Reconstructing Phylogenetic Networks

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Amsterdam

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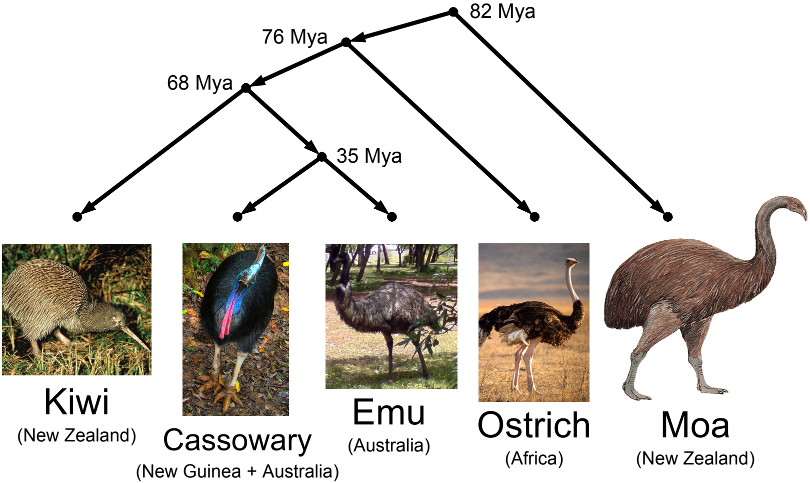
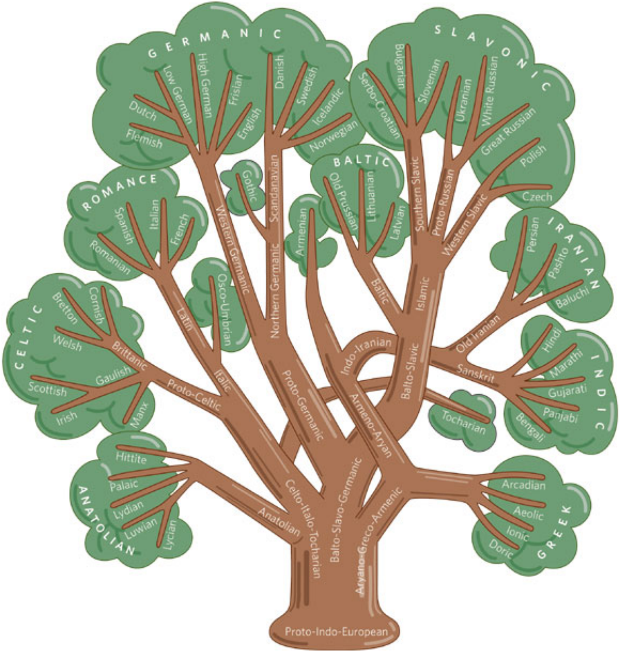
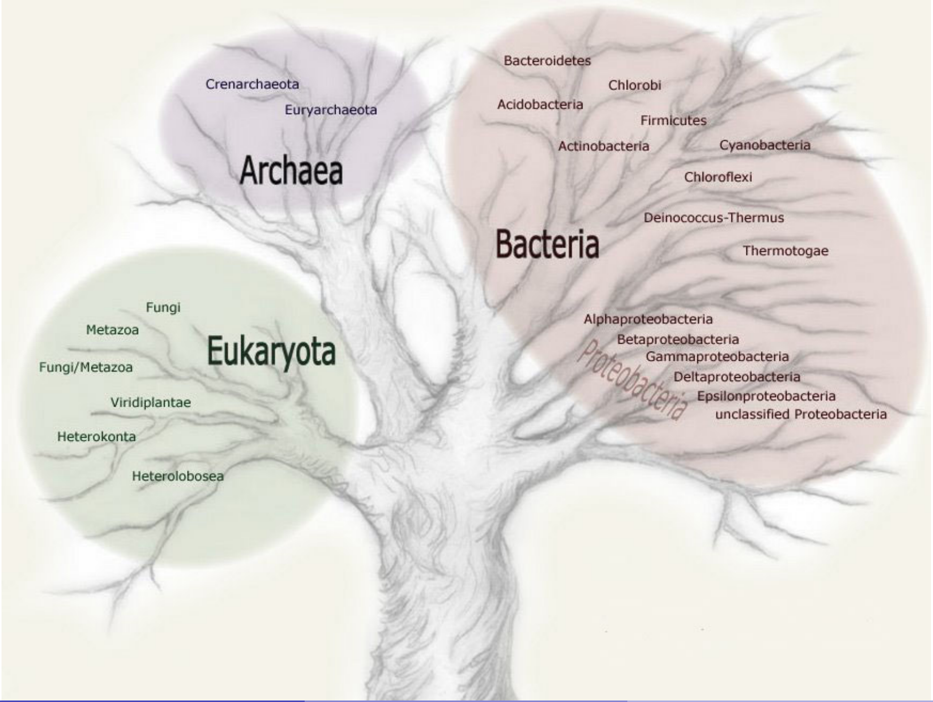
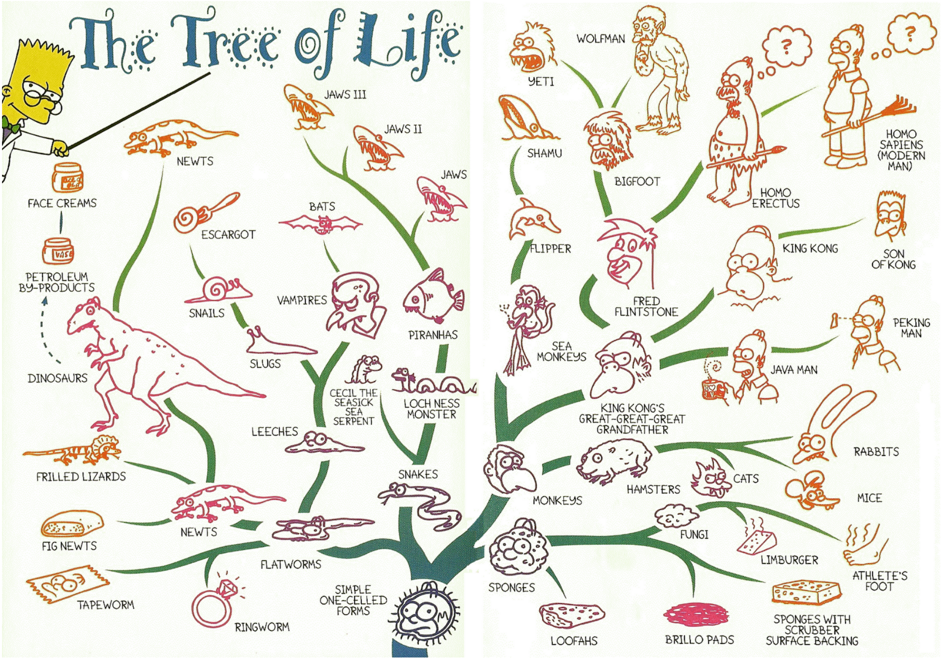
Definition

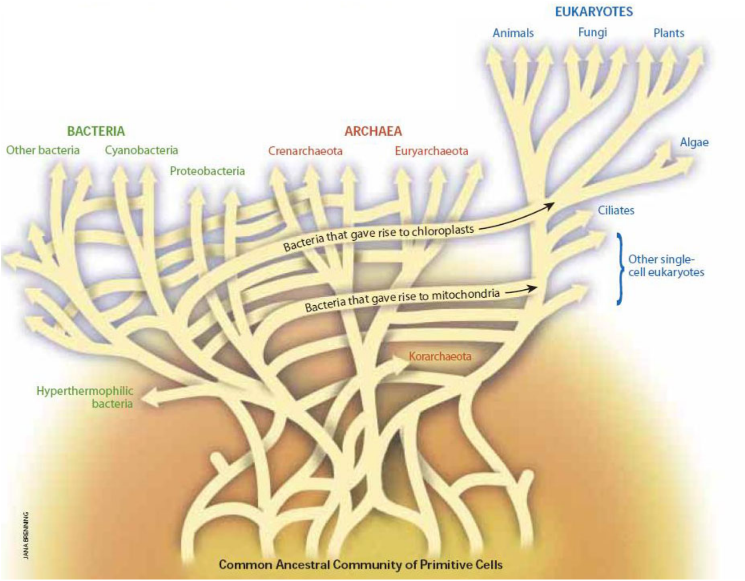
Let X be a finite set. A **(rooted) phylogenetic tree** on X is a rooted tree with no indegree-1 outdegree-1 vertices whose leaves are bijectively labelled by the elements of X.




GERMANIC
Low German
High German
Frisian
Danish
Swedish
Icelandic
Norwegian
English
Dutch
Flemish
SLAVONIC
Bulgarian
Serbo-Croatian
Slovenian
Ukranian
White Russian
Great Russian
Polish
Czech
BALTIC
Old Prussian
Lithuanian
Latvian
ROMANCE
Spanish
Italian
French
Romanian
Gothic
Scandanavian
Western Germanic
Northern Germanic
Armenian
Southern Slavic
Proto-Russian
Western Slavic
IRANIAN
Persian
Pashto
Baluchi
CELTIC
Bretton
Cornish
Welsh
Gaulish
Scottish
Irish
Manx
Brittanic
Osco-Umbrian
Latin
Italic
Proto-Celtic
Baltic
Islamic
Old Iranian
Indo-Iranian
Balto-Slavic
Sanskrit
INDIC
Hindi
Marathi
Gujarati
Panjabi
Bengali
Tocharian
Proto-Germanic
Armeno-Aryan
ANATOLIAN
Hittite
Palaic
Lydian
Luwian
Lycian
Anatolian
Celto-Italo-Tocharian
Balto-Slavo-Germanic
Aryano-Greco-Armenic
GREEK
Arcadian
Aeolic
Ionic
Doric
Proto-Indo-European


Crenarchaeota
Euryarchaeota
Archaea
Bacteroidetes
Chlorobi
Acidobacteria
Firmicutes
Actinobacteria
Cyanobacteria
Chloroflexi
Deinococcus-Thermus
Bacteria
Thermotogae
Fungi
Metazoa
Eukaryota
Fungi/Metazoa
Viridiplantae
Heterokonta
Heterolobosea
Alphaproteobacteria
Betaproteobacteria
Proteobacteria
Gammaproteobacteria
Deltaproteobacteria
Epsilonproteobacteria
unclassified Proteobacteria


The Tree of Life
JAWS III
JAWS II
JAWS
NEWTS
FACE CREAMS
ESCARGOT
BATS
PETROLEUM BY-PRODUCTS
SNAILS
VAMPIRES
PIRANHAS
DINOSAURS
SLUGS
CECIL THE SEASICK SEA SERPENT
LOCH NESS MONSTER
LEECHES
FRILLED LIZARDS
SNAKES
NEWTS
FIG NEWTS
FLATWORMS
SIMPLE ONE-CELLED FORMS
TAPEWORM
RINGWORM
YETI
WOLFMAN
?
?
SHAMU
BIGFOOT
HOMO SAPIENS (MODERN MAN)
HOMO ERECTUS
FLIPPER
KING KONG
SON OF KONG
FRED FLINTSTONE
SEA MONKEYS
PEKING MAN
JAVA MAN
KING KONG'S GREAT-GREAT-GREAT GRANDFATHER
RABBITS
CATS
HAMSTERS
MONKEYS
MICE
FUNGI
LIMBURGER
ATHLETE'S FOOT
SPONGES
SPONGES WITH SCRUBBER SURFACE BACKING
LOOFAHS
BRILLO PADS

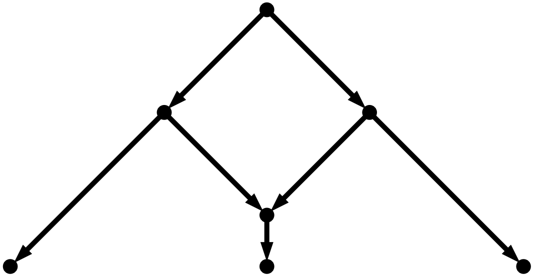


EUKARYOTES
Animals
Fungi
Plants
BACTERIA
Other bacteria
Cyanobacteria
Proteobacteria
ARCHAEA
Crenarchaeota
Euryarchaeota
Algae
Ciliates
Bacteria that gave rise to chloroplasts
Other single-cell eukaryotes
Bacteria that gave rise to mitochondria
Korarchaeota
Hyperthermophilic bacteria
JANA BRENNING
Common Ancestral Community of Primitive Cells

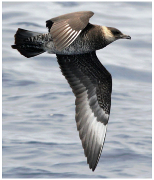
W.F. Doolittle et al. (2000)

Definition

Let X be a finite set. A **(rooted) phylogenetic network** on X is a rooted directed acyclic graph with no indegree-1 outdegree-1 vertices whose leaves are bijectively labelled by the elements of X.



Parasitic Jaeger



Pomarine Skua

Great Skua

The first phylogenetic network (Buffon, 1755)

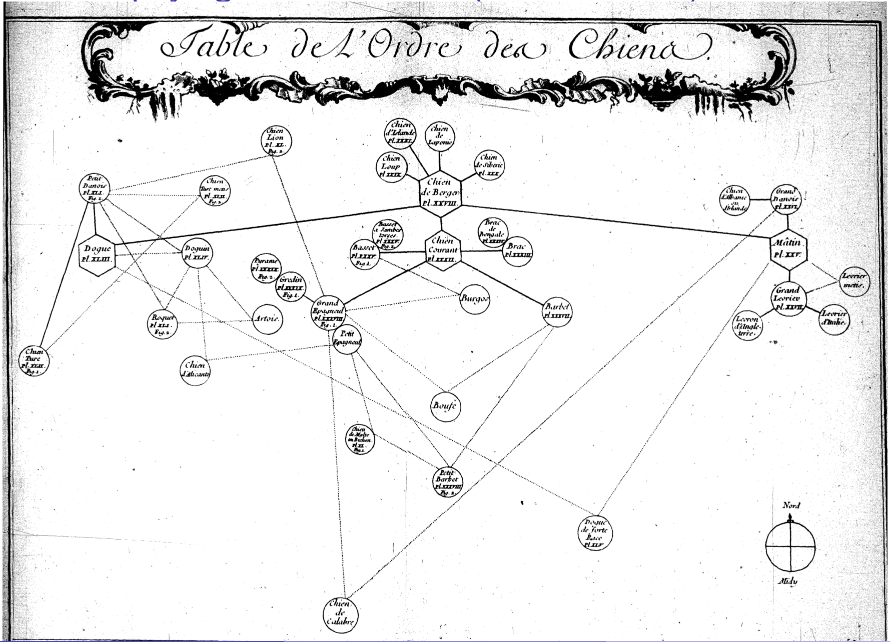
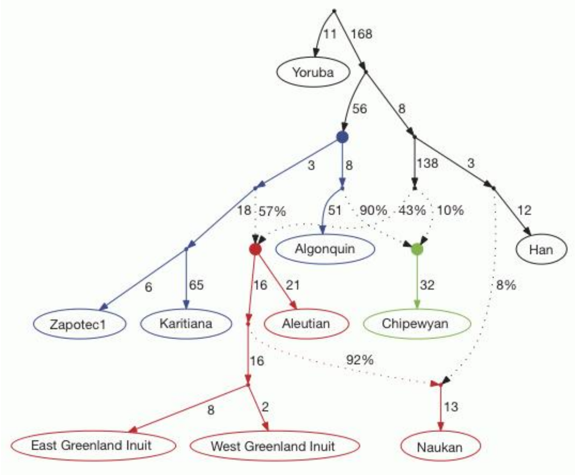


Table de L'Ordre des Chiens
Chien Lion pl. XL. Fig. 2.
Chien d'Islande pl. XXXI.
Chien de Laponie
Chien Loup pl. XXIX
Chien de Siberie pl. XXX.
Chien de Berger pl. XXVIII.
Petit Danois pl. XLI. Fig. 1.
Chien Turc metis pl. XLII Fig. 2.
Dogue pl. XLIII.
Doguin pl. XLIV.
Basset a Jambes torses pl. XXXV. Fig. 2.
Basset pl. XXXV. Fig. 1.
Chien Courant pl. XXXII.
Brac de Bengale pl. XXXIV.
Brac pl. XXXIII.
Chien d'Albanie ou d'Irlande
Grand Danois pl. XXVI.
Mâtin pl. XXV.
Levrier metis.
Grand Levrier pl. XXVII.
Levron d'Angleterre.
Levrier d'Italie.
Pyrame pl. XXXIX Fig. 2.
Gredin pl. XXXIX Fig. 1.
Grand Epagneul pl. XXXVIII Fig. 1.
Petit Epagneul
Burgos
Barbet pl. XXXVII.
Roquet pl. XLI. Fig. 2.
Artois.
Chien Turc pl. XLII. Fig. 1.
Chien d'Alicante
Boufe
Chien de Malte ou Bichon pl. XL. Fig. 1.
Petit Barbet pl. XXXVIII Fig. 2.
Dogue de forte Race pl. XLV
Chien de Calabre
Nord
Midy

Phylogenetic network for humans (Reich et al., 2011)



Definition

A **reticulation** is a vertex with indegree at least 2.

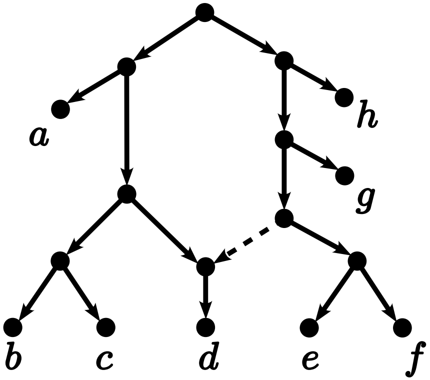
Tree-based methods

1. Compute trees from DNA sequences.
   - Different parts of DNA might give different trees.
2. Try to induce a phylogenetic network from the trees.

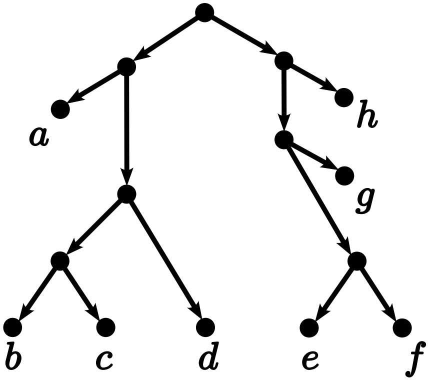
Definition

A phylogenetic tree T is **displayed** by a phylogenetic network N if T can be obtained from a subgraph of N by contracting edges.

Example: tree T is displayed by network N

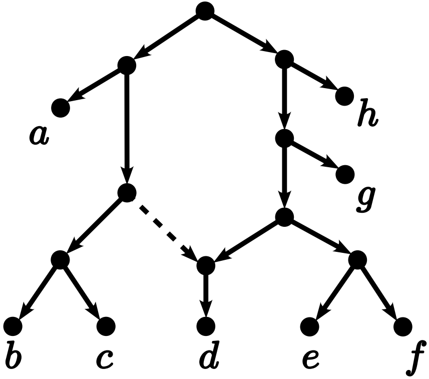


N

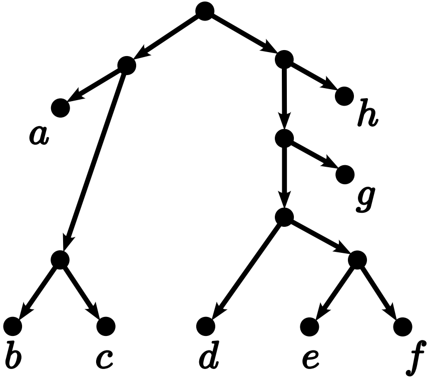


T

The other binary tree T' displayed by network N

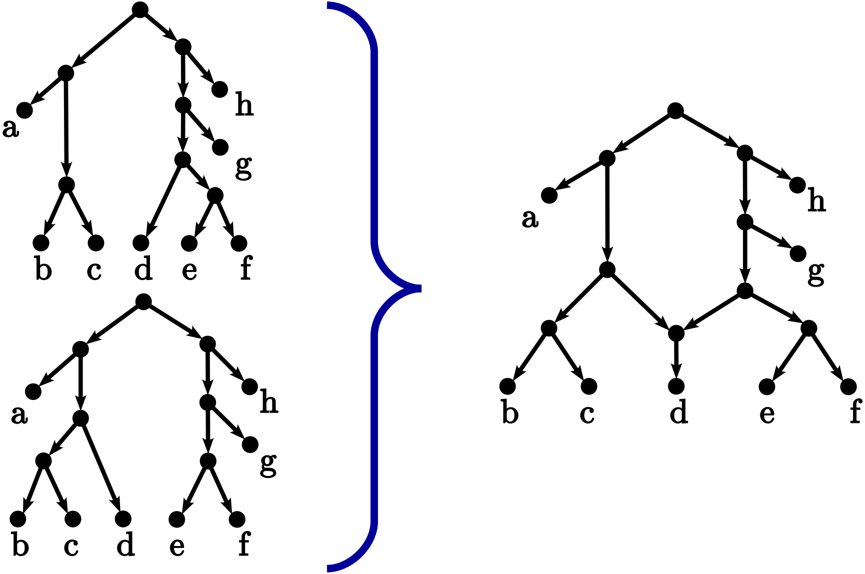


N



T'

Challenge: try to reconstruct the network from the trees



Definition

The **reticulation number** of a phylogenetic network N is

$$\sum_{v \in V \setminus \{\text{root}\}} d^-(v) - 1.$$

Problem

Minimum Reticulation

- **Instance:** *phylogenetic trees T_1, T_2*
- **Solution:** *phylogenetic network that displays T_1 and T_2*
- **Minimize:** *reticulation number of the network.*

Theorem

There exists a constant factor approximation algorithm for Minimum Reticulation *if and only if there exists a constant factor approximation algorithm for* Directed Feedback Vertex Set.

Open question: how to handle more than two trees (efficiently)?

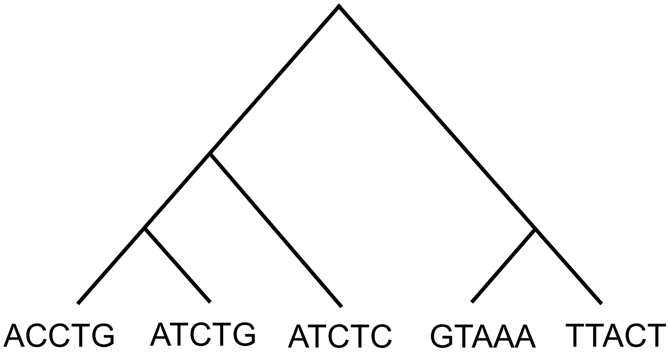
Reconstructing phylogenetic networks

- Tree-based methods
  1. Construct trees from DNA sequences.
  2. Find a network that displays the trees and has minimum reticulation number.

- Sequence-based methods
  - Find a network directly from the DNA sequences.
  - Optimize **Parsimony** or Likelihood score of network.

Maximum Parsimony for **trees**

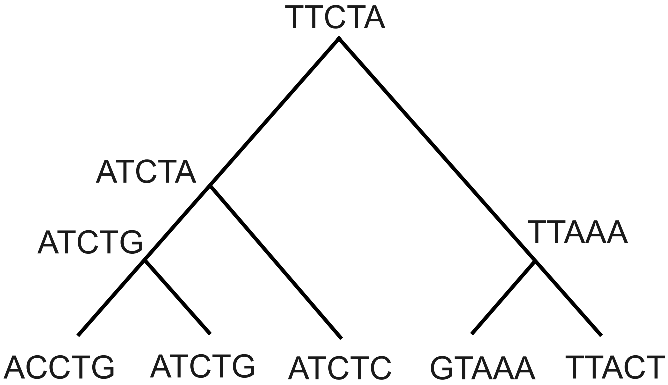
Small parsimony problem: given a tree and a sequence for each leaf, assign sequences to the internal vertices in order to **minimize** the total number of **mutations**.



Example input

Maximum Parsimony for trees

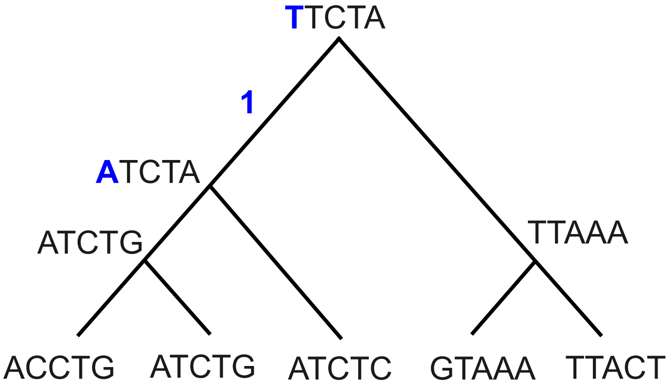
Small parsimony problem: given a tree and a sequence for each leaf, assign sequences to the internal vertices in order to **minimize** the total number of **mutations**.



Example labelling of internal vertices

Maximum Parsimony for trees

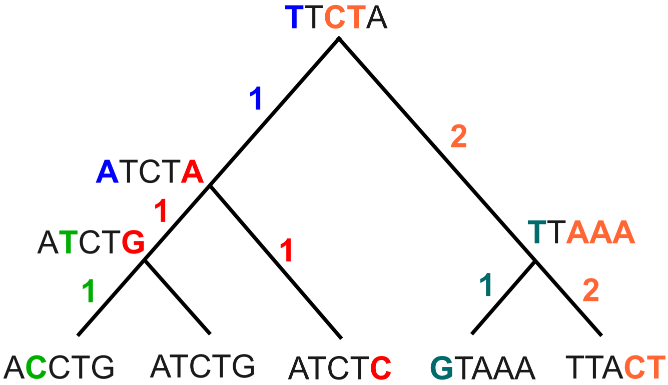
Small parsimony problem: given a tree and a sequence for each leaf, assign sequences to the internal vertices in order to **minimize** the total number of **mutations**.



Example of one mutation

Maximum Parsimony for trees

Small parsimony problem: given a tree and a sequence for each leaf, assign sequences to the internal vertices in order to **minimize** the total number of **mutations**.



All 9 mutations.

Maximum Parsimony for trees

Small parsimony problem: given a tree and a sequence for each leaf, assign sequences to the interior vertices in order to **minimize** the total number of **mutations**.

- Polynomial-time solvable:
  - Consider each character separately.
  - Use dynamic programming (Fitch, 1971).
- Two possible extensions to networks:
  - **hardwired**
  - **softwired**

Hardwired Maximum Parsimony on **Networks**

- A p-state **character** on X is a function $\alpha : X \to \{1, \dots, p\}$.
- The **change** $c_\tau(e)$ on edge $e = (u, v)$ w.r.t. a p-state character τ on $V(N)$ is defined as:

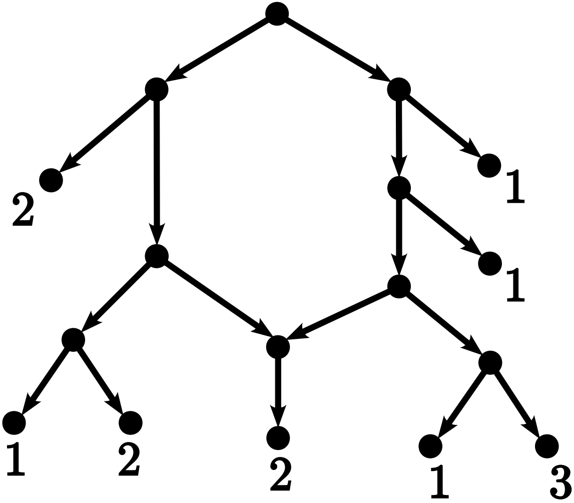
$$c_\tau(e) = \begin{cases} 0 \text{ if } \tau(u) = \tau(v) \\ 1 \text{ if } \tau(u) \neq \tau(v). \end{cases}$$

- The **hardwired parsimony score** of a phylogenetic network N and p-state character α is given by

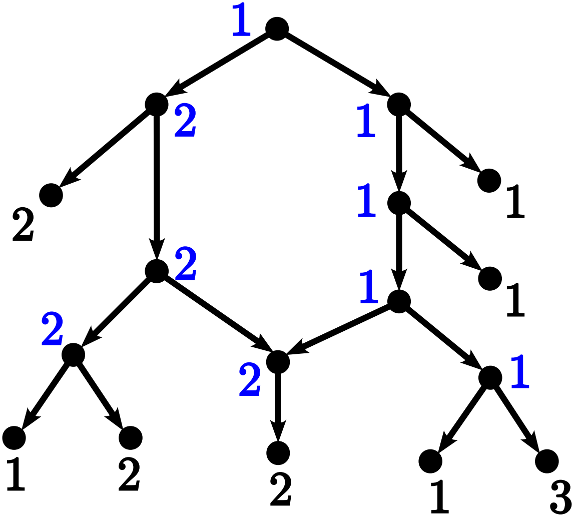
$$PS_{\text{hw}}(N, \alpha) = \min_\tau \sum_{e \in E(N)} c_\tau(e),$$

where the minimum is taken over all p-state characters τ on $V(N)$ that extend α.

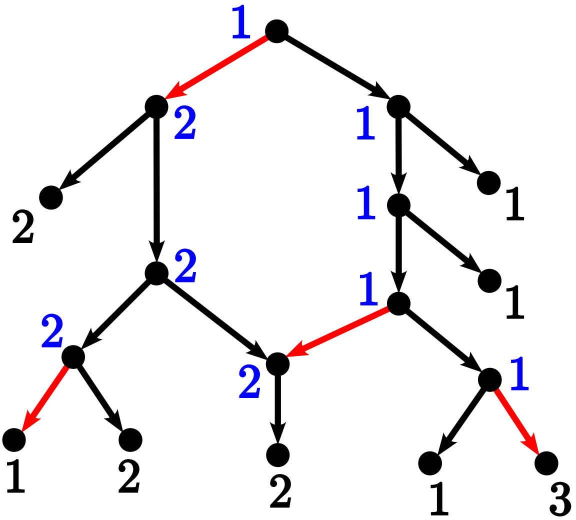
Example input: (N, α)



A 3-state character τ on $V(N)$ that extends α.



$PS_{\mathrm{hw}}(N, \alpha) = 4$



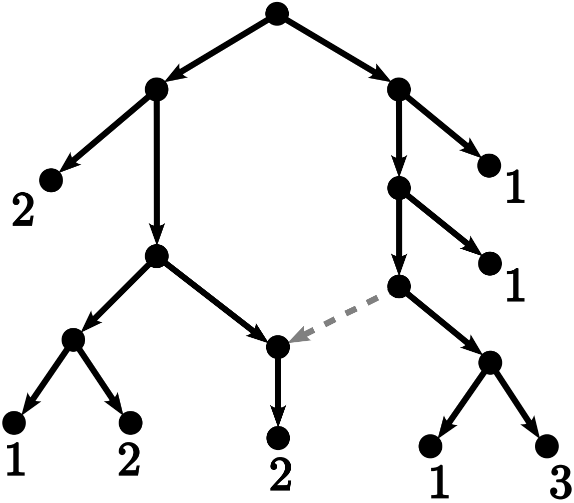
Softwired Maximum Parsimony on Networks

The **softwired parsimony score** of a phylogenetic network N and p-state character α is given by

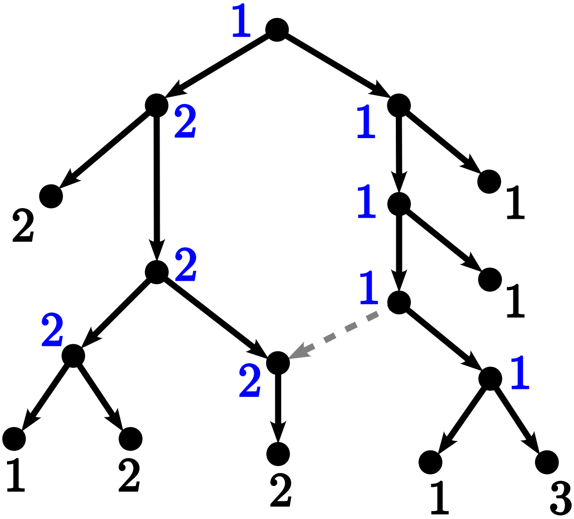
$$PS_{\text{sw}}(N,\alpha) = \min_{T \in \mathcal{T}(N)} PS(T,\alpha),$$

where $\mathcal{T}(N)$ is the set of trees on X displayed by N.

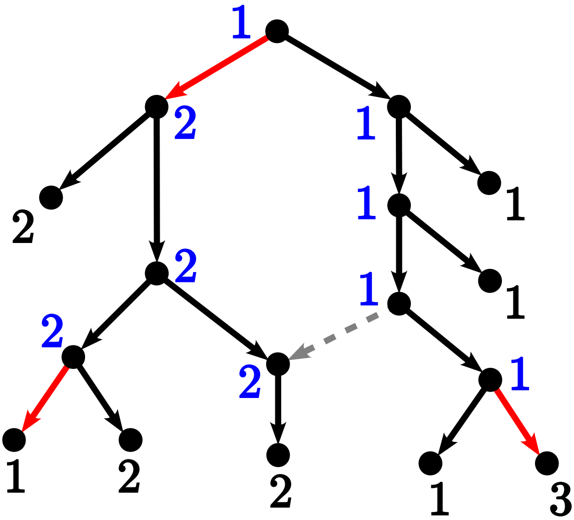
One of the two trees on X displayed by the network



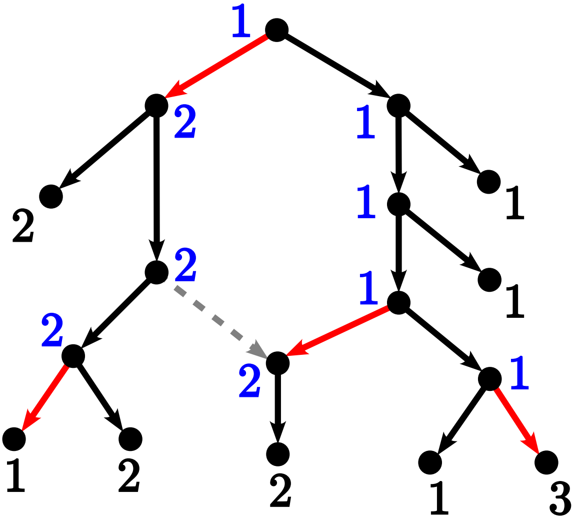
A 3-state character τ on $V(T)$ that extends α.



There are 3 changes



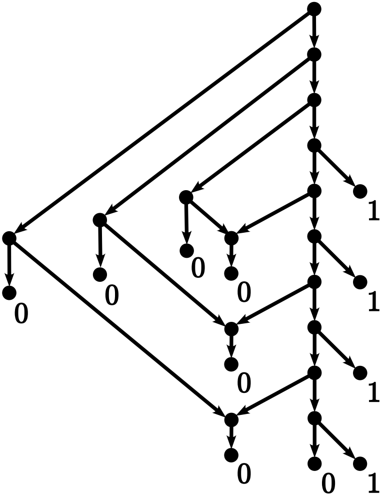
The other tree needs 4 changes



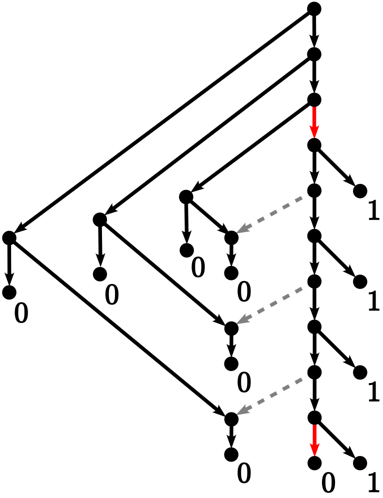
The minimum over the two trees is 3, so $PS_{\mathrm{sw}}(N, \alpha) = 3$.

Proposition

$PS_{hw}(N,\alpha)$ is not an $o(n)$-approximation of $PS_{sw}(N,\alpha)$.

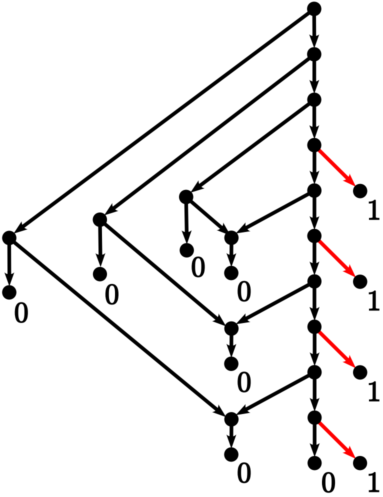


Softwired Parsimony Score



$$PS_{\text{sw}}(N,\alpha)=2$$

Hardwired Parsimony Score



$$PS_{\mathrm{hw}}(N, \alpha) = 4 = r + 1$$

with r the number of reticulations.

Proposition

Let G be the graph obtained from network N by merging all leaves x with $\alpha(x) = i$ into a single node γ_i, for $i = 1, \ldots, p$.
Then, $PS_{hw}(N, \alpha)$ equals the size of a **minimum multiterminal cut** *in G with terminals $\gamma_1, \ldots, \gamma_p$.*

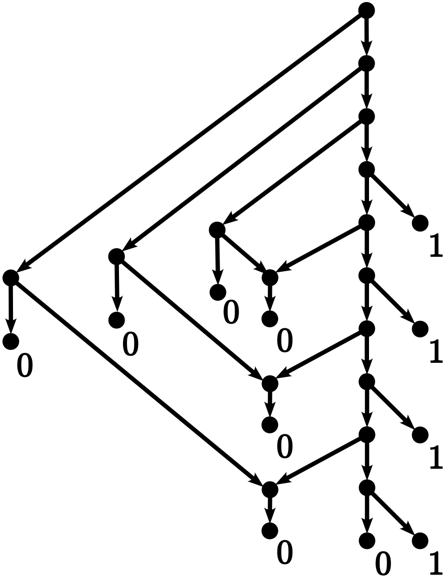
Corollary

Computing the hardwired parsimony score of a phylogenetic network and a **binary character** *is* **polynomial-time solvable***.*

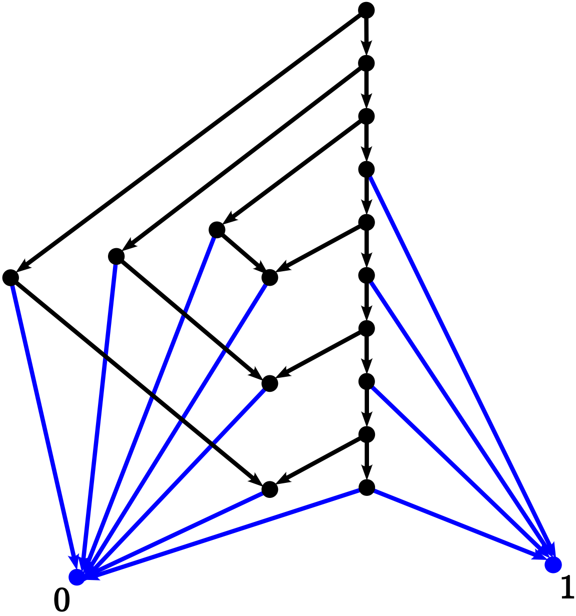
Corollary

Computing the hardwired parsimony score of a phylogenetic network and a p-state character, for $p \geq 3$, is NP-hard and APX-hard but fixed-parameter tractable (FPT) in the parsimony score, and there exists a polynomial-time 1.3438-approximation for all p and a $\frac{12}{11}$-approximation for $p = 3$.

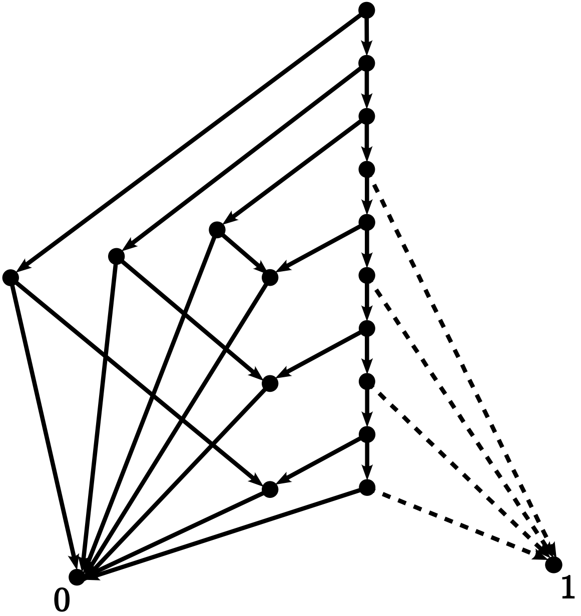
Example



Merge 0-leaves and 1-leaves



Hardwired Parsimony Score is 4



Observation

There exists a (trivial) $|X|$-approximation for computing the softwired parsimony score of a phylogenetic network.

Theorem

For every constant $\epsilon > 0$ there is **no polynomial-time approximation algorithm** *that approximates $PS_{sw}(N, \alpha)$ to a factor $|X|^{1-\epsilon}$, for a phylogenetic network N and a binary character α, unless $P = NP$.*

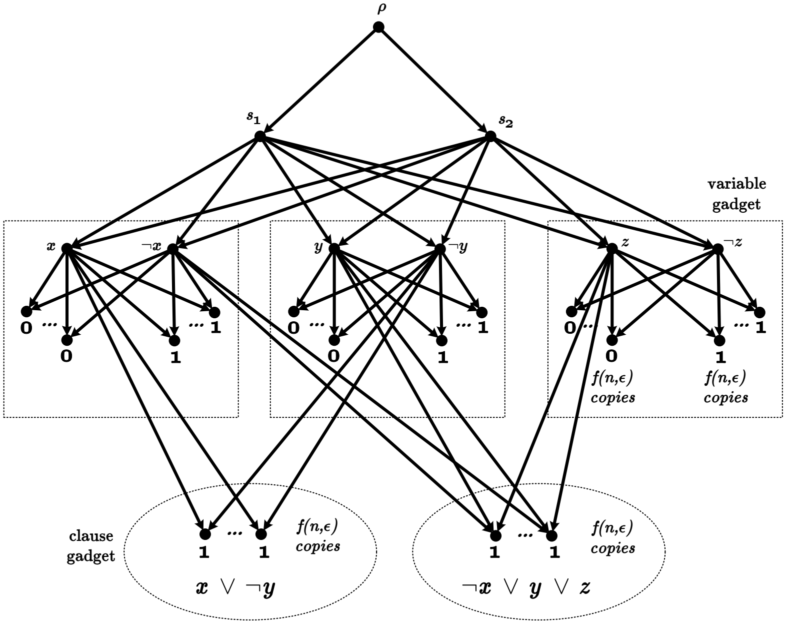
Definition

A phylogenetic network is **binary** if the root has outdegree 2 and all other vertices have total degree 1 or 3.

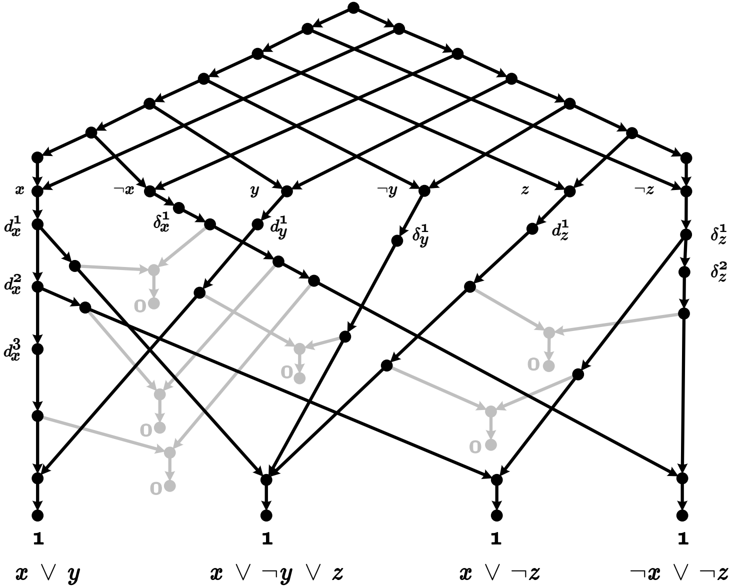
Theorem

For every constant $\epsilon > 0$ there is no polynomial-time approximation algorithm that approximates $PS_{sw}(N, \alpha)$ to a factor $|X|^{\frac{1}{3}-\epsilon}$, for a **binary** *phylogenetic network N and a binary character α, unless $P = NP$.*

Proof: reduction from 3SAT



Binary case



x
$\neg x$
y
$\neg y$
z
$\neg z$
d_x^1
δ_x^1
d_y^1
δ_y^1
d_z^1
δ_z^1
δ_z^2
d_x^2
d_x^3
0
0
0
0
0
0
0
1
1
1
1
$x \vee y$
$x \vee \neg y \vee z$
$x \vee \neg z$
$\neg x \vee \neg z$

Theorem

There is **no FPT** *algorithm for computing the softwired parsimony score, with the score as parameter, unless $P = NP$.*

Definition

A phylogenetic network is **level-**k if each biconnected component has reticulation number at most k.

Theorem

There is an **FPT** *algorithm for computing the softwired parsimony score, with the* **level** *of the network as parameter.*

ILP for softwired parsimony score

$$
\begin{aligned}
&\min \sum_{e \in E} c_e && \\
&\text{s.t.} \sum_{s \in \mathcal{P}} x_{v,s} = 1 && \text{for all } v \in V \\
&\quad c_e \geq x_{u,s} - x_{v,s} - (1 - y_e) && \text{for all } e = (u,v) \in E, s \in \mathcal{P} \\
&\quad c_e \geq x_{v,s} - x_{u,s} - (1 - y_e) && \text{for all } e = (u,v) \in E, s \in \mathcal{P} \\
&\quad \sum_{v:(v,r) \in E} y_{(v,r)} = 1 && \text{for each reticulation } r \\
&\quad y_e = 1 && \text{for each non-reticulate edge } e \\
&\quad x_{v,\alpha(v)} = 1 && \text{for each leaf } v \\
&\quad c_e, y_e \in \{0,1\} && \text{for all } e \in E \\
&\quad x_{v,s} \in \{0,1\} && \text{for all } v \in V, s \in \mathcal{P}
\end{aligned}
$$

with $\mathcal{P} = \{1, \ldots, p\}$ and $\alpha(v)$ the given character state of a leaf v.

Both parsimony scores can be computed quickly using ILP

$\lvert X\rvert$	Avg.	Average computation time (s)					
	num. of	Hardwired PS			Softwired PS		
	retic.	2-state	3-state	4-state	2-state	3-state	4-state
50	17.0	0.0	0.0	0.1	0.1	0.1	0.3
100	37.0	0.0	0.0	0.2	0.0	0.1	0.6
150	54.1	0.0	0.1	0.6	0.1	0.2	0.8
200	72.8	0.0	0.1	1.1	0.1	0.4	1.4
250	91.3	0.0	0.1	3.5	0.1	0.4	2.2
300	112.6	0.0	0.2	5.2	0.1	0.6	3.7

Future Work

- Are there approximation or FPT algorithms for computing the softwired parsimony score of **restricted classes** of networks?
- How to **search** for an optimal **network**?
- What if the different characters are **not independent**?

Thanks

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- Leen Stougie (Amsterdam)
- Nela Lekić (Maastricht)