SPhyR: Tumor Phylogeny Estimation from Single-Cell Sequencing Data under Loss and Error

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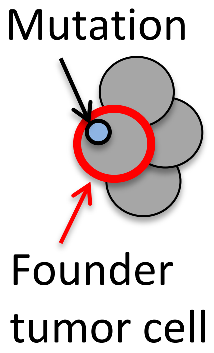
Tumorigenesis: (i) Cell Mutation

Clonal Evolution Theory of Cancer

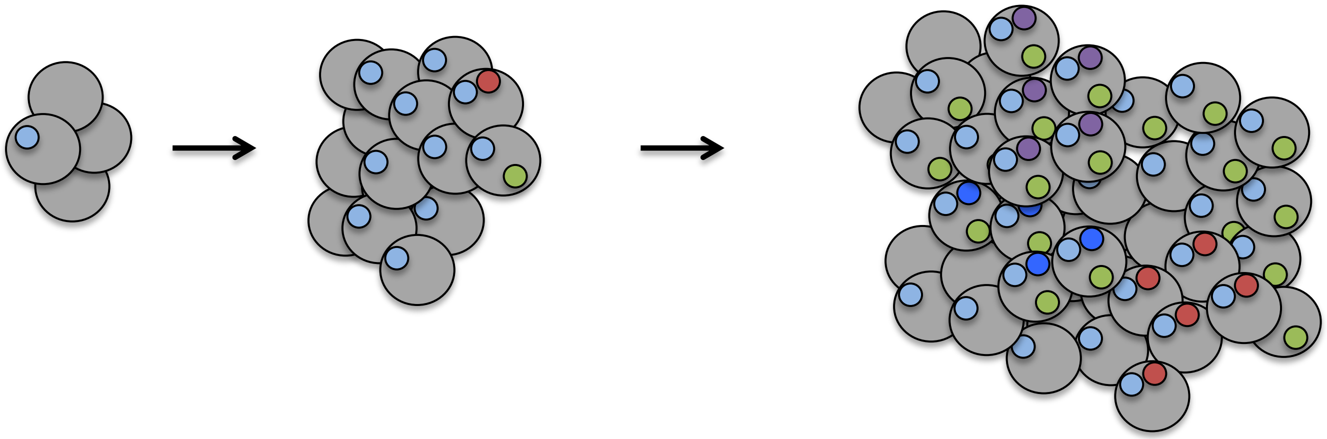
[Nowell, 1976]



Tumorigenesis: (i) Cell Mutation & (ii) Cell Division

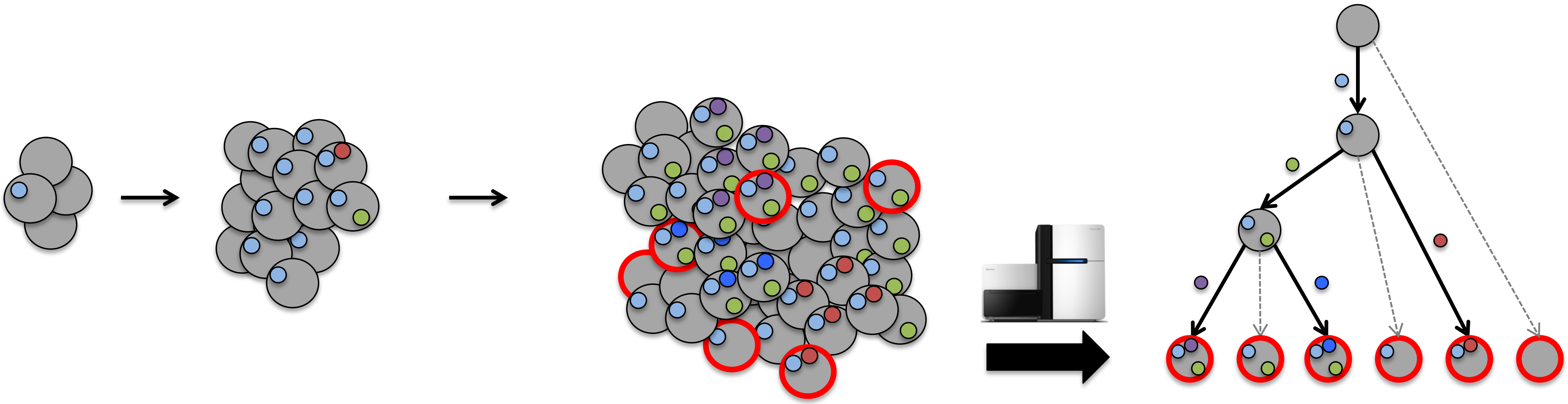
Clonal Evolution Theory of Cancer

[Nowell, 1976]



Heterogeneous Tumor

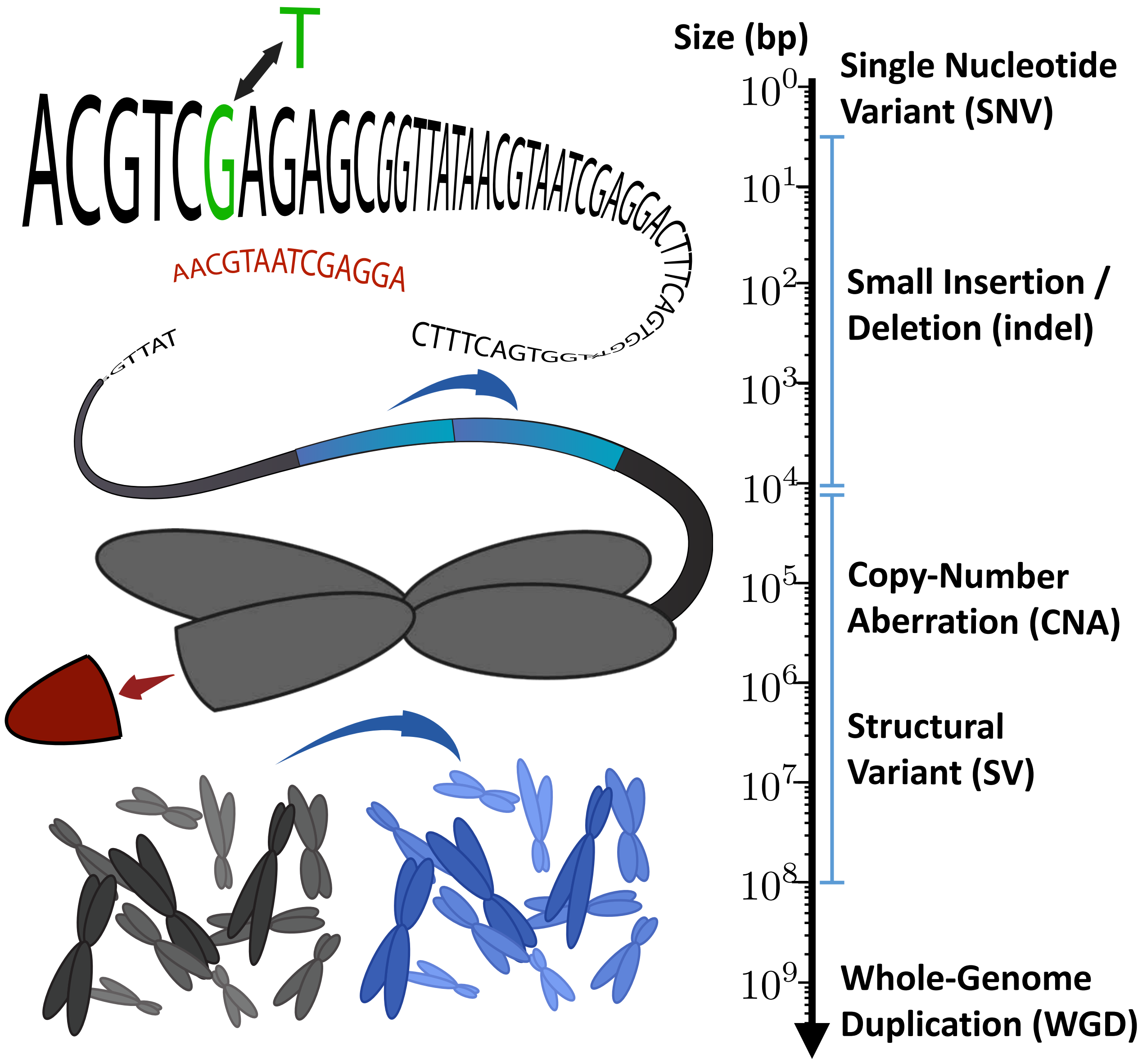
Tumorigenesis: (i) Cell Mutation & (ii) Cell Division



Goal: Given single-cell DNA sequencing data, find phylogenetic tree ***T***

Requirement: Evolutionary model

Somatic Mutations Occur at Different Genomic Scales



Size (bp)

Single Nucleotide Variant (SNV)

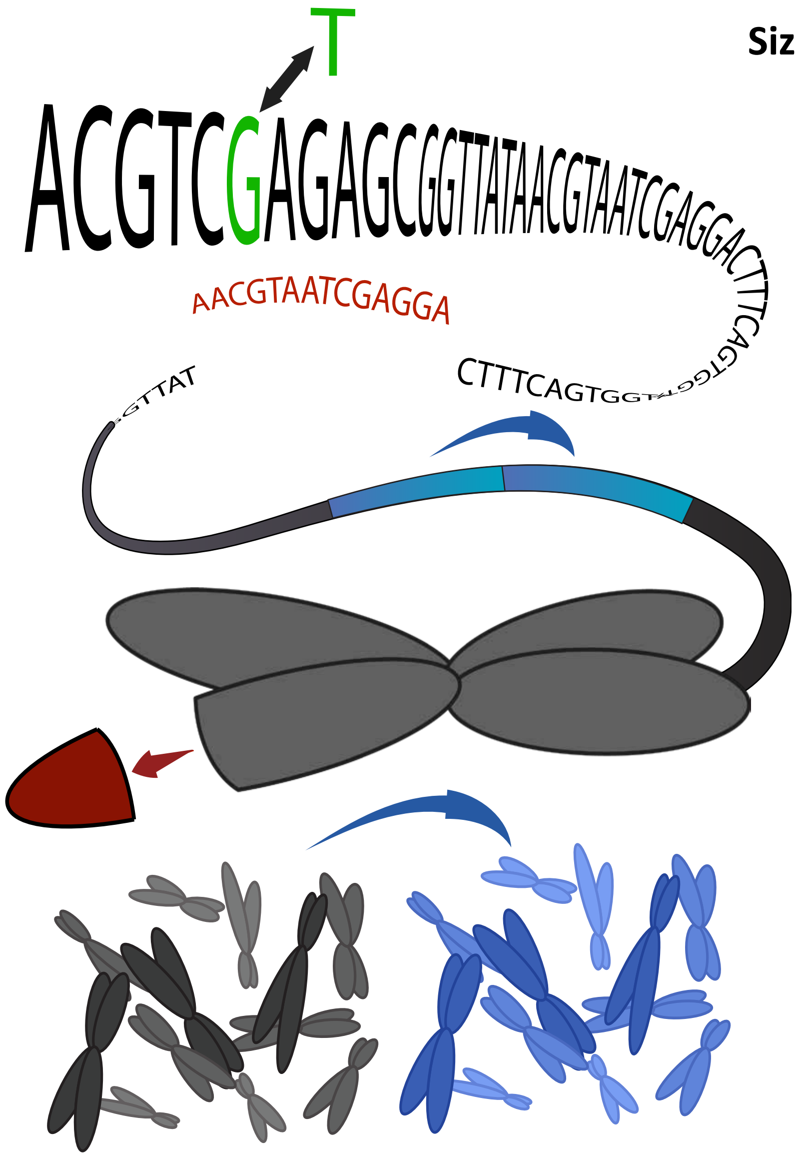
Small Insertion / Deletion (indel)

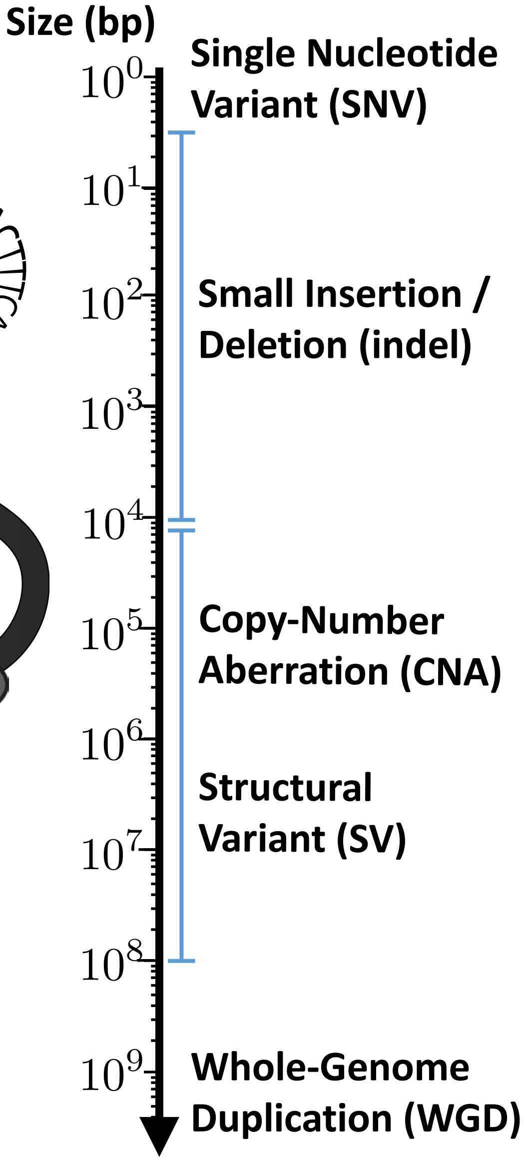
Copy-Number Aberration (CNA)

Structural Variant (SV)

Whole-Genome Duplication (WGD)

Infinite Sites Assumption is too Restrictive for SNVs





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Single Nucleotide Variant (SNV)

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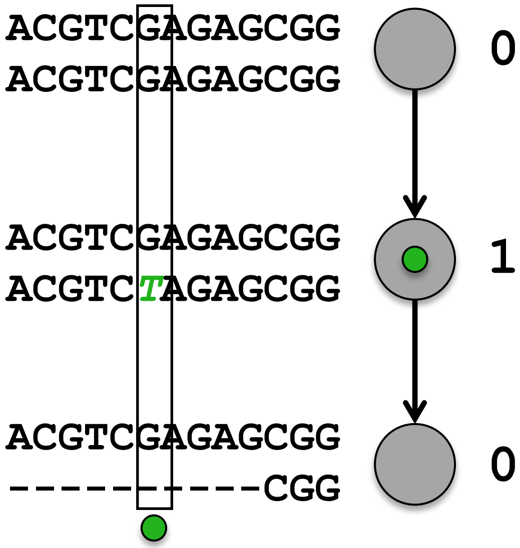
SNVs can be **lost** due to CNAs



Infinite sites assumption:

- No parallel evolution of SNVs
- No loss of SNVs
- SCITE [Jahn et al. 2016]
- OncoNEM [Ross and Markowetz, 2016]

Outline

- Perfect data (error free)
  - Problem statement
  - Combinatorial characterization of solutions
  - Exact algorithm
  - Results

- Real data (with errors)
  - Problem statement
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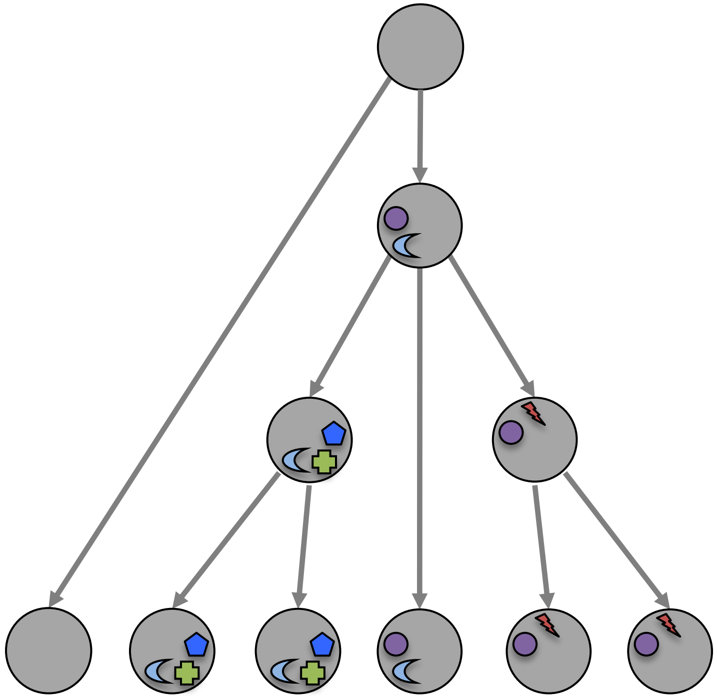
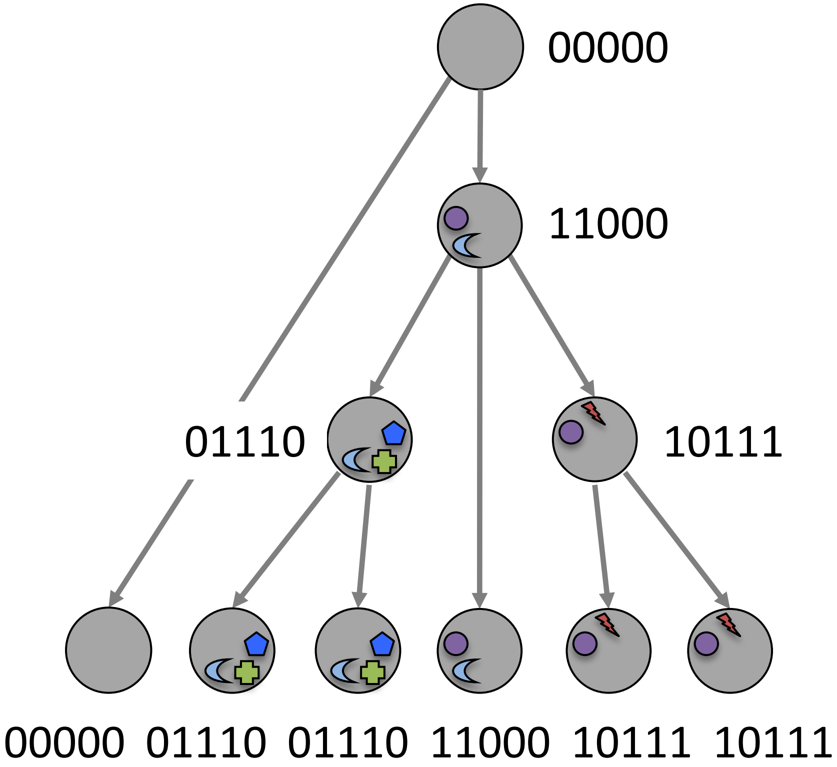
- Conclusions



k-Dollo Phylogeny (*k*-DP) Problem

Definition 1. A *k-Dollo phylogeny* T is a rooted, node-labeled tree subject to the following conditions.

1. Each node v of T is labeled by a vector $\mathbf{b}_v \in \{0,1\}^n$.
2. The root r of T is labeled by vector $\mathbf{b}_r = [0,\ldots,0]^T$.



k-Dollo Phylogeny (k-DP) Problem

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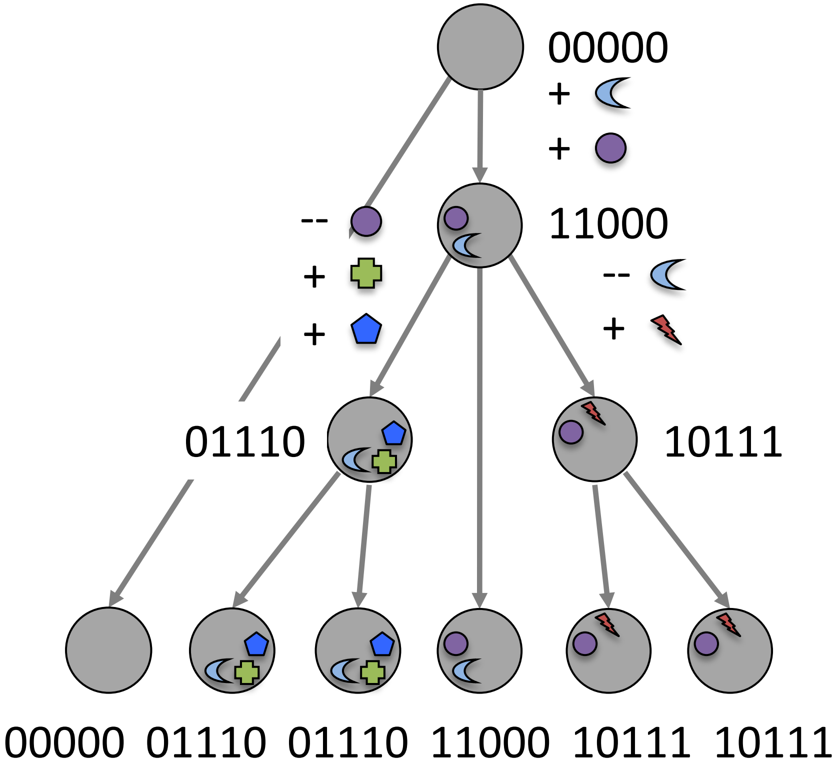
1. Each node v of T is labeled by a vector $\mathbf{b}_v \in \{0,1\}^n$.
2. The root r of T is labeled by vector $\mathbf{b}_r = [0,\ldots,0]^T$.
3. For each character $c \in [n]$, there is exactly one *gain edge* (v,w) in T such that $b_{v,c} = 0$ and $b_{w,c} = 1$.
4. For each character $c \in [n]$, there are at most k *loss edges* (v,w) in T such that $b_{v,c} = 1$ and $b_{w,c} = 0$.



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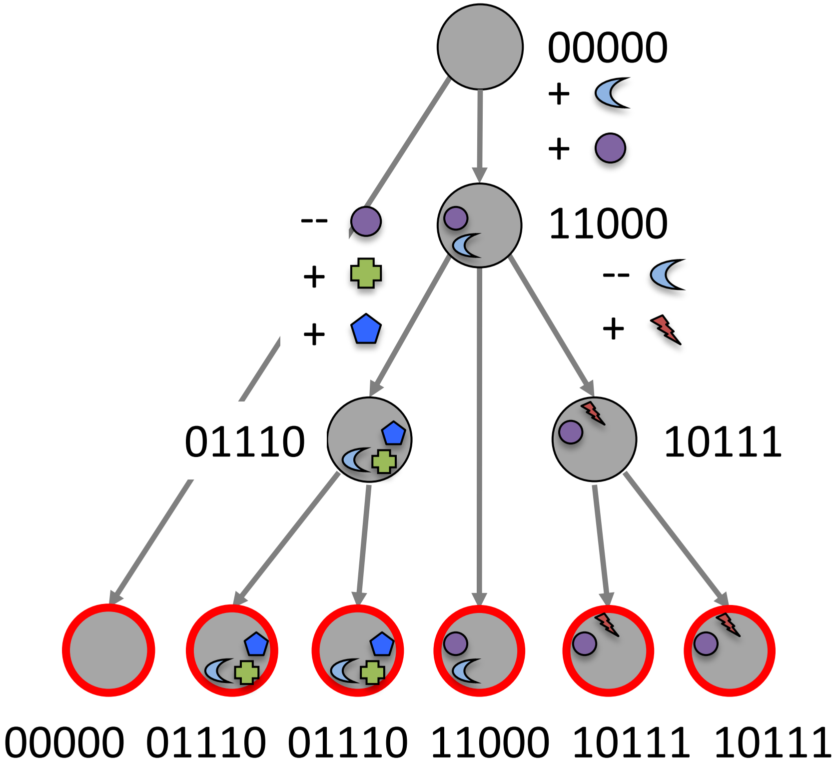
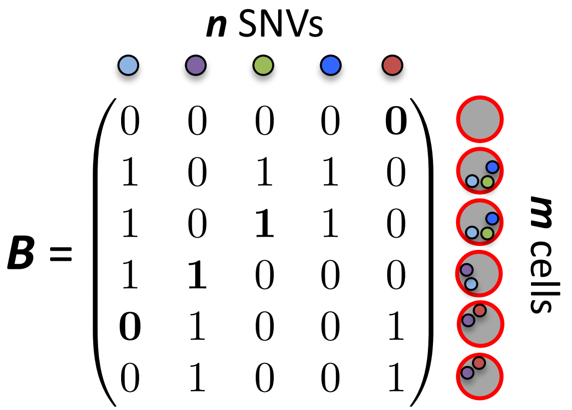


k-Dollo Phylogeny problem (k-DP). Given a binary matrix $B \in \{0,1\}^{m \times n}$ and parameter $k \in \mathbb{N}$, determine whether there exists a k-Dollo phylogeny for B, and if so construct one.

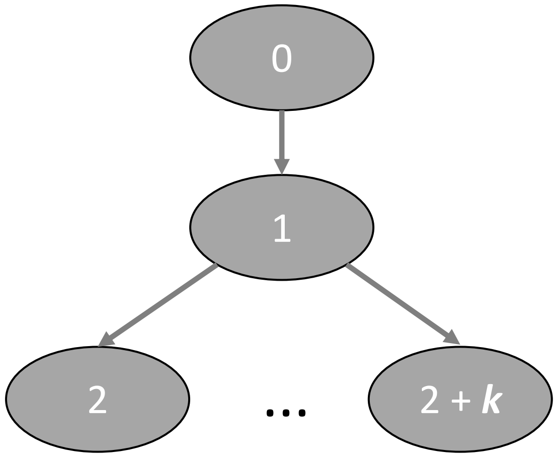


$$\boldsymbol{B} = \begin{pmatrix} 0 & 0 & 0 & 0 & \mathbf{0} \\ 1 & 0 & 1 & 1 & 0 \\ 1 & 0 & \mathbf{1} & 1 & 0 \\ 1 & \mathbf{1} & 0 & 0 & 0 \\ \mathbf{0} & 1 & 0 & 0 & 1 \\ 0 & 1 & 0 & 0 & 1 \end{pmatrix}$$

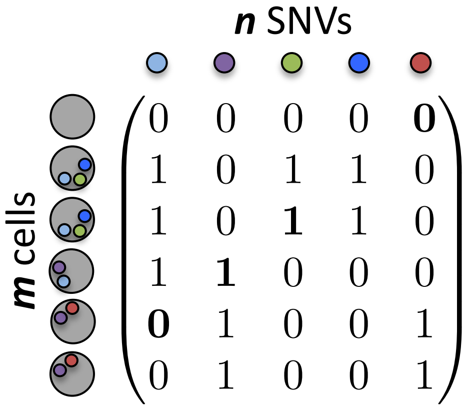
Combinatorial Characterization of *k*-DP

Theorem 3. Let $B \in \{0,1\}^{m \times n}$. The following statements are equivalent.

1. There exists a k-Dollo phylogeny T for B.
2. There exists a k-Dollo completion A of B.
3. There exists a k-completion A of B, and perfect phylogeny T for A whose characters are consistent with $S[k]$.

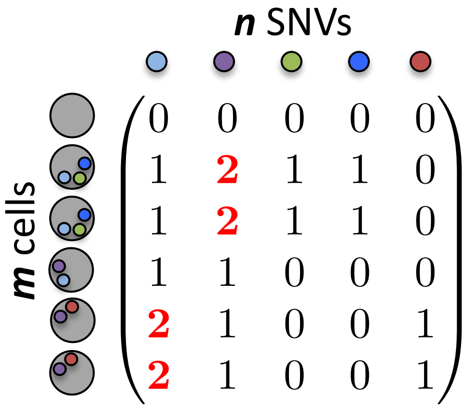


***k*-Dollo State Tree *S*[*k*]**



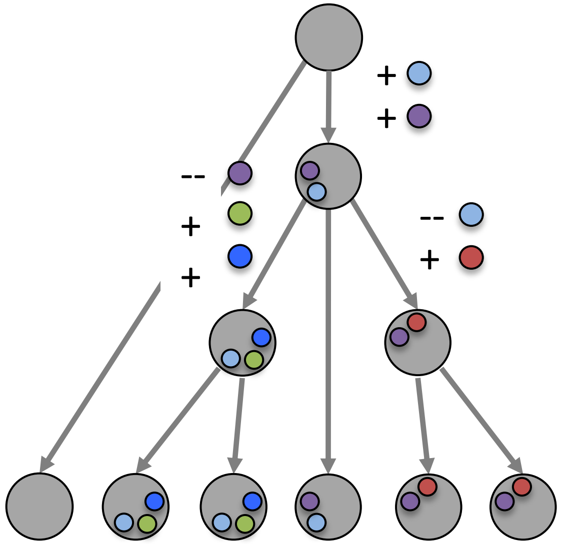
$$\begin{pmatrix} 0 & 0 & 0 & 0 & \mathbf{0} \\ 1 & 0 & 1 & 1 & 0 \\ 1 & 0 & \mathbf{1} & 1 & 0 \\ 1 & \mathbf{1} & 0 & 0 & 0 \\ \mathbf{0} & 1 & 0 & 0 & 1 \\ 0 & 1 & 0 & 0 & 1 \end{pmatrix}$$

Input Matrix ***B***



$$\begin{pmatrix} 0 & 0 & 0 & 0 & 0 \\ 1 & \mathbf{2} & 1 & 1 & 0 \\ 1 & \mathbf{2} & 1 & 1 & 0 \\ 1 & 1 & 0 & 0 & 0 \\ \mathbf{2} & 1 & 0 & 0 & 1 \\ \mathbf{2} & 1 & 0 & 0 & 1 \end{pmatrix}$$

k*-Dollo Completion *A



k*-Dollo Phylogeny *T

Forbidden Submatrices in Solutions ***A*** to ***k***-DP

$$\begin{pmatrix}1 & 0\\0 & 1\\1 & 1\end{pmatrix}$$

k **= 0**

$$\begin{pmatrix}1 & 0\\0 & 1\\1 & 1\end{pmatrix}\quad\begin{pmatrix}1 & 0\\0 & 1\\1 & 2\end{pmatrix}\quad\begin{pmatrix}1 & 0\\0 & 2\\1 & 1\end{pmatrix}\quad\begin{pmatrix}1 & 0\\0 & 2\\1 & 2\end{pmatrix}\quad\begin{pmatrix}1 & 0\\0 & 1\\2 & 1\end{pmatrix}\quad\begin{pmatrix}1 & 0\\0 & 1\\2 & 2\end{pmatrix}\quad\begin{pmatrix}1 & 0\\0 & 2\\2 & 1\end{pmatrix}\quad\begin{pmatrix}1 & 0\\0 & 2\\2 & 2\end{pmatrix}$$

$$\begin{pmatrix}2 & 0\\0 & 1\\1 & 1\end{pmatrix}\quad\begin{pmatrix}2 & 0\\0 & 1\\1 & 2\end{pmatrix}\quad\begin{pmatrix}2 & 0\\0 & 2\\1 & 1\end{pmatrix}\quad\begin{pmatrix}2 & 0\\0 & 2\\1 & 2\end{pmatrix}\quad\begin{pmatrix}2 & 0\\0 & 1\\2 & 1\end{pmatrix}\quad\begin{pmatrix}2 & 0\\0 & 1\\2 & 2\end{pmatrix}\quad\begin{pmatrix}2 & 0\\0 & 2\\2 & 1\end{pmatrix}\quad\begin{pmatrix}2 & 0\\0 & 2\\2 & 2\end{pmatrix}$$

$$\begin{pmatrix}1 & 1\\0 & 2\\1 & 2\end{pmatrix}\quad\begin{pmatrix}1 & 1\\0 & 2\\2 & 2\end{pmatrix}\quad\begin{pmatrix}2 & 1\\0 & 2\\1 & 2\end{pmatrix}\quad\begin{pmatrix}2 & 1\\0 & 2\\2 & 2\end{pmatrix}\quad\begin{pmatrix}2 & 0\\1 & 1\\2 & 1\end{pmatrix}\quad\begin{pmatrix}2 & 0\\1 & 1\\2 & 2\end{pmatrix}\quad\begin{pmatrix}2 & 0\\1 & 2\\2 & 1\end{pmatrix}\quad\begin{pmatrix}2 & 0\\1 & 2\\2 & 2\end{pmatrix}$$

$$\begin{pmatrix}2 & 1\\1 & 2\\2 & 2\end{pmatrix}$$

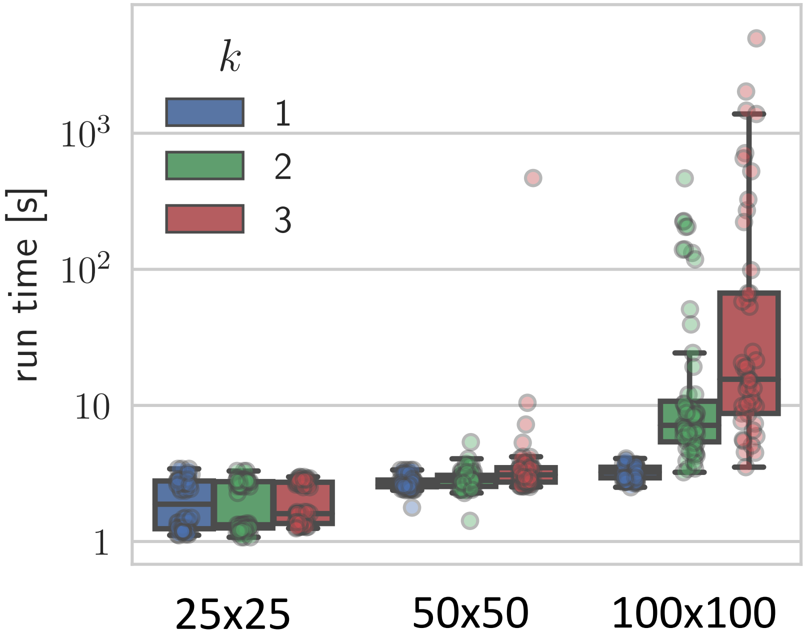
k **= 1**

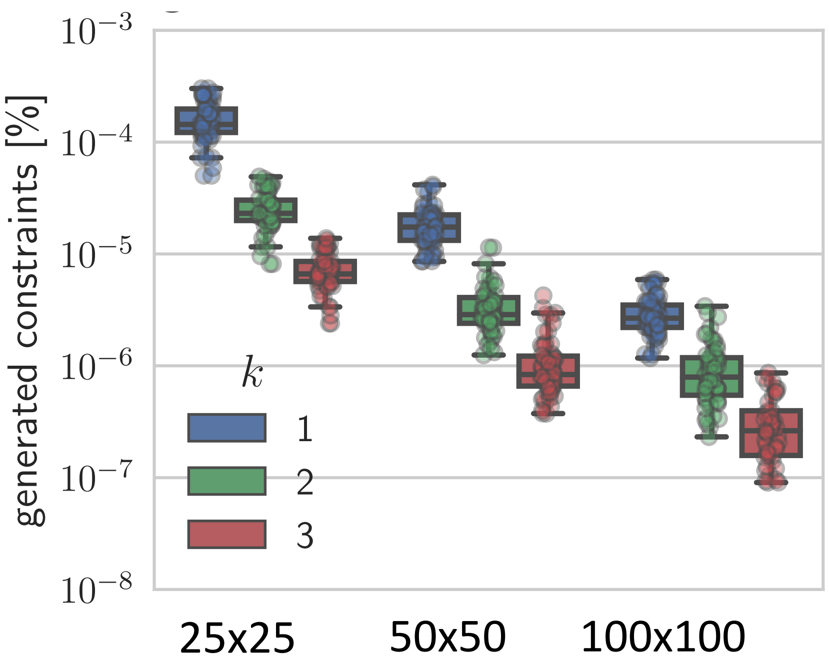
Number of forbidden submatrices is $4k^4 + 8k^3 + 8k^2 + 4k + 1$

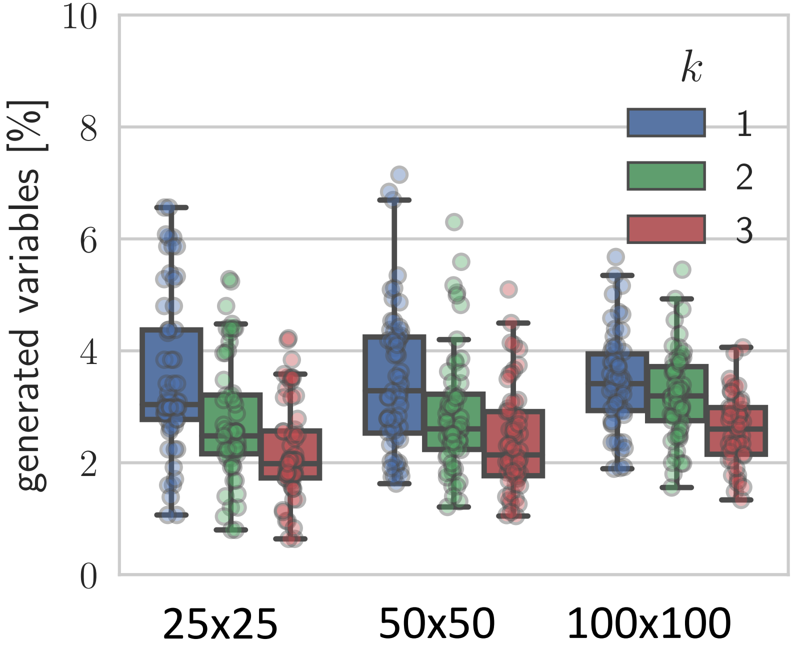
Open question: Hardness of deciding whether ***B*** admits a ***k***-Dollo completion ***A***

Results for *k*-DP

- Naive ILP does not scale and has O(*mnk*) variables and O($m^3n^2k^4$) constraints
- Column and cutting plane generation
    - Introduce variables and constraints only when needed
- Simulations with 60 instances for each each m, n and k







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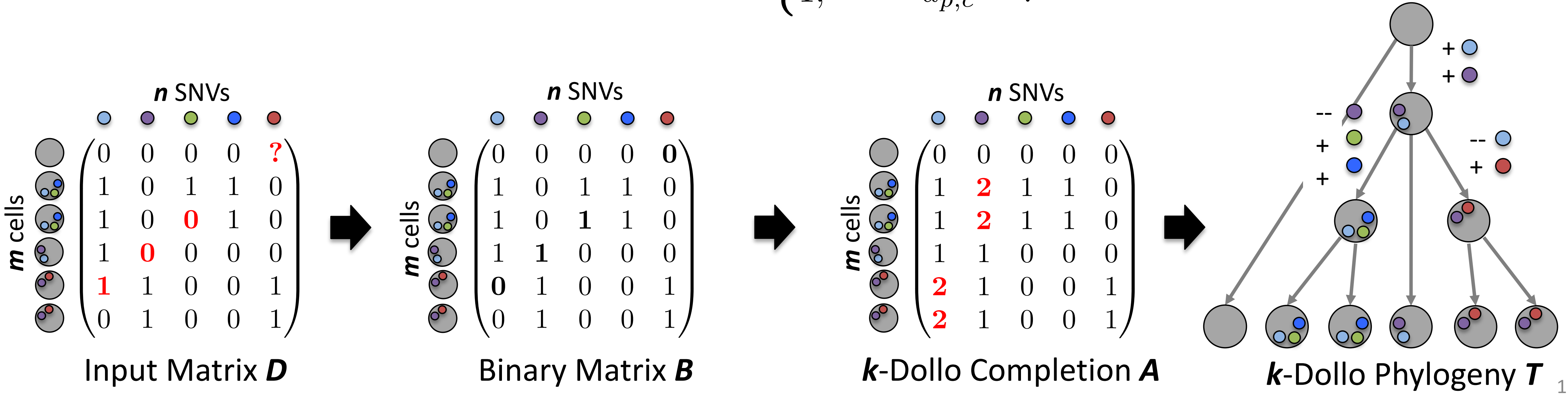
k-Dollo Phylogeny Flip and Cluster (k-DPFC) problem. Given matrix $D \in \{0,1,?\}^{m \times n}$, error rates $\alpha, \beta \in [0,1]$, integers $k, s, t \in \mathbb{N}$, find matrix $B \in \{0,1\}^{m \times n}$ and tree T such that: (1) B has at most s unique rows and at most t unique columns; (2) $\Pr(D \mid B, \alpha, \beta)$ is maximum; and (3) T is a k-Dollo phylogeny for B.

$$\Pr(D \mid B, \alpha, \beta) = \prod_{p=1}^{m} \prod_{c=1}^{n} \begin{cases} \alpha, & d_{p,c} = 1 \text{ and } b_{p,c} = 0 \\ 1-\alpha, & d_{p,c} = 1 \text{ and } b_{p,c} = 1, \\ \beta, & d_{p,c} = 0 \text{ and } b_{p,c} = 1, \\ 1-\beta, & d_{p,c} = 0 \text{ and } b_{p,c} = 0, \\ 1, & d_{p,c} = ? \end{cases}$$



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

Input Matrix ***D***

$$\begin{pmatrix} 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & 1 & 1 & 0 \\ 1 & 0 & 1 & 1 & 0 \\ 1 & 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 1 \\ 0 & 1 & 0 & 0 & 1 \end{pmatrix}$$

Binary Matrix ***B***

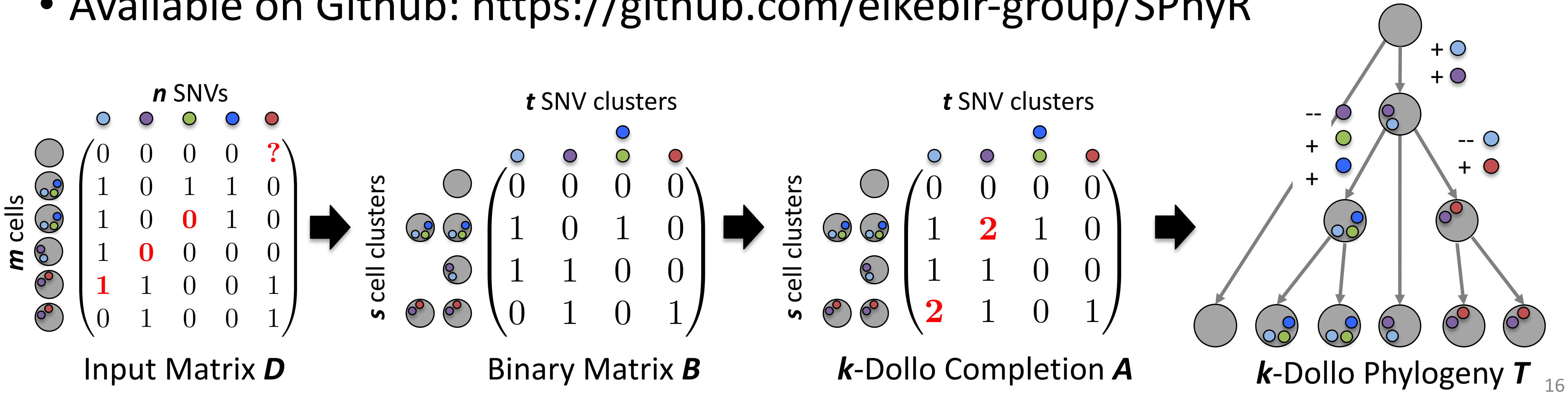
$$\begin{pmatrix} 0 & 0 & 0 & 0 & 0 \\ 1 & 2 & 1 & 1 & 0 \\ 1 & 2 & 1 & 1 & 0 \\ 1 & 1 & 0 & 0 & 0 \\ 2 & 1 & 0 & 0 & 1 \\ 2 & 1 & 0 & 0 & 1 \end{pmatrix}$$

k*-Dollo Completion *A

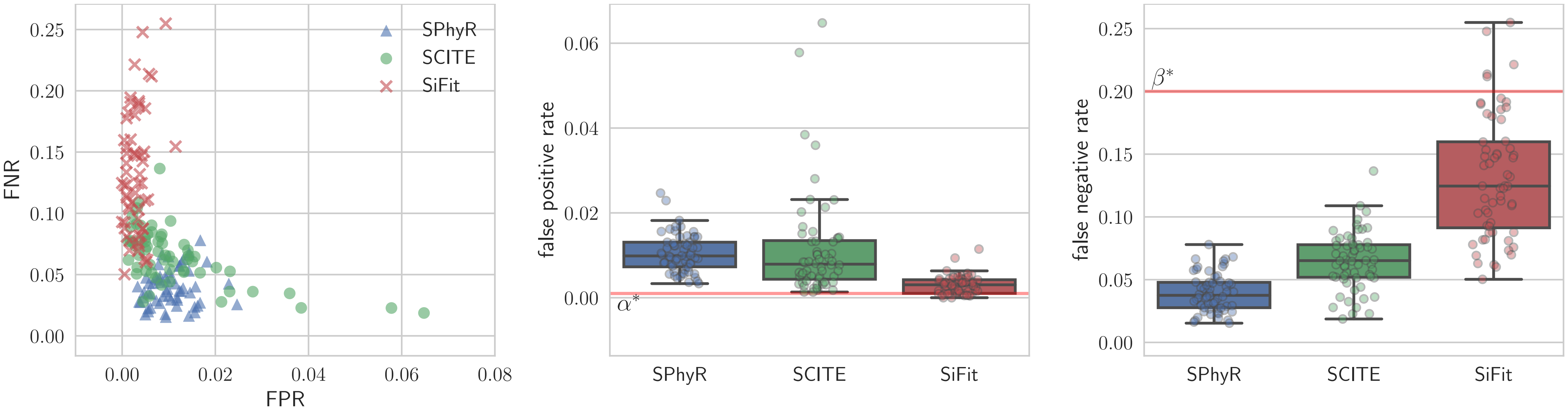
k*-Dollo Phylogeny *T

SPhyR: Single-cell Phylogeny Reconstruction

- Coordinate ascent:
  1. k-Means with random seed to obtain cell clustering ***π*** and SNV clustering ***ψ***
  2. ILP to obtain maximum likelihood ***k***-Dollo completion ***A*** given ***D***, ***π*** and ***ψ***
  3. Identify maximum likelihood ***π*** given ***A*** and ***ψ***
  4. Identify maximum likelihood ***ψ*** given ***A*** and ***π***
  5. Repeat until convergence
- Available on Github: https://github.com/elkebir-group/SPhyR



Simulation Results (m = 50, n = 50, k = 1)



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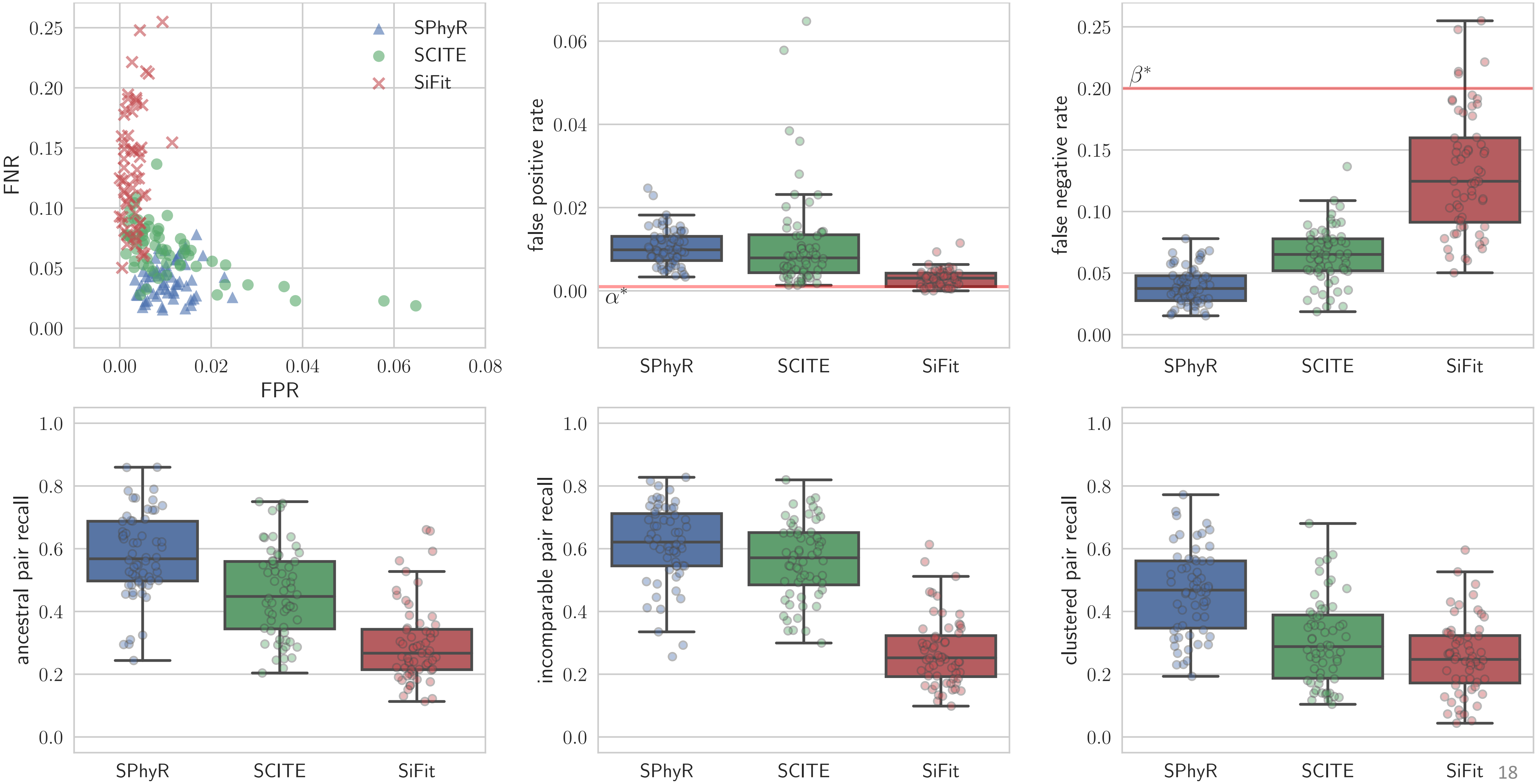


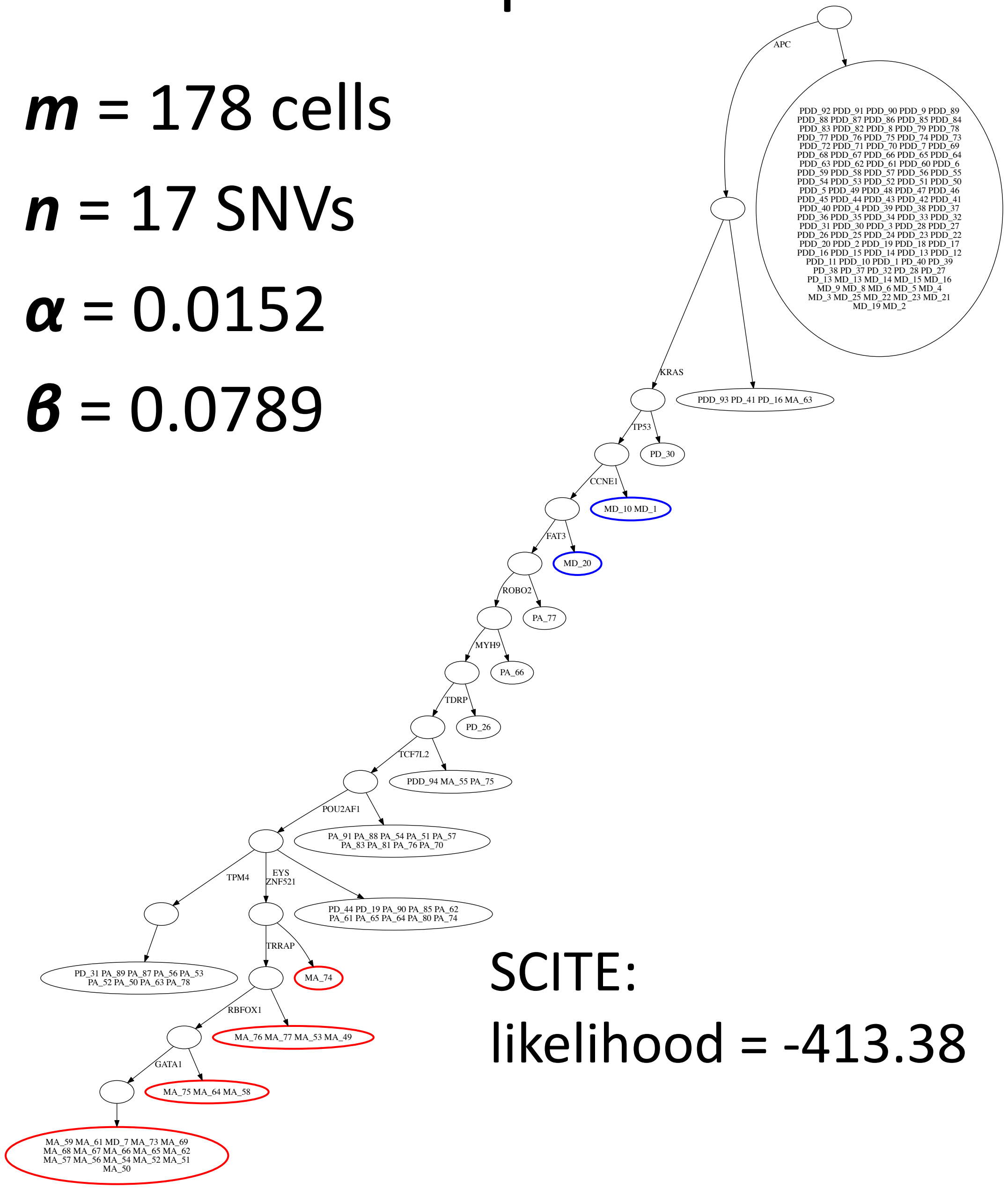
Colorectal patient CRC1 [Leung et al., 2017]

m = 178 cells

n = 17 SNVs

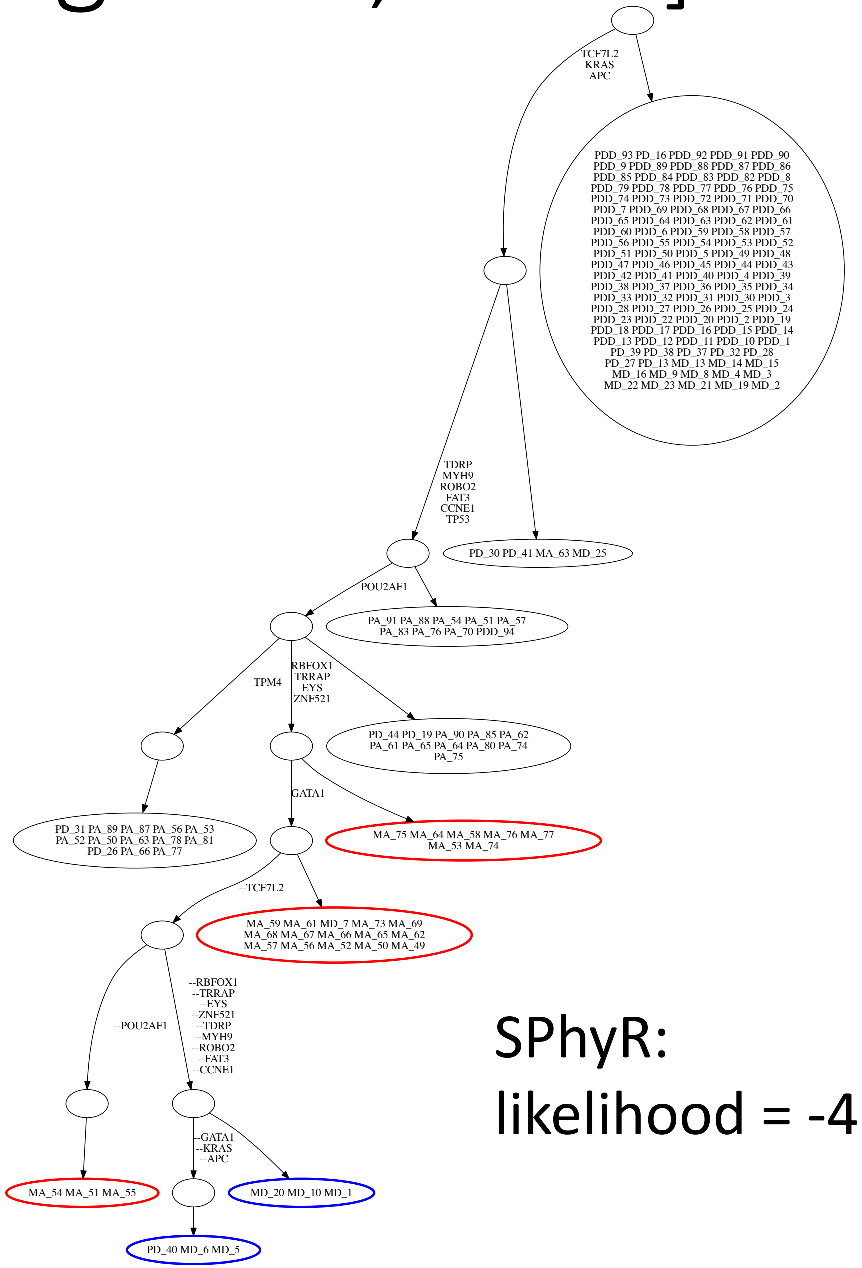
α = 0.0152

β = 0.0789



SCITE:

likelihood = -413.38

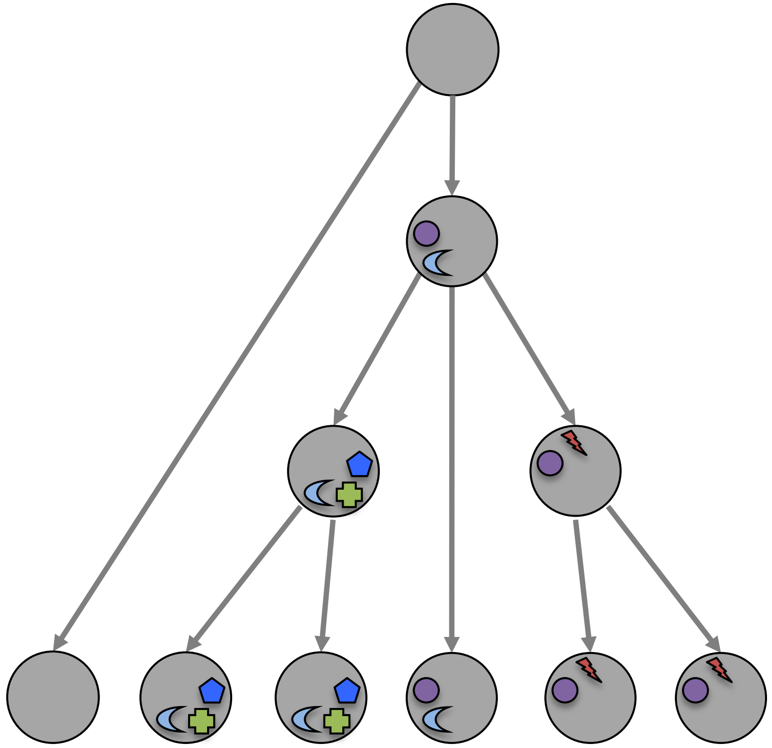


SPhyR:

likelihood = -450.70

Conclusions

- ***k***-Dollo parsimony model strikes a balance between realistic and yet sufficiently constrained
- Solutions are integer matrix completions
- SPhyR outperformed existing methods



Future work:

- Include ***α*** and ***β*** into optimization
- Model selection for ***s***, ***t*** and ***k***
- Hardness is open