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Alzheimer's Disease under the Purview of Graph Theory Centric Genetic Networks

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Abstract: *Notice that the synapsis of brain is a form of communication. As communication demands connectivity, it is not a surprise that "graph theory" is a fastest growing area of research in the life sciences. It attempts to explain the connections and communication between networks of neurons. Alzheimer's disease (AD) progression in brain is due to a deposition and development of amyloid plaque and the loss of communication between nerve cells. Graph/network theory can provide incredible insights into the incorrect wiring leading to memory loss in a progressive manner. Network in AD is slanted towards investigating the intricate patterns of interconnections found in the pathogenesis of brain. Here, we see how the notions of graph/network theory can be prudently exploited to comprehend the Alzheimer's disease. We begin with introducing concepts of graph/network theory as a model for specific genetic hubs of the brain regions and cellular signalling. We begin with a brief introduction of prevalence and causes of AD followed by outlining its genetic and signalling pathogenesis. We then present some of the network-applied outcome in assessing the disease-signalling interactions, signal transduction of protein-protein interaction, disturbed genetics and signalling pathways as compelling targets of pathogenesis of the disease.*

Keywords: *Alzheimer's disease, Cell signalling networks, Genetic networks, Graph Centrality measures, Characteristic path length, Clustering coefficient.*

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1. Introduction

There are 1011 neurons and 104 synaptic links in a human brain. Each of which contributes to the formation of a connectome with cellular connections of magnitude one Quadrillion. To access such a huge complex network e it is irredundant to design simple models of the brain network. Graph theory serves to the creation of one such class of simple model. Graph theory is a tool to extract topological attributes of brain network models, viz., "Graphs". Graphs comprise of two vital elements called vertices or nodes and edges or links. The former stands for functional units/information sources/brain regions while the latter stands for the connections among them.

Graphs accord pertinent measures depend on the path lengths between graph vertices. It is the number of edges among them with the understanding that two vertices separated by the path of length one is adjacent or neighbors. Network hubs are formed by those vertices that are part of many paths among other vertices. In view of this, by efficiency of a network we mean the inverse of average path lengths among all pairs of vertices. So lesser average path lengths are a characteristic for higher efficiency of the network. Also, path lengths between can be employed to narrate network clustering. Paths of short length in sub graphs with adjacent vertices are features for networks with huge size clique and modularity (Latora & Marchiori, 2001; 2003). By a clique we mean a subgraph in which every vertex is adjacent with every other vertex.

Small-worldness is a crucial property that all brain networks hold in common is. Regular networks in general possess high clustering but exhibit low efficiency. By introducing only a few more random links to a regular network its efficiency can be altered from a meagre 4% to 40% (Watts & Strogatz, 1998). Further as axonal wiring is not cost effective the success of an evolutionary process depends on small-world attribute in brains.

Brain acquires counsel from systems that are attentional, perceptual, and evaluative. Integration of these distinct types of counsel is mandatory for controlled behavior (Baars, 1997; Dehaene et al., 1998). Brain is made of regions that are distinct both functionally and anatomically. Counsel is divided as per various attributes and processed in distinct brain regions. Graph theory-based observations of high clustering and integrity explain brain architecture. This tunes graphs as brain models to access brain topology.

To create a graph, one need to specify the data base based on which vertices and edges emanate. The former stand for various sources and the

latter for various connectivity metrics (Bullmore & Sporns, 2009). Intrinsic suddenly oscillation that are robust and strong induce brain activity in resting state across individuals and result in functional coherence patterns in a frequency range less than 10-1 Hz. In this frequency range the correlation values of the signal time courses are the metric measures of connectivity and exhibit between the signal sources high functional coupling. The graphs constructed on this database denote configurations of the brain functional network at rest.

When we apply the techniques of Graph theory it has to be borne in mind that a single complex graph alone will not suffice. So, it is irredundant to look for graphs with same vertex/edge cardinality for comparison. A probe (Zalesky et al., 2010) proved that basic features like network efficiency and clustering are conserved across networks with nodes size between 100 and 5000s. By vertex/edge cardinality we mean the number of elements in the vertex/edge set respectively.

One common method of defining the edge set construction is by setting cost levels of a network. A graph's cost level denotes its density and is set as the percentage of all possible edges. That is, a graph with $n = 1000$ vertices has $(1000\times 999)/2 = 999000$ possible edges and at a cost level of 5%, this graph can have 49950 edges of all possible edges. This setting could allow comparison of graphs constructed at the identical cost level. The challenge is to determine the appropriate edge cardinality of a functional brain network. Due to the dynamic nature of brain network it has spontaneous pattern of coherence and hence very hard to address the above challenge. On one side we encounter lesser to huge population of neurons and on the other side on the option of seed regions coupled with varying sources as option for vertices. As for as the option of choosing the edges of a brain network/graph is concerned a justifiable lower and upper bound could dictated by two riddles. In a brain graph no region functions and gives the lower bound and the upper bound is set by a cost level of 50%.

As of now no gold standard exists to choose an edge in the process of graph construction. However, edge selection is done depending on the correlation value with the constraint that the resulting graph should be connected. This is because brain networks cannot be disconnected. So, edge addition is done every time with the assurance that every vertex can be reached from a given vertex by a path. The first edges selected for each vertex were the one with the large correlation value between this vertex and another vertex. Next edge as per the next largest correlation value until the graph is connected. This process yields the minimum spanning tree (MST) of a graph/network. By a tree in a graph we mean the subgraph that relates

to no cycles. For each vertex further edges were included as per the correlation values among this vertex and all other vertices. This plan is called the k-nearest neighbor graph with k denoting the number of edges per vertex. This plan guarantee graph growing on equal foot (Alexander-Bloch et al., 2010). At last the edges among the vertices employed in a graph at some cost level, gives the highest order percent of edges. Graphs with huge cost level mostly consist edges at the lesser cost price. So, while averaging over a cost range on graph parameters, edges with higher correlation values in relative sense gain more weight.

For well-known graphs, several graph parameters can be determined. They can be region specific such as the degree of a vertex or the number of paths going through a vertex also refereed as hubs or collection of more densely connected vertices or subgraph that exhibit less dense coherence to the rest of the graph or (path lengths among neighbored vertices refereed as clustering. At last measures that point to the whole graph/network such as average path lengths among all pairs of vertices refereed as efficiency and Euclidean distances between vertices. To sum up, clustering and vertex efficiency describe cognitive capacity through biomarker for and exhibit brain's endurance to behavior adapt and adjustment. Euclidian distances among joined vertices describe communication pathways' length in real space. Communication through real pathways of least path length was agreed as a plan of the brain to reduce metabolic costs (Kitzbichler et al., 2011; Niven & Laughlin, 2008). Hence preferring communication through short distance is strongly visible in patients with poor performance and is viewed as a sequel of the affected brain that has to conserve energy to uphold intrinsic state values.

Processing and transport of information in the brain takes place with the help of neurons by a series of electrical and chemical signal interactions. A neuron is structured with dendrites and axons and the signals are transmitted via synapses found between two neurons that allows them to receive and transmit information. The signals used in this information processing are neurotransmitters which are transported between neurons via synaptic cleft through a mechanism of action potential. Neurons contain ion channels found in the lipid bi-layer of neuronal cells and these ion-channels are known for transportation of Na+ and K+ ions on electrochemical gradient basis across the membrane. More data on axonal communication can be referred from (Arotaritei, 2013). The axon is a cylindrical structure made up of microtubules and these microtubules are connected to each other by tau proteins making up a cytoskeleton structure. To minimize the redundancy and increase the reliability of any interaction model, Moore and

Shannon proposed Hammocks networks which could be applied to brain interaction models. A reliable model is an error free model that would function with high precision even when applied to complex structures. The human brain consists of millions of neurons (nodes/vertices) connected to each other for information transmission via axons and dendrites (edges). In the articles (Beiu et al., 2017; Rohatinovici et al., 2018), the significance of application of hammock networks in the axonal communication and the model's reliability were established.

As seen through literature, graph theory is a very relativistic technique. Its parameters are useful in comparison. A lot needs to happen while setting rules for graph construction. Also, for the probe of brain regions, algorithms for identification and classification must be developed. Graph analysis opens new vistas into how the brain network is made and how it ensures efficient counsel flow. It has potential for application in clinical research. The advances made in explaining brain networks in patients provide the way for using graph metrics as supportive tool in diagnosis of psychological brain related diseases.

Brain being a critical part of a human organ function rapidly to the requirements of the environment and adjust its behavior. While performing a task it is inclined to reconfigure its functional networks in milliseconds. Processes such as reconfiguration cannot be done with poorly sampled fMRI temporal data.

2. Cellular Signalling Networks

Network is a graphical representation of objects considered as nodes connected to each other through edges or links. Network has found its major position in biological concepts that helps in understanding the structural and functional organization of cells. A biological network represents the biological interaction of ecosystem describing relationship between same or different biological species, epidemiology describing spread of infectious diseases world-wide, immune system describing the process that takes places within an organism to protect against foreign antigens, neural networks representing the functional and structural interactions of brain, protein-protein interaction and gene regulation found in cells during DNA replication, transcription and translation processes, metabolic reactions determining the biochemical and physiological reactions inside an organism (Barabasi & Oltvai, 2004; Rangel et al., 2016). Several biology related databases are established to study and unravel the human body and its interplay in terms of cellular functions, molecular components, and

genetic interactions. The information retrieved from these biological databases are integrated into a model of gene ontology (GO). Gene ontologies helps in delineating the features of genes and its products dealing with molecular functions and cellular interaction (Gene Ontology Consortium, 2006).

Interpretation of high-throughput analysis of genomic data to explore gene regulation and gene expression is of greater interest to the data related to GO and functional association of a set of genes retrieved from biological databases such as Reactome, Kyoto Encyclopedia of Genes and Genomes (KEGG), Pathway commons the intricate direct/indirect interactions among all sorts of macromolecules. Proteins, genes, protein-protein interactions, and signal transduction mechanism can be well described using network science (Barabasi & Oltvai, 2004; Diao et al., 2007; Rangel et al., 2016; Gene Ontology Consortium, 2006).

Cell signalling better defines the cellular activity, interaction between cellular components and their coordination, which can be represented as cell signalling networks. Depending on the functions of genes and proteins, a network system may elucidate each of the specified and unstated interactions with the other surrounding molecules called as neighbours. And the biological process of transmission of array of instructions is called signal transduction inside or outside the cell. In a normal biological process, each molecule relays a message to the others and the process continues until the final target molecule is activated or expressed. Any deviations in this array of aligned signal transduction can contribute to many human diseases. The network biology helps in elucidation of functional and interactional properties of genes and proteins in definite pathways and thus their end phenotypes between healthy and diseased individuals (Aggarwal et al., 2010; Chen et al., 2010). Taking advantage of the topological data of a network, functional analysis of each component in these biological processes can be presented as gene clusters and the methods employed to determine and analyse gene clusters can be referred (Everitt et al., 2011).

3. Alzheimer's disease (AD)

Even though a precise mechanism of AD is vague, a complicated mix of factors attributable to environment, natural process of aging, routine living style of the individual, factors due to epigenetic and genetic are construed to be cause in general. AD is a dementia induced disorder that is neurodegenerative. It is characterized by impaired cognition with difficulties in the reasoning, problem solving abilities. A lot of research happened to address this global burden. This review gives an overview on genetic factors,

epidemiology and clinical symptoms employed in the diagnosis of AD. This is followed by the significance of Graph theory and networks application in understanding the complexities Alzheimer's disease progression and management is described and concluding with few open problems of possible neurobiological research questions solved by mathematical graph-network models.

We are much grateful to James M. Ellison for nicely describing about the history of AD in (2018). We provide here a brief outline of his exposition. Emil Sioli brought to the notice of Alzheimer's, the death of one of his patient Auguste Deter by sending her brain material. Alzheimer's examined her brain material microscopically with new stains to announce what we coin as amyloid plaques and neurofibrillary tangles. It was Kraepelin who honoured Alzheimer's contribution and named this type of dementia as AD. As Auguste is middle aged this disease was classified at that time (in the first decade of 20th century) as presenile dementia. However, in 1976 Robert Katzman a noted neurologist preferred to eliminate this distinction and AD is considered as main cause of dementia in older adults from early 1980's.

The historical context of Alzheimer's disease dates back to 1906.The cognitive impairment in individuals with less than 65 years of age presented as presenile dementia and subjects above 65 years of age with vascular disease presented as senile dementia. Later, around 1950, vascular explanation of senile dementia was abandoned. In 1984, the clinical characteristics and pattern of neuropathology after death was formulated which can be referred at (Dubois et al., 2007).

3.1. Epidemiology

The neuro-pathogenesis of AD is linked to complex sets of molecular mechanisms, proteins and genes. This condition is not a single gene disorder. The function of different signalling pathways and various genes linked in cognitive impairment and disease progression are being addressed, yet, there is no definite explanation of specific mechanism and genetic predisposition to the disease development and progression. The research on this disease is long way to go for therapeutic development. The molecular interaction with disease progression varies with age, genetic susceptibility, geographical location, lifestyle and ethnicity. It is believed that AD appears 15-20 years before the actual cause of mild cognitive impairment is noticed.

AD is progressive with time and diagnosed only in the later age of 60 years or above. Facts and data from the literature shows the number of older

people aged 60 years or above will increase from 420 million to 1 billion from 2000-2030 (Reitz et al., 2011). World Health Organization (WHO) has estimated that the world-wide cases of dementia are 50 million with 10 million new cases every year. Prevalence of a disease is the proportion of population with that particular condition found at a specific time. Through literature survey, the number of prevalent cases of dementia has increased by 117% from 1990 – 2016. The global prevalence of AD was 701 cases per hundred thousand in 1990 which then increased by the rate of 1.7% leading to 712 cases per 100,000 population in 2016. Also, it is observed 1.17 times greater in women than in men. The incidence rate also increases exponentially with older age of 70 – 80 years (Robinson et al., 2017). The prevalence, death and disability-adjusted life years of AD is recorded in the Table 1. Yet, the prevailing rates of AD are age-adjusted and may vary with different geographical locations, sex and ethnicity.

Table 1. Prevalence and death for dementia associated Alzheimer's disease calculated by percentage rates of age adjusted rates by location, 1990-2016.

Source: Authors' own conception

Populations	Prevalence (%)	Death (%)
High Income North America	-1.6	9.9
Southern Latin America	-4.4	-3.5
Central Latin America	-5.2	-7.2
Tropical Latin America	5	0.1
Andean Latin America	-6	-3.2
Western Europe	-8.1	-7.4
Eastern Europe	-1.2	-0.3
Central Europe	-3.5	-2.9
Caribbean	-4.9	-3.5
North Africa-Middle East	-1.0	-1.8
Southern Sub Saharan	-3	9.9
Western Sub Saharan	-2.7	3.7
Eastern Sub Saharan	-4.1	6.5
Central Sub Saharan	-2.5	8.1
Australasia	-9.1	-6.2
High Income Asia Pacific	15.6	9.2
Central Asia	-0.9	-1
East Asia	5.4	-0.5
South Asia	-4.6	16.6
South East Asia	-1.5	6.5
Oceania	-1.6	-7.3

3.2. Contribution of Risk factors in AD onset

As dementia associated AD is age-related, with rise in geriatric population will have greater impact on global public health. This disorder requires lot of care in its later stages and it is fatal. The disadvantage of the disease is that there is no definite diagnosis (biomarker detection) apart from clinical assessment (Nichols et al., 2019). The major causative factors of AD are given in the Figure 1.

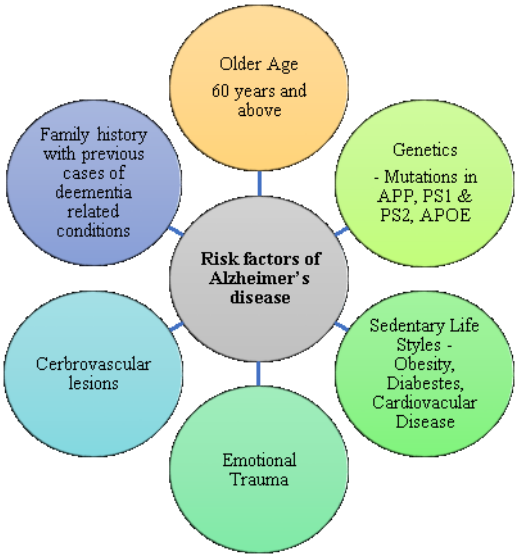

Figure 1. Potential risks factors that causes the onset of Alzheimer's's disease
APP – Amyloid Precursor Protein; PS 1 – Presenilin; PS 2 – Presenilin 2;
APOE – Apolipoprotein E
Source: Authors' own conception

3.3. Clinical Symptoms of AD

Although the memory loss is a part of aging, few other symptoms are exclusively observed in the dementia and AD patients due to the degeneration of neurons and loss of synapses in the hippocampal regions of central nervous systems. Table 2 gives different signs of impaired cognition observed in AD patients. As the disease is slowly progressive there is a long duration of disease before mortality which weakens the patients from being normal and makes them more dependent. This calls for more attention, care and time.

Table 2. Symptoms of AD and dementia in advanced form found in the moderate and later phases of cognitive impairment
Source: Authors' own conception

Age-related clinical cause of AD
Loss of Memory
Difficulty in completing routine tasks and planning
Loss of solving-problem ability
Confusion with time and place
Trouble in Vision – Cataract, Glaucoma, macular degeneration
Loss of ability to differentiate color images
Difficulty in speaking –employing appropriate word
Loosing objects easily and problems in retracing/recalling the location where the object is lost
Loss of judgmental ability
Behavioral changes - mood and personality fluctuates
Become socially insecure and inactive
Withdrawal from work

3.4. Cause of Alzheimer's disease

Pathological features of AD are: a) aggregation of amyloid b peptides referred to as amyloid plaques collected in the extracellular regions of the brain, b) aggregation of hyper-phosphorylated tau proteins contributing to the development of neurofibrillary tangles identified in spatial patterns in the intracellular regions of the hippocampus and cortical areas of the central nervous system. These proteins build up contributes to neuronal and synaptic dysfunction which promotes cognitive impairment to develop (Combs et al., 2016; Magalingam et al., 2018).

Since the discovery of AD, heterogeneous causes and recognized theories (Kocahan & Doğan, 2017) have led to the neuronal impairments of AD. A ton of new knowledge has emerged that establishes the causes, disease mechanisms and prospective therapeutics, but no impactful solution has been described to help treat the diseases. This could be due to the unpredictability of the pathophysiology of the brain, as it includes different causal genetic and epigenetic predispositions. The demanding high-level genetic techniques such as Genome wide Association Studies (GWAS), CRISPR-CAS9, RNA sequencing, Next Generation Sequencing (NGS), help to transcribe the genetic sequence of different organisms. These technologies have pulled out various genes and their alleles involved in several human diseases along with the frequency data of specific forms of

mutations. The AD-associated genes were investigated by IGAP through GWAS. Some of the gene sets reported in AD include ABCA7, BIN1, CD33, CR1, CASS4, CD2AP, CLU, DRB5, DSG2, EPHA1, FERMT2, HLA-DRB5- HLA-DRB1, INPP5D, PTK2B, SLC24A4, TREM2 and ZCWPW1). Rare variants of some AD-connected genes such as APP, APOE, TREM2 have also been reported. While they study the multiple functionalities of these genes through various biological pathways, their functions in AD pathophysiology have yet to be studied (Kim, 2018; Rosenthal & Kamboh, 2014). One may refer (Andrews et al., 2020; Jansen et al., 2019) to know the various risk gene / loci and the functional pathways associated with AD discovered through GWAS and meta-analyses experiments. The Figure 2 handles some of the popular biological mechanisms studied in the phenomenon of AD (Bobba et al., 2013, Bota et al., 2005; Chouliaras et al., 2013; Esterbauer et al., 1991; Goedert & Spillantini, 2006; Hickman & El Khoury, 2014; Keck et al., 2003; McGeer et al., 1988; Okamoto et al., 2014; Priller et al., 2006; Yakes & Van Houten, 1997).

Though numerous facets recognized to cause AD are established, not all these abnormalities are recorded together in the cases of AD. There are reported cases of co-existence of multiple other disorders along with AD. The triggering or common causal factors of such diseases are to be researched deeply. The similarities found in various disease biology, pathways and genomic data has to be further investigated to unravel each one's function and interlinks in the pathological development of the disease. In order to achieve early detection of the disease, provide personalized medical approach, identify the prompt therapeutic target and establish disease management, it is significant to correlate and understand the hidden underlying concepts of the disease. This lays an emphasis on delineating the complexity and intricate details of disease mechanism through the right pavement of network biology.

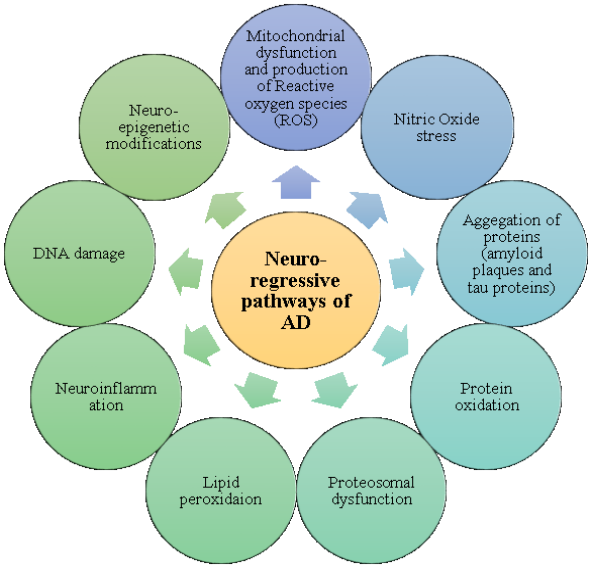

Figure 2. Prevailing neuro-regressive pathways
Source: Authors' own conception

4. Network approaches for AD

A recent study on association of disease-pathway in human diseases was carried out by employing a bipartite Random Walk with Restart on heterogeneous network (RWRH). Network of disease similarity and pathway similarity and their association was constructed by retrieving data from various biological databases such as GO, KEGG, Reactome, OMIM. Based on the similarity scores and linkage analysis, primary and intermediate nodes were detected, and edges were linked to adjacent nodes and formed a specified disease-pathway network (Ghulam et al., 2020). This network of disease-pathways defines the genetic connections in different biological pathways with varied disease. The combination of biological experiment findings with graphical methods will aid in forecasting potential relationships in a disease between genes, proteins and signalling pathways. The cumulative principles of graph theory and cellular signalling have helped to define the relationship between TGF-β signalling and AD pathway incorporating clustering and semantic mining. The signalling pathway graph was created based on social network analysis (SNA) for cluster identification. This analysis gives the network of semantically enriched common genes and protein linked to both pathways (Rangel et al., 2016). Similarly, exploiting graph principles such as centrality, modularity, and mining, we might find

essential biological pathways, analyze the functional similarities between gene communities, and build protein interaction networks. Another study revealed relationships between AD and type 2 diabetes through the use of shared causal pipelines. Through the data collected from GWAS, GO, Reactome, random directed acyclic networks were created by linking some of the common genes and employed a graphical approach of causal network to assess the associations between these two diseases. This approach established 13 genes and 16 common pathways between AD and type 2 diabetes, including 101 associated methylated genetic nodes linked to both the diseases described by causal networks (Zixin et al., 2020). This causal network approach can establish close association within/between genes and proteins denoted as nodes in graph theory.

4.1. Genetic Networks and AD

The genetics of Alzheimer's disease at the molecular level has evolved as alterations one after the other as interactions that are molecular centric in pathways to elucidate processes governing the states that are pathophysiological. Investigations of late onset Alzheimer's disease have exposed critical genomic regions connected to the disease and it is even today not known the actual reasons. A vast quanta of genetic data governing late onset has enables us to understand causally described processes to it. In (Zhang et al., 2016) the authors have discussed distinct features network-based methods pointing to devising network of genes linked to AD from post-mortem samples of tissues of brain. They explained at length replica of network methods that are multi scalar that combines interaction and causal gene to probe gene expression, DNA. They made use of co-expressed weighted gene network study to build networks that are multi-tissue centric to explain interactions that are gene to gene to assess the connectivity changes due to late onset of co-expressed genes in comparison with the normal case. Regulatory connections that are causal between the genes along every module are found by framework of inference through Bayesian approach in network form. It is used to collate the counsel due to gene expression (Zhang et al., 2016). In (Kelly et al., 2020) the authors carried out a huge up to date probe of AD network in blood depending on its gene expressions. They located among the networks of disease and healthy control, the un-conserved modules and pertinent genes as hub with transcription factors. The module corresponding to lipolysis regulation in adipocytes and interaction that is neuroactive in ligand-receptor are not conserved in AD networks of both cases of healthy and mild cognitive impairment. Here the vital TRPC5 and BRAP lots are conceived as main

targets for treatments of therapeutic type. Their investigation showed that AD possess in common genetics that are impaired and located pathways that are interesting (Kelly et al., 2020).

4.2. Google Knowledge Graph for AD

Graph theory is capable of briefly estimating the attributes of complex structure and replicating interconnections (denoted by edges) among brain lots (denoted by vertices). It can bring out the topological attributes and scrutinize the various brain network states through measures such as the vertex degree, clustering coefficient, characteristic path length, small-world attribute, betweenness centrality and global/local efficiency (Bullmore & Sporns, 2009).

To reap the benefit from graph theory and pattern recognition, these two can be mingled through knowledge graph measures that could act as trained classifiers features. It further expands the classifiers to determine functional data from various group of cases that are unseen. This well explains hard brain conditions such as pathology. Because of high dimensional type of the fMRI data, features that are of graph theoretical type about brain network are also of higher dimensional and hence resorting to selection procedure is irredundant. Various options are weighed and the best one is chosen for the algorithm-based handling.

The automated anatomical labelling technique divides the whole brain into 90 distinct lots. These lots are represented as vertices to build brain network. The signal corresponding to each vertex is achieved by expected value of the time series of all voxels within the lots. Then edges of the brain network are functional linking of all pairs of automated anatomical labelling lots through the correlation coefficient due to Karl Pearson. The resulting functional matrix that is undirected and weighted is a dense knowledge graph. It has to be made sparse with the setting threshold value p to lie between 0 and 1. Set diagonal weights that are self-links to zero. If value of p is high, then it becomes a dense knowledge graph by allowing weaker edges with respect to low and noisy correlations. Else, set a low value to p to drop more edges and it leads to a knowledge graph that is disconnected and hence its metrics cannot be found.

Hence for the classifiers, it is clinically recommended to employ measures of brain network as input features. When the knowledge graphs are built, compute various metrics that are knowledge graph centric to explain the functional state of the brain and employ them as features to subject the classifier to test and train. Clustering coefficient normalized local efficiency and local efficiency are the three measures of functional

segregation to characterize the brain ability for processing to occur within densely interlinked cluster of distinct brain lots. Characteristic path length and global efficiency are two measures of functional integration to assess the brain strength for integrating the counsel from distributed lots. Then the three local vertex centred measures such as betweenness centrality, degree, and participation coefficient along with the small-world attribute of the network to probe the attributes of 90 automated anatomical labelling brain lots. These graph measures are found depending on the weightiness of the graph corresponding to its adjacency matrices through the toolbox of Brain link (Rubinov & Sporns, 2010).

The clustering coefficient in weighted sense is an expanded version of binary clustering coefficient. Binary clustering coefficient of vertex x is the proportion of edge count among pairs of adjacent elements of the vertex x to the neighbour to neighbour edge count admissible. The mean clustering coefficient was determined through clustering coefficients of individual vertices which points to the existence of clustered linking about individual vertices. Local efficiency assesses the capacity of a network to transfer counsel at the local level. Normalized local efficiency is determined as the proportion of local efficiency to the global efficiency. These measures pertain to functional segregation of the brain knowledge graph. The characteristic path length is often employed measure of the network integration. It is conceived as the expected value of least path lengths among each pair of vertices in the network. Path length for a weighted knowledge graph is determined as the total sum of reciprocal of weights of each edge. Global efficiency is conceived as the expected value of the reciprocal of least path length and it finds the capacity of a network to transfer counsel at the global level (Rubinov & Sporns, 2010).

The degree is a viable measure of centrality for a weighted undirected knowledge graph and is conceived as the sum of weights of links joined to a vertex. Large value of the degree implies more interaction. The knowledge graph's modular system is found by looking at the node arrangement into huge modules so that highest count of links lies within groups and least count of links lies between groups. When the knowledge graph modules are spelled, the diversity of links among vertices can be found by the participation coefficient. Vertices with a huge participation coefficient implies varied links agreed as link hubs. It facilitates integration in between-module of the knowledge graph. But vertices with high-degree and low participation coefficient are known as provincial hubs they take part in interactions of within-module type. Then one more measure of centrality called betweenness centrality is dependent on the concept of least paths. It is

conceived as the normalized sum of estimated proportion of all least paths that pass through that vertex. The brain knowledge is designed obeying small world attribute. It gives a wise mix of functional segregation and integration. Small-worldness are conceived as the ratio of clustering coefficient and characteristic path length. The values of clustering coefficient and characteristic path length are normalized by their corresponding random knowledge graph values (Bullmore & Sporns, 2009; Rubinov & Sporns, 2010).

A statement in biology can be given a visual treatment by denoting by denoting it as a triple consisting of [subject, predicate, and object]. Note that here a subject point to a statement in a biology and the predicate points to the relation that links the subject and the object. Interpreted using the terminology of graph theory, a subject corresponds to vertex; a predicate corresponds to the incidence relation between vertex and edge; an object corresponds to edge. By following this convention one can create a knowledge graph exploiting the statements from biology. Lately, Google has undertaken a massive exercise to create such a knowledge graph for the purpose of ease and visual treat for further probe and analysis. A very useful counsel can be drawn by looking at the subgraphs or subnetworks of protein-protein interaction networks of both normal and AD affected people. One can extract the data of protein-protein interaction of healthy people, the following inference which is a union of two connected components A and B, where A consists of 6 vertices denoting the genes: APP, ADAM10, BACE1, MIF, MAPT, LRP1 and B consist of 2 vertices denoting the genes PTGS2 and IL1B. Here A is a star graph and B is a tree on two vertices. See Figure 3.

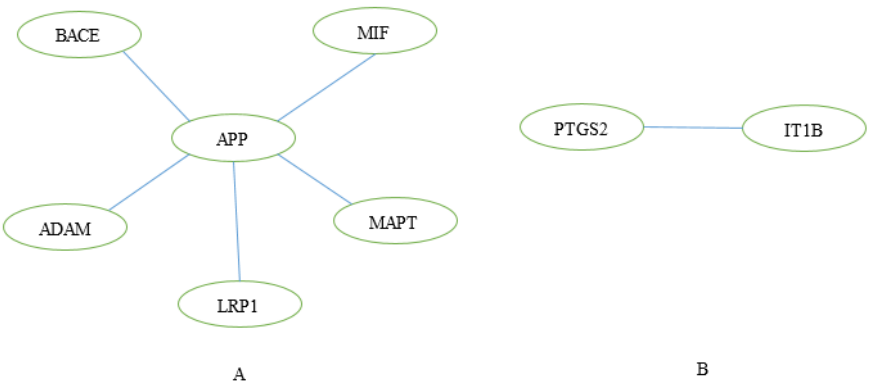

Figure 3. Subgraph from normal person's protein-protein interaction network
Source: Authors' own conception

One can extract the protein-protein interaction network of an AD affected person, the following inference which is a union of tree connected components A, B, C where A consists of 4 vertices denoting the genes: STAT4, JUN, MAPK3, STMN2; B consists of 5 vertices denoting the genes: APP, BACE1, LRP1, DLG4, TGFB1; C consists of 2 vertices denoting the genes: MAPT, TUBA4A (Iyappan et al., 2016). See Figure 4.

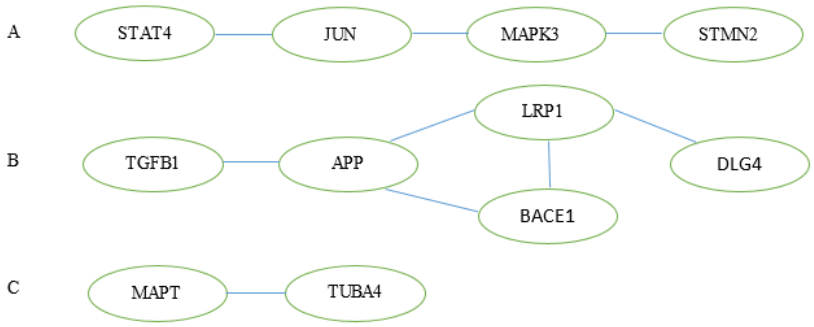

Figure 4. Subgraph from AD affected person's protein-protein interaction network
Source: Authors' own conception

5. Graph/Network dependent proposition of AD

Network outlook make use of muti-omic data to find out pathways and susceptibility genes in AD. The following networks are associated with AD. 1) Clathrin-mediated receptor endocytosis and MAPK/ERK. Here turn upside down of the pathway receptor conciliated by clathrin result in improved levels of APP paying way to progression of disease (Hallock & Thomas, 2012), 2) microglia and Immune system (Zhang et al., 2013), 3) microglia-enriched modules and Astrocyte-specific (Miller et al., 2013), 4) innate immune response and Myelination (Humphries et al., 2015), 5) AD progression network modules (Kikuchi et al., 2013), 6) APOEε4 stratification dependent co-expression modules (Jiang et al., 2016), 7) metastable proteins susceptible to aggregation inducing down regulated gene network (Ciryam et al., 2016), 8) myelination network with hypomethylation patterns (Humphries et al., 2015). In literature one can see umpteen instances on how networks could hasten personalized treatment. Scrutiny of network modules that are unstable in various brain regions due to protein interaction, specifically, in the AD patient's entorhinal cortex. At different Braak stages presence or otherwise of a lot of protein interactions give indication regarding upward progression of AD through network modules

(Kikuchi et al., 2013). Similarly network exploration of 6 critical brain regions observed in AD patients' unravelled a hub of 136 genes where 72 of them well agree with the Mental State diagnose test and cognitive scores confirming progression dreadfulness of AD. APOEε4 is a grave risk factor for late onset of AD and responsible for greater than fifty percent of the affected cases. The carriers of APOEε4 exhibit clinical and pathological traits unlike in non-carriers. Further APOEε4 carriers' co-expression modules are full of a) disorders that are hereditary, b) diseases that are neurological and c) function of nervous system. However, modules of non-carriers were enhanced in diseases that are cardiovascular and immunological thereby conveying that several processes that are biological could cause a havoc with late onset of AD (Jiang et al, 2016). Network scrutiny other than determining genetic confederacy in share mode, enrol the evaluation of a similarity matrix spot clusters of gene associated to repair of DNA, metabolism due to RNA, and metabolism induced by glucose in AD (Calderone et al., 2016). Pertinently, conventional gene ontology is not used to detect these pathways. Latest meta-scrutiny of brain tissue of approximately 1600 microarrays of AD affected patients pronounce a set of genes that are down regulated related to metastable proteins accord to aggregation (Ciryam et al., 2016). So, proteome homeostasis network targeting components could facilitate therapeutic moment for diseases that are neurodegenerative. Temporally regulated Gene expression that are also spatial is created by DNA methylation. Such epigenetic changes could impact a global gene expression. Neurodegenerative disorders and aging can be scrutinized through epigenetic changes in gene expression. Further positive correlation was detected in AD affected individuals regarding cognitive repair, working memory, and acceleration epigenetic age coupled with episodic memory. For this various tool that are computational are put in place to integrate data that is epigenetic in networks.

6. Conclusion

Through network approach aided by graph theory attributes and the advantages of visual representation and pathway-centred strategy, we reviewed various mechanisms that are of genetic and pathogenetic types governing AD. Our review provides significant ideas for comprehending the mechanisms that are molecular with reference to AD. The article provides the applied concepts of graph theory principles of centrality, betweeness, pathlength, small-worldness, clustering coefficient, bipartite random network, causal path network, social network analysis with semantic mining, weighted network analysis and knowledge graph in accommodating genetics

and signalling interactions in the clinical course of development of AD. This gives an impression of the significance of network theory applications in neuroscience and disease biology mechanisms. More combined work of graph theory and biology can help elaborate the unknown causes and interaction networks in the study of any human disease.

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