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).

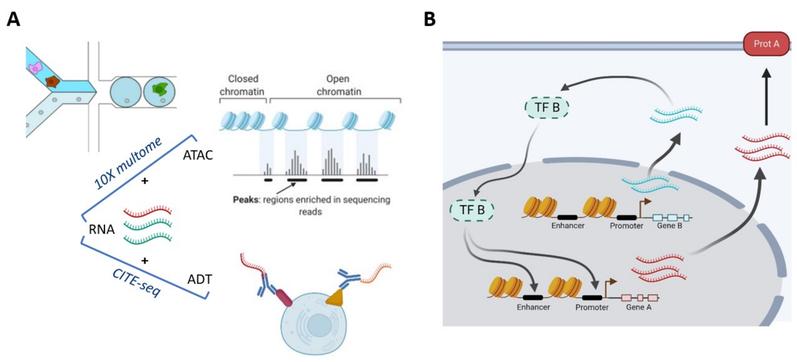


Figure 1: Single-cell multiomics (A) can be used to study cell-type specific transcriptional regulation (B).

- **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).

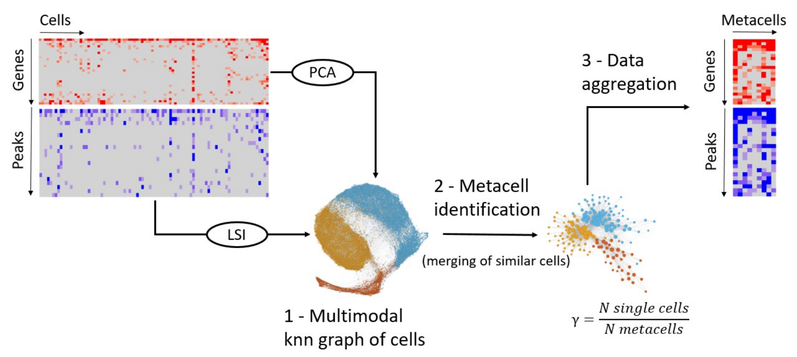


*Figure 2: SuperCell workflow to identify multiomics metacells at a graining level γ. The multimodal knn graph is computed using the WNN method from Seurat **(Hao et al. 2021)**.*

Benchmark

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

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

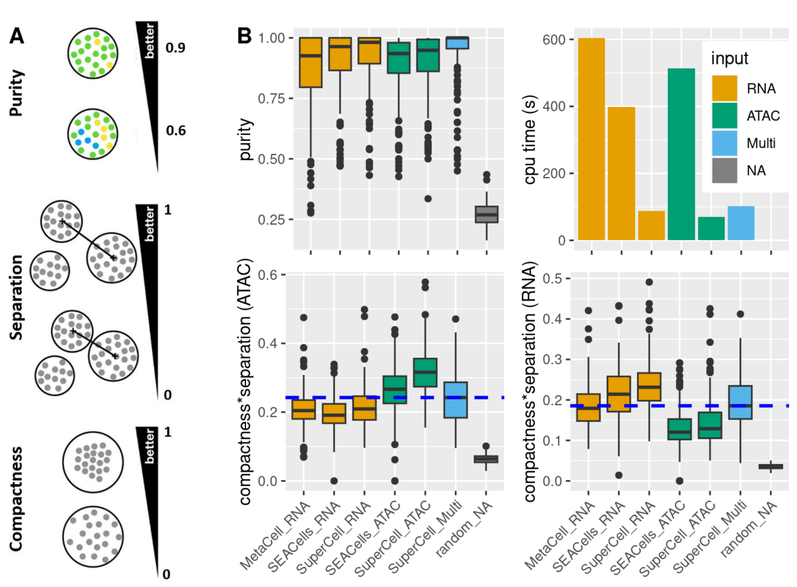


*Figure 3: **A** Benchmark metrics. **B** Benchmark results of metacell tools on a 10x multiome (RNA + ATAC) dataset of PBMCs, graining level γ=75. Tools: new version of SuperCell, SEACells **(Persad et al. 2023)**, MetaCell2 **(Ben-Kiki et al. 2022)**.*

SuperCell Analyses

10X multiome dataset of PBMCs

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

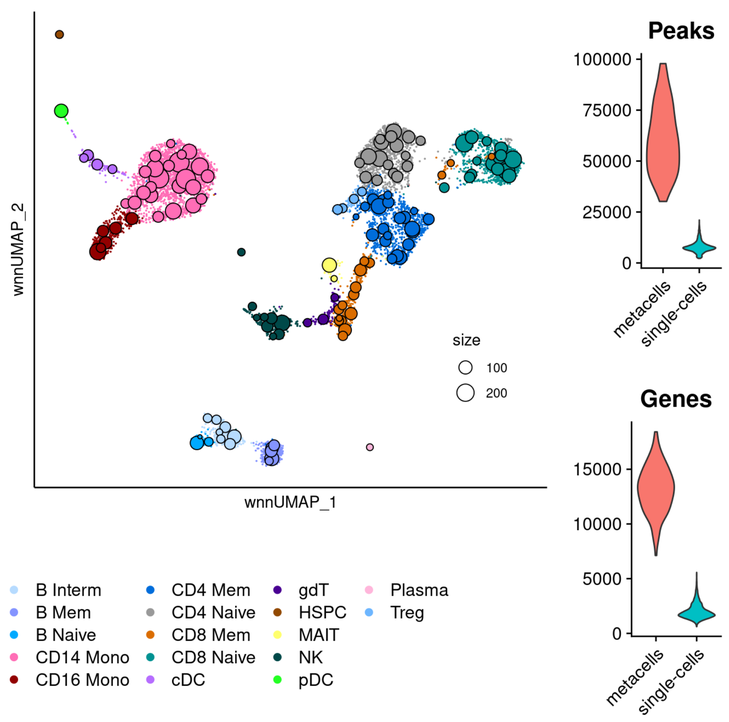


Figure 4: Identified metacells in the multiomic space of PBMCs, graining level γ = 75.

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

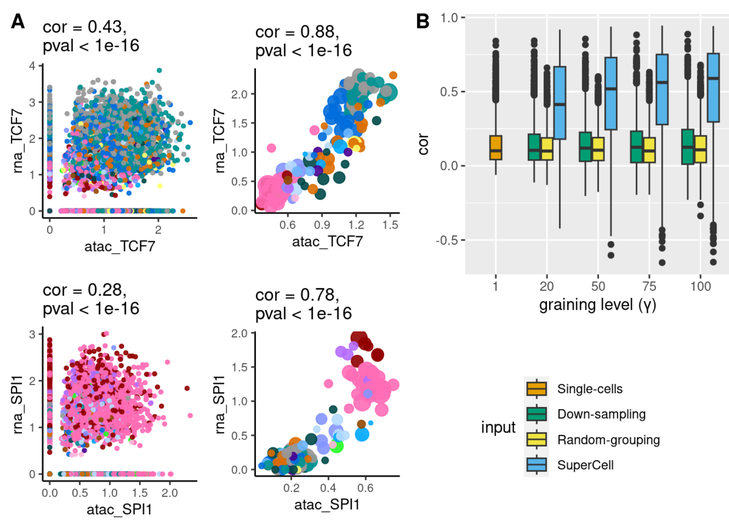


*Figure 5: **A**. Gene accessibility - gene expression correlation for TCF7 and SPI1. Left: Single-cell level, right: metacells γ = 75. Same color legend as in Fig.4. **B**. Same correlations for the 2000 highly variable genes (on RNA) with increasing γ.*

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

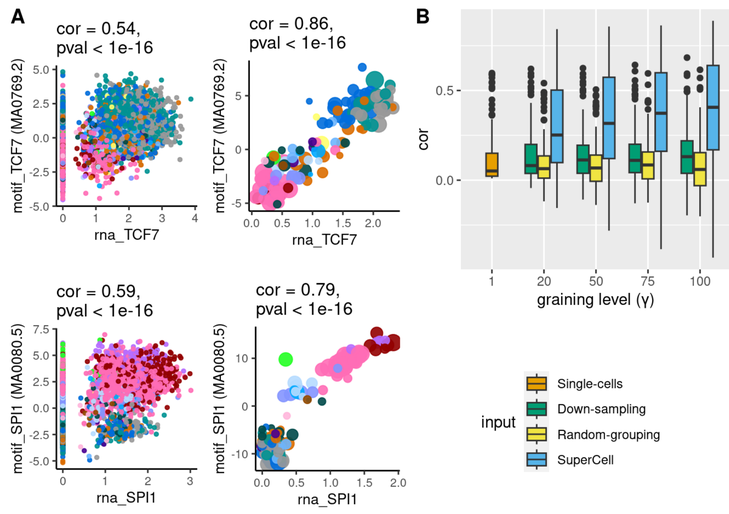


*Figure 6: **A.** TF expression (RNA) - motif accessibility (ATAC) correlation for TCF7 and SPI1. Left: single-cell, right: metacells, γ = 75. Same color legend as in Fig.4. **B.** Same correlations for 200 TFs (with cor > 0.01 in single-cells) with increasing γ.*

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).

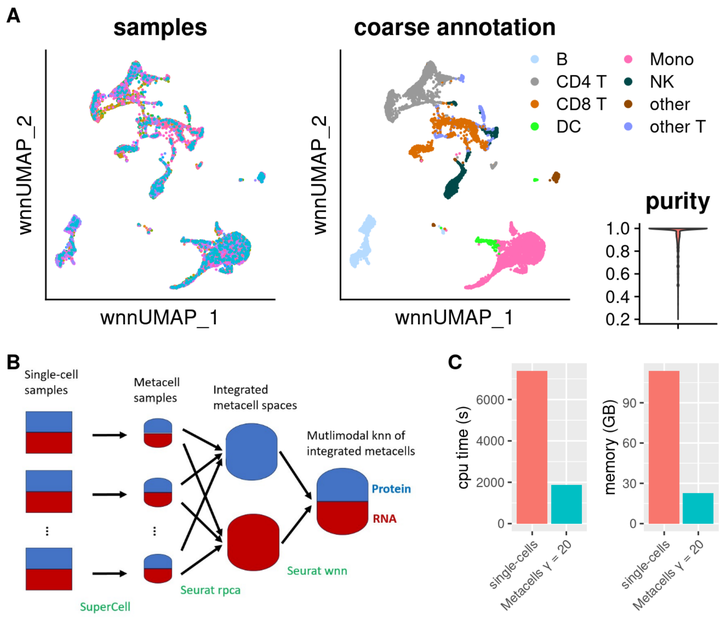


*Figure 7: **A.** UMAP visualizations of 8,000 multiomic metacells, metacell purities with respect to original annotation from **(Hao et al. 2021)**. **B.** Metacell workflow. **C.** Computational resources used by single-cell and metacell workflows.*

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

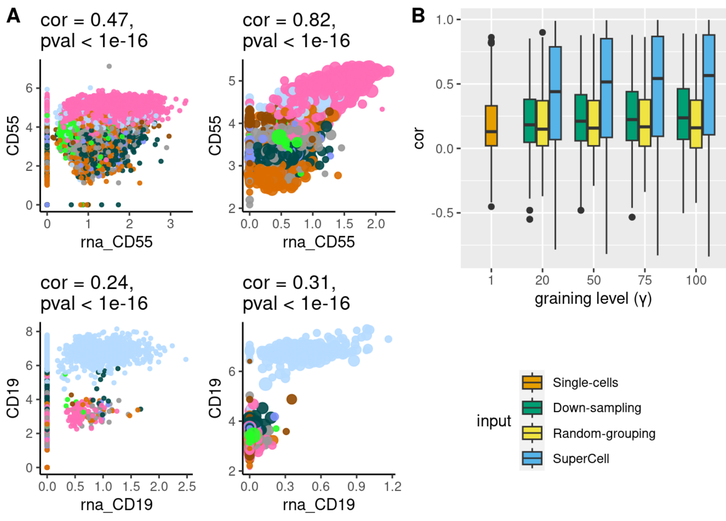
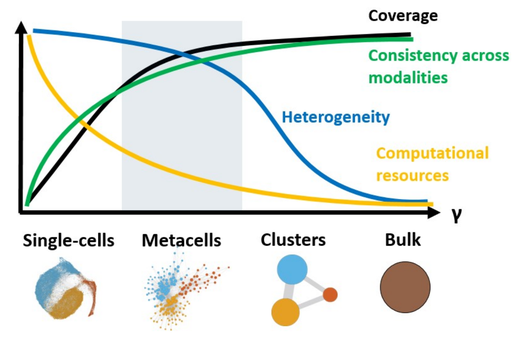


*Figure 8: **A.** RNA-protein correlation for CD55 and CD19 in the 8 reference samples. Left: Single-cell level, right: metacells γ = 20 Same color legend as in Fig.7. **B.** RNA-Protein correlation for 213 gene-protein pairs with increasing γ.*

Conclusion



Perspectives

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

References

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