

# **Recent developments in single-cell multi-omics and spatial transcriptomics sequencing**

**Dr. Qin Ma  
Ohio State University**

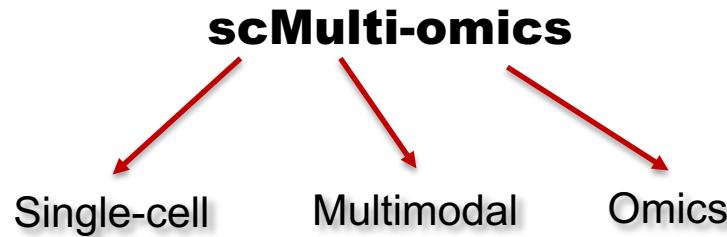
## What is scMulti-omics?

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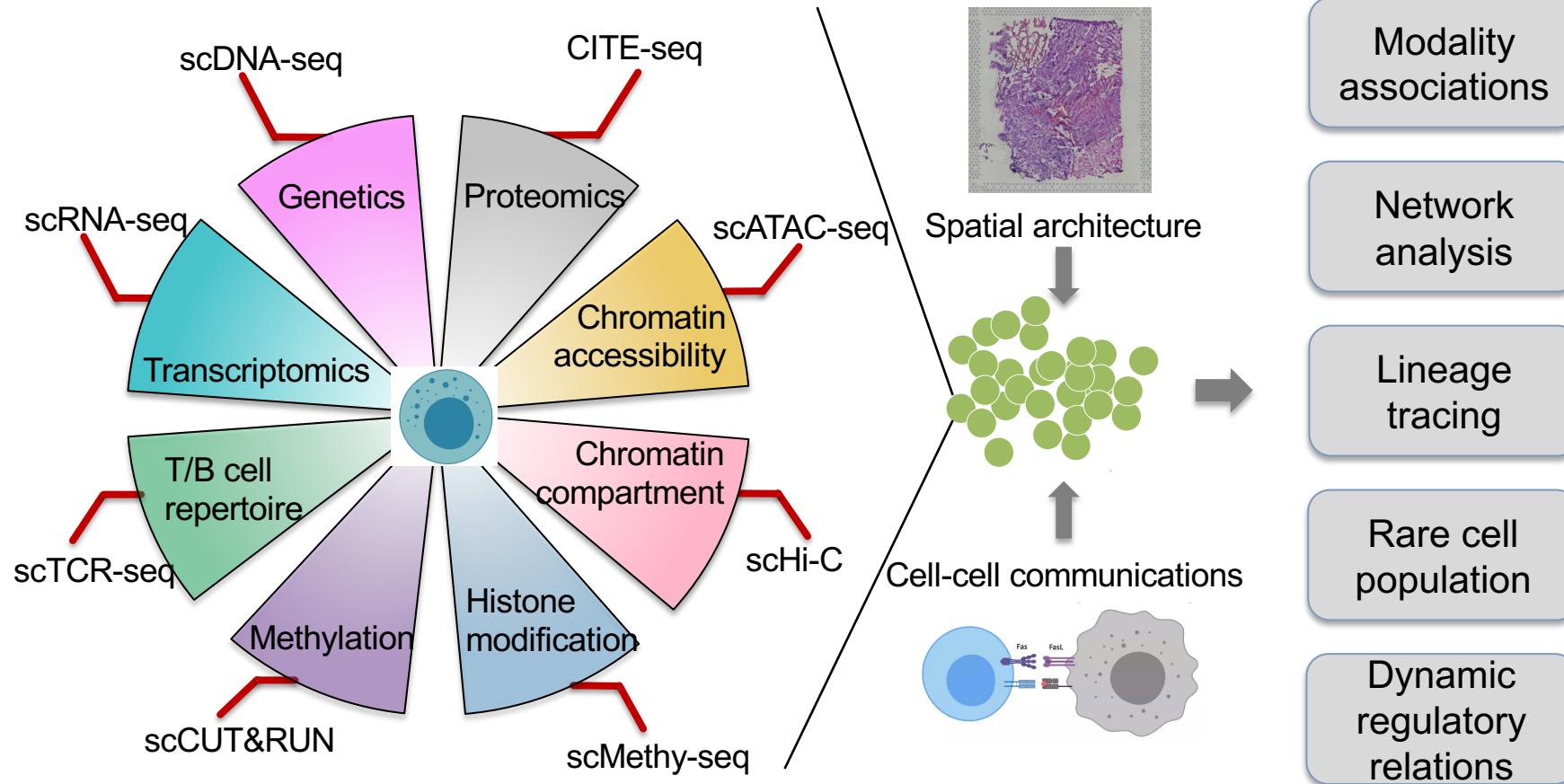
**Single-cell data  $\neq$  scRNA-seq data**

**scRNA-seq is only one modality**

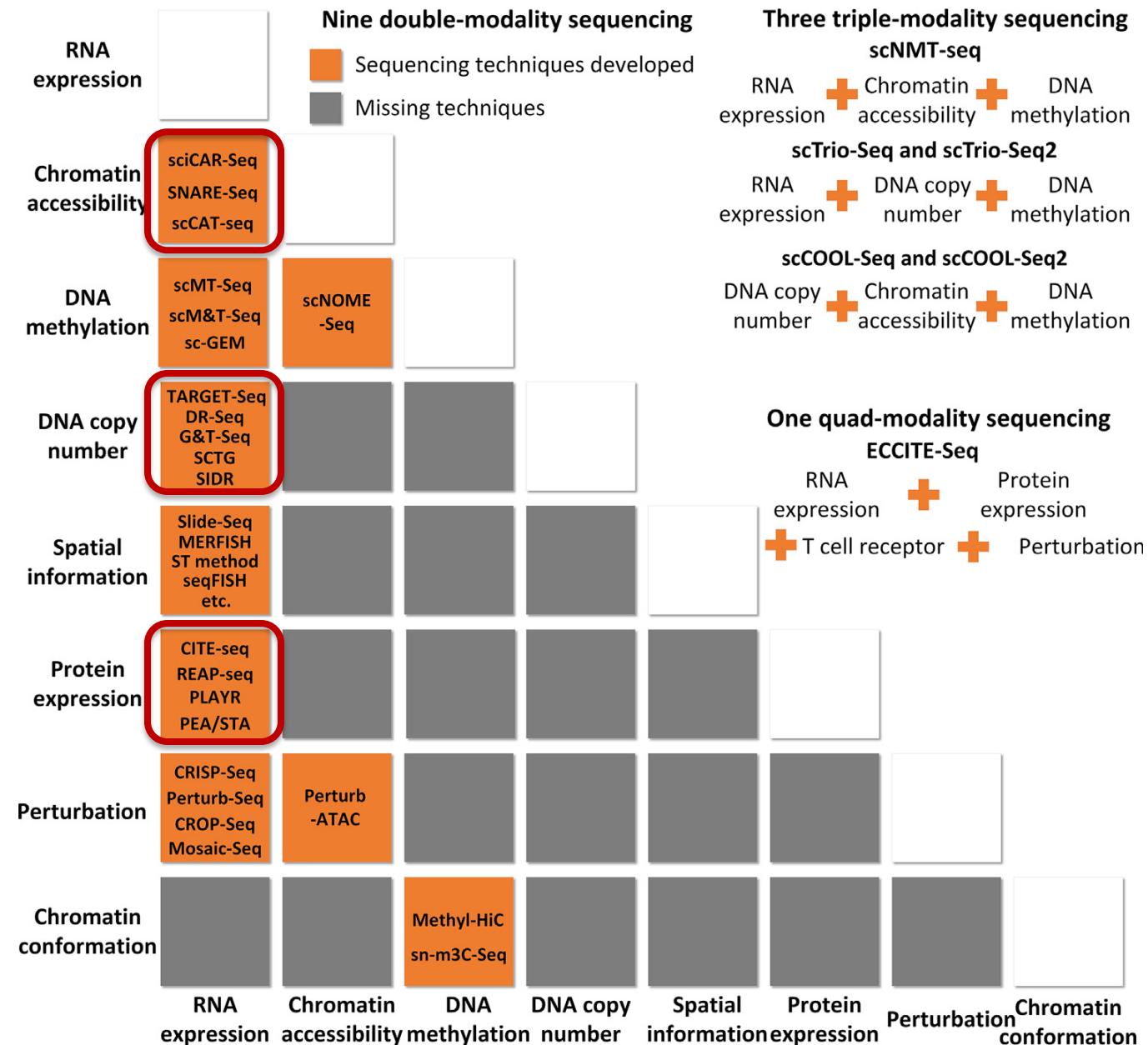
**We have multiple modalities**



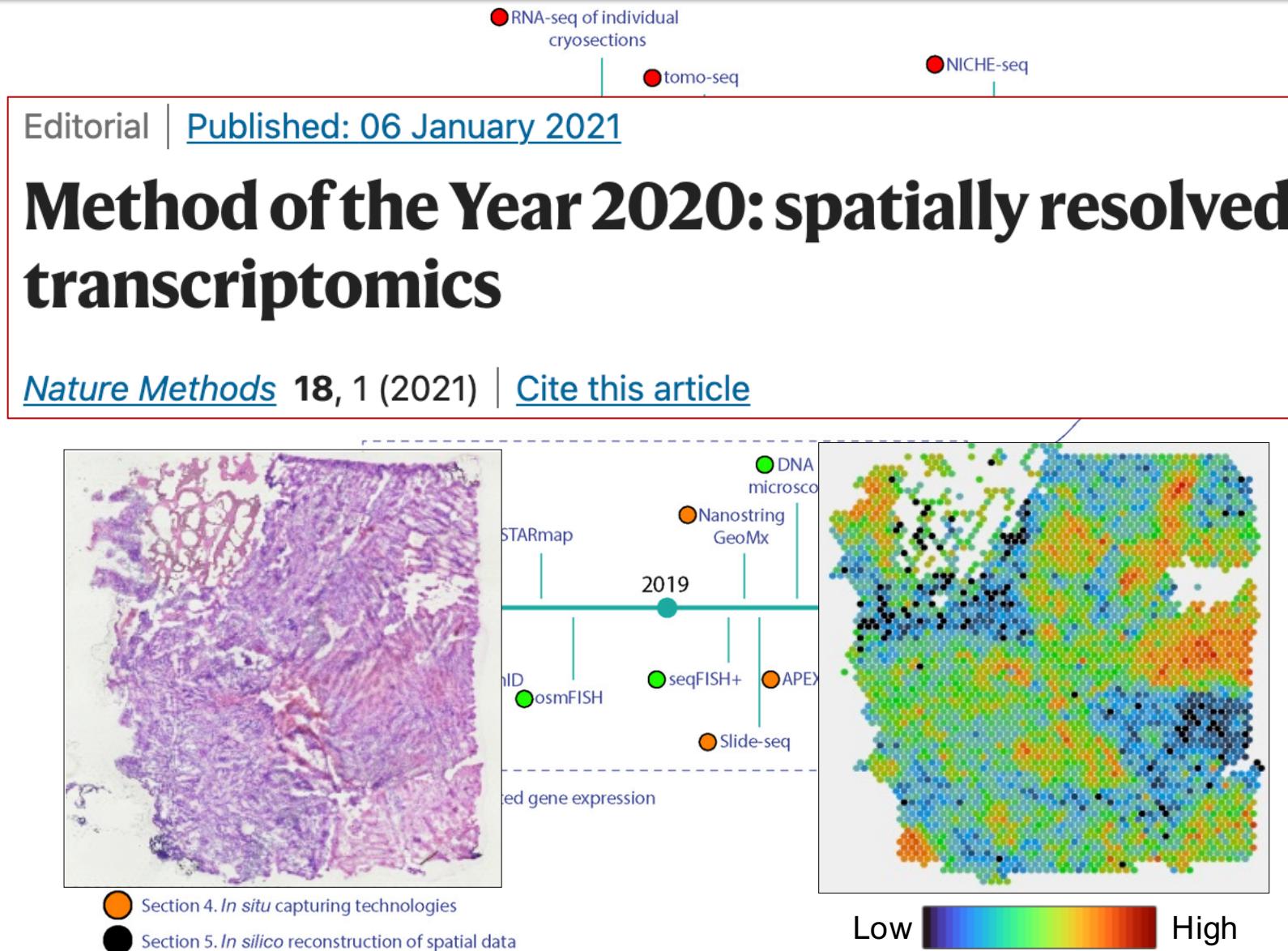
# scMulti-omics enhance and enable various biological analyses



# What scMulti-omics profiling techniques do we have?



# What is spatially resolved transcriptomics?



# Spatial transcriptomics vs others

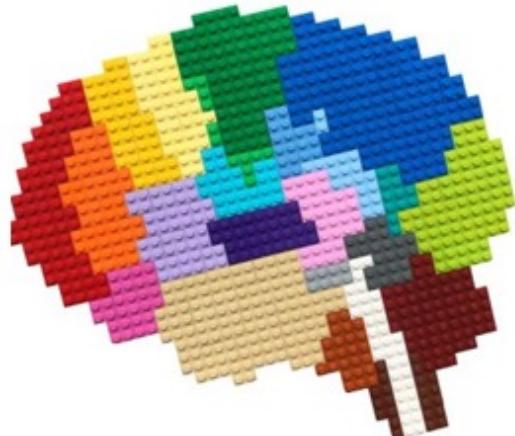
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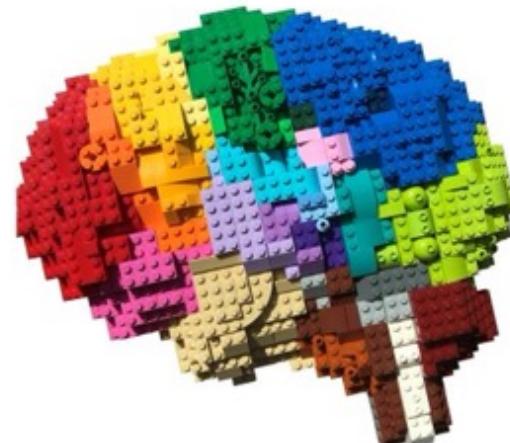
bulk RNA-seq



single-cell RNA-seq

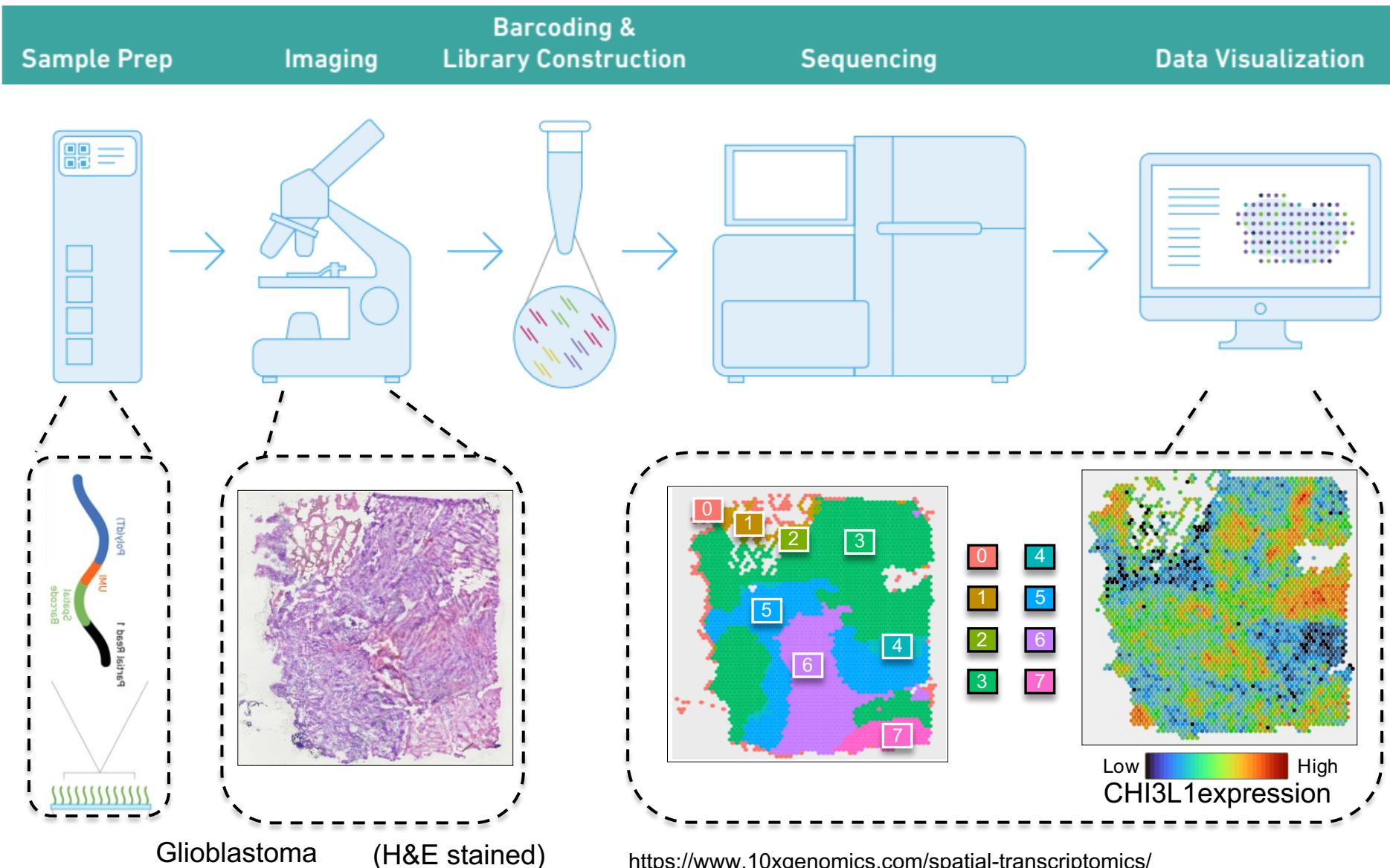


spatial transcriptomics

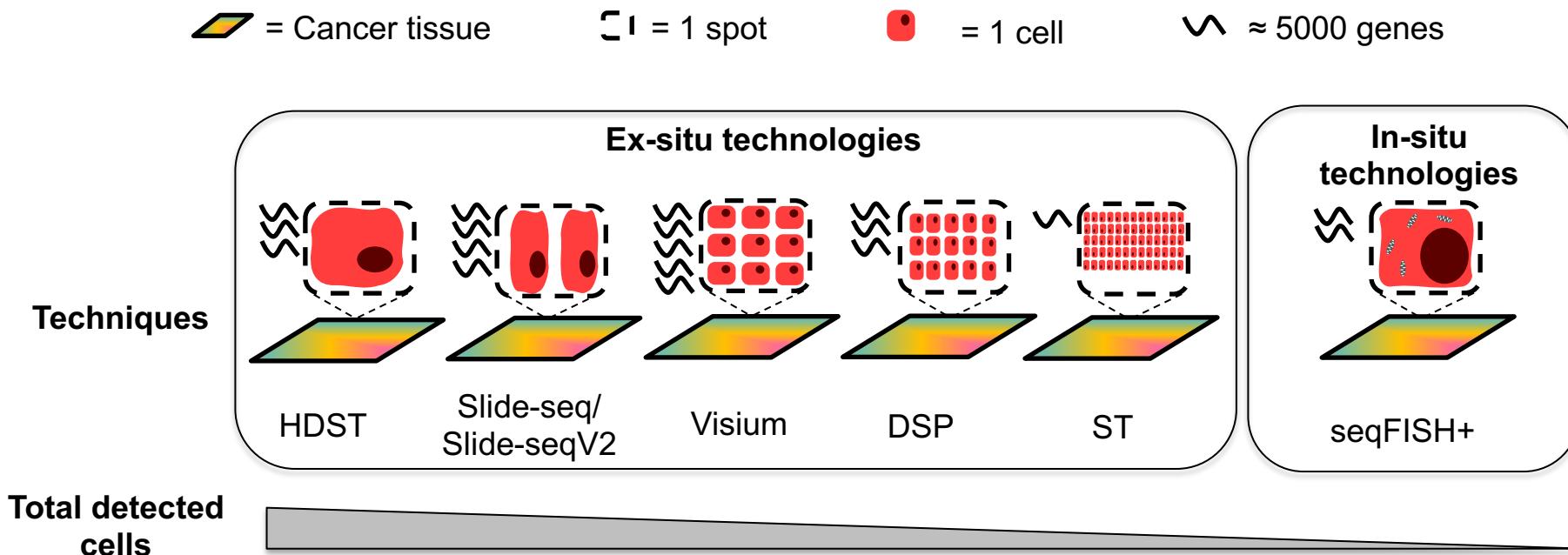


functional tissue

# Technology: 10X Visium



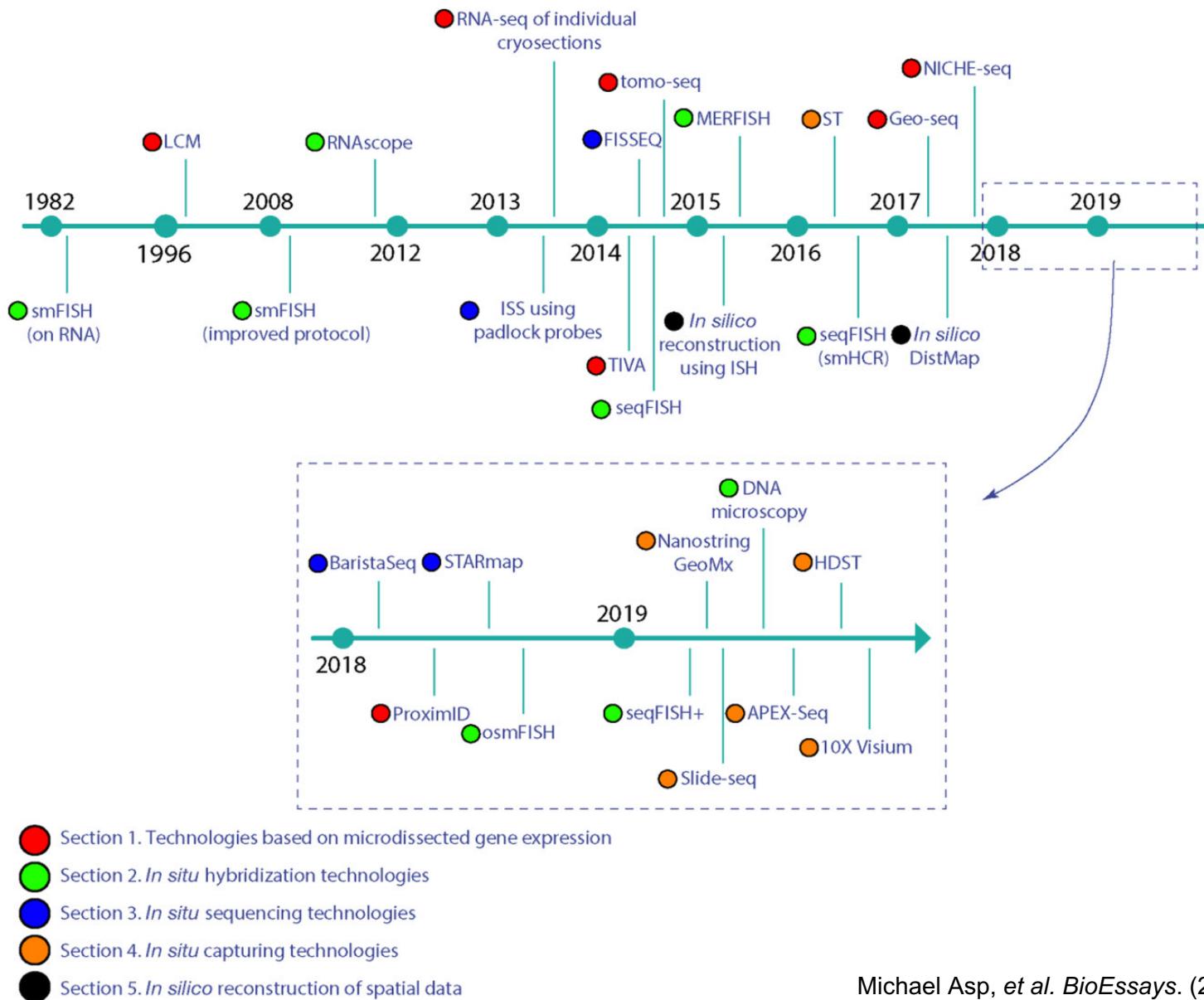
# Spatial transcriptomics technologies



Take home message:

- In-situ technology (image-based) have a higher resolution.
- Ex-situ technology (sequencing-based) have a higher cell throughput and higher gene depth.

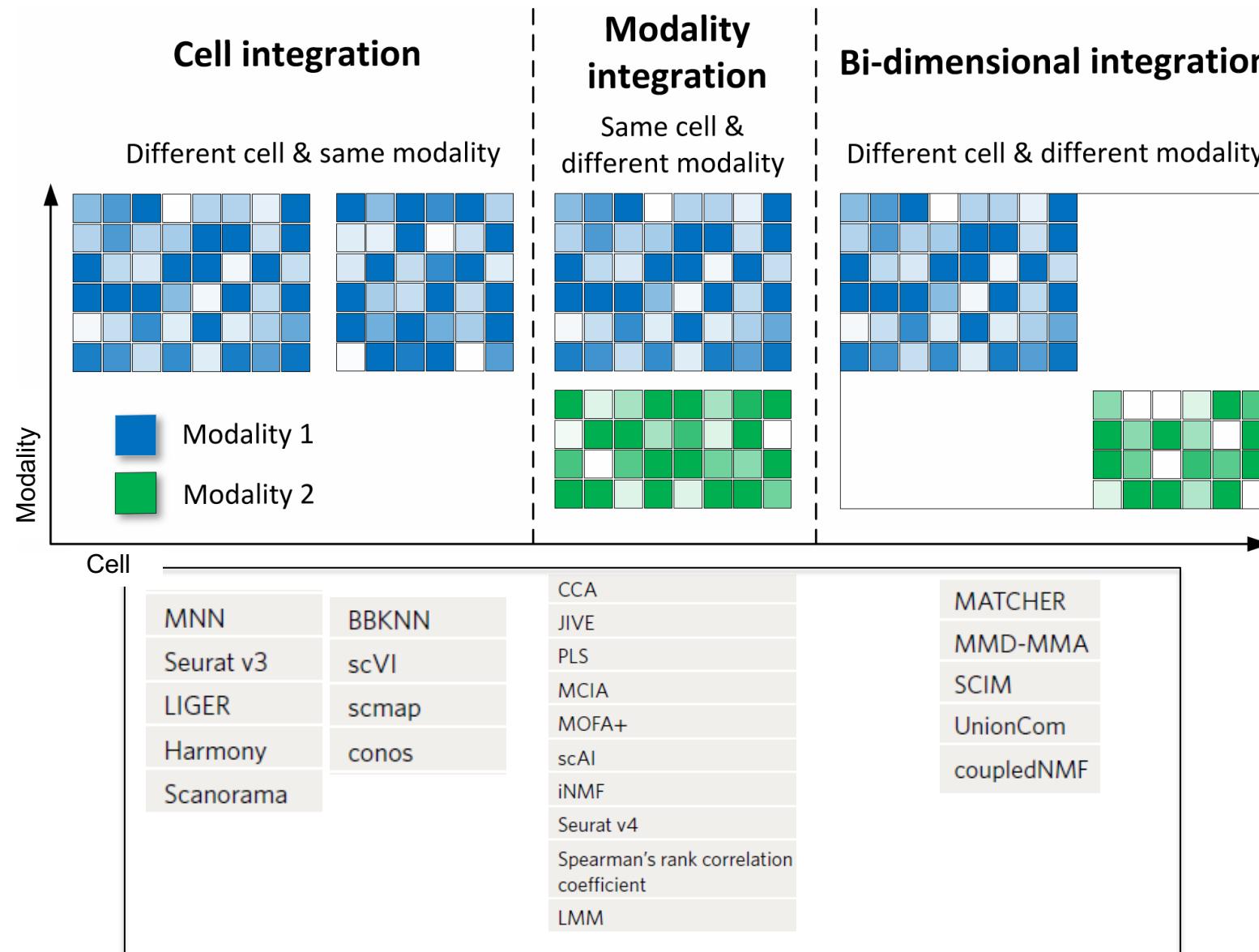
# Technology development history



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## General computational approaches in data modeling

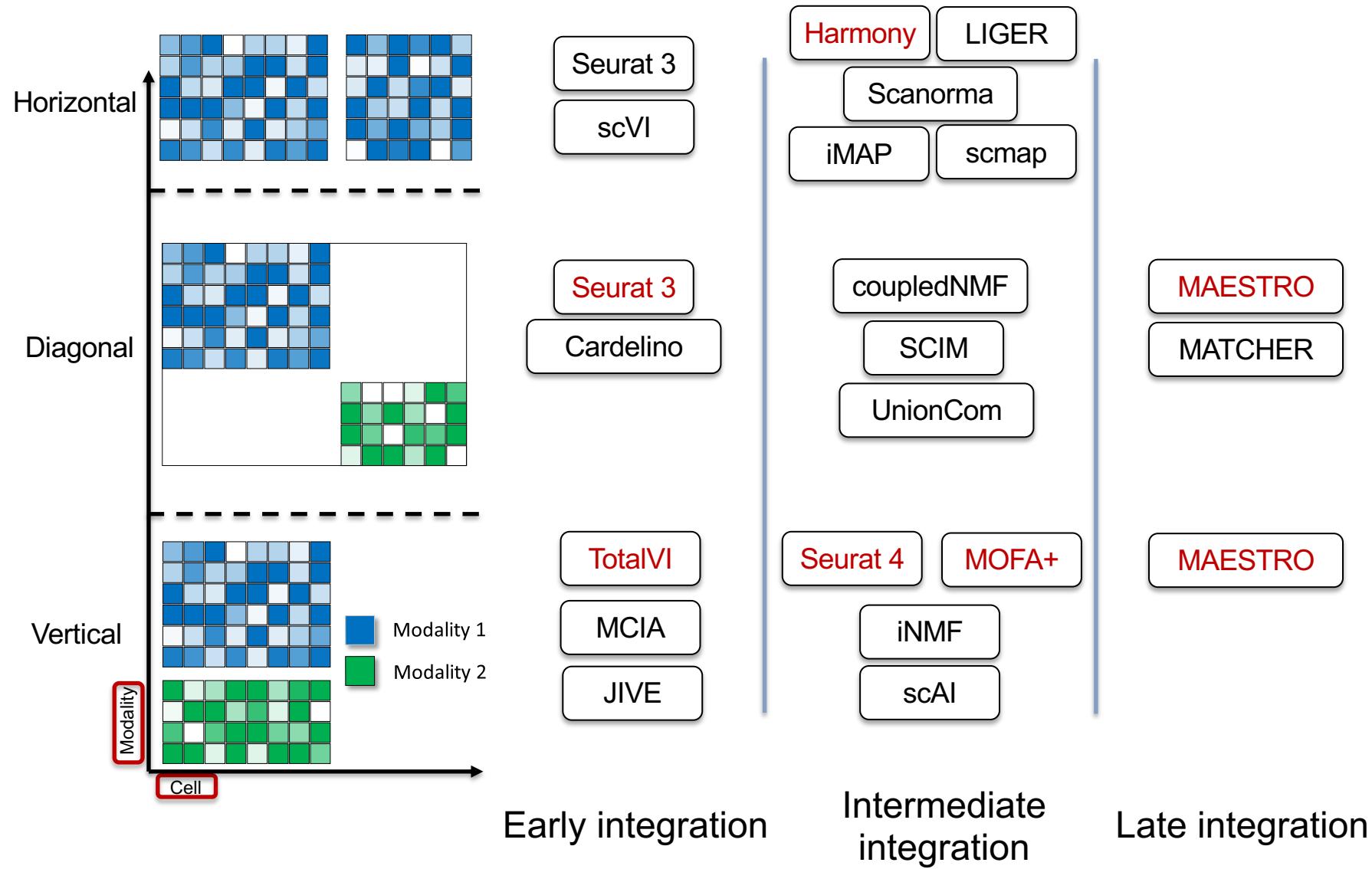
# Method of the Year 2019: scMulti-omics



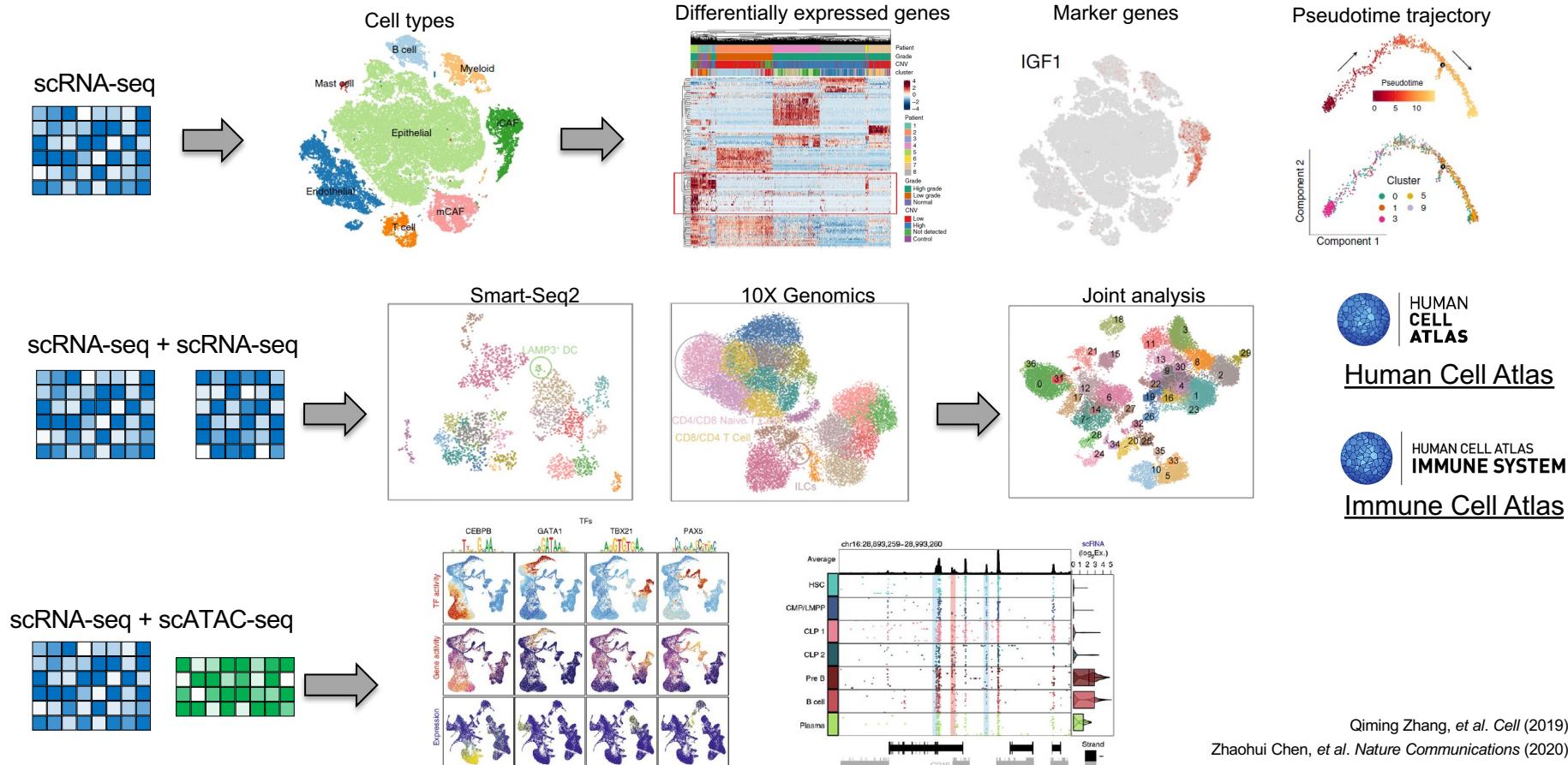
Most tools focus on:

- Data integration
- Batch correction
- Downstream modality association

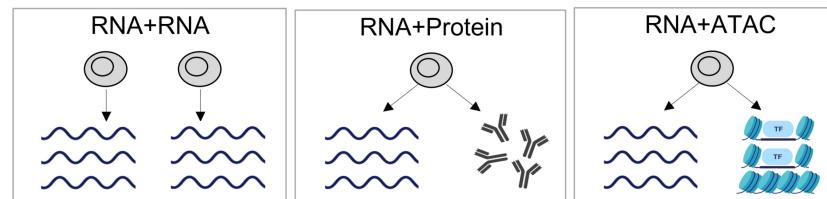
## What integration strategies and corresponding tools are available?



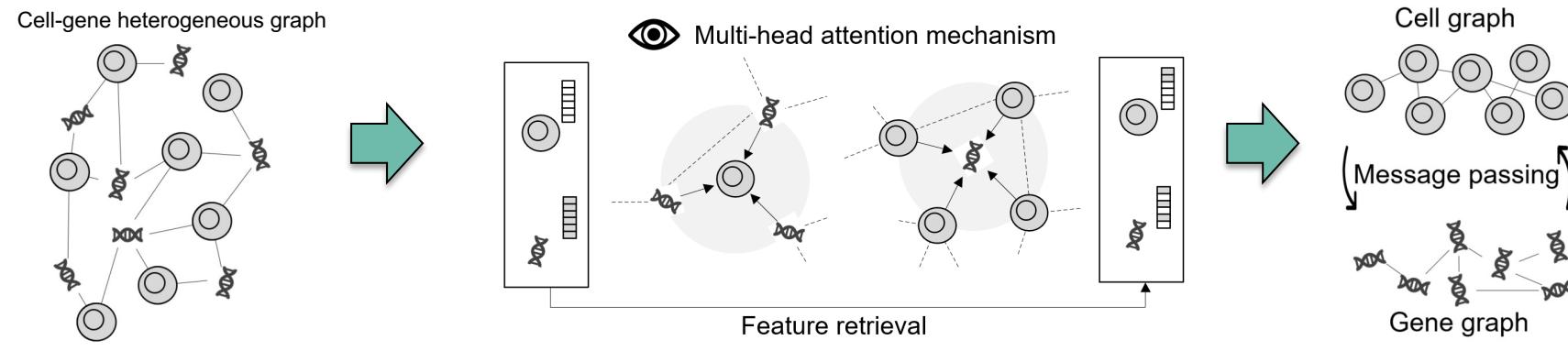
# scMulti-omics analysis refines knowledge of cell heterogeneity



# DeepMAPS: Deep learning based Multi-omics Analysis platform for Single cells



- First-of-its-kind for simultaneous cell clustering and biological network inference on a heterogeneous graph.



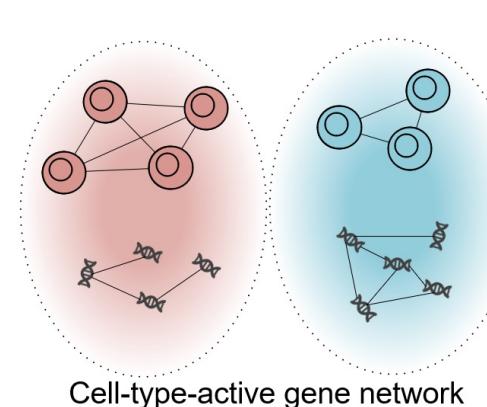
Dr. Qin Ma  
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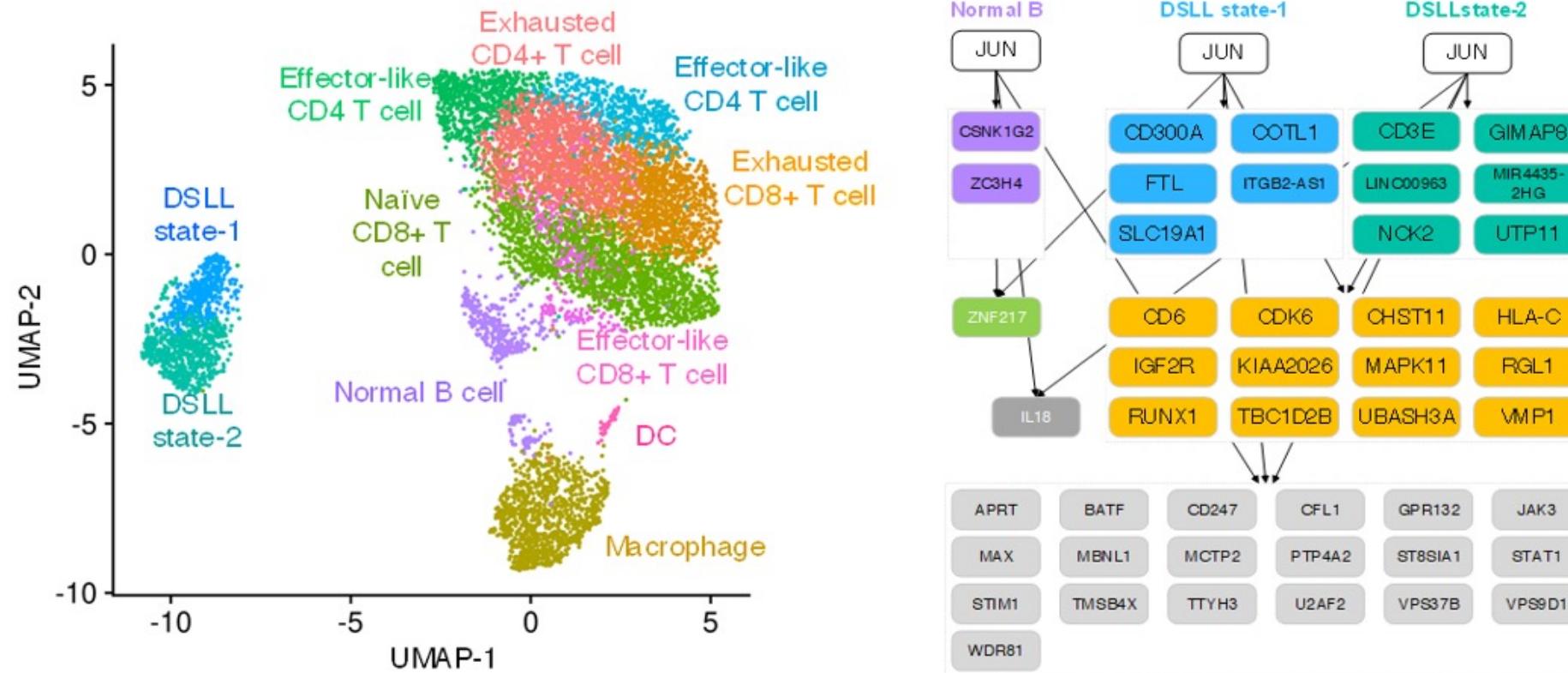
Dr. Dong Xu  
U of Missouri, US



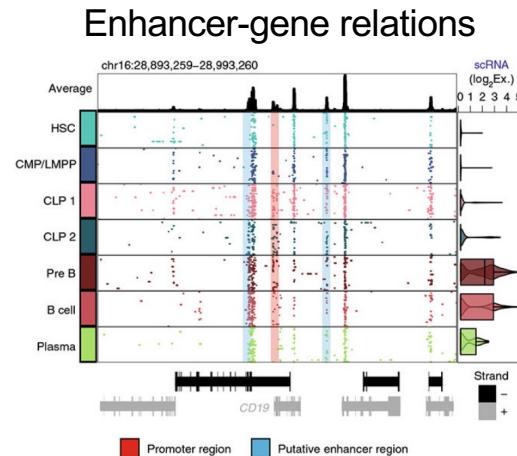
Dr. Bingqiang Liu  
Shandong U, China



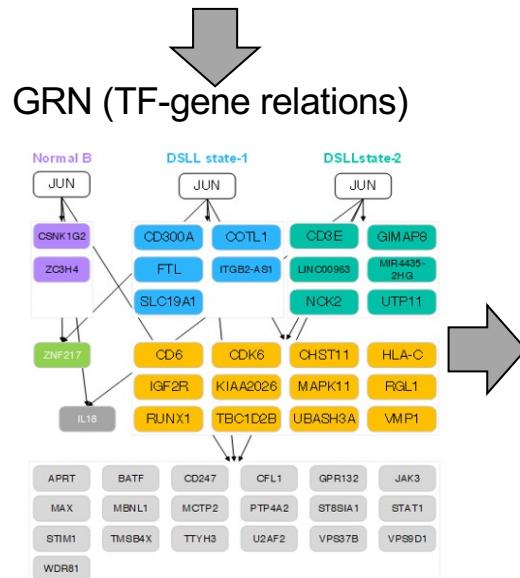
# DeepMAPS identifies state-specific GRNs in B lymphoma



# What else? – enhancer-driven GRN



Dr. Stein Aerts



nature

## Decoding gene regulation in the fly brain

<https://doi.org/10.1038/s41586-021-04262-z>  
Received: 30 December 2020  
Accepted: 17 November 2021  
Published online: 5 January 2022

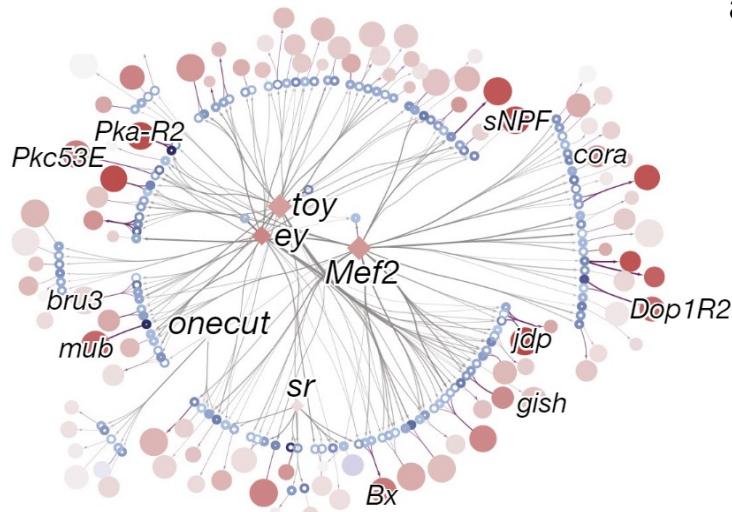
Jasper Janssens<sup>1,2</sup>, Sara Albar<sup>1,2</sup>, Ibrahim Ihsan Taskiran<sup>1,2</sup>, Joy N. Ismail<sup>1,2</sup>, Alicia Estacio Gomez<sup>2</sup>, Gabriel Aughey<sup>3</sup>, Katina I. Spanier<sup>1,2</sup>, Florian V. De Rop<sup>1,2</sup>, Carmen Bravo González-Blas<sup>1,2</sup>, Marc Dionne<sup>3</sup>, Krista Grimes<sup>3</sup>, Xiao Jiang Quan<sup>1,2</sup>, Dafni Papasokrati<sup>1,2</sup>, Gert Hulselmans<sup>1,2</sup>, Samira Makhzami<sup>1,2</sup>, Maxime De Waegeneer<sup>1,2</sup>, Valerie Christiaens<sup>1,2</sup>, Tony Southall<sup>1</sup> & Stein Aerts<sup>1,2</sup>

### SCENIC+: single-cell multiomic inference of enhancers and gene regulatory networks

Carmen Bravo González-Blas, Seppe De Winter, Gert Hulselmans, Nikolai Hecker, Irina Matetovici, Valerie Christiaens, Suresh Poovathingal, Jasper Wouters, Sara Aibar, Stein Aerts

doi: <https://doi.org/10.1101/2022.08.19.504505>

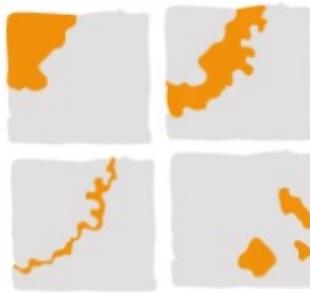
## Enhancer-driven GRN (TF-enhancer-gene relations)



eGRN is an advanced and accurate form of expression for TF regulatory relations that maximize the value of scRNA-seq and scATAC-seq data

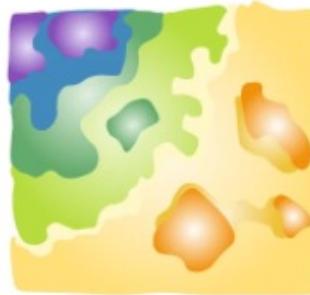
# Spatial transcriptomics data analysis

## Spatially variable gene (SVG)



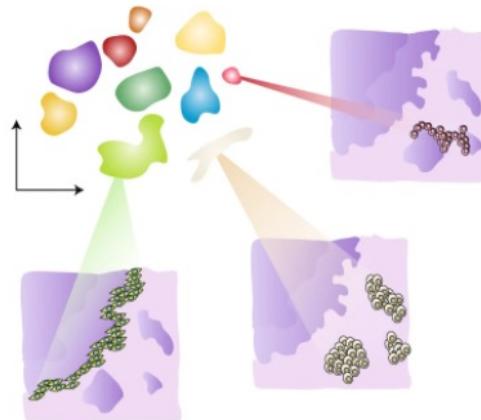
- Find spatial patterns
- Investigate biological insight of patterns

## Tissue architecture



- Define tissue heterogeneity
- Associate with biological functions

## Deconvolution



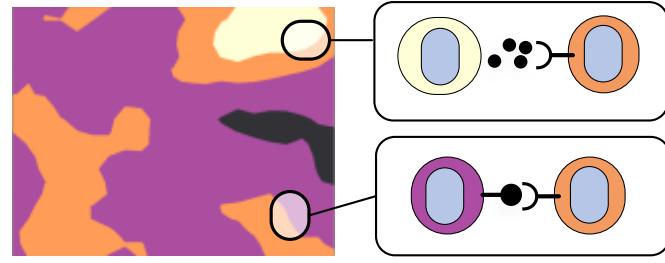
- Interpreted cell type composition and localization

## DEG analysis



- Obtain transcriptional changes between two niches

## Cell-cell communication (CCC)



- Decipher cell-cell communication
- Reveal outcomes after CCC

## Another analysis:

- Impute gene expression based on H&E stain images.
- Infer fusion gene via RNA
- Integrate with proteomics.
- .....

## SVG identification

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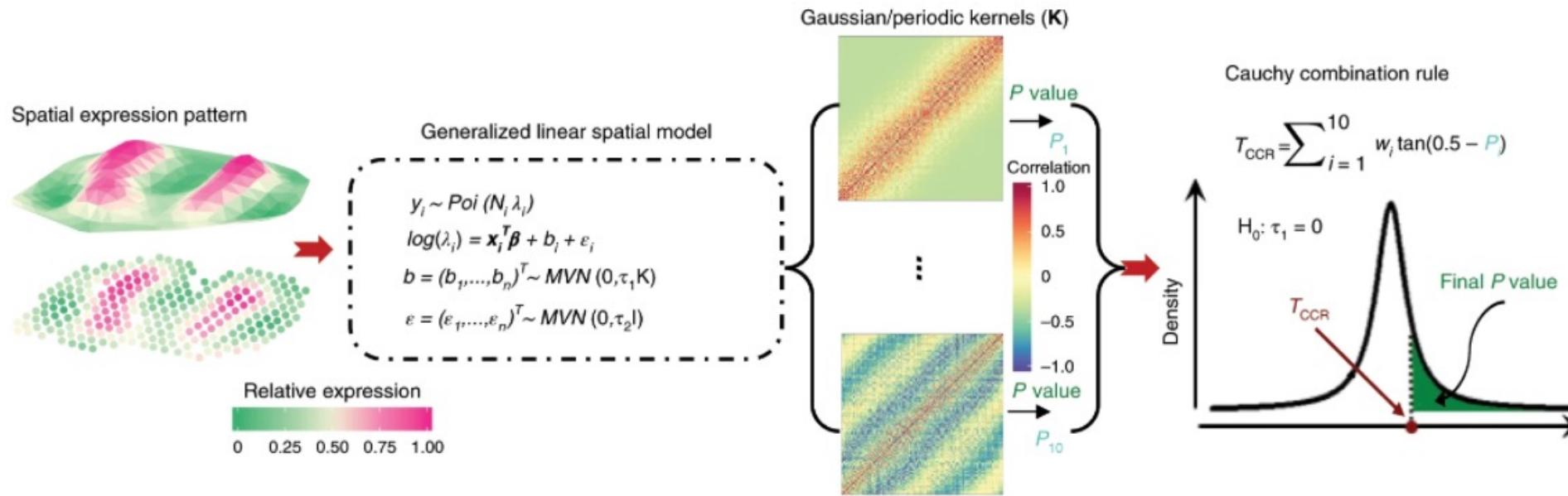
### Spatially variable gene identification:

- From data analysis point of view, spatially variable gene (SVG) identification corresponds to feature selection.
- In scRNA-seq, we use highly variable genes (HVGs), which shows significant variation in gene expression among cells.
- In the case of spatial transcriptomics, in addition to variability in gene expression, it is desirable to also consider their spatial co-localization patterns, i.e., spatially variable genes.
- Relevant algorithms have been significantly researched recently, where examples include SPARK-X, trendseek, SpatialDE, etc.
- Qin Lab proposed a novel algorithm in this direction (e.g., SpaGFT), which will be discussed more in detail in the second part.

### Marker detection



## SVG identification: SPARK



### Features:

- SPARK is a statistical framework developed to identify genes with spatial expression pattern in spatially resolved transcriptomic studies.
- Gene expression is modeled by a Poisson distribution.
- Spatial correlation is modeled using Gaussian process with different kernels and bandwidths.

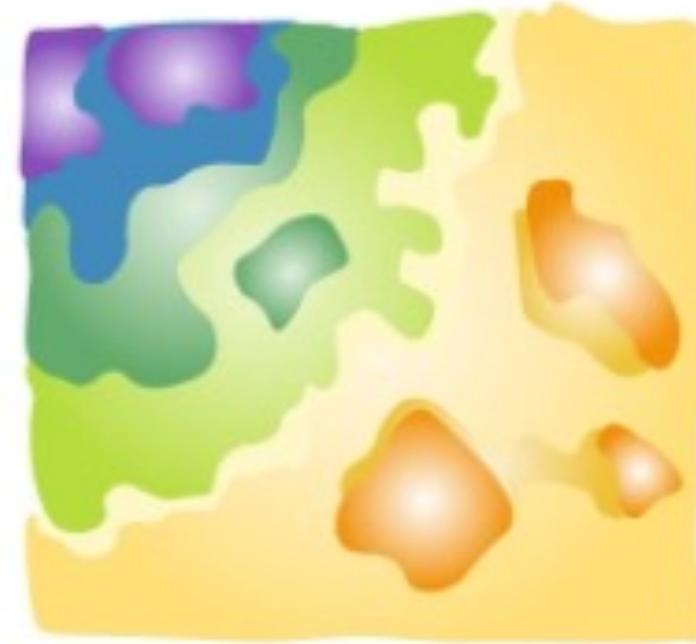
## Tissue architecture identification

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### Tissue architecture identification:

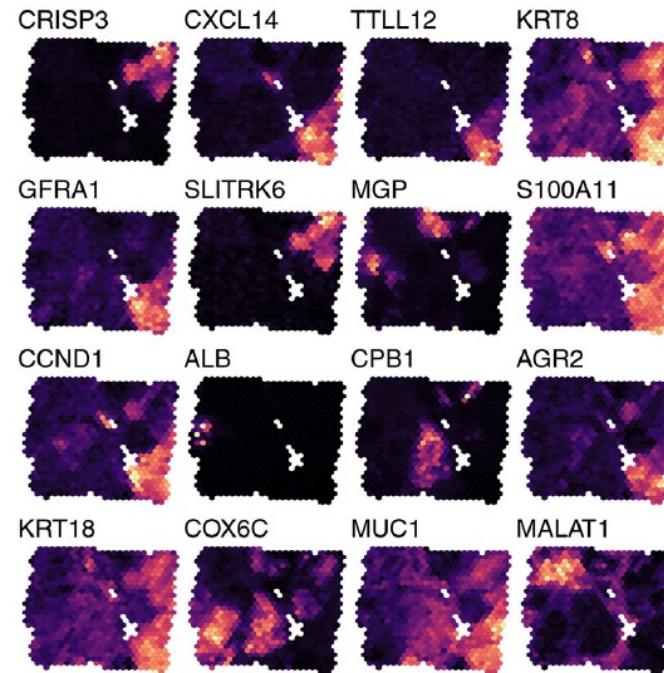
- From data analysis point of view, tissue architecture identification corresponds to cell/spot clustering.
- In scRNA-seq, similarity in gene expression is the main driver for this clustering.
- In the case of spatial transcriptomics, in addition to similarity in gene expression, it is desirable to also consider spatial proximity between cells/spots.
- Relevant algorithms have been significantly researched recently, where examples include Seurat 4.0, BayesSpace, Giotto, stLearn, etc.
- Chung Lab and Qin Lab proposed multiple novel algorithms in this direction (e.g., SPRUCE, MAPLE, BANYAN, RESEPT), which will be discussed more in detail in the second part.

Unsupervised clustering

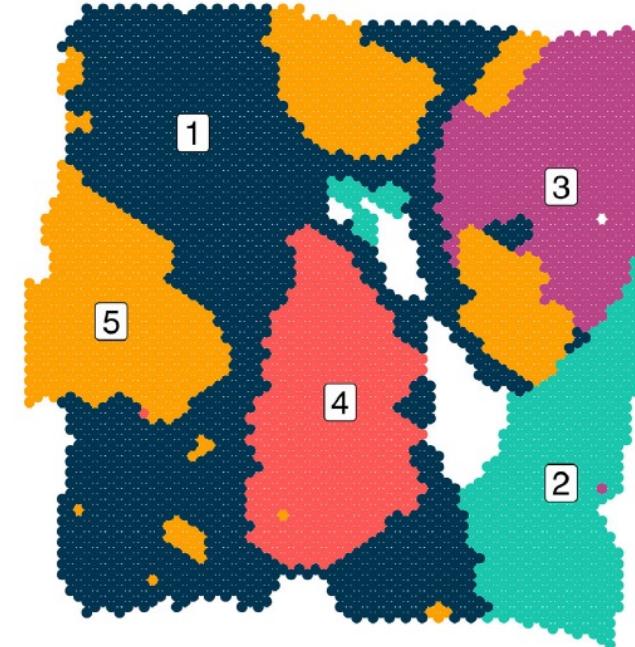


## Tissue architecture identification: SPRUCE

(A) Spatially Variable Features



(B) Estimated Cluster Labels



Features:

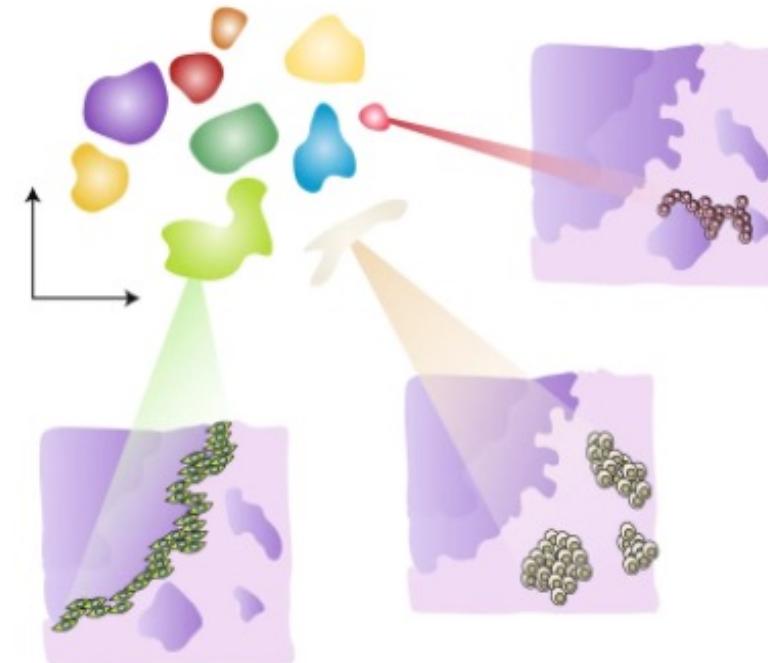
- SPRUCE is a statistical framework developed to identify the tissue architecture using the spatially resolved transcriptomics data.
- SPRUCE considers spatial correlation in gene expression patterns and cluster membership using conditional autoregressive (CAR) approach.
- In addition, it also considers correlation among genes and skewness in gene expression, and provides uncertainty quantification.

# Deconvolution

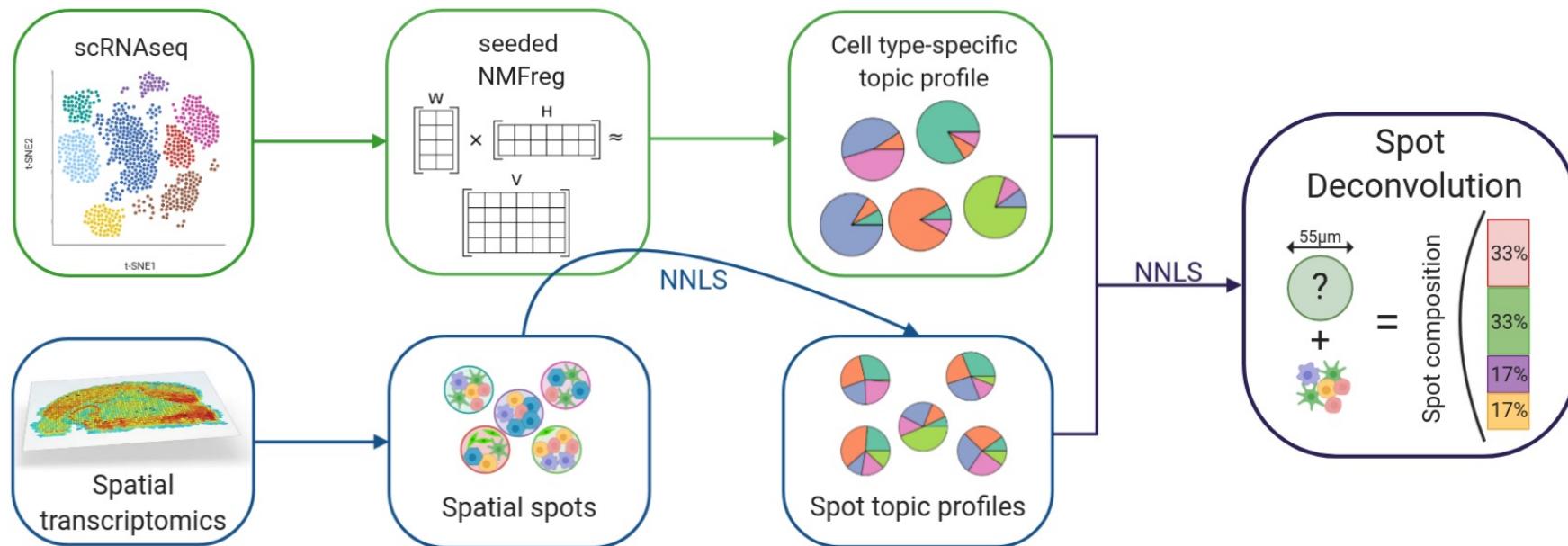
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## Deconvolution:

- In the case of 10X Visium, each spot consists of several cells and we can observe only the averaged expression of these cells.
- This can be a critical issue, especially when we implement cell-level investigation, e.g., cell-cell communication analysis.
- Deconvolution analysis aims to “decompose” genes expression in each spot and predict which cell types constitute the spot.
- Relevant algorithms have been significantly researched recently, where examples include RCTD, Cell2location,Tangram, CARD, etc.



## Deconvolution: SPOTlight



### Features:

- Require scRNA-seq and spatial transcriptomics as input.
- Use matrix factorization to decompose scRNA-seq and spatial transcriptomics matrices and produce topic-signatures.
- SPOTlight learns topic signatures from single-cell data and finds the optimal weighted combinations of cell types to explain a spot's cellular composition.
- Output cell type proportion in each spot.

# Deconvolution

ANALYSIS

<https://doi.org/10.1038/s41592-022-01480-9>

nature methods

 Check for updates

## Benchmarking spatial and single-cell transcriptomics integration methods for transcript distribution prediction and cell type deconvolution

Bin Li<sup>1,7</sup>, Wen Zhang<sup>1,2,7</sup>, Chuang Guo<sup>1,7</sup>, Hao Xu<sup>1,2</sup>, Longfei Li<sup>3</sup>, Minghao Fang<sup>3</sup>, Yinlei Hu<sup>4</sup>, Xinye Zhang<sup>3</sup>, Xinfeng Yao<sup>1</sup>, Meifang Tang<sup>1</sup>, Ke Liu<sup>1</sup>, Xuetong Zhao<sup>5</sup>, Jun Lin<sup>1,2</sup>, Linzhao Cheng<sup>3</sup>, Falai Chen<sup>4</sup>, Tian Xue<sup>3</sup> and Kun Qu<sup>1,2,6</sup> 

nature communications



Article

<https://doi.org/10.1038/s41467-023-37168-7>

## A comprehensive benchmarking with practical guidelines for cellular deconvolution of spatial transcriptomics

Received: 30 September 2022

Accepted: 3 March 2023

Published online: 21 March 2023

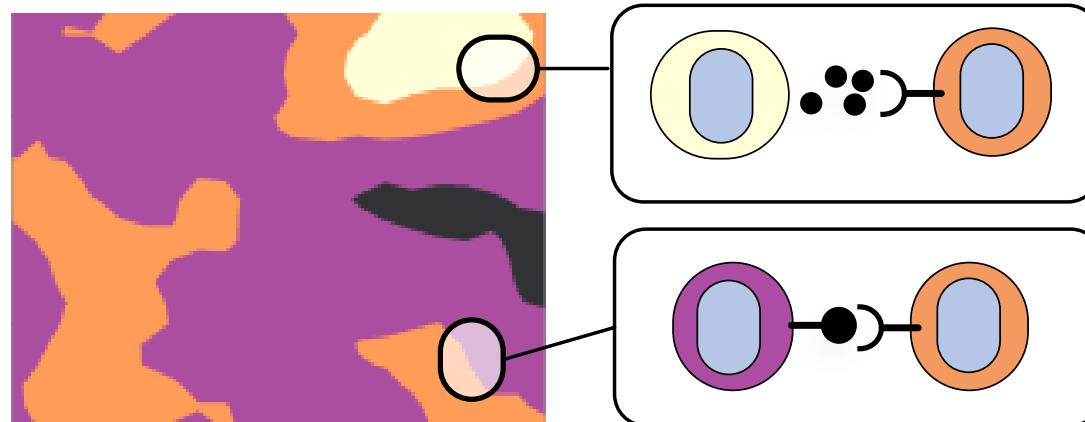
Haoyang Li , Juexiao Zhou<sup>1,2,6</sup>, Zhongxiao Li , Siyuan Chen , Xingyu Liao , Bin Zhang<sup>1,2</sup>, Ruochi Zhang<sup>3</sup>, Yu Wang<sup>3</sup>, Shiwei Sun<sup>4,5</sup> & Xin Gao 

## Cell-cell communication

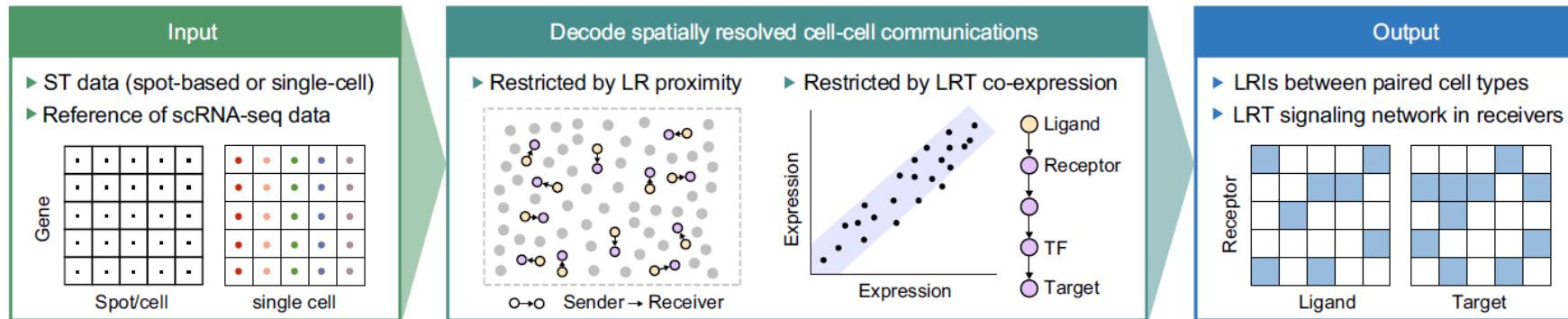
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### Cell-cell communication identification:

- We aim to identify pairs of sender and receiver cells that interact with each other.
- In scRNA-seq, we make predictions mainly based on expression of sender and receiver marker genes.
- In the case of spatial transcriptomics, in addition to sender/receiver marker expression, it is desirable to also consider their spatial proximity.
- Relevant algorithms have been significantly researched recently, where examples include COMMOT, SpaTalk, CellChat, Giotto, etc.
- Qin Lab proposed a novel algorithm in this direction (e.g., SAGE), which will be discussed more in detail in the second part.



# Cell-cell communication: SpaTalk



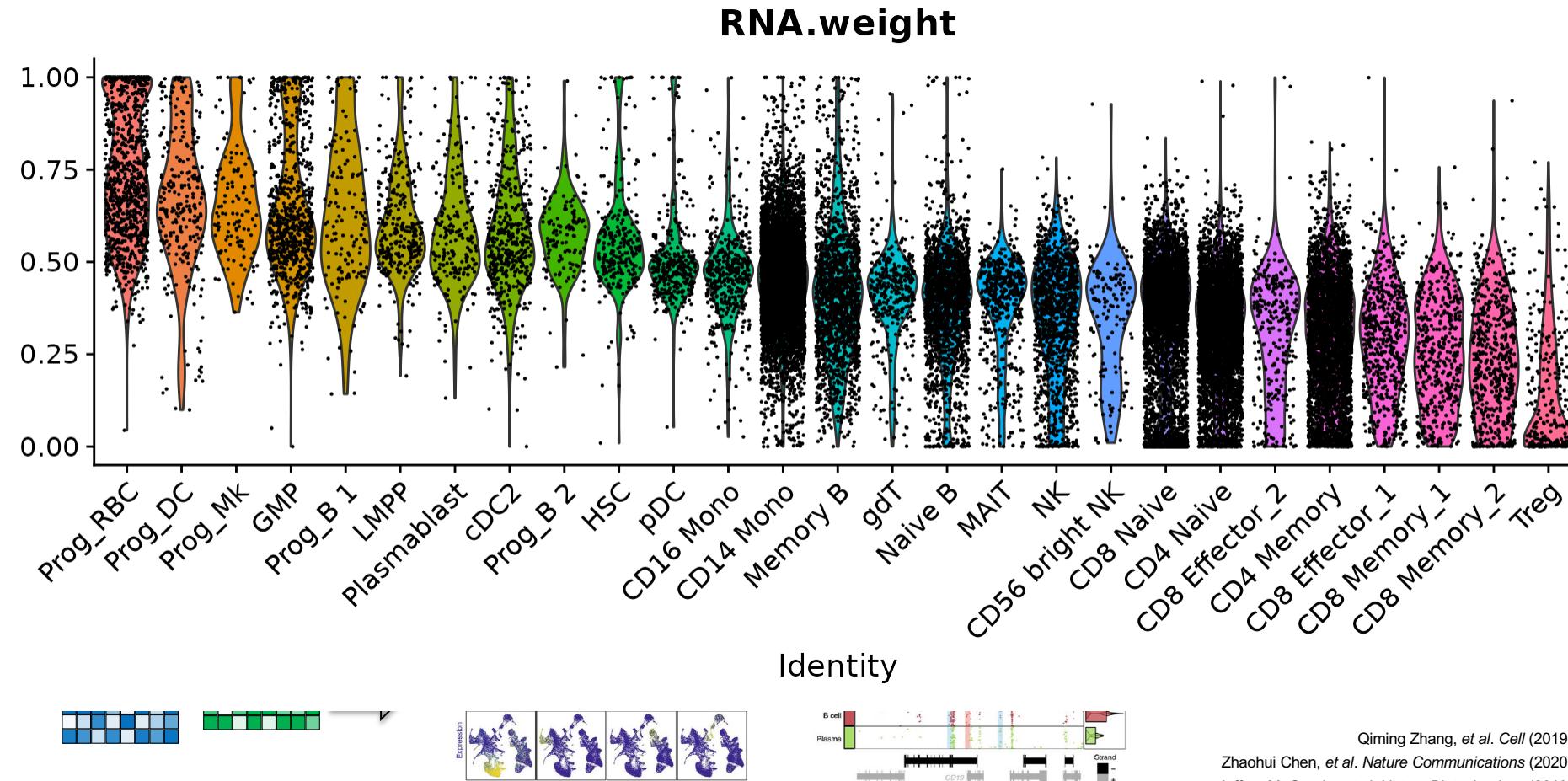
## Features:

- SpaTalk is a network-based model to detect ligand-receptor interaction.
- In Step 1, using the reference scRNA-seq data, SpaTalk first applies deconvolution.
- In Step 2, SpaTalk considers both ligand-receptor-transcription factor co-expression and their spatial proximity to identify ligand-receptor interaction.

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**The impact of advanced machine learning approaches  
on discovering cell types, regulatory relations, and key  
markers in complex diseases and other biological  
phenomena**

# scMulti-omics analysis refines knowledge of cell heterogeneity



# Significance: why should we use spatially resolved transcriptomics?

nature > review articles > article

Review Article | Published: 11 August 2021

## Exploring tissue architecture using spatial transcriptomics

Anjali Rao, Dalia Barkley, Gustavo S. França & Itai Yanai 

Nature 596, 211–220 (2021) | Cite this article

21k Accesses | 174 Altmetric | Metrics

nature > nature methods > review articles > article

Review Article | Published: 18 June 2021

## Integrating single-cell and spatial transcriptomics to elucidate intercellular tissue dynamics

Sophia K. Longo, Margaret G. Guo, Andrew L. Jj & Paul A. Khavari 

Nature Reviews Genetics 22, 627–644 (2021) | Cite this article

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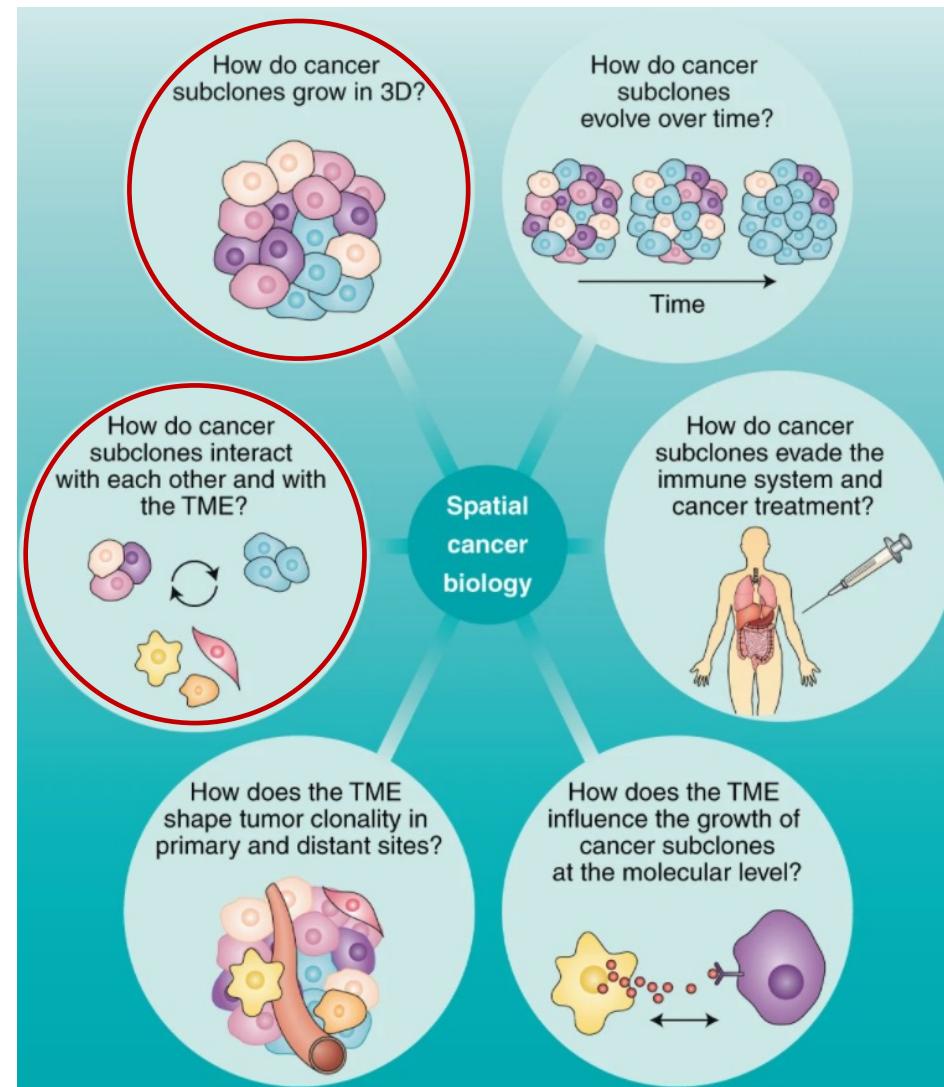
Review Article | Published: 02 August 2021

## Spatial omics and multiplexed imaging to explore cancer biology

Sabrina M. Lewis, Marie-Liesse Asselin-Labat, Quan Nguyen, Jean Berthelet, Xiao Tan, Verena C. Wimmer, Delphine Merino, Kelly L. Rogers  & Shalin H. Naik 

Nature Methods 18, 997–1012 (2021) | Cite this article

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Sabrina, et al., *Nature Methods*. (2021)

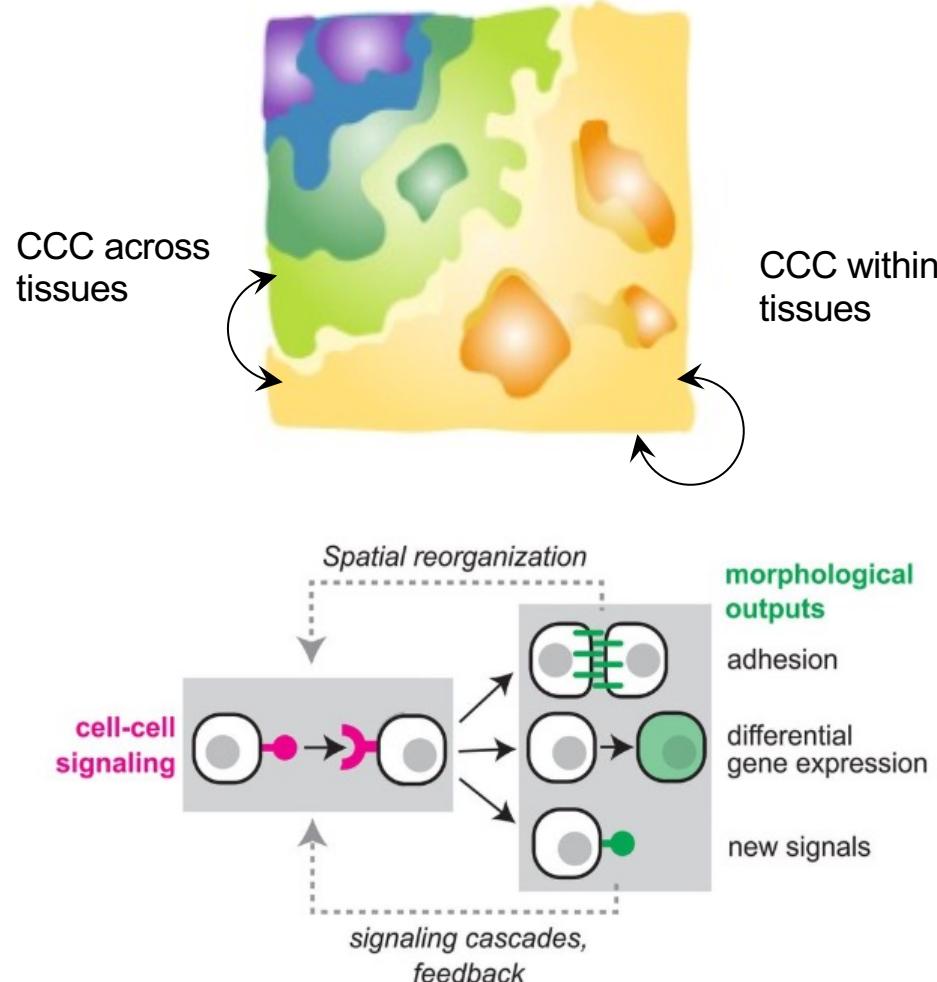
# What key insights can be derived from spatial transcriptomics?

**Spatial variable gene (SVG)**— a gene with an uneven pattern on spatial distribution

**Tissue architecture** – It is the foundation of spatial heterogeneity with complex tissues or organs (e.g., tumor and brain).

**Cell-cell communication (CCC)**— a biological process mediated by ligand-receptor pairs for a sender cell and a receiver cell.

We can infer CCC **within or across** tissue architectures, and assess CCC's activity, biological functions.



## Significance in terms of neuroscience

- Generate Brain atlas.
- Investigate molecular identity, connectivity, morphology and physiology.
- Understand the mechanism of brain diseases. (e.g., Alzheimer's disease)

nature neuroscience

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nature > nature neuroscience > reso

Resource | Published: 08 February 202

### Transcriptome-scale human dorsolateral

Kristen R. Maynard, Leonardo Collado-  
R. Williams, Joseph L. Catallini II, Matth  
Yin, Joel E. Kleinman, Thomas M. Hyde,

Jaffe

PNAS

Proceedings of the  
National Academy of Sciences  
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Keywords

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Cell

Volume 182, Issue 4, 20 August 2020, Pages 976-991.e19



RESEARCH ARTICLE

Spatial trans-  
subcellular  
dependent

Resource

### Spatial Transcriptomics and *In Situ* Sequencing to Study Alzheimer's Disease

Chenglong Xia, + See all authors at

Wei-Ting Chen <sup>1, 2, 11</sup>, Ashley Lu <sup>1, 2, 11</sup>, Kathleen Craessaerts <sup>1, 2</sup>, Benjamin Pavie <sup>1, 2, 3, 4</sup>, Carlo Sala Frigerio <sup>1, 2, 10</sup>,  
Nikky Corthout <sup>1, 2, 3, 4</sup>, Xiaoyan Qian <sup>5</sup>, Jana Laláková <sup>5</sup>, Malte Kühnemund <sup>5</sup>, Iryna Voytyuk <sup>1, 2</sup>, Leen Wolfs <sup>1, 2</sup>,  
Renzo Mancuso <sup>1, 2</sup>, Evgenia Salta <sup>1, 2</sup>, Sriram Balusu <sup>1, 2</sup>, An Snellinx <sup>1, 2</sup>, Sebastian Munck <sup>1, 2, 3, 4</sup>, Aleksandra Jurek  
<sup>6</sup>, Jose Fernandez Navarro <sup>6</sup>, Takaomi C. Saito <sup>7</sup>, Inge Huitinga <sup>8, 9</sup>, Joakim Lundeberg <sup>6</sup>, Mark Fiers <sup>1, 2, 10</sup>, Bart  
De Strooper <sup>1, 2, 10, 12</sup>

## Significance in terms of developmental biology

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- Learn the spatial dynamics of organogenesis.
- Observe molecular changes among functional zonation.
- Support Human Cell Atlas project

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**nature**

Article | Open

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between single-cell and whole-organ approaches

Madhav Mantri

Benjamin Grodski

Nature Communications

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Article | Preprint

Single-cell

somatic

> [Cell](#). 2019 Dec 12;179(7):1647-1660.e19. doi: 10.1016/j.cell.2019.11.025.

## A Spatiotemporal Organ-Wide Gene Expression and Cell Atlas of the Developing Human Heart

Michaela Asp <sup>1</sup>, Stefania Giacomello <sup>2</sup>, Ludvig Larsson <sup>3</sup>, Chenglin Wu <sup>4</sup>, Daniel Fürth <sup>5</sup>,  
Xiaoyan Qian <sup>4</sup>, Eva Wärdell <sup>6</sup>, Joaquin Custodio <sup>7</sup>, Johan Reimegård <sup>8</sup>, Fredrik Salmén <sup>9</sup>,  
Cecilia Österholm <sup>10</sup>, Patrik L Ståhl <sup>3</sup>, Erik Sundström <sup>11</sup>, Elisabet Åkesson <sup>11</sup>, Olaf Bergmann <sup>12</sup>,  
Magda Bienko <sup>7</sup>, Agneta Måansson-Broberg <sup>6</sup>, Mats Nilsson <sup>4</sup>, Christer Sylvén <sup>6</sup>,  
Joakim Lundeberg <sup>13</sup>

Affiliations + expand

PMID: 31835037 DOI: 10.1016/j.cell.2019.11.025

Free article

## Significance in terms of diseases

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- Understand how normal region changes to disease states.
- Study gene signatures of pathological region and decipher heterogenous cells.
- Investigate relations among heterogeneous cell types.

➤ [Science](#). 2019 Apr 5;364(6435):89-93. doi: 10.1126/science.aav9776.

### Spatiotemporal dynamics of molecular pathology in amyot:

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Annelie Moll [nature](#)

Gonzalo Saiz

Richard Boni [Article](#)

Affiliations ·

PMID: 30948

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H. Hajd

Margaret G Guo <sup>2</sup>, Benson M George <sup>5</sup>, Annelie Mollbrink <sup>3</sup>, Joseph Bergenstråhle <sup>3</sup>,

Nature

Ludvig Larsson <sup>3</sup>, Yunhao Bai <sup>4</sup>, Bokai Zhu <sup>4</sup>, Aparna Bhaduri <sup>6</sup>, Jordan M Meyers <sup>2</sup>,

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Paul A Khavari <sup>7</sup>