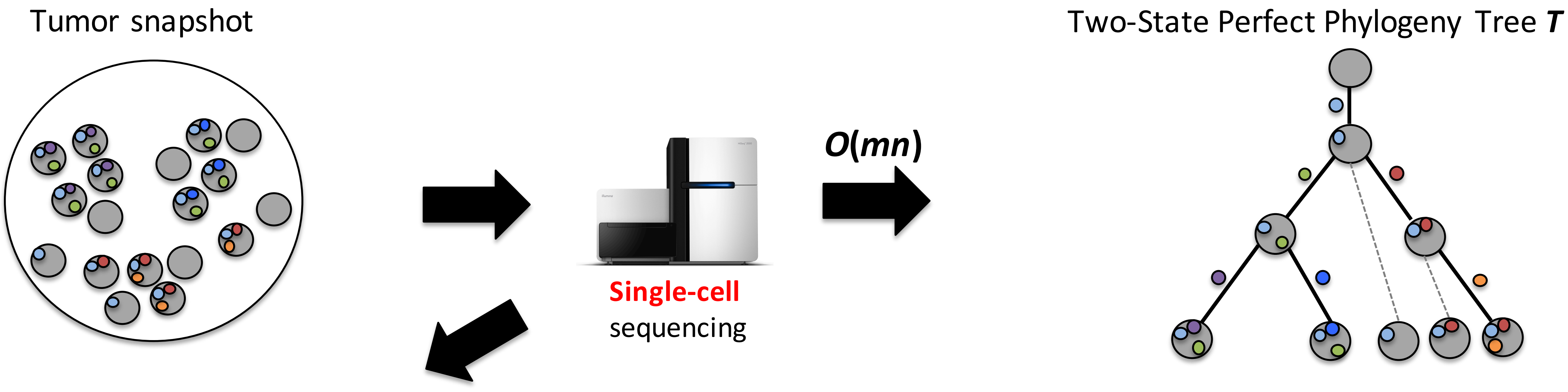
Multi-State Perfect Phylogeny Mixture Deconvolution and Applications to Cancer Sequencing

Mohammed El-Kebir

BROWN

CCMB

Tumor Evolution as a Two-State Perfect Phylogeny



Given:

SNVs

$$
\boldsymbol{M} = \begin{array}{c}
\begin{array}{cccccc} \bullet & \bullet & \bullet & \bullet & \bullet & \bullet \end{array} \\
\begin{bmatrix}
1 & 1 & 1 & 0 & 0 & 0 \\
1 & 1 & 0 & 1 & 0 & 0 \\
1 & 0 & 0 & 0 & 0 & 0 \\
1 & 0 & 0 & 0 & 1 & 0 \\
1 & 0 & 0 & 0 & 1 & 1
\end{bmatrix}
\end{array}
$$

leaves of ***T***

Find:

Two-state perfect phylogeny tree ***T***

Assumptions:

- No copy number aberrations
- Infinite sites assumption

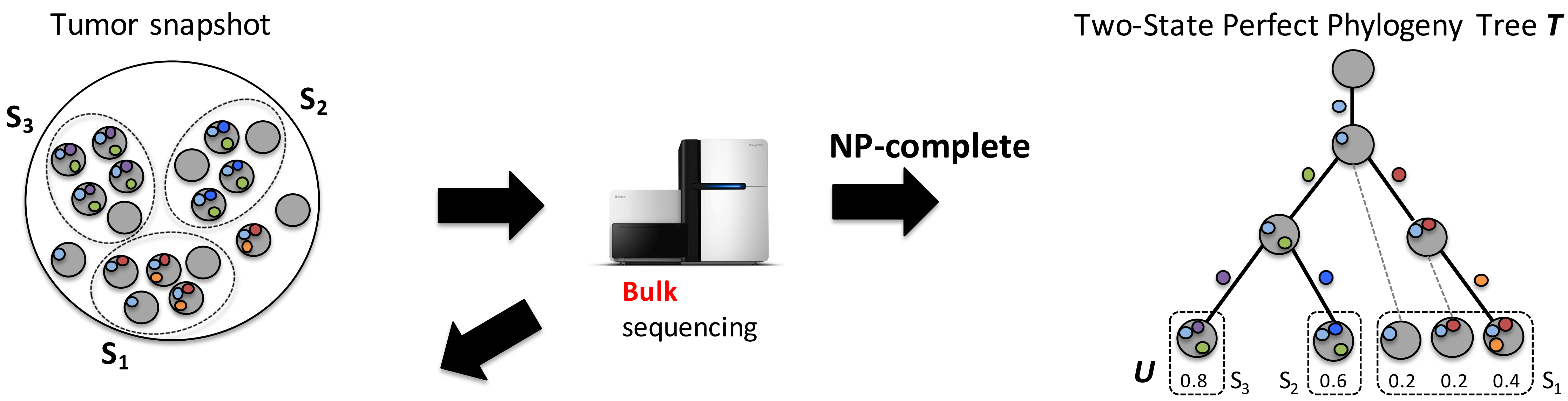
States:

0 : non-mutated

1 : mutated

Seq. method	Mixing	Inferring *T*
single-cell	no	two-state perfect phylogeny [Gusfield, 1991]

Tumor Evolution as a Two-State Perfect Phylogeny



Given:

mutations

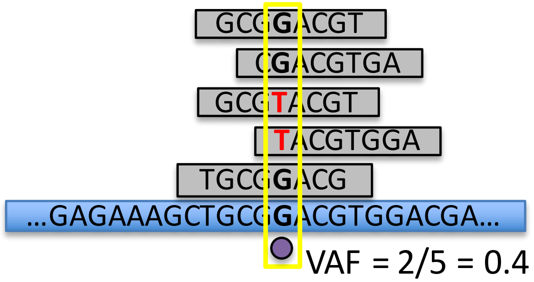
$$\text{VAFs } \boldsymbol{F} = \begin{array}{c|c|c|c|c|c|l} \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \\ 0.4 & 0.0 & 0.0 & 0.0 & 0.3 & 0.2 & s_1 \\ 0.3 & 0.3 & 0.0 & 0.3 & 0.0 & 0.0 & s_2 \\ 0.4 & 0.4 & 0.4 & 0.0 & 0.0 & 0.0 & s_3 \end{array}$$

samples

Find:

Two-state perfect phylogeny tree ***T***
Mixing proportions ***U***

Variant Allele Frequency (VAF):
Fraction of reads covering position of single-nucleotide variant (SNV) that contain ***variant*** allele

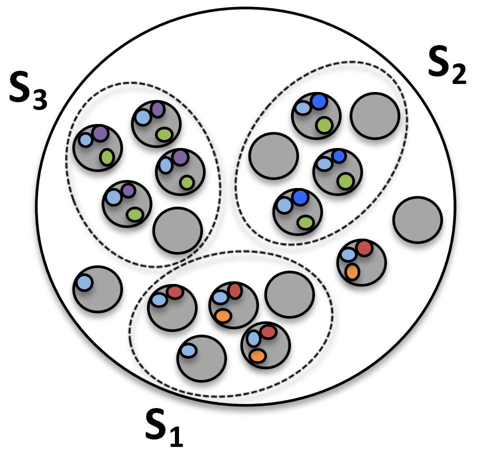


VAF = 2/5 = 0.4

Seq. method	Mixing	Inferring *T*
single-cell	no	two-state perfect phylogeny [Gusfield, 1991]
bulk	yes	TrAp [Strino *et al.*, 2013] Rec-BTP [Hajirasouliha *et al.*, 2014] PhyloSub [Jiao *et al.*, 2014] Clomial [Zare *et al.*, 2014] Binary ***F*** [Hajirasouliha *et al.*, 2014] CITUP [Malikic *et al.*, 2015] BitPhylogeny [Yuan *et al.*, 2015] LICHeE [Popic *et al.*, 2015] AncesTree [El-Kebir, Oesper *et al.*, 2015] …

Tumor Evolution as a Two-State Perfect Phylogeny

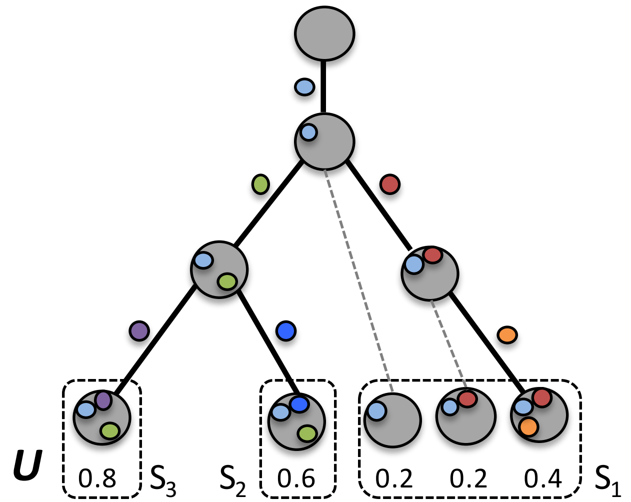
Tumor snapshot



Bulk sequencing

NP-complete

Two-State Perfect Phylogeny Tree ***T***



Given:

mutations

$$
\text{VAFs } \boldsymbol{F} = \begin{array}{c}
\begin{array}{cccccc} \bullet & \bullet & \bullet & \bullet & \bullet & \bullet \end{array} \\
\left[\begin{array}{c|c|c|c|c|c} 0.4 & 0.0 & 0.0 & 0.0 & 0.3 & 0.2 \\ 0.3 & 0.3 & 0.0 & 0.3 & 0.0 & 0.0 \\ 0.4 & 0.4 & 0.4 & 0.0 & 0.0 & 0.0 \end{array}\right]
\end{array}
\begin{array}{c} \\ s_1 \\ s_2 \\ s_3 \end{array}
$$

samples

Find:

Two-state perfect phylogeny tree ***T***
Mixing proportions ***U***

States: rescale VAFs to CCFs

0 : non-mutated

1 : mutated

2 : CN loss-of-heterozygosity

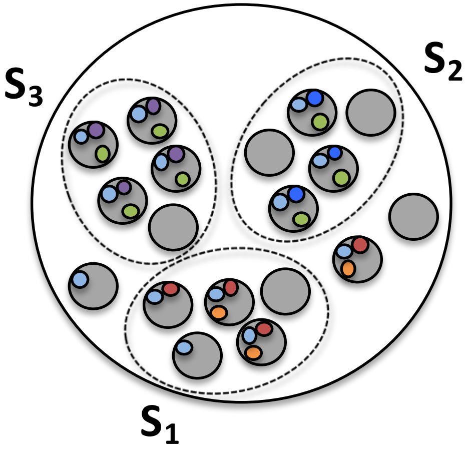
3 : amplification

… ….

Seq. method	Mixing	Inferring *T*
single-cell	no	two-state perfect phylogeny [Gusfield, 1991]
bulk	yes	TrAp [Strino *et al.*, 2013] Rec-BTP [Hajirasouliha *et al.*, 2014] PhyloSub [Jiao *et al.*, 2014] Clomial [Zare *et al.*, 2014] Binary ***F*** [Hajirasouliha *et al.*, 2014] CITUP [Malikic *et al.*, 2015] BitPhylogeny [Yuan *et al.*, 2015] LICHeE [Popic *et al.*, 2015] AncesTree [El-Kebir, Oesper *et al.*, 2015] …

Tumor Evolution as a Multi-State Phylogeny

Tumor snapshot



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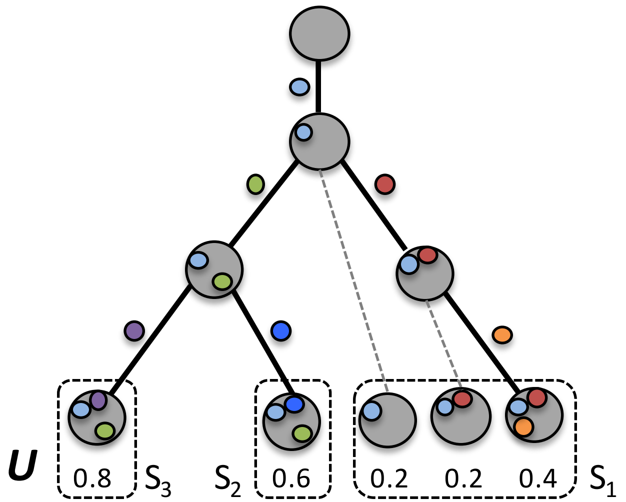
Two-State Perfect Phylogeny Tree ***T***



Given:

mutations

$$\text{VAFs } \boldsymbol{F} = \begin{array}{c|c} \begin{matrix} ● & ● & ● & ● & ● & ● \end{matrix} & \\ \hline \begin{bmatrix} 0.4 & 0.0 & 0.0 & 0.0 & 0.3 & 0.2 \\ 0.3 & 0.3 & 0.0 & 0.3 & 0.0 & 0.0 \\ 0.4 & 0.4 & 0.4 & 0.0 & 0.0 & 0.0 \end{bmatrix} & \begin{matrix} s_1 \\ s_2 \\ s_3 \end{matrix} \end{array} \text{ samples}$$

Find:

Two-state perfect phylogeny tree ***T***

Mixing proportions ***U***

States: more than > 2 states

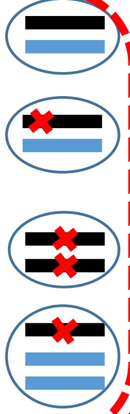
0 : non-mutated

1 : mutated

2 : CN loss-of-heterozygosity

3 : amplification

...



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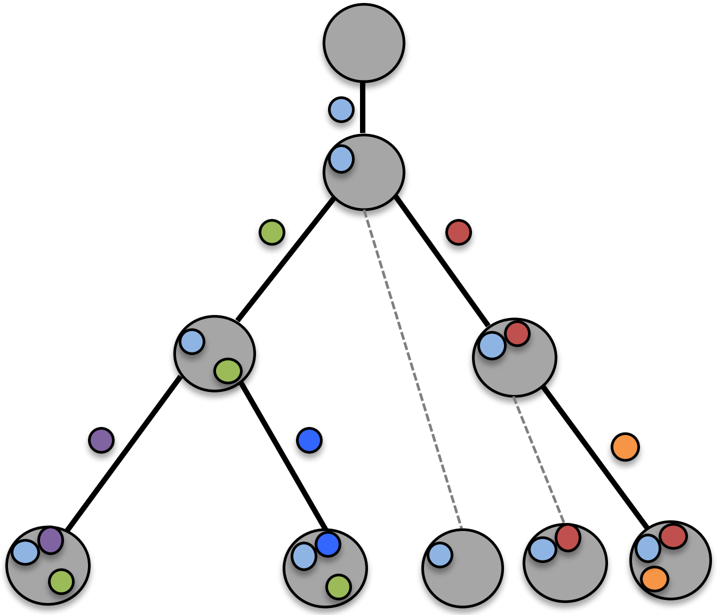
Outline

- Problem Statement
- Combinatorial Characterization of Solutions
- Application to Cancer Sequencing



Problem Statement

Two-State Perfect Phylogeny:

Infinite sites assumption: a character changes state once

n mutations

$$\boldsymbol{F} = \left(\begin{array}{cccccc} \bullet & \bullet & \bullet & \bullet & \bullet & \bullet \\ 0.8 & 0.8 & 0.8 & 0.0 & 0.0 & 0.0 \\ 0.6 & 0.6 & 0.0 & 0.6 & 0.0 & 0.0 \\ 0.8 & 0.0 & 0.0 & 0.0 & 0.6 & 0.4 \end{array}\right)$$

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Infinite sites assumption: a character changes state once

n mutations

$$\boldsymbol{F} = \begin{array}{c} \begin{array}{cccccc} ● & ● & ● & ● & ● & ● \end{array} \\ \begin{pmatrix} 0.8 & 0.8 & 0.8 & 0.0 & 0.0 & 0.0 \\ 0.6 & 0.6 & 0.0 & 0.6 & 0.0 & 0.0 \\ 0.8 & 0.0 & 0.0 & 0.0 & 0.6 & 0.4 \end{pmatrix} \end{array}$$

m samples

taxa

$$= \text{samples} \begin{array}{c} \begin{array}{cccccc} ◉ & ◉ & ◉ & ◉ & ◉ & ◉ \end{array} \\ \begin{pmatrix} 0.0 & 0.0 & 0.8 & 0.0 & 0.0 & 0.0 \\ 0.0 & 0.0 & 0.0 & 0.6 & 0.0 & 0.0 \\ 0.2 & 0.0 & 0.0 & 0.0 & 0.2 & 0.4 \end{pmatrix} \end{array}$$

Usage Matrix ***U***

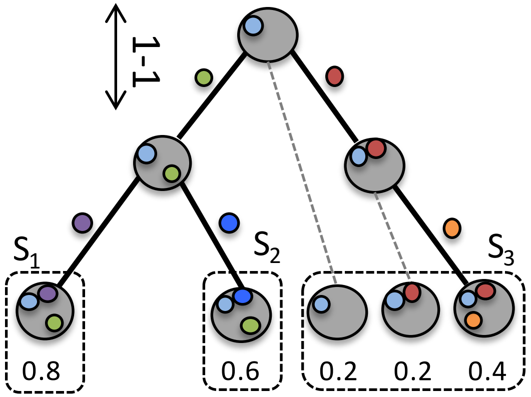
mutations

$$\begin{array}{c} \begin{array}{cccccc} ● & ● & ● & ● & ● & ● \end{array} \\ \begin{pmatrix} 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 0 & 0 \\ 1 & 1 & 1 & 0 & 0 & 0 \\ 1 & 1 & 0 & 1 & 0 & 0 \\ 1 & 0 & 0 & 0 & 1 & 0 \\ 1 & 0 & 0 & 0 & 1 & 1 \end{pmatrix} \end{array} \begin{array}{c} ◉ \\ ◉ \\ ◉ \\ ◉ \\ ◉ \\ ◉ \end{array} \text{taxa}$$

Complete Two-State Perfect Phylogeny ***B* / *T***

U=[u_{pj}] is a ***usage matrix*** iff

$$u_{pj} \geq 0 \text{ and } \sum_j u_{pj} \leq 1$$



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$$\boldsymbol{F} = \begin{pmatrix} 0.8 & 0.8 & 0.8 & 0.0 & 0.0 & 0.0 \\ 0.6 & 0.6 & 0.0 & 0.6 & 0.0 & 0.0 \\ 0.8 & 0.0 & 0.0 & 0.0 & 0.6 & 0.4 \end{pmatrix}$$

m samples

taxa

mutations

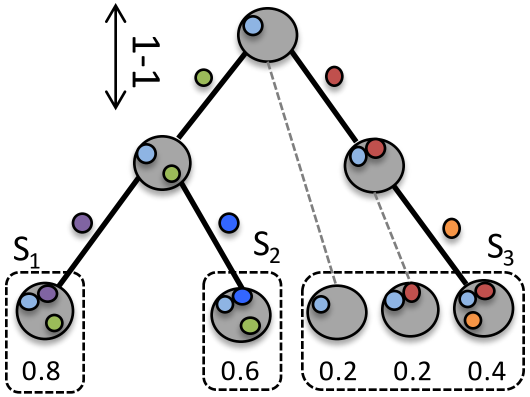
$$= \begin{pmatrix} 0.0 & 0.0 & 0.8 & 0.0 & 0.0 & 0.0 \\ 0.0 & 0.0 & 0.0 & 0.6 & 0.0 & 0.0 \\ 0.2 & 0.0 & 0.0 & 0.0 & 0.2 & 0.4 \end{pmatrix} \begin{pmatrix} 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 0 & 0 \\ 1 & 1 & 1 & 0 & 0 & 0 \\ 1 & 1 & 0 & 1 & 0 & 0 \\ 1 & 0 & 0 & 0 & 1 & 0 \\ 1 & 0 & 0 & 0 & 1 & 1 \end{pmatrix}$$

samples

taxa

Usage Matrix ***U***

Complete Two-State Perfect Phylogeny ***B* / *T***



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VAF Factorization Problem (VAFFP): [El-Kebir, Oesper et al., 2015]

Given ***F***, find ***U*** and ***B*** such that ***F* = *U B***

Problem Statement

Two-State Perfect Phylogeny:

Infinite sites assumption: a character changes state once

n mutations

$$\boldsymbol{F} = \begin{array}{c} \begin{array}{cccccc} ● & ● & ● & ● & ● & ● \end{array} \\ \begin{pmatrix} 0.8 & 0.8 & 0.8 & 0.0 & 0.0 & 0.0 \\ 0.6 & 0.6 & 0.0 & 0.6 & 0.0 & 0.0 \\ 0.8 & 0.0 & 0.0 & 0.0 & 0.6 & 0.4 \end{pmatrix} \end{array} \quad \boldsymbol{m} \text{ samples}$$

taxa

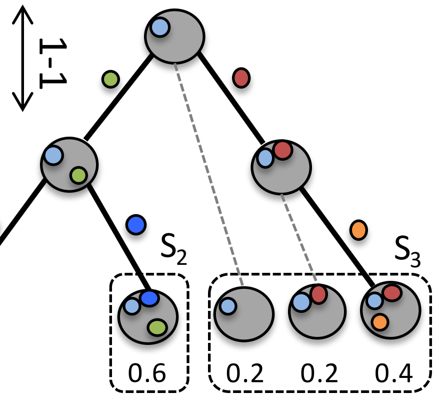
$$= \text{samples} \begin{array}{c} \begin{array}{cccccc} ● & ● & ● & ● & ● & ● \end{array} \\ \begin{pmatrix} 0.0 & 0.0 & 0.8 & 0.0 & 0.0 & 0.0 \\ 0.0 & 0.0 & 0.0 & 0.6 & 0.0 & 0.0 \\ 0.2 & 0.0 & 0.0 & 0.0 & 0.2 & 0.4 \end{pmatrix} \end{array}$$

Usage Matrix ***U***

mutations

$$\begin{array}{c} \begin{array}{cccccc} ● & ● & ● & ● & ● & ● \end{array} \\ \begin{pmatrix} 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 0 & 0 \\ 1 & 1 & 1 & 0 & 0 & 0 \\ 1 & 1 & 0 & 1 & 0 & 0 \\ 1 & 0 & 0 & 0 & 1 & 0 \\ 1 & 0 & 0 & 0 & 1 & 1 \end{pmatrix} \end{array} \begin{array}{c} ● \\ ● \\ ● \\ ● \\ ● \\ ● \end{array} \text{ taxa}$$

Complete Two-State Perfect Phylogeny ***B*** / ***T***



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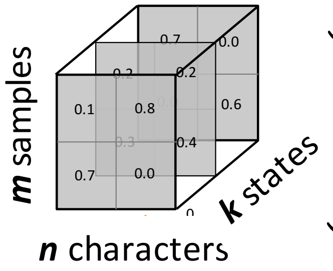
Multi-State Perfect Phylogeny:

Infinite alleles assumption: a character changes to a state once



Frequency Tensor ***F***

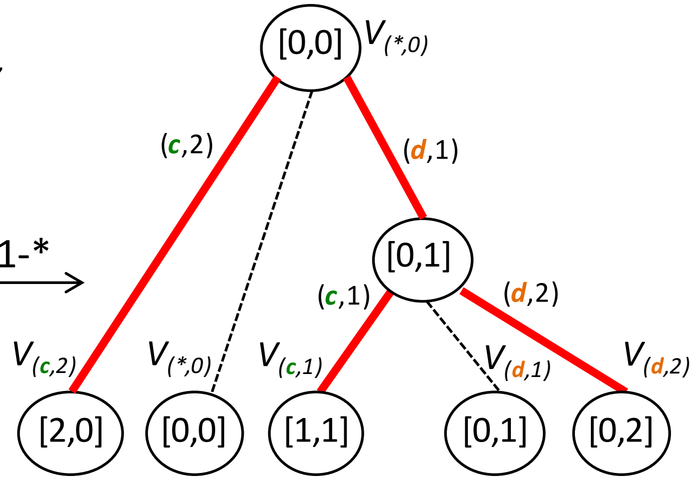
characters

$$\underbrace{\begin{pmatrix} 0.1 & 0.8 \\ 0.7 & 0.0 \end{pmatrix}}_{F_0} \text{ samples}$$

$$\underbrace{\begin{pmatrix} 0.2 & 0.2 \\ 0.3 & 0.4 \end{pmatrix}}_{F_1}$$

$$\underbrace{\begin{pmatrix} 0.7 & 0.0 \\ 0.0 & 0.6 \end{pmatrix}}_{F_2}$$

$$\underbrace{\begin{pmatrix} 1 & 1 \\ 0 & 0 \\ 0 & 1 \\ 1 & 0 \\ 1 & 0 \end{pmatrix}}_{A_0} \underbrace{\begin{pmatrix} 0 & 0 \\ 1 & 1 \\ 0 & 0 \\ 0 & 1 \\ 0 & 0 \end{pmatrix}}_{A_1} \underbrace{\begin{pmatrix} 0 & 0 \\ 0 & 0 \\ 1 & 0 \\ 0 & 0 \\ 0 & 1 \end{pmatrix}}_{A_2} \quad \overset{1\text{-}*}{\longleftrightarrow}$$



Complete Multi-State Perfect Phylogeny ***A*** / ***T***

Problem Statement

Two-State Perfect Phylogeny:

Infinite sites assumption: a character changes state once

n **mutations**

$$\boldsymbol{F} = \begin{pmatrix}0.8 & 0.8 & 0.8 & 0.0 & 0.0 & 0.0\\ 0.6 & 0.6 & 0.0 & 0.6 & 0.0 & 0.0\\ 0.8 & 0.0 & 0.0 & 0.0 & 0.6 & 0.4\end{pmatrix} \quad \textit{m} \text{ samples}$$

taxa

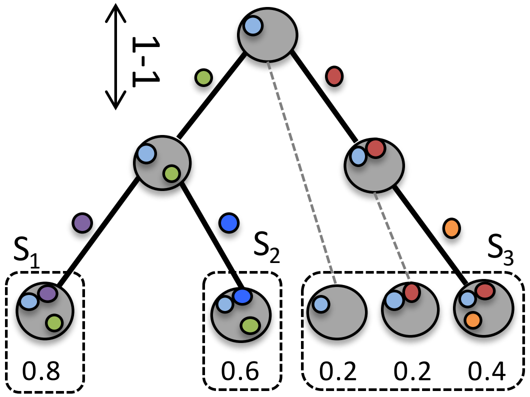
$$= \text{samples} \begin{pmatrix}0.0 & 0.0 & 0.8 & 0.0 & 0.0 & 0.0\\ 0.0 & 0.0 & 0.0 & 0.6 & 0.0 & 0.0\\ 0.2 & 0.0 & 0.0 & 0.0 & 0.2 & 0.4\end{pmatrix}$$

Usage Matrix ***U***

mutations

$$\begin{pmatrix}1 & 0 & 0 & 0 & 0 & 0\\ 1 & 1 & 0 & 0 & 0 & 0\\ 1 & 1 & 1 & 0 & 0 & 0\\ 1 & 1 & 0 & 1 & 0 & 0\\ 1 & 0 & 0 & 0 & 1 & 0\\ 1 & 0 & 0 & 0 & 1 & 1\end{pmatrix} \quad \text{taxa}$$

Complete Two-State Perfect Phylogeny ***B / T***



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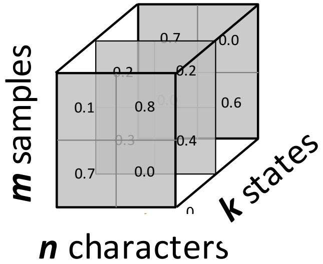


Frequency Tensor ***F***

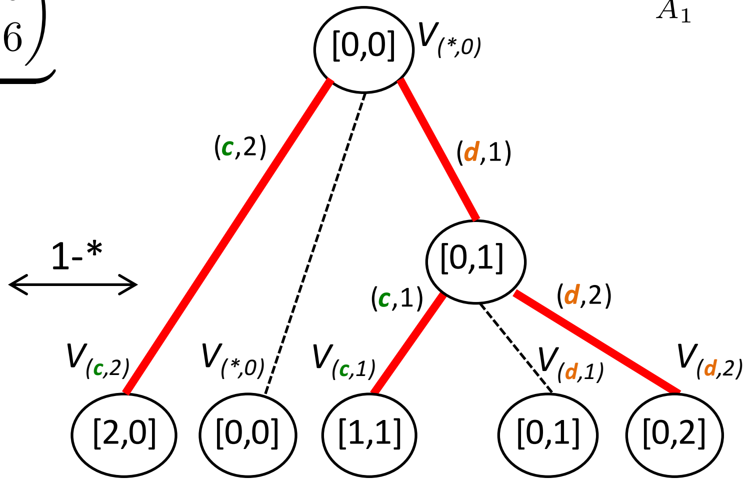
characters

$$\underbrace{\begin{pmatrix}0.1 & 0.8\\ 0.7 & 0.0\end{pmatrix}}_{F_0} \quad \text{samples}$$

$$\underbrace{\begin{pmatrix}0.2 & 0.2\\ 0.3 & 0.4\end{pmatrix}}_{F_1} = \underbrace{\begin{array}{ccccc} V_{(*,0)} & V_{(c,1)} & V_{(c,2)} & V_{(d,1)} & V_{(d,2)}\\ \end{array} \begin{pmatrix}0.1 & 0.2 & 0.7 & 0.0 & 0.0\\ 0.0 & 0.3 & 0.0 & 0.1 & 0.6\end{pmatrix}}_{\text{Usage Matrix } \boldsymbol{U}} \underbrace{\begin{pmatrix}0 & 0\\ 1 & 1\\ 0 & 0\\ 0 & 1\\ 0 & 0\end{pmatrix}}_{A_1}$$

$$\underbrace{\begin{pmatrix}0.7 & 0.0\\ 0.0 & 0.6\end{pmatrix}}_{F_2}$$

$$\underbrace{\begin{pmatrix}1 & 1\\ 0 & 0\\ 0 & 1\\ 1 & 0\\ 1 & 0\end{pmatrix}}_{A_0} \underbrace{\begin{pmatrix}0 & 0\\ 1 & 1\\ 0 & 0\\ 0 & 1\\ 0 & 0\end{pmatrix}}_{A_1} \underbrace{\begin{pmatrix}0 & 0\\ 0 & 0\\ 1 & 0\\ 0 & 0\\ 0 & 1\end{pmatrix}}_{A_2}$$



Complete Multi-State Perfect Phylogeny ***A / T***

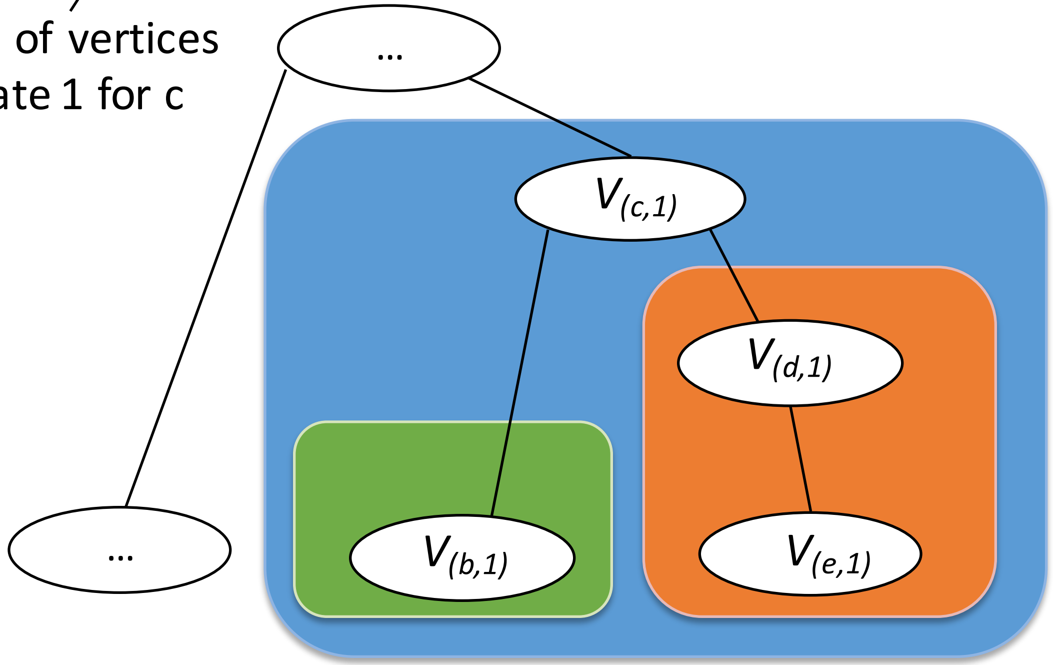
Perfect Phylogeny Mixture Deconvolution Problem (PPMDP)
[El-Kebir et al., 2016]: Given ***F***, find ***U*** and ***A***
such that ***F_i = U A_i*** for all states ***i***

Combinatorial Characterization

Two-State Perfect Phylogeny:

- A character changes state once
  - Once a mutation happens it persists
- Thus $T_{(c,1)} = \overline{T}_{(c,1)}$ subtree rooted at $V_{(c,1)}$

subtree of vertices with state 1 for c



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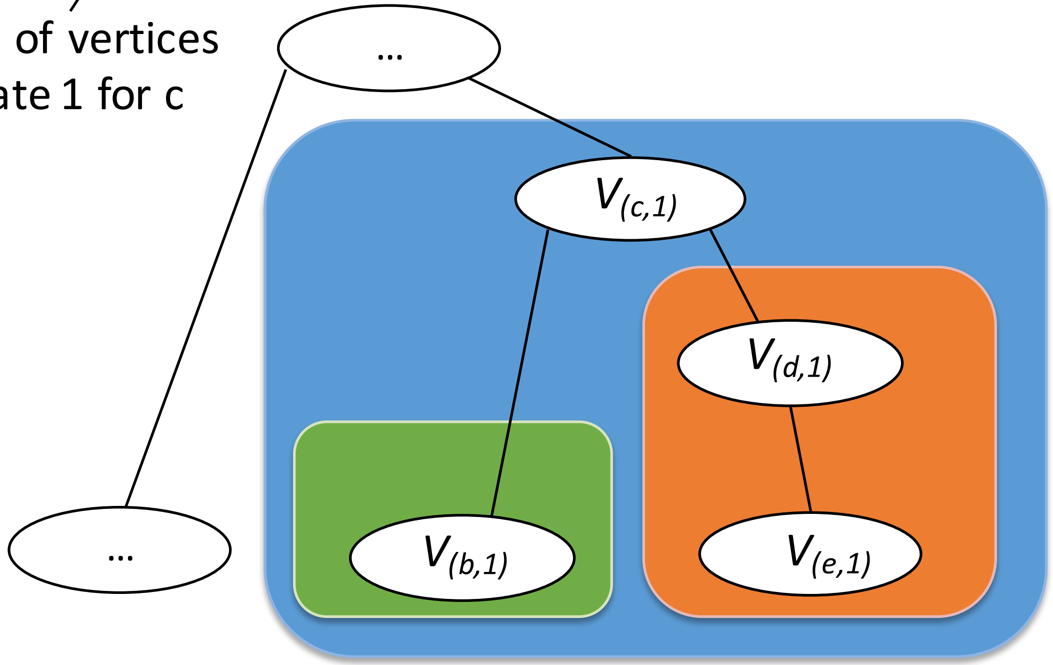

Sum Condition (SC)

$$f_{p,(c,1)} \geq \sum_{(d,1)\in\delta(c,1)} f_{p,(d,1)}$$

Combinatorial Characterization

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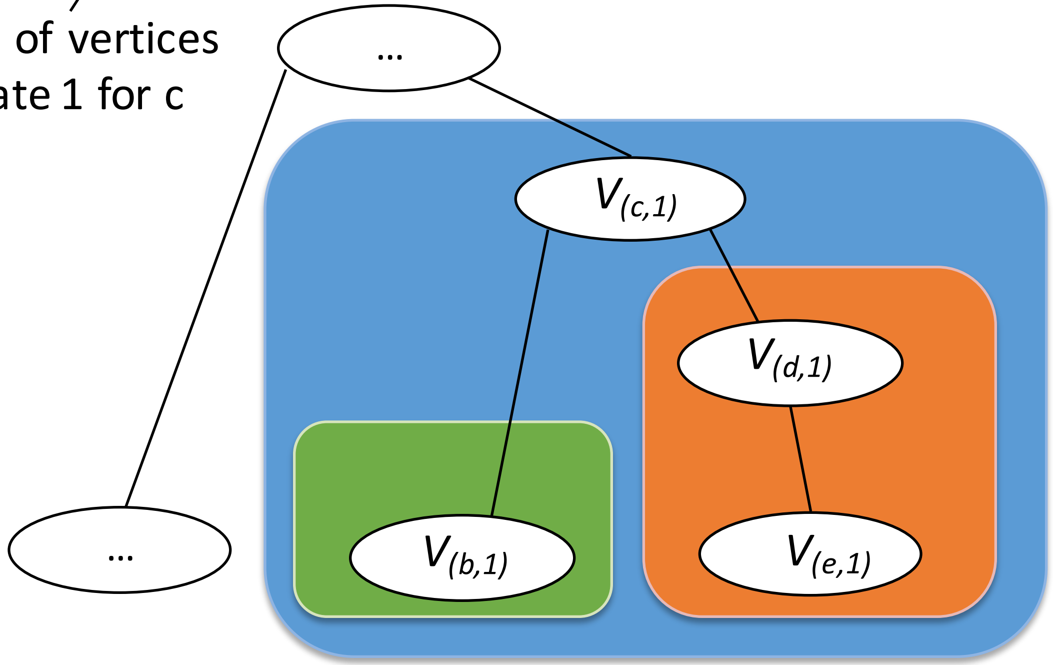

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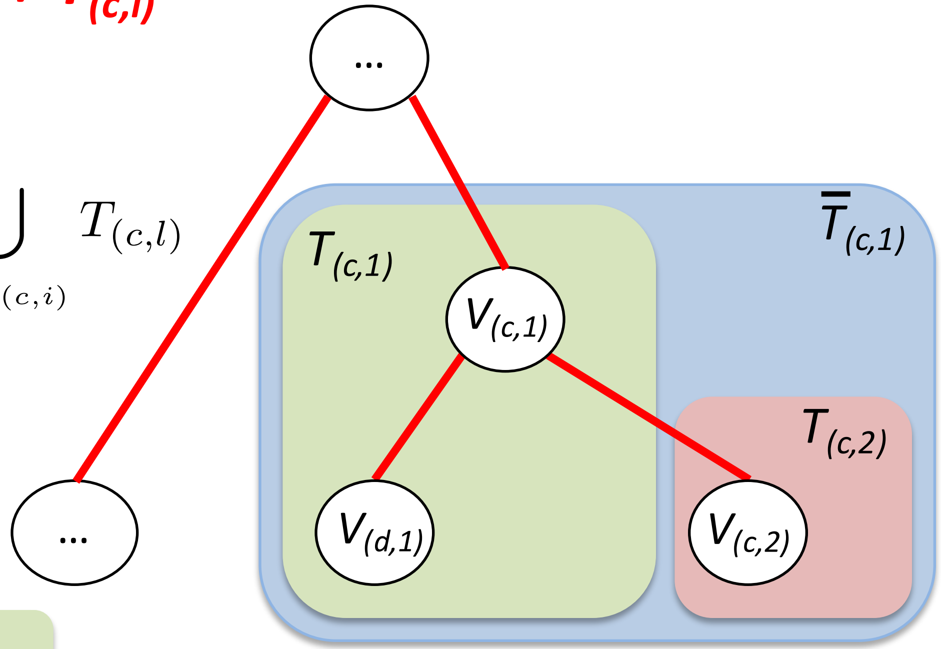
Multi-State Perfect Phylogeny:

- A character changes to a state once
- Thus, $T_{(c,i)} \neq \overline{T}_{(c,i)}$
- Instead:

$$\overline{T}_{(c,i)} = \bigcup_{l\in D_{(c,i)}} T_{(c,l)}$$



$\overline{T}_{(c,1)} \neq T_{(c,1)}$

$\overline{T}_{(c,1)} = T_{(c,1)} \cup T_{(c,2)}$

Descendant set

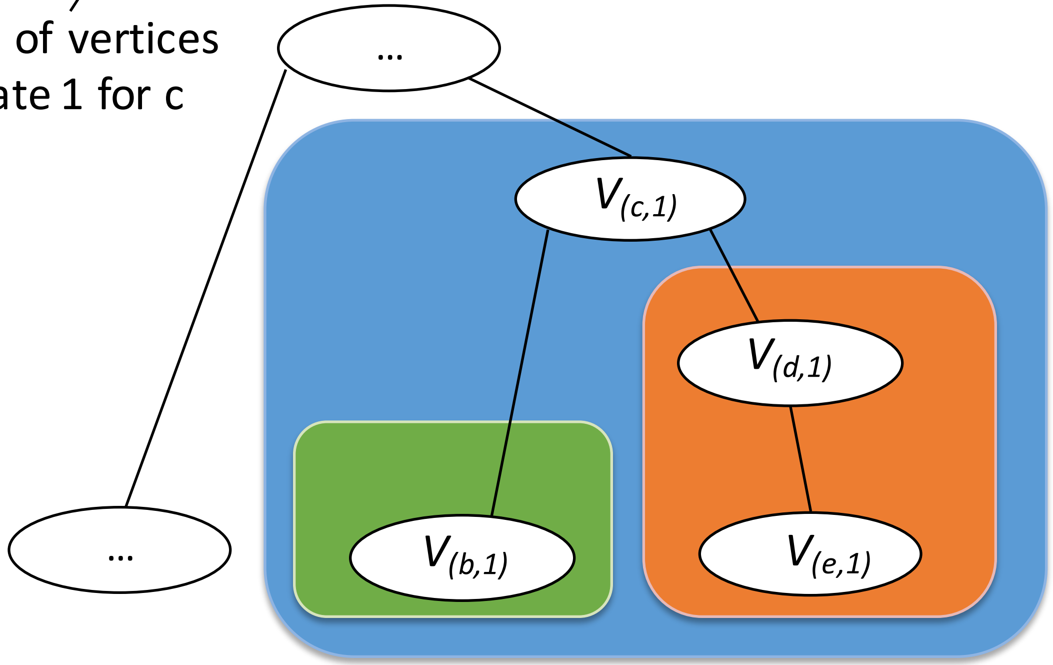
$D_{(c,1)} = \{1,2\}$

Combinatorial Characterization

Two-State Perfect Phylogeny:

- A character changes state once
  - Once a mutation happens it persists
- Thus $T_{(c,1)} = \overline{T}_{(c,1)}$ — subtree rooted at $V_{(c,1)}$

subtree of vertices with state 1 for c



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- Thus, $T_{(c,i)} \neq \overline{T}_{(c,i)}$
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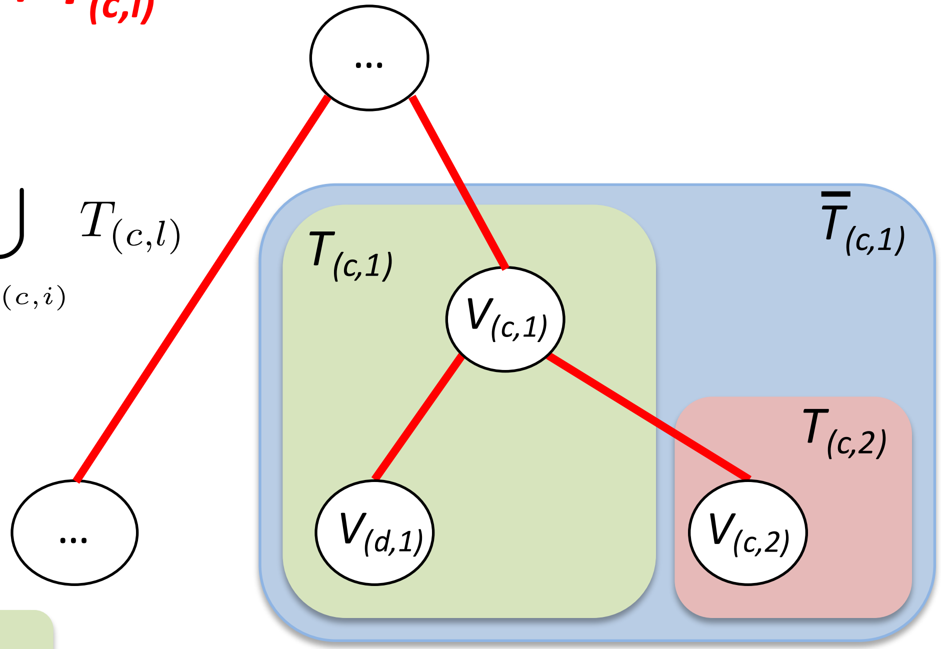

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$$\overline{T}_{(c,1)} = T_{(c,1)} \cup T_{(c,2)}$$

Descendant set

$D_{(c,1)} = \{1,2\}$

Multi-State Sum Condition (MSSC) [El-Kebir et al., 2016]

cumulative frequency

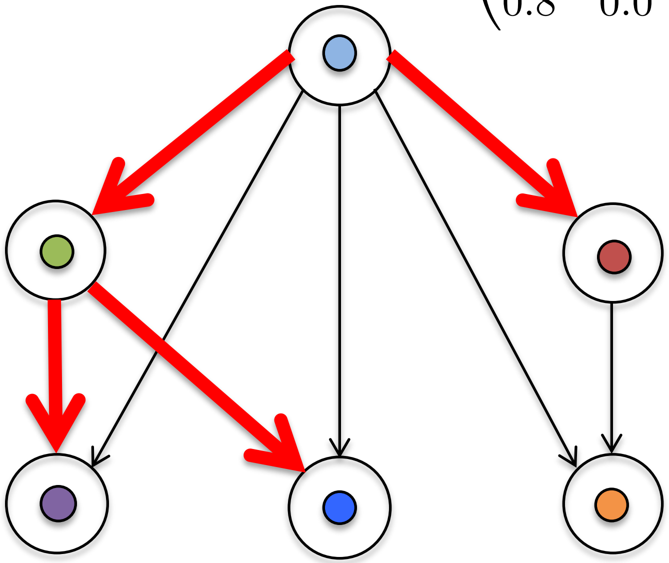
$$f_p^+(D_{(c,i)}) \geq \sum_{(d,j)\in\delta(c,i)} f_p^+(D_{(d,j)})$$

Spanning Trees in Ancestry Graph

Two-State Perfect Phylogeny:

mutations

$$\begin{array}{c c} \begin{array}{cccccc} ● & ● & ● & ● & ● & ● \end{array} & \\ \begin{pmatrix} 0.8 & 0.8 & 0.8 & 0.0 & 0.0 & 0.0 \\ 0.6 & 0.6 & 0.0 & 0.6 & 0.0 & 0.0 \\ 0.8 & 0.0 & 0.0 & 0.0 & 0.6 & 0.4 \end{pmatrix} & \text{samples} \end{array}$$



- Simple directed graph (DAG)
- Vertices are characters
- Edges are potential ancestral relationships

Theorem 1 [El-Kebir, Oesper et al., 2015; Popic et al., 2015]
Solutions are spanning trees that satisfy (SC)

Theorem 2 [El-Kebir, Oesper et al., 2015]
VAFFP is NP-complete for $m = O(n)$

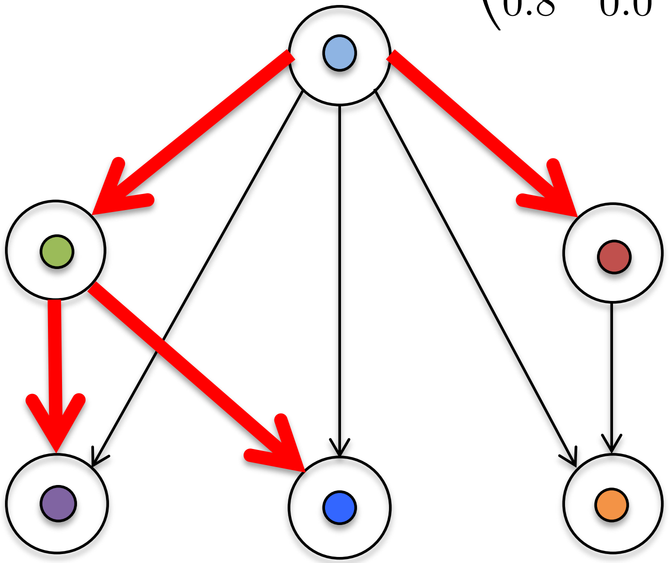
Spanning Trees in Ancestry Graph

Two-State Perfect Phylogeny:

mutations

$$\begin{array}{c} \\ \text{samples} \end{array} \begin{array}{cccccc} \bullet & \bullet & \bullet & \bullet & \bullet & \bullet \\ \end{array}$$

$$\begin{pmatrix} 0.8 & 0.8 & 0.8 & 0.0 & 0.0 & 0.0 \\ 0.6 & 0.6 & 0.0 & 0.6 & 0.0 & 0.0 \\ 0.8 & 0.0 & 0.0 & 0.0 & 0.6 & 0.4 \end{pmatrix} \text{samples}$$



- Simple directed graph (DAG)
- Vertices are characters
- Edges are potential ancestral relationships

Theorem 1 [El-Kebir, Oesper et al., 2015; Popic et al., 2015]
Solutions are spanning trees that satisfy (SC)

Theorem 2 [El-Kebir, Oesper et al., 2015]
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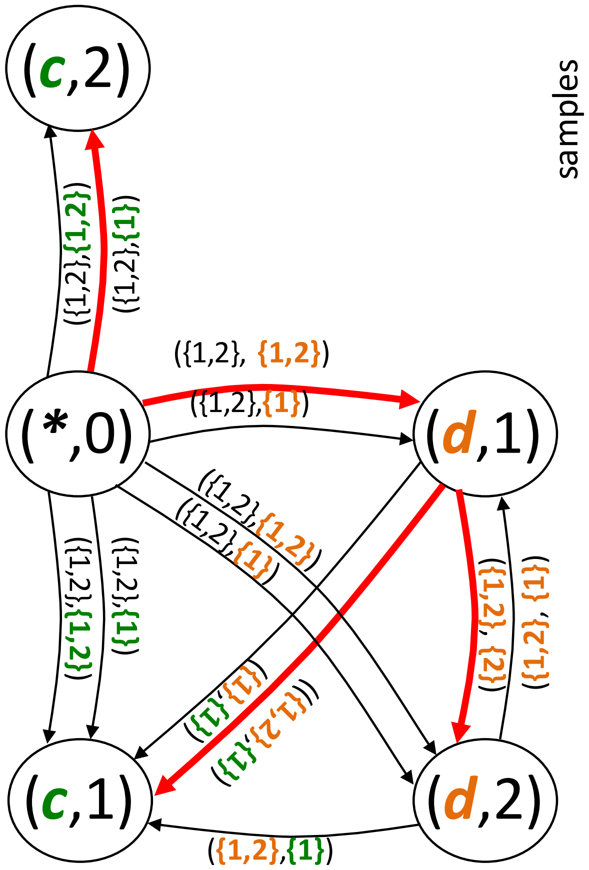
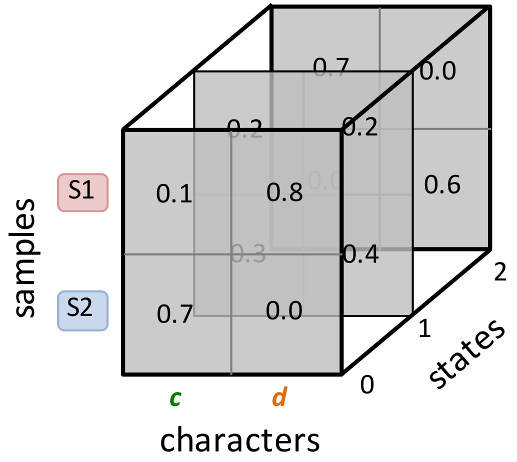
Multi-State Perfect Phylogeny:





- Directed multi-graph
- Vertices are character-state pairs
- Edges are labeled by valid descendant set pairs

Theorem 1 [El-Kebir et al., 2016]
Solutions are *threaded* spanning trees satisfying (MSSC)

Theorem 2 [El-Kebir et al., 2016]
PPMDP is NP-complete even for *m* = 2 and *k* = 2

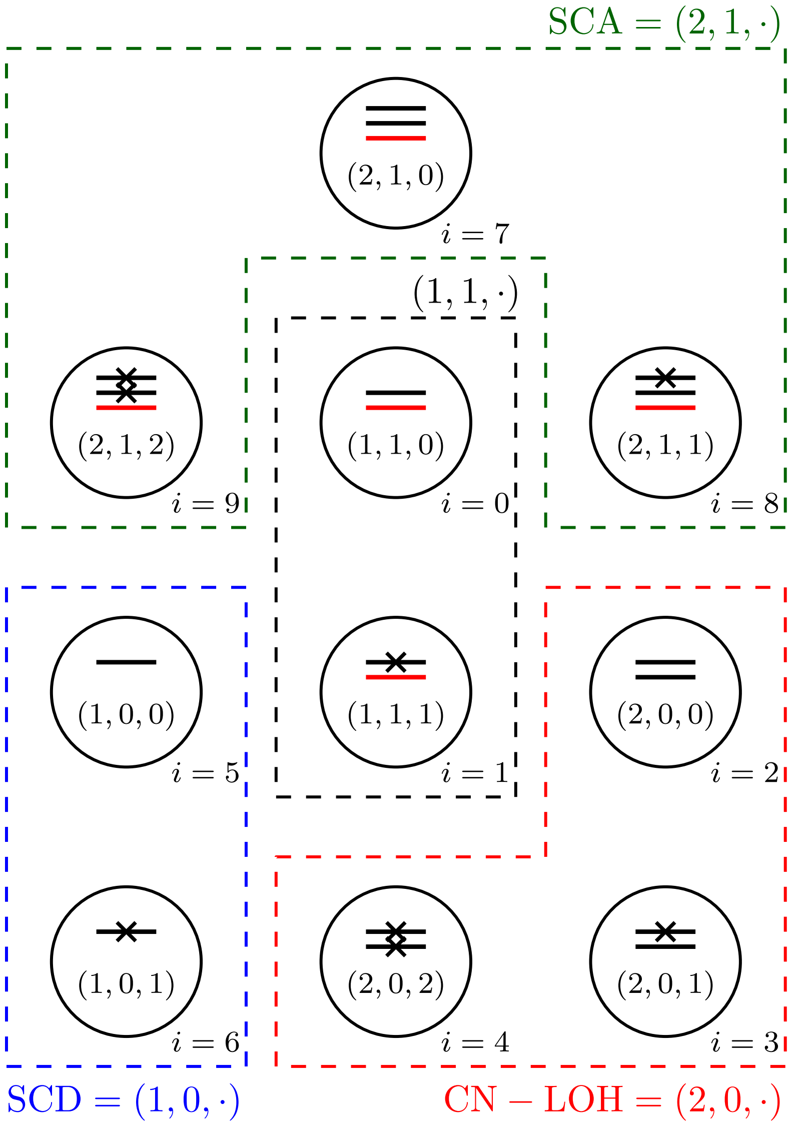
Application to Cancer Sequencing

Input

- Read-depth ratio
- B-allele frequencies
- Variant allele frequencies

Model

- Character is a genomic position (SNV)
- State is a triple (*x, y, z*) where
  - *x* is # maternal copies
  - *y* is # paternal copies
  - *z* is # mutated copies
- Cladistic characters



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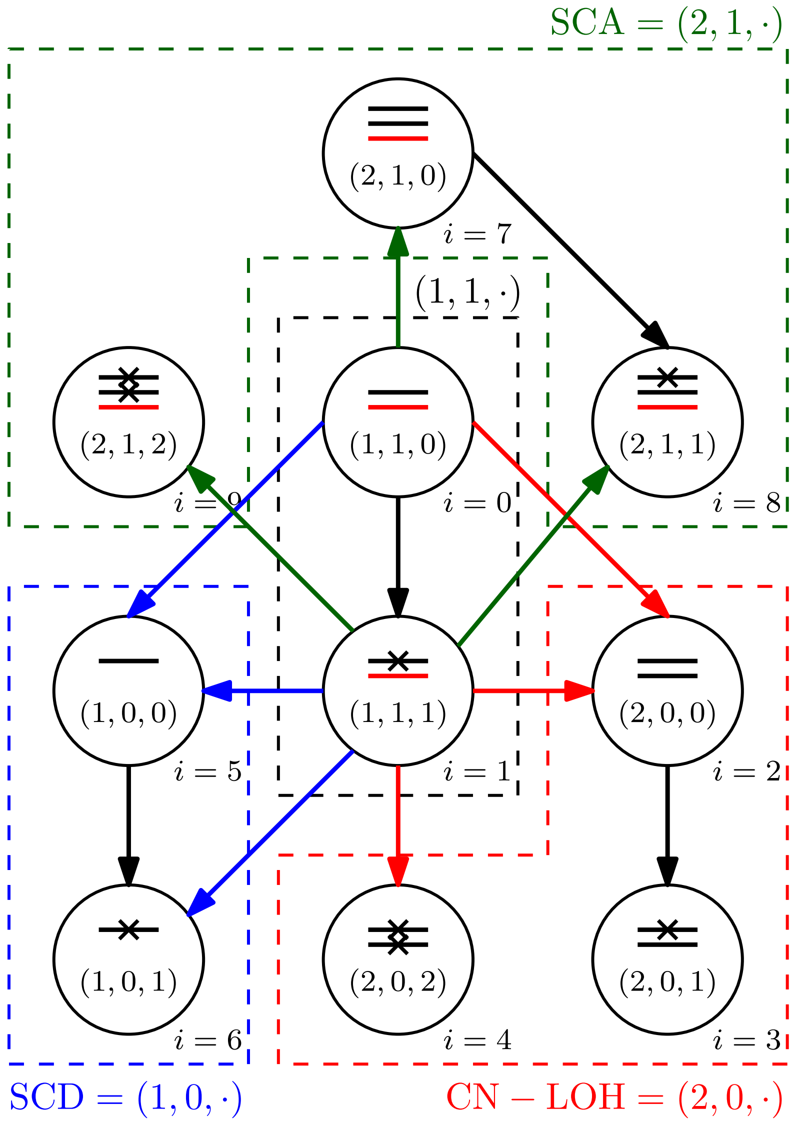

Application to Cancer Sequencing

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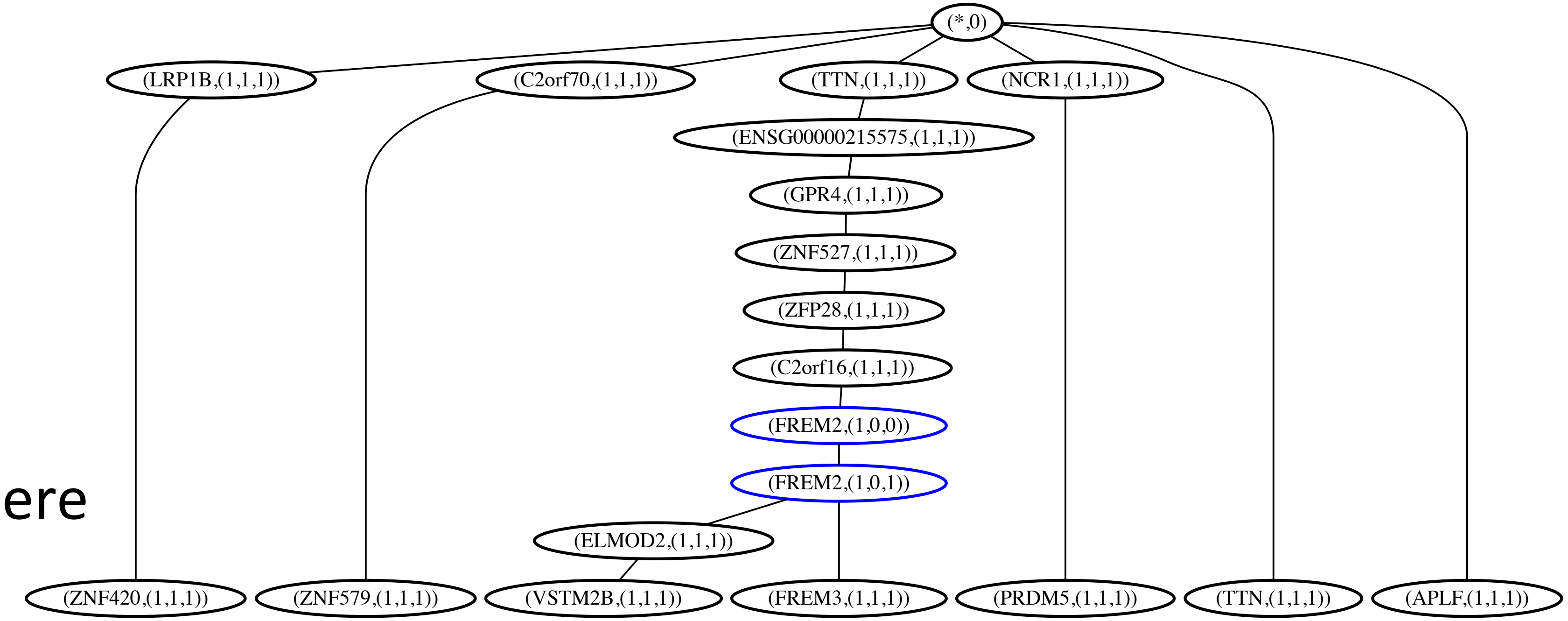


Conclusions

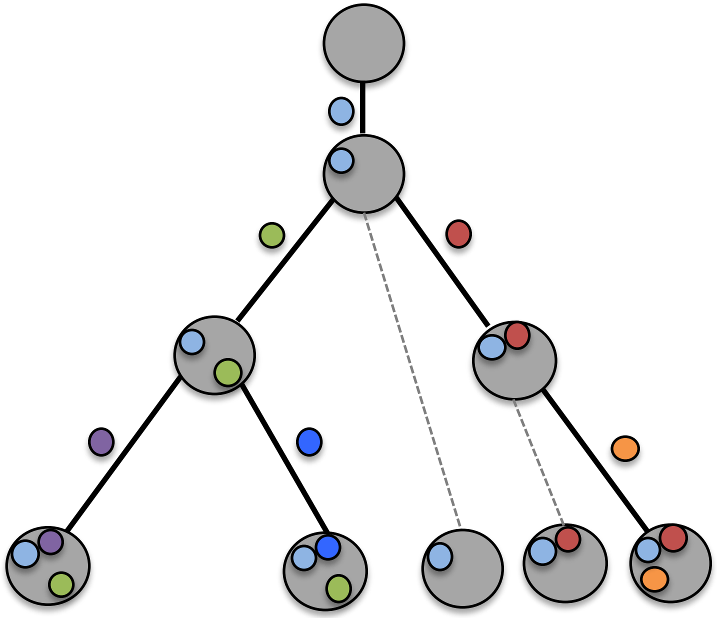
- Generalization of infinite sites model for SNVs is infinite alleles model for SNVs + CNAs

- Introduced Perfect Phylogeny Mixture Deconvolution Problem (PPMDP) for multi-state characters

- Combinatorial characterization of solutions

- PPMDP is NP-complete for *k* = 2 and *m* = 2

- Application to cancer sequencing
  - Metagenomics, somatic hypermutations, mtDNA, …



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Preprint will be available soon on arXiv