Graph Theory: A Primer to Understanding Resting State fMRI

Tulane University SCHOOL OF MEDICINE

Tulane University School of Medicine Department of Radiology

Millie Yu MS2, Quan Nguyen, MS3, Jeremy Nguyen MD, Enrique Palacios MD, Mandy Weidenhaft MD

What is Graph Theory?

- Simple stated, graph theory is the study of graphs.
- Graphs are mathematical structures that can be utilized to model pairwise relations between objects.
- A graph in this context is made up of nodes or points which are connected by edges or arcs.

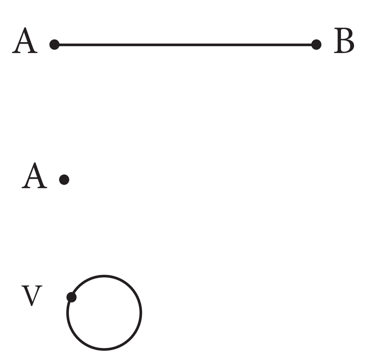
GRAPH THEORY has extensive applications:
- Applied Mathematics
- Electrical Engineering
- Computer Science
- Computer Network
- Medical Science
- Linguistics
- Sociology

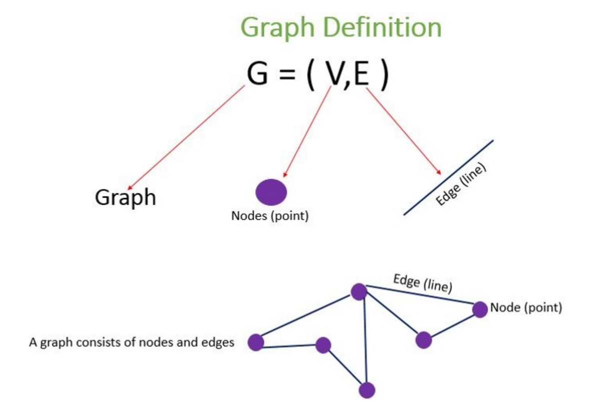
What are the fundamental constructs in Graph Theory?

Edge
- A line that connects two nodes
- Must have a starting node and ending node
- A single node may form many edges

Node
- A point where multiple edges meet
- Represented by a letter

Loop
- An edge drawn from a node to itself

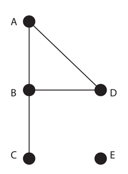




What are adjacent nodes and what are parallel edges?

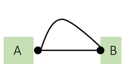
Two nodes are adjacent if there is an edge between the two nodes.

Example:
'A' and 'B' are adjacent nodes that share the common edge 'AB'
'A' and 'D' are adjacent nodes that share the common edge 'AD'
'B' and 'D' are adjacent nodes that share the common edge 'BD'
'B' and 'C' are adjacent nodes that share the common edge 'BC'



Parallel edges are a pair of nodes connected by more than one edge.

Example:
'A' and 'B' are adjacent nodes by two edges, 'AB' and 'AB', thus this is a parallel edge.



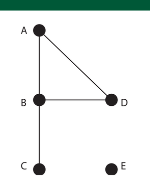
What's a Degree of Node?

The degree of node is the number of nodes adjacent to a particular node(V), denoted as deg(V).

Example:
Node A has 2 adjacent nodes (B,D) → deg(A)=2
Node B has 3 adjacent nodes (A,D,C) → deg(B)=3
Node E has zero adjacent node → deg(E)=0

Special types of nodes

There are special types of nodes include pendant nodes and isolated nodes:
- A pendant node is a node with one degree.
- An isolated node is a node with zero degrees.



<u>Example:</u>
Node C has one adjacent node, deg(C)=1, C is a pendant node
Node E has no adjacent node, deg(E)=0. E is an isollated node

What are the basic properties of a graph?

Distance between two nodes:
- The number of edges in the shortest path between two nodes.
- Example: distance between Node A and Node B is denoted as d(A,B) = 1

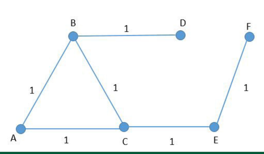
Eccentricity of a node:
- The maximum distance between a node to all other nodes.
- Example: eccentricity of Node A is denoted as e(A) = 3, since maximum distance from node A to F is 3

Radius of a graph:
- The minimum eccentricity from all the nodes. From all the eccentricities of the nodes in a graph, the radius of the graph is the minimum of all those eccentricities.
- Example: radius of Graph G is denoted as r(G) = 1, since the minimum distance is 1 from all eccentricities

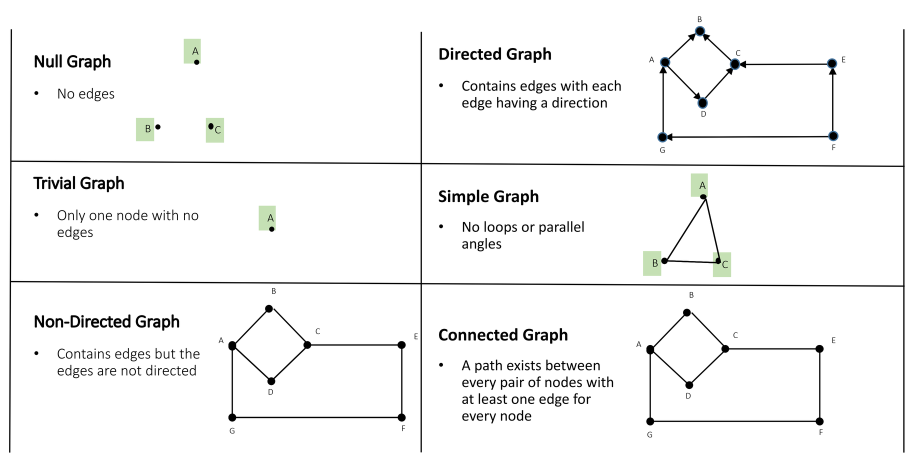
Diameter of a graph:
- The maximum eccentricity from all the nodes. From all the eccentricities of the nodes in a graph, the diameter of the graph is the maximum of all those eccentricities
- Diameter of Graph G is denoted as d(G).
- Example: e(A) = 3, e(B) = 3, e(C) = 2, e(D) = 4, e(E) = 3, e(F) = 4
- Therefore, diameter of the graph is 4

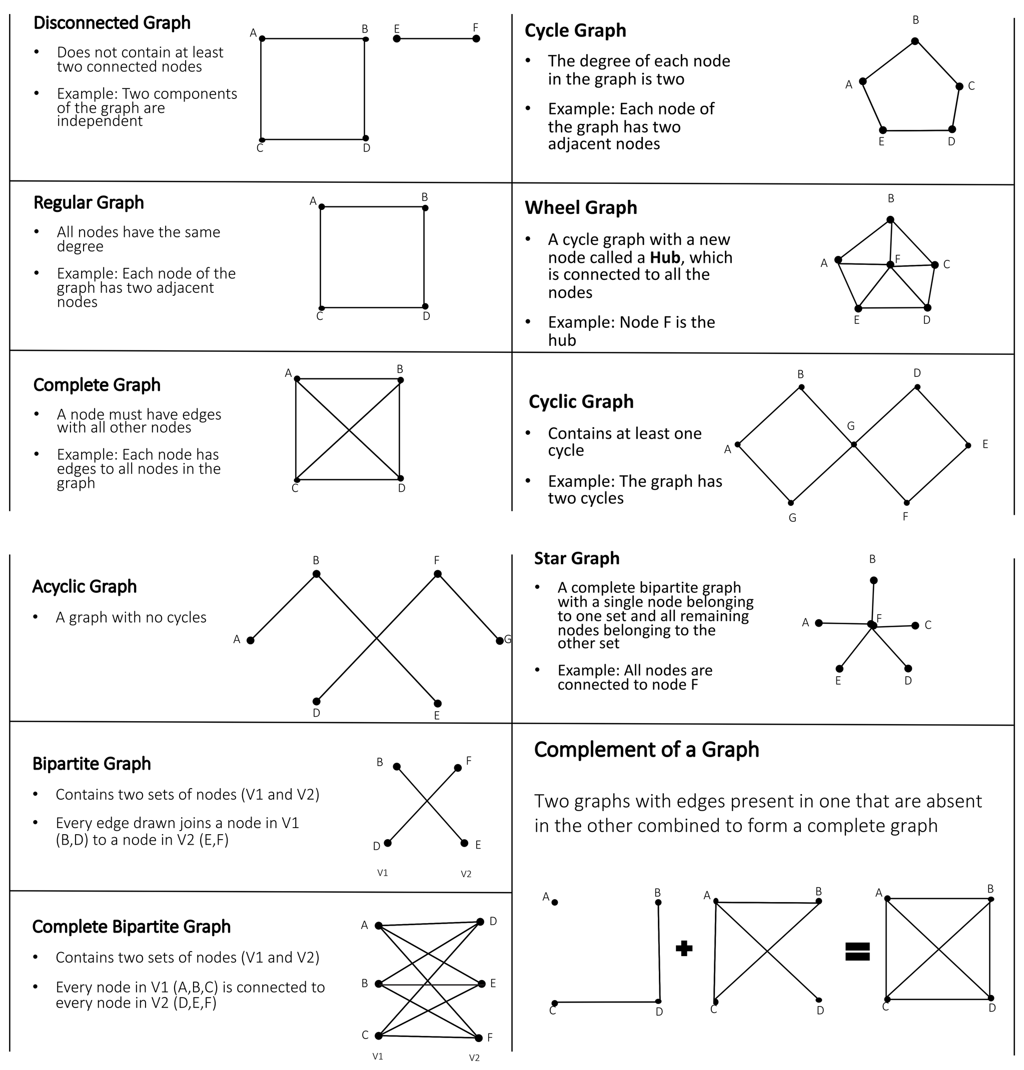
Distances between nodes:
d(A,B) =1
d(A,C) =1
d(A,D) = 2
d(A,E) = 2
d(A,F) = 3

Using this graph for example to calculate the distance, eccentricity of a node and radius, and diameter of a graph:



Graphs can take simple or complex forms. Some basic types of graphs





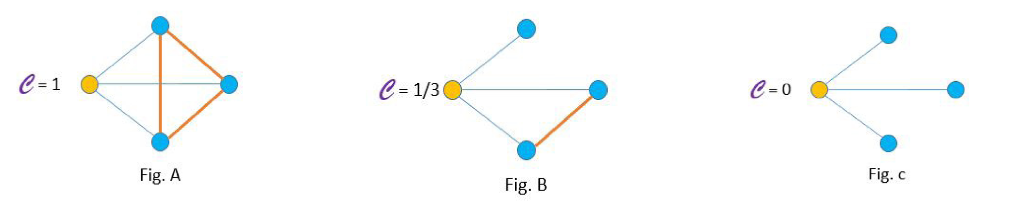
Some important key graph properties

- Clustering (clustering coefficient)
- Characteristic path length
- Node degree and degree distribution
- Centrality
- Modularity

Clustering coefficient

- Clustering reflects the level of local connectedness within a graph.
- A clustering coefficient is a measure of the degree to which nodes in a graph tend to cluster together.
- The local clustering coefficient of a node in a graph quantifies how close its neighbors are to being a complete graph. The value of clustering coefficient ranges from zero (0) to one (1)

To explain the concept of clustering, consider the examples of three graphs below.
The yellow node in each graph has three adjacent blue nodes, which can have a maximum of 3 connections among them.
- Figure A, all three possible connections are constructed (red edges), giving a local clustering coefficient C = 3/3 = 1.
- Figure B, only one red edge is constructed and 2 red edges are absent, giving a local cluster coefficient C = 1/3.
- Figure C, none of the edges are constructed among the blue nodes, giving a local clustering coefficient C = 0/3 = 0.



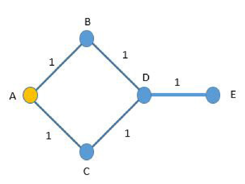
Characteristic path length

- Characteristic path length is defined as the average number of steps along the shortest paths for all possible pairs of network nodes.
- This basically tells you how close a node of the graph is connected to every other node in the network.
- This will give you insight on the level of global connectivity of the graph and tell you how efficient information can be integrated between different regions.

The characteristic path length (CPL) of node A equals to the average of the steps of AB, AC , AD and AE.

CPL = (1 + 1 + 2 + 3)/ 4 = 1.75

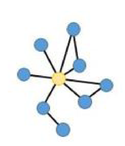
Distance of AB → d(A,B) = 1
Distance of AC → d(A,C) = 1
Distance of AD → d(A,D) = 2
Distance of AE → d(A,D) = 3



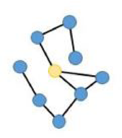
Centrality

Centrality is used to indicate the most IMPORTATNT nodes in the graph.

There are different ways that one can characterize Centrality:
- **Degree Centrality:** Number of edges incident on a node
- **Closeness Centrality:** The average length of the shortest path between a node and all other nodes in the graph. The more central a node is, the closer it is to all other nodes.
- **Betweenness Centrality:** The number of times a node acts as a bridge along the shortest path between two other nodes.
- **Eigenvector Centrality:** A measure of the influence of a node in a graph



Seven (7) edges to yellow node

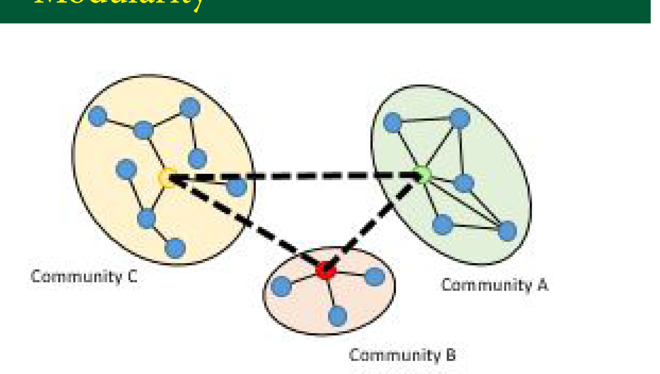


Three (3) edges to yellow node

The simplest Centrality is the Degree Centrality which is simply the number of edges to a node. The remaining Centrality types are more abstract requiring higher mathematical representation

Modularity

Modularity depicts to which extent groups of nodes in the graph are connected to the members of their own group (formation of communities), thus indicating the formation of sub-networks within the full network.



Fundamental concept of Functional MRI (fMRI)

- fMRI is a magnetic resonance imaging technique that measures the change in blood oxygenation over time
- Blood oxygenation levels can change rapidly following the activities of neurons in a brain region
- fMRI allows for localization of brain activities on a second-by-second basis and within short distance of its origin

What is BOLD imaging?

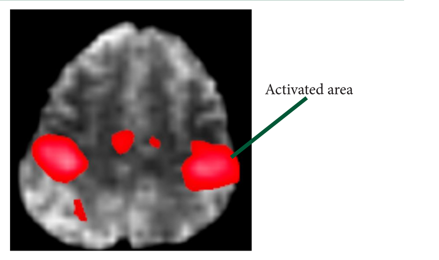
- BOLD stands for blood oxygen level dependent
- BOLD imaging is the standard technique used in fMRI
- BOLD fMRI utilizes T2* sequence
- BOLD signal is strongly influenced by hemoglobin (Hb) and deoxy-hemoglobin (dHb) in blood
- Hb is diamagnetic with small susceptibility effect → small signal loss
- dHb is paramagnetic with large susceptibility effect → large signal loss

Neuronal activity is associated with following physiologic processes:
- Cerebral blood flow (CBF)
- Cerebral blood volume (CBV)
- Cerebral metabolic rate of oxygen (CMRO2)
- Blood oxygenation

An increase in neural activity leads to the following events:
- Increased CMRO2 results in increased oxygen extraction → increased dHb → rapid dephasing → increased signal loss
- Concomitant increase in CBF which overshoots the increased demand of oxygen → increased influx of Hb
- Resultant increased Hb/dHb → signal gain

BOLD imaging principle

BOLD Images are generated by differentiating between regional discrepancies in cerebral blood flow to delineate regional activity.
Cerebral blood flow discrepancies give rise to local magnetic field inhomogeneities arising from different states of hemoglobin, which are used to create an image



What is the difference between fMRI and resting-state fMRI?

- fMRI uses task based or stimulus driven actions performed by the subject to measure brain function.
- Resting state fMRI is a method of functional brain imaging that measures the level of co-activation between anatomically separate brain regions during when a subject is not performing an explicit task.
- Resting state fMRI measures spontaneous, low frequency fluctuations through BOLD imaging.

How do fMRI findings correlate to brain functional activity?

- Functional connectivity is defined as the temporal dependence of neuronal activity patterns of anatomically separated brain regions.
- fMRI studies have shown the feasibility of utilizing time-series signal measured during resting state to examine the functional connectivity between brain regions.
- Resting state fMRI experiments have shown that a vast amount of spontaneous activity that is highly correlated between multiple brain regions.

How do we utilize the fMRI data to analyze the brain connectivity?

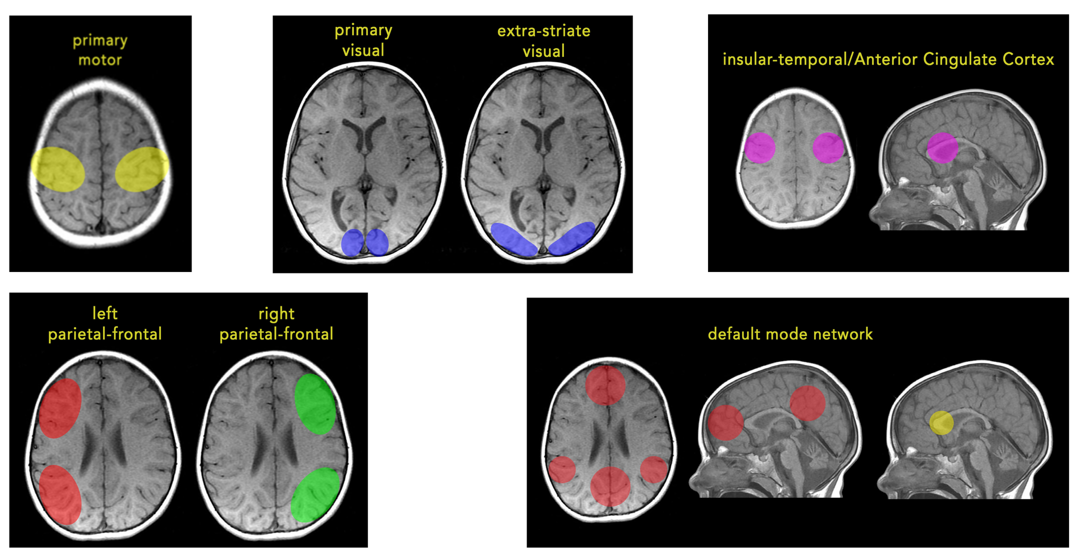
Using fMRI data, a technique called "MODEL-FREE METHOD" is used to explore the connectivity of the brain as a whole.
- Model-free methods are designed to look for general patterns of unique connectivity across brain regions.

Several model-free methods have been suggested and successfully applied to resting-state time-series, including:
- Principal component analysis (PCA)
- Independent component analysis (ICA)
- Laplacian and normalized cut clustering

Resting State fMRI Networks

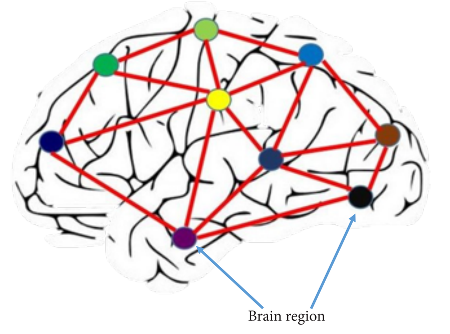
The resting-state networks features:
- Anatomically separated
- Functionally linked brain regions
- High level of ongoing functional connectivity during resting state

The most consistent reported resting-state networks across these studies include:
- Primary sensorimotor network
- Primary visual and extra-striate visual network
- A network consisting of bilateral temporal/insular and anterior cingulate cortex (ACC) regions
- Left and right lateralized networks consisting of superior parietal and superior frontal regions (*reported as one single network)
- Default mode network consisting of precuneus, medial frontal, inferior parietal cortical regions and medial temporal lobe



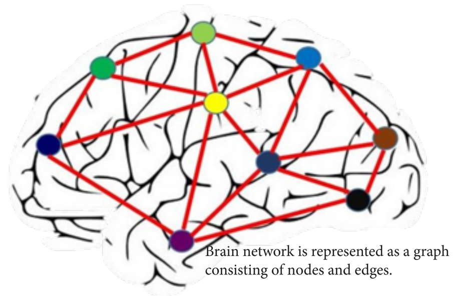
Brain Functional Connectivity

- The brain forms a very efficient network.
- This so-called brain network consists of a large number of different brain regions that each have their own task and function, which continuously sharing information with each other.
- The brain regions thus form a complex integrative network in which information is continuously processed and transported between structurally and functionally linked brain regions.



Graph Theoretical Model of the Brain Network

- Graph theory provides a theoretical framework to examine the topology of complex networks in general.
- Graphical analysis is a specific approach to analyzing brain networks in which the brain network is represented in the mathematical "graph."
- Graphical analysis can reveal important information about both the local and global organization of functional brain networks.



Brain network is represented as a graph consisting of nodes and edges.

Brain Network Scale

Microscale organization → The organization of nodes and edges in the network

Mesoscale organization → The arrangement of nodes into modules or communities

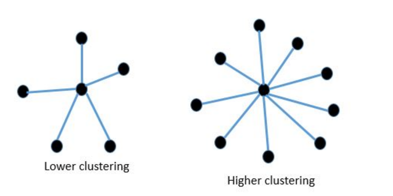
Macroscale organization → Single scalar values representing a property of the network

Key Properties of Brain Network

Some key properties of brain networks that can be described graph theory are:
- Clustering (clustering coefficient)
- Node degree and degree distribution
- Node centrality
- Characteristic path length
- Modularity

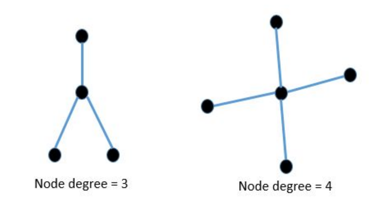
Clustering

- Clustering provides Information about the level of local neighborhood clustering within a graph.
- This describes how close the neighbors of node are connected themselves.
- This indicates the level of local connectedness of a graph.
- Clustering is characterized by clustering-coefficient.



Node degree

- K = the number of edges linked to a node
- This is a measurement of the connectivity of a node with the rest of the nodes in a network.

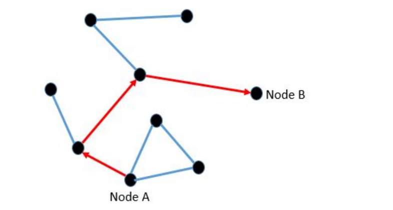


Degree distribution

- This is the probability that a node chosen uniformly at random has degree k.
- This is equivalent to calculating the fraction of nodes in the graph having degree k.
- Networks can be classified into different categories based on degree distribution.

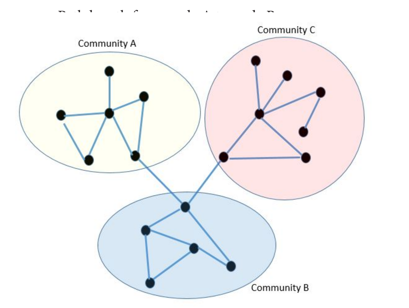
Characteristic path length

- This is the path length describing how close on average a node is connected to every other node in the network.
- This provides information about the level of global connectivity of the network.



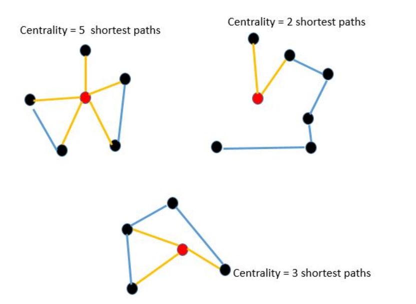
Modularity

- Modularity is the degree to which a network is organized into a modular or community structure.
- Modules consist of a set of nodes with denser links among them but sparser links with the rest of the network.
- Detection and characterization of modular structure in the brain system can help to identify groups of anatomically and/or functionally associated components that perform specific biological functions.



Node Centrality

- Node centrality indicates the number of shortest travel routes within a network pass through a specific node of the network.
- This quantifies how important a node is within a network.
- A node with high level of centrality indicates that it has a key role in the overall communication efficiency of a network.

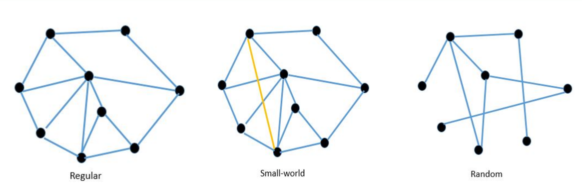


Several different metrics exist for measuring nodal centrality:
- Node degree = the number of edges linked directly to it
- Nodal efficiency = the ability of a node to propagate information with the other nodes in a network
- Closeness centrality = the average distance from a node to all the other nodes in a network
- Betweenness centrality = the influence that one node has over the flow of information between all other nodes in the network.

A node with high centrality is considered a hub in the network.

Major Types of Networks

Three major types of networks:
- **Regular organization (lattice)**
  - High local clustering, high path length
- **Small world organization**
  - High local clustering, low path length
- **Random organization**
  - Low local clustering, low path length



- Graph theoretical analysis of the brain revealed that the brain network showed a small-world network.
- Small-world network features:
  - High level of local clustering → High level of local connectedness
  - Short path lengths linking different brain regions → short average travel distance (i.e. low path length) between the nodes of the network
- Small world organization combines a high level local efficiency with a high level of global efficiency.

Conclusion

- Graph Theory is the study of graphs consisting of nodes and edges.
- Graph Theory can be utilized to perform mathematical analysis of the brain networks.
- Important graph properties in the analysis of brain networks include clustering, node degree and degree distribution, characteristic path length, centrality, and modularity.
- Resting state fMRI can be utilized to map the functional connectivity of the brain networks.
- Graph theoretic analysis of resting state fMR imaging is recognized as a significant analytical tool for describing the human brain networks.
- Graphical theoretic analysis can reveal important information about both the local and global organization of functional brain networks.
- Brain network consists of a large number of different brain regions that each have their own task and function, which continuously share information with each other.
- Brain network can be characterized as a small-world network that has high level local efficiency with a high level of global efficiency.

References

1. Van den Heuvel M, Hulshoff Pol H. Exploring the brain network: A review on resting-state fMRI functional connectivity. European Neuropsychopharmacology. 2010;20:519-34.
2. Graph Theory Tutorial. https://www.tutorialspoint.com/graph_theory/. Accessed December 9, 2017.
3. Smith S, Vidaurre D, Beckmann C, et al. Functional connectomics from resting-state fMRI. Trends in Cognitive Sciences. 2013;17(12):666-82.
4. Bullmore E, Sporns O. Complex brain networks: graph theoretical analysis of structural and functional systems. Nature Reviews Neuroscience. 2009;10(3):186-98.
5. Ruohonen K. Graph Theory. TUT Finlandia MAT-62756 Graph Theory course.
6. Wang J. Graph-based network analysis of resting-state functional MRI. Frontiers in Systems Neuroscience. 2010;4(16).
7. Sadaghiani S. Graph analysis of fMRI data. UCLA/Semel Advanced Neuroimaging Summer Program 2015.
8. Lee M, Smyser C, Shimony J. Resting-state fMRI: a review of methods and clinical applications. American Journal of Neuroradiology. 2012;34(10):1866-72.

Author Contact Information:

Nguyen, Jeremy; MD, MS – Associate Professor of Radiology, Vice Chair of Academics, Tulane University School of Medicine, New Orleans, LA jnguye2@tulane.edu
Yu, Millie; MS – Second Year Medical Student, Tulane University School of Medicine, New Orleans, LA myu2@tulane.edu
Quan Nguyen, MS – Third Year Medical Student, LSU Health Science Center, New Orleans, LA
Enrique Palacios; MD –Professor of Radiology, Tulane University School of Medicine, New Orleans, LA epalaci@tulane.edu
Mandy Weidenhaft; MD - Assistant Professor of Radiology, Radiology Residency Program Director Tulane University School of Medicine, New Orleans, LA mcrause@tulane.edu

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