

# Cell-cell communication in single-cell omics

2023/09/28

**Pau Badia i Mompel  
Saez-Rodriguez Group**



[www.saezlab.org](http://www.saezlab.org)



@saezlab  
@PauBadiaM



**HEIDELBERG**  
UNIVERSITY  
HOSPITAL

 **cellzome**  
A GSK Company



# Introduction



# Background



- 2014 - 2018: **BSc in Biology**



Universitat Autònoma  
de Barcelona

- 2018 - 2020: **MSc in Bioinformatics**



Universitat  
Pompeu Fabra  
Barcelona



- 2017: **Erasmus**



HEIDELBERG  
UNIVERSITY  
HOSPITAL

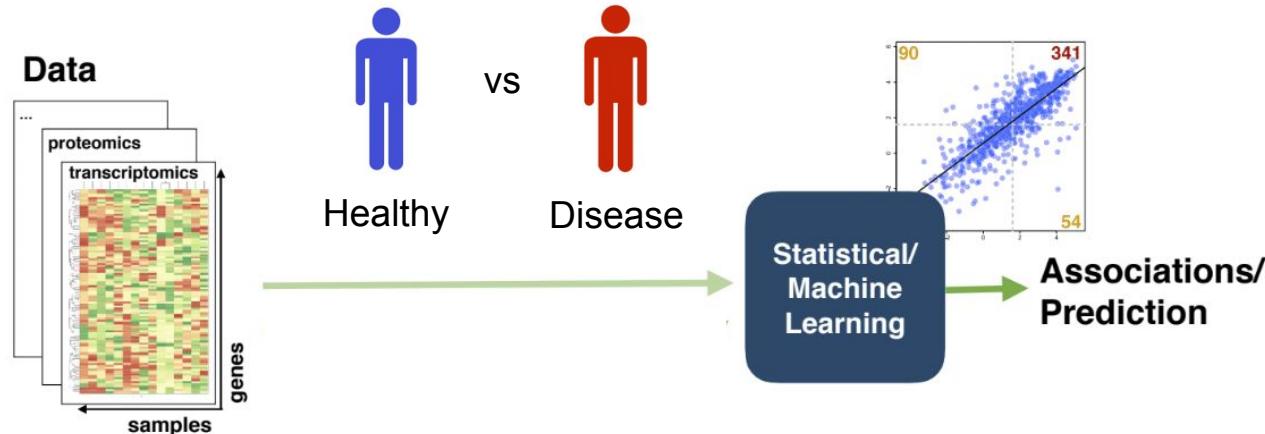
- 2020 - Present: **PhD Candidate**



# Saezlab: Supporting statistics with biological knowledge

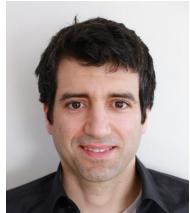


Prof. Julio  
Saez-Rodriguez

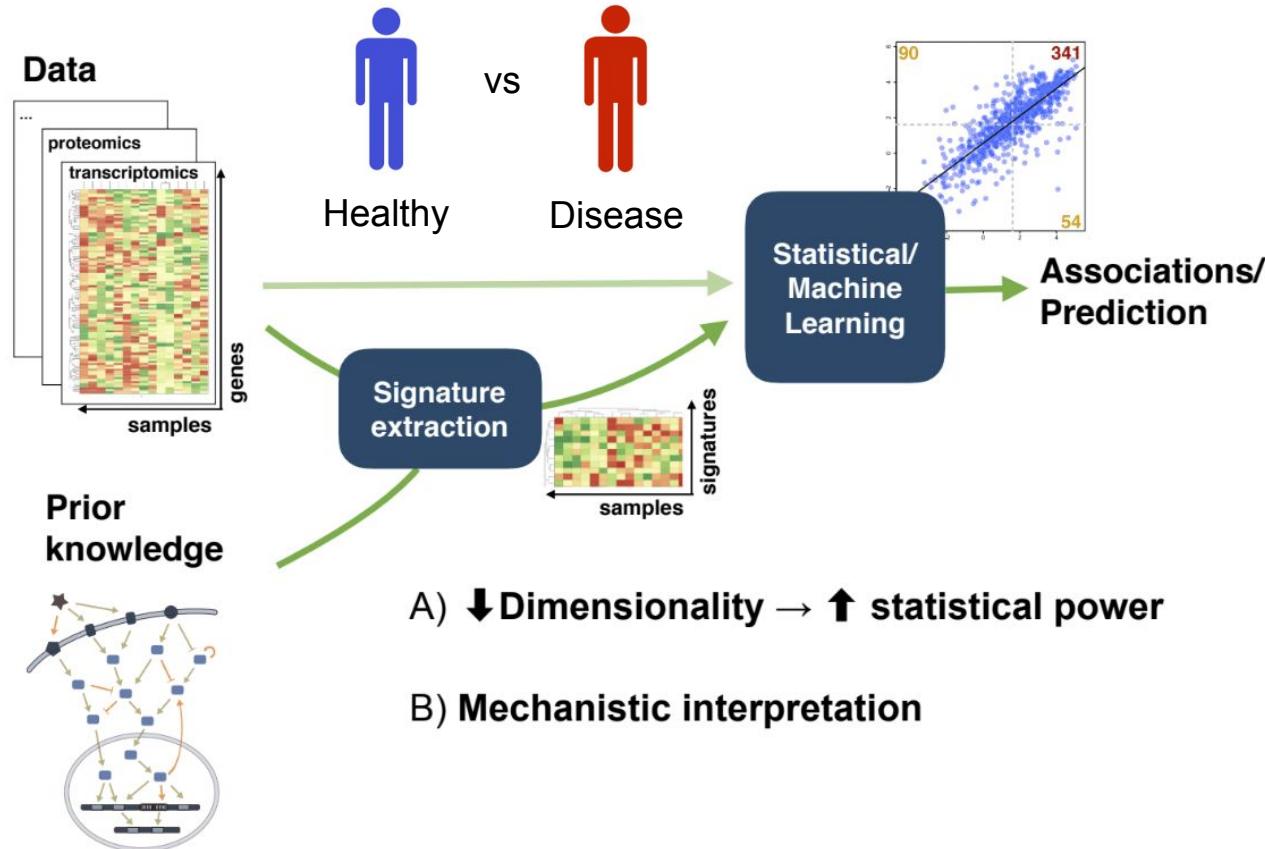




# Saezlab: Supporting statistics with biological knowledge



Prof. Julio  
Saez-Rodriguez





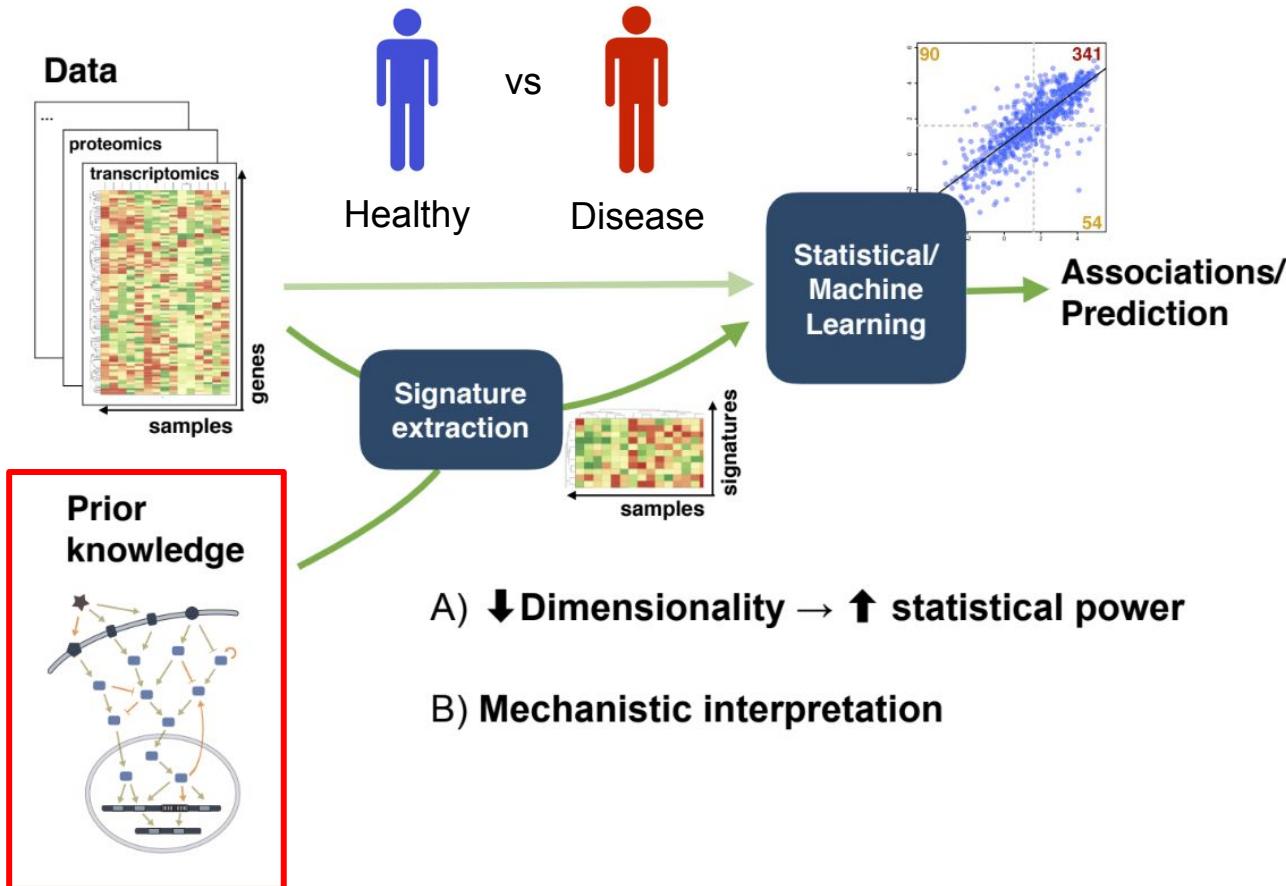
# Saezlab: Supporting statistics with biological knowledge



Prof. Julio  
Saez-Rodriguez

Gene regulatory  
networks

Cell-cell  
interaction  
networks

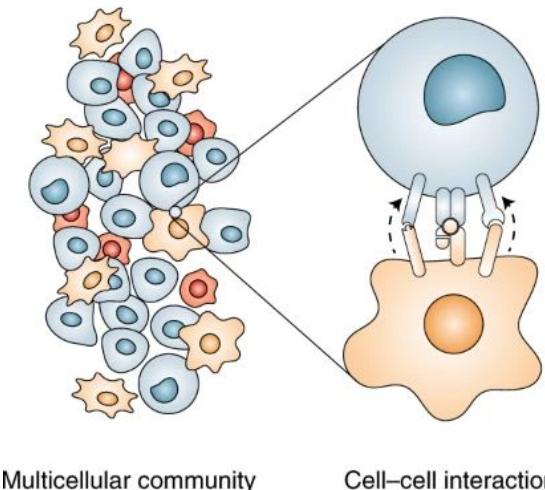




# What are cell-cell interactions?



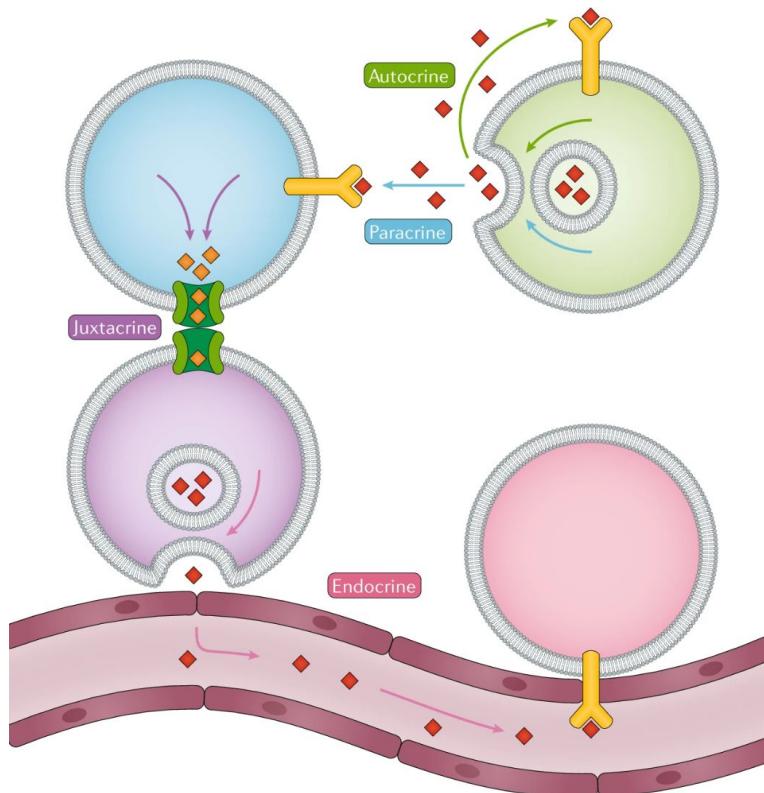
# Cell signaling



- Cells are organized in communities
- Communicate in response to changes in their environment
- **Cell-Cell Communication (CCC)** via the interaction between proteins or molecules
- **Source** cell has a **ligand** that interacts with a **receptor** in the **target** cell



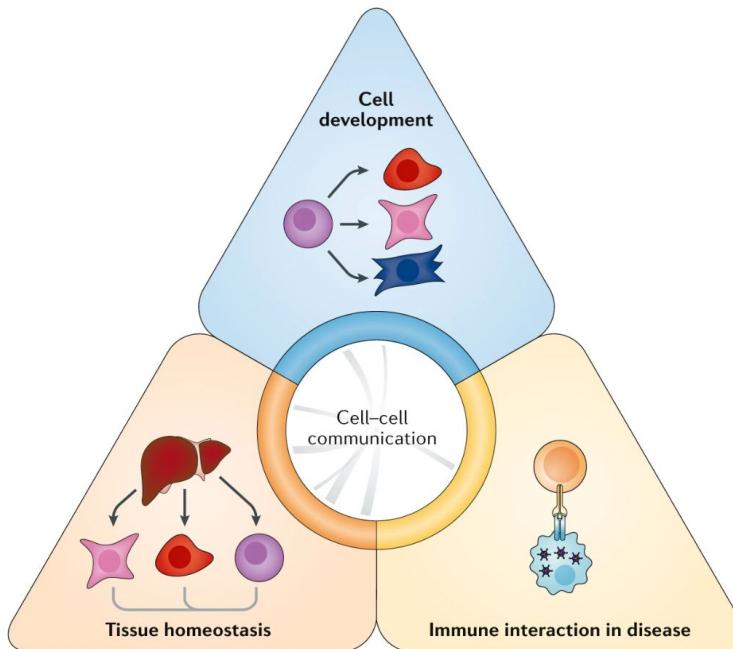
# Types of cell signaling



- **Autocrine:** intracellular communication
- **Paracrine:** diffusion of molecules after secretion.
- **Juxtacrine:** contact-dependent without secretion
- **Endocrine:** long distance through fluids



# Cell signaling regulates cell function



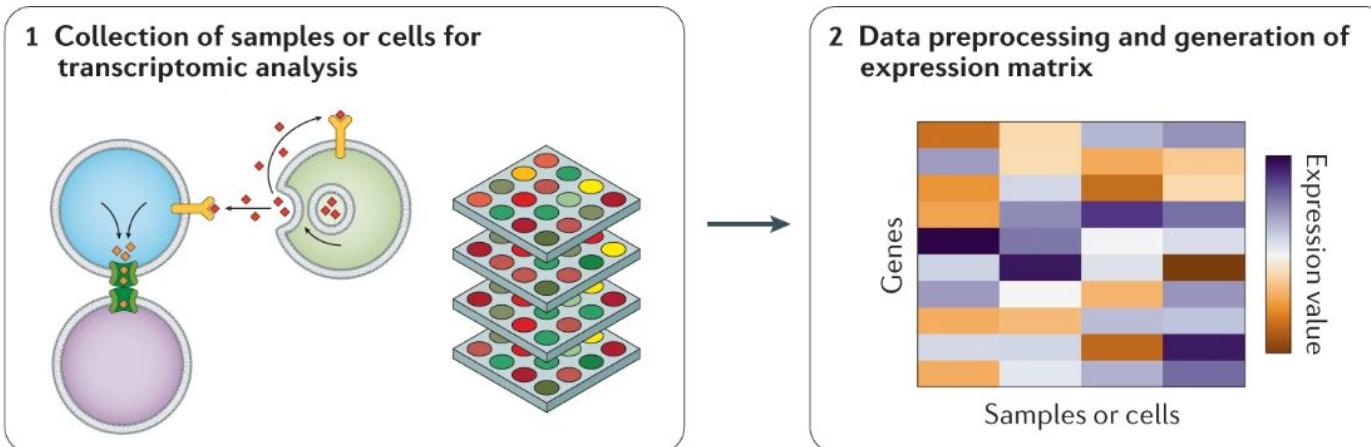
- **Cell development:** temporally and locally precise communication.  
Microglia-*APOE* + Neuron-*LRP1* in developing brain (Sheikh 2019)
- **Tissue homeostasis:** organ function  
Endothelia-*CST3* + Microglia-*CXCL12* in brain ageing (Ximerakis 2019)
- **Immune interaction:** activation or inhibition of immune response  
*PDL1* + *PD1* inhibition as cancer therapy (Zitvogel 2012)



# **Computational workflow to infer CCC from RNA-seq**



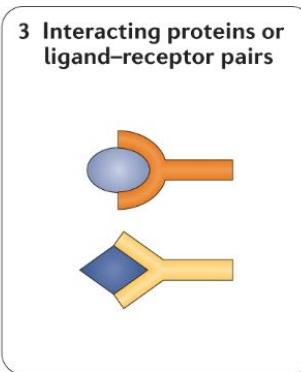
# Generation of transcriptomics data



scRNA-seq  
snRNA-seq  
RNA-seq  
...



# Prior knowledge of Ligand-Receptor pairs



## Primary sources of Ligand-Receptor interactions:

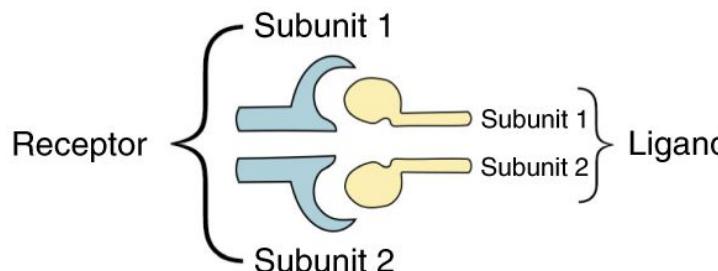
- Protein-Protein interactions (STRING, IntAct, ...)
- Annotated in gene sets (REACTOME, KEGG, ...)
- Manual curation from literature (FANTOM5, HMPR, ...)

## Meta-resources:

- CellPhoneDB
- iTALK
- connectomeDB
- OmniPath
- ...



# Prior knowledge of Ligand-Receptor pairs

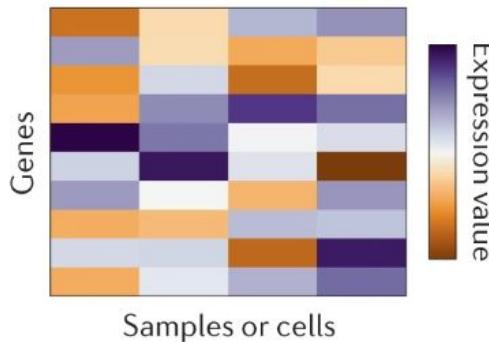


- Some resources contain Ligand-Receptor complexes:
  - CellPhoneDB
  - CellCall
  - CellChatDB
  - Cellinker
  - OmniPath
  - ...

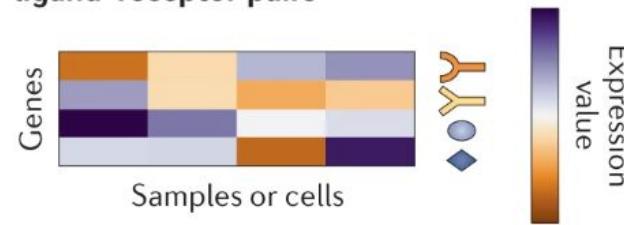


# Filtering by prior knowledge

## 2 Data preprocessing and generation of expression matrix



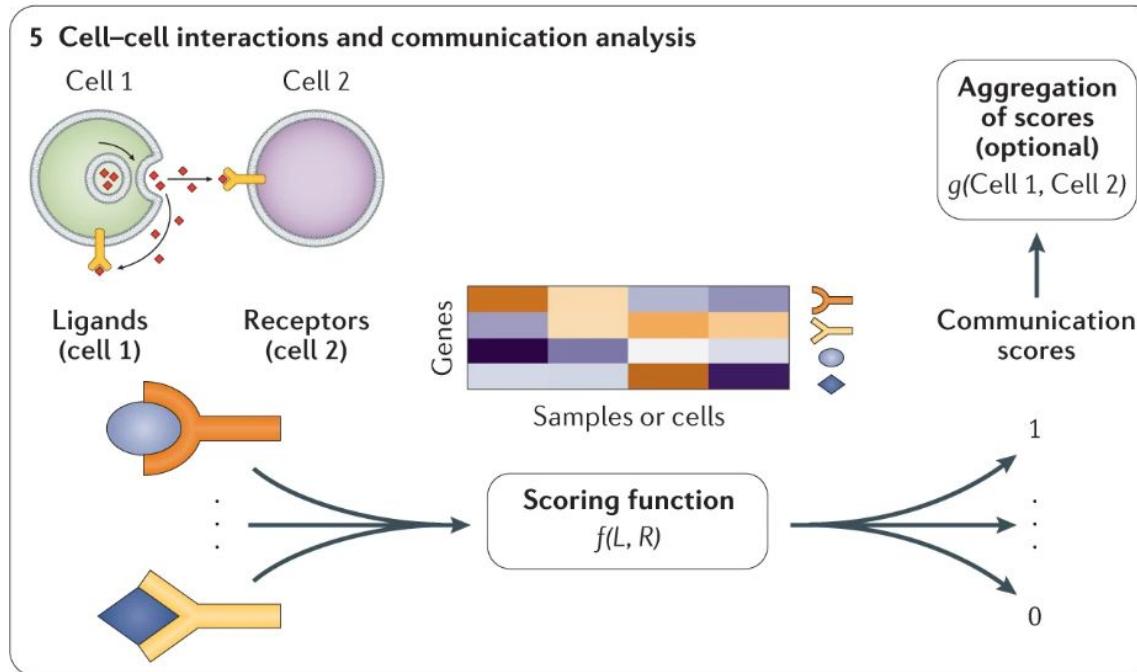
## 4 Filtering by interacting proteins or ligand-receptor pairs



~ 2k genes in Human  
(depends on the  
resource used)

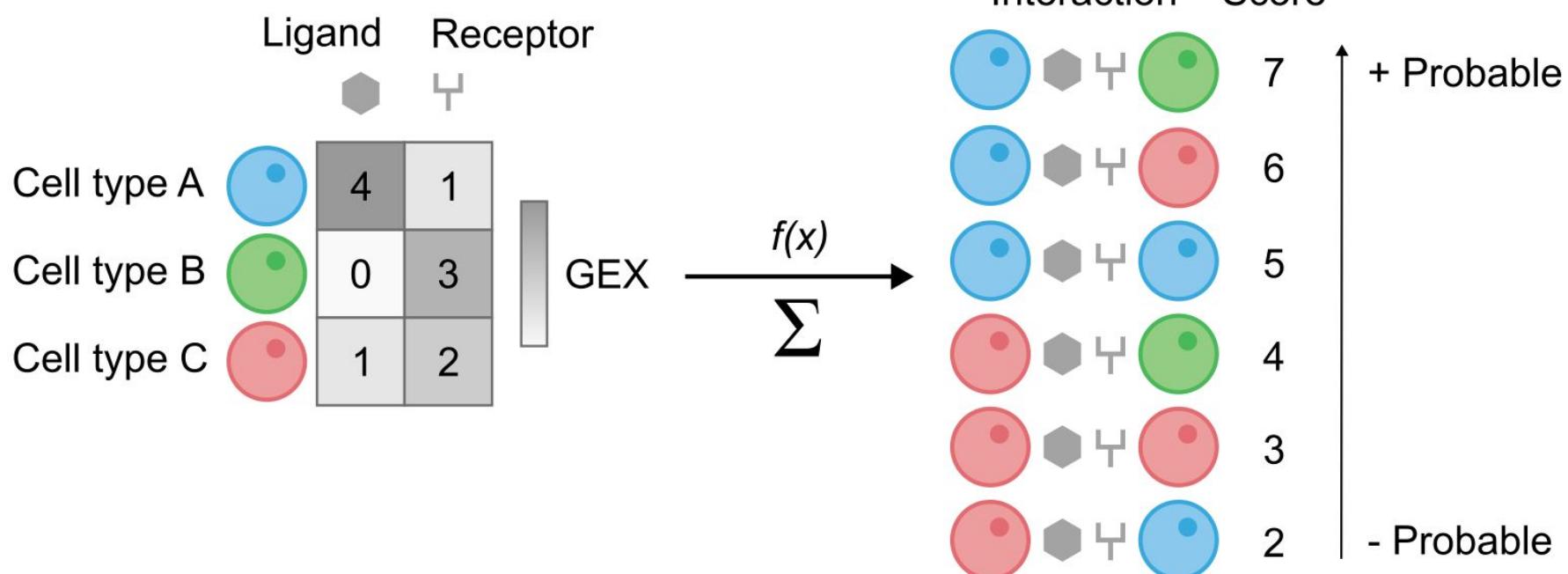


# Filtering by prior knowledge



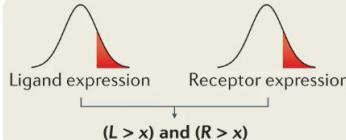
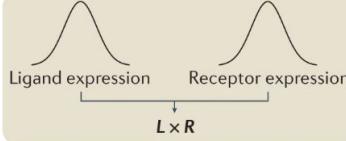
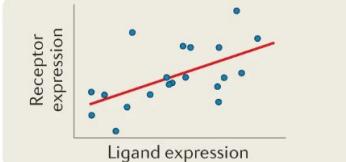
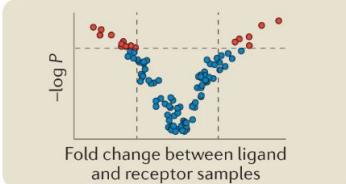


# Example





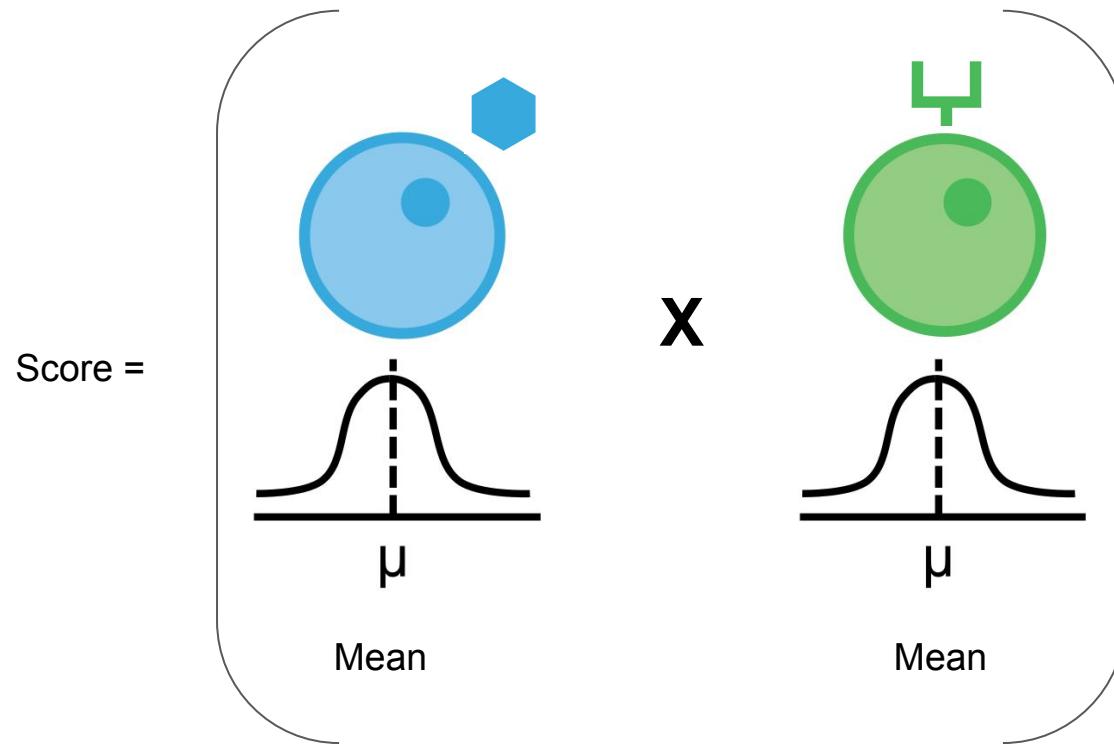
# Strategies for scoring functions

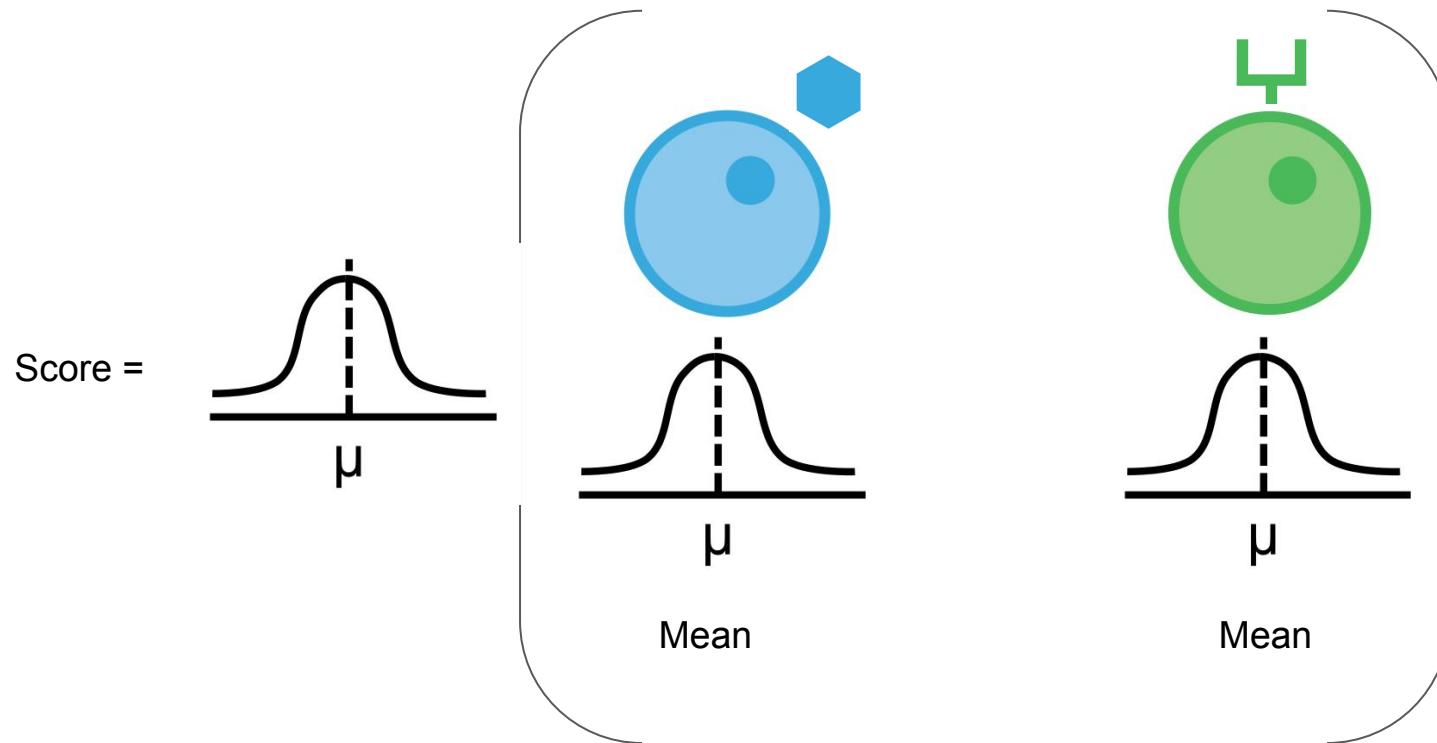
Communication score		
Expression thresholding		Binary
Expression product		Continuous
Expression correlation		Continuous
Differential combinations		Binary

- **2 types of scores:**
  - Magnitude (strength)
  - Specificity (uniqueness across cell types)



# **Methods for CCC inference**







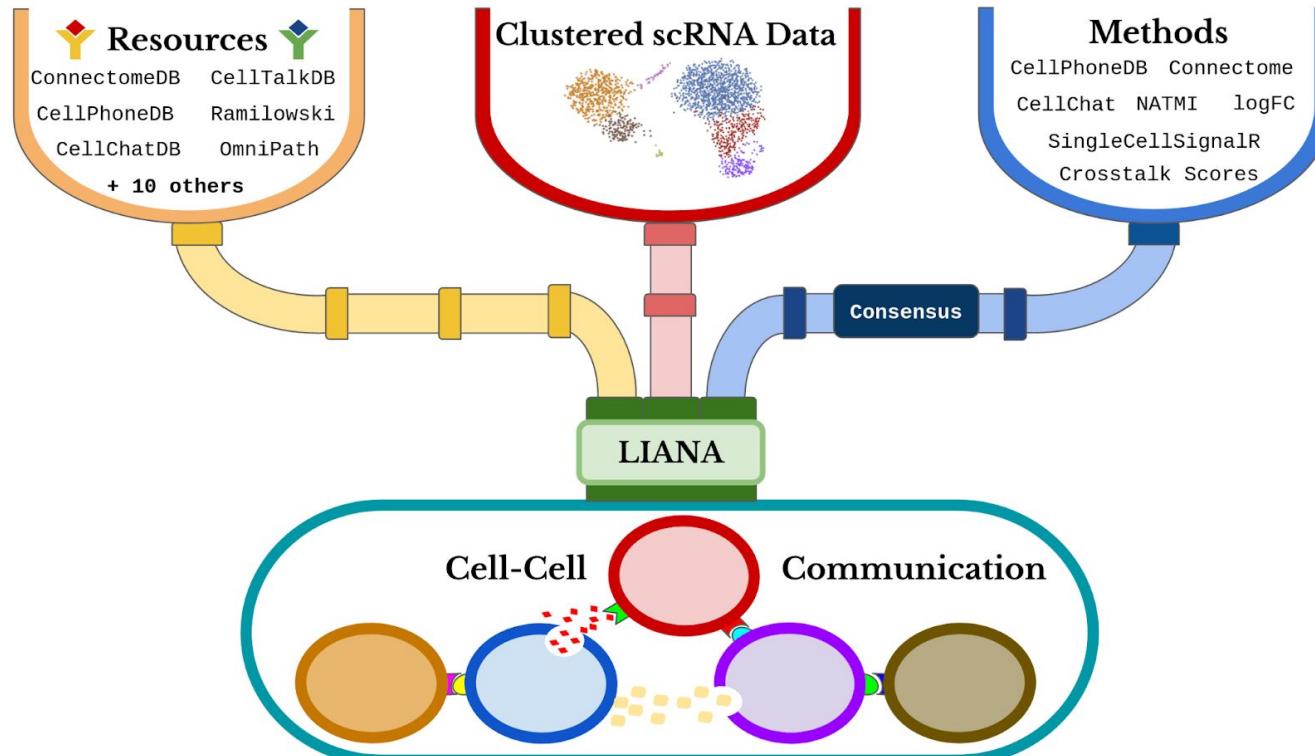
# Which method and database to use?



# LIANA: a unified Ligand-receptor ANalysis frAmework.

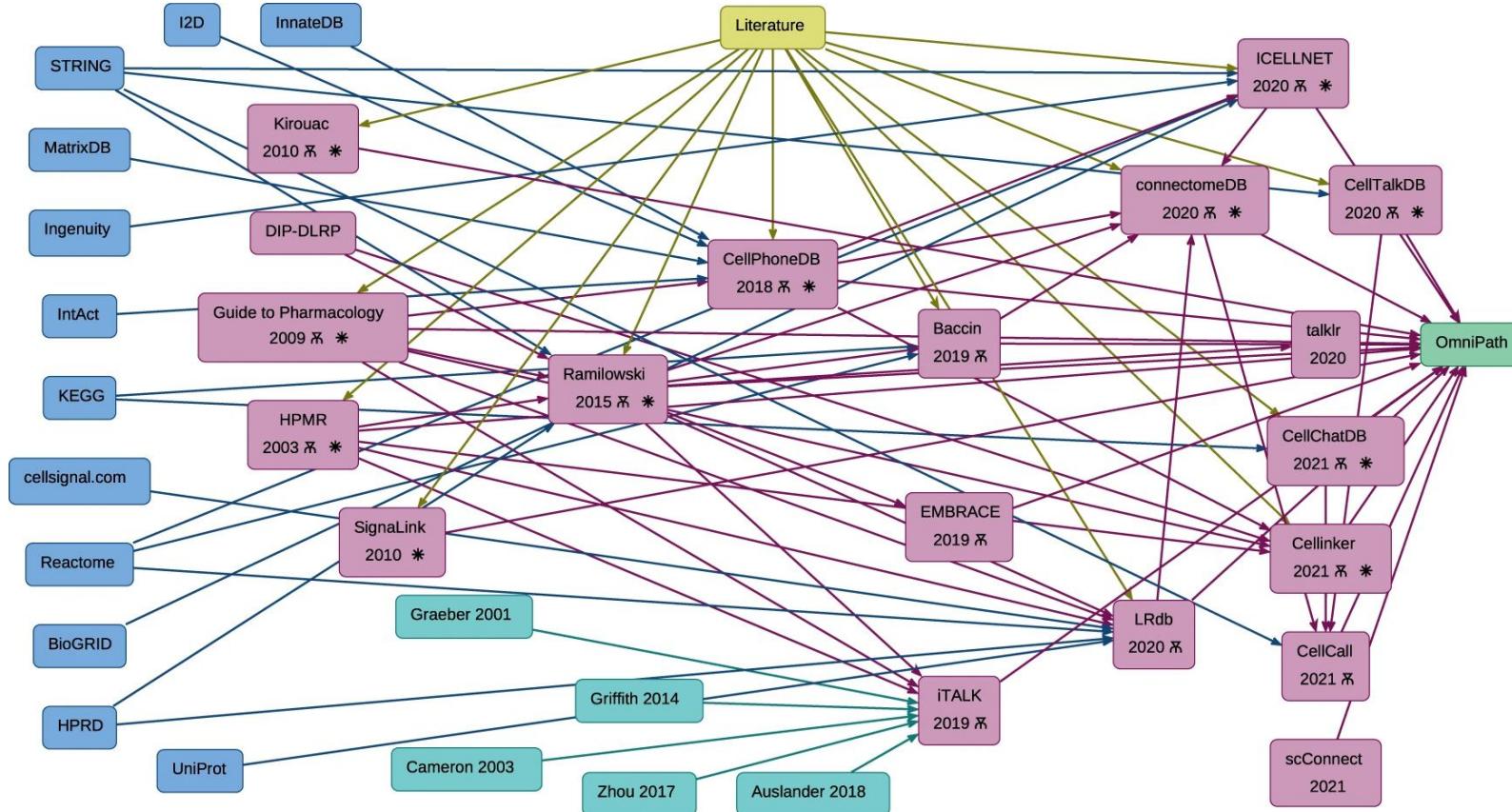


Daniel Dimitrov



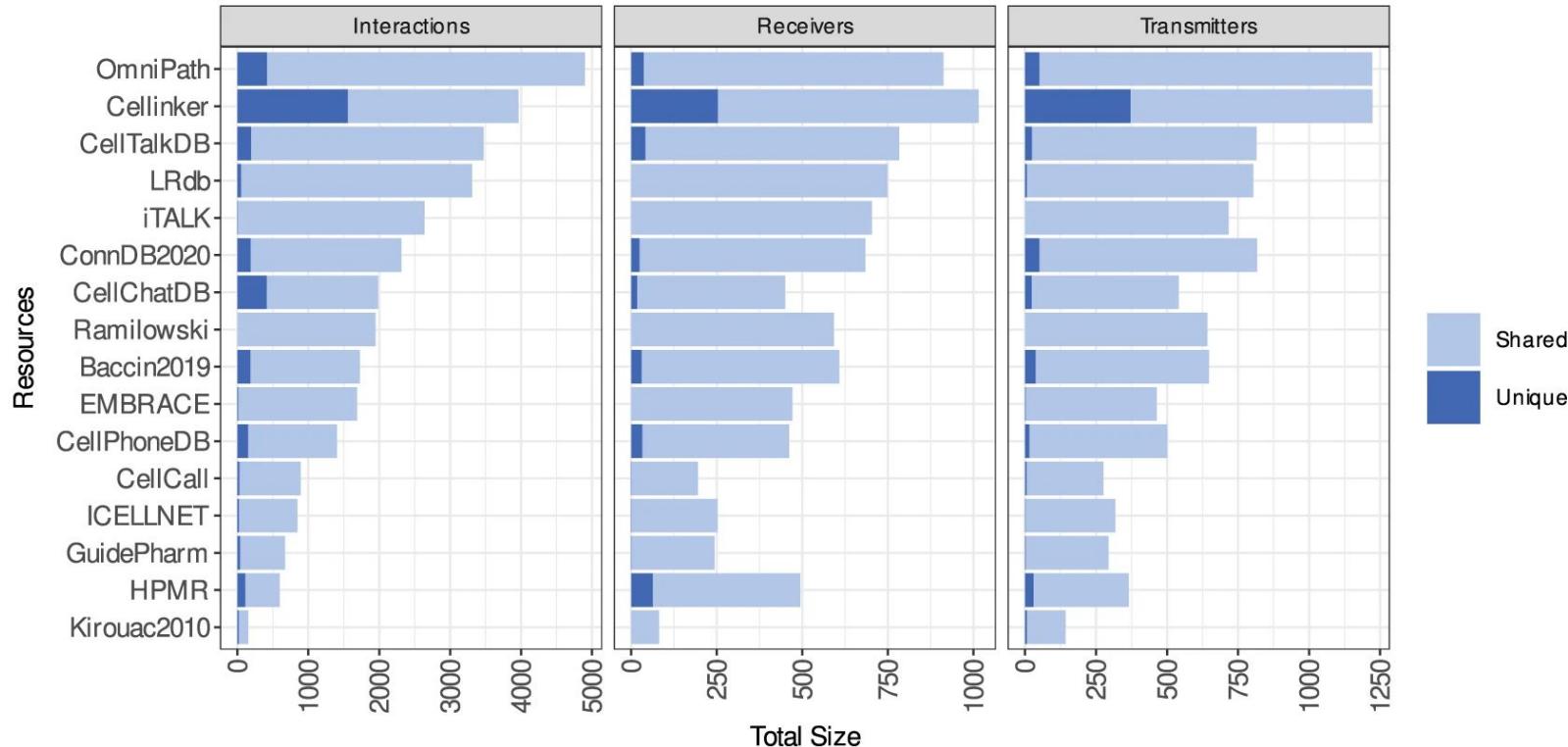


# Dependencies and overlap between CCC resources



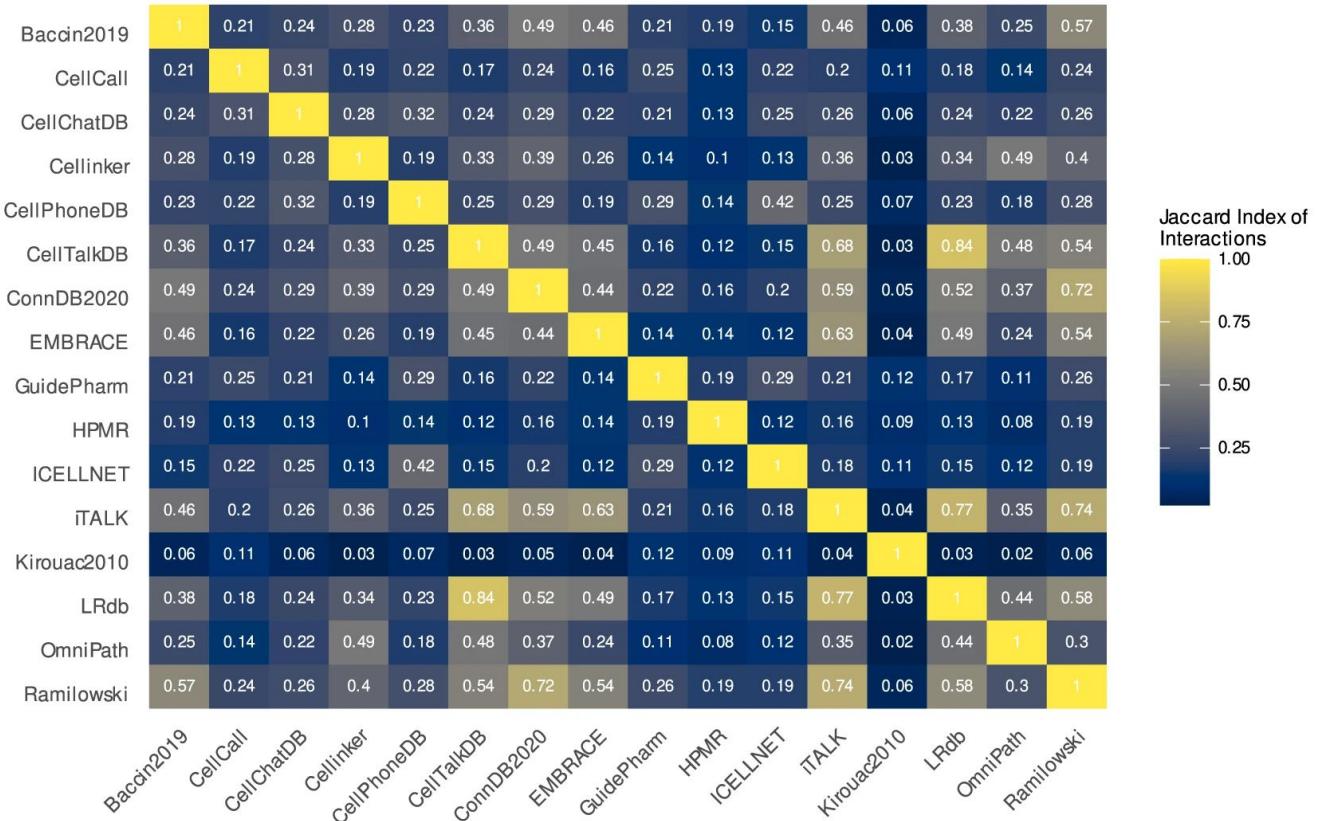


# Limited uniqueness across the resources





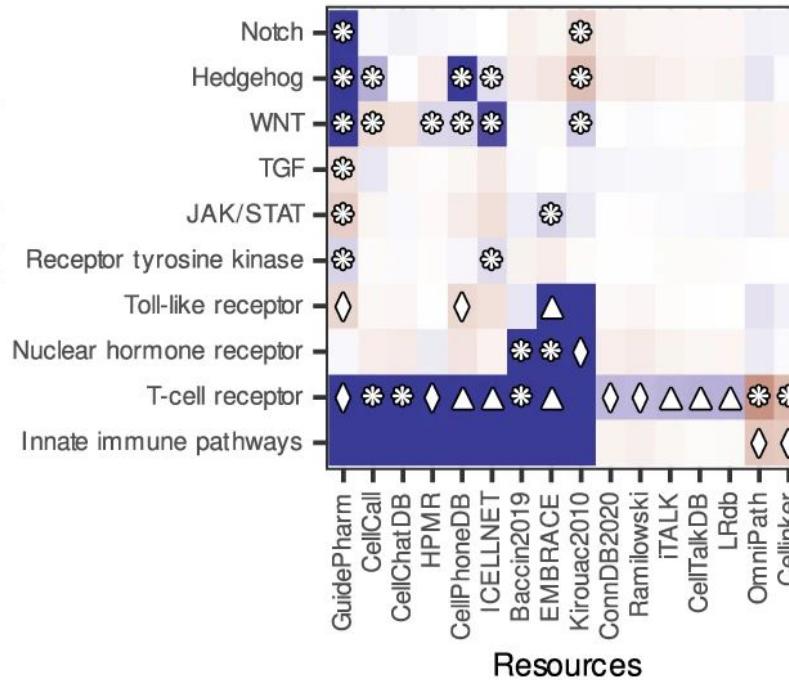
# Pairwise similarity between resources



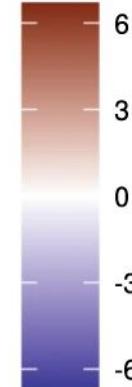


# Biases in Ligand-Receptor databases

Pathway (SignalLink)



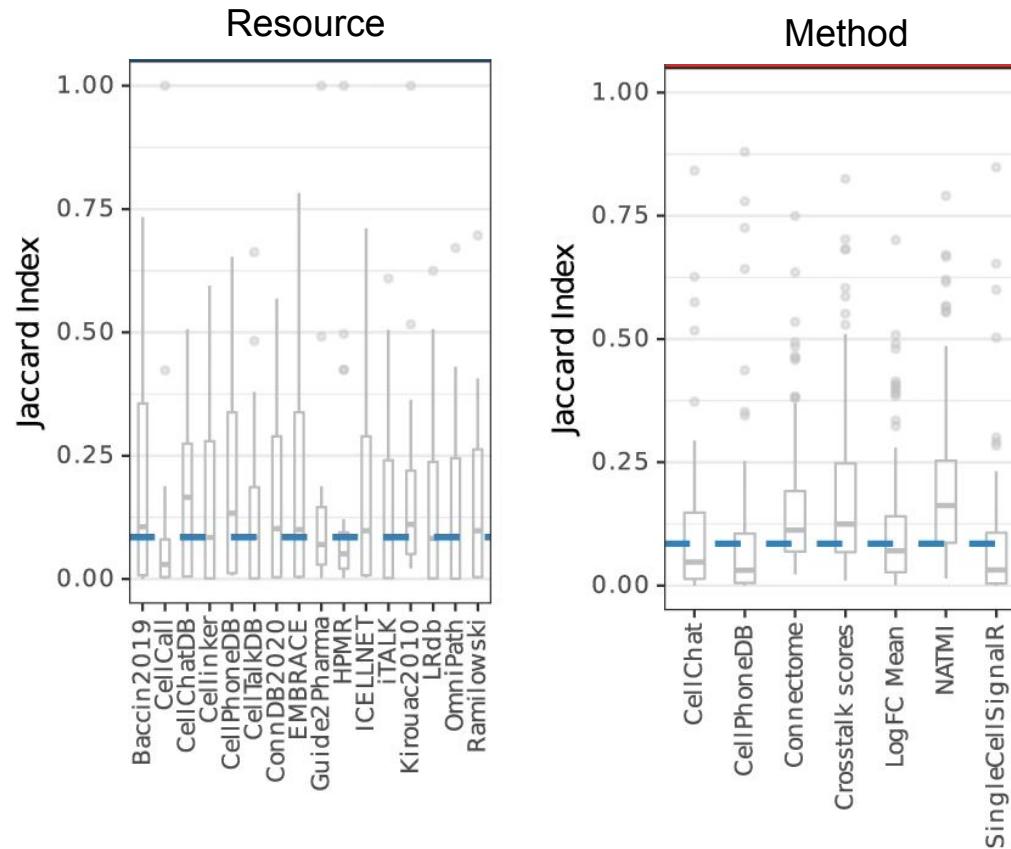
log<sub>2</sub>(Odds Ratios)  
of interactions



- Many resources are over or underrepresented by certain biological processes

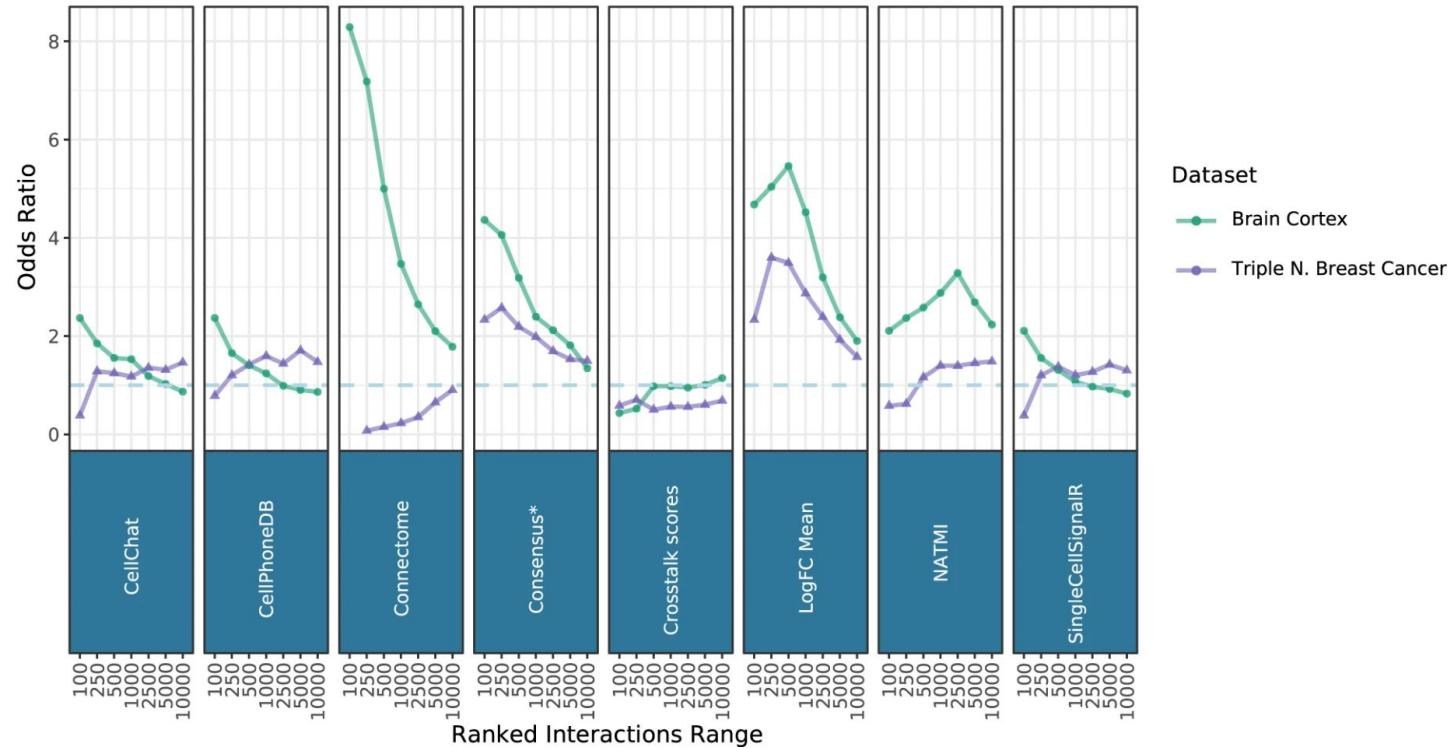
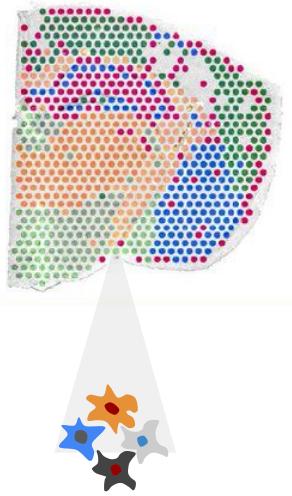


# Low overlap in predicted interactions





# Benchmark with spatial transcriptomics



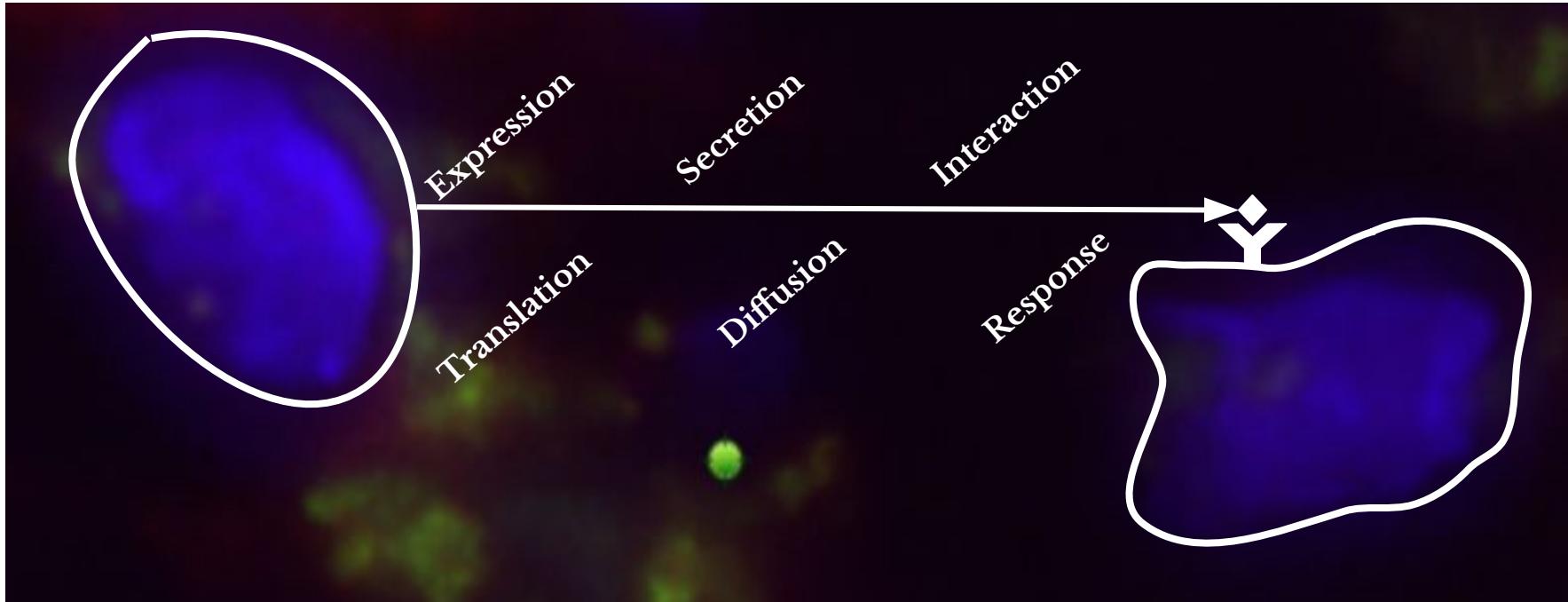
- **Consensus score and LogFC mean recover more spatial interactions**



# Caveats of CCC inference and how to mitigate them



# CCC inference requires huge assumptions



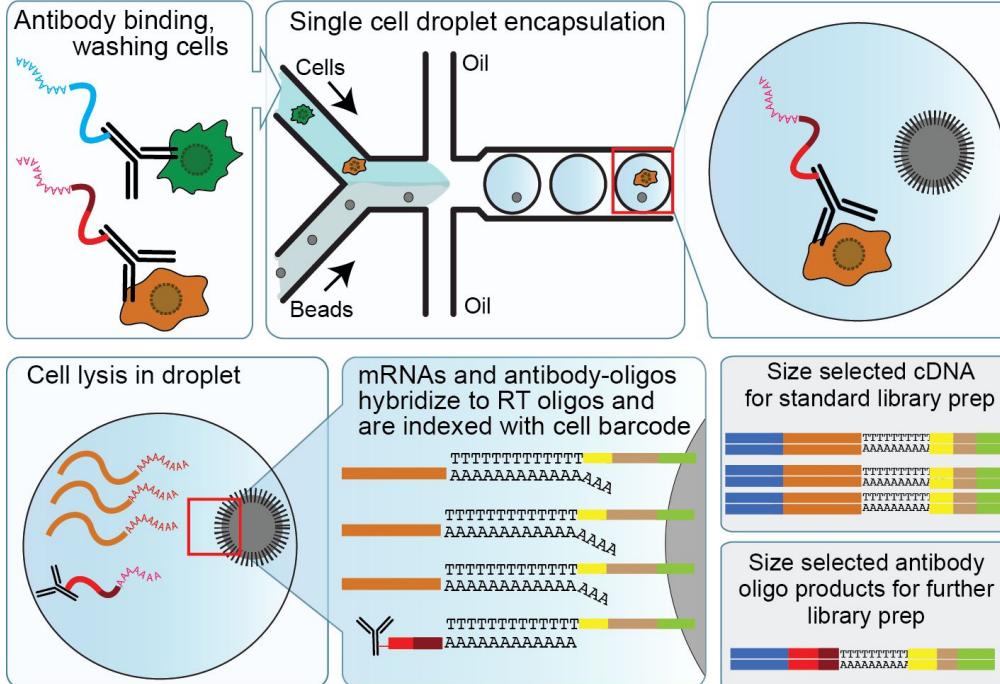
- Choice of method and resource can affect the results
- Due to heavy assumptions potentially there are many false positives in our predictions
- We can use other data modalities to refine our predictions

Adapted from Kartal et al., *Gut* (2022)



# Usage of CITE-seq data

Cellular Indexing of Transcriptomes and Epitopes by Sequencing (CITE-seq)

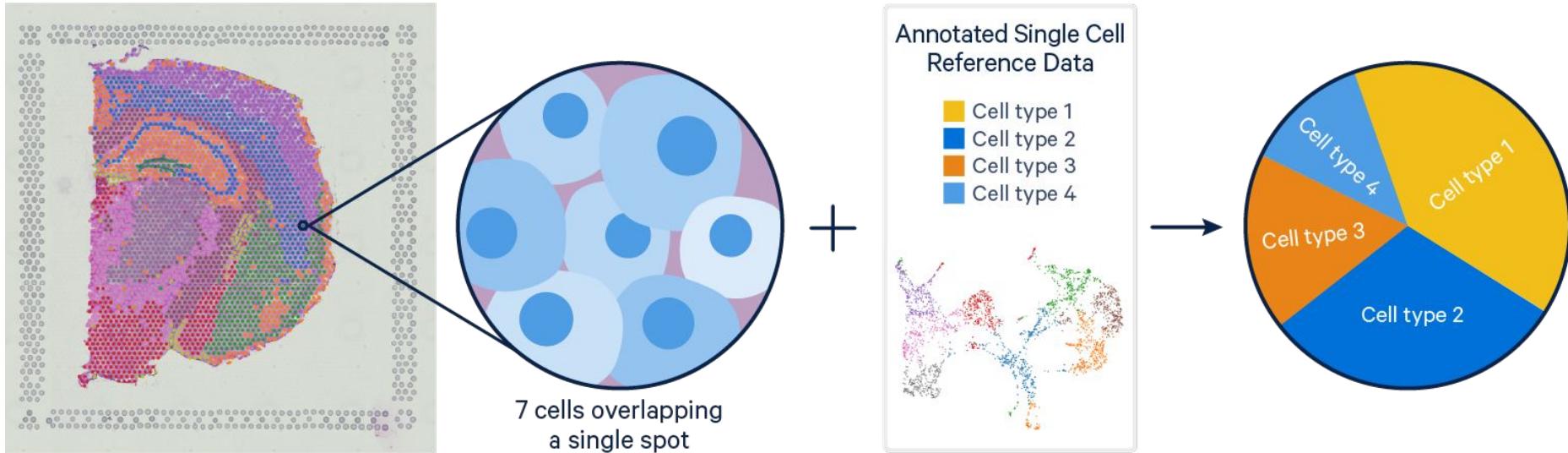


- **Profiles both gene expression and protein abundance of a collection of receptors**
- **Allows to filter out receptors that are not present at the protein level**
- **Still does not mean that they are interacting**

Adapted from <https://cite-seq.com/>



# Usage of spatial transcriptomics data



- Profiles gene expression with spatial coordinates
- Allows to filter out distal interactions (assuming diffusion and no endocrine signaling)
- Still does not mean that they are interacting

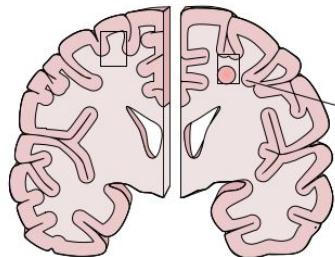


## Example of CCC analysis

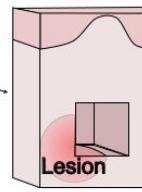


# Spatial cell type mapping of multiple sclerosis lesions

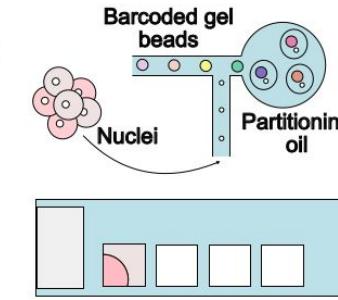
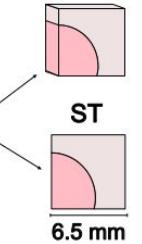
6 CTRL donors 9 MS donors



Tissue block



snRNA-seq



Conditions

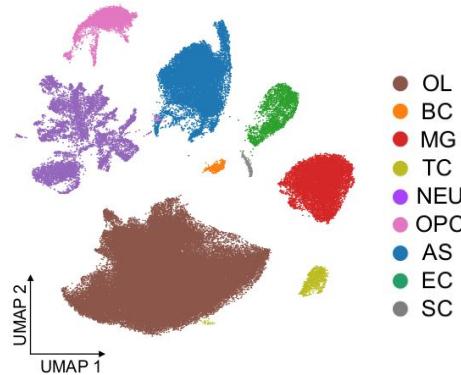
CTRL	MS-CA	MS-Cl
------	-------	-------

snRNA-seq sample size

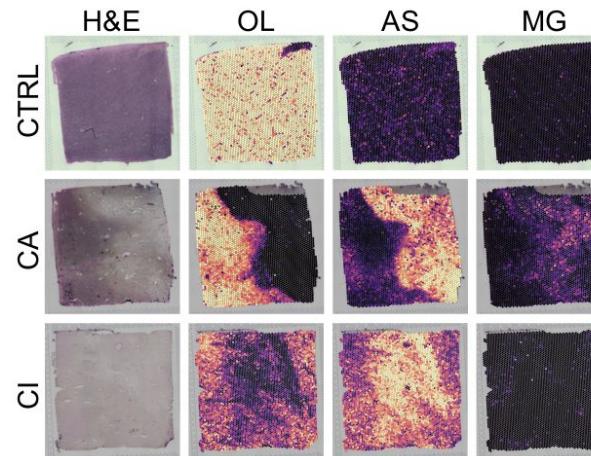
n=6	n=6	n=4
-----	-----	-----

ST sample size

n=6	n=8	n=4
-----	-----	-----



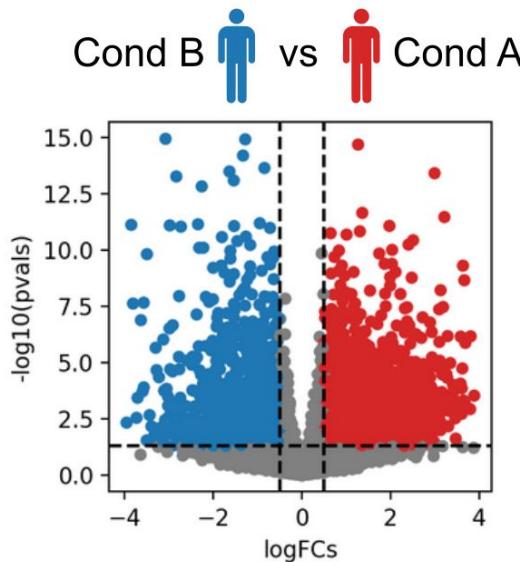
Deconvolution





# Example: CCC in Multiple Sclerosis

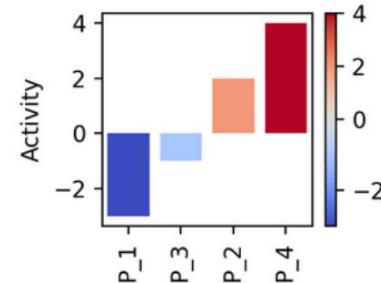
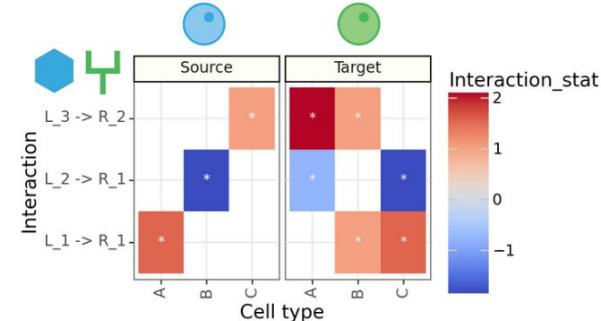
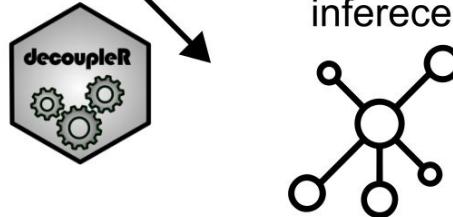
DEA across cell types



Cell-cell comm.  
inference

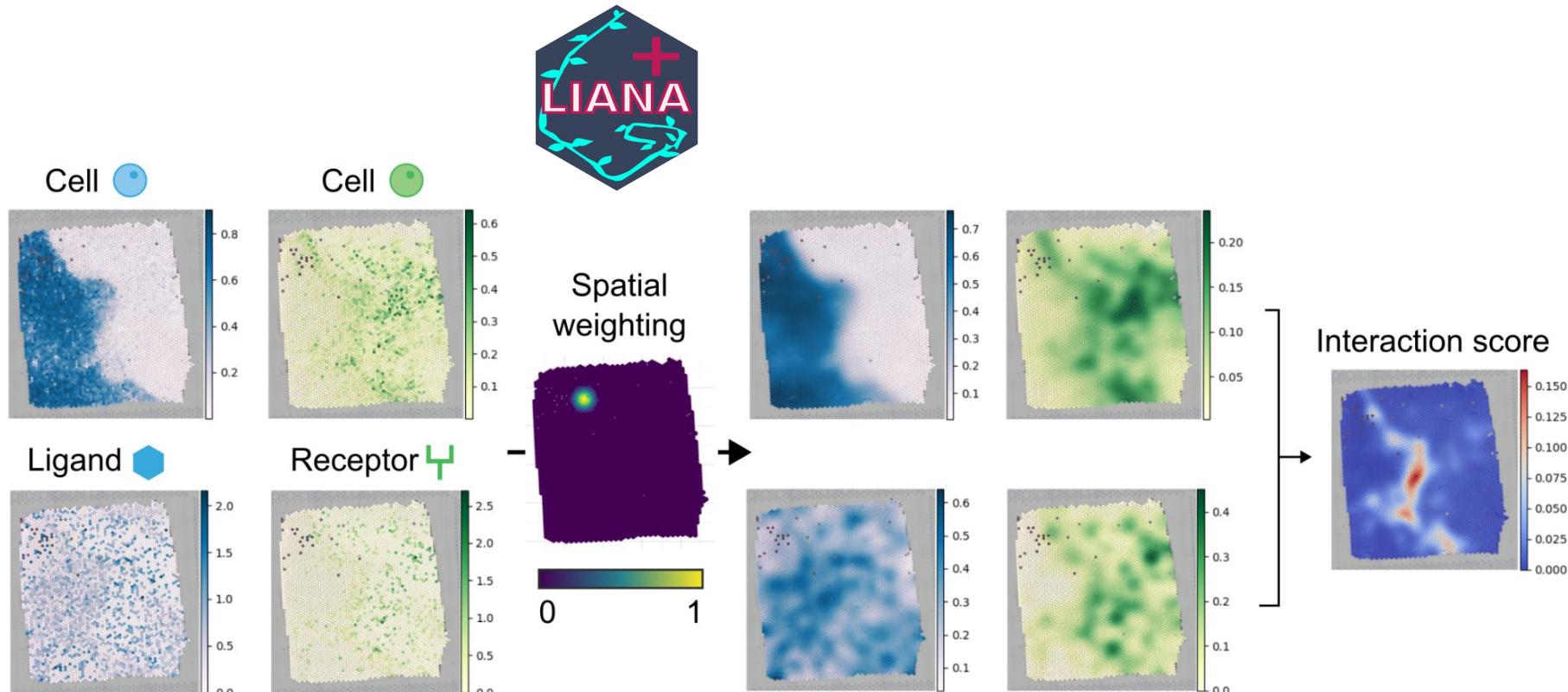


Pathway activity  
inferece



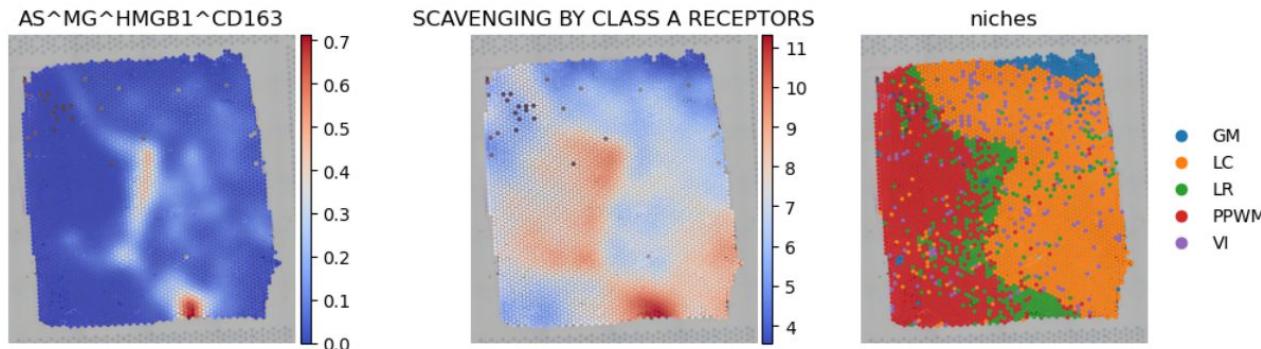
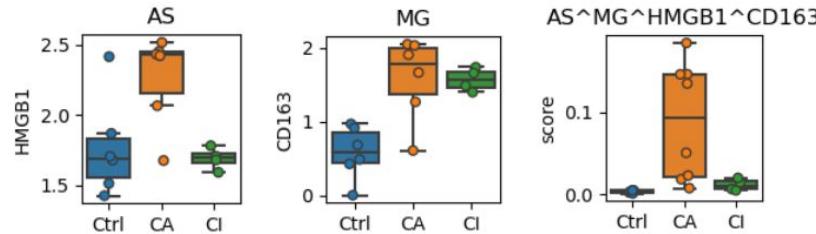


# Inference of spatial local scores for significant interactions





# Association of AS-MG signaling to scavenging





# Thank you for your attention

Take home messages:

- Cell-cell communication (CCC) drives many biological processes
- CCC inference is based on the presence of transcripts from ligands and receptors
- The choice of method and resource will affect the final results
- CCC results are never proof and have to be validated in the lab



X @saezlab  
@PauBadiaM

HEIDELBERG  
UNIVERSITY  
HOSPITAL

cellzome  
A GSK Company