A Tutorial on Deep Learning Research in Alzheimer's Disease

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***Abstract*—This tutorial explains the evolving approaches on Deep Learning (DL) modeling and their dependence on statistically comprehensive datasets as input in various forms of brain scan neuroimages. Powerful visual modalities, e.g., Magnetic Resonance Images (MRI) and Positron Emission Tomography (PET), can show neural changes during Alzheimer's Diseases (AD) development. The recent success in computer vision has lent impetus to numerous deep learning modeling publications reporting accuracy above 90%, using AD NeuroImage (ADNI) datasets. However, several limitations exist when using DL for AD image interpretation. Due to lack of a comprehensive dataset and the complexity of medical images, there is little to no clinical value in such DL approaches. Furthermore, without well-accepted evaluation criteria, many of the published research results in the field are not comparable in experimenting with the ADNI datasets. This tutorial describes the fundamentals and gaps in applying DL methodology over ADNI datasets.**

I. Introduction

Alzheimer's Disease (AD) is irreversible, progressive neurological disorder common in late life, slowly destroying brain cells leading to memory loss. It is the leading cause of death among the elderly in developed countries and the number of AD patients is expected to triple to 152 million by 2050 globally[1]. Consequently, the patient is unable to perform communication and normal daily activities, e.g., speaking, dressing up oneself, etc. Moreover, the cost of nursing for AD patients is expected increasingly expensive. AD is the most common type of dementia, attributing to 60-80% of the total number of dementia cases. Early and accurate diagnose capturing the initial stage of AD plays a crucial role in providing appropriate treatments. A reasonable goal is to prolong senior's independence by avoiding AD.

Rapid advances in Graphics Processing Units (GPUs) and the large amount of labelled data facilitate deep learning to dominate the field of computer vision, as manifested in Figure 1. In recent year, deep learning, especially convolutional neural network (CNN), has appeared as promising tools in medical imaging domain problems including organ segmentation [1], [2] or disease detection [3], [4]. Thanks to the capability to capture hidden visual features from large amount of data, CNN has successfully applied in different types of medical images in the shape of structural MRI, functional MRI, PET, CT, and Diffusion Tensor Imaging (DTI.) Researchers have also dived into deep learning to tackle issues of Alzheimer's's Disease (AD). Hundred of papers have been published in the last 3 years using the most popular datasets from ADNI [5]. Some promising results leading to Alzheimer diagnosis have been shown based on ADNI images [6]–[8]. However, there exist plenty of unknowns and resistance for deep learning modeling to become practical in disease diagnosis[2].

II. Objectives

This tutorial is designed to introduce the fundamentals of CNN with essential access tips to ADNI as the input. It further examines on-going advancements which hinge on multi-disciplinary approaches. It highlights the current state-of-the-art neuroimage research, uncovering some oversights and leveling the input and output metrics. It further advocates the importance of having a brain data bank following a meaningful compilation of multi-modal and longitudinal brain datasets for expert's acceptance.

III. Methods

A significant amount of deep learning techniques has been applied to AD diagnosis. Different from traditional machine learning approaches, deep learning combines all three main steps: feature extraction, feature dimension reduction, and classification in neural network modeling. Even though CNN is designed to specifically handle image data, many explorations involve diverse biomarkers, including demographic information, e.g., gender or age of non-image types into the model to strive for a convincing performance. Thus, deep learning approaches have been categorized based on the CNN models employed, types of biomarkers used, and resources managed. For example, Deep learning techniques anchored on the ADNI datasets can be classified into two main categories: unsupervised and supervised learning.

The goal of unsupervised deep learning model is to extract high-level features with lower dimensionality which is later used for classification by the Support Vector Machine (SVM.) Auto-Encoder (AE) and Restricted Boltzmann (RB) machine are two primary unsupervised deep learning models. AE consists of two modules: an encoder mapping the input data into

[1] https://www.who.int/news-room/detail/07-12-2017-dementia-number-of-people-affected-to-triple-in-next-30-years

[2] https://www.raps.org/news-and-articles/news-articles/2020/7/radiologists-to-fda-autonomous-ai-not-ready-for-pr

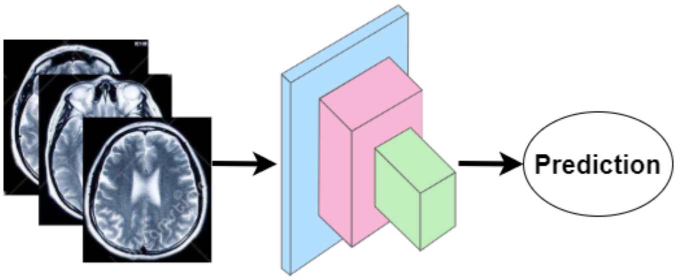

Fig. 1. Deep Learning Modeling

most definitive representation space and a decoder attempting to reconstruct the data from the encoded subspace. RB is an undirected graphical model which learns the probability distribution from the set of data. Unsupervised learning is not popular in computer vision because the process does not merge feature extraction with classification. This merging process represents the most advantage of deep learning over traditional machine learning modeling.

In terms of supervised learning in deep learning, CNN and Recurrent Neural Network (RNN) have been the dominated mechanisms. CNN currently is deemed the most successful deep learning model in computer vision and image analysis. CNN models are composed of several import components: convolutional layers, max pooling layers, activation layers, softmax layers. The architecture utilizes stack of layers which gradually extract abstract spatial features for 2D or 3D image data. RNN, consisting of complex units such as LSTM (Long Short- Term Memory) or GRU (Gated Recurrent Unit), specialized in extracting temporal information in time series data such as voice or video. 2D CNN models reduce the number of parameters as opposed to 3D CNN; but 2D CNN can only handle 2D images. To work with 3D or stack of 2D images, researchers usually merge multiple 2D CNN into RNN to fuse the multiple features from stacks. 3D CNN is much more popular than 2D when examining AD because neuroimaging provides 3D images with spatial relation among stack of 2D images.

Deep learning models could also be categorized by what biomarkers are processed in the input. Since deep learning is sort of a black-box approach, qualifying the input and output plays the most crucial role in evaluating the model's performance. Voxel-based approaches rely on the voxel intensity from the tissue component in MRI images. This requires preprocessing steps to align spatial information from full brain images into standard 3D space. Slice-based methods extract 2D image slices (the central part of the brain) that deemed most relevant to AD, while ignoring the rest of the image. In Region of Interest (ROI)-based approaches, only particular parts of the brain known to be most affected by AD are used to extract features. Patch-based preprocessing focuses on the 3D cube images that capture most of the AD information. Different from the above approaches which only utilize part of the brain, thus requiring knowledge of abnormal regions to furnish full brain models with the full 3D images as the input. Consequently, ROI-based approaches usually require much larger number of parameters in place of insufficient information about the full brain. This tutorial will explain the above definitions and approaches per Syllabus as follows.

IV. SYLLABUS

1) Machine Learning Basics
   - Learning Algorithms
   - The Performance Measure
   - Overfitting and Underfitting
   - Validation approaches
   - The Curse of Dimensionality
2) Deep learning Introduction
   - Hyper-parameters
     - Batch size
     - Learning rate
     - Optimizer
   - Convolution Neural Network (CNN)
     - Convolution operation
     - Batch normalization
     - Activation
     - 2D CNN vs 3D CNN
   - Recurrent Neural Network (RNN)
     - Fully recurrent
     - Long short-term memory
     - Bi-directional
3) Deep learning in ADNI
   - Voxel-based approach
   - Slice-based approach
   - Patch-based approach
   - ROI-based approach
   - Full brain approach
4) Summary and future direction

V. TARGET AUDIENCE

Researchers as well as students interested in building deep learning models to understand brain and its functions using data will find the information presented here useful. This tutorial acts like a bridge between the fields of deep learning and neuroimaging. It is of specific advantage to those who participate in the IEEE Brain Data Bank Challenge 2020.

VI. FURTHER NOTES

The Instructor has been engaged in BDBC and CNN since 2016, becoming part of the Champion team in BDB-Boston in 2018. He is also contributing to BDBC-2020 challenge platform since its inception as well as the SPCN-2020 conference.

The instructor believes that the material shared here will also benefit the audience in Big Data and Deep Learning related research and applications.

Special acknowledgment is bestowed to Saumil Dhankar. Without his dedication and volunteering effort, this tutorial and the companion tutorial on ADNI would not have been put in place as detailed.

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