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Insights on Early Diagnosis of Alzheimer Disease Using Graph Theory

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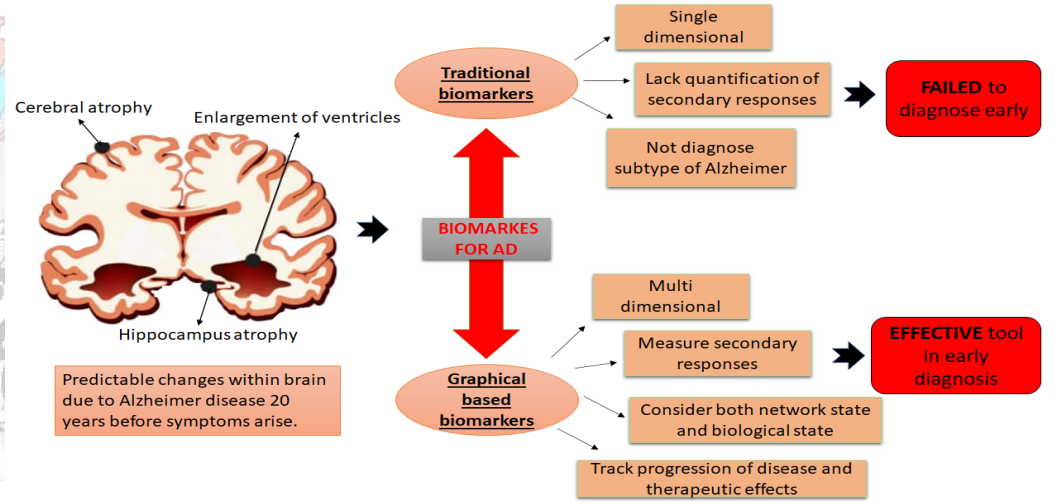
Abstract:

Alzheimer is a step wise and progressive neurodegenerative disorder caused by neuronal cell death. The predictable changes within the brain due to Alzheimer disease (AD) usually turn out almost two decades prior to the emergence of symptoms. This slightest phase of symptoms offers a great chance for therapeutic potential which can be directed to predict the progression of clinical AD. Mild cognitive impairment is the stage before AD. The transformation from MCI to AD has been of agreeable interest for the analysis of biomarkers that are beneficial for early AD detection. Determination of causative agents is a necessary step for the understanding and to figure out the effective treatment of a disease. The aassessment of significant biomarkers can be overriding for the prompt pre-clinical diagnosis, therapeutics, examining and treatment, monitoring, and continuing phases of AD analysis, for that graph theoretical measures can be utilized to infer neurobiological mechanisms leading to loss of cognitive functions, behavioural and other brain disorders. Also, complex networks of brain can be well characterized by graph functions that distinguish Alzheimer brain from the normal ones. This paper highlights the role of graph theory as an emerging tool for the early diagnosis of AD.

Graphical abstract:



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Introduction

Alzheimer's disease (AD) is a neurodegenerative, inevitable, progressive disorder that affects memory, thinking behavior and other potential activities, the early symptoms of which include trouble in recalling recent talks, names or events; depression; lack of interest (apathy) and later signs are confusion, hindered communication, disorientation, behavioural changes and poor judgement (Bondi et al., 2017). It is perceived as a disease of neural network dysfunction and disconnection syndrome where connectivity type based on structure and function of the complex system is steadily altered by various pathological mechanisms (Brier et al., 2014).

Worldwide, more than 25 million people are suffering from dementia, in which more of them are from AD. It has been estimated that approximately about 5 million fresh/ new cases happening each year and this figure is expected to become two-fold after every two decades (20 years) and thus prominent the need of AD detection at an early stage. The underlying and foremost step of the disease is to strike the brain's memory center leading to the individuals of AD more forgetful and distracted. The initial stage of AD is difficult to be diagnosed as its symptoms are noticeable usually at an advanced stage (Knopman et al., 2001). The sequential cleavage of APP, Amyloid Precursor protein, results in the formation of peptide Amyloid beta by beta secretase followed by gamma secretase. This is known as Amyloidogenic pathway. The enzyme alpha secretase competes with gamma secretase to stop this amyloidogenic pathway. Competition of alpha secretase with gamma secretase is non-amyloidogenic pathway (Dawkins et al. 2014; Zhang et al., 2015). Based on the hypothesis of amyloid cascade, imbalances between formation and removal of amyloid beta results in the dysfunctioning of neurons and ultimately cell death. Different forms of amyloid beta in terms of structure can occur such as oligomeric, protofibrillar, and fibrils (Mohamed et al., 2016; Macchi et al., 2014). Accumulation of deposits of beta amyloid protein outside nerve cells results in the formation of hard plaque. Simultaneously, accumulation of malformed versions of tau proteins inside the neurons results in the collapsing of neuron's transport microtubules (Boutajangout and Wisniewski, 2014). As time passes, the functioning of neurons become less efficient or die, ultimately fail to communicate with one another causing the shrinkage of brain tissue. One's own judgment becomes awful as the disease spreads to the outer layer of the brain (Knopman et al., 2001).

Food and drugs administration (FDA) approved drugs to treat symptoms related to Alzheimer's disease, that includes the class of drugs called "cholinesterase inhibitors". The cholinesterase inhibitors halt the process of disintegration and breakdown of a chemical messenger in the brain that is important for learning and memory. Examples of such drugs are donepezil, galantamine and rivastigmine approved for the treatment of mild to moderate Alzheimer disease (Mirjana et al., 2013). Other classes of drugs include M drugs (Memantine, melatonin, minocycline, modafinil). Meantime that has been to manage mild and severe form of AD is the antagonist of N-methyl-d-aspartic acid, also known as uncompetitive NMDA. Melatonin is a neuroprotector and antioxidant and anti-inflammatory in nature, Minocycline reduces neuroinflammation and CNS pathology and prevents cell death and Modafinil has been registered for treating sleep apnea and narcolepsy and it promotes wakefullness in a diagnosed individual. Further, improvement in the neurogenesis of hippocampus, cognition, mental status and attention has been reported (Daulatzai, 2016). Enzymes associated with degradation of amyloid beta including neprilysin, insulin-degrading enzyme and enzyme that converts endothelin decrease the levels of amyloid beta is also one

of the medications approved for Alzheimer treatment (Miners et al., 2011). But still, any of these medicines is not that efficient against the disease due to lack of effective and early diagnosis.

The fact that the individuals with MCI not possibly make a switch to dementia and if the diagnosis done at the stage prior to Alzheimer, fruitful therapeutics can be achieved. In order for the identification to be done at early stage to obstruct further advancement of disease, its compelling necessity of improving the diagnosis rate of AD.

Available diagnostic procedures and biomarkers

The traditional non-invasive methods/biomarkers for AD detection includes:

Amyloid beta- The most important trademark of AD is the agglomeration of amyloid beta peptides (hard plaques) between and outside the nerve cells. Cleavage of APP results in the formation of amyloid beta and the modifications in APP molecule produces amyloid beta (Aβ1-40 and Aβ1-42) in multiple quantities. Aβ1-40 is a harmless peptide and is detected in non-AD patients. However, Aβ1-42 is a non-soluble peptide and when produced in huge quantity, aggregates and thus created hard plaques of amyloid beta (Scheuner et al., 1996).

Phosphorylated protein Tau- It stabilizes neuronal microtubule (MT). In certain pathological situations, tau protein undergoes modification through phosphorylation that generates aggregates that are toxic to neurons (Avila et al., 2004). Phosphorylated tau (p-tau181) is capable of differentiating the cognitively normal groups (normal brains) from the Alzheimer brains and thus have assured its potential in early detection (Schaffer et al., 2015).

Glucose- The occurrence of metabolic deficits has long been suggested in Alzheimer's diseases. In this way, glucose can be utilized as one of a metabolic biomarker in the diagnosis of AD (Leon et al., 1983). The advances in neuro imaging technology have allowed analyzing the intimate connection between brain energy metabolism and progression of AD. Using tracers such as 18F-fluorodeoxyglucose (FDG) and 11C-Pittsbergh compound (PiB) in Positron emission tomography (PET), the activity associated with energy metabolism in brain can be detected which is now becoming the foremost and economical in vivo approach. Moreover, this technique is also applicable to determine the amyloid-related pathology and performance of neuronal circuits (Leon et al., 1983).

Cerebrospinal fluid- The reason for CSF as an ideal in AD biomarkers is the direct interaction of CSF with the ECS (Extra Cellular Space) of brain. Due to the direct interaction, CSF is capable enough to reflect the biochemical or pathological changes associated with AD. The reduced concentrations of CSF of peptide Aβ1-42 along with high concentrations of tau (normal and phosphorylated) are potent and responsive biomarkers in the early detection of AD (Blennowa et al., 2015)

Apo E and telomere length- Another biomarker that is effective in diagnosing AD is apo E, in particular, apo E4 isoform. Decreased levels of apo E4 can be correlated with neuronal degradation. The association of end length, also called telomeric length (telomere length) of mono ytes and lymphocytes with neural structure has been inspected in various studies. Studies found that shortened telomeric length in humans is indicative of emotional and mental burden, more particularly, chronic stress (Patel et al., 2011).

Magnetic Resonance Imaging (MRI)- The measures of cerebral atrophy on MRI are authoritative prognosticators that represents the progression of disease from MCI to AD (Jack et al., 1999). By MRI 3-D physical picture of the brain can be evaluated. The degree of cerebral atrophy determines the neurodegenerative track of an individual (Jack et al., 2010).

RNA Interference- A process where regulatory mechanism of gene that either restrict the pathway of transcription or by activating post transcriptional gene silencing. It has been discovered to identify different functional genes responsible for causing AD. There is a procedure designed that identify quantitatively an effective siRNA that caused inhibition of

targeted gene expression and this includes RNAi probes, fluorescent or enzymatic reporter (Orlacchio et al., 2007).

These biomarkers are non-invasive methods and detect severe stages of AD; however, these biomarkers are single dimensional, they are unable to quantify additional/ secondary responses such as oxidative stress. Thus, they lack the ability to diagnose early. Also, these for AD detection.

Further, brain imaging techniques like PET to determine metabolic changes; fMRI to detect the changes in BOLD (blood oxygenation level-dependent) responses; DTI to capture the structural pathways by the application of MRI to trace myelinated tracts; EEG to evaluate the activity of brain by measuring magnetic and electrical signals are used for the diagnosis of Alzheimer. (Bihan et al., 2001; Ogawa et al., 1990; Chugani et al., 1987; Pfurtscheller and Lopes,Chugani 1999).

Moreover, there exists a diagnostic challenge that interferes with the early diagnosis process that includes distinguishing dementia syndromes from depression, delirium, and mild cognitive impairment, diagnosing the subtype of AD (pre-dementia, mild, moderate or severe), detecting the characteristic changes that occurs within the brain almost 20 years before symptoms arise. This emerges the need of finding or identifying such biomarkers that are potent enough to indicate biological and pathogenic processes or pharmaceutical actions in response to therapeutic drugs; reflect a core pathogenic process; measure levels of amyloid beta, tau and secondary responses such as inflammation, immune responses and oxidative stress and their associated interaction with pathogenic processes, track both the progression of disease and therapeutic effects coherently. With that goal, a graphical or network-based approach for biomarker discovery can be employed as a tool. The rationale behind the idea of graphical approach is that in addition to focussing on individual node, discovery of biomarker should consider both the complex state of network plus the biology related content plus the the network state and the biological content where network revolves.

Graph theory referred to as graph analysis. Graph is the mathematical representation of functions that is used to describe or model the relation between two or more variables. The characteristic features of graphs include modelled elements (nodes) and their connections (edges). Nodes can be compared with neurons and the connections that are edges can be compared with synapses (synapse- a point of communication, from where information flows from one point to another). The motivation behind the use of graphical methods in the field of Neurosciences is the conceptualizing of brain as network. The brain can be considered as a network on multiple scales. Three main forms of connectivity have been established by neurophysiological and neuroimaging studies and are named as anatomical, functional and effective (Yang and others 2016a, 2016b). Anatomical connectivity concerns with the physical connections between areas of brain. The study of neural interactions with the neural ensembles excluding the physical connection is termed as functional connectivity (Ahmadlou and others 2014; Yuvaraj and others 2016). Effective connectivity deals with the features of functional connectivity and assess how different domains of brain affects the other brain's regions (Friston 2011). The points that attract the use of graph theory is its simplified network that can quantify brain connectivity with minimum loss of information, easy generation of graphs via data obtained from techniques like MRI, fMRI, EEG, PET, its potential to/in retrieve/retrieving information on spatial and temporal dynamics.

Role of Graph theory in Neurosciences

With reference to Neuroscience research, the graphs represent the population of specialized neurons such as temporal or prefrontal lobe. They reveal relevant details about the networking structure and functions of the brain like small worldness, connected hubs and modular organization (Bullmore and Bassett, 2011; He and Evans, 2010; Heuvel and Sporns, 2013; Bullmore and Sporns, 2009, 2012; Meunier et al., 2010). In small-worldness, nodes in

the networks reach to other node in just a small number of steps but they don't share neighbourhood (nodes are not neighbours of each other). This property can be accommodated well for the study of complex dynamics of brain. It also validates the effective segregation of information and brain network integration at very low wiring costs and energy (Watts and Strogatz, 1998). There are studies documented which suggests the topological alterations in the small-worldness property of human brain networks under several cognitive impairments; neurological and mental disorders. These studies are very much insightful for understanding the cognition's mechanisms (Braun et al., 2015; Liang et al., 2016, Bassett et al., 2011; Cao et al., 2016)

Graph theory in Alzheimer disease

In particular to Alzheimer disease, many graph theory related works have been done. The changes in graphical theoretical metrics at various stages of Alzheimer studies by M R and their colleagues. They studied path length, modularity, nodal hub and clustering coefficient as four basic measures of metrics. Path length describes an estimation of integrated node; modularity represents the discreteness of node; nodal hub is associated with the complex network structure and clustering coefficient relate to the segregation of node. Their results suggested Alzheimer as a disconnection syndrome because of the decrease in clustering coefficient and as the disease advance, the connecting phases from the anterior cingulate and medial prefrontal cortex in three important brain centers disorientated (Brier et al., 2014).
The synchronization likelihood measure was used by Sanz-Arigita et al to create their functional coupling network. They analyzed functional connectivity within the brain using path length and clustering coefficient metrics. They observed the disconnections between the occipital, frontal and parietal lobes; long distance disconnections, thus supporting the hypothesis that AD is a disconnection syndrome (Arigita et al., 2010).
The consequences of tau pathology on the brain functions were investigated by Cope, T. E. et.al. They created their network model using functional MRI (fMRI) and comprehend the pathophysio mechanisms of AD by comparing to graph metrics. They found the direct (positive) correlation between the microtubules tau and the weighted degree, meaning stronger the connection of the nodes, more the disorientated microtubules are there between and within the functional networks of brain (Cope, T. E. et.al., 2018). The low efficiency was found due to the accumulation of tau proteins in long distance connections.
Raj A, et al developed a diffusion model using network heat equation based on prion-like hypothesis in order to determine the pattern of disease advancement in which they estimate the patterns of AD atrophy development in Hippocampus from the standard information. They also validated the results of atrophy progression patterns with the data assembled in Alzheimer's Disease Neurodegenerative Initiative database (Newman, 2010; Raj, A. et.al., 2015).
The patterns of AD progression were reproduced by Peraza, L. et.al. using a susceptible-infected model. They discovered hippocampus as the probable site for the AD origination and closeness and strength as centrality measures by finding the infected and degraded connected network node's probability (Peraza, L. R. et al., 2019). These network model studies help scientists to understand Alzheimer's etiology and pathophysiological mechanisms.

Graph theory as an early diagnostic method for AD

Due to the fact that the predictable changes within brain happens about twenty years prior to the symptoms emerge and this slightly characteristic stage of symptoms offers a possible chance for restorative cures. Assessment of significant biomarkers is important for early (preclinical) diagnosing, treatment, monitoring, and continuing phases of Alzheimer's analysis. Graph theory along with rs-fMRI has been playing a key role as a biomarker for early diagnosis due to which disconnections can be disclosed at a very early phase even prior to the emergence of symptoms. For instance, it is providing a precise and validated

foundation to examine the connectivity pattern of cognitive networks quantitatively at either a local or global level.

The early signs and expressions of amyloid accumulation in ApoE4 carriers can be detected well using resting state fMRI and thus acts as promising tool for early identification and improved disease modifications.

Altered biomarkers of functional connectivity in resting state can distinguish Alzheimer's patients with the healthy ones that too with high specificity and sensitivity.

Imaging with R-fMRI can detect altered particular connections of the network and determine disruption of metabolic pathways, depositions of abnormal protein levels and atrophic patterns.

The preliminary and asymptomatic phases can be depicted with the help of graph theoretical models. Also, the modifications in the connections affecting functions of brain (functional connectivity) can be traced with graph theory and thus is capable of being employed as a tool or a biomarker for early diagnosis and disease modifying therapies (Brier et al., 2014; Botha and Jones, 2018; Wang et al., 2013; Dai and He, 2014).

Conclusion and future directions

In this paper, firstly we have reported the insights about the epidemiology, causes, available drugs, failure of dugs and the importance of early diagnosis of AD. Next, we have covered the available diagnostic procedures and biomarkers and the reason why they are not sufficient for the Alzheimer determination. Then, focussing the main motive of the paper, the detailed information on graphical theoretical measures for the pattern connectivity in network state of brain in addition with the relevancy in Neurosciences was demonstrated. Further, the studies related to graph theory with special consideration to AD has been included well along with the highlights of graph theory as an early diagnostic marker for AD. However, there are some unaddressed issues faced by Neuroscience sector in working with graphical methods that is limiting their application and potential. Result heterogeneity, node specification, ignoring the connection strength and variability in network density, inattentiveness to the association between the structure and functions of brain, ignoring the discrepancies in the density of complex network are some of the examples. Tackling the addressed issues in upcoming years can help to understand well about the neural networks functionally which will be beneficial for the early detection and thus prevention of various neurological disorders.

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