REPRODUCIBLE PIPELINE for VISUALIZING METABOLIC PATHWAYS from SINGLE-CELL TRANSCRIPTOMICS: Application to Schizophrenia

Alba Coto Escofet

Master Thesis in Bioinformatics

June 2024

Supervisors: Postdoc, Romain de Oliveira. PhD candidate, Isabel Evi Naumann.

Professor Konstantin Khodosevich

Biotech Research & Innovation Centre (BRIC)

Khodosevich Group

ABSTRACT:

This thesis presents a reproducible and modular computational pipeline. The pipeline integrates single-cell RNA sequencing (scRNA-seq) data with genome-scale metabolic modeling using the Recon3D model and Escher visualization platform.

The pipeline created in this project enables researchers to translate transcriptomic differences into functional interpretations of metabolic activity across biological conditions. As proof of concept, the pipeline is validated using a curated bacterial model (E. coli) and then applied to human brain single-cell data from schizophrenia (SZ) and control samples.

The brain single-cell data are raw and must therefore undergo demultiplexing and clustering with Seurat. Subsequently, differential gene expression is mapped to metabolic reactions in Recon3D, and condition-specific models are generated using Flux Balance Analysis (FBA).

The nucleotide interconversion pathway is prioritized due to its transcriptional dysregulation and relevance to neuronal signaling. Simulations revealed elevated flux through enzymes such as ADK3, PDE1, and PDE4 in schizophrenia, indicating disease-associated changes in energy metabolism and cyclic nucleotide signaling.

Importantly, the pipeline also identified reactions where gene expression and metabolic activity diverged, offering insight into the multifactorial nature of metabolic dysregulation.

This integrative approach aims to demonstrate the potential of combining scRNA-seq data with metabolic modeling to explore disease mechanisms and offer a generalizable framework for studying metabolic alterations in complex disorders.

TABLE OF CONTENTS: