An exact and polynomial distance-based algorithm to reconstruct single copy duplication trees

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Tandemly repeated sequences

- two or more adjacent and approximate copies of a same DNA sequence
- the successive duplications form a tandem duplication tree
- we seek to reconstruct the duplication tree of tandemly repeated sequences

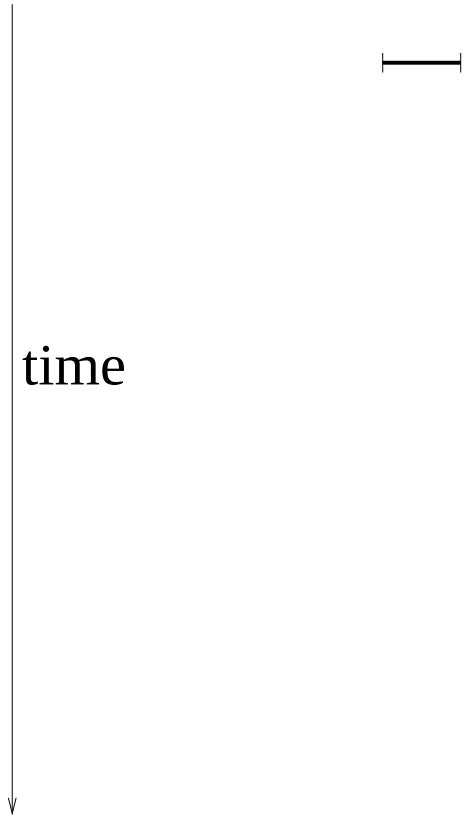
Reconstructing single copy tandem duplication trees

- Jaitly et al, 2002 : the problem of reconstructing single copy duplication trees is NP-hard, in a parsimony framework
- Benson et al, 1999 : heuristic algorithms using the parsimony criterion
- Tang et al, 2002 ; Jaitly et al, 2002 : PTAS using DP in a parsimony framework

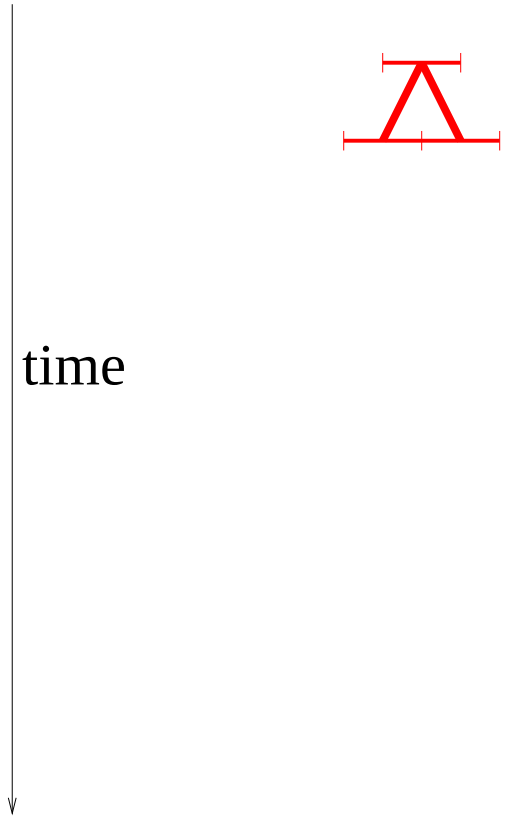
Outline

- Tandem duplication trees (DT)
- Minimum Evolution principle
- recurrence equation for estimating the length of a DT given a matrix of pairwise distances using Ordinary Least Squares
- use this equation in a DP framework to find the optimal DT (the tree with shortest length)

Tandem duplication trees



Tandem duplication trees



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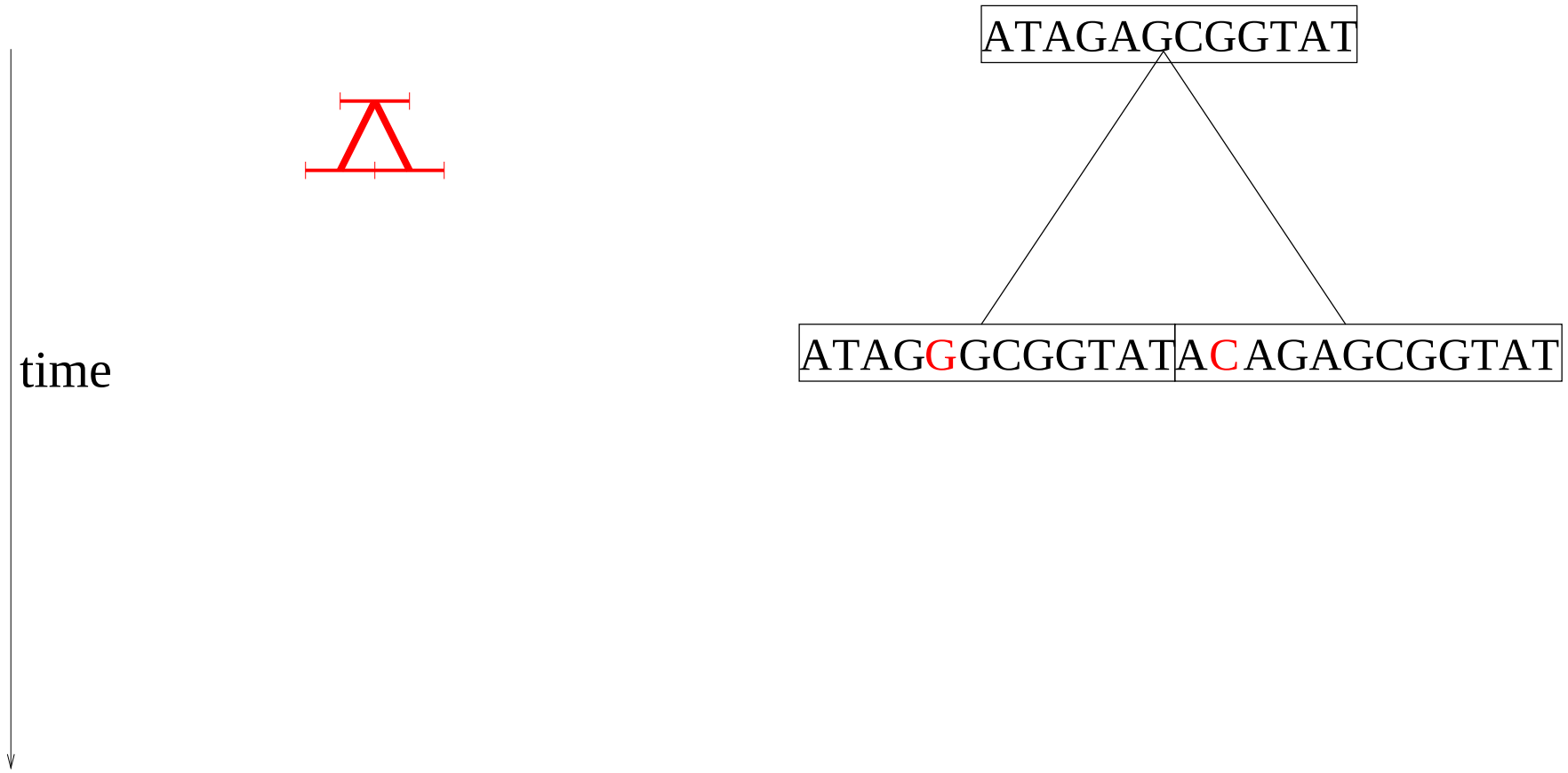
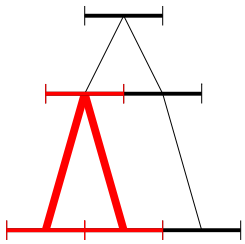


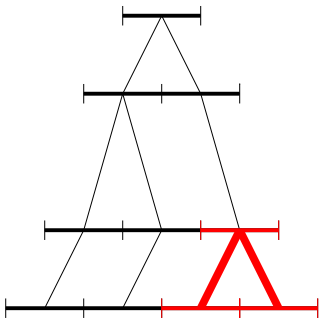
Tandem duplication trees



time

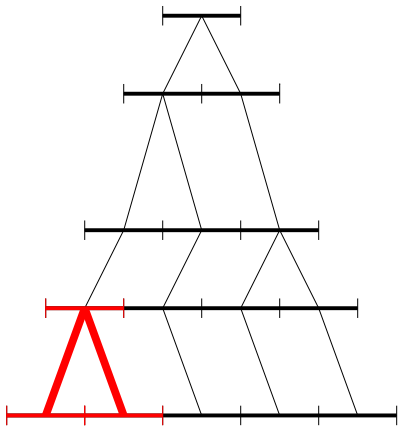
Tandem duplication trees

time

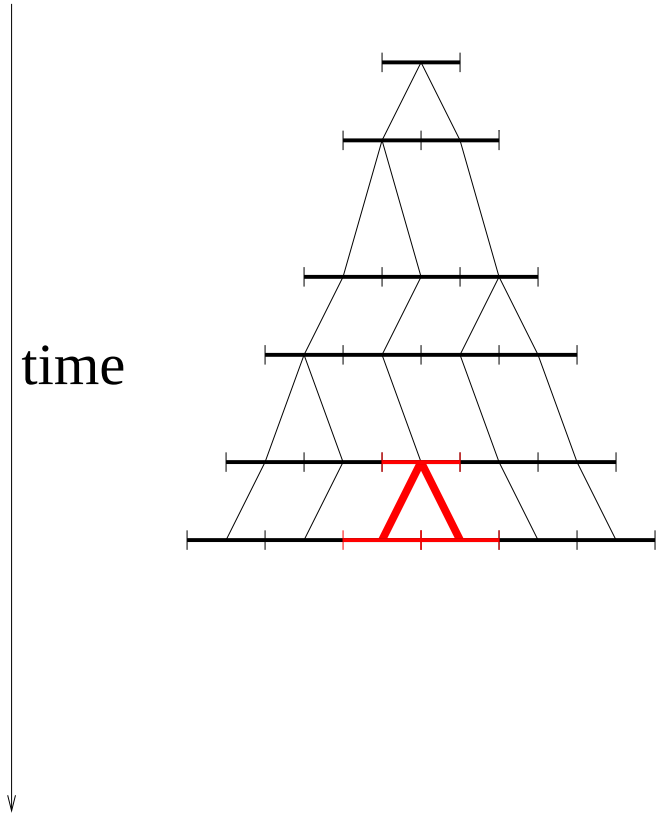


Tandem duplication trees

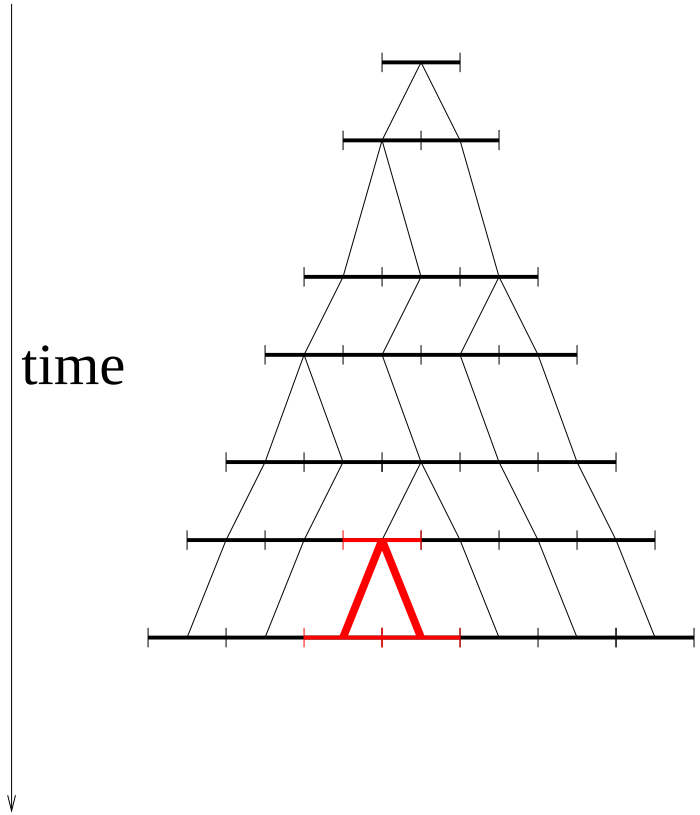
time



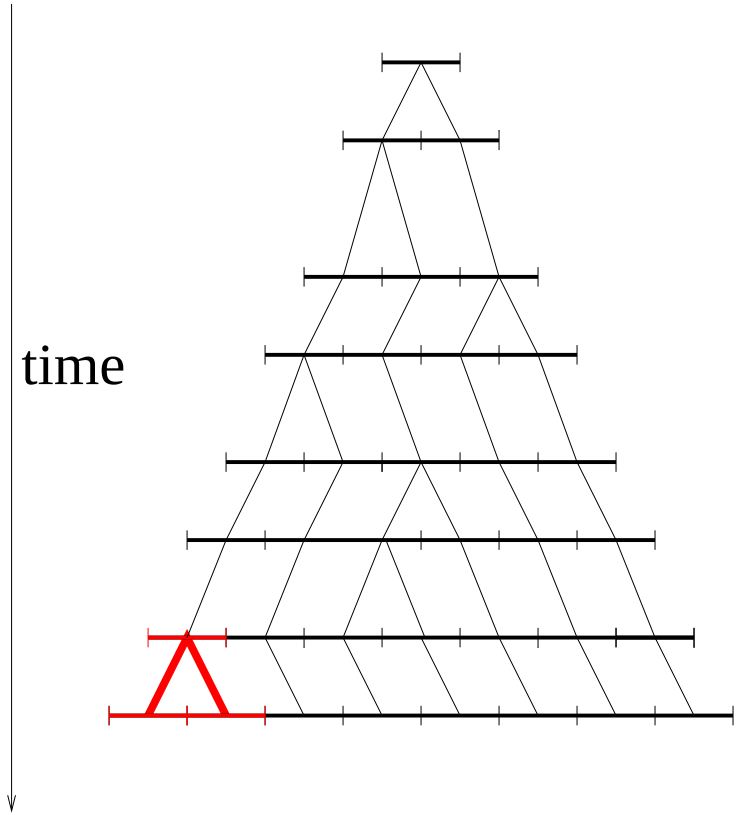
Tandem duplication trees



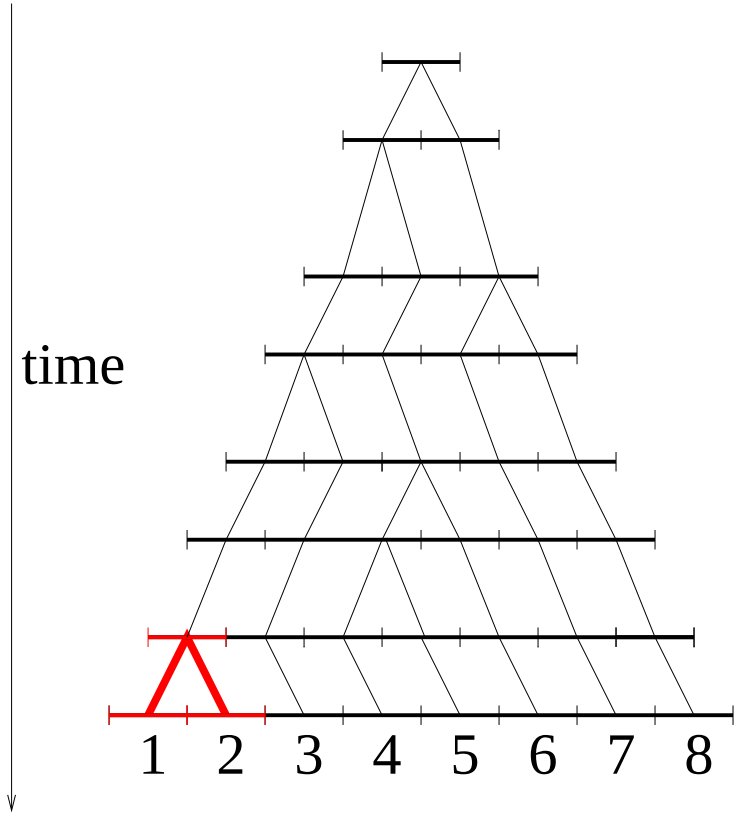
Tandem duplication trees



Tandem duplication trees

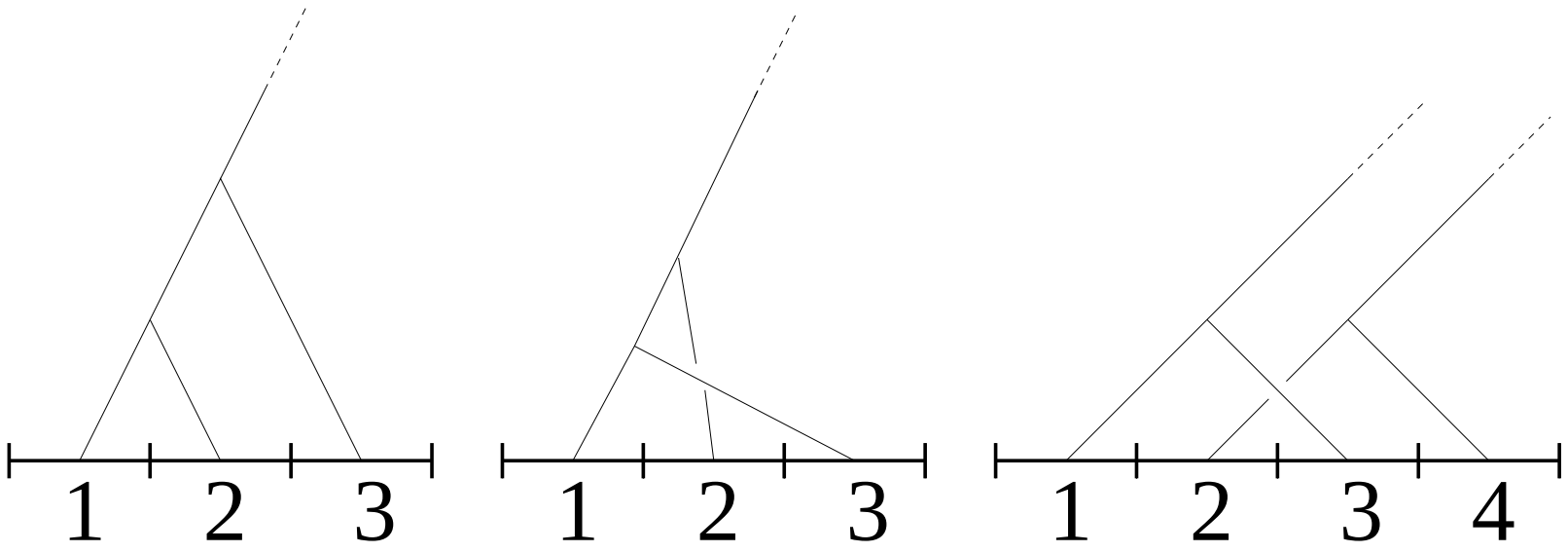


Tandem duplication trees



- induces a phylogeny
- order between the leaves
- not all duplications are allowed
- only single copy tandem duplications

Tandem duplication trees



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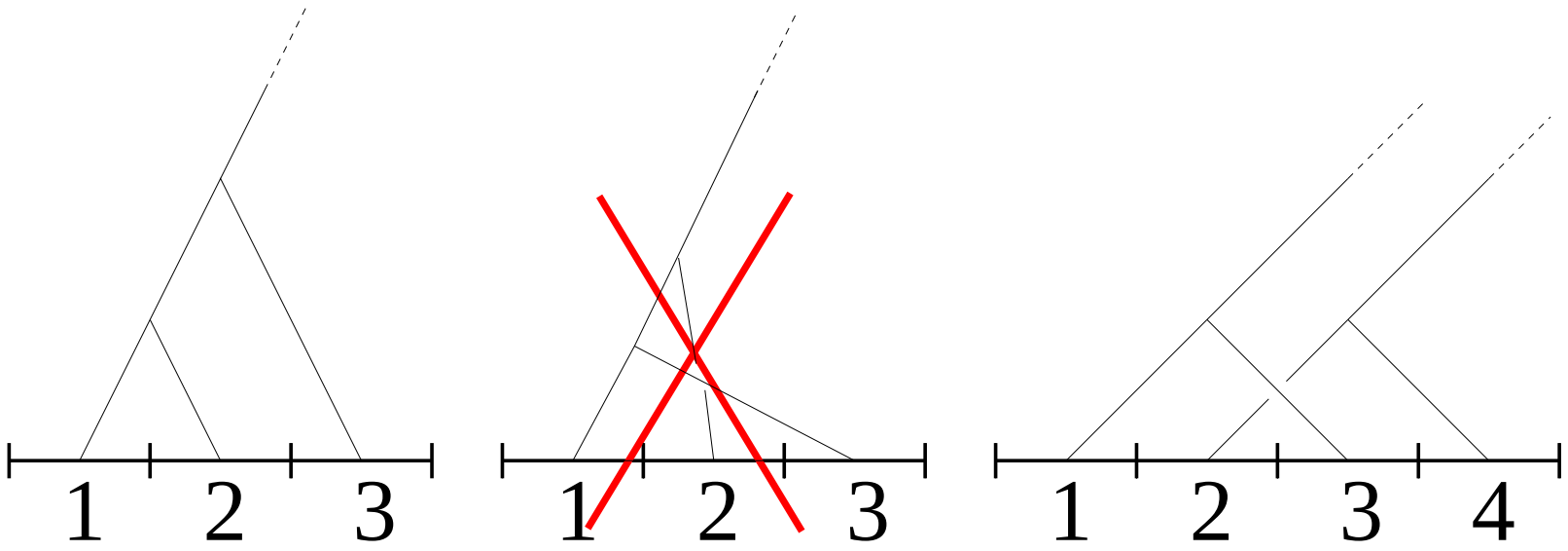
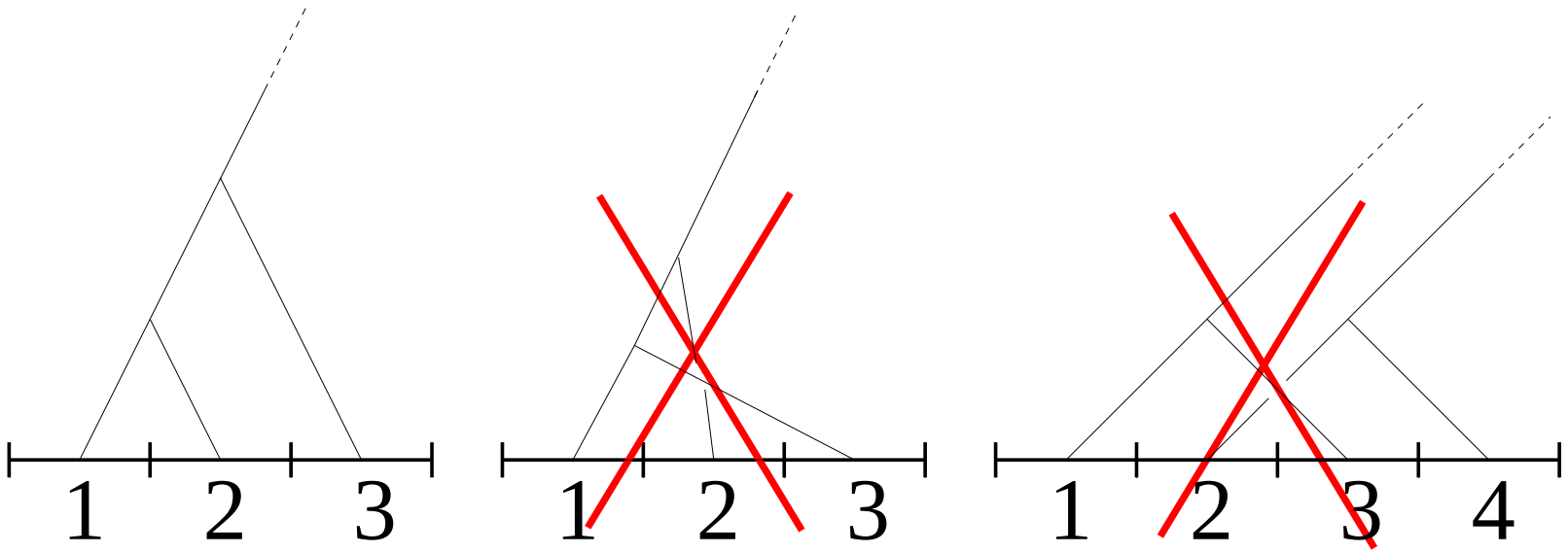
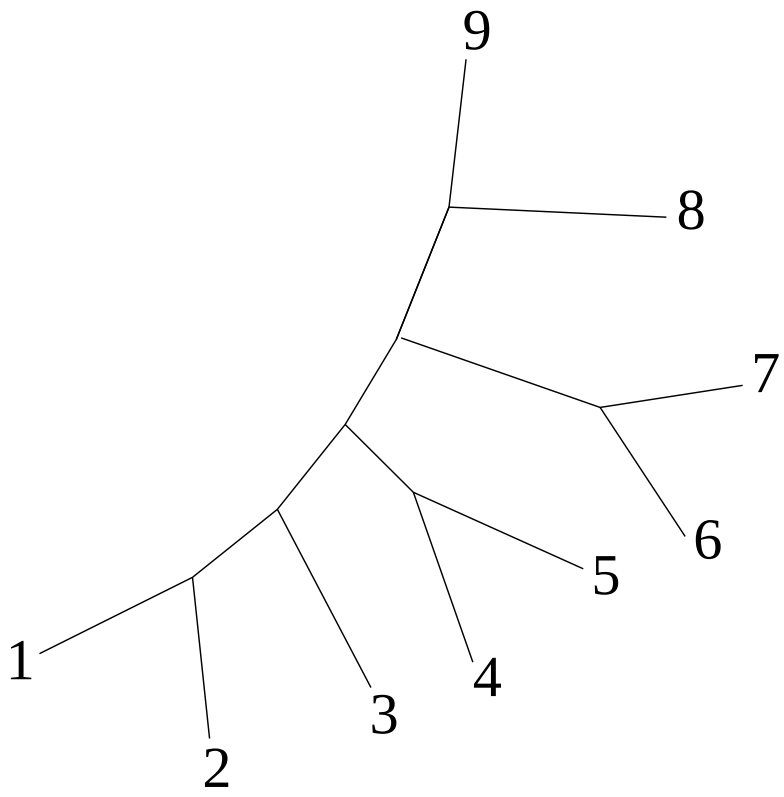


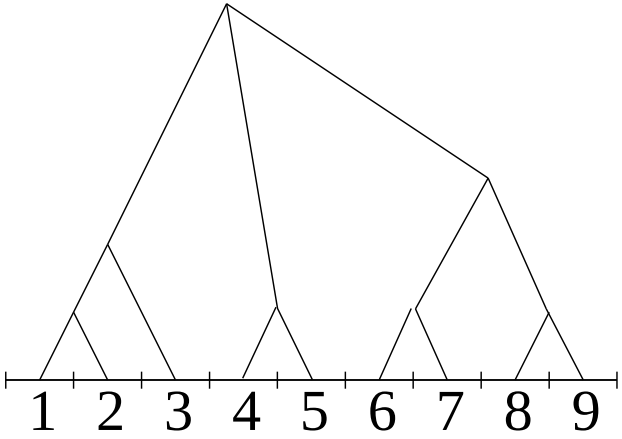
Tandem duplication trees



Tandem duplication trees

- we can only recover an unrooted DT (no molecular clock)





Counting single copy duplication trees

- the Catalan recursion (binary search trees)

$$C_n = \sum_{k=1}^{n-1} C_k C_{n-k} = \frac{(2n)!}{n!(n+1)!} \sim \frac{4^n}{\sqrt{\pi} n^{3/2}}.$$

- we cannot search exhaustively for the best single copy duplication tree

Minimum Evolution principle

- search for the tree with shortest length (sum of individual branch lengths)
- example : Neighbor-Joining (Saitou and Nei, 1987), heuristic, agglomerative method ($O(n^3)$)

Minimum Evolution principle and OLS tree length estimation

- ME with Ordinary Least Squares tree length estimation is statistically consistent (Rzhetsky and Nei, 1993 ; Denis and Gascuel, 2003)

Minimum Evolution principle and OLS tree length estimation

- Given a topology T and a distance matrix Δ, the OLS branch length estimation of T (valued tree with topology T, inducing a tree distance Δ^T) is obtained by minimizing :

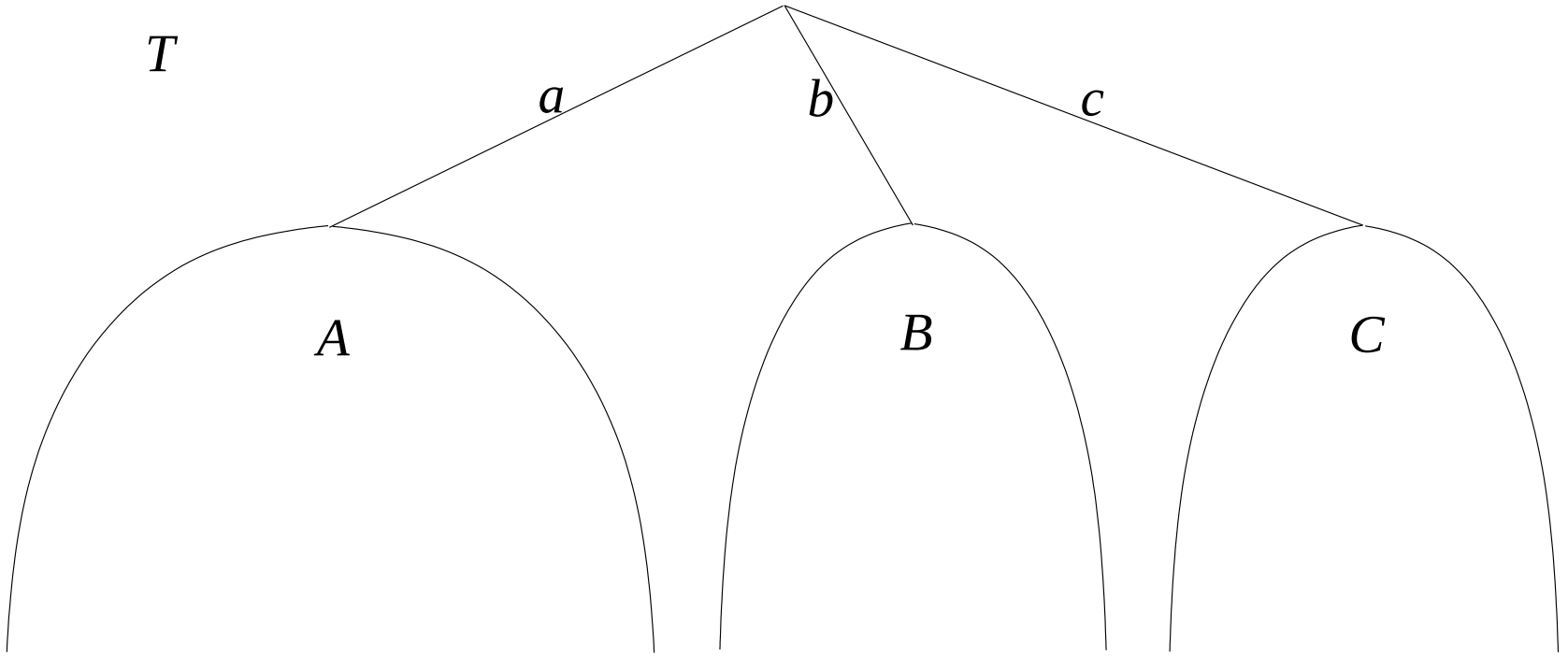
$$\sum_{i,j \in T} (\delta_{ij}^T - \delta_{ij})^2.$$

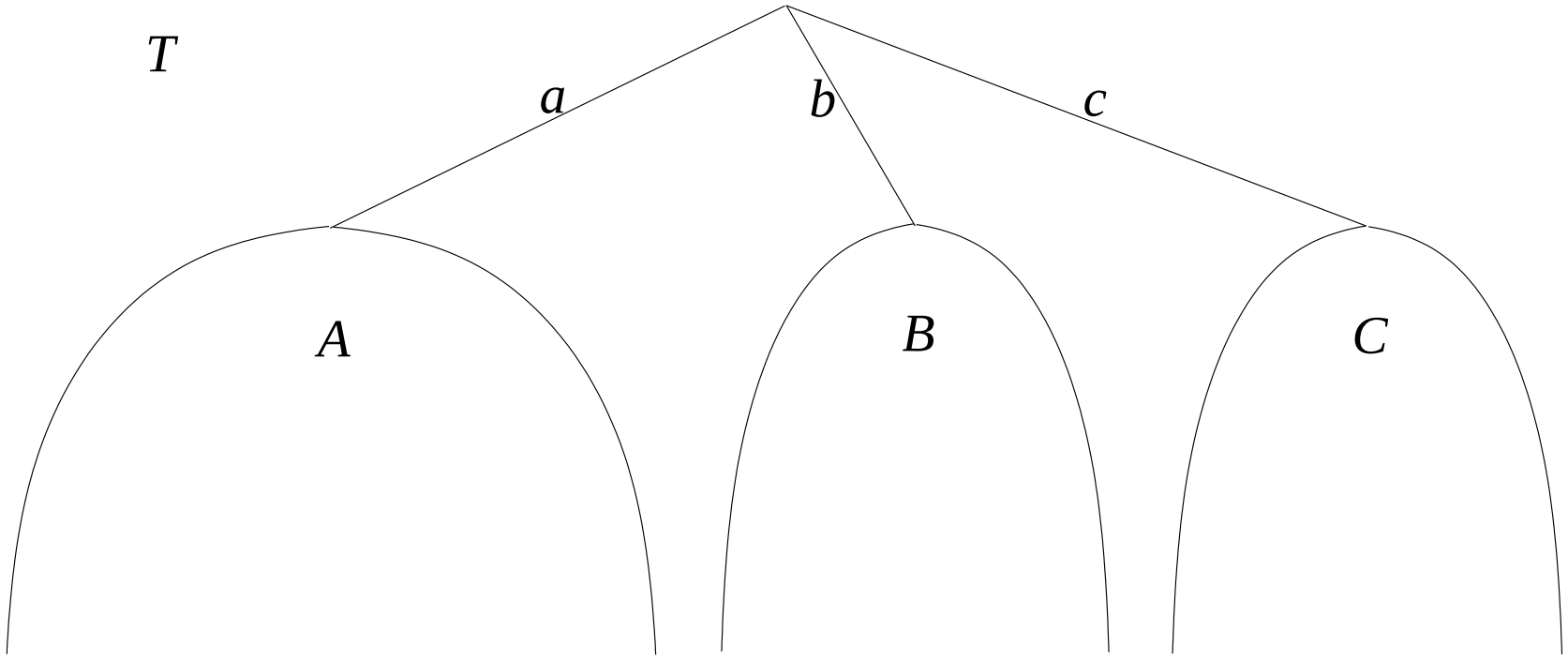
OLS estimation of tree length

- recurrence equation for calculating the length of a tree topology using OLS, given a matrix of pairwise evolutionary distances

Δ	matrix of evolutionary distances (eg K2P)
δ_{ij}	distance between copy i and copy j
T	(unrooted) tree topology
T	valued tree with topology T
n	number of leaves in T
Δ^T	tree distance induced by T
δ_{ij}^T	distance between copy i and copy j
$L(T)$	sum of branch lengths of T

OLS estimation of tree length

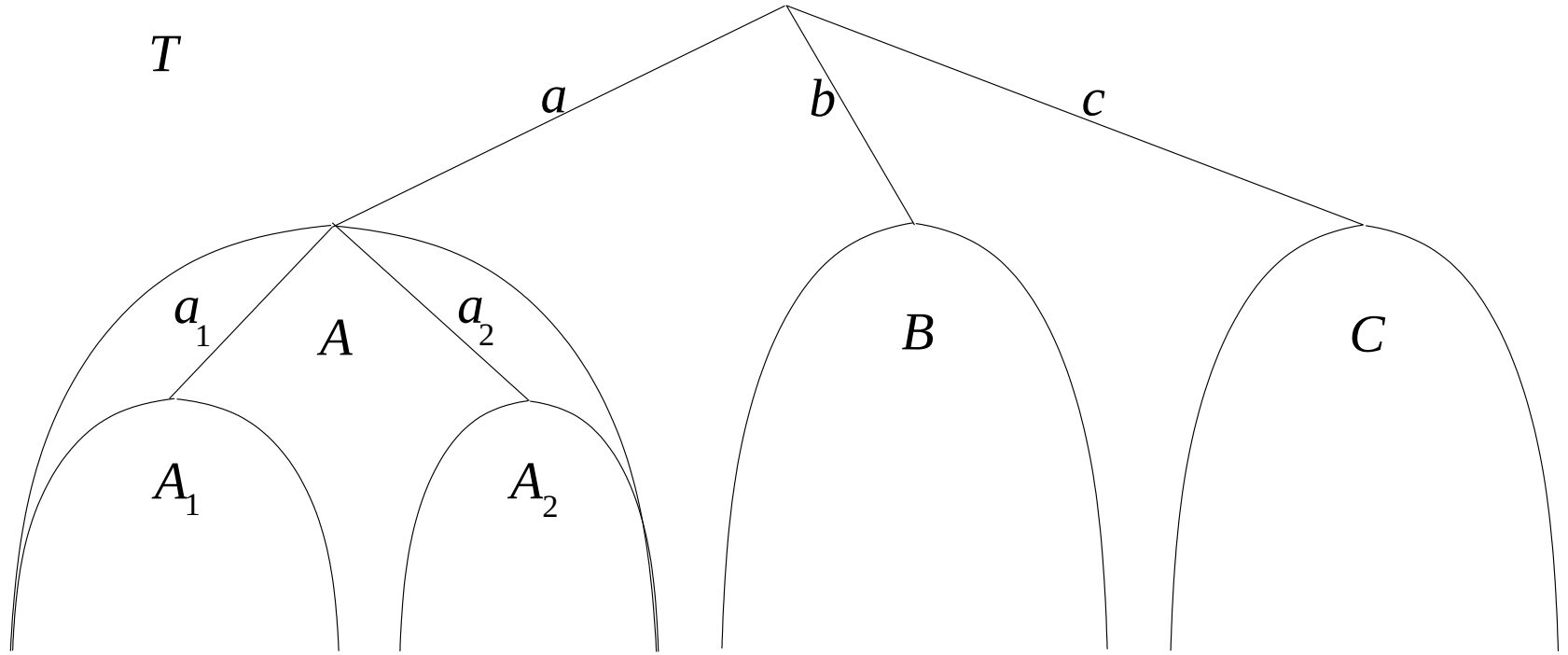




R is the subset of leaves which do not belong to A

$(R = B \cup C)$

OLS estimation of tree length



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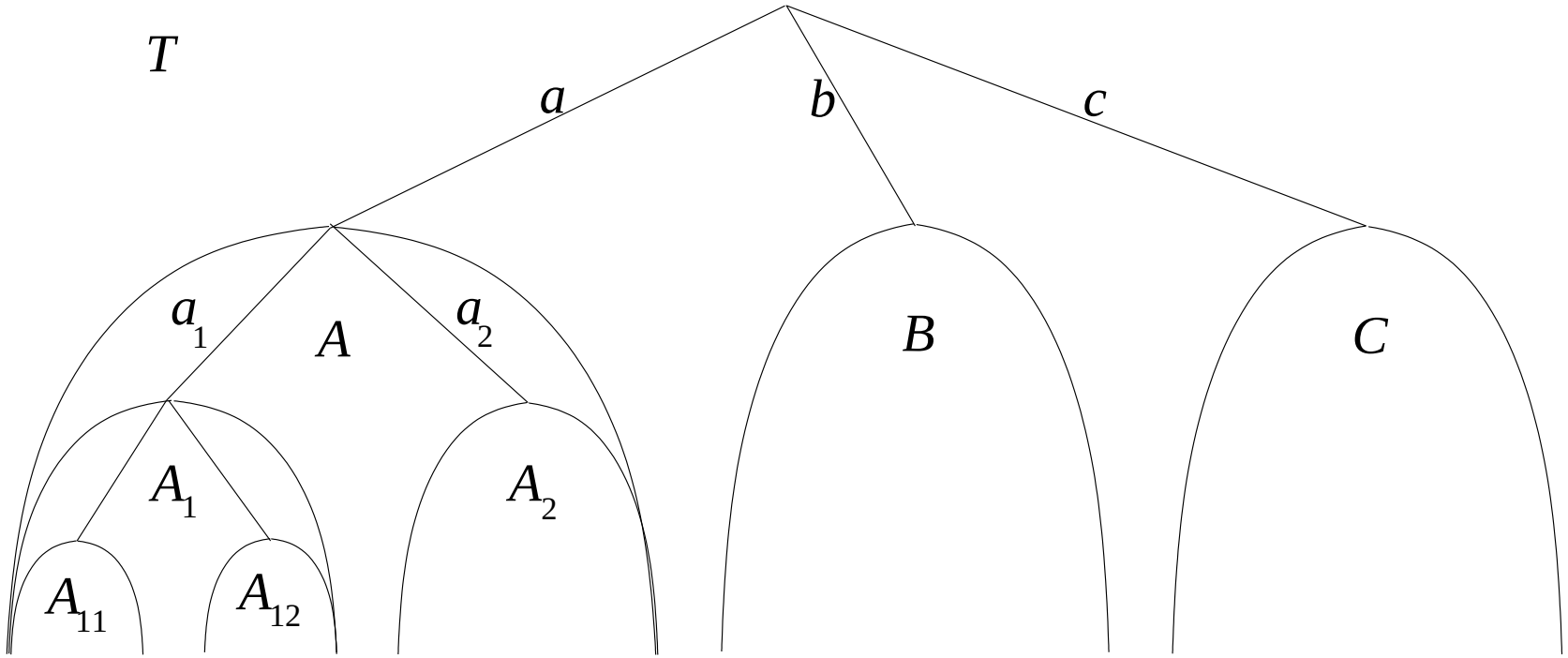
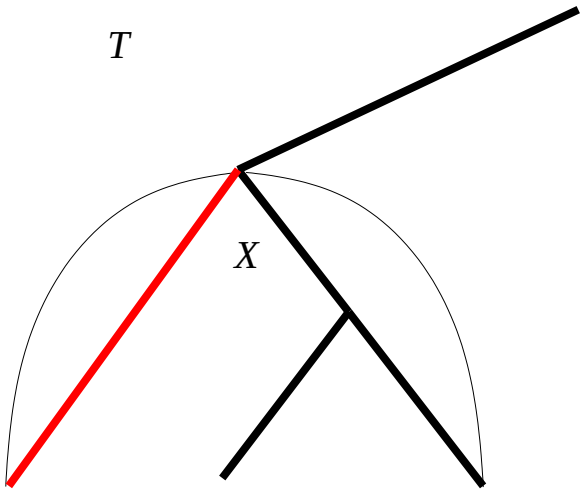


Notations

- X any subtree of T
- $\overline{X}$ average distance in T between the root of X and its leaves



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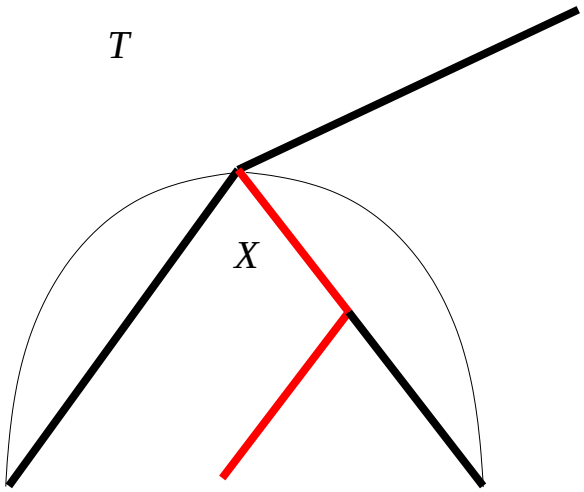

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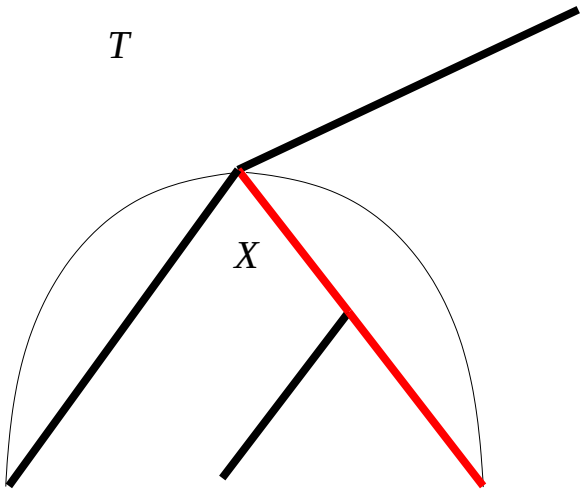


Notations

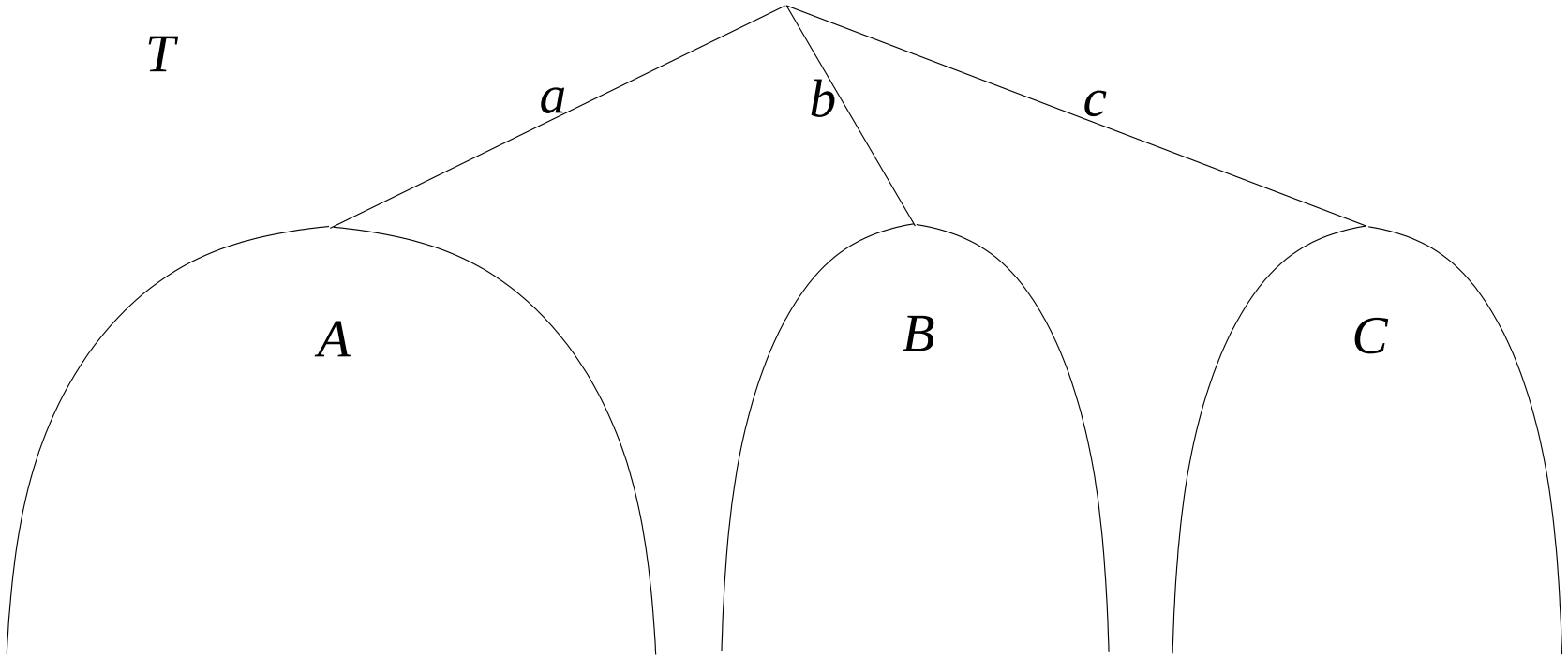
- X, Y two non-intersecting subtrees
- Δ_{XY} average distance in Δ between the leaves of X and Y

$$\Delta_{XY} = \frac{1}{|X|\,|Y|} \sum_{i \in X, j \in Y} \delta_{ij}$$

- Δ^T_{XY} average distance in T (or Δ^T) between the leaves of X and Y

$$\Delta^T_{XY} = \frac{1}{|X|\,|Y|} \sum_{i \in X, j \in Y} \delta^T_{ij}$$

OLS estimation of tree length



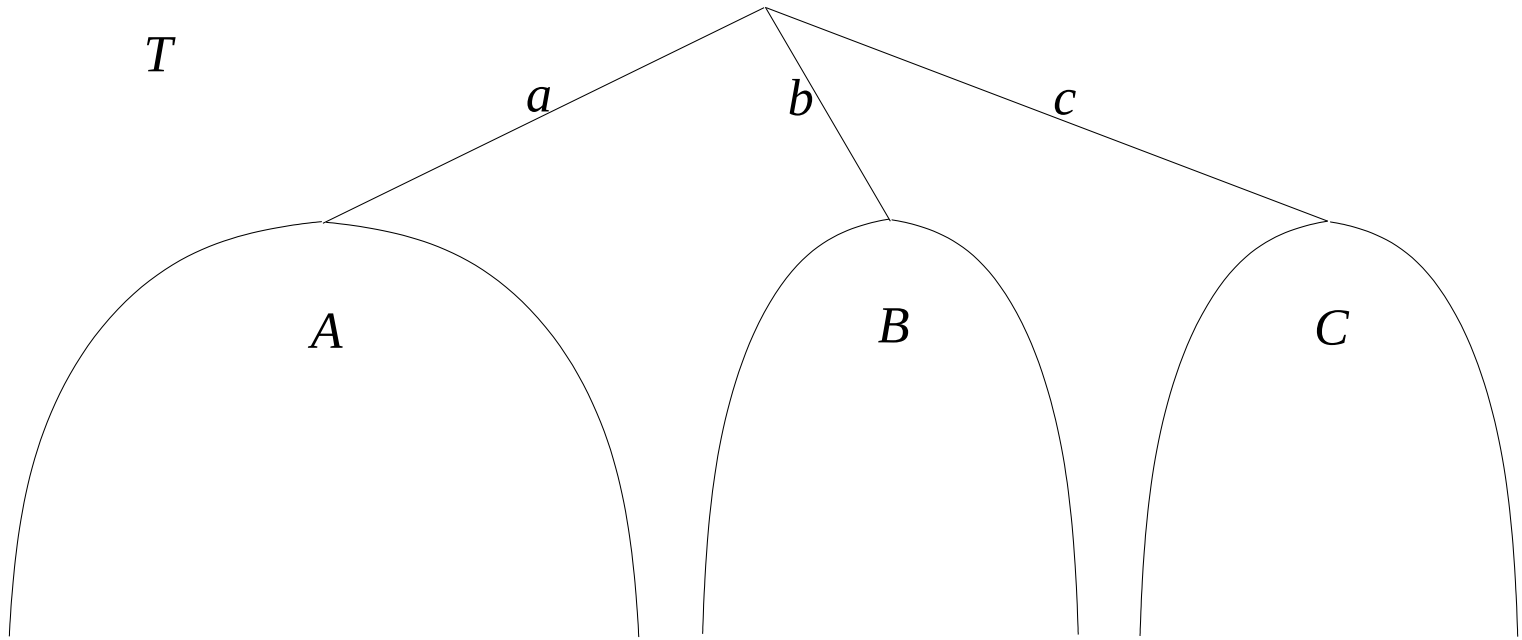
$$L(T) = L(A) + L(B) + L(C) + a + b + c$$

OLS property (Vach, 1989 ; Gascuel, 1997)

- the average distance between (non-intersecting subtrees) X and Y is preserved between Δ and Δ^T, when X and Y are adjacent to a common ternary node

$$\Delta_{XY} = \Delta^T_{XY}$$

OLS estimation of tree length



$$\Delta_{AB} = \Delta^{T}_{AB} = \overline{A} + a + b + \overline{B}$$

$$L(T) = L(A) + L(B) + L(C) + a + b + c$$

$$(i) \quad \Delta_{AB} = \overline{A} + a + b + \overline{B},$$

$$(ii) \quad \Delta_{AC} = \overline{A} + a + c + \overline{C},$$

$$(iii) \quad \Delta_{BC} = \overline{B} + b + c + \overline{C},$$

$$L(T) = L(A) + L(B) + L(C) + a + b + c$$

$$(i) \quad \Delta_{AB} = \overline{A} + a + b + \overline{B},$$

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$$L(T) = (L(A) - \overline{A}) + (L(B) - \overline{B}) + (L(C) - \overline{C}) + \frac{1}{2}(\Delta_{AB} + \Delta_{AC} + \Delta_{BC})$$

$$L(T) = L(A) + L(B) + L(C) + a + b + c$$

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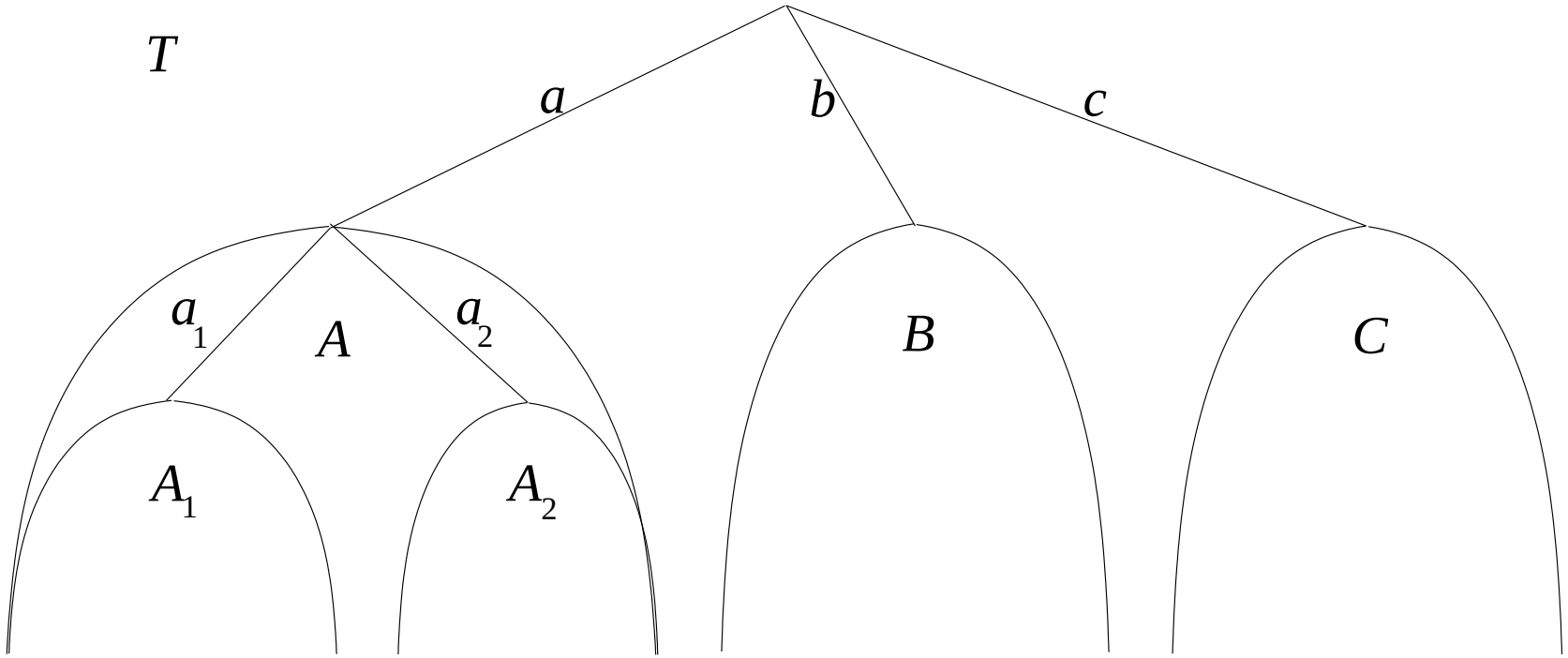
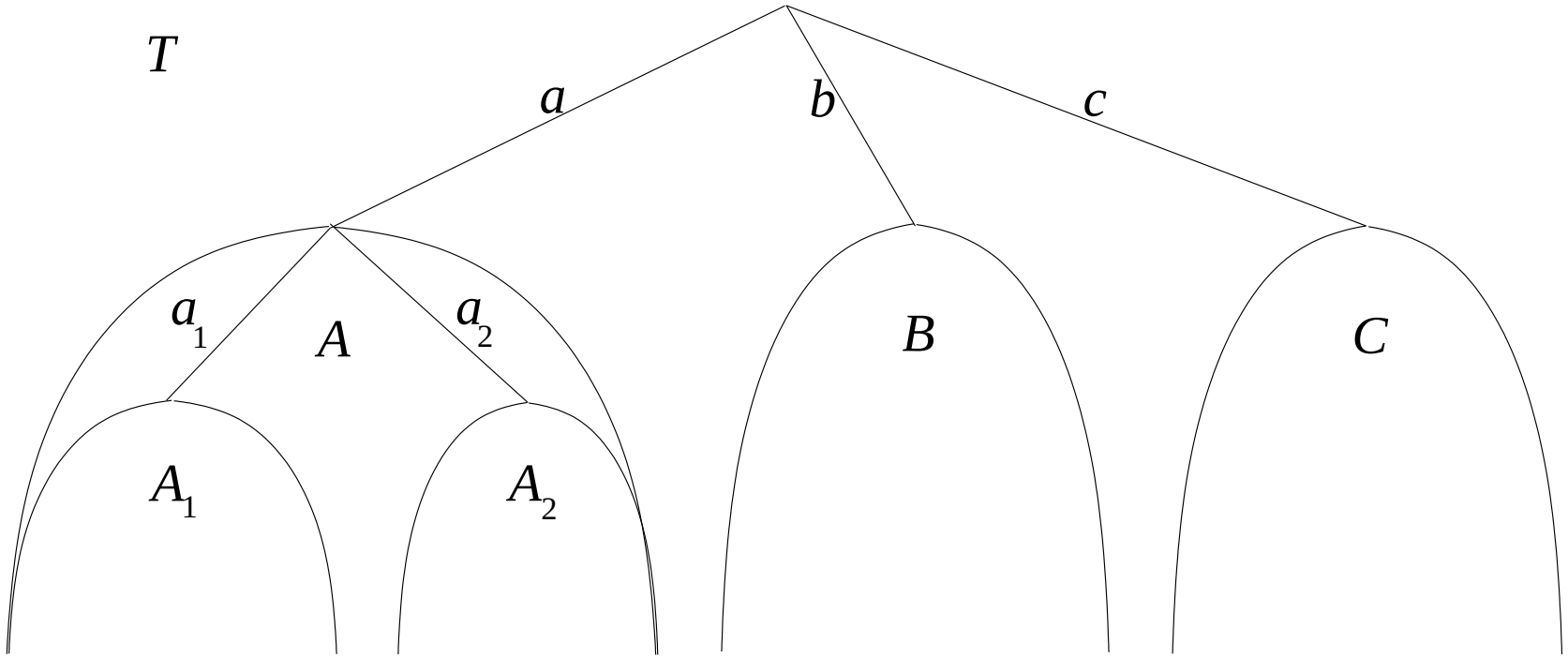
OLS estimation of tree length



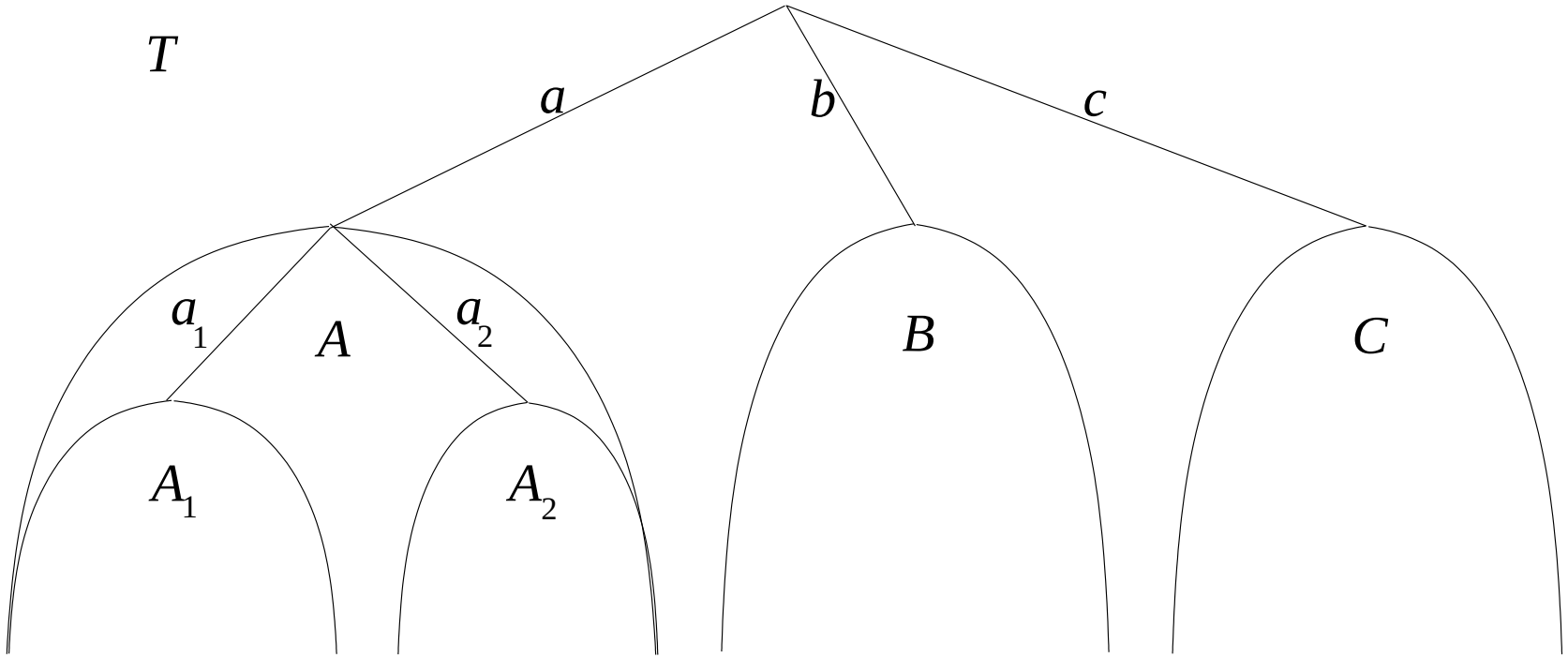
$$L(A) = L(A_1) + L(A_2) + a_1 + a_2$$

OLS estimation of tree length



$$\overline{A} = \frac{|A_1|}{|A|}(a_1 + \overline{A_1}) + \frac{|A_2|}{|A|}(a_2 + \overline{A_2})$$

OLS estimation of tree length



$$\Delta_{A_1A_2} = \Delta^T_{A_1A_2} = \overline{A_1} + a_1 + a_2 + \overline{A_2}$$

$$
\begin{aligned}
(i)' \quad & \Delta_{A_1 A_2} = \overline{A_1} + a_1 + a_2 + \overline{A_2}, \\
(ii)' \quad & \Delta_{A_1 R} = \overline{A_1} + a_1 + a + \overline{R}, \\
(iii)' \quad & \Delta_{A_2 R} = \overline{A_2} + a_2 + a + \overline{R},
\end{aligned}
$$

- solve to get an expression for a_1 and a_2

$$a1 = \frac{1}{2}\Delta_{A_1A_2} + \frac{1}{2}\Delta_{A_1R} - \frac{1}{2}\Delta_{A_2R} - \overline{A_1}$$

$$a2 = \frac{1}{2}\Delta_{A_1A_2} + \frac{1}{2}\Delta_{A_2R} - \frac{1}{2}\Delta_{A_1R} - \overline{A_2}$$

$$a1 = \frac{1}{2}\Delta_{A_1A_2} + \frac{1}{2}\Delta_{A_1R} - \frac{1}{2}\Delta_{A_2R} - \overline{A_1}$$

$$a2 = \frac{1}{2}\Delta_{A_1A_2} + \frac{1}{2}\Delta_{A_2R} - \frac{1}{2}\Delta_{A_1R} - \overline{A_2}$$

$$\overline{A} = \frac{|A_1|}{|A|}(a_1 + \overline{A_1}) + \frac{|A_2|}{|A|}(a_2 + \overline{A_2})$$

$$a1 = \frac{1}{2}\Delta_{A_1A_2} + \frac{1}{2}\Delta_{A_1R} - \frac{1}{2}\Delta_{A_2R} - \overline{A_1}$$

$$a2 = \frac{1}{2}\Delta_{A_1A_2} + \frac{1}{2}\Delta_{A_2R} - \frac{1}{2}\Delta_{A_1R} - \overline{A_2}$$

$$\overline{A} = \frac{|A_1|}{|A|}(a_1 + \overline{A_1}) + \frac{|A_2|}{|A|}(a_2 + \overline{A_2})$$

$$L(A) = L(A_1) + L(A_2) + a_1 + a_2$$

- combine to get an expression for $(L(A) - \overline{A})$

$$
\begin{aligned}
(L(A)-\overline{A}) = \; & (L(A_1) - \overline{A_1}) + (L(A_2) - \overline{A_2}) \\
& + \tfrac{1}{2}\Delta_{A_1 A_2} \\
& + \tfrac{1}{2}\left(\tfrac{|A_2|-|A_1|}{|A|}\right)\Delta_{A_1 R} + \tfrac{1}{2}\left(\tfrac{|A_1|-|A_2|}{|A|}\right)\Delta_{A_2 R}
\end{aligned}
$$

$$L(T) = (L(A) - \overline{A}) + (L(B) - \overline{B}) + (L(C) - \overline{C}) + \frac{1}{2}(\Delta_{AB} + \Delta_{AC} + \Delta_{BC}),$$

$$(L(A) - \overline{A}) = (L(A_1) - \overline{A_1}) + (L(A_2) - \overline{A_2}) + \frac{1}{2}\Delta_{A_1 A_2} + \frac{1}{2}\left(\frac{|A_2| - |A_1|}{|A|}\right)\Delta_{A_1 R} + \frac{1}{2}\left(\frac{|A_1| - |A_2|}{|A|}\right)\Delta_{A_2 R},$$

$(L(A) - \overline{A}) = 0$ if A is a leaf.

$$L(T) = (L(A) - \overline{A}) + (L(B) - \overline{B}) + (L(C) - \overline{C}) + \frac{1}{2}(\Delta_{AB} + \Delta_{AC} + \Delta_{BC}).$$

- $(L(A) - \overline{A})$ only depends on the structure of subtree A (not on the structure of $R = B \cup C$), idem for $(L(B) - \overline{B})$, $(L(C) - \overline{C})$
- to compute $L(T)$, we only have to compute (independently) $(L(A) - \overline{A})$, $(L(B) - \overline{B})$ and $(L(C) - \overline{C})$, then to apply the above equation.

$$
\begin{aligned}
(L(A)-\overline{A}) = \; & (L(A_1) - \overline{A_1}) + (L(A_2) - \overline{A_2}) \\
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& + \tfrac{1}{2}\left(\tfrac{|A_2|-|A_1|}{|A|}\right)\Delta_{A_1 R} + \tfrac{1}{2}\left(\tfrac{|A_1|-|A_2|}{|A|}\right)\Delta_{A_2 R},
\end{aligned}
$$

- $(L(A_1) - \overline{A_1})$ only depends on the structure of A_1, not on the structure of $R' = R \cup A_2$
- to compute $(L(A) - \overline{A})$, we only have to compute (independently) $(L(A_1) - \overline{A_1})$, $(L(A_2) - \overline{A_2})$ then to apply the above equation.

$$L(T) = (L(A) - \overline{A}) + (L(B) - \overline{B}) + (L(C) - \overline{C}) + \frac{1}{2}(\Delta_{AB} + \Delta_{AC} + \Delta_{BC}),$$

$$(L(A) - \overline{A}) = (L(A_1) - \overline{A_1}) + (L(A_2) - \overline{A_2}) + \frac{1}{2}\Delta_{A_1 A_2} + \frac{1}{2}\left(\frac{|A_2| - |A_1|}{|A|}\right)\Delta_{A_1 R} + \frac{1}{2}\left(\frac{|A_1| - |A_2|}{|A|}\right)\Delta_{A_2 R},$$

$(L(A) - \overline{A}) = 0$ if A is a leaf.

Reconstructing the optimal single duplication tree under the ME principle

- we want to find the tree whose length is minimum among all possible duplication trees, when calculated with this equation

$$L(T) = (L(A) - \overline{A}) + (L(B) - \overline{B}) + (L(C) - \overline{C}) + \frac{1}{2}(\Delta_{AB} + \Delta_{AC} + \Delta_{BC})$$

- we divide the n copies into 3 adjacent subsets (intervals) A, B and C
- we then (independently) compute the 3 subtree structures which minimize $(L(A) - \overline{A})$, $(L(B) - \overline{B})$, $(L(C) - \overline{C})$
- we then apply the above equation
- we consider all possible combinations of A, B, C

$$L(T) = (L(A) - \overline{A}) + (L(B) - \overline{B}) + (L(C) - \overline{C}) + \frac{1}{2}(\Delta_{AB} + \Delta_{AC} + \Delta_{BC})$$

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$$
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& + \tfrac{1}{2}\left(\tfrac{|A_2|-|A_1|}{|A|}\right)\Delta_{A_1 R} + \tfrac{1}{2}\left(\tfrac{|A_1|-|A_2|}{|A|}\right)\Delta_{A_2 R},
\end{aligned}
$$

- we divide subset A into 2 adjacent sets A_1 and A_2
- we then (independently) compute the 2 subtree structures which minimize $(L(A_1) - \overline{A_1})$, $(L(A_2) - \overline{A_2})$
- we then apply the above equation

- we consider all possible combinations of A_1, A_2

Reconstruction algorithm

$S \leftarrow n \times n$ matrix
$M \leftarrow n \times n$ matrix
for l from 1 to $n-3$ **do**
  for i from 1 to $n-l$ **do**
    compute $S_{i,i+l}$ and $M_{i,i+l}$
  end for
end for
$L^*(T) \leftarrow \infty$
for m_1 from 1 to $n-2$ **do**
  for m_2 from m_1+1 to $n-1$ **do**
    compute $L(T)$ for X_{1,m_1}, X_{m_1+1,m_2}, $X_{m_2+1,n}$
    if $L(T) < L^*(T)$ **then**
      $L^*(T) \leftarrow L(T)$, $m_1^* \leftarrow m_1$, $m_2^* \leftarrow m2$
    end if
  end for
end for
recreate T using M, starting from M_{1,m_1^*}, $M_{m_1^*+1,m_2^*}$ and $M_{m_2^*+1,n}$

First part

- consider an interval $X_{p,q}$
- $S_{p,q}$ stores the minimum value of $(L(X_{p,q}) - \overline{X_{p,q}})$ (calculated with the recurrence equation)
- computing $S_{p,q}$ requires evaluating all combinations $X_{p,m}$ and $X_{m+1,q}$ (using values in S from smaller interval sizes)
- $M_{p,q}$ stores the value of m for which $(L(X_{p,q}) - \overline{X_{p,q}})$ is minimum

Reconstruction algorithm

$S \leftarrow n \times n$ matrix
$M \leftarrow n \times n$ matrix
for l from 1 to $n-3$ **do**
  for i from 1 to $n-l$ **do**
    compute $S_{i,i+l}$ and $M_{i,i+l}$
  end for
end for
$L^*(T) \leftarrow \infty$
for m_1 from 1 to $n-2$ **do**
  for m_2 from m_1+1 to $n-1$ **do**
    compute $L(T)$ for X_{1,m_1}, X_{m_1+1,m_2}, $X_{m_2+1,n}$
    if $L(T) < L^*(T)$ **then**
      $L^*(T) \leftarrow L(T)$, $m_1^* \leftarrow m_1$, $m_2^* \leftarrow m2$
    end if
  end for
end for
recreate T using M, starting from M_{1,m_1^*}, $M_{m_1^*+1,m_2^*}$ and $M_{m_2^*+1,n}$

Complexity of the first part

- $O(n^2)$ intervals to consider in the first step
- each interval requires the evaluation of $O(n)$ combinations of adjacent sub-intervals
- each combination requires the 3 average distances to be calculated, takes $O(n^2)$ operations
- the time complexity is in $O(n^5)$, $O(n^3)$ with refinements, and $O(n^2)$ space

Complexity of the second part

- $O(n^2)$ combinations of 3 adjacent intervals to consider

- each combination requires the 3 average distances to be calculated, takes $O(n^2)$ operations

- the complexity is in $O(n^4)$, $O(n^2)$ with refinements

Complexity of the third part

- depth first tree traversal through the best intervals, takes $O(n)$ time

Algorithmic refinements

- calculating $(L(A) - \overline{A})$ requires 3 average distances to be calculated
- we consider growing intervals
- most of the work has already been done at previous interval sizes
- we only need to "update" average distances for new intervals
- reduces the complexity from $O(n^5)$ to $O(n^3)$

Summary

- single copy tandem duplication trees
- new recurrence equation to calculate the length of a given tree using OLS
- $O(n^3)$ time, $O(n^2)$ space exact algorithm using a DP framework to reconstruct the shortest single copy duplication tree

The future

- compare the topological accuracy with NJ, DTSCORE (Elemento and Gascuel, 2002)

- extend to multiple copy duplications

- use other distance criteria (eg weighted least-squares)