Bioinformatics Program

Automated Cell Type Re-Annotation for Enhanced Reproducibility and Meta-analysis in Single-Cell Brain Studies

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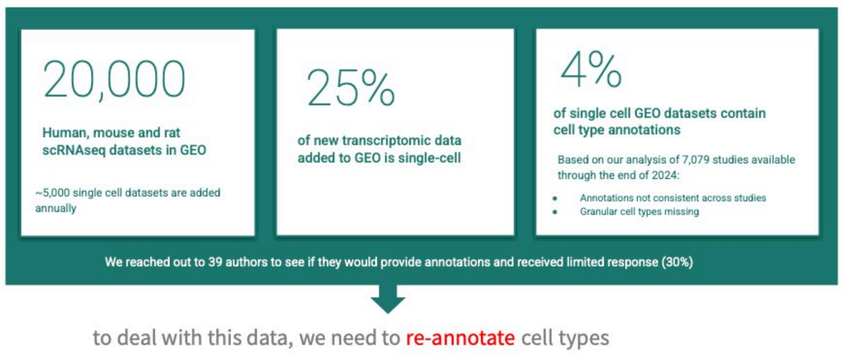
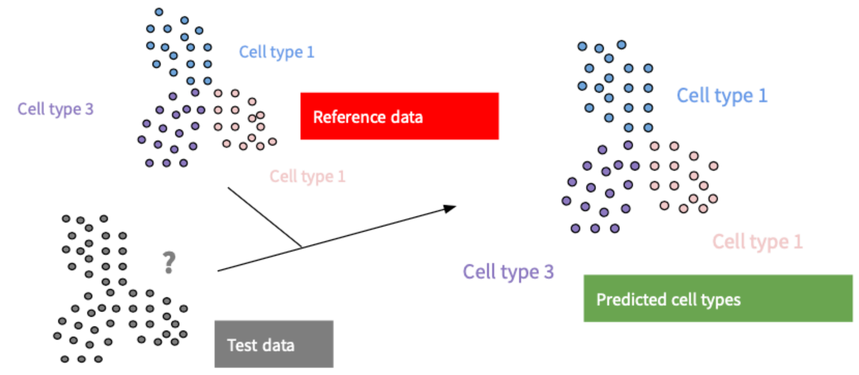
Introduction

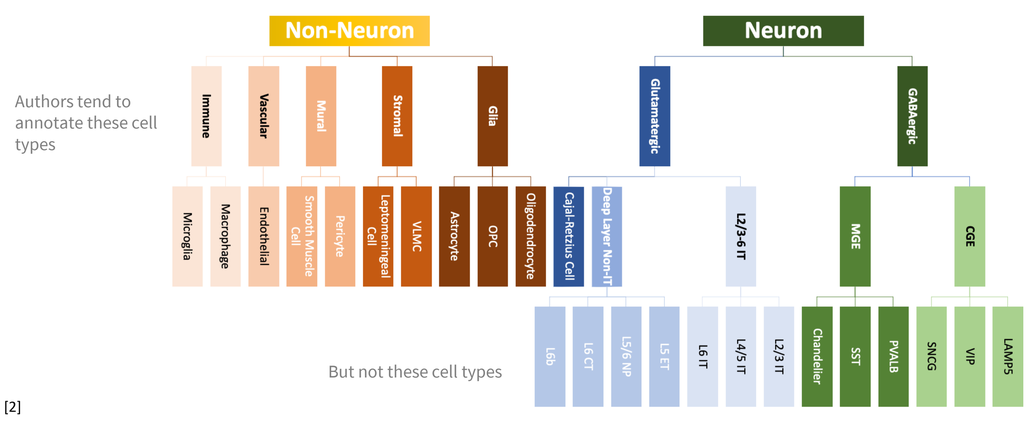
•**Challenge:** Inconsistency and lack of cell-type annotations hinder meta-analysis of single-cell data and limit reproducibility across studies.
•**Approach:** We a pipeline for automated annotation of public single-cell transcriptomes, focusing on human and mouse neocortex under a unified cell type taxonomy.
• **Methods:** We benchmarked several approaches to automated re-annotation, focusing on the impact of method, reference dataset, confidence thresholding, and experimental factors.
•**Impact:** Re-annotation enables robust identification of overlooked cell types, exposing them to meta-analysis in the context of brain disease.

Lack of consistent cell-type annotations challenges meta-analysis of single-cell data



Leveraging BICCN cell type taxonomy for re-annotation of human and mouse neocortex



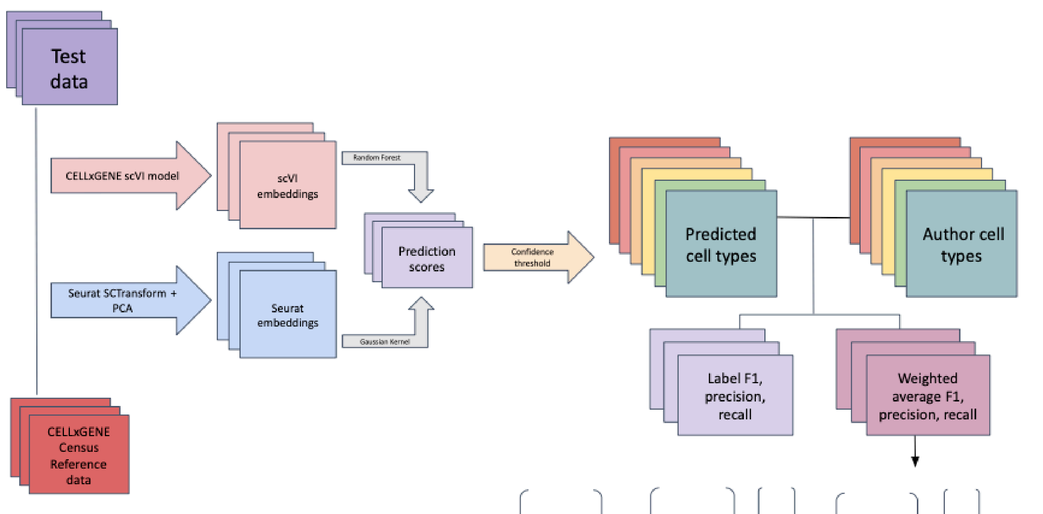


Authors tend to annotate these cell types

But not these cell types

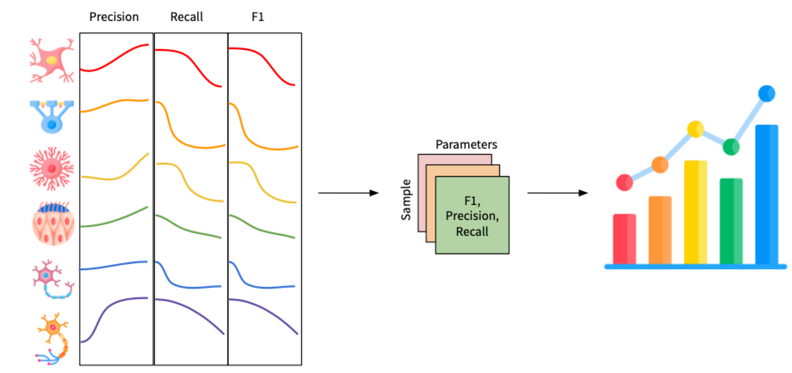
[2]

Benchmarking of label transfer methods from BICCN references in diverse public datasets

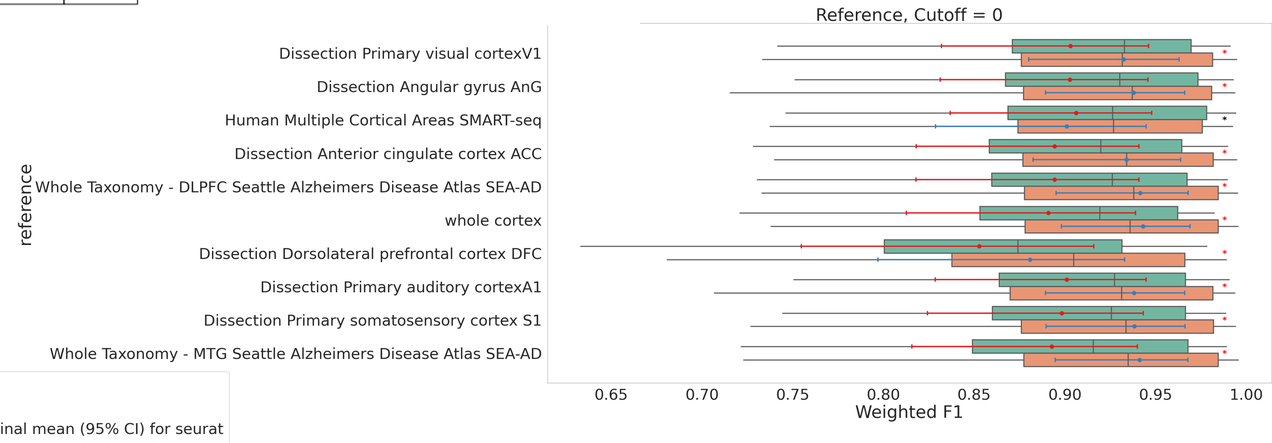


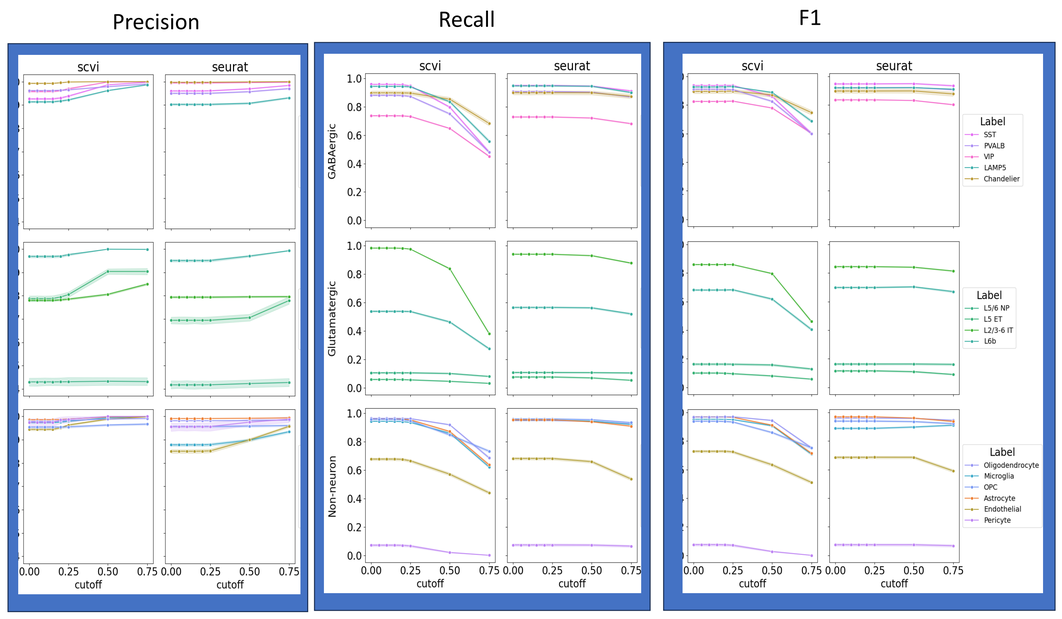
[3][5][6]

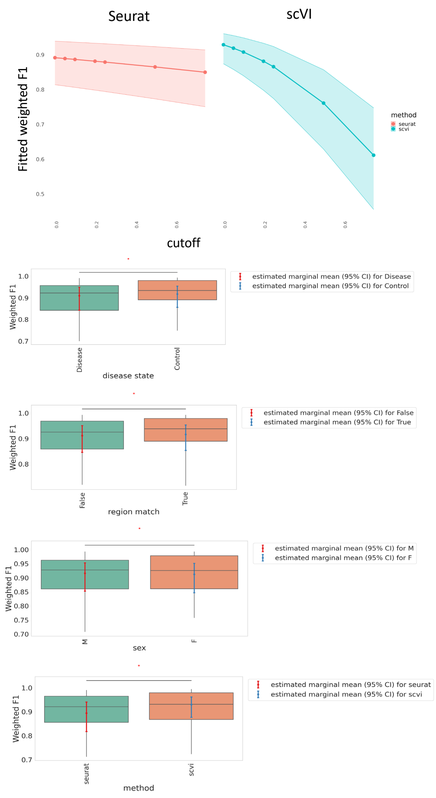
Evaluation of label transfer across 15 cell types in 198 human neocortex samples



factor	contrast	OR	SE	Tukey's p-value
method	seurat / scvi	0.63	0.004	<0.001
sex	F / M	0.95	0.004	<0.001
region match	False / True	0.94	0.008	<0.001
disease state	Control / Disease	1.11	0.005	<0.001

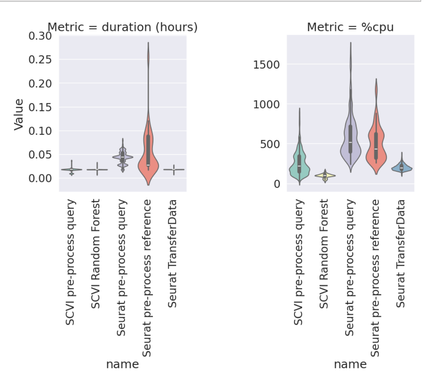




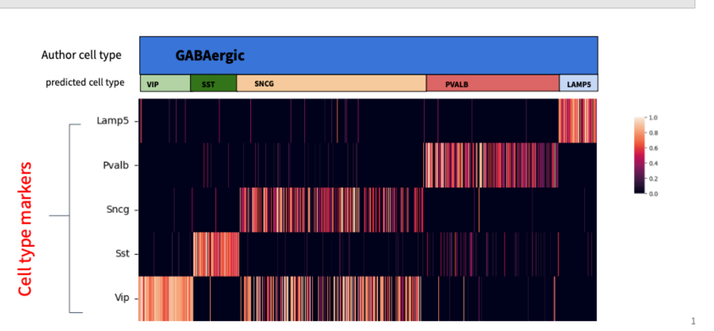


Precision, recall, and F1 scores for 15 cell subclasses across 8 confidence thresholds (cutoff) were generated for 7 studies comprising 198 individual samples. Weighted average F1 scores for each sample were fit to a beta-logit generalized linear model treating study as a random effect. Marginal means for parameters (reference, method, disease state, and region matching) were estimated from the model and compared with Tukey's post-hoc tests.

scVI is faster and more efficient than Seurat



Re-annotation exposes granular cell types



Re-annotation of GABAergic cell types in [1].

Conclusions

- Using an scVI-trained classifier without confidence thresholding achieves highest overall performance for human data; Seurat classifier is more robust to thresholds
- Cortical region, sex, disease state have little overall effect on performance when accounting for the effects of individual studies
- We implemented a Nextflow pipeline informed by benchmarking results to re-annotate experiments using an aggregate "whole cortex" reference [4]
- So far, we have re-annotated 79 scRNAseq experiments in human and mouse with harmonized cell types in the Pavlidis lab's Gemma database [7]
- Future work will expose harmonized cell types to meta-analysis across human and mouse studies of neurodegenerative and psychiatric disease

References
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