Developing algorithms for single cell genomics

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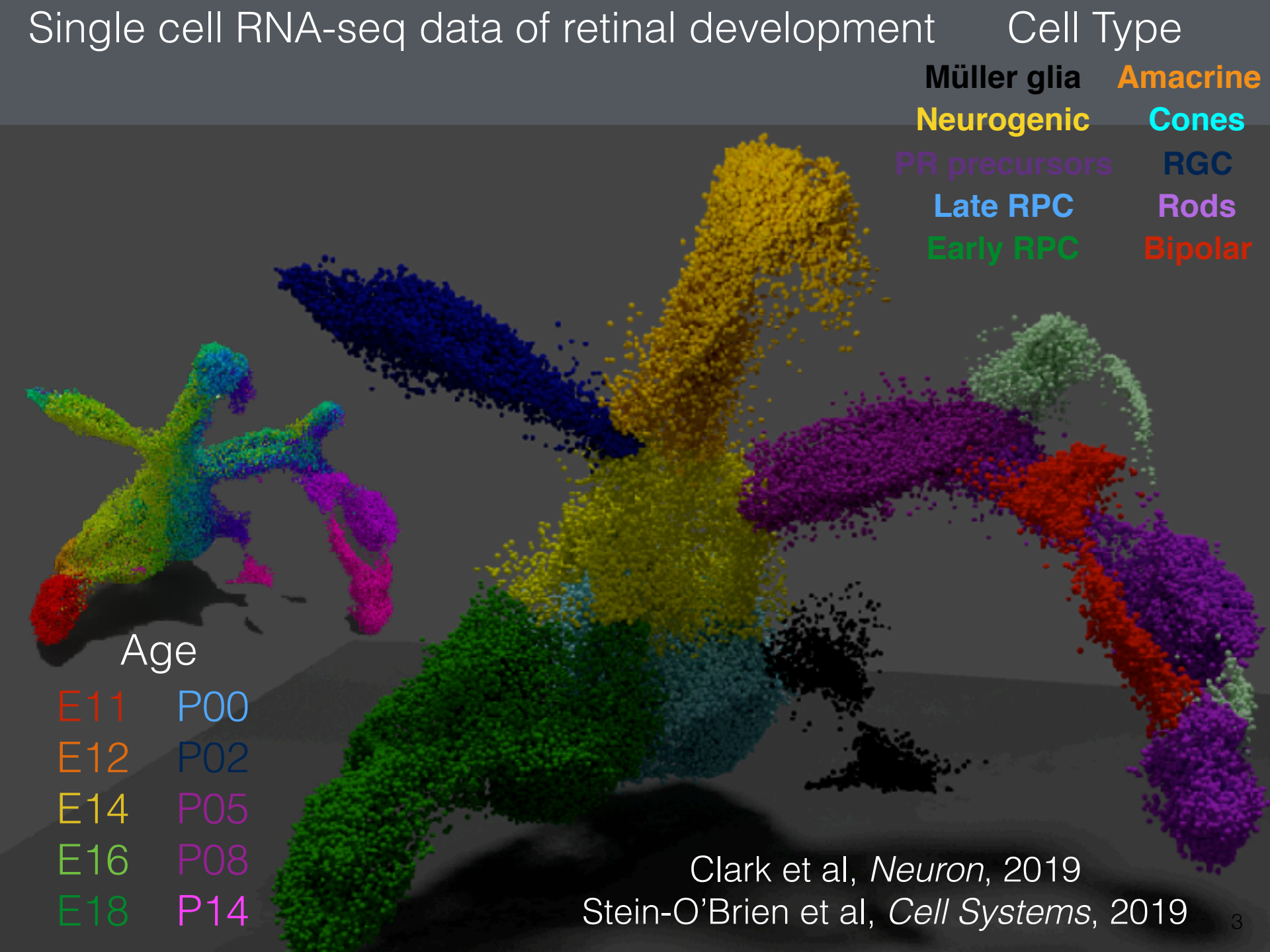
What are single cell technologies?

Bulk RNA-Seq

Single cell RNA-Seq

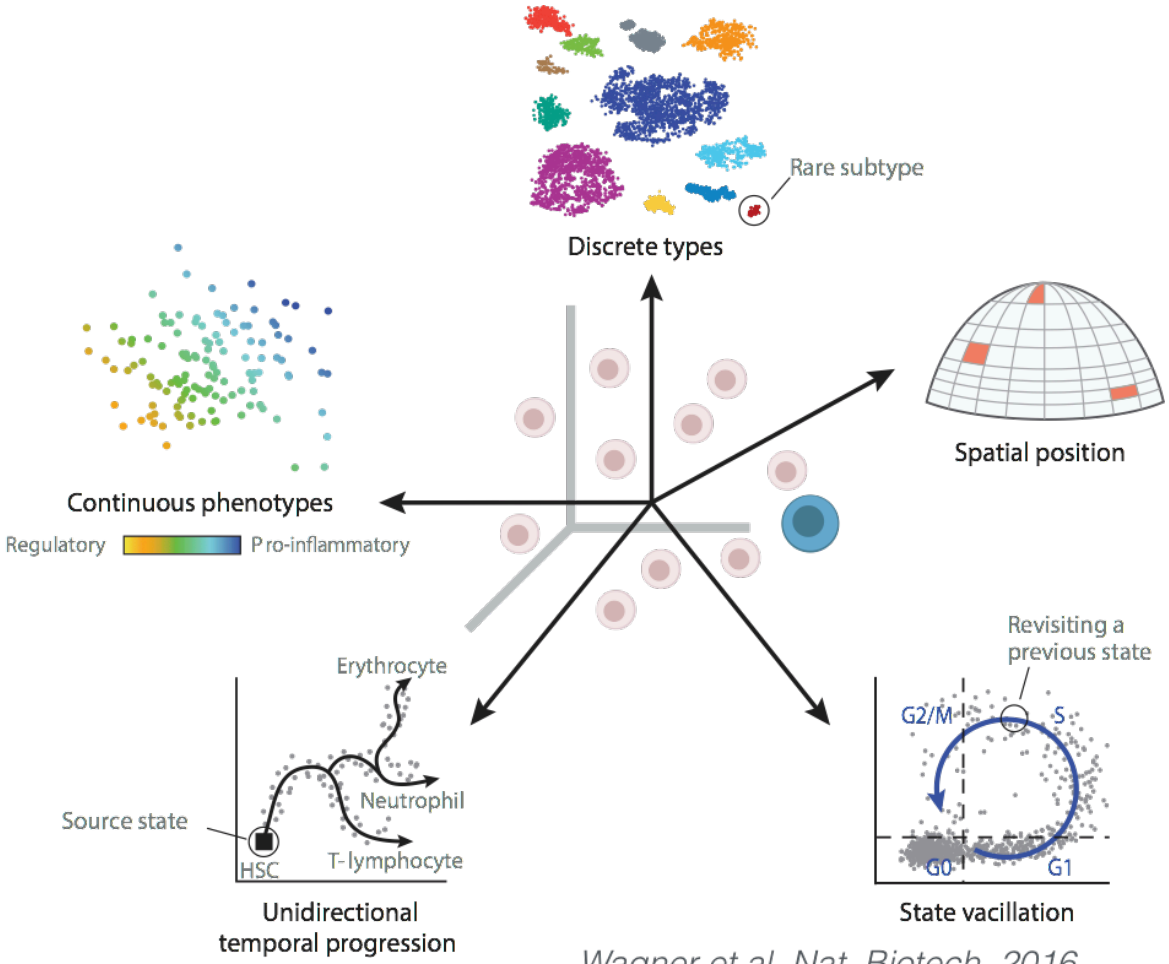
Spatial transcriptomics

Single cell RNA-seq data of retinal development



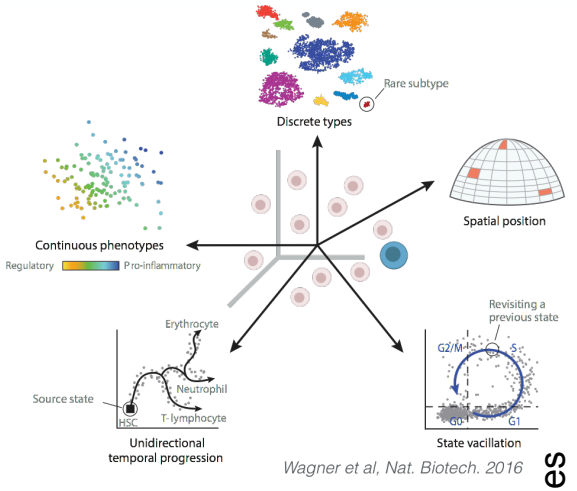
Clark et al, *Neuron*, 2019
Stein-O'Brien et al, *Cell Systems*, 2019

In addition to cell types, single cell data also captures axes of cellular activity

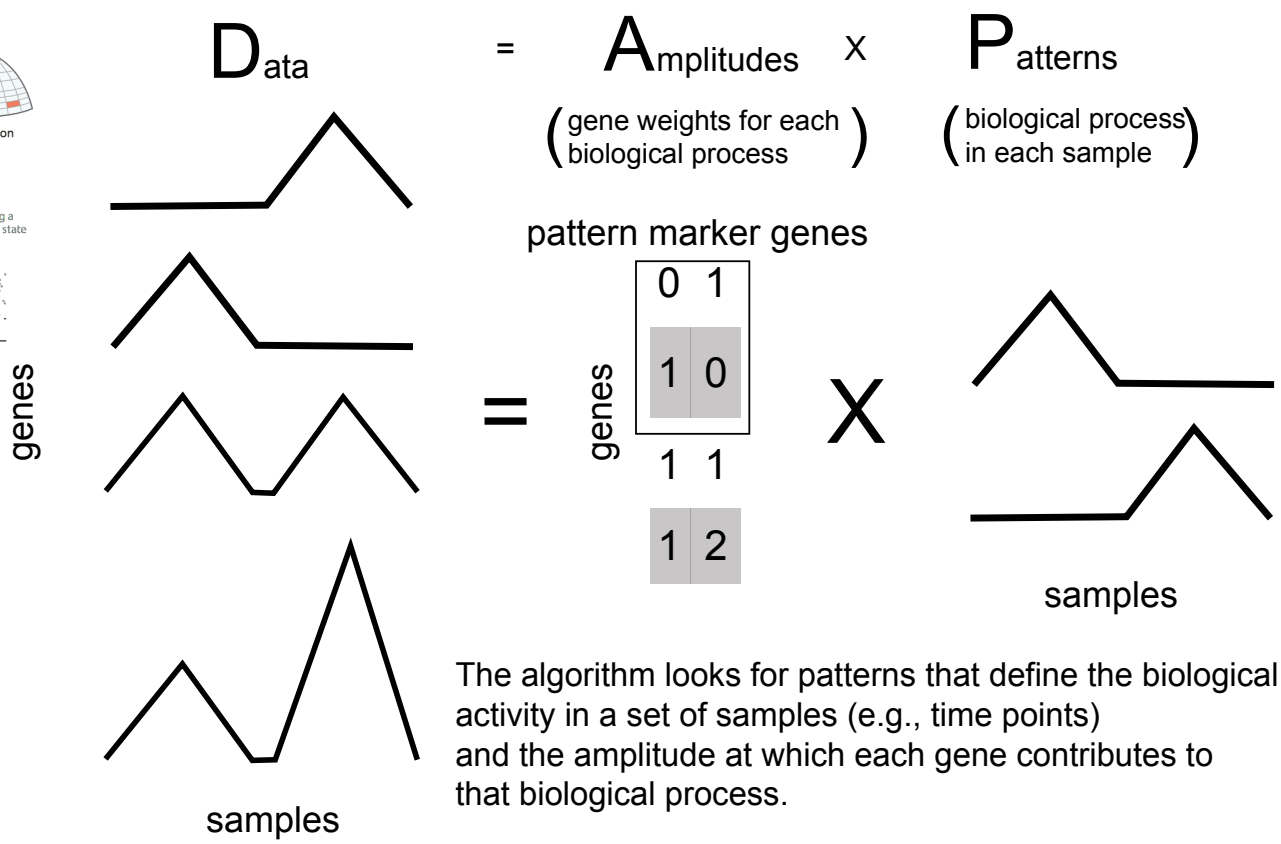


Wagner et al, Nat. Biotech. 2016

Axes of cellular identity mirrored by CoGAPS matrix factorization



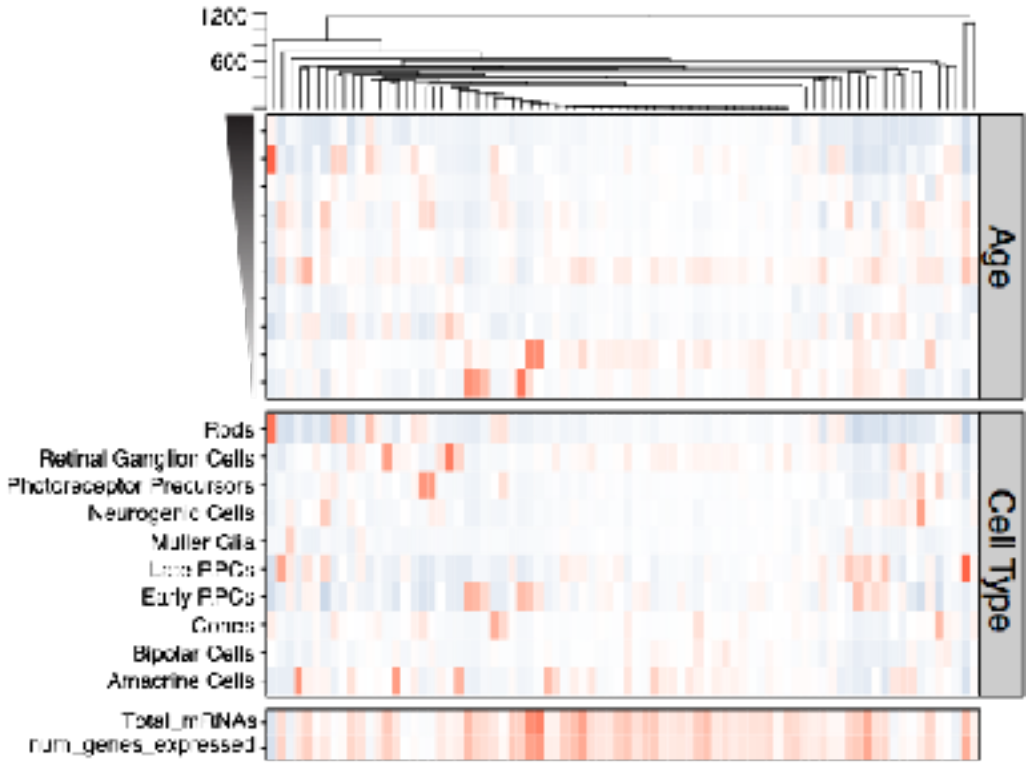
Wagner et al, Nat. Biotech. 2016



The algorithm looks for patterns that define the biological activity in a set of samples (e.g., time points) and the amplitude at which each gene contributes to that biological process.

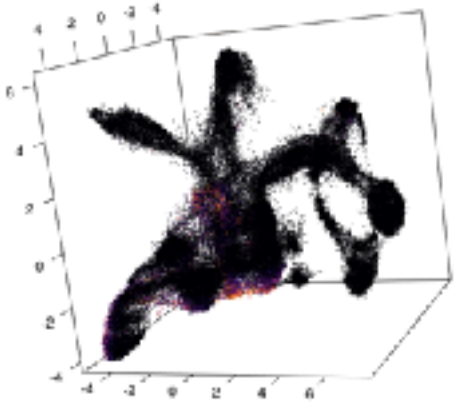
Stein-O'Brien et al, *Trends in Genetics*, 2018

Example of how matrix factorization uncovers axes of cellular identity in retinal development

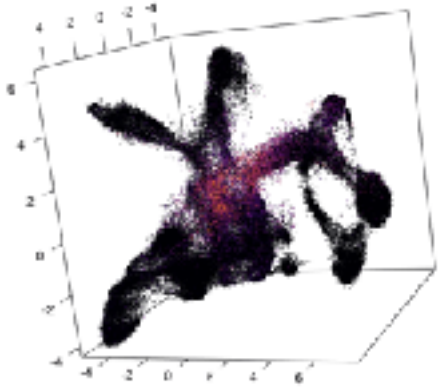


Clark et al, *Neuron*, 2019
Stein-O'Brien et al, *Cell Systems*, 2019

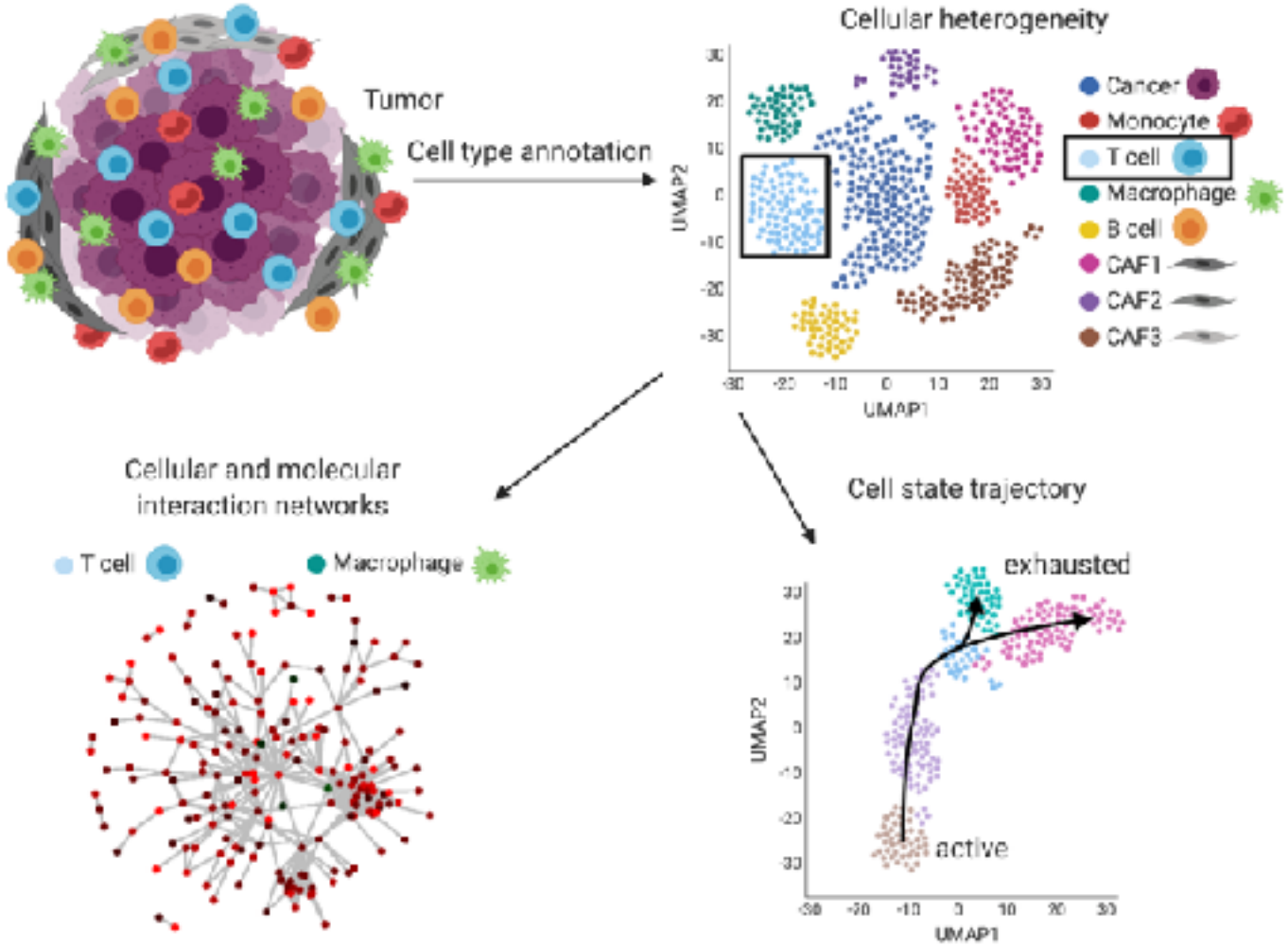
Cell Cycle - G1/S



Neurogenic

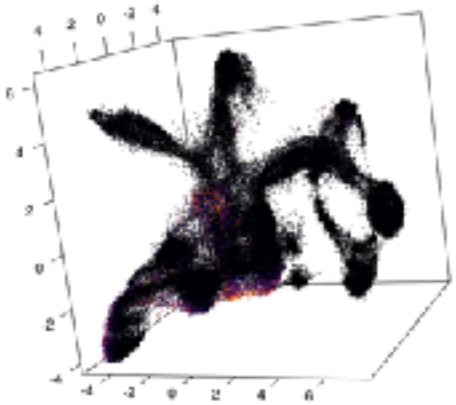


Inference of cellular state transitions and interactions requires new algorithms

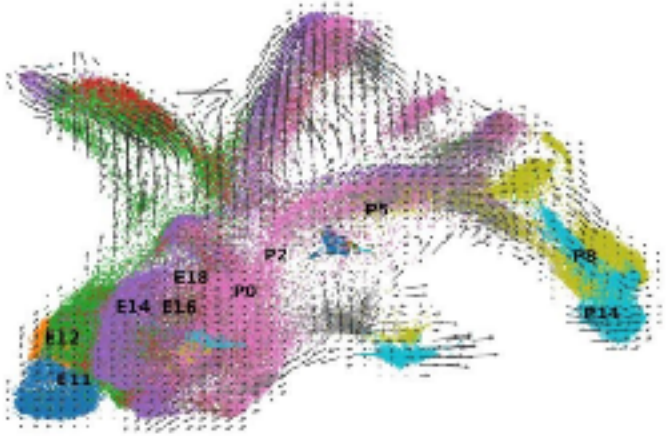


Cell state transitions

Patterns of cell cycle - G1/S

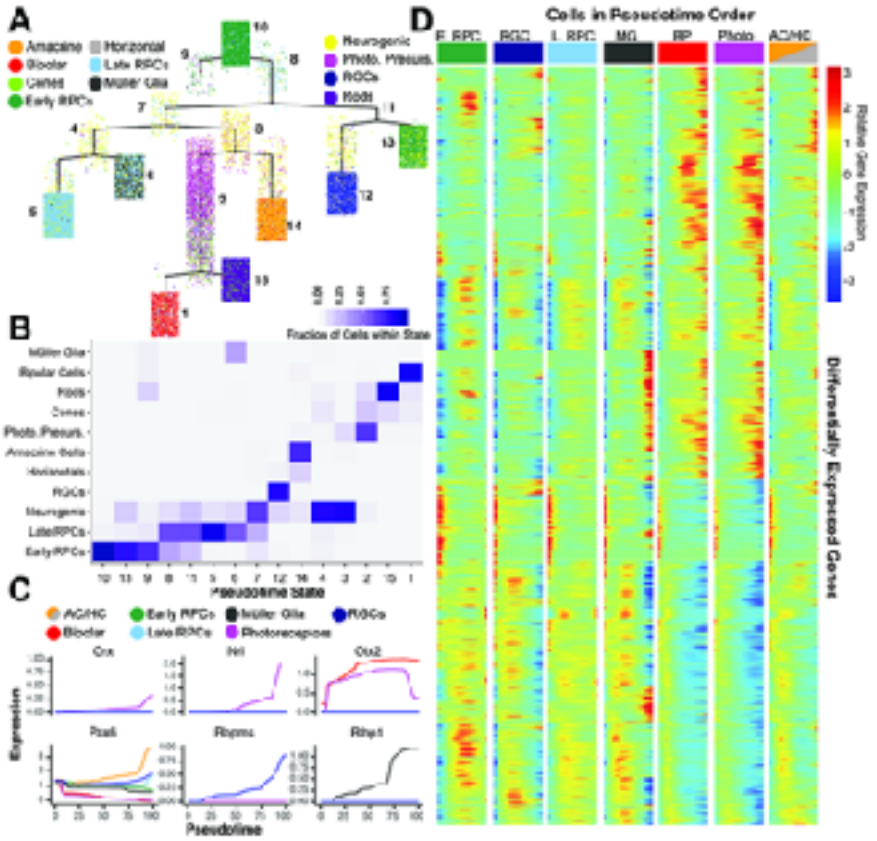


RNA velocity



Melsted et al, *BioRxiv*, 2019

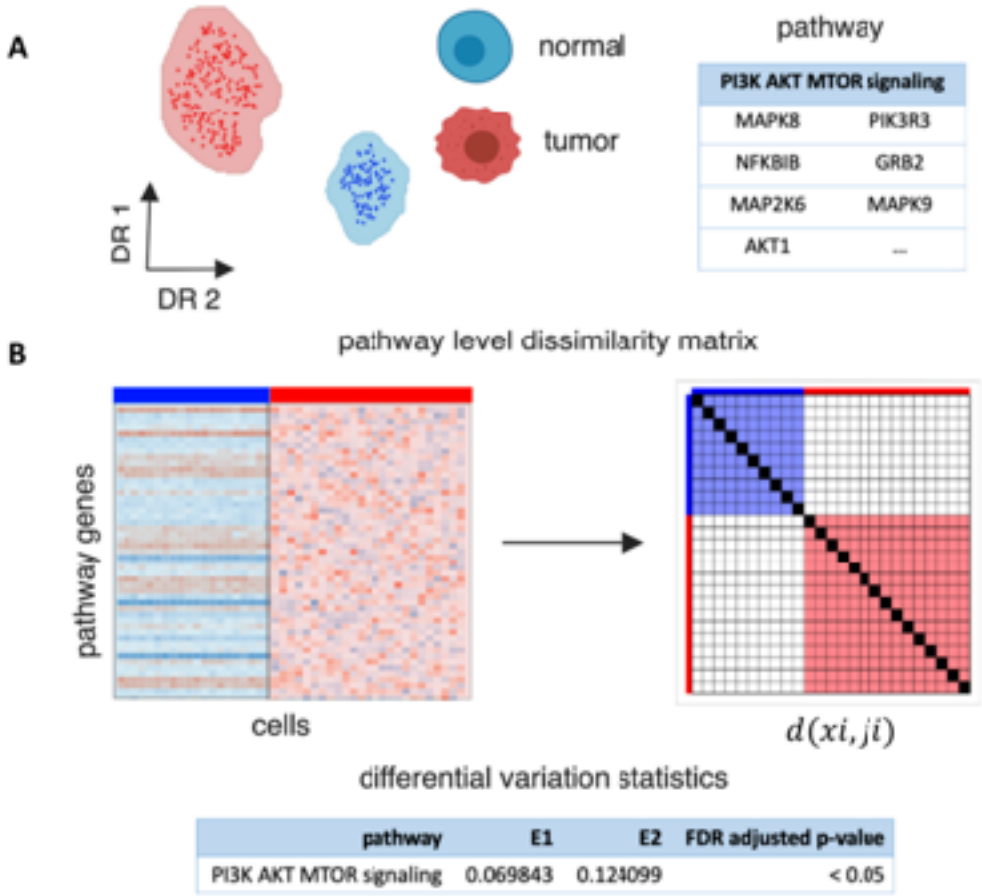
Trajectory inference or pseudotime



Clark et al, *Neuron*, 2019

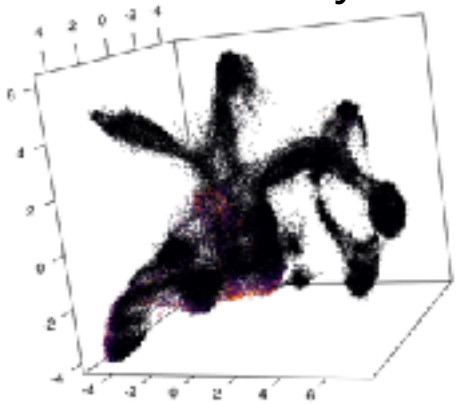
Stein-O'Brien et al, *Cell Systems*, 2019

Molecular heterogeneity can occur within distinct cellular subtypes

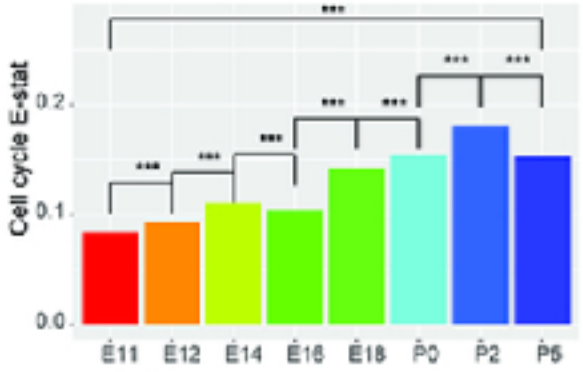


Davis-Marcisak et al, *Cancer Research*, 2019

Patterns of cell cycle - G1/S

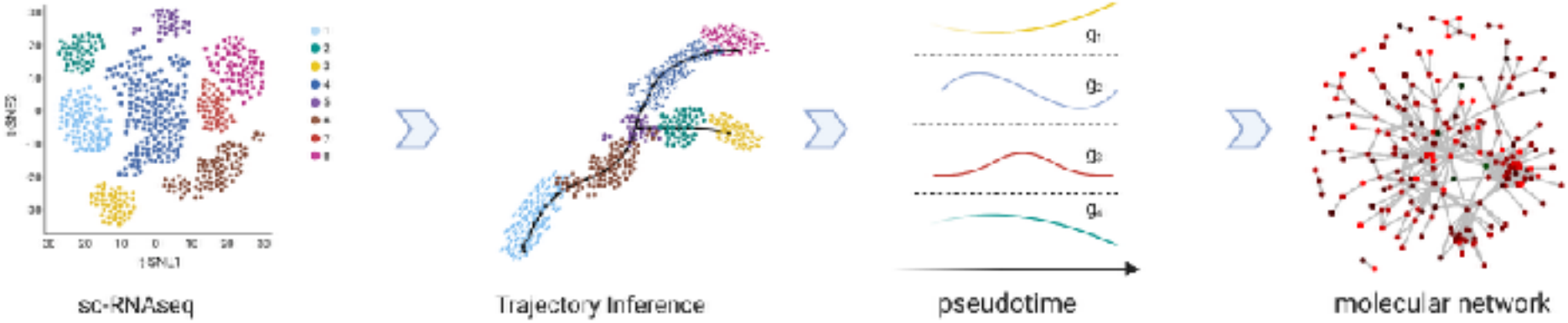


Temporal dysregulation of cell cycle

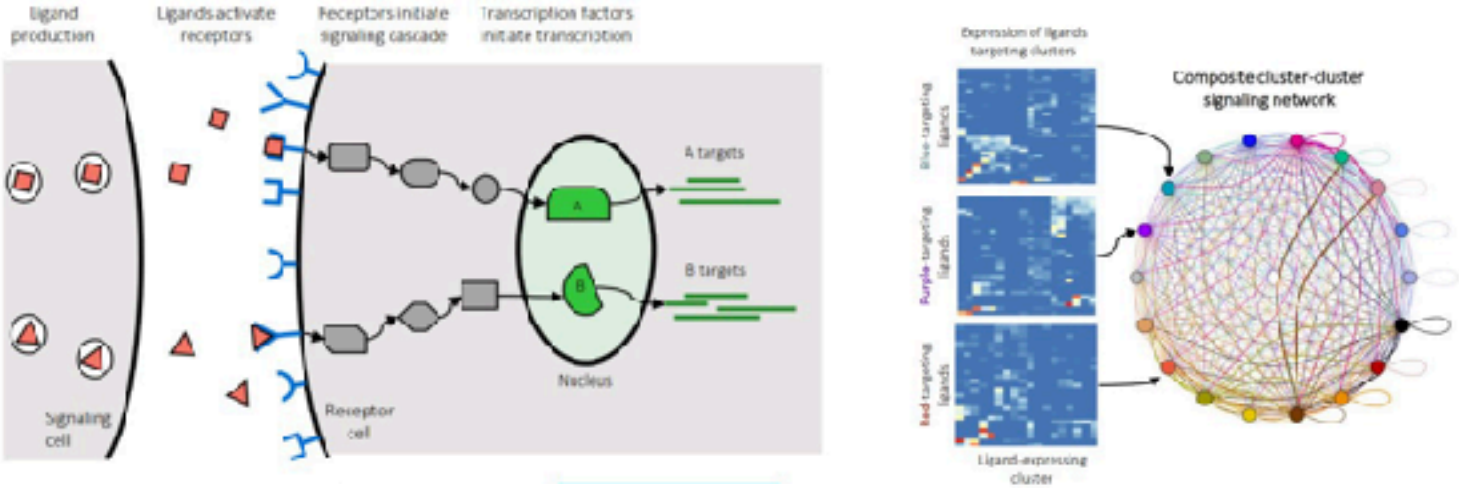


Clark et al, *Neuron*, 2019

Interaction networks can be informed by cell state transitions or regulatory networks



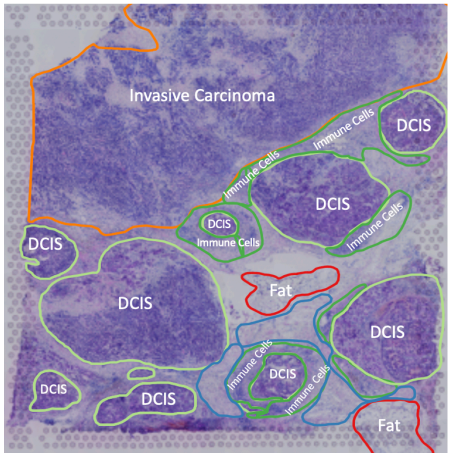
Deshpande et al, *BioRxiv*, 2019



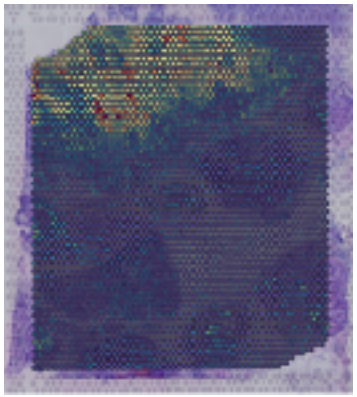
Cherry et al, *BioRxiv*, 2020

Inter-cellular interactions can be further inferred with spatial transcriptomics

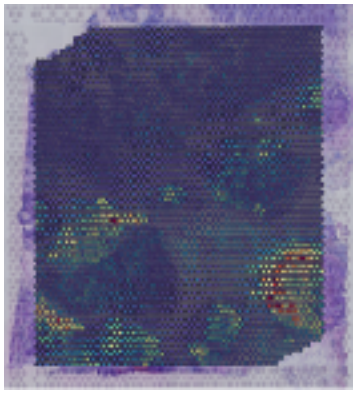
Visium
IHC + expression



tumor patterns

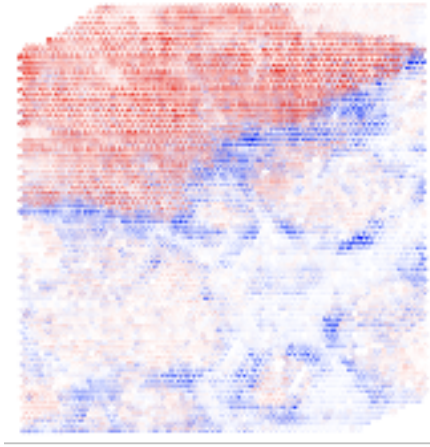


TGFBI, VEGFA, FGFR1



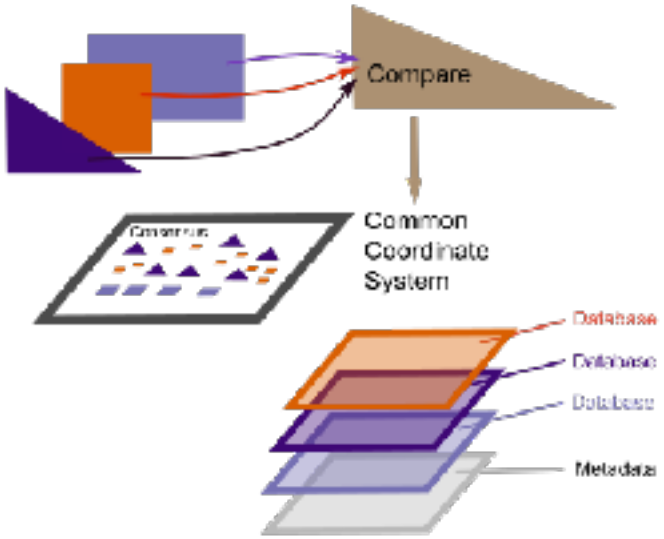
PIK3R3

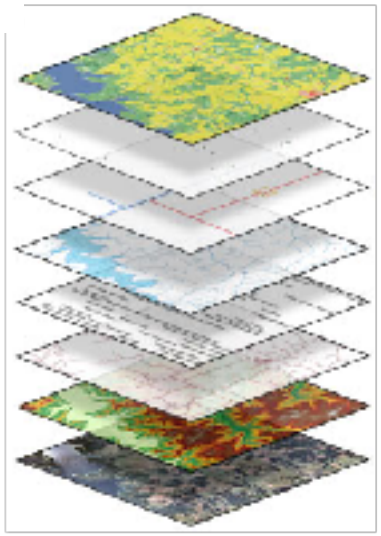
immune / tumor interactions

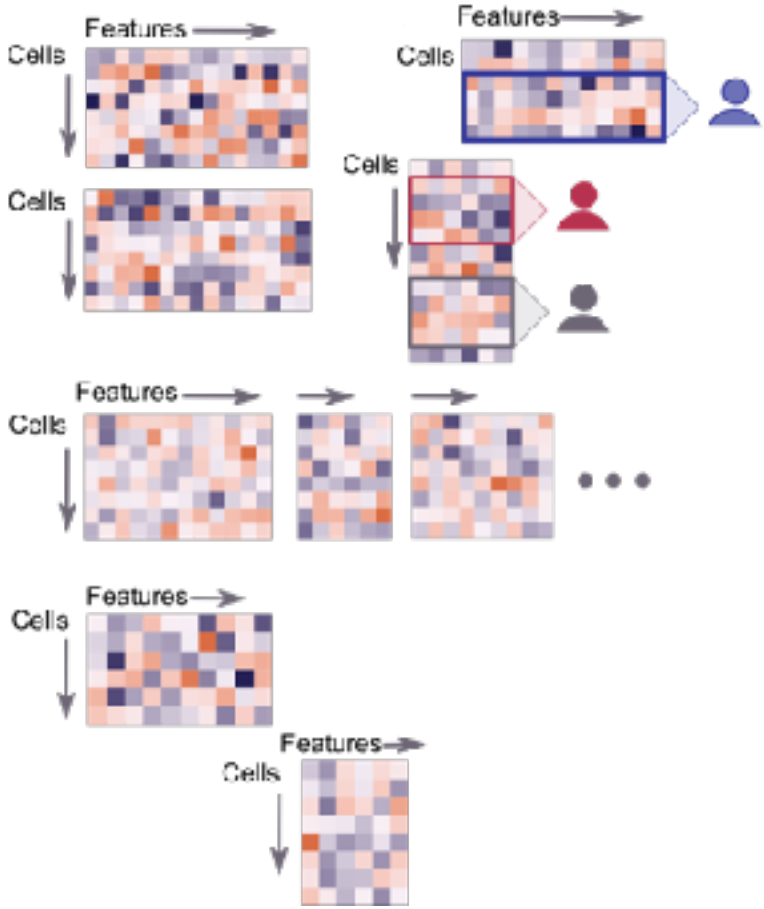


Melanie Loth, Atul Deshpane in collaboration with 10X Genomics

Multi-omics enables regulatory network inference and cross-study validation







Le Cao et al, 2019, https://birsbiointegration.github.io/whitePaper/

Summary of methods and references

- **Matrix factorization and latent space analysis**
  - Cleary et al, 2017
  - Zhu et al, 2017
  - Townes et al, 2017
  - Stein-O'Brien et al, 2018
  - Stein-O'Brien et al, 2019
  - Welch et al, 2019
  - Mohammadi et al, 2019
  - Svensson et al, 2020
- **Heterogeneity analysis**
  - Azizi et al, 2018
  - Davis-Marcisak et al, 2019
- **Trajectory and velocity analyses**
  - Trapnell et al, 2014
  - Ji et al, 2016
  - La Mannno et al, 2018
  - Bergen et al, 2020
  - Saalens et al, 2019
- **Network analyses**
  - Efremova et al, 2020
  - Browaeys et al, 2020
  - Cherry et al, BioRxiv, 2020
  - Deshpande et al, BioRxiv, 2019