Master Thesis summary

732A64-Master Thesis

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Contents

During this paper we will present the results obtained so far alongside with critic and future steps.

Lets consider again the questions of interest during this project

Role of derivatives

What is the relation of the derivatives in the classification? We are interested to know if a certain derivative or derivative combination gives better classification

Data augmentation

What kind of 3D augmentation (e.g. rotations, scaling of each volume) are most important in the 3D CNN training?

Architecture

What is the best architecture of the 3D CNN? We wish to know how many layers to use and number of filters in each layer in the model architecture.

1 Training and Evaluation

To begin with, at first we decide to create some combinations of derivatives and test which combination or single derivative can result a better classification. The choice of the combinations of interest include i) one combination with only the dual regression derivative (10-channels) ii) one combination with all the derivatives except dual regression (9-channels) and iii) one combination with all the derivatives (19-channels). In order to increase the size of the datasets a series of augmentations is performed with the following methods considered

Augmentations

1. rotation
2. flip
3. center crop
4. blur
5. elastic deformation

Following up, the discovery of the best CNN architecture is performed within the concept of grid search with predefined discrete values for the parameters of interest. During this project the following hyper-parameters are considered

Hyper-parameters

- number of convolutional layers $\in [3, 4, 5]$
- number of filters int the convolutional layers $\in [32, 64, 128]$
- dropoout rate $\in [0.4, 0.5, 0.6]$

- dense nodes $\in [128, 256, 512, 1024]$

The process of evaluating each combination is performed with MC dropout were the model is exposed to a hold-out dataset for 100 times and the average accuracy/loss is reported as test accuracy/loss

2 Results so far

This section is dedicated to the presentation of the results obtained so far with some illustrations. The proper visualization in order to present the combinations tested for each architecture is suggested to be a parallel coordinate plot. For the results presented in the following sections the hyper-parameters1 previously presented were used with the exception in the number of convolutional layers where only 4 layers tested.

2.1 Dual Regression Derivative

One of the first combination of derivatives that tested was dual regression derivative. The figure 1 shows the obtained pair accuracy/loss for each combination

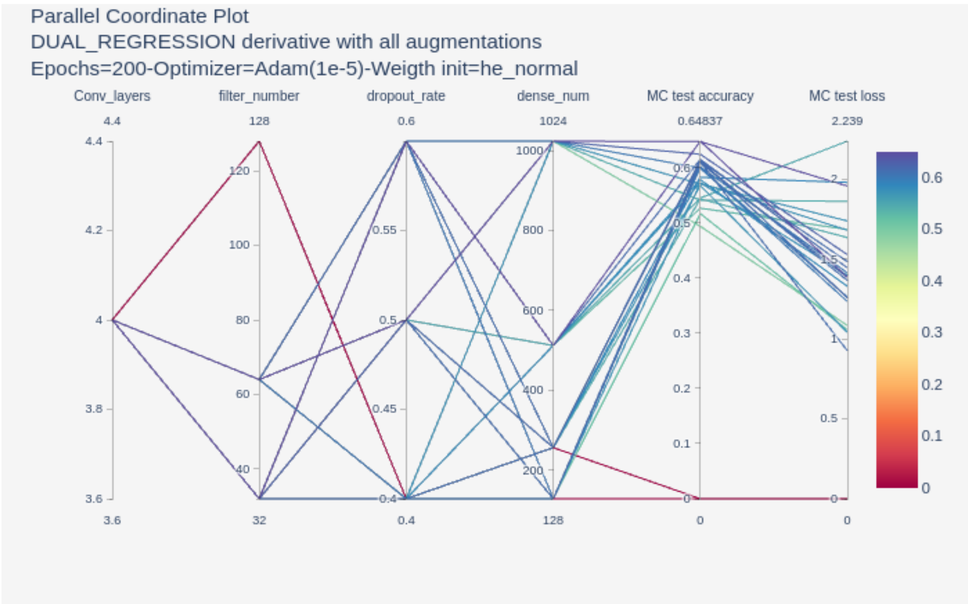

Figure 1: Parallel coordinates plot dual regression

As we can see from the above plot the best accuracy was roughly 0.65% and achieved with the following settings

ConvLayers	nFilts	dropoutRate	denseNodes	loss	accuracy
4	32	0.6	512	0.13875	0.6483

The next plot provides an illustration of the MC dropout evaluation

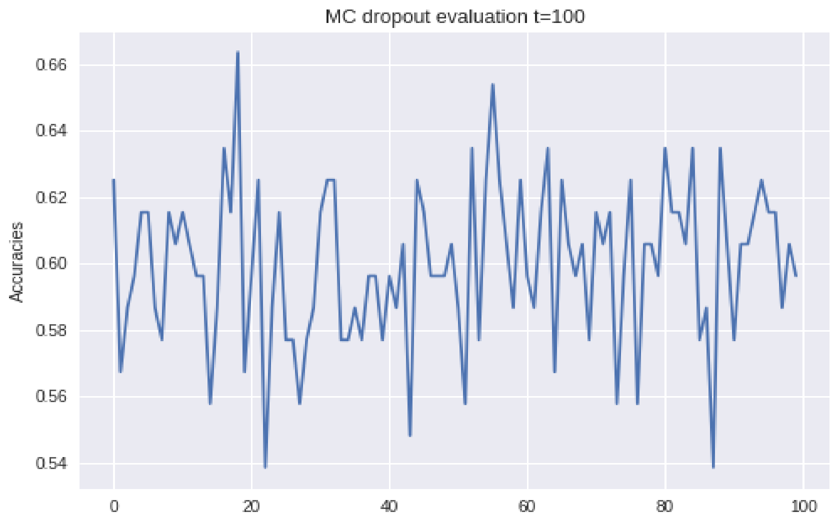

Figure 2: MC evaluation for dual regression

2.2 All 9 Derivatives except Dual Regression

The next combination tested was all 9 derivatives combined without dual regression. The figure 3 shows the obtained pair accuracy/loss for each combination

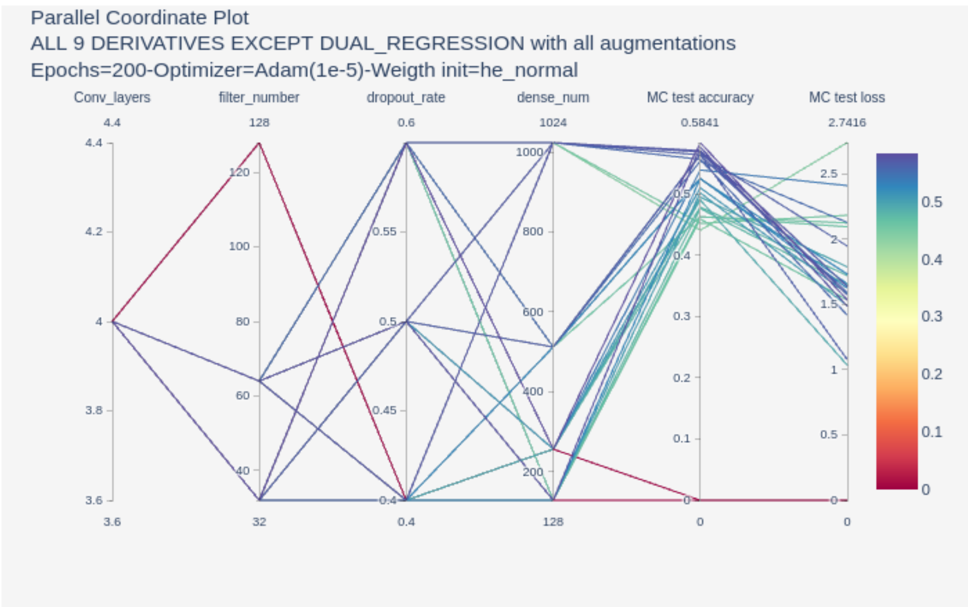

Figure 3: Parallel coordinates plot 9 derivatives

As we can see from the above plot the best accuracy was roughly 0.58% and achieved with the following settings

ConvLayers	nFilts	dropoutRate	denseNodes	loss	accuracy
4	32	0.6	256	0.15357	0.5841

The next plot provides an illustration of the MC dropout evaluation

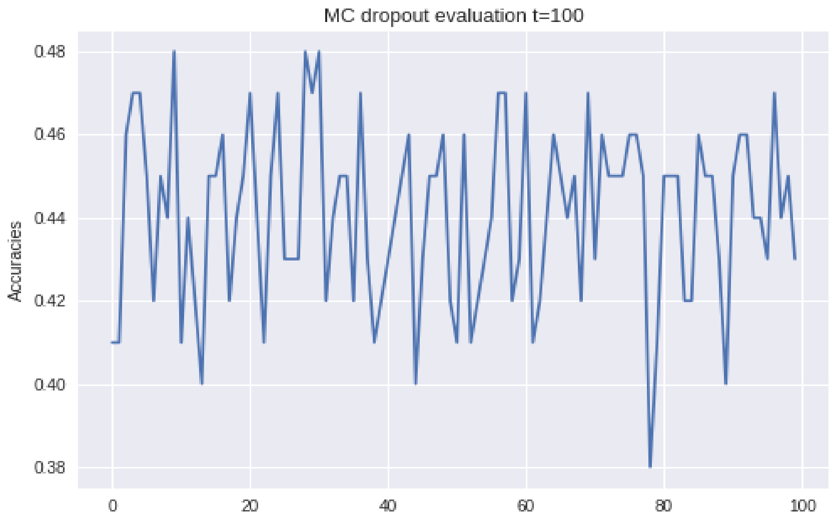

Figure 4: MC dropout 9 derivatives

3 Critic and Future plan

In this section we provide a critic on the methods applied and an overview of the future work to be implemented. The results presented in the previous section have been applied with the settings mentioned in the introduction besides the ConvLayers hyper-parameter where only 4 layers where tested. This was a decision made in order to test the implementation and the computational time. The results seem to be consistent and the future work involves the following steps

Next steps

- test the combinations of interest with all and some augmentations
- perform the training using the entire search space
- investigate the performance of another activation function (PRELU)

1 Introduction

1.1 Motivation

Neuroimaging has offered a non-invasive method to map the structure of the human brain and the etiology of complex diseases related to it. The traditional clinical methods of diagnosing brain disorders (e.g. Alzheimer, Mild Cognitive Impairment (MCI), Attention Deficit Hyper Activity Disorder (ADHD), Autism Spectrum Disorder (ASD)), as described in (DSM-5) are relying heavily on behavioural investigation and interview evaluations of symptoms. However, due to the high complexity of the symptoms and potential overlapping with other psychiatric disorders (e.g. Depression, Anxiety) these methods require lots of expertise, are prone to misdiagnosis and not quantifiable. Thus, phychiatric research has been swifted in brain image analysis and focuses on identification of quantitative biomakers that can assist diagnosis and treatment of brain diseases. Many different techniques are used in medical imaging and can be summarized in two categories, structural and functional, figure 1.1 illustrates images from the two categories.

Among these methods, functional techniques such as resting state fMRI (rs-fMRI) in brain disease diagnosing have proven more effective compared to structural because they can better reflect the brain abnormalities. The fMRI images are able to measure brain functionality though changes in blood flow between different brain regions. These scans are taken every 1 or 2 seconds resulting 4D data tensor, 3D-(brain volume)$\times$*time*. Somewhere in those high dimensional spatio-temporal signals are hidden the biomakers that can be used to diagnose between healthy and ill subjects. Analyzing fMRI scans and finding patterns can be challenging for the human eye because of the complexity of the different patterns. Another challenge rises from the heterogeneity of clinical samples and the replication of findings across larger populations. Recent advancements in machine learning (ML) and especially deep learning (DL) methods in computer vision alongside the rising computational power coming from hardware improvements(e.g. graphical processing units (GPUs)) have been introduced in medical imaging as an effort to automate and improve the accuracy of diagnosing process.

The successful application of DL methods in medical imaging is limited not only by the lack of medical data due to to ethics and data protection regulations (e.g. GDPR) but also because they are expensive and hard to annotate. Autism Brain Imaging Data Exchange (ABIDE) *(Di Martino et al., 2014[3])* is a project that has aggregated images from 17 medical centers around the world of individuals with Autistic Spectrum Disorder (ASD) and healthy

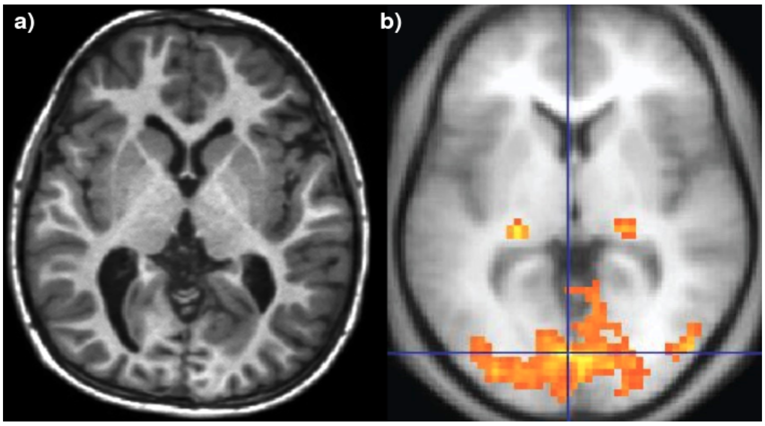

Figure 1.1: Structural techniques (e.g. Magnetic Resonance Imaging(MRI), Doppler, Computed Tomography (CT)) are used for anatomic region identification, while functional (e.g. functional MRI (fMRI), Magnetoencephalography (MEG)) demonstrate the organic process of a specific region of interest. Figure shows a T1-weighted MRI [1]image on the left (a)) and an fMRI[2]image on the right (b))

controls (CON) in an effort to engage research and increase awareness in special diseases such as ASD. Autistic Spectrum Disorders are neurodevelopment disabilities associated with difficulties and deficits in the development of social communication and interaction skills and restricted, repetitive patterns in behavior, interest and activities *(Grzadzinsk et al., 2013[9])*. The variation in symptoms is causing individuals experience ASD in a non uniform way requiring different assessment and support in their daily routines. Some individuals are able to navigate world, living independent and satisfying lives, while others have intellectual disability that significantly affect the quality of their lives requiring constant supervision. Although the behavioural composition of ASD has been thoroughly portrayed the exact aitiology and pathogenesis remains still unknown. As indicated by research, genetic and environmental elements appears to have a noteworthy impact.

These disabilities can occur in all races, nations and socioeconomic groups but males are 4-times more likely to females *(Baio et al., [1])*. It is estimated based on a systematic research on epidemiological surveys *(Elsabbagh et al., 2012 [4])*, supported by World Health Organization[3], that at a worldwide average, one in 160 children has an ASD with the estimate not containing many low- and middle-income countries because of the lack of systematic report on the cases. The estimate in adults of all ages has been around 1% in the high-income countries *(Lai et al., 2015 [15])* placing these disorders as one of the most common developmental disorders and according to epidemiological studies been increasing globally. Initial symptoms appear during early childhood and tend to be long-life present thus timely diagnosis is crucial for the relief of the symptoms.

In this project we wish to combine the successful application of DL in medical imaging with recent studies that have shown that ASD affects brain connectivity, studies report hyperconnectivity between amygdala regions in adolescents and adults with autism compared with healthy control *(Rausch et al., 2016[20])* while others report decreased functional connectivity *(Xiaonan et al., 2016[10])*. Mining the ABIDE fMRI images for patterns that can distinguish between ASD and CON subjects and generalize results across different populations is the motivation of this project.

[1]https://en.wikipedia.org/wiki/Magnetic_resonance_imaging
[2]https://en.wikipedia.org/wiki/Functional_magnetic_resonance_imaging
[3]https://www.who.int/news-room/fact-sheets/detail/autism-spectrum-disorders

1.2 Aim

In the present study the main aim is to use DL algorithms and develop a system than can distinguish between ASD and CON subjects. The backbone of DL methods are Artificial Neural Networks (ANN), a learning algorithm that its structure is inspired by human brain. They consists of a connected computational nodes, known as neurons arranged in layers. The first layer is the input layer where the data enter the network an is followed by one or more hidden layers that are transforming the data as they flow though reaching the final output layer which outputs the predictions. A set of training data and labels are fed to the network which is trained with the data to identify patterns and produce useful predictions while an objective function is used to evaluate the outputs with the true labels. Model parameters are updated during training in accordance to the objective function in order to result good predictions. While ANN are able to solve complicated problems they require a lot of data to train properly making them very computationally expensive. In recent years, a new structure of ANN has attracted a lot of attention and further improved the learning abilities of ANNs.

Convolutional Neural Networks (CNNs) have specifically high performances in the field of pattern recognition and especially in Computer Vision tasks. Their design is an extension of the ANN where the fully connected layers are been replaced with convolutional layers. CNN are able to preserve spatial relationships in the data with fewer node connections between layers. The input data to CNN are arranged in grid structure and each layer operates in a small region of the previous layer.

This unique capability of the CNNs to accept high dimensional data we wish to leverage in this project to train a model using the ABIDE-I dataset and learn useful patterns in the rs-fMRI images. The rs-fMRI images from ABIDE have already been processed with different pipelines in order to remove unwanted noise. Moreover, different methods have been applied to the processed images removing the time component from the images and reducing the dimensions resulting 3D images. These methods have extracted different aspects of the spatio-signals and are commonly known as statistical derivatives. Those calculated derivatives will be the inputs to our CNNs and since they are 3D images the proper structure to use are 3D-CNN. Moreover, inspired by ensemble learning methods which use the concept of learning from the wisdom of the crowd and weak learners wish to combine the calculated derivatives resulting multi-channel inputs to the 3D-CNN. Increasing the number of filters will require a deeper network in order to learn patterns from different images. A potential problem we need to address especially when using medical images which have limited samples and training deep networks with many parameters is over-fitting. In order to avoid over-fitting we will use data augmentation techniques such as rotation, scaling e.t.c to artificially increase the sample size.

1.3 Research questions

During this project we are interested in answering the following questions :

- What is the relation of the resting state derivatives in the classification?
  Is there a specific combination of derivatives that gives better classification?
- What kind of 3D augmentation (e.g. rotations, scalings of each volume) are most important for training the 3D CNN ?
- What is the best architecture of the 3D CNN?
  More specifically we wish to know how many layers and filters to use. Also, what is the best regularization method for the network?

1.4 Related Work

Since the publication of the ABIDE dataset on 2013 lots of research has been made in the discovery of a method for classifying ASD and control subjects. One of the first studies was performed by *(Nielsen et al., 2013[19])*, using a glm model for classification. According to their method first they processed the images with numerous preprocessing steps with some of them include slice time correction, realigning and resclising each volume, gray matter segmentation, voxelwise regression and mean time extraction of time courses from ROI masks. Using the preprocessed BOLD images and 7266 gray matter ROIs they construct a 726×726 matrix of Fisher-transformed Pearson correlation coefficient for each subject. Each ROI is a representation of an association matrix of functional connectivity in each subject between all ROI pairs. The different pairs of ROIs are refereed to as *connections* from the authors. These connections were grouped into multiple bins and used as inputs to a leave-one-out classifier alongside covariates such as age, age-squared and handedness. Then a general linear model was fitted separately for autism and control subjects. With their implementation they produced an overall accuracy of 60% with specificity 58%.

In similar fashion *(Sherkatghanad et al., 2020[23])* they used a functional parcellation atlas of brain for constructing functional connectivity matrices of each subject. Each cell in the matrix is a Pearson correlation coefficient between the mean values of time series obtained eith ROI and each row is the ROI representation. The matrices produced have 392×392 size representing the co-activation correlations of 392 brain areas of interest. These matrices were used as inputs into a CNN structure. Their model is consider a single convolutional layer with maxpooling followed by densely connected layers (Dropout, FC, softmax) achieving an accuracy of 70.22%. During their research they considered also ML algorithms and explored SVM, KNN and RF with 69, 62, 60% respectively.

Most recently a research that inspired the present study was performed by *(Thomas et al., 2020[25])*. This research is performed on both ABIDE I and II datasets and tested 3D CNNs. In their method they considered one dataset with all the 9 derivatives and one combination with only ReHo derivative obtaining roughly 66% accuracy on both datasets. Additionally, they also used ML algorithms by applying SVM in order to compare the performance of the CNNs. For their study the datasets were used have been preprocessed with CPAC pipeline and 4 additionally custom preprocessing steps. The additional steps used are motion correction, nuisance regression, coregistration of the resulting rs-fMRI images using medical imaging software and finally normalization of the images onto standard Montreal Neurological Institute (MNI) space (4mm). For their model they considered an architecture that consists of an average pooling layer of size 2 and stride 2 at the beginning of the network followed by 2 convolutional layers with exponential linear unit (ELU) as activation function. The number of filters in the first layer were set to 64 and 16 for the second while the kernel size was set to 3. Following up, a flatten layer that feeds to a fully connected layers with 16 nodes and ELU activation feeding the results on the dense layer with one node for the final label output. As it will be presented in the upcoming chapters the idea of combining together the different derivatives can be used to create more datasets constructing multi-channel images as inputs to the CNN architecture.

1.5 Thesis Outline

The rest of the thesis is organized as follows:

- Data chapter introduces the more detailed overview of the data used in this project
- Theory chapter presents the theoretical background related to the methods that are formulated and developed in this thesis.

- Method chapter explains the methods in detail along with details about their implementation
- Results chapter reports all the evaluations in terms of the performance metrics, visualizations, examples of image retrieval and an analysis of the obtained results.
- Discussion chapter discusses the methods developed in this thesis in a wider context and attempts to reason about the results obtained.
- Conclusion provides the conclusions drawn regarding the research questions that this thesis aimed to answer.

1.6 Delimitations

The dataset that will be used in this project is freely available in accordance to HIPAA guidelines and 1000 Functional Connectomes Project / INDI protocols. All the collected images are anonymous and no protected information has been exposed. Usage of the data is restricted to reasearch non-commercial purposes only. Thus no special consideration is ewquired according to delimitations and ethical considerations. With respect to the funder donors as well as to the ABIDE consortium founders we acknowledge Simons Foundation and the National Institute of Mental Health, Adriana Di Martino and Stefan Mostofsky respectively.