Benchmarking single cell RNA sequencing integration

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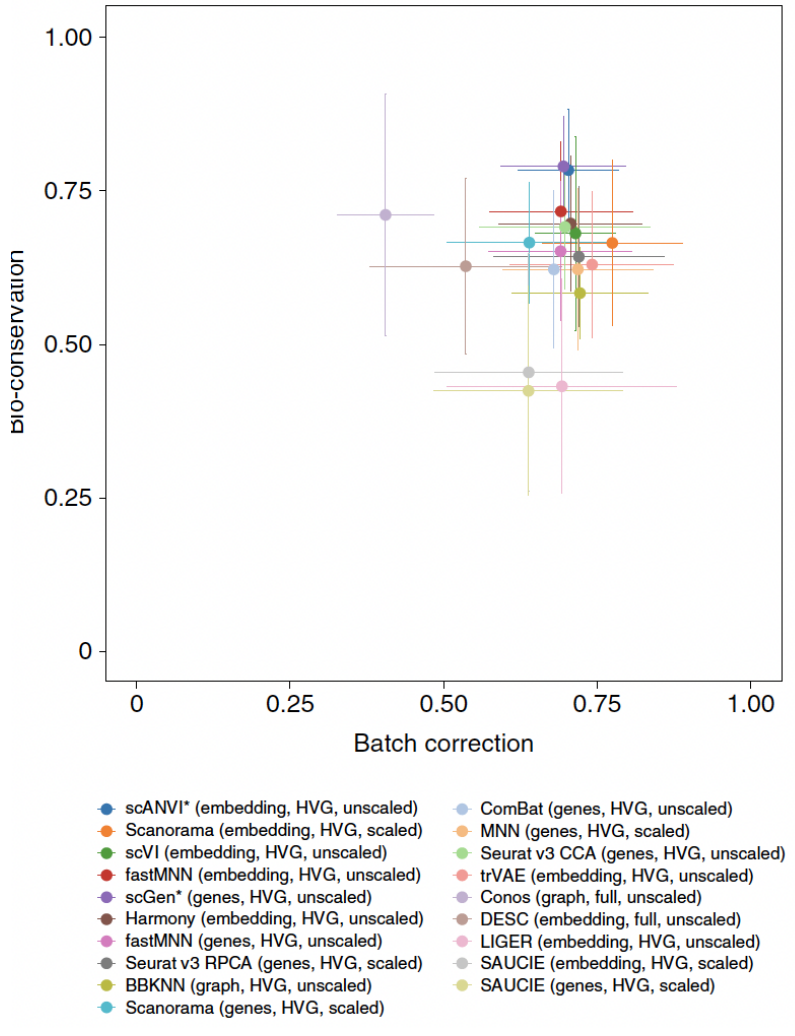
Background

- **Dataset**: Single-cell RNA sequencing (scRNA-seq) datasets.
  - each dataset consists of a `cell` by `gene` expression matrix, where cells are annotated with batches and labels.
- **Goal**: Combining high-throughput sequencing datasets to produce a self-consistent version of the data for downstream analysis.
- **Reason**: Integrating scRNA-seq helps biological findings.
- **Challenges**:
  - Dealing with noise, sparsity, batch effects and rare cell types.
  - Evaluating integration methods.

Background

- (Luecken, Büttner, Chaichoompu, Danese, Interlandi, Müller, Strobl, Zappia, Dugas, Colomé-Tatché, and others, 2022) benchmarked 19 methods in 13 integration tasks.
- They used 14 metrics to evaluate integration methods on their ability to
  - **remove batch effects**, and
  - **conserve biological variations**.
- They provided guidelines to choose an integration method given a task.
- For all methods, they used default parameters.



Methods

- Integrating scRNA-seq datasets usually include two parts:
  - jointly **embedding** high-dimensional input onto a shared latent space, and
  - (soft) **clustering** cells that incorporates annotated information (e.g. cell type).
- In this presentation, we aim to study the dependence of integration methods on the dimension of latent space.
- We focus on three methods that build deep generative models:
  - `scVI`(Lopez, Regier, Cole, Jordan, and Yosef, 2018),
  - `scGen` (Lotfollahi, Wolf, and Theis, 2019), and
  - `scANVI`(Xu, Lopez, Mehlman, Regier, Jordan, and Yosef, 2021).

Evaluation

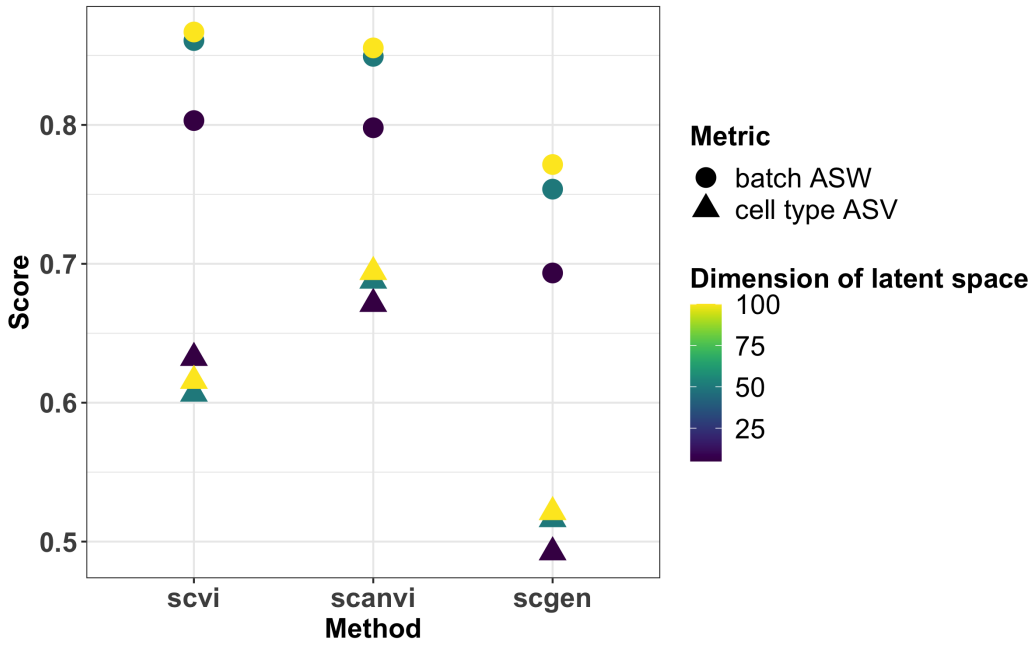
- Average silhouette width (ASW) measures the separation of clusters.
- We use modified **batch ASW** and **cell type ASW** to evaluate the ability of batch removal and biogical conservation, respectively.
- For both, the larger ASW we have, the better.

Real-data analysis: human immune cell integration

- Task: integrating 5 datasets of 10 batches (donors) with cells from peripheral blood and bone marrow, annotated by cell types
- According to (Luecken, Büttner, Chaichoompu, et al., 2022), `scANVI` is one of the best methods, evaluated by a weighted mean of 14 metrics.

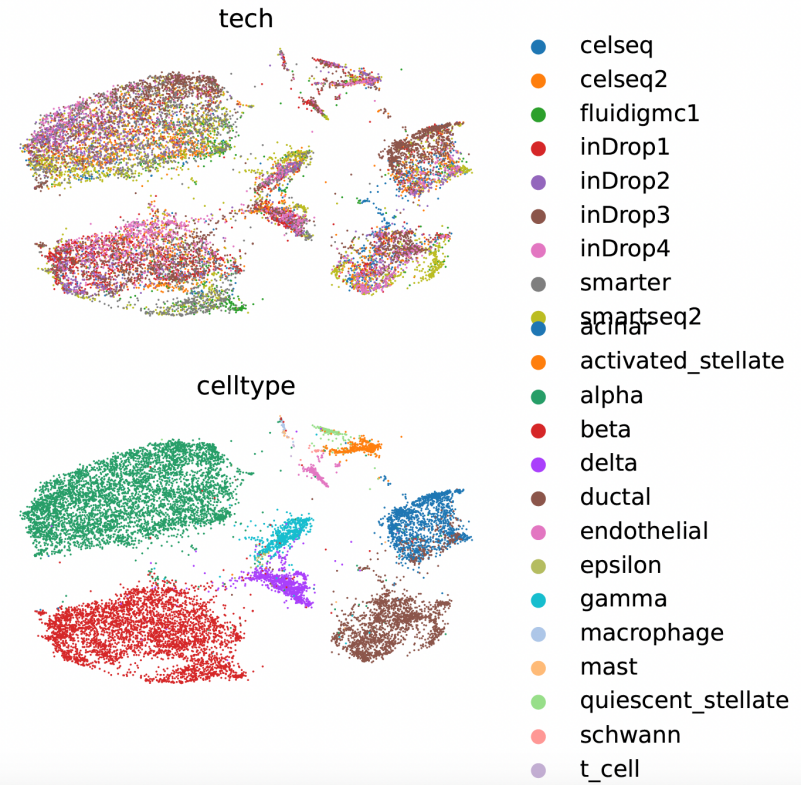
Results

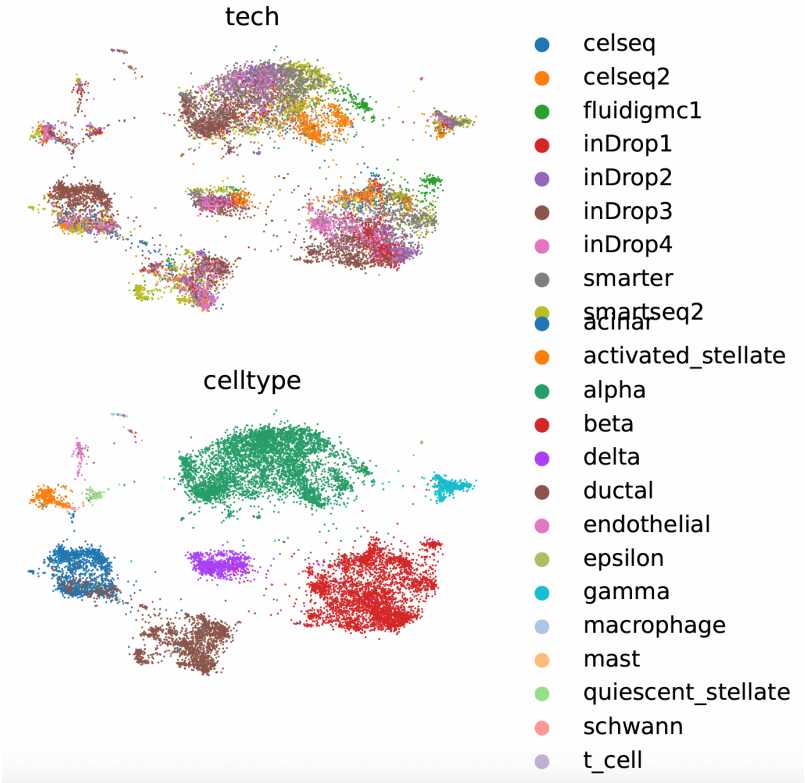
- We vary the dimension of latent space, and evaluate `scvi`, `scanvi` and `scgen` using batch ASW and cell type ASW.
- Overall, `scgen` works worst.
- For `scvi` and `scanvi`, there is a trade-off between removing batch effects and conserving biological variations.
  - Higher-dimensional latent space tends to have better batch correction.
  - For conservation of biological variations, the choice of dimension is unclear (may present opposite order in other datasets).



Results

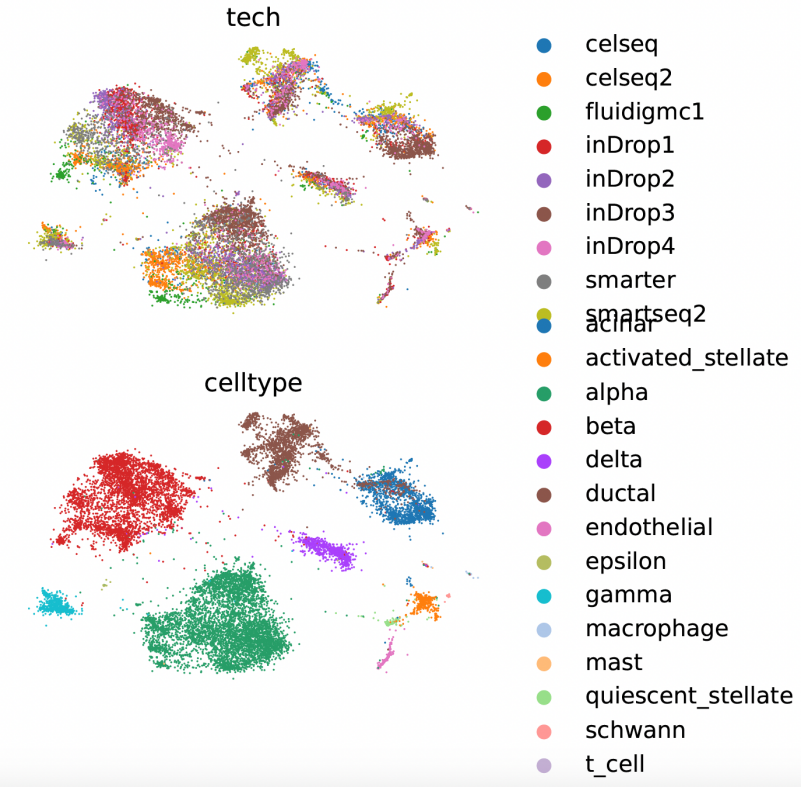
Latent space fitted by `scvi` projected onto 2d space, with dimension of latent space (left) 5 and (right) 100, colored by (top) batches and (bottom) cell types.

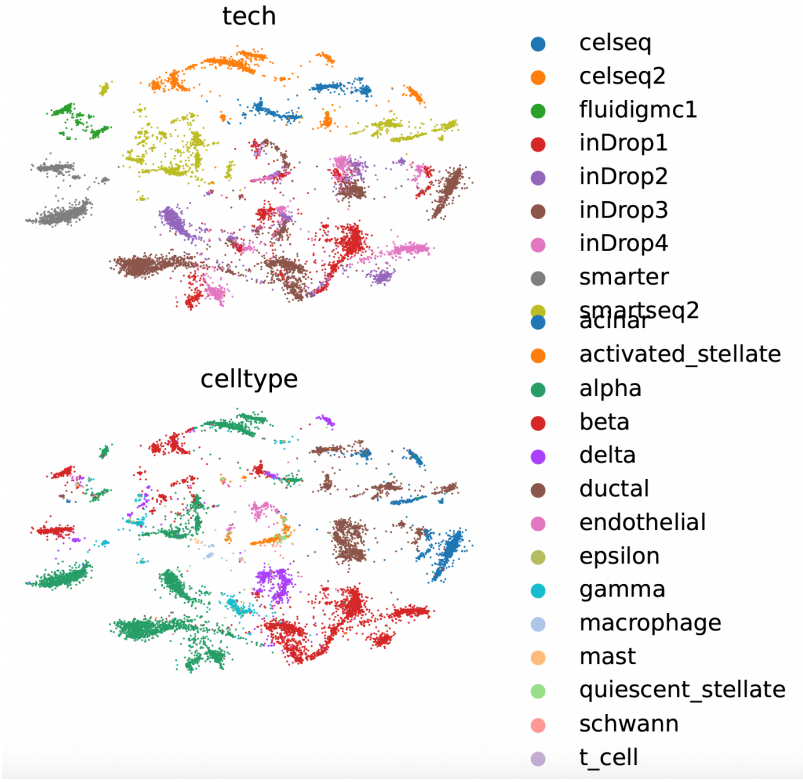




Results

Latent space fitted by (left) `scanvi` and `scgen` projected onto 2d space, , colored by (top) batches and (bottom) cell types.





Takeaways

- Across methods, there is a trade-off between batch removal and conservation of biological variations.
- The choice of latent space dimension doesn't affect the rank across methods.
- For each method, the performance of integration methods is dependent on the dimension of latent space.
  - High-dimensional latent space leads to better batch removal.
  - That being said, it's hard to tell the difference in visualizations on 2d space.

Reproducibility

- Results can be reproduced via https://github.com/XinranMiao/scRNA_int (not yet finished).


Thank You!
Questions?

References

Luecken, M. D., M. Büttner, K. Chaichoompu, et al. (2022). "Benchmarking atlas-level data integration in single-cell genomics". In: *Nature methods* 19.1, pp. 41-50.