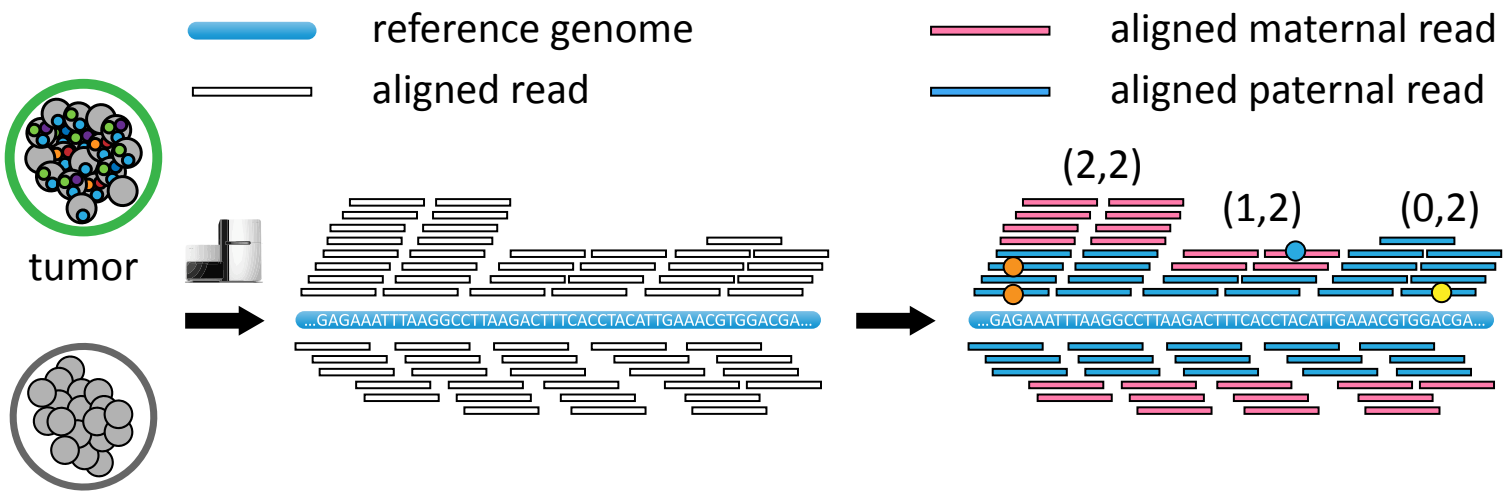
CS 598MEB
Computational Cancer Biology
Lecture 13

Mohammed El-Kebir

February 26, 2019

Cancer Phylogenetics Pipeline



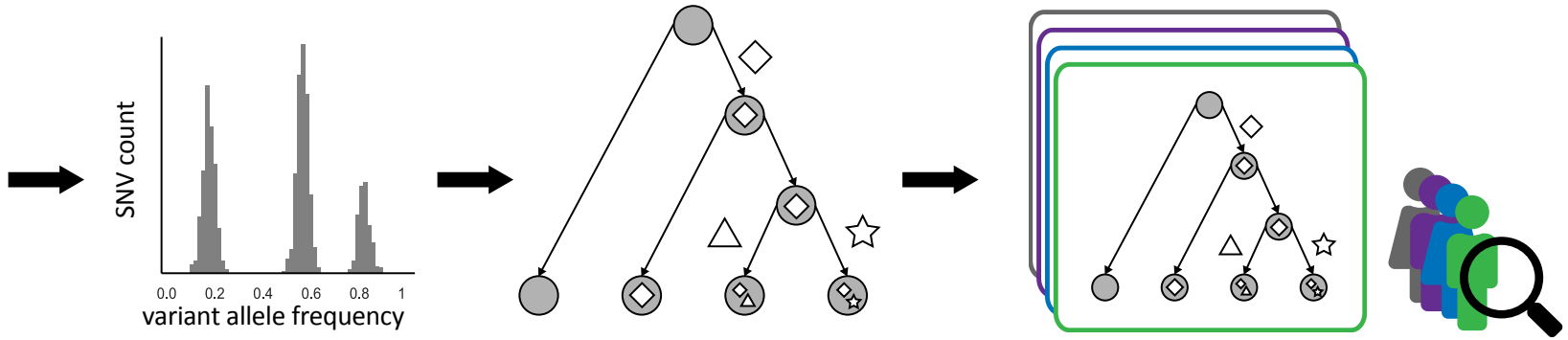
(i) Alignment

(ii) Somatic variant calling

single nucleotide variant (SNV)

SNV cluster

(x, y) copy number state (# maternal, # paternal copies)

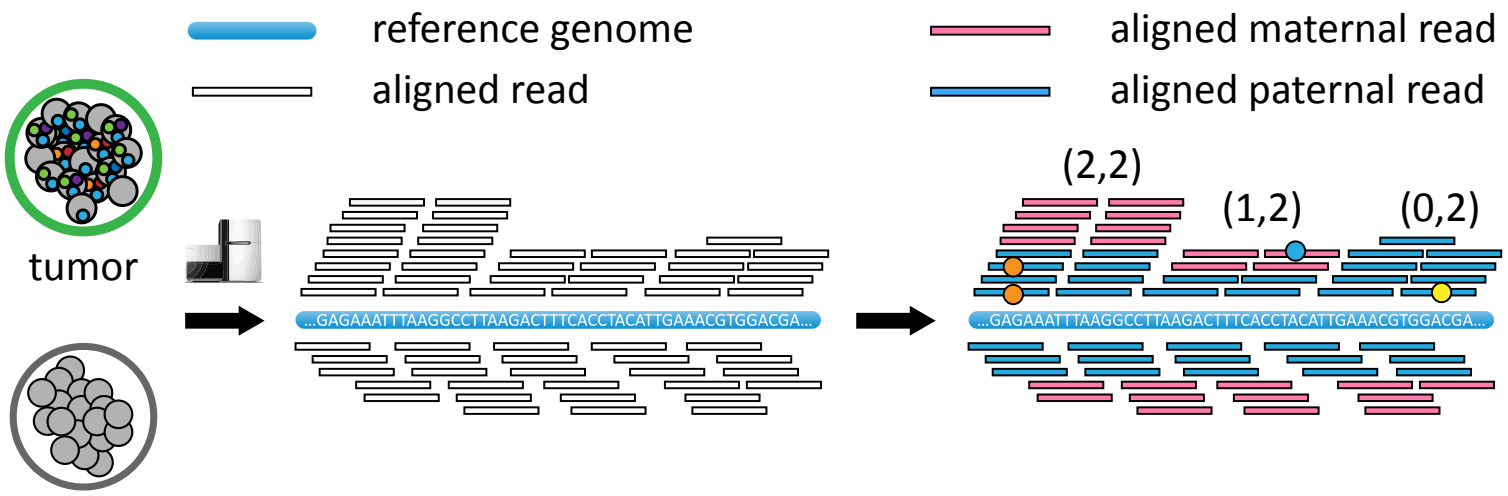


(iii) SNV clustering

(iv) Phylogeny inference

(v) Downstream analysis

Cancer Phylogenetics Pipeline



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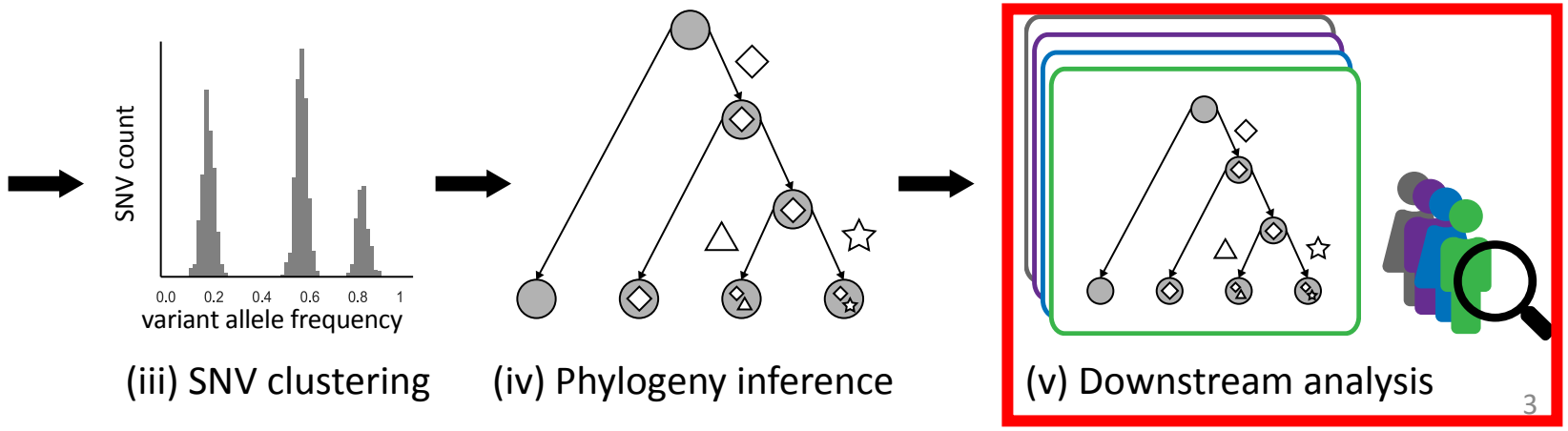

(iii) SNV clustering

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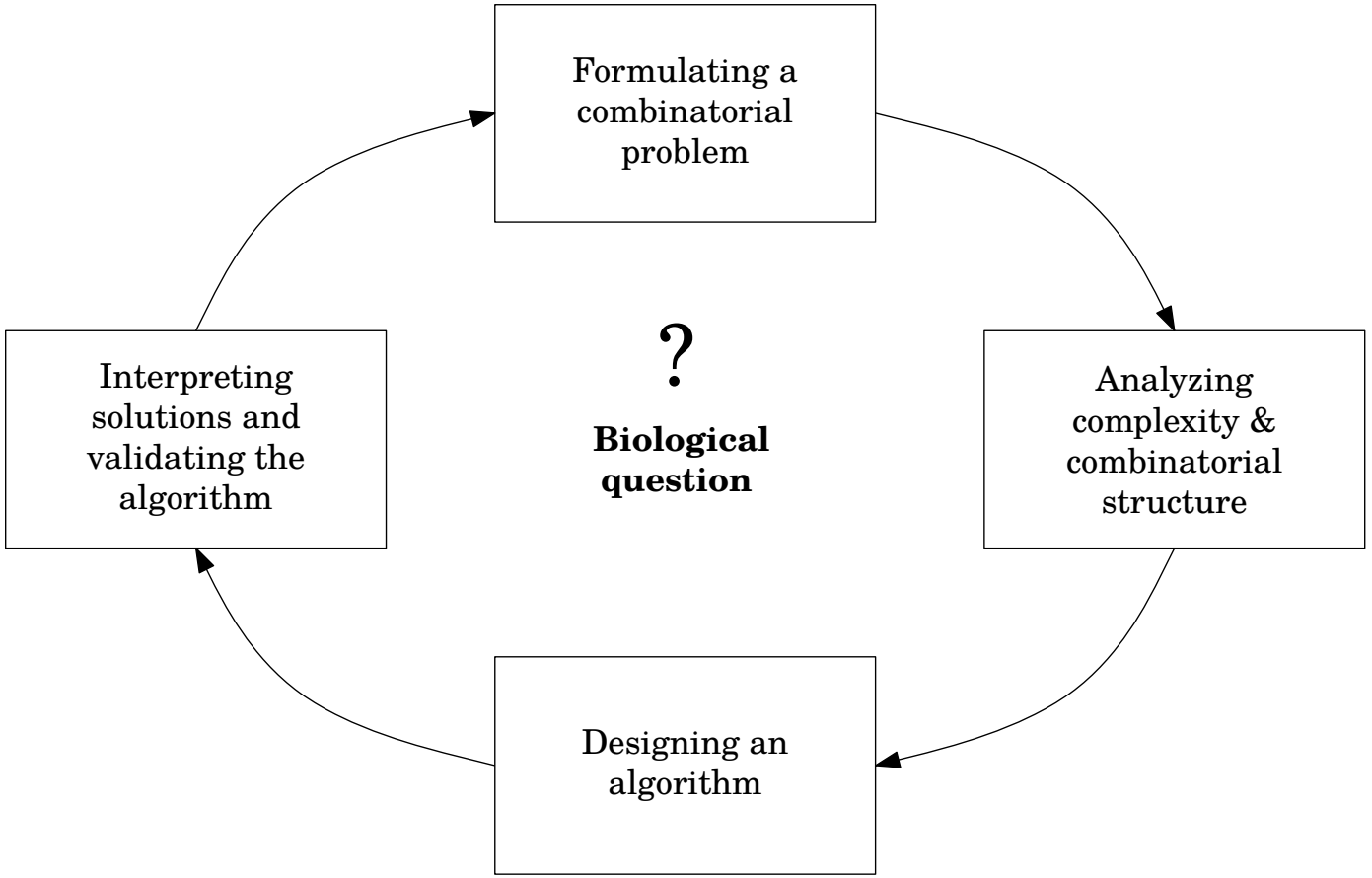
(v) Downstream analysis

Outline

- Metastasis
- Maximum parsimony
- Problem statement
- Complexity
- Algorithm & results
- Problem variants



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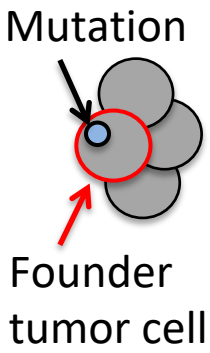
- **M. El-Kebir**†. Parsimonious Migration History Problem: Complexity and Algorithms. WABI 2018, Helsinki, Finland, August 20-22, 2018.

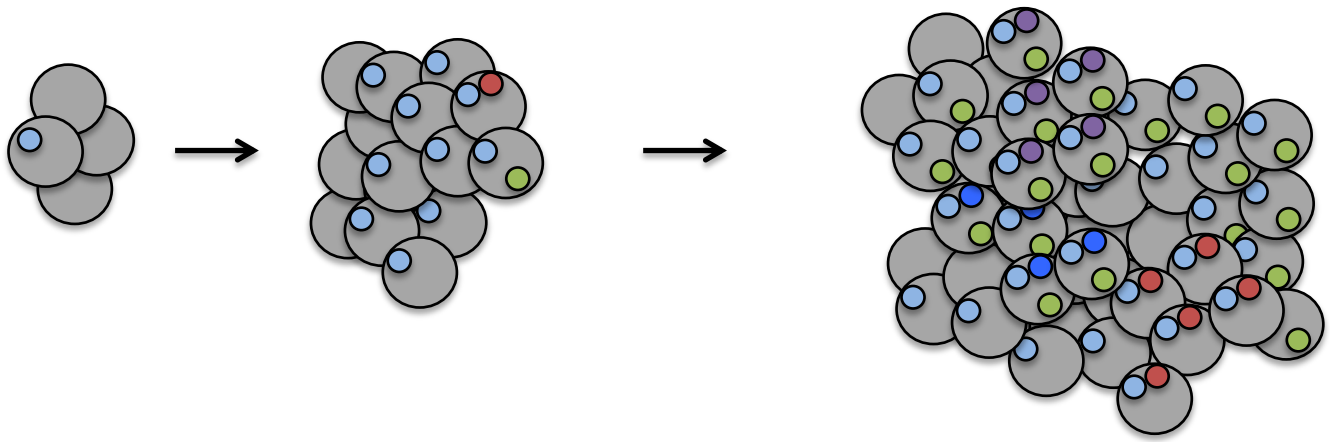
Tumorigenesis: (i) Cell Mutation

Clonal Theory of Cancer
[Nowell, 1976]



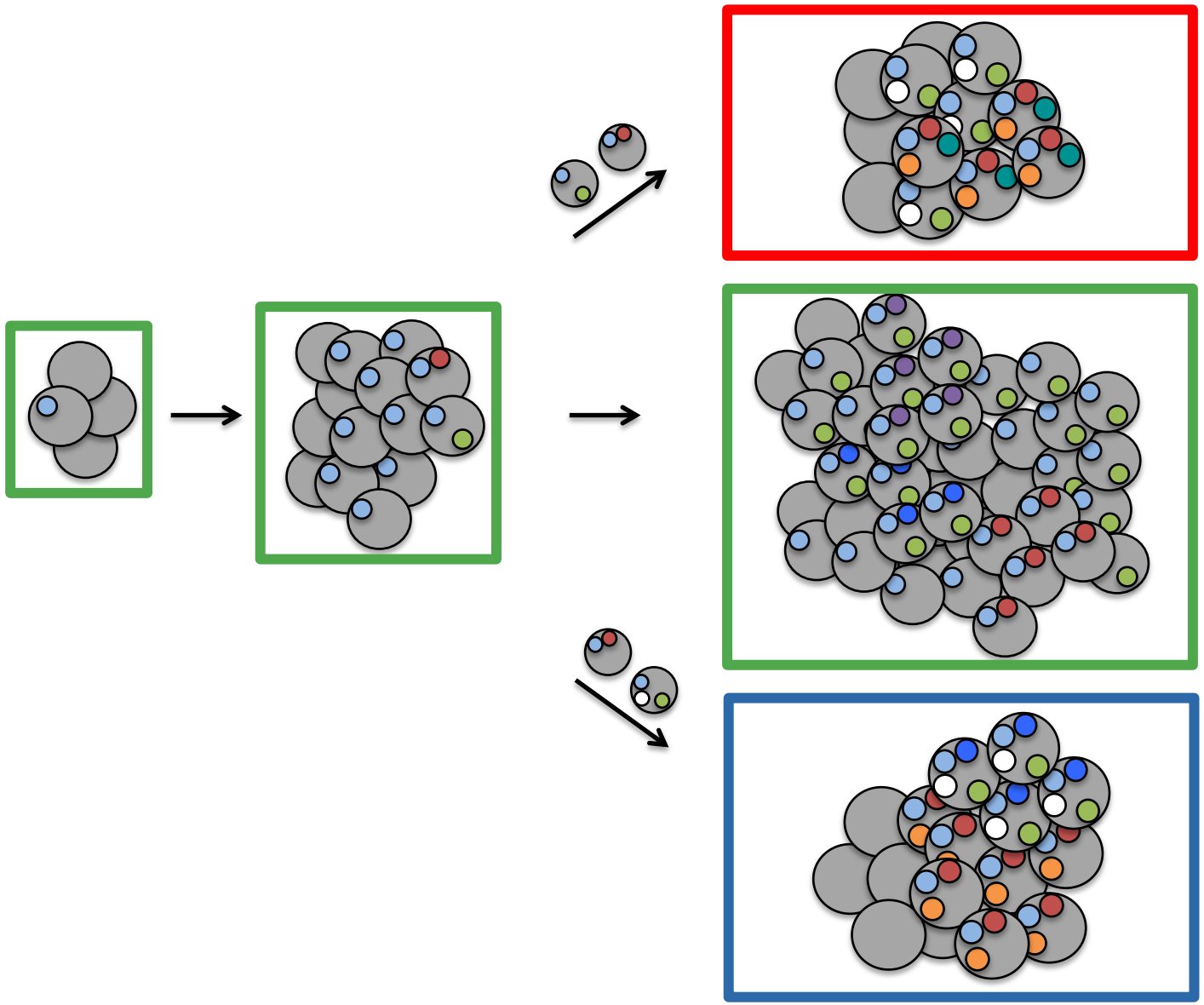
Tumorigenesis: (i) Cell Mutation, (ii) Cell Division

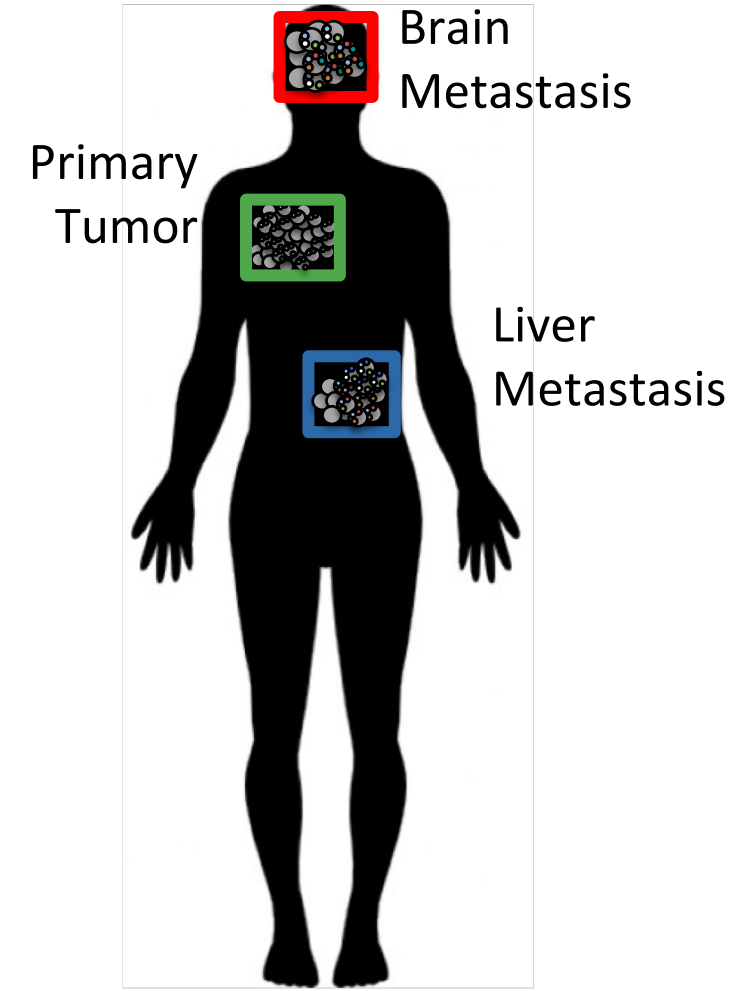
Clonal Theory of Cancer
[Nowell, 1976]



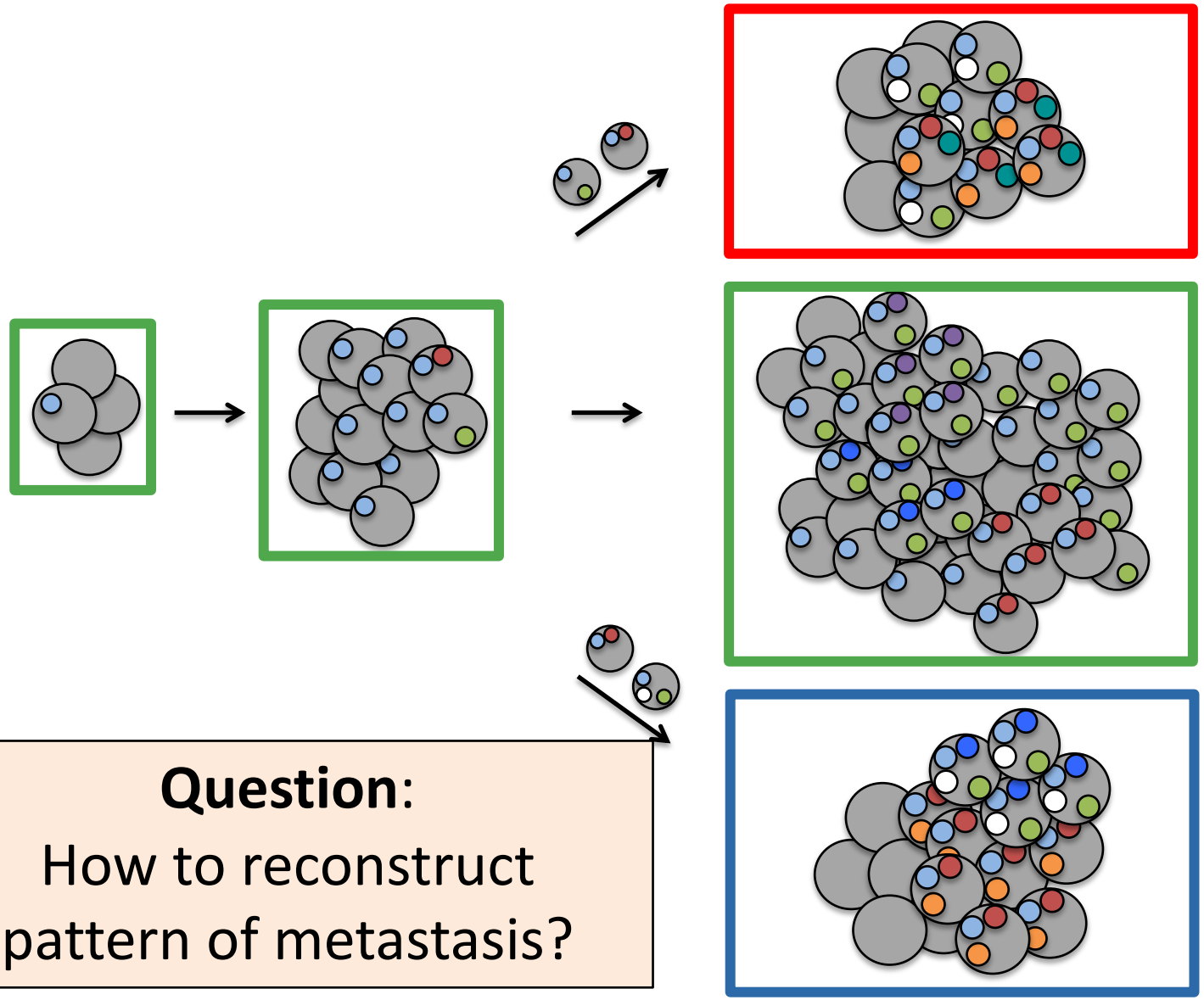
Heterogeneous Tumor

Tumorigenesis: (i) Cell Division, (ii) Mutation & (iii) Migration

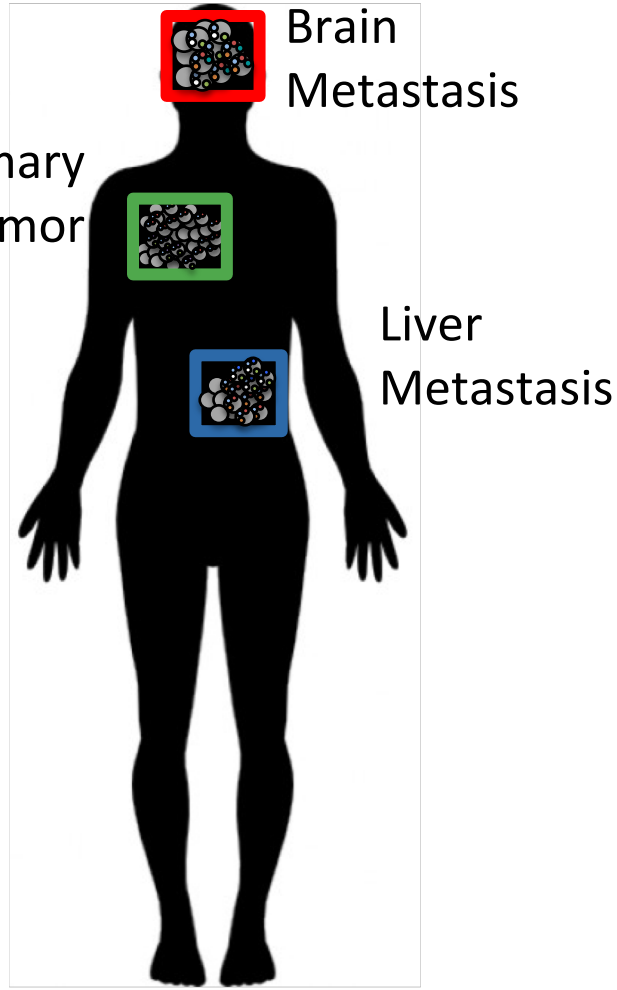




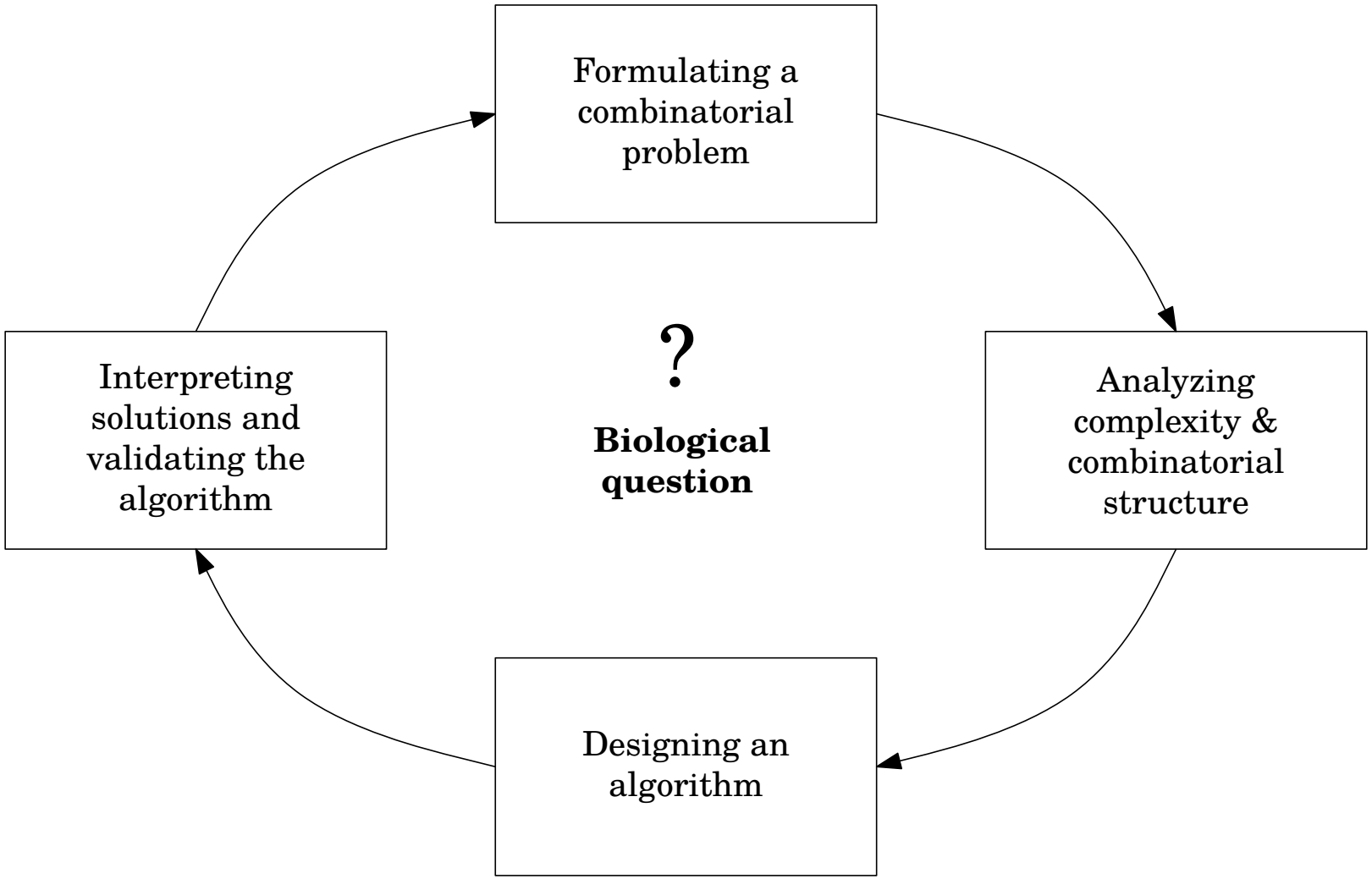
Tumorigenesis: (i) Cell Division, (ii) Mutation & (iii) Migration



Question:
How to reconstruct pattern of metastasis?

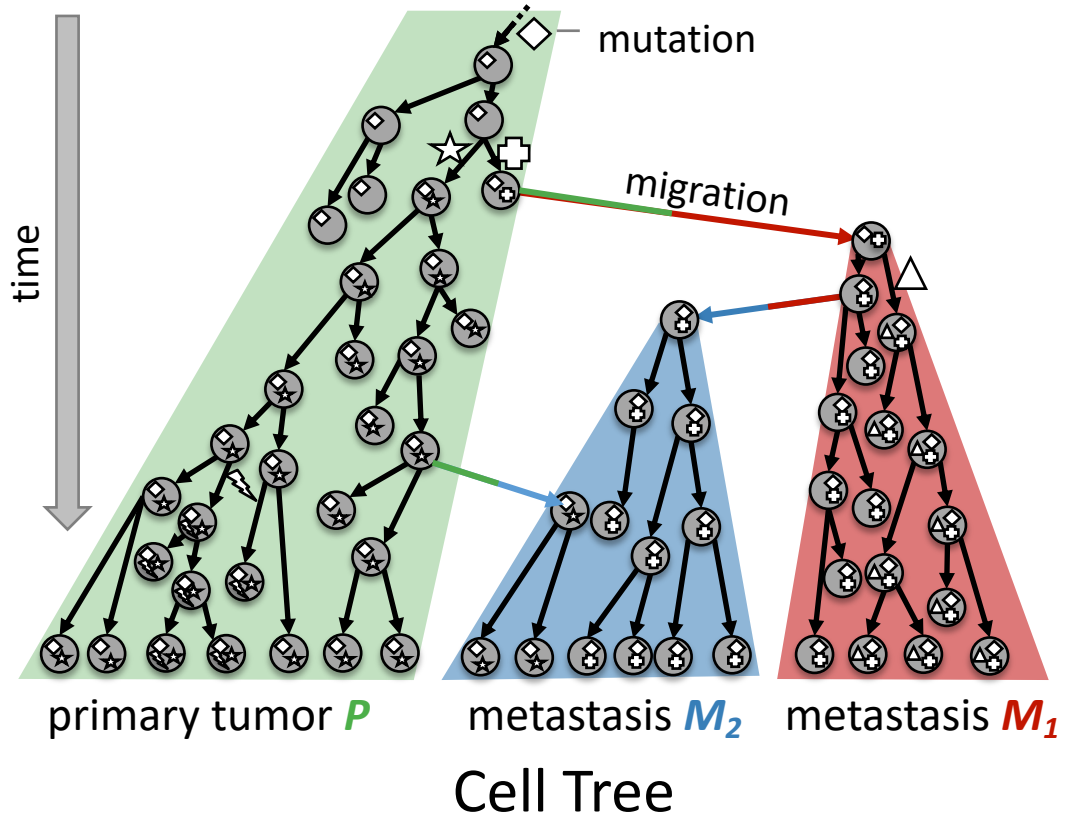


Key Challenge in Computational Biology

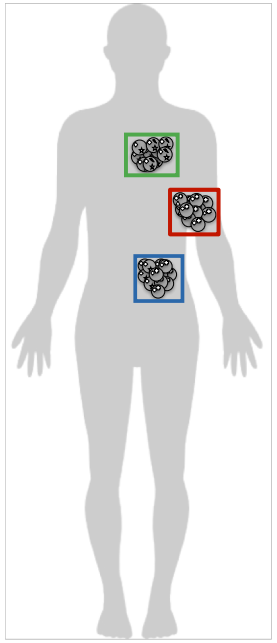


Translating a biological problem into computer science

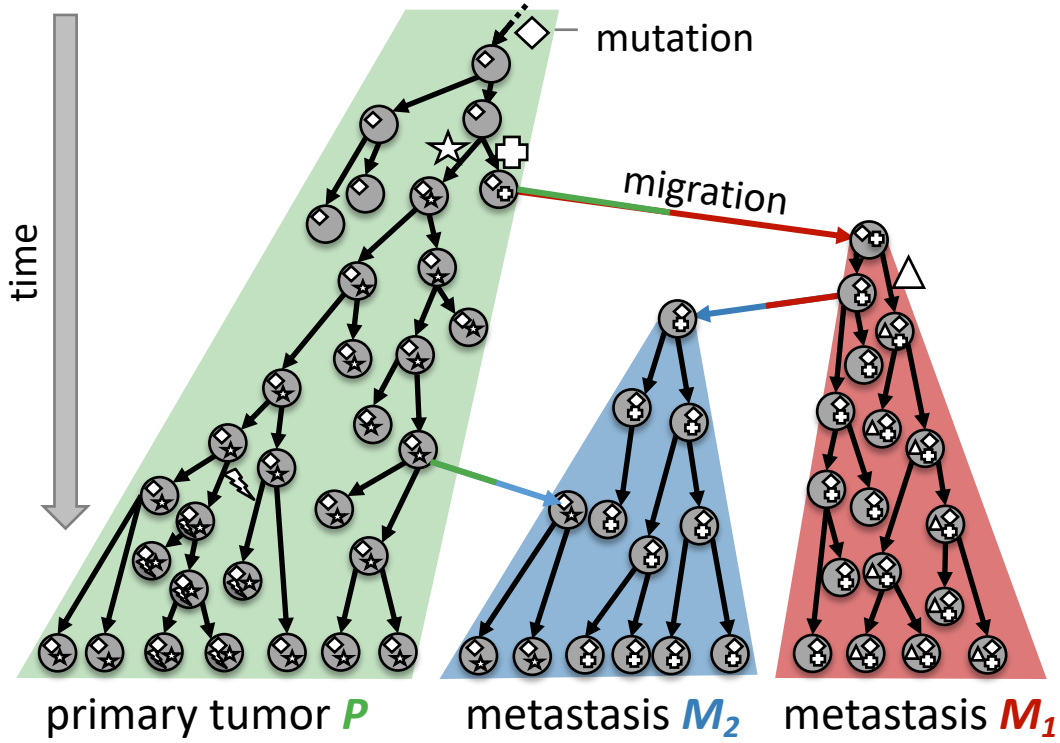
Tumorigenesis: (i) Cell Division, (ii) Mutation & (iii) Migration



Cell Tree



Tumorigenesis: (i) Cell Division, (ii) Mutation & (iii) Migration



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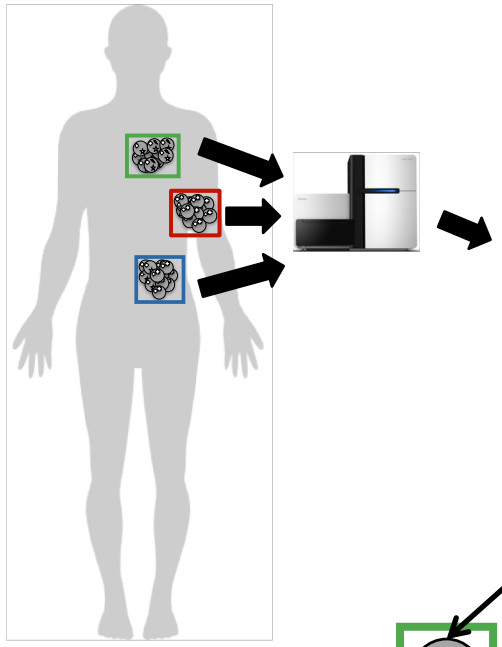
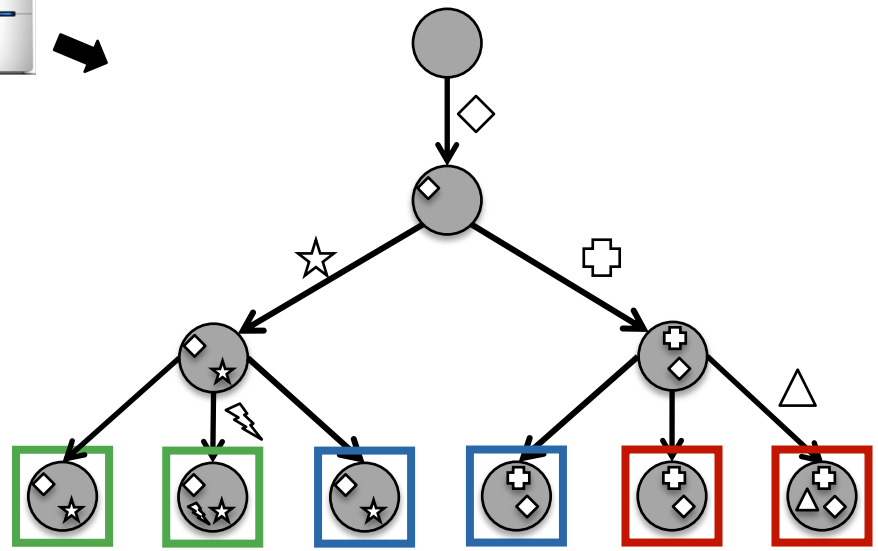
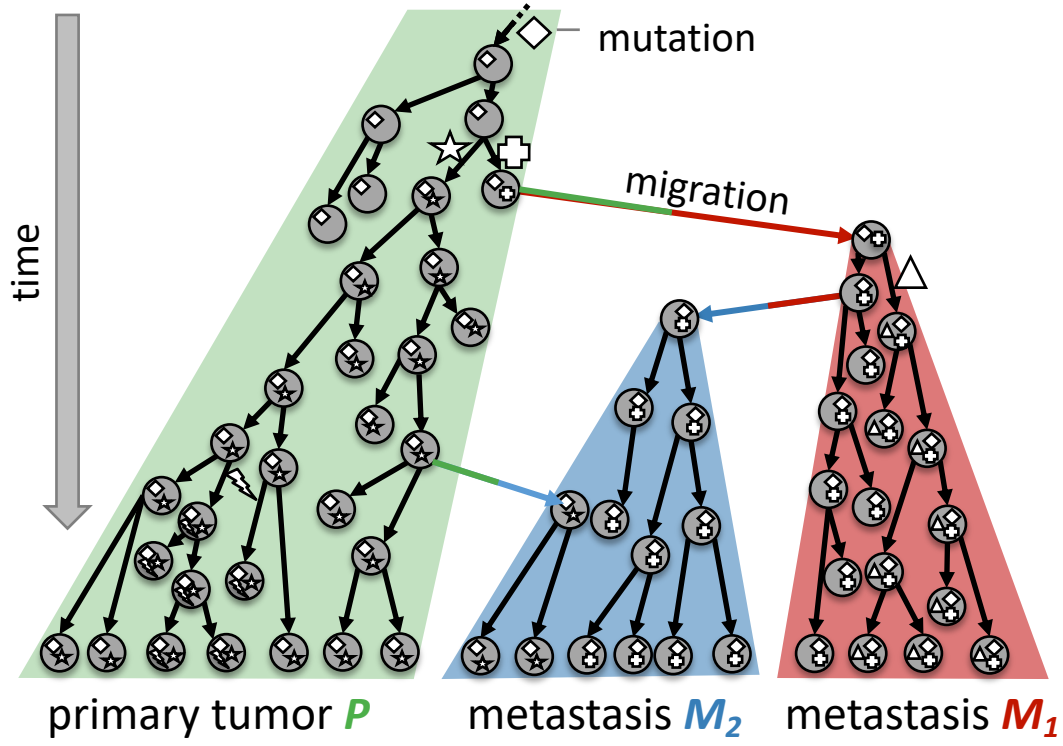




Phylogenetic Tree *T*

Tumorigenesis: (i) Cell Division, (ii) Mutation & (iii) Migration



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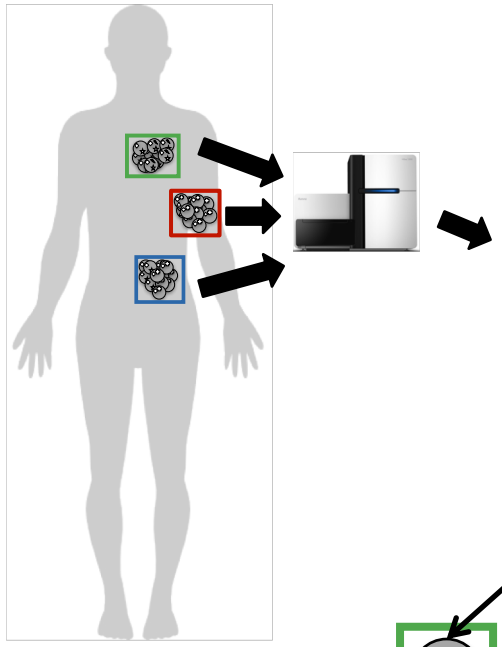
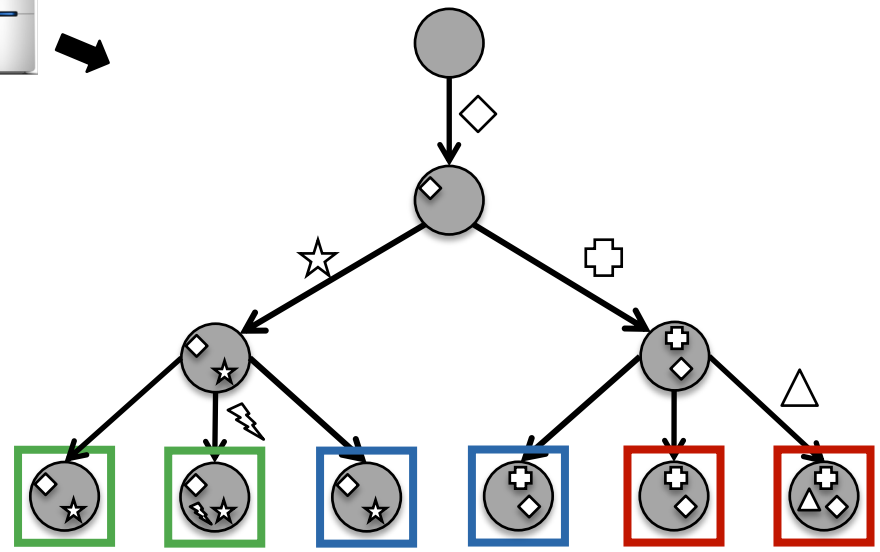
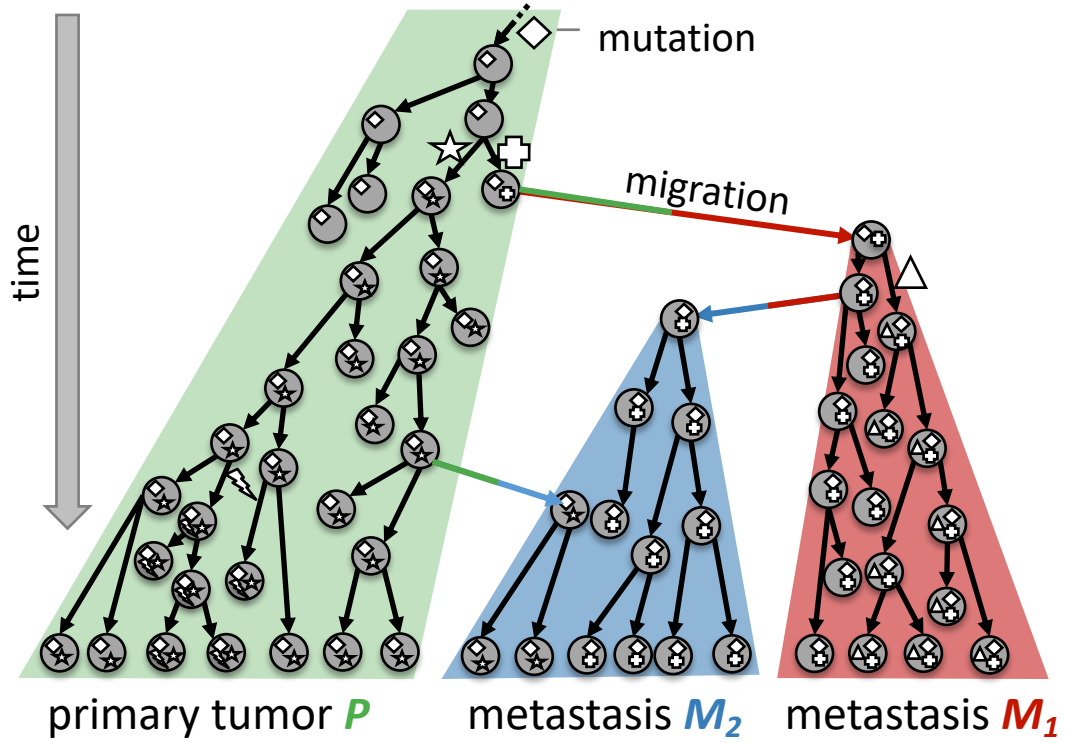




Phylogenetic Tree ***T***

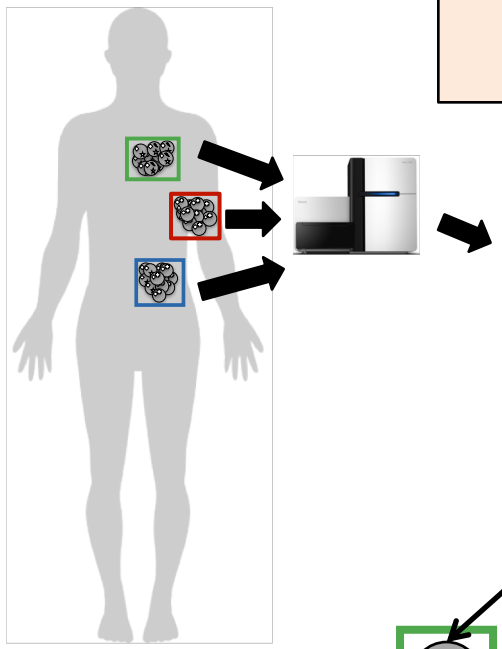
Goal: Given phylogenetic tree ***T***, find ***parsimonious*** vertex labeling ℓ with fewest migrations

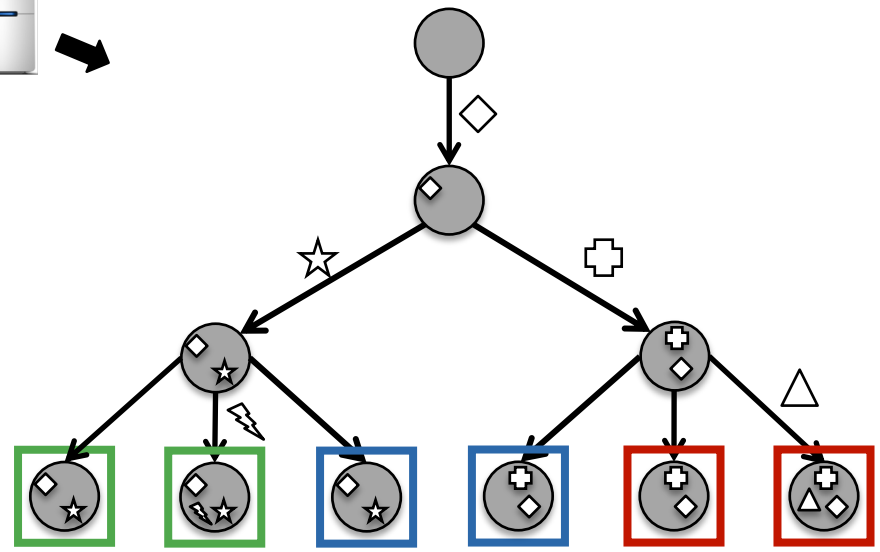
Tumorigenesis: (i) Cell Division, (ii) Mutation & (iii) Migration



Cell Tree

Question: Find parsimonious vertex labeling





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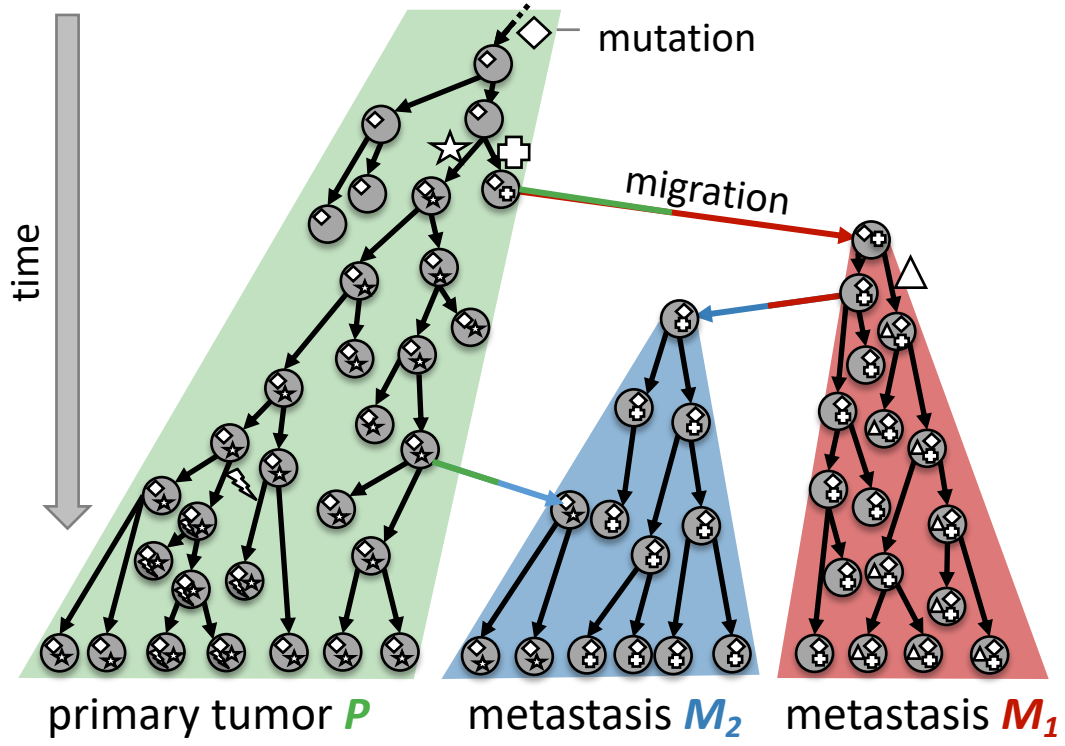

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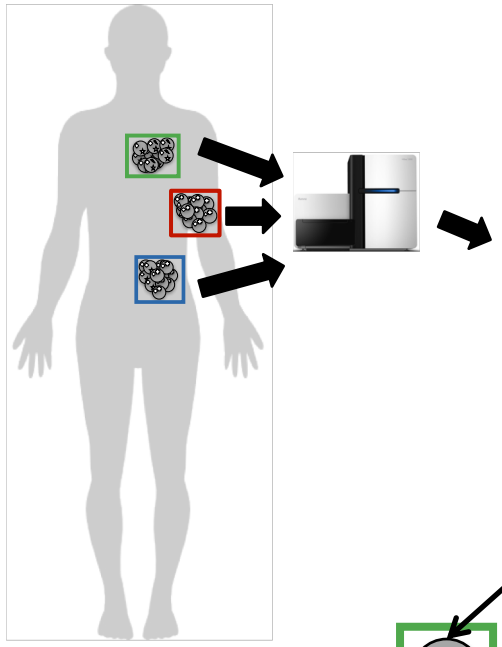

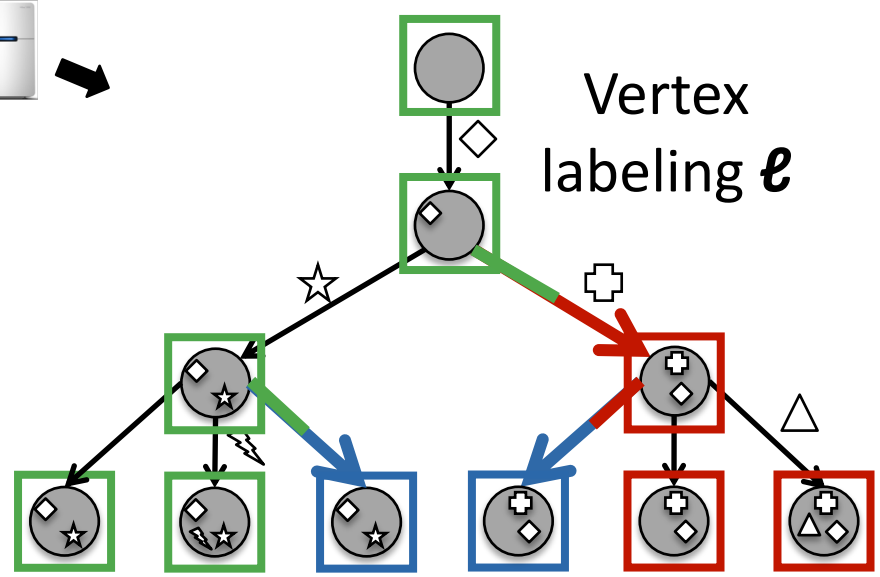

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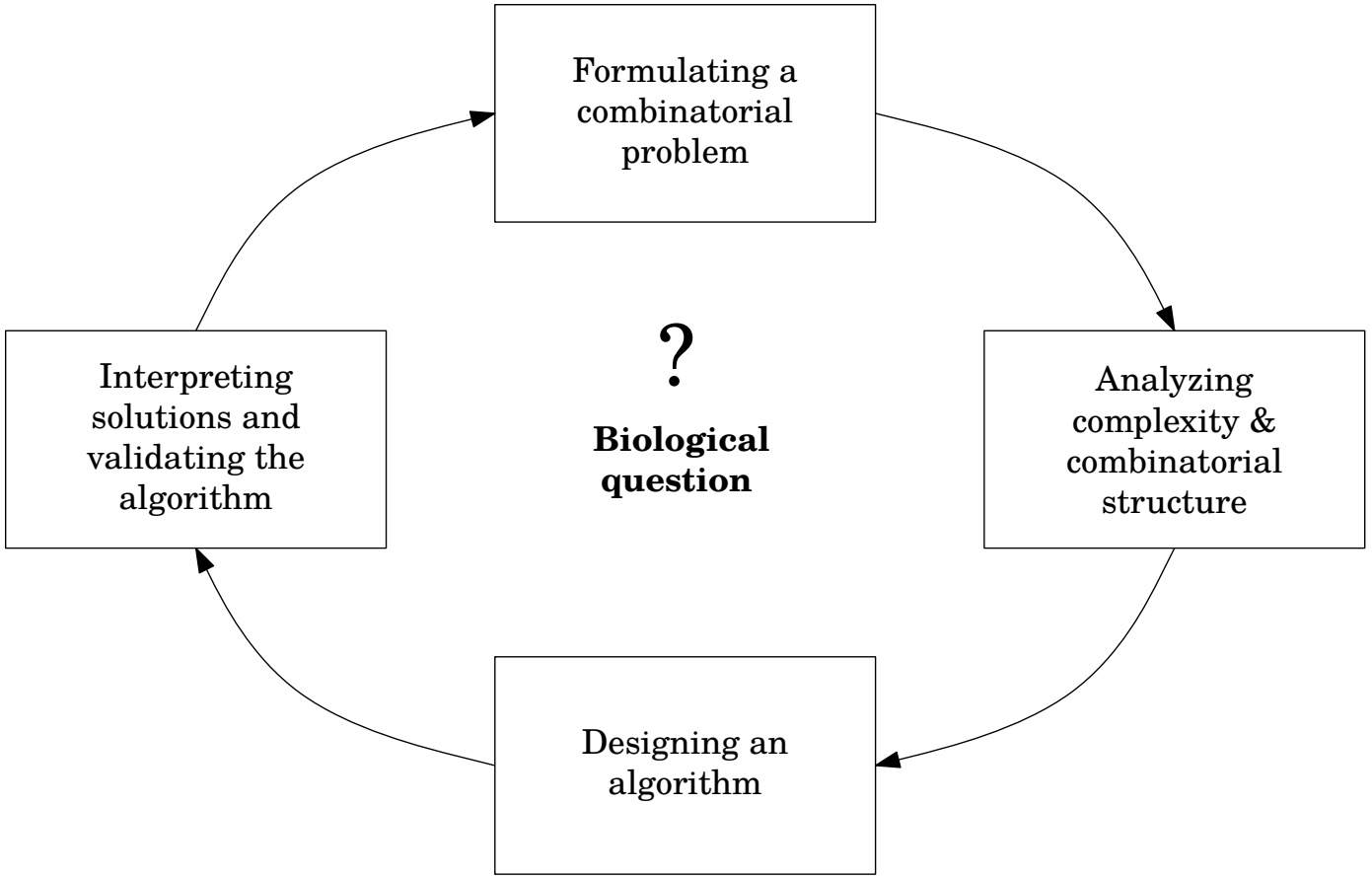

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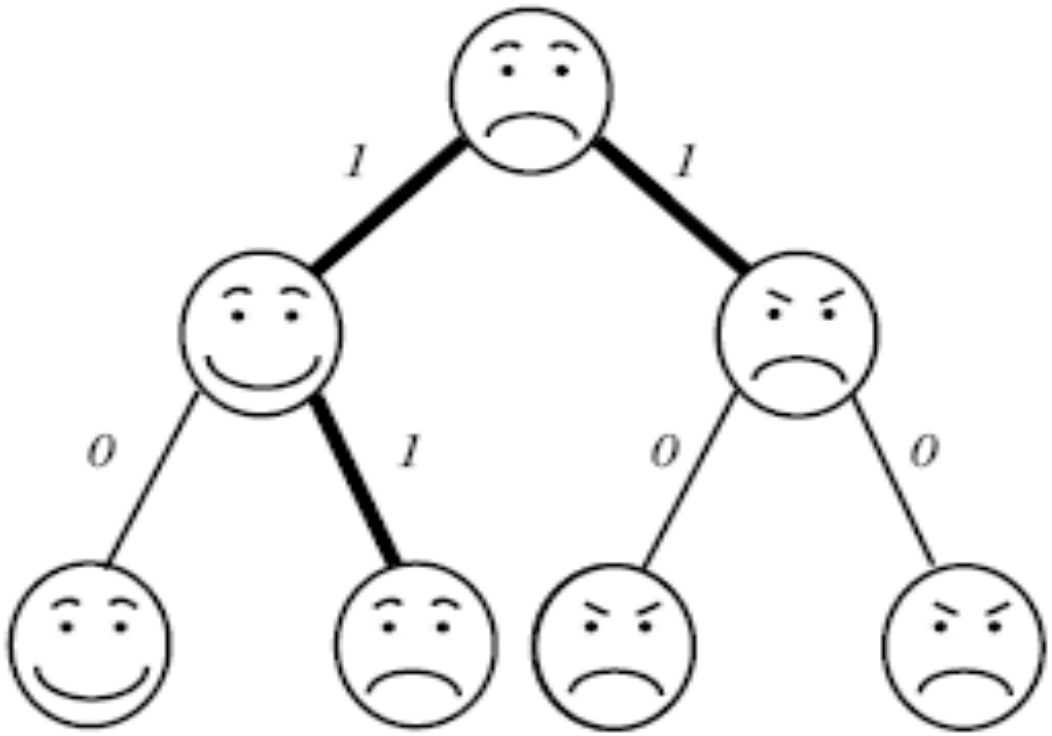
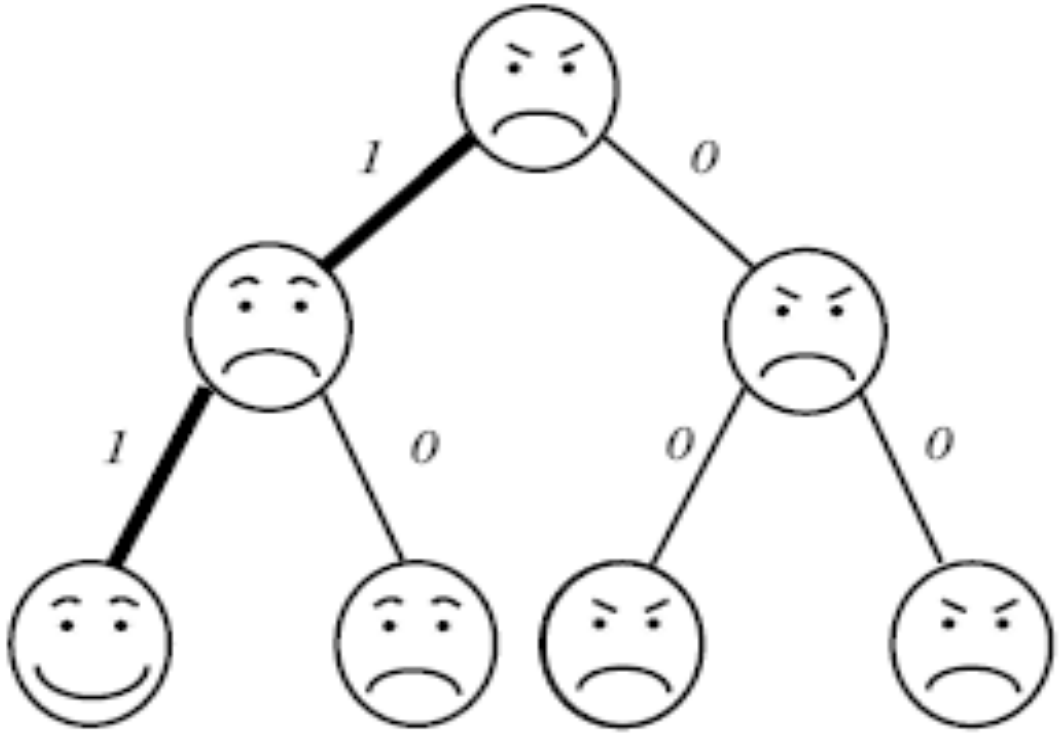
Character-Based Phylogeny Reconstruction: Criterion



(a) *Parsimony Score=3*



(b) *Parsimony Score=2*

Parsimony: minimize number of changes on edges of tree

A Small and a Large Problem

Small Maximum Parsimony Phylogeny Problem:

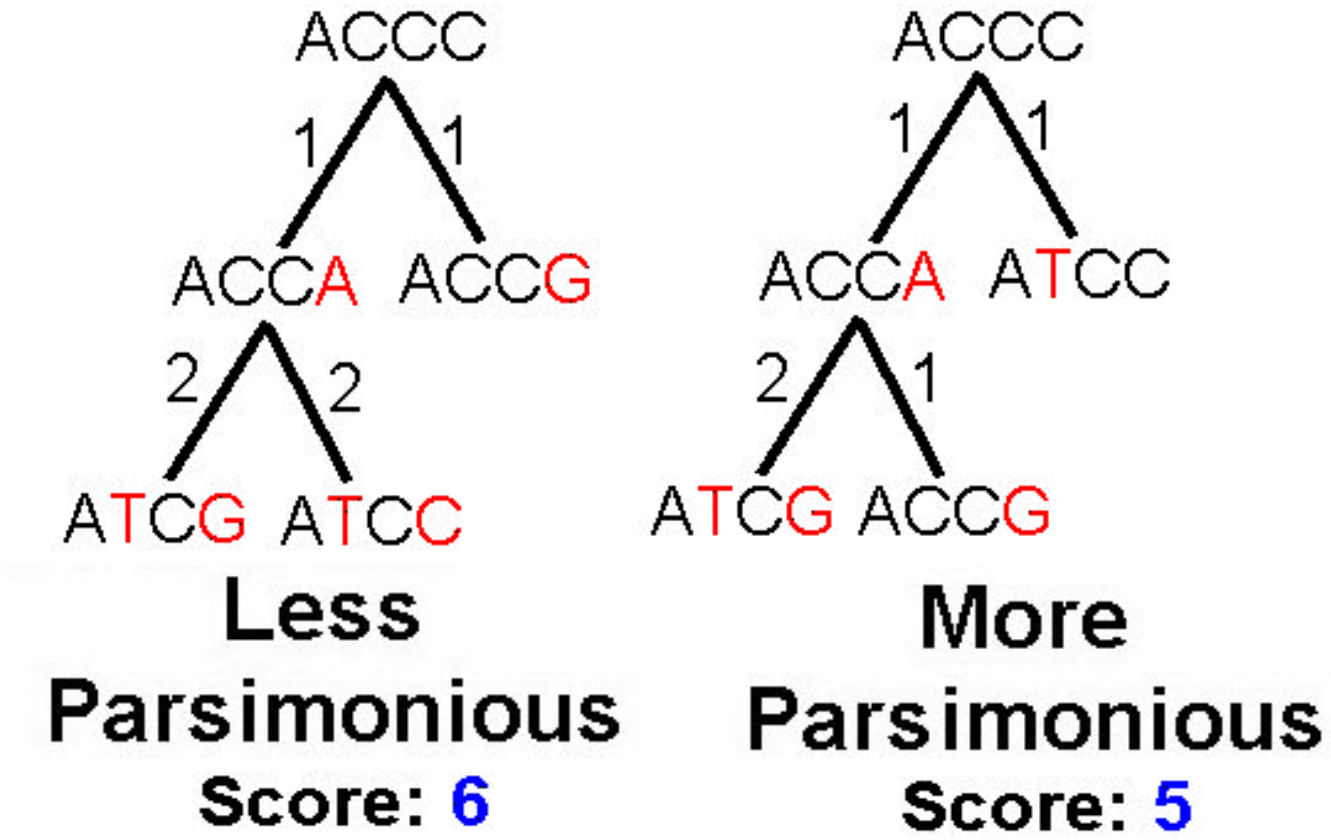
Given $m \times n$ matrix $A = [a_{i,j}]$ and tree T with m leaves, find assignment of character states to each internal vertex of T with minimum parsimony score.

Large Maximum Parsimony Phylogeny Problem:

Given $m \times n$ matrix $A = [a_{i,j}]$, find a tree T with m leaves labeled according to A and an assignment of character states to each internal vertex of T with minimum parsimony score.

Question: Are both problems easy (i.e. in P)?

Small Maximum Parsimony Phylogeny Problem



Key observations: (1) Characters can be solved independently.
(2) Optimal substructure in subtrees.

Recurrence for Small Maximum Parsimony Problem

Small Maximum Parsimony Phylogeny Problem:

Given rooted tree T whose leaves are labeled by $\sigma : L(T) \rightarrow \Sigma$, find assignment of states to each internal vertex of T with minimum parsimony score.

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Let $\mu(v, s)$ be the minimum number of mutations in the subtree rooted at v when assigning state s to v.

Let $\delta(v)$ be the set of children of v.

Recurrence for Small Maximum Parsimony Problem

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Let $\mu(v, s)$ be the minimum number of mutations in the subtree rooted at v when assigning state s to v.

$$c(s,t) = \begin{cases} 0, & \text{if } s = t \\ 1, & \text{if } s \neq t, \end{cases}$$

Let $\delta(v)$ be the set of children of v.

$$\mu(v,s) = \min \begin{cases} \infty, & \text{if } v \in L(T) \text{ and } s \neq \sigma(v), \\ 0, & \text{if } v \in L(T) \text{ and } s = \sigma(v), \\ \sum_{w \in \delta(v)} \min_{t \in \Sigma} \{c(s,t) + \mu(w,t)\}, & \text{if } v \notin L(T). \end{cases}$$

Filling out DP Table and Traceback

Filling out μ

Fill$(T, r(T), \sigma, \Sigma)$ $O(n|\Sigma|^2)$

```
Fill(T, v, σ, Σ)
if v ∈ L(T) then
    For s ∈ Σ
        if s = σ(v) then
            μ(v,s) = 0
        else
            μ(v,s) = ∞
else
    For w ∈ δ(v)                    // children
        Fill(T, w, σ, Σ)
    μ(v,s) = 0
    For w ∈ δ(v)
        μ(v,s) += min_{t∈Σ} {c(s,t) + μ(w,t)}
```

Backtrace(T, v, μ)

```
if v = r(T)
    σ(r(T)) = arg min_{s∈Σ} {μ(r(T), s)}      = σ(v)
else let u be the parent of v and let s be the state of u
    σ(v) = arg min_{t∈Σ} {c(s,t) + μ(v,t)}
For w ∈ δ(v)
    Backtrace(T, w, μ)
```

Let $r(T)$ be the root vertex

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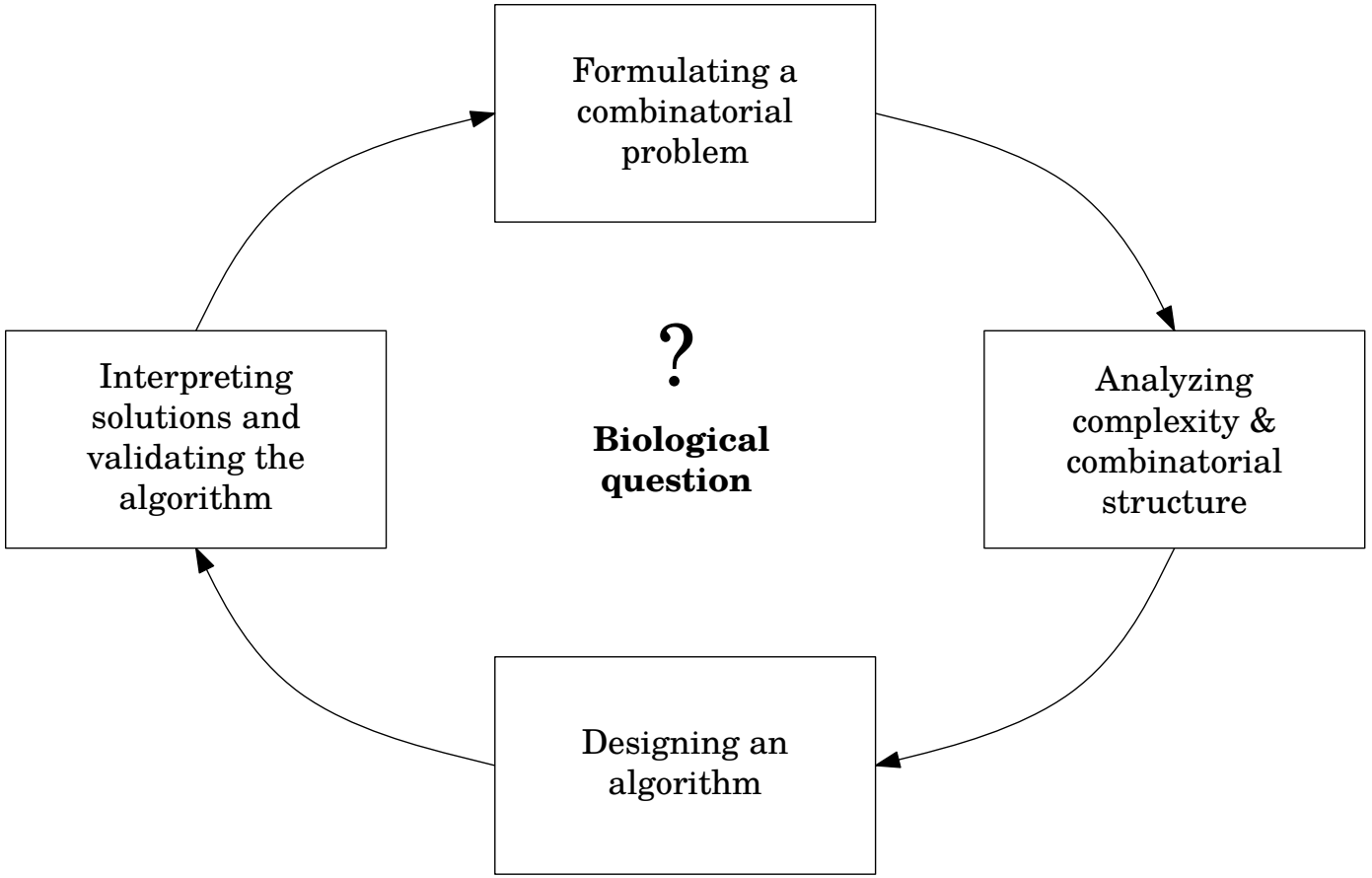

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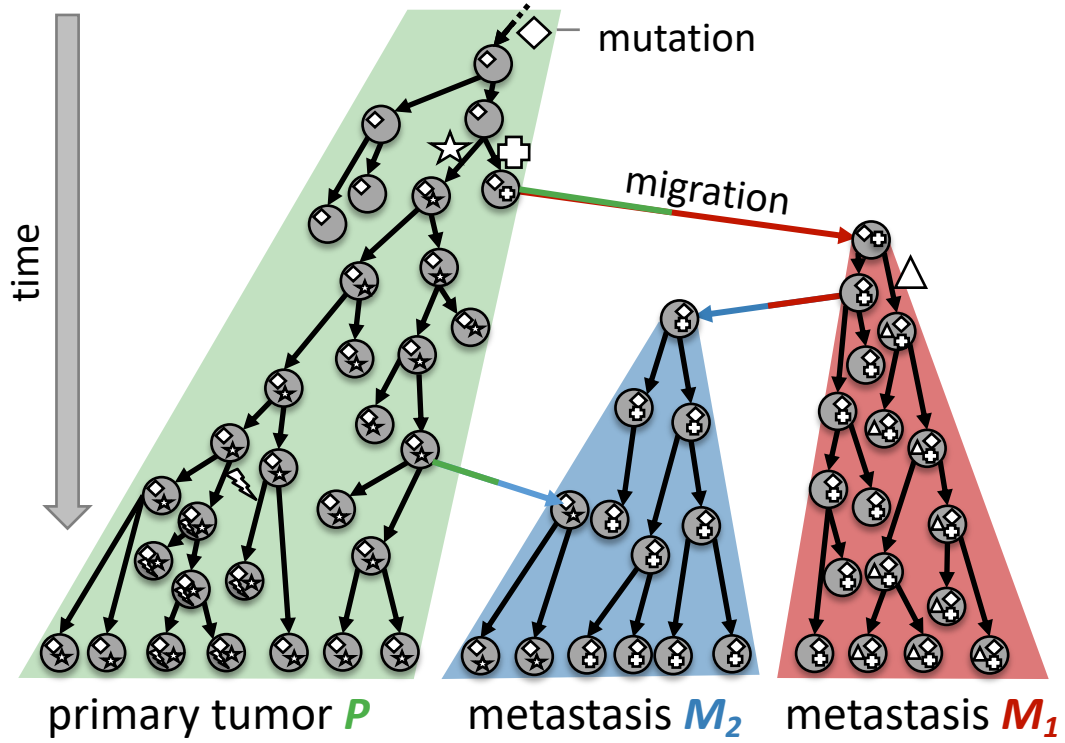
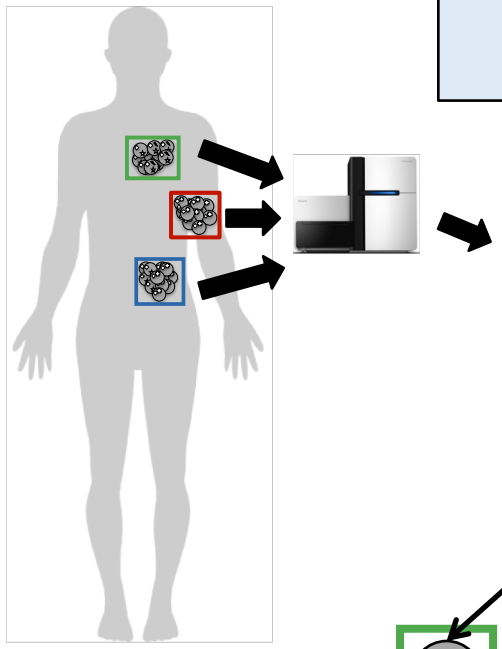
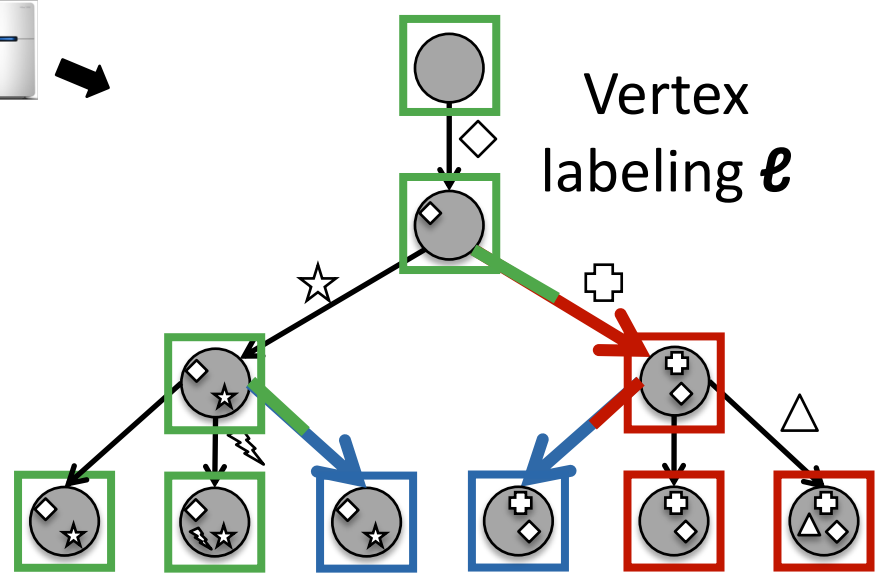


Cell Tree



Instance of small maximum parsimony problem



Phylogenetic Tree T

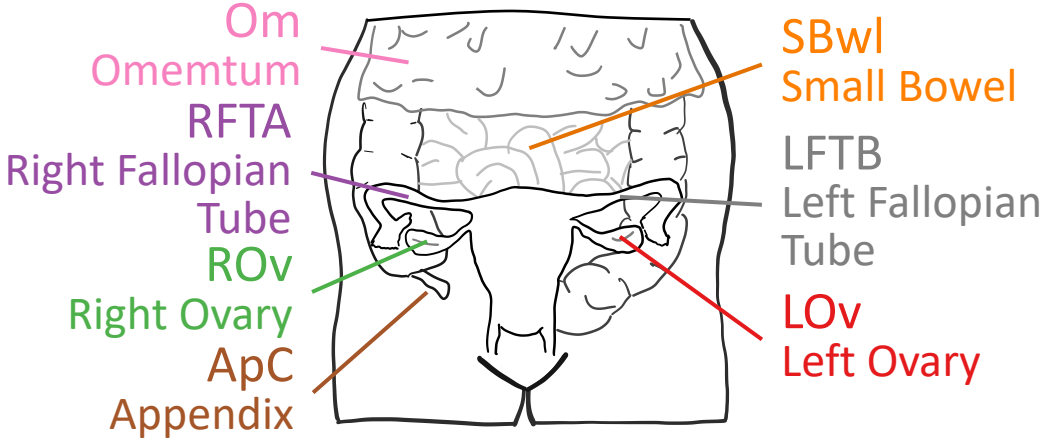
Goal: Given phylogenetic tree T, find ***parsimonious*** vertex labeling ℓ with fewest migrations

Slatkin, M. and Maddison, W. P. (1989). A cladistic measure of gene flow inferred from the phylogenies of alleles. *Genetics*, *123*(3), 603–613.

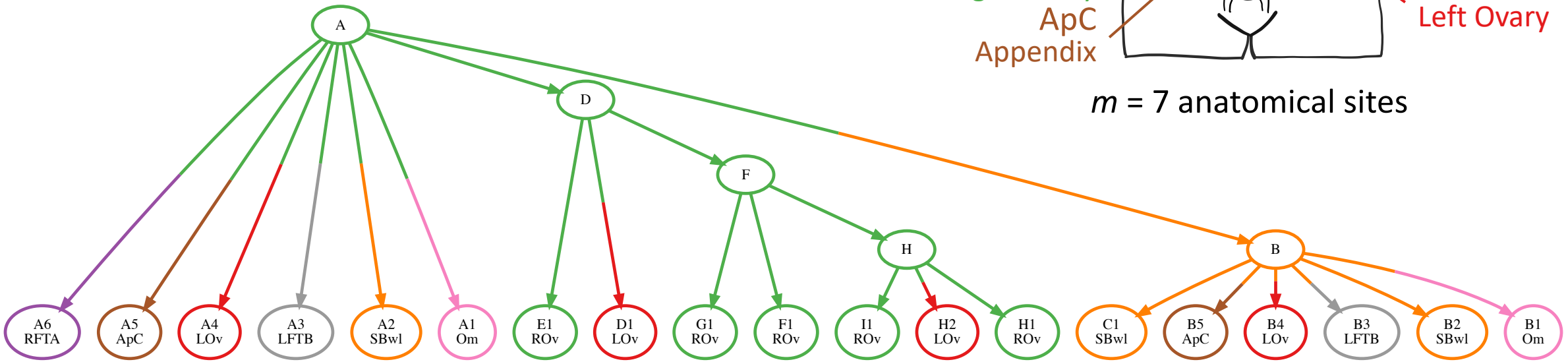
Minimum Migration Analysis in Ovarian Cancer

McPherson et al. (2016). Divergent modes of clonal spread and intraperitoneal mixing in high-grade serous ovarian cancer. *Nature Genetics*.

- Instance of the maximum parsimony small phylogeny problem [Fitch, 1971; Sankoff, 1975]



m = 7 anatomical sites



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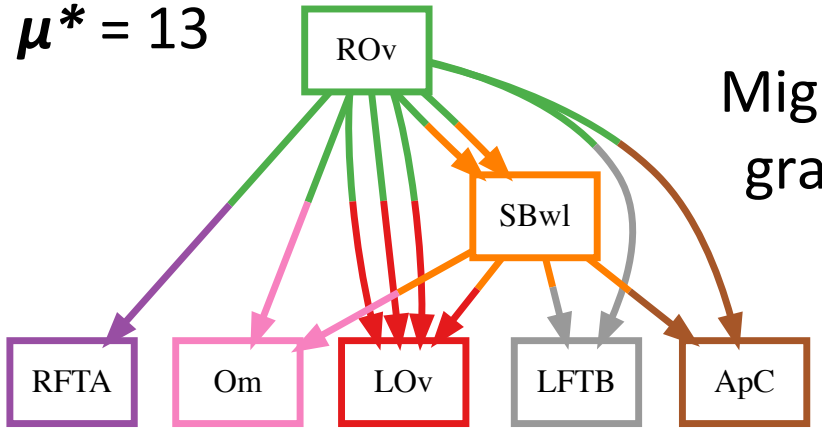
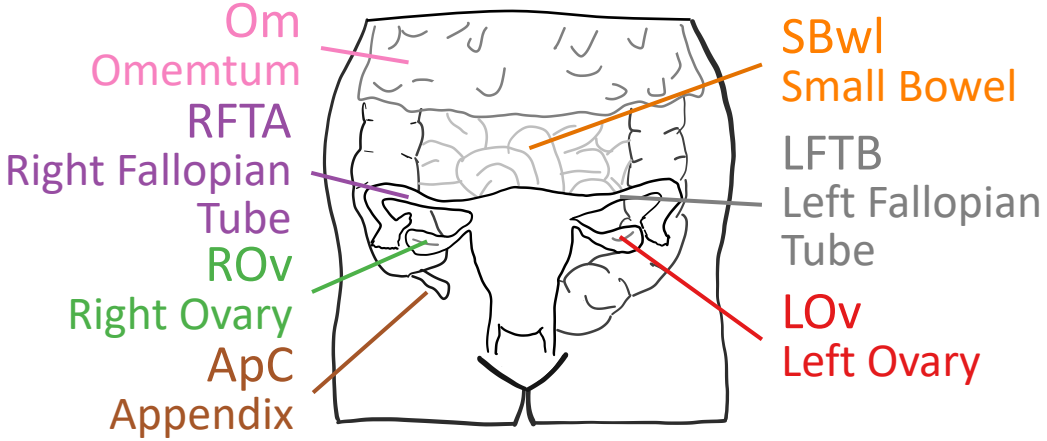
$\mu^* = 13$



Migration graph **G**



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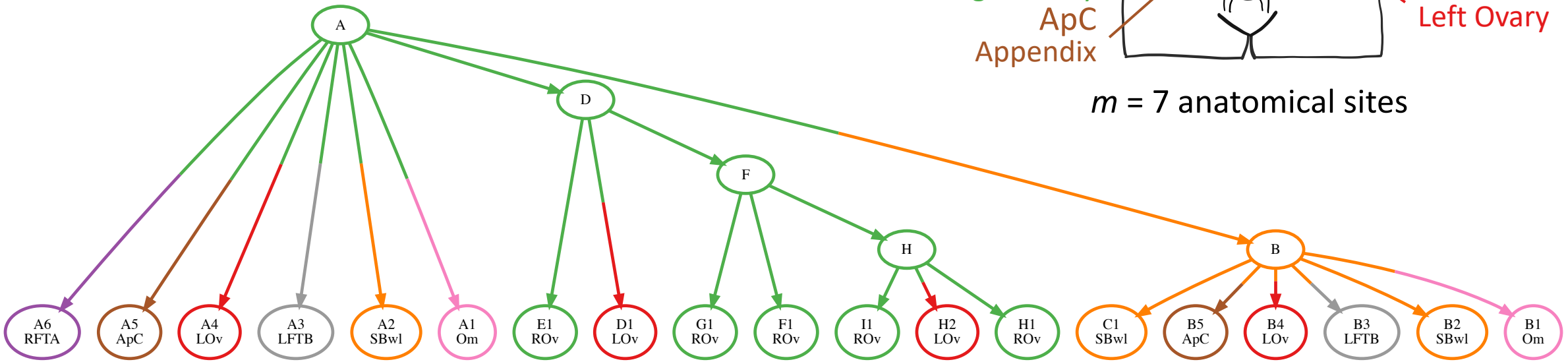
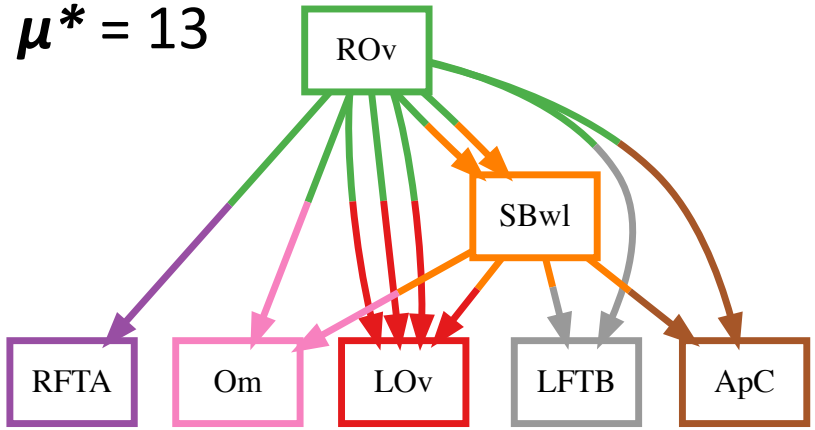


Minimum Migration History is ***Not*** Unique

- Enumerate all minimum-migration vertex labelings in the backtrace step

$\mu^* = 13$



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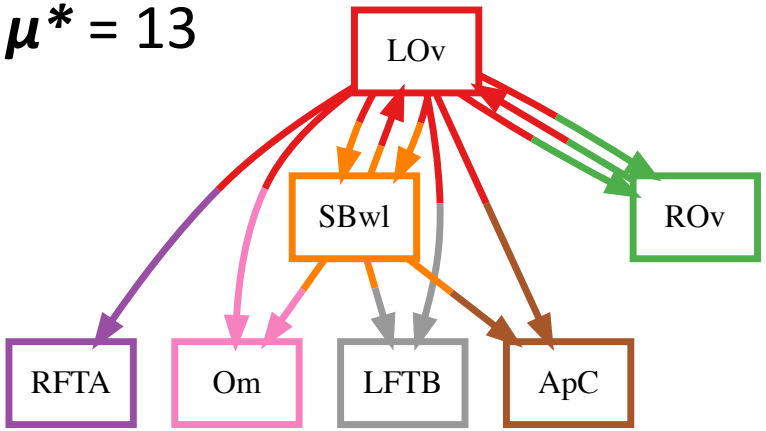
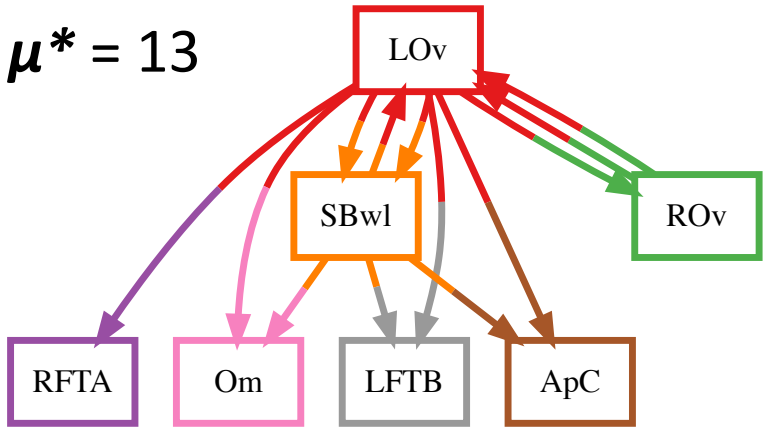


$\mu^* = 13$



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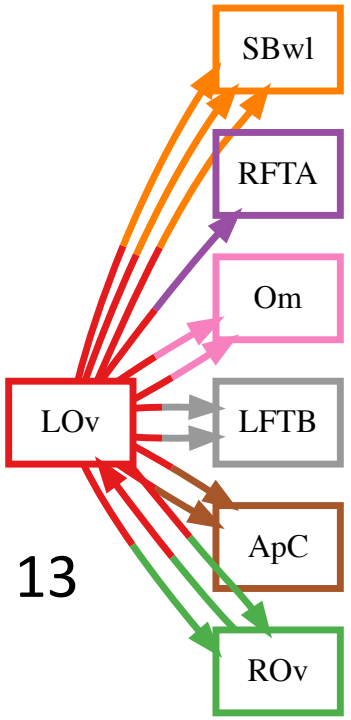

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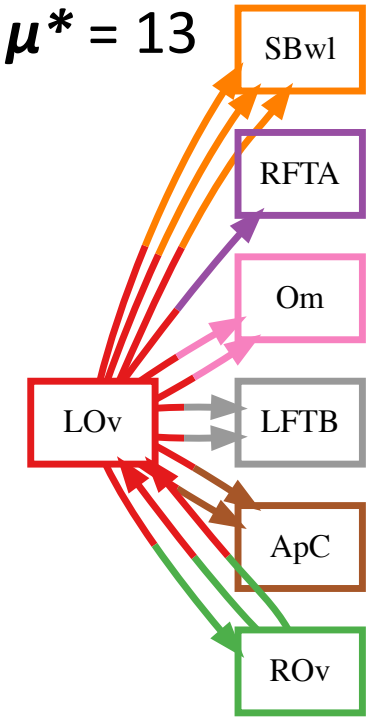

ApC	Appendix
LFTB	Left Fallopian Tube
LOv	Left Ovary
RFTA	Right Fallopian Tube
ROv	Right Ovary
SBwl	Small Bowel
Om	Omentum

Comigrations: Simultaneous Migrations of Multiple Clones

- Multiple tumor cells migrate simultaneously through the blood stream [Cheung et al., 2016]
- Second objective: number γ of comigrations is the number of multi-edges in migration graph G †

† Not necessarily true in the case of directed cycles

$\mu^* = 13$

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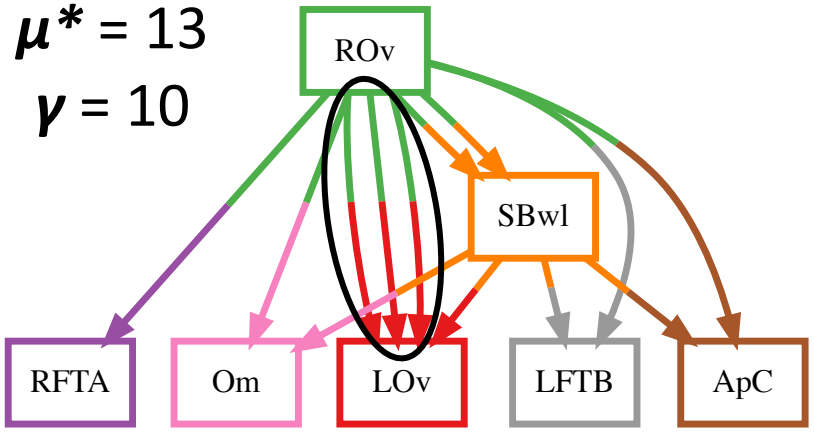
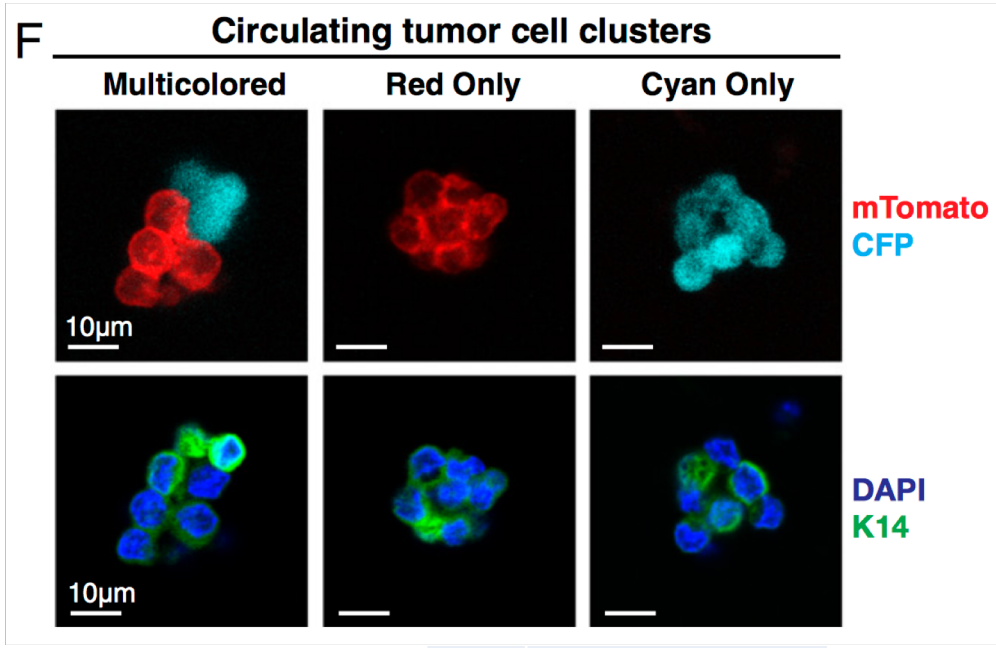
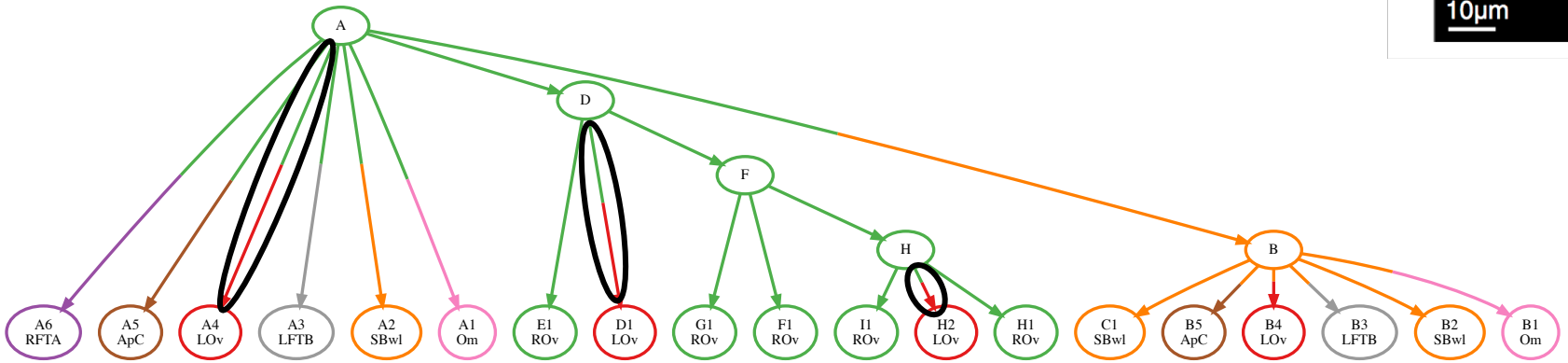


Migration Graph G



Clone Tree T



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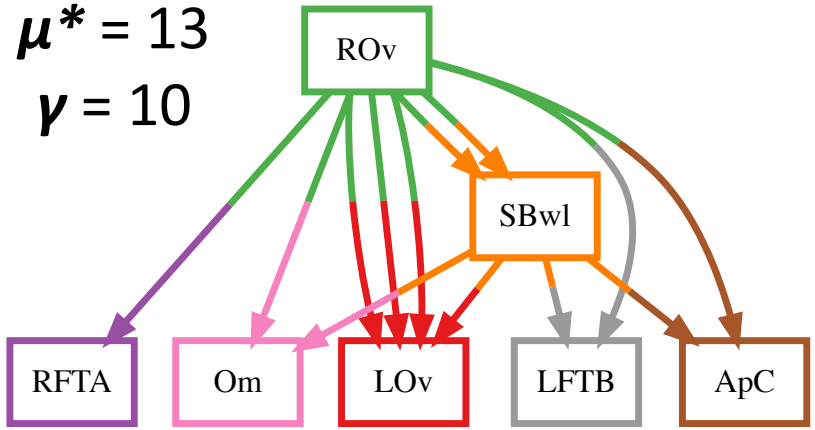
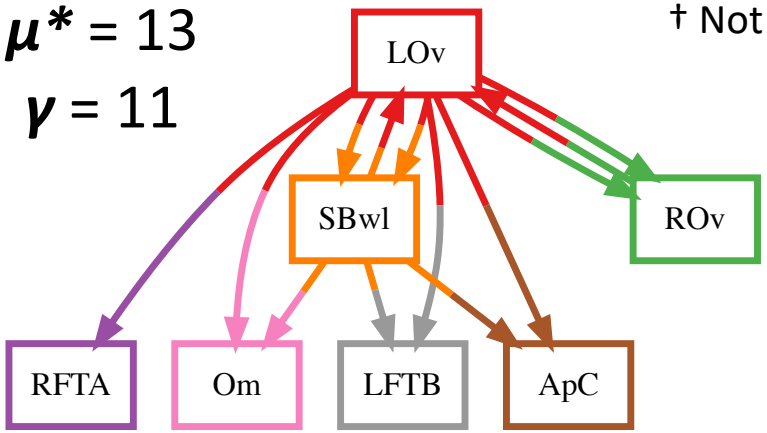


$\mu^* = 13$
$\gamma = 11$



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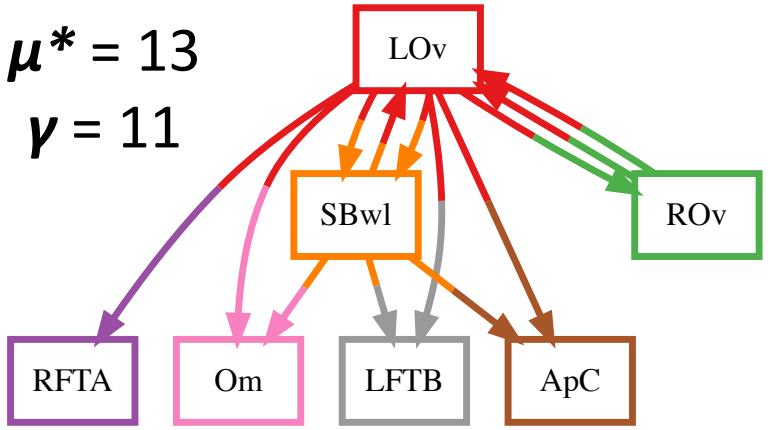
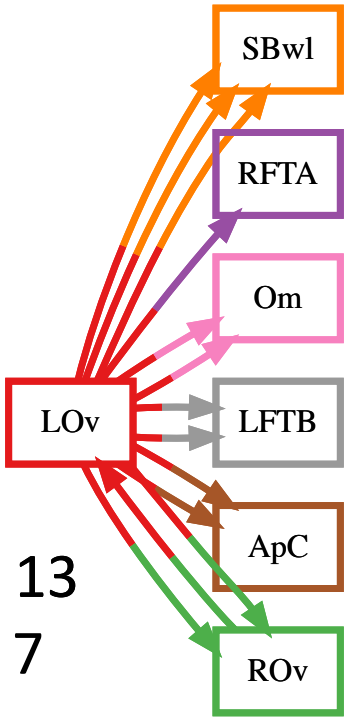


$\mu^* = 13$
$\gamma = 7$



$\mu^* = 13$
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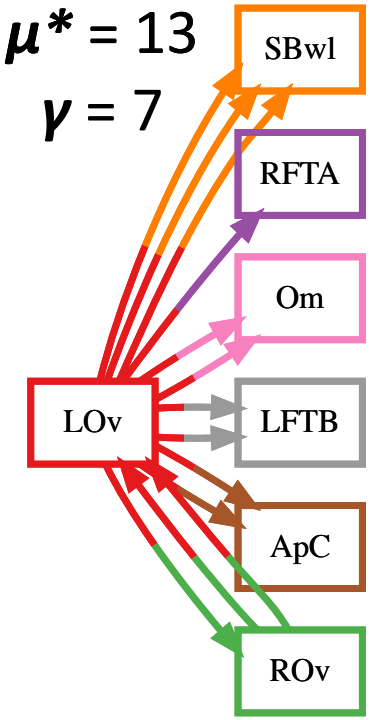
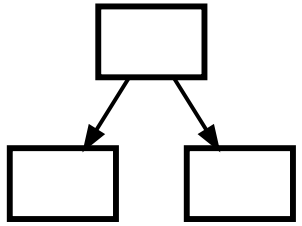
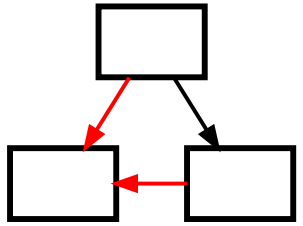
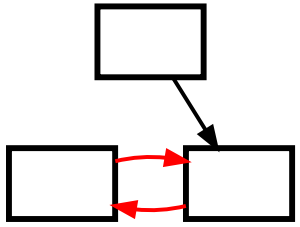
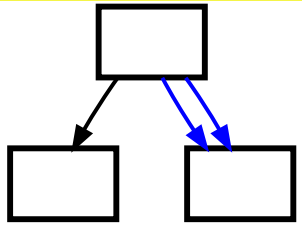
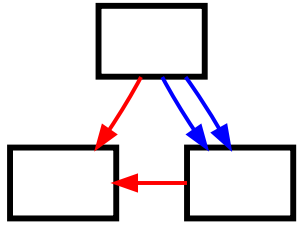
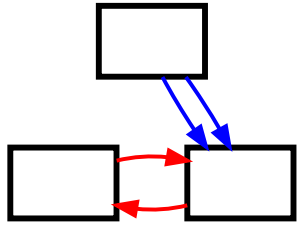
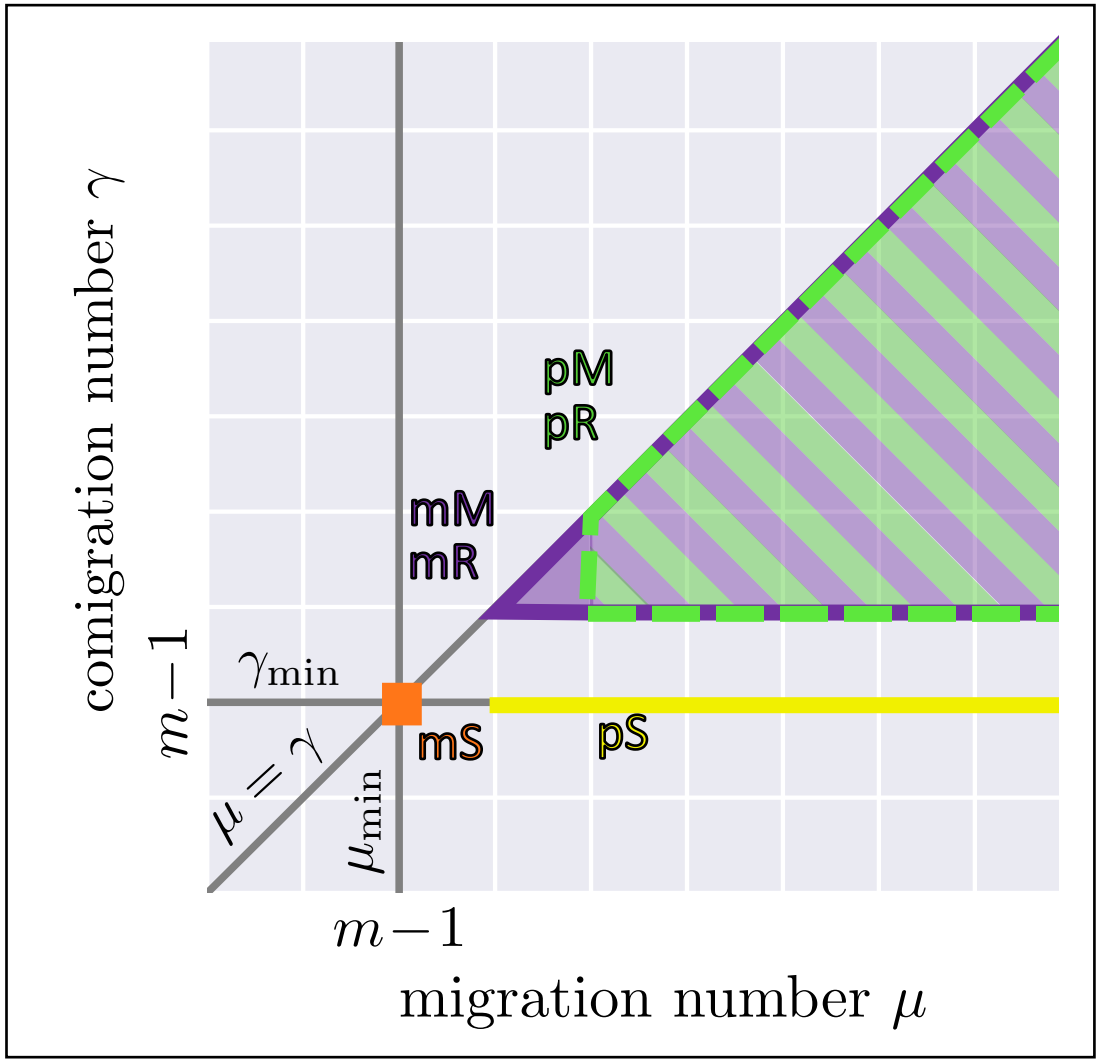


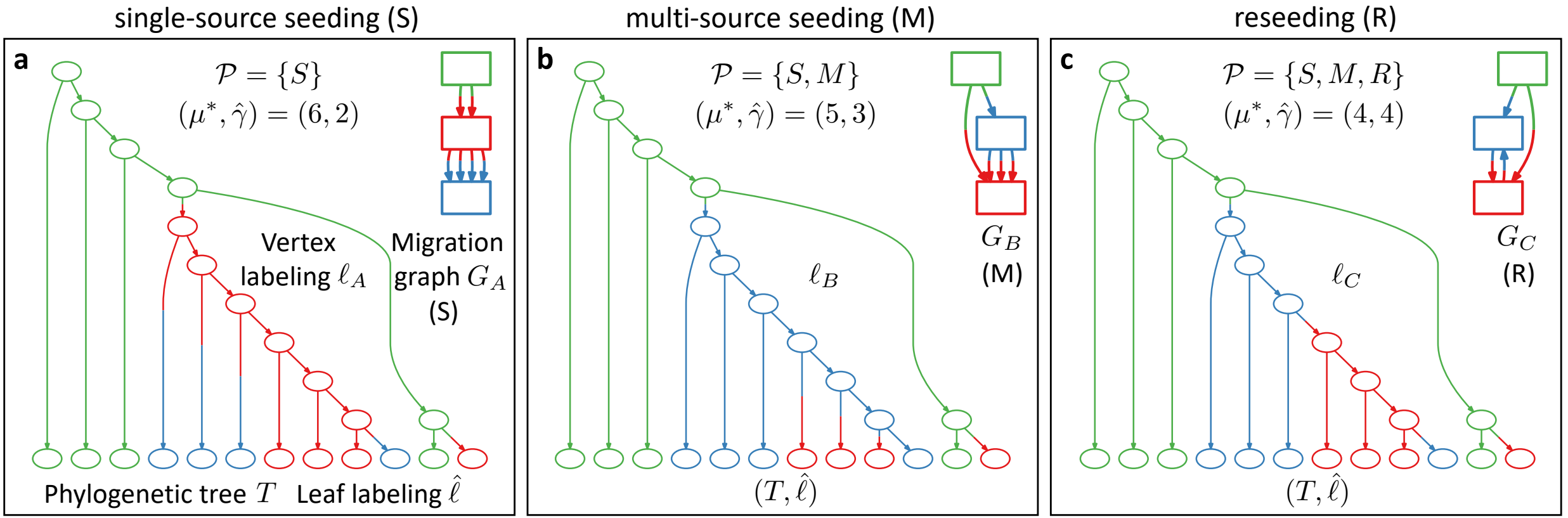
Tradeoffs between Migrations, Comigrations and Migration Pattern

	single-source seeding (S)	multi-source seeding (M)	reseeding (R)
monoclonal (m)	 tree	 directed acyclic graph	 directed graph
polyclonal (p)	 multi-tree	 directed acyclic multi-graph	 directed multi-graph



Constrained Multi-objective Optimization Problem

Parsimonious Migration History (PMH): Given a phylogenetic tree T and a set $\mathcal{P} \subseteq \{\mathrm{S}, \mathrm{M}, \mathrm{R}\}$ of allowed migration patterns, find vertex labeling ℓ with minimum migration number $\mu^*(T)$ and smallest comigration number $\hat{\gamma}(T)$.



El-Kebir, M., Satas, G., & Raphael, B. J. (2018). Inferring parsimonious migration histories for metastatic cancers. *Nature Genetics*, *50*(5), 718–726.

Outline

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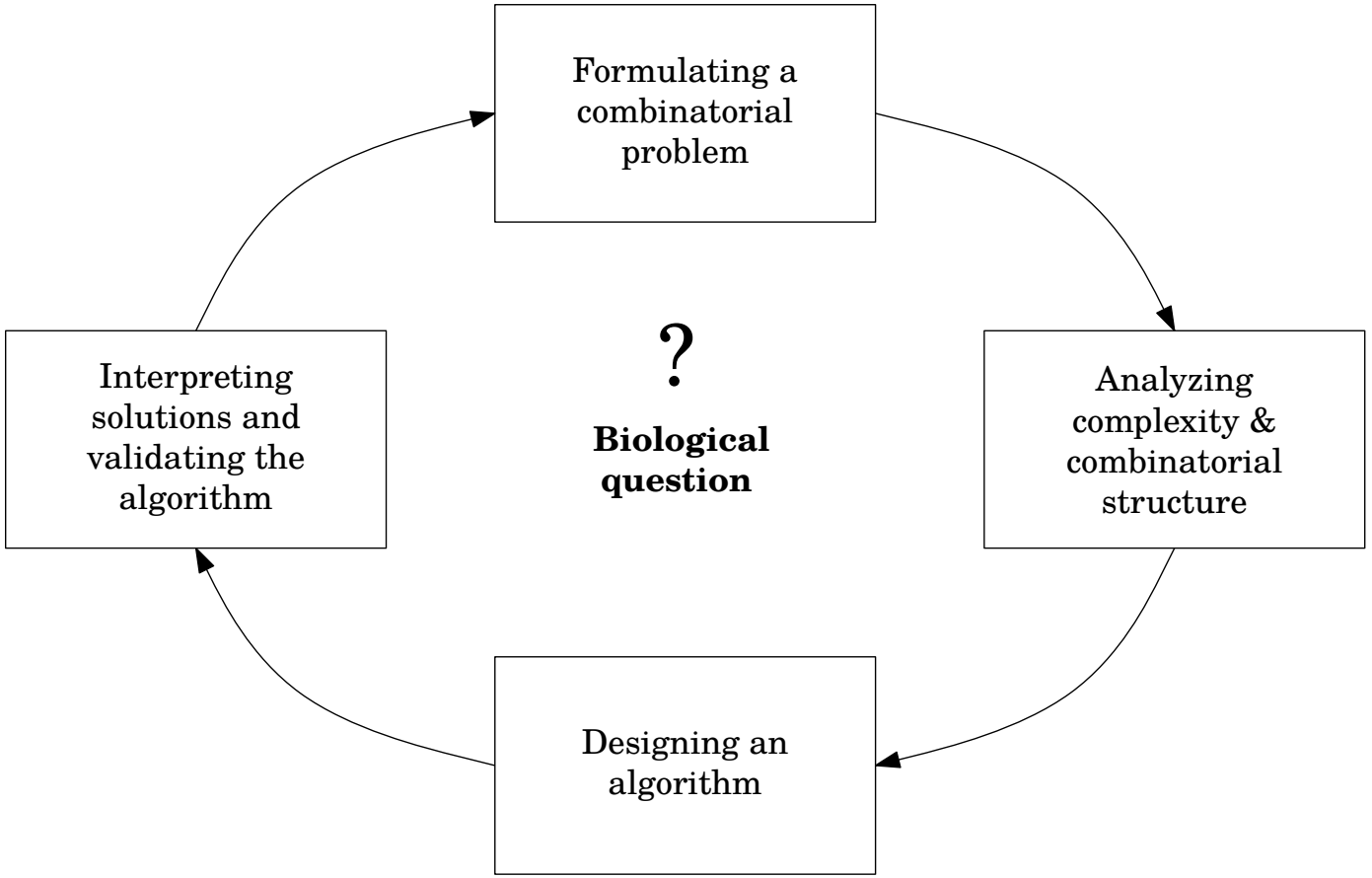
- Problem variants



Reading:

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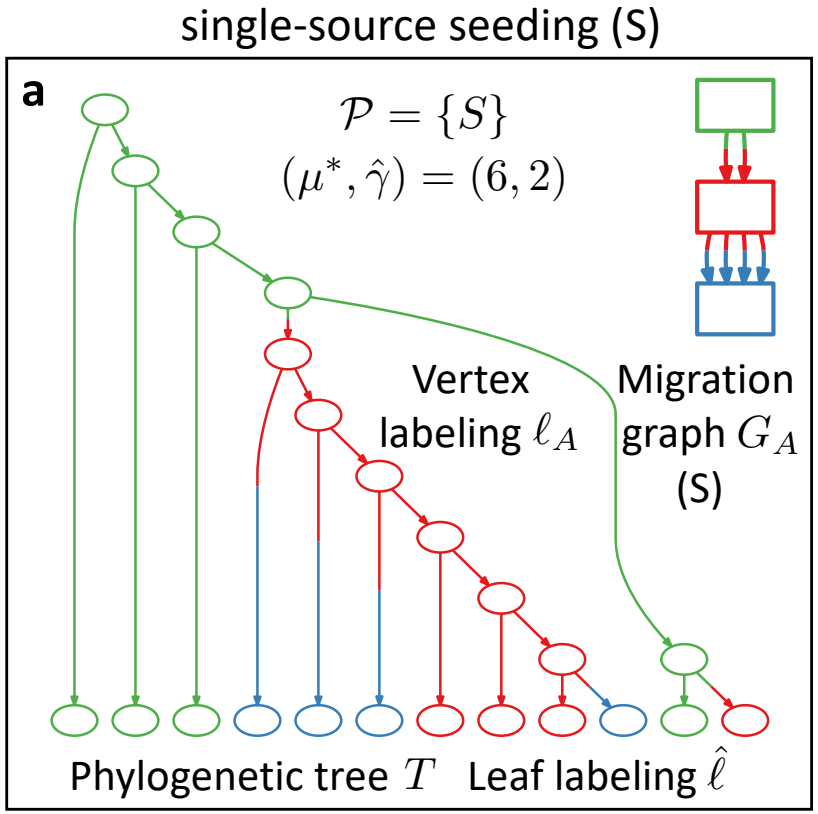
- **M. El-Kebir**†. Parsimonious Migration History Problem: Complexity and Algorithms. WABI 2018, Helsinki, Finland, August 20-22, 2018.

Results [El-Kebir, WABI 2018]

Parsimonious Migration History (PMH): Given a phylogenetic tree T and a set $\mathcal{P} \subseteq \{\mathrm{S}, \mathrm{M}, \mathrm{R}\}$ of allowed migration patterns, find vertex labeling ℓ with minimum migration number $\mu^*(T)$ and smallest comigration number $\hat{\gamma}(T)$.

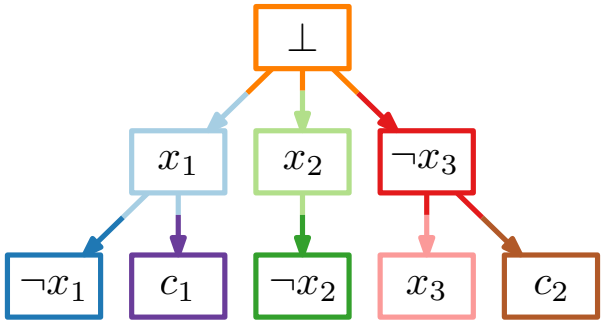


Theorem 1: PMH is NP-hard when $\mathcal{P} = \{\mathrm{S}\}$

Theorem 2: PMH is fixed parameter tractable in the number m of locations when $\mathcal{P} = \{\mathrm{S}\}$

PMH is NP-hard when $\mathcal{P} = \{S\}$

3-SAT: Given $\varphi = \Lambda_{i=1}^{k}(y_{i,1} \vee y_{i,2} \vee y_{i,3})$ with variables $\{x_1, \dots, x_n\}$ and k clauses, find $\phi : [n] \to \{0,1\}$ satisfying φ



$$\Sigma = \{x_1, \dots, x_n, \neg x_1, \dots, \neg x_n, c_1, \dots c_k, \bot\}$$

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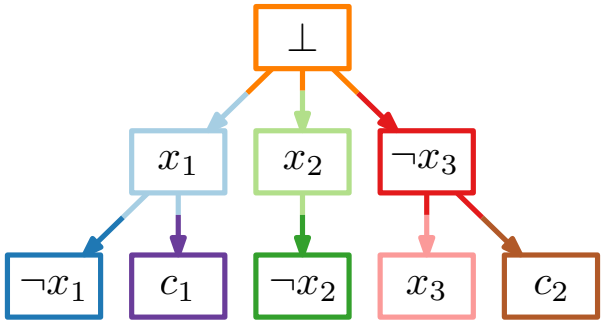
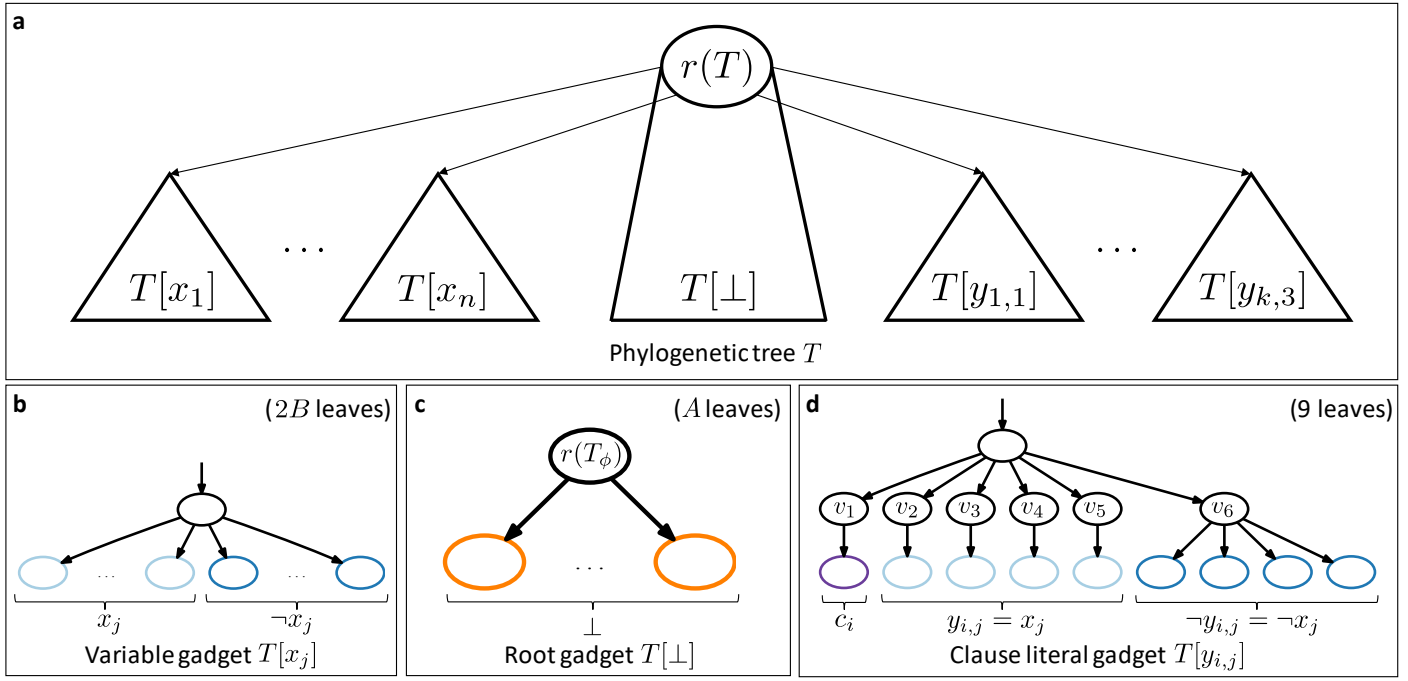


$$\Sigma = \{x_1, \ldots, x_n, \neg x_1, \ldots, \neg x_n, c_1, \ldots c_k, \bot\}$$

Three ideas:

1. Ensure that $(x, \neg x) \in E(G)$ or $(\neg x, x) \in E(G)$
2. Ensure that $\ell^*\big(r(T)\big) = \bot$
3. Ensure that φ is satisfiable if and only if ℓ^* encodes a satisfying truth assignment



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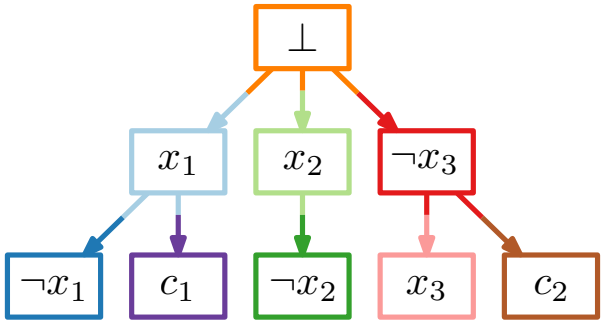

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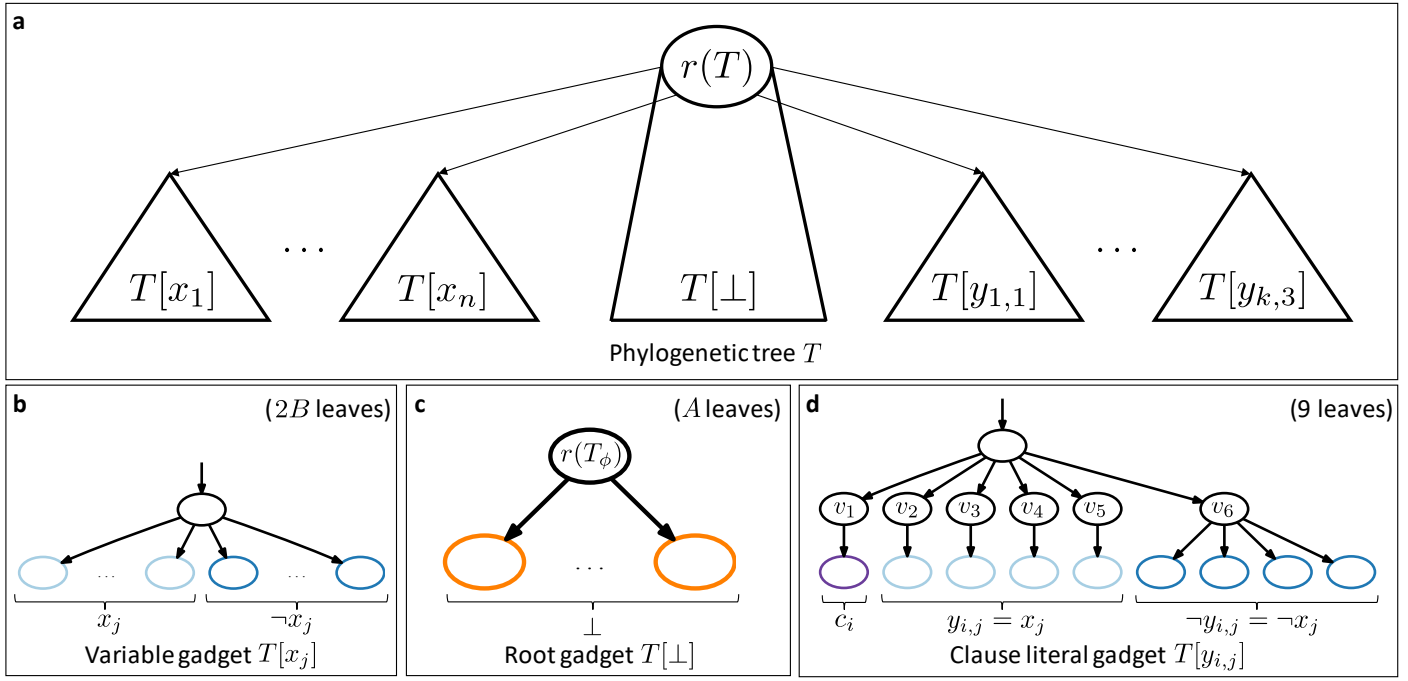


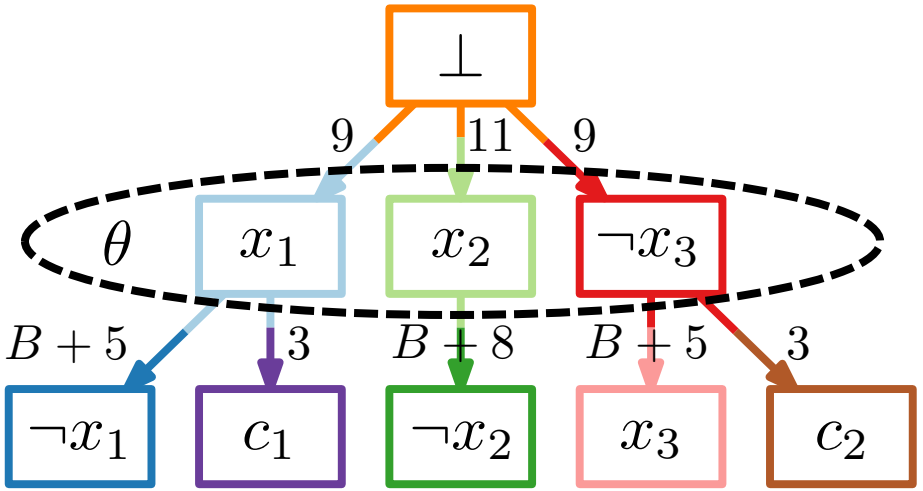
Lemma: Let $B > 10k + 1$ and $A > 2Bn + 27k$.
Then, φ is satisfiable if and only if $\mu^*(T) = (B + 1)n + 25k$

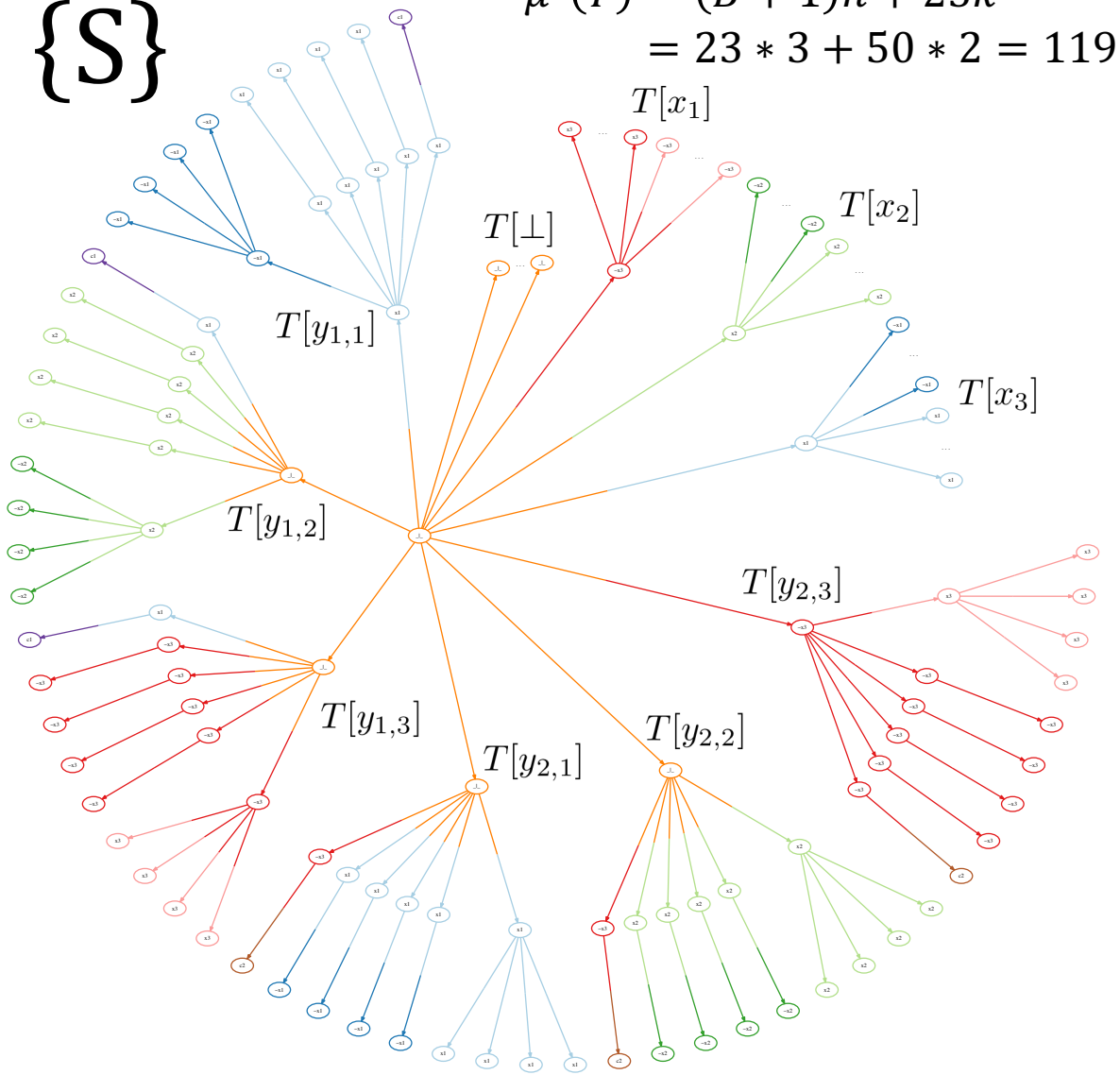
PMH is NP-hard when $\mathcal{P} = \{S\}$

$$\mu^*(T) = (B+1)n + 25k$$
$$= 23 * 3 + 50 * 2 = 119$$

$$\varphi = (x_1 \vee x_2 \vee \neg x_3) \wedge (\neg x_1, \neg x_2, \neg x_3)$$

$$k = 2, n = 3$$
$$B = 10k + 2 = 22$$
$$A = 2Bn + 27\mathrm{k} + 1 = 187$$





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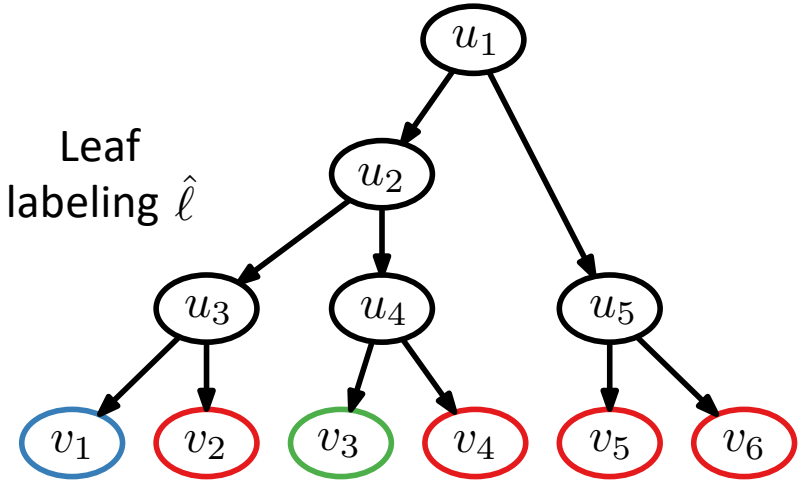
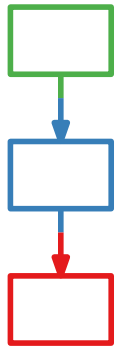
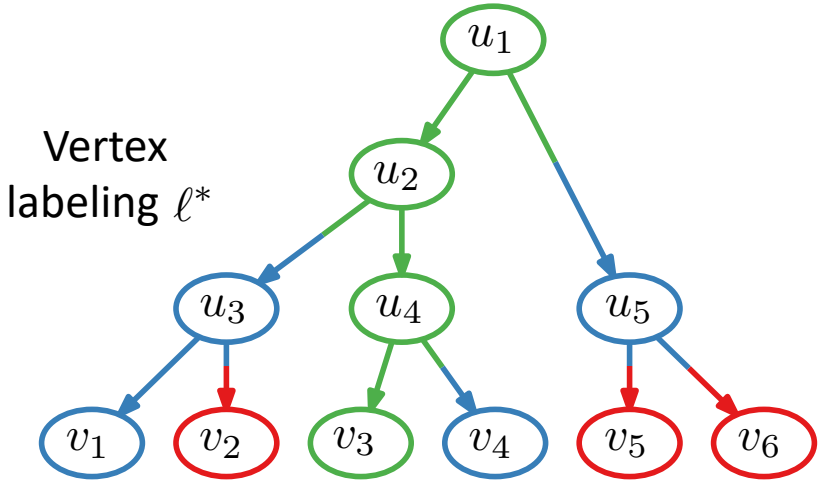


Phylogenetic tree T



Migration tree $\hat{G}$



Phylogenetic tree T

Lemma: If there exists labeling ℓ consistent with $\hat{G}$ then

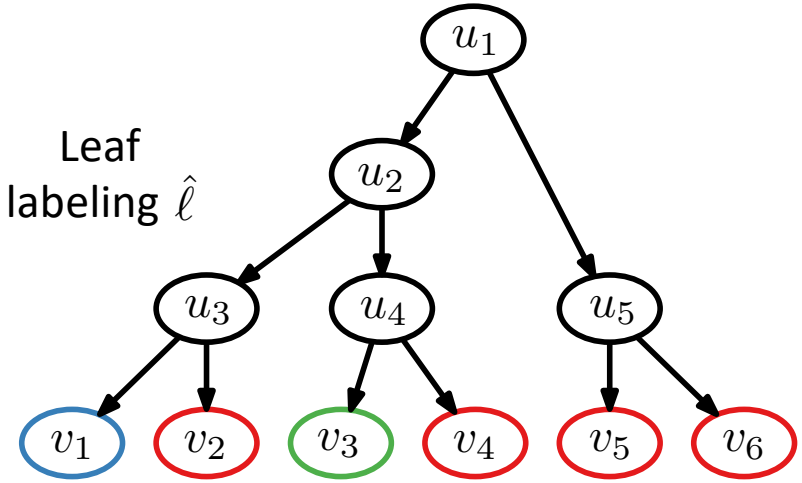
$$d_T(u,v) \geq d_{\hat{G}}(\mathrm{lca}_{\hat{G}}(u), \hat{\ell}(v)) \qquad \forall u, v \in V(T) \text{ such that } u \preceq_T v. \quad (1)$$

$$\ell^*(v) = \begin{cases} \mathrm{LCA}_{\hat{G}}(r(T)), & \text{if } v = r(T), \\ \sigma(\ell^*(\pi(v)), \mathrm{LCA}_{\hat{G}}(v)), & \text{if } v \neq r(T), \end{cases}$$

where $\sigma(s,t) = s$ if $s = t$ and otherwise $\sigma(s,t)$ is the unique child of s that lies on the path from s to t in $\hat{G}$.

Lemma: If (1) holds then ℓ^* is a minimum migration labeling consistent with $\hat{G}$.

PMH is FPT in number m of locations when $\mathcal{P} = \{S\}$



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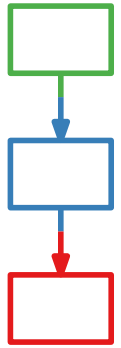

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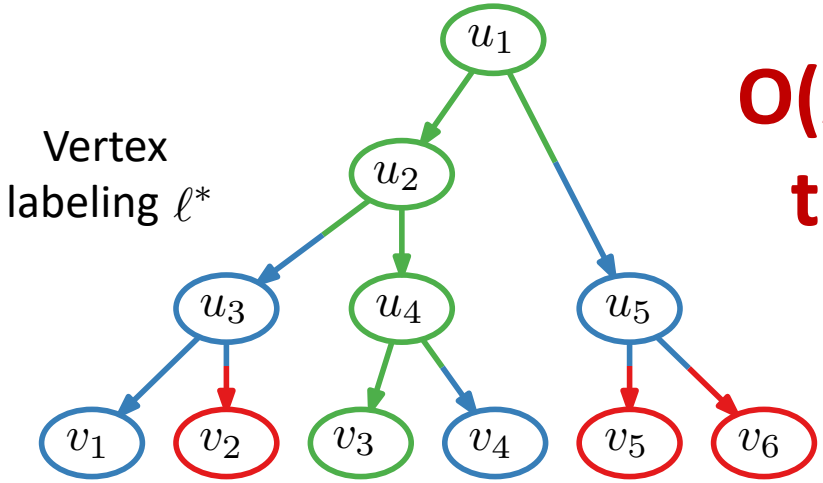

Phylogenetic tree T

O(nm^m) time

Lemma: If there exists labeling ℓ consistent with $\hat{G}$ then

$$d_T(u,v) \geq d_{\hat{G}}(\mathrm{lca}_{\hat{G}}(u), \hat{\ell}(v)) \qquad \forall u, v \in V(T) \text{ such that } u \preceq_T v. \quad (1)$$

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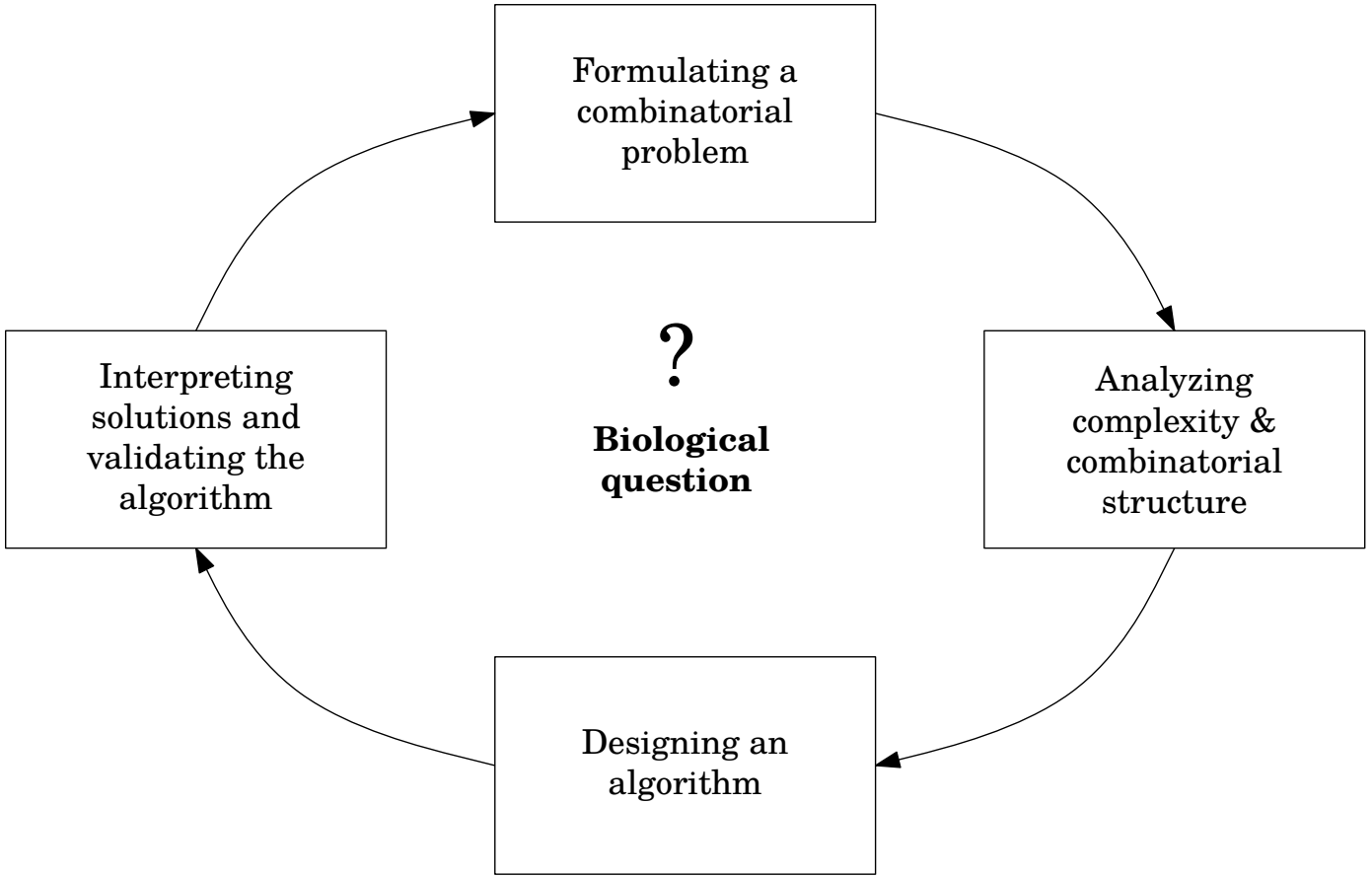

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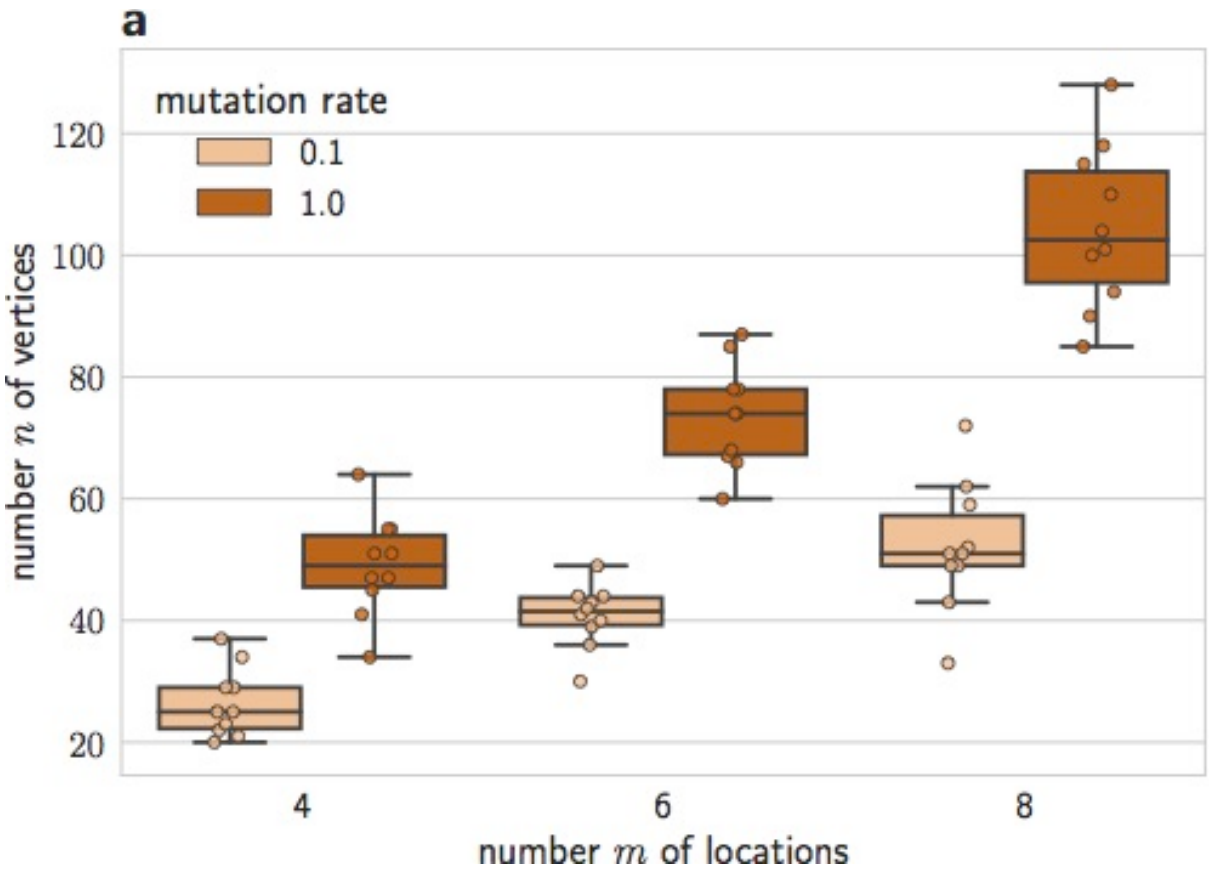
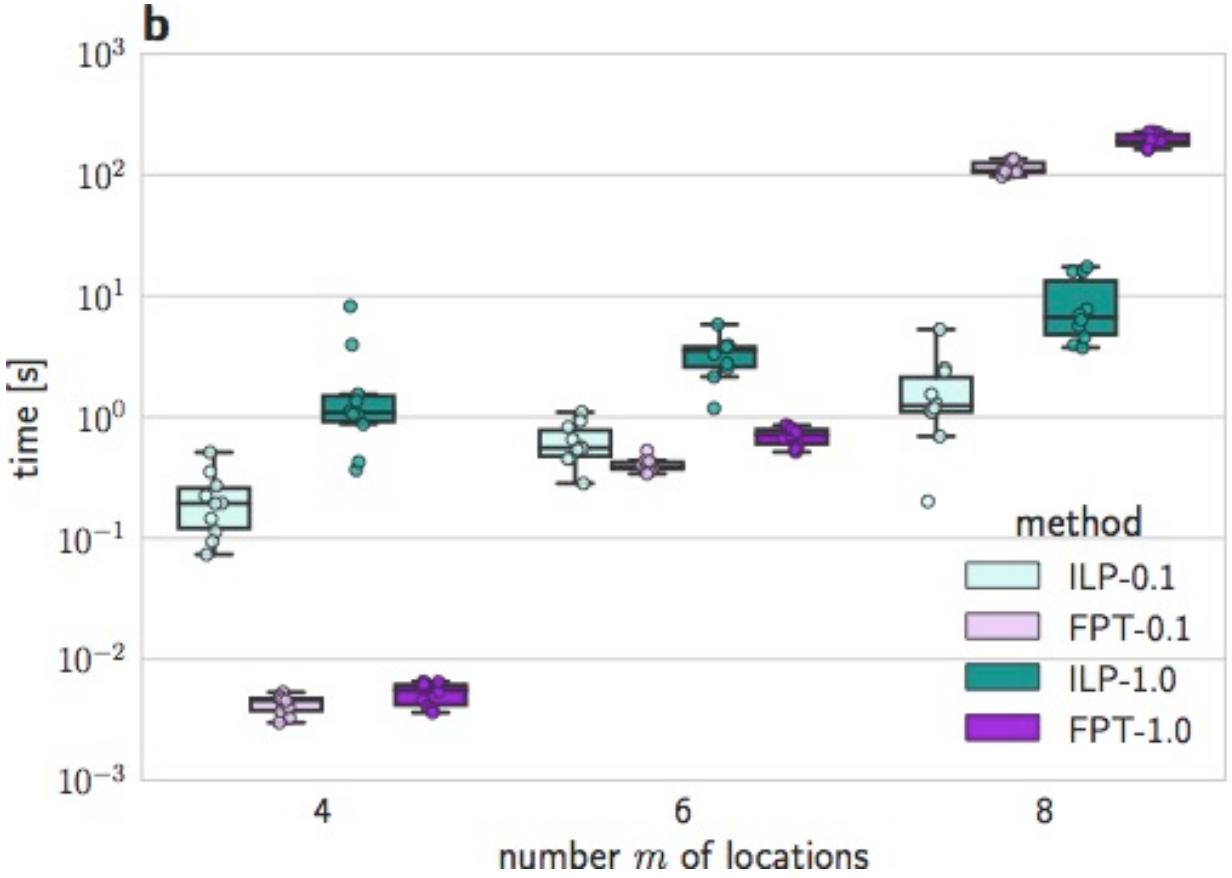
Simulations





Available on: https://github.com/elkebir-group/PMH-S

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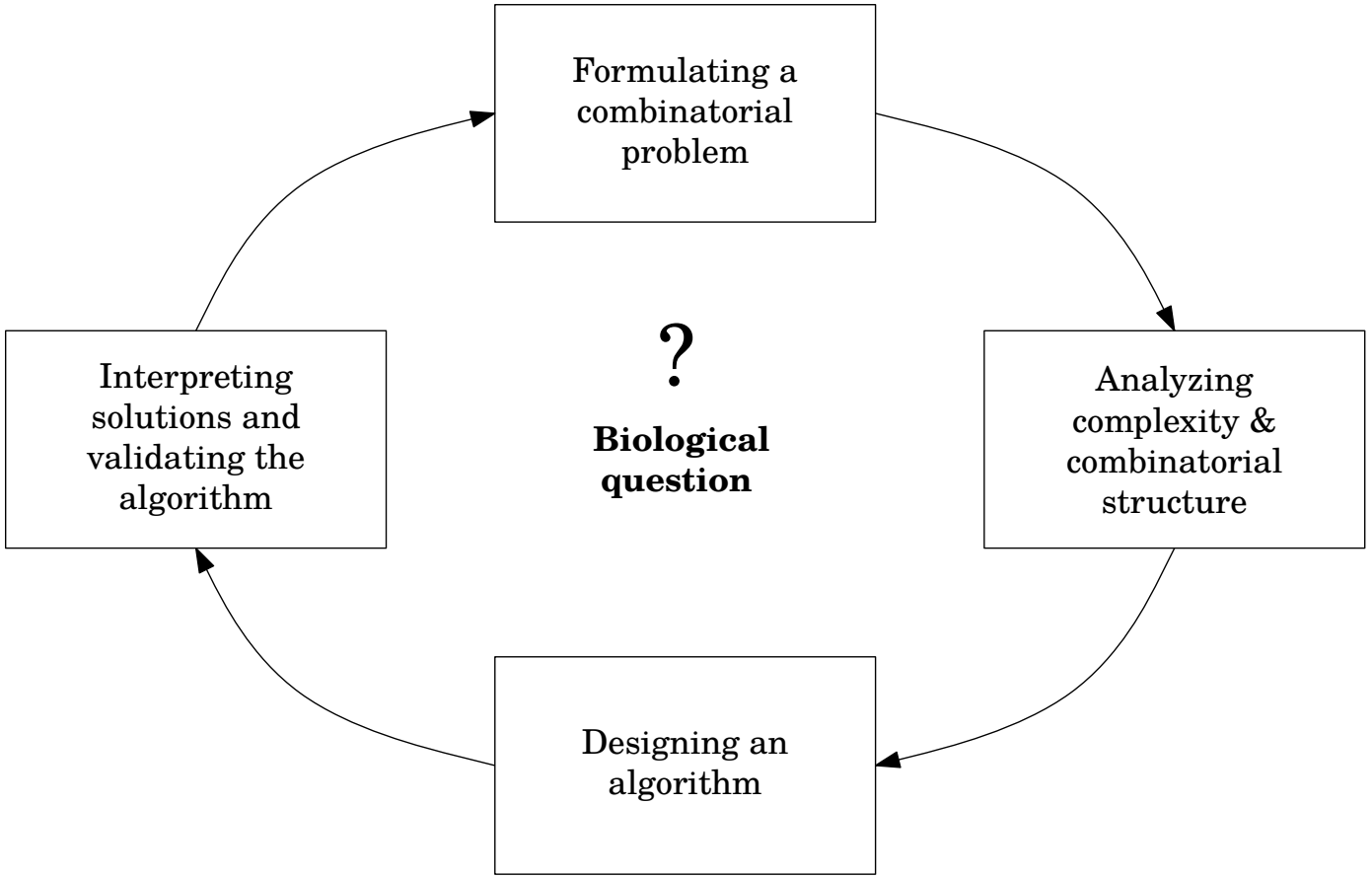

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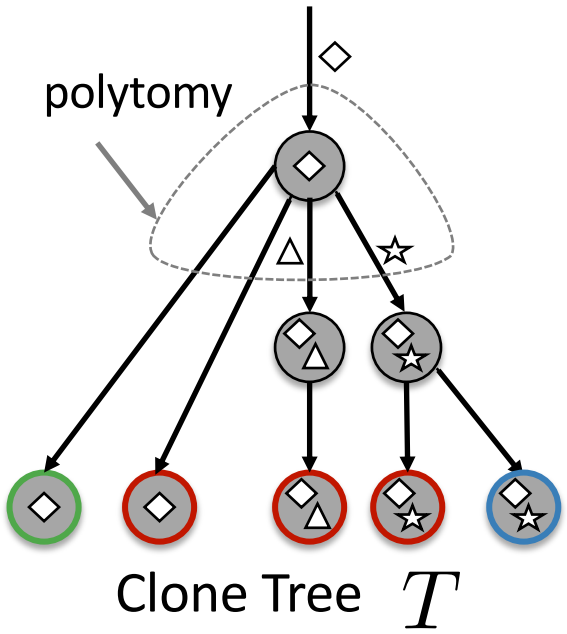
- **M. El-Kebir**†. Parsimonious Migration History Problem: Complexity and Algorithms. WABI 2018, Helsinki, Finland, August 20-22, 2018.

Resolving Clone Tree Ambiguities

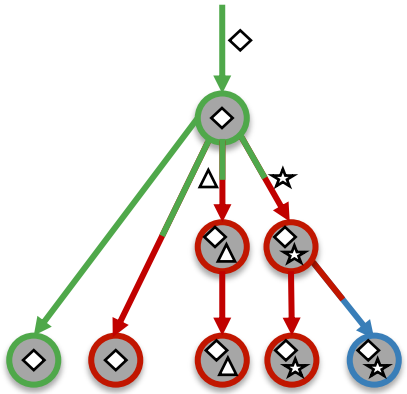


Clone Tree T

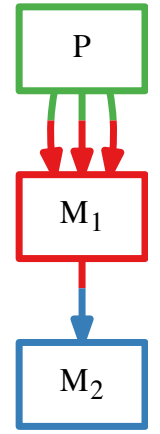
PMH Problem
Parsimonious Migration History

Allowed patterns $\mathcal{P}$
$\{S, M, R\}$

PMH-TR Problem
Parsimonious Migration History with Tree Resolution

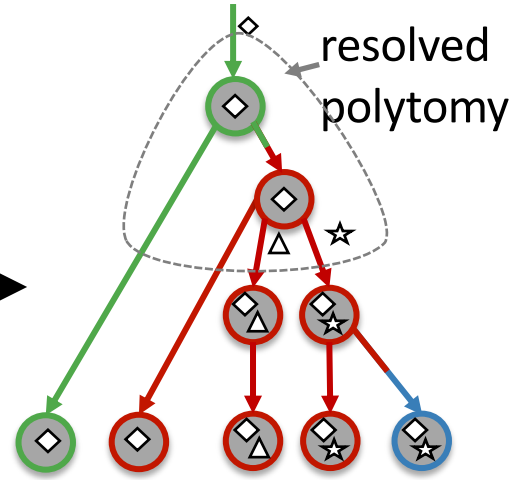


polyclonal single source seeding (pS)

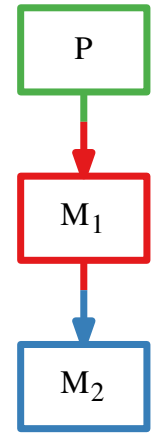


$\mu = 4$

$\gamma = 2$



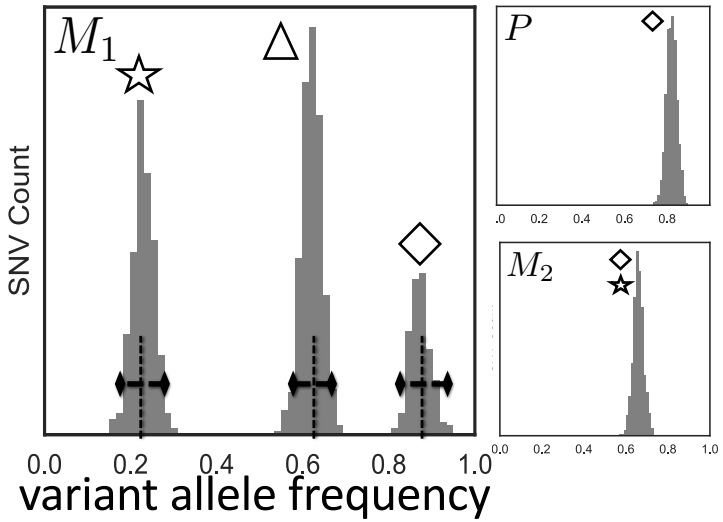
monoclonal single source seeding (mS)



$\mu = 2$

$\gamma = 2$

Resolving Clone Tree Ambiguities

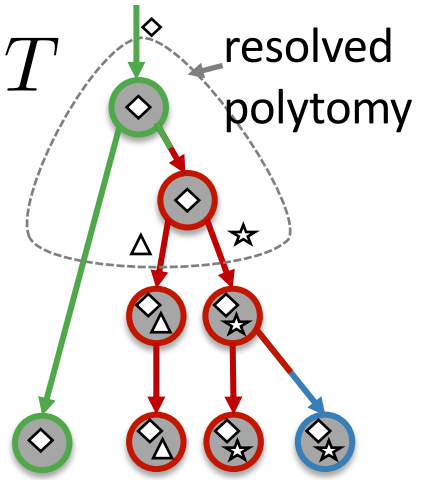


confidence intervals

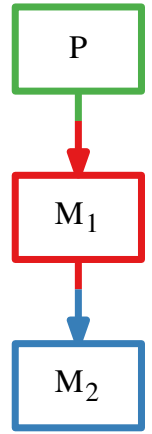
$$F^- = \begin{array}{c} \\ P \\ M_1 \\ M_2 \end{array} \begin{array}{c} \diamond \quad \triangle \quad \star \\ \begin{bmatrix} 0.75 & 0 & 0 \\ 0.82 & 0.15 & 0.56 \\ 0.66 & 0 & 0.68 \end{bmatrix} \end{array}$$

$$F^+ = \begin{array}{c} \\ P \\ M_1 \\ M_2 \end{array} \begin{array}{c} \diamond \quad \triangle \quad \star \\ \begin{bmatrix} 0.86 & 0 & 0 \\ 0.92 & 0.30 & 0.68 \\ 0.78 & 0 & 0.77 \end{bmatrix} \end{array}$$

Clone Tree T



$$\begin{array}{c} \\ P \\ M_1 \\ M_2 \end{array} \begin{array}{c} \diamond \quad \triangle \quad \star \\ \underbrace{\begin{bmatrix} 0.82 & 0 & 0 \\ 0.88 & 0.24 & 0.64 \\ 0.73 & 0 & 0.73 \end{bmatrix}}_{\hat{F}} \end{array} = \begin{array}{c} \\ P \\ M_1 \\ M_2 \end{array} \begin{array}{c} \\ \underbrace{\begin{bmatrix} 0.82 & 0 & 0 \\ 0 & 0.24 & 0.64 \\ 0 & 0 & 0.73 \end{bmatrix}}_{U} \end{array} \begin{array}{c} \diamond \quad \triangle \quad \star \\ \underbrace{\begin{bmatrix} 1 & 0 & 0 \\ 1 & 1 & 0 \\ 1 & 0 & 1 \end{bmatrix}}_{B} \end{array}$$



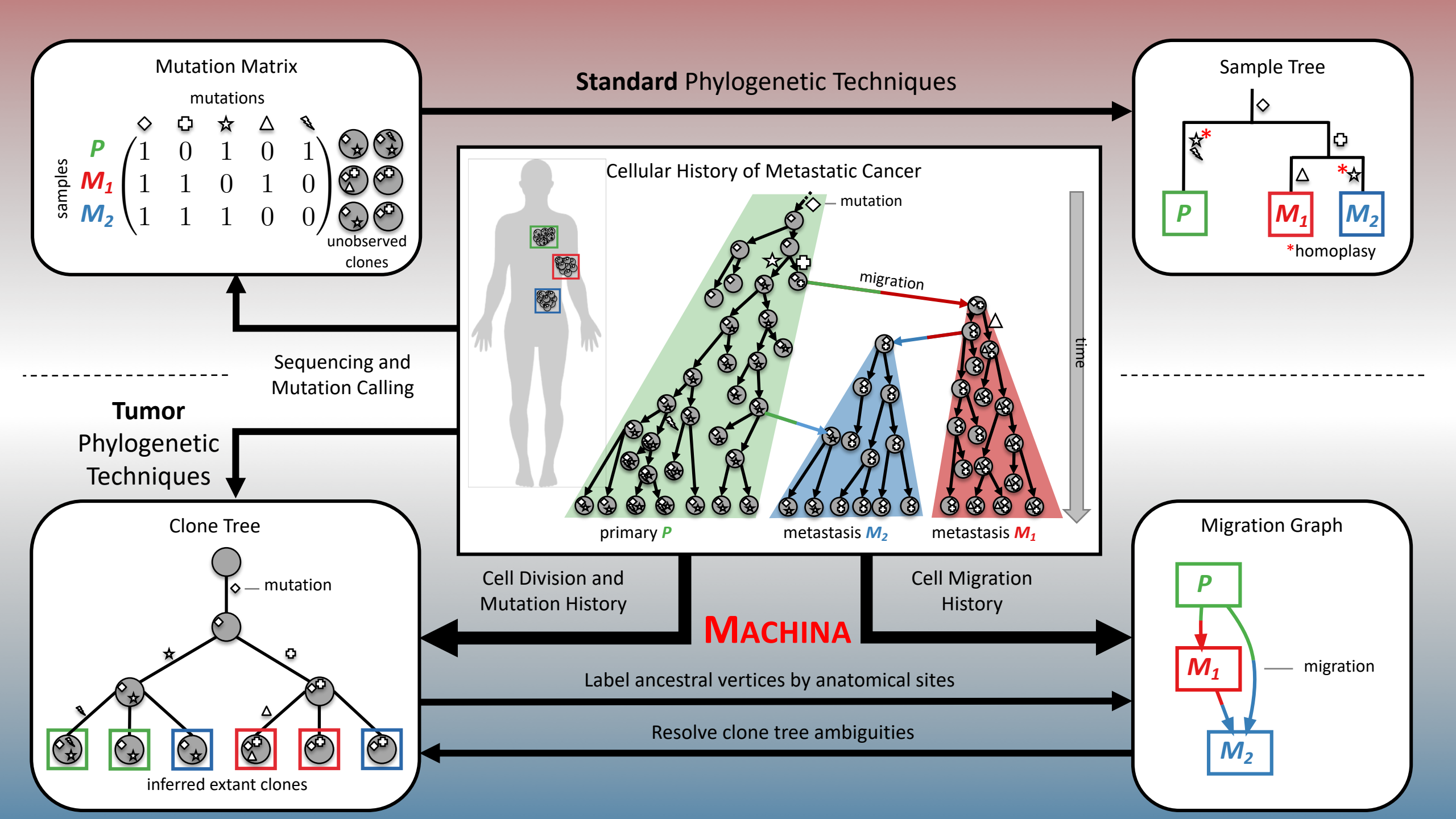
$\mu = 2$

$\gamma = 2$

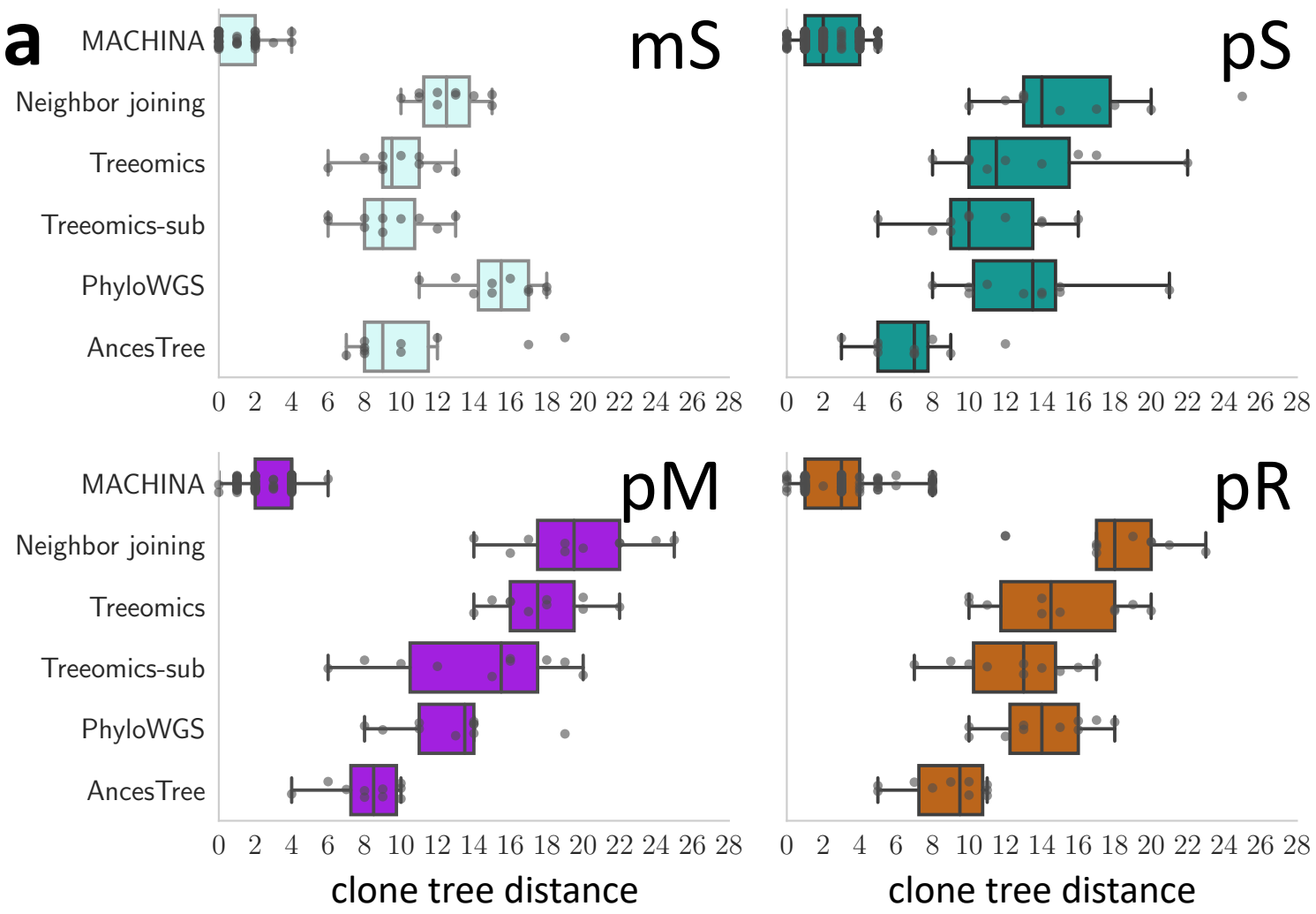
monoclonal single source seeding (mS)

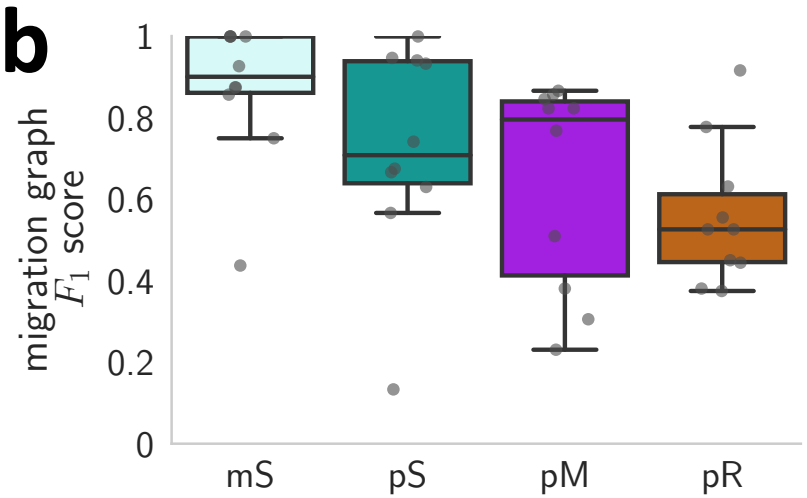
PMH-TI Problem
Parsimonious Migration History with Tree Inference

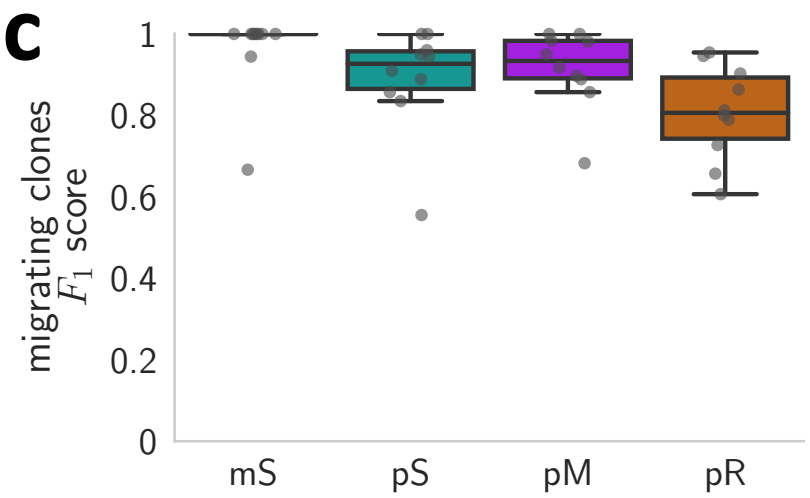
$\mathcal{P}$


Mutation Matrix
mutations
samples
P
M1
M2
1 0 1 0 1
1 1 0 1 0
1 1 1 0 0
unobserved clones
Standard Phylogenetic Techniques
Sample Tree
P
M1
M2
*homoplasy
Cellular History of Metastatic Cancer
mutation
migration
time
primary P
metastasis M2
metastasis M1
Sequencing and Mutation Calling
Tumor Phylogenetic Techniques
Clone Tree
mutation
inferred extant clones
Cell Division and Mutation History
MACHINA
Cell Migration History
Label ancestral vertices by anatomical sites
Resolve clone tree ambiguities
Migration Graph
P
M1
M2
migration

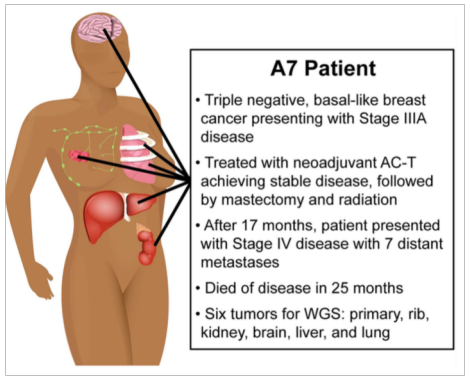
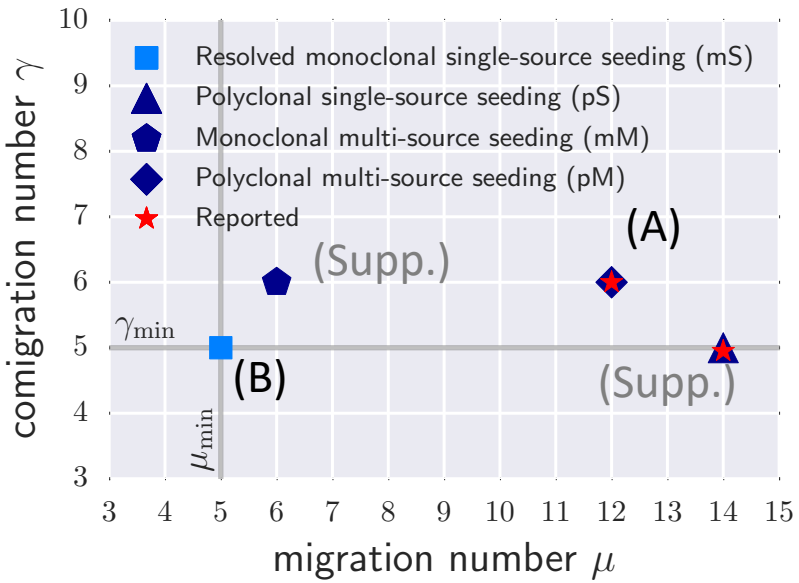
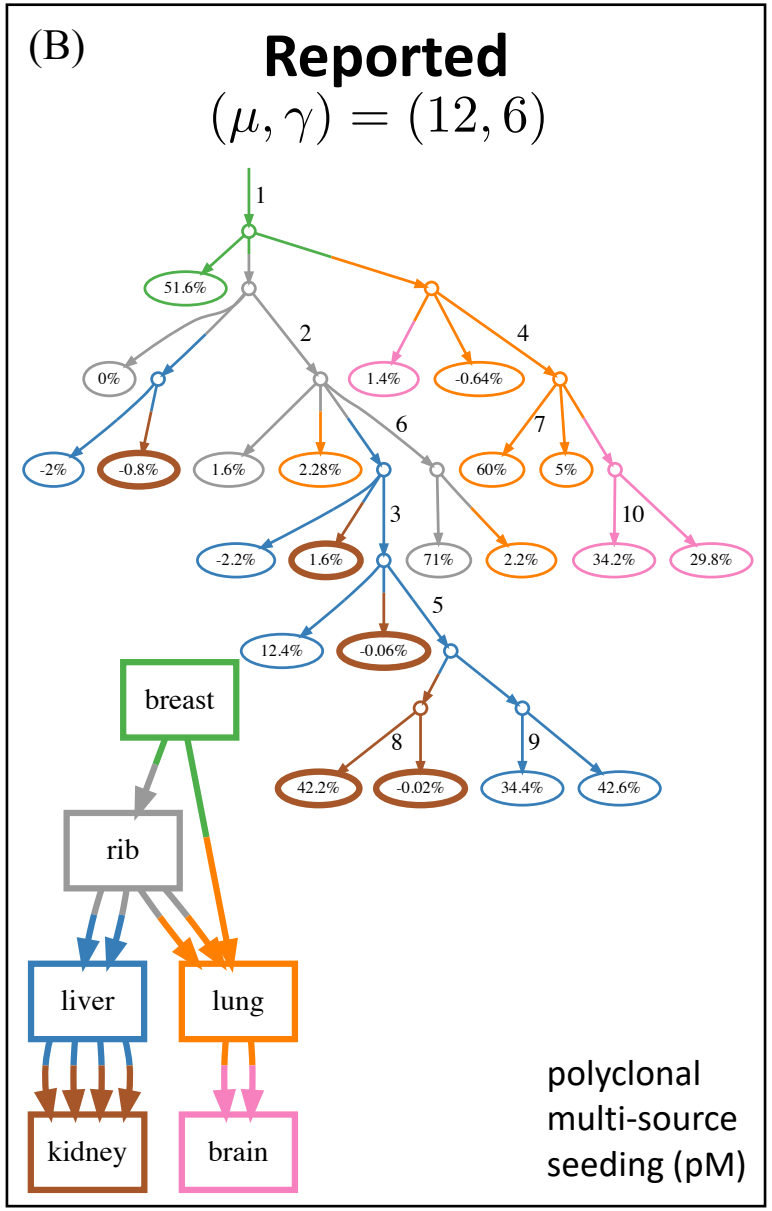
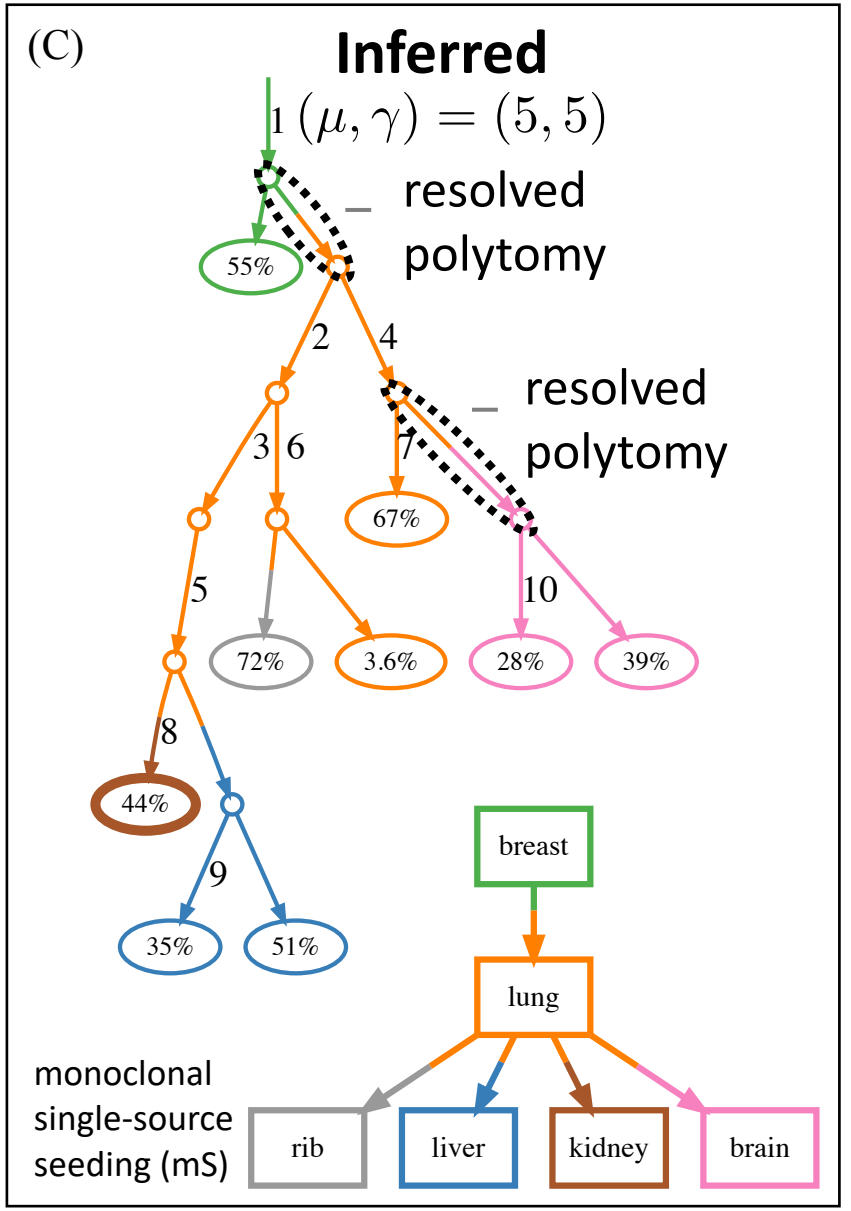
MACHINA accurately infers clone trees and migration histories on simulated data







Applying MACHINA to Metastatic Breast Cancer



Hoadley et al. Tumor Evolution in Two Patients with Basal-like Breast Cancer: A Retrospective Genomics Study of Multiple Metastases. *PLOS Med*, *13*(12) 2016