Consistency Index (CI)

- minimum number of changes divided by the number required on the tree.
- CI=1 if there is no homoplasy
- negatively correlated with the number of species sampled

Retention Index (RI)

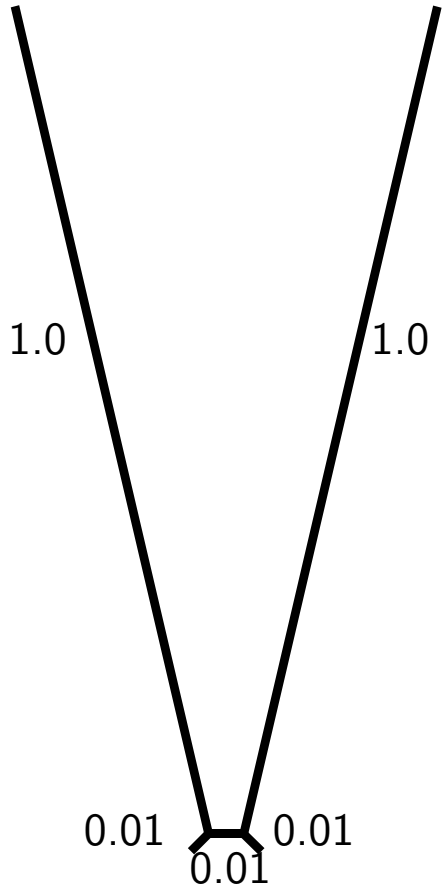
$$\mathrm{RI} = \frac{\mathrm{MaxSteps} - \mathrm{ObsSteps}}{\mathrm{MaxSteps} - \mathrm{MinSteps}}$$

- defined to be 0 for parsimony uninformative characters
- RI=1 if the character fits perfectly
- RI=0 if the tree fits the character as poorly as possible

Qualitative description of parsimony

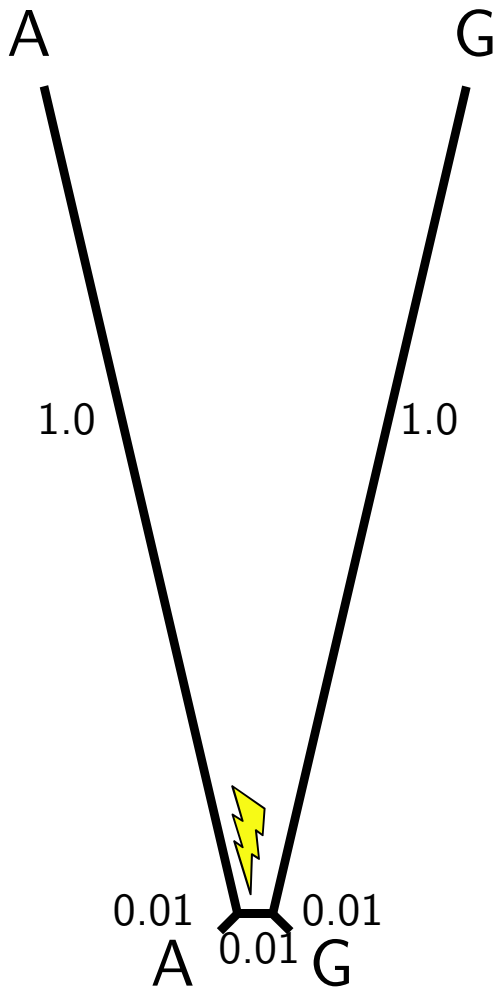
- Enables estimation of ancestral sequences.
- Even though parsimony always seeks to minimizes the number of changes, it can perform well even when changes are not rare.
- Does not "prefer" to put changes on one branch over another
- Hard to characterize statistically
  - the set of conditions in which parsimony is guaranteed to work well is very restrictive (low probability of change and not too much branch length heterogeneity);
  - Parsimony often performs well in simulation studies (even when outside the zones in which it is guaranteed to work);
  - Estimates of the tree can be extremely biased.

Long branch attraction



Felsenstein, J. 1978. Cases in which parsimony or compatibility methods will be positively misleading. *Systematic Zoology* **27**: 401-410.

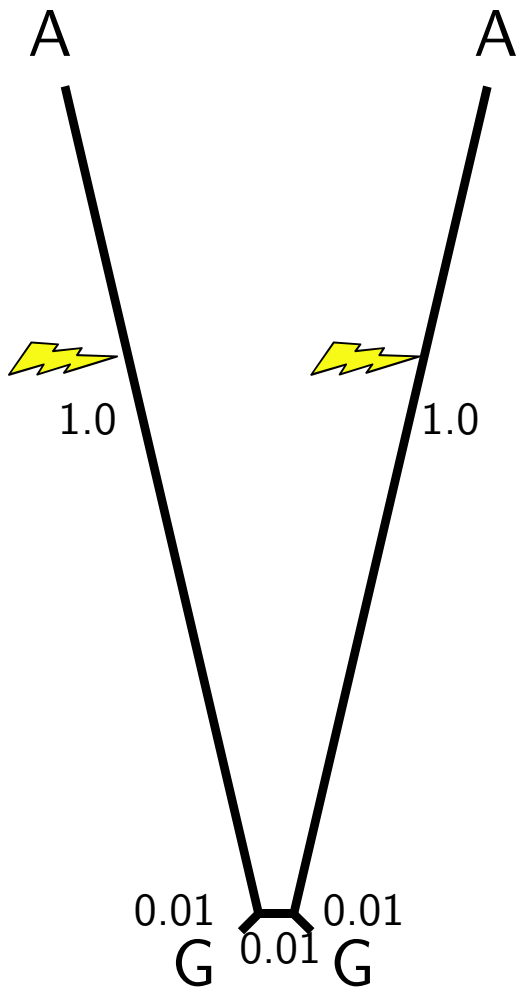
Long branch attraction



Felsenstein, J. 1978. Cases in which parsimony or compatibility methods will be positively misleading. *Systematic Zoology* **27**: 401-410.

The probability of a parsimony informative site due to inheritance is very low, (roughly 0.0003).

Long branch attraction



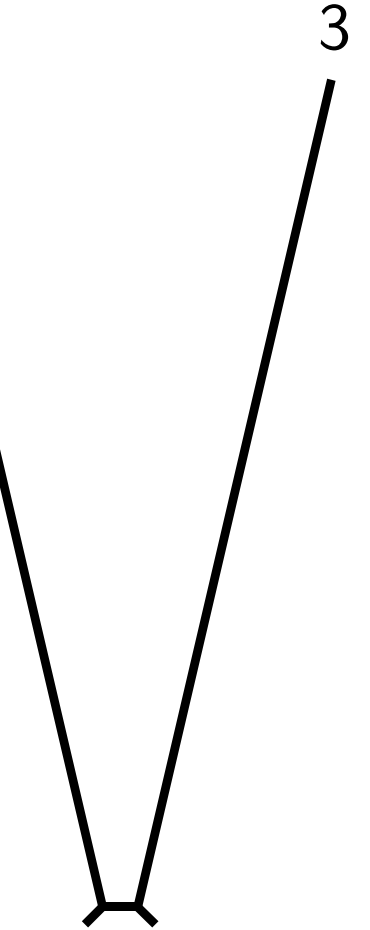
Felsenstein, J. 1978. Cases in which parsimony or compatibility methods will be positively misleading. *Systematic Zoology* **27**: 401-410.

The probability of a parsimony informative site due to inheritance is very low, (roughly 0.0003).

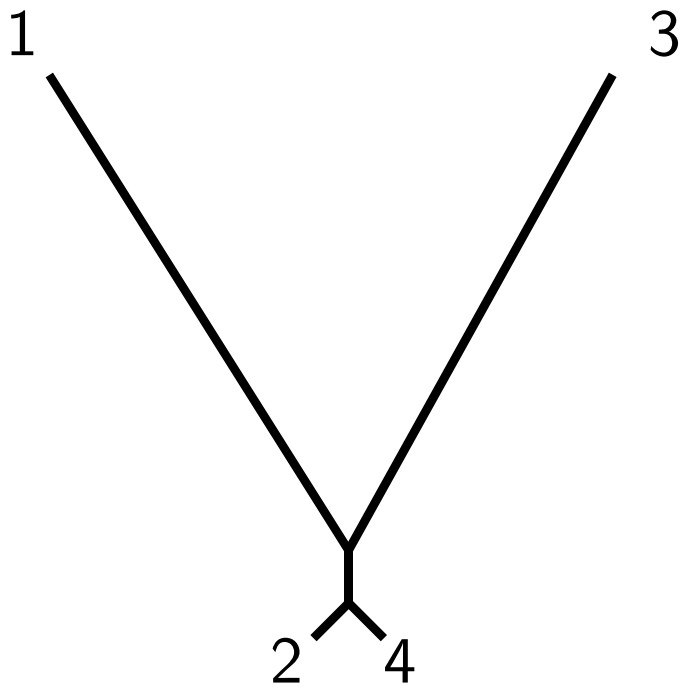
The probability of a misleading parsimony informative site due to parallelism is much higher (roughly 0.008).

Long branch attraction

Parsimony is almost guaranteed to get this tree wrong.



True



Inferred

Inconsistency

- Statistical Consistency (roughly speaking) is converging to the true answer as the amount of data goes to ∞.

- Parsimony based tree inference is *not* consistent for some tree shapes. In fact it can be "positively misleading":
  - "Felsenstein zone" tree
  - Many clocklike trees with short internal branch lengths and long terminal branches (Penny *et al.*, 1989, Huelsenbeck and Lander, 2003).

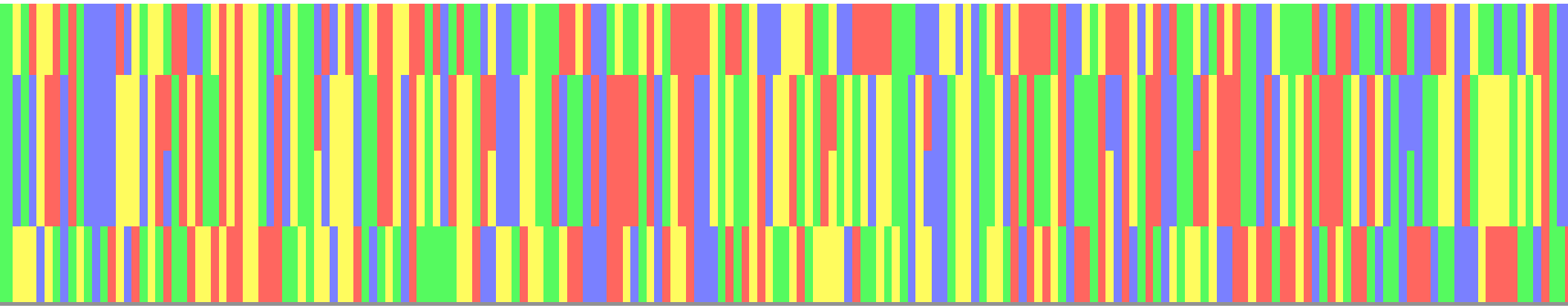
- Methods for assessing confidence (e.g. bootstrapping) will indicate that you should be very confident in the wrong answer.

If the data is generated such that:

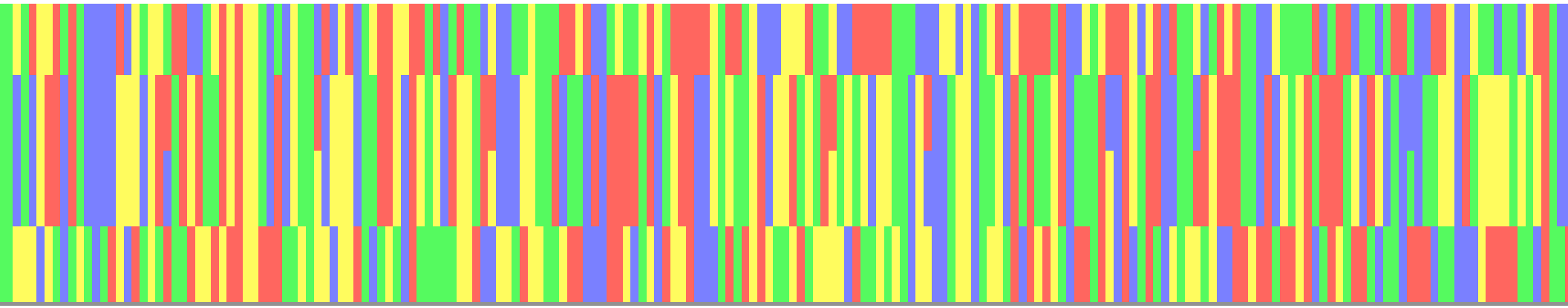
$$\Pr\begin{pmatrix} A \\ A \\ G \\ G \end{pmatrix} \approx 0.0003 \quad \text{and} \quad \Pr\begin{pmatrix} A \\ G \\ G \\ A \end{pmatrix} \approx 0.008$$

then how can we hope to infer the tree ((1,2),3,4) ?

Looking at the data in "bird's eye" view (using Mesquite):



Looking at the data in "bird's eye" view (using Mesquite):



We see that sequences 1 and 4 are clearly very different.
Perhaps we can estimate the tree if we use the branch length information from the sequences...

Distance-based approaches to inferring trees

- Convert the raw data (sequences) to a pairwise distances
- Try to find a tree that explains these distances.
- *Not* simply clustering the most similar sequences.

	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

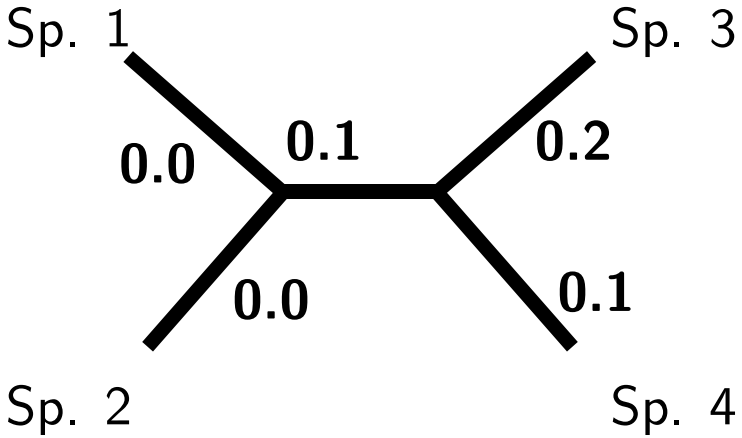
. . . so we can just use the lower triangle.

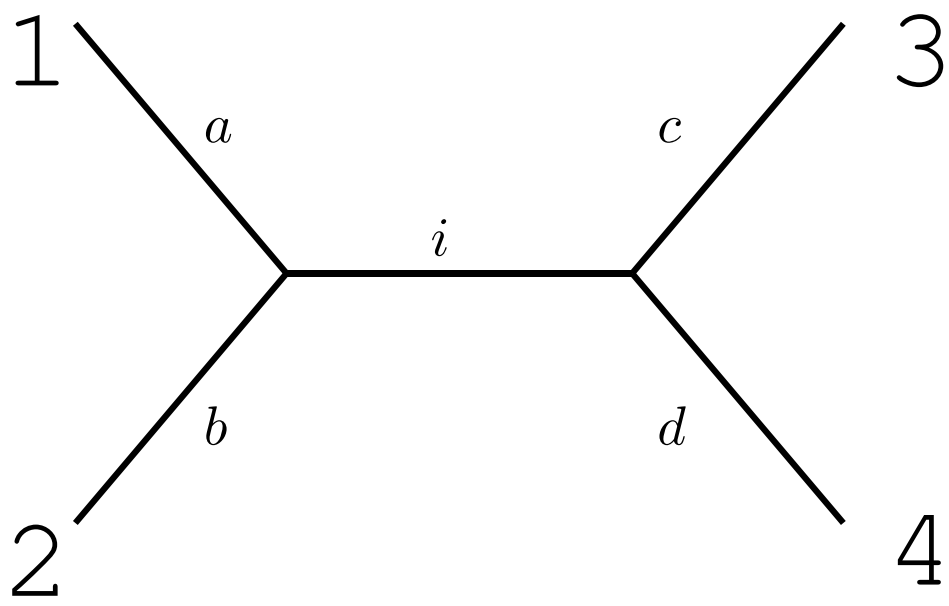
	Species 1	Species 2	Species 3
Species 2	0		
Species 3	0.3	0.3	
Species 4	0.2	0.2	0.3

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

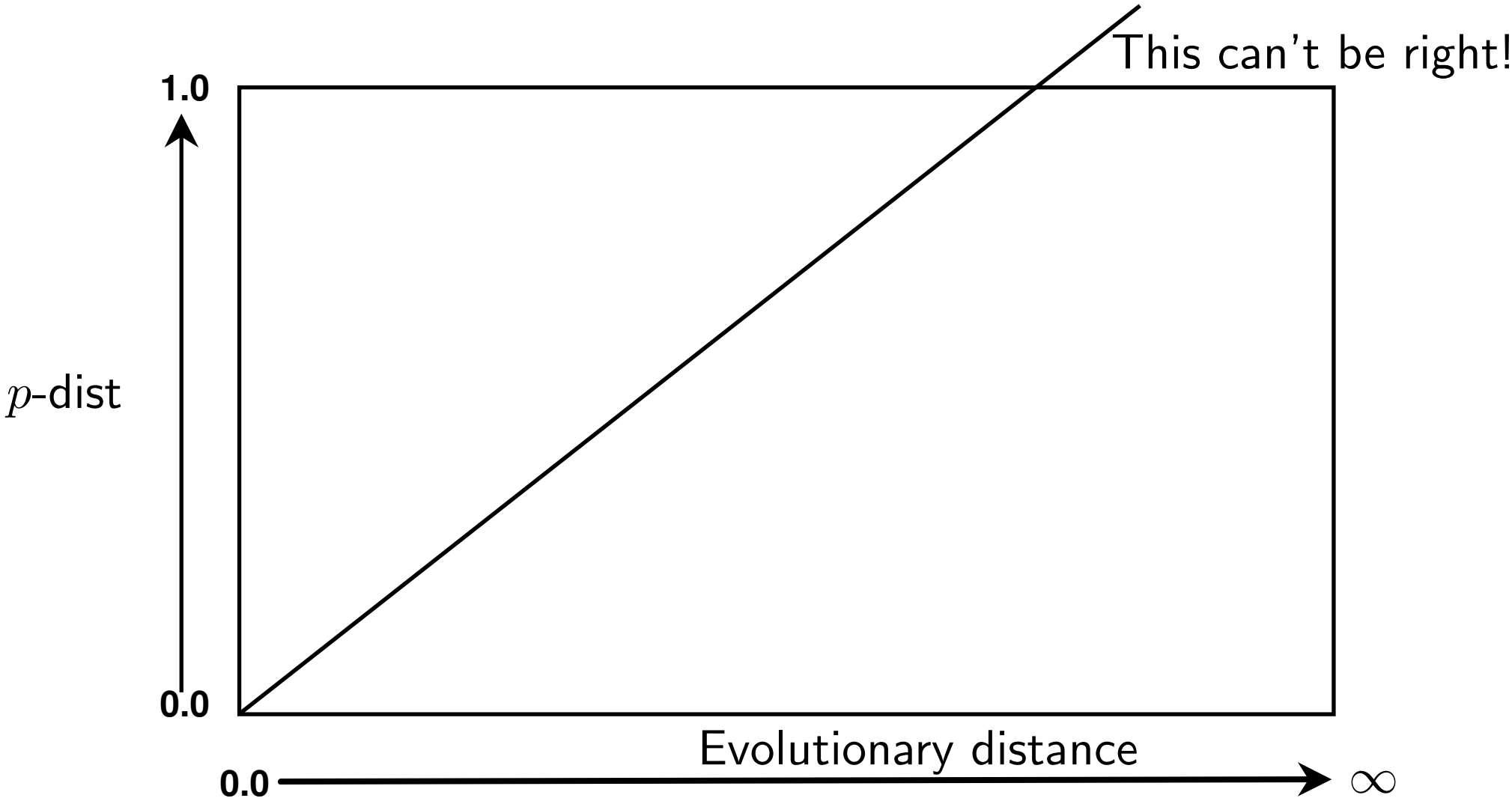
	1	2	3
2	d_{12}		
3	d_{13}	d_{23}	
4	d_{14}	d_{24}	d_{34}

If our pairwise distance measurements were error-free estimates of the *evolutionary distance* between the sequences, then we could always infer the tree from the distances.

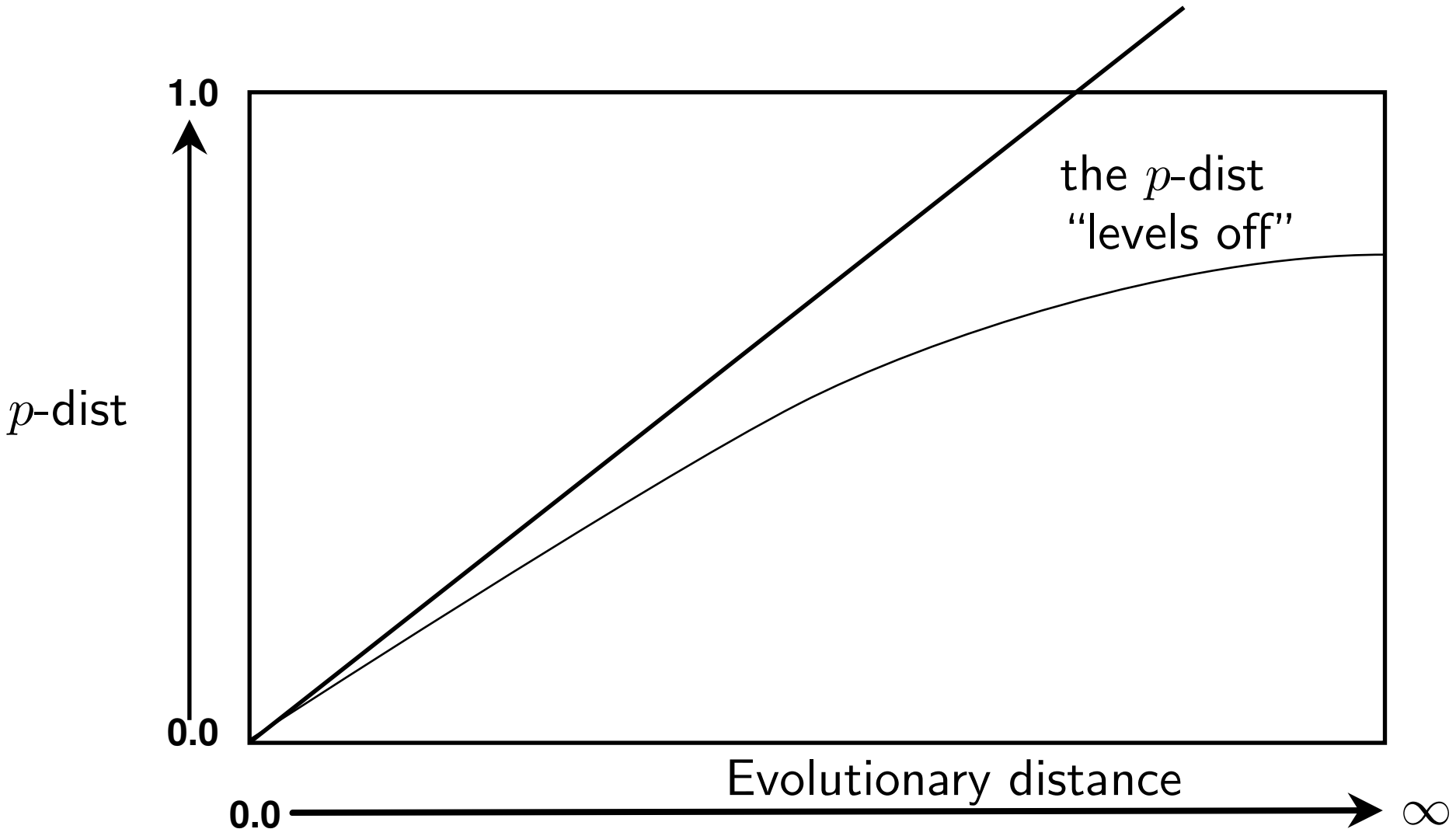
The evolutionary distance is the number of mutations that have occurred along the path that connects two tips.

We hope the distances that we measure can produce good estimates of the evolutionary distance, but we know that they cannot be perfect.

Intuition of sequence divergence vs evolutionary distance

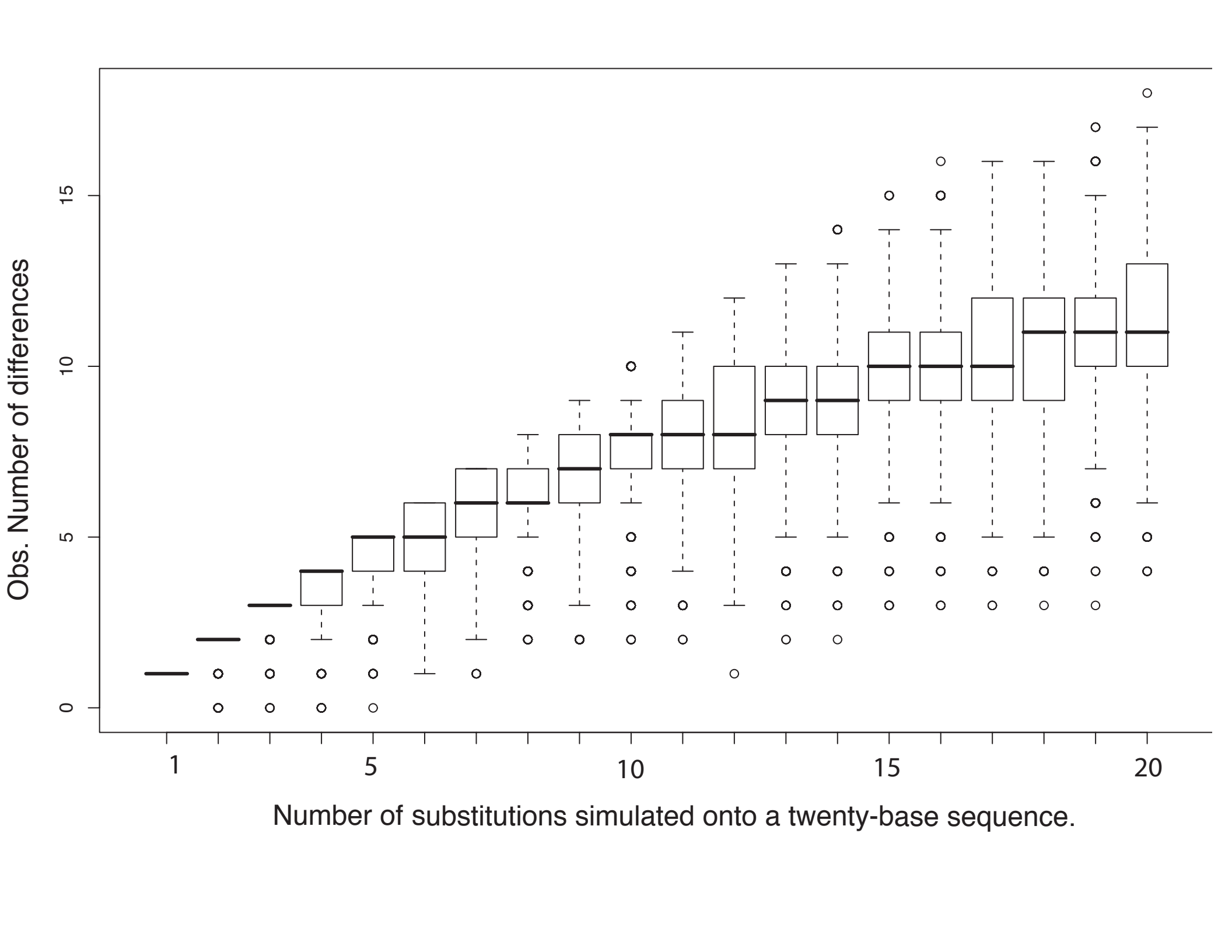


Sequence divergence vs evolutionary distance



"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.
- Large p-distances respond more to model-based correction – and there is a larger error associated with the correction.


Obs. Number of differences
0
5
10
15
1
5
10
15
20
Number of substitutions simulated onto a twenty-base sequence.

Distance corrections

- applied to distances before tree estimation,
- converts raw distances to an estimate of the evolutionary distance

$$d = -\frac{3}{4} \ln\left(\frac{4c}{3} - 1\right)$$

"raw" p-distances

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

corrected distances

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

$$d = -\frac{3}{4} \ln\left(1 - \frac{4c}{3}\right)$$

"raw" p-distances

	1	2	3
2	0.0		
3	0.3	0.3	
4	0.2	0.2	0.3

corrected distances

	1	2	3
2	0		
3	0.383	0.383	
4	0.233	0.233	0.383

Least Squares Branch Lengths

$$\text{Sum of Squares} = \sum_i \sum_j \frac{(p_{ij} - d_{ij})^2}{\sigma_{ij}^k}$$

- minimize discrepancy between path lengths and observed distances
- σ_{ij}^k is used to "downweight" distance estimates with high variance

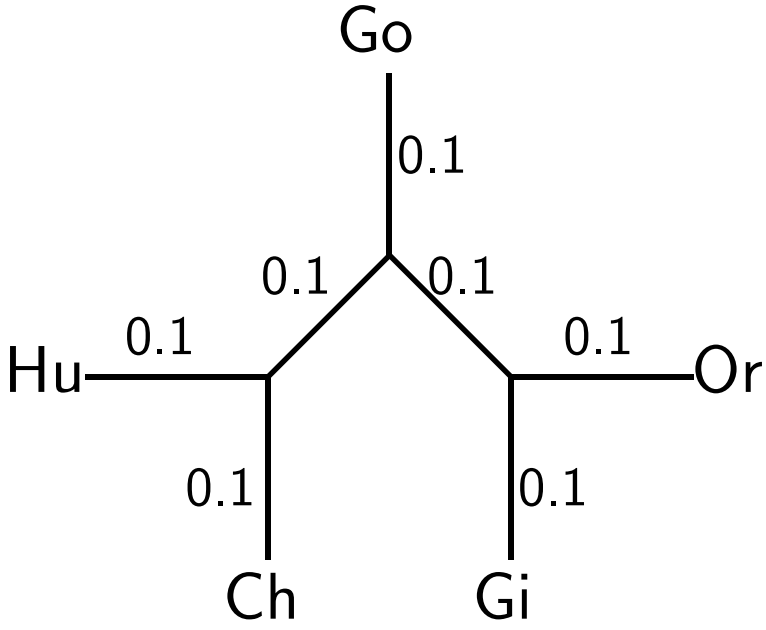
Least Squares Branch Lengths

$$\text{Sum of Squares} = \sum_i \sum_j \frac{(p_{ij} - d_{ij})^2}{\sigma_{ij}^k}$$

- in unweighted least-squares (Cavalli-Sforza & Edwards, 1967): $k = 0$
- in the method Fitch-Margoliash (1967): $k = 2$ and $\sigma_{ij} = d_{ij}$

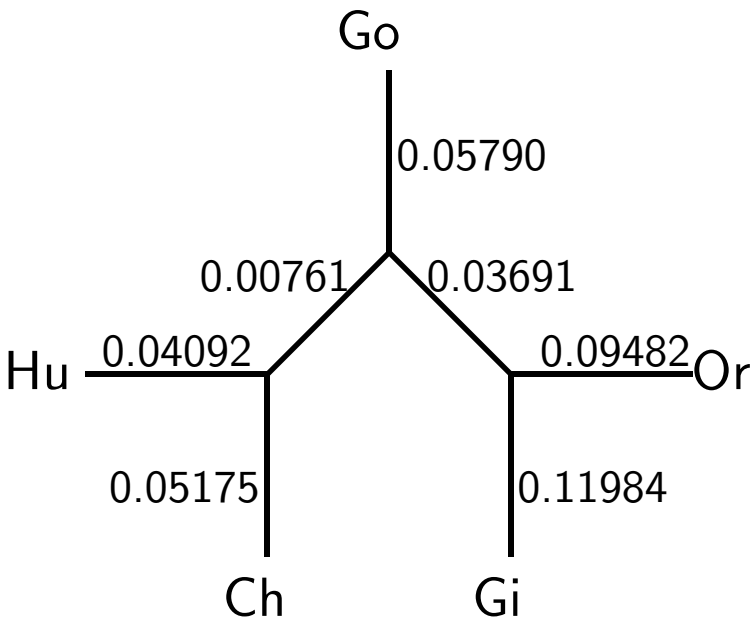
Poor fit using arbitrary branch lengths

Species	d_{ij}	p_{ij}	$(p-d)^2$
Hu-Ch	0.09267	0.2	0.01152
Hu-Go	0.10928	0.3	0.03637
Hu-Or	0.17848	0.4	0.04907
Hu-Gi	0.20420	0.4	0.03834
Ch-Go	0.11440	0.3	0.03445
Ch-Or	0.19413	0.4	0.04238
Ch-Gi	0.21591	0.4	0.03389
Go-Or	0.18836	0.3	0.01246
Go-Gi	0.21592	0.3	0.00707
Or-Gi	0.21466	0.2	0.00021
		S.S.	**0.26577**

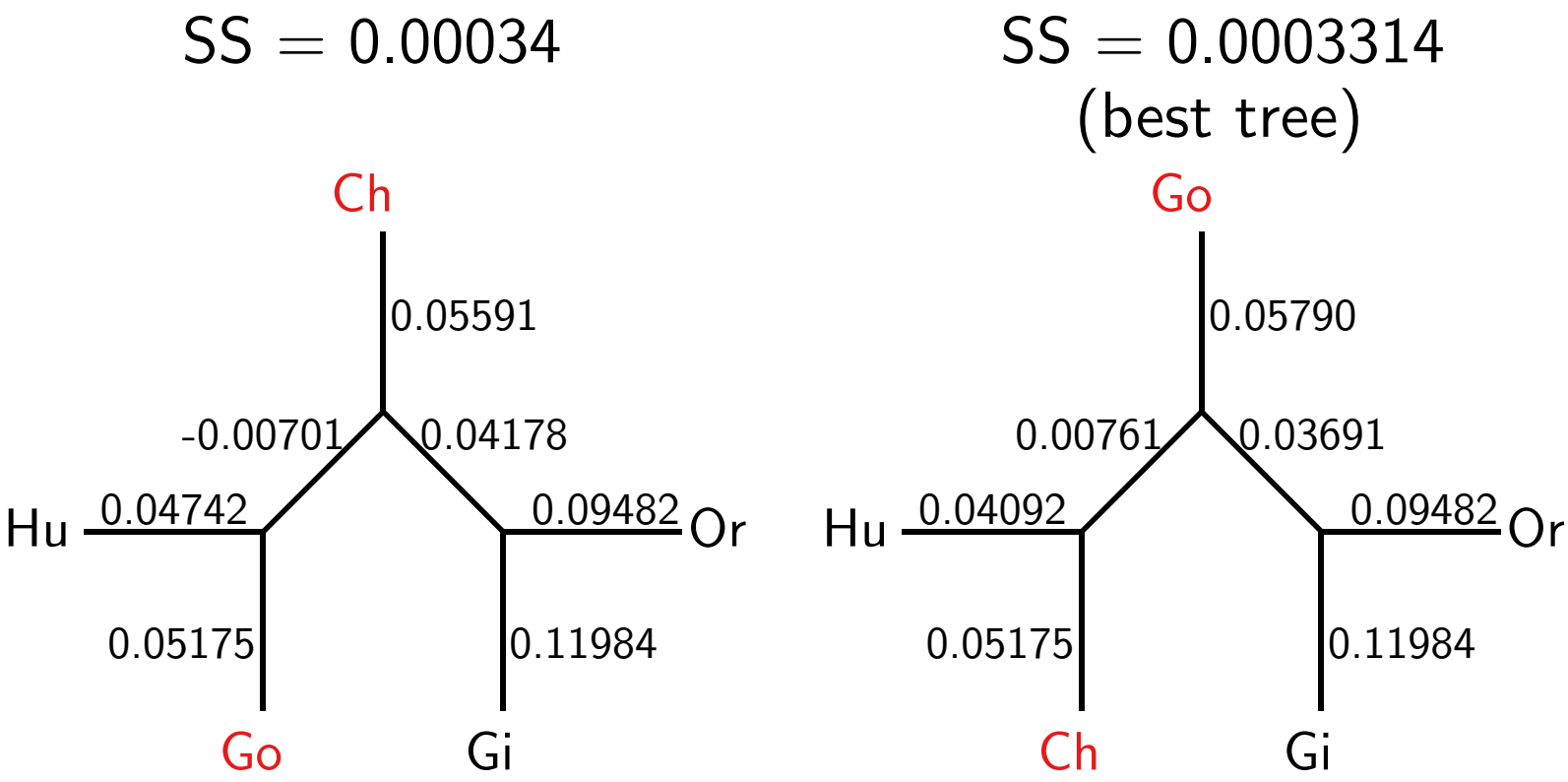


Optimizing branch lengths yields the least-squares score

Species	d_{ij}	p_{ij}	$(p-d)^2$
Hu-Ch	0.09267	0.09267	0.000000000
Hu-Go	0.10928	0.10643	0.000008123
Hu-Or	0.17848	0.18026	0.000003168
Hu-Gi	0.20420	0.20528	0.000001166
Ch-Go	0.11440	0.11726	0.000008180
Ch-Or	0.19413	0.19109	0.000009242
Ch-Gi	0.21591	0.21611	0.000000040
Go-Or	0.18836	0.18963	0.000001613
Go-Gi	0.21592	0.21465	0.000001613
Or-Gi	0.21466	0.21466	0.000000000
		S.S.	**0.000033144**

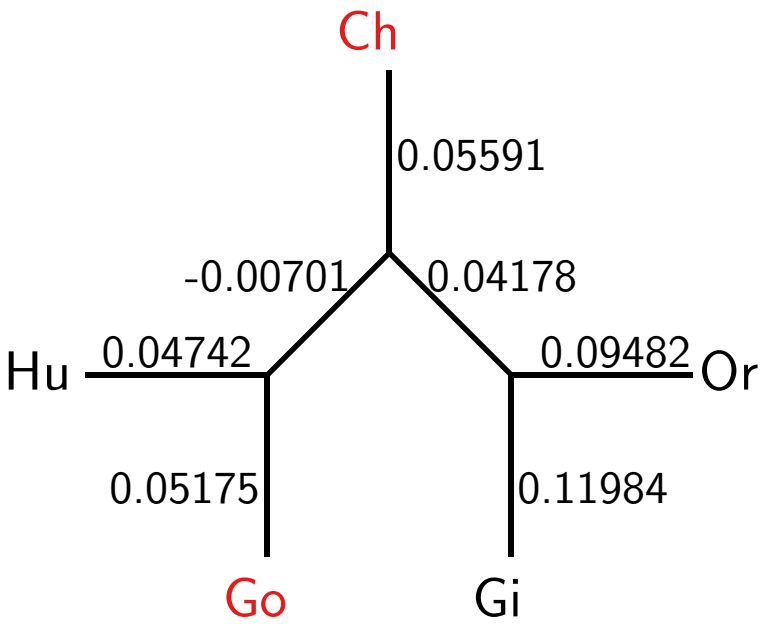


Least squares as an optimality criterion

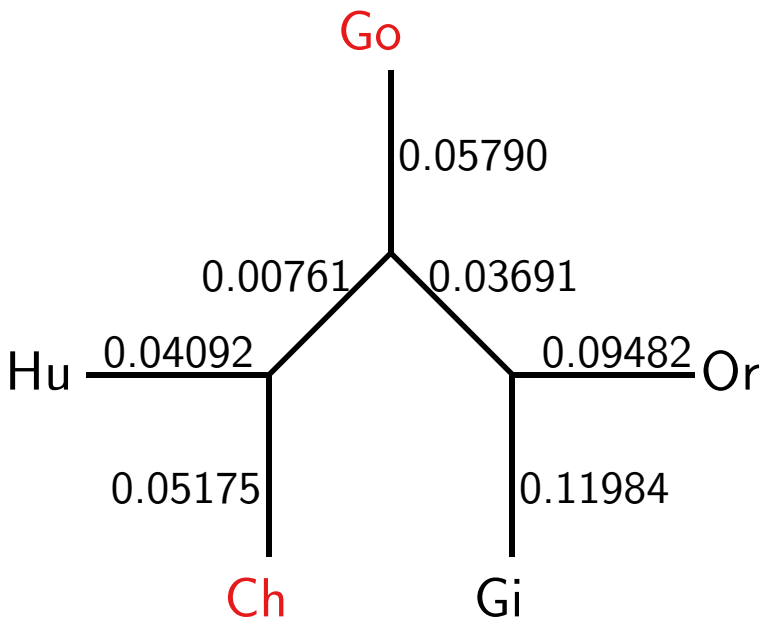


Minimum evolution optimality criterion

Sum of branch lengths
=0.41152



Sum of branch lengths
=0.40975
(best tree)



We still use least squares branch lengths when we use Minimum Evolution

Huson and Steel – distances that perfectly mislead

Huson and Steel (2004) point out problems when our pairwise distances have errors (do not reflect true evolutionary distances). Consider:

Taxon	Characters						
A	A	A	C	A	A	C	C
B	A	C	A	C	C	A	A
C	C	A	G	G	G	A	A
D	C	G	A	A	A	G	G

Taxa	Taxa			
	A	B	C	D
A	-	6	6	5
B	6	-	5	6
C	6	5	-	6
D	5	6	6	-

Homoplasy-free on tree $AB|CD$, but additive on tree $AD|BC$ (and not additive on any other tree).

Huson and Steel – distances that perfectly mislead

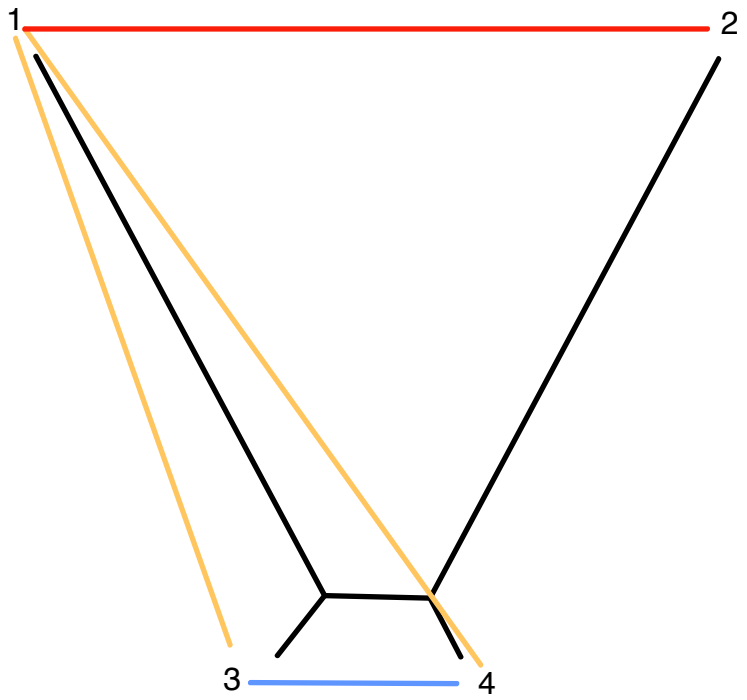
Clearly, the previous matrix was contrived and not typical of realistic data.
Would we ever expect to see additive distances on the **wrong** tree as the result of a reasonable evolutionary process?

Yes.

Huson and Steel (2004) show that under the equal-input model(more on this later), the **uncorrected** distances can be additive on the wrong tree leading to long-branch attraction. The result holds even if the number of characters $\rightarrow \infty$

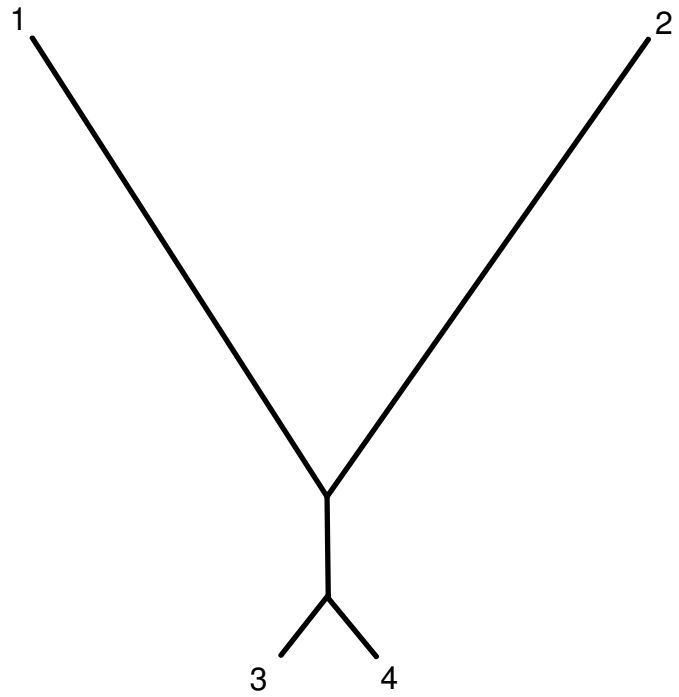
Failure to correct distance sufficiently leads to poor performance

"Under-correcting" will underestimate long evolutionary distances more than short distances



Failure to correct distance sufficiently leads to poor performance

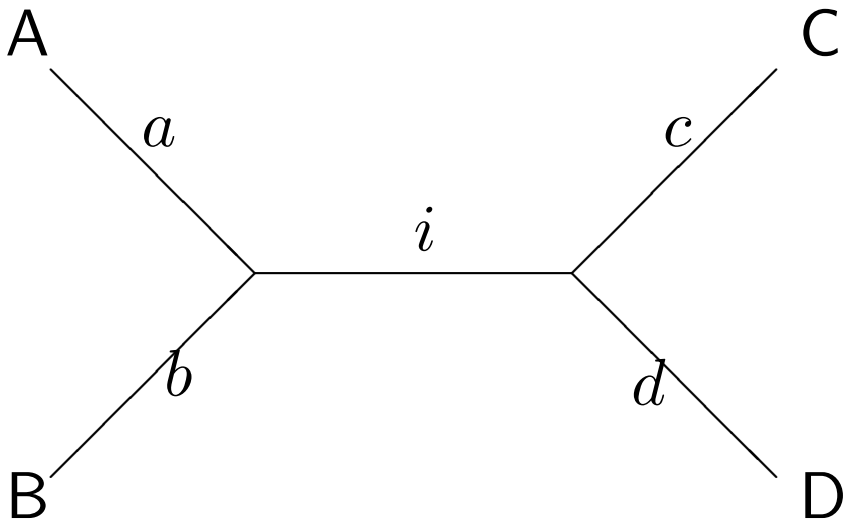
The result is the classic "long-branch attraction" phenomenon.



Distance methods – summary

We can:

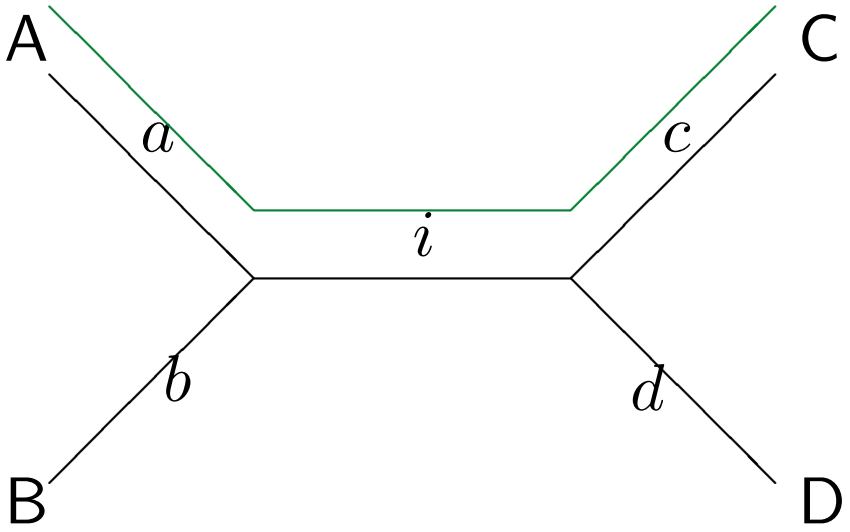
- summarize a dataset as a matrix of distances or dissimilarities.
- correct these distances for unseen character state changes.
- estimate a tree by finding the tree with path lengths that are "closest" to the corrected distances.



	A	B	C
B	d_{AB}		
C	d_{AC}	d_{BC}	
D	d_{AD}	d_{BD}	d_{CD}

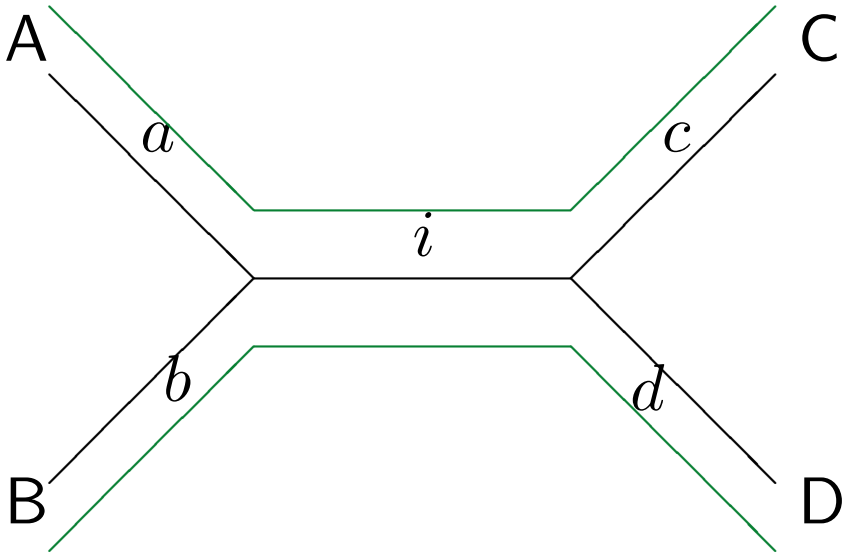
If the tree above is correct then:

$$
\begin{aligned}
p_{AB} &= a + b \\
p_{AC} &= a + i + c \\
p_{AD} &= a + i + d \\
p_{BC} &= b + i + c \\
p_{BD} &= b + i + d \\
p_{CD} &= c + d
\end{aligned}
$$



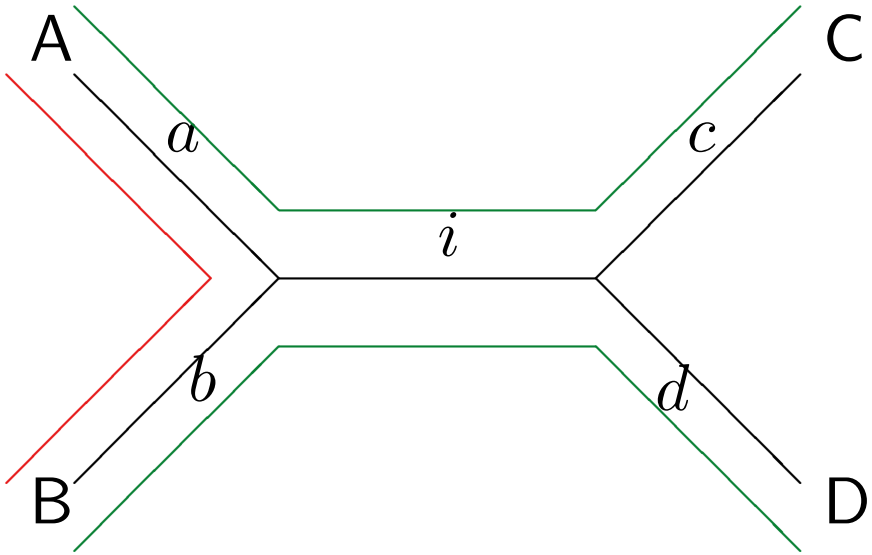
	A	B	C
B	d_{AB}		
C	d_{AC}	d_{BC}	
D	d_{AD}	d_{BD}	d_{CD}

d_{AC}



	A	B	C
B	d_{AB}		
C	d_{AC}	d_{BC}	
D	d_{AD}	d_{BD}	d_{CD}

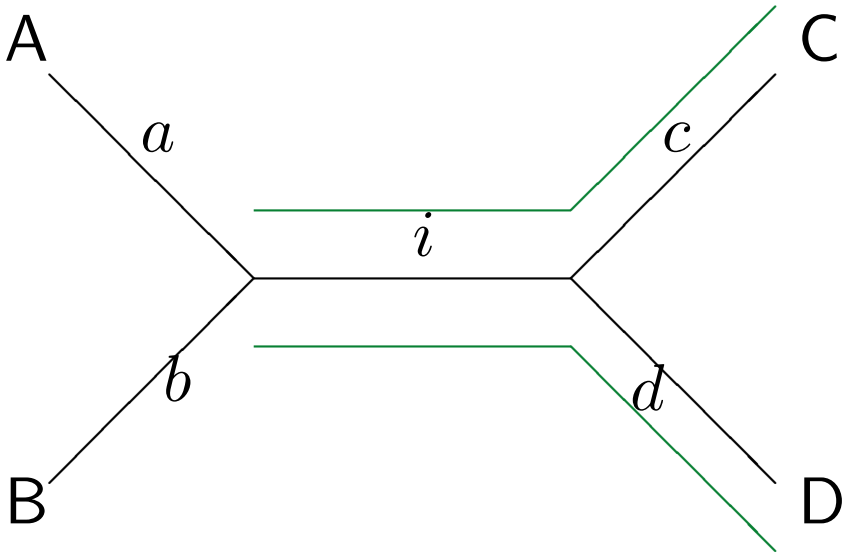
$$d_{AC} + d_{BD}$$



	A	B	C
B	d_{AB}		
C	d_{AC}	d_{BC}	
D	d_{AD}	d_{BD}	d_{CD}

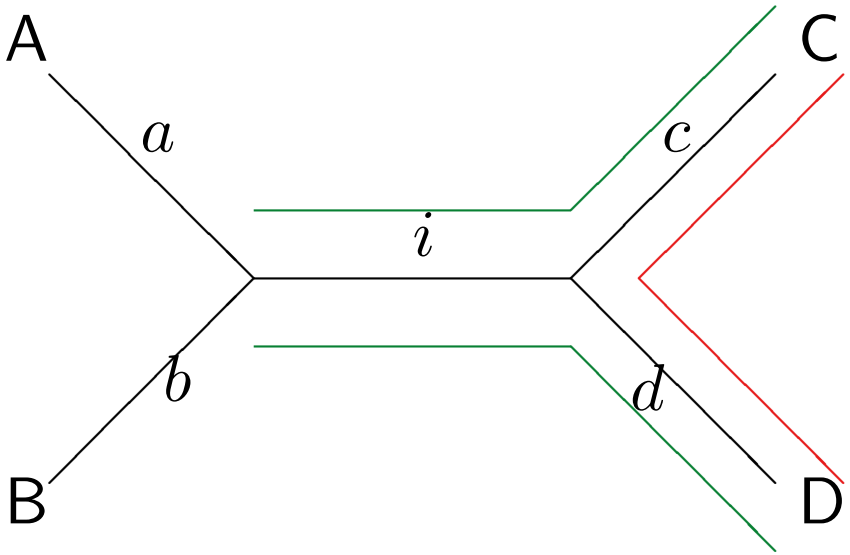
$$d_{AC} + d_{BD}$$

$$d_{AB}$$



	A	B	C
B	d_{AB}		
C	d_{AC}	d_{BC}	
D	d_{AD}	d_{BD}	d_{CD}

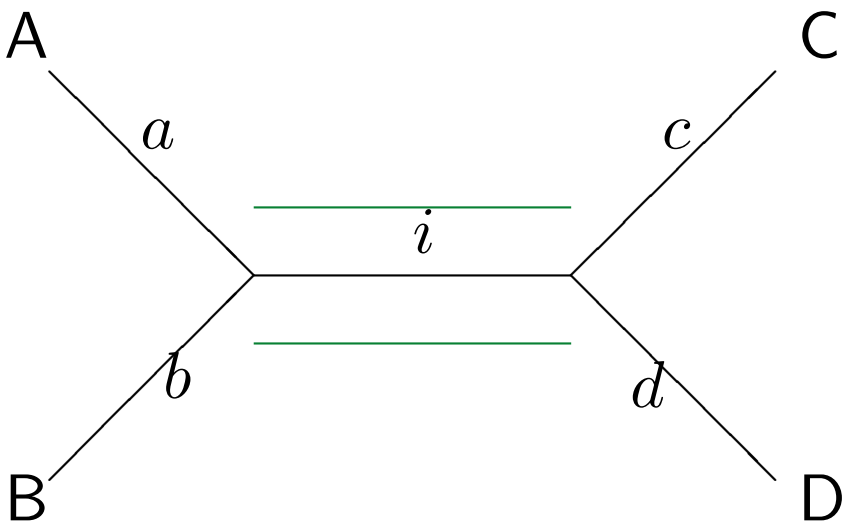
$$d_{AC} + d_{BD} - d_{AB}$$



	A	B	C
B	d_{AB}		
C	d_{AC}	d_{BC}	
D	d_{AD}	d_{BD}	d_{CD}

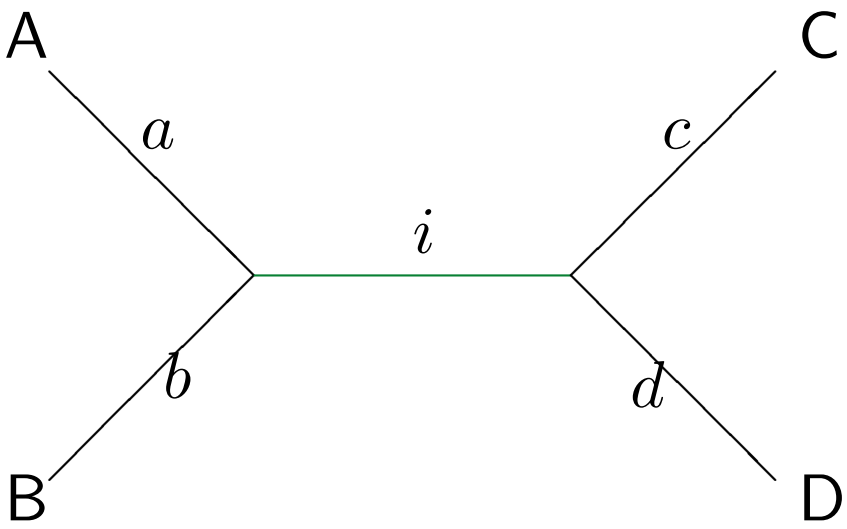
$$d_{AC} + d_{BD} - d_{AB}$$

$$d_{CD}$$



	A	B	C
B	d_{AB}		
C	d_{AC}	d_{BC}	
D	d_{AD}	d_{BD}	d_{CD}

$$d_{AC} + d_{BD} - d_{AB} - d_{CD}$$



	A	B	C
B	d_{AB}		
C	d_{AC}	d_{BC}	
D	d_{AD}	d_{BD}	d_{CD}

$$i^{\dagger} = \frac{d_{AC}+d_{BD}-d_{AB}-d_{CD}}{2}$$

Note that our estimate

$$i^{\dagger} = \frac{d_{AC} + d_{BD} - d_{AB} - d_{CD}}{2}$$

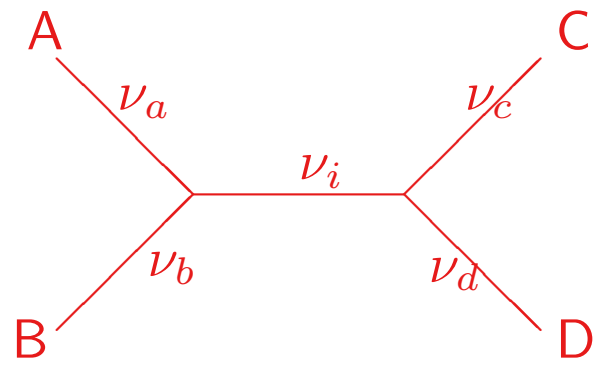
does not use all of our data. d_{BC} and d_{AD} are ignored!

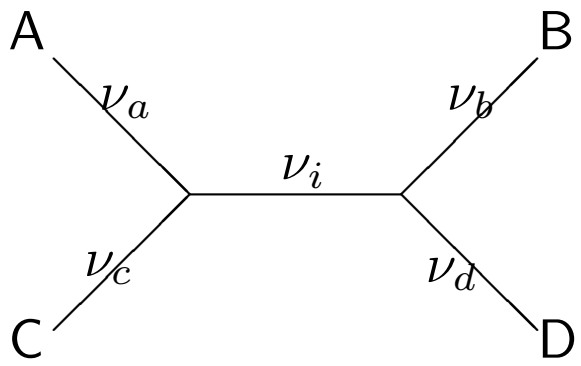
We could have used $d_{BC} + d_{AD}$ instead of $d_{AC} + d_{BD}$ (you can see this by going through the previous slides after rotating the internal branch).

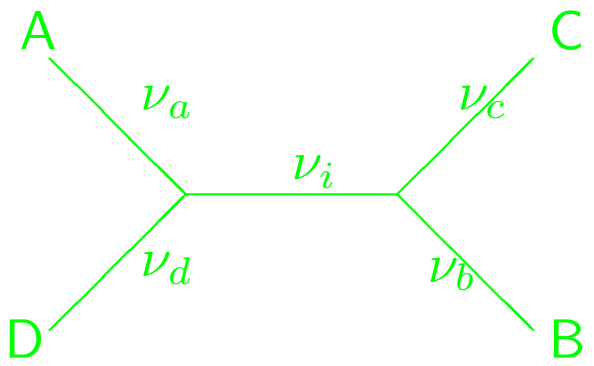
$$i^{*} = \frac{d_{BC} + d_{AD} - d_{AB} - d_{CD}}{2}$$

A better estimate than either i or i^* would be the average of both of them:

$$i' = \frac{d_{BC} + d_{AD} + d_{AC} + d_{BD}}{4} - \frac{d_{AB} - d_{CD}}{2}$$



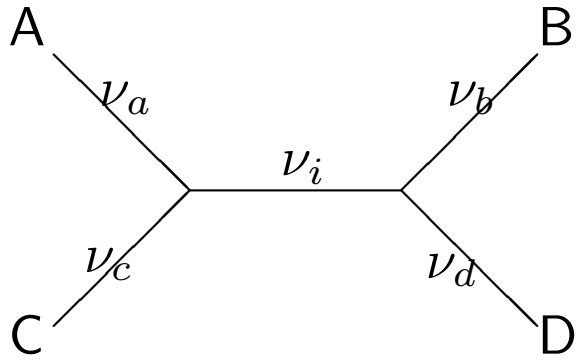




$d_{AB} + d_{CD}$	$\nu_a + \nu_b + \nu_c + \nu_d$	$\nu_a+\nu_b+\nu_c+\nu_d+2\nu_i$	$\nu_a + \nu_b + \nu_c + \nu_d + 2\nu_i$
$d_{AC} + d_{BD}$	$\nu_a+\nu_b+\nu_c+\nu_d+2\nu_i$	$\nu_a + \nu_b + \nu_c + \nu_d$	$\nu_a + \nu_b + \nu_c + \nu_d + 2\nu_i$
$d_{AD} + d_{BC}$	$\nu_a+\nu_b+\nu_c+\nu_d+2\nu_i$	$\nu_a+\nu_b+\nu_c+\nu_d+2\nu_i$	$\nu_a + \nu_b + \nu_c + \nu_d$

The four point condition of Buneman (1971).

This assumes additivity of distances.



$d_{AB} + d_{CD}$	$\nu_a + \nu_b + \nu_c + \nu_d + 2\nu_i + \epsilon_{AB} + \epsilon_{CD}$
$d_{AC} + d_{BD}$	$\nu_a + \nu_b + \nu_c + \nu_d + \epsilon_{AC} + \epsilon_{BD}$
$d_{AD} + d_{BC}$	$\nu_a + \nu_b + \nu_c + \nu_d + 2\nu_i + \epsilon_{AD} + \epsilon_{BC}$

If $|\epsilon_{ij}| < \frac{\nu_i}{2}$ then $d_{AC} + d_{BD}$ will still be the smallest sum – So Buneman's method will get the tree correct.

Worst case: $\epsilon_{AC} = \epsilon_{BD} = \frac{\nu_i}{2}$ and $\epsilon_{AB} = \epsilon_{CD} = -\frac{\nu_i}{2}$ then

$$d_{AC} + d_{BD} = \nu_a + \nu_b + \nu_c + \nu_d + \nu_i = d_{AB} + d_{CD}$$

Both Buneman's four-point condition and Hennigian logic, return the tree given perfectly clean data. But what does "perfectly clean data" mean?

1. Hennigian analysis $\rightarrow$ no homoplasy. The infinite alleles model.
2. Buneman's four-point test $\rightarrow$ no multiple hits to the same site. The infinite sites model.

The guiding principle of distance-based methods

If our data are true measures of evolutionary distances (and the distance along each branch is always > 0) then:

1. The distances will be additive on the true tree.
2. The distances will **not** be additive on any other tree.

This is the basis of Buneman's method and the motivation for minimizing the sum-of-squared error (least squares) too choose among trees.

Balanced minimum evolution

The logic behind Buneman's four-point condition has been extend to trees of more than 4 taxa by Pauplin (2000) and Semple and Steel (2004).

Pauplin (2000) showed that you can calculate a tree length from the pairwise distances without calculating branch lengths. The key is weighting the distances:

$$l = \sum_{i}^{N} \sum_{j=i+1}^{N} w_{ij} d_{ij}$$

where:

$$w_{ij} = \frac{1}{2^{n(i,j)}}$$

and $n(i,j)$ is the number of nodes on the path from i to j.

Balanced minimum evolution

"Balanced Minimum Evolution" Desper and Gascuel (2002, 2004) – fitting the branch lengths using the estimators of Pauplin (2000) and preferring the tree with the smallest tree length

BME = a form of weighted least squares in which distances are down-weighted by an exponential function of the topological distances between the leaves.

Desper and Gascuel (2005): neighbor-joining is star decomposition (more on this later) under BME. See Gascuel and Steel (2006)

FastME

Software by Desper and Gascuel (2004) which implements searching under the balanced minimum evolution criterion.

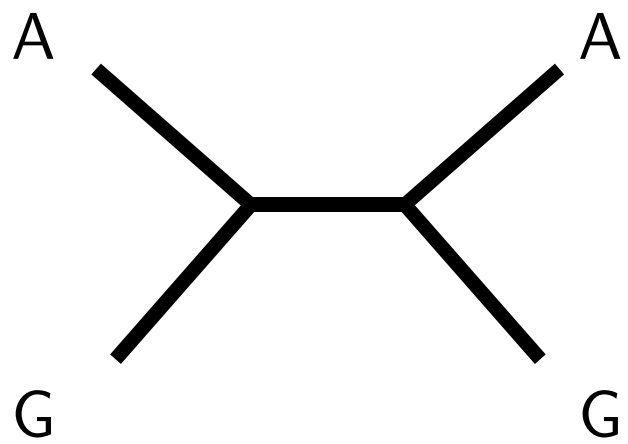
It is extremely fast and is more accurate than neighbor-joining (based on simulation studies).

Distance methods: pros

- Fast – the new FastTree method Price et al. (2009) can calculate a tree in less time than it takes to calculate a full distance matrix!
- Can use models to correct for unobserved differences
- Works well for closely related sequences
- Works well for clock-like sequences

Distance methods: cons

- Do not use all of the information in sequences
- Do not reconstruct character histories, so they not enforce all logical constraints



Neighbor-joining

Saitou and Nei (1987). r is the number of leaves remaining. Start with $r = N$.

1. choose the pair of leaves x and y that minimize $Q(x, y)$:

$$Q(i, j) = (r - 2)d_{ij} - \sum_{k=1}^{r} d_{ik} - \sum_{k=1}^{r} d_{jk}$$

2. Join x and y with at a new node z. Take x and y out of the leaf set and distance matrix, and add the new node z as a leaf.

Neighbor-joining (continued)

3. Set the branch length from x to z using:

$$d_{xz} = \frac{d_{xy}}{2} + \left(\frac{1}{2(r-2)}\right)\left(\sum_{k=1}^{r} d_{xk} - \sum_{k=1}^{r} d_{yk}\right)$$

   (the length of the branch from y to z is set with a similar formula).
4. Update the distance matrix, by adding (for any other taxon k) the distance:

$$d_{zk} = \frac{d_{xk} + d_{yk} - d_{xz} - d_{yz}}{2}$$

5. return to step 1 until you are down to a trivial tree.

Neighbor-joining (example)

	A	B	C	D	E	F
A	-					
B	0.258	-				
C	0.274	0.204	-			
D	0.302	0.248	0.278	-		
E	0.288	0.224	0.252	0.268	-	
F	0.250	0.160	0.226	0.210	0.194	-

Neighbor-joining (example)

$\sum_k d_{ik}$		A	B	C	D	E	F
1.372	A	0.0	0.258	0.274	0.302	0.288	0.25
1.094	B	0.258	0.0	0.204	0.248	0.224	0.16
1.234	C	0.274	0.204	0.0	0.278	0.252	0.226
1.306	D	0.302	0.248	0.278	0.0	0.268	0.21
1.226	E	0.288	0.224	0.252	0.268	0.0	0.194
1.040	F	0.25	0.16	0.226	0.21	0.194	0.0

$Q(A, B)$	-1.434
$Q(A, C)$	-1.510
$Q(A, D)$	-1.470
$Q(A, E)$	-1.446
$Q(A, F)$	-1.412
$Q(B, C)$	-1.512
$Q(B, D)$	-1.408
$Q(B, E)$	-1.424
$Q(B, F)$	-1.494
$Q(C, D)$	-1.428
$Q(C, E)$	-1.452
$Q(C, F)$	-1.370
$Q(D, E)$	-1.460
$Q(D, F)$	-1.506
$Q(E, F)$	-1.490

Neighbor-joining (example)

	A	D	E	F	(B,C)
A	0.0	0.302	0.288	0.25	0.164
D	0.302	0.0	0.268	0.21	0.161
E	0.288	0.268	0.0	0.194	0.136
F	0.25	0.21	0.194	0.0	0.091
(B,C)	0.164	0.161	0.136	0.091	0.0

Neighbor-joining (example)

$\sum_k d_{ik}$		A	D	E	F	(B,C)
1.004000	A	0.0	0.302	0.288	0.25	0.164
0.941000	D	0.302	0.0	0.268	0.21	0.161
0.886000	E	0.288	0.268	0.0	0.194	0.136
0.745000	F	0.25	0.21	0.194	0.0	0.091
0.552000	(B,C)	0.164	0.161	0.136	0.091	0.0

Neighbor-joining (example)

$Q(A, D)$	-1.039000
$Q(A, E)$	-1.026000
$Q(A, F)$	-0.999000
$Q(A, (B, C))$	-1.064000
$Q(D, E)$	-1.023000
$Q(D, F)$	-1.056000
$Q(D, (B, C))$	-1.010000
$Q(E, F)$	-1.049000
$Q(E, (B, C))$	-1.030000
$Q(F, (B, C))$	-1.024000

Neighbor-joining (example)

	D	E	F	(A,(B,C))
D	0.0	0.268	0.21	0.1495
E	0.268	0.0	0.194	0.13
F	0.21	0.194	0.0	0.0885
(A,(B,C))	0.1495	0.13	0.0885	0.0

Neighbor-joining (example)

$\sum_k d_{ik}$		D	E	F	(A,(B,C))
0.627500	D	0.0	0.268	0.21	0.1495
0.592000	E	0.268	0.0	0.194	0.13
0.492500	F	0.21	0.194	0.0	0.0885
0.368000	(A,(B,C))	0.1495	0.13	0.0885	0.0

Neighbor-joining (example)

$Q(D, E)$	-0.683500
$Q(D, F)$	-0.700000
$Q(D, (A, (B, C)))$	-0.696500
$Q(E, F)$	-0.696500
$Q(E, (A, (B, C)))$	-0.700000
$Q(F, (A, (B, C)))$	-0.683500

$$((D, F), E, (A, (B, C)))$$

Neighbor-joining is special

Bryant (2005) discusses neighbor joining in the context of clustering methods that:

- Work on the distance (or dissimilarity) matrix as input.
- Repeatedly
  - select a pair of taxa to agglomerate (step 1 above)
  - make the pair into a new group (step 2 above)
  - estimate branch lengths (step 3 above)
  - reduce the distance matrix (step 4 above)

Neighbor-joining is special (cont)

Bryant (2005) shows that if you want your selection criterion to be:

- based solely on distances
- invariant to the ordering of the leaves (no *a priori* special taxa).
- work on linear combinations of distances (simple coefficients for weights, no fancy weighting schemes).
- statistically consistent

then neighbor-joining's Q-criterion as a selection rule is the *only* choice.

Neighbor-joining is not perfect

- BioNJ (Gascuel, 1997) does a better job by using the variance and covariances in the reduction step.
- Weighbor (Bruno et al., 2000) includes the variance information in the selection step.
- FastME (Desper and Gascuel, 2002, 2004) does a better job of finding the BME tree (and seems to get the true tree right more often).

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