# CS 598MEB
# Computational Cancer Genomics
## Lecture 3

Mohammed El-Kebir

January 28, 2020

# 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

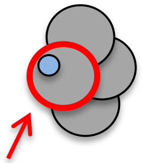
- Recap
- Two-state Perfect Phylogeny Mixtures

**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

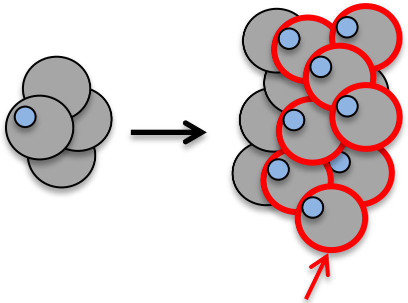
**Clonal Evolution Theory of Cancer**
[Nowell, 1976]



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**
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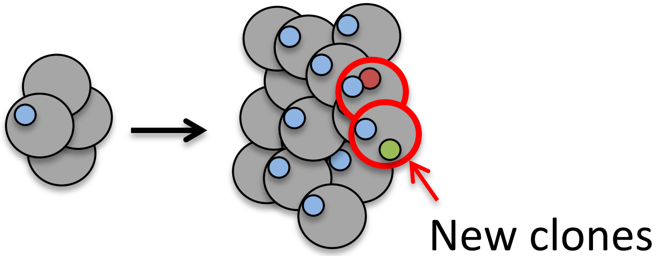
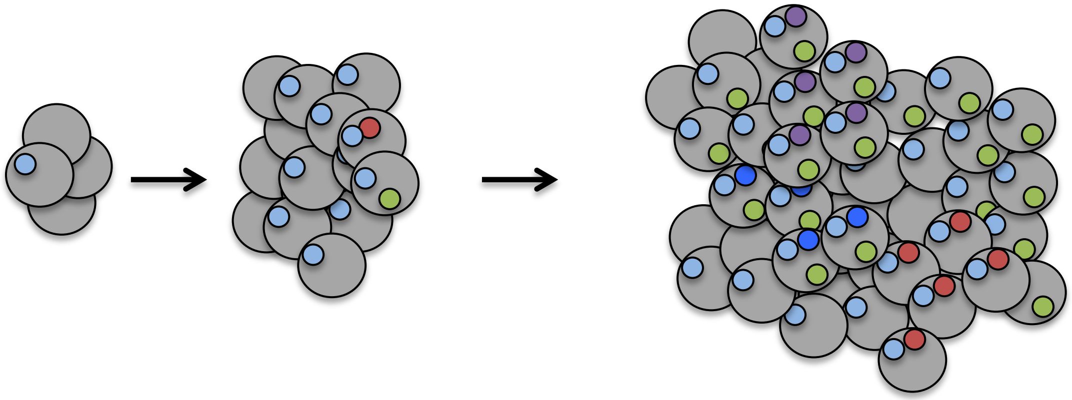


# Tumorigenesis: Cell Mutation & Division

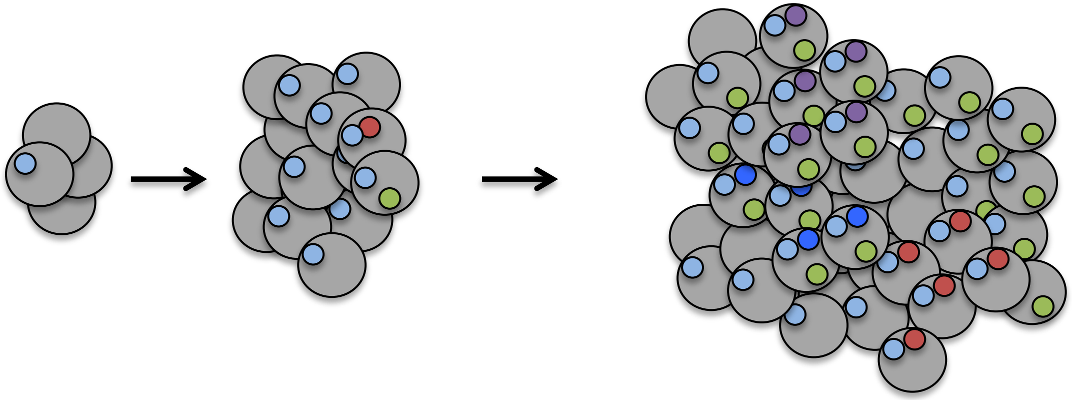
**Clonal Evolution Theory of Cancer**
[Nowell, 1976]



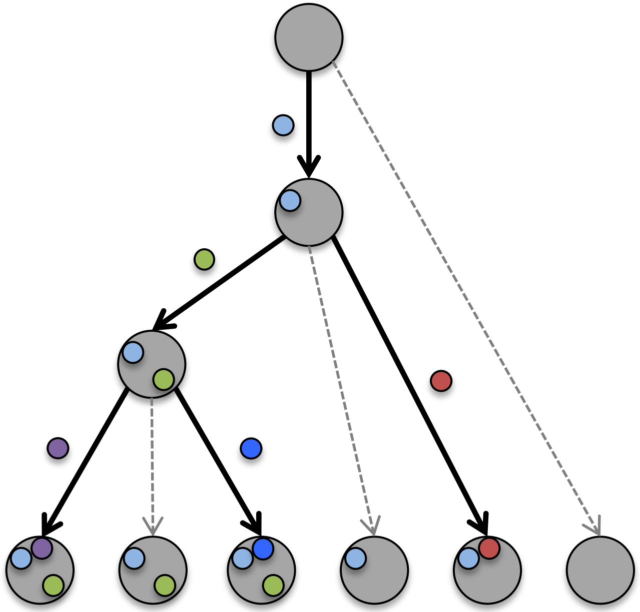
Intra-Tumor
Heterogeneity

# Tumorigenesis: Cell Mutation & Division

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

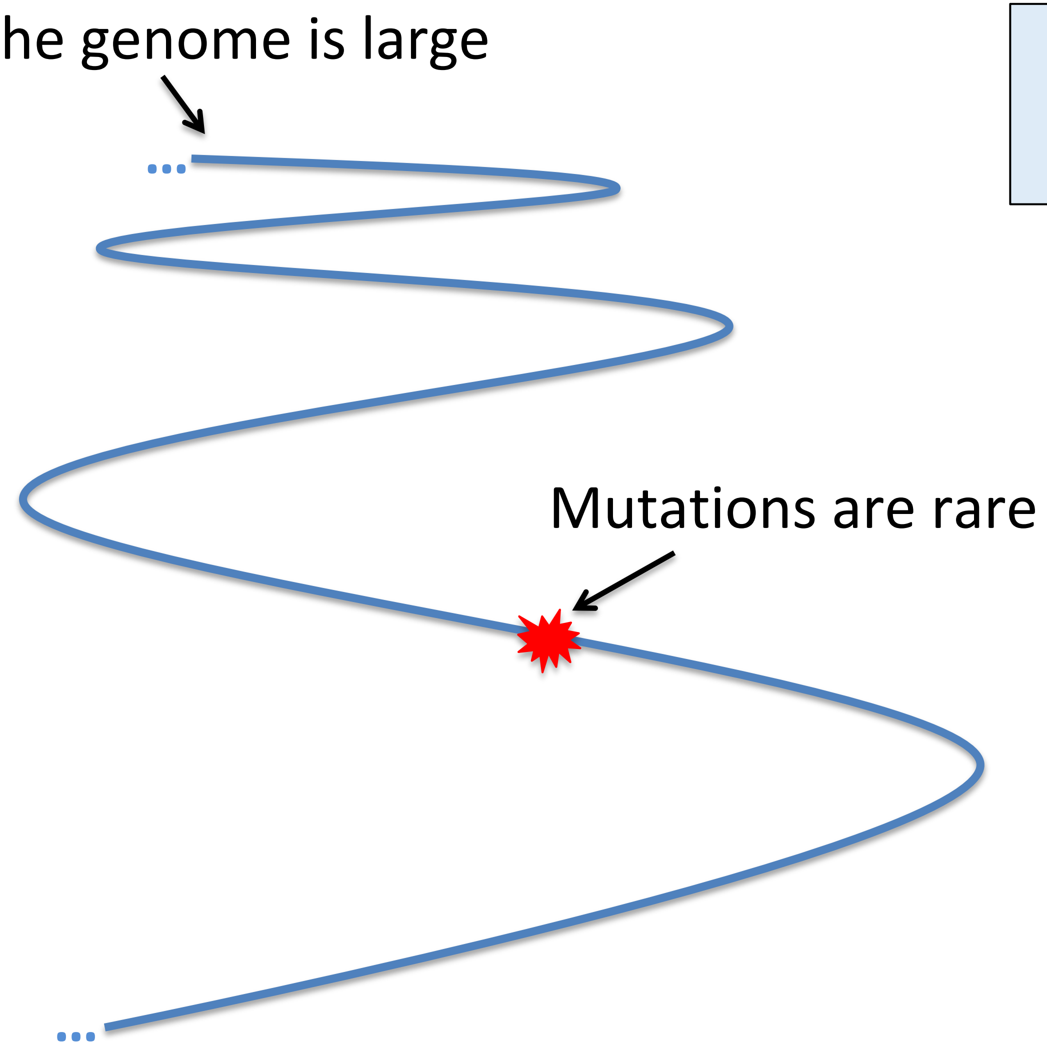


Intra-Tumor
Heterogeneity



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

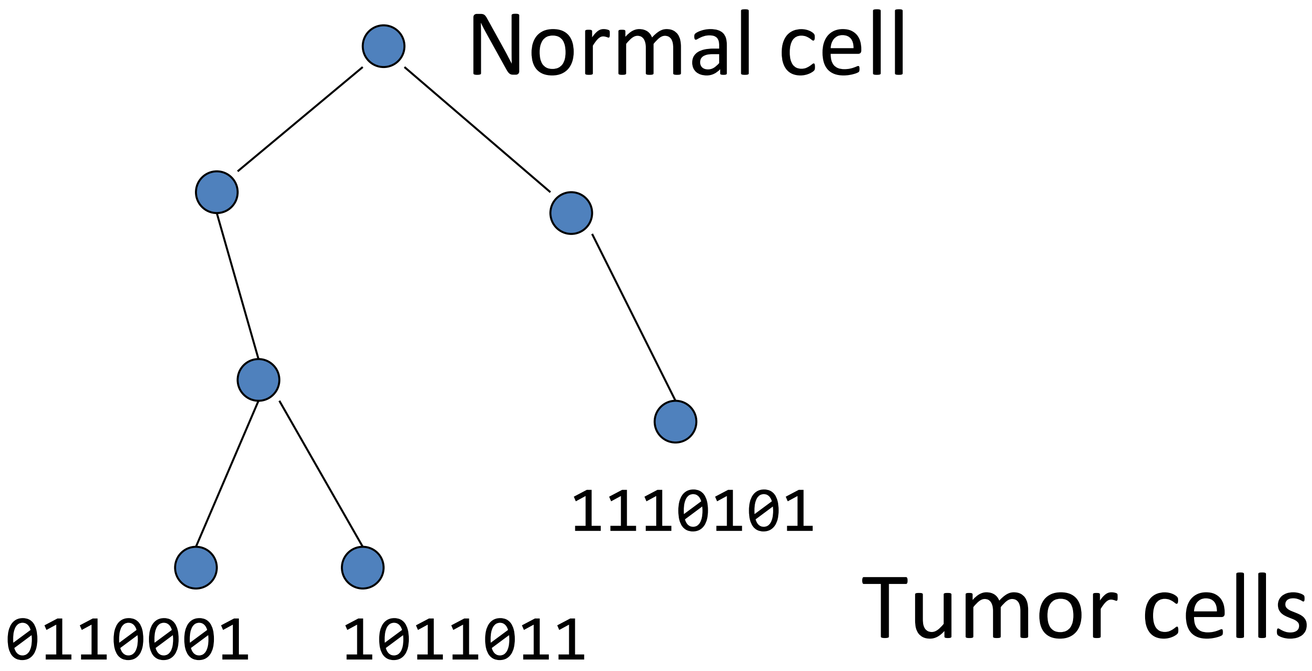
**Single nucleotide mutation**

… CGTAATTAG …

… CGTCATTAG …

0 = normal

1 = mutated



Normal cell

1110101

0110001 1011011

Tumor cells

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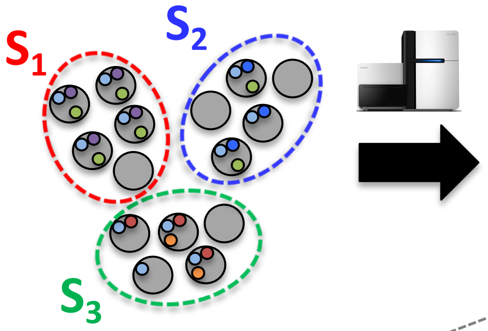
- Y. Qi, D. Pradhan and M. El-Kebir. Implications of non-uniqueness in phylogenetic deconvolution of bulk DNA samples of tumors. Algorithms for Molecular Biology, 14:19, 2019.

# Sequencing and Tumor Phylogeny Inference

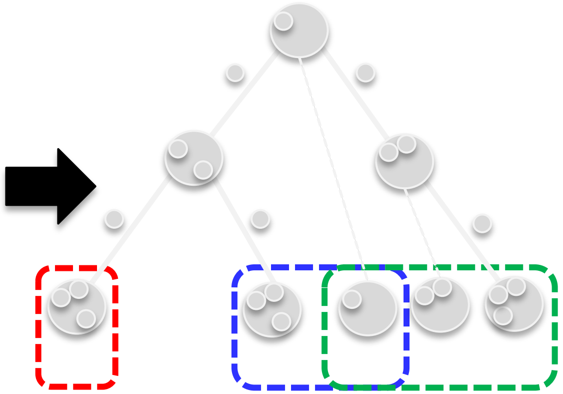


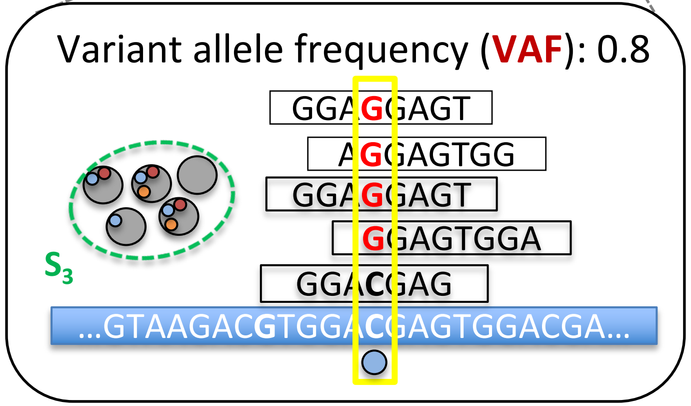
***n*** mutations

***m*** samples

$$\begin{array}{cc} & \begin{array}{cccccc} \bullet & \bullet & \bullet & \bullet & \bullet & \bullet \end{array} \\ \begin{array}{c} S_1 \\ S_2 \\ S_3 \end{array} & \begin{pmatrix} 0.8 & 0.8 & 0.8 & 0.0 & 0.0 & 0.0 \\ 0.7 & 0.6 & 0.0 & 0.6 & 0.0 & 0.0 \\ \boxed{0.8} & 0.0 & 0.0 & 0.0 & 0.6 & 0.4 \end{pmatrix} \end{array}$$

Frequency Matrix ***F***

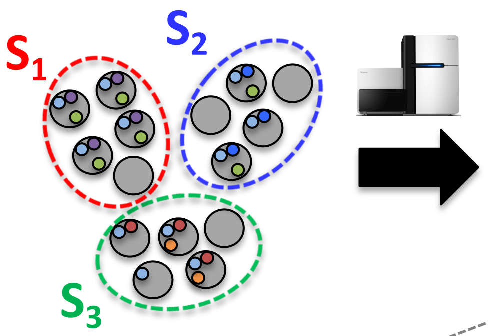




Variant allele frequency (**VAF**): 0.8

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

# Sequencing and Tumor Phylogeny Inference



***n*** mutations

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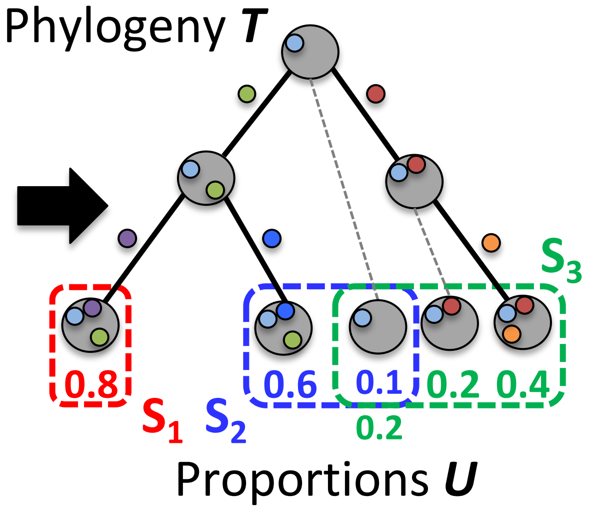
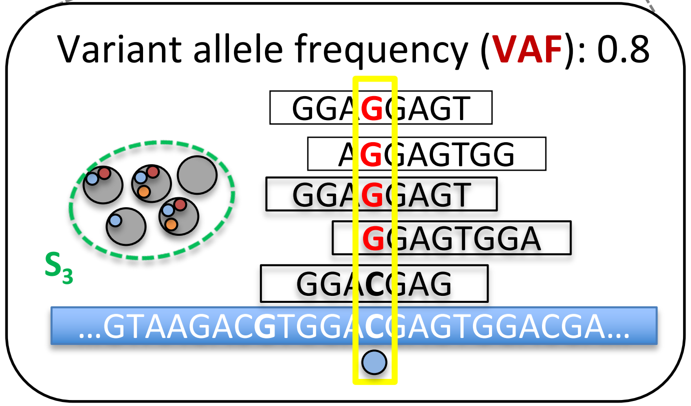
Frequency Matrix ***F***

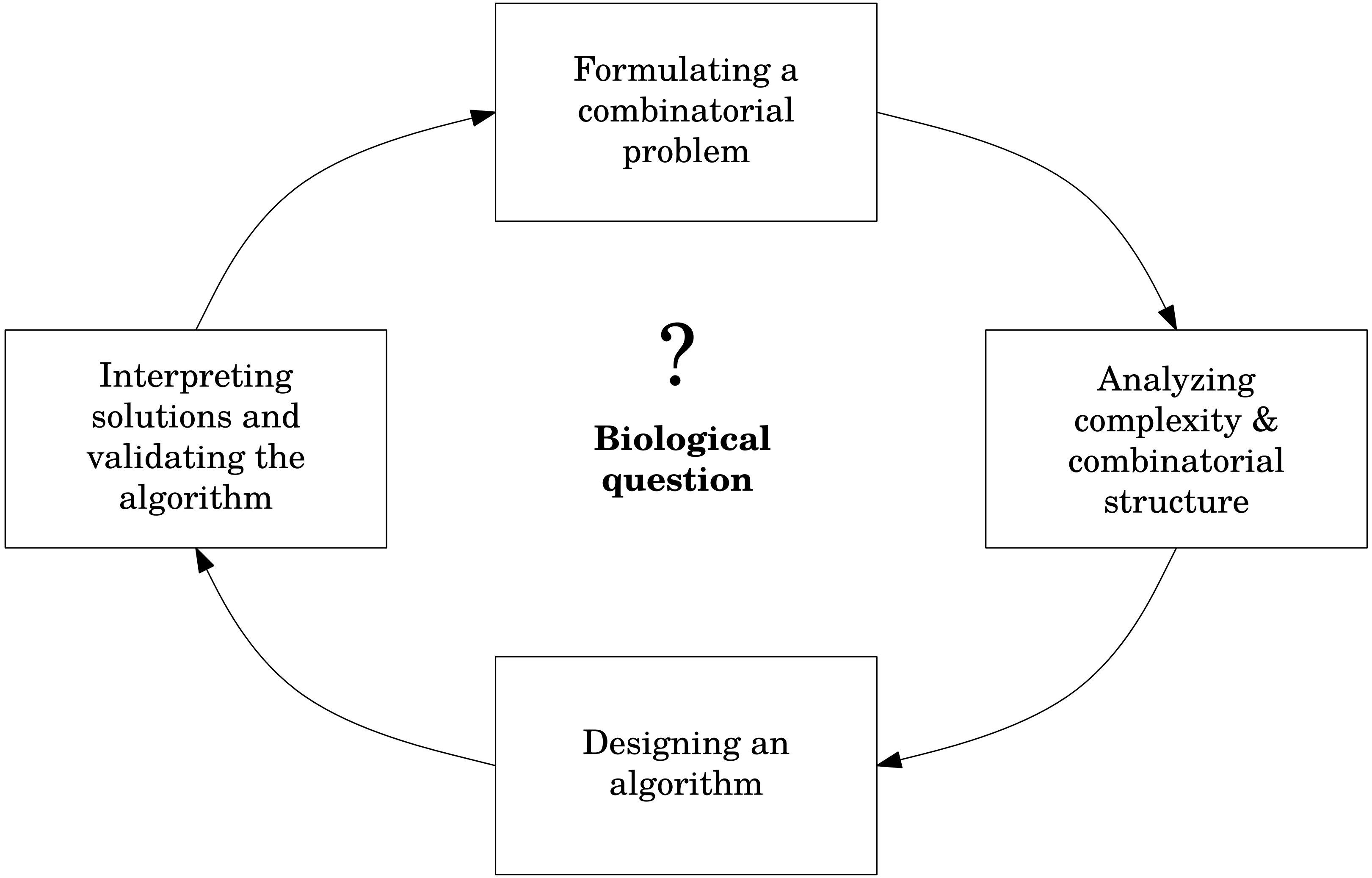




**Mixtures** of unknown leaves ***L(T)***
of an unknown tree ***T***
in unknown proportions ***U***

**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

?

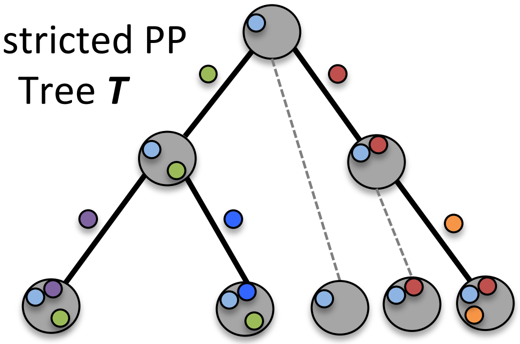
**Biological question**

Translating a biological problem into a computational biology

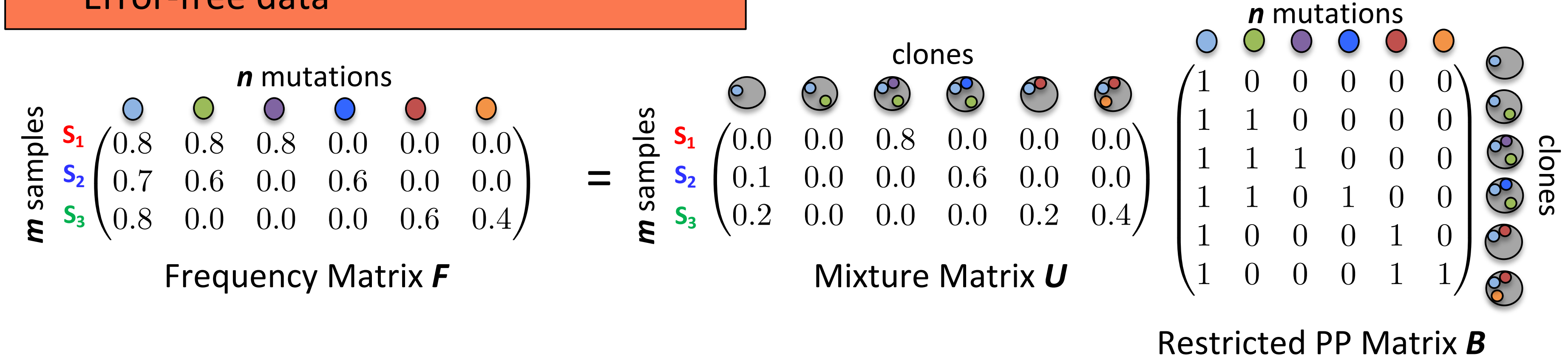
# Perfect Phylogeny Mixture

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

Restricted PP Tree ***T***



1-1 ↕ **Equivalent**



***n*** mutations

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

***m*** samples

clones

Frequency Matrix ***F***

Mixture Matrix ***U***

Restricted PP Matrix ***B***

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

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

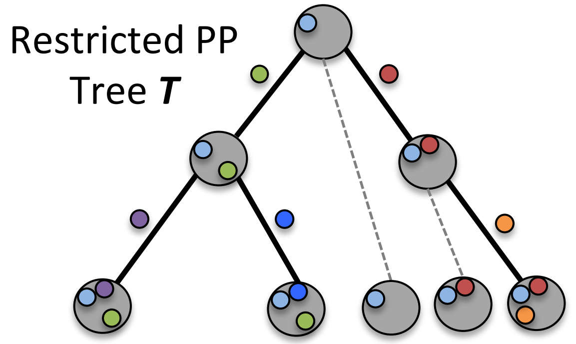
Perfect Phylogeny Theorem
[Estabrook, 1971]
[Gusfield, 1991]

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

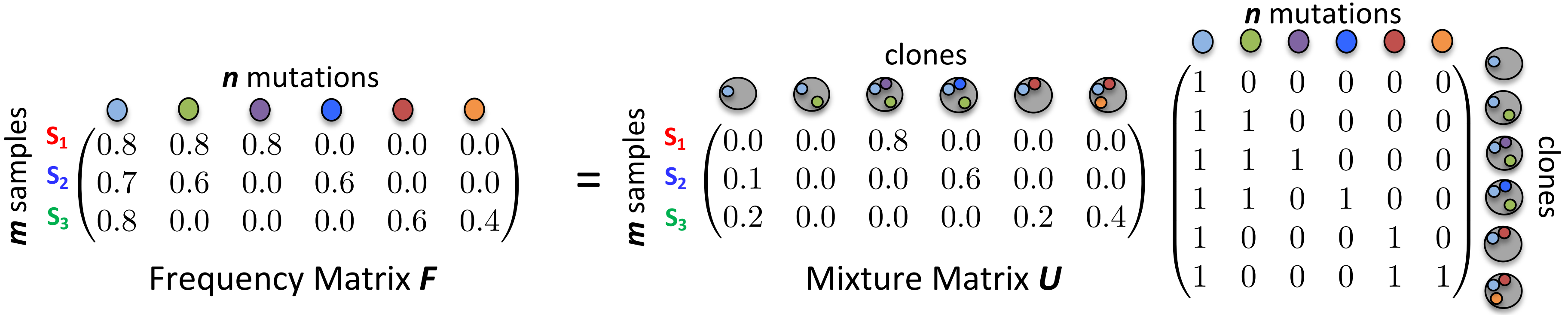
# Previous Work

**Variant of PPM:**

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], …



1-1 ↕ **Equivalent**



$$\underbrace{\begin{array}{c|cccccc} & \text{●} & \text{●} & \text{●} & \text{●} & \text{●} & \text{●} \\ \hline s_1 & 0.8 & 0.8 & 0.8 & 0.0 & 0.0 & 0.0 \\ s_2 & 0.7 & 0.6 & 0.0 & 0.6 & 0.0 & 0.0 \\ s_3 & 0.8 & 0.0 & 0.0 & 0.0 & 0.6 & 0.4 \end{array}}_{\text{Frequency Matrix } \boldsymbol{F}} = \underbrace{\begin{array}{c|cccccc} s_1 & 0.0 & 0.0 & 0.8 & 0.0 & 0.0 & 0.0 \\ s_2 & 0.1 & 0.0 & 0.0 & 0.6 & 0.0 & 0.0 \\ s_3 & 0.2 & 0.0 & 0.0 & 0.0 & 0.2 & 0.4 \end{array}}_{\text{Mixture Matrix } \boldsymbol{U}} \underbrace{\begin{array}{cccccc} \text{●} & \text{●} & \text{●} & \text{●} & \text{●} & \text{●} \\ \hline 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 0 & 0 \\ 1 & 1 & 1 & 0 & 0 & 0 \\ 1 & 1 & 0 & 1 & 0 & 0 \\ 1 & 0 & 0 & 0 & 1 & 0 \\ 1 & 0 & 0 & 0 & 1 & 1 \end{array}}_{\text{Restricted PP Matrix } \boldsymbol{B}}$$

***n*** mutations (columns); ***m*** samples (rows of ***F*** and ***U***); clones (columns of ***U***, rows of ***B***)

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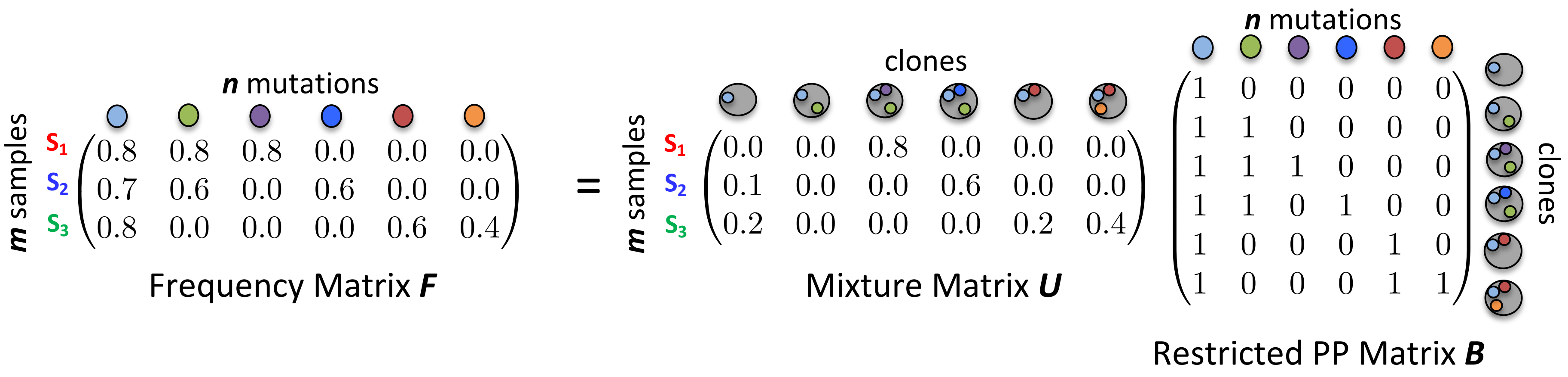
**Perfect Phylogeny Mixture:** [El-Kebir*, Oesper* et al., 2015]
Given ***F***, find ***U*** and ***B*** such that ***F* = *U B***

# 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***

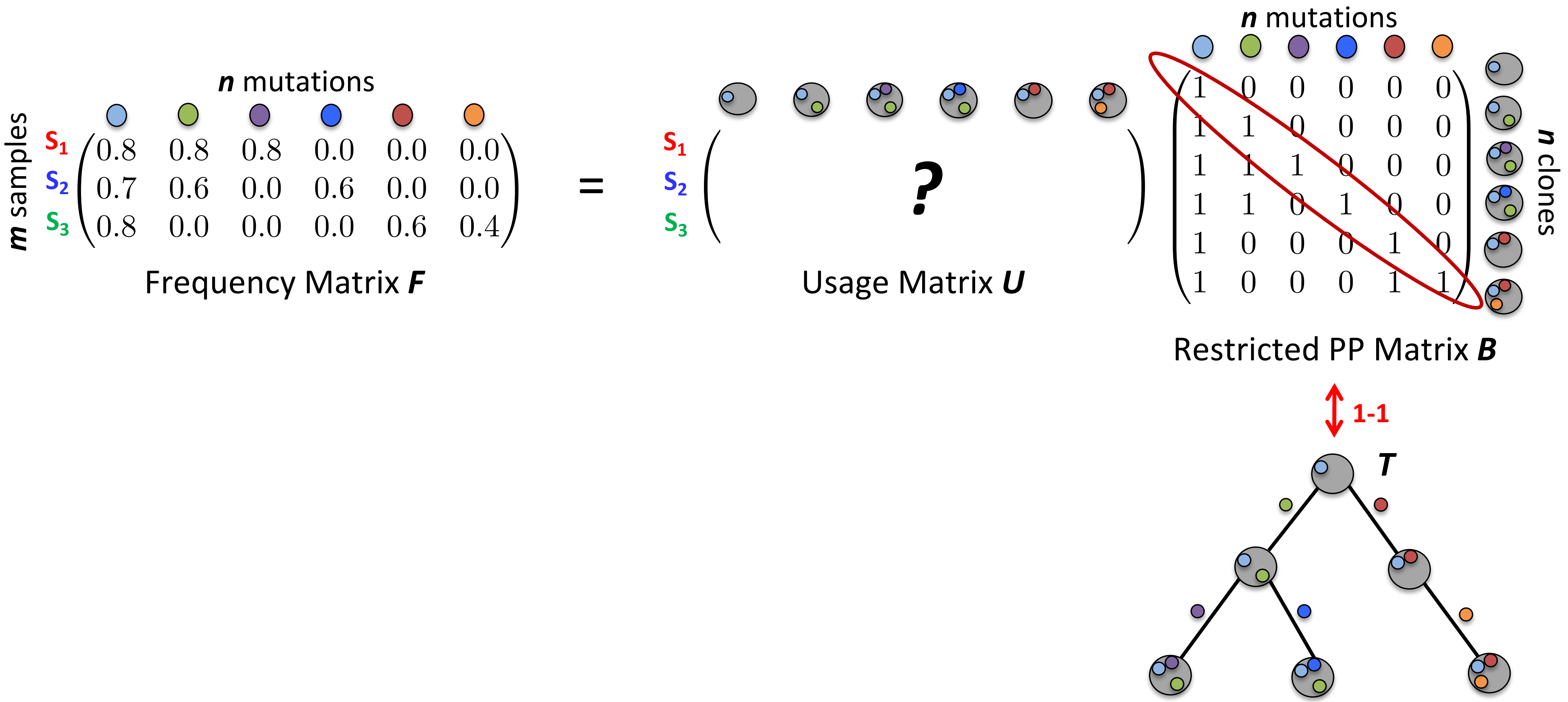
Mixture Matrix ***U***

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

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

Frequency Matrix ***F***

Usage Matrix ***U***

***n*** mutations

***n*** clones

Restricted PP Matrix ***B***

# 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

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

Frequency Matrix ***F***

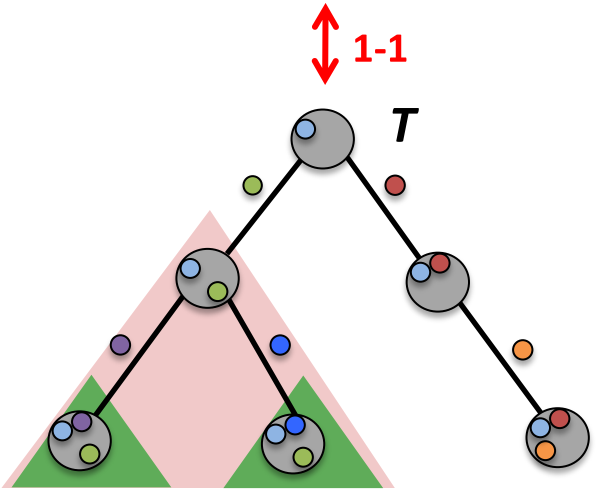
Usage Matrix ***U***

***n*** mutations

$$\begin{array}{cccccc} ● & ● & ● & ● & ● & ● \\ \hline 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 0 & 0 \\ 1 & 1 & 1 & 0 & 0 & 0 \\ 1 & 1 & 0 & 1 & 0 & 0 \\ 1 & 0 & 0 & 0 & 1 & 0 \\ 1 & 0 & 0 & 0 & 1 & 1 \end{array}$$

***n*** 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***

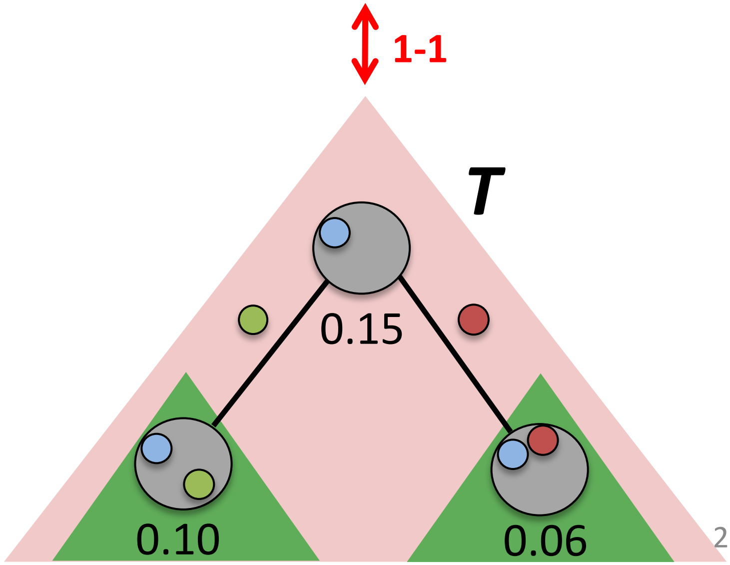
$$\begin{array}{ccc} ● & ● & ● \end{array}$$

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

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:**

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

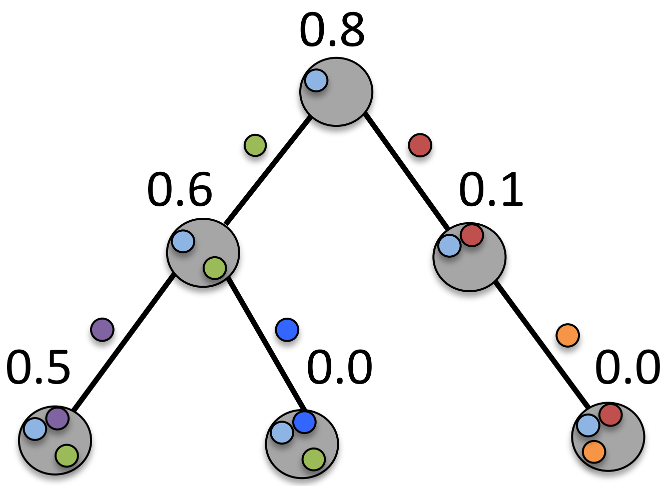
**Lemma (Sum Condition):**

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

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

***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

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

***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

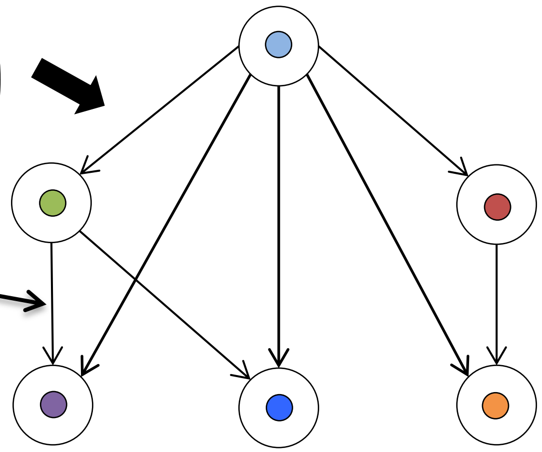
**Lemma (Ancestry Condition):**
Given ***F*** and ***T***, for all samples *p* and mutations *k* child of *j*, $f_{pj} \geq f_{pk}$

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*, $f_{pj} \geq \sum_{k \text{ child of } j} f_{pk}$

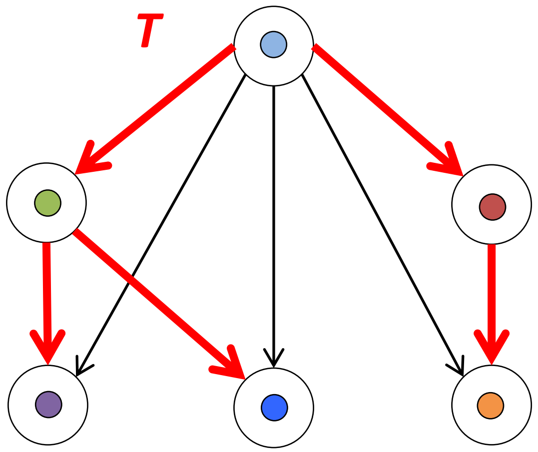
necessary
sufficient

**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***



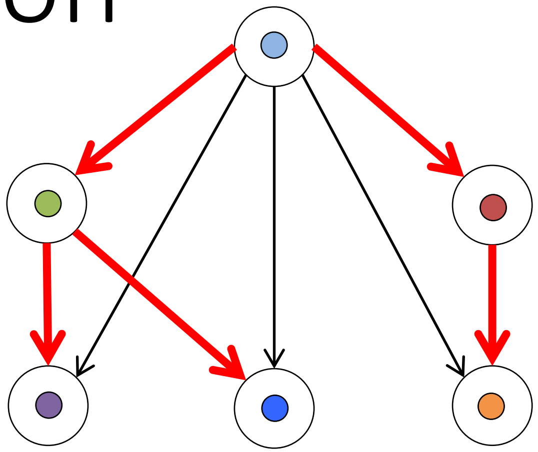
Ancestry Graph ***G* = (*V*, *A*)**

**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**

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

**Connectivity**

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

**Tree**

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

**Sum condition**

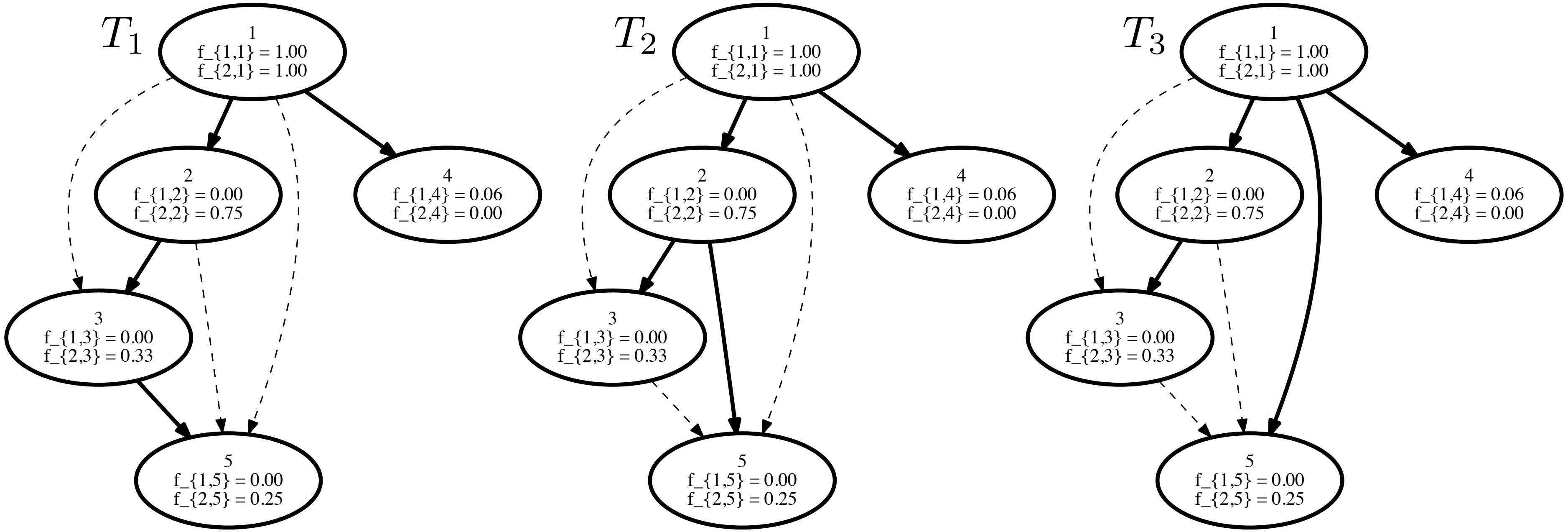
$$x_{jk} \in \{0,1\} \qquad \forall (v_j, v_k) \in A'$$

# 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 $\Pi$ 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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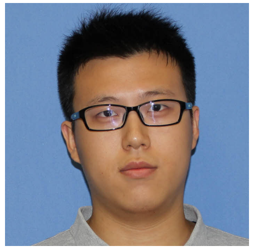
**Theorem**: #PPM is #P-complete

**Theorem**: There is no FPRAS for #PPM

**Theorem**: There is no FPAUS for PPM



Yuanyuan Qi

# Outline

**Background and theory:**

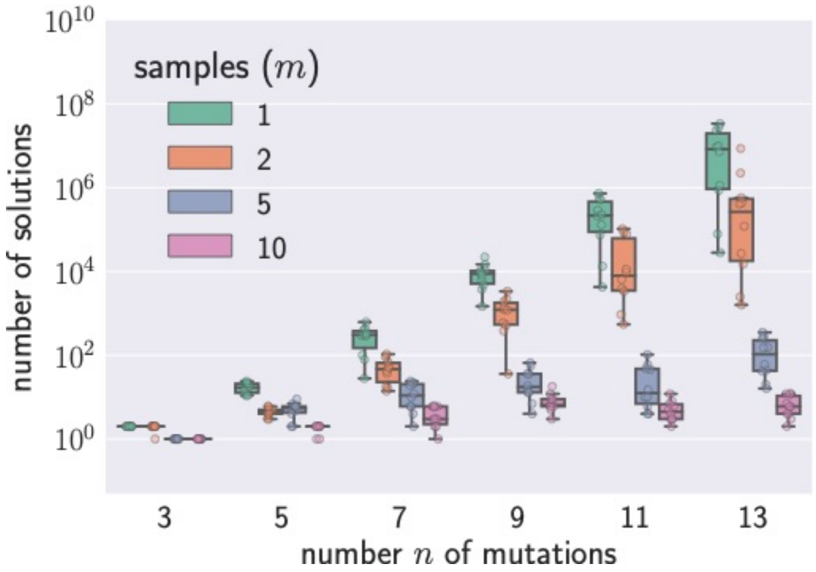
- Perfect Phylogeny Mixture (PPM) problem
- Combinatorial characterization of solutions
- #PPM: exact counting and uniform sampling

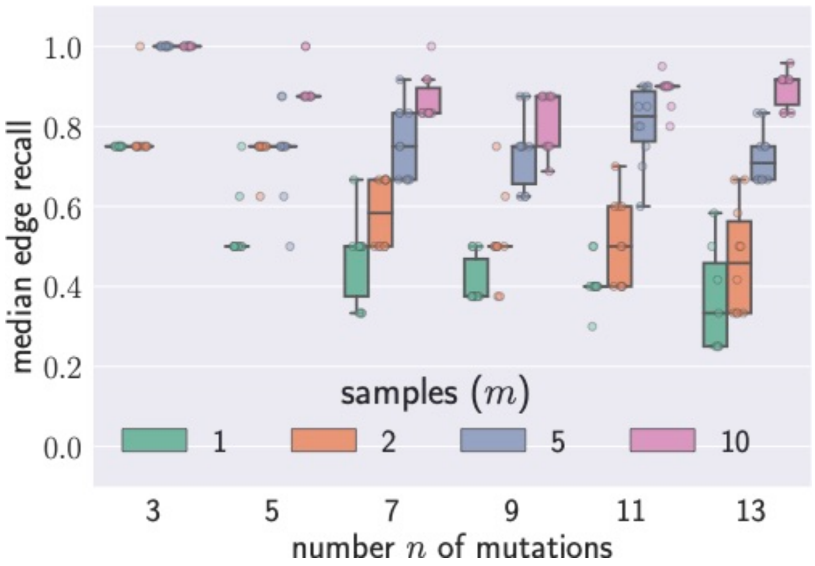
**Simulation results:**

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

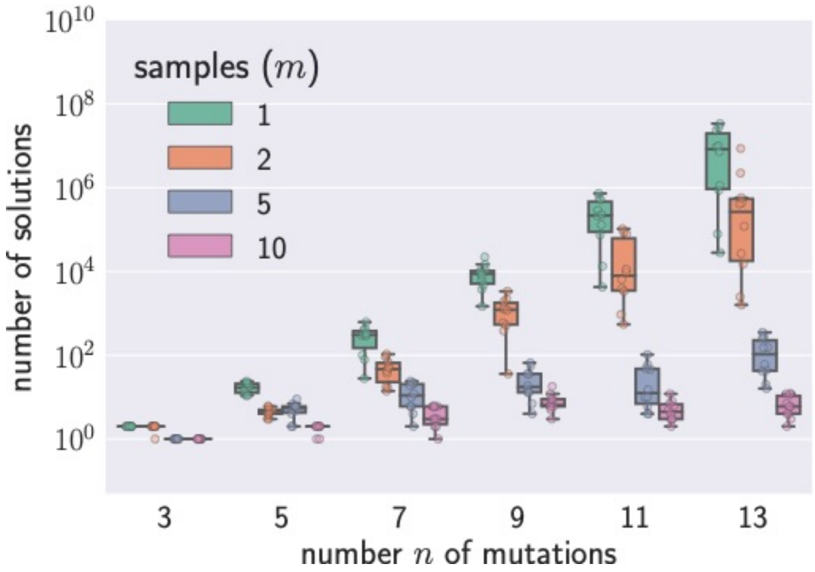
Dikshant Pradhan

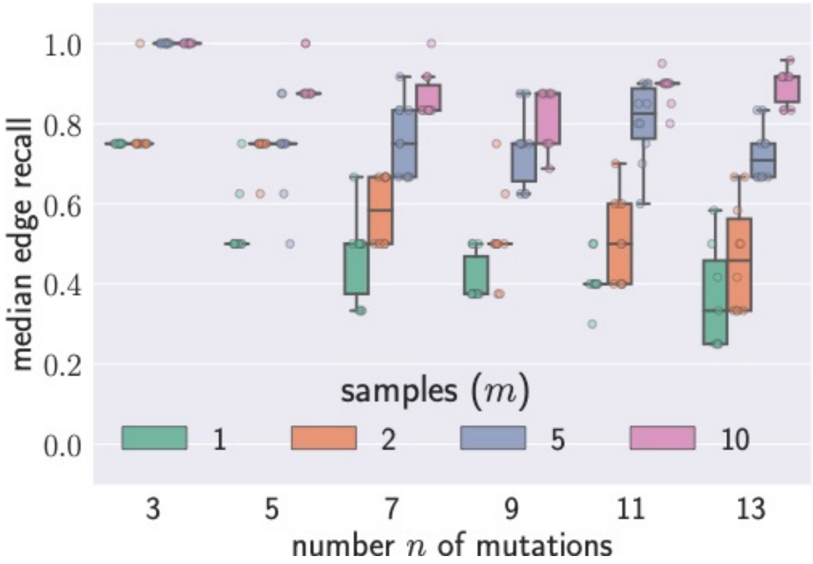
# What Contributes to Non-uniqueness?

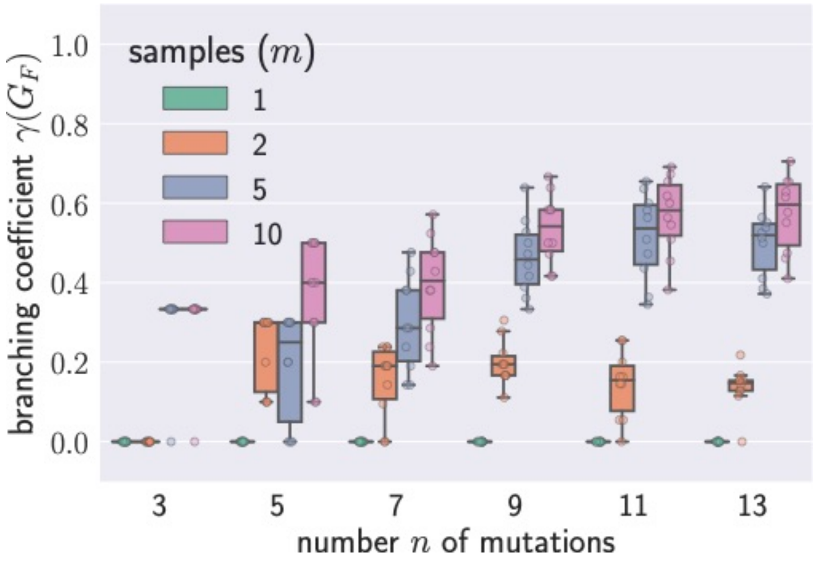


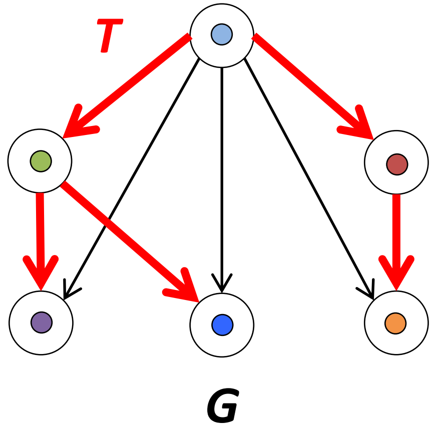


# What Contributes to Non-uniqueness?

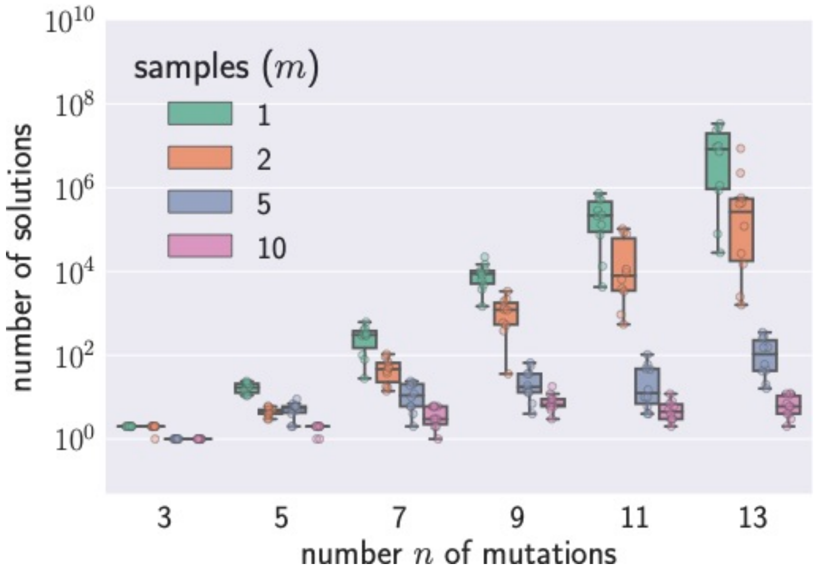


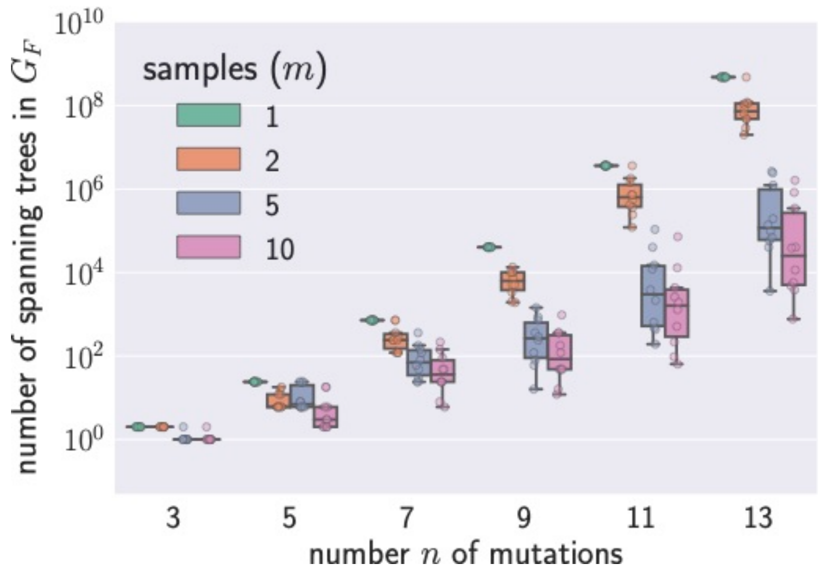


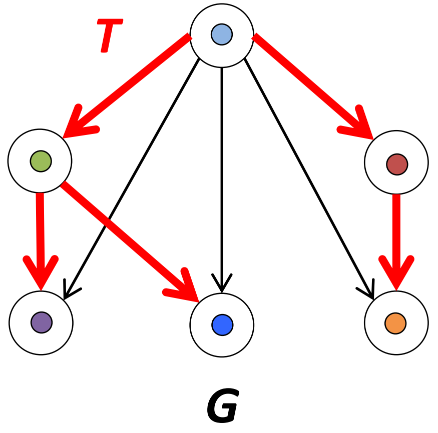




# An Upper Bound for Number of Solutions







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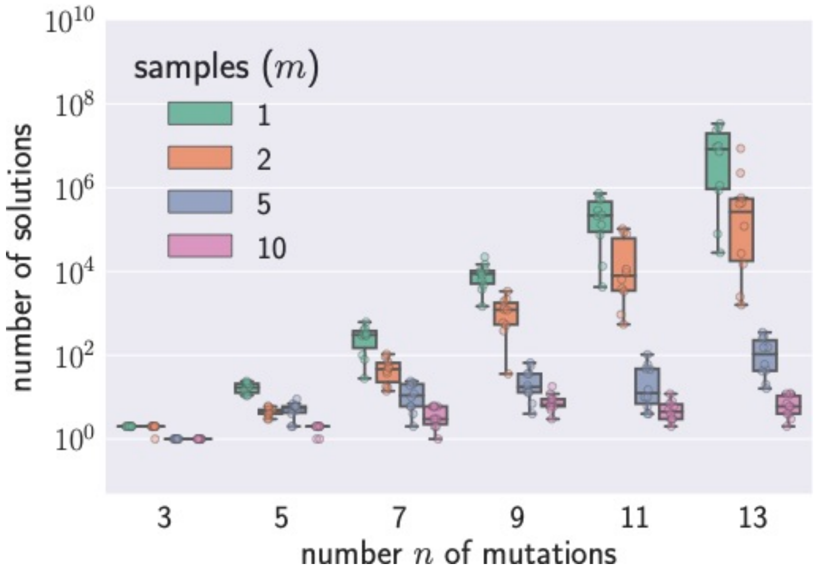
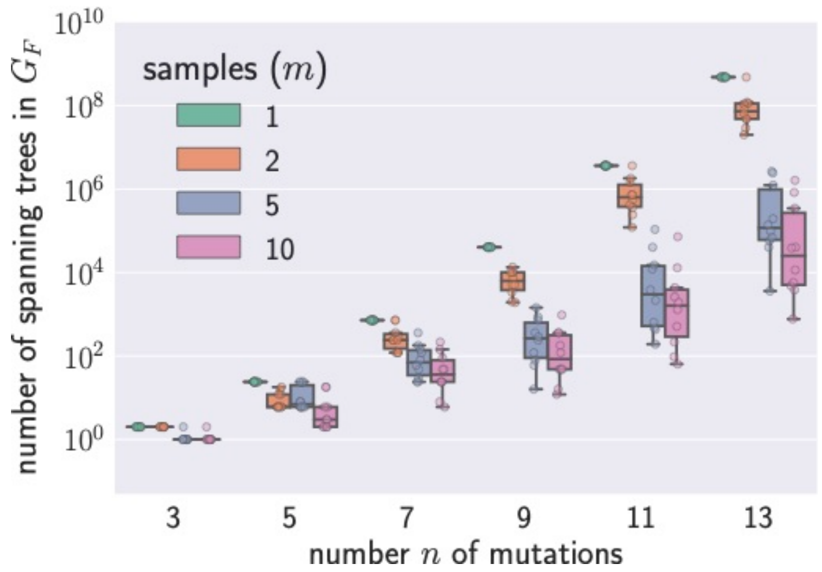
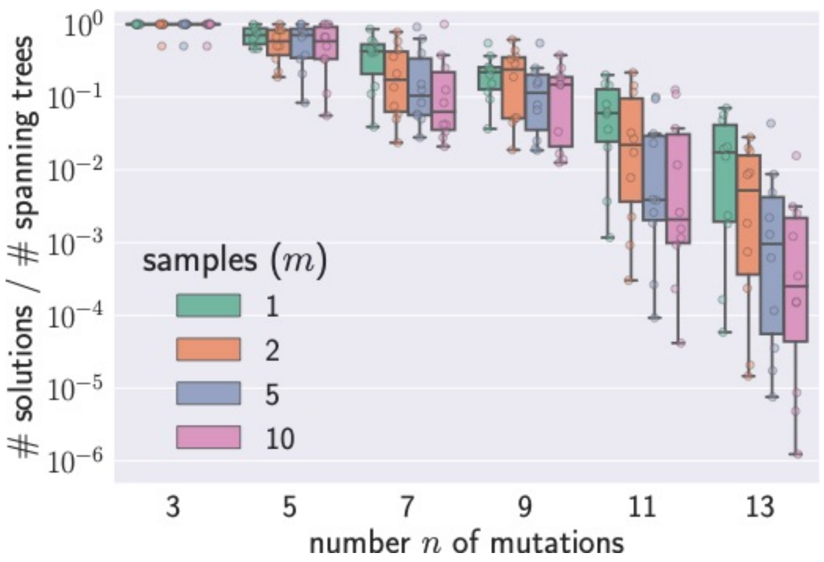
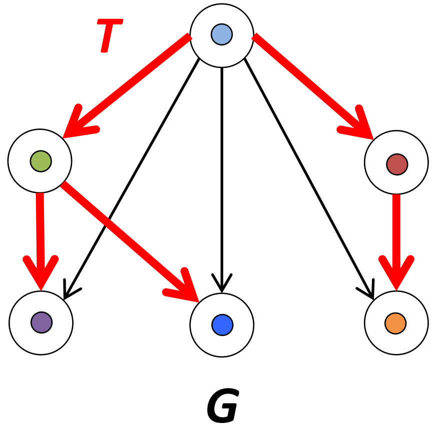
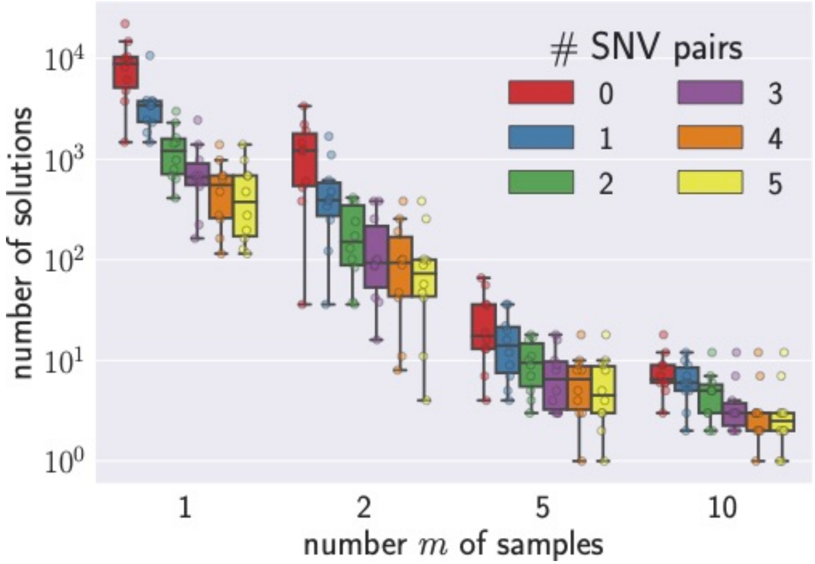


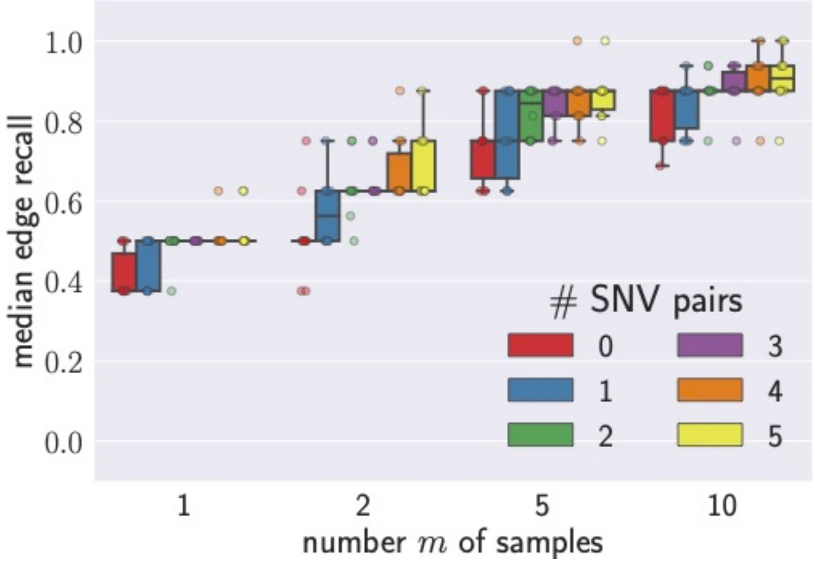


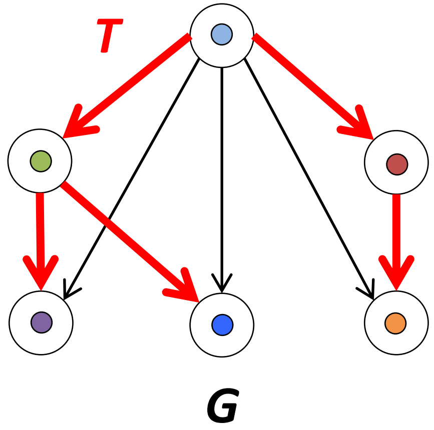




# How to Reduce Non-Uniqueness?







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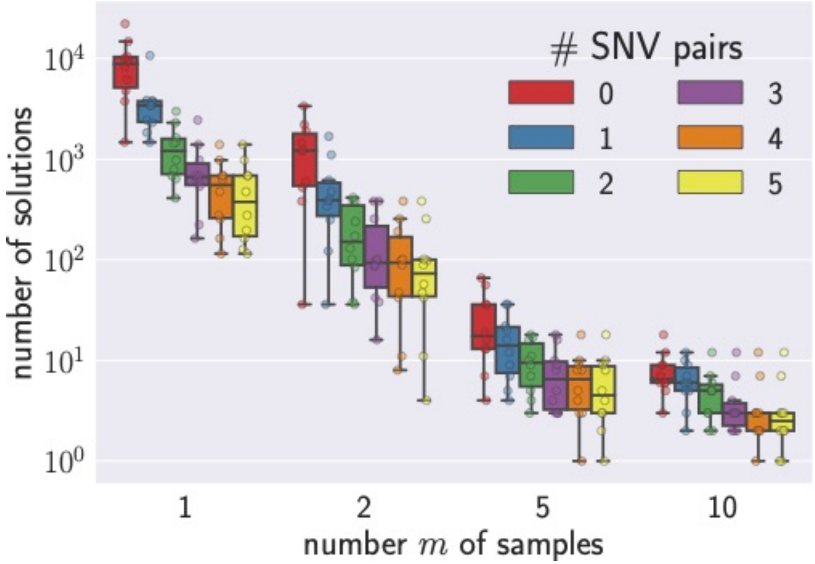

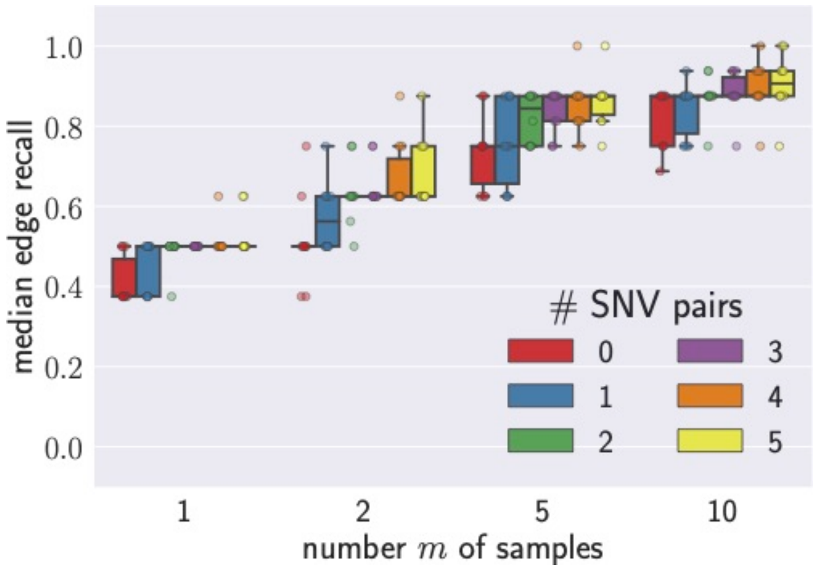

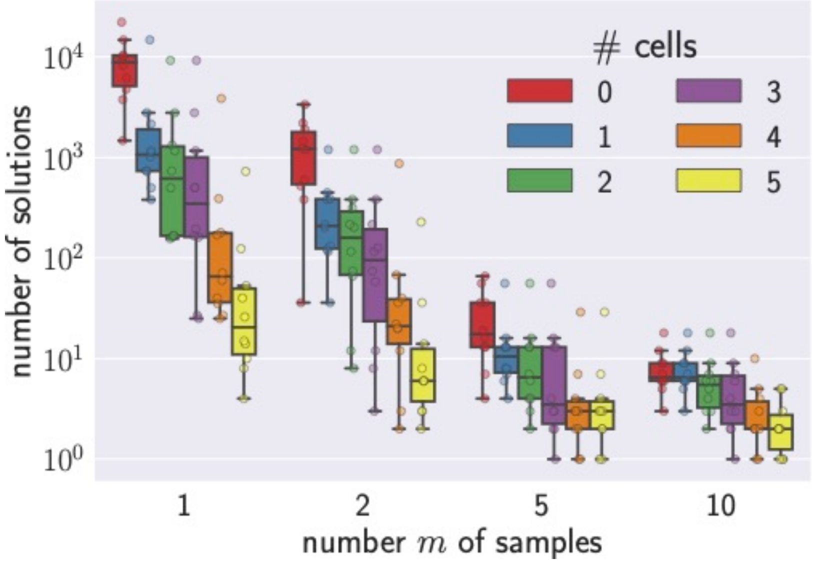

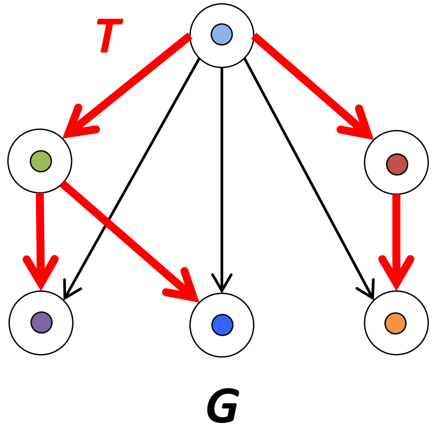

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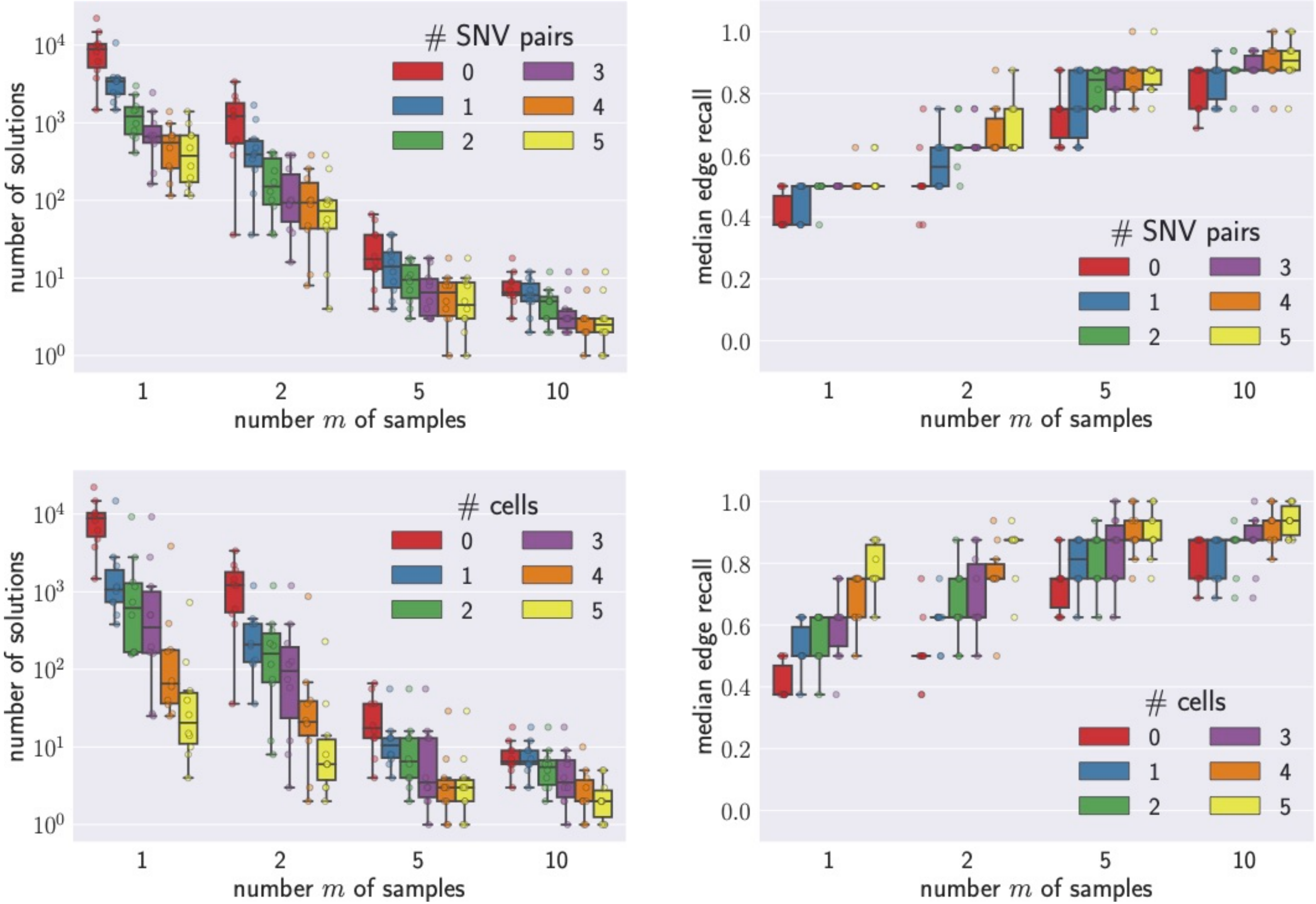
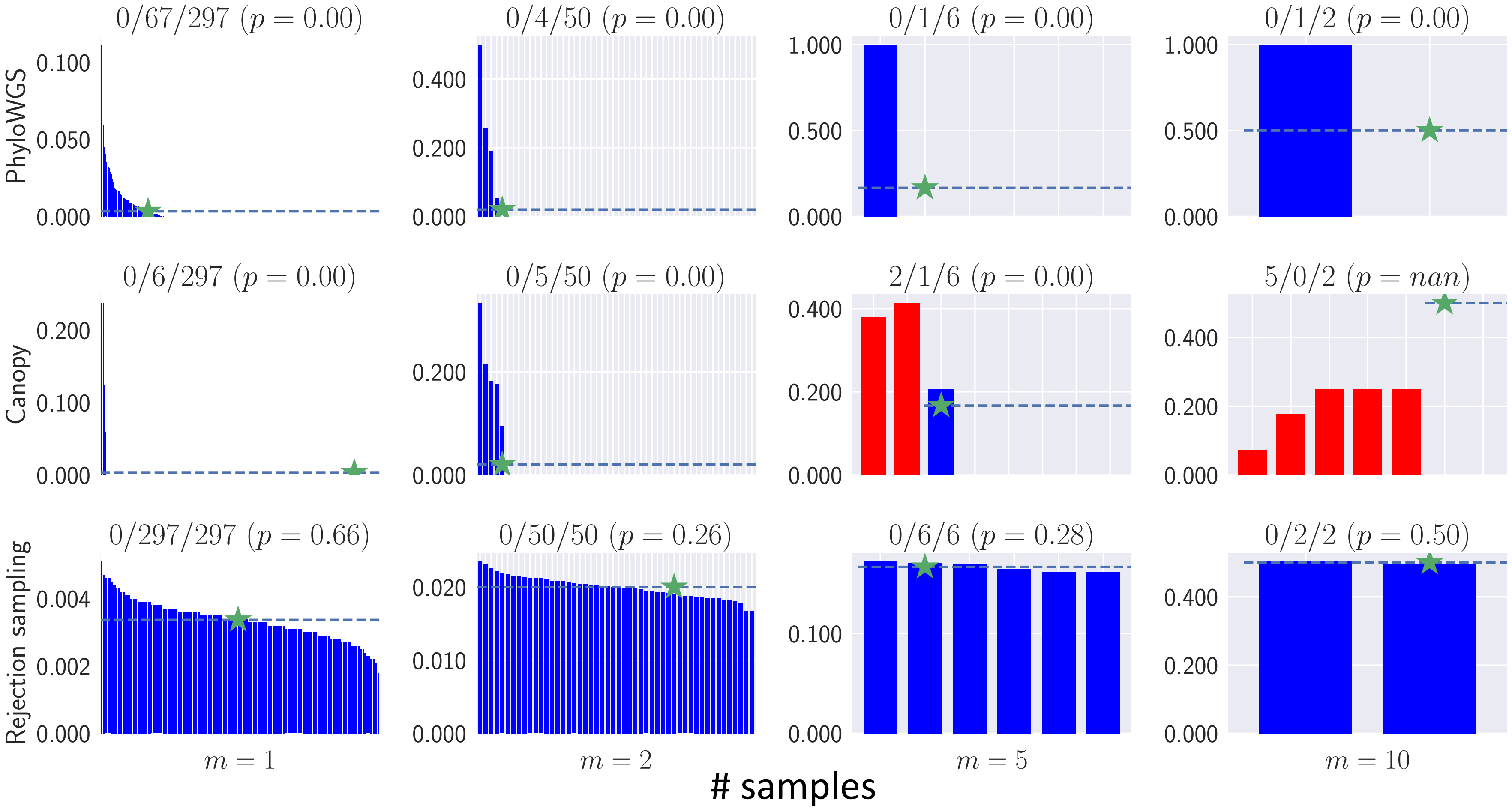


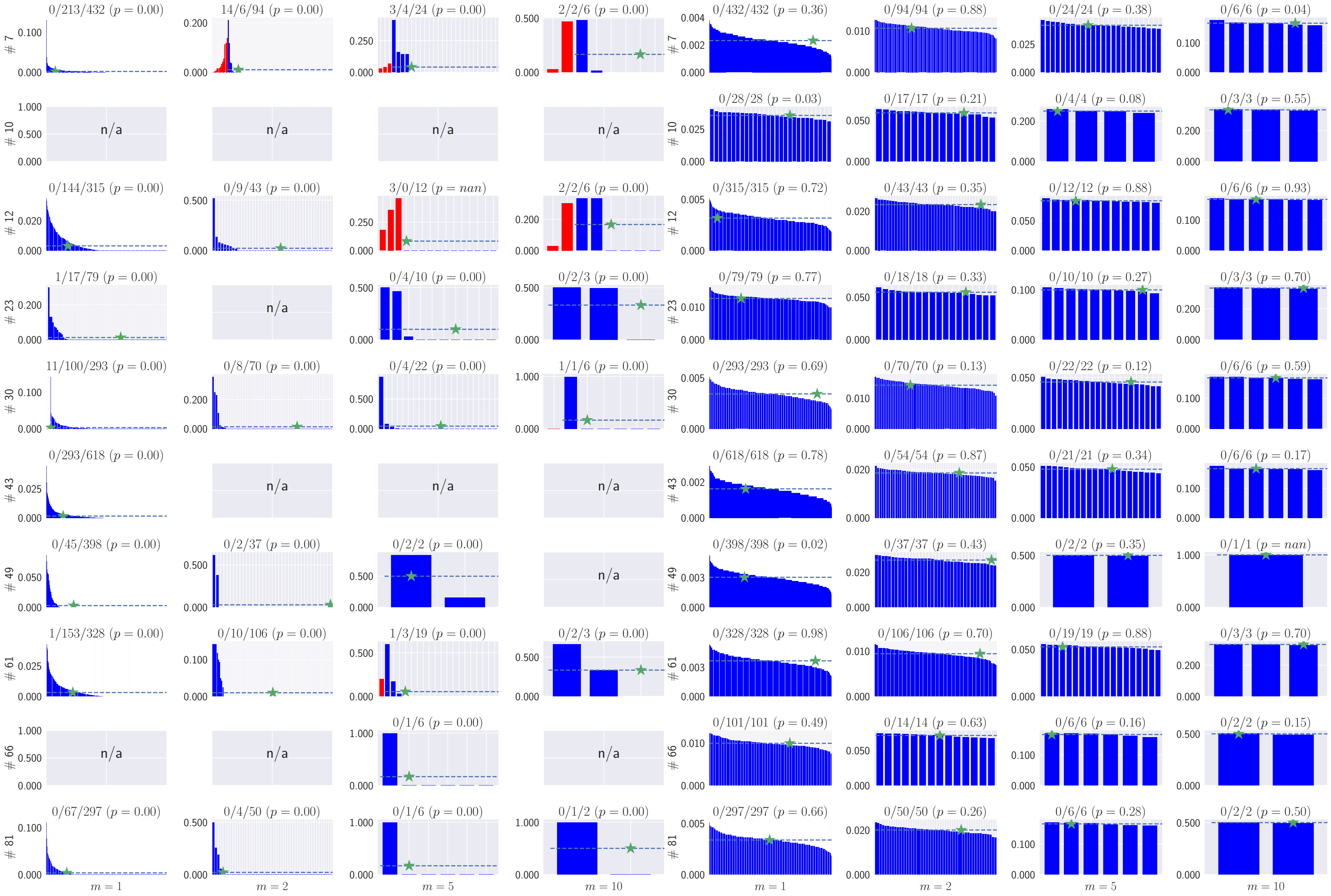
# How Does Non-uniqueness affect Methods?

Two current MCMC methods using default parameters:

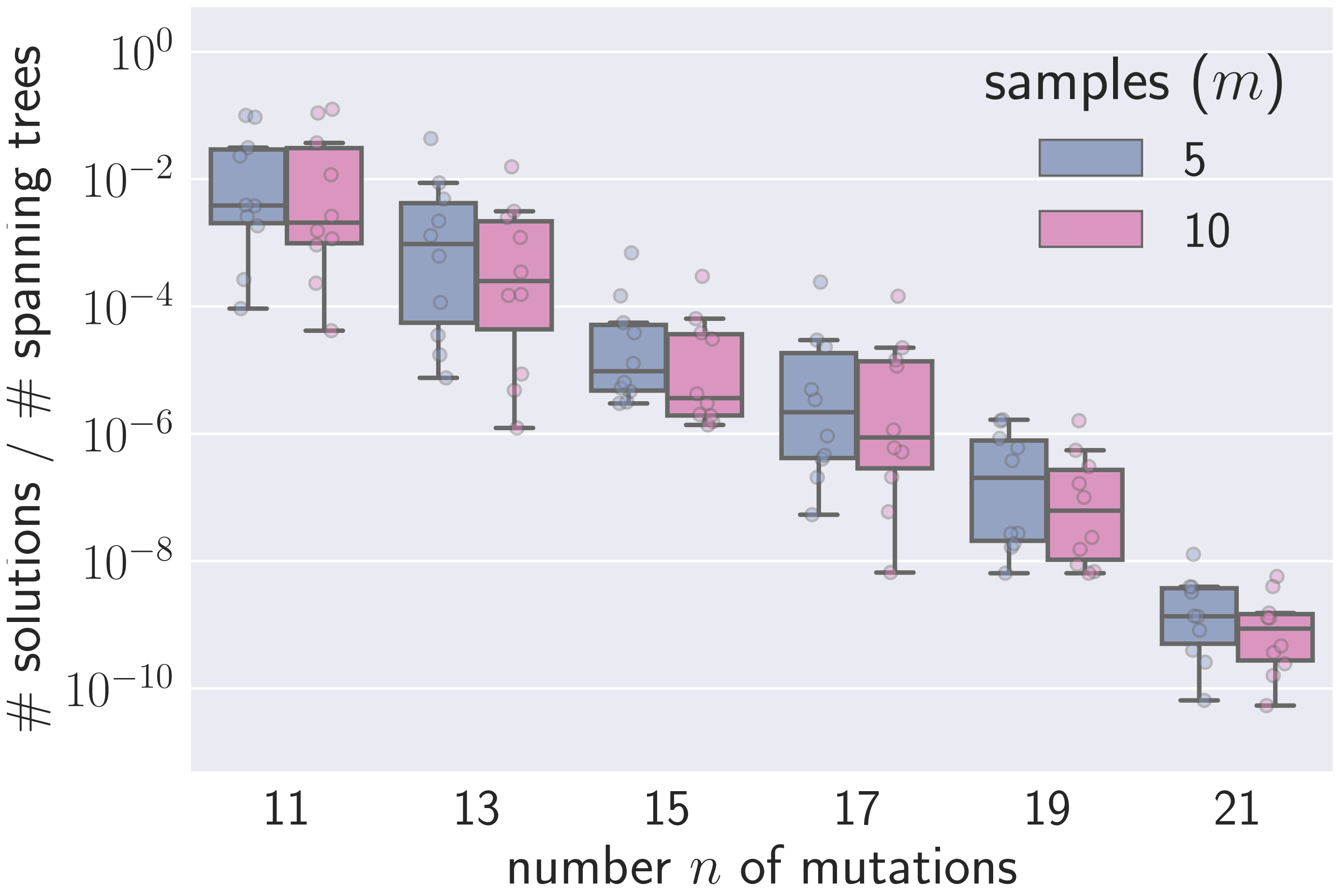
- PhyloWGS, Deshwar et al., Genom. Biol., 2015 [10,000 samples]
- Canopy, Jiang et al., PNAS, 2016 [~300 samples]



PhyloWGS Rejection Sampling



# Rejection Sampling Does Not Scale



# Probabilistic Model for Noisy Measurements

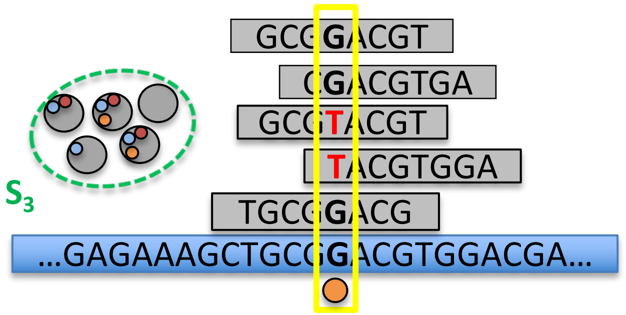
mutations

$$\boldsymbol{F} = [f_{pi}] = \begin{array}{cc} \begin{array}{cccccc} \bullet & \bullet & \bullet & \bullet & \bullet & \bullet \end{array} & \\ \begin{pmatrix} 0.8 & 0.8 & 0.8 & 0.0 & 0.0 & 0.0 \\ 0.7 & 0.6 & 0.0 & 0.6 & 0.0 & 0.0 \\ 0.8 & 0.0 & 0.0 & 0.0 & 0.6 & \boxed{0.4} \end{pmatrix} & \begin{array}{c} s_1 \\ s_2 \\ s_3 \end{array} \end{array}$$

samples

VAF of mutation *i* in sample *p*

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

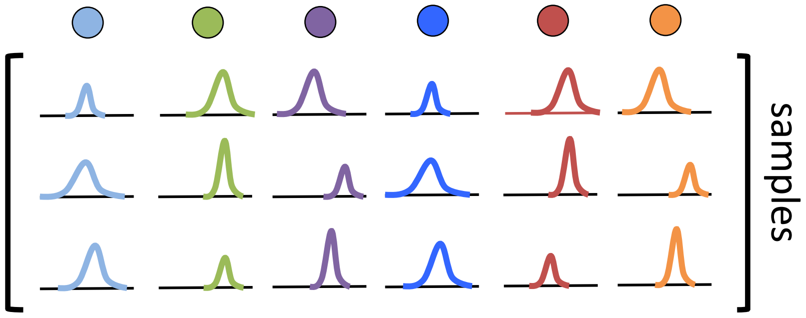


$$\mathrm{VAF}(\bullet) = \frac{\#\text{ reads with } \bullet}{\#\text{ reads}}$$

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

mutations

$[\boldsymbol{X}_{pi}] =$



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

# Probabilistic Model for Noisy Measurements

mutations

$$\boldsymbol{F}^{-} = [f^{-}_{pi}] = \begin{array}{ccccccc} \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \\ 0.75 & 0.78 & 0.77 & 0.0 & 0.0 & 0.0 & s_1 \\ 0.55 & 0.43 & 0.0 & 0.54 & 0.0 & 0.0 & s_2 \\ 0.56 & 0.0 & 0.0 & 0.0 & 0.57 & 0.34 & s_3 \end{array}$$

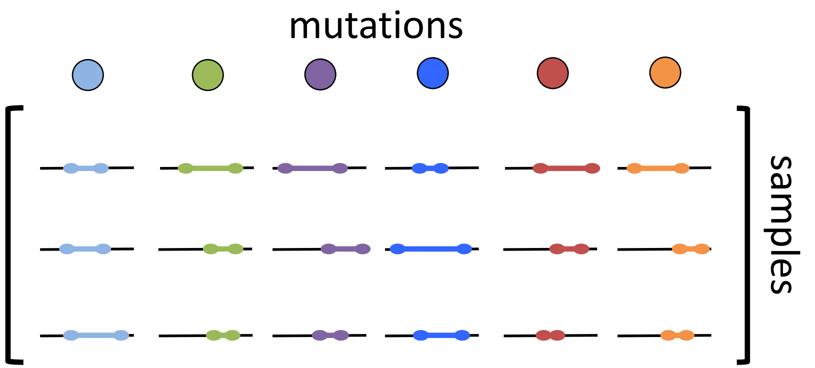
samples

**Consider (1 - α) confidence intervals:**

**Interval PPM (I-PPM)**

Given $\boldsymbol{F}^{-}$ and $\boldsymbol{F}^{+}$, find $\boldsymbol{F}$, $\boldsymbol{U}$ and $\boldsymbol{B}$ such that $\boldsymbol{F} = \boldsymbol{U}\boldsymbol{B}$ and $f^{-}_{pi} \leq f_{pi} \leq f^{+}_{pi}$ for all samples *p* and mutations *i*

$[\boldsymbol{X}_{pi}] =$



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

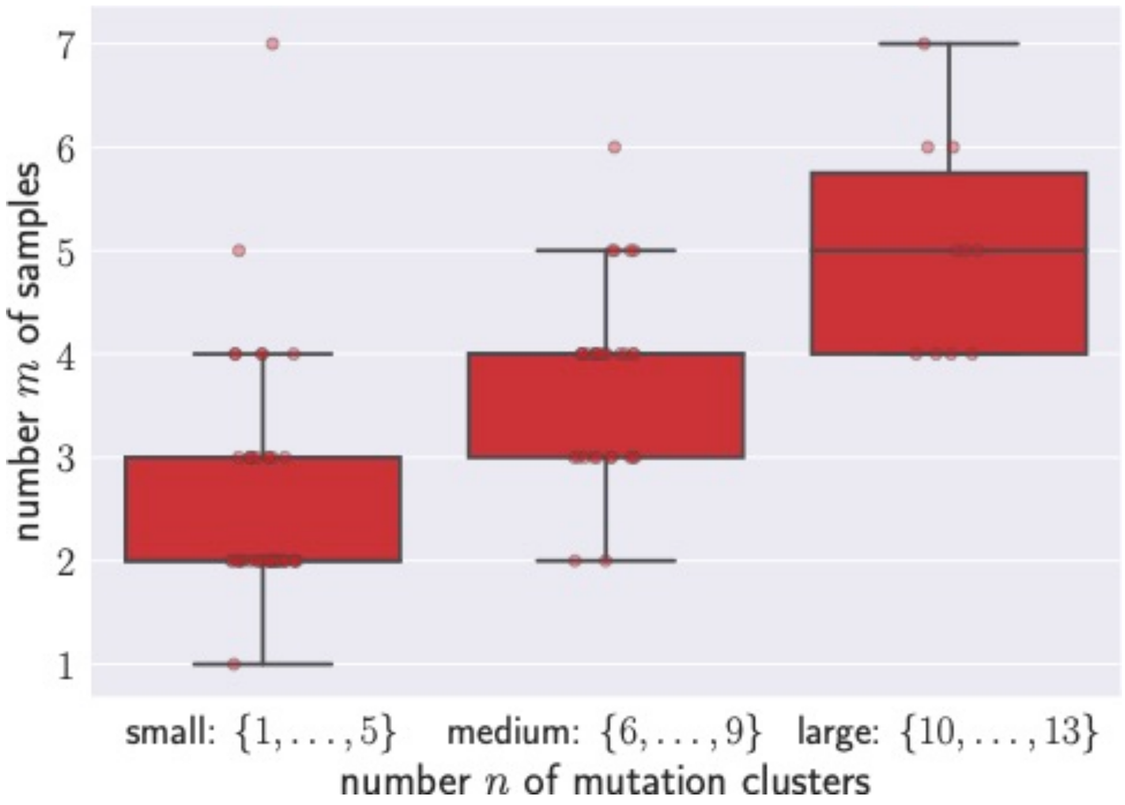
mutations

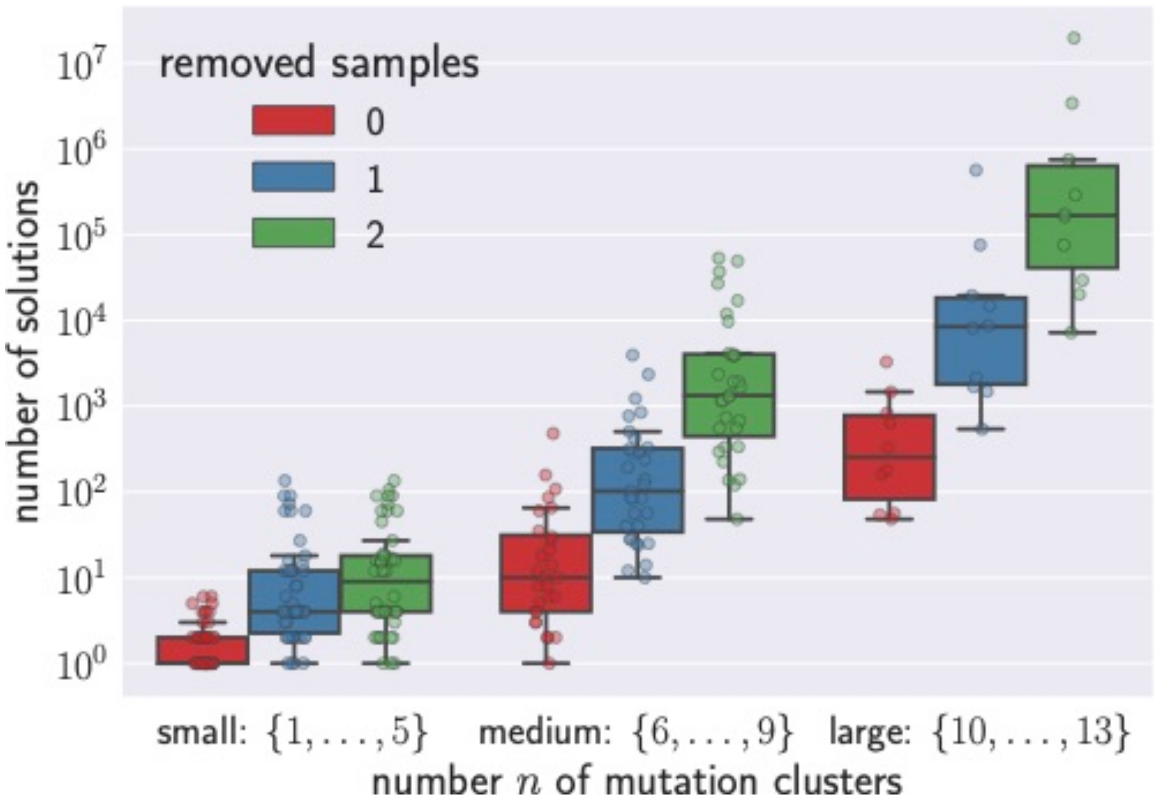
$$\boldsymbol{F}^{+} = [f^{+}_{pi}] = \begin{array}{ccccccc} \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \\ 0.9 & 0.85 & 0.87 & 0.05 & 0.0 & 0.0 & s_1 \\ 0.75 & 0.65 & 0.05 & 0.68 & 0.0 & 0.0 & s_2 \\ 0.83 & 0.0 & 0.04 & 0.0 & 0.67 & 0.48 & s_3 \end{array}$$

samples

# Real Data

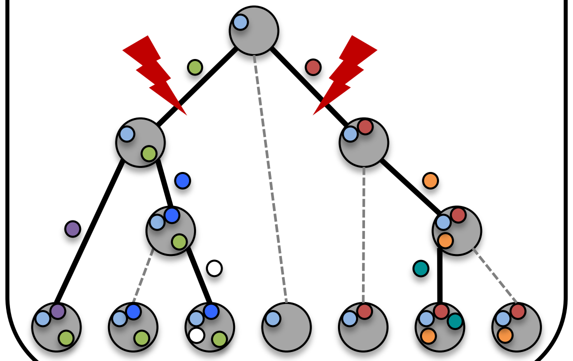
- Cohort of 100 lung cancers [Jamal-Hanjani, NEJM 2017]
- 90% confidence intervals



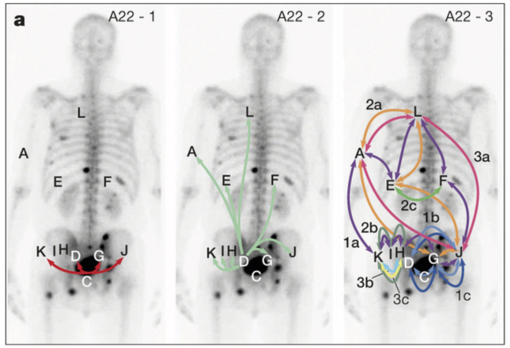


# Challenges

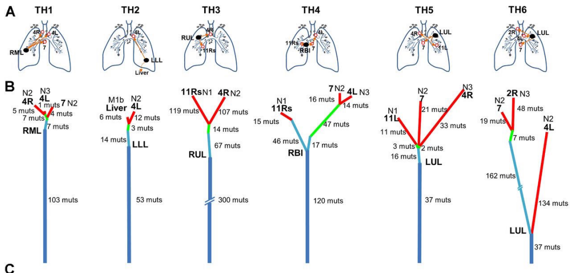
**Identify targets for treatment**



**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**