IMPROVING DEEP LEARNING APPROACH FOR FMRI DATA

BY

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ABSTRACT

Functional magnetic resonance imaging (fMRI) has become one means to understand the epicentre of the human nervous system, the brain. It represents intrinsic haemodynamic signals in high-dimensional data that linked to neuronal activities. Numerous studies such as statistical parametric analysis, multivariate pattern analysis and few machine learning techniques have demonstrated significant results that suggested the links between human activities and the haemodynamic signals and which sections of the brain that got activated. In this research, deep learning, a recently discovered method that broke many benchmark records in areas such as object and speech recognition, is used. One of the significant advantages of deep learning is that it avoids the problem of labour-intensive work, such as feature extractions. With that, various deep learning algorithms were studied and experimented. Contribution to the knowledge sphere in this thesis revolves around the data division for deep learning approach to classify high-dimensional fMRI when a rather low volume of data was adopted in the classification approach. High dimensionality and low signal-to-noise-ratio (SNR) are the biggest challenges in fMRI classification. Using a single centre slice of data reduces the anatomical variability dependence and curse of dimensionality degree. First, a minimal preprocessing stage is proposed for the two types dataset compilations; randomised and separated validation data of 1029 control fMRI individual subjects data. Convolutional neural network (CNN), studied and chosen deep learning method, has been assessed under three aspects: convolutional layers size; feature map sizes selection, and inception model blocks insertion. These aspects are few of many uncertainties in CNN modelling. The minimal preprocessing stage was proposed as opposed to lengthy conventional methods. Division of data shows the capabilities of deep learning to overfit the classification algorithm, though many adjustments were included. Besides, the model training step in processing stage formulates the problem as a single optimisation problem in which all the components of the model share a similar goal. It is an end-to-end deep learning algorithm reliability testing. This research requires very demanding computational capabilities with any increase in data volume. As a result, high accuracy was acquired with tested CNN models but inversely proportional for validation data accuracy when separated validation set was used. Although this research is designed for one slice of 3D fMRI data, an impressive set of computation resource such as a high-performance computer with stacked of dedicated graphic cards may have the ability to analyse a much higher volume of the whole-brain fMRI data. As a conclusion, this research shows that deep learning is reliable for classification but has the tendency to overfit and overgeneralisation. This was suggested when higher validation loss acquired with low volume of high-dimensional fMRI data employment. The data division strategy proposed in this research for end-to-end deep learning solution should be one of the keypoints for the data processing model.

خلاصة البحث

أصبح التصوير بالرنين المغناطيسي الوظيفي (fMRI) أحد وسائل فهم مركزالجهاز العصبي البشري ، الدماغ. وهو يمثل إشارات الدورة الدموية الفعلية على شكل بيانات كثيرة الأبعاد مرتبطة بالأنشطة العصبية. أظهرت العديد من الدراسات مثل التحليل البارامتري الإحصائي وتحليل الأنماط متعدد المتغيرات و بعض تقنيات التعلم الآلي ، نتائج في غاية الأهمية تشير إلى الروابط بين الأنشطة البشرية وإشارات الدورة الدموية وأجزاء الدماغ التي تم تنشيطها. تم في هذا البحث استخدام التعلم العميق وهو منهج تم اكتشافه مؤخراً وقد تفوق على العديد من السجلات القياسية في مجالات التعرف على الأشياء والكلام. أحد المزايا المهمة في التعلم العميق هي تجنب مشكلة العمل كثيف الجهد كاستخراج الميزات. وبذلك ، تمت دراسة وتجريب خوارزميات مختلفة للتعلم العميق. في هذه الأطروحة ، تدور المساهمة في مجال المعرفة حول تقسيم البيانات في نهج التعلم العميق لتصنيف التصوير بالرنين المغناطيسي الوظيفي كثير الأبعاد باستخدام حجم بيانات منخفض نوعًا ما في التصنيف. إن التحديات الأكبر في تصنيف التصوير بالرنين المغناطيسي الوظيفي هي الأبعاد الكثيرة والنسبة المنخفضة للإشارة بالنسبة للضجيج (SNR) . يؤدي استخدام شريحة مركزية واحدة من البيانات إلى تقليل الاعتماد على التباين التشريحي ولعنة درجة الأبعاد. تم في البداية اقتراح الحد الأدنى من مرحلة المعالجة المسبقة لنوعين من مجموعات البيانات : البيانات العشوائية و بيانات منفصلة للتحقق لـ 1029 موضوع فردي متحكم بها للتصوير بالرنين المغناطيسي الوظيفي. تم تقييم الشبكة العصبونية التلافيفية (CNN) ، التي تم دراستها واختيارها كطريقة للتعلم العميق من خلال ثلاثة جوانب: حجم الطبقات التلافيفية ، اختيار أحجام خريطة الميزات ، وإدخال كتل من نموذج البداية inception. إن هذه الجوانب هي بعض من العديد من أوجه عدم اليقين في نمذجة الشبكة العصبونية التلافيفية. تم اقتراح الحد الأدنى من مرحلة المعالجة المسبقة كبديل للطرق التقليدية الطويلة. يُظهر تقسيم البيانات قدرات التعلم العميق في الإفراط بملائمة خوارزمية التصنيف على الرغم من تضمين العديد من التعديلات. إلى جانب ذلك ، فإن خطوة تدريب النموذج في مرحلة المعالجة تعمل على صياغة المشكلة كمشكلة وحيدة للأمثلة بحيث تتشارك جميع مكونات النموذج بهدف مماثل. إنه اختبار موثوقية لخوارزمية التعلم العميق من نهاية إلى نهاية. يتطلب هذا البحث قدرات حسابية متطلبة للغاية مع أي زيادة في حجم البيانات. نتيجة لذلك ، تم الحصول على دقة عالية مع نماذج الشبكة العصبونية التلافيفية المختبرة ولكنها تتناسب عكسياً مع دقة بيانات التحقق عند استخدام مجموعة منفصلة من بيانات التحقق. على الرغم من أن هذا البحث مصمم لشريحة واحدة من البيانات ثلاثية الأبعاد للتصوير بالرنين المغناطيسي الوظيفي ، إلا أن تواجد مجموعة كبيرة من الموارد الحسابية مثل جهاز كمبيوتر عالي الأداء مزود ببطاقات رسومية مخصصة قد يكون لديها القدرة على تحليل حجم أكبر بكثير من بيانات التصوير بالرنين المغناطيسي الوظيفي لكامل للدماغ. في الختام ، يوضح هذا البحث أن التعلم العميق جدير بالثقة في التصنيف ولكنه يميل إلى الإفراط في الملائمة و الإفراط في التعميم. تم اقتراح هذا عندما تم الحصول على خسارة تحقق أكبر بعد توظيف حجم قليل من البيانات كثيرة الأبعاد للتصوير بالرنين المغناطيسي الوظيفي. لذا ينبغي على استراتيجية تقسيم البيانات المقترحة في هذا البحث لحلول التعلم العميق من نهاية إلى نهاية أن تكون أحد النقاط الرئيسية لنموذج معالجة البيانات .

APPROVAL PAGE

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DECLARATION

I hereby declare that this thesis is the result of my own investigations, except where otherwise stated. I also declare that it has not been previously or concurrently submitted as a whole for any other degrees at IIUM or other institutions.

Nur Farahana Mohd Suhaimi

Signature:........................... Date:...........................

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LIST OF ABBREVIATIONS

AD	Alzheimer's Disease
$ADHD$	Attention Deficit Hyperactivity Disorder
AI	Artificial Intelligence
ANN	Artificial Neural Network
BCI	Brain Computer Interface
$BOLD$	Blood-oxygen-level-dependent
CNN	Convolutional Neural Network
CNS	Central Nervous System
DBN	Deep Belief Network
EEG	Electroencephalography
FFT	Fast Fourier Transform
$fMRI$	Functional Magnetic Resonance Imaging
GLM	General Linear Model
GPU	Graphical Processing Unit
HRF	Haemodynamic Response Function
ICA	Independent Component Analysis
MEG	Magnetoencephalography
MRI	Magnetic Resonance Imaging
$MVPA$	Multivoxel Pattern Analysis
NMT	Neural Machine Translation
RNN	Recurrent Neural Network
ROI	Region of Interest
SPM	Statistical Parametric Map
SVM	Support Vector Machine
$t-SNE$	T-Distributed Stochastic Neighbour
$voxel$	Volumetric Pixel

LIST OF SYMBOLS

$H(p)$	entropy
W	updated weights
f_c	fully-connected layer
η	learning rate

CHAPTER 1

INTRODUCTION

1.1 OVERVIEW

This thesis is the documentation for a Doctoral research program that was undertaken at the International Islamic University Malaysia in Kuala Lumpur, Malaysia, between the years of 2015 and 2019. This Doctoral research program was a part of a larger program of research, undertaken in collaboration with researchers of the University of Malaya for the first two years. The next two years then were spent for analysis, publications and thesis writing. This Doctoral research investigates the relationship between high-dimensional and high-temporal data for classification approach.

The specific goal of this research is to demonstrate the ability of a deep learning approach to classify high-dimensional functional magnetic resonance imaging (fMRI) data. FMRI is one of the neuroimaging modalities in neuroscience field.

1.2 BACKGROUND

Neuroimaging is a branch of neuroscience, a study to understand human's brain. The brain is a human central nervous system (CNS). It is the most complex and elegant computing device that exists and weights less than most desktop computer (Waxman, 2009). Studying how the brain can make complex decisions even under various loads, think and produce something creative, and feel, are the neuroscience subjects of interest. Neuroimaging is the method that encompasses various technology to gain and visualise the brain for prognosis, diagnosis, and clinical procedures. Recent advances in neuroimaging have made it workable to examine the whole brain network for multiple individual subjects. Anderson et al. (2016) suggested a single-node implementations of the data, Thirion (2016) reviewed the general framework for multiple subjects inference and Vieira et al. (2017) hypothesised that the new algorithm that are going to be discussed extensively in this thesis, the deep learning, is a powerful tool for biomarkers and neurologic disease.

Other neuroimaging modalities to collect the brain informations are magnetoencephalography (MEG), electroencephalography (EEG) and magnetic resonance imaging (MRI). These modalities have different procedures and data type. Many have made tremendous efforts to integrate information across multiple modalities. The integration is generally based on the same stimuli and performed by the specific subject or multiple subjects to set up a groundwork for early detection and prevention of a particular disease, for example Dementia. Most familiar integrations were MRI/fMRI, MRI/EEG and MEG/MRI. High resolution data of MRI provides a good framework for many other modalities.

Networks of neurons in the brain communicate with each other by means of electrical impulses. It has similar working principle as transmission and receiver operations in network servers. These imaging techniques are non-invasive and capable of recording electricity in the brain (Cabeza et al., 2016; Just et al., 2017). The process is known as bioelectrical activity (B. He, 2010). A standard experiment in neuroimaging is to name associations between bioelectrical activities and the subject's perception towards stimulus or resting state. These impulses then capture for analysis. Capturing method on the impulses introduced by the different neuroimaging modalities and how researchers infer results from experiments and their objectives specifically.

These impulses were captured either by electrical potentials (i.e., EEG) or magnetic fields (i.e., MEG, MRI and fMRI) methods. Electric potentials passed through scalp distorted and captured by EEG test. The recorded EEG signals represent the summation firing of millions of neurons synchronously (B. He & Lian, 2005). On the other hand, MEG could detect magnetic field outside of the scalp and not as distorted as bioelectrical detection by EEG test. Despite that, it is sufficed to have detection done on an alive or dead brain using the EEG machine. This brain detection is possible due to its machine sensitivity of firing neurons intensity recorded in the brain (Buzsaki, 2006). In some medical practices, such mentioned standard analysis using EEG and MEG was insufficient. EEG and MEG are not capable of producing distinguishable images of white and grey matter such as size predictions of brain tumours.

MRI and fMRI, the magnetic resonance imaging technology, both has an improved spatial and temporal resolution compared to electrical and magnetic potential energy detection. The desired temporal resolution for the analysis of bioelectrical activities is the operation speed of neurons in the brain networks; which is in millisecond scale (Buzsaki, 2006). Researchers had tested that fMRI has the capability of capturing little less than the speed of neurons by having a trade-off with image quality (Goense et al., 2016; Vu et al., 2017). MRI, on the other hand, has a high spatial resolution but suffered meagre temporal resolution (Glover, 2011).

As one of the most fascinating and least understood organ in the human body, brain and its underlying networks introduces vast topics in many research fields. Psychology, prognosis and disease diagnosis are a few examples of brain studies that manipulate MRI and fMRI. The accurate prognosis and diagnosis of a disease in medical imaging especially neuroimaging technologies depends on both careful image acquisition and deliberate image interpretation (Razzak et al., 2018). Acquisition of the images has improved substantially over recent years, with devices acquire data at faster rates and increased resolution (Greenspan et al., 2016). However, fMRI (the other main topic of discussion in this thesis) image interpretation is in rapid development stage when computer technology just recently increased in computability capabilities. Though, it is a step forward to manipulate the fMRI data to the ability not only in prognosis and diagnosis but it could pave a way to understand further and treat theses problems. For instance, psychological problem such as Schizophrenia (Stam, 2014) treatment and vegetative state patient communication using brain-computer interfaces (BCI) (Owen et al., 2006; LaConte, 2011).

This challenging task is also motivated by the ability to answer a long-standing goal of human existence, the conscience (Decety & Jackson, 2004; Ochsner et al., 2002; Owen, 2013). Monti et al. (2010) had detected five patients out of 54 patients, who had shown match response on motor imagery task in a vegetative state or minimally conscious state using fMRI data. fMRI has become one of the means to do the task as it can capture the signals of human activity despite a low signal-to-noise ratio (Welchman, 2016). Besides, the acquired data from this imaging modality had a cause-and-effect approach. The approach is implemented by stimulus activation of the designed experiment to the subject. The translated millions of neurons firing from the subject's activity in the brain (James et al., 2014) then acquired in images type. Because of that, each stimulus was designed to investigate and understand the associated areas (i.e., activated by stimulus) of the brain.

Specifically, fMRI measures haemodynamic response of activated areas which are the changes in blood flow. The measurement is known as blood-oxygen-level-dependent (BOLD) due to the response (Ogawa et al., 1990). Data from fMRI images are not easily recognised or interpreted by radiologists. The response that the brain makes is changing over time of experiment that then translated to series of images. Ogawa et al. (1990) reported the haemodynamic response due to blood oxygen changes in the brain. It suggests that the BOLD or level of oxygen in the blood could map the brain in real-time. The research was done on female rats, and blood was periodically sampled during the time of scanning. Images of the rat brain are easily identified when it is induced with insulin which was an invasive type of experiment. On the contrary, fMRI acquisition on any human subject is a non-invasive technique. The only physical interactions by the subject was such as doing day-to-day activities like reading and watching a movie. There should be no physical intervention by the experimenters such as insulin injections into the subject's brain.

The haemodynamic responses highly depend on the state of blood oxygenation and the effects of physiological events surrounding the subject on experiment. These events could be any physical or non-physical actions, which could then be captured by the MRI scanner, at any given moment. For instance, a resting and a stimulated human subject during the time of scanning will give different brain response accordingly. Stimulation event is an essential step in paradigm design because the brain as central nervous system reacts differently to each stimulation (James et al., 2014). The problem arose when noises were accumulated, and images produced not only holds high-dimension (3D) due to volumetric characteristics of the brain but added dimension of each time stamp the data captured. Nevertheless, many studied have proposed various methods to treat these noisy and high-dimensional problems.

The conventional but significant fMRI interpretation approach to-date is the statistical parametric map (SPM). It is a complex approach where many child steps are fundamental that could be grouped as preprocessing, processing and postprocessing stages. Importance of these steps lies in work to reduce the varied sources of noises and simultaneously accentuate salient signals. The general statistical algorithm used based on the General Linear Model (GLM), where the end result is to have statistical value (e.g., t-value) for every voxel in the images. However, many published papers had proposed new approaches that encompass in machine learning approaches such as naive Bayesian model (Stephan et al., 2009; Penny et al., 2011) and support vector regression (SVR) (Mete et al., 2016), and dimension reduction approaches such as independent component analysis (ICA) and principal component analysis (PCA) (Dohmatob et al., 2016; Bzdok et al., 2015).

Furthermore, the machine learning and artificial intelligence (AI) have progressed rapidly in recent years with very notable published and commercialised algorithms. Both fields have contributed in many domains such as natural language translation, image interpretation, image segmentation and also in medical areas such as computer-aided diagnosis and medical image processing (Kamnitsas et al., 2017; Bojarski et al., 2016). With the approach of maximising the ability to make predictions about unobserved data, it used many types of approaches such as minimising loss and probability comparison (Poldrack et al., 2011). For example, a particular machine learning approach has help doctors in determining the size of a tumour but also optimally reduces the time of extracting the tumour (Havaei et al., 2014).

Deep learning is one of the fields for both machine learning and AI. Deep learning-based algorithms have shown promising performance in such fields mentioned above. The three most promising algorithms are Convolutional Neural Network (CNN), recurrent neural network (RNN) and Generative Adversarial Networks (GANs) that have dramatically breaks some benchmark records in many applications (LeCun et al., 2015). LeCun et al. (2015) showed deep learning as an excellent tool to learn the intrinsic structure of high dimensional data. Deep learning in MRI classification has shown remarkable results which Kamnitsas et al. (2017) had published an improved state-of-the-art of lesion segmentation in the brain. Moreover, Standford Team lead by

Andrew Ng, one of the founders of deep learning, had published pneumonia diagnosing algorithms which surpassed the accuracy of radiologists diagnosis (Rajpurkar et al., 2017). This advancement is one of medical image processing applications where many other research groups are working forward to assist radiologists and physicians.

1.3 PROBLEM STATEMENTS

Power et al. (2017) briefly explained the problem of fMRI analyses. However, in this research, the process of setting a relationship between fMRI data, that is known to be high dimensional, with rapid improvements of deep learning field, contributed to wider problems and challenges. Thus, given is four main problem statements for this Doctoral research which includes:

- lengthy preprocessing steps for the established and widely used statistical fMRI analysis (i.e., SPM);
- lack of underlying neural activity ground truth of fMRI data where it itself is in the active research areas;
- high-dimensional nature of fMRI data with blended multiple sources of noises which reduces recorded signals relatively that eventually make harder classification approach and
- investigators hold diverse medical imaging analysis hypotheses and conclusions that intrinsically create onerous knowledge aggregation and contribute to varied challenges.

Thus, the research question arises whether deep learning is viable for high dimensional fMRI data classification by reducing preprocessing steps, establishing the anatomical maps dissimilarities by standard ground truth and restricting deep learning configurations scope. On the other hand, a new strategy should be imposed on high dimensional deep learning current methods. The diverse medical imaging analysis conclusions should be aggregated in comprehensive manners where other researchers could move forward from there. In this research, it is hypothesized that small dataset volume suggests higher training accuracy with larger validation loss on multiple subjects fMRI data classification due to massive generalisation of deep learning approach. Thus, a new strategy for data division is researched for robust deep learning classification techniques.

1.4 OBJECTIVES

Classifying the brain areas to specific cognitive states is one of the main goals for most machine learning researchers and practitioners in the neuroimaging field. Knowledge on specific states of areas eases the work in medical and non-medical applications such as mental abnormalities treatment for Dementia and Autism Spectrum Disorder and future brain computer interface between human and industrial robots. With that motivation, the central objective of this research is to classify the high-dimensional fMRI data based on deep learning approach. Following are objective milestones to be completed through out this Doctoral research program:

i To investigate previous machine learning techniques capabilities to reduce fMRI preprocessing steps;

ii To develop deep learning classification technique on high-dimensional fMRI data;

iii To test and validate the data division strategy on deep learning technique using fMRI validation set; and iv To test and verify the hypothesis.

1.5 RESEARCH PHILOSOPHY

Improving deep learning approach for high dimensional fMRI data may reduce many steps of the conventional GLM method with statistical parametric mapping classification approach. This is because deep learning is befitting in learning the intrinsic structure of high dimensional data when deeper layers were employed. However, the nature of deep learning algorithms that learn the low to high abstraction of data intrinsically might be overwhelmed by fMRI data. As such that it learns to classify the brain shape which is the high abstraction of fMRI data rather than the main objective which is to classify and interpret the brain state. Brain states, most of the time, are combination of low abstractions of high-dimensional fMRI data.

1.6 RESEARCH METHODOLOGY

A wide range from the fMRI origin, preprocessing steps, classification approaches and challenges for low signal-noise-to-ratio were studied extensively. Then, the experiment start with the data collection. High dimensional fMRI data was downloaded and expected to have big data size with proper randomly selected subjects from 1200 subjects of Human Connectome Project dataset. Big data was used to reduce the curse of dimensionality between the high counts of voxels and the number of subjects. Thus, a relatively fast workstation was prepared to process this data. Besides, the volume of data has an important role in the hypothesis testing. However, as a small scale research group, an intermediate level of workstation was acquired for this research purposed. The previous works were reviewed endlessly to ensure the best approach taken in dealing with this high-dimensional fMRI data. An immeasurable length signifies the importance of testing the best approach for deep learning configurations such as long hours of trial and error during the training and testing stage. Furthermore, specified training and validation sets of fMRI data were employed to ensure the validity of taken classification approach and robust to inter-subject of high-dimensional fMRI. In the end, an expected new strategy for fMRI data division was verified for different deep learning configuration approaches.

1.7 SCOPE OF RESEARCH

An off-line approach is taken in this research study where data of fMRI were downloaded for training stage preparation. Data was divided in two manner, randomised and separated validation set. Various deep learning approach were studied to delineate grey areas of various deep learning configurations. It is fixed to have end-to-end method for each deep learning model tested. It was done qualitatively where the ending result is compared and statistically tested with p-test for hypothesis testing.

Feasibility and reliability is of important characteristic for high-dimensional fMRI classification. Those two characteristics were investigated on various deep learning models that comparable architectures were taken into hypothesis testing. Moreover, the small dataset volume used in investigation is hypothesised to have higher training accuracies with larger validation loss when multiple inter-subjects employed. Then, the feasibility and reliability of deep learning approach on fMRI will be concluded.

1.8 ORGANISATION OF THE THESIS

The structure of this thesis is broken down into five chapters. Chapter one is an introductory part of the thesis. It focused on the details of the thesis in simple and brief manner as described in previous sections.

Chapter 2 provides a general overview of deep learning and its previous achieve-