Progression of Degenerative Connectivity in Alzheimer's Disease

Michael Aviles
Department of Physics and Astronomy
Youngstown State University

Advisor:
A. Prieto-Langarica

Department of Mathematics and
Statistics Youngstown State University

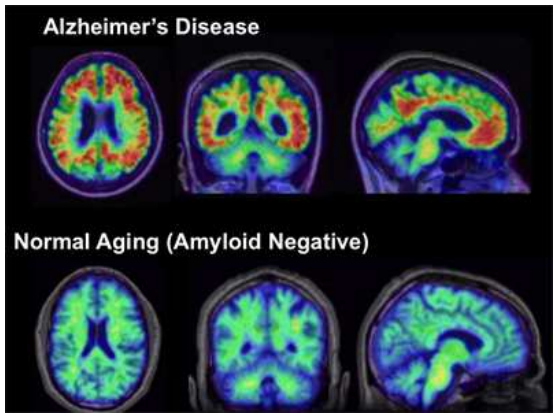
Senior Thesis

What is Alzheimer's Disease?

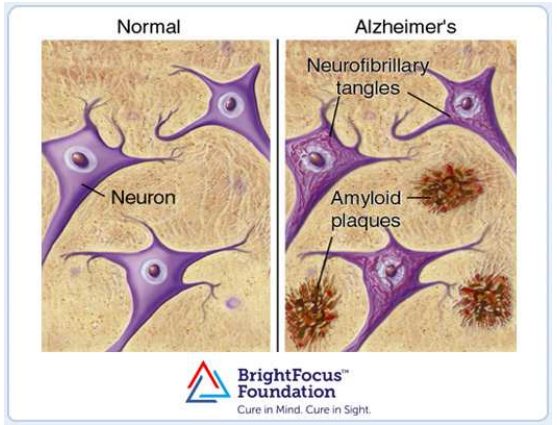
- Alzheimer's disease is a progressive degenerative disease that attacks the brain's neurons, resulting in memory loss, thinking language skills, and behavioral changes.
- These neurons break connections with other nerve cells and ultimately die. For example, short-term memory fails when Alzheimer's disease first destroys nerve cells in the hippocampus, and language skills and judgment decline when neurons die in the cerebral cortex.

Cause of AD

The exact cause of Ad is unknown. It is thought that the progression of amyloid-β plaques and neurofibrillary tangles is what causes AD.



FigureAmyloid-β Plaques



FigureNeurofibrillary Tangles and Amyloid-β Plaques

Life Expectancy

- Alzheimer's disease typically progress over a span of 2 to 20 years, and people live on average for 8 to 10 years with the disease.
- Top 10 leading cause of death in U.S.

Diagnosis

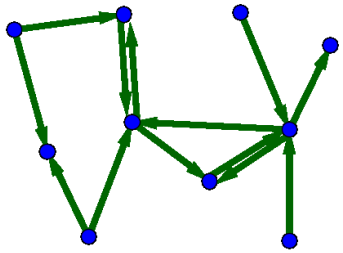
- Only 90% accurate
- Only a 'probable' diagnosis can be made
- Early detection is key to treating AD
- AD is currently confirmed by autopsy

Graph Theory

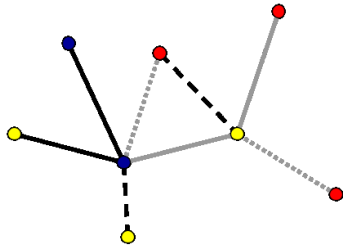
Grapgh theory is the study of graphs!!!

- Useful to study relationships
- Points called nodes
- Lines called edges
- Directed and undirected graphs
- Weighted and unweighted graphs

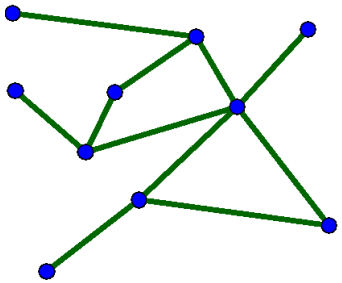
Graph Theory



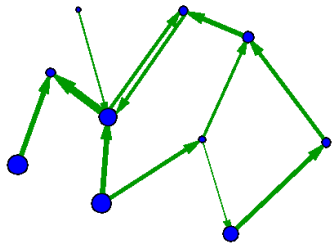
FigureDirected Graph



FigureUndirected Graph with Different Nodes



FigureUndirected Graph



FigureWeighted Graph

Synchronization Likelihood (SL)

Synchronization Likelihood (SL)

- The SL is a general measure of the correlation or synchronization between 2 time series, which is sensitive to linear as well as nonlinear interdependencies.
- The SL is then the chance that there is a pattern recurrence in time series X which coincides with a pattern recurrence in time series Y.
- The end result of computing the SL for all pairwise combinations of channels is a square N$\times$N matrix of size 21 (the number of EEG channels), where each entry N i,j contains the value of the SL for the channels i and j.
- We replace this sychronization matrix with a random adjacency matrix

Average Path Length

Average Path Length

- Calculated by finding the shortest path between all pairs of nodes, adding them up, and then dividing by the total number of pairs
- This shows the number of steps it takes to get from one part of the network to another

Calculating the Average Path Length

Random 4×4 matrix

	A	B	C	D
A	1	0	1	0
B	0	1	0	1
C	1	0	1	1
D	0	1	1	1

C$\Rightarrow$ pathlength 1 A$\Rightarrow$D; A$\rightarrow$C, C$\rightarrow$D pathlength 2 B$\Rightarrow$C; B$\rightarrow$D, D$\rightarrow$B pathlength 2 A$\rightarrow$B; A$\rightarrow$C, C$\rightarrow$D, D$\rightarrow$B pathlength 3

Cluster Coefficients

Cluster Coefficients

- Ratio of N / M,
- N is the number of edges between all of the neighbors of a node
- M is the maximum number of edges that could possibly exist between the neighbors of a node

Cluster Coefficients

Cluster Coefficients

- Clustering coefficient of a node is always a number between 0 and 1
- Clustering coefficient for the entire network is the average of the clustering coefficients of all the nodes
- High clustering coefficient for a network is another indication of a small world

Calculating Cluster Coefficient

	A	B	C	D
A	1	0	1	0
B	0	1	0	1
C	1	1	1	0
D	0	0	1	1

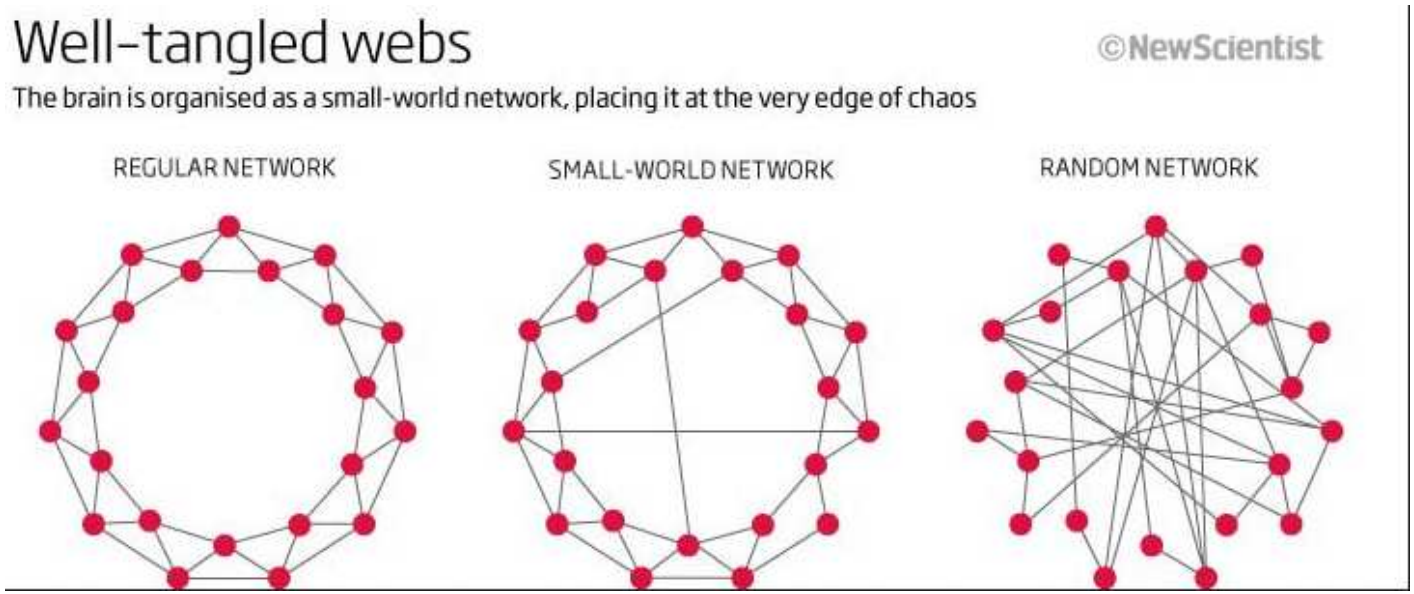
$2 \div 4 = 0.5$

$3 \div 4 = 0.75$

Average clustering coefficient for this random adjacency matrix is $C_{ave} = 0.75$ All nodes for our adjacency matrix have non-zero clustering coefficients since all nodes are weighted

What are Small World Networks?

- Have a shortest mean path length that is similar to a matched random graph (same number of nodes and edges)
- The difference being that a small world network also has a high clustering coefficient
- Small -World networks are domains



FigureType of Networks

Background Information

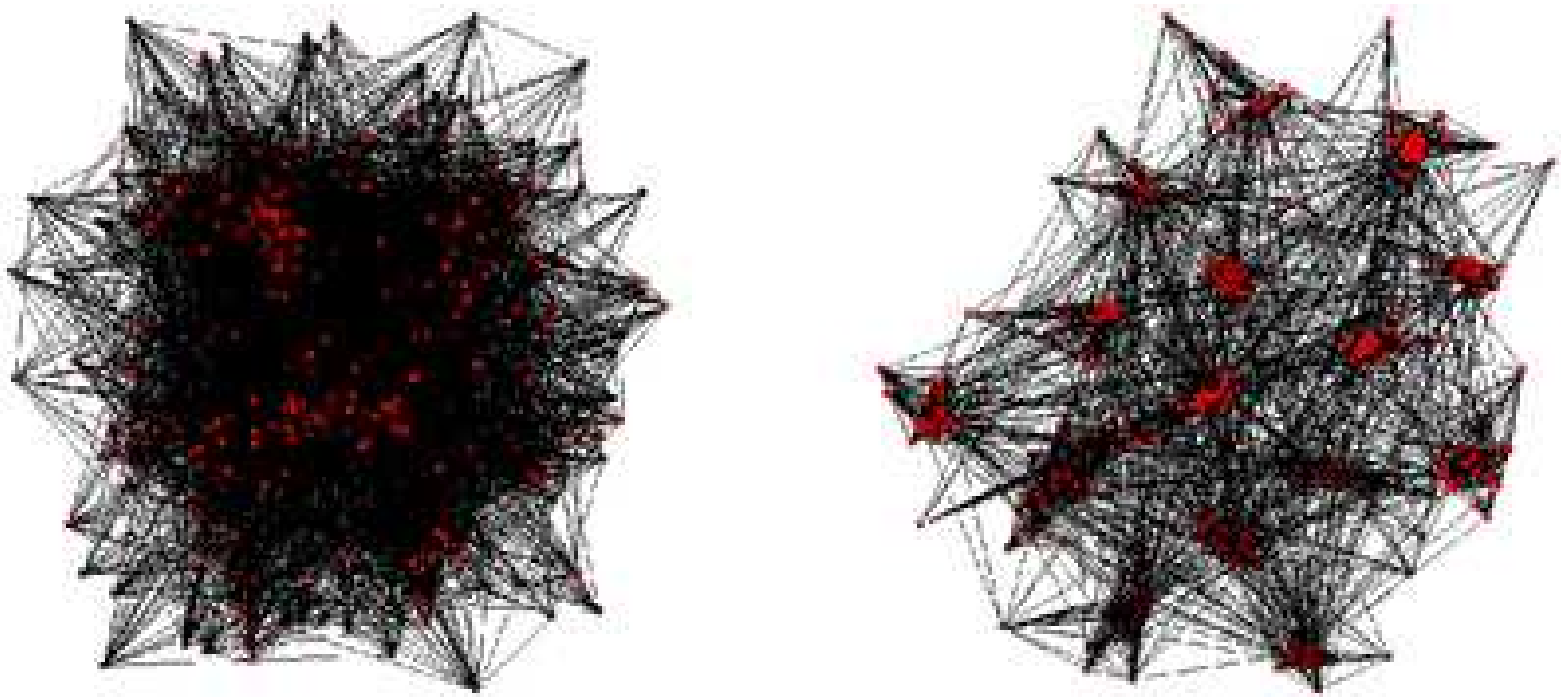
- Researchers at the Alzheimer Center at the VU University Medical Center looked at functional brain networks that were abnormally organized in Alzheimers disease (AD).
- Graph theory was used on matrices of functional connectivity of beta band filtered electroencephalography (EEG) channels
- 15 Alzheimer patients and 13 control subjects were used
- Correlations between EEG channels were determined with the synchronization likelihood

Background Information

- Resulting synchronization matrices were converted to graphs by applying a threshold
- Cluster coefficients and path lengths were computed as a function of threshold

Background Information-Results

- Their results showed a longer path length with a relatively constant cluster coefficient means a loss of complexity and a less optimal organization
- Average path length decreases due to the fact that the graph divides into 2 or more subgraphs (graph fragmentation)
- Graph fragmentation occurs earlier in AD patients than control patients
- Also supports that AD is characterized by the loss of small-world network characteristics
- Percolation tells us that a small decline in connectivity can lead to a sudden breakdown of global network coherence

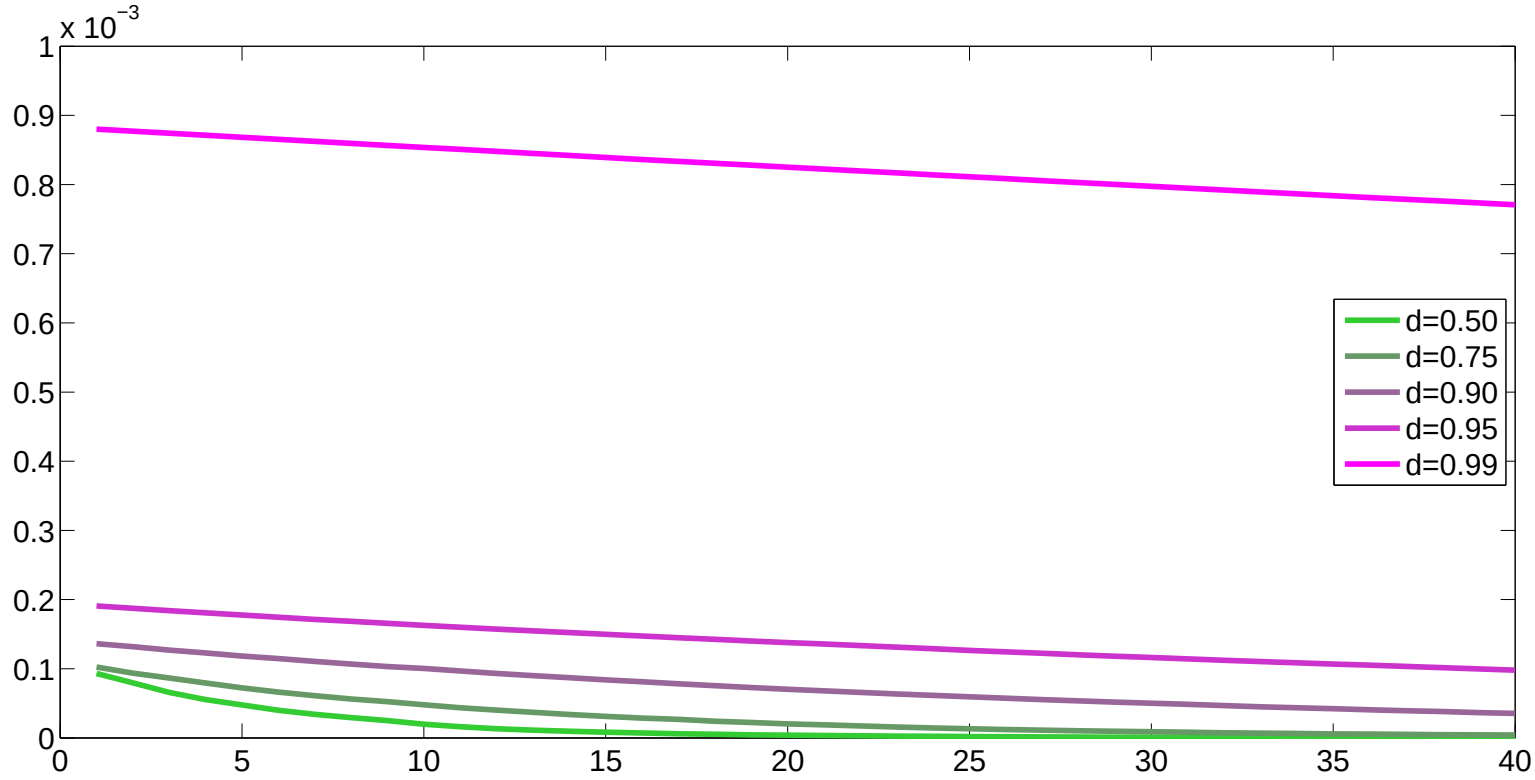


FigureGraph Fragmentation

Improvements

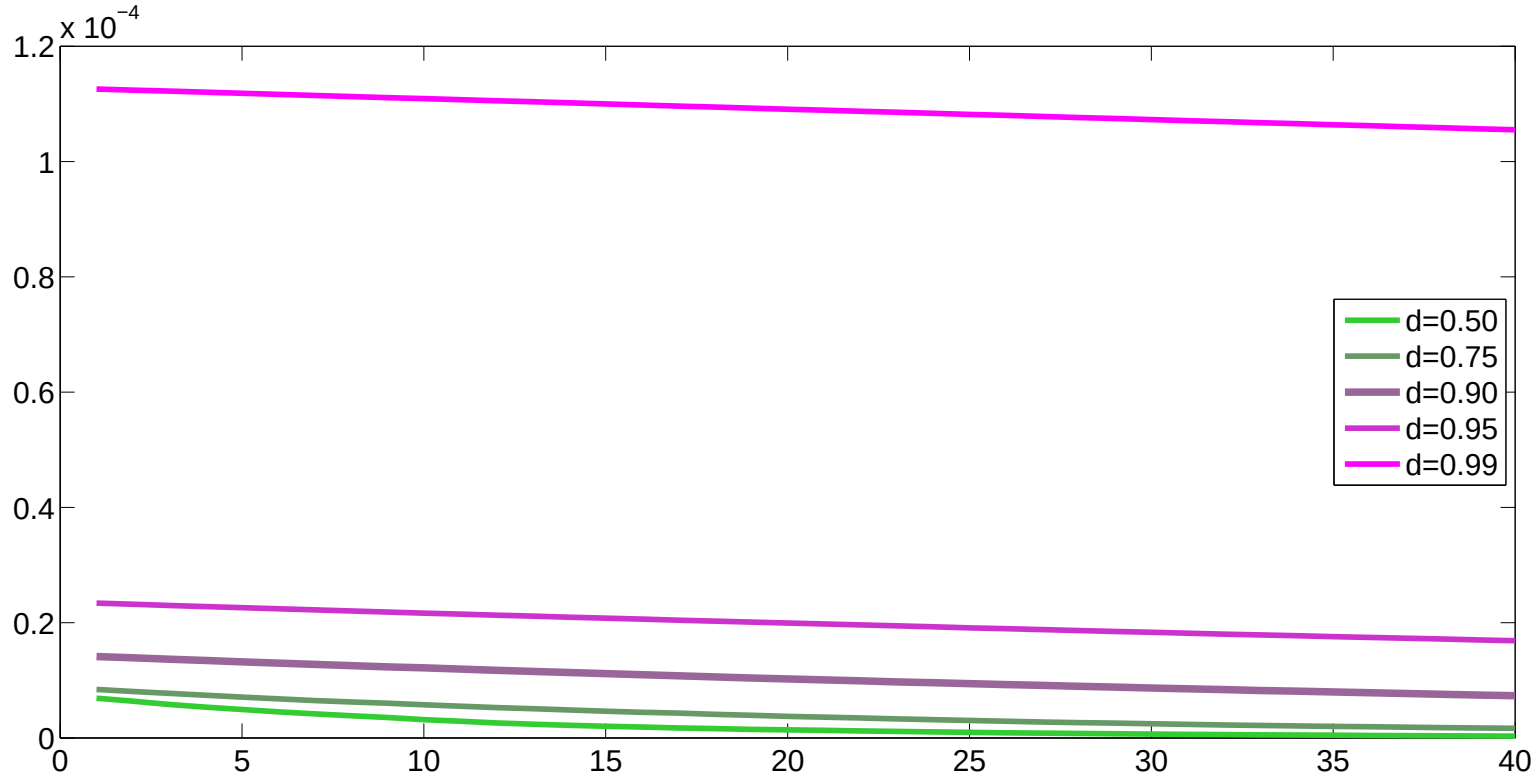
- The clustering coefficients and pathlengths are explicit functions, no longer a function of the threshhold
- The threshhold is too generic because it takes the connection between two nodes to be either 0 or 1

Results-Average Pathlength Degradation



FigureAverage Pathlength Degradation

Results- Clustering Degradation



FigureClustering Degradation

Future Directions

- Obtain EEG channels of a suspected Alzheimer's Disease patient
- Calculate synchronization matrix
- Calculate clustering coeffecients and average pathlength
- Compare to theoretical results
- Design a GUI for inputting EEG channels and outputting results
- To be used as a statistical diagnostic test in place of the probable diagnostic test currently in use
- Later to be used to statistically predict the progression of a patients disease

Conclusions

- What is Alzheimer's Disease?
- Causes
- Life Expectancy
- Diagnosis
- Types of Networks
- Synchronization Likelihood
- Calculating Average Pathlength
- Calculating Clustering Coefficients
- What are Small-World Networks?
- Background Information
- Improvements
- Results for Average Pathlength, Clustering, and Brain Degradation
- Future Directions

Work Cited

- C.J. Stam, B.F. Jones, G. Nolte, M. Breakspear and Ph. Scheltens, "Small-World Networks and Functional Connectivity in Alzheimer's Disease", **Cerebral Cortex**, 17:92-99, January 2007.
- Daan van den Berg, Pulin Gong, Michael Breakspear and Cees van Leeuwen, "Fragmentation: loss of global coherence or breakdown of modularity in functional brain architecture?", **Front. Syst. Neurosci**, 30 March 2012.
- http://www.alzfdn.org/
- http://sph.berkeley.edu/uc-berkeley-receives-18m-alzheimer
- http://mathinsight.org/network_introduction