Robust and Accurate Deconvolution of Tumor Populations Uncovers Evolutionary Mechanisms of Breast Cancer Metastasis

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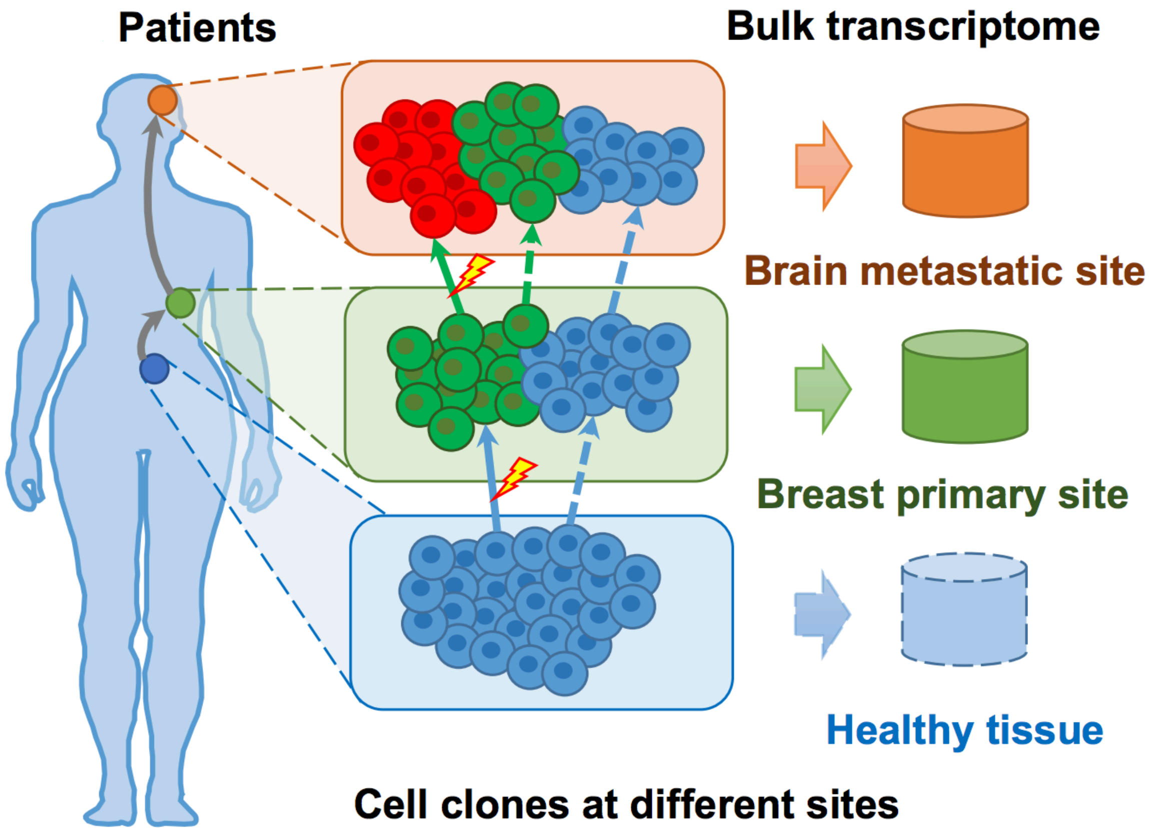
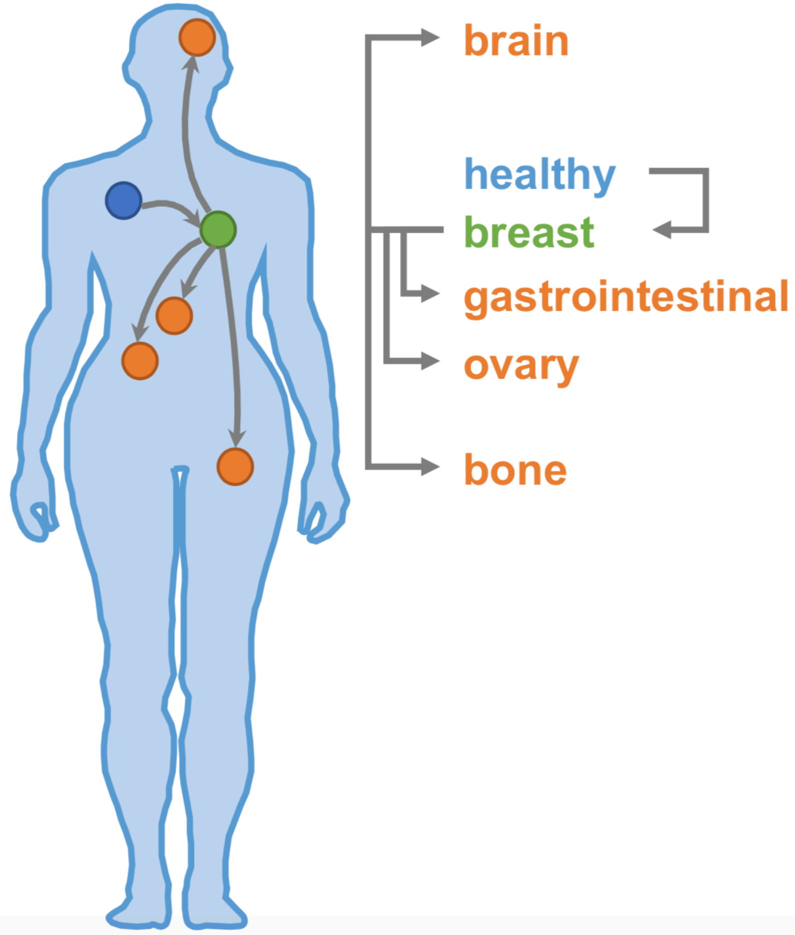
Background: cancer progression and metastasis

- Tumor phylogeny: tumor cells follow a clonal evolution process
- Metastasis: transfer from primary site to other sites
- Heterogeneous tumor populations/clones even from same tissue



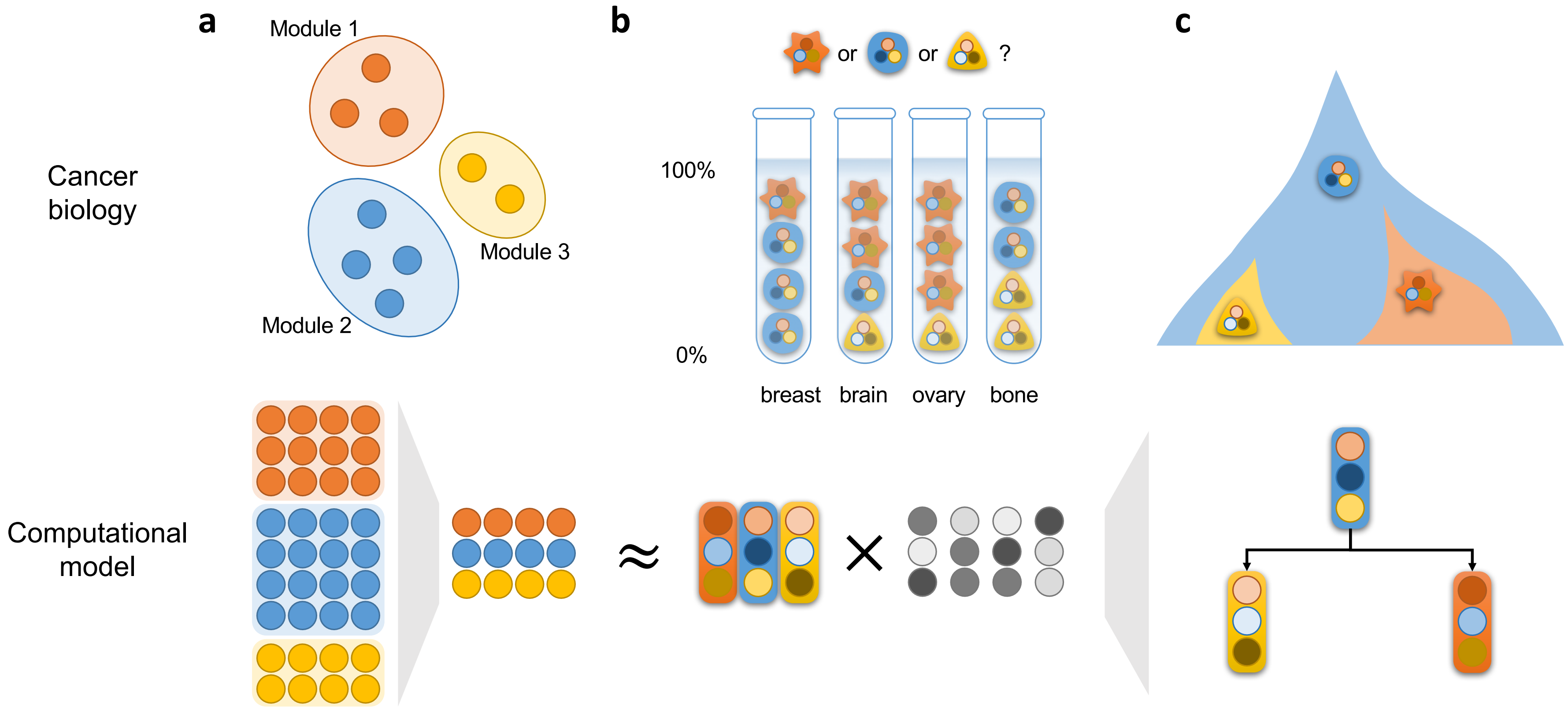
Background: breast cancer metastasis and bulk data

- Breast cancer: second common cause of death from cancer in women
- Breast cancer metastasis (BrM) causes majority of those deaths
- Mechanism of tumor progression during metastasis relies on phylogenetic analysis
- scRNA rarely available due to years between sample collection
- Robust and accurate deconvolution (RAD) of bulk tumor samples is essential



Approach: evolution inference of BrM from bulk RNA

- To boost RAD: knowledge-based gene module (DAVID; DW Huang et al. 2009)
- Core of RAD: bulk sample deconvolution
- Based on RAD-unmixed populations: phylogeny inference (MEP; Tao et al. 2019)

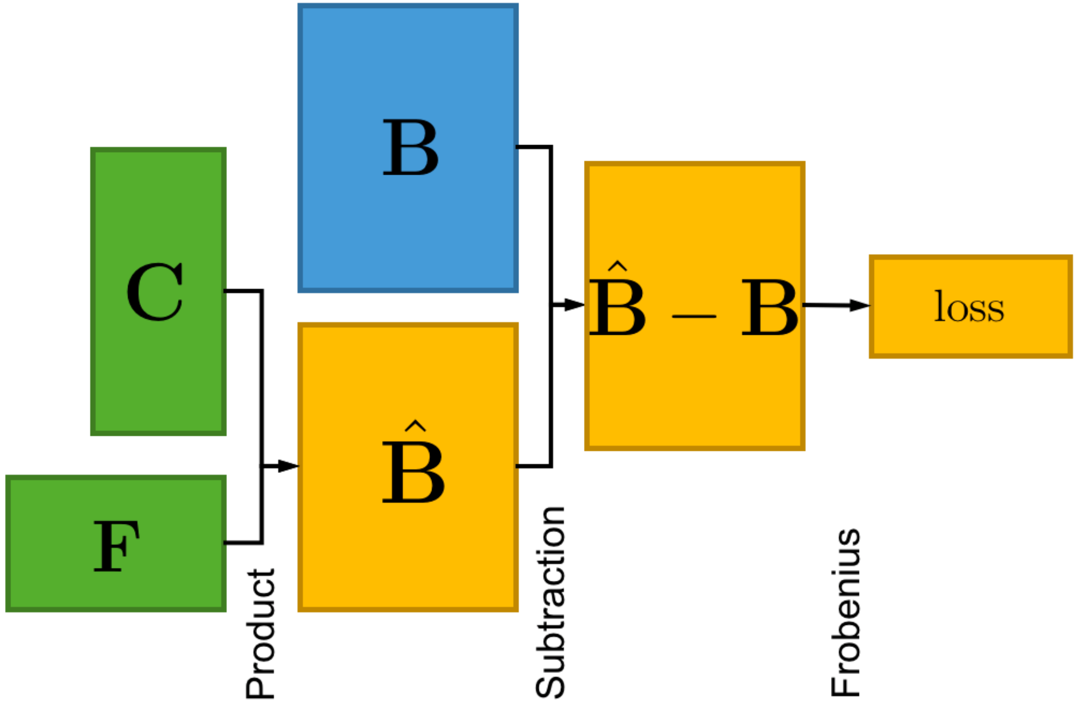


RAD formulation: biologically inspired NMF

- RAD formulated as non-negative matrix factorization (NMF)
  - B: bulk RNA of samples; C: RNA of populations; F: fractions of populations
  - Data noisy and correlated → gene module compression
  - Non-convex and no efficient optimizer → RAD three-phase optimizer
  - *k* not known in prior → cross-validation

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

$$\begin{aligned} \text{s.t.} \quad & \mathbf{C}_{il} \geq 0, \quad i=1,\ldots,m,\ l=1,\ldots,k, \\ & \mathbf{F}_{lj} \geq 0, \quad l=1,\ldots,k,\ j=1,\ldots,n, \\ & \textstyle\sum_{l=1}^{k} \mathbf{F}_{lj} = 1, \qquad j=1,\ldots,n \end{aligned}$$



RAD phase 1: multiplicative update warm-start

- Revised multiplicative update (MU) rules
  - Loop until objective stops decreasing

$$\mathbf{C} \leftarrow \mathbf{C} \odot (\mathbf{B}\mathbf{F}^{\intercal}) \oslash (\mathbf{C}\mathbf{F}\mathbf{F}^{\intercal})\,,$$

$$\mathbf{F} \leftarrow \mathbf{F} \odot (\mathbf{C}^{\intercal}\mathbf{B}) \oslash (\mathbf{C}^{\intercal}\mathbf{C}\mathbf{F})\,,$$

$$\boxed{\mathbf{F}_{lj} \leftarrow \mathbf{F}_{lj} \Big/ \sum_{l'=1}^{k} \mathbf{F}_{l'j}\ , \quad l = 1, ..., k,\ j = 1, ..., n}$$

  - MU is non-increasing objective only for general NMF problem (DD Lee et al. 2000)
  - Fast to converge to a reasonable solution

RAD phase 2: coordinate descent

- Coordinate descent
  - Optimizes over C and F iteratively until convergence

$$
\begin{aligned}
\mathbf{C} \leftarrow \arg\min_{\mathbf{C}} \quad & \|\mathbf{B} - \mathbf{C}\mathbf{F}\|_{\mathrm{Fr}}^2 \,, \\
\text{s.t.} \quad & \mathbf{C}_{il} \geq 0, \quad i = 1, ..., m, \; l = 1, ..., k \\
\mathbf{F} \leftarrow \arg\min_{\mathbf{F}} \quad & \|\mathbf{B} - \mathbf{C}\mathbf{F}\|_{\mathrm{Fr}}^2 \,, \\
\text{s.t.} \quad & \mathbf{F}_{lj} \geq 0, \quad l = 1, ..., k, \; j = 1, ..., n, \\
& \textstyle\sum_{l=1}^{k} \mathbf{F}_{lj} = 1, \qquad\qquad j = 1, ..., n
\end{aligned}
$$

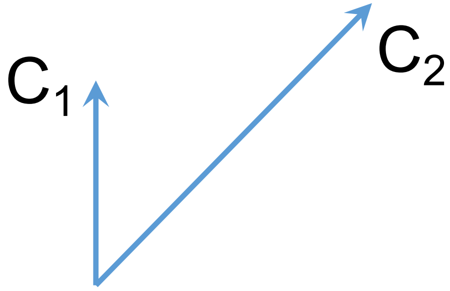
  - Subproblems solved as quadratic programming problems (MS Andersen et al. 2013)
  - Computationally expensive compared with MU warm-start
  - Further reduces loss by ~5-30%

RAD phase 3: minimum similarity selection

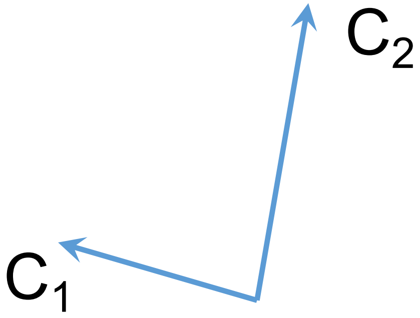
- Minimum similarity selection
  - Repeat random initialization, phase 1 and phase 2 for multiple (e.g., 10) times
  - Select solution with minimum similarity

$$\mathrm{cosim}(\mathbf{C}) = \sum_{l=1}^{k-1} \sum_{l'=l+1}^{k} \mathbf{C}_{\cdot l}^{\intercal} \mathbf{C}_{\cdot l'}$$

  - Better solution: components/populations orthogonal from each other



Solution 1: ✗



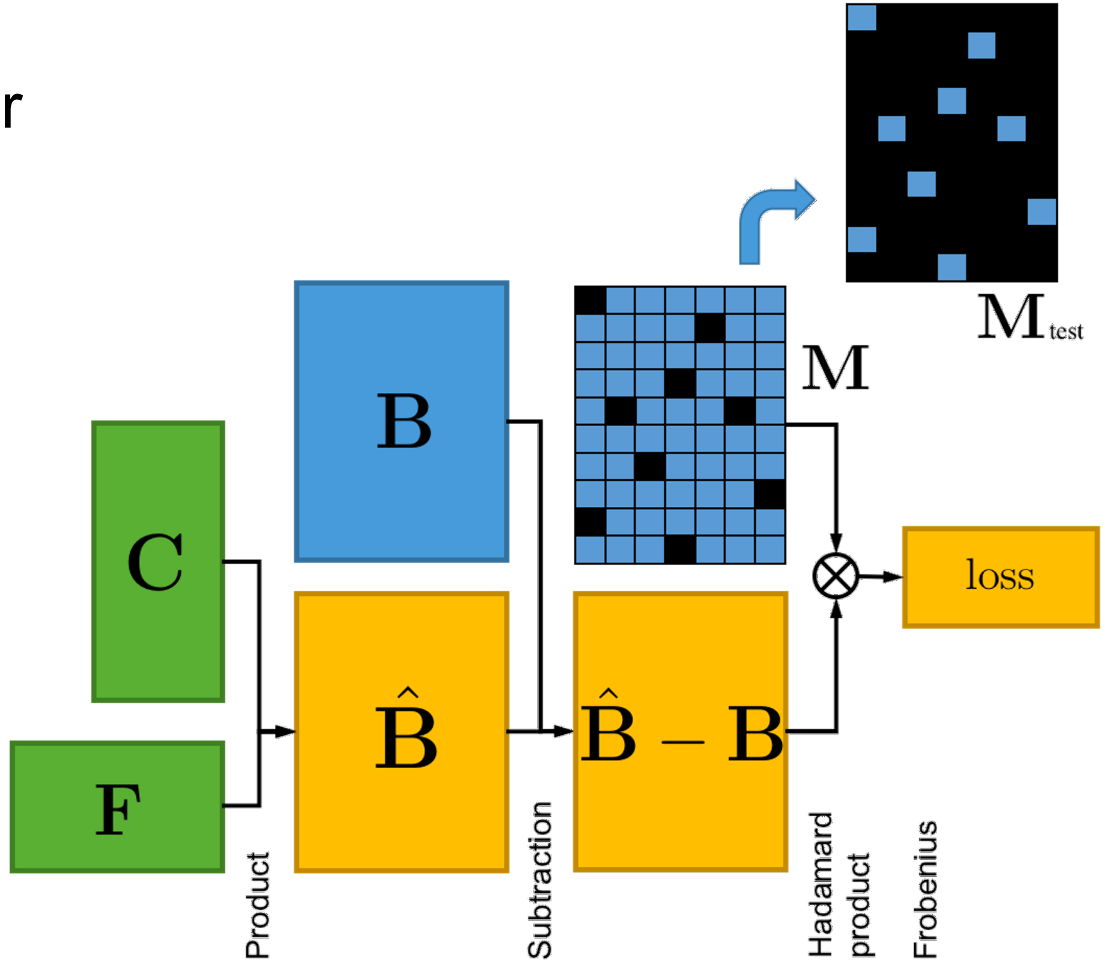
Solution 2:

Population number estimation via RAD

- Masking trick for cross-validation (CV)
- Select *k* that achieves minimum CV error
- Masked RAD algorithm exits!

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

$$\begin{aligned} \text{s.t.} \quad & \mathbf{C}_{il} \geq 0, \quad i = 1, \ldots, m,\ l = 1, \ldots, k, \\ & \mathbf{F}_{lj} \geq 0, \quad l = 1, \ldots, k,\ j = 1, \ldots, n, \\ & \textstyle\sum_{l=1}^{k} \mathbf{F}_{lj} = 1, \qquad j = 1, \ldots, n \end{aligned}$$

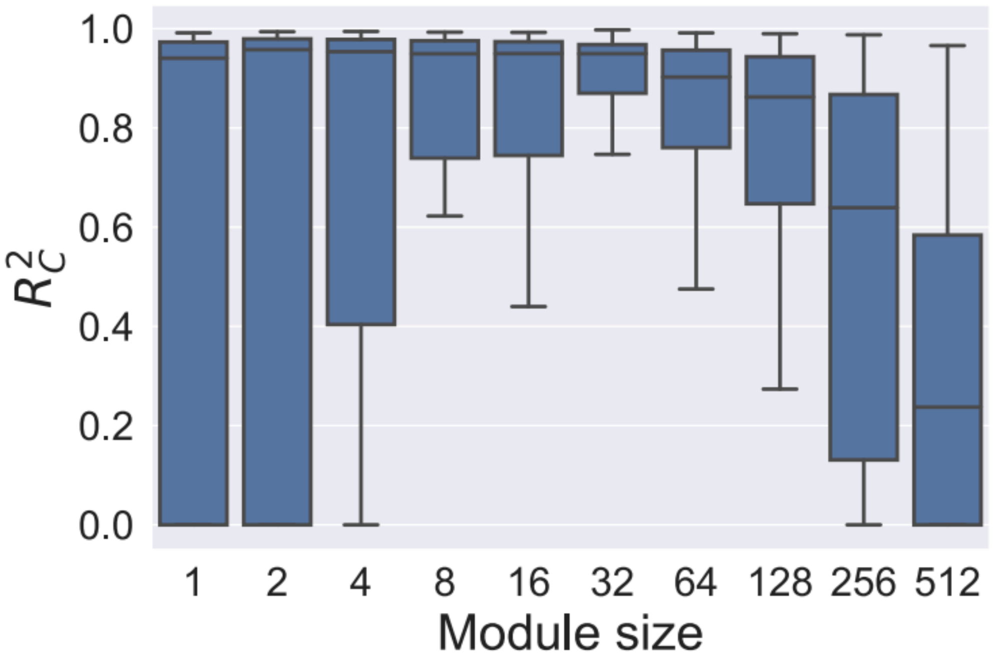


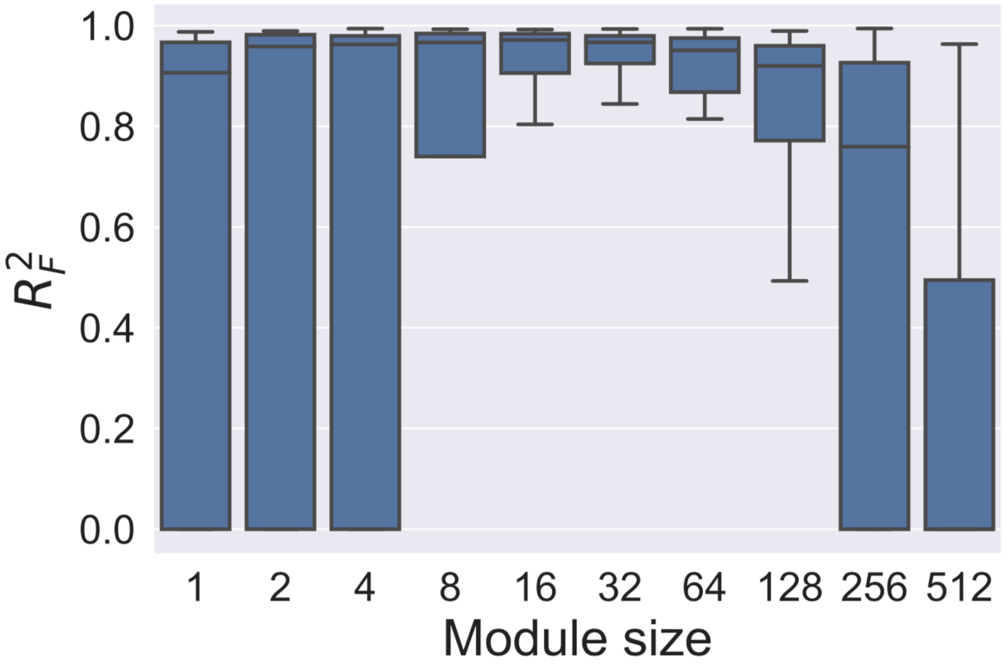
Datasets and experiment design

Dataset	Gene module	Ground truth C and F	Purpose
Simulated (K Zaitsev et al. 2019)	Known	Known	• Evaluate effect of gene module
GSE19830 (SS Shen-Orr et al. 2010)	Knowledge base	Known	• Evaluate effect of gene module • Evaluate RAD accuracy on estimating C, F, and *k*
BrM (L Zhu et al. 2019)	Knowledge base	Unknown	• Understand breast cancer metastasis mechanism

Gene modules facilitate robust deconvolution

- Simulated datasets: gene module known
  - Too small module size → fragile deconvolution
  - Too large module size → worse estimation

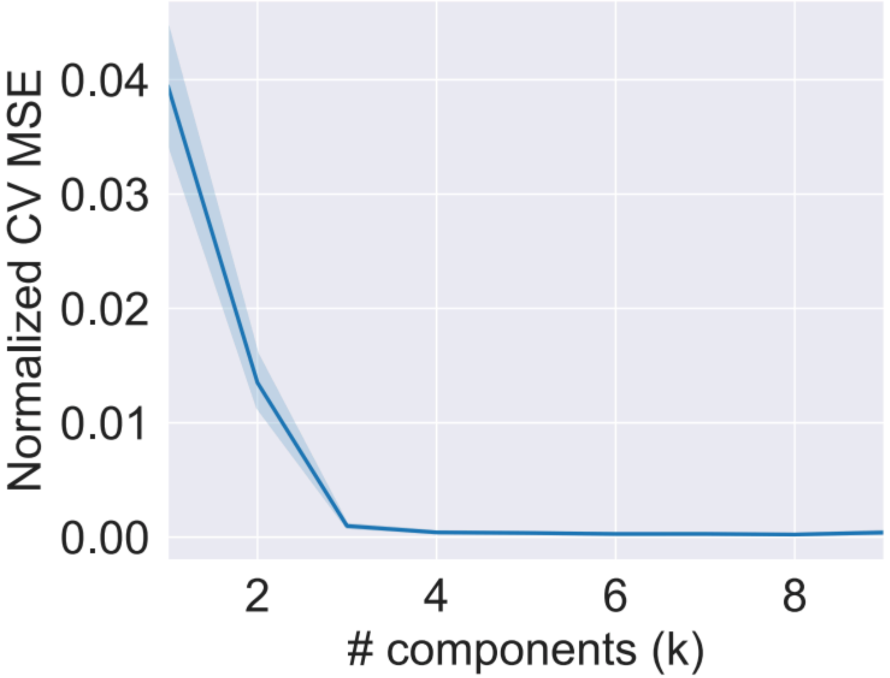




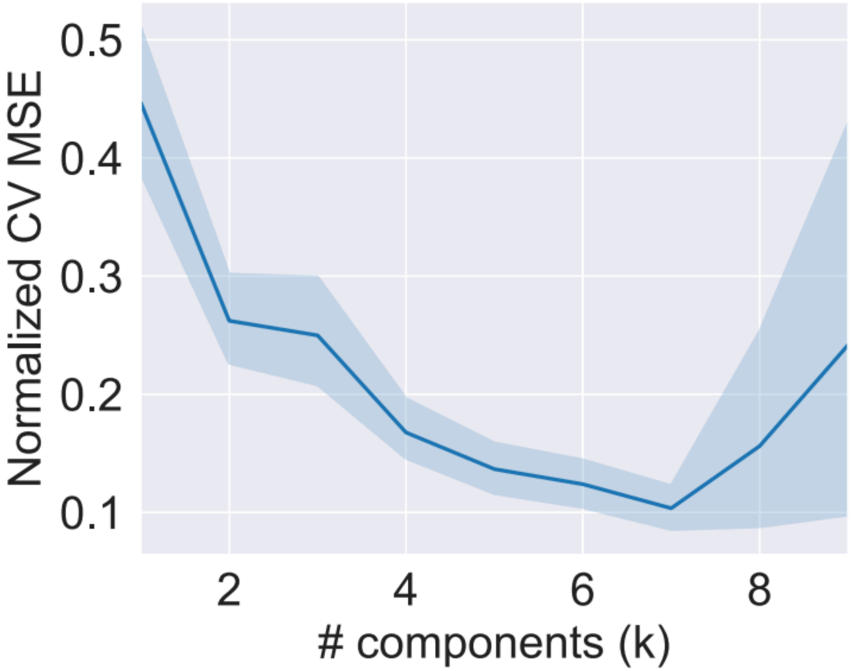
RAD detects correct number of cell components

- GSE19830: three cell types known in advance
- BrM: ground truth cell types unknown

GSE19830

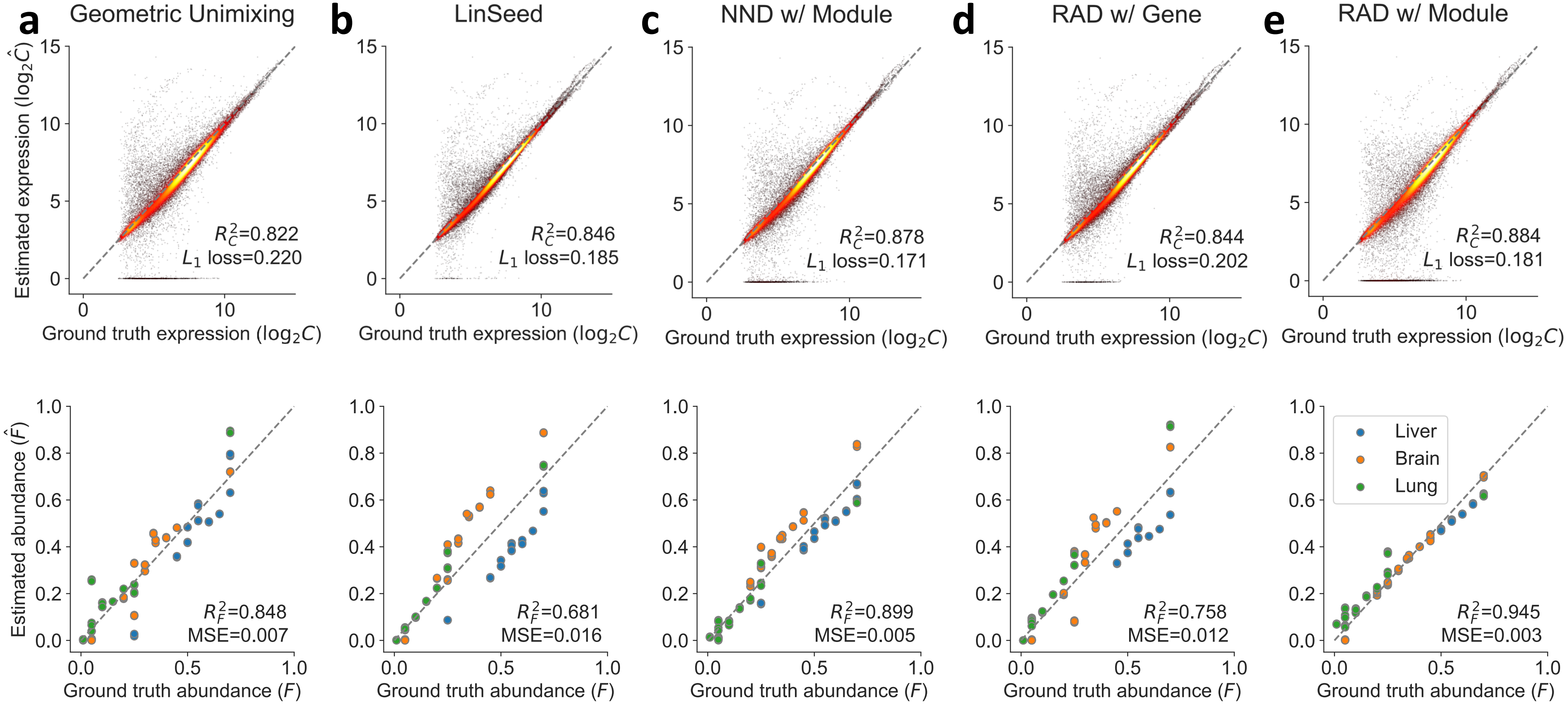


BrM



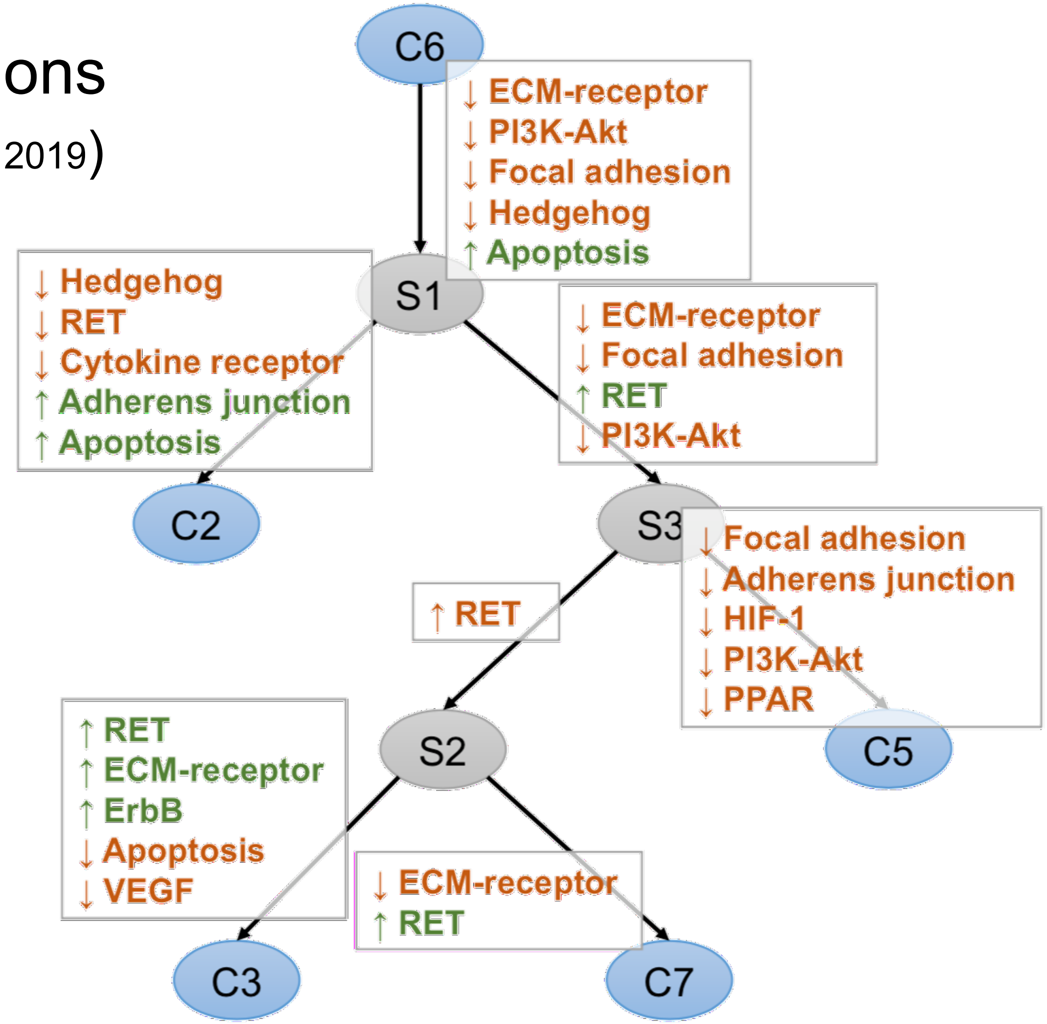
RAD estimates populations more accurately

- Outperforms three competing methods on GSE19830 dataset
- Gene module inferred from knowledge base improves RAD as well



Common evolutionary mechanisms of BrM

- Infer phylogenies from RAD-unmixed populations
  - Minimum elastic potential (MEP; Nei et al. 1987, Tao et al. 2019)
  - Four cases in total (one shown)
- Common early pathway-level events
  - ↓ PI3K-Akt (PK Brastianos et al. 2015)
  - ↓ Extracellular matrix (ECM)-receptor interaction
  - ↓ focal adhesion (M Nagano et al. 2012)



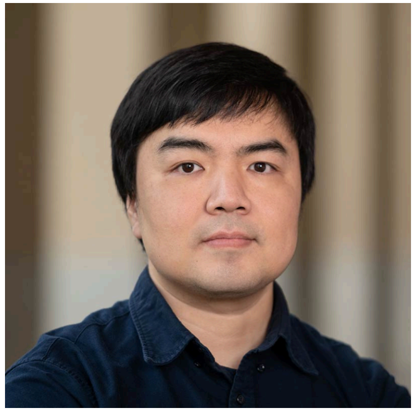
Conclusion and future work

- Deconvolution of bulk data is the key to understanding the BrM progression
- We propose RAD, a toolkit that accurately and robustly estimates the number of cell populations (*k*), expression profiles of cell populations (C), and fractions of populations (F)
- Through RAD, we find the loss of PI3K-Akt, ECM-receptor interaction, and focal adhesion emerge as the common early pathway-level events of BrM

- Integrate single cell data of metastatic samples to improve RAD performance

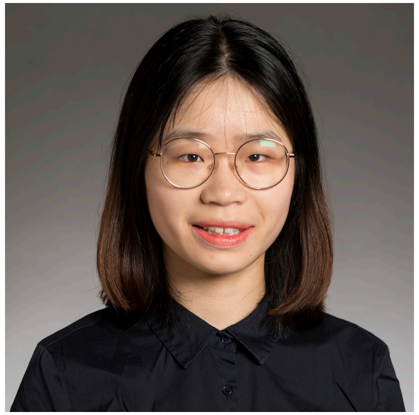
Acknowledgments

Dr. Russell Schwartz


Dr. Jian Ma

Dr. Adrian V. Lee

Haoyun Lei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