Phylogenetic Reconstruction and Applications

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collaborations with

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Corinaldo 2010

Outline

Outline

- The problem

Outline

- The problem
- Additive trees

Outline

- The problem
- Additive trees
- Iterative algorithms

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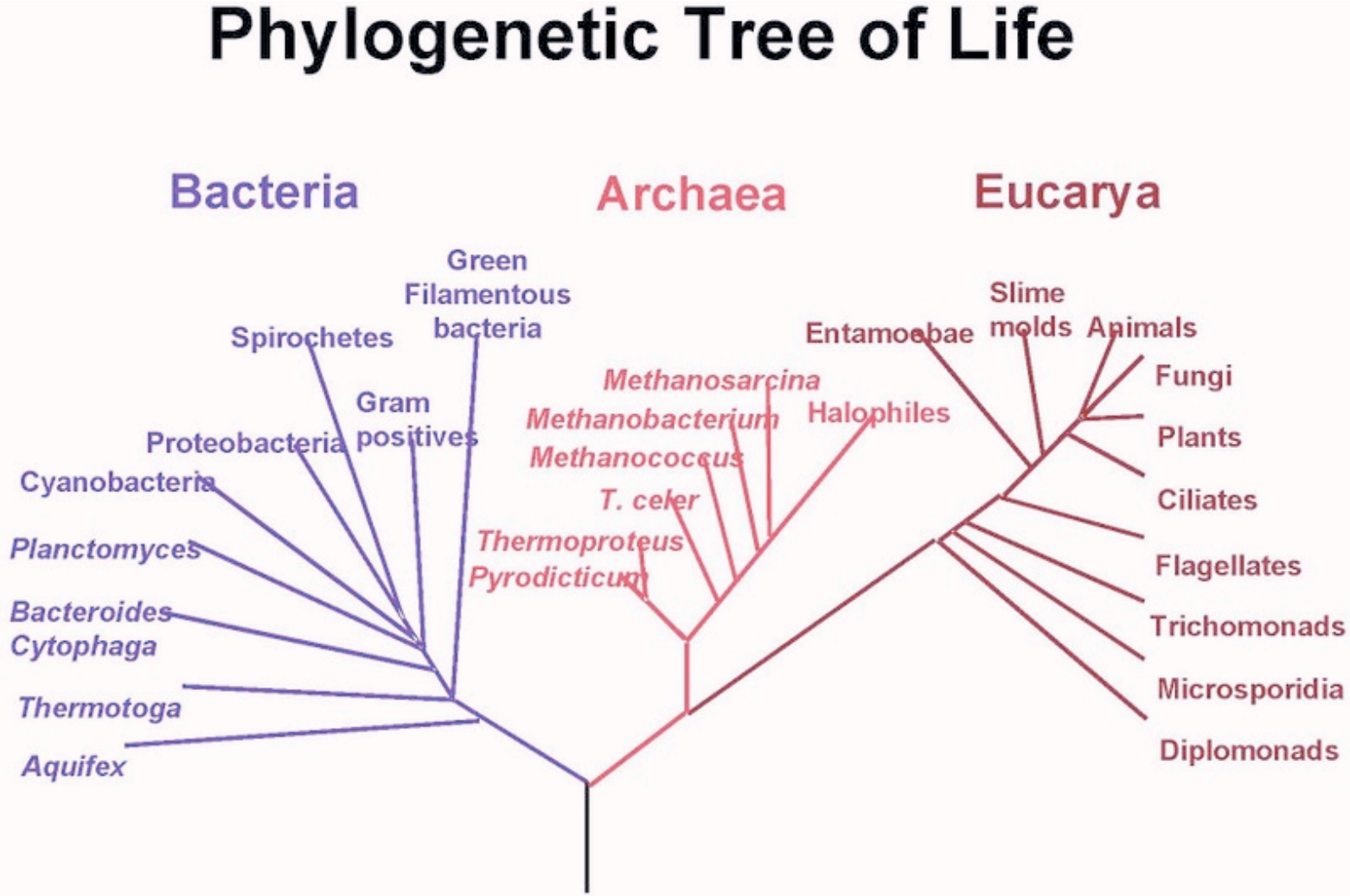
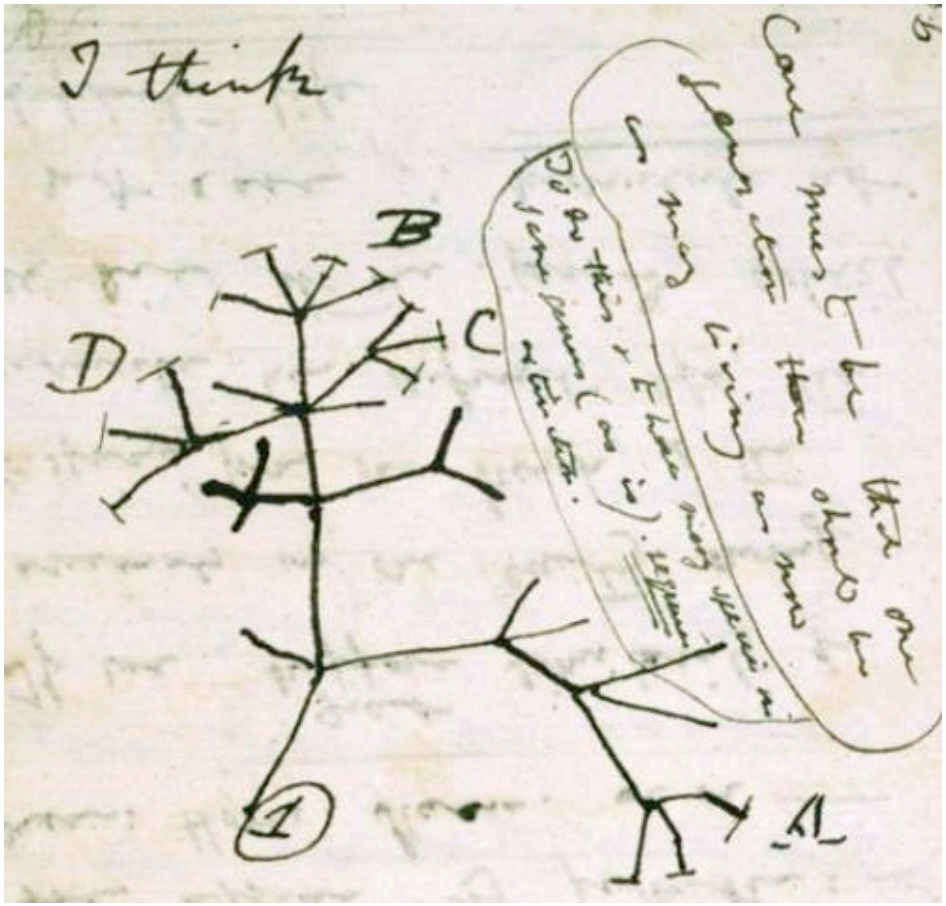
- The problem
- Additive trees
- Iterative algorithms
- Global (variational) algorithms


Phylogenetic Tree of Life
Bacteria
Archaea
Eucarya
Green
Filamentous
bacteria
Spirochetes
Gram
positives
Proteobacteria
Cyanobacteria
Planctomyces
Bacteroides
Cytophaga
Thermotoga
Aquifex
Methanosarcina
Methanobacterium
Methanococcus
T. celer
Halophiles
Thermoproteus
Pyrodicticum
Slime
molds
Entamoebae
Animals
Fungi
Plants
Ciliates
Flagellates
Trichomonads
Microsporidia
Diplomonads

Darwin's tree of life




nel mezzo del cammin di nostra vita
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nel mezzo di cammin di vostra vita
nel mezzo di cammin di nostra via
nel mezzo di cammin di nostra vita
a mezzo di cammino di nostra vita
mutation
back mutation

A simple evolutionary model

A simple evolutionary model

Simulate the evolution changing randomly binary sequences with a certain mutation rate per site and branching at Poisson times

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mutation

back mutation

Algorithms for Phylogenetic reconstruction

Algorithms for Phylogenetic reconstruction

Distance based

Characters based

Algorithms for Phylogenetic reconstruction

Distance based

Infer the tree using the distance matrix only

UPGMA

Neighbor Joining

Fitch

Weighbor

FASTME

Characters based

Algorithms for Phylogenetic reconstruction

Distance based

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Characters based

Compare different sequences character by character

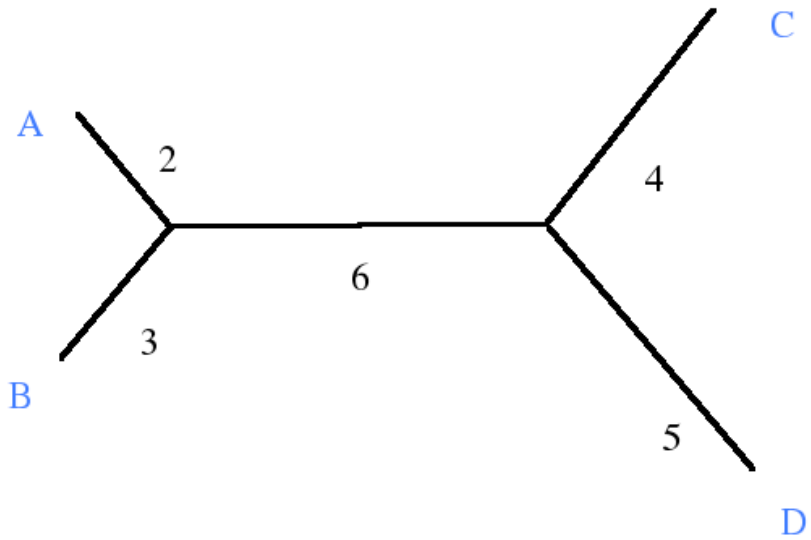
Parsimony

MrBayes

Additivity

Definition. A distance matrix is additive if there exists a tree on which, for each pair of taxa X, Y, $d_{X,Y}$ is the sum of the length of the branches connecting X and Y

Additivity



	A	B	C	D
A	0	5	12	13
B	5	0	13	14
C	12	13	0	9
D	13	14	9	0

Four Point Condition

Definition.

A distance is additive iff for any four taxa A,B,C,D it is

$$d_{A,B} + d_{C,D} < d_{A,C} + d_{B,D} = d_{A,D} + d_{B,C}$$

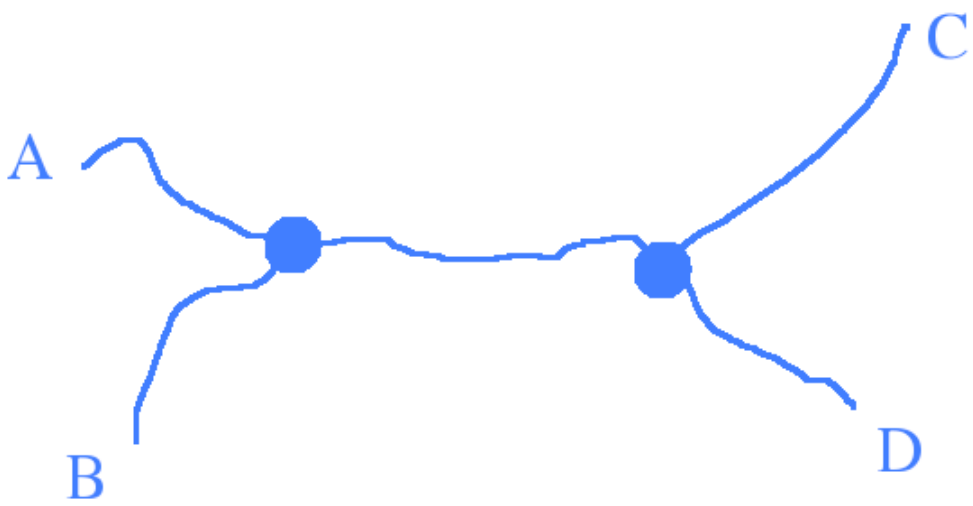
or

$$d_{A,C} + d_{B,D} < d_{A,B} + d_{C,D} = d_{A,D} + d_{B,C}$$

or

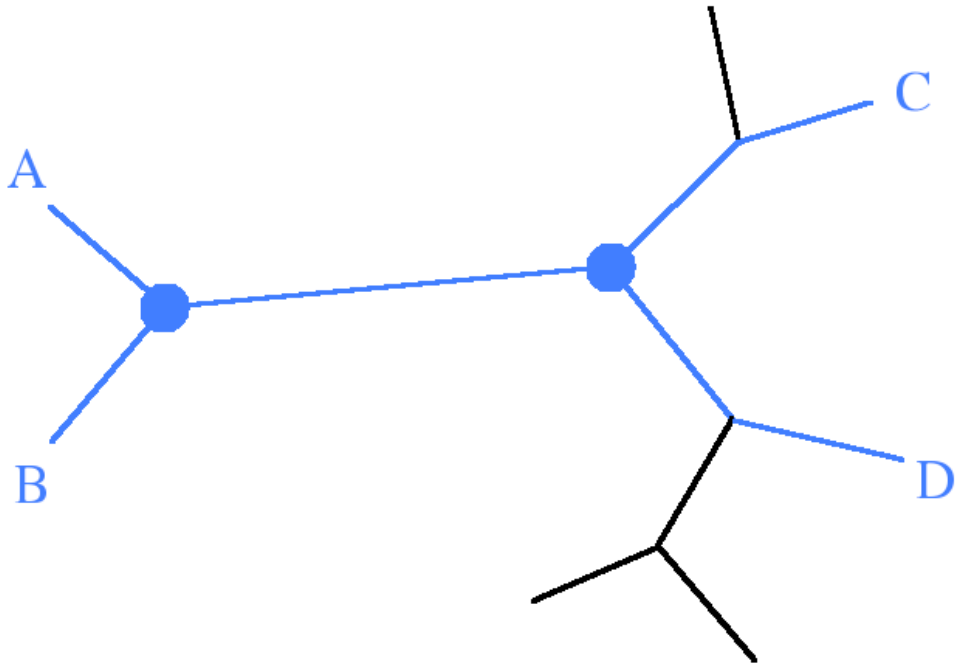
$$d_{A,D} + d_{B,C} < d_{A,C} + d_{B,D} = d_{A,B} + d_{C,D}$$

Four Point Condition



$$d_{A,B} + d_{C,D} < d_{A,C} + d_{B,D} = d_{A,D} + d_{B,C}$$

Four Point Condition



$$d_{A,B} + d_{C,D} < d_{A,C} + d_{B,D} = d_{A,D} + d_{B,C}$$

Iterative Algorithms

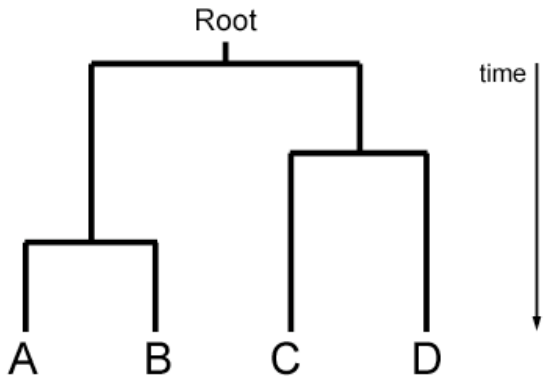
UPGMA

- connect the two nearest taxa XY
- compute the distance between the new taxa and the other taxa
- iterate till there remain only 3 taxa

Neighbor Joining

UPGMA works for ultrametric trees but not for additive trees in general

ultrametricity $\leftrightarrow$ constant evolutive speed



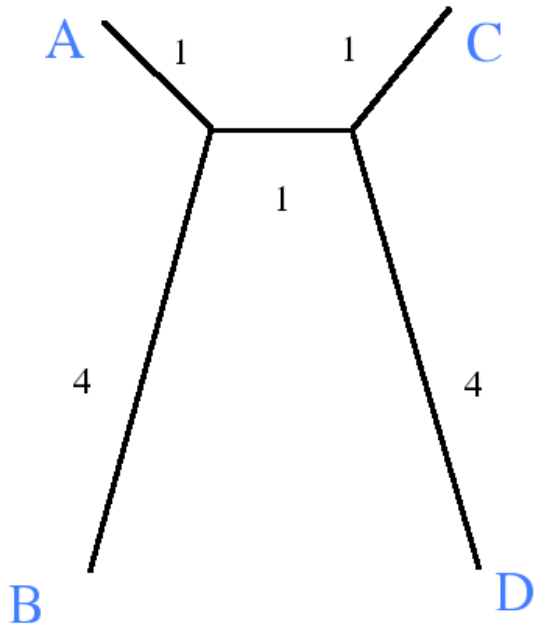
ultrametricity: for any three leaves a, b, c

$$d_{a,b} \leq \max(d_{a,c}, d_{b,c})$$

Neighbor Joining

UPGMA works for ultrametric trees but not for additive trees in general

ultrametricity $\leftrightarrow$ constant evolutive speed



$$d_{A,C} < d_{A,B}$$

Neighbor Joining

Define the matrix D as

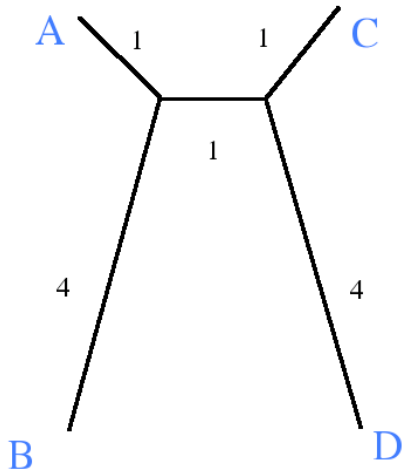
$$D_{X,Y} = d_{x,y} - r_X - r_Y$$

where

$$r_X = \frac{1}{N-2} \sum_Y d_{X,Y}$$

- connect the two taxa which minimizes $D_{X,Y}$
- compute D between the new taxa and the other taxa
- iterate till there remain only 3 taxa

Saitou and Nei 1987



$$r_A = r_C = \frac{5+3+6}{2} = 7, \qquad r_B = r_D = \frac{5+6+9}{2} = 10$$

$$d = \begin{pmatrix} 0 & 5 & 3 & 6 \\ 5 & 0 & 6 & 9 \\ 3 & 6 & 0 & 5 \\ 6 & 9 & 5 & 0 \end{pmatrix} \qquad D = \begin{pmatrix} 0 & -12 & -11 & -11 \\ -12 & 0 & -11 & -11 \\ -11 & -11 & 0 & -12 \\ -11 & -11 & -12 & 0 \end{pmatrix}$$

Properties of NJ

- Theorem (Saitou and Nei)
  If the tree is additive then NJ reconstruct the correct tree.
  Main ingredient: if X.Y minimizes D then X,Y is a cherry

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- Theorem (Saitou and Nei)
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  Main ingredient: if X.Y minimizes D then X,Y is a cherry
- Stability Theorem (K. Atteson 1997) If the distance estimates are at most half of the minimal edge length of the tree away from their true value then Neighbor-Joining will reconstruct the correct tree
- Neighbor Joining runs in $O(N^3)$ time

Pauplin Formula

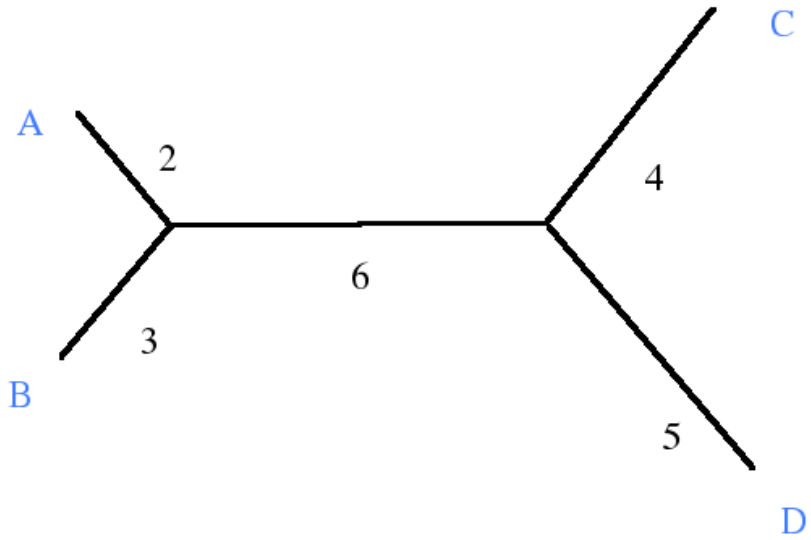
If a distance is additive than the total length of the corresponding tree is given by

$$P = \sum_{\{X,Y\}} 2^{-t_{X,Y}} d_{X,Y}$$

where $t_{X,Y}$ is the number of nodes between X and Y

Pauplin Formula

$$L = \frac{1}{2}d_{A,B} + \frac{1}{4}d_{A,C} + \frac{1}{4}d_{A,D} + ... = 20$$



Y. Pauplin 2000

Proof of Pauplin formula

Let L be the length of the tree: i.e.

$$L = \sum_{k:k\ edge} l_k$$

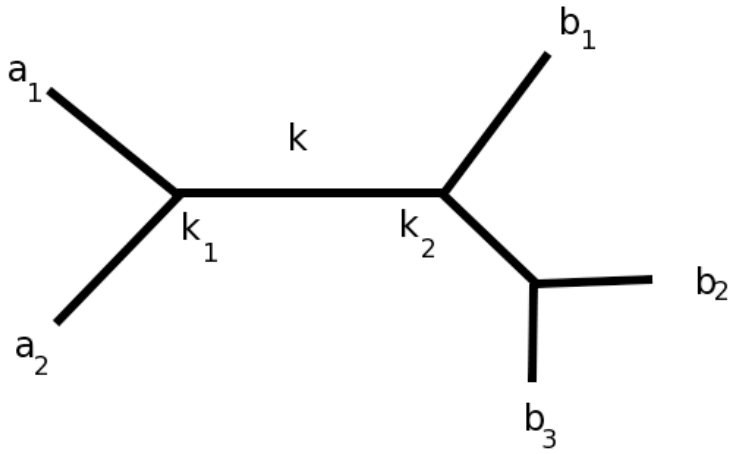
where we denoted with l_k the length of the edge k.
The Pauplin expressione P can be written as

$$\begin{aligned} P = & \sum_{a,b} 2^{-t_{a,b}} d_{a,b} \\ = & \sum_{a,b} \sum_{k \in w_{a,b}} 2^{-t_{a,b}} l_k \\ = & \sum_k l_k \sum_{a,b} 1_{k \in w_{a,b}} 2^{-t_{a,b}} \end{aligned}$$

where $\sum_{a,b}$ denotes the sum on distinct pair of leaves a, b and where we denoted with $W_{a,b}$ the set of edges connecting the leaf a with the leaf b.
Given an edge k, let us denote with k_1 and k_2 the two nodes connected by k, and let us denote with T_1 and T_2 the two trees which has roots in k_1 and k_2 , respectively.
We can notice that

$$\sum_{a,b} 1_{k \in W_{a,b}} 2^{-t_{a,b}} = \sum_{a \in T_1} \sum_{b \in T_2} 2^{-t_{a,b}}$$

in fact all the pairs which contribute to the above sum have one leaf in T_1 and the other in T_2.



Now we can notice that for any $a \in T_1$, and $b \in T_2$ we can write

$$t_{a,b} = z_a + z_b$$

where z_a is the the number of branches in the path between a and k_1 and where z_b is the number of branches in the path between b and k_2.

Therefore

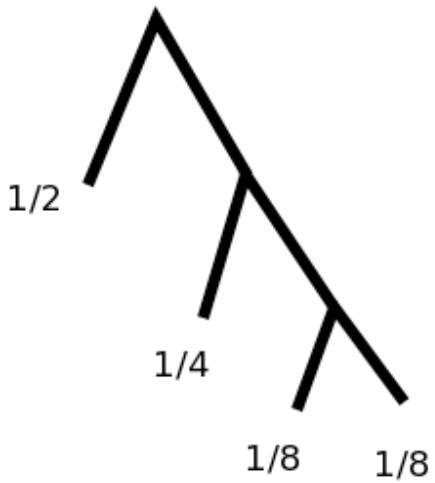
$$\sum_{a\in T_1}\sum_{b\in T_2} 2^{-t_{a,b}} = \sum_{a\in T_1}\sum_{b\in T_2} 2^{-z_a-z_b} = \sum_{a\in T_1} 2^{-z_a}\sum_{b\in T_2} 2^{-z_b} = 1\cdot 1 = 1 \tag{1}$$

by Kraft equality.

Kraft Equality

In a binary tree let z_k be the depth of the leaf k. Then

$$\sum_k 2^{-z_k} = 1$$



Balanced Minimum Evolution Principle

If a distance is additive the right tree T is the one that minimizes

$$L_T = \sum_{\{X,Y\}} 2^{-t_{X,Y}} d_{X,Y}$$

R. Desper, O.Gascuel 2003

A BME Algorithm

A BME Algorithm

Define an Energy:

$$E = \sum_{a,b} 2^{-t_{a,b}} d_{a,b}$$

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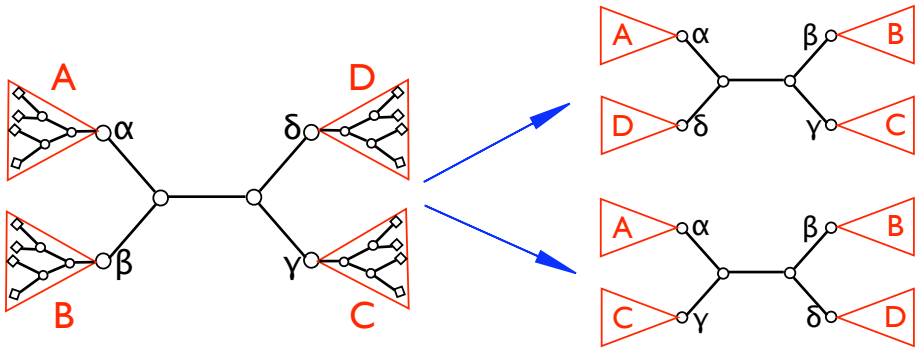
Define an elementary move



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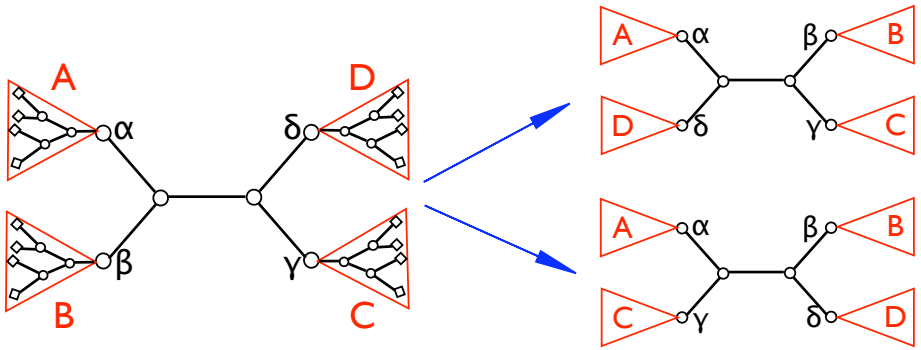

- start from a reasonable tree (NJ tree)

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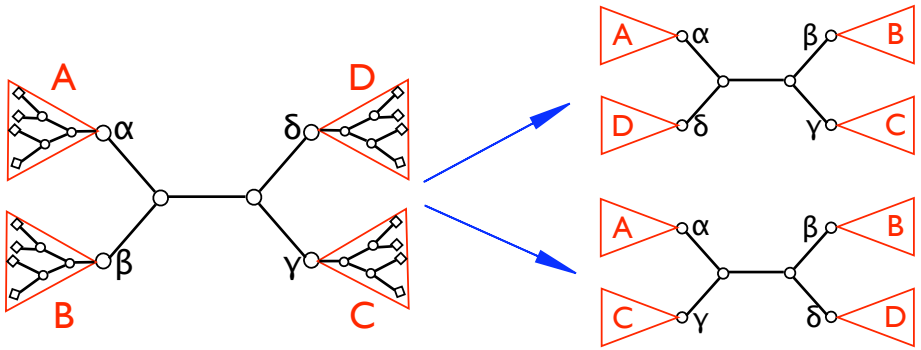

- start from a reasonable tree (NJ tree)
- extract a link

A BME Algorithm

Define an Energy:

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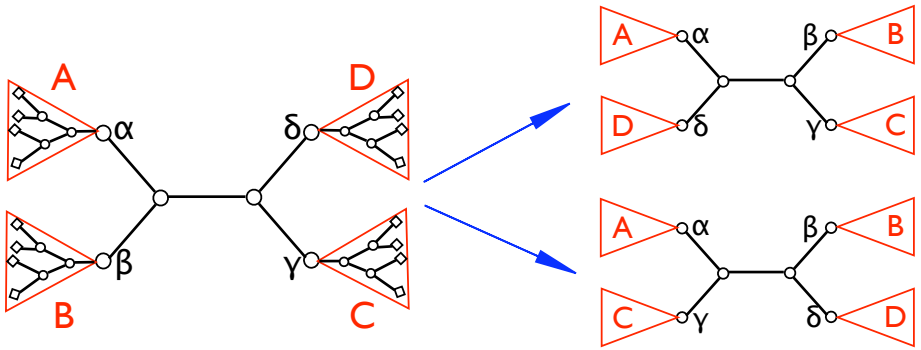
Define an elementary move



- start from a reasonable tree (NJ tree)
- extract a link
- extract an elementary move

A BME Algorithm

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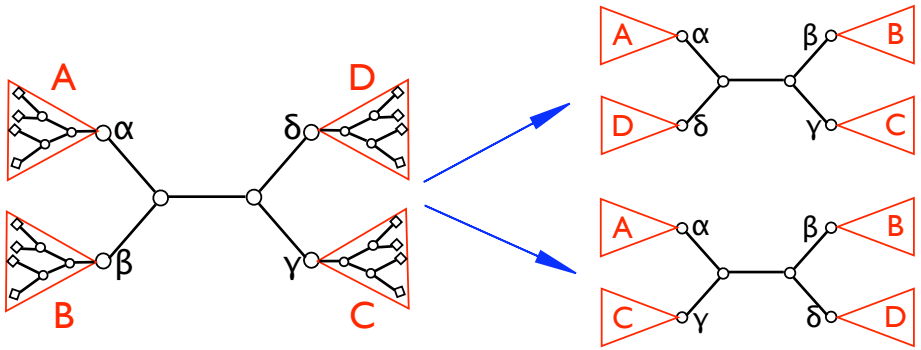
Define an elementary move



- start from a reasonable tree (NJ tree)
- extract a link
- extract an elementary move
- accept the move if $\Delta E < 0$

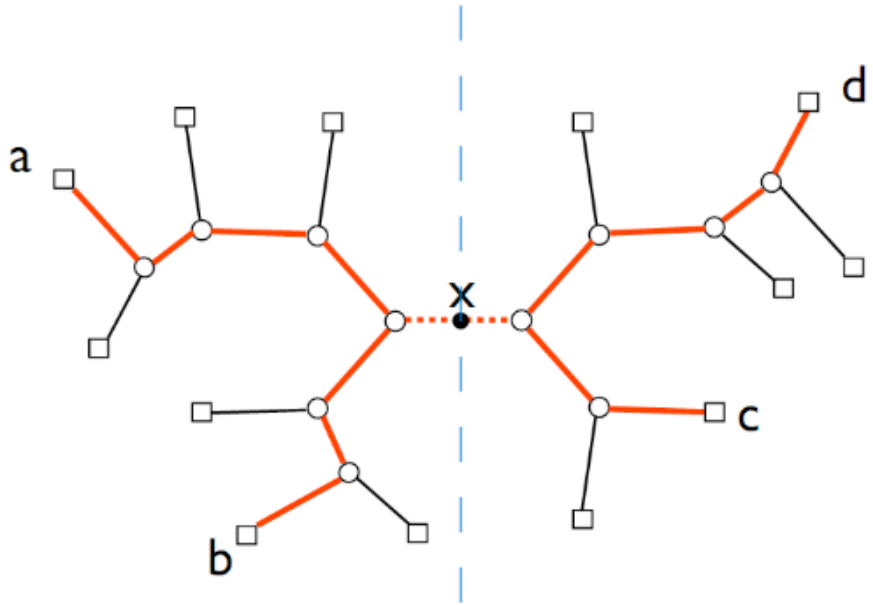
FASTME algorithm

$$\sum_{\{X,Y\}} 2^{-t(X,Y)} d(X,Y)$$

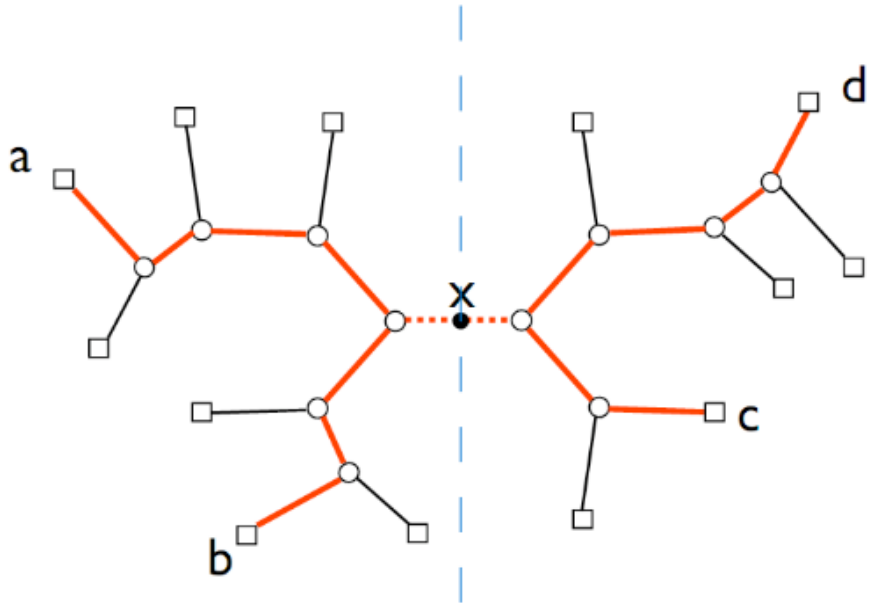
The algorithm FASTME starts form a reasonable tree (NJ tree) and then makes suitable elementary moves to minimize the formula above

O. Gascuel and M. Steel 2006

Quartet Based Algortihms



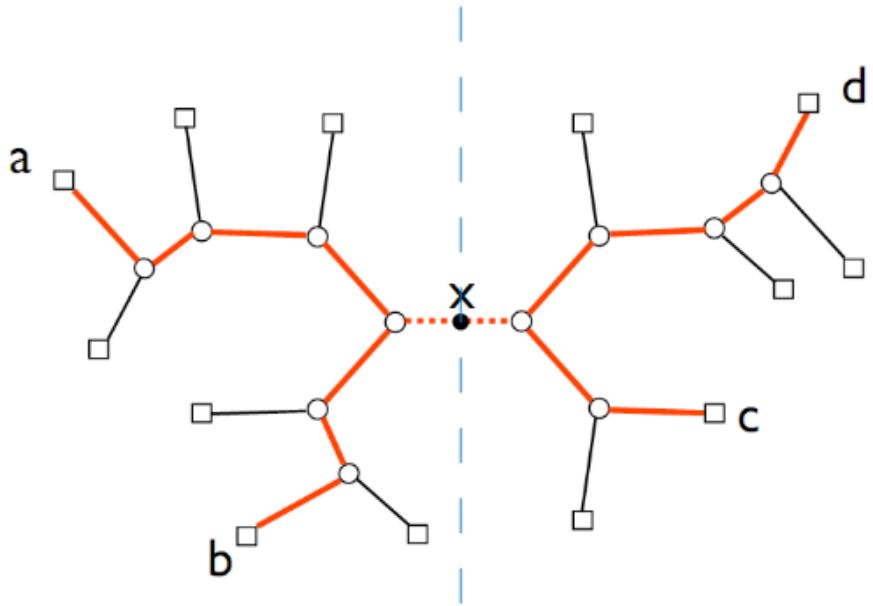
Quartet Based Algortihms



strong four points condition

$$d_{A,B} + d_{C,D} < d_{A,C} + d_{B,D} = d_{A,D} + d_{B,C}$$

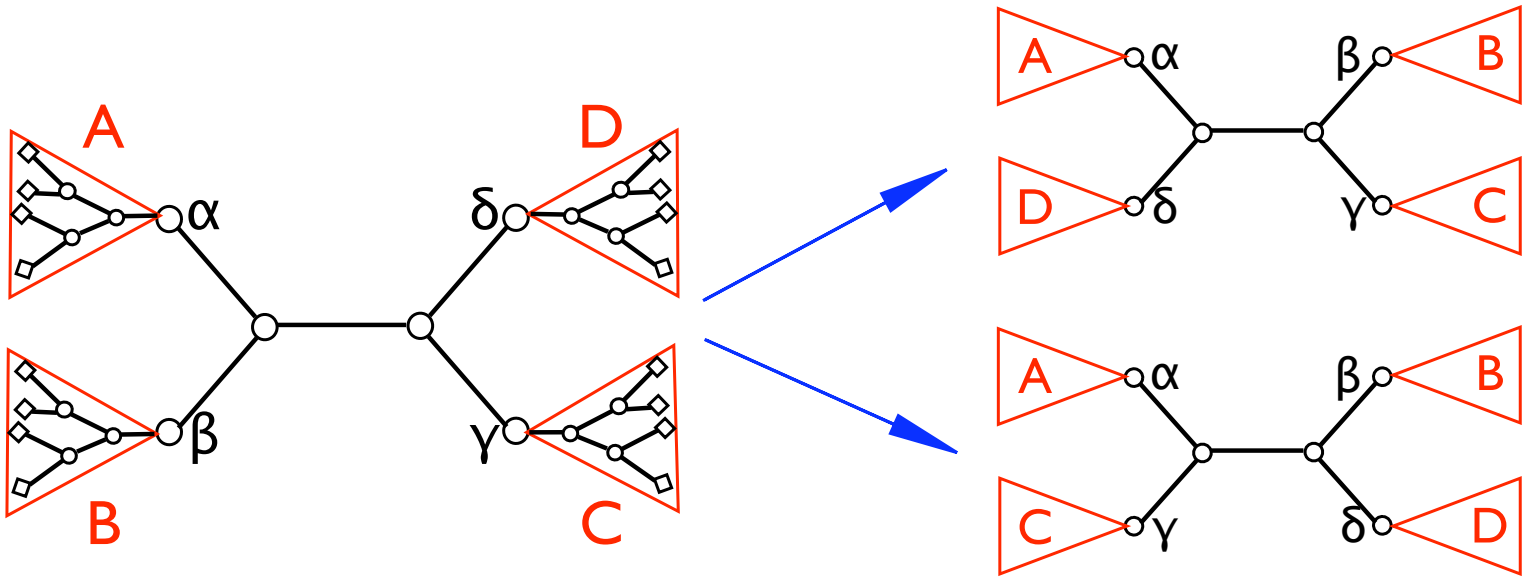
Quartet Based Algortihms



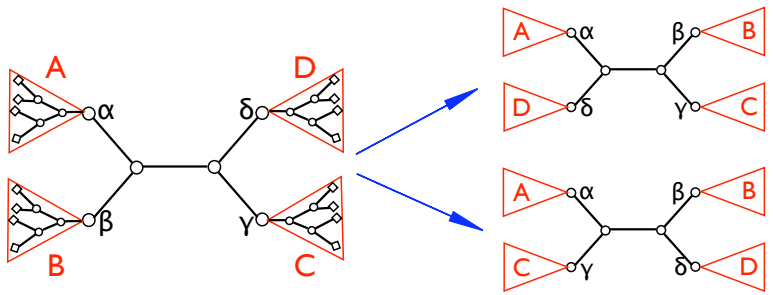
soft four points condition

$$d_{A,B} + d_{C,D} < min(d_{A,C} + d_{B,D}, d_{A,D} + d_{B,C})$$

A Quarted Based Algorithms: Elementary Move



A Quarted Based Algorithms: Elementary Move



for any $a \in A, b \in B, c \in C, d \in D$

define $D_1 = d_{a,b} + d_{c,d}, D_2 = d_{a,c} + d_{c,d}, D_3 = d_{a,d} + d_{b,c}$

define quartet frustration as

$$f_{(a,b)(c,d)} = max(0, D_1 - min(D_2, D_3))$$

A Quartet Based Algorithm

define configuration energy

$$E_{(A,B),(C,D)} = \sum_{a\in A, b\in B, c\in C, d\in D} 2^{-n(a,\alpha)-n(b,\beta)-n(c,\gamma)-n(d,\delta)} f_{(a,b),(c,d)}$$

A Quartet Based Algorithm

define configuration energy

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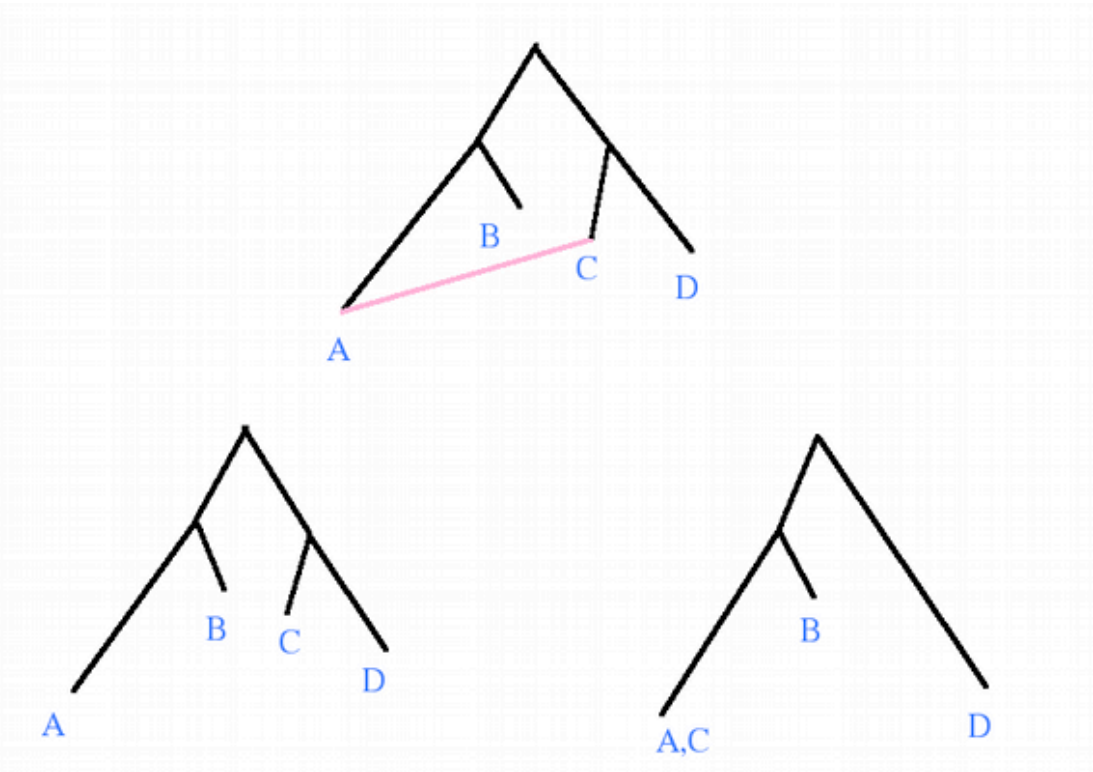
ΔE is the variation of a functional and the functional is the Pauplin length L_T

Horizontal Transfer

An entire part of sequence A is copied in sequence C
As a result the distance matrix is the convex combination of two additive matrices, then it is not an additive matrix



Phylogeny reconstruction with applications in linguistics and biology

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joint work with

Vittorio Loreto Sapienza Università di Roma & ISI

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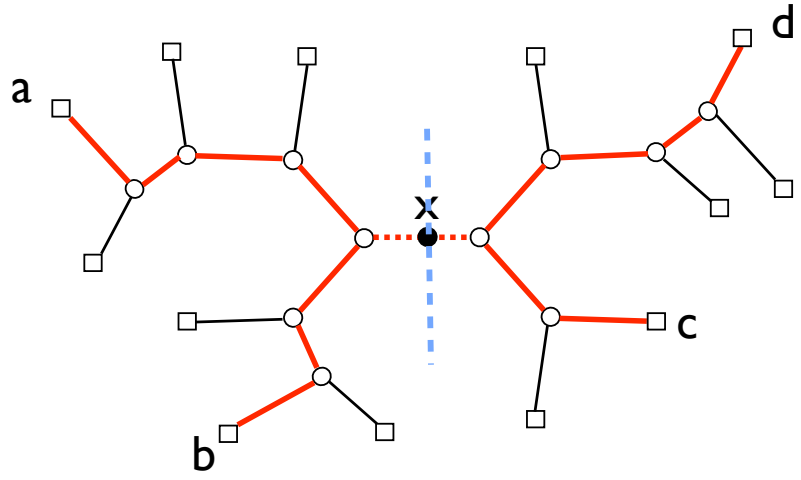
- Algorithms
- An application in linguistics

Outline

- Algorithms
- An application in linguistics
- A biology related problem

A recall

Soft four points condition

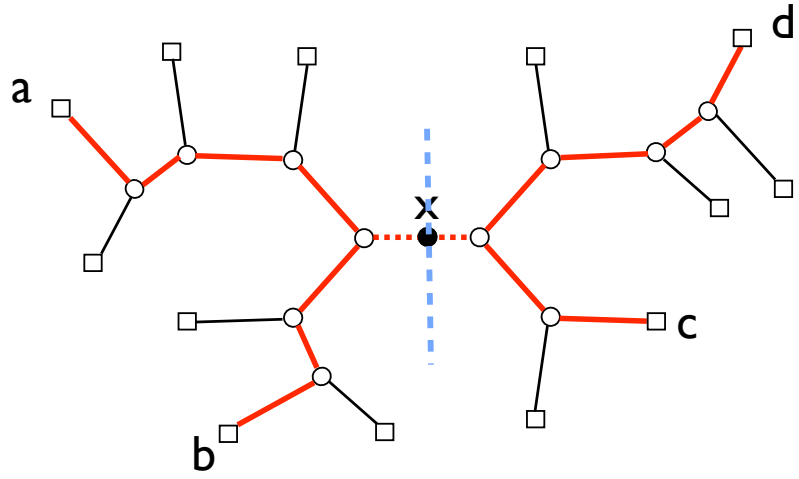


$$D_1 = d_{a,b} + d_{c,d}, D_2 = d_{a,c} + d_{c,d}, D_3 = d_{a,d} + d_{b,c}$$

$$D_1 = \min(D_1, D_2, D_3)$$

A recall

Soft four points condition

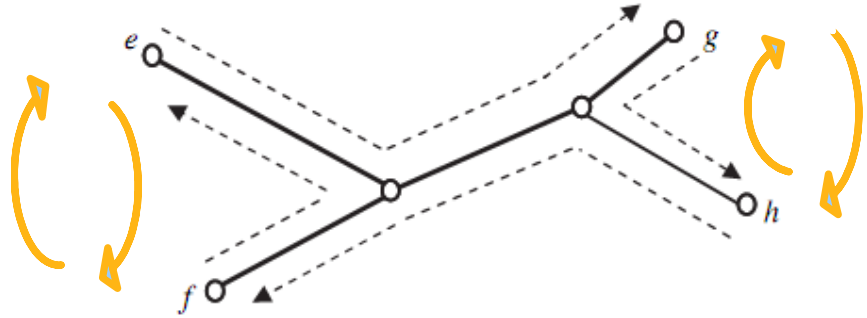


$$D_1 = d_{a,b} + d_{c,d}, D_2 = d_{a,c} + d_{c,d}, D_3 = d_{a,d} + d_{b,c}$$

$$D_1 = \min(D_1, D_2, D_3)$$

Pauplin's formula

$$L_P = \sum_{a<b} 2^{-t(a,b)} \mathcal{D}(a,b)$$

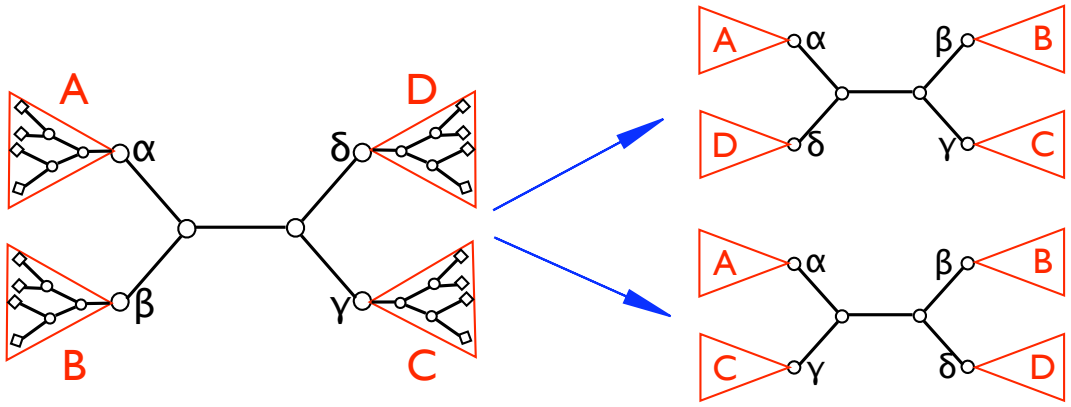


O. Gascuel and M. Steel 2006

$$l = \frac{1}{2}[d(e,g) + d(g,h) + d(h,f) + d(f,e)]$$

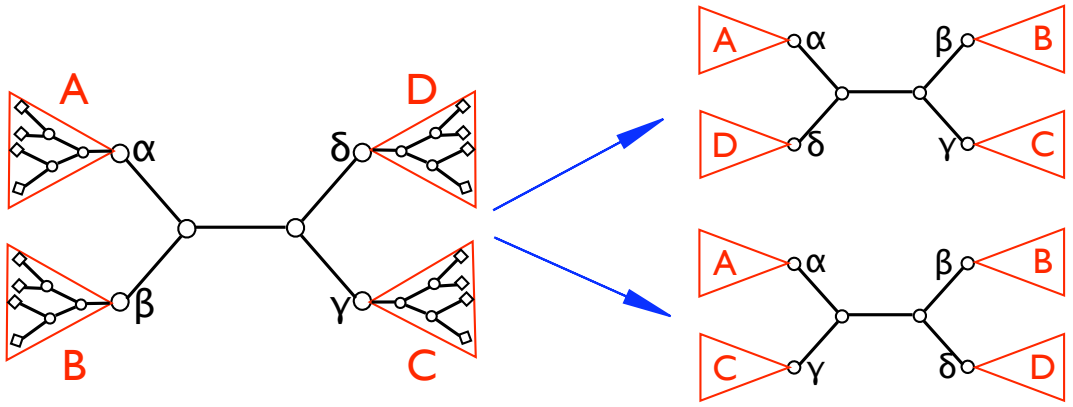
$$L_P = \frac{1}{2}[d(e,f) + d(g,h)] + \frac{1}{4}[d(e,g) + d(e,h) + d(f,h) + d(f,g)] \qquad L_P = l$$

Stochastic local search algorithms (SLS)



elementary moves (NNI)

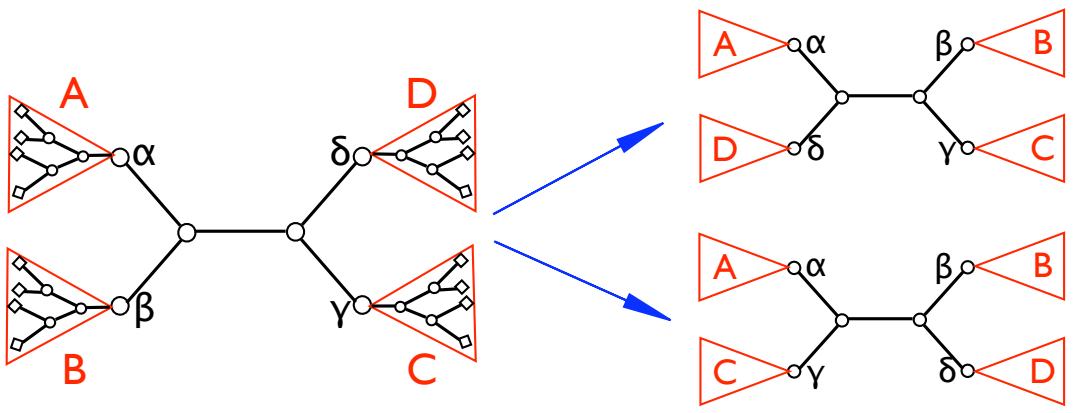
Stochastic local search algorithms (SLS)



elementary moves (NNI)

1. extract a link
2. extract an elementary move
3. accept the move with probability $e^{-\beta \Delta E}$

Stochastic local search algorithms (SLS)



elementary moves (NNI)

1. extract a link
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simulated annealing-like procedure:

β (*inverse temperature*) increases with time

zero temperature procedure:

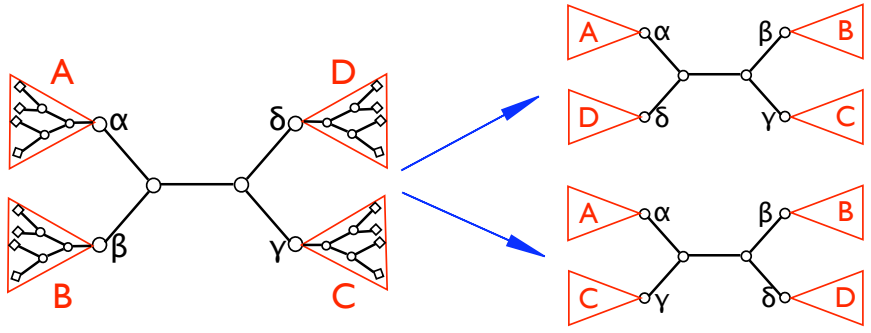
$\beta = +\infty \longleftrightarrow$ accept the move iff $\Delta E < 0$

Local (configurational) energy definition based on the soft four points condition

Local (configurational) energy definition based on the soft four points condition

for any

$$a \in A, b \in B, c \in C, d \in D$$



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Local (configurational) energy definition based on the soft four points condition

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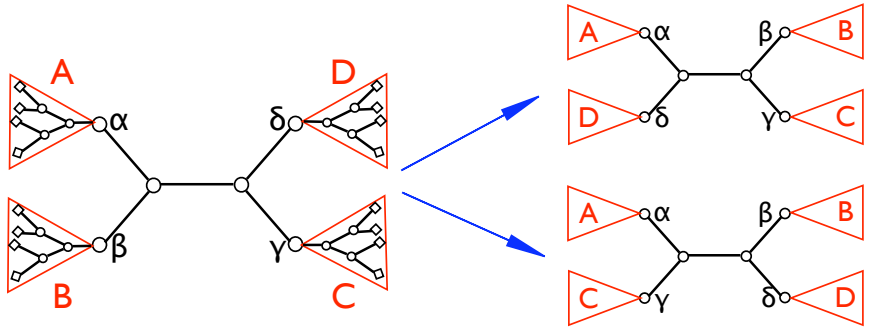

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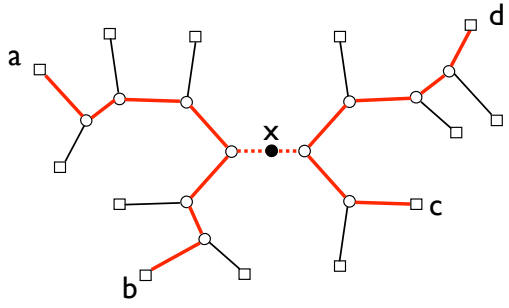

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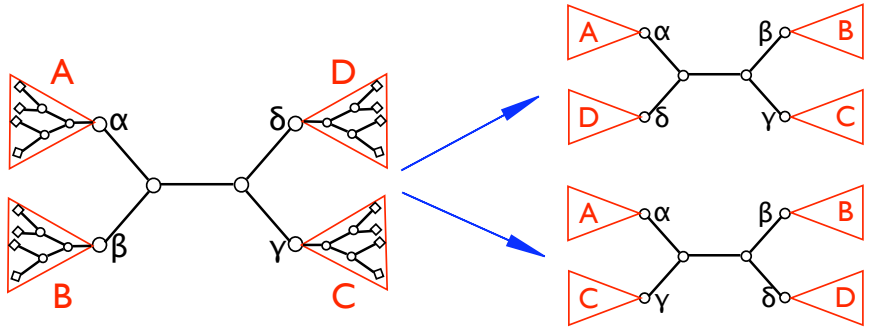

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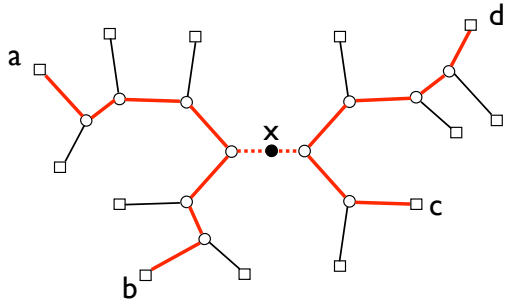

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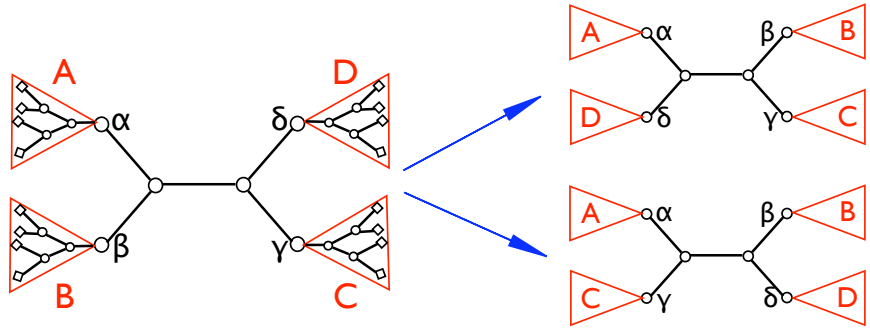

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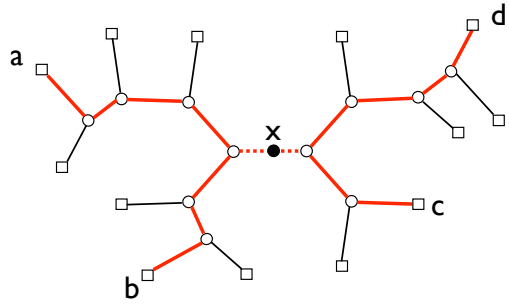

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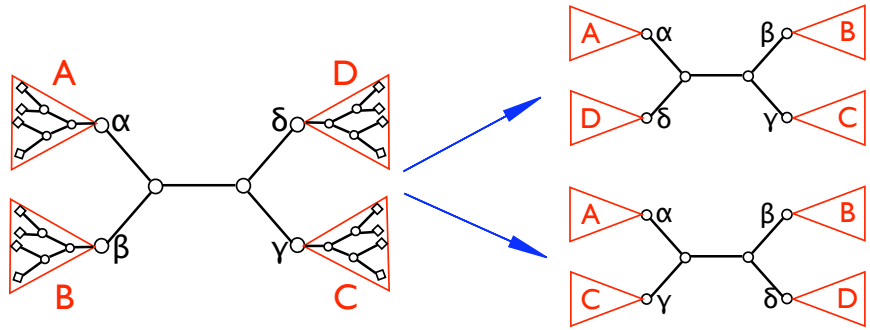

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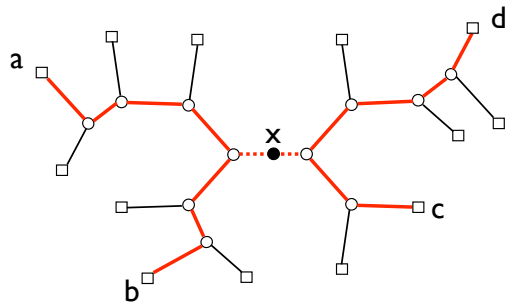

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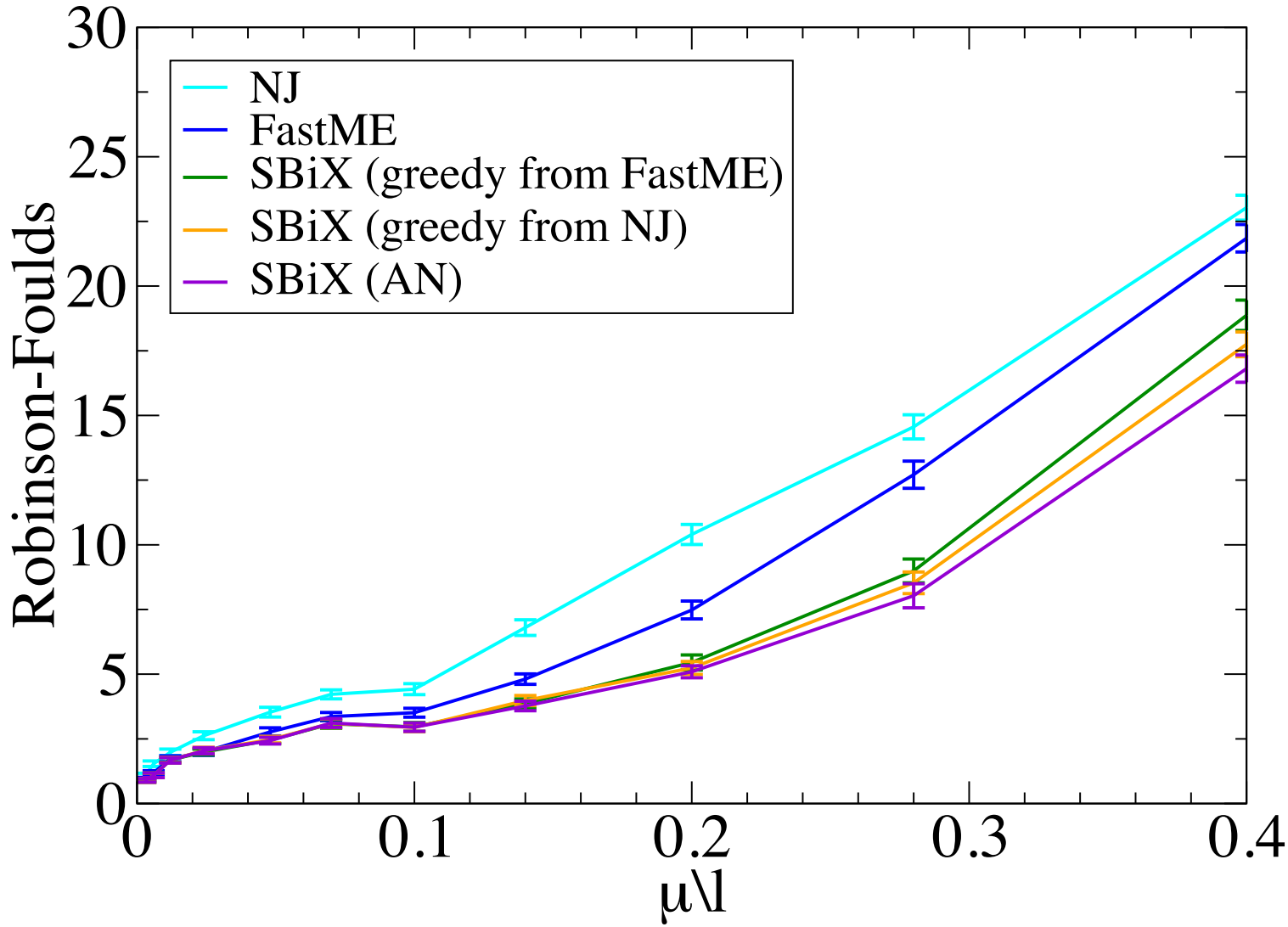
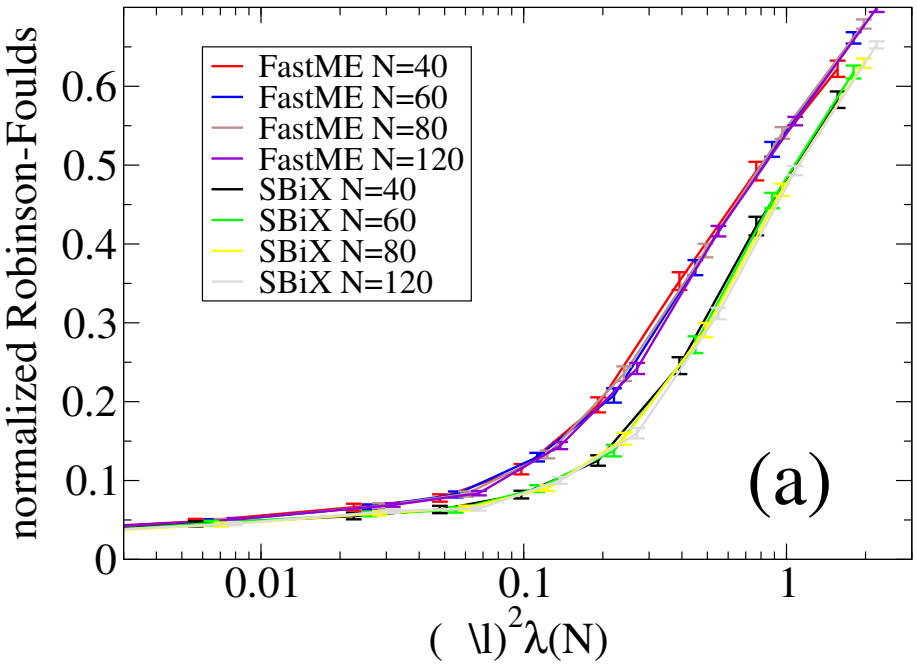
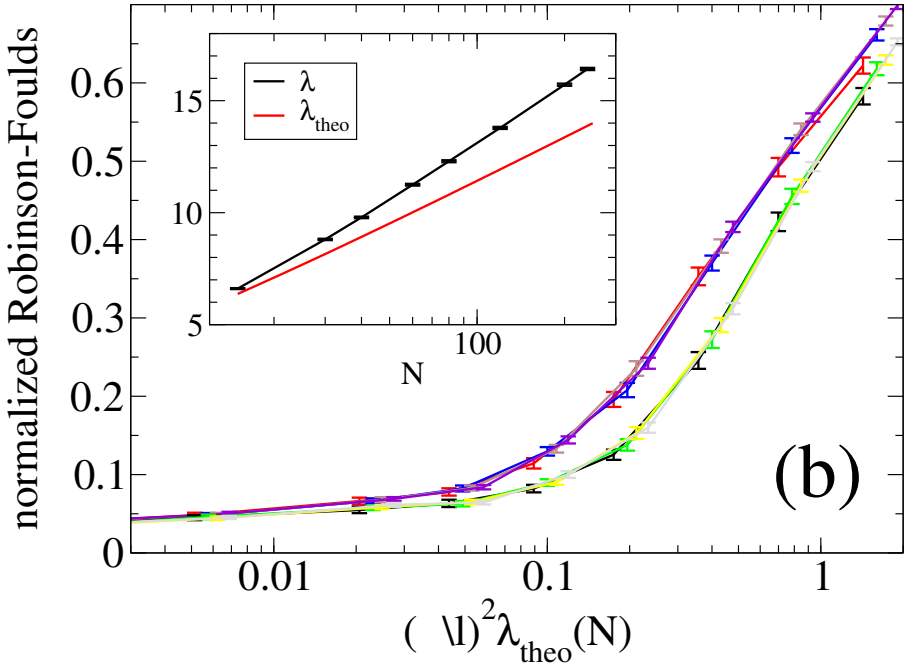
Why choosing 2.? It works better

Performances of distance-based reconstruction algorithms as a function of mutation rate per site



Scaling behavior with the number of taxa N





dependence on $\mu^2\lambda(N)$

$\lambda(N)$ mean distance between leaves

$$\lambda_{\text{theo}}(N) = \frac{2N(\log_2 N + 1) - 4N + 2}{N - 1}$$ for completely balanced trees

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still good for large phylogenies (~ 1000 taxa)

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In general, areas where the phylogeny
is important for prediction

Subtree representatives

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$$\mathcal{M}_1 = M_{\alpha,\beta} + M_{\gamma,\delta}$$
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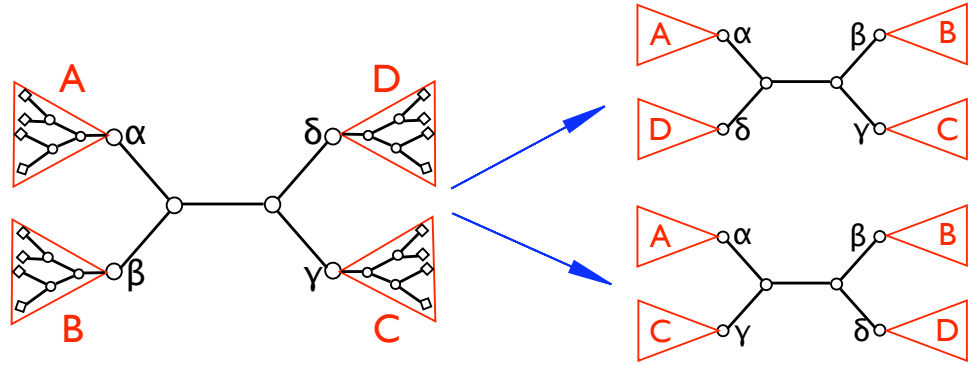

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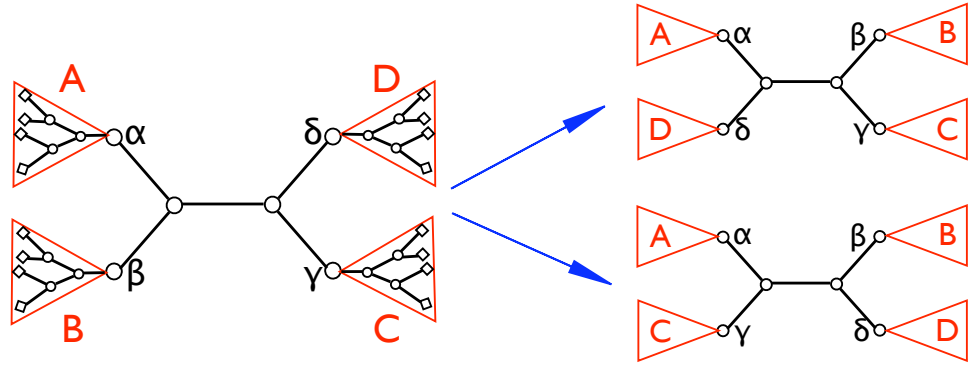

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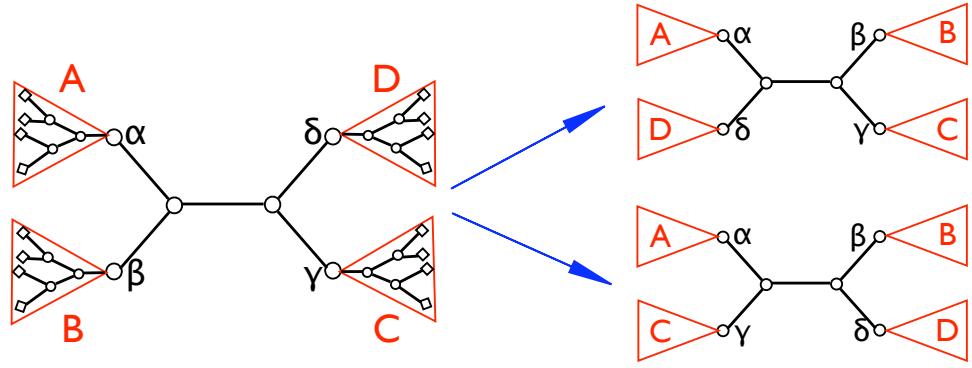

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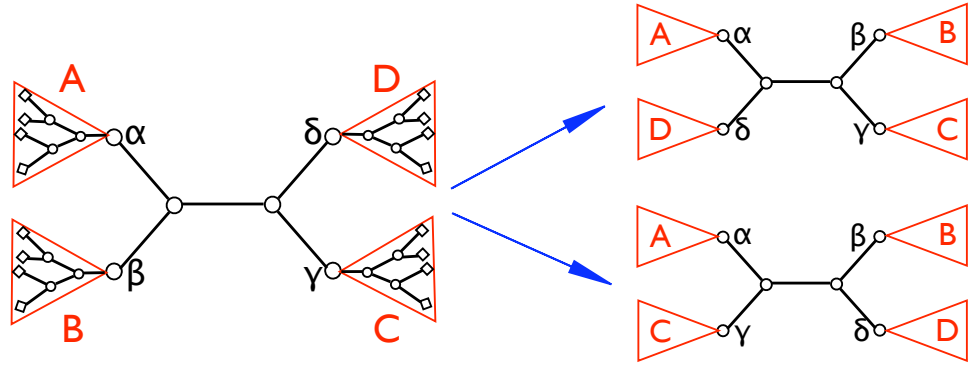

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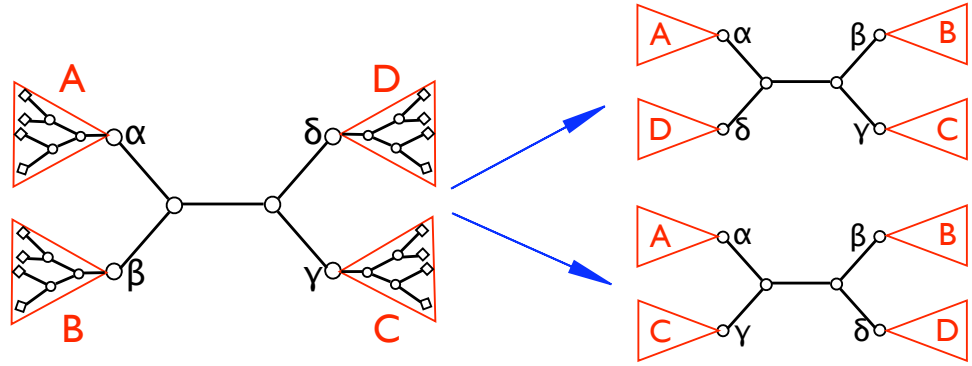

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Introduce the idea that longer distances have larger fluctuations

for each leaf *a* we define a *length*

$$l_a = \frac{1}{N_B}\sum_{b\in B}\mathcal{D}(a,b) + \frac{1}{N_C}\sum_{c\in C}\mathcal{D}(a,c) + \frac{1}{N_D}\sum_{d\in D}\mathcal{D}(a,d)$$

the idea is filtering leaves' contributions using this length

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Identify the weight p_a with the probability of considering the leaf *a* when defining the subtree representative

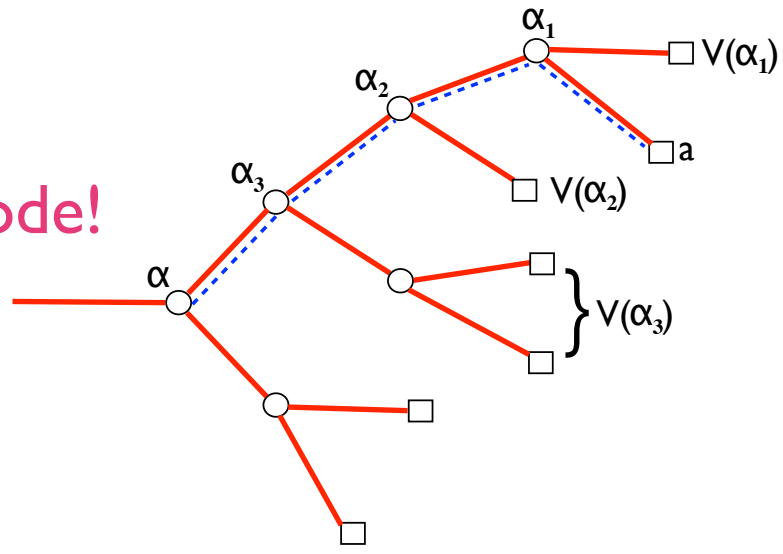
Compute the effective Pauplin weights
by using a suitable partition function

$$w_a = \sum_{\{\sigma(\alpha_i)\}} \mathrm{P}(\alpha_1, \alpha_2, \alpha_3) 2^{-\sigma(\alpha_1)-\sigma(\alpha_2)-\sigma(\alpha_3)}$$

$$\sigma(\alpha_i) \in \{0, 1\}$$

but the probability factorizes on each node!

$$w_a = \frac{1}{2^{n(\mathcal{P}_a)}} \prod_{\alpha_i \in \mathcal{P}_a} \left(1 + \prod_{a_i \in V(\alpha_i)} (1 - p_{a_i}) \right)$$



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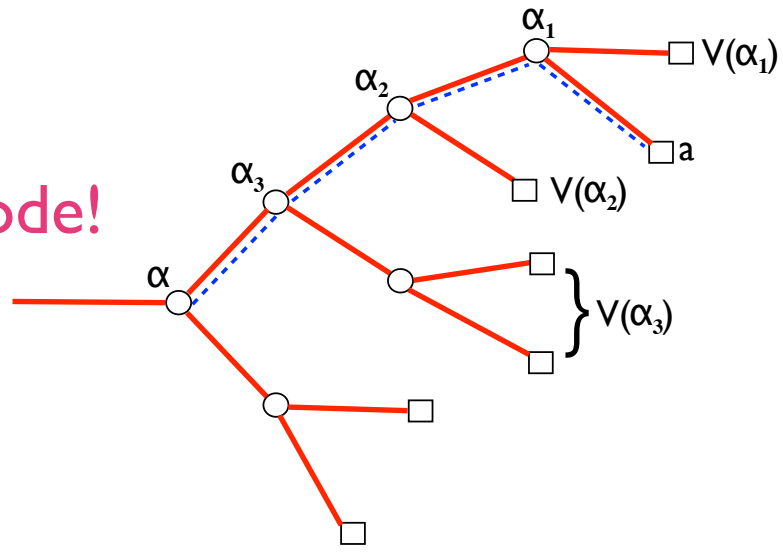

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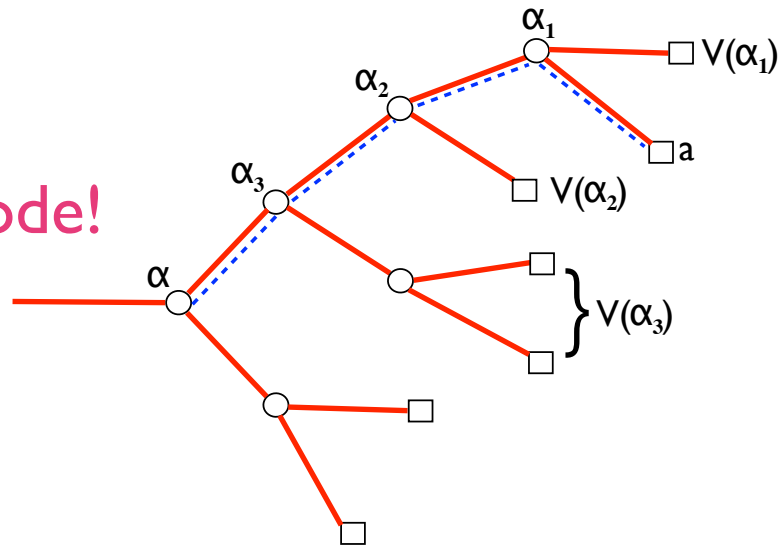

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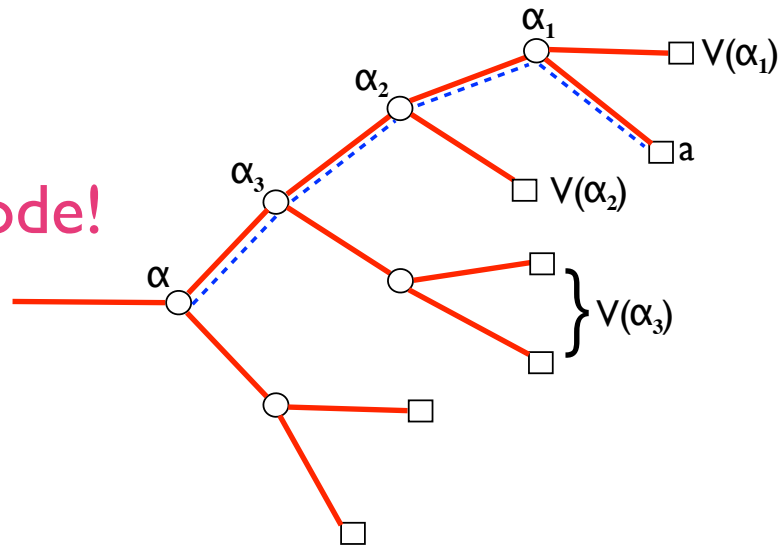

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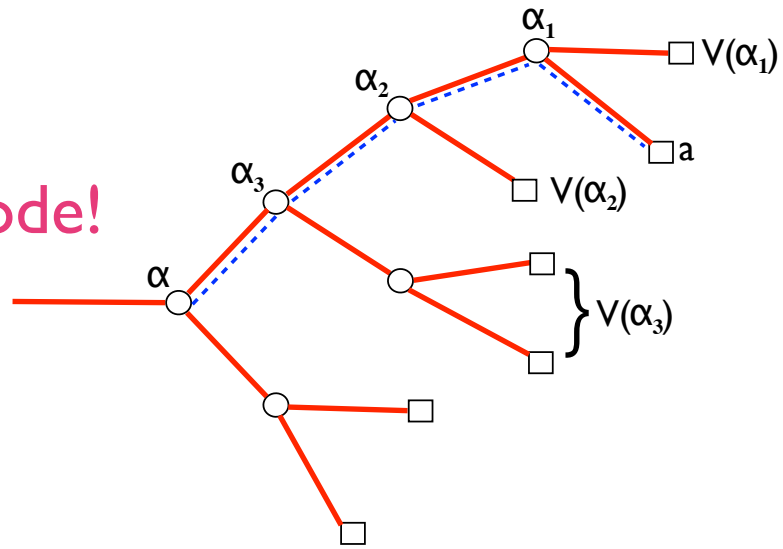

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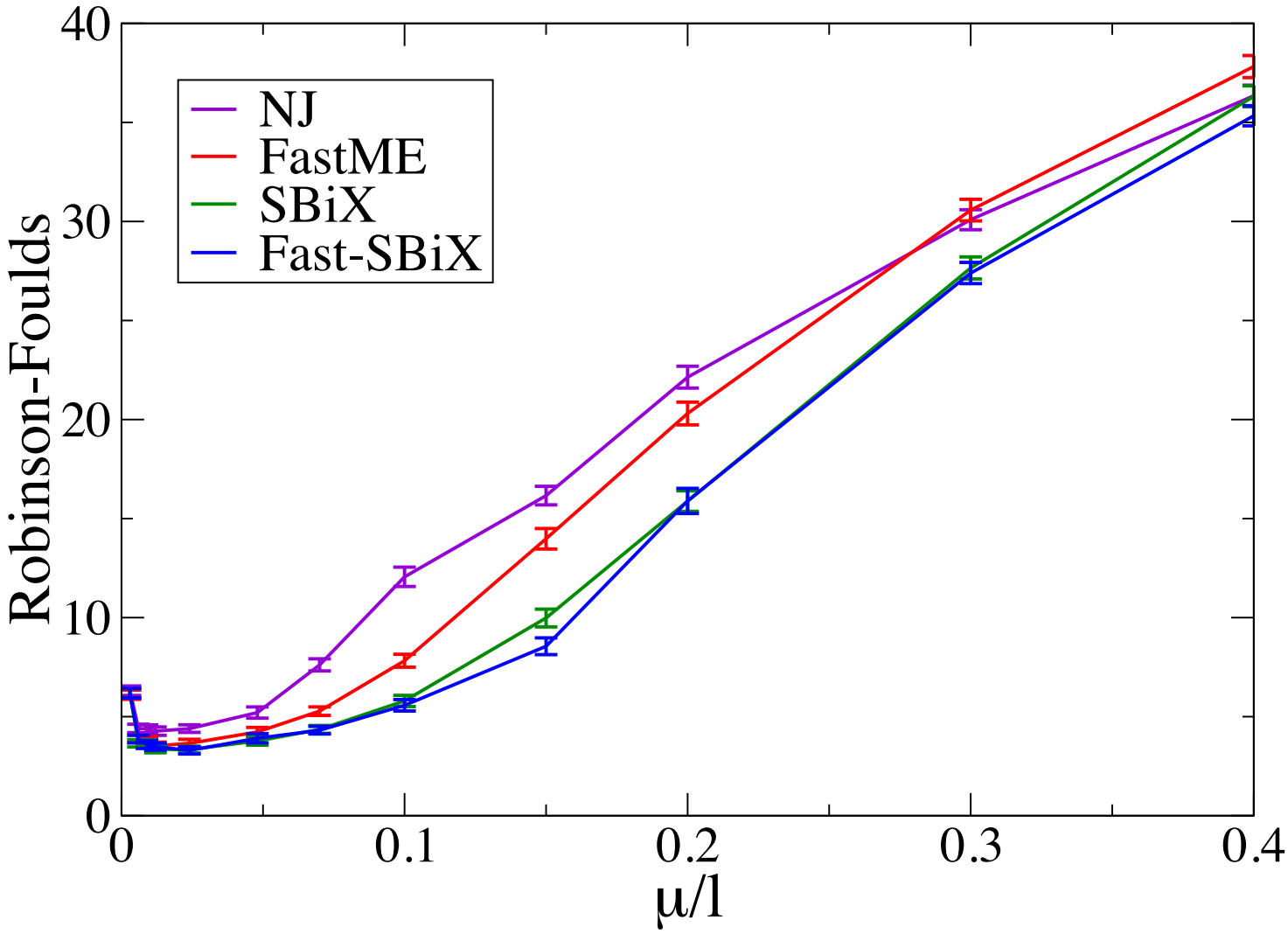
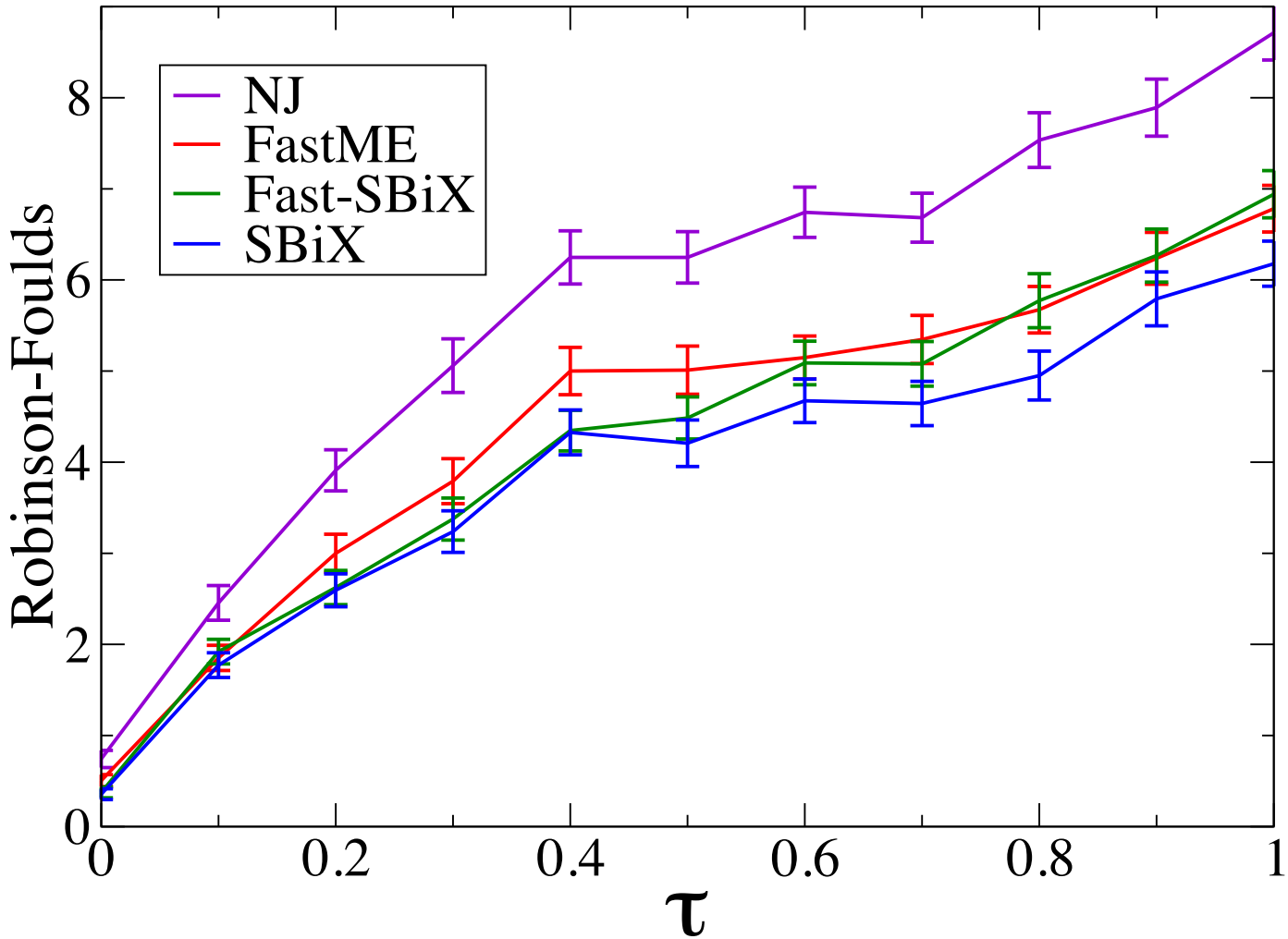
positive facts:

1. It works
2. computational complexity *O*(N^2 log(N))
3. general method to weigh taxa

Performances of distance-based reconstruction algorithms as a function of mutation rate per site



Performances of distance-based reconstruction algorithms as a function of the horizontal transfer rate



The benchmarking problem

Copystree

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O dolce amor de caritate, pregote che me te lassi tenere, se te piace che da ti non me deggia mai partire. Lo dolce amore che me se è dato, madonna, puoi che me l'hai prestato, non me lo tollere questa fiata puoi che l'agio desiderato; puoi che ce so' venuta e che me te si' dato, non me voglio più partire. O dolce amore smesurato che te si' umiliato ed a questa misera te si dato. O dolce matre non me lo retollere, lo voglio tenere che me confuorti e che ma mea mente allustri. Puoi che m'hai reconsolata ed ame allustrata, no lo retollere se te piace. O dolce amore de grande confuorto che resusciti chi è muorto. O dolce amor de veritate che dai lume alli accecati, illuminame se te piace.

Copystree

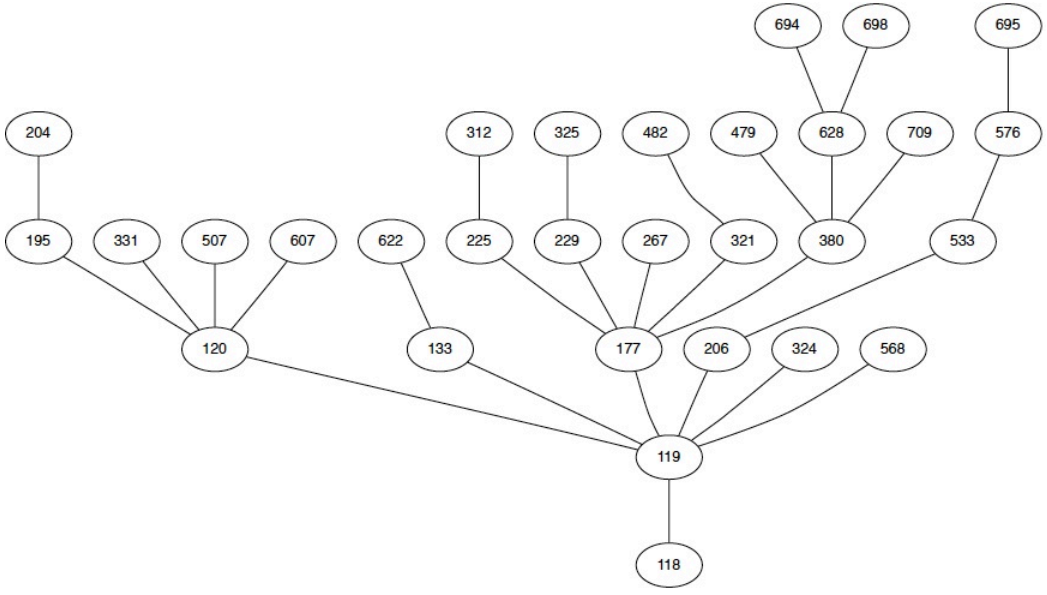
Is a web experiment -game- aimed to provide
a completely controlled and model-free phylogeny

Players (copysts) have few minutes to copy a given text.
Texts evolve by:

- copying ⟵ human ability
- degradation ⟵ parameters

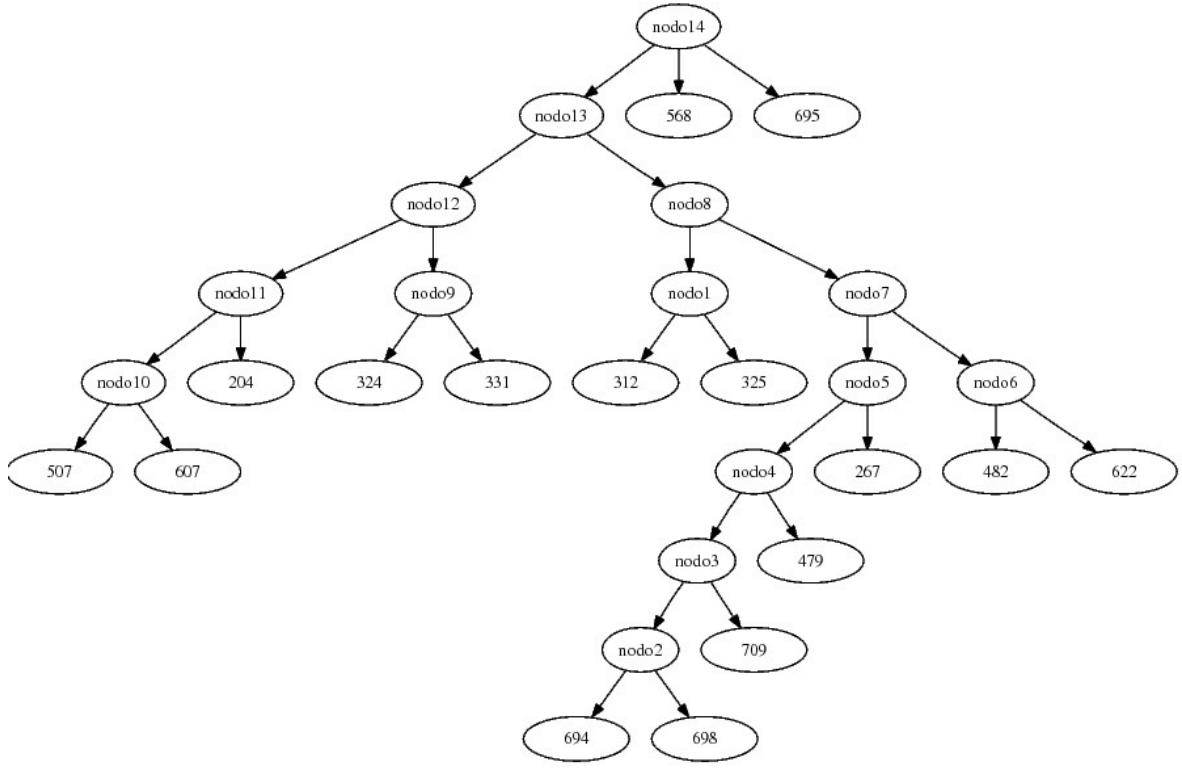
TIME

O dolce amor de caritate, pregote che me te lassi tenere, se te piace che da ti non me deggia mai partire. Lo dolce amore ch[illegible]e se è dato, madonna, puoi che me l'hai prestato, non me lo tollere questa fiata puoi che l'agio desider[illegible]uoi che ce so' venuta e che [illegible]i' dato, non me voglio più partire. O dolce [illegible] smesurato che te si' umiliat[illegible] questa misera te si da[illegible] O dolce matre non me lo retollere, lo voglio tenere che me confuorti e che ma[illegible]nea mente allustri. Puoi che m'hai reconsolata ed ame allustrata, no lo retollere se te piace. O dolce amore de grande confuorto che resusciti chi è muorto. O dolce amor de veritate che dai lume alli accecati, illuminame se te piace.



real phylogeny

reconstructed phylogeny



An application in linguistics: The tree of languages

Swadesh lists

Lists of words representing a language

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- First attempt: cognate words → distance 0/1
- phonological characters

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Ear	ir	oreky~o
Eye	ei	oky~o

→ Levenshtein (edit) distance:
number of insertions, deletions or substitutions
to go from a word to another

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distance between languages:
average Levenshtein distance
between homologous words

→ Levenshtein (edit) distance:
number of insertions, deletions or substitutions
to go from a word to another

ASJP (*Automated Similarity Judgment Program)* database

50 language families
languages per family varing from *O*(10) to *O*(100)
each language list 100 homologous words (but incomplete!)

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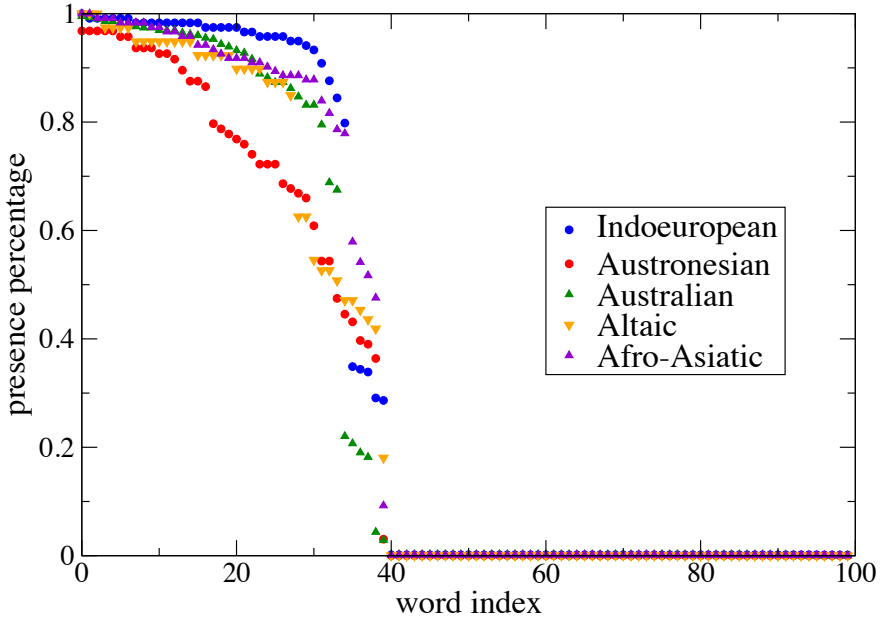

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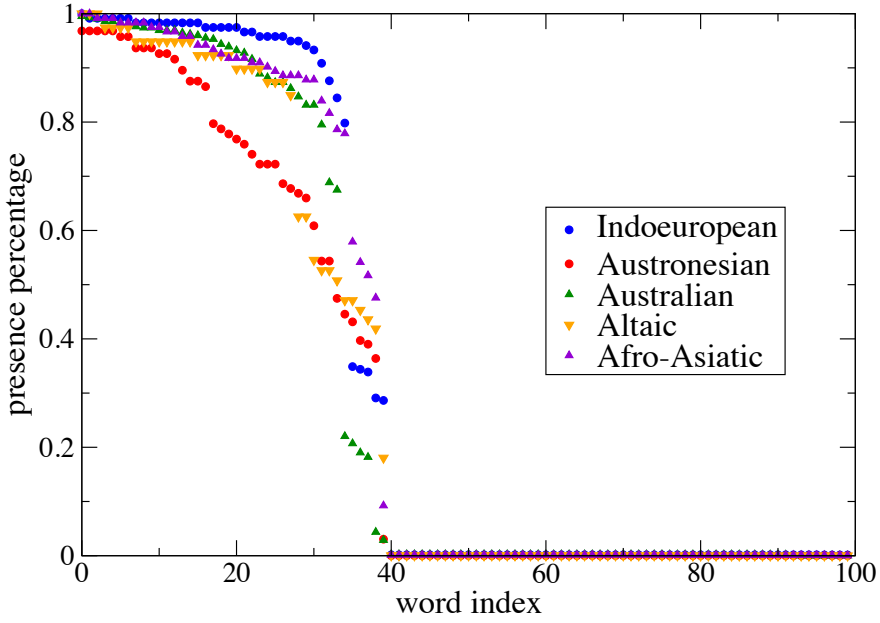
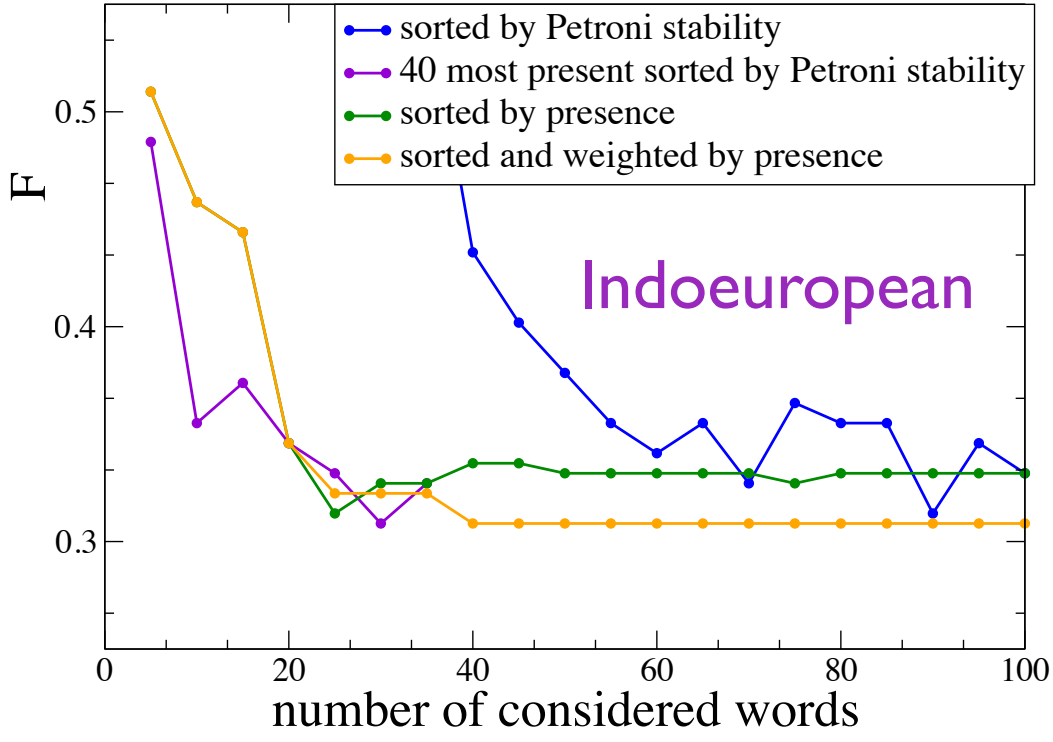
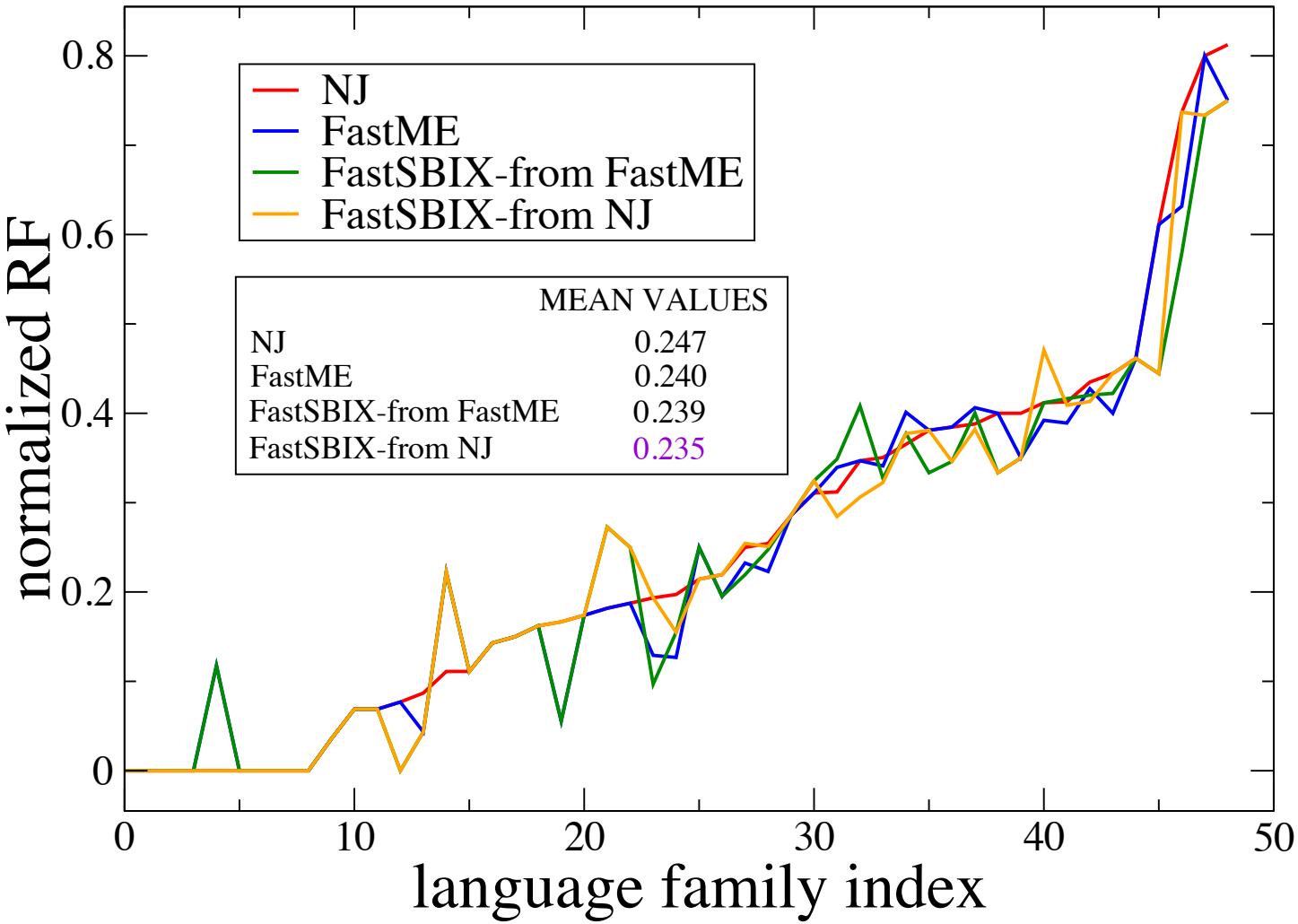




need of complete dataset!

Comparison with Ethnologue (experts) classification



No much difference in performances between reconstruction algorithms: too much noise or too short and/or incomplete lists?

Artificial lists of words

evolving through mutation, deletion and insertion

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N=100 languages, lists of 100 words
common to all languages
+100 words of which 80%
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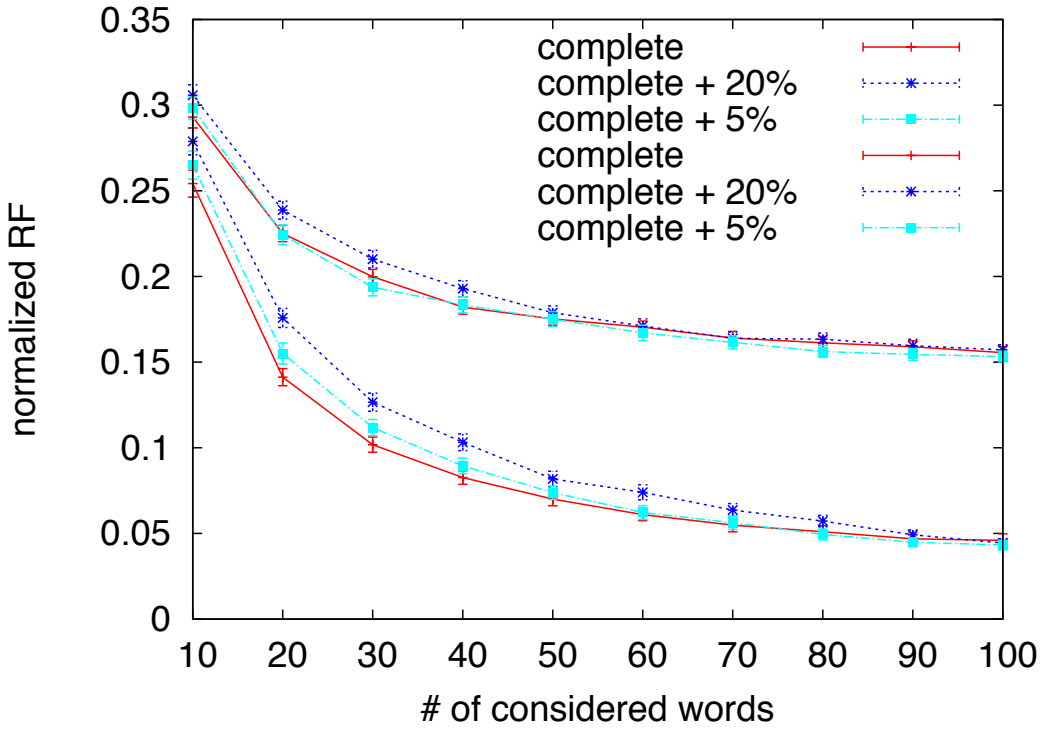

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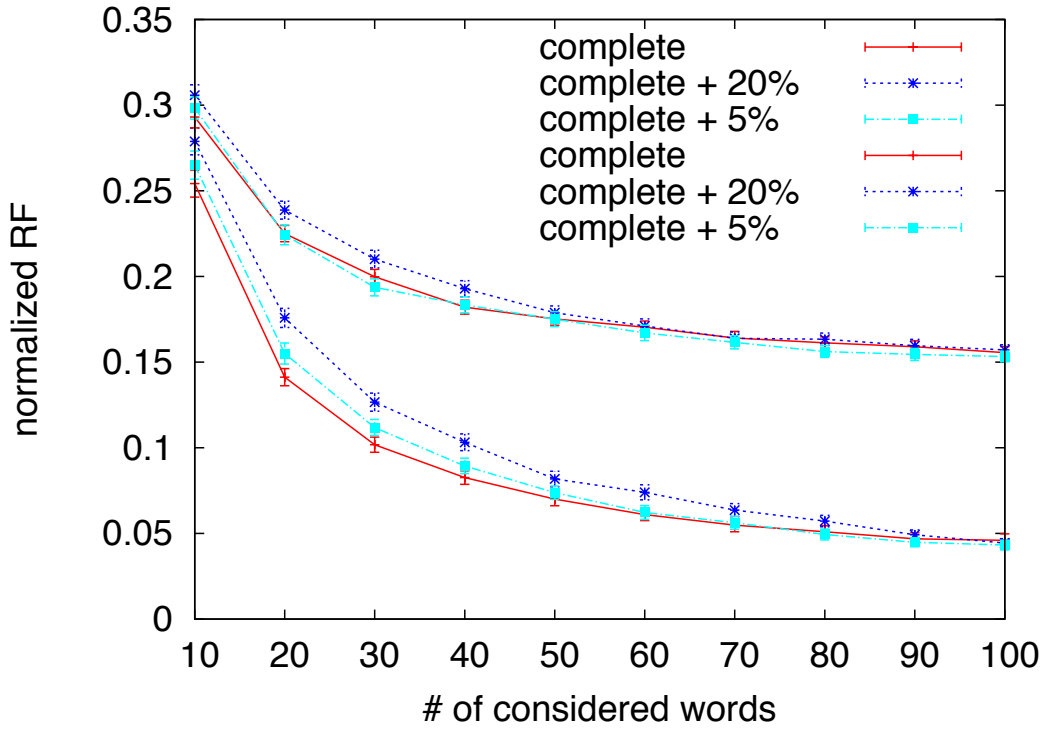
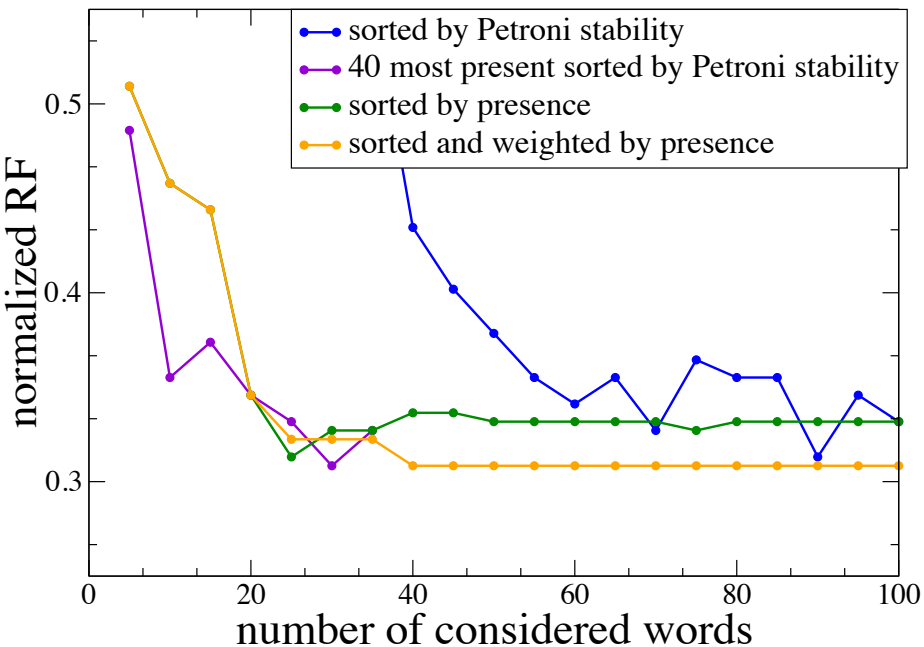
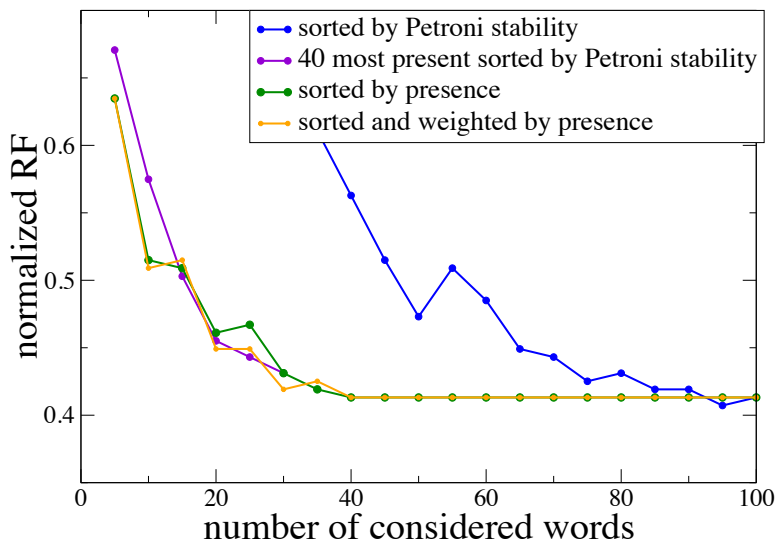
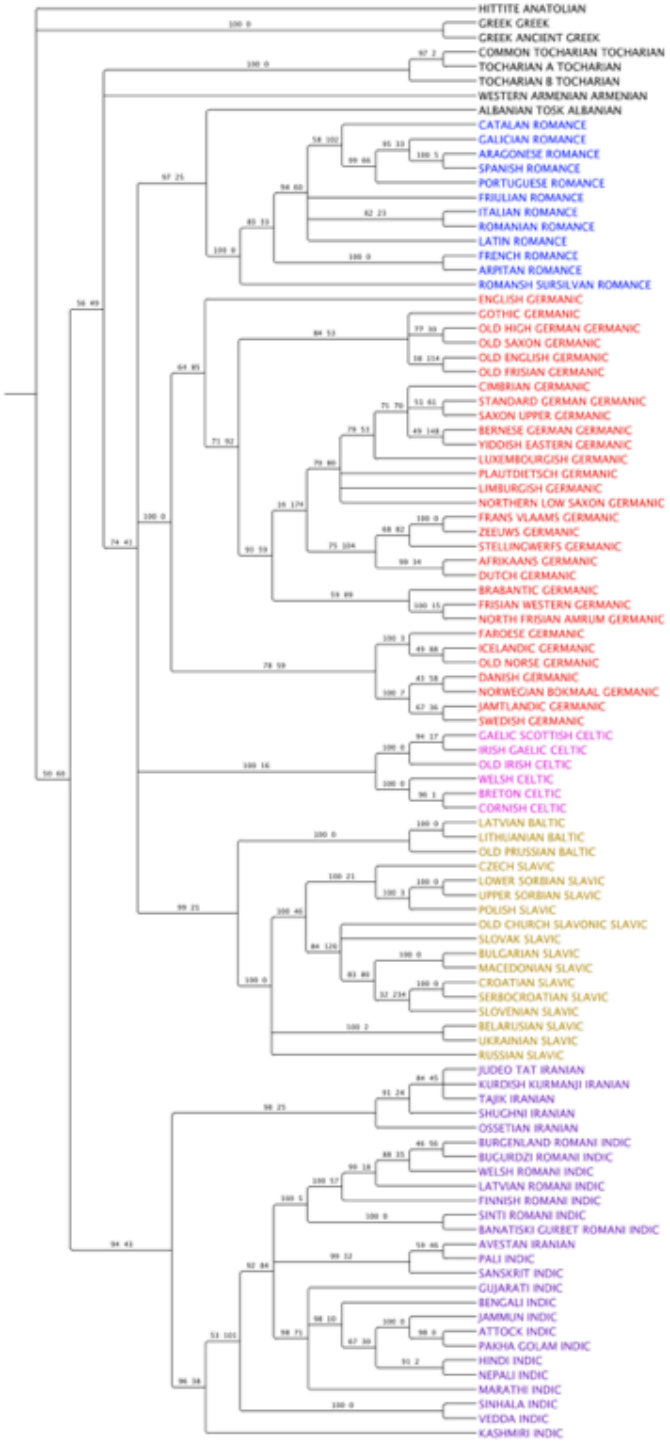








INDO-EUROPEAN

Romance

Germanic

Celtic

Balto-Slavic

Indo-Iranian

An application in biology: Influenza virus evolution

Extract information about the phylogenetic process from phylogenetic tree shape

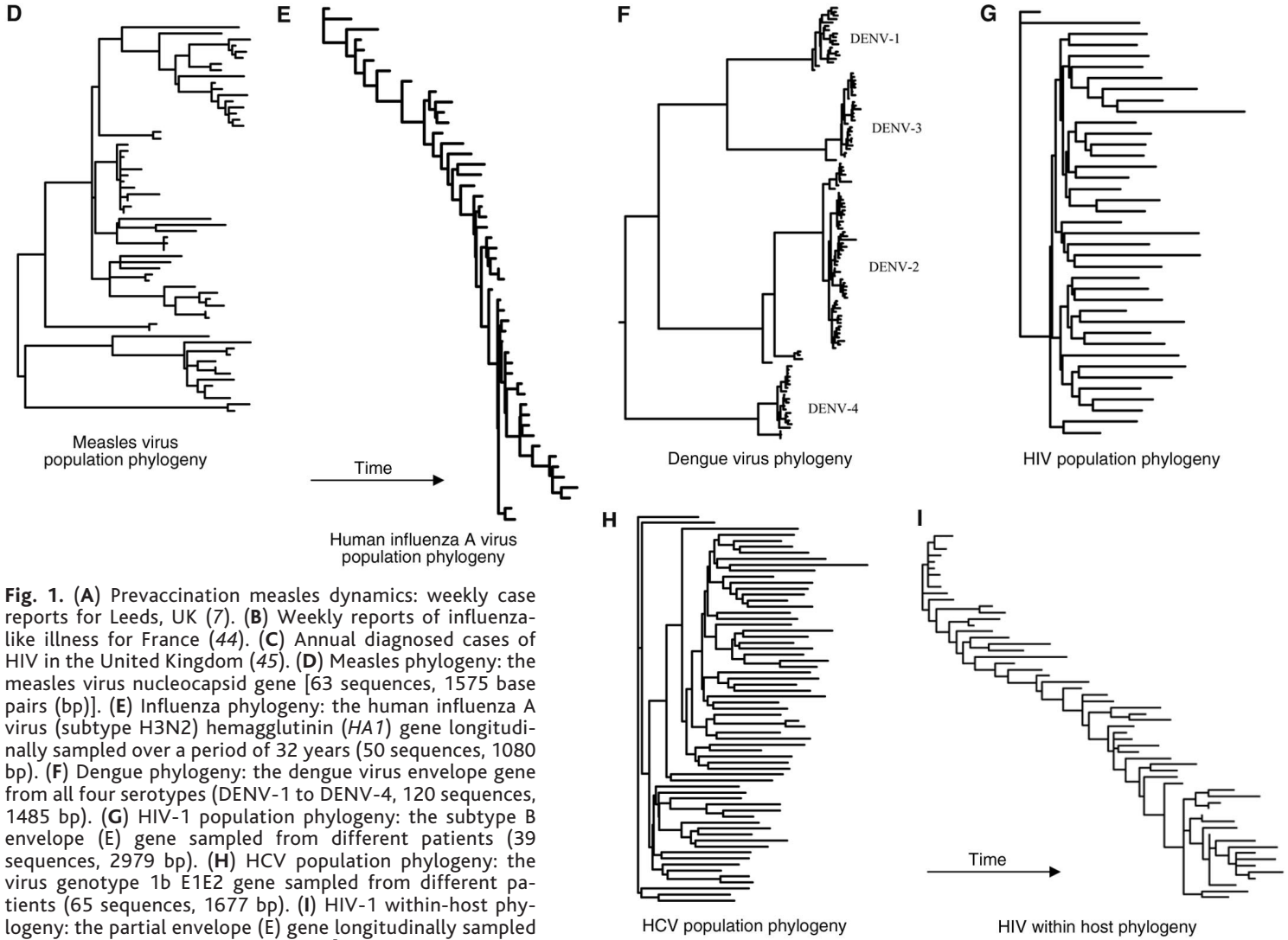
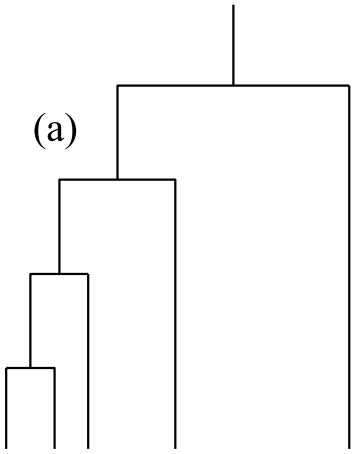


Fig. 1. (**A**) Prevaccination measles dynamics: weekly case reports for Leeds, UK (*7*). (**B**) Weekly reports of influenza-like illness for France (*44*). (**C**) Annual diagnosed cases of HIV in the United Kingdom (*45*). (**D**) Measles phylogeny: the measles virus nucleocapsid gene [63 sequences, 1575 base pairs (bp)]. (**E**) Influenza phylogeny: the human influenza A virus (subtype H3N2) hemagglutinin (*HA1*) gene longitudinally sampled over a period of 32 years (50 sequences, 1080 bp). (**F**) Dengue phylogeny: the dengue virus envelope gene from all four serotypes (DENV-1 to DENV-4, 120 sequences, 1485 bp). (**G**) HIV-1 population phylogeny: the subtype B envelope (E) gene sampled from different patients (39 sequences, 2979 bp). (**H**) HCV population phylogeny: the virus genotype 1b E1E2 gene sampled from different patients (65 sequences, 1677 bp). (**I**) HIV-1 within-host phylogeny: the partial envelope (E) gene longitudinally sampled from a single patient over 5.8 years [58 sequences, 627 bp; patient 6 from (*26*)]. All sequences were collected from GenBank and trees were constructed with maximum likelihood in PAUP* (*46*). Horizontal branch lengths are proportional to substitutions per site. Further details are available from the authors on request.

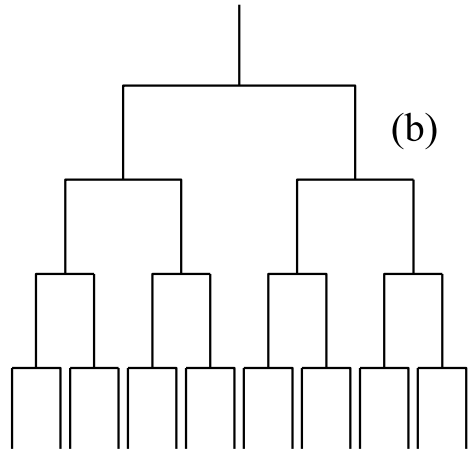
Balance/unbalance measures

A_i number of taxa diversifying from node *i*, including itself

$$C_i = \sum_j A_j$$

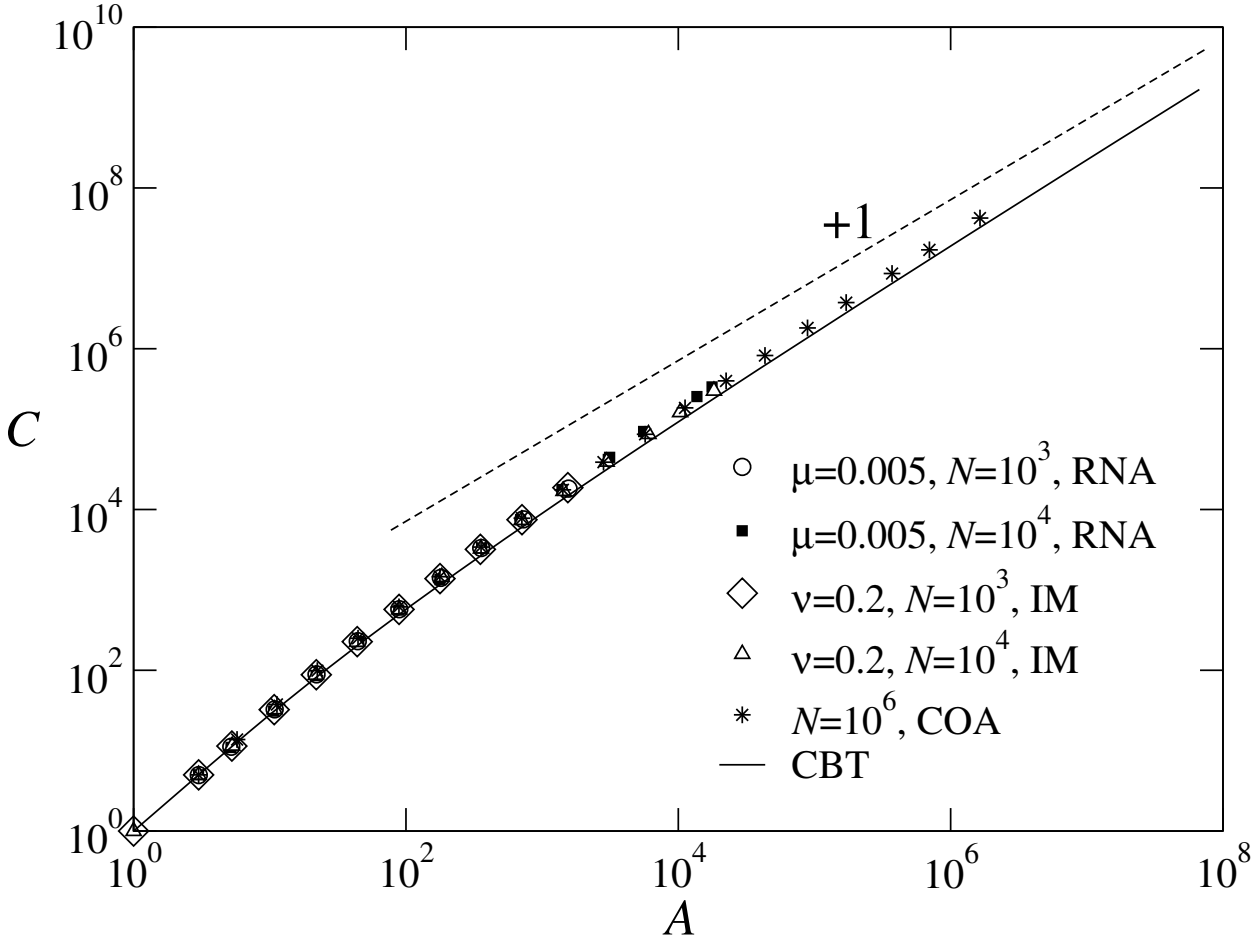


$N_u(l)$	$A_u(l)$	$C_u(l)$	l	$N_b(l)$	$A_b(l)$	$C_b(l)$
1	9	29	5	$n/16$	31	129
1	7	19	4	$n/8$	15	49
1	5	11	3	$n/4$	7	17
1	3	5	2	$n/2$	3	5
n	1	1	1	n	1	1



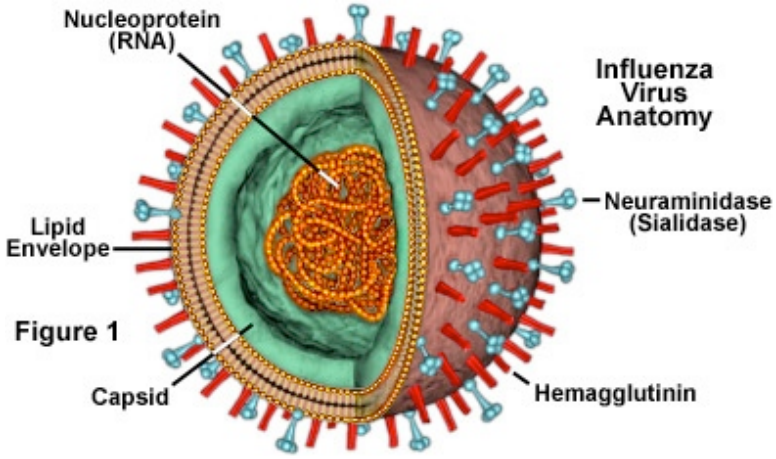
Asymptotic behavior

$$P(A) \propto A^{-\alpha} \quad P(C) \propto C^{-\gamma} \quad C(A) \propto A^{\eta}, \;\; \eta = \frac{1-\alpha}{1-\gamma}$$

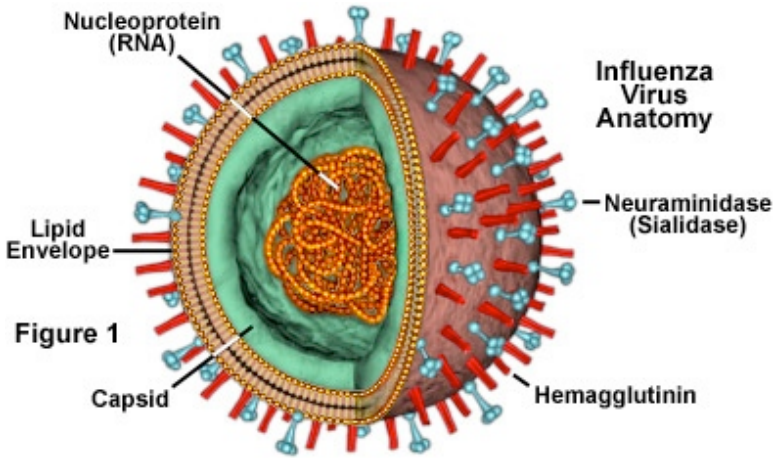


M. Stich and S.C. Manrubia:
Eur. Phys. J. B **70**, 583–592 (2009)

Almost all evolutive process produce asymptotically balanced tress



Influenza A virus
RNA in 8 segments
(~10000 nucleotides)



Influenza A virus
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HA (Hemagglutinin) and
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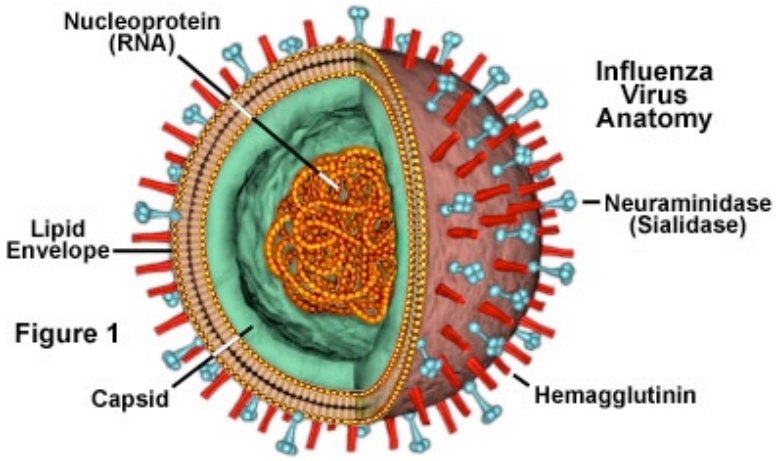
are the surface proteins
responsible for the interaction
with host immune system
(~1000 nucleotides each)

e.g. H3N2 (from 1968)



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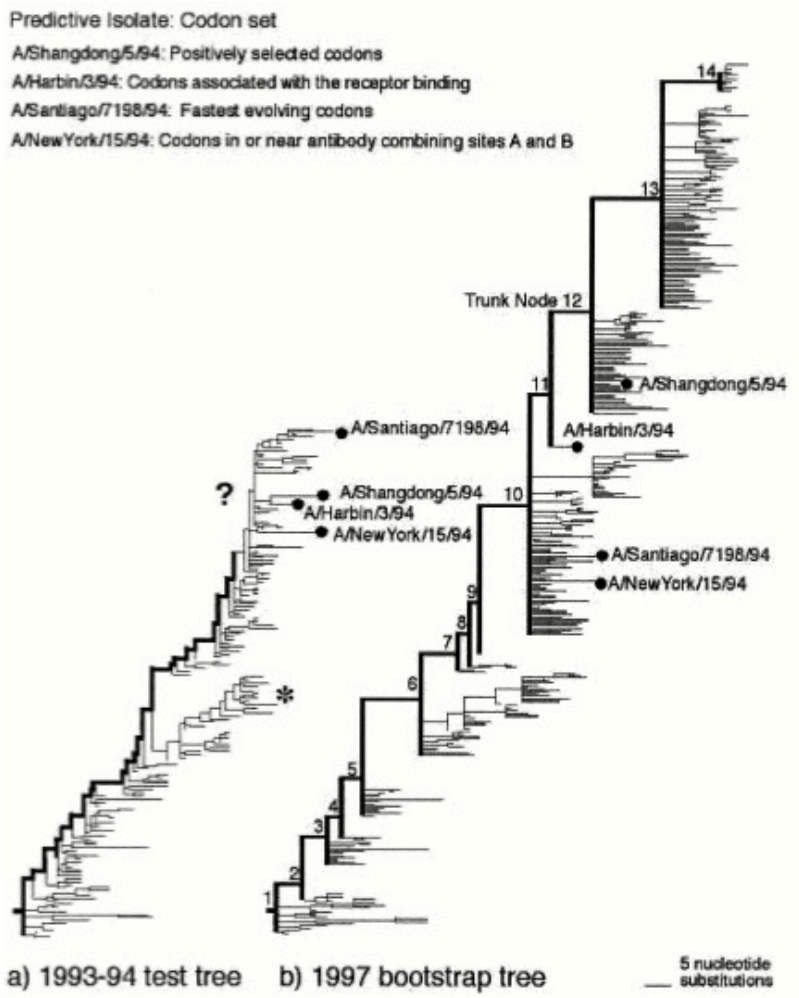

Open question:

Which evolutive process produces
the comb-like (or unbalanced) tree?
virus - host immune system interaction?

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More general open questions:

taking into account deviations from additivity
in algorithms (horizontal transfer)

exploiting additional information
(internal nodes)

modeling evolutionary processes leading to
real phylogenies

Thank you