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Prediction of expression changes in single cell RNA using style transfer variational autoencoder

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Motivation and Aim: Single cell transcriptomics is already a well-established method for unbiased profiling of complex and heterogeneous systems [1]. The produced data is usually used to explain phenotypes based on the composition and dynamics of cells. The dynamics of individual cells in response to perturbations, like treatments or gene knockouts, are of particular interest. While the discovery of genes affected by a perturbation has been made possible by developments in single cell differential expression analysis [2], generative modeling of perturbation response goes one step further since it allows generating data *in silico*. The ability to generate data that was previously unseen (not present in the training data, out-of-sample) is particularly challenging and enticing.

Methods and Algorithms: In this study, we've polished the architecture and evaluated the performance of stVAE [3], a deep learning model that uses Conditional Variational Autoencoder [4] and Y-Autoencoder [5] training approaches. The stVAE architecture allows to disentangle the variables representing a needed 'style' from the hidden variables. We've applied stVAE to the single cell dataset of peripheral blood mononuclear cells (PBMCs) derived from patients with pericarditis, some of which received IL-1β blocker treatment. We've analyzed the distribution and composition characteristics of the predicted data, and also performed differential expression and pathway analyzes.

Results: Our goal was to train the model to predict treatment effects for specific cell types. As a first test, we trained the model on all the cell types present in the dataset and analyzed the predictions for the validation set of cells, left out during training. Then we also experimented by restricting the training data to a subset of cell types (e.g. training only on B cells, CD4 T cells, etc.) and then validating on the cell types hold out during training. Results from both approaches showed high correlations of predicted gene expressions and ground truth (mean R2 over all genes in cell types ≥0.93, mean R2 over differentially expressed genes in monocytes ≥0.87). We've proposed several metrics to evaluate the accuracy of perturbation predictions in comparison to the ground truth

(experimental data), for example, correlation of differentially expressed gene sets or fold changes and intersection or semantic similarity of enriched pathways.
Conclusion: We have demonstrated that stVAE is able to accurately predict single-cell perturbation response out-of-sample. Obtained predictions are cell-type- and patient-specific. To enable this, the model is required to capture features that differentiate genes and cells that respond weakly from those that respond strongly. Building biological interpretations of the features could, for instance, aid in comprehending how patients react to medications and thus advancing the personalized treatments.

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