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Hyper-Synchronization, De-Synchronization, Synchronization and Seizures

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1. Introduction

Ranging from its most basic mechanisms to the clinical symptoms, epilepsy is tightly associated with the word "synchronization". In fact, synchronization phenomena underlying epilepsy are described in several mechanisms at different temporal and spatial scales. At the lowest spatial scale, hippocampal and neocortical interictal spikes appear as the result of synchronized activity of pyramidal cells. At a larger spatial scale, epileptic seizures are usually described as a state of "hypersynchrony" encompassing extended cortical areas. Synchronization and epilepsy are so associated one to each other that lack of synchronization, or desynchronization, has been highlighted in recent years as a key aspect of the underlying dynamic in this pathology. The word synchronization comes from two Greek words, $\chi\rho\nu\nu\omicron\varsigma$ (chronos) and $\sigma\upsilon\nu$ (same), which means "sharing the same time"; therefore, a synchronized event is always composed by the temporal coincidence of two or more actions. However, it is usually understood the existence of an underlying mechanism that cause the synchronization itself. In this sense, synchronization is assumed differently from chance, because no deterministic causal effect exists in the last one. On the other hand, the use of the word synchronization is generally associated with a mechanism, known or not, that makes possible the temporal coincidence. In the above sense, and from the very beginning of epilepsy research, the word synchronization is found in many aspects of this pathology. Every time we found the word synchronization in epilepsy, one is tempted to think in a pathological substrate that would make it possible. However, it seems that synchronization in epilepsy has suffered from bifurcating routes since the beginnings of the quantitative descriptions of epileptic phenomena. The very clever and insightful descriptions made by the epilepsy researches in the late 40's and 50's (Penfield & Jasper, 1954) were plagued by the words synchronization and hypersynchronization, and today they are still used almost in the same fashion that were originally used. However, since the first description of the synchronization phenomena by Christian Huygens in 1673 to nowadays, there has been a profound revision and enlargement of the concept of synchronization especially in the last years (Pikovsky et al., 2001). Chaos theory, complex networks methodologies and nonlinear time series analysis have dug into the traditional concept of synchronization with the net result of a completely new proposal of what synchronization actually is. Today, in fact, there is no more a single synchronization phenomena, but instead, the traditional term has been split in several, more specific terms to characterize the numerous forms of the underlying mechanism but also, of the different kind of synchronized objects. It seems that the new understanding we have today of

synchronization is far from being adopted by the epileptologists, especially by the physician community. New terms as lag or full synchronization are rarely seen in clinical works, which is rather frustrating, because synchronization research in the last years has opened up new and powerful techniques, which would very useful in the improvement of diagnostic or therapeutic techniques.

This chapter is intended to review some of the new advances in synchronization in general and specifically in epilepsy research. A very brief mathematical introduction will be presented in order to fully understand the whole range of synchronization concepts presented in the chapter, either in the theoretical or empirical fields. Our aim thus is to show only the most basic methods and applications of synchronization and epilepsy.

2. Contemporary concepts of synchronization

In general terms, *synchronization between two systems is defined as the adjustment of their internal rhythms due to an existing (weak) interaction between them* (Pikovsky et al., 2001). Therefore, the following ingredients are essential for synchronization:

- a. There must exist two or more self-sustained oscillators, i.e., systems capable of generating their own rhythms,
- b. The systems adjust their own rhythms due to a (weak) interaction between them, and
- c. The adjustment of rhythms occurs in a certain range of systems' mismatch; in particular, if the frequency of one oscillator is slowly varied, the second system follows this variation.

The presence of self-sustained oscillators is needed for synchronization. This requirement is fundamental at the time of differentiating actual synchronization from other phenomena, for instance resonance. Self-sustained oscillators typically are represented mathematically by nonlinear differential equations, as for example Van der Pol oscillator. This kind of oscillator is able to oscillate with its own rhythm without external driving. Moreover, self-sustained oscillators can adjust their frequency, which is the key concept in synchronization. Two isolated different self-sustained oscillators, with different intrinsic frequencies can oscillate at the same frequency when they interact with each other. Note that synchronization refers to a dynamical process instead of a stationary state. Synchronization is a process by which two or more systems adjust their rhythms in the course of time. This means that the interaction allows (generally small) variations of the intrinsic rhythms, but always try to reach the common frequency. One aspect of the formal synchronization definition worth of mentioning is point b), which states that the rhythms are adjusted by a weak interaction. Although this is the very general concept, adjustment of rhythms through the weak interaction allows differentiating activity raised due to a true synchronization between two or more systems from, the activity derived from a compound system in which several subsystems are tightly connected. Note lastly that the synchronization definition used encompass the case of a unidirectional synchronization known as synchronization by driving. We will review below basically the most important concepts of oscillators and synchronization.

2.1 Linear, nonlinear, and chaotic oscillations

The simplest of all oscillators is the harmonic oscillator, described mathematically by:

$$\frac{d^2z}{dt^2} + \omega^2 z = 0$$

(1)

The Equation (1), which is a single second-order differential equation, can also be written as a system of two first-order differential equations, that is:

$$\begin{aligned} \frac{dx_1}{dt} &= x_2 \\ \frac{dx_2}{dt} &= -\omega^2 x_1 \end{aligned}$$

(2)

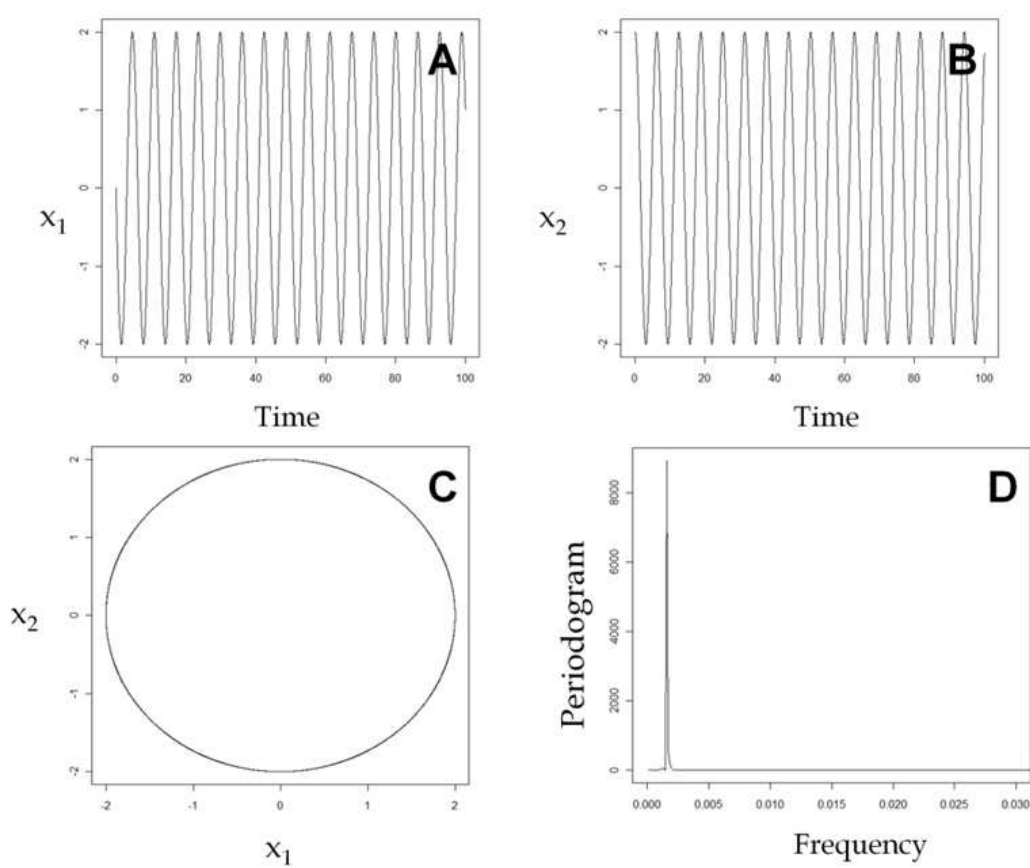


Fig. 1. Harmonic oscillator, solution of Equation 2.

The solution of both equations, (1) and (2), is the well-known $z(t) = A_0 \sin(\omega t + \varphi)$ a periodic function with a fixed frequency $f = \omega / 2\pi$, amplitude A_0 , phase $(\omega t + \varphi)$, and an initial phase φ . This kind of oscillator has an intrinsic frequency that cannot be varied. In Figure 1 is displayed the time series from x_1 (panel A) and x_2 (panel B). Also displayed in the phase portrait, that is, the evolution of the system in the phase space of variables, x_1 and x_2 (panel C). In panel C, Figure 1, is depicted the power spectrum of this system, which obviously consists of only one frequency. As we have stated above, two or more oscillators of this type cannot be synchronized because they cannot adjust its intrinsic frequency f . It turns out that equation (1) needs a nonlinear term in order to achieve self-sustained oscillations. Perhaps the best-known nonlinear oscillator is the Van der Pol oscillator with parameter μ ,

$$\frac{d^2z}{dt^2} + \mu(z^2 - 1)\frac{dz}{dt} + z = 0 \quad (3)$$

or

$$\begin{aligned} \frac{dx_1}{dt} &= x_2 \\ \frac{dx_2}{dt} &= -x_1 - \mu(x_1^2 - 1)x_2 \end{aligned} \quad (4)$$

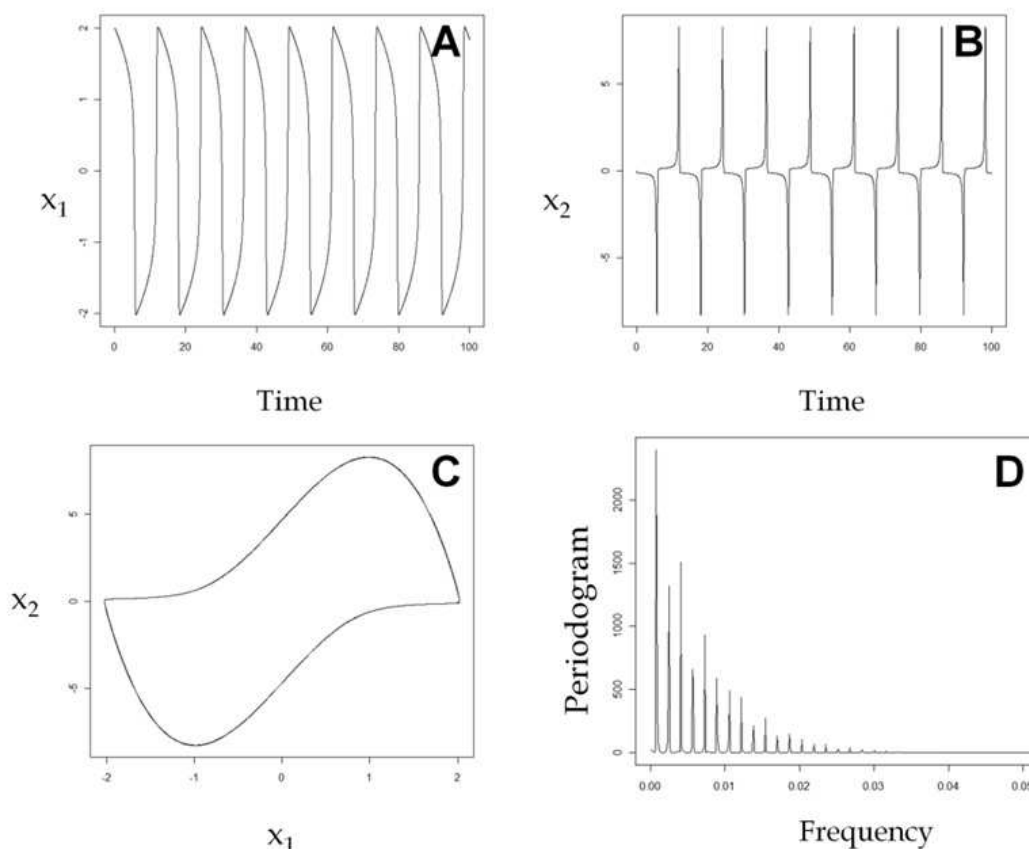


Fig. 2. Van der Pol oscillator for a value of $\mu=5.5$.

In this case, an analytical solution cannot be obtained, so numerical solutions must be calculated. The Van der Pol oscillators, like many other nonlinear oscillators, possess an intrinsic frequency that can be adjusted or entrained by an external driver. In this sense, these kinds of oscillators are fundamentally different from the harmonic one. In Figure 2 is displayed the time series from both coordinates, x_1 (panel A) and x_2 (panel B). Note the clear deviation from a pure sine solution of Equation (2). This fact is also evident in panel C of Figure 2, displaying the characteristic limit cycle. Departure from a pure sine is more evident in the power spectrum, panel D, Figure 2. In this case, the main frequency, corresponding to the fundamental period of the oscillator is accompanied with several harmonic frequencies, due to the non-harmonic character of the time series. Note that in this case it is still possible to define a phase of the oscillator, as in the case of the harmonic oscillator, but in rotating from 0 to 2π the amplitude will change (Figure 3C).

Furthermore, there exists another kind of oscillators, chaotic oscillators, which are fundamentally different from the linear and nonlinear ones, mainly because its behavior does not possess anymore a fundamental frequency. Instead, a chaotic oscillator typically displays a behavior with many different frequencies. Perhaps the best known of all of chaotic oscillators is the Lorenz system, which takes the following form:

$$\begin{aligned}\frac{dx_1}{dt} &= \sigma(x_2 - x_1) \\ \frac{dx_2}{dt} &= x_1(\rho - x_3) - x_2 \\ \frac{dx_3}{dt} &= x_1 x_2 - \beta x_3\end{aligned}\tag{5}$$

where typically $\sigma=10$, $\rho=28$ and $\beta=8/3$. With these parameters values, Equation (5) displays chaotic behavior. Note that in this case, three first order differential equations are needed to describe the complex dynamic of the oscillator, an essential difference needed for a chaotic regime.

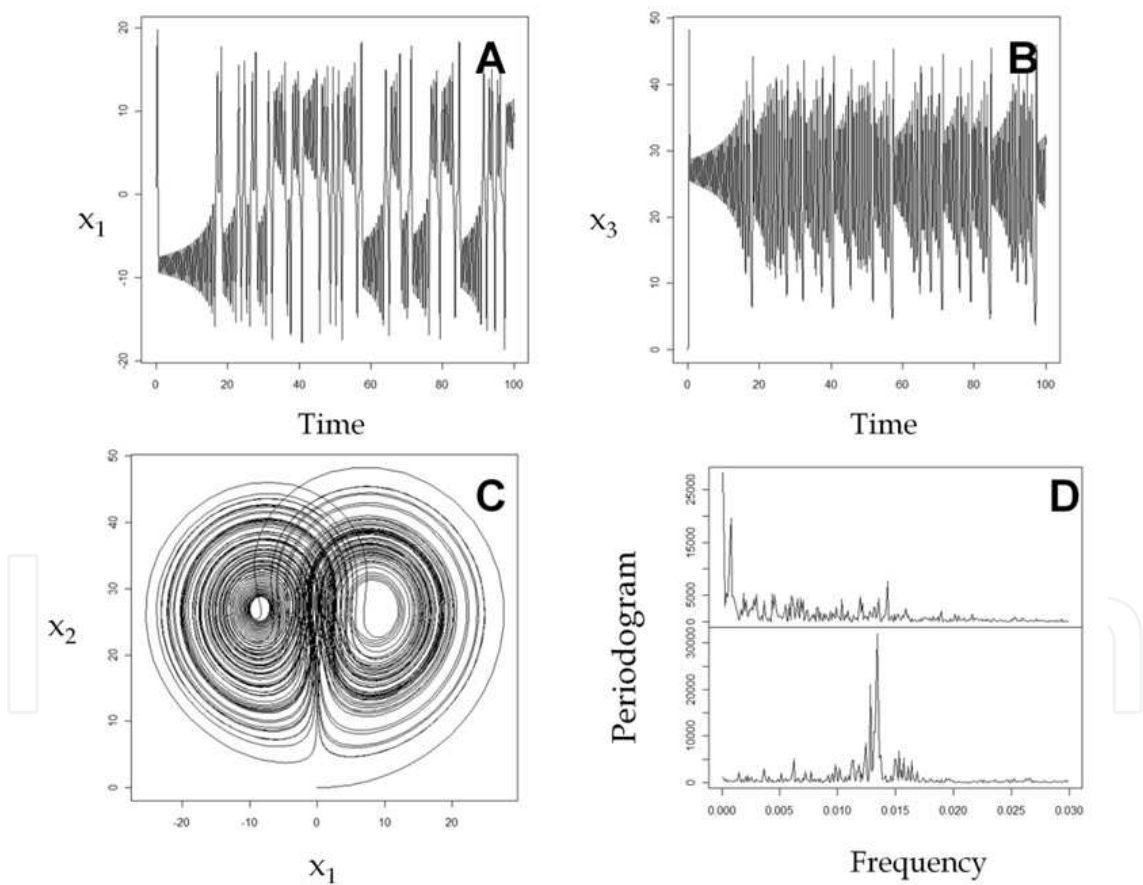


Fig. 3. Lorenz system

In Figure 3, time series of variables x_1 (panel A) and x_3 (panel B) are displayed, drastically different from the linear and nonlinear oscillators. The phase portrait in panel C shows complex oscillations in a bounded region, called attractor, which are very different from the typical limit cycle of nonlinear oscillators, whereas Panel D shows the power spectra of both

coordinates, x_1 and x_3 . Note the great difference between the power spectrum of variable x_1 (upper) from the power spectrum of variable x_3 (lower). In this last case, the system may be practically considered with a unique, or several but similar frequencies. This is an important point in chaotic systems because, unlike regular oscillators, it is sometimes impossible to define an instantaneous frequency and, in this case, an average frequency is defined. This point will be clear at the time to differentiate frequency from phase synchronization.

Considering the three cases, the linear oscillator (2), the nonlinear oscillator (4) and the chaotic one (5), it is always possible to write these equations in a more general form:

$$\frac{d\mathbf{x}}{dt} = \mathbf{F}(\mathbf{x}) \quad (6)$$

where $\mathbf{x}=(x_1, x_2)$ for (2) and (4), and $\mathbf{x}=(x_1, x_2, x_3)$ for the Lorenz equations (5). For a system like (6), \mathbf{x} is called the state variable and completely determines the state of the system at each time t . Note that experimentally one usually can only access one or a few variables of the system through the experimental time series recorded.

Now, we can express the general form of coupling between two systems, \mathbf{F} with state variable \mathbf{x} and \mathbf{G} with state variable \mathbf{y} , in the form:

$$\begin{aligned} \frac{d\mathbf{x}}{dt} &= \mathbf{F}(\mathbf{x}) + \mathbf{c}_1(\mathbf{x}, \mathbf{y}) \\ \frac{d\mathbf{y}}{dt} &= \mathbf{G}(\mathbf{y}) + \mathbf{c}_2(\mathbf{x}, \mathbf{y}) \end{aligned} \quad (7)$$

Systems \mathbf{F} and \mathbf{G} for example could be a Van der Pol oscillator and a Lorenz system, respectively, where both systems would interact each one the other through the coupling terms $\mathbf{c}_1(\mathbf{x}, \mathbf{y})$ and $\mathbf{c}_2(\mathbf{x}, \mathbf{y})$. The existence of both terms implies a bidirectional coupling. In the case of a unidirectional coupling, for example from \mathbf{F} to \mathbf{G} only $\mathbf{c}_2(\mathbf{x}, \mathbf{y})$ will remain.

2.2 Nonlinear systems and experimental records

Up to now, theoretical considerations have been made regarding oscillators and coupling between them. However, when dealing with neurophysiological records from patients with epilepsy, one cannot access the underlying interacting systems, like those of Equation 7. Instead, experimental time series from the various types of neurophysiological records are readily obtained in most epilepsy centers. These time series are in fact a "window" to the underlying dynamic, which formally can be considered as function of it. For instance, given a neurophysiological time series $\text{eeg}(t)$, it is always possible to consider that record as generated by an underlying system, as the one of Equation (6). In this sense, the experimental record $\text{eeg}(t) = \Phi[\mathbf{x}(t)]$, where Φ is a function which maps the, generally unknown, multivariate system state \mathbf{x} onto the univariate time series $\text{eeg}(t)$. The simplest of all Φ would be the one which gives a coordinate of the system, $\text{eeg}(t) = x_1(t)$. In Figure 4 is sketched the process in the upper curved arrow, which maps state variable \mathbf{x} in the underlying system to the experimental record $\text{eeg}(t)$.

The opposite process is nevertheless possible, due to the famous "embedding theorem" of Takens (Stam, 2005), which is at the heart of the modern approach of time series analysis.

The embedding theorem allows reconstructing an equivalent dynamical system to the original one. If we have a univariate neurophysiological record $eeg(t)$, it is possible to reconstruct an equivalent state variables $\mathbf{x}'(t)$ of the original $\mathbf{x}(t)$, in such a way that $\mathbf{x}'(t) = \psi[eeg(t)]$ by means of a function ψ . There exist many ways to choose ψ , but the simplest and most common way to go from the time series to the reconstructed dynamics is by means of the time delays methods (Stam, 2005). In Figure 4 is sketched the process of dynamics' reconstruction from the experimental time series $eeg(t)$.

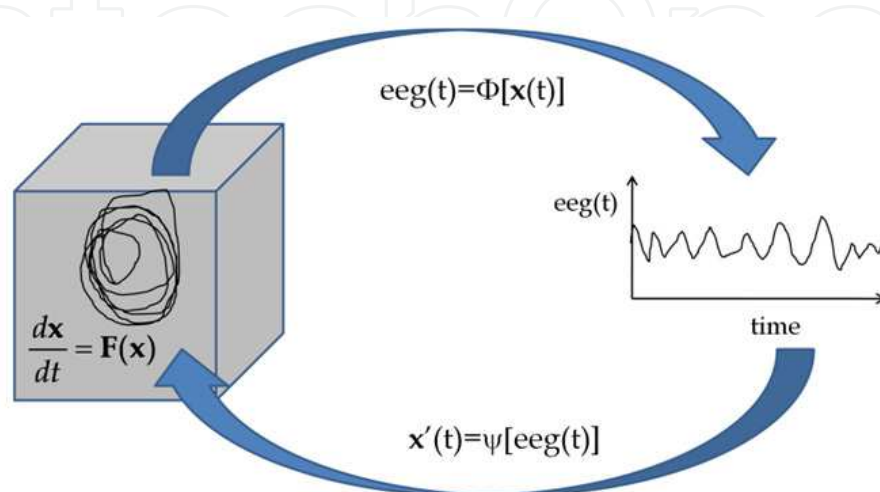


Fig. 4. Go and back from time series to dynamical system.

The above considerations are of special importance at the time to address the synchronization issue. Synchronization of time series was the main objective in the past, whether in time or frequency domain. However, with the advent of nonlinear and chaos theory, the concept of synchronization has been extended to the underlying dynamic. Therefore, is important to take into account what kind of synchronization one is dealing with. It may happen that one kind of synchronization implies another, as we will see below, but in other cases, this is not.

2.3 Synchronization

2.3.1 Frequency synchronization

This is perhaps the most intuitive form of synchronization in which two systems, for instance oscillators like Van der Pol, adjust their rhythms through their mutual interaction in order to share the same frequency or period. One important point to highlight is that frequency synchronization does not need that exactly the same frequency be shared by two synchronized systems with state variables \mathbf{x} and \mathbf{y} respectively. Instead, the following relation is valid: $n_x \omega_x - n_y \omega_y = 0$, where n_x and n_y are integers and ω_x and ω_y are the frequencies of systems \mathbf{x} and \mathbf{y} respectively.

Frequency synchronization can also be achieved in chaotic systems. For instance, Lorenz systems can synchronize another oscillator through its strong frequency displayed in the x_3 component (Figure 3D, lower panel). This frequency, which corresponds to the alternations between the two lobes in the "attractor" (Figure 3C), may be used to entrain a regular oscillator with periodic motion. However, when looking at the power spectrum of this

variable or at the variable itself, it is clear that the frequency is not as well defined as in the case of the Van der Pol oscillator, due to its chaotic dynamic. Therefore, it is usual to define an average frequency in these systems and synchronization through frequency does not need an exact instantaneous frequency. In this last sense, frequency synchronization, at least in chaotic systems seems to be less restrictive than other types of synchronization (phase or identical), because instantaneous values of variables may be different.

2.3.2 Phase synchronization

When considering non-chaotic systems, this is a very intuitive notion of synchronization. Two oscillators are phase synchronized when their phases are entrained, that is:

$$\left| n_x \varphi_x(t) - n_y \varphi_y(t) \right| \leq \text{const}$$

where $\varphi_x(t)$ and $\varphi_y(t)$ are the phases of the oscillators. As in the case of frequency synchronization, n_x and n_y stand for possible integers, but we can eliminate them, yielding $\left| \varphi_x(t) - \varphi_y(t) \right| \leq \text{const}$. That is, the difference between the phases in the oscillations remain constant through time. In particular, if $\text{const}=0$, we get $\varphi_x(t) = \varphi_y(t)$, both systems have the same phase for every time. This is called in-phase synchronization. One important point to highlight is that phase synchronization is irrespective of amplitude, thus, two phase-synchronized systems may have different trajectories with their amplitudes totally uncorrelated. In the case of chaotic systems, however, the phase is a more complex concept. For the existence of phase synchronization however, frequency synchronization of needed and therefore is more restricted.

2.3.3 Identical synchronization

In this case the state variables of the systems become identical, that is, $\mathbf{x}(t) = \mathbf{y}(t)$. However, in order to achieve a complete synchronization between two systems **F** and **G**, both must be identical, in form and parameters values. This is therefore the most restrictive form of synchronization. Identical synchronization implies phase and frequency synchronization.

2.3.4 Lag synchronization

This type of synchronization is a generalization of the identical synchronization in which the state variables of a system $\mathbf{x}(t)$ are identical to the state variables of another $\mathbf{y}(t)$, but with lag difference of τ ,

$$\mathbf{x}(t) = \mathbf{y}(t+\tau)$$

Note that for $\tau = 0$, identical synchronization is recovered.

2.3.5 Generalized synchronization

The concept of generalized synchronization arises in the case of unidirectional coupling between two systems that establish a relation known as “master-slave”, when one system (slave) obeys the dynamics of the other (master). In Equation (7) for example making $c_2(\mathbf{x},\mathbf{y})=0$ we will have a unidirectional coupling from **G(y)** to **F(x)**. In this case, we will

expect that the state variables \mathbf{x} will be determined from the interplay between its own dynamic (\mathbf{F}) and the coupling $c_1(\mathbf{x}, \mathbf{y})$. However, when a generalized synchronization is established between both systems, the state variable \mathbf{x} will be completely determined from the state variables from the other system, \mathbf{y} . In this case, it is possible to write the master-slave relation in the following way:

$$\mathbf{x}(t) = \Gamma[\mathbf{y}(t)] \quad (8)$$

where Γ is a general (vectorial) function which maps the state variable \mathbf{y} , of system \mathbf{G} to state variable \mathbf{x} of system \mathbf{F} . Because Γ is unknown, this kind of synchronization is difficult to detect, especially because the experimental series coming from the system, one of the state variables for example, do not must follow one each other. However, by using nonlinear time series techniques, such as the embedding methodology (Stam, 2005) it is possible to reconstruct state variables from a single time series and therefore to assess the existence of a functional relation between both systems.

2.3.6 Full (complete) synchronization

Up to now, the aforementioned synchronization types were described in the case of two interacting systems, which can obviously be generalized to the case of more. However, when dealing with a large number of interacting oscillators it may be more practical to quantify the average synchronization in the whole set rather than specifying synchronization between every pair of them. The study and characterization of synchronization in a large set of oscillators is an active field of research today, which has been pioneered by the works of Winfree (1967) and Kuramoto (1975). In the case of a population of interacting systems, Equation 7 should be generalized to include N oscillators instead of two, the kind of coupling between the systems, the underlying topology of the network of oscillators, etc. Trying to characterize such a system from a dynamical point of view is a colossal task, so in order to simplify as much as possible the problem, but capturing the essential phenomenology, the following system is studied:

$$\frac{d\vartheta_i}{dt} = \omega_i + \frac{K}{N} \sum_{j=1}^N \sin(\vartheta_i - \vartheta_j) \quad (i, j = 1, \dots, N) \quad (9)$$

where K is a normalization factor. Every oscillator is now replaced by its instantaneous phase ϑ_i and its natural or intrinsic frequency ω_i , as in the case of nonlinear oscillators. Doing this way, the model does not consider the amplitude evolution. The system therefore is composed of N limit cycle oscillators mutually coupled each other through the terms $\sin(\vartheta_i - \vartheta_j)$. However, Equation 9 does not take into account the spatial distribution of the oscillators, a relevant information that should be considered and which opens a whole world of possibilities (Arenas et al., 2008).

$$\frac{d\vartheta_i}{dt} = \omega_i + \sum_{j=1}^N \sigma_{ij} a_{ij} \sin(\vartheta_i - \vartheta_j) \quad (i, j = 1, \dots, N) \quad (10)$$

where σ_{ij} is the coupling strength between adjacent oscillators in the underlying network and a_{ij} are the elements of the connectivity matrix, that is, 1's or 0's whether the links exist or not and which determine much of the network topology.

Finally, the degree of synchronization in the whole network is evaluated by using the *order parameter*,

$$r(t)e^{i\phi(t)} = \frac{1}{N} \sum_{i=1}^N e^{i\theta_i(t)} \quad (11)$$

where the modulus $0 \leq r(t) \leq 1$ measures the average phase coherence of the oscillators and the degree of synchronization. When $r \sim 1$, a full or complete synchronization is obtained, and the oscillators are said to be phase locked.

2.4 Synchronization measures

Synchronization has been traditionally detected by several numerical methods, the most common of all the cross-correlation (Press et al., 2007) in the time domain. In electroencephalographic (EEG) analysis the cross-spectrum, which is nothing else but a cross-correlation in the frequency domain, dominates the field for several years. The search of brain *functional connectivity* and *effective connectivity* (Friston et al., 1993) boosts many researchers to introduce the use of non-traditional techniques. Functional connectivity is defined as “a temporal correlation between spatially remote neurophysiological events”, whereas effective connectivity is defined as “the influence that one neural system exerts over another either directly or indirectly”. This distinction between both concepts allows to clearly dividing the existing methods in two main classes. On the one hand, methods to quantify functional connectivity overpass the causality issue, focusing only in the existence of a deterministic relation between two systems. In this sense, synchrony detection is generally thought as an indication of a functional connectivity between two distinct brain regions. On the other hand, effective connectivity involves temporal causation, so appropriate methods must be used in this case. Traditionally, cross-correlation has been also used, fundamentally at the cellular level, to detect effective connectivity between, for instance, two neurons, by looking the time lag which maximizes the cross-correlation estimate. New and powerful methods have been developed in the last years to infer the effective connectivity, as the Granger causality (Granger, 1969) and transfer entropy (Schreiber, 2000) to mention a few.

We will briefly describe some of the most used methods to calculate synchronization in neurophysiological records, in particular those coming from epileptic patients. Cross-correlation was one of the first methods used to calculate synchronization. Being a linear method and with the increasing use of nonlinear time series analysis techniques (Stam, 2005), it was replaced by other, more subtle methods. However, in the last years, cross-correlation has suffered a revival in its use to quantify functional connectivity between cortical areas, powered mostly by developments in complex networks techniques. Dynamics and synchronization in complex networks (Arenas, 2008) from neurophysiological systems need fast and reliable estimates of synchronization between huge quantities of pairs, in order to compare estimates of functional connectivity against large databases of anatomical connectivity from human data (Hilgetag & Kaiser, 2004). Cross-correlation offers both properties. Moreover, the discovery that cross-correlation, although a linear statistic, perform as well as nonlinear synchronization measures when applied to neurophysiological data (Netoff & Schiff, 2002; Quiñan Quiroga et al., 2002; Ortega et al., 2008) justifies in most cases its first use, at least as an initial exploratory task. As is well-known in the field of time

series analysis, it is always mandatory to employ a full battery of methods to estimate an underlying quantity. In the case of synchronization, several methods would bring different aspect of the true functional connectivity.

There exists many excellent books and reviews of time series and synchronization methods, just to mention few (Pereda et al. 2005; Lehnertz et al., 2009).

We will not get into details about statistical validation of the results obtained in each of the following methods, a topic which is of paramount importance. Many times, synchronization calculations generate significant but otherwise false indications of connectivity between two systems, due to the limited quantity of analyzed data or its lack of stationarity. Statistical testing of the results should always be performed, by the classical methods or with the use of surrogate methodology. We will only describe here the basic concept underlying each of them and its use in epilepsy research.

Synchronization is a bivariate measure, and most often measures of synchronization between more than two systems is needed. Almost every modern neurophysiological equipment produce multivariate time series, recorded from different brain areas, so special techniques and methods should be developed to deal with these kinds of spatially extended data. Moreover, the recent developments in complex networks (Boccaletti et al., 2006) and synchronization over them (Arenas et al., 2008) have made researchers to discover new methods or rediscover traditional ones. This is the case for example the searching of community structures in networks i.e., the organization in groups of tightly connected members. New (Girvan & Newman, 2002) and traditional clustering analysis (Boccaletti et al., 2006) methods are used with the aim to describe in the most succinct and comprehensive fashion the synchronization pattern in a complex network. In the last part of this section we will show only one classical method, hierarchical clustering, which allows to organize the synchronized activity in more than two interacting systems.

Whatever kind of neurophysiological record we wish to analyze, typically it will consist of a multivariate data set \mathbf{x} with the recorded electrical activity of N_{chan} channels, and N_{dat} data points in each channel:

$\mathbf{x} = x_i(k), i = 1, N_{chan}$ and $k = 1, N_{win}$ where index i represents the channel number and k is the discretized time.

2.4.1 Linear correlation

Cross-correlation analysis is perhaps the most used method to estimate synchronization between two variables. It was the favourite choice during the 50's and 60's of the past century at the time of measuring correlation between spikes discharges in microelectrodes studies. However, in the mid-60's with the advent of the Cooley-Tukey method (Press et al., 2007) to quickly calculate the Fourier Transform, the fast Fourier transform algorithm, moves synchronization search to the frequency domain in many fields. Given two continuous signals $x(t)$ and $y(t)$, the cross-correlation function between both signals is defined as:

$$\rho_{xy}(\tau) = \frac{\text{cov}[x(t), y(t + \tau)]}{\sqrt{\text{var}[x(t)]} \sqrt{\text{var}[y(t + \tau)]}} \quad (12)$$

where *cov* stands for covariance and *var* for variance. Cross correlation is a function of τ , the lag between both signals. In looking for synchronization at the same time thus $\tau=0$. One can easily estimate the cross-correlation for two discretized time series, x_i and x_j , at times k , with the Pearson correlation coefficient (Press et al., 2007),

$$\rho_{ij}(0) = \frac{\sum_{k=1}^{N_{win}} (x_i(k) - \bar{x}_i)(x_j(k) - \bar{x}_j)}{\sqrt{\sum_{k=1}^{N_{win}} (x_i(k) - \bar{x}_i)^2 \sum_{k=1}^{N_{win}} (x_j(k) - \bar{x}_j)^2}} \quad (13)$$

Where $\rho_{ij}(0)$ implies that no lag between x_i and x_j exists. Correlation coefficient range in $-1 \leq \rho_{ij} \leq 1$, where a value of -1 implies a perfect inverse linear correlation between both time series, and a value of 1 implies a perfect linear relation. The linear character of (13) resides in the fact it is a fit to a straight line and ρ_{ij} gives its slope. The case of zero correlation however, implies only the *inexistence of linear correlation*, but a nonlinear interaction between both signals may be present. 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. When the signals are similar Equation (13) gives robust results, which is not the case for example when both signals have very different amplitudes. As many methods, it also requires the stationarity of the time series, both in its means and variance. While many modern techniques specifically designed to deal with nonlinear time series flourish in the epilepsy literature, cross-correlation analysis is still being used to detect synchronization, mostly for its intuitive interpretation, ease of implementation and statistical evaluation.

While (12) or (13) evaluate correlation in the time domain, there exists an equivalent way to do the same thing in the frequency domain, through the cross-spectrum, and in particular by using the coherence function:

$$Coh_{xy}(f) = \frac{|P_{xy}(f)|^2}{P_{xx}(f)P_{yy}(f)} \quad (14)$$

where $P_{xy}(f)$ is the cross-spectrum of variables x and y , and P_{xx} and P_{yy} correspond to the power spectrum of x and y respectively. Unfortunately, coherence is a measure that does not separate the effects of amplitude and phase in the interrelations between the signals and, as in the case of time correlation; it can be applied only to stationary signals.

2.4.2 Phase synchronization

The concept of phase synchronization was introduced by Rosenblum *et al.* (1996) in relation with chaotic oscillators. It has been also extended to the case of noisy oscillators. The power of the method resides in that it measures the phase relationship, independently on the signal amplitude. In order to evaluate differences between phases in two signals, one must firstly define the *instantaneous phase* of the signal, by means of the analytical signal concept. For a continuous signal $x_i(t)$ the associated analytical or complex signal is defined as:

$$z_i(t) = x_i(t) + i\tilde{x}_i(t) = A_i(t)e^{i\phi_i(t)}$$

where $\tilde{x}_i(t)$ is the Hilbert transform of $x_i(t)$

$$\tilde{x}_i(t) = \frac{1}{\pi} p.v. \int_{-\infty}^{\infty} \frac{x(t')}{t-t'} dt' \quad (15)$$

where *p.v.* stands for (Cauchy) Principal Value. The instantaneous phase is thus,

$$\phi_i(t) = \arctan \frac{\tilde{x}_i(t)}{x_i(t)} \quad (16)$$

Therefore, in the case of two signals $x_i(t)$ and $x_j(t)$, phase difference between both can be calculated as

$$\phi_i(t) - \phi_j(t) = \arctan \frac{\tilde{x}_i(t)x_j(t) - x_i(t)\tilde{x}_j(t)}{\tilde{x}_i(t)x_j(t) + x_i(t)\tilde{x}_j(t)} \quad (17)$$

This gives the instantaneous phase difference between both signals.

In order to implement numerically the above definition over two time series $x_i(k)$ and $x_j(k)$, the mean phase coherence R_{ij} was introduced (Mormann et al., 2000):

$$R_{ij} = \left| \frac{1}{N_{win}} \sum_{k=1}^{N_{win}} e^{i\Delta\alpha_{ij}(k)} \right| \quad (18)$$

calculated in the time window N_{win} , where $\Delta\alpha_{ij}(k) = \phi_i(k) - \phi_j(k)$ is the instantaneous phase difference at the discretized time k . It is clear from Equation (18) that R_{ij} follows $0 \leq R_{ij} \leq 1$. The literature (Pikovski et al., 2000) gives useful hints for the numerical calculation of the Hilbert Transform of a time series, i.e. Equation (15).

2.4.3 Mutual information

A very different kind of approach to evaluate association between two variables is through the information theory approach (Cover & Thomas, 2006). For a single time series, x_i one can estimate its probability distribution, $P(x_i)$ by partitioning the entire range of values taken by x_i in N_{bins} bins and then, count the number of points n_i falling in each bin l . In this way, the relative occurrence n_i/N_{win} estimate $p_i(l)$ the probability that a point in the time series i fall in the bin l . Then, the Shannon entropy is defined as:

For a single time series, x_i of length N_{win} one can estimate its probability distribution, $P(x_i)$ by partitioning the entire range of values taken by x_i in N_{bins} bins and then, count the number of points n_i falling in each bin l . In this way, the relative occurrence n_i/N_{win} estimate $p_i(l)$ the probability that a point in the time series i fall in the bin l . Then, the Shannon entropy is defined as:

$$H[P(x_i)] = H(x_i) = - \sum_{l=1}^{N_{bins}} p_i(l) \log_2 p_i(l) \text{ for time series } x_i, \text{ and likewise} \quad (19)$$

$$H[P(x_j)] = H(x_j) = - \sum_{l=1}^{N_{bins}} p_j(l) \log_2 p_j(l) \text{ for time series } x_j \quad (20)$$

Analogously, using the joint probability distribution $P(x_i, x_j)$, the joint entropy between x_i and x_j (or properly between $P(x_i)$ and $P(x_j)$) is

$$H[P(x_i, x_j)] = H(x_i, x_j) = - \sum_{l=1}^{N_{bins}} \sum_{k=1}^{N_{bins}} p_{ij}(l, k) \log_2 p_{ij}(l, k) \quad (21)$$

Finally, the mutual information $MI(x_i, x_j)$ between x_i and x_j is

$$MI(x_i, x_j) = H(x_i) + H(x_j) - H(x_i, x_j) \quad (22)$$

which clearly shows that it is a symmetric function of x_i and x_j . MI is positive, being zero when the probabilities distributions of x_i and x_j are independent. MI can be thought as a generalization of the linear correlation coefficient. It gives the reduction in the uncertainty in x_i due to the knowledge of x_j .

Although MI is bounded from below, giving $MI = 0$ when there is statistical independence between x_i and x_j , it is not bounded from above. In this context it is useful to define a mutual information statistic with the property of $0 \leq R_{ij} \leq 1$.

$$\lambda_{ij} = \sqrt{1 - e^{-2MI_{ij}}} \quad (23)$$

which now satisfies $0 \leq \lambda_{ij} \leq 1$.

2.4.4 Spatial synchronization

When dealing with spatially extended system, as it most the case with neurophysiological signals, especial methods should be used in order to organize synchronization between every pair of interacting systems. One traditional method is the hierarchical clustering (Boccaletti et al., 2006) that allows to arrange a group of, say N objects into smaller groups, such that objects belonging to these groups are more tightly linked with member of the same group than with the other groups. The net result is to obtain a set of groups, or clusters, such that members within each cluster are more closely related to one another than objects assigned to different clusters. Formally, it is better to work with "distances" instead of "correlations" between objects, such that a tight correlation between objects is equivalent to a closer distance, so this transformation is usually performed. The whole same procedure is able to be extended in the case of synchronization between time series. When dealing with multivariate records, firstly, a measure of synchronization is chosen, typically Pearson coefficient (Zhou et al., 2006), Equation (13), though other measures are also used (Ortega et al., 2008; Ortega et al., 2010) to check the results' reliability, and then a transformation to distances is performed. Then, a favorite clustering algorithm is used in order to create the hierarchical organization, which will uncover the synchronization clusters present in the data. See section 3.5 for a concrete example. This is only one of the many existing methods to organize synchronization in a set of time series.

3. Synchronization in epilepsy

3.1 Interictal epileptogenic discharges (IED)

Epilepsy is a synchronization/desynchronization pathology and the first indication of an abnormal synchronization process is in the most basic clinical sign of epilepsy, the appearance of IED, in the form of spikes and/or sharp waves in electrophysiological records. IED are usually present in epileptic patients and rarely in normal subject (Noatchar & Rémi, 2009; Walczak et al., 2008). In the case of temporal lobe epilepsy (TLE) epilepsy, spikes and sharp waves are frequently found in EEG records at both sides, even though strictly unilateral occurrence of IED has an excellent predictive value for a successful resective surgery. There is no difference in the diagnostic information between spikes and sharp waves. Although IED are difficult to define precisely, there exist widespread consensus about two or three criteria IED should meet, namely (Noatchar & Rémi, 2009; Walczak et al., 2008; Pastor et al., 2010):

- a. IED should be clearly distinguishable from the background activity,
- b. Duration must be <200 msec. The Committee on Terminology distinguishes between spikes, which have a duration <70 msec, and sharp waves, which have a duration between 70 and 200 msec, and
- c. The IED must have a physiologic field. Practically, this means that the IED are recorded by more than one electrode and has a voltage gradient across the scalp. This requirement helps distinguish IEDs from artifacts.

IED are the mesoscopic manifestation of the cellular paroxysmal depolarizing shift (PDS) (McCormik & Contreras, 2001; Timofeev & Steriade, 2004; Speckmann et al., 2011), which occurs at the cellular level in the pyramidal cells. A single PSD is a sudden neuronal depolarization of large amplitude of 20-40 mV and long-lasting duration of 50-200 ms. During the depolarizing shift, a train of action potentials are triggered. Although intra as well extracellular recordings can detect a single PDS, it would be impossible to identify it by macroelectrodes, as those of EEG and/or electrocorticography (ECoG). The appearance of IED in these kinds of records is actually the overt activity in several pyramidal cells suffering PSD at the same time. The mechanisms underlying this synchronized activity are diverse, for instance:

- a. Highly coupled large cortical network: interictal spikes appear to be generated through a brief period of runaway excitation that spreads rapidly through a large local network of neurons, lasting 80–200 ms and being terminated largely by the activation of inhibitory synaptic conductances and intrinsic K^+ currents (McCormik & Contreras, 2001).
- b. Ephaptic (non-synaptic) interaction: This is another influence identified in the generation of IED. The close proximity of cell bodies and dendrites in the hippocampus results in a direct activation of neighbor cells by currents circulating in the extracellular space (an electrical field effect). The entry of positive charges into one neuron results in a negative charge in the extracellular space causing a decrease in the potential difference (e.g. depolarization) across the membrane of neighboring neurons. This apparent depolarization may then influence the timing of action potential generation in neighboring cells and therefore bring the network into synchrony
- c. Change in the extracellular concentration of ions: Also a non-synaptic mechanism in which periods of intense activity, from brief synchronized bursts of action potentials in

a population of neurons to more prolonged discharges, result in significant increases in K^+ and decreases in Ca^{2+} . These changes in ion concentration may significantly increase neuronal excitability and promote epileptogenesis.

From the above three possible mechanism of IED generation, it is possible to identify three different classes of synchronization mechanisms. The first one clearly corresponds to the case of synchronization due to a strong coupling between oscillators. A strong coupling between pyramidal and interneurons, which in many cases is through gap junctions (Traub et al., 2004), would make a system of interconnected groups of oscillatory neurons behave as a unique system. In this case, the presence of IED in macroscopic records appears in fact as the overt activity of bigger cluster of neurons than the basic unit of oscillatory behavior does. Therefore, synchronized activity in the form of IED is mainly due to a structural characteristic of the underlying network. Numerical simulations in the dentate gyrus (Morgan & Soltesz, 2008) with 50000 granulate cells shows that hyperexcitability in the network, which promotes de appearance of network synchronization is enhanced by the presence of a small number of highly and strongly interconnected "hubs" in the whole network ("scale-free" networks). The presence of these hubs in the network will promote de appearance of full synchronization in the whole network which will manifest as and IED in macroscopic records.

On the other side, the other two possible mechanisms for the generation of IED are, nor mediated by gaps junctions, but neither by chemical synapses. In these cases instead, synchronization of oscillatory activity at the cellular level is mediated by weak interaction through the extracellular space. However, weak interaction does not mean that full synchronization in the IED generating network will not be achieved. On the contrary, weak interaction may promote full synchronization in the network depending fundamentally of the underlying topology (Arenas et al., 2008).

Perhaps both properties in pyramidal-interneurons and granulate-interneurons networks are present whether in physiological and pathological situations. However, the interaction between both mechanisms of synchronization may be different in each situation, and the appearance of IED, as the result of full synchronization between small groups of neurons will be determined by a particular enhancement between them.

3.2 Hypersynchronization

The word hypersynchronization is traditionally used to describe two of the main characteristics of epilepsy. On the one hand, IED are described as "hypersynchronous" events due to excessive simultaneous neuronal discharge (Chang et al., 2011). As we have review in the above section, IED are produced by a full synchronization of PDS of neurons in a small cortical network, mediated by two synchronization mechanisms. In these sense, the term hypersynchronization should be replaced, we think, for a more appropriate *local full synchronization*, because IED are caused by a small spatial coordination of several neurons suffering PDS at the same time, due to both, strong and weak interactions.

On the other side, hypersynchronization is also used to describe global, high amplitude patterns in electroencephalographic recordings, that is epileptic seizures. Firstly, as we have stated above, neither synchronization nor hypersynchronization are "states", but dynamical process. In this sense, individual neurons adjust their rhythms during the ictal event, and the overt activity varies strongly in the elapsed time of the seizure. At the cellular level for

instance, it has been shown that only 30 % of neurons change their firing frequency (Babb et al., 1987) during partial seizures. At larger scales, electrodecremental seizure onset (Chang et al., 2011), which displays a desynchronized neuronal activity at the seizure onset, as well as the whole correlation changes (Schindler et al. 2007) during the seizures. In this last case, synchronization, measured through zero-lag correlation, remains constant or even decreases during the first part of the seizure's development in the case of a secondary generalization, and increases only in the second half of the seizure.

3.3 Desynchronization

Although synchronization and hypersynchronization are at the heart of epilepsy, desynchronization has emerged in recent years as a property of neurophysiological signals, playing a central role in several issues. However, desynchronization in epilepsy may be traced back as far as 1963 (Gastaut et al., 1963) in the description of electrodecremental seizures (Arroyo et al., 1993; Chang et al., 2011; Tatum et al., 2008), described in both partial and generalized seizures. Electrodecremental seizures display an EEG pattern with low-voltage and fast activity which progresses by increasing voltage and decreasing frequency. Due to the obvious lack of automatic or quantitative methods at that time (Gastaut et al., 1963), desynchronized activity was simply referred to as an abolishment of fundamental rhythms at the onset of seizures. It is interestingly to note that some EEG seizure patterns were commonly described as desynchronization-synchronization or desynchronization-hypersynchronization processes, stressing the importance of the dynamical changes, and thus highlighting that synchronization is a process, not a state. Further research (Arroyo et al., 1993) denied the existence of desynchronization, favoring instead the existence of synchronized activity at higher frequencies. This fact could not be observed originally due to the formerly paper-based analysis performed, inadequate for a quantitative assessment.

More recently, desynchronization has entered into epileptology with new strength, not only at the macroscale, as in the cases of EEG patterns, but at the cellular level (Netoff & Schiff, 2002) too.

Perhaps the first methodological reference to desynchronization process in epileptic signals was that of Mormann *et al.* (Mormann et al., 2000), where intracranial EEG (iEEG) records from TLE patients were analyzed with phase synchronization methodology. Two kinds of findings were reported regarding des/synchronization activity, spatial and temporal results. Spatial findings showed that ipsilateral synchronization is greater than contralateral one in 14 out of 17 TLE patients during the interictal period. However, as those iEEG electrodes record activity coming from entorhinal cortex and hippocampal body, comparison between both temporal sides is difficult. As it was showed (Mormann et al., 2000) synchronization matrix is highly modular in each side due to the high synchronization within each structure, entorhinal cortex and hippocampus. Thus, the spatial average for the whole set of electrodes in each side is difficult to understand. The temporal findings, however, are easier to interpret. They found a clear difference between the synchronization behavior during the interictal and pre-ictal periods. There exists an abrupt drop in the mean phase coherence 15-20 minutes prior to the seizure onset, displaying therefore a very important desynchronization mark in the seizure process. The interpretation behind these findings is that the whole recorded area is in a state of increased susceptibility for pathological synchronization, that is, desynchronization, and an abrupt temporal drop in synchronization seems to favor the recruitment of neuronal tissue for a pathological

synchronization. A second hypothesis underlying desynchronization prior to seizures seems to be favored by a second work (Mormann et al., 2003). In this case, the seizure preceding desynchronization appears to be caused by the existence of two different kinds of regions in the recording areas. One region is in the physiological levels of synchronization and the other one is already involved in the progressive pathological synchronization coming from the epileptic focus. In this way, phase synchronization between electrodes located at both areas will give abnormal lower values of synchronization. Worthy to note, synchronization drop prior to seizure allows anticipating seizure onset in one hour (on average). Similar results were presented by (Le Van Quyen et al., 2003), although only for the β -band (10-25 Hz).

These last results jointly with the earliest findings of the decremental, desynchronizing-synchronizing seizures seem to point out that a seizure by itself is a pure synchronizing process. Schindler et al. (Schindler et al., 2007) have dug into the focal seizure's dynamical structure, finding that desynchronization also play a key role in the seizure development. They analyzed the correlation matrix constructed with the zero-lag correlation coefficients (Equation 13) between every pair of electrodes (depth and subdural), during seizure with focal onset. Their results show that during the clinical seizure onset, synchronization structure remains unchanged, and then progressively increase before the seizure terminate. Interestingly, in the case of seizure with secondary generalization, desynchronization dominates during the first half of the seizure extent, a finding also observed by Wendling et al. (Wendling et al., 2003). How a localized synchronous activity inside the seizure onset zone may progress toward a more extended desynchronized activity during the first part of the seizure? The authors (Schindler et al., 2007) provide the answer by proposing that due to different conduction times, and perhaps traveling by different paths (Milton et al., 2007), synchronous activity at the seizure onset zone reach distant cortical areas with time delay relative to each other. In this way, the seizure correlation structure during the spreading will be mostly desynchronized. Because secondary generalization have more extensive spreading than complex partial seizures, this hypothesis explain why desynchronization is greater in the former. However, causality may also be reversed in the sense that an already present desynchronization may be the cause of the seizure spreading (Schindler et al., 2007). This interpretation is supported by recent findings (Ortega et al., 2010) in TLE, where there exists an intrinsic imbalance in the synchronized activity between both temporal lobes, being the ipsilateral lobe more desynchronized than the contralateral one.

The above mesoscopic findings seem to be reproduced at the cellular scale. In an *in vitro* experimental seizure-like events in hippocampal slices, Netoff and Schiff showed (2002) that desynchronization between pairs of neurons, is tightly associated to the seizure-like events. Comparing, by using a battery of linear and nonlinear methods, interictal and seizure-like periods, they were able to demonstrate the existence of desynchronization during the seizures. Therefore, desynchronization appears as essential for seizure initiation and maintenance, at least at the cellular level. Beyond the important results concerning desynchronization during seizures, the work of Netoff and Schiff also illuminates about two fundamental aspects of synchronization. The first one is related with the methodology employed to quantify synchronization. The finding reported shows that synchronization estimates strongly depends upon the numerical method employed and the underlying analyzed signal. A linear method, as the Pearson correlation used over nonlinear signals, like neuronal activity, may gives better results than a nonlinear method, like phase

synchronization or mutual information. In any case, the morale is to employ a battery of synchronization methods, which examine different aspects of the underlying synchronization. The second issue raised by the work of Netoff and Schiff is related with the controversy of broad-band versus narrow-band analysis. As it was showed (Netoff & Schiff, 2002), only in the case of dominant-frequency signals, narrow band analysis seem to perform better than broad-band. On the contrary, when faced with compound signals, synchronization should be quantified by using the broad-band signal.

A more recent work (van Drongelen et al., 2005) combining modeling and electrophysiological experiments confirms and explains cellular desynchronization during the seizures. A network model of 656 cortical neurons can generate and sustain seizure-like activity if the excitatory coupling strength falls below a certain threshold. This fact certainly contradicts the common belief that strong excitatory coupling is needed to synchronize neurons.

3.4 Background interictal activity and IED synchronization

In order to identify IEDs, they must appear simultaneously in several neighboring electrodes, as it was mentioned in a previous section. However, this fact does not imply the existence of a true synchronization of IED ("conduction synchrony" in Lachaux et al., 1999), but merely it reproduces the field of the brain source, which is captured by several, neighboring electrodes at the same time. Characterization and tracking of IED have a long history in epilepsy due to its clinical importance (Bourien et al., 2005 and references therein). Source localization (Townsend & Ebersole, 2008), the search of IED generators, is perhaps the main electroencephalographic task in the pre-surgical studies of drug-resistant epileptic patients. Simultaneous occurrence of IED in distant areas, however, is considered as true synchronization phenomena and in fact, it was one of the earliest demonstrations of synchronization at a large scale (Spencer & Spencer, 1994) in epileptic patients, demonstrating hippocampal-entorhinal interaction. Since then, IED and synchronization have being side by side many times. This fact contrasts with the much more recent works which use instead the full interictal background signal to assess synchronization (Mormann et al., 2000). Furthermore, it is known that IED are present in records from epileptic patients, and for instance, they usually appear more frequently in the focal side than the contralateral side, in temporal lobe epilepsy. Thus, one question, to our best knowledge not being explored until very recently (Ortega et al., 2010) is the relation between interictal background signal and the IED content of the signal. It would be nice to know, for instance, if and how the presence of interictal spikes affects synchronization calculations in an EEG record.

One further issue that must be addressed before to compare IED synchronization against interictal background activity is the difference between the kind and quantity of IED present at the several neurophysiological records: EEG, foramen ovale electrodes (FOE), ECoG, depth electrodes, etc. An EEG IED (Walczak et al., 2008) must have a duration < 200 ms. In particular, a sharp wave has a temporal structure between 70 ms and 200 ms and spikes must have a duration < 70 ms. These values seem to be invariant along neurophysiological techniques, while the amount of IED present in these records may vary largely depending of the selected procedure. Although the EEG spikes' frequency varies largely, a typical epileptic record with frequent spikes has a spikes' frequency > 60 spike/hour or 1

spike/min, but it can be as high as 4 spikes/min or more. In FOE, a typical record shows approximately 3.5 spikes/min (Clemens et al., 2003; Ortega et al., 2010), but it can be as high as 30 spikes/min. We can estimate roughly a proportion of 4 FOE/EEG, that is, there are 4 FOE spikes for a single EEG spike. This ratio is extreme in the case of ECoG. It has been showed (Tao et al., 2005) that most of intracranial spikes, recorded with subdural electrodes, are missing in the EEG record. Only 10% of cortical spikes, with a source $< 10 \text{ cm}^2$ are also recorded in scalp EEG. We can therefore estimate a relation of 10 ECoG/EEG. Thus, it is safe to estimate a higher frequency of 40 spikes/min for a ECoG record. Depth electrodes seem to possess the highest spike rate (Bourien et al., 2005), 3322 spikes/hour, or equivalently, 55.3 spikes/min, with a maximum of approximately 6100 spikes/hour, or 100 spikes/min.

The above numbers allow us to estimate the "percentage of time" that spikes occupies in the background signal. Considering the maximum duration of a spike as 200 ms, or 0.2 seconds, we will get for each recording technique the following:

$$\text{EEG: } 0.2 \text{ sec} \times 4 / 60 \text{ sec} = 0.012$$

$$\text{FOE: } 0.2 \text{ sec} \times 30 / 60 \text{ sec} = 0.1$$

$$\text{ECoG: } 0.2 \text{ sec} \times 40 / 60 \text{ sec} = 0.133$$

$$\text{Depth: } 0.2 \text{ sec} \times 100 / 60 \text{ sec} = 0.33$$

The above numbers yields the following conclusions: IED structures "occupy", at most 1.2% of the total time in an EEG record, at most 10% in a FOE record, at most 13.3% in an ECoG record and a maximum of 33.3 % for a depth electrode record. Note that our assumptions have been extremely conservative by excess, taking maxima number of spikes in each case. With those percentages of time that spikes occupy in each type of neurophysiological record, we have implemented the following simulation, in order to evaluate the potential influence of IED in the full signal synchronization. A single IED structure typically last at most 200 ms. We then generate two Gaussian stochastic processes with a given value of correlation and we have replaced part of the records by a simulated IED. The simulated IED, represented by a sine wave cycle, is inserted at the same time in both time series. In this way we can study the influence of IED time, on the synchronization estimate by increasing the proportion of the IED time in the records, ranging from 0% (no IED) to 100% (a whole IED). Lastly we have plotted the ratio between $\rho(\text{stoch}, \text{stoch})$, that is, the correlation between both purely stochastic process, to $\rho(\text{stoch} + \text{IED}, \text{stoch} + \text{IED})$, the correlation between the processes with the inserted simulated IED. This ratio, $\rho(\text{stoch}, \text{stoch}) / \rho(\text{stoch} + \text{IED}, \text{stoch} + \text{IED})$ allows to compare a given value of correlation between a pair of experimental signals against a pair of signals with theoretical IED inserted. This is showed in Figure 5. As can be seen, for small levels of correlation between both signals the influence of IED time is much higher (left part of the figure) than the case of high levels of correlation (right part), and also for high proportion of IED time (upper left part). Horizontal lines indicate the maximum percentage of IED times contained in the typical neurophysiological records, as calculated before. By knowing the calculated values of synchronization, in this case Pearson correlation, it is possible to know whether IED are affecting the synchronization estimate or not. For example, in the case of EEG, practically there are no correlation values in the experimental series which can be influenced by the IED contained. With as lower values as 1.2% of the EEG time series occupied by IED, the value of the correlation is due to the

background. The case of depth electrodes is different. Due to the high quantity of spikes integrated in the background activity, which can account as much as 33 % of the record time, alert that full signal synchronization may be due to the occurrence of synchronized spikes instead of the background activity. In this case, it would be mandatory to carefully analyze the correlation values obtained from signals. As it is clear from the Figure 5, values of correlation around 0.4 (x-axis) for instance, for depth electrodes (dot-dashed line), gives a value approximately of 0.7 (right scale). This value implies that 70% of the correlation is due to the background activity and 30% due to the synchronized spikes. These values are rather high and must be analyzed in detail.

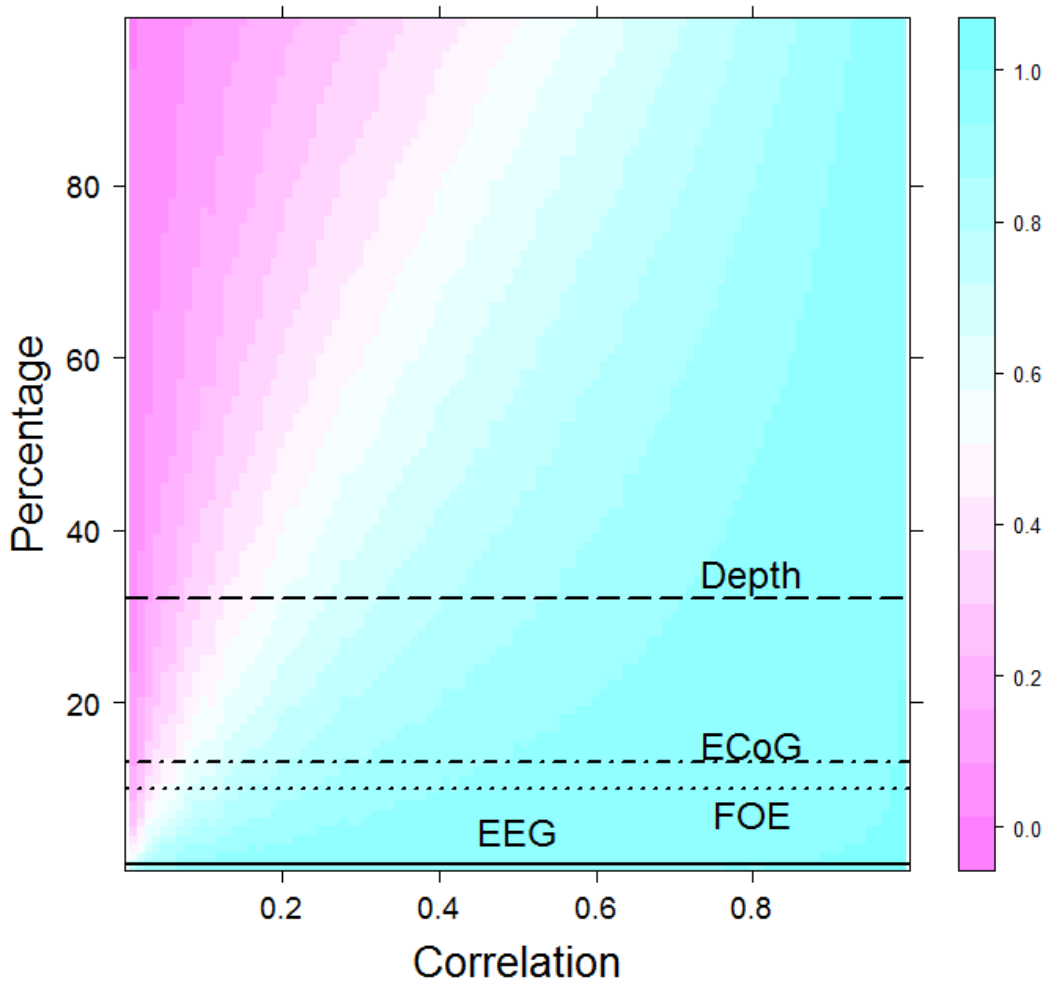


Fig. 5. Background interictal and IED synchronization

The above procedure is aimed to demonstrate that neurophysiological records from epileptic patients, which usually contain large quantities of IED, in the form of spikes or sharp waves, can be used safely for synchronization calculations because the presence of these IED hardly affect the results. For example, in the case of TLE, there exist reports that interictal synchronization is augmented in the hemisphere ipsilateral to epileptic seizures, calculated by using EEG records. From the above discussion, it must be discarded the influence of the greater quantities of IED in the ipsilateral side as a cause of the higher synchronization in the epileptic side. Furthermore, recent findings (Ortega et al., 2010) show the existence of lower values of synchronization in the ipsilateral side, as compared against

the contralateral one, measured by FOE at the entorhinal cortex. In this case, the ipsilateral side contain higher quantities of IED, being the epileptic side, but with a decreased value of synchronization. This last fact seems soundly corroborate the minimal influence of IED over the background activity for the synchronization calculation purposes.

For the sake of completeness, we may generalize the above issue, in which we have compared IED synchronization with background synchronization, with the issue of broadband synchronization versus narrow-band synchronization. In general, cortical and scalp data, which are weighted space averages of many cortical rhythms (Nunez & Srinivasan, 2005) display broadband spectrum, from 0 to 80 Hz. This range is even greater, up to 500 Hz, when considering fast ripples in epileptic patients. However, many studies on synchronization, whether neurophysiological or not, are carried out on data coming from narrow-band systems, where typically a single dominant frequency prevails among the other. In these cases phase synchronization methods, for instance, are more sensitive, because the prevailing frequency is relatively stable in time. Theoretically, this is the case of synchronization between two nonlinear oscillators. However, when the interacting systems contain several frequencies, synchronization among them should be assessed with extreme caution. Interaction between frequencies in different bands may be overlooked if synchronization is calculated independently in each of the standard bands, δ , θ , α , β and γ . In these cases, standard methods of synchronization will fail in identify synchronization, and more general methods, or higher order spectral analysis should be used. One of them, for instance, which is applied in the case of assessing synchronization between chaotic oscillators, uses the concept of generalized synchronization. Because generalized synchronization relies in a functional relation between the underlying systems, techniques from nonlinear time series analysis, as it is the embedding methodology (Stam, 2005), must be used. This is particularly important in the case of systems with variable-dependent power spectra. In some cases, a chaotic system may shows a sharp frequency in one variable, but a broadband spectrum in the other variables (Ortega, 1995, Ortega, 1996). This broadband spectrum may hide the fundamental frequency of the underlying system, which however may synchronize with other systems through that frequency. In this case, a solely time series synchronization would also ignore this interaction. From the above comments, when dealing with neurophysiological data, especially from epileptic patients, synchronization may be best characterized from this broadband approach (Netoff & Schiff, 2002).

3.5 Seizures: Hypersynchronization, desynchronization, propagation or lag-synchronization?

Although seizures are the most prominent symptoms in the epileptic patient, few attempts to characterize seizures from a dynamical point of view have been done. It would be very valuable to know how synchronization evolves during the whole period of a typical seizure. The classical association of hypersynchronization with seizure events does not seems appropriate today, in the light of recent advances in this field (Schiff et al., 2005; Netoff & Schiff, 2002; Schindler et al., 2007). Augmented synchronization, as compared with pre-ictal stages, is only a small part of the seizure dynamic, where desynchronized activity dominates in the first part (Schindler et al., 2007), and in some cases at the end (Schiff et al., 2005) of the seizure. Bearing in mind that synchronization is usually measured by the zero-lag correlation coefficient, one may speculate that desynchronization is actually due to the spread of seizure activity. If seizures, starting at the particular focus, propagate by different

routes and with different lags (Milton et al., 2007), one would expect that epileptogenic activity at different cortical points be zero-decorrelated, but lag-correlated instead. Although we have not enough data to support that desynchronization is caused by an "inhomogenous" propagation, we have some clues to support the hypothesis that interictal desynchronization, at least in TLE patients, may be the cause of desynchronized spread. Recently (Ortega et al., 2010), we have shown the existence of an imbalance in the mesial synchronization in TLE patients by using a cluster methodology (see sec. 2.4.4.). FOE records of interictal activity at the entorhinal cortex show the existence of lower levels of synchronization in the ipsilateral side of the epileptic seizures than the contralateral one. Figure 6 display the distance matrix, from a right TLE patient, among all the electrodes calculated from the correlation matrix (Equation (13)). It is apparent the existence of a great synchronization cluster among almost all the FOE electrodes, except three right electrodes (small circles), R4, R5 and R6. These electrodes are declusterized and desynchronized from the rest. If, as is believed (Kandel et al., 2000), the spread of seizures follows normal cortical circuits, it would be expected that seizure propagation will be desynchronized, at least at the onset stage, due to the synchronization inhomogeneity of the cortical substrate. Moreover, interictal synchronization inhomogeneities have been reported in the lateral cortex (Ortega et al., 2008) in TLE patients. Therefore, it is highly expected that during the seizure onset, the seizure spreading, both in the mesial and in the lateral side of the temporal lobe, display a desynchronized activity, at least through the intracortical propagation. As the seizure develops, and in the case of secondary generalization, ictal activity spread to sub-cortical structures which came back to cortex, perhaps reinforcing synchronization.

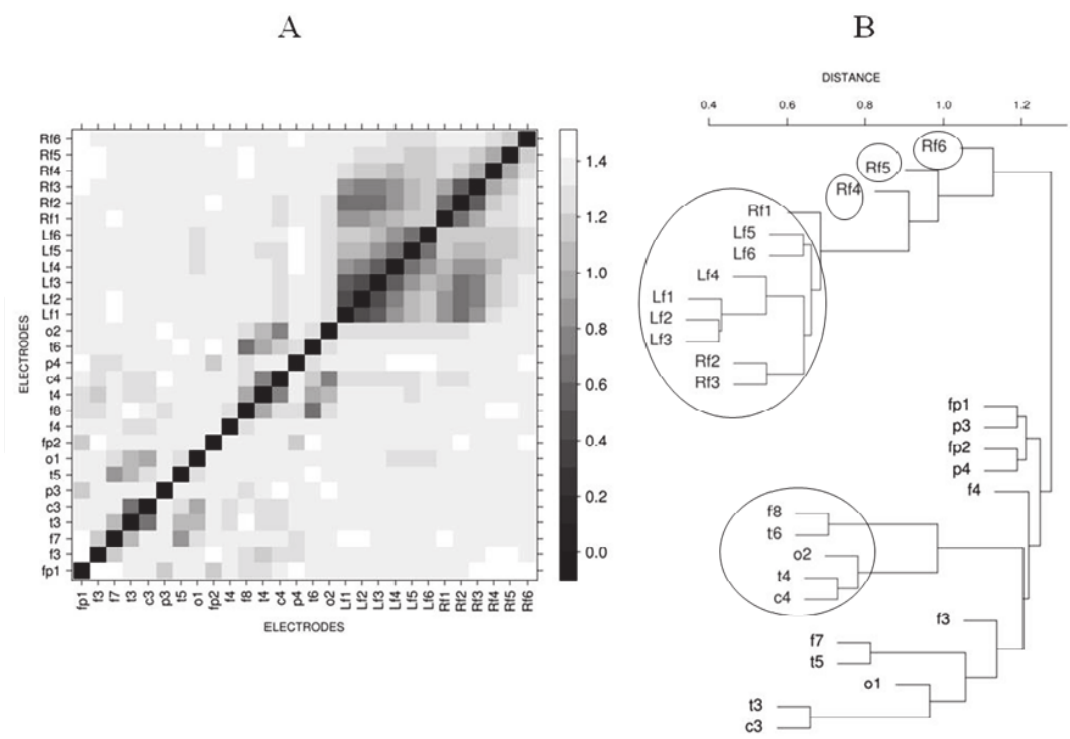


Fig. 6. Distance matrix (A) and hierarchical clusters (B) of scalp and FOE electrodes in TLE patients.

4. Conclusions

Recurrent seizures are the hallmark of epilepsy. They are usually termed as "hypersynchronized" events in the same fashion as the interictal epileptogenic discharges, which are the traditional EEG signatures of epilepsy. However, the term hypersynchronization seems to be misleading. In the case of seizures, a complex dynamics involving transitions from desynchronization to synchronization and perhaps distant and final lag synchronization seems to be the principal manifestation. In the case of interictal epileptogenic discharges, it seems more appropriate to justify its appearance due to the synchronizability of small cellular networks in the hippocampus and neocortex. In this last case perhaps, a correct term to be used would be full synchronization of all the participants in the underlying network.

With the support of chaos and network theories, the classical concept of synchronization has evolved substantially in the last decade. This fact has made possible recognize and differentiate new types of synchronizing mechanisms between two or more systems, even in the cases with very different corresponding signals. These new theoretical and methodological advances seem to be far from the epileptology realm yet. Although the number of new synchronization techniques applied in the analysis of neurophysiological data is growing, the step toward the introduction of these concepts in the daily language of clinical practice seems distant however. This is a disappointing situation, because the correct characterization of every synchronization process in epilepsy would boost new research, both in direction and deepness, certainly improving the fragmented knowledge we have of this disease today.

We believe that the recent advances in network theory and in particular, dynamics and synchronization in complex networks are crucial issue to be applied in the epilepsy field. Epilepsy is a neurological disorder and the brain is a network at its various scales. Seizure is intrinsically a synchronization/desynchronization manifestation, the correct characterization and dynamical properties of synchronization in the underlying cellular and cortical networks is the appropriate ground where this pathology should be considered. Characterizing the mesoscale synchronizability in the limbic system, for instance would be a step forward in the understanding of the appearance of seizures in the TLE. The study of the stability of synchronization, would further understand the seizure propagation and generalization. Synchronizability and synchronization stability should be therefore considered as new paradigms and future efforts should be addressed in that direction.

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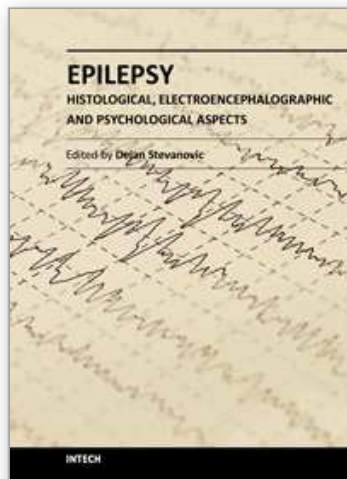
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