Identify Spatially Variable Genes using BSP and scBSP

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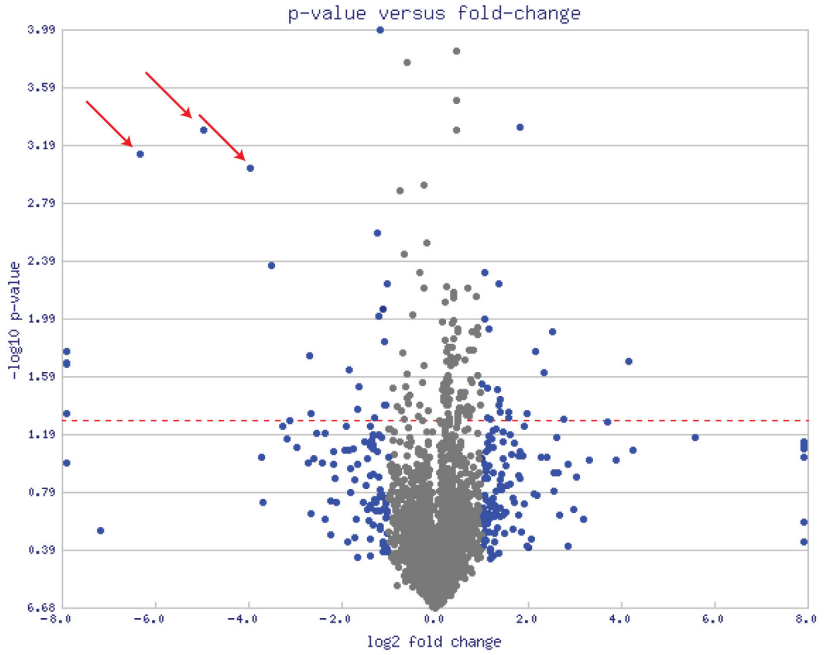
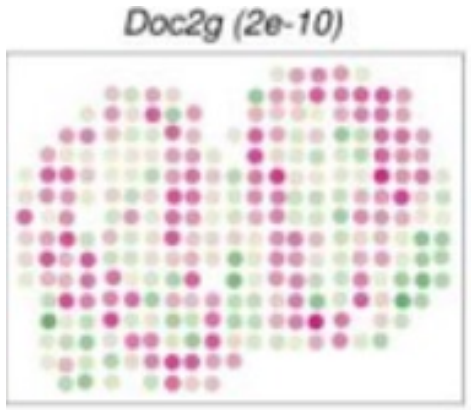
Spatial Variable Genes (SVGs) (spatial context of DEG)

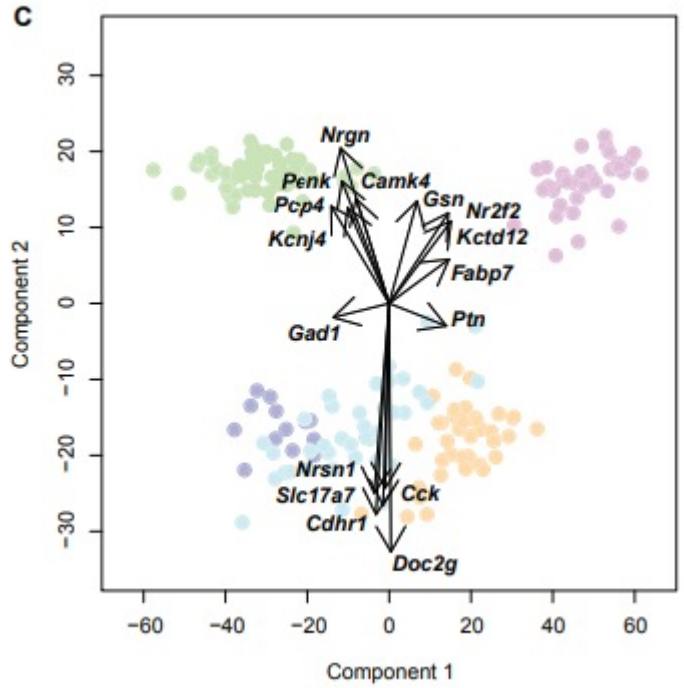
- Differential Expressed Gene -> Spatial Variable Gene
- **Spatial Variable Gene**: Gene differential expressed because of spatial (condition as DEG)
- SVGs are defined as genes with **a highly spatially correlated pattern of expression**, which varies along with the spatial distribution of a tissue structure of interest.
- Spatial expression variation can reflect communication between adjacent cells, position-specific states, or cells that migrate to specific tissue locations to perform their functions.

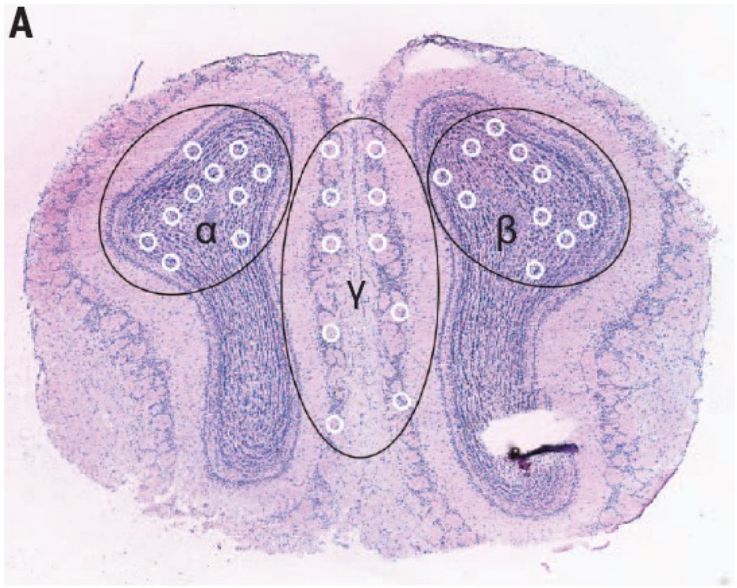


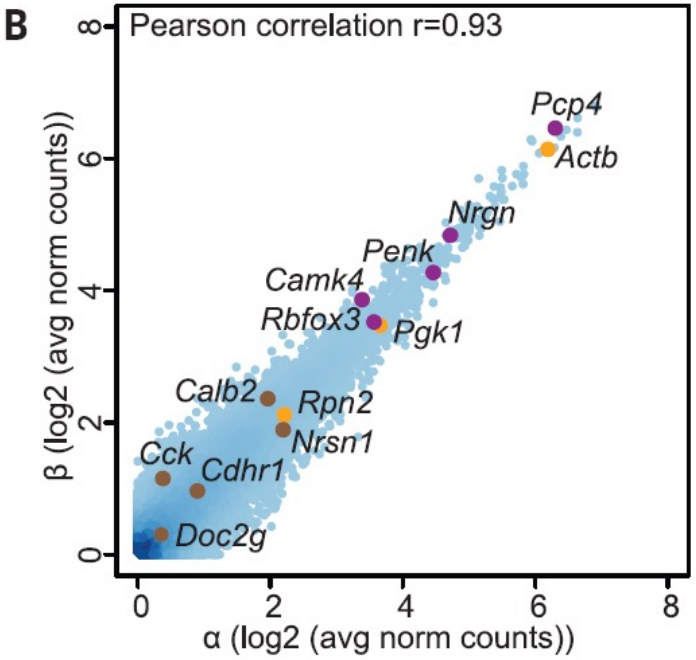


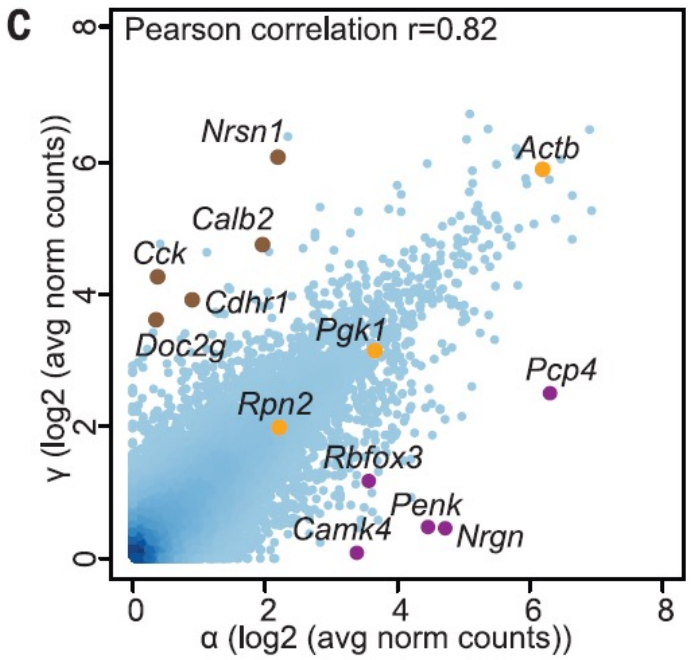
Earlier days: Ad-hoc methods

- Union of both PCA and domain correlation
- Ståhl, Patrik L., et al. "Visualization and analysis of gene expression in tissue sections by spatial transcriptomics." *Science* 353.6294 (2016): 78-82.



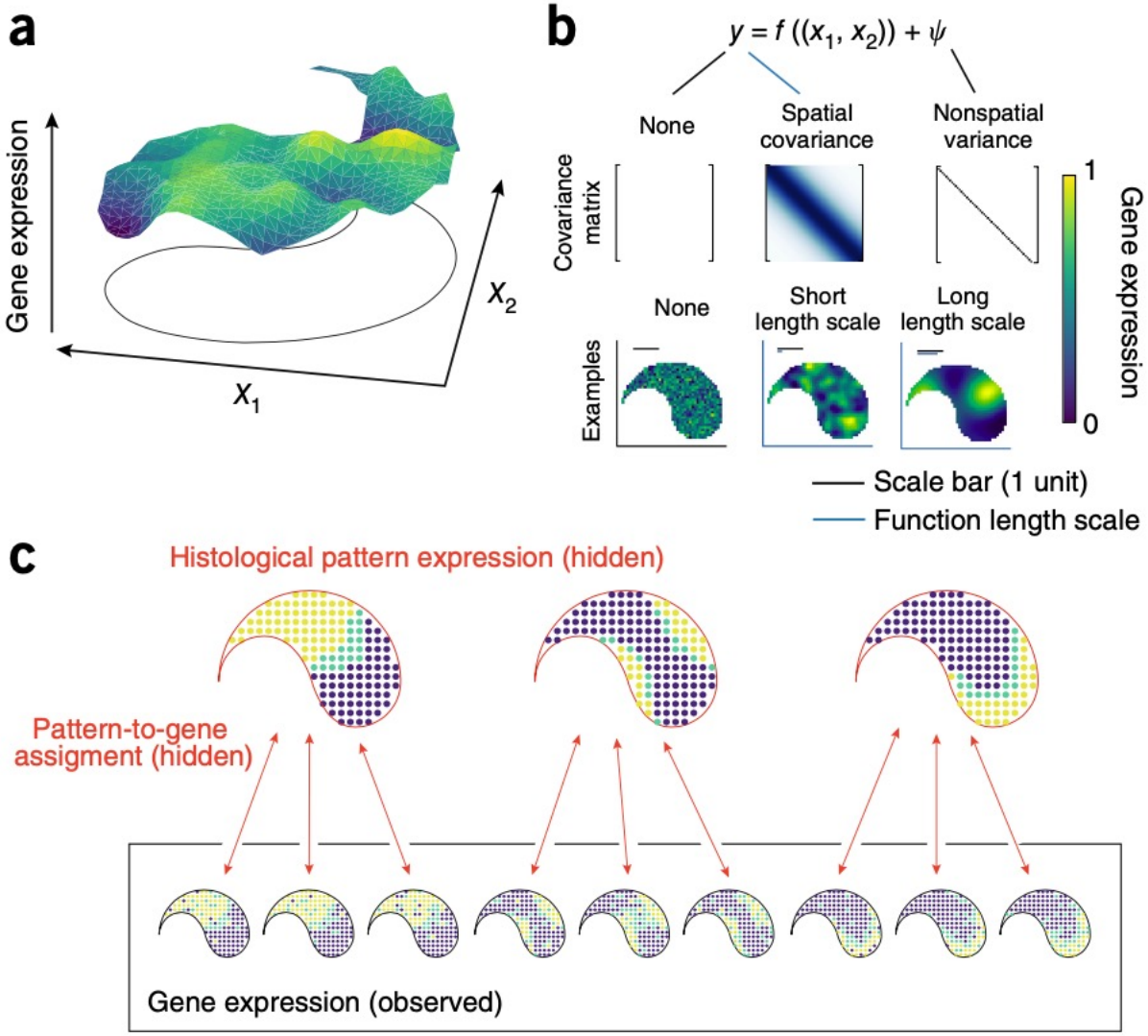






SpatialDE

- Gaussian process regression; decomposes expression variability into spatial and nonspatial components
- SpatialDE defines spatial dependence for a given gene by using a nonparametric regression model, **testing whether gene expression levels at different locations covary in a manner that depends on their relative location**, and thus are spatially variable.



Svensson, Valentine, Sarah A. Teichmann, and Oliver Stegle. "**SpatialDE**: identification of spatially variable genes." *Nature methods* 15, no. 5 (2018): 343-346.

Trendsceek

- **Tests for significant dependency between** the **spatial distributions** of points and their associated marks (**expression levels**) through pairwise analyses of points as a function of the distance *r* (radius) between them.
- Permutation test

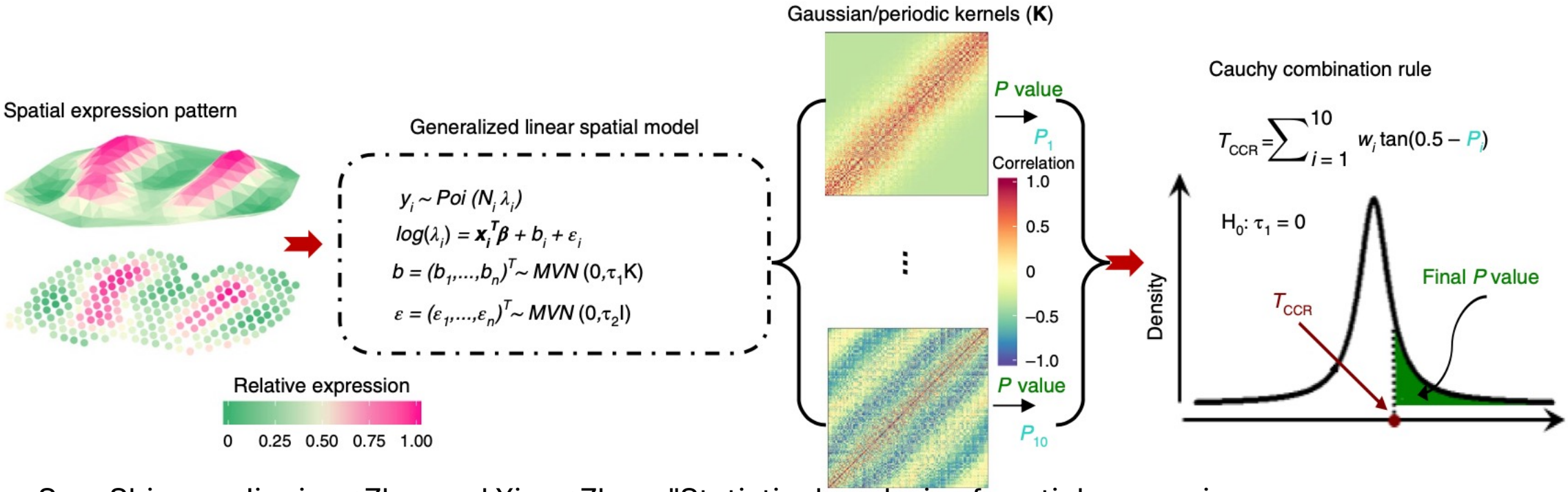
$$M_2(m_1, m_2 \mid r) = \frac{f_2(m_1, m_2, r)}{f_2(r)}$$

$$M_2(m_1, m_2 \mid r) \neq M_1(m_1) M_1(m_2)$$

Edsgärd, Daniel, Per Johnsson, and Rickard Sandberg. "Identification of spatial expression trends in single-cell gene expression data." *Nature methods* 15, no. 5 (2018): 339-342.

Spark

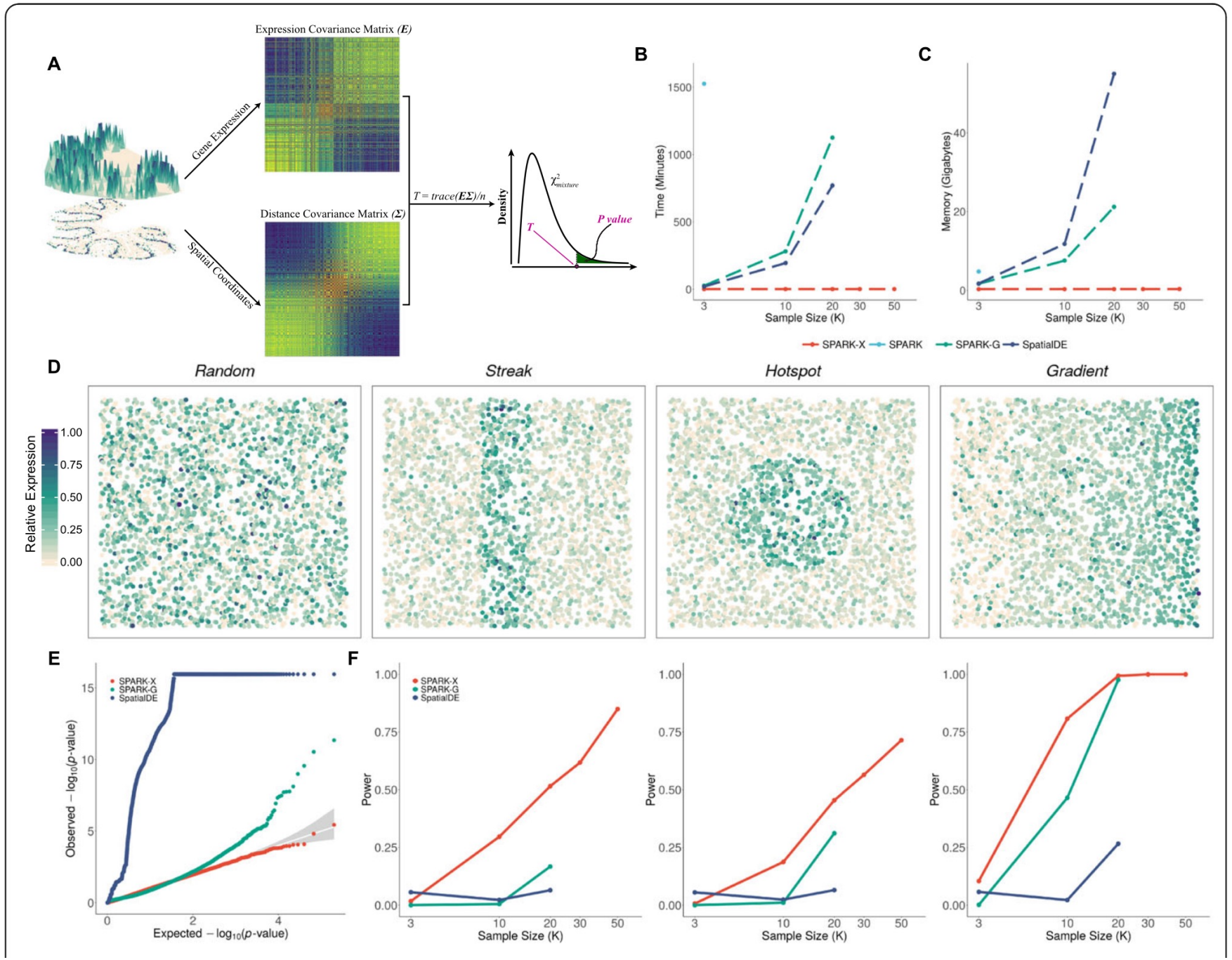
- **Generalized linear spatial model** with a variety of spatial kernels. Chi-square as the exact test statistics distribution; **Cauchy combination rule to combine across multiple spatial kernels**



Sun, Shiquan, Jiaqiang Zhu, and Xiang Zhou. "Statistical analysis of spatial expression patterns for spatially resolved transcriptomic studies." *Nature methods* 17, no. 2 (2020): 193-200.

Spark-X

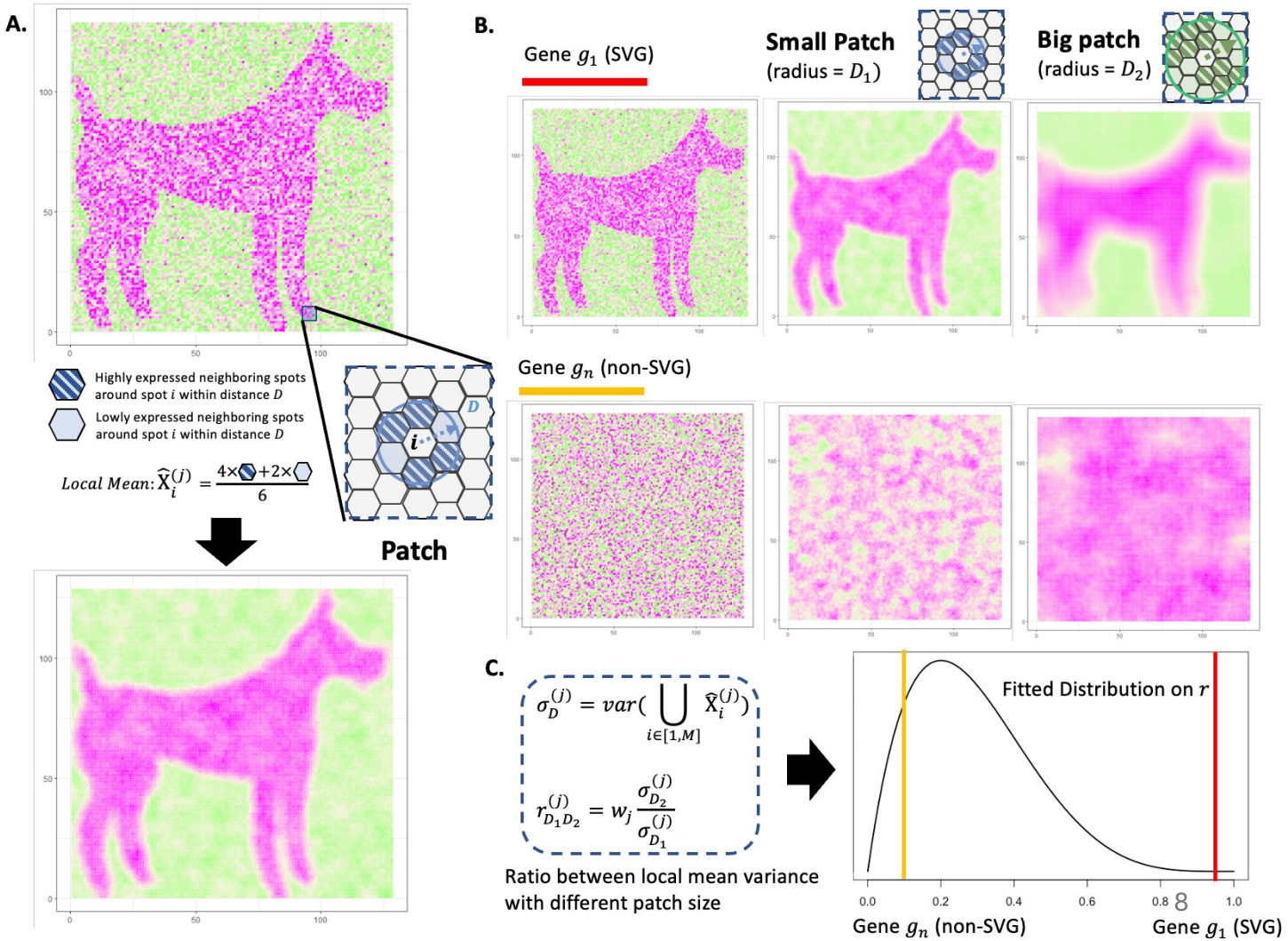
- Non-parametric, check dependence between expression and spatial.
- Simple Statistics
- Designing for Large data



Zhu, Jiaqiang, Shiquan Sun, and Xiang Zhou. "SPARK-X: non-parametric modeling enables scalable and robust detection of spatial expression patterns for large spatial transcriptomic studies." *Genome Biology* 22, no. 1 (2021): 1-25.

BSP: Dimension-agnostic and granularity-based spatially variable gene identification

- BSP (big-small patch), a non-parametric model by comparing gene expression pattens at two spatial granularities to identify SVGs from two or three-dimensional spatial transcriptomics data in a fast and robust manner.
- **Velocity of change in variances of local means in different granularity can be used to distinguish SVGs and non-SVGs**
- Data driven, model free, any dimension
- Highlighted by Editor's choices

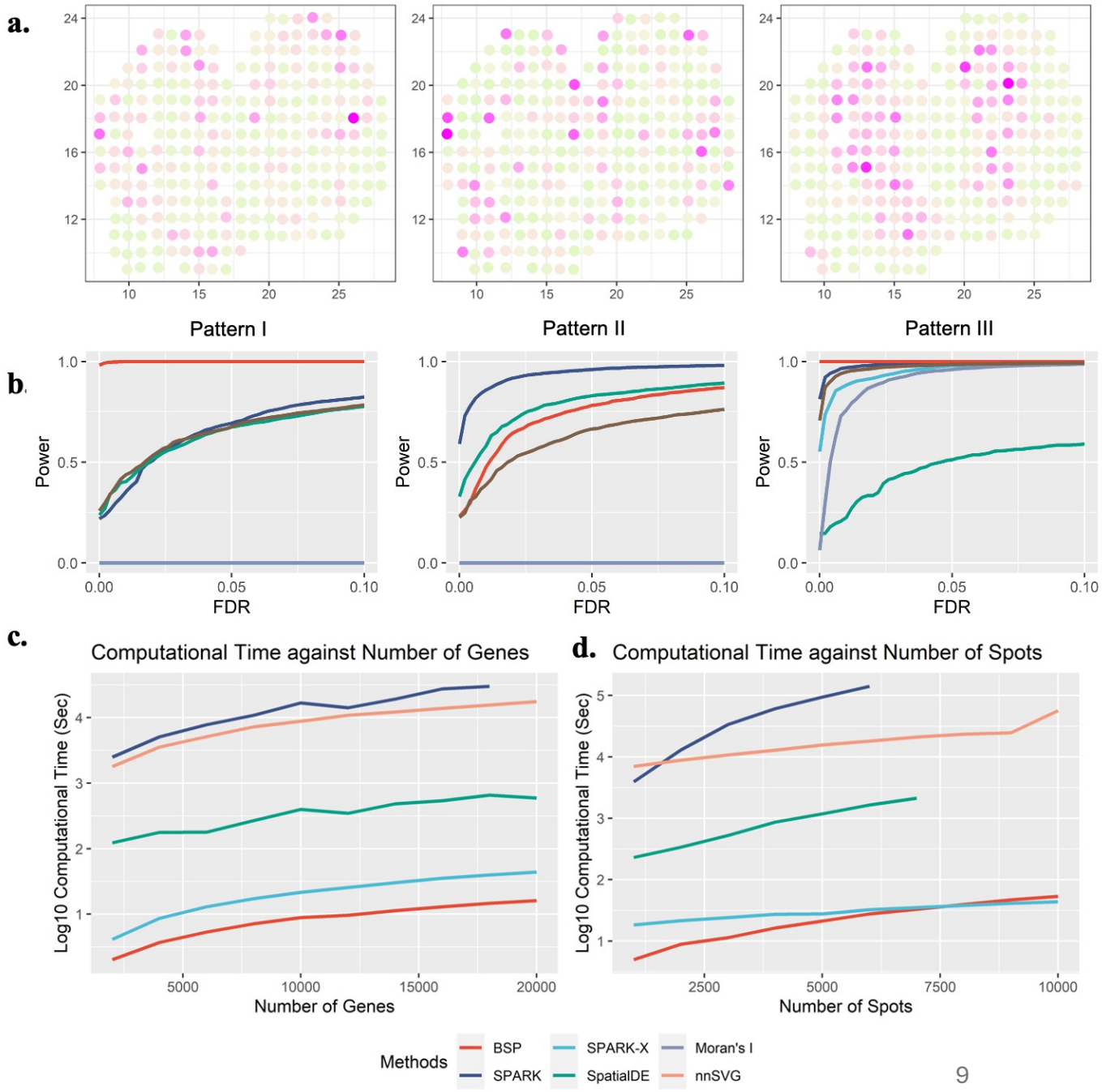


Wang, J., Li, J., Kramer, S.T. *et al.* Dimension-agnostic and granularity-based spatially variable gene identification using BSP. *Nat Commun* **14**, 7367 (2023).

2D simulations

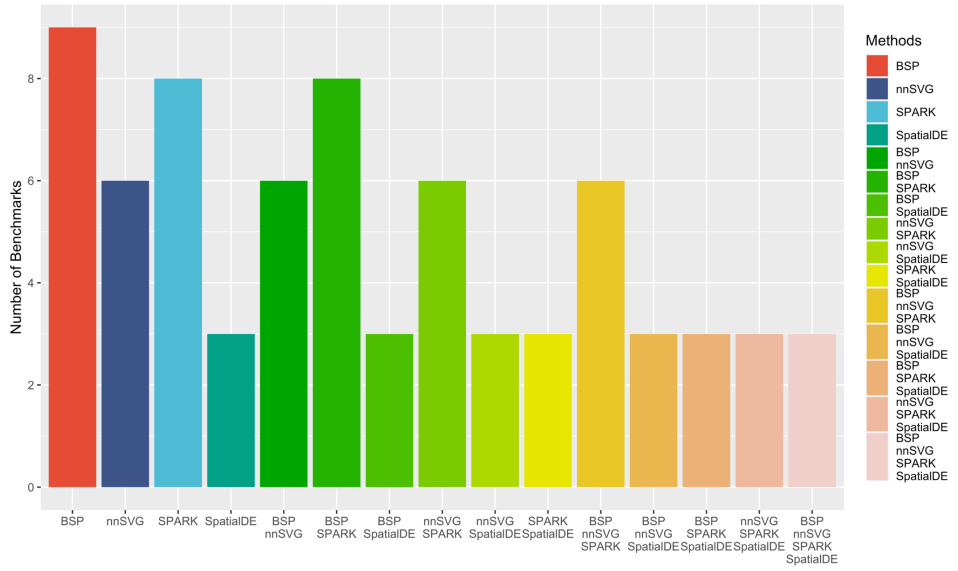
- Better performances on most scenarios varying spatial patterns, size of the pattern, signal strength, and noise level
- Fast and accurate

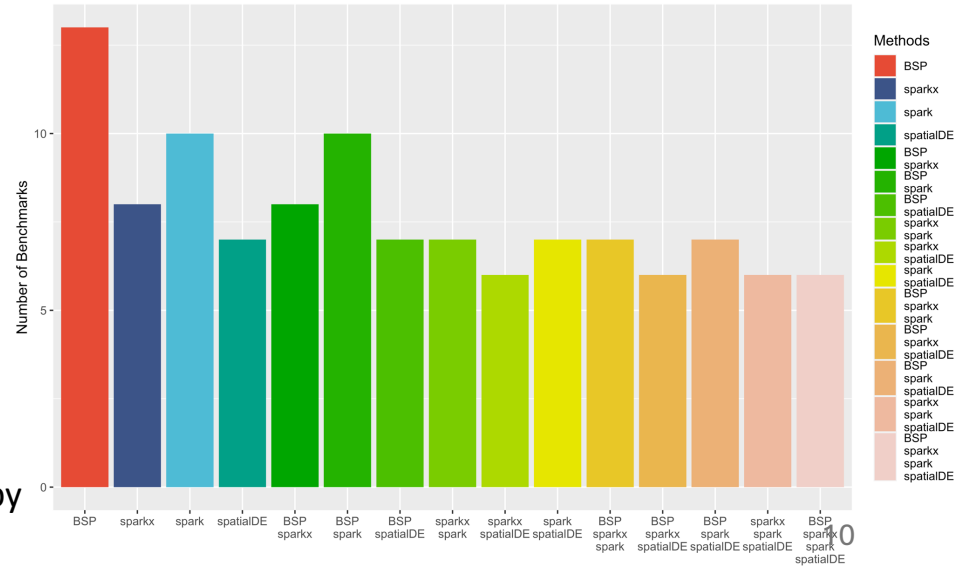
Mouse olfactory bulb (simulation)



2D Real datasets

- Mouse factory bulb study
  - ST platform
  - 10 marker genes
  - BSP detected 9
  - SpatialDE detected 3, SPARK detected 8, nnSVG detected 6, and SPARK-X detected 0
- Human breast cancer
  - ST platform
  - 14 marker genes
  - BSP detected 13
  - SpatialDE detected 7, SPARK detected 10, and SPARK-X detected 8

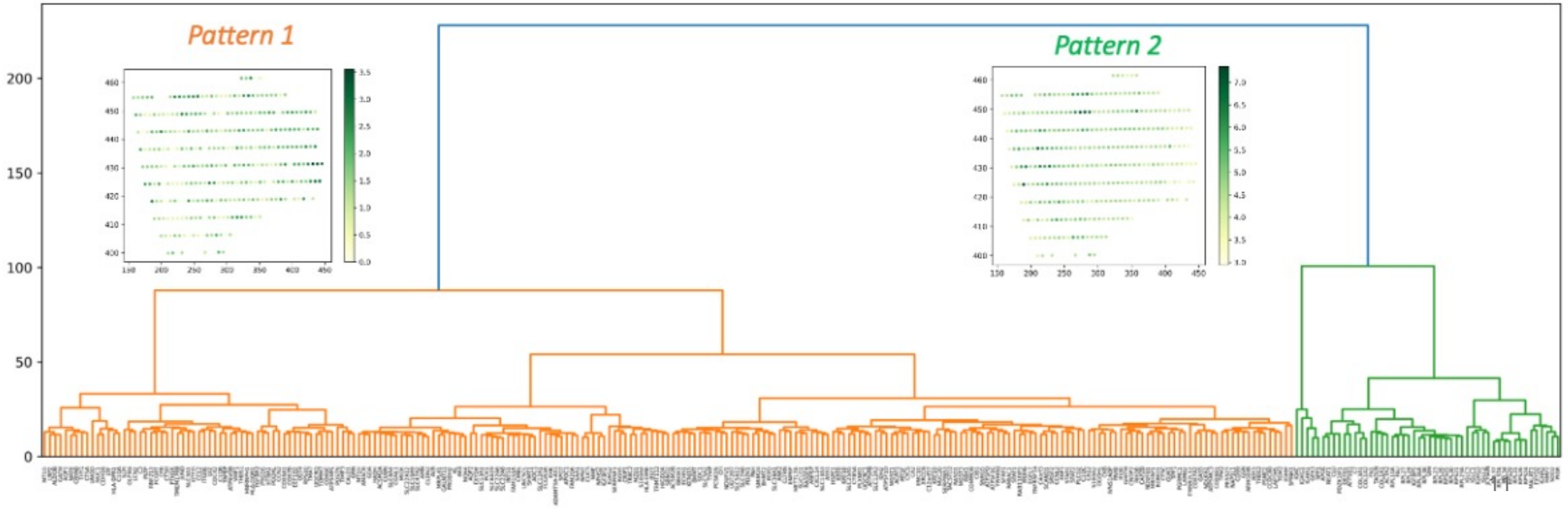




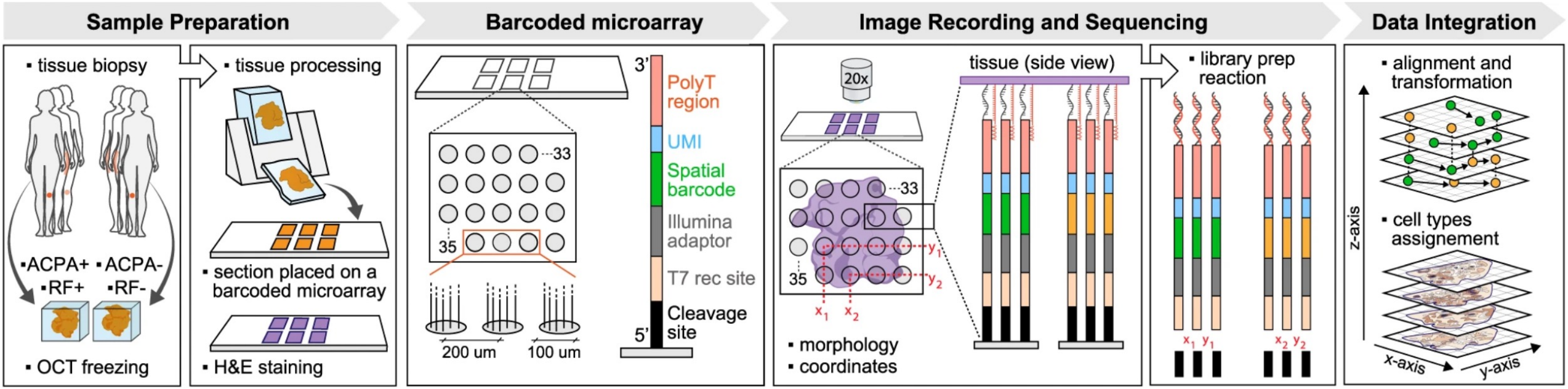
Stahl, P. L. *et al.* Visualization and analysis of gene expression in tissue sections by spatial transcriptomics. *Science* **353**, 78-82 (2016).

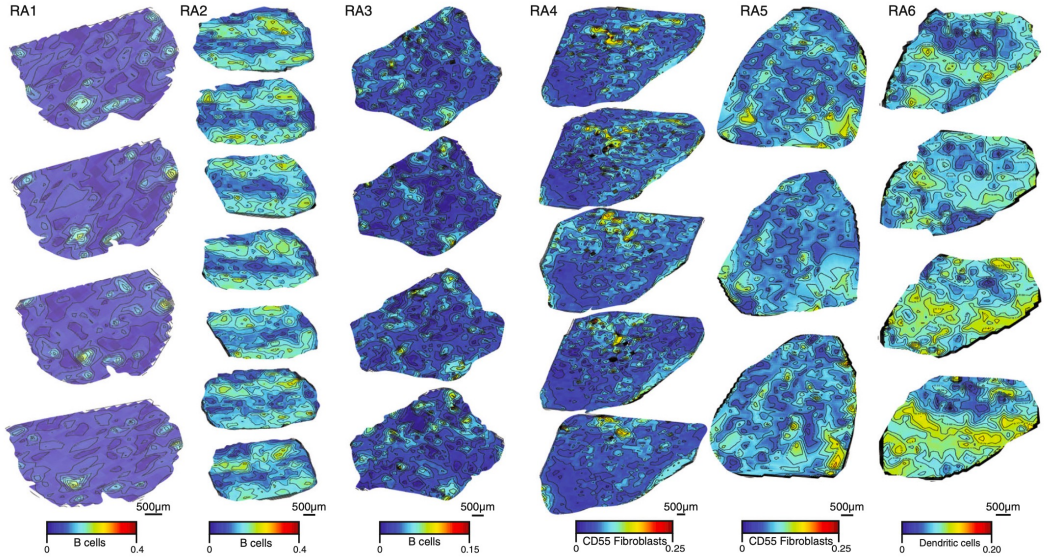
2D case study: Acute Kidney Injury (10X Visum)

- Pattern 1
  - Aerobic respiration (q-value 1.04e-09) and oxidative phosphorylation (q-value 4.69e-09), consistent with hypoxic or nephrotoxic acute tubular necrosis, the most common tubulointerstitial form of AKI.
  - Pathways of early recovery were enriched including **kidney development** (q-value 8.56e-07) and **metanephric nephron epithelium development** (q-value 2.30e-06), which included genes like PAX8.
- Pattern 2
  - Humoral immune response (q-value 5.15e-05) and tissue homeostasis (q-value 5.15e-05).
  - Several **immune responses** were activated (q-value 3.51e-04) including B cell receptor signaling pathway (q-value 4.72e-07).



3D spatial transcriptomics is on the way





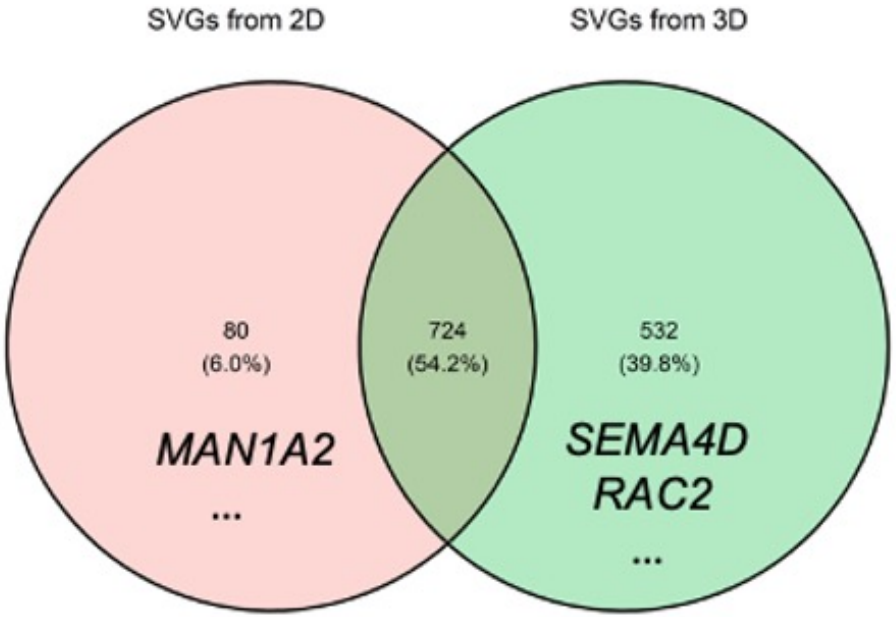
Cut onions in slices

27 slices of 6 RA patients

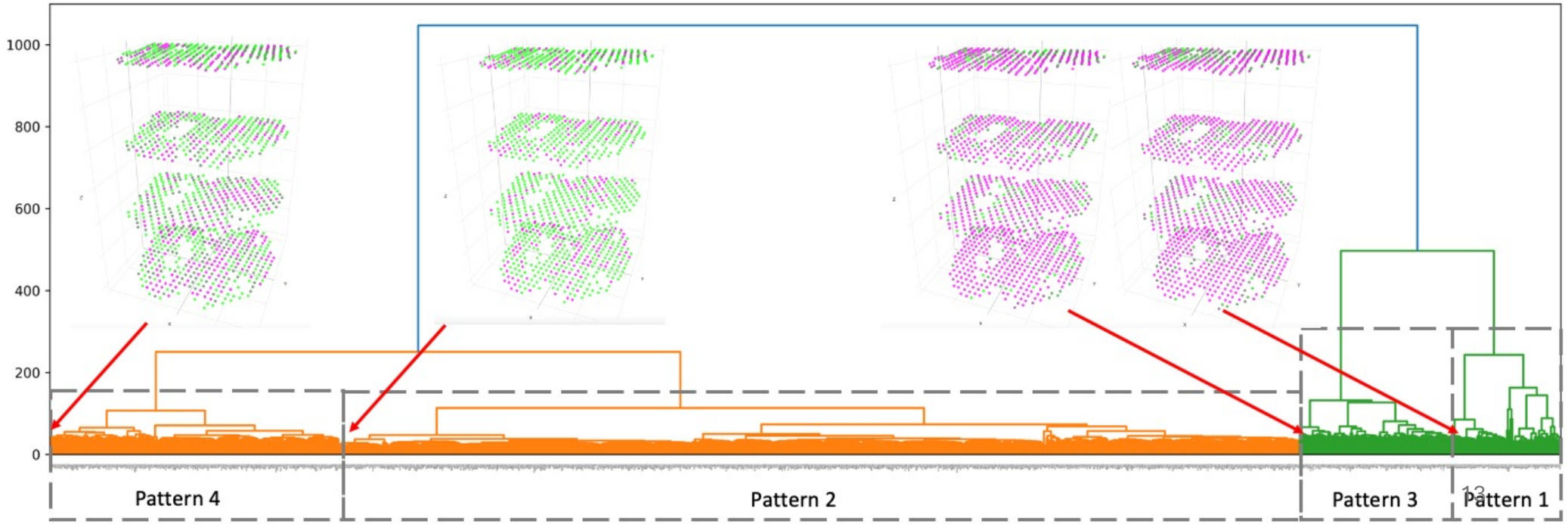
Vickovic,…, **Aviv Regev** & Patrik L. Ståhl "Three-dimensional spatial transcriptomics uncovers cell type localizations in the human rheumatoid arthritis synovium." *Communications Biology* 5.1 (2022): 1-11.

3D case study: Rheumatoid Arthritis

- Identified more biological meaningful genes than 2D meta-analysis

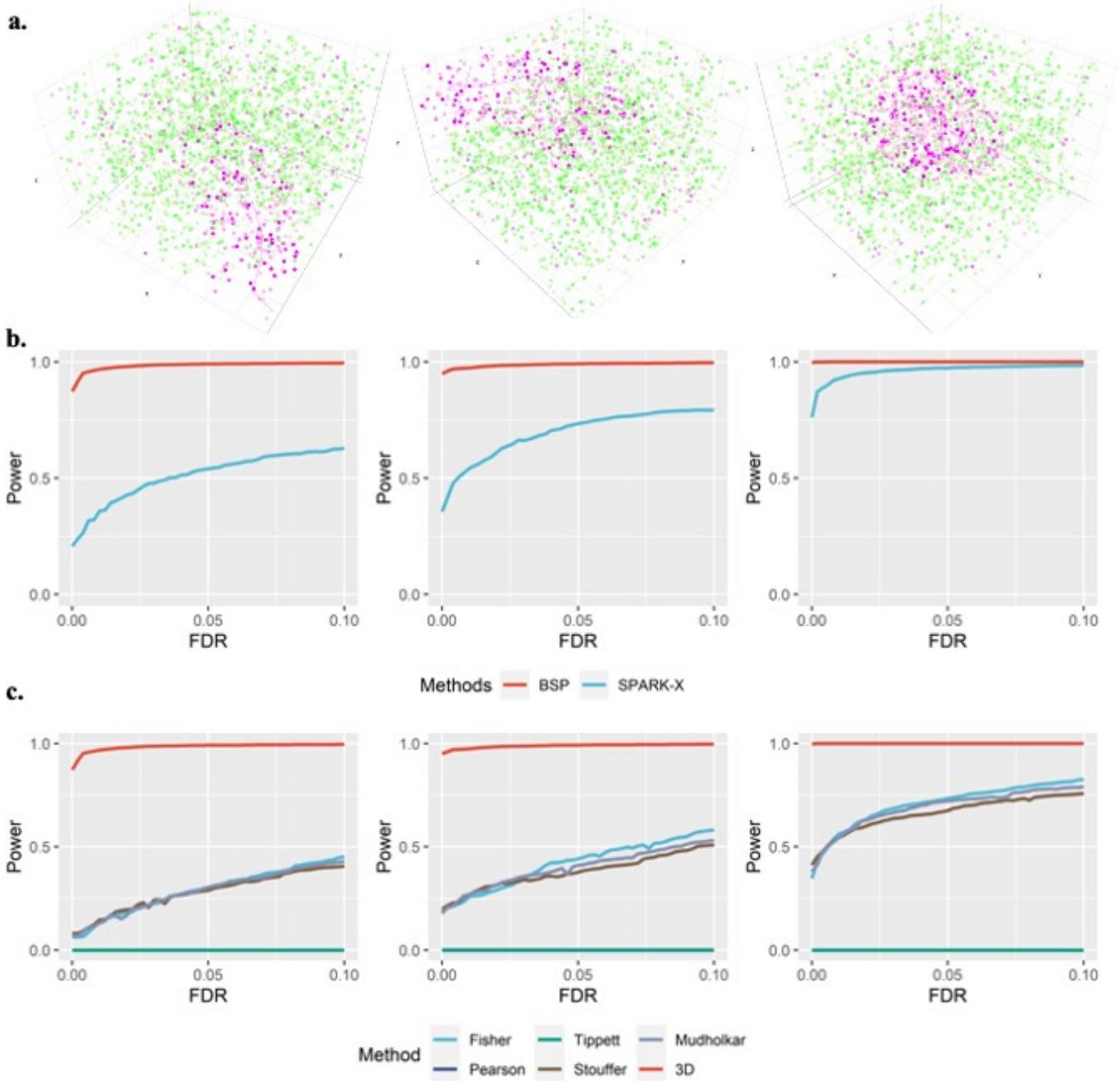


Vickovic, S. *et al.* Three-dimensional spatial transcriptomics uncovers cell type localizations in the human rheumatoid arthritis synovium. *Commun Biol* **5**, 129 (2022)

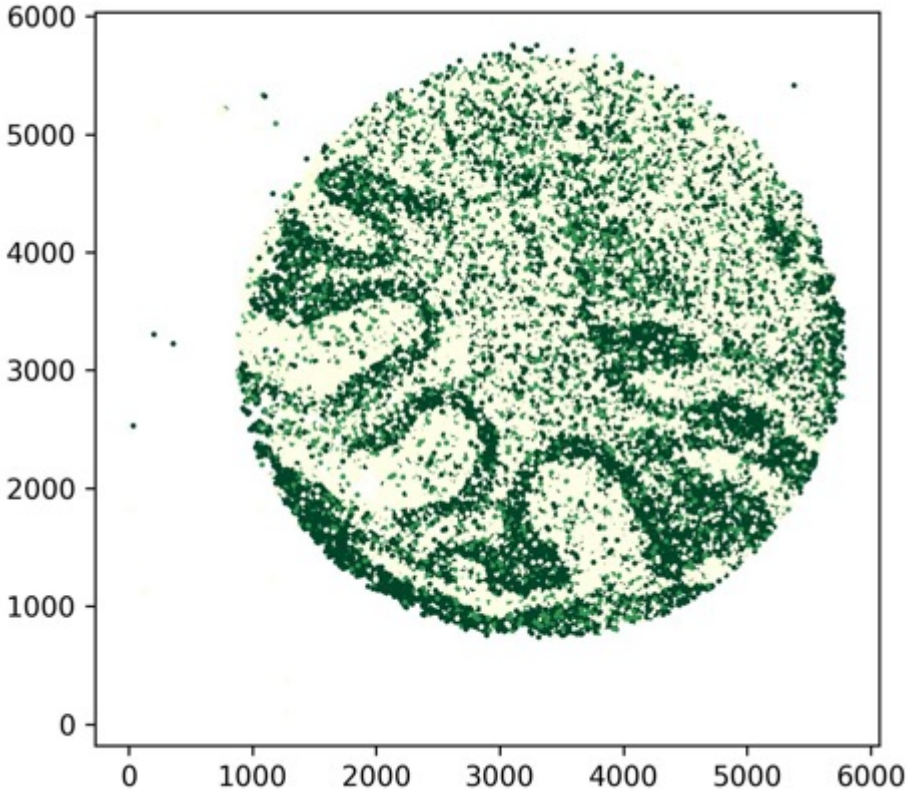


3D simulation

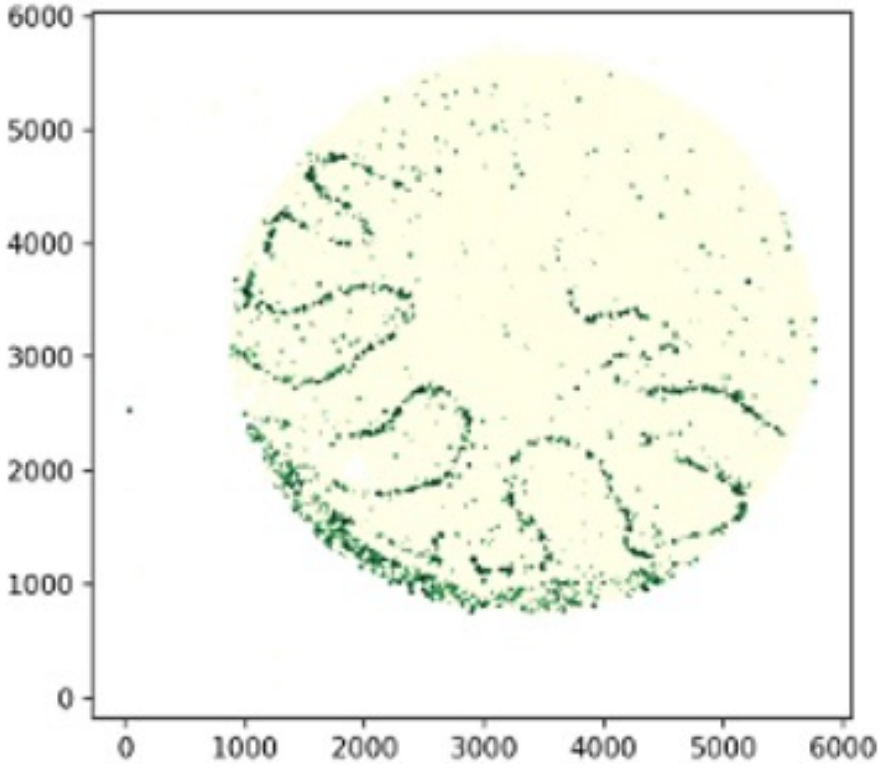
- Three 3D patterns:
- curved stick (Pattern I), thin plate (Pattern II), and irregular lump (Pattern III)
- Power analysis varying pattern size, signal strength, and noise.
- 3D outperforms meta-analysis on 2D slides



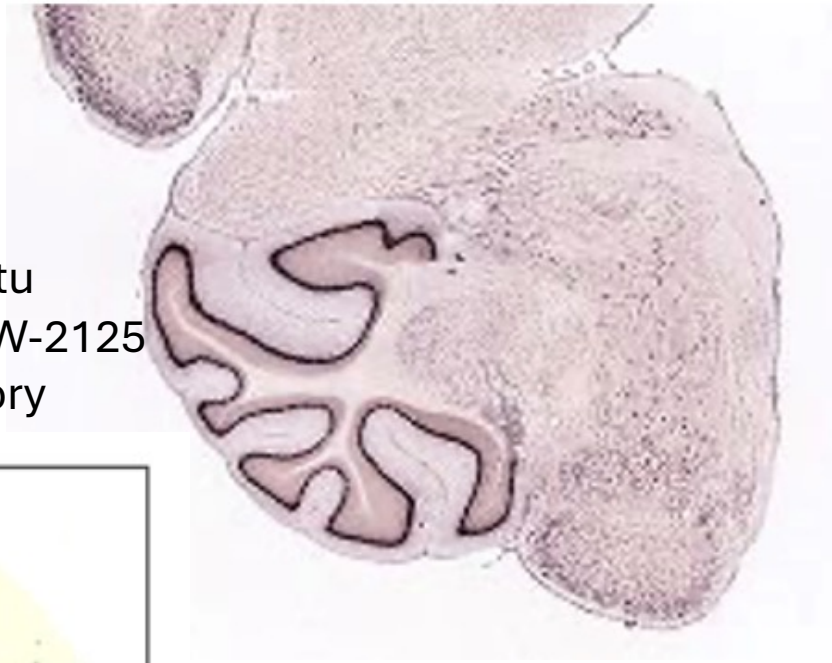
Challenges from large scale data



23,096 genes and 39,496 beads
Running time: **18 min** on an Ubuntu workstation with Intel(R) Xeon(R) W-2125 CPU @ 4.00GHz and 32 GB memory



Malat1 **(left) and Calb1 (right) as SVG identified by BSP**



ISH of *Calb1* in an adult mouse brain from a separate study

2D slide-seq v2

scBSP (BSP 2.0): Improve computational efficiency on BSP

- Using sparse matrix operation to accelerate the computing.
- Targeting subcellular Xenium/CosMx/MERSCOPE data

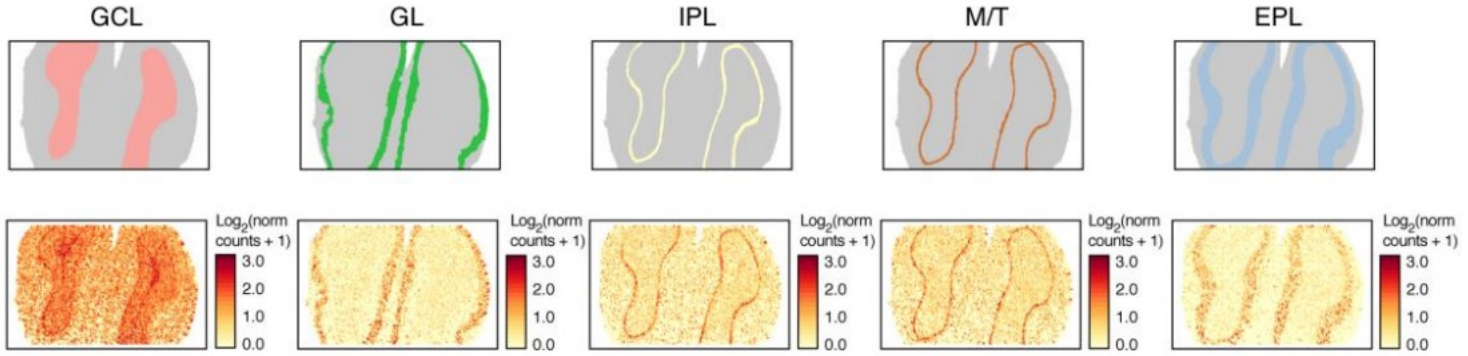
	BSP			scBSP		
Process	**Method**	**Time Complexity**	**Space Complexity**	**Method**	**Time Complexity**	**Space Complexity**
Data Pre-processing	Min-max Scaling	$O(NM)$	$O(NM)$	Maximum Absolute Scaling	$O(M)$	$O(NM)$
Patch Determination	Exhaustive Search	$O(NM^2)$	$O(NM)$	Approximate Nearest Neighbor Search*	$O(NMlogM)$	$O(NM)$
Expression Matrix Calculation	Dense Matrix	$O(M)$	$O(NM)$	Sparse Matrix	$O(SM)$	$O(SNM)$
Local Expression Calculation	Loop Operation	$O(NM)$	$O(NM)$	Matrix Operation	$O(SNM)$	$O(SNM)$

* The Approximate Nearest Neighbor Search in Python is based on HNSW implementation.

Table 1: Time and space complexity of BSP and scBSP. M: number of spots; N: number of genes; S: data sparsity (proportion of non-zero values in the expression matrix).

Li, Jinpu, et al. "scBSP: A fast and accurate tool for identifying spatially variable genes from spatial transcriptomic data." *bioRxiv* (2024): 2024-05.

Performance on a laptop

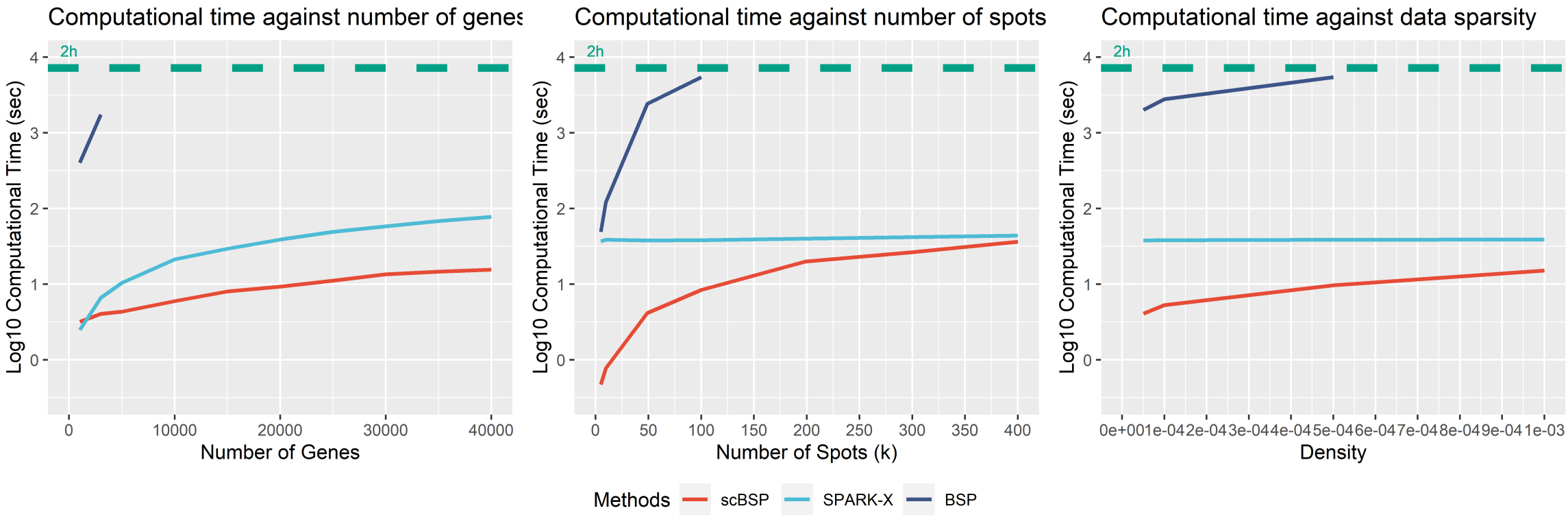


- HDST data:
- ~200,000 spots, 20,000 genes, 0.0003 density

- BSP: 4 hours, 90GB
- scBSP: ~3 sec, 2GB

Vickovic, S., Eraslan, G., Salmén, F. *et al.* High-definition spatial transcriptomics for in situ tissue profiling. *Nat Methods* **16**, 987–990 (2019).

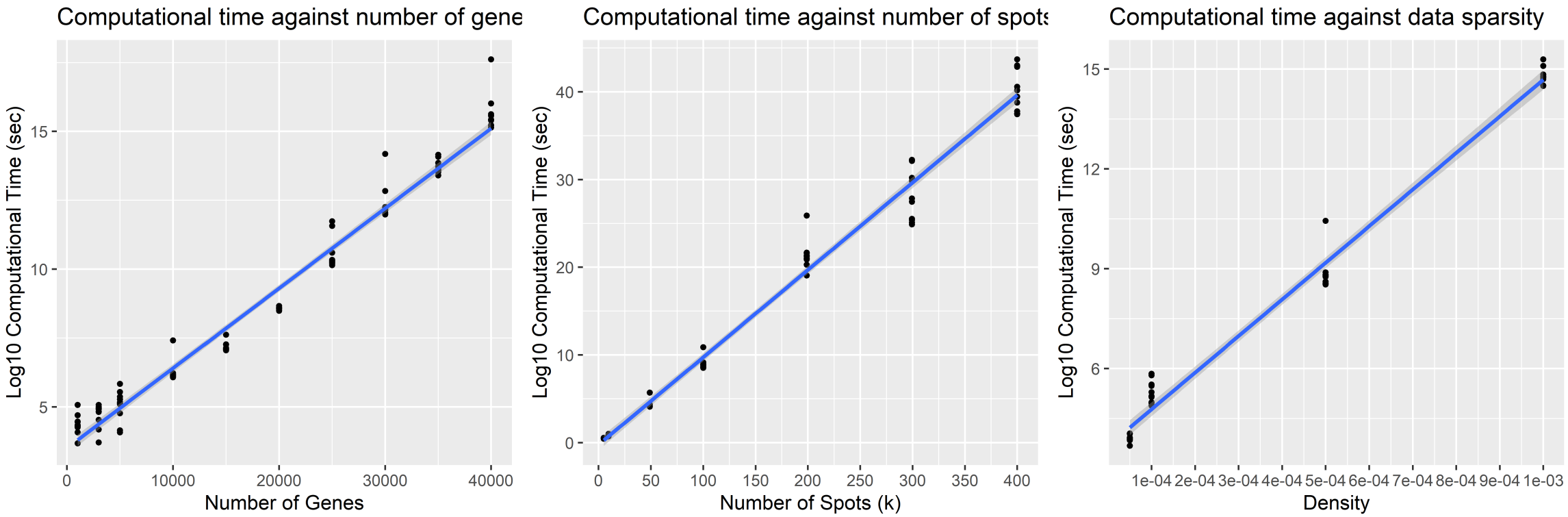
Results – running time



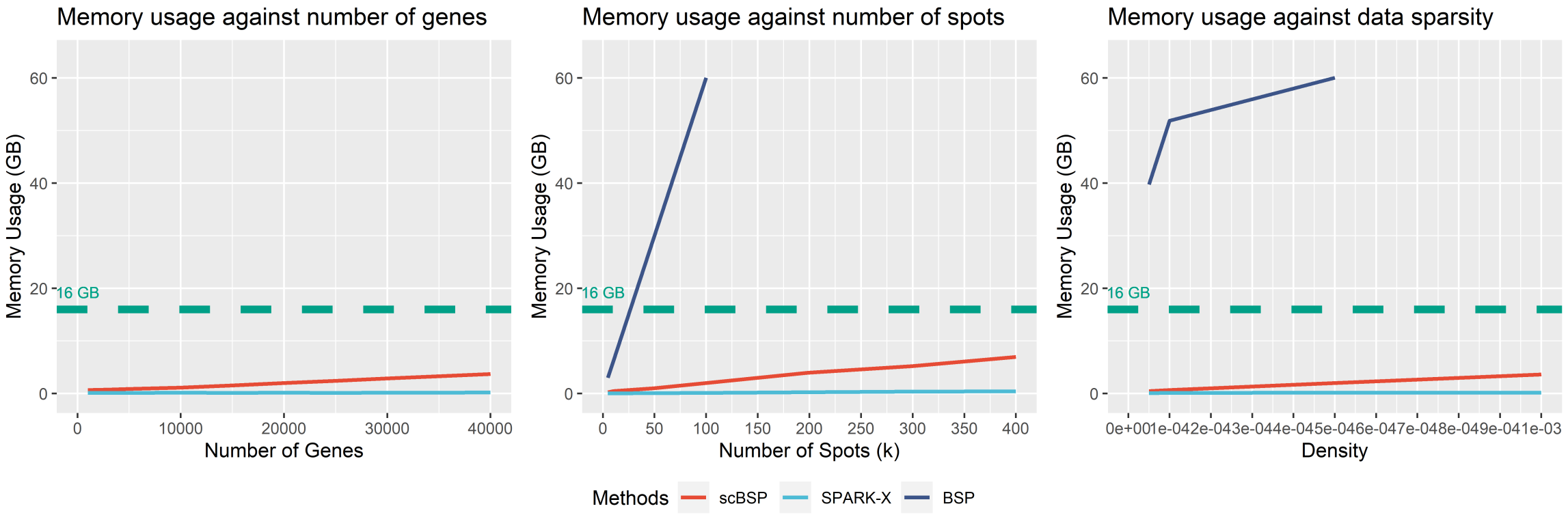
Left: Computational time with an increasing number of genes and fixed 100, 000 spots and density of 0.0005.
Middle: Computational time with an increasing number of spots and fixed 20, 000 genes and density of 0.0005.
Right: Computational time with an increasing density and fixed 100, 000 spots and 20,000 genes.

Results – running time

Computational time scales linearly with number of genes, number of spots, and data density



Results – memory usage



Required RAM memory < 10 GB for most data

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ML and Data analysis

Dr. **Dong Xu** at University of Missouri
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Dr. **Qin Ma** at OSU
Dr. Yuzhou Chang
Yi Jiang
…
Dr. Anjun Ma at OSU

Kidney Study

Dr. Michael Eadon at IU SOM
Dr. Krzysztof Kiryluk at Columbia

Tutorial: https://github.com/juexinwang/Tutorial_DahShu2024

R: https://cran.r-project.org/web/packages/scBSP/index.html
Python: https://pypi.org/project/scbsp/

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