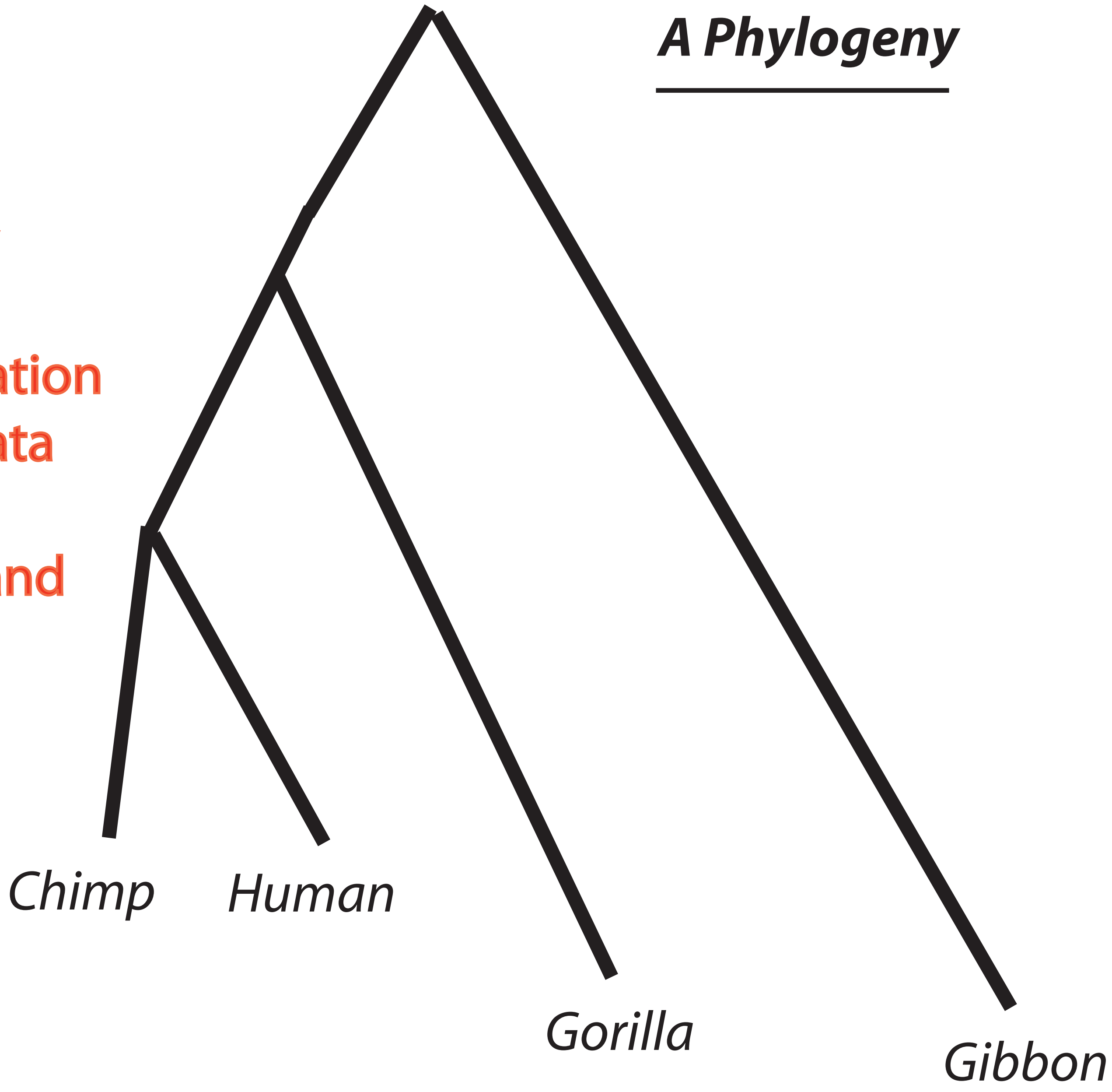
Biologists care about phylogenies because

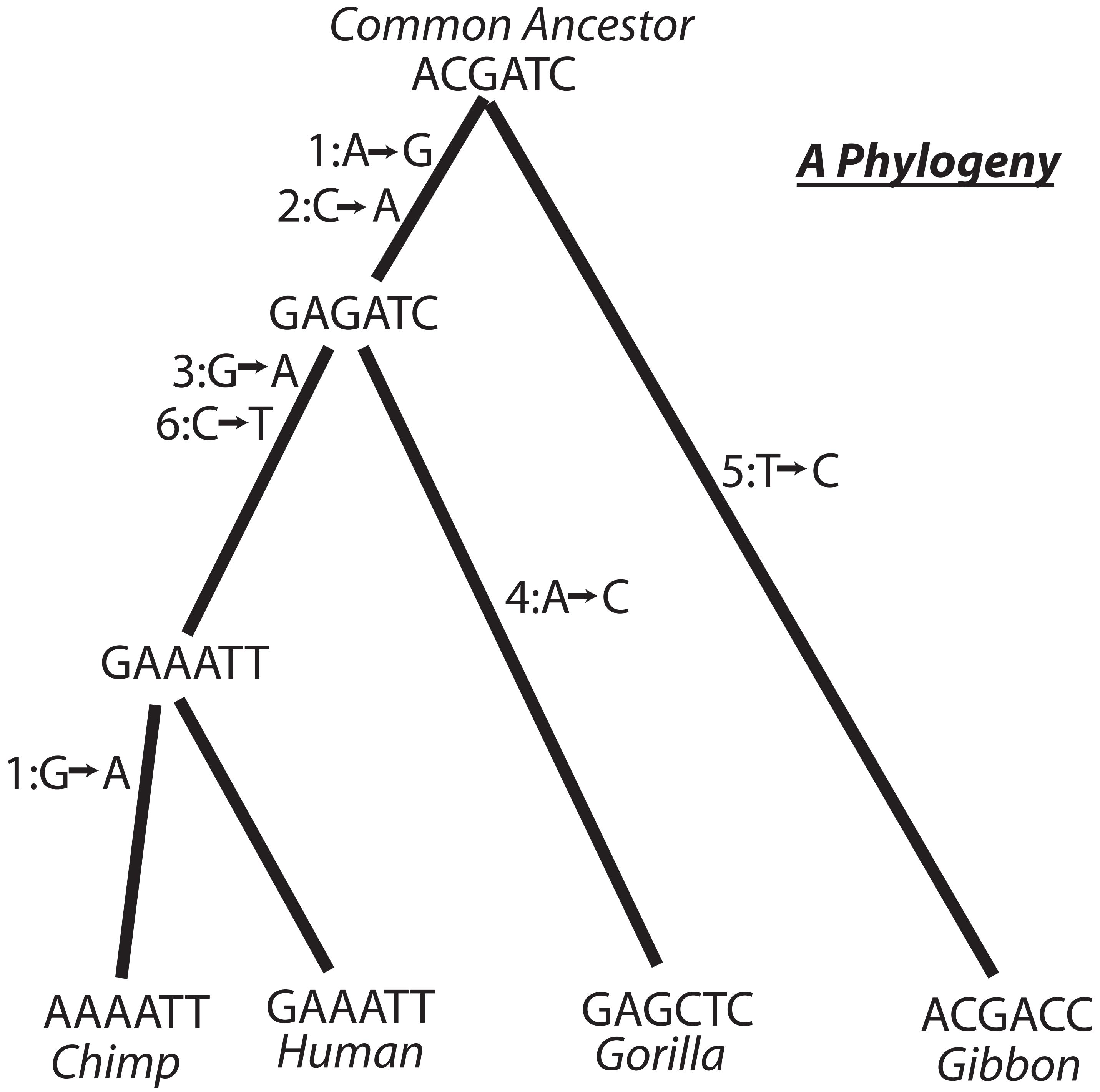
1. They represent history

2. They represent correlation structure of biological data

3. They help us understand biological process

A Phylogeny




A Phylogeny
Common Ancestor
ACGATC
1:A→G
2:C→A
GAGATC
3:G→A
6:C→T
GAAATT
1:G→A
4:A→C
5:T→C
AAAATT
Chimp
GAAATT
Human
GAGCTC
Gorilla
ACGACC
Gibbon

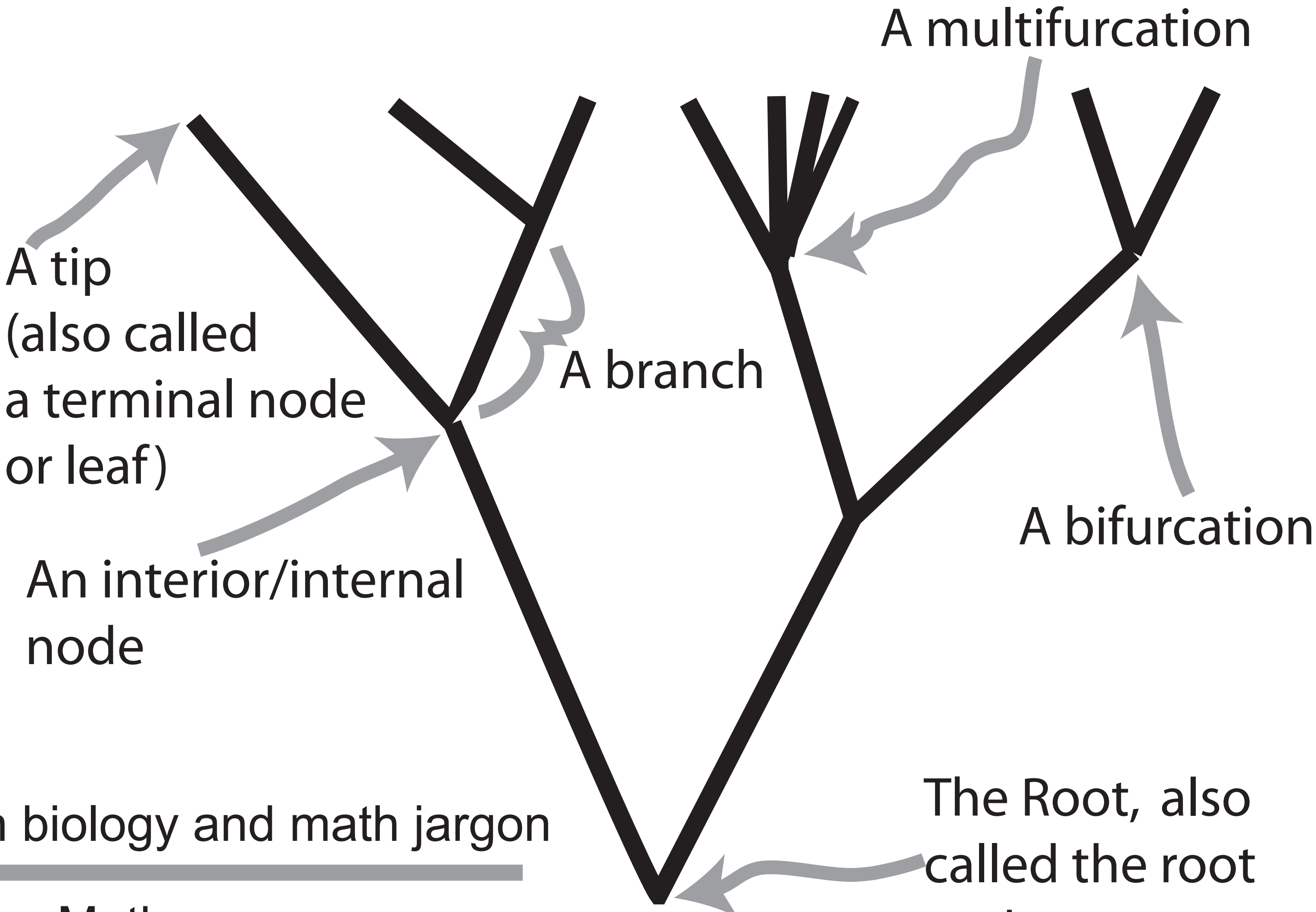
AAAATT
Chimp

GAAATT
Human

GAGCTC
Gorilla

ACGACC
Gibbon

Tree Anatomy



A multifurcation

A tip (also called a terminal node or leaf)

A branch

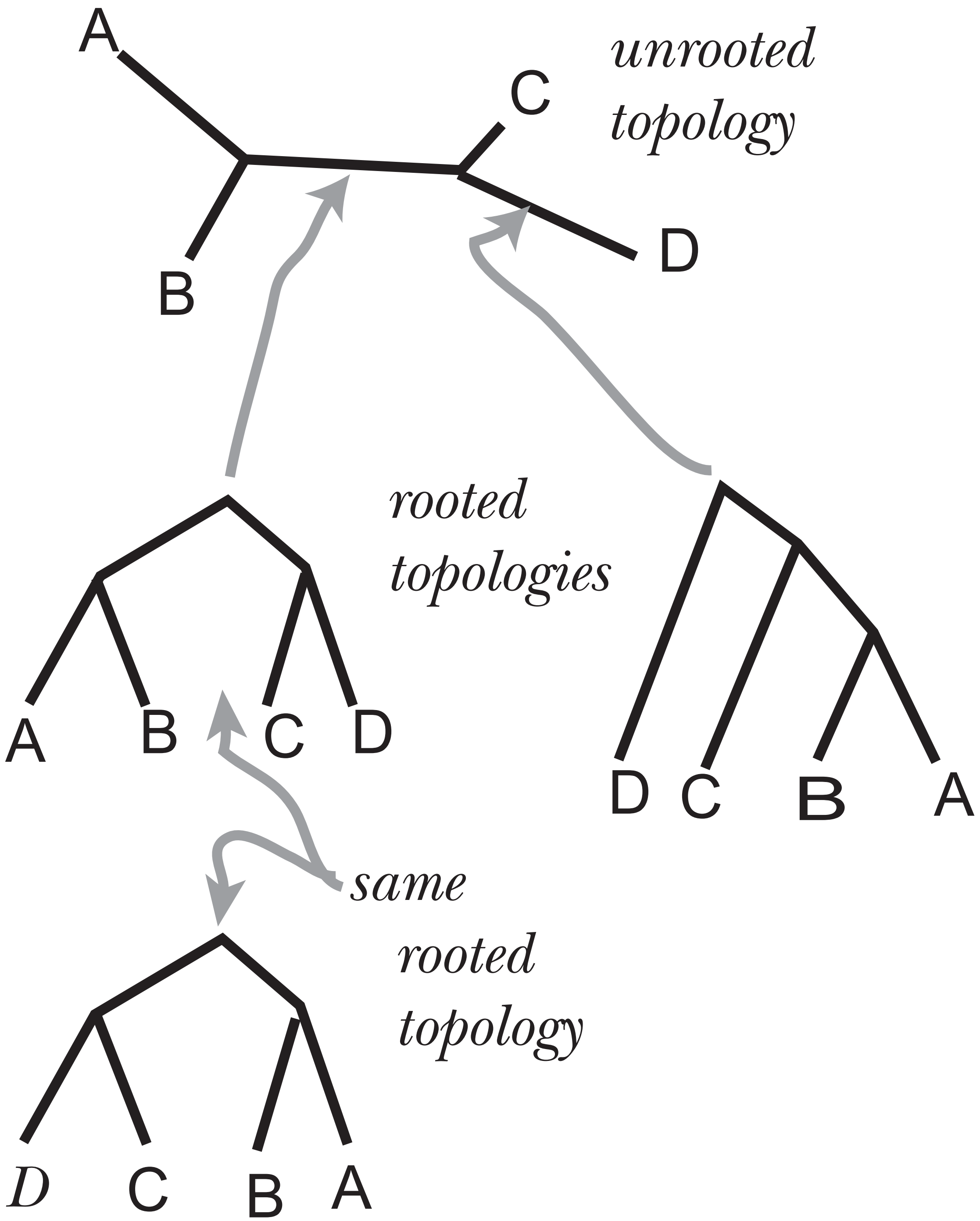
An interior/internal node

A bifurcation

The Root, also called the root node

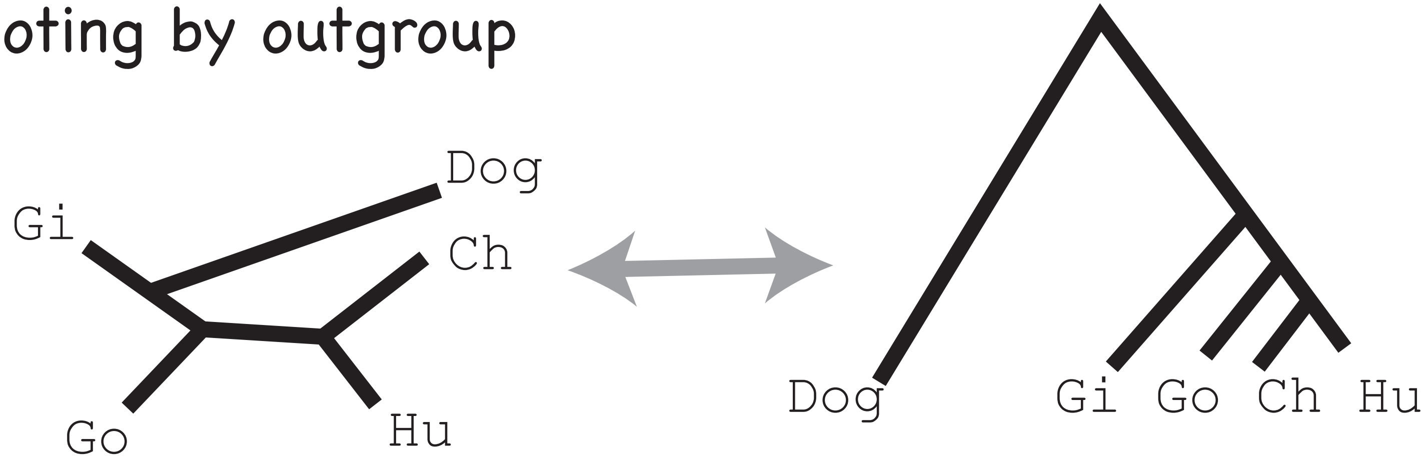
Translating between biology and math jargon

Biology	Math
Tree	Graph
Branch	Edge
Node	Vertice


A
C
unrooted
topology
B
D
rooted
topologies
A
B
C
D
D
C
B
A
same
rooted
topology
D
C
B
A

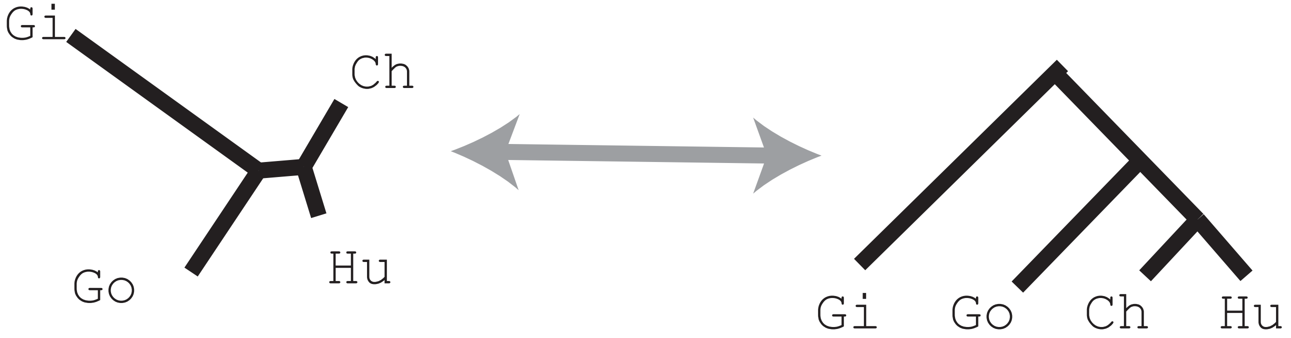
The two common ways phylogenies are rooted:

1. Rooting by outgroup

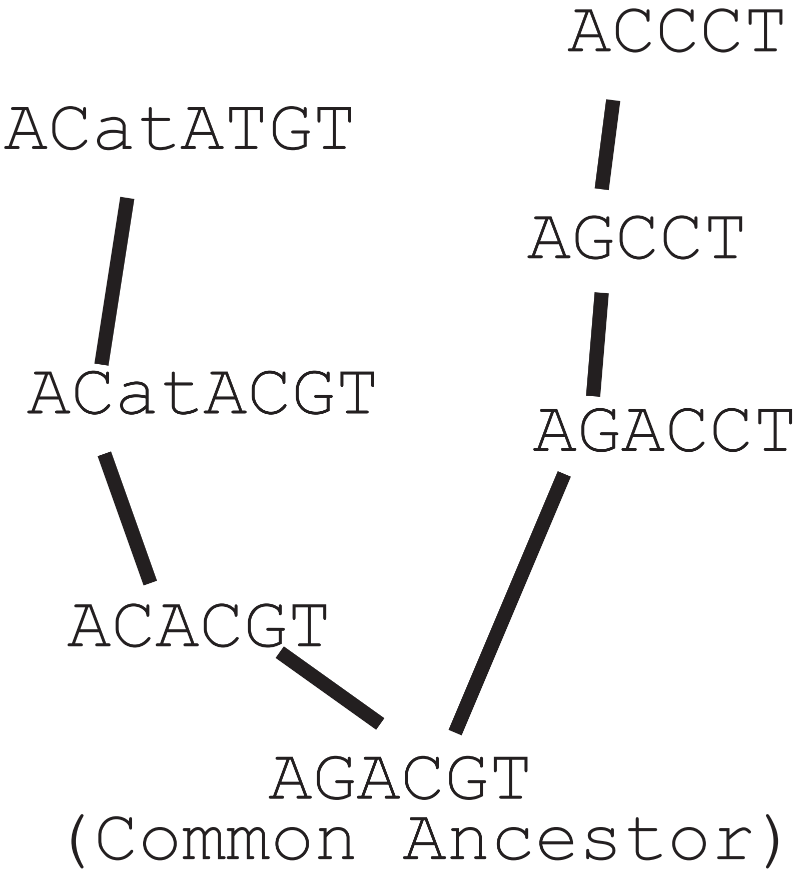


“Outgroup” = Dog “Ingroup” = Gi & Go & Ch & Hu

2. Rooting by molecular clock



All "tips" should be equally far from root



ACCCT

ACatATGT

AGCCT

ACatACGT

AGACCT

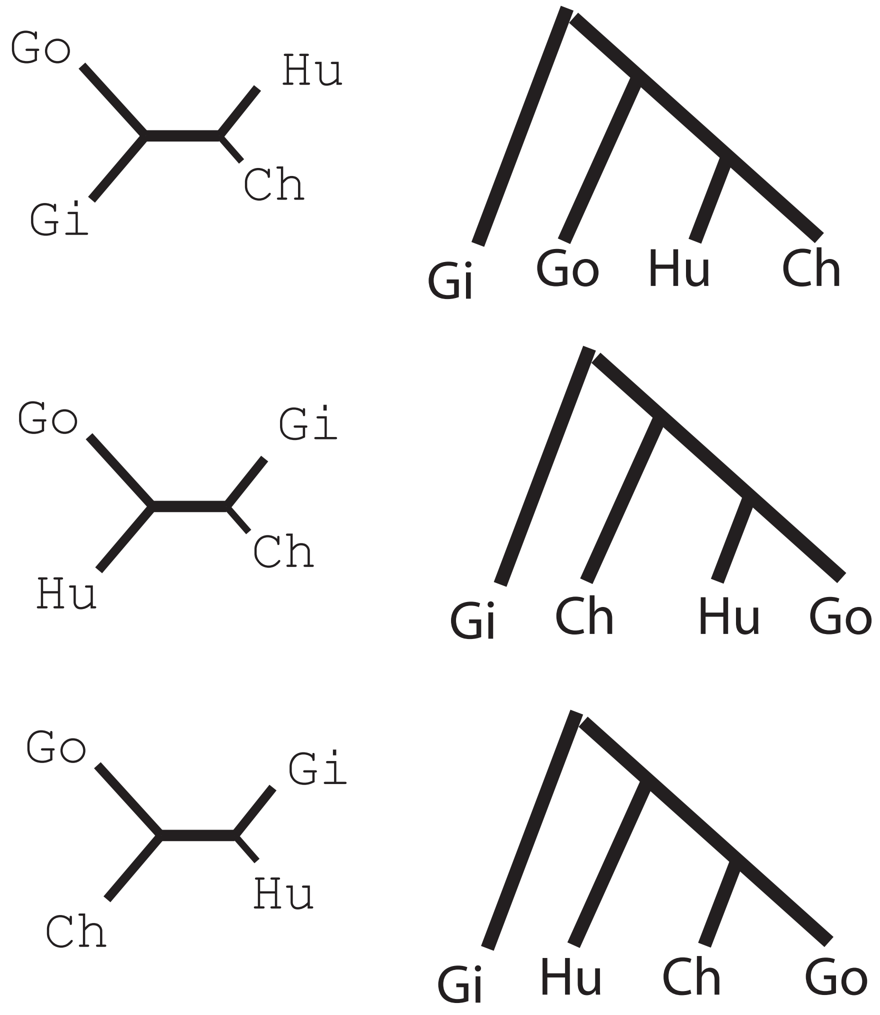
ACACGT

AGACGT
(Common Ancestor)

The "true" alignment:

```
ACATATGT
AC---CCT
```

```
     Character:  123456
(Go) Gorilla:  GAGCTC
(Gi)  Gibbon:  ACGACC
(Hu)   Human:  GAAATT
(Ch)   Chimp:  AAAATT
```



Maximum Parsimony Principle: The best explanation is the simplest.

Basic assumptions of parsimony as applied to phylogeny reconstruction:

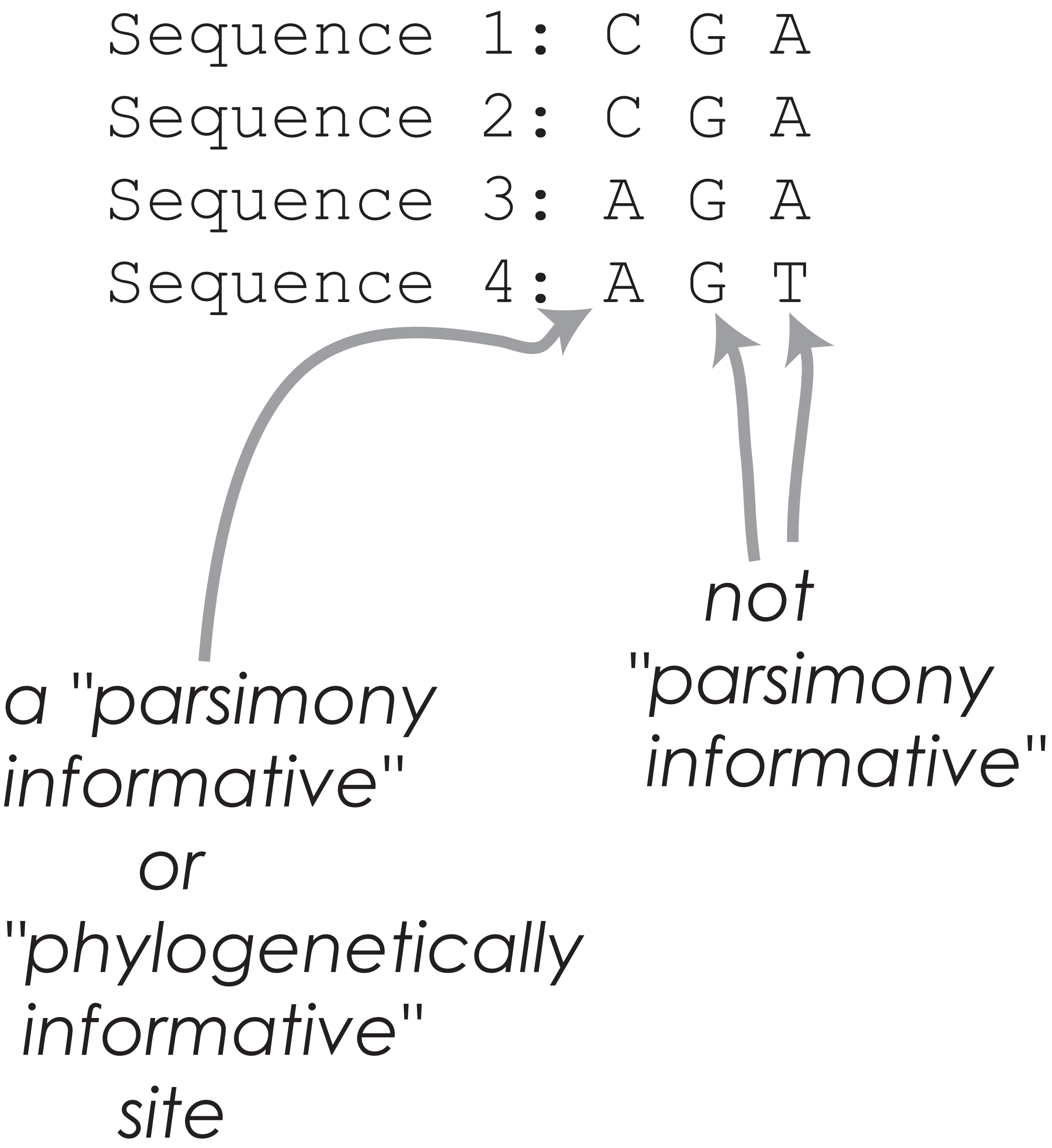
1. For a particular topology and a particular character (i.e., alignment column), the most reasonable explanation of how the character evolved on the tree is the one that requires the smallest "amount" of evolutionary change.

2. The best topology is the topology that requires the smallest "amount" of evolutionary change.

the parsimony definition of ***Phylogenetically Informative Characters*** -- characters for which the most parsimonious number of changes is different among unrooted topologies.

Characters that do not vary among taxa (sequences) are not phylogenetically informative according to parsimony.

Characters where all but one taxon have same state are not phylogenetically informative **according to parsimony**.



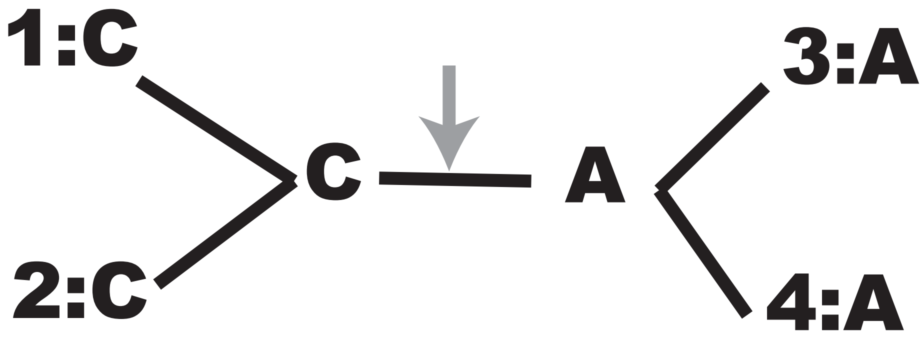
```
Sequence 1: C G A
Sequence 2: C G A
Sequence 3: A G A
Sequence 4: A G T
```

a "parsimony informative" or "phylogenetically informative" site

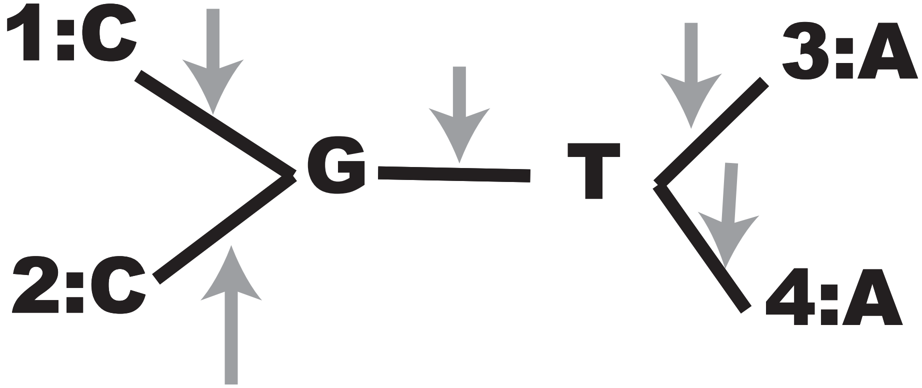
not "parsimony informative"

(column 1 will reappear on next slide)

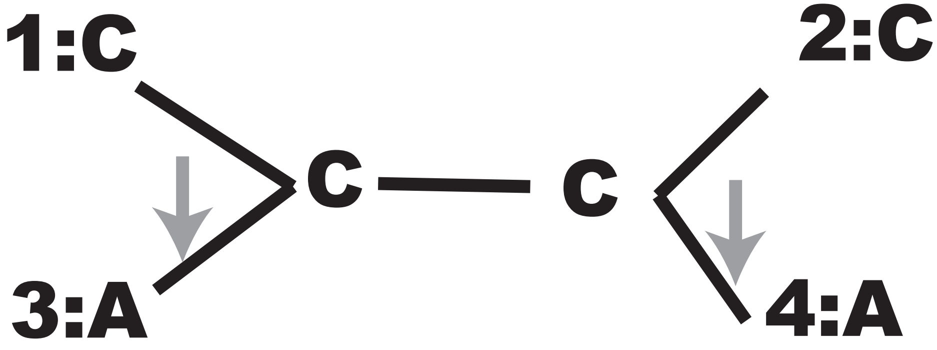
Parsimony Idea



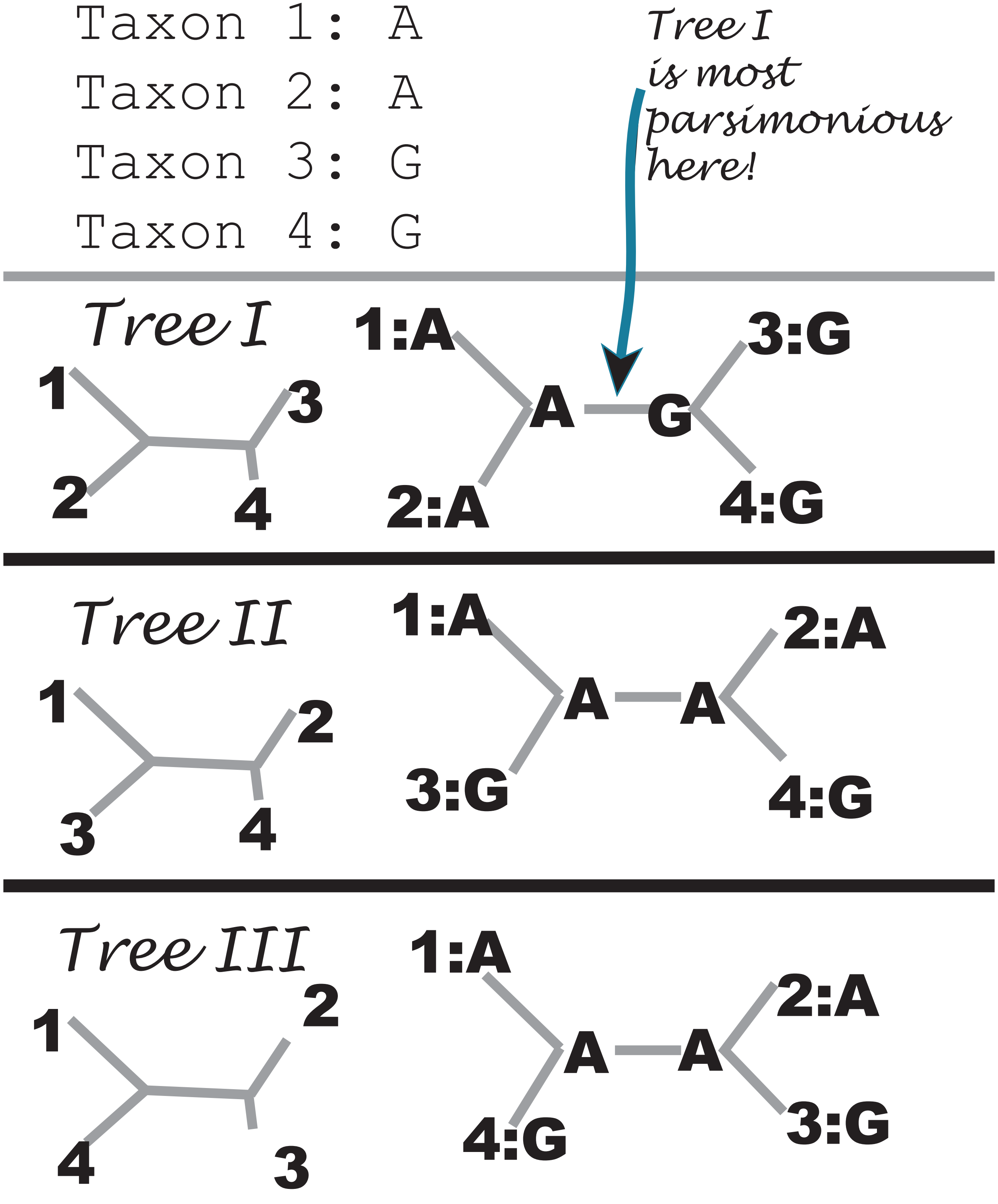
is more reasonable than



or

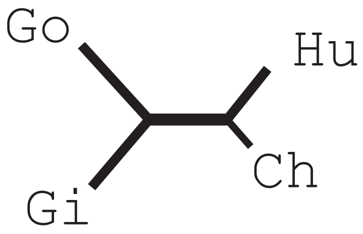


Taxon 1: A
Taxon 2: A
Taxon 3: G
Taxon 4: G

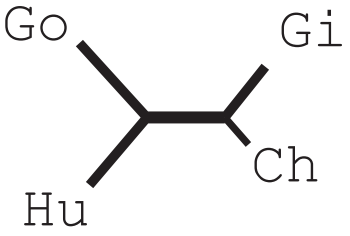


	Character:	123456
(Go)	Gorilla:	GAGCTC
(Gi)	Gibbon:	ACGACC
(Hu)	Human:	GAAATT
(Ch)	Chimp:	AAAATT

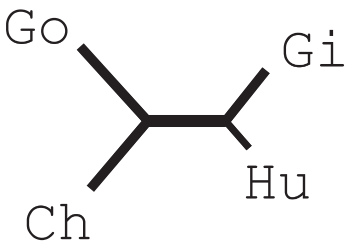
Parsimony Scores



123456: Total
211111: 7



112112: 8



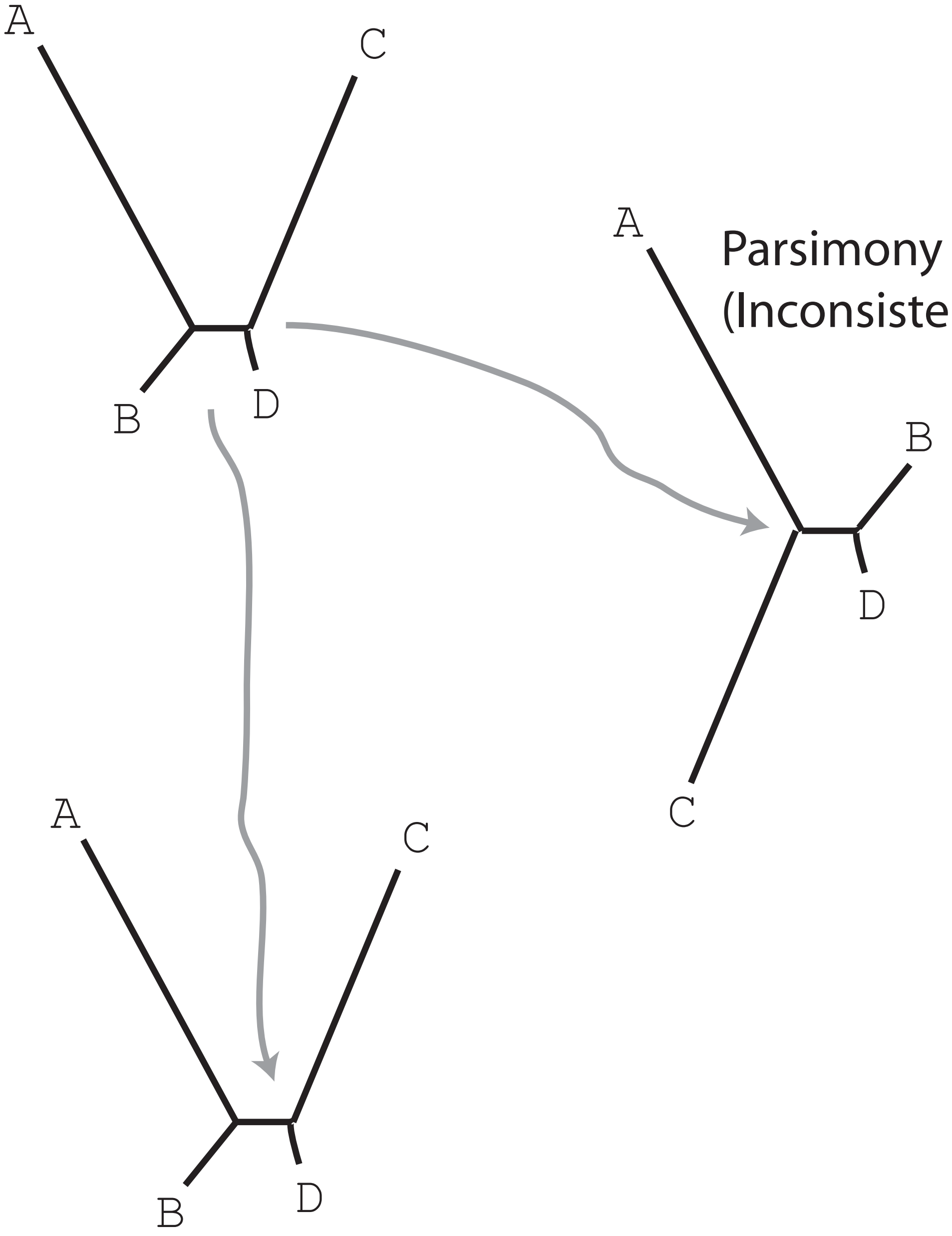
212112: 9

Step Matrices

		To			
		A	**C**	**G**	**T**
From	**A**	0	1	1	1
	C	1	0	1	1
	G	1	1	0	1
	T	1	1	1	0

Step matrix for Fitch parsimony

Slide borrowed with permission from
Paul Lewis



Parsimony Inference (Inconsistency)

Correct model of sequence evolution with maximum likelihood or with some distance-based procedures (e.g. neighbor-joining) leads to consistent inference of topology.

Distance Methods for Phylogeny Inference

Most slides courtesy of ...

Dr. Mark Holder, University of Kansas

...with a few slides courtesy of ...

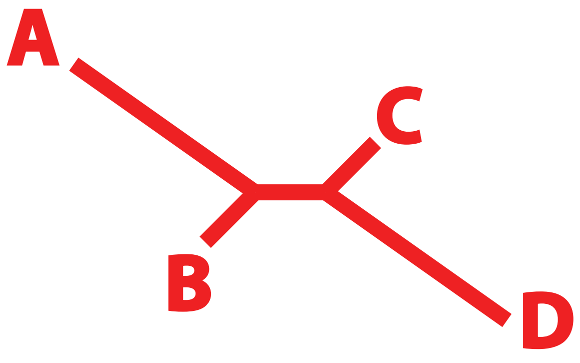
Dr. Paul Lewis, University of Connecticut

Distance-based approaches to inferring trees

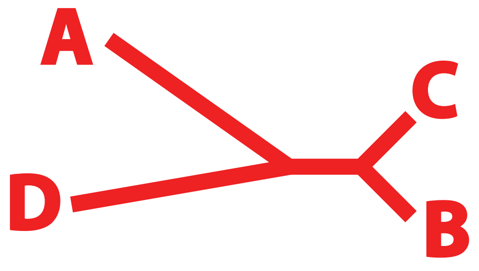
(1) Convert the raw data (sequences) to pairwise distances

(2) Find a tree that best explains these distances.

- **Do Not** simply cluster the most similar sequences



Versus



	1	2	3	4	5	6	7	8	9	10
Species 1	C	G	A	C	C	A	G	G	T	A
Species 2	C	G	A	C	C	A	G	G	T	A
Species 3	C	G	G	T	C	C	G	G	T	A
Species 4	C	G	G	C	C	A	T	G	T	A

Can be converted to a distance matrix:

	Species 1	Species 2	Species 3	Species 4
Species 1	0	0	0.3	0.2
Species 2	0	0	0.3	0.2
Species 3	0.3	0.3	0	0.3
Species 4	0.2	0.2	0.3	0

Note that the distance matrix is symmetric.

	Species 1	Species 2	Species 3	Species 4
Species 1	0	0	0.3	0.2
Species 2	0	0	0.3	0.2
Species 3	0.3	0.3	0	0.3
Species 4	0.2	0.2	0.3	0

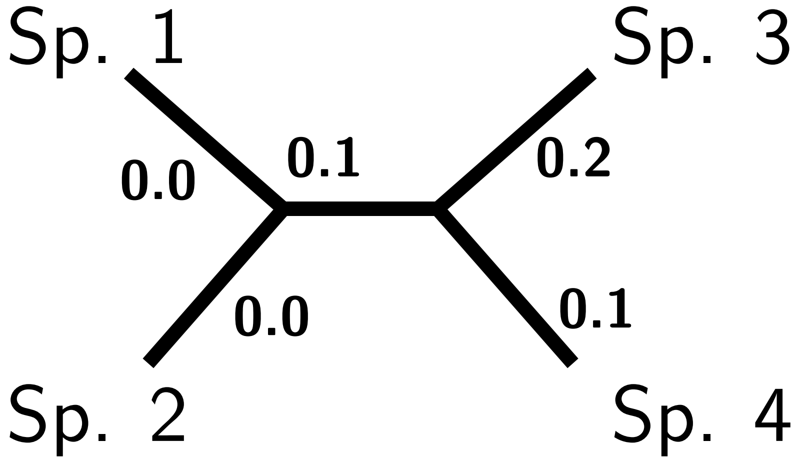
. . . so we can just use the lower triangle.

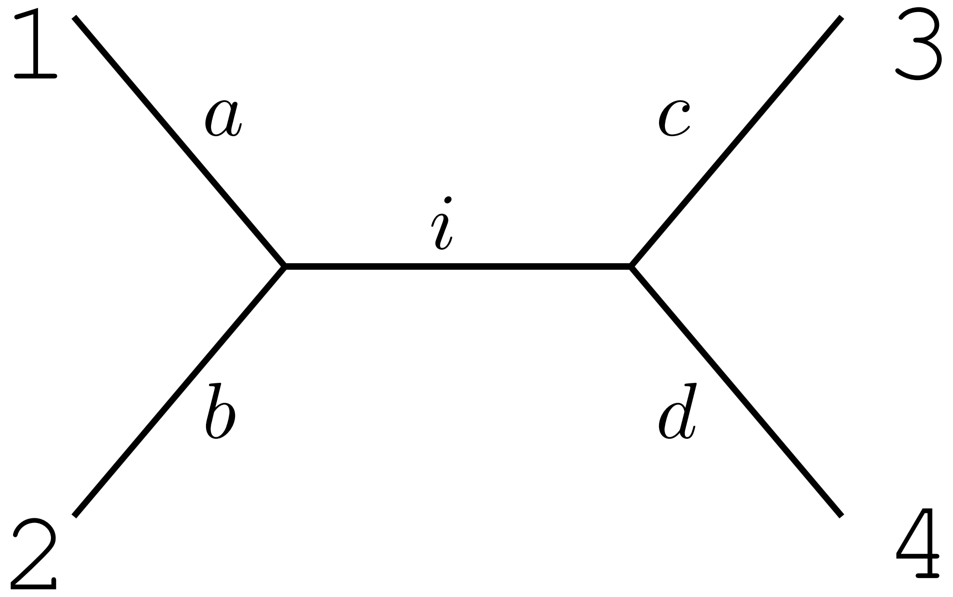
	Species 1	Species 2	Species 3
Species 2	0		
Species 3	0.3	0.3	
Species 4	0.2	0.2	0.3

Can we find a tree that would predict these observed character divergences?

	Species 1	Species 2	Species 3
Species 2	0		
Species 3	0.3	0.3	
Species 4	0.2	0.2	0.3

Can we find a tree that would predict these observed character divergences?





parameters

$$p_{12} = a + b$$
$$p_{13} = a + i + c$$
$$p_{14} = a + i + d$$
$$p_{23} = b + i + c$$
$$p_{23} = b + i + d$$
$$p_{34} = c + d$$

data

	1	2	3
2	d_{12}		
3	d_{13}	d_{23}	
4	d_{14}	d_{24}	d_{34}

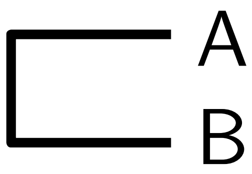
Why doesn't simple clustering work?

Step 1: use sequences to estimate pairwise distances between taxa.

	A	B	C	D
A	-	0.2	0.5	0.4
B		-	0.46	0.4
C			-	0.7
D				-

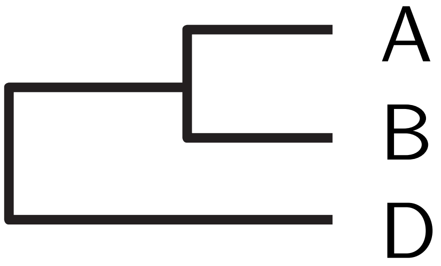
Why doesn't simple clustering work?

	A	B	C	D
A	-	**0.2**	0.5	0.4
B		-	0.46	0.4
C			-	0.7
D				-



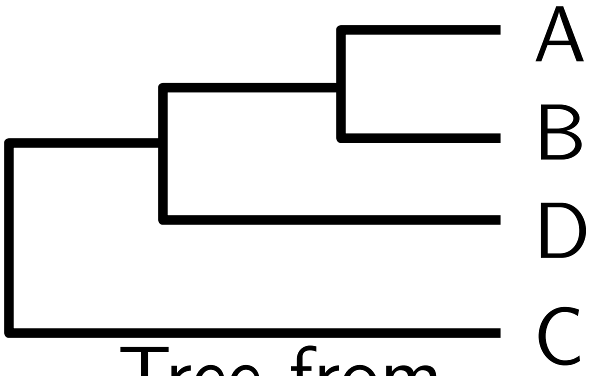
Why doesn't simple clustering work?

	A	B	C	D
A	-	0.2	0.5	**0.4**
B		-	0.46	**0.4**
C			-	0.7
D				-



Why doesn't simple clustering work?

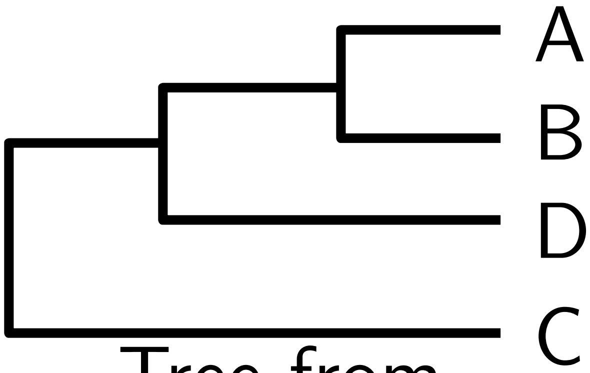
	A	B	C	D
A	-	0.2	0.5	**0.4**
B		-	0.46	**0.4**
C		-	-	**0.7**
D				0



Tree from clustering

Why doesn't simple clustering work?

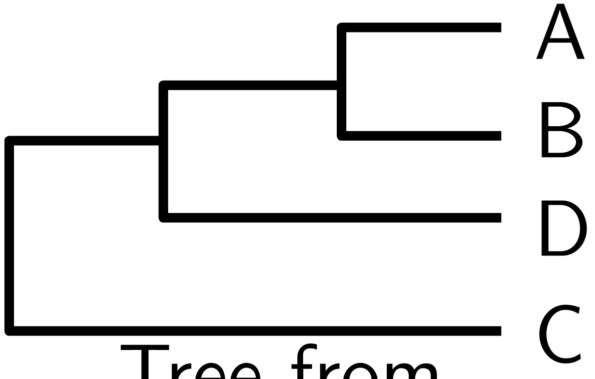
	A	B	C	D
A	0	0.2	**0.5**	0.4
B	0.2	0.2	**0.46**	0.4
C	**0.5**	**0.46**	0	**0.7**
D	0.4	0.4	**0.7**	0



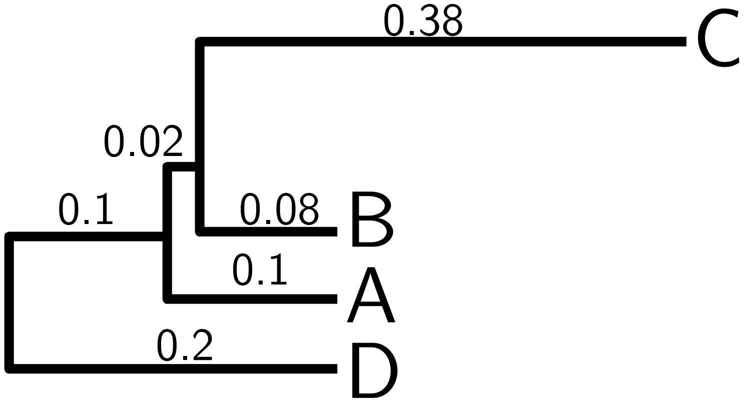
Tree from clustering

Why doesn't simple clustering work?

	A	B	C	D
A	0	0.2	0.5	0.4
B	0.2	0.	0.46	0.4
C	0.5	0.46	0	0.7
D	0.4	0.4	0.7	0



Tree from clustering

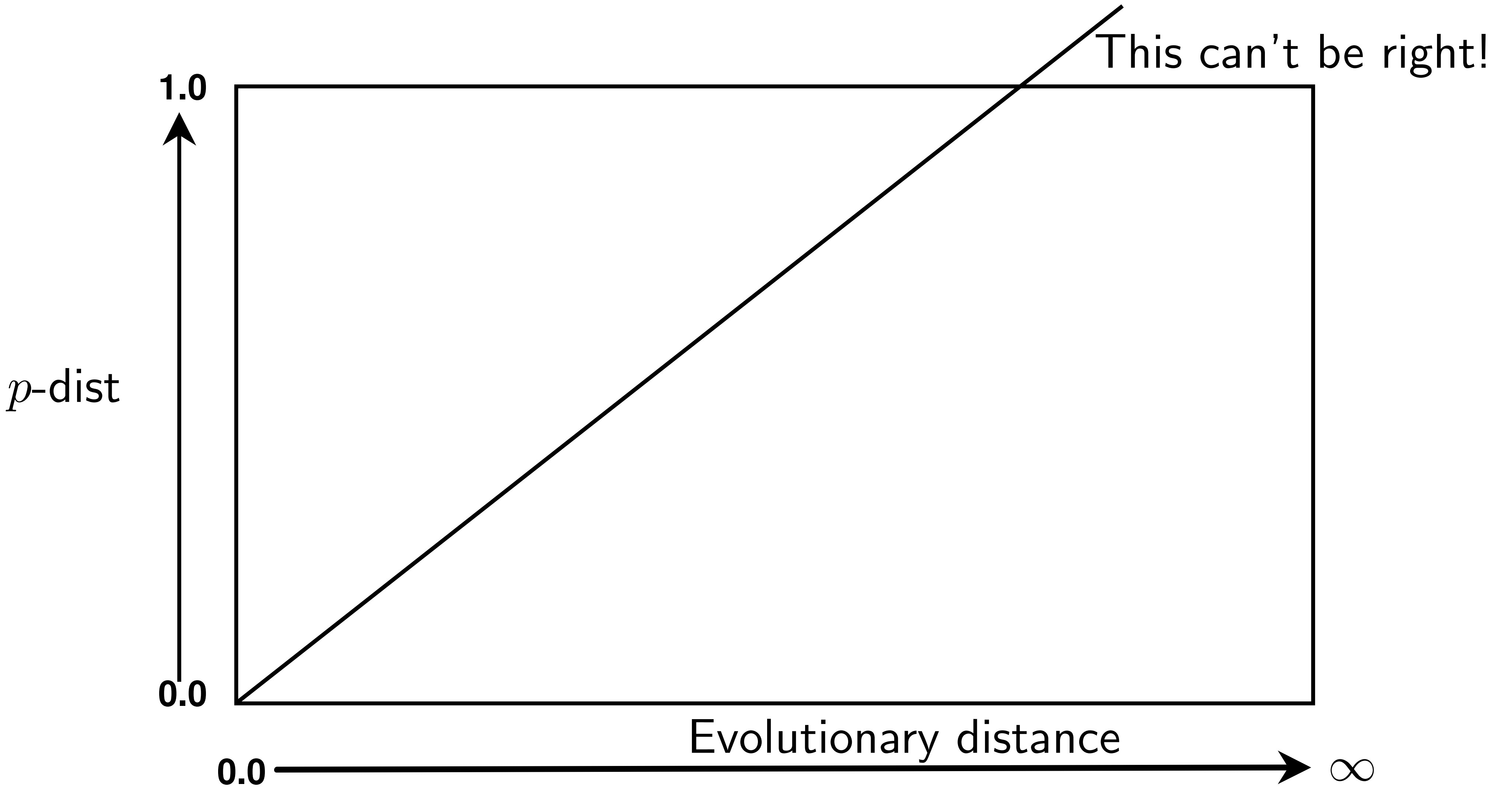


Tree with perfect fit

p-distance = proportion of positions that
are different in 2 sequences.

Hamming distance = number of positions
at which two sequences
(”strings”) differ.

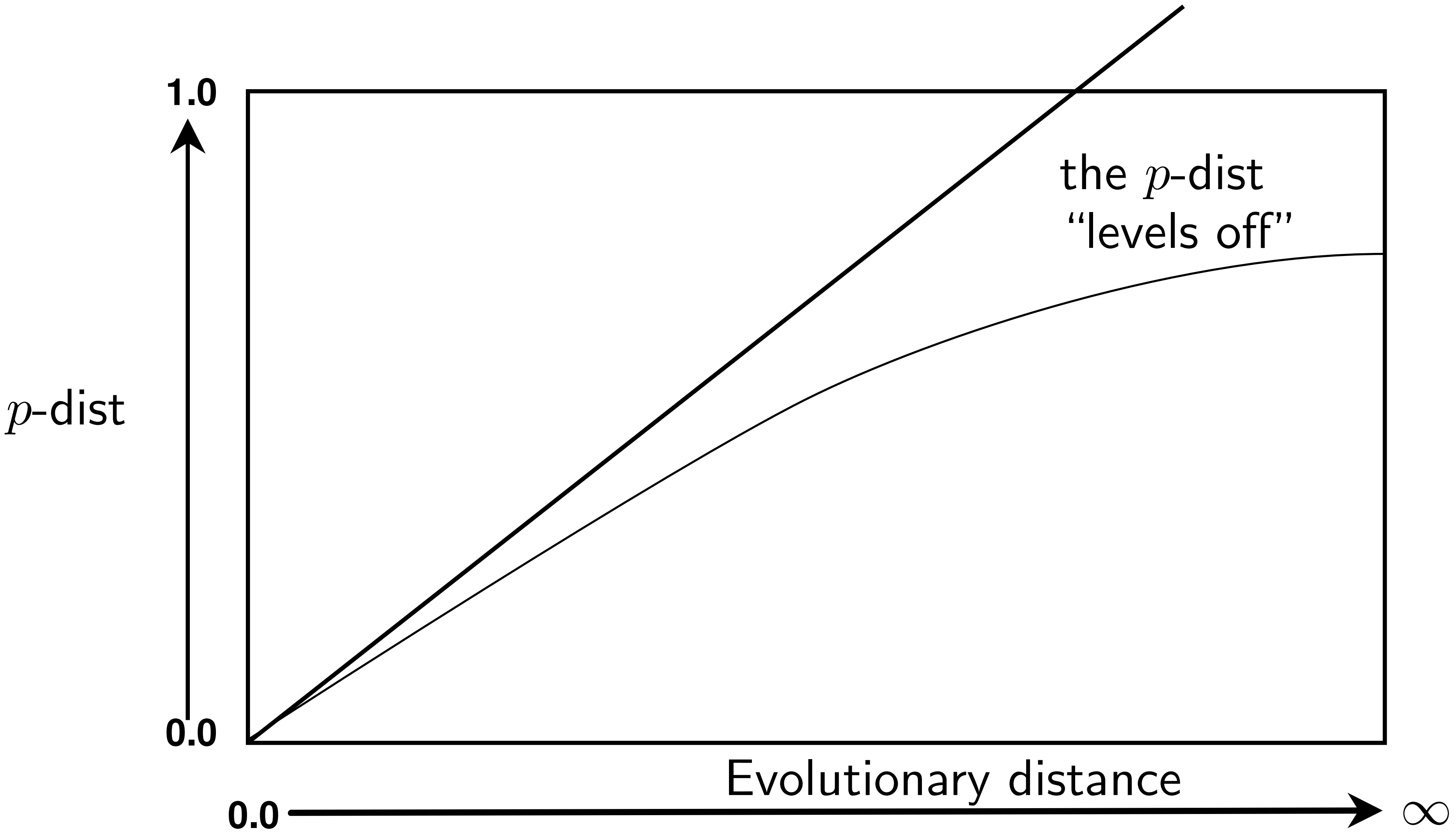
Intuition of sequence divergence vs evolutionary distance



“Multiple hits” problem (also known as saturation)

- Levelling off of sequence divergence vs time plot is caused by multiple substitutions affecting the same site in the DNA.
- At large distances the “raw” sequence divergence (also known as the p-distance or Hamming distance) is a poor estimate of the true evolutionary distance.
- Statistical models must be used to correct for unobservable substitutions
- Large p-distances respond more to model-based correction – and there is a larger error associated with the correction.

Sequence divergence vs evolutionary distance



Besides parsimony and distance-based methods for inferring evolutionary trees, there are two additional widely-used categories of methods.

Both of the other two rely on probabilistic models of sequence change and they therefore have some connection to each other.

One of these categories of method is known as maximum likelihood and the other is known as Bayesian inference.

Bayesian inference and maximum likelihood methods are more statistically sound than parsimony and distance-based methods.

Maximum likelihood uses only the probabilistic model and the data. Bayesian inference uses these plus prior information.

However, they are both computationally more demanding and so sometimes data sets are too big to use them.

Phylogeny Reconstruction is computationally difficult

Number of Tips	Number of Rooted Trees	Number of Unrooted Trees
2	1	1
3	3	1
4	15	3
5	105	15
6	945	105
7	10,395	945
8	135,135	10,395
9	2,027,025	135,135
10	34,459,425	2,027,025
...		
N	$\frac{(2N-5)!}{2^{N-3}\ (N-3)!}$	$\frac{(2N-3)!}{2^{N-2}\ (N-2)!}$