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Predicting upstream ligands from gene expression at the single-cell level with PULSO

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Although the widespread adoption of single-cell RNA sequencing has enabled researchers to decipher complex biological processes via cell-cell interaction, current methods suffer from loss of cell-level signals via bulk aggregation and inference of surface signaling molecule level from high dropout gene expression. To address this, we introduce PULSO (Predictive Upstream Ligands using Single-cell transcriptOmics), a novel methodology that infers upstream ligand signaling activity at the single-cell level using transcriptomic data. PULSO employs a two-step approach. First, the user-provided batch-corrected latent space is used in the attention operations that capture the relationships between multiple cells simultaneously and increase computational efficiency. Combined with positive and negative sampling for classification model training, this approach generates gene importance scores for individual cells that preserve the batch correction information. These values reflect both a single cell's similarity with other cells and gene expression, facilitating the imputation of weak biological signals. Second, PULSO evaluates the per-cell gene importance scores against a curated ligand-target gene relationship database to predict upstream ligand activity. The cell-specific values derived from PULSO enable the discovery of multicellular programs relevant to different biological contexts. We highlight this potential to advance our understanding of complex biological interactions at single-cell resolution by uncovering insights into immunotherapy response in primary liver cancer.