A new statistical approach for the simultaneous clustering of genes and cells in spatial transcriptomic experiments

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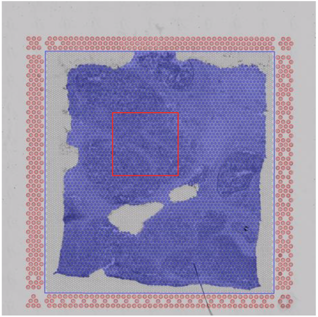
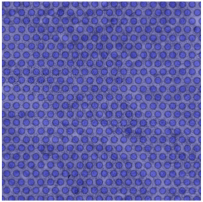
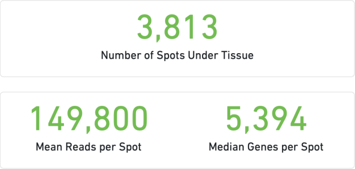
WORK IN PROGRESS

The 10x Genomics Visium technology



$\Downarrow$





3,813
Number of Spots Under Tissue

149,800
Mean Reads per Spot

5,394
Median Genes per Spot

- $j = 1, \ldots, p$ spots, each of which is spatially located;
- Number of spots $\approx$ number of cells;
- for each spot, $i = 1, \ldots, n$ gene expressions are available.

Spatially expressed genes and research motivations

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however...

- These methods do not account for the presence of different cell types.
- Some (clusters of) genes might be *s.e.* just in some specific cell types.

Some aspects to consider

- Let

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Some aspects to consider:

1. correlation of the genes → $Cor(x_{ij}, x_{i'j})$,
2. (spatial) correlation of the spots → $Cor(x_{ij}, x_{ij'})$.

A statistical model

We assume that the experiment matrix $\mathbf{X}$ distributes as

$$\mathbf{X} \sim \mathcal{MVN}_{n,p}(\boldsymbol{\mu}, \boldsymbol{\Sigma}, \boldsymbol{\Delta}),$$

where $\mathcal{MVN}$ denotes the Matrix Variate Normal distribution [Gupta and Nagar, 2018]:

- $\boldsymbol{\mu} = \mu \cdot \mathbf{1}_{n \times p}$ is the mean matrix;
- $\boldsymbol{\Sigma}$ is an $n \times n$ matrix which express the **correlation of the genes** (rows);
- $\boldsymbol{\Delta}$ is an $p \times p$ matrix which express the **correlation of the cells** (columns).

A statistical model

Regarding the rows,

$$\mathbf{\Sigma} := \begin{cases} \sigma_i^2 \text{ in position } (i,i); \\ 0 \text{ elsewhere}; \end{cases} \qquad \sigma_i^2 \sim \mathcal{IG}(\alpha, \beta).$$

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Regarding the columns,

$$\mathbf{\Delta} = \tau \cdot \mathbf{K}(\phi) + \xi \cdot \mathbb{1}_{p \times p}.$$

- $\tau \in \mathbb{R}^+$ is the amount of spatial expression;
- $\mathbf{K}(\cdot)$ is the spatial kernel matrix: example,

$$\mathbf{K}_{j,j'} = \exp\{-||\mathbf{s}_j - \mathbf{s}_{j'}||^2/(2\phi^2)\};$$

- $\phi \in \mathbb{R}^+$ is the spatial scale;
- $\xi \in \mathbb{R}^+$ is the nugget effect (variance not imputable to the spatial structure);

The Co-clustering problem

- K gene clusters → $\mathcal{C}_i = k$ means that gene i belongs to the k-th gene cluster;
- R cell clusters → $\mathcal{D}_j = r$ means that cell j belongs to the r-th cell type.

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$$\mathbf{X} = \begin{array}{c|c|c|c|c|}
 & r=1 & r=2 & \dots & r=R \\ \cline{2-5}
k=1 & \mathbf{X}_{11} & \mathbf{X}_{12} & \dots & \mathbf{X}_{1R} \\ \cline{2-5}
k=2 & \mathbf{X}_{21} & \ddots & \dots & \vdots \\ \cline{2-5}
\dots & \vdots & \dots & \ddots & \vdots \\ \cline{2-5}
k=K & \mathbf{X}_{K1} & \dots & \dots & \mathbf{X}_{KR} \\ \cline{2-5}
\end{array}$$

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$$\Downarrow$$

$$\mathbf{X}_{kr} \sim \mathcal{MVN}_{n_k, p_r}(\boldsymbol{\mu}_{kr}, \boldsymbol{\Sigma}_{kr}, \tau_{kr} \cdot \mathbf{K}(\phi_r) + \xi_{kr} \cdot \mathbb{1}_{p_r \times p_r}),$$

$$\sigma^2_{kr,i} \sim \mathcal{IG}(\alpha_{kr}, \beta_{kr})$$

for $k = 1, \dots, K$ and $r = 1, \dots, R$.

spatialLIBD data

- We exploit the human dorsolateral prefrontal cortex (DLPFC) spatial transcriptomics data generated with the 10x Genomics Visium technology by [Maynard et al., 2020] and contained in the R package spatialLIBD [Collado-Torres et al., 2020].
- We reduced the dataset size, using the first **1000** most variable **genes** measured in **1585 spots**.
- We run our model on $\log$-counts data using $K = 1$ and $R = 4$.
- The estimation procedure is initialized using the results from k-means.

spatialLIBD data - clustering

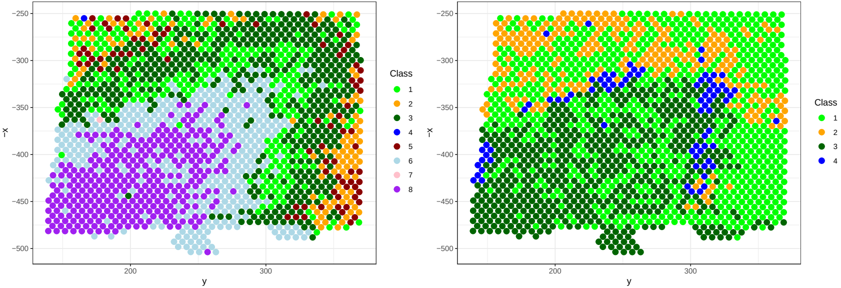

Figure 1: Data: subject 151673. Left: clustering provided by spatialLIBD. Right: Clustering from our method.

cell cluster	$\hat{\mu}$	$\hat{\tau}/\hat{\xi}$	$\hat{\phi}$
1	0.863	0.479	19.159
2	0.451	0.304	21.232
3	0.501	0.357	19.283
4	0.198	0.200	31.440

`spatialLIBD` data - genes variance

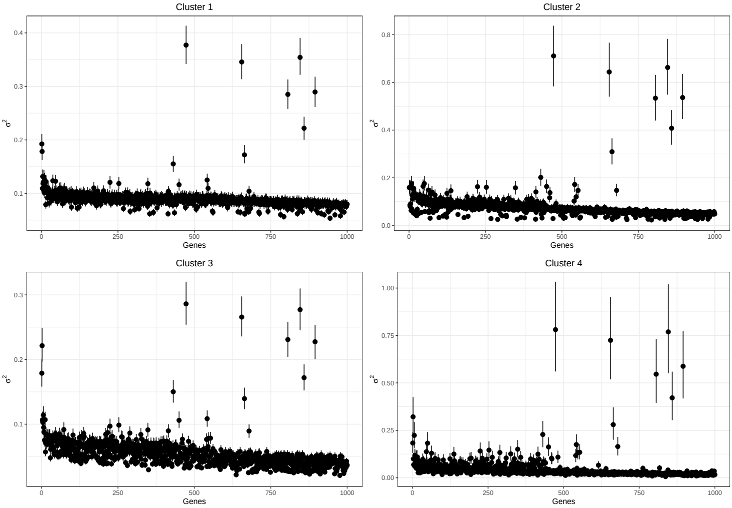

Figure 2: Expected value and 95% interval of σ_i^2 in every cell cluster, given the data the parameter estimates. The first two highly variable genes are $\mathrm{ENSG00000123560}$ and $\mathrm{ENSG00000197971}$.

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