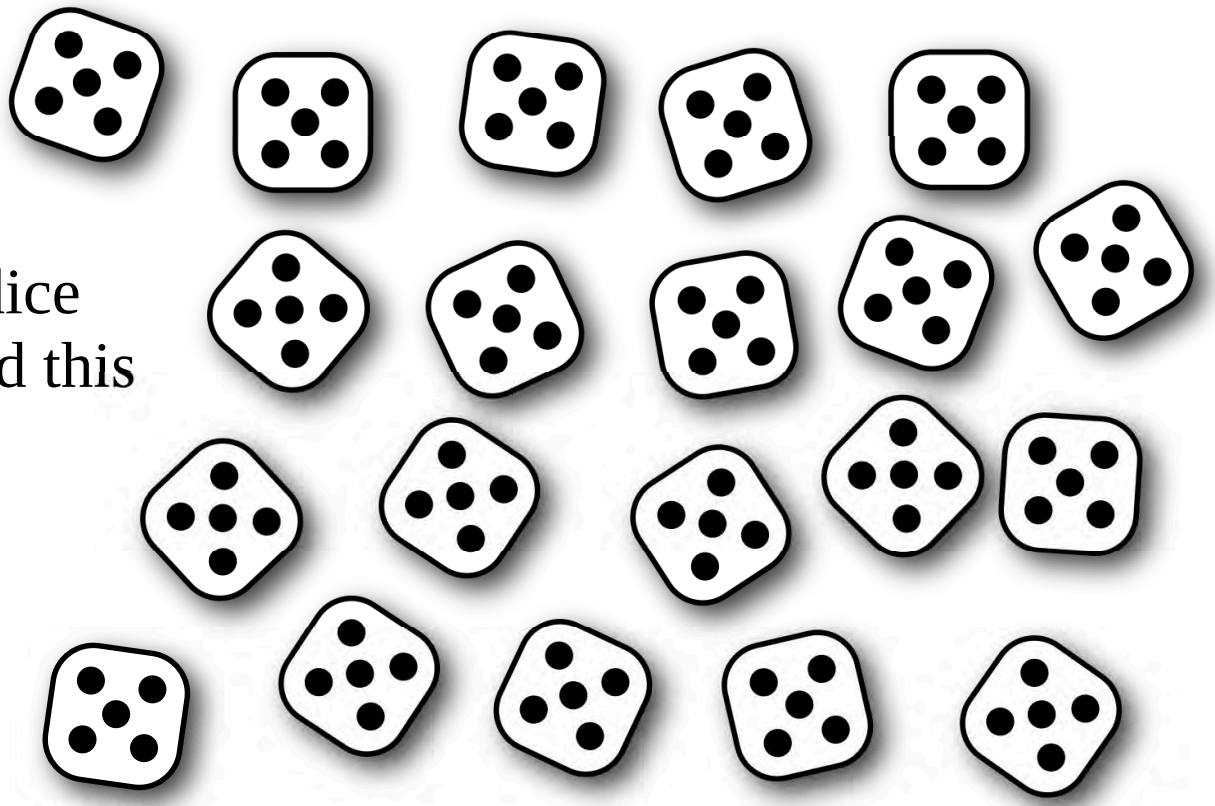
- We need to apply an error model
- Likelihood provides a measure of surprise under different models

The Likelihood Criterion

The probability of the observations computed using a model tells us how surprised we should be.

The preferred model is the one that surprises us least.

Suppose I threw 20 dice down on the table and this was the result...



Combining probabilities

- *Multiply* probabilities if the component events must happen **simultaneously** (i.e. where you would naturally use the word AND when describing the problem)

Using 2 dice, what is the probability of

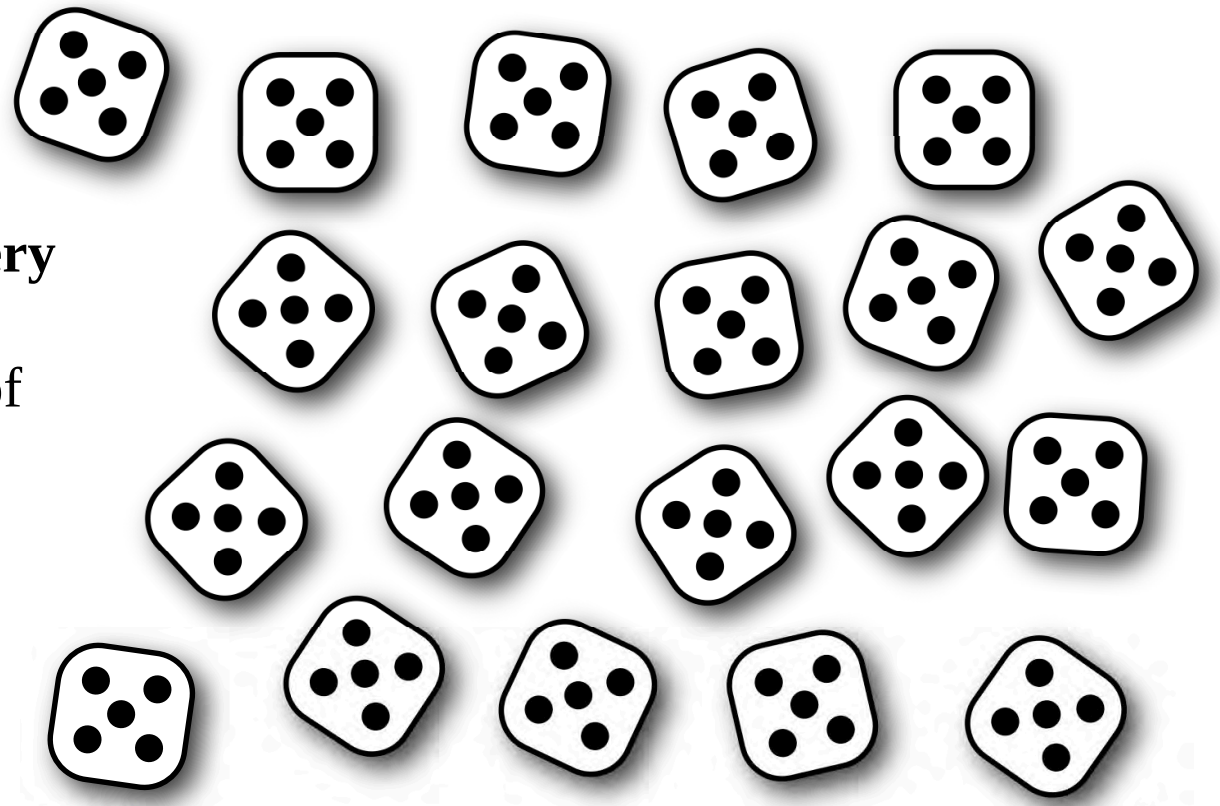
 AND ?

$(1/6) \times (1/6) = 1/36$

The Fair Dice model

$$\Pr(\text{obs.}|\text{fair dice model}) = \left(\frac{1}{6}\right)^{20} = \frac{1}{3,656,158,440,062,976}$$

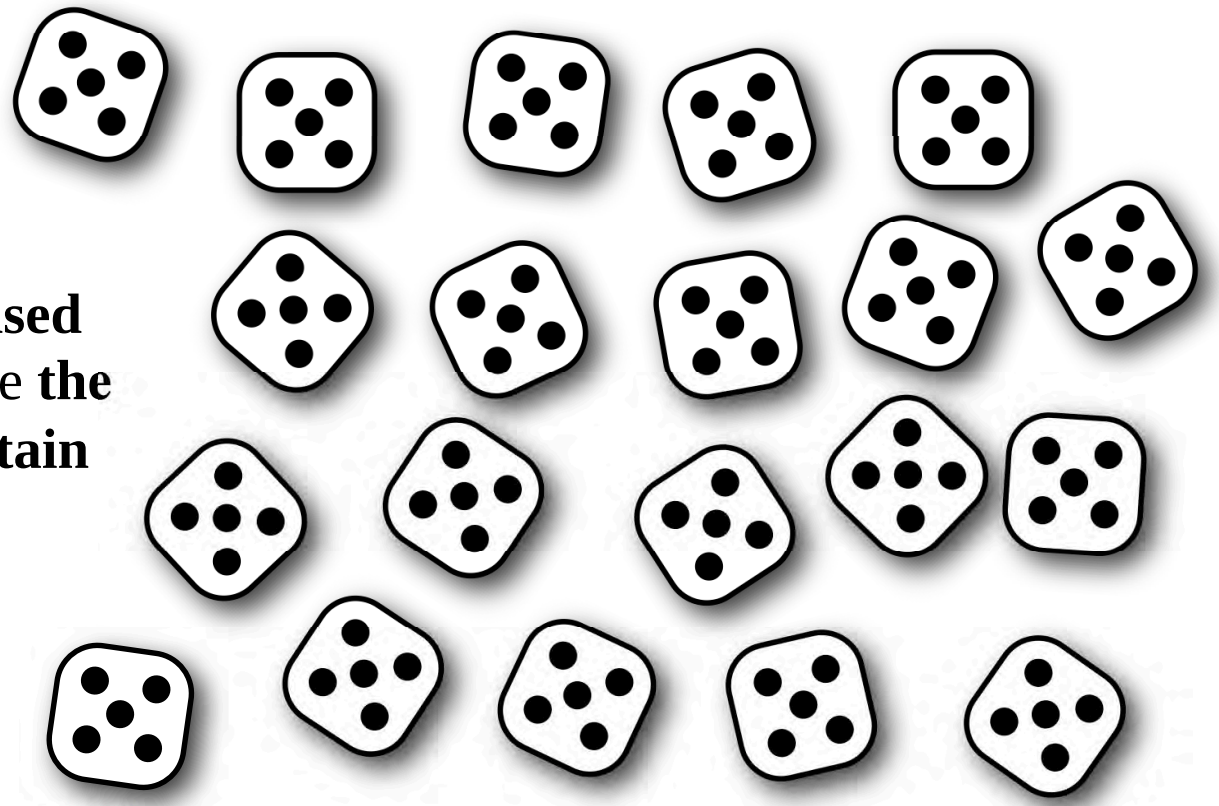
You should have been **very surprised** at this result because the probability of this event is **very small**: only 1 in 3.6 quadrillion!



The Trick Dice model

(assumes dice each have 5 on every side)

$$\Pr(\text{obs.}|\text{trick dice model}) = 1^{20} = 1$$



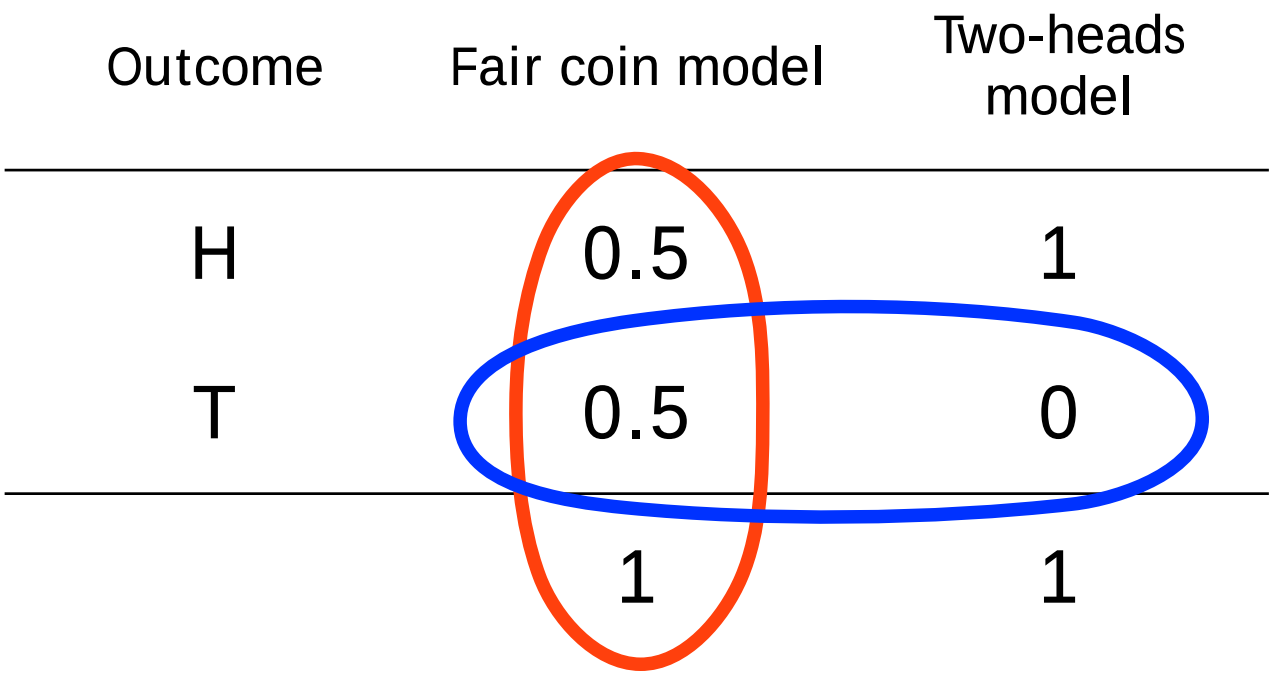
You should **not be surprised at all** at this result because **the observed outcome is certain** under this model

Results

Model	Likelihood	Surprise level
Fair Dice	$\frac{1}{3{,}656{,}158{,}440{,}062{,}976}$	Very, *very*, ***very*** surprised
Trick Dice	1	Not surprised at all

winning model maximizes likelihood (and thus minimizes surprise)

Likelihood: why a new term?



Likelihoods of models given one particular data outcome are *not* expected to sum to 1.0

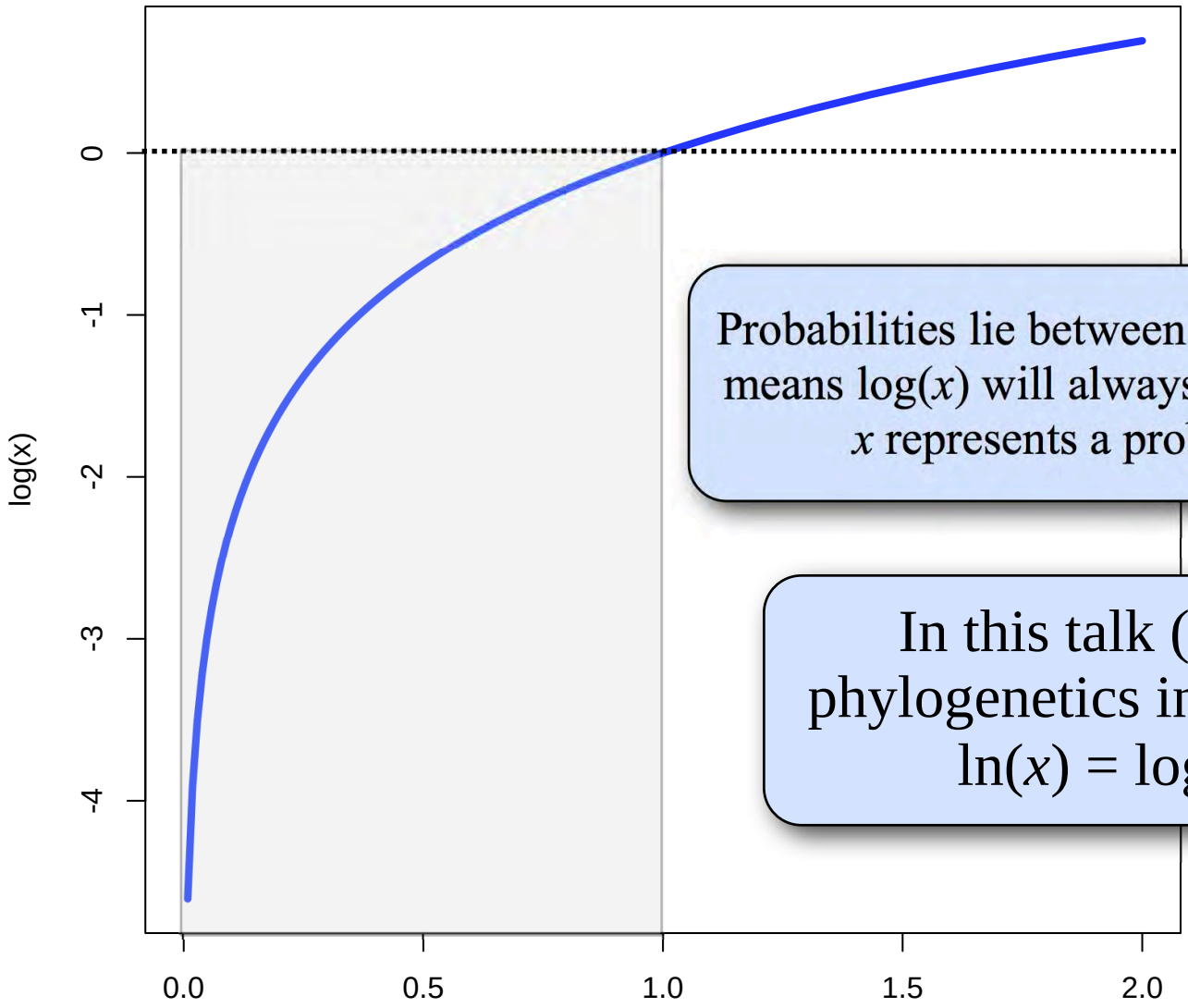
Probabilities of data outcomes given one particular model sum to 1.0

Likelihood and model comparison

- Analyses using likelihoods ultimately involve **model comparison**
- The models compared can be **discrete** (as in the fair vs. trick dice example)
- More often the models compared differ **continuously**:
  - Model 1: branch length is 0.01
  - Model 2: branch length is 0.02
  - Model 3: branch length is 0.03

Rather than having an infinity of models, we instead think of the branch length as a **parameter** within one model

Likelihoods vs. log-likelihoods



Probabilities lie between 0 and 1, which means $\log(x)$ will always be negative if x represents a probability.

In this talk (and in phylogenetics in general), $\ln(x) = \log(x)$

Likelihood calculated from a single sequence

$$\Pr(A) = \pi_A$$
$$\Pr(C) = \pi_C$$
$$\Pr(G) = \pi_G$$
$$\Pr(T) = \pi_T$$

First 32 nucleotides of the ψη-globin gene of gorilla:

GAAGTCCTTGAGAAATAAACTGCACACACTGG

$$L = \pi_G \pi_A \pi_A \pi_G \pi_T \pi_C \pi_C \pi_T \pi_T \pi_G \pi_A \pi_G \pi_A \pi_A \pi_A \pi_T \pi_A \pi_A \pi_A \pi_C \pi_T \pi_G \pi_C \pi_A \pi_C \pi_A \pi_C \pi_A \pi_C \pi_T \pi_G \pi_G$$
$$= \pi_A^{12} \pi_C^{7} \pi_G^{7} \pi_T^{6}$$

Note that we are assuming independence among sites here

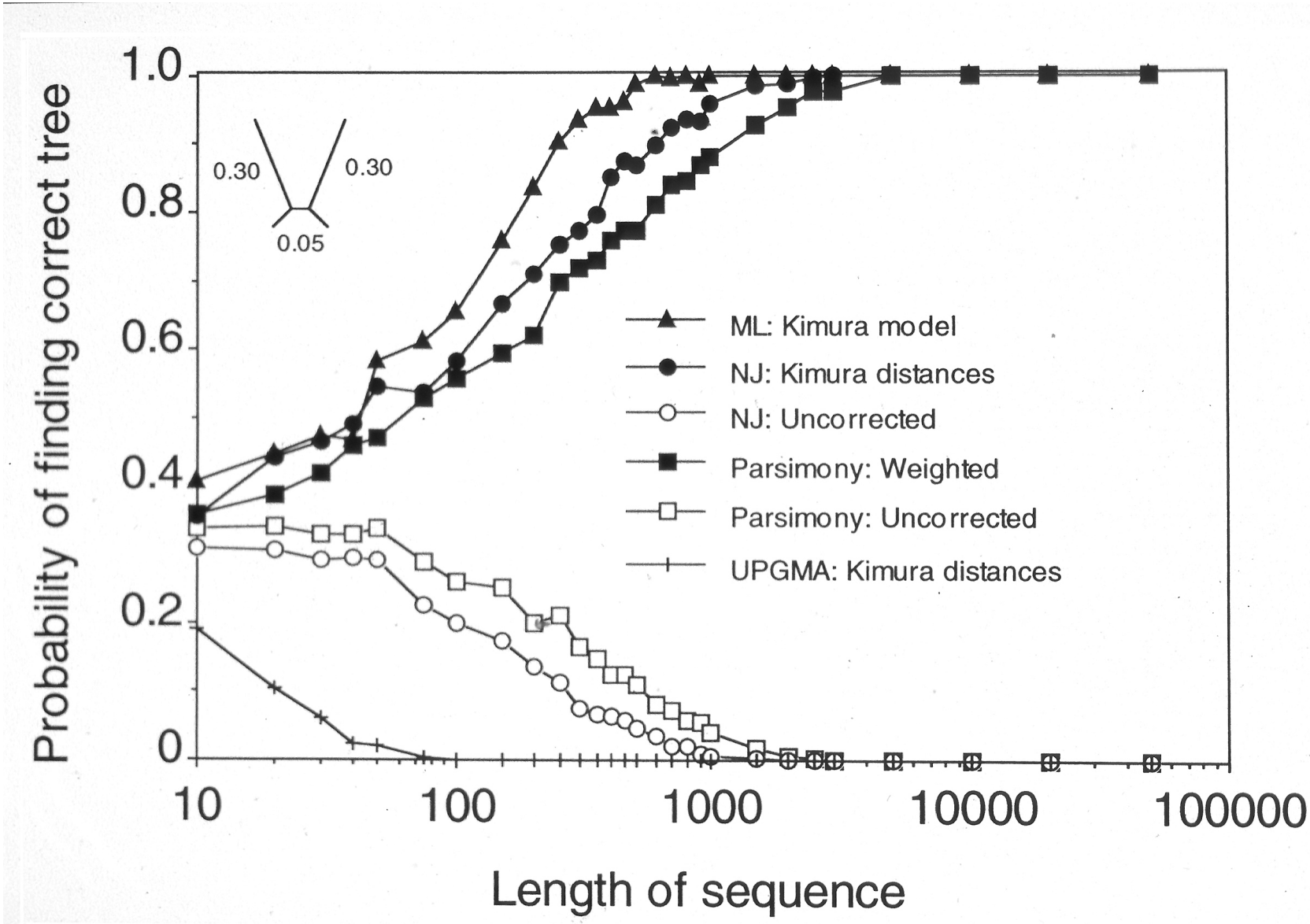
$$\log L = 12 \log(\pi_A) + 7 \log(\pi_C) + 7 \log(\pi_G) + 6 \log(\pi_T)$$

We can already see by eye-balling this that a model allowing **unequal** base frequencies will **fit better** than a model that assumes **equal** base frequencies because there are about twice as many As as there are Cs, Gs and Ts.

Discussion Question

Is it possible for the EQUAL model to fit a data set better (using the likelihood to measure model fit) than the FLEXIBLE model? Why or why not?

Historical aside



Hillis, D. M., J. P. Huelsenbeck, and D. L. Swofford. 1994. Hobgoblin of Phylogenetics? Nature 369:363-364.

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Model ranking using LRT or AIC

Likelihood Ratio Tests (LRT) and the Akaike Information Criterion (AIC) provide two ways to evaluate whether an **unconstrained** model fits the data significantly better than a **constrained** version of the same model.

Find *maximum* logL under the *unconstrained* model:

$$\begin{aligned}\log L_{\text{unconstrained}} &= 12\log(\pi_A) + 7\log(\pi_C) + 7\log(\pi_G) + 6\log(\pi_T) \\ &= 12\log(0.375) + 7\log(0.219) + 7\log(0.219) + 6\log(0.187) \\ &= -43.1\end{aligned}$$

This model has 3 estimated parameters

Find *maximum* logL under the *constrained* model:

$$\begin{aligned}\log L_{\text{constrained}} &= 12\log(\pi_A) + 7\log(\pi_C) + 7\log(\pi_G) + 6\log(\pi_T) \\ &= 12\log(0.25) + 7\log(0.25) + 7\log(0.25) + 6\log(0.25) \\ &= -44.4\end{aligned}$$

This model has 0 estimated parameters

Likelihood Ratio Test (LRT)

Calculate the likelihood ratio test statistic:

$$
\begin{aligned}
R &= -2\left[\log(L_{\text{constrained}}) - \log(L_{\text{unconstrained}})\right] \\
&= -2\left[-44.4 - (-43.1)\right] \\
&= 2.6
\end{aligned}
$$

(Note that the log-likelihoods used in the test statistic have been *maximized* under each model separately)

"unconstrained" does fit better than "constrained" (-43.1 > -44.4), but not significantly better (P = 0.457, chi-squared with 3 d.f.*)

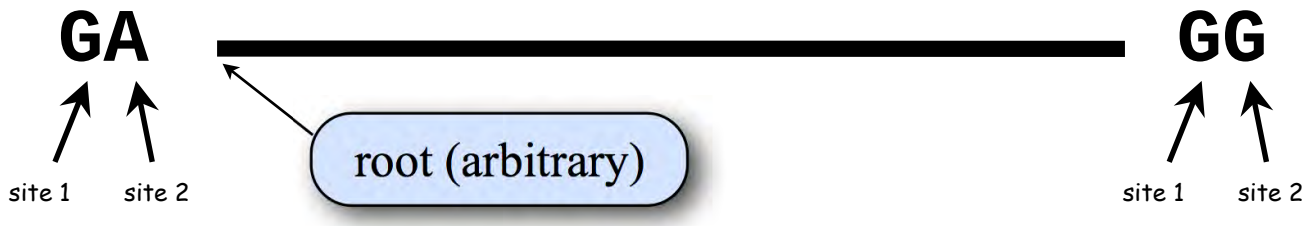
*The number of degrees of freedom equals the difference between the two models in the number of estimated parameters. In this case, unconstrained has 3 parameters and constrained has 0, so d.f. = 3 – 0 = 3

Comparing models in phylogenetics can be challenging, as topologies are not nested within one another.
We will discuss appropriate statistical approaches later in the course.

Likelihood of the simplest tree

sequence 1 ——— sequence 2

To keep things simple, assume that the sequences are only 2 nucleotides long:



$$
\begin{aligned}
L &= L_1 \, L_2 \\
&= \left[\left(\frac{1}{4}\right) \left(\frac{1}{4} + \frac{3}{4}e^{-4\alpha t}\right)\right] \left[\left(\frac{1}{4}\right) \left(\frac{1}{4} - \frac{1}{4}e^{-4\alpha t}\right)\right]
\end{aligned}
$$

Pr(G) Pr(G|G, αt) Pr(A) Pr(G|A, αt)

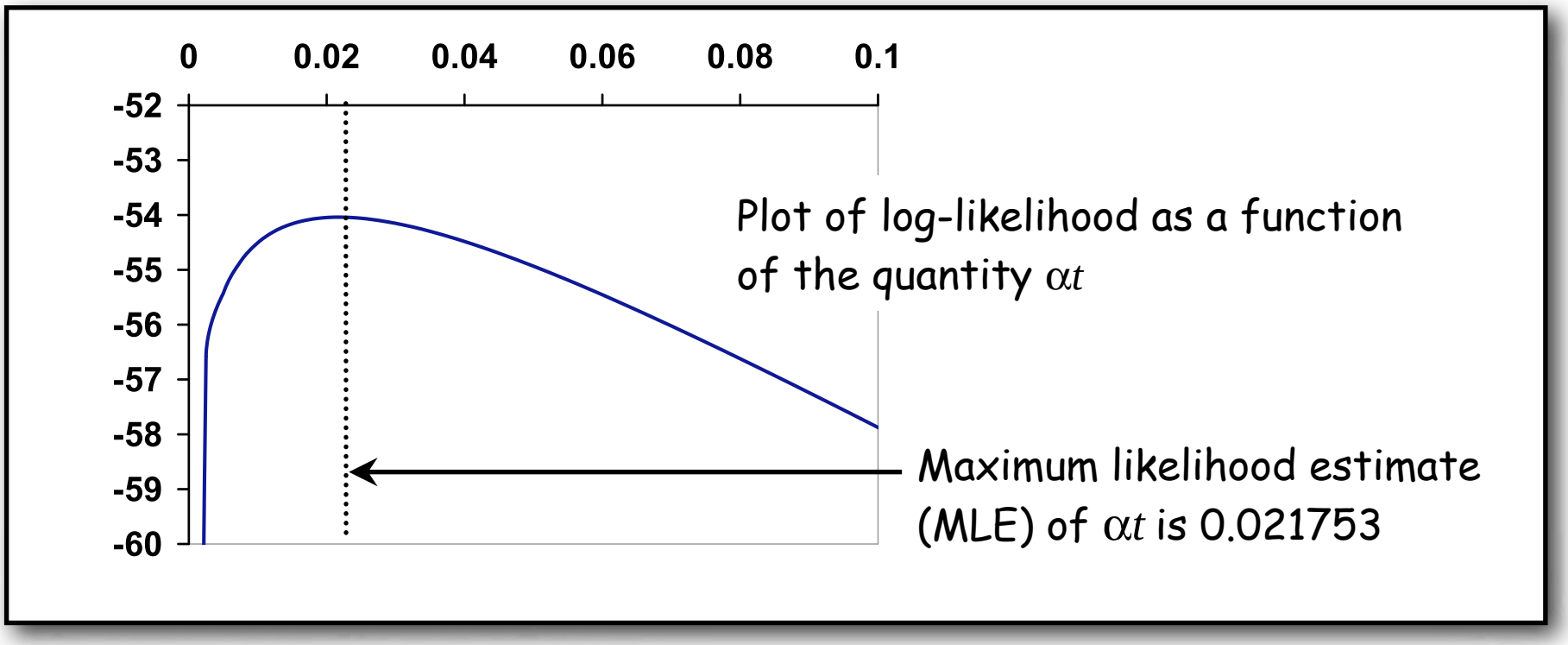
Note that we are NOT assuming independence here

Maximum likelihood estimation

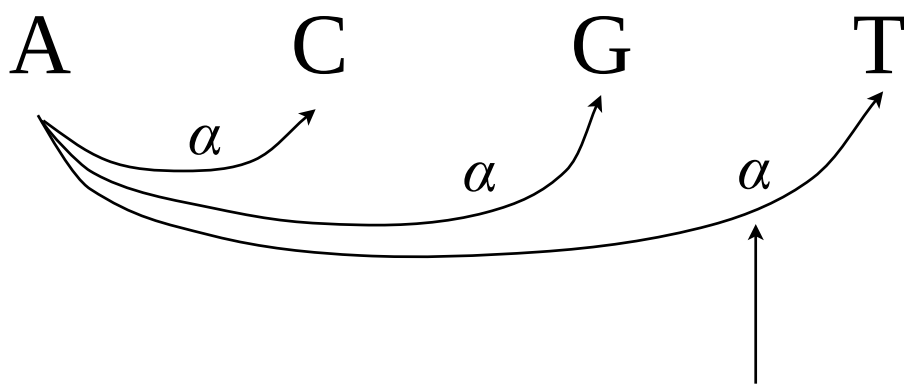
First 32 nucleotides of the ψη-globin gene of gorilla and orangutan:

```
gorilla   GAAGTCCTTGAGAAATAAACTGCACACACTGG
orangutan GGACTCCTTGAGAAATAAACTGCACACACTGG
```

$$L = \left[\left(\tfrac{1}{4}\right)\ \left(\tfrac{1}{4}+\tfrac{3}{4}e^{-4\alpha t}\right)\right]^{30}\left[\left(\tfrac{1}{4}\right)\ \left(\tfrac{1}{4}-\tfrac{1}{4}e^{-4\alpha t}\right)\right]^{2}$$



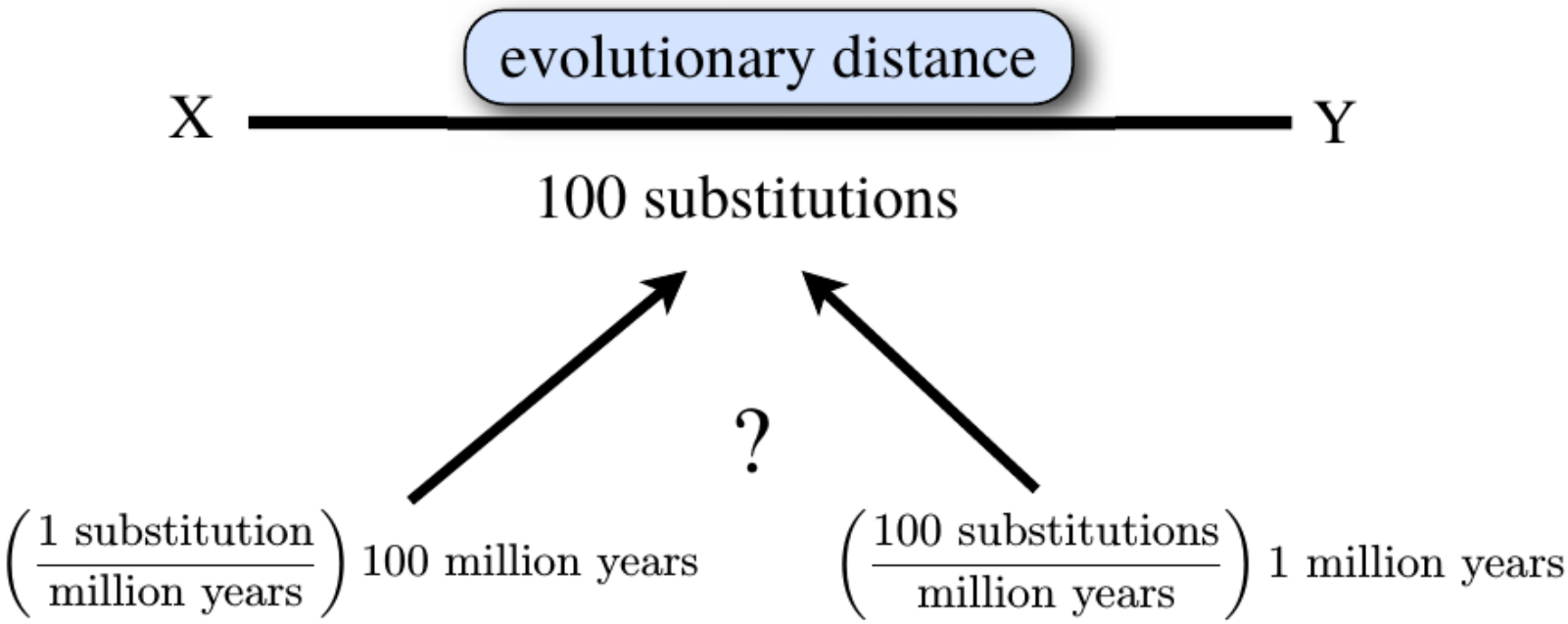
number of substitutions = rate × time



Overall substitution rate is 3α, so the expected number of substitutions (v) is

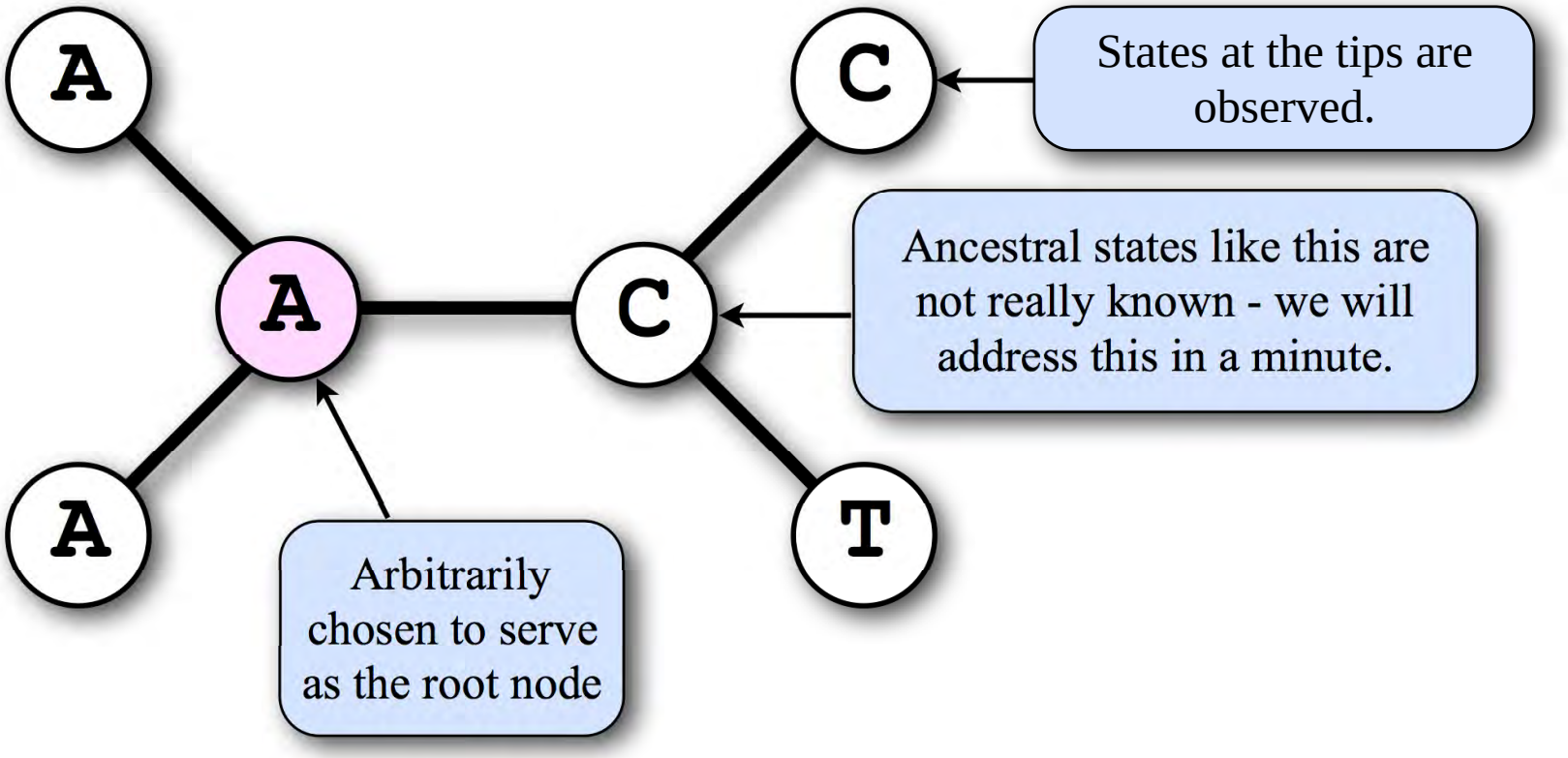
$$v = 3\alpha t$$

Rate and time are confounded

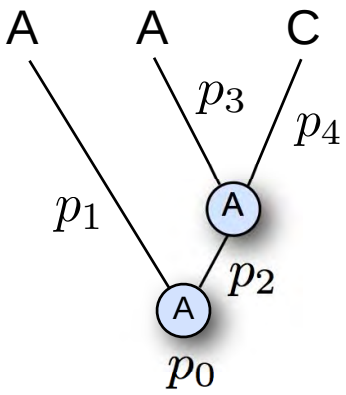


Likelihood of an unrooted tree

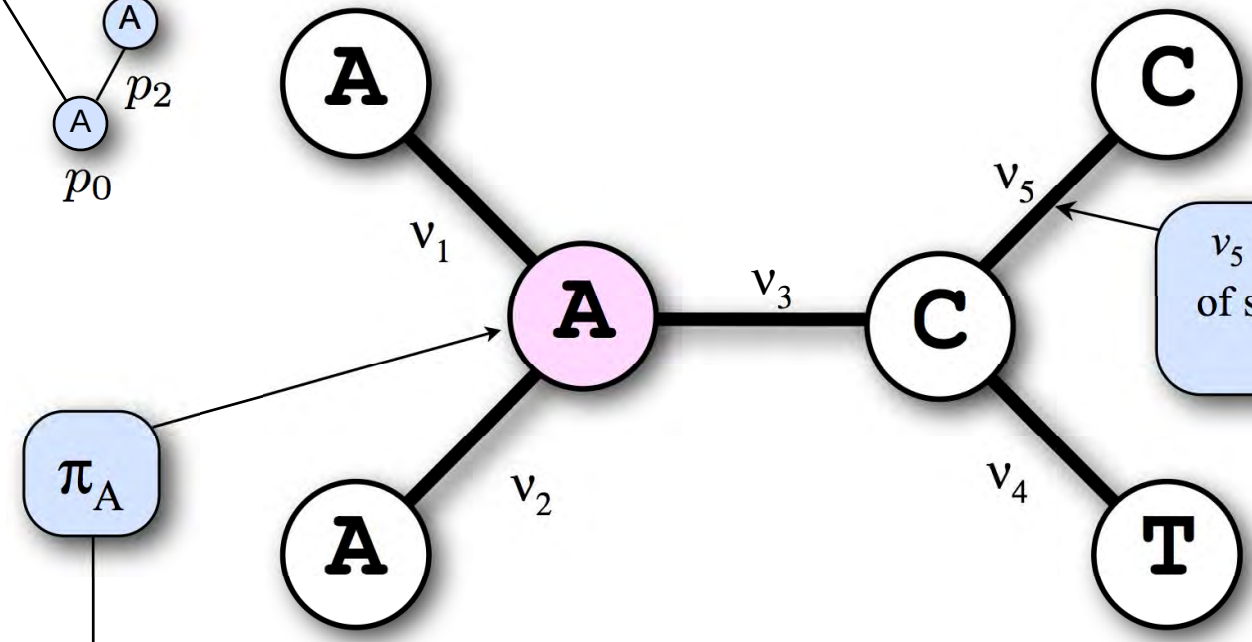
(data shown for only one site)



From slide 6



Likelihood for site *k*



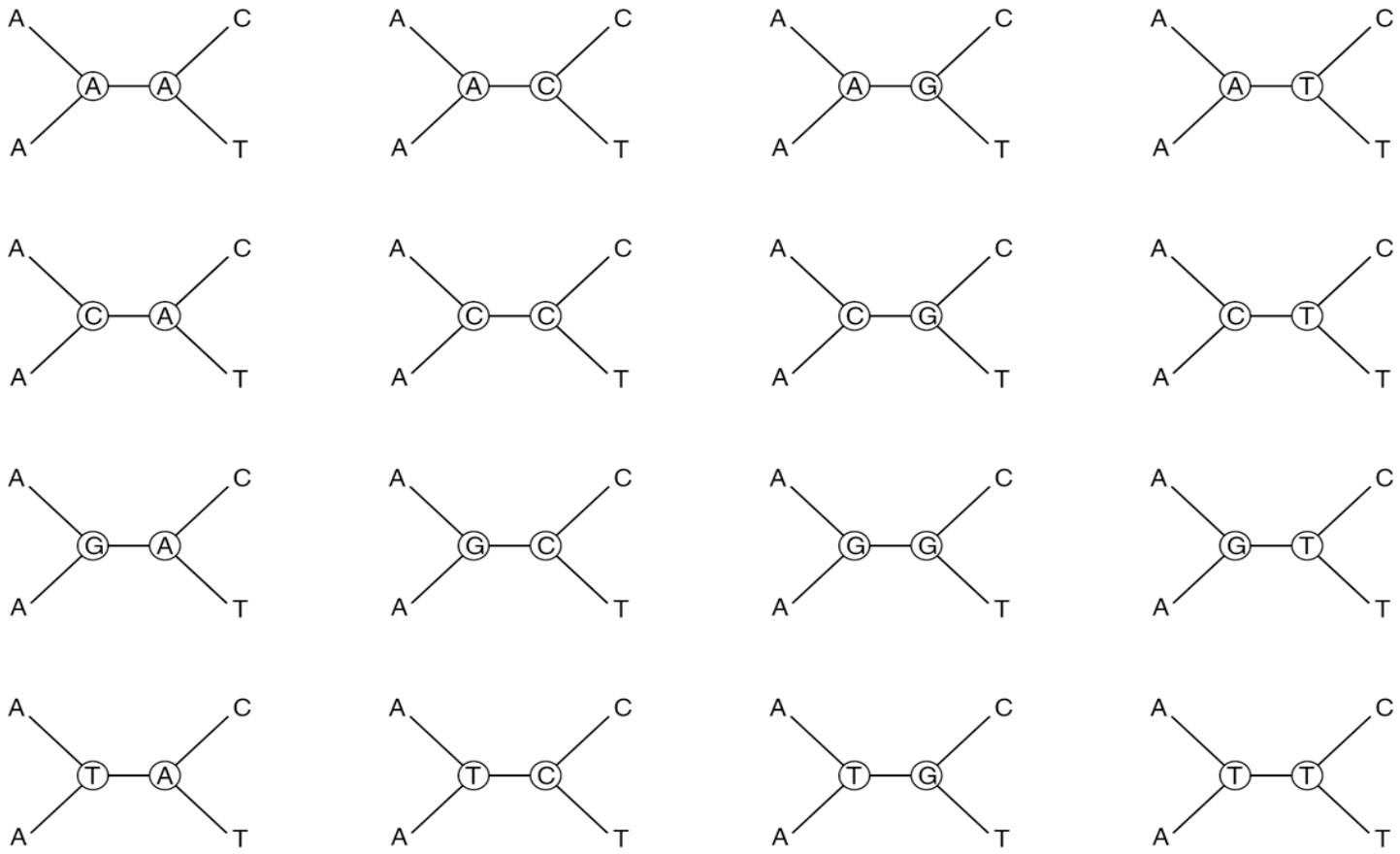
v_5 is the expected number of substitutions for just this one branch

$$L_k = \frac{1}{4}\left[\frac{1}{4}+\frac{3}{4}e^{-4\nu_1/3}\right]\left[\frac{1}{4}+\frac{3}{4}e^{-4\nu_2/3}\right]\left[\frac{1}{4}-\frac{1}{4}e^{-4\nu_3/3}\right]\left[\frac{1}{4}-\frac{1}{4}e^{-4\nu_4/3}\right]\left[\frac{1}{4}+\frac{3}{4}e^{-4\nu_5/3}\right]$$

$P_{AA}(v_1)$ $P_{AA}(v_2)$ $P_{AC}(v_3)$ $P_{CT}(v_4)$ $P_{CC}(v_5)$

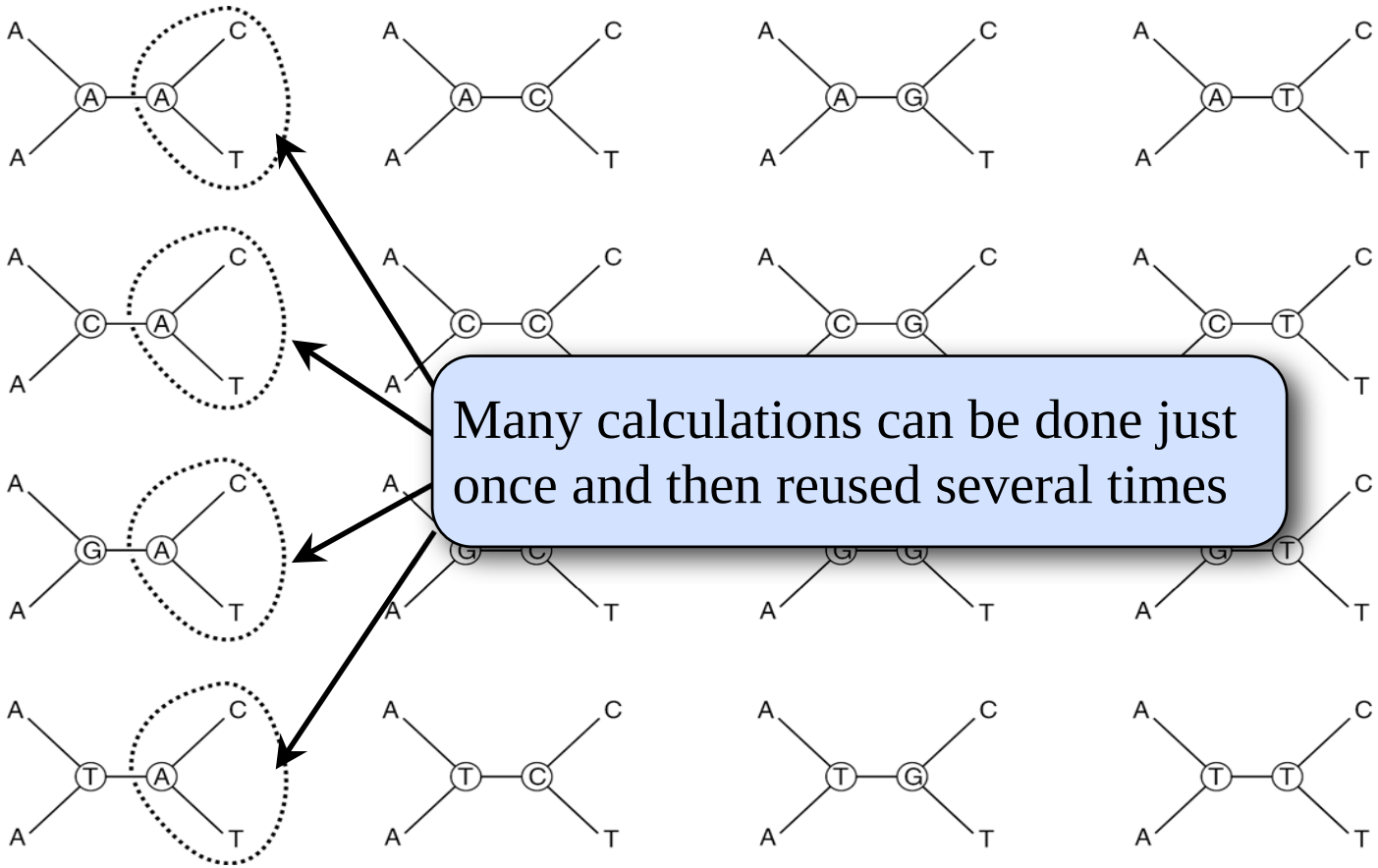
Note use of the AND probability rule

Brute force approach would be to calculate L_k for all 16 combinations of ancestral states and sum them



Note use of the OR probability rule

Pruning algorithm
(same result, less time)



Felsenstein, J. 1981. Evolutionary trees from DNA sequences: a maximum likelihood approach. *Journal of Molecular Evolution* **17**:368-376

We will explore likelihood of different trees using these uper cool widgets developed by Mark Holder:

- `http://phylo.bio.ku.edu/mephytis/barcharts.html`
- `http://phylo.bio.ku.edu/mephytis/brlen-opt.html`
- `http://phylo.bio.ku.edu/mephytis/tree-opt.html`

and using sequence simulation and analyses using `seq-gen` and `paup`

Bootstrapping

- Draw new data sets from your original data by sampling with replacement
- For each pseudoreplicate dataset estimate the best tree
- Calculate how often each split is recovered
- If not close to 100% may be sampling error
- If close to 100% likely not sampling error... but could still be a lot of other kinds of error!! Bootstraps are usually very high in very large (genomic) data sets.

https://phylo.bio.ku.edu/mephytis/boot-sample.html