Chapter 4

Network Theoretical Approach to Describe Epileptic Processes

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Abstract

Epilepsy is characterized by recurrent unprovoked seizures. Recent studies suggest that seizure generation may be caused by the abnormal activity of the entire network. This new paradigm requires new tools and methods for its study. In this sense, synchronization by linear as well as nonlinear measures are used to determine network structure and functional connectivity of neurophysiological data. Electroencephalography (EEG) data can be analyzed using each electrode's activity as a node of the underlying cortical network. The information provided by the synchronization matrix is the basic brick upon which several lines of analysis can be performed thereafter. Detection of community structures, identification of centrality nodes, transformation of the underlying network into a simpler one, and the identification of the basic network architecture are only some of the many lines of basic works that can be done in order to characterize the epilepsy as a network disease. This chapter describes new approaches in network epilepsy, provides mathematical concepts in order to understand the complex network analyses, and reviews the advances in network analyses and its application to epilepsy research.

Keywords: synchronization, temporal lobe epilepsy, electroencephalography, electrocorticography, graph theory, centrality measures, community structures, small-world

1. Introduction

Epilepsy is one of the most common neurological disorders characterized by recurrent unprovoked seizures. It has an incidence of 50–100 cases per 100,000 persons/year in devel-

oped countries, and about 50 million people around the world suffer from epilepsy [1]. The most common type of epilepsy is temporal lobe epilepsy (TLE). Unfortunately, a high percentage of TLE patients are resistant to drug treatment presenting the so-called drug-resistant epilepsy (DRE). Surgery is recommended in such cases as the only curative/palliative alternative. Meta-analyses from literature indicate that 66% of the patients are seizure free in the first two years following the surgery [2]. However, seizures persist in one third of the operated patients; thus, an accurate localization of the epileptogenic zone (EZ) is vital for a good surgery outcome.

Traditionally, seizures in partial epilepsy have been considered to arise from a single focus that recruits other regions in order to spread. Very recently however, an alternative point of view has suggested that ictogenesis (seizure generation) may be caused by the abnormal activity of the entire network instead of being provoked by pathological isolated areas, such as the EZ [3–7]. In fact, the Commission on Classification and Terminology from the International League Against Epilepsy (ILAE) has proposed a new approximation for the classification of seizures and epilepsy types [8]. The new recommended terminology redefines focal seizures as those originating at some points within networks spatially limited to only one hemisphere, or bilaterally distributed in the case of generalized seizures. This new perspective has been mostly inspired, on one hand from the network analyses of data obtained from several diagnostic tools that are routinely used nowadays in the pre-surgical evaluation of epilepsy, such as functional magnetic resonance imaging (MRI) (for review see [9]) or even from the classical one, the electroencephalography (EEG) [4,6,9]. On the other hand, the development of the connectome concept, which describes the connectivity among different brain areas in physiological conditions, has boosted this new perspective. In this regard, three types of connectivity have been defined: the anatomical, which are the structural connections linking the neurons or brain regions; the functional, which describes the statistical relations between activity of different neurons or brain regions; and lastly, the effective connectivity, which assesses the causal effects of one region or neuron to another [10].

Similarly to the impact of network analyses in seizure definition and classification, this new perspective on epilepsy has also modified the traditional pre-surgical evaluation of TLE patients. The traditional zone-oriented approach [11] has been complemented with the recent advent of the network perspective [4,5]. The zone-oriented concept of the EZ can be interpreted under this new point of view as a key property, yet unknown, of the network in charge of generating and sustaining the seizures. The new aim in epilepsy surgery would be now targeted at destroying this particular property of the network instead of being aimed at resecting a cortical area such as the EZ, as it is traditionally done. The importance of identification, delimitation and characterization of the epileptic network clearly shows up when the above considerations are taking into account and justify the great number of works devoted to this issue [12–18].

In this regard, EEG data obtained either invasively or non-invasively, can be now analyzed using each electrode's activity as a node of the underlying cortical network. In this framework, it is fashionable to estimate functional connectivity between cortical areas covered by neurophysiological electrodes through the correlation or synchronization – both terms are used interchangeably through the chapter, although their meanings are not exactly the same

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– matrix of the electrodes' time series. The information provided by the synchronization matrix is the basic brick upon which several lines of research can be built. One of them is the study of hierarchical organization, which through the construction of hierarchical trees provides insightful information of closeness and farness of node's neurophysiological activity. The application of this technique characterizes the underlying dynamical behavior of the whole network and allows to easily reveal those regions of highly synchronized nodes, i.e. synchronization clusters. Also, by combining the information provided by the synchronization matrices, and several techniques borrowed from graph theory, give us the opportunity to study the underlying cortical network as a whole entity.

It is important to emphasize that the network perspective is not only limited to EEG studies but functional MRI (fMRI) also provides evidences of this emerging view. Despite fMRI possesses a lower temporal resolution and is an indirect measure of neuronal activity, as compared with EEG, fMRI has a good spatial resolution and obviously provides critical data about the functional connectivity of the whole brain. In this regard, simultaneous fMRI and EEG studies have revealed the validity of the BOLD analysis [19], showing that changes in the epileptic network actually occur (for a review see [9]). In line with fMRI and EEG data, pathological and structural studies also corroborate the study of epilepsy as a network disorder, since histological studies have revealed neuronal cell loss, gliosis, axonal sprouting, among others in hippocampus of the TLE patients [20]. Indeed, similar changes have been described in adjacent areas to the hippocampus, as the amygdala, the entorhinal cortex, the parahippocampal cortex, certain areas of the temporal cortex, and even other cortical and thalamic areas [9]). All these results suggest that network reorganization occurs in epilepsy from a histological point of view. Similarly, anatomical and diffusion MRI studies supported the histological results, showing loss of grey matter and disorganization of fibers.

In this chapter, we review in a first step, the synchronization concept, its different types and estimators in order to provide an overview of the basic element needed to perform a network analysis of neurophysiological data. Secondly, we present the new network epilepsy approach with detailed and comprehensive explanations of the underlying mathematical concepts needed to fully understand the involved concepts and methodologies. Our aim, thus, is to present the recent advances in network analyses, covering issues such as hierarchical classifications, community detection, centrality measures identification and topological organization in order to state their outstanding relevance in a particular field of biomedical signal processing as it is the evaluation of pre-surgical neurophysiological recordings coming from DRE patients.

2. Synchronization

2.1. Concepts

Synchronization is the building block upon which functional networks are constructed. Once a functional relation between any two cortical areas is established, for all of the recording

electrodes, the first step in the network construction can be confidently performed. This is the main reason why synchronization estimation is so critical. In recent years there has been a rising number of works dealing with this issue, and in particular in their application to brain functional connectivity. It is important to emphasize that not a single method can accurately provide the true, if something like this exists, underlying synchronization, because each one possesses its drawbacks and benefits. In any case, several methods should be employed.

Synchronization is closely related to epilepsy, as commented Section 1. Conceptually, synchronization is the adjustment of the internal rhythms of two systems due to an existing (weak) interaction between them [21]. Furthermore, it is essential for synchronization to be established, the presence of two or more self-sustained oscillators with their own rhythms.

2.2. Types of synchronization

The most intuitive form of synchronization is the *frequency synchronization*. That is, two systems, e.g. x and y, through mutual interaction adjust their own rhythms to share a similar frequency $\omega_x = \omega_y$. Frequency synchronization does not need that exactly the same frequency be shared by two synchronized systems, however. Instead, the following relation is valid: $n_x\omega_x - n_y\omega_y = 0$, where n_x and n_y are integers. Moreover, in chaotic systems it seems to be less restrictive than other types of synchronization (phase or identical), because instantaneous values of variables may be different.

In addition to frequency synchronization, phase can also become synchronized, this occurs when the phases of both systems are similar. Similar to the frequency synchronization, both phases do not have to be necessarily equal since *phase synchronization* also occurs when a constant time difference exists between them. The synchronization of both frequency and phase is called *identical synchronization*; likewise, when a lag exists between them it is termed *lag synchronization*.

When a system, slave, is under governance of another system, master, there is a unidirectional relation. In this condition, the synchronization is called *generalized synchronization*. To describe this type of synchronization in EEG data is necessarily to use the embedding theorem which allows to reconstruct an equivalent system of the original one.

The different types of synchronization described above can be used for the analysis of synchronization of more than two systems. However, in those cases it is better to use the *full synchronization* in order to determine the synchronization of the whole oscillators' interaction rather than the interaction between each pair. The oscillator is replaced by its instantaneous phase and intrinsic synchrony, and the spatial distribution is added. The spatial distribution is formed by the coupling strength between adjacent oscillators and the existence or absence of each link. The whole system synchronization is achieved by an order parameter that provides information about the phase coherence of the oscillator and the degree of synchronization.

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2.3. Synchronization estimation

Several numerical methodologies have been used to determine the synchronization; the most common are the cross-correlation [22] and the cross-spectrum analysis. However, new methodologies have gradually been introduced to evaluate networks connectivity. This is, to address the temporal correlation between spatially separated nodes or the influence of one neural system over another, i.e. the functional and effective connectivity, respectively (see Section 3).

Broadly speaking, two types of correlation exist, the linear and nonlinear correlations [23]. Both have its pros and cons, however. Usually, a tradeoff between accuracy and speed appear at the time of deciding which method to use. These two premises are critical, mainly the first one, because of the high number of comparisons, which increases the number of false positive, i.e. the number of significant correlation that does not correspond to real signification. In these cases, statistical methods have to be used in order to improve the sensitivity, for instance, the classical methodology, such as Bonferroni correction, or more sophisticated systems as the surrogate data testing.

Cross-correlation is essentially an amplitude method in the sense that it quantifies co-movements in two time series by "comparing" amplitudes in the signals. Pearson correlation coefficient [22] is the best known method for synchrony calculation by cross-correlation since it is a function of the lag between signals; the lag has to be specified. For two discretized time series, x_i and x_j, at times k, in a 0 lag condition the ρ_{ij} is calculated as follows,

$$\rho_{ij}(0) = \frac{\sum_{k=1}^{N_{wins}} (x_i(k) - \overline{x_i})(x_j(k) - \overline{x_j})}{\sqrt{\sum_{k=1}^{N_{wins}} (x_i(k) - \overline{x_i})^2 \sum_{k=1}^{N_{wins}} (x_j(k) - \overline{x_j})^2}} \tag{1}$$

Correlation coefficient range is between $-1 \leq \rho_{ij} \leq 1$, calculated in the time window N_{win}. Higher negative values mean a higher inverse linear correlation whereas higher positive values indicate a higher linear relation between time series.

A zero cross-correlation in Eq. (1) does not mean that there is no correlation because nonlinear correlation could also exist; this is because nonlinear analyses compare other parameters rather than amplitude [24]. For instance, phase synchronization measures the differences in phases. In two time series x_i and x_j, at times k, the phase synchronization is calculated by the mean phase coherence, R_{ij},

$$R_{ij} = \left| \frac{1}{N_{wins}} \sum_{k=1}^{N_{wins}} e^{\Delta\alpha_{ij}(k)} \right| \tag{2}$$

Correlation coefficient range is between $0 \leq R_{ij} \leq 1$, calculated in the time window N_{win}, where $\Delta\alpha_{ij}(k)$ is the instantaneous phase difference at the discretized time k.

Information theory [25], through mutual information, has been used to evaluate the association between the two variables. Roughly speaking, if the (Shannon) entropy of a time series x_i quantifies the degree of uncertainty about future values of it, the mutual information between x_i and y_i quantifies the reduction of uncertainty in x_i knowing y_i. Thus, mutual information between two time series evaluates the statistical association between them. Mutual information range from zero to positive values, such that zero means that the two systems are statistically independent.

Figure 1 displays the typical synchronization patterns calculated from a typical recording of a scalp EEG. In **Figure 1A**, the correlation matrix calculated through the Pearson estimate is depicted. **Figure 1B** shows a similar calculation but using Eq. (2), corresponding to the phase synchronization. On the contrary, **Figure 1C** shows the synchronization calculation carried out by using the mutual information measure. Note that in this last case diagonal elements have been eliminated because they have not upper bound.

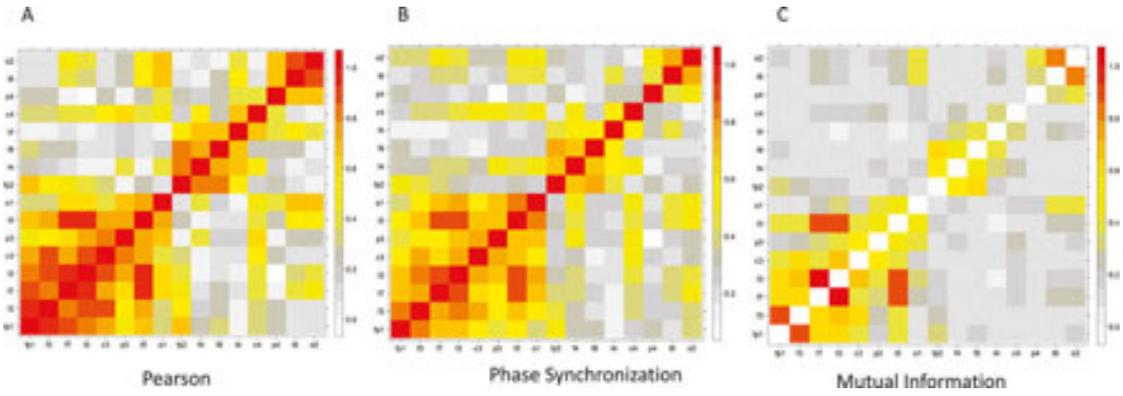

Figure 1. Synchronization patterns: synchronization matrices for three different measures calculated over 10 s of scalp recordings. (A) Pearson correlation, (B) phase synchronization using the mean phase coherence (Eq. (2)), (C) mutual information with diagonal elements set to 0 in order to make it clear the interaction between different elements (see main text).

Finally, the integration of these different synchrony measurements in a spatially extended system is what is called spatial synchronization. It is especially useful when dealing with neurophysiological data in order to gain insight of the underlying network, and becomes the main concept for several network analyses that are the subject of this chapter. The spatial synchronization is the organization of the whole network based on their nodes interaction, i.e. correlation between every pair of nodes. Firstly, transformation of the synchrony matrix to distance is required, i.e. higher correlations mean closer distances between nodes, in order to perform a hierarchical organization (see Section 3.4.1). Several methods and algorithms exist to perform the hierarchical tree; the best known is the hierarchical clustering [26]. It organizes nodes in smaller groups based on their higher correlation, or more properly their closer distance, to generate groups of highly linked nodes, known as cluster.

2.4. Synchronization and epilepsy

Late 1940s and early 1950s descriptions [27] presented epilepsy as a neurological disorder associated with excessive synchrony leading to a state of "hypersynchrony", an idea maintained recently. However, recent advances in chaos theory, complex networks and nonlinear time series analyses have reviewed this classical interpretation of synchronization and its application to seizure characterization. Nowadays, epilepsy is far from being considered as a merely hypersynchronized "state". Extent data from literature present epilepsy as a synchronization/desynchronization process, remarkably active during seizures. Dramatic changes in synchronization have been quantified during the seizure extent, highlighting thus the concept of synchronization as a truly process instead of a particular state [24,28,29]. This section will approach the relations between synchronization and epilepsy.

2.4.1. Synchronization and hypersynchronization

From a classical [30,31] and a fundamental point of view, the epileptic activity starts as a paroxysmal depolarization shift (PDS) in thousands of hypersynchronously neurons causing a mesoscopic manifestation in the EEG recordings – the well-known interictal epileptogenic discharges (IEDs) [32–34]. The spread of this activity, which in physiological conditions would remain confined due to weakened inhibition of the surrounding areas, induces the seizure start. This means that large population of neurons far from the seizure onset zone ones triggered synchronously. Synchronization thus can be studied at two different scales, i.e. local and global.

Although seizures are the pathophysiological definition of epilepsy, other EEG disturbances are considered as clinical signs. IEDs are widely accepted as an EEG marker of epilepsy since they are present in 80–90% of the patients. IEDs present different patterns in the EEG recordings, such as spikes, poly-spikes and/or sharp waves [35, 36]. The way in which PDS manifest as IEDs can be explained by local synchronization mechanisms, specifically, strong and weak mechanisms of interaction. The strong mechanism involves the direct communication between neurons by chemical or electrical (gap junctions) synapses [37]. In this regard, computational simulations of the dentate gyrus, one of the components of the hippocampal formation and an area highly involved in temporal lobe epilepsy, have demonstrated that the incorporation of a small number of highly interconnected hubs greatly increase the hyperexcitability of the network [38], modifying the network topology toward a scale-free one. Therefore, it is suggested that the strong mechanisms increase the synchronization of the whole network inducing IEDs manifestation. On the contrary, weak interactions are due to the extracellular space changes of ions concentration or electrical field transmission induced by the activity of neighboring cells [39]. Both interactions are present in physiological processes and are needed to an appropriate brain function; however, an enhancement of this processes due to the several pathological issues produces the IEDs. To summarize, IEDs can be considered as the result of a small number of neurons triggering simultaneously driven by weak and strong interactions in a process considered as hypersynchronization, or suitably, a local full synchronization process.

The clinical relevance of IEDs is reflected in the huge efforts made by the researchers to describe and identify them [40]. In fact, most of the past publications use traditional raw EEG analysis in order to lateralize and localize the seizure by the presence of IEDs, since the ipsilateral side presents a higher number of IEDs as compared to the contralateral [41–43]. The first evidence of distant synchronization in epilepsy occurred by the analyses of IEDs, demonstrating a hippocampal–entorhinal cortex interaction [44]. However when a synchronization analysis of the interictal period is performed, a critical issue has to be considered: the role of IEDs and the background interictal activity in the synchronization of interictal period. In reference [45], the authors deal with this question; they demonstrated that IEDs are a 1.2, 10, 13.3, 33.3% of the total time in scalp EEG, foramen ovale electrodes (FOE), electrocorticography (ECoG) and depth electrode recordings, respectively. These results give an idea of the contribution of IEDs in each type of recording to the synchronization measurement. Surprisingly, the intuitive association of a higher presence of IEDs in the ipsilateral side with a higher synchrony in the same side presents controversial results, with works favoring this possibility [46–48] and others not [49]. Perhaps this disagreement can be explained by the above-explained synchronization bias of the depth electrodes as compared to FOE, since works favoring higher synchronization in the ipsilateral side were performed in depth electrodes recordings.

The classical definition describes seizure as a hypersynchronization of a large amount of neurons; however, recent evidences present it as a more complex phenomena. As stated earlier, synchronization has to be considered a dynamical process and that is what happens in a seizure. An increase of desynchronization is observed in the first stages [50] followed by a large-scale increase in synchronization. Hypersynchronization has also been proposed as a seizure termination process, since excessive activation of neurons induces several mechanism of autoregulation entailing seizure termination [29]. Seizure synchronization depends on the spatial scale, the type of synchrony and the EEG patterns analyzed, among others. Despite hypersynchronization also occurs in seizure at cellular level, only a 30% of neurons change its firing rate [50] during partial seizures. This suggests that a dynamical approach is more appropriate to analyze seizure synchronization.

2.4.2. Desynchronization

The role played by desynchronization in epilepsy has been well documented in the literature [49–53]. Far from challenging the classical point of view, desynchronization has been integrated into the epilepsy facts providing a new perspective. It occurs not only at a global scale but also at the cellular level, since desynchronization has also been found in seizure-like events of cellular studies [52].

First evidences of desynchronization in seizure were reported by Gastaut et al. [54], by describing the electrodecremental seizures. Since then, several works have reported desynchronization prior to seizures onset. Desynchronization has been described in the analyses of depth electrodes recordings by using phase synchronization methodology. A decrease in the mean phase coherence occurs 15–20 min after seizure onset [53]. Similar results were found only in the beta-band [55]. Two hypotheses were derived from these results; one suggests that desynchronization favors the recruitment of regions until full synchronization is achieved [46],

and the other suggests that desynchronization is the result of an adjustment process between two different recorded areas, one with physiological synchronization levels and the other with higher levels because of being part of the seizure onset zone [53]. Surprisingly, desynchronization was also described in the first half of seizures during secondary generalization [56,50]. The authors suggest that this is due to different routes and lags during the seizure propagation [57].

Not only in seizures but also during the interictal period, desynchronization also seems to play an important role in the epilepsy dynamics. Lower levels of synchronization were reported [49,58] in the ipsilateral side, as compared with the contralateral one, to seizures in TLE patients. These lower levels were maintained also during the seizures [58].

Desynchronization also occurs at the cellular level as it was demonstrated in an elegant study of Netoff and Schiff [52] in *in vitro* hippocampal slices. They show the existence of decreased synchronization immediately after ictal-like activity. They observed this change using both linear and nonlinear methods. The initial desynchronization can be explained because of the presence of microdomains of highly synchronized neuronal clusters present in ictogenesis in *in vitro* studies [59,60]. Moreover, microseizures have been described prominently in the seizure onset zone in human recordings [61–63]. Zones that present microseizures are good candidates of being part of the seizure onset. However, instead of single initial onset zone, multiple distant microdomains that synchronize and produce the macroseizure could also be another mechanism of seizure onset [29]. In both cases, the presence of different regions disturbs the synchronization estimation, that is, if synchrony is measured in a region that includes areas generating ictal activity and others remain unaffected the global results will be a desynchronization [64]. These results were also confirmed by the computational and electrophysiological models, demonstrating that seizure-like activity can be induced even when the synaptic strength of neurons is small, suggesting that higher excitatory strength is not needed to seizure induction [65].

This new perspective of epilepsy as a dynamical process has provided new insights of epilepsy and seizures, bringing more evidences that justify the complex network analyses. Although the use of synchronization measures by epileptologists is still rather marginal, a raising interest in this decade has appeared to perform analyses by using linear as well as nonlinear methods. The next section introduces concepts and methodologies of the complex network analysis, mainly based on synchronization methods, applied to neurophysiological data.

3. Networks

Traditionally the brain has been considered as a compartmentalized structure with particular functions in each area. However, over the last decade a network approach has been proposed as a more accurate model for brain functioning, leading to the appearance of the connectome concept [66], a connectivity map derived from the neurophysiological and imaging data.

Besides the network-oriented study of physiological brain connectivity, the study of several pathologies, such as epilepsy, has also been focused on the network paradigm. Evidences from

EEG studies have raised this alternative point of view. In fact, the ILAE proposed a new terminology including the network concept for the classification of seizures and epilepsies [8]. Moreover, several studies of the ictogenesis [3–6] suggested that seizures are caused by the abnormal activity of a network rather than by an isolated area malfunction. All these information, in particular the last statement, has boosted a large amount of re-analysis of EEG recordings under this new perspective [4,5,11]. Indeed, a rising number of works have appeared in the recent years supporting this idea [12–18].

To deal with this new paradigm, studies are increasingly using graph theory, a mathematical framework that studies the general properties – graphical, topological, statistical, etc. – of a set of nodes interconnected by links. Any kind of system can be described and characterized under this framework as long as the system's elements can adequately be represented by network´s nodes and their relations by links. In the case of the brain, and in particular with respect to the neurophysiological characterization, network nodes are represented by cortical areas covered by the electrodes' contacts and the links between them by the existing synchronization level in their electrical activity. As shown below, the type of links considered between the cortical areas determines the type of network.

Considering the brain as a connectome, three main categories of parameters can be used to extract valuable information of the network activity. These three categories correspond to the three scales where a network can be evaluated, the most basic, centrality or nodal measures; the intermediary, community structures; and the most global, the topological organization. Centrality measures study the significance of the nodes inside the network by determining its characteristics; community structures are based on the recognition or assessment of communities of nodes, so-called clusters or modules; and topological organization uses the average of some of the centrality parameters to determine the properties and architectures of a given network. These variables can be correlated with behavioral data (task performing results), clinical data (treatment or surgery outcome) or different pathologies providing a valuable knowledge or a key target in the pathological network. Thus, in the next section, network parameters have been explained providing definitions and mathematical notations, and its use in epilepsy has been discussed.

A final remark regarding the nature of the network approach is in order here. When dealing with very large networks, like networks of networks, composed of a very large number of nodes, the proper approach to network characterization is by the statistical mechanics of network. In this sense, network characterization is preferably done by the statistical properties of their nodes and/or links. The most common examples are for instance to look at the statistical distribution of the nodes connectivity ("degree", see below) and ask whether these distributions fit in any of the standard distributions: random networks, scale-free networks, small-world networks, etc. However, these kinds of networks have typically a huge quantity of nodes, which allows to study their properties across several scales. A typical example of these kinds of networks is the internet, composed of routers and computers as nodes, and the wires and cables, which connect them as the physical links. The kind of networks we are able to characterize in studying neurophysiological records is nonetheless of a very different kind.

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3.1. Types of networks

We briefly summarize here some basic types of networks. The most basic representation of a network is by considering only the nodes and links the network is made of. **Figure 2A** represents a network of this type composed of 34 nodes and 77 links between some of the nodes.

A step into a more complete description of a network is by adding "weights" to the links, that is, it is not only relevant whether or not two different nodes are connected by a link, but also the intensity of the links does also matter. This is represented in **Figure 2B** in such a way that links' weights are represented by lines width, such that more intense connections are represented by thicker lines.

In the case we are working on, this is represented by the estimation of the synchronization level between the electrical activities covered by the corresponding contacts.

More complex representations may be achieved when directionally is introduced in the interaction between two different nodes, as it is represented in **Figure 2C**.

Other situation including finer details is represented in **Figure 2D** such that nodes' characteristics are also included in the description, represented in this case by the nodes' sizes. Other, more complex situations can be represented in the network descriptions.

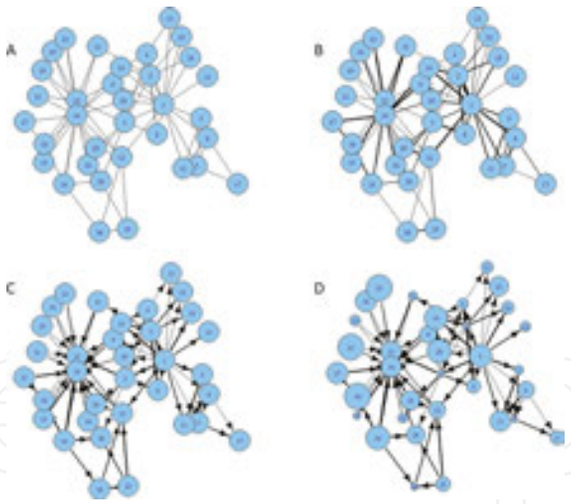

Figure 2. Different types of networks constructed with 34 nodes: (A) unweighted undirected network with equally important nodes; (B) weighted undirected network with equally important nodes; (C) weighted directed nodes with equally important nodes and (D) weighted directed network with unequally important nodes.

From a mathematical point of view, a "simple" network, as the one of **Figure 2A**, is fully characterized by giving the "adjacency matrix" whose elements are binary numbers a_{ij} denoting the presence or absence of edges, or links, between nodes *i*and *j*, that is $a_{ij} = 1$ if a link between node i and node j does exist and $a_{ij} = 0$ if not. Because the adjacency matrix is a symmetric matrix, that is, if a link between nodes i and j exists, then $a_{ij} = a_{ji} = 1$, the total number

of links in network with adjacency matrix a_{ij} is the sum of 1's in a_{ij} divided by 2 (because of symmetry) minus the number of nodes in the networks (diagonal elements).

When dealing with networks like the one depicted in **Figure 2B**, the adjacency matrix contains the weights, that is, the 1's in the adjacency matrix are replaced by the corresponding weights w_{ij}. These kinds of networks are called weighted networks. Both kinds of networks, weighted and unweighted, are typical examples of functional connectivity representation in the neurophysiological realm. Effective connectivity on the contrary, when directionality counts are typically represented with the networks, is depicted in **Figure 2C** and **D** [10].

3.2. Networks from time series

Having described the basic properties of networks, the following step is to know how to construct the network from the recording time series. This is a critical step when the objective is to analyze neurophysiological recordings under a network perspective.

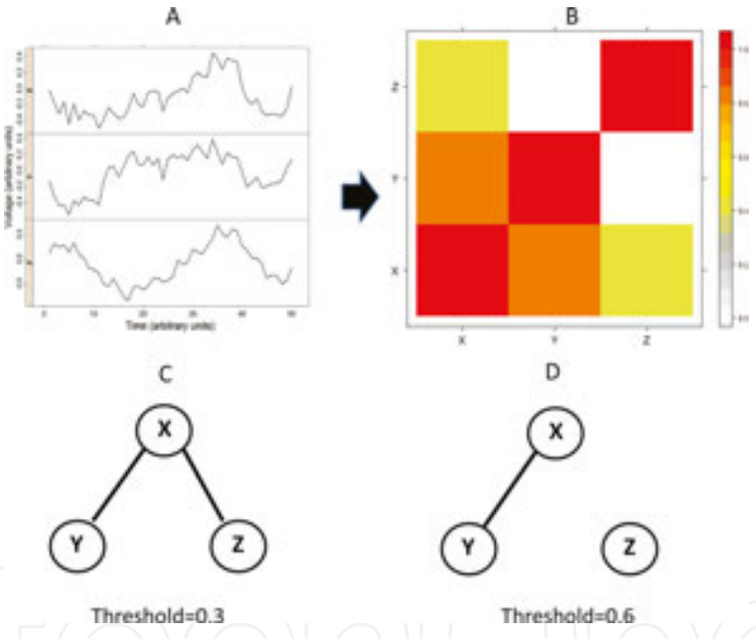

Figure 3. Network construction from simulated time series: (A) three correlated time series, X, Y and Z, (B) correlation (Pearson) matrix of time series of panel A, (C) network corresponding to the correlation matrix of panel B (threshold = 0.3) and (D) network corresponding to the correlation matrix of panel B (threshold = 0.6).

In **Figure 3**, the basic steps of constructing a simple network from simulated time series are displayed. Three synthetic time series X, Y and Z are shown in **Figure 3A**. With the objective to know whether any kind of functional connectivity exists between these time series, a synchronization measure (see Section 2.3) is calculated. In this way, an estimation of the potential relations between these recordings is assessed. **Figure 3B** shows a simple correlation estimate, Eq. (1), between these three time series. This figure shows the existence of a correlation close to 0.8, a rather intense value, between X and Y time series; the correlation between X and Z is close to 0.5, and between Y and Z is close to 0.2. Note that the correlation calculation

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accomplished in this way provides connectivity between any pair of time series even for the cases with very low values, giving rise to a fully connected network. This means that apparently uncorrelated time series, with a correlation values close to 0, will nonetheless be linked. Several methods can be used to eliminate these weak links. The first and more obvious is to select only those statistically significant correlations. On the contrary, one can choose an arbitrary threshold and eliminate those correlations below this particular value. This is what is displayed in **Figure 3C** where a threshold equal to 0.3 has been used. The basic network constructed in this way possesses only two links, X-Y and X-Z, because the link Y-Z, equal to 0.2, has been eliminated by the used threshold of 0.3. Whether a more stringent threshold is used, for instance equal to 0.6 as in **Figure 3D**, one of the former links is also discarded, X-Z, and the new network possess only one link, X-Y and one isolated node, Z. We have constructed in this way a non-connected network, because it possesses isolated nodes.

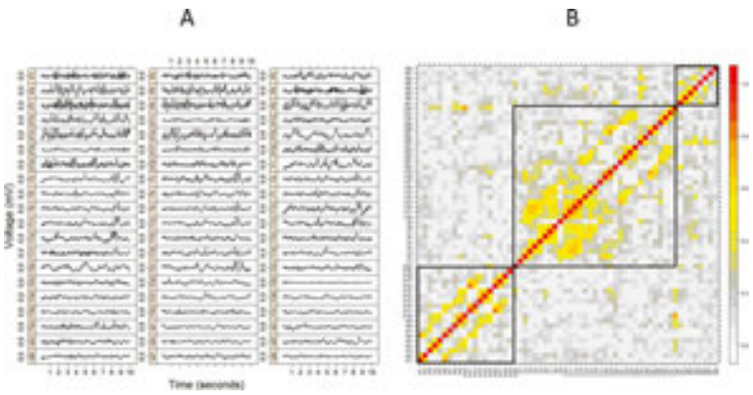

Figure 4. Network construction from neurophysiological time series: (A) actual time series from subdural electrodes and (B) matrix of absolute values of the correlation (Pearson) measure. Solid black squares delimit intra-area interactions.

A more complex and real example is depicted in **Figure 4**, taken from a typical neurophysiological recording of subdural electrodes. The set of electrodes comprises two subdural grids of 5×4 and 4×8 electrodes and a strip of 1×8 electrodes. A typical recoding lasting 10 s is displayed in **Figure 4A** and the correlation matrix in panel B. Note that all of the correlations values are positive. This is so because we have plotted, and also used, the absolute value of the correlation estimate. No matter in which "direction" the relation exists as long as it exists. It is easy to recognize in this figure the approximate boundaries of intra-area correlations (black solid lines). As mentioned above, the next step is in the selection of a threshold with the objective of simplifying the network. In **Figure 5A** and **B**, two examples of thresholded correlation matrices with 0.2 and 0.5, respectively, are displayed. Using this information the last step is to construct the network as the ones displayed in **Figure 6**. In the first case, **Figure 6A**, the correlation matrix with a threshold of 0.2 was used to construct the network. Due to the low value of threshold employed, 0.2, too many links populate the network. When greater threshold value is employed, as 0.5, only those stronger links remain (**Figure 6B**). As a final remark, note that both networks displayed in **Figure 6** seem to be of the kind unweighted (see Section 3.1), because no apparent differences exist between the links' width. However,

every link has a weight associated with it, which is given by the corresponding correlation value. Thus, from this point on one can choose between two different scenarios to work, whether on an unweighted or weighted network. Different network properties and measures are explained in the next sections.

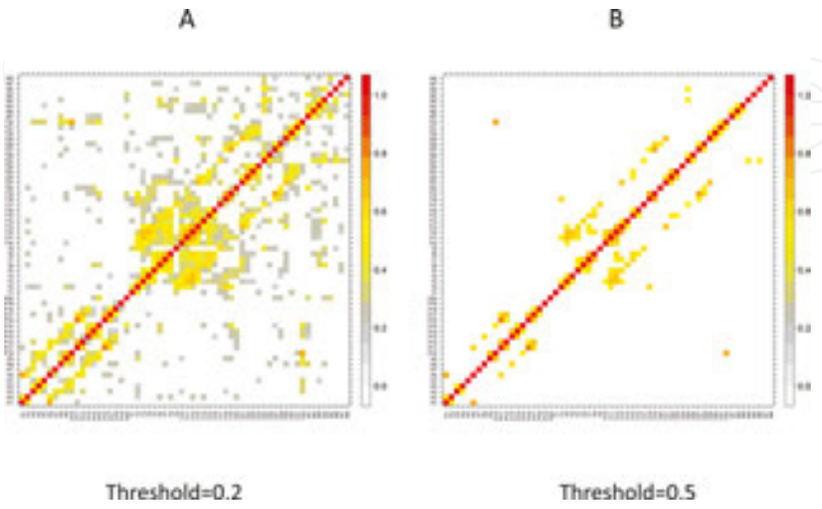

Figure 5. Network construction from neurophysiological time series: (A) Filtered (thresholded) correlation matrix when a threshold equal to 0.2 is applied and (B) filtered (thresholded) correlation matrix when a threshold equal to 0.5 is applied.

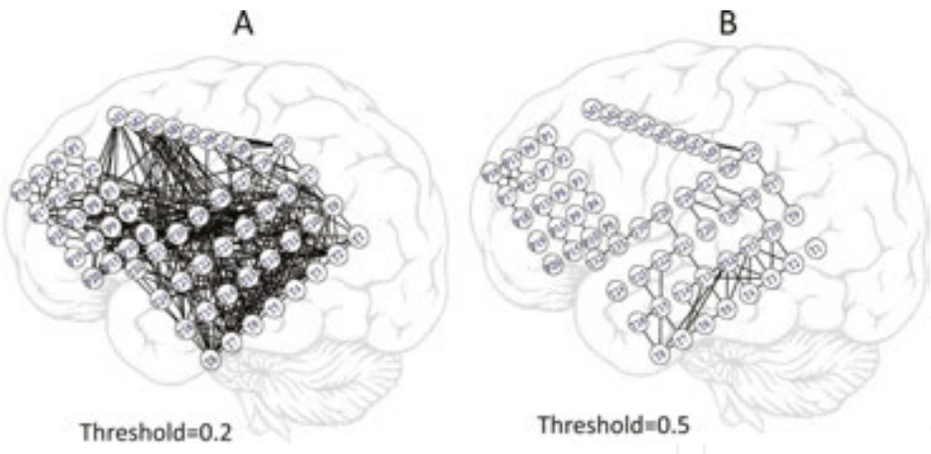

Figure 6. Network construction from neurophysiological time series: (A) network from time series of **Figure 4**, derived from the correlation matrix of **Figure 5A** and **(B)** network from time series of **Figure 4**, derived from the correlation matrix of **Figure 5B**.

3.3. Centrality measures

Centrality measures aim to study the nodes' characteristics and their relevance inside the network (**Figure 7**). Centrality measures characterize hubs nodes inside the network, a fact of surmount importance regarding seizure onset and spread. There are several centrality

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measures classified accordingly with the characteristics they measure, but we will only present here the most used in the literature, namely: degree, betweenness and local synchronization strength (for review see [10,26,67–69]). All these measures can be calculated for both weighted and unweighted graphs, although we only include here those corresponding to unweighted graphs. When appropriate, weighted definitions are going to be explained. For an extended review of weighted definitions, see [69].

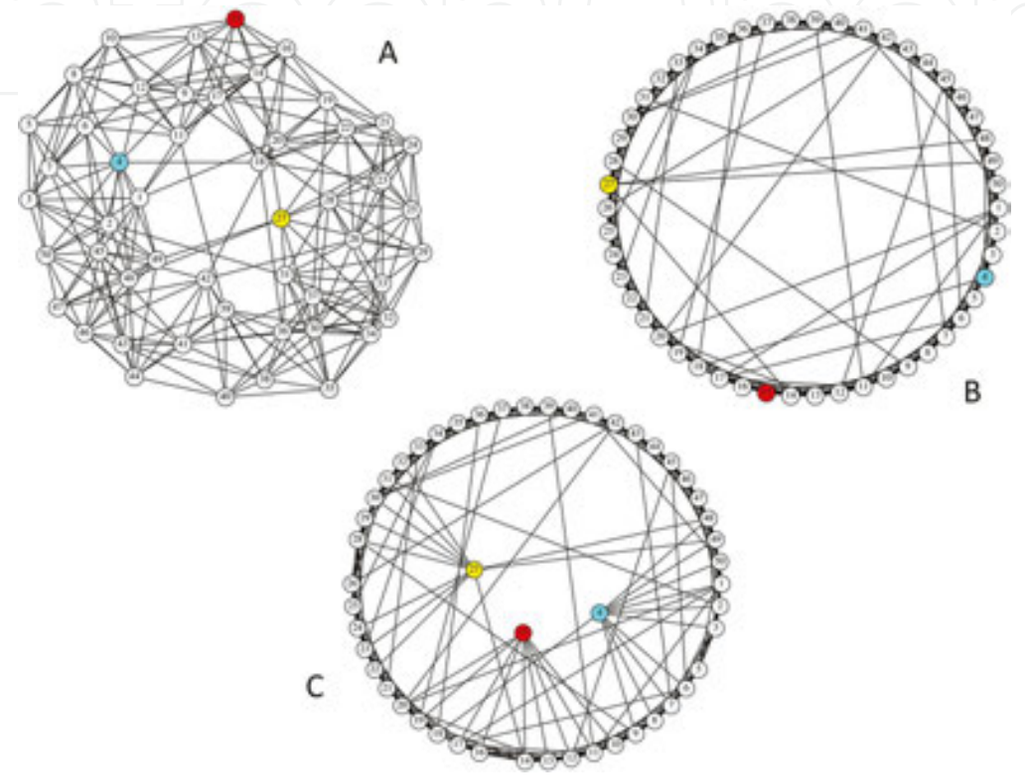

Figure 7. Centrality measures in a simulated network. In red, the node with maximum clustering coefficient. In blue, the node with maximum degree and, in yellow, the maximum betweenness. (a) Disordered network. (b) ordered network according to numeration, i.e. nodes are numbered according to their neighborhood. (c) ordered network according to numeration highlighting nodes with maximum values of centrality measures.

3.3.1. Concepts

As shown in Section 3.1, an unweighted network is fully described by the adjacency matrix a_{ij}. The number of links of a particular network node is called *node's degree*. The degree k_i of a node i is the number of edges that connect to other nodes

$$k_i = \sum_{j \in N} a_{ij}, \tag{3}$$

where N is number of network's nodes and a_{ij} are the binary element of the adjacency matrix. In a directed graph, the node's degree corresponds to the sum of ongoing k_i^{in} and outgoing

k_i^{out} edges, $k_i = k_i^{in} + k_i^{out}$. The importance of a node inside the network is directly linked to its degree level, i.e. a node with high degree possesses a great number of connections with other nodes of the network, increasing substantially connectivity with the rest of the network.

Betweenness can be defined as the capability of a node to facilitate the communication across the network. Betweenness of a node is defined as the number of shortest pathways that pass through this node. The betweenness b_i of a node i is

$$b_i = \sum_{j,k \in N, j \neq k} \frac{n_{jk}(i)}{n_{jk}} \tag{4}$$

being $n_{jk}(i)$ the number of shortest pathways passing through node i, and n_{jk} the total number of shortest pathways between nodes j and k. The betweenness concept is also applicable to edges, being the number of shortest pathways passing through a particular edge. A node with high betweenness has a great influence in the communication between other network nodes serving itself as an in-between relay. A node with a high degree may have a high betweenness; however, a node with high betweenness may have a low degree if it is located in a strategic position in the network.

Local synchronization, also known as *strength*, is the sum of weights of a particular node with its first neighbors divided by its degree. Thus, the local synchronization is represented as [70]

$$s_i = \frac{1}{n_i} \sum_{j=1}^{n_i} w_{ij}, \tag{5}$$

being w_{ij} the synchronization value between nodes i and j, and n_i is the number of first neighbors of node i. Local synchronization gives an idea of the contribution of each node to the total synchronization activity; a node with a higher local synchronization will contribute greatly to the global synchronization and perhaps to determine role in a network as a hub.

Clustering coefficient is defined as the proportion of neighbors' nodes that are also neighbor one of each other, characterizing the local connectedness in a network. According to [71], the clustering properties can be overestimated if weights are not considered when calculating clustering coefficient. So, the weighted clustering coefficient of node i is

$$c_i = \frac{1}{s_i(k_i - 1)} \sum_{j,k} \frac{w_{ij} + w_{ik}}{2} a_{ij} a_{ih} a_{jh}, \tag{6}$$

where k_i is the degree of i, s_i is its strength, a_{ij} are the binary elements of the adjacency matrix and w_{ij} are the weights between nodes i and j. The clustering is considered a segregation

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parameter because it describes the existence of specialized nodes, i.e. higher clustering coefficient means a higher connection density in the local subnetwork that surrounds the given node.

The following measure is not exactly a centrality measure, but nonetheless its importance has been explained in the following sections. The *Shortest path lengths* is the smallest number of edges that connect two nodes i and j, that is

$$d_{ij} = \sum_{a_{uv} \in g_{i \leftrightarrow j}} a_{uv}, \tag{7}$$

where $g_{i \leftrightarrow j}$ is the shortest path between i and j across the network nodes. The shortest path lengths is considered a measure of integration because it describes connectivity between distant nodes. This is why shortest path lengths is more informative as a global parameter, providing information about the global network integration through the average path length (see Section 3.5).

3.3.2. Applications

The most basic application of centrality nodes in epilepsy is in localizing areas involved in seizures. In [70] an approximation to this critical issue was carried out with the objective to assess whether nodes with high local synchronization participate in seizures in one way or another. In this study, functional connectivity was evaluated during intra-operatory ECoG by using three different measures: cross-correlation, phase synchronization and mutual information (Section 2.3), with a better performance of the two firsts [70]. Those cortical areas covered by electrodes with higher local synchronization seem to be deeply involved in seizures appearance because when these areas were resected during the surgery, patients remained without post-operative seizures. These results agree with other groups that observed higher synchrony in seizure onset zone [6,46,72].

Moreover, those areas with higher local synchronization also display low temporal variability, suggesting that their stability is also critical at the time to be involved in seizure generation [15]. It is argued [15] that the existence of particular areas with both high local synchronization and low temporal variability increase *seizurability*, i.e. the capability of the network to seize. On the contrary, no correlation could be established between these high synchronization areas and seizure onset zones. Altogether, these results seem to favor the hypothesis about seizures generation, which postulates that desynchronization is a preexistent state of the cortical areas and a transient synchronization help to spread the seizures.

The above-reported findings were all accomplished during the interictal period. However, long-run analysis carried out on subdural electrodes was also performed with the objective to explore the dynamics of these high local synchronization areas. In one study [18] of a patient with partial seizures – with and without secondary generalizations – a similar analysis was carried out. The analysis during partial seizures revealed temporal changes in those areas with higher local synchronization. Both types of seizures start in areas with high interictal local

synchronization and both seizures present similar patterns in the first part of the seizure. These data support the hypothesis of the role of interictal local synchronization areas in seizure formation.

To summarize, altogether these data demonstrate how the centrality measures are a valuable tool for the analysis of invasive neurophysiological recordings, since it makes possible the characterization of the cortical dynamics in epilepsy patients. Specifically, these kinds of works prove the existence of stable local synchronization areas, which are involve in seizures generation because if they are surgically removed, the patients present better outcomes. The existence of these local synchronization areas implies the existence of areas with no high connectivity but also very intense and temporally stable local synchronization. It seems therefore that the cortex of epilepsy patients presents a highly heterogeneous connectivity, something that has been proved by immunohistochemistry, genetics and electrophysiological studies [73–75]. In addition, computational studies have shown that those areas of high local synchrony facilitate the global synchronization processes [24]. The stability of those local synchrony areas has been demonstrated that induce a change in network topology, to a small-world architecture (see Section 3.5.1), simplifying the synchronous activity between regions and favoring seizure onset.

3.4. Community structures

Detection of community structures is aimed to study the topological organization of a network accordingly with its subnetworks [26]. Community structures characterize clusters of tightly connected nodes inside the entire network. There are several community measures, the most used are motifs and modularity [69]. In the last years several methods to detect community structures have been published with great differences in both performances and capabilities, some of them using highly sophisticated algorithms [26].

3.4.1. Concepts

Modularity determines how well a given partition or division in a complex network corresponds to a natural or expected sub-division, i.e. which groups of nodes are more connected between them than with other nodes of the network. Thus modularity is defined as [69]

$$Q = \frac{1}{2m}\sum_{i,j}(a_{ij} - \frac{k_i k_j}{2m})\sigma(c_i, c_j), \tag{8}$$

where m is the number of edges, a_{ij} is the element of the adjacency matrix, k_i and k_j are the degree of node i and j, respectively; c_i is the type (or component) of i, c_j that of j, the sum goes over all i and j pairs of vertices, and σ (x, y) is 1 if $x = y$ and 0 otherwise.

In addition to the above-mentioned definition of community, an important issue in community structures is the method to be used to find them. Unlike other network parameters that are computed exactly, community structure calculations are obtained by optimizing algorithms.

Although several and highly sophisticated algorithms to calculate community exist [26], one of them, based on cutting a hierarchical tree, will be explained in the following section to understand its importance. A *Hierarchical clustering* algorithm is a method based on the construction of a hierarchy or tree based in similarities. The lower branches of the tree are composed of those more closely related nodes. In order to construct a hierarchical tree, a "distance" between objects is firstly defined and then, an ordering of distances is performed with the aim to construct the tree. A typical measure of distance is the so-called Gower distance

$$d_{(i,j)} = \sqrt{2(1-\rho_{ij})}, \tag{9}$$

based on the Pearson correlation (Eq. (1)) ρ_{ij}. In doing so, elements highly correlated with ρ_{ij} close to 1 attain distances close to 0. Then, one can construct a hierarchical tree by grouping those elements with similar distances. The process of assignations of nodes to a group or cluster can be done by combining nodes into groups by using an agglomerative method, or by separating groups into smaller ones by means of divisive methods. The single-linkage, complete-linkage and the average-link are the most common agglomerative methods. Once a hierarchical tree, also known as dendrogram, is constructed, the last step is simply to cut the tree at a particular level, obtaining the clusters or communities. A simple example can be observed in [26].

3.4.2. Applications

Communities or cluster detection has been successfully applied to neurophysiological data coming from scalp and FOE [28,49]. In these works, clustering detection was done by hierarchical clustering using a single-linkage clustering method. The aim of clustering detection was used to detect exactly the opposite, that is, those electrodes which do not belong to any cluster, or declustered nodes. Detection of declustered electrodes is important because it allows to correctly lateralize the ipsilateral side to seizures during the interictal period in TLE patients [28,49]. This calculation is performed through a lateralization index, quantifying which lobe possesses more declusterized/desynchronized electrodes. However, some controversy exists about the synchronization level of the ipsilateral side, since there are works describing higher synchronization in the ipsilateral side [76,77]. This controversy could be explained because of the different kinds of invasive electrodes, and different recording areas, used in those studies.

Community structures detection has been also used over subdural electrodes as in [18] in order to calculate the modularity. In this work it is shown that the value of modularity decreases during the seizures as compared with the preictal levels. Similar results are found by using a combination of scalp and FOE.

These results provide evidence that community detection is a promising diagnostic tool for network epilepsy, since it could help to determine the side of the seizure in TLE patients in semi-invasive interictal recordings of 1 or 2 h, saving time and using a less disturbing and a

cheaper technique. Community detection can also help to determine the ictal dynamics through the analysis of modularity in ECoG and scalp and FOE. In addition to the above-mentioned community structures measures, others parameters can also help to analyze communities. Those are the network resilience measures, which define the resistance of a network to remove the random or critical nodes, as occurs in epilepsy surgery, for review see [69].

3.5. Topological organization

The epileptic network can also be characterized by changes in its topological organization which is reflected in the changes of other several parameters. One way to quantifying these changes is through averages, over the whole network, of certain measures, as for instance the shortest path length (Eq. (7)). Another way consists of transforming the entire network into a simplified network, called the minimum spanning tree, in order to study the main properties of the actual network by using the simplified one, instead.

3.5.1. Concepts

Average shortest path length (APL) is a network parameter employed to provide information of how fast or slow is the communication transfer through the network nodes, i.e. the average number of steps along the shortest paths through the network nodes. APL is defined as

$$APL = \frac{1}{n(n-1)} \sum_{i \neq j} d(v_i, v_j), \tag{10}$$

being n the number of nodes and $d(v_i, v_j)$ the shortest path lengths between nodes v_i and v_j, calculated by Eq. (7).

The *density of links* (DoL) is the ratio between the actual number of links and all possible links of the network. It provides information of how globally connected is the network. DoL is calculated as follows

$$DoL = \frac{\#of\ existing\ links}{\#of\ \ possible\ links}. \tag{11}$$

Both APL and DoL are related, i.e. a high DoL implies a low APL because a higher number of links entails higher possibilities to interconnect nodes and reaching this connection by using shortest paths. On the other hand, one cannot assume that a low APL implies a high DoL, because the presence of long-distance connected nodes favor the low APL without a high number of links, this is measured by the next parameter, the clustering coefficient.

Average clustering coefficient (ACC) measures how well neighbors nodes of a particular node are connected between them, characterizing local connectedness. ACC is defined as

$$ACC = \frac{1}{n}\sum_{i=1}^{n} c_i, \tag{12}$$

being n the number of nodes and c_j clustering coefficient of node i, calculated by Eq. (6).

The use of these three parameters allows a broad classification of networks in three groups: random, small-world and scale-free networks. *A random network* is a network with a uniform distribution of links, i.e. every node is connected with other every network's node with uniform probability. On the contrary, *small world network* is that network in which nodes have high local connectivity, i.e. high clustering coefficient, and some nodes also have long-distance connections. This last property represents that these small-world networks have a small average path length. Lastly, a *scale-free network* is that network in which most of the nodes have few local connections but some of them, called hubs, have a high number of connections. In the context of the average parameters, all three types can also be defined: random networks presented a low ACC and APL, regular networks showed a high ACC and low APL, small-world presented a high ACC and a low APL and scale-free presented similar characteristics to the small-world network.

The *minimum spanning tree* (*MST)* is a simplification of the full network into another, simpler, network. It is a tree without closed paths, i.e. from a node *i* to a node *j* always exists a unique path. The MST is obtained by the construction of a matrix based on the distance matrix, in the same way the construction of a hierarchical tree is done (see Section 3.4.1). The MST possesses the feature of retaining the more important links in the original network under the simplest topology.

3.5.2. Applications

To consider the topological aspects of networks, especially their changes, is of critical importance in its relation with epilepsy as it was demonstrated in several works [12,17,78]. A typical example of the application of network changes during seizures was recently presented by Vega-Zelaya et al. [18]. In this work differences in the network structure, constructed upon subdural recordings, between preictal, ictal and postictal stages were found. It is shown that after seizure onset of a partial seizure with secondary generalization, a decrease in both the modularity and the APL jointly with an increase in the DoL and the ACC exists.

Recently, the study of the transition from the preictal to the ictal period, recorded in scalp and FOE, reported that in 72% of the cases, an increase in the DoL during seizures with a decrease in the APL in 68% of cases exists. This fact suggests an increase in connectivity in the underlying functional network likely provoked by the small-world ictal architecture [58]. Although other works show a shift toward a regular network during the preictal-ictal transition [12,13,16], the difference could be explained by the use of FOE, which records electrical activity at the extrahippocampal areas [28]. In this regard, Mormann et al. [79] has revealed a different synchronization levels in the entorhinal cortex and hippocampus areas. Vega-Zelaya et al. [58] also reported an imbalance between ipsilateral and contralateral side, resulting in lower DoL

and ACC and a higher APL in the ipsilateral side than the contralateral one. These results are also supported by fMRI studies [77,80], and even by results of studies of patients with extratemporal seizures, which presented lower connectivity in the seizure area [81].

The application of topological parameters to the analysis of epilepsy turned out to be a great tool for network characterization, either in ECoG, scalp or FOE recordings. It has uncovered the dynamics and connectivity of the brain in TLE as well in the extratemporal ones. In fact, these works showed a lack of connectivity in the seizure area. In particular, in TLE the lack of connectivity in the ipsilateral side could be somehow related to the ipsilateral impairment found in the community structures analysis of FOE [49]. Moreover, loss of connectivity within specific network structures has been involved in seizure generation [82], and computational models has revealed that connections deletion increases seizure likelihood [83].

Also, the use of the MST has provided to be of great importance in describing different types of functional architecture [68]. In that work, the MST was used to simplify the underlying network with the objective to localize particular areas of interest, as the node's degree, betweenness and local synchronization. As it was shown, critical nodes in the MST are those with highest local synchronization. Moreover, when different types of critical parameters, as maximum local synchronization, maximum betweenness, concur at a particular cortical area, resection of these area correlates with a goof post-operative outcome. **Figure 8** displays three different MST architectures with the critical nodes marked in each case. In the last case, **Figure 8C**, the three nodes with maximal local synchronization, betweenness and degree concur at the same location, that is node #2. During the surgery, a minimal cortical resection involved this cortical area and the patient remained free of seizures [68].

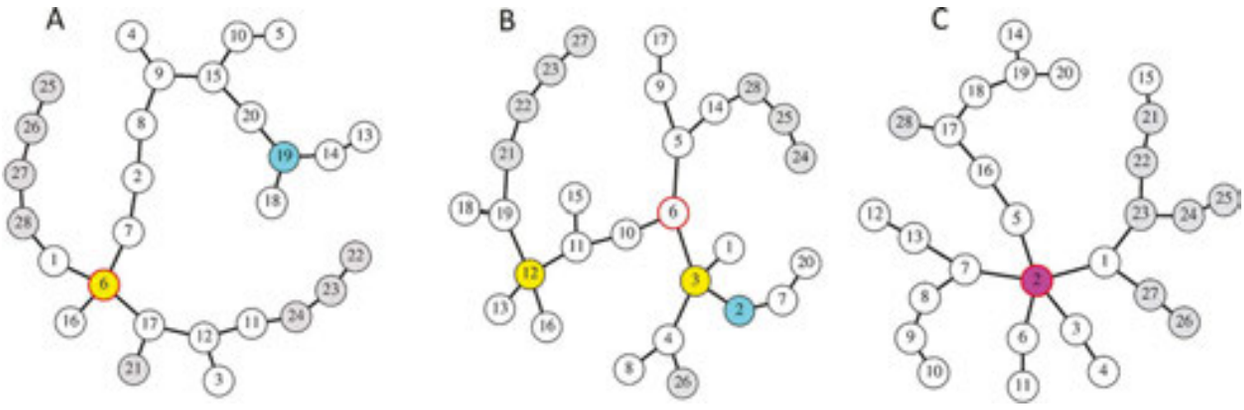

Figure 8. Centrality measures and minimum spanning tree (MST) constructed from ECoG data from two different locations. (A, B, C) Represent three examples from three patients. Electrodes are represented by gray circles (location 1) and white circles (location 2). The node with maximun local synchronization is represented by a cyan circle, the node with maximun degree by a yellow circle and The node with maximun betweenness by a red-border circle. Magenta circle represents superposition of the three centrality measures in the same node.

4. Conclusions

Although the advent of digital computation has revolutionized the whole realm of biomedical signal acquisition and preprocessing, particularly of scalp and invasive EEG, the clinical analysis and interpretation has not accompanied the rapid development experienced by the technological counterpart. Many of the current epilepsy-related protocols performed in the specialized centers around the world still rely on purely observational analyses of raw signals, depending subjectively on the neurophysiologist background and capabilities. Visual technique developed during the early years of epileptology, when computers were not yet available, has rooted so deeply in the clinical practice that it seems it could only be replaced by very efficient and objective techniques. In doing that, the new techniques should demonstrate that they performed at least as well as the classical ones. Moreover, they should provide a new framework under which the traditional view could be encompassed, but uncovering new concepts and models. Probably the little familiarity of neurophysiologists with numerical methods would help to explain to some extent the sparse use in clinical practice.

We feel that in the near future the complex network approach of epileptic processes will fit both requirements of being an encompassing framework under which the epileptogenesis and seizure spread could be fully understood and more important, it could become into a reliable therapeutic methodology to evaluate drug resistant epileptic patients, at least partially. As we have shown in this chapter, the traditional zone-oriented approach, with the seizure onset zone occupying the central position, is now shifting toward a network perspective, where network critical properties are becoming more relevant. This new framework would be applied to idiopathic or cryptogenic epilepsies, although symptomatic epilepsies (i.e. tumor induced, dysplasias, cavernomas or some types of post-traumatic seizure) probably remain better explained by the old or classical vision. In this regard, the graph theory jointly with the concept of functional connectivity is bringing new ways of thinking about the epilepsy.

Synchronization, of critical importance in constructing functional networks, has also evolved since its first use describing epileptic processes. Although epilepsy was initially related with hypersynchronization processes, today it is known that desynchronization also plays a dramatic role in the seizures dynamics. Moreover, as we have revised in this chapter, not only a single concept of synchronization exists but, on the contrary, several types of them are described.

One point which should be highlighted is the great difference existing between the traditional neurophysiological signal analysis in the field of epilepsy and the one performed under the network approach. As it is well known, interictal analysis is performed mainly in search of epileptogenic activity, i.e. sharp waves and spikes. On the contrary, synchronization of the full signals is made in construction networks.

Besides the novel knowledge provided by synchronization, the recent connectome concept has also added evidences to support the epilepsy as a truly network pathology. The analysis of EEG recordings from epilepsy patients reveals dynamical process in which network changes favor seizure creation. Centrality parameters show the presence of stable local synchronized

areas that present a small-world architecture; community structures analysis revealed an increase in the ipsilateral side of desynchronized clusters, which can be related to the lower connectivity of the ipsilateral side as shown by topological parameters. All these results are at some points controversial mainly due to the different electrodes used for recordings and the small number of studies. However, they provide critical dynamical evidences to understand the underlying mechanism of epilepsy.

Although today we have the fragmented knowledge of the epilepsy as a complex network pathology, the new advances in network-related methodologies and the growing literature of its application to biomedical signals make network analyses a promising and yet powerful tool for epilepsy research with potential applications either in the diagnostic or in the therapeutic realms.

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