Algorithms for constructing hybridization networks from multiple gene trees

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Hybridization Networks

Gene trees: phylogenetic trees from gene sequences

- Assume: **Binary** and **rooted**
- **Different** topologies at different genes

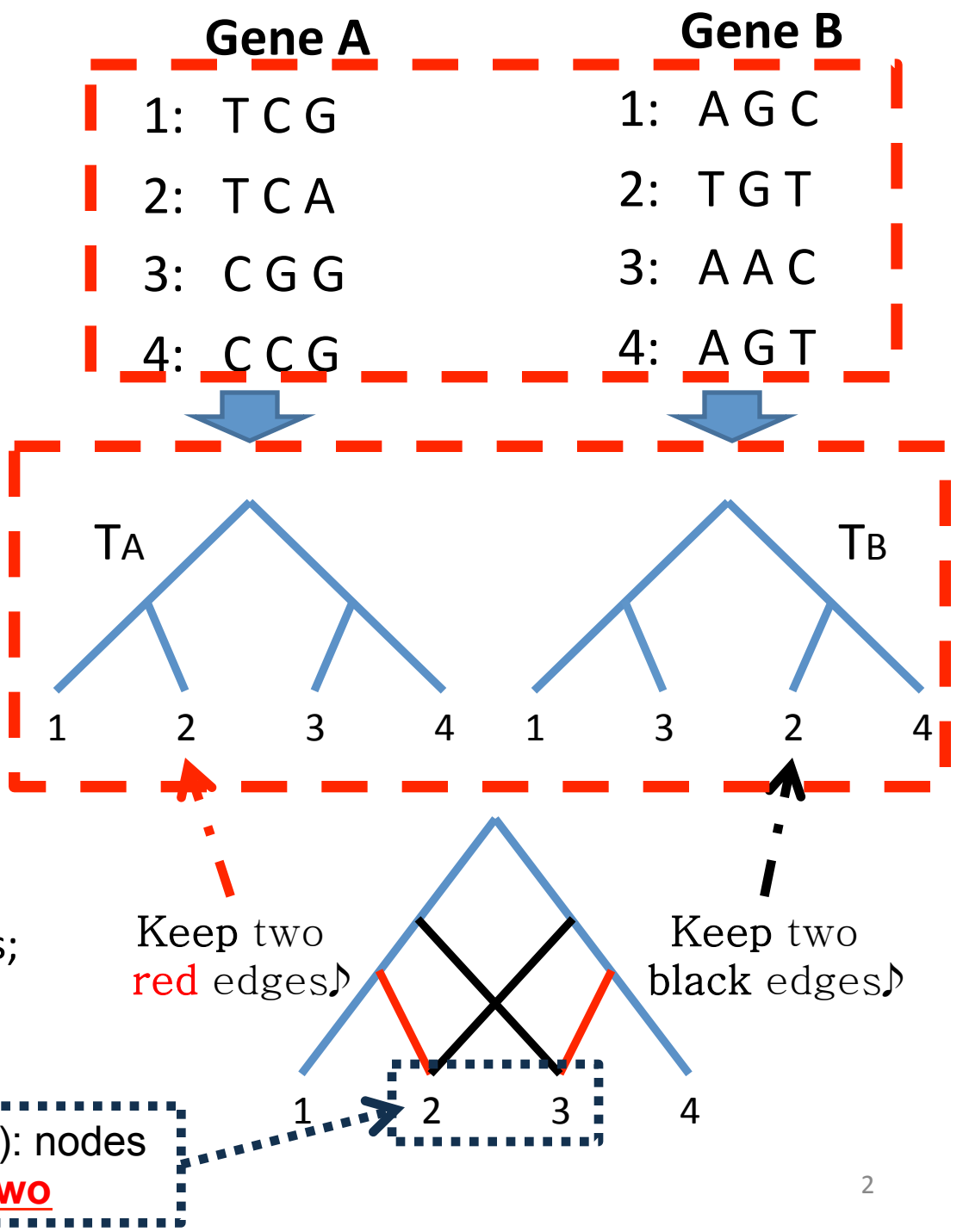
Reticulate evolution:

one explanation

- Hybrid speciation, horizontal gene transfer

Hybridization network:

A directed acyclic graph displaying **each** of the gene trees; each node with one or two incoming edges.



Hybridization Networks

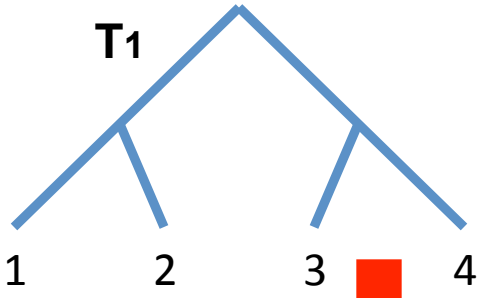
Given: a set of **K** binary gene trees **G**.

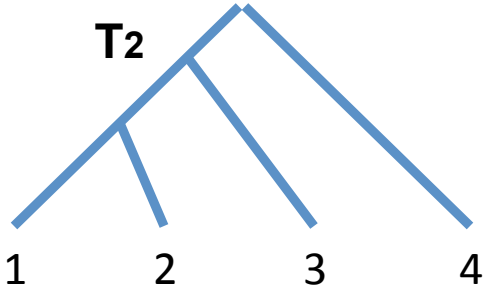
Problem: reconstruct hybridization networks with Rmin(**G**), the **minimum** number, reticulation events ***displaying*** each gene tree

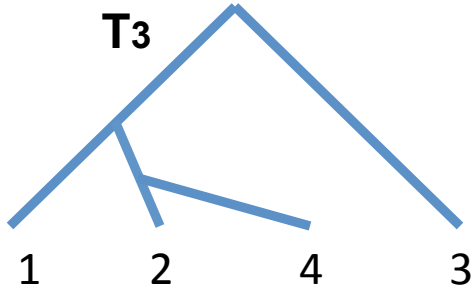
NP complete: even for **K=2**

Current approaches:

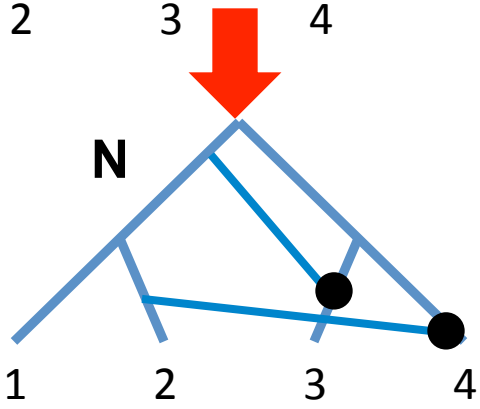
- exact methods for K=2 case (see Semple, Linz, et al) or K ≥2 (Wu, RECOMB 2013)
- impose topological constraints (e.g. galled networks, see Huson, Kelk, Van Iersel, et al.)







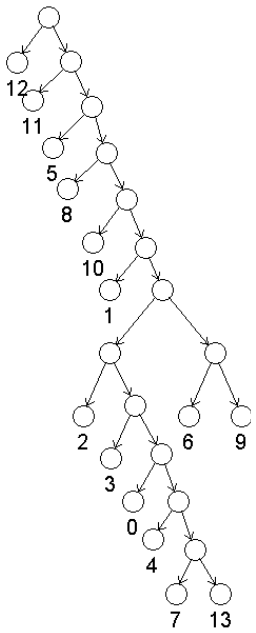
reticulation



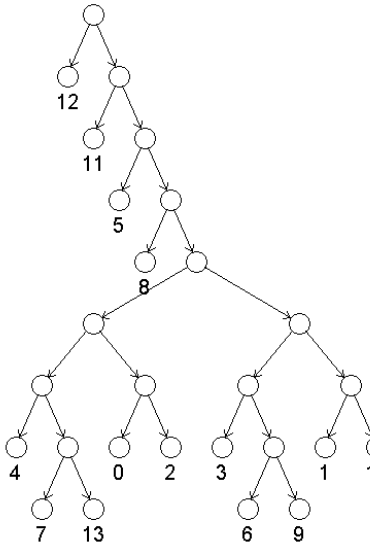
Two reticulation events**. Claim: minimum.**

Optimality: more difficult for **larger trees.**

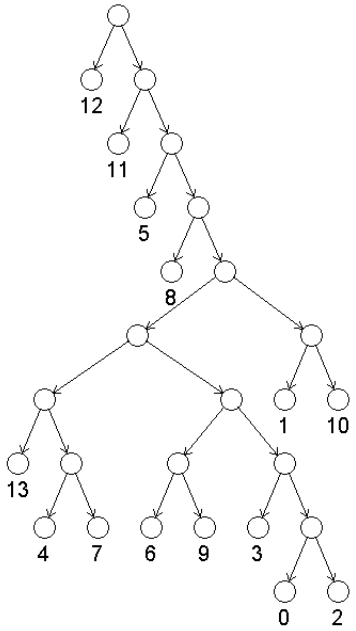
Five Poaceae Trees (13 taxa): how many reticulation events do we need?



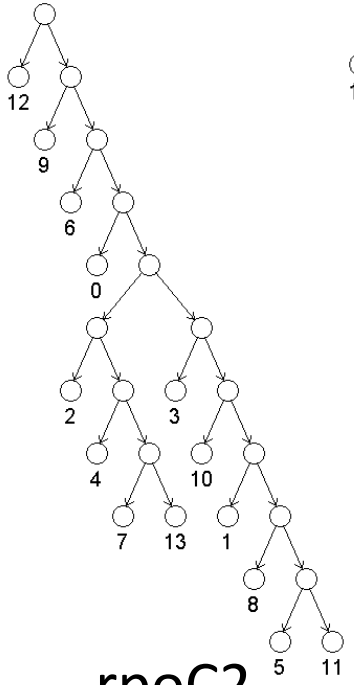
ndhF



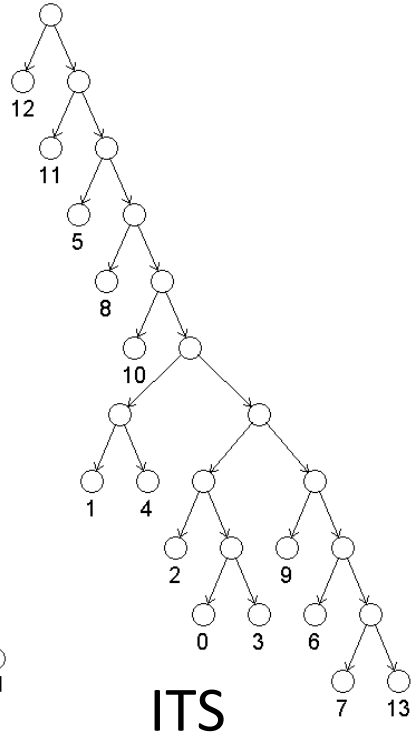
phyB



rbcL



rpoC2



ITS

Disclaimer: obtained from S. Linz

Key question: how to build good networks? Exact (but slow) method or **heuristics**.

Key question: how good is a given network? A **lower bound** for optimality.

Challenge: exact network is **infeasible** by existing methods.

Our idea: estimate **lower and upper bounds** on these trees instead

Close Lower and Upper Bounds for Minimum **Reticulation** of **Multiple** Gene Trees (Wu, ISMB 2010)

Key idea: developing novel lower and upper bounds for Rmin(**G**): G is the set of **K** gene trees.

$$RH(\mathbf{G}) \leq R_{min}(\mathbf{G}) \leq SIT(\mathbf{G})$$

RH(G): Lower bound
First non-trivial bound

Rmin(G): Minimum
Challenging for K ≥ 3

SIT(G): Upper Bound
Works for any K

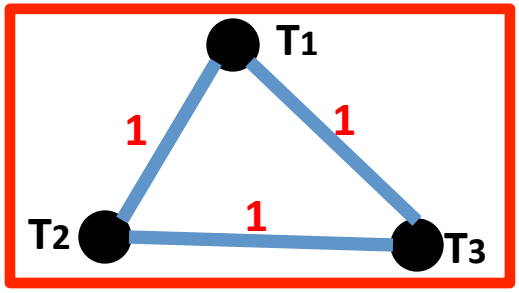
Bounds provides **range** of $R_{min}(G)$

If RH(G)=SIT(G), then **R_{min}(G) = RH(G) = SIT(G)**

RH Lower Bounds from **Pairwise** Distance

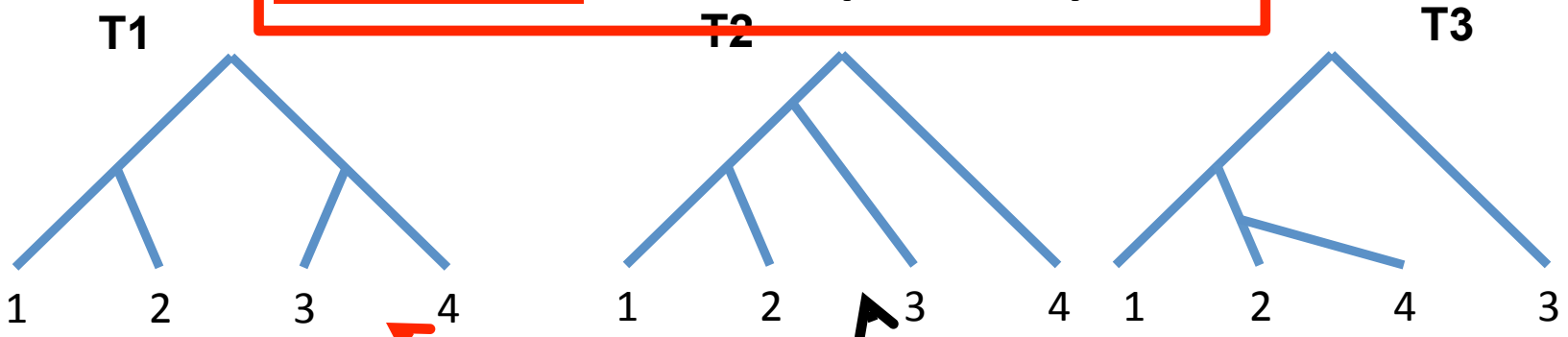
Pairwise reticulation distance of T_1 and T_2: **$d(T_1,T_2)$**, the **minimum** reticulation in any reticulate network for T_1 and T_2. Exists several methods for this.

Pairwise distances for **T_1, T_2 and T_3**

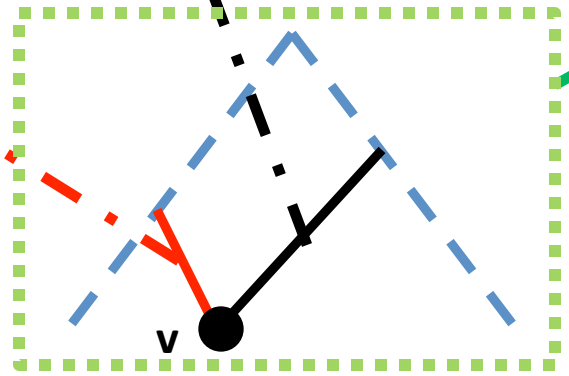


$R_{min}(T_1,T_2,T_3) \geq \max(1,1,1) = 1$

Question: can **$R_{min}(T_1,T_2,T_3) = 1$**?



Choosing same reticulate edge ➔ same gene trees

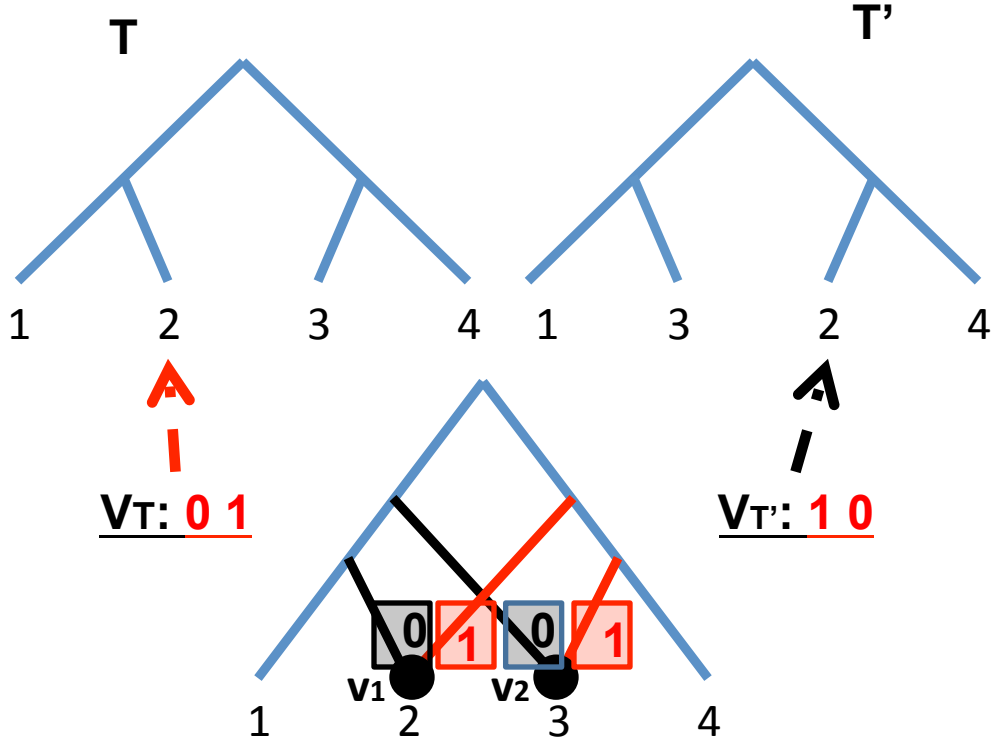


?

Imaginary network with one reticulation node

$R_{min}(T_1, T_2$ and $T_3) \geq 2$!

Display Vector



Tree T is **displayed** in a network

Each tree has a display vector

V_T : **Display vector** of T, how T is displayed in the network

- **one** bit per reticulation node ➔ length of display vector = number of reticulation nodes in the network
- value 0/1: at each reticulation node, which edge (the 0-edge or 1-edge) is kept for T?

Intuition: display vectors can *not* be too similar for two different trees

Lemma: $D(V_{T1},V_{T2}) \geq d(T_1,T_2)$ for *any* network displaying T_1 an T_2.

$D(V_{T1},V_{T2})$: Hamming distance of V_{T1} and V_{T2}.

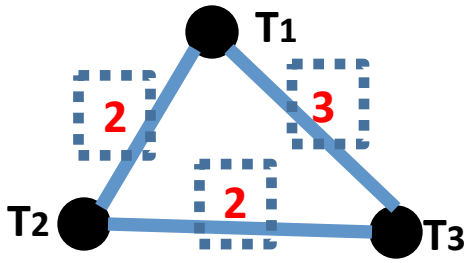
$d(T_1,T_2)$: pairwise reticulation distance of T_1 and T_2

The RH Lower Bound

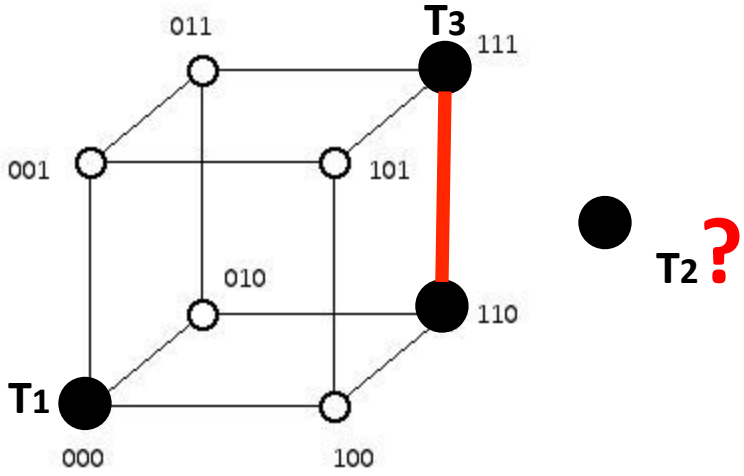
Key: if **R** reticulation events possible, then exist K length **R** display vectors, satisfying the **distance constraints**: Hamming distance D(VT,VT') ≥ d(T,T')

- **Analogy**: Selecting K points on R dimensional binary **hypercube** s.t. the points can *not* be too close
- If such K points do not exist, then we must need at least R+1 reticulation events.

RH lower bound: the **smallest** R s.t. K points can be selected on R-dimensional hypercube satisfying the distance constraints.



Question: can $R_{min}(T_1,T_2,T_3) = 3$?



$R_{min}(T_1, T_2, T_3) \geq 4$!

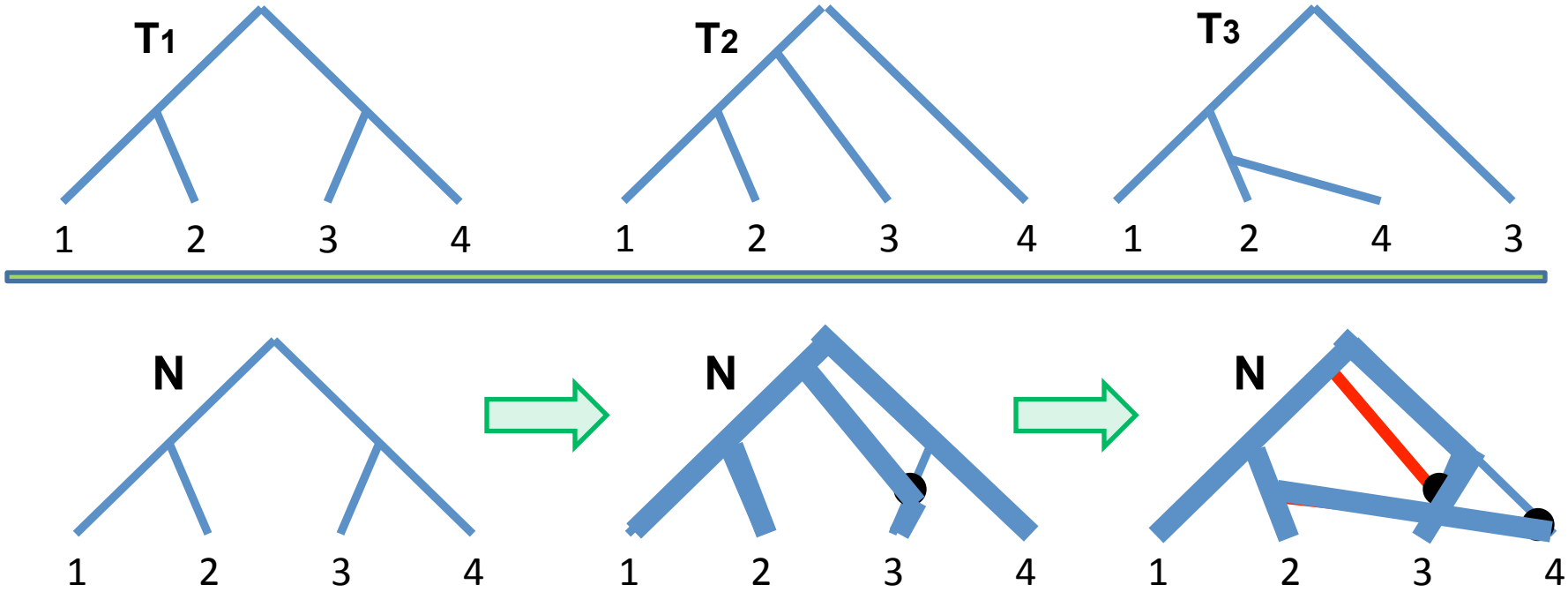
We use **integer linear programming** to solve it.
Closed-form formula of RH bound for K=3.

SIT Bound Heuristic for Constructing Networks (implemented in program PIRN)

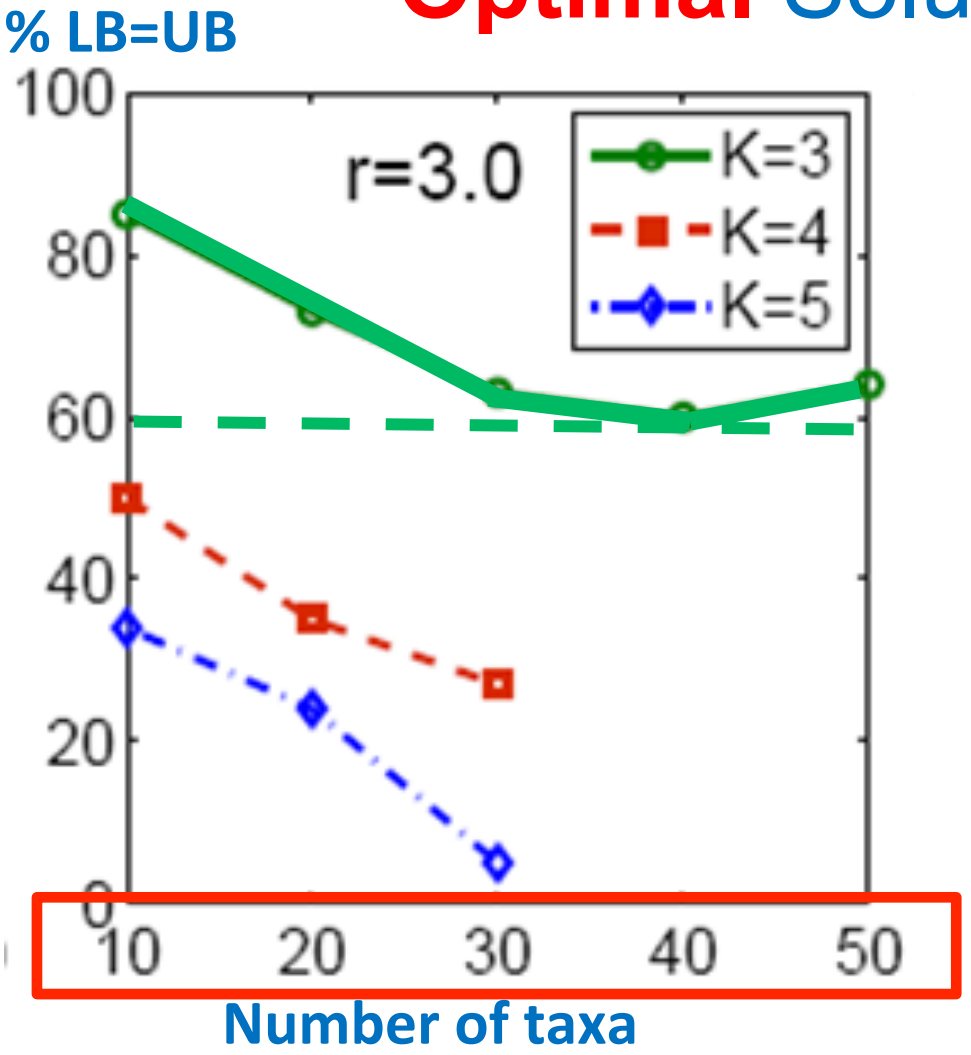
Heuristic: how to reconstruct a network for $T_1, T_2, \ldots, T_K$ using small (may *not* be minimum) number, U, of reticulation events?

Key idea (1) try all ordering of T_i to find the **best**; (2) for each order of $T_1, T_2, \ldots$, sequentially **insert** gene trees T_i into a **growing** network **N.**

- Each step inserts a tree into N by **new** reticulation to *display* T_i in N.
- **Minimize** the new reticulation events at each step (i.e. making smallest changes to accommodate the new tree Ti).



Performance of PIRN: % of Datasets **Optimal** Solution Found



Horizontal axis: *number* of taxa

Vertical axis: % of datasets lower = upper bounds

K: *number* of gene trees

r: *level* of reticulation

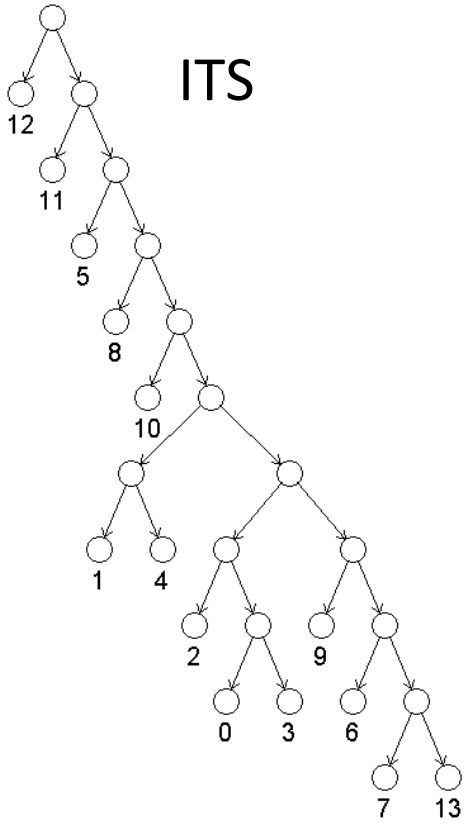
Average over 100 datasets

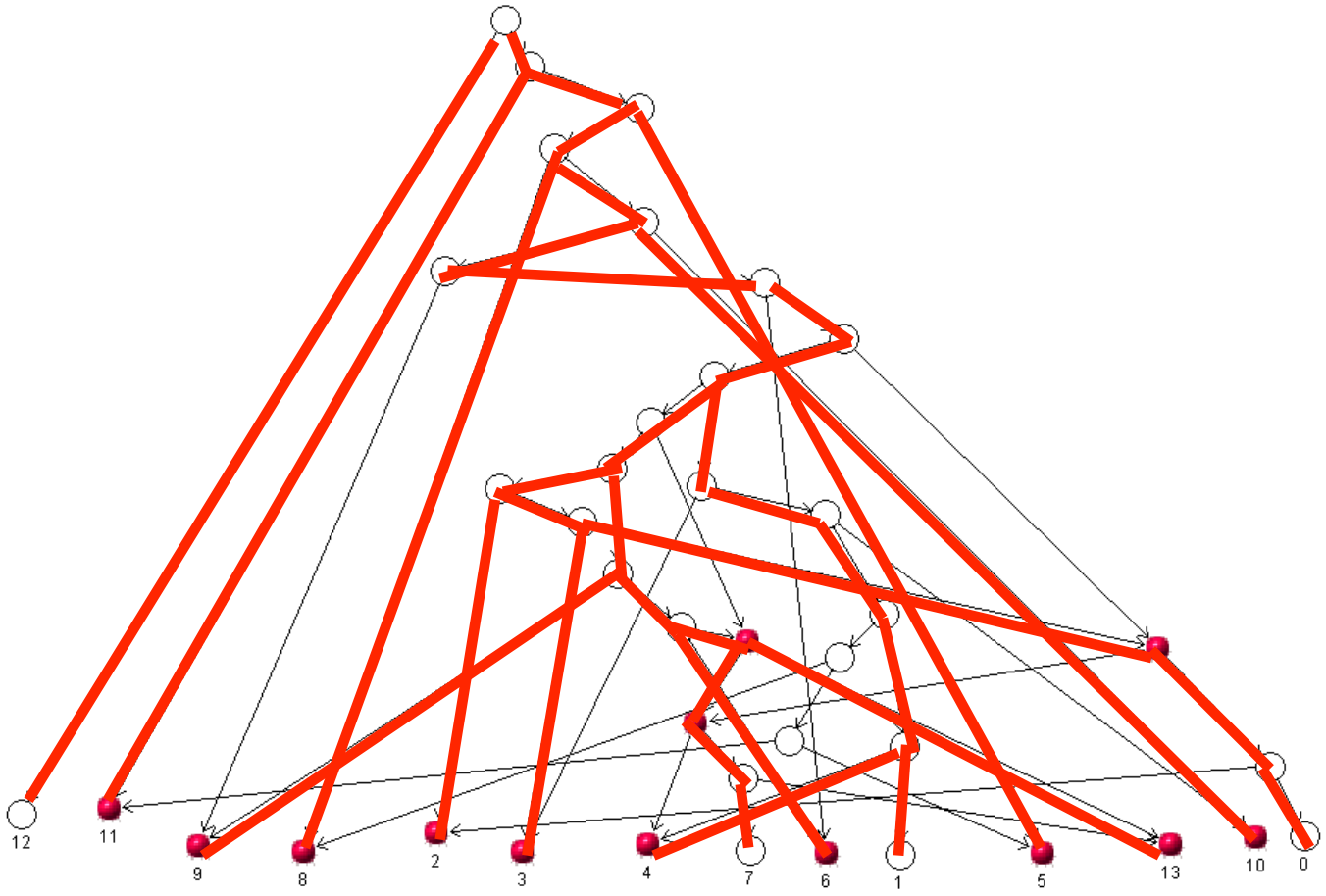
Lower and upper bounds often **match** for many data

When the number of trees **K** increases, performance *declines*.

PIRN: cannot handle large number of gene trees

Hybridization Network for Five Poaceae Trees





RH bound for five Poaceae trees: **11**

SIT bound: **13** reticulation events used in the constructed network.

Question: is this network optimal?

Lower bound: no stronger bound is known

Upper bound: a new method by Mirzaei and Wu

PIRNc: Exact algorithm for hybridization networks with unbounded K (Wu, RECOMB 2013)

PIRNc: allow arbitrary num of gene trees and taxa; no assumption on network topology, etc.

Constraint: Practical for networks with **4** (*maybe* 5) hybridization events.

	n=10			n=20			n=30		
	K=3	K=4	K=5	K=3	K=4	K=5	K=3	K=4	K=5
#Data ≤ 4	98	98	93	88	77	65	84	76	65
$PIRN_C$ = RH	96	93	90	88	74	63	84	75	61
$PIRN_C$ > RH	2	5	3	0	3	2	0	1	4
$PIRN_C$ < SIT	0	1	0	0	1	0	0	1	0
$PIRN_C$ = SIT	98	97	93	88	76	65	84	75	65
$PIRN_C$ > SIT	0	0	0	0	0	0	0	0	0
#Data not optimal by SIT	2	*6*	3	0	4	2	0	1	4
Time	13.4	49.9	92.6	276.8	705.8	1686.6	606.7	2227.1	2811.5

n: number of taxa. K: number of trees

Time: seconds

#Data <= 4: # of data w/ 4 or less reticulations among 100 simulations

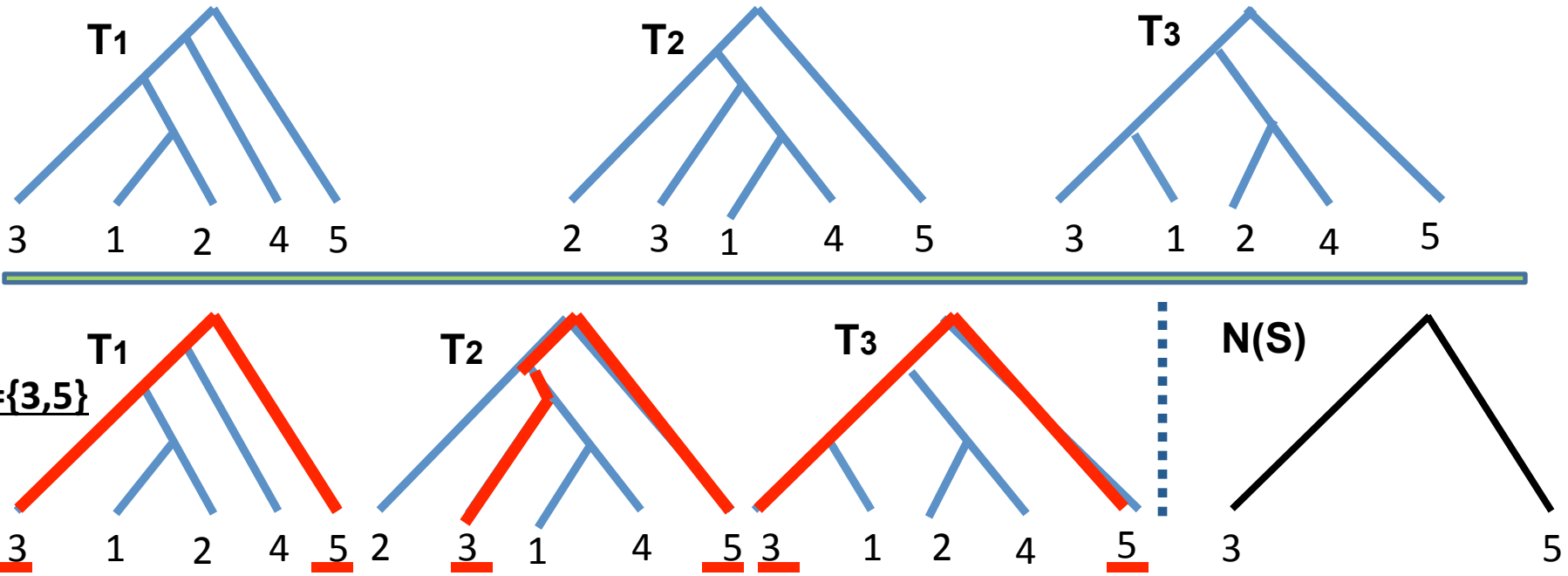
PIRNs: a new heuristic for large number (K) of trees (Mirzaei and Wu, TCBB, 2015 to appear)

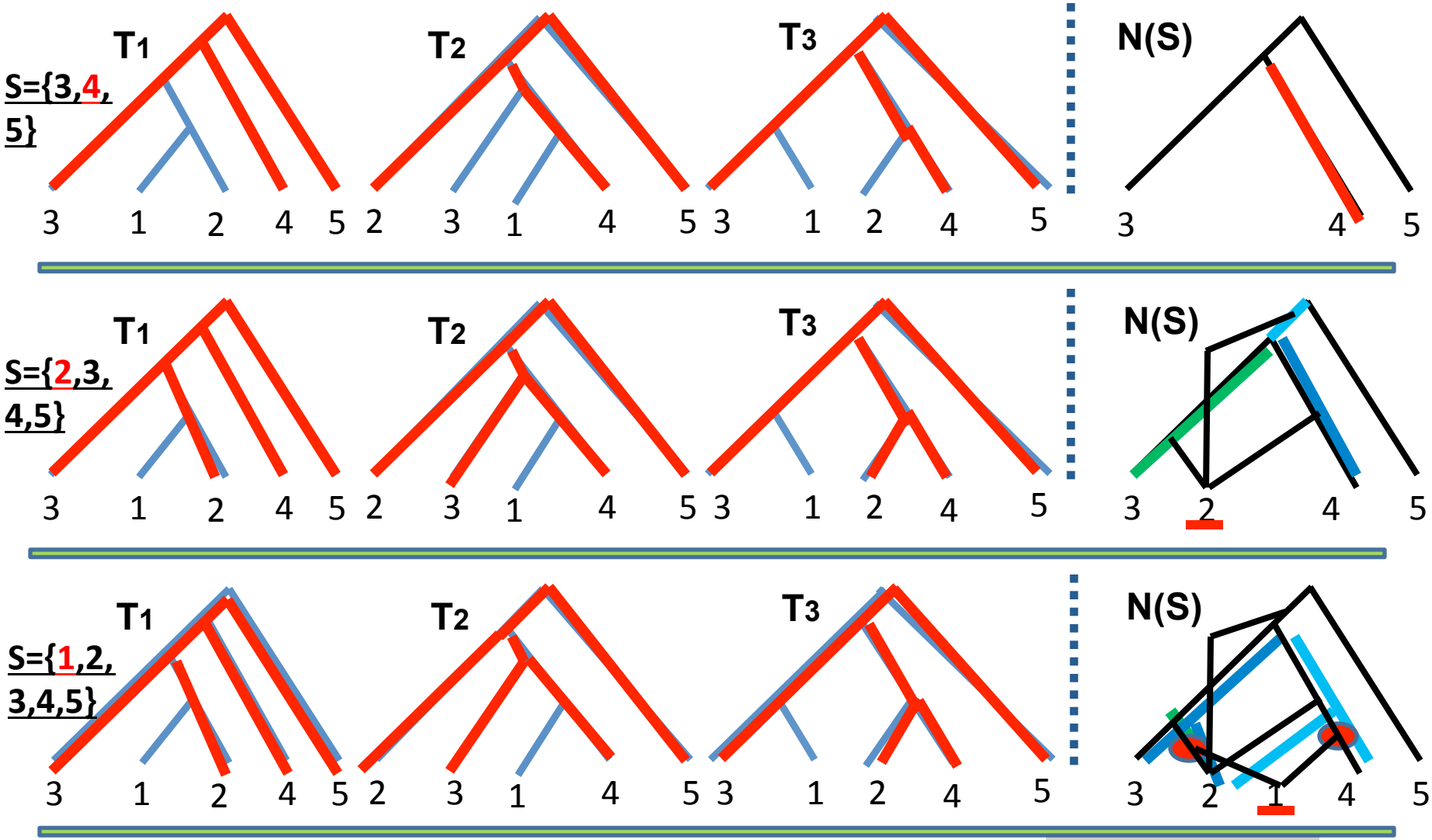
Key idea: consider **subsets** of taxa ***S***

Networks for *S*: display *subtrees* of Ti with taxa only from ***S***

Grow network for larger S by modifying networks for small subsets by adding as few reticulation events as possible

More efficient when **K** (num of trees) is large and num of taxa is not too large





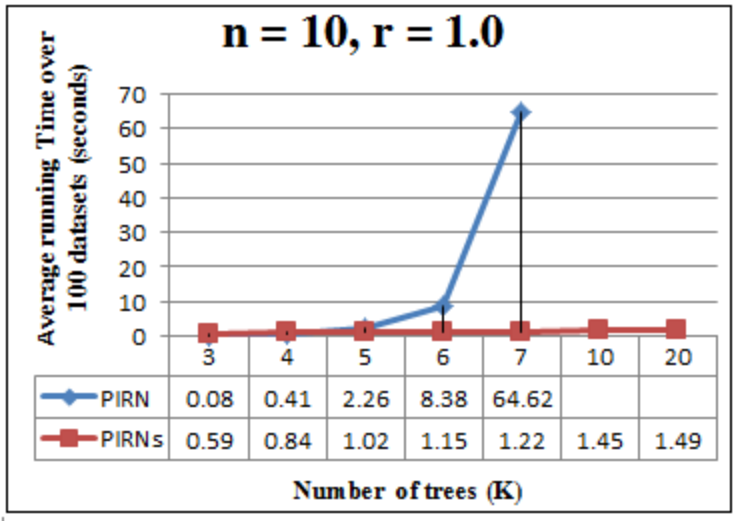
Share reticulation: choose the smallest number of edges to attach reticulation edges (a hitting set problem)

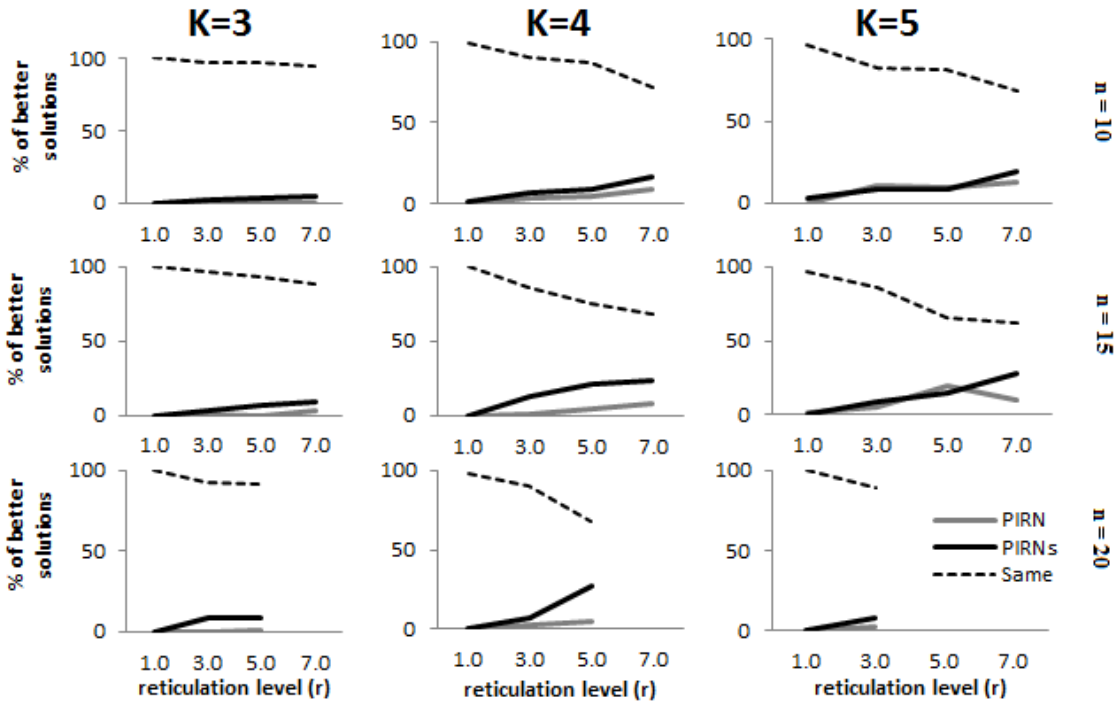
Share a common edge with T1

- For each tree Ti, find the set of edges to attach edges from the new taxa to display T
- This is based on how Ti is displayed in the network

Performance of PIRNs

Running time: PIRNs is much faster for larger K values.

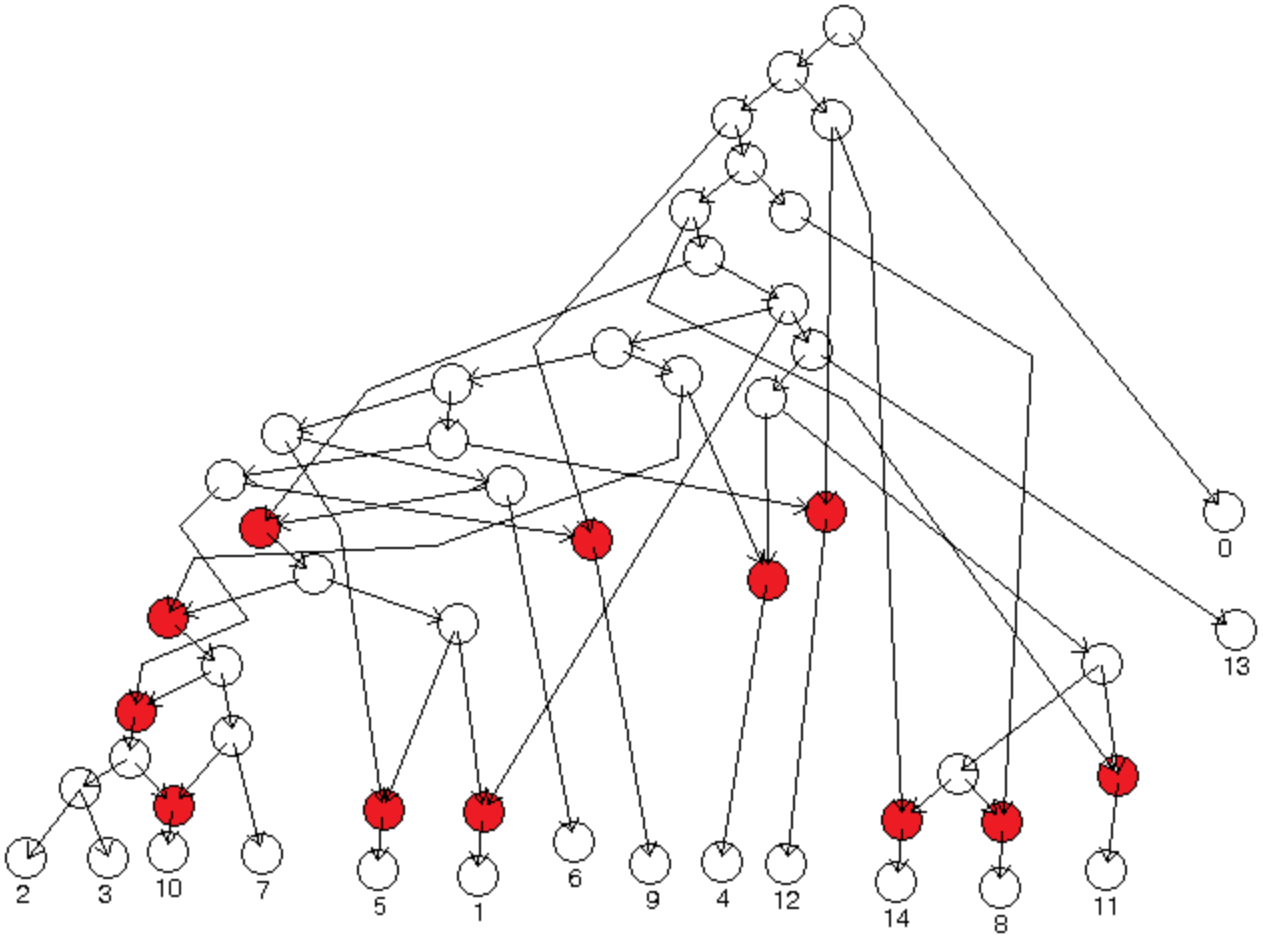




Parsimony: PIRNs produces more parsimonious networks when K increases than PIRN (the SIT bound).

K: number of trees. Dashed lines: PIRN=PIRNs. **Dark solid line**: PIRNs better. Light solid line: PIRN better.

A Better Network for Five Poaceae Trees



PIRNs: 12 reticulation events used in the constructed network (lower bound is 11). Optimality: still not known

- Papers from me and my student
  - Yufeng Wu: **Close lower and upper bounds for the minimum reticulate network of multiple phylogenetic trees**. Bioinformatics [ISMB] (2010)
  - Yufeng Wu: An Algorithm for Constructing Parsimonious Hybridization Networks with Multiple Phylogenetic Trees. Journal of Computational Biology (RECOMB, 2013)
  - Sajad Mirzaei and Yufeng Wu: **Fast Construction of Near Parsimonious Hybridization Networks for Multiple Phylogenetic Trees**, IEEE/ACM TCBB, accepted, 2015
- Related work from other groups: Park and Nakhleh (2012), Chen and Wang (2012), Albrecht (2015)
- More information available at: **http:// www.engr.uconn.edu/~ywu**
- Research supported by National Science Foundation (CCF-1116175 and IIS-0953563)