Phylogenies Derived from Matched Transcriptome in Breast Cancer Brain Metastases

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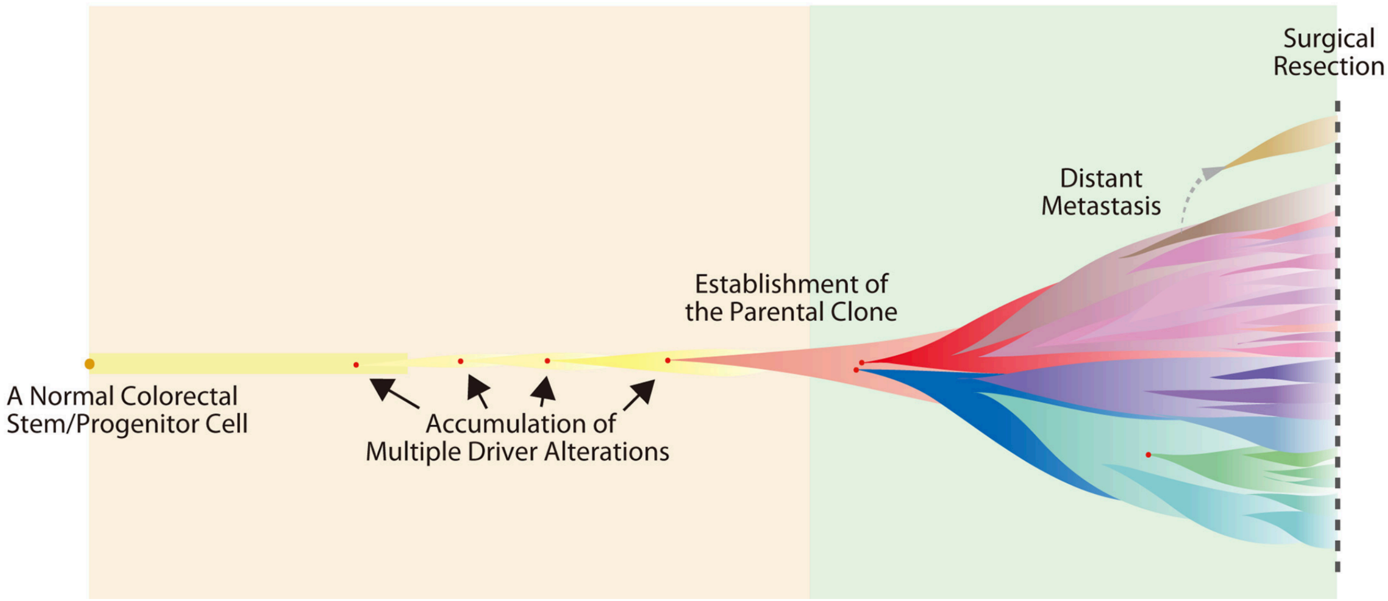
Background: Cancer Progression

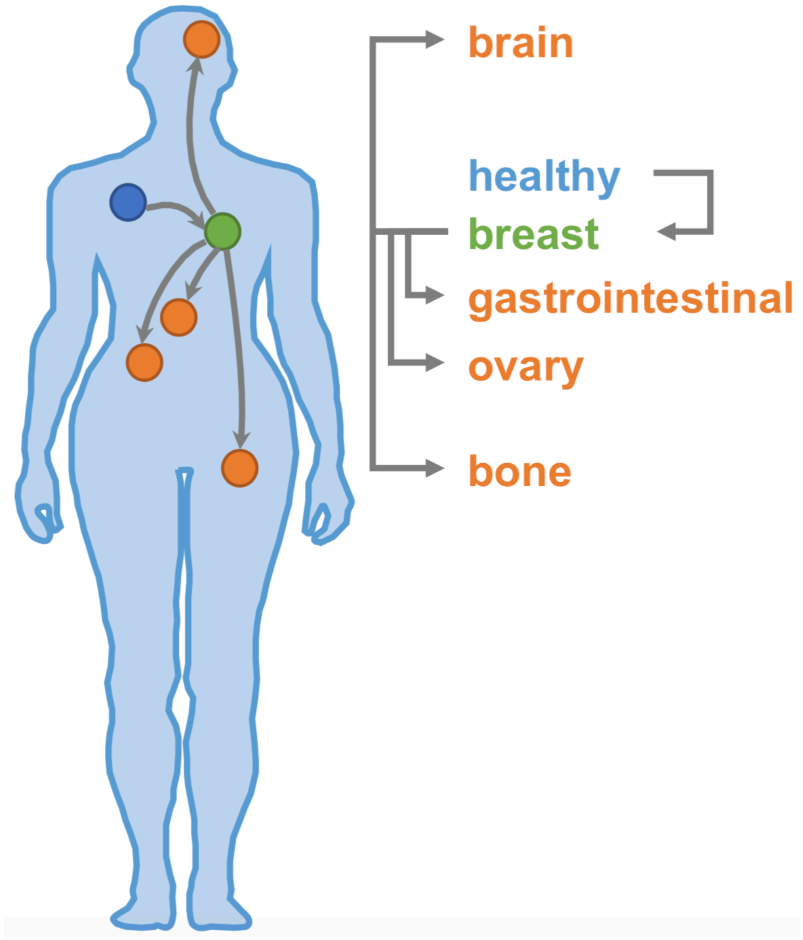


[Uchi, R. et al., *PLOS Genetics*. 2016]

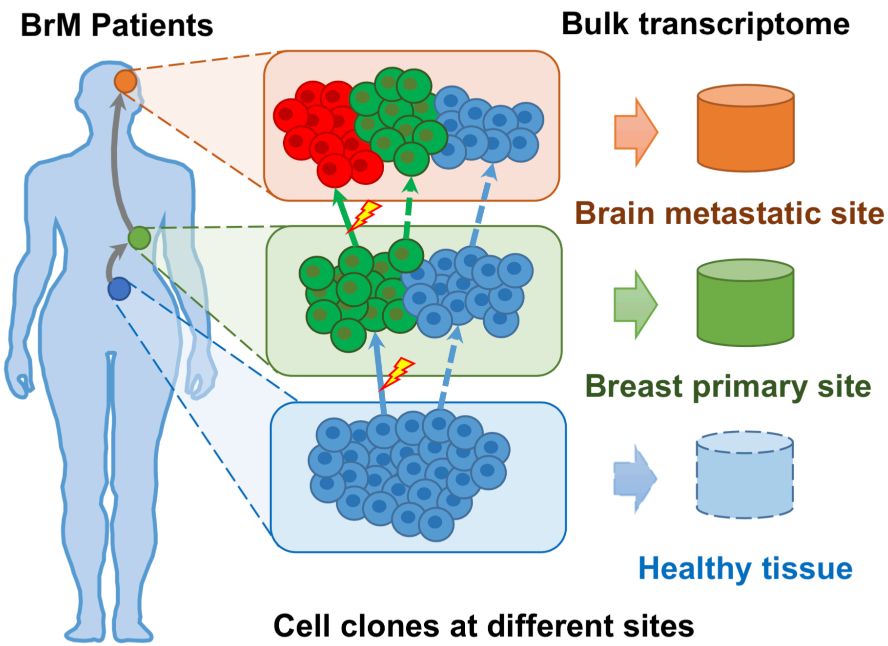
- Cancer: mainly caused by accumulated somatic alterations
- Tumor cells: heterogeneous populations/clones
- Tumor phylogeny: tumor cells follow a clonal evolution
- Metastasis: transfer from primary site to other sites
- Cell communities vs. cell clones

Background: Breast Cancer Metastasis

- Breast cancer: 2nd common cause of death from cancer in women
- Metastatic breast cancer
  - Causes majority of those deaths
  - Limited viable treatment options
  - Early detection is important
- Mechanism of tumor progression/evolution during metastasis?



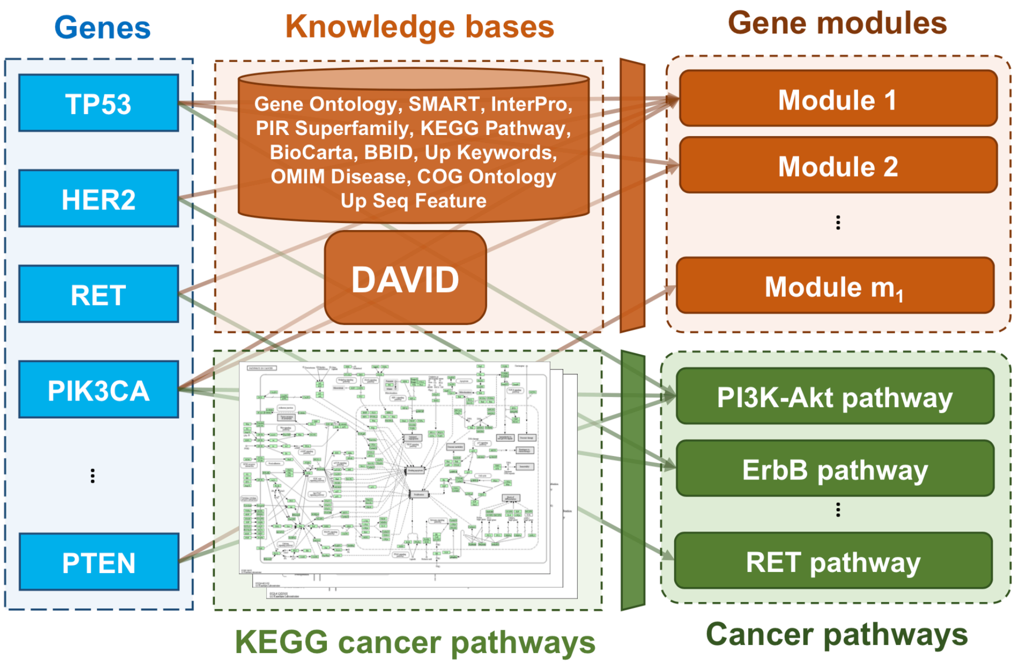
Tumor Evolution Derived from Match Bulk Transcriptome



[Vareslija, D. et al., *Journal of the National Cancer Institute*. 2018]

- Given matched primary and metastatic bulk transcriptome:
  - Q1: How to cope with high-dim, noisy, and uninformative transcriptome?
  - Q2: What model and solver to unmix/deconvolve clones?
  - Q3: How to infer evolutionary trajectory and perturbed pathways/functions?
- Yes! We proposed a three-step pipeline.

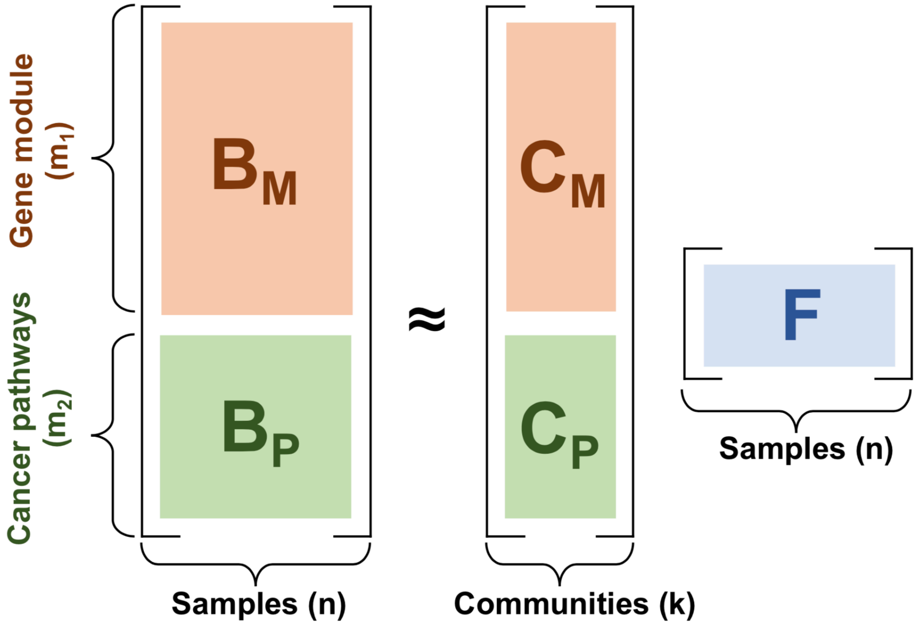
Step 1: Mapping to Gene Modules and Cancer Pathways



[Desmedt, C. et al., *Clinical Cancer Research*. 2008]

- Q1: How to cope with high-dim, noisy, and uninformative RNA?
  - Gene modules
    - Compress high dimensional and noisy data → accurate deconvolution
  - Cancer pathways
    - Markers/probes → interpretation purpose

Step 2: Deconvolution of Cell Communities



$$\min_{\mathbf{C},\mathbf{F}} \quad \|\mathbf{B} - \mathbf{CF}\|_{\mathrm{Fr}}^2 ,$$

$$\text{s.t.} \quad \mathbf{F}_{lj} \geq 0,$$

$$\sum_{l=1}^{k} \mathbf{F}_{lj} = 1$$

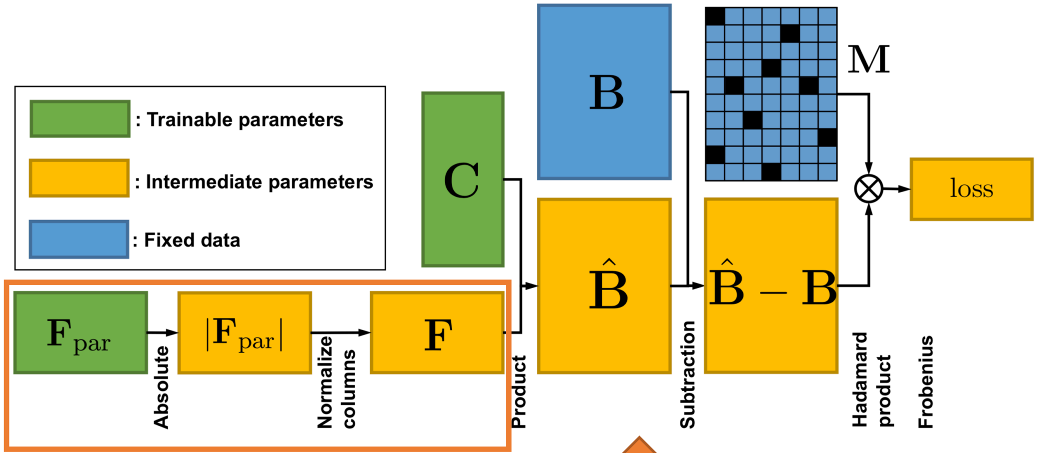
[Lee, D.D. et al., *NIPS*. 2000]

- Q2: What model to unmix/deconvolve clones?
  - Matrix factorization
  - C: expression profiles of communities
  - F: fractions of communities in samples
- However, it is non-convex and not trivial to solve…

Step 2: Deconvolution of Cell Communities

Gradient descent
by backpropagation

[Rumelhart, D.E. et al., *Nature*. 1986]



$$\min_{\mathbf{C},\mathbf{F}} \quad \|\mathbf{B} - \mathbf{CF}\|_{\mathrm{Fr}}^2 ,$$

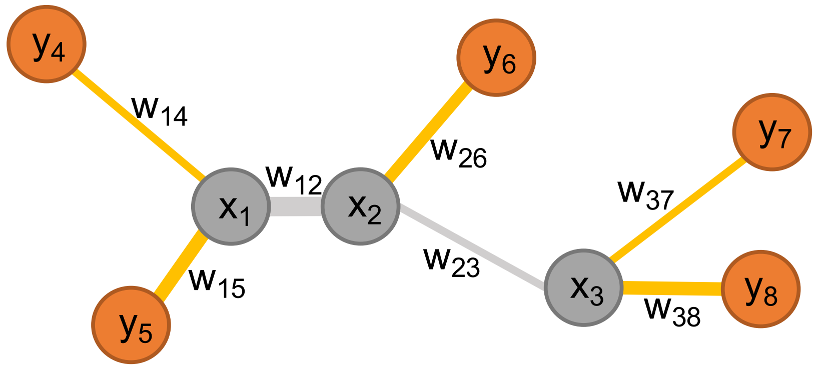
$$\text{s.t.} \quad \boxed{\begin{array}{l} \mathbf{F}_{lj} \geq 0, \\ \sum_{l=1}^{k} \mathbf{F}_{lj} = 1 \end{array}}$$

$$\min_{\mathbf{C},\mathbf{F}_{\mathrm{par}}} \quad \|\mathbf{B} - \mathbf{CF}\|_{\mathrm{Fr}}^2 ,$$

$$\text{s.t.} \quad \boxed{\mathbf{F} = \mathrm{cwn}\left(|\mathbf{F}_{\mathrm{par}}|\right)}$$

- Q2: What model and solver to unmix clones?
  - Neural network deconvolution (NND)
  - # components: trade-off of model complexity vs. sample size
    - Mask matrix for cross-validation in NND

Step 3: Inference of Phylogeny



$$\mathcal{G} = (\mathcal{V}, \mathcal{E})$$

[Nei, M. et al., *Molecular Biology and Evolution*. 1987]

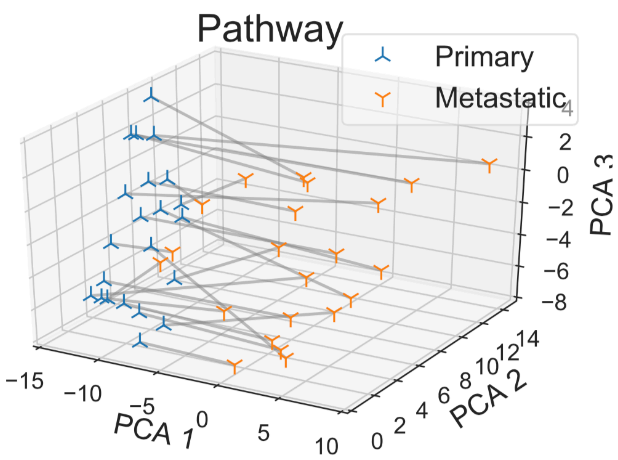
- Q3: How to infer evolutionary trajectory and perturbed pathways?
  - Phylogeny skeleton built using neighbor-joining algorithm
  - Pathway of Steiner nodes inferred by minimizing the elastic potential energy:

$$\min_{\mathbf{x}} \quad U(\mathbf{x}, \mathbf{y};\ \mathcal{W}) = \sum_{\substack{(u,v)\in\mathcal{E} \\ v\leq k-2}} \frac{1}{2} w_{uv}(x_u - x_v)^2 + \sum_{\substack{(u,v)\in\mathcal{E} \\ v\geq k-1}} \frac{1}{2} w_{uv}(x_u - y_v)^2$$

$$\Updownarrow$$

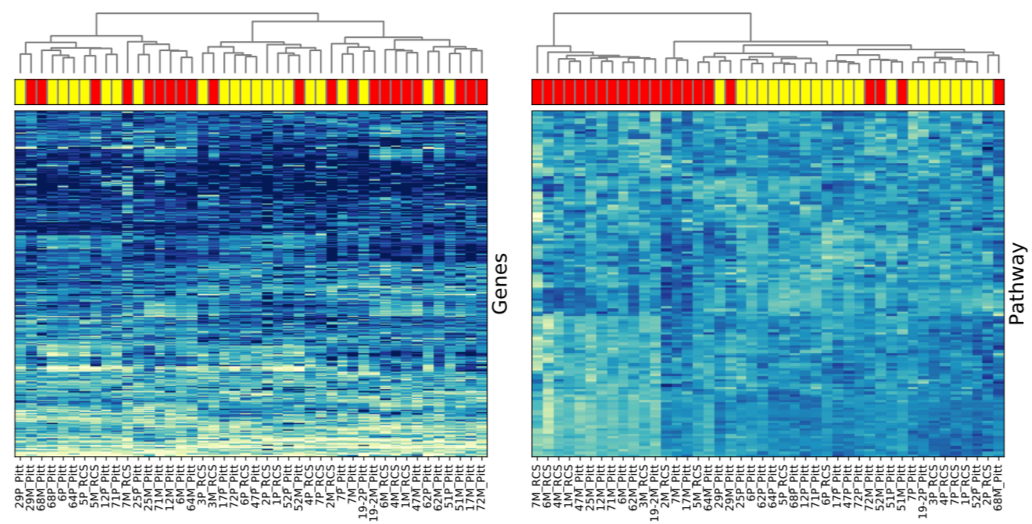
$$\min_{\mathbf{x}} \quad \frac{1}{2}\mathbf{x}^\intercal \mathbf{P}(\mathcal{W})\mathbf{x} + \mathbf{q}(\mathcal{W}, \mathbf{y})^\intercal \mathbf{x}$$

Effective Pathway Representation



Gene expression z_{MSD}=-2.6

Pathway z_{MSD}=-13.4

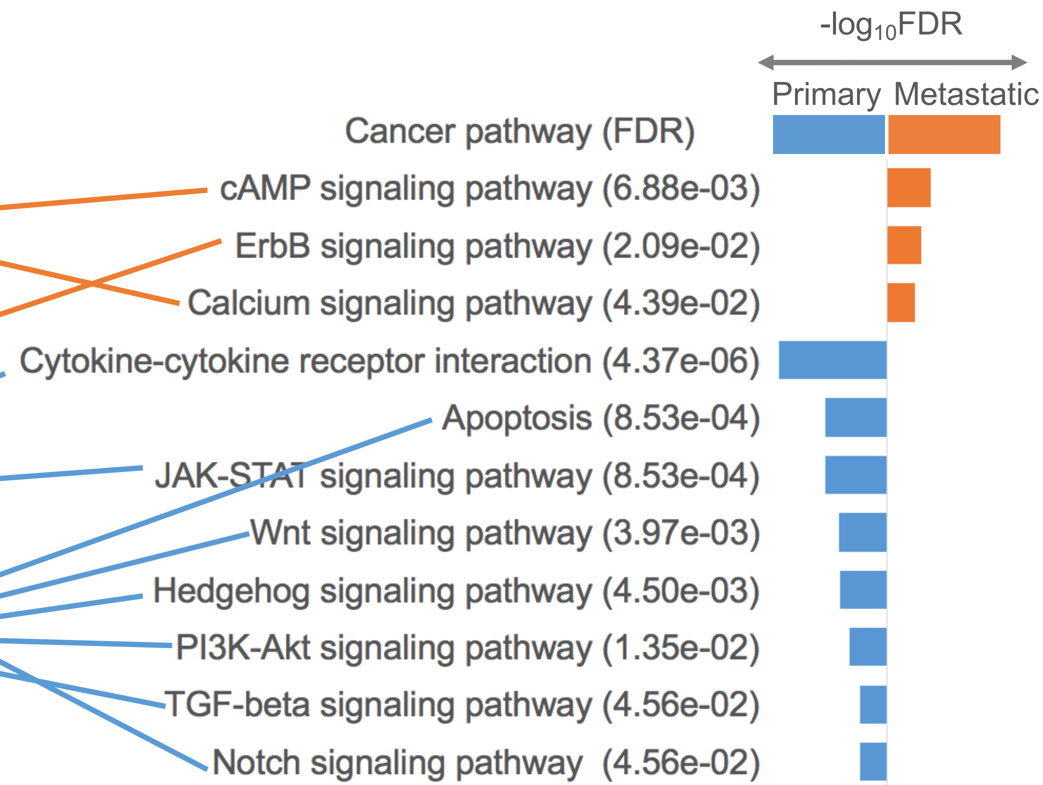


[Park, Y. et al., *Transactions on Computational Biology and Bioinformatics*. 2009]

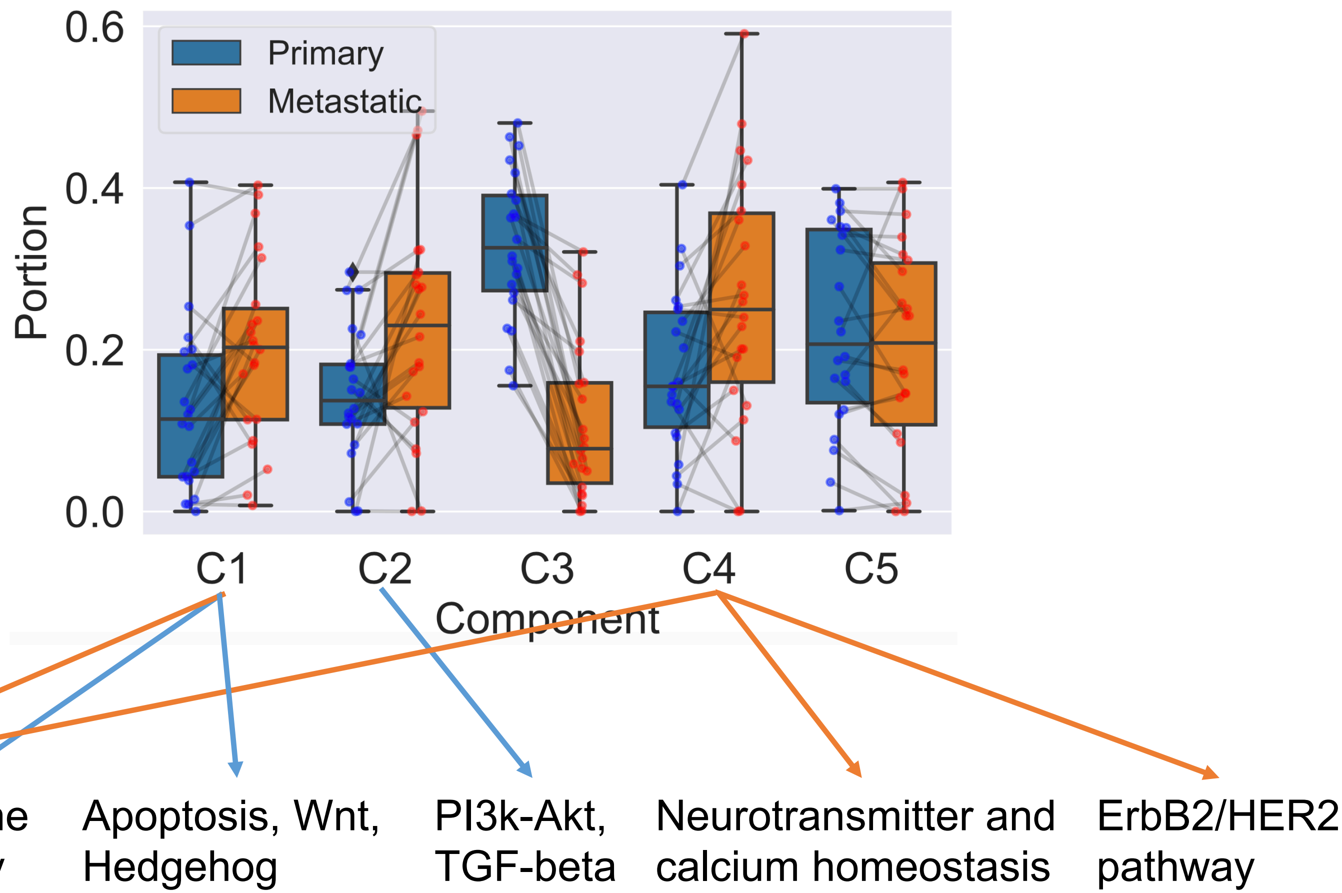
- PC1: recurrent feature between primary and metastatic samples
- PC2+PC3: variability between patients
- Effective in separating primary tumors from metastatic tumors

Differentially Expressed Cancer Pathways

- Neurotransmitter and calcium homeostasis
- ErbB2/HER2 pathway
- Immune activity
- Dysregulation promotes tumor growth

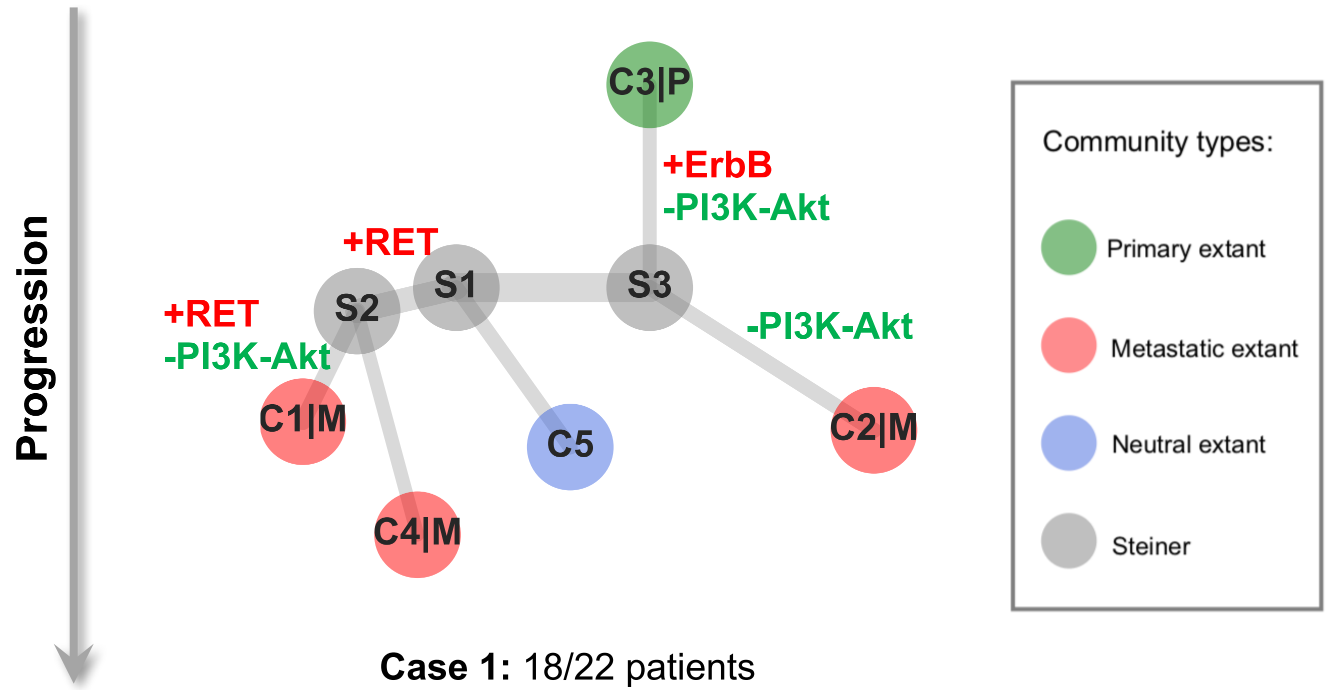


Landscape of Cell Communities



- The deconvolution provides more fine-grained landscape of tumor cell communities

Phylogenies of Cell Communities



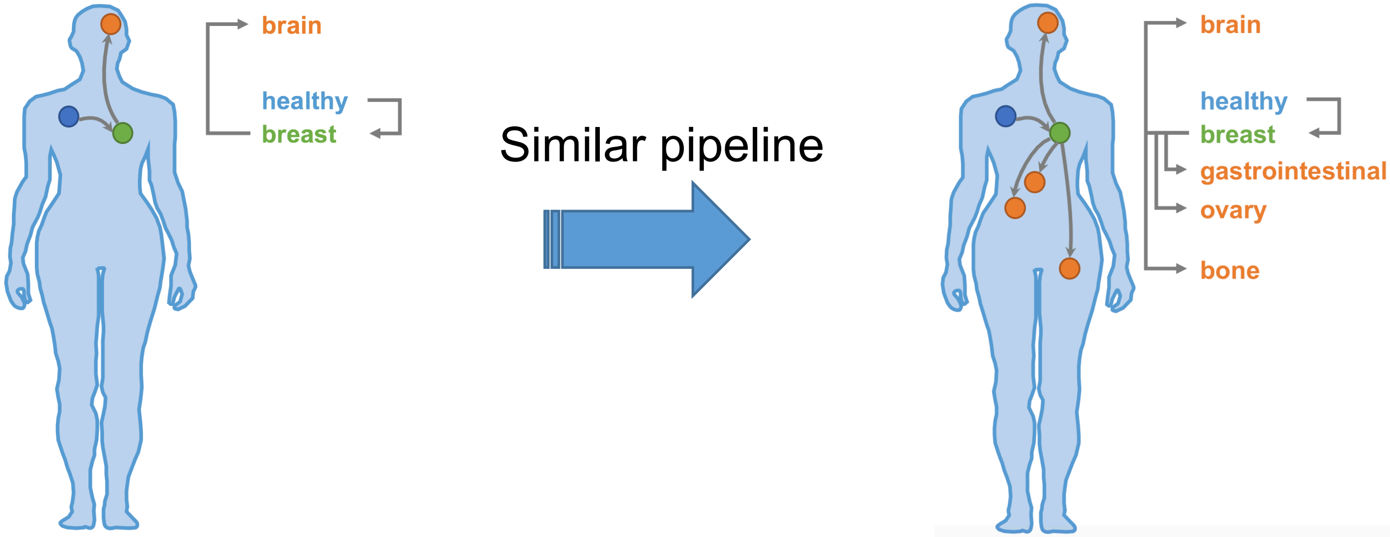
Case 1: 18/22 patients

- Common temporal order of perturbed pathways during metastasis
  - Gained ErbB caused by early events
  - Expansion of minor clonal populations with lost PI3K-Akt and gained RET

Conclusion and Future Work

- Conclusion
  - Pipeline to infer tumor evolution using matched bulk transcriptome
  - Common temporal order of perturbed pathways in breast cancer brain metastases
- Open source code, data and supp:

  https://github.com/CMUSchwartzLab/BrM-Phylo
- Further exploration: multiple metastatic sites



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○ Authors

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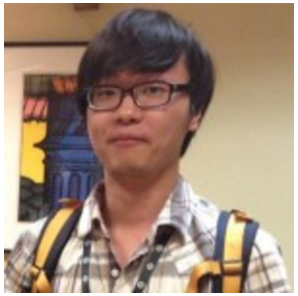

Haoyun Lei

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