

Comp790-166: Computational Biology

Lecture 26

April 18, 2022

Good Morning Question

- ① How did the 'correct' step work in the correct and smooth approach?
What was the assumption about errors (residuals) and edges in the graph?
- ② How were information about node features used (e.g. at the beginning, middle, or end.. which one?)

Announcements

- Homework 2 is due Friday.
 - Yes, the k hop business unfortunately takes a long time because these are large graphs.
- Projects - how are they going?
 - Presentations next week. See rubric about projects and writeup,
https://docs.google.com/document/d/1FKh4_9VK6CHwqLs2V3mTo457FwELEFYNrXwEqNbGlBk/edit?usp=sharing

Today

- Spatial regularization – single-cell + tissue information from imaging.
- LEAPH

CyTOF + Spatial Resolution

An upgrade of regular CyTOF to image 32 proteins and their modifications at cellular resolution.

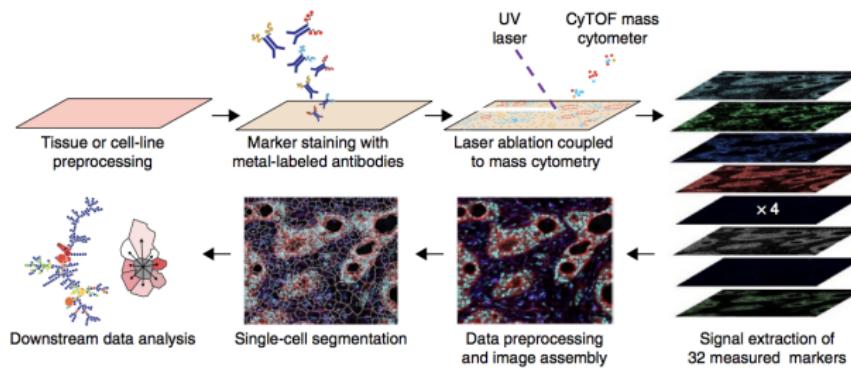


Figure: from Giesen *et al.* Nature Methods. 2016

Why Do We Care?

Understanding the spatial organization of cells (for example, tumor and immune cells) can provide a more mechanistic understanding of the underlying biology. This can further translate to more accurate prediction of prognostic outcomes.

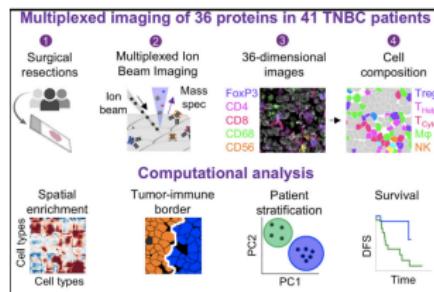


Figure: from Keren *et al.* Cell. 2018.

Recent Advances in Study The Relationship Between Immune Cells and Tumor

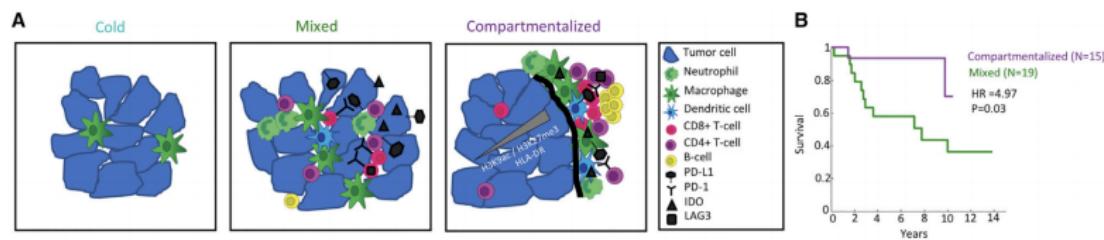


Figure: from Keren *et al.* Cell. 2018.

Studying Aging

Older mice were observed to have infiltrating T-cells in their neurogenic niches (the collection of neuronal progenitor cells)

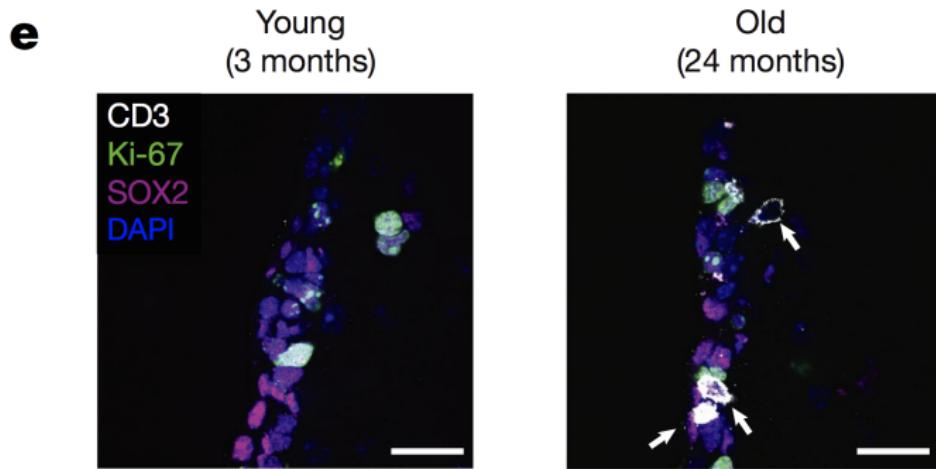
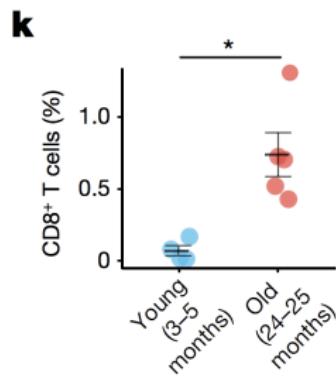


Figure: from Dulken *et al.* Nature 2019

Counting CD8+ T-cells

You can even compare the proportion of CD8+ T-cells there are in neurogenic niches between young and old mice. It's a pretty striking difference.



General Steps in Analyzing These Data

- Segmentation of cells
- Phenotype cells
- Identify microenvironments or characteristic co-occurrences of particular cell-types within a region.

Example-Cell Phenotype Map

Cells are clustered and phenotyped according to protein expression.

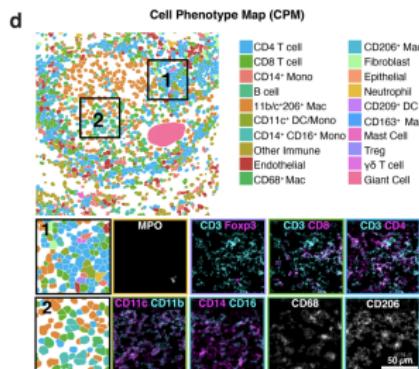


Figure: from <https://www.biorxiv.org/content/10.1101/2020.06.08.140426v1.full.pdf>

End-Goal of Identifying Particular Microenvironments

Ultimately, an objective is to identify ‘micro-environments’ or spatially-localized subsets of cells with characteristic frequency patterns that are predictive of some outcome of interest.

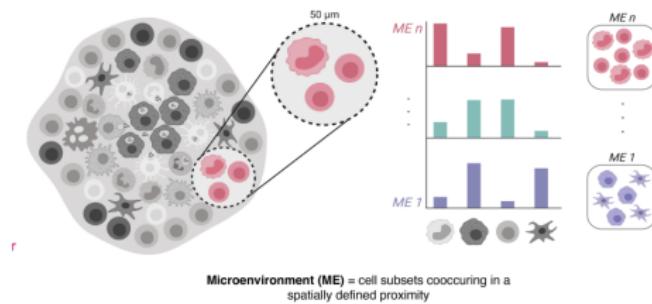


Figure: from <https://www.biorxiv.org/content/10.1101/2020.06.08.140426v1.full.pdf>

A New Problem: Identifying Microenvironments

Welcome LEAPH. One of the first methods out there to identify phenotypically distinct microdomains of spatially configured cell phenotypes.

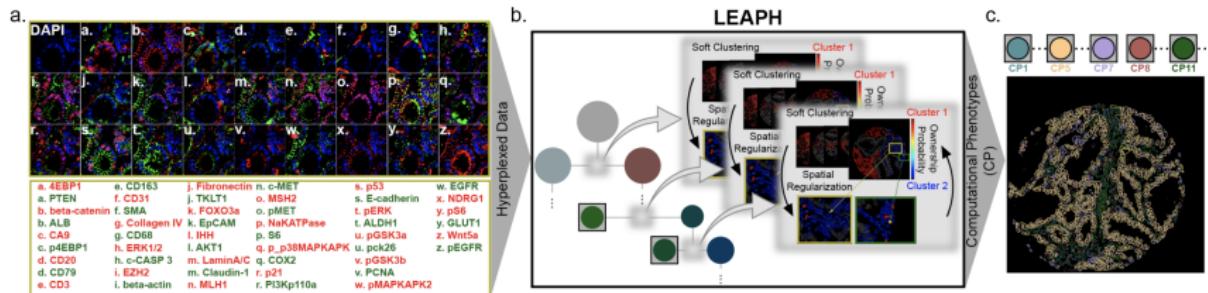


Figure: from Furman *et al.* BioArXiv. 2020.

LEAPH Overview

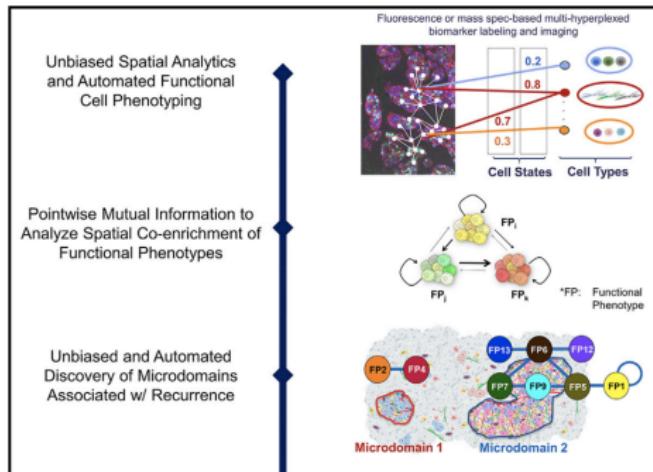


Figure: from Furman *et al.* BioArXiv. 2020.

Notation in LEAPH

- For cell i , let its protein expression be represented as $\mathbf{x}_i \in \mathbb{R}^p$.
- Mixture of factors setup, with k dimensions in the latent space, with
$$\mathbf{x}_i = \Lambda \mathbf{z} + \boldsymbol{\mu} + \mathbf{v}$$
 - Loadings in $\Lambda \in \mathbb{R}^{p \times k}$
 - Latent variables, $\mathbf{z} \in \mathbb{R}^{k \times 1}$
 - Noise term via, $\mathbf{v} \sim \mathcal{N}(0, \Psi)$
 - Mean vector, $\boldsymbol{\mu} \in \mathbb{R}^{p \times 1}$

Mixture Model

Each $p(\mathbf{x}_i)$ is computed as

$$p(\mathbf{x}_i) = \sum_{j=1}^M \pi_j \mathcal{N}(\mathbf{x}_i | \boldsymbol{\mu}_j, \Lambda_j \Lambda_j^T + \Psi)$$

- π_j is the mixing weight for cluster j .

Practicalities

- Overall, parameters being estimated are $\{\pi_j, \mu_j, \Lambda_j\}_{j=1}^M, \Psi$.
- They 2-dimensions for each latent space, so, $k = 2$.
- Ultimately, they get a prediction that each cell belongs to of the M components, and in particular for class j , $p(j | \mathbf{x}_i) = \frac{p(\mathbf{x}_i|j)p(j)}{\sum_{c=1}^M p(\mathbf{x}_i|c)p(c)}$
- Use the estimated probability between a cell i and a cluster c and create a matrix, $\Omega \in \mathbb{R}^{N \times M}$ where Ω_{ic} gives the probability that cell i belongs to cluster c .
- This gives a soft clustering interpretation for each cell.

Spatial Regularization Intuition

- Based on prior biological knowledge, there are known properties that for example, epithelial/tumor cells should be surrounded by or spatially proximal to other epithelial/tumor cells.
- There should also be some allowance for tumor-infiltrating cells, such as lymphocytes and other stromal cells.

A new Ω is optimized that encodes spatial information as follows,

$$\min_{\Omega} - \sum_{i=1}^N \sum_{j=1}^M \Omega_{ij} \log_2 (\Omega_{ij}) + \lambda \sum_{(j,k)} w_{jk} \|\Omega_j - \Omega_k\|_2$$

Unpacking

$$\min_{\Omega} - \sum_{i=1}^N \sum_{j=1}^M \Omega_{ij} \log_2 (\Omega_{ij}) + \lambda \sum_{(j,k)} w_{jk} \|\Omega_j - \Omega_k\|_2$$

- w_{jk} is a weight, calculate as the reciprocal of distance between cells j and k in the image
- The first term is basically an entropy term of ownership confidence
- The second term is promoting spatial coherence.
- λ controls the tradeoff between spatial coherence and membership confidence.

Effect of Spatial Regularization

In particular in the first example, a cell with a highly predicted assignment towards CP1 transitioned towards a phenotype of CP2 after spatial regularization.

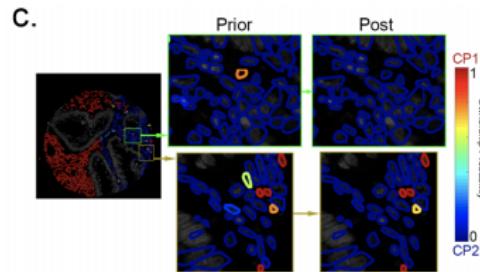


Figure: from Fig. 2 of <https://www.biorxiv.org/content/10.1101/2020.10.02.322529v3.full.pdf>

Determining Specialized Cells

- Based on the Ω , assign each cell to one of the M phenotypes based on the j that gives the maximum probability.
- For a particular patient, p , create a feature vector \mathbf{f}_p which gives the proportion of its cells assigned to each of the cell phenotypes.
- At times, the authors refer to specialized cell-types (membership probability $> 95\%$) in contrast to transitional and rare cells.

Recap and Transition

- The clustering part is straight-forward : Assume each cell is from one of M 2-dimensional latent factors
- Calculate a probability that each cell was from each of these latent factors
- Add penalties that enforce spatial coherence and certainty of assignment
- **Next step:** Identify microdomains with a collection of cells that are predictive of some phenotype of interest.

Predicting Time to Recurrence in Breast Cancer

- Consider cohorts of patients with the following properties.
 - 45 patients in 'NED-8' category that have no evidence of disease for over 8 years
 - 46 patients in 'NED-3', where cancer came back within 3 years.

The goal is to translate the distributions of cell phenotypes that spatially co-occur to a signal that can be used for prediction.

Constructing a Cell Network For Each Patient

- Connectivity is determined by proximity in the image of the tissue
- For a pair of cells, m , and n , connect them with a weights, $w_{mn} = 1$ if their spatial distance, $d_{mn} < 1$.
- Otherwise, $w_{mn} = 0$ and there are no edge between the cells

Identifying Spatial Co-Occurrence Between Cell Phenotype Pairs

Consider two phenotypes, f_i and f_j for a given set (e.g. a subset of patients, etc). The pairwise mutual information between these two phenotypes is defined as,

$$\text{PMI}_s(f_i, f_j) = \log_2 \left(\frac{p(f_i^s, f_j^s)}{p(f_i^t) p(f_j^t)} \right)$$

- $p(f_i^s)$ is the probability of a particular phenotype, i occurring in a network set, s .
- $p(f_i^t)$ is the background probability of phenotype i .

Calculating Joint Phenotypic Probability for a Single Patient

Letting Ψ encode the set of edges for a particular patient, the joint probability of phenotypes i and j is given as,

$$p(f_i^s, f_j^s) = \frac{1}{z} \left(\sum_{(m,n) \in \Psi} w_{mn} \left(\vec{\Omega}_{mf_i} \vec{\Omega}_{nf_j} + \vec{\Omega}_{mf_j} \vec{\Omega}_{nf_i} \right) \right)$$

*Here z is a normalization over all combinations of i and j according to the computational phenotypes.

Specifying a Background Distribution

The background probability for a phenotype, i is simply the mean assignment probability over all cells, or,

$$p(f_i^t) = \frac{1}{N} \sum_{c=1}^N \Omega_{ci}$$

Ultimately, for each cell phenotype pair, (f_i, f_j) compute the PMI for each sample and consider how this relates to the patient re-occurrence outcomes.

Looking at Significant Microdomains Between Groups

There were a few cellular phenotypes that tended to co-occur between the two patient groups.

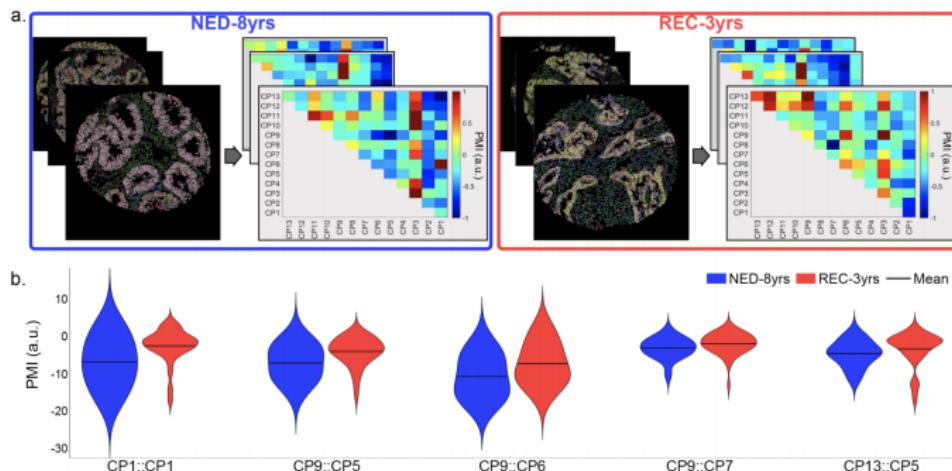


Figure: from Fig. 4 in <https://www.biorxiv.org/content/10.1101/2020.10.02.322529v3.full.pdf>