ETH zürich

Department of Biosystems Science and Engineering

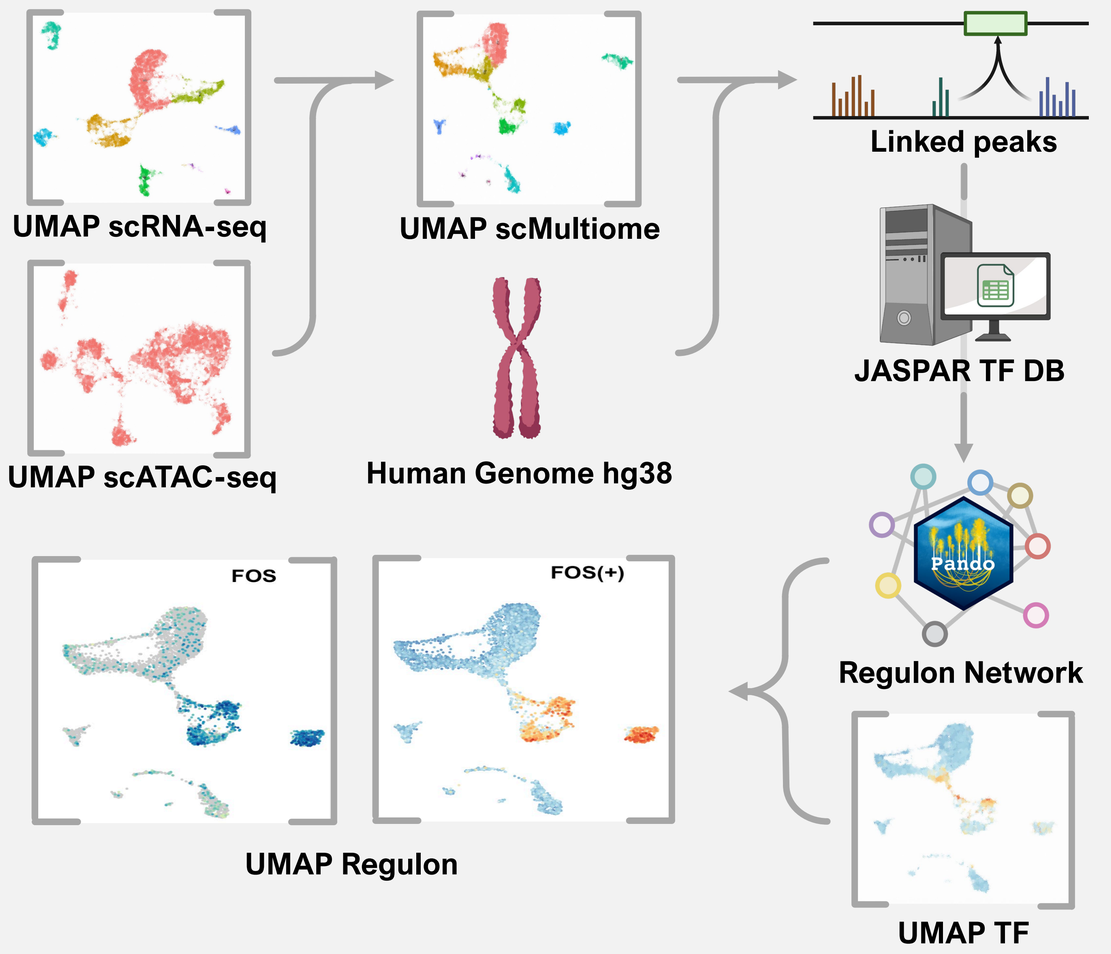
Single-cell multiome analysis of retinal organoid data

Jannik Neumann[1], Lucas Merlicek[1], Arthur Theuer[1] and Moritz Ullhofen[1]
[1]Department of Biosystems Science and Engineering, ETH Zurich

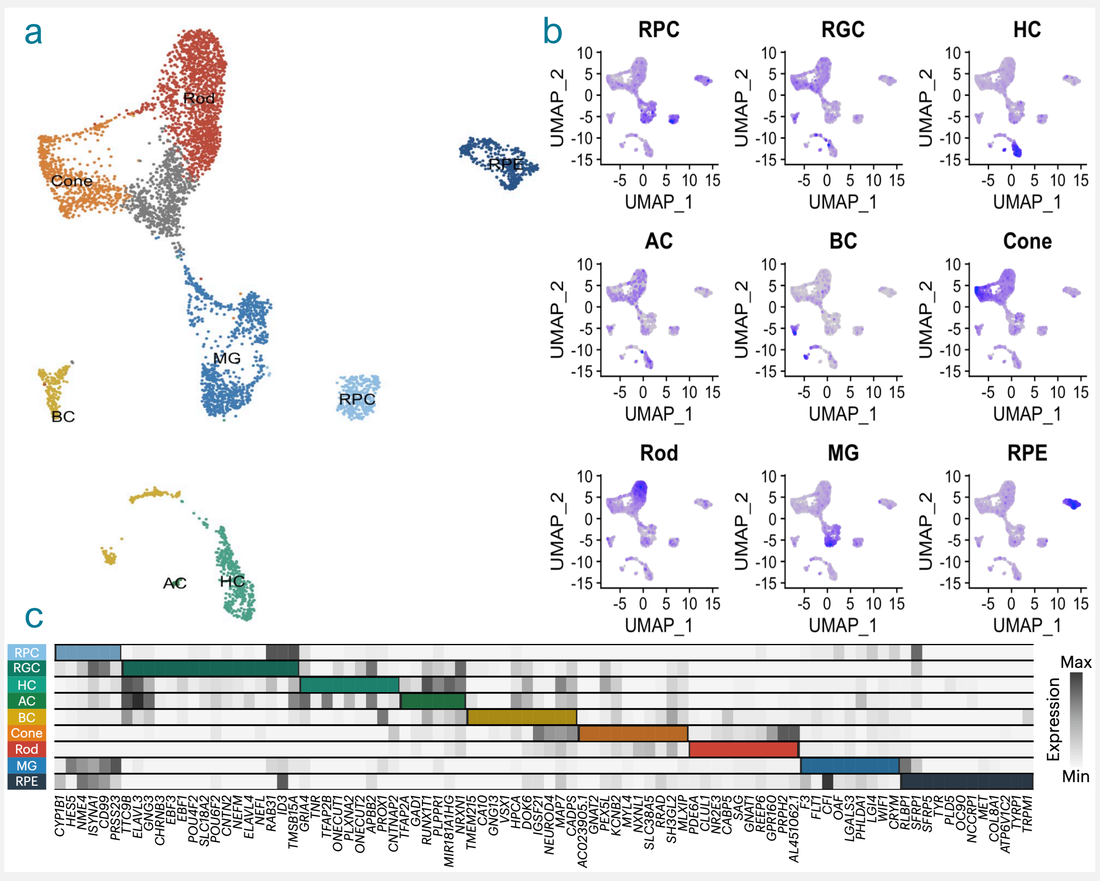
1 Introduction

We performed individual analysis of the scRNA-seq data, including feature selection, 2D embedding, and cell-type annotation. Additionally, we conducted a separate 2D embedding analysis of the scATAC-seq data. Furthermore, we carried out a bi-modal integrative analysis of both modalities, incorporating peak-gene linkage and enrichment of transcription factor binding motifs. Finally, we analyzed TF regulomes using PANDO.

2 Method overview

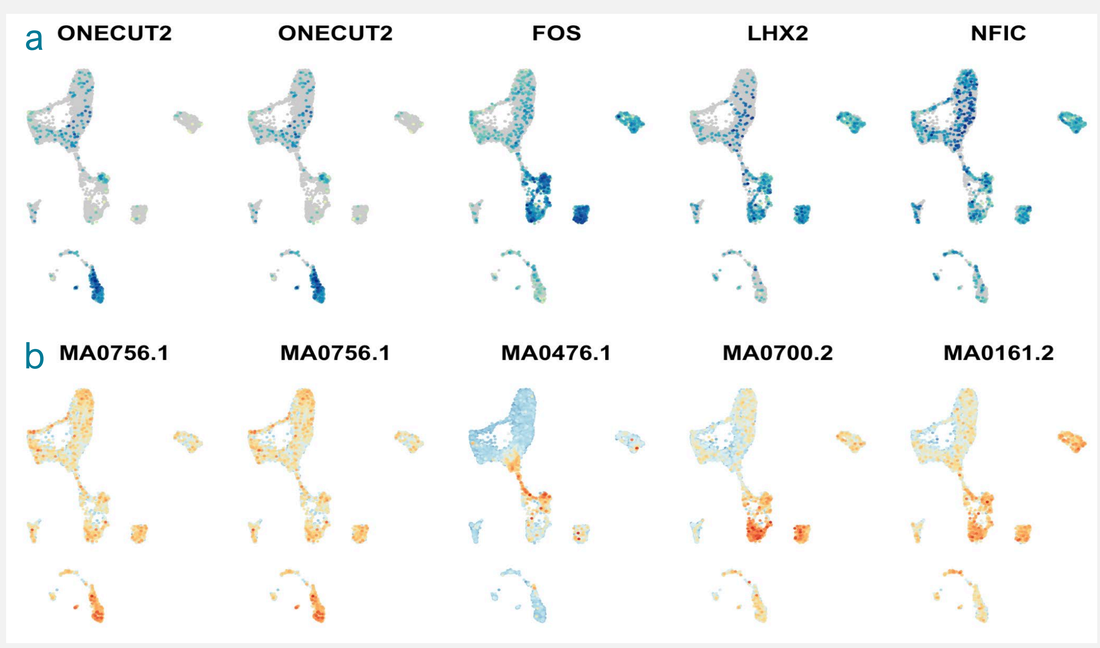


3 Results Bimodal cell type annotation

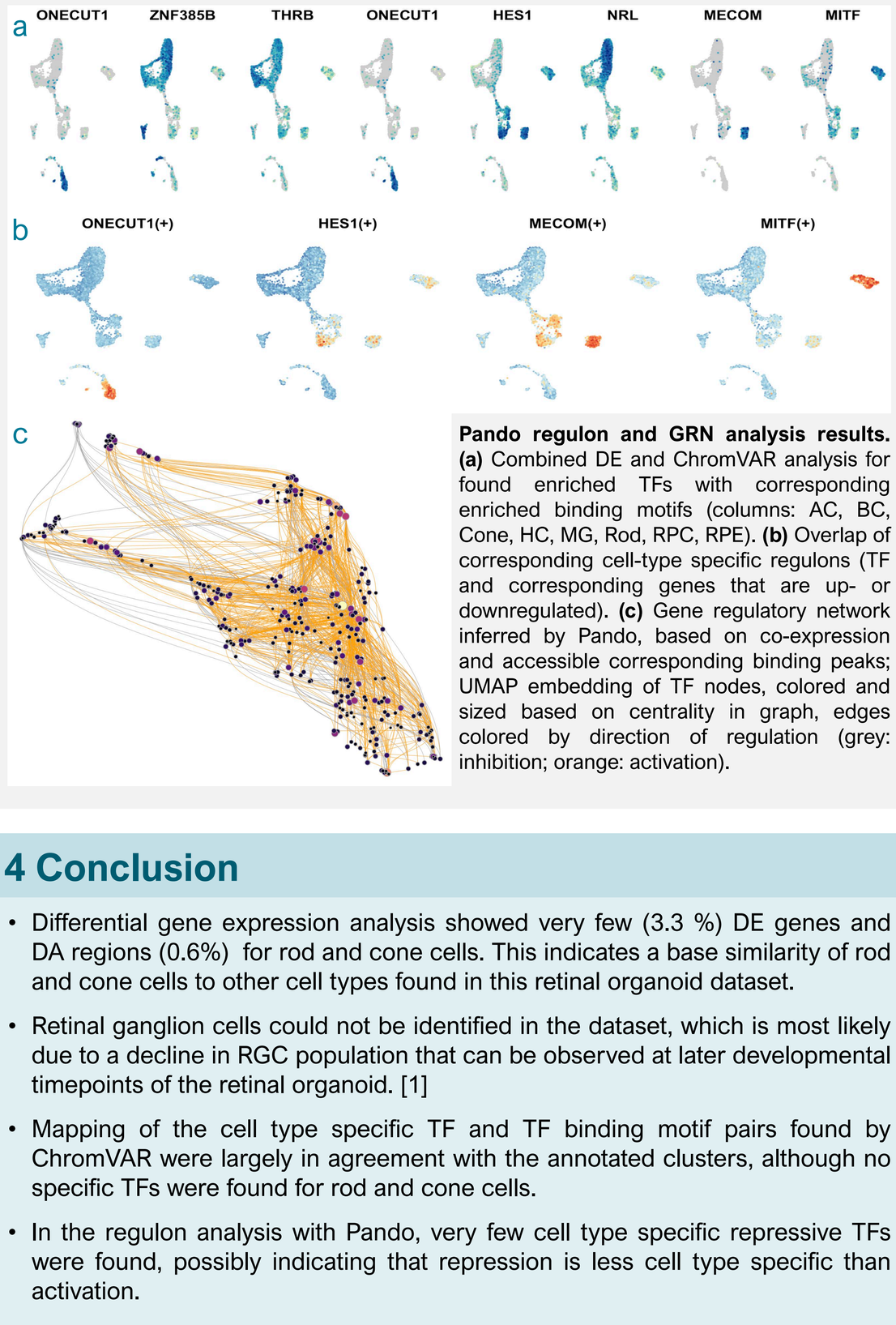


(a) ATAC and RNA scMultiome data were used to construct a weighted nearest neighbor graph. These relationships were used to generate bimodal clusters and a UMAP embedding. **(b)** Expression of retinal cell type markers was mapped to infer the cell identity of the generated clusters. **(c)** Canonical retinal organoid cell type markers were taken from Wahle, P., Brancati, G., Harmel, C. et al., 2023.

Cell-type specific TF/binding-motif enrichment



ChromVAR motif enrichment analysis. Columns correspond to cell types AC, HC, MG, RPC, RPE; pairs of cell-type specific differentially expressed TF based on animalTFDB database (top row) with corresponding cell-type specific enriched TF binding motifs based on ChromVAR estimated differential accessibility score.



Pando regulon and GRN analysis results. **(a)** Combined DE and ChromVAR analysis for found enriched TFs with corresponding enriched binding motifs (columns: AC, BC, Cone, HC, MG, Rod, RPC, RPE). **(b)** Overlap of corresponding cell-type specific regulons (TF and corresponding genes that are up- or downregulated). **(c)** Gene regulatory network inferred by Pando, based on co-expression and accessible corresponding binding peaks; UMAP embedding of TF nodes, colored and sized based on centrality in graph, edges colored by direction of regulation (grey: inhibition; orange: activation).

4 Conclusion

- Differential gene expression analysis showed very few (3.3 %) DE genes and DA regions (0.6%) for rod and cone cells. This indicates a base similarity of rod and cone cells to other cell types found in this retinal organoid dataset.
- Retinal ganglion cells could not be identified in the dataset, which is most likely due to a decline in RGC population that can be observed at later developmental timepoints of the retinal organoid. [1]
- Mapping of the cell type specific TF and TF binding motif pairs found by ChromVAR were largely in agreement with the annotated clusters, although no specific TFs were found for rod and cone cells.
- In the regulon analysis with Pando, very few cell type specific repressive TFs were found, possibly indicating that repression is less cell type specific than activation.

References

[1] Wahle, P., Brancati, G., Harmel, C. et al. Multimodal spatiotemporal phenotyping of human retinal organoid development. Nat Biotechnol (2023).

Partner/Sponsor: Quantitative Developmental Biology Lab

D BSSE