On the Non-uniqueness of Solutions to the Perfect Phylogeny Mixture Problem

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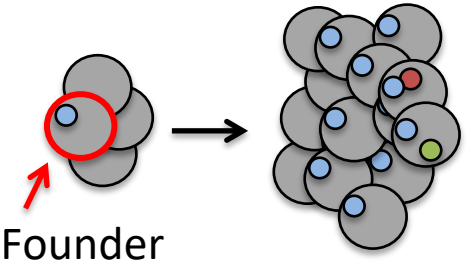
RECOMB-CG 2018

Tumorigenesis: Cell Mutation

Clonal Evolution Theory of Cancer
[Nowell, 1976]



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

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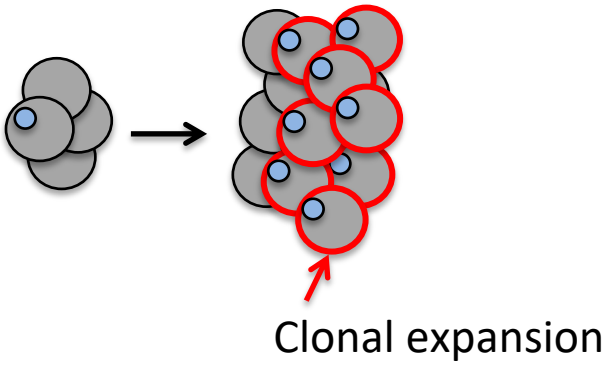

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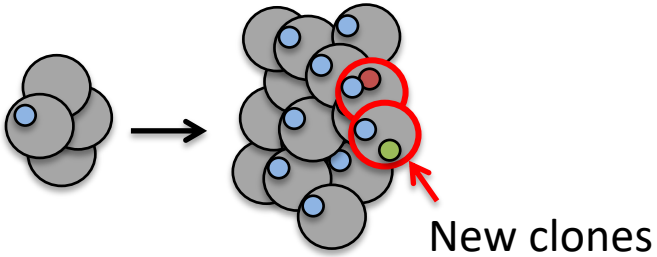

Tumorigenesis: Cell Mutation & Division

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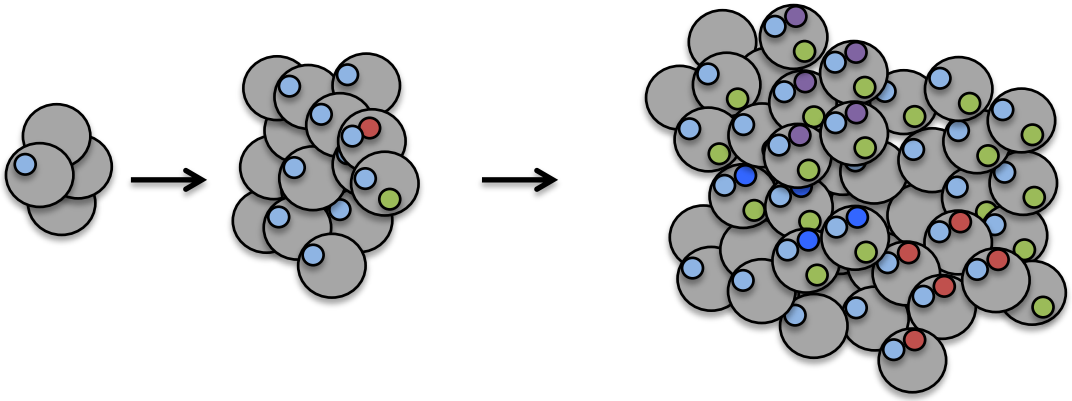

Intra-Tumor
Heterogeneity

Tumorigenesis: Cell Mutation & Division

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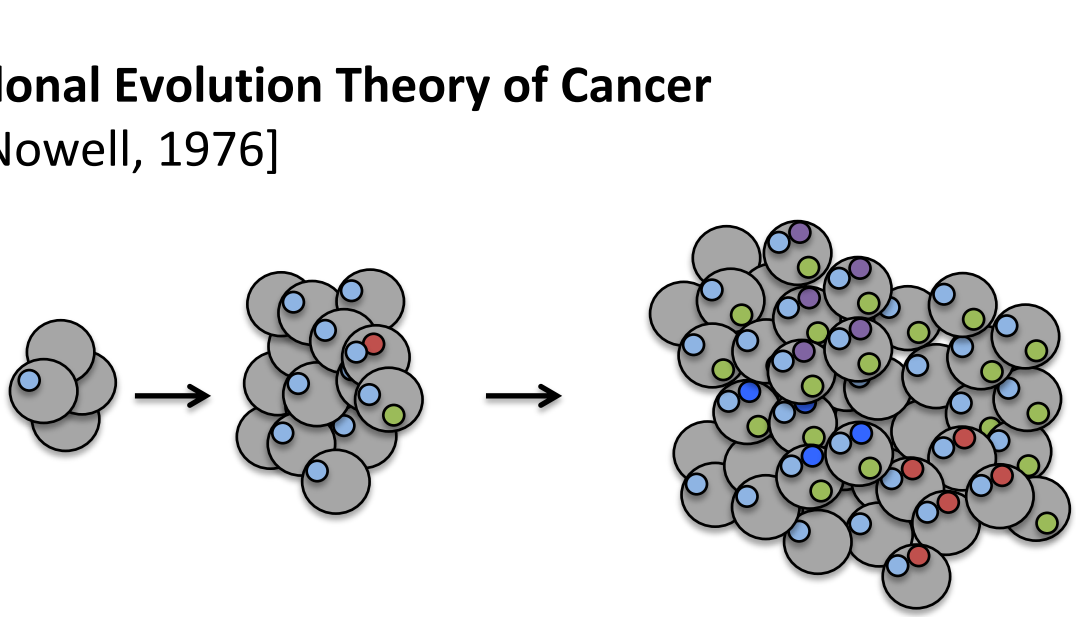

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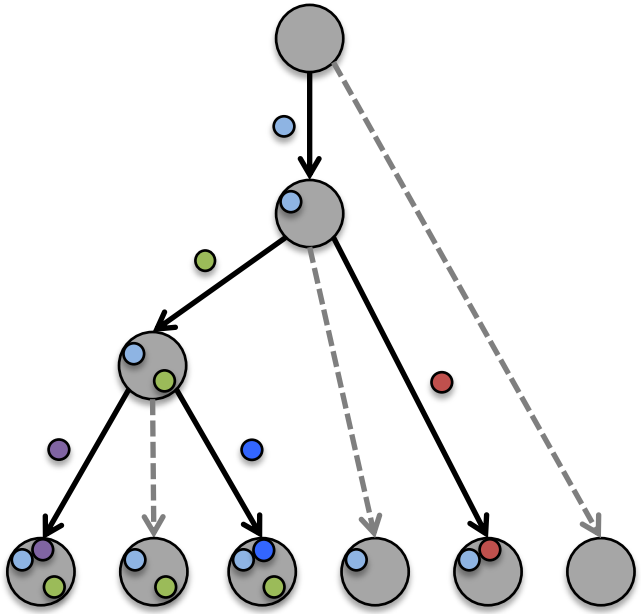
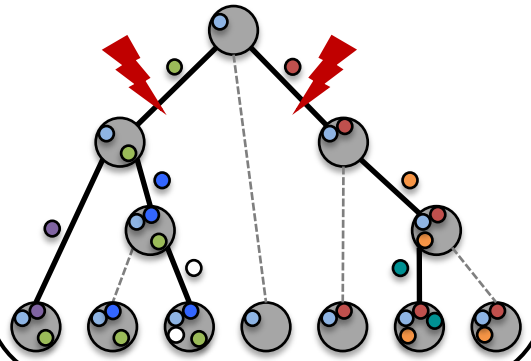


Phylogenetic Tree ***T***

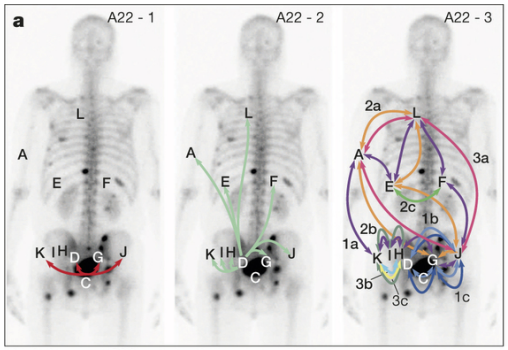
Question: Why are tumor phylogenies important?

Phylogenies are Key to Understanding Cancer

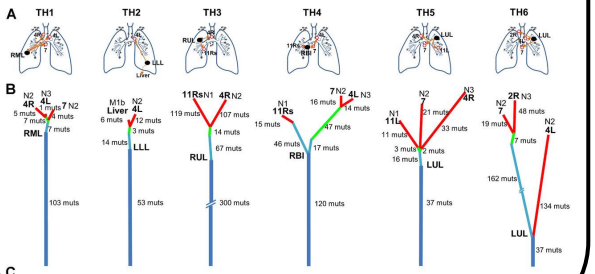
Identify targets for treatment



Understand metastatic development



Recognize common patterns of tumor evolution across patients



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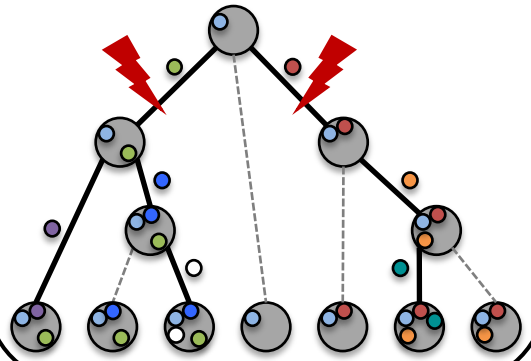

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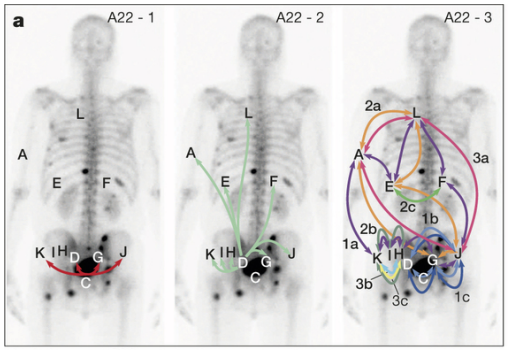

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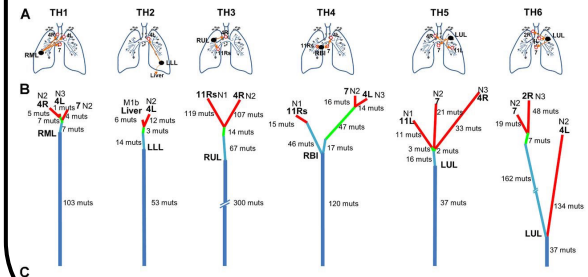

These downstream analyses **critically rely** on accurate tumor phylogeny inference

Phylogenies are Key to Understanding Cancer

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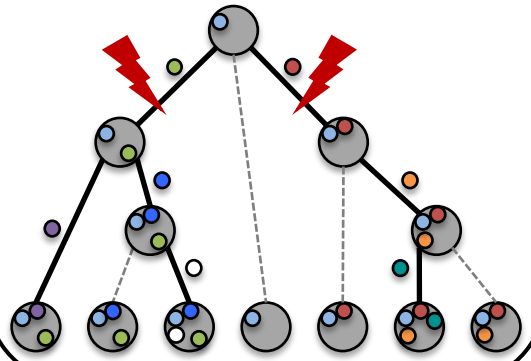

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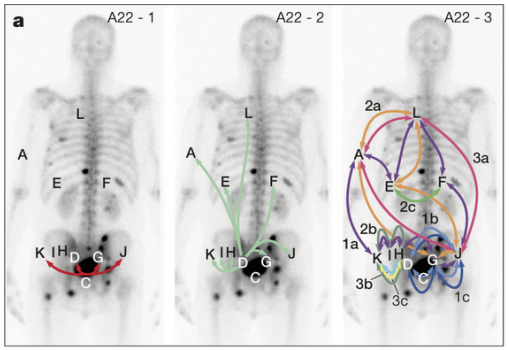

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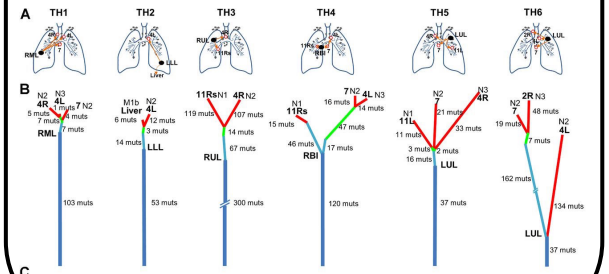

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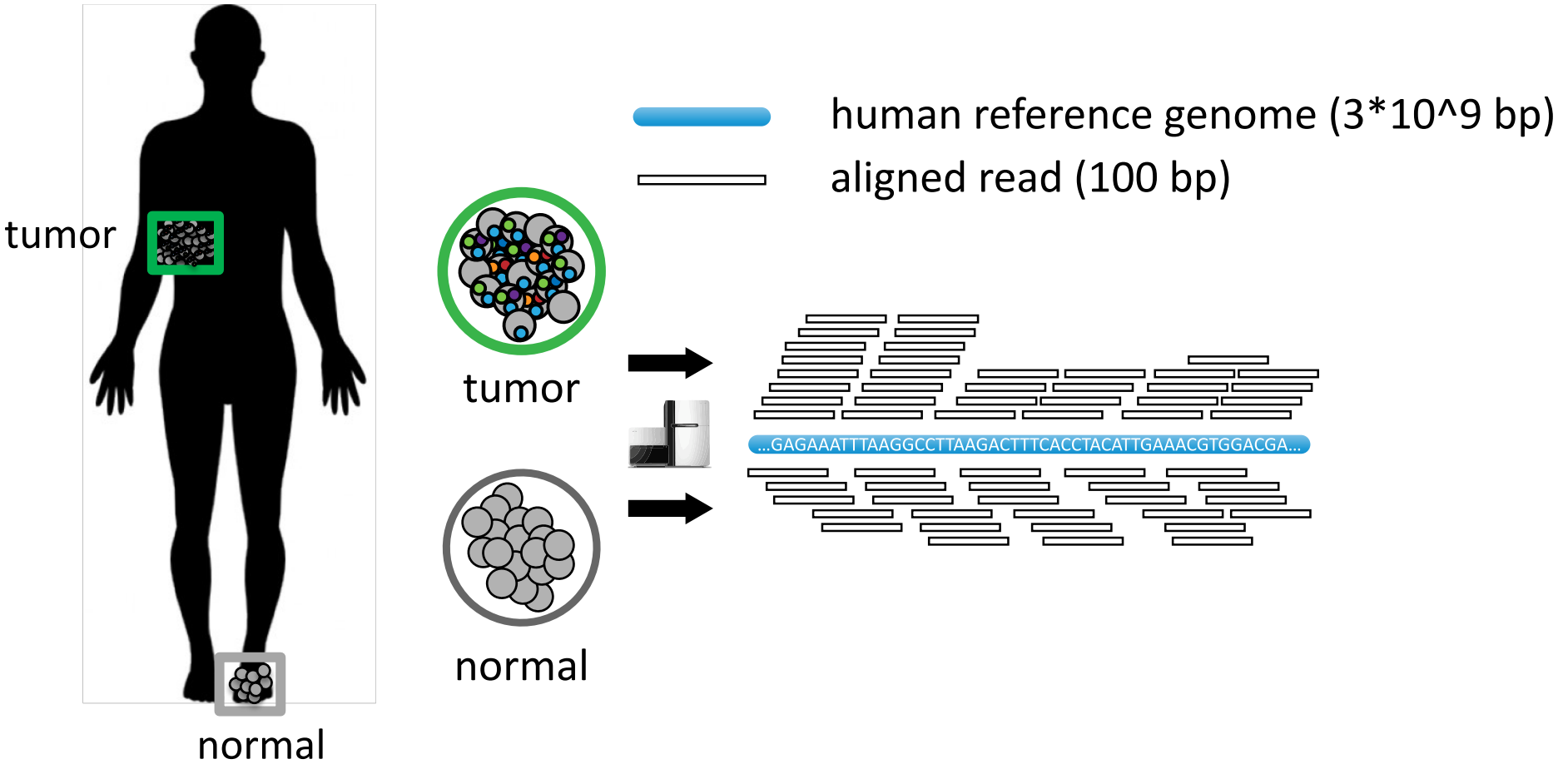
Key challenge in phylogenetics:
Accurate phylogeny inference from data at present time

Additional Challenge in Cancer Phylogenetics



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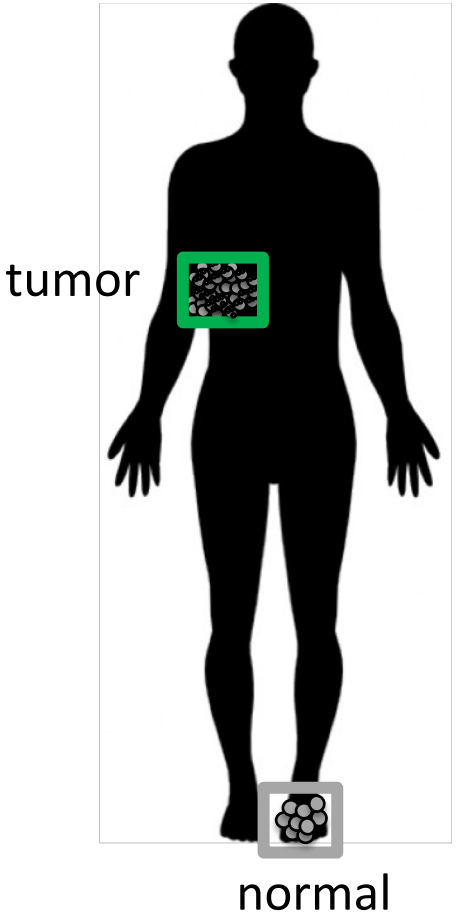

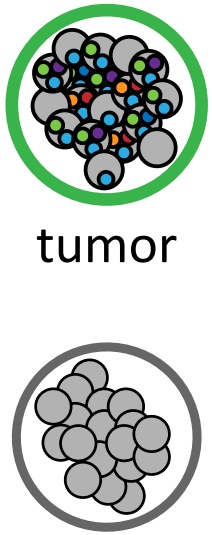

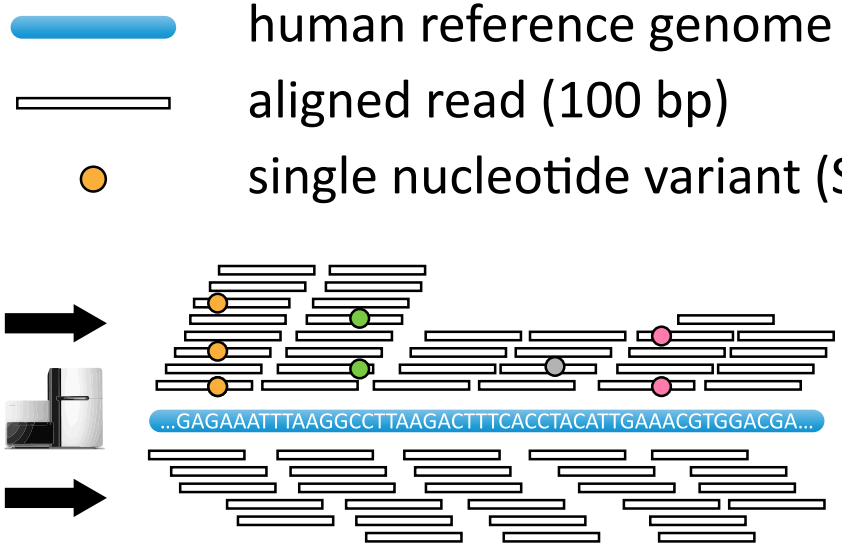

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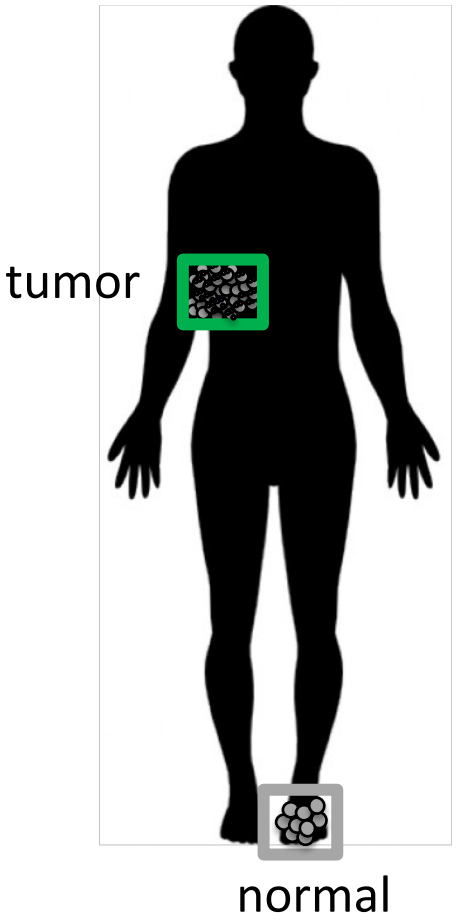
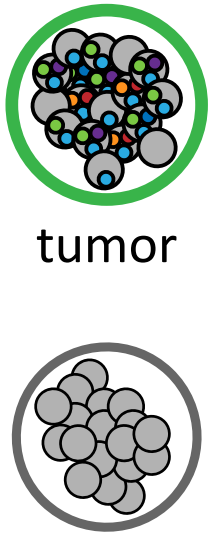




human reference genome (3*10^9 bp)

aligned read (100 bp)

single nucleotide variant (SNV)

Additional challenge in cancer phylogenetics:

Phylogeny inference from **mixed bulk samples** at present time

Outline

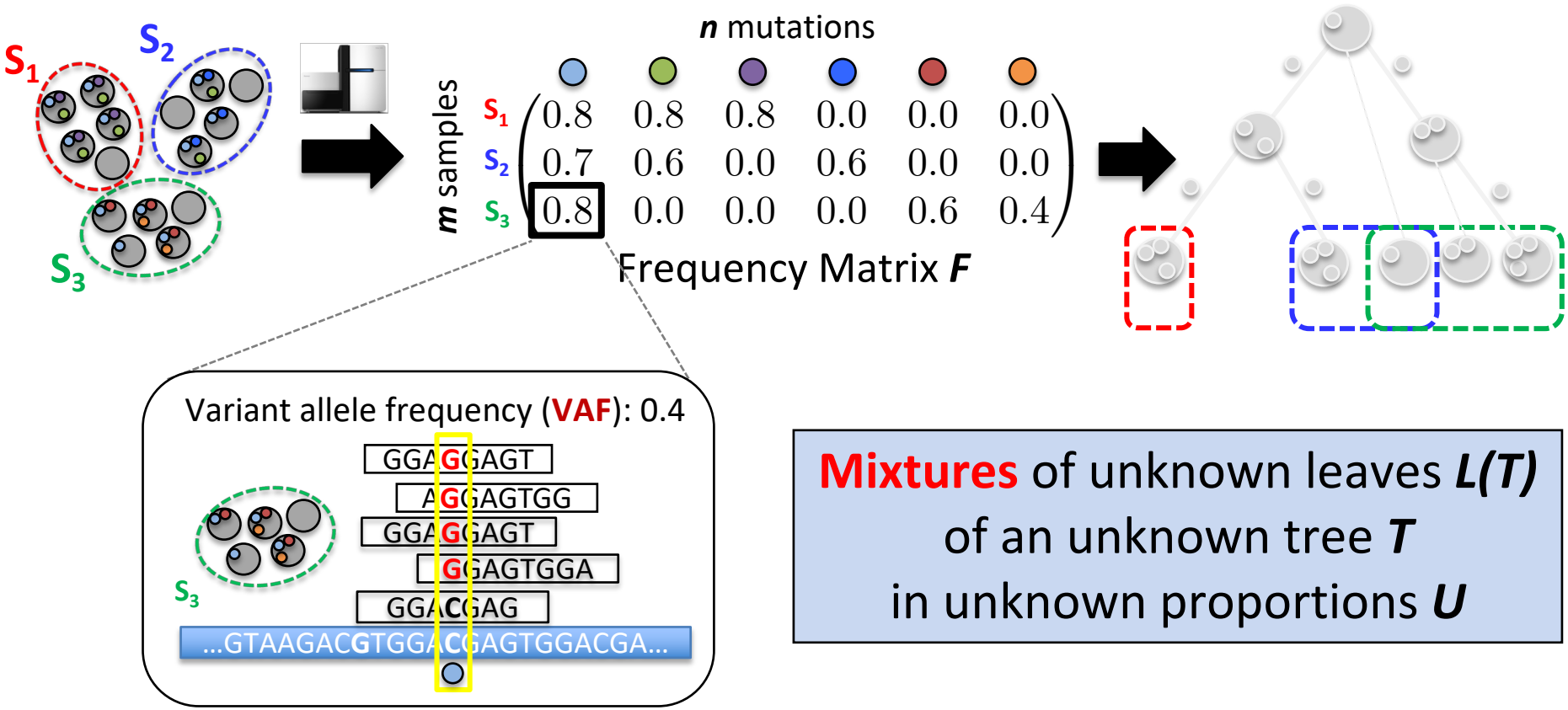
Background and theory:

- 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?

Sequencing and Tumor Phylogeny Inference



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

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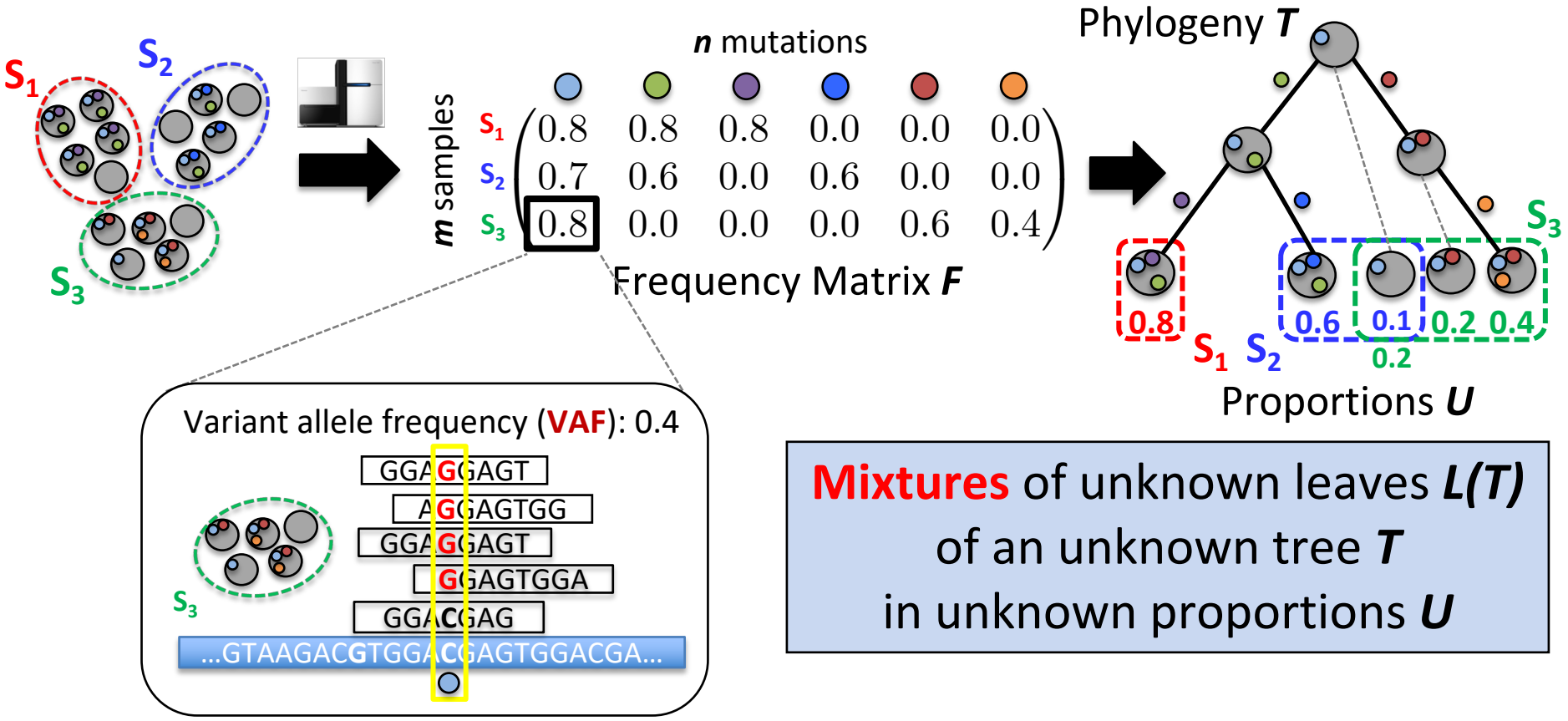

Mixtures of unknown leaves ***L(T)***
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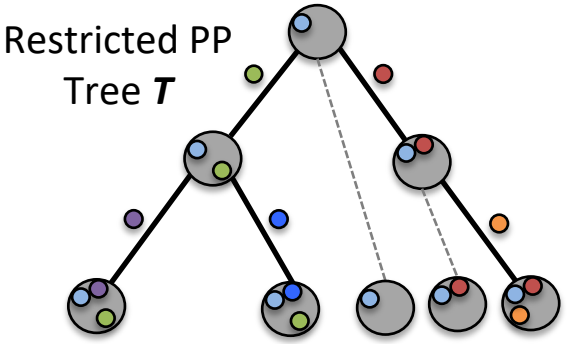
Tumor Phylogeny Inference: Given frequencies ***F***, find phylogeny ***T*** and proportions ***U***

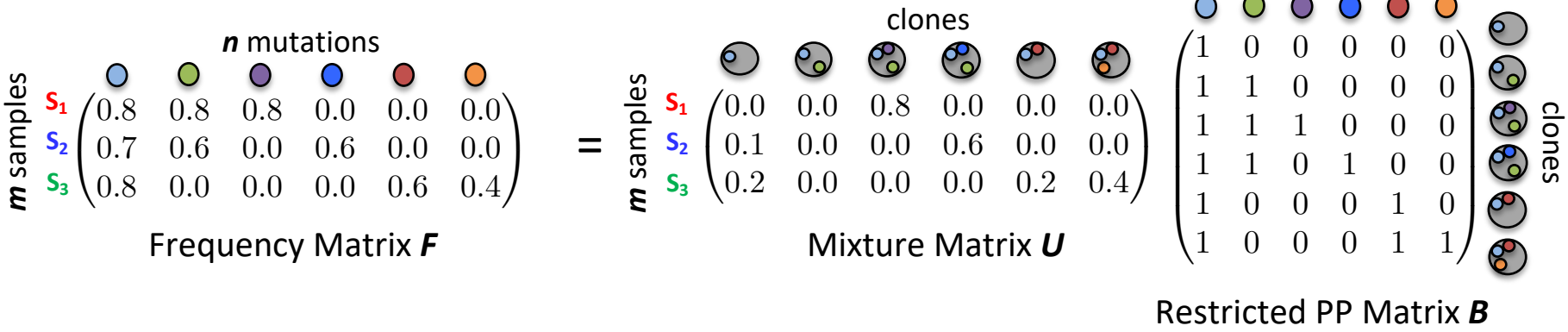
Perfect Phylogeny Mixture



Assumptions:

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

1-1 Equivalent



Rows of U are proportions:

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

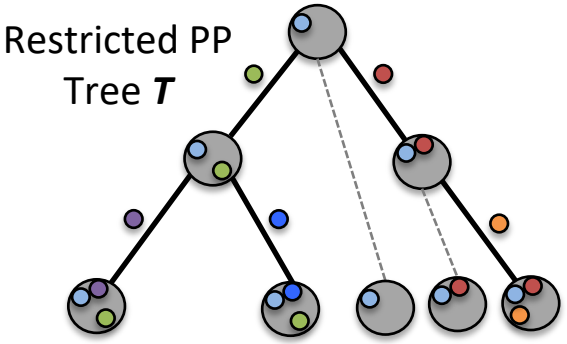
Perfect Phylogeny Theorem
[Estabrook, 1971]
[Gusfield, 1991]

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], …



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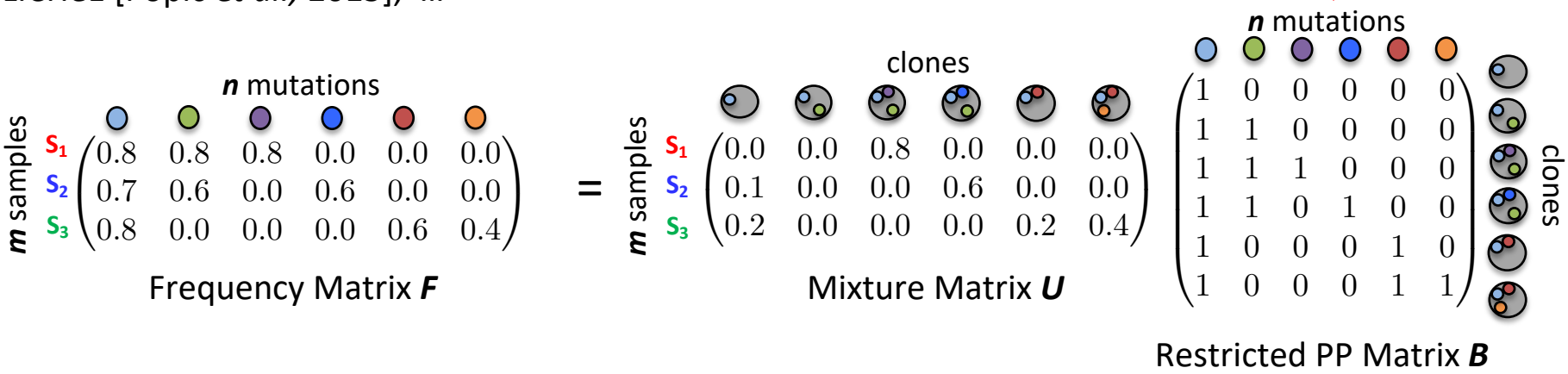

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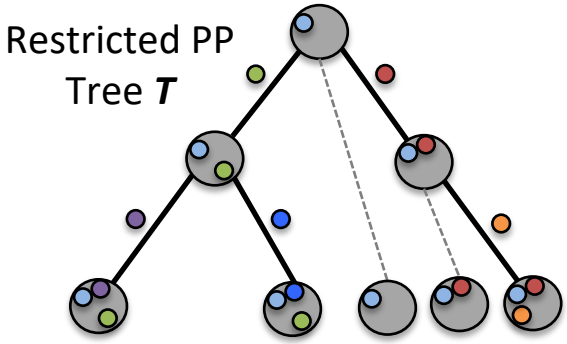
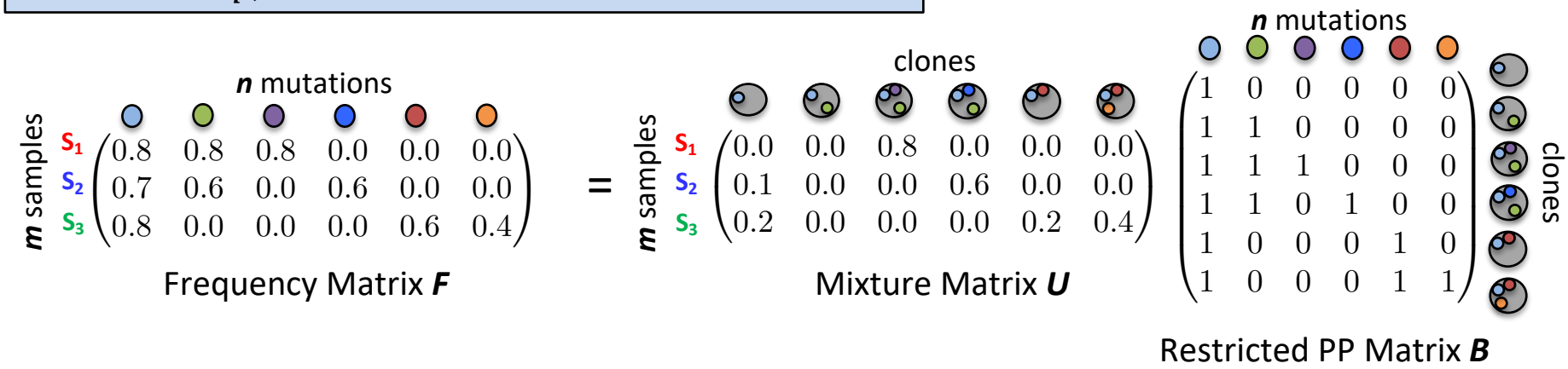
Combinatorial Characterization



- Frequency $f_{p,i}$ is mass of subtree rooted at node that introduced i
- Usage $u_{p,i}$ is mass of node that introduced i

1-1 **Equivalent**



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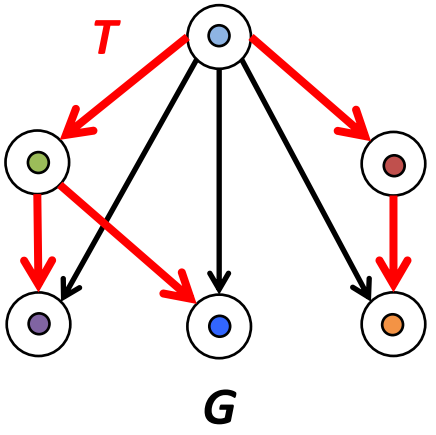

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n mutations

m samples

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

Frequency Matrix ***F***

=

clones

m samples

$$\begin{array}{c} \\ S_1 \\ S_2 \\ S_3 \end{array} \begin{pmatrix} 0.0 & 0.0 & 0.8 & 0.0 & 0.0 & 0.0 \\ 0.1 & 0.0 & 0.0 & 0.6 & 0.0 & 0.0 \\ 0.2 & 0.0 & 0.0 & 0.0 & 0.2 & 0.4 \end{pmatrix}$$

Mixture Matrix ***U***

n mutations

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

clones

Restricted PP Matrix ***B***

Theorem 1:

T is a solution to the PPM if and only if ***T*** is a spanning tree of ***G*** satisfying the sum condition

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

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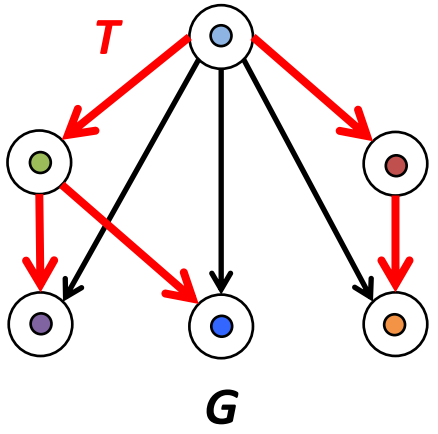
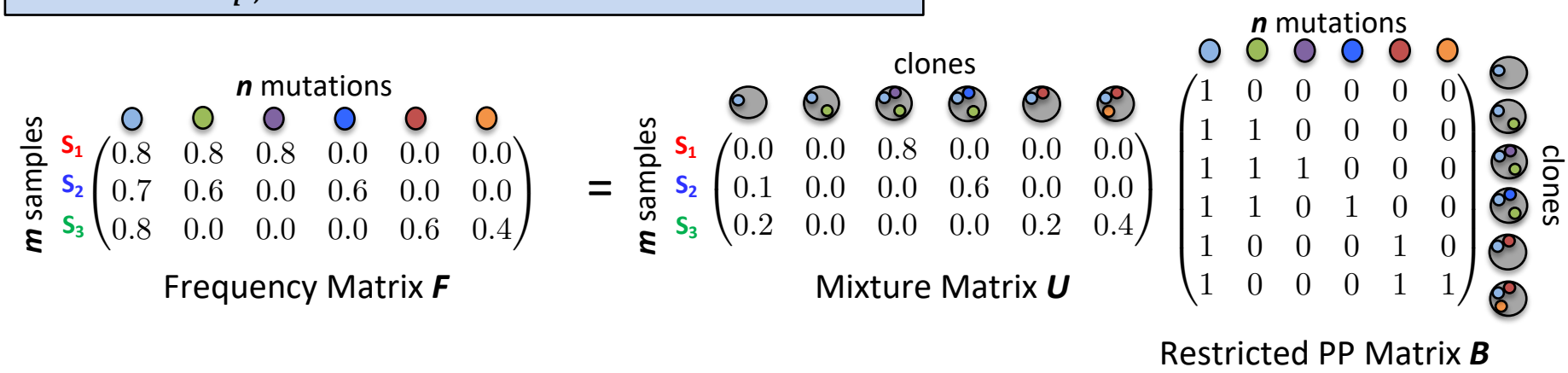


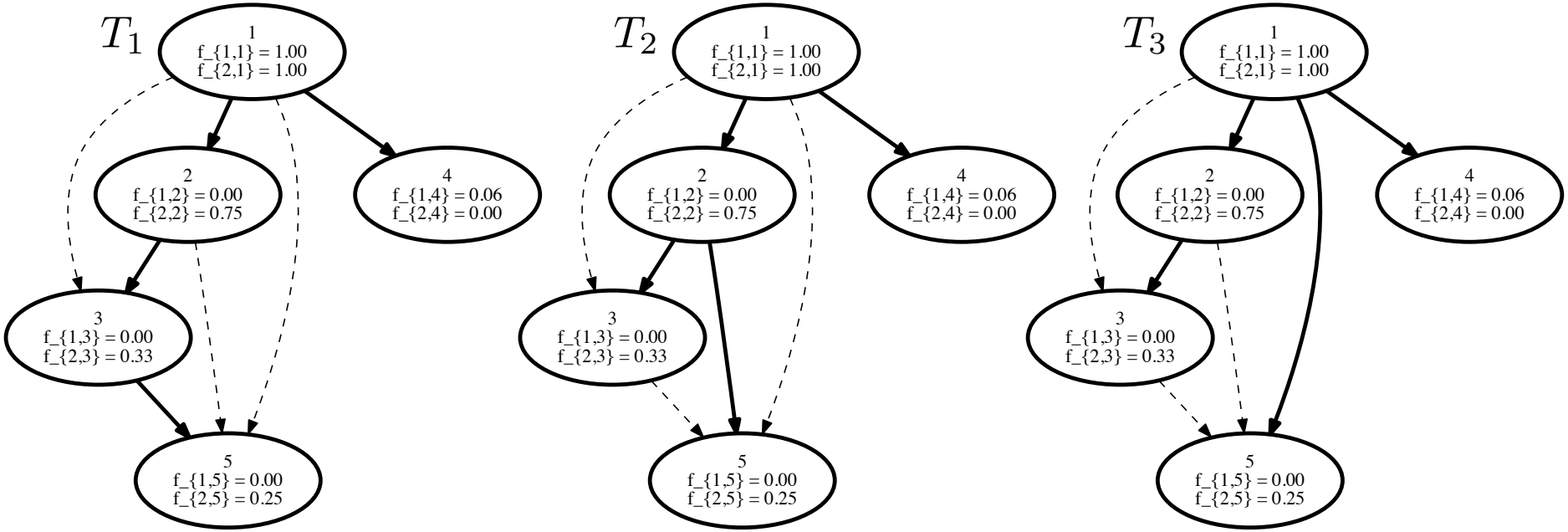


Theorem 1:
T is a solution to the PPM if and only if ***T*** is a spanning tree of ***G*** satisfying the sum condition

Theorem 2:
PPM is NP-complete even for ***m***=2

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

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?

On the Complexity of #PPM (new results)

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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

Every problem in #P can be reduced in polynomial time to any problem in #P-complete, preserving cardinalities

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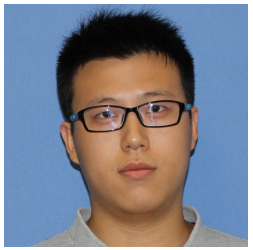
Theorem: #PPM is #P-complete

Theorem: There is no FPRAS for #PPM

Theorem: There is no FPAUS for PPM



Yuanyuan Qi

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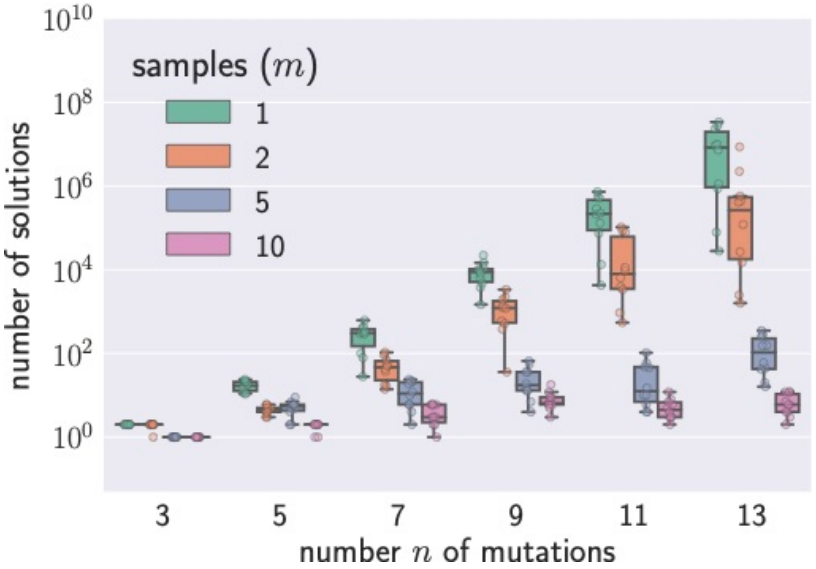
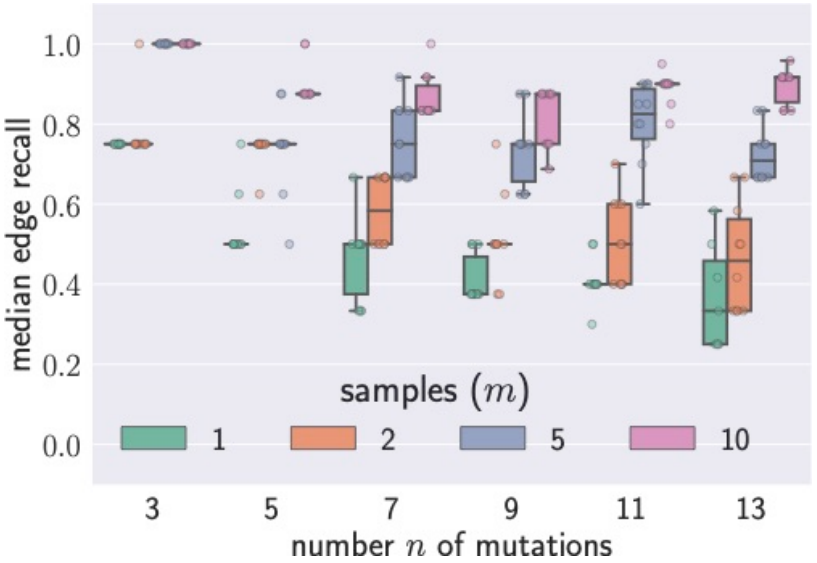
Dikshant Pradhan

What Contributes to Non-uniqueness?





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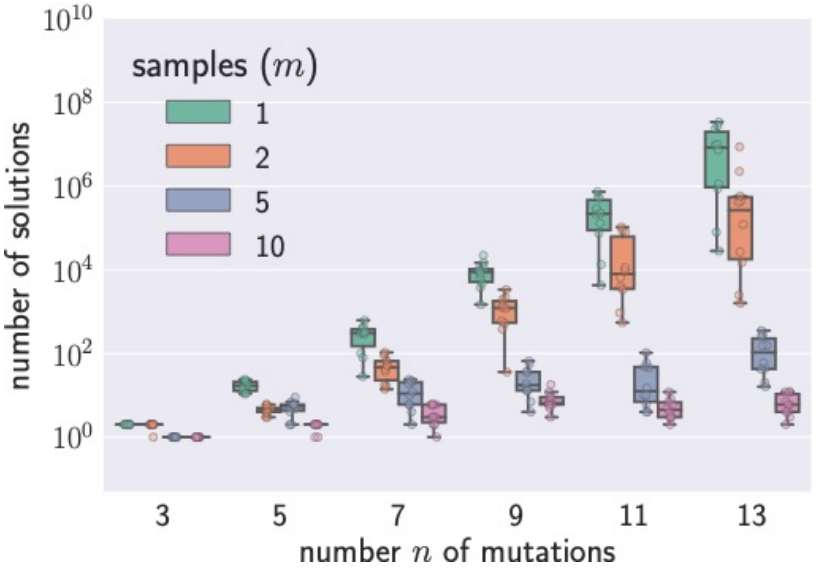
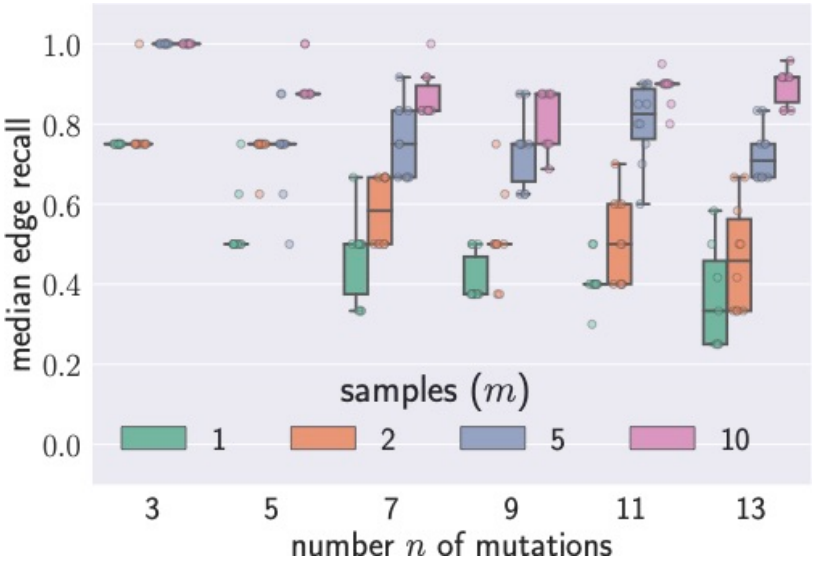
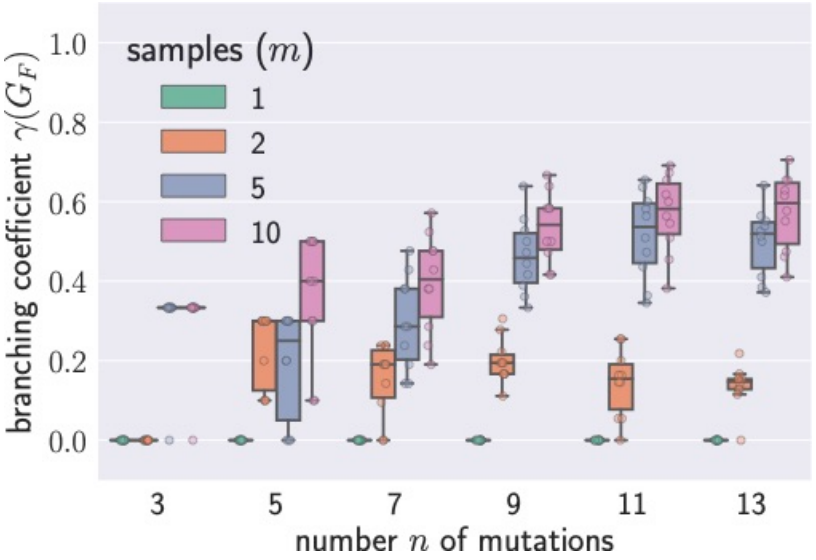
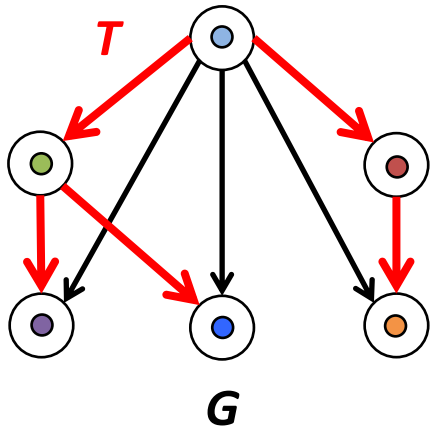
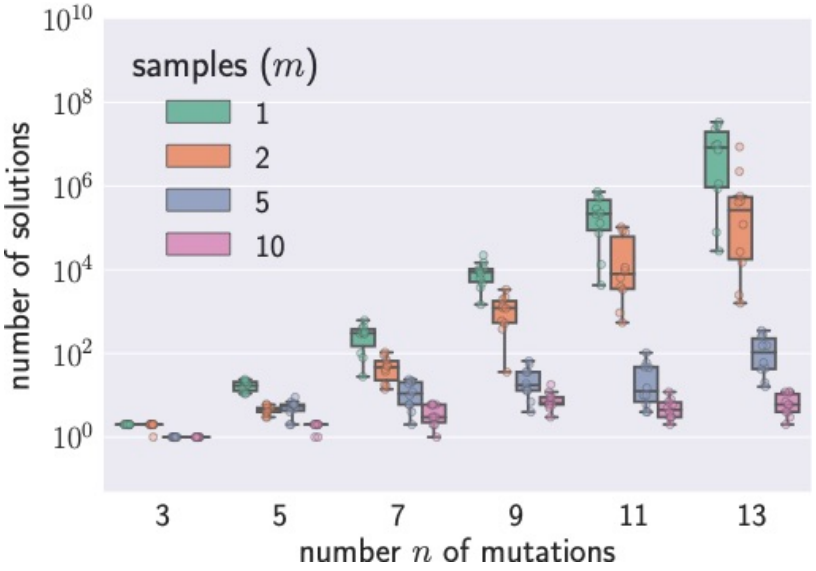


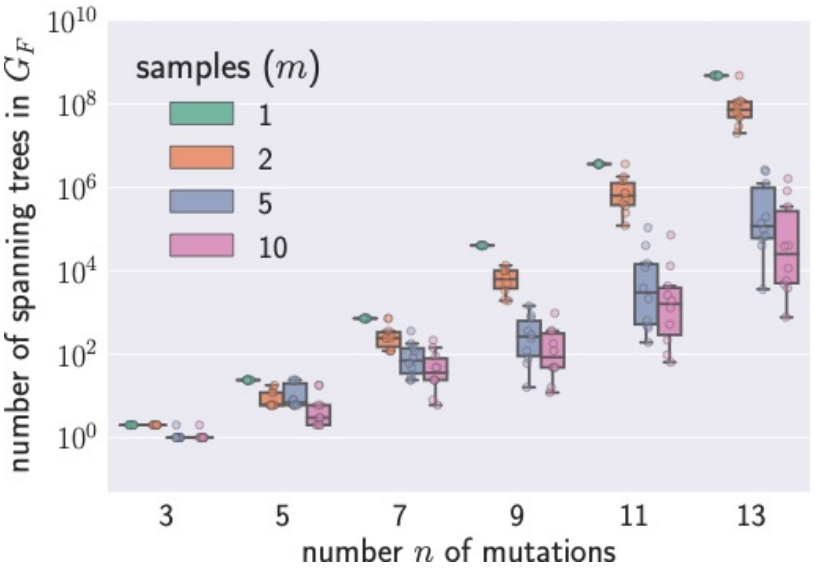


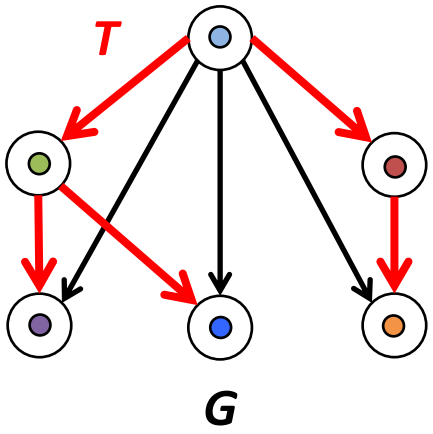




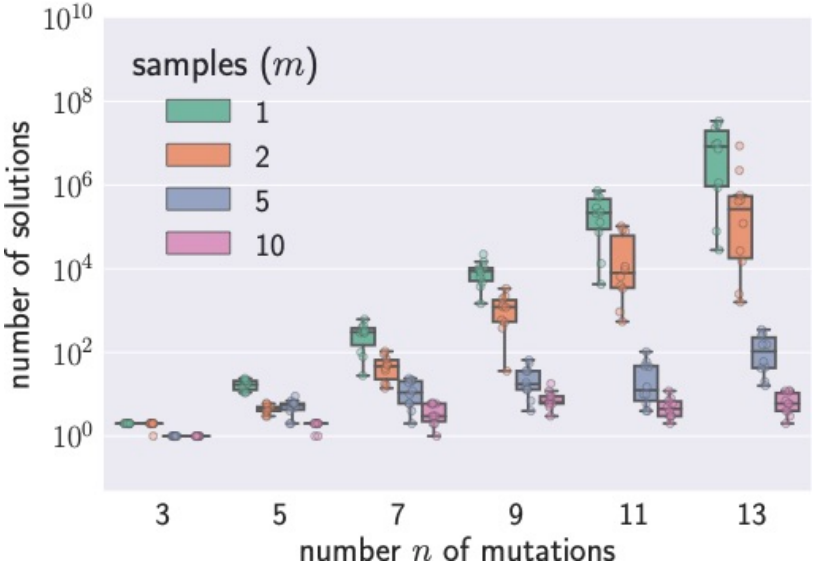
An Upper Bound for Number of Solutions

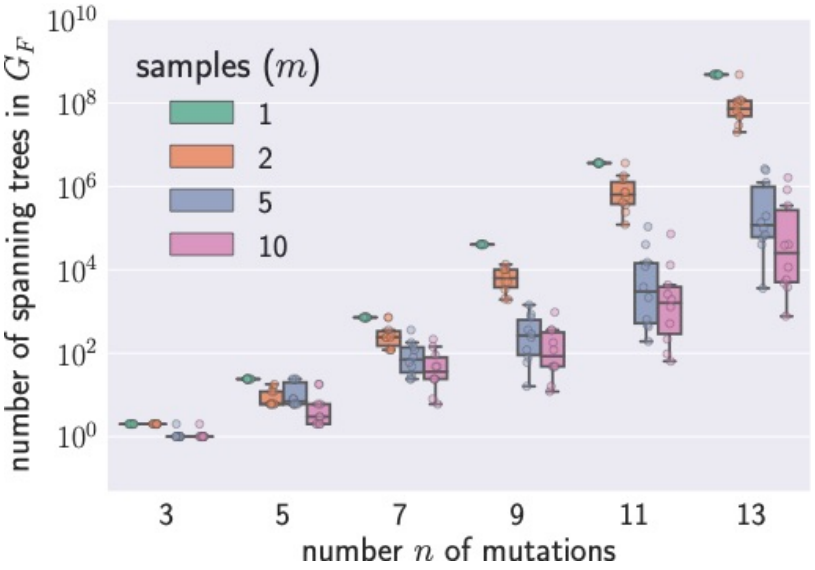


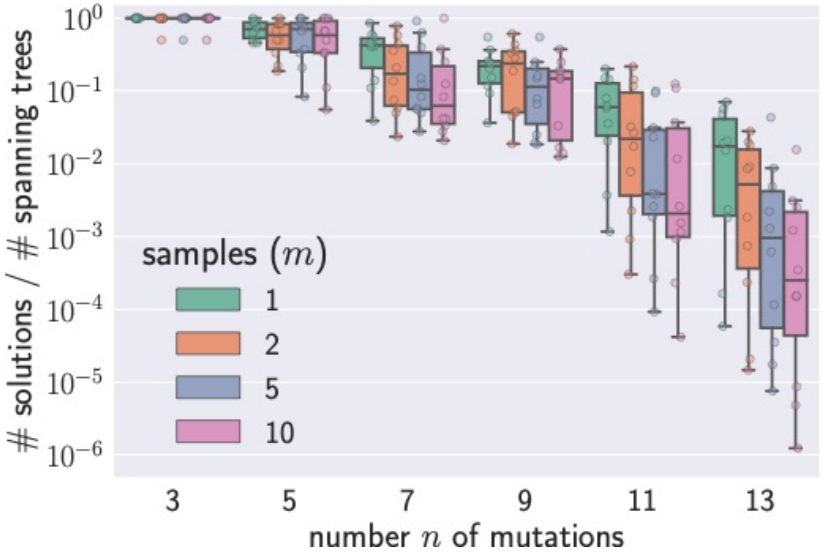


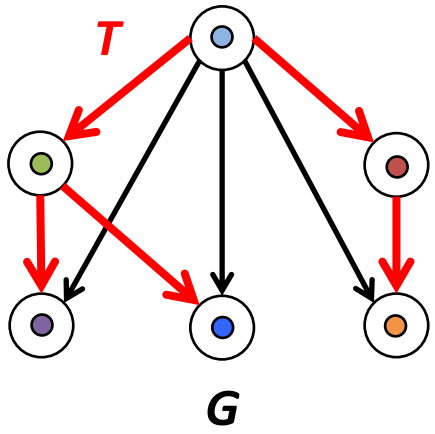


An Upper Bound for Number of Solutions

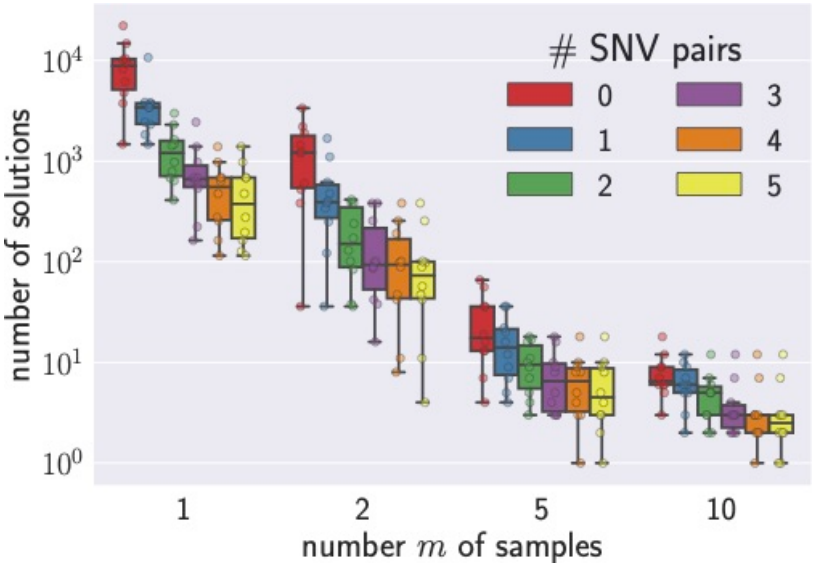


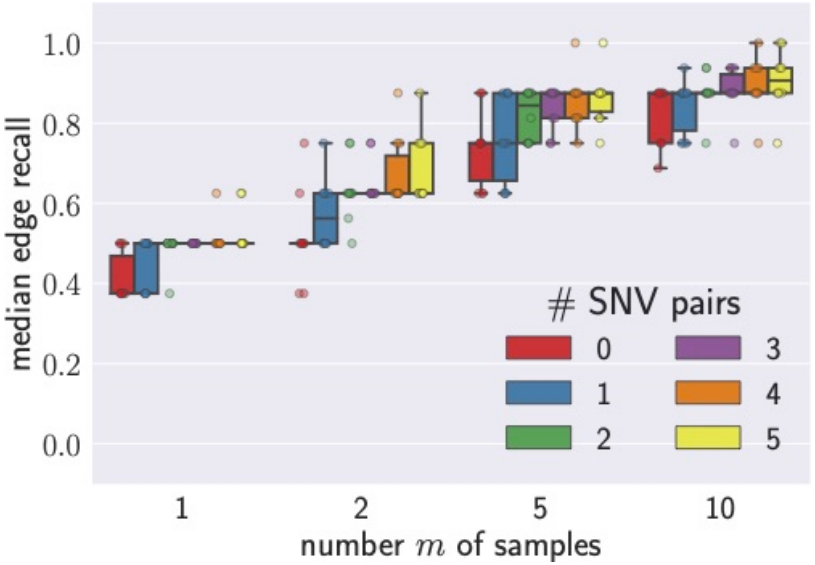


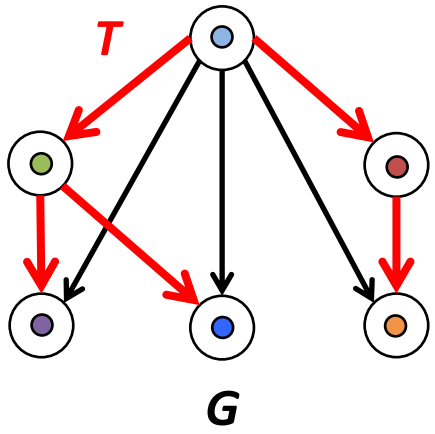




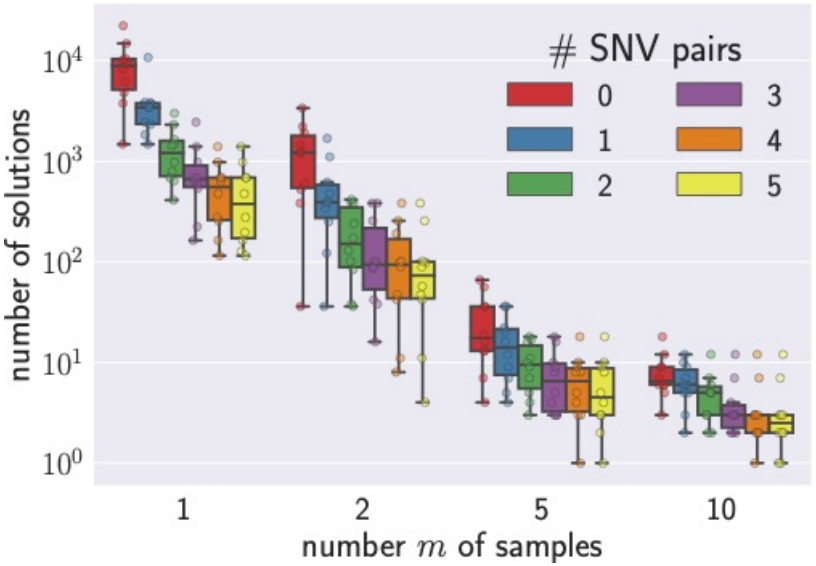
How to Reduce Non-Uniqueness?

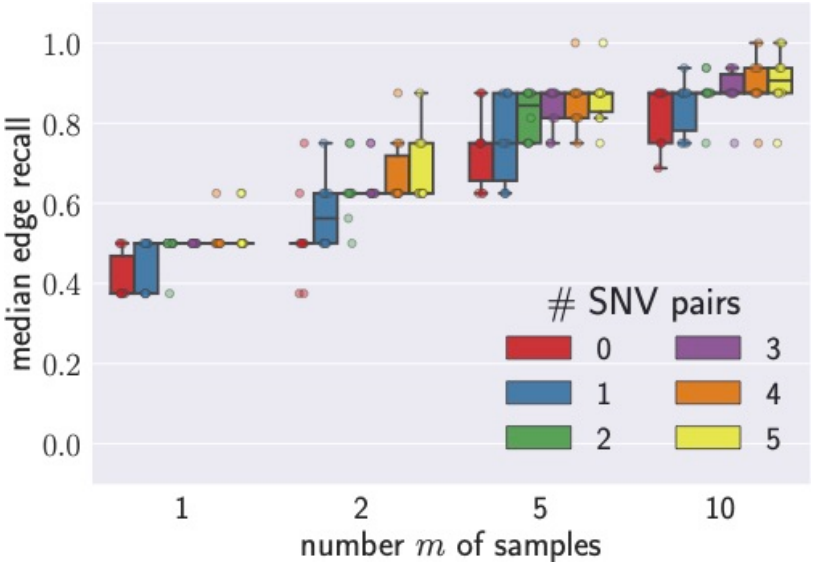


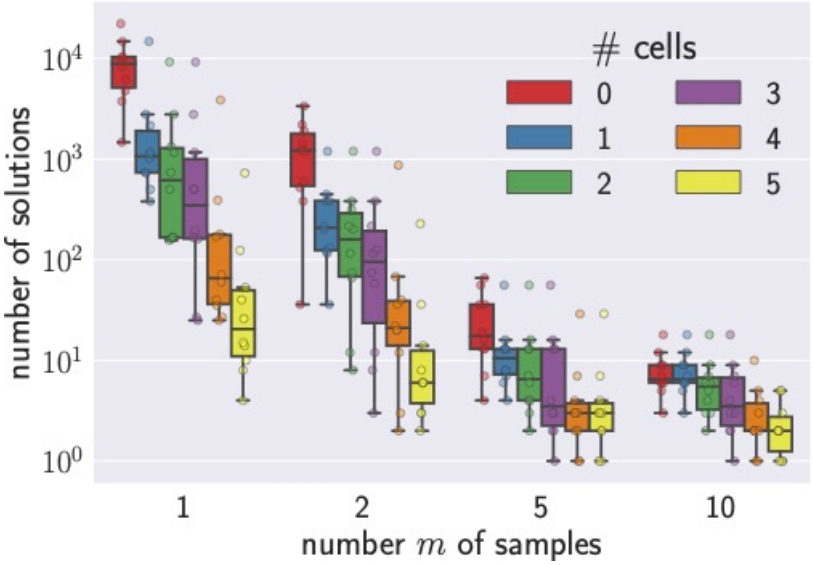


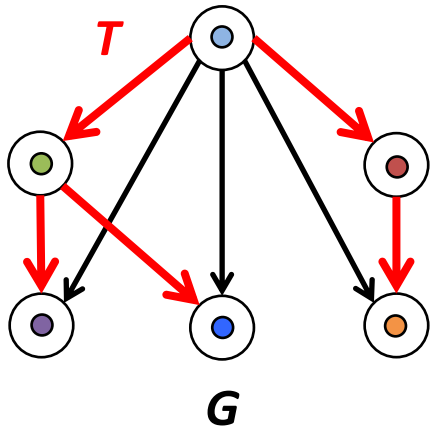


How to Reduce Non-Uniqueness?

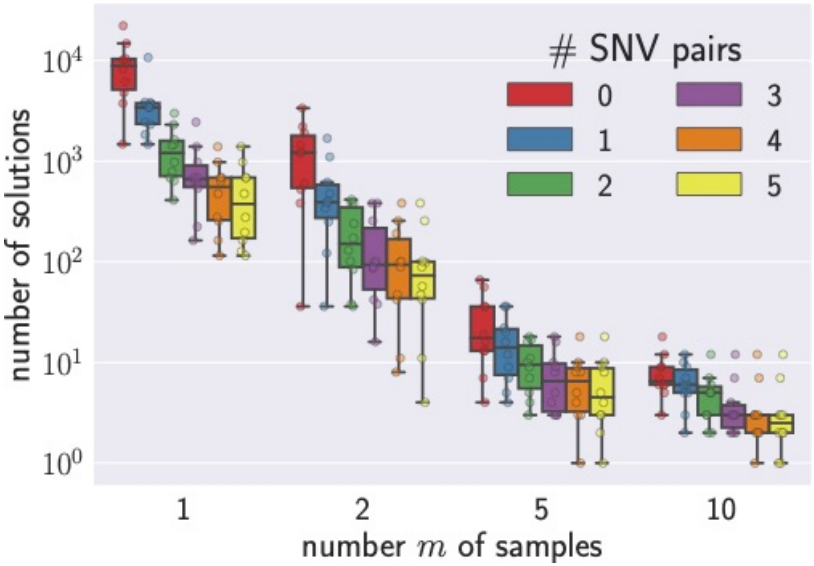


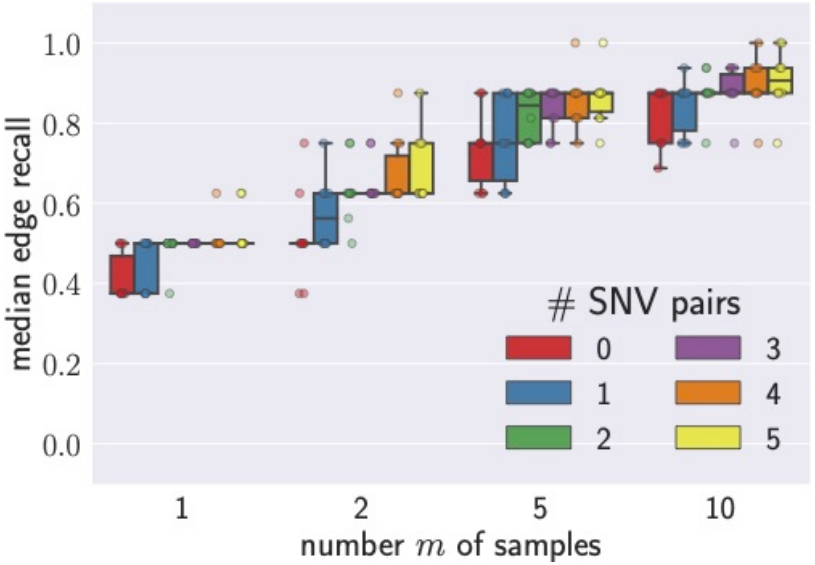


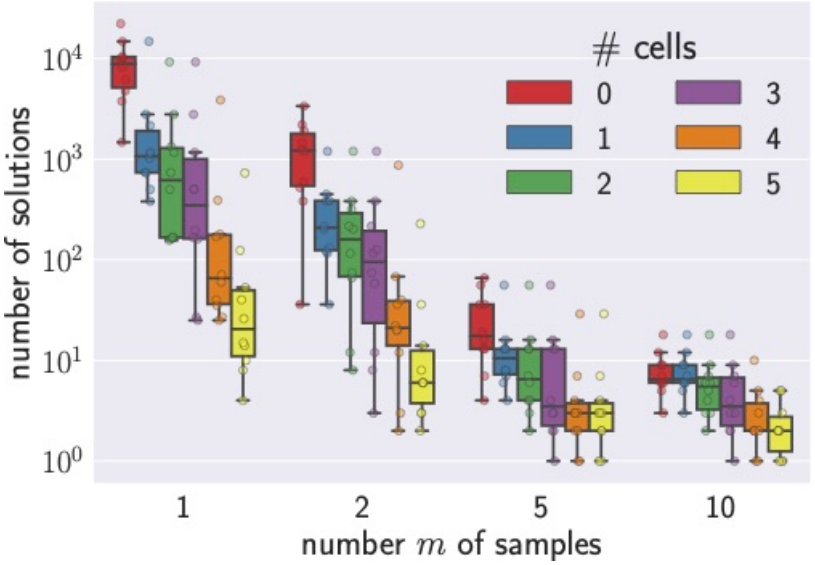


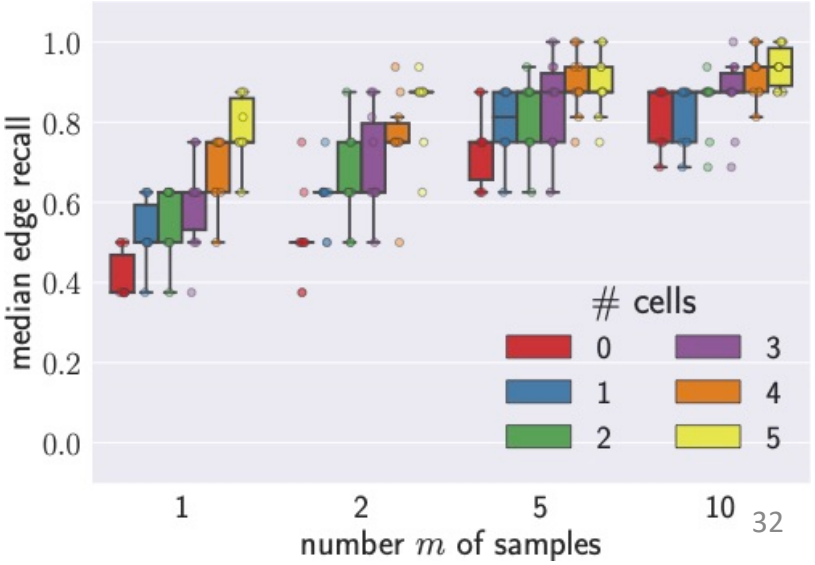


How to Reduce Non-Uniqueness?





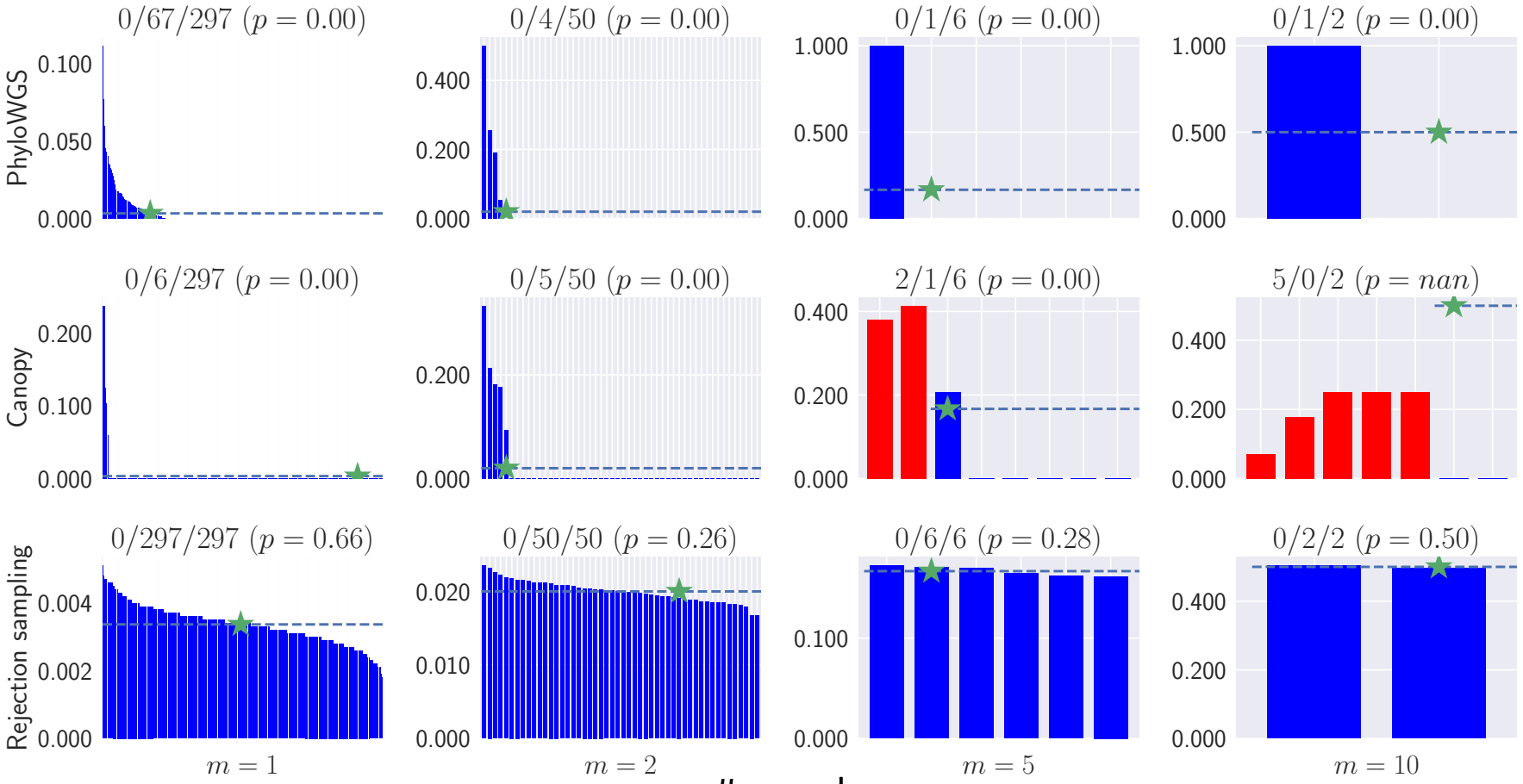


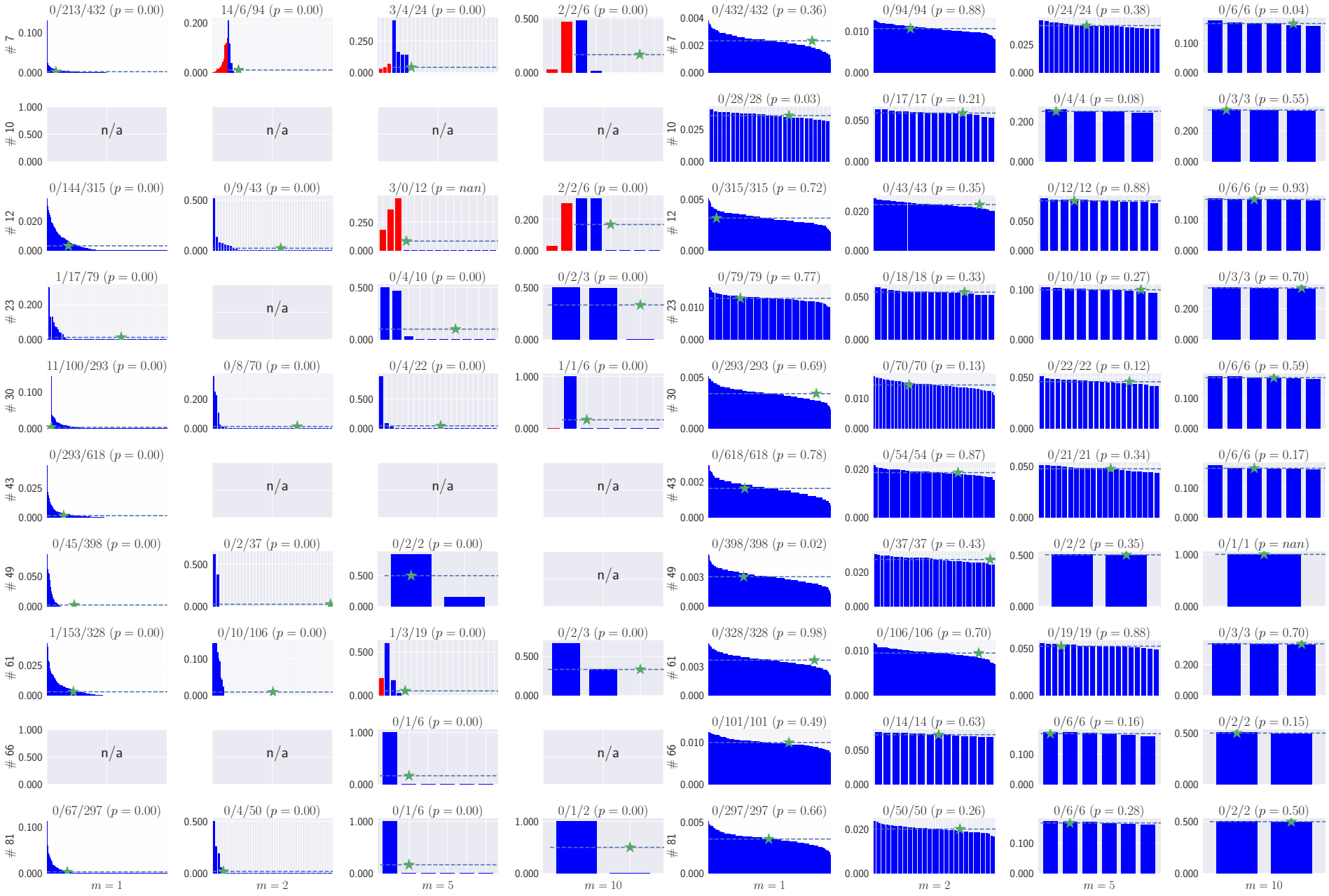


How Does Non-uniqueness affect Methods?

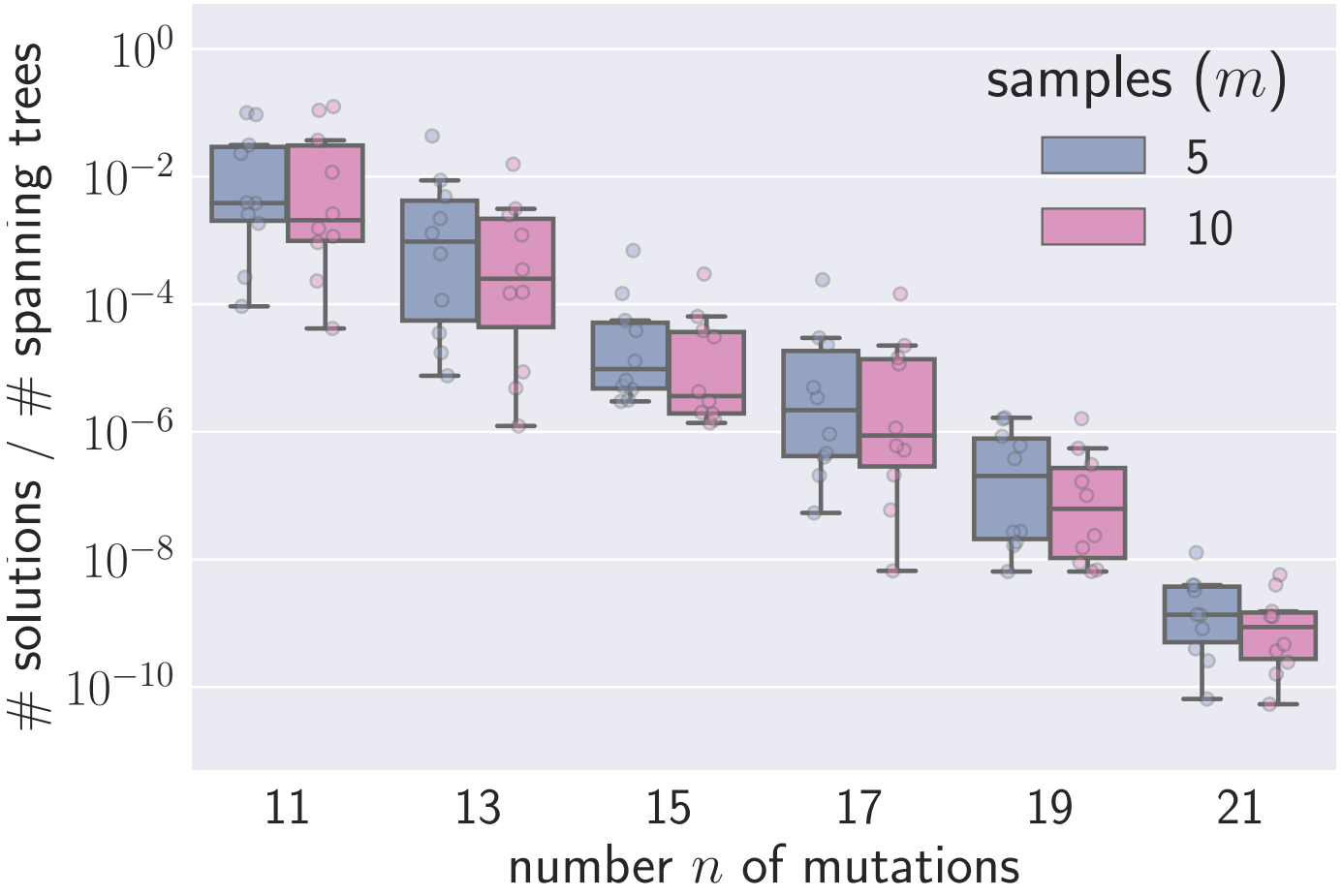
Two current MCMC methods using default parameters:

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



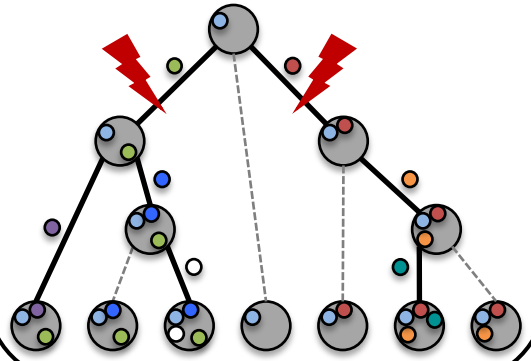

PhyloWGS
Rejection Sampling
0/213/432 (p = 0.00)
14/6/94 (p = 0.00)
3/4/24 (p = 0.00)
2/2/6 (p = 0.00)
0/432/432 (p = 0.36)
0/94/94 (p = 0.88)
0/24/24 (p = 0.38)
0/6/6 (p = 0.04)
7
n/a
0/28/28 (p = 0.03)
0/17/17 (p = 0.21)
0/4/4 (p = 0.08)
0/3/3 (p = 0.55)
10
0/144/315 (p = 0.00)
0/9/43 (p = 0.00)
3/0/12 (p = nan)
2/2/6 (p = 0.00)
0/315/315 (p = 0.72)
0/43/43 (p = 0.35)
0/12/12 (p = 0.88)
0/6/6 (p = 0.93)
12
1/17/79 (p = 0.00)
0/4/10 (p = 0.00)
0/2/3 (p = 0.00)
0/79/79 (p = 0.77)
0/18/18 (p = 0.33)
0/10/10 (p = 0.27)
0/3/3 (p = 0.70)
23
11/100/293 (p = 0.00)
0/8/70 (p = 0.00)
0/4/22 (p = 0.00)
1/1/6 (p = 0.00)
0/293/293 (p = 0.69)
0/70/70 (p = 0.13)
0/22/22 (p = 0.12)
0/6/6 (p = 0.59)
30
0/293/618 (p = 0.00)
0/618/618 (p = 0.78)
0/54/54 (p = 0.87)
0/21/21 (p = 0.34)
0/6/6 (p = 0.17)
43
0/45/398 (p = 0.00)
0/2/37 (p = 0.00)
0/2/2 (p = 0.00)
0/398/398 (p = 0.02)
0/37/37 (p = 0.43)
0/2/2 (p = 0.35)
0/1/1 (p = nan)
49
1/153/328 (p = 0.00)
0/10/106 (p = 0.00)
1/3/19 (p = 0.00)
0/2/3 (p = 0.00)
0/328/328 (p = 0.98)
0/106/106 (p = 0.70)
0/19/19 (p = 0.88)
0/3/3 (p = 0.70)
61
0/1/6 (p = 0.00)
0/101/101 (p = 0.49)
0/14/14 (p = 0.63)
0/6/6 (p = 0.16)
0/2/2 (p = 0.15)
66
0/67/297 (p = 0.00)
0/4/50 (p = 0.00)
0/1/6 (p = 0.00)
0/1/2 (p = 0.00)
0/297/297 (p = 0.66)
0/50/50 (p = 0.26)
0/6/6 (p = 0.28)
0/2/2 (p = 0.50)
# 81
m = 1
m = 2
m = 5
m = 10

Rejection Sampling Does Not Scale

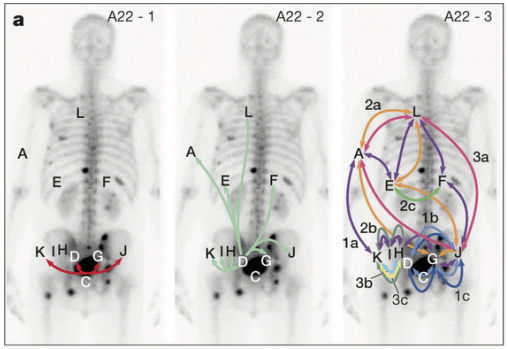


Challenge

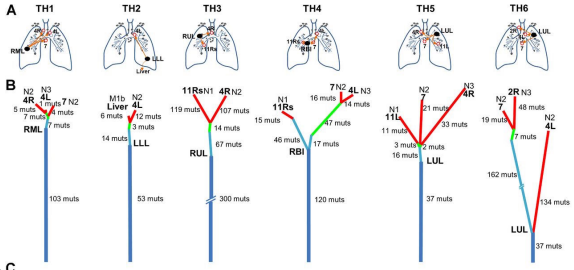
Identify targets for treatment



Understand metastatic development



Recognize common patterns of tumor evolution across patients



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

Key challenge:

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

Conclusion

Background and theory:

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

Simulation results:

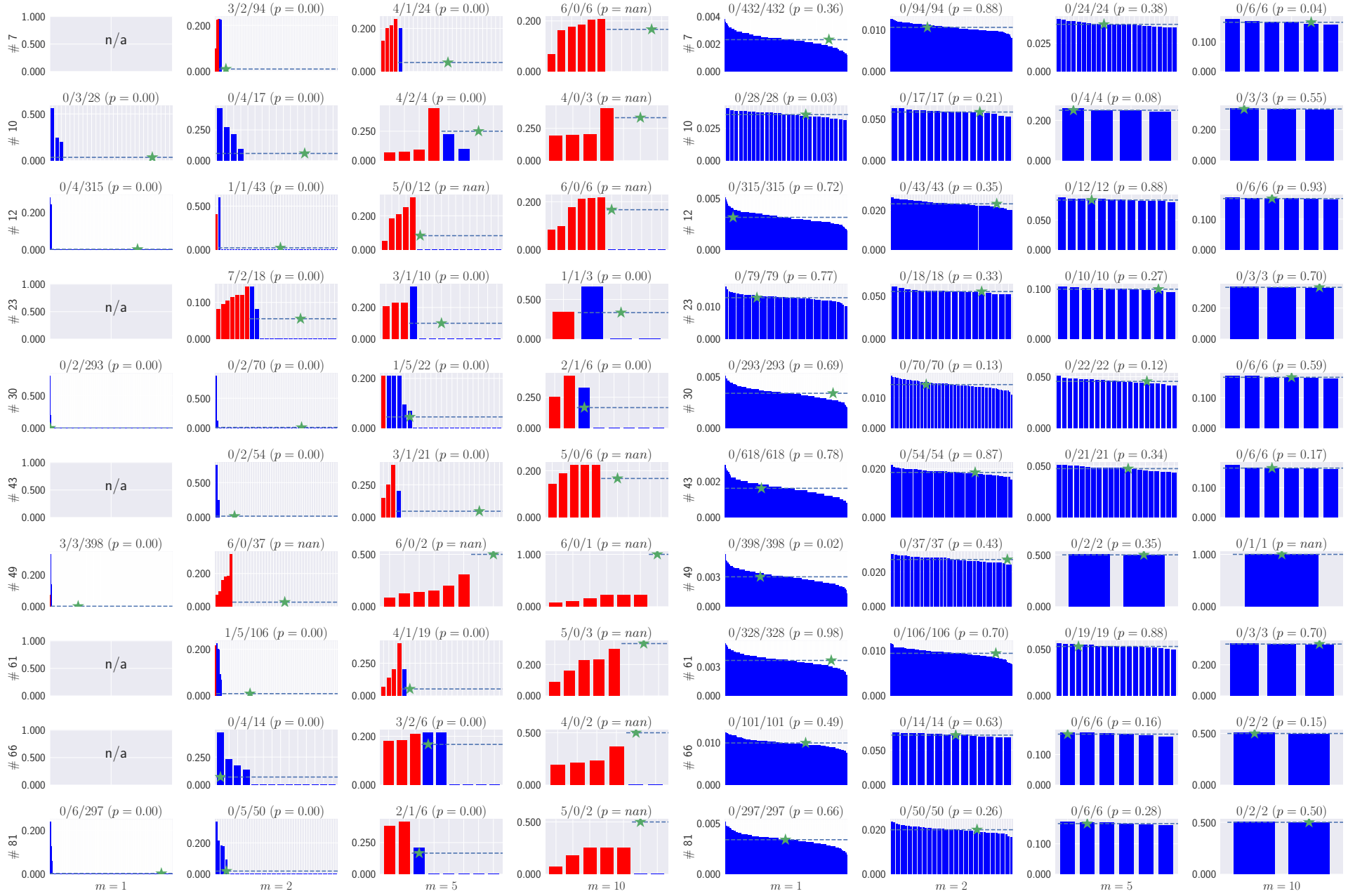
- What contributes to non-uniqueness?
- How to reduce non-uniqueness?
- How does non-uniqueness affect current methods?

Future Work

- Better sampling and counting algorithms
- Non-uniqueness in an infinite setting: characterize statistical consistency
- Constrained tumor phylogeny inference
  - Metastasis [El-Kebir, Satas & Raphael, Nature Genetics, 2018]
  - SCS + bulk, long-read sequencing
  - Other constraints…

Acknowledgments:

- Experiments were run on NCSA's Blue Waters supercomputer


Canopy
Rejection Sampling
7
10
12
23
30
43
49
61
66
81
n/a
3/2/94 (p = 0.00)
4/1/24 (p = 0.00)
6/0/6 (p = nan)
0/432/432 (p = 0.36)
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0/6/6 (p = 0.93)
7/2/18 (p = 0.00)
3/1/10 (p = 0.00)
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0/18/18 (p = 0.33)
0/10/10 (p = 0.27)
0/3/3 (p = 0.70)
0/2/293 (p = 0.00)
0/2/70 (p = 0.00)
1/5/22 (p = 0.00)
2/1/6 (p = 0.00)
0/293/293 (p = 0.69)
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0/22/22 (p = 0.12)
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0/2/54 (p = 0.00)
3/1/21 (p = 0.00)
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0/618/618 (p = 0.78)
0/54/54 (p = 0.87)
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6/0/37 (p = nan)
6/0/2 (p = nan)
6/0/1 (p = nan)
0/398/398 (p = 0.02)
0/37/37 (p = 0.43)
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1/5/106 (p = 0.00)
4/1/19 (p = 0.00)
5/0/3 (p = nan)
0/328/328 (p = 0.98)
0/106/106 (p = 0.70)
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m = 1
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Somatic Mutations Occur at Different Genomic Scales