Class Imbalance Applied to Medical Neuroimaging for Classification of Alzheimer's Disease

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Abstract

Class imbalance is an issue that naturally occurs when a database is sparse or incomplete. This can occur in medical diagnostics when a large percentage of tests ran to return negative results rather than a positive. Classification models are sensitive to an imbalanced training set, and training on one can cause undesirable biases. This work presents an overview of the effects of class imbalance on classification models in Alzheimer's detection utilizing voxel based-morphometry (VBM). MRI scans are processed by FreeSurfer where cerebral volumetric and thickness are taken as feature vectors. The effcts of class imbalances on multiple machine learning models were compared to one another. Furthermore, different biomarkers were studied for their effect on different metrics of trained models. The classification models were trained to detect the following categories: Alzheimer's disease (AD), mild cognitive impairment (MCI), and normal controls (NC). SVM, KNN, MLP, Random Forest, etc. algorithms were evaluated for the prediction analysis. It was observed that class imbalance did not produce any significant effects on the disease classification process.

Keywords: *Classifiers, Alzheimer's disease, Mild cognitive Impairment, Voxel-Based Morphometry*

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder that presents with symptoms including memory impairment, executive dysfunction, and other deficits in other cognitive domains. Normal neuron activity creates amyloid precursor protein, but in AD, a dysfunctional enzyme creates a shorter protein. A build-up of these form of beta-amyloid plaques, which are toxic to and inhibits neuron function by injuring synapses and neurites.[1] Beta-amyloid plaques also promote the formation of neurofibrillary tangles that stops neuron function.[2] Both result in neurons disconnecting from others, they stop communicating and die, resulting in memory loss.[3] As this continues, those brain regions shrink and function is impaired.

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Neuroimaging technology such as magnetic resonance imaging (MRI) has significantly contributed to further understanding of brain regions, and associated diseases such as AD. Despite the limits to detail in images, (units called voxels make up an image, and a single voxel can represent a million brain cells)[4] predictions can be made from observations of activity among groups of voxels correlating to specific brain regions. MRI is also able to accurately measure the size of brain structures, in three-dimensional volume.[3]

Classifiers

Recently, machine learning has been applied to the medical field.[5] A decrease in the cerebral volumetric and thickness are physiological symptoms of Alzheimer's disease.[6] These biomarkers can be utilized as indicators for machine learning algorithms to detect AD.[6,7] Although several classification methods have been utilized, Support Vector Machines (SVM) is the most common approach in practice, along with both the MRI images [8,9,10] and PET images.[11,12] For instance, Davatzikos et al.[13] implemented SVM in MRI imaging and cerebrospinal fluid (CSF) biomarkers and applied it for MRI, FDG-PET, and CSF as in.[14]

However, only the binary classifier has been discussed in many of the earlier referred researches. As an example,[13] regarded the only AD vs NC classifications, while Cui et al.[15] considered investigating both MCI vs NC and AD vs NC. In[16] the author has dealt with the transition of MCI to AD, whereas, Vounou et al.[17] reported the differences in progressive p-MCI and stable s-MCI patients that were discussed as a binary issue. As noted by Amir et al. in their study on the use of convolutional neural networks (CNN) for classification of spinal MRIs, and as discussed in recent papers on utilizing SVM [18,19,20] valuated diffusional MRI images using multilayer perceptron (MLP) and Kohonen self-organizing map (SOM) classifiers to improve the standard analysis of apparent diffusion coefficient (ADC) maps. MLPs are a staple artificial neural network (ANN) architecture that utilizes a feed-forward system with multiple layers of nodes that have a linear or nonlinear activation function. These nodes are typically trained with some variation of back propagation. Kohonen SOM is a different ANN architecture that utilizes unsupervised learning to create a map, which is a form of dimensionality reduction.

The research group utilized 3 different images with varying exponent diffusions to calculate an ADC map. What they found was a Kohonen organization map of 99.9% accuracy and MLP with an accuracy of 88.5% [20]. Similar studies by Hamou, et al.,[21] in 2010 utilized clustering techniques and decision trees to determine whether or not participants with AD or MCI states from MRI images. Their study revealed that that standard K-means clustering was not accurate enough and they were able to obtain a better representation by further refining the results with decision trees.[21] Even though the binary classification is easier and far less complex, AD treatment is a multi-class problem, and multi-class methods should, therefore, be studied.

Class Imbalance

The class imbalance is often a case wherein the category allocation is complicated. This case is frequently observed within the data of Alzheimer's disease, that differentiates conventional models from various greater categories.[22] In order to evaluate the pair of results from each class, training of the binary classifiers has been suggested [22,23,24,], and therefore, both groups also add to the selection criteria. In a multi-class analysis that was outlined in[25], deliberately included class allocation for AD prediction. The analysis primarily depended on multi-class segregation of the problem into binary problems. The findings, thus, acquired were promising. Though, their strategy did not significantly addressed the class imbalance, that motivates the current study.

Materials and Method

Table 1: Stages of cognition and size of samples used with a train/test split of 80:20.

Stages	Number of Samples	Train/Test
Alzheimer's Disease (AD)	65	52/13
Mild Cognitive Impairement (MCI)	116	93/23
Normal Cognition (MC)	96	84/12

Datasets

Data used in the preparation of this article were obtained from the Alzheimer's disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu).[26] The ADNI sample comprising pooled ADNI1, ADNIGO, and ADNI2 subjects was used to perform primary analysis comprising modeling and prediction tasks.[27] ADNI has 3 phases: ADNI-1, ADNI-GO, ADNI-2 that varied in their goals and cognitive stages. The stages given in the dataset are normal control (NC), significant memory concern (SMC), early mild cognitive impairment (EMCI), mild cognitive impairment (MCI), late mild cognitive impairment (LMCI), and Alzheimer's disease (AD). In this research, MCI, NC, and AD data sets from ADNI were studied with their quantities highlighted in Table 1.

Validation of Data for the Study

Many researchers have identified specific neuropathic behaviors linked to the cognitive and functional decline in Alzheimer's disease and its prodromes[28] in search of the detection of accurate biomarkers. The absence of manifestations of localized canonical atrophy may be related to behavioural, biological and environmental factors.[29] Therefore, models with an ensemble of imaging characteristics, genotypic and diagnostic information were delivered.[30] The improvements in performance delivered by the image details however are ambiguous in some of these multimodal systems.

MRI Processing

After the data was received from ADNI, the data was processed further using FreeSurfer. A set of software tools released by FreeSurfer has allowed researchers to study cortical and subcortical brain anatomy in a streamlined method. Here, the three types of probabilities are computed at each point (voxel): the probability that a point belongs to each of the label class, probability of the spatial configuration, and the probability of the intensity/curvature.

Feature Vectors

For our work, the trained prediction models use three distinct sets of features. In the first feature set, aseg.stats files were utilized containing 45-dimensional vectors. The volumes of the anatomical structures were then normalized with the subject's intracranial volume to account for variance in head-size. The left and right cerebral white matter, cerebral cortex, 3rd and 4th ventricle, lateral ventricle, inferior lateral ventricle, cerebellum white matter, cerebellum cortex, thalamus proper, caudate, putamen, pallidum, hippocampus, and the amygdala were a part of this set. For the second feature set, aparc.stats files were used containing 68-dimensional vectors. This second feature set contained the average thickness for the various structures like superior frontal, rostral middle frontal, caudal middle frontal etc. And finally, the last feature set contained a combination of the two aforementioned feature sets

In the case of MRI images, FreeSurfer was utilized to extract important features and then utilized principal component analysis (PCA) where a trained classification model can be used to query new images.

Results and Discussion

One is more inclined to believe that a stronger model is easier to create with a larger dataset. That is, however, not necessarily the case. As seen in Table 1, the largest data provided were for MCI and NC patients; it is observed that MCI vs NC was the most difficult to model. Moreover, drastic changes in biological structures as seen in AD vs NC patients are more readily classified. Alzheimer's disease classification versus patients who show mild cognitive impairments are also moderately detectable. What this alludes to is that the progression from MCI to Alzheimer's disease is severe. EE and BC are shown to have moderate performance in all three binary classification problems in comparison to other classifiers. Although EE and BC were incorporated specifically to mitigate class imbalances, it was found that the model either performed moderately or generally under performed.

In contrast, SVM drastically decreases in overall metrics when classifying NC vs. MCI while it excels at classifying AD vs. NC and AD vs. MCI. In the case of MCI vs. NC, MLP architecture has shown to be slightly more favorable. This slight advantage could be attributed to MLPs' advantage of extracting complicated trends from data. What is surprising is that the imbalanced dataset has no drastic effects seen in AD vs. NC and AD vs. MCI, as their F-1 and MCC scores show adequate values. From the cross-validation results for AD vs. NC classification, there is a clear distinction that can be made for the binary classification and that it generalizes well. Moreover, SVM seems to continually indicate strong cross-validation results. Furthermore, there is a decrease in the ability of classification when both biomarkers are used to train the models as seen by low MCC numbers. EE and BC are shown to have moderate performance in all three binary classification problems in comparison to other classifiers.

Although, EE and BC were incorporated specifically to mitigate class imbalances, it was found that the model either performed moderately or generally underperformed. In contrast, SVM shows a drastic decrease in metrics when classifying NC vs. MCI while excels at AD vs. NC and AD vs. MCI. In the case of MCI vs. NC, MLP architecture has shown to be slightly more favorable.

Moreover, the ROC analysis coincides with the confusion matrix analysis. In general, the ROC curves for MCI vs. NC lies either below linear or oscillate around a slope of 1. This indicates that the methods either under-performed or were no better than random search.

Conclusion

SVM demonstrated a drastic decrease in metrics when classifying NC vs. MCI while excelled during the classification of AD vs. NC and AD vs. MCI. In the case of MCI vs. NC, MLP architecture was slightly more favorable. Consecutively, it was surprising that the imbalanced dataset had no significant effects in AD vs. NC and AD vs. MCI, as their F-1 and MCC scores. However, the differences in an MRI image between patients that shows MCI versus one that is not impaired is subtle. Therefore, more advanced neural network architecture may prove to be advanced classifiers. Advanced classifiers will allow us to create significant CBIR systems that are more robust, where a robust CBIR system is one of many requirements to deploy a query image for classification.

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