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End-to-End Framework for Condition-Specific Gene Regulatory Network Inference via Multi-View Attention from Single-Cell Multi-Omics

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Deciphering how transcriptional regulation varies across cell types and disease states at single-cell resolution remains a major challenge in molecular biology and systems medicine. Existing methods for gene regulatory networks (GRNs) inference often rely heavily on bulk-derived reference networks or use single-cell data only through gene co-expression. Bulk priors overlook differences between cellular states, while co-expression approaches suffers from data sparsity and limited interpretability. These limitations restrict discovery of the regulatory programs that drive cell identity and disease. Here, we present a scalable, end-to-end deep learning framework that infers GRNs in the context of input single-cell RNA-seq or multi-omics data. The pipeline integrates multi-omics preprocessing, graph construction, representation learning, and prediction in a unified workflow. The core model employs a multi-view attention mechanism that integrates curated regulatory network topology with data-specific gene expression features, capturing both global regulatory structure and condition-dependent signals. Our framework reconstructs regulatory networks tailored to the input condition, avoiding cross-type biases from bulk-derived prior networks. For example, it identified the bone marrow(BM)-specific interaction between BCL11A and DNMT1, absent in umbilical cord blood(UCB) data predictions and not annotated in prior networks. This finding aligns with BCL11A's known repressive role in adult erythroid cells through DNMT1-mediated hypermethylation, underscoring the biological interpretability of our results. Altogether, our approach advances condition-specific, biologically grounded single cell GRN inference with broad applicability to multi-omics integration and cell type-focused regulatory discovery.