Spatial transcriptomics algorithms and the trend of spatial omics

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10/18/2022

Bioinformatics and Mathematical Biosciences Lab

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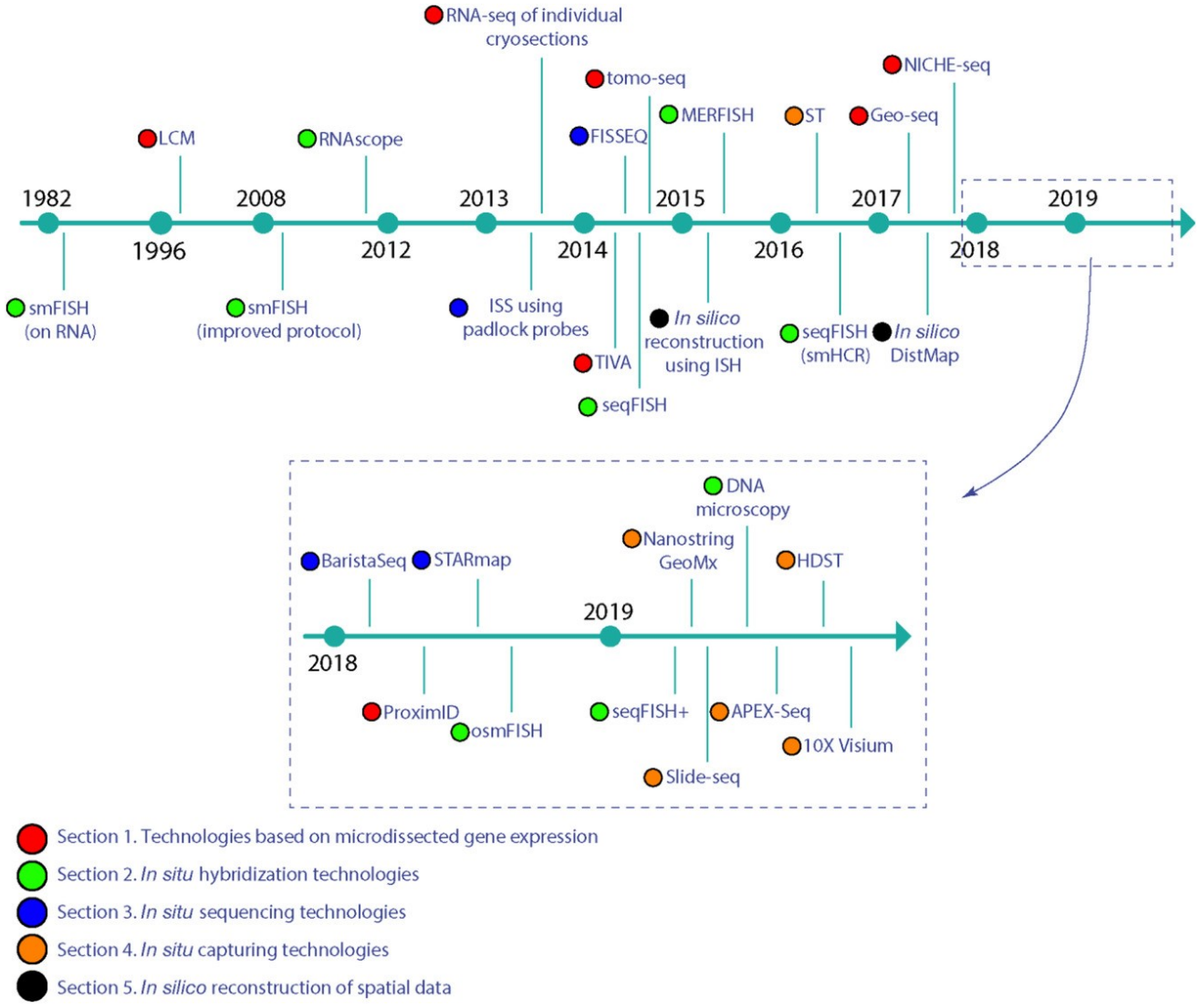
Background: what is spatially resolved transcriptomics?



Spatially resolved transcriptomics: Quantifying transcripts while keeping spatial context of samples within tissue or cell.

Nature Methods:

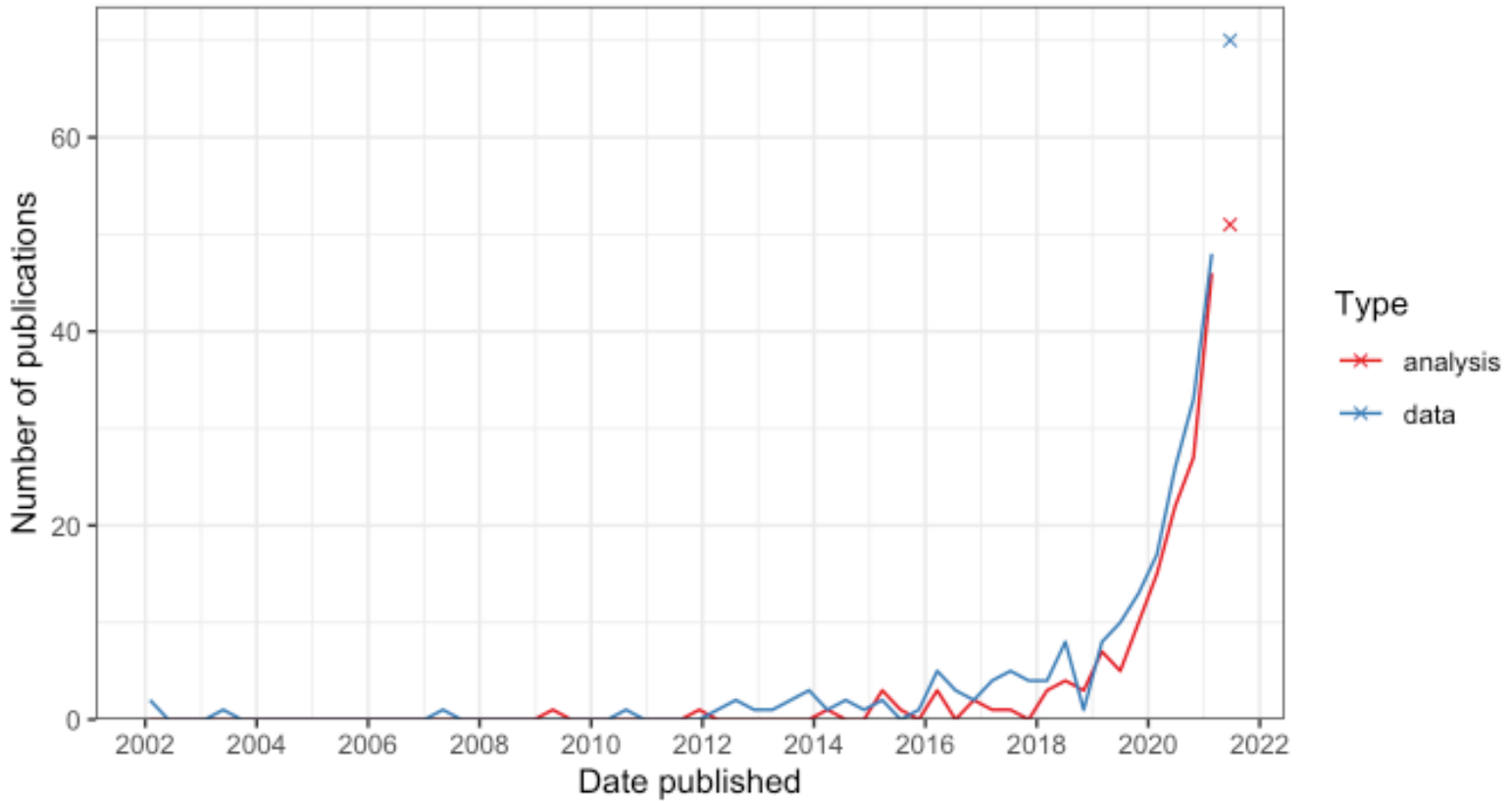
FOCUS | 06 JANUARY 2021

Method of the Year 2020: spatially resolved transcriptomics

Spatially resolved transcriptomics is our Method of the Year 2020, for its ability to provide valuable insights into the biology of cells and tissues while retaining information about spatial context.

Michael Asp, *et al. BioEssays*. (2020)

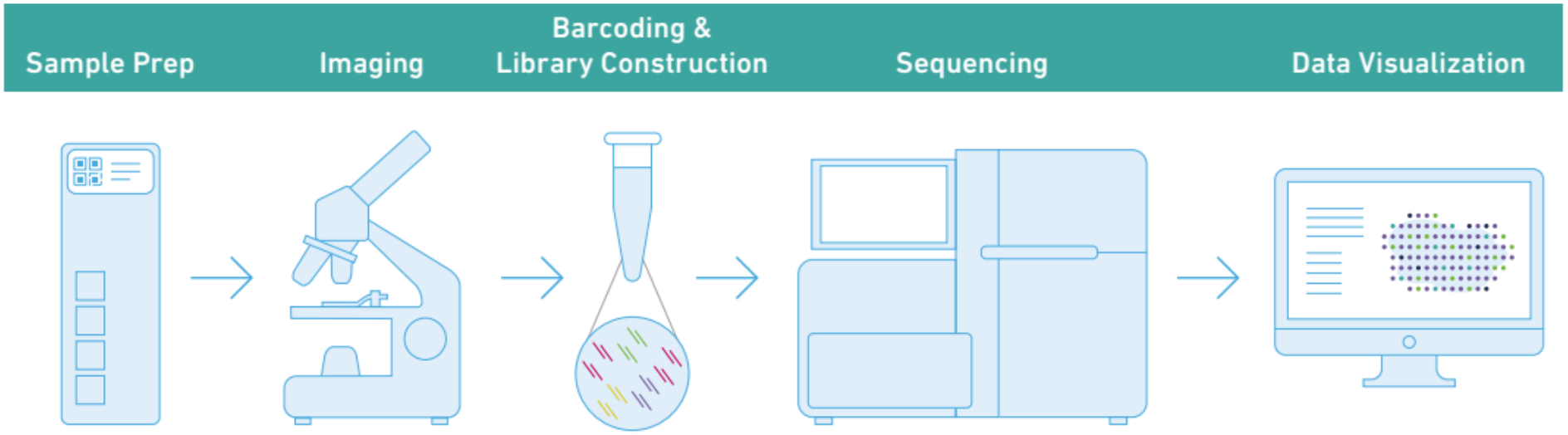
About spatial transcriptomics

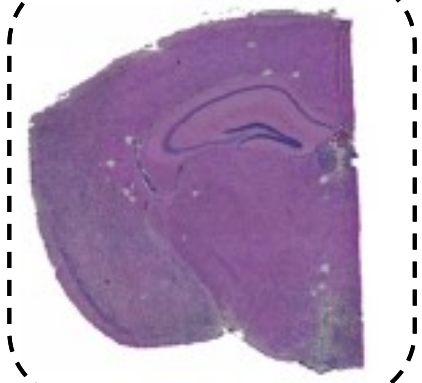


Museum of spatial transcriptomics, *online book (2021)*

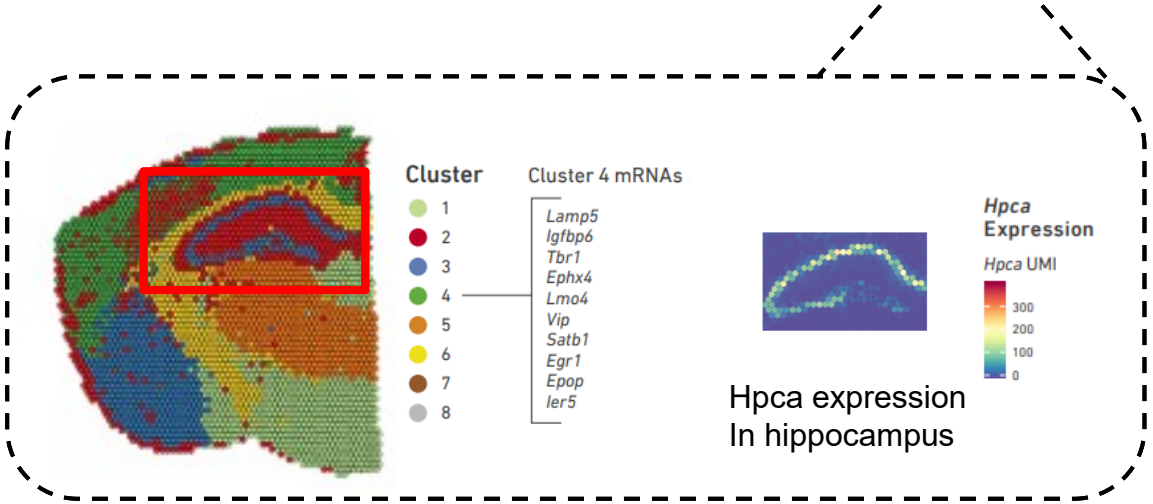
- Trend of spatial transcriptomics is increasing.
- The number is stilling going up.
- Gold era for spatial transcriptomics.

Spatial transcriptomics example: Visium





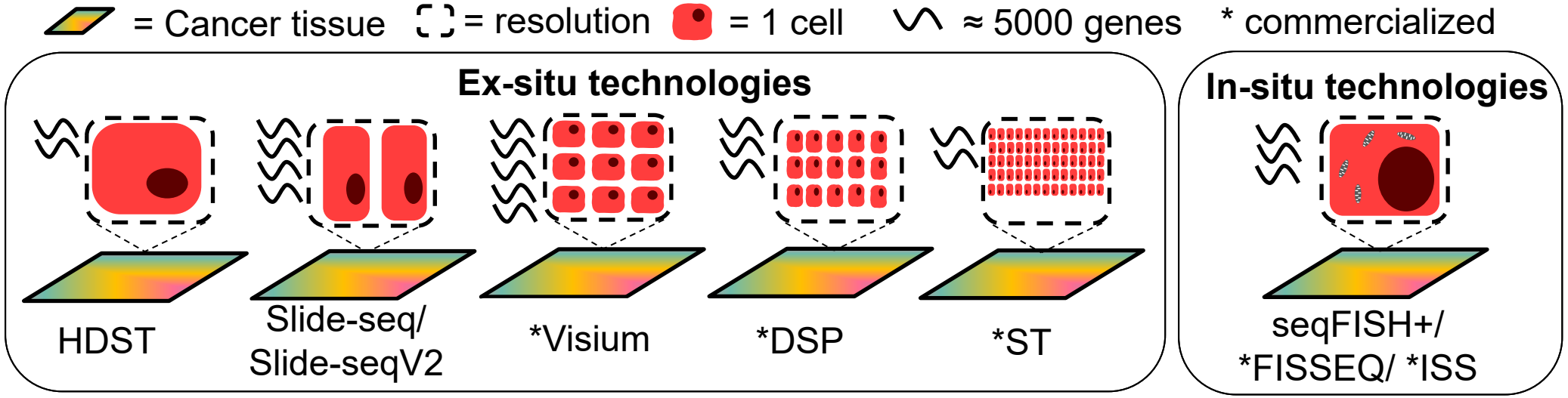
A coronal mouse brain section
H&E stained



Hpca expression
In hippocampus

https://www.10xgenomics.com/spatial-transcriptomics/

Spatial transcriptomics technologies (before Jan 2022)



	In- & Ex-	In- & Ex-	Ex-	Ex-	Ex-	Ex-
Tools	Giotto	Trendsceek	BayesSpace	SPOTlight	STARCH	STfusion
	MERINGUE	SpatialDE	SpaGCN	Stereoscope		
	SPARK	SPARK	RESEPT	Cell2location		
	SAPRK-X	SAPRK-X	STATEGATE	Tangram		
Related questions	Spatial variable gene Tissue architecture Cell-cell communication	Spatial variable gene	Tissue architecture	Deconvolution	Copy number inference	Fusion genes

Jie Liao, et al., *Trends in Biotechnology* (2020)

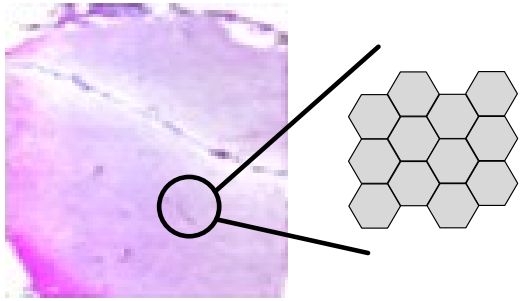
Sabrina M. Lewis, et al., *Nature Methods* (2021)
Rania Bassiouni, et al., *Molecular Cell* (2021)

https://www.nature.com/webcasts/event/applications-of-single-cell-multi-omics-techniques-in-molecular-biology-genetics-and-cancer-research/

Golden age for spatial transcriptomics

nature methods

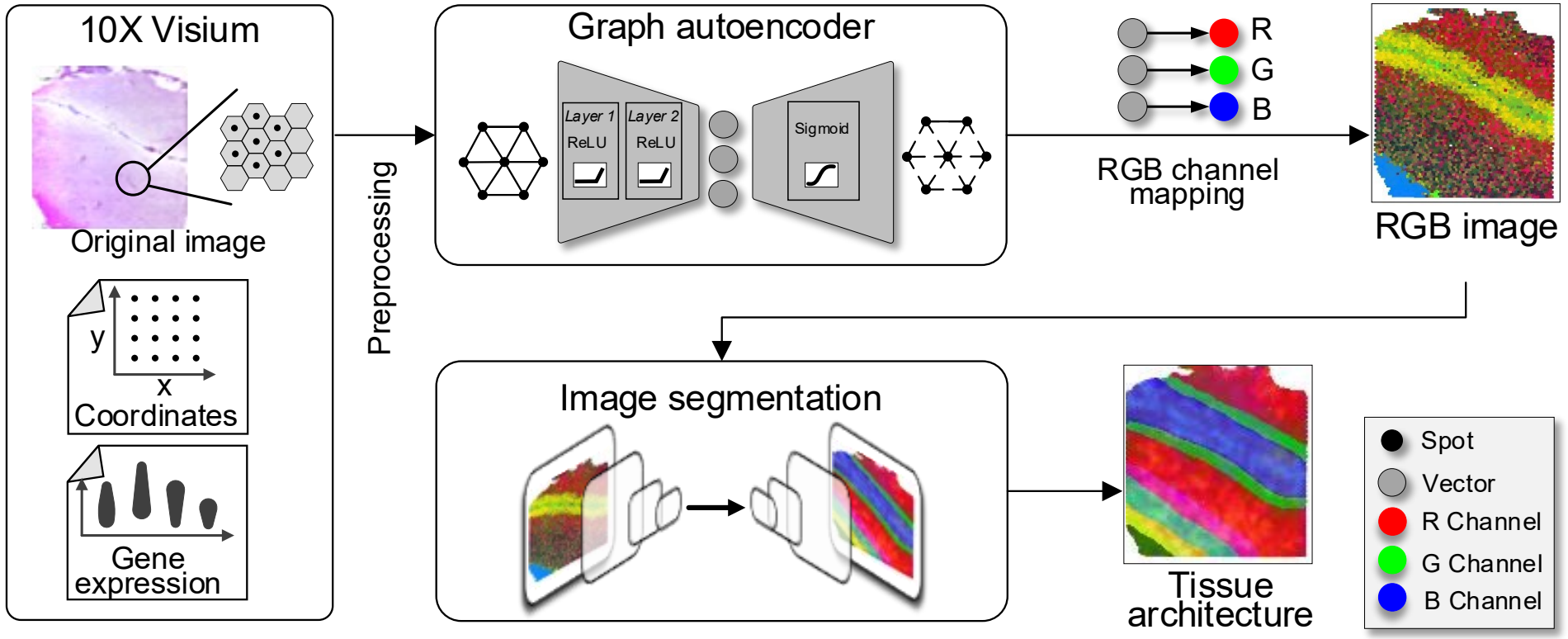
Method of the Year
2020: spatially resolved transcriptomics



Unique questions to be answered

- Assess spatial heterogeneity and tissue architecture
- Characterize cell-cell communication events in a specific region
- Towards spatial omics technologies

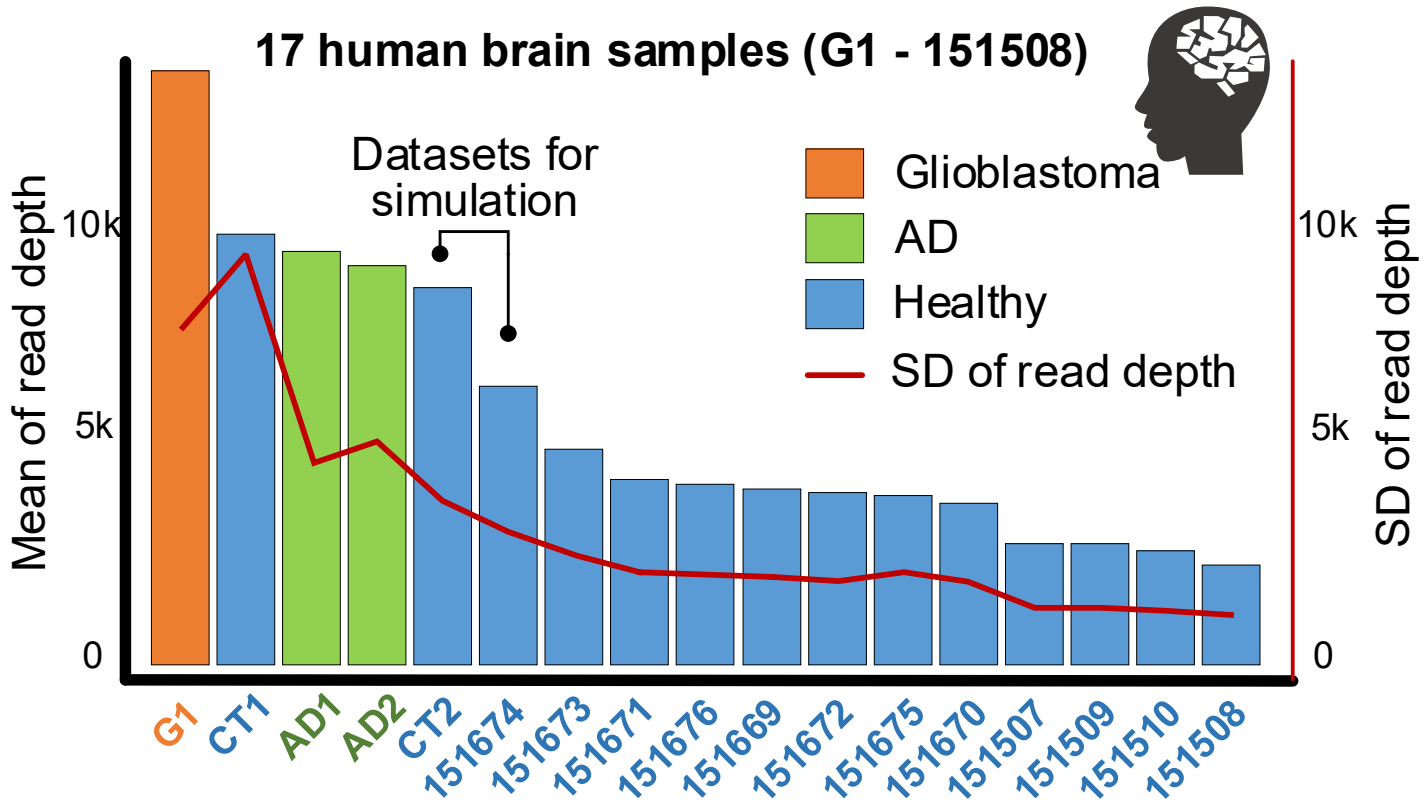
RESEPT: REconstructing and Segmenting Expression mapped RGB images based on sPatially resolved Transcriptomics



1. Input gene expression and spatial location.
2. 3D embedding.
3. Embeddings convert to RGB image.
4. Pseudo-color image segmentation, using16 human brain datasets which include 14 healthy and 2 Alzheimer's disease (AD) datasets.

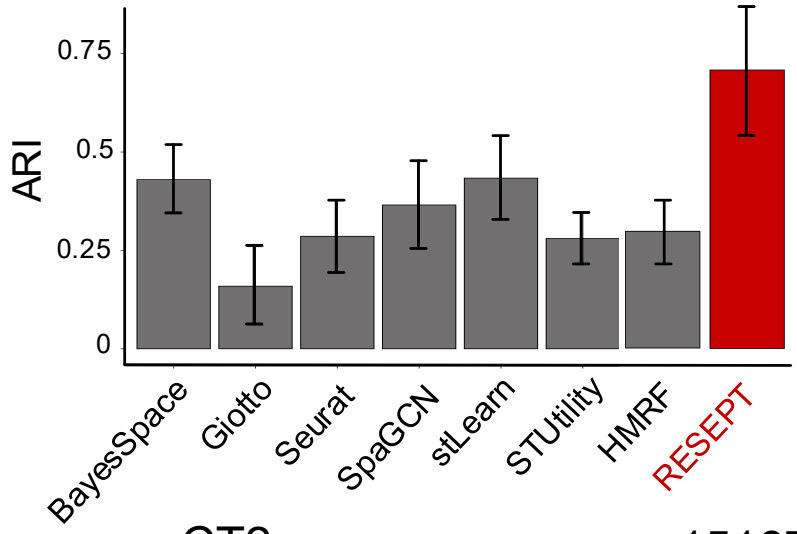
Yuzhou Chang, Computational and Structural Biotechnology Journal, (2022)

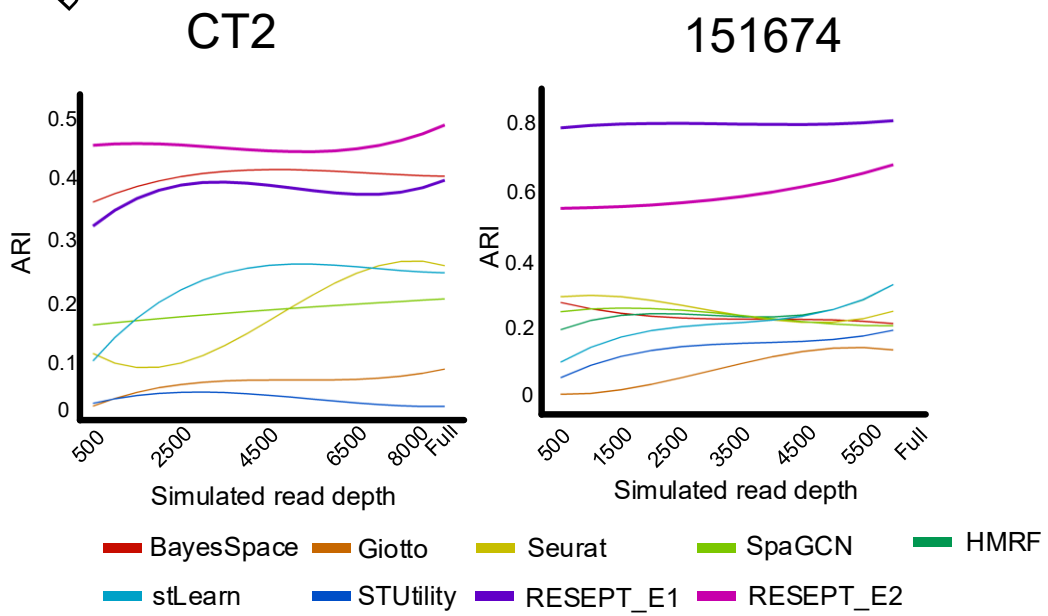
16 Datasets used in RESEPT training and testing



- 16 Visium data were used for model training and testing (from CT1 to 151508).
- The data includes health (14) and Alzheimer's disease sample (2).
- G1 was used for case study.
- CT2 and 151674 were selected to simulate different read depth for stability test.

RESEPT outperformed other computational tools





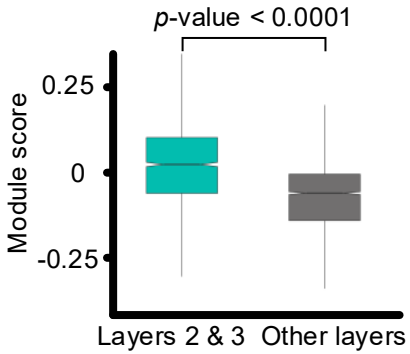
Performance on 16 real datasets by a fix cluster number

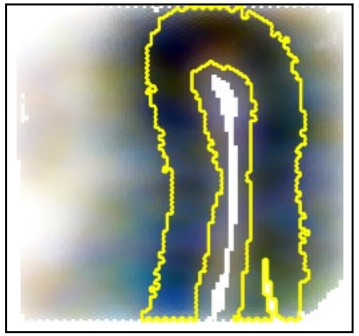
- Outperform other tools

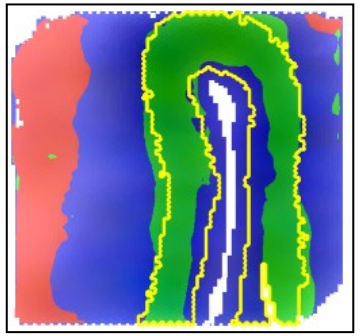
Performance on simulation datasets (grid sequencing depth)

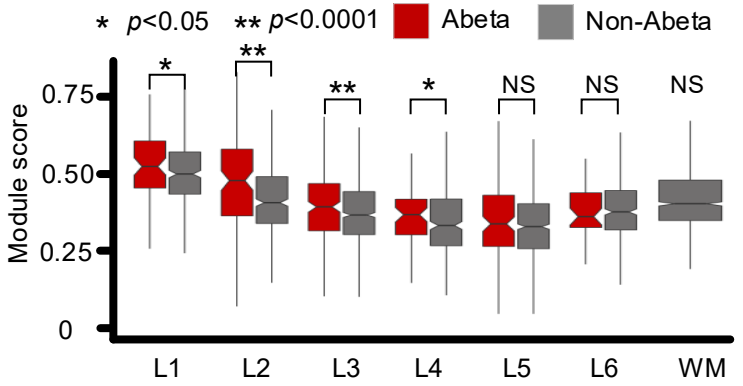
- Stable and high performance

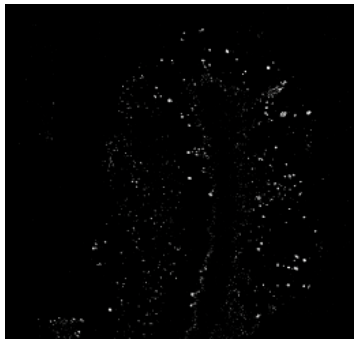
RESEPT can capture specific region by a given gene list

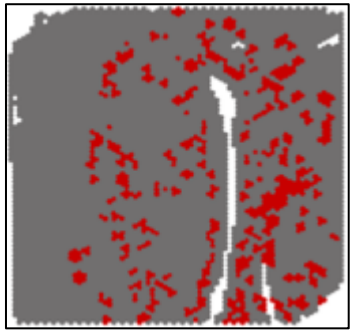


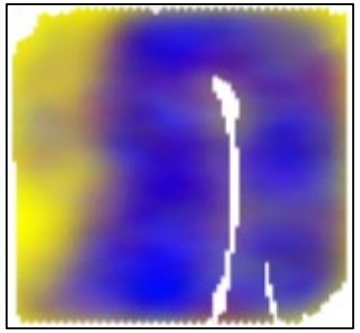


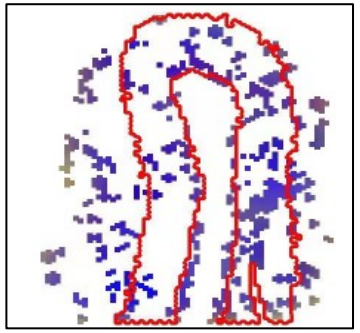


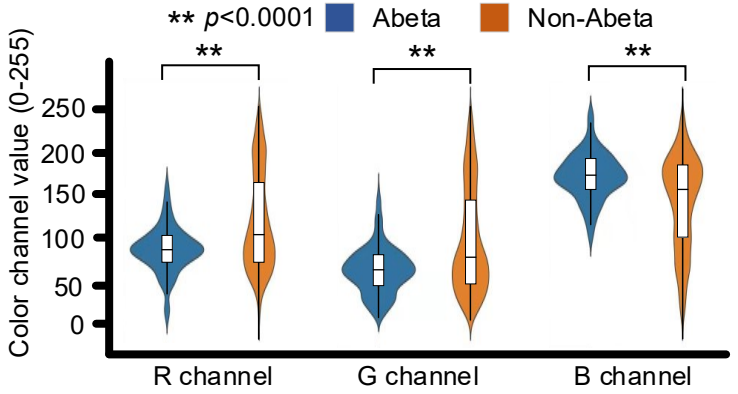








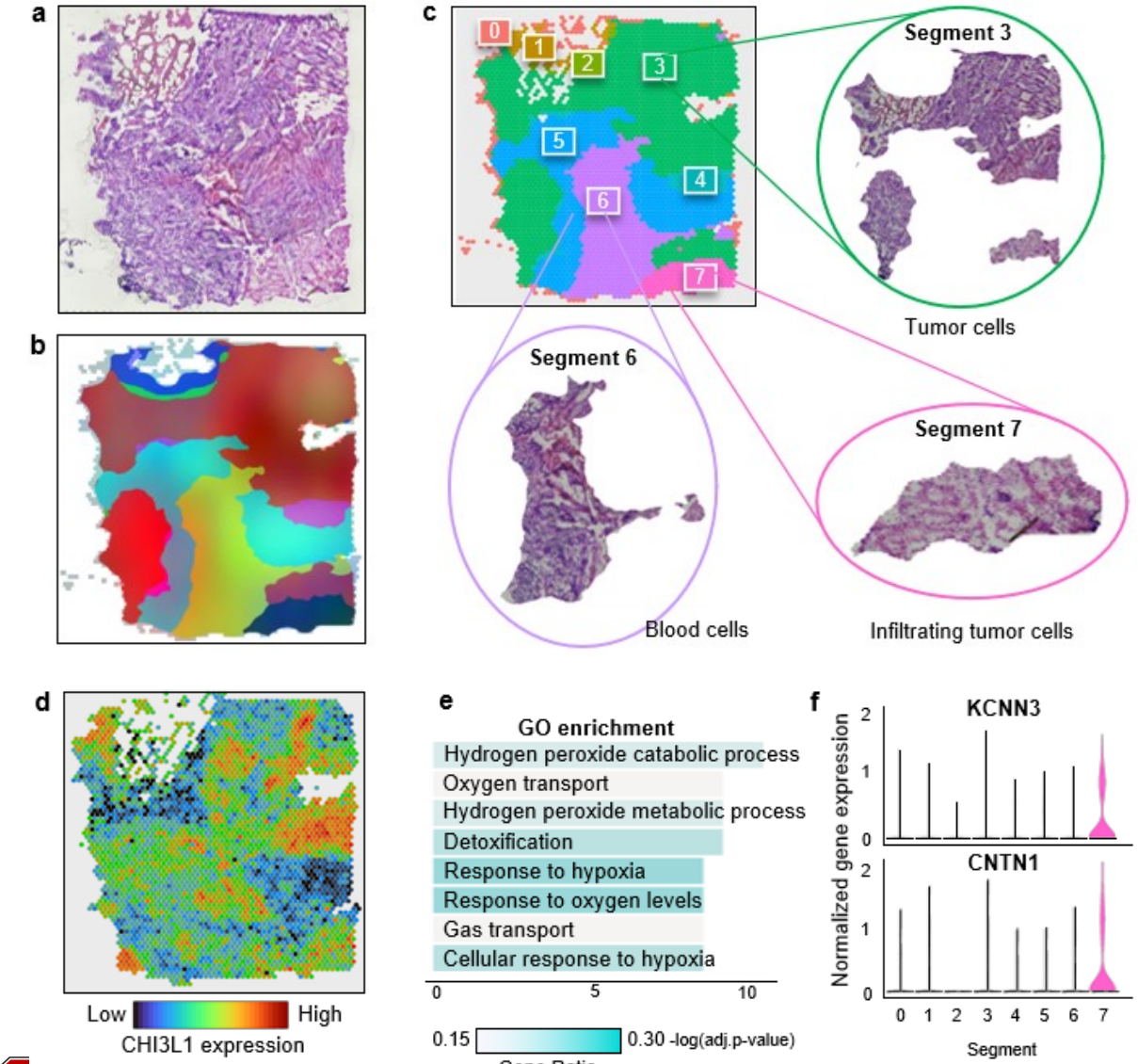




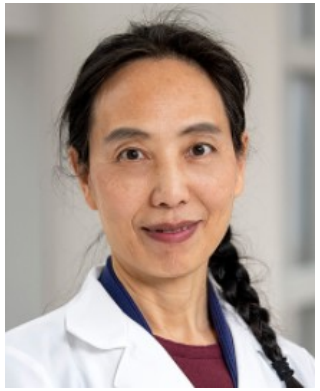
Conclusion: RESEPT could confidently reflect layer-specific, cell-type-specific, and pathological region-specific architecture regarding well-studied marker genes, which indicated significant potentials to localize and present important spatial architecture contributing to AD development.

Kristen R. Maynard, Nature Neuroscience (2021)
Wei-Ting Chen, Cell (2020)

Glioblastoma case demonstrates RESEPT can be used on cancer tissue



Dr. Jose Otero



Dr. Shaoli Sun

Conclusion:

1. Identify tumor, non-tumor, and infiltrating tumor region.
2. Validate the three regions by pathological features.
3. Validate the three regions by transcriptional features.

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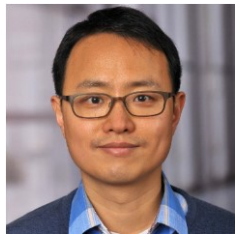
Summary of RESEPT

Conclusion:

- RESPT is a deep learning framework for tissue heterogeneity visualization and architecture identification.
- The core concept of converting three-dimensional representations to RGB images and being associated with spatially variable genes will potentially enable explainable AI.
- RGB image can associated with certain spatially variable genes which can support main architecture of each RGB channels.
- It can generalize to other tissues (e.g., cancer)
- We apply on Alzheimer's' disease and glioblastoma to visualize and reveal pathological region.



Collaboration with
Dr. Dongjun Chung

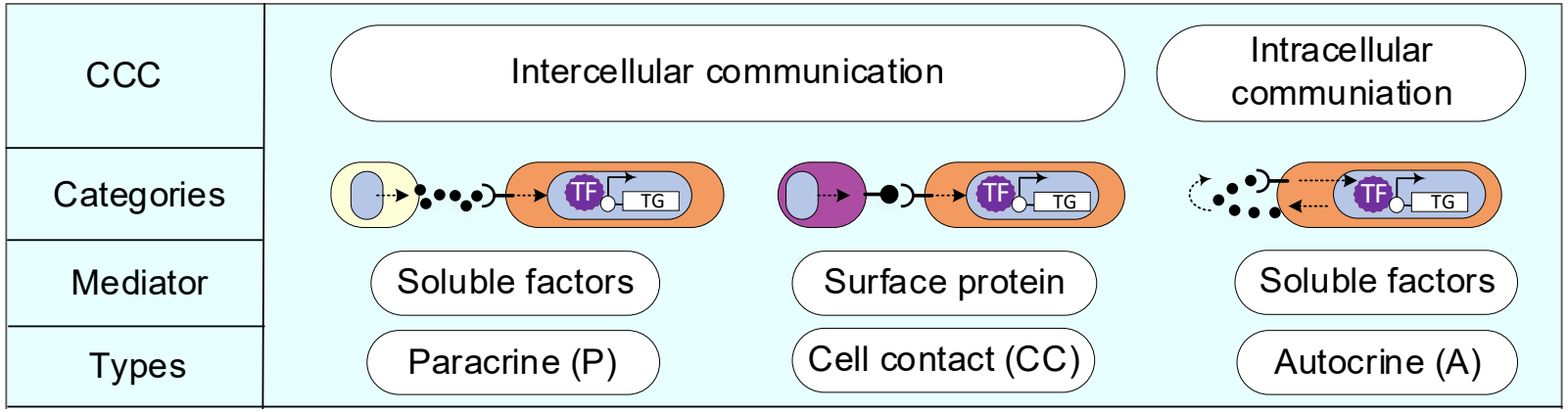
Allen C, Chang Y, Neelon B, Chang W, Kim HJ, Li Z, Ma Q, Chung D. A Bayesian multivariate mixture model for high throughput spatial transcriptomics. Biometrics. 2022 Jul 27. doi: 10.1111/biom.13727. Epub ahead of print. PMID: 35895854.

Output:

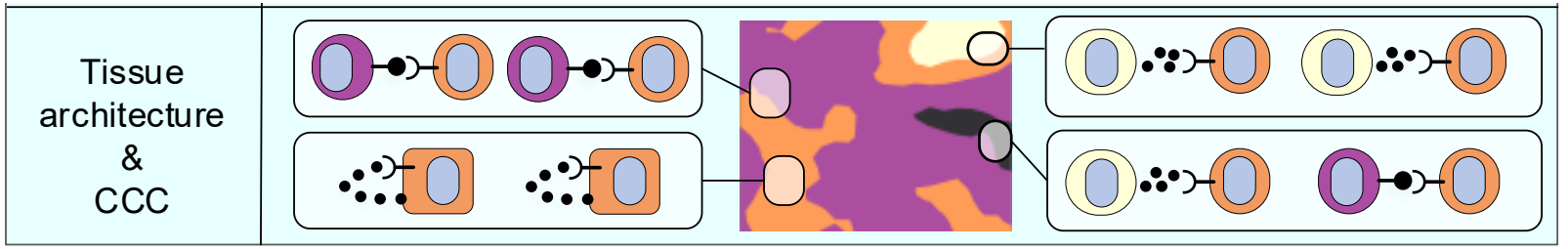
- Tissue architecture identification.
- Distinct cellular sub-populations (cell uncertainty measurement)

Characterize cell-cell communication (CCC) events in a specific region

Cell-cell communication categories

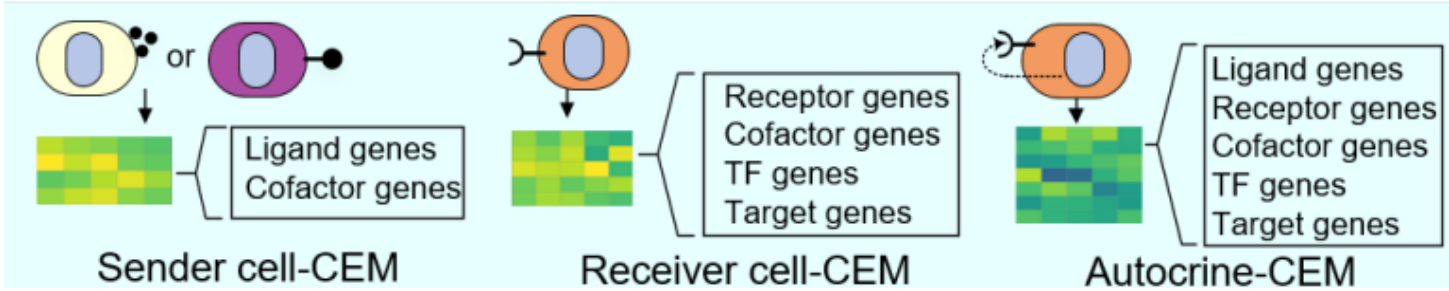


Cell-cell communication within or across tissue architectures



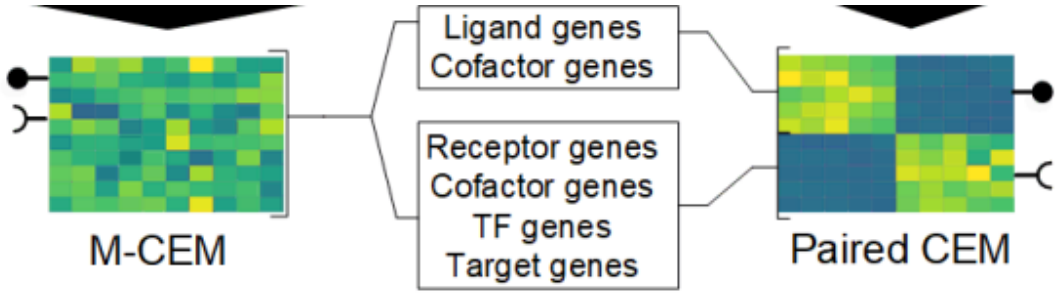
Hypothesis and observation

Hypothesis 1:



Hypothesis 2:

S-CEM, R-CEM, and A-CEM will form two patterns in SRT data: paired-CEM (P-CEM) and mixed-CEM (M-CEM).

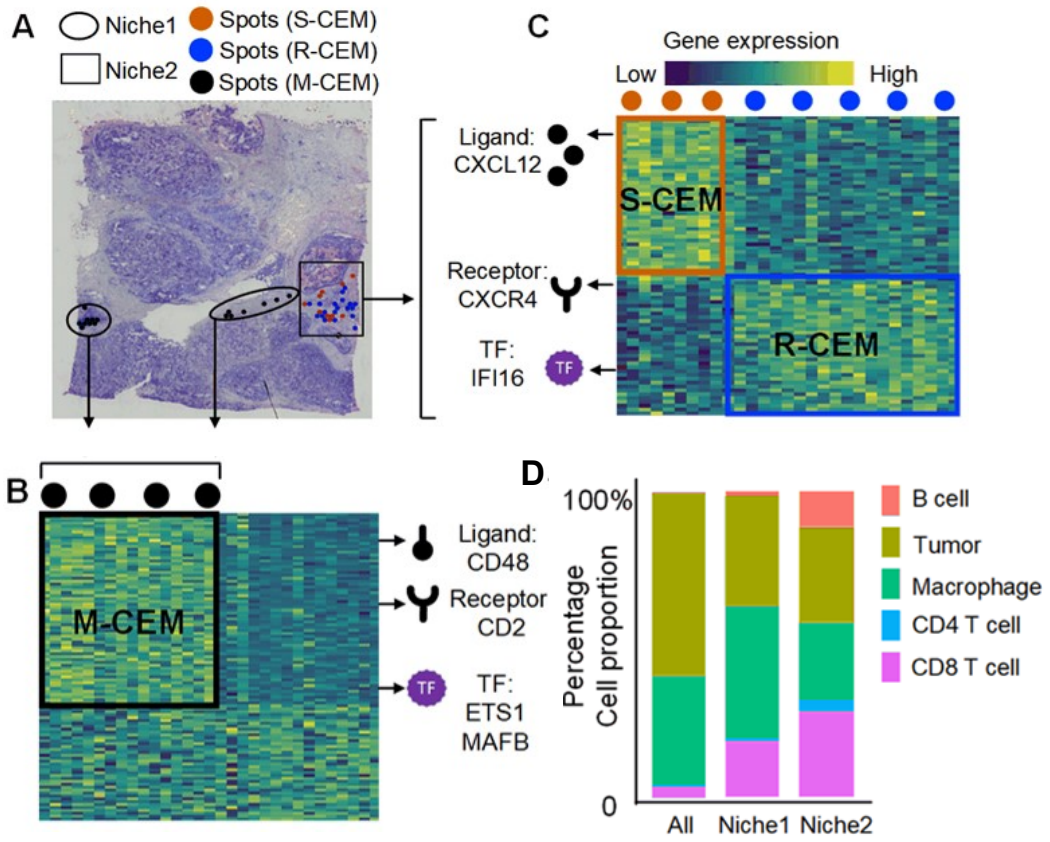


Purpose:

Identify a group of spots that subject to the following conditions:

1. They are M-CEM and P-CEM
2. These spots are spatially clustered

Hypothesis and observation



Conclusion:

1. M-CEM (mixed co-expression gene modules) capture CD48-CD2 ligand receptor pairs, associating T cell and B cell activation gene signatures.

2. S(sender)-CEM/R(receiver)-CEM capture motility-related LRP coding genes (CXCL12-CXCR4), which were reported to associate with tumor suppression in T cells.

3. Niches 1 and 2 had a higher proportion of CD8+ T cells and B cells and a lower proportion of cancer cells compared to those of all the spots.

4. Pathway of Niche 1 and 2 were associated with T cell and B cell activation functions.

5. The data were unpublished results generated by in-house IRIS-FGM.

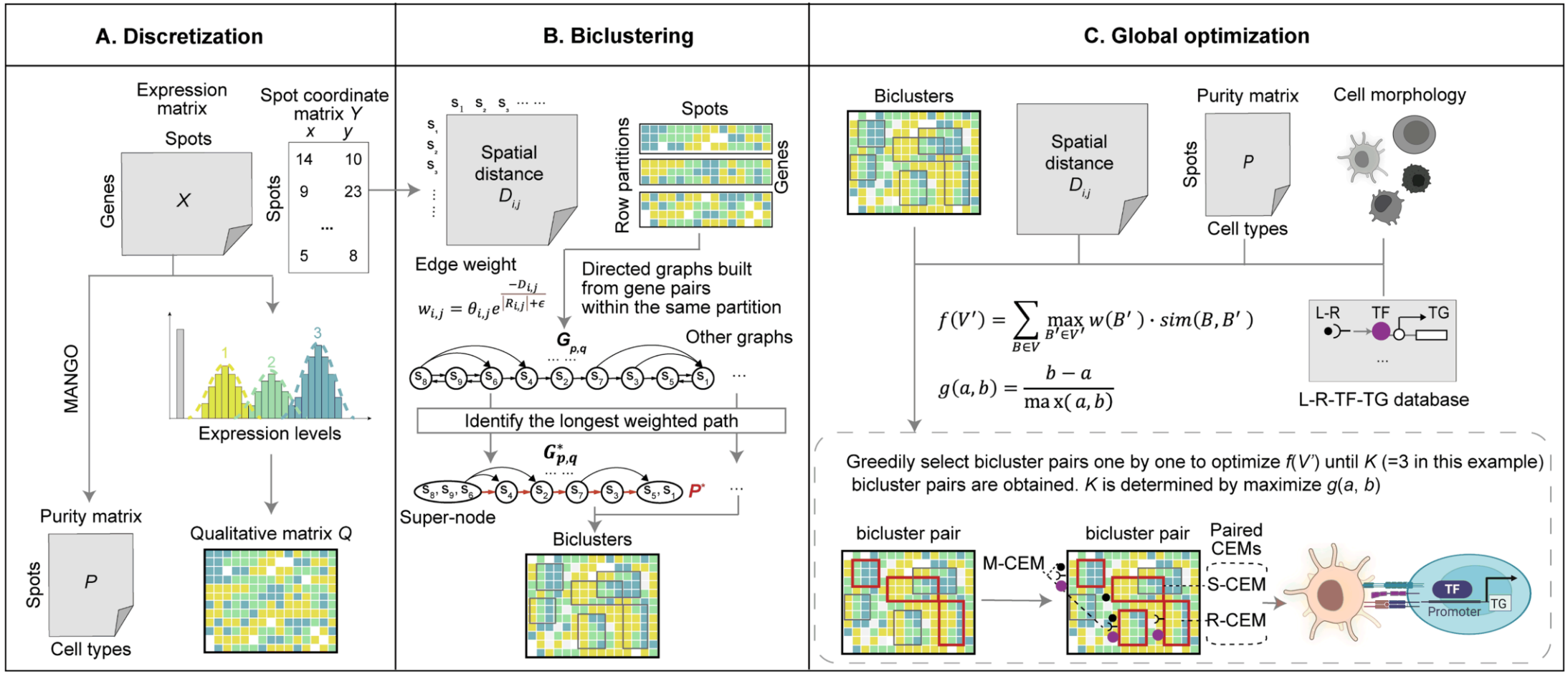
Mathematic formulation for CCC

- The mathematic formulation is to find local-low rank matrix from gene expression matrix (row is gene and column is spot)
- Solution of determining local-low rank matrix is NP-hard.
- Approximate solution is to find a set of heavy subgraphs in a weighted graph G,
  - nodes is gene,
  - edge is connecting every pair of genes
  - edge weight is determined by spatial distance and transcripts similarity.

$$w_{i,j} = e^{-\frac{D_{i,j}}{|R_{i,j}|+\epsilon}}$$

Where $\boldsymbol{D}$ is spot-to-spot spatial distance matrix; $\boldsymbol{R}$ is the spot-to-spot similarity matrix computed by Spearman correlation based on gene expression value, and ϵ is a pseudo-number to improve computational stability.

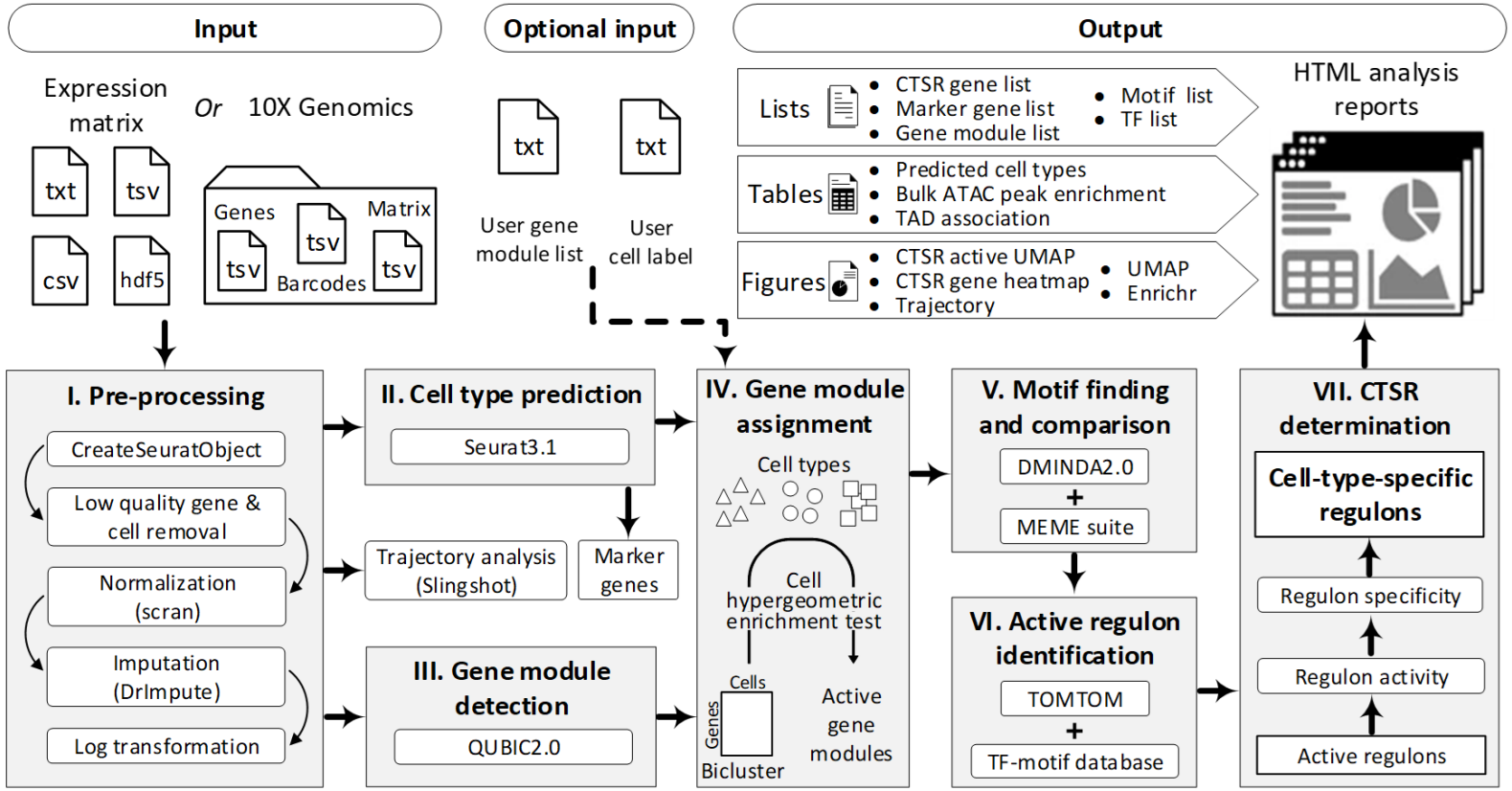
SAGE: a spatially-guided pattern recognition algorithm for simultaneous detection of CCC and CCC-associated CEM signatures



Yuzhou Chang, Carter Allen, Changlin Wan, Dongjun Chung, **Chi Zhang[$], Zihai Li[$], Qin Ma[$]** . *IRIS-FGM: an integrative single-cell RNA-Seq interpretation system for functional gene module analysis*. **Bioinformatics**. 2021.

Downstream analysis of SAGE algorithm

- Determine the potential regulator (i.e., transcriptional factors) for Pair-CEMs and M-CEM using IRIS3.



- Decipher cell type composition using Cell2location.
- Assess CCC directionality using the linear graph neural network-based causality model.

Anjun Ma, et al., Nucleic Acids Research (2020)
David S. Fischer, et al., bioRxiv (2021)
Vitalii Kleshchevnikov, et al., Nature biotechnology (2022)

Spatial omics is coming!

nature

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Article | Open Access | Published: 17 August 2022

Spatial profiling of chromatin accessibility in mouse and human tissues

Yanxiang Deng, Marek Bartosovic, Sai Ma, Di Zhang, Petra Kukanja, Yang Xiao, Graham Su, Yang Liu, Xiaoyu Qin, Gorazd B. Rosoklija, Andrew J. Dwork, J. John Mann, Mina L. Xu, Stephanie Halene, Joseph E. Craft, Kam W. Leong, Maura Boldrini, Gonçalo Castelo-Branco & Rong Fan

Nature **609**, 375–383 (2022) | Cite this article

29k Accesses | **248** Altmetric | Metrics

Cell

CellPress

Volume 183, Issue 6, 10 December 2020, Pages 1665-1681.e18

Resource

High-Spatial-Resolution Multi-Omics Sequencing via Deterministic Barcoding in Tissue

Yang Liu [1, 2, 5], Mingyu Yang [1, 2, 5], Yanxiang Deng [1, 2, 5], Graham Su [1, 2], Archibald Enninful [1], Cindy C. Guo [1], Toma Tebaldi [2, 4], Di Zhang [1], Dongjoo Kim [1], Zhiliang Bai [1], Eileen Norris [1], Alisia Pan [1], Jiatong Li [1], Yang Xiao [1], Stephanie Halene [2, 4], Rong Fan [1, 2, 3, 6]

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REPORT | SPATIAL EPIGENOMICS

Spatial-CUT&Tag: Spatially resolved chromatin modification profiling at the cellular level

YANXIANG DENG, MAREK BARTOSOVIC, PETRA KUKANJA, DI ZHANG, YANG LIU, GRAHAM SU, ARCHIBALD ENNINFUL, ZHILIANG BAI, GONÇALO CASTELO-BRANCO, [...] RONG FAN +1 authors Authors Info & Affiliations

SCIENCE · 10 Feb 2022 · Vol 375, Issue 6581 · pp. 681-686 · DOI: 10.1126/science.abg7216

20,484 CHECK ACCESS

RONG FAN

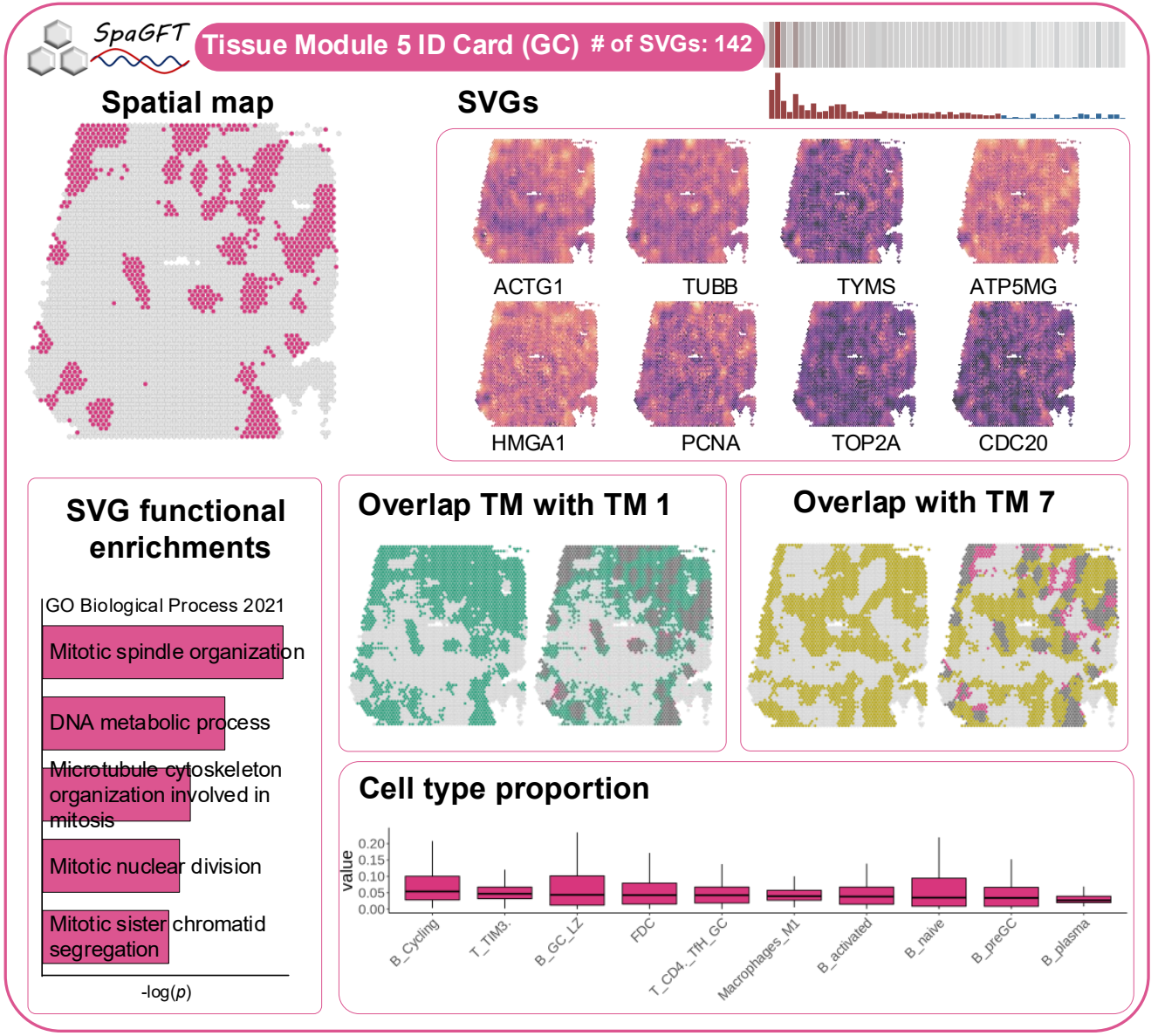
Harold Hodgkinson Professor of Biomedical Engineering

Spatial proteomics (e.g., CODEX)
Spatial ATAC-seq
Spatial CITE-seq
Spatial CUT & Tag
…..

Tissue module identification (Ongoing)

TM ID interpretation

1. SVG number.
2. Fourier coefficient as unique identifier.
3. Spatial map to show the TM distribution.
4. SVGs and functional enrichment.
5. Overlapped TMs show the interaction with other TMs.
6. Cell proportion (using cell2location) show the cell type composition in this TM.
7. More spatial-omics interpretation.



Yuzhou Chang, et al., Nature biotechnology (under revision)

Algorithms based on spatial omics

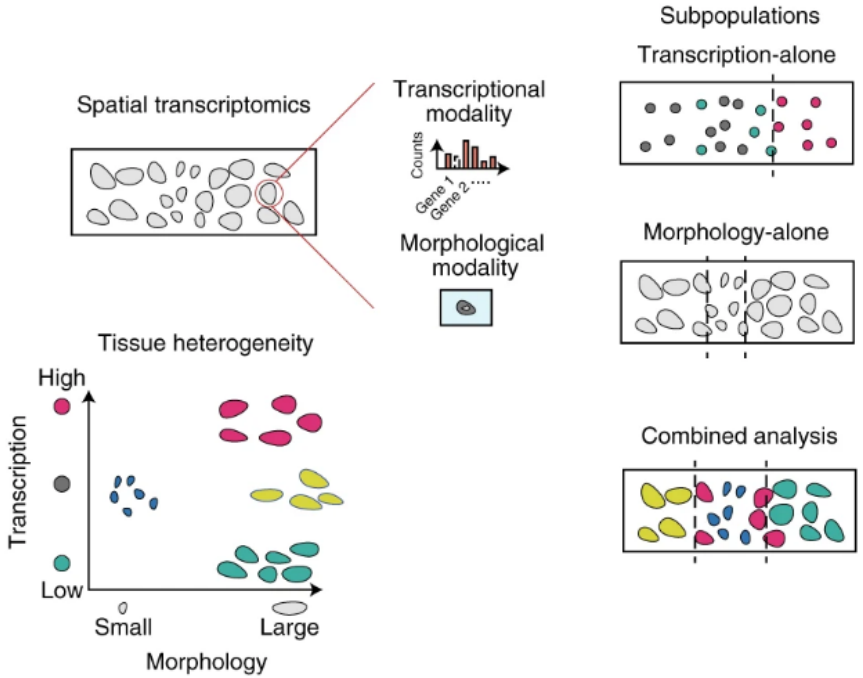
Article | Published: 28 March 2022

Integrative spatial analysis of cell morphologies and transcriptional states with MUSE

Feng Bao, Yue Deng, Sen Wan, Susan Q. Shen, Bo Wang, Qionghai Dai, Steven J. Altschuler & Lani F. Wu

Nature Biotechnology **40**, 1200–1209 (2022) | Cite this article

9180 Accesses | **2** Citations | **35** Altmetric | Metrics



Main idea: Identify new cell type by considering morphology and transcriptional information.

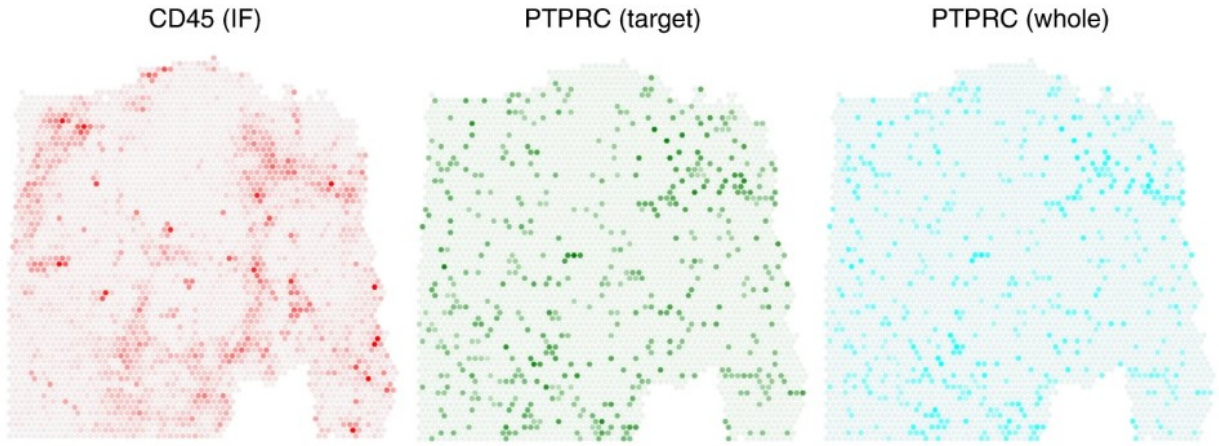
Article | Published: 04 August 2022

Sprod for de-noising spatially resolved transcriptomics data based on position and image information

Yunguan Wang, Bing Song, Shidan Wang, Mingyi Chen, Yang Xie, Guanghua Xiao, Li Wang & Tao Wang

Nature Methods **19**, 950–958 (2022) | Cite this article

3889 Accesses | **42** Altmetric | Metrics



Main idea: de-noise gene expression using protein or histology information.

Acknowledgement

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Ma Lab:
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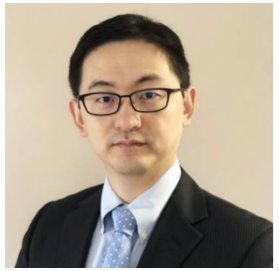
Tong Xiao
Nojoon Song

Dr. Dongjun Chung

Chung Lab:
Dr. Carter Allen



Dr. Gang Xin

Xin Lab:
Jianying Li

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Construction of cell-specific gene co-regulation signatures based on single-cell transcriptomics analysis (R01-GM131399)

Thrombocytes in Cancer Immunity (R01-CA188419)

Statistical Power Calculation Framework for Spatially Resolved Transcriptomics Experiments (R21-HG012482-01, Dr. Dongjun Chung, and Dr. Qin Ma)

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THANK YOU