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

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RECOMB-CCB 2019

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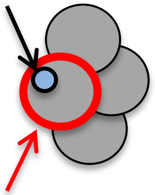
# Viewing Cancer Through the Lens of Evolution

**Clonal Evolution Theory of Cancer**
[Nowell, 1976]

Mutation



Founder
tumor cell
with somatic mutation:
(e.g. BRAF V600E)

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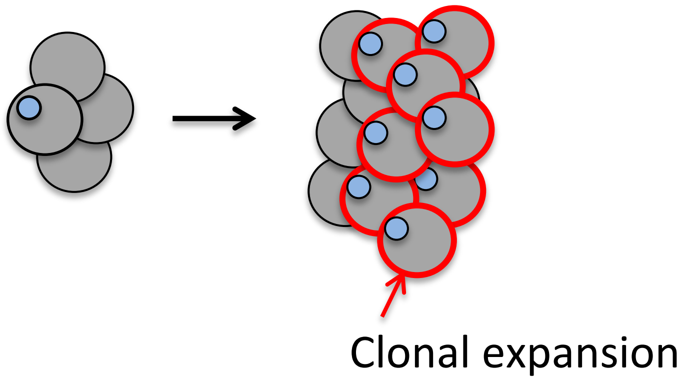

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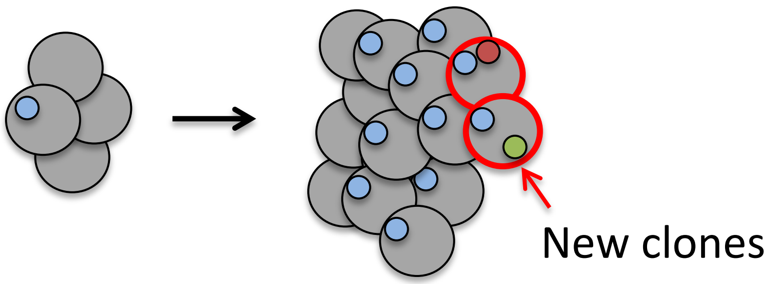

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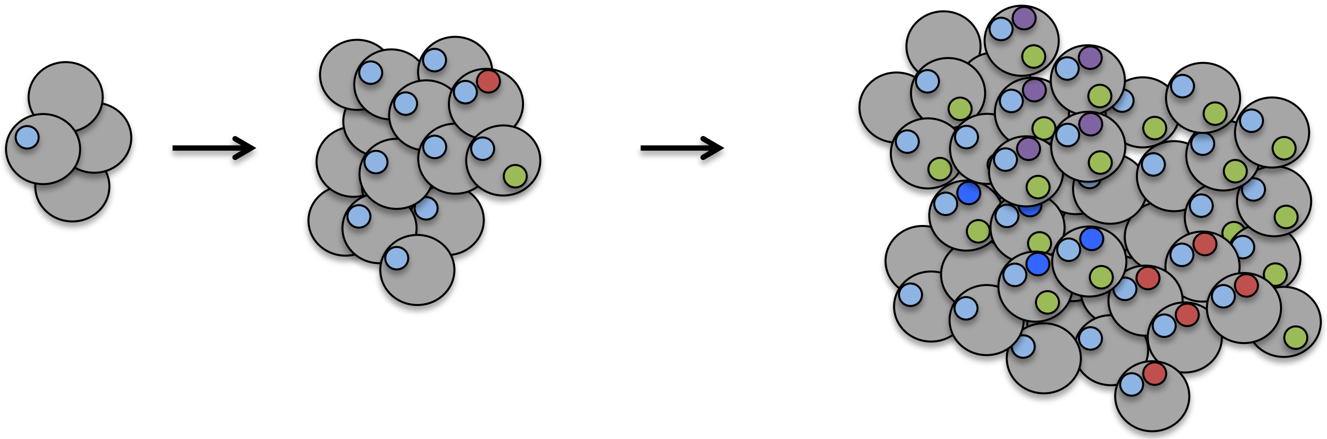
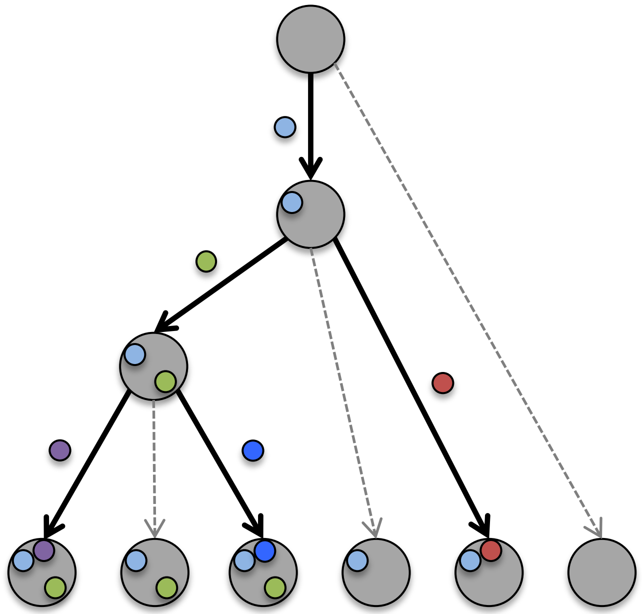


Heterogeneous Tumor

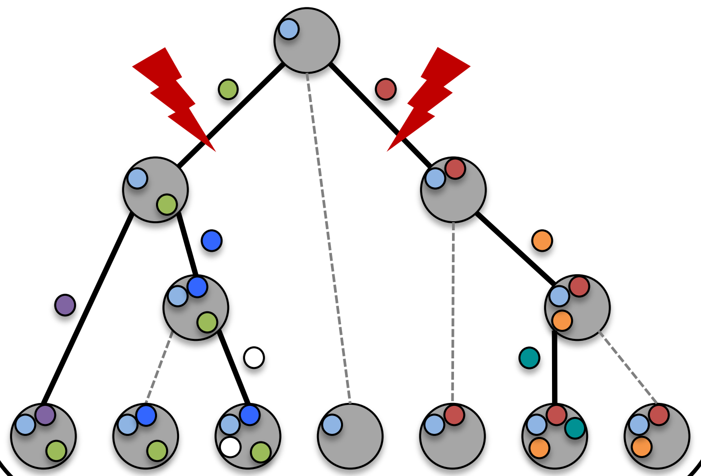


Phylogenetic Tree ***T***

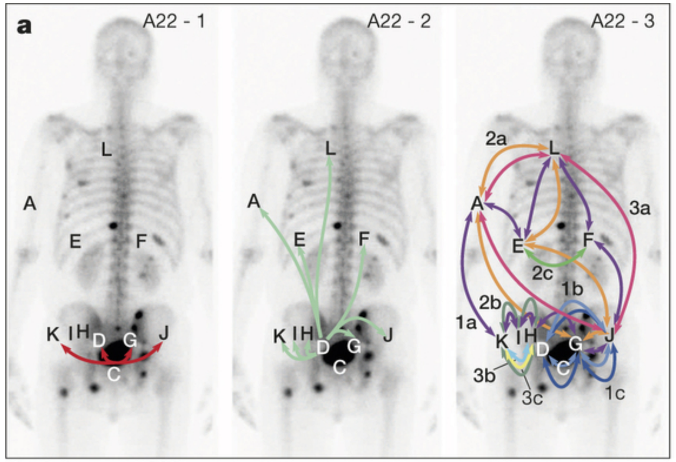
**Question:** Why are tumor phylogenies important?

# Phylogenies are Key to Understanding and Treating Cancer

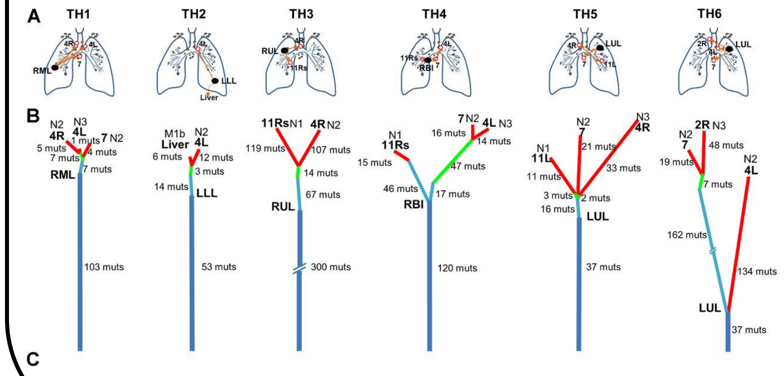
**Identify targets for treatment**



**Understand metastatic development**




**Recognize common patterns of tumor evolution across patients**




These downstream analyses **critically rely** on accurate tumor phylogeny inference

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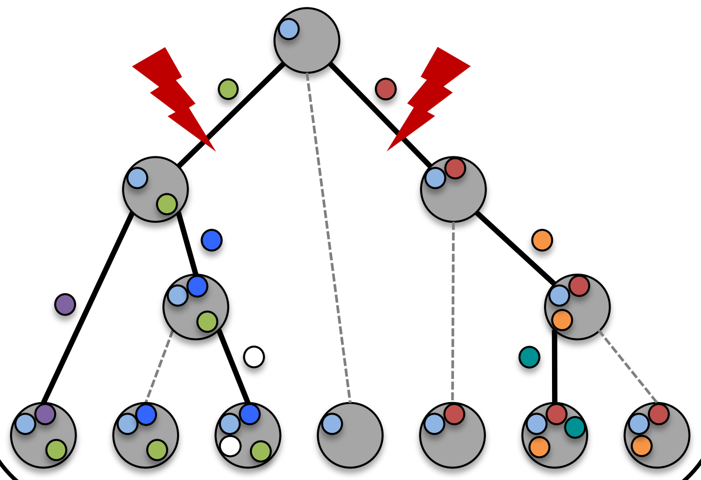

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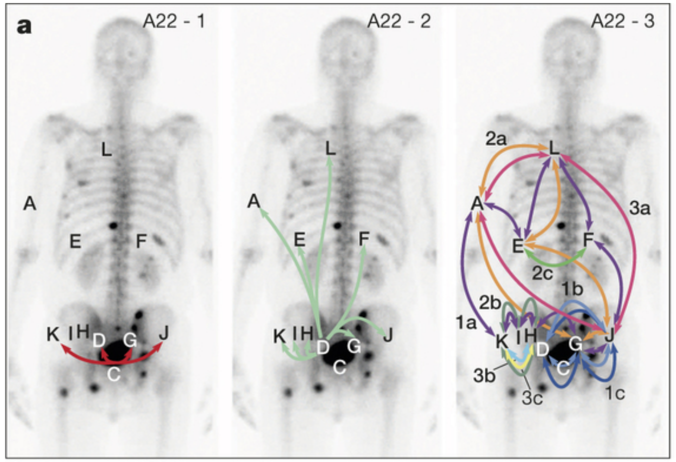


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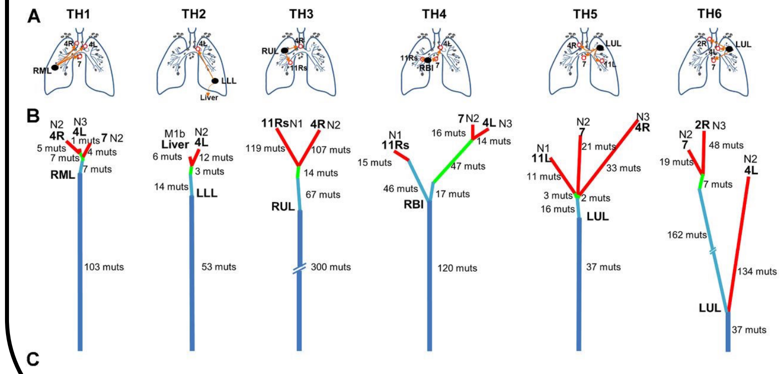


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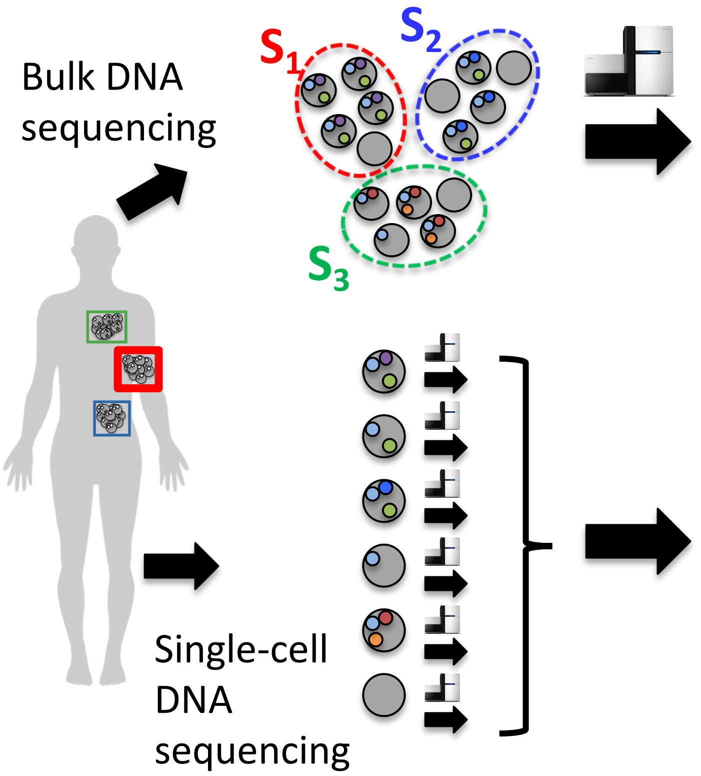
**Key challenge in phylogenetics:**
Accurate phylogeny inference from data at present time

# Additional Challenge in Cancer Phylogenetics




***n*** **mutations**

$$
\begin{array}{c}
\\ \color{red}{S_1} \\ \color{blue}{S_2} \\ \color{green}{S_3}
\end{array}
\begin{pmatrix}
0.8 & 0.8 & 0.8 & 0.0 & 0.0 & 0.0 \\
0.7 & 0.6 & 0.0 & 0.6 & 0.0 & 0.0 \\
0.8 & 0.0 & 0.0 & 0.0 & 0.6 & 0.4
\end{pmatrix}
$$

***m*** **samples**

***n*** **mutations**

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

***m*** **cells**

**Incorrect entries:**
0: false negative
1: false positive

**Missing entries: ?**

Phylogeny inference from mixtures of/incomplete measurements of leaves

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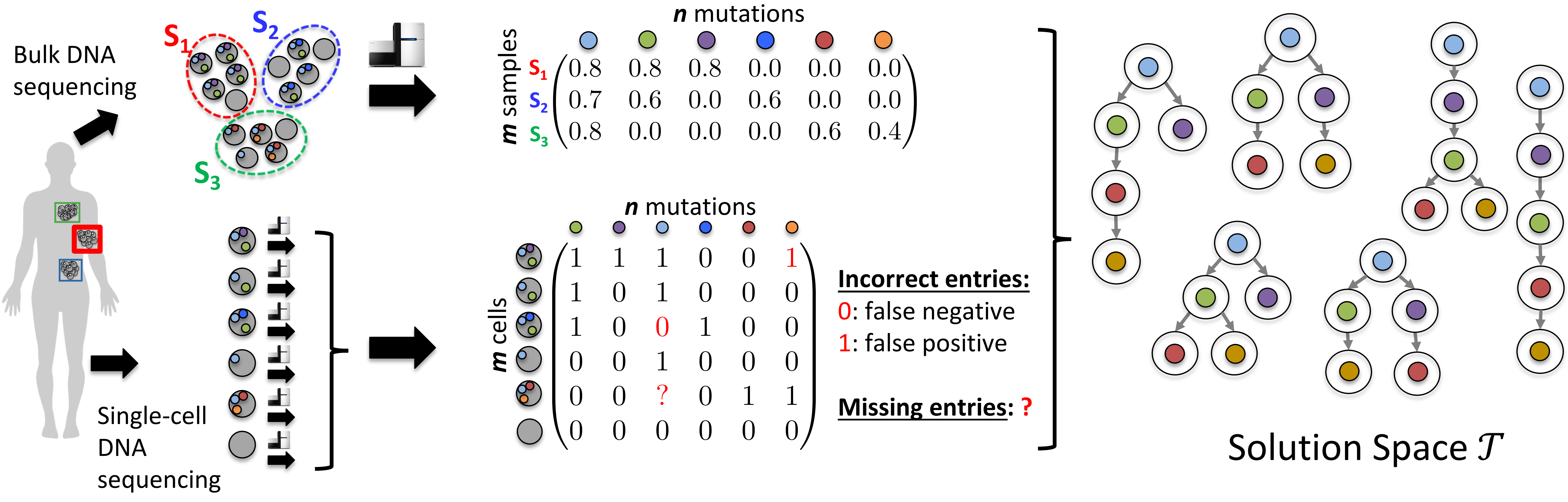


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Non-uniqueness of solutions: alternative solutions with varying leaf sets

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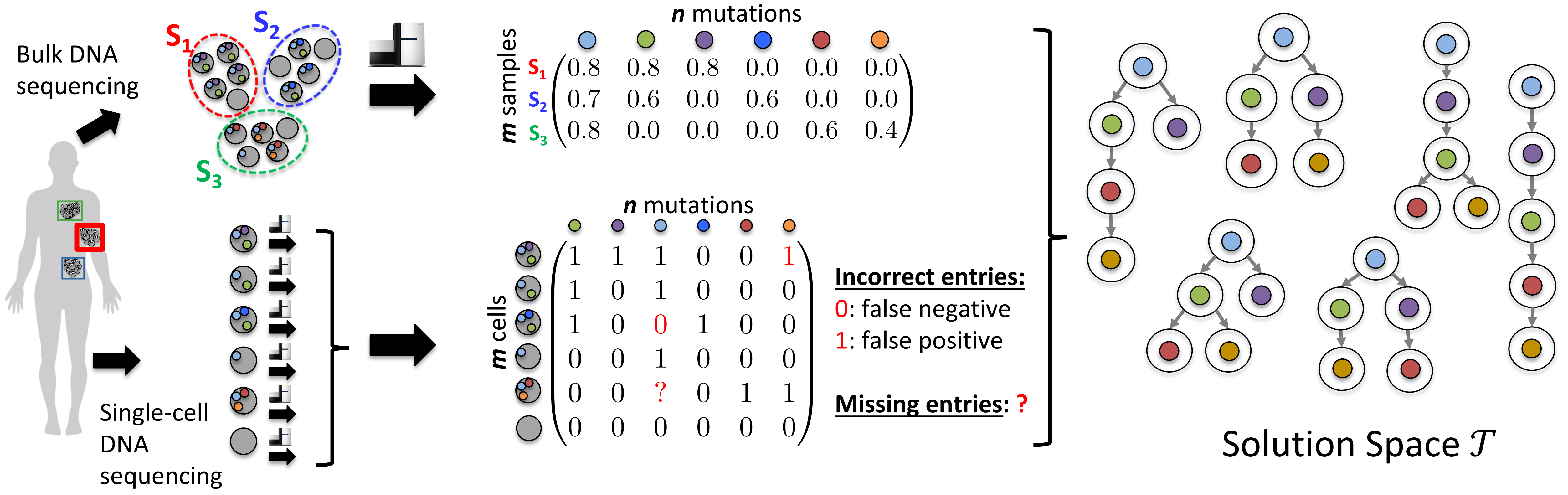


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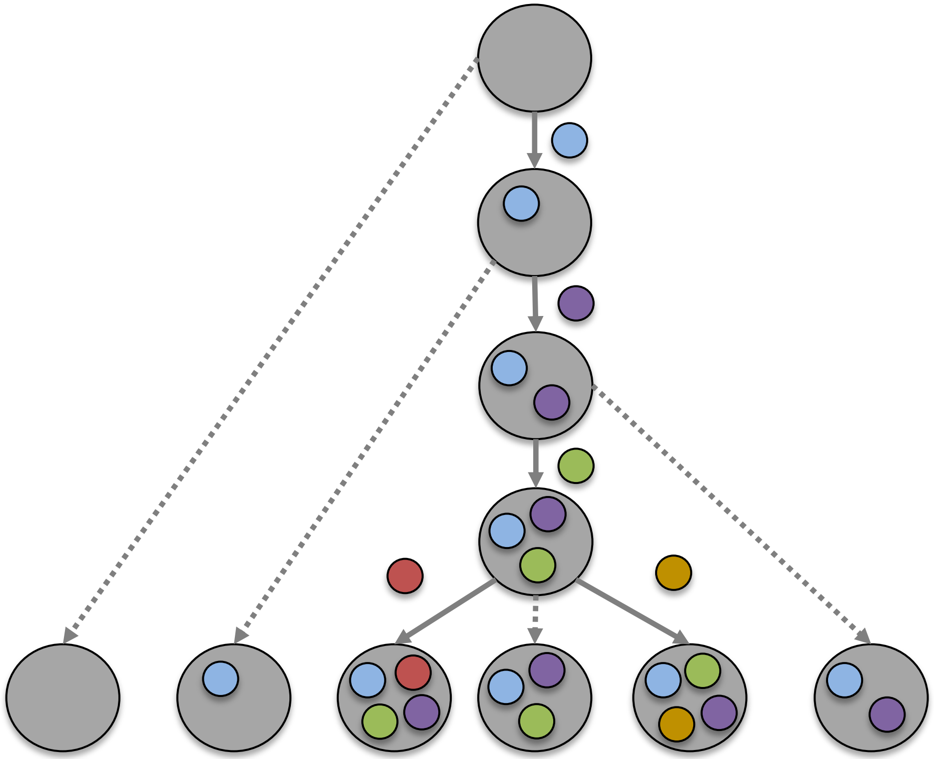
**Question:** How to **summarize solution space** $\mathcal{T}$ in order to remove inference errors and identify dependencies among mutations?

# 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

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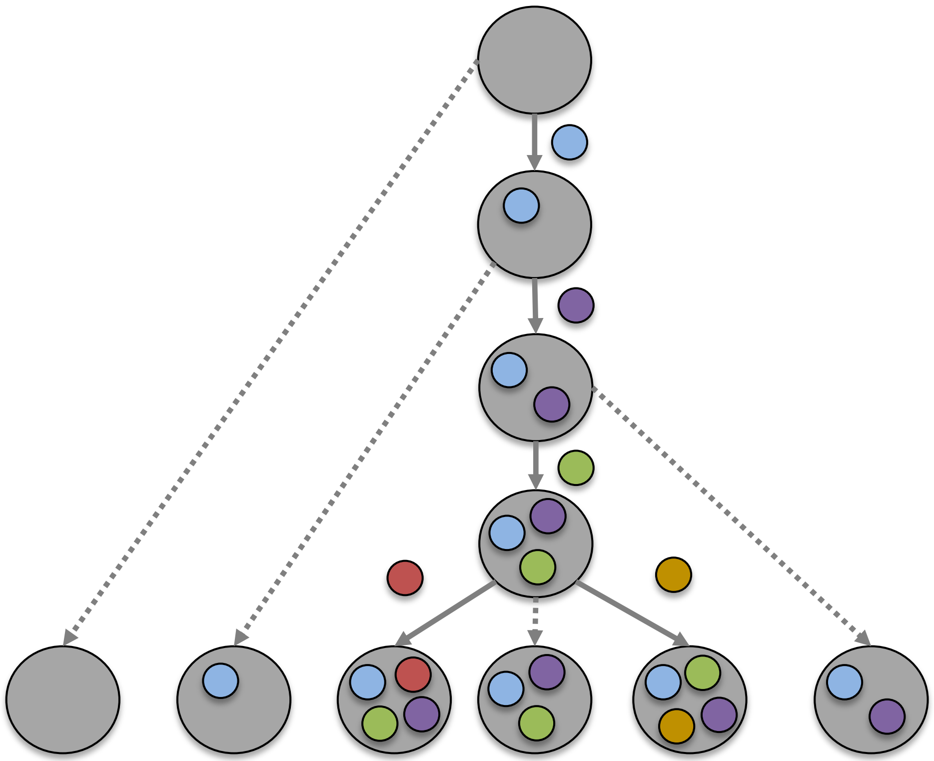

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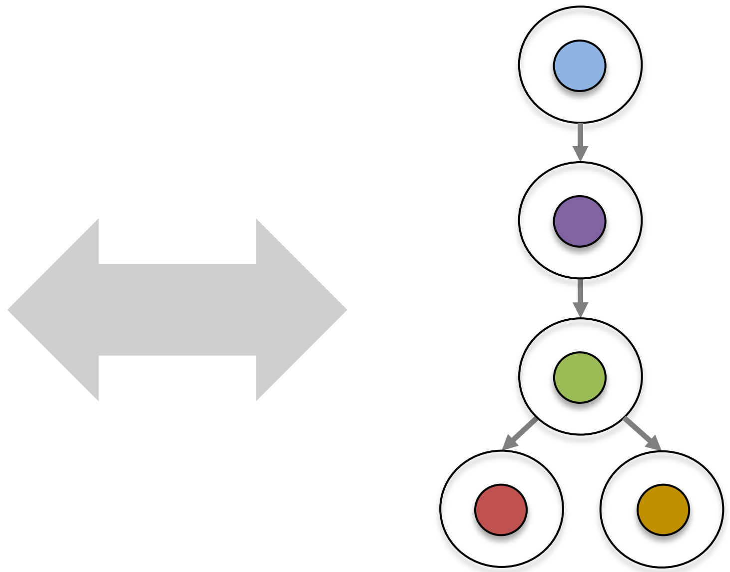


Mutation Tree

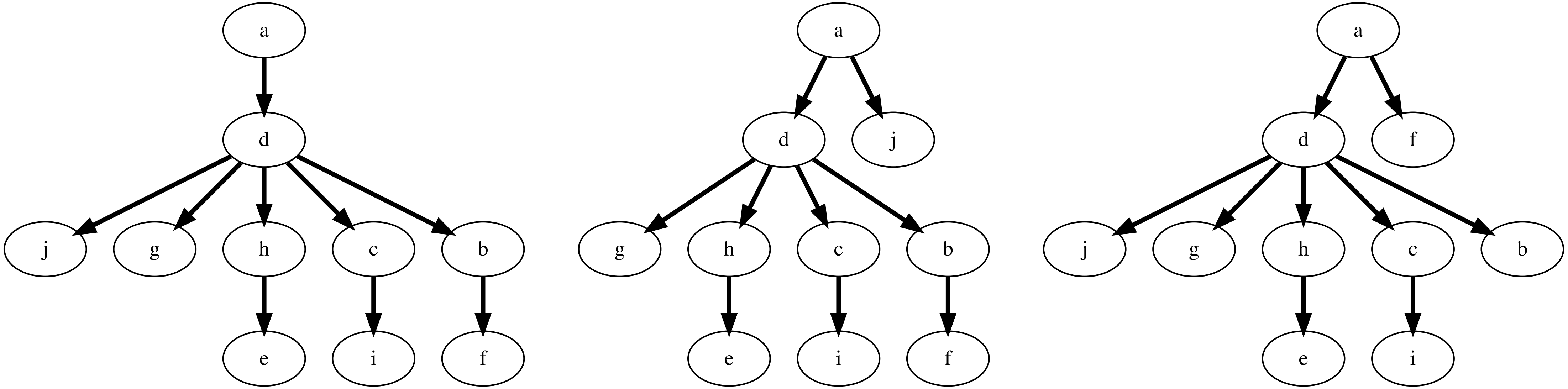
Infinite sites assumption (ISA): each mutation is introduced once and never subsequently lost

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




...
[14 more]

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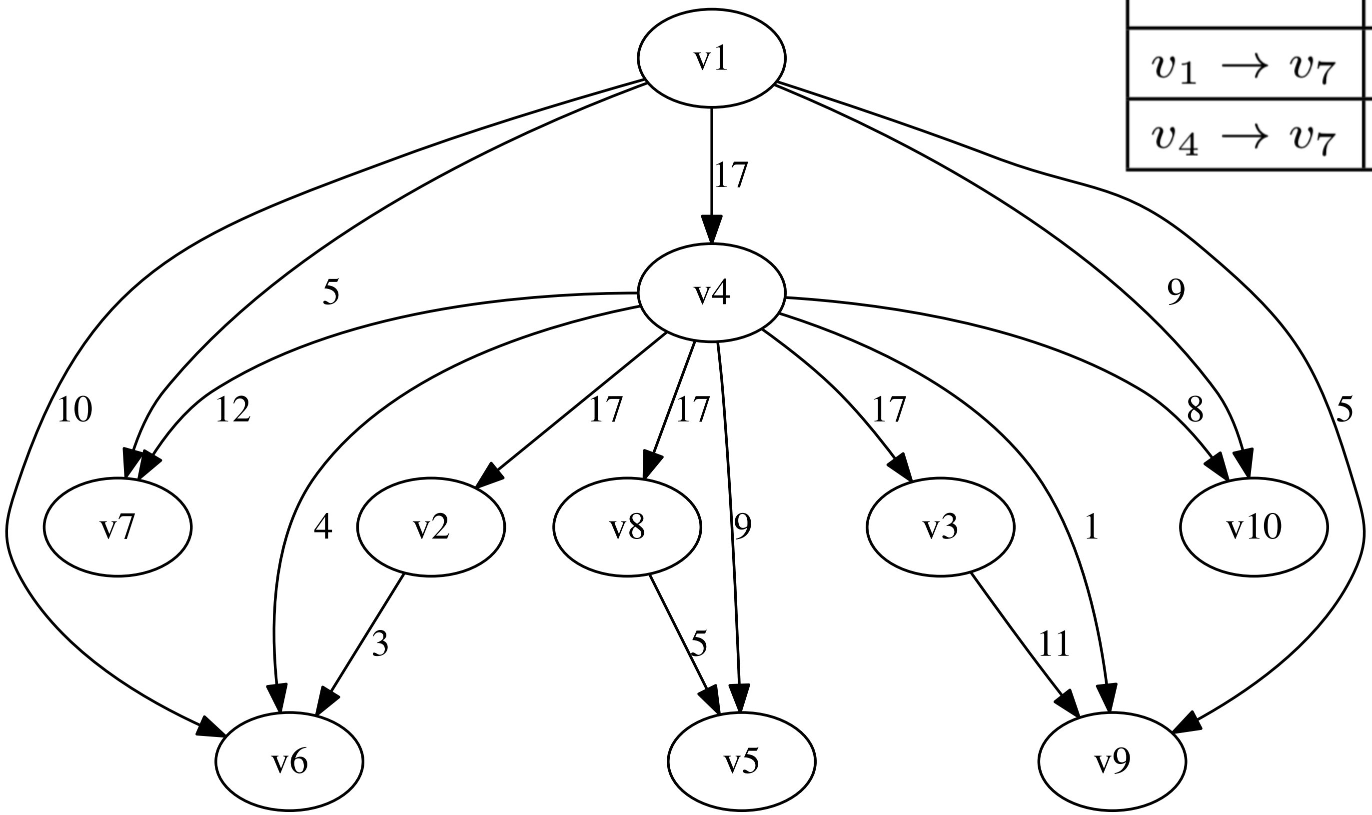
# Parent-child Graph: Union of all Edges in $\mathcal{T}$




| | $v_4 \to v_5$ | | $v_8 \to v_5$ | |
|---|---|---|---|---|
| | $v_1 \to v_{10}$ | $v_4 \to v_{10}$ | $v_1 \to v_{10}$ | $v_4 \to v_{10}$ |
| $v_1 \to v_7$ | 2 | 0 | 3 (d) | 0 |
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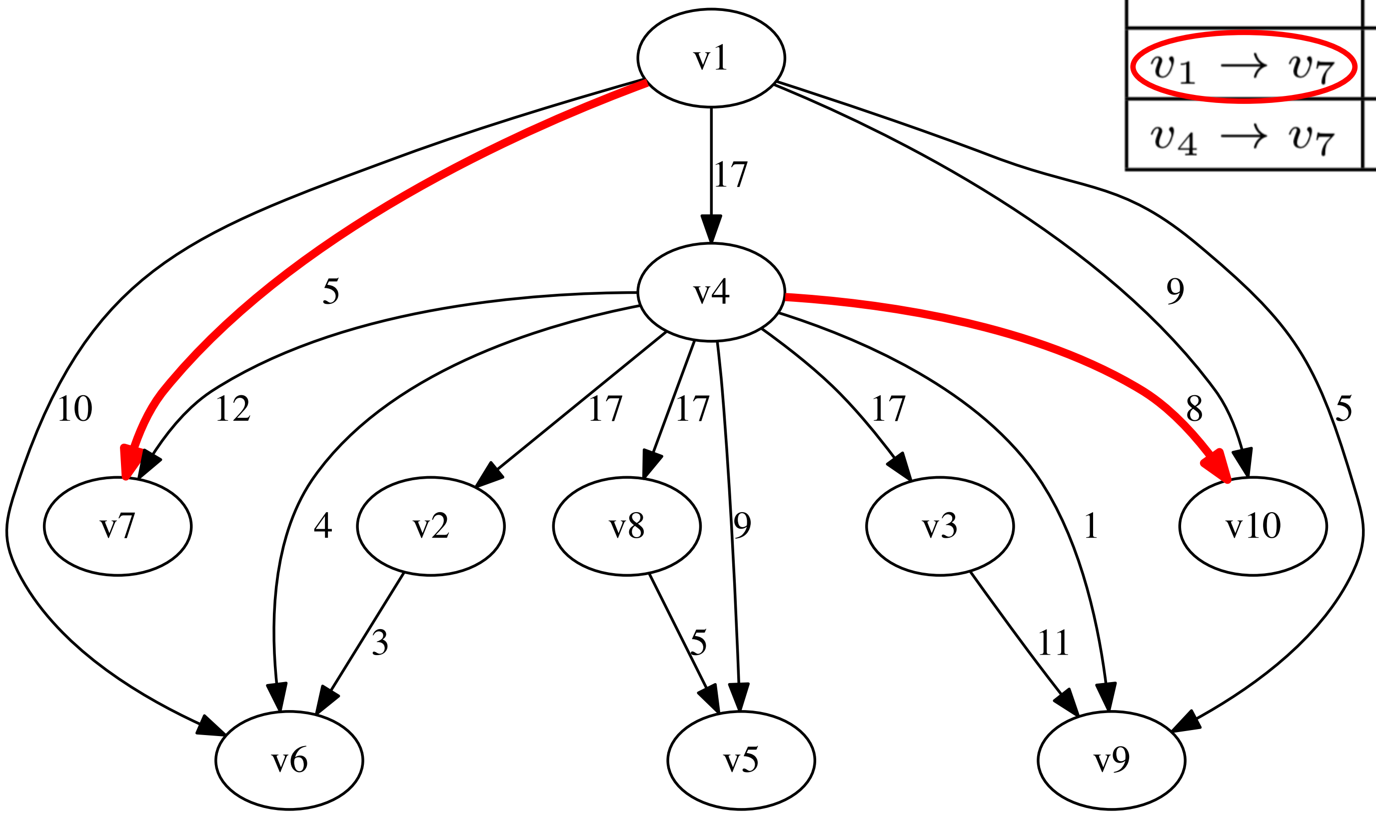


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The parent-child graph does not capture patterns of mutual exclusivity

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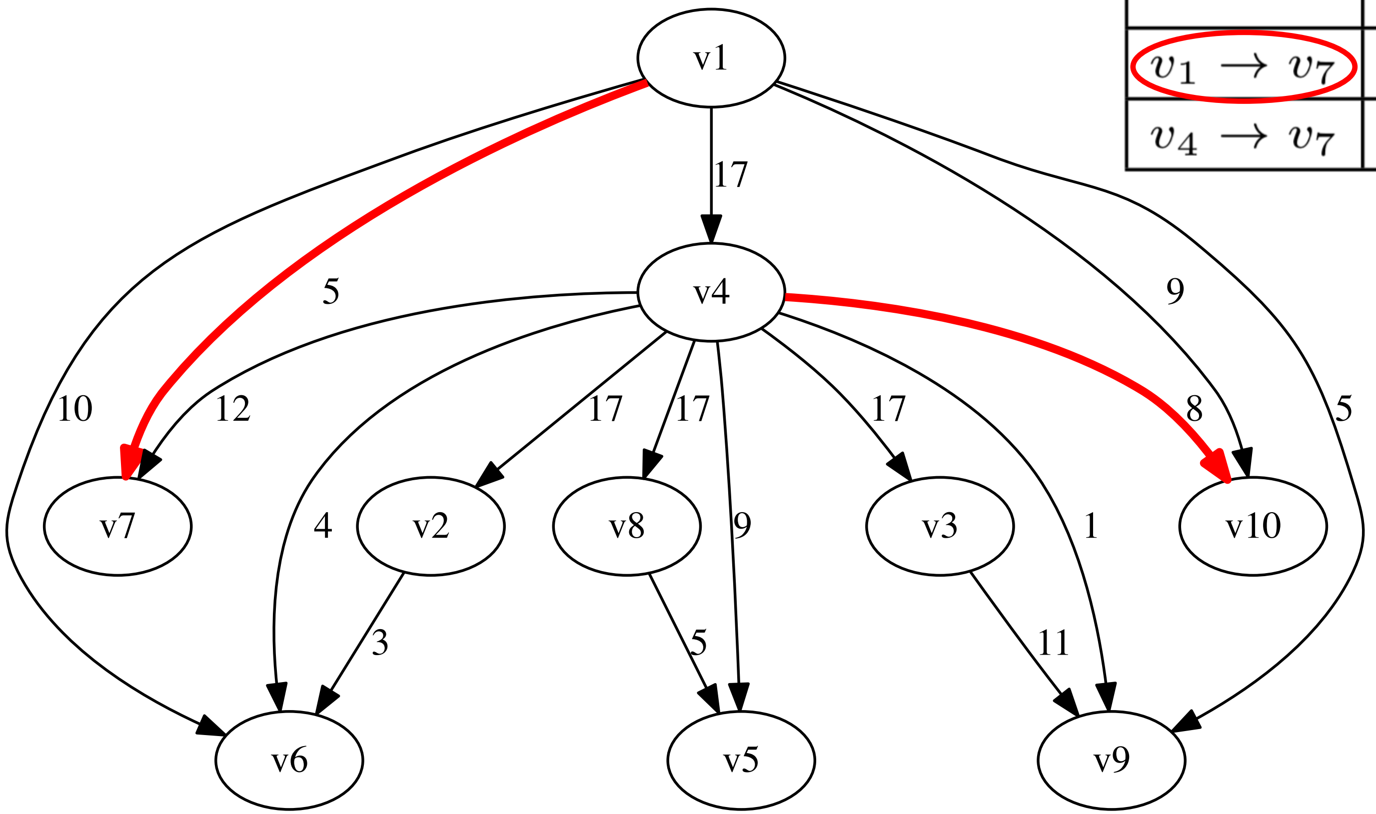


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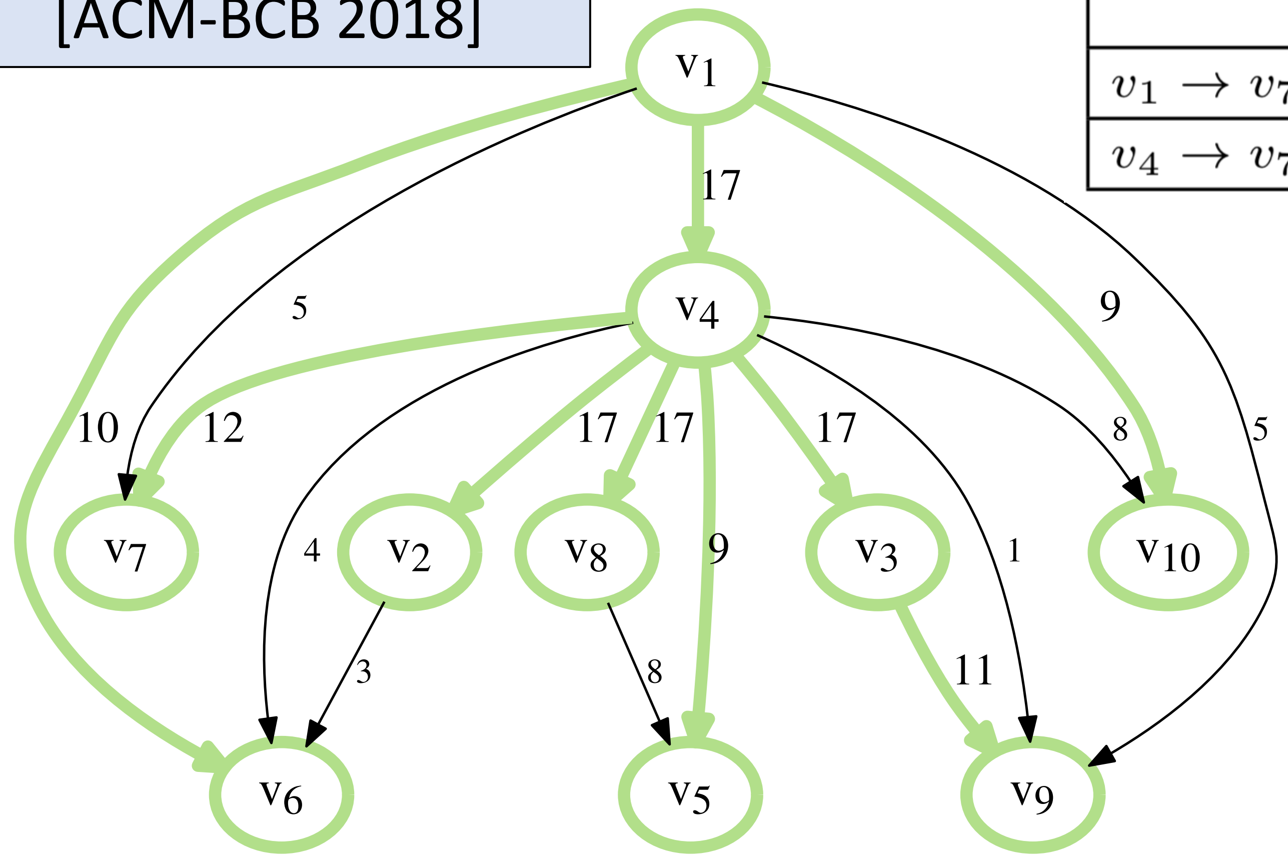
The parent-child graph does not capture patterns of mutual exclusivity

**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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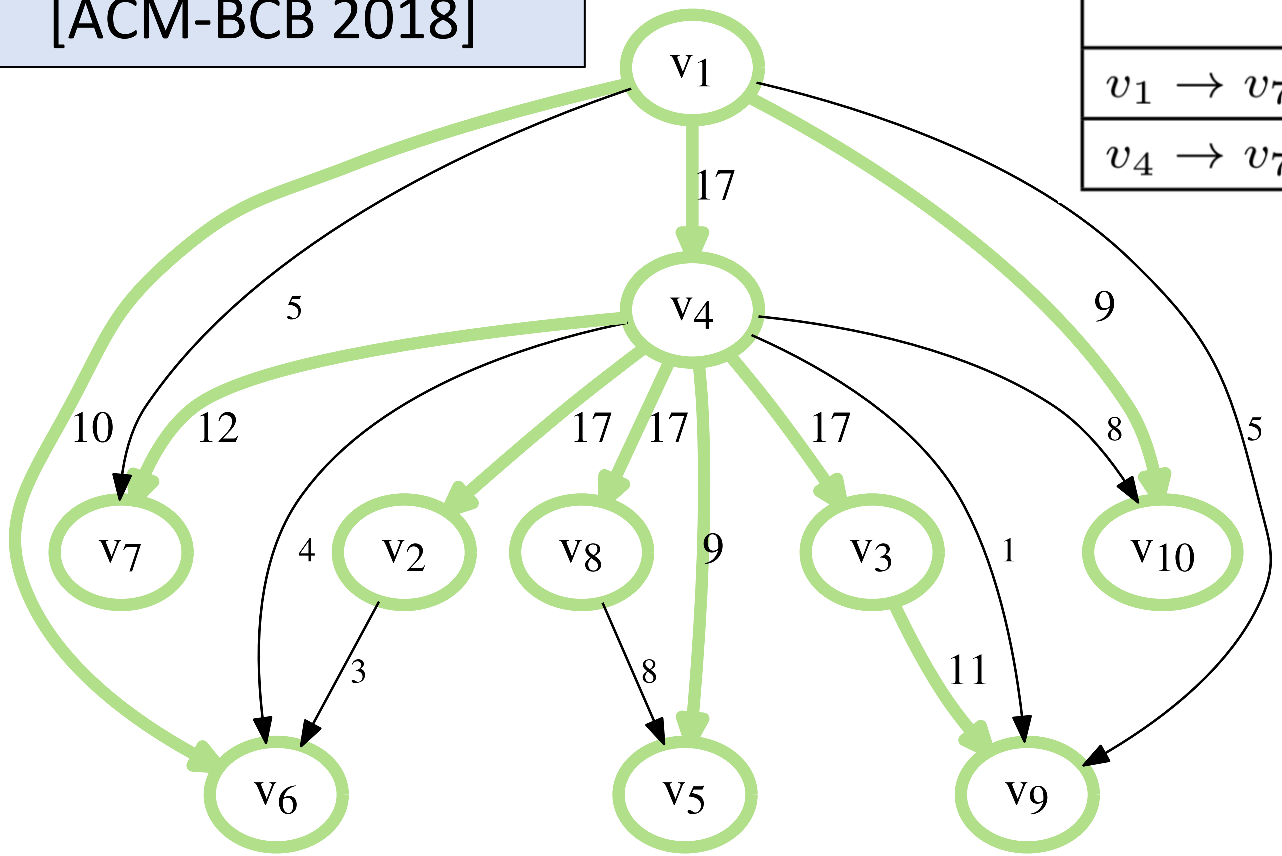
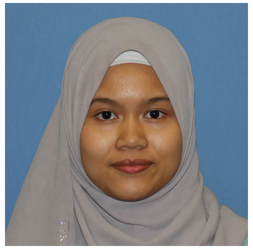



Inaccurate summary for diverse solution spaces

**Question:** How about inferring multiple consensus trees?

# Multiple Consensus Trees Problem

Simultaneous clustering and consensus tree inference



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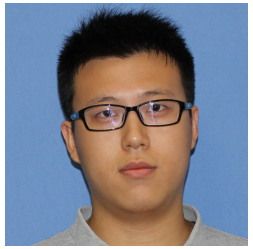

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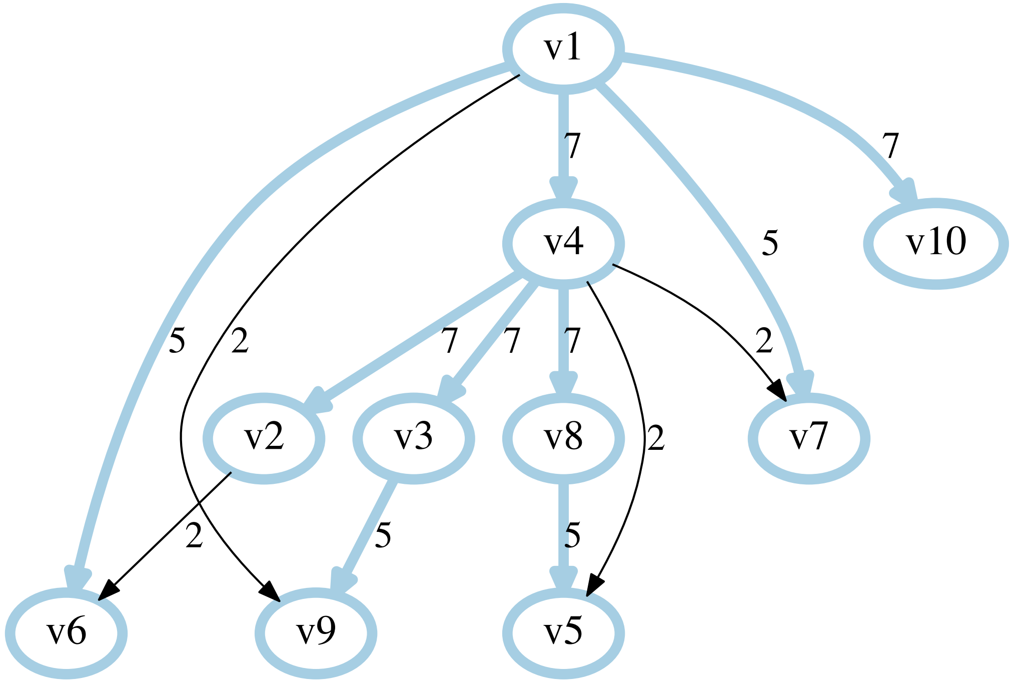


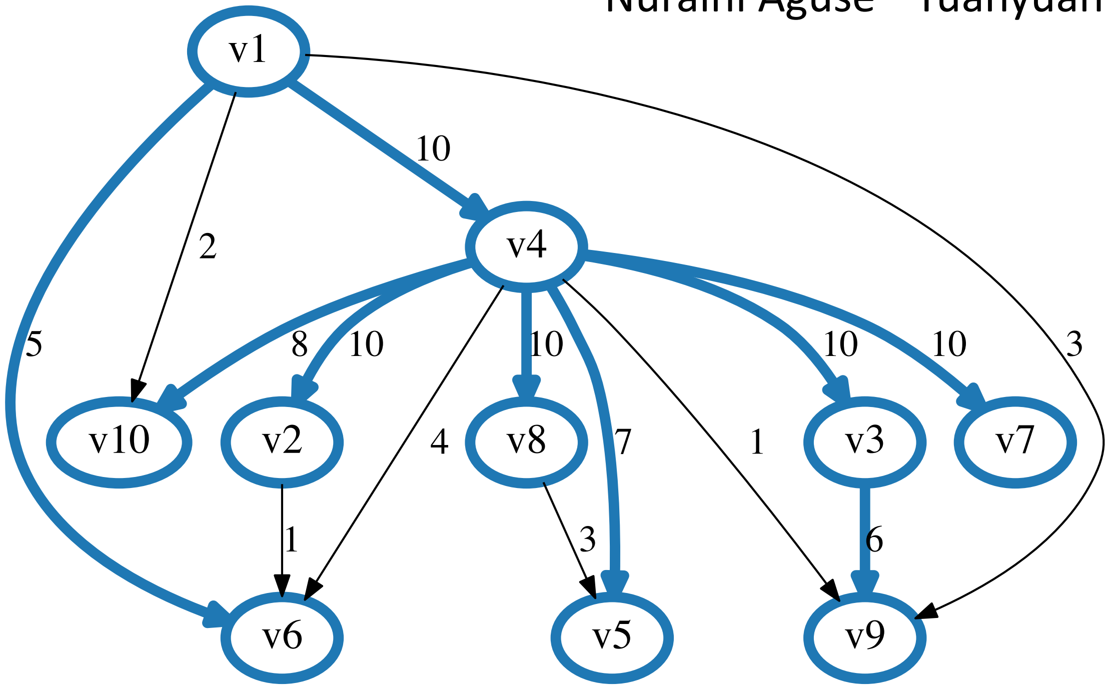

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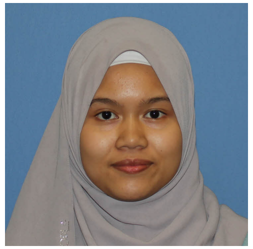

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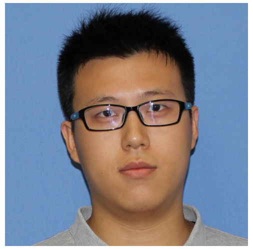

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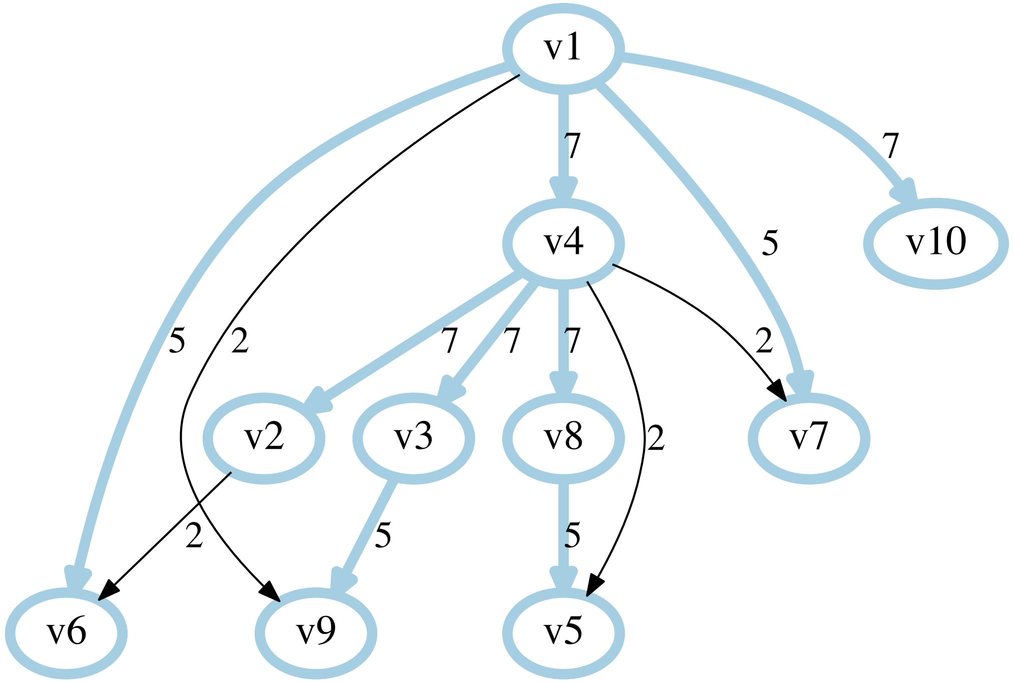


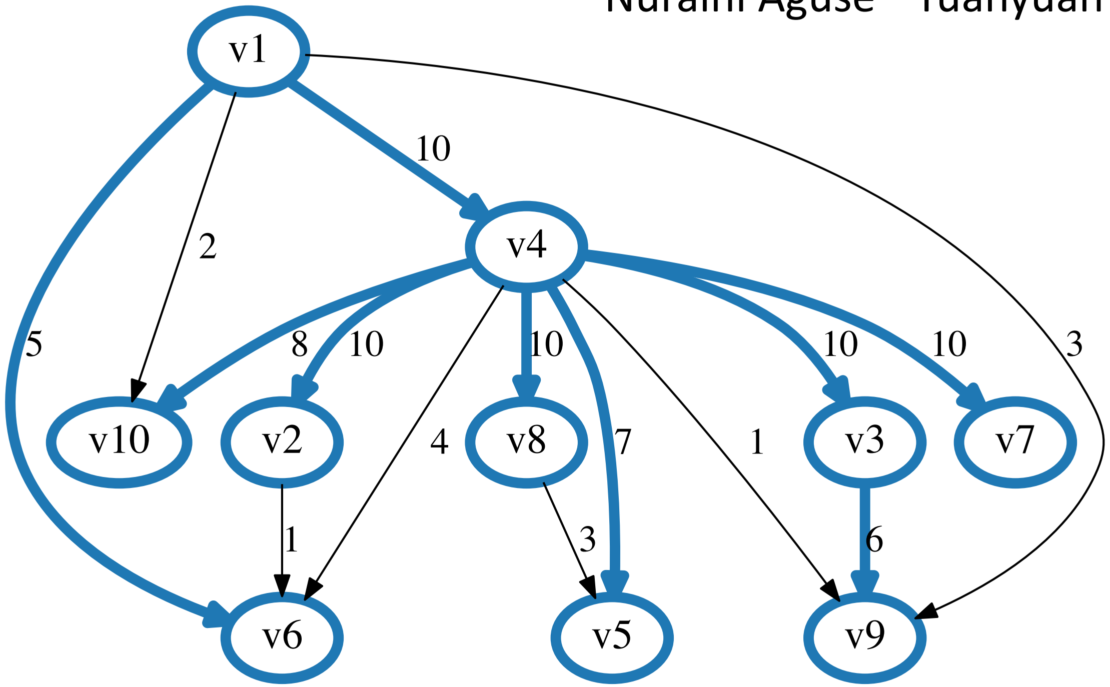


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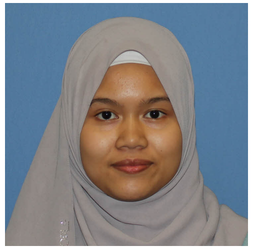

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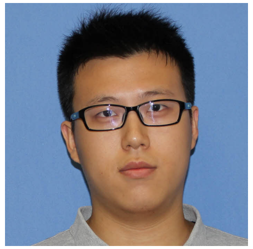

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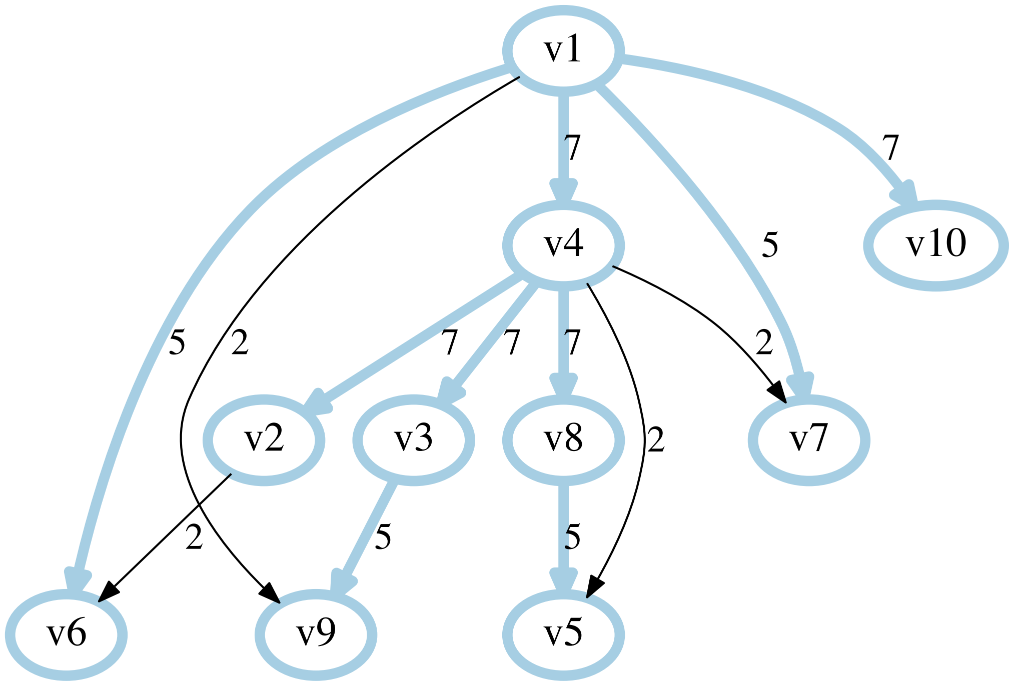


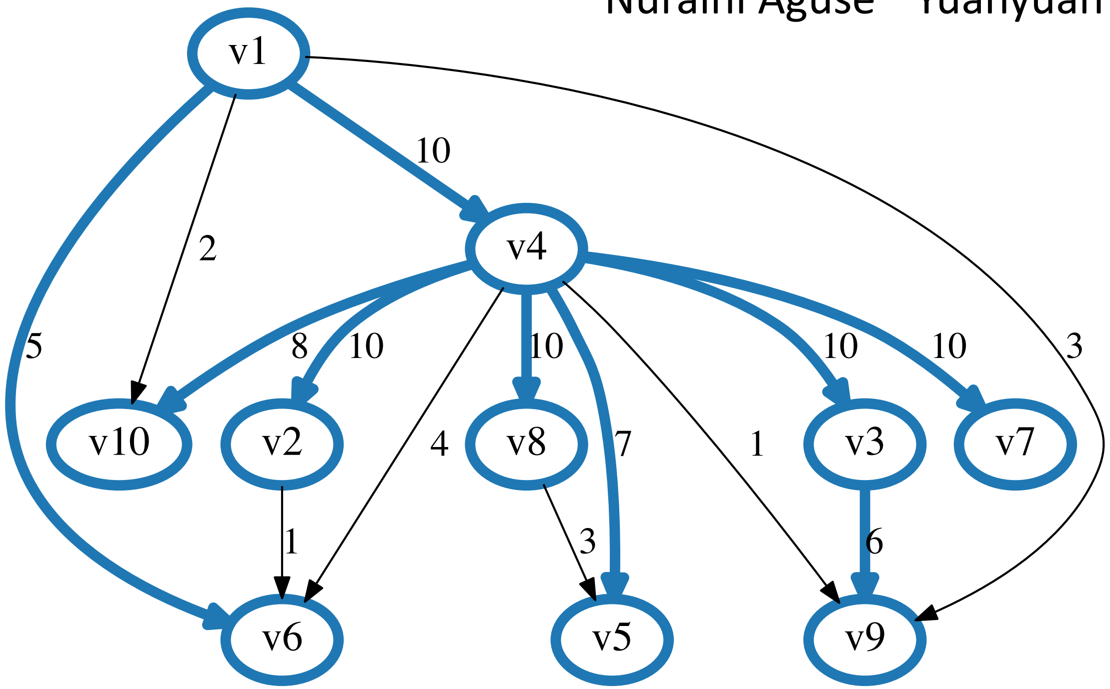


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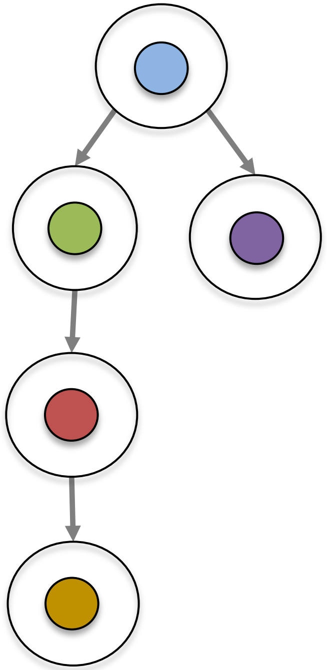
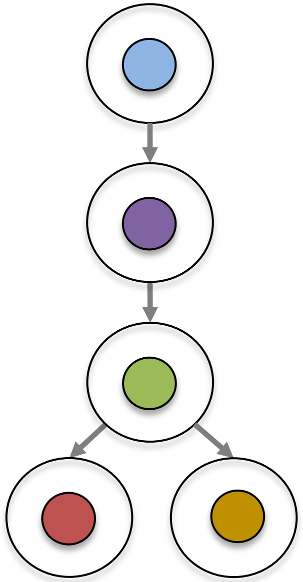
# Parent-child Distance Function

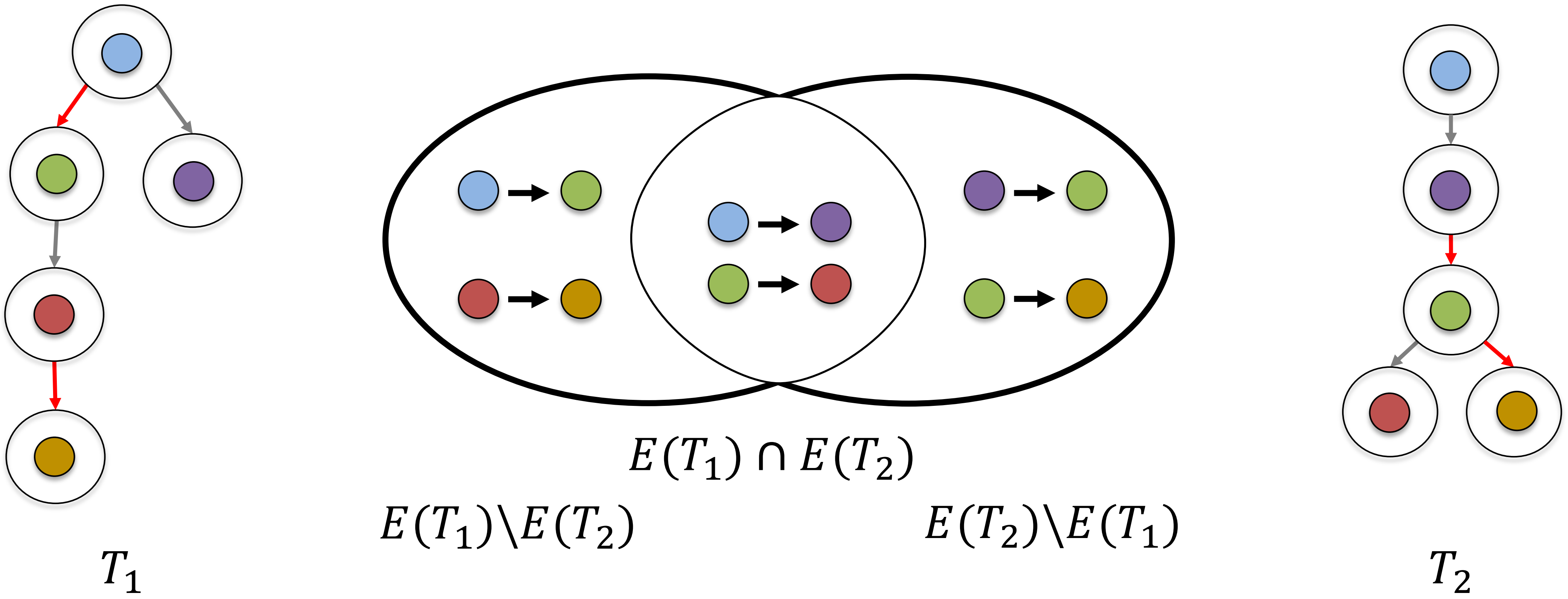


$T_1$



$T_2$

# Parent-child Distance Function



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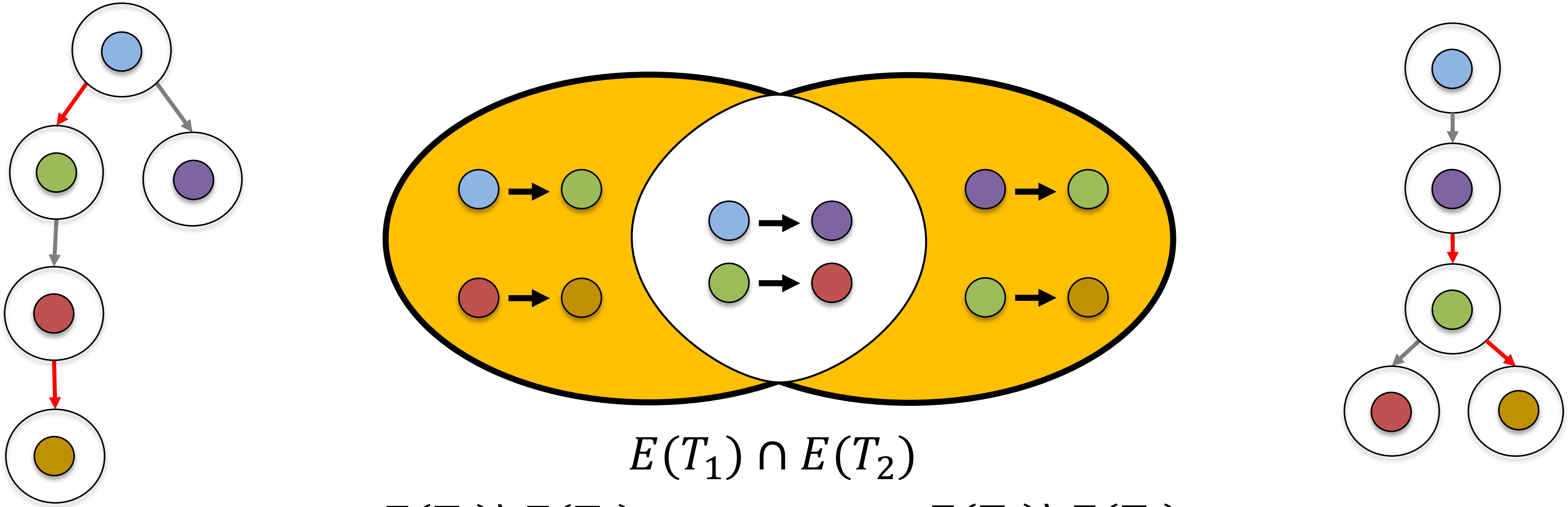


$E(T_1) \cap E(T_2)$

$E(T_1) \backslash E(T_2)$ $E(T_2) \backslash E(T_1)$

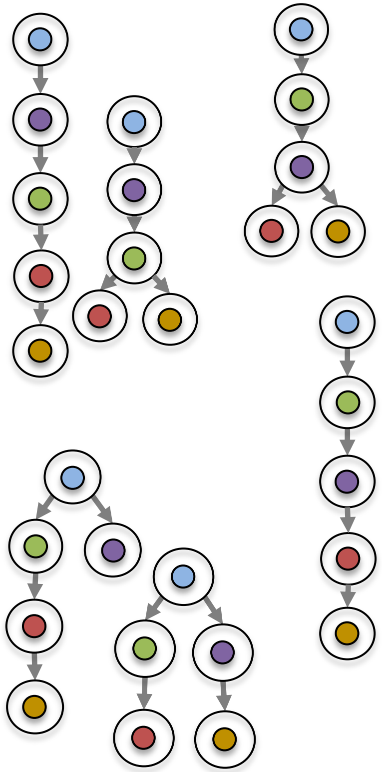
$T_1$ $T_2$

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

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

# 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. $\sum_{i=1}^{n} d(T_i, R)$ is minimum



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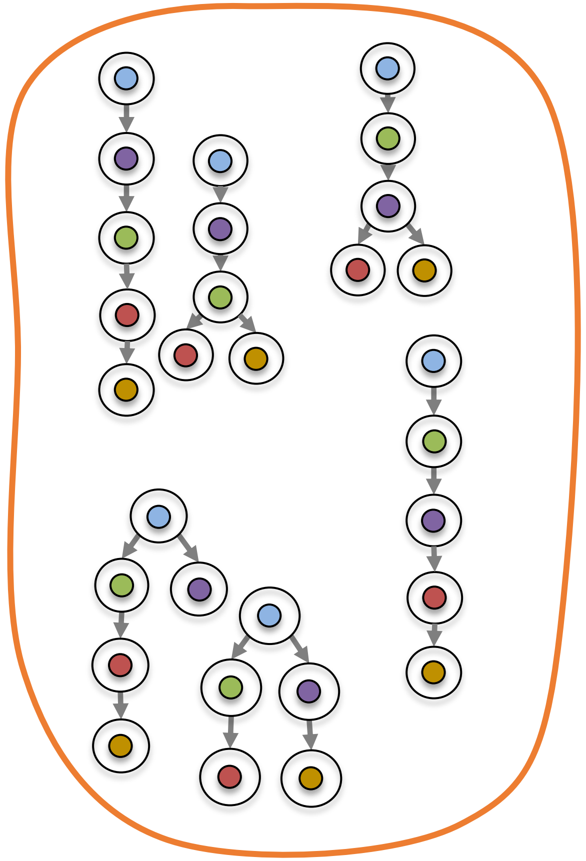
Max weight spanning arborescences
of parent-child graph $G_{\mathcal{T}}$ are solutions to SCT



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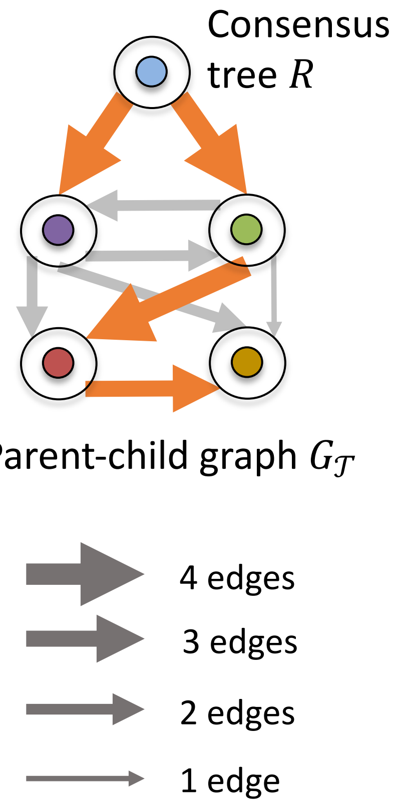


Parent-child graph $G_{\mathcal{T}}$

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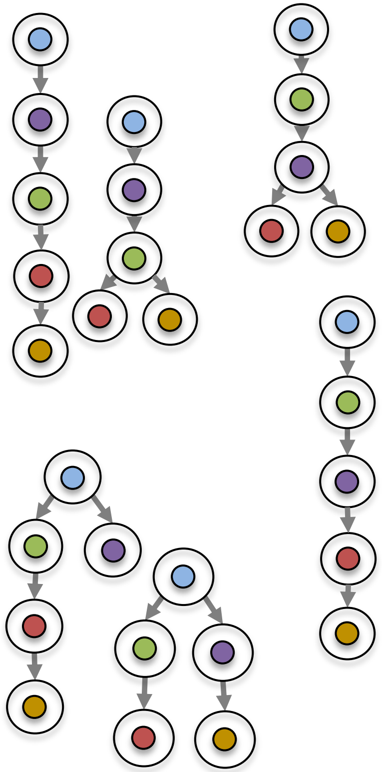

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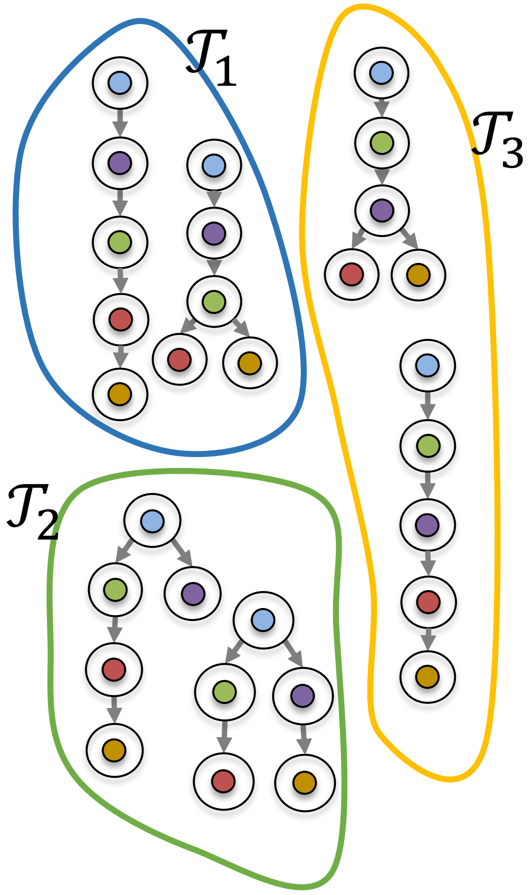
**Proposition:** [Aguse et al., ISMB 2019]
Given fixed clustering $\sigma : [n] \rightarrow [k]$, MCT decomposes into $k$ independent SCT instances

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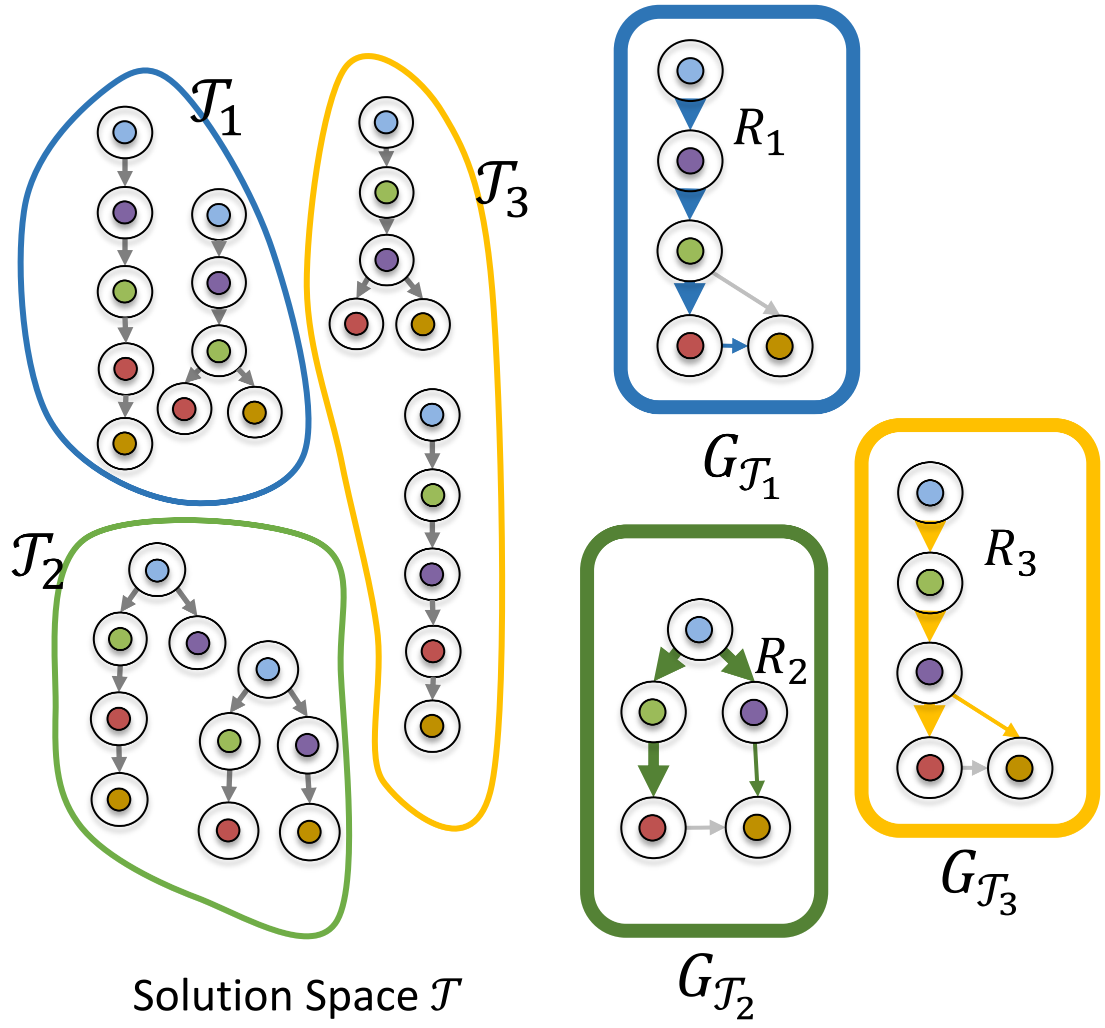
where $R_{\sigma(i)}$ is max weight spanning arborescence of $G_{\mathcal{T}_{\sigma(i)}}$

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




Solution Space $\mathcal{T}$

# 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.
$\sum_{i=1}^{n} d(T_i, R)$ is minimum

**Theorem:** [Govek et al., ACM-BCB 2018]
Max weight spanning arborescences
of parent-child graph $G_{\mathcal{T}}$ are solutions to SCT

**Multiple Consensus Trees (MCT):** [Aguse et al., ISMB 2019]
Given $\mathcal{T} = \{T_1, \dots, T_n\}$ and $k > 0$, find surjective clustering
$\sigma : [n] \rightarrow [k]$ ~~and consensus trees $\mathcal{R} = \{R_1, \dots, R_k\}$~~
s.t. $\sum_{i=1}^{n} d(T_i, R_{\sigma(i)})$ is minimum
where $R_{\sigma(i)}$ is max weight spanning arborescence of $G_{\mathcal{T}_{\sigma(i)}}$

**Proposition:** [Aguse et al., ISMB 2019]
Given fixed clustering $\sigma : [n] \rightarrow [k]$, MCT decomposes into
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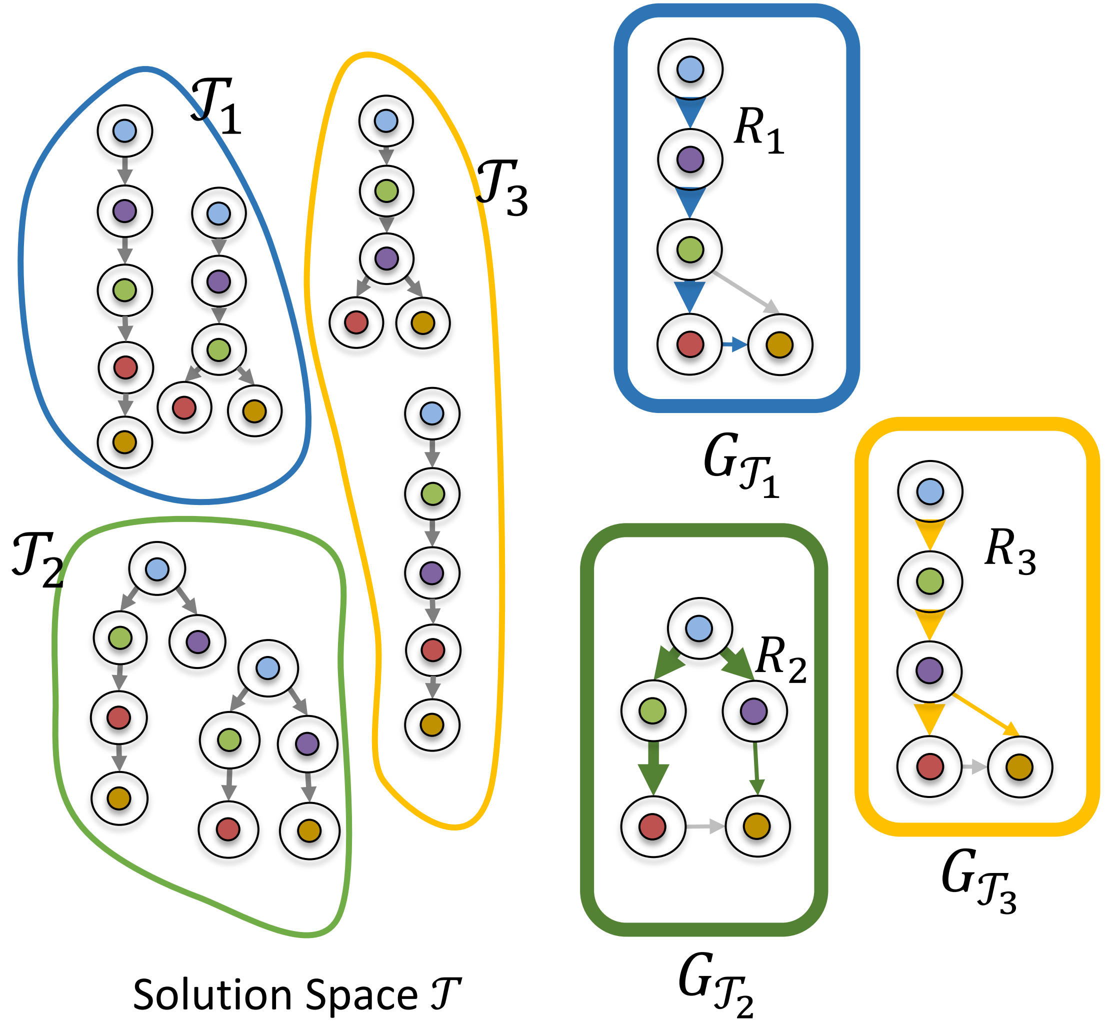


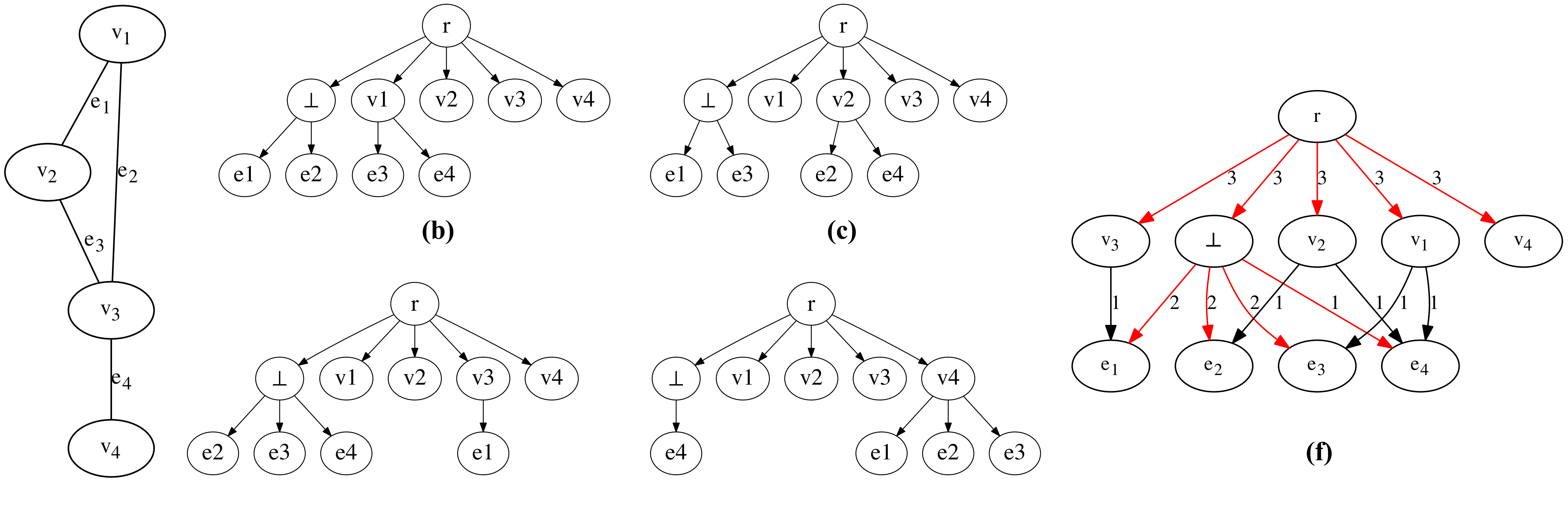

**Question:** How to find $\sigma^*$?

# Complexity

**Multiple Consensus Trees (MCT):**

Given $\mathcal{T} = \{T_1, \dots, T_n\}$ and $k > 0$, find surjective clustering $\sigma : [n] \to [k]$

s.t. $\sum_{i=1}^{n} d(T_i, R_{\sigma(i)})$ is minimum where $R_{\sigma(i)}$ is max weight spanning arborescence of $G_{\mathcal{T}_{\sigma(i)}}$



(a) (b) (c) (d) (e) (f)

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

# Outline

- Problem Statement
  - Previous work
  - Problem statement
  - Combinatorial characterization of solutions
  - Complexity
- Method & Results
  - Exact algorithm
  - Heuristic algorithm
  - Model selection

# 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 $R_s$

$$\min n(m-1) - \sum_{i=1}^{n}\sum_{s=1}^{k}\sum_{p=1}^{m}\sum_{q=1}^{m} w_{i,s,p,q}$$

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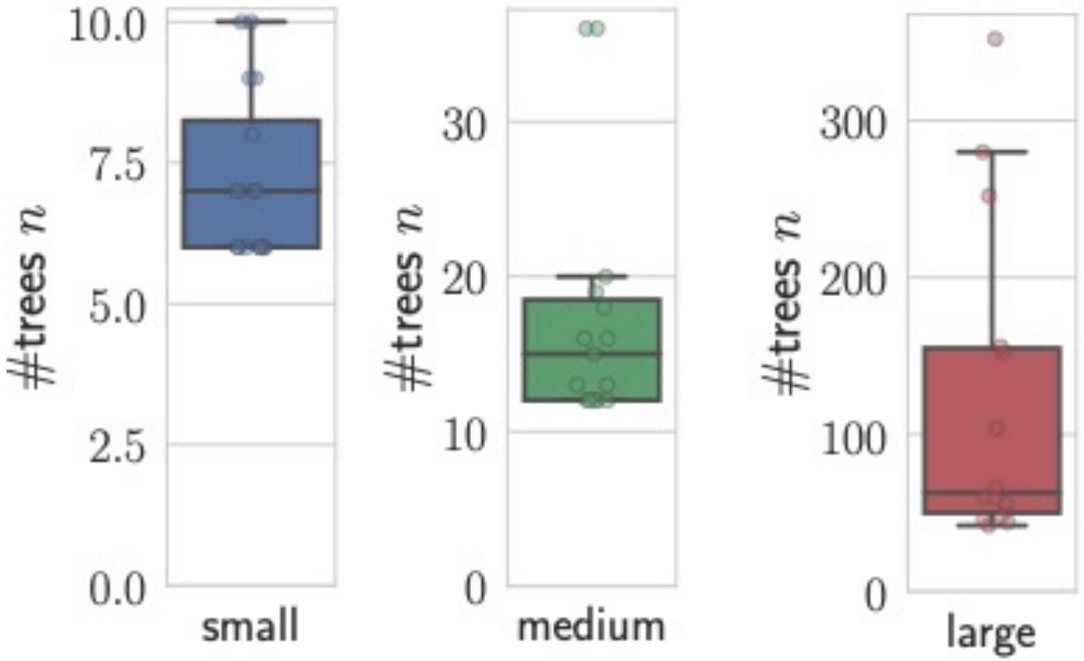
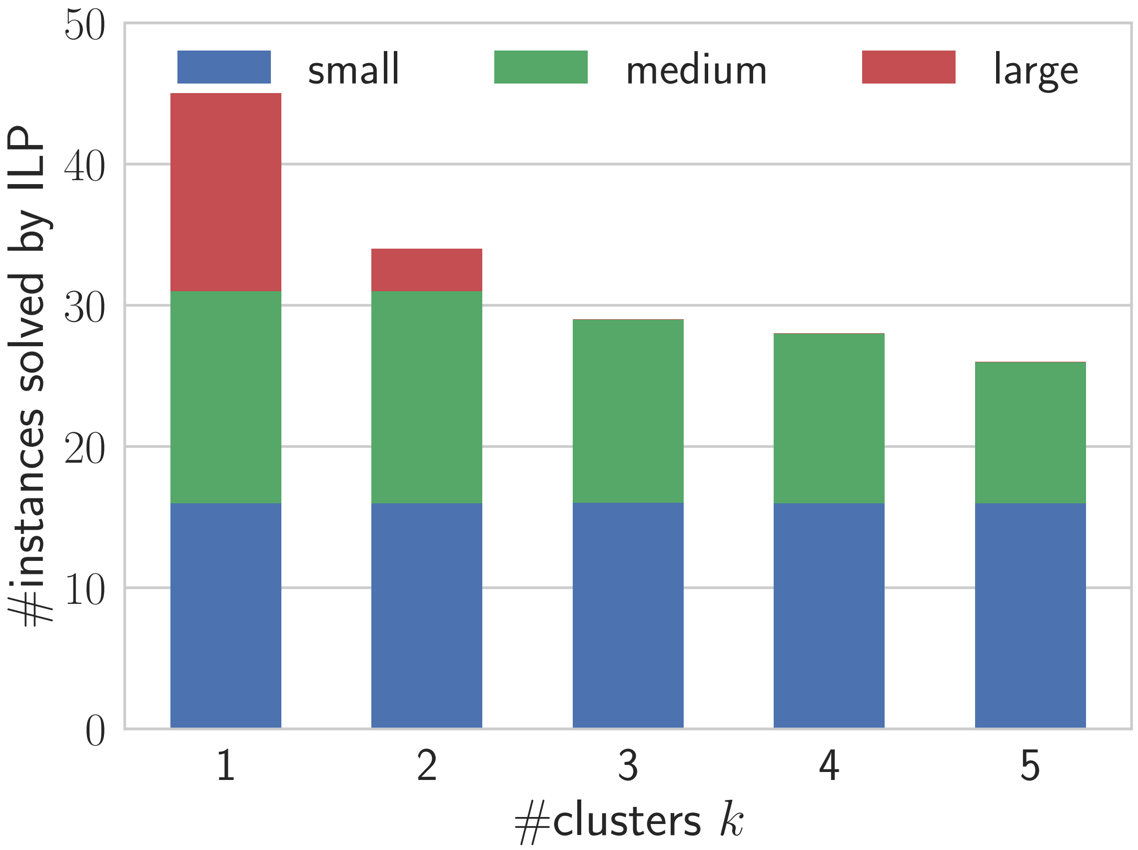
& w_{i,s,p,q} \leq x_{i,s} && \forall i \in [n], s \in [k], p,q \in [m]\\
& w_{i,s,p,q} \leq y_{s,p,q} && \forall i \in [n], s \in [k], p,q \in [m]\\
& w_{i,s,p,q} \geq 0 && \forall i \in [n], s \in [k], p,q \in [m]\\
& y_{s,p,q} \leq \sum_{i=1}^{n} a_{i,p,q} x_{i,s} && \forall s \in [k], p,q \in [m]\\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

# MILP does not scale well with $k$ and $n$



# Coordinate Ascent (akin to k-means)

**Proposition:** [Aguse et al., ISMB 2019]
Given fixed clustering $\sigma : [n] \rightarrow [k]$, 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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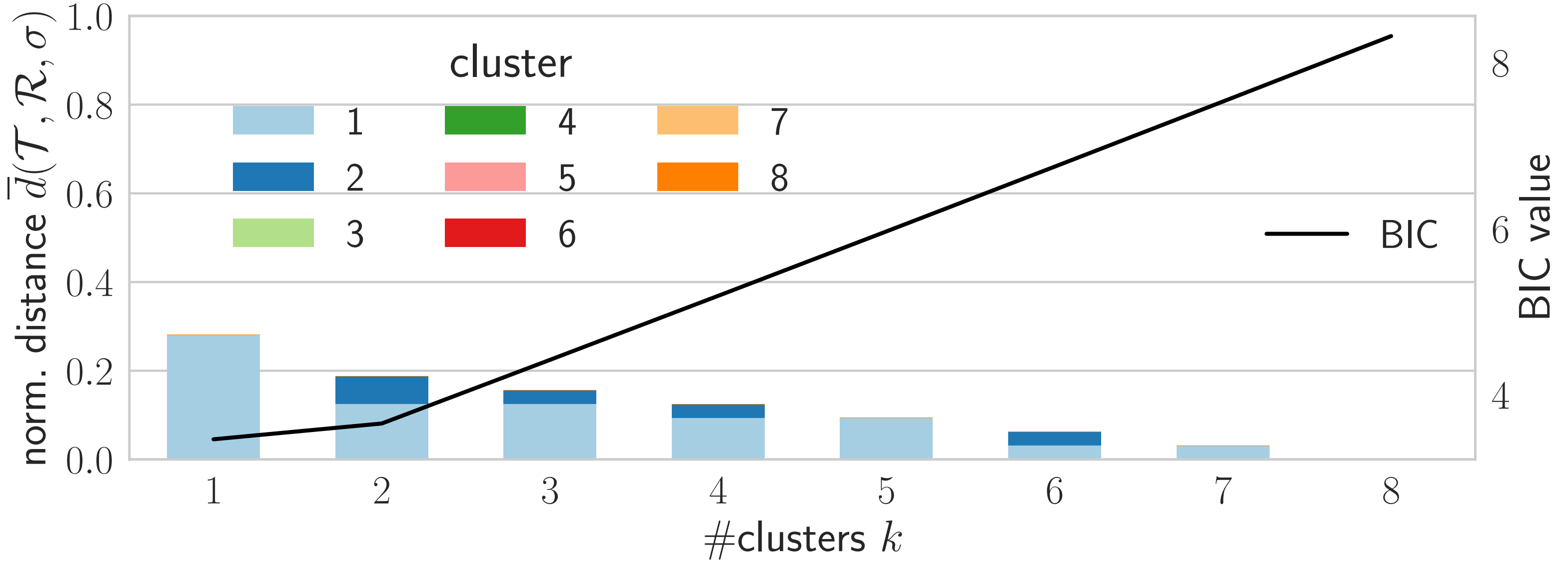
4. Go to 2

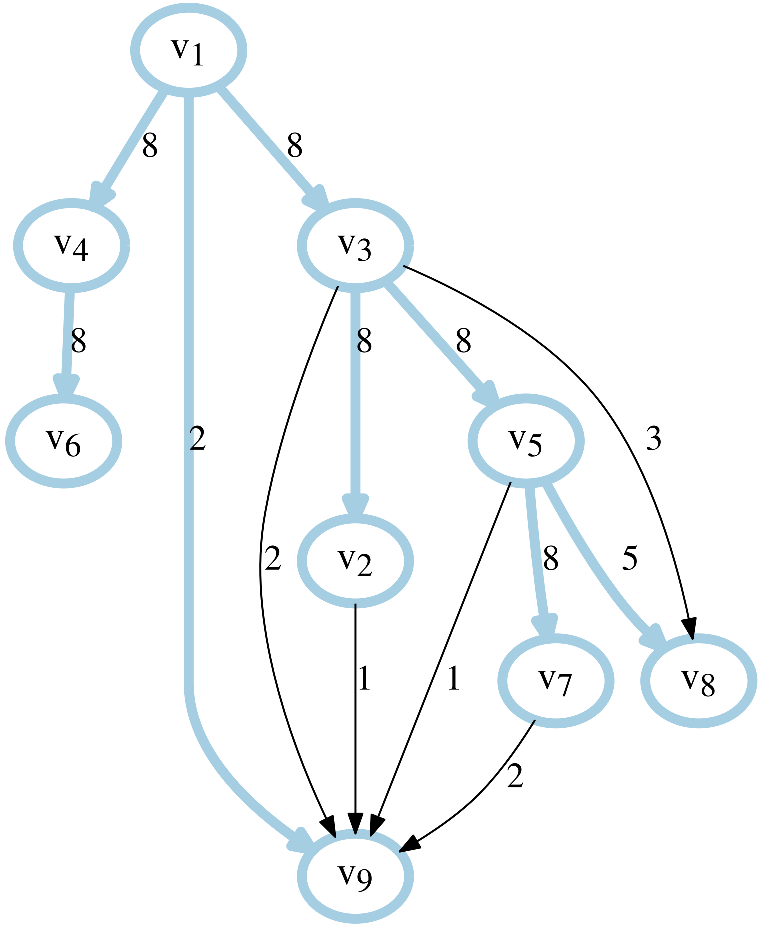
| | #clusters $k$ | MILP (1 h) | BF (1 h) | CA (1 h) | CA (100 r.) |
|---|---|---|---|---|---|
| small (16) | 2 | 16 | 16 | 16 | 16 |
| | 3 | 16 | 16 | 16 | 16 |
| | 4 | 16 | 16 | 16 | 16 |
| | 5 | 16 | 14 | 16 | 16 |
| medium (15) | 2 | 15 | 13 | 15 | 15 |
| | 3 | 13 | 7 | 13 | 13 |
| | 4 | 12 | 0 |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

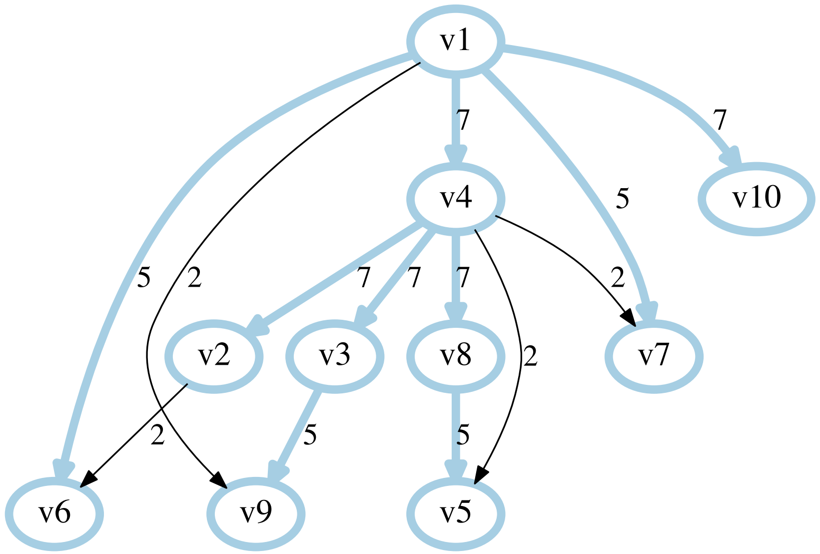


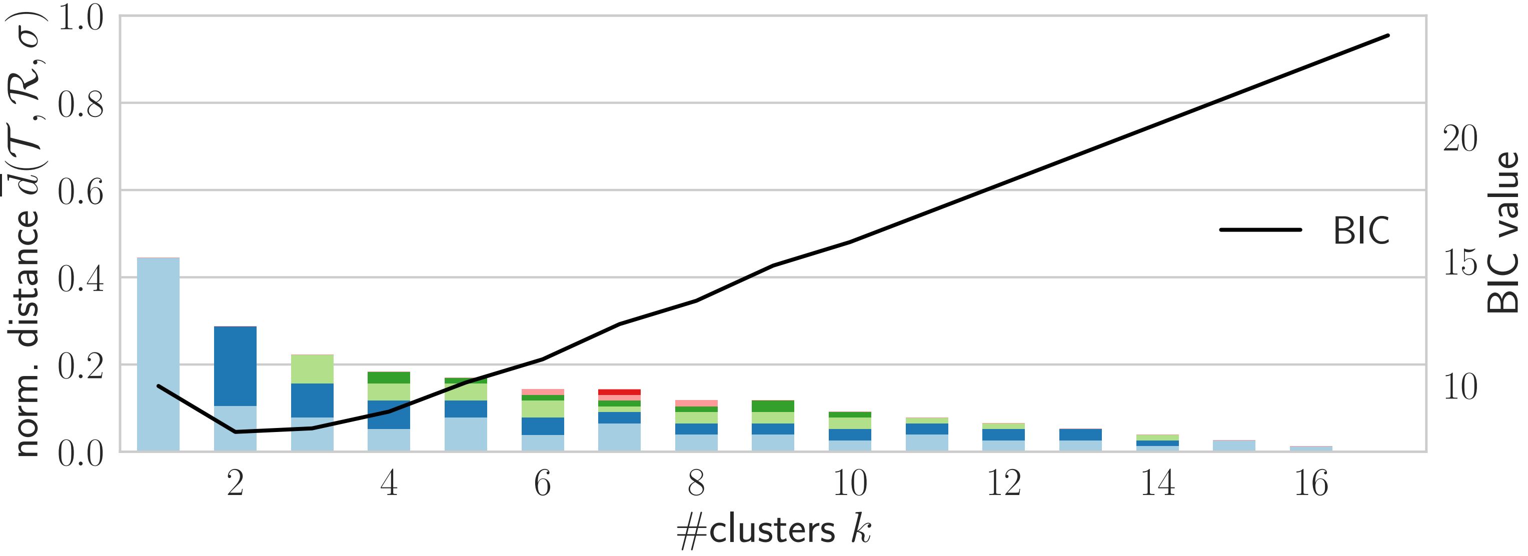



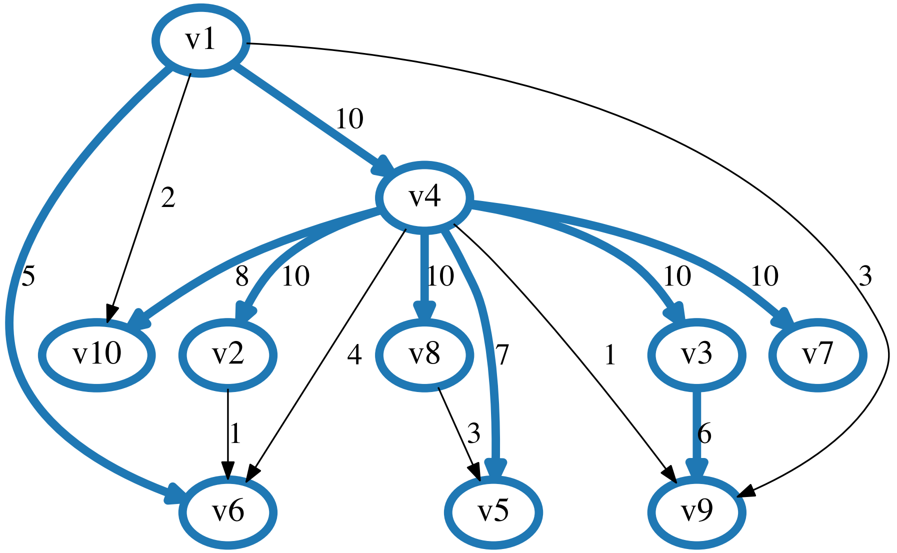
# Bayesian Information Criterion

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

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



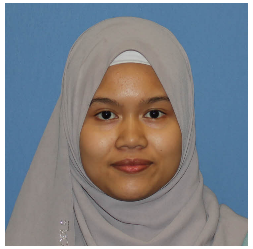
# Conclusion

- 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

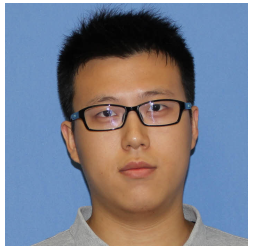
**Future directions**

- Relax infinite sites assumption
- Use medoids rather than centroids

# Acknowledgments



Nuraini Aguse



Yuanyuan Qi

**<u>El-Kebir group</u>**

- **Nuraini Aguse**
- Juho Kim
- **Yuanyuan Qi**
- Jiaqi Wu

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Available at: https://github.com/elkebir-group/MCT