PREDICTING PATIENT-LEVEL PHENOTYPES FROM SINGLE-CELL DATA

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ABSTRACT

Deep learning approaches have seen increased use in several functional genomics applications, often meeting or exceeding the performance of state-of-the-art methodologies [1]. Over the course of this project, we intend to use a convolutional neural network architecture to predict patient-level phenotypes from B cell mass cytometry data.

1. INTRODUCTION

High-dimensional single-cell technologies (such as single-cell RNA sequencing, single-cell ATAC-sequencing, mass cytometry, among many others) have become useful tools in understanding the heterogeneity and molecular profile of cells in both health and diseased states [2], as a result these technologies now play an important role in the development of more effective and precise therapies to diseases such as cancer [3, 4]. Single-cell technologies also enable the detection and description of diverse cell population in both healthy and diseased states - including the identification of rare cell populations which traditional biological experiments may fail to detect. This ability to map out the genomic and proteomic profile of cells in different states, such as in development, healthy and diseased states, is crucial in improving our understanding of cellular processes and the human biology .

Unsupervised clustering is a machine learning approach, which utilizes single-cell omics analysis to identify and define cell clusters (and subsequently cell types) [5, 6, 7] . While this learning approach has aided our understanding of the heterogeneity of cell types in development, health and diseased states, unsupervised clustering is still limited in directly associating identified cell clusters with disease status, as this is usually done manually with the aid of literature, wet-lab experiments and expertise knowledge. Furthermore, with unsupervised learning associating cell cluster to a disease phenotype usually requires an additional step of condition-specific differences introduced in wet-lab experiments (or differences introduced as a function of individuals having a disease and thus altered biology relative to healthy individuals),which in turn is represented in unsupervised clustering of single-cell data by the increased or decreased abundance of a given cell cluster(s) compared to healthy controls or healthy individual.

The limitation of unsupervised clusterings' inability to predict phenotype(s) (such as disease condition, expected survival, developmental stage) from single-cell data is one which is expensive and time consuming when relying on the combination of literature, expertise knowledge and wet-lab experiments to associate cell types with phenotypes.

Our project aims to address this problem using supervised learning, specifically deep convolutional neural networks with multiple layers and transfer learning. In a recent study done by Arvaniti and Claassen, a computational framework, called CellCNN, was developed to facilitate the detection of rare- disease associated subsets and their phenotype [8]. CellCNN combined multi instance learning and convolutional neural network using a single layer to identify cell clusters and also the associated disease status of clusters. Our project aims to further extend on this using additional techniques such as dimensionality reduction and saliency maps to extract information which could then be used for predictions.

2. RELATED PAPERS

2.1. Deep Learning for Phenotype Prediction

Recent applications of convolutional neural networks (CNNs) on single-cell inputs have demonstrated CNN utility for both the classification (multi-node output) and regression (single node output) task.

Specifically, Claasen et. al adapted CNN architecture for processing groups of single-cell inputs (collectively, multi-cell inputs), where each of these multi-cell inputs was associated with a phenotype [8]. The group was able to demonstrate efficacy of their CellCNN architecture in a variety of phenotype prediction tasks. Their architecture was used to classify whether peripheral blood mononuclear cells (PBMC) samples had been stimulated or unstimulated by paracrine agents, based on the samples intra-cellular markers. Additionally, the group was able to use CellCNN for the regression task, to identify T-cell subpopulations that were at higher risk of AIDS onset following infection to HIV. CellCNN was shown to predict comparably to state-of-the-art approaches, with lower computational costs.

Chen et. al. were able to use a deep learning approach to predict gene expression patterns of cells [9]. Their model,

dubbed D-GEX, predicts the expression of a "target" gene based on known expressions of a group of "landmark" genes. Comparing their RNN based models to other state-of-the-art methods (linear regression), resulted in D-GEX significantly outperforming other methodologies.

2.2. Datasets

A study done by the Pe'er and Nolan lab groups employed mass cytometry to study the development trajectory of B cells, as well as the behaviour of B cells in response to stimuli [10]. The group developed an unsupervised learning algorithm, Wanderlust, a nearest-neighbor (NN) based graph trajectory detection algorithm. Wanderlust takes multiparameter single-cell events as input, and maps them onto a cell developmental trajectory [10]. As part of their experiment, Pe'er et. al collected a B cell centric, mass cytometry dataset from human bone marrow. Their dataset includes records of multiple B cell cellular features, such as activation of regulatory signaling molecules, and phenotypic proteins. We will be using their publicly available data of mass cytometry and scRNA seq from the same group to reduce technical variations such as batch effects.

We would develop and train our model using mass cytometry data of B cells. Since the development of B cells and its response to stimuli results in differential expression of B cell types and phenotypes, we would test the sensitivity and efficiency of our model in detecting phenotype(s) associated with observed cell types. This intended data set is already publicly available on https://reports.cytobank.org/1/v1

3. ML TECHNIQUES

Our network will take in single cell data as input and attempt to identify the phenotype-associated cell subpopulations. We will be using supervised learning via variety of different model architectures.

3.1. Preprocessing and Feature Engineering

We will attempt numerous feature engineering techniques. Dimensionality reduction techniques such as linear discriminant analysis and principal component analysis have been used to reduce the raw data size (and by extension the computational cost) of genomics data sets [11]. Outside of functional genomics, dimensionality reduction of input data has been shown to improve performance of image classification models. We will try dimensionality reduction for pre-processing to cell distribution. Another way to extract information is to use saliency maps to see which cells/genes are contributing to the predictions.

3.2. Model Architecture

For our network, we will be using deep convolutional neural networks (CNN). CNNs broadly consist of series of convolutional layers followed by pooling layers. In the case of Cell-CNN, the architecture consisted of max-pooling and mean-pooling layers following the convolutional layer. One avenue of exploration is to integrate an expectation pooling layer, developed for using CNNs as probabilistic models [12]. We plan on expanding the number of layers, as well as implementing state of the art architectures such as UNet [13]. We will also use transfer learning, applying trained models from other single celled states models, as well as from other fields of study such as computer vision and natural language processing [7] [14].

4. DELIVERABLES

Deliverables for the midcourse report include:

1. Download, process and understand the data. The Pe'er Lab's B cell data will need to be processed into single-cell inputs with corresponding phenotype classification (in this case, B cell response to stimuli).

2. Perform mass cytometry analysis and unsupervised clustering to identify cell population and deferentially expressed proteins representative of each cluster.

3. Perform some EDA, and possibly run a baseline method or code from a related method. Open source CellCNN [8] code

5. MEASURING RESULTS

How will you assess performance compared to existing/baseline approaches?

1. Comparison to Truth Data: Pe'er et. al [10] documented the responses of B cells to certain stimuli. Difference from this baseline truth data will be used as a point of preformance comparison for different model architectures.

2. Ablation: in order to assess the performances of our model we would perform ablation specific features/nodes are removed and the change in accuracy is measured to see how the model performs in the presence vs absence of selected features/nodes.

3. Comparative Analysis: Another method of assessing and increasing performance of our model is by comparing output accuracy and run time for different model architectures on a single data set.

6. REFERENCES

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