Modeling Patient Variability in scRNA Sequence Data

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Games Engineering

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Motivation

&

Variability in cellular profiles

?

Disease progression and treatment outcomes

Dataset

	Stephenson et al. dataset From "Single-cell multi-omics analysis of the immune response in COVID-19"	Wang et al. dataset From "COMBATdb: a database for the COVID-19 Multi-Omics Blood ATlas"
Patients	130	140
Number of cells	781,123	783,704
Variable of interest	'Status' - 4 categories	'Outcome' - 6 ranks
Batch Variable	'Site' - 3 categories	'Institute'- 2 categories

Methods

Pseudobulk analysis

- Aggregating of cells
- Established method, but not standardized
    - Input Type
    - Aggregation Method
    - Distance Metric

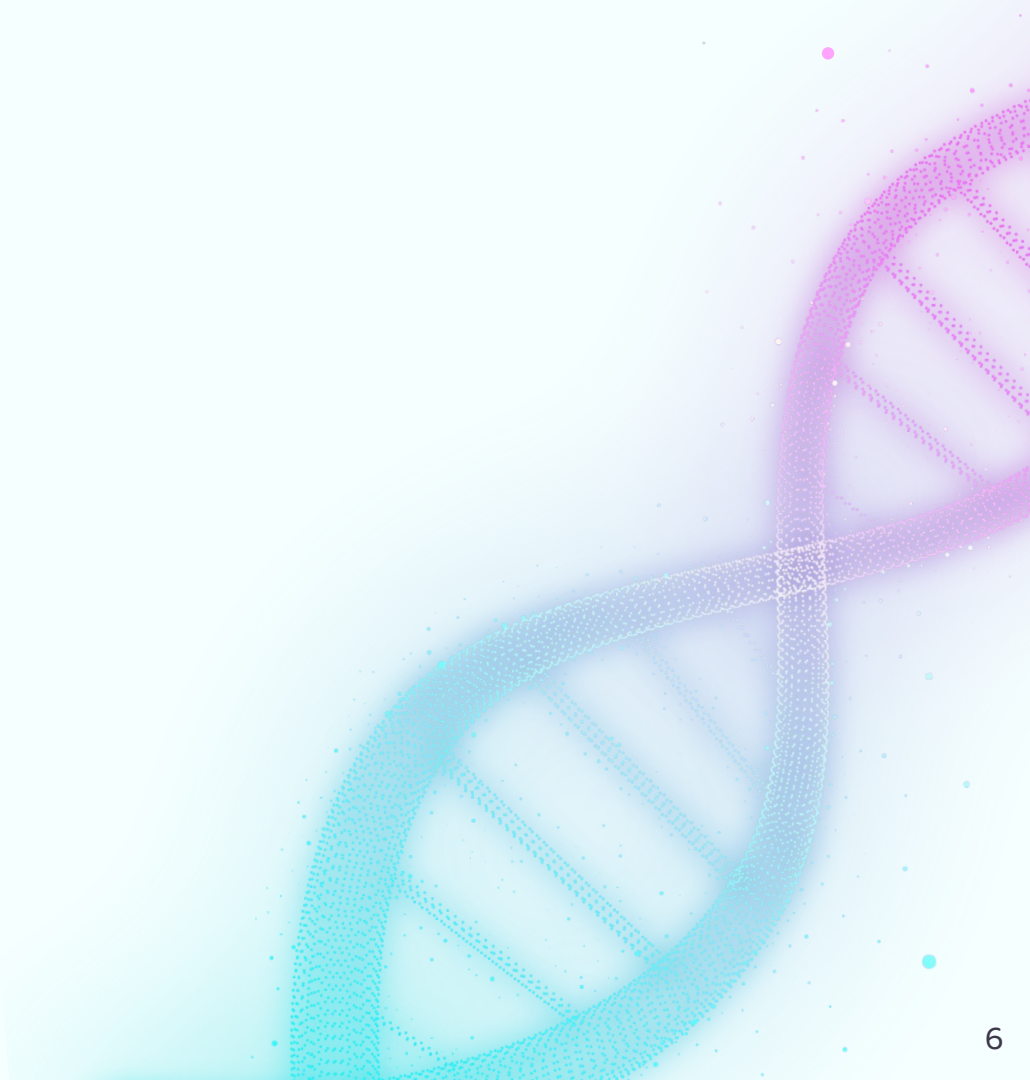
Aim: Establish best combination for described datasets

Develop a superior model with SSL approach

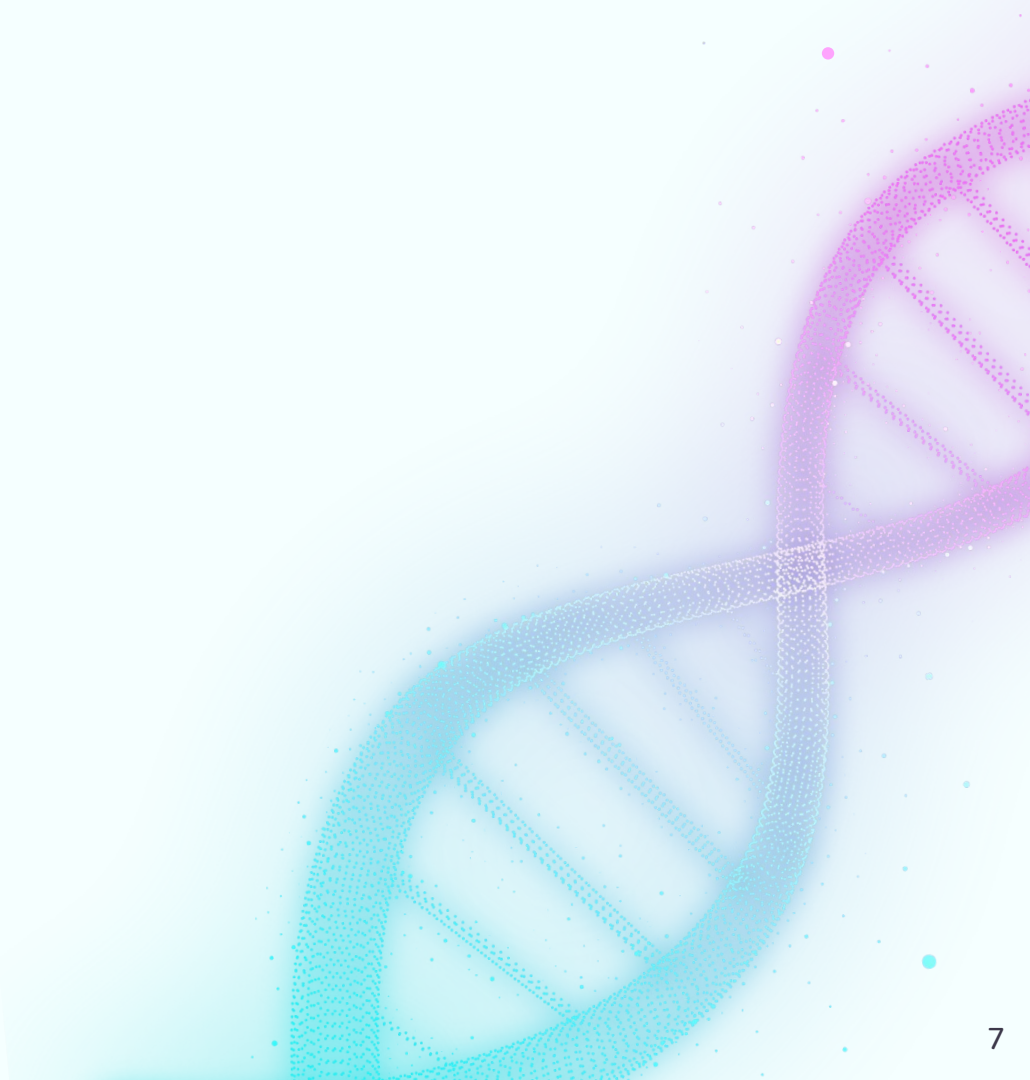
Methods

Pseudobulk analysis

- Metrics
  - Euclidean
  - Cosine
  - Manhattan
- Aggregation methods
  - Mean
  - Median
  - Sum
- Input types
  - PCA
  - Harmony
  - scVI
  - scANVI



Results



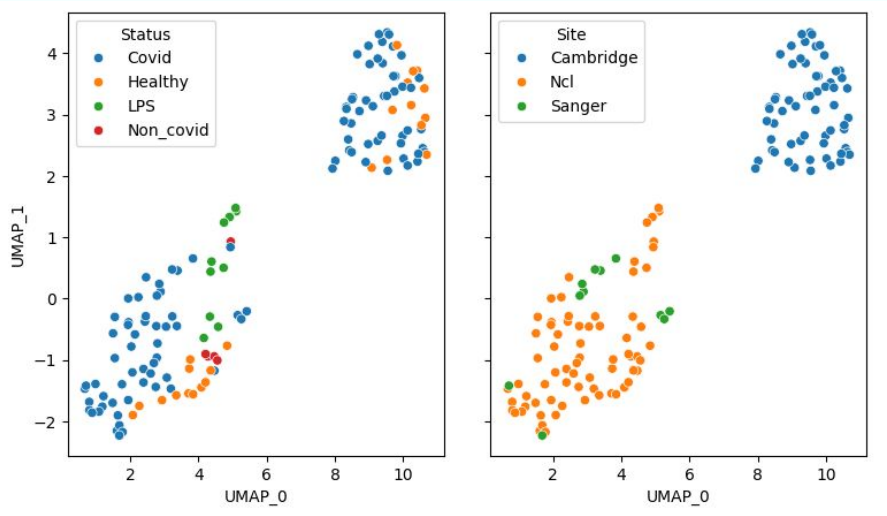
UMAP-Visualization of pseudobulk analysis

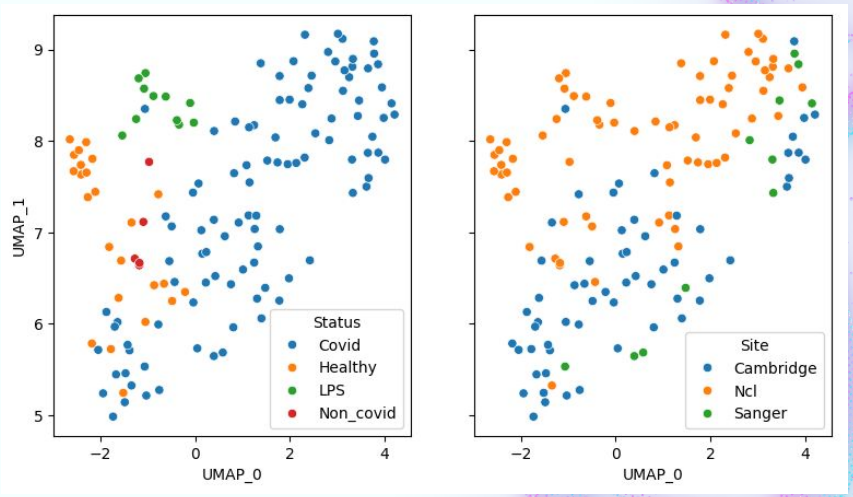
Dataset: Stephenson, Metric: Manhattan, Aggregation method: Mean

One point represents one patient

Input layer : PCA
→ grouping is highly associated with "Site" (batch effect)

Input layer: scVI
→ Batch effect reduced
→ "Status" has a better grouping





What is the best aggregation method, metric and input layer for pseudobulk analysis? *in the Stephenson et al. dataset*

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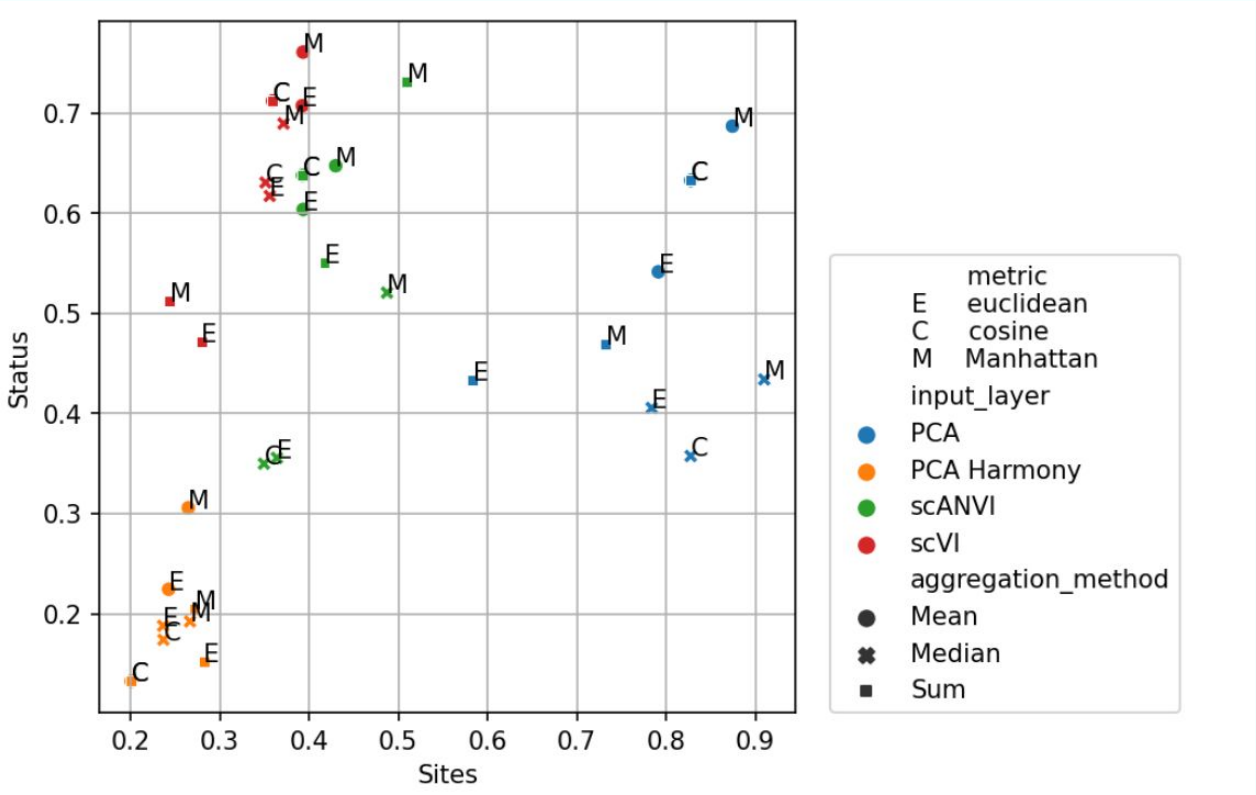
Wish: **high** f1-score for Status **low** f1-score for Sites

	Variable of interest (Status)			Batch variable (Site)		
	PCA					
	Euclidean	Cosine	Manhattan	Euclidean	Cosine	Manhattan
Mean	0.54151	0.632808	0.686977	0.791361	0.827601	0.874412
Median	0.40556	0.357604	0.434042	0.783896	0.827601	0.909976
Sum	0.433725	0.632808	0.469745	0.583315	0.827601	0.732368
	Harmony					
	Euclidean	Cosine	Manhattan	Euclidean	Cosine	Manhattan
Mean	0.224486	0.132722	0.305832	0.242647	0.200623	0.264706
Median	0.188022	0.17412	0.192379	0.236453	0.236871	0.266608
Sum	0.15187	0.132722	0.204667	0.282047	0.200623	0.272118
	scVI					
	Euclidean	Cosine	Manhattan	Euclidean	Cosine	Manhattan
Mean	0.707433	0.712192	0.760904	0.392442	0.359047	0.393295
Median	0.617309	0.630713	0.689542	0.355944	0.351271	0.371429
Sum	0.472193	0.712192	0.51284	0.279238	0.359047	0.243897
	scANVI					
	Euclidean	Cosine	Manhattan	Euclidean	Cosine	Manhattan
Mean	0.603802	0.637872	0.647453	0.393452	0.392703	0.429846
Median	0.355749	0.349893	0.520704	0.363946	0.349461	0.487325
Sum	0.551104	0.637872	0.731716	0.417208	0.392703	0.509288


Status
Sites
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
0.2
0.3
0.4
0.5
0.6
0.7
metric
E euclidean
C cosine
M Manhattan
input_layer
PCA
PCA Harmony
scANVI
scVI
aggregation_method
Mean
Median
Sum

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Wish: **high** Spearman-score for Status **low** f1-score for Institute

	Variable of interest (Outcome)			Batch variable (Institute)		
	PCA					
	Euclidean	Cosine	Manhattan	Euclidean	Cosine	Manhattan
Mean	0.516954	0.5106	0.531117	0	0.059732	0
Median	0.441388	0.47462	0.470388	0	0	0
Sum	0.573073	0.5106	0.556205	0.443746	0.059732	0.283117
	scVI					
	Euclidean	Cosine	Manhattan	Euclidean	Cosine	Manhattan
Mean	0.601517	0.6444	0.636751	0	0	0
Median	0.520509	0.59924	0.549614	0	0	0
Sum	0.564765	0.64441	0.576705	0.443746	0	0.415254
	scANVI					
	Euclidean	Cosine	Manhattan	Euclidean	Cosine	Manhattan
Mean	0.582703	0.60337	0.600343	0	0	0
Median	0.56566	0.55544	0.542906	0	0	0
Sum	0.56356	0.60335	0.625822	0.634921	0	0.660308

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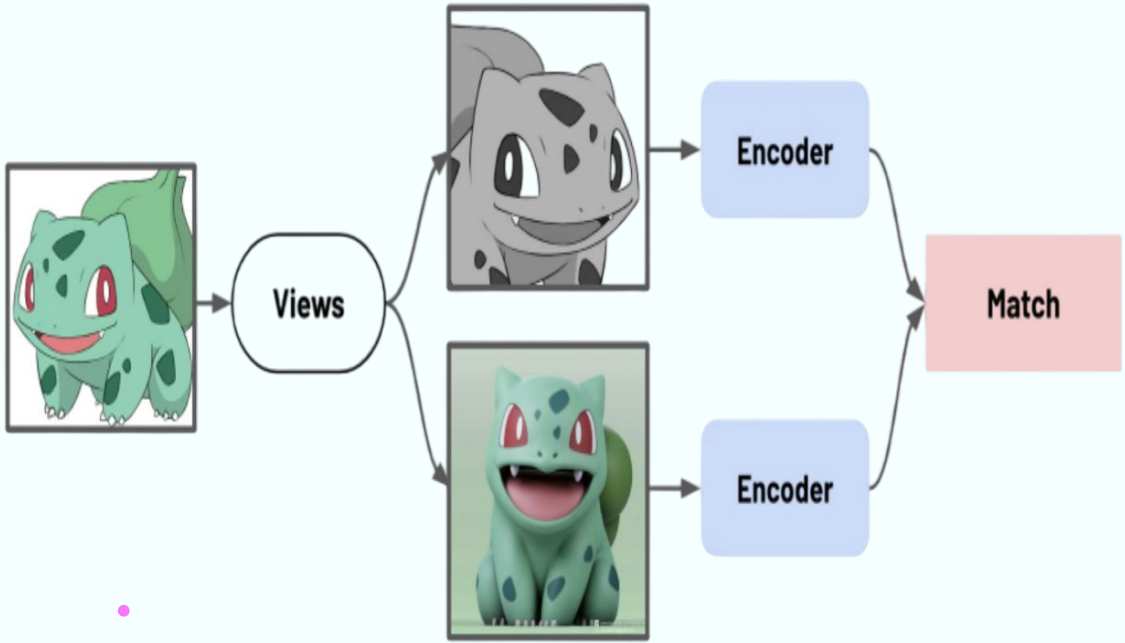
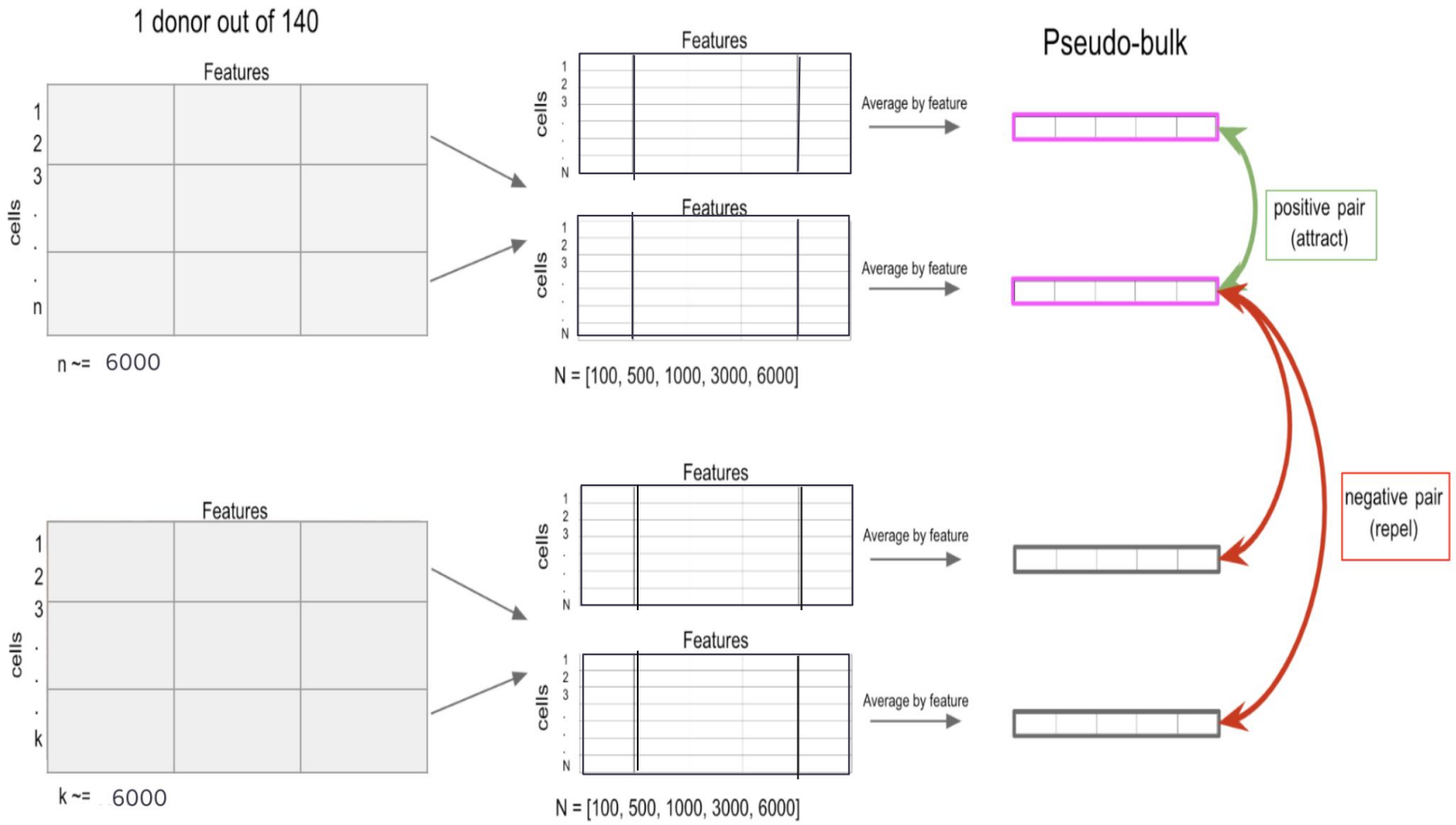
Self-Supervised Learning (SSL) via Contrastive Learning

- Maximizing agreement between differently augmented views of the same data point while minimizing it between unrelated points



Now,
how can we leverage these techniques to infer patient representation?


1 donor out of 140
Features
cells
1
2
3
n
n ~= 6000
Features
cells
1
2
3
N
Average by feature
Features
cells
1
2
3
N
Average by feature
N = [100, 500, 1000, 3000, 6000]
Pseudo-bulk
positive pair
(attract)
Features
cells
1
2
3
k
k ~= 6000
Features
cells
1
2
3
N
Average by feature
Features
cells
1
2
3
N
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negative pair
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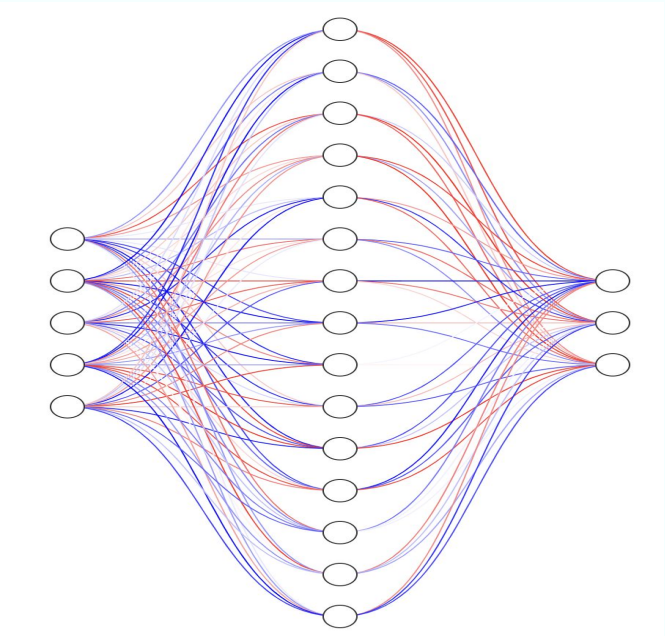
Contrastive Loss

InfoNCE Loss: $$\mathcal{L} = -\log \frac{\exp(\mathrm{sim}(z_i, z_j)/\tau)}{\sum_{k=1}^{N} \exp(\mathrm{sim}(z_i, z_k)/\tau)}$$

Cauchy-based similarity measure: $$\frac{1}{1 + (\mathrm{cdist}(a, b) \cdot \tau)^2}$$



Best hyperparameters

For **scVI** :
{'learning_rate': 0.0431
'weight_decay': 4.48e-05,
'temperature': 0.904,
'batch_size': 4,
'num_layers': 1,
'hidden_size': 192,
'cell_subset_size': 5486}

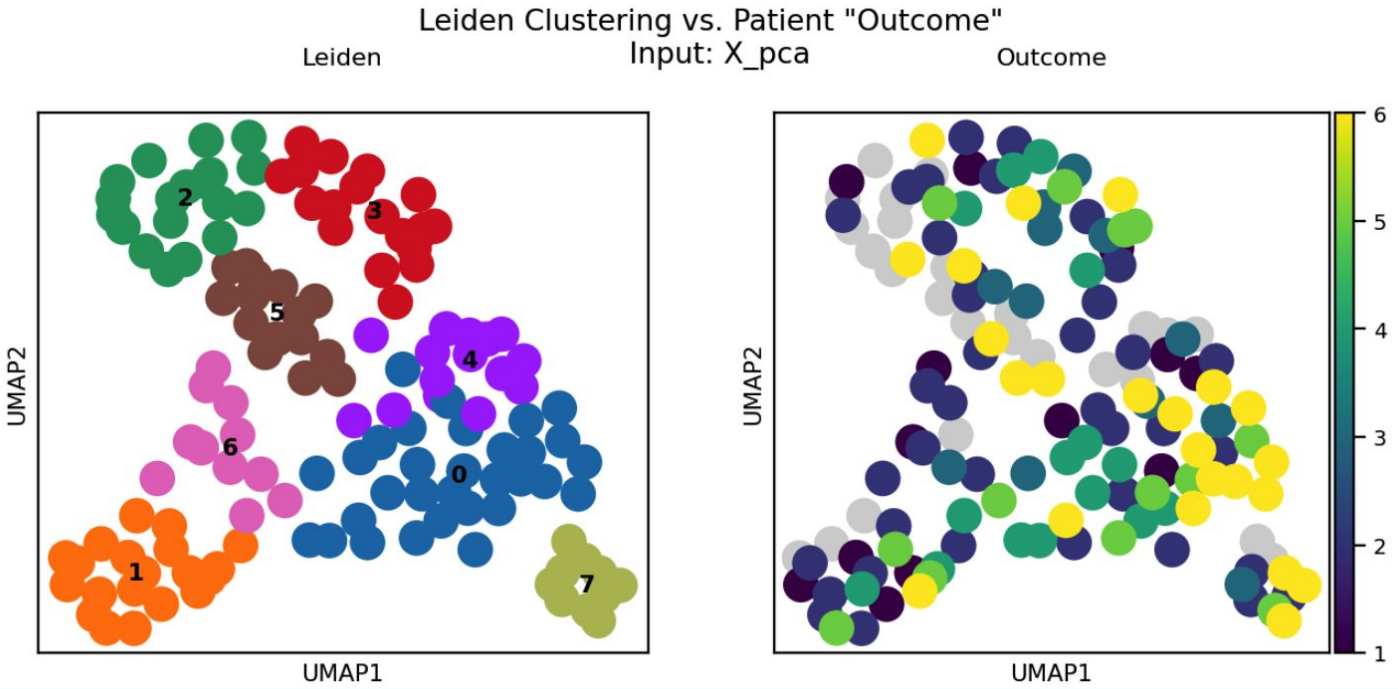
For **scANVI**:
{'learning_rate': 0.052,
'weight_decay': 5.43e-06,
'temperature':0.428
, 'batch_size': 4,
'num_layers': 2,
'hidden_size': 257,
'cell_subset_size':5848}

Performance Assessment On Unseen Data

- Performed k-NN evaluation with **2 metrics**: F1-Macro, Spearman correlation coefficient (SCC)
- **scVI** and **scANVI** demonstrated superior performance over **PCA** in both datasets

Dataset/ Layer/ score	Input Layer	SCC	F1-Macro
COMBAT	**scVI**	**0.602**	**0.208**
	scANVI	0.555	0.205
	PCA	0.372	0.081
Stephenson	scVI	0.718	0.389
	scANVI	0.754	0.579
	PCA	0.584	0.466

Performance of ‘PCA’ input for Contrastive Learning model on COMBAT



- **SCC score: 0.37**
- No meaningful clustering

1 = Death
2 = Intubated, ventilated
3 = Non-invasive ventilation
4 = Hospitalized, O2
5 = Hospitalized, no O2
6 = Not hospitalized

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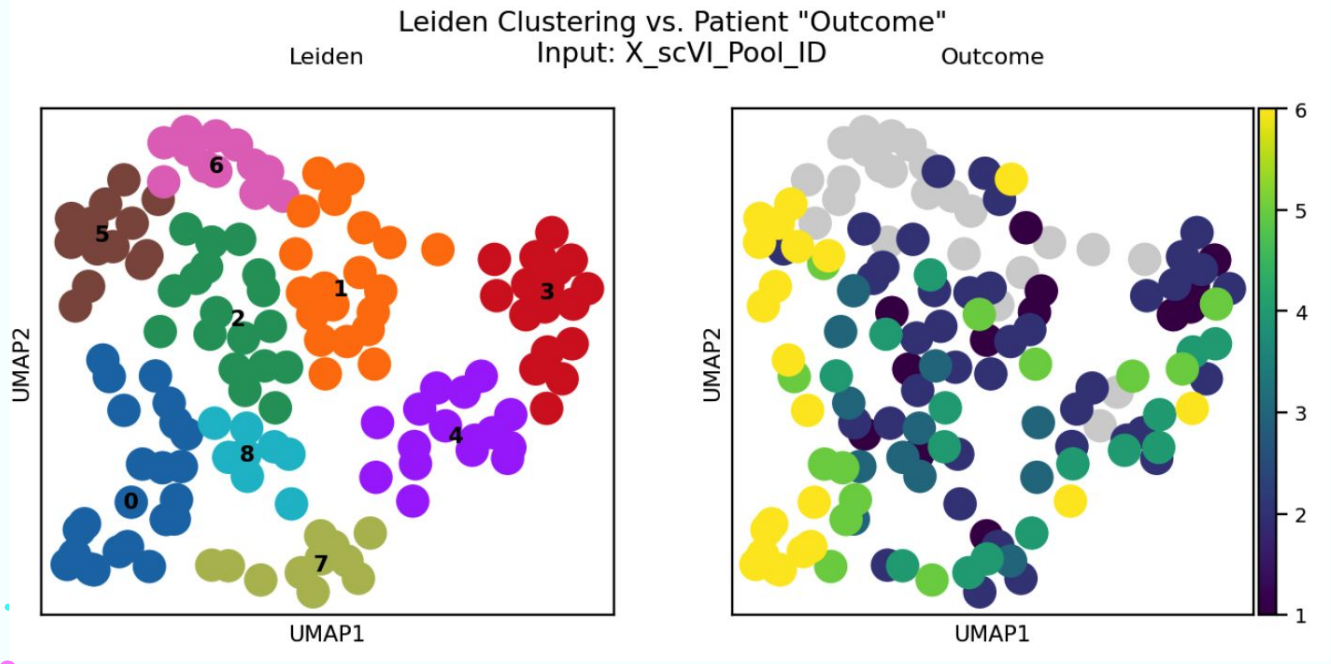
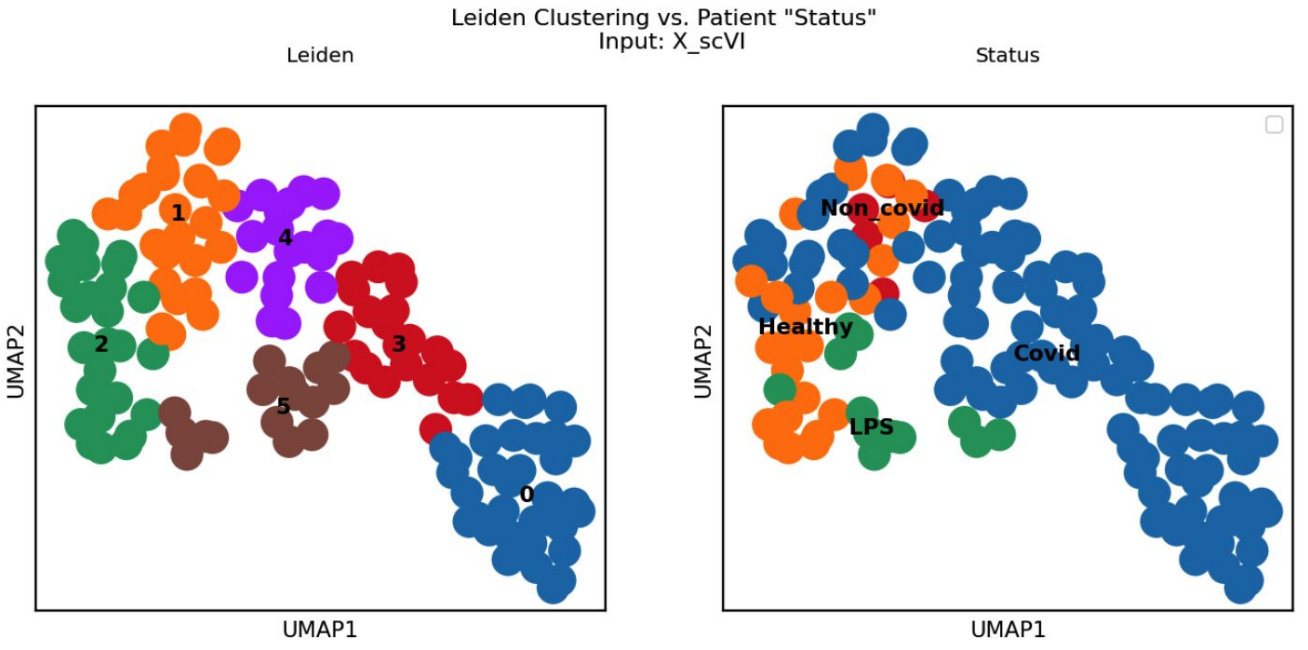


- **SCC score: 0.60**
- Clustering of healthy vs deceased patients are observed (yellow dots)
- Distinct clustering of patients with conditions unrelated to the primary study (gray dots)

Performance of ‘scVI’ input for Contrastive Learning model on Stephenson dataset



- **F1-Macro score: 0.38**
- Patients of the similar categories are grouped together

Conclusion

- Pseudobulk vs SSL based approach
  - F1-Macro score using SSL: 0.38
  - F1-Macro score using pseudobulk: 0.76
  - Contrastive learning model did not outperform the pseudobulk method

- Exploring other Contrastive Losses and similarity functions?
  - Triplet loss
  - Margin loss
  - Gaussian similarity
  - Dot product similarity

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Please refer to the written report for a comprehensive bibliography

THANK YOU :)

Any Questions ?