Summarizing the Solution Space in Tumor Phylogeny Inference by Multiple Consensus Trees

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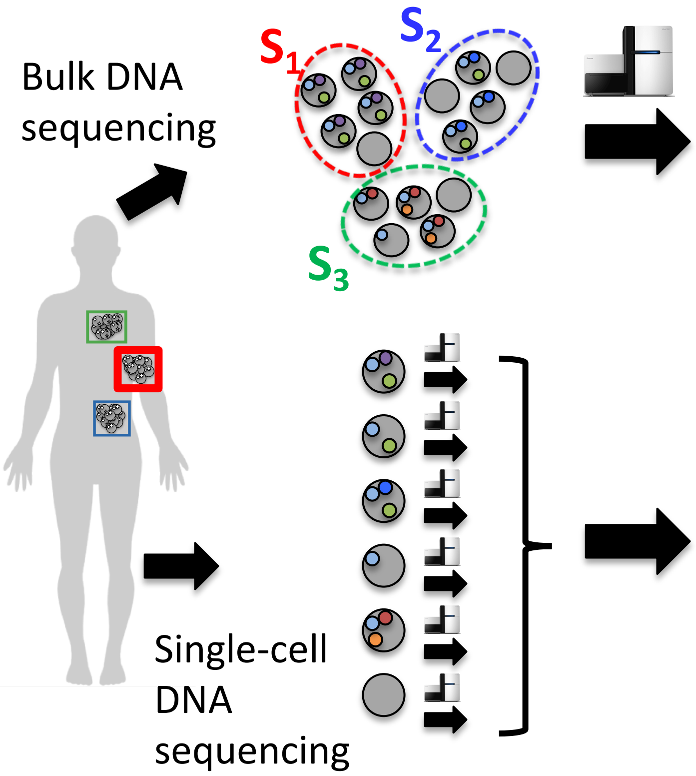
Additional Challenge in Cancer Phylogenetics



n **mutations**

$$
\begin{array}{c} \\ \\ m \text{ samples} \end{array}
\begin{array}{c} S_1 \\ S_2 \\ S_3 \end{array}
\begin{pmatrix}
0.8 & 0.8 & 0.8 & 0.0 & 0.0 & 0.0 \\
0.7 & 0.6 & 0.0 & 0.6 & 0.0 & 0.0 \\
0.8 & 0.0 & 0.0 & 0.0 & 0.6 & 0.4
\end{pmatrix}
$$

n **mutations**

$$
m \text{ cells}
\begin{pmatrix}
1 & 1 & 1 & 0 & 0 & \color{red}{1} \\
1 & 0 & 1 & 0 & 0 & 0 \\
1 & 0 & \color{red}{0} & 1 & 0 & 0 \\
0 & 0 & 1 & 0 & 0 & 0 \\
0 & 0 & \color{red}{?} & 0 & 1 & 1 \\
0 & 0 & 0 & 0 & 0 & 0
\end{pmatrix}
$$

Incorrect entries:

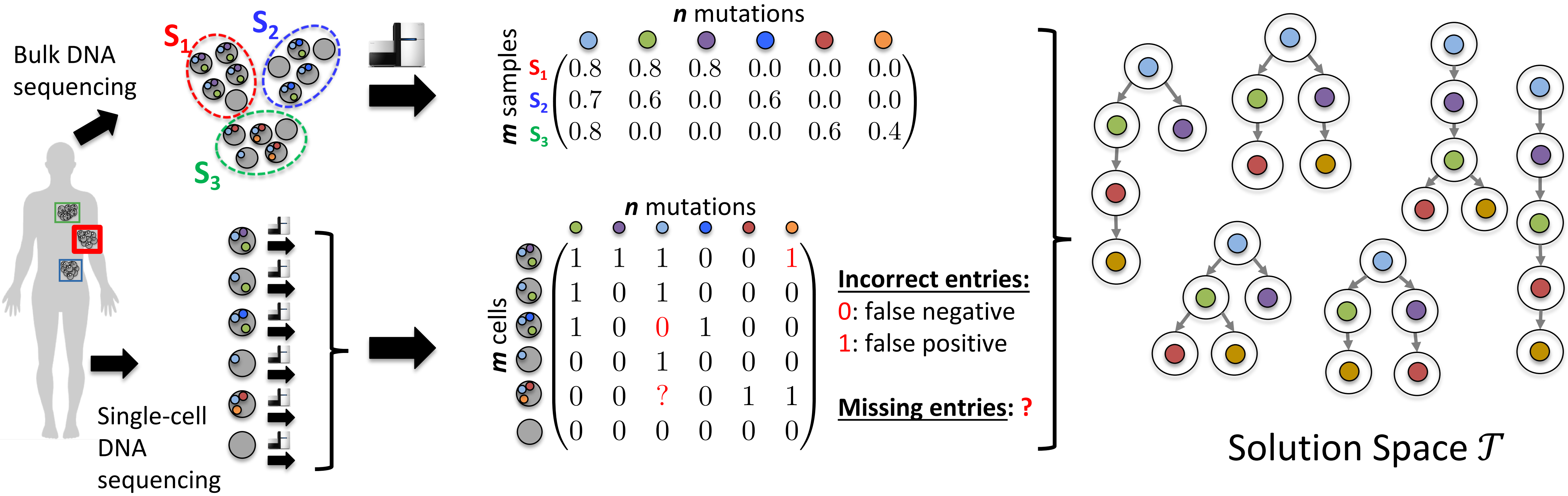
0: false negative

1: false positive

Missing entries: ?

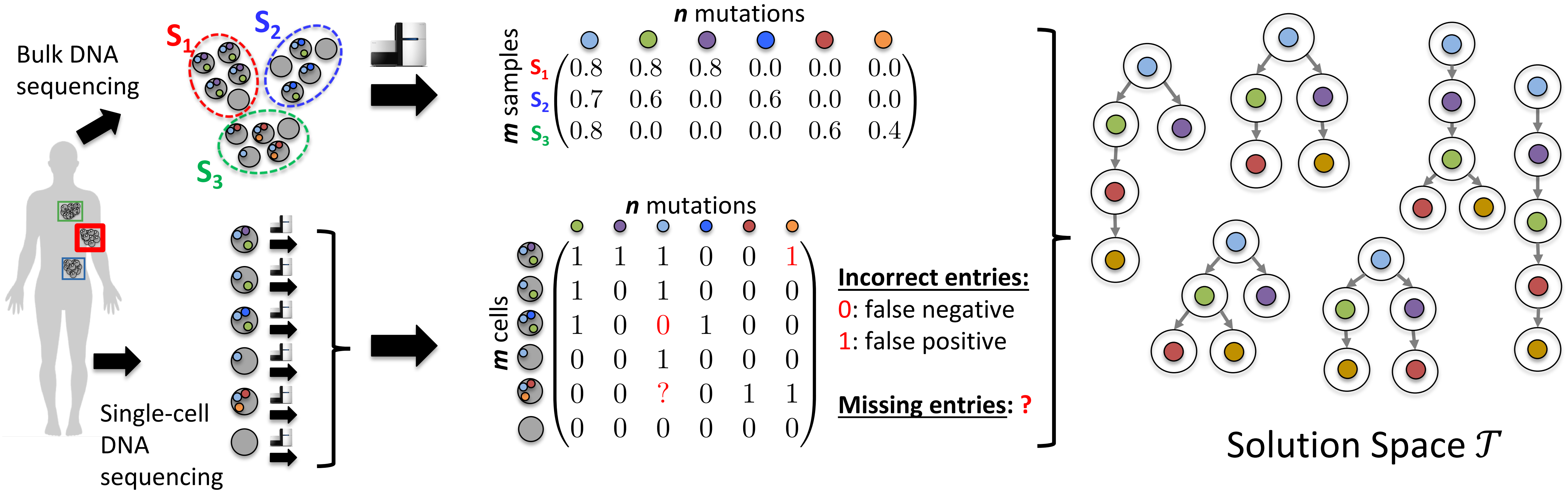
Phylogeny inference from mixtures of/incomplete measurements of leaves

Additional Challenge in Cancer Phylogenetics



Phylogeny inference from mixtures of/incomplete measurements of leaves	Non-uniqueness of solutions: alternative solutions with varying leaf sets

Additional Challenge in Cancer Phylogenetics



Phylogeny inference from mixtures of/incomplete measurements of leaves

Non-uniqueness of solutions: alternative solutions with varying leaf sets

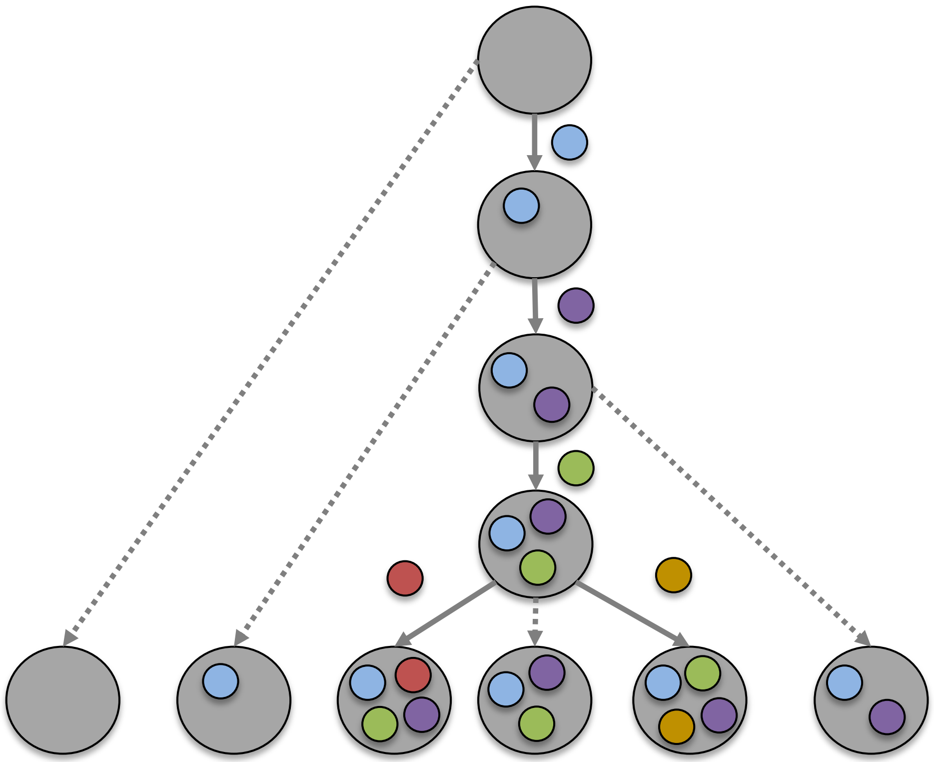
Question: How to **summarize solution space $\mathcal{T}$** in order to remove inference errors and identify dependencies among mutations?

Outline

- Problem Statement
  - Previous work
  - Problem statement
  - Combinatorial characterization of solutions
  - Complexity

- Method & Results
  - Exact algorithm
  - Heuristic algorithm
  - Model selection

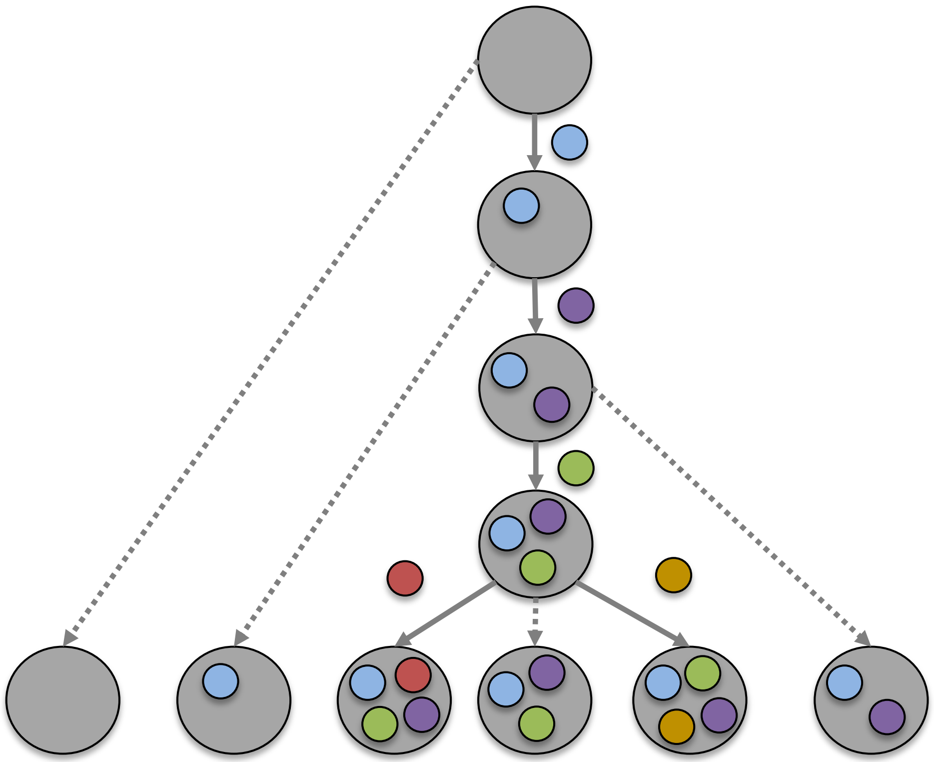
Phylogenetic Trees vs. Mutation Trees



Phylogenetic Tree

Infinite sites assumption (ISA): each mutation is introduced once and never subsequently lost

Phylogenetic Trees vs. Mutation Trees



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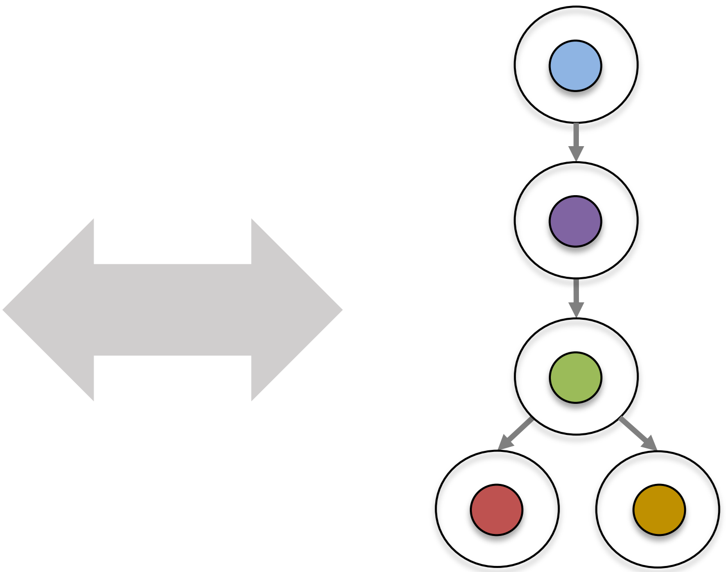


Mutation Tree

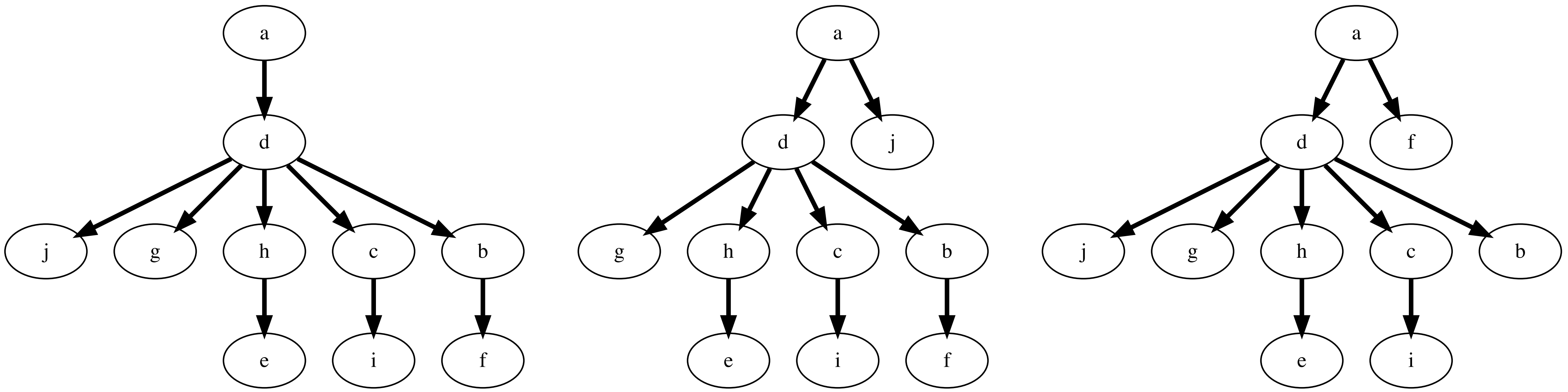
Infinite sites assumption (ISA): each mutation is introduced once and never subsequently lost

Under ISA, a phylogenetic tree may be equivalently* represented by a mutation tree

Solution Space of Lung Cancer Patient CRUK0037

Jamal-Hanjani et al. (2017). *New England Journal of Medicine*, *376*(22), 2109–2121.

Jamal-Hanjani et al. inferred 17 trees for patient CRUK0037



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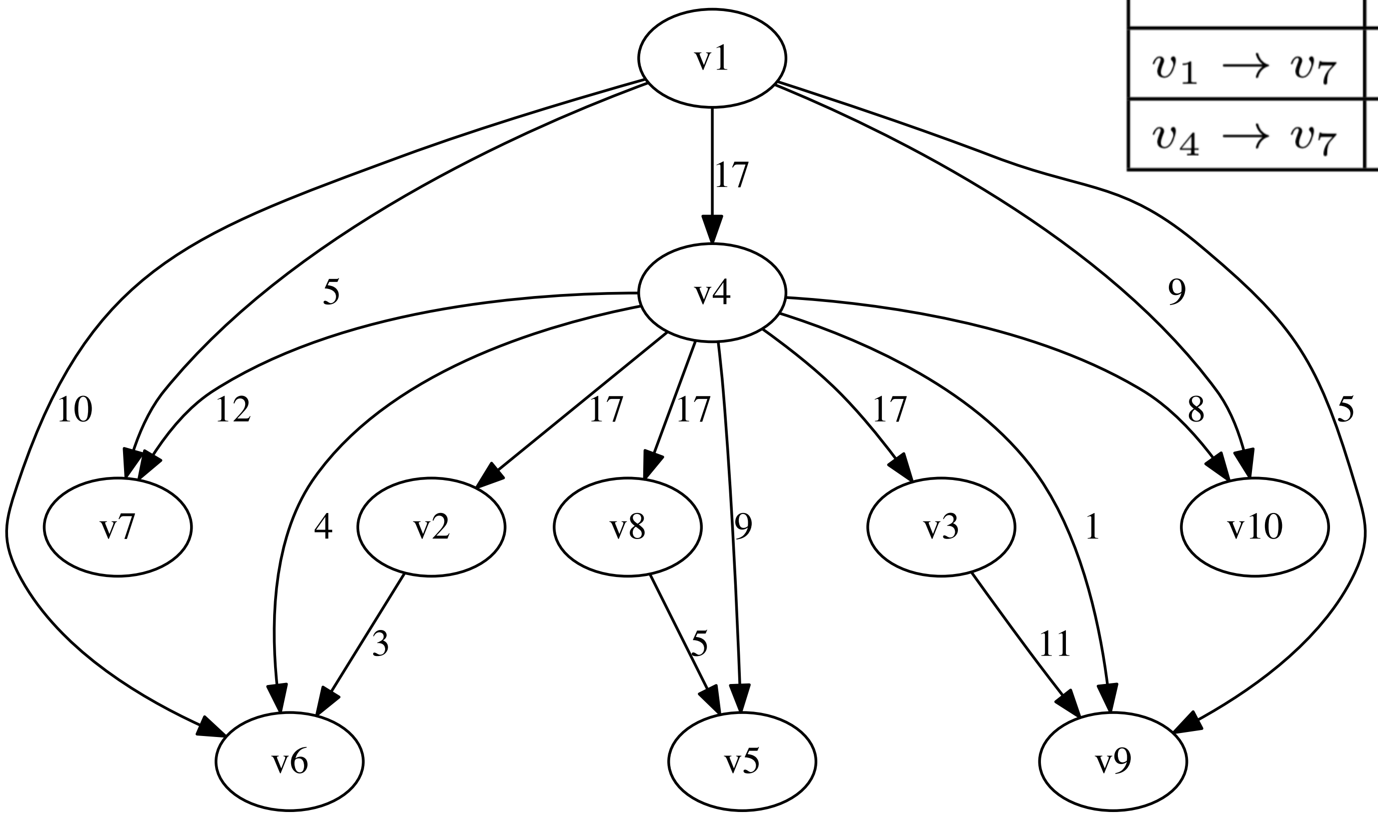
[14 more]

Question: How to **summarize solution space** in order to remove inference errors and identify dependencies among mutations?

Parent-child Graph: Union of all Edges in $\mathcal{T}$



	$v_4 \to v_5$		$v_8 \to v_5$	
	$v_1 \to v_{10}$	$v_4 \to v_{10}$	$v_1 \to v_{10}$	$v_4 \to v_{10}$
$v_1 \to v_7$	2	0	3 (d)	0
$v_4 \to v_7$	2 (b)	5 (e)	2	3

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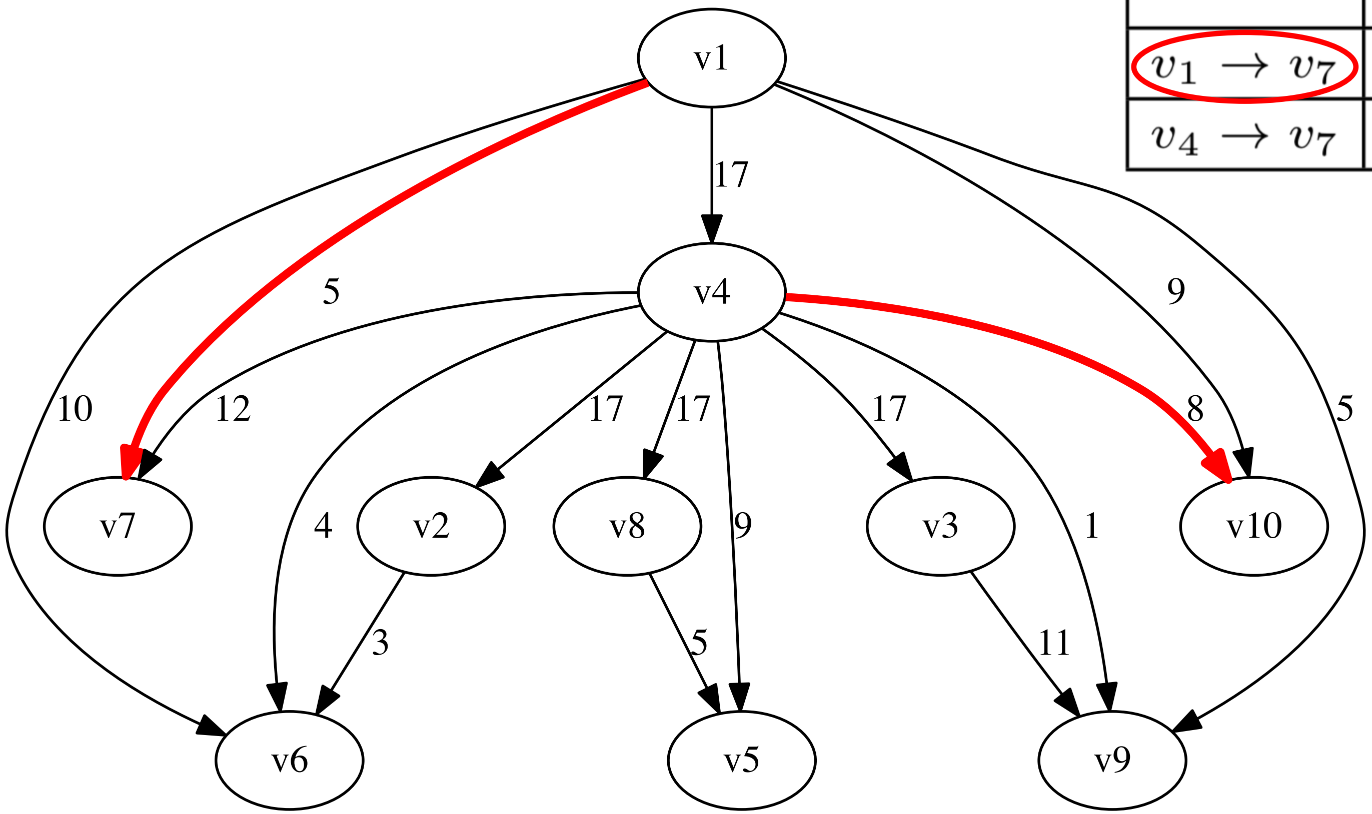

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The parent-child graph does not capture patterns of mutual exclusivity

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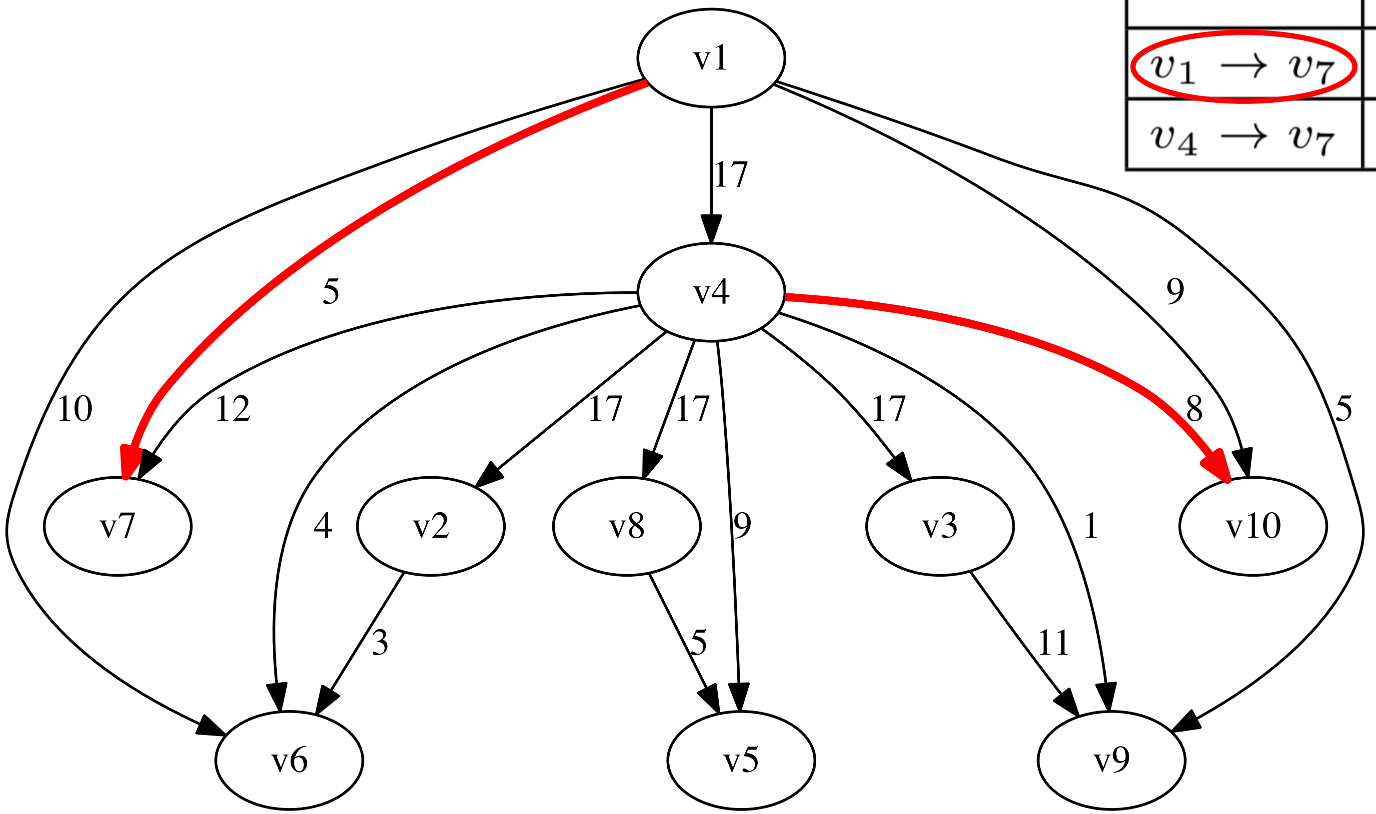

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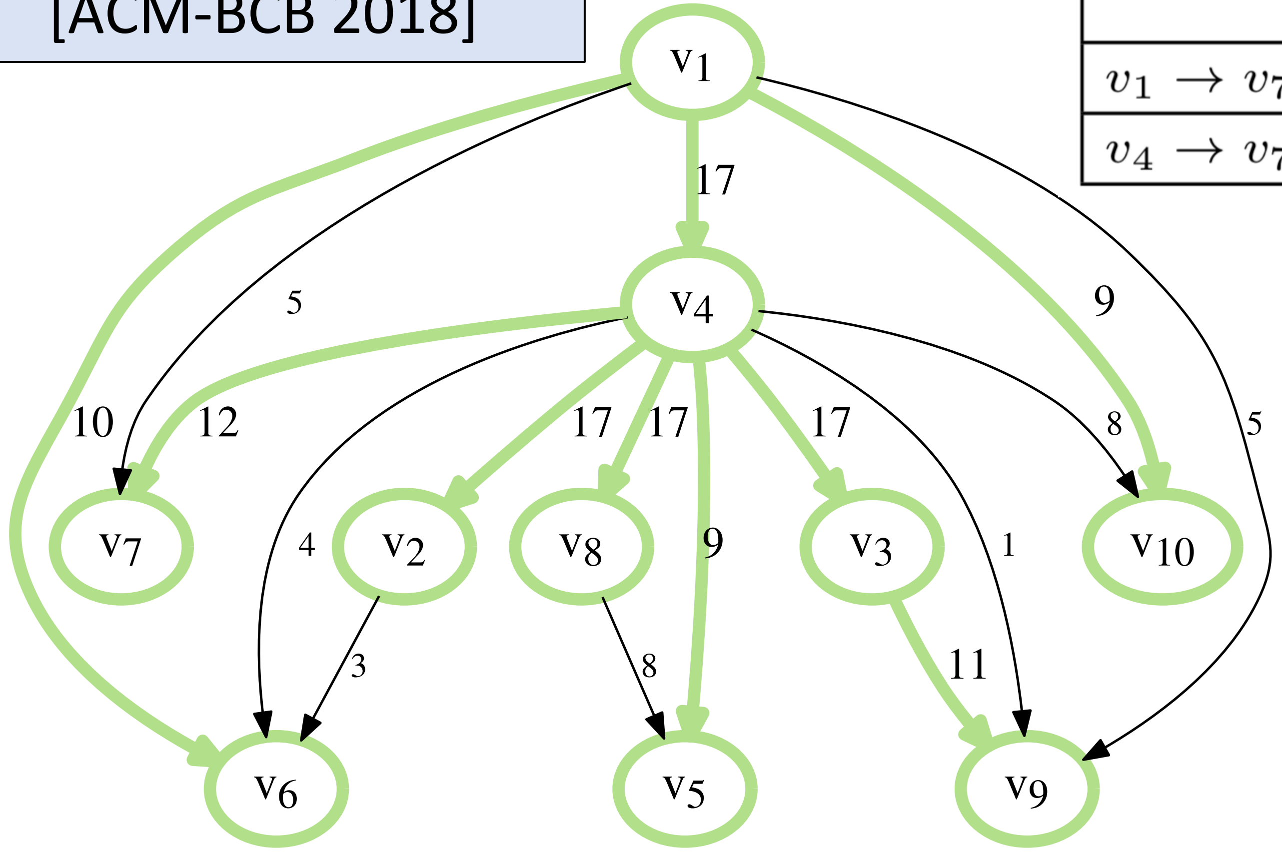
The parent-child graph does not capture patterns of mutual exclusivity

Question: Can we infer a single consensus tree?

Single Consensus Tree: Max Weight Spanning Tree

Oesper and colleagues. [ACM-BCB 2018]



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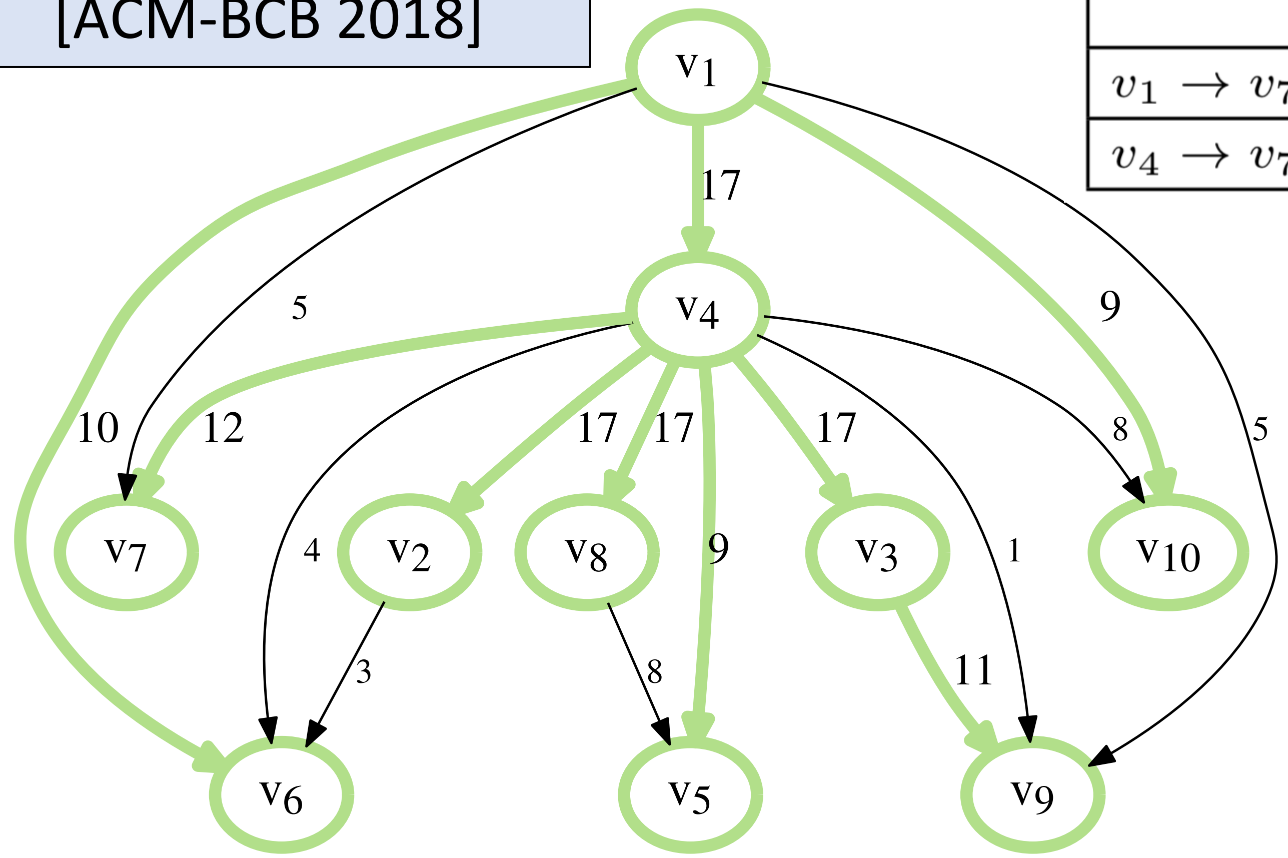

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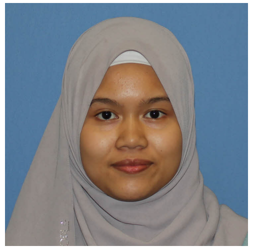
Inaccurate summary for diverse solution spaces

Question: How about inferring multiple consensus trees?

Multiple Consensus Trees Problem

Simultaneous clustering and consensus tree inference



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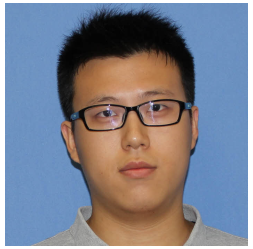
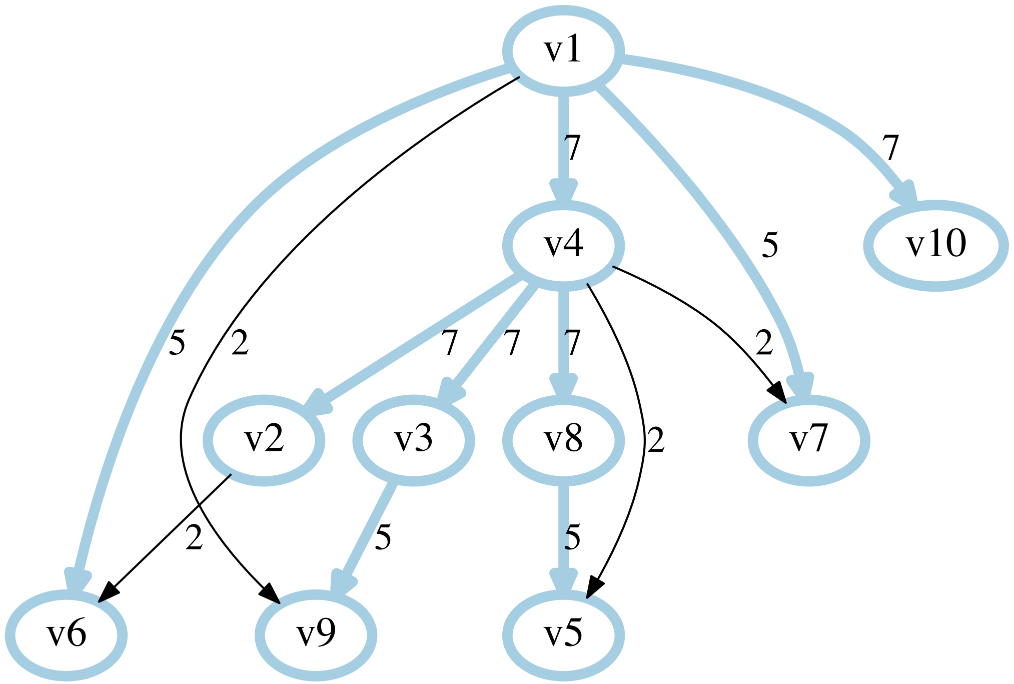
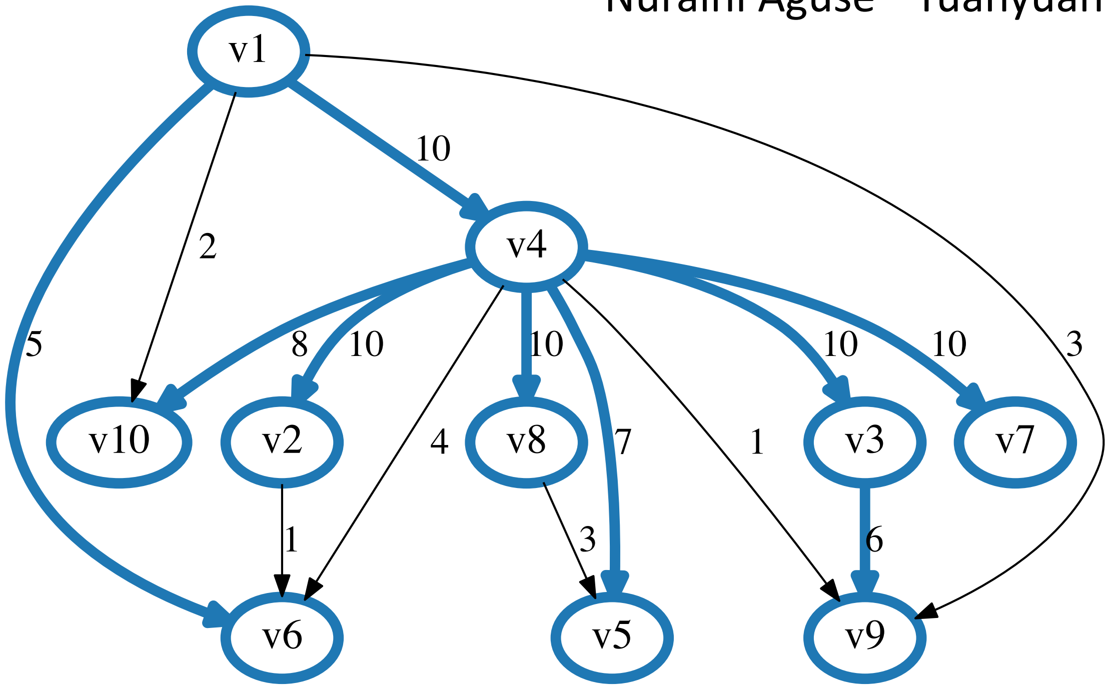
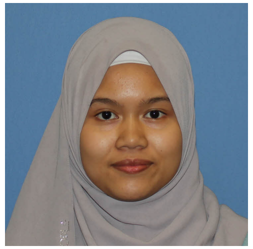
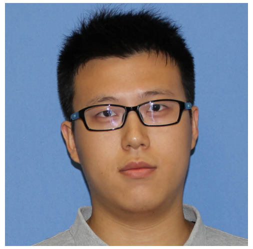


Yuanyuan Qi



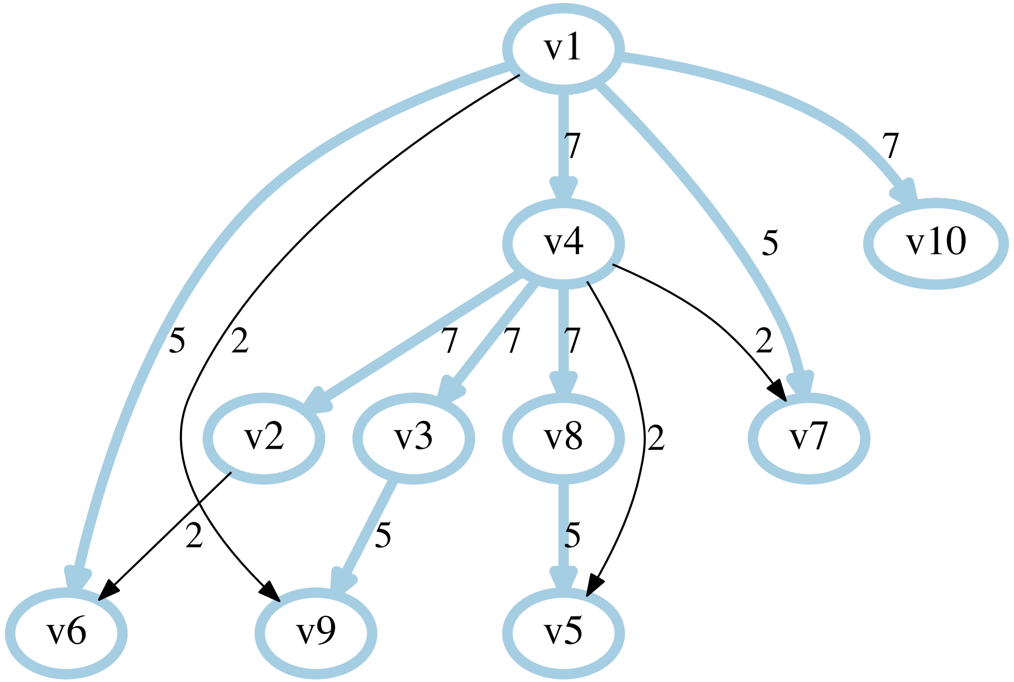


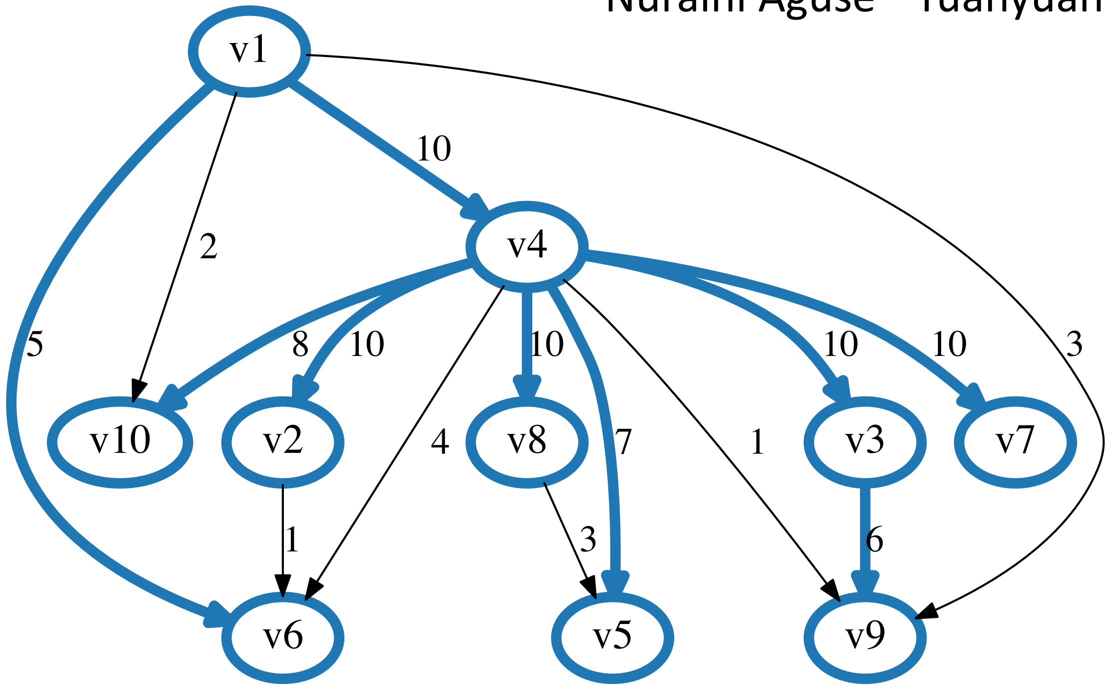
Multiple Consensus Trees Problem

Nuraini Aguse Yuanyuan Qi

Simultaneous clustering and consensus tree inference





Multiple Consensus Trees (MCT): [ISMB/ECCB 2019]

Given trees $\mathcal{T} = \{T_1, \dots, T_n\}$ and $k > 0$, find surjective clustering $\sigma : [n] \to [k]$ and consensus trees $\mathcal{R} = \{R_1, \dots, R_k\}$ s.t. $\sum_{i=1}^{n} d(T_i, R_{\sigma(i)})$ is minimum

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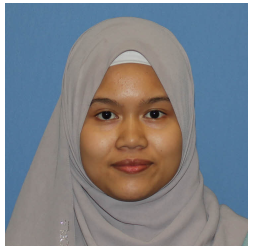
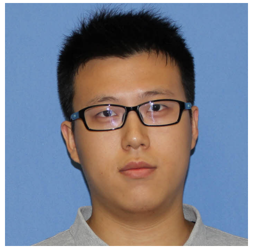

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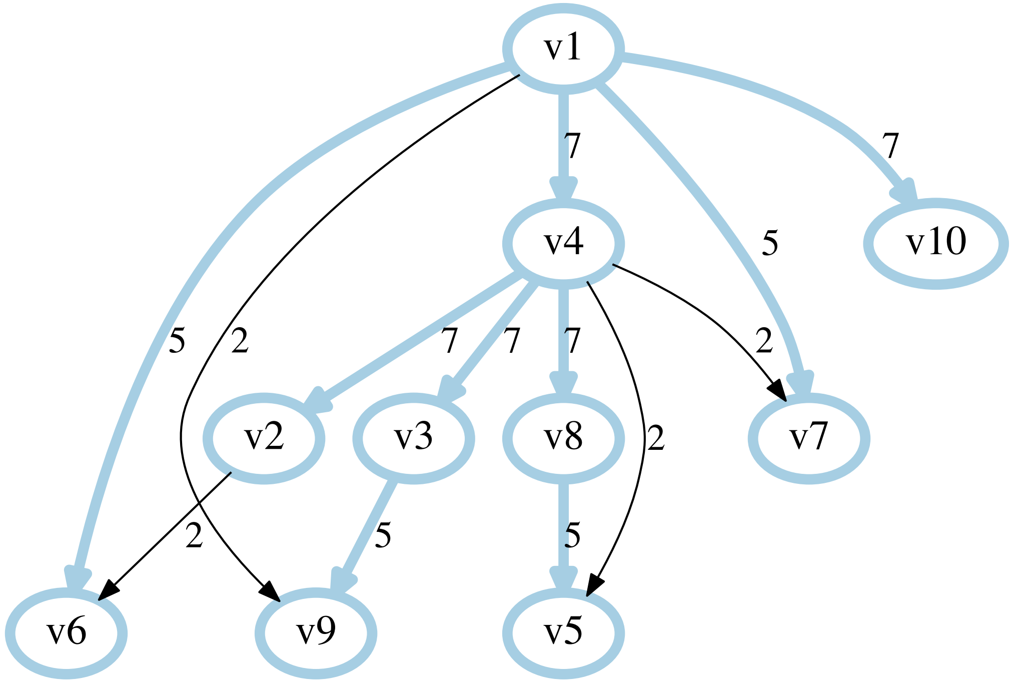

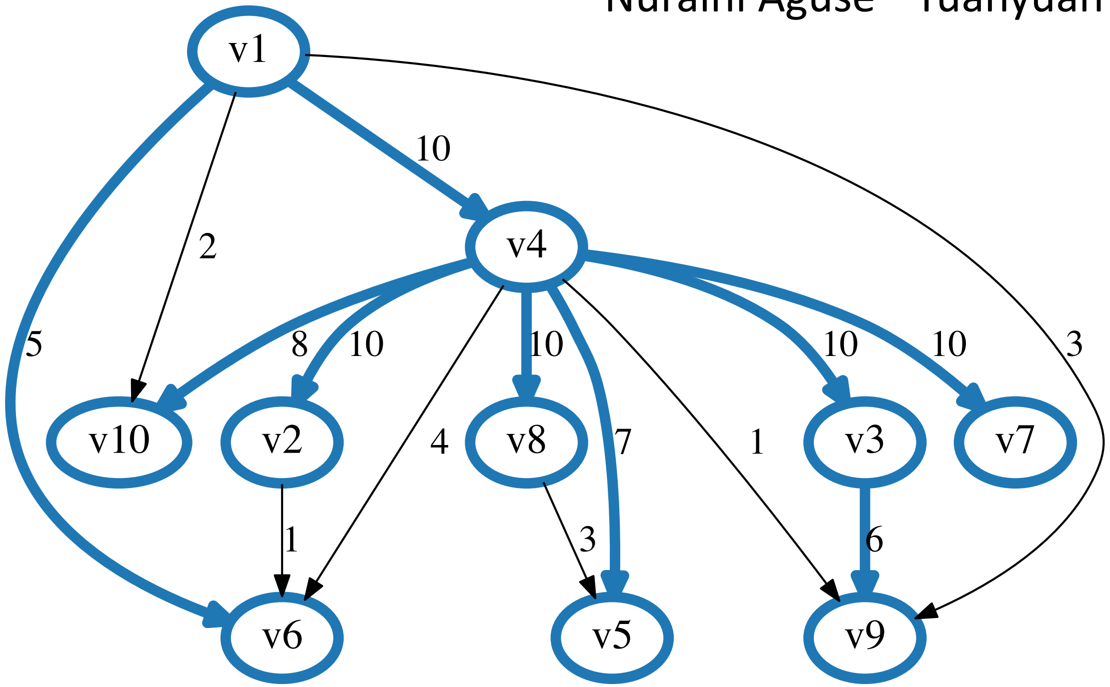

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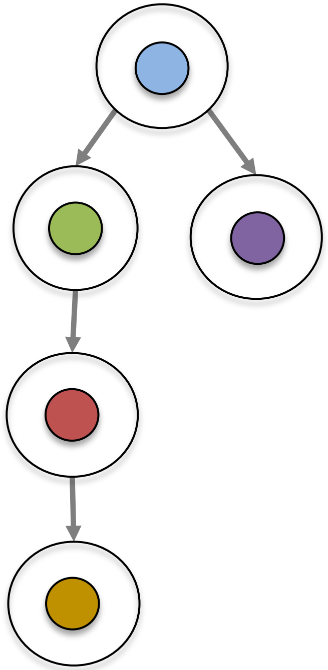
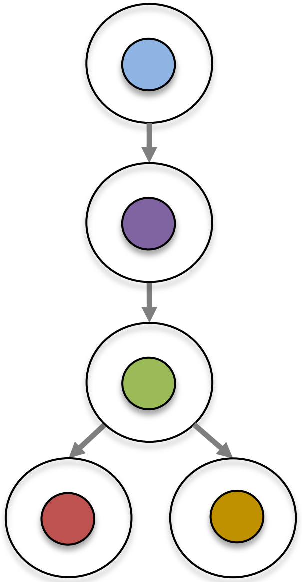
Parent-child Distance Function

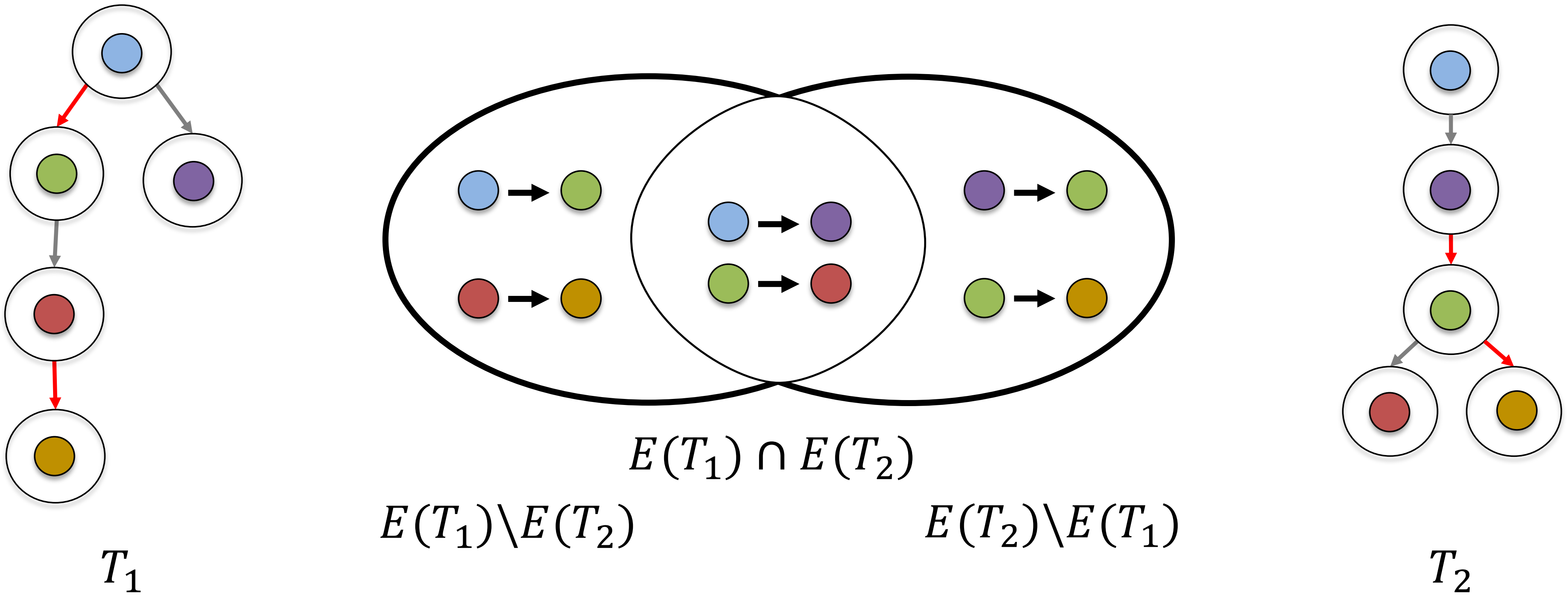


T_1



T_2

Parent-child Distance Function



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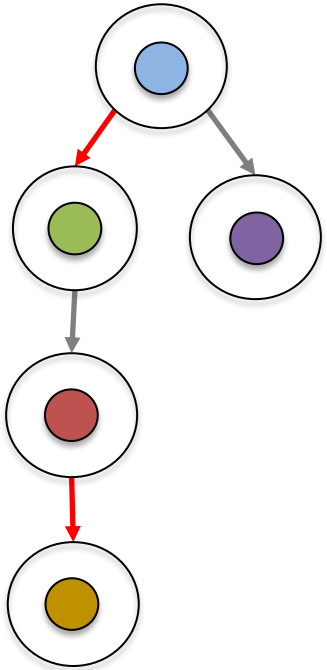

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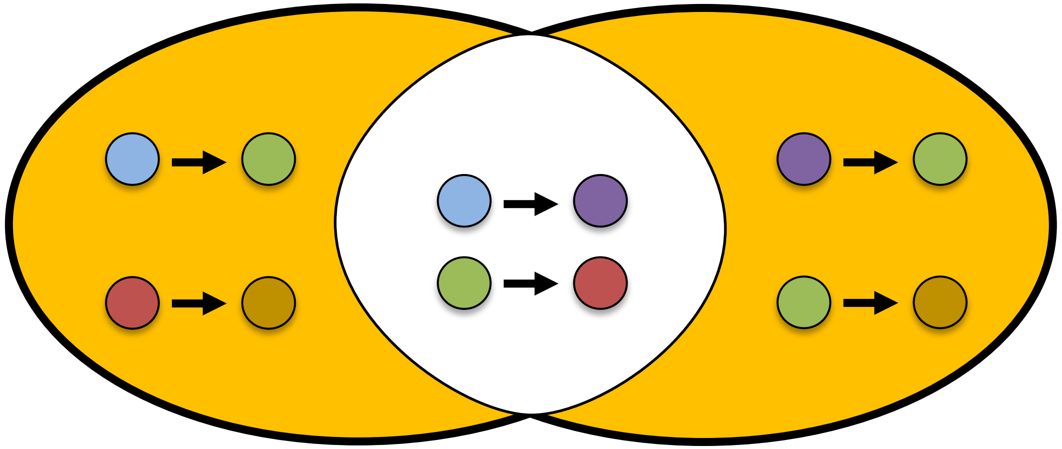
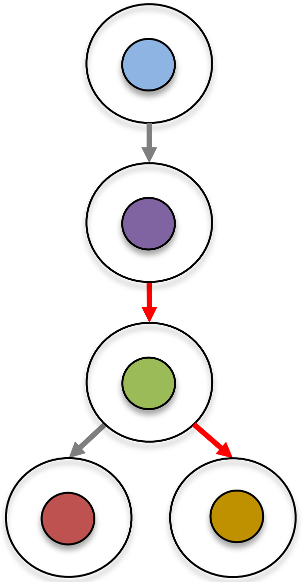


$E(T_1) \cap E(T_2)$

$E(T_1) \setminus E(T_2)$ $E(T_2) \setminus E(T_1)$



T_2

Parent-child distance $d(T_1, T_2)$ is the size of the symmetric difference of the edge sets

Here, $d(T_1, T_2) = |E(T_1) \setminus E(T_2)| + |E(T_2) \setminus E(T_1)| = 4.$

Combinatorial Characterization of Solutions to MCT

Single Consensus Trees (SCT): [Govek et al., ACM-BCB 2018]
Given $\mathcal{T} = \{T_1, \dots, T_n\}$, find consensus tree R s.t.
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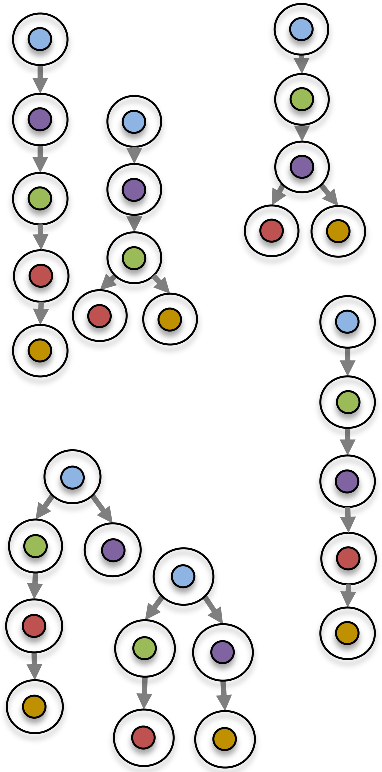

Solution Space $\mathcal{T}$

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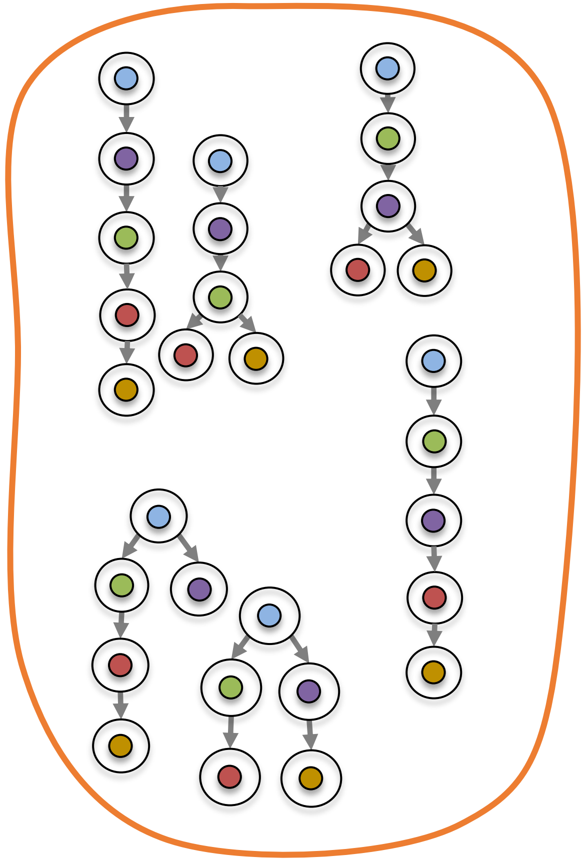
Max weight spanning arborescences of parent-child graph $G_{\mathcal{T}}$ are solutions to SCT



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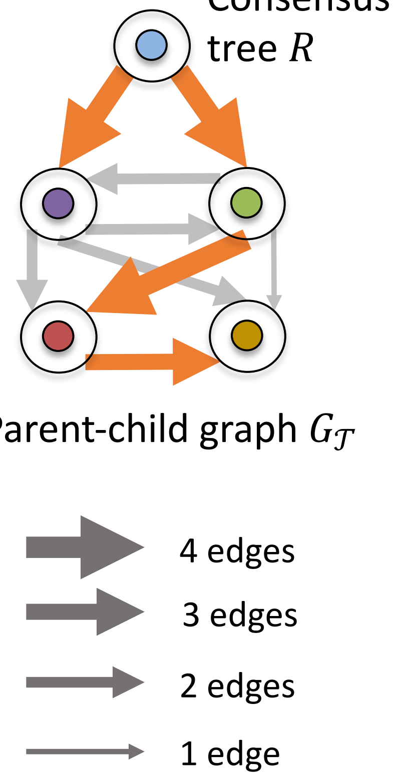

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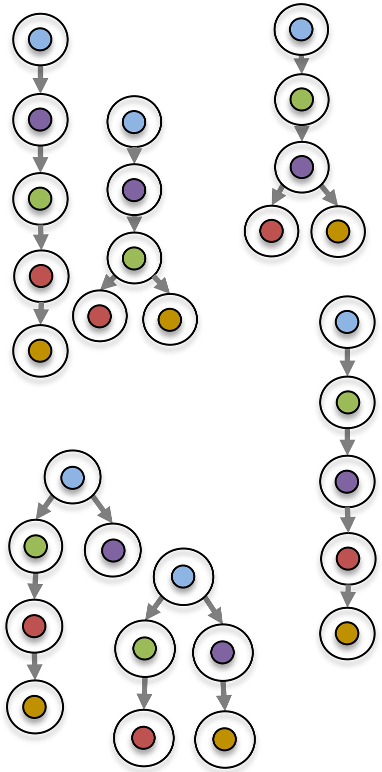

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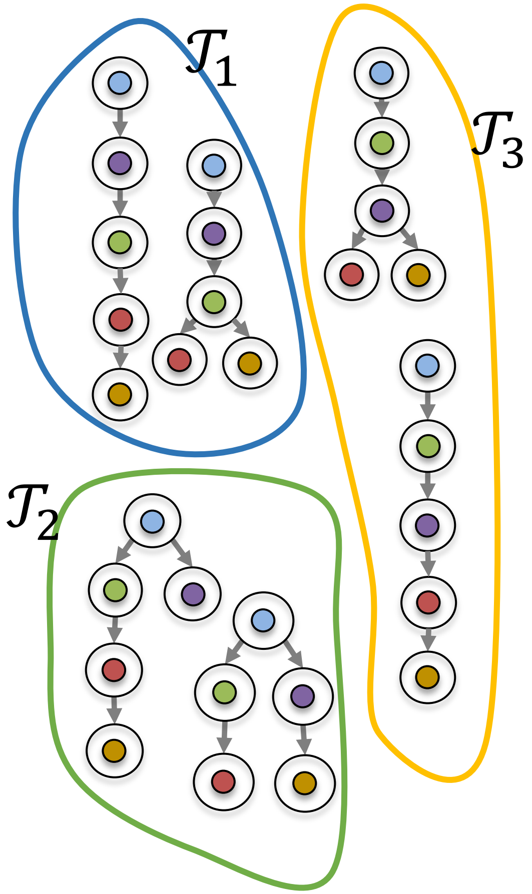
Proposition: [Aguse et al., ISMB 2019]
Given fixed clustering $\sigma : [n] \to [k]$, MCT decomposes into k independent SCT instances



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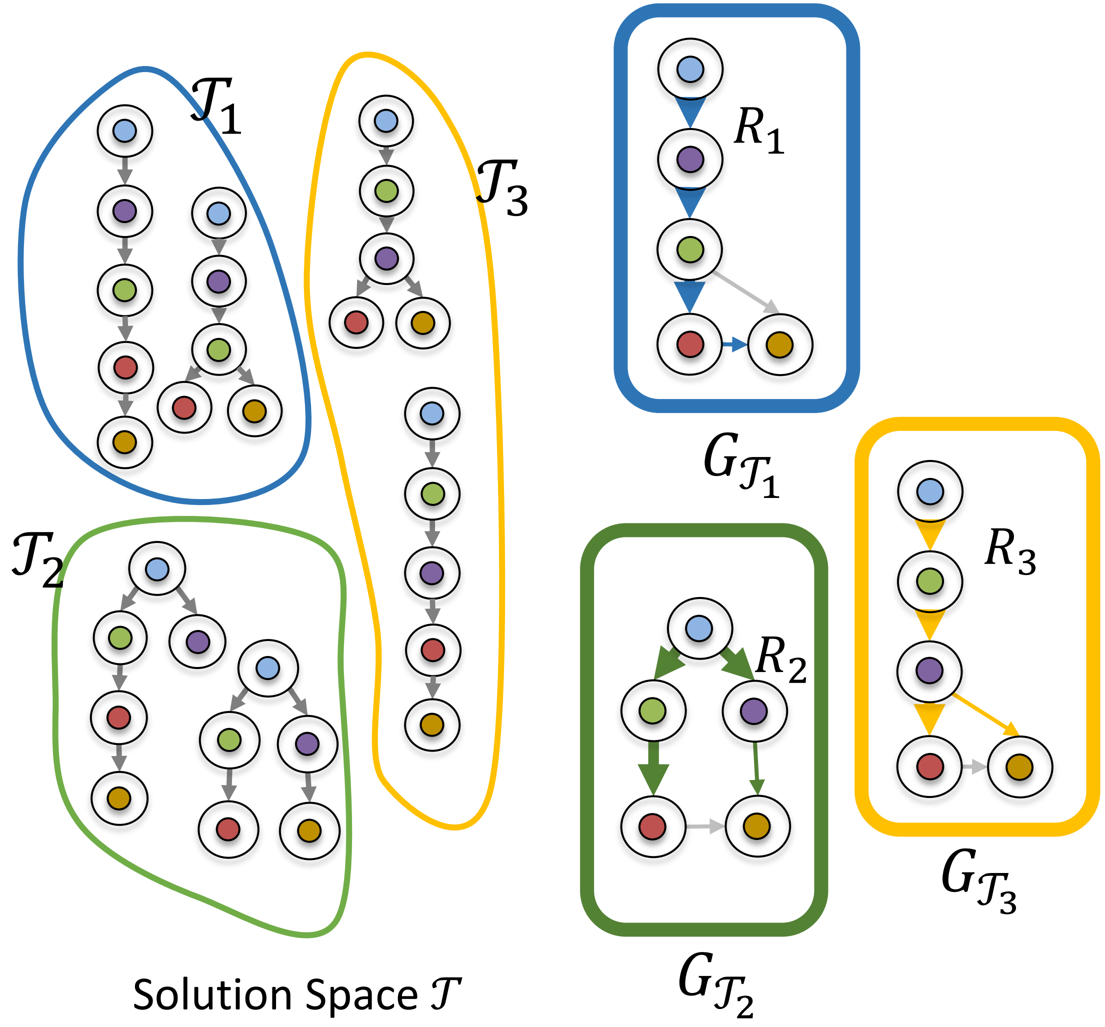

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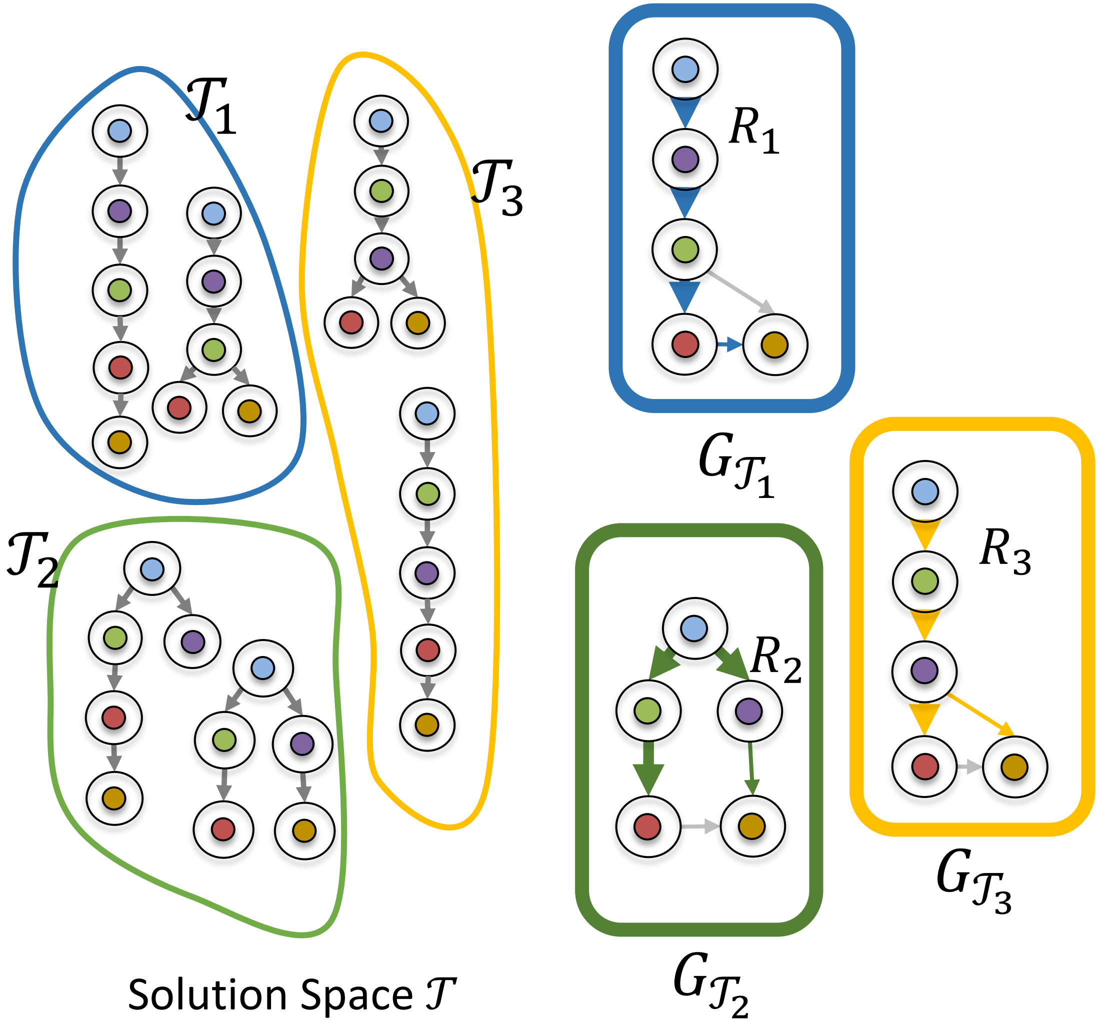

Question: How to find σ^*?

Complexity

Multiple Consensus Trees (MCT):
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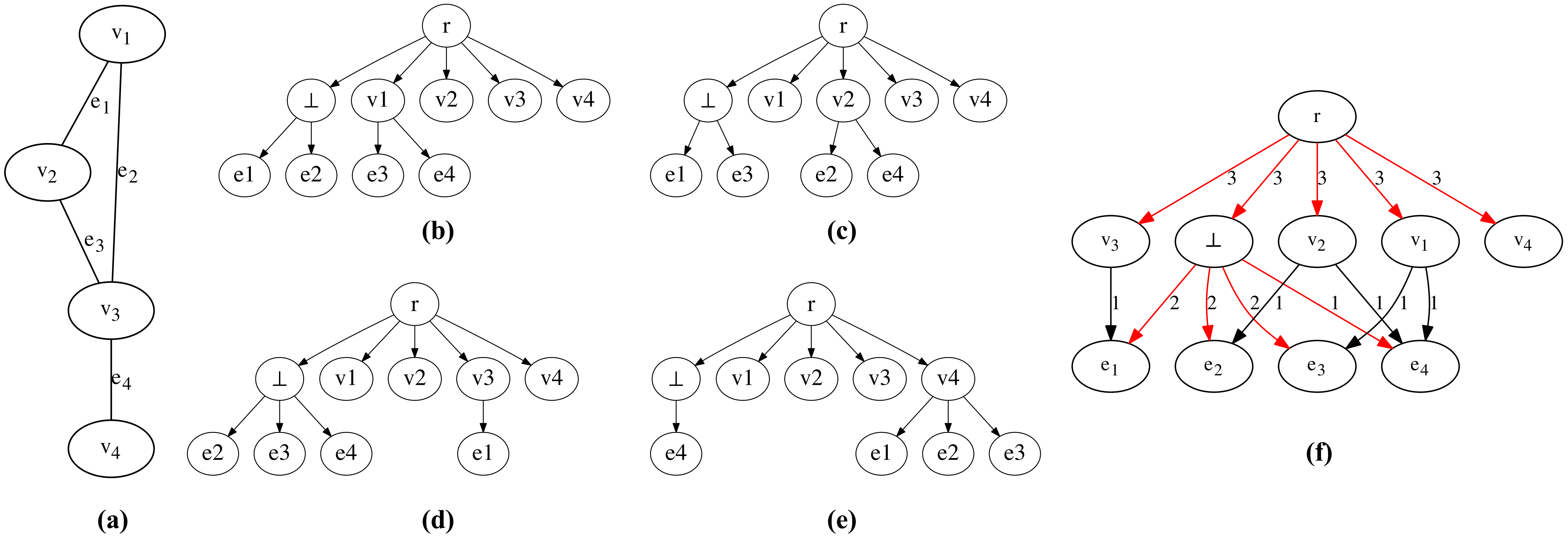

Theorem: MCT is NP-hard for general k (by reduction from CLIQUE).

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    - Previous work
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Mixed Integer Linear Program

Theorem: MCT is NP-hard for general k (by reduction from CLIQUE).

$$
\begin{aligned}
\min\ & n(m-1) - \sum_{i=1}^{n}\sum_{s=1}^{k}\sum_{p=1}^{m}\sum_{q=1}^{m} w_{i,s,p,q} \\
\text{s.t.}\ & \sum_{s=1}^{k} x_{i,s} = 1 && \forall i \in [n] \\
& \sum_{i=1}^{n} x_{i,s} \geq 1 && \forall s \in [k] \\
& \sum_{p=1}^{m} z_{s,p} = 1 && \forall s \in [k] \\
& \sum_{q=1}^{m} y_{s,p,q} = 1 - z_{s,p} && \forall s \in [k], p \in [m] \\
& y_{s,p,q} \leq b_{p,q} && \forall s \in [k], p, q \in [m] \\
& \sum_{(p,q)\in\delta^-(U)} y_{s,p,q} + \sum_{p\in U} z_{s,p} \geq 1 && \forall s \in [k], U \subseteq [m] \\
& w_{i,s,p,q} \leq a_{i,p,q} && \forall i \in [n], s \in [k], p, q \in [m] \\
& w_{i,s,p,q} \leq x_{i,s} && \forall i \in [n], s \in [k], p, q \in [m] \\
& w_{i,s,p,q} \leq y_{s,p,q} && \forall i \in [n], s \in [k], p, q \in [m] \\
& w_{i,s,p,q} \geq 0 && \forall i \in [n], s \in [k], p, q \in [m] \\
& y_{s,p,q} \leq \sum_{i=1}^{n} a_{i,p,q} x_{i,s} && \forall s \in [k], p, q \in [m] \\
& y_{s,p,q} \geq \sum_{i=1}^{n} a_{i,p,q} x_{i,s} - \sum_{i=1}^{n} x_{i,s} + 1 && \forall s \in [k], p, q \in [m] \\
& \sum_{i=1}^{n} x_{i,s} \geq \sum_{i=1}^{n} x_{i,s+1} + 1 && \forall s \in [k-1] \\
& x_{i,s} \in \{0,1\} && \forall i \in [n], s \in [k] \\
& y_{s,p,q} \geq 0 && \forall s \in [k], p, q \in [m] \\
& z_{s,p} \geq 0 && \forall s \in [k], p \in [m]
\end{aligned}
$$

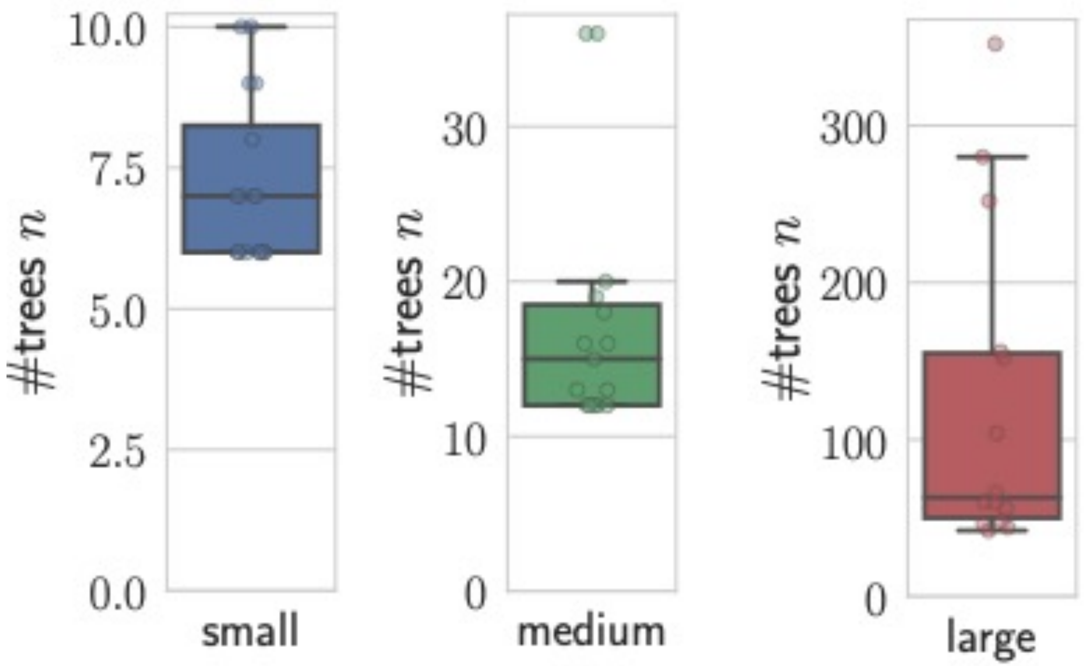
Mixed Integer Linear Program

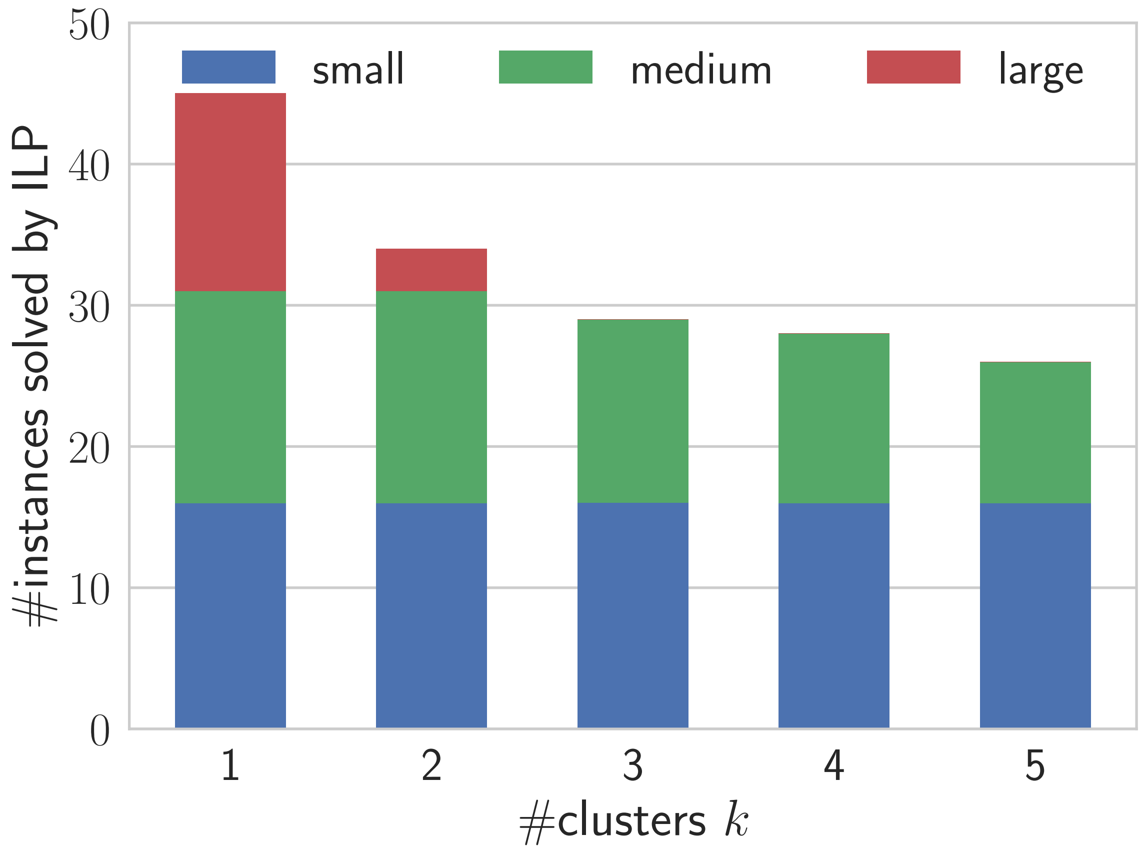
Theorem: MCT is NP-hard for general k (by reduction from CLIQUE).

$x_{i,s} \in \{0,1\}$	Tree T_i is assigned to cluster s
$y_{s,p,q} \geq 0$	Edge (p,q) is present in consensus tree R_s
$z_{s,p} \geq 0$	Vertex p is root of consensus tree R_s

$$
\begin{aligned}
\min\ & n(m-1) - \sum_{i=1}^{n}\sum_{s=1}^{k}\sum_{p=1}^{m}\sum_{q=1}^{m} w_{i,s,p,q} & \\
\text{s.t. } & \sum_{s=1}^{k} x_{i,s} = 1 & \forall i \in [n] \\
& \sum_{i=1}^{n} x_{i,s} \geq 1 & \forall s \in [k] \\
& \sum_{p=1}^{m} z_{s,p} = 1 & \forall s \in [k] \\
& \sum_{q=1}^{m} y_{s,p,q} = 1 - z_{s,p} & \forall s \in [k], p \in [m] \\
& y_{s,p,q} \leq b_{p,q} & \forall s \in [k], p,q \in [m] \\
& \sum_{(p,q)\in\delta^-(U)} y_{s,p,q} + \sum_{p\in U} z_{s,p} \geq 1 & \forall s \in [k], U \subseteq [m] \\
& w_{i,s,p,q} \leq a_{i,p,q} & \forall i \in [n], s \in [k], p,q \in [m] \\
& w_{i,s,p,q} \leq x_{i,s} & \forall i \in [n], s \in [k], p,q \in [m] \\
& w_{i,s,p,q} \leq y_{s,p,q} & \forall i \in [n], s \in [k], p,q \in [m] \\
& w_{i,s,p,q} \geq 0 & \forall i \in [n], s \in [k], p,q \in [m] \\
& y_{s,p,q} \leq \sum_{i=1}^{n} a_{i,p,q} x_{i,s} & \forall s \in [k], p,q \in [m] \\
& y_{s,p,q} \geq \sum_{i=1}^{n} a_{i,p,q} x_{i,s} - \sum_{i=1}^{n} x_{i,s} + 1 & \forall s \in [k], p,q \in [m] \\
& \sum_{i=1}^{n} x_{i,s} \geq \sum_{i=1}^{n} x_{i,s+1} + 1 & \forall s \in [k-1] \\
& x_{i,s} \in \{0,1\} & \forall i \in [n], s \in [k] \\
& y_{s,p,q} \geq 0 & \forall s \in [k], p,q \in [m] \\
& z_{s,p} \geq 0 & \forall s \in [k], p \in [m]
\end{aligned}
$$

MILP does not scale well with k and n





Coordinate Ascent (akin to k-means)

Proposition: [Aguse et al., ISMB 2019]
Given fixed clustering $\sigma : [n] \to [k]$, MCT decomposes into k independent SCT instances

1. Fix clustering σ at random
2. Compute consensus tree R_s for each cluster s
3. Reassign each input trees T_i to cluster s where $d(T_i, R_s)$ is minimum
4. Go to 2

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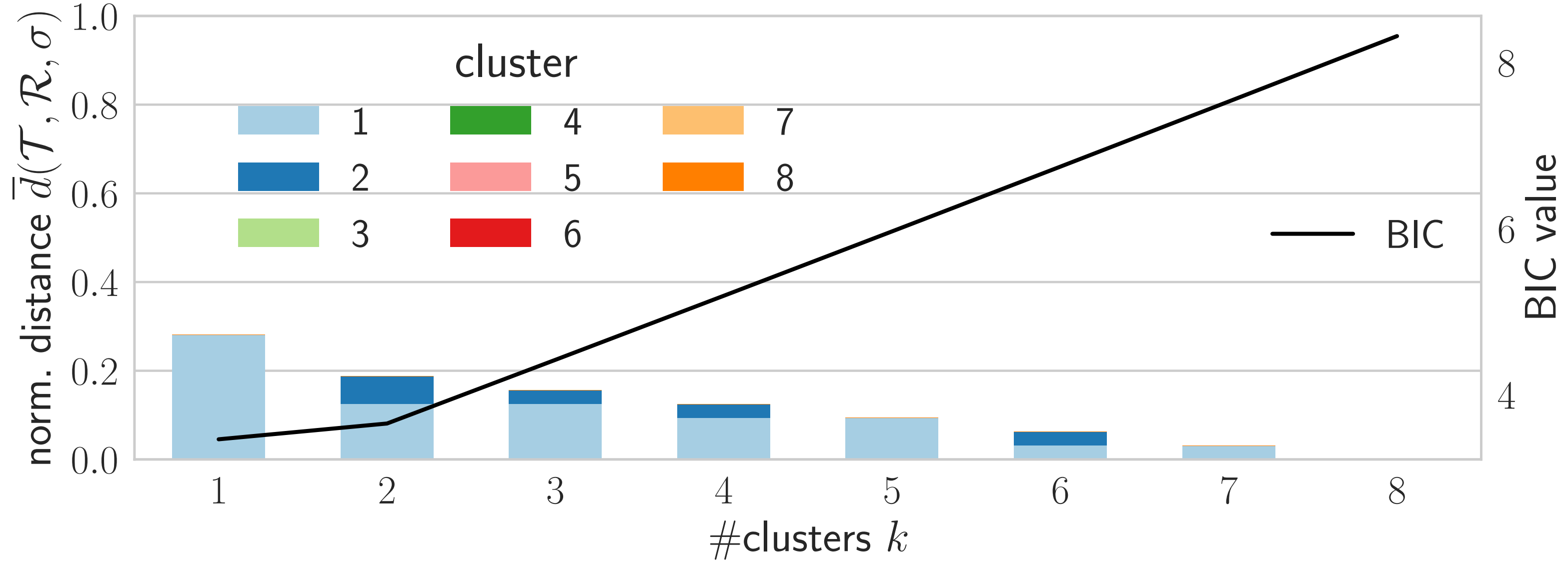
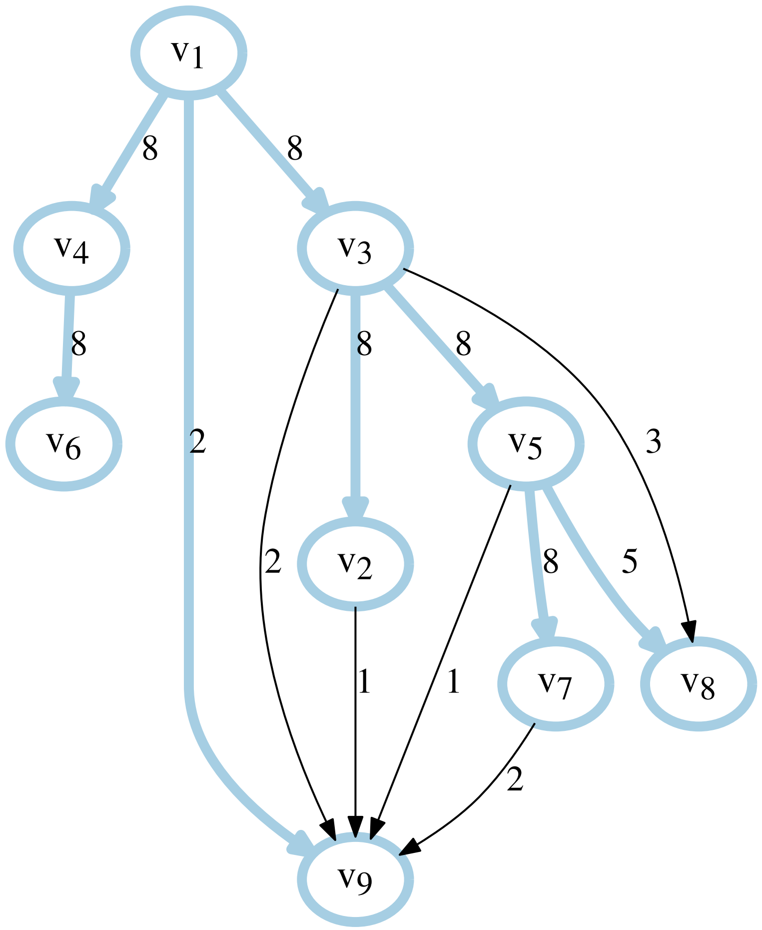
	#clusters k	MILP (1 h)	BF (1 h)	CA (1 h)	CA (100 r.)
small (16)	2	16	16	16	16
	3	16	16	16	16
	4	16	16	16	16
	5	16	14	16	16
medium (15)	2	15	13	15	15
	3	13	7	13	13
	4	12	0	12	12
	5	10	0	10	10
large (14)	2	3	0	3	3
	3	0	0	0	0
	4	0	0	0	0
	5	0	0	0	0

Bayesian Information Criterion

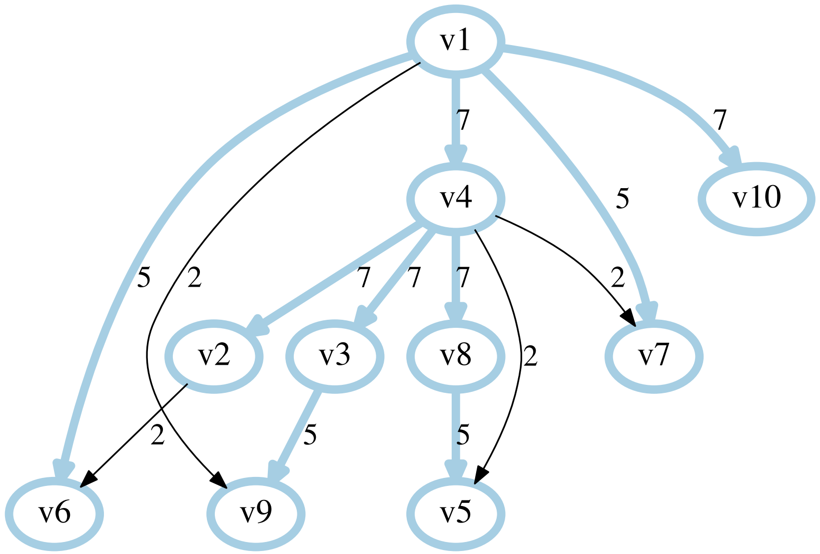
Jamal-Hanjani et al. (2017). *NEJM*.

Jamal-Hanjani et al. inferred 8 trees for patient CRUK0013



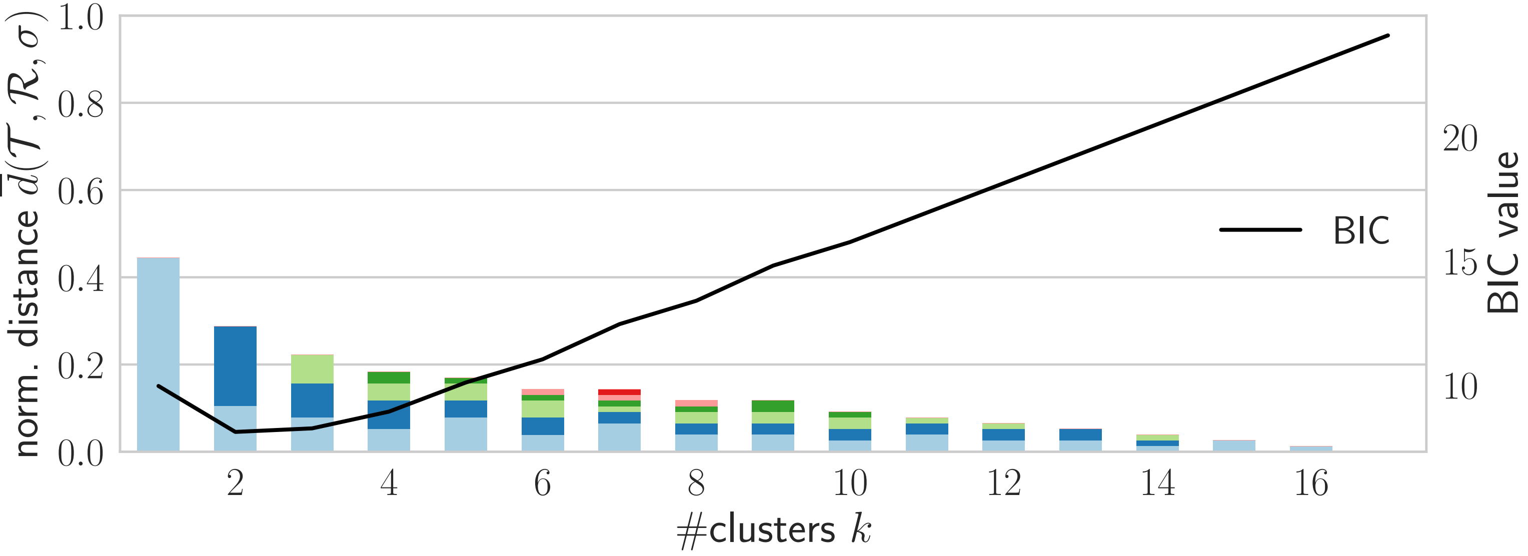


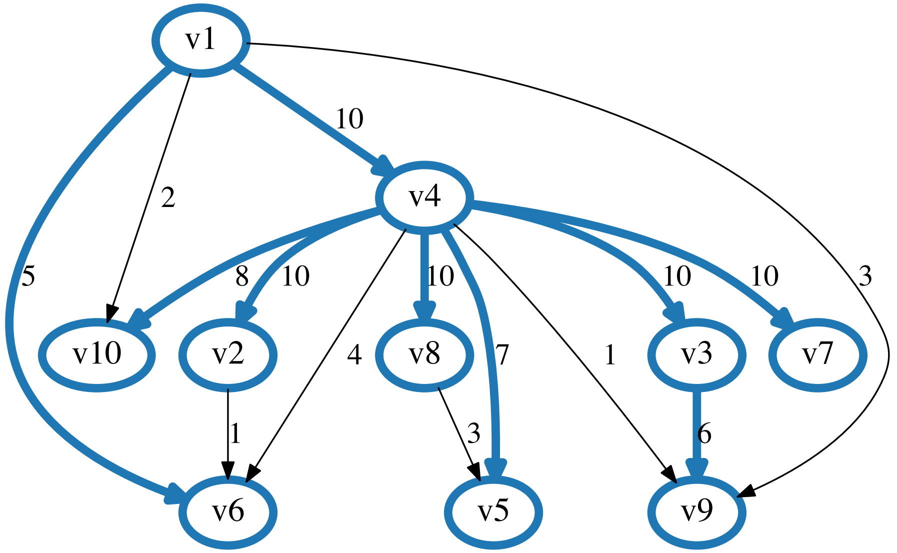
Bayesian Information Criterion



Jamal-Hanjani et al. (2017). *NEJM*.

Jamal-Hanjani et al. inferred 17 trees for patient CRUK0037





Conclusion

- Introduced the Multiple Consensus Tree (MCT) problem
- Characterized combinatorial structure of optimal solutions
- Showed that MCT is NP-hard
- Presented a mixed integer linear program
- Presented an efficient heuristic and showed that it finds optimal solutions
- Model selection for the number of clusters

Future directions

- Relax infinite sites assumption
- Use medoids rather than centroids