

Transcriptional landscape of fate choices in the sensory lineages

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Corresponding author: Saida Hadjab

Igor Adameyko



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**Karolinska
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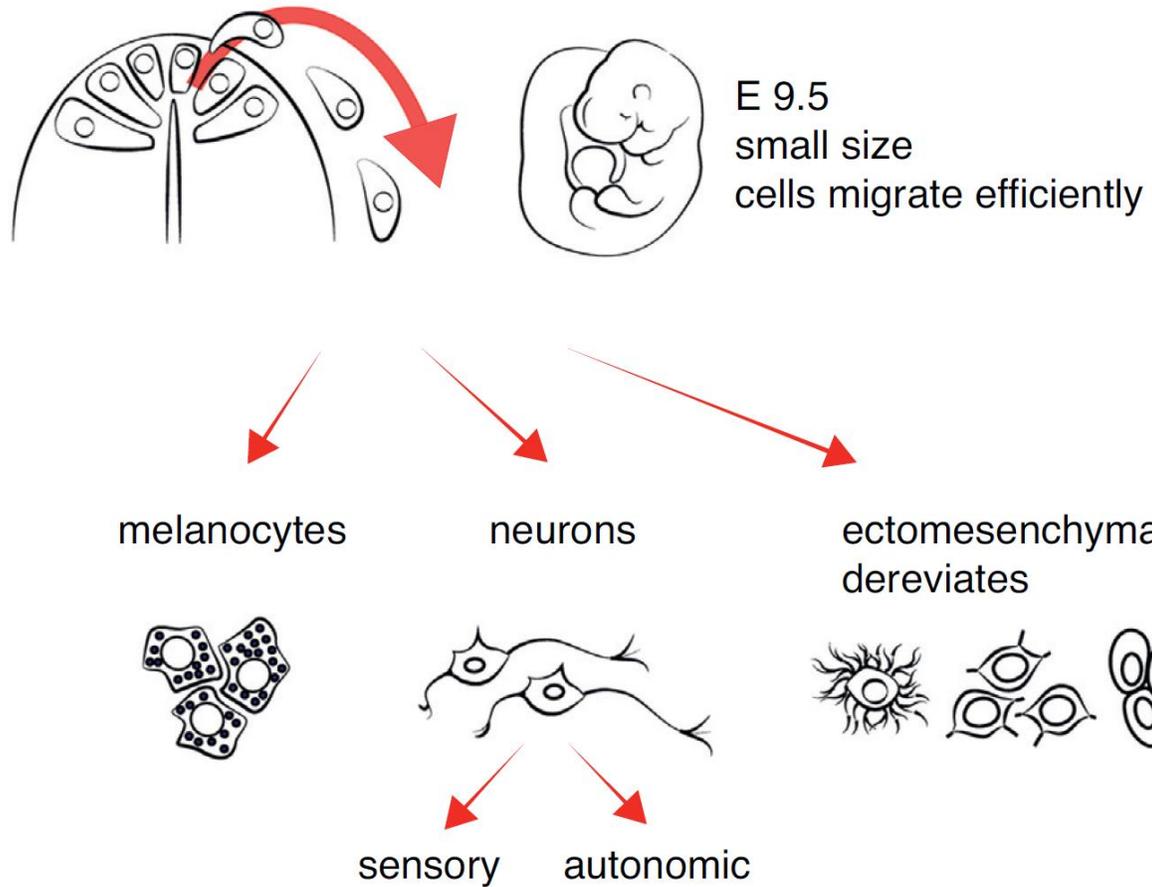
Saida Hadjab



François Lallemand

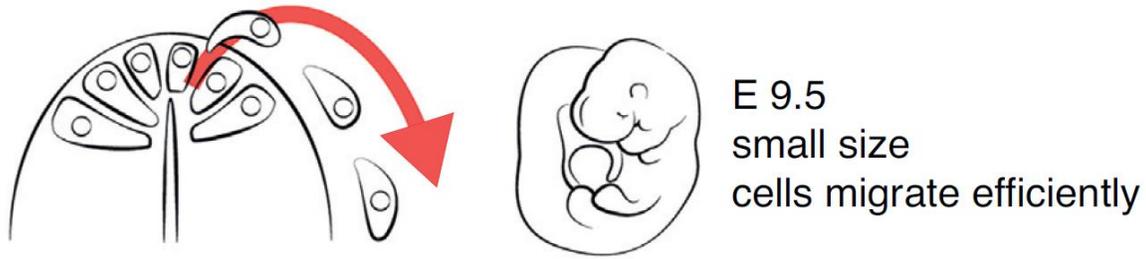


Neural crest



Petersen, J. & Adameyko, I. Nerve-associated neural crest: peripheral glial cells generate multiple fates in the body. *Curr. Opin. Genet. Dev.* 45, 10-14 (2017).

Neural crest



melanocytes



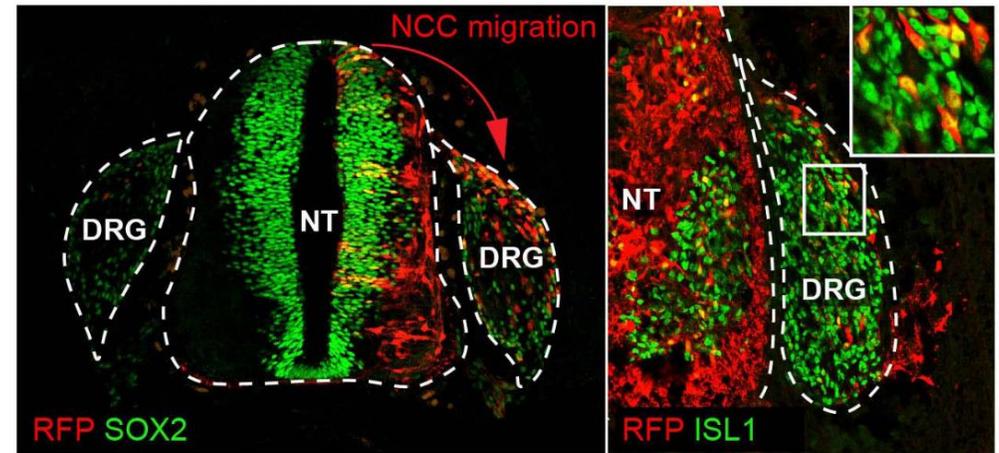
neurons



sensory

autonomic

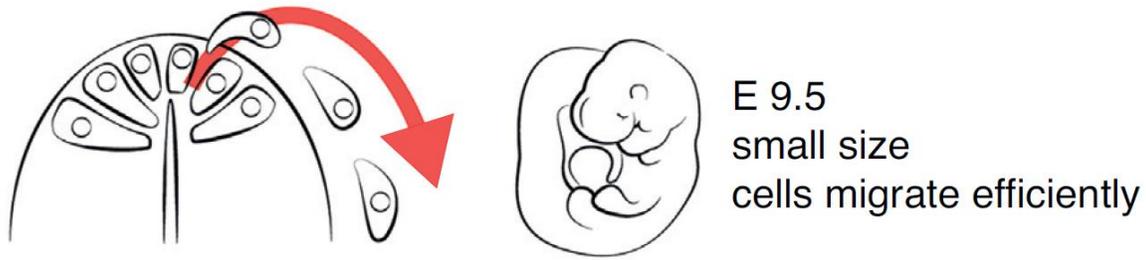
ectomesenchymal
derivates



Soldatov, R. *et al.* Spatiotemporal structure of cell fate decisions in murine neural crest. *Science* (80-.). 364, (2019).

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Neural crest



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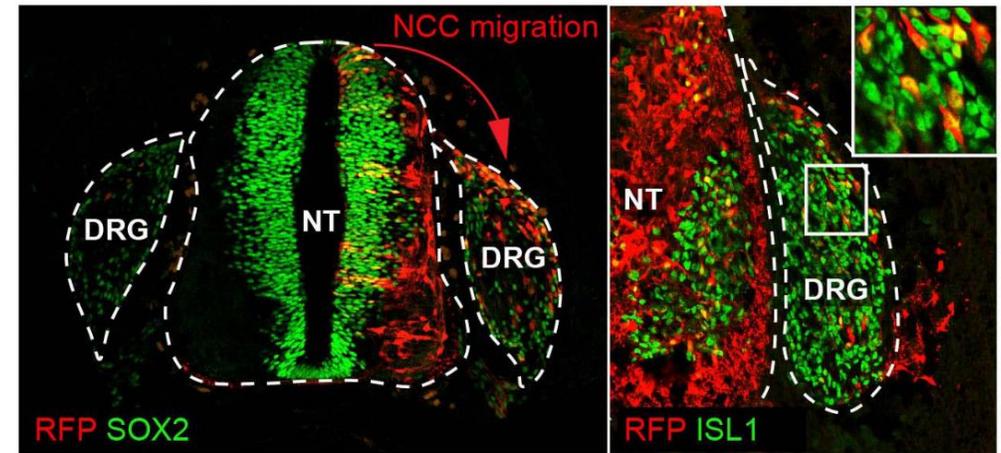
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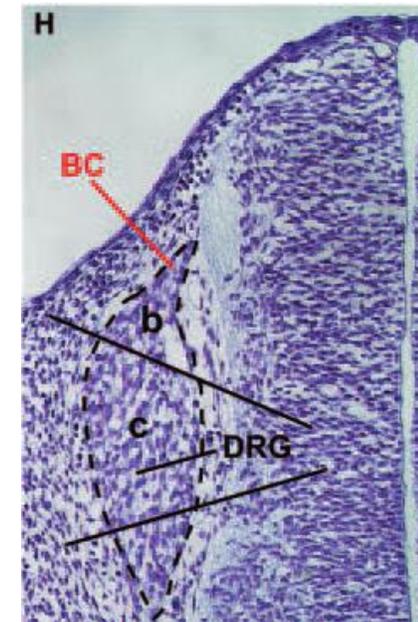
sensory

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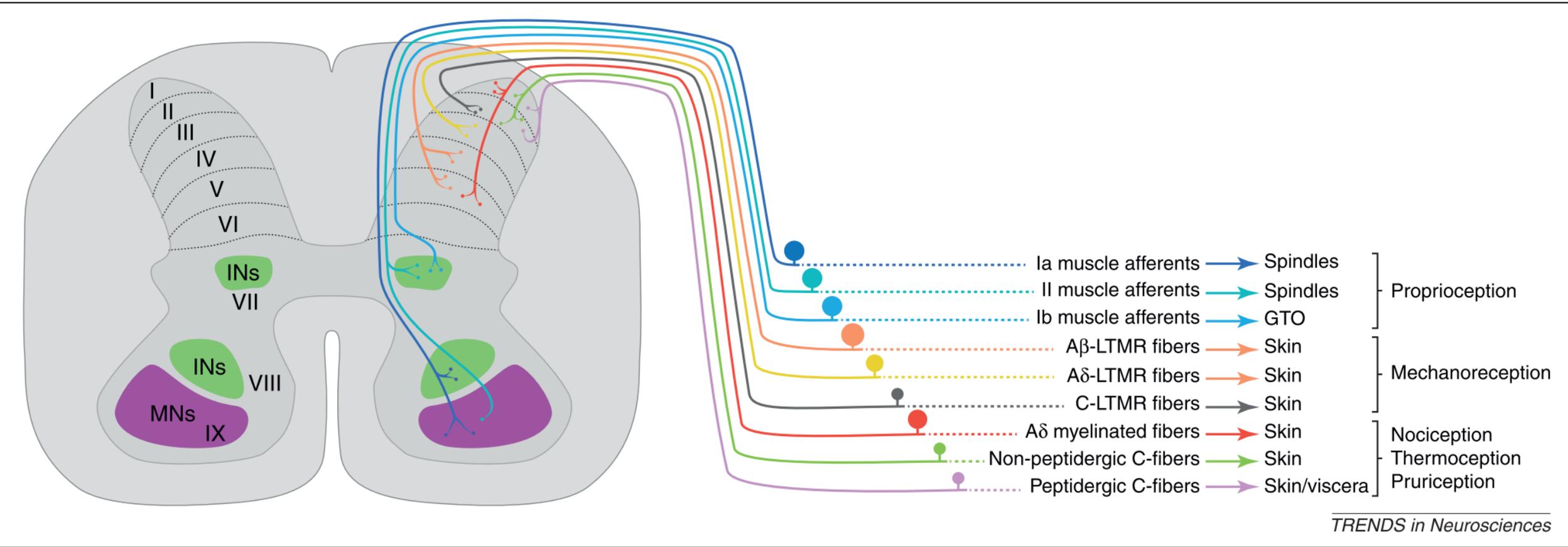
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derivates



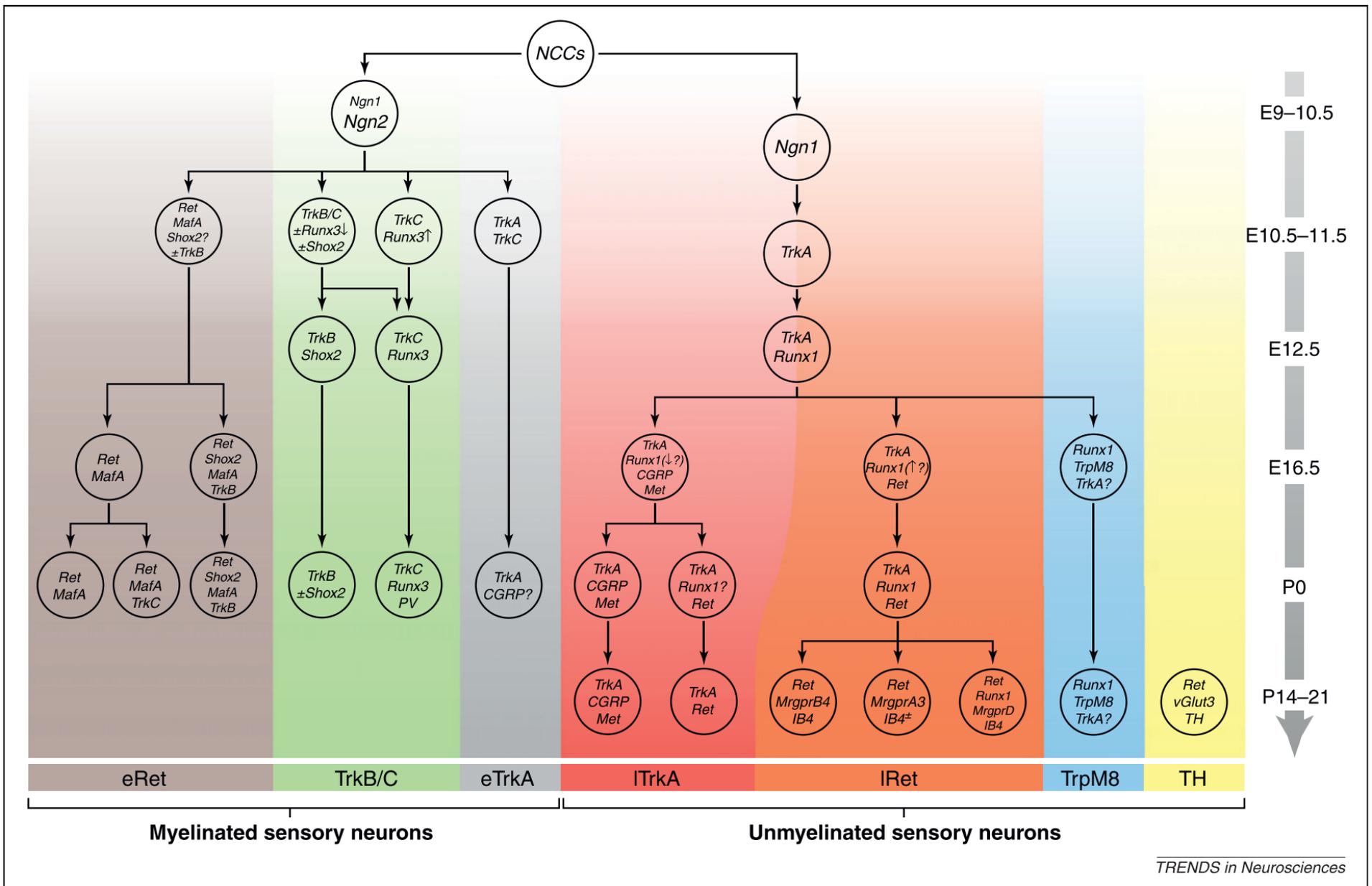
Soldatov, R. *et al.* Spatiotemporal structure of cell fate decisions in murine neural crest. *Science* (80-.). 364, (2019).



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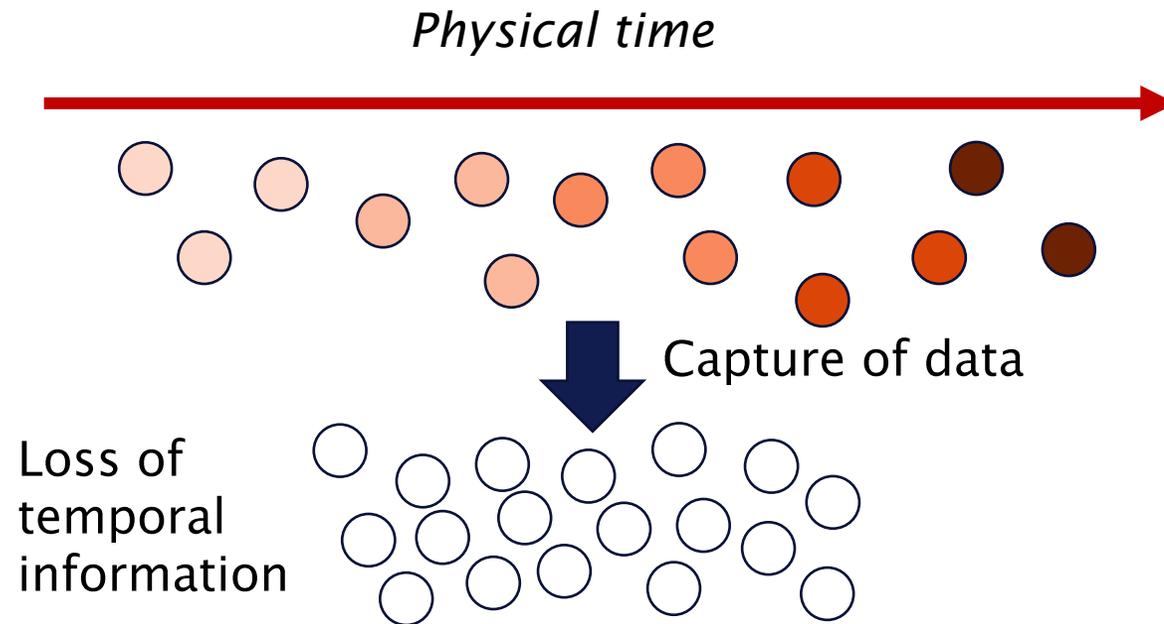
Lallemend, F. & Ernfors, P. Molecular interactions underlying the specification of sensory neurons



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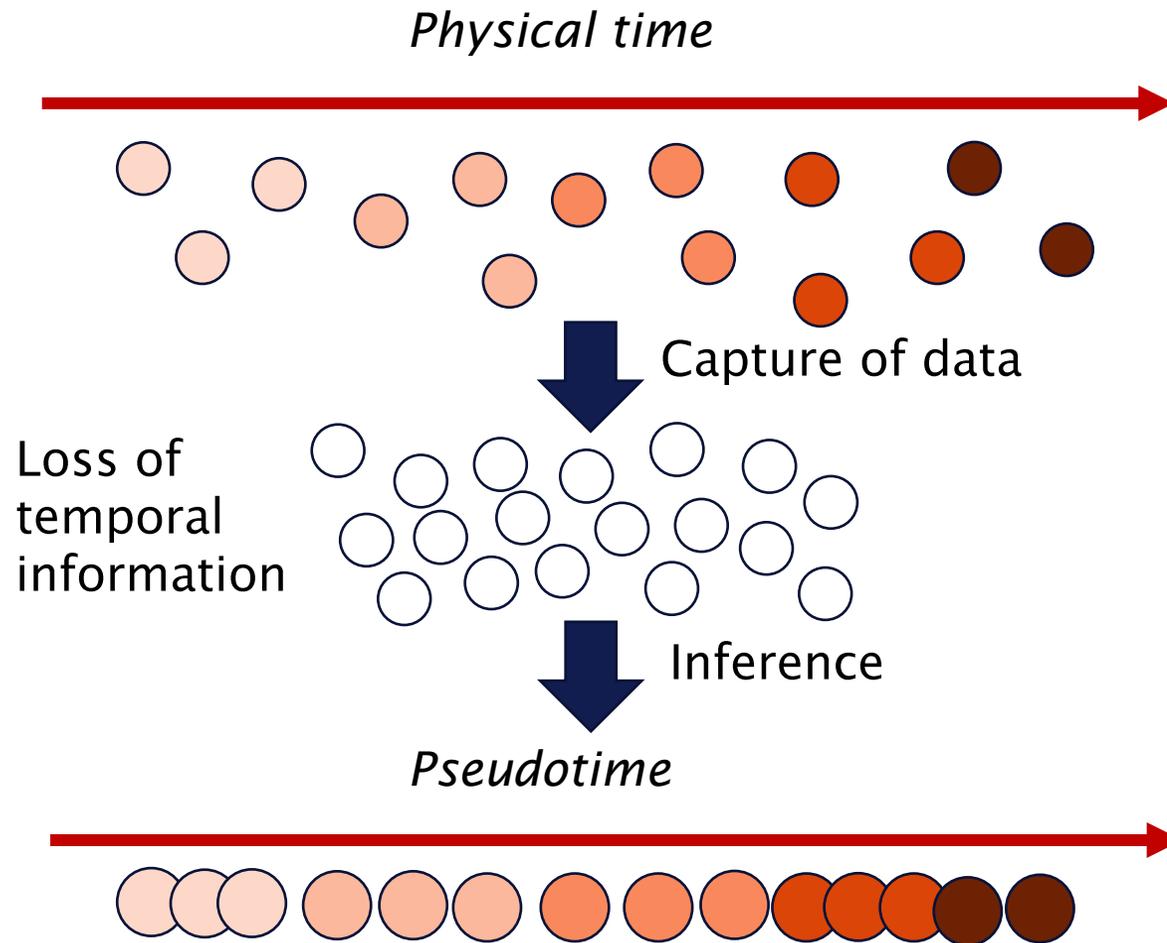
Pseudotime ordering

Ordering of the cell along a trajectory inferred in transcriptional space (Curve, Branching)



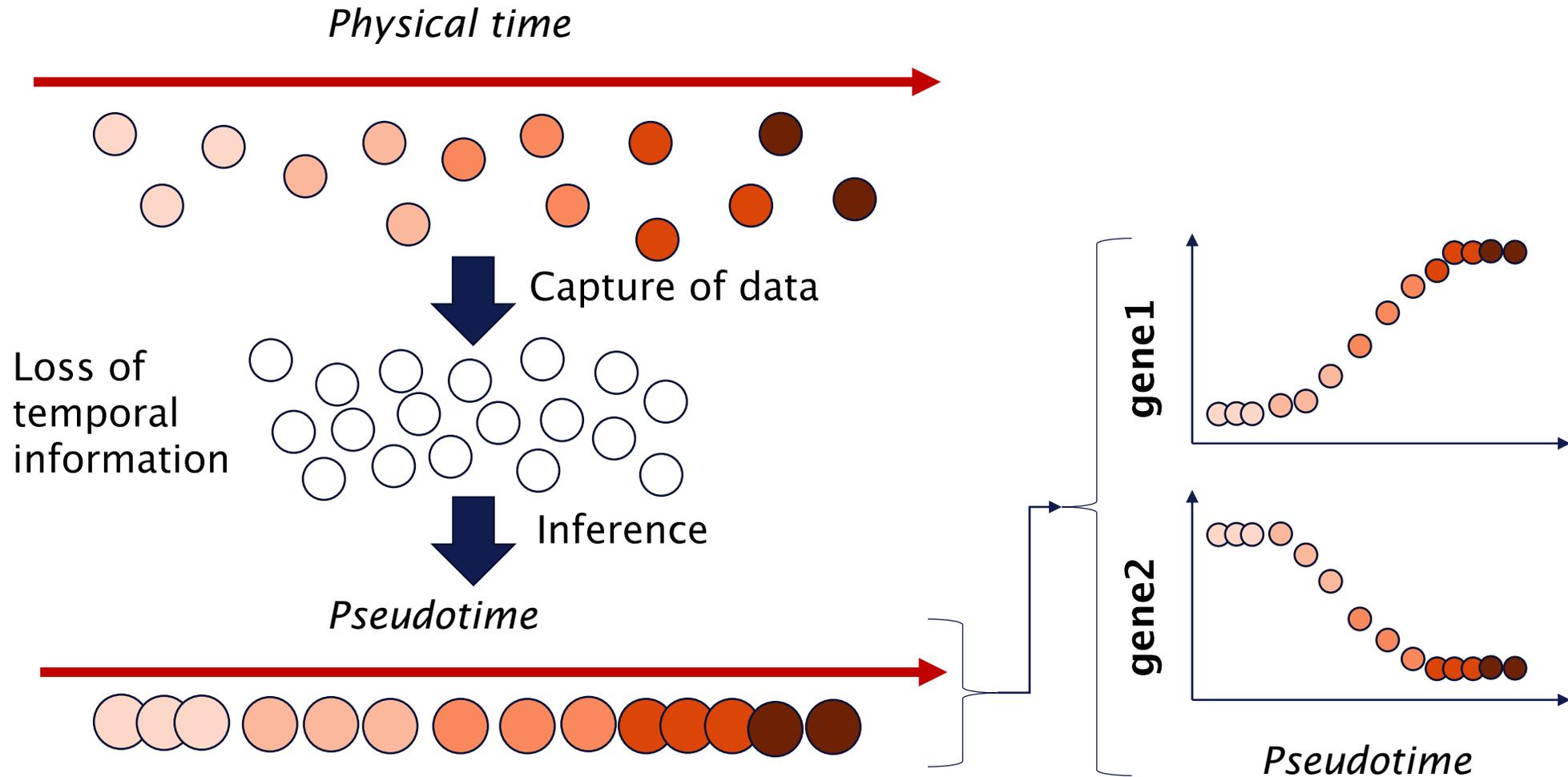
Pseudotime ordering

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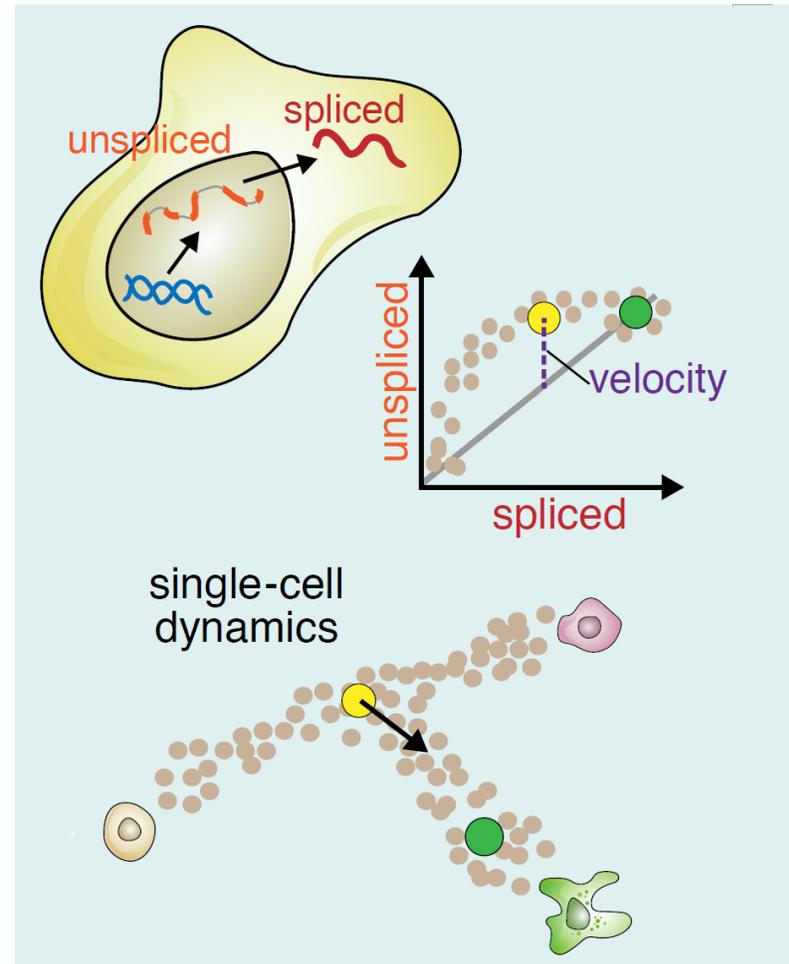
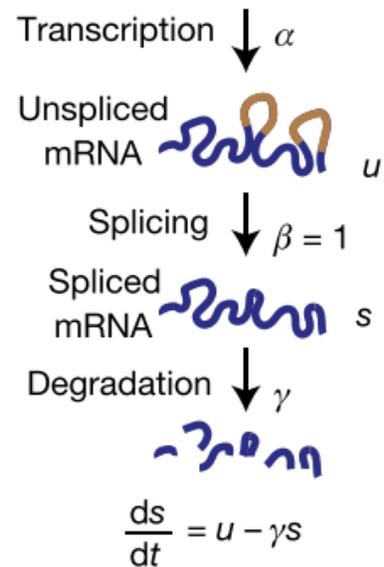
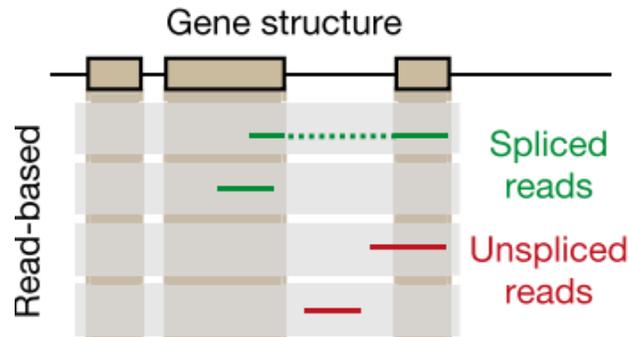


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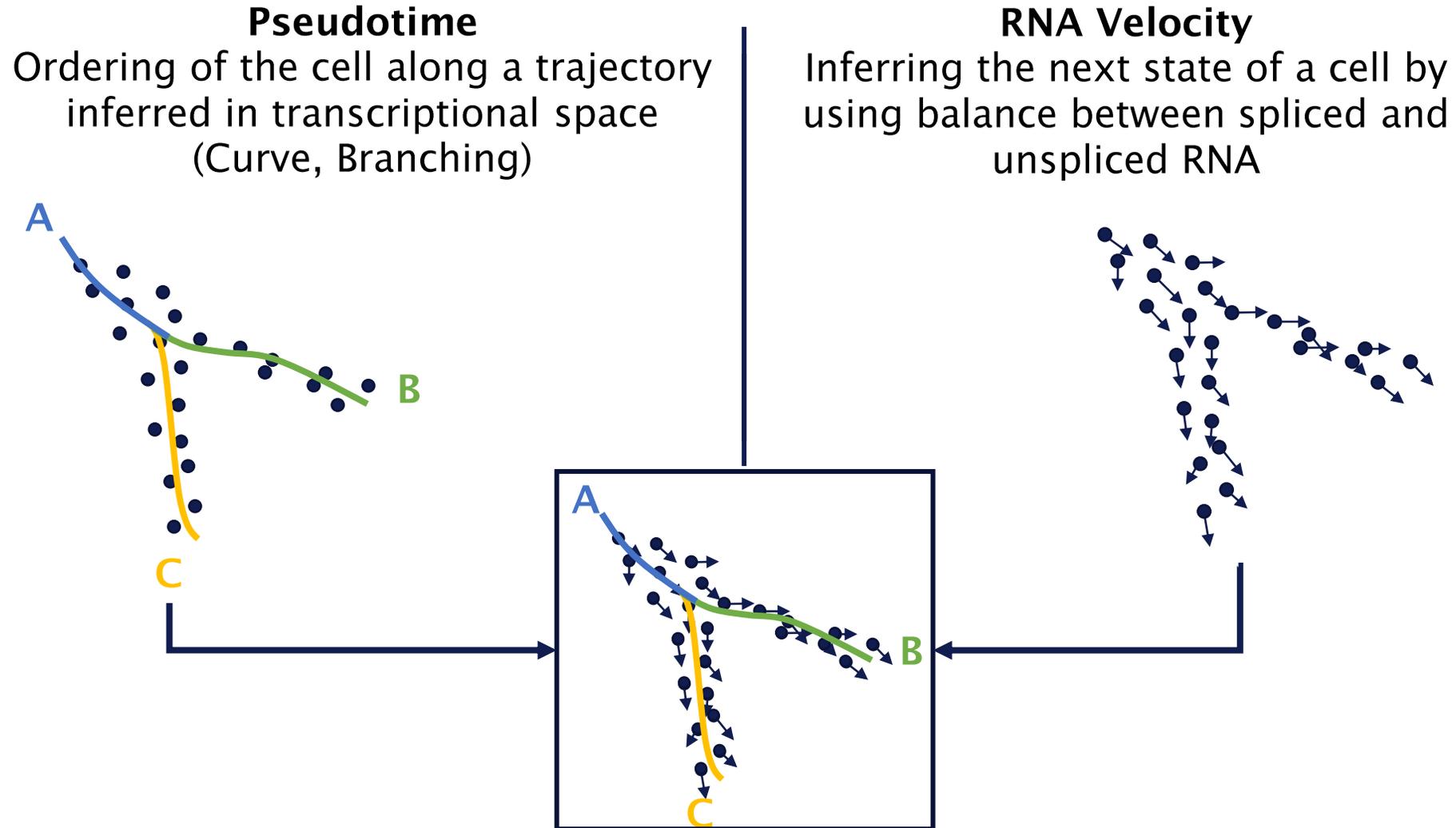


RNA velocity: inferring cell's future state



Edited from: Lederer, A. R. & La Manno, G. The emergence and promise of single-cell temporal-omics approaches. *Current Opinion in Biotechnology* (2020). doi:10.1016/j.copbio.2019.12.005

Uncovering trajectories: two complementary methods



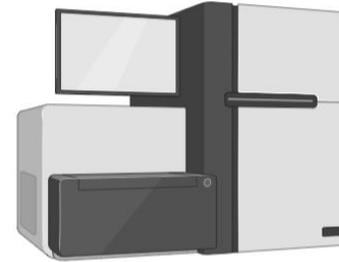
Single-cell sequencing strategy

Cell selection

- Brachial DRGs**
Isl1Cre (E10.5)
Ntrk3Cre (E11.5-12.5)
- Whole Trunk**
Wnt1Cre (E9.5-10.5)
- Above Otic vesicle**
Plp1CreERT2 (E12.5)



FACS



SciLifeLab

Dissociated cells

Reverse transcription of mRNA

cDNA amplification and sequencing

Gene x cell matrix

Dimensionality reduction

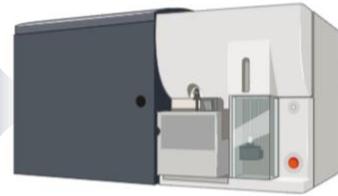
Trajectory inference

Ordering of cells along trajectory
(a cell = a pseudotime value)

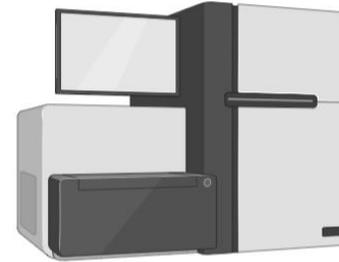
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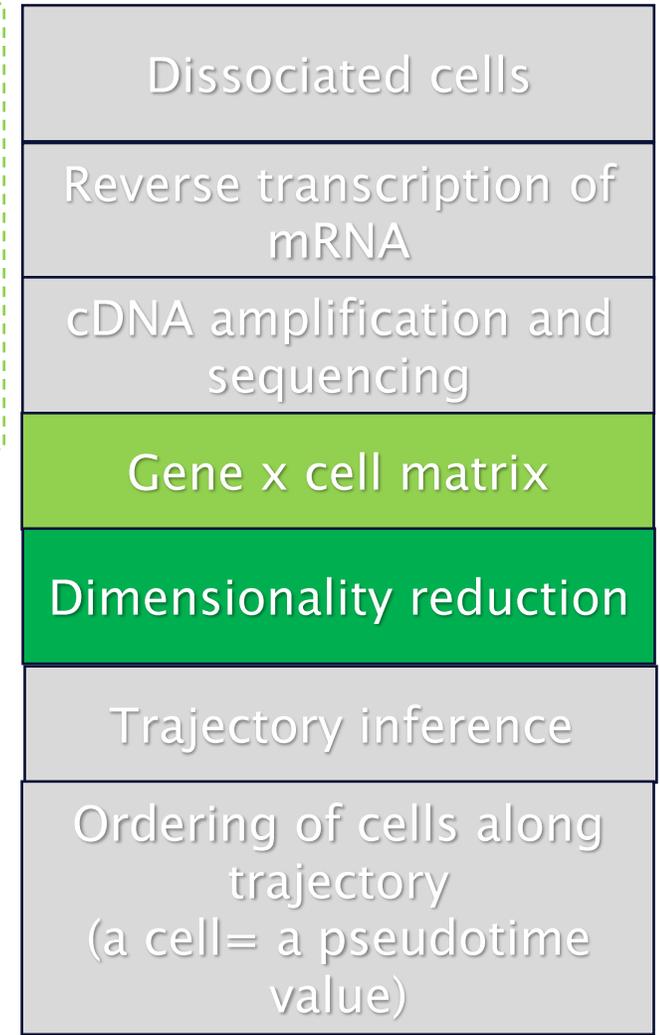
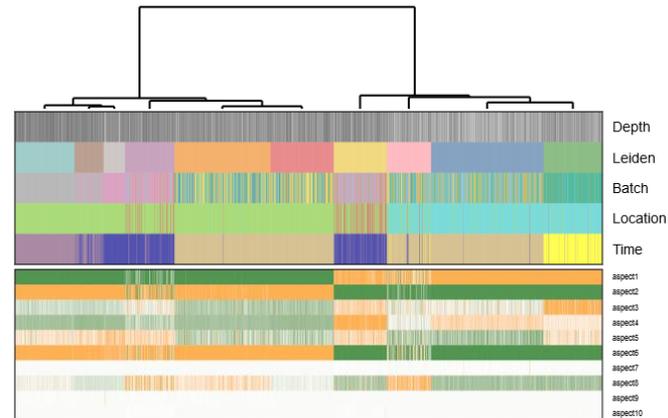
FACS



SciLifeLab



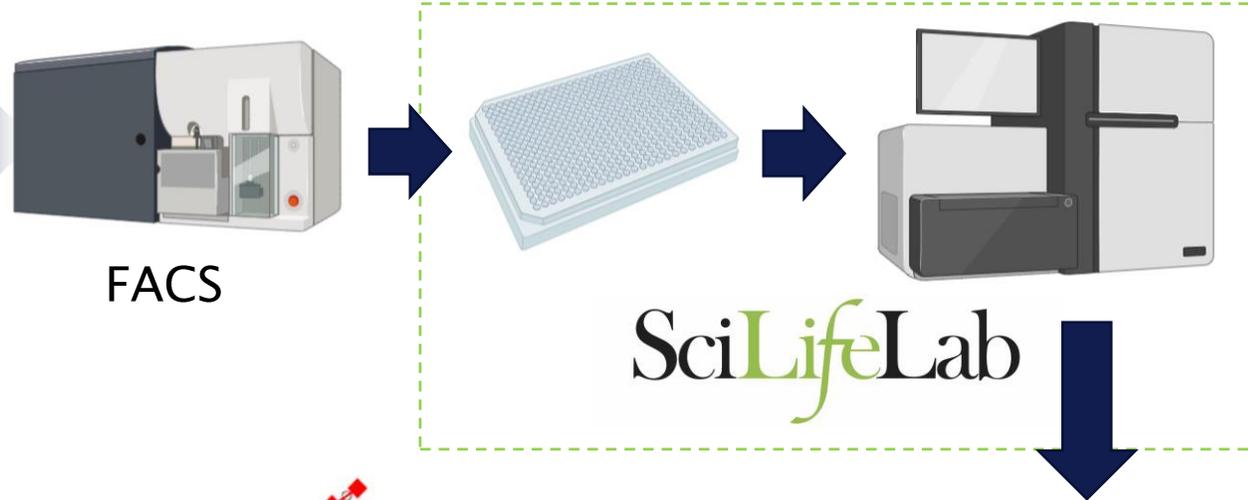
Processing data using
Pagoda2 and scvelo



Single-cell sequencing strategy

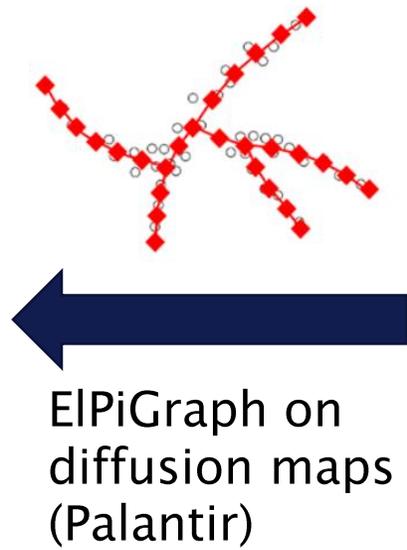
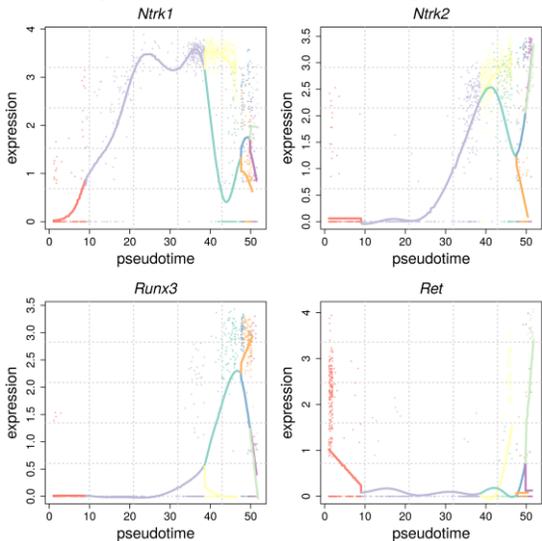
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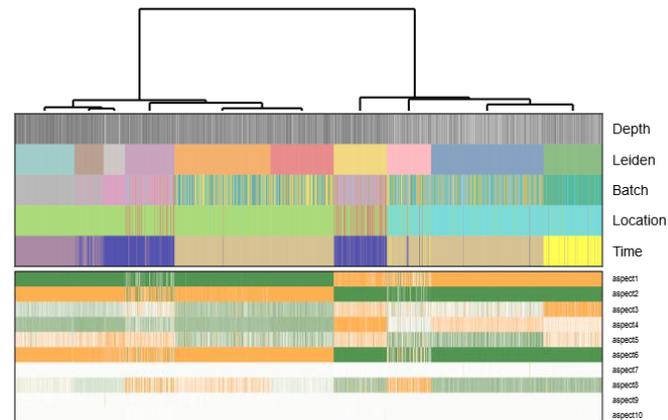


Dissociated cells
Reverse transcription of mRNA
cDNA amplification and sequencing
Gene x cell matrix
Dimensionality reduction
Trajectory inference
Ordering of cells along trajectory (a cell = a pseudotime value)

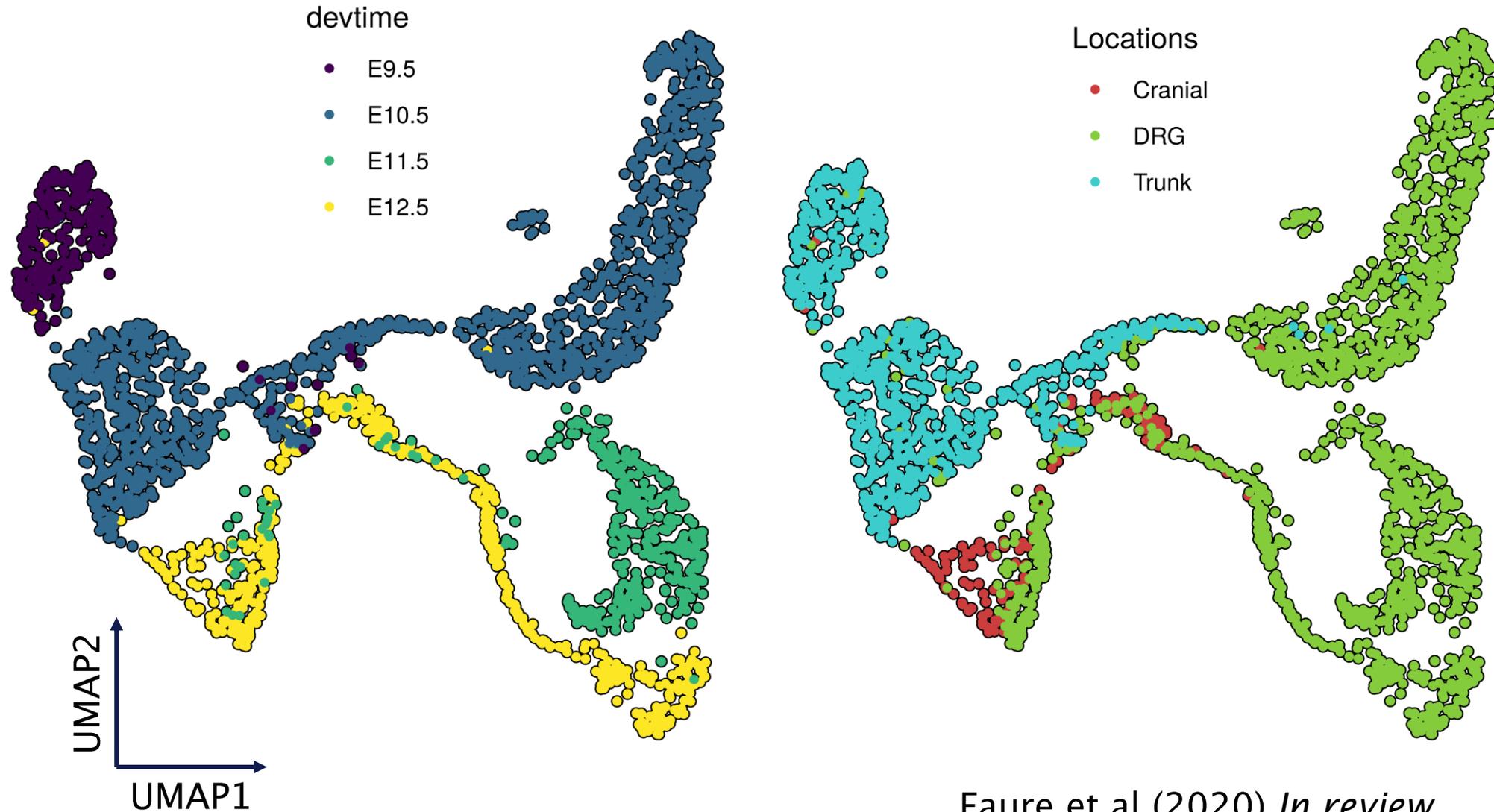
Dynamical gene Expression analysis



Processing data using Pagoda2 and scvelo

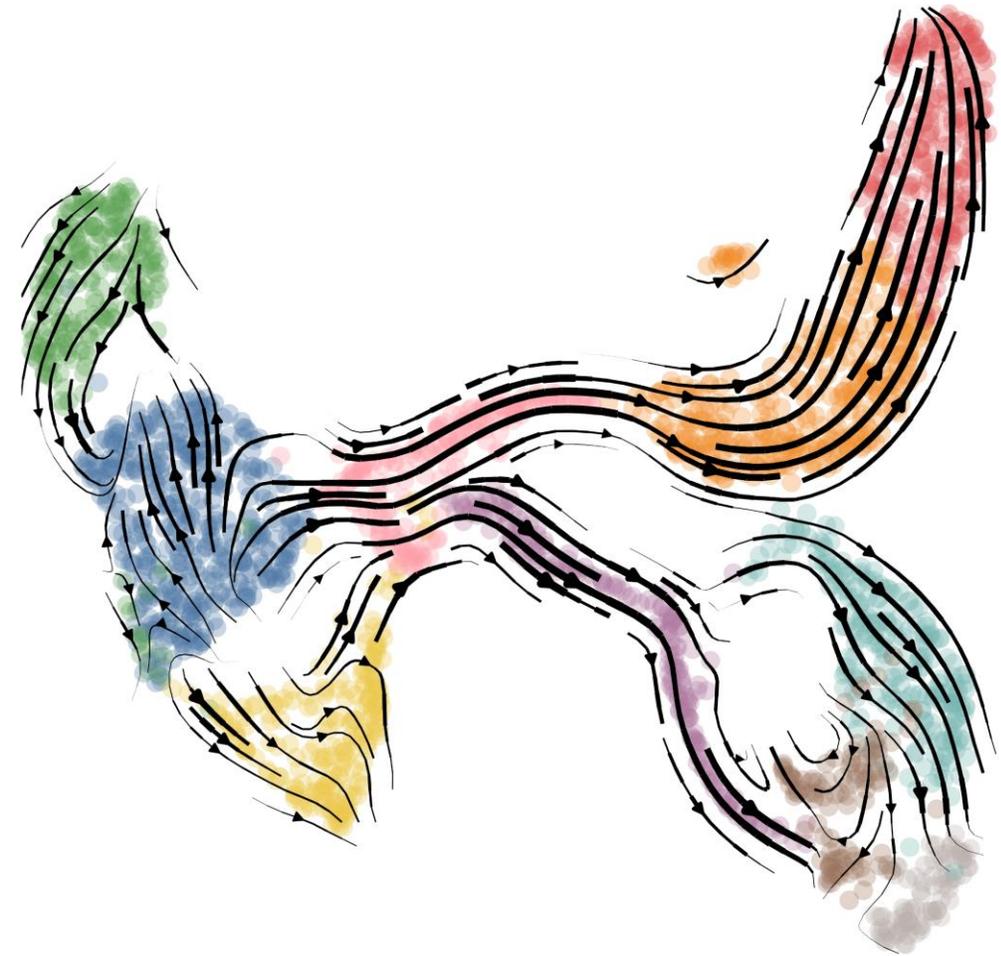
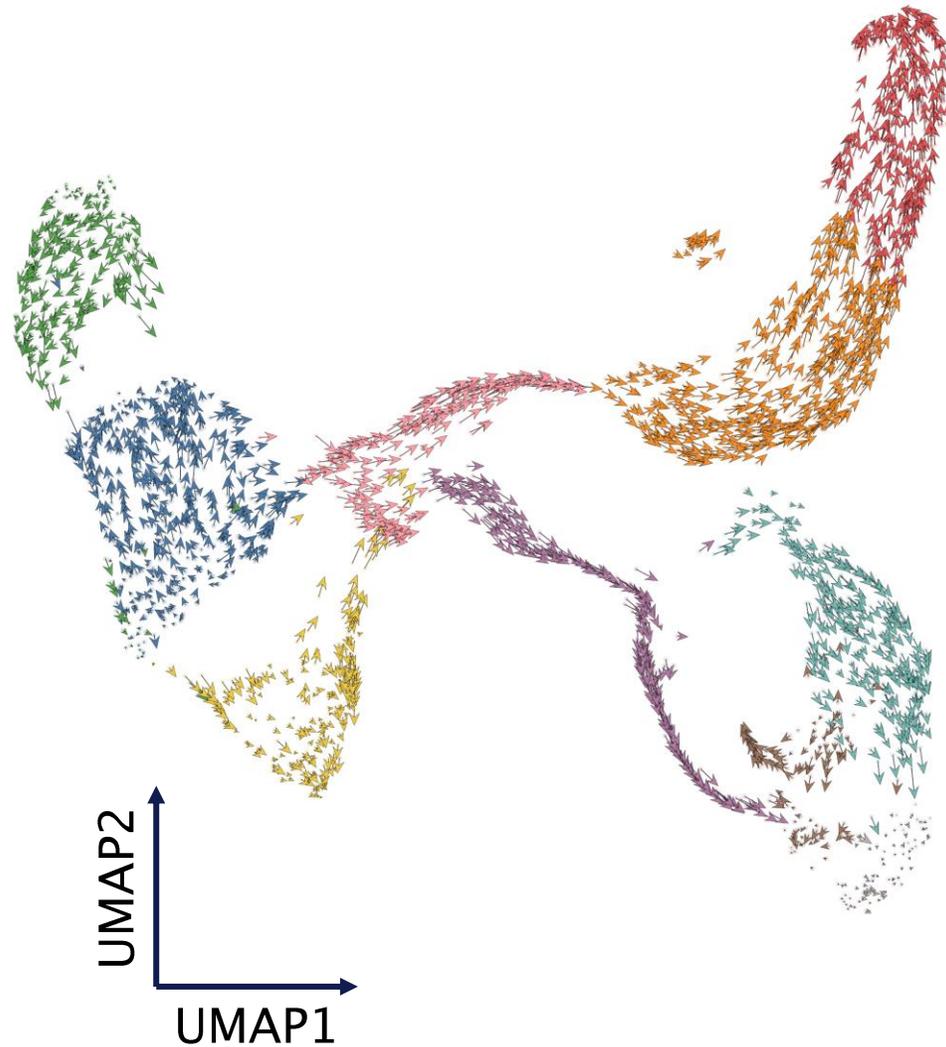


Overview of the sequencing data



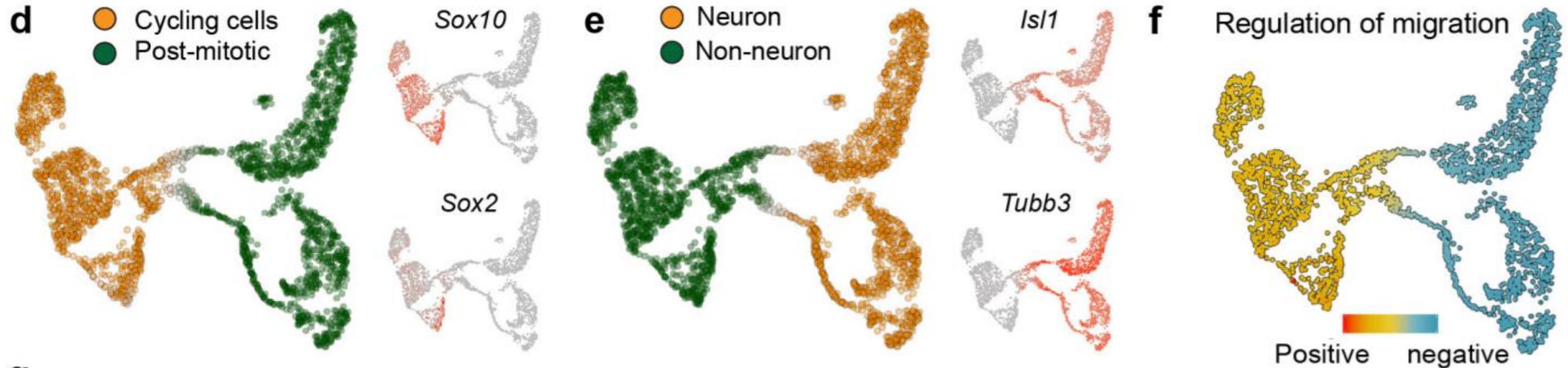
Faure et al (2020) *In review*

Overview of the sequencing data



Faure et al (2020) *In review*

Main sources of variation and relevant biological aspects



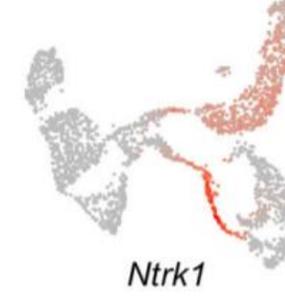
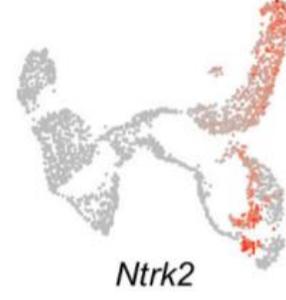
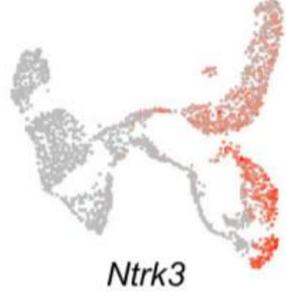
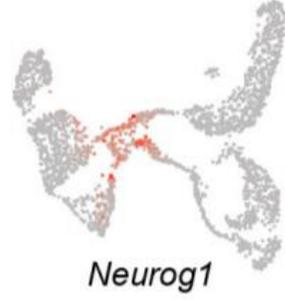
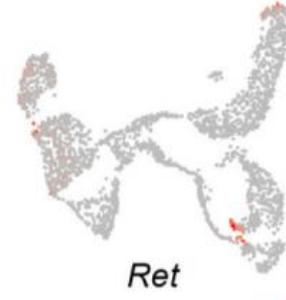
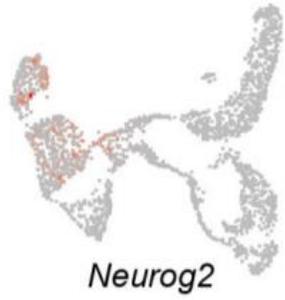
Faure et al (2020) *In review*

Neurogenic niche

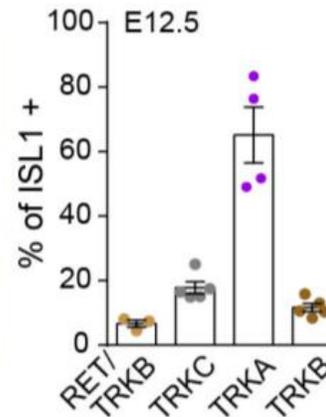
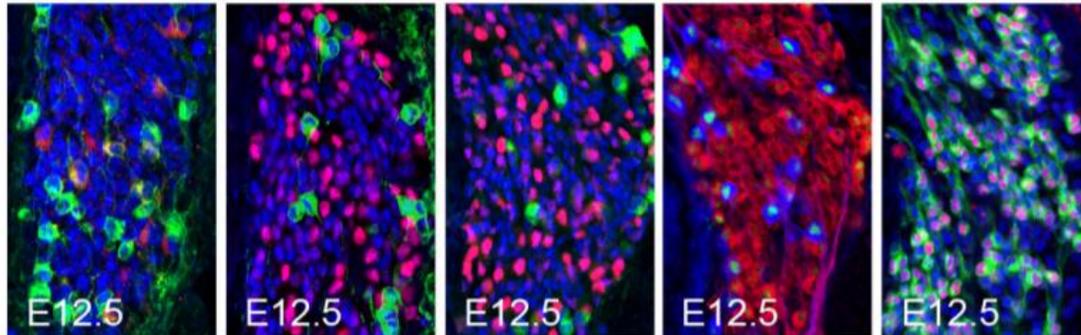
Proprioceptors

Mechanoreceptors

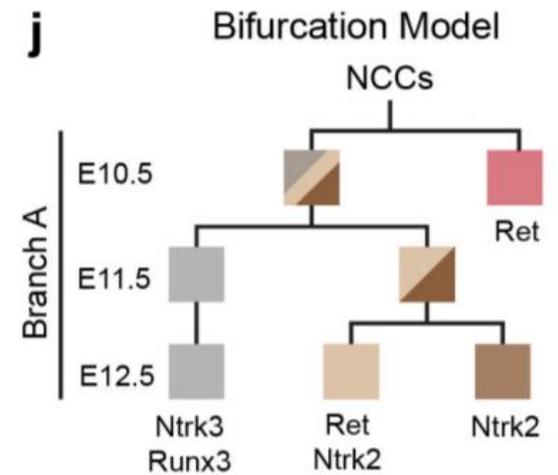
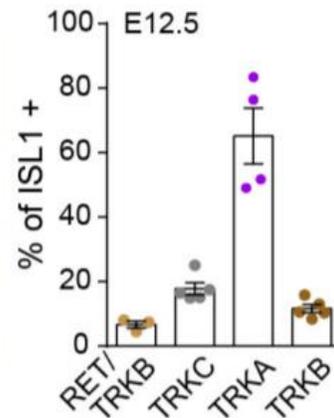
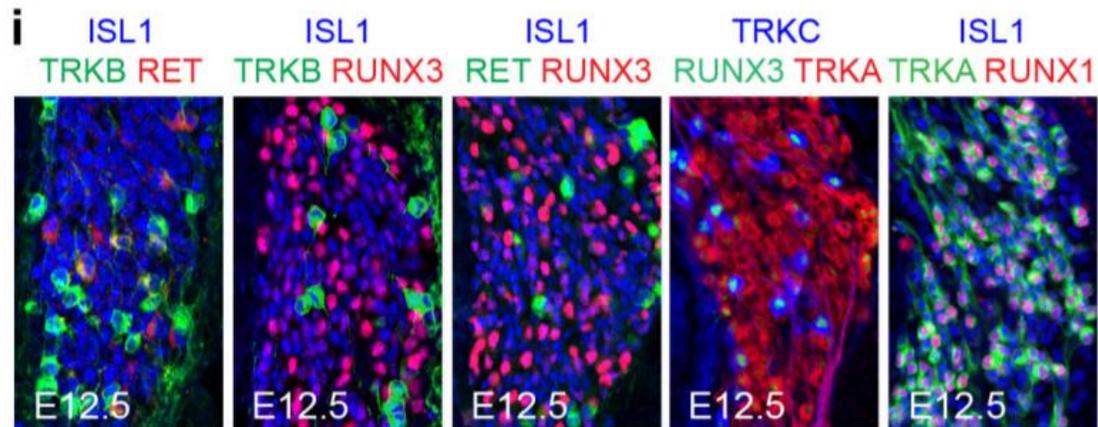
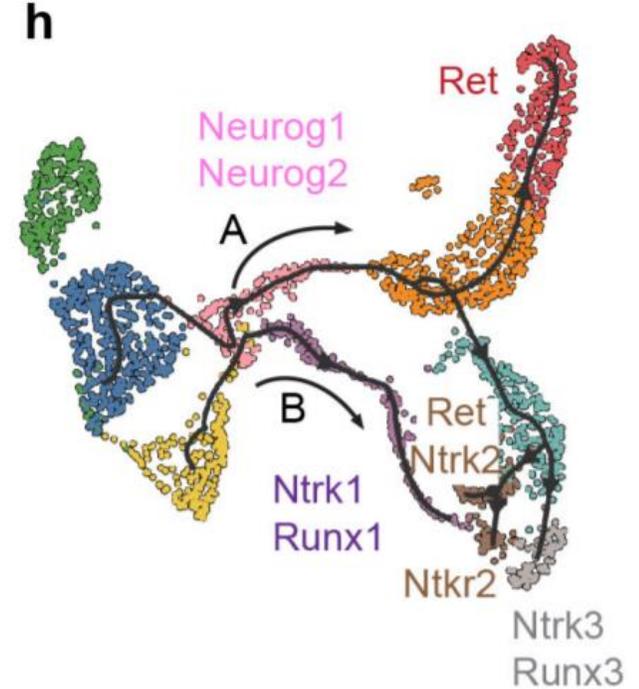
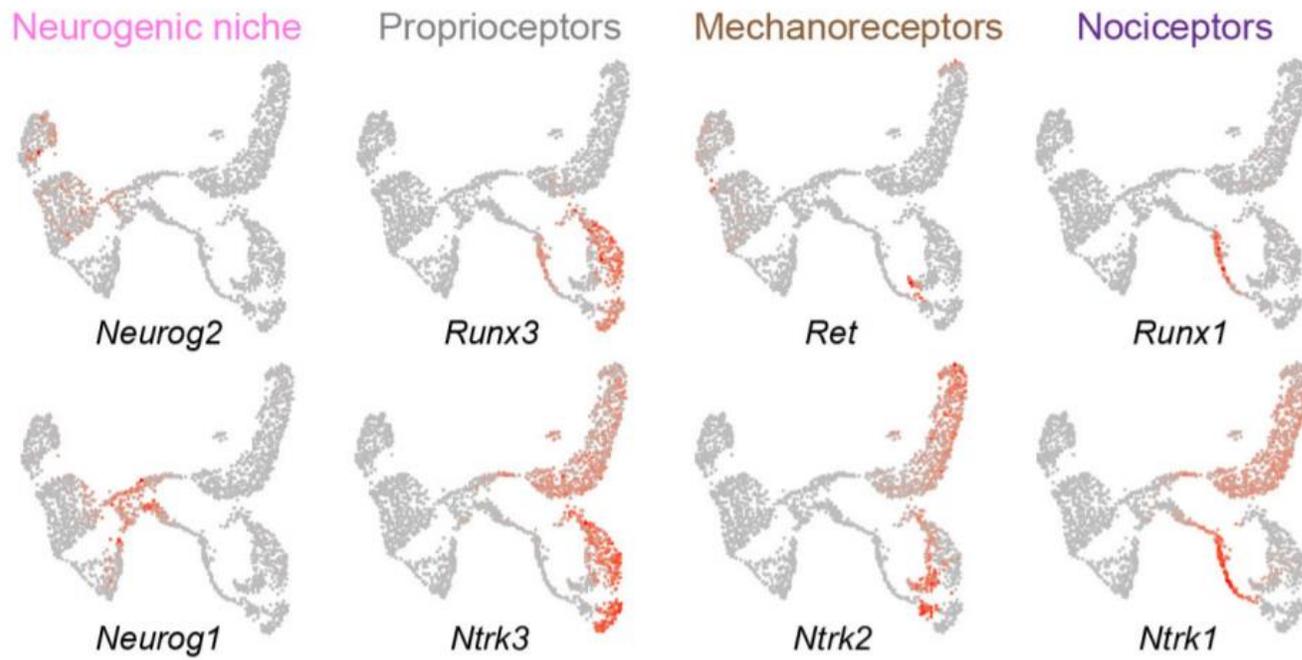
Nociceptors



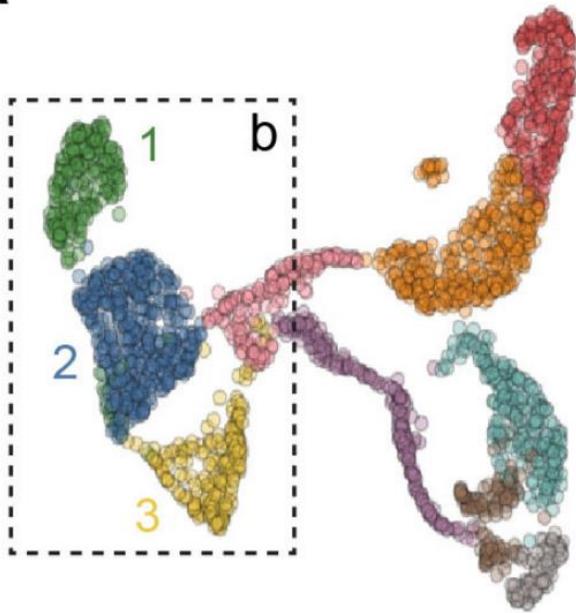
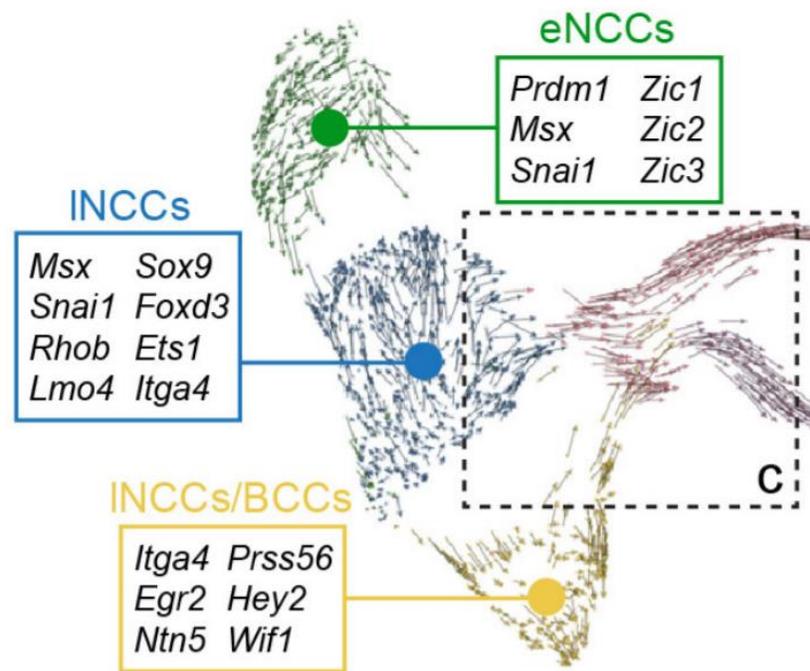
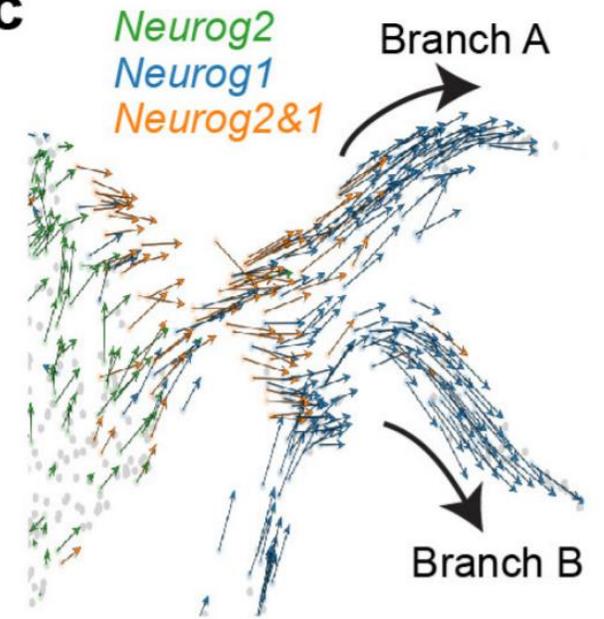
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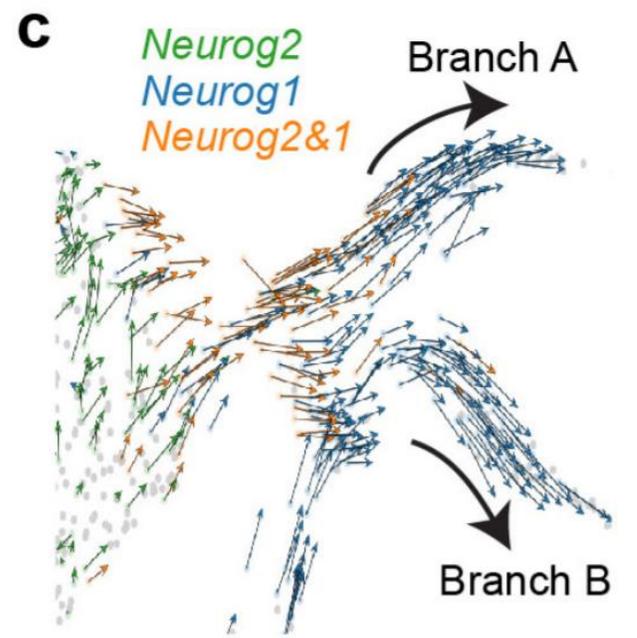
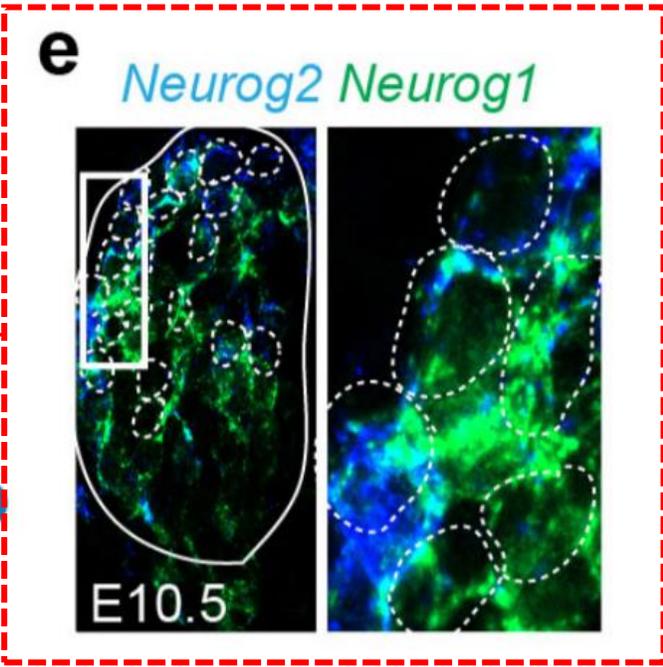
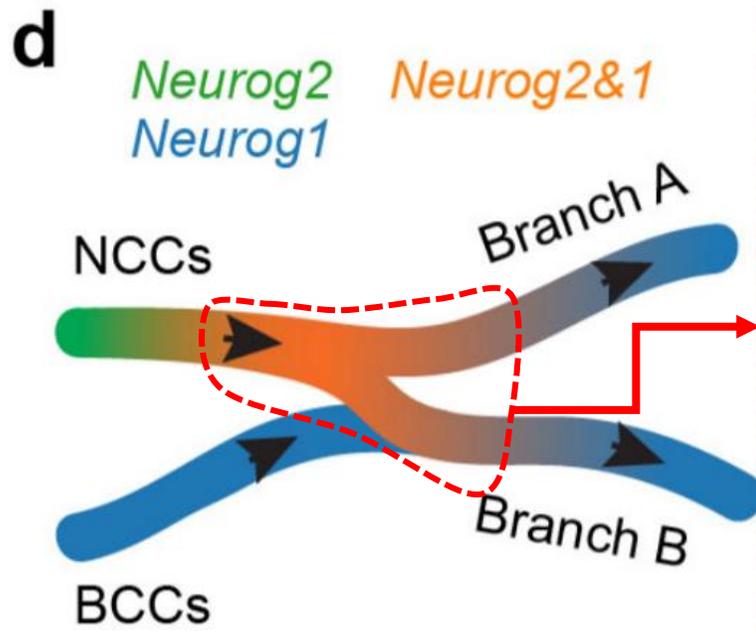


Faure et al (2020) *In review*

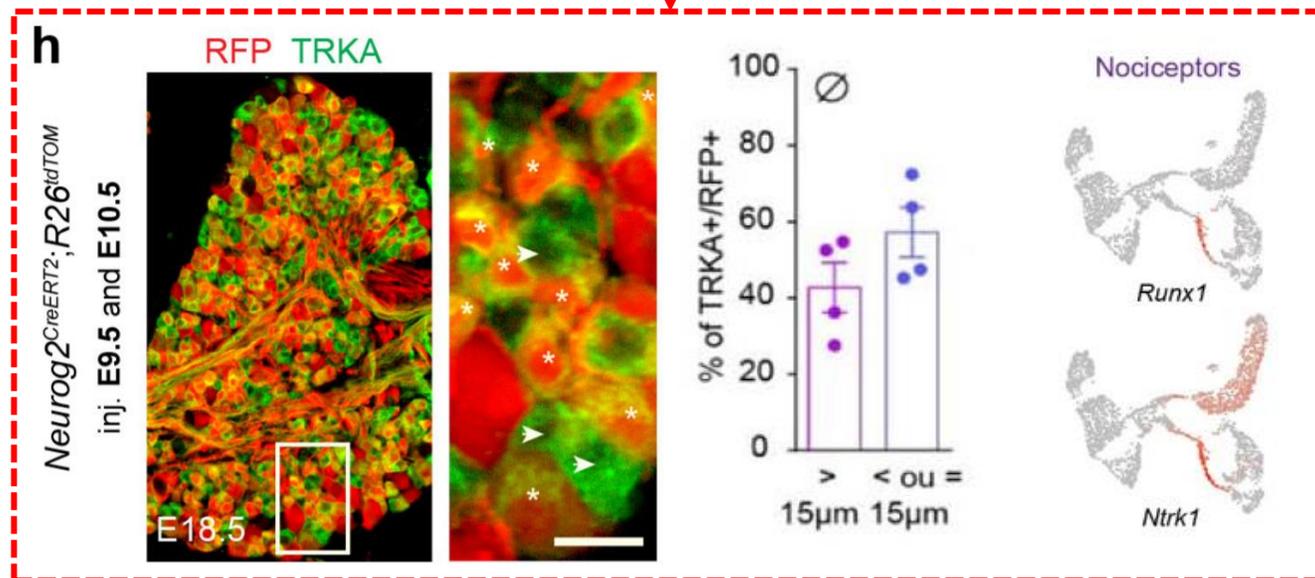
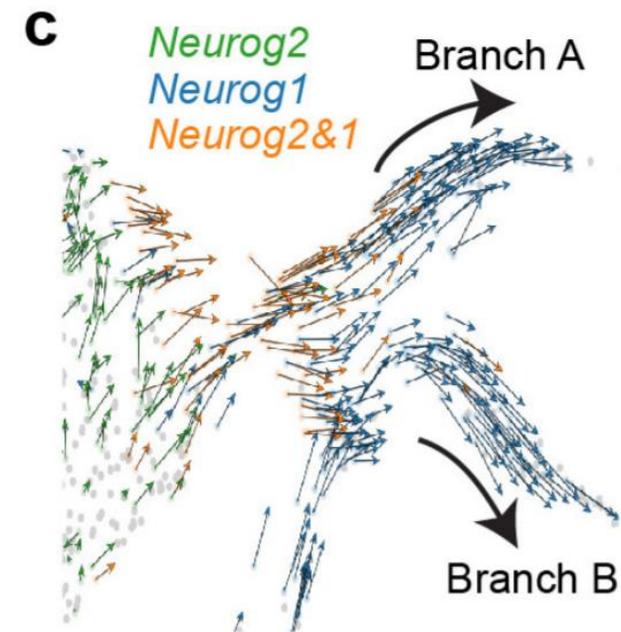
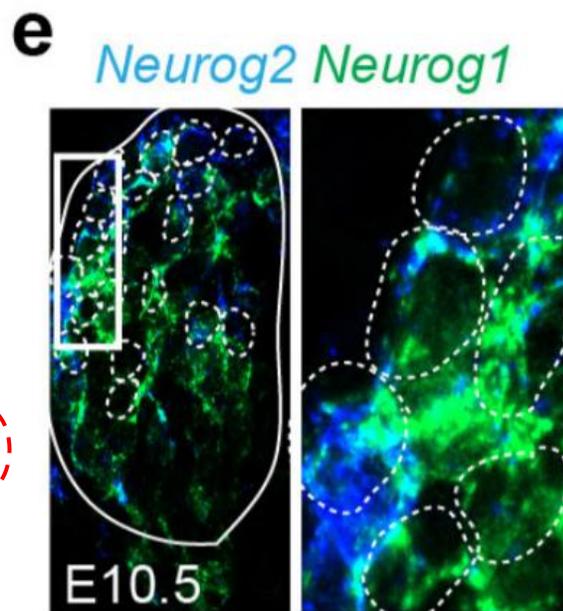
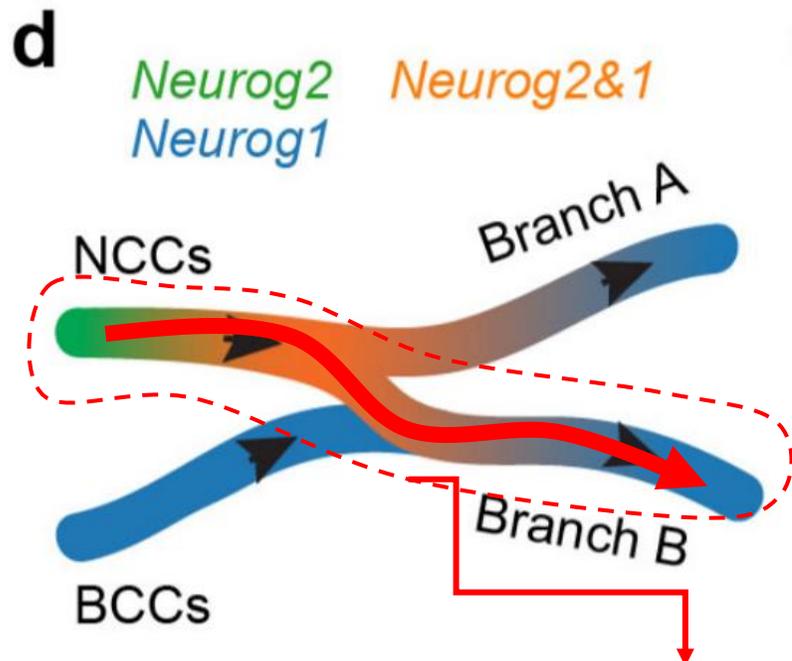


Faure et al (2020) *In review*

a**b****c**Faure et al (2020) *In review*

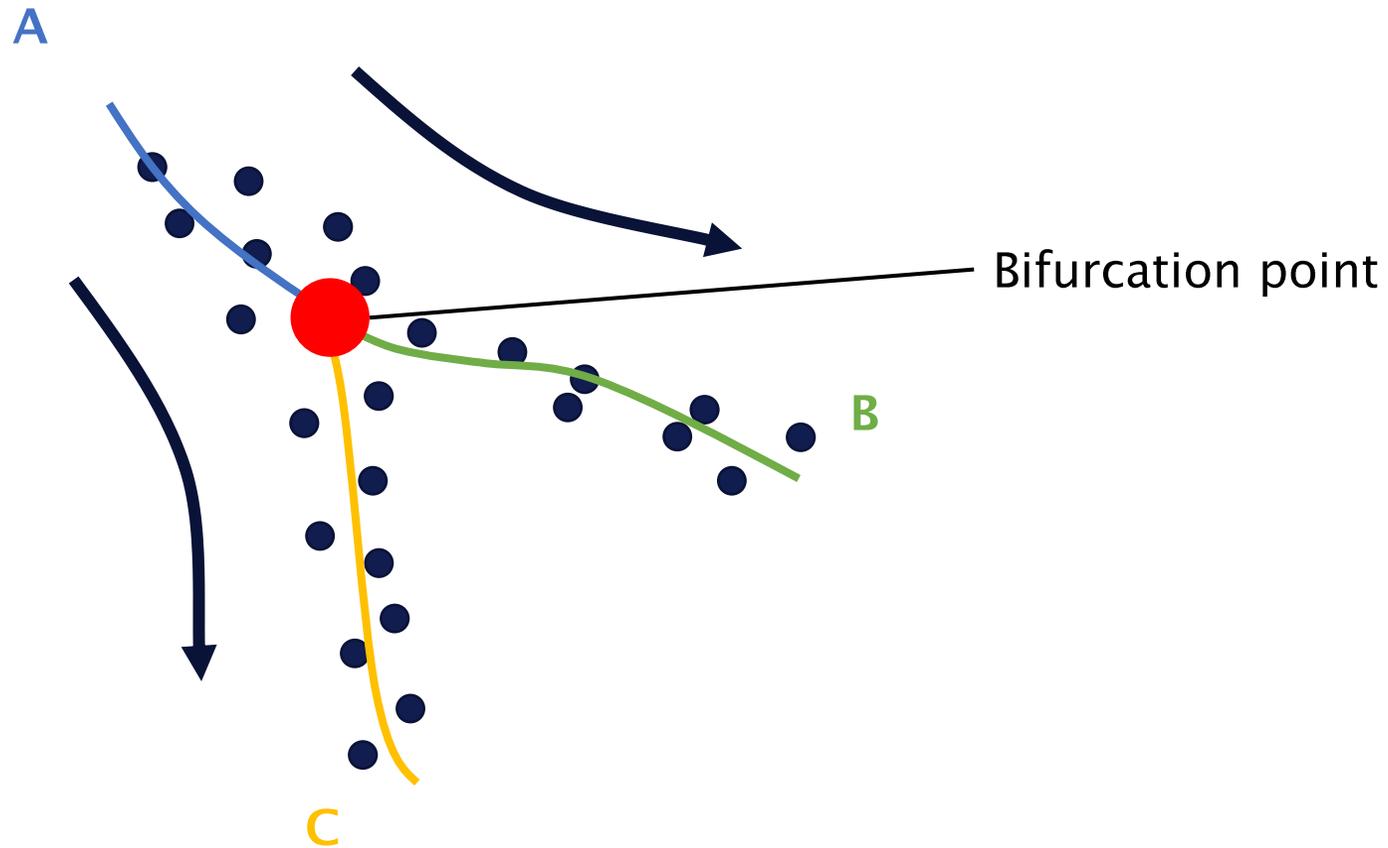


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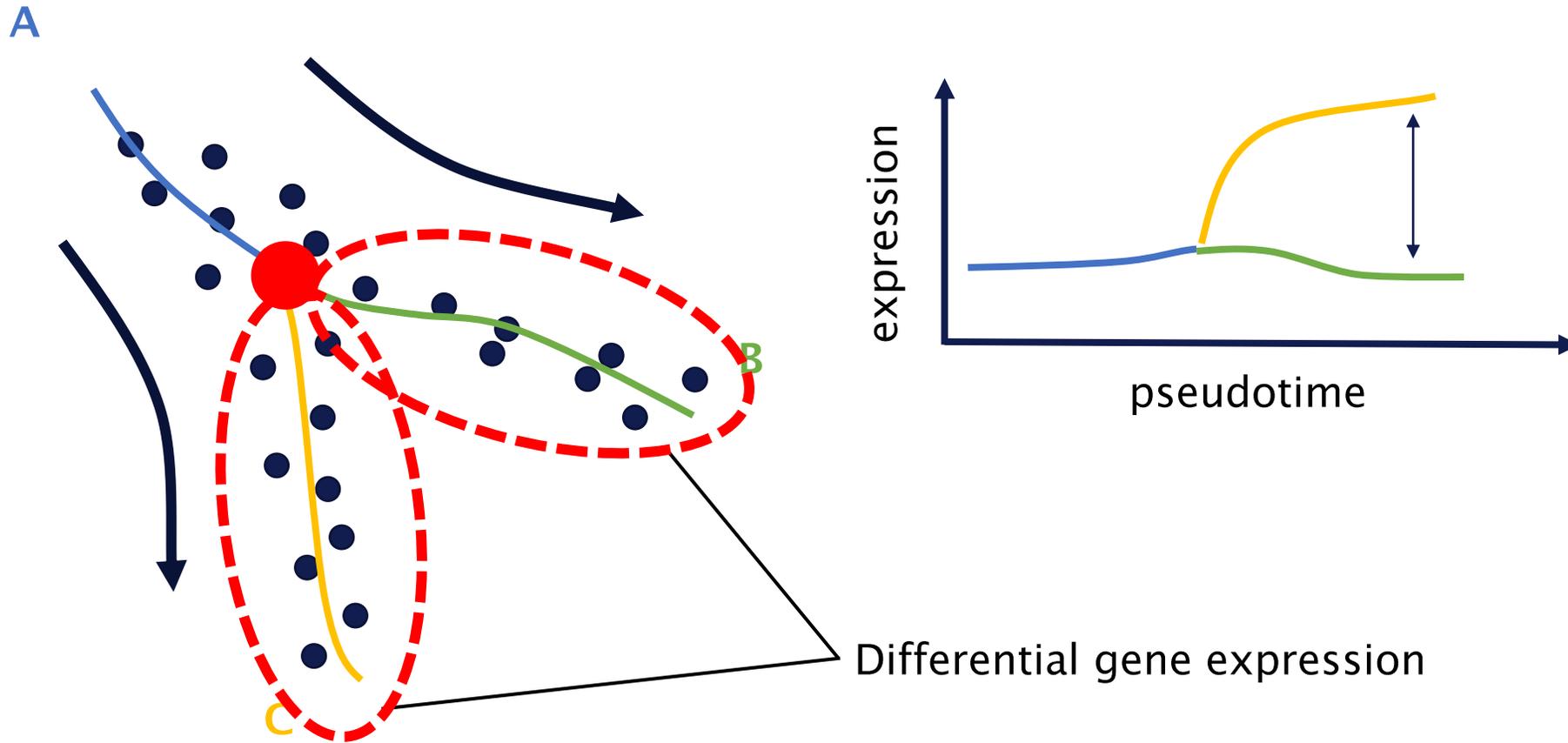


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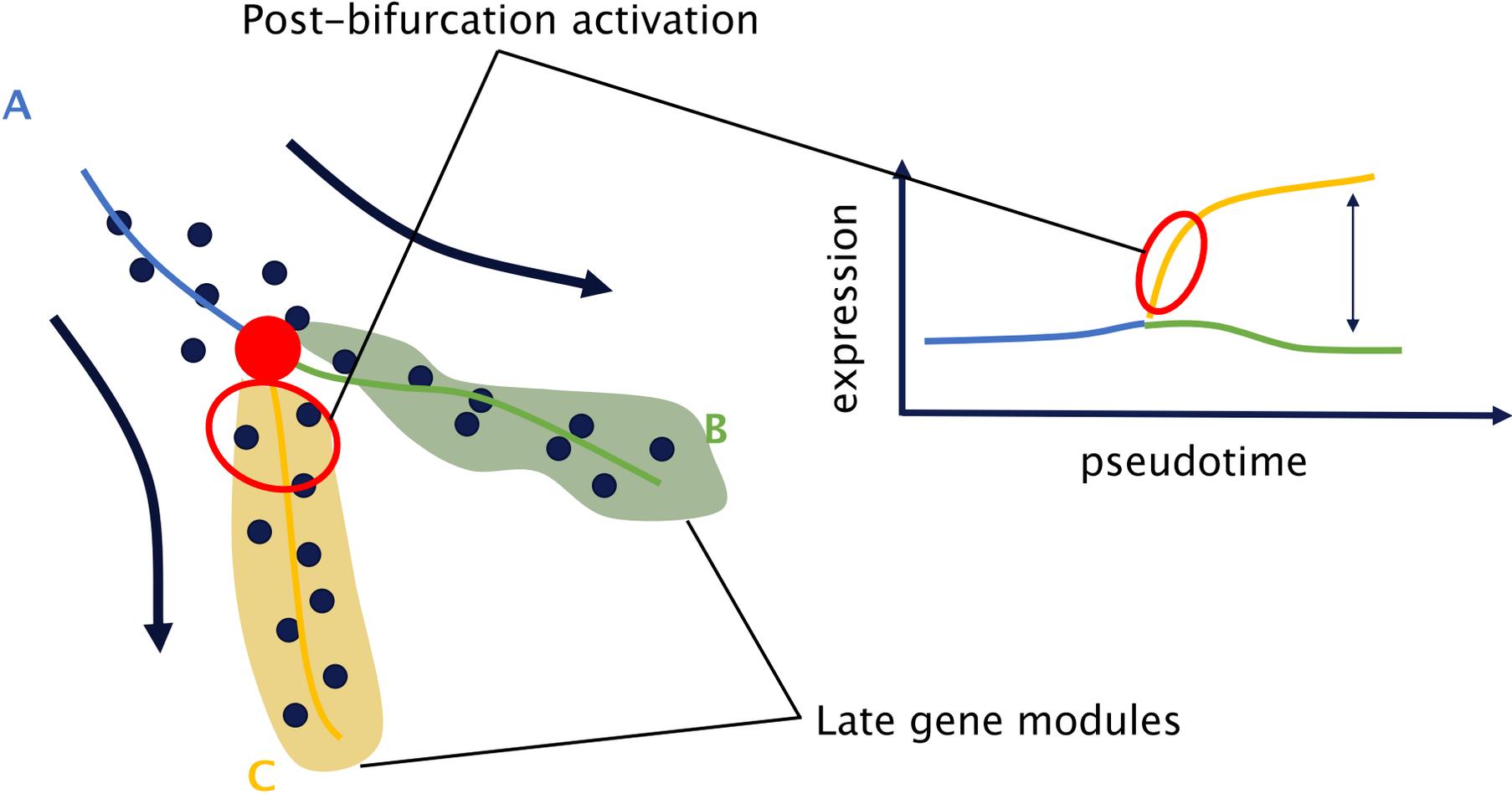
Bifurcation analysis



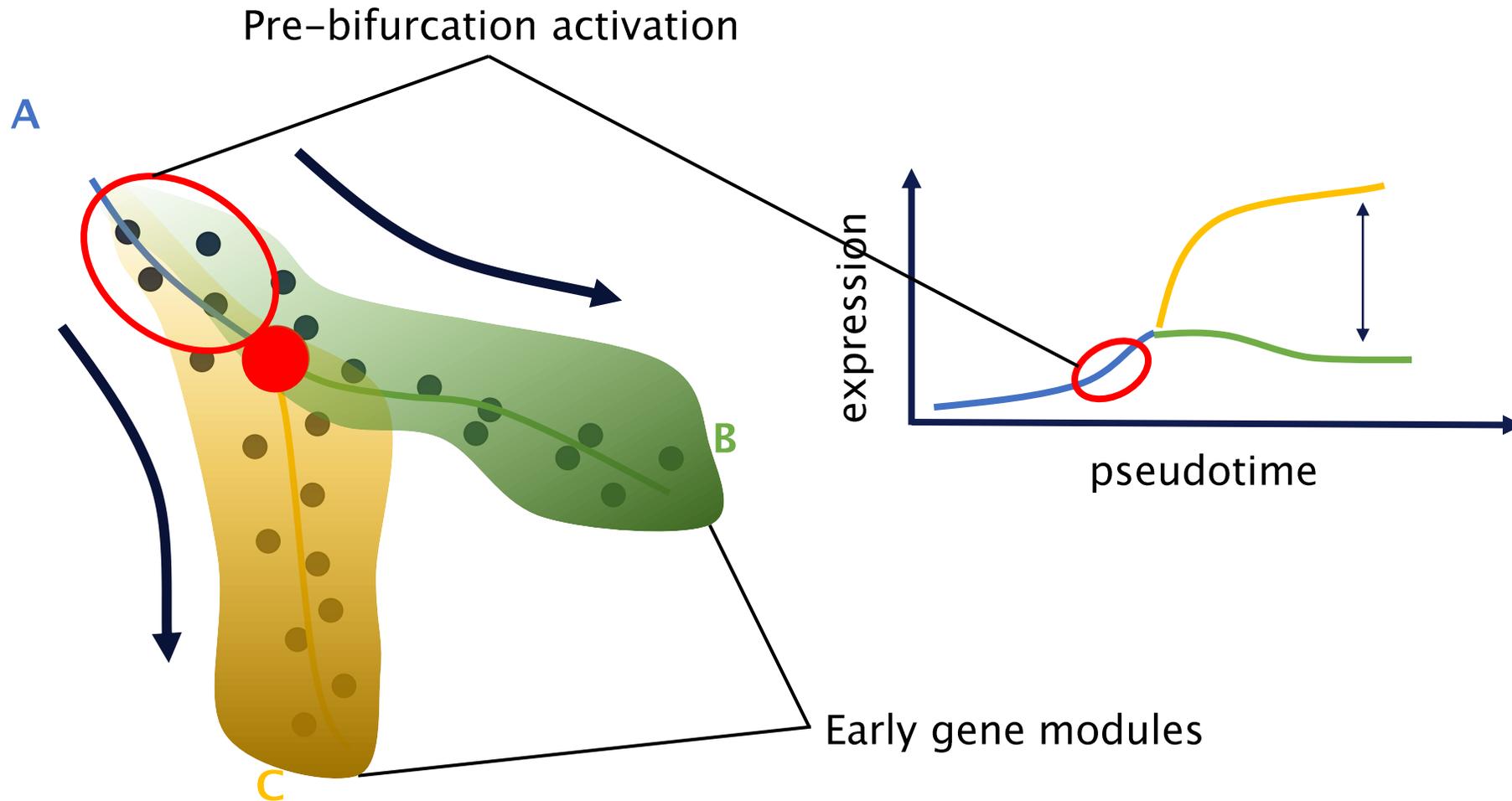
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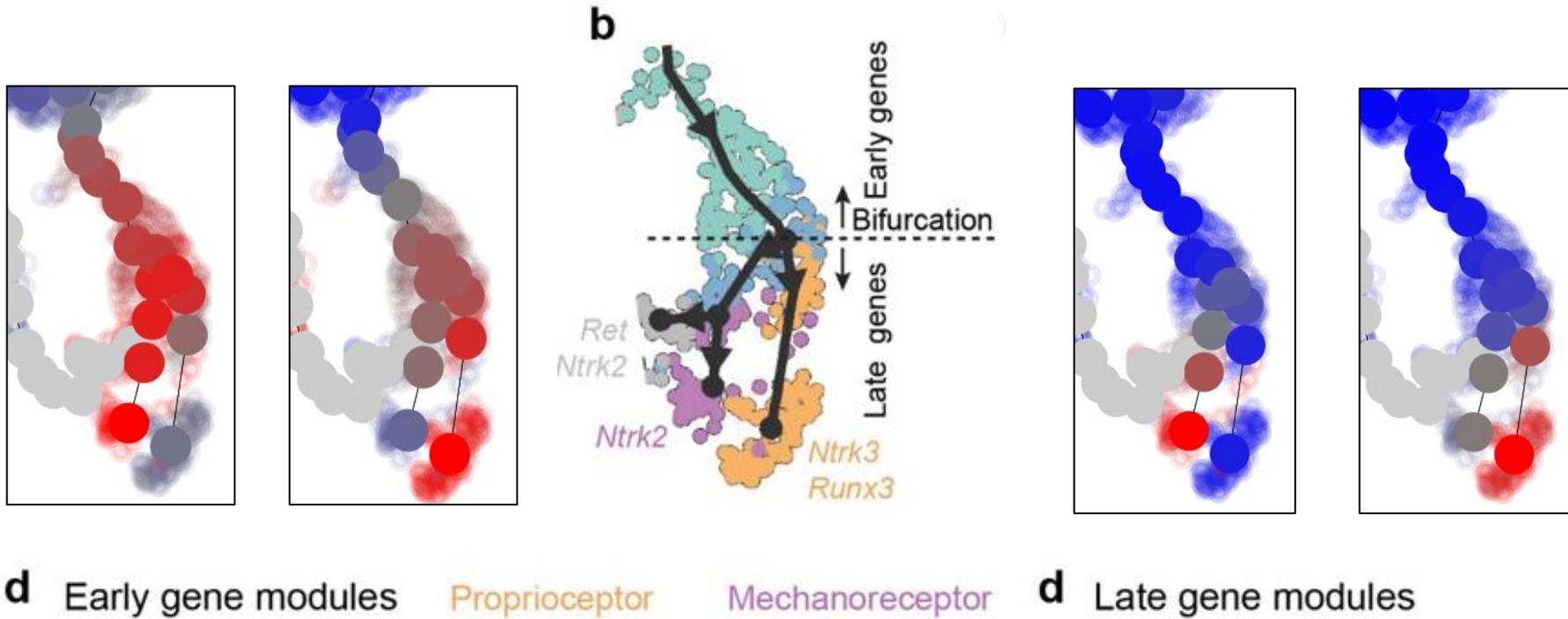


Bifurcation analysis

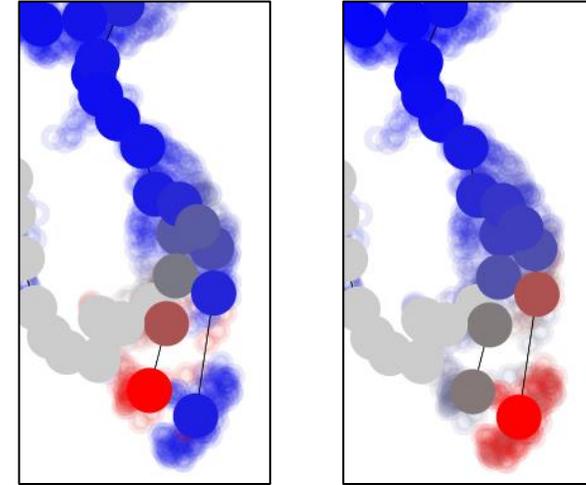
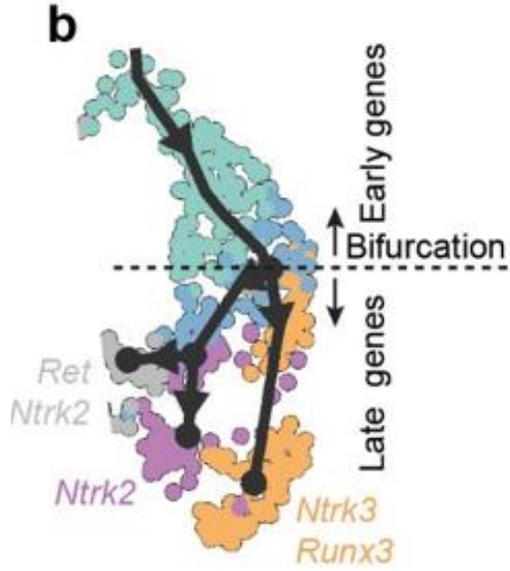
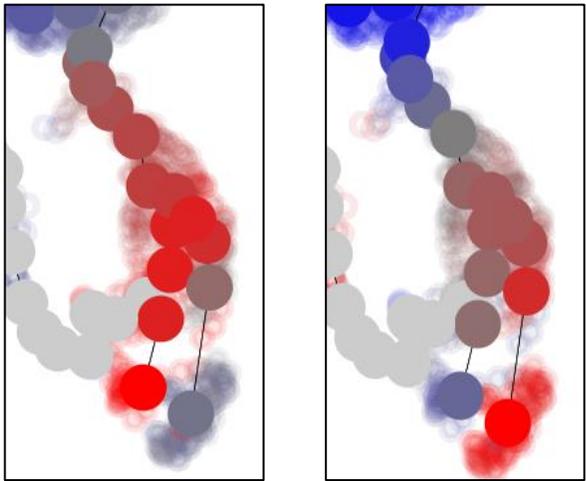


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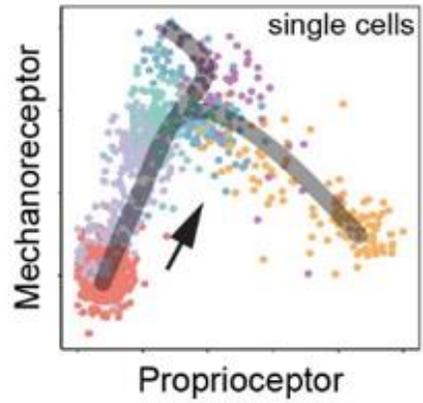




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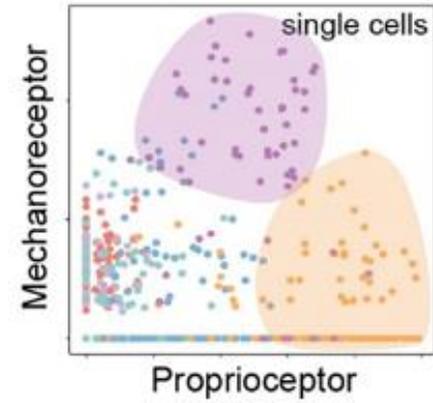
d Early gene modules



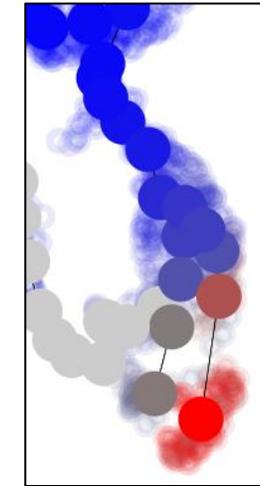
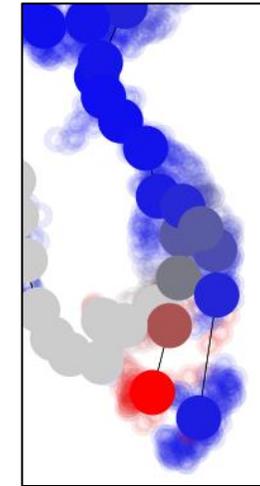
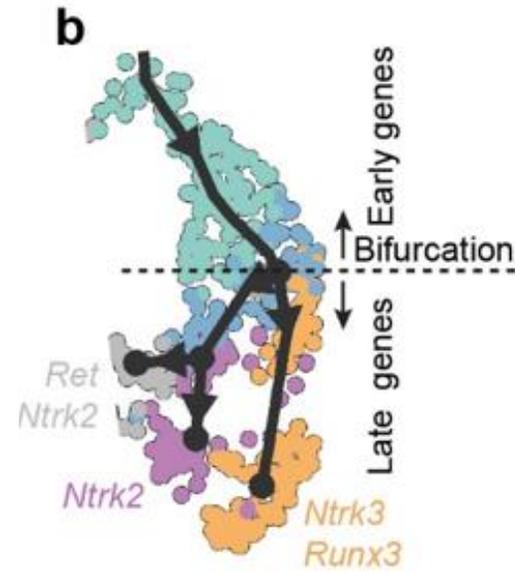
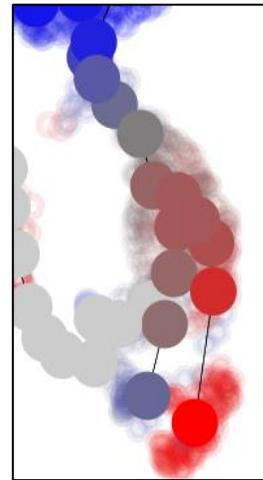
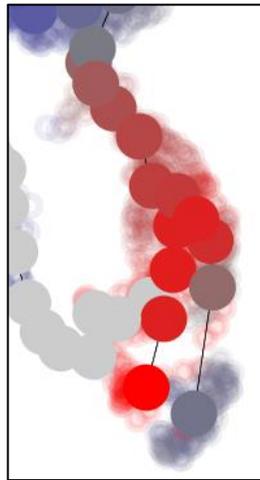
Proprioceptor

Mechanoreceptor

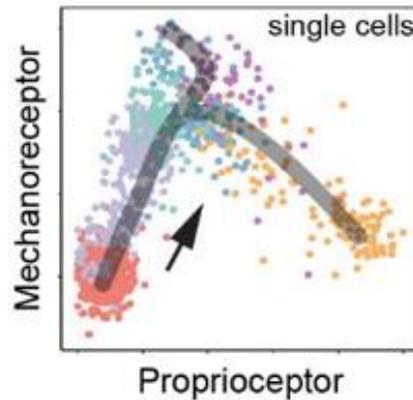
d Late gene modules



Faure et al (2020) *In review*



d Early gene modules



Proprioceptor

- Top 10
Pcdh9
Tshz2
Ncam2
Ntrk3
Pcp4
Fam19a4
Gm20597
Gm11549
Runx3
Lgals9

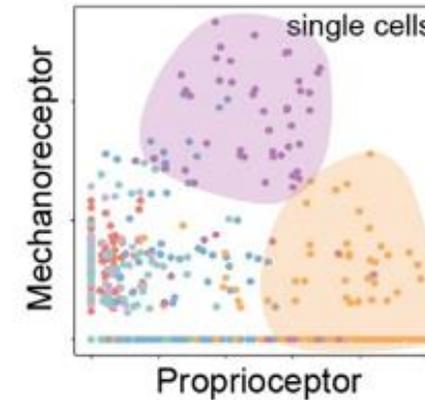
- TF
Runx3
Nfia

Mechanoreceptor

- Top 10
Dixdc1
Shank2
Ntrk2
Sgsm2
Spf1
Syt13
Rgs4
Gfra2
Sgk1
Nptx1

- TF
Pou6f2
Nr5a2
Hoxb5
Pdlim1
Egr1
Junb

d Late gene modules



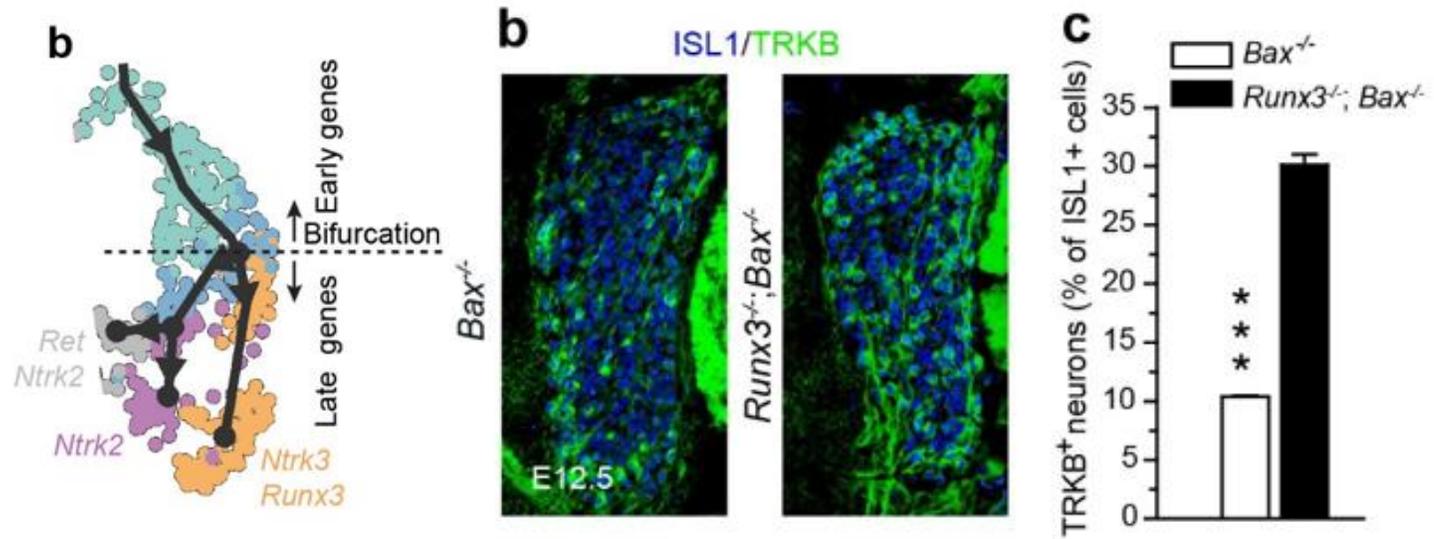
Top Genes

- Ramp3*
Plcd4
Frmpd4
Mdga2
Rbfox1
Kirrel3
Syt9

- Gpm6a*
Ntng1
Prokr2

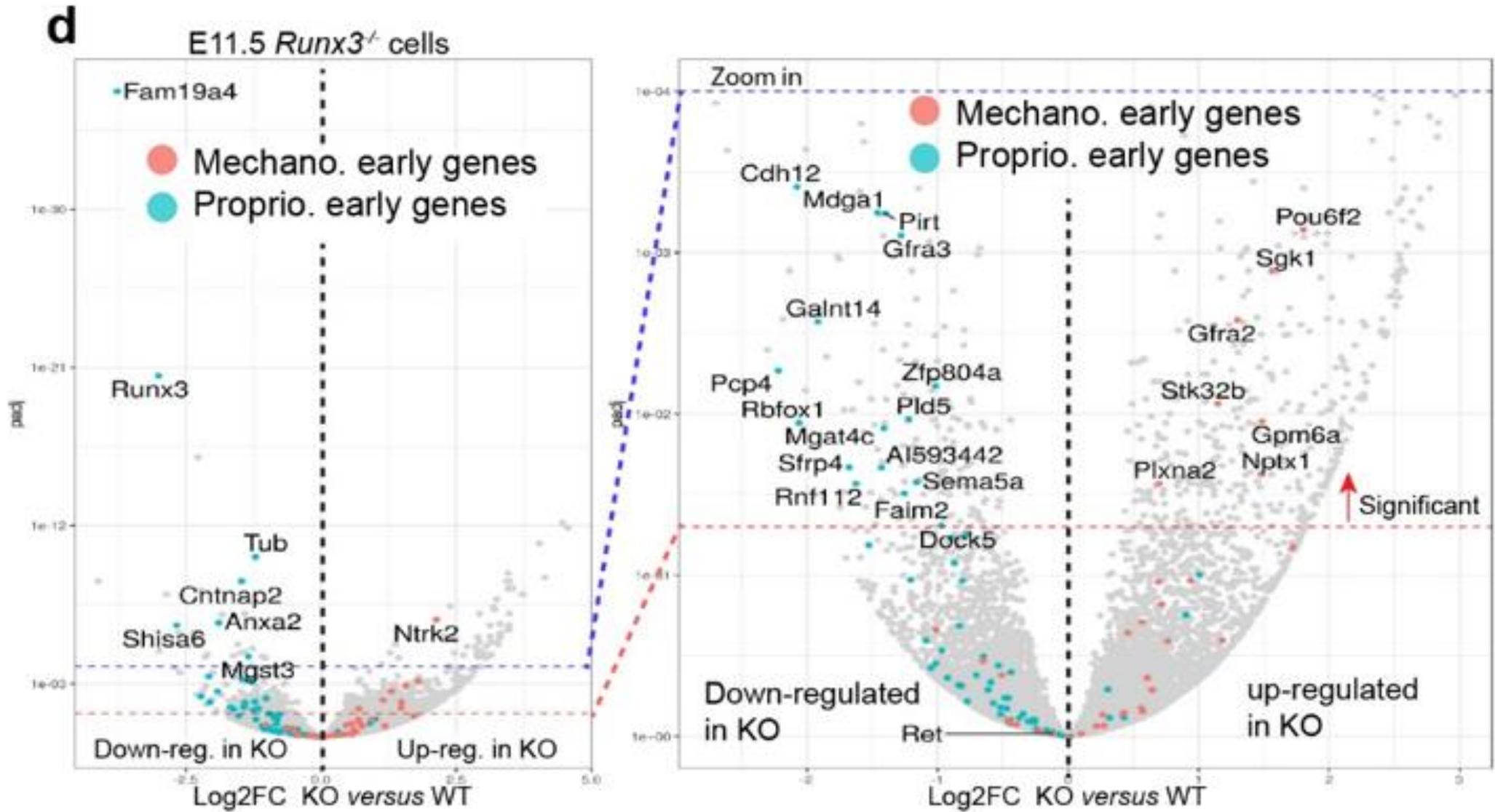
Faure et al (2020) *In review*

In vivo validation of gene module involved in fate decision



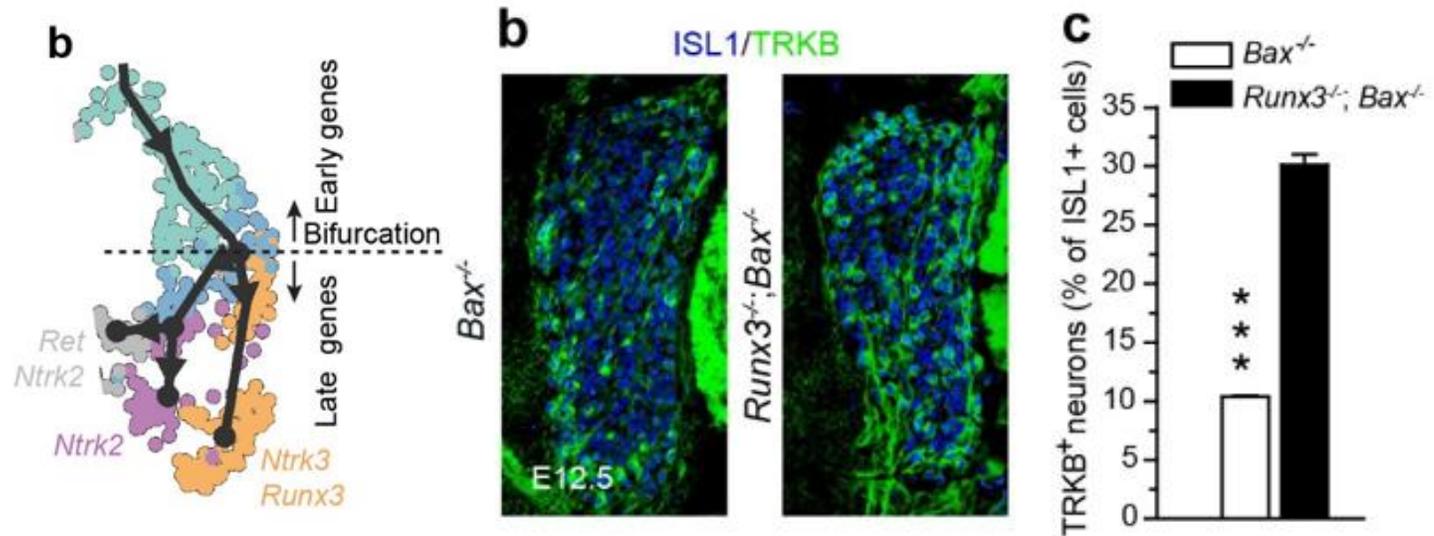
Faure et al (2020) *In review*

In vivo removal of TF of pro-proprioceptive fate lead to mechanoreception fate

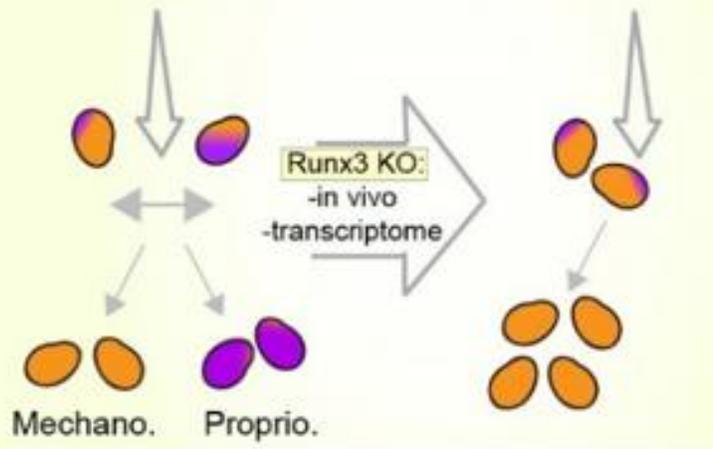


Faure et al (2020) *In review*

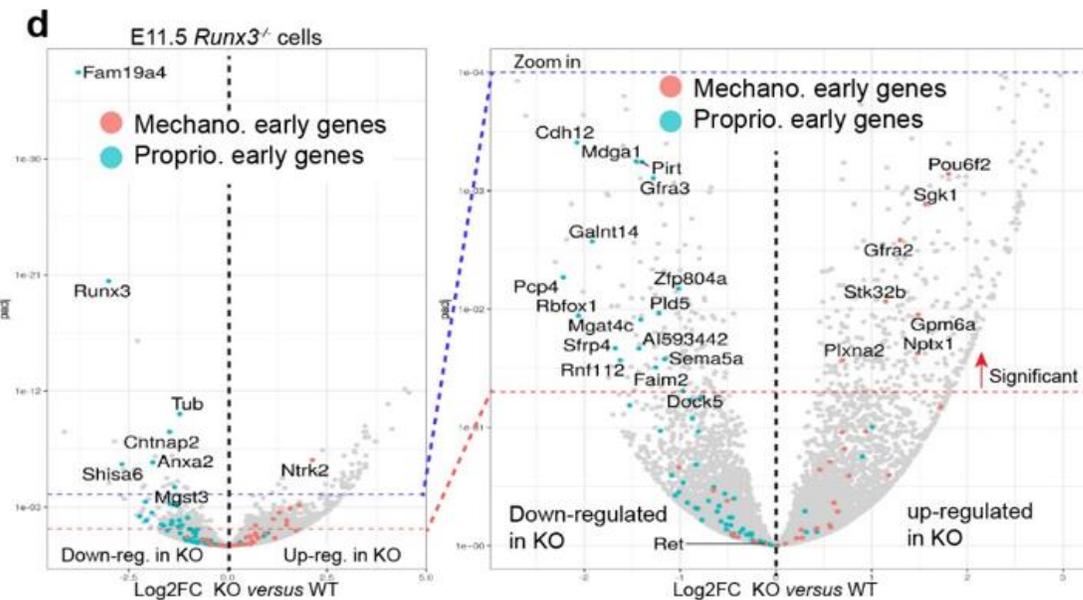
In vivo validation of gene module involved in fate decision



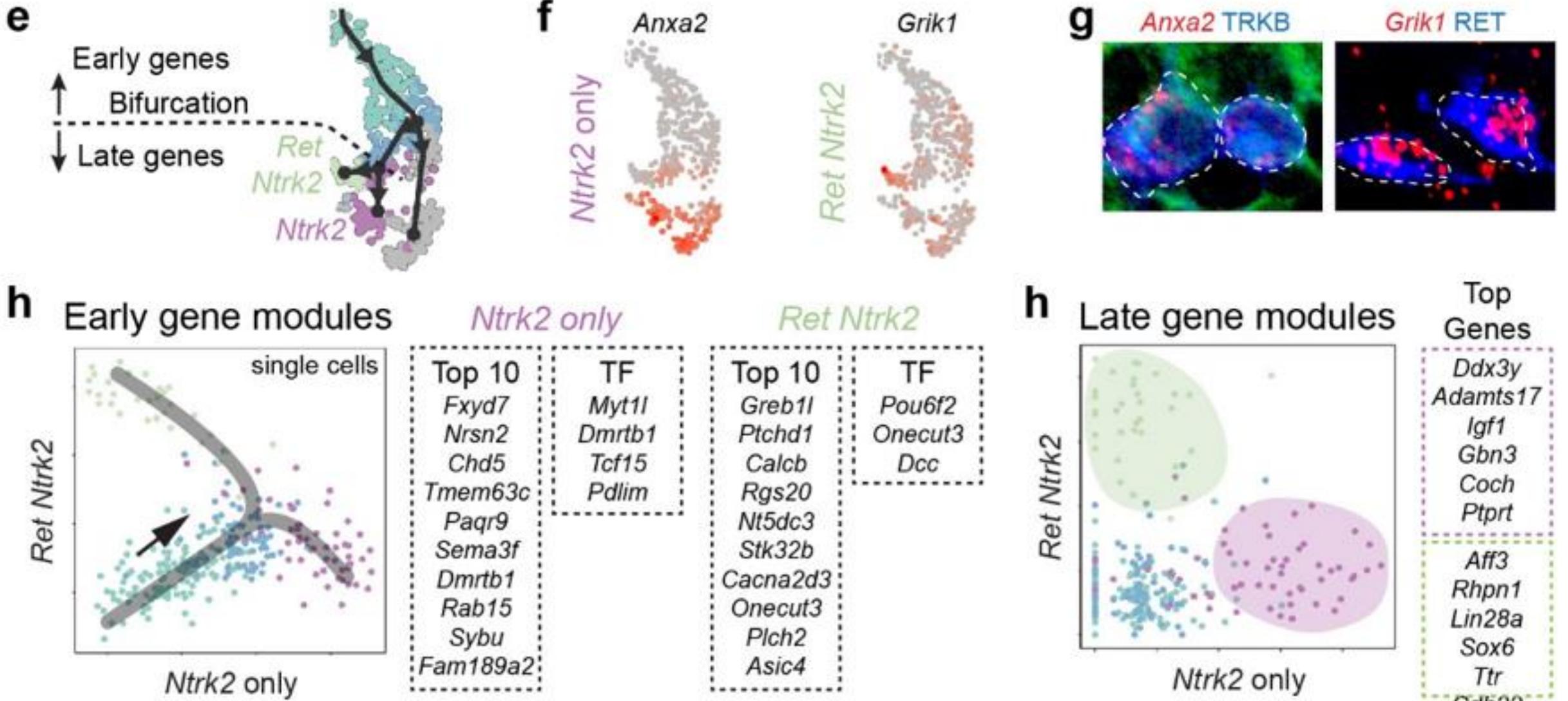
Conversion of proprioception neurons into mechanoreception neurons profiles



In vivo removal of TF of pro-proprioceptive fate lead to mechanoreception fate

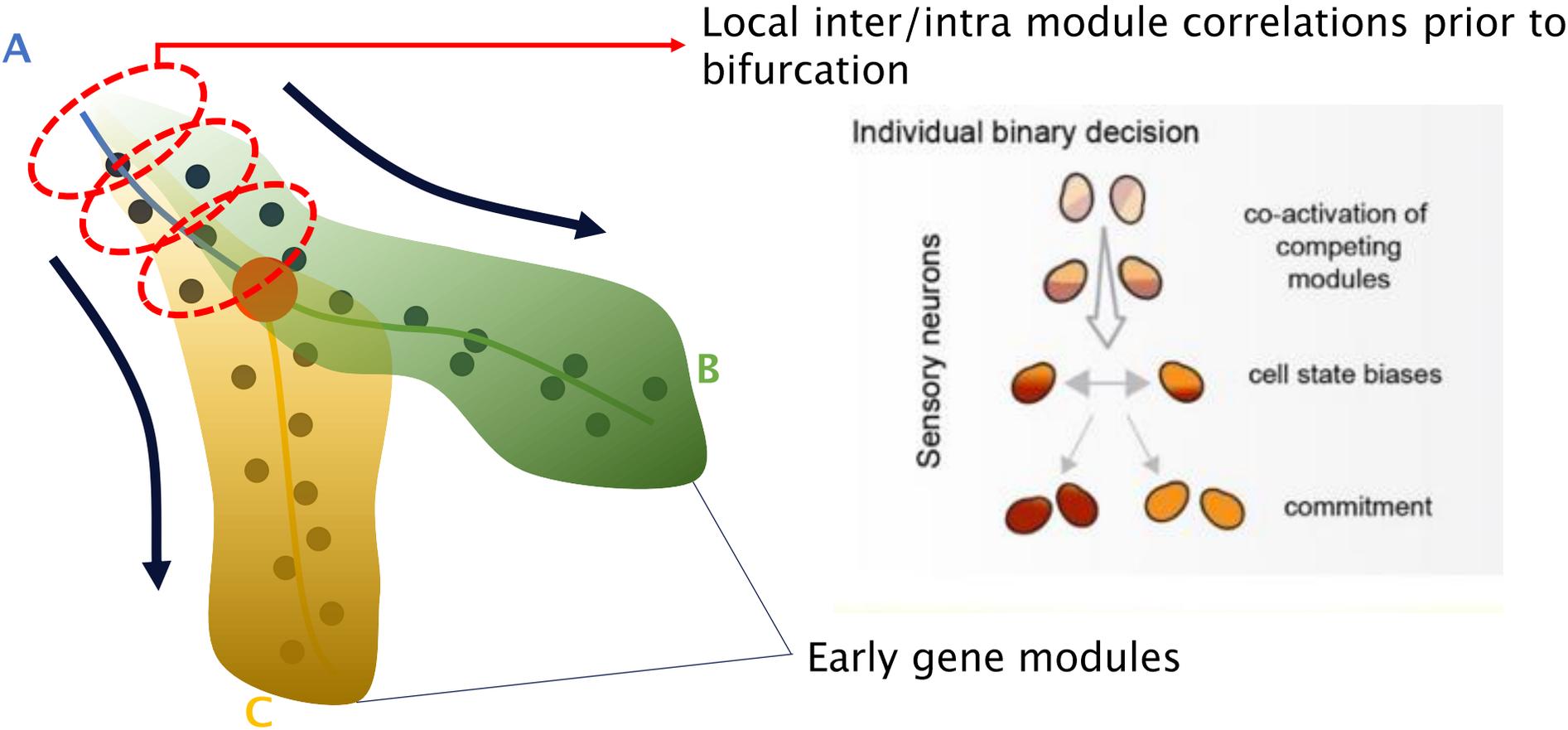


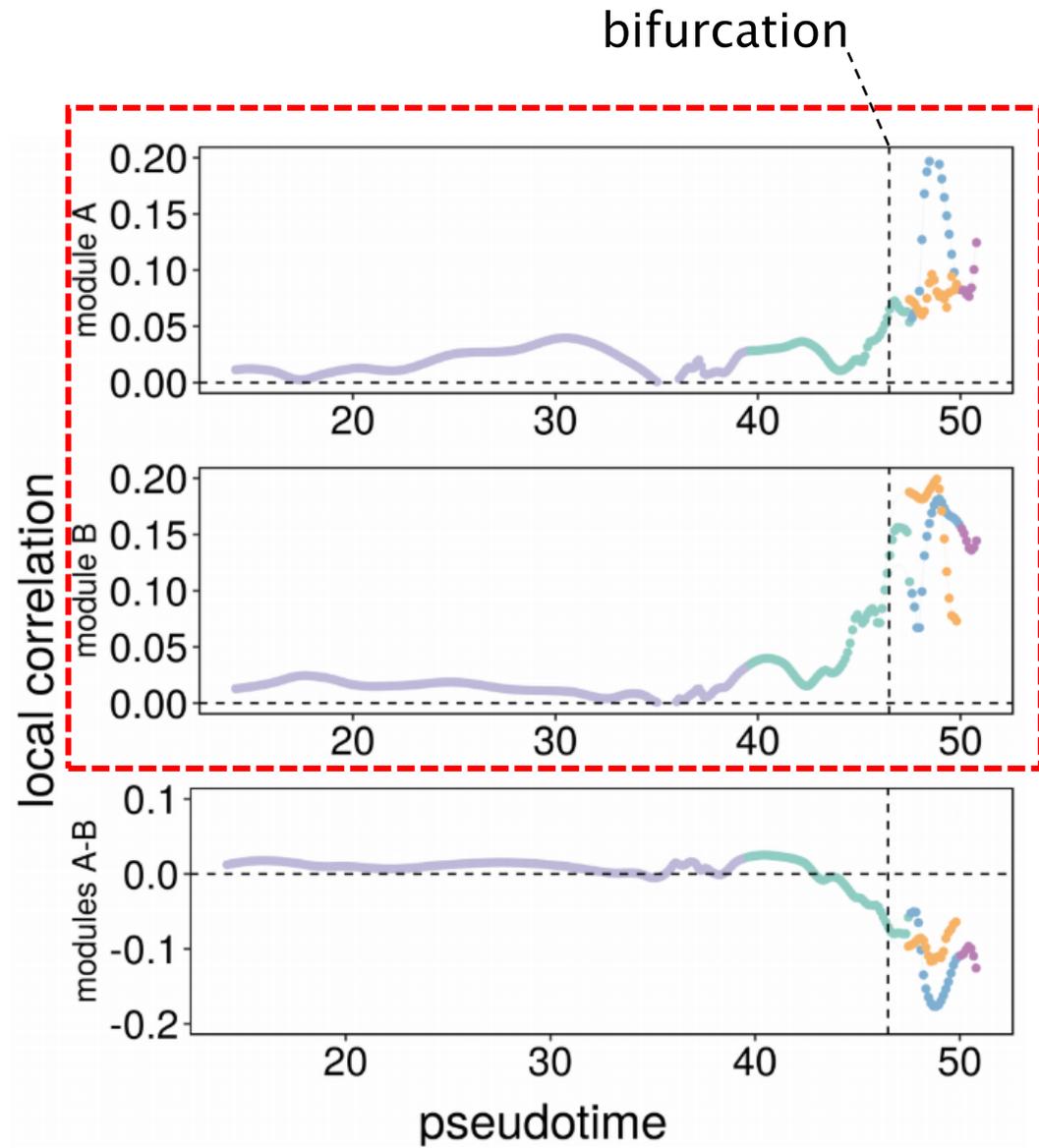
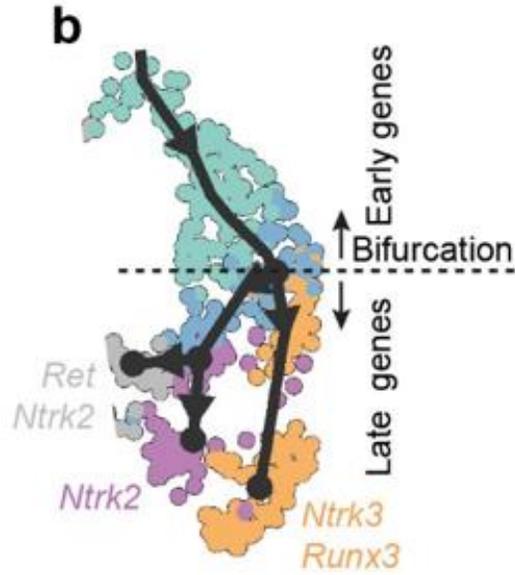
Faure et al (2020) *In review*



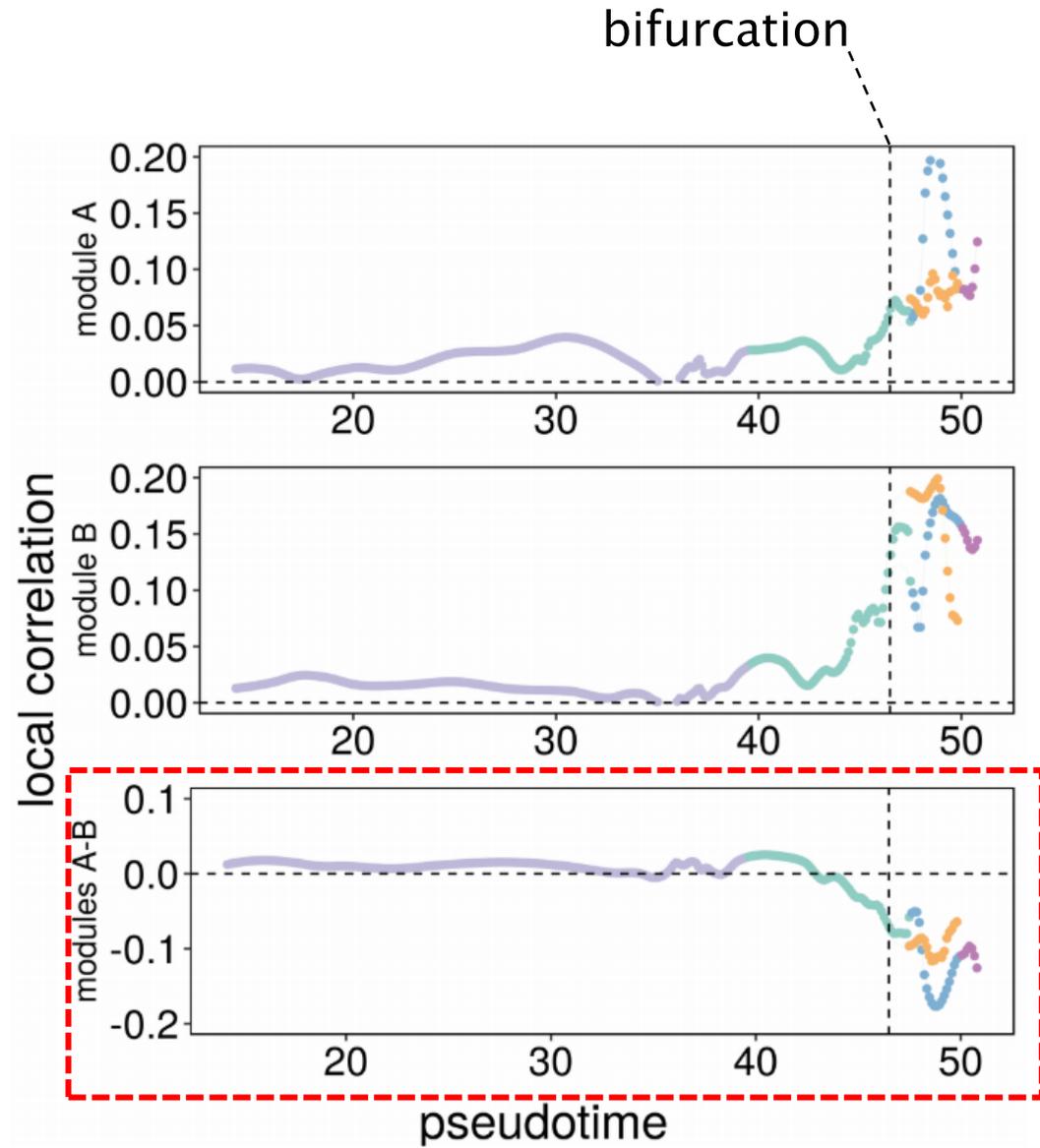
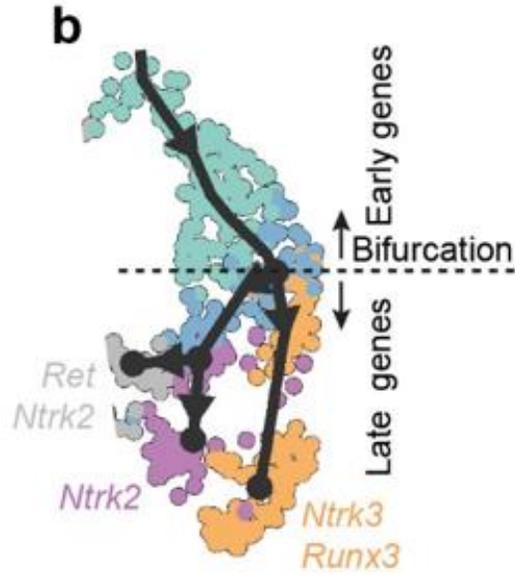
Faure et al (2019) *In review*

Inferring commitment prior to bifurcation

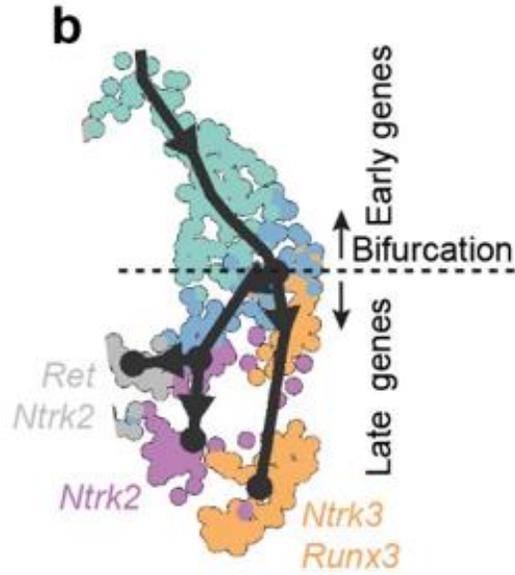




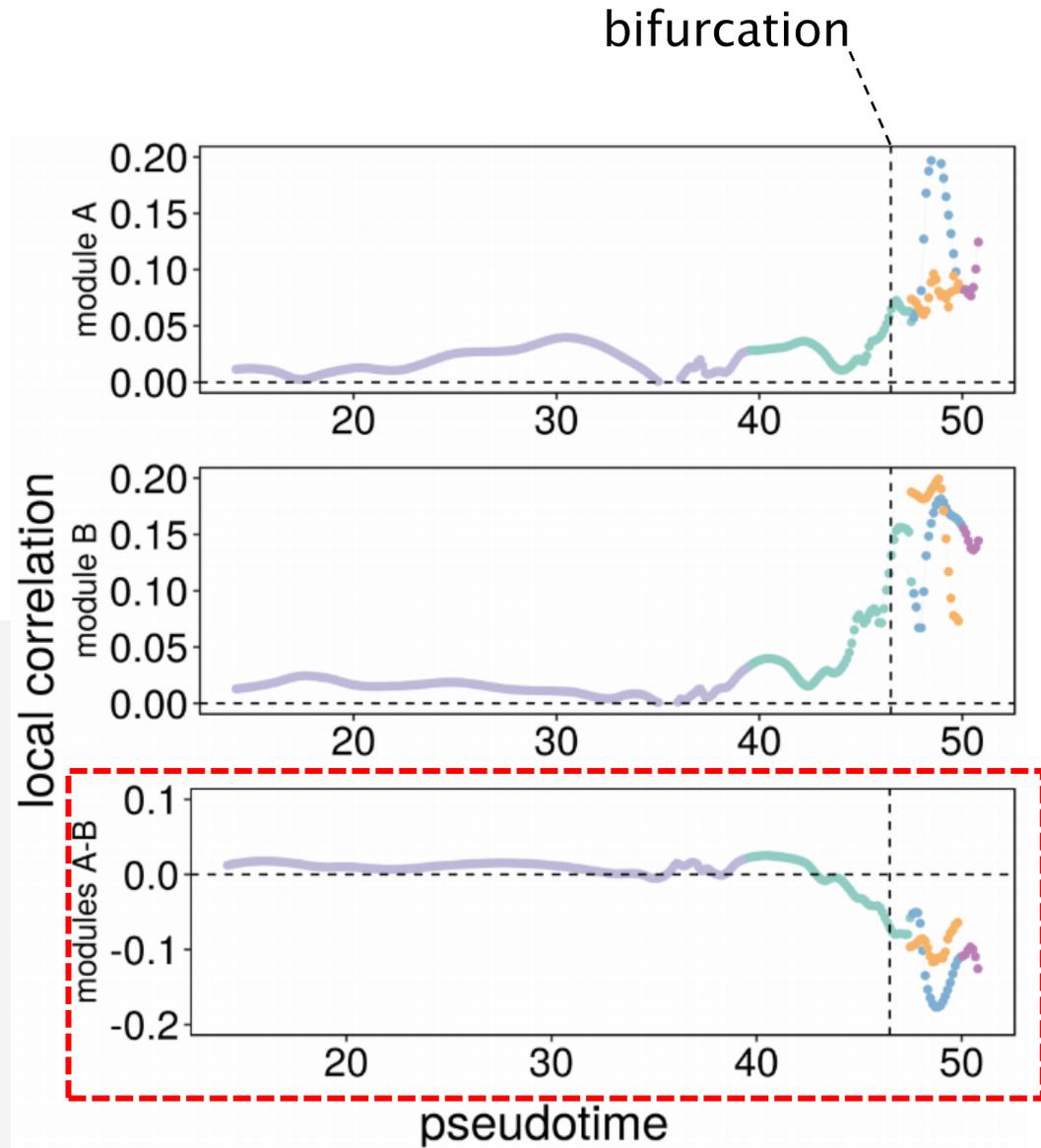
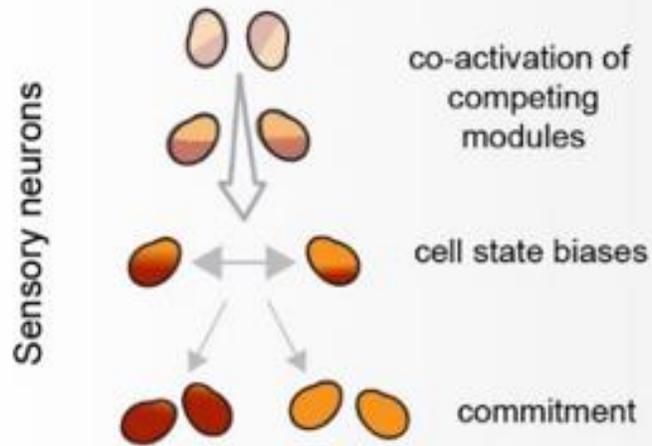
Faure et al (2019) *In review*



Faure et al (2020) *In review*

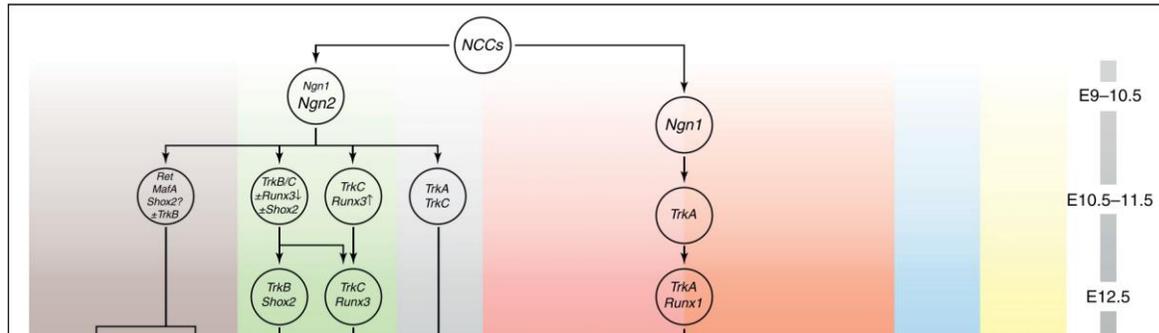


Individual binary decision

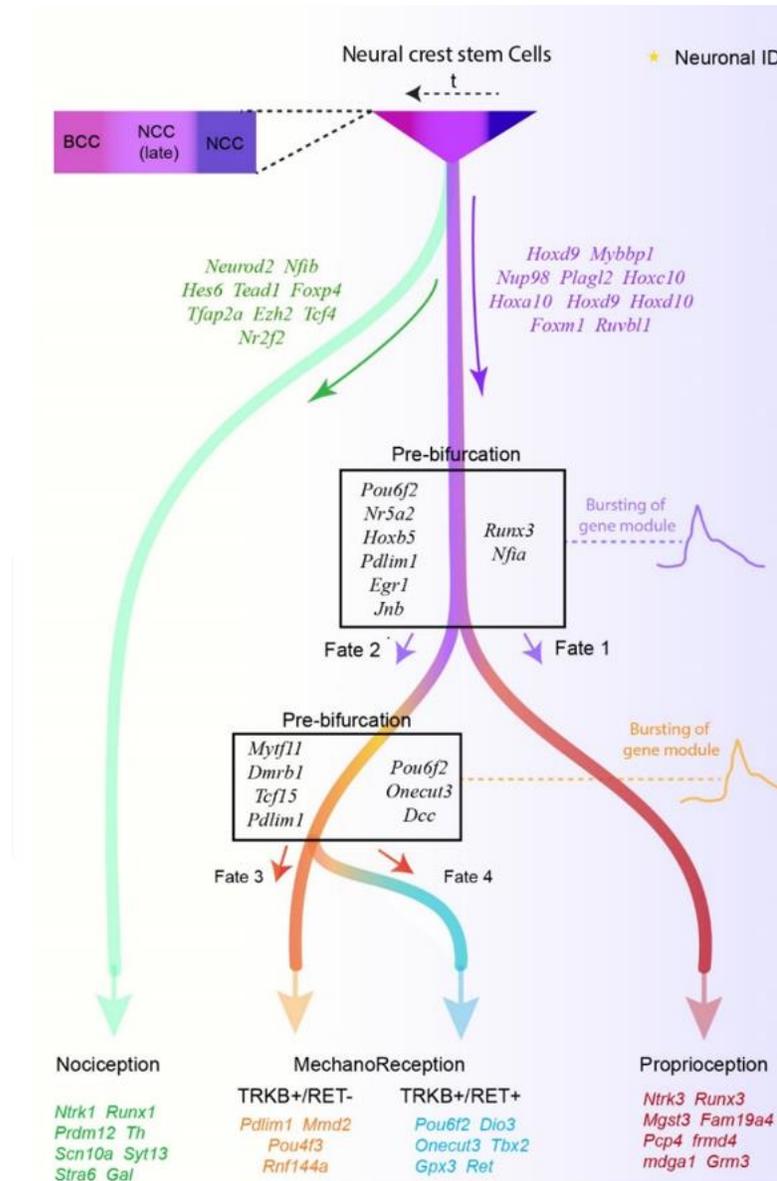


Faure et al (2020) *In review*

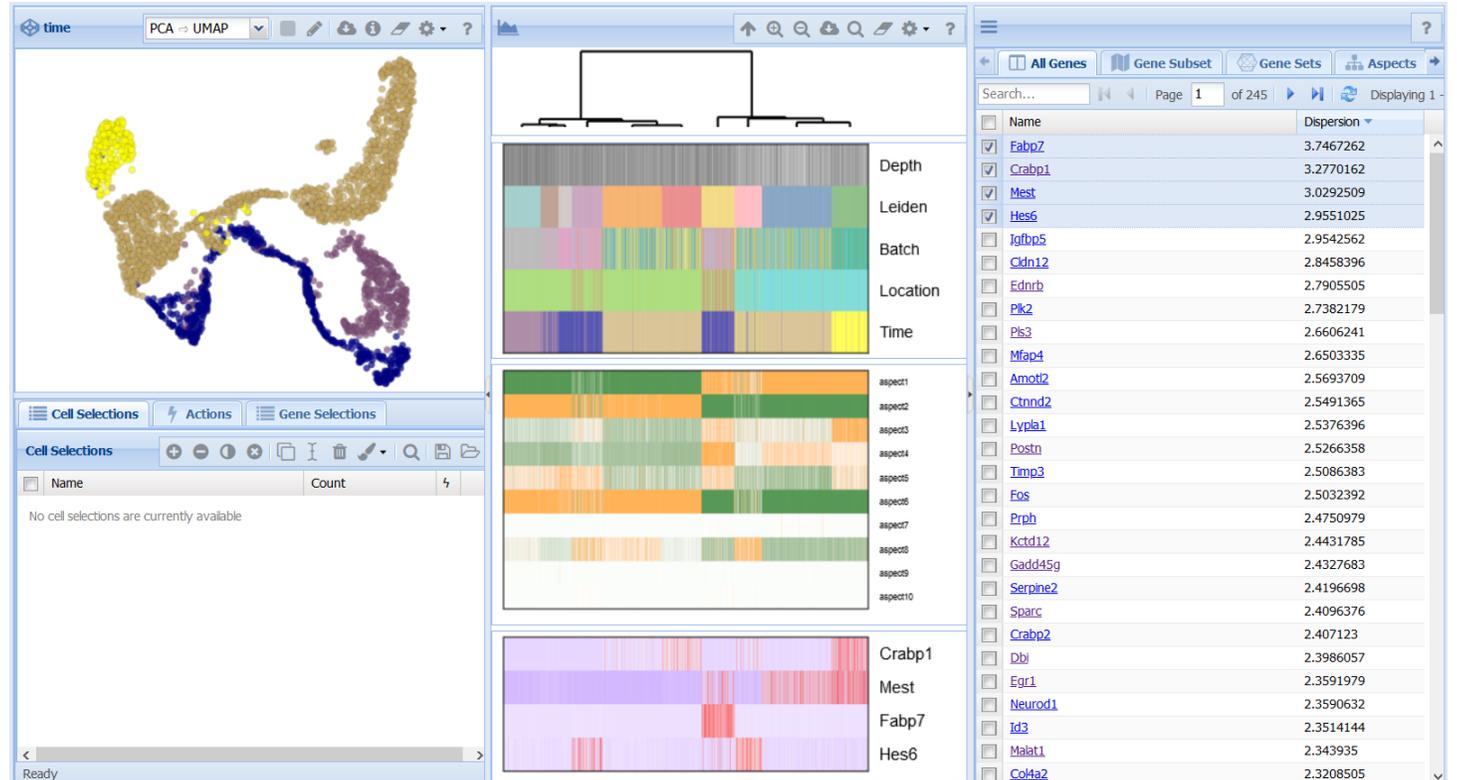
Classical model



New model



Data exploration and code reproducibility



Thank you!

Igor Adameyko



Saida Hadjab



François Lallemand



Maria Eleni Kastriti

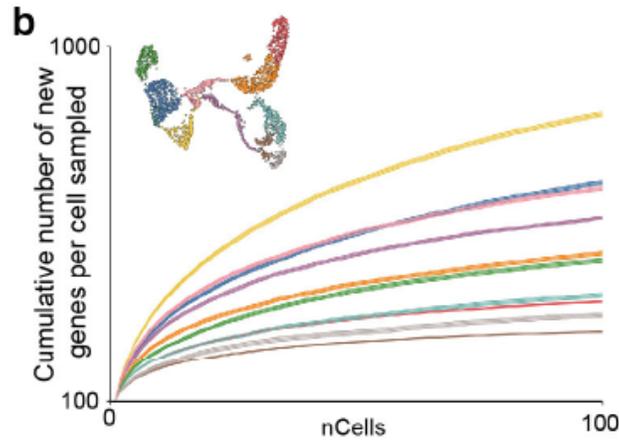
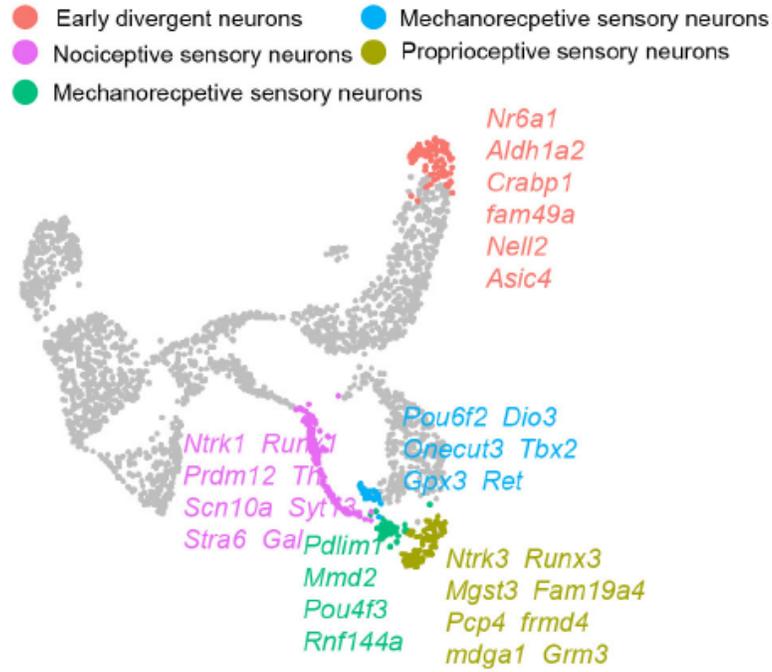


FWF

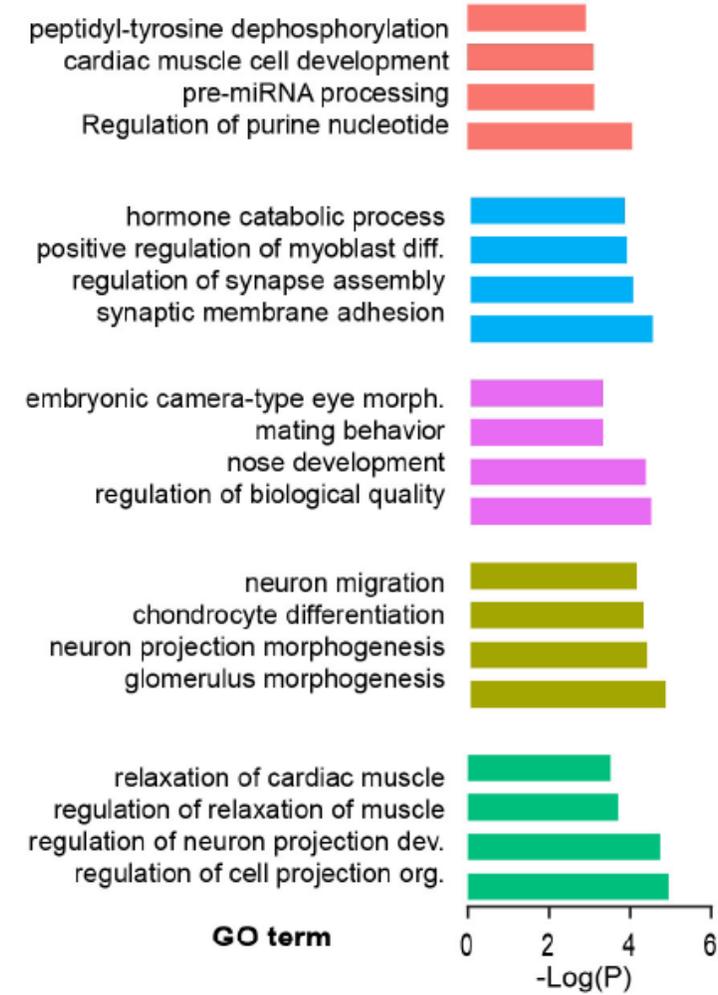


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a Differentially expressed genes in sensory neurons lineages



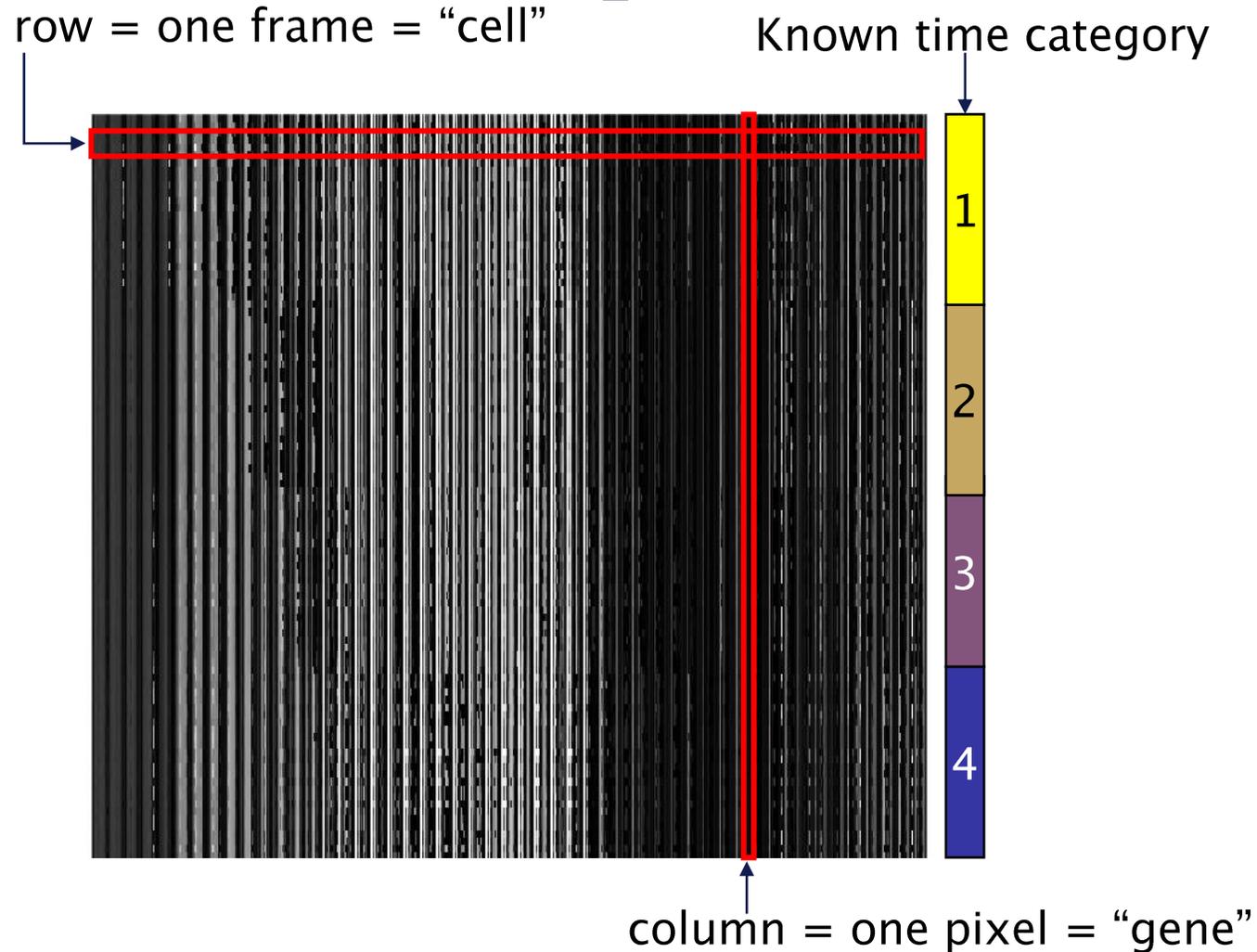
c Top GO term of sensory neurons lineages



Concept of pseudotime: recovering lost time information



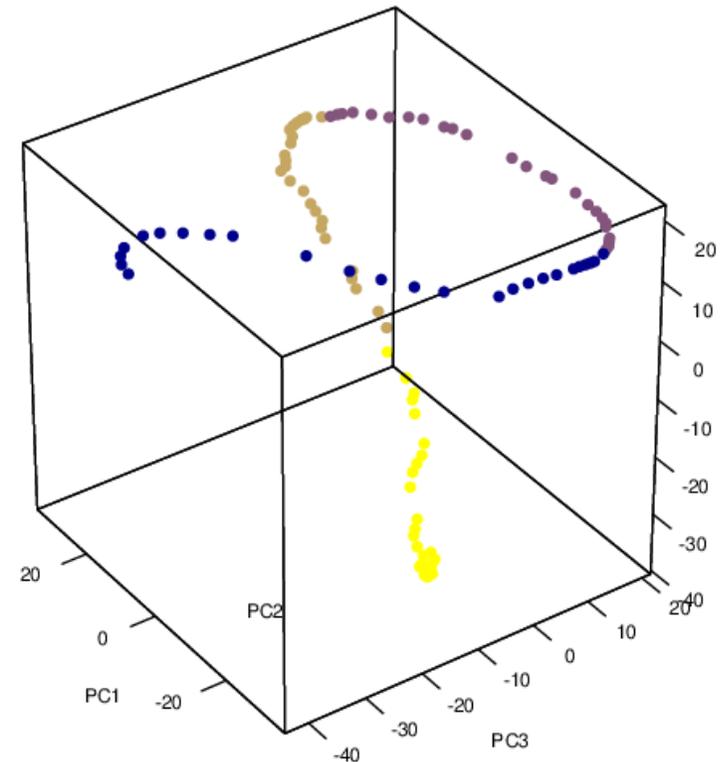
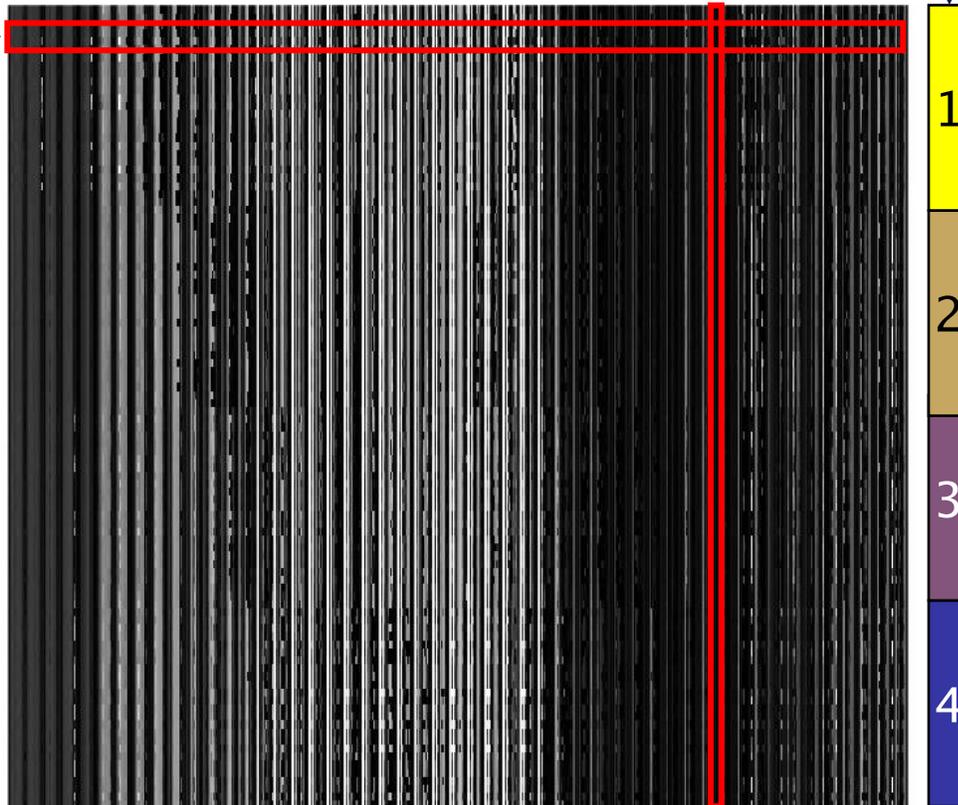
Considering the video as an expression matrix



Applying PCA reveals low dimensional latent structure!

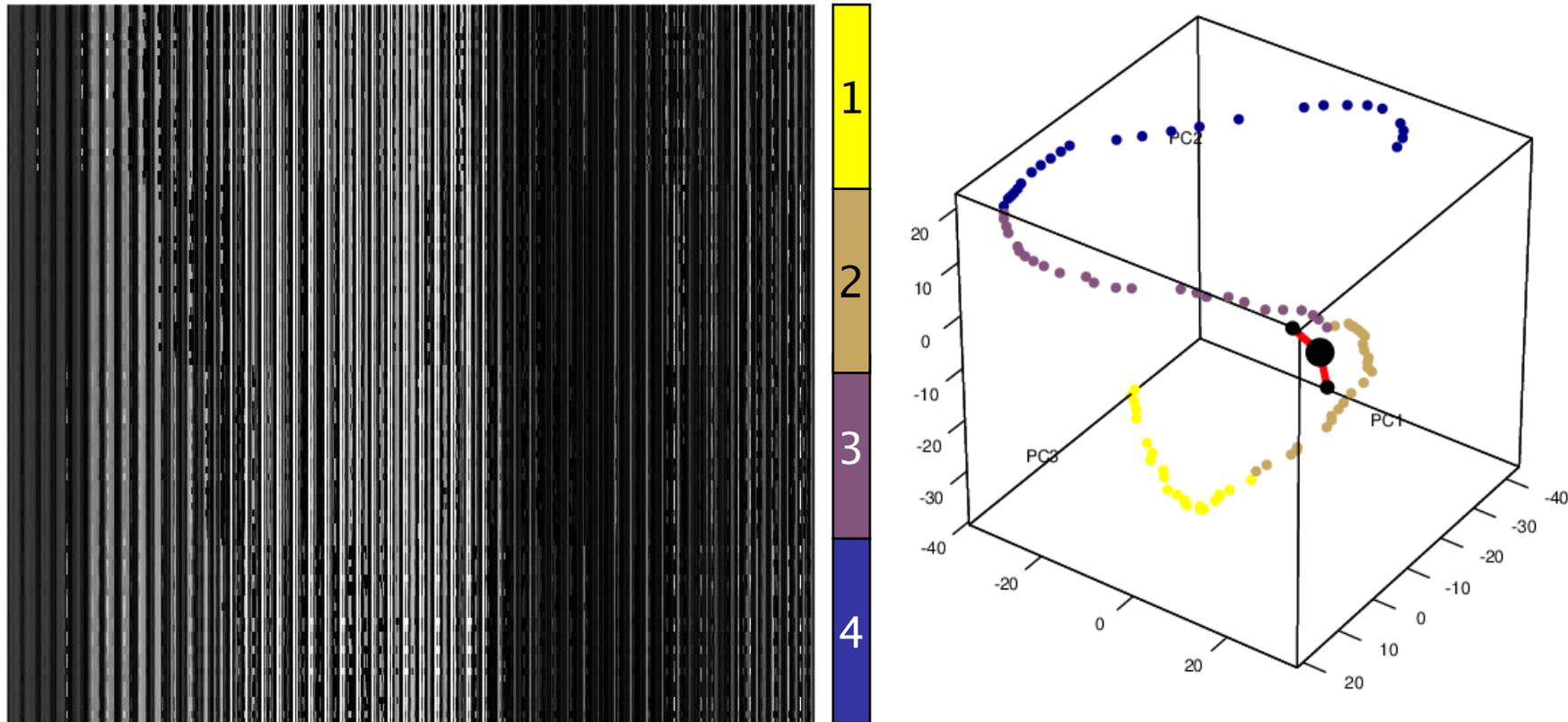
row = one frame = "cell"

Known time category



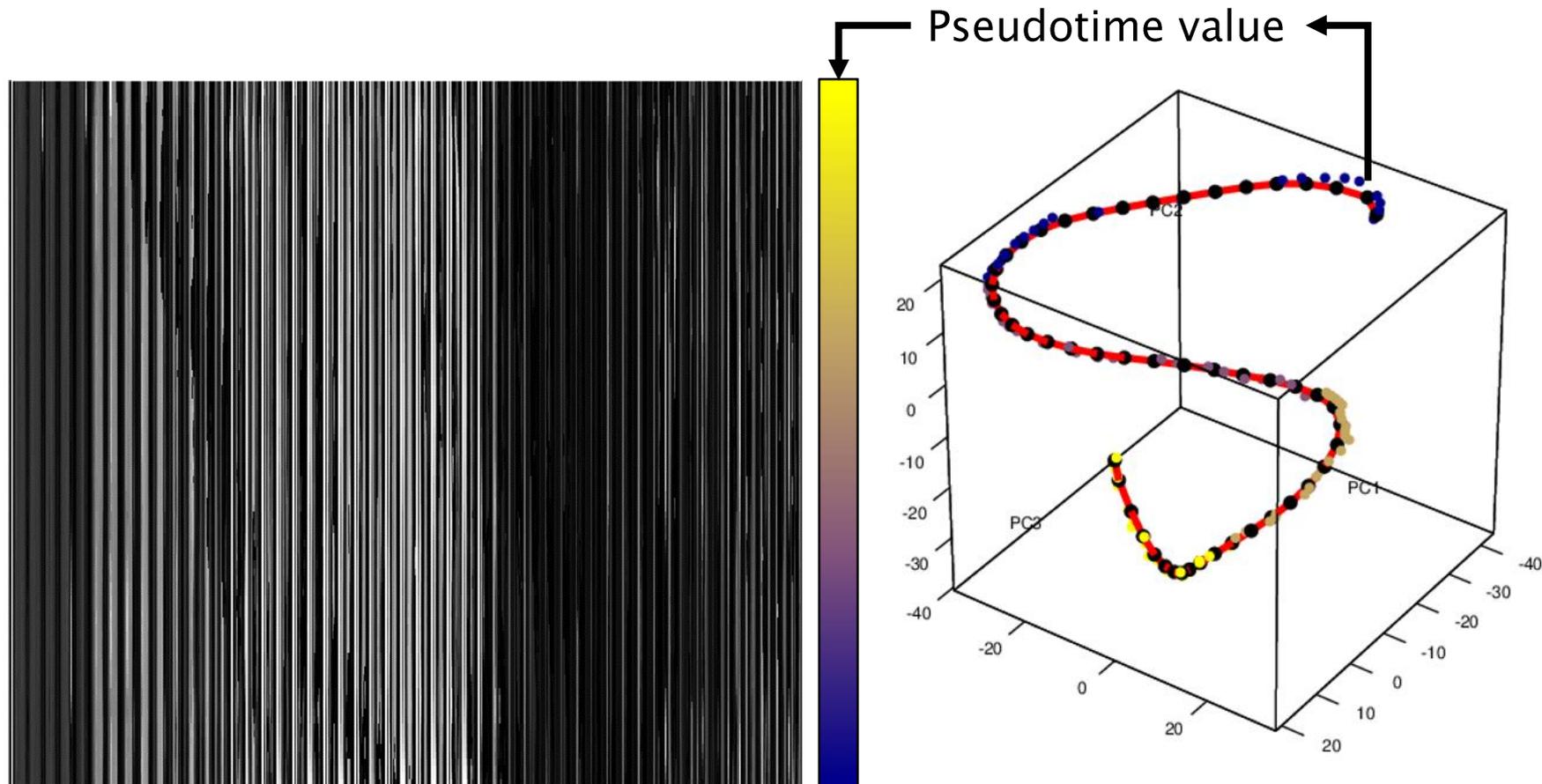
column = one pixel = "gene"

This latent structure can be approximated using principal curves



↑
column = one pixel = “gene”

Ordering frames along the principal curve recovers lost time information!



Recovered time!



