CS 598MEB
Computational Cancer Genomics

Lecture 3

Mohammed El-Kebir

February 2, 2021

Course Project

- 1-2 students per project
- First write a proposal, which will receive feedback from instructor and fellow students
- Then, conduct research and write a paper
- Pick venue (conference/journal) and use LaTeX style for your paper

Lecture Outline

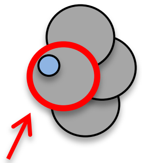
- Recap
- Two-state Perfect Phylogeny Mixtures

Reading

- M. El-Kebir, L. Oesper, H. Acheson-Field and B. J. Raphael. Reconstruction of clonal trees and tumor composition from multi-sample sequencing data. Bioinformatics (Special Issue: Proceedings of ISMB), 31(12):i62-i70, 2015
- Y. Qi, D. Pradhan and M. El-Kebir. Implications of non-uniqueness in phylogenetic deconvolution of bulk DNA samples of tumors. Algorithms for Molecular Biology, 14:19, 2019.

Tumorigenesis: Cell Mutation

Clonal Evolution Theory of Cancer
[Nowell, 1976]

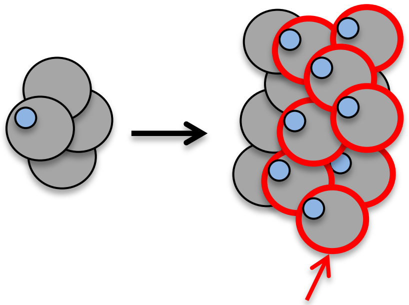


Founder
tumor cell
with somatic mutation: ●
(e.g. BRAF V600E)

Tumorigenesis: Cell Mutation

Clonal Evolution Theory of Cancer

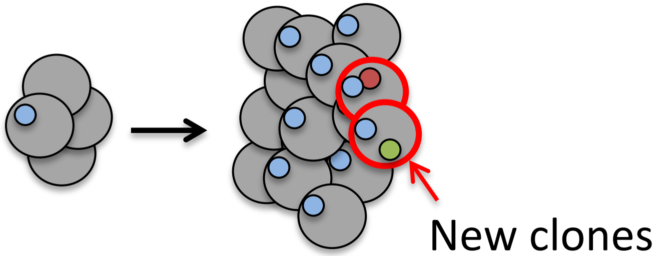
[Nowell, 1976]



Clonal expansion

Tumorigenesis: Cell Mutation

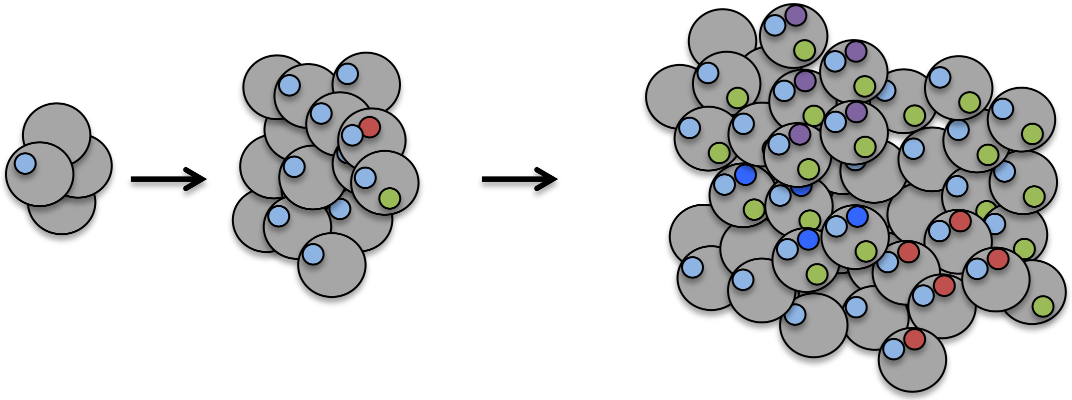
Clonal Evolution Theory of Cancer
[Nowell, 1976]



Tumorigenesis: Cell Mutation & Division

Clonal Evolution Theory of Cancer

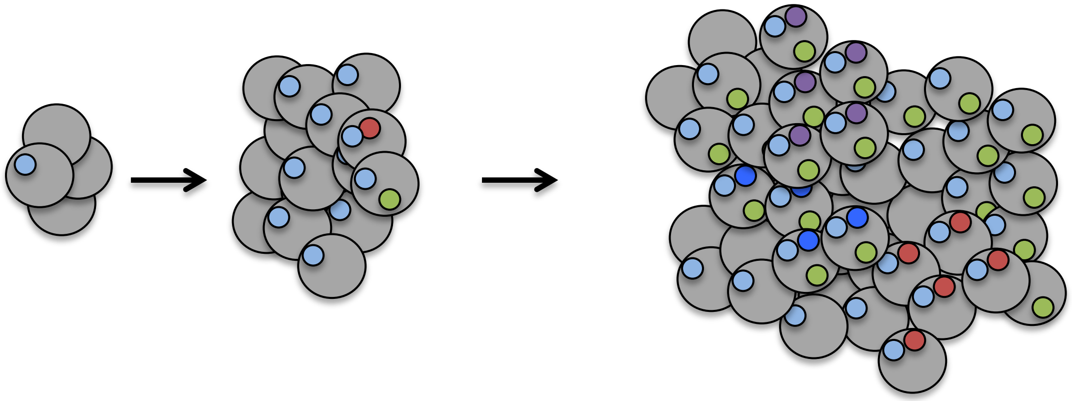
[Nowell, 1976]



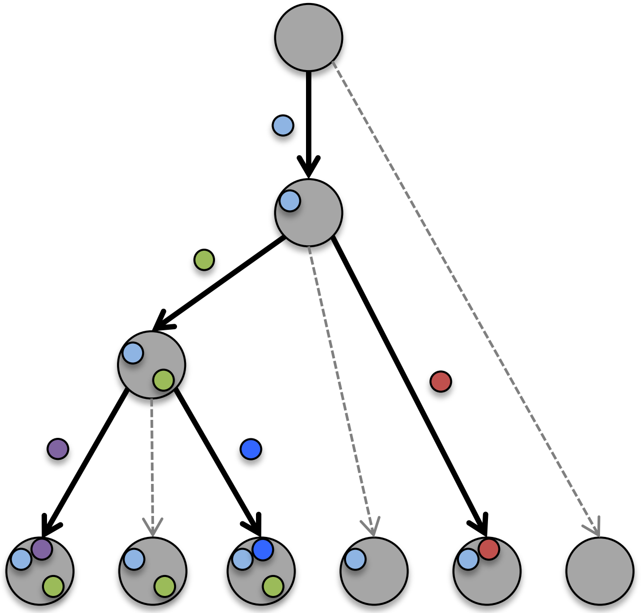
Intra-Tumor Heterogeneity

Tumorigenesis: Cell Mutation & Division

Clonal Evolution Theory of Cancer
[Nowell, 1976]

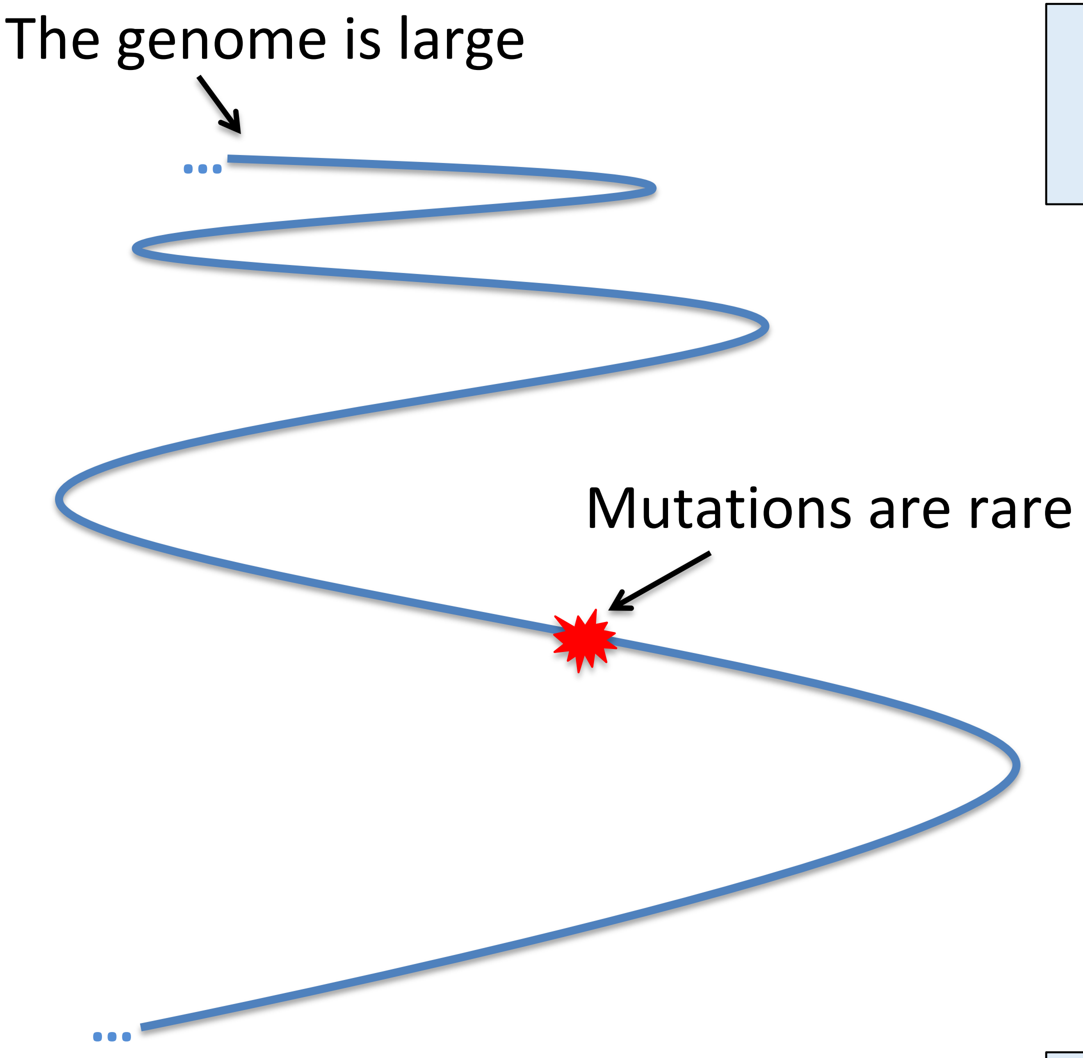


Intra-Tumor
Heterogeneity



Phylogenetic
Tree ***T***

Infinite Sites Model



[Kimura, 1969]

Infinite sites model: multiple mutations never occur at the same position

Mutated Loci

Species (cancer cells)

	🟥	🟦	🟩	🟪	🟧	🟨
A	0	0	0	0	1	1
B	0	0	0	1	1	1
C	0	0	1	0	1	0
D	1	0	0	0	0	0
E	1	1	0	0	0	0

1: mutated
0: not

All sites are bi-allelic: mutated or not.

Progression of Somatic Mutations

Single nucleotide mutation

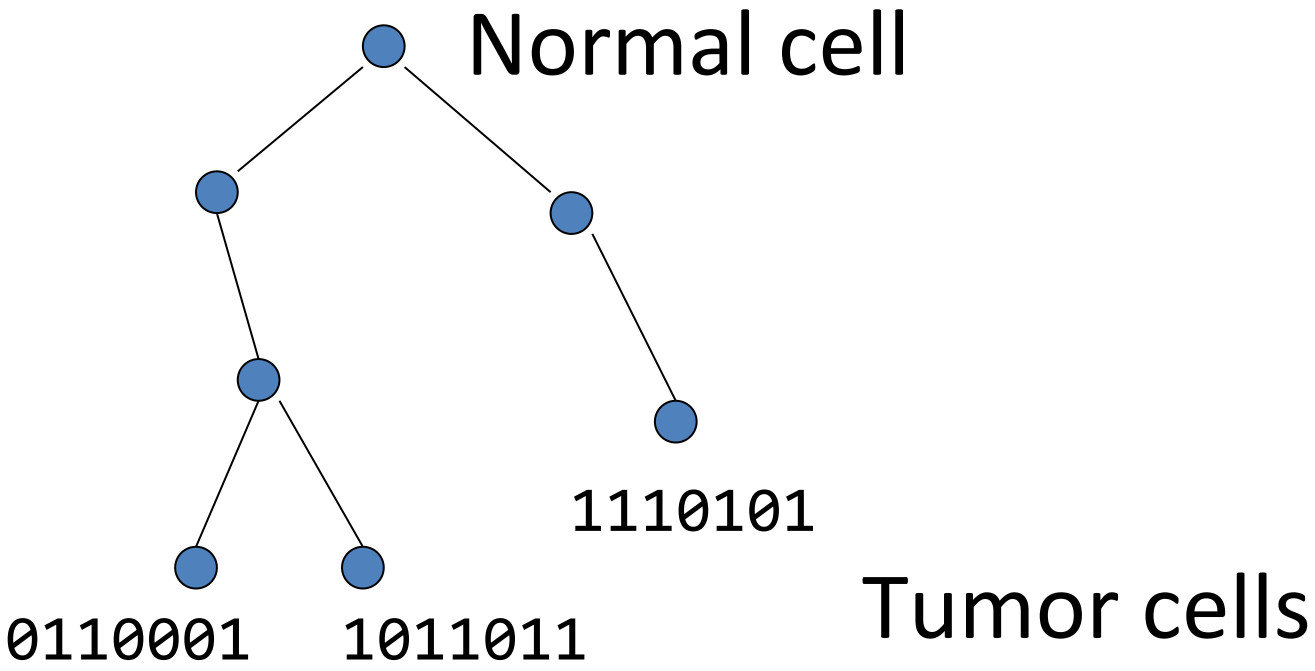
… CGTAATTAG …

↓

… CGTCATTAG …

0 = normal

1 = mutated



Root is the normal, founder cell and leaves are cells in tumor.

Infinite sites assumption: each locus mutates only once.

Lecture Outline

- Recap
- Two-state Perfect Phylogeny Mixtures

Reading

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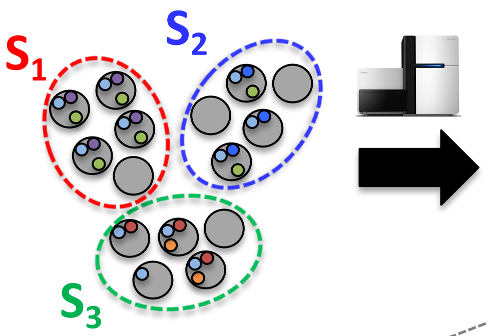
- Y. Qi, D. Pradhan and M. El-Kebir. Implications of non-uniqueness in phylogenetic deconvolution of bulk DNA samples of tumors. Algorithms for Molecular Biology, 14:19, 2019.

Sequencing and Tumor Phylogeny Inference

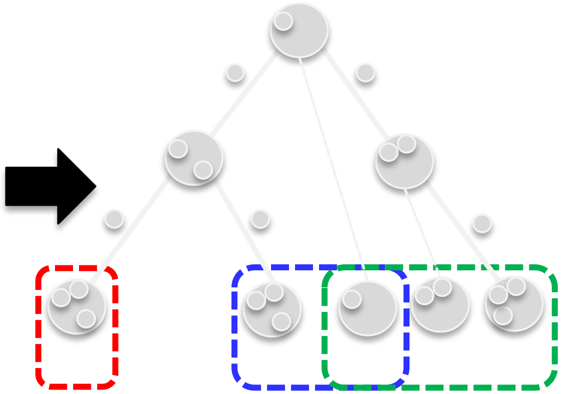


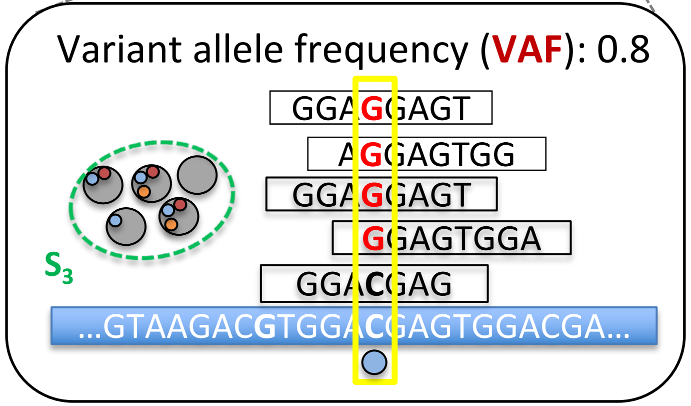
n **mutations**

m **samples**

$$\begin{array}{c|cccccc} & ● & ● & ● & ● & ● & ● \\ \hline S_1 & 0.8 & 0.8 & 0.8 & 0.0 & 0.0 & 0.0 \\ S_2 & 0.7 & 0.6 & 0.0 & 0.6 & 0.0 & 0.0 \\ S_3 & \boxed{0.8} & 0.0 & 0.0 & 0.0 & 0.6 & 0.4 \end{array}$$

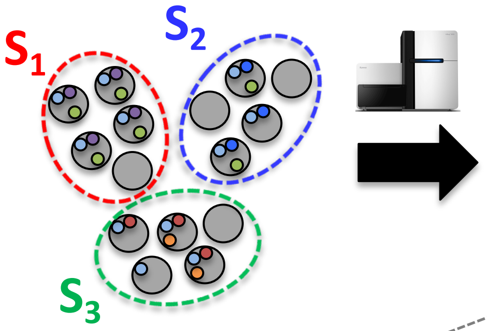
Frequency Matrix ***F***




Variant allele frequency (**VAF**): 0.8

Mixtures of unknown leaves ***L(T)***
of an unknown tree ***T***
in unknown proportions ***U***

Sequencing and Tumor Phylogeny Inference

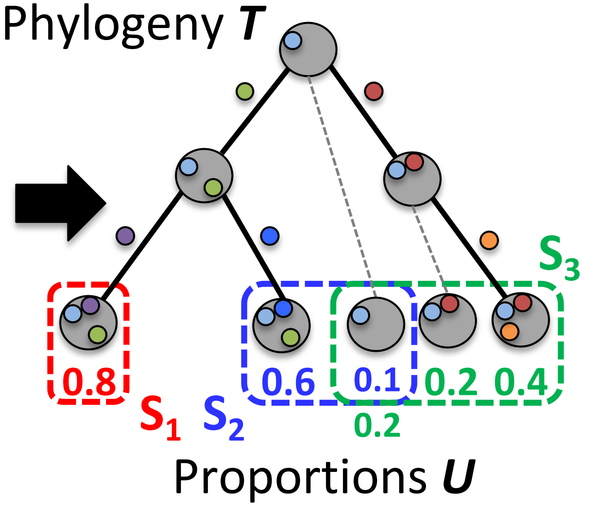


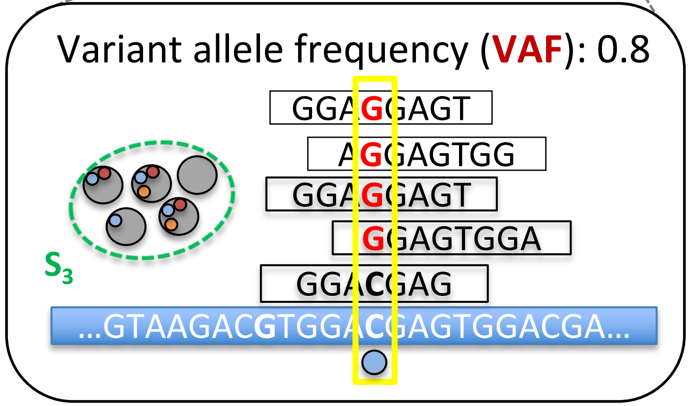
n mutations

$$\begin{array}{c|cccccc} & ● & ● & ● & ● & ● & ● \\ \hline S_1 & 0.8 & 0.8 & 0.8 & 0.0 & 0.0 & 0.0 \\ S_2 & 0.7 & 0.6 & 0.0 & 0.6 & 0.0 & 0.0 \\ S_3 & \boxed{0.8} & 0.0 & 0.0 & 0.0 & 0.6 & 0.4 \end{array}$$

m samples

Frequency Matrix ***F***



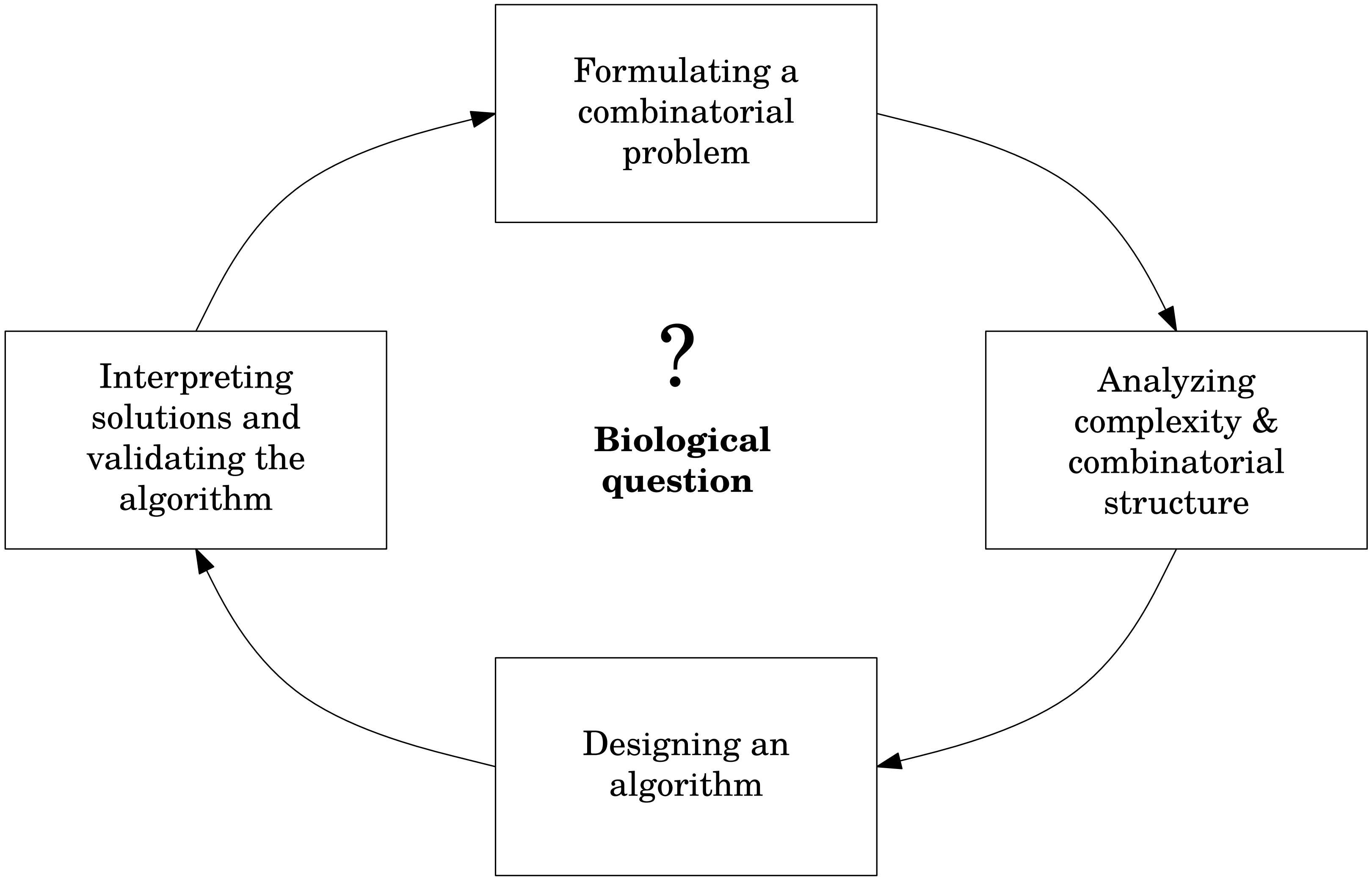


Variant allele frequency (**VAF**): 0.8

Mixtures of unknown leaves ***L(T)***
of an unknown tree ***T***
in unknown proportions ***U***

Tumor Phylogeny Inference: Given frequencies ***F***, find phylogeny ***T*** and proportions ***U***

Key Challenge in Computational Biology



Formulating a combinatorial problem

Analyzing complexity & combinatorial structure

Designing an algorithm

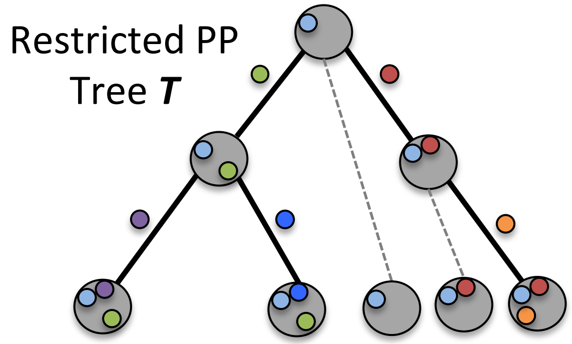
Interpreting solutions and validating the algorithm

?

Biological question

Translating a biological problem into a computational biology

Perfect Phylogeny Mixture



Restricted PP Tree ***T***

Assumptions:

- Infinite sites assumption:
  a character changes state once
- Error-free data

1-1 ↕ **Equivalent**

n mutations

$$\text{\textbf{\textit{m}} samples}\quad \begin{array}{c|cccccc} & ● & ● & ● & ● & ● & ● \\ \hline S_1 & 0.8 & 0.8 & 0.8 & 0.0 & 0.0 & 0.0 \\ S_2 & 0.7 & 0.6 & 0.0 & 0.6 & 0.0 & 0.0 \\ S_3 & 0.8 & 0.0 & 0.0 & 0.0 & 0.6 & 0.4 \end{array} \quad = \quad \text{\textbf{\textit{m}} samples}\quad \begin{array}{c|cccccc} & ◉ & ◉ & ◉ & ◉ & ◉ & ◉ \\ \hline S_1 & 0.0 & 0.0 & 0.8 & 0.0 & 0.0 & 0.0 \\ S_2 & 0.1 & 0.0 & 0.0 & 0.6 & 0.0 & 0.0 \\ S_3 & 0.2 & 0.0 & 0.0 & 0.0 & 0.2 & 0.4 \end{array} \quad \begin{array}{cccccc|c} ● & ● & ● & ● & ● & ● & \\ \hline 1 & 0 & 0 & 0 & 0 & 0 & ◉ \\ 1 & 1 & 0 & 0 & 0 & 0 & ◉ \\ 1 & 1 & 1 & 0 & 0 & 0 & ◉ \\ 1 & 1 & 0 & 1 & 0 & 0 & ◉ \\ 1 & 0 & 0 & 0 & 1 & 0 & ◉ \\ 1 & 0 & 0 & 0 & 1 & 1 & ◉ \end{array}$$

clones

Frequency Matrix ***F***

Mixture Matrix ***U***

Restricted PP Matrix ***B***

Rows of ***U*** are proportions:

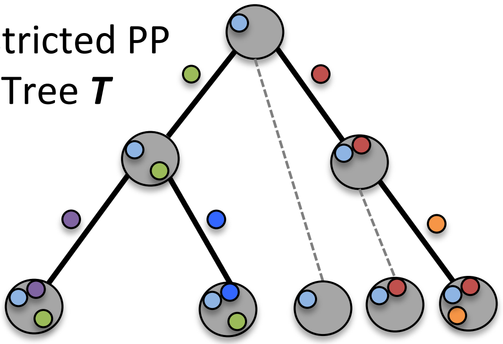
$$u_{pj} \geq 0 \text{ and } \sum_j u_{pj} \leq 1$$

Perfect Phylogeny Theorem
[Estabrook, 1971]
[Gusfield, 1991]

Perfect Phylogeny Mixture: [El-Kebir*, Oesper* et al., 2015]

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

Previous Work



Restricted PP Tree ***T***

1-1 ↕ **Equivalent**

<u>Variant of PPM:</u>

TrAp [Strino *et al.*, 2013], PhyloSub [Jiao *et al.*, 2014]
CITUP [Malikic *et al.*, 2015], BitPhylogeny [Yuan *et al.*, 2015]
LICHeE [Popic et *al.*, 2015], …

n mutations

$$\begin{array}{c|cccccc} & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet \\ \hline S_1 & 0.8 & 0.8 & 0.8 & 0.0 & 0.0 & 0.0 \\ S_2 & 0.7 & 0.6 & 0.0 & 0.6 & 0.0 & 0.0 \\ S_3 & 0.8 & 0.0 & 0.0 & 0.0 & 0.6 & 0.4 \end{array} = \begin{array}{c|cccccc} & \circ & \circ & \circ & \circ & \circ & \circ \\ \hline S_1 & 0.0 & 0.0 & 0.8 & 0.0 & 0.0 & 0.0 \\ S_2 & 0.1 & 0.0 & 0.0 & 0.6 & 0.0 & 0.0 \\ S_3 & 0.2 & 0.0 & 0.0 & 0.0 & 0.2 & 0.4 \end{array} \quad \begin{array}{cccccc|c} \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \\ \hline 1 & 0 & 0 & 0 & 0 & 0 & \circ \\ 1 & 1 & 0 & 0 & 0 & 0 & \circ \\ 1 & 1 & 1 & 0 & 0 & 0 & \circ \\ 1 & 1 & 0 & 1 & 0 & 0 & \circ \\ 1 & 0 & 0 & 0 & 1 & 0 & \circ \\ 1 & 0 & 0 & 0 & 1 & 1 & \circ \end{array}$$

m samples — Frequency Matrix ***F***

m samples — clones — Mixture Matrix ***U***

n mutations — clones — Restricted PP Matrix ***B***

Rows of ***U*** are proportions:

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

Perfect Phylogeny Theorem
[Estabrook, 1971]
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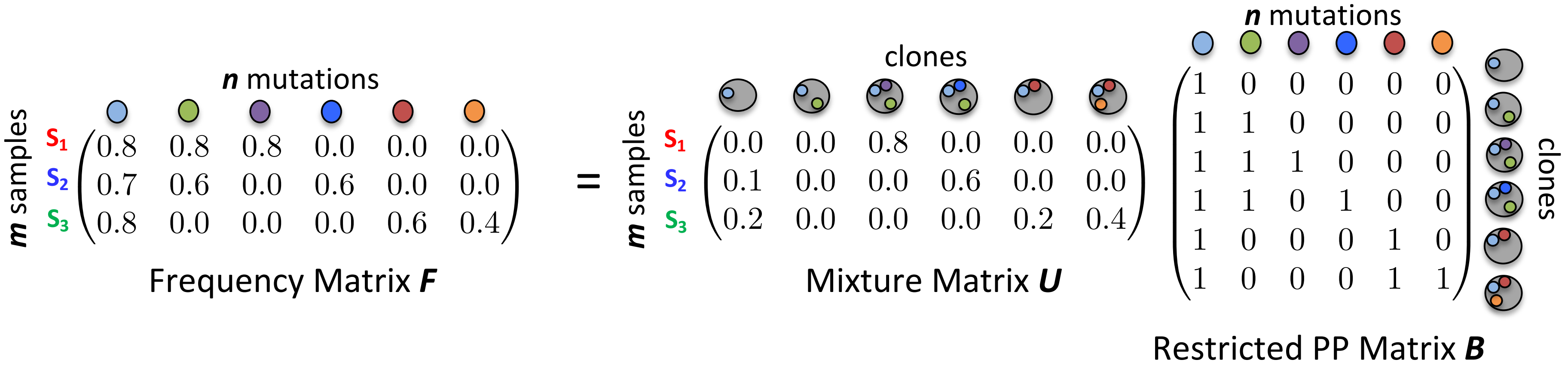
Perfect Phylogeny Mixture: [El-Kebir*, Oesper* et al., 2015]

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

Combinatorial Characterization

Perfect Phylogeny Mixture: [El-Kebir*, Oesper* et al., 2015]
Given ***F***, find ***U*** and ***B*** such that ***F = U B***



$$\begin{array}{c} s_1 \\ s_2 \\ s_3 \end{array}\begin{pmatrix} 0.8 & 0.8 & 0.8 & 0.0 & 0.0 & 0.0 \\ 0.7 & 0.6 & 0.0 & 0.6 & 0.0 & 0.0 \\ 0.8 & 0.0 & 0.0 & 0.0 & 0.6 & 0.4 \end{pmatrix} = \begin{array}{c} s_1 \\ s_2 \\ s_3 \end{array}\begin{pmatrix} 0.0 & 0.0 & 0.8 & 0.0 & 0.0 & 0.0 \\ 0.1 & 0.0 & 0.0 & 0.6 & 0.0 & 0.0 \\ 0.2 & 0.0 & 0.0 & 0.0 & 0.2 & 0.4 \end{pmatrix} \begin{pmatrix} 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 0 & 0 \\ 1 & 1 & 1 & 0 & 0 & 0 \\ 1 & 1 & 0 & 1 & 0 & 0 \\ 1 & 0 & 0 & 0 & 1 & 0 \\ 1 & 0 & 0 & 0 & 1 & 1 \end{pmatrix}$$

Frequency Matrix ***F***

Mixture Matrix ***U***

Restricted PP Matrix ***B***

- **Combinatorial characterization** involves investigating what (optimal) solutions look like
- This starts by asking questions!

Given *F* and *T* (or *B*), is there a usage matrix *U*?

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

n mutations

m samples

$$\begin{array}{c|cccccc} & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet \\ \hline S_1 & 0.8 & 0.8 & 0.8 & 0.0 & 0.0 & 0.0 \\ S_2 & 0.7 & 0.6 & 0.0 & 0.6 & 0.0 & 0.0 \\ S_3 & 0.8 & 0.0 & 0.0 & 0.0 & 0.6 & 0.4 \end{array}$$

Frequency Matrix ***F***

=

$$\begin{array}{c|c} S_1 & \\ S_2 & ? \\ S_3 & \end{array}$$

Usage Matrix ***U***

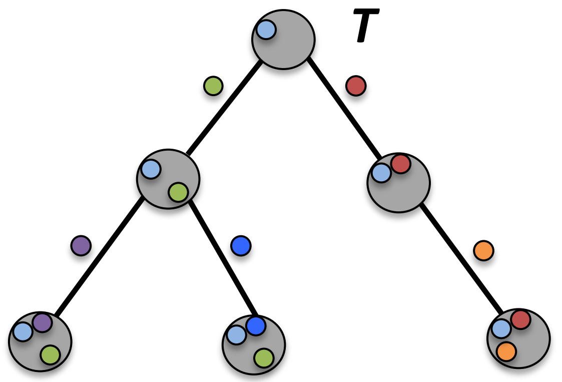
n mutations

n clones

$$\begin{array}{c|cccccc} & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet \\ \hline \bullet & 1 & 0 & 0 & 0 & 0 & 0 \\ \bullet & 1 & 1 & 0 & 0 & 0 & 0 \\ \bullet & 1 & 1 & 1 & 0 & 0 & 0 \\ \bullet & 1 & 1 & 0 & 1 & 0 & 0 \\ \bullet & 1 & 0 & 0 & 0 & 1 & 0 \\ \bullet & 1 & 0 & 0 & 0 & 1 & 1 \end{array}$$

Restricted PP Matrix ***B***

↕ **1-1**



Given *F* and *T* (or *B*), is there a usage matrix *U*?

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

$$\begin{array}{c|cccccc} & ● & ● & ● & ● & ● & ● \\ \hline S_1 & 0.8 & 0.8 & 0.8 & 0.0 & 0.0 & 0.0 \\ S_2 & 0.7 & 0.6 & 0.0 & 0.6 & 0.0 & 0.0 \\ S_3 & 0.8 & 0.0 & 0.0 & 0.0 & 0.6 & 0.4 \end{array} = \begin{array}{c|cccccc} & ● & ● & ● & ● & ● & ● \\ \hline S_1 & 0.0 & 0.0 & 0.8 & 0.0 & 0.0 & 0.0 \\ S_2 & 0.1 & 0.0 & 0.0 & 0.6 & 0.0 & 0.0 \\ S_3 & 0.2 & 0.0 & 0.0 & 0.0 & 0.2 & 0.4 \end{array} \begin{array}{cccccc|c} ● & ● & ● & ● & ● & ● & \\ \hline 1 & 0 & 0 & 0 & 0 & 0 & ● \\ 1 & 1 & 0 & 0 & 0 & 0 & ● \\ 1 & 1 & 1 & 0 & 0 & 0 & ● \\ 1 & 1 & 0 & 1 & 0 & 0 & ● \\ 1 & 0 & 0 & 0 & 1 & 0 & ● \\ 1 & 0 & 0 & 0 & 1 & 1 & ● \end{array}$$

n mutations

m samples

Frequency Matrix ***F***

Usage Matrix ***U***

n mutations

n clones

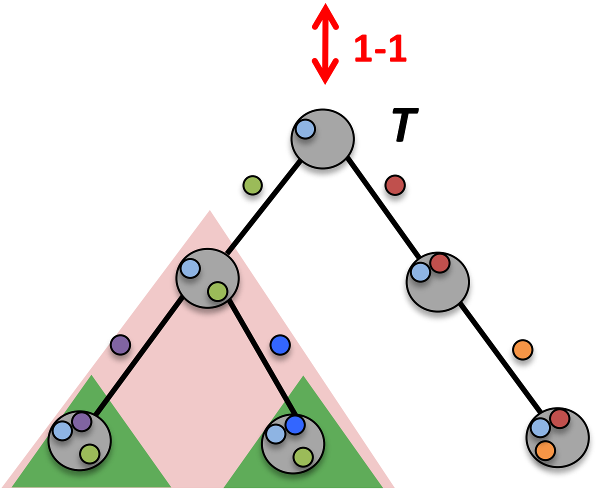
Restricted PP Matrix ***B***

Lemma: *B* is invertible

➡ Given ***F*** and ***B***, ***U*** is **unique**: ***U* = *F B*$^{-1}$**

Lemma:

$$u_{pj} = \boxed{f_{pj}} - \boxed{\sum_{k \text{ child of } j} f_{pk}}$$



Given *F* and *T* (or *B*), is there a usage matrix *U*?

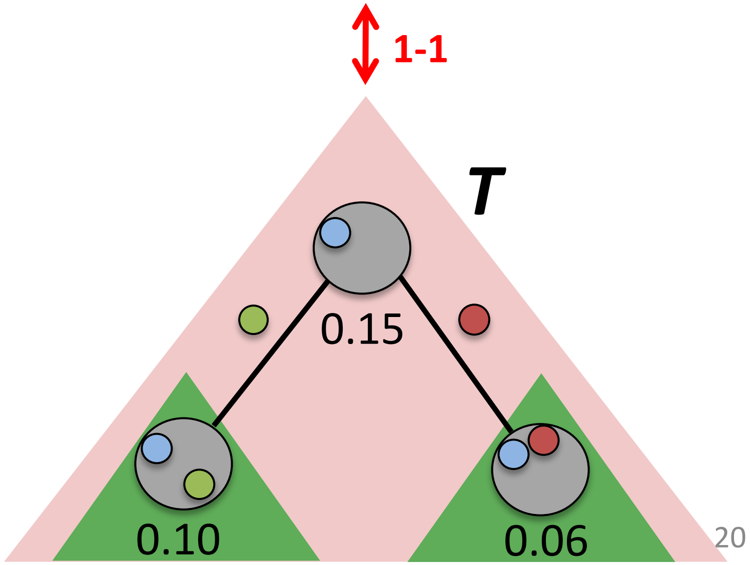
PPM: Given ***F***, find ***U*** and ***B*** such that ***F* = *U B***

$$\begin{array}{ccc} ● & ● & ● \\ 0.15 & 0.1 & 0.06 \\ 0.2 & 0.05 & 0.04 \end{array} = \begin{pmatrix} \boxed{-0.01} & 0.1 & 0.06 \\ 0.11 & 0.05 & 0.04 \end{pmatrix} \begin{pmatrix} 1 & 0 & 0 \\ 1 & 1 & 0 \\ 1 & 0 & 1 \end{pmatrix}$$

Frequency Matrix ***F***

Usage Matrix ***U***

Restricted PP Matrix ***B***



Lemma:

$$u_{pj} = \boxed{f_{pj}} - \boxed{\sum_{k \text{ child of } j} f_{pk}}$$

Combinatorial Characterization of Solutions

Lemma:

$$u_{pj} = \boxed{f_{pj}} - \boxed{\sum_{k \text{ child of } j} f_{pk}}$$

Lemma (Sum Condition):

Given ***F*** and ***T***, for all samples *p* and mutations *j*, $\boxed{f_{pj}} \geq \boxed{\sum_{k \text{ child of } j} f_{pk}}$

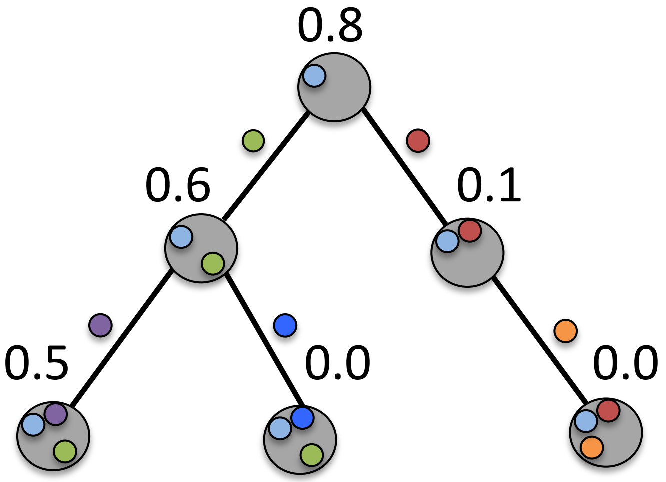
necessary

sufficient

$$\begin{array}{cccccc}
● & ● & ● & ● & ● & ● \\
\end{array}$$

$$\begin{pmatrix}
0.8 & 0.6 & 0.5 & 0.0 & 0.1 & 0.0 \\
0.7 & 0.6 & 0.0 & 0.6 & 0.0 & 0.0 \\
0.8 & 0.0 & 0.0 & 0.0 & 0.6 & 0.4
\end{pmatrix}$$

F



T

Combinatorial Characterization of Solutions

Lemma (Sum Condition):

Given ***F*** and ***T***, for all samples *p* and mutations *j*, $$f_{pj} \geq \sum_{k \text{ child of } j} f_{pk}$$

necessary

sufficient

Lemma (Ancestry Condition):

Given ***F*** and ***T***, for all samples *p* and mutations *k* child of *j*, $$f_{pj} \geq f_{pk}$$

necessary

$$\begin{array}{cccccc} \bullet & \bullet & \bullet & \bullet & \bullet & \bullet \\ \end{array}$$
$$\begin{pmatrix} 0.8 & 0.6 & 0.5 & 0.0 & 0.1 & 0.0 \\ 0.7 & 0.6 & 0.0 & 0.6 & 0.0 & 0.0 \\ 0.8 & 0.0 & 0.0 & 0.0 & 0.6 & 0.4 \end{pmatrix}$$

F

Combinatorial Characterization of Solutions

Lemma (Sum Condition):
Given ***F*** and ***T***, for all samples *p* and mutations *j*, $f_{pj} \geq \sum_{k \text{ child of } j} f_{pk}$

necessary

sufficient

Lemma (Ancestry Condition):
Given ***F*** and ***T***, for all samples *p* and mutations *k* child of *j*, $f_{pj} \geq f_{pk}$

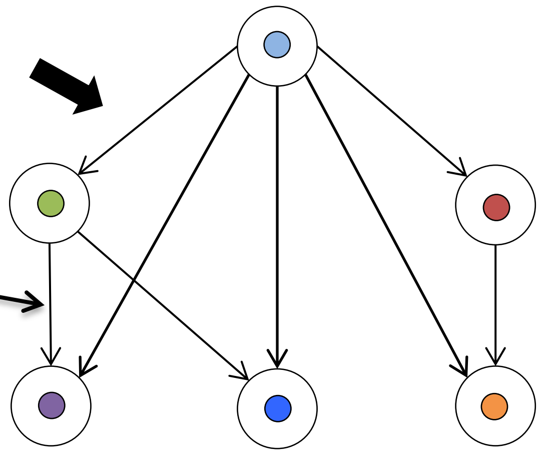
necessary

Ancestry graph *G* = (*V*, *A*); given ***F***

- Vertex for every mutation
- Edge $(j, k) \in A$ iff $f_{pj} \geq f_{pk}$ for all samples *p*

$$\begin{array}{cccccc} ● & ● & ● & ● & ● & ● \\ \end{array}$$
$$\begin{pmatrix} 0.8 & 0.6 & 0.5 & 0.0 & 0.1 & 0.0 \\ 0.7 & 0.6 & 0.0 & 0.6 & 0.0 & 0.0 \\ 0.8 & 0.0 & 0.0 & 0.0 & 0.6 & 0.4 \end{pmatrix}$$

F



potential parental relationship

Ancestry Graph ***G* = (*V, A*)**

Combinatorial Characterization of Solutions

Lemma (Sum Condition):
Given ***F*** and ***T***, for all samples *p* and mutations *j*, $f_{pj} \geq \sum_{k \text{ child of } j} f_{pk}$

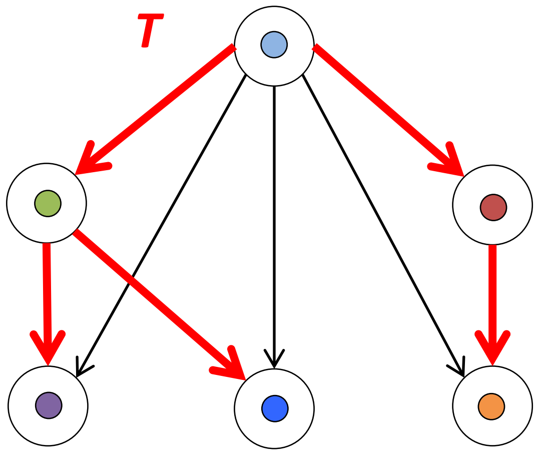
necessary
sufficient

Lemma (Ancestry Condition):
Given ***F*** and ***T***, for all samples *p* and mutations *k* child of *j*, $f_{pj} \geq f_{pk}$

necessary

$$\begin{array}{cccccc} \bullet & \bullet & \bullet & \bullet & \bullet & \bullet \\ \end{array}$$
$$\begin{pmatrix} 0.8 & 0.6 & 0.5 & 0.0 & 0.1 & 0.0 \\ 0.7 & 0.6 & 0.0 & 0.6 & 0.0 & 0.0 \\ 0.8 & 0.0 & 0.0 & 0.0 & 0.6 & 0.4 \end{pmatrix}$$

F



Ancestry Graph ***G*** **= (*V, A*)**

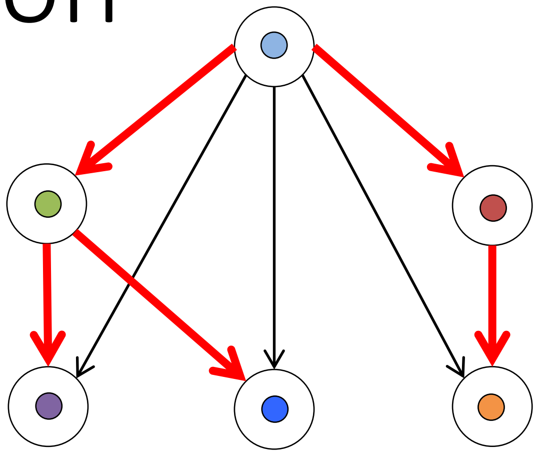
Ancestry graph *G* = (*V, A*); given ***F***

- Vertex for every mutation
- Edge $(j, k) \in A$ iff $f_{pj} \geq f_{pk}$ for all samples *p*

Theorem 1:
T is a solution to the PPM if and only if ***T*** is a spanning tree of ***G*** satisfying the Sum Condition

Theorem 2:
PPM is NP-complete

Solving the PPM problem: ILP formulation



G = (V, A)

$$\max \sum_{(v_j,v_k)\in A'} x_{jk}$$

Find the largest set of edges in *G*

$$\text{s.t.} \sum_{v_j\in\delta^+(v_r)} x_{rj} = 1$$

Exactly one root node

$$x_{kl} \le \sum_{v_j\in\delta^-(v_k)} x_{jk} \qquad \forall (v_k, v_l) \in A$$

Connectivity

$$\sum_{v_j\in\delta^-(v_k)} x_{jk} \le 1 \qquad \forall v_k \in V$$

Tree

$$\sum_{v_j\in\delta^-(v_k)} f_{pk}x_{jk} \ge \sum_{v_l\in\delta^+(v_k)} f_{pl}x_{kl} \qquad \forall p\in[m],\, v_k\in V$$

Sum condition

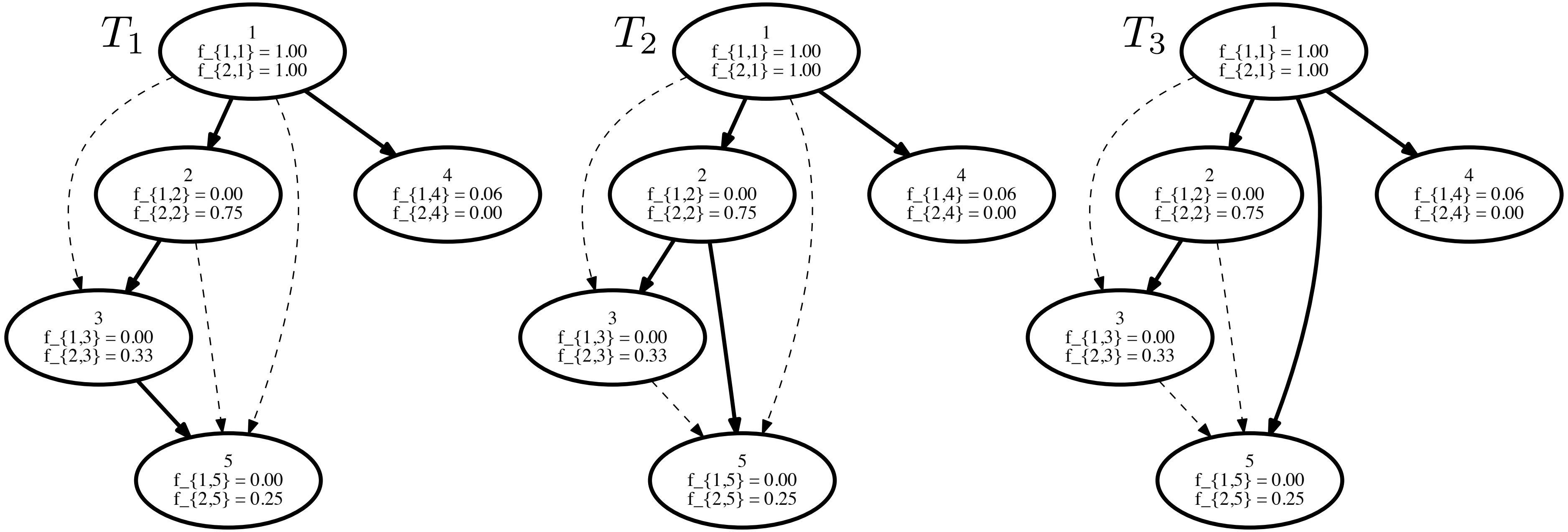
$$x_{jk}\in\{0,1\} \qquad \forall (v_j, v_k)\in A'$$

Non-uniqueness of Solutions to PPM

$$F = \begin{pmatrix} 1 & 0 & 0 & 0.06 & 0 \\ 1 & 0.75 & 0.33 & 0 & 0.25 \end{pmatrix}$$

Question 0: Reconstruct all solutions?

Non-uniqueness of Solutions to PPM



$$F = \begin{pmatrix} 1 & 0 & 0 & 0.06 & 0 \\ 1 & 0.75 & 0.33 & 0 & 0.25 \end{pmatrix}$$

Question 1: Can we determine the number of solutions?

Question 2: Can sample solutions uniformly at random?

Question 3: How to enumerate solutions?

Recall: Different Types of Problems!

Problem Π with instance X and solution set $\Pi(X)$:

- Decision problem:
  - Is $\Pi(X) = \emptyset$?
- Optimization problem:
  - Find $y^* \in \Pi(X)$ s.t. $f(y^*)$ is optimum.
- Counting problem:
  - Compute $|\Pi(X)|$.
- Sampling problem:
  - Sample uniformly from $\Pi(X)$.
- Enumeration problem:
  - Enumerate all solutions in $\Pi(X)$

Algorithms:

Set of instructions for solving problem.

- Exact
- Heuristic

On the Complexity of #PPM (new results)

Question 1: Can we determine the number of solutions?

Question 2: Can sample solutions uniformly at random?

#PPM: Given ***F***, count the number of pairs ***(U, B)*** composed of mixture matrix ***U*** and perfect phylogeny matrix ***B*** such that ***F* = *U B***

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#P is the complexity class of counting problems whose decision problems are in NP

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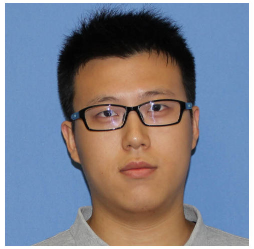
Theorem: #PPM is #P-complete

Theorem: There is no FPRAS for #PPM

Theorem: There is no FPAUS for PPM


Yuanyuan Qi

Outline

Background and theory:

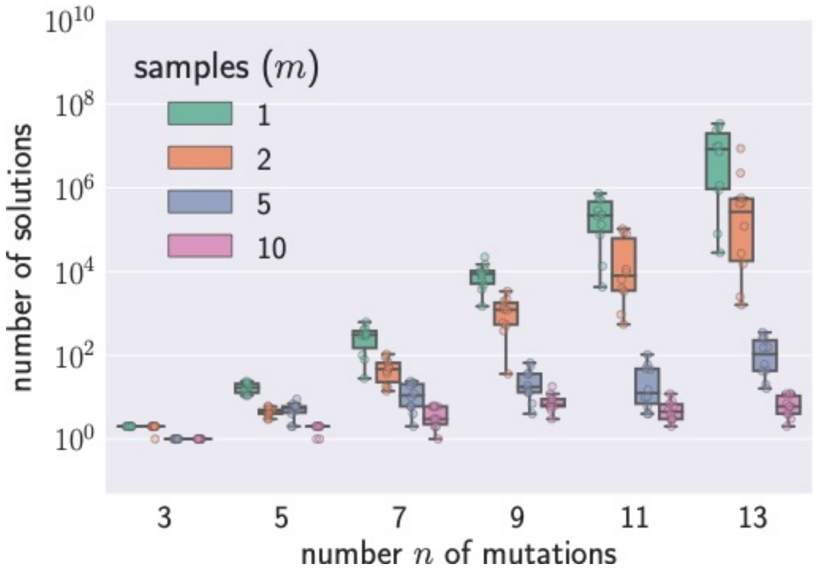
- Perfect Phylogeny Mixture (PPM) problem
- Combinatorial characterization of solutions
- #PPM: exact counting and uniform sampling

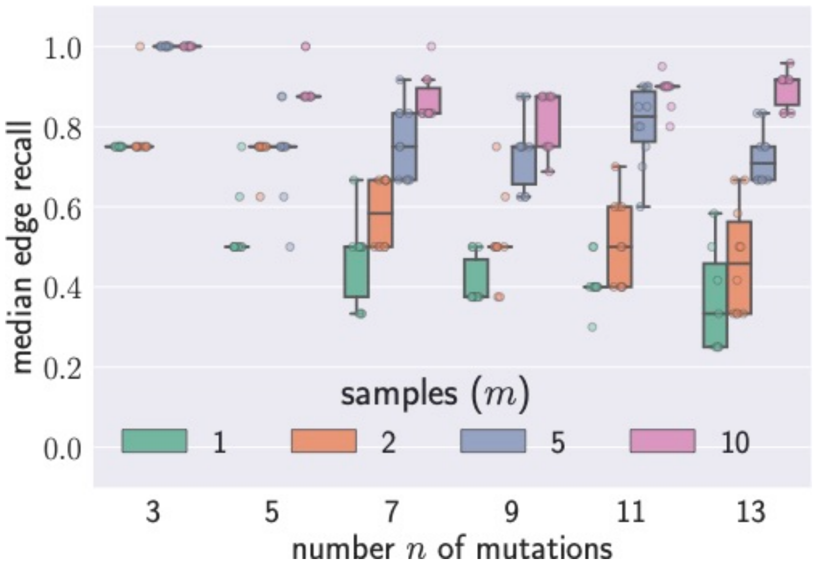
Simulation results:

- What contributes to non-uniqueness?
- How to reduce non-uniqueness?
- How does non-uniqueness affect current methods?

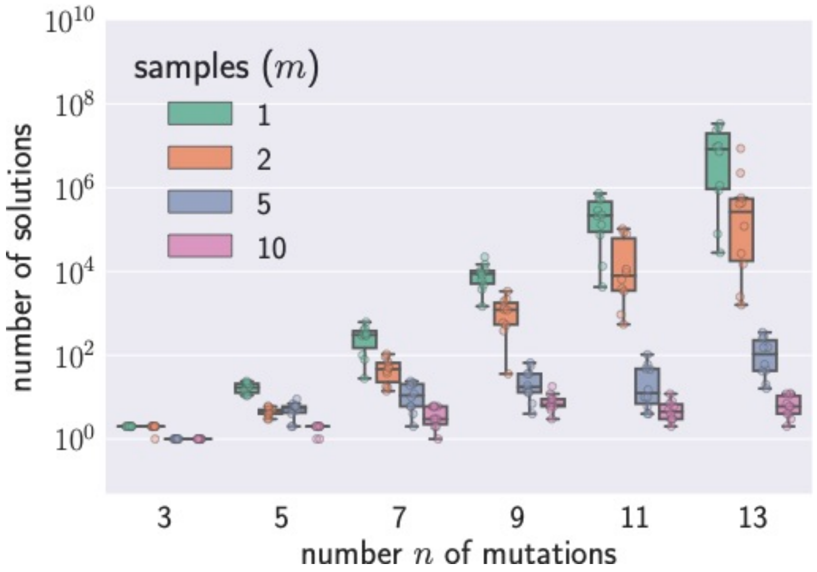
Dikshant Pradhan

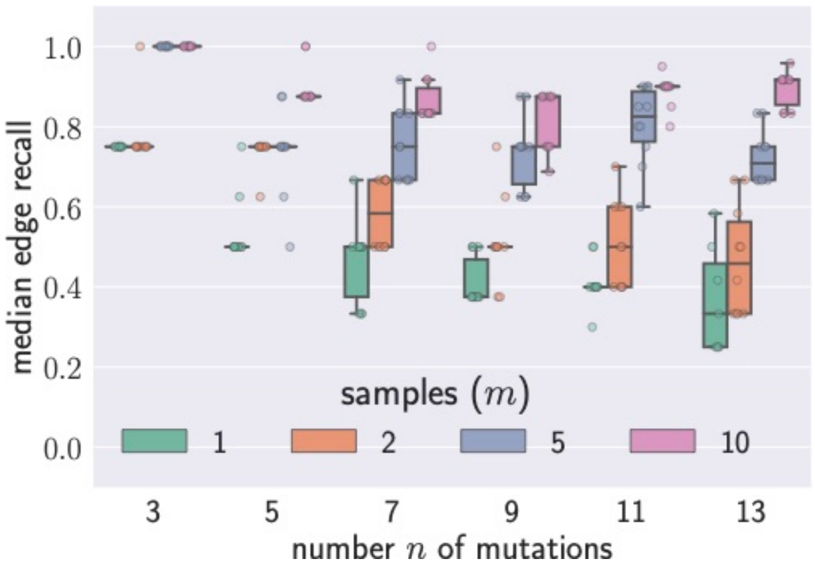
What Contributes to Non-uniqueness?

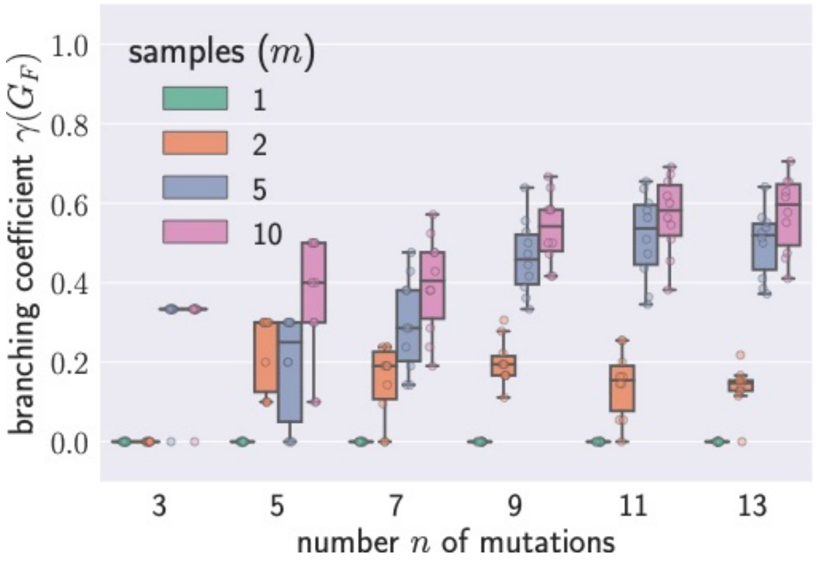


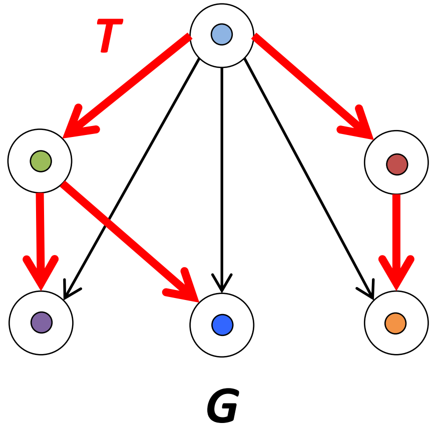


What Contributes to Non-uniqueness?

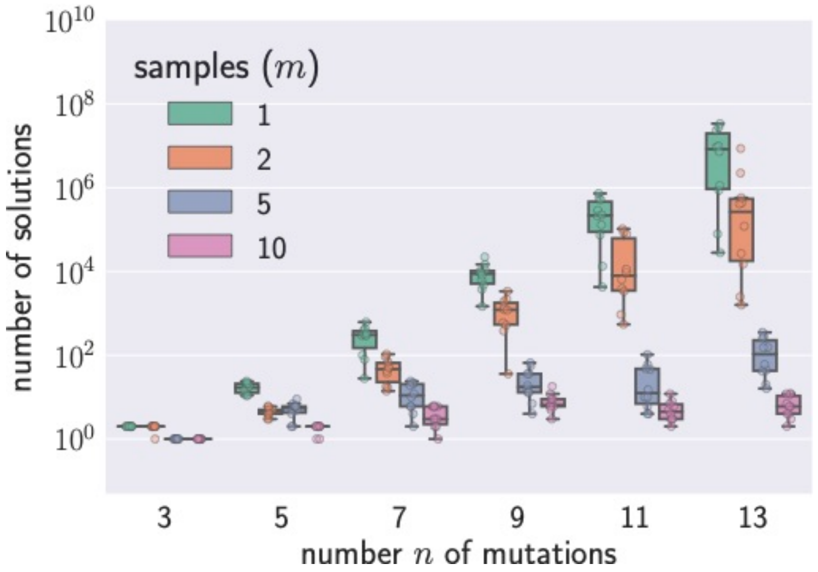


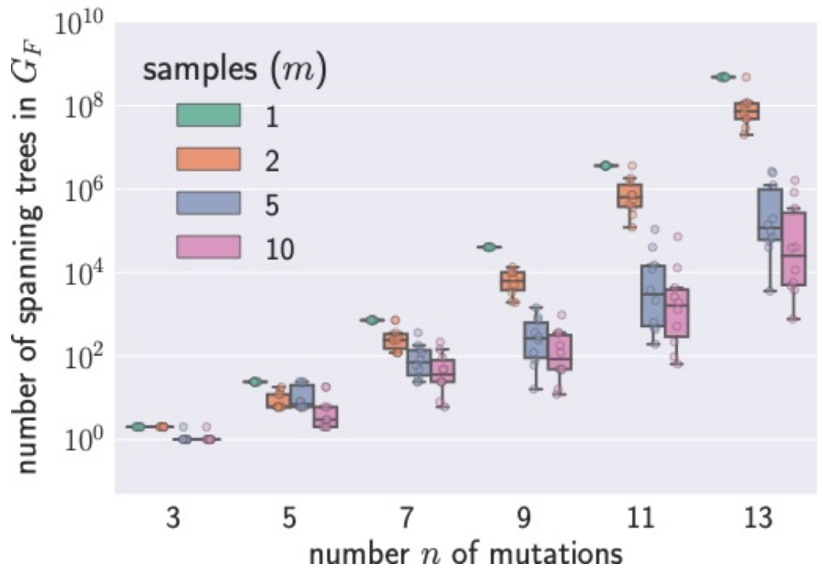


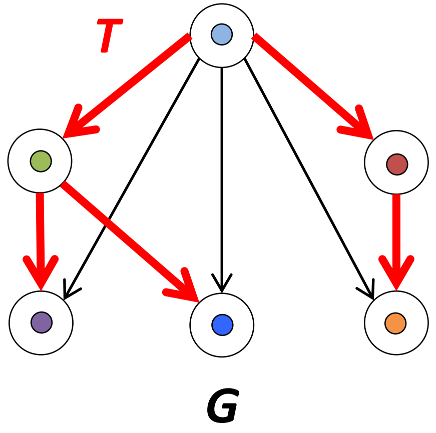




An Upper Bound for Number of Solutions







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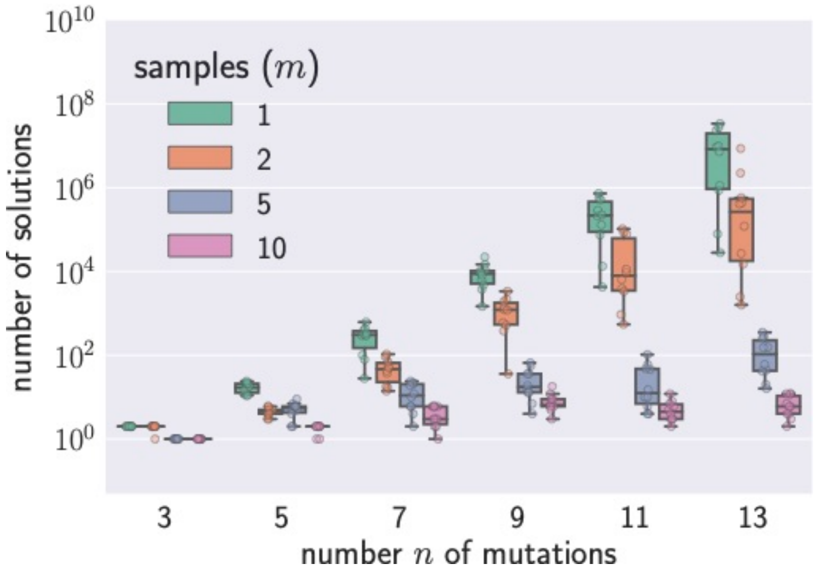
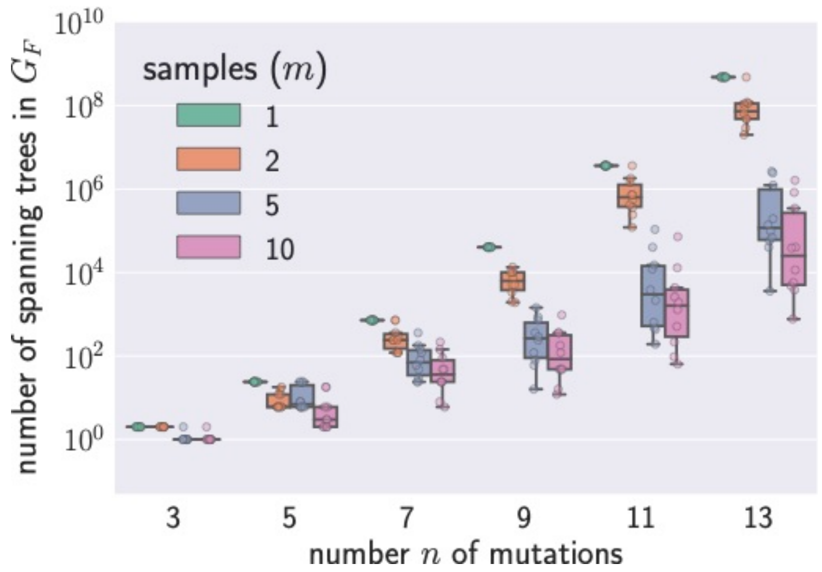
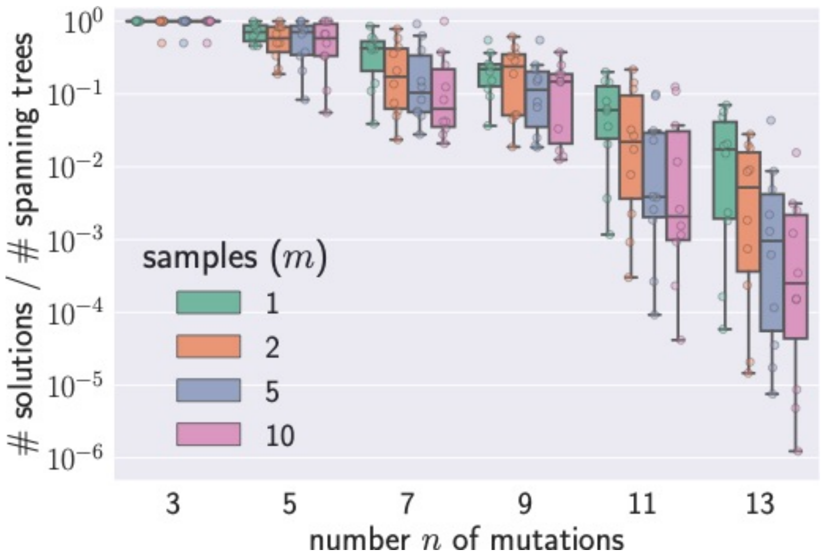
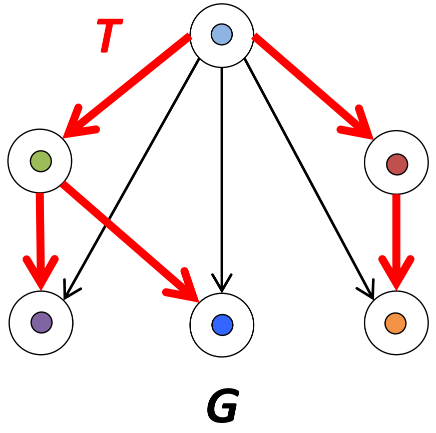
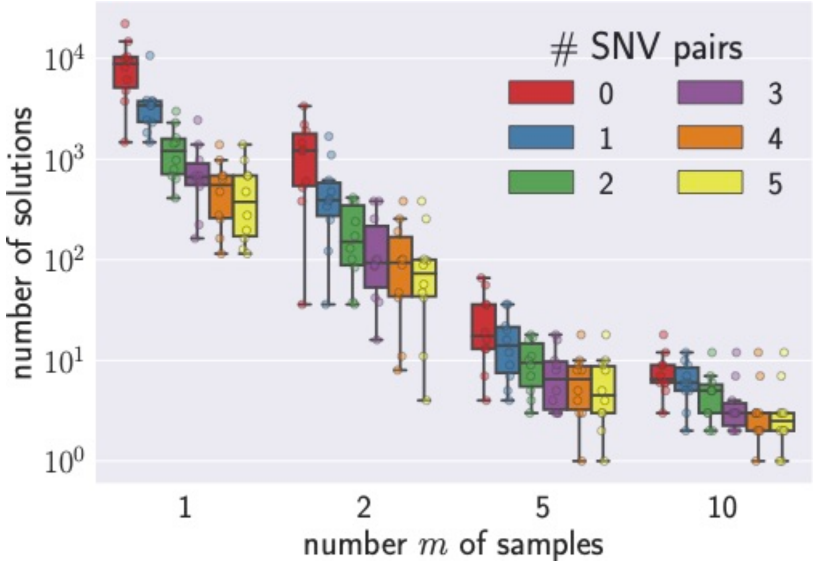


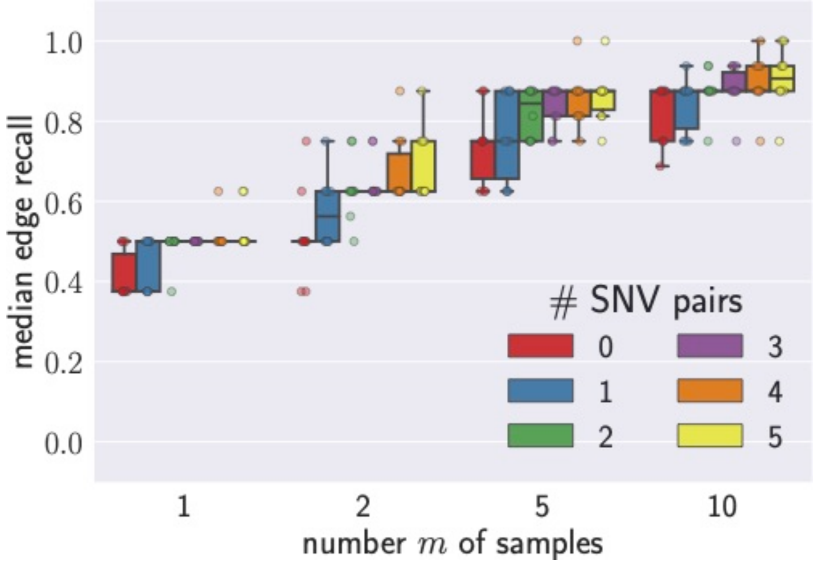


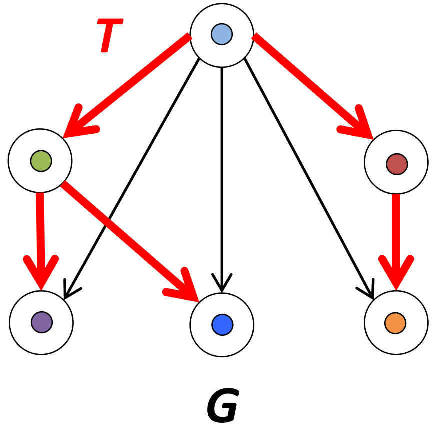




How to Reduce Non-Uniqueness?







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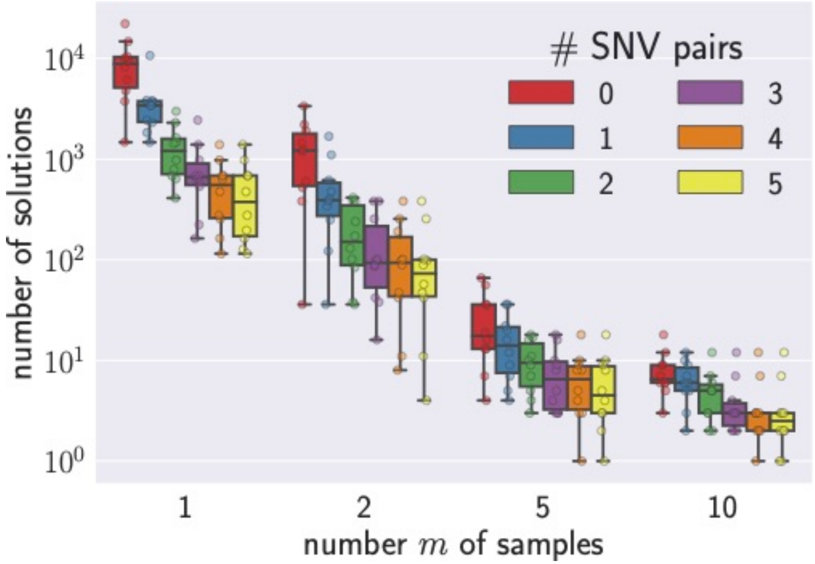

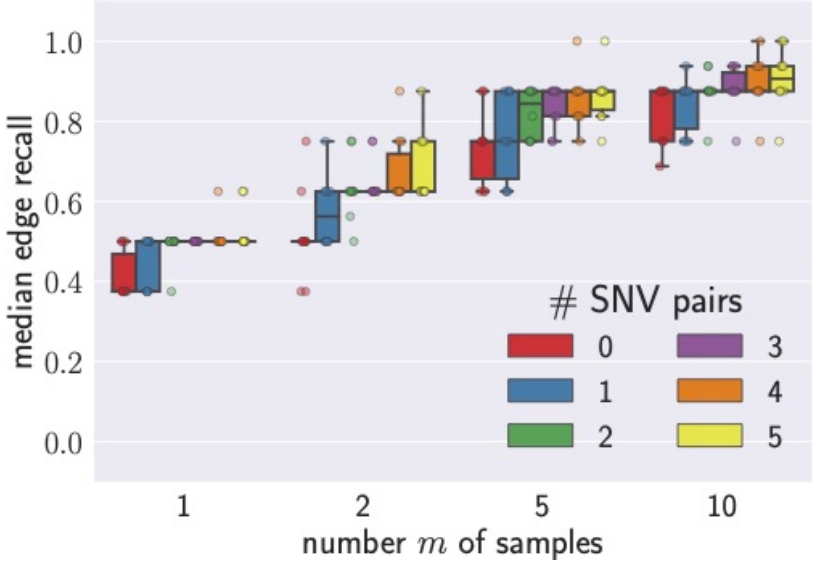

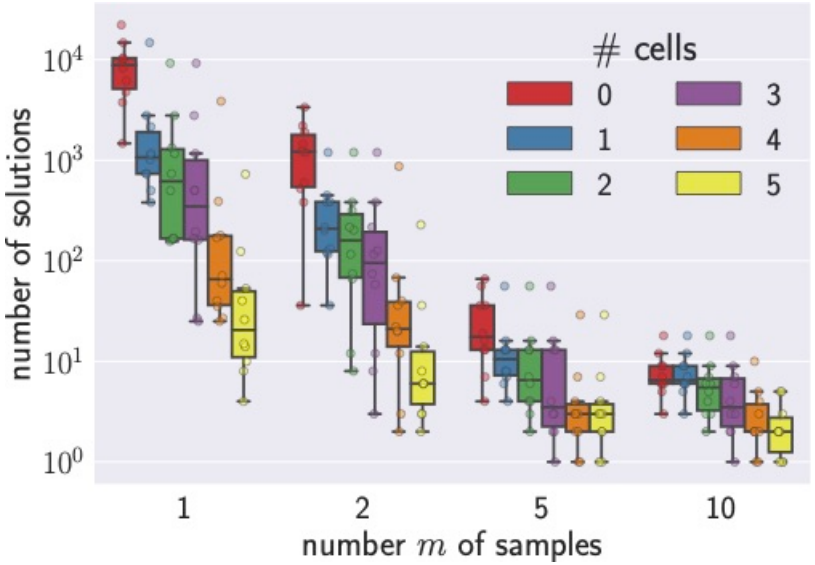

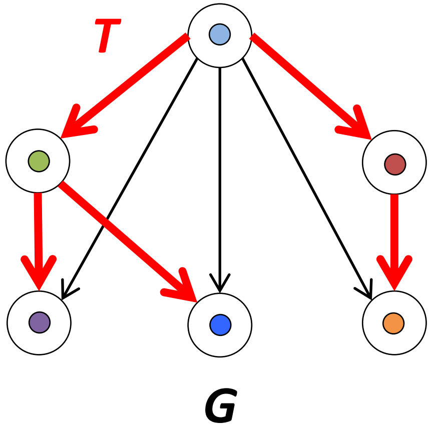

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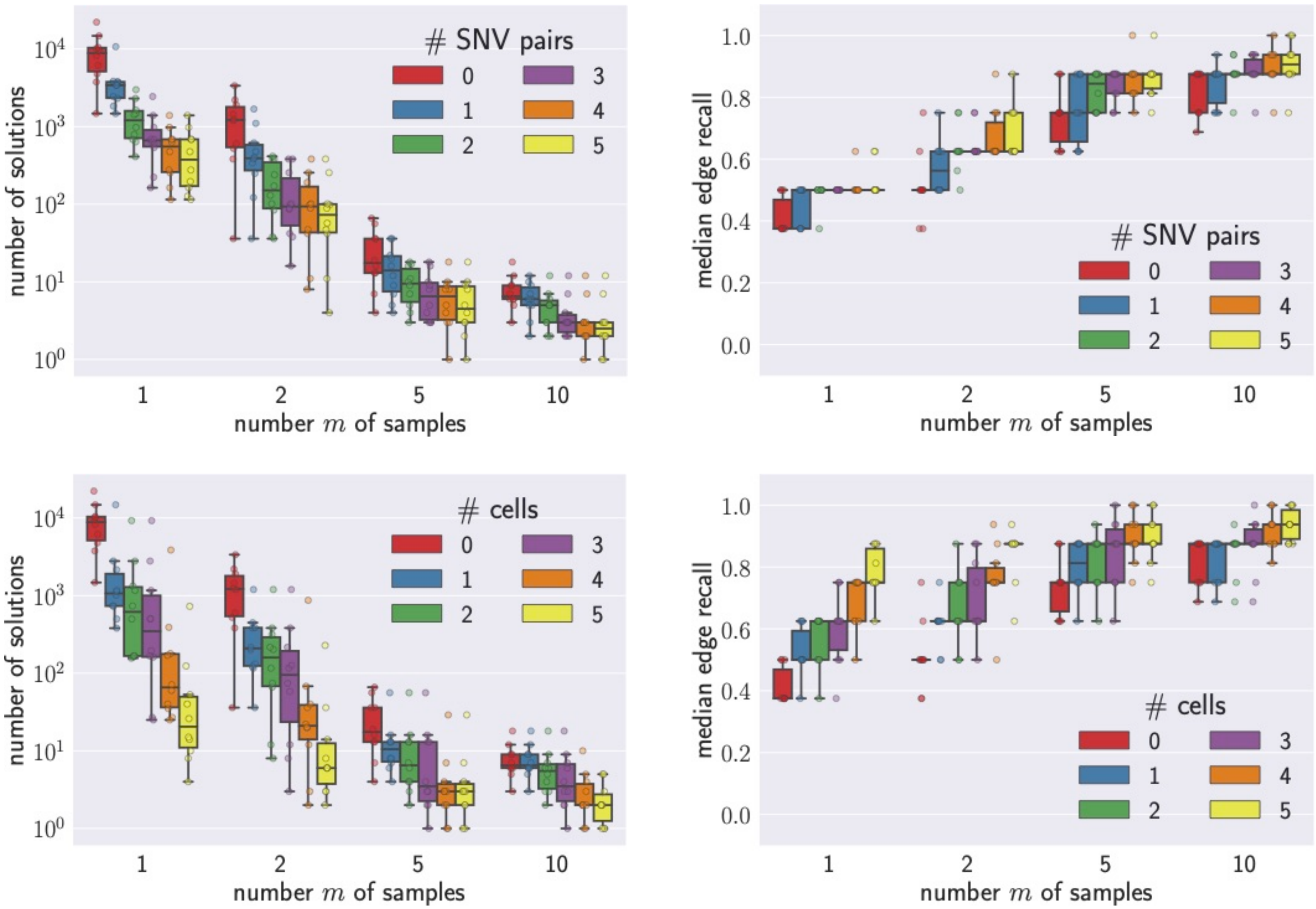
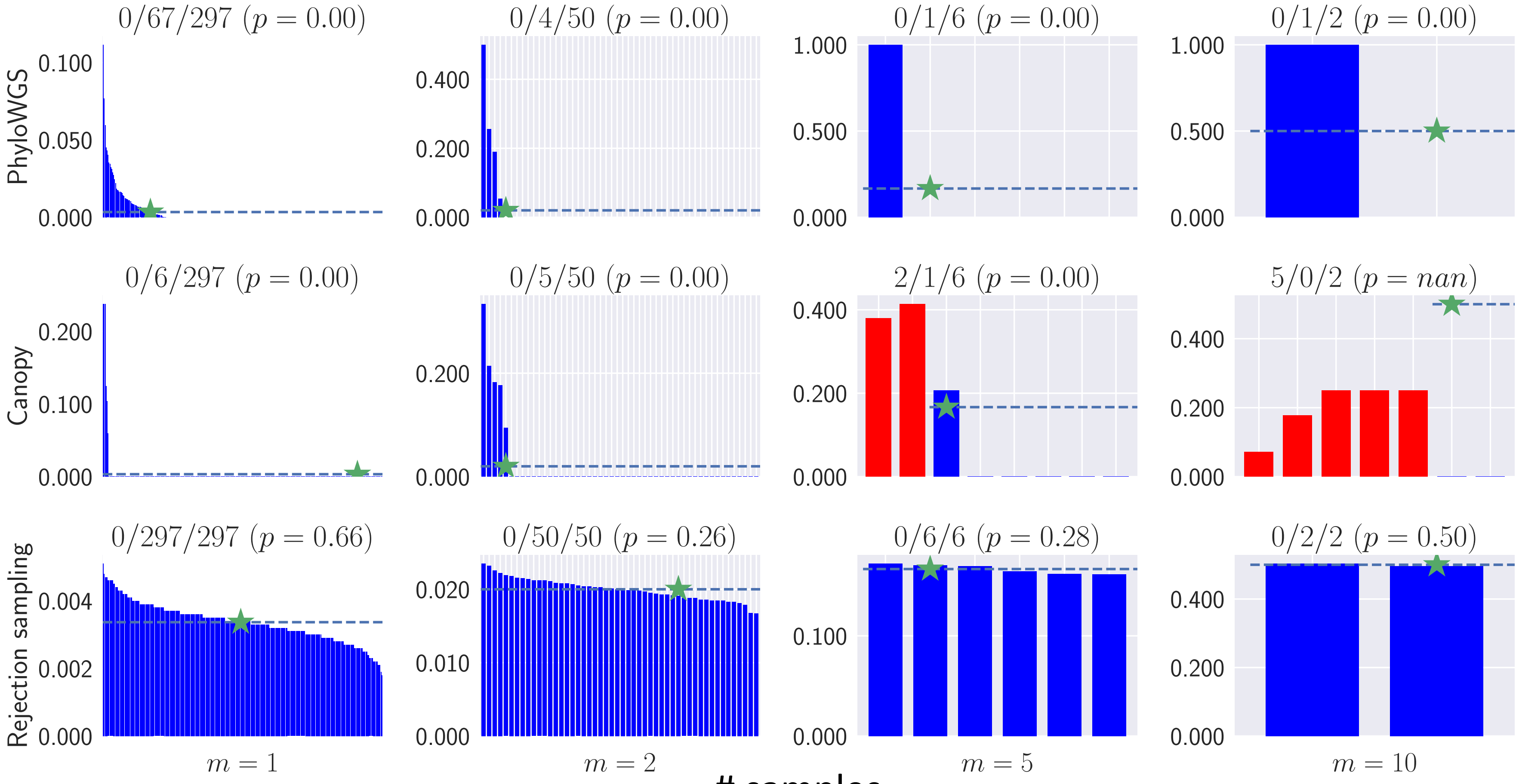


How Does Non-uniqueness affect Methods?

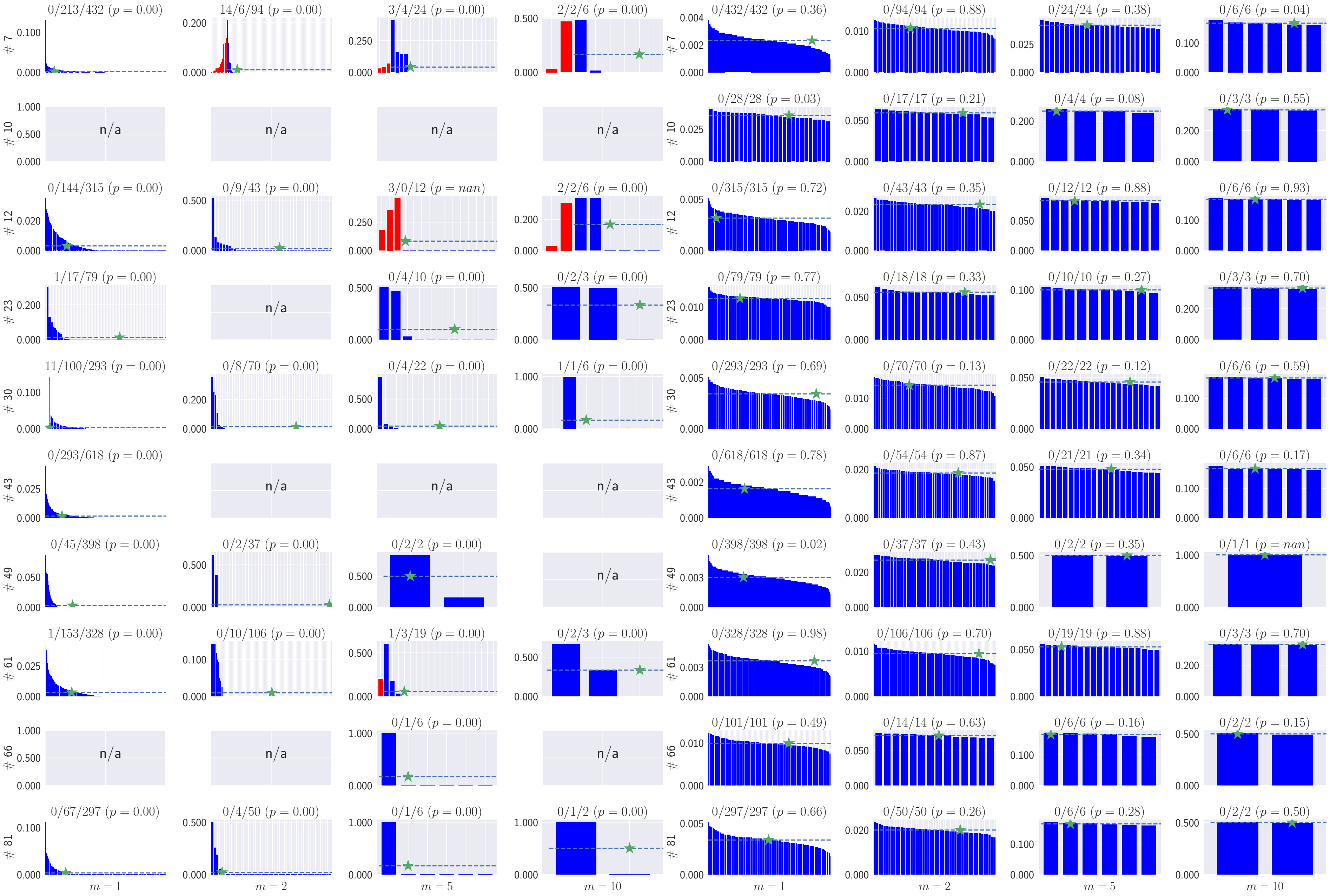
Two current MCMC methods using default parameters:

- PhyloWGS, Deshwar et al., Genom. Biol., 2015 [10,000 samples]
- Canopy, Jiang et al., PNAS, 2016 [~300 samples]

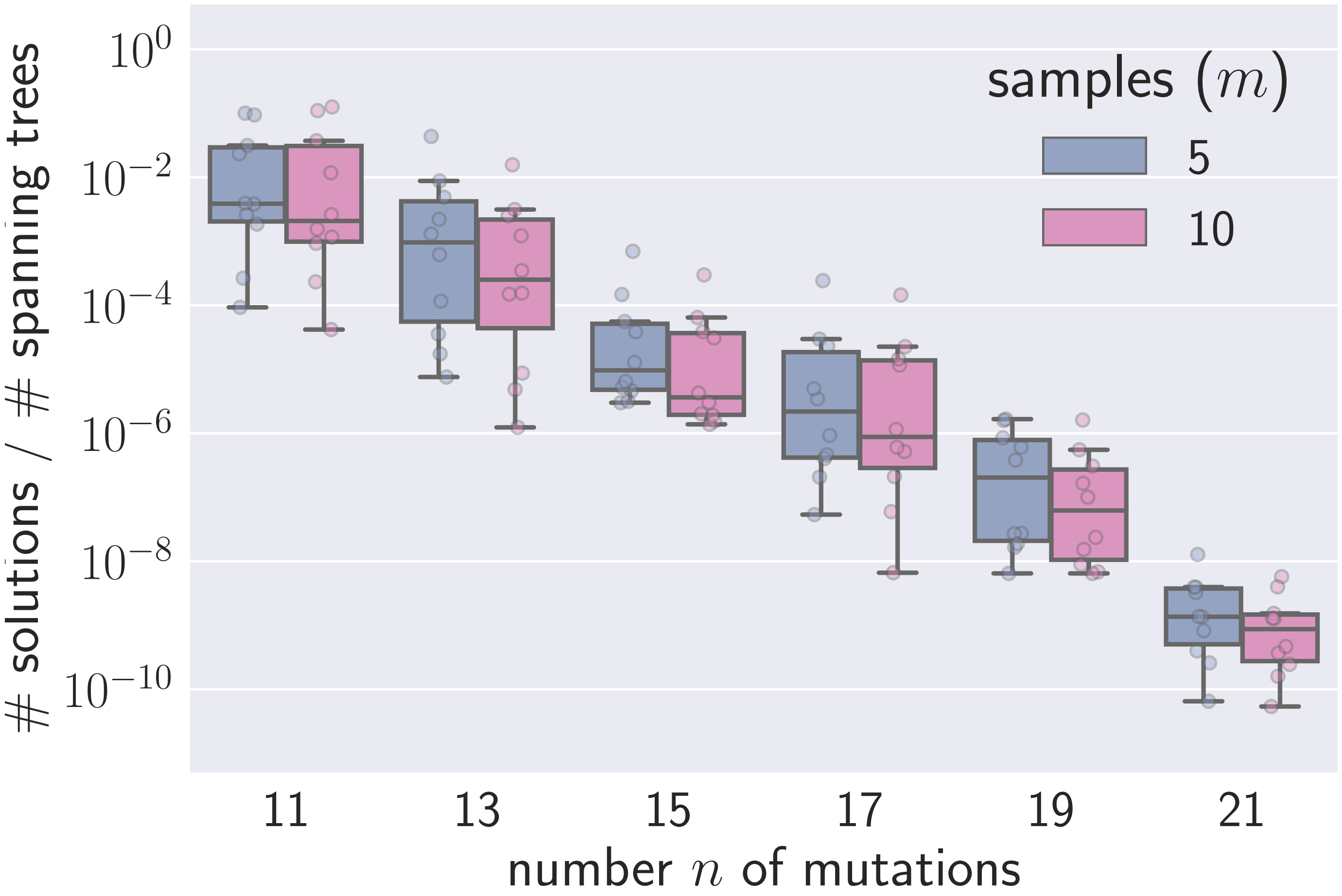


# samples

PhyloWGS Rejection Sampling



Rejection Sampling Does Not Scale



Probabilistic Model for Noisy Measurements

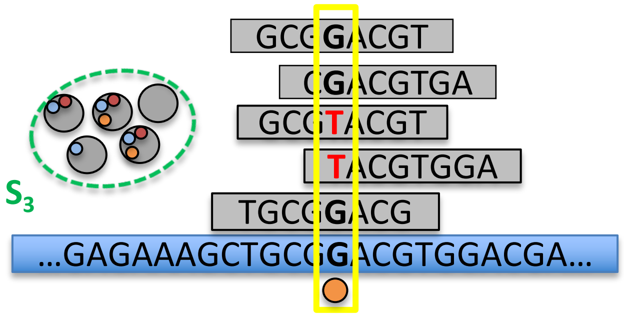
mutations

$$\boldsymbol{F} = [f_{pi}] = \begin{array}{cccccccc} \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & & \\ 0.8 & 0.8 & 0.8 & 0.0 & 0.0 & 0.0 & s_1 & \\ 0.7 & 0.6 & 0.0 & 0.6 & 0.0 & 0.0 & s_2 & \text{samples} \\ 0.8 & 0.0 & 0.0 & 0.0 & 0.6 & \boxed{0.4} & s_3 & \end{array}$$

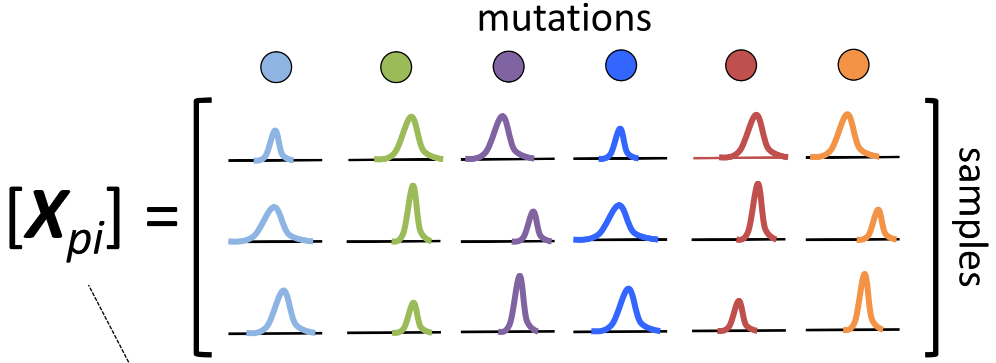
VAF of mutation *i* in sample *p*

Uncertainty due to:
(i) sequencing errors
(ii) mapping errors
(iii) sampling

Variant allele frequency (**VAF**): 0.4



$$\text{VAF}(\bullet) = \frac{\#\text{ reads with } \bullet}{\#\text{ reads}}$$



VAF posterior distribution (beta) given the reads of mutation *i* in sample *p*

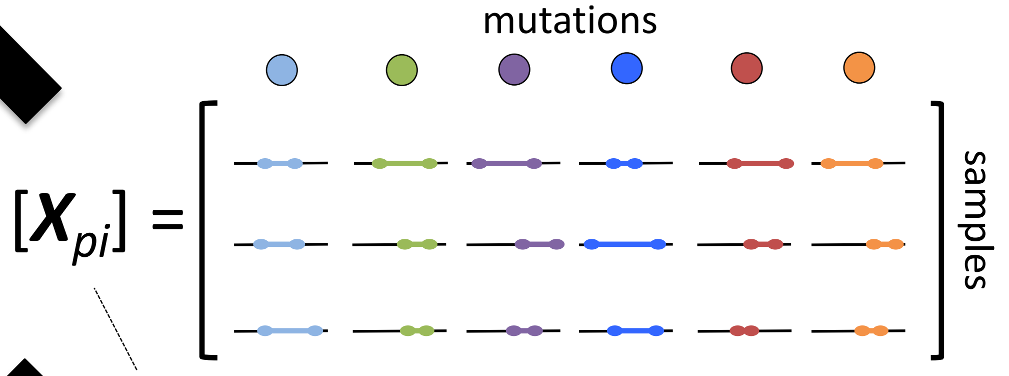
Probabilistic Model for Noisy Measurements

mutations

$$\boldsymbol{F}^{-} = [f^{-}_{pi}] = \begin{array}{cc} \begin{matrix} \bullet & \bullet & \bullet & \bullet & \bullet & \bullet \end{matrix} & \\ \begin{pmatrix} 0.75 & 0.78 & 0.77 & 0.0 & 0.0 & 0.0 \\ 0.55 & 0.43 & 0.0 & 0.54 & 0.0 & 0.0 \\ 0.56 & 0.0 & 0.0 & 0.0 & 0.57 & 0.34 \end{pmatrix} & \begin{matrix} S_1 \\ S_2 \\ S_3 \end{matrix} \end{array}$$

samples

Consider (1 - α) confidence intervals:



VAF posterior distribution (beta) given the reads of mutation *i* in sample *p*

Interval PPM (I-PPM)

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

and $f^{-}_{pi} \leq f_{pi} \leq f^{+}_{pi}$ for all samples *p* and mutations *i*

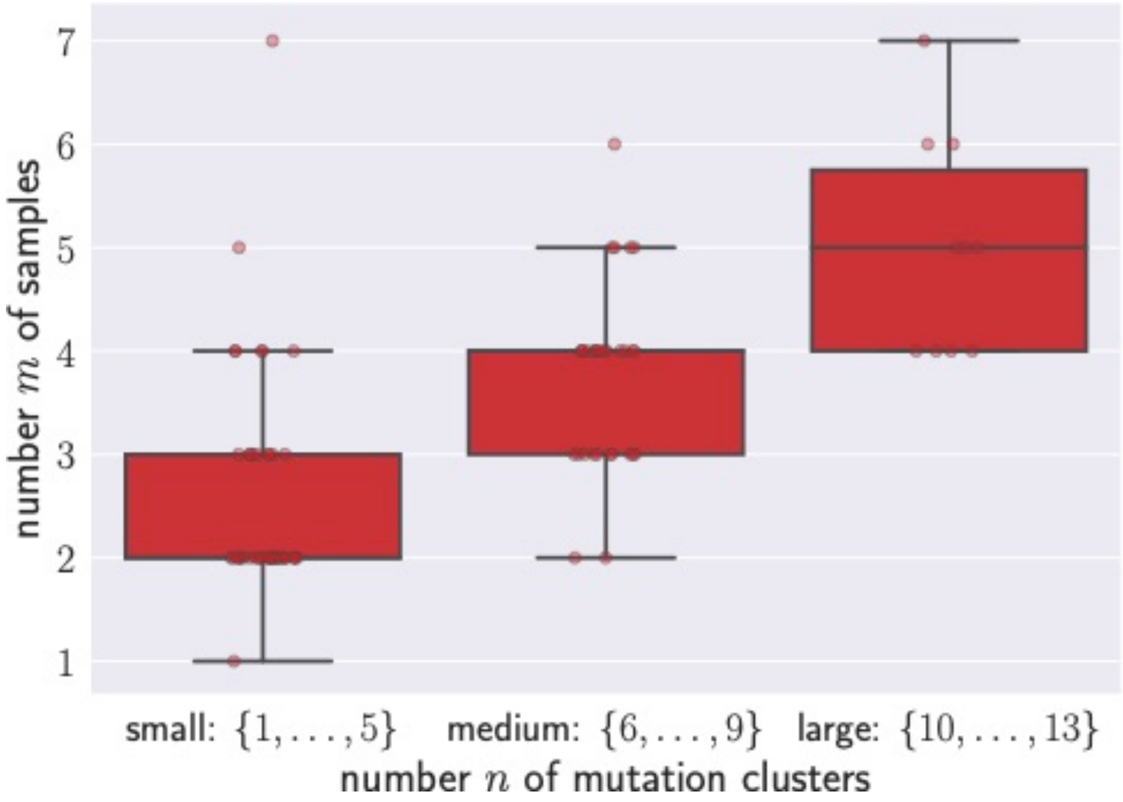
mutations

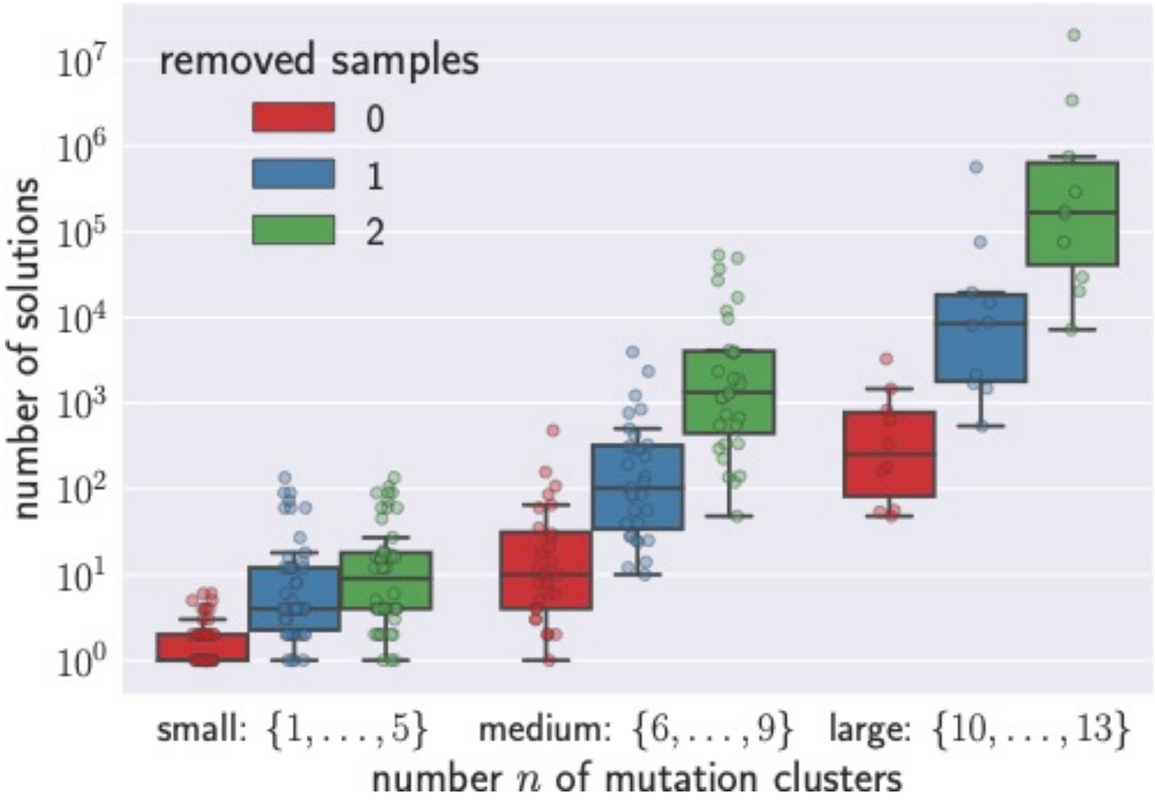
$$\boldsymbol{F}^{+} = [f^{+}_{pi}] = \begin{array}{cc} \begin{matrix} \bullet & \bullet & \bullet & \bullet & \bullet & \bullet \end{matrix} & \\ \begin{pmatrix} 0.9 & 0.85 & 0.87 & 0.05 & 0.0 & 0.0 \\ 0.75 & 0.65 & 0.05 & 0.68 & 0.0 & 0.0 \\ 0.83 & 0.0 & 0.04 & 0.0 & 0.67 & 0.48 \end{pmatrix} & \begin{matrix} S_1 \\ S_2 \\ S_3 \end{matrix} \end{array}$$

samples

Real Data

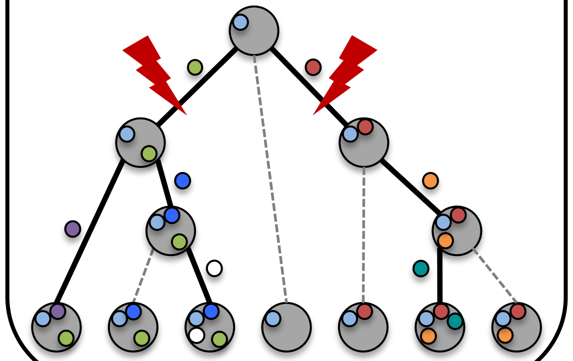
- Cohort of 100 lung cancers [Jamal-Hanjani, NEJM 2017]
- 90% confidence intervals



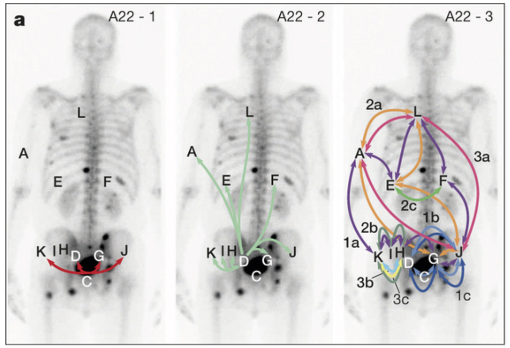


Challenges

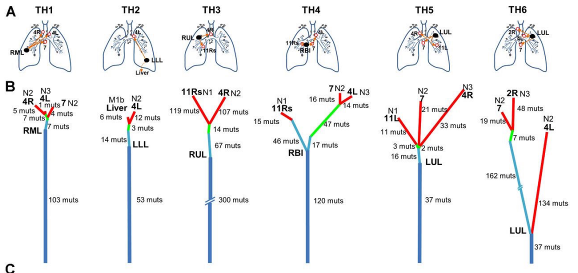
Identify targets for treatment



Understand metastatic development



Recognize common patterns of tumor evolution across patients



Downstream analyses in cancer genomics **critically rely** on accurate tumor phylogeny inference

Challenge I

Novel algorithms that sample uniformly at random from the space of PPM solutions

Challenge II

Algorithms to accurately summarizing solution space (consensus trees)

Conclusion

Background and theory:

- Perfect Phylogeny Mixture (PPM) problem
- Combinatorial characterization of solutions
- #PPM: exact counting and uniform sampling

Simulation results:

- What contributes to non-uniqueness?
- How to reduce non-uniqueness?
- How does non-uniqueness affect current methods?

Summary of Lectures 1, 2 and 3

- DNA, RNA and proteins are sequences
  - Central dogma of molecular biology: DNA -> RNA -> protein
- Problem != algorithm
- Key challenge in computational biology is translating a biological problem into a computational problem
- Cancer is a genetic disease caused by somatic mutations
- Inter-tumor heterogeneity and intra-tumor heterogeneity:
  - *Not only is every tumor different, but so is every tumor cell…*
- **Non-uniqueness of solutions in phylogeny reconstruction from bulk DNA samples**