Multimodal Analysis in Biomedicine

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Abstract

The current and future challenge for BCI centers is to develop methods and systems to remove noise, extract meaningful features and learn from big data [26]. Generally, there are three main steps to develop such a system and to make biosignals useful in real-world settings. These include real-time data collection, data processing (e.g., feature extraction and classification) by computer and biofeedback to apply the desired action. The requirements of a practical BCI system include methods for signal processing, machine learning and brain-state analysis in large data sets collected from user populations in real-time and in combination with their health records [25]. Learning applications of big data in the form of real-time acquisition with the background of the electronic healthcare record (EHR) provide for the generation of new knowledge that will aid in detection of outcome and, therefore, prognosis [27]. This situation calls for the safe storage of a large archive and for high computational resources to process big data. Accordingly, next generation BCI systems must be connected to high-performance computing servers in order to be able to adopt predictive models and to execute computation in real-time for large incoming datasets. Cloud computing and edge computing are a new Information and Communications Technology (ICT) that enables ubiquitous and on-demand access to healthcare databases and computational resources through the global Internet.

1 Medical Big Data

As technology gets more advanced throughout all industries, there is an increasing interest to measure and analyze human behavior. Data mining in retail, finance, and medicine are among the industries where information about consumers will have a huge impact on the way businesses operate. Whether this data will be used to increase profits or to better our quality of life, it is certain that all of this data will lead to changes in our society in every aspect.

In particular, big data in medicine has greatly changed the way in which we analyze and manage information. The advancements in the medical device industry has allowed physicians to collect vast amounts of data about our personal well being. The transformation and digitization of information drives a more proactive healthcare model creating more accessible information for both the patient and the physician. The generation of this data also comes from advances in the medical device industry as well as a shift in our culture and how we are choosing to manage our own health. Patient-generated health data is a large contributor to the amount of information that is being generated. This has been made possible by the growth in wearable technologies in recent years. This includes everyday lifestyle monitoring that tracks the number of steps taken in a day or monitors our blood pressure as we perform our normal daily functions. As the number of wearable medical devices increases, individuals will have growing access to information on their own well-being.

Additionally, large amounts of data from medical equipment such as neuroimaging and electrodiagnostic analytic tasks provide a platform for deep learning techniques to be trained with a single model without the need for manual, labor-intensive screenings. Applications of big data in the healthcare can increase our effectiveness in diagnosing disease and on the prediction of outcomes. Current computer applications available to physicians only allow for basic functions such as context-sensitive warning messages, reminders, suggestions for economical prescribing, and results of quality improvement activities. The following five characteristics that will have to be differentiated in order to facilitate the use of big data: first, the standardize the patient groups that are being compared; second, the analysis would have to be automated; third, the data analysis would have to happen rapidly to include new incoming data; fourth, performing the data analysis would have to be user-friendly; fifth, the analysis result would be translated in a readable manner for both the clinician and patient [27]. These five characteristics are important in applying analytics to health datasets because of the wide variation that a single disease can have on different patients.

A potential issue in the field of medical big data analysis in the manner in which much of this data is stored [27] Because of privacy concerns, a patient's information is distributed over several databases. For example, as genetic sequencing gets cheaper and more accessible, there would be an increasing number of individuals that choose to sequence their DNA. This detailed genetic information, however, would not be included in their medical record. Having the ability to form connections between these datasets would allow a more informed analysis that can apply to a larger population across different geographical cultures. Big data in medicine will provide a new frontier in healthcare; however, without the proper algorithms for analysis, this data will mean nothing.

2 Big Data Analysis with Machine Learning

Machine learning methods have been increasingly used in the medical imaging field for computer-aided analysis of diagnostics and prognostic models. Several of these methods such as supervised, unsupervised, and deep learning have more recently been employed to solve medical imaging related problems. Machine learning is a subset of artificial intelligence that allows machine algorithms to be programmed to an optimized performance criterion with the use of a known training dataset. The learning happens when an algorithm is trained to go

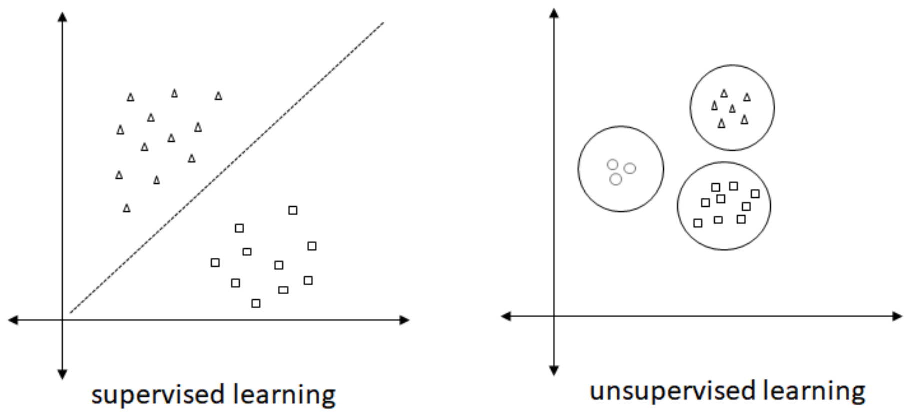

Figure 1: A representation of supervised learning compared to unsupervised learning. Supervised learning develops a model based on data from both the input and the output. Types of supervised learning include classification and regression. Unsupervised learning only depends on the input data. Clustering is an example of unsupervised learning.

through data and iterate through until it is able to correctly identify characteristics an labels. This machine learning is used mostly in cases where human expertise does not exist or are unable to quickly process and understand data. The unique advantage to machine learning is the ability take in large amounts of data and be able to recognize patterns that are beyond the human ability.

Two main applications of machine learning are supervised and unsupervised learning. Supervised learning is when an algorithm or function is trained on a set of labeled data. The supervised learning algorithm analyzes a dataset and makes an inferred function from the generalized data. Classification and regression are two types of supervised learning. In classification, the algorithm attempts to separate the data into distinct groups. For example, classification is used in pattern recognition and facial recognition the lighting, hair style, pose and structure. In medical context, certain symptoms can be grouped together to and linked to a particular illness. Supervised learning is one of the basic learning methods that uses simple rules to predict an outcome from an input data set. A slightly more complicated concept is that of unsupervised learning. This method forms inferences without a labeled outcomes. An example of unsupervised learning is anomaly detection and clustering. Objects that are similar to on another are grouped together. These types of methods are very common for pattern recognition, image and data analysis.

3 Multimodal Analysis

Multimodal imaging combines two or more imaging techniques in a single examination to allow for the integration of several analysis in order to have a better understanding of disease biology. A synchronous image acquisition is the best solution to achieve consistency in time and position of the scan. Common multimodal imaging techniques include SPECT-CT, PET-CT, and more recently PET-MR [21]. For example, one of the most common combinations is the PET-CT scan where the PET would provide information about how the body is functioning while the CT scan relays information about anatomical structure. This type of imaging acquisition allows physicians to better pinpoint any problems in the body. Additionally, EEG, MEG, and fMRI are used to study neural activity and interactions. EEG/MEG is know for it ability to have a high temporal resolution and fMRI is know for using blood oxygenation level dependent (BOLD) contrast that provides high spatial resolution. When these two modalities are combined, it has the potential to significantly i ncrease the spatial resolution of electromagnetic source imaging and to be able to pinpoint rapid neural responses in the brain [19].

The use of machine learning in multimodal imaging aids in processing the data from systems that are able to detect two modality signals at the same time. Combination of methods involves the use of two or more of the machine learning algorithms to take advantage of the unique characteristics that each method possesses. This allows the multimodal algorithm to extract additional desired features. The significance o f m ultimodal i ntegration i s that it allows high resolution classification u sing p rimarily a lready e xisting methods [?]. Additionally, this resolution will generally be higher than that of the individual methods separately. However, multimodal extraction is not without limitations. Due to the increased complexity of the algorithm, it may be difficult to determine the true accuracy as it is not directly comparable to existing methods. An example of this application in EEG is the diagnosis of multiple sclerosis patients. In the paper, T-test and Bhattacharyya were used for feature extraction as part of the preprocessing. Following this a combination of KNN and SVM as the primary classification a lgorithm. T his r esulted i n an total accuracy of 93% [?]. While other sections above have dedicated tables with reviewed literature, we wanted to bring attention to multimodal analysis as some literature above already demonstrated the application of the combination of methods. Multimodal imaging techniques are often differentiated into two categories: asymmetric and symmetric data analysis approaches. In an asymmetric approach, the analysis uses one modality to bias the estimates of another modality˜ []biessmann2011analysis. Many asymmetric analysis works similarly to the supervised learning method of regression where one modality is used to extract features of the other modality. For example, the amplitude of an ERP component from EEG/MEG data can be extracted and correlated with the fMRI data. Asymmetric analysis leverages one of the modalities to bias the other. By doing this, there is potential to lose information from the second modality. However, asymmetric analysis is advantageous in that one modality

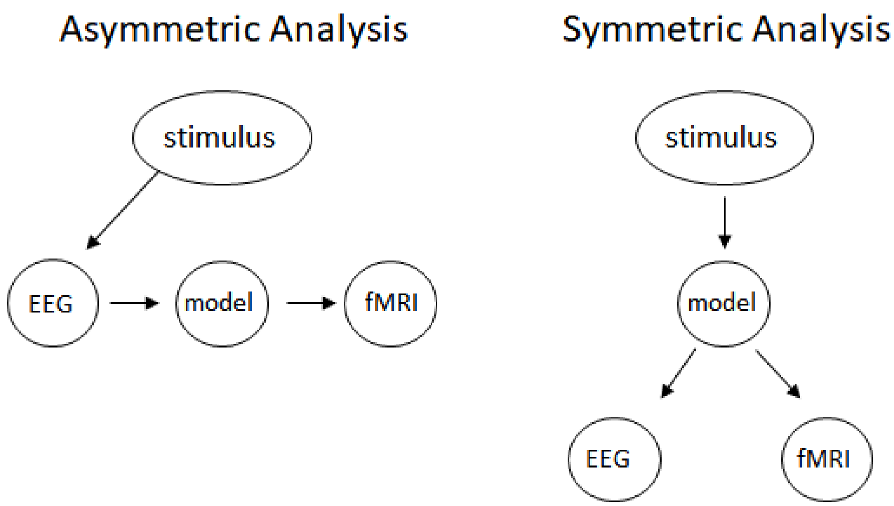

Figure 2: Multimodal methods usually have either a asymmetric or symmetric approach. In asymmetric analysis, features from one modality are used to improve on the features of another modality. Symmetric approaches analyzes both modalities jointly. [3].

is able to create a model of measurement noise. This noise models allows for subtle artifacts to be removed from the analysis.

In contrast, symmetric analysis processes both modalities at the same time. Because they are done at the same time thy are able to reveal certain aspects that the other modalities are not able to catch. For symmetric analysis, there is careful consideration for some "pre-analysis" steps such as the feature selection in multimodal methods. An option would be to employ unsupervised methods in order to learn the important features rather than rely on the model assumptions or a manual feature selection. For example, unsupervised methods are able to learn features that are important for the neurovascular coupling process [2]. Unsupervised models are used to find s tructure i n t he d ata w hen n o stimulus variable exists.

There are several unsupervised learning models that are being used in multimodal data analysis. This includes principal component analysis (PCA), independent component analysis (ICA), functional connectivity analysis, and canonical correlation analysis (CCA) [3]. Clustering has also been used in many multimodal analysis. This is where groups of objects that are found similar to one another are grouped together. A well-known clustering analysis is called the k-means algorithm. In the k-means algorithm, each data point in the set is assigned a label (k) and assigned in groups where datapoints within each group have similarities. Clustering is commonly used for data exploration and to understand the structure of data.

4 Multimodal Processing in Neuroscience

Functional changes in the brain may precede detectable structural changes [12] and may be detected by existing noninvasive modalities. Functional connectivity analysis through EEG and rs-fMRI [6], complemented by diffusion tensor imaging (DTI), has provided such meaningful input in cases of temporal lobe epilepsy (TLE) [17]. To this end, the brain is modeled as a connected network of nodes and connectivity matrices are estimated from EEG and rs-fMRI data. The nodes may be selected based on structural or functional parcellation of the brain using model-based or model-independent (data-driven) methods. The entire connectivity matrix or specific connections between any two groups of nodes may be compared between two groups of subjects. Whole brain connectivity analysis can reveal major differences between the two groups and requires more samples and more complicated statistical analysis [31].

Multimodal analysis of brain images to diagnose neurological disorders can also be paired with nonimaging factors to discover underlying correlations between illnesses. Schizophrenia and bipolar disorder are genetically related and are leading causes of disability worldwide [30]. Multimodal imaging along with clinical and behavioral variables would need to be analyzed because a simple MRI signal can often be influenced by lifestyle choices (smoking, substance abuse, etc.) [22]. Therefore multivariate covariation between nonimaging and imaging variables were analyzed to obtain measures of cortical thickness, subcortical volume, task-related brain activation, resting-state functional connectivity and white matter fractional anisotropy (FA) [23]. Factors that were known to be associated with the MRI signal were included in the nonimaging data set. This included lifestyle factors, physical health, IQ, substance abuse, BMI, and medication. A sparse canonical correlation analysis (sCCA) was applied because of the varying sources of each data set. Canonical correlation analysis (CCA) is a multimodal analysis method that is very useful in determining correlations between multiple sets of variables. The sCCA analysis between the imaging and non imaging data sets demonstrated a substantial covariation between the multiple variables. The results highlight the association between BMI and neuroimaging phenotypes. The relation of an individual's lifestyle to the brain characteristics emphasize the importance of of these associations in possibly leading to early intervention that can mitigate risk.

Multimodal analysis is also used in the diagnosis of Alzheimer's disease for treatment and possibly delay of the illness. A deep polynomial network (DPN) is a deep learning algorithm that is able to perform well on both large data sets as well as being able to learn effective feature representations on small data sets [29]. This is a new concept that is able to provide better performance on large datasets compared to deep belief networks and stacked autoencoder algorithms [20]. A multimodal stacked DPN is able to fuse and learn features from multimodal neuroimaging data for Alzheimer's disease diagnosis. The analysis first learns high level features of MRI and PET images. These features are extracted from only their corresponding imaging modality and therefore would not have any correlation between PET and MRI. Because of this, the

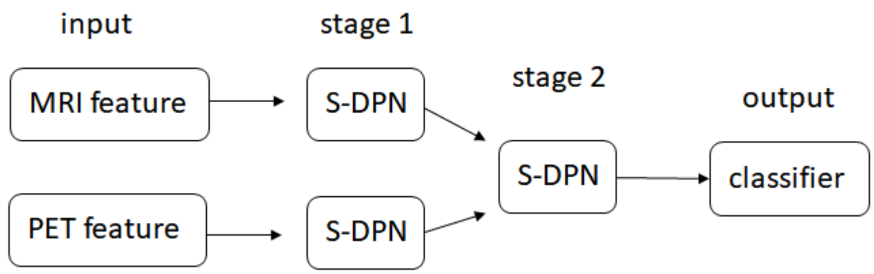

Figure 3: A representation of the multi-modality framework using stacked Deep Polynomial Networks (S-DPN) for Alzheimer's Disease classification with PET and MRI features. Image adopted from Zheng et al. [32].

high-level features from PET and MRI are fed into another DPN network to combine the two analysis algorithms. [28]. This creates a stacked, two staged DPN network that is able to correlate information from features of both imaging modalities. In the analysis done by Zheng et al. the stacked DPN network was able to demonstrate superior performance over the original DPN algorithm for both imaging modalities and achieved an accuracy of over 97% [32].

Before a deep learning algorithm is applied to the dataset, there is usually some preprocessing steps that need to take place prior to the analysis. Neuroimaging data was taken from the Alzheimer's disease Neuroimaging Initiative (ADNI) [1]. These images from PET and MR scans were fused together in order to align the different modalities and improve the overall quality of the image. Noise reduction filters are applied such as the Wiener filter to reduce the amount of additive noise in the PET and MR images [1]. After the filtering, the images go through a feature extraction step then through the Elman Back propagation Network for pattern classification [1]. Elman Back propagation Networks are Recurrent Neural Networks that go through a supervised training algorithm [24]. Feature extraction was performed on the MR and PET images to classify the normal data set as "No disease" and the subjects with Alzheimer's disease as "Alzheimer's disease." Because there is no single biomarker that can predict Alzheimer's disease with 100% certainty, image analysis from multiple modalities increase the diagnosing accuracy for Alzheimer's disease.

5 Multimodal Analysis in Epilepsy, An Application

Functional changes in the brain may precede detectable structural changes [12] and may be detected by existing noninvasive modalities. Functional connectivity analysis through EEG and rs-fMRI [6], complemented by diffusion tensor imaging (DTI), has provided such meaningful input in cases of temporal lobe epilepsy (TLE) [17]. To this end, the brain is modeled as a connected network of nodes and connectivity matrices are estimated from EEG and rs-fMRI data. The nodes may be selected based on structural or functional parcellation of the brain using model-based or model-independent (data-driven) methods. The entire connectivity matrix or specific c onnections b etween a ny t wo g roups of nodes may be compared between two groups of subjects. Whole brain connectivity analysis can reveal major differences between the two groups and requires more samples and more complicated statistical analysis [31]. In unilateral TLE patients, increased functional connectivity of the default mode network (DMN) with other brain regions has been shown in left TLE along with decreased connectivity in right TLE.

A means of therapeutic interaction with an area of epileptogenicity, that does not entail removal of a portion of the brain, first r equires a dequate d etection of ictal onset. The use of computers to help physicians in the acquisition, management, storage, and reporting of brain (i.e., EEG) signals is well established. To this end, there are computer-aided detection applications that use a BCI. In order for an autonomic computing system to work effectively, computational algorithms must reliably identify periods of increased probability of an impending ictal occurrence in order to abort its development. Such preictal periods may be of variable duration and may not afford suitable latency to provide current methodologies with sufficient time for signal deployment to achieve control in all circumstances. The development of an autonomic method for detection and epileptogenicity localizing would optimize seizure control and bring about an improved quality of life.

Efficiently handling and processing of medical big data can provide useful information about a patient and about diseases. To understand the task at hand, it is useful to review the current investigational aspects involved in elucidating the patient's epilepsy. In those patients declared to have an epileptogenicity that can be further investigated to establish its location in the brain, a number of standard neuroimaging, functional and electroencephalographic studies are undertaken. These include magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT), positron emission tomography (PET), inpatient scalp EEG and video monitoring (phase I), sodium amobarbital study and a neuropsychological profile. In select cases, a variety of further MR postprocessing applications and magnetoencephalography (MEG) are applied. Several quantitative neuroimaging metrics have been applied to provide greater precision and reproducibitlity in defining putative sites of epileptogenicity particularly as it applies to the most common area of involvement, the mesial temporal lobe. These are correlated with EEG data to render an initial assumption of the site of epileptogenicity and these may be reported with varying degrees of certainty.

Based upon our previous studies [7–11, 13–16], definitive t herapy m ay be decided in the form of resective surgery or entirely discounted on the basis of multifocality suggesting greater than two sites of independent epileptogenicity. When uncertainty exists regarding the location of a particular focality or a need exists to establish the eloquence of cerebral function in the vicinity of a putative site, then intracranial electrographic investigation (i.e., phase II) is required in the form of extraoperative electrocorticography (eECoG). This requires the intracranial placement of surface and/or depth electrode arrays in specific locations of the brain to better understand the distribution of the epileoptogenic network and a further admission to the Epilepsy Monitoring Unit (EMU). The results will often declare the approach to be taken therapeutically.

The shape of the brain network using rs-fMRI and EEG data is shown in recent publications such as [5] and [4]. The rs-fMRI data can determine the temporal dynamic of functional connectivity, which is limited to the scanning time which is usually less than 10 minutes. In contrast, EEG/iEEG can be used for long-term analysis of dynamic changes in functional connectivity and finding IED. Also, temporal sampling rate of EEG is higher than rs-fMRI. Therefore, the combination of rs-fMRI and EEG/iEEG can reveal more information about dynamic functional connectivity. However, simultaneous fMRI imaging and EEG data acquisition present challenges [18].

6 Conclusion

Multimodal anaysis of big data in healthcare will continue to grow and unveil more efficient diagnostics and evaluation of many difficult to treat diseases. Neuroimaging is an example where machine learning analysis has made a lasting impact on the way we are able to diagnosis disease. Neurological disorders are very difficult to treat which makes early diagnosis even more important. There are many different imaging techniques that are available (ie. EEG, fMRI, MEG). By incorporating multiple different imaging techniques into the same analysis, it is likely that there are certain features that will not be able to be recognized by one modality. As more images are fed into machine learning algorithms, it is able to learn rules from the data. The algorithms are able to combine and correlate predictors in interactive and nonlinear ways. As more data gets generated, machine learning will become indispensible in solving complex problems in medical disgnostics.

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