A multi-omic approach to uncover enhancer-gene interactions in the human brain

MIT Primes Conference

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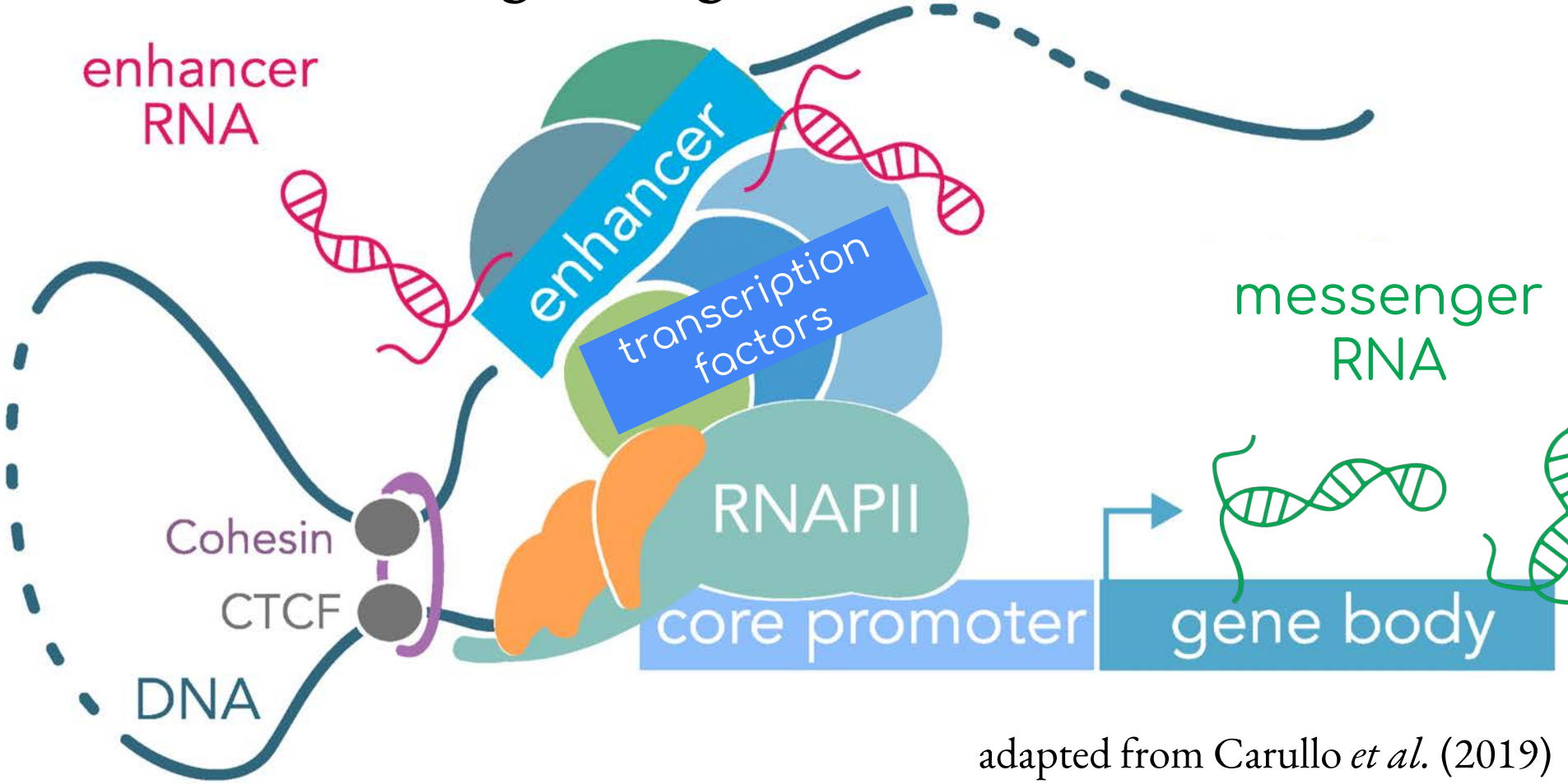
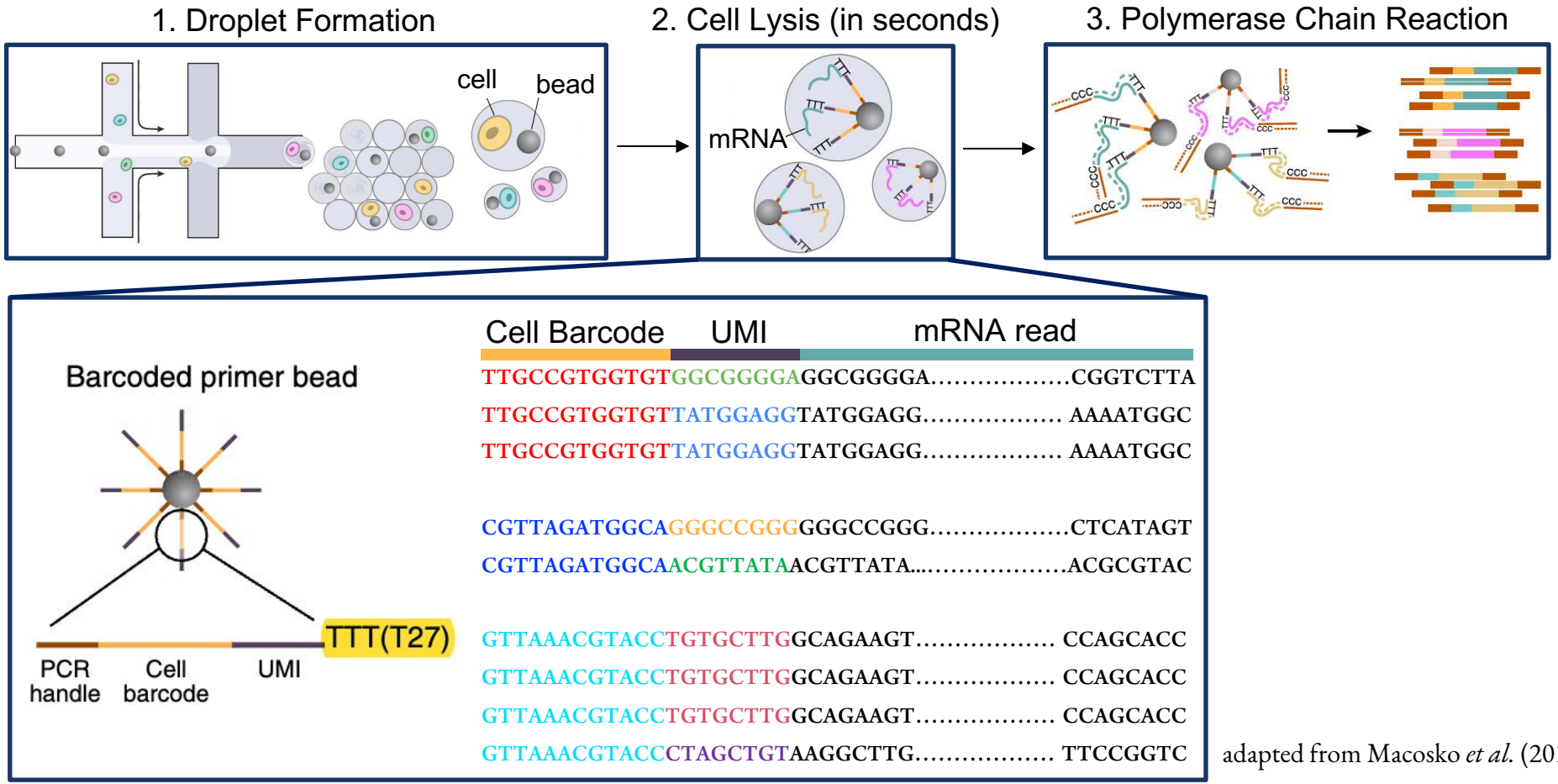
Enhancer-driven gene regulation



adapted from Carullo *et al.* (2019)

Single nucleus RNA sequencing (snRNA-seq)

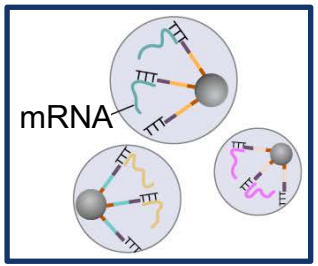


adapted from Macosko *et al.* (2015)

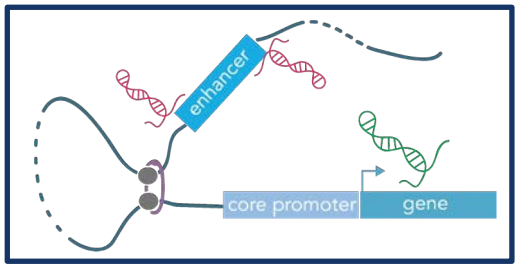
Project overview

Objectives

a) Detect eRNA from snRNA-seq data



b) Link putative active enhancers back to their target genes



Motivation

a) Ability to explore active enhancers at the cell-type specific level

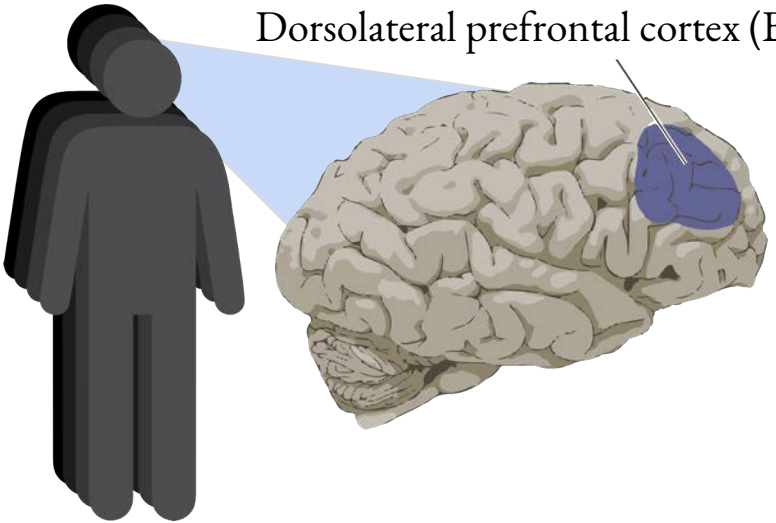
Challenges

a) eRNA is unstable

b) snRNA-seq is not optimized to target eRNA

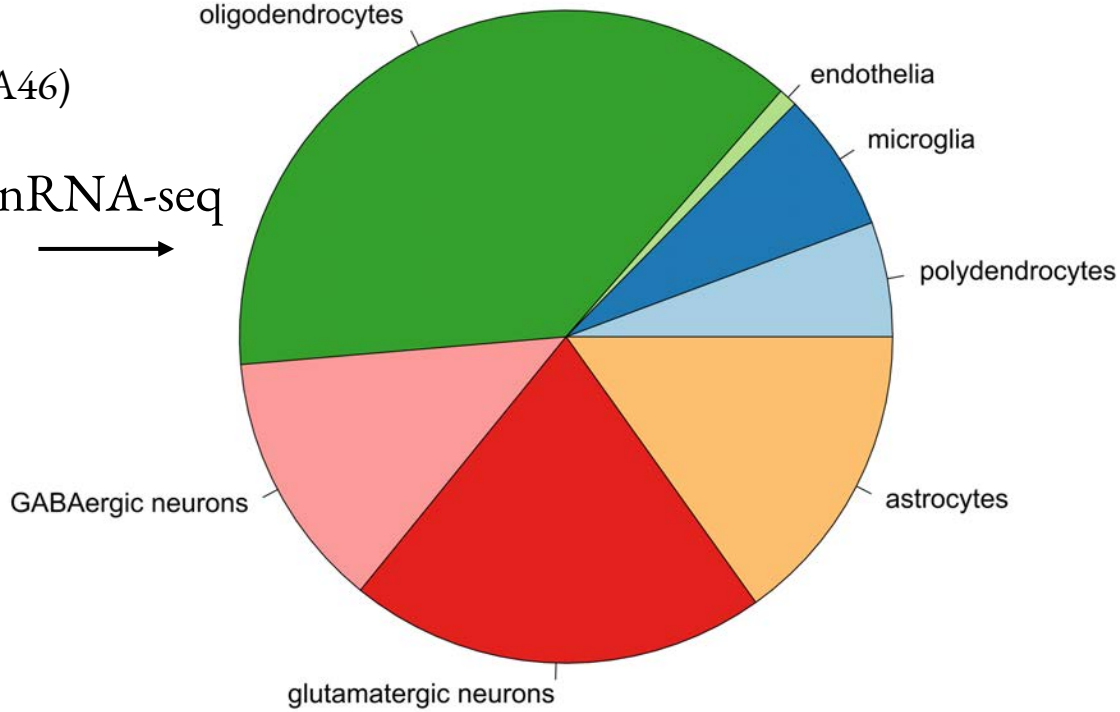
Our snRNA-seq dataset

20 donors



snRNA-seq

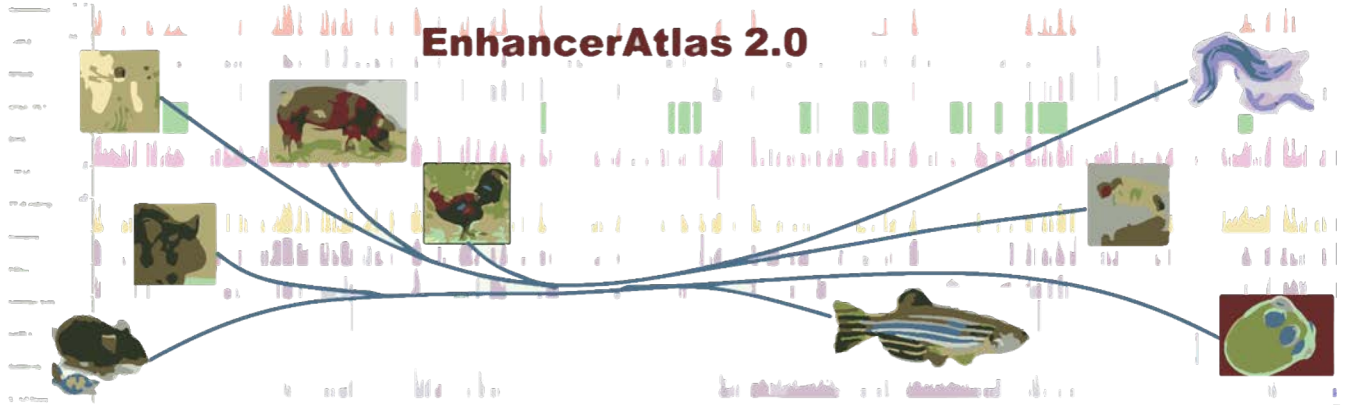
Cell-type composition of
79k total nuclei



Identifying 29k putative brain enhancers from reference databases

62k brain enhancers

129k brain enhancers

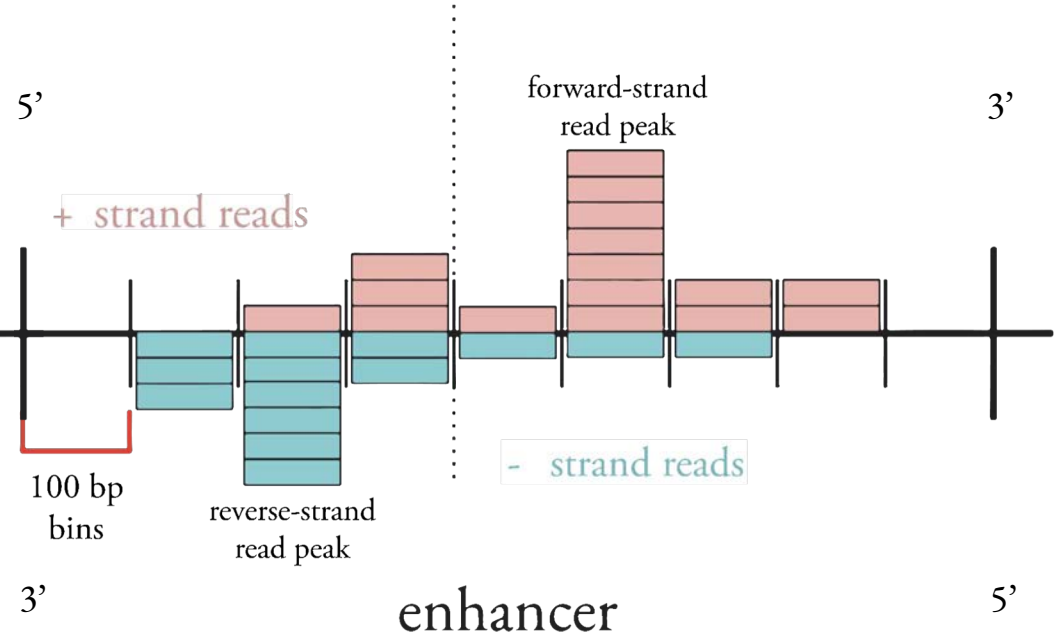


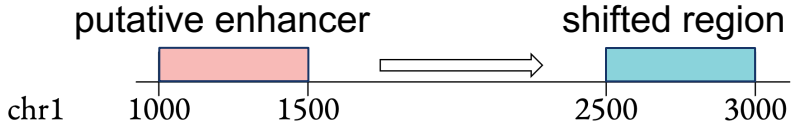
filtered to exclude enhancers that overlapped other regulatory regions

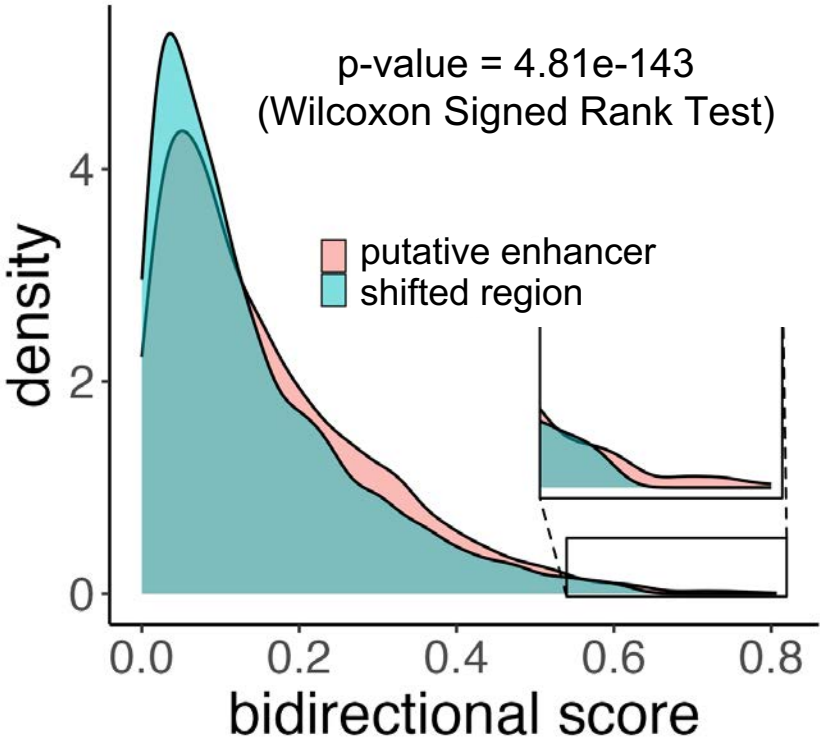
29k putative brain enhancers

Greater bidirectional activity at putative enhancers than nearby intergenic regions

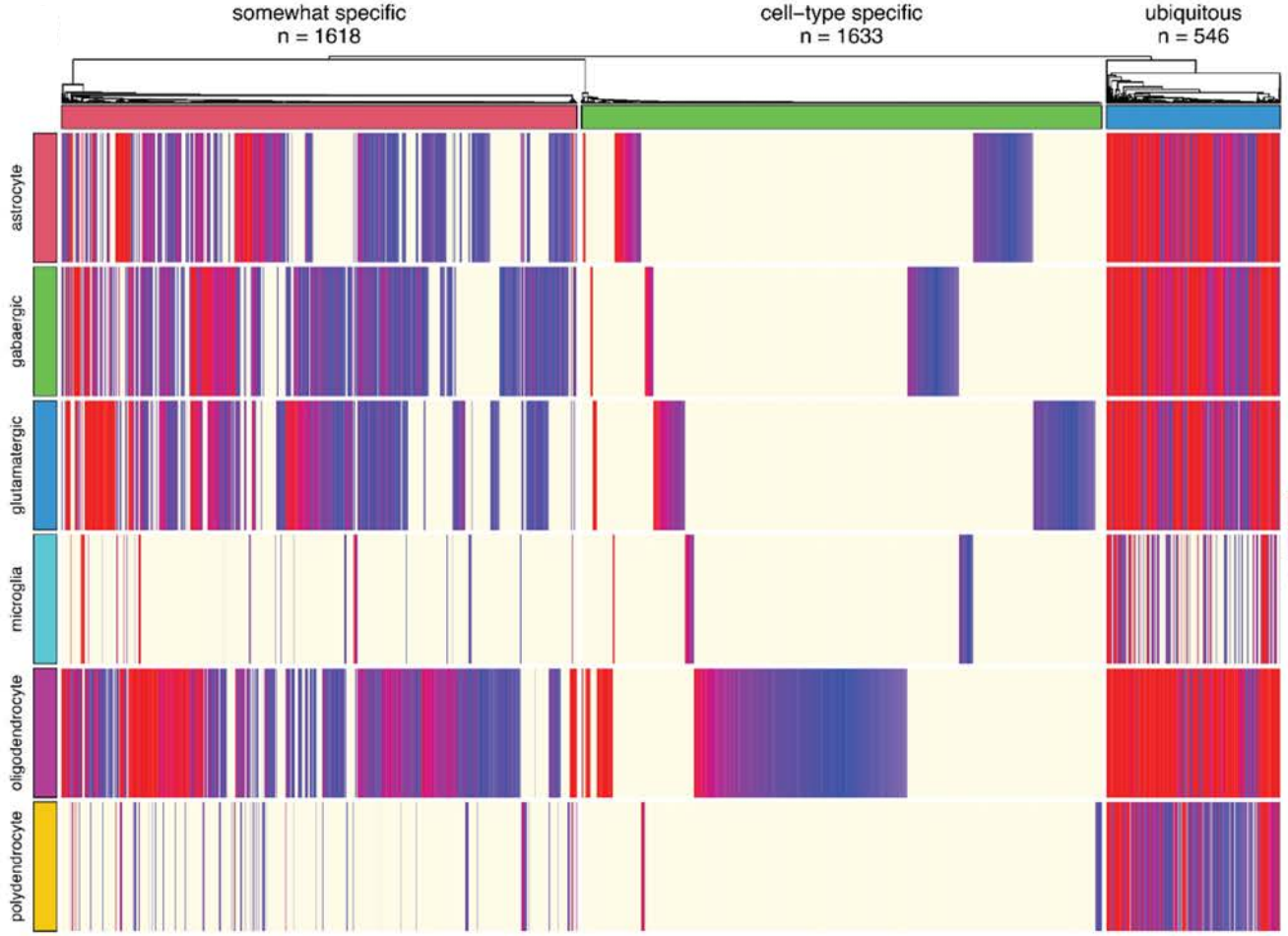
$$S_{bidirectional} = S_{divergence} \cdot (1 - |S_{balanced}|)$$

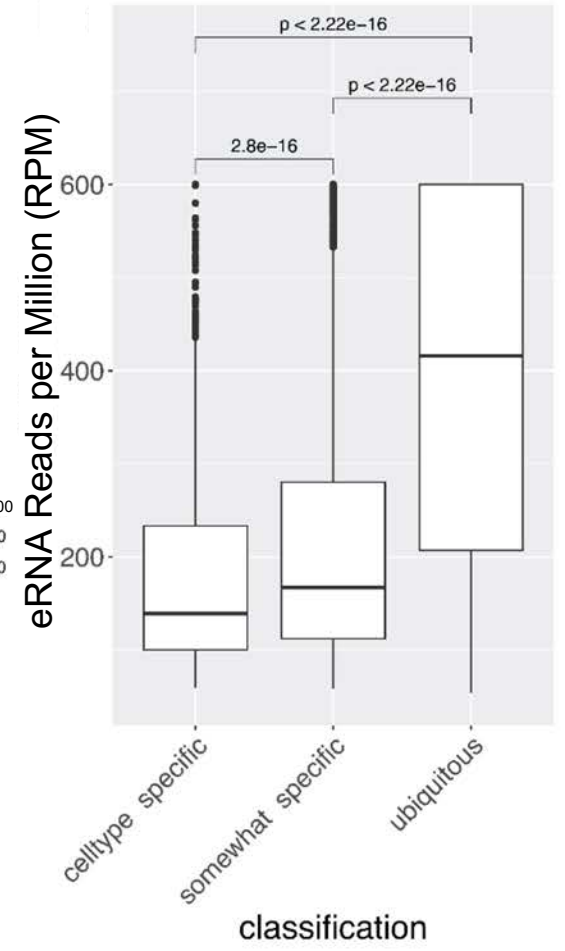




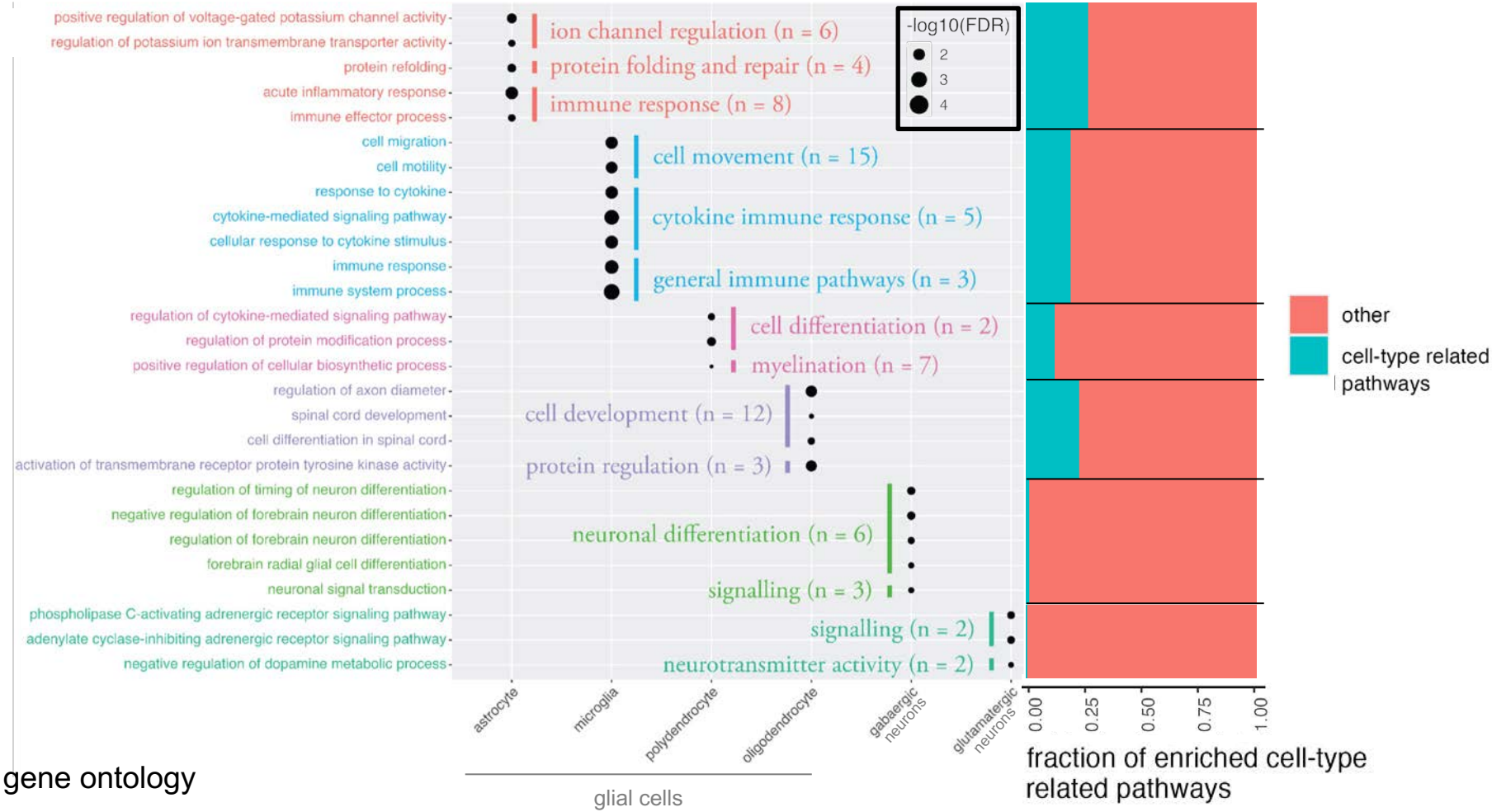


Enhancer expression varies across cell-type



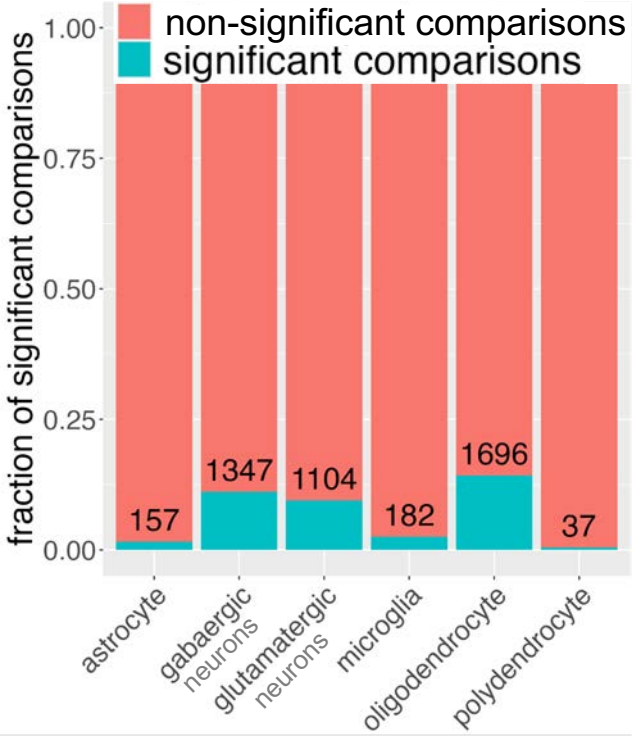


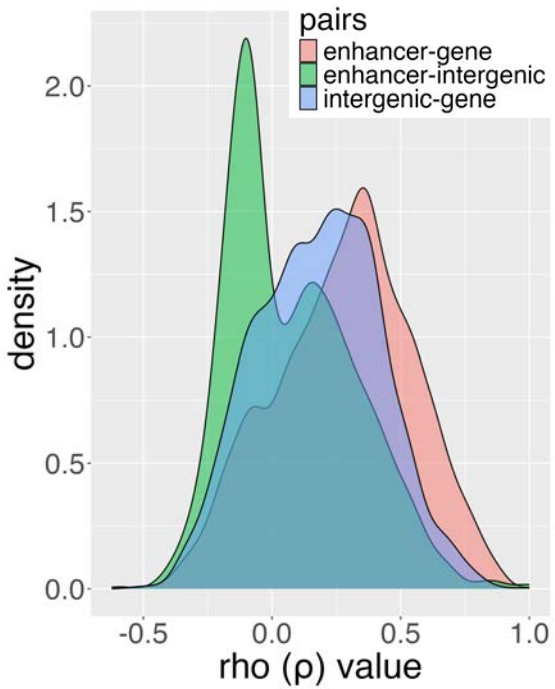
Enhancer cell-type specificity is revealed by GO analysis

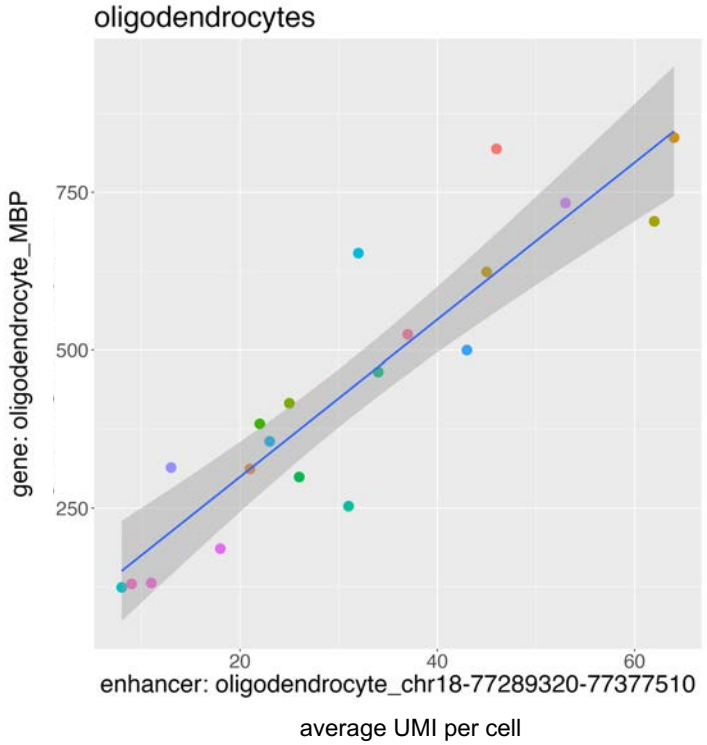


GO: gene ontology

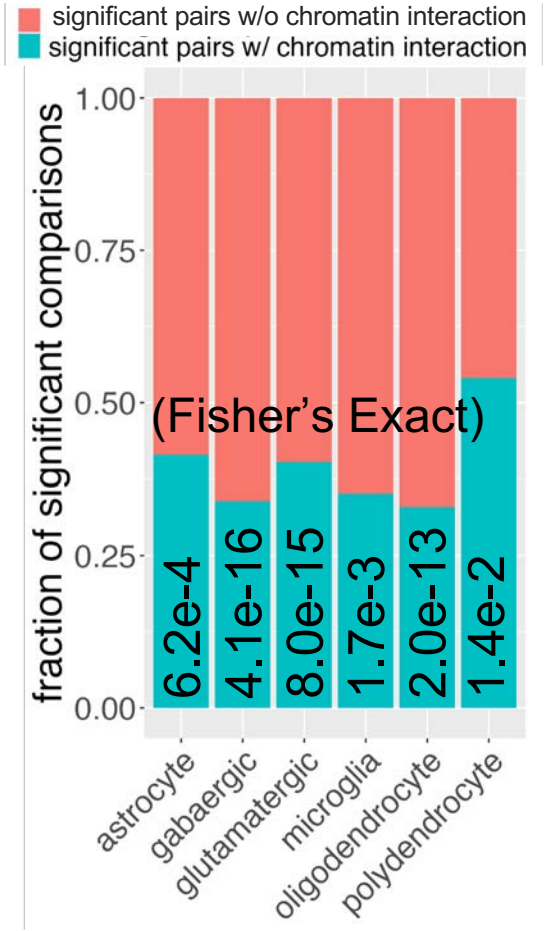
Mapping enhancers to genes

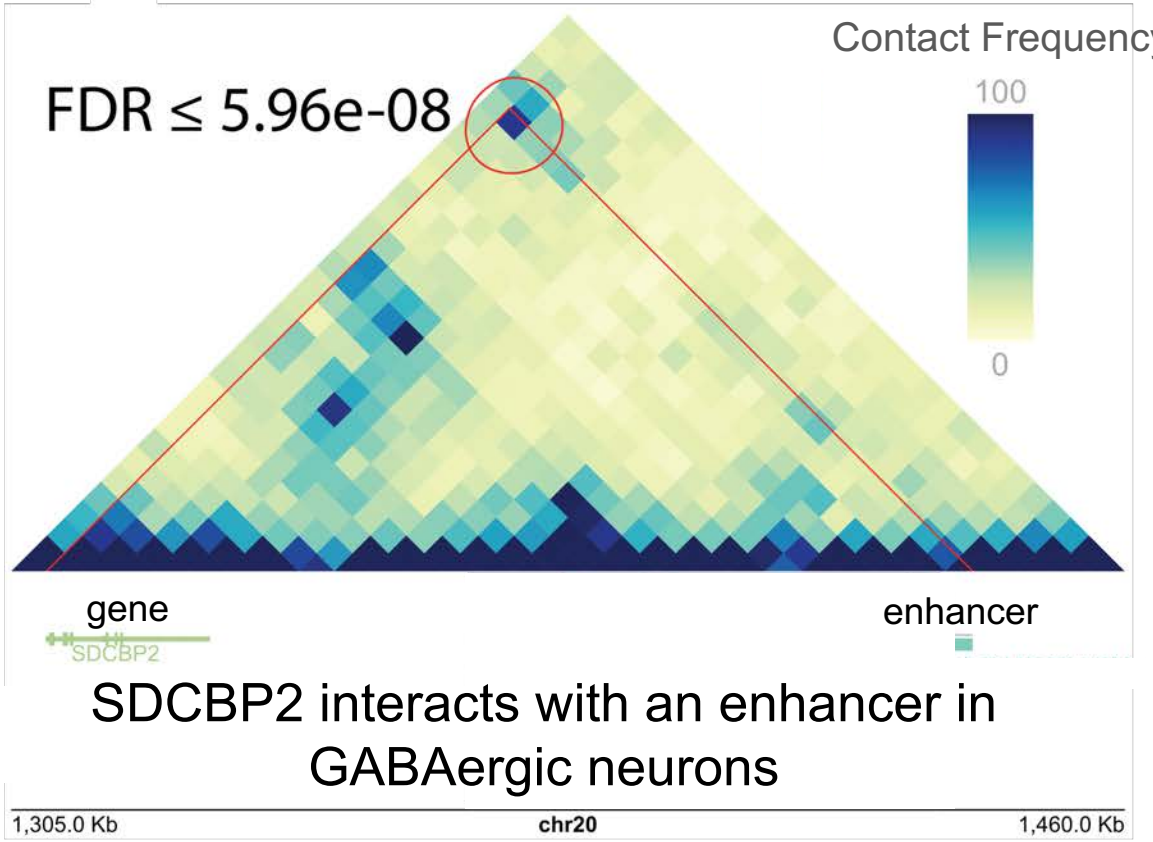






Enhancer-gene pairs bolstered with Hi-C data



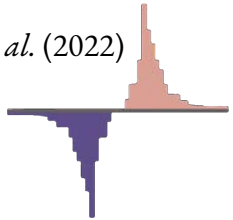


SDCBP2 interacts with an enhancer in GABAergic neurons

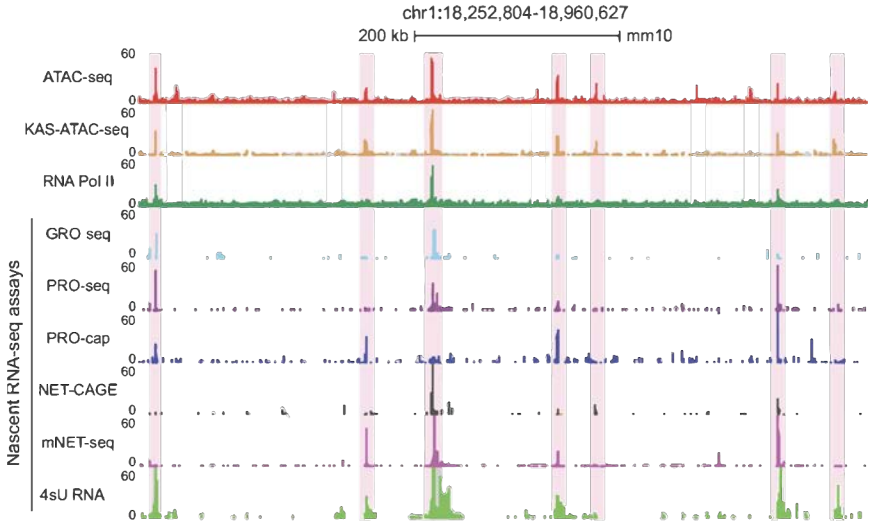
Implications and future plans

1. Assessing our framework in comparison to other datasets

Lyu *et al.* (2022)

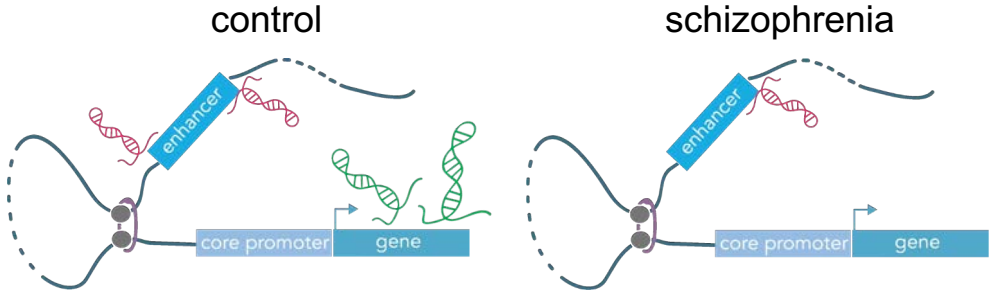


PINTS web portal



Yao *et al.* (2024)

2. Evaluating the role of our enhancer-gene pairs in diseases



Artistic image modified from MedKart

Acknowledgements

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I'd like to thank the members of the McCarroll lab for introducing me to their work environment and making me feel at ease.

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