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# GRAPH THEORY APPLICATIONS IN BIOLOGY

**[1]*S. Naga Durga and [2]M. Durgadevi and K. Rama devi**

[1]Lecturer in Msc Mathematics, Ch. S.D. St Theresa's College for Women, Eluru.
[2]Research Scholar, Ch. S.D. St Theresa's College for Women, Eluru.
[3]Student in Msc Mathematics, Ch. S.D. St Theresa's College for Women, Eluru.

***Corresponding Author: S. Naga Durga**
Lecturer in Msc Mathematics, Ch. S.D. St Theresa's College for Women, Eluru.

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**ABSTRACT**
Mathematics plays a key role in many disciplines of science, primarily as a mathematical modeling tool. A survey of the use of graph theoretical techniques in Biology is presented. In particular, recent work on identifying and modeling the structure of bio-molecular networks is discussed, as well as the application of centrality measures to interaction networks and research on the hierarchical structure of such networks and network motifs. One can think is mathematics has that same important role or even lesser important role in the field of biology and is mathematics and biology could possibly have anything in common. As an effective modeling, analysis and computational tool, graph theory is widely used in biological mathematics to deal with various biology problems. In the field of microbiology, graph can express the molecular structure, where cell, gene or protein can be denoted as a vertex, and the connect element can be regarded as an edge.

**KEYWORDS:** Mathematical modeling, Biological Networks, Graph, Vertex, Edge.

## INTRODUCTION AND MOTIVATION

Mathematical biology or biomathematics is a fast-growing well-recognized and the most exciting modern application of mathematics. This is an interdisciplinary research area with a range of applications in biology, biotechnology and biomedical science. The filed may be referred to as mathematical biology or biomathematics to stress the mathematical side or theoretical biology to stress the biological side. A variety of mathematical techniques are used in mathematical biology to model biological researches. Mathematical areas such as calculus, probability theory, statistics, linear algebra, graph theory, combinatorics, algebraic geometry, topology, dynamical systems, differential equations and coding theory are now being applied in this field.

The theory of complex networks plays an important role in a wide variety of disciplines, ranging from communications and power systems engineering to molecular and population biology.[1–8] Although the focus of this article is on biological applications of the theory of graphs and networks, there are also several other domains in which networks play a crucial role. For instance, the Internet and the World Wide Web (WWW) have grown at a remarkable rate, both in size and importance, in recent years, leading to a pressing need both for systematic methods of analyzing such networks as well as a thorough understanding of their properties. Moreover, in sociology and ecology, increasing amounts of data on food-webs and the structure of human social networks are becoming available. Given the critical role that these networks play in many key questions relating to the environment and public health, it is hardly surprising that researchers in ecology and epidemiology have focused attention on network analysis in recent years. In particular, the complex interplay between the structure of social networks and the spread of disease is a topic of critical importance. The threats to human health posed by new infectious diseases such as the SARS virus and the Asian bird flu[9,10], coupled with modern travel patterns, underline the vital nature of this issue.

Thus, it is now possible to investigate the structural properties of networks in living cells, to identify their key properties and to hopefully shed light on how such properties may have evolved biologically. Given the special nature of biological systems, there is a pressing need for tailored analysis methods which can extract meaningful biological information from the data becoming available through the efforts of experimentalists. This is all the more pertinent given that the network structures emerging from the results of high-throughput techniques are too complex to analyze in a non-systematic fashion. A knowledge of the topologies of biological networks, and of their impact on biological processes, is needed if we are to fully understand, and develop more sophisticated treatment strategies for, complex diseases such as cancer.[12] Also, recent work

suggesting connections between abnormal neural synchronization and neurological disorders such as Parkinson's disease and Schizophrenia[11] provides strong motivation for studying how network structure influences the emergence of synchronization between interconnected dynamical systems.

The mathematical discipline which underpins the study of complex networks in Biology and elsewhere is graph theory.[13] The complexity of the networks encountered in cellular biology and the mechanisms behind their emergence presents the network researcher with numerous challenges and difficulties. The inherent variability in biological data, the high likelihood of data inaccuracy[14] and the need to incorporate dynamics and network topology in the analysis of biological systems are just some of the obstacles to be overcome if we are to successfully understand the fundamental networks involved in the operation of living cells. A substantial literature dedicated to the analysis of biological networks has emerged in the last few years, and some significant progress has been made on identifying and interpreting the structure of such networks. Our primary goal in the present article is to provide as broad a survey as possible of the major advances made in this field in the recent past, highlighting what has been achieved as well as some of the most significant open issues that need to be addressed. It is particularly hoped that the article will serve as a useful introduction to the field for those unfamiliar with the literature.

**Example 1. DNA graphs**

The study of DNA sequence is the most important issue in biology science, and there are lots of contributions on DNA analysis and computation from mathematical and algorithmic point of view, out that Hartree- Fock exchange percentage of density functional has a key factor in getting the structure electronic properties. The notable features sequencing platform based on a mathematical framework and it working mechanism has some characteristics, such as: optimizing cost, implement, and sensitivity analysis to different parameters. The demography and reproductive success and by means of coalescent theory to compute mitochondrial DNA sequences from the Japanese sardine. The DNA storage channel and modeled the read process considering profile vectors. They raised new asymmetric coding tricks to combat the effects of sequencing noise and synthesis, and an asymptotic analysis of the number of profile vectors was also presented. At last, two families of codes for this channel model were constructed. To effectively store FASTQ files raised by big DNA sequencers, determined a specialized compressor designing. The ionization potential with single and double excitations was estimated by means of equation of motion coupled cluster trick, and VIEs is estimated in terms of density functional theory with dispersion corrected omega B97x-D. A studied on how to build independent spanning trees on hypercubes and how to use them to predict mitochondrial DNA sequence parts through paths on the hypercube. An alignment-free technology for DNA sequence similarity analysis based on graph theory concepts and genetic codes. The new approach to test the DNA sequences using optical joint Fourier transform. Theoretically studied the transverse electron transport through all four DNA nucleotide bases by electron propagator theory.

Let k $\geq 2$ be an integer. The DNA graph is defined, and it said that a directed graph $D=(V(D),E(D))$ is DNA graph whether it can assign a label $(l_1(x),l_2(x).....,l_k(x))$ of length k to each vertex $x\in V(D)$ as follows

(i) $l_i(x)\in\{A,C,T,G\}$ where i $\in$ {1,2,…..,k}

(ii) $(l_1(x),l_2(x),.....,l_k(x))\neq(l_1(y),l_2(y),...l_k(y))$ if $x\neq y$;

(iii) $(x,y)\in E(D)$ if and only if $(l_2(x),....l_k(x))=(l_1(y),....,l_{k-1}(y))$

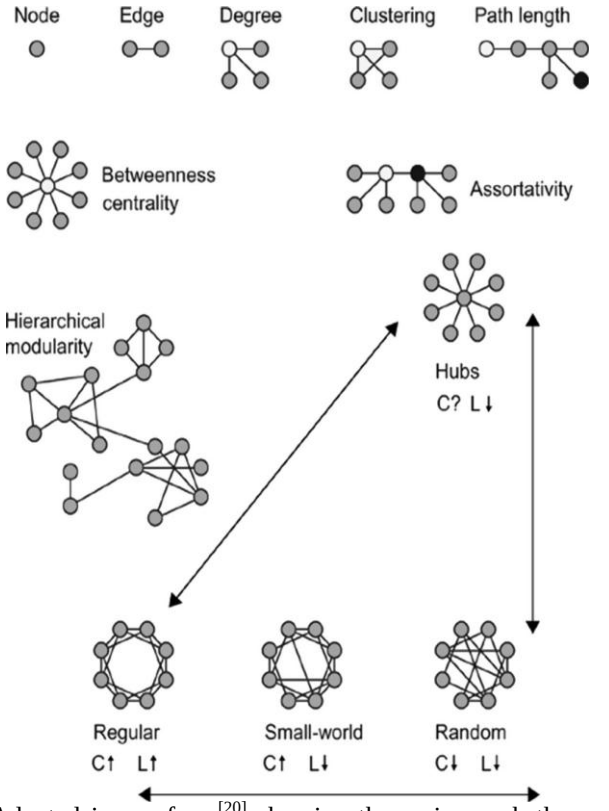
For a multi set consists of oligonucleotides with length k, a DNA graph can be constructed as follows: set each oligonucleotide with length k from the multi set as a vertex; add an arc between two vertices if the k--1 rightmost nucleotides of first vertex overlap with the k -1 leftmost nucleotides of the second one. Several contributions on DNA graph and DNA mathematical expression.

Biological sequence analysis and comparison is another important problem in bioinformatics which replies to the emergence and need for the analysis of different types of data generated through biological research. Molecular sequence and structure data of DNA, RNA and proteins, gene expression profiles or micro array data, metabolic pathway data are some of the major types of data being analyzed in bioinformatics. Among them, sequence data are increasing at the exponential rate due to advent of next-generation sequencing technologies. Since the origin of bioinformatics, sequence analysis has remained the major area of research with wide range of applications in database searching, genome annotation, comparative genomics, molecular phylogeny and gene prediction. The pioneering approaches for sequence analysis were based on sequence alignment, global or local, pairwise or multiple sequence alignment. Alignment-based approaches generally give excellent results when the sequences under study are closely related and can be reliably aligned, but when the sequences are divergent, a reliable alignment cannot be obtained and hence the applications of sequence alignment are limited. Another limitation of alignment-based approaches is their computational complexity when dealing with large-scale sequence data. The advent of next generation sequencing technologies has resulted in generation of voluminous sequencing data. The size of

this sequence data poses challenges on alignment-based algorithms in their assembly, annotation and comparative studies. Thus, alignment-free sequence analysis approaches provide attractive alternatives over alignment-based approaches. In this paper, we will discuss about applications of product of graphs and overlap graphs to compare DNA sequences based on an alignment-free method.


## 2. **Graph theory approach**

The human brain is probably the most complex container of interconnected networks in nature, and the ‘‘network science of the brain,” or network neuroscience, remains a very recent venture in its starting exploring phase. It defines the connection matrix of the human brain as the human ‘‘Connectome.” Network-based algorithms provide parameters that define the global organization of the brain and its alterations at different levels of investigation.[15] Previous studies have applied graph theory to EEG data for the investigation of brain network organization during aging and, in particular, along the continuous line that connects normal aging (Nold), mild cognitive impairment (MCI), and dementia.[16-17] Thus, it was observed that both measures of global integration (path length as an index of information transfer efficiency) and local segregation(clustering as an index of local interconnectedness and network segregation) can discriminate cortical network features, which represent the boundaries separating physiological from pathological neurodegenerative brain aging. On the basis of how both specialized and integrated information processing in the brain are supported by the small-world model[18], this new approach allows the evaluation of functional connectivity patterns and aims to specify whether an optimal balance can be found between local independence and global integration as a favorable condition for information processing.[19]




Adapted image from[20] showing the main graph theory concepts. Reproduced with permission.

Fig. 1 help the readers in the comprehension of the graph theory concepts. A brain graph theory network is a mathematical representation of the real brain architecture that consists of a set of nodes (vertices) and links (edges) interposed between them. Nodes usually represent brain regions, while links represent anatomical, functional, or effective connections, depending on the problem under investigation. In general, the number of nodes is important, but it is not clear whether a minimum number is required. Mathematically speaking, a network is a matrix, where each row represents a node and each column represents the relationship between the current node and every other node in the network. Links between nodes can be weighted or un weighted. Weighted links can represent the size, density, or coherence of anatomical tracts in anatomical networks, whereas these links can represent the strength of correlation or causal interactions in functional networks. Un weighted (binary) networks are often used by applying a threshold to a weighted network, with links indicating the presence or absence of connection. Although in literature most studies use un weighted networks, interest in weighted network analysis is increasing because of the more specific information they can provide. In this review, network analyses on resting-state EEG data, which are considered undirected and weighted or un weighted networks, are reported, focusing on their applications to physiological aging and neurological diseases such as AD and epilepsy. Analysis from EEG in a resting-state condition was chosen because it provides a measure of

connectivity based on the level of co activation between the functional time series of brain regions.[21]

Finally, although MRI technique is not discussed in the present review, the potential usefulness of combining EEG and MRI technologies should be critically considered, particularly MRI, which provides much higher spatial resolution and detailed structural information. The use of functional MRI techniques, including activation and resting-state studies, has reduced the use of EEG in clinical research also, but the reasons for using EEG for connectome analysis instead of MRI could be as follows: the low cost and large diffusion of EEG in clinical centers. Furthermore, the physiological meaning of connectivity within different frequency bands should be obtained just in EEG data and could be more correlated with behavioral pathologies.

## 3. Graph theory applications to EEG data

Considering the above methodological remarks, in the following sections, network studies of physiological aging and neurological disorders, such as AD and epilepsy, are explored.

### 3.1. EEG for the study of physiological aging

This first section reviews studies aimed at understanding whether graph theory application can reveal how normal aging affects the network structure. Boersma and colleagues recorded resting-state eye-closed EEG of young children (5–7 years). The graphs were weighted using synchronization likelihood (SL); the results showed an increase in average clustering and path length, suggesting that a shift from random to more organized small-world functional networks characterizes normal brain maturation.[22] Micheloyannis and colleagues studied SL in the EEG of children (8–12 years) and young students (21–26 years). They found that beta and gamma values of C in children were higher than those in students. They also found that in beta band SW was significantly higher in children than in students. They concluded that the higher synchronization of fast frequencies observed in children reflects brain maturational processes.[23] Smit and colleagues found that connectivity was more random in adolescence and old age but was more ‘‘structured” in middle age. Decrease in SW was also observed in older adults.[24] When we analyzed.[25] EEG data in a sample of 113 healthy human volunteers divided into three groups depending on their ages (young, adult, and elderly), we found that in physiological aging, the normalized characteristic path length showed the pattern Young > Adult > Elderly in the higher alpha band. Furthermore, elderly subjects showed an increase in delta and theta bands unlike young subjects (Fig. 2). This alpha result extends those of previous clinical EEG studies[27-28], in which a reduction in the characteristic path length in the alpha band was observed in patients with AD, compared with that in normal elderly subjects. The increase in normalized alpha path length characterizing AD was also interpreted as a loss of efficiency of communication between distant brain regions. An increase in delta connectivity might therefore reflect a progressive disconnection process of the aging brain as a loss of efficiency of communication between distant brain regions. The loss of structure, as partially expressed by the lower path length in the higher alpha frequency bands, supports, together with the well-known slowing of EEG brain activity and the loss of functional connectivity, the idea that brain aging is –at least in part- a process of progressive disconnection.

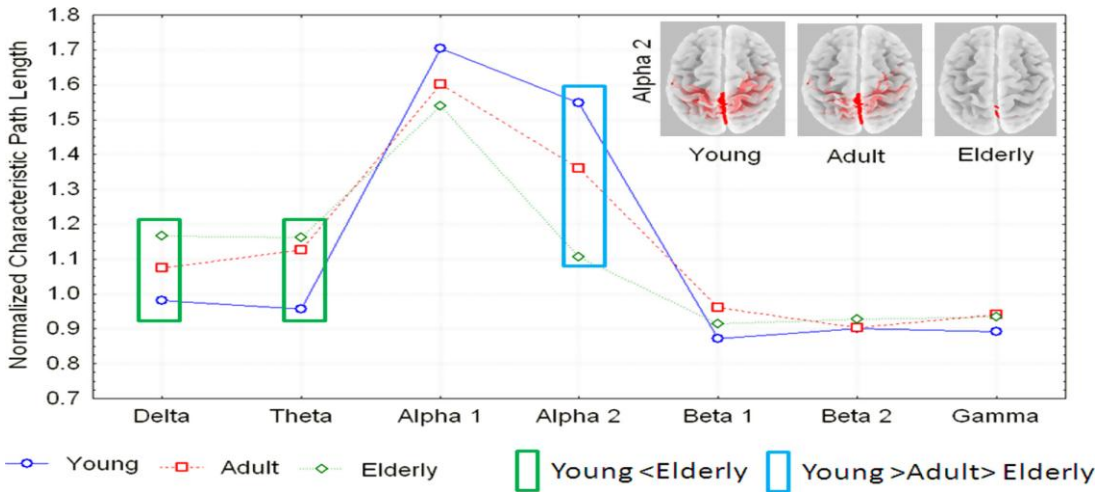



**Fig. 2: ANOVA interaction of the normalized characteristic path length (k) among the factors group (young, adult, and elderly) and band (delta, theta, alpha 1, alpha 2, beta 1, beta 2, and gamma). The lower panel of the figure shows the concomitant cerebral connectivity, mapped by eLORETA, for the alpha 2 band in the three groups, in which the red tract representation belongs to ROIs well connected over the cut-off threshold.**

Of note, a shorter path length related to physiological aging seems counter-intuitive. However, at least in theory, a shorter path length is not necessarily an advantage in a complex network affected by age because it might increase the processing time and the background ‘‘noise” and because the overall structure must maintain

an effective balance between local specialization and global integration. In this context, the modulation of the global but not of the local network parameters during the aging process could be considered a loss in the balancing of the most efficacious type of brain connectivity of the young-adult group. A possible interpretation of the present results is that aging processes provoke progressive disconnection among brain areas. This effect has been revealed in older subjects by an increase in slow and a decrease in fast EEG characteristic path length values, which measure the average shortest path length of a network. This indicates a progressive loss of efficiency in a global index of transfer of information from one part of the network to another.

### 3.2. EEG for the study of pathological aging

Searching for signs of pathological aging, several studies tested whether it was possible to find a trend linking different conditions such as normal elderly subjects (Nold) and demented (AD) patients passing through MCI, by applying graph theory methodology in cortical sources of EEG data.

AD is considered a disease that initially affects synaptic transmission with an overall disconnection, which could be investigated using a network approach because the structural elements of the brain form an intricate network at different spatial scales (ranging from neurons to anatomical regions) from which functional dynamics emerge. In this way, graph theory approach could provide a general language that enables to understand the association of the various pathological processes interacting with each other in AD, such as spatial patterns of cortical atrophy and functional disruptions, and why the disease propagates along specific routes.

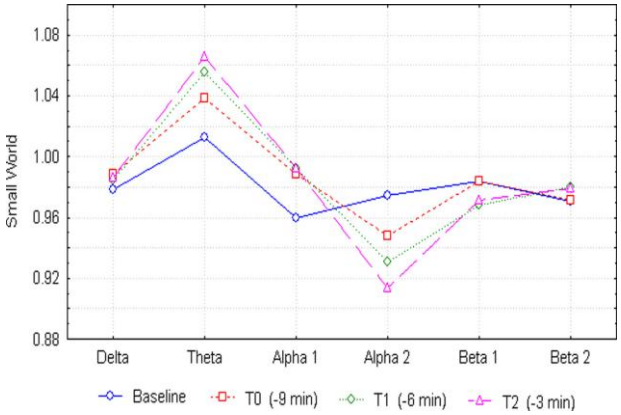
Stam and colleagues applied graph theory to functional connectivity EEG data in beta band of patients with AD and control subjects. Results showed that a loss of small-world network features typifies AD. In fact, in patients with AD, the cluster coefficient C did not significantly change, whereas the characteristic path length L increased. These data suggest a loss of complexity and a less optimal organization. Furthermore, by applying graph theory on EEG data of patients with AD and healthy controls, de Haan and colleagues demonstrated in the first group a reduction in both the clustering coefficient, especially in the lower alpha and beta bands, and the characteristic path length, especially in the lower alpha and gamma bands. Because of the decrease in both local and global connectivity parameters, the functional brain network organization in AD deviates from the optimal small-world network structure toward a more random type. This is associated with less efficient information exchange between brain areas, supporting the disconnection hypothesis of AD.

We analyzed a dataset of 378 EEGs (174 AD, 154 MCI, and 50 Nold). Significant differences between normal cognition and dementia were identified in cortical sources' connectivity. Normalized characteristic path length significantly increased for AD patients compared with those for MCI and Nold subjects in the theta band alone. Instead, normalized clustering coefficient significantly increased in the theta band of AD patients compared with those of MCI and Nold groups and in the alpha 1 band of AD patients and MCI subjects compared with those of Nold group. The slow EEG frequency increase in both global (clustering coefficient) and local (characteristic path length) parameters could be seen as the disease's effect on network's edges and as a sign of functional disconnection. With regard to the outcome observed at low alpha rhythm (8– 10.5 Hz) – which is supposed to reflect the regulation of global cortical arousal[28] – there is a general consensus that the high-frequency alpha rhythms reflect the functional modes of thalamo-cortical and cortico-cortical loops that facilitate/inhibit the impulse transmission and the retrieval of sensorimotor information processing. Because a decrease in path length implies a shift toward network randomness, it can be argued that an increase in high-frequency normalized clustering coefficient for both AD and MCI subjects could reflect compensatory neuroplastic mechanisms. The fact that AD patients are more impaired than MCI subjects in theta but not in alpha band is in line with the hypothesis of an intermediate status of MCI between normal condition and overt dementia, in which the alpha bands are the first to be affected by neurodegenerative mechanisms.

### 3.3. EEG for the study of epilepsy

Brain networks constantly change their dynamic state, switching between movement and rest, behavioral and cognitive tasks, and wakefulness and sleep. The epileptic brain represents a further network's feature with the transient occurrence of paroxysmal firing within neuronal assemblies, which end up with a seizure as time progresses. Characterization of neural networks in epilepsy has gained relevance through time because localized forms of epilepsy are related to an abnormal functioning of specific brain networks without structural damage. Seizures and EEG spiking are considered the result of an imbalance between inhibitory and excitatory signals, thus leading to a hyperexcitable state in which the abnormal rhythms of neural firing cannot be sufficiently controlled by the physiological inhibition mechanism, generating a paroxysmal depolarization shift. In a recent study, we focused on the exploration of the interictal network properties of EEG signals from temporal lobe structures in the context of fronto-temporal lobe epilepsy. Therefore, the graph characteristics of the EEG data of 17 patients suffering from focal epilepsy of the fronto-temporal type, recorded during interictal periods, were examined and compared in terms of affected versus unaffected hemispheres. In this study, EEG connectivity analysis was performed using eLORETA software in 15 fronto-temporal regions (Brodmann Areas BAs 8,9,10,11,20,21,22,37,38,41,42,44,45,46, and 47) on both affected and unaffected hemispheres.

Evaluation of the graph analysis parameters, such as characteristic path length and clustering coefficient—indices of global and local connectivity, respectively—showed a statistically significant interaction among side (affected and unaffected hemispheres) and band (delta, theta, alpha, beta, and gamma). Statistical testing showed that local and global graph theory parameters increased in the alpha band in the affected hemisphere. This could result from the combination of overlapping mechanisms, including reactive neuroplastic changes, seeking to maintain constant integration and segregation properties and trying to contrast the progressive loss of the natural complexity of EEG signals.




Small-world parameter among the factors time (Baseline, T0, T1, and T2) and band (delta, theta, alpha 1, alpha 2, beta 1, and beta 2).

Furthermore, epilepsy is characterized by unpredictable and sudden paroxysmal neuronal firing and/or synchronization occurrences eventually evolving into a seizure. To predict the seizure event, small-world characteristics of a 9-min time epoch immediately preceding individual seizures, each epoch fragmented in three 3-min periods (T0, T1, and T2), were investigated on stereo taxic EEG of drug-resistant epileptic patients explored with depth electrodes before surgery. In work, the importance of using a large number of nodes was evidenced; in this case, the number of contacts was about 100. Seizures are caused by a progressive hyper synchronization of the firing of a critical mass of neuronal assemblies. This implies that a single neuron cannot cause a seizure; instead, a population of cells or – better – a network of neuronal assemblies is needed. Effective connectivity and optimal network structure are believed essential for proper information processing in the brain. Indeed, an association exists between functional abnormalities of the brain and pathological changes in connectivity and network structures. Intra cerebral recordings were obtained for 10 patients with drug-resistant focal epilepsy examined by stereo tactically implanted electrodes; analysis was performed in a seizure-free period of low spiking (Baseline) and during two seizures. Networks' architecture is undirected and weighted. Electrodes' contacts close to epileptic focus are the vertices, and edges are weighted by mscohere (=magnitude squared coherence). Differences were observed (Fig. 2) between Baseline and T1 and between Baseline and T2 in theta band; and between Baseline and T1, between Baseline and T2, and near-significant difference between T0 and T2 in alpha 2 band. Moreover, an intra-band index was computed for small world as difference between theta and alpha 2. An increasing trend of index was observed from Baseline to T2. The more seizure onset was approaching, the less SW characteristics were evident, with an overall progressive loss of complexity of neural network architecture sustaining the EEG signals. According to the results of this study, cortical network features significantly modify their configuration up to about 10 min before seizure onset. Additionally, a proof-of-concept attempt suggests that this type of analysis could predict the incoming epileptic seizure with good performance, thus representing an interesting marker of epileptic risk factor.

## CONCLUSION

Evidence from this review confirms the utility of an innovative mathematical approach to investigate relevant neurological features in real complex brain networks through EEG data. We chose EEG in all our studies because it is a widely used, noninvasive, and low-cost procedure and is an ideal candidate to functional connectivity analysis with a time frame appropriate for brain function (from seconds to tens of milliseconds). Network analysis in neuroscience could help understand how human cognitive functions are linked to neuronal network structure and how they deal with time varying networks' dynamics, thus providing a window for an online view on brain complexity and dynamics. As human brains vary largely in size and surface shape, network analysis is appropriate for assessing this variability and can characterize brain network organization. The characterization of brain networks using connectivity matrices and graphs has the advantage of obtaining a rich structural description that allows an efficient computation and comparison of different connection topologies within a common theoretical framework

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