Metacells facilitate the analysis of single-cell multiomics data

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Introduction

- Single-cell multiomics: measurement of different modalities (e.g., ATAC, RNA, proteins) in the same cell (Fig.3A)
- Precise analysis of cell-type specific transcriptional regulation (Fig.3B).

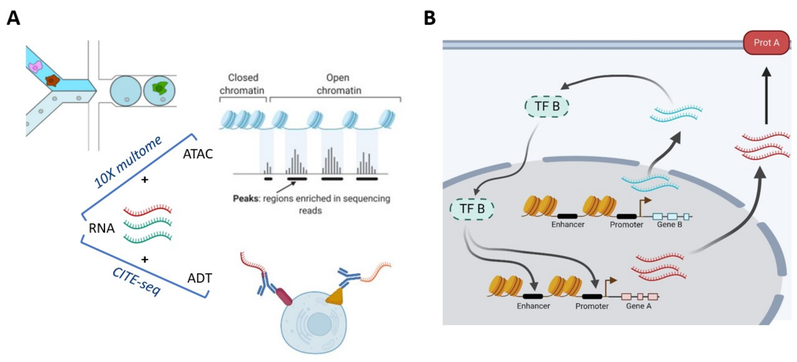


Figure 1: Single-cell multiomics (A) can be used to study cell-type specific transcriptional regulation (B)

- **Limitations:** Large size, high sparsity of the data.
- **Solution:** Merging highly similar cells in metacells, proposed for scRNA-seq **(Baran et al. 2019)**.
- **Aim:** Extension of `SuperCell` **(Bilous et al. 2022)**, to single-cell multiomics. (Fig.2B).

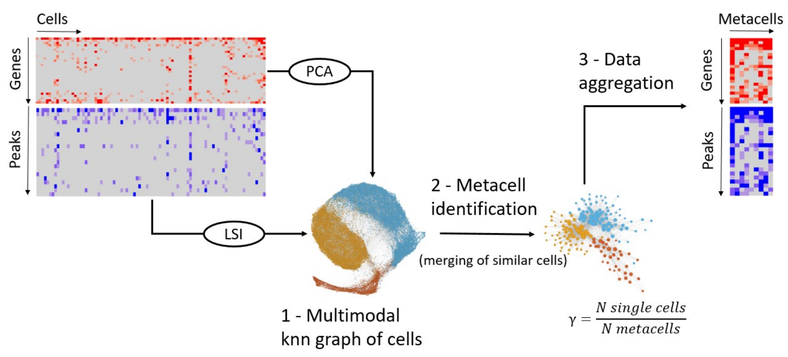


*Figure 2: SuperCell workflow to identify multiomics metacells at a graining level γ. The multimodal knn graph is computed using the WNN method from Seurat **(Hao et al. 2021)**.*

Benchmark

Multiomodal version of `SuperCell` versus unimodal tools (Fig.3):

- Purer metacells
- Compact and separated metacells in both modalities
- Faster

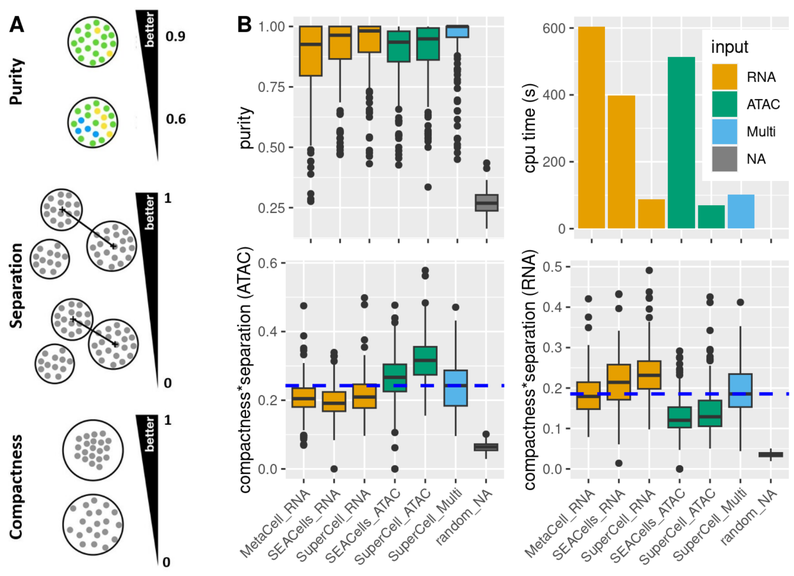


*Figure 3: **A** Benchmark metrics. **B** Benchmark results of metacell tools on a 10x multiome (RNA + ATAC) dataset of PBMC, graining level γ=75. Tools: new version of SuperCell, SEACells **(Persad et al. 2022)**, MetaCell2 **(Ben-Kiki et al. 2021)**.*

SuperCell Analyses

10X multiome dataset of PBMCs

`SuperCell` identifies robust metacells in the PBMC multiomic space (Fig.4).

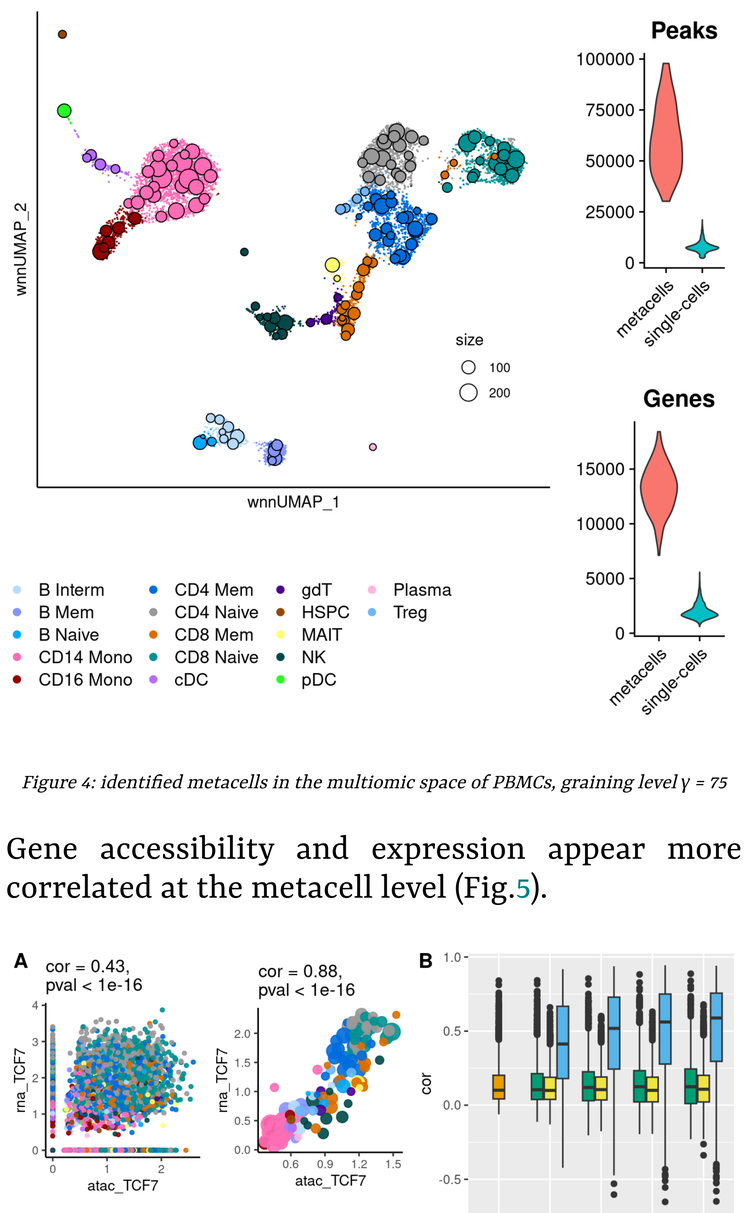


Figure 4: identified metacells in the multiomic space of PBMCs, graining level γ = 75

Gene accessibility and expression appear more correlated at the metacell level (Fig.5).

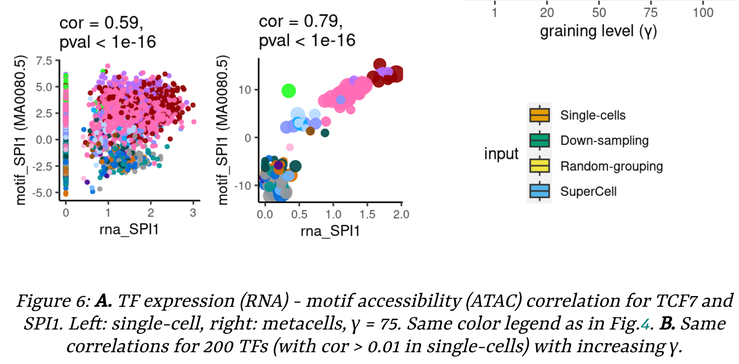


*Figure 5: **A**. gene accessibility - gene expression correlation for TCF7 and SPI1. Left: Single-cell level, right: metacell γ = 75. Same color legend as in Fig.4. **B**. Same correlations for the 2000 highly variable genes (on RNA) with increasing γ.*

Correlation between transcription factor (TF) expression and corresponding motif accessibility also becomes clearer using metacells (Fig.6).

*Figure 6: **A.** TF expression (RNA) - motif accessibility (ATAC) correlation for TCF7 and SPI1. Left: single-cell, right: metacells, γ = 75. Same color legend as in Fig.4. **B.** Same correlations for 200 TFs (with cor > 0.01 in single-cells) with increasing γ.*

CITE-seq atlas of 160,000 PBMCs

- Identification of metacells by sample (γ = 20)
- Correction of the batch effect at the metacell level (Fig.7A&B).
- This workflow runs on a standard laptop (Fig.7C).

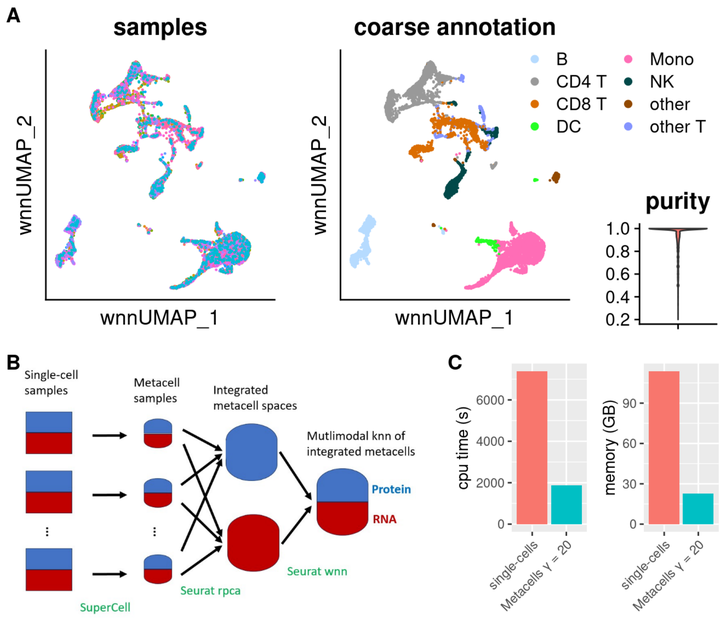


*Figure 7: **A.** UMAP visualizations of 8,000 multiomic metacells, metacell purities with respect to original annotation from **(Hao et al. 2021)**. **B.** Metacell workflow. **C.** Computational resources used by single-cell and metacell workflows.*

RNA-protein correlation in the CITE-seq atlas is increased with metacells (Fig.8).

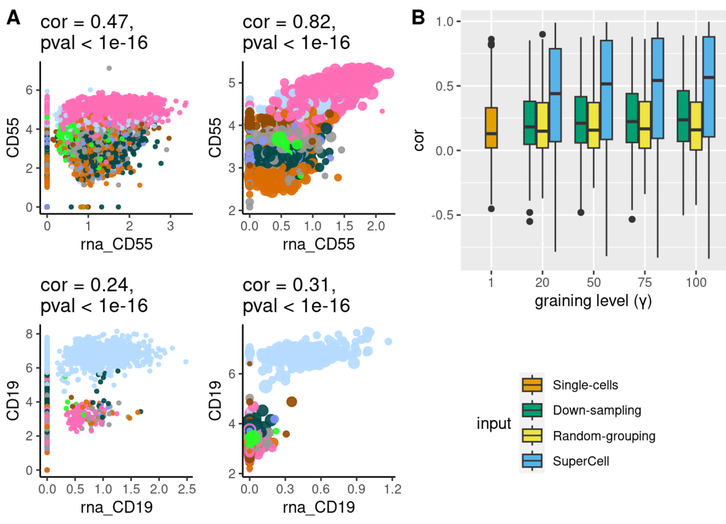
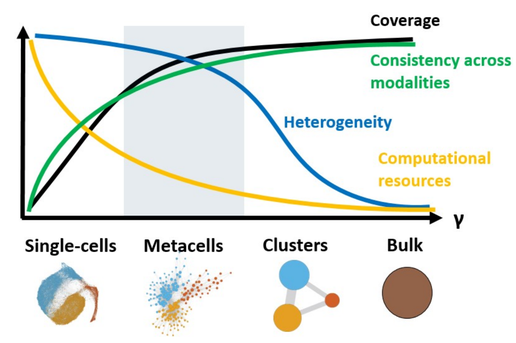


*Figure 8: **A.** RNA-protein correlation for CD55 and CD19. Left: Single-cell level, right: metacell γ = 75 Same color legend as in Fig.7. **B.** RNA-Protein correlation for 213 gene-protein pairs with increasing γ*

Conclusion



Perspectives

- **Downstream analyses** of sc-multiomics:
  - gene regulatory network inference
  - multiomic velocity
- **Metaspots** for spatial-omics

References

Baran, Yael, Akhiad Bercovich, Arnau Sebe-Pedros, Yaniv Lubling, Amir Giladi, Elad Chomsky, Zohar Meir, Michael Hoichman, Aviezer Lifshitz, and Amos Tanay. 2019. "MetaCell: Analysis of Single-Cell RNA-Seq Data Using K-Nn Graph Partitions." *Genome Biology* 20 (1): 206. https://doi.org/10.1186/s13059-019-1812-2.

Ben-Kiki, Oren, Akhiad Bercovich, Aviezer Lifshitz, and Amos Tanay. 2021. "A Divide and Conquer Metacell Algorithm for Scalable scRNA-Seq Analysis." Preprint. Bioinformatics. https://doi.org/10.1101/2021.08.08.453314.

Bilous, Mariia, Loc Tran, Chiara Cianciaruso, Aurélie Gabriel, Hugo Michel, Santiago J. Carmona, Mikael J. Pittet, and David Gfeller. 2022. "Metacells Untangle Large and Complex Single-Cell Transcriptome Networks." *BMC Bioinformatics* 23 (1): 336. https://doi.org/10.1186/s12859-022-04861-1.

Hao, Yuhan, Stephanie Hao, Erica Andersen-Nissen, William M. Mauck, Shiwei Zheng, Andrew Butler, Maddie J. Lee, et al. 2021. "Integrated Analysis of Multimodal Single-Cell Data." *Cell* 184 (13): 3573–3587.e29. https://doi.org/10.1016/j.cell.2021.04.048.

Persad, Sitara, Zi-Ning Choo, Christine Dien, Ignas Masilionis, Ronan Chaligné, Tal Nawy, Chrysothemis C. Brown, Itsik Pe'er, Manu Setty, and Dana Pe'er. 2022. "SEACells: Inference of Transcriptional and Epigenomic Cellular States from Single-Cell Genomics Data." bioRxiv. https://doi.org/10.1101/2022.04.02.486748.

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