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

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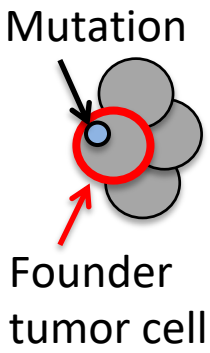
ECCB 2018

Tumorigenesis: (i) Cell Mutation

Clonal Evolution Theory of Cancer
[Nowell, 1976]



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

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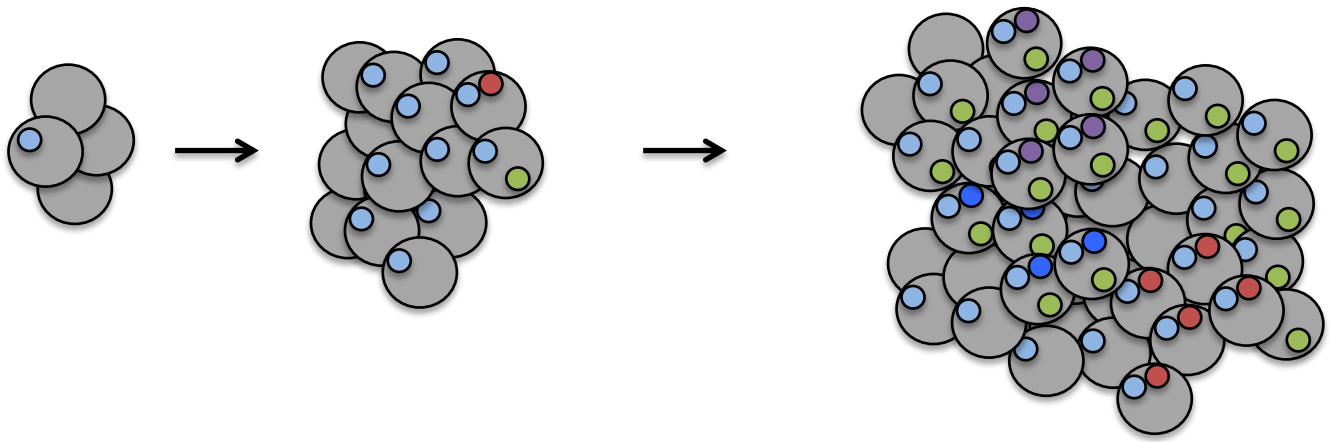
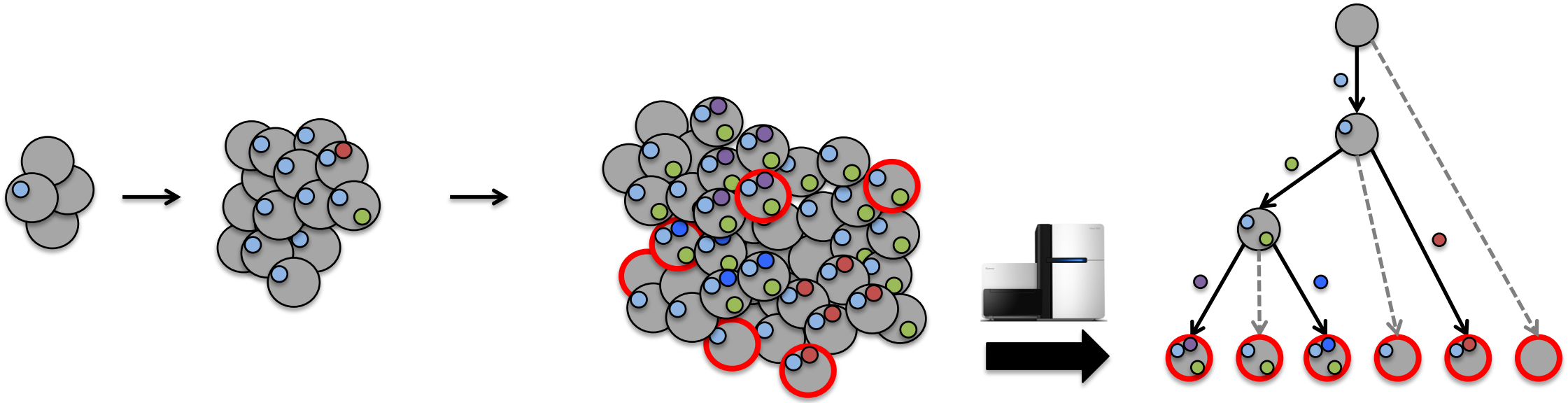
[Nowell, 1976]



Heterogeneous Tumor

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

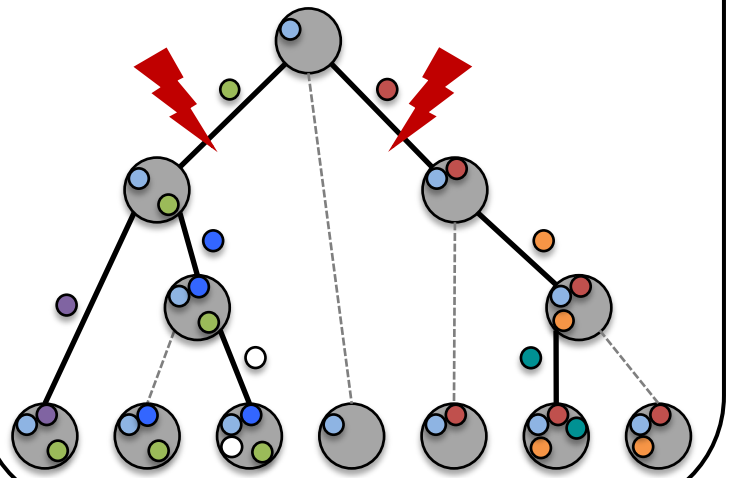


Heterogeneous Tumor

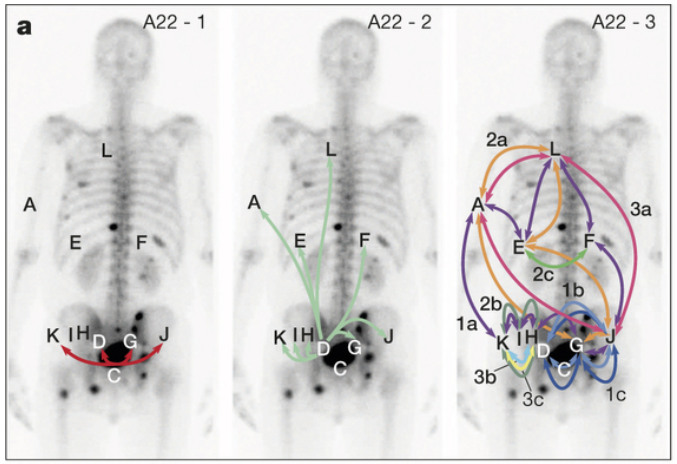
Phylogenetic Tree ***T***

Phylogenies are Key to Understanding Tumorigenesis

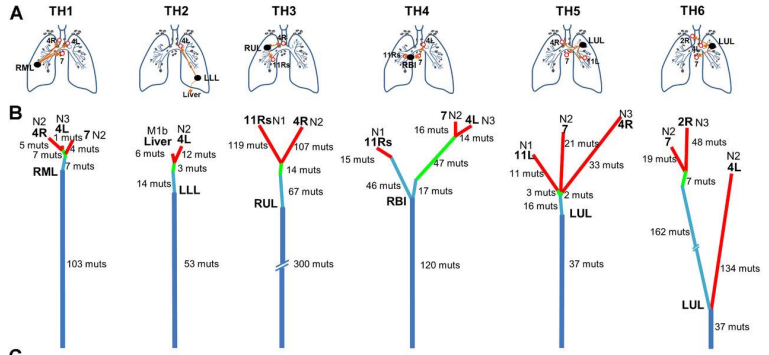
Identify targets for treatment



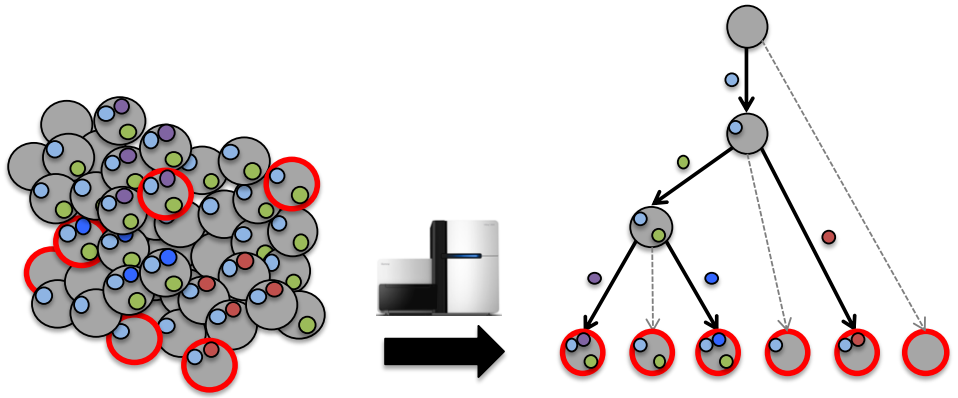
Understand metastatic development



Recognize common patterns of tumor evolution across patients



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



Heterogeneous Tumor

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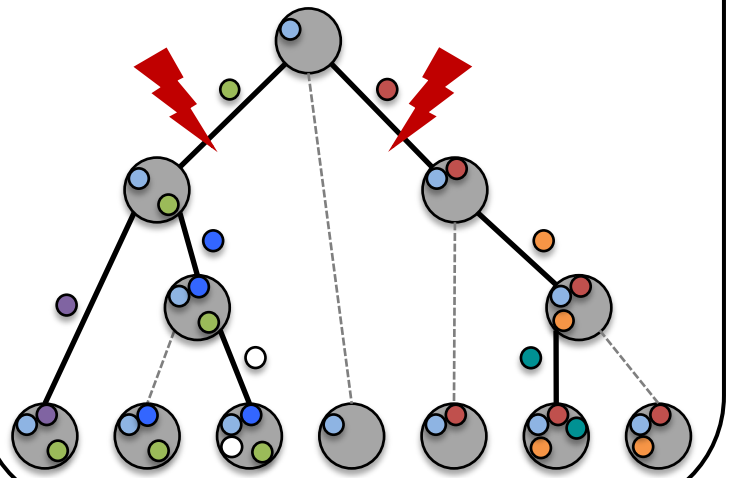

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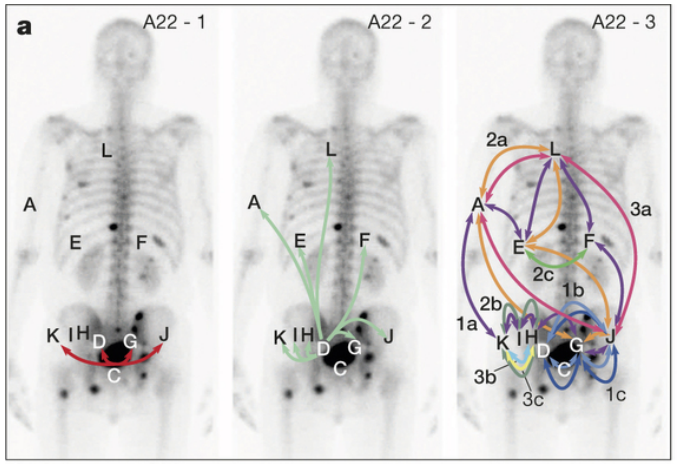

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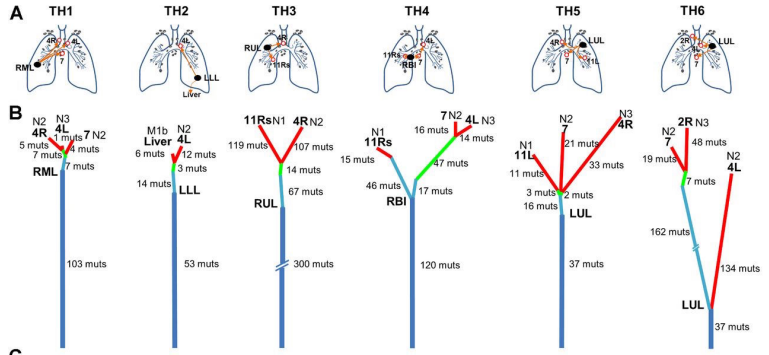
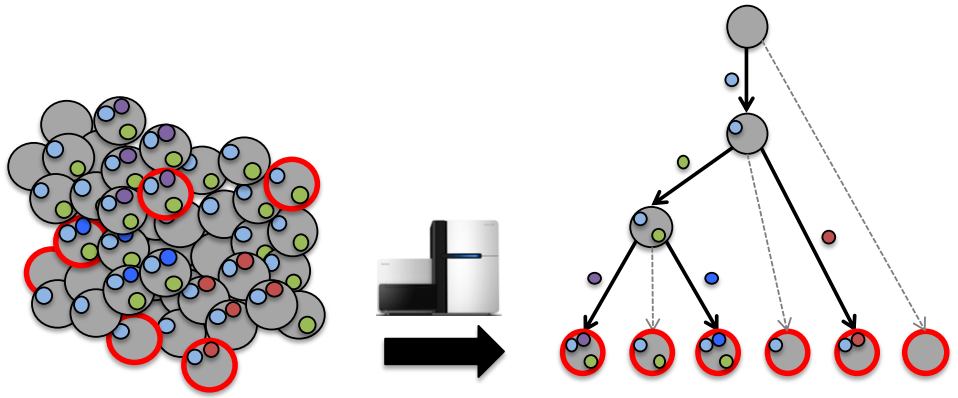


Goal: Given single-cell DNA sequencing data, find phylogenetic tree ***T***

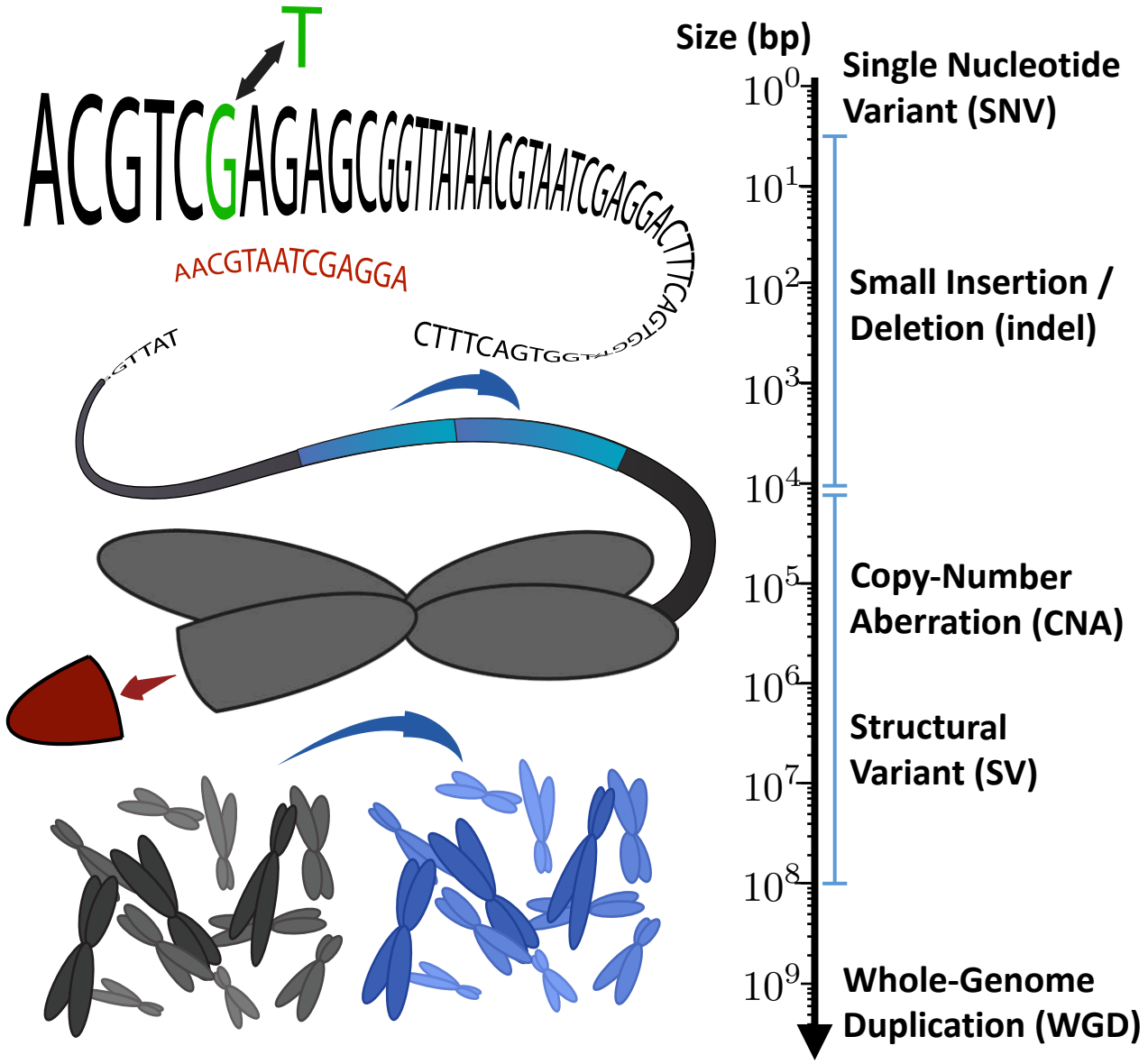
Requirement: Evolutionary model for somatic mutations



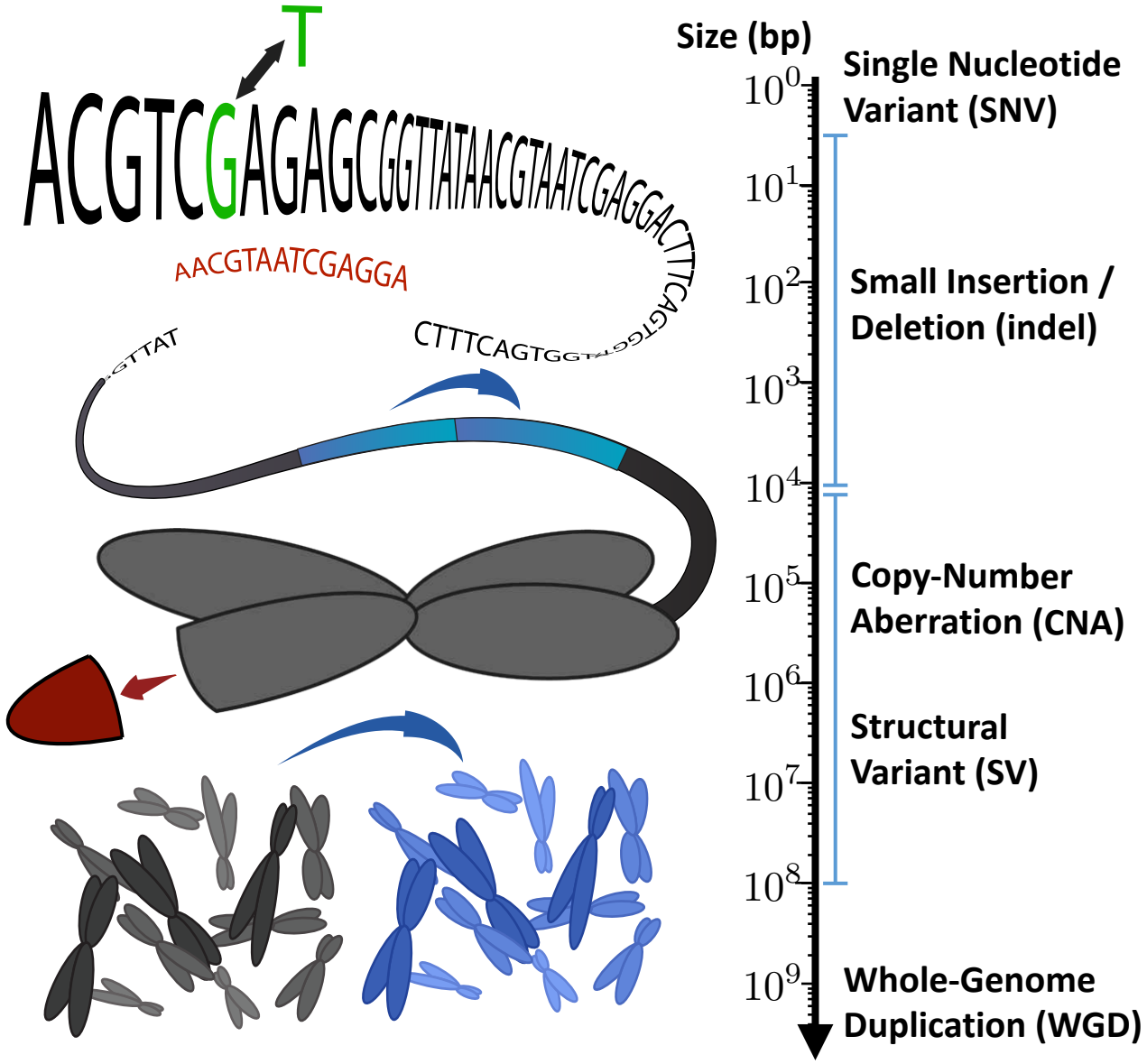
Heterogeneous Tumor

Phylogenetic Tree ***T***

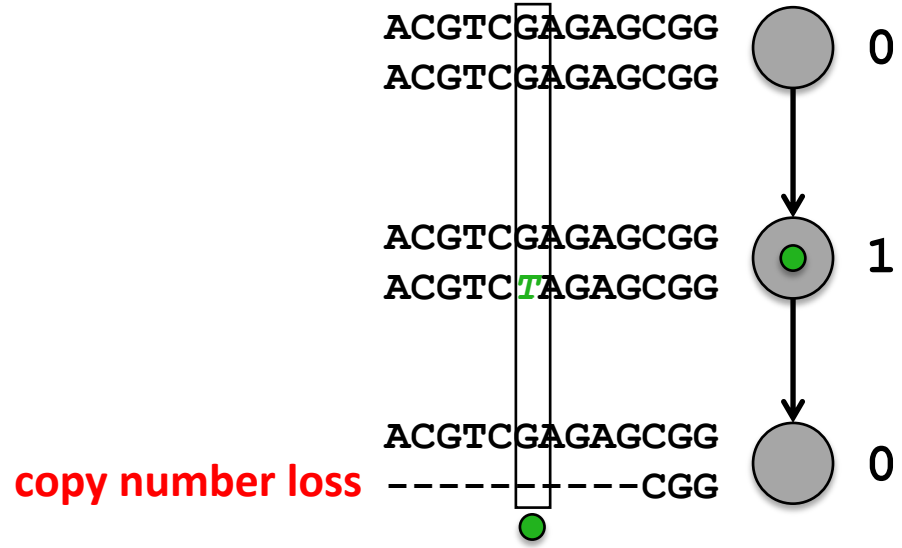
Somatic Mutations Occur at Different Genomic Scales



Infinite Sites Assumption is too Restrictive for SNVs



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)
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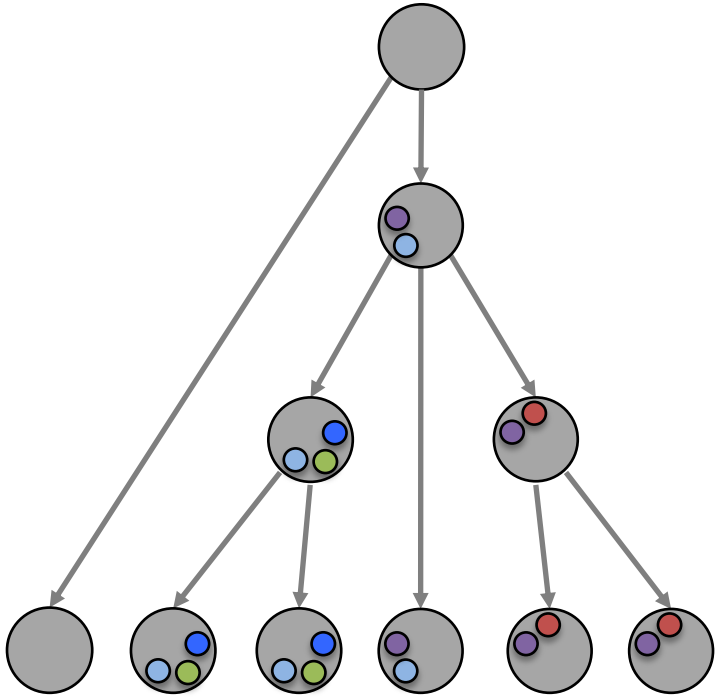
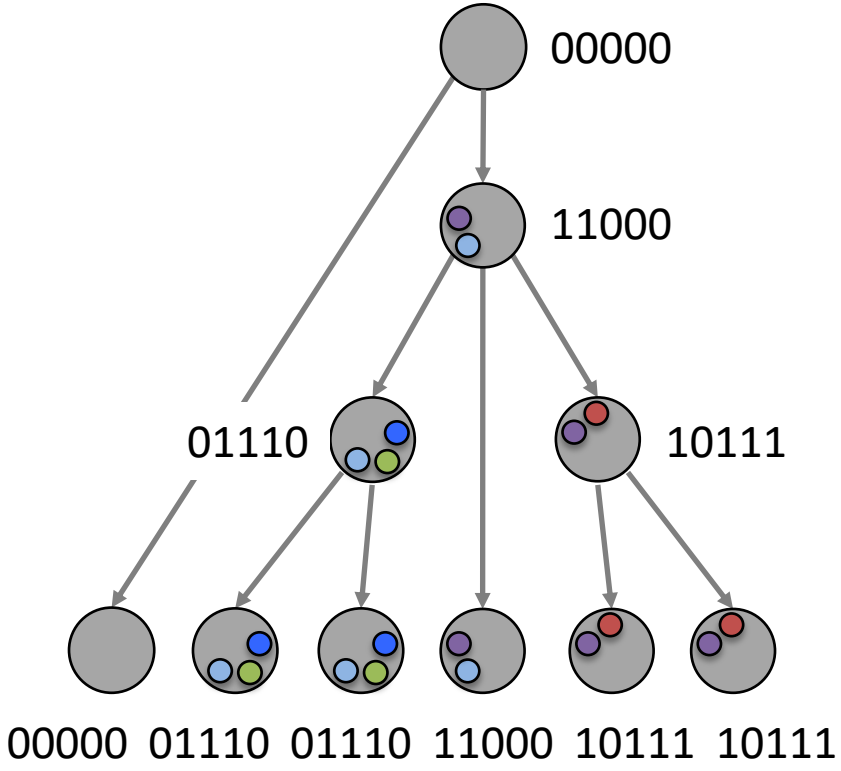
  - Heuristic algorithm
  - Results
- Conclusions



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 $\mathbf{b}_r = [0,\ldots,0]^T$.



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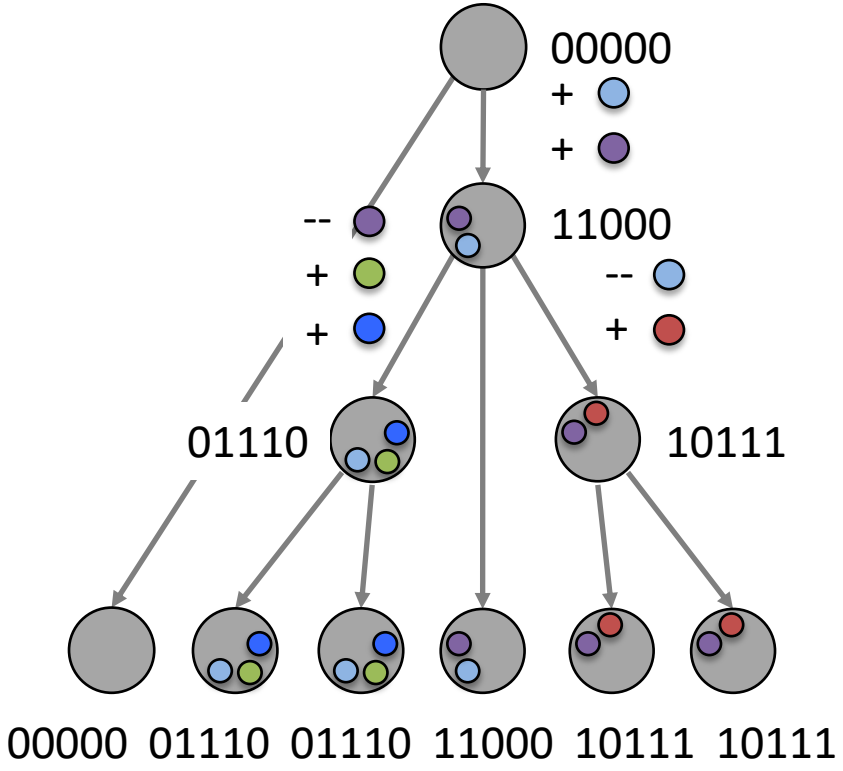
2. The root r of T is labeled by vector $\mathbf{b}_r = [0,\ldots,0]^T$.
3. For each character $c \in [n]$, there is exactly one *gain edge* (v,w) in T such that $b_{v,c} = 0$ and $b_{w,c} = 1$.
4. For each character $c \in [n]$, there are at most k *loss edges* (v,w) in T such that $b_{v,c} = 1$ and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



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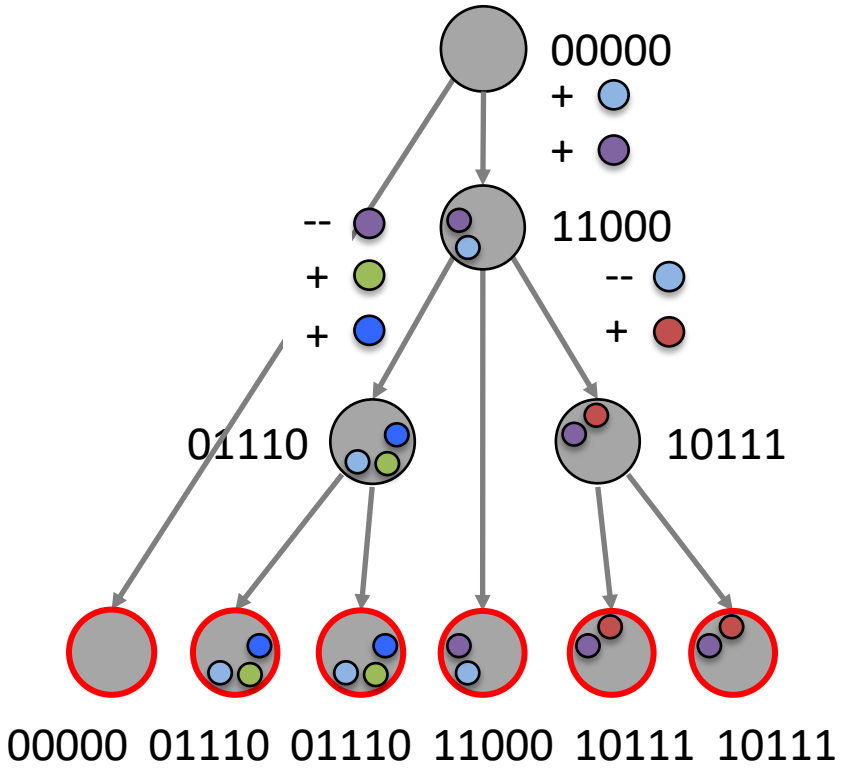
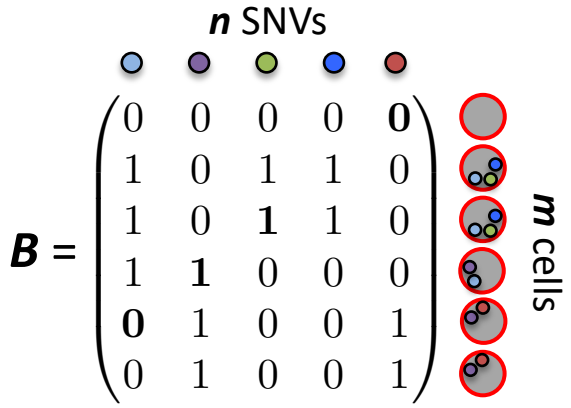


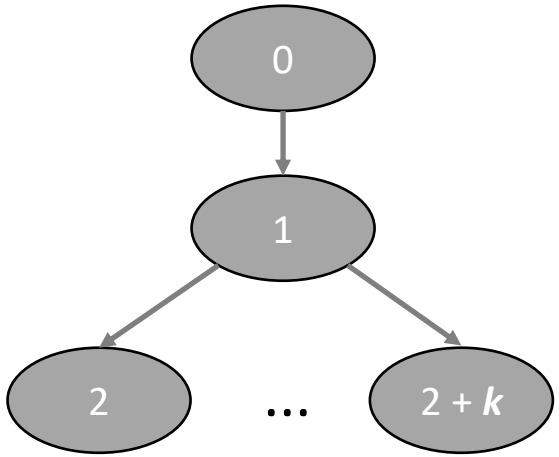
***k*-Dollo Phylogeny problem** (*k*-DP). Given a binary matrix $B \in \{0,1\}^{m\times n}$ and parameter $k \in \mathbb{N}$, determine whether there exists a *k*-Dollo phylogeny for B, and if so construct one.



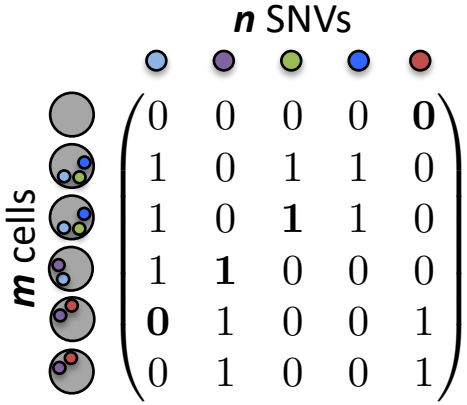
Combinatorial Characterization of *k*-DP

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

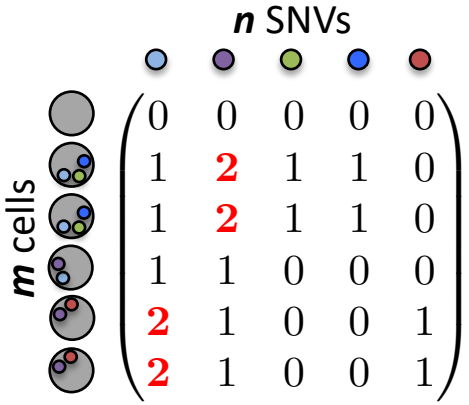
1. There exists a k-Dollo phylogeny T for B.
2. There exists a k-Dollo completion A of B.
3. There exists a k-completion A of B, and perfect phylogeny T for A whose characters are consistent with $S[k]$.



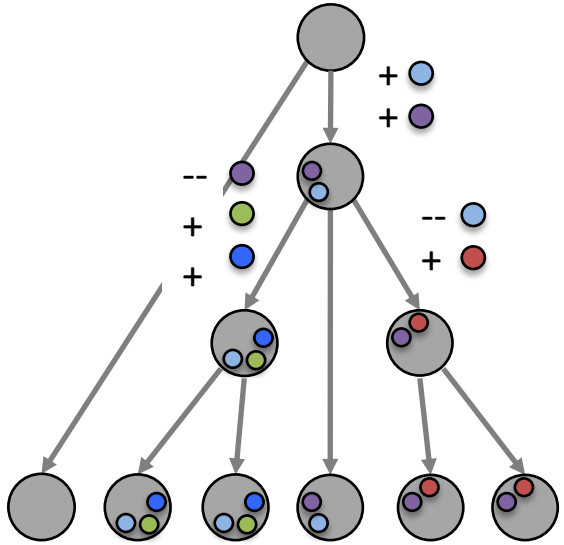
***k*-Dollo State Tree *S*[*k*]**



Input Matrix ***B***



k*-Dollo Completion *A



k*-Dollo Phylogeny *T

Forbidden Submatrices in Solutions A to k-DP

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

$k = 0$

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

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

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

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

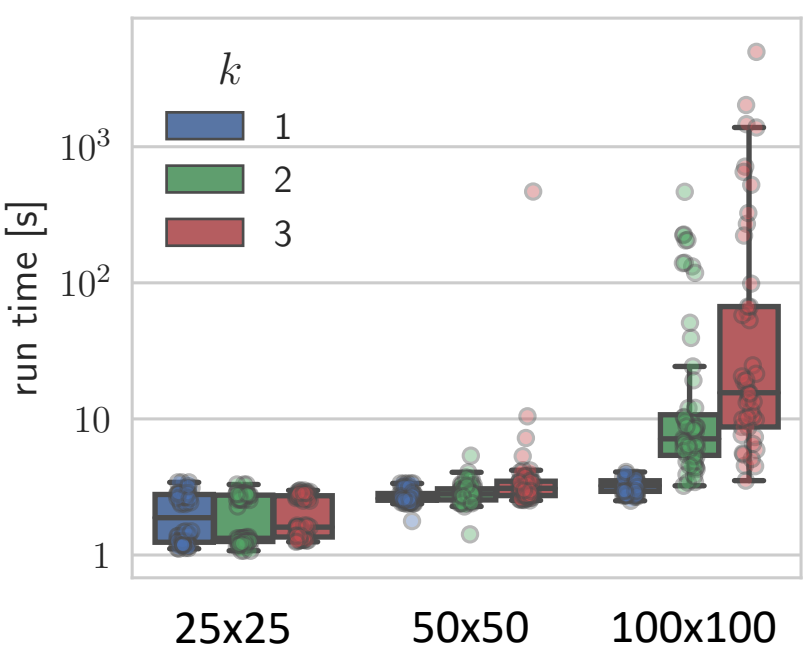
$k = 1$

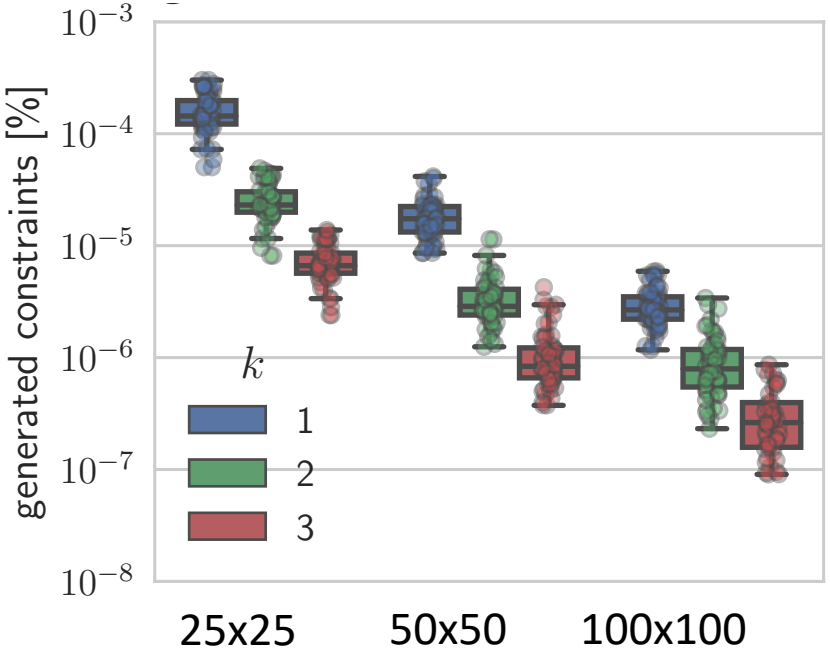
Number of forbidden submatrices is $4k^4 + 8k^3 + 8k^2 + 4k + 1$

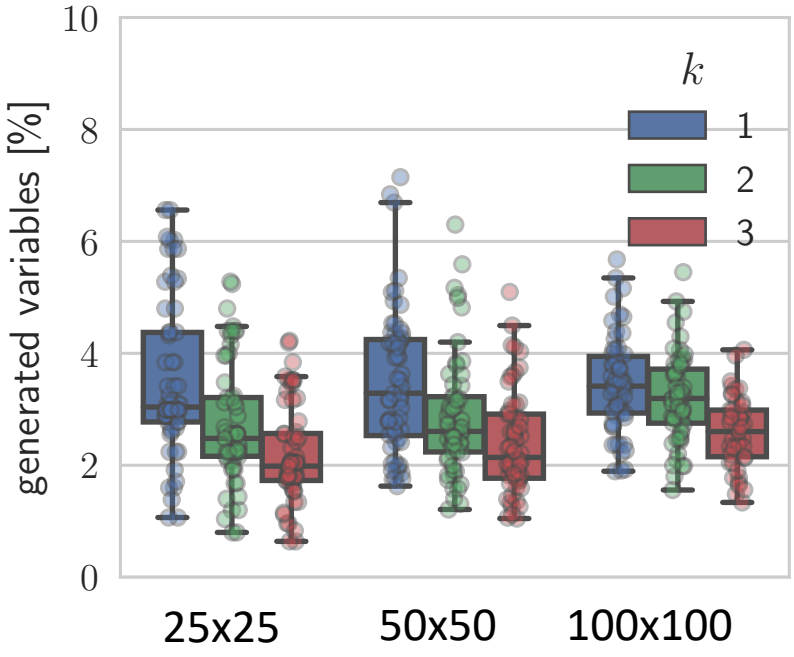
Open question: Hardness of deciding whether B admits a k-Dollo completion A

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 *m*, *n* and *k*







Outline

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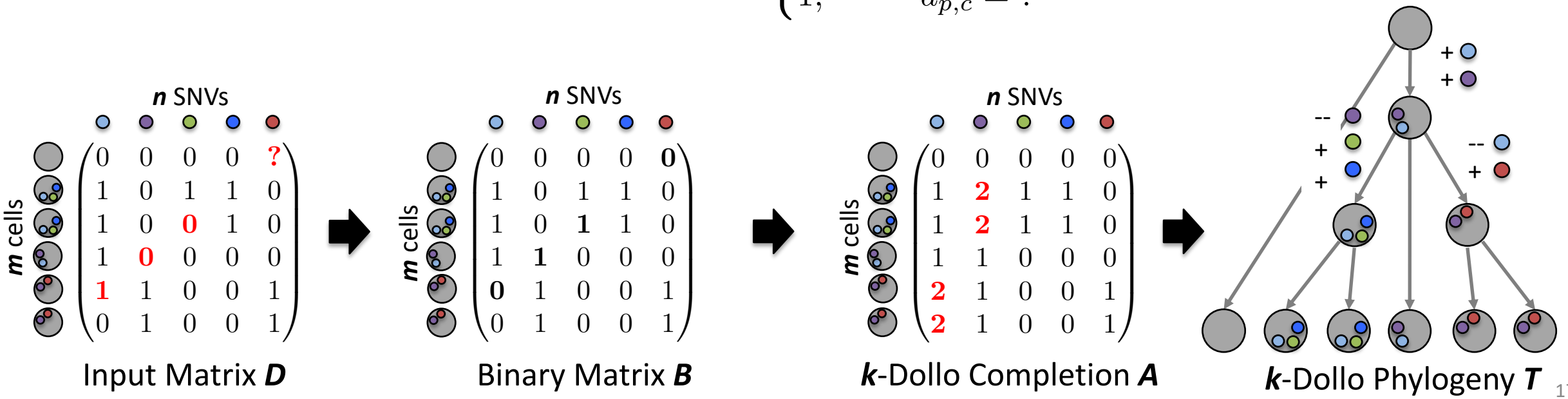
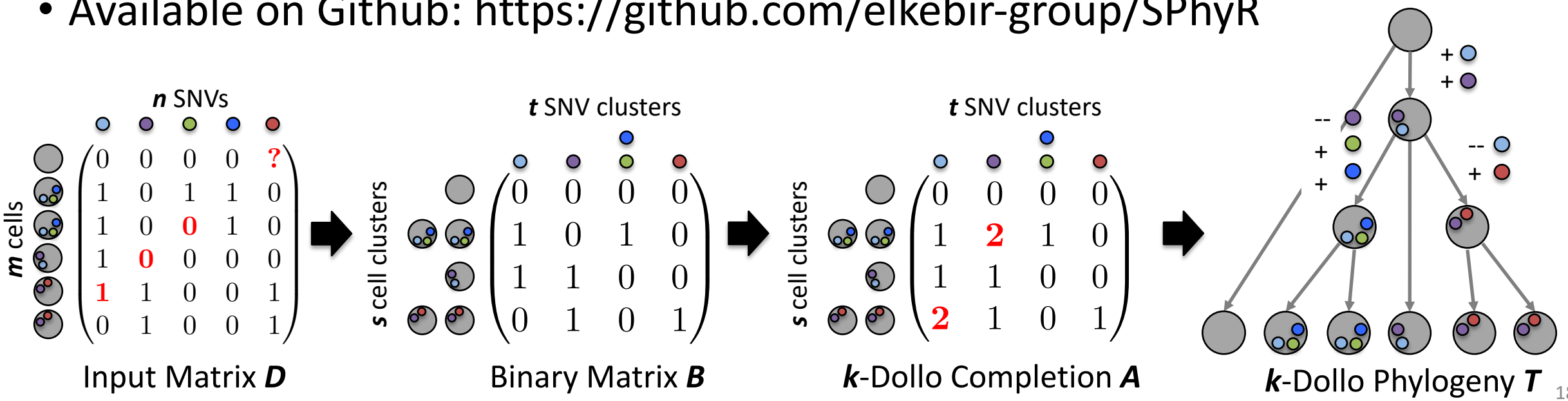
k-Dollo Phylogeny Flip and Cluster (k-DPFC) problem. Given matrix $D \in \{0,1,?\}^{m \times n}$, error rates $\alpha, \beta \in [0,1]$, integers $k, s, t \in \mathbb{N}$, find matrix $B \in \{0,1\}^{m \times n}$ and tree T such that: (1) B has at most s unique rows and at most t unique columns; (2)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

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

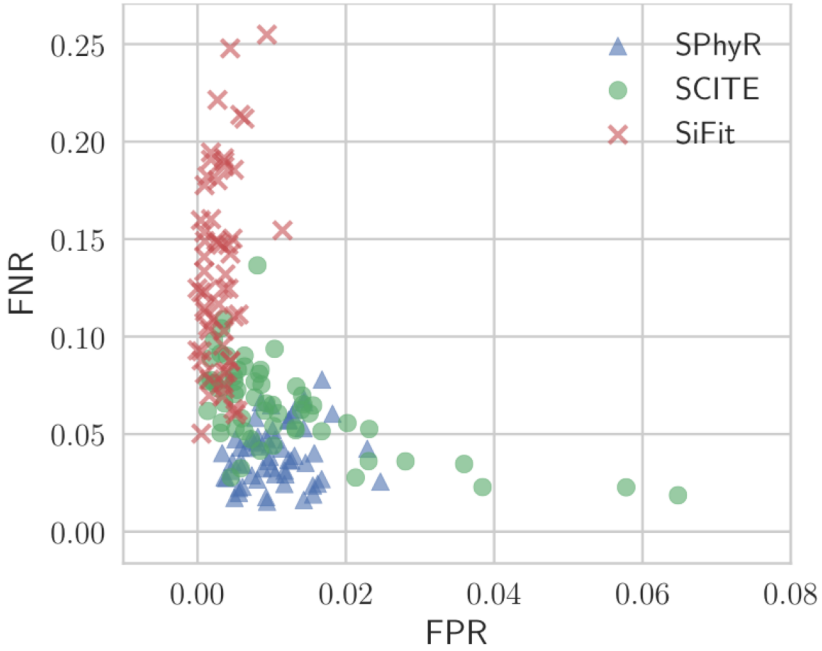


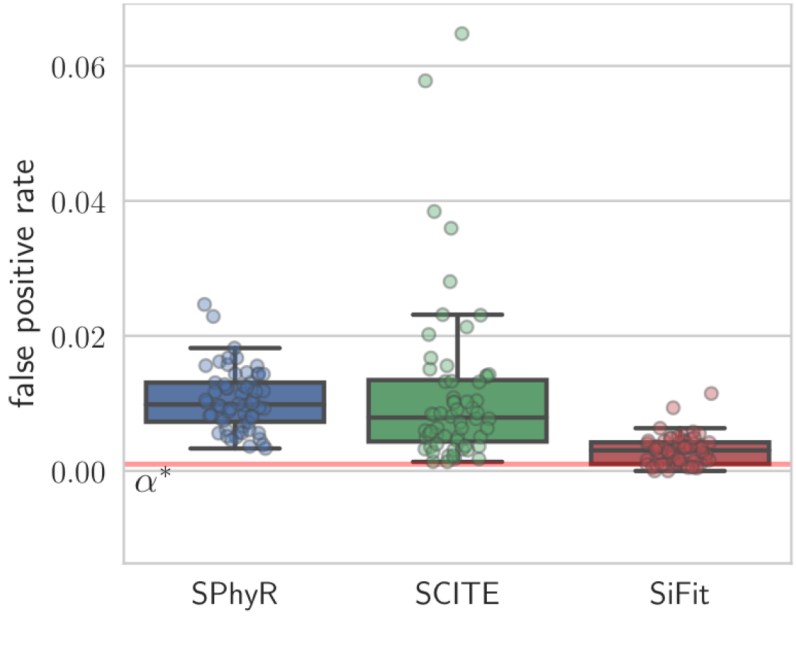
SPhyR: Single-cell Phylogeny Reconstruction

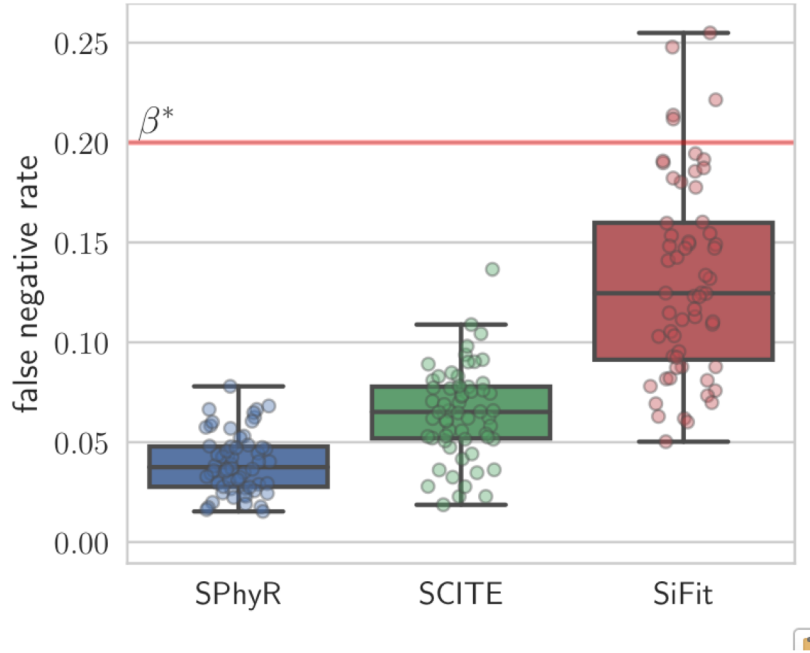
- Coordinate ascent:
  1. k-Means with random seed to obtain cell clustering $\boldsymbol{\pi}$ and SNV clustering $\boldsymbol{\psi}$
  2. ILP to obtain maximum likelihood $\boldsymbol{k}$-Dollo completion $\boldsymbol{A}$ given $\boldsymbol{D}$, $\boldsymbol{\pi}$ and $\boldsymbol{\psi}$
  3. Identify maximum likelihood $\boldsymbol{\pi}$ given $\boldsymbol{A}$ and $\boldsymbol{\psi}$
  4. Identify maximum likelihood $\boldsymbol{\psi}$ given $\boldsymbol{A}$ and $\boldsymbol{\pi}$
  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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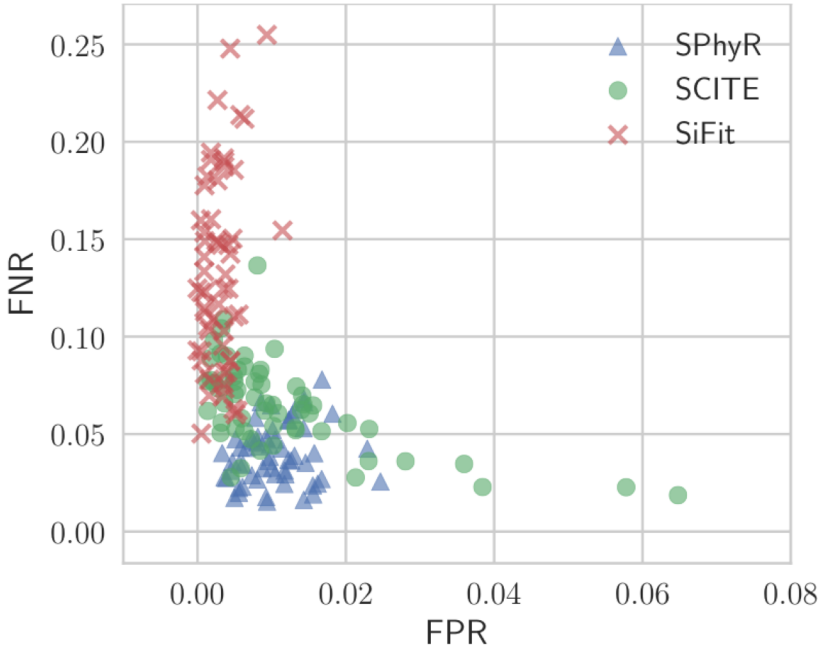
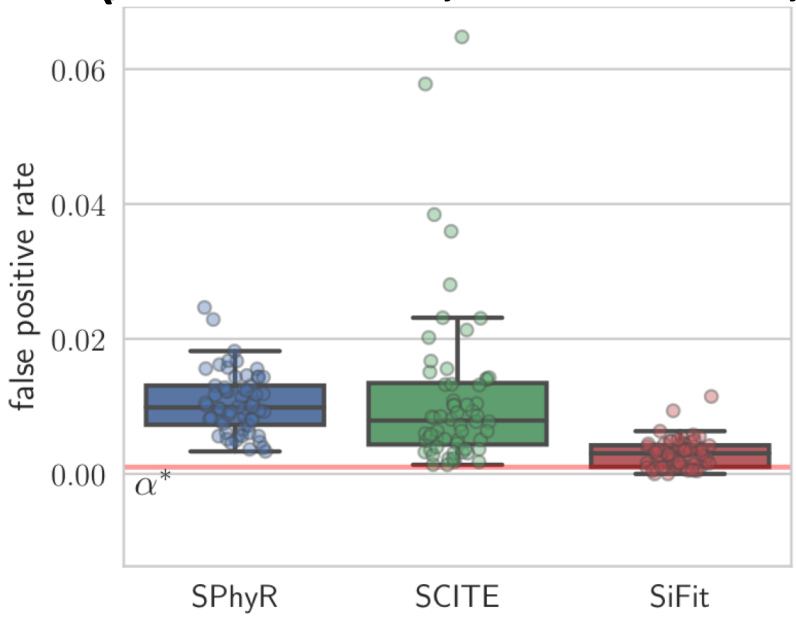
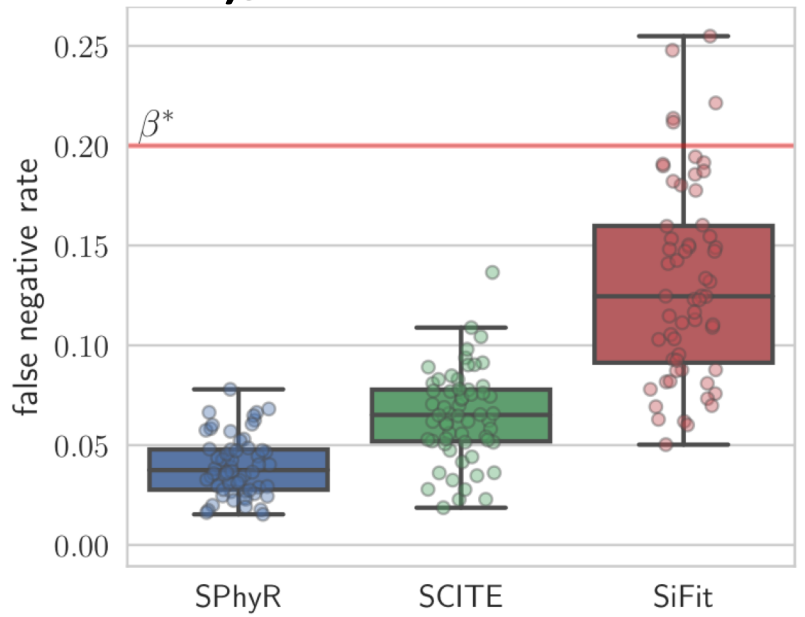
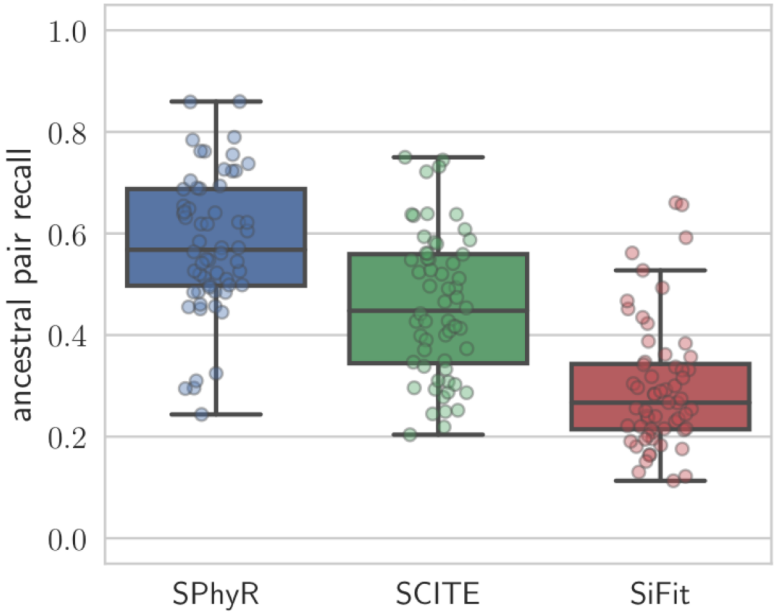
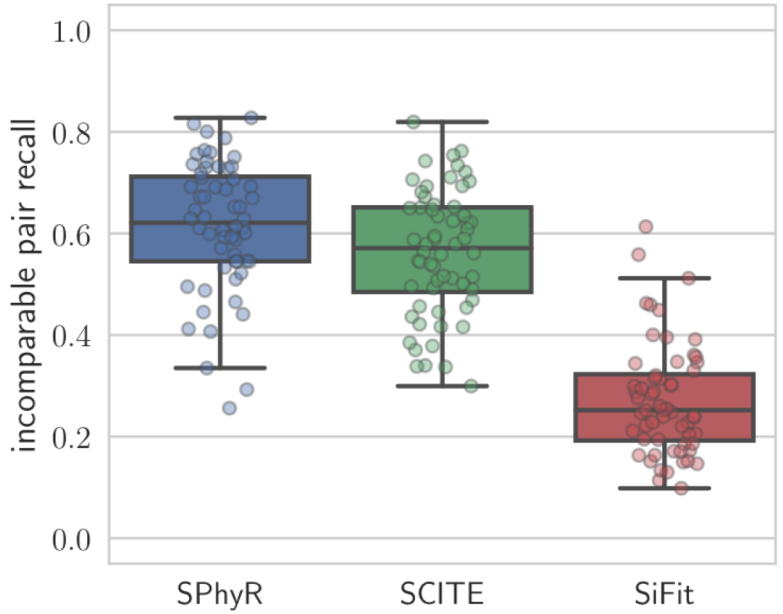
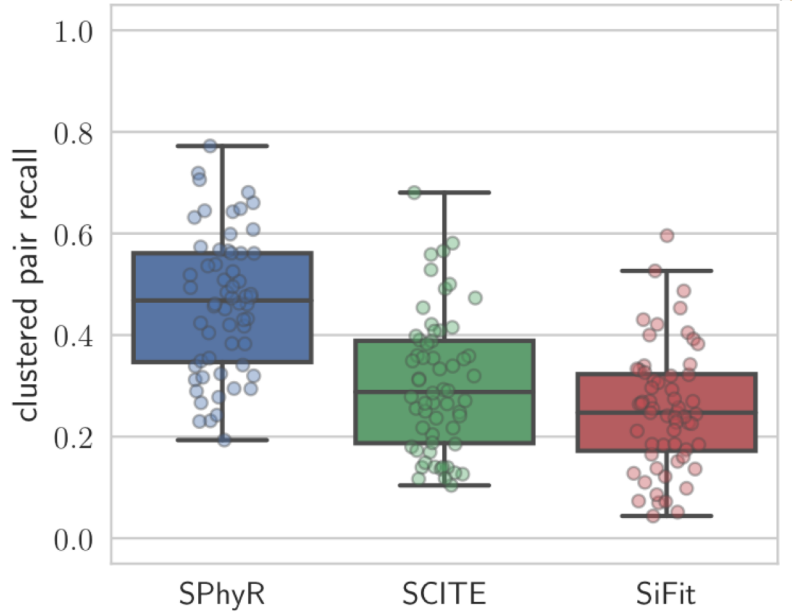












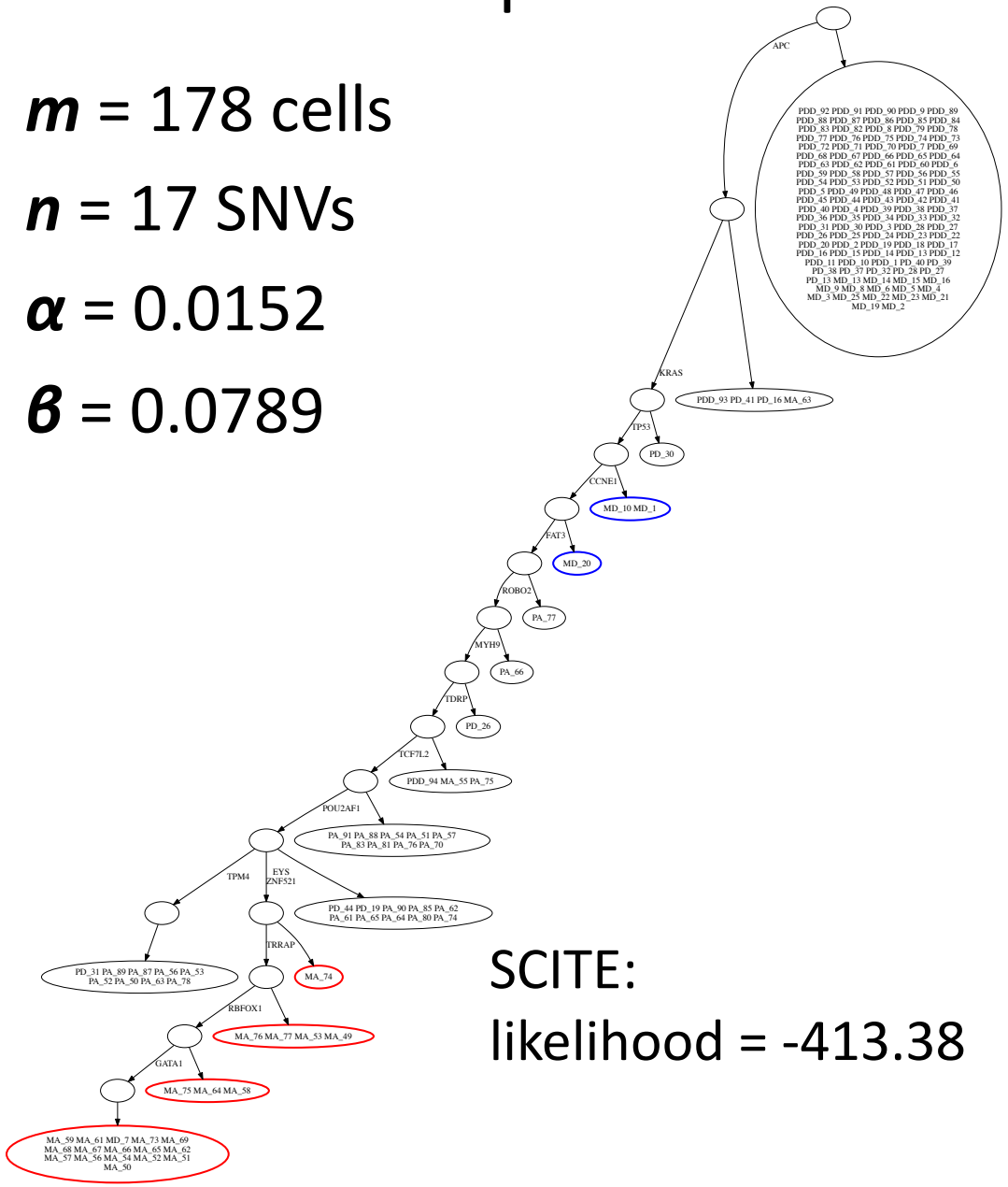
Colorectal patient CRC1 [Leung et al., 2017]

m = 178 cells

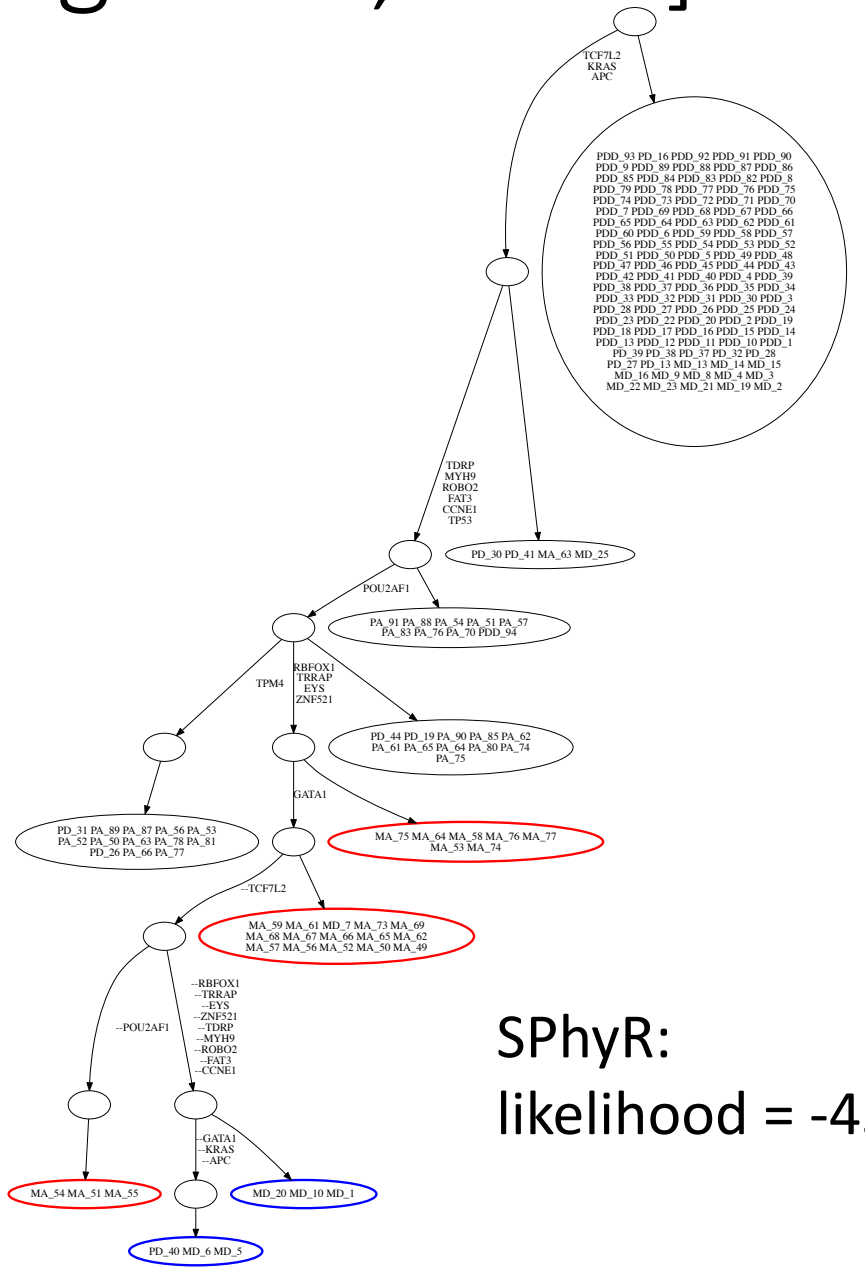
n = 17 SNVs

α = 0.0152

β = 0.0789



SCITE:
likelihood = -413.38



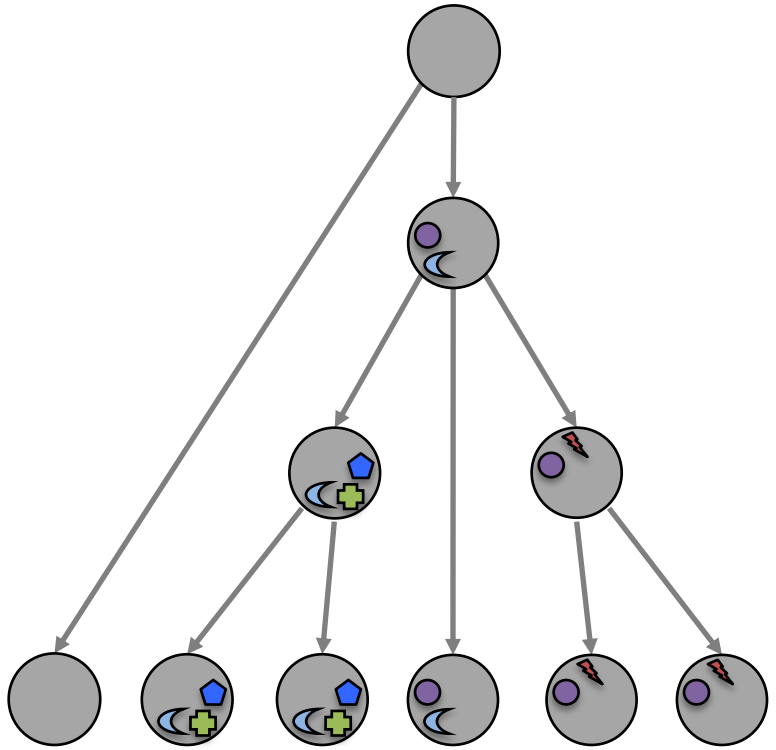
SPhyR:
likelihood = -450.70

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 $\boldsymbol{\alpha}$ and $\boldsymbol{\beta}$ into optimization
- Model selection for ***s***, ***t*** and ***k***
- Hardness is open



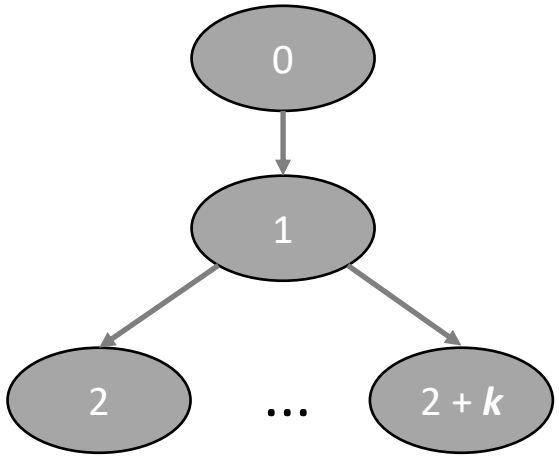
Acknowledgments

- Experiments were run on NCSA Blue Waters

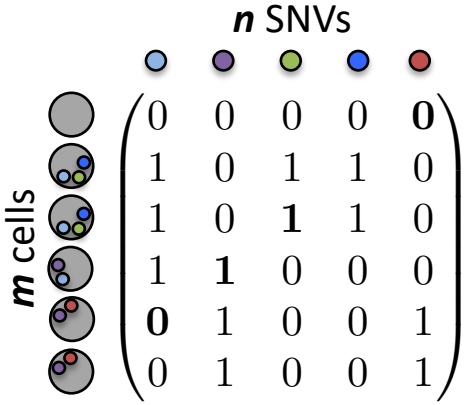
Combinatorial Characterization of *k*-DP

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

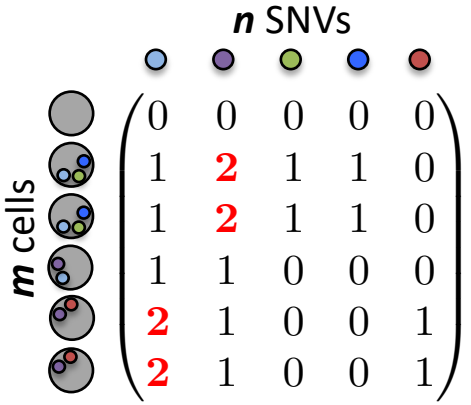
1. There exists a k-Dollo phylogeny T for B.
2. There exists a k-Dollo completion A of B.
3. There exists a k-completion A of B such that the binary factor matrix B' of $(A, \mathcal{S}[k])$ is a perfect phylogeny matrix.
4. There exists a k-completion A of B, and perfect phylogeny T for A whose characters are consistent with $S[k]$.



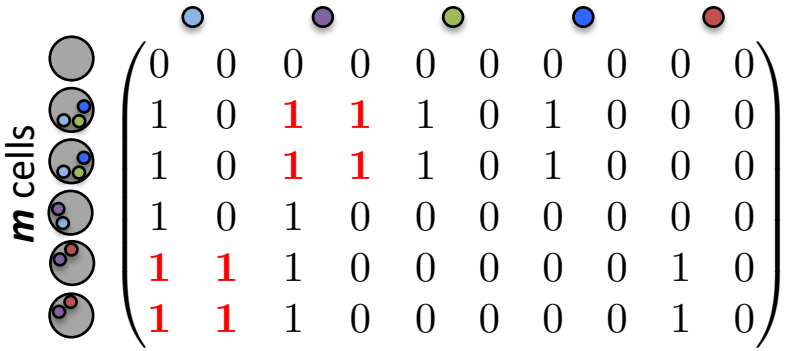
***k*-Dollo State Tree *S*[*k*]**



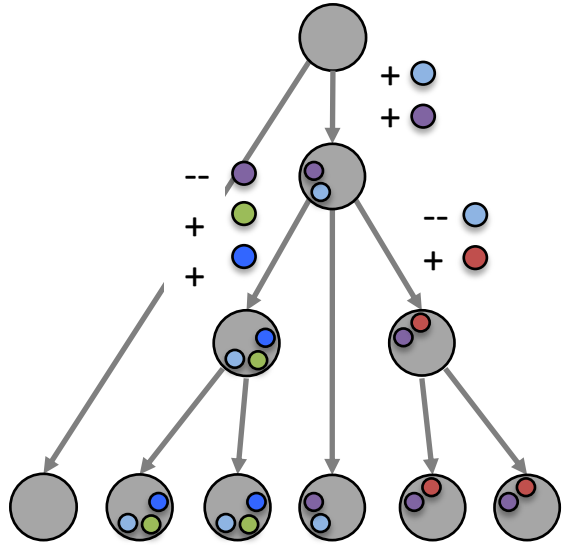
Input Matrix ***B***



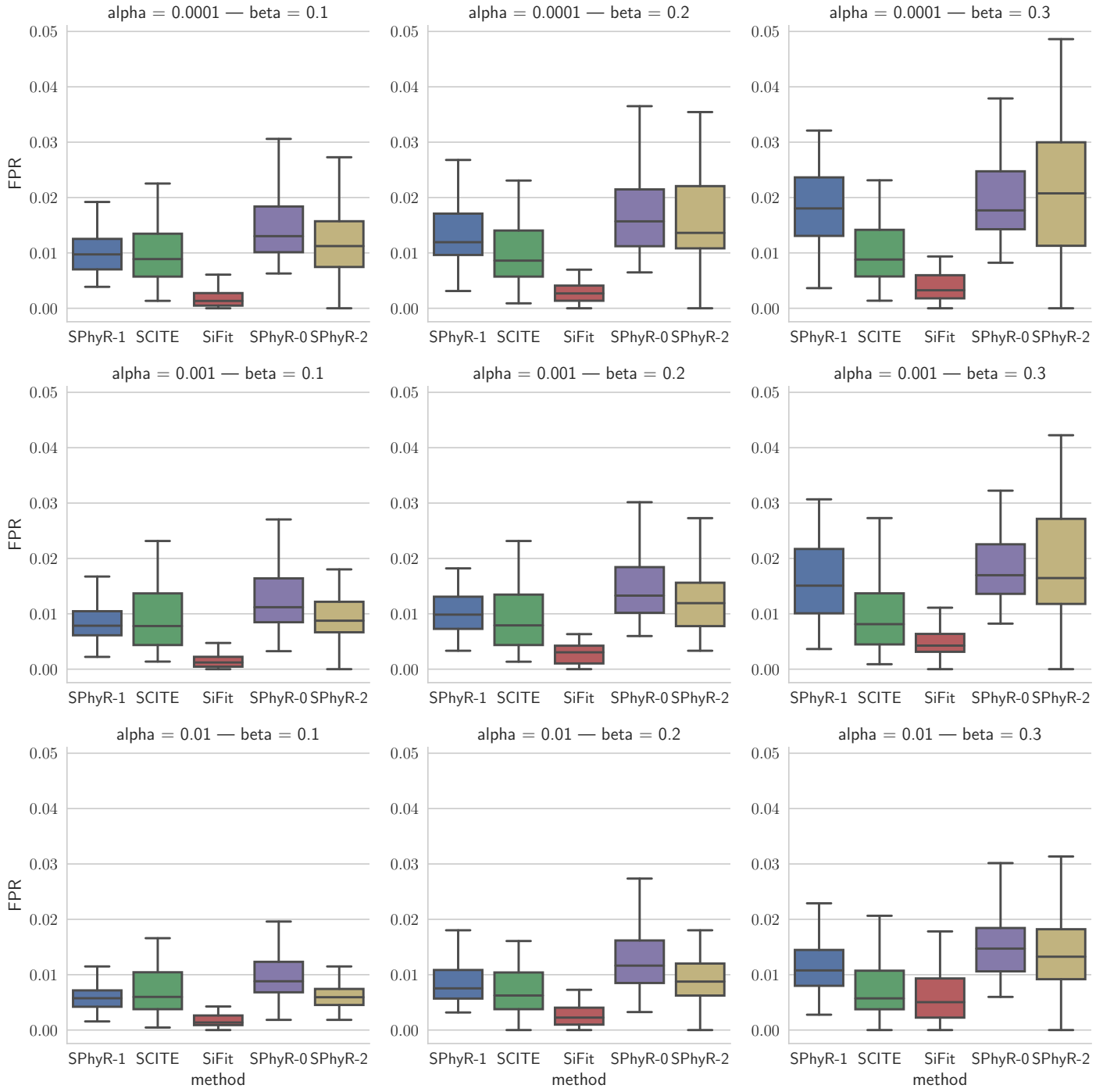
k*-Dollo Completion *A

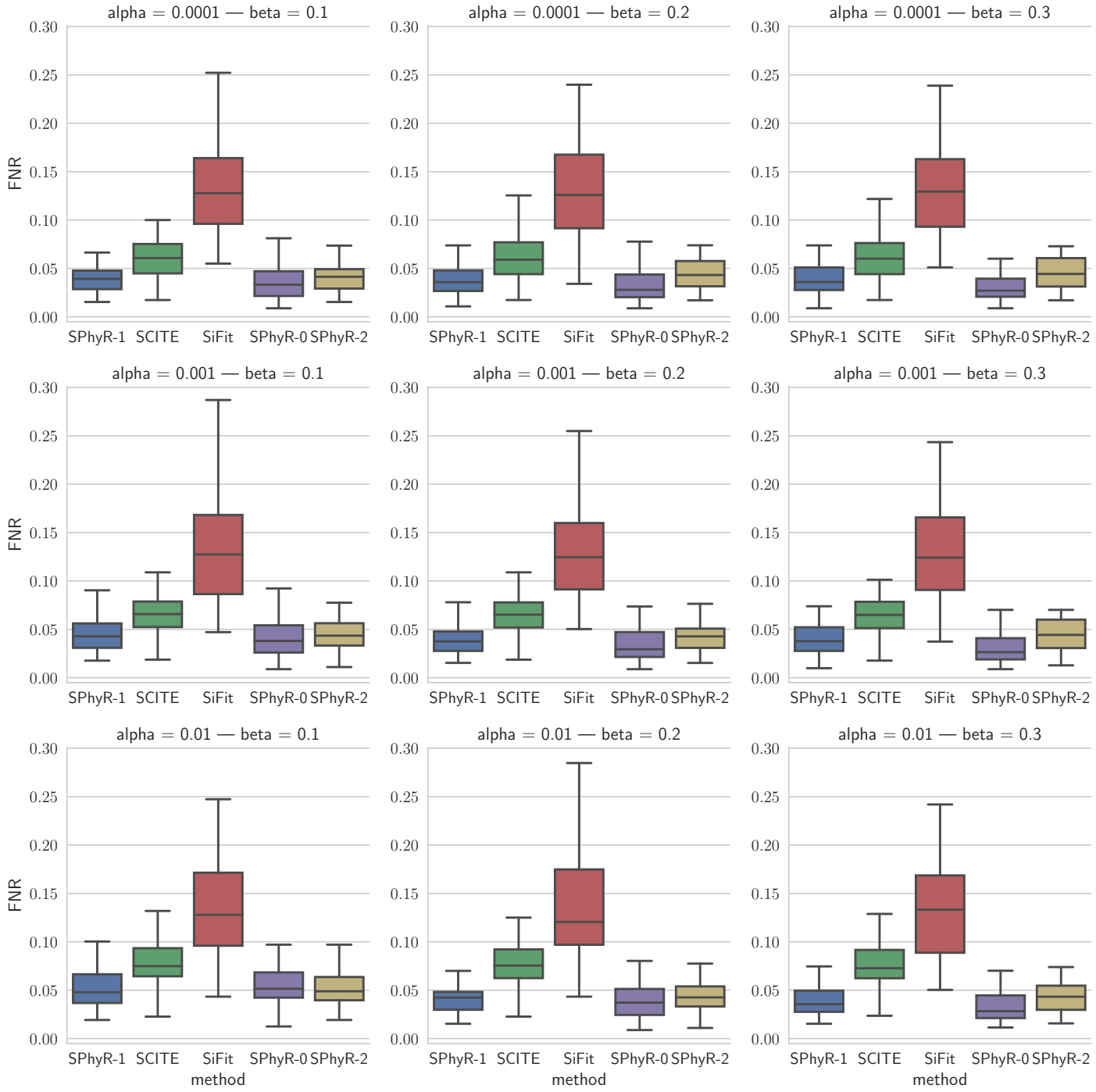


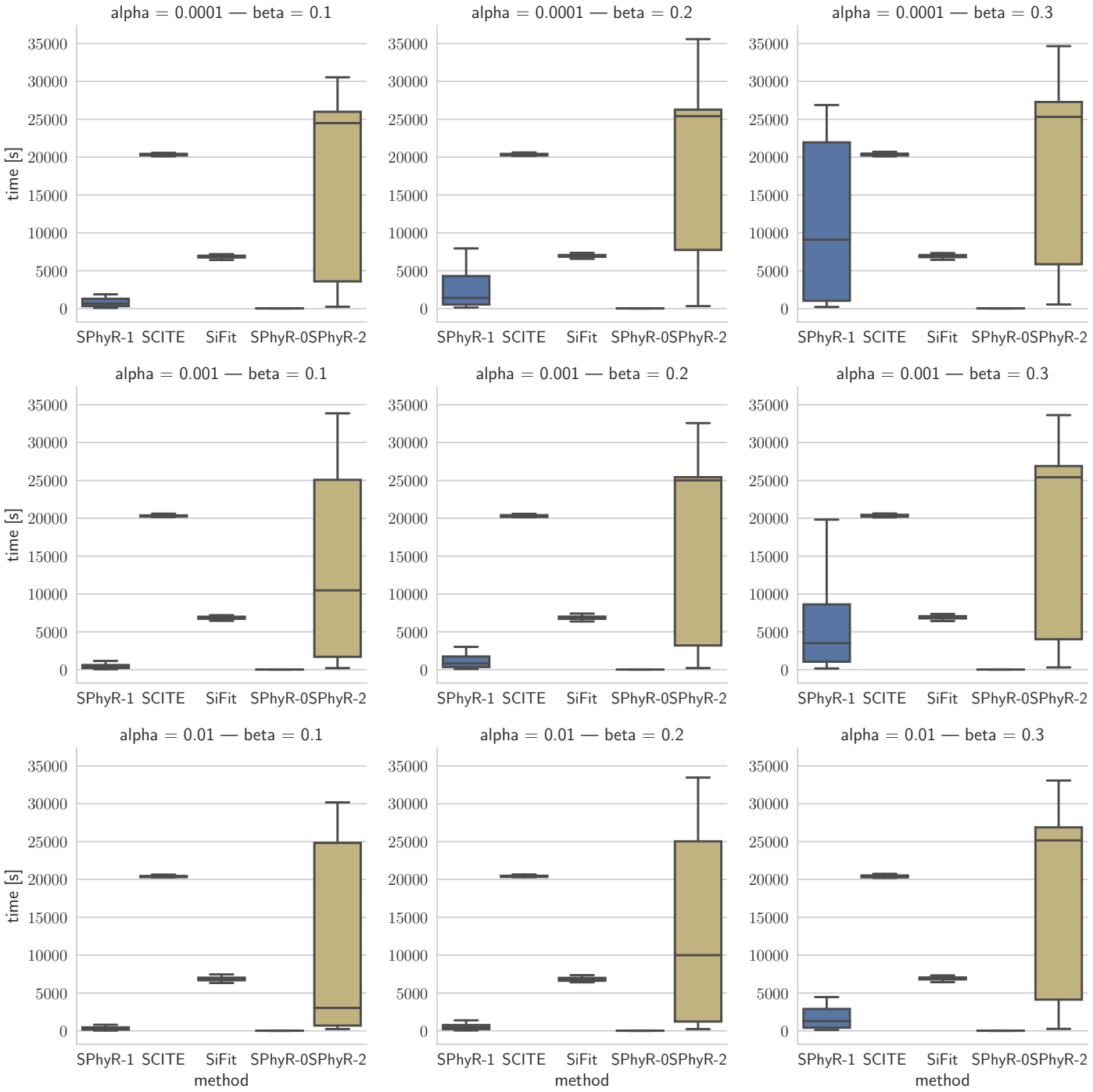
Binary Factor Matrix ***B'***

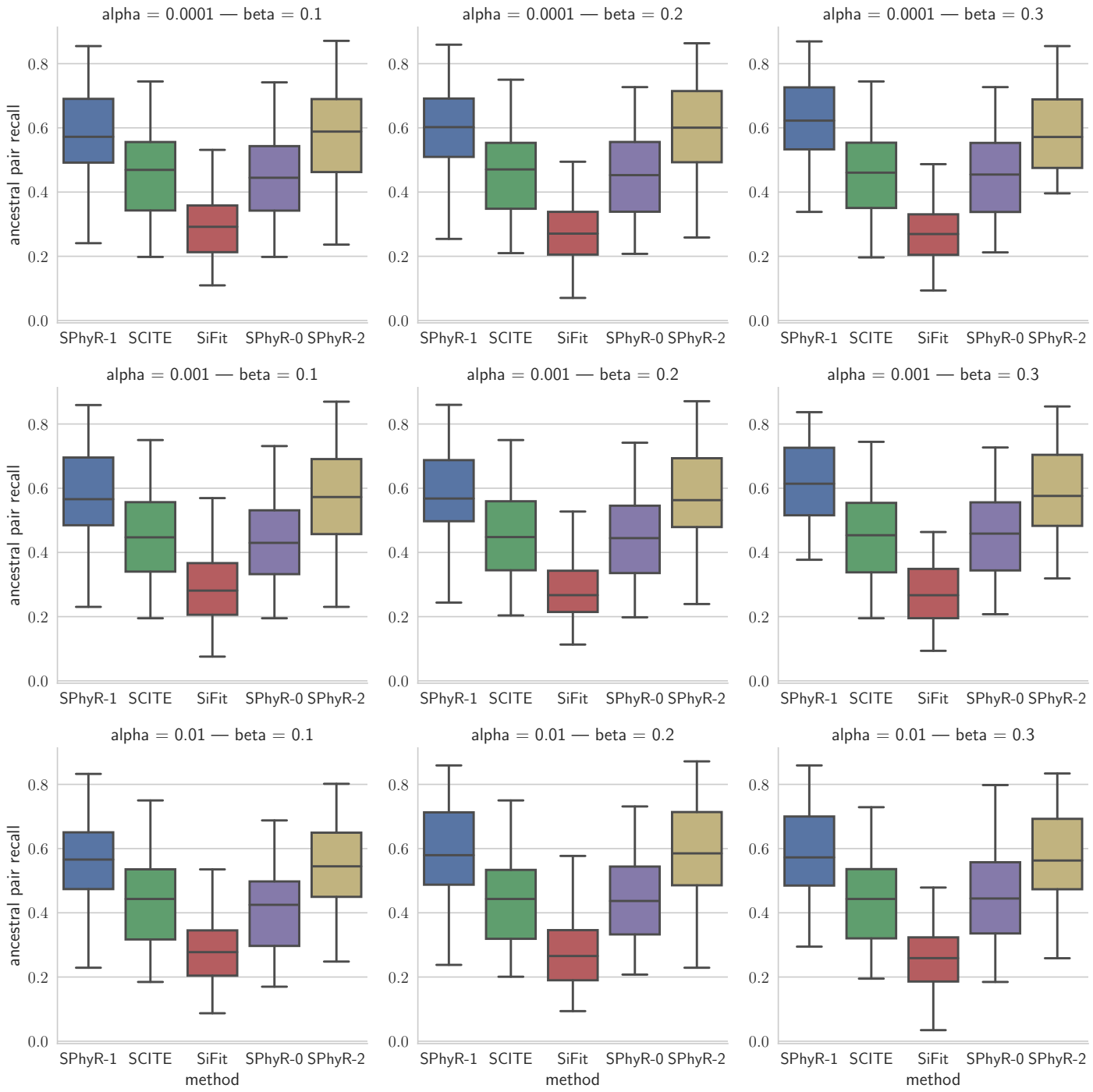


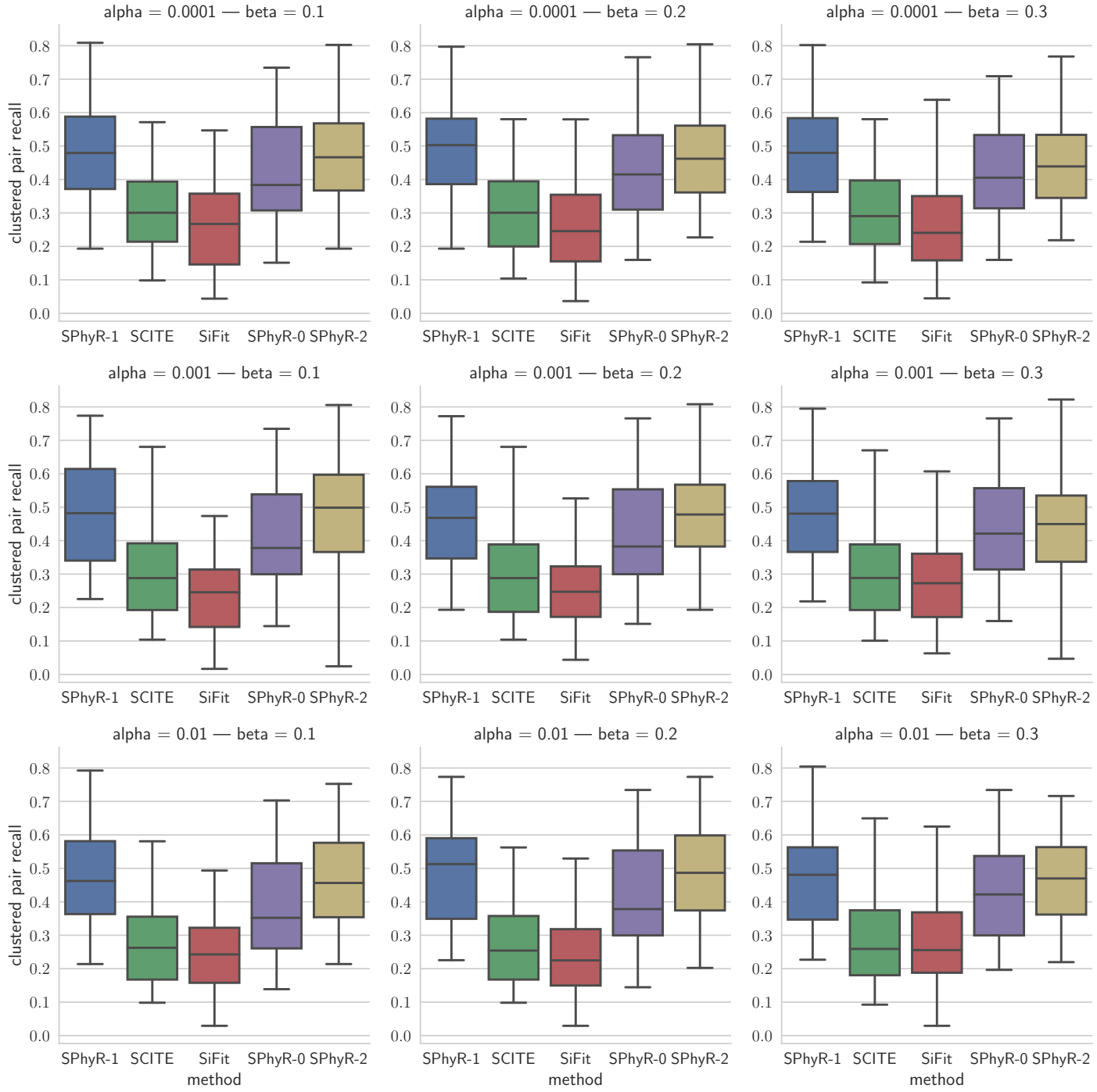
k*-Dollo Phylogeny *T

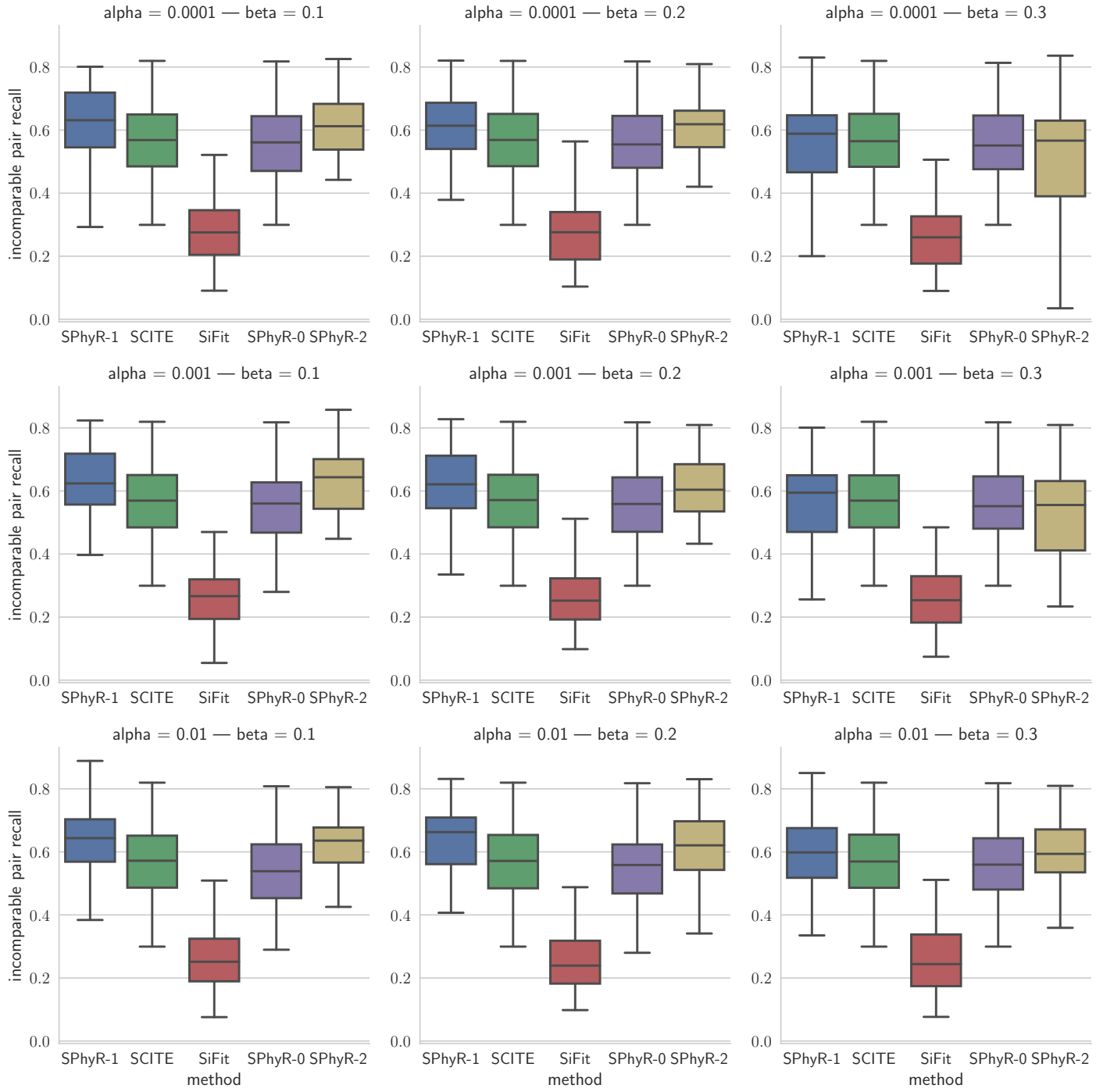

alpha = 0.0001 — beta = 0.1
alpha = 0.0001 — beta = 0.2
alpha = 0.0001 — beta = 0.3
alpha = 0.001 — beta = 0.1
alpha = 0.001 — beta = 0.2
alpha = 0.001 — beta = 0.3
alpha = 0.01 — beta = 0.1
alpha = 0.01 — beta = 0.2
alpha = 0.01 — beta = 0.3
FPR
0.05
0.04
0.03
0.02
0.01
0.00
SPhyR-1
SCITE
SiFit
SPhyR-0
SPhyR-2
method


alpha = 0.0001 — beta = 0.1
alpha = 0.0001 — beta = 0.2
alpha = 0.0001 — beta = 0.3
alpha = 0.001 — beta = 0.1
alpha = 0.001 — beta = 0.2
alpha = 0.001 — beta = 0.3
alpha = 0.01 — beta = 0.1
alpha = 0.01 — beta = 0.2
alpha = 0.01 — beta = 0.3
FNR
0.00
0.05
0.10
0.15
0.20
0.25
0.30
SPhyR-1
SCITE
SiFit
SPhyR-0
SPhyR-2
method


alpha = 0.0001 — beta = 0.1
alpha = 0.0001 — beta = 0.2
alpha = 0.0001 — beta = 0.3
alpha = 0.001 — beta = 0.1
alpha = 0.001 — beta = 0.2
alpha = 0.001 — beta = 0.3
alpha = 0.01 — beta = 0.1
alpha = 0.01 — beta = 0.2
alpha = 0.01 — beta = 0.3
time [s]
0
5000
10000
15000
20000
25000
30000
35000
SPhyR-1
SCITE
SiFit
SPhyR-0
SPhyR-2
method


alpha = 0.0001 — beta = 0.1
alpha = 0.0001 — beta = 0.2
alpha = 0.0001 — beta = 0.3
alpha = 0.001 — beta = 0.1
alpha = 0.001 — beta = 0.2
alpha = 0.001 — beta = 0.3
alpha = 0.01 — beta = 0.1
alpha = 0.01 — beta = 0.2
alpha = 0.01 — beta = 0.3
ancestral pair recall
0.0
0.2
0.4
0.6
0.8
SPhyR-1
SCITE
SiFit
SPhyR-0
SPhyR-2
method


alpha = 0.0001 — beta = 0.1
alpha = 0.0001 — beta = 0.2
alpha = 0.0001 — beta = 0.3
alpha = 0.001 — beta = 0.1
alpha = 0.001 — beta = 0.2
alpha = 0.001 — beta = 0.3
alpha = 0.01 — beta = 0.1
alpha = 0.01 — beta = 0.2
alpha = 0.01 — beta = 0.3
clustered pair recall
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
SPhyR-1
SCITE
SiFit
SPhyR-0
SPhyR-2
method


alpha = 0.0001 — beta = 0.1
alpha = 0.0001 — beta = 0.2
alpha = 0.0001 — beta = 0.3
alpha = 0.001 — beta = 0.1
alpha = 0.001 — beta = 0.2
alpha = 0.001 — beta = 0.3
alpha = 0.01 — beta = 0.1
alpha = 0.01 — beta = 0.2
alpha = 0.01 — beta = 0.3
incomparable pair recall
0.0
0.2
0.4
0.6
0.8
SPhyR-1
SCITE
SiFit
SPhyR-0
SPhyR-2
method