Poster #B-845

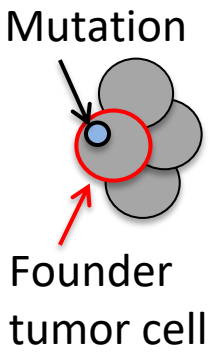
Inferring Parsimonious Migration Histories for Metastatic Cancers

Mohammed El-Kebir, Gryte Satas and Ben Raphael

El-Kebir, M., Satas, G., & Raphael, B. J. (2018). Inferring parsimonious migration histories for metastatic cancers. *Nature Genetics*, *50*(5), 718–726. http://doi.org/10.1038/s41588-018-0106-z

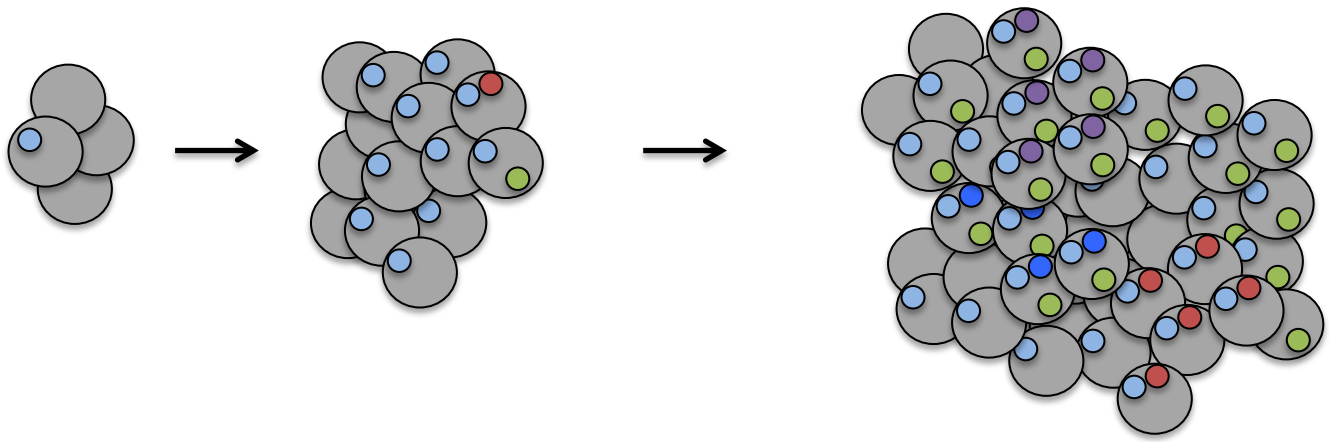
Tumorigenesis: (i) Cell Mutation

Clonal Theory of Cancer
[Nowell, 1976]



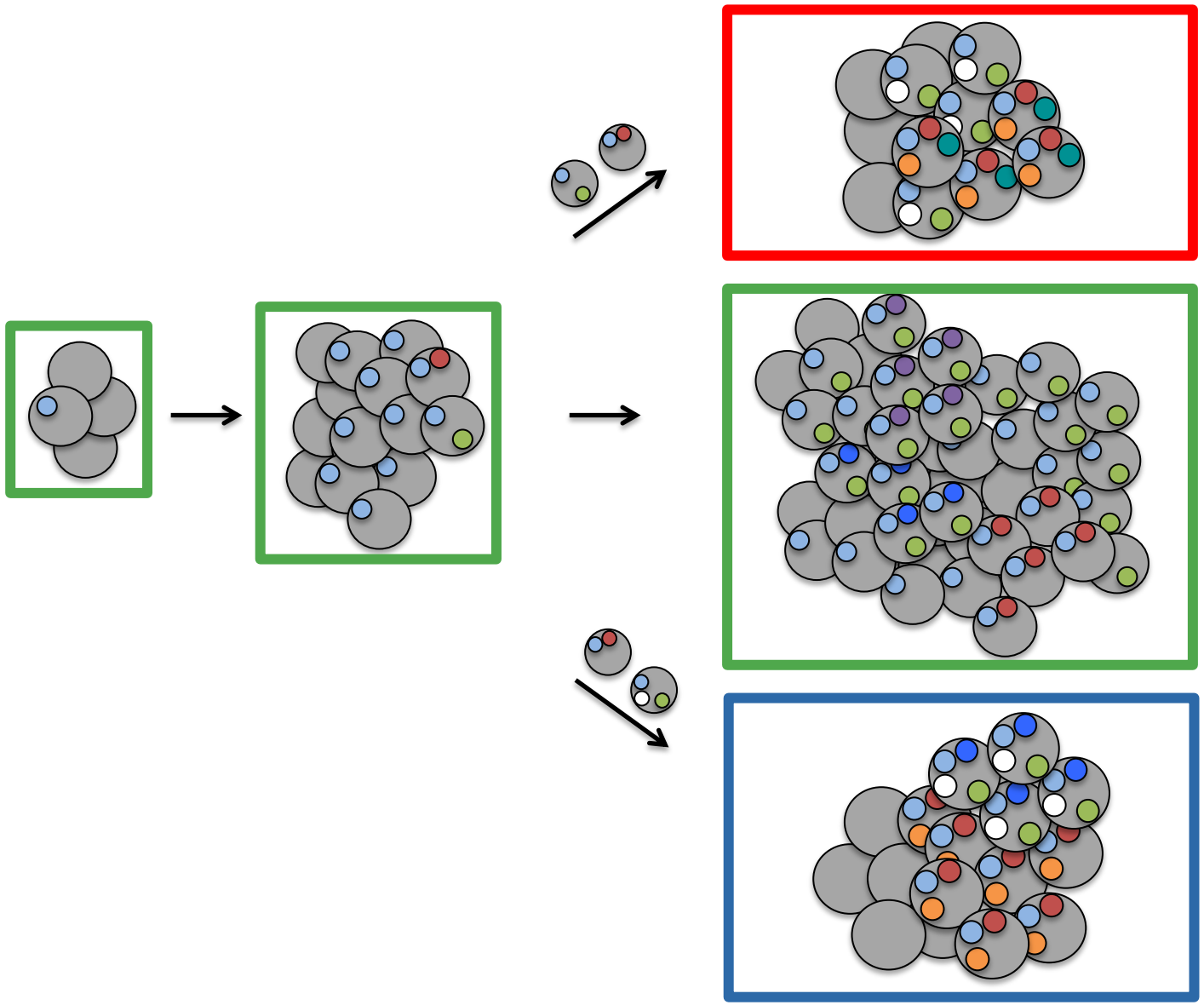
Tumorigenesis: (i) Cell Mutation, (ii) Cell Division

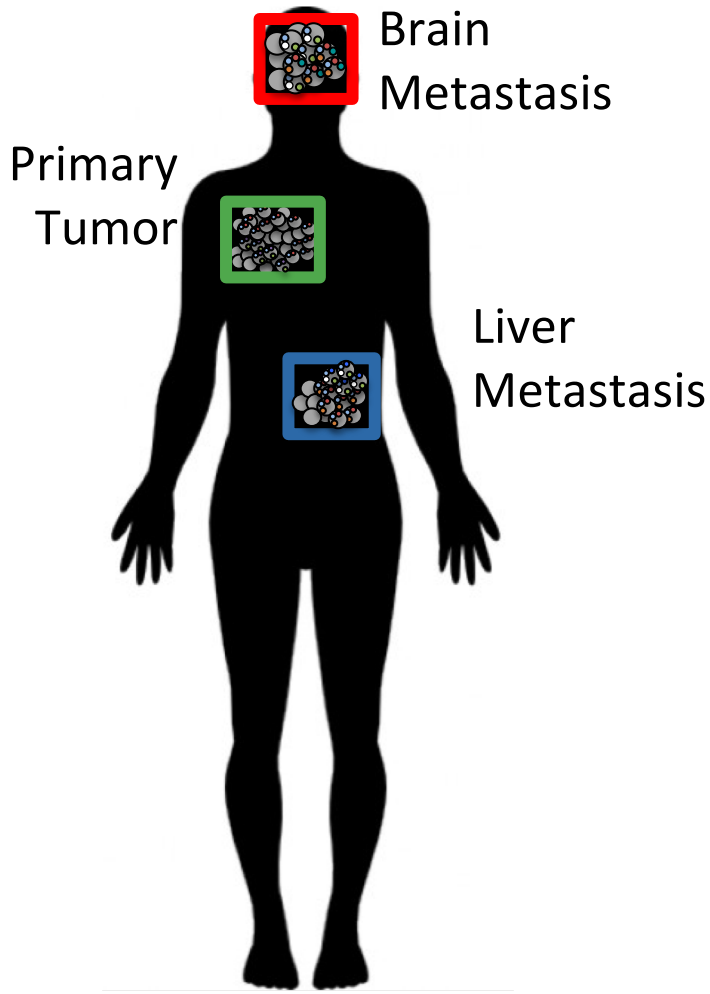
Clonal Theory of Cancer
[Nowell, 1976]



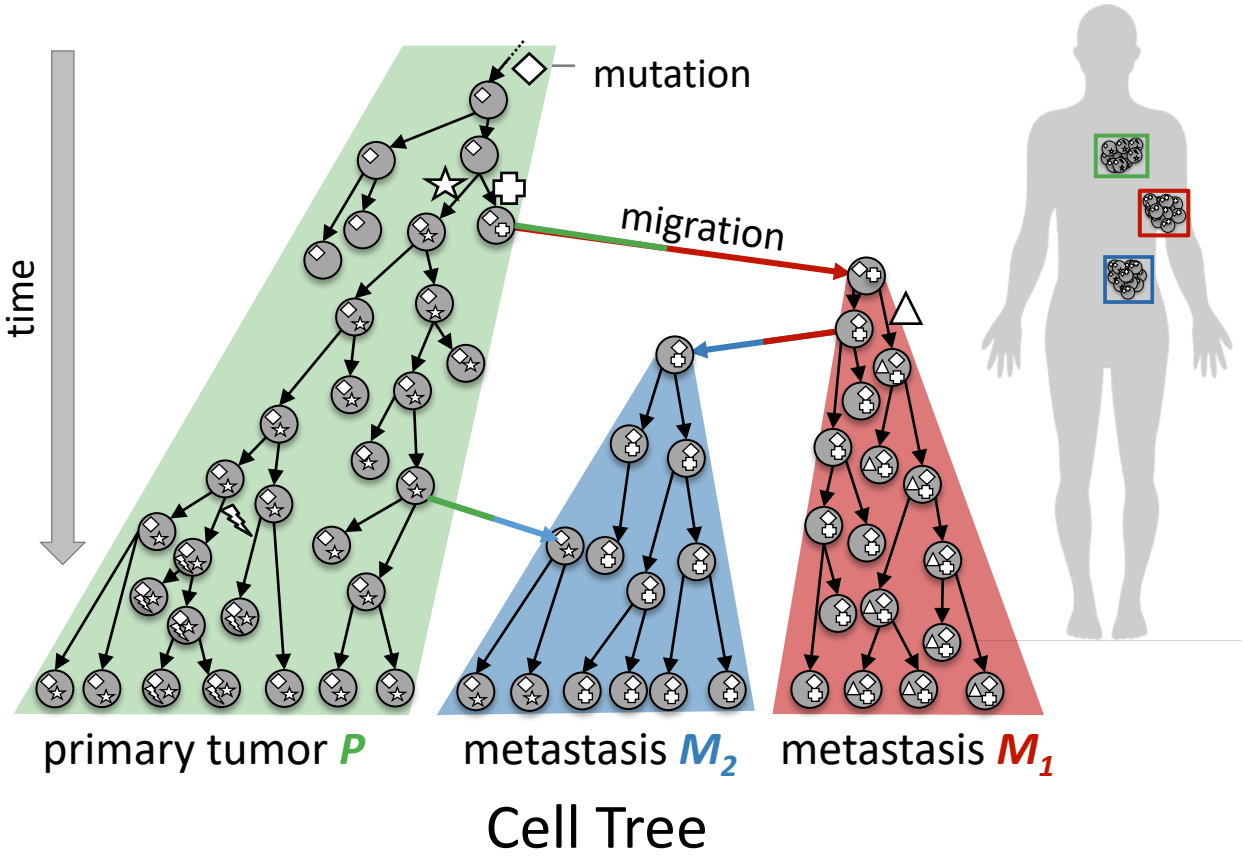
Heterogeneous Tumor

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



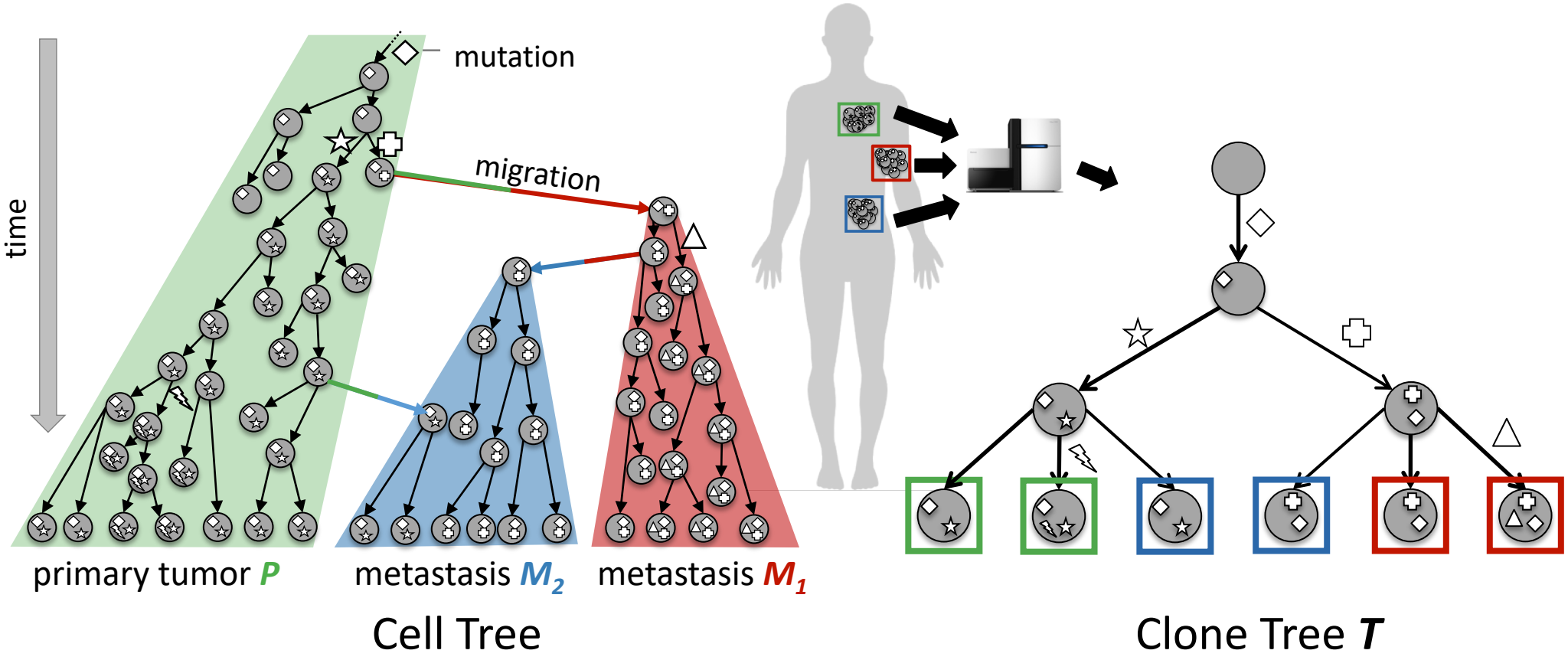


Mathematical Model for Cell Division, Mutation & Migration

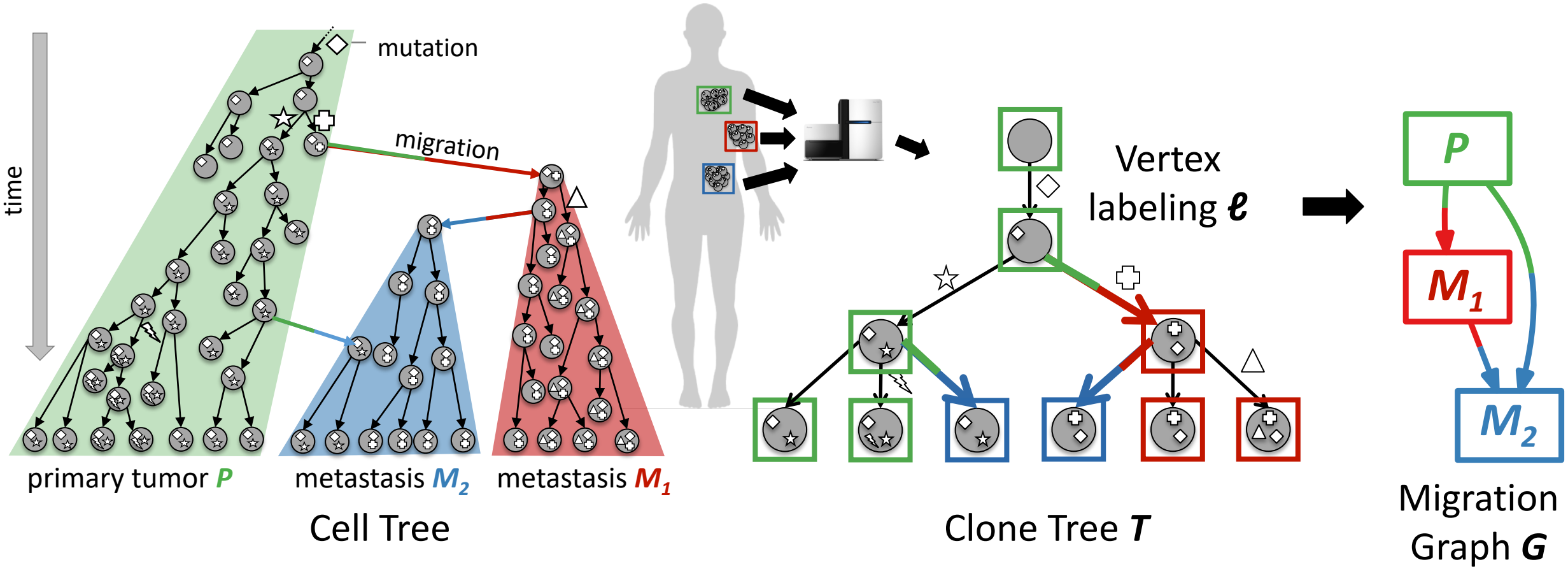


Cell Tree

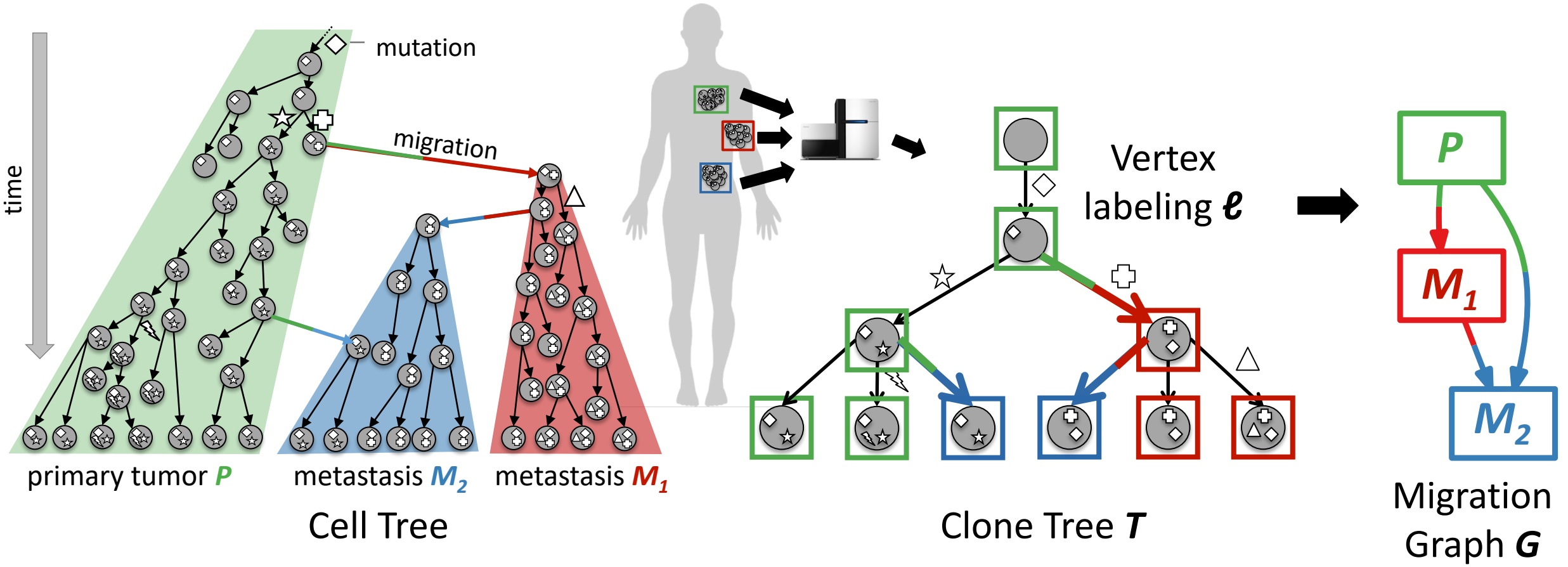
Mathematical Model for Cell Division, Mutation & Migration



Mathematical Model for Cell Division, Mutation & Migration



Mathematical Model for Cell Division, Mutation & Migration

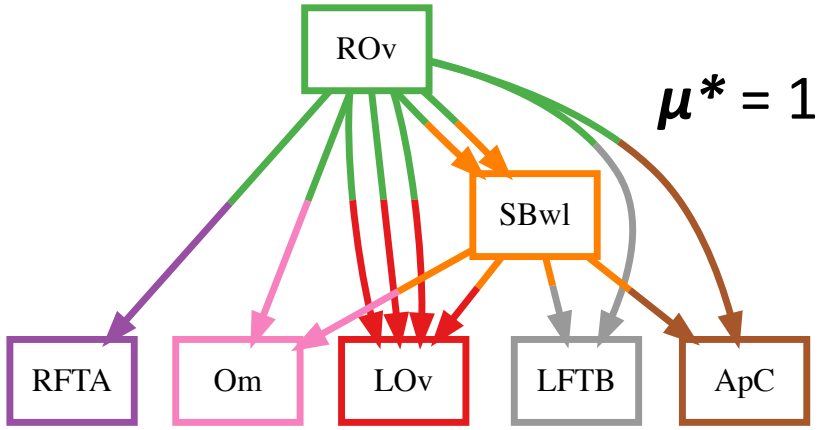


Goal: Given clone tree ***T***, find ***parsimonious*** vertex labeling ℓ with fewest migrations

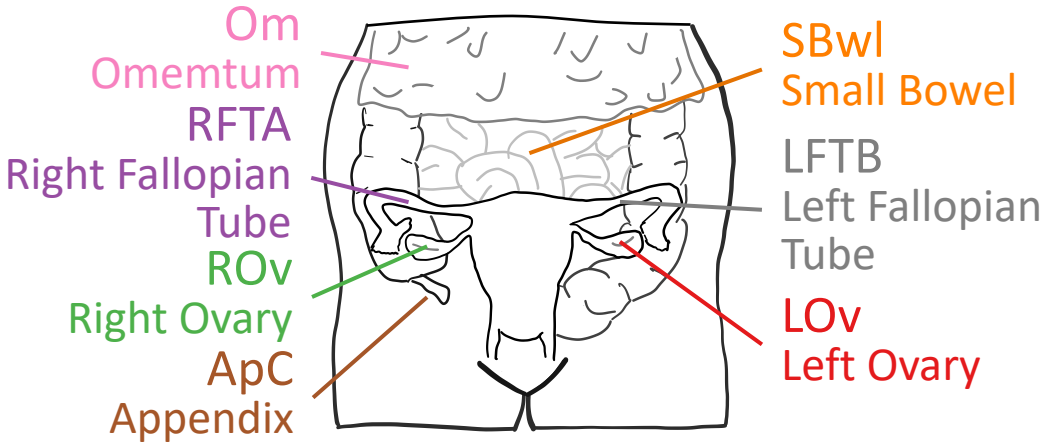
Minimum Migration Analysis in Ovarian Cancer

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

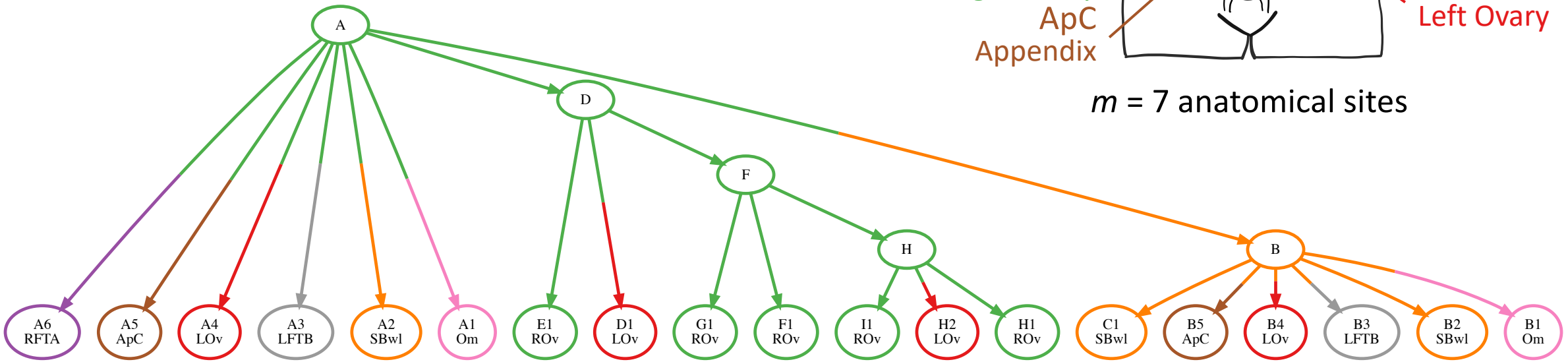
- Instance of the maximum parsimony small phylogeny problem [Fitch, 1971; Sankoff, 1975]



$\mu^* = 13$



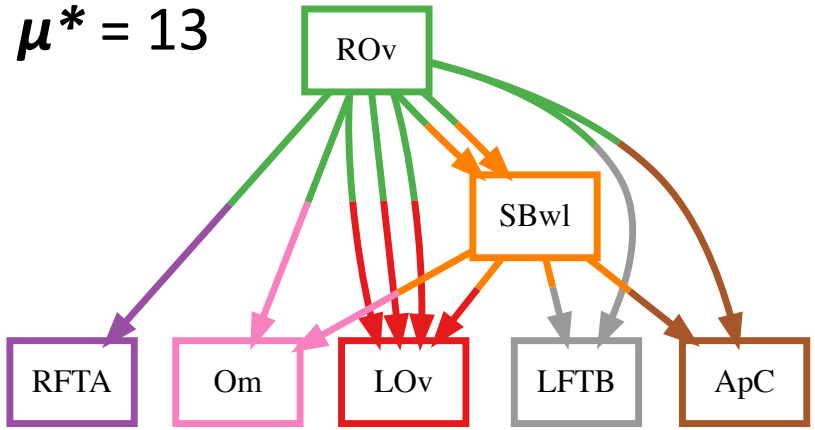
m = 7 anatomical sites



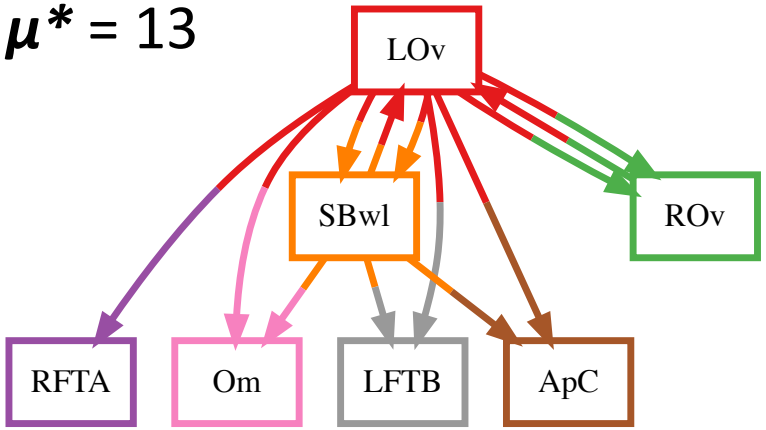
Minimum Migration History is ***Not*** Unique

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

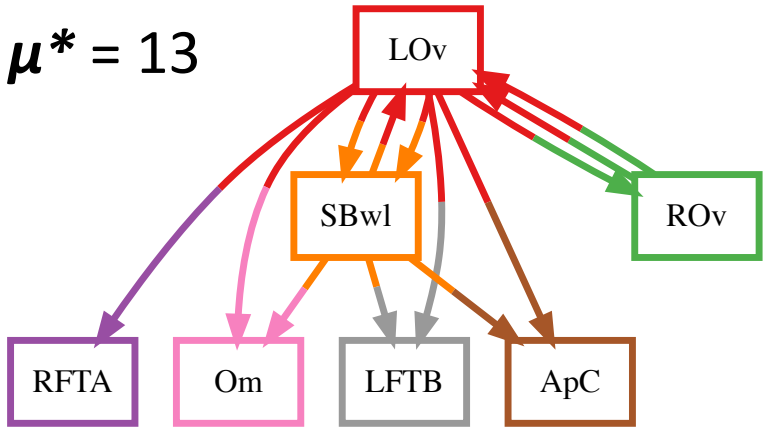
$\mu^* = 13$



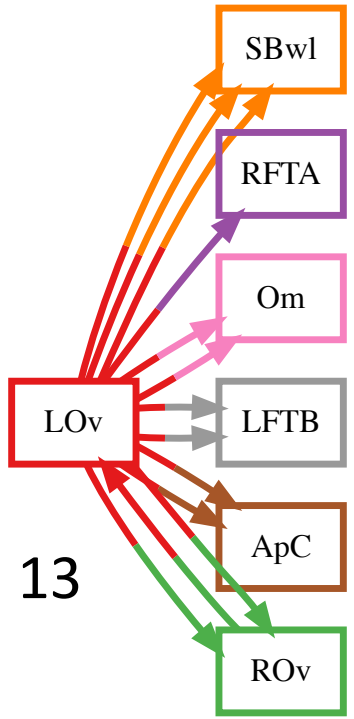
$\mu^* = 13$



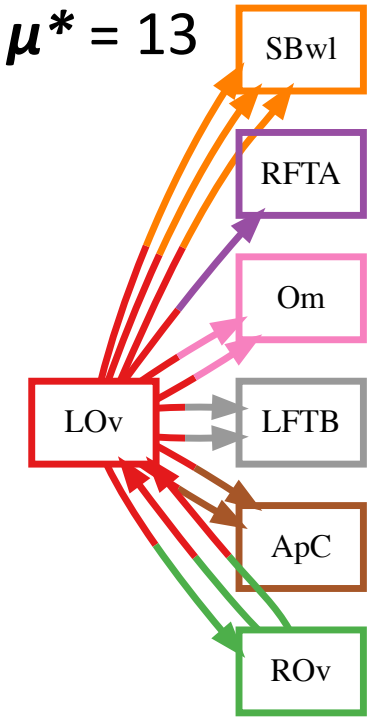
$\mu^* = 13$



$\mu^* = 13$



$\mu^* = 13$



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

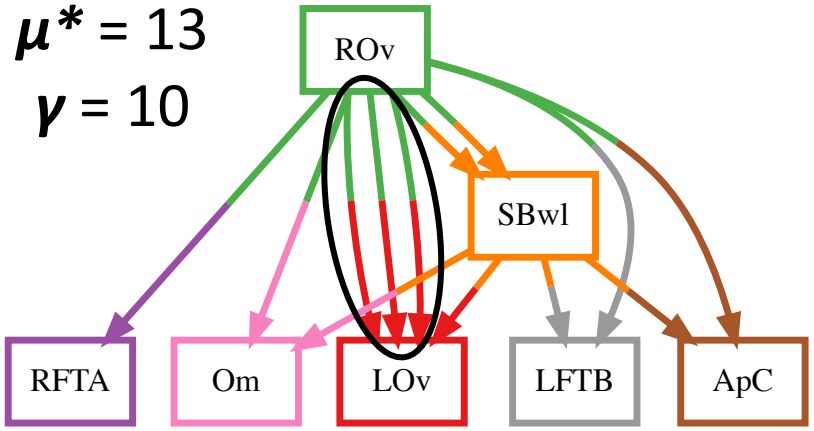
Comigrations: Simultaneous Migrations of Multiple Clones

- 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 †

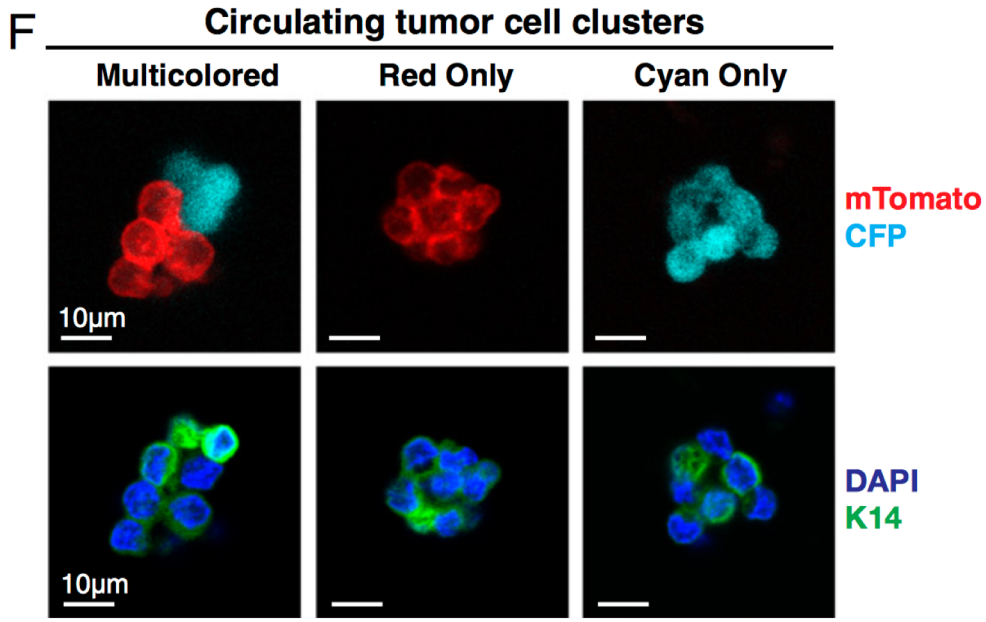
† Not necessarily true in the case of directed cycles

$\mu^* = 13$

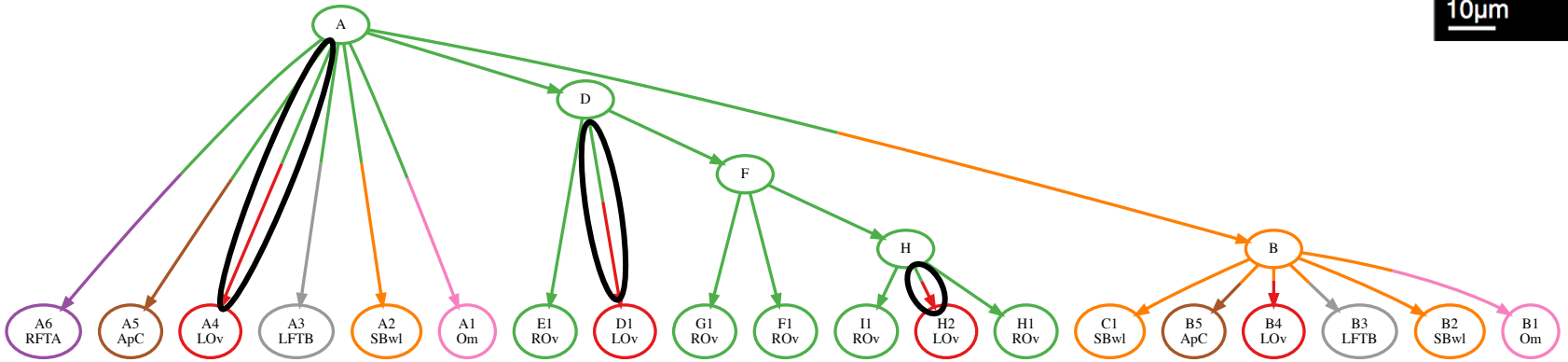
$\gamma = 10$



Migration Graph G



Clone Tree T



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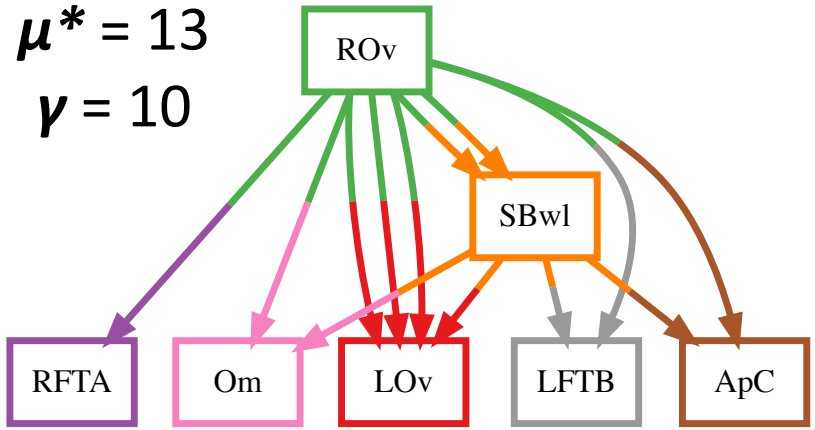
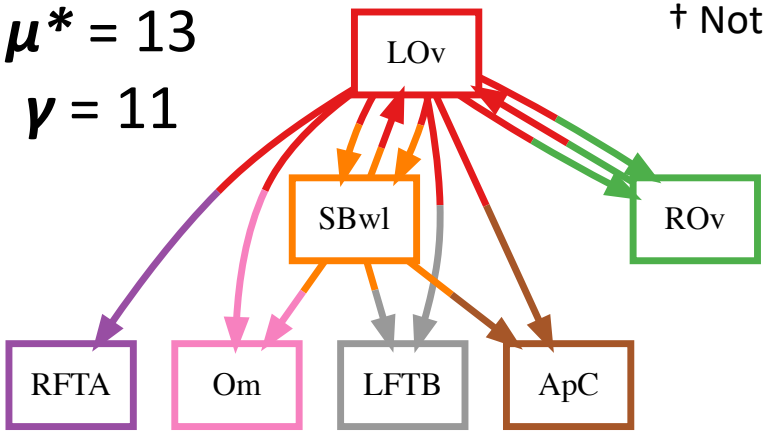
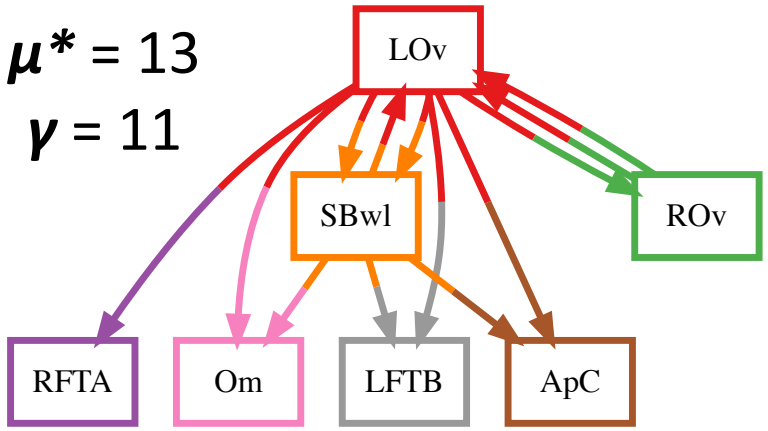
$\mu^* = 13$
$\gamma = 10$



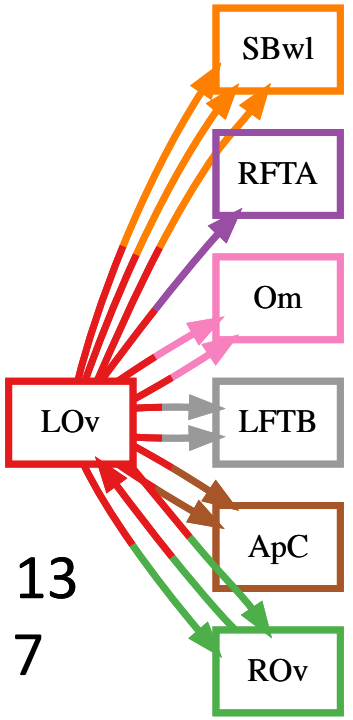
$\mu^* = 13$
$\gamma = 11$



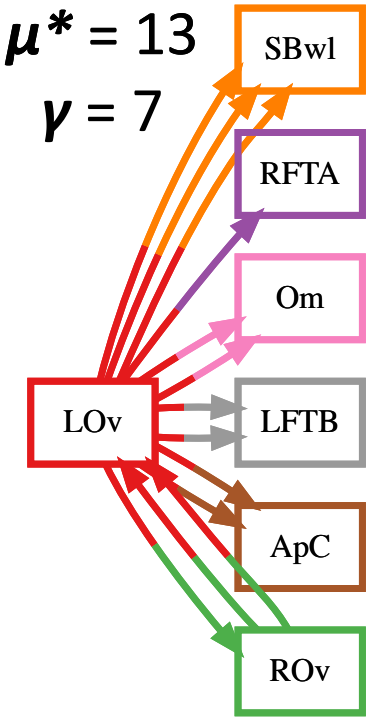
$\mu^* = 13$
$\gamma = 11$



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



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



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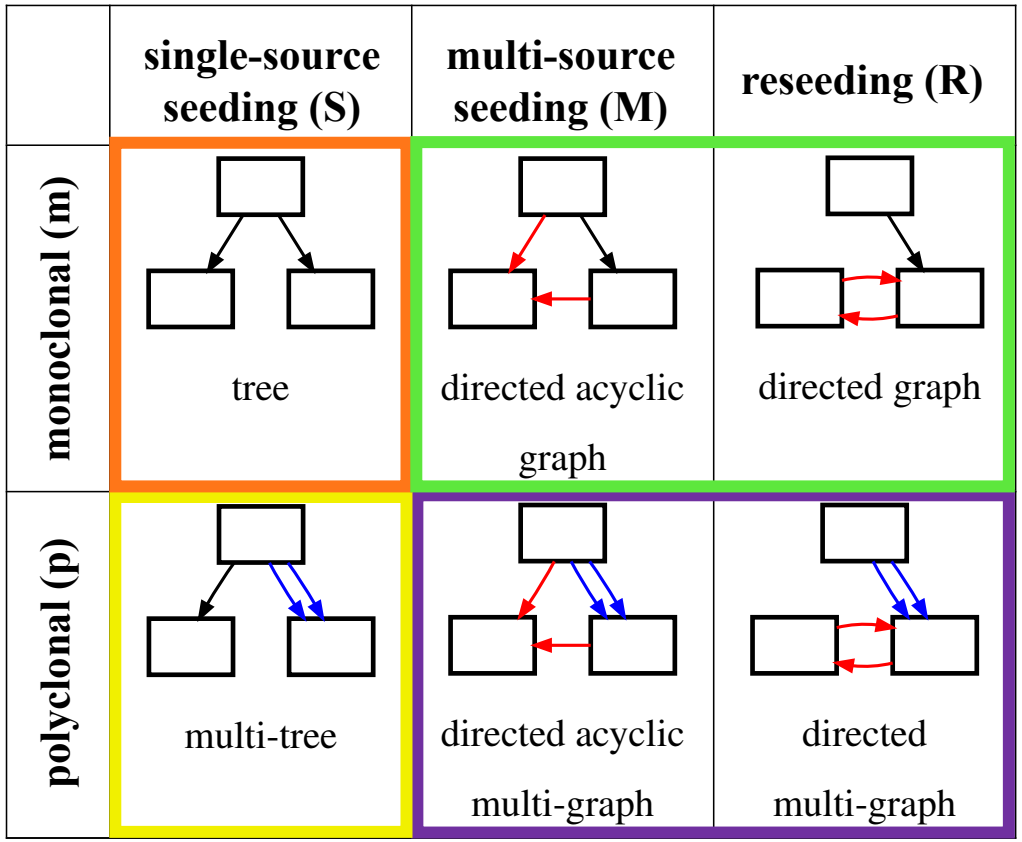
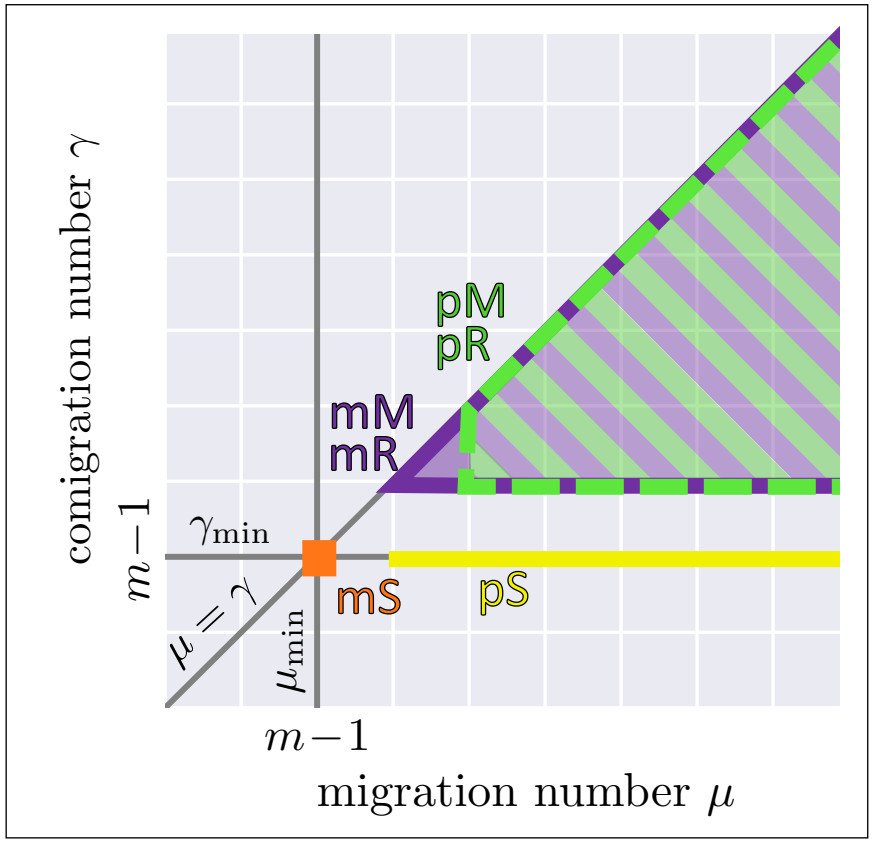
Tradeoffs between Migrations, Comigrations and Migration Pattern

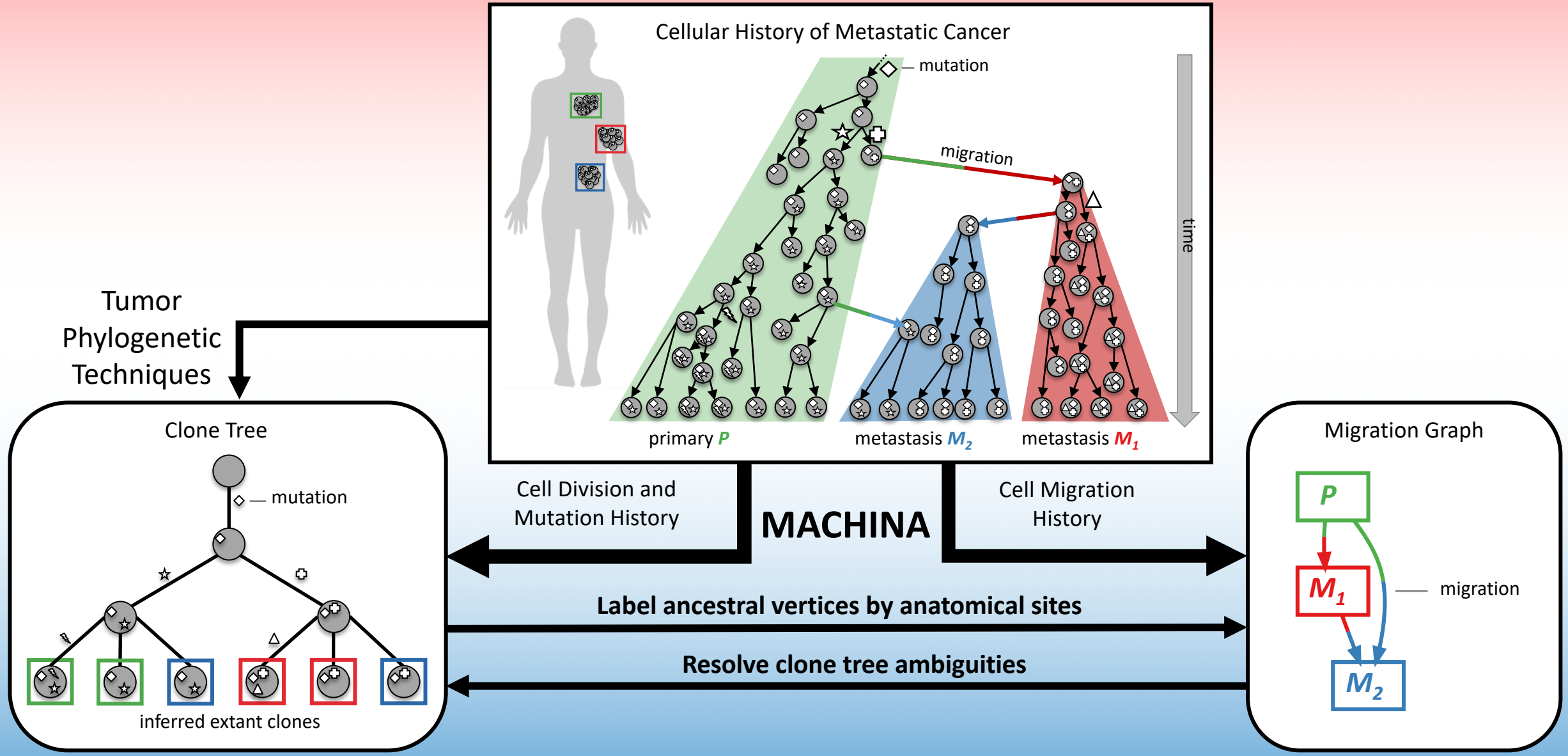




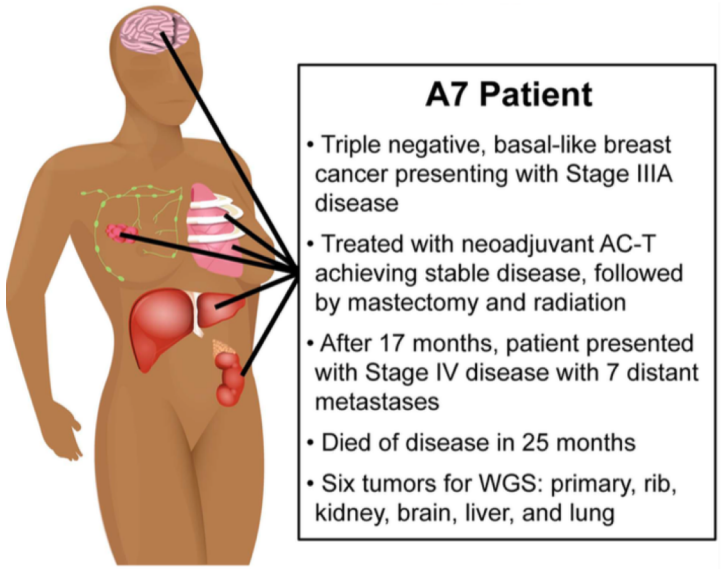
Parsimonious Migration History (PMH): Given a clone tree T and a set $\mathcal{P}$ of allowed migration patterns, find vertex labeling ℓ with minimum migration number $\mu^*(T)$ and smallest comigration number $\hat{\gamma}(T)$.

PMH is NP-hard
[El-Kebir, WABI 2018]

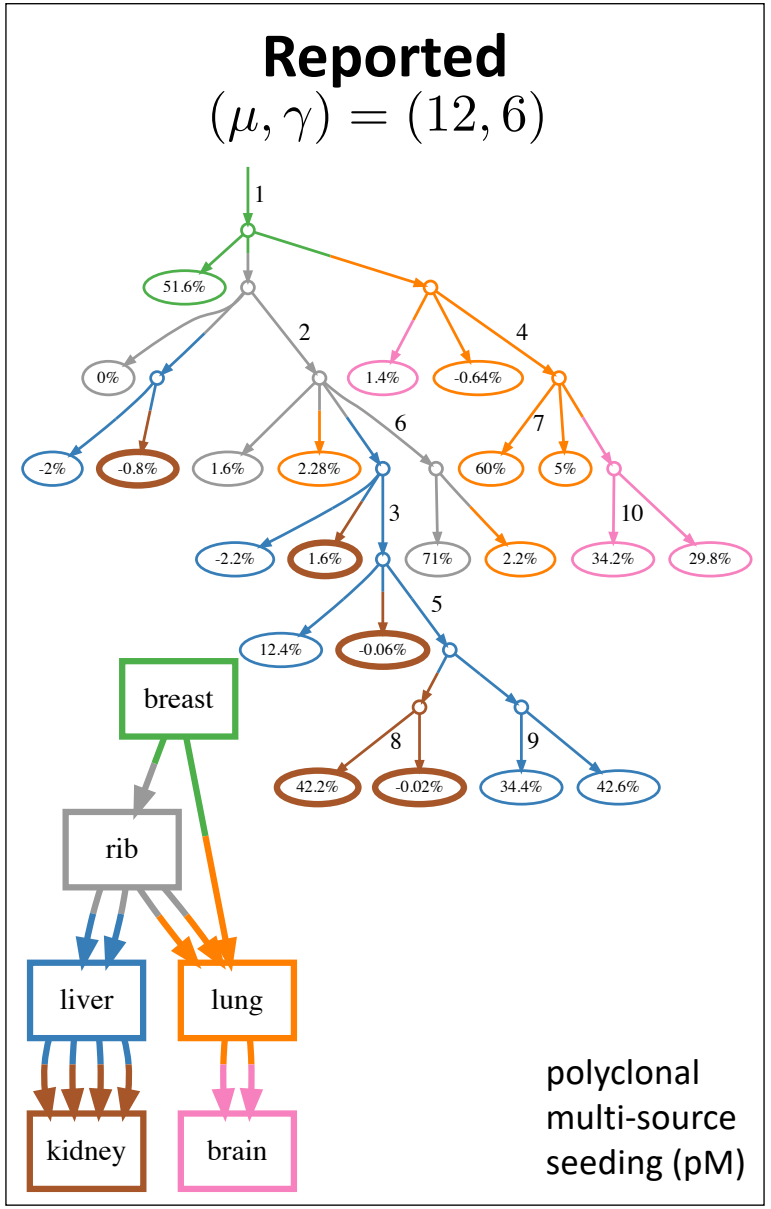
MACHINA: Joint Clone Tree and Migration History Inference

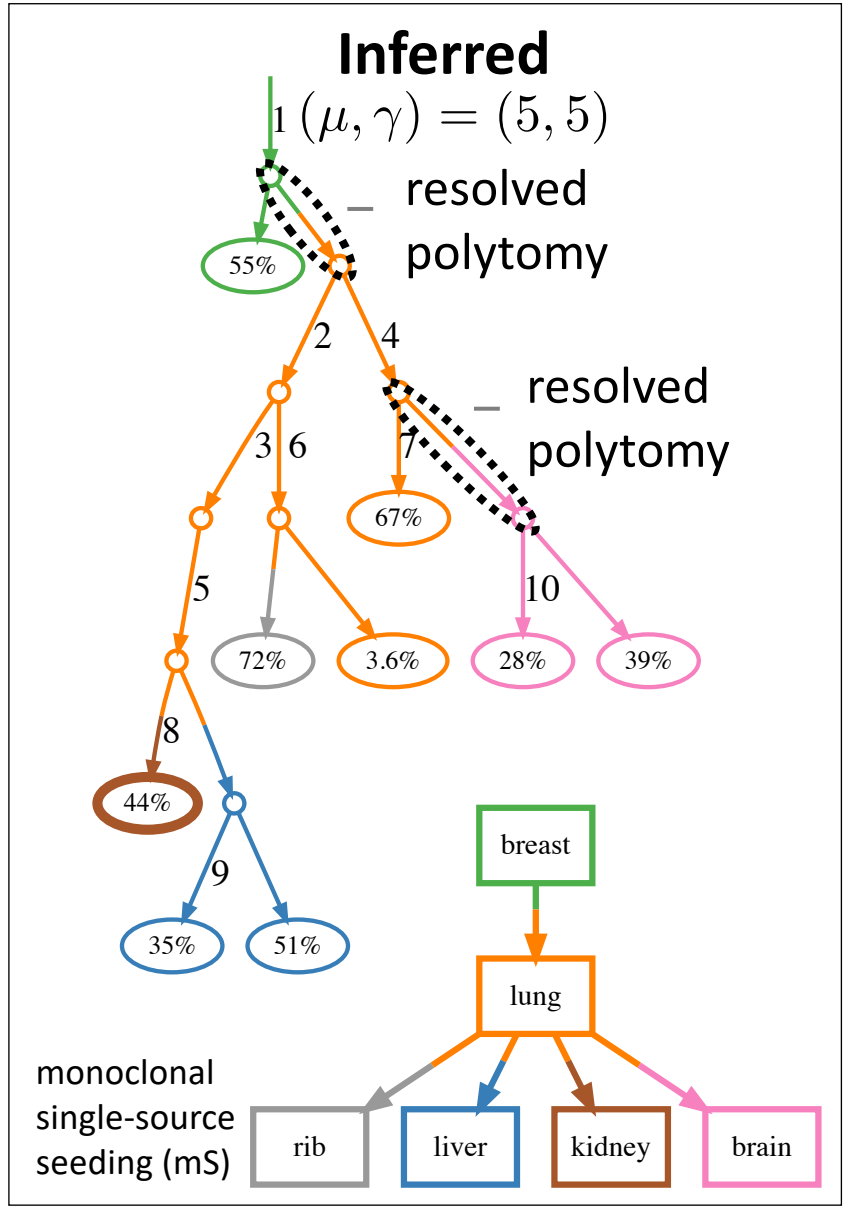


Applying MACHINA to Metastatic Breast Cancer



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





Conclusions & Acknowledgments

Poster #B-845

- Migration history not determined by migration number
- Group of cells from distinct clones may comigrate
- Tradeoff between migrations, comigrations and migration pattern
- MACHINA: algorithm for joint clone tree and migration history inference from bulk DNA sequencing data

https://github.com/raphael-group/machina

Research Group

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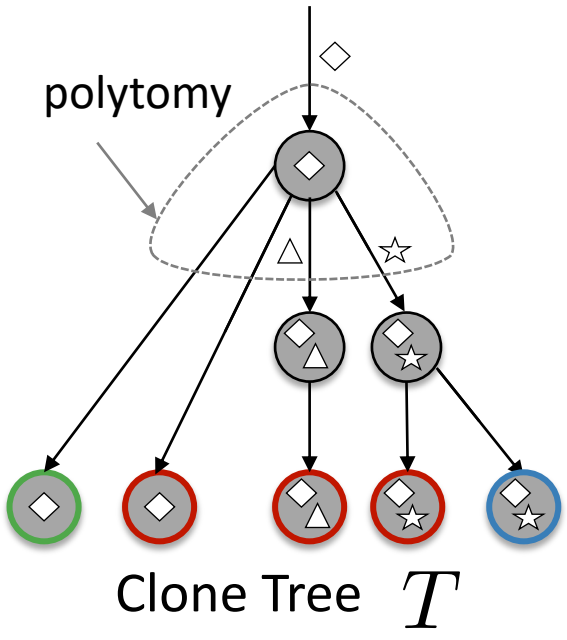
Funding

El-Kebir, M., Satas, G., & Raphael, B. J. (2018). Inferring parsimonious migration histories for metastatic cancers. *Nature Genetics*, *50*(5), 718–726. http://doi.org/10.1038/s41588-018-0106-z

Resolving Clone Tree Ambiguities

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

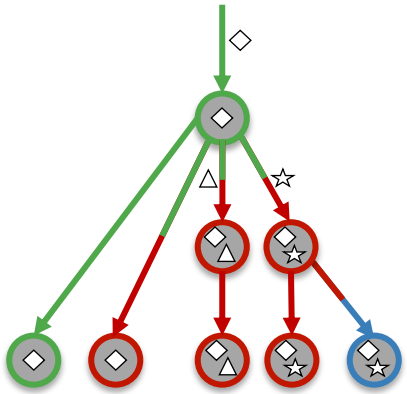


Clone Tree T

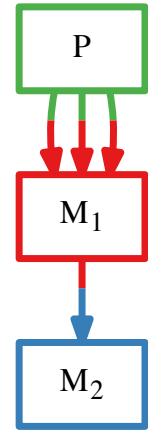
PMH

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

PMH-TR

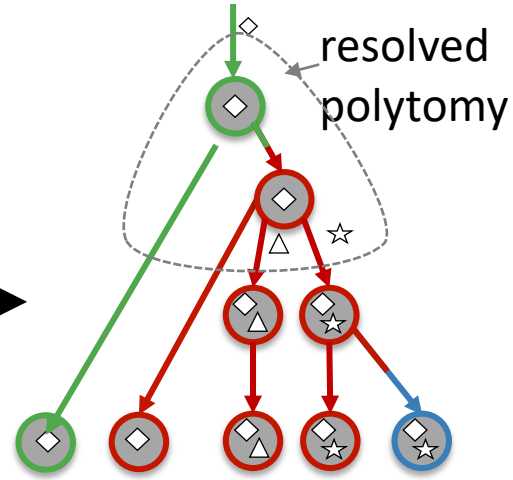


polyclonal single source seeding (pS)

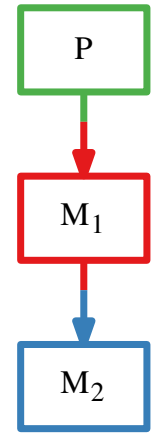


$\mu = 4$

$\gamma = 2$



monoclonal single source seeding (mS)



$\mu = 2$

$\gamma = 2$

Parsimonious Migration History with Tree Refinement (PMH-TR): Given a clone tree T and a set $\mathcal{P}$ of allowed migration patterns, find a refinement T' of T and vertex labeling ℓ of T' with the minimum migration number $\mu^*(T')$, and subsequently smallest comigration number $\hat{\gamma}(T')$.

MACHINA accurately infers clone trees and migration histories on simulated data