Statistical Discovery of Transcriptomic Cancer Signatures using Multimodal Local Search

Emile Zakiev, Johann Dreo, Mara Santarelli, Benno Schwikowski

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Statistical Discovery of Transcriptomic Cancer Signatures using Multimodal Local Search

• E. Zakiev/ J. Dreo • 29/11/2022

The problem

What causes cancer to be resistant?

While killing most of the cells, monodrug chemotherapy doesn't kill all, allowing remaining cells proliferate

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Why not mixing multiple drugs to be sure?

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What causes cancer to be resistant?

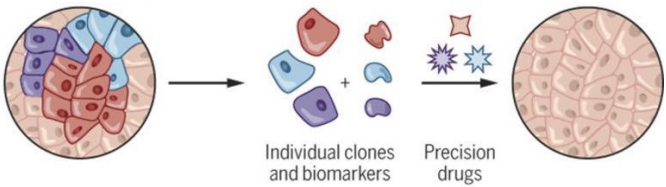
While killing most of the cells, monodrug chemotherapy doesn't kill all, allowing remaining cells proliferate

Why not mixing multiple drugs to be sure? Because of excessive toxicity

The problem

What causes cancer to be resistant?

Need for precision drugs fine-tailored to each subpopulation of cells in each patient



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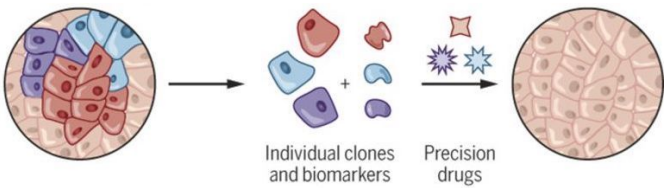

- the subpopulations of cells defined by their scRNAseq profile

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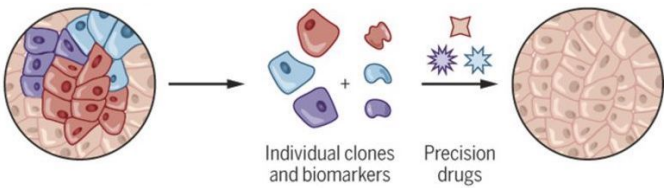

- the subpopulations of cells defined by their scRNAseq profile
  - by their characteristic *signatures* (ensembles of genes)

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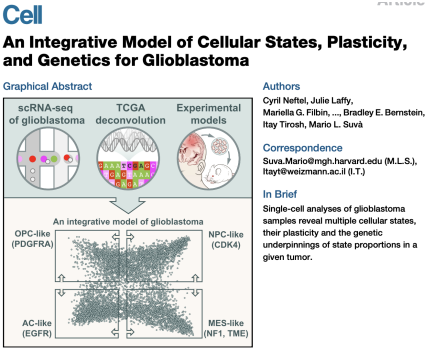
Inspired by...

...the glioblastoma paper by Neftel et al. (2019) where they searched for *signatures* using **global hierarchical clustering** of cells and genes in each sample **separately**



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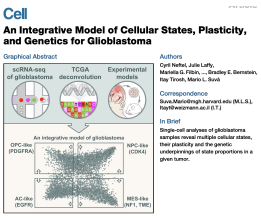
Cell

An Integrative Model of Cellular States, Plasticity, and Genetics for Glioblastoma

Graphical Abstract

scRNA-seq of glioblastoma | TCGA deconvolution | Experimental models

An integrative model of glioblastoma

OPC-like (PDGFRA) | NPC-like (CDK4) | AC-like (EGFR) | MES-like (NF1, TMD)

Authors

Cyril Neftel, Julie Laffy, Mariella G. Filbin, ..., Bradley E. Bernstein, Itay Tirosh, Mario L. Suvà

Correspondence

Suva.Mario@mgh.harvard.edu (M.L.S.), Itay@weizmann.ac.il (I.T.)

In Brief

Single-cell analyses of glioblastoma samples reveal multiple cellular states, their plasticity and the genetic underpinnings of state proportions in a given tumor.

Were able to show benefit of certain gene inhibitors in glioblastoma xenografts on mice

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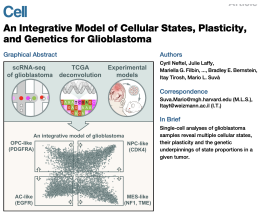

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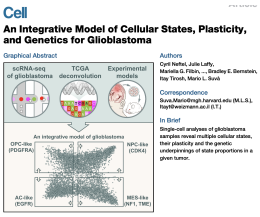

Were able to show benefit of certain gene inhibitors in glioblastoma xenografts on mice

- Hierarchical clustering of cells to form *partitions* of each sample into up-regulated and "the rest of the sample" parts
- Avoiding batch effects: integrated common genesets instead

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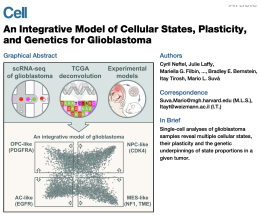
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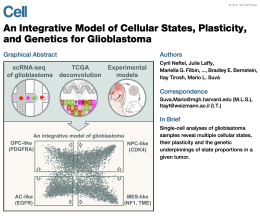

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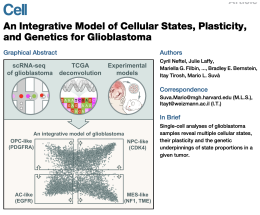

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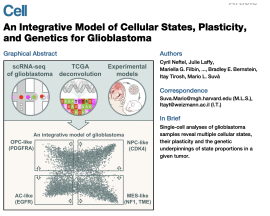

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- Global clustering (dominated by global similarities)
- Search in each sample separately, missing out on a synchronized unified search
- Dichotomous clustering: cell can belong to only 1 cluster (like many methods)
- Extremely ad-hoc, overabundance of dubious thresholds

Optimization search for the best contrast

Our method

- Is not a mere clustering of the cells

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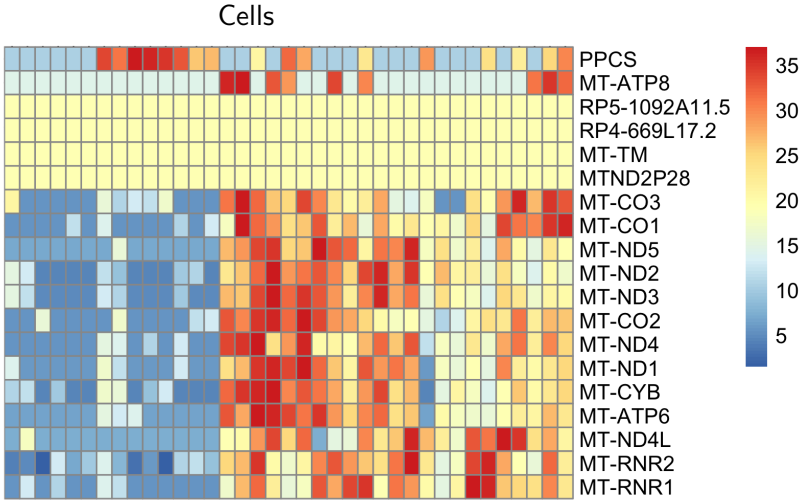
- Looks for signatures in all samples at the same time
- Each cell can support multiple programs
- No ad-hoc thresholds, no parameters

Optimization search for the best contrast

find such partition of sample's cells and genes that confers the highest contrast from the rest of the sample



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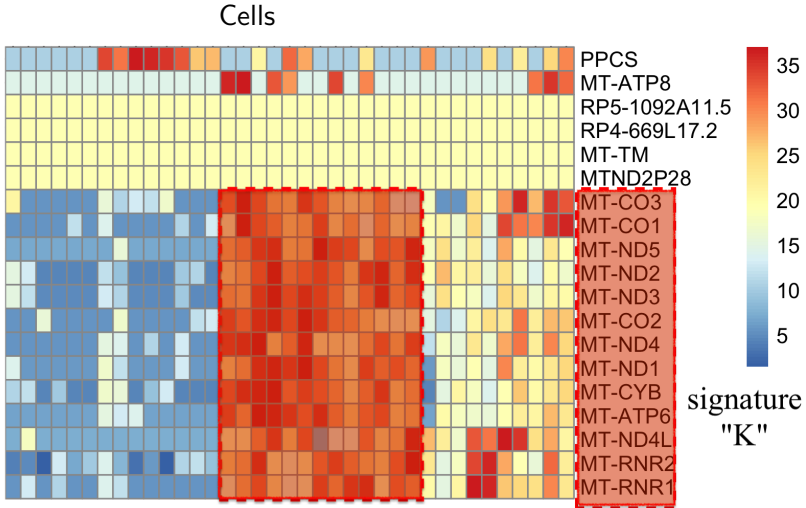

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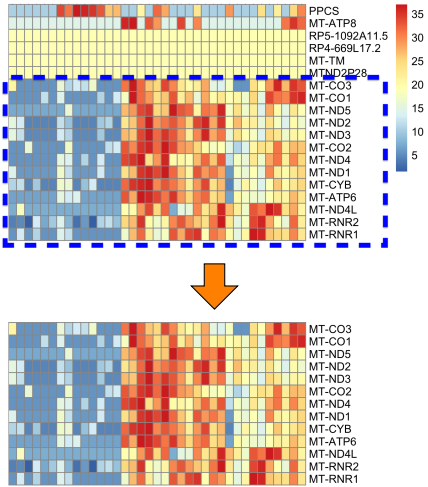

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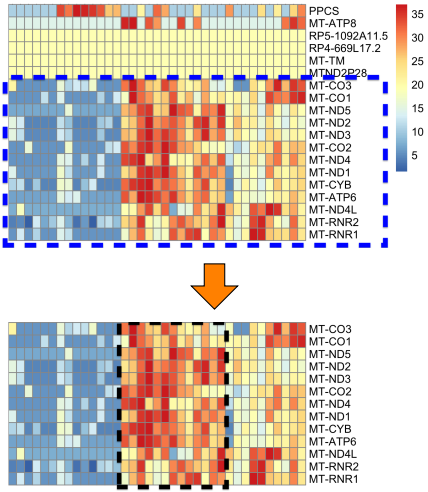

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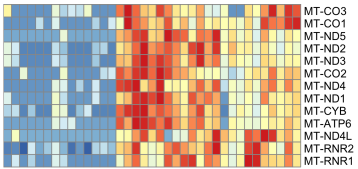
Friedman Statistic



$$S = \frac{12n}{k(k+1)} \sum_{j=1}^{k} \left(R_{.j} - \frac{k+1}{2} \right)^2$$

where

$$R_j = \sum_{i=1}^{n} r_{ij} \quad \text{and} \quad R_{.j} = \frac{R_j}{n}.$$

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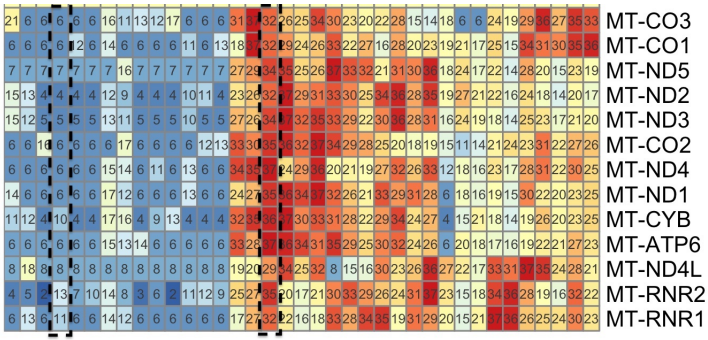

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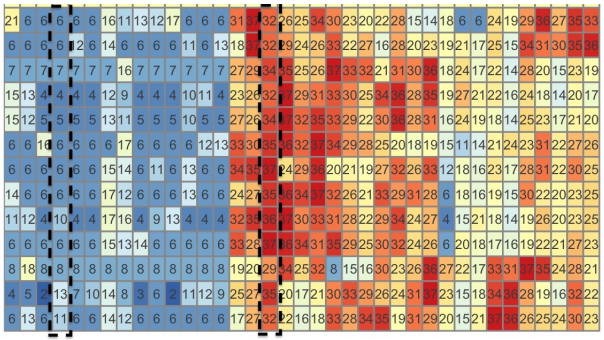

$$S = \frac{12n}{k(k+1)} \sum_{j=1}^{k} \left(R_j - \frac{k+1}{2} \right)^2$$

$$= 370.1$$

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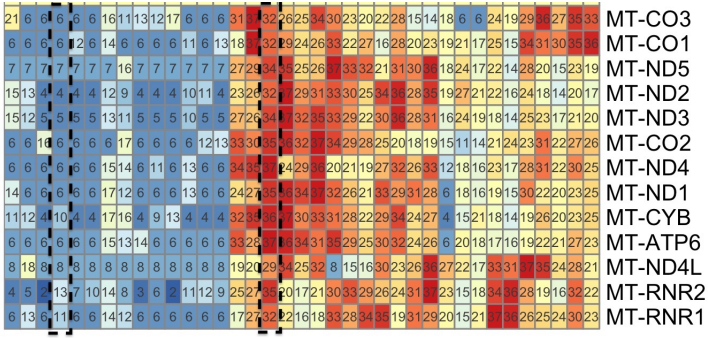
Friedman Statistic



$$-\log p(S, df) = -\log p(370.1, 36) = 129.7 \quad (1)$$

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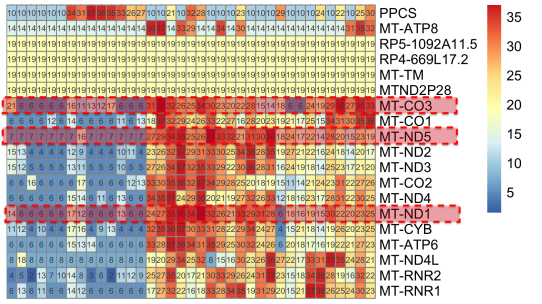
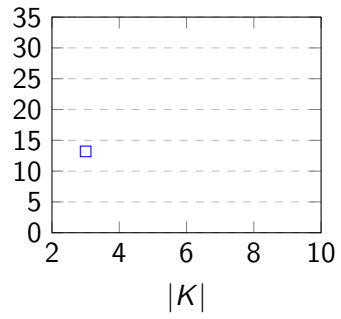
Selecting Genes



Currently selected genes highlighted

Friedman's logP vs # of genes



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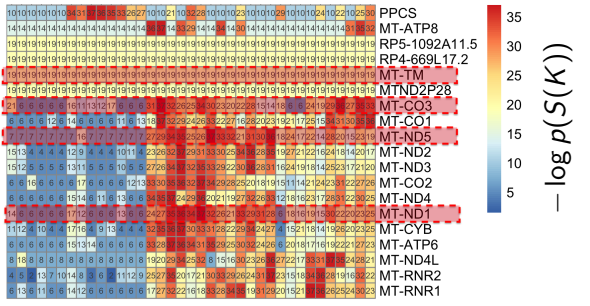
Optimization Process



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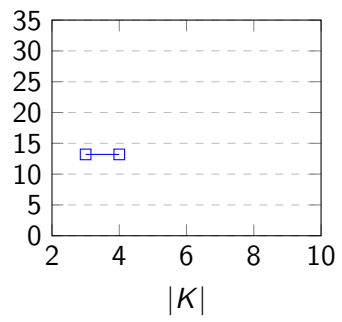

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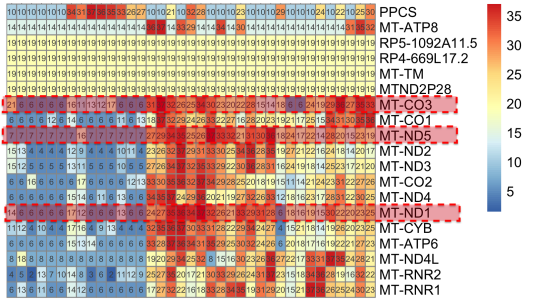
Selecting Genes

(rolling back)



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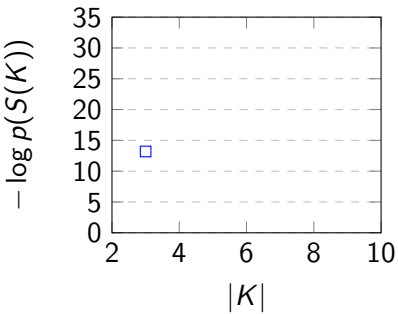

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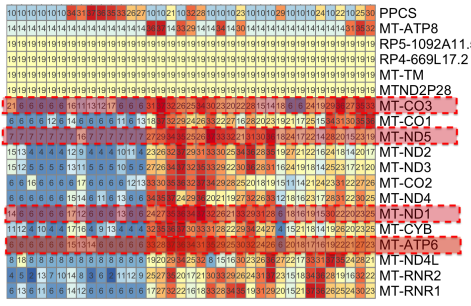

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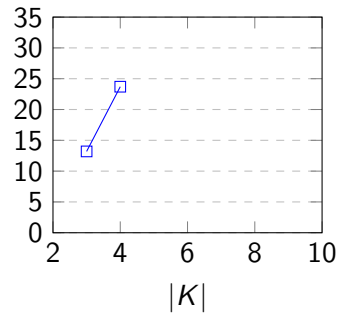

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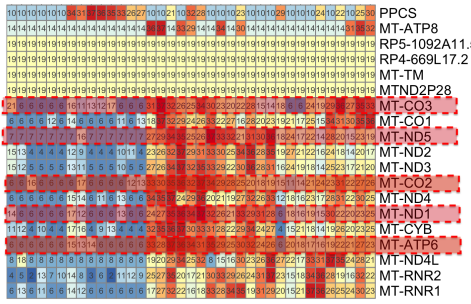

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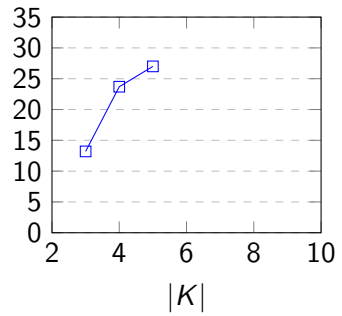

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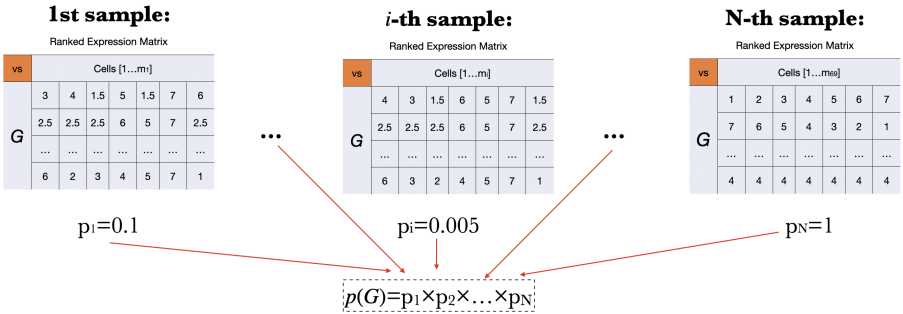
Objective to Optimize

Find signatures $\hat{K}$ which maximize the objective function over N samples

Easily expanded over multiple samples by multiplying individual p values



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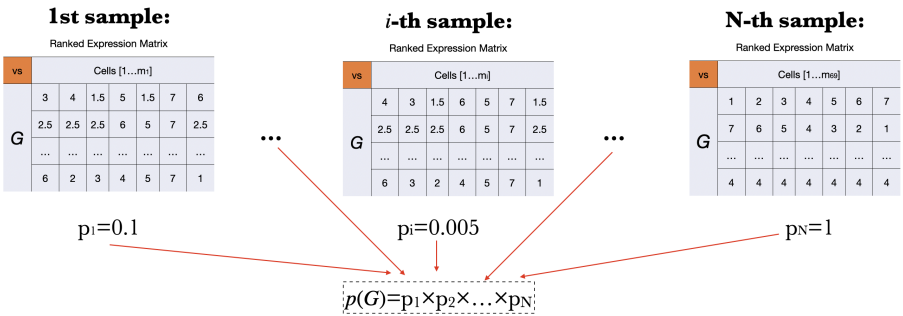

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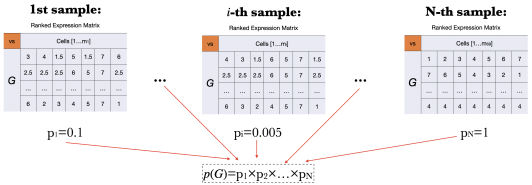

Optimize the objective function

$$g(K) = \sum_{i=1}^{N} (-\log p_i(K)) \tag{2}$$

so that

$$\hat{K} = \arg\max_{K \in \mathfrak{G}} g(K) \tag{3}$$

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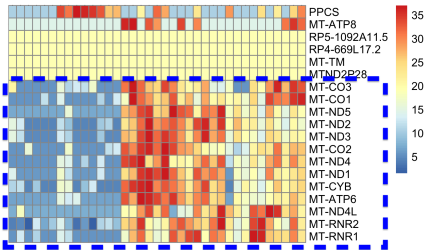
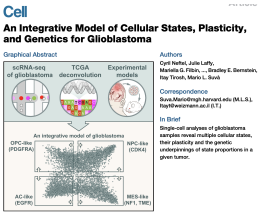
Objective to Optimize

Optimal signature $\hat{K}$



Results

Glioblastoma Smartseq2 data from Nefel et al.



27 samples, 8k cells x 23 k genes. Known ground truth, known signatures

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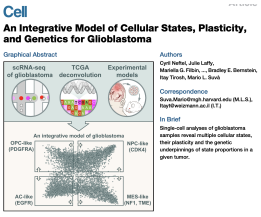

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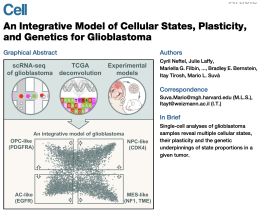

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  - enrichments from MSigDB check out as well

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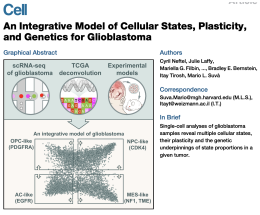

27 samples, 8k cells x 23 k genes. Known ground truth, known signatures

- Our method discovers similar signatures as Neftel et al, Seurat, HARMONY, LIGER and cNMF
  - enrichments from MSigDB check out as well
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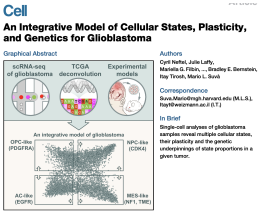
Cell

An Integrative Model of Cellular States, Plasticity, and Genetics for Glioblastoma

Graphical Abstract

scRNA-seq of glioblastoma | TCGA deconvolution | Experimental models

An integrative model of glioblastoma

OPC-like (PDGFRA) | NPC-like (CDK4) | AC-like (EGFR) | MES-like (NF1, TMIC)

Authors

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In Brief

Single-cell analyses of glioblastoma samples reveal multiple cellular states, their plasticity and the genetic underpinnings of state proportions in a given tumor.

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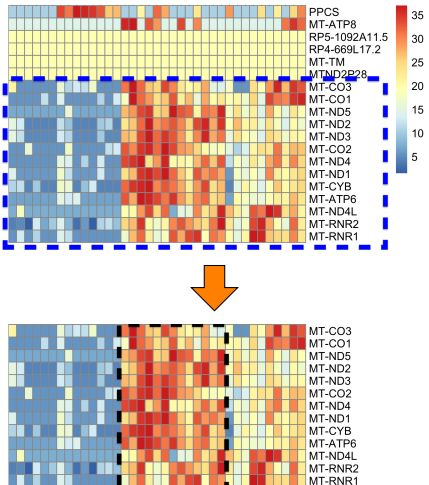
- Our method discovers similar signatures as Neftel et al, Seurat, HARMONY, LIGER and cNMF
  - enrichments from MSigDB check out as well
- On top of that it discovers small signatures not found by any of the methods above, and their enrichments are highly relevant to glioblastoma
- Our signatures are on average enriched for smaller pathways/genesets than the competitors' signatures

Solutions

	starting loss	No of iter	Final score	Geneset
1	start_loss was 91.7711	48 iterations locally	969.918	AURKB BIRC5 BUB1B CDCA5 CDK1 CENPF FAM64A KIF...
2	start_loss was 105.185	48 iterations locally	969.918	AURKB BIRC5 BUB1B CDCA5 CDK1 CENPF FAM64A KIF...
3	start_loss was 107.669	38 iterations locally	969.918	AURKB BIRC5 BUB1B CDCA5 CDK1 CENPF FAM64A KIF...
4	start_loss was 113.993	29 iterations locally	623.992	ATP1B2 BCAN CST3 DBI EDNRB GATM GPM6B HEPACA...
5	start_loss was 113.502	33 iterations locally	969.918	AURKB BIRC5 BUB1B CDCA5 CDK1 CENPF FAM64A KIF...
6	start_loss was 125.488	48 iterations locally	969.918	AURKB BIRC5 BUB1B CDCA5 CDK1 CENPF FAM64A KIF...
7	start_loss was 101.827	47 iterations locally	969.918	AURKB BIRC5 BUB1B CDCA5 CDK1 CENPF FAM64A KIF...
8	start_loss was 109.972	49 iterations locally	969.918	AURKB BIRC5 BUB1B CDCA5 CDK1 CENPF FAM64A KIF...
9	start_loss was 114.923	48 iterations locally	969.918	AURKB BIRC5 BUB1B CDCA5 CDK1 CENPF FAM64A KIF...
10	start_loss was 122.534	47 iterations locally	969.918	AURKB BIRC5 BUB1B CDCA5 CDK1 CENPF FAM64A KIF...

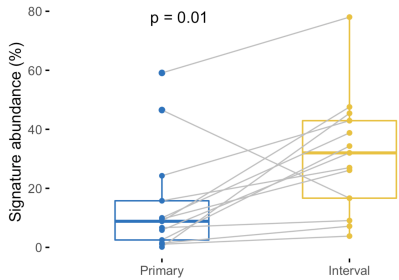
Addendum 1: Tricky part

how to define "abundance" of a signature in a given sample?



Addendum 1: Functional testing of the signatures

After obtaining all the signatures, test them for association with resistance.



"a desirable signature"

Signature's **abundance** goes up in "after" treatment vs "before" treatment?
Potential chemoresistance signature

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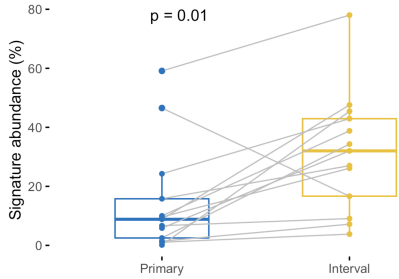

"a desirable signature"

Signature's **abundance** goes up in "after" treatment vs "before" treatment?
Potential chemoresistance signature

- Only 11 pairs :(

Addendum 1: Compound Objective Function

Sum over all samples of Friedman Statistic log-p values

$$g(K) = \sum_{i=1}^{n} (-\log p_i(K)) \tag{4}$$

where n is the number of samples

$$f(K) = \delta \cdot h(K) + g(K) \tag{5}$$

$$\hat{K} = \underset{K \in \mathfrak{G}}{\arg\max}\, f(K) \tag{6}$$

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Addendum 2: A Brief Note on Performance

How we make the algo work faster

- embarrassingly parallel, ready-to-deploy on an HPC cluster

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Resulting algo scales as O(n) where n is the number of cells
One full iteration on Pasteur's Maestro Cluster core:
49 microseconds for 27 samples of 8000 cells
169 microseconds for 63 samples of 25k cells

Addendum 3: Friedman Statistic Quick Update

Friedman statistic with n genes:

$$S'_n = \frac{12\sum_{j=1}^{m} R_j^2 - 3n^2m(m+1)^2}{nm(m+1) - [1/(m-1)]\sum_{i=1}^{n}\{(\sum_{j=1}^{g_i} t_{i,j}^3) - m\}} \tag{7}$$

Denote

$A_n = 12\sum_{j=1}^{m} R_j^2$, $B_n = 3n^2m(m+1)^2$, $C_n = nm(m+1)$,
$D_n = [1/(m-1)]\sum_{i=1}^{n}\{(\sum_{j=1}^{g_i} t_{i,j}^3) - m\}$,

so that

$$S'_n = \frac{A_n - B_n}{C_n - D_n} \tag{8}$$

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so that When adding a gene: n $\rightarrow n+1$

$\mathrm{A}_{n+1} = 12\sum_{j=1}^{m}(R_{j,n} + r_j)^2 = A_n + 24\sum_{j=1}^{m} R_{j,n}r_j + 12\sum_{j=1}^{m} r_j^2$
$B_{n+1} = 3(n+1)^2m(m+1)^2 = B_n + 3m(m+1)^2(2n+1)$
$C_{n+1} = (n+1)m(m+1) = C_n + m(m+1)$
$D_{n+1} = D_n + [1/(m-1)]\{(\sum_{j=1}^{g_{n+1}} t_{n+1,j}^3) - m\}$

$$S'_{n+1} = \frac{(A_n + 24\sum_{j=1}^{m} R_{j,n}r_j + 12\sum_{j=1}^{m} r_j^2) - (B_n + 3m(m+1)^2(2n+1))}{(C_n + m(m+1)) - (D_n + [1/(m-1)]\{(\sum_{j=1}^{g_{n+1}} t_{n+1,j}^3) - m\})} \quad (9)$$

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Challenge: non-fixed size signatures

- in reality we use fixed size signatures, swapping genes in and out

Challenge: non-fixed size signatures

- in reality we use fixed size signatures, swapping genes in and out
- size-restriction-free variant ends up in absorbing all the genes in the dataset
  - even when penalizing the Friedman's S by the number of currently selected genes n :
    - $S' = S/n^{alpha}$ (where alpha is a real number [0.5...2])

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