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scDECA: Intergrating Gene-Cell interactions with Global Priors and Local Structures in Single-Cell Transcriptomics.

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Single-cell RNA sequencing (scRNA-seq) is a powerful approach for dissecting cellular heterogeneity and disease-specific transcriptional programs using large-scale atlases. Because of the inherent dropout, sparsity, and high dimensionality of scRNA-seq data, extracting meaningful biological signals is challenging. Recently, foundation models trained on large atlases have provided global priors that offer useful guidance, but they fail to capture condition-specific signals in study-specific datasets. Moreover, conventional clustering emphasizes cell–cell relationships without accounting for the biological context of individual genes and gene groups.

To address these limitations, we introduce scDECA (Single-cell Dual-Encoder with Cross-Attention), a representation learning framework that integrates the global priors of foundation models with graph-based local context to jointly encode genes and cells, explicitly capturing gene–cell interactions. Our method employs a gene encoder that integrates foundation model–based token embeddings with graph-derived features from protein–protein interaction (PPI) networks constructed on raw gene expression, and a cell encoder that models transposed gene expression using k-nearest neighbor (KNN) graphs to capture both expression patterns and neighborhood structure. Each representation is refined by self-attention, while cross-attention explicitly models gene–cell interactions beyond simple concatenation. Gene representations are decoded to reconstruct PPI networks, and cell representations are used to reconstruct gene expression.

Experiments on four condition-specific datasets—Malaria-associated B cell, Melanoma, SARS-CoV-2, and Glioblastoma—demonstrate that our method captures functional relevance at the gene level, as shown by functional annotation and network-based analyses (including pathway reconstruction and gene–gene relational profiling), while improving cellular structure delineation and clustering robustness. Furthermore, reconstructed gene expression reveals differential patterns and condition-specific pathways, supporting the biological validity of the learned representations.