Exponential-family embedding with application to cell developmental trajectories for single-cell RNA-seq data

Kevin Lin

with Kathryn Roeder and Jing Lei

We are interested in studying the developmental trajectory of oligodendrocytes using single-cell RNA-seq data.

Previous technology:
Many cells investigated at once

New technology (Popularized 2015+):
Single cell

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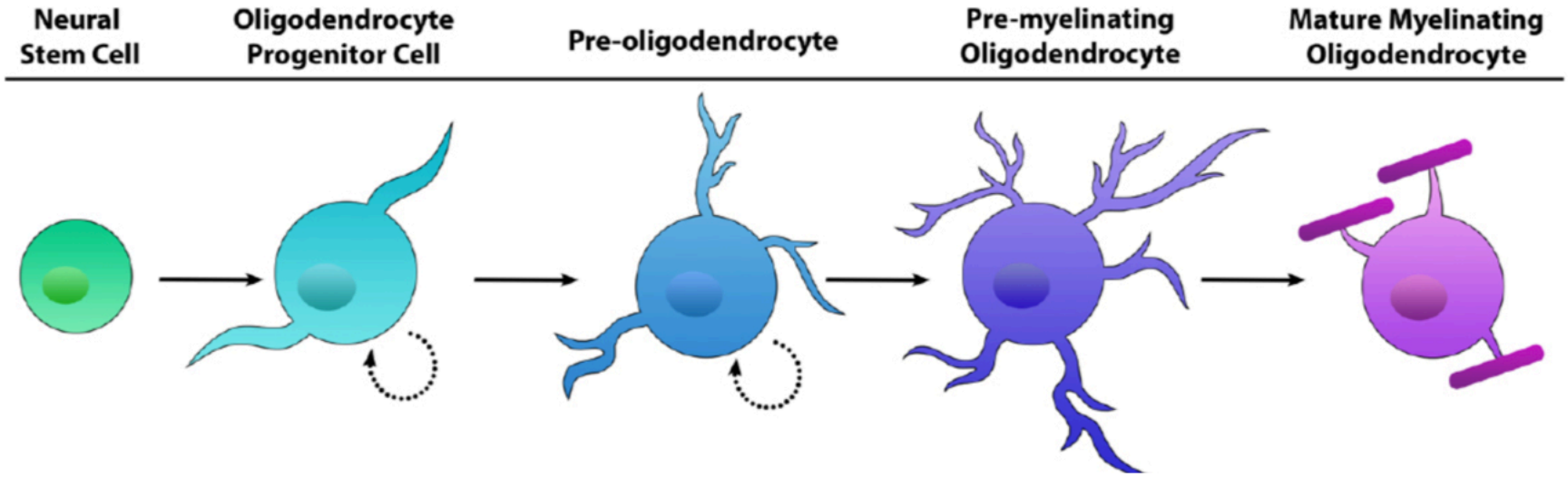

We use the dataset from Marques et al. (2016), which divides the cells into 6 major cell types and 13 sub-types.

Major Cell Type (6 total)	Count (5000+ total)	Number of cell sub-types (13 total)
Pdgfra+ precursor		
Oligodendrocyte precursor cell		
Differentiation-committed oligodendrocyte precursors		
Newly formed oligodendrocytes		
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Oligodendrocyte precursor cell	300+	1
Differentiation-committed oligodendrocyte precursors	100+	1
Newly formed oligodendrocytes	500+	2
Myelin-forming oligodendrocytes	1200+	2
Mature oligodendrocyte	2700+	6

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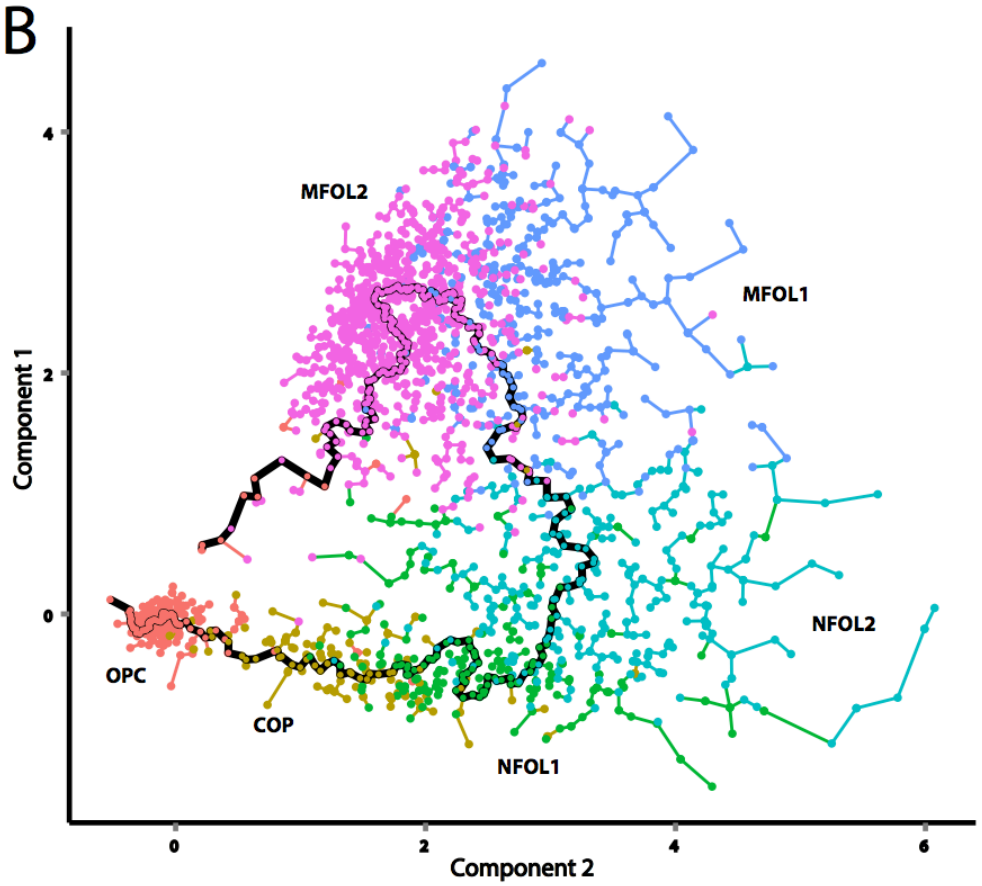

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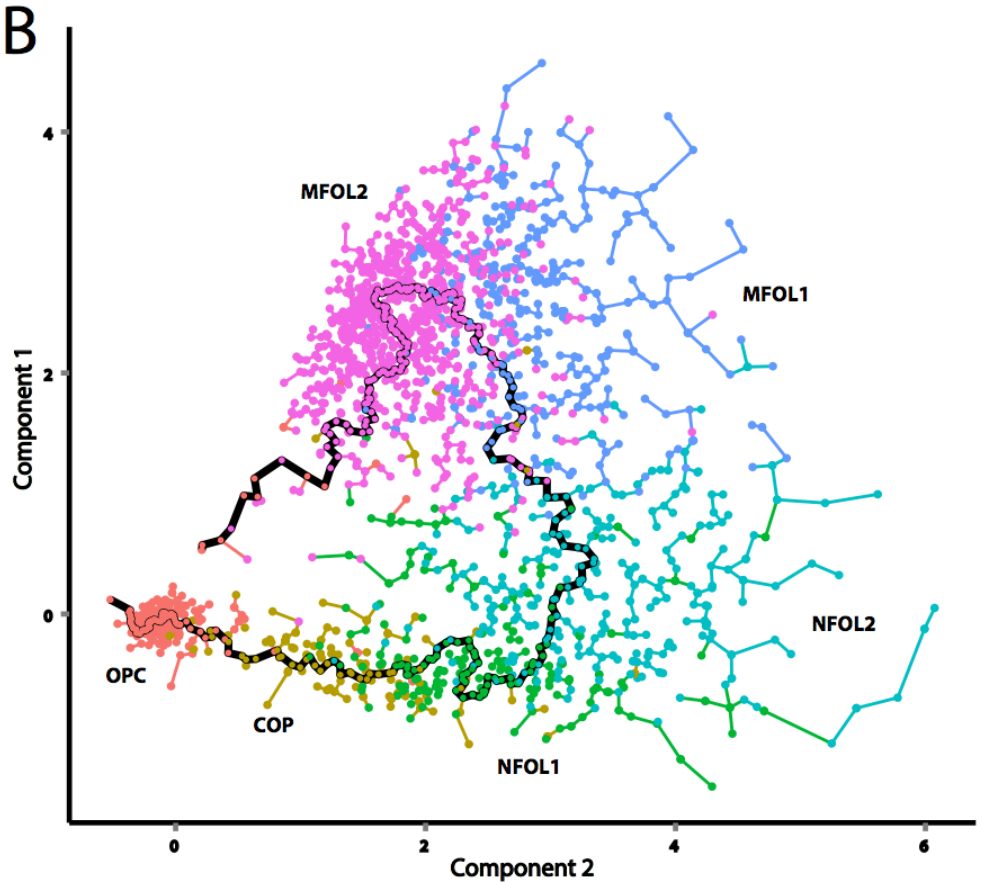

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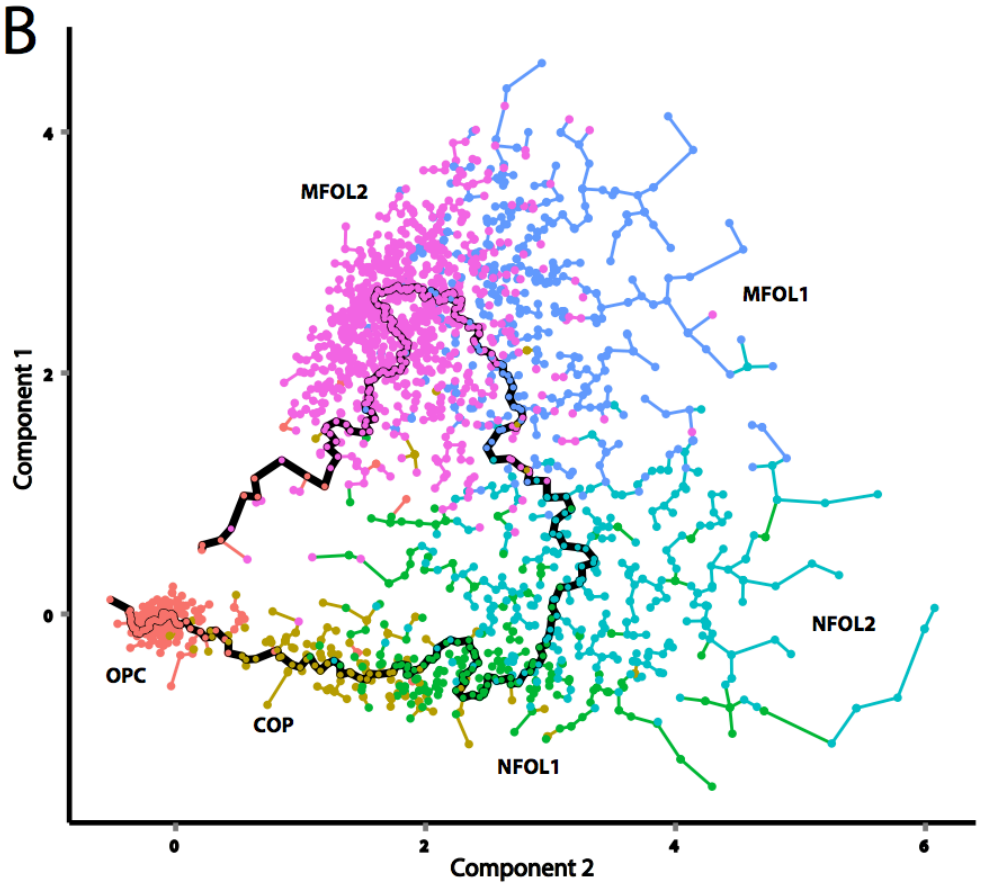

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To estimate this low-dimensional embedding, we impose a hierarchical, latent space model.

$$\boldsymbol{X}_1, \ldots, \boldsymbol{X}_n \overset{i.i.d.}{\sim} G, \quad \text{and} \quad \boldsymbol{Y}_1, \ldots, \boldsymbol{Y}_p \overset{i.i.d.}{\sim} H$$

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n cells and *p* genes

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Exponential-family distribution

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Latent low-dimensional distr. of interest

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ZIFA (Pierson et al. 2015): Gaussian
ZINB-WaVE (Risso et al. 2018): Negative binomial
pCMF (Durif et al. 2017): Poisson

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Exponential-family distribution

Natural idea: For a given distribution family *F*, find the factorization that maximizes the log-likelihood based on ***A*** in order to recover *G*

SVD's implicitly assumes a Gaussian model with fixed variance, which does not seem to be a great model.

Minimize over two low-rank matrices:

$$\mathcal{L}(\boldsymbol{X}, \boldsymbol{Y}) = \frac{1}{np} \sum_{(i,j)} \left[g(\boldsymbol{X}_i^\top \boldsymbol{Y}_j) - A_{ij}^\top (\boldsymbol{X}_i^\top \boldsymbol{Y}_j) \right]$$

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Plugging in the appropriate form for fixed-variance Gaussian

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Solved exactly by SVD

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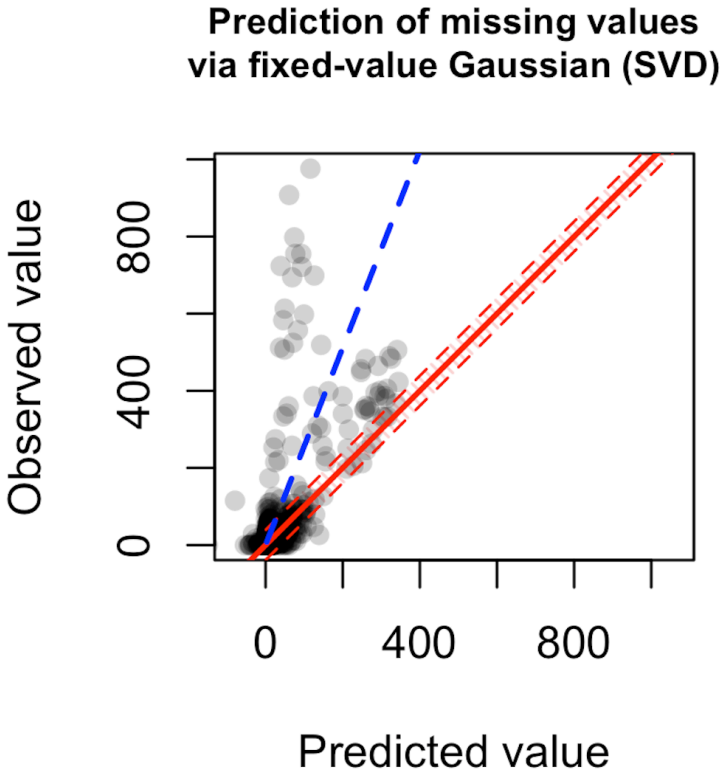

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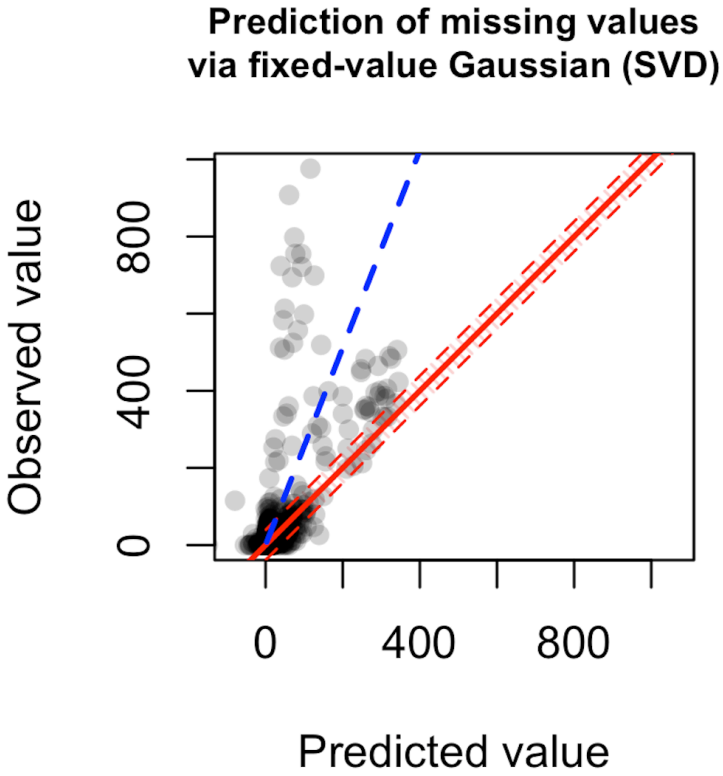
- Blue: Principal component vector between predicted and observed values



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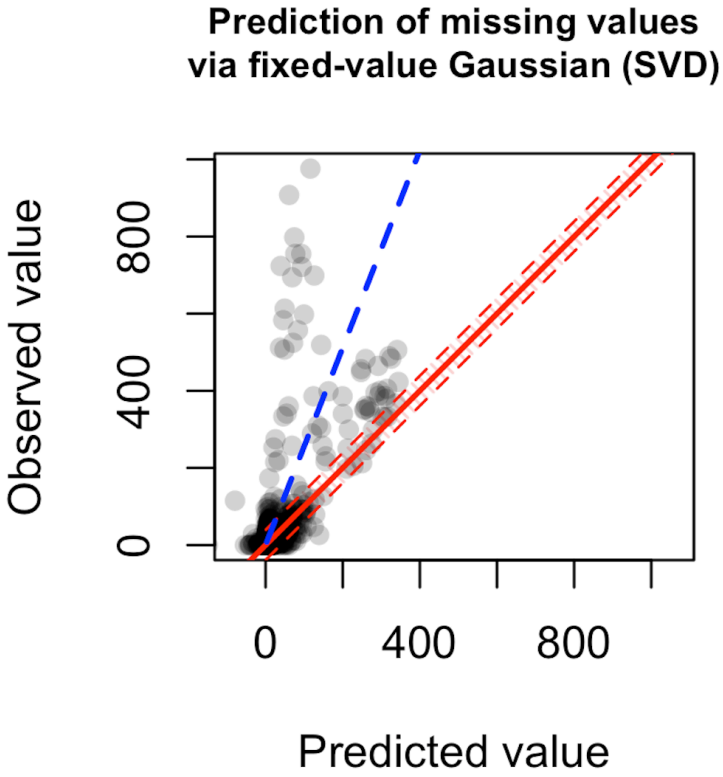
- Blue: Principal component vector between predicted and observed values
- Red: Theoretical band if model were correctly specified



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We provide a more flexible way to embed cells into a lower-dimensional space, backed by statistical theory.

- **Statistical goal:**
  - Estimate the latent vectors $\boldsymbol{X}_1, \ldots, \boldsymbol{X}_n$ (and $\boldsymbol{Y}_1, \ldots, \boldsymbol{Y}_p$) from the observed matrix $\boldsymbol{A}$ where each entry A_{ij} is drawn from an exponential-family distribution parameterized by the inner product $\boldsymbol{X}_i^\top \boldsymbol{Y}_j$

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- **Scientific goal:**
  - Apply our method to aid with estimating oligodendrocytes' lineages

Method

(eSVD, for exponential-family SVD)

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- Stage 3: Reparameterization
  - Ensure identifiability conditions are met

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- Stage 2: Alternating minimization

$$\boldsymbol{X}^{(t)} = \underset{\boldsymbol{X} \in \mathbb{R}^{n \times k}}{\arg\min}\, \mathcal{L}(\boldsymbol{X}, \overline{\boldsymbol{Y}}^{(t)}) \;:\; \boldsymbol{X}_i^\top \overline{\boldsymbol{Y}}_j^{(t)} \in \mathcal{R}, \quad \forall (i,j),$$

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Minimizing one of the factors based on the log-likelihood (Convex problem)

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$$X^{(t)} =$$
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Need to ensure the inner product still yields a valid natural parameter

We use Frank-Wolfe to do this constrained optimization

$$\boldsymbol{X}_i^\top \overline{\boldsymbol{Y}}_j^{(t)} \in \mathcal{R}, \quad \forall (i,j),$$

$$: (\overline{\boldsymbol{X}}_i^{(t+1)})^\top \boldsymbol{Y}_j \in \mathcal{R}, \quad \forall (i,j),$$

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$$\overline{\boldsymbol{X}}^{(t+1)} = \text{LeftSVD}(\boldsymbol{X}^{(t)}),$$

We reparameterize each estimate by its left singular vectors for identifiability reasons

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We then move to the next factor. We keep alternating between the two factors until convergence.

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- Handling the extra source of randomness due to the hierarchical model:
  - Requires careful study of identifiability conditions and perturbation bounds (Lei 2019)

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- Handling the extra source of randomness due to the hierarchical model:
  - Requires careful study of identifiability conditions and perturbation bounds (Lei 2019)
- Applying these generic bounds to a specific model:
  - Requires deploying statistical machinery from other high-dimensional papers (Sur et al. 2019)

Results

(We estimate two lineages for oligodendrocytes.)

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- Recall: To use eSVD, you simply need to plug in the appropriate terms from the exponential family distribution that model *F*.

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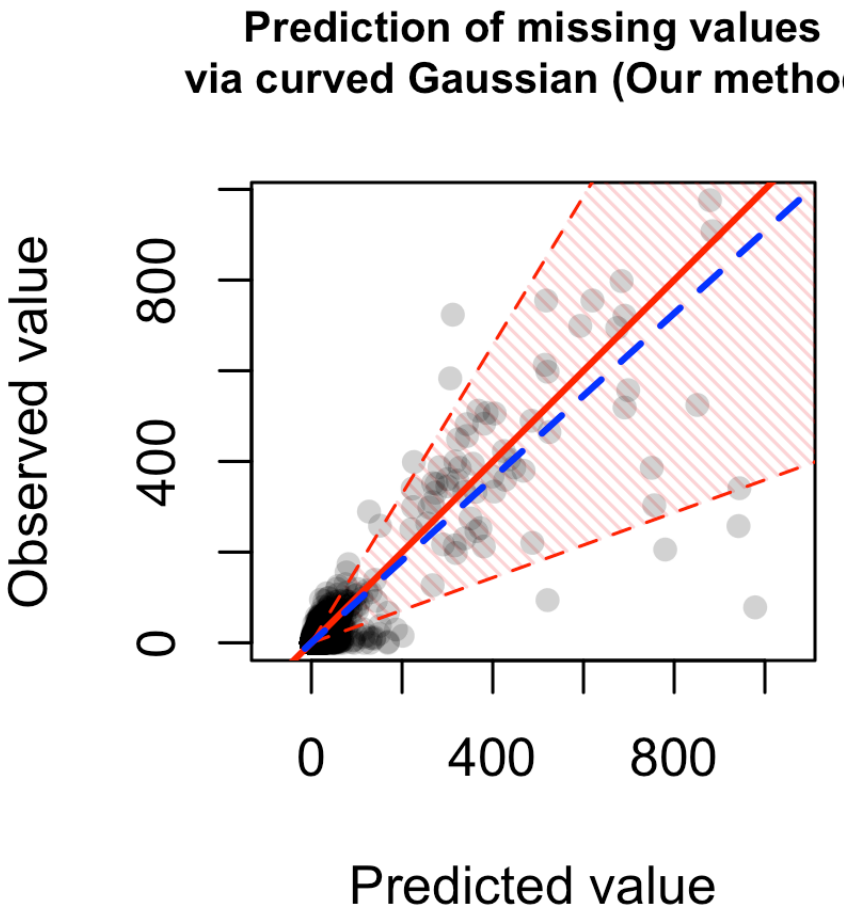

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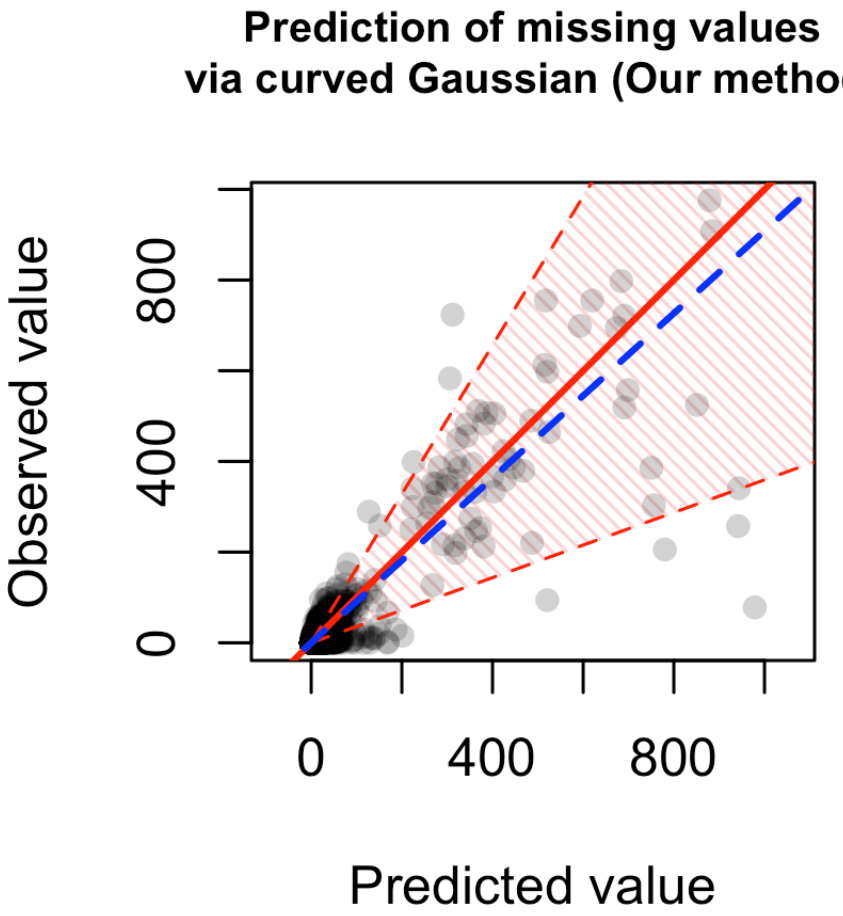
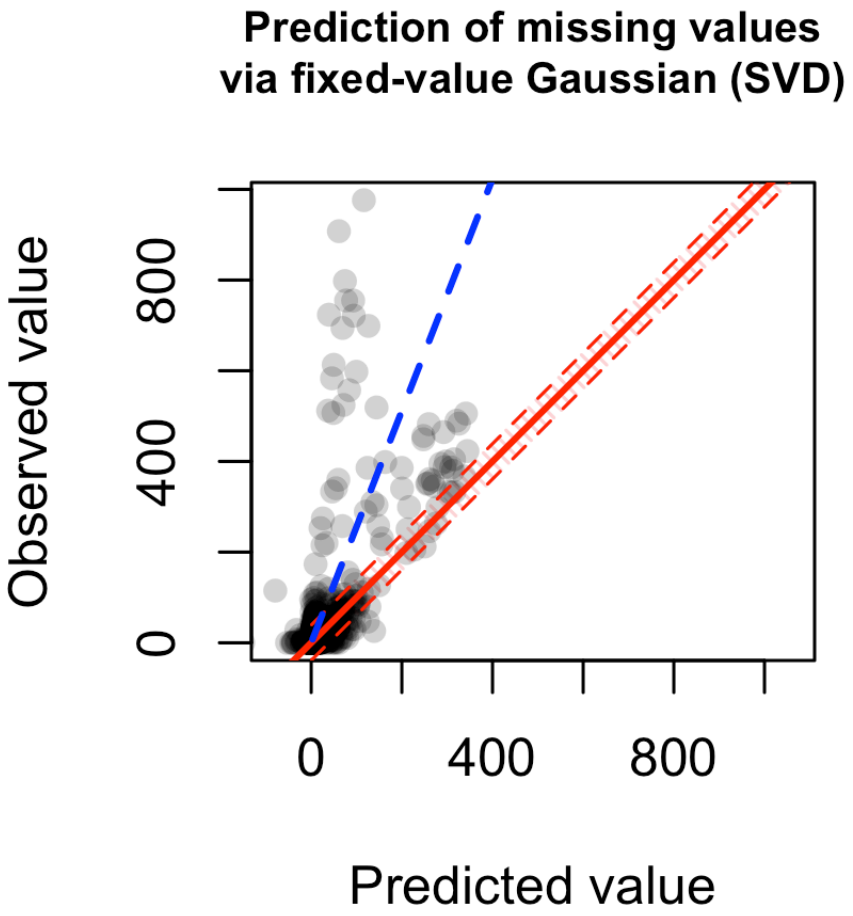
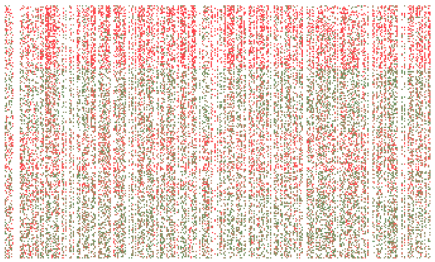


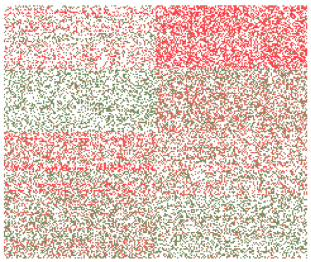


In our pipeline, we screen to keep only the important genes, depth-normalize but do not impute the data.



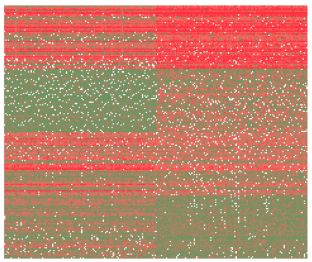
Single-cell RNA-seq data

(Cells as rows, genes as columns)



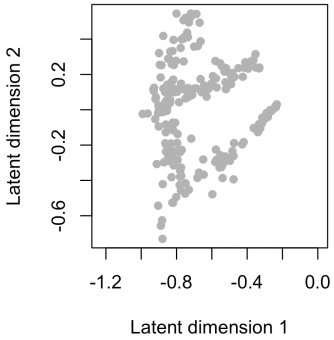
1. Screening relevant genes

(Sparse PCA (Whitten et al., 2009) and DESCEND (Zhu et al., 2018))



2. Imputing suspected dropout values

(scImpute (Li and Li, 2018))



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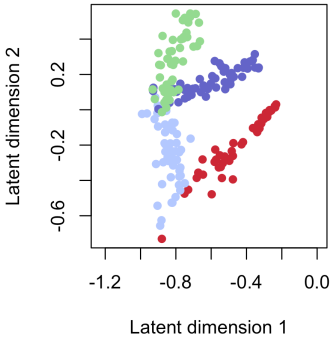

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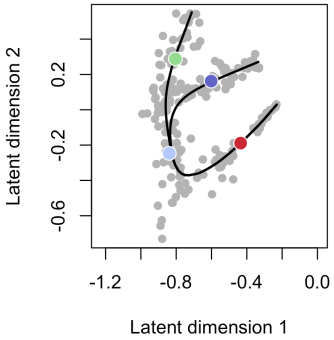

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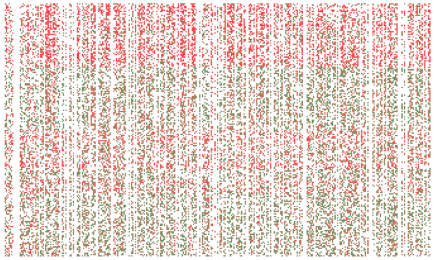

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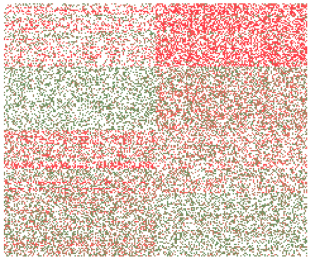

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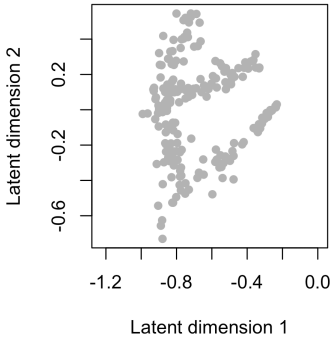

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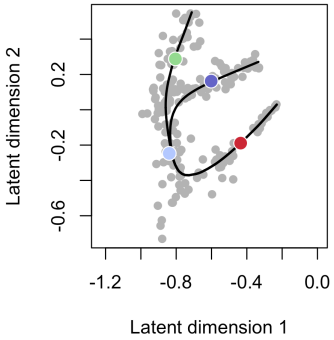

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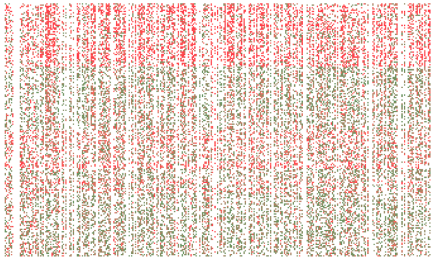

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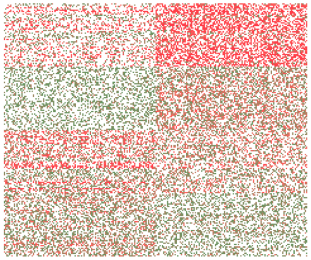

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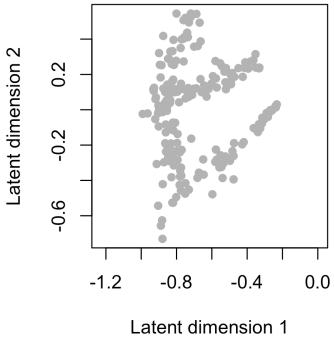

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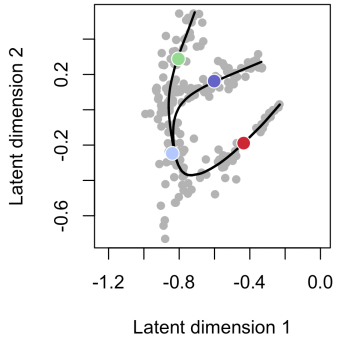

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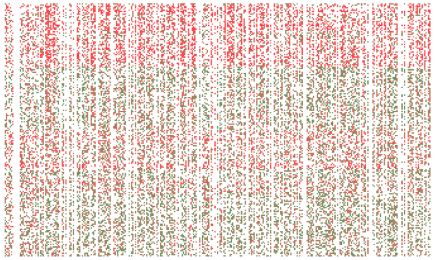

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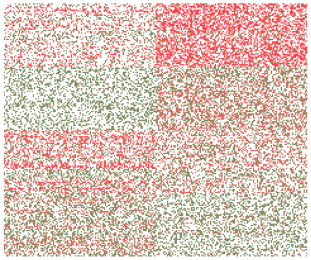

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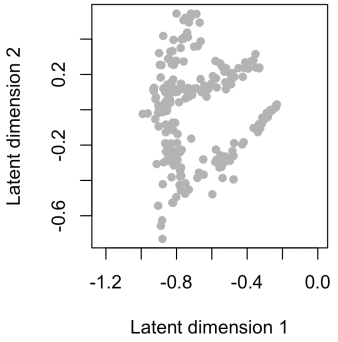

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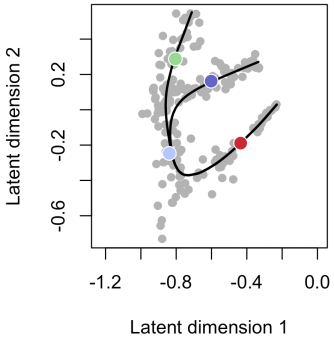

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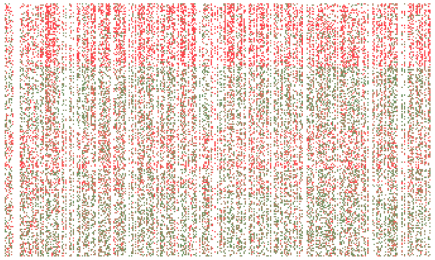

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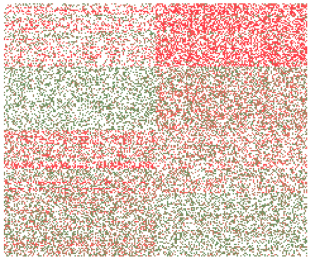

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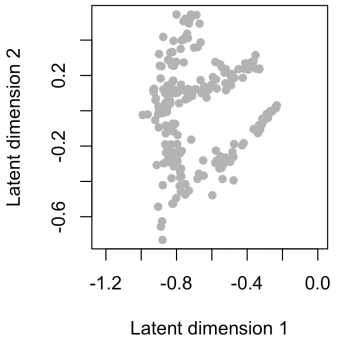

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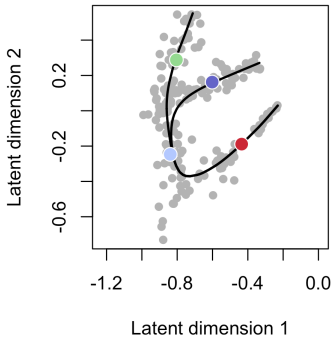
We use the cell sub-types as the given clustering



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(Slingshot (Street et al., 2018))

We estimate two trajectories in the oligodendrocytes, which diverge at the mature oligodendrocytes.

Major Cell Type (6 total)	Count (5000+ total)	Number of cell sub-types (13 total)
Pdgfra+ precursor	70+	1
Oligodendrocyte precursor cell	300+	1
Differentiation-committed oligodendrocyte precursors	100+	1
Newly formed oligodendrocytes	500+	2
Myelin-forming oligodendrocytes	1200+	2
Mature oligodendrocyte	2700+	6

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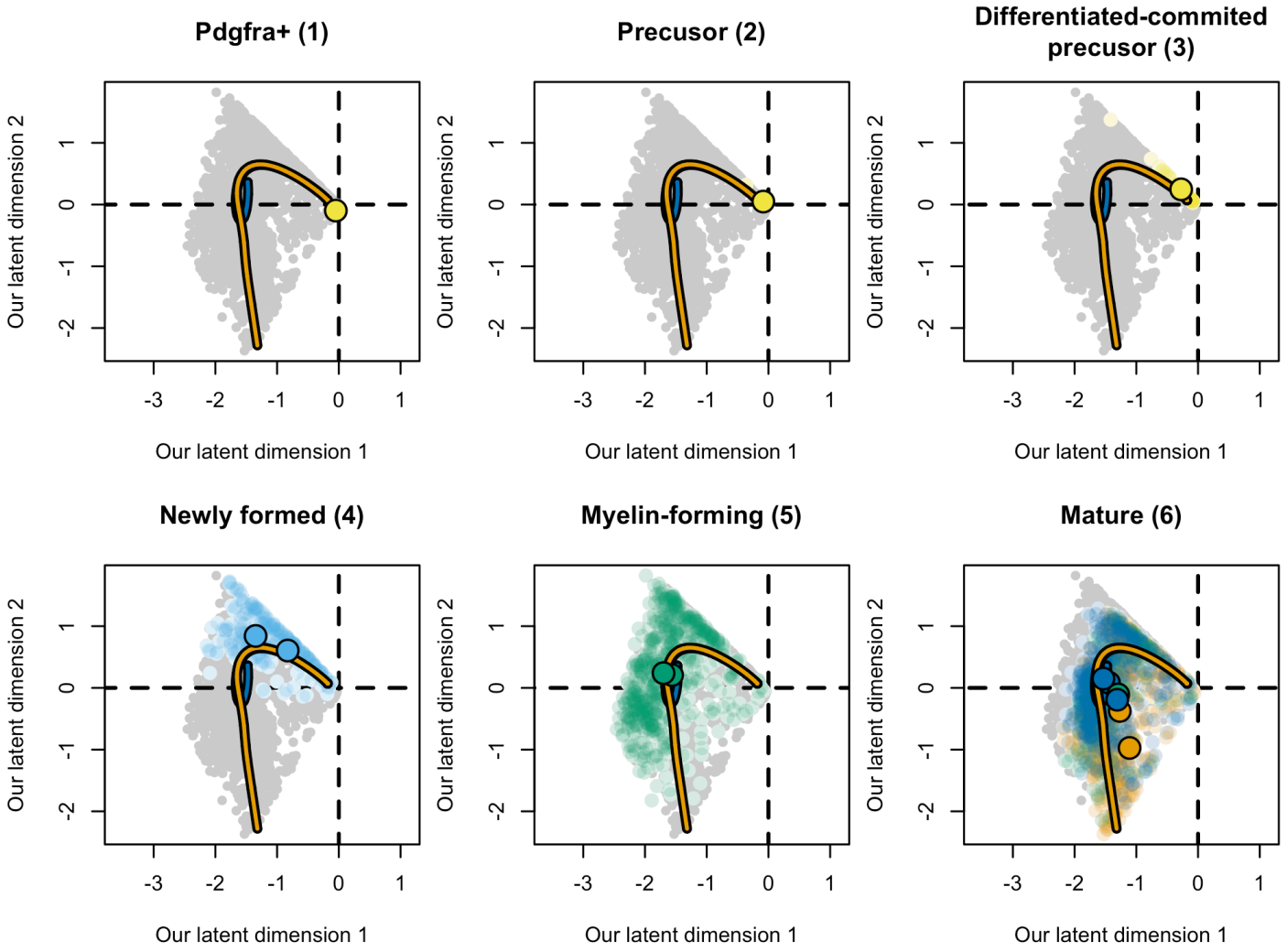

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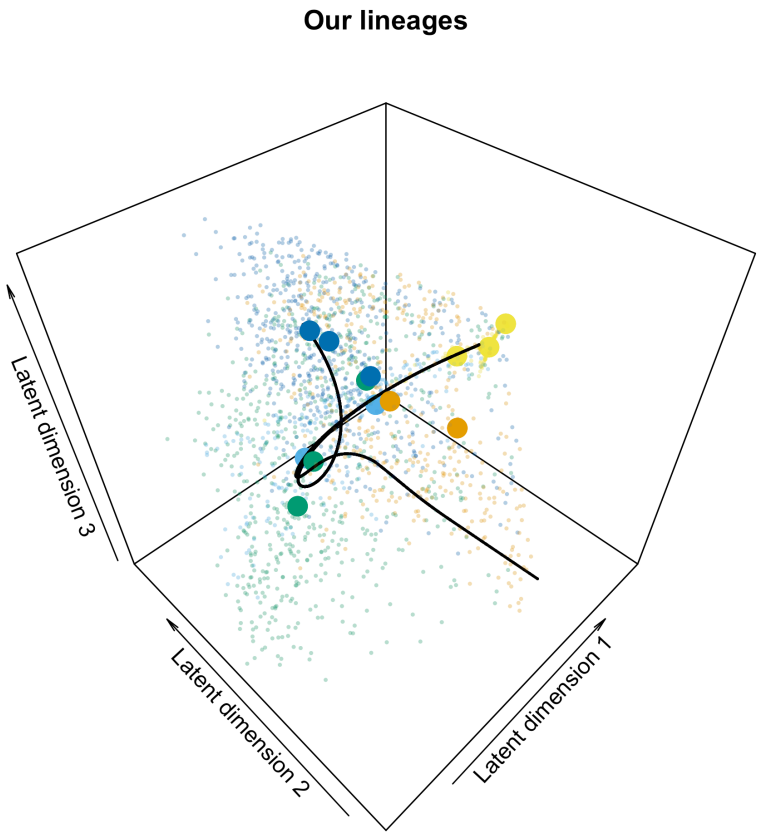
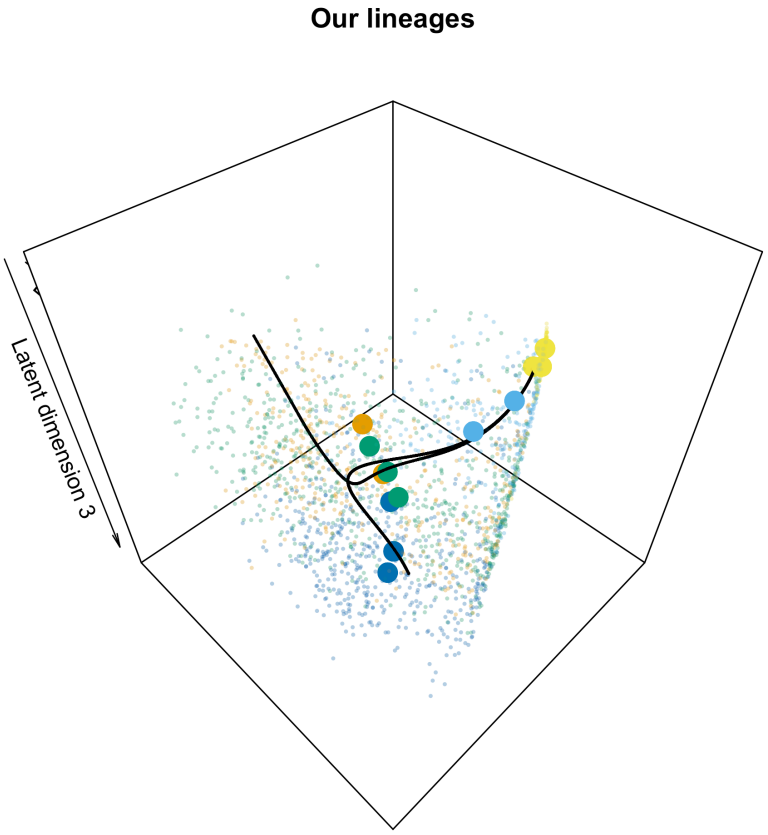
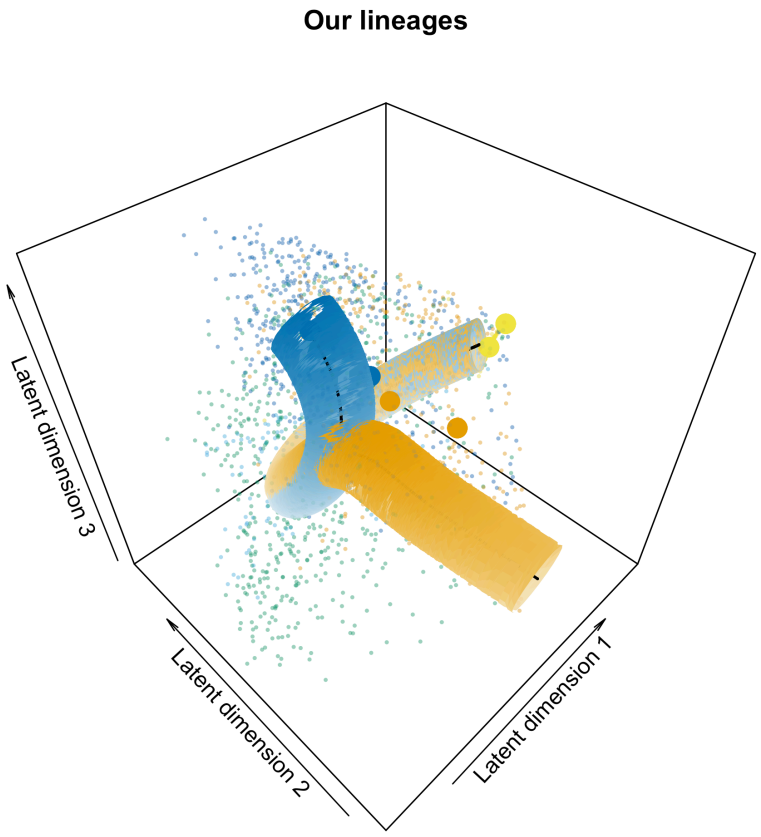
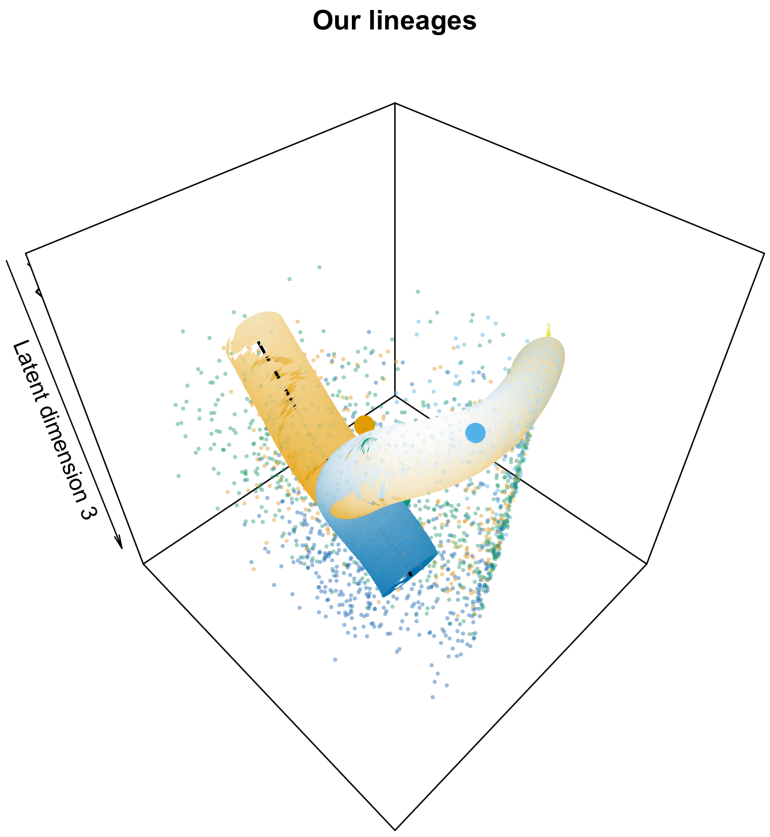




We use a bootstrap-based heuristic to build a “uncertainty tube” to see if the trajectories are indistinguishable.





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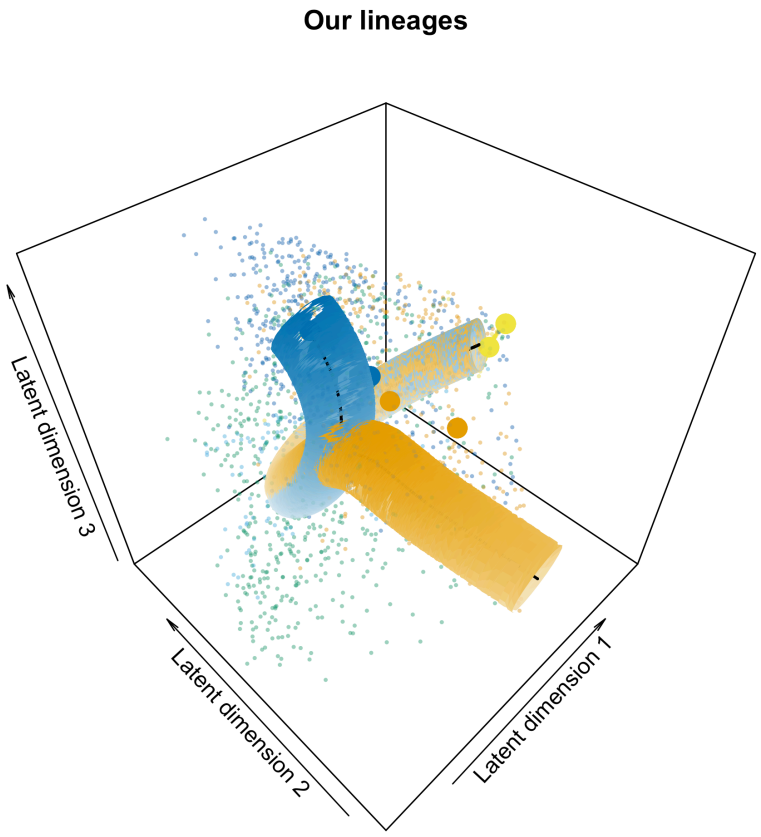

- Not a formal confidence set, but a useful visual diagnostic nonetheless
- Visible divergence of the two trajectories at the mature oligodendrocytes

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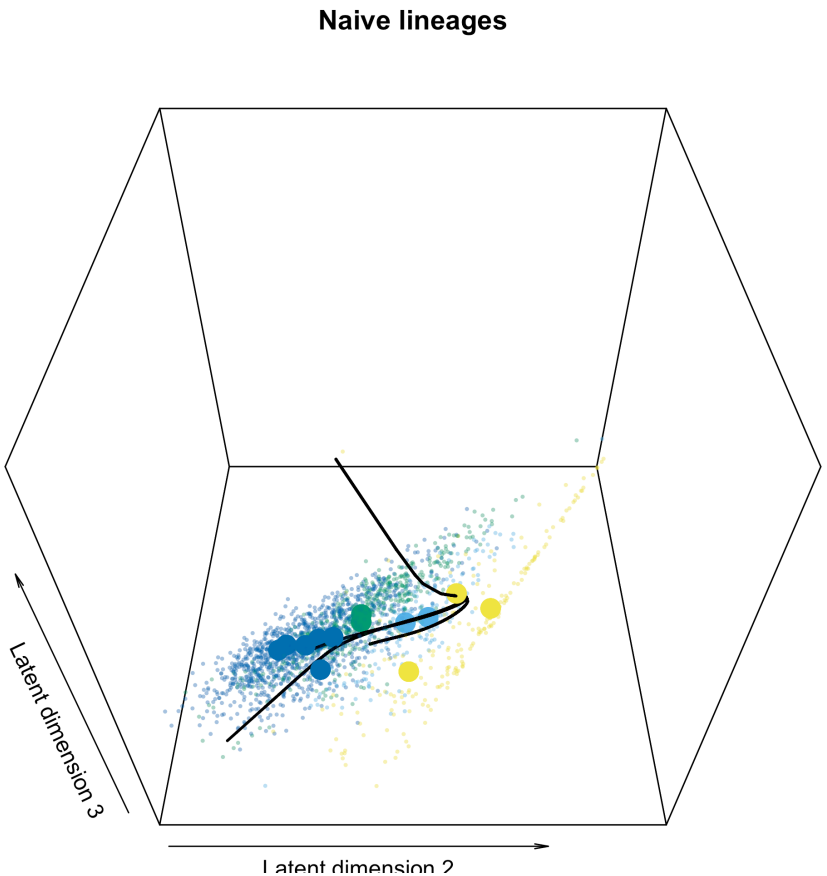

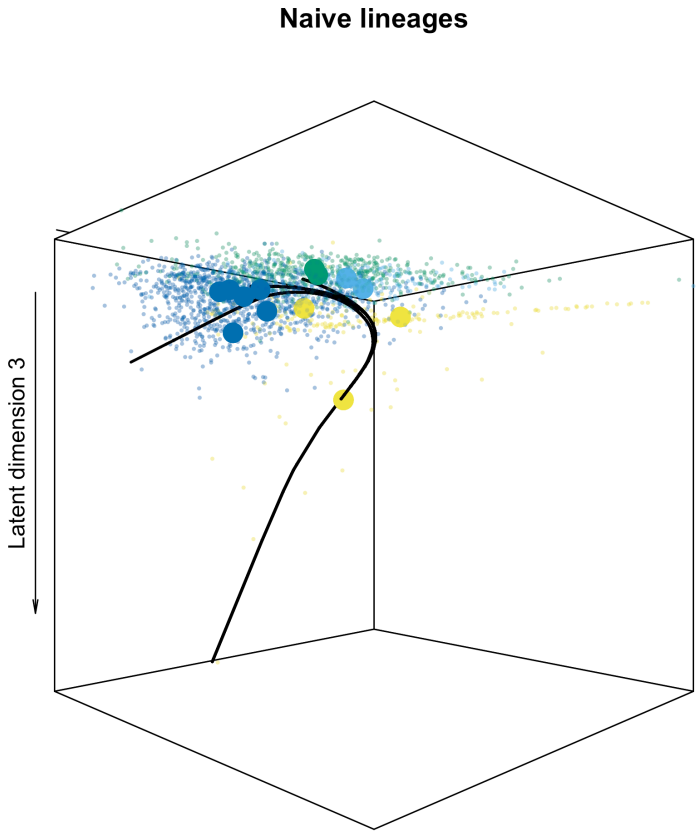

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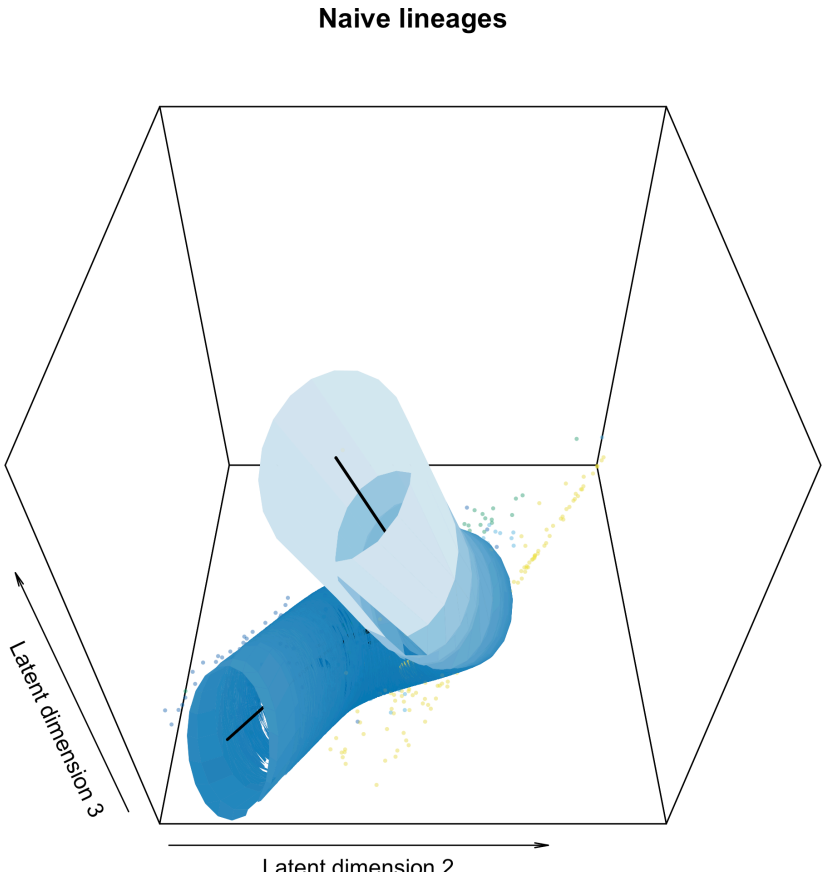

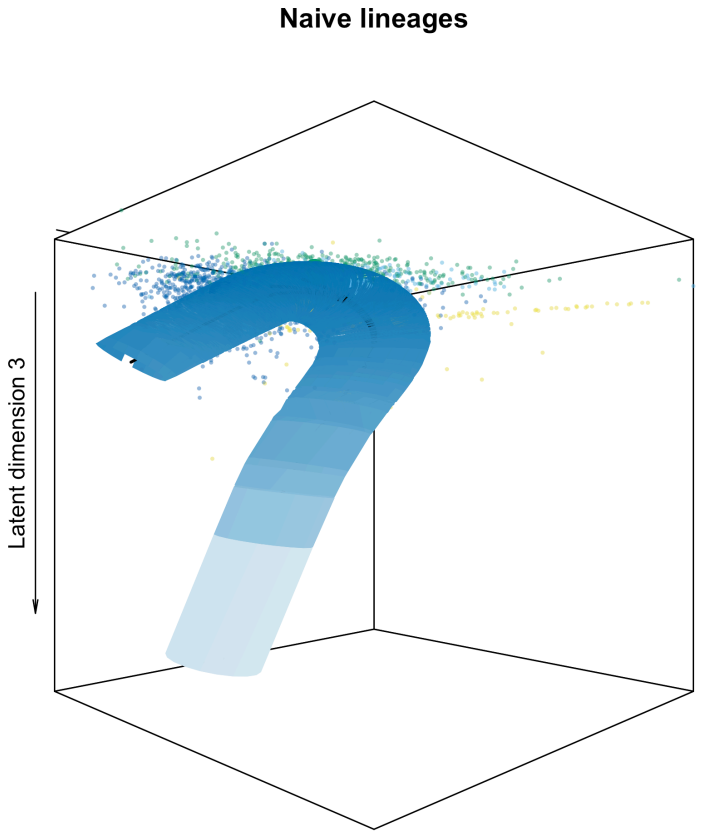

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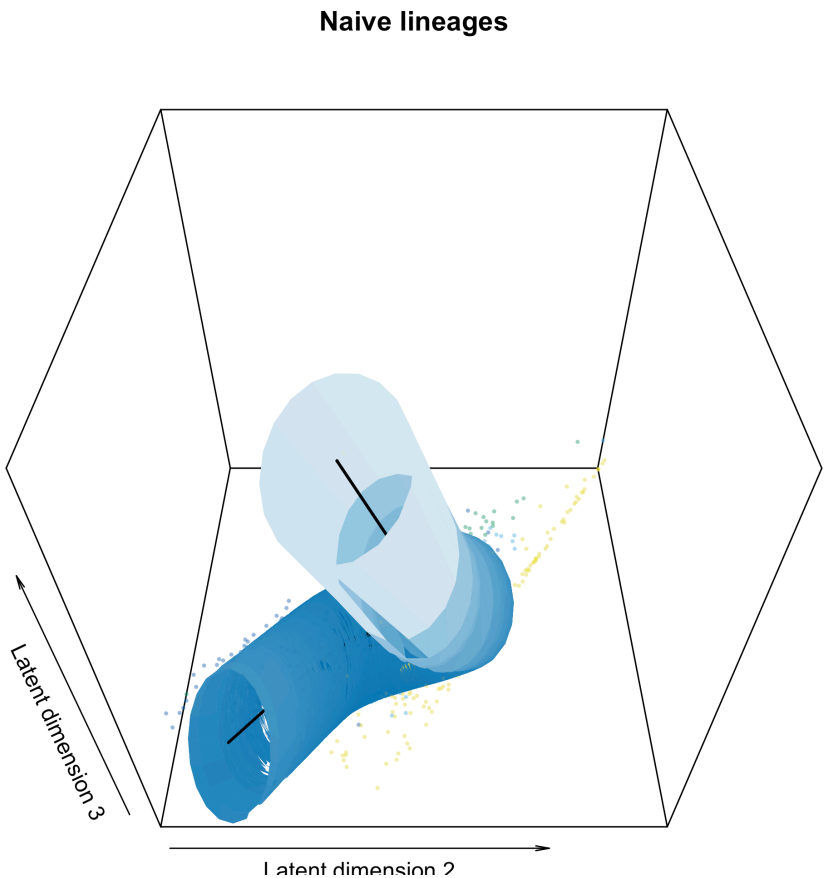

- All five trajectories are contained in the same uncertainty tube
- When using SVD (fixed-variance Gaussian), we recover similar results from previous work that suggest only one lineage

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