

DIPLOMA THESIS

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# TOWARDS GENE EXPRESSION PREDICTION IN MOUSE BRAINS

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proper title?

**Abstract**

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## To include in some chapter

Predict gene expression per section/structure:

Take region as input and predict gene expression

Challenges:

- how to normalize expression intensity (see discussion in DeepMOCCA paper, Sara Alghamdi), as there are regions with much more activity than others (e.g. bone narrow vs. bone boarder); thresholds for intensity varies across genes
  - over all intensities →
  - per structure →
  - per gene →

Our model also allows us to test different ways of representing omics data. We tested different ways to normalize values assigned to genes as these normalizations convey different biological information; in the matrix of values assigned to genes from cancer samples, we can normalize values across the entire matrix, across each row (cancer sample), or across each column (gene). While a global normalization is more common, row-based normalization allows us to highlight values that are significantly higher or lower within one sample (e.g., which genes are expressed at high or low levels within a single sample), and column-based normalization allows us to highlight values assigned to a particular gene that are significantly higher or lower within one sample (e.g., whether a gene is expressed at higher or lower levels within one sample compared to all others). We find that column-based normalization performs better than row-based normalization, while the global normalization approach performs close to random. The best results are achieved when combining both row- and column-based normalization (Supplementary Table 2).

- transfer learning working for other structure/regions
- dataset: Allen Mouse brain atlas vs.
  - phenoview impc data
  - mousephenotype
  - HPO/MP project expression data
- structure specific features?
  - structural ontology / closeness
  - developmental hierarchy of tissue
- how descriptive are the following for gene expression? How to encode structural properties
  - molecular protein function (DeepGPlus)
  - phenotypical features
  - fix-point stuff
- predict knock-out of genes, does this relate over
  - functional graph [Valk et al., 2020]
  - structural ontology?
  - developmental ontology
- graph autoencoders for

**Possible hypotheses**

- predict gene expression for a given single structure
- predict structure from gene expression pattern
- predict structure from gene expression and image
- predict cancer type from morphology/pathologic image of cancer
- simulate loss of function/expression by removing one node of graph

**Ideas for page-filling plots**

- show distribution (histo, mean, median, boxplot?) of expression densities see ‘get\_ge\_structure\_mat’
- show predictability of gene expression across over multiple structure vs. distance over onto?

## 1 Introduction

- Works on mouse brain in general and potential tasks
- works on gene expression in mouse brains
- conservative approaches
- neural networks for this purpose
- gene expression for general tissue
- 

## 2 Literature review

### 2.1 To be searched

- read across citations of DeepMOCCA/Takata et al. [2021]
- find other papers on
  - gene expression patterns within mouse brain and both possible hypothesis and tasks, and models over this
  - gene knockout models and whether they can learn propagation of those?
  - connection of FC and gene expression patterns and how to prove such interaction/correlation?
  - possible gene knockout targets within mouse brain and possible structural influences

### 2.2 To be sorted somewhere

- Variability and different interpretations of different graph convolutional neural filters [Kipf and Welling, 2016, Li et al., 2020, Hamilton et al., 2017] etc.
- Guilt by association over gene networks [Oliver, 2000, Gillis and Pavlidis, 2012]
- protein function prediction from PPI networks [Vazquez et al., 2003]
- DeepGOPlus for feature generation [Kulmanov and Hoehndorf, 2019]
- discussion of DeepMocca by Sara [Althubaiti et al., 2021]
- discussion of different PPI network databases [Szklarczyk et al., 2014]
- discussion of potential databases associating gene expression data with their spatial distribution [Hawrylycz et al., 2011]
- discussion of best neural learning/graph convolutional methods [Paszke et al., 2019, Fey and Lenssen, 2019]
- how to handle highly imbalanced data, metrics, preprocessing, sampling, modification of loss function [Jeni et al., 2013] and optimization over them (with Adam [Kingma and Ba, 2015])
- maybe introduction of PhenomeNET for MP/GO for more sophisticated protein representation [Hoehndorf et al., 2011, Ashburner et al., 2000, Carbon et al., 2020, Smith and Eppig, 2009] and derive features from DL2vec [Chen et al., 2020, Mikolov et al., 2013]

- evaluation of „Using ontology embeddings for structural inductive bias in gene expression data analysis“ [Trebacz et al., 2020]
- take some ideas from Zitnik and Leskovec [2017] with title „Predicting multicellular function through multi-layer tissue networks“. (OhmNet)
- potentially group results based on InterPro [Blum et al., 2020] families eventually
- RayTune [Liaw et al., 2018] for automated hyperparameter tuning

## 2.3 Spatial patterns of gene expression

Data discussion, hypotheses and traditional approaches:

- [noa]
- Possible effects of rabies virus on gene expression [Prosniak et al., 2001] for potential knockout targets
- Review paper on regional variation in gene expression in mouse brain [Pavlidis and Noble, 2001]

Modern approaches on learning from gene expression patterns in mouse brain:

- Deep learning methods for capturing spatiality w.r.t. gene expression withing the brain [Zeng et al., 2015]
- R package for simulating gene expression from graph structures over general biological pathways [Kelly and Black, 2020]

[Read this](#)

## 2.4 Gene knockout and pathology hypotheses

- Gene expression for different kinds of stress within mouse brain [Flati et al., 2020]

# 3 Methods

## 3.1 Problem description

## 3.2 Datasets

- Allen mouse brain atlas [Lein et al., 2006]
- STRING for PPI network and how we chose suitable interactions [Szklarczyk et al., 2014]

## 3.3 Model

### 3.3.1 Feature generation

### 3.3.2 Graph convolutional neural layers

We include these molecular and ontology-based sub-models within a graph neural network (GNN) [Kipf and Welling, 2016]. The graph underlying the GNN is based on the protein–protein interaction (PPI) graph. The PPI dataset is represented by a graph  $G = (V, E)$ , where each protein is represented by a vertex  $v \in V$ , and each edge  $e \in E \subseteq V \times V$  represents an interaction between two proteins. Additionally, we introduce a mapping  $x : V \rightarrow \mathbb{R}^d$  projecting each vertex  $v$  to its node feature  $x_v := x(v)$ , where  $d$  denotes the dimensionality of the node features.

A graph convolutional layer [Kipf and Welling, 2016] consists of a learnable weight matrix followed by an aggregation step, formalized by

$$\mathbf{X}' = \hat{\mathbf{D}}^{-1/2} \hat{\mathbf{A}} \hat{\mathbf{D}}^{-1/2} \mathbf{X} \Theta \quad (1)$$

where for a given graph  $G = (V, E)$ ,  $\hat{\mathbf{A}} = \mathbf{A} + \mathbf{I}$  denotes the adjacency matrix with added self-loops for each vertex,  $\hat{\mathbf{D}}$  is described by  $\hat{D}_{ii} = \sum_{j=0} \hat{A}_{ij}$ , a diagonal matrix displaying the degree of each node, and  $\Theta$  denotes the learnable weight matrix. Added self-loops enforce that each node representation is directly dependent on its own preceding one. The number of graph convolutional layers stacked equals the radius of relevant nodes for each vertex within the graph.

The update rule for each node is given by a message passing scheme formalized by

$$\mathbf{x}'_i = \Theta \sum_j^N \frac{1}{\sqrt{\hat{d}_j \hat{d}_i}} \mathbf{x}_j \quad (2)$$

where both  $\hat{d}_i, \hat{d}_j$  are dependent on the edge weights  $e_{ij}$  of the graph. With simple, single-valued edge weights such as  $e_{ij} = 1 \forall (i, j) \in E$ , all  $\hat{d}_i$  reduce to  $d_i$ , i.e., the degree of each vertex  $i$ . We denote this type of graph convolutional neural layers with GCNCONV.

While in this initial formulation of a GCNConv the node-wise update step is defined by the sum over all neighboring node representations, we can alter this formulation to other message passing schemes. We can rearrange the order of activation function  $\sigma$ , aggregation AGG, and linear neural layer MLP with this formulation as proposed by [Li et al., 2020]:

$$\mathbf{x}'_i = \text{MLP}(\mathbf{x}_i + \text{AGG}(\{\sigma(\mathbf{x}_j + \mathbf{e}_{ji}) + \epsilon : j \in \mathcal{N}(i)\})) \quad (3)$$

where we only consider  $\sigma \in \{\text{ReLU}, \text{LeakyReLU}\}$ . We denote this generalized layer type as GENCONV following the notation of PyTorch Geometric [Fey and Lenssen, 2019]. While the reordering is mainly important for numerical stability, this alteration also addresses the vanishing gradient problem for deeper convolutional networks [Li et al., 2020]. Additionally, we can also generalize the aggregation function to allow different weighting functions such as learnable SoftMax or Power for the incoming signals for each vertex, substituting the averaging step in GCNCONV. Hence, while GCNCONV suffers from both vanishing gradients and signal fading for large scale and highly connected graphs, each propagation step in GENCONV emphasizes signals with values close to 0 and 1. The same convolutional filter and weight matrix are applied to and learned for all nodes simultaneously. We further employ another mechanism to avoid redundancy and fading signals in stacked graph convolutional networks, using residual connections and a normalization scheme [Li et al., 2019] [Li et al., 2020] as shown in Supplementary 3. The residual blocks are reusable and can be stacked multiple times.

### 3.3.3 Combined prediction model

### 3.3.4 Hyperparameter tuning

## 3.4 Evaluation and metrics

# 4 Results

# 5 Discussion

# 6 Conclusion



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