Biologically-informed self-supervised learning for segmentation of subcellular spatial transcriptomics data

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work lead by
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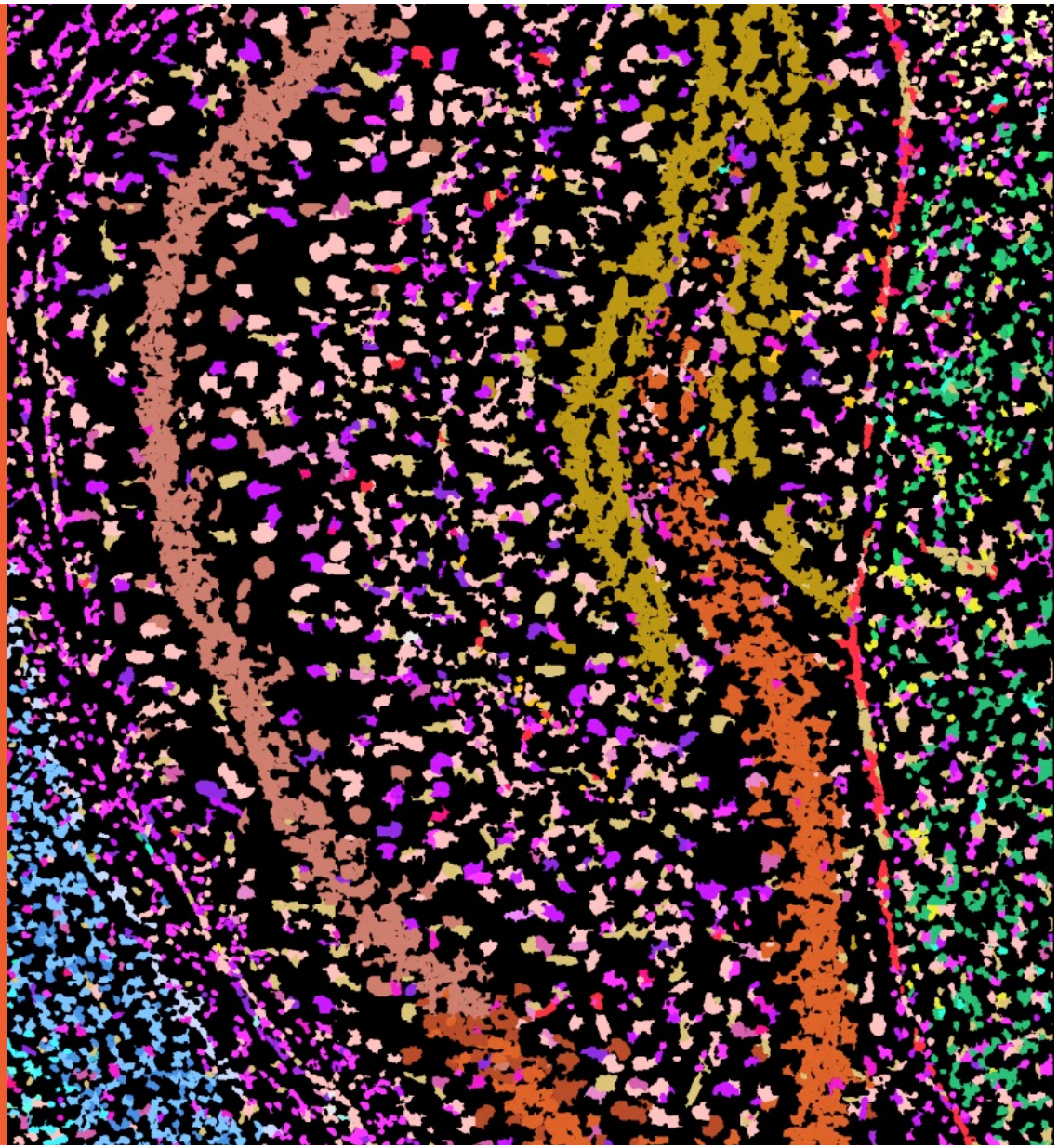
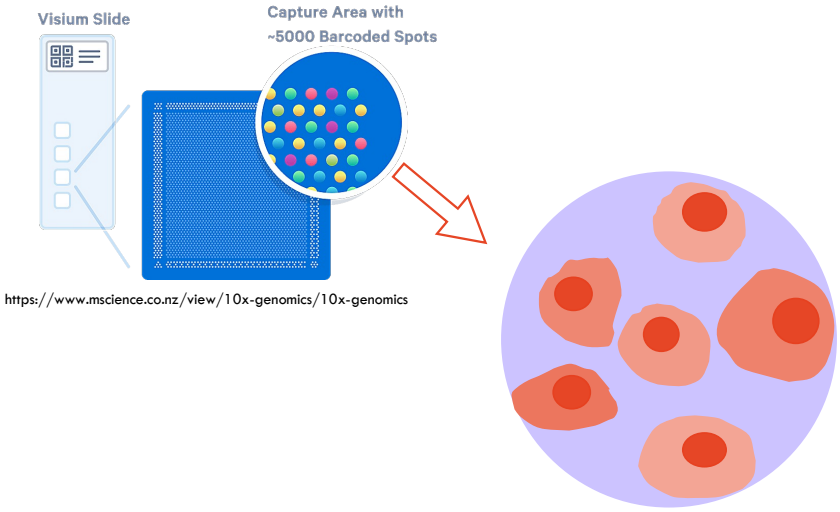
Sydney Precision Data Science Centre

THE UNIVERSITY OF SYDNEY



Spatially resolved transcriptomics

Nature Method of the Year 2020



https://www.mscience.co.nz/view/10x-genomics/10x-genomics

1-10 cells in 1 spot

Spatially resolved transcriptomics

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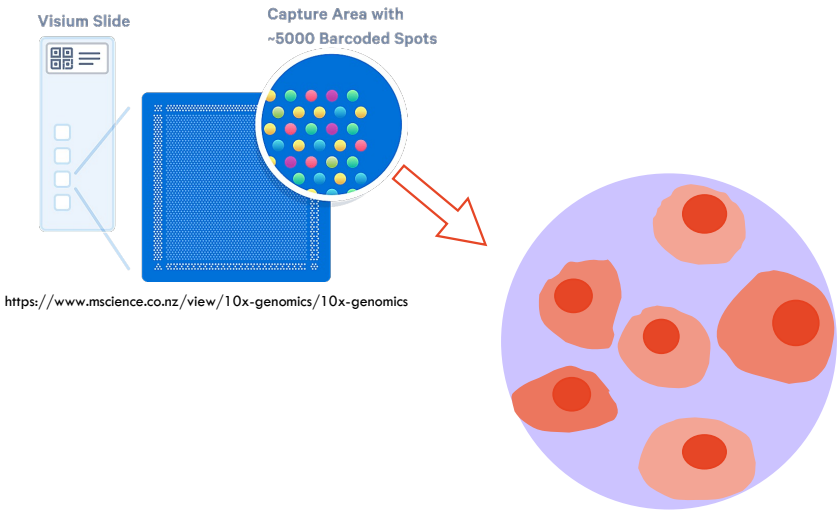

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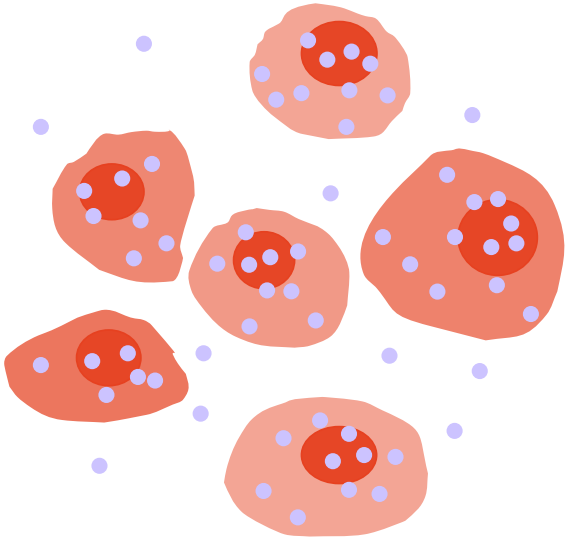
Subcellular spatially resolved transcriptomics



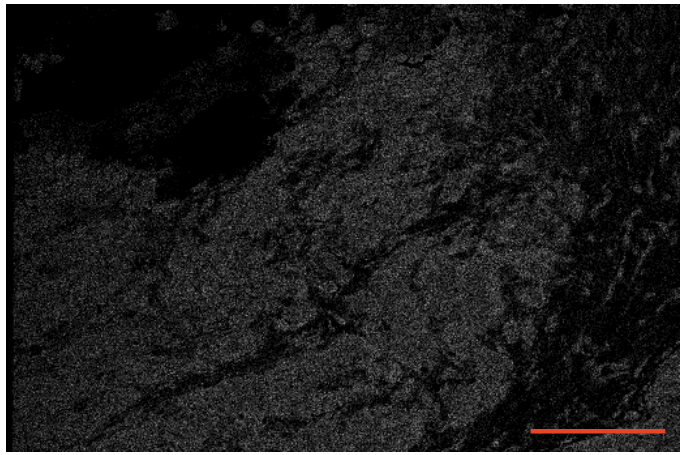
Subcellular detections

10x Genomics Xenium
NanoString CosMx
Vizgen MERSCOPE

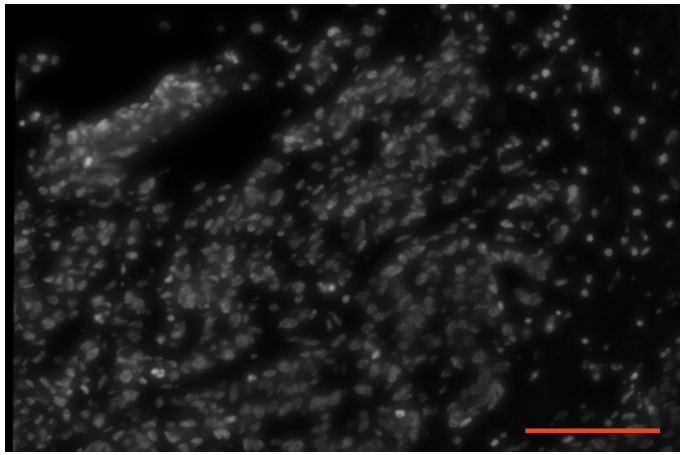
Subcellular spatially resolved transcriptomics (SST)

- Detect expression of hundreds of genes at subcellular resolution *in situ*
- Capture multi-channel **spatial transcriptomic maps** and **DAPI** images

Transcripts (Summed channels)



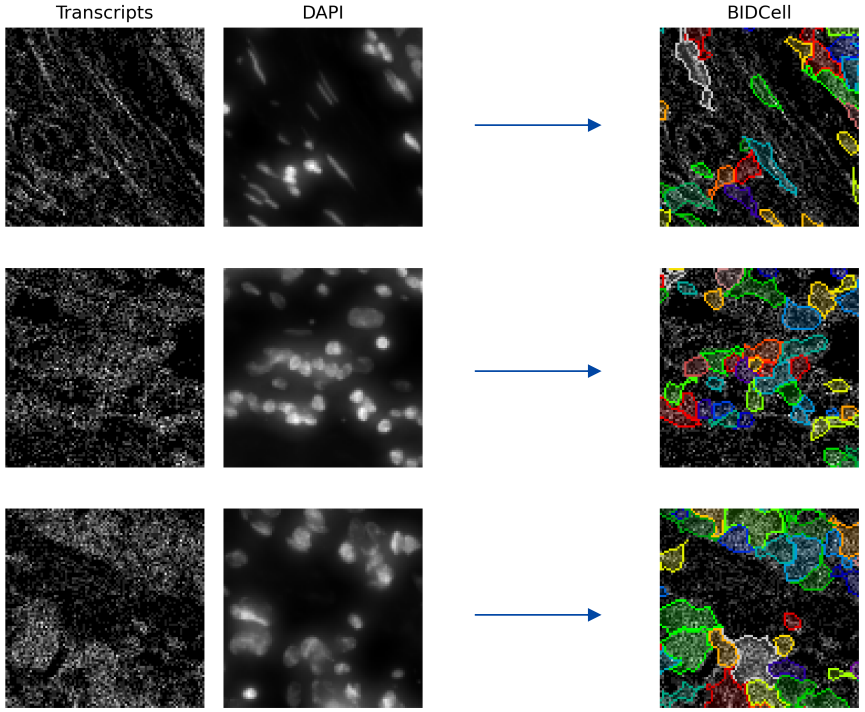
DAPI (Nuclei)



Scale: 100 µm
10x Genomics Xenium (breast cancer, 313 genes)

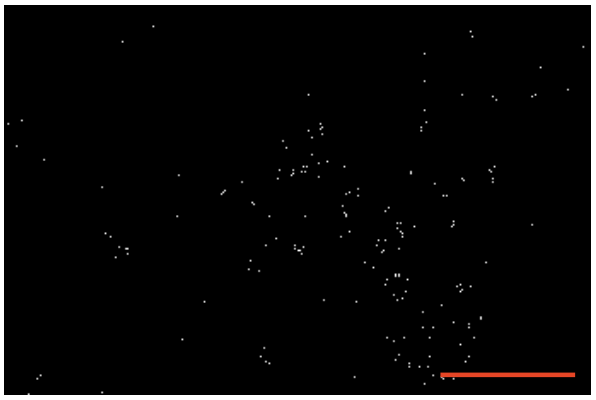
Cell segmentation

- Task: Identify all the pixels belonging to a cell in the form of a mask
- Do this for every unique cell in the image – i.e., instance segmentation
- The segmentation is used to quantify gene expression of each cell, by collecting the detected transcripts that falls inside the pixels belonging to a cell's mask

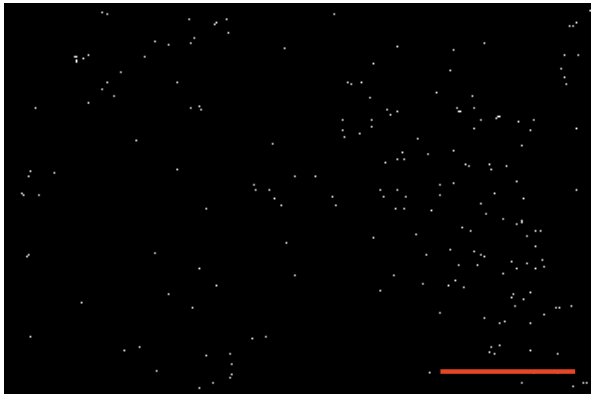


Challenges of SST images

- High dimensionality (hundreds of channels)
- High sparsity within each channel
- Lack of visual boundaries
- Densely-packed together cells
- No ground truth



CD3D



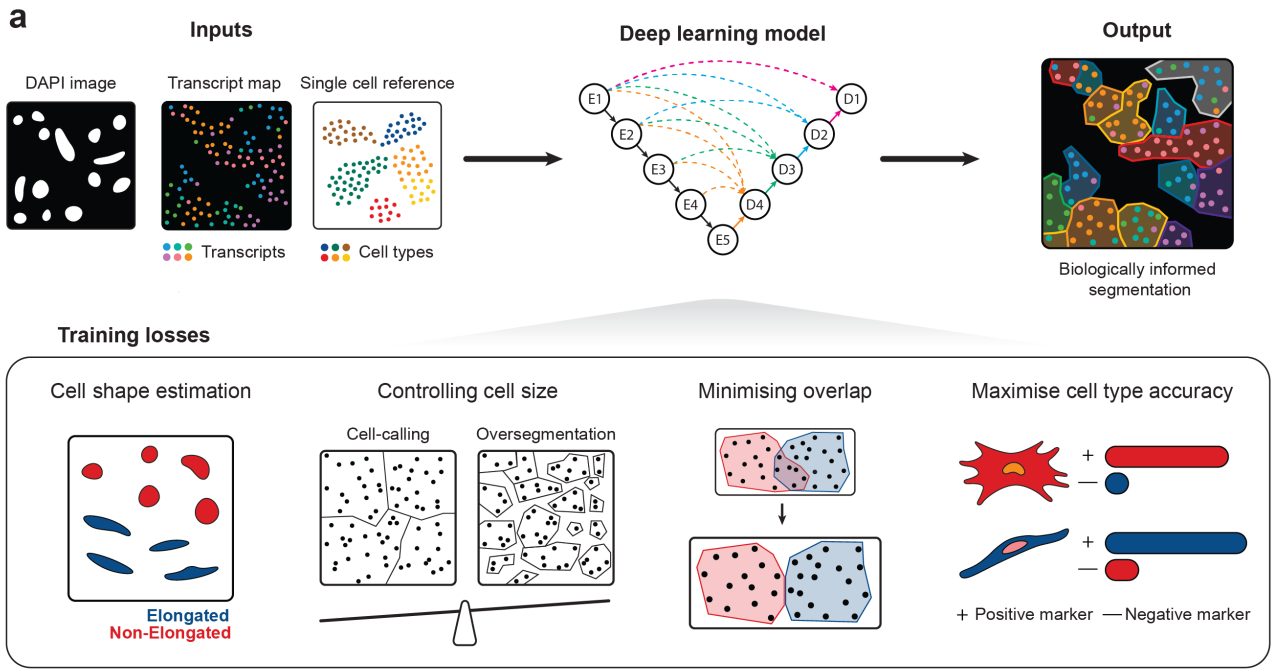
EGFR

Scale: 100 μm
10x Genomics Xenium (breast cancer, 313 genes)

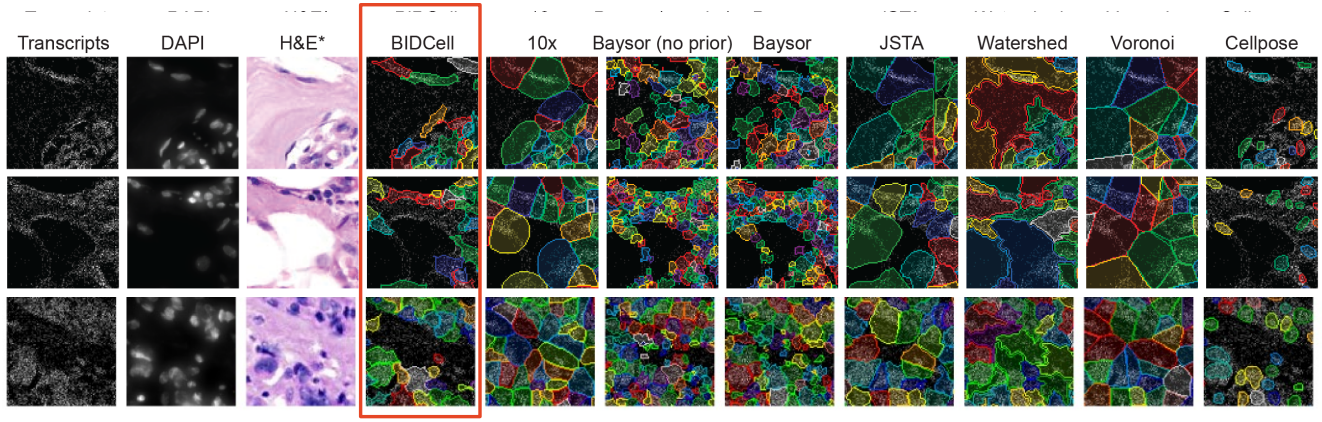
Existing methods

- **Classical**: watershed, Voronoi expansion, dilation from nuclei boundary
  - Spatial gene expression is irrelevant, tend to rely on nuclei/distance-based
- **Clustering/Transcript-based:** Baysor, ClusterMap
  - Disregard cell morphologies, sensitive to hyperparameters, slow, assume cells are homogeneous
- **Deep learning** (e.g., convolutional neural networks (CNNs)): Cellpose
  - SST images are considerably different to other modalities
    - Models pre-trained on other datasets are unsuitable
  - How to learn? There are no cell annotations, and manual annotation is impractical

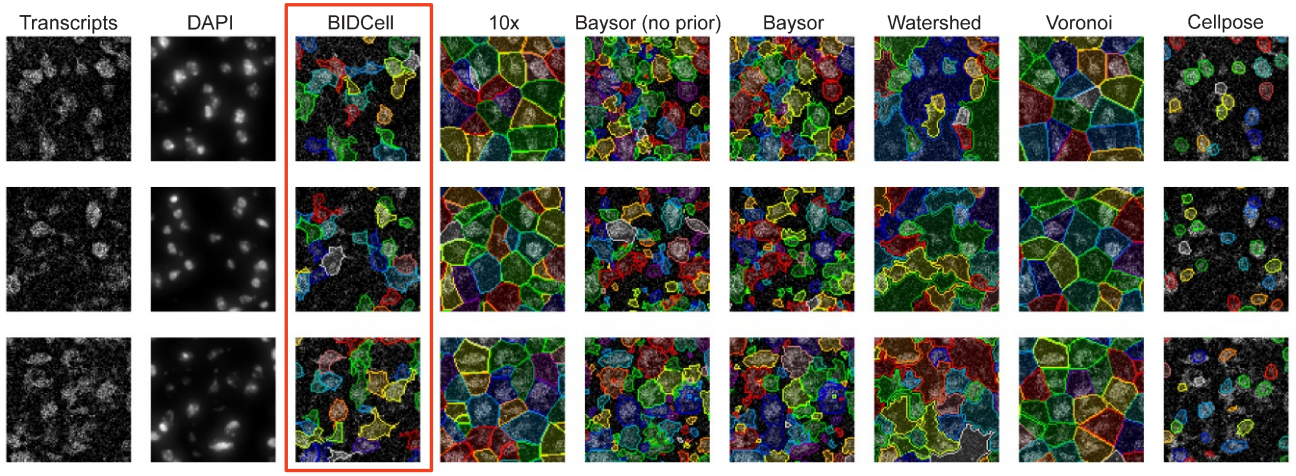
Biologically-informed deep learning-based cell segmentation (BIDCell)



Results



(a) Xenium-BreastCancer1



(b) Xenium-MouseBrain

Cell Segmentation Performance Assessment (CellSPA)

Baseline characteristics

Overall characteristics
cells;
% cells overlapped with nuclei;
% transcript assigned

Cell-level QC metrics
Density; Cell area;
# of genes expressed
# of total transcripts

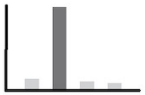
Cell morphology metrics
Elongation; Convexity; ...

Gene-level QC metrics
% of cells expressed

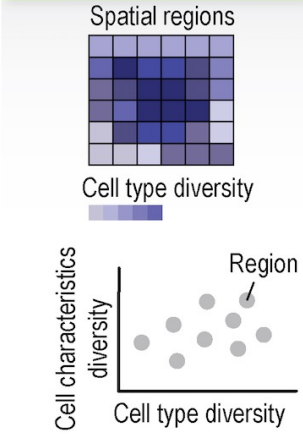
Segmented cell expression purity

Expression concordance with scRNA-seq

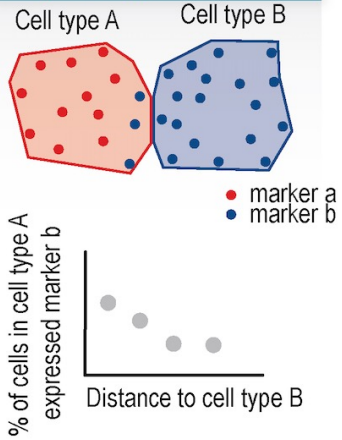
Expression purity in positive/negative markers



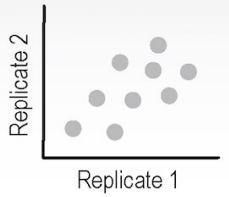
Spatial characteristics diversity



Neighbouring contamination



Replicability



Cell type proportion
Cell-level QC metrics
Gene-level QC metrics
...

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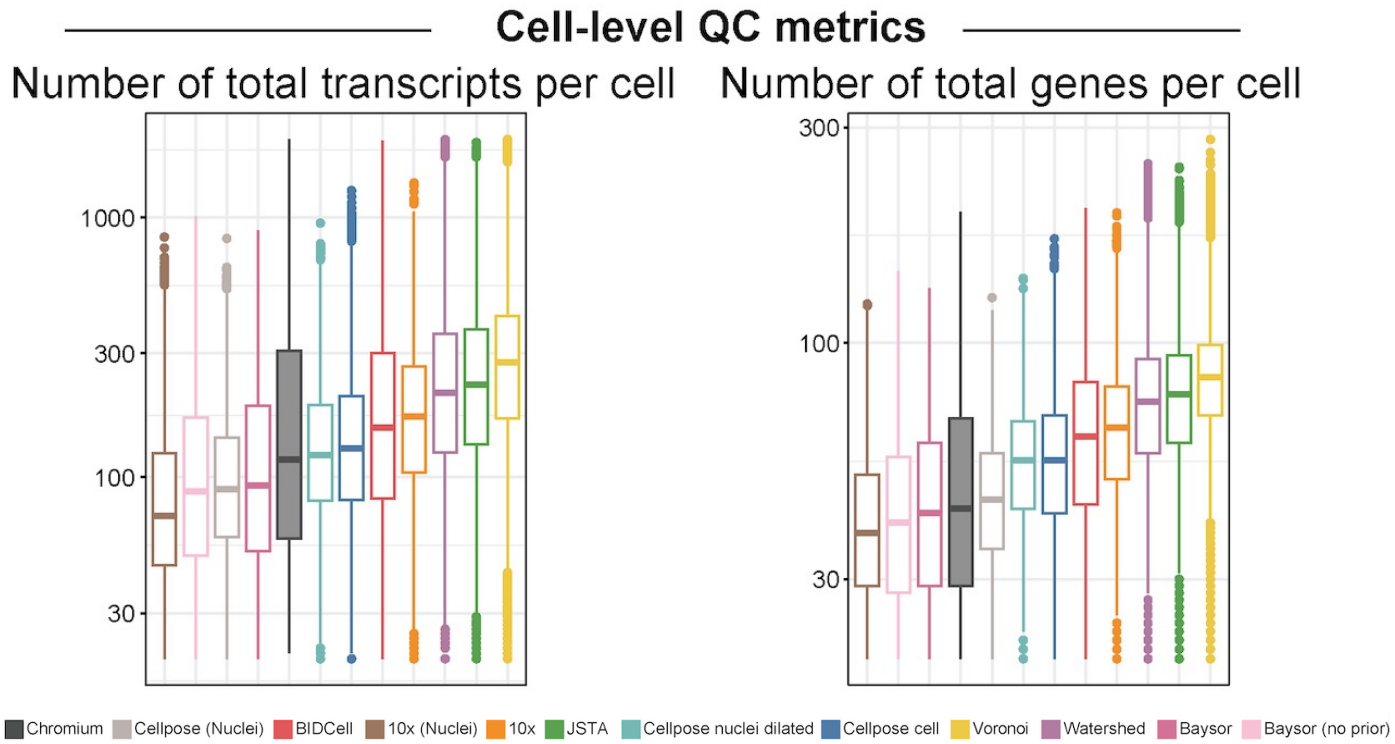

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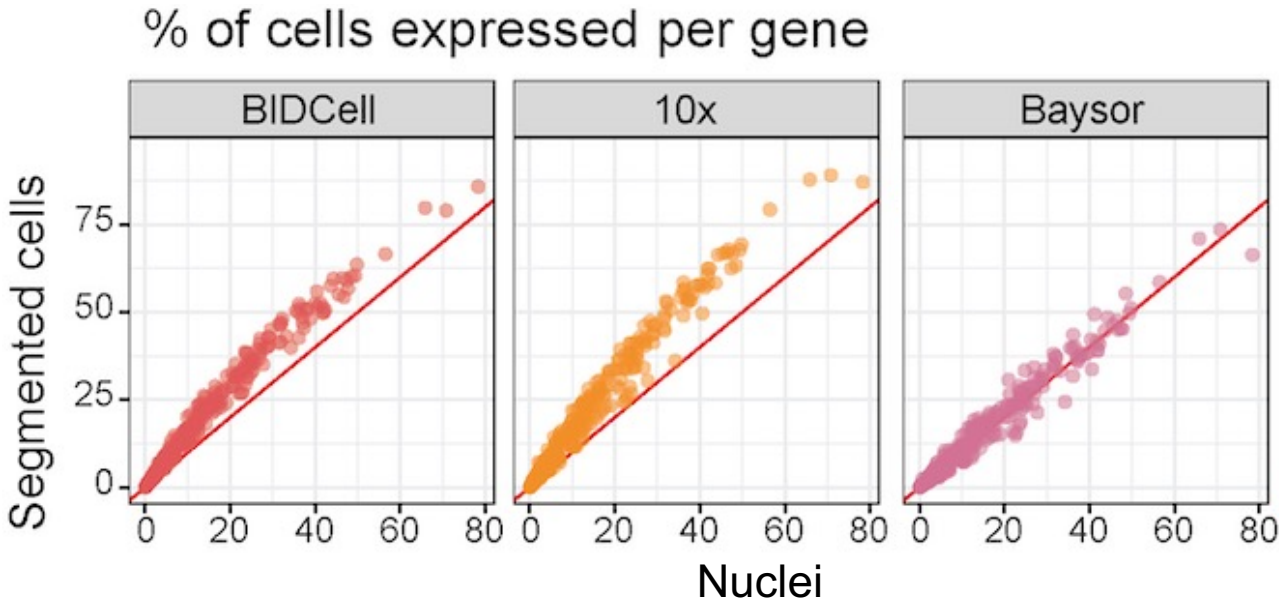

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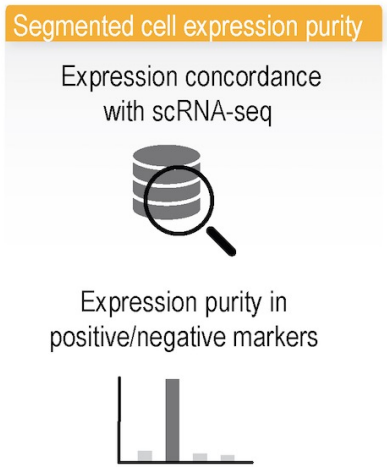
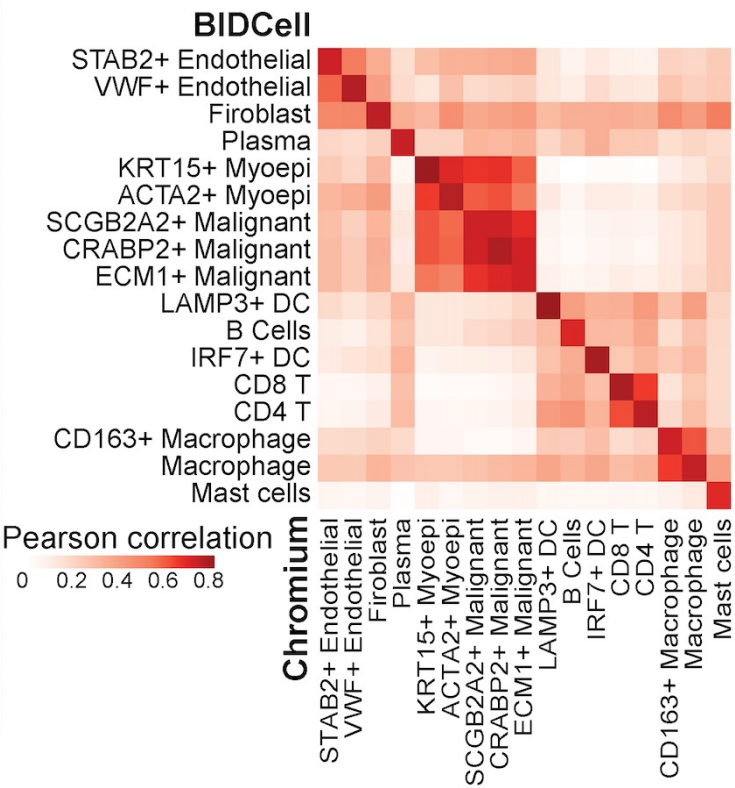
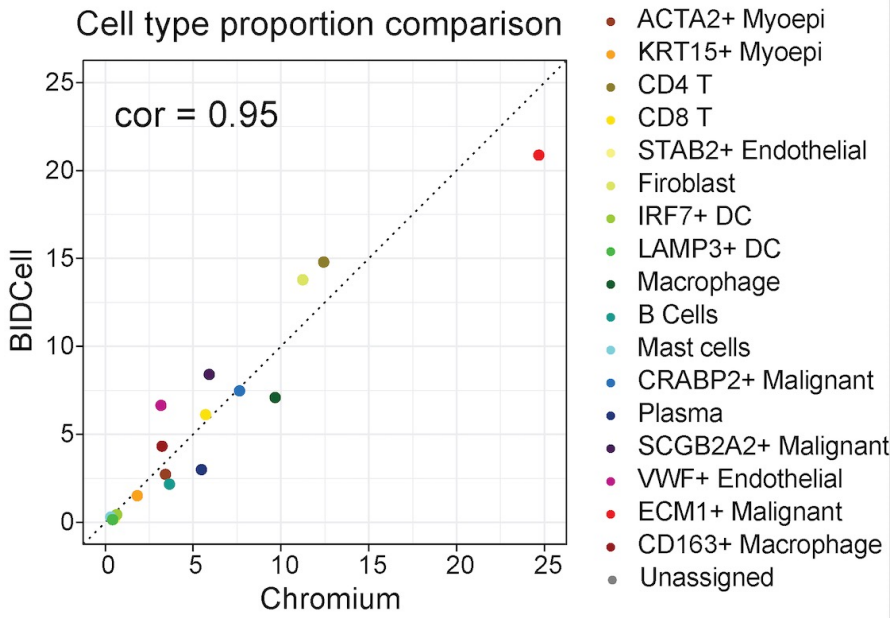
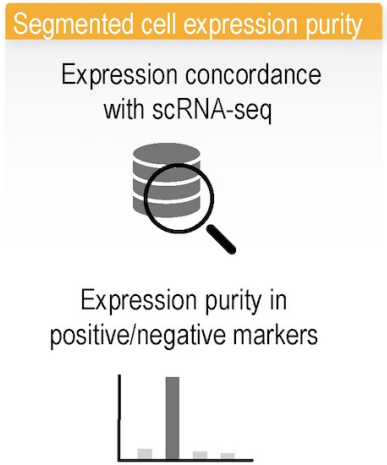
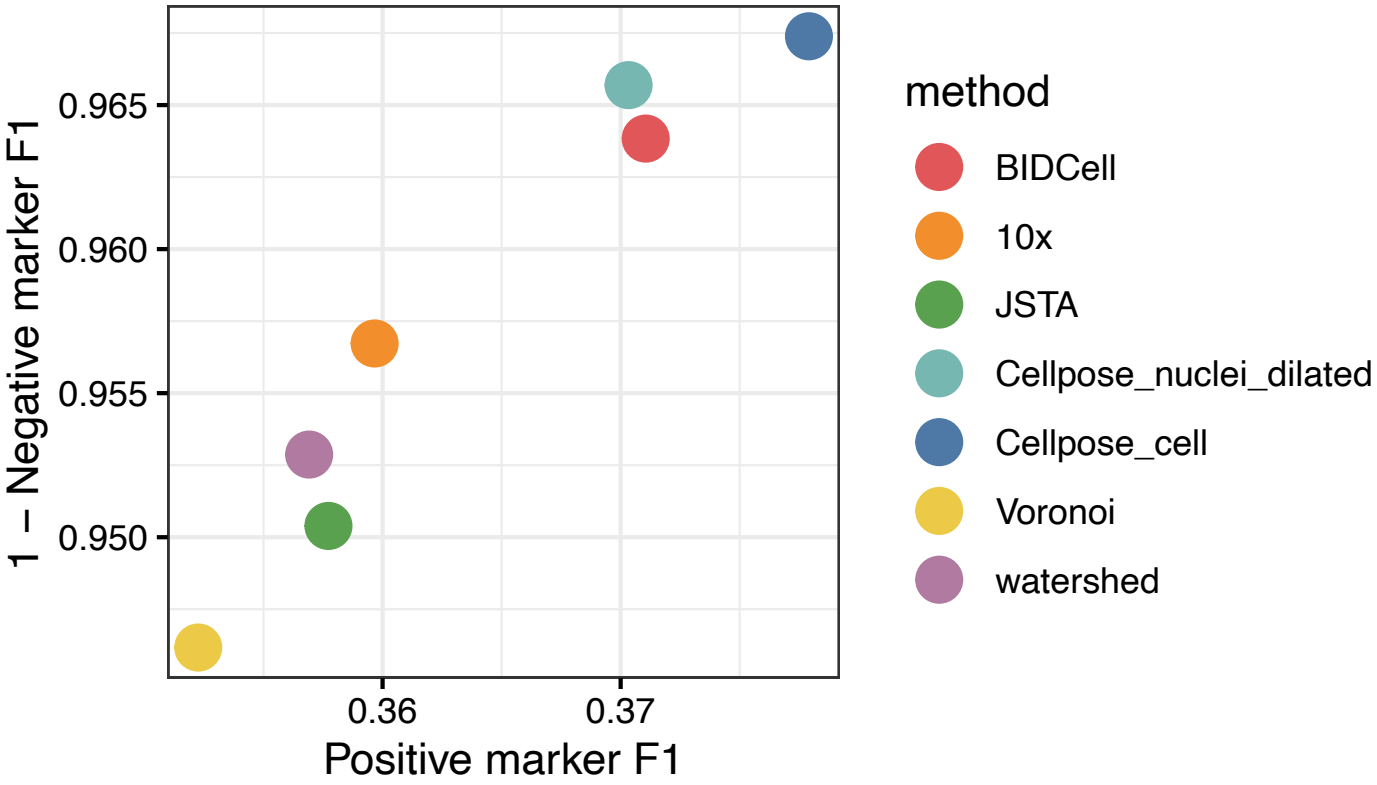






Evaluation – Trade-off between expression purity and size of cell





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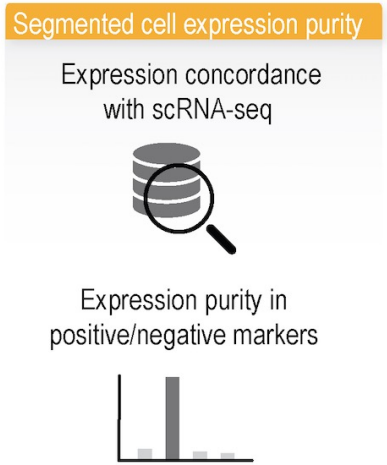

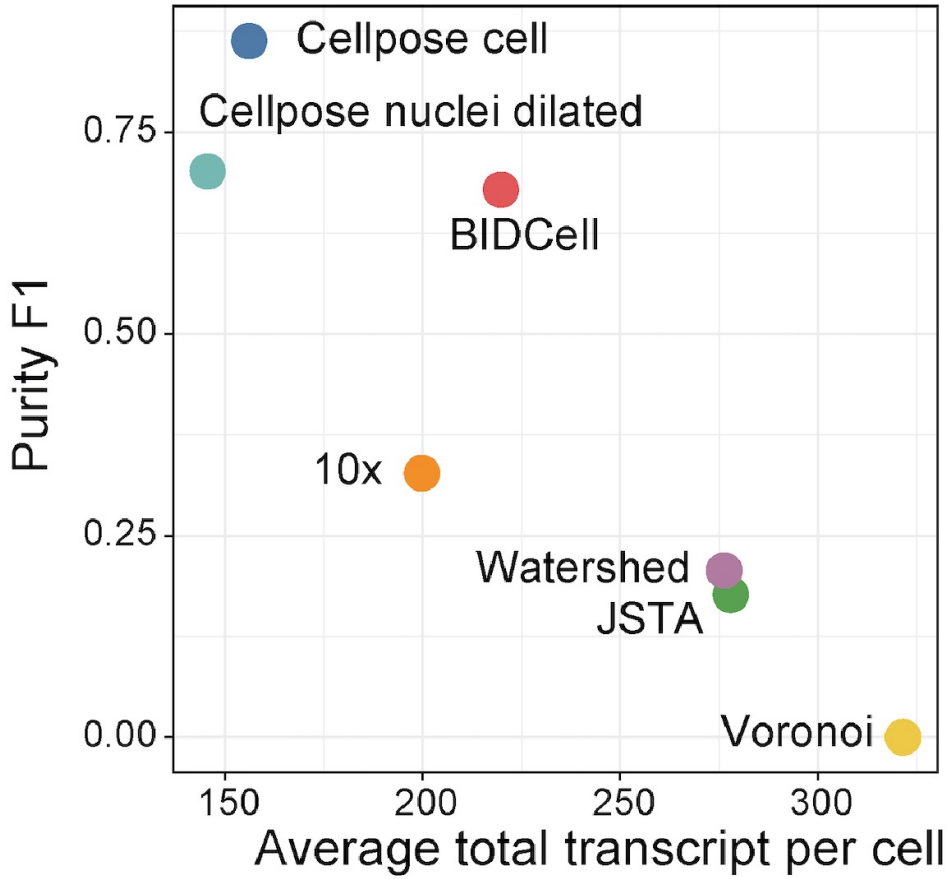

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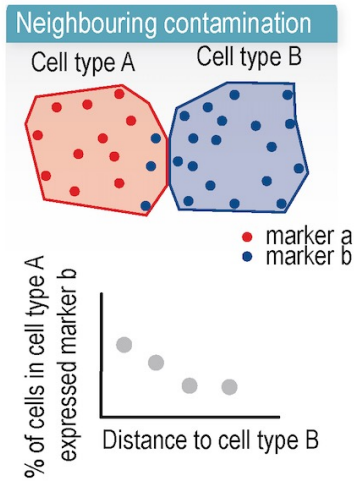

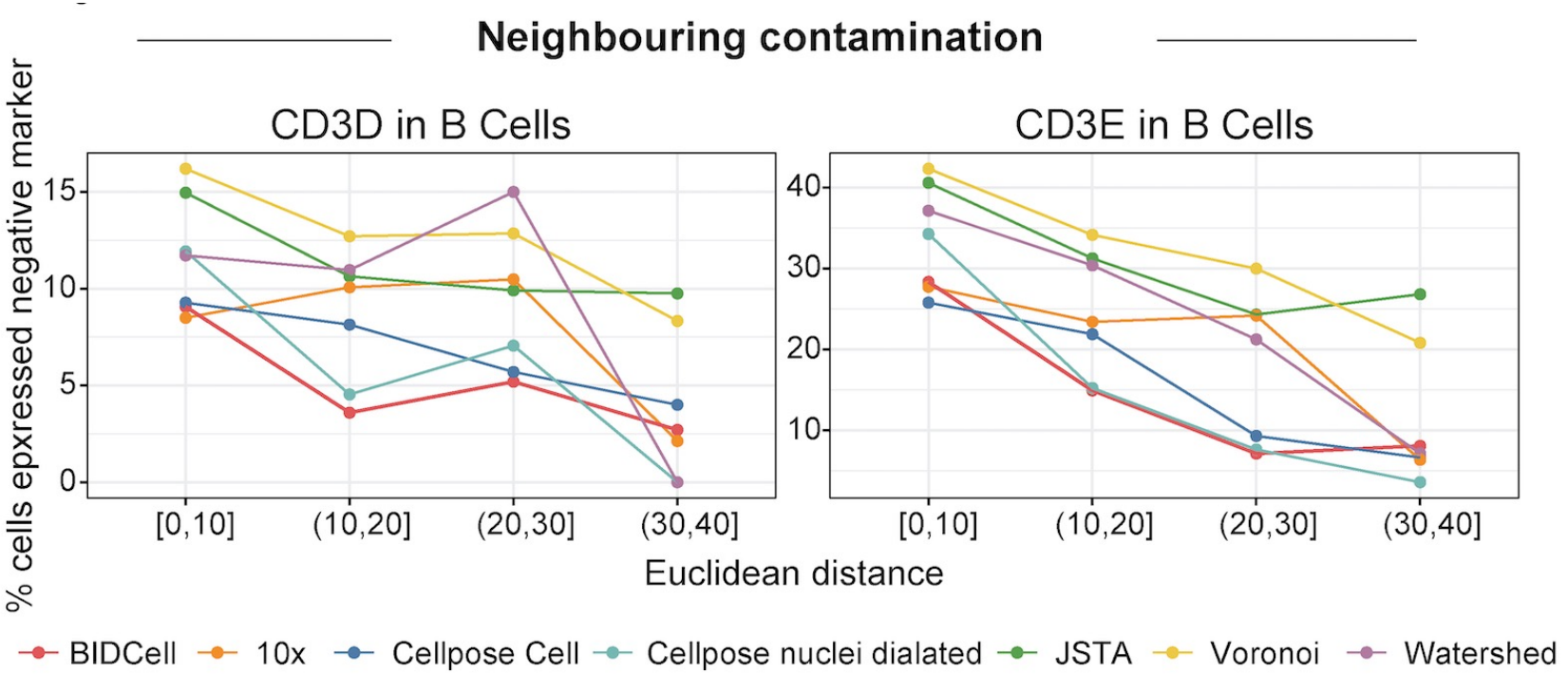

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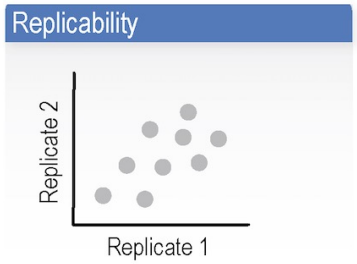

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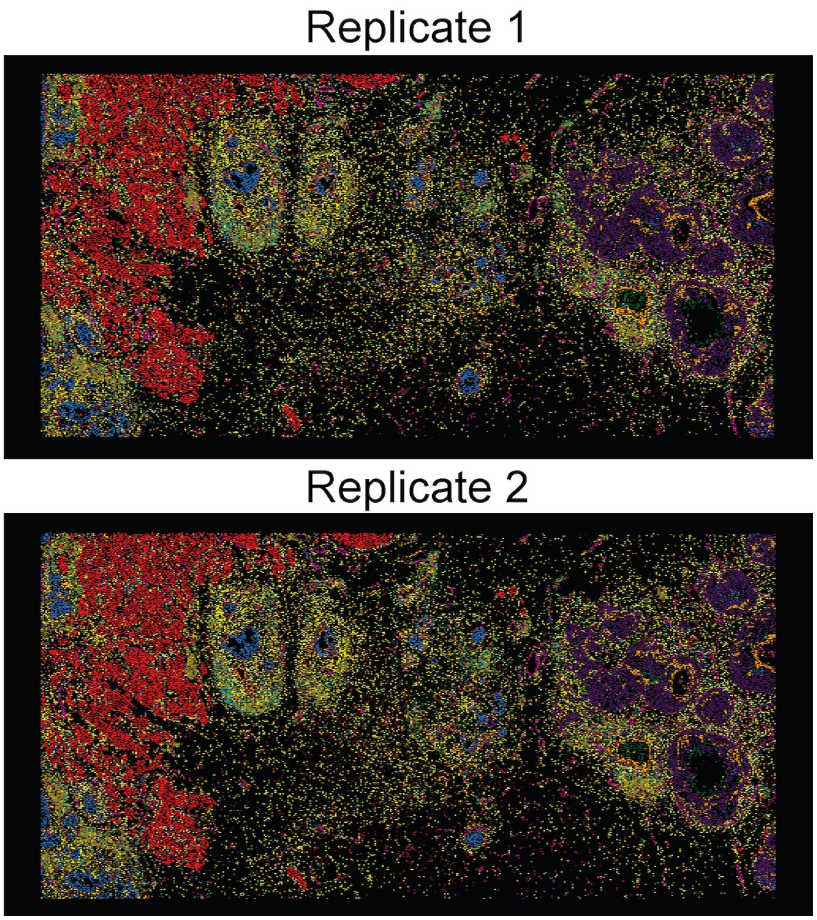
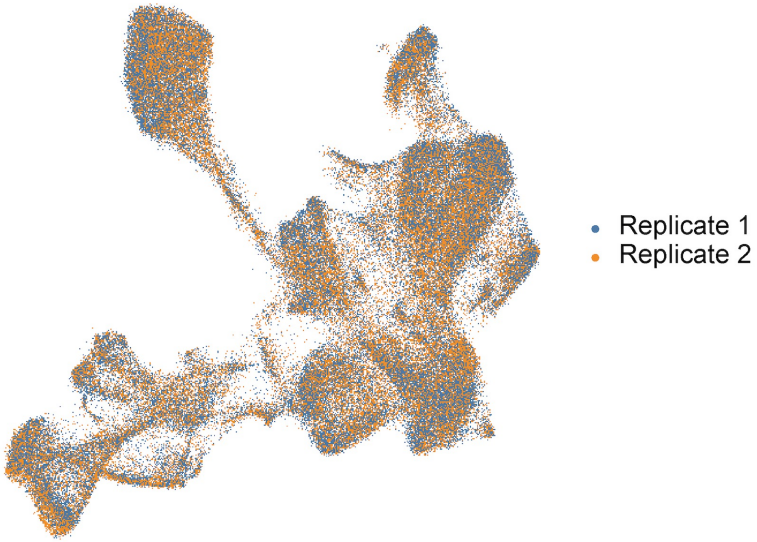
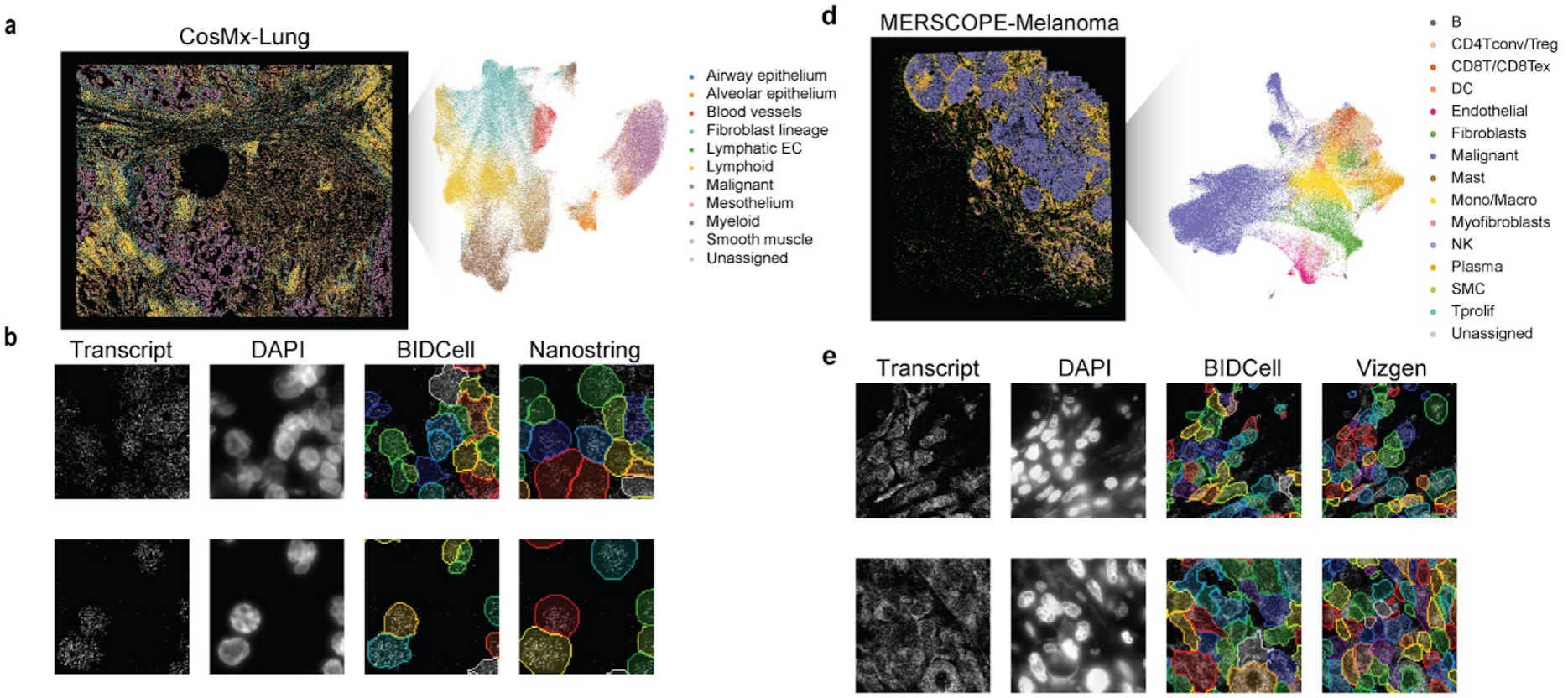


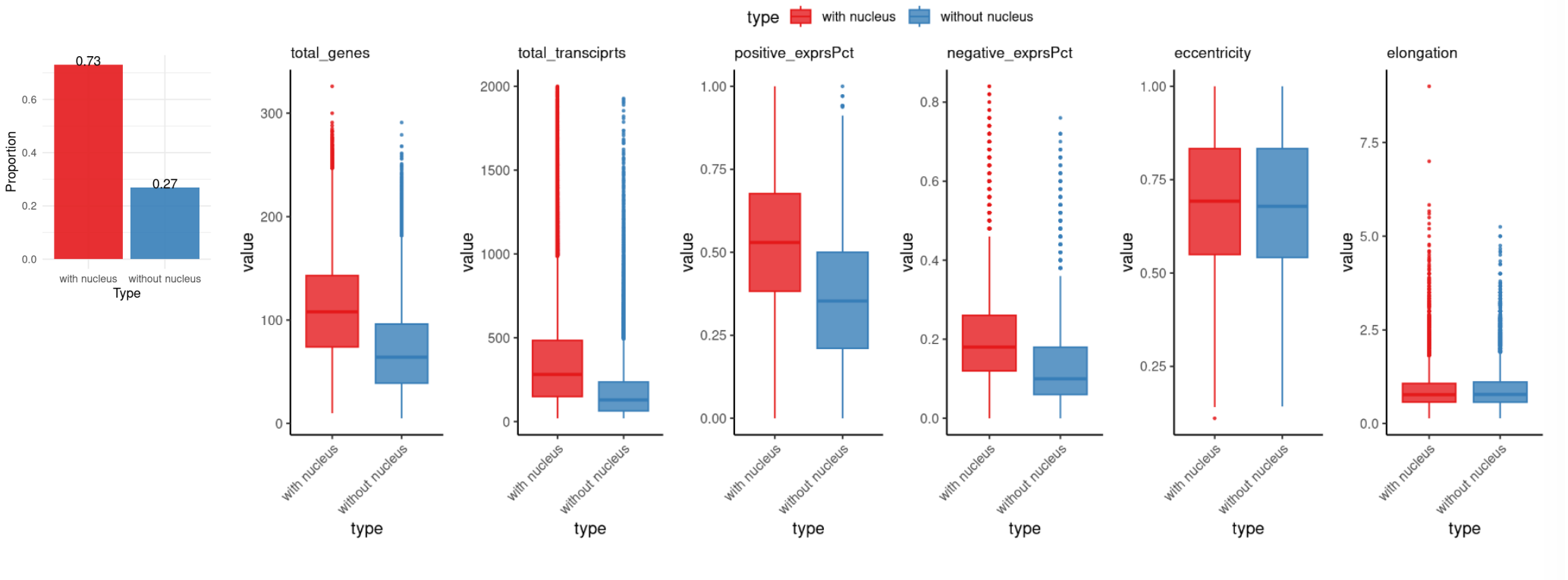


Flexibility



Worked in Stero-seq from BGI

BIDCell2 - What is the difference ?



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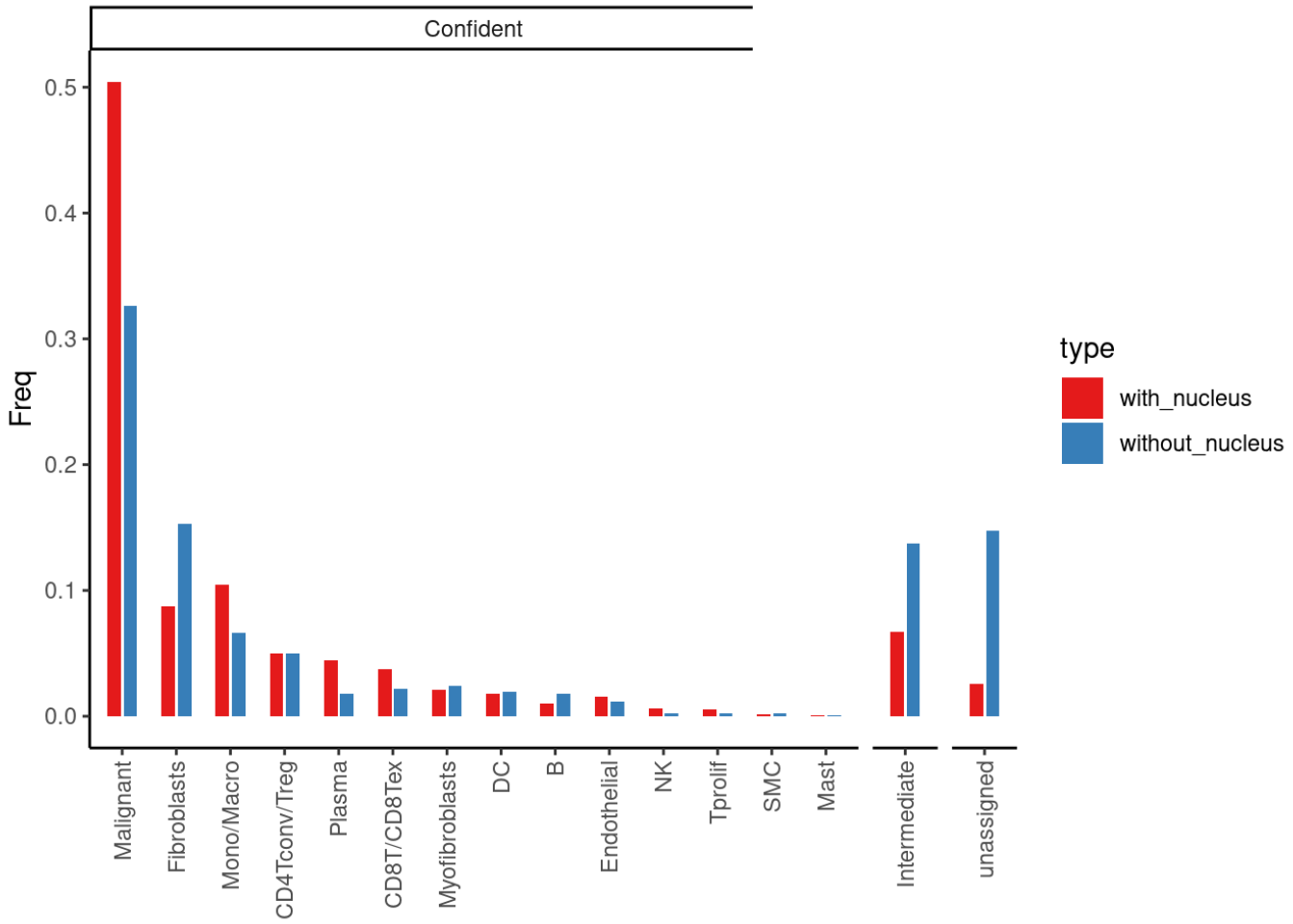

Lin etal Molecular System Biology 2020

Data and Code

Manuscript:
https://www.biorxiv.org/content/10.1101/2023.06.13.544733v1

Code:
- BIDCell training and inference in https://github.com/SydneyBioX/BIDCell

- We provide our CellSPA framework in https://github.com/SydneyBioX/CellSPA.

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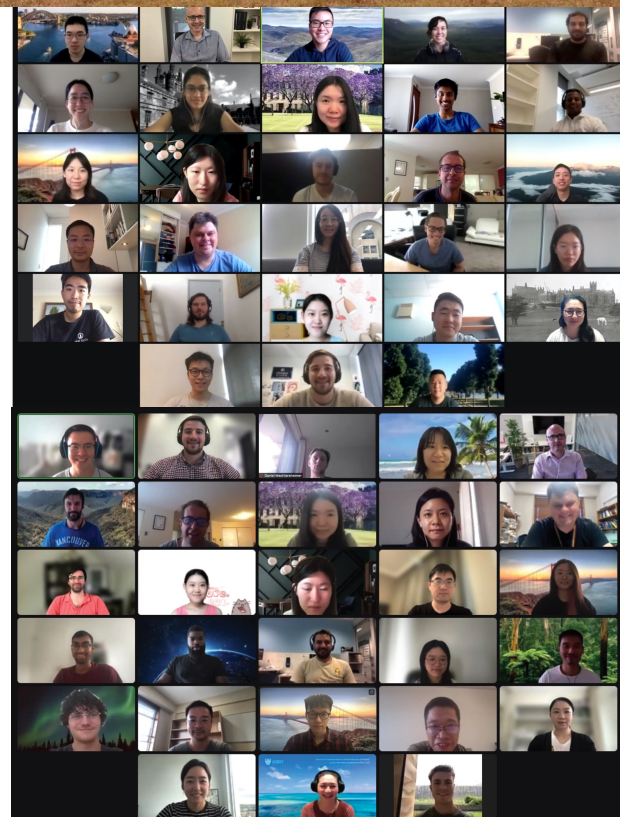

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