

Maximum Likelihood in Phylogenetics

23 January 2013

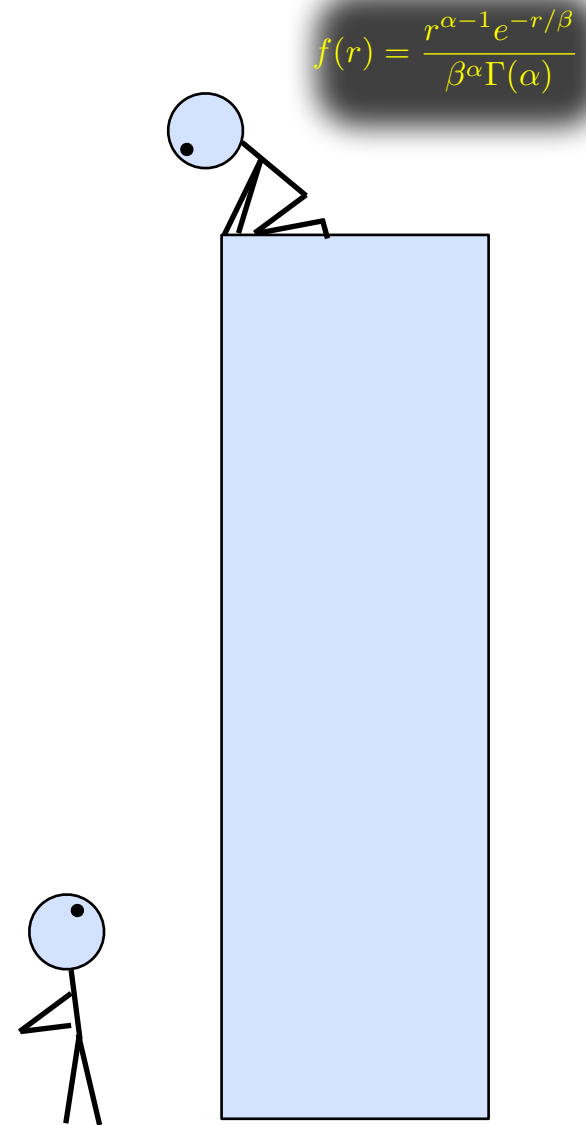
Workshop on Molecular Evolution
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Goals

Explain jargon
Increase comfort level
Provide background
In other words...give a hand up



The Plan

- Probability review
- Likelihood
- Substitution models



Combining probabilities

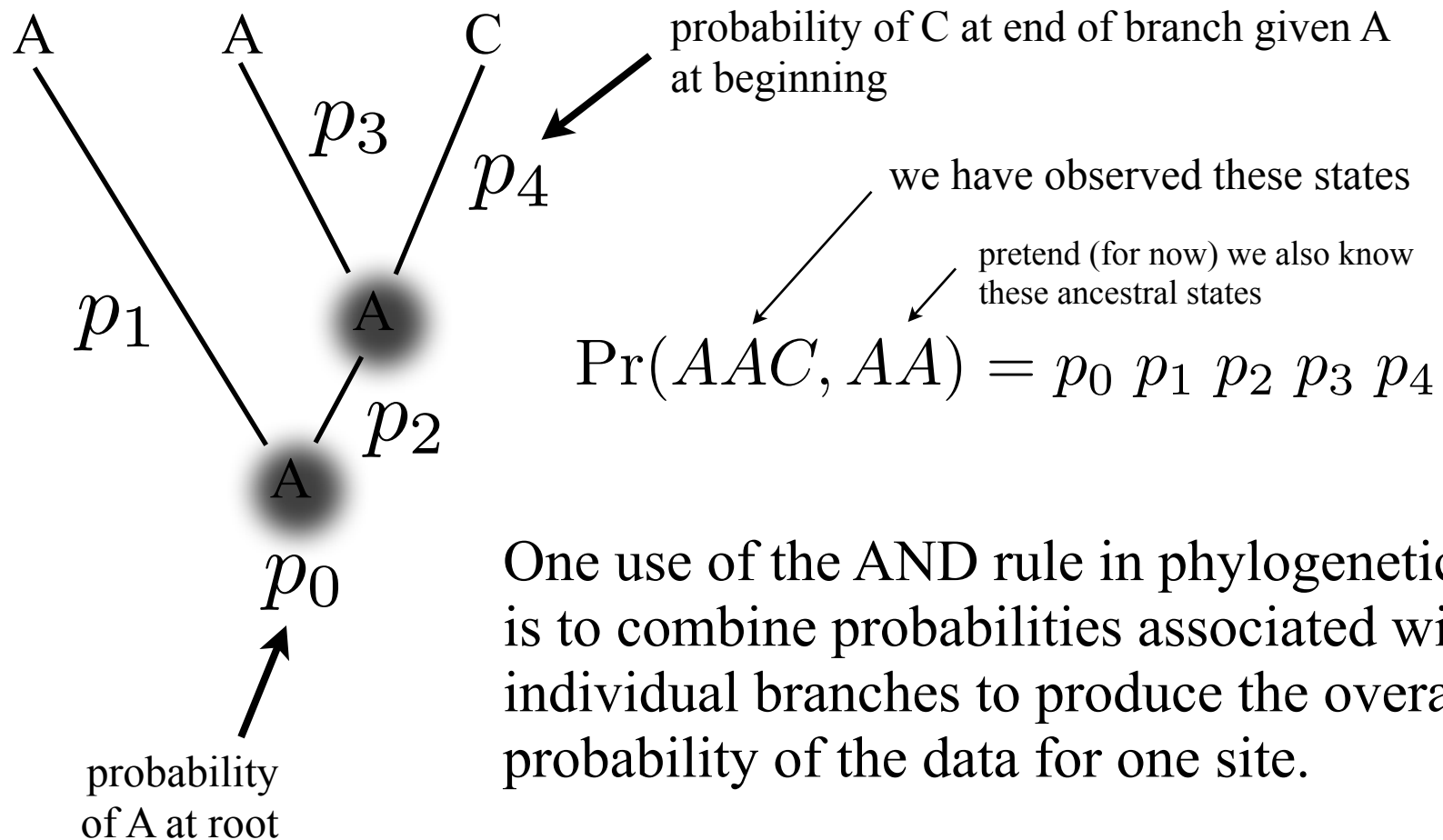
- *Multiply* probabilities if the component events must happen **simultaneously** (i.e. where you would naturally use the word AND when describing the problem)

Using 2 dice, what is the probability of

• AND ■■■ ?

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

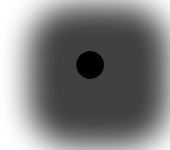
AND rule in phylogenetics



Combining probabilities

- *Add* probabilities if the component events are **mutually exclusive** (i.e. where you would naturally use the word OR in describing the problem)

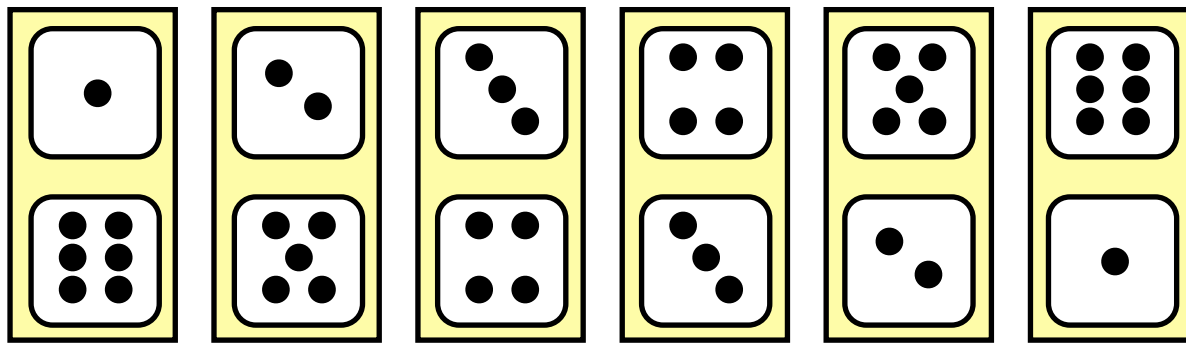
Using one die, what is the probability of

 OR  ?

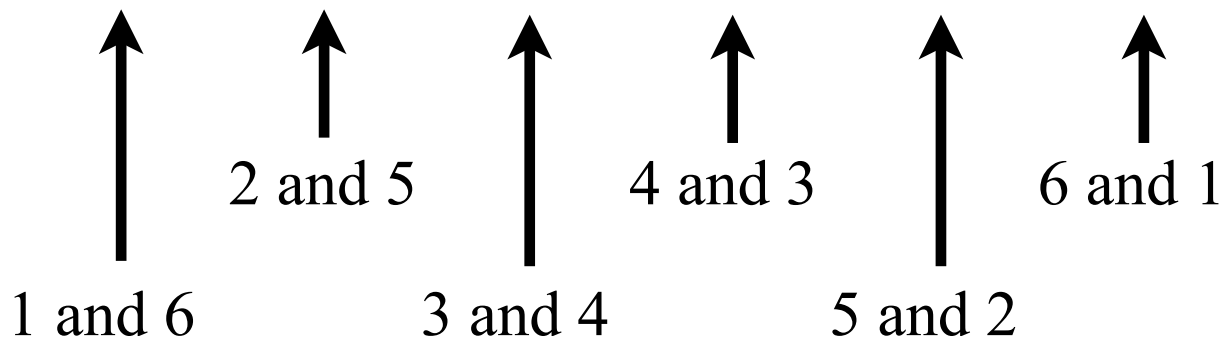
$$(1/6) + (1/6) = 1/3$$

Combining AND and OR

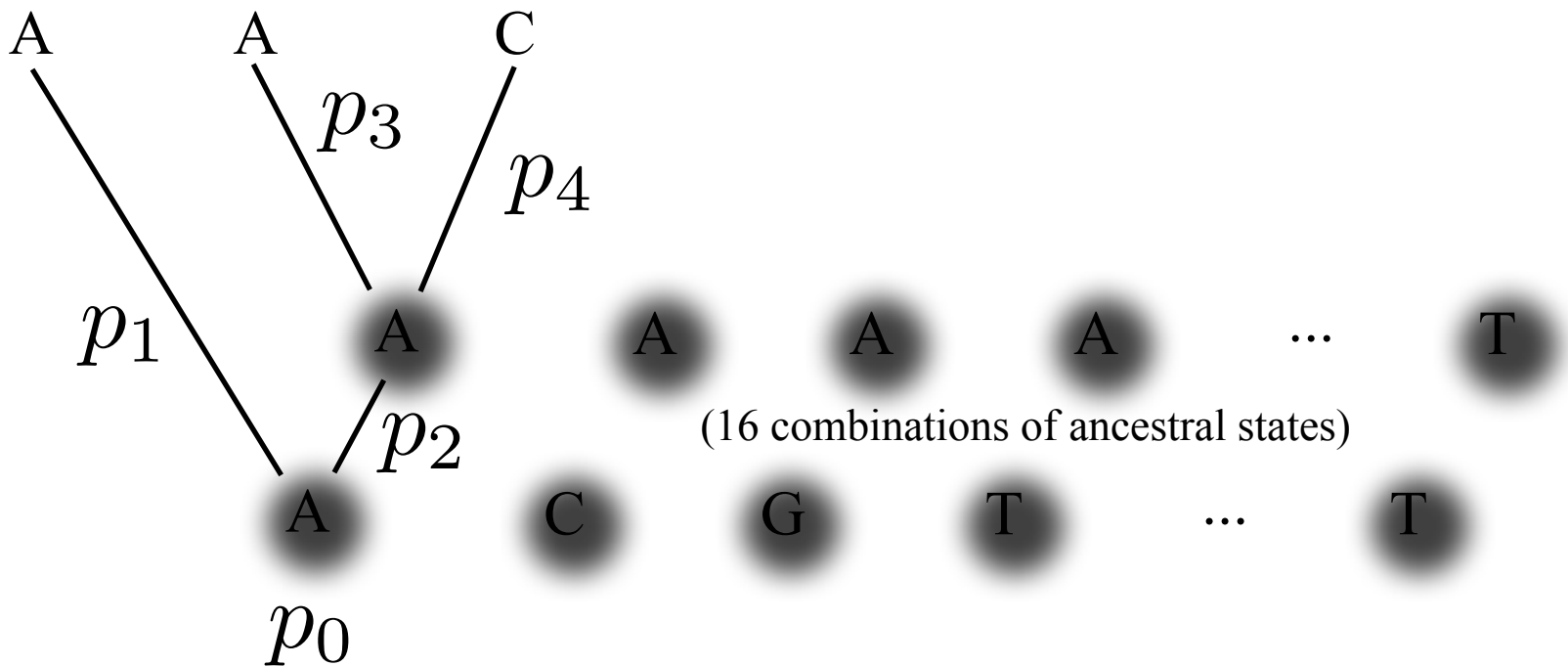
What is the probability that the sum of two dice is 7?



$$(1/36) + (1/36) + (1/36) + (1/36) + (1/36) + (1/36) = 1/6$$



Using both AND and OR in phylogenetics



AND rule used to compute probability of the observed data for *each combination* of ancestral states.

OR rule used to combine different combinations of ancestral states.

Independence

This is always true...

$$\underset{\text{joint probability}}{\Pr(\text{A and B})} = \Pr(\text{A}) \underset{\substack{\text{conditional} \\ \text{probability}}}{\Pr(\text{B}|\text{A})}$$

If we can say this...

$$\Pr(\text{B}|\text{A}) = \Pr(\text{B})$$

...then events A and B are **independent** and we can express the joint probability as the product of $\Pr(\text{A})$ and $\Pr(\text{B})$

$$\Pr(\text{A and B}) = \Pr(\text{A}) \Pr(\text{B})$$

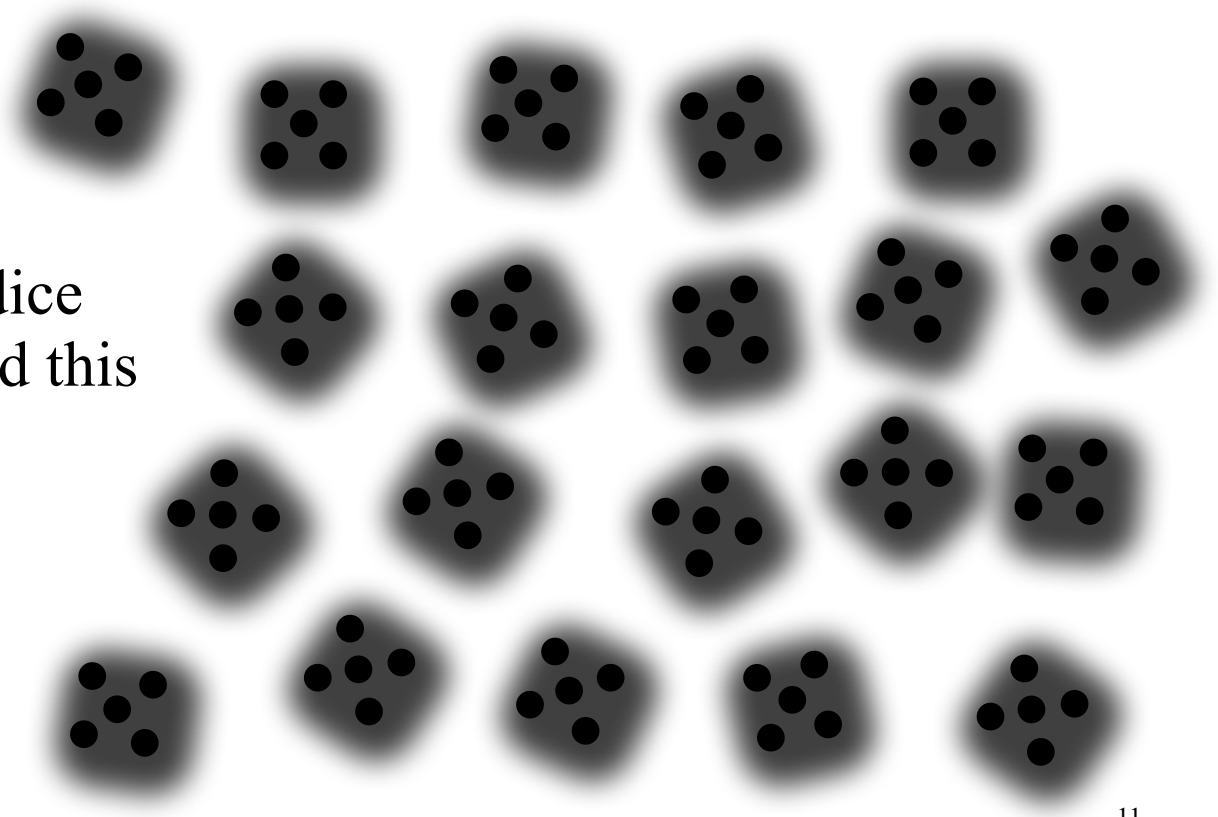
Likelihood

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.

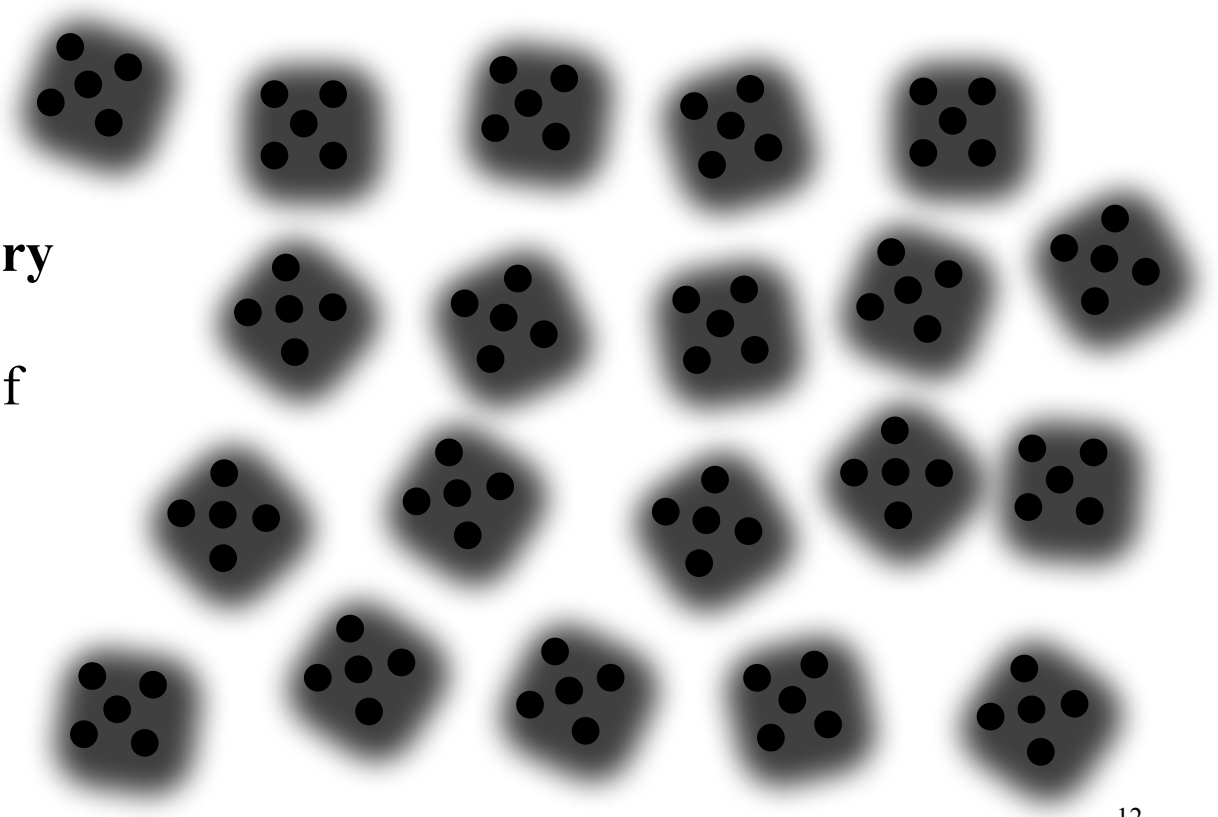
Suppose I threw 20 dice down on the table and this was the result...



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!

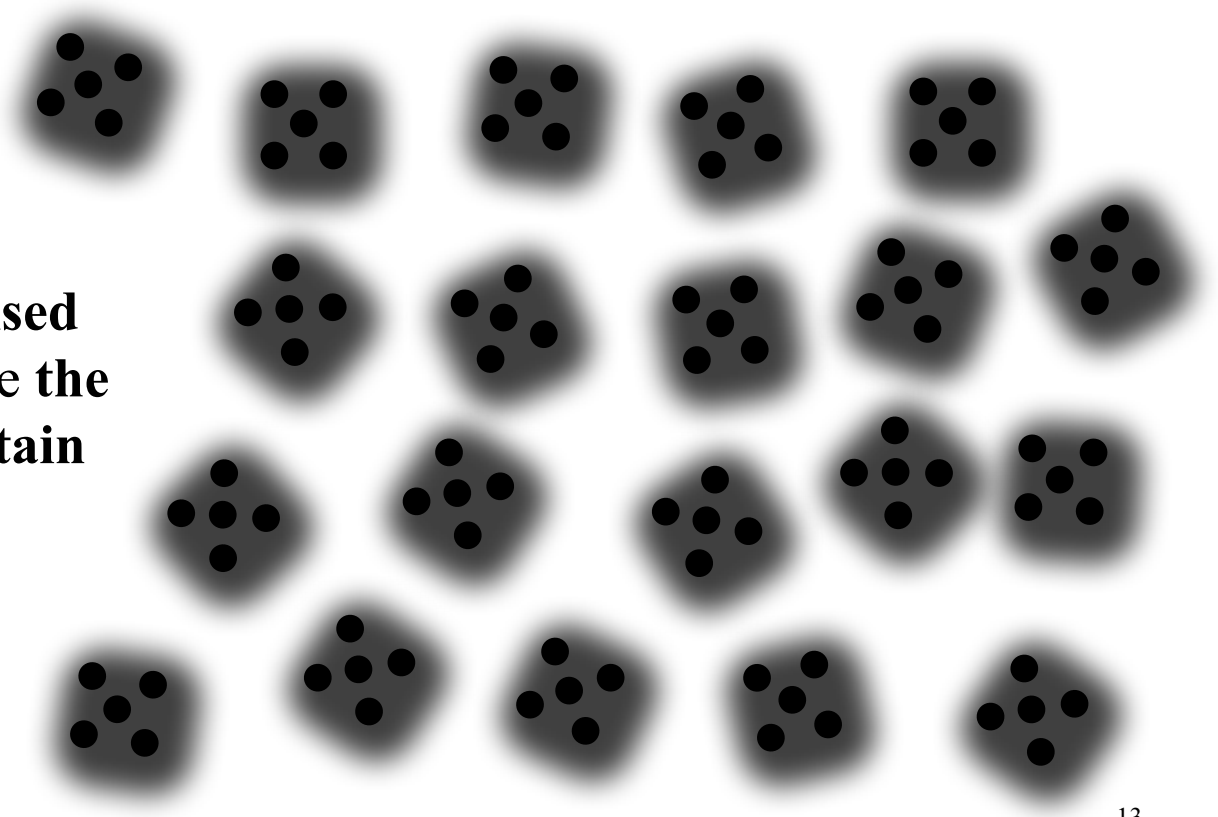


The Trick Dice model

(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, <i>very</i> , <i>very</i> surprised
Trick Dice	1.0	Not surprised at all

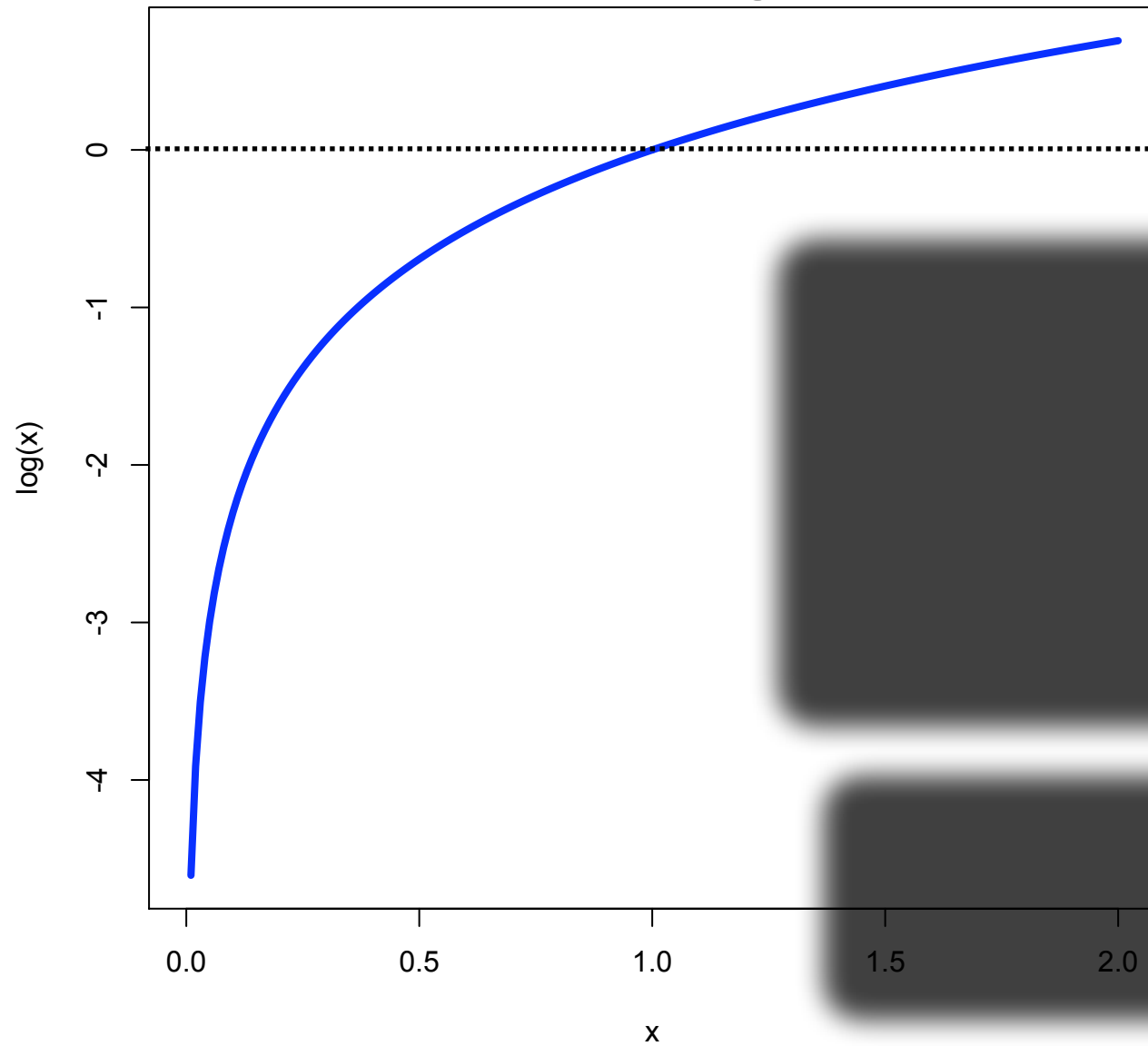
winning model maximizes likelihood
(and thus minimizes surprise)

Likelihood and model comparison

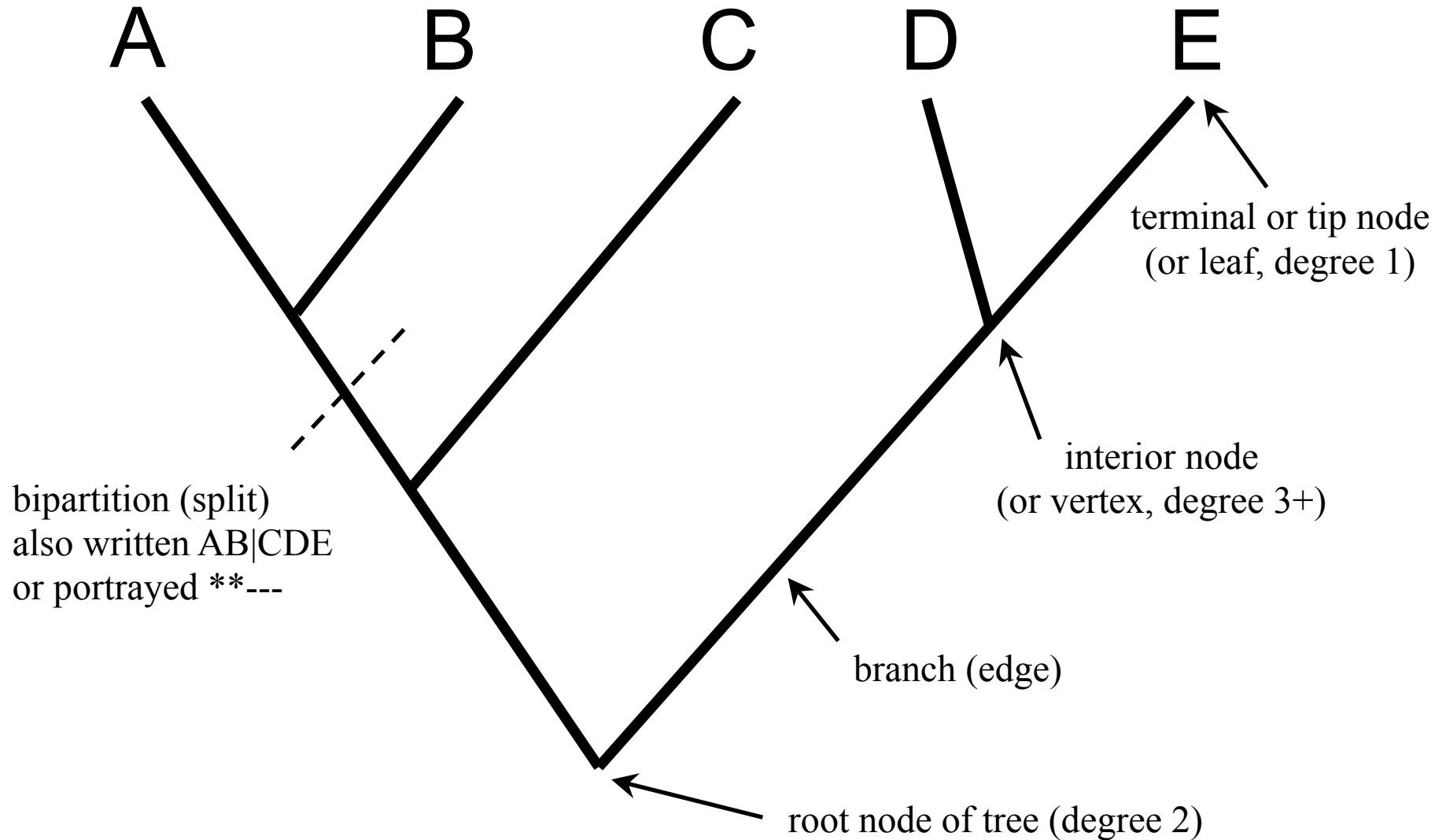
- Analyses using likelihoods ultimately involve **model comparison**
- The models compared can be **discrete** (as in the fair vs. trick dice example)
- More often the models compared differ **continuously**:
 - Model 1: branch length is 0.05
 - Model 2: branch length is 0.06



Likelihoods vs. log-likelihoods



Tree jargon



Likelihood of a single tip node

First 32 nucleotides of the $\psi\eta$ -globin gene of gorilla:

GAAGTCCTTGAGAAATAAACTGCACACACTGG

$$L = \pi_G \pi_A \pi_A \pi_G \pi_T \pi_C \pi_C \pi_T \pi_T \pi_G \pi_A \pi_G \pi_A \pi_A \pi_A \pi_T \pi_A \pi_A \pi_A \pi_C \pi_T \pi_G \pi_C \pi_A \pi_C \pi_A \pi_C \pi_A \pi_C \pi_T \pi_G \pi_G$$

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

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

Model ranking using AIC

The Akaike Information Criterion (AIC) can be used to evaluate whether an **unconstrained** model ("free") fits the data significantly better than a **constrained** version ("equal") of the same model.

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

$$\begin{aligned}\log L_{\text{free}} &= 12 \log(\pi_A) + 7 \log(\pi_C) + 7 \log(\pi_G) + 6 \log(\pi_T) \\ &= 12 \log(0.375) + 7 \log(0.219) + 7 \log(0.219) + 6 \log(0.188) \\ &= -43.1\end{aligned}$$

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

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

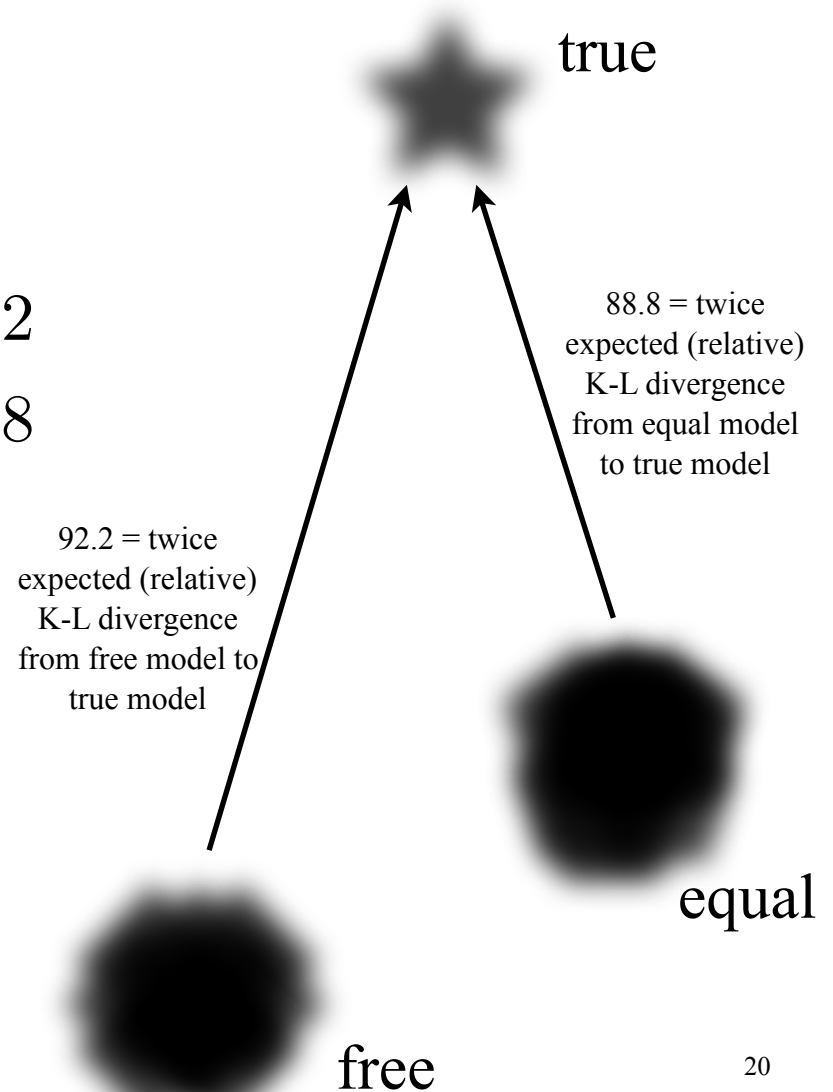
Model ranking using AIC

Calculate AIC for each model:

$$AIC = 2k - 2 \log(L_{\max})$$

$$AIC_{\text{free}} = 2(3) - 2(-43.1) = 92.2$$

$$AIC_{\text{equal}} = 2(0) - 2(-44.4) = 88.8$$



(K-L stands for
Kullback-Leibler)

Likelihood of the simplest tree

sequence 1  sequence 2

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



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



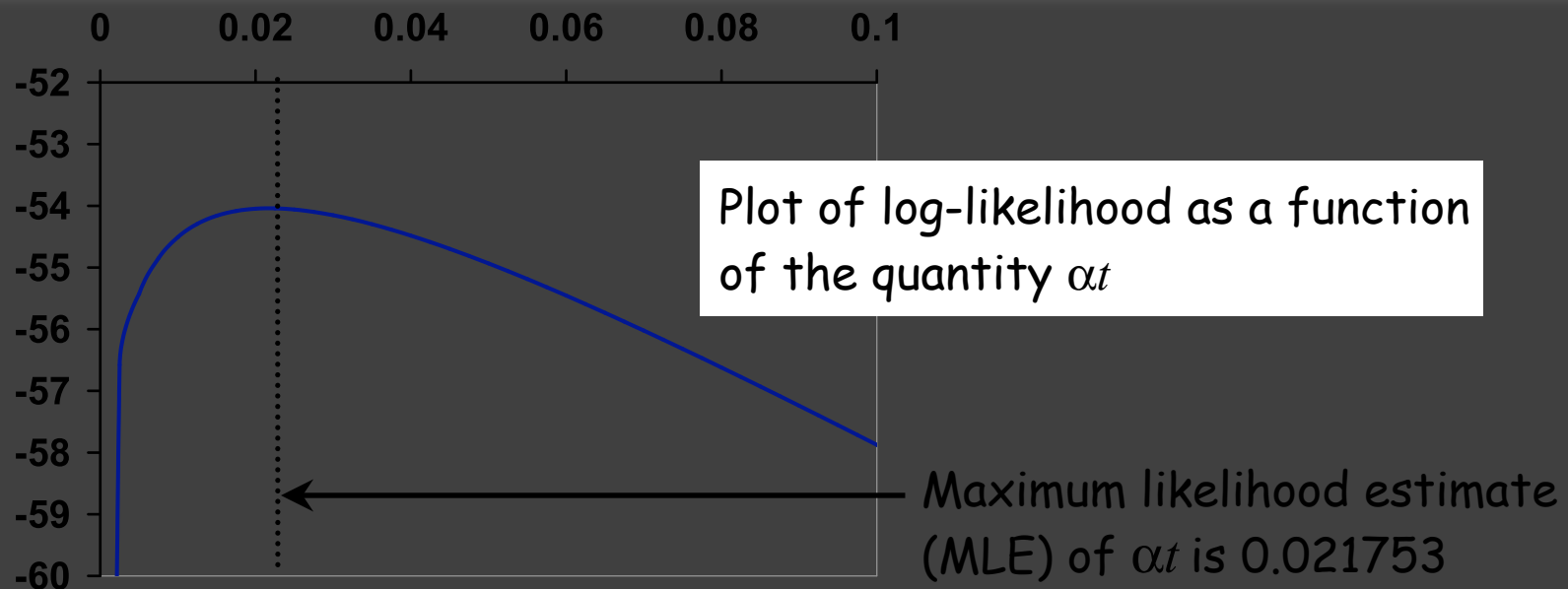
Maximum likelihood estimation

First 32 nucleotides of the $\psi\eta$ -globin gene of gorilla and orangutan:

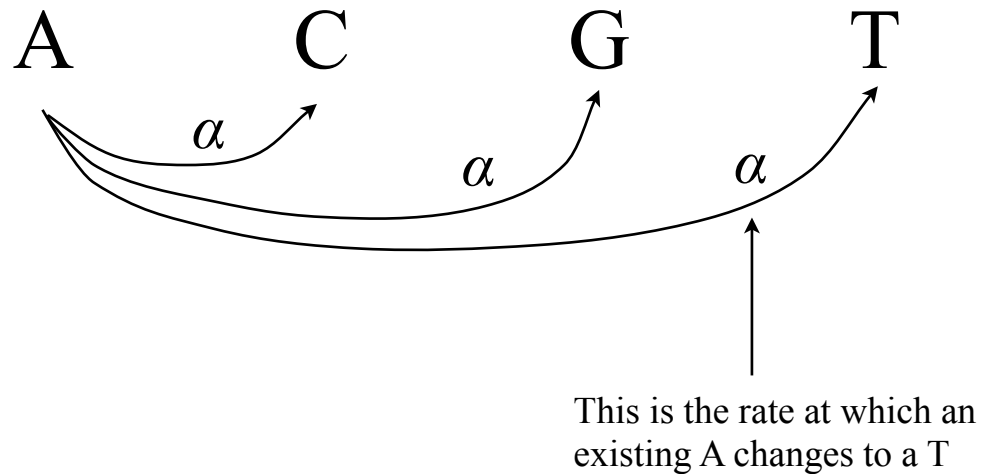
gorilla **G****A****G**TCCTTGAGAAATAAACTGCACACACTGG

orangutan **G****G****A**TCCTTGAGAAATAAACTGCACACACTGG

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



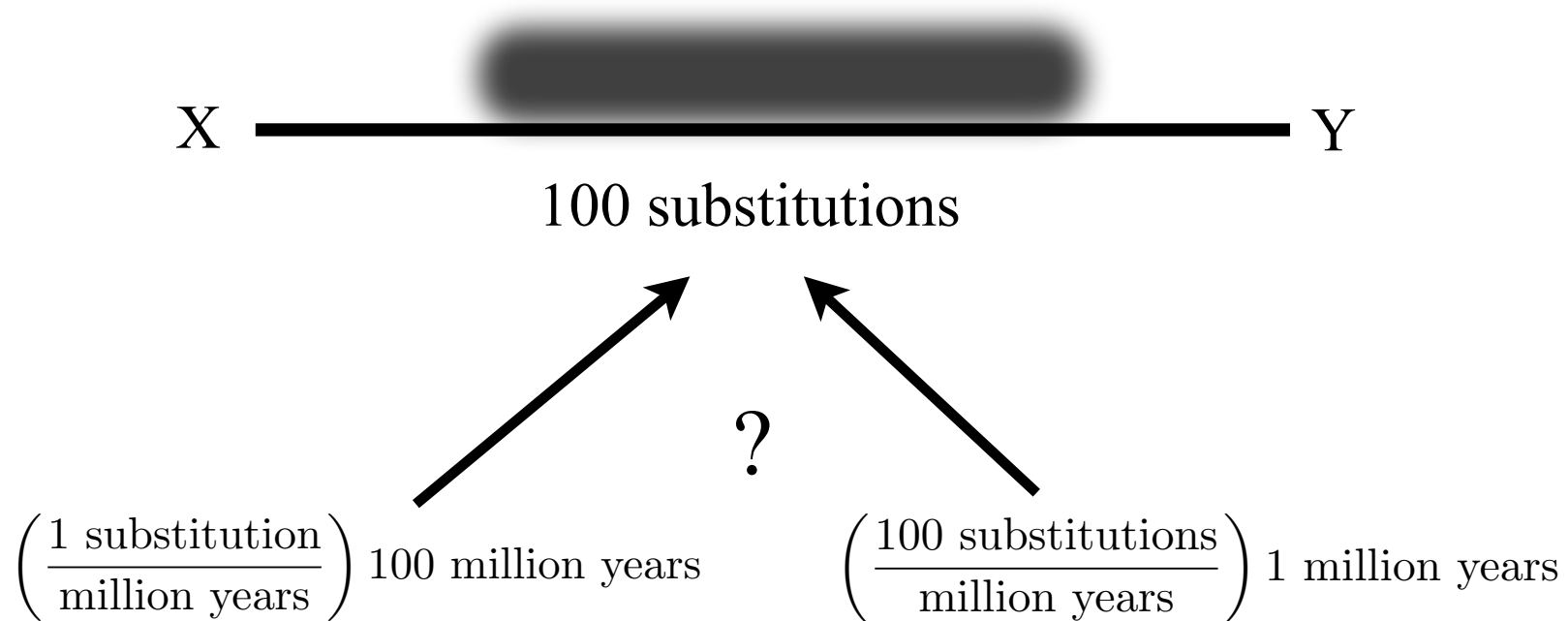
number of substitutions = rate $\times$ time



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

$$v = 3\alpha t$$

Rate and time are confounded



Later this week you will be introduced to models in which constraints on times can be used to infer rates (and vice versa), but without some extra information or constraints, sequence data allow only estimation of the **number** of substitutions.

A convenient convention

Because rate and time are confounded, it is convenient to arbitrarily standardize things by setting the rate to a value such that **one substitution** is expected to occur in **one unit of time** for each site.

This results in “time” (the length of a branch) being measured in units of **evolutionary distance (expected number of substitutions per site)** rather than years (or some other calendar unit).

evolutionary distance $v = 3\alpha t$

$$v = 3 \left(\frac{1}{3} \right) t$$

Setting $\alpha=1/3$ results in v equalling t

Evolutionary distances for several common models

Model	Expected no. substitutions: $v = \{r\}t$
JC69	$v = \{3\alpha\} t$
F81	$v = \{2\mu(\pi_R\pi_Y + \pi_A\pi_G + \pi_C\pi_T)\} t$
K80	$v = \{\beta(\kappa + 2)\} t$
HKY85	$v = \{2\mu[\pi_R\pi_Y + \kappa(\pi_A\pi_G + \pi_C\pi_T)]\} t$

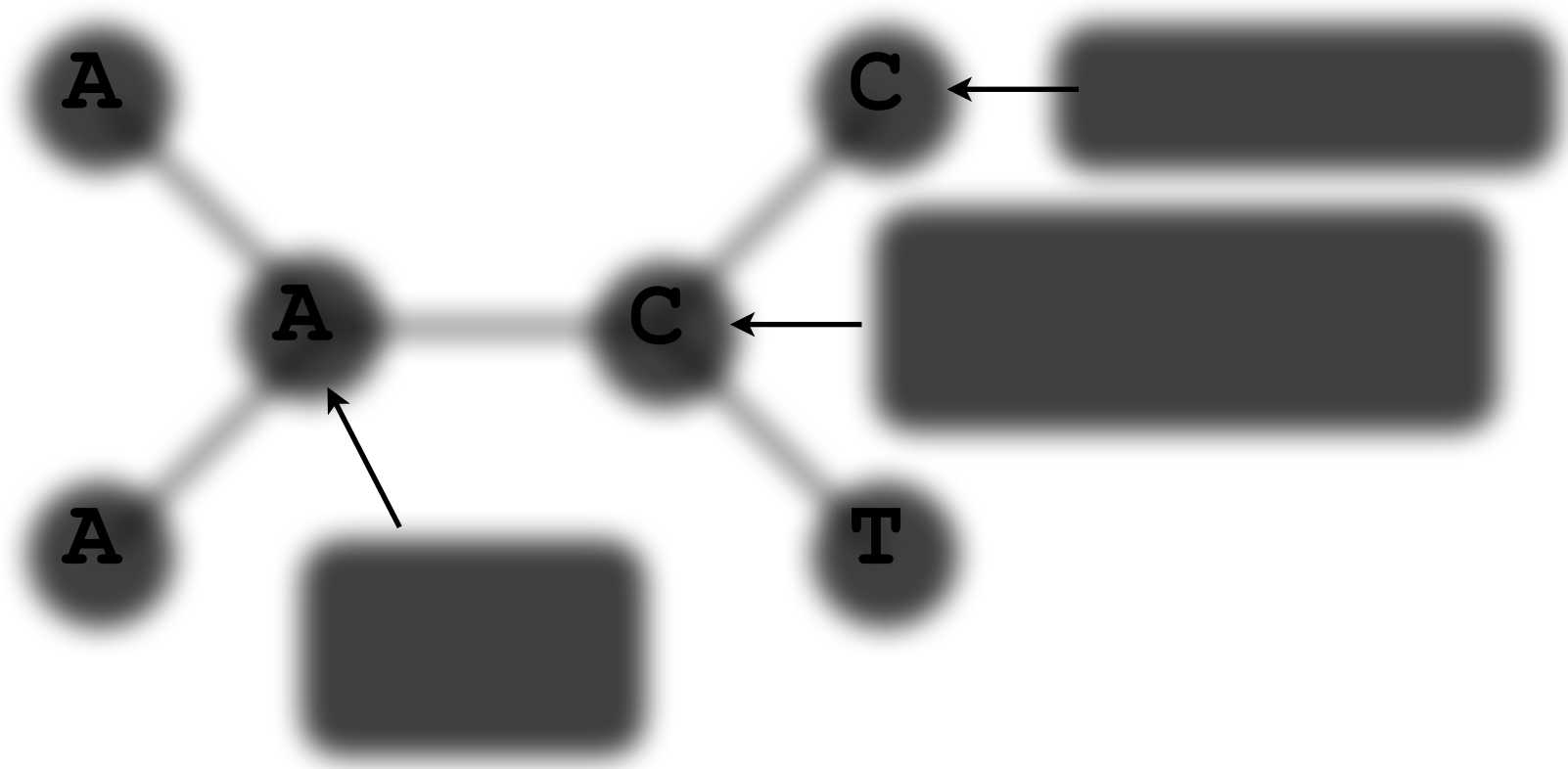
In the formulas above, the overall rate r (in curly brackets) is a function of all parameters in the substitution model.

Note that one of the parameters of the substitution model can always be *determined from the branch length* (using our convention that $v = t$).

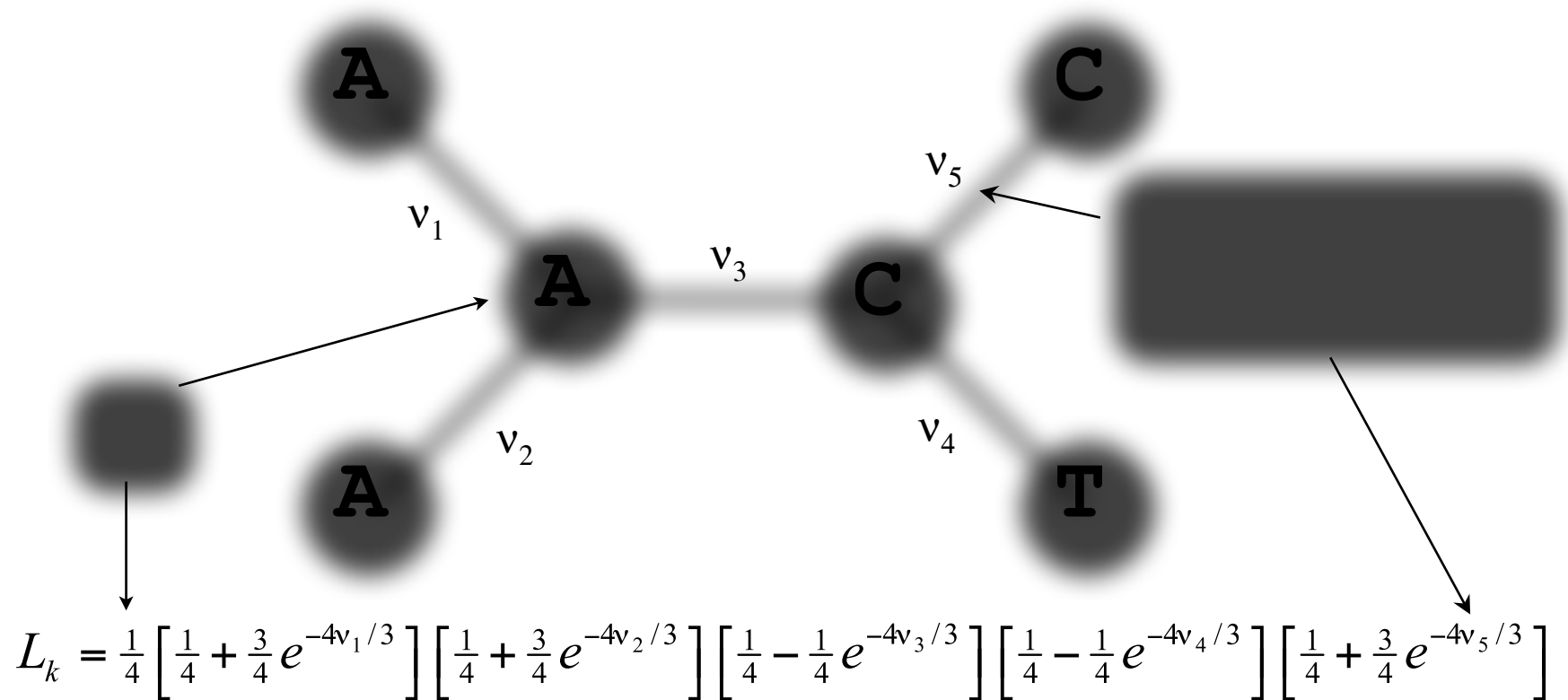
Typically, all other model parameters are estimated for the *entire tree* (for example, each branch uses the same value of κ)

Likelihood of an unrooted tree

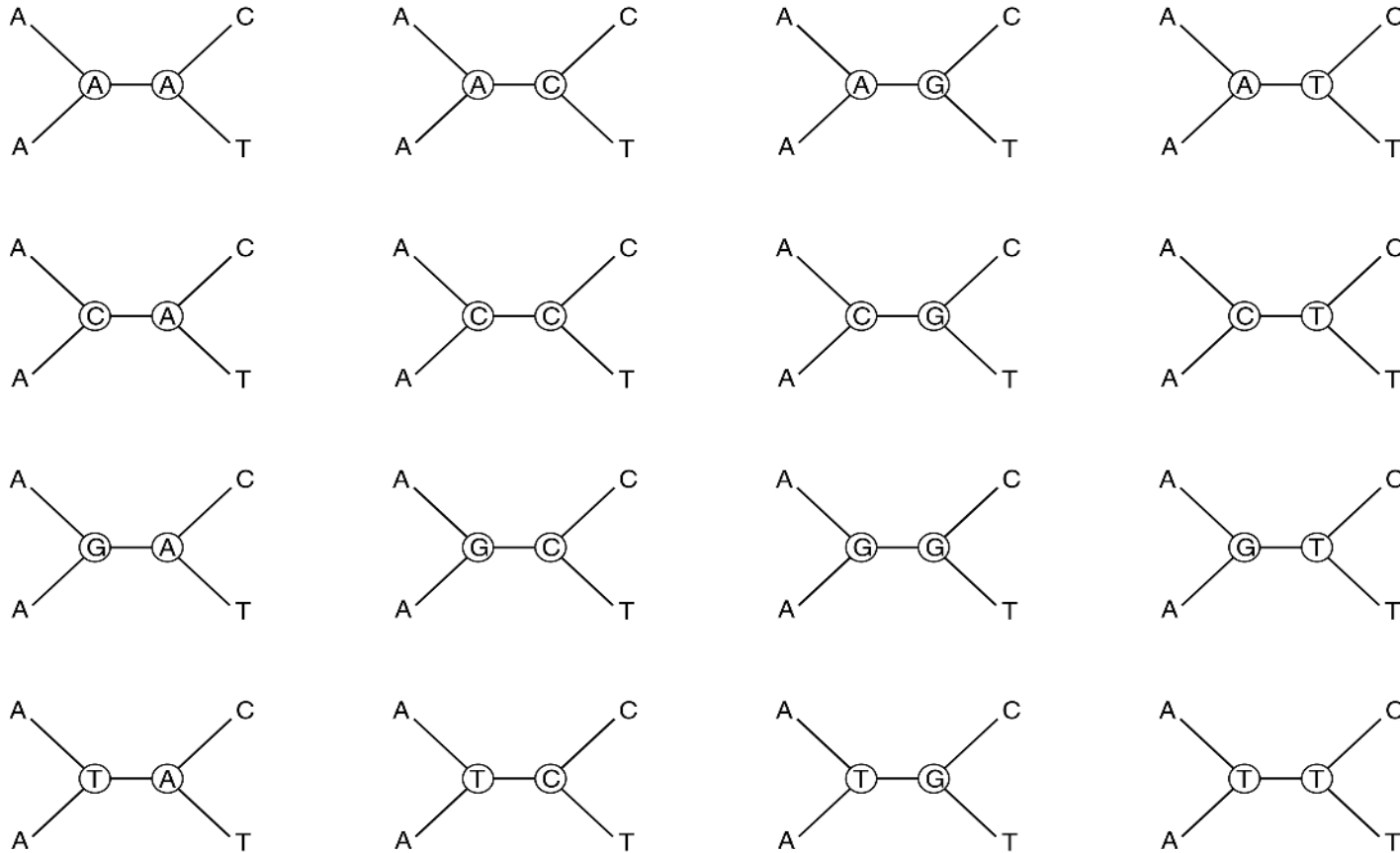
(data shown for only one site)



Likelihood for site k

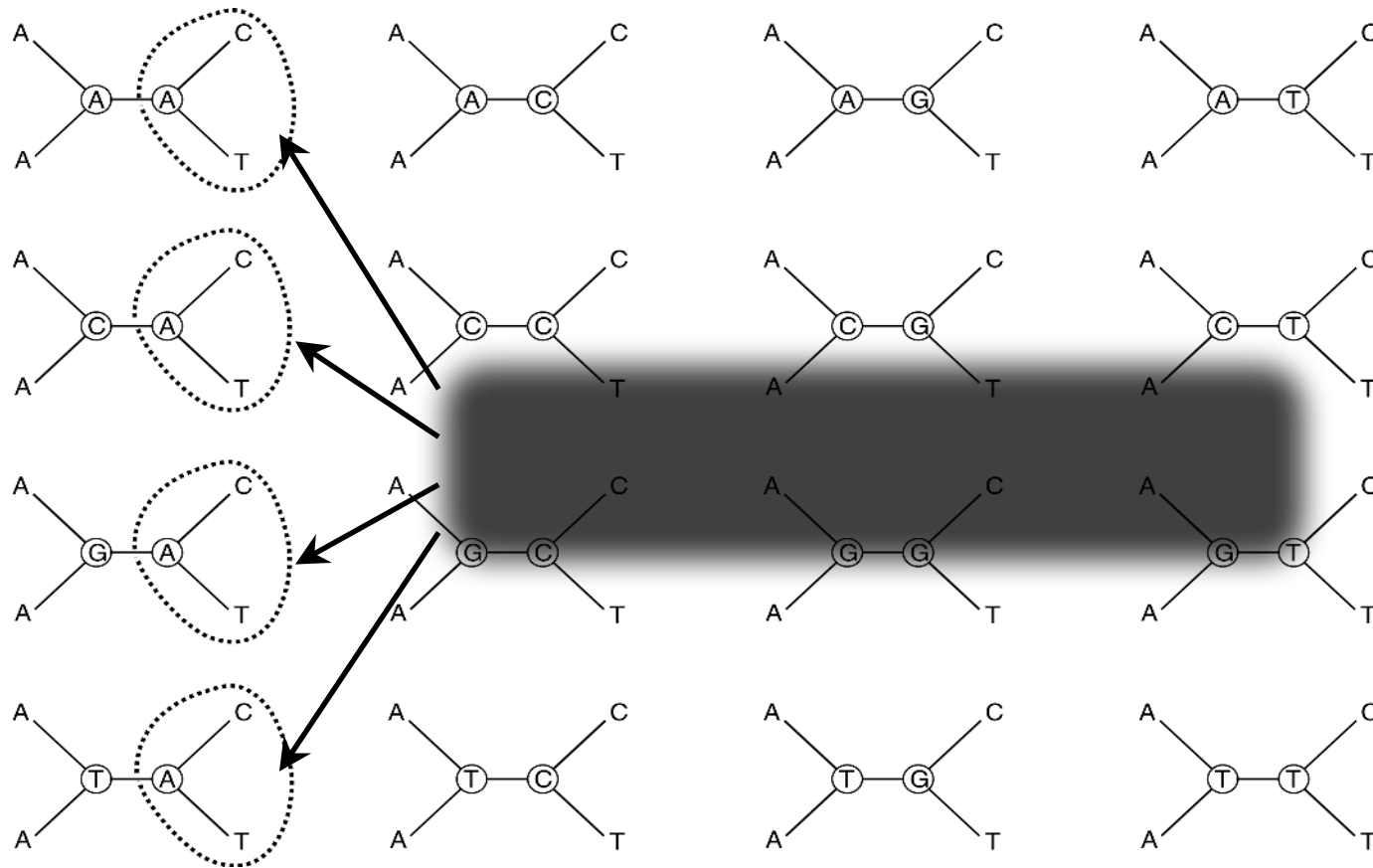


Brute force approach would be to calculate L_k for all 16 combinations of ancestral states and sum them



Pruning algorithm

(same result, less time)



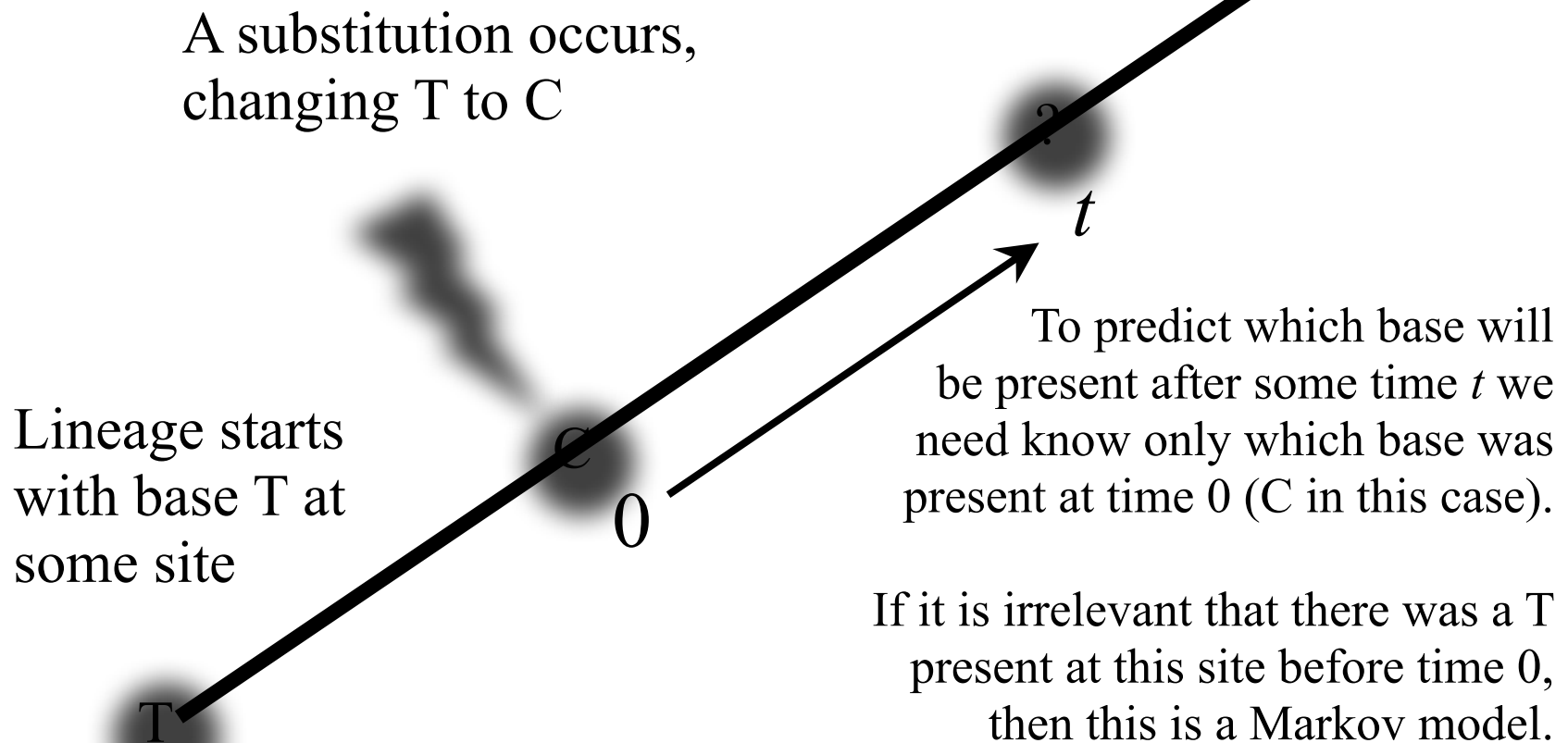
Felsenstein, J. 1981. Evolutionary trees from DNA sequences:
a maximum likelihood approach. *Journal of Molecular Evolution* 17:368-376

Substitution Models

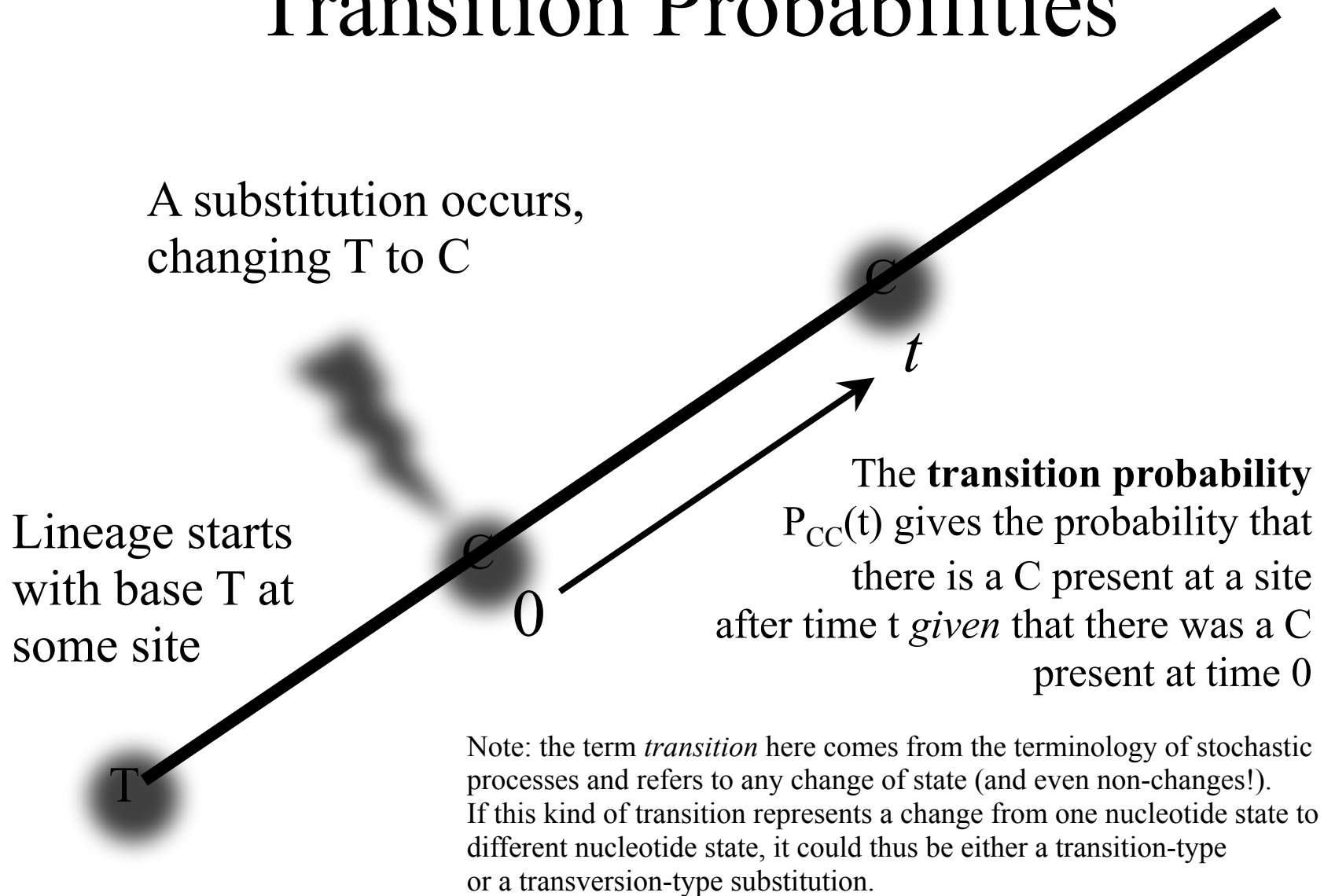
Jukes-Cantor (JC69) model

- The four bases (A, C, G, T) are expected to be **equally frequent** in sequences ($\pi_A = \pi_C = \pi_G = \pi_T = 0.25$)
- Assumes **same rate** for all types of substitution ($r_{A \rightarrow C} = r_{A \rightarrow G} = r_{A \rightarrow T} = r_{C \rightarrow G} = r_{C \rightarrow T} = r_{G \rightarrow T} = \alpha$)
- Usually described as a **1-parameter** model (the parameter being the branch length)
 - Remember, however, that each branch in a tree can have its own length, so there are really as many parameters in the model as there are edges in the tree!
- Assumes substitution is a **Markov** process...

What is a Markov model?



Transition Probabilities



Jukes-Cantor transition probabilities

Here is the probability that a site starting in state T will end up in state G after time t when the individual substitution rates are all α :

$$P_{TG}(t) = \frac{1}{4} (1 - e^{-4\alpha t})$$

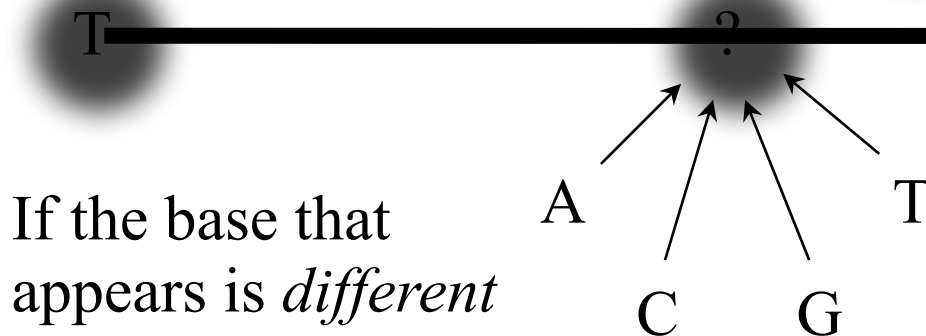
The JC69 model has only one unknown quantity: αt

(The symbol e represents the base of the natural logarithms: its value is 2.718281828459045...)

"ACHNyons" vs. substitutions

ACHN =
"Anything
Can Happen
Now"

When an *achnyon* occurs, any
base can appear in a sequence.



If the base that
appears is *different*
from the base that
was already there, then a
substitution event has occurred.

The rate (α) at which any
particular substitution
occurs will be 1/4 the
achnyon rate (μ).
That is, $\alpha = \mu/4$
(or $\mu = 4\alpha$)

Deriving a transition probability

Calculate the probability that a site currently T will change to G over time t when the rate of this particular substitution is α :

$$\Pr(\text{zero achnyons}) = e^{-\mu t} \quad (\text{Poisson probability of zero events})$$

$$\Pr(\text{at least 1 achnyon}) = 1 - e^{-\mu t}$$

$$\Pr(\text{last achnyon results in base G}) = \frac{1}{4}$$

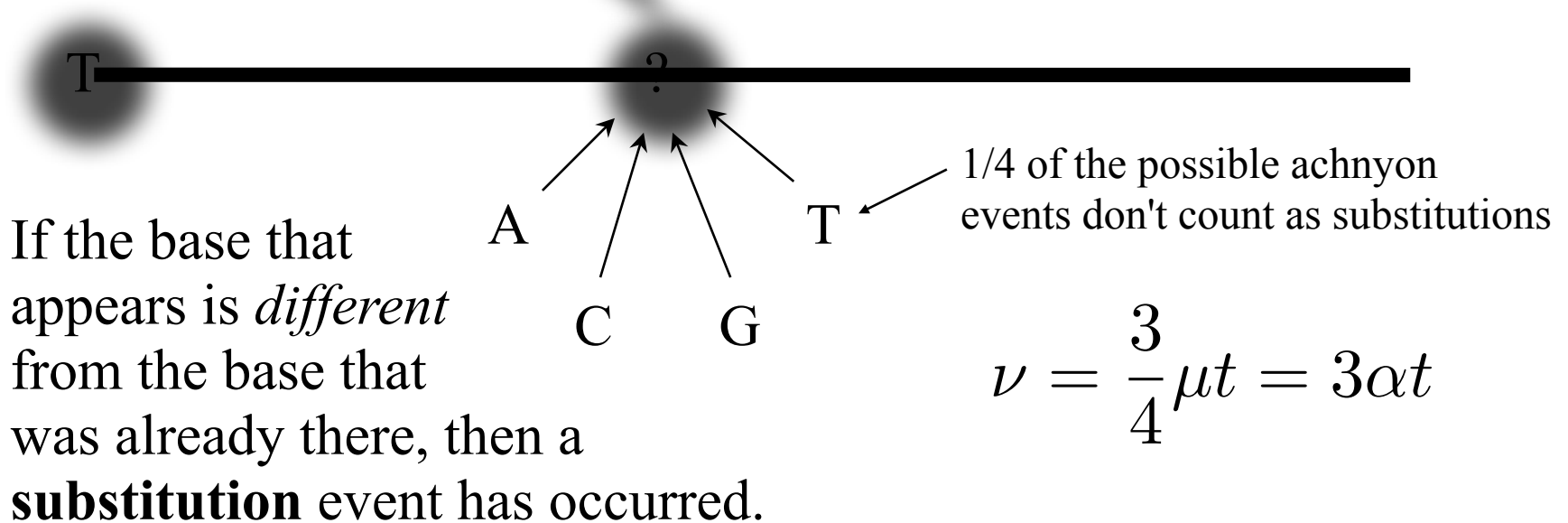
$$\Pr(\text{end in G} \mid \text{start in T}) = \frac{1}{4} (1 - e^{-\mu t})$$

Remember that the rate (α) of any particular substitution is one fourth the achnyon rate (μ):

$$P_{GT}(t) = \frac{1}{4} (1 - e^{-4\alpha t})$$

Expected number of substitutions

The overall substitution rate will be 3/4 the achnyon rate



$$\nu = \frac{3}{4}\mu t = 3\alpha t$$

Transition Probabilities: Remarks

$$P_{TA}(t) = \frac{1}{4}(1 - e^{-4\alpha t})$$

$$P_{TC}(t) = \frac{1}{4}(1 - e^{-4\alpha t})$$

$$P_{TG}(t) = \frac{1}{4}(1 - e^{-4\alpha t})$$

$$P_{TT}(t) = \frac{1}{4}(1 - e^{-4\alpha t})$$

$$1 - e^{-4\alpha t}$$

Transition Probabilities: Remarks

$$P_{TA}(t) = \frac{1}{4}(1 - e^{-4\alpha t})$$

$$P_{TC}(t) = \frac{1}{4}(1 - e^{-4\alpha t})$$

$$P_{TG}(t) = \frac{1}{4}(1 - e^{-4\alpha t})$$

$$P_{TT}(t) = \frac{1}{4}(1 - e^{-4\alpha t}) + e^{-4\alpha t}$$



Equilibrium frequencies

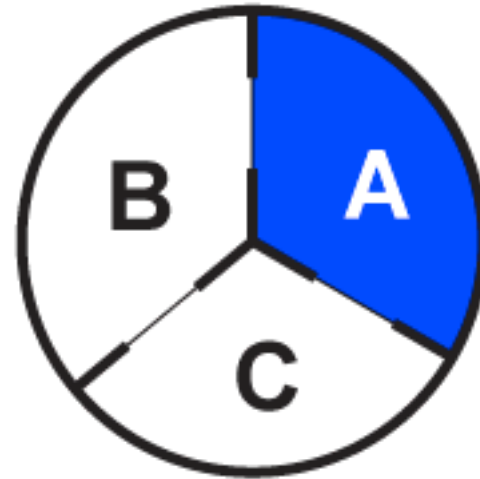
- The JC69 model assumes that the frequencies of the four bases (A, C, G, T) are equal
- The equilibrium relative frequency of each base is thus 0.25
- Why are they called *equilibrium* frequencies?

Equilibrium Frequencies

Imagine a bottle of perfume has been spilled in room A.

The doors to the other rooms are closed, so the perfume has, thus far, not been able to spread.

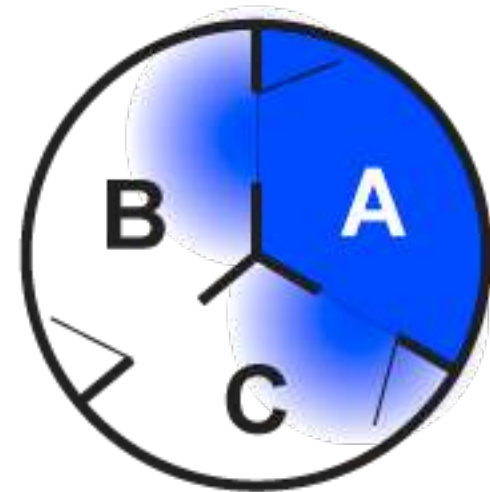
What would happen if we opened all the doors?



Equilibrium Frequencies

If the doors are suddenly opened, the perfume would begin diffusing from the area of highest concentration to lowest.

Molecules of perfume go both ways through open doors, but more pass one way than another, leading to a net flow from room A to rooms B and C.

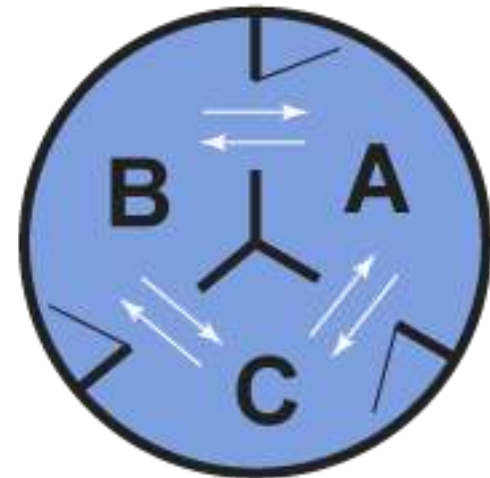


In the instant that the doors are opened, A is losing perfume molecules at *twice the rate* each of the other rooms is gaining molecules. As diffusion progresses, however, the rate of loss from A drops, approaching an equilibrium.

Equilibrium Frequencies

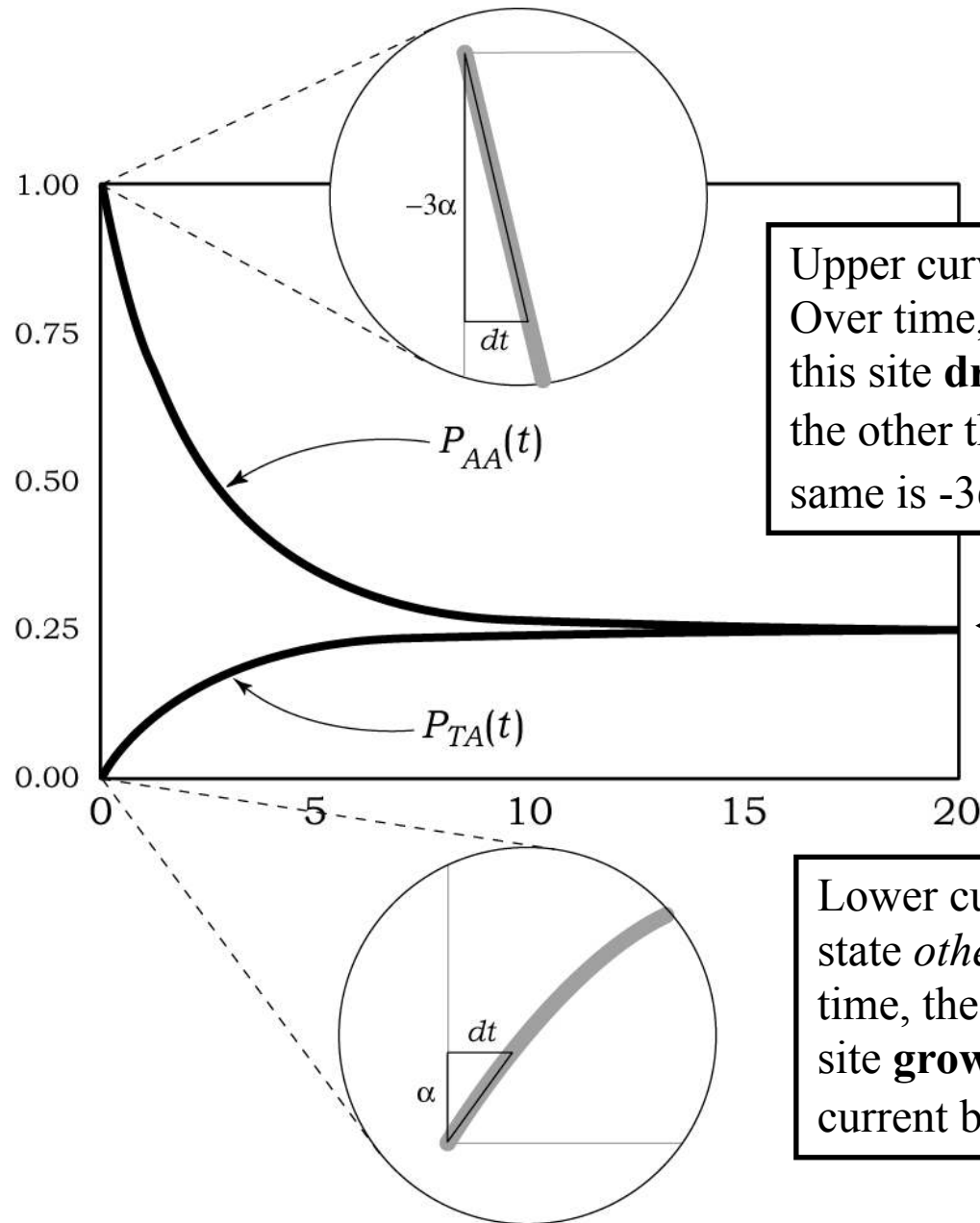
Eventually, all four rooms have essentially the same concentration of perfume.

Molecules still move through doors, but now the rates are the same in all directions.



Back to sequence evolution: assume a sequence began with only A nucleotides (a poly-A sequence). Over time, substitution would begin converting some of these As to Cs, Gs, and Ts, just as the perfume diffused into adjacent rooms.

$\Pr(A|A)$ and $\Pr(A|T)$ as a function of time



Upper curve assumes we started with A at time 0. Over time, the probability of still seeing an A at this site **drops** because rate of changing to one of the other three bases is 3α (so rate of staying the same is -3α).

The equilibrium relative frequency of A is 0.25

Lower curve assumes we started with some state *other* than A (T is used here). Over time, the probability of seeing an A at this site **grows** because the rate at which the current base will change into an A is α .

JC69 rate matrix

		To			
		A	C	G	T
From	A	-3α	α	α	α
	C	α	-3α	α	α
	G	α	α	-3α	α
	T	α	α	α	-3α

Jukes, T. H., and C. R. Cantor. 1969. Evolution of protein molecules. Pages 21-132 in H. N. Munro (ed.), *Mammalian Protein Metabolism*. Academic Press, New York.

K80 (or K2P) rate matrix

		To			
		A	C	G	T
From	A	$-\alpha - 2\beta$	β	α	β
	C	β	$-\alpha - 2\beta$	β	α
	G	α	β	$-\alpha - 2\beta$	β
	T	β	α	β	$-\alpha - 2\beta$

$\uparrow$
 transition rate

$\uparrow$
 transversion rate

Kimura, M. 1980. A simple method for estimating evolutionary rate of base substitutions through comparative studies of nucleotide sequences. Journal of Molecular Evolution 16:111-120.

K80 rate matrix

(looks different, but actually the same)

	A	C	G	T
A	$-\beta(\kappa + 2)$	β	$\kappa\beta$	β
C	β	$-\beta(\kappa + 2)$	β	$\kappa\beta$
G	$\kappa\beta$	β	$-\beta(\kappa + 2)$	β
T	β	$\kappa\beta$	β	$-\beta(\kappa + 2)$

All I've done is re-parameterize the rate matrix,
 letting κ equal the *transition/transversion rate ratio* $\longrightarrow \kappa = \frac{\alpha}{\beta}$

F81 rate matrix

	A	C	G	T
A	$-\mu(1 - \pi_A)$	$\pi_C\mu$	$\pi_G\mu$	$\pi_T\mu$
C	$\pi_A\mu$	$-\mu(1 - \pi_C)$	$\pi_G\mu$	$\pi_T\mu$
G	$\pi_A\mu$	$\pi_C\mu$	$-\mu(1 - \pi_G)$	$\pi_T\mu$
T	$\pi_A\mu$	$\pi_C\mu$	$\pi_G\mu$	$-\mu(1 - \pi_T)$

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

HKY85 rate matrix

	A	C	G	T
A	—	$\pi_C \beta$	$\pi_G \beta \kappa$	$\pi_T \beta$
C	$\pi_A \beta$	—	$\pi_G \beta$	$\pi_T \beta \kappa$
G	$\pi_A \beta \kappa$	$\pi_C \beta$	—	$\pi_T \beta$
T	$\pi_A \beta$	$\pi_C \beta \kappa$	$\pi_G \beta$	—

A dash means
equal to negative
sum of other
elements on the
same row

F84 vs. HKY85

F84 model:

μ rate of process generating *all types of substitutions*

$k\mu$ rate of process generating *only transitions*

Becomes F81 model if $k = 0$

HKY85 model:

β rate of process generating *only transversions*

$\kappa\beta$ rate of process generating *only transitions*

Becomes F81 model if $\kappa = 1$

F84 first used in Felsenstein's PHYLIP package in 1984, first published by: Kishino, H., and M. Hasegawa. 1989. Evaluation of the maximum likelihood estimate of the evolutionary tree topologies from DNA sequence data, and the branching order in hominoidea. Journal of Molecular Evolution 29: 170-179.

GTR rate matrix

	A	C	G	T
A	—	$\pi_C a \mu$	$\pi_G b \mu$	$\pi_T c \mu$
C	$\pi_A a \mu$	—	$\pi_G d \mu$	$\pi_T e \mu$
G	$\pi_A b \mu$	$\pi_C d \mu$	—	$\pi_T f \mu$
T	$\pi_A c \mu$	$\pi_C e \mu$	$\pi_G f \mu$	—

Rate Heterogeneity

Green Plant *rbcL*

First 88 amino acids (translation is for *Zea mays*)

M--S--P--Q--T--E--T--K--A--S--V--G--F--K--A--G--V--K--D--Y--K--L--T--Y--Y--T--P--E--Y--E--T--K--D--T--D--I--L--A--A--F--R--V--T--P--	
Chara	(green alga; land plant lineage) AAAGATTACAGATTAACCTTACTTACTCCTGAGTATAAACTAAAGATACTGACATTTTAGCTGCATTTCGTGTAAGTCCA
Chlorella	(green alga)C...C.T.....T..CC..C.A....C....T...C.T..A..G..C...A.G....T
Volvox	(green alga)TC.T....A....C..A....C...GT.GTA....C.....C.....A.....A.G....
Conocephalum	(liverwort)TC.....T.....G..T...G.....G..T.....A.....A.AA.G....T
Bazzania	(moss)T.....C..T....G....A..G.G..C....G..A..T....G..A.....A.G....C
Anthoceros	(hornwort)T.....CC.T....C....T..CG.G..C..G.....T....G..A..G.C.T.AA.G....T
Osmunda	(fern)TC...G...C.....C..T...G.G..C..G.....T....G..A.....C..AA.G....C
Lycopodium	(club "moss") .GG.....C.T..C.....T...G..C....A..C..T...C.G..A.....AA.G....T
Ginkgo	(gymnosperm; Ginkgo biloba)G....T.....A...C...C.....T..C.G..A....C..A.....T
Picea	(gymnosperm; spruce)T.....A...C.G..C.....G..T....G..A....C..A.....T
Iris	(flowering plant)G....T.....T..CG...C.....T..C.G..A....C..A.....T
Asplenium	(fern; spleenwort)TC..C.G....T..C..C..C..A..C..G..C.....C..T..C.G..A..T..C..GA.G..C...
Nicotiana	(flowering plant; tobacco)G...A..G....T.....CC...C..G.....T..A..G..A....C..A.....T

Q--L--G--V--P--P--E--E--A--G--A--A--V--A--A--E--S--S--T--G--T--W--T--T--V--W--T--D--G--L--T--S--L--D--R--Y--K--G--R--C--Y--H--I--E--	
CAACCTGGCGTTCCACCTGAAGAAGCAGGGGCTGCAGTAGCTGCAGAATCTTCTACTGGTACATGGACTACTGTTTGGACTGACGGATTAACTAGTTTGGACCGATACAAAGGAAGATGCTACGATATTGAA	
.....A..T.....A.....G..T..G.....A.....A.....T.....G....A.....T..T.....A.....TC.T..T..T..C..C..G	
.....A..T.....TGT..T....T..T....T.....A..A..A....T.....A.....A.....T..T....A...C.T....T.....TC.T..T..T..C..C..G	
..G....G..A..G.A.....A..A....T....T.....A.....T..TC.T....ACC.T..T..T..T....TC.....T.G.....C	
.....G..A..A.....A..G.....T.....A..C....G....C..G.....C..T..GC.T..A...C.C..T..T.....TC.....T..C..C..	
T...A..G..G.....A..C.....T.....A.....C.....C..T...C.T..C..CC.T...T.....TC.....C.....	
.....C..A..A..GG...G....T..A.....G.....A....G....C....A....G..T..C.T..C..C.T..T..T..G..TC.....	
...T...A..A....C..G....G..A..C.....T.....C.....C.....C..T...C.T..C..C.C..T..C.....TC.G....T..A.....	
.....A..G.....G....G..A.....C.....C.....C.....C..T...C.T..C..C.C..T..T..T..G....T..C..C..G	
.....A..G..G..C..G....G..A..A.....T.....C..C.....C.....C..T...C.T..T..T..T..G..GC.....T..C..C..G	
.....C..A....TG....G....C..G.....C.....A..A..G.....T..C.T..C..C.T..T..T..C.....C.C..C..G	
.....C..A..A..G.....C..A.....G..C....A.....C....G....A....G..G..C..CC.T...T...G..CC.....C..G	
.....A.....C..G.....C.....A.....A.....C..T...C.T..C..CC.T..T..T.....GC.....CGC..C..G	



Site-specific rates

Each defined subset (e.g. gene, codon position) has its own relative rate

Subset 1

Subset 2

r_1 applies to subset 1
(e.g. sites 1 - 1000)

r_2 applies to subset 2
(e.g. sites 1001-2000)

Site-specific rates

$$L = \underbrace{\Pr(D_1|r_1) \cdots \Pr(D_{1000}|r_1)}_{\text{Gene 1}} \underbrace{\Pr(D_{1001}|r_2) \cdots \Pr(D_{2000}|r_2)}_{\text{Gene 2}}$$


$$r_1 = 1.2$$


$$r_2 = 0.8$$

Site-specific rates

JC69 transition probabilities that would be used for every site if rate *homogeneity* were assumed:

$$P_{ii}(t) = \frac{1}{4} + \frac{3}{4}e^{-4\alpha t}$$

$$P_{ij}(t) = \frac{1}{4} - \frac{1}{4}e^{-4\alpha t}$$

Site specific rates

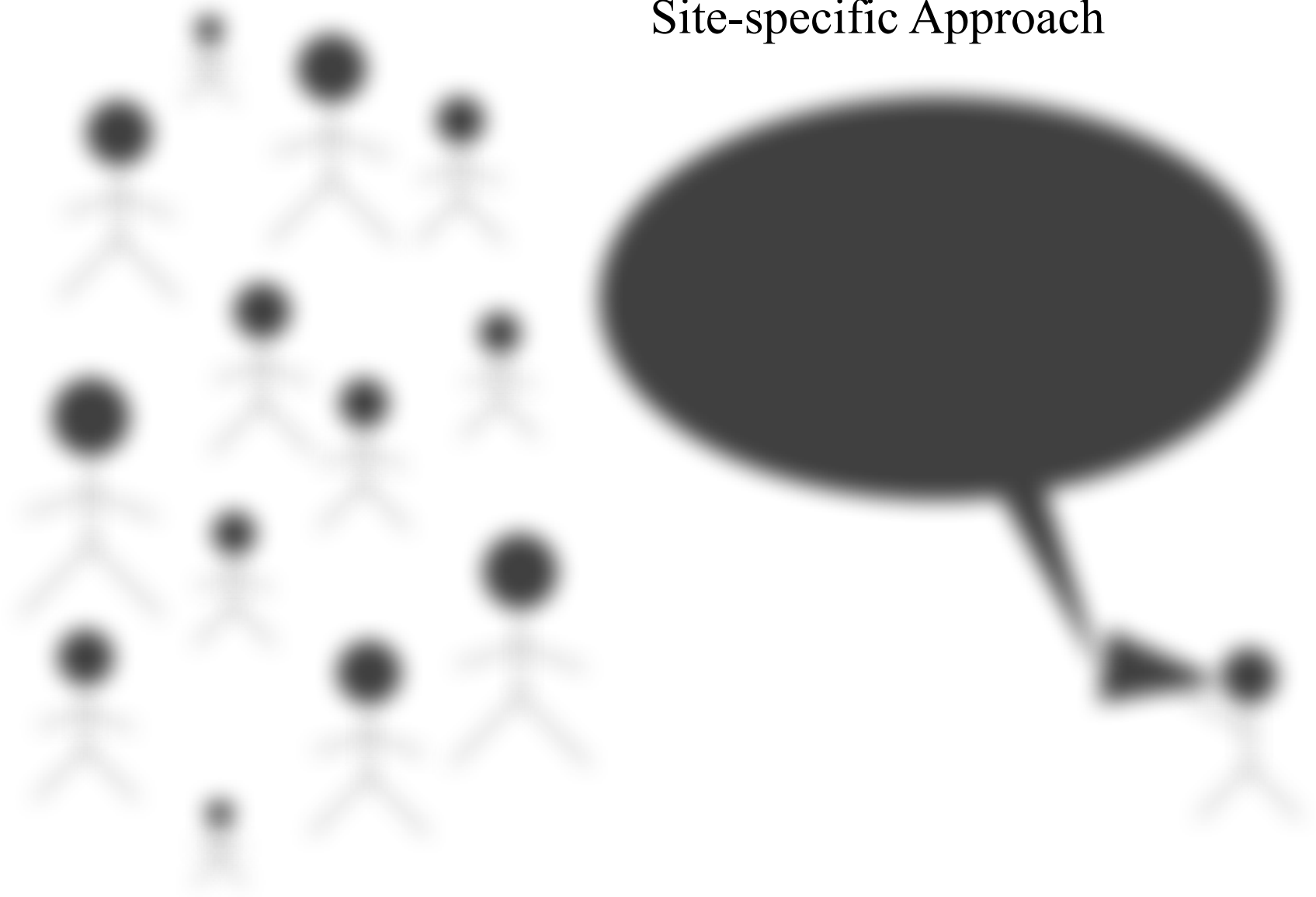
JC69 transition probabilities that would be used for sites in **gene 1**:

$$P_{ii}(t) = \frac{1}{4} + \frac{3}{4}e^{-4r_1\alpha t}$$
$$P_{ij}(t) = \frac{1}{4} - \frac{1}{4}e^{-4r_1\alpha t}$$

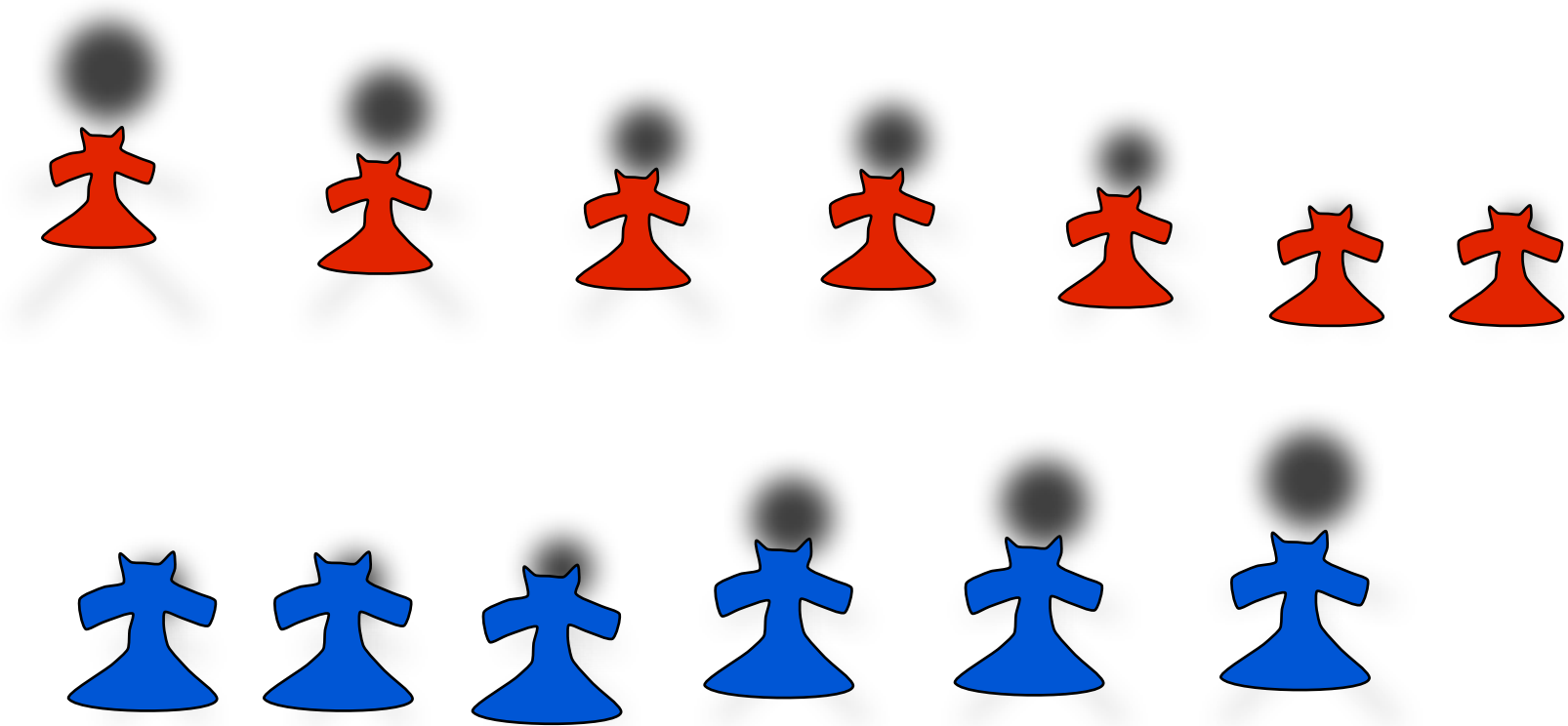
JC69 transition probabilities that would be used for sites in **gene 2**:

$$P_{ii}(t) = \frac{1}{4} + \frac{3}{4}e^{-4r_2\alpha t}$$
$$P_{ij}(t) = \frac{1}{4} - \frac{1}{4}e^{-4r_2\alpha t}$$

Site-specific Approach



Site-specific Approach

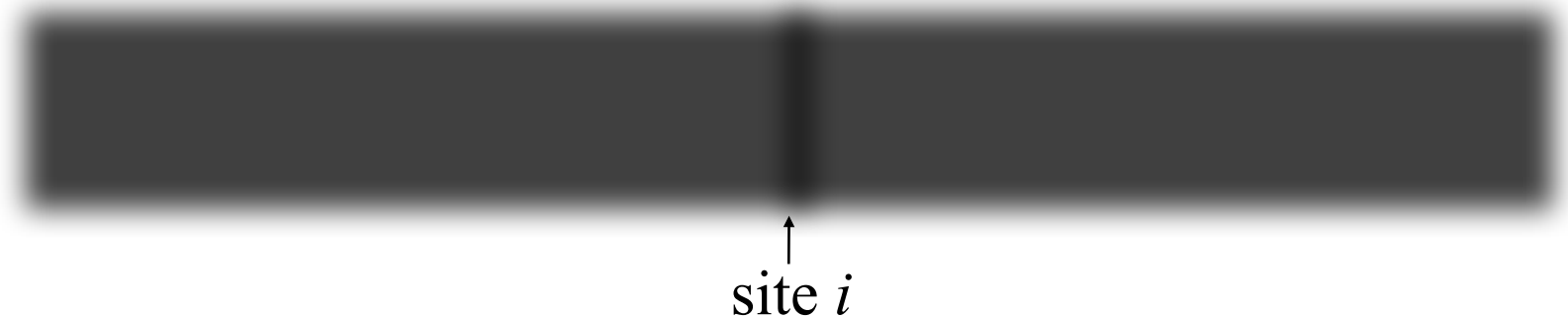


Pro: costs less: need to buy just one coat for every person

Con: every person in a group has to wear the same size coat, so the fit will be poor for some people if they are much bigger or smaller than the average size for the group in which they have been placed

Mixture Models

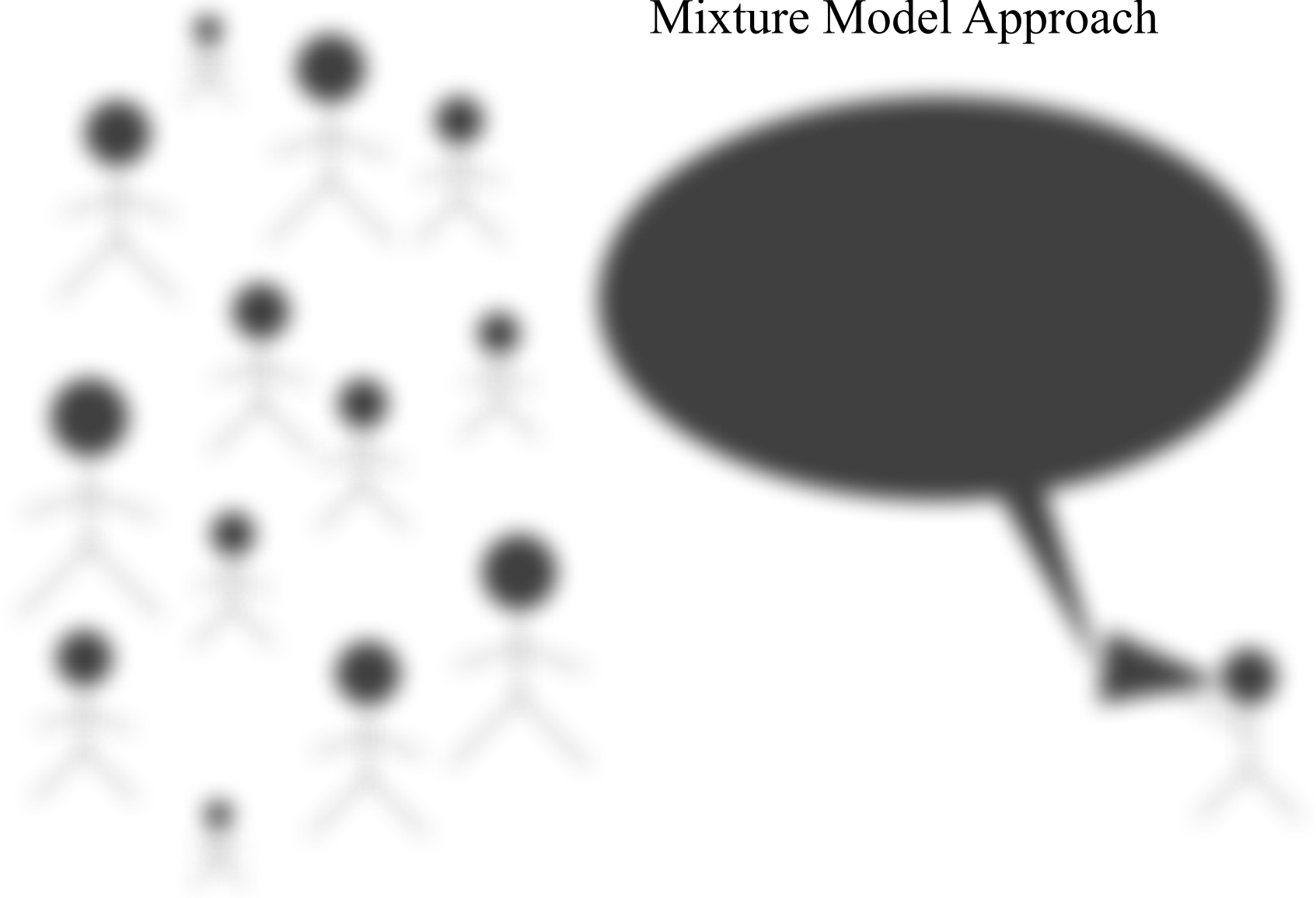
All relative rates applied to every site



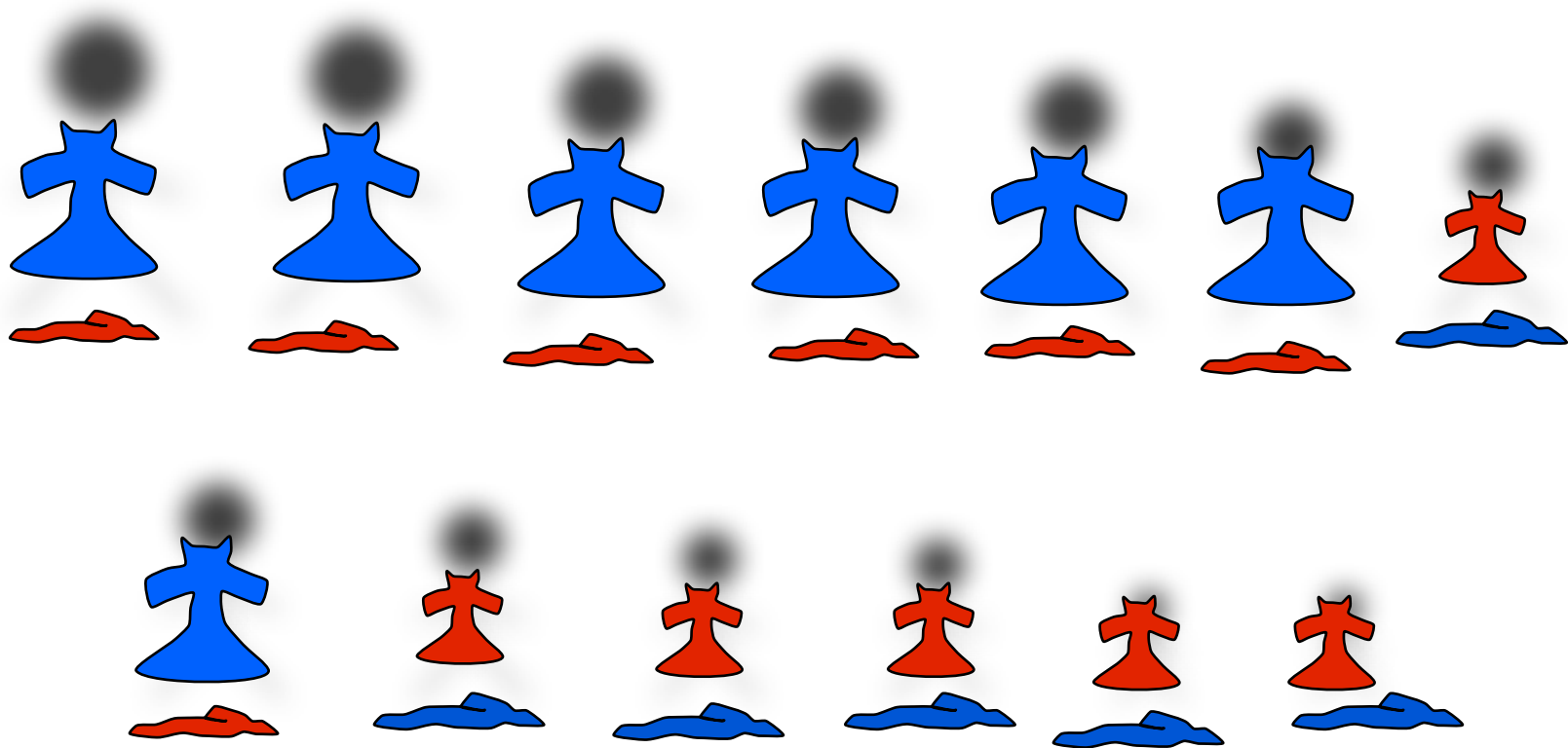
$$L_i = \Pr(D_i|r_1) \Pr(r_1) + \Pr(D_i|r_2) \Pr(r_2)$$

Common examples $\left\{ \begin{array}{l} \text{Invariable sites (I) model} \\ \text{Discrete Gamma (G) model} \end{array} \right.$

Mixture Model Approach



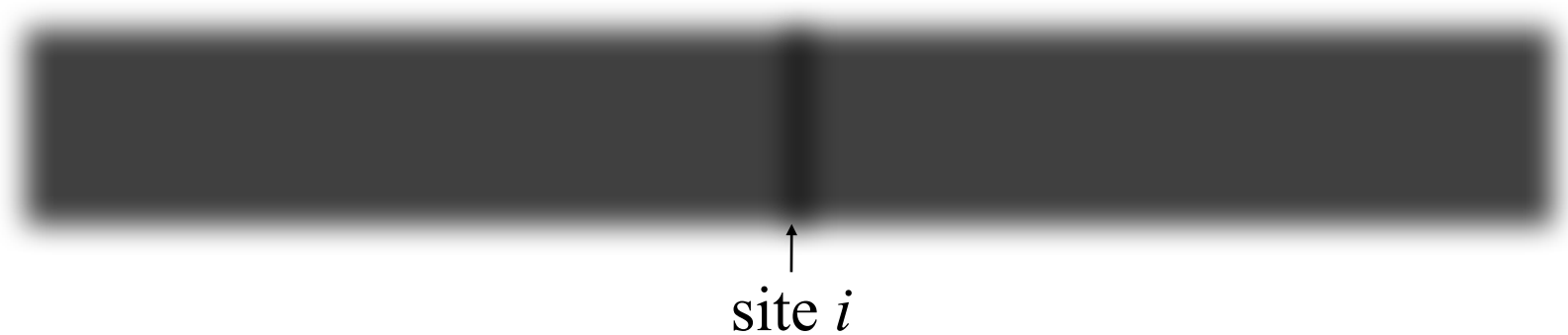
Mixture Model Approach



Pro: every person experiences better fit because they can choose the size coat that fits best
Con: costs more because two coats must be provided for each person

Invariable Sites Model

A fraction p_{invar} of sites are assumed to be invariable (i.e. rate = 0.0)



$$L_i = \text{Pr}(D_i|r_1)p_{invar} + \text{Pr}(D_i|r_2)(1 - p_{invar})$$

$$r_1 = 0.0$$

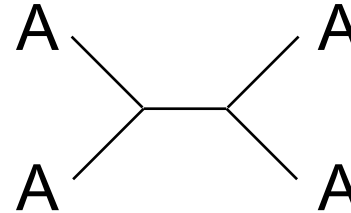
$$r_2 = \frac{1}{1 - p_{invar}}$$

Allows for the possibility that any given site could be variable or invariable

Reeves, J. H. 1992. Heterogeneity in the substitution process of amino acid sites of proteins coded for by mitochondrial DNA. *Journal of Molecular Evolution* 35:17-31.

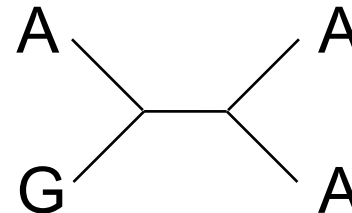
Invariable sites model

If site i is a *constant* site, both terms will contribute to the site likelihood:



$$L_i = \Pr(D_i|0.0)p_{\text{invar}} + \Pr(D_i|r_2)(1 - p_{\text{invar}})$$

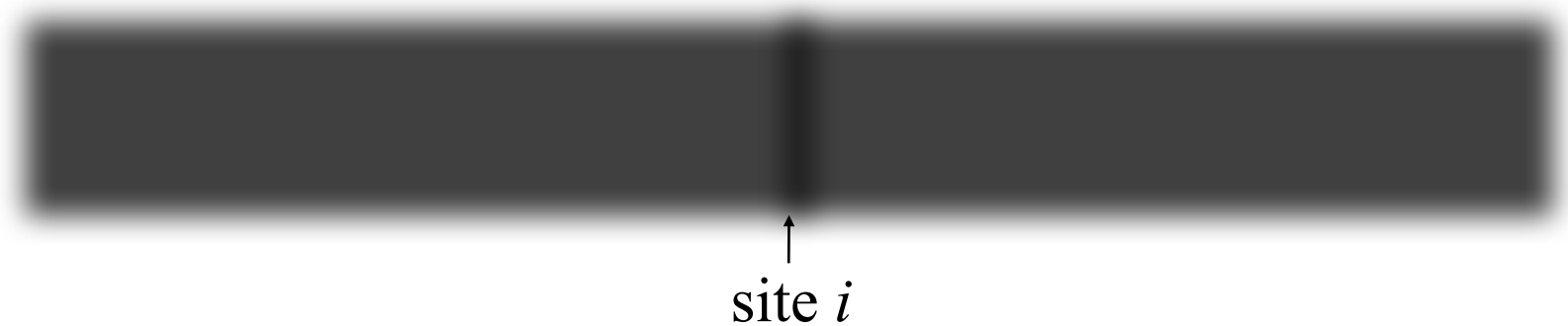
If site i is a *variable* site, there is no way to explain the data with a zero rate, so the first term is zero:



$$L_i = \cancel{\Pr(D_i|0.0)p_{\text{invar}}} + \Pr(D_i|r_2)(1 - p_{\text{invar}})$$

Discrete Gamma Model

No relative rates are exactly 0.0, and all are equally probable



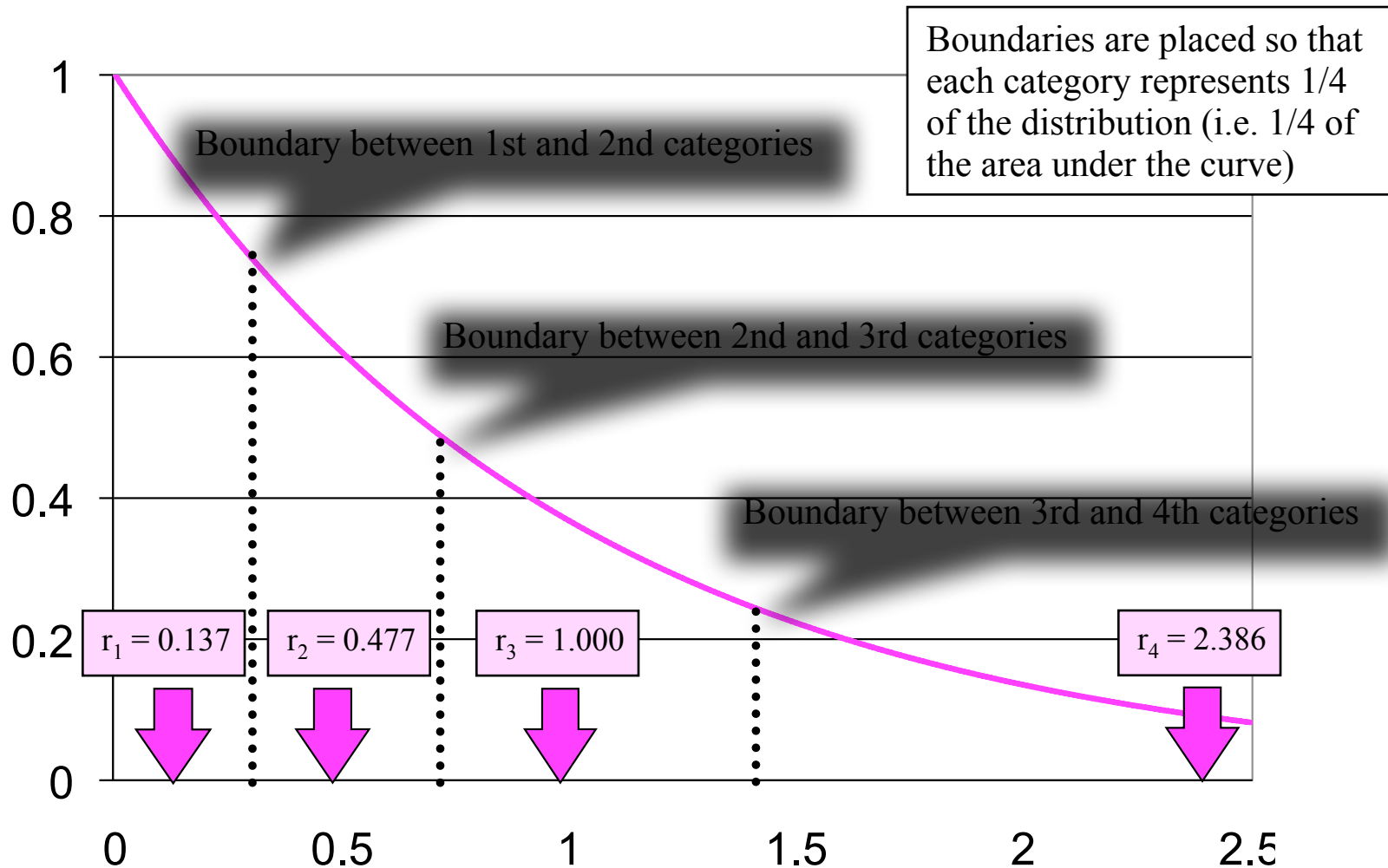
$$L = \left(\frac{1}{4}\right) \Pr(D_i|r_1) + \left(\frac{1}{4}\right) \Pr(D_i|r_2) + \left(\frac{1}{4}\right) \Pr(D_i|r_3) + \left(\frac{1}{4}\right) \Pr(D_i|r_4)$$

Relative rates are constrained to a discrete gamma distribution
Number of rate categories can vary (4 used here)

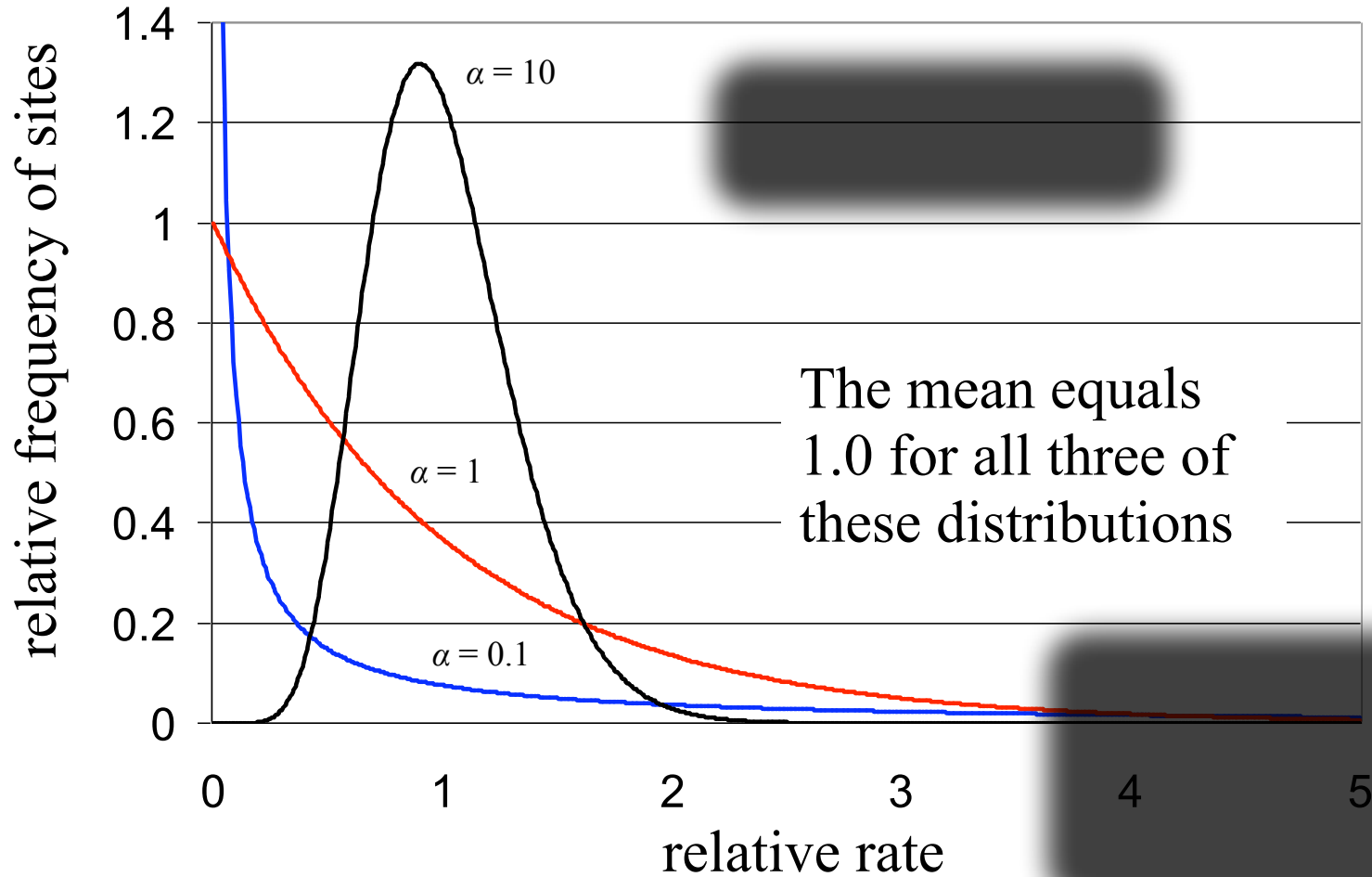
Yang, Z. 1993. Maximum-likelihood estimation of phylogeny from DNA sequences when substitution rates differ over sites. *Molecular Biology and Evolution* 10:1396-1401.

Yang, Z. 1994. Maximum likelihood phylogenetic estimation from DNA sequences with variable rates over sites: approximate methods. *Journal of Molecular Evolution* 39:306-314.

Relative rates in 4-category case



Gamma distributions



Codon models

The Genetic Code

First 12 nucleotides at the 5' end of the *rbcL* gene in corn:

5' -ATG | TCA | CCA | CAA-3' coding strand
 3' -TAC | AGT | GGT | GTT-5' template strand

} DNA double helix

transcription

5' -AUG | UCA | CCA | CAA-3' mRNA

translation

N-Met | Ser | Pro | Gln-C polypeptide

Codon models treat codons as the independent units, not individual nucleotide sites.

Genetic Code

	U	C	A	G	
U	UUU Phe UUC Phe UUA Leu UUG Leu	UCU Ser UCC Ser UCA Ser UCG Ser	UAU Tyr UAC Tyr UAA Stop UAG Stop	UGU Cys UGC Cys UGA Stop UGG Trp	U C A G
C	CUU Leu CUC Leu CUA Leu CUG Leu	CCU Pro CCC Pro CCA Pro CCG Pro	CAU His CAC His CAA Gln CAG Gln	CGU Arg CGC Arg CGA Arg CGG Arg	U C A G
A	AUU Ile AUC Ile AUA Ile AUG Met	ACU Thr ACC Thr ACA Thr ACG Thr	AAU Asn AAC Asn AAA Lys AAG Lys	AGU Ser AGC Ser AGA Arg AGG Arg	U C A G
G	GUU Val GUC Val GUA Val GUG Val	GCU Ala GCC Ala GCA Ala GCG Ala	GAU Asp GAC Asp GAA Glu GAG Glu	GGU Gly GGC Gly GGA Gly GGG Gly	U C A G

<http://www.langara.bc.ca/biology/mario/Assets/Geneticcode.jpg>

First codon models

- Muse and Gaut model (MG94) is simplest
 - α = synonymous substitution rate
 - β = nonsynonymous substitution rate
 - $\pi_A, \pi_C, \pi_G, \pi_T$ = base frequencies
- Goldman and Yang model (GY94) similar
 - accounts for synon./nonsynon. *and* trs/trv bias *and* amino acid properties (later simplified, see Yang et

Muse, S. V., and B. S. Gaut. 1994. A likelihood approach for comparing synonymous and nonsynonymous substitution rates, with application to the chloroplast genome. *Molecular Biology and Evolution* 11:715-724.

Goldman, N., and Z. Yang. 1994. A codon-based model of nucleotide substitution for protein-coding DNA sequences. *Molecular Biology and Evolution* 11:725-736.

Yang, Z., Nielsen, R., and Hasegawa, M. 1998. Models of amino acid substitution and applications to mitochondrial protein evolution. *Molecular Biology and Evolution* 15:1600-1611.

Table I. Part of Muse and Gaut's 61×61 instantaneous rate matrix^a

Codon before substitution (the 'from' state)	Codon after substitution (the 'to' state)							
	TTT (Phe)	TTC (Phe)	TTA (Leu)	TTG (Leu)	CTT (Leu)	CTC (Leu)	...	GGG (Gly)
TTT (Phe)	---	$\alpha\pi_C$	$\beta\pi_A$	$\beta\pi_G$	$\beta\pi_C$	0	...	0
TTC (Phe)	$\alpha\pi_T$	---	$\beta\pi_A$	$\beta\pi_G$	0	$\beta\pi_C$	...	0
TTA (Leu)	$\beta\pi_T$	$\beta\pi_C$	---	$\alpha\pi_G$	0	0	...	0
TTG (Leu)	$\beta\pi_T$	$\beta\pi_C$	$\alpha\pi_A$	---	0	0	...	0
CTT (Leu)	$\beta\pi_T$	0	0	0	---	$\alpha\pi_C$	...	0
CTC (Leu)	0	$\beta\pi_T$	0	0	$\alpha\pi_T$	---	...	0
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮
GGG (Gly)	0	0	0	0	0	0	...	---

Instantaneous rate is 0.0 if two or more nucleotides must change during the codon transition

Interpreting codon model results

$\omega = \beta/\alpha$ is the nonsynonymous/synonymous rate ratio

omega	mode of selection	example(s)
$\omega < 1$	stabilizing selection (nucleotide substitutions rarely change the amino acid)	functional protein coding genes
$\omega = 1$	neutral evolution (synonymous and nonsynonymous substitutions occur at the same rate)	pseudogenes
$\omega > 1$	positive selection (nucleotide substitutions often change the amino acid)	envelope proteins in viruses under active positive selection