An orientation in the spatial transcriptomics landscape

2021 :: Summer School Advanced Topics in Single Cell Analysis

https://github.com/almaan

https://almaan.github.io

@aalmaander

Who am I?

- **Name** : Alma Andersson
- **Part of** : Lundeberg Lab (PhD Student)
- **Works with** : Computational Method Development
  - Mainly focus on spatial transcriptomics data
- **Background :**
  - Engineer by training
  - **Before**: Molecular Dynamics
  - **Now**: Spatial Transcriptomics
- **Work :**
  - Single cell and spatial transcriptomics data integration (*stereoscope)*
  - Model to find spatially variable genes (*sepal)*
  - Spatial characterization of HER2 breast cancer samples
  - Common coordinate frameworks for spatial data
- **Non-scientific Interests**
  - Trail/Ultrarunning, Hiking, Outdoor stuff

SciLifeLab KTH

My vision for today

Introduction

- Broad overview of experimental spatial transcriptomics techniques
- A Recap on Visium
- Data character - what are we working with?

Computational methods and frameworks

- Different flavors of currently available methods
- Example methods
- Extra focus on single cell mapping and integration
- Squidpy : a framework for handling spatial data

Observations from the wild

- General advice
- Example : A spatial survey of HER2-positive breast cancer
- Example : Spatial gene expression dynamics in the mouse liver

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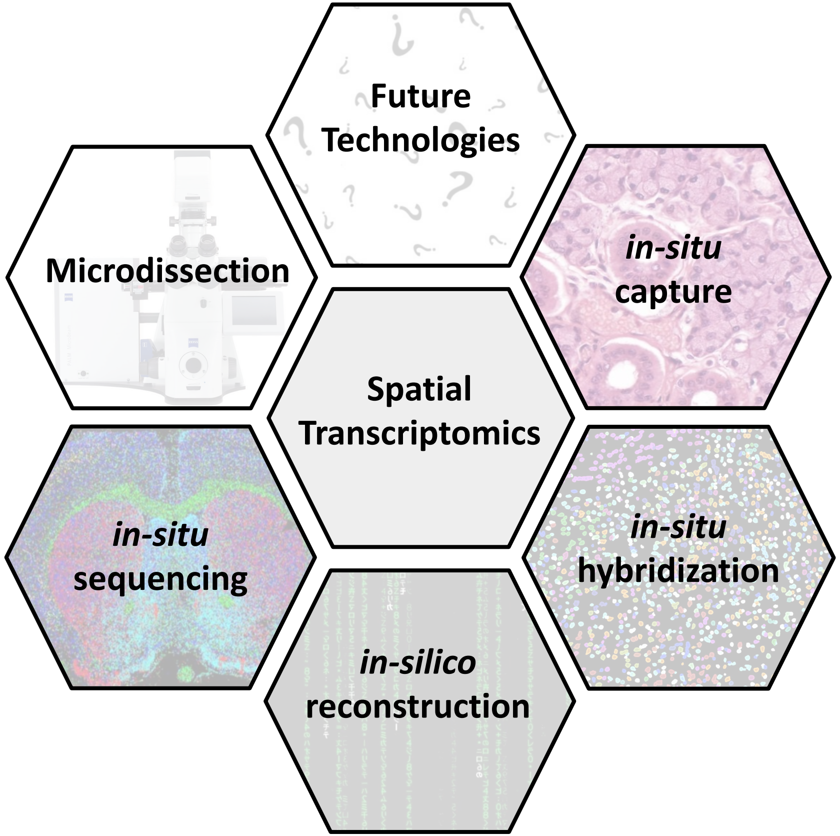
Slides ::
lectures/spatial_transcriptomics.pdf

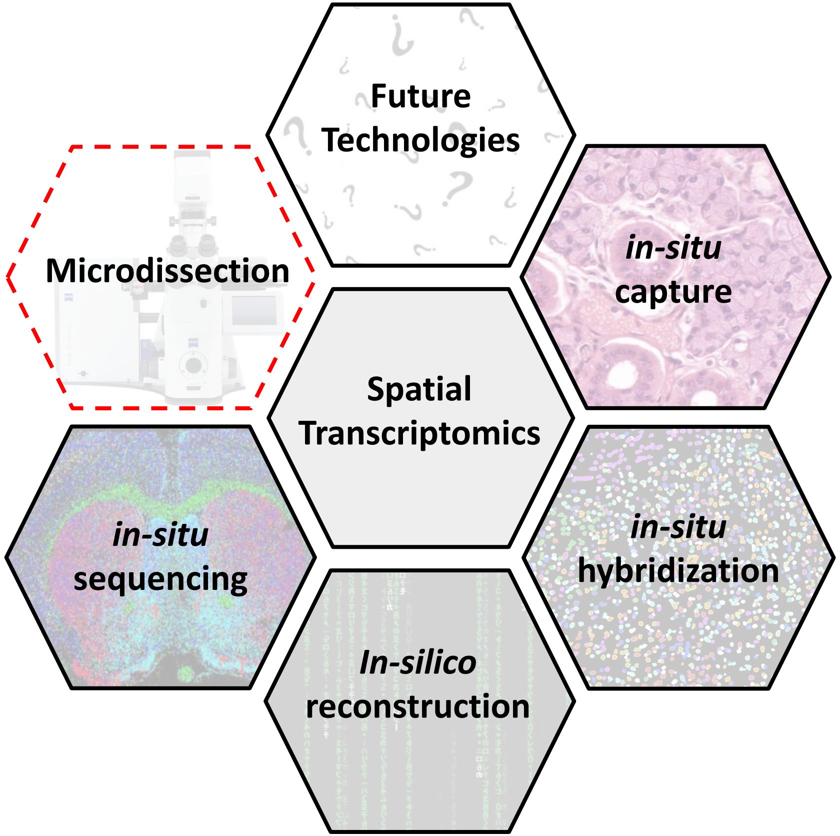
Links ::
https://almaan.github.io/extras/advsc-info/

Experimental techniques



Categories from : **Spatially Resolved Transcriptomes—Next Generation Tools for Tissue Exploration, Asp et al.**

Experimental techniques



Microdissection-based technologies

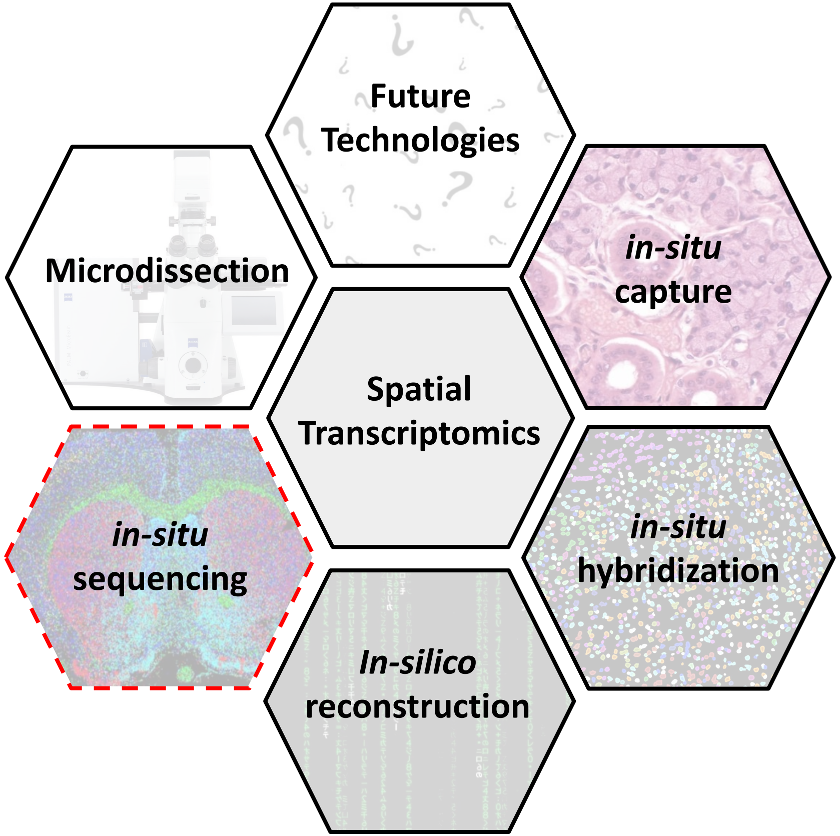
Isolate a region of interest, place isolate in separate well and sequence (either by bulk or single-cell methods).

A "Brute Force" approach.

Examples : LCM, Tomo-seq, TIVA, ProximID, Niche-seq

Categories from : **Spatially Resolved Transcriptomes—Next Generation Tools for Tissue Exploration, Asp et al.**

Experimental techniques



In-situ sequencing based methods

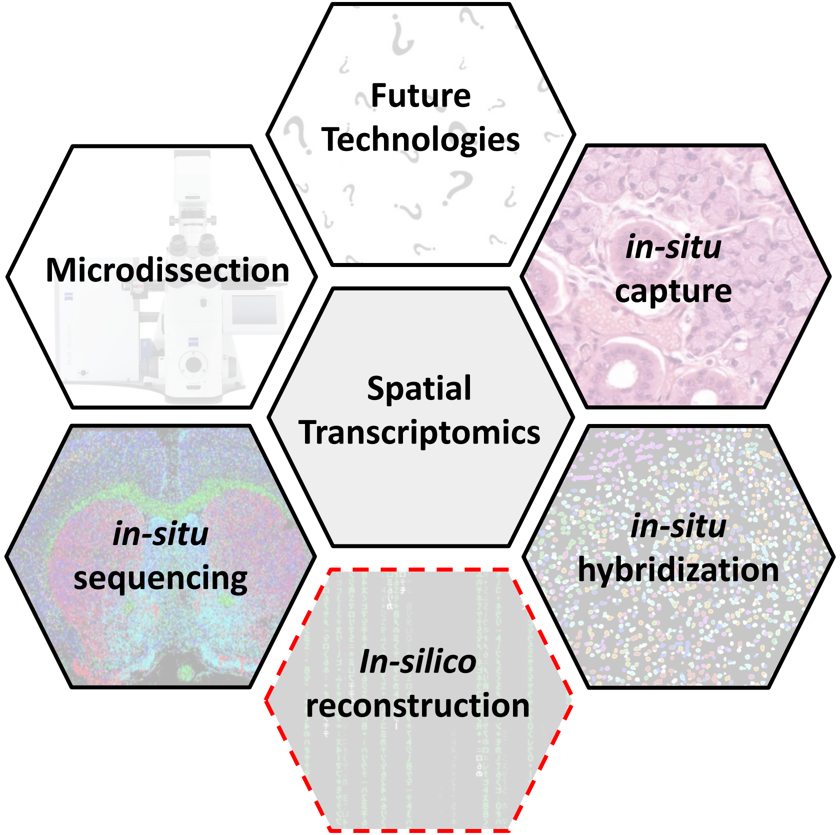
Sequence the transcripts in place.

Offer sub-cellular resolution. Some relies on "*a priori*" defined targets, but not all.

Examples : ISS/Cartana (padlock probes), BaristaSeq, STARmap, FISSEQ

Categories from : **Spatially Resolved Transcriptomes—Next Generation Tools for Tissue Exploration, Asp et al.**

Experimental techniques



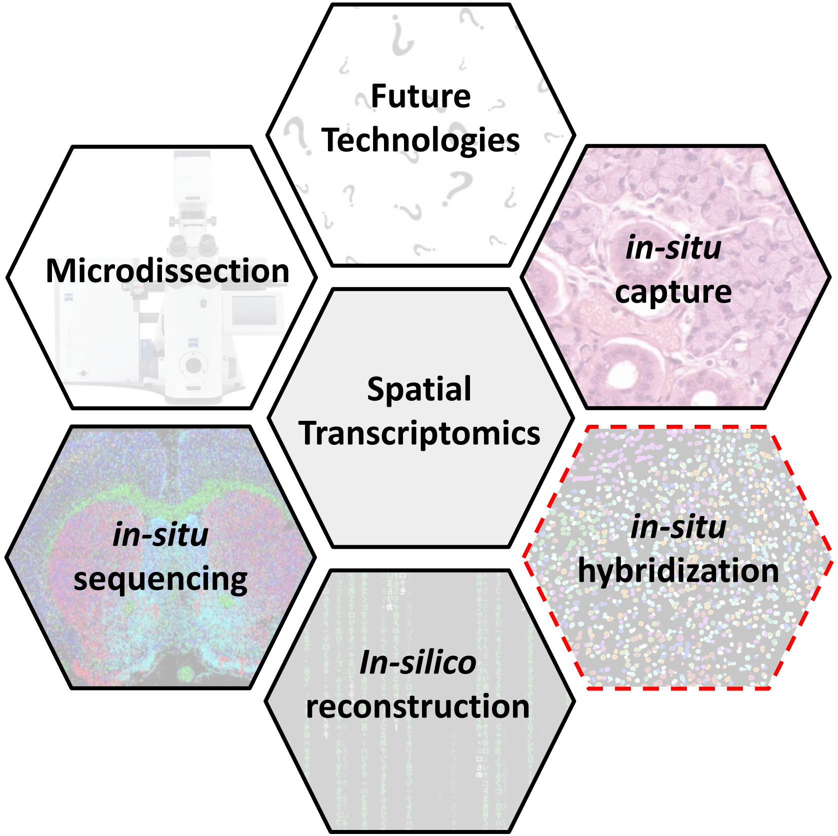
In-silico reconstruction

Infer and reconstruct spatial structure from non-spatial data (e.g., single cell).

Examples : novoSpaRc, CSOmap, Seurat v3

Categories from : **Spatially Resolved Transcriptomes—Next Generation Tools for Tissue Exploration, Asp et al.**

Experimental techniques



In-situ hybridization based methods

Labeled probes for specific targets, hybridize in place.

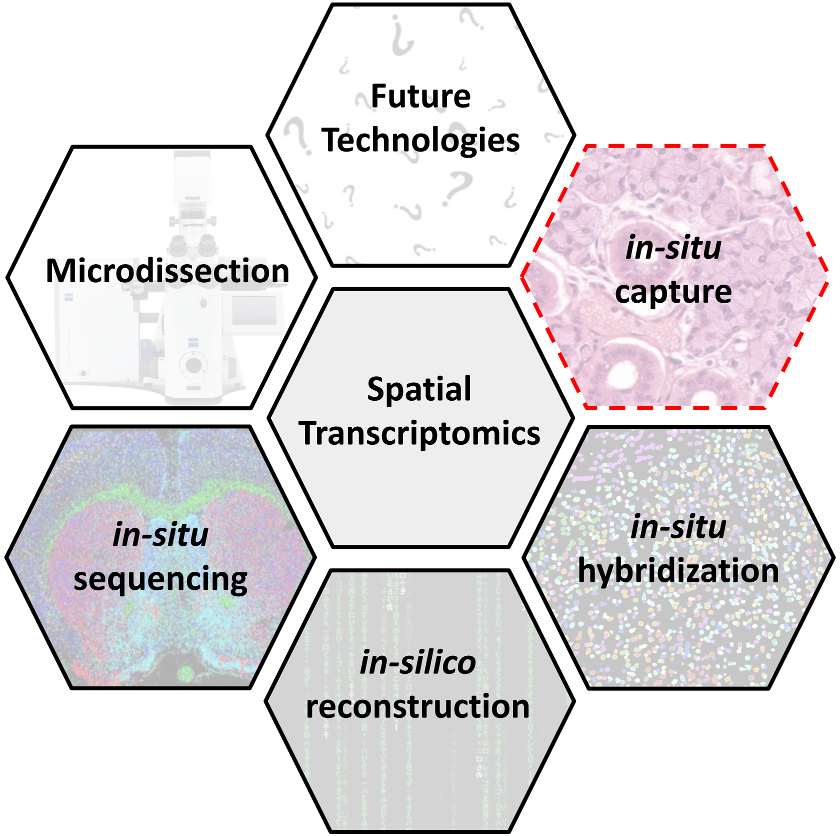
Requires "*a priori*" defined targets.

Expansion strategies and smart decoding scheme has helped to overcome spectral overlap.

Examples : smFISH, seqFISH, MERFISH, seqFISH+, osmFISH, RNA Scope, DNA microscopy

Categories from : **Spatially Resolved Transcriptomes—Next Generation Tools for Tissue Exploration, Asp et al.**

Experimental techniques



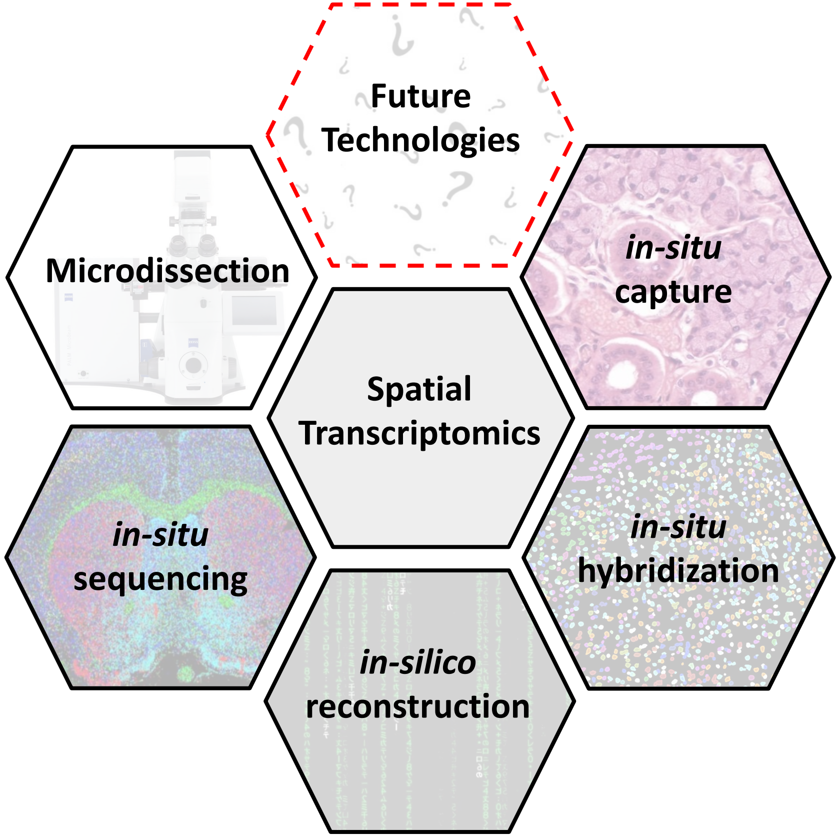
In-situ capture based methods

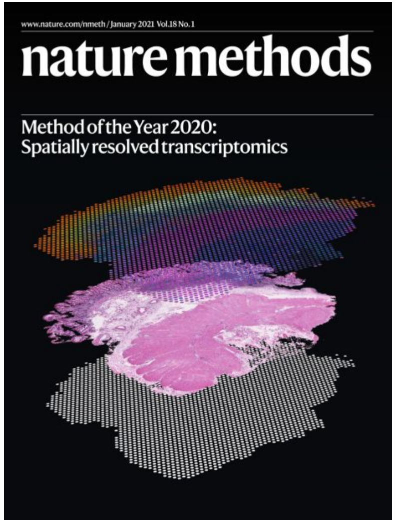
Capture transcripts *in situ* but sequence *ex situ*. Usually less dependent on prior selection of targets.

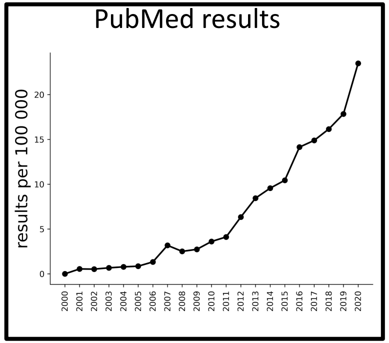
Examples : Visium, ST, Slide-Seq, HDST, GeoMX, Apex-Seq, Stereo-SEQ

Categories from : **Spatially Resolved Transcriptomes—Next Generation Tools for Tissue Exploration, Asp et al.**

Experimental techniques



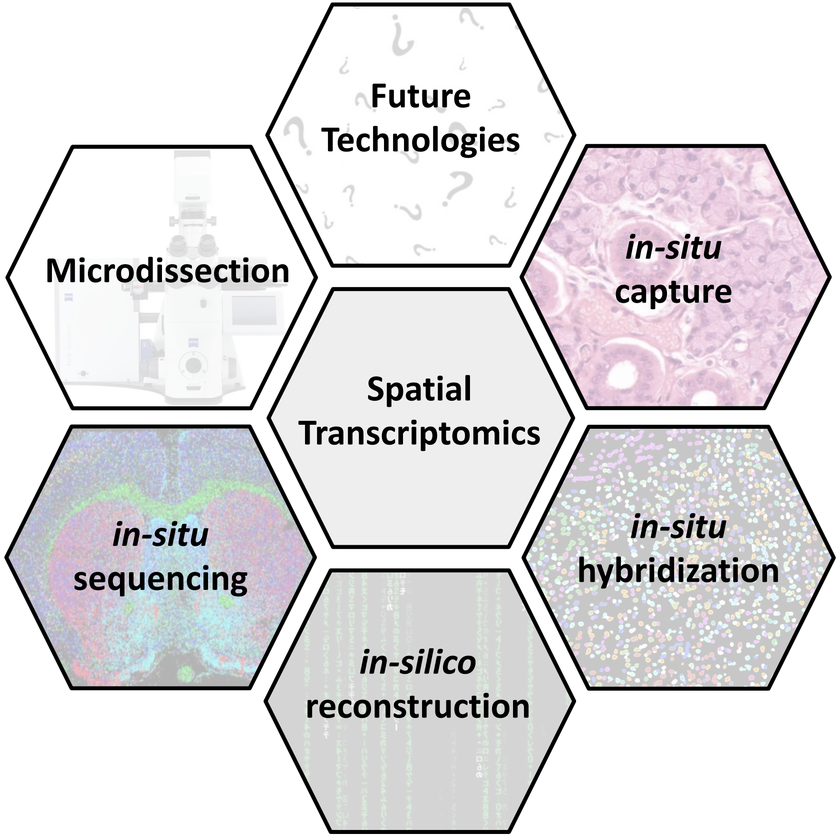




Search: Spatial Transcriptomics

Categories from : **Spatially Resolved Transcriptomes—Next Generation Tools for Tissue Exploration, Asp et al.**

Experimental techniques



Further Readings

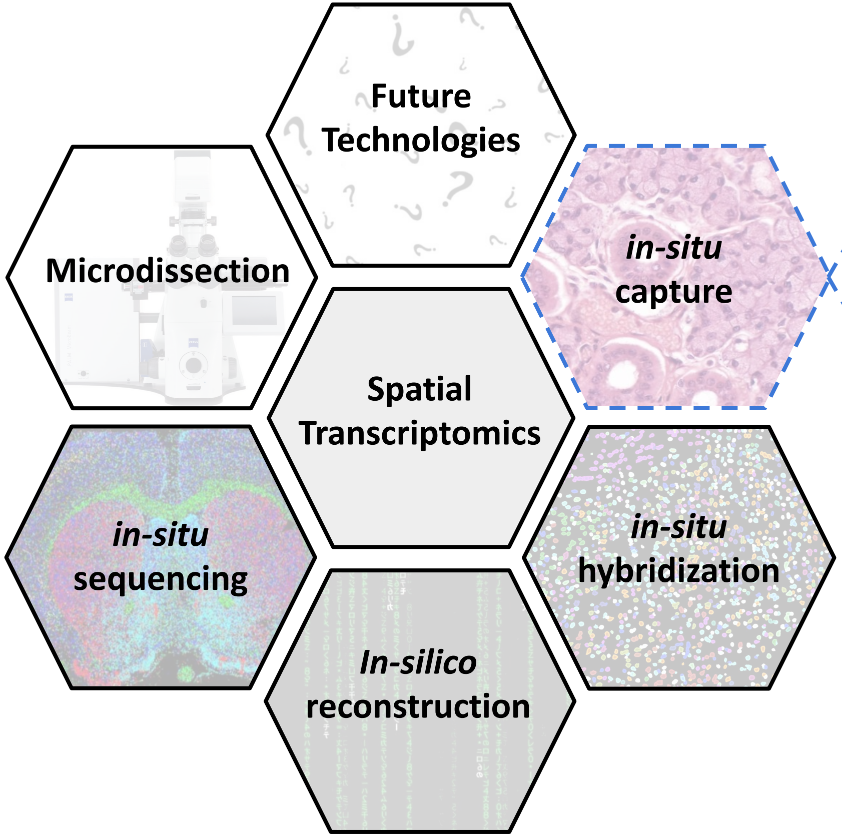
Spatially Resolved Transcriptomes—Next Generation Tools for Tissue Exploration
Authors : Michaela Asp, Joseph Bergenstråhle, Joakim Lundeberg
Published : 2020-05-04
DOI: 10.1002/bies.201900221

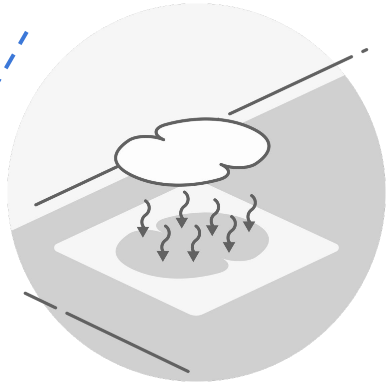
Spatially resolved transcriptomics adds a new dimension to genomics
Authors : Ludvig Larsson, Jonas Frisén & Joakim Lundeberg
Published : 2021-01-06
DOI: 10.1038/s41592-020-01038-7

Museum of Spatial Transcriptomics
Authors : Lambda Moses and Lior Pachter
Published : 2021-05-12
Link: https://pachterlab.github.io/LP_2021/

Categories from : **Spatially Resolved Transcriptomes—Next Generation Tools for Tissue Exploration, Asp et al.**

Experimental techniques



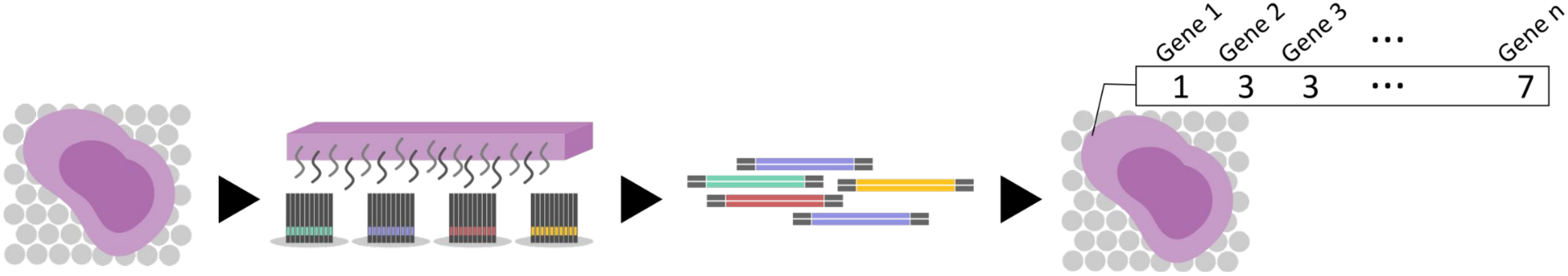


10x GENOMICS

Visium

Image from : https://www.10xgenomics.com/products/spatial-gene-expression

Visium :: Recap



Tissue +
Visium array

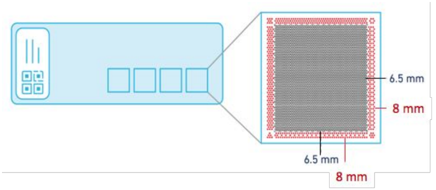
Permeabilize and
capture mRNA

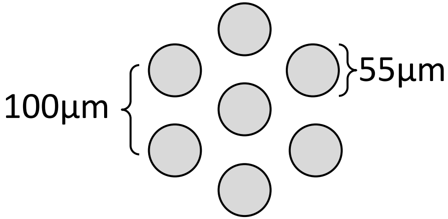
Sequence cDNA with
spatial barcodes

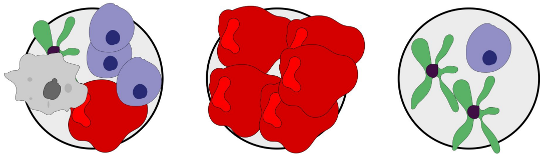
Relate gene
expression to physical
location

Visium :: Recap

- Array based technique
- 6.5mm x 6.5mm area to put sample on
- 4992 spots arranged in hexagonal grid
- Array specs:
  - Spot diameter : 55µm
  - Center to center distance : 100 µm
- Successor to Spatial Transcriptomics (ST)
- Data processing often includes :
  - Genome mapping and annotation
  - Spatial barcode demultiplexing
- Approx. 1-10 cells contribute to each spot
  - **NOTE** : Not single cell resolution!
- Data represented as [spot] x [gene] matrix
- You also get HE-image of the **same** tissue





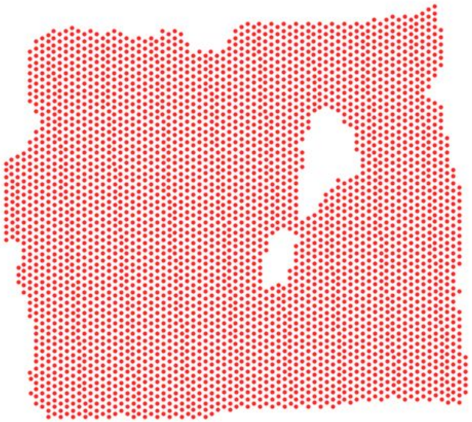


https://kb.10xgenomics.com/hc/en-us/articles/360035487572-What-is-the-spatial-resolution-and-configuration-of-the-capture-area-of-the-Visium-Gene-Expression-Slide-

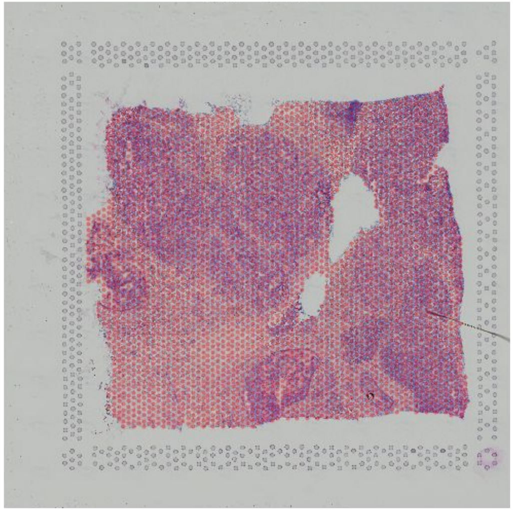
Visium :: Recap

- Example with Human Breast cancer data
  - Public data : Available at 10x website

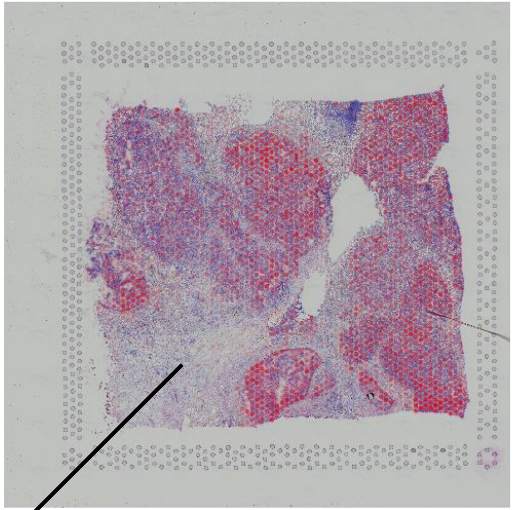
Spots Only



Spots + HE image



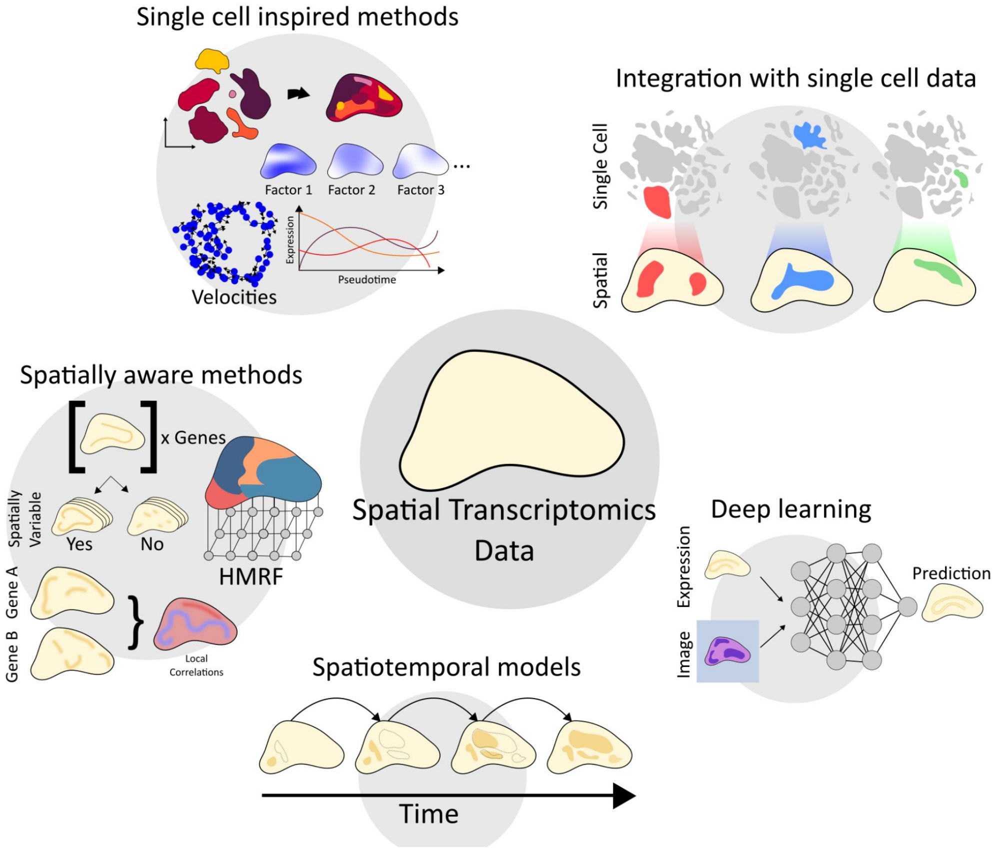
Spots + ERBB2 expression + HE image



Facecolor intensity proportional
to gene expression value

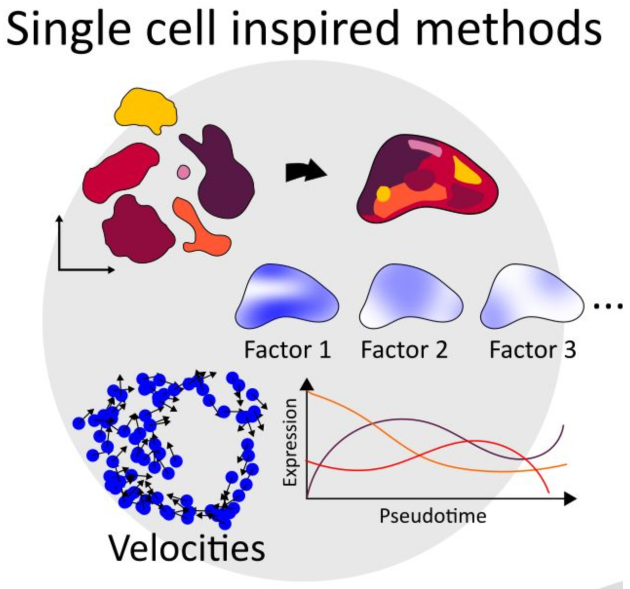
Computational Analysis

A motley crew of diverse methods



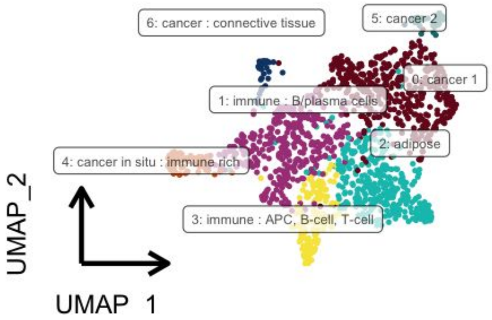
Single Cell Inspired methods

- **Basic idea :** apply existing methods and tools developed for single cell data.
- **Examples** :
  - Cluster spatial data, show clusters in space
  - Decompose expression profiles using factor models
  - Trajectory Inference :
    - Alt 1 : treat as single cell data
    - Alt 2 : reconstruct algorithm
- **Suites/Tools:**
  - Seurat : added support for spatial data
  - Scanpy : added support for spatial data
  - STUtility : built on Seurat tailored for spatial data
  - stLearn : built on scanpy tailored for spatial data
  - SpatialExperiment : (similar to SingleCellExperiment)
  - And many many more...

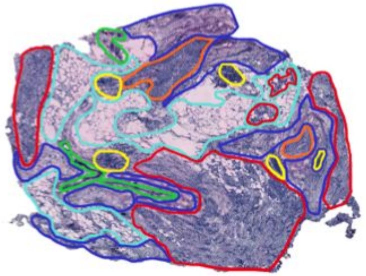


Clustering :: Human Breast Cancer Data

UMAP embedding



Pathologist annotation (for reference)



Spatial distribution of Clusters

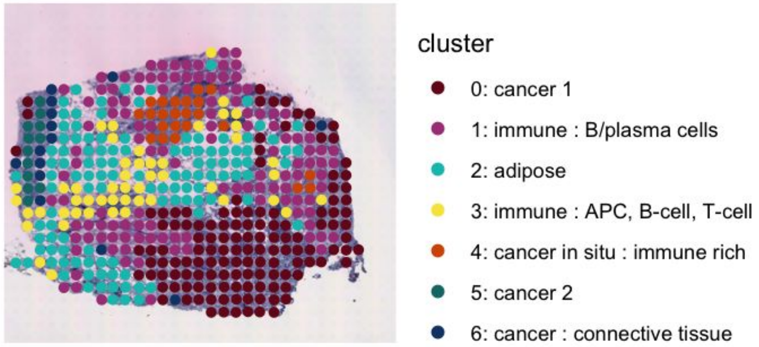
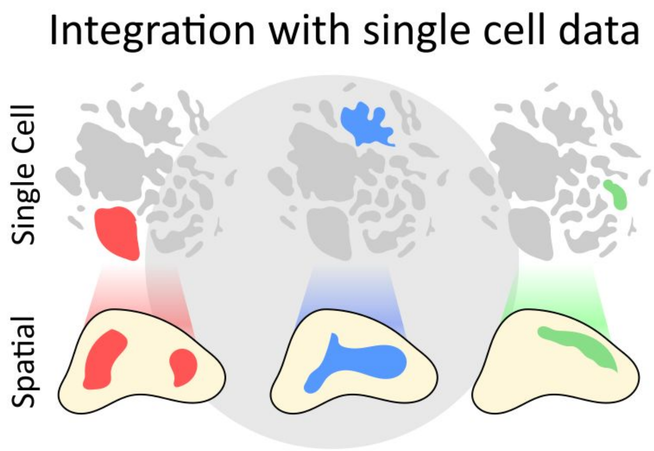


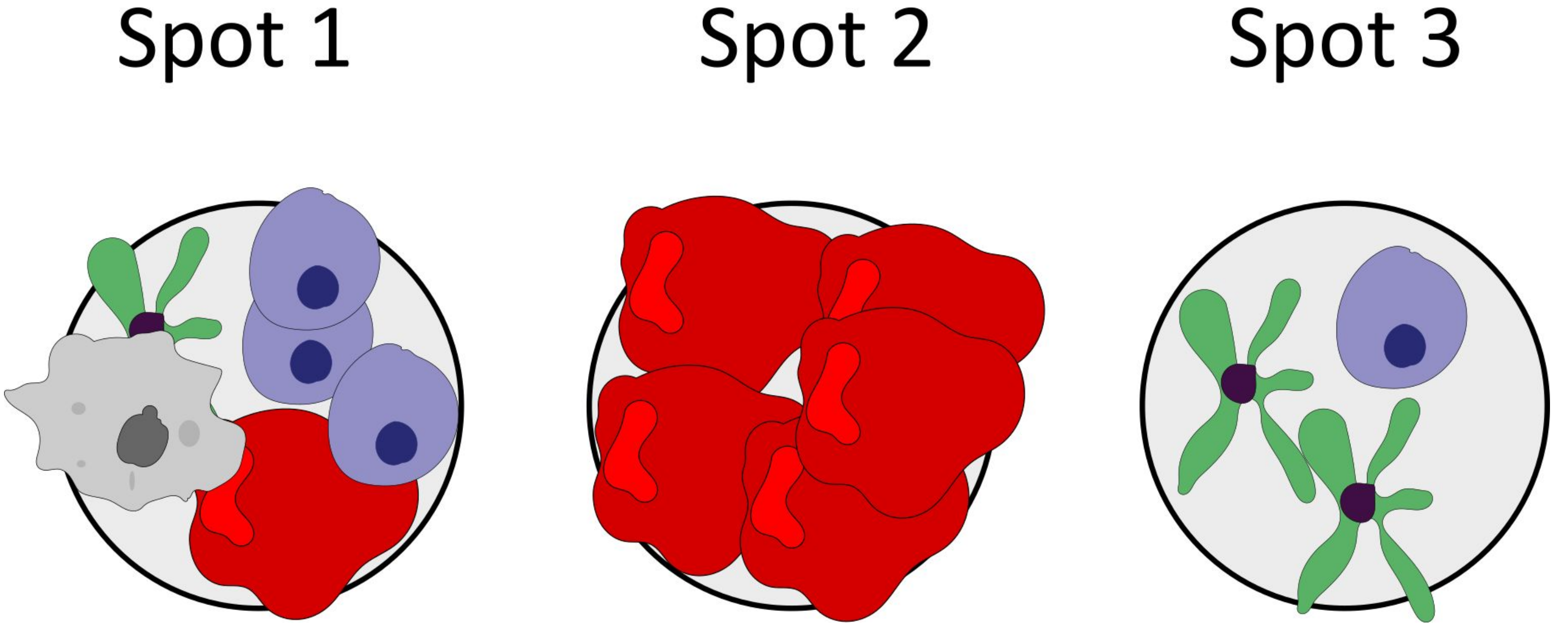
Figure from : Spatial Deconvolution of HER2-positive Breast Tumors Reveals Novel Intercellular Relationships, Andersson et al.

Integration with single cell data

- **Basic idea :** use single cell data as a *reference* when working with spatial data.
- **Answers :** Where are cell types in SC data found in space?
- **But why?** Two main reasons :
  - Efficient use of resources. Leverage extensive annotation work done for single cell data.
  - Problem of mixed contributions (in Visium)

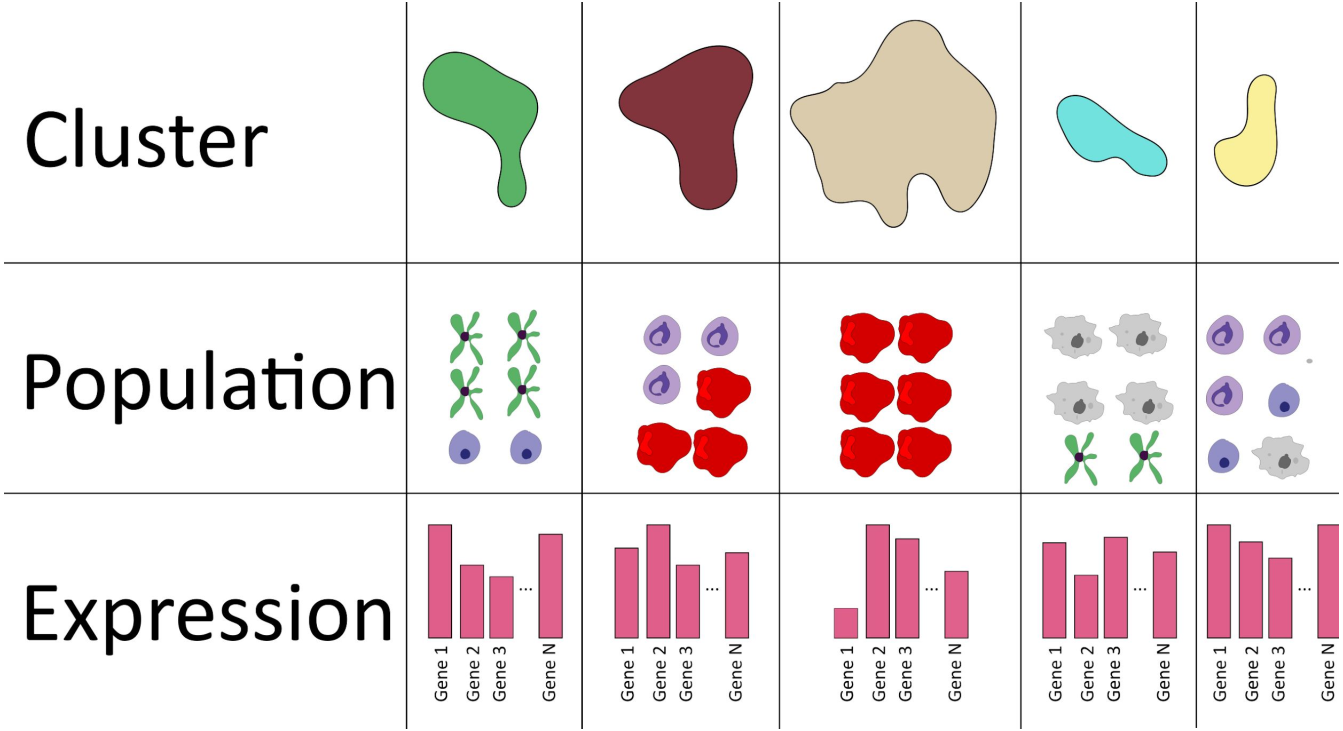


Mixed contributions



In several of the **capture based techniques** (e.g., Visium and Slide-seq), observed expression values are **contributions from multiple cells**. Not all necessarily of the same type.

Mixed contributions



- Clusters **do not represent cell types**
- Clusters are more an assembly of spots with **similar composition** of cell types.
- We have no idea what the cell type population looks like. **Only observe expression**

Mixed contributions

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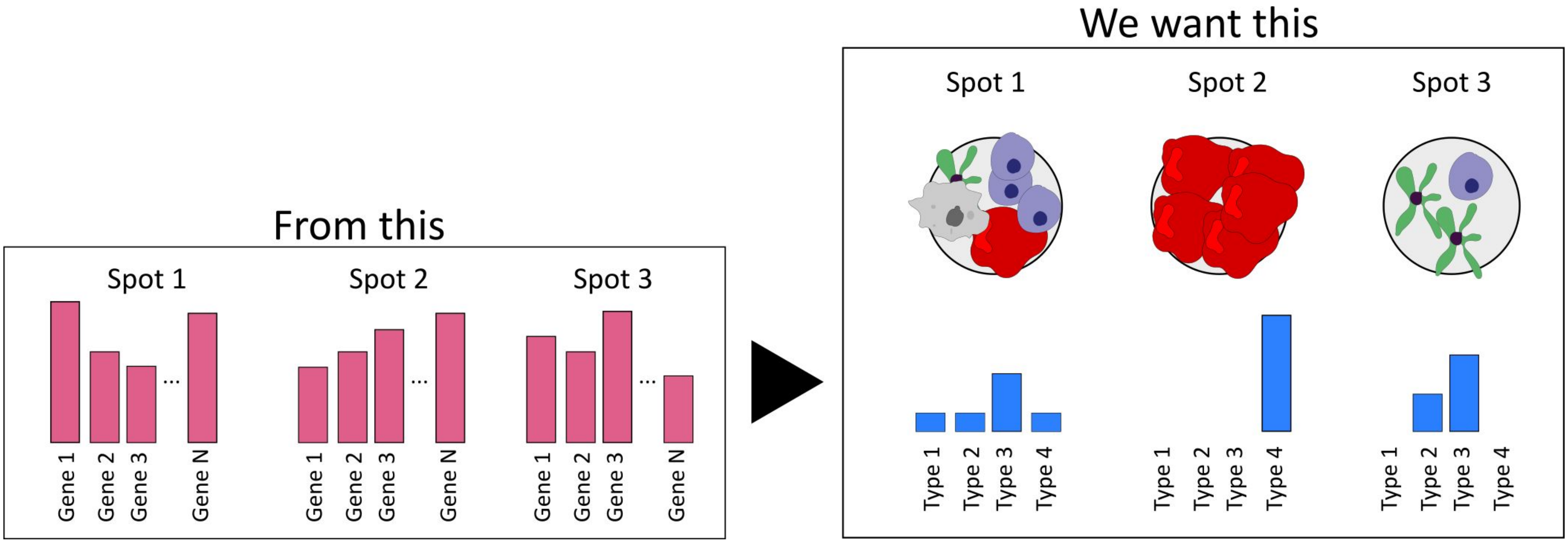
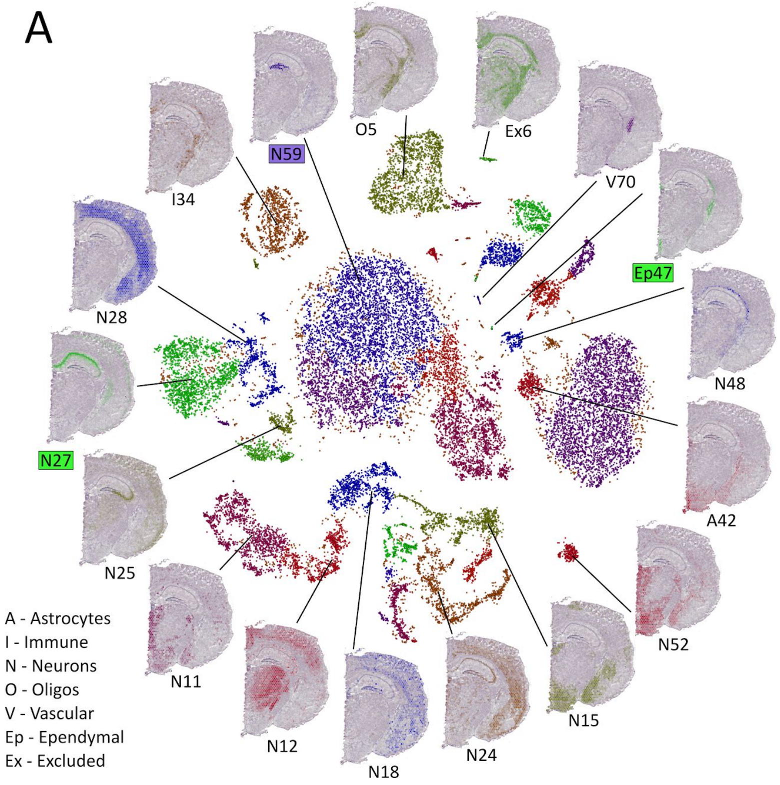
Our objective : deconvolve expression data



Integration with single cell data



(generated with *stereoscope*)

- **Inner** : Single cell data from mouse brain, gt-SNE embedding. Colored by cluster.
- **Outer** : Visium data of mouse brain. Facecolor intensity indicates proportion value of cluster.

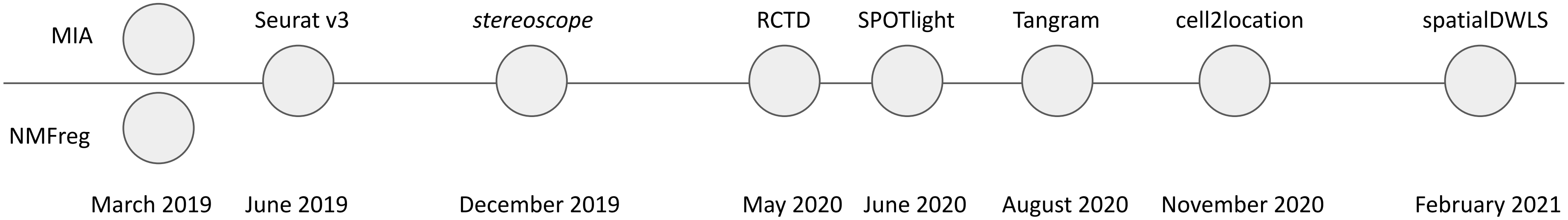
Figure 2 from "*Single-cell and spatial transcriptomics enables probabilistic inference of cell type topography*", Andersson et al.

Integration with single cell data

Marker gene based	Anchor based	Probabilistic Modelling	Optimization based
Extract marker genes (MG) for each cell type from SC data Compute enrichment score for each set of MGs in spatial locations Normalize to make scores sum to 1 **Ex:** Moncada et al.	Find anchors between modalities (MNNs). Create correction vector based on differences in expression. Use correction vectors to remove platform effects. Integrated data sets. Transfer labels of single cells to spatial data points. **Ex:** Seurat	Assume gene expression follows certain statistical distributions. Joint model for SC and spatial data. Learn cell type parameters from SC data, use to deconvolve spatial data (when mixed). Correct for eventual platform differences **Ex:** *stereoscope,* RCTD, cell2location	Find spatial location where each cell is most likely to reside. Tries to simultaneously optimize terms such as: ● Cell density ● UMI distribution across genes within spots ● gene distribution across spots **Ex:** Tangram

Integration with single cell data

A non-comprehensive overview based on bioRxiv releases



Integration with single cell data

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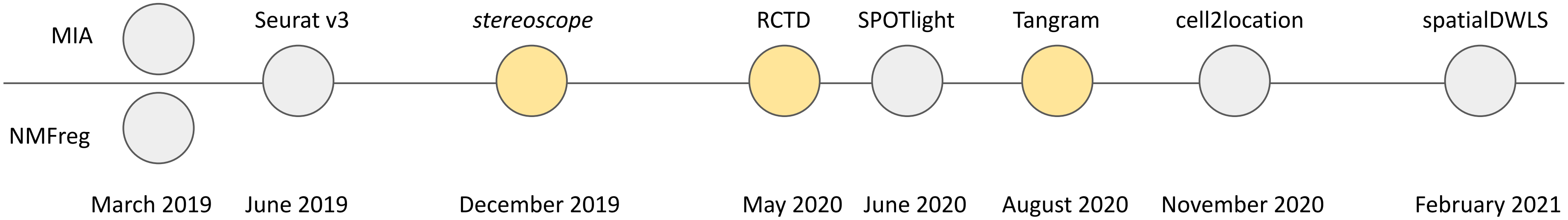
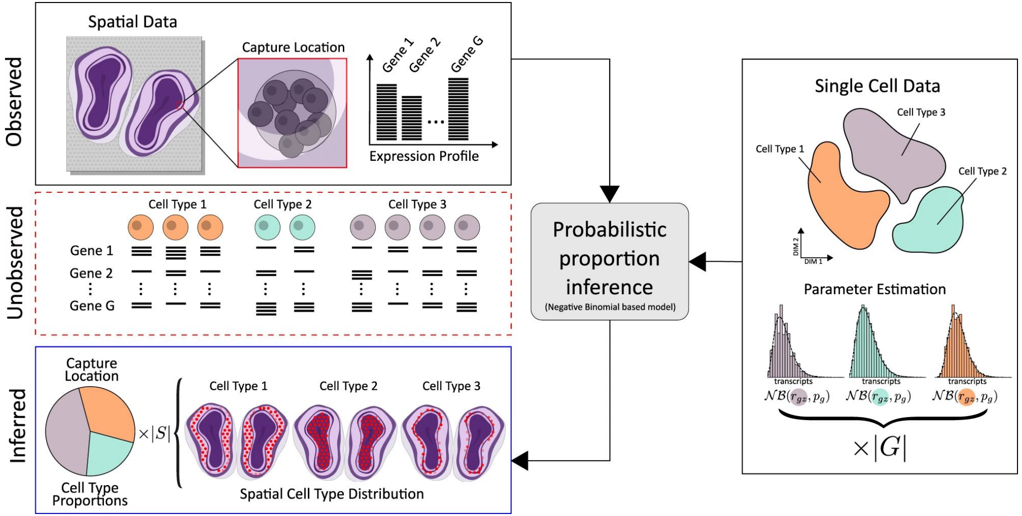


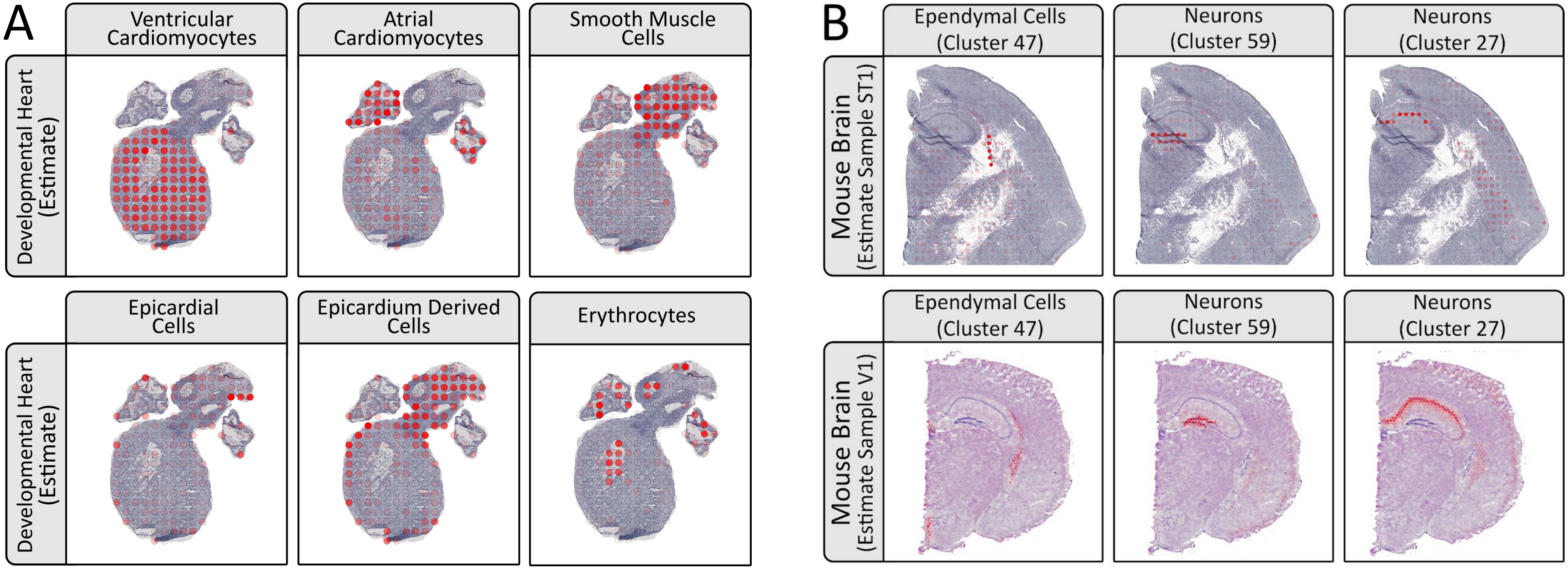
Integration with single cell data :: *stereoscope*

- Probabilistic, models single cell and spatial transcriptomics data with **negative binomial** distribution
- Two-step process:
  1. Learn parameters from sc-data
  2. Infer proportions in spatial data
- Parameters from single cell data can be reused, cut computational time in half.
- Accounts for missing cell types by including a “dummy cell types”
- *“Single-cell and spatial transcriptomics enables probabilistic inference of cell type topography”*, Communications Biology, Andersson et al.



https://github.com/almaan/stereoscope

Integration with single cell data :: *stereoscope*



Developmental heart : DOI: [10.1016/j.cell.2019.11.025](https://doi.org/10.1016/j.cell.2019.11.025)
Mouse Brain : 10X Genomics website + mousebrain.org

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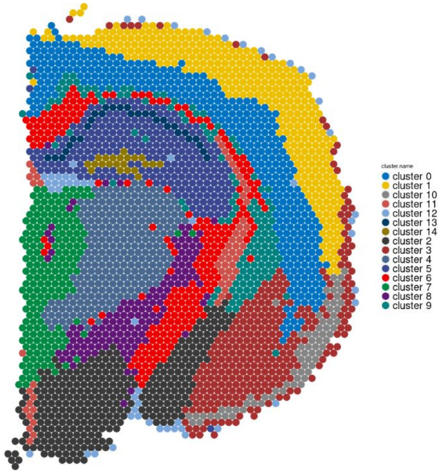
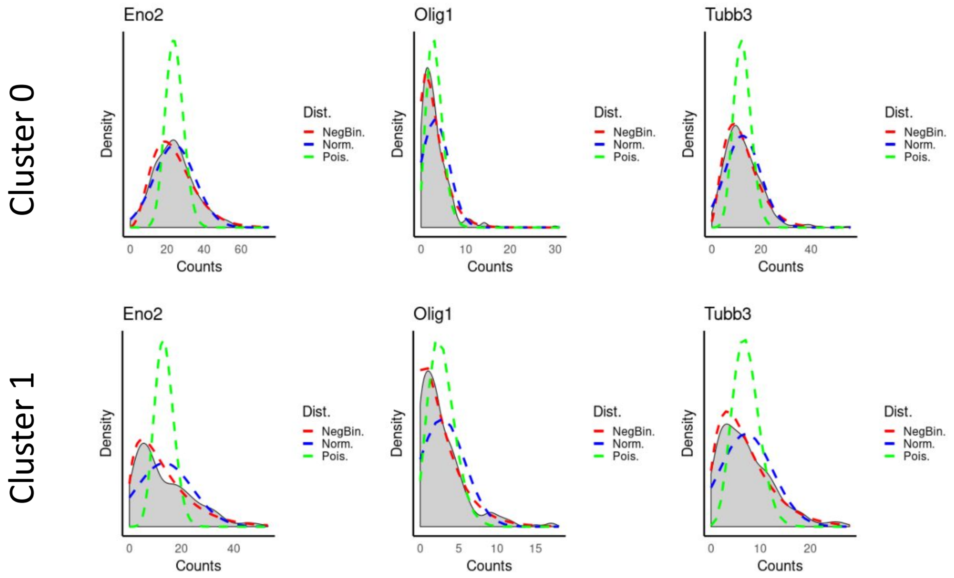
Integration with single cell data :: *stereoscope*

- Single cell data usually modelled as overdispersed Poisson distribution (Negative Binomial). Basis for several analysis methods (Normalization, DE, etc.)
- Applicable to ST/Visium data as well



Visium data Mouse Brain
Colored by cluster

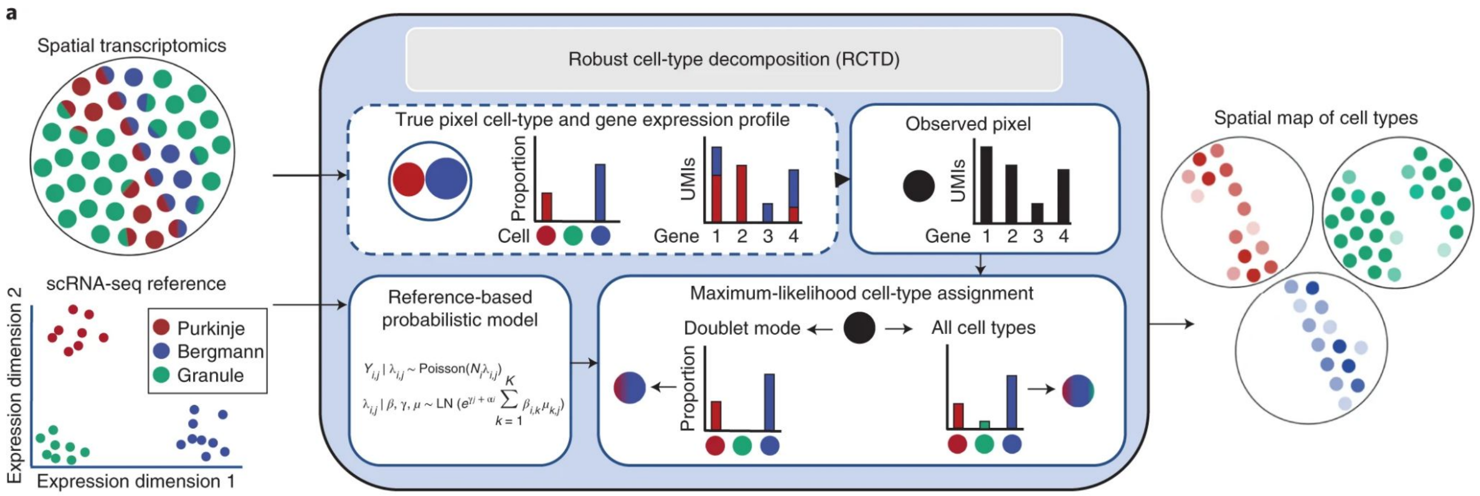


Similar trends for all clusters and genes.

Supports NB distribution, also when corrected for increased parameter number compared to Poisson).

Figure Supplementary *"Single-cell and spatial transcriptomics enables probabilistic inference of cell type topography"*, Andersson et al.

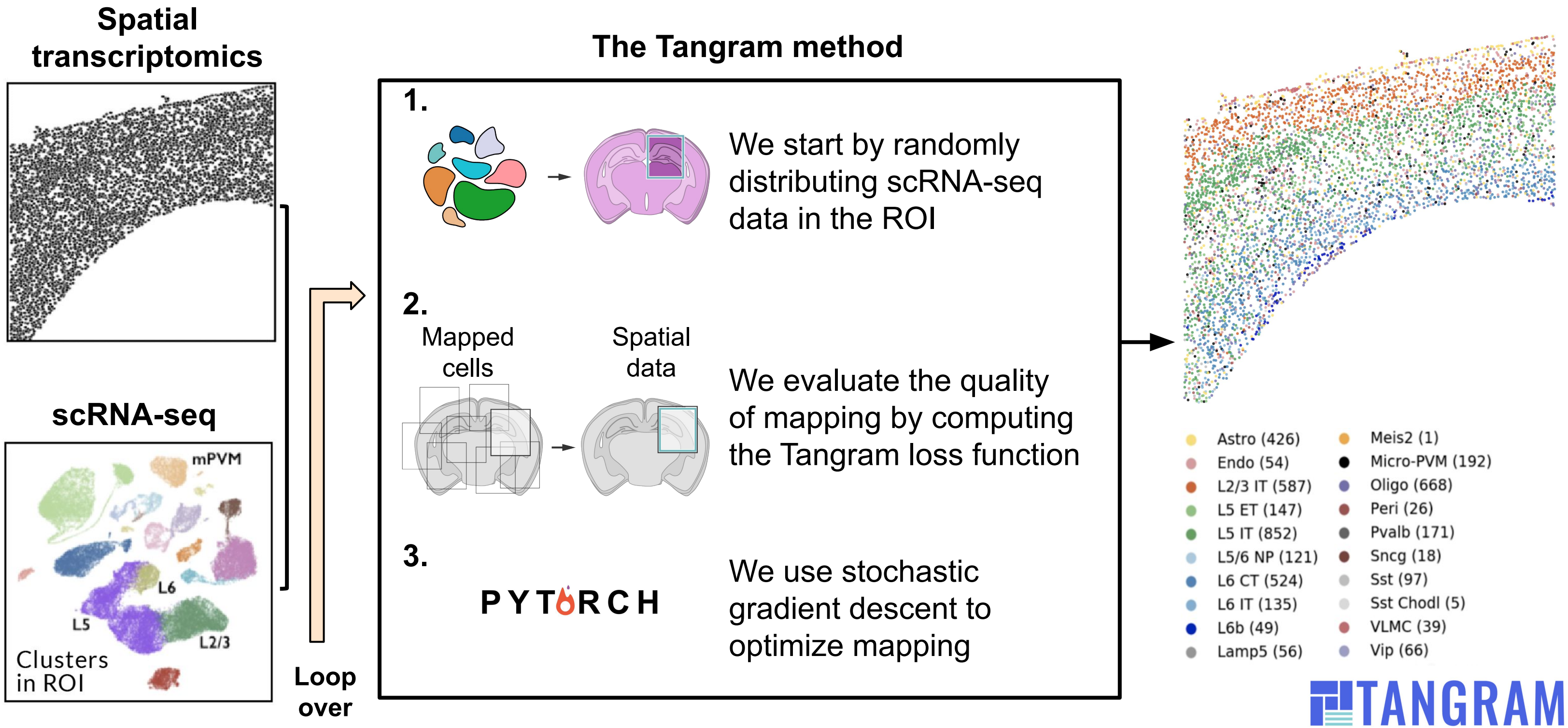
Integration with single cell data :: RCTD



- Probabilistic model for **inferring cell types in spatial transcriptomics data**, supervised with a labeled single-cell RNA-seq reference.
- Infers **platform effects** (or technical differences across sequencing platforms) in order to correct for differences between the single-cell reference and the spatial target dataset.
- RCTD uses maximum likelihood estimation to **identify cell types present on each spatial** transcriptomics spot, **in addition to estimating cell type proportions**.
- Robust decomposition of cell type mixtures in spatial transcriptomics, Nat. Biotech, Cable et al.

Slide courtesy of Dylan Cable.

Integration with single cell data :: Tangram



TANGRAM

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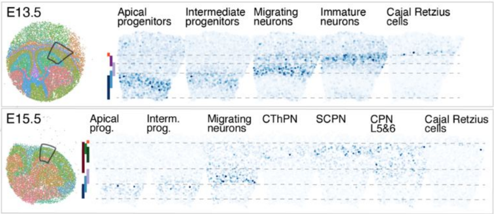
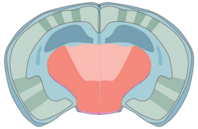
Deep learning and alignment of spatially-resolved whole transcriptomes of single cells in the mouse brain with Tangram, Biancalani, Scalia* et al. - Nature Methods (in press), 2021.* Slide courtesy of Tommaso Biancalani.

Integration with single cell data :: Tangram

Spatial maps of cell types in developmental mouse brain

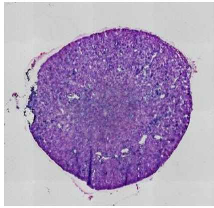




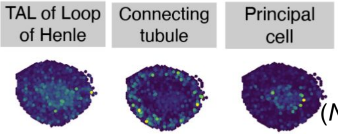
with Paola Arlotta lab (*Nature* 2021 *in press*)

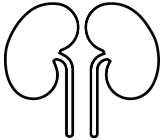
Assessing cross-species conservation in kidney

Mouse kidney histology



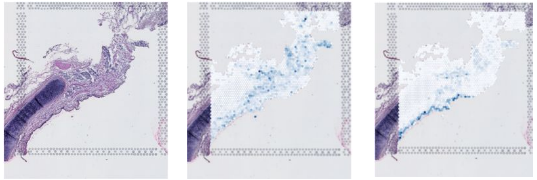
Cell type maps in kidney

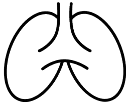




with Aviv Regev lab (*Nature Methods* 2021 *in press*)

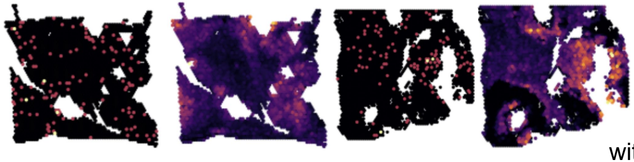
Localization of epithelial cell types in human lung

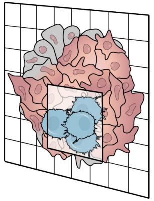




with Jay Rajagopal lab (*in preparation*)

Correction of gene expression in colorectal cancer



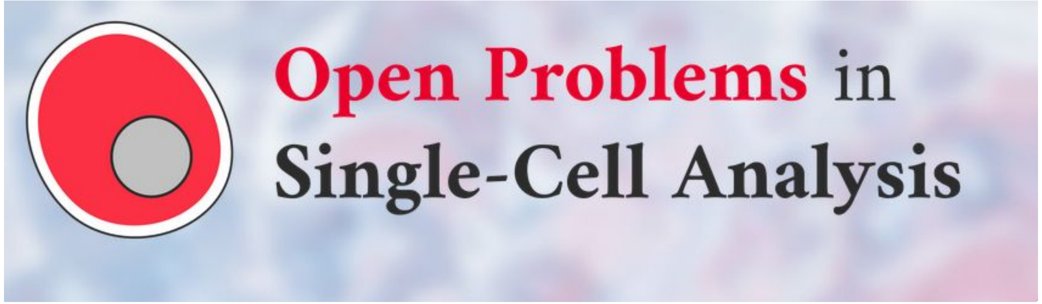


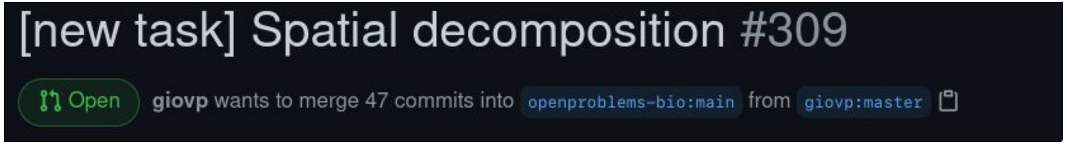
with Fred De Sauvage

Slide courtesy of Tommaso Biancalani.

Integration with single cell data :: which one to choose?

- Initiative to formalize problems in single cell (and spatial) analysis. Includes *proper* definition.
- Provide datasets for unbiased evaluation of data, and define metrics to be used.
- Build framework for said evaluation.
- Allows you to make informed choice.
- https://openproblems.bio/



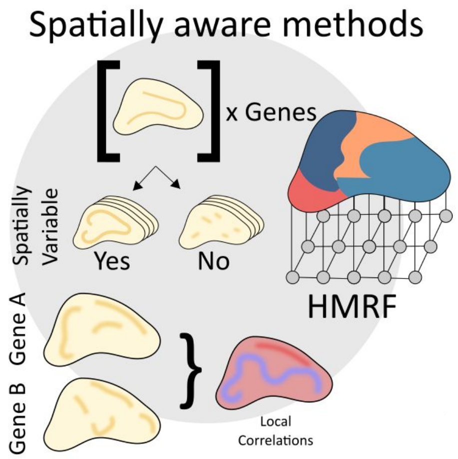


Spatially aware methods

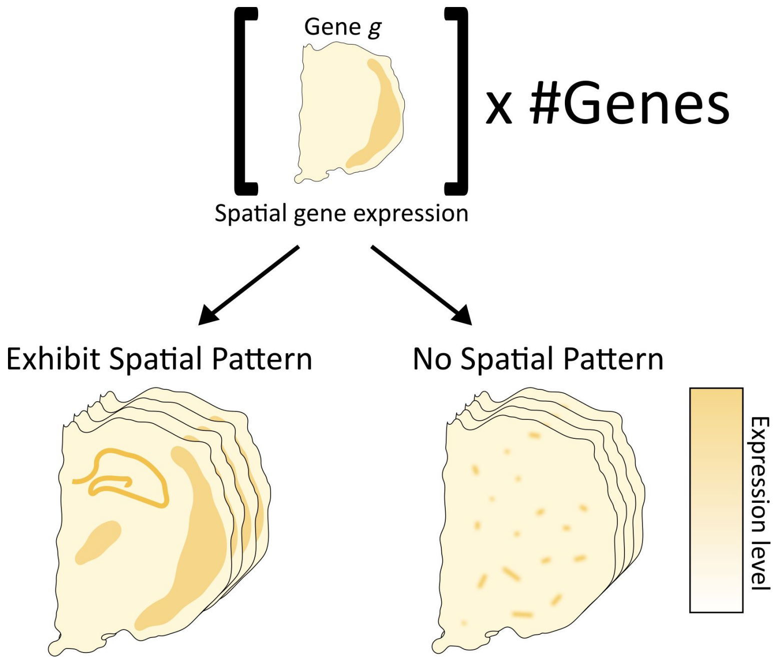
Basic Idea : Attempts to include knowledge of spatial structure in the analysis, not only to visualize results.

Designed for tasks like :

- Identifying *spatially* variable genes and features
  - Why not just select highly variable genes (more later)
- Finding spatially coherent expression domains
- Leverage spatial proximity to increase robustness of inference (e.g., CNA inference)
- Find *local* correlations between features

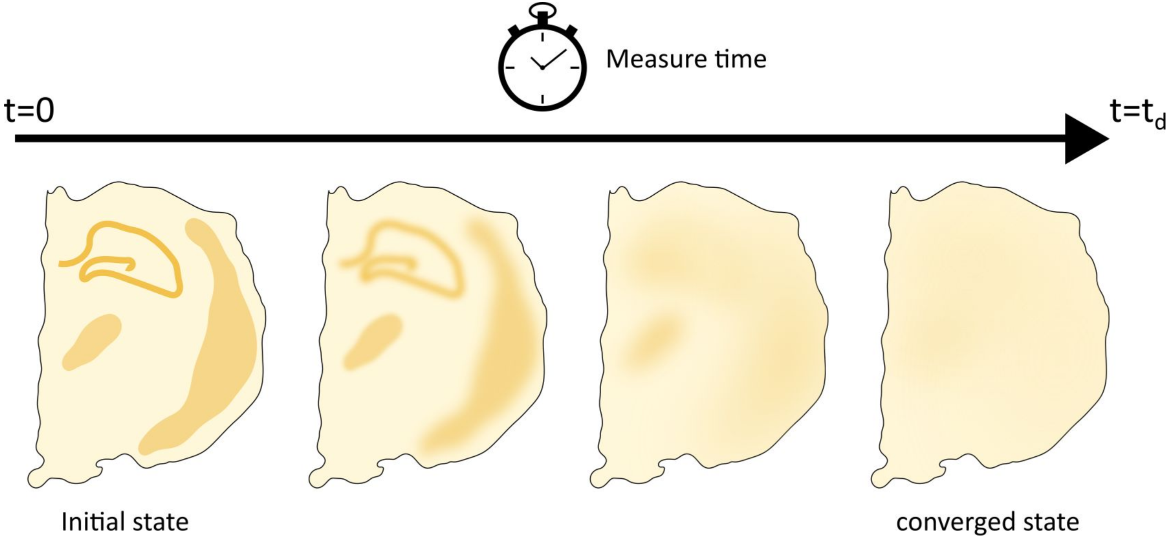


Spatially Variable Genes



- Sort expression profiles into spatially variable or not.
- SpatialDE, SVCA and SPARK use probabilistic models
- Leverage *Gaussian Processes* to model data
- Essentially, test whether a "spatial" term in the covariance function significantly increase model's ability to explain data

Spatially Variable Genes



- *sepal* is not probabilistic
- Uses finite differences to simulate diffusion of transcripts.
- Measures time util converges
- Ranks genes by the time it takes to converge.
- **Key Idea** : The longer the time, the more structured the initial state.

sepal: identifying transcript profiles with spatial patterns by diffusion-based modeling, Andersson and Lundeberg (Oxford Bioinformatics)

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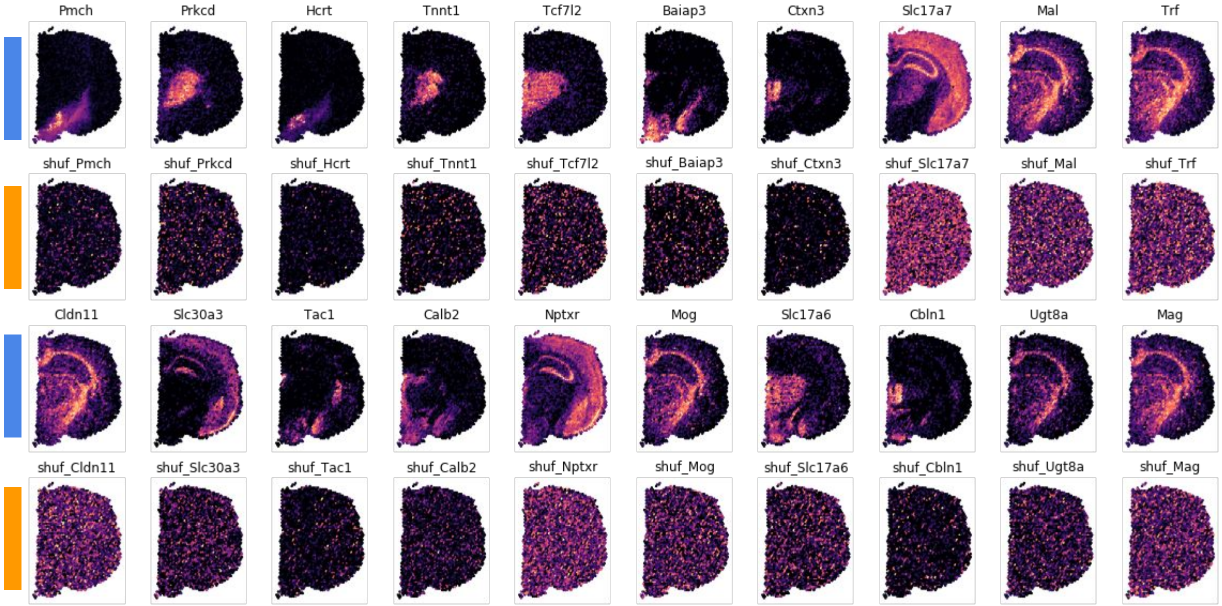
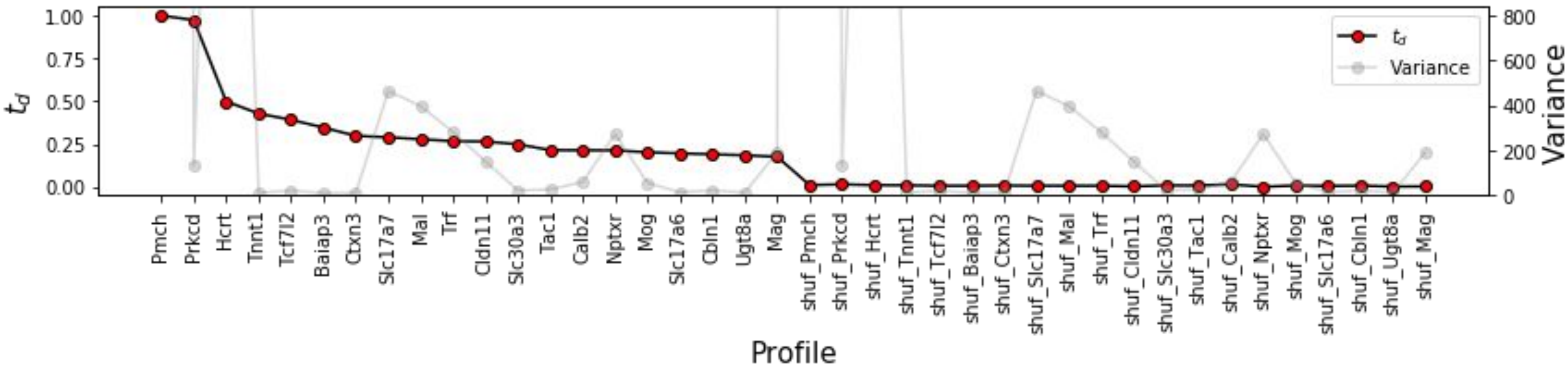
Spatially Variable Genes



- 20 Expression profiles from mouse brain
- Shuffle spots to get random expression profiles. Has “shuf” prefix.

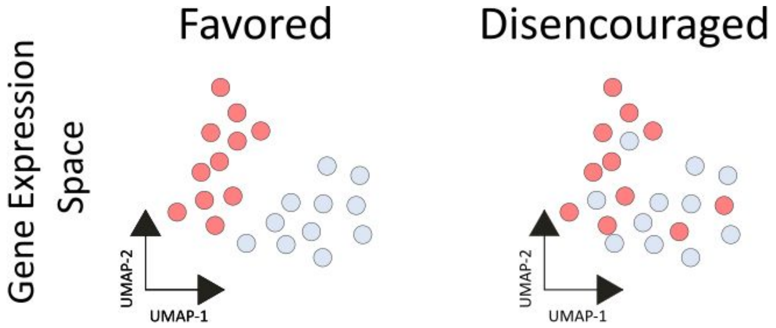
Observed Profiles   Shuffled Profiles

Spatially Variable Genes



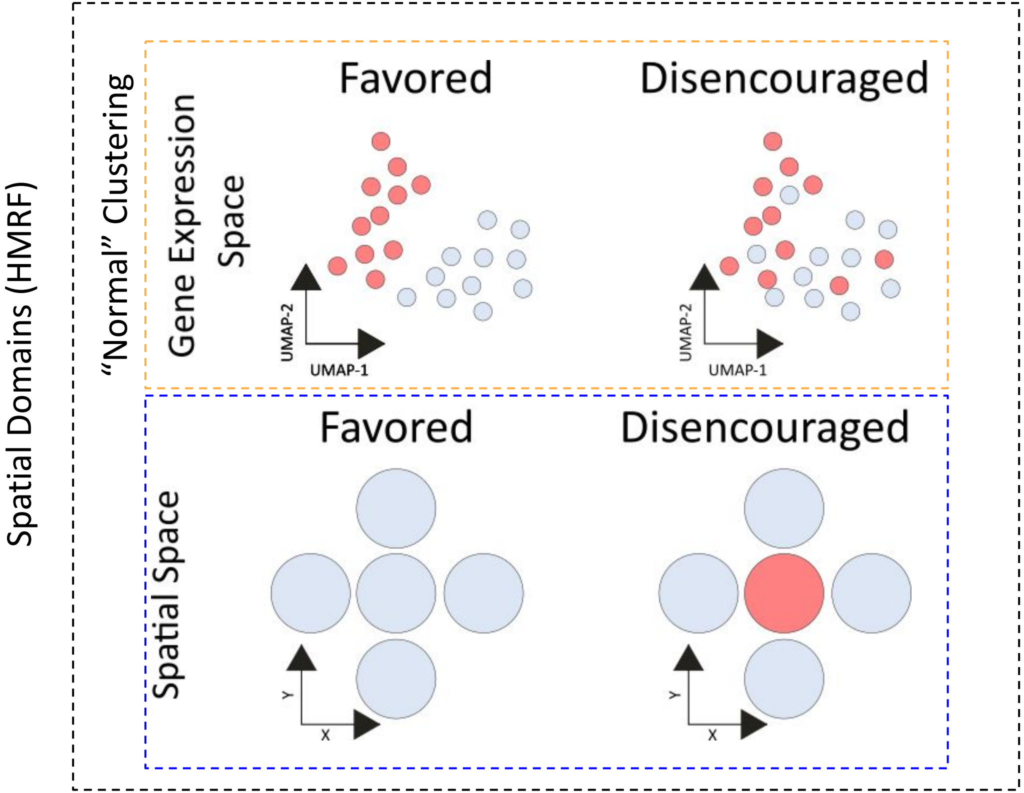
- Variance or dispersion metrics renders exactly the same value (gray) for shuffled and non-shuffled profiles
- *sepal's* ranks real profiles higher than shuffle ones (spatial structure considered)
- Similar results obtained for other methods as well (SpatialDE, SPARK, etc)

Spatials domain patterns



- Normal clustering mainly focus on gene expression

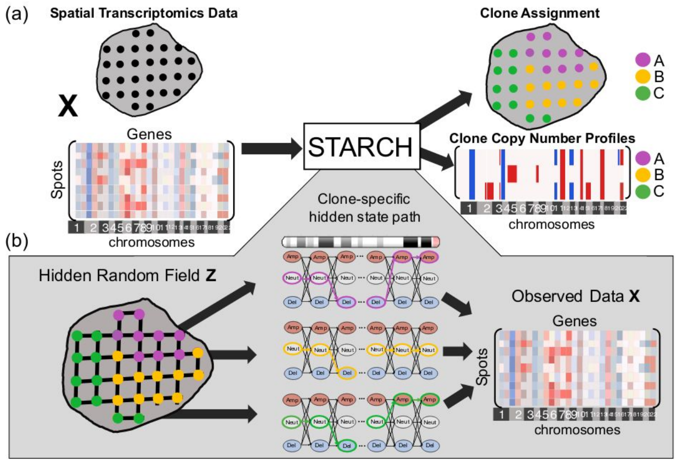
Spatials domain patterns



- Normal clustering mainly focus on gene expression
- Leverage spatial information to find spatially coherent clusters (domains)
- Common to use HMRF (Hidden Markov Random Field)
- Construct a graph based on spatial proximity
- Probability of node (spot) belonging to a specific domain depends on:
  - Agreement with domain expression profile
  - Coherence with neighbors

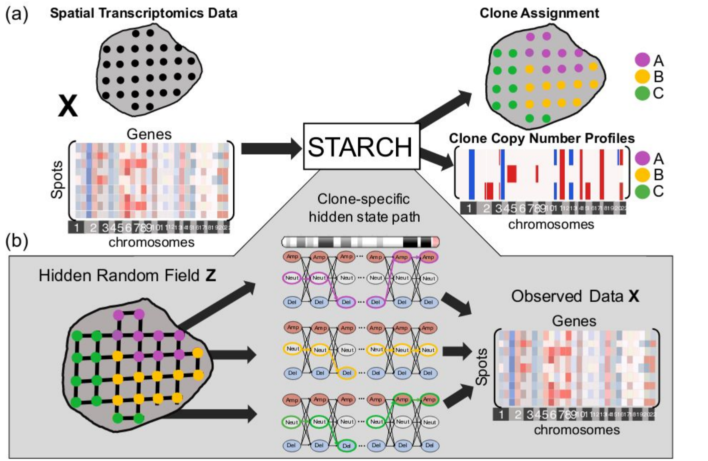
Example : Identification of spatially associated subpopulations by combining scRNAseq and sequential fluorescence in situ hybridization data", Zhu et al.

Spatially aware methods :: STARCH and scHOT



- **Name** : STARCH
- Infer Copy Number Aberrations (CNA) from spatial transcriptomics data
- Increase robustness of inference by aggregating data in same domains (similar profiles)
- Also uses Hidden Markov Random Fields (HMRF)
- "*STARCH: Copy number and clone inference from spatial transcriptomics data*", Elyanow et al.

Spatially aware methods :: STARCH and scHOT



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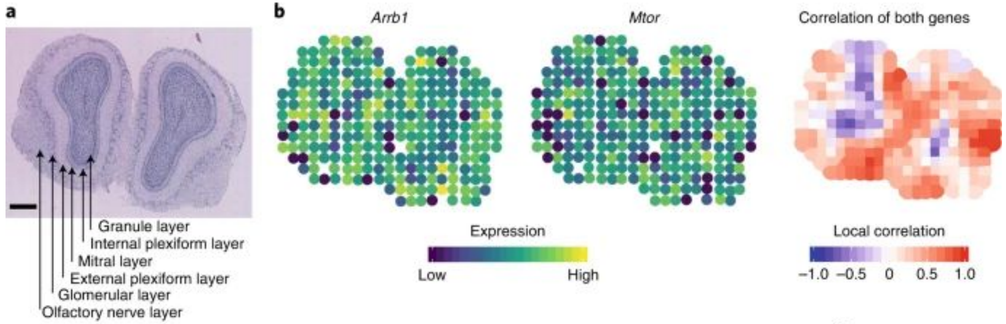
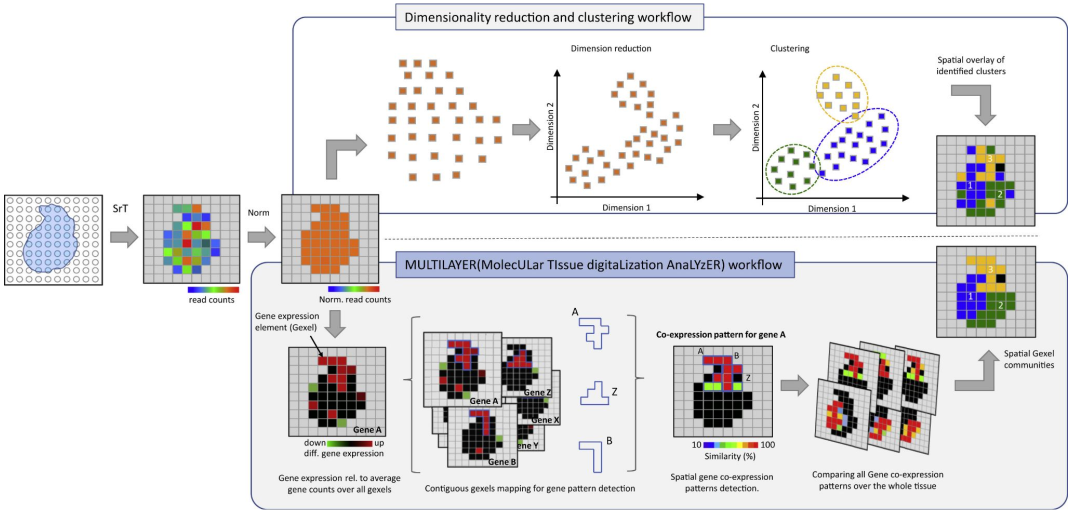
- **Name** : scHOT
- Computes (spatially) weighted correlations to find local correlations.
- "*Investigating higher-order interactions in single-cell data with scHOT*", Ghazanfar et al.



Spatially aware methods :: MULTILAYER

- Inspired by digital image processing, aggregated contiguous pixels. Introduces “gexels”.
- Looks at relative gene expression of each gexel compared to remainder. Up and down-regulated genes.
- Uses agglomerative clustering to find contiguous patterns that share similar structures (co-expression modules)
- Extracts communities (think clusters) from co-expression modules by using Louvain clustering.



“Inferring biologically relevant molecular tissue substructures by agglomerative clustering of digitized spatial transcriptomes with multilayer”, J Moehlin

Spatiotemporal Modeling :: Splotch

- Hierarchical generative probabilistic model for analyzing Spatial Transcriptomics data
- Uses Zero Inflated Poisson (ZIP) regression model to account for:
  - Tissue region context
  - Local components
  - Spot effects
- Also aligns sections
- Can identify genes that changes over both space and time

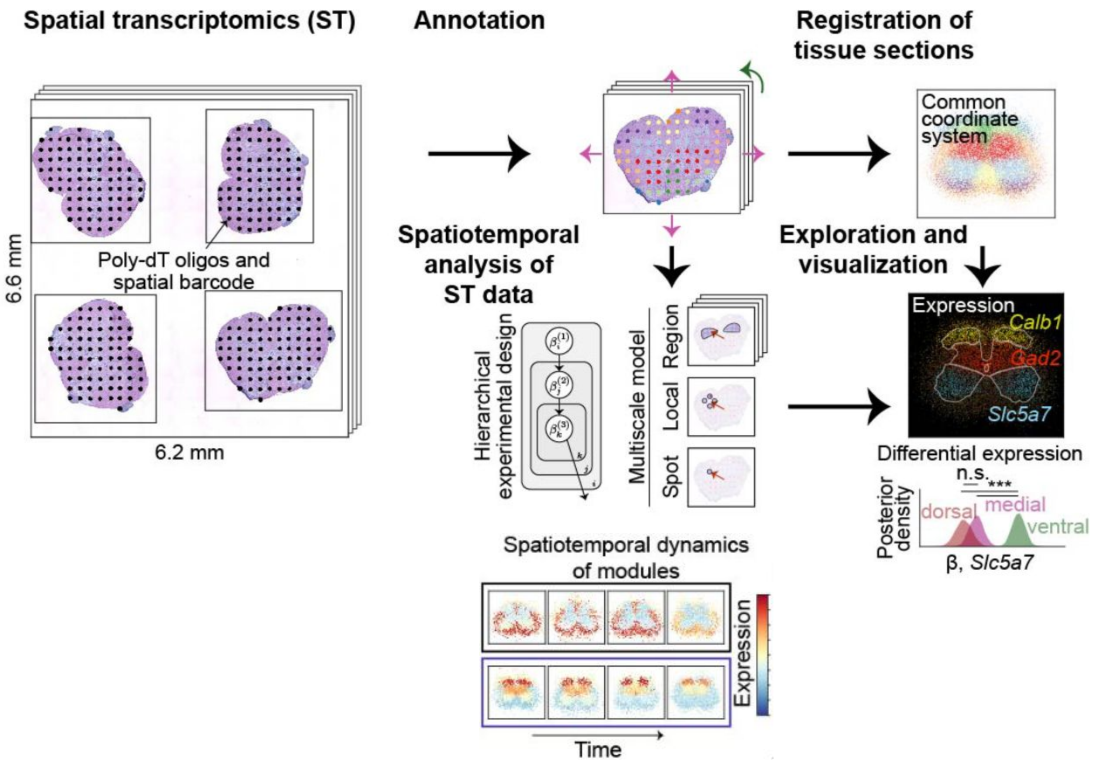


Image adaptation from : Splotch: Robust estimation of aligned spatial temporal gene expression data, T Äijö et al. (Supplementary Figure 1,2)

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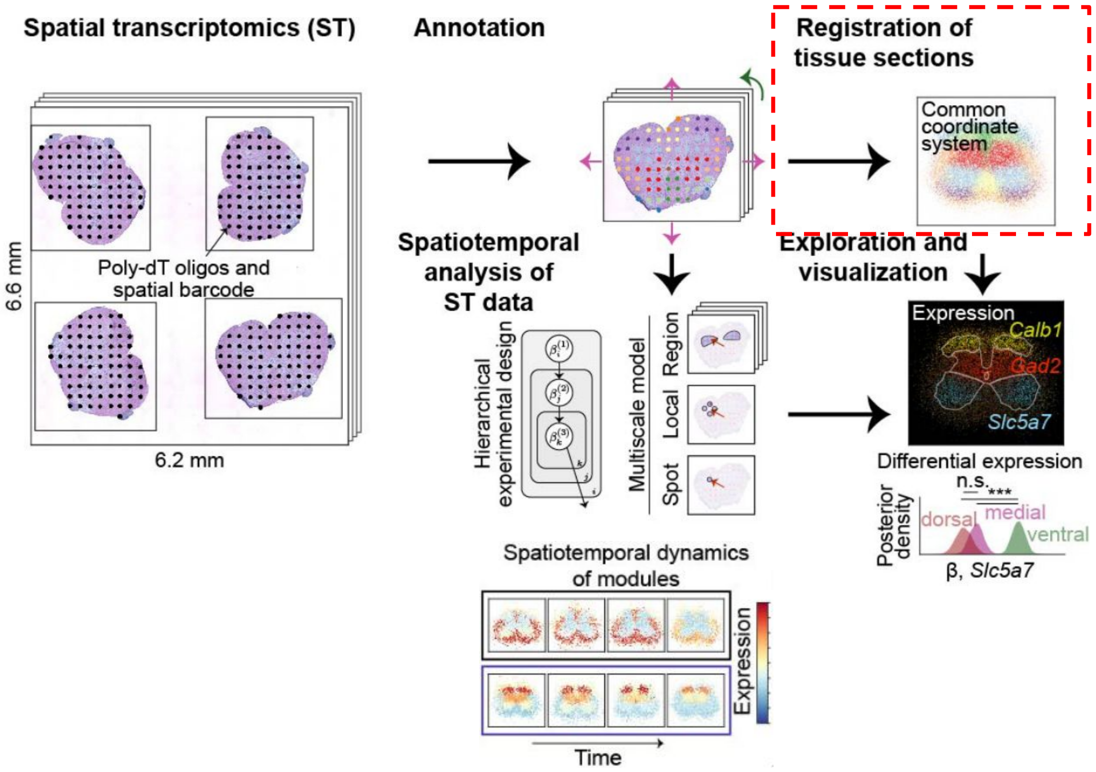
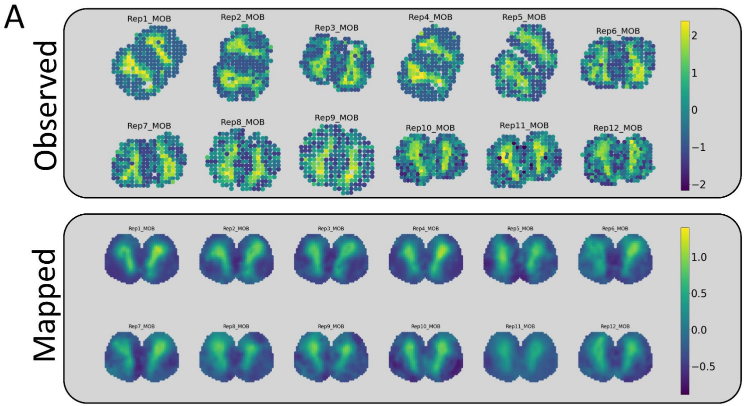
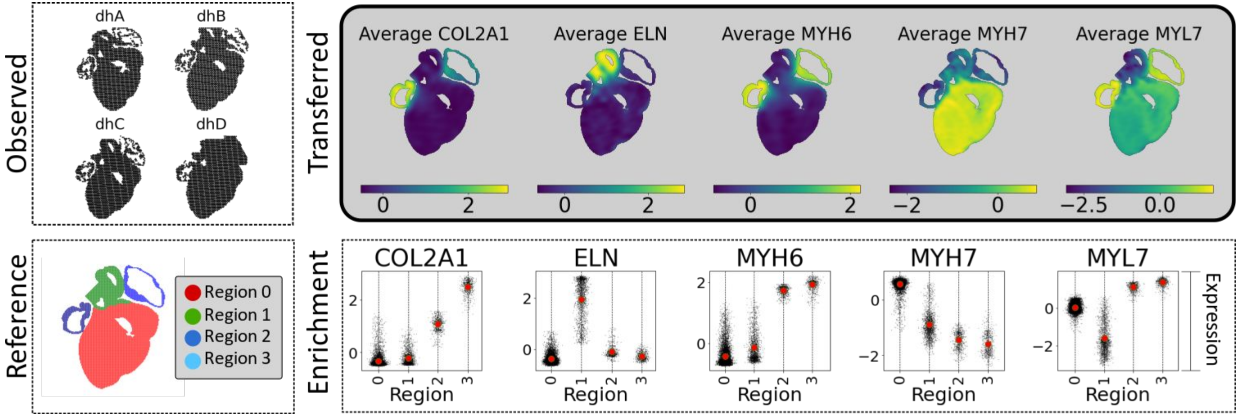


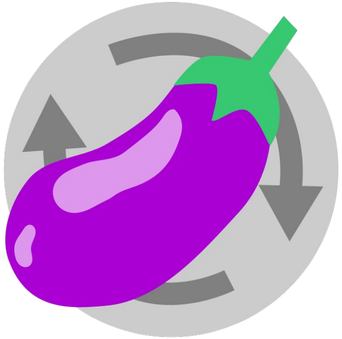
Image adaptation from : Splotch: Robust estimation of aligned spatial temporal gene expression data, T Äijö et al. (Supplementary Figure 1,2)

Sneak Peek :: *eggplant*



- New method (*eggplant)* that maps features (gene expression, cell type proportions) to a common coordinate framework (CCF)
- Allows user to define a reference and then transfer feature values to it
- Enables spatiotemporal modeling and construction of atlases





Andersson et al. In preparation. Developmental Heart data by Andrusivová Ž.

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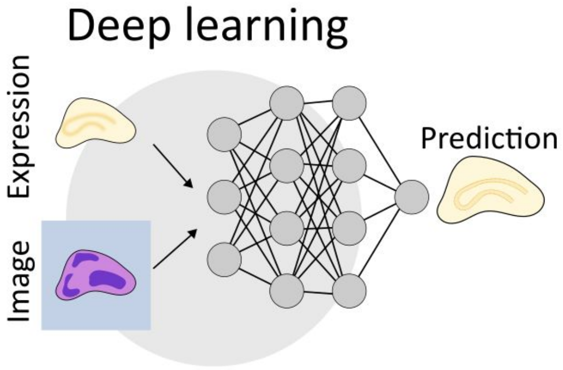
Deep Learning

Basic Idea : Apply deep learning to spatial data (very broad)

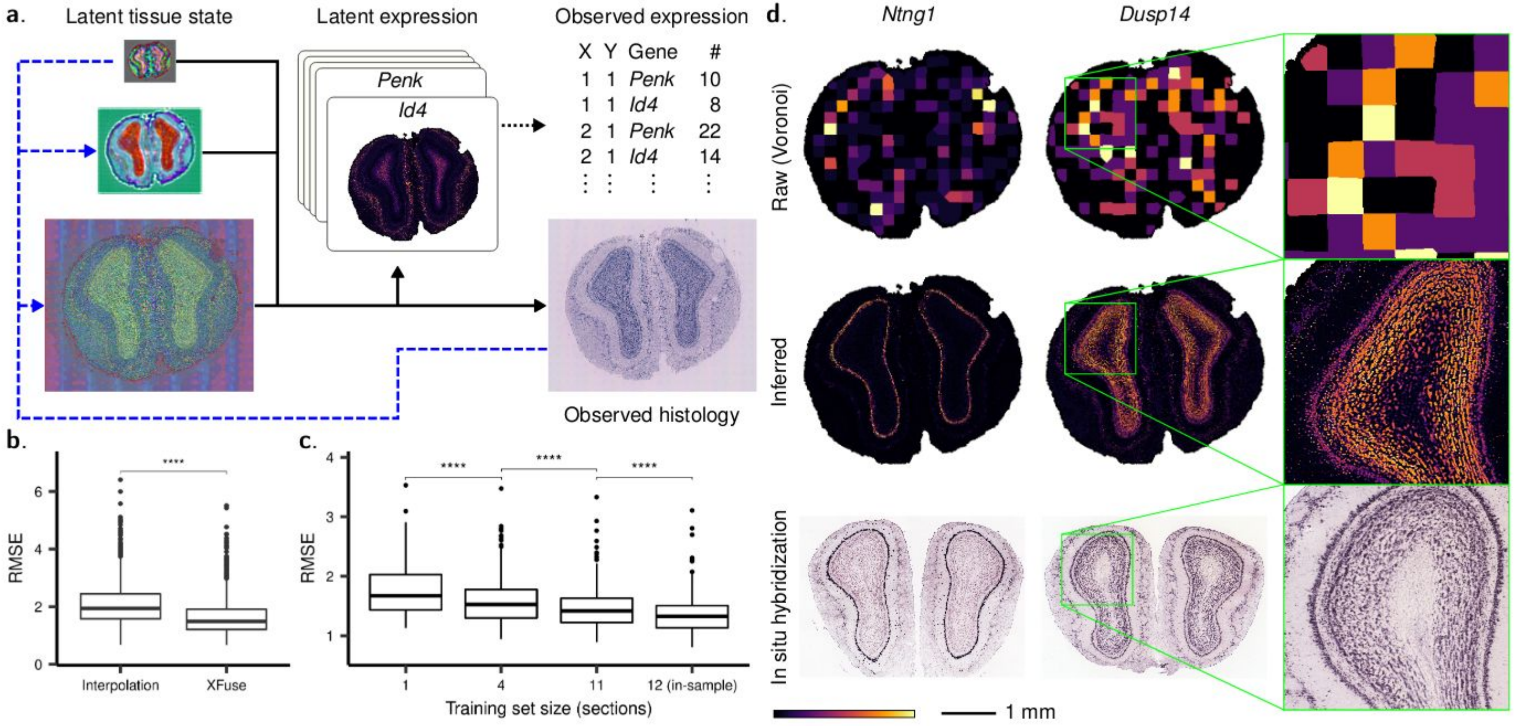
Fairly nascent : Relatively few examples. Limited amount of high quality available data.

Current examples :

- **XFuse :** "*superresolution*" (pixel) of gene expression by learning joint representation of image and expression data.
- **stPlus :** Uses scRNA-seq data and autoencoders to enhance spatial transcriptomics data
- **SpaGCN :** simultaneous domain and SVG detection using graph convolution layers
- **RESEPT :** Uses graph convolutional network to embed spatial data in RGB space, then uses a CNN to segment data into spatially coherent tissue domains



Deep Learning :: XFuse



From : *"Super-resolved spatial transcriptomics by deep data fusion"*, Bergenstråhle et al. *(in press Nature Biotechnology)*

Computational suites :: squidpy

"One framework to rule them all, one framework to find them…"

- Similar philosophy as scanpy, uses same kind of API, built on AnnData objects
- Tailored towards spatial data with support for multiple different experimental platforms (not only Visium)
- Easy to construct spatial graphs and perform graph operations
- Has great interface with ML ecosystems such as PyTorch, TensorFlow and sklearn
- Simplified my life a lot and something I tend to use now in method development
- (Also has sepal integrated into the suit)

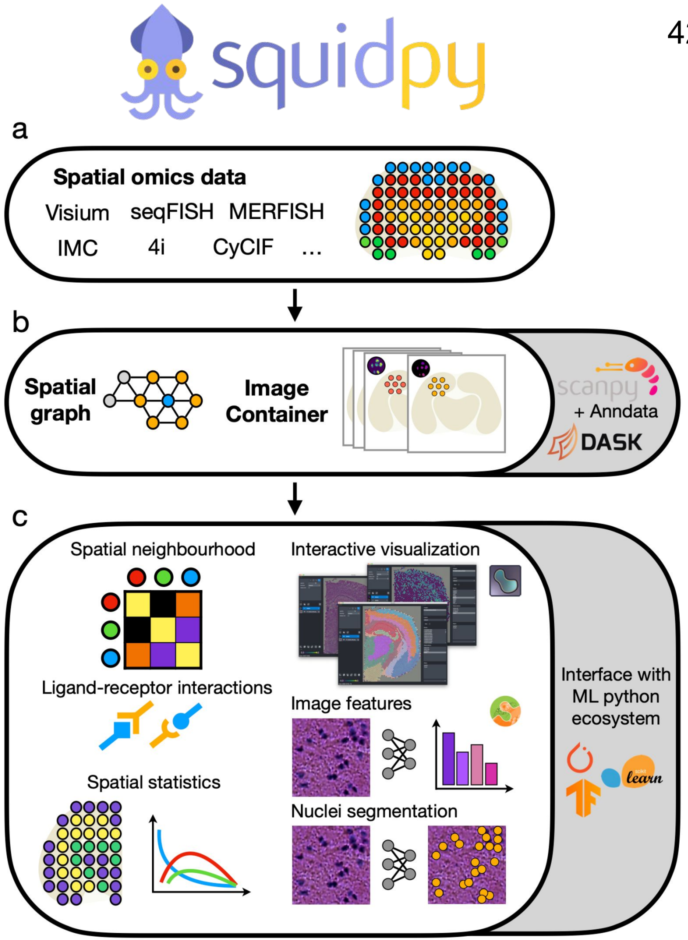


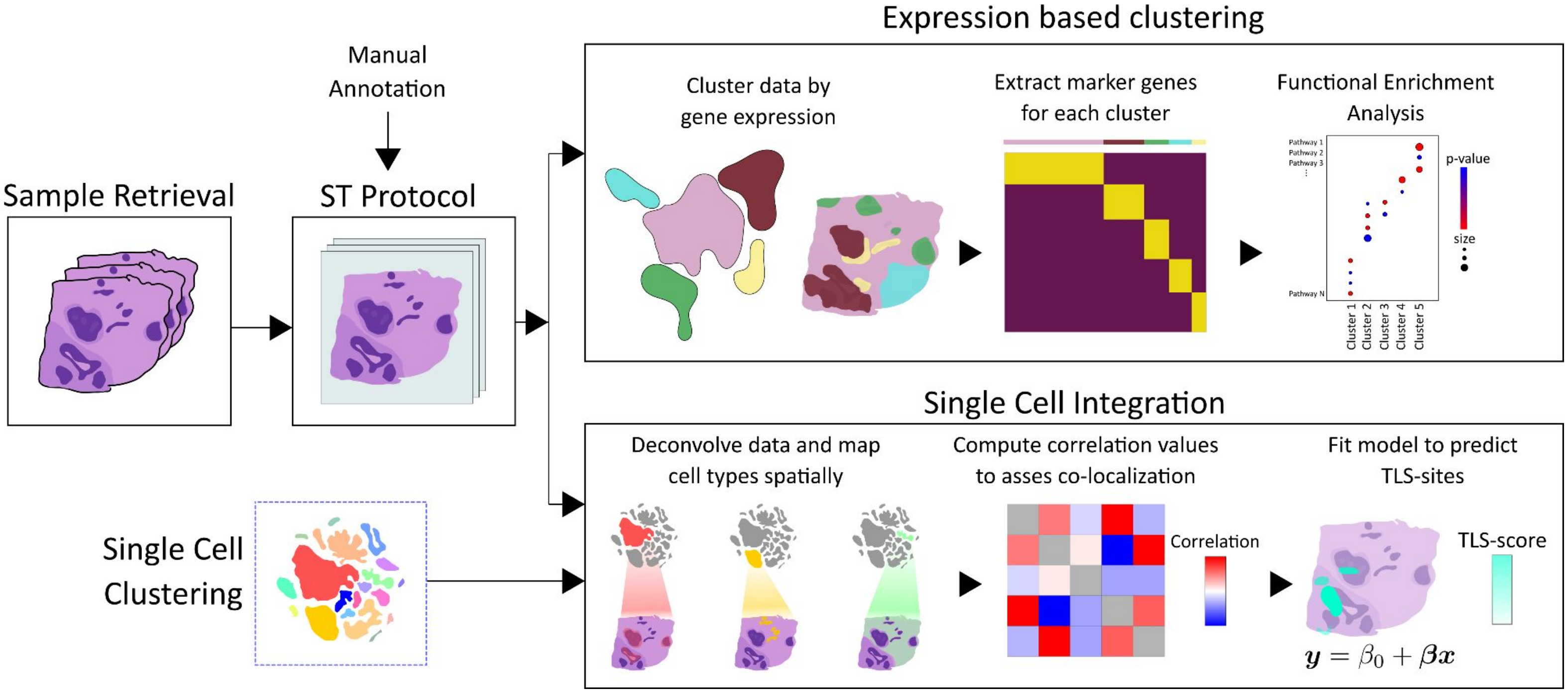
Image from: https://squidpy.readthedocs.io/

Observations from the wild

General advice

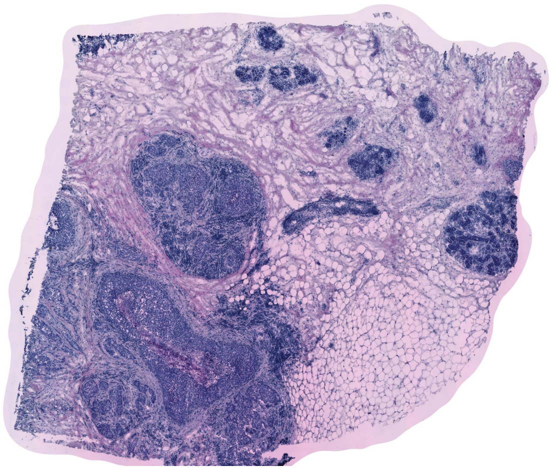
- **Batch effects** between sections are usually observed, try to account for this. Single cell methods have worked great so far.
- **Cell density** is often not homogeneous across tissue. Good idea to normalize based on the library size to account for this.
- Keep in mind that expression profiles are **mixtures**, often it makes more sense to analyze them accordingly; looking at **factor** contributions rather than hard cluster identities.
- Single cell mapping is often **improved by use of HVG** genes or curated lists
- **Trajectory inference is tricky**, no method that I'm aware of accounts for the fact that several temporal states might be present at each observation. Incorporation of spatial information has been done fairly heuristically so far.
- Filtering **ribosomal, mitochondrial and Hb-genes** usually have a positive effect on the result. They usually constitute irrelevant sources of variation. However, keep them if relevant!
- Use the image to visualize and inspect your data, one of the best quality checks there is. Always ask yourself: "does this make sense"?

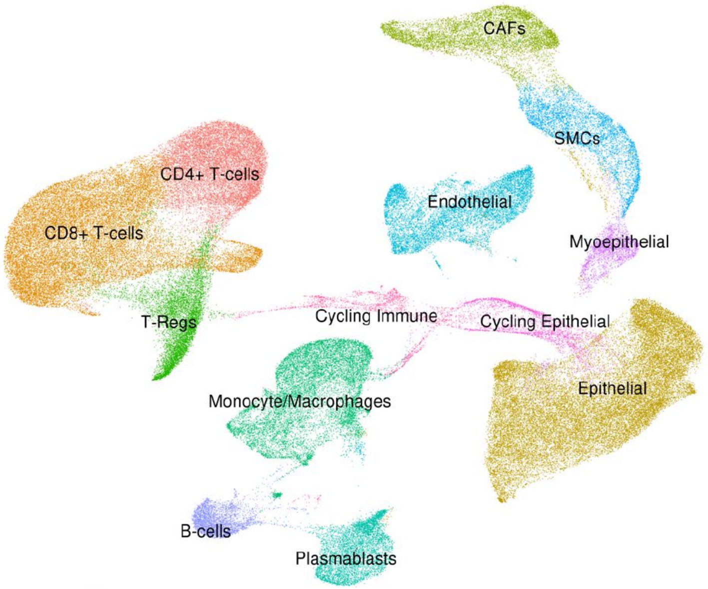
A spatial survey of HER2-positive breast cancer



"Spatial deconvolution of HER2-positive Breast cancer delineates tumor-associated cell type interactions", Andersson et al. (*in press* Nature Communications)

Human HER2-positive breast cancer





Spatial Data
Human Breast Cancer
HER2-positive

SC Data
Human Breast Cancer
Multiple types (incl. HER2)

Spatial data : Linnea Stenbeck | **SC data** : Swarbrick Lab

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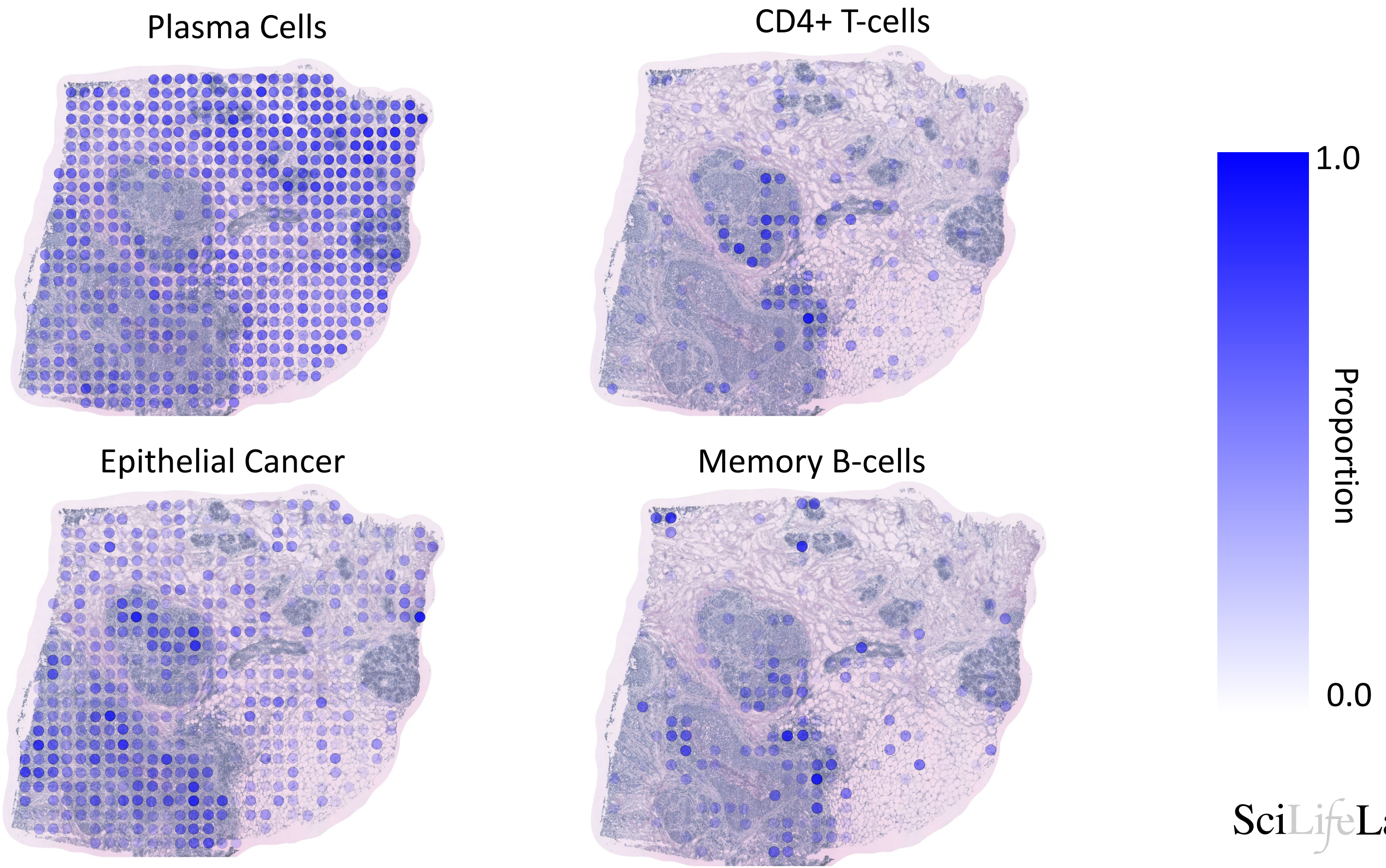
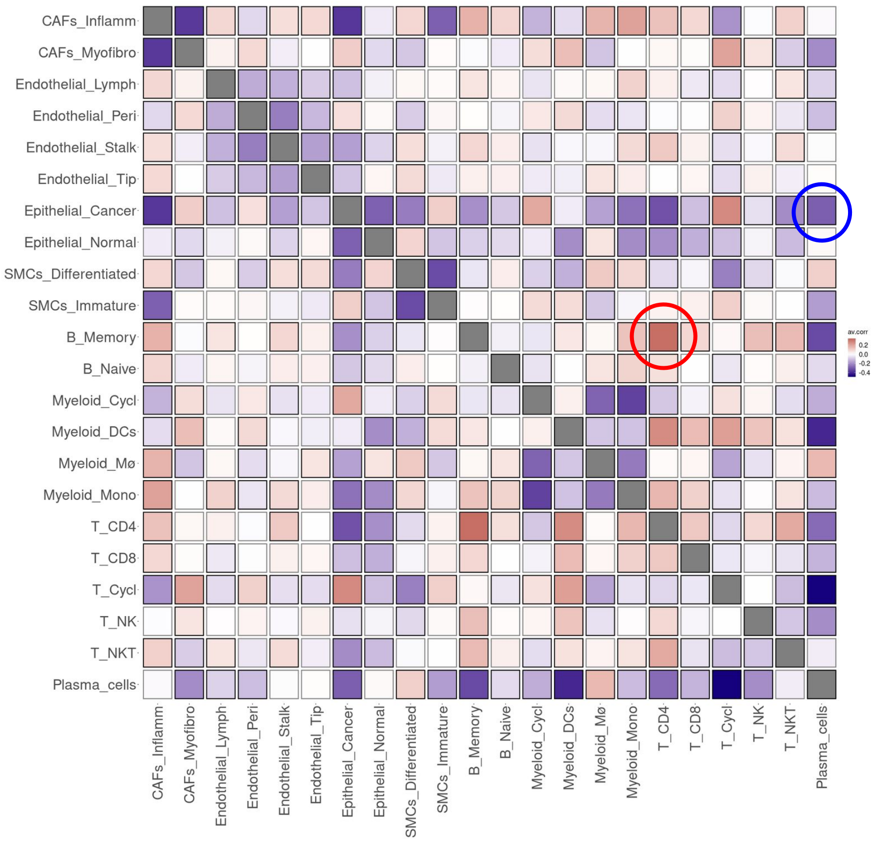
Proportion estimated overlaid on tissue

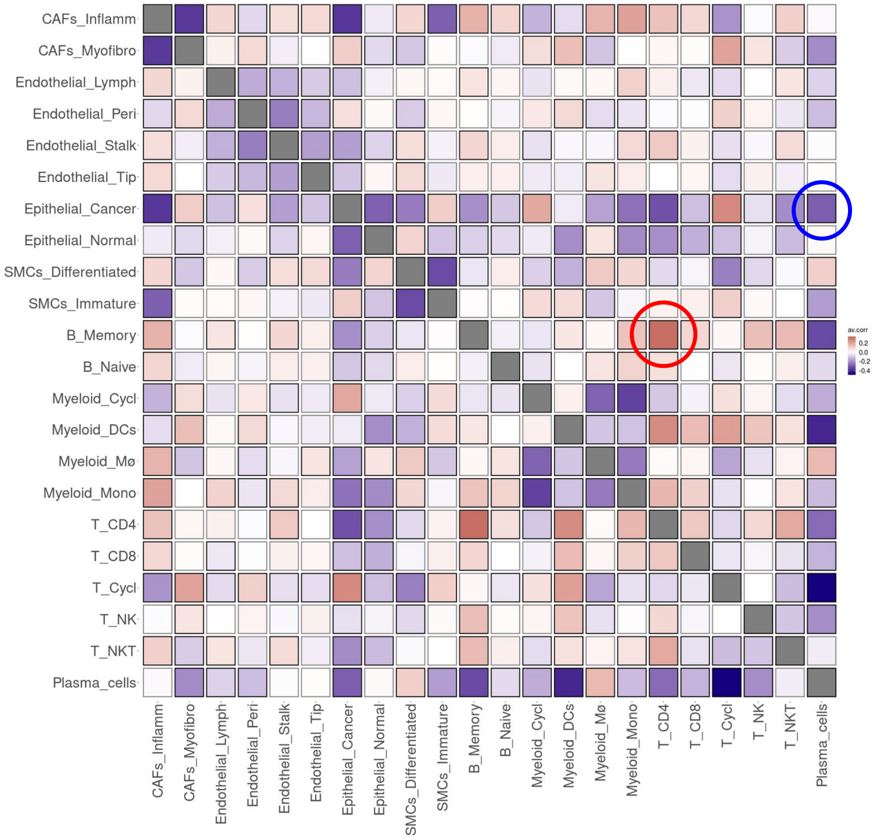


Cell type co-localization



- Find cell types with similar spatial distributions
- Confirms previous observations
  - Plasma cells and Epithelial Cancer anticorrelate
  - Memory B-cells and CD4+ T-cells co-localize

Cell type co-localization



- Find cell types with similar spatial distributions
- Confirms previous observations
  - Plasma cells and Epithelial Cancer anticorrelate
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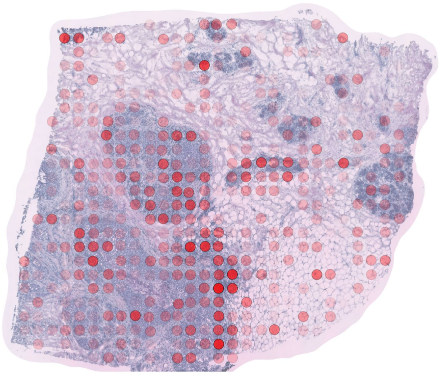
TLS : Tertiary Lymphoid Structures

- Characterized by high presence of B and T-cells
- Interesting for several reasons
    - Partially dictates degree of TILs (Tumor Infiltrating Lymphocytes)
    - Implications in tumor treatment and outcome
- **Question :** Can we locate TLSs in our samples?

Searching for TLS-sites

B-cells



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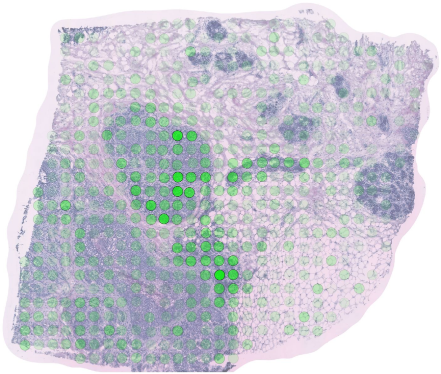
T-cells



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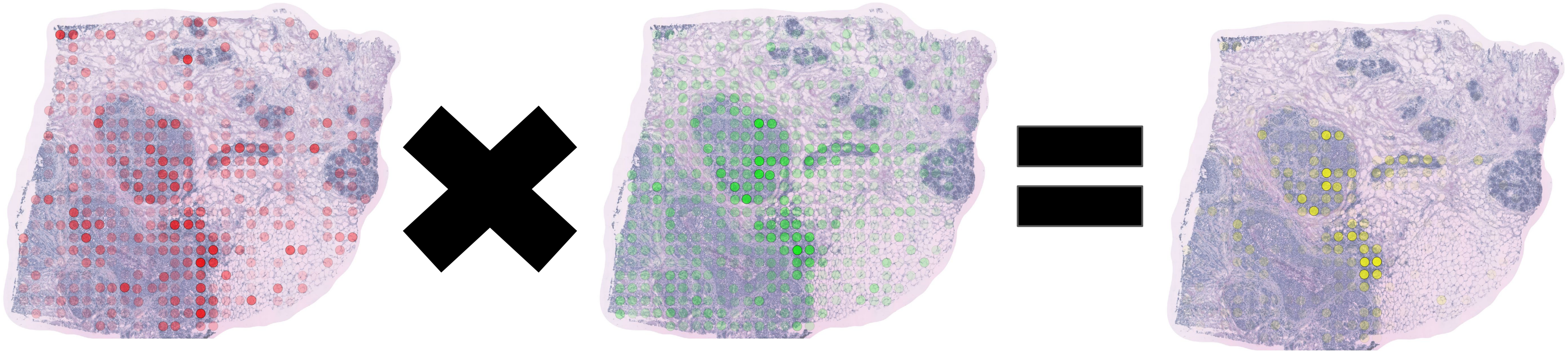
Searching for TLS-sites

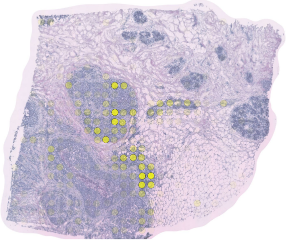
B-cells × T-cells = TLS



Characterizing the expression landscape of TLSs

TLS-score

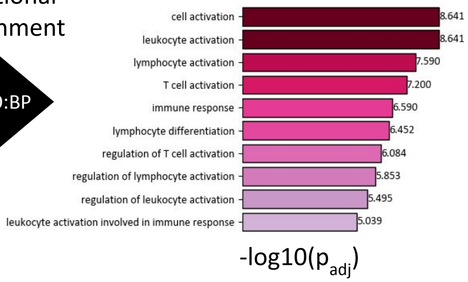
$$\beta_0 + \beta_1[\text{Gene 1}] + \ldots. + \beta_N[\text{Gene N}] = $$



Set of
TLS-related genes:
CXCL13
LTB
CXCR5
...

Functional
Enrichment

GO:BP



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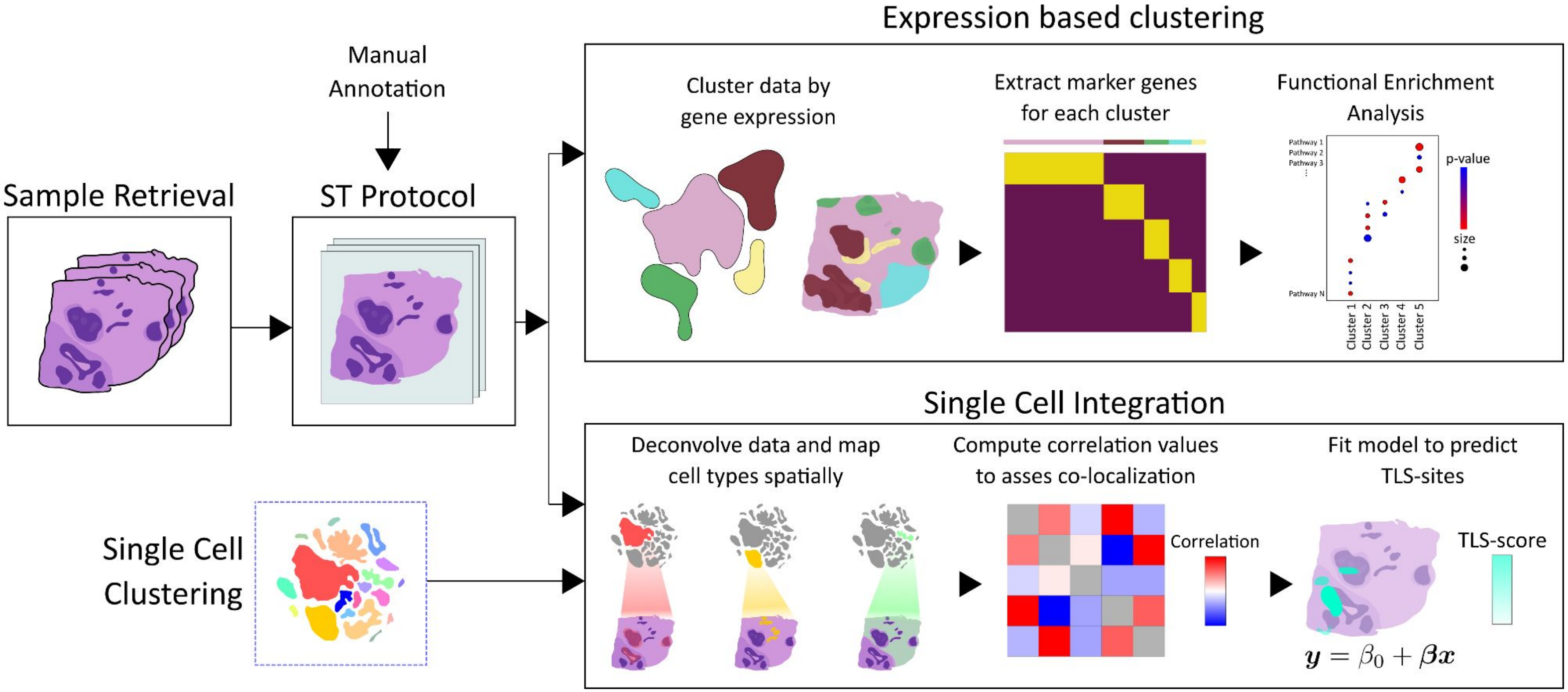

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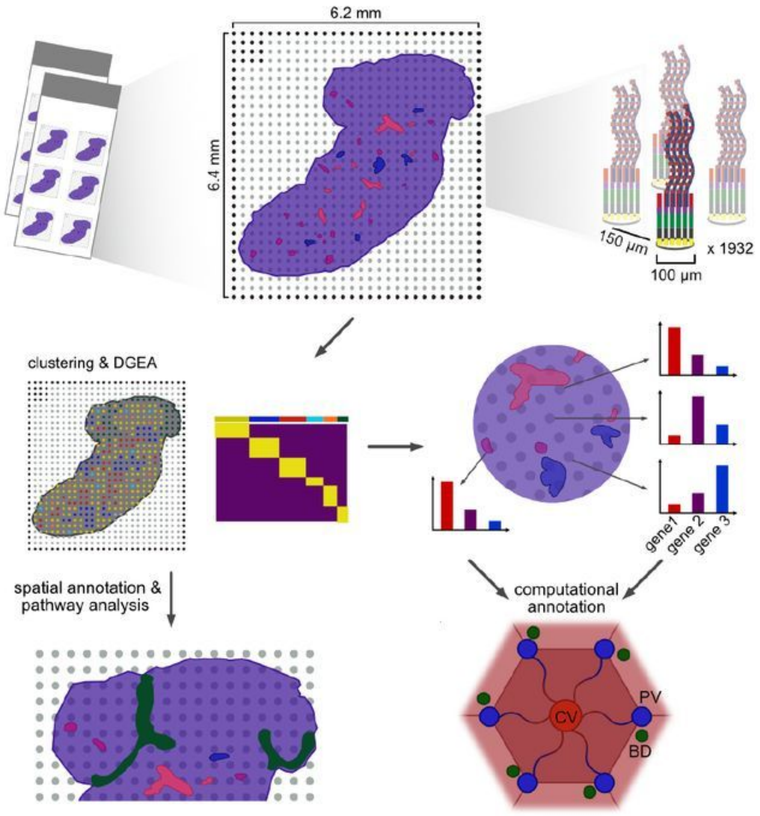
bioRχiv https://doi.org/10.1101/2020.07.14.200600

Spatial gene expression dynamics in the mouse liver



"Spatial Transcriptomics to define transcriptional patterns of zonation and structural components in the liver", Hildebrandt and Andersson et al.

bioRχiv https://doi.org/10.1101/2021.01.11.426100

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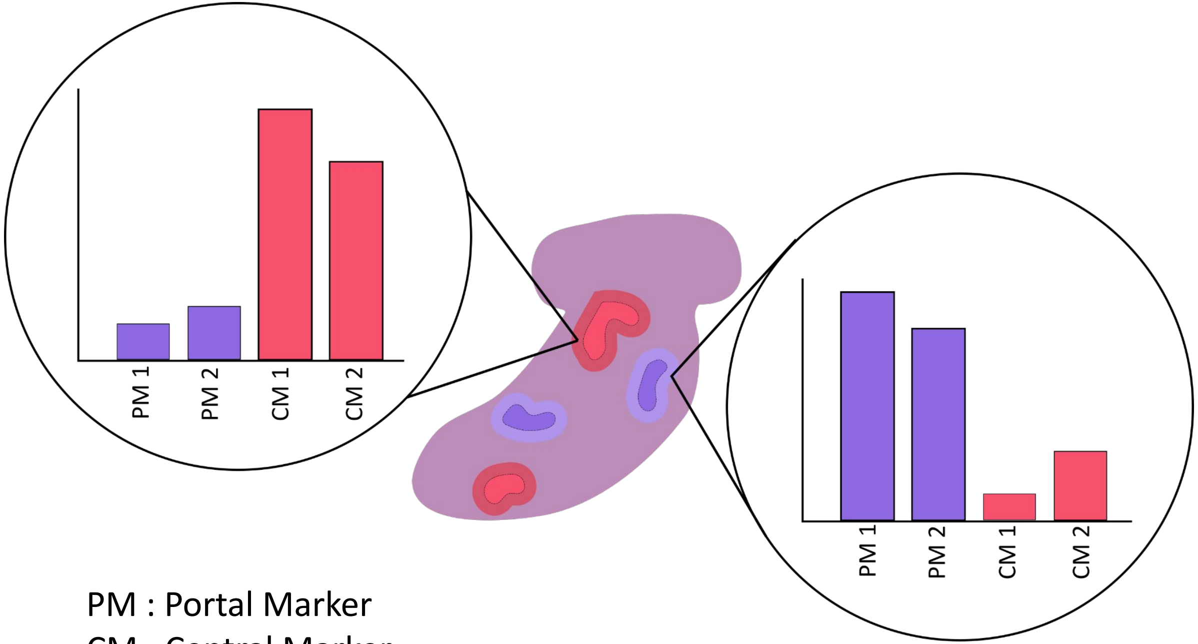
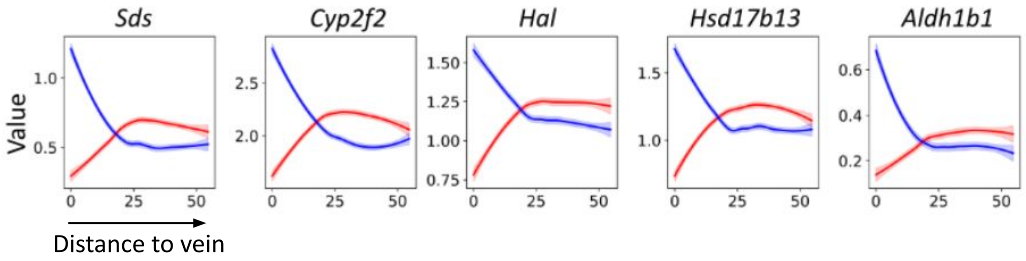
Spatial gene expression dynamics in the mouse liver



PM : Portal Marker
CM : Central Marker

- Portal and central veins have certain marker genes associated with them
- **Key concept :** Marker gene expression is dependent on distance to the veins

Expression as function of distance

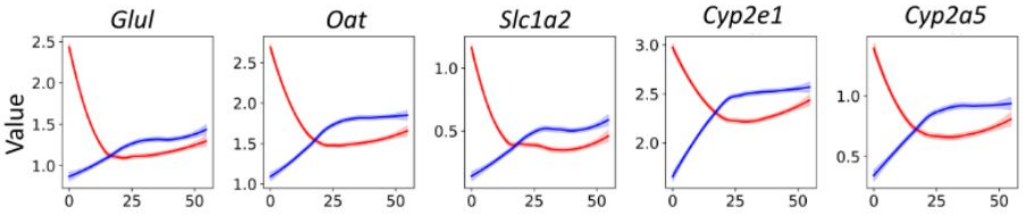


- Model gene expression as a ***function of the distance*** to respective vein

Blue curves : expression as a function of distance to portal veins
Red curves : expression as a function of distance to central veins

Figure adapted from *"Spatial Transcriptomics to define transcriptional patterns of zonation and structural components in the liver"*, by Hildebrandt and Andersson et al.

Expression as function of distance



Distance to vein

Blue curves : expression as a function of distance to portal veins
Red curves : expression as a function of distance to central veins

- Model gene expression as a ***function of the distance*** to respective vein

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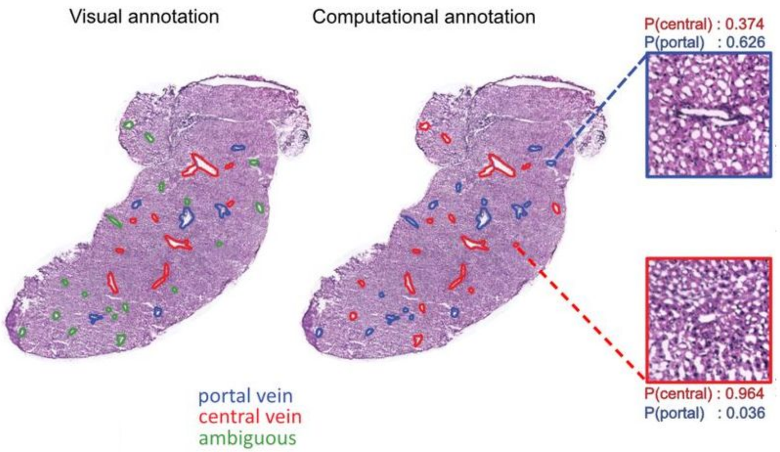
Expression as function of distance



- **Objective :** Unsupervised classification of vein types
- **Implementation :**
    - Construct neighborhood expression profile (NEP).
    - Train logistic classifier on NEPs from (expert annotated) veins
    - Predict vein type based on NEP for un-annotated veins. Gives probabilistic assignment.

From "*Spatial Transcriptomics to define transcriptional patterns of zonation and structural components in the liver*", by Hildebrandt and Andersson et al.

Summary

- Tons of spatial techniques
    - I'm very fond of Visium, but you should always pick whatever is best for you!
- Ever increasing repertoire of computational methods!
    - Be **careful** when transferring single cell methods, make sure the methods' assumptions are valid
    - A lot of tools out there, but sometimes beneficial to construct **custom solutions**
- Don't just treat spatial data as a different form of single data, it has much more to offer

Acknowledgements

Spatial research group : www.spatialresearch.org
Organizers : NBIS and SIB
External slide contributions : Tommaso Biancalani and Dylan Cable

Thank **you** for the attention!

https://github.com/almaan

https://almaan.github.io

@aalmaander