Novel Metrics Of Functional Network Structure And Their Application to the Detection and Characterisation of Alzheimer's Disease

Athanasios Anastasiou, Emmanuel Ifeachor *Member, IEEE*

Abstract - Metrics of network structure obtained using Graph Theory can provide valuable insights into the functioning and overall operation of neuronal networks in the brain. The objectives of this paper are to highlight the shortcomings of commonly used network structure metrics in the study of functional connectivity networks today and to propose a methodology for deriving more sensitive metrics which may be used to detect and characterize dementia and other disconnection syndromes.

***Index Terms*—Functional connectivity, Alzheimer's Disease, modeling, simulation**

I. INTRODUCTION

GRAPH Theory represents an important tool for the study of functional neuronal networks of the brain. The current consensus from studies with functional modalities, such as EEG, MEG and fMRI, is that brain networks are most likely to exhibit "Small-World" properties at structural and functional levels, which is associated with efficient information exchange and minimization of total "wiring" length [1,2]. The importance of this finding is further underlined by recent research showing that the deviation of a brain functional network from Small-World properties is associated with a diseased state [3]. A widely accepted theory of the functioning brain is that it does not operate as a single organ and there does not exist a single "command centre" [4,5-pp471-522]. Instead, due to functional integration, several areas of the brain are incorporated into a temporary functional network, which exchange and process information depending on the cognitive task.

The study of functional connectivity is of particular importance in brain diseases such as Alzheimer's disease (AD). Normal aging and AD affect both the structure, the intricate way that the neurons are connected with each other, and the cognitive processes or function of a human brain. However, the impact on functional processes, that are more dynamic, is more pronounced than the structural changes [6-p331-332]. Certain network metrics provide valuable insights into the role of network structure in the overall operation of neuronal network. Clustering Coefficient, Path Length [7,8,9], Global Efficiency and Cost [10,11] are the most frequently used metrics in the study of functional networks and to some extent they have also been successfully employed in research into the ageing brain [10]. However, these metrics are limited especially in relation to monitoring disease progression. Previous work in monitoring disease progression through structural imaging modalities such as Computed Tomography (CT)[12] and Magnetic Resonance Imaging (MRI) [13, 14-p334] have revealed the accelerated reduction of volume in diseased brains. However, the corresponding evolution of functional connectivity metrics versus disease progression has not being investigated sufficiently.

The main objectives of this paper are to highlight the shortcomings of commonly used network structure metrics in the study of functional connectivity networks and to propose a novel methodology for deriving more sensitive metrics which may be used to detect and follow progression of diseases such as AD and other disconnection syndromes.

From the perspective of early detection and characterization of Alzheimer's disease through serial data collection and assessment the following questions arise:

- Which metrics are the most suitable for the early detection and monitoring response to treatment for AD for a given dataset modality?
- How sensitive are the metrics and how many dataset acquisitions should occur before small network structure changes can be detected?
- How does the value of a metric vary in relation to disease progression? Is this monotonic?
- What is the impact of different kinds of disconnection syndromes on the brain? Can we discriminate between them as early as possible to help a clinician in their decision making process?

The work reported here forms part of a programme of research aimed at the development of new and robust methods to allow early detection and monitoring of progression of brain diseases and response to treatment through modeling and studies of the brain using functional modalities. The programme of work takes place within the framework depicted in Figure 1.

Manuscript received 02/07/2001. Authors are with the Signal Processing and Multimedia Communications Research Group, University of Plymouth, Drake Circus, Plymouth, PL4 8AA.

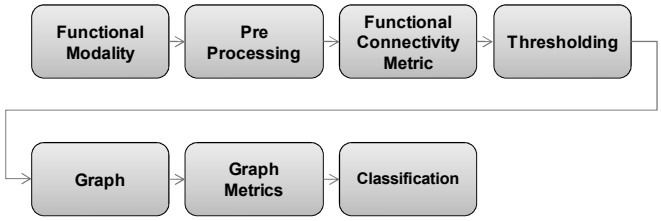

Figure 1 – Workflow of network metrics extraction

The emphasis of this paper is on 'graph metrics' in Figure 1 to put this in the context. Conceptually, in Figure 1, functional networks of the brain associated with cognition are extracted from datasets using a suitable functional modality. Although the particular phenomenon that each functional modality is monitoring is important for making inferences about brain activity, the actual workflows for processing the dataset are similar. Thus, development in any part of the workflow in Figure 1 has a significant implication across all functional modalities. As shown in the figure, the datasets first undergo some form of pre-processing. In the case of EEG and MEG, this may involve a form of filtering or artefact processing to minimize the effects of noise or artefacts (e.g. muscle and eye movements) or to isolate specific brain activity [3,15] . In the case of functional modalities such as fMRI, preprocessing may involve spatial alignment to minimize correlations that might be induced because of head movement [16] and parcellation [17,18] to reduce the computational load of subsequent processing stages.

The estimation of functional connectivity is performed through suitable linear and non-linear metrics and may lead to directed or undirected brain functional networks. Thresholding produces an Adjacency Matrix which in essence describes the structure of the functional network. The majority of network structure metrics applied to the study of functional brain networks operate on this matrix and are also used as classification features in the subsequent classification block.

The paper is structured as follows: first, we demonstrate the shortcomings of the most commonly used metrics of network structure today in the context of early detection of AD. We then undertake an evaluation of their sensitivity and propose new metrics based on specific structural properties of the network that can be used to monitor network structure much more efficiently. Finally, the discussion section summarizes the key issues arising from our approach.

II. Materials And Methods

A. Network Metrics

Currently, only a subset of known metrics is systematically used to estimate functional network structure and to some extent used for disease detection.

These metrics are the Clustering Coefficient, Mean Path Length, Efficiency and Cost. Less significant metrics of network structure such as average vertex degree have also being used [19]. Although these particular metrics are useful when studying the properties of brain functionality in general, they are not sensitive enough to be used as biomarkers of Brain diseases. In the following sections we explain why.

B. Clustering Coefficient

Clustering coefficient was defined by Strogatz and Watts [20,21] and applied within the context of sociology research. The researchers, used the abstract model of a Graph composed of a set of nodes V connected through a set of Edges E to represent social contacts and developed the Clustering Coefficient metric (C_p) to estimate the connectivity of each node and through this the connectivity of the network as a whole.

Each individual node's Clustering Coefficient is defined as:

$$Cv_i = \frac{\left|E(\Gamma_i)\right|}{\binom{k_i}{2}} \quad (1)$$

Where $|E(\Gamma_u)|$ is the number of edges in the subgraph defined by the vertices that V_u is connected to and K_i is the degree of vertex V_i .

This is essentially a metric of how far is $E(\Gamma_u)$ from an equal order clique K_{ki}.

The Clustering Coefficient of the network is defined as the expectation of (1) as follows:

$$C(G) = \frac{1}{|V|}\sum_{i=1}^{|V|} Cp_i \quad (2)$$

By definition the clustering coefficient is only defined over connected Graphs which does not necessarily have to be the case with neuronal networks. Additionally, the low sensitivity of this metric is due to the fact that it is defined as the expectation of each V_i.

1) Clustering Coefficient Issues

The specific structural element that the Clustering Coefficient responds to more is the clique (K_n) and specifically the smallest of cliques which is the K_3 , also known as the 'triangle'. From (1), it is clear that as the order of the clique increases, the term $\binom{k_i}{2}$ grows much faster. Therefore, the fraction that each edge contributes to the value of the metric per subgraph vertex is small. The sensitivity of this metric is further decreased by the fact that the average clustering coefficient is obtained as the expectation over all C_{Vi}. Therefore, the term $\frac{1}{|V|}$ introduced in (2) contributes further to decreased sensitivity particularly as the network size increases as is depicted in Figure 2. This makes the clustering coefficient unlikely to respond to changes in functional brain structure especially based on high spatial resolution functional modality datasets.

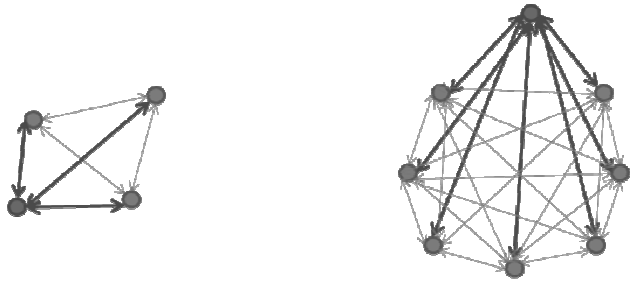

Figure 2 – The sensitivity of the Clustering Coefficient is decreasing as the order of the network is increasing.

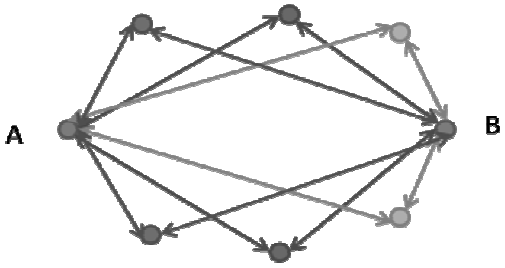

Figure 3 – The shortest path between vertices A & B will remain at 2 hops until most of the alternative paths are severed

C. Path Length Metrics

Path length metrics refers to all metrics that employ a graphs distance matrix d(G) as in (3).

$$d(i,j) \forall i,j \in V(G) \quad (3)$$

This is an NxN matrix with each element d(i,j) describing the distance (in number of vertices) between vertex V_i and vertex V_j. Obviously, in the case of directed graphs this matrix is symmetric around the main diagonal. A number of statistics is defined over this matrix. For example, to obtain the Average Path Length, the average (modal or algebraic) of d is obtained whereas to obtain the Characteristic Path Length the median of d is obtained [22-p27].

Characteristic Path Length was also used by Strogatz and Watts [21] and applied within sociological research as well. Path Length along with Clustering Coefficient were the two features of network structure by which the Small World property that some networks exhibit was revealed. The mean path length represents the average distance between any two nodes V_i, V_j of a network G. For graphs that are not embedded in some space R, distance refers to the order of the shortest path (number of vertices or hops) that connects any two vertices

1) Path Length Issues

The Path Length is another statistic obtained over the entirety of the network. In undirected networks (Figure 3), the structures it is more sensitive to are unique open paths of a given length between any two V_i, V_j. However, if two vertices V_i, V_j participate in more than one paths connecting them, a large number of them would have to be severed before the value of the metric changes considerably.

As with the Clustering Coefficient, this metric is also defined only for connected graphs.

D. Network Efficiency

Efficiency was first defined by Latora and Marchiori [23,24] and later employed in the neuroscience research context by Achard et al [10], Basset et al [11] and others. Efficiency is a statistic that depicts how well information can be transferred between the nodes of a network and is very closely coupled with the distance matrix d(G) defined by equation 3 above.

However, contrary to the Mean Path Length, the Efficiency refers to the mean of the inverse of the distance matrix d(G). Efficiency is defined as:

$$L_E(G) = \frac{1}{N(N-1)} \sum_{i \neq j \in G} \frac{1}{d(i,j)} \quad (4)$$

Where L_E denotes the efficiency, N the number of vertices and d(i,j) is the distance matrix as it was defined in (3).

This inversion of the distance matrix is an important detail which makes this metric suitable for application to weakly connected Graphs. That is because, in this type of graphs, every pair of unreachable vertices will simply contribute a zero to the overall efficiency.

1) Network Efficiency Issues

Network efficiency is an improvement, in terms of its usefulness to the study of neuronal networks, against Mean Path Length because it can be applied to networks with disconnected components. However, it shares the same negative remarks as Mean Path Length when examined from the sensitivity point of view.

E. Cost

Cost is a metric which is closely associated with Network Efficiency and provides an estimate of resources trade-off to achieve a particular Efficiency. Its original definition by Latora and Marchiori [25] is:

$$Cost(G) = \frac{\sum_{i \neq j \in G} a(i,j)\gamma(d(i,j))}{\sum_{i \neq j \in G} \gamma(d(i,j))} \quad (4)$$

Where, a(i,j) is the weight of an edge connecting V_i with V_j and γ is a function of the cost versus length associated with the same edge. The function cost(G) is context dependent and depicts resource expenditure to establish a particular link between any two nodes. This definition is a departure from the networks considered so far in that it operates over the weights of the edges E(G) and it also introduces the function γ. This function depends on the context of the network and it can be used to add other length dependent parameters to cost that could potentially increase the sensitivity of this metric.

However when examining simple unweighted graphs that are not embedded in some geometric space, the definition of cost is reduced to the ratio of existing edges divided by the number of possible edges that could have existed in a graph of a given size as in (5):

$$Cost(G) = \frac{2|E|}{N^2 - N} \quad (5)$$

Where |E| is the total number of edges in a graph and N is the total number of vertices.

Through this definition, cost provides a crude metric of how far is any Graph of order N from a corresponding K_n (Clique of size n) which additionally has an efficiency of 1.

1) Cost Issues

The Cost is the statistic with the potential for high sensitivity over all statistics mentioned so far. This is because of the inclusion of the gamma function to its calculation and through this additional context information can be used to increase the sensitivity of the metric. However, simple application of the Cost metric, where the gamma function is effectively omitted, does not result in a metric with increased sensitivity especially in networks with a high number of vertices N.

F. Simulating Alzheimer's Disease Progression

In order to evaluate the performance of these metrics as biomarkers of Alzheimer's disease a simulation framework was established. The objective of this is to allow the derivation of the metrics' value versus the corresponding change in the structure of the network. The idea is to enable the estimation of how long a subject suspected of AD should undergo serial data collection before the clinician is in the position to confirm significant changes in the brain's functional networks. Another reason that necessitates the use of such simulations is the fact that the derivation of analytic expressions for the scaling of these metrics is very difficult. [22 p28-29]

This framework is inspired by observations of the macroscopic effects of Alzheimer's disease on the human brain. The brain is represented by a Small World network as it would have been extracted by a suitable functional modality dataset. The Watts-Strogatz model of Small World networks is employed and similarity with realistic brain functional networks is ensured by choosing the size (N) and average connections $\bar{k}$ according to data found in the available literature [26]. The size of the network is closely related to the modality that would have produced the connectivity data. Therefore, a modality like EEG can produce a network of 16-32 nodes, fMRI can produce a network of up to 90 areas and MEG can produce a network of up to 192 areas or more. Once a network is constructed, a minimal change of structure signifying early onset of Alzheimer's disease is applied. This network structure change can be defined in three different ways corresponding to the processes occurring in the brain.

- Elimination of a Vertex
- Elimination of an Edge
- Rewiring of two Edges

In the context of functional brain networks derived from functional modalities having the current spatial resolution limits, elimination of a vertex corresponds to a large area of the brain being damaged. This usually happens in the case of stroke conditions and it has an adverse effect on cognitive performance. It is less relevant for the specific purposes of our research and will not be considered any further here.

Edge elimination and rewiring is of particular interest to tracking changes in the brain as reduced connectivity between brain areas has been closely linked with specific brain diseases[27,28,29]. Finally, edge rewiring corresponds in this model to brain plasticity. In any case, the selection of edges is totally random over the set of edges already existing in the network. The simulation proceeds by calculating the difference of metric values before and after this elementary change in network structure. In mathematical terms we are attempting to estimate:

$$S_M(G) = \frac{dM(G)}{d(G-e)} \qquad with\, e \in E(G) \quad (5)$$

Where M(G) represents each structural metric (Clustering coefficient, path length, etc) and d(G-e) represents the change in graph structure after one edge has been removed. This process is repeated over a number of networks and an average change versus the network size is obtained.

In other words, we estimate the least variation of the metric's value for the smallest change in network structure versus network size.

At a later stage we attempt to evaluate the disease tracking capabilities of each metric by allowing the random process of edge elimination to occur over a representative functional network over a number of simulation steps until the critical point where the network develops more than one component. This corresponds to the equivalent of serial data collection and extraction of functional networks as depicted in Figure 1 and provides a view of the expected values for a particular metric.

The metrics are calculated according to the published formulas by Strogatz and Watts [20,21] and Latora and Marchiori[24,25] respectively.

G. Sensitive Structure Metrics

As outlined in Section II, the primary shortcomings of the existing metrics are in their low sensitivity to structure change. The primary reason for this is that their derivation depends on structures that might be less abundant in a particular type of network.

To alleviate this we propose here a methodology for deriving sensitive metrics for both undirected and directed networks. The main idea underpinning our derivation is the construction of a metric from a subset of coefficients of the cycle or motif spectrum of a network.

The cycle spectrum of a graph |G| is a histogram showing the frequency of occurrence of a cycle of length **n** in a graph. A cycle is defined as a closed nontrivial path [30 p39]. That is, a unique sequence of non-repeated Vertices (V(G)) and Edges (E(G)) connecting them. Cycles and their distribution within a graph is an important characteristic of network structure [22 p24] and has many applications in chemistry [31], genomics and other domains [30 p43-46]

The complexity of counting these cycles in a graph is growing explosively and depends on the number of vertices,

edges and cycles existing in a given graph [32]. For relatively small graphs, algebraic methods such as the powers of the Adjacency Matrix, number theory based derivations [33], and the minimum Cycle Basis can be used. For larger networks (a few hundred nodes), it is unavoidable to count the cycles directly with efficient search algorithms usually based on some form of Depth First Search [32, 33] . When the size of the network becomes too large (thousands of vertices) then cycle counting relies more on statistical sampling of the network [34].

An important point that has an impact on the sensitivity of network metrics that are based on the cycle spectrum is the actual set of cycles enumerated by each class of algorithms mentioned above. Generally speaking, the concept of the "cycle" is somewhat loosely used in the literature adding to confusion. For example, algebraic methods tend to count the number of walks that could possibly exist between two given nodes returning a large amount of redundant (duplicated) data. This redundancy contributes negatively to the sensitivity of a metric that estimates structural changes in a very similar way to the averaging of the distance matrix d(G).

In this work we are particularly interested in the set of elementary cycles in a graph and this generally means counting each cycle just once. Counting algorithms based on Depth First Search (DFS) are the most efficient for this task. The results in this paper have been obtained with a modified DFS algorithm. The modifications were primarily done to reject any duplicates found in the data produced by the original algorithm. We achieve this by constructing a unique hash code once a cycle is discovered. This code is then checked against a binary tree of all the codes that have been discovered up to that point and if it is found, the cycle is rejected.

The problems of cycle and motif counting are similar in nature although Motif counting is a slightly harder problem. This is because, in the case of Motifs, picking up a path from the original network and determining if it leads back to the starting vertex is not enough.

The methods that have been developed to efficiently count motifs are usually based on variants of the DFS algorithm and random sampling of edges. In this work, motif counting tools developed by Milo [35] were adapted and used in order to extract network motifs.

Simply extracting the cycle or motif spectrum though is not practical. Although the total differences observed across the whole spectrum could provide a sensitive network structure metric, this could contain unwanted variations. It is therefore proposed that a novel metric of network structure is extracted by the combination of a small subset of coefficients of the spectrum. The question now becomes which and how many coefficients?

A simple strategy was adopted throughout the simulations at this stage. This was to select a small number of coefficients corresponding to the most frequent elementary structures from each spectra (either motifs or cycles) with an additional component from the most frequent and longest cycle.

That is, given the spectrum H of either cycles or motifs (denoted here generally as (H_M)) :

$$H_M(n) = \left|F_i(G)\right| \forall F_i \in G \quad (6)$$

The new metric I_M is obtained as:

$$I_M = \frac{1}{3}\left(H_M(i) + H_M(j) + H_M(k)\right) \quad (7)$$

Where F_i is the set of elementary cycles and motifs defined over the network G and i,j,k are the selected indexes from the spectra.

This approach also takes into account the fact that Graphs of different sizes exhibit different distributions. For the simulations found in the 'Results' section, two coefficients corresponding to the elementary structures with the highest frequency of occurrence where selected for the case of Motifs of size 4. For the special case of cycles [22 p28], an additional coefficient corresponding to the longest and most frequent cycles was included. The rationale behind this third coefficient for the case of cycles is that long cycles in a connected network are the first to be lost as edges are removed from the graph. Coefficient selection occurs at the first simulation cycle which represents a baseline scan at a subject's first admission and tracked in the subsequently produced networks.

III. Results

A. Metric Sensitivity

In order to demonstrate the sensitivity of various metrics at detecting small structural changes versus network size, the results from a series of simulations were obtained.

In the context of AD, the data obtained, demonstrate the least amount of metric variation one can expect, between two successive acquisitions, at baseline and sometime later.

These simulations were performed on Small World graphs using the model of Watts-Strogatz [21]. The size of the networks was varied from 28 to 90 which closely follows the corresponding networks produced by modalities such as EEG, MEG and fMRI [1]. The results are summarized in Figure 4. Each point on this curve is obtained by averaging the metric variation after at least $N^*\bar{k}$ repetitions to ensure that the variation due to the removal of any edge is accounted for properly.

Figure 4 shows the scaling properties of the four commonly used metrics along with their standard deviation. Global Efficiency is a scaled down and inversed image of the path length owing to their similarities in definition. It also is apparent that the sensitivity of these metrics is getting worst as the size of the network is increased. Therefore, although fMRI offers much better spatial resolution and is more accurate in localising brain activity, subsequent analysis based on network structure metrics would fail in capturing the subtle changes occurring in a diseased brain.

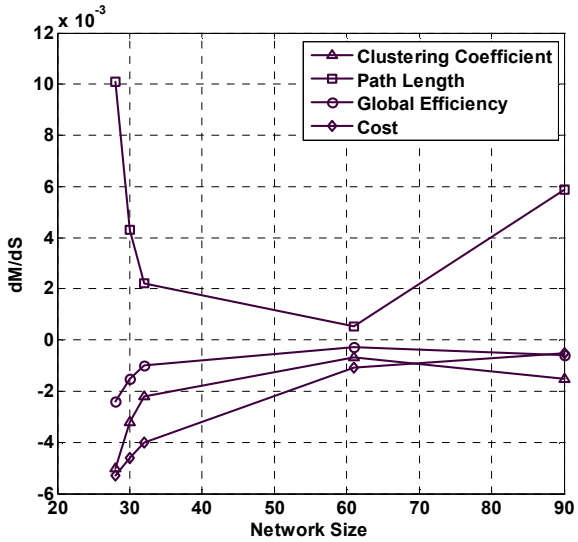

Figure 4 – Metric value variation versus network size for Clustering Coefficient, Path Length, Global Efficiency and Cost (Note: Values for N=60, k=14 and N=90, k=6 have been obtained after 100 repetitions due to the large number of edges)

It is worth noting at this point that the networks used to produce these statistics from do not have similar average connection densities and this the reason for the deviations from a smooth logarithmic curve.

The corresponding variation of the metrics derived by the Cycle and Motif spectra is depicted in Figure 5.

A much wider variation for the same minimal changes in network structure induced by random edge removal is observed. In order to investigate how these metrics would behave in long term disease tracking, another simulation was performed where the variation of the metrics is examined while the process of edge removal is allowed to continue until the critical point when the network becomes disconnected.

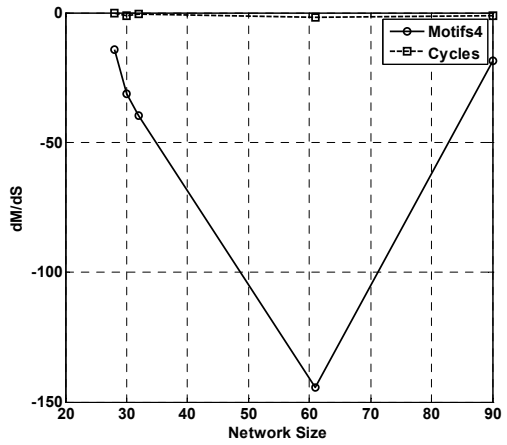

Figure 5 – Average metric value variation versus network size for the two most frequent motifs of size 4 and cycles. (Note: Values for N=60, k=14 and N=90, k=6 have been obtained after 100 repetitions due to the large number of edges)

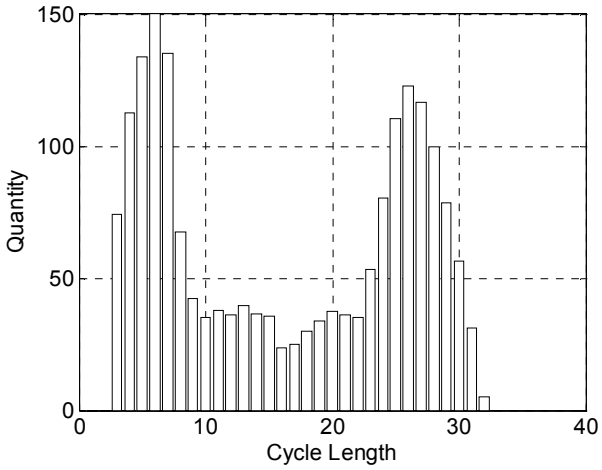

Figure 6 – Cycle Spectrum at baseline for a Small-World network with N=32, k=14

Figure 6 depicts the averaged cycle spectrum at an assumed baseline scan over three realizations of Small-World networks with N=32, $\bar{k} = 14$. This corresponds to a possible functional network obtained through an fMRI dataset as in [1].

The two most frequent cycle lengths in this graph are those of length 6,7 and the longest and most frequent cycle is of length 26. Because of their high frequency of occurrence within the network these cycles are most susceptible to changes. For the same network Figure 8 shows the corresponding size 4 motif distribution also at baseline. Because the graph is undirected not all possible motif classes appear in its spectrum and the most frequent class is #107 (hub) followed by class #124 (kite). It is worth noting here that the full K4 (motif #199) which has the strongest contribution to the Clustering Coefficient is only a tiny fraction (599) of the two most frequent classes in the network (10894). It is therefore bound to fluctuate slower than class #107.

The populations of cycles and motifs described by the distributions in figures 6 and 7 will progressively change as one edge is removed at random at each simulation cycle.

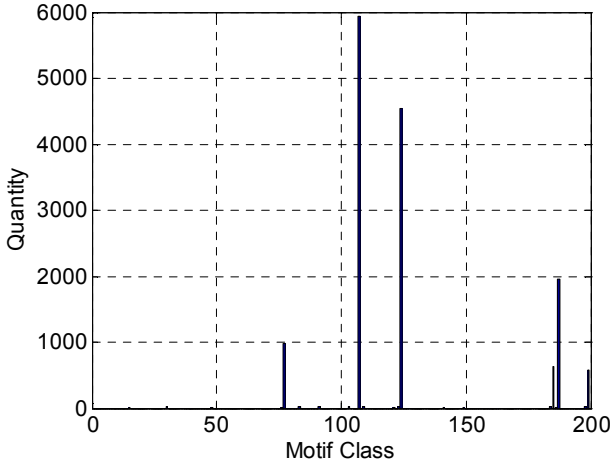

Figure 8 – Motifs of Class 4 at baseline

The variation of the metric that results as a combination of the three most frequent spectra coefficients versus edge

removal is depicted in Figures 9 and 10. Included in these is the variation of C3 (Fig 9) which is the structure that the Clustering Coefficient depends on and the variation of K4 (Fig 10) which also has the strongest contribution to the clustering coefficient. The slope of the combined cycle coefficients is steeper compared to the variation of C3 alone which means that a metric depending on a combination of these structures would be more sensitive to subtle variations in network structure. A similar situation is depicted by Figure 10. In this case, the small number of K4s in the network decreases slower than M124 and M107 combined.

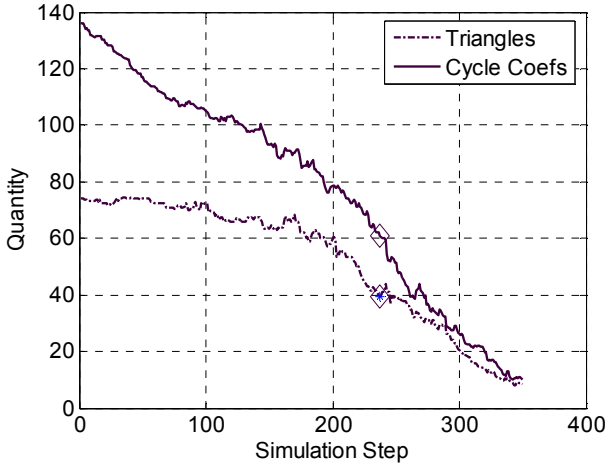

Figure 9 – Metric variation for C3,C4,C28

IV. Discussion

From the simulations carried out so far, the sensitivity of metrics based on cycles and motifs have been found superior to that of simple statistics over the networks.

The shortcomings of the clustering coefficient and path length when applied to the early diagnosis of AD come from the fact that these metrics are averaged over the size of the network. This introduces the 1/|V| factor which grows smaller much faster than the respective increase in clusters as the size of the network is growing.

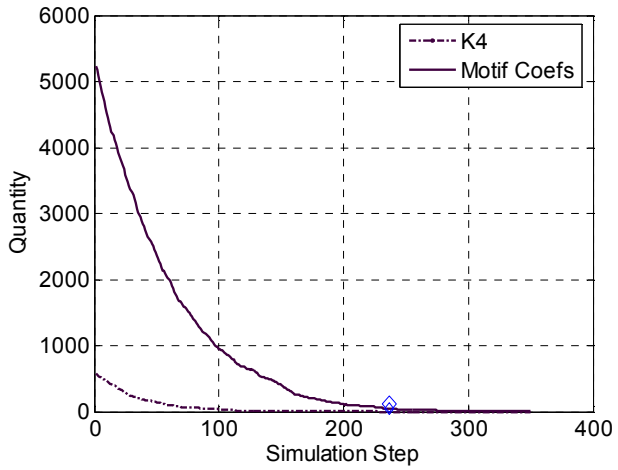

Figure 10 – Variation of motifs versus network deterioration.

Additionally, the expressions of the four metrics discussed in the introductory section respond to specific structures and miss others whose variation might be much wider as the network progresses. Between the cycle and motif spectra, motifs offer much more coefficients in the case of undirected networks which exhibit a larger variety of motif classes from which to choose from. An example is that from the 199 classes of M4, an undirected small-world network (N=90, $\bar{k}$ =6,p=0.08) would exhibit only 6.

An important point in the selection of a good set of coefficients is the differences in the way that the Cycle and Motif spectra change versus subsequent edge removal. As the network deteriorates, a process corresponding to disease progression, the distribution of the coefficients changes in a certain way. This process is quite different for Cycle and Motif spectra. In general, all the coefficients of the cycle spectrum are decreasing monotonically as a proportion of the total number of edges with each subsequent edge removal. This is expected since every edge in a connected network (that is not a tree) contributes to one or more cycles. The same though is not true for Motif counting which occurs over a set of subgraphs with specific structure. Therefore, deletion of an edge might increase the population of a class that did not even exist before.

The additional benefit from using either the cycle or motif distribution is that a biomarker could be optimized to track the specific way that a disease attacks a functional network. However, more data from experiments is needed to establish this relationship rigorously.

As far as the simulation framework is concerned, it provides a useful tool to gain an insight to the timescales involved in AD. As it is visible from figure 7, there comes a point after n simulation steps that it is unavoidable for the network to remain connected and is broken down into two distinct parts. From a physiological point of view, very progressed Alzheimer's disease results in Schizofrenia which is a disconnection syndrome as well. Therefore taking the average time that it takes for patients to reach this advanced state can provide a hint of the time scale of the simulations. Although the Cycle and Motif spectra are two good choices to monitor the structural changes of a network, these metrics are not without some negative remarks. The primary of these being the high computational load for counting these elementary structures in a graph. For example, the calculation of the cycle and motif spectra for the case of a Small World network with N=90, $\bar{k} = 6$ takes about 34 seconds in MATLAB and that is to produce only one iteration. Future recoding of the algorithms in more efficiently compiled code is expected to increase the speed of execution for the sizes of networks involved in this paper.

V. Conclusion

This paper has demonstrated the rather low sensitivity of the most commonly used metrics for analyzing the structure of functional brain networks when applied to a framework of serial data collection for the early detection of Alzheimer's disease. Furthermore two new metrics were proposed that appear to be more sensitive to subtle changes of network structure.

References

[1] D.S. Bassett and E. Bullmore, "Small-World Brain Networks," Neuroscientist, vol. 12, Dec. 2006, pp. 512-523.

[2] O. Sporns, G. Tononi, and G.M. Edelman, "Connectivity and complexity: the relationship between neuroanatomy and brain dynamics," Neural Networks, vol. 13, Nov. 2000, pp. 909-922.

[3] C. Stam et al., "Small-World Networks and Functional Connectivity in Alzheimer's Disease," Cereb. Cortex, vol. 17, Jan. 2007, pp. 92-99.

[4] G. Tononi, O. Sporns, and G. Edelman, "A Measure for Brain Complexity: Relating Functional Segregation and Integration in the Nervous System," Proceedings of the National Academy of Sciences, vol. 91, May. 1994, pp. 5033-5037.

[5] R. Frackowiak et al., Human Brain Function, Academic Press, 2003; http://www.fil.ion.ucl.ac.uk/spm/doc/books/hbf2/.

[6] Abosch, "Handbook of Functional Neuroimaging of Cognition: Roberto Cabeza, Alan Kingstone (Eds.), The MIT Press, 2001, GBP 41.50, ISBN: 0-262-03280-5," Journal of Chemical Neuroanatomy, vol. 27, Jul. 2004, pp. 283-284.

[7] C.J. Stam, "Functional connectivity patterns of human magnetoencephalographic recordings: a 'small-world' network?, Neuroscience Letters, vol. 355, Jan. 2004, pp. 25-28.

[8] R. Salvador et al., "Neurophysiological Architecture of Functional Magnetic Resonance Images of Human Brain," Cereb. Cortex, vol. 15, Sep. 2005, pp. 1332-1342.

[9] S. Achard et al., "A Resilient, Low-Frequency, Small-World Human Brain Functional Network with Highly Connected Association Cortical Hubs," J. Neurosci., vol. 26, Jan. 2006, pp. 63-72.

[10] S. Achard and E. Bullmore, "Efficiency and Cost of Economical Brain Functional Networks," PLoS Computational Biology, vol. 3, Feb. 2007, p. e17.

[11] D.S. Bassett and E. Bullmore, "Small-World Brain Networks," Neuroscientist, vol. 12, Dec. 2006, pp. 512-523.

[12] N.C. Fox, P.A. Freeborough, and M.N. Rossor, "Visualisation and quantification of rates of atrophy in Alzheimer's disease," The Lancet, vol. 348, Jul. 1996, pp. 94-97.

[13] P. Freeborough and N. Fox, "MR image texture analysis applied to the diagnosis and tracking of Alzheimer's disease," Medical Imaging, IEEE Transactions on, vol. 17, 1998, pp. 475-478.

[14] Abosch, "Handbook of Functional Neuroimaging of Cognition: Roberto Cabeza, Alan Kingstone (Eds.), The MIT Press, 2001, GBP 41.50, ISBN: 0-262-03280-5," Journal of Chemical Neuroanatomy, vol. 27, Jul. 2004, pp. 283-284.

[15] S. Micheloyannis et al., "Small-world networks and disturbed functional connectivity in schizophrenia," Schizophrenia Research, vol. 87, Oct. 2006, pp. 60-66.

[16] J. Ashburner and K. Friston, "Rigid body registration," Human Brain Function, R. Frackowiak et al., ed., Academic Press, 2003.

[17] G. Flandin et al., "Parcellation of brain images with anatomical and functional constraints for fMRI data analysis," Biomedical Imaging, 2002. Proceedings. 2002 IEEE International Symposium on, 2002, pp. 907-910.

[18] S. Achard et al., "A Resilient, Low-Frequency, Small-World Human Brain Functional Network with Highly Connected Association Cortical Hubs," J. Neurosci., vol. 26, Jan. 2006, pp. 63-72.

[19] V. Sakkalis et al., "Time-significant Wavelet Coherence for the Evaluation of Schizophrenic Brain Activity using a Graph theory approach," Engineering in Medicine and Biology Society, 2006. EMBS '06. 28th Annual International Conference of the IEEE, 2006, pp. 4265-4268.

[20] D.J. Watts and S.H. Strogatz, "Collective dynamics of /`small-world/' networks," Nature, vol. 393, Jun. 1998, pp. 440-442.

[21] S.H. Strogatz, "Exploring complex networks," Nature, vol. 410, Mar. 2001, pp. 268-276.

[22] D.J. Watts, Small worlds : the dynamics of networks between order and randomness, Princeton, N.J.: Princeton University Press, 1999.

[23] V. Latora and M. Marchiori, "Economic Small-Wolrd Behaviour In Weighted Networks," The European Physical Journal B, vol. 32, 2003, pp. 249-263.

[24] P. Crucitti et al., "Error and attack tolerance of complex networks," Physica A: Statistical Mechanics and its Applications, vol. 340, Sep. 2004, pp. 388-394.

[25] V. Latora and M. Marchiori, "Efficient Behavior of Small-World Networks," Physical Review Letters, vol. 87, Oct. 2001, p. 198701.

[26] C. Stam and J. Reijneveld, "Graph theoretical analysis of complex networks in the brain," Nonlinear Biomedical Physics, vol. 1, 2007, p. 3.

[27] S.E. Rose et al., "Loss of connectivity in Alzheimer's disease: an evaluation of white matter tract integrity with colour coded MR diffusion tensor imaging," J Neurol Neurosurg Psychiatry, vol. 69, Oct. 2000, pp. 528-530.

[28] C.L. Grady et al., "Altered brain functional connectivity and impaired short-term memory in Alzheimer's disease," Brain, vol. 124, Apr. 2001, pp. 739-756.

[29] X. Delbeuck, M. Van der Linden, and F. Collette, "Alzheimer' Disease as a Disconnection Syndrome?," Neuropsychology Review, vol. 13, Jun. 2003, pp. 79-92.

[30] J. Gross and J. Yellen, Graph theory and its applications, CRC Press, Inc., 1999.

[31] Zamora, "An Algorithm for Finding the Smallest Set of Smallest Rings," J. Chem. Inf. Comput. Sci., vol. 16, 1976, pp. 40-43.

[32] R. Tarjan, "Enumeration of the Elementary Circuits of a Directed Graph," SIAM Journal on Computing, vol. 2, 1973, pp. 211-216.

[33] J.C. Tiernan, "An efficient search algorithm to find the elementary circuits of a graph," Commun. ACM, vol. 13, 1970, pp. 722-726.

[34] Sebastian Wernicke, "Efficient Detection of Network Motifs," Computational Biology and Bioinformatics, IEEE/ACM Transactions on, vol. 3, 2006, pp. 347-359.

[35] R. Milo et al., "Superfamilies of Evolved and Designed Networks," Science, vol. 303, Mar. 2004, pp. 1538-1542.