Lecture 1.2:
Substitution Models

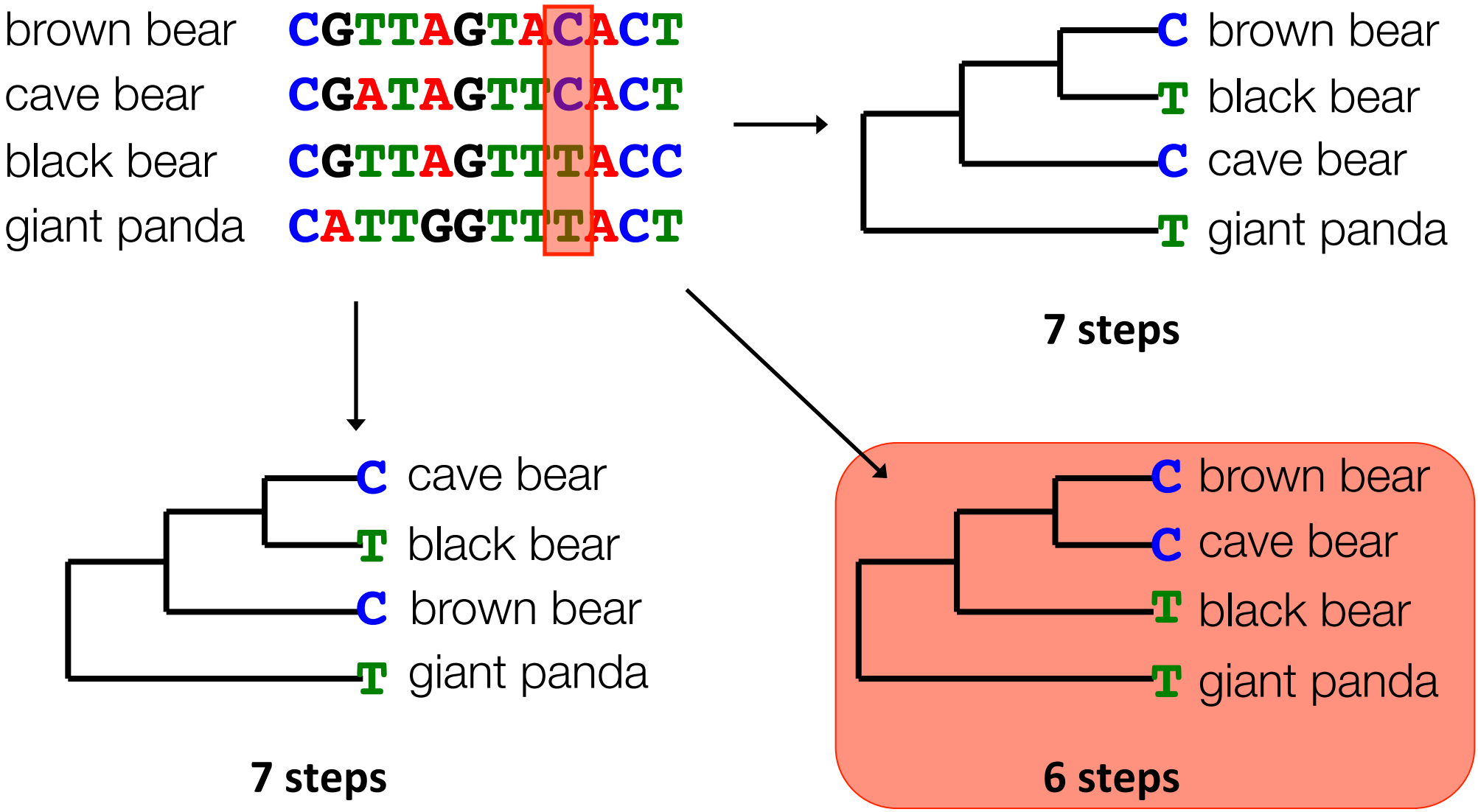
Popular phylogenetic methods

1. Maximum parsimony
2. Distance-based methods
3. Maximum likelihood
4. Bayesian inference

Model-based methods

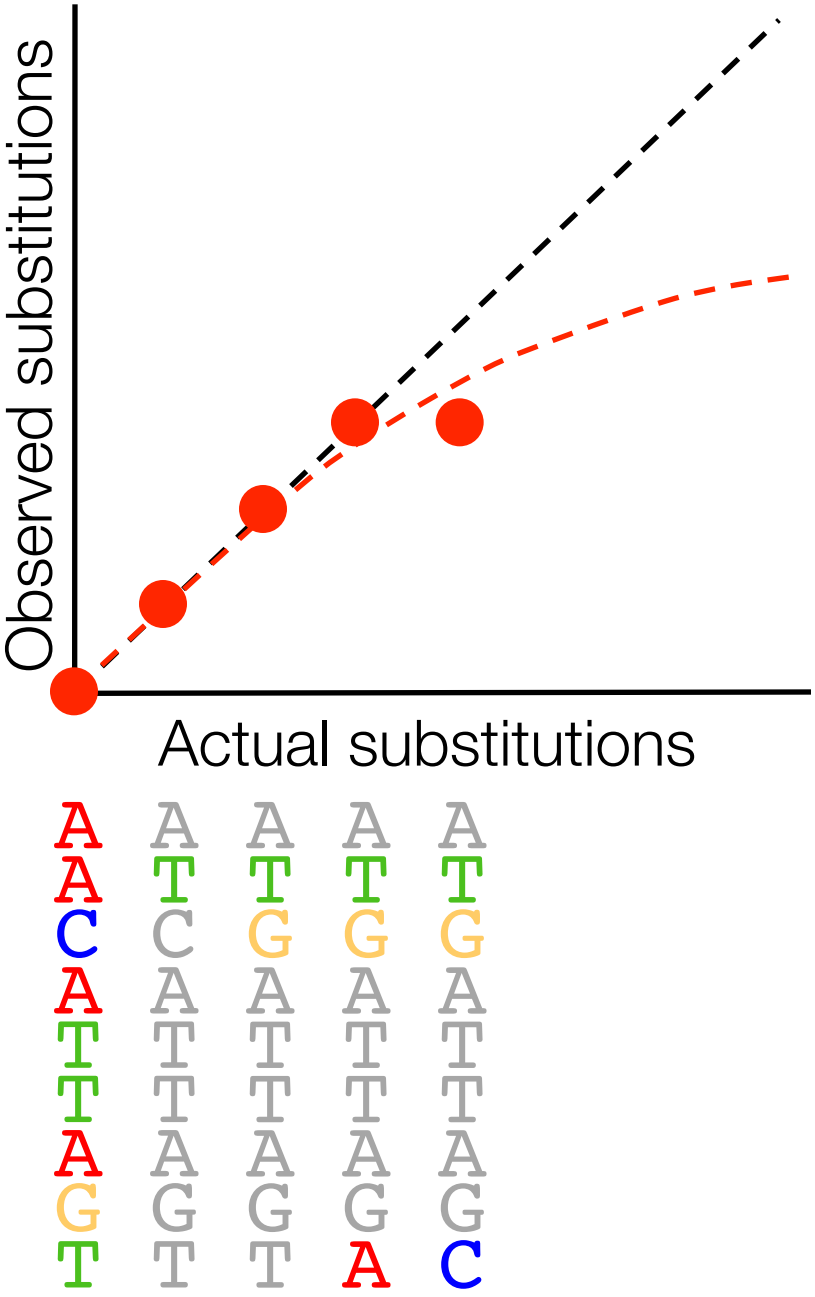
Maximum Parsimony

Maximum parsimony



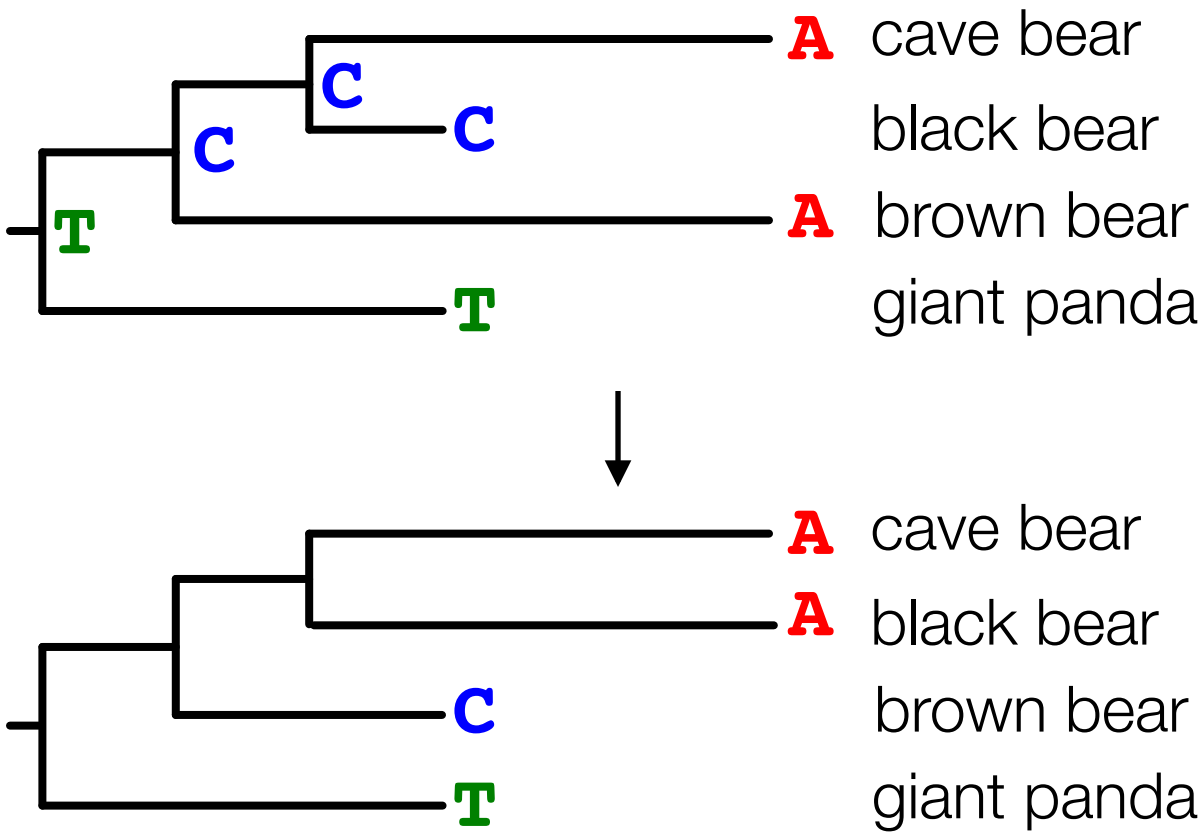
Maximum parsimony

- Identifies the tree topology that can explain the sequence data, using the smallest number of inferred substitution events
- Commonly used for morphological data
- Now rarely used for analysing genetic data
  - Cannot estimate evolutionary rates or timescales
  - Effects of multiple substitutions



- Maximum parsimony does not correct for multiple substitutions at the same site
- This leads to a problem known as ‘long-branch attraction’
  - Long branch = many substitutions
  - Similarities arise by chance
  - Long branches cluster together

Long-branch attraction



We can correct for multiple hits using substitution models

Weaknesses

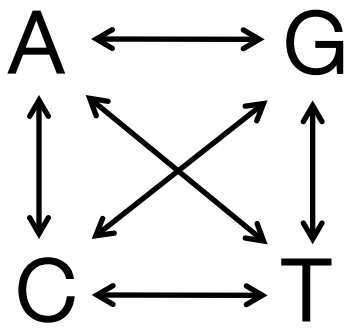
- Maximum parsimony does not correct for multiple substitutions at the same site
- This leads to a problem known as ‘long-branch attraction’
  - Long branches in the tree tend to group together

We can correct for multiple substitutions using **models** of the molecular evolutionary process

Evolutionary Models

Nucleotide substitution models

Rate Matrix



Base Frequencies

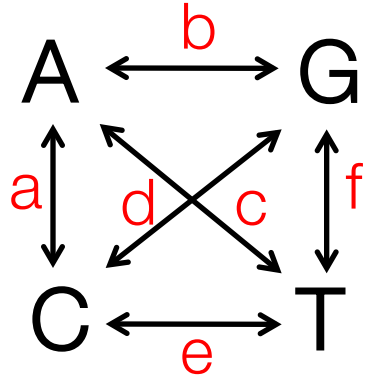
$\pi_A + \pi_C + \pi_G + \pi_T = 1$

Site Rates

+ I + G

Nucleotide substitution models

Rate Matrix



Base Frequencies

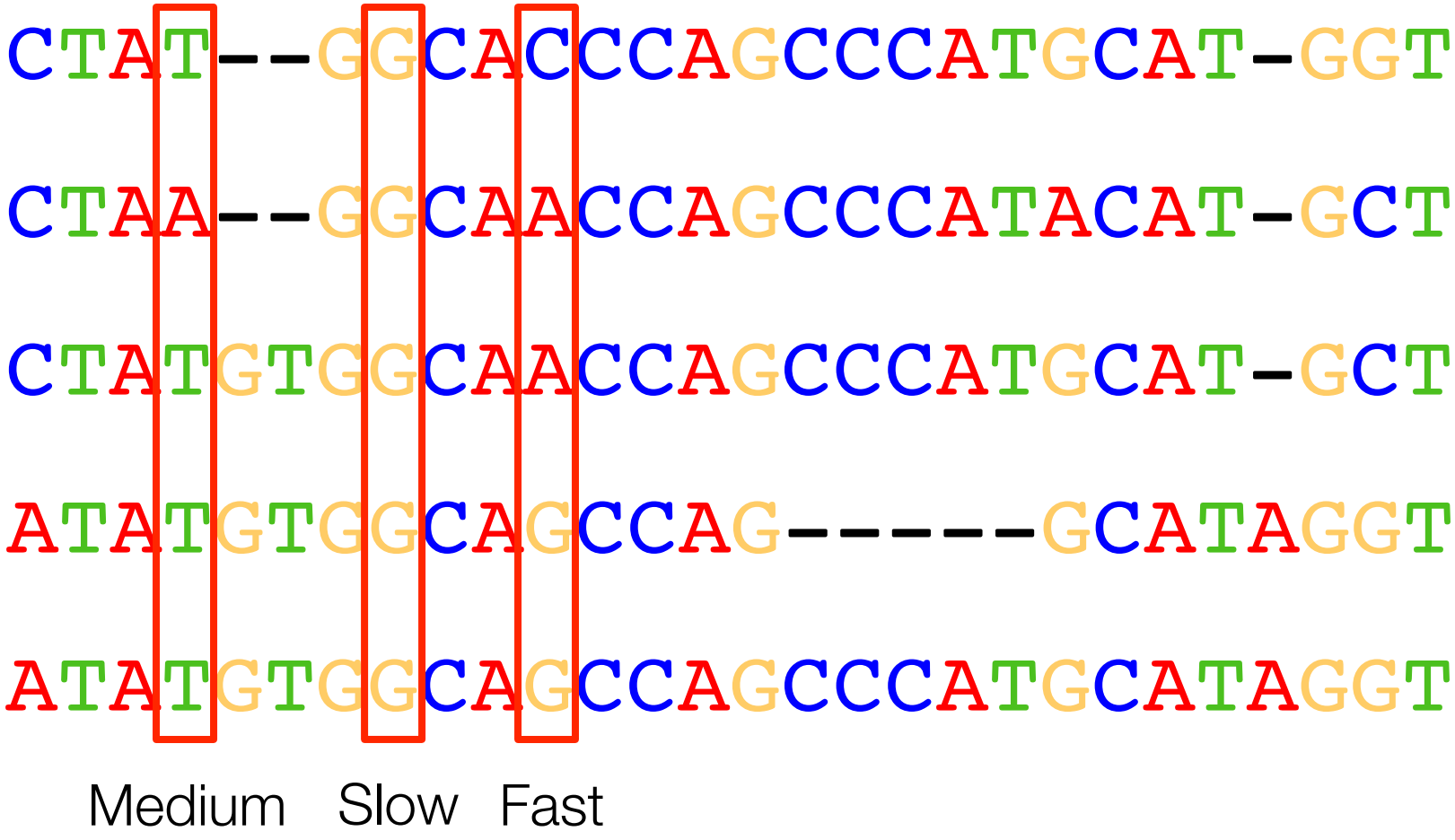
$\pi_A + \pi_C + \pi_G + \pi_T = 1$

Site Rates

$+ I + G$

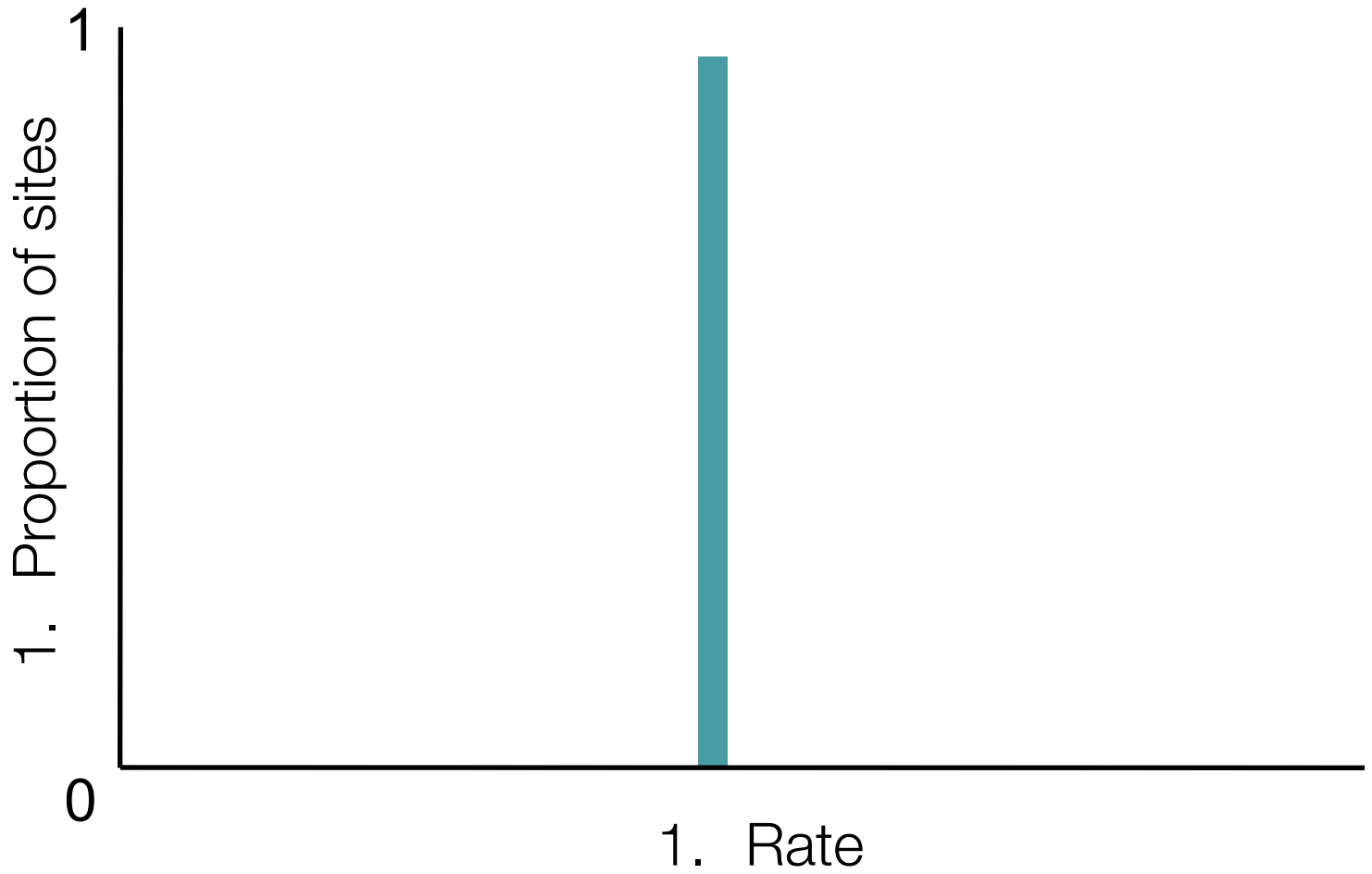
JC	HKY	GTR	GTR+I+G
a=b=c=d=e=f	a=c=d=f, b=e	a, b, c, d, e, f	a, b, c, d, e, f
$\pi_A=\pi_C=\pi_G=\pi_T$	π_A, π_C, π_G, π_T	π_A, π_C, π_G, π_T	π_A, π_C, π_G, π_T
No I or G	No I or G	No I or G	I, G
0 free parameters	4 free parameters	8 free parameters	10 free parameters

Rate variation across sites



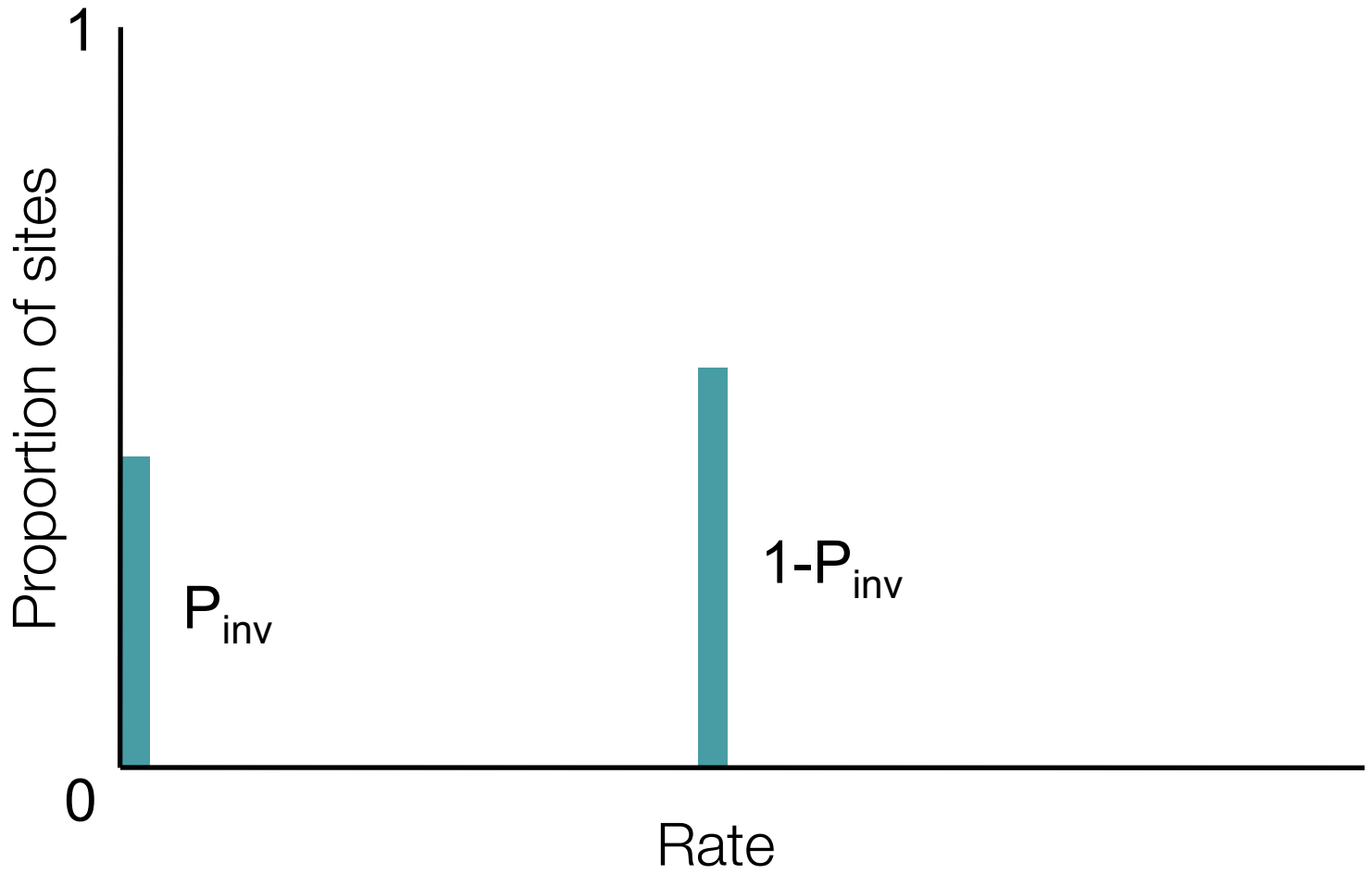
1. Rate variation among sites

1. Equal rates among sites (e.g., **JC**, **GTR**, **HKY** models)



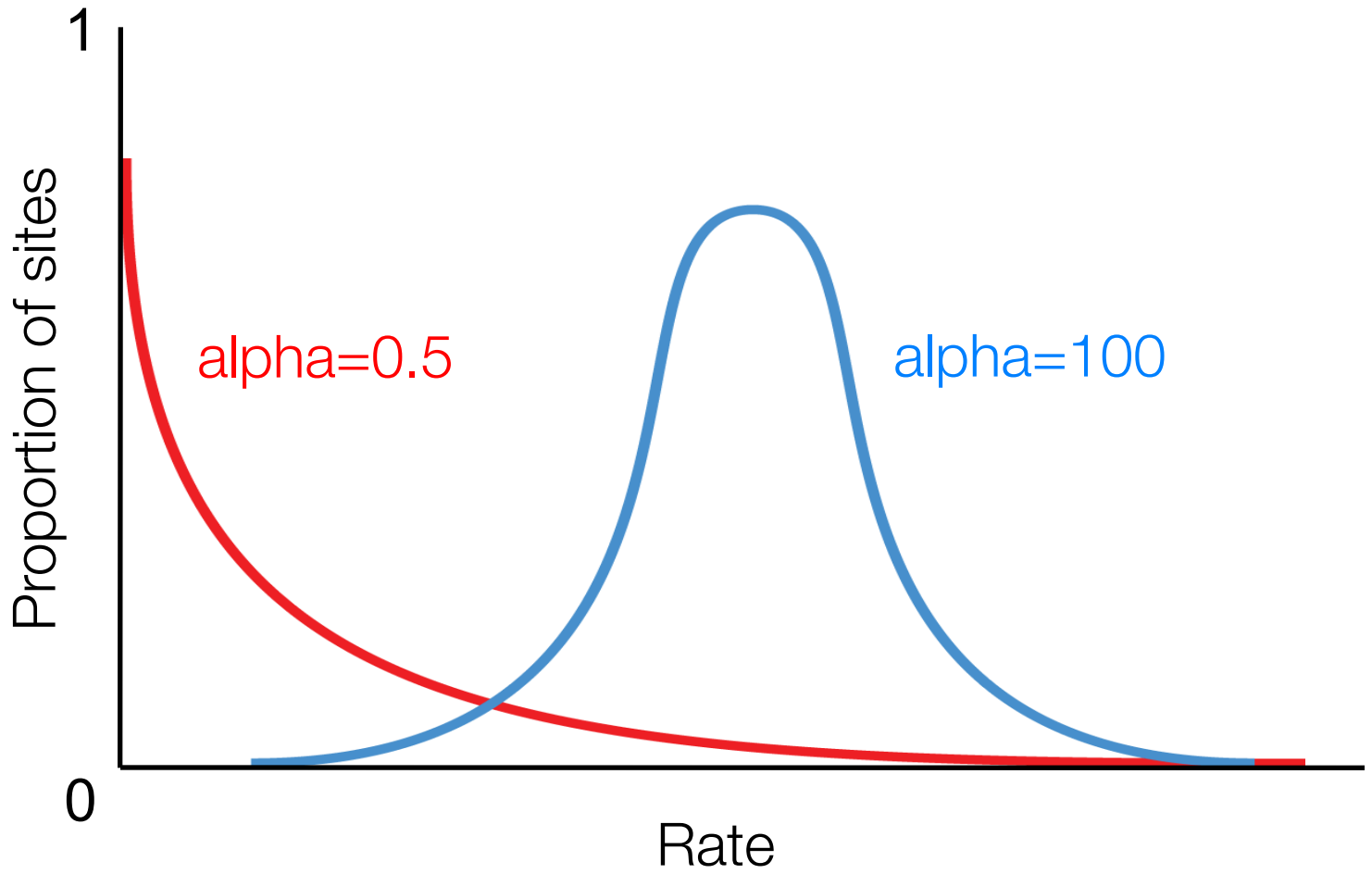
Rate variation among sites

- Proportion of invariable sites (e.g., **JC+I**, **GTR+I**, **HKY+I** models)



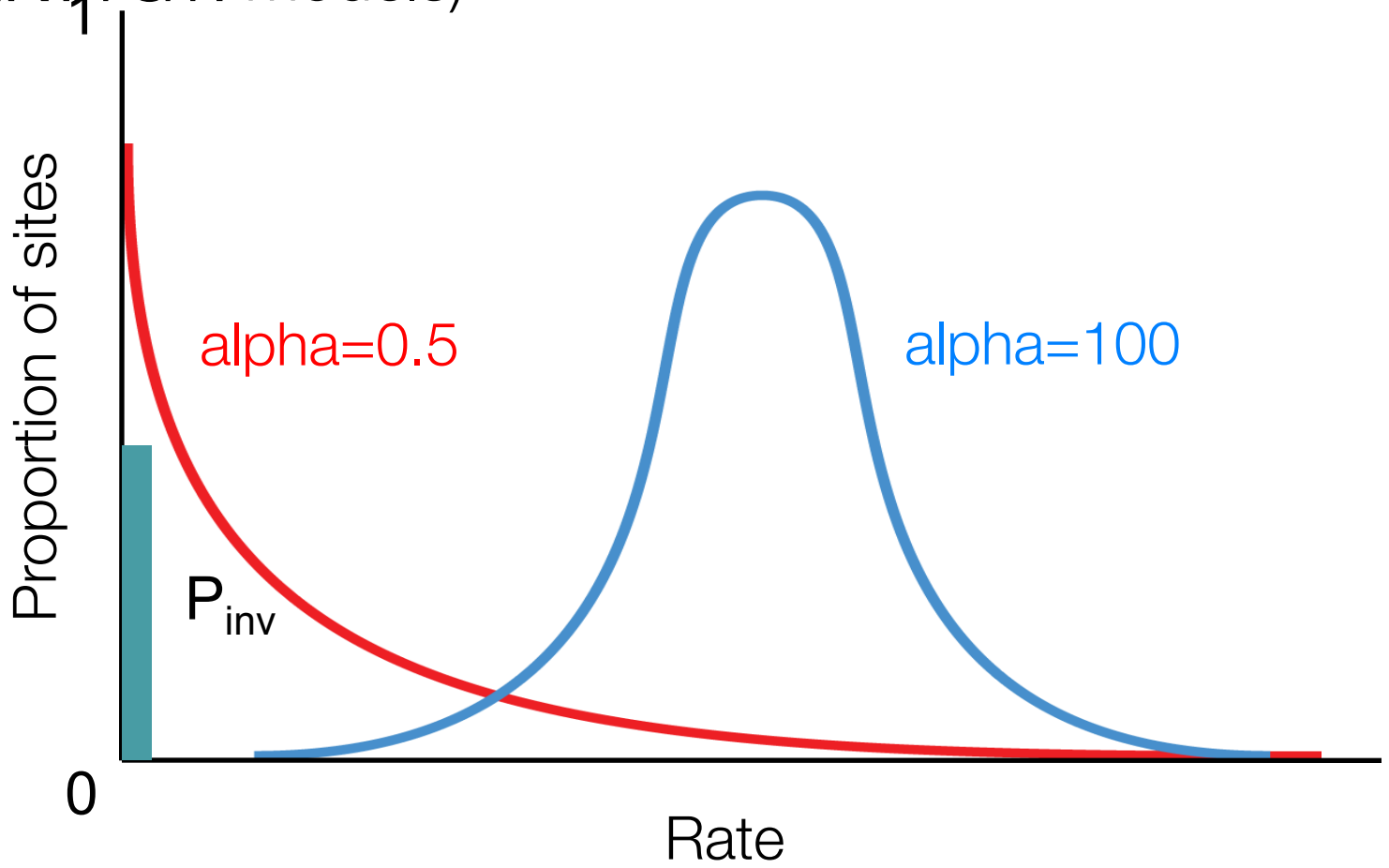
Rate variation among sites

- Gamma-distributed rate variation among sites (e.g., **JC+G**, **GTR+G**, **HKY+G** models)



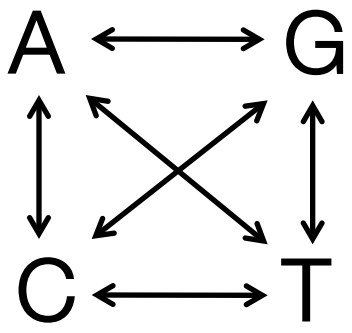
Rate variation among sites

- Gamma-distributed rate variation among sites and a proportion of invariable sites (e.g., **JC+G+I**, **GTR+G+I**, **HKY+G+I** models)



Nucleotide substitution models

Rate Matrix



Base Frequencies

$\pi_A + \pi_C + \pi_G + \pi_T = 1$

Site Rates

$+ I + G$

#Models

203 x 15 x 4 = 12,180

In phylogenetics, we typically consider a small subset of these

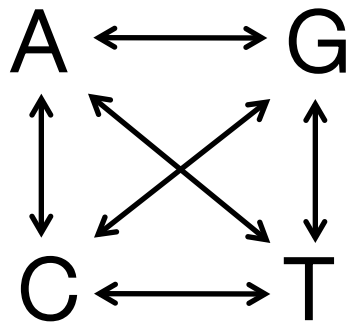
Amino acid substitution matrices

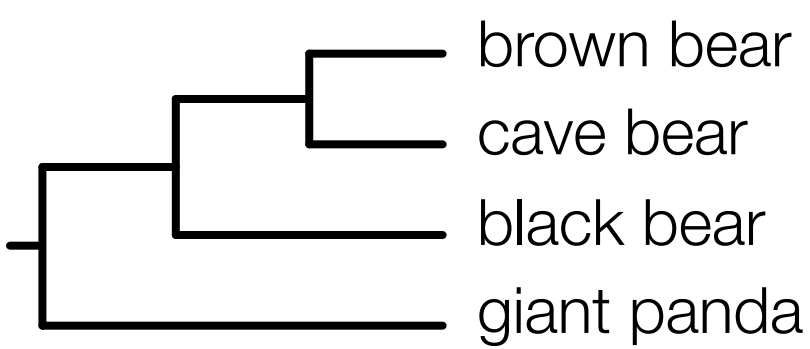
- 20x20 matrix of substitution probabilities
- Too many parameters to estimate
  - GTR model for DNA: 6 parameters
  - GTR model for proteins: 190 parameters
- Estimate substitution probabilities using a large data set
- Standard matrices:
  - PAM, BLOSUM, etc.

Fundamental assumptions

- Stationary
- Reversible
- Homogeneous
- Independent across sites

$\pi_A \quad \pi_C \quad \pi_G \quad \pi_T$

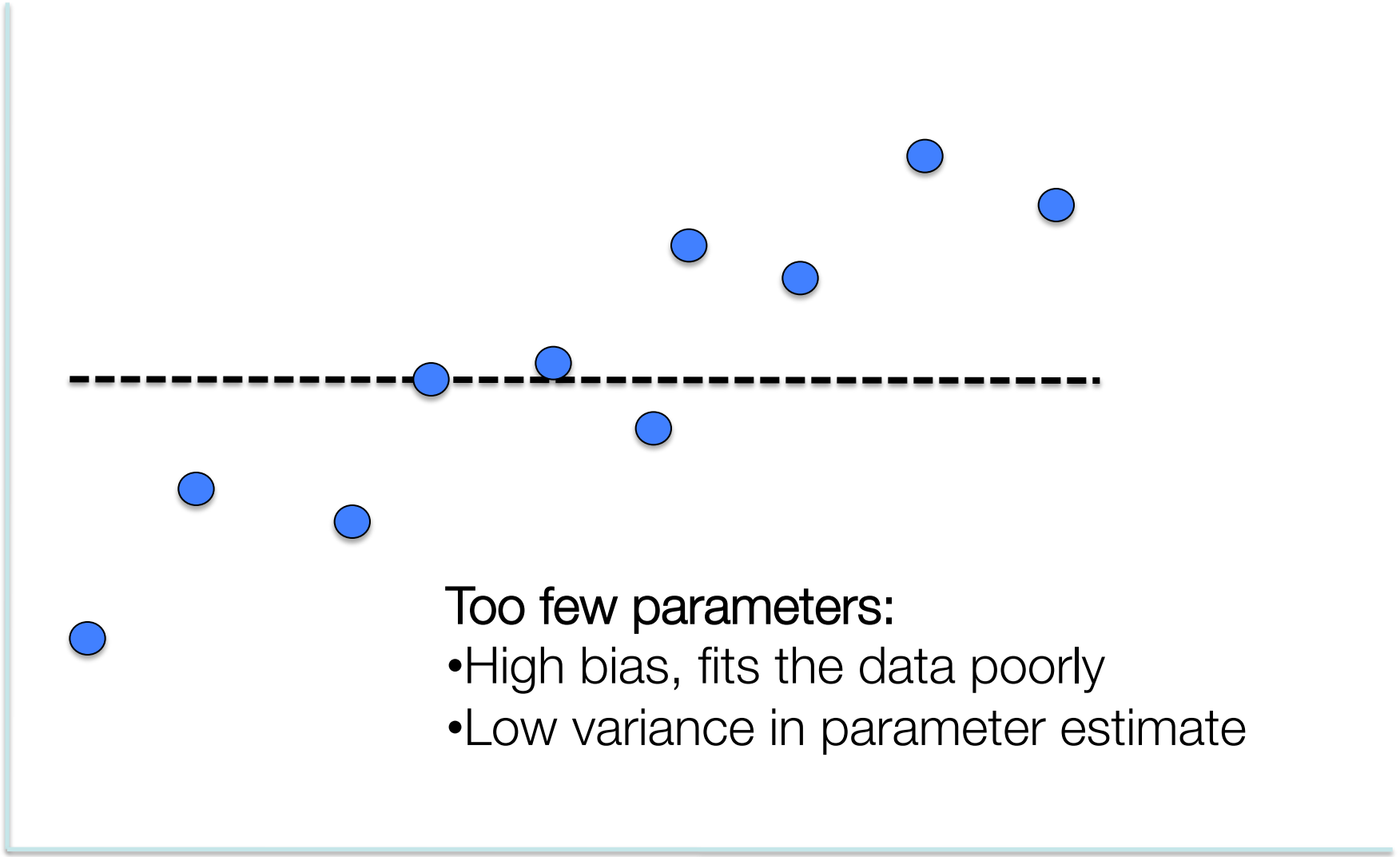




CGTTAGTACACT
CGATAGTTCACT
CGTTAGTTTACC
CATTGGTTTACT

Model Selection

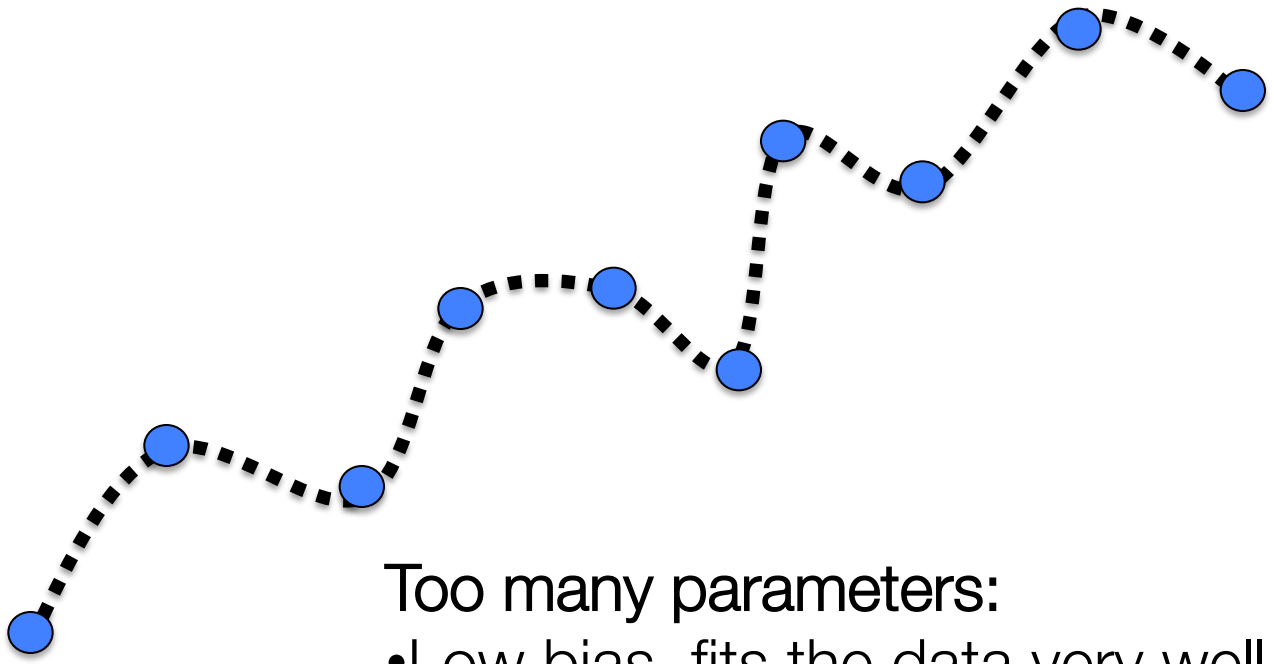
Model selection



Too few parameters:

- High bias, fits the data poorly
- Low variance in parameter estimate

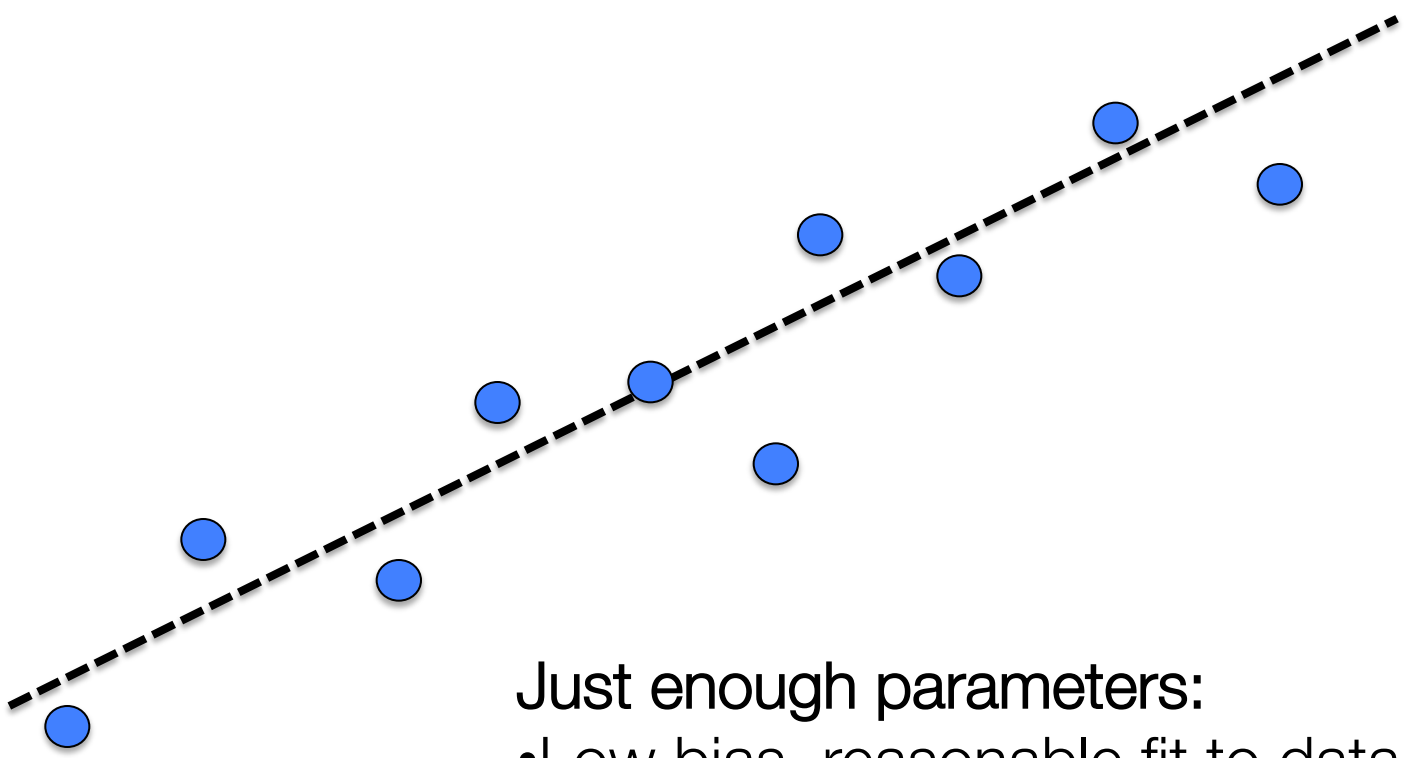
Model selection



Too many parameters:

- Low bias, fits the data very well
- Too many parameters, tell us little about the biological process that gave rise to the data

Model selection

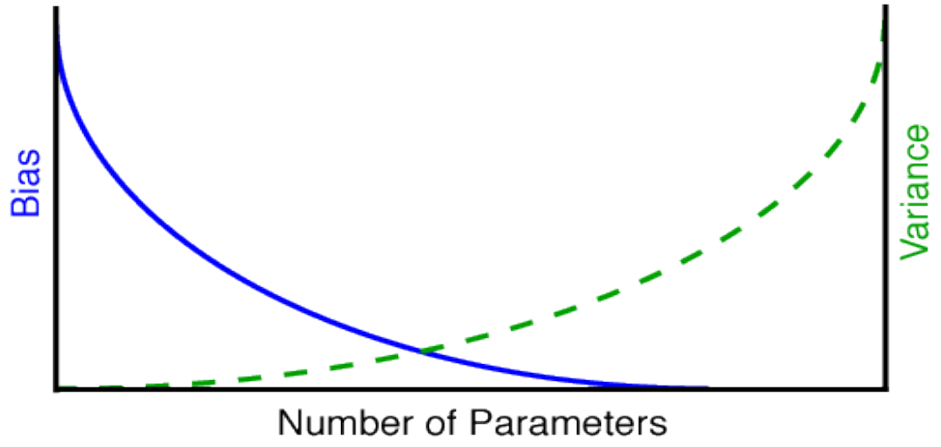


Just enough parameters:

- Low bias, reasonable fit to data
- Low variance, parameters have biological meaning

Model selection

- Adding more parameters *always* improves the fit of the model to the observed data
- More parameters → higher R^2 and better likelihood
- But it doesn't necessarily improve the model!
- Goal is to find the best balance between bias and variance



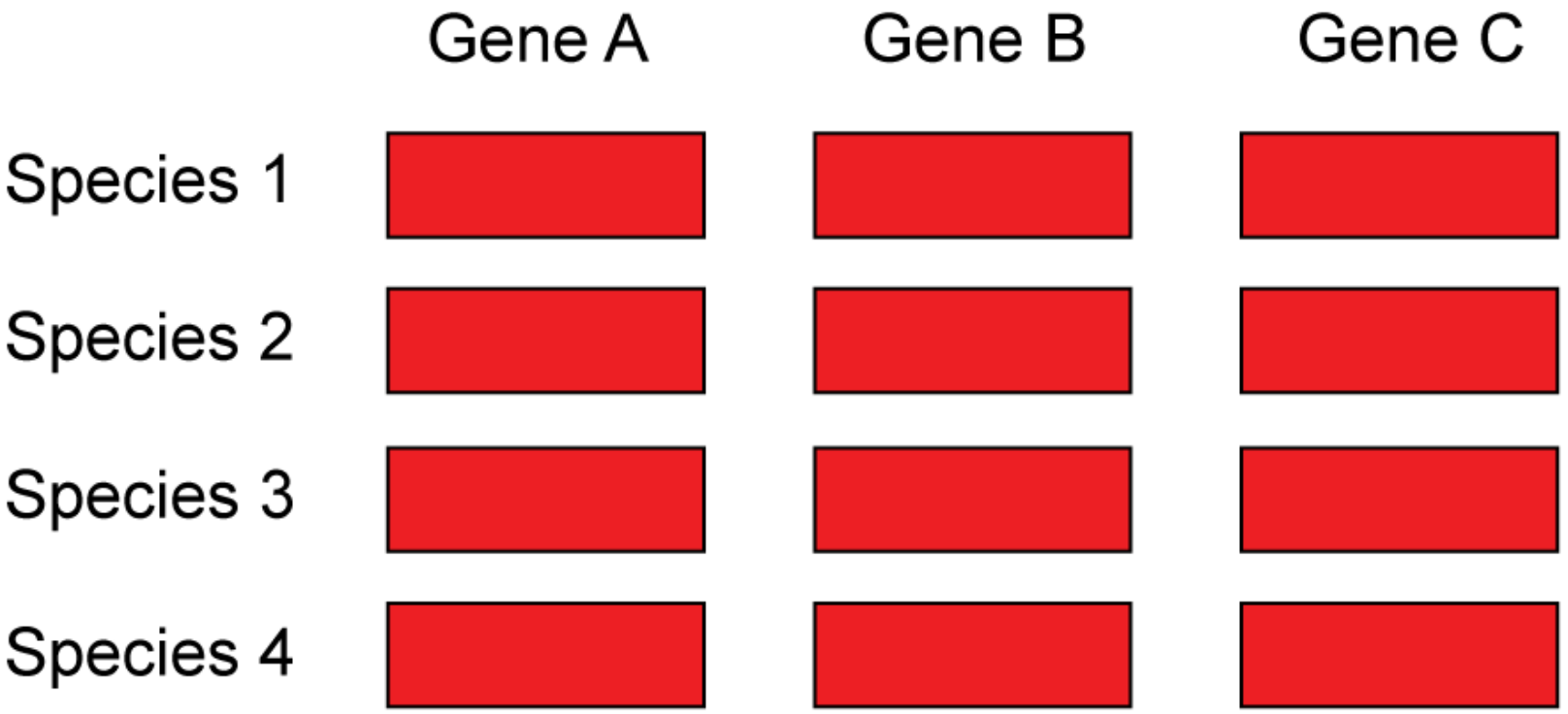
Model selection

- Adding a parameter to the model:
  - Is the improvement in likelihood worth the cost of adding a parameter?
- Model selection methods
  - **Likelihood-ratio test (LRT)**
    Used to compare nested models
  - **Akaike information criterion (AIC)**
    AIC = -2ln(likelihood) + k
  - **Bayesian information criterion (BIC)**

Data Partitioning

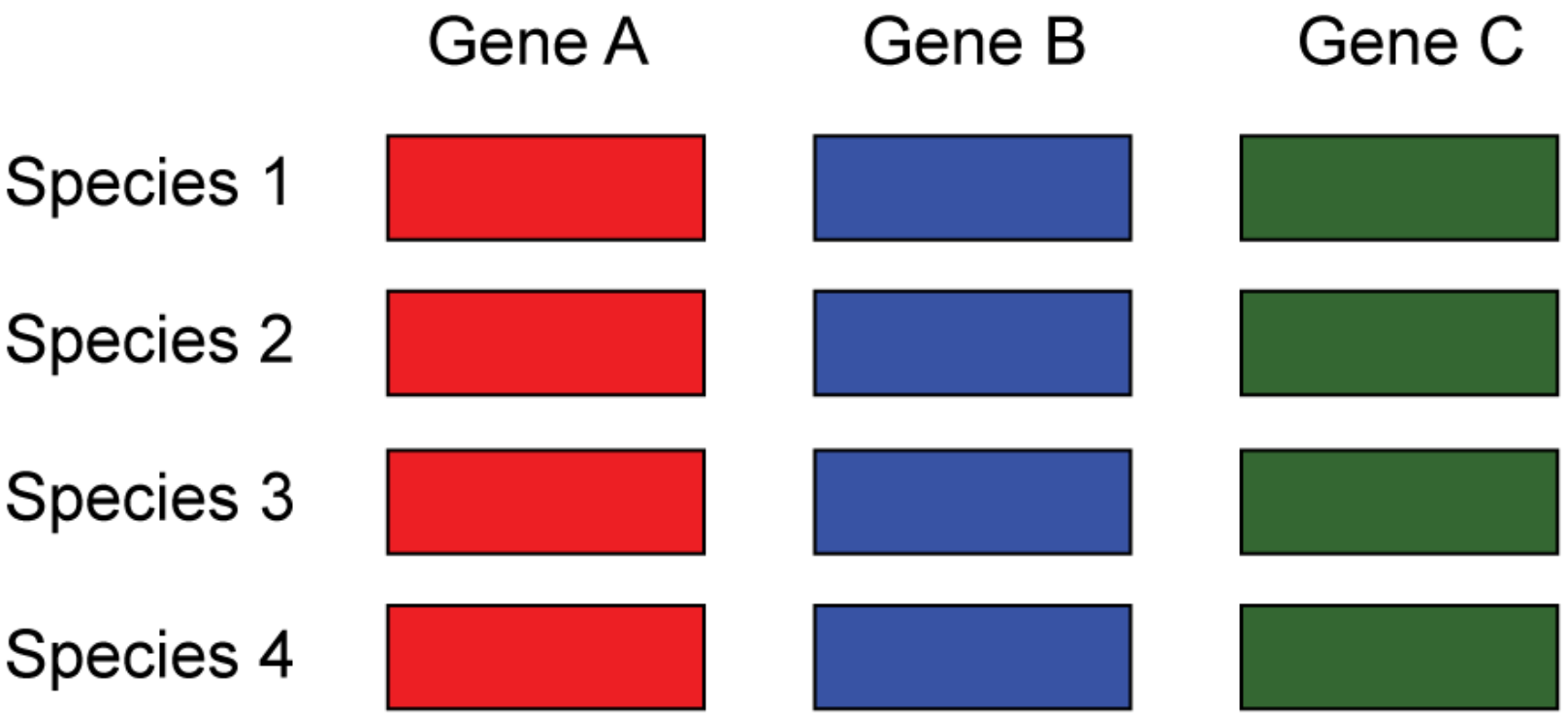
Data partitioning

- Single substitution model across 3 genes



Data partitioning

- Separate substitution model for each gene



Data partitioning

- Separate substitution model for each gene and codon position