Gaining insight into SARS-CoV-2 infection and COVID-19 severity using self-supervised edge features and Graph Neural Networks

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Abstract

Graph Neural Networks (GNN) have been extensively used to extract meaningful representations from graph structured data and to perform predictive tasks such as node classification and link prediction. In recent years, there has been a lot of work incorporating edge features along with node features for prediction tasks. In this work, we present a framework for creating new edge features, via a combination of self-supervised and unsupervised learning which we then use along with node features for node classification tasks. We validate our work on two biological datasets comprising of single-cell RNA sequencing data of in vitro SARS-CoV-2 infection and human COVID-19 patients. We demonstrate that our method achieves better performance over baseline Graph Attention Network (GAT) and Graph Convolutional Network (GCN) models. Furthermore, given the attention mechanism on edge and node features, we are able to interpret the cell types and genes that determine the course and severity of COVID-19, contributing to a growing list of potential disease biomarkers and therapeutic targets.

1. Introduction

Graph neural networks (GNN) have been widely used and developed for predictive tasks such as node classification and link prediction [35] and have been shown to learn from any sparse and discrete relational structure in data [12]. GNNs typically use message passing, or recursive neighborhood aggregation, to construct a new feature vector for a particular node by collecting its neighbor’s feature vec-

tors [36, 20]. However, most GNN schemes do not use edge features in learning new representations of graphical data. Recently, edge features have been incorporated into GNNs to harness information describing different aspects of the relationships between nodes [15, 13]. However, there are very few frameworks for creating de novo edge feature vectors in a domain agnostic manner. In this article, using Graph Attention Networks, we propose a self-supervised learning framework to create new edge features which can be used to improve GNN performance in downstream node classification tasks.

Given the devastating impact of the coronavirus disease of 2019 (COVID-19) caused by infection of SARS-CoV-2 and the gap in our understanding of the molecular mechanisms of the disease, we sought to focus our efforts on COVID-19 datasets that can generate hypotheses related to these gaps [37, 39]. Our focus on single-cell transcriptomic data relating to COVID-19 was motivated by recent work showing that Graph Attention Networks are effective at predicting disease states on an individual cell-to-cell basis [29]. Single-cell RNA sequencing (scRNA-seq) is a technology that yields large datasets comprising many thousands of cells’ gene expression in a variety of conditions [38, 18, 31]. However, identifying factors important for determining an individual cell’s pathophysiological trajectory or response to viral insult remains a challenge as single-cell data is noisy, sparse, and multi-dimensional [8, 21]. We reasoned that our framework’s improved performance could extract useful insights into the genes and cell types that might be important determinants of COVID-19 severity and SARS-CoV-2 infection.

2. Related works

There is a wealth of research on Graph Neural Networks. A significant amount of work has been focused on graph embedding techniques, representation learning and various predictive analyses using node features. There has been recent interest in using edge features to improve the performance of Graph Neural Networks [15, 9, 1]. In this work we use an unique multi–tasking approach in creating these edge features.
Since our work focuses on biological applications, it becomes necessary to be able to interpret the results of our network to inform further study of biology and medicine. One of the most common and popular ways to interpret machine learning models is via Shapley values [26] and it’s various generalizations [27]. However Shapley values require independence of features which is generally hard to guarantee. There is an excellent library [22] that allows us to interpret PyTorch models. In this work we follow the approach of [29, 2] in using attention mechanisms for interpretability. Thus even though set2set [34] is a popular mechanism to encode sets and has been previously used in the graph domain [14, 3], our view is that it is hard to interpret the hidden state of a LSTM. The transformer used in the graph domain [14, 3], our view is that it is hard to interpret the results by looking at their attention heads. Even though GNNs have been extensively used in biomedical research to predict medications, diagnoses, and outcomes from graphical representations of electronic health records [10], protein-protein and drug-protein interactions and molecular activity [28, 7, 17, 33] there is only one recent work that uses GAT models to predict the disease state of individual cells derived from clinical samples [29]. However they do not consider multiple disease states or severity nor do they account for the confounding bias of batch effects. Here, we use the information contained within the dataset to construct edge features and a graph-structure that is balanced across batches, which reduces the bias of cell source while preserving biological variation [25]. To the best of our knowledge, this is the first attempt to apply a GNN model to gain insight into multiple pathophysiological states, merging time-points, severity, and disease-state prediction into a multi-label node classification task from single-cell data.

3. Our Model

In this subsection we describe our model which consists of two components: (1) Set Transformer and (2) GAT layers.

3.1. Set Transformer

We use a Set Transformer as in [23]. The Set Transformer is permutation invariant so it is an ideal architecture to encode sets. The building block of our Set Transformer is the multihead attention, as in [32]. Given $n$ query vectors $Q$ of dimension $d_q$, a key-value pair matrix $K \in R^{n \times d_k}$ and a value matrix $V \in R^{n \times d_v}$ and for simplicity, let $d_q = d_v = d$, the multihead attention is computed by first projecting $Q, K, V$ onto $h$ different $d_q, d^h_q, d^h_k, d^h_v$ dimensional vectors. For simplicity, let $d^h_q = d^h_v = \frac{d}{h}$, where $h$ is the number of heads.

$$ \text{Multihead}(Q, K, V) := \text{concat}(O_1, \cdots, O_h)W^O $$

$$ O_j := \text{softmax}\left( \frac{(QW^Q_j)(KW^K_j)^T}{\sqrt{d}} \right)VW^V_j $$

and $W^Q_j, W^K_j, W^V_j$ are projection operators of dimensions $R^{d_q \times d^h_q}, R^{d_k \times d^h_k}$ and $R^{d_v \times d^h_v}$ respectively and $W^O$ is a linear operator of dimension $d \times d$. Now, given a set $S$, the Set Transformer Block (STB) is given the following formula:

$$ \text{STB}(S) := \text{LayerNorm}(X + rFF(X)) $$

where $X = \text{LayerNorm}(S + \text{Multihead}(S, S, S))$. rFF is a row-wise feedforward layer and LayerNorm is layer normalization [4].

A Set Transformer takes as input a 3d tensor of the form $[\text{batch}, \text{seq}-\text{length}, \text{input-dim}]$ and outputs 3d tensor of the form $[\text{batch}, \text{seq}-\text{length}, \text{output-dim}]$, i.e. it outputs sets of the same size as the input sets. If, for a batch $b_i$, the set transformer outputs a set of the form $\{w_{i1}, ..., w_{ij}\}$, we modify the output of the transformer to a fixed length vector

$$ w_i := \sum_j \lambda_j w_{ij} $$

where $\lambda_j$ are learnable weights. This step is necessary for us because our downstream tasks require vectors of fixed length.

3.2. Graph Attention Network

We also use the popular Graph Attention Network (GAT) [33]. The input to a GAT layer are the node features and it outputs a new set of node features (of possibly different dimension). The heart of this layer is multi-head self-attention like in [32, 33]. If $h_i$ is the feature vector of node $i$, then self-attention is computed on the nodes

$$ e^l_{ij} = \alpha^l(\bar{W}^l h_i, \bar{W}^l h_j) $$

where $\bar{W}^l$ is a linear transformation called the weight matrix for the head $l$, $\alpha^l$ is a feedforward network outputting a scalar indexed by the head $l$. We then normalize these attention coefficients.

$$ \alpha^l_{ij} = \text{softmax}_j(e^l_{ij}) = \frac{\exp(e^l_{ij})}{\sum_{k \in N_i} \exp(e^l_{ik})} $$

where $N_i$ is a 1-neighborhood of the node $i$. The normalized attention coefficients are then used to compute a linear combination of the features corresponding to them, to serve as the final output features for every node (after applying a nonlinearity, $\sigma$):

$$ h^l_i = \sigma\left( \sum_{j \in N_i} \alpha^l_{ij} \bar{W}^l h_j \right). $$
We concatenate the features of these heads to produce a new node feature, \( h_i^t := ||h_i^1 \). However, for the final prediction layer, we average the representations over the heads and apply a logistic sigmoid non-linearity. Thus the equation for the final layer is: \( h_i^t = \sigma \left( \frac{1}{K} \sum_{l=1}^{K} \sum_{j \in N_i} \alpha_{ij}^l \mathbf{w}^l h_j \right) \), where \( K \) is the number of heads. We create new edge features \( \Lambda_{ij} \) for the node \( e_{ij} \) by concatenating the \( \alpha_{ij}^l \) across all heads resulting in a \( K \)-dimensional edge feature, i.e.

\[
\Lambda_{ij} := \| \|_{l=1}^{K} \alpha_{ij}^l
\] (6)

3.3. Our model

In this section we will describe our model that combines edge features, obtained as described above, with node features for our main node classification tasks. We use two GAT layers to encode the node representations. In the case of the GAT layers, we concatenate the representations obtained by different heads resulting in a 64-dimensional node feature vector. For each node \( i \), we construct a set \( S_i := \{ e_{ij} : j \in N_i \} \), where \( e_{ij} \) is the vector representing the edge features of the edge connecting nodes \( i \) and \( j \). We then encode this set, \( S_i \), which we call the edge feature set attached to the node \( i \) via our modified Set Transformer. We use 2 heads and 1 block of Set Transformer outputting a 8-dimensional vector. This 8-dimensional vector is concatenated with the 64-dimensional node representation. We call this new representation an enhanced node feature vector. This enhanced node feature vector is then passed through a dense layer with a logistic sigmoid non-linearity for classification. Note that instead of GAT layers, we can also use GCN layers. Thus our method can be used by a variety of message passing architectures.

4. Experiments

| Datasets       | SARS-CoV-2 infected organoids | COVID-19 patients |
|----------------|-------------------------------|-------------------|
| # Nodes        | 54353/11646/11648            | 63486/13604/13605 |
| # Node features | 24714                         | 25626             |
| # Edges        | 1041226/230429/228630         | 2746280/703217/707529 |
| # Edge features| 18                            | 18                |
| # Classes      | 7                             | 3                 |

We validate our model on the following scRNA-seq datasets: (I) 4 human bronchial epithelial cell cultures or “organoids” that were inoculated with SARS-CoV-2 and co-cultured for 1, 2, and 3 days post-infection [30]; (II) Bronchoalveolar lavage fluid samples from 12 patients enrolled in a study at Shenzhen Third People’s Hospital in Guangdong Province, China of whom 3 were healthy controls, 3 had a mild or moderate form of COVID-19 and 6 had a severe or critical COVID-19 illness [24]. Table 1 gives a summary of our datasets.

Creating new edge features: We cluster our datasets using Louvain clustering [6], and annotate these clusters as “cell types,” as commonly done in single-cell analysis [21]. Then, we use a 2-layer GAT with 8 attention heads in each layer to predict the cell type label. We extract the edge attention coefficients from the first layer of our trained model as edge features. Thus we get an 8-dimensional edge feature vector by equation 6. All of our biological datasets have a batch ID associated to it, i.e. some metadata that keeps track of the origin of the cell. We use the same method as before to create another 8-dimensional edge feature vector. We also use the Forman-Ricci curvature [11] as a measure of local geometry of the graph. Finally we use node2vec [16] to embed the nodes in 16-dimensional space and then we calculate the dot product between the node embeddings, which share an edge, as a measure of similarity. We concatenate the above vectors to create a 18 dimensional edge feature vector.

| Models                  | SARS-CoV-2 infected organoids | COVID-19 patients | P (Welch’s t-test) |
|-------------------------|-------------------------------|-------------------|-------------------|
| GCN                     | 65.43 (65.21-65.65)           | 89.26 (89.06-89.47) | -                 |
| GCN + Edge Features (Ours) | 81.61 (79.34-83.87)           | 92.84 (91.95-93.74) | < 0.001           |
| GAT                     | 73.10 (70.93-75.27)           | 92.25 (91.27-93.24) | -                 |
| GAT + Edge Features (Ours) | 82.95 (81.75-84.15)           | 95.12 (94.02-96.22) | < 0.001           |

5. Discussion

We achieved significant improvements using self-supervised edge features when comparing our model to the two popular GNN architectures, GCN and GAT. This suggests that using edge features derived from self-supervised learning and local graph information, with no requirement for hand-crafted edge features, can improve graph neural network performance on challenging node classification tasks. Our models are simple, easy to train and can be used with various graph neural network architectures. Additionally, our edge feature creation framework is applicable to any graphical data.

Given the excellent performance of our GAT with added edge features at predicting the disease-state at single-cell level, we sought to use the insight learned from our model to better understand SARS-CoV-2 infection dynamics and COVID-19 disease severity on an individual gene and cell basis. We show the various aspects of model interpretability that we can glean from our model in Figure 1. First, we extract the learned, edge attentions from our Set Transformer and average the coefficients across heads and dimensions to construct a new adjacency matrix. Then, using a cosine distance metric, we learn a new embedding of the cells (1A). In addition, to evaluate the importance of different types of
edge features, we plot the average weights of the query layer in the set transformer (1B). Learning a manifold in this way shows better segregation of cell types than typically used for embedding high-dimensional single-cell data, possibly because our models give weight to cell type labels via their edge feature representation. In addition, we also extract the learned weights from our models’ first GAT layer in order to investigate our model’s feature saliency with respect to gene importance. In predicting COVID-19 severity from patient samples, our model gives high weight to genes involved in the innate immune system response to type I interferon (CCL2, CCL7, IFITM1), regulation of signaling (NUPR1, TAOK1, MTRNR2L12), a component of the major histocompatibility complex II (HLA-DQA2), which is important for developing immunity to infection, and a marker of eosinophil cells, which are involved in fighting parasites (RETN). In predicting SARS-CoV-2 infection, our model finds saliency in counts of viral transcript, which is encouraging, as well as genes that are involved in inflammatory response and cell death (NFKBIA) and signaling (IFI27, HCLS1, NDRG1, NR1D1, TF), which may provide clues as to the dynamic regulatory response of cells in the lung’s airways to SARS-CoV-2. The learned embedding for the SARS-CoV-2 infected organoids dataset highlights that our model segregates infected ciliated cells, which is the reported SARS-CoV-2 cell tropism, validating our models’ interpretability [30]. In predicting COVID-19 severity, it is interesting that our model learns to mix macrophages and monocytes in a predominantly severe patient cell cluster while cells derived from mild and severe COVID-19 patients are mixed in a T cell cluster. Monocytes derived from macrophages are thought to be enriched in severe COVID-19 cases and T cells are proposed targets for immune checkpoint therapy of COVID-19, despite lack of understanding as to the transcriptional differences between mild and severe COVID-19 illness [5, 24, 19]. Lastly, it is interesting that our models find that genes involved in type I interferon signaling are important in predicting both COVID-19 severity and susceptibility to SARS-CoV-2 infection. Interferon signaling is involved in pro-inflammatory immune responses and it is suspected that type I interferon signaling may cause immunopathology during SARS-CoV-
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2 infection, leading to critical illness [30, 19]. Further study into the interaction partners and the subtle transcriptional differences between the cells and cell types that we identified may provide complementary hypotheses or avenues for therapeutic intervention to mitigate the impacts of COVID-19. However, we are not medical professionals so we do NOT claim that interpretation of our model will bear any fruit. Rather, we hope that the approach of seeking state-of-the-art results on predicting disease states at single-cell resolution will enhance study of biology and medicine and potentially accelerate our understanding of critical diseases during crises like the COVID-19 pandemic.

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