Statistically consistent estimation of level-1 phylogenetic networks from SNPs

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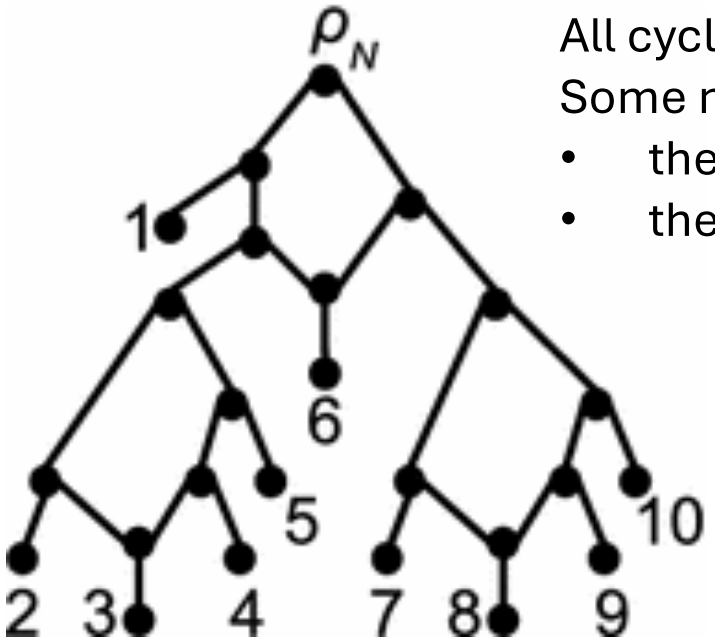
Phylogenetic networks

- Models evolution of a group of species (or individuals)
- Handles hybridization and lateral gene transfer, unlike trees
- Internal nodes that have indegree greater than 1 are “reticulate nodes”
- Substantial literature
- “Level-1” phylogenetic networks are a very simple version
- Estimating more complex networks is difficult, due to non-uniqueness

Level-1 phylogenetic network (aka “galled tree”)



All cycles are node-disjoint

Some nodes have indegree > 1

- these are the “reticulate nodes”
- they are also the “bottom nodes” of cycles

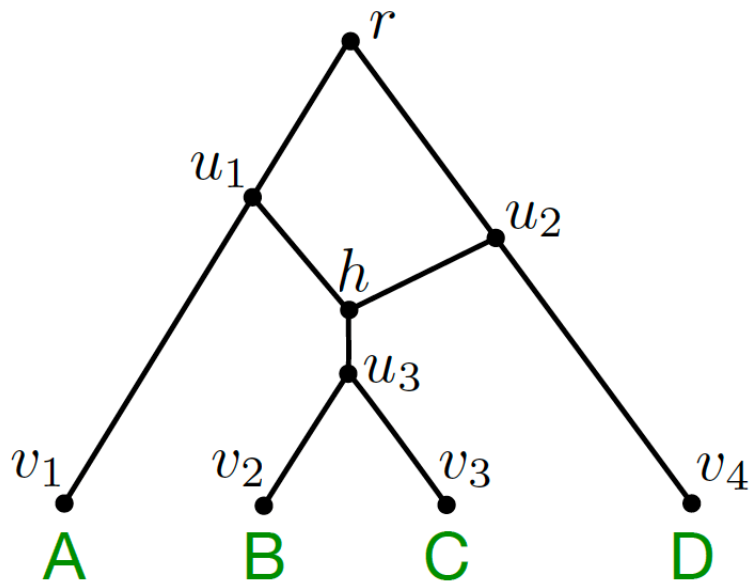
Figure from Gambette et al. 2015, On the challenge of reconstructing level-1 phylogenetic networks from triplets and clusters, https://arxiv.org/abs/1511.08056v2

Constructing rooted level-1 networks

Assuming N has no cycles of size less than 5, guaranteed correct and polynomial time reconstruction of the rooted network topology if given

- the set of all rooted trees in N
- the set of all clades in N
- the set of all rooted triplet trees in N

Rooted trees, rooted triplet trees, and clades inside rooted networks



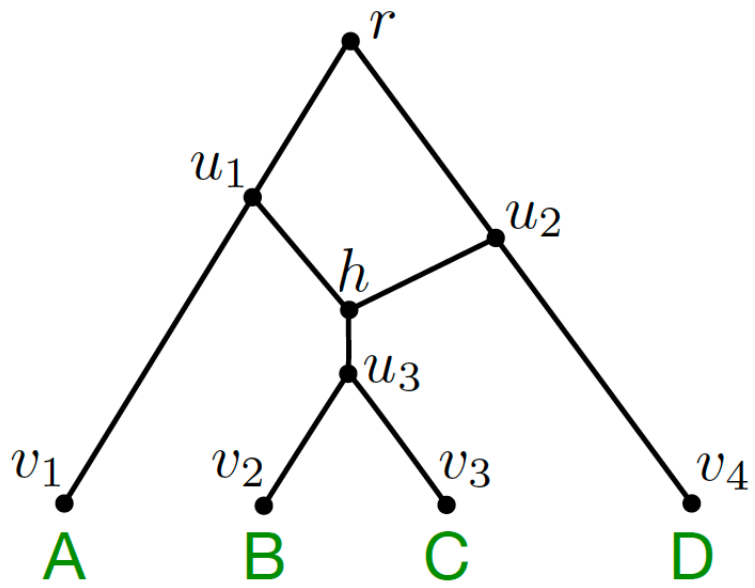
This network N is rooted at r and has one reticulate node, h

For each way of removing one edge entering h, we obtain a rooted tree:

- (A, (D,(B,C))) – if we remove (u_1, h)
- ((A,(B,C)),D) – if we remove (u_2, h)

The set of rooted trees is denoted $\mathcal{T}(N_r)$

Rooted trees, rooted triplet trees, and clades inside rooted networks



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Clades(N_r) = {{B,C}, {A,B,C}, {B,C,D}, {A,B,C,D}}

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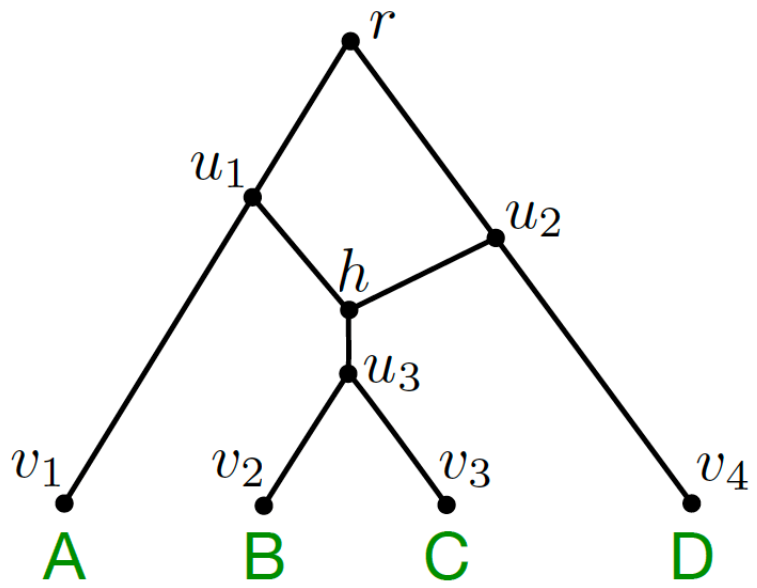

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Triplet trees: induced from the rooted trees.
A|BC – but not AB|C or AC|B
AB|D, A|BD – but not B|AD
AC|D, A|CD – but not C|AD
BC|D – but not BD|C or CD|B

Our problem: Estimating networks from SNPs

- Sequences evolve down a level-1 phylogenetic network N, some of which are SNPs (defined here to be binary sequences that evolve without homoplasy)
- Question: Can we infer the topology of N from the data, under the assumption of access to an Oracle that tells us which sites are SNPs?

- Version 1: We know the ancestral state for every SNP
  - We can try to estimate the rooted topology
- Version 2: We do not know the ancestral state for any SNP
  - We can only try to estimate the unrooted topology

Constructing rooted level-1 networks from SNPs?

If we have SNPs with known ancestral state, then we can get clades.

Therefore: given SNPs with known ancestral state that evolve down a level-1 network without cycles of size less than 5, we can construct the correct rooted network topology, if they cover all the clades of N

But: if the ancestral state is not known?

- The biologically more realistic case is when we do not know the ancestral state. We just have two states, 1 and 2.
- Hence, we cannot infer trees, clades, or rooted triplet trees
- Remember: each SNP evolves down a tree in $\mathscr{T}(N_r)$
- Therefore, the SNPs can provide
  - Bipartitions: splits of leafset into state 1 and state 2 for some SNP
  - $Q(N_r)$: quartet subtrees AB|CD induced in $\mathscr{T}(N_r)$
  - These can be inferred from SNPs: A and B exhibit state 1 and C and D exhibit state 2 for some SNP

But: if the ancestral state is not known?

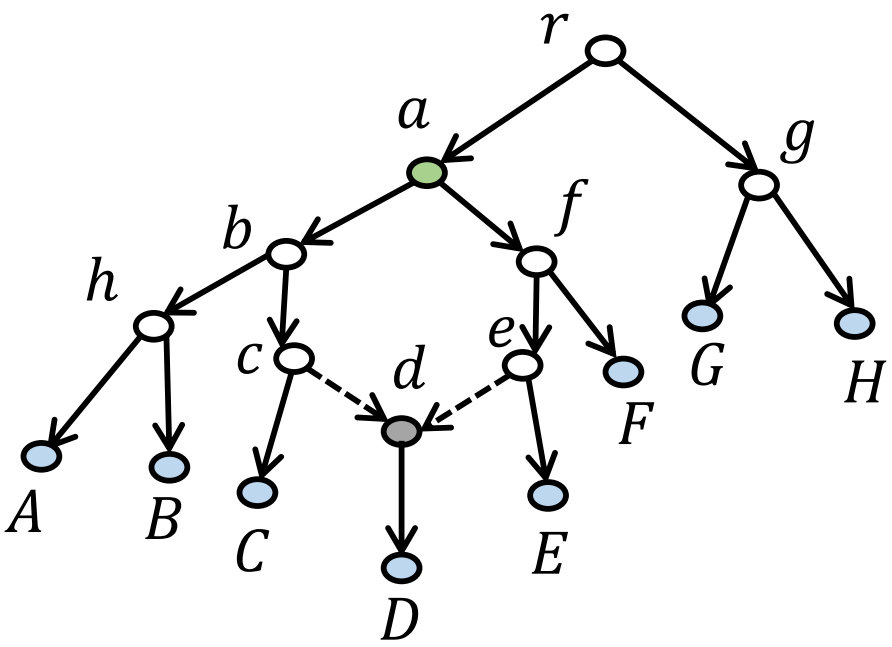
- The biologically more realistic case is when we do not know the ancestral state. We just have two states, 1 and 2.
- Hence, we cannot infer trees, clades, or rooted triplet trees
- But we can use the SNPs to obtain:
  - Bipartitions: splits of leafset into those that exhibit state 1 and those that exhibit state 2
  - $Q(N_r)$: quartet subtrees of trees in $\mathscr{T}(N_r)$
- Question: Can we infer the unrooted topology of a level-1 phylogenetic network from SNPs without known ancestral state?

Prior results relevant to SNPs without known ancestral state

- Gusfield (JCSS 2005): polynomial time algorithm to construct an unrooted level-1 phylogenetic network consistent with input set of SNPs (without known ancestral state), but no proof of uniqueness

- Gambette, Berry, and Paul (JBCB 2012): poly time algorithm to construct the true unrooted level-1 phylogenetic network when given Q(N), the set of all quartet trees in N

Q(N): quartet trees of network N (unrooted)



Ignore the root!
Then we can define Q(N):

- The set of all UV|XY so that there are node-disjoint paths from U to V and from X to Y

Question: which of the following are in Q(N)?

- AC|EF
- CD|AE
- AF|CE
- AD|CE

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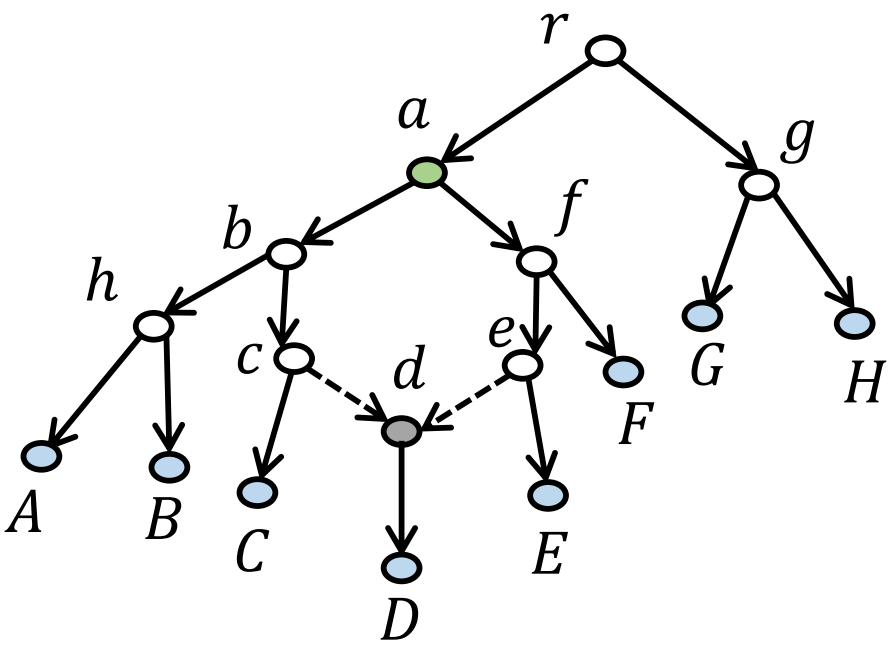

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Question: which of the following are in Q(N)?

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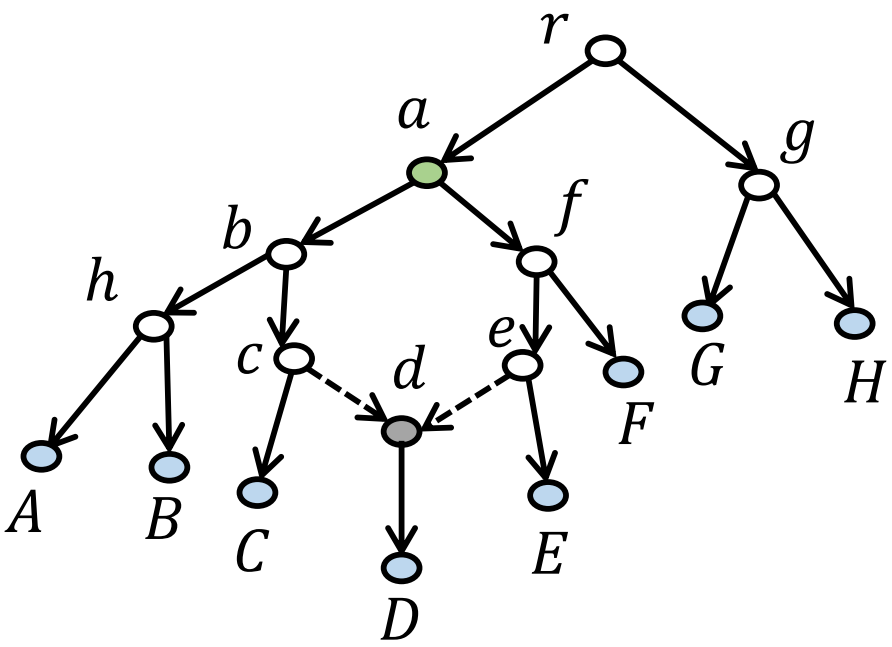
- AD|CE - no

$Q(N_r)$: quartet trees of network N (rooted)



Given the set $\mathcal{T}(N_r)$ of trees in the network, we can define $Q(N_r)$:

- The set of all UV|XY so that there are node-disjoint paths from U to V and from X to Y within some tree in $\mathcal{T}(N_r)$

Question: which of the following are in $Q(N_r)$?

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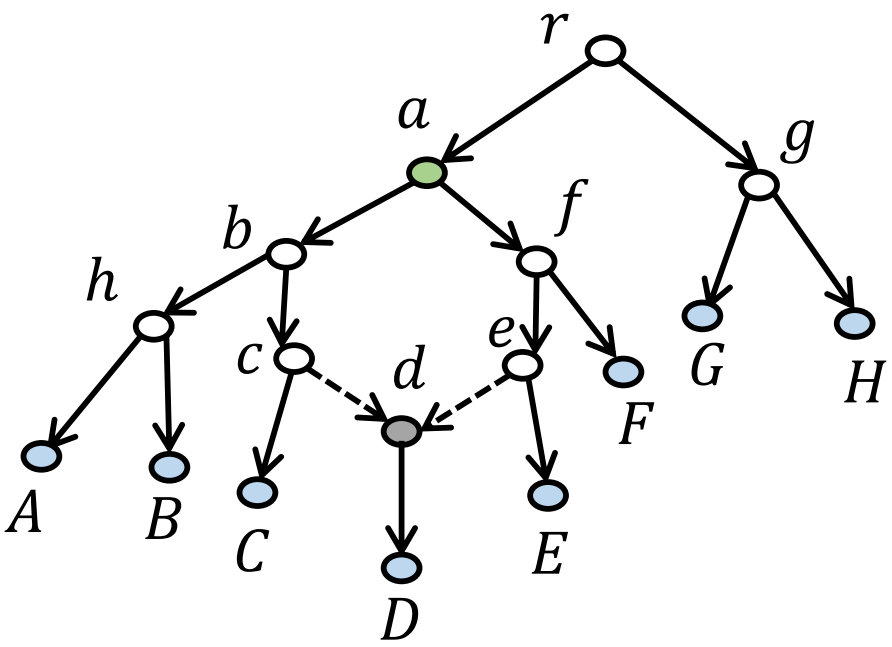

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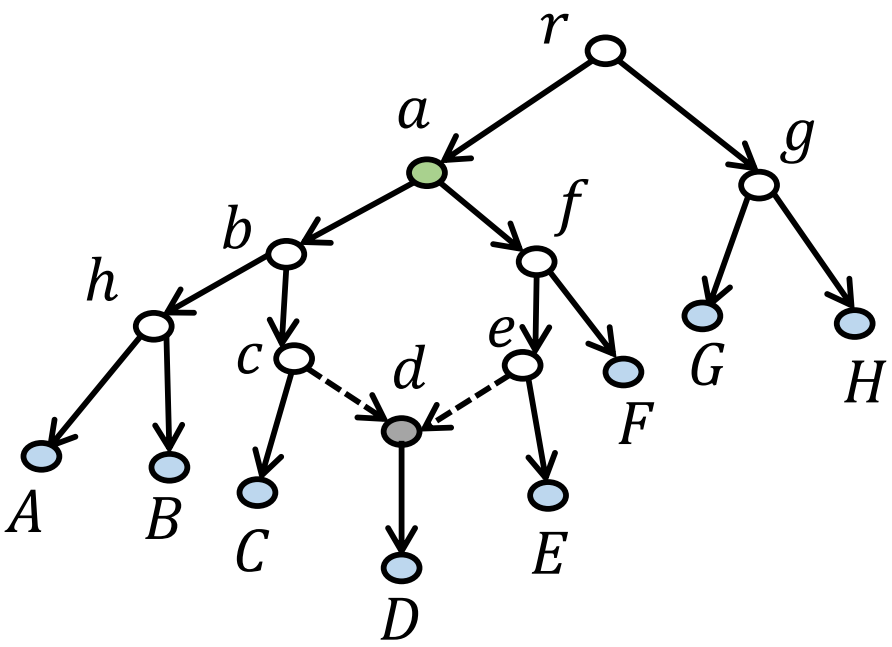
Q(N) vs. $Q(N_r)$

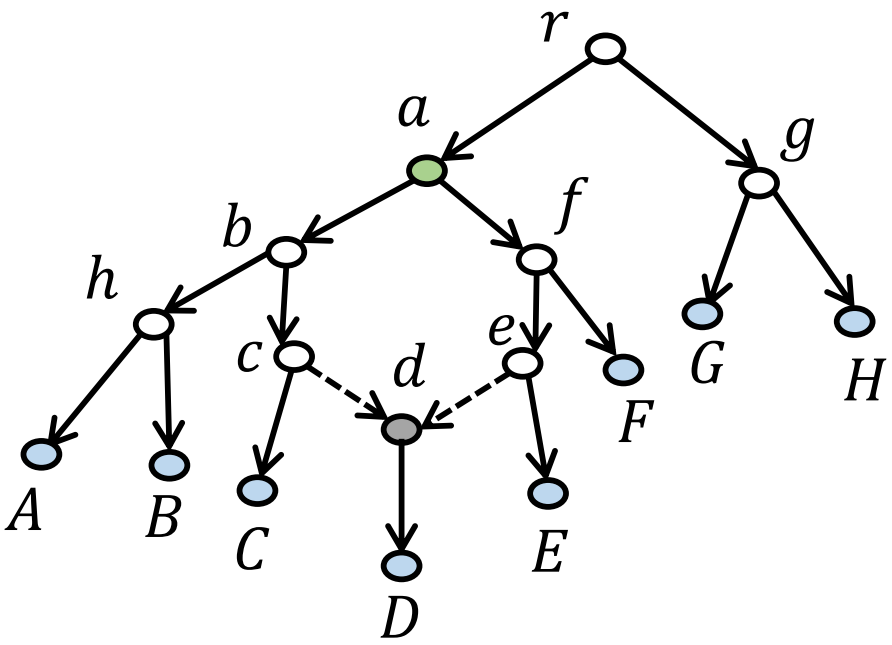


Question: which of these are in Q(N) and/or $Q(N_r)$?

- AC|EF - in both
- CD|AE - in both
- AF|CE - only in Q(N), not in $Q(N_r)$
- AD|CE – not in either

Thus: $Q(N_r)$ is a subset of Q(N), and can be a proper subset.

Q(N) vs. Q(N_r): *Not the same!*



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Our contributions: algorithms

- Our problem: unrooted level-1 network topology reconstruction given SNPs without known ancestral state, where cycles are of length at least 5, and we assume the SNPs cover the clades of N.
- We use quartet trees and bipartitions from SNPs
- We prove:
  - The algorithm from Gambette, Berry, and Paul (GBP) can fail
  - SNPs suffice to identify the unrooted topology of N.
  - Gusfield's algorithm correctly reconstructs N

Our contributions: statistical estimation

- We provide a model of site evolution down level-1 phylogenetic networks
- Given an Oracle that determines which sites are SNPs, we establish that Gusfield's algorithm can be used in a statistically consistent and polynomial time pipeline
- We provide a sample complexity for this approach

This talk

I will cover:

- Why GBP doesn't work for constructing networks from SNPs without known ancestral state
- Proof that SNPs suffice to construct unique network if they cover all clades and N has no cycles of length less than five
- The CUPNS algorithm (Constructing Unrooted Phylogenetic Networks from SNPs) correct for level-1 network construction
- Proof that Gusfield's algorithm is also correct

I will not cover the stochastic model, proof of statistical consistency, or sample complexity (not enough time)

GBP: Gambette, Berry, and Paul, JBCB 2012

- GBP prove that their algorithm returns the unrooted topology of N if given Q(N), where N is a level-1 phylogenetic network.

GBP: Gambette, Berry, and Paul, JBCB 2012

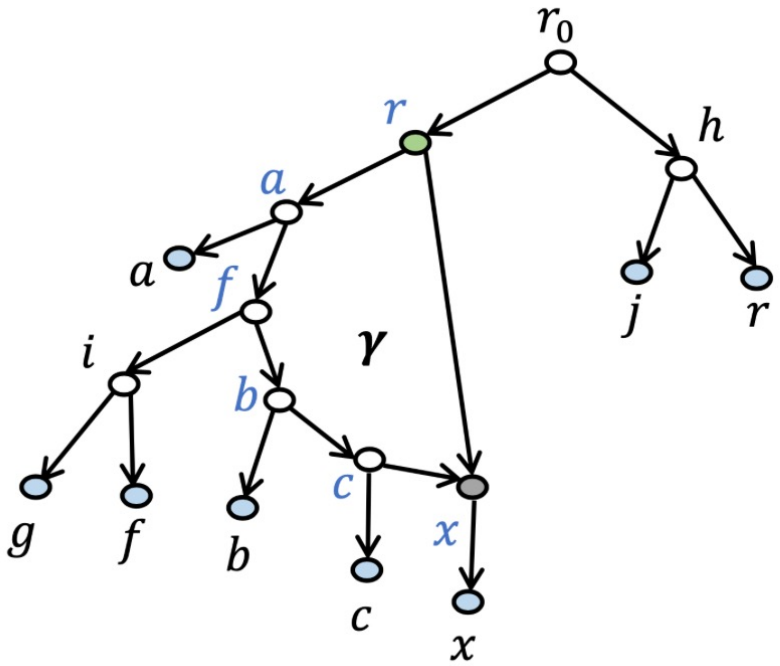
- Given set Q of quartet trees:
  - Phase 1: Construct "SN-tree" (maximally refined tree T all of whose resolved quartets are in Q, and no resolved quartet tree in T conflicts with any quartet tree in Q)
  - Phase 2: Replace each polytomy by a cycle, using the "node ordering algorithm"
  - Return the resultant graph

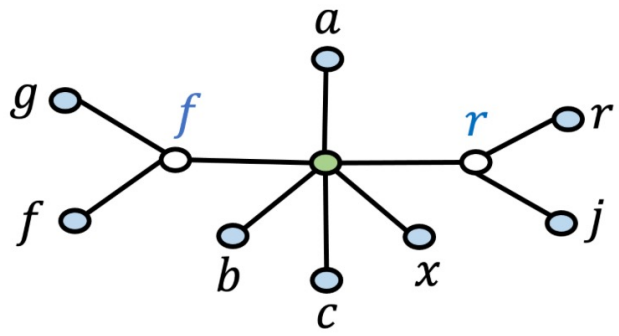
Phase 2 of GBP

Given a polytomy v in the SN-tree, and given set Q of quartet trees:

- Label the neighbors of v by leaves
- Determine that nodes a,b,c appear consecutively, in that order, in the cycle expansion of the polytomy if and only if there does not exist a label z such that ac|bz is a quartet in Q.
- Return the cycle if and only if information is consistent with a unique cycle.

Phase 1: Constructing the SN-tree given Q(N)





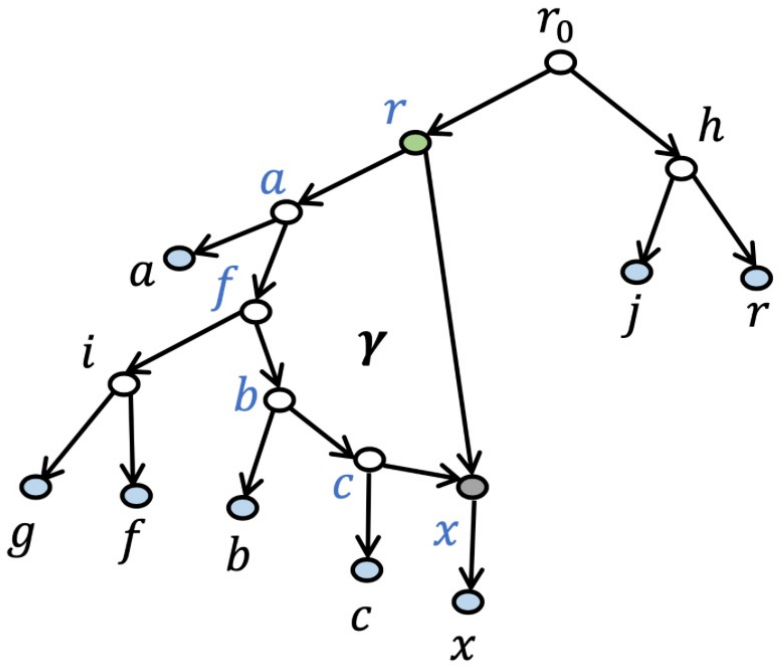
The SN-tree given Q(N)

- The cycle has been collapsed to a polytomy,
- The nodes adjacent to the polytomy are labelled by leaves.

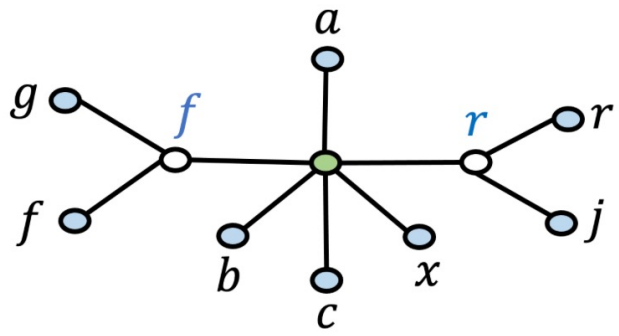
Network N with cycle γ

The internal nodes of γ are labelled by leaves that attach to the cycle at those nodes.

Phase 2: Refining the polytomy given Q(N)



Network N with cycle



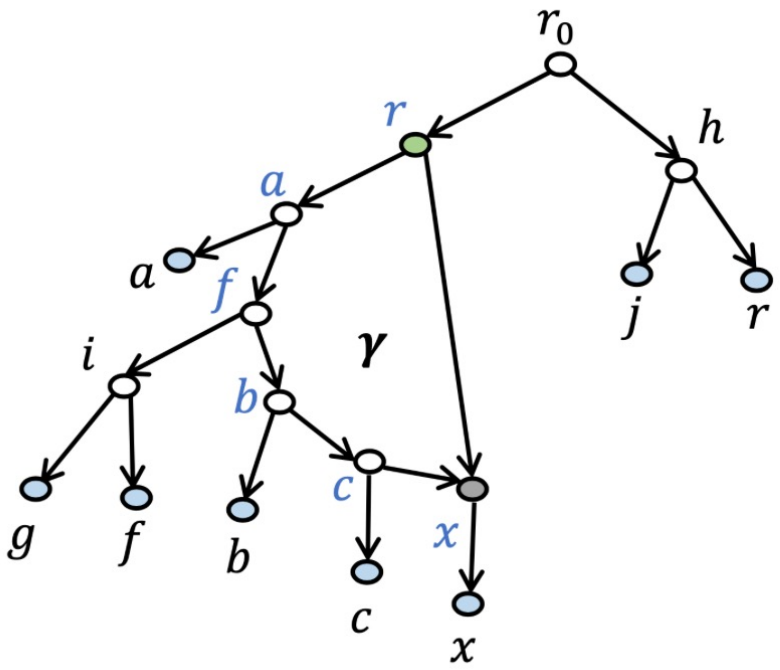
The SN-tree given Q(N)

Given Q(N), the node ordering algorithm will replace the polytomy in the SN-tree by the correct cycle—and so returns the unrooted topology of N.

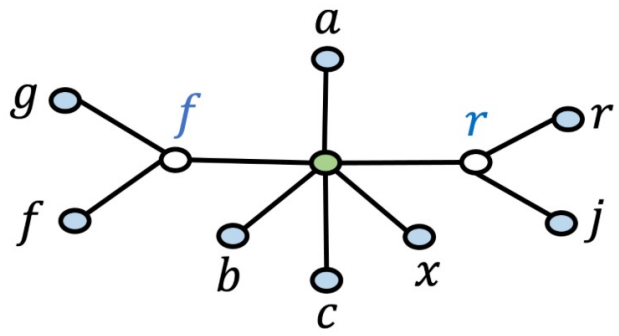
GBP: usable from SNPs?

- Remember: the SNPs define $Q(N_r)$
  - Each SNP defines a bipartition of the leaves into two sets
  - Hence we can get quartet trees AB|CD where A and B share one state, and C and D share the other state.
- But we already showed $Q(N_r)$ can be a proper subset of $Q(N)$
- So: what happens if we give GBP the set $Q(N_r)$ instead of $Q(N)$?

We proved the SN-tree given Q(N) is the same as the SN-tree given Q(N_r)



Network N with one cycle.



The SN-tree given Q(N_r) or Q(N)

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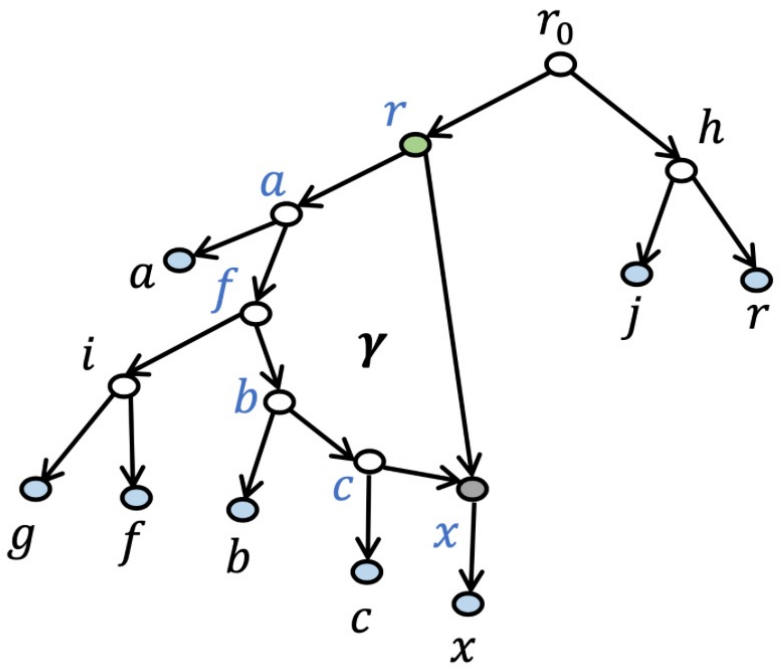
Phase 2: Refining the polytomy given $Q(N_r)$



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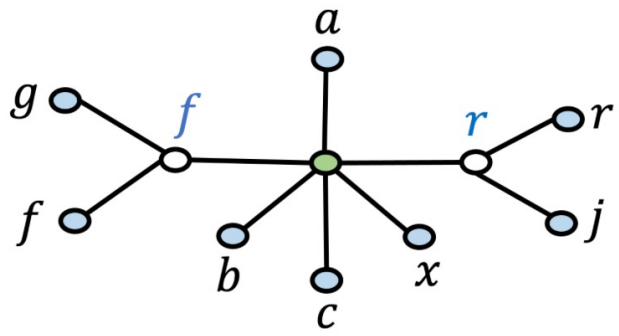

The SN-tree given $Q(N_r)$

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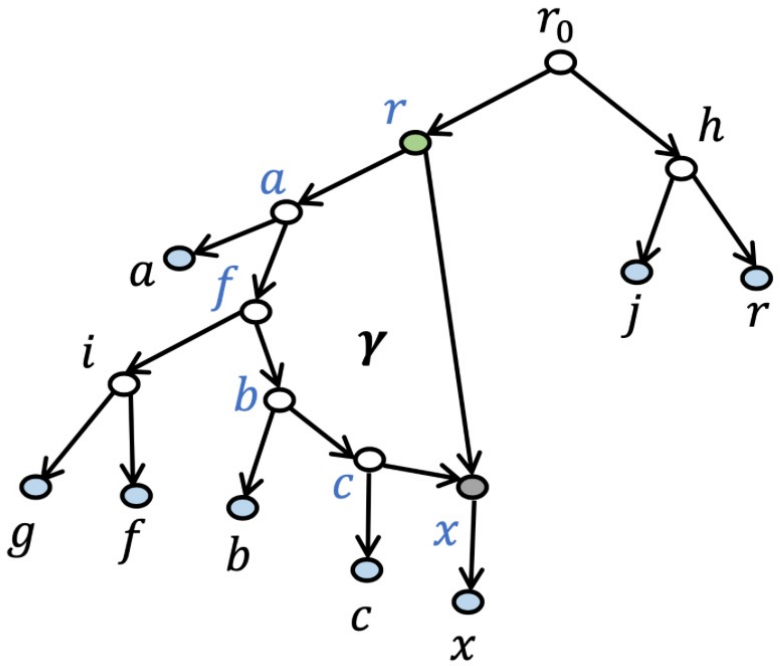

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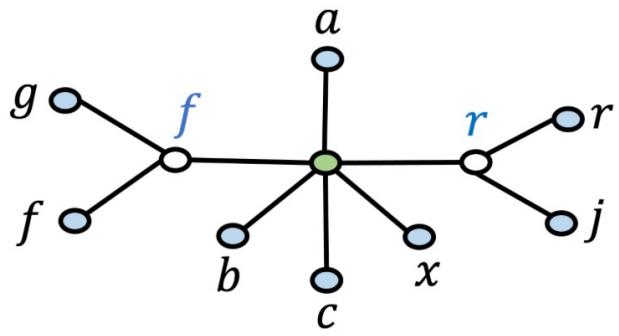

The SN-tree given $Q(N_r)$

Note: bf|ac is in Q(N), but bf|ac is NOT in $Q(N_r)$!

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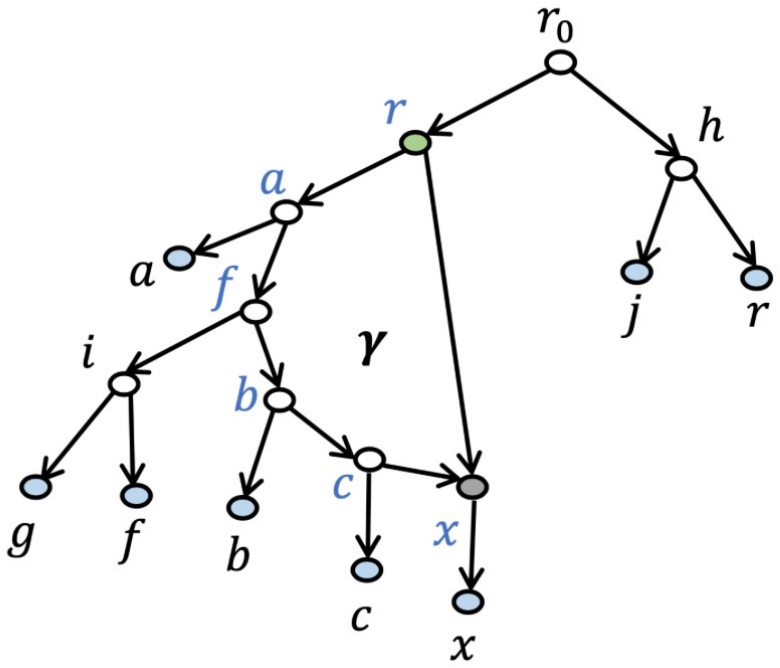

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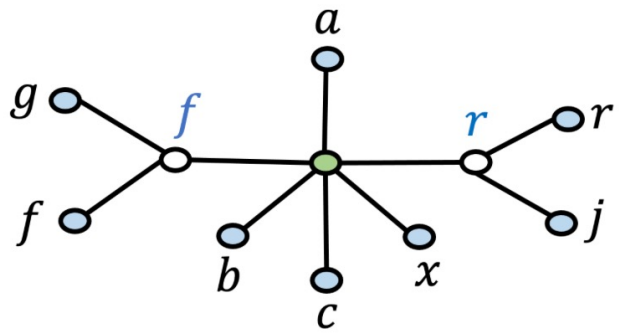

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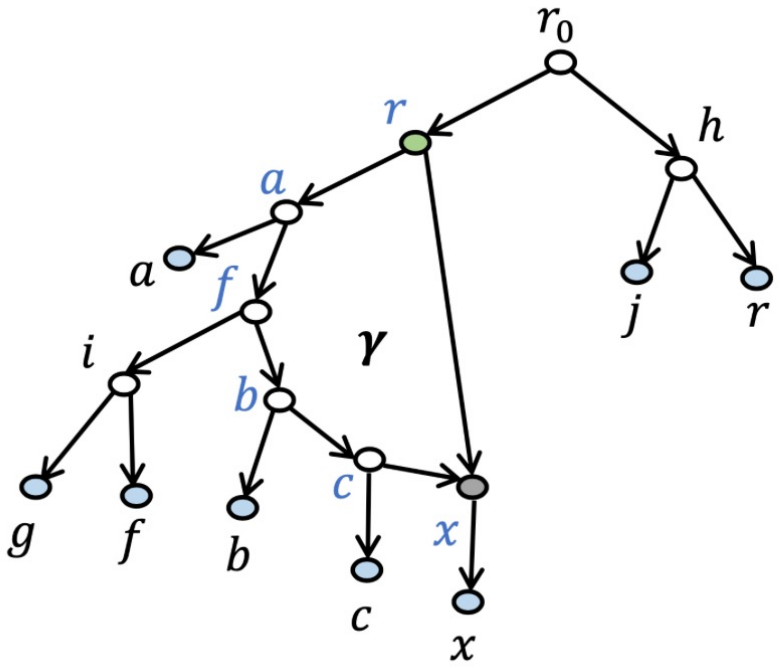
Phase 2: Refining the polytomy given $Q(N_r)$



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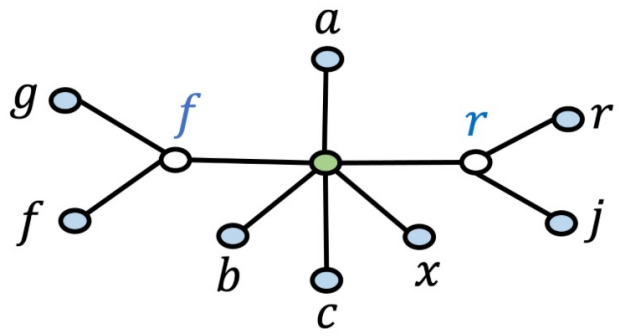

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Thus, the node-ordering algorithm can fail on $Q(N_r)$!

Estimating level-1 networks from SNPs

- With known ancestral state, many algorithms are correct (provided cycles not below size 5, SNPs cover the clades)
- Without known ancestral state, GBP can fail

- But we can use $Q(N_r)$ to obtain the level-1 network even without known ancestral state, as we now show (CUPNS method)

CUPNS: Constructing Unrooted Phylogenetic Networks from SNPs

- Input: SNPs without known ancestral state
- Output: network N if required conditions hold
  - Level-1
  - No cycles of size less than 5
  - The SNPs cover the clades of N

CUPNS method

- Input: SNPs without known ancestral state
- Steps:
  - Construct set Q of quartet trees
  - Construct SN-tree for Q, and label neighbors of each polytomy
  - For each polytomy,
    - Use Q to find “bottom node” (unique leaf x for which two quartet trees exist in Q for any set of four leaves including x)
    - Let Q’ be result of removing quartets involving x from Q.
    - Construct tree T on Q’. If $Q=Q(N_r)$, this will be a caterpillar tree.
    - Use Q to close T into a cycle including x.

CUPNS method

- Theorem: Suppose N is level-1, all cycles are of size at least five, and the SNPs are given without known ancestral state but cover the clades of N. Then CUPNS will return N, and uses polynomial time.
- Corollary: There is only one unrooted level-1 network that is consistent with $Q(N_r)$ when the required conditions hold.
- Corollary: Gusfield's algorithm is correct when the required conditions hold.

Contributions: algorithms when SNPs are given without known ancestral state

Method	Comments if required conditions hold	Runtime
Gusfield–Construct-Unrooted	Guaranteed correct	$O(mn + n^3)$
CUPNS	Guaranteed correct	$O(mn^4)$
GBP-SNPs	Will fail on some networks	$O(mn^4)$

Notes: m is the number of SNPs and n is the number of leaves.

Required conditions:
(1) the SNPs cover the bipartitions of N,
(2) N is level-1, and
(3) every cycle in N is of length at least 5

Statistical estimation

- We also provide a parametric model of character evolution down level-1 phylogenetic networks
- We assume existence of a perfect oracle (tells us which sites are SNPs)
- Under these assumptions, we prove that CUPNS and Gusfield's algorithms are statistically consistent estimators of the unrooted level-1 network.
- We also provide sample complexity analysis.

Future work

- Evaluate robustness to oracle error
- Evaluate on simulated data, especially under model misspecification
- Determine outcome when SNPs do not cover the clades (or develop better methods for that case)