

Existing Work on Large-linear Models in Neuro-genomics

In prior work from co-PIs Mark Gerstein and Jonathan Warrell, we have established a strong foundation in developing large integrative genomics and multiomics models of genetic risk, highlighted by our contributions to major consortia such as the PsychENCODE Consortium. In this work, we generated a detailed mapping of gene expression and regulatory networks across a large sample size, which helps the understanding of the genomic basis of psychiatric disorders. We developed the **Linear Network of Cell-Type Phenotypes (LNCTP) model**, an innovative omics-based deep-learning approach designed to predict various psychiatric phenotypes from genotypes and detailed single-cell data, while preserving a linear model structure at all levels of the model.

The **LNCTP model** utilizes a multi-level architecture incorporating a Boltzmann-machine gene expression imputation engine and hierarchical linear predictors. This analysis enabled us to explore the gene expression and chromatin states across a diverse cohort, including individuals diagnosed with various psychiatric disorders. Moreover, the framework generates a model that is directly interpretable at multiple scales, avoiding many of the difficulties arising in the interpretation of deep neural networks, while maintaining a hierarchical structure. The **linear architecture** also allowed prioritization of intermediate phenotypes by both gradient-based saliency and co-heritability. Additionally, the ability to impute cell-type gene expression allows the model to simulate the effects of gene perturbations, demonstrated to be in high agreement with experimental CRISPR perturbations in neural-related cell-lines.

Polygenic Subgroups for Improved Prediction of Cancer Patient Responses to Immunotherapy

In prior work, co-PIs Gerstein and Warrell have shown that using spatial transcriptomics can allow highly predictive compact gene signatures to be learned, which accurately stratify cancer patients who will respond best to immunotherapy treatments from clinical trials.