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A Framework for Pathway-Based Dimension Reduction for Drug Response Prediction at Single-Cell Resolution

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Predicting drug responses at single-cell resolution is a critical yet challenging task in precision oncology due to the vast variability in gene expression profiles among individual cells. This heterogeneity complicates effective treatment strategies as it often eludes traditional bulk-level analysis methods. To address this challenge, we propose the PathFinder, a transfer learning-based framework that integrates the single-cell data with bulk-level pharmacogenomic profiles. PathFinder, our transfer learning framework, addresses this challenge by integrating single-cell data with bulk-level pharmacogenomic profiles, bridging a significant gap in current methodologies. The framework introduces a pathway-based dimension reduction strategy that aligns high-dimensional single-cell gene expression data with well-curated bulk drug response profiles. To enhance this alignment, PathFinder incorporates a drug response label–guided contrastive loss, ensuring that single-cell representations with same sensitivity or resistance labels are embedded more closely in the latent space. Leveraging a weight transfer mechanism, the framework adapts bulk-derived knowledge to single-cell scenarios, thereby improving prediction accuracy and biological interpretability. This learning strategy improved both prediction accuracy along with the biological interpretability by maintaining pathway-level embeddings. Throughout rigorous benchmarking analysis, PathFinder has demonstrated its robustness and outperformed previously released state-of-the-art models In summary, PathFinder offers a scalable solution that significantly improves our understanding and prediction of drug responses at the single-cell level, presenting a valuable tool for advancing personalized treatment plans in clinical oncology.