The Physical Mechanism in Epilepsy - Understanding the Transition to Seizure

Dorian Aur[1]
[1]Dept of Comparative Medicine, Stanford University, Palo Alto, CA

Abstract: The occurrence of seizures is a rare event with a very low probability of incidence therefore; a new paradigm is required to understand how epileptic seizures are generated. Specifically, analytical models and experimental data analysis show that the process underlying seizure generation is a severe dysfunctional regulation of neuronal activity inside epileptogenic region. Translated in significant changes of endogenous electric field this dysfunction acts at fundamental level of charge dynamics and leads to chaotic diffusion and electrical resonances within clustered regions with high frequency oscillations (HFO). Since the alteration in regulation can be modeled by perturbed Hamiltonian systems with many degrees of freedom that describe the motion of charged particles in electric field the Kolmogorov Arnold Moser theory (KAM) provides a physical model for the mechanism of epileptogenesis. Contrary to common belief, either inhibitory or excitatory function models of chronic epilepsy are incomplete and inconsistent.

Key words: epilepsy, seizure generation, KAM theory, seizure prediction neuroelectrodynamics

1. Introduction

Rhythmic repeatable states in terms of signal-dependent phase and magnitude of EEG fluctuations constitute a prominent dynamic feature of brain activity, which develop continuously during neuronal activity. Epilepsy leads to alterations in normal electric rhythms which can be recorded and analyzed. Several electrophysiological phenomena originating from different epileptic brain regions precede the ictal discharge. Importantly, during interictal periods in epileptic focal regions quasi-localized clusters of high-frequency oscillations (HFO) have been previously revealed based on EEG analysis (Bragin et al., 1999, Staba et al., 2002, Worrell et al., 2004; Crépon, et al., 2010, Bragin et al., 2010).

High frequency oscillations appear periodically in the epileptic brain and they manifest on a scale of centimeters that are generated by abnormal hyper-synchronization of large neuronal ensembles. The formation of HFO clusters that become broader after the application of $GABA_A$ receptor antagonist bicuculine was firstly reported by (Bragin et al., 2002). The presence of HFO in the seizure-generating structures is highly related to temporal and spatial location of seizure onsets (Crépon, et al., 2010). On the other hand few analyses have highlighted the presence of focal low frequency oscillations that precede ictal discharge in EEG or MEG data (Adeli et al., 2003).

[1] To whom correspondence should be addressed. E-mail: DorianAur@gmail.com

The mechanism that generates epileptic seizure is still unknown. Several factors govern the excitability of neurons including changes in intra or extracellular ion concentration (increased extracellular K^+ concentration) (Bazhenov et al., 2004; Park and Durand, 2006; Fröhlich,2008; D'Ambrosio, 2004) increased excitatory synaptic neurotransmission (Chu et al., 2010) decreased inhibitory neurotransmission (Turnbull et al., 2005), alteration in voltage-gated ion channels (Claes et al., 2001; Fujiwara et al., 2003; Wallace et al., 1998; Escayg and Goldin, 2010) complex changes in the neurochemistry of glutamate metabolism (e.g. alterations in the metabolism of glutamate, Tani et al., 2007) and modulation of transmitter metabolism by glial cells (Seifert et al., 2006). The existence of a distorted transport mechanism (ionic transport between neurons and neuroglial cells) increases potassium concentration excess of glutamate that accumulates outside cells (due to impaired glutamate reuptake by astrocytes, Moritani et al., 2005). Other hypotheses include remodeling of synaptic contacts due to different causes including axon sprouting (Tauck and Nadler, 1985) and relate these changes to an increase of the long-term potentiation-LTP coupling between the pre- and post-synaptic elements.

All these changes are important characteristics that distinguish epileptogenic regions from non-epileptogenic ones. However, many changes at synapse level, inhibition or alteration in voltage-gated ion channels are common phenomena that occur during learning and behavior. Additionally, most activities in the brain are non-epileptic. While alterations at different levels can always facilitate abnormal neuronal activities, the occurrence of seizures is a rare event with a very low probability of occurrence. Therefore, a new paradigm is required in order to explain a transition from non-epileptic state to seizure generation.

There are several studies that have analyzed the nonlinear dynamics and chaos occurrence in epilepsy. However a theoretical framework that links the activity of neurons, changes in firing rate and presence of HFO in epileptogenic regions is still missing. The existence of chaotic attractors was evidenced by estimated fractal dimensions or Lyapunov exponent (Babloyantz and Destexhe, 1986; Iasemidis et al., 1990). A rigorous demonstration of chaos existence within biological data is far from being achieved.

Important information that describes local dynamics and interaction of electric charges in the brain can be obtained by analyzing recorded local field potentials (LFPs). The activity of excitable neurons can be mathematically described using the general framework of reaction diffusion systems. Synchronization, clustering and spatio-temporal chaos are phenomena specific to reaction-diffusion systems, where localized Turing patterns and standing waves can develop (Turing, 1952). Experimental evidence of Turing patterns in chemical and biological systems show a direct relationship with reaction diffusion theory (Petrov et al., 1997). The existence of a transport mechanism, which in many cases is diffusion combined with sources of excitation, presence of chemical reactants and nonlinear effects can transform microscopic short term interactions in long term macroscopic order and oscillations (see the Belousov Zhabotinsky, BZ reaction).

From gene to gliogenesis (Bonni et al., 1997) and neurotransmitter release (Cartmell, and Schoepp, 2000) to neurogenessis (Zhao et al.,2008) all these mechanisms are highly regulated in the brain. This regulation extends further to synaptic activity (Newman, 2003) and firing activity of neurons in different brain regions (see Appendix 4). Therefore, changes in regulation are likely to have broad consequences and influence rhythmic patterns of neuronal activity.

1.1 Background from system theory

From van der Waals interactions and quantum theory (Møller and Plesset, 1934) to studies of celestial mechanics (Lerner and McDonald, 2010) the study of transitory regimes and perturbation theory have been successfully applied to various fields. The alteration in system regulation can be modeled by a response to a perturbation (Figure 1).When the system is linear the resulting behavior after a perturbation can be easily modeled (see Appendix 2). Globally, the impulse response (perturbation) of a regulatory system can be approximated with a sinc function which represents the impulse response of an ideal low-pass filter (Figure 1, b, c). If the system is nonlinear this response and the resulting shape can become more complex (see Appendix 2). However the main phases, the raising phase when the amplitudes of the signals increase, the peak phase when signal harmonics reach maximum values and the falling phase when there is a decrease in the amplitude are generally common features for systems that respond to perturbations. The development of brain rhythms (Buzsáki, 2006) nonlinear dynamics and the occurrence of deterministic diffusion often expressed as chaotic dynamics exhibit broadband spectral features and generate specific waveforms with low-frequency and high amplitudes (Kennel and Isabelle, 1992, Qingchao et al., 2010).

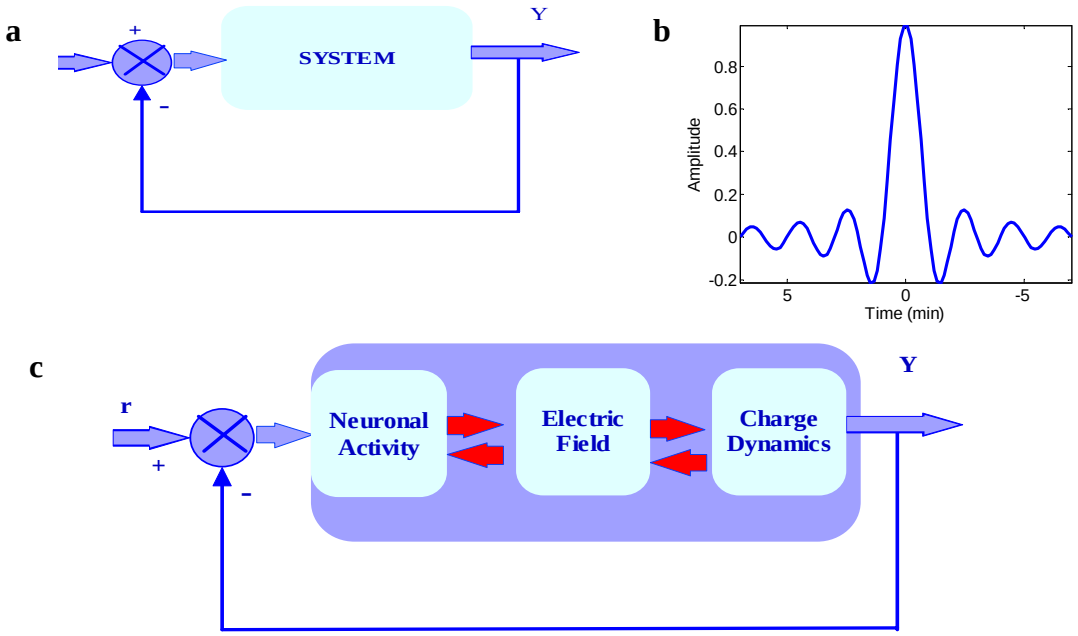


Figure 1: **a.** A schematic representation of a regulatory mechanism; **b**, The response to an impulse of an ideal low-pass filter (the sinc function) includes three distinct phases. The first phase when the amplitude of the signal increases, the peak phase when the signal reaches a maximum value and the falling phase, the decrease in amplitude **c.** Schematic representation of interconnected changes of neuronal activity, electric field and dynamics of electric charges

Recent focus on local field potentials and information transfer in spikes has shown that information can be carried non-synaptically by weak endogenous electric fields a result of non-uniform, transient charge density dynamics during action potential generation (Hausser et al., 2000; Buzsáki, 2002; Golding et al., 2002; Aur et al., 2005).

These interactions between neuronal activity, electric field and dynamics of electric charges are schematically represented in (Figure 1, c). Such premise has brought new investigations regarding the presence of nonlinear electric oscillations and rhythmic neuronal activity (Deans et al., 2007, Fries et al., 2008). The endogenous electric field influences the dynamics of electric charges, the diffusion of ions as well as the neurotransmitter release resulting in changes in the local neuronal activity (Fröhlich and McCormick, 2010).

Therefore, we hypothesize that dysfunctional regulation of neuronal activity inside epileptogenic regions alters endogenous electric field, changes relevant characteristics of charge dynamics and leads to seizure generation.

The main goal of this paper is to highlight the fundamental physical mechanism involved in seizure generation by correlating changes from several different measures including firing rate, local field potentials and dynamics of electric charges. Another objective is to relate nonlinear theoretical framework of charge dynamics with early experimental observations regarding abnormal synchrony (Penfield et al., 1954), high frequency oscillations (Fisher et al., 1992; Bragin et al., 1999; Worrell et al., 2004) phase synchrony and preictal desynchronization (Le Van Quyen et al., 2003) impairment of higher cognitive functions (Niedermeyer, 2005) inhibition.

2. Materials and Methods

Current models hypothesize that several factors which govern the excitability of neuron, intrinsic neurochemistry are involved in the mechanism of epileptogenesis, however little is yet known about how these factor operate and determine the seizure onset. To address this issue, recorded local field potentials from several regions were analyzed using wavelet and FFT power spectrum. Tetrodes recording during 12 spontaneous seizures selected from 4 pilocarpine-treated, epileptic rats from HFO epileptogenic regions (Bower and Buckmaster, 2008) were analyzed. The seizure onset was identified electrographically from one of the tetrodes based on changes in the spectral power. An automated unsupervised classification of multidimensional data in the tetrode setup was used (KlustaKwik, Harris K. D. et al., Rutgers University) followed by manual selection of final clusters was performed (MClust-3.5, Redish A. D. et al., University of Minnesota). Recorded local field potentials were analyzed using wavelet and FFT power spectrum one hour prior to spontaneous seizure onset with the following algorithm:
1. The windowed Fourier transform of local field potential $x(t)$ is performed:

$$S(\omega,u)=\lim_{T\to\infty}\frac{1}{T}\int_0^T e^{i\omega t}x(t)g(t-u)dt \qquad (1)$$

where g is the Hanning window function. The power spectrum measures the amount of energy per unit time as a function of frequency. The algorithm uses fast Fourier transform (FFT) of $x(t)g(t-u)$ over time period T.

2. Compute the power spectrum for different bandwidths: high frequency oscillations (HFO, 200<f<300 Hz) main frequency oscillations (FO, 2-100Hz) and low frequency oscillations (LFO-0.1<f<2 Hz):

$$|S(\omega,u)|^2=\mathrm{Re}^2\{S(\omega,u)\}+\mathrm{Im}^2\{S(\omega,u)\} \qquad (2)$$

3. Extract the harmonic components within a specific band:

$$A_i=\max_{\omega_{\min}<\omega<\omega_{Max}}|S(\omega,u)| \qquad (3)$$

and the phase of spectrum:

$$ph_i = \max_{\omega_{\min}<\omega<\omega_{Max}} (\arctan(\frac{\mathrm{Im}\, S(\omega,u)}{\mathrm{Re}\, S(\omega,u)})) \quad (4)$$

For all three different bandwidths, the values of harmonics are extracted between $\omega_{\min}$ and ω_{Max} then averaged. These values are the minimum respectively the maximum values of pulsation for every considered bandwidth. The phase unwrapping technique is used to remove the 2π discontinuities of the phase map by adding or subtracting an integer offset of 2π (Tribolet, 2003).

4. The envelope are extracted from four different electrodes by using a principal component analysis (PCA) and a zero phase-shift band pass digital filter to suppress the noise and improve the signal-to-noise ratio (Urbach and Pratt, 1986; Moller, 1988). Since in many cases the analysis include longer periods, one hour and over and only the envelope of HFO, LFO or FO events are represented. Therefore, further discussion and statistical analyses refer to filtered envelope.

5. Select a baseline time period and analyze changes in the amplitude of harmonics and phase compared to baseline period using a windowed t-test or one way ANOVA for all seizures with window size of 5 min. The widowed t-test is used to detect the existence of rare events in activity compared to a baseline period (first 10 min). In each case the t-test indicates a rejection of the null hypothesis at the 5% significance level.

6. Analyze LFP signal using measures of complexity to detect the presence of chaotic dynamics. In these analyses we used Kolmogorov complexity (Small, 2005). Several details regarding Kolmogorov complexity with a complete list of resources are provided in (Vitányi, and Li, 2000; Feldman and Crutchfield, 1998). Different entropy measures (Pezard et al., 1997; Pincus et al., 1991; Palus, 1996; Torres et al., 2001), the largest Lyapunov exponent, along with correlation dimension (Rosenstein et al., 1993, Grassberger and Procaccia, 1983) can be used to detect the presence of chaotic dynamics of electric field. The differences between different algorithms in estimating signal complexity is beyond the goal of this paper and will be addressed elsewhere.

3. Results

The presence of HFO spikes is a specific marker of epileptogenic regions and was detected in 12 selected seizures recorded from four pilocarpined treated rats. These data were further analyzed. We found that statistically significant changes in the amplitude/phase of power spectrum harmonics precede the seizure onset and reflect the presence of nonlinear resonances and perturbed dynamics within HFO epileptogenic regions. The resonances occur in distinct frequency domains, high frequency oscillations (HFO, 200<f<300 Hz), main frequency oscillations (FO, 2-100 Hz) and low frequency oscillations (LFO-0.01<f<2 Hz). One way ANOVA test was performed during 60 min before seizure assuming independent estimates for groups of 5 min window. The estimated F-ratio and p-values summarize the result of statistical analysis. The ANOVA analysis shows a statistically significant change in HFO (p=3.78e-7, F=5.76) and LFO (p=0.0091, F=2.52). A post-hoc pairwise comparison is performed in order to reveal where in time these differences are significant (see Supplementary Figure 10). On average the significant change in HFO and LFO harmonics occurs between 5 to 10 min

before the seizure onset (Figure 2). However, there is no significant trend in the main frequency bandwidth (p=0.821, F=0.58).

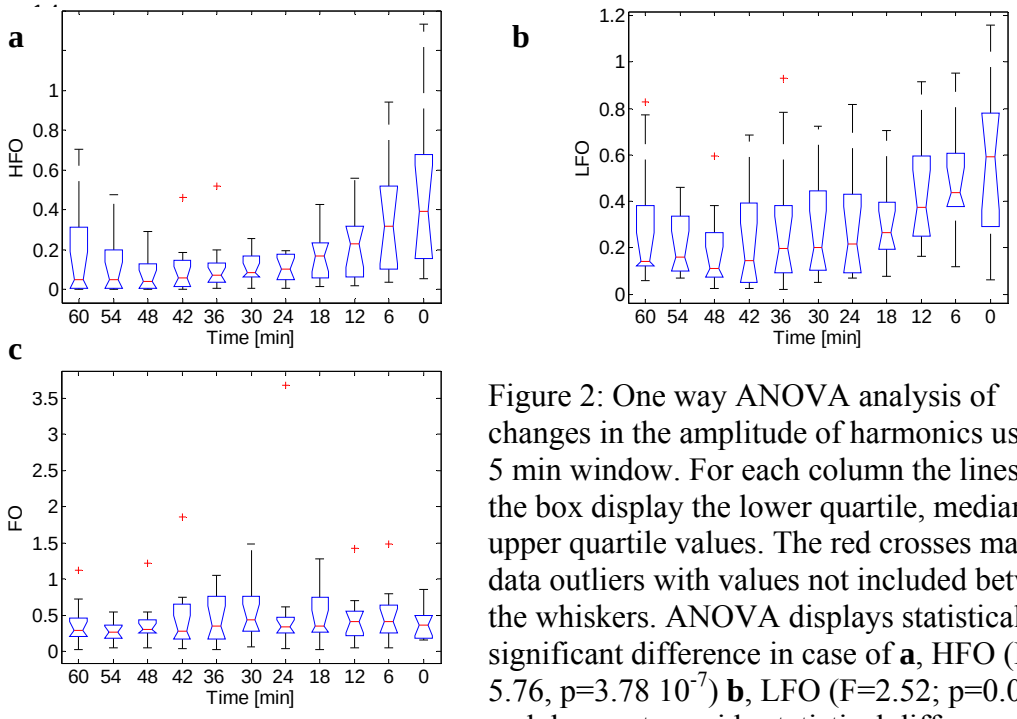


Figure 2: One way ANOVA analysis of changes in the amplitude of harmonics using a 5 min window. For each column the lines of the box display the lower quartile, median and upper quartile values. The red crosses mark data outliers with values not included between the whiskers. ANOVA displays statistically significant difference in case of **a**, HFO (F 5.76, p=3.78 10^{-7}) **b**, LFO (F=2.52; p=0.0091) and does not provide statistical difference **c**, for FO (F=0.58, p=0.821)

This result shows that a broadband spectrum develops before seizure onset by 'adding' HFO and LFO bandwidths and reveals changes in the dynamics of electric charges determined by the development of HFO spikes and chaotic charge diffusion. Specifically, the increase in amplitude of LFO harmonics is related to chaos generation that reflects a universal behavior of nonlinear systems known as the period doubling route to chaos (Pritchard and Duke, 1992; Cvitanovic, 2005).

While these ANOVA analyses of 5 min window display a general trend of averages from several seizures it is likely that important details regarding the dynamics before seizure onset can be hidden within every seizure. Therefore, in order to understand how seizures are generated it is important to separately analyze some seizures using several different measures (firing rate, changes in local field potentials).

There is a close relationship between spiking activity of individual neurons, changes in the mean firing rate and alterations of local field potentials (LFPs). Significant changes in the firing rate of an ensemble of neurons are correlated with changes in HFO and LFO before the seizure onset. Large amplitudes of HFO with local maxima (peaks) or minima (valleys) can be observed in HFO values determined by sudden increase/decrease "kicks" in the firing rate of granule cell units that precede the seizure onset (Figure 3, a, b, c). It is likely that high firing rate values represented in top red color is generated by interneurons (mean firing rate > 5Hz) (Figure 3, a) while lower firing rates are generated

by granule cells. Importantly, all these recorded cells show similar oscillatory dynamics of firing rate before the seizure onset. This period of synchronous firing in large neuronal ensembles provides a clear explanation for increased signal energy observed during the ictal state. The analysis of HFO data with a windowed t-test shows that a statistically significant changes in HFO (in red) occurs 20 min before seizure followed by significant changes in LFO and main frequency band and correspond to changes in the firing rate. Most of the time a bounded trajectory in the frequency domain is maintained, which reflects a regulatory process that rarely is altered (Figure 3, c).The t-test outcome for LFO signal is represented in black color and for FO in blue color (Figure 3, d).
Preliminary data from analyzed seizures show variability of seizure propagation and a high degree of inhomogeneity. Even seizures that develop within the same epileptogenic region seem to have highly heterogeneous propagation properties for HFO and LFO.

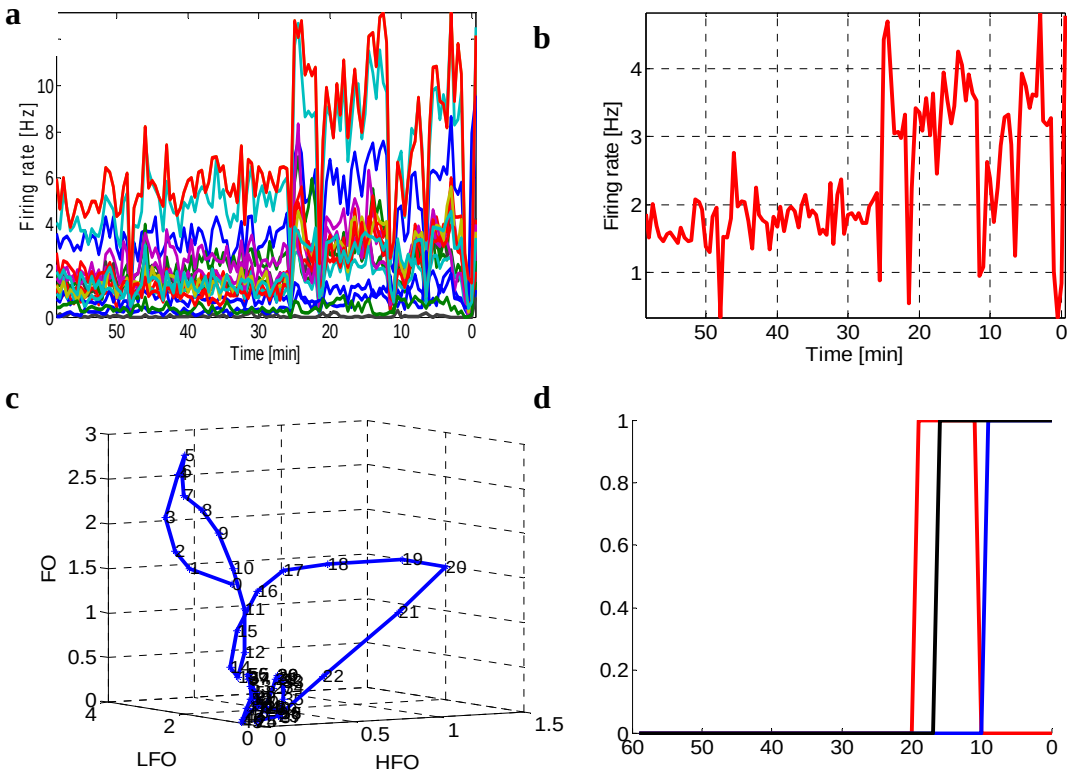


Figure 3 : Significant changes in the firing rate of an ensemble of neurons are correlated with HFO fluctuations and precede the seizure onset.
a, The evolution of changes in firing rate in granule cell layer one hour prior to seizure represented in different colors.
b, The average of firing rate for neurons represented in **a**
c, The corresponding trajectory in LFO, HFO, FO space during 60 min before seizure. Most of the time the trajectory is bounded and rarely is perturbed (min 20 and min 6 precedes the seizure)
d, The corresponding windowed t-test shows that statistically significant changes in HFO (in red) occur 20 min before seizure followed by significant changes in LFO and in the main frequency band. The T-test outcome for LFO is represented in black and for FO in blue color.

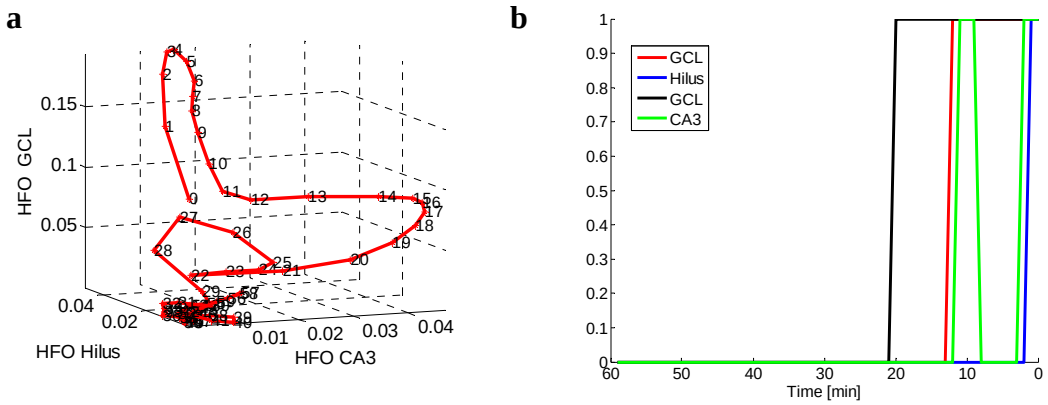


Figure 4: Statistically significant changes in HFO envelope occur 20 min before seizure.

a. The propagation of HFO between GCL, hilus and CA3.

b. Statistically significant changes in HFO occur first in GCL (black and red color for two different tips of tetrodes implanted in GCL) and they expand to CA3 region and hilus

A representative example of HFO propagation between GCL, hilus and CA3 during 60 min before the seizure onset is shown in Figure 3, a. A statistically significant change in HFO occurs first in GCL layer then expands to CA3 region and hilus (Figure 3, b). Additionally, along with these changes in amplitudes, alterations in the phase of harmonics occur (Figure 5). This significant increase in phase before seizure onset can be related to alteration in endogenous electric field and diffusion mechanisms that alters the dynamics of electric charges (Arnold diffusion, resonance overlap). Important details regarding seizure generation can be revealed only if one analyses correlated changes in firing rate and the development of chaotic dynamics. The increase in firing rate and the presence of HFO reduces the chaotic charge diffusion. Additionally, since electrical patterns occur within spikes (see Figure 7, a) the increase in synchronous firing generates extended spread of resonant patterns which determine a more ordered dynamics of electric field revealed by low values of complexity. However, due to resonance overlap, chaos develops and its presence becomes evident during the decrease, absence of firing when high values of complexity can be estimated (Figure 6 a).

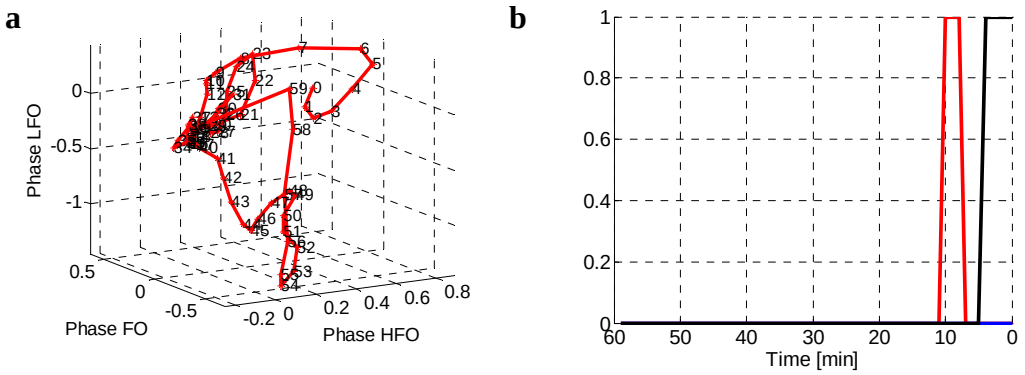


Figure 5: An example of seizure generation that displays statically significant change in the phase of harmonics.

a. The trajectory in phase space during 60 min before seizure

b. The windowed t-test shows that a statistically significant changes in the HFO phase occur earlier (in red color) followed by a significant change of phase of low frequency oscillations which occurs 5 min before seizure (in black color)

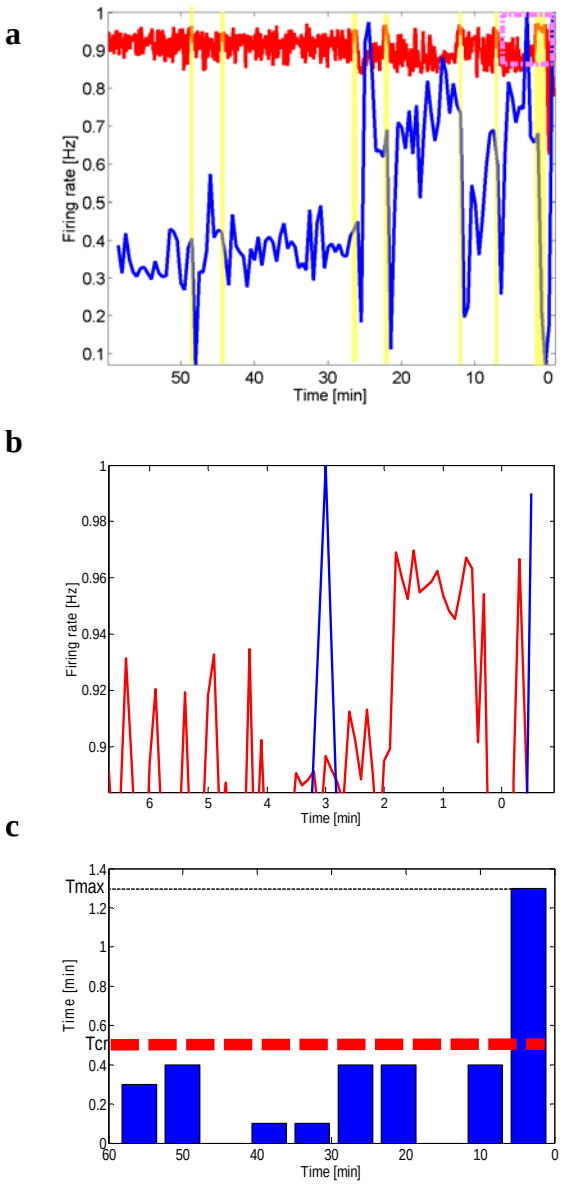


Figure 6: Specific transitory behavior precedes the seizure.

a. The normalized change of firing rate in blue color and scaled Kolmogorov complexity (in red) one hour prior to seizure. The changes that occur in firing rate correlate with alterations in the dynamics of electric charges. High values of Kolmogorov complexity correspond to increased chaotic dynamics (yellow marked regions).

b. Details of chaos persistence before the seizure onset represented in red color 6 min before the seizure (the rectangle from Figure 6, a)

c. The presence of persistent chaotic dynamics one hour before the seizure. The dysfunction in regulation occurs right before the seizure onset. The horizontal dashed red line marks the critical time ($T_{cr} \cong 0.5$ min) of persistent chaotic diffusion and is required to elicit the seizure onset. Each bar in blue color represents the duration of persistent chaotic dynamics

The periods when chaotic dynamics are persistent can be detected since they have high values of complexity. The presence of chaotic charge diffusion reflects less order in the dynamics of electric field (Figure 6, c). The occurrence of chaotic dynamics is followed by an increase of firing rate. Right before the seizure a detail of increased complexity shows that persistent chaotic charge dynamics is longer and precedes the seizure (Figure 6, b). The decrease in firing rate, absence of firing longer time reveals the dysfunctional regulation of neuronal activity (Figure 6, a) translated in periods of persistent chaotic diffusion. If the chaotic dynamics lasts over 0.5 min (30 s) the generation of ictal state is certain in this specific region (focal region) and expands very fast. Different electric patterns develop within every action potential (Figure 7 a, Aur and Jog, 2006) that may lead to extended resonances if the neurons fire in synchrony.

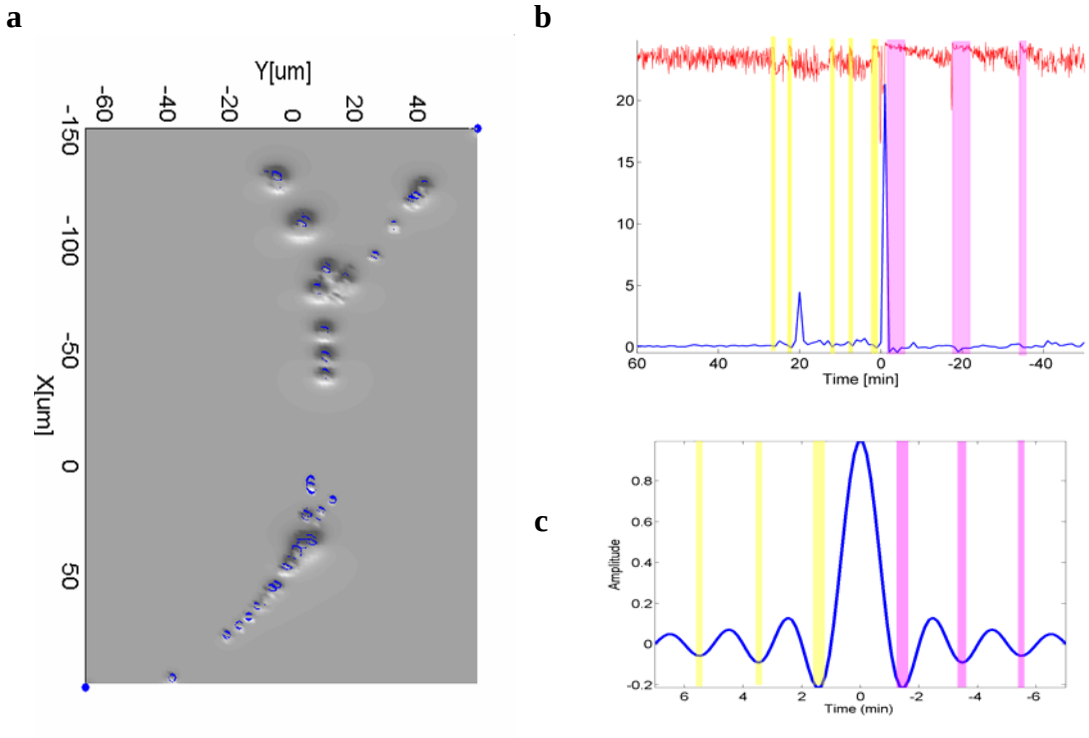


Figure 7: **a.** The development of electrical patterns (resonances, Turing patterns) during action potential propagation (Aur and Jog, 2006; Aur and Jog 2010)

b, The response to an internal perturbation determines a transitory regime. The scaled changes of complexity are shown in red color. The transition in HFO envelope represented in blue color includes brief periods when chaos develops during preictal period marked in yellow and postictal period marked in magenta. An increase of low frequency ripples can be detected in HFO envelope before the seizure

c. A reductionist representation of regulation with a sinc function. During the periods that correspond to lower neuronal activity chaos develops and is marked in yellow and magenta color while peaks in the amplitude define the corresponding resonant periods.

All three phases appear in the amplitudes of HFO envelope (Figure 7, b). The raising phase (preictal) shows an increased trend in the firing rate and HFO amplitude, ictal when HFO reach the maximum value and the postictal period when the trend is decreasing. The transitory regime that precedes seizure generation (preictal state) is followed by a longer transition that occurs after the seizure (postictal phase). The maximum value of HFO envelope represented in blue color defines the ictal phase. The preictal state is characterized by brief periods when chaotic dynamics occurs in HFO epileptogenic regions (Figure 7, b). Longer periods of chaotic dynamics marked in magenta with higher values of complexity develop during post-ictal phase. Excessive order occurs during the ictal phase and may determine cognitive and motor impairment or loss of consciousness. The transitory regime that follows after the seizure includes large periods with chaotic diffusion prolonged over 20 minutes. A schematic reductionist representation of the regulation by a sinc function is represented in (Figure 7, c) .The

corresponding periods of lower electrical activity are marked in yellow and magenta color.

4. Discussion

The mechanisms of generating epileptic seizures are elusive. Previous models have highlighted inhibitory or excitatory mechanisms or their balance in seizure generation. Several factors which govern the excitability of neurons along with complex changes in the neurochemistry are currently examined in different labs, however, little is yet known regarding the dynamics that leads to seizure generation.

This paper proposes a paradigm shift, a more general model that leads to seizure generation. Specifically, the fundamental source of seizure generation is the impaired regulation of neuronal activity in the epileptogenic region (see Appendix4). Since dysfunctional regulation does not always severely occur in the epileptogenic region, then indeed *the ictal state is a rare event*.

Alterations in the brain rhythms, abrupt changes in firing rate and neuronal activity translates to significant changes in endogenous electric fields and alterations of dynamics and interactions of electric charges that generate chaotic charge diffusion and electric resonances in epileptogenic regions. Standard averaging and filtering techniques that use many different seizures can show indeed a certain trend (Figure 2a, b), however these analyses may hide significant details regarding nonlinear dynamics in every seizure (see Figure 6 a,b,c). Importantly, there is a close relationship between changes in firing rate and changes in HFO. The correlation can be easily observed if one compares the average of firing rate for neurons (Figure 3b) and the profile of extracted HFO envelope one hour before the seizure (Figure 6,b). If the recordings are made in the focal source of the seizure, similar increase of low frequency ripples can be detected in HFO envelope and in the average of firing rate of neurons. Far from this focal region these ripples are small and the problem of neuronal regulation cannot be perceived (Figure 11).

It is likely that anytime a significant number of neurons fire in synchrony there are significant changes in the energy level of HFO envelope. *Electric resonances are specific to peaks of HFO envelope and the persistent chaotic dynamics of electric field, charge diffusion characterize the valleys of the HFO envelope.* Large peaks of HFO envelope include brief periods when high frequency oscillations develop. There is equivalence between the power spectrum outcome and generated ripples that can be evidenced in the filtered signal (Staba et al, 2002). Therefore, for any peak in the HFO envelope substantial ripples of high frequency oscillations within the given bandwidth of 200 - 300Hz can be detected with durations between (20-100ms). This result is an intrinsic characteristic of Fourier expansion of periodic functions. The best example of increased value of HFO envelope due to synchronous firing is the period of seizure development when the level of HFO harmonics attains the highest level. If many cells fire together in synchrony the local endogenous electric field changes significantly in the epileptogenic region, rapidly spreads further and determines changes in the dynamics of electric

charges and resonant regimes in large brain areas. This result points to critical mass hypothesis (Iasemidis, 2003) and reinforces the idea that a certain number of cells have to fire simultaneously (in synchrony) in order to generate the ictal state. Additionally, this observation suggests that in the epileptogenic region the occurrence/persistence of chaotic dynamics in electric field is still regulated. Only a severe dysfunctional regulation of neuronal activity leads to seizure generation. *The transition to seizure in epileptogenic region is generated in absence of neuronal activity, low firing rate when chaotic dynamics becomes persistent.*

We predict that the loss of consciousness is related to excessive order (redundant information) generated in the electric field by hyper-synchronous spiking in large areas during the ictal state (about 2 min, Figure 7,b). This result shows that *the measure of complexity provides a coherent model of the neural correlates of consciousness* generally unavailable for spike timing measures (Crick, and Koch, 1990, Crick and Koch, 2003).

We predict that confusion and lack of responsiveness after a seizure (Fagan et al., 1990) is determined by the transitory regime that follows every seizure which includes *large periods with chaotic dynamics (charge diffusion) that impair information processing and communication in large brain areas* (magenta marked periods, Figure 7,b).

Correlating this outcome with perturbation theory framework, an increase in the firing rate is equivalent to a 'perturbation' where developed resonances overlap and give raise to chaotic dynamics of electric field. This theoretical framework is particularly relevant since the existence of patterns (resonant regimes) within action potentials has been previously revealed in single spikes (Figure 7 a, Aur and Jog, 2006). Importantly, the results show that the regulatory mechanism is present in the frequency domain. Dominant frequency oscillations of electric field (FO, 2-60 Hz) are continuously built by neuronal activities. The occurrence of strong harmonics of HFO and LFO in epileptogenic region demonstrate the presence of dysfunctional neuronal activity. However, even in HFO epileptogenic regions neuronal activity is still regulated, only longer time persistence of chaotic dynamics, chaotic diffusion makes the ictal state a rare event.

This work elucidates the nature of seizure generation by providing evidence of dysfunctional regulation of neuronal activity and corresponding physical mechanism. Therefore, aberrant changes in firing activity in epileptogenic region are translated into a physical mechanism which acts at fundamental level of charge dynamics, electric field variability and leads to chaotic diffusion and electric resonances.

We identified at least two different important levels where the analysis can be performed and shows similar results. First, the temporal rhythm of spiking activity can be disrupted in the epileptogenic region and strong alterations of neuronal firing are involved in the process of epileptogenesis. Second, these significant changes in neuronal activity in the epileptogenic region alter the dynamics of electric field and electric charges.

In this case the KAM theory refers to Hamiltonian systems with many degree of freedom that describe the motion of charged particles in electric field. The KAM approach provides a theoretical framework of how chaos and electric resonances occur under dysfunctional regulation in neuronal activity seen as an occurring perturbation (Appendix1). We combined analytical models and experimental data analysis and we predict that high frequency oscillations (HFO clusters) from epileptogenic regions are the main sources of seizures. This approach provides a theoretical framework for the process

of seizure generation, the required relation with endogenous electric field, perturbation theory, resonance and chaos occurrence in nonlinear Hamiltonian systems via Kolmogorov Arnold Moser (KAM) theory.
Since the seizure occurrence can be explained as a result of perturbation theory and nonlinear dynamics, this framework demonstrates that alone, either inhibitory or excitatory function models of chronic epilepsy are incomplete and inconsistent. Under endogenous electric field development, extensive chaotic charge diffusion occurs, relevant differences between different types of neurons disappear and all cells fire together in synchrony inside HFO clusters.

The evidence for a synchronous activity in different types of neurons is presented in Figure 3, a. In the epileptogenic HFO region different types of cells including interneurons begin to show similar fluctuations of firing rate 10-20 minutes earlier before the seizure onset. Several controversies regarding synchrony can occur if the analyses are not made in the seizure focus, if averages from different experiments are considered all together or the time-scale of analyses is not large enough.
A classification of many causes that facilitate changes in nonlinear dynamics can be made based on different characteristics of a diffusion process (see Appendix 3). In this case the diffusion across the resonance lines is a result of synchronous firing (perturbation) with fast development strong electric fields which can be generated by aberrant synaptic connectivity (Jacobs, et al., 1999) recurrent excitatory and inhibitory synaptic connectivity (Huguenard, 1999) terminal sprouting (Buckmaster et al., 2002). Arnold diffusion is a different mechanism that slowly develops and can be caused by a failure of glutamate reuptake from the extracellular space facilitated by Belousov-Zhabotinsky (BZ) reaction (Bentzen et al., 2009,2010) or extracellular potassium concentration (Haglund and Schwartzkroin, 1990, Heinemann et al., 1986; Jensen and Yaari, 1997; Korn et al., 1987; Lux, 1974; Moody et al., 1974) potassium lateral diffusion coupling models and glial buffering on extracellular potassium (Bazhenov et al., 2004; Park and Durand, 2006; Fröhlich,2008; D'Ambrosio, 2004) and highlights the importance of glial regulation.
The paper clarifies the possibility of short time seizure prediction in the context of nonlinear behavior. *The horizon of prediction* can be computed as a measure of persistent chaotic diffusion over a specific critical time period (T_{cr}) as exemplified in Figure 6, c, Aur et al. 2010. Since the electrode acts as a sensor in a noisy environment and high frequencies are likely to be more attenuated (Bédard and Destexhe, 2009) then the seizure prediction can be accurately performed only if the electrodes are implanted close to the region where the seizures originates.
Additionally, this work shows that sensitivity and specificity measures currently used to test the seizure prediction algorithms may not necessarily reflect the algorithm properties if the recordings are not made close to HFO epileptogenic regions (Litt and Lehnertz, 2002; Mormann et al. 2005, Sackellares et al. 2006; Schad et al. 2008).
The presented framework provides a direct possibility to enhance neuromodulatory treatment based on closed loop phase control using HFO stimulation to prevent seizure generation in patients with chronic drug-resistant epilepsy (Aur et a., 2010). Since in this case the idea of neurostimulation exploits a physical mechanism, we predict that this type

of high frequency stimulation in Parkinson disease and depression will reduce local chaotic diffusion and switch off the pathological disrupted activity.
Importantly, the theoretical framework of seizure generation provides a window to understand the neural correlates of consciousness in terms of dynamics and interaction of electric charges. We predict that *altered states of consciousness correspond to 'excessive' order recorded during the ictal phase (hyper-synchrony) or persistent chaotic diffusion in the postictal phase*. Therefore, the conscious state is maintained as long as the dynamics of electric charges are regulated by neuronal activity in specific brain regions (e.g. anterior hypothalamus Adamantidis et al., 2007; sleep the altered state vs awake state).

Since information is read, written, processed and stored at molecular level within neurons the interaction of electric charges, their dynamics and corresponding electric field has to be highly regulated. The paper introduces a new paradigm regarding seizure generation, explains chaotic dynamics as a result of resonance overlap and Arnold diffusion. Dysfunctional regulation of neuronal activity in the epileptogenic region translates into a physical mechanism of transition to ictal state. Persistent chaotic diffusion periods and strong electric resonant regimes can occasionally develop and make the seizure generation a rare event. This process of seizure generation revealed as a nonlinear phenomenon built-in by the dynamics of electric charges and endogenous electric fields *reinforces the view presented in neuroelectrodynamics where universal physical laws can characterize complex computational processes in the normal and diseased brain* (Aur and Jog, 2010). Quoting Albert Einstein, it seems that the physical phenomena reflect God's thoughts and.... "the rest are details".

Summary of principal concepts

- *The occurrence of seizures is a rare event with a very low probability of incidence generated by a dysfunction of neuronal activity in the epileptogenic region*
- *The dysfunctional regulation of neuronal activity inside epileptogenic regions alters endogenous electric field, changes relevant characteristics of charge dynamics and leads to seizure generation.*
- *'The details' that contribute to dysfunctional regulation are many changes in gene expression, aberrant synaptic connectivity, terminal sprouting, failure of glutamate reuptake, potassium lateral diffusion just to mention a few.*
- *The alteration in regulation can be modeled by perturbed Hamiltonian systems with many degrees of freedom that describe the motion of charged particles in electric field via Kolmogorov Arnold Moser theory (KAM) and provides a physical model for the mechanism of epileptogenesis.*
- *The presence and a longer persistence of chaotic dynamics of electric field right before the ictal state characterizes the transition to seizure*
- *Chaotic dynamics is a result of physical phenomena (resonance overlap, Arnold diffusion) and is generated when the required conditions are met*
- *This transition is generated in absence of neuronal activity, low firing rate that determines chaotic dynamics to become persistent.*

- *The presence and persistence of HFO and LFO harmonics in the epileptogenic are markers of neuronal activity dysfunction.*
- *If the recording electrode is far from the focal region where the ripples occur (see* Figure 11*) the problem of neuronal regulation cannot be perceived in advance and the seizure cannot be predicted.*
- *Therefore, sensitivity and specificity measures currently used to test the seizure prediction algorithms may not necessarily reflect the algorithm properties if the recordings are not made close to HFO epileptogenic regions*
- *Contrary to common belief under electric field fluctuations or extensive chaotic charge diffusion, relevant differences between different types of neurons disappear and all types of cells fire together in synchrony inside epileptogenic regions.*
- *Since the seizure occurrence can be explained as a result of perturbation theory and nonlinear dynamics, this framework demonstrates that alone, either inhibitory or excitatory function models of chronic epilepsy are incomplete and inconsistent.*
- *The measure of complexity provides a coherent model of the neural correlates of consciousness generally unavailable for spike timing measures*
- *A balance between chaotic dynamics and order is sustained by steady regulatory mechanisms that act to maintain neuronal activity*
- *The confusion and lack of responsiveness after a seizure is determined by the transitory regime that follows every seizure characterized by large periods with chaotic dynamics (charge diffusion) that impair information processing and communication in large brain areas*
- *The loss of consciousness is related to excessive order (redundant information) generated in electric field by hyper-synchronous spiking in large areas during the ictal state*
- *The physical mechanism points to a direct methodology to enhance neuromodulatory treatment based on closed loop phase control using HFO stimulation (Aur et a., 2010).*
- *Since the idea of neurostimulation exploits a physical mechanism, we predict that similar control of high frequency stimulation can be performed in Parkinson disease or to treat symptoms depression*
- *Importantly, the paper explains the transition to ictal state based on physical processes, relates the dynamics and interaction of electric charges, changes in electric field with information processing and reflects a neuroelectrodynamic model of computation in the brain*

Appendix 1: The perturbation model: Nonlinear Hamiltonian dynamics

The physical phenomenon of diffusion can be related to processes that develop at microscopic scale, dynamics of charges and transport properties of biological membranes (Mateos, 2000). The 'noise' is generally supposed to have a thermal origin which is consistent with Brownian view of motion and can also be associated with diffusion. The presence of chaotic dynamics and deterministic diffusion are related phenomena, however deterministic diffusion at microscopic scale doesn't necessarily have a 'thermal origin'. The phenomenon of diffusion can be directly connected to the theory of nonlinear dynamical

systems and chaos generation (Feigenbaum, 1983; Pritchard and Duke, 1992; Cvitanovic, 2005). In the early sixties Kolmogorov Arnold and Moser have demonstrated that under very small perturbations the quasiperiodic dynamics of an integrable system is preserved (KAM Theory, Kolmogorov, 1954; Arnold, 1963; Moser 1967). An existent perturbation with higher energy determines the transition to chaotic dynamics and deterministic diffusion due to resonance overlap. Additionally, deterministic diffusion can occur based on Arnold diffusion mechanism which significantly changes the dynamics of the system (Chirikov, 1979; Gaspard, 1996).

The perturbation framework provides a model of charge motion in a potential V of periodic perturbation. The Hamiltonian dynamics can be expressed in the form of action angle variable (Chirikov, 1979; Reichl, 1992):

$$H = \sum_{i=1,N} H_0(I_i) + \varepsilon V(I_1, I_2, ..., I_N, \theta_1, \theta_2, ...\theta_N) \quad \textbf{(5)}$$

where N represents the degree of freedom and H_0 the unperturbed dynamics (non-interacting charges). The potential representing the perturbation V is expanded in Fourier series:

$$V(\mathrm{I}_1, I_2, ...I_N, \theta_1, \theta_2, ..., \theta_N) = \sum_{n_1, n_2, ..n_N} V_{n_1, n_2, ...n_N}(I_1, I_2, ...I_N) e^{i(n_1\theta_1 + n_2\theta_2 + ... + n_N\theta_N)} \quad \textbf{(6)}$$

where n_i are integers. In a general case this periodic perturbation can be a result of synaptic activity. For each decoupled Hamiltonian the energy distribution can be written in the form:

$$E_i = H_0(I_i) + \varepsilon V(I_i, \theta_i),\ i = 1, N \quad \textbf{(7)}$$

where E_i is the energy. The Hamiltonian equation of motion in the form of action angle variable is:

$$\dot{I}_i = -\frac{\partial H}{\partial \theta_i} = -\sum_{n_1, n_2, ..n_N} i n_i V_{n_1, n_2, ...n_N}(I_1, I_2, ...I_N) e^{i(n_1\theta_1 + n_2\theta_2 + ... + n_N\theta_N)} \quad \textbf{(8)}$$

and:

$$\dot{\theta}_i = \frac{\partial H}{\partial I_i} = \frac{\partial H_0}{\partial I_i} + \frac{\partial V(I_1, I_2, ..., I_N, \theta_1, \theta_2, ..., \theta_N)}{\partial I_i} \quad \textbf{(9)}$$

and $\frac{\partial H_0}{\partial I_i} = \omega_i(I_i)$ represent the oscillations of unperturbed motion. The presence of perturbation leads to the following condition for internal nonlinear resonances (Chirikov, 1979; Reichl, 1992) :

$$n_1\omega_1(I_{10}) + ... + n_N\omega_N(I_{N0}) = 0 \quad \textbf{(10)}$$

where n_1,.., n_N are natural numbers and:

$$\omega_i = \frac{dH_i}{\partial I_i} \quad \textbf{(11)}$$

Due to periodic perturbations various resonances can occur for different actions (I_{10} , I_{20} ,.., I_{N0}). The effect of perturbation over external stability of the system can be assessed using Kolmogorov –Arnold - Moser (KAM) approach where the perturbation ΔH determines a low 'deformation' of the Hamiltonian:

$$H = H_0 + \varepsilon H \quad \textbf{(12)}$$

If the perturbation is null $\varepsilon = 0$ then the trajectories of the system lie on an invariant tori generating quasiperiodic motions which corresponds to KAM-stable Hamiltonians (Sevryuk, 1995, Broer et al., 2007).

For small perturbations $\varepsilon \cong 0$ most of these trajectories (non-resonant trajectories) are preserved and only slight deformation of the tori occurs (Sevryuk, 2006). Any additional periodic perturbation Ωt (e.g. HFO perturbation) generated by neuronal activity or electrical stimulation changes the condition for nonlinear resonance:

$$n_1 \omega_1(J_{10}) + \ldots + n_N \omega_N(J_{N0}) + m_1\Omega_1 + \ldots m_p\Omega_p = 0 \quad \textbf{(13)}$$

Since many resonances may occur near the separatrix they may determine instabilities and the appearance of chaotic regimes.

Appendix2: Linear and Nonlinear Oscillations

Every system has a fundamental frequency, which for linear systems is known to be the natural frequency. Nonlinear systems are a special category of dynamic systems that exhibit complex behavior. In a nonlinear system the component which collects almost all the energy is considered to be the fundamental frequency. Compared to linear systems the behavior of nonlinear systems is not always predictable. In order to test the behavior of nonlinear oscillations in a nonlinear dynamic system is considered under the influence of a periodic forcing frequency:

$$m\frac{d^2x}{dt^2} + k_v\frac{dx}{dt} + k\sin(x) = A\cos\Omega t \quad \textbf{(14)}$$

The forcing input can be any excitation (perturbation) that influences the dynamics of electric charges. In a nonlinear system resonances may occur at different frequencies and are multiple and submultiples of forcing frequency. The condition for resonance is:

$$m\omega = n\Omega \quad \textbf{(15)}$$

where $m \in N, n \in N$ and Ω is the excitation frequency. Since the global system's fundamental frequency depends on the energy, nonlinear systems can exhibit resonances at frequencies that are multiples or submultiples of the forcing frequency. Therefore, the resonance frequency ω_r is a fraction of forcing frequency Ω:

$$\omega_r = \frac{n}{m}\Omega \quad \textbf{(16)}$$

There is an important difference in the nonlinear case; the amplitude of spectral components and their frequency depend on the amplitude of excitation. Therefore, the resonance frequency ω_i depends on the amplitude of forcing signal:

$$\omega_i = \omega_i + f_i(A) \quad \textbf{(17)}$$

Importantly, in a nonlinear system changes in the amplitude of excitation can be perceived as alterations that occur in the power spectrum.

.

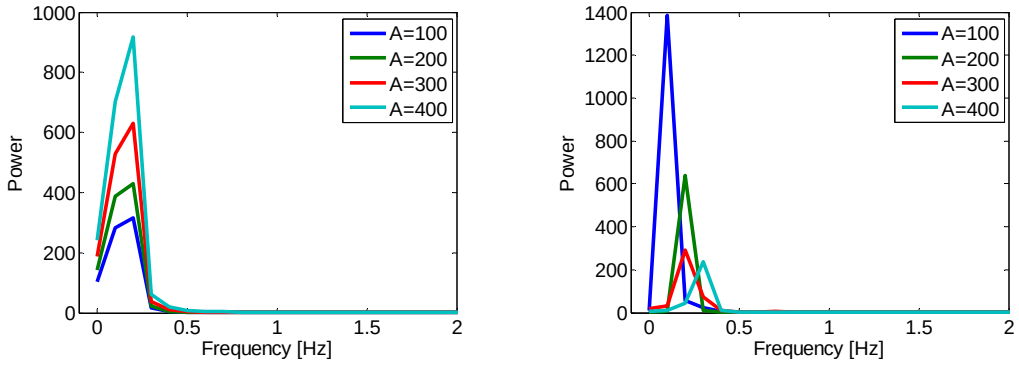


Figure 8: Significant difference between the power spectrum of linear resonance and nonlinear resonance. (Ω =0.3Hz)

a. In a linear system the existence of a single resonant frequency is independent of the amplitude of excitation
b. In a nonlinear system the amplitude of spectral components and their frequency depend on the amplitude of excitation

In general the dynamics of linear systems do not include the presence of chaotic regimes. In a nonlinear system a perturbation (the change in excitation) can be detected and causes changes in the amplitude of power spectrum harmonics (Figure 8). Since a change in the amplitude of perturbation is followed by a change in the amplitude of power spectrum harmonics, the above result shows that the investigation of transition to chaos as a result of a perturbation in a nonlinear system can be fully revealed by a power spectrum analysis.

Appendix 3: Internal Resonances and Chaotic Dynamics

Since the resonance frequency in a nonlinear system depends on action, then changes in action (perturbations) are reflected in the alterations of power spectrum harmonics. Therefore, the analysis of power spectrum harmonics provides information regarding ongoing changes in action.
The chaotic behavior is an essential property of charge dynamics that occurs during diffusion. One possibility is a slow, gradual transition to chaotic behavior that occurs by diffusion *along the resonance lines* called Arnold diffusion. Another possibility is a fast transition that occurs when a strong perturbation in the electric field is generated and determines diffusion across *the resonances lines* due to resonance interference. A combination of both mechanisms starting with Arnold diffusion process that can progressively grow and generates resonance overlap is also possible.

Resonance interference

In general the process of diffusion across resonant layer (resonance overlap) is a result of an external perturbation. If the Hamiltonian is expressed by a Fourier series expansion (Lichtenberg and Lieberman, 1992) then for two close consecutive resonance harmonics

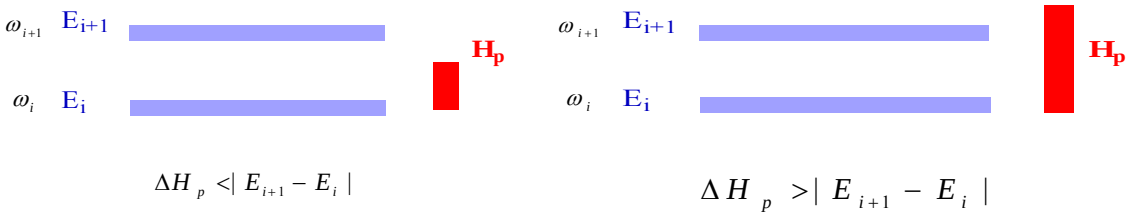


Figure 9: Resonance overlapping and chaos generation occur when the energy of perturbation ΔH_p exceeds the energy difference between the two closest unperturbed resonant orbits

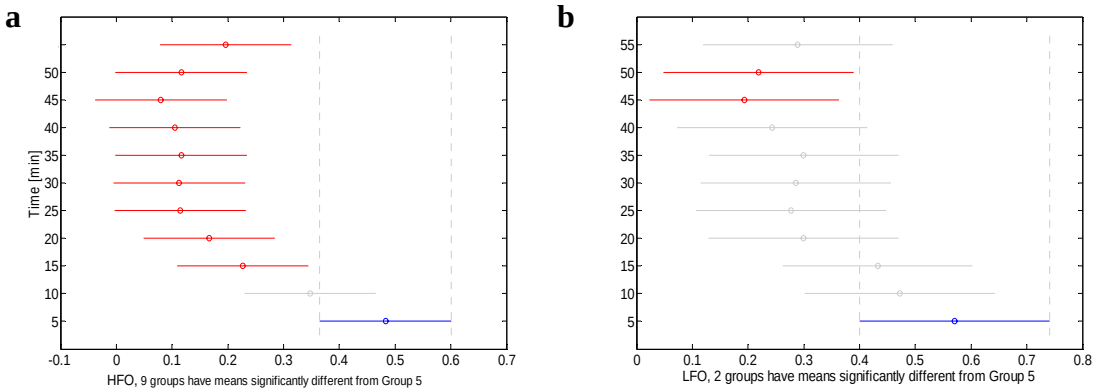
ω_i and ω_{i+1} the process of resonance interference occurs if the perturbation energy due to perturbation is higher than the energy difference between the two closest unperturbed resonant orbits (Luo, 1995):

$$\Delta H_i > E_{i+1} - E_i \qquad \textbf{(18)}$$

The interaction between resonances in perturbed and unperturbed orbits destroys the KAM tori and generates a transitory regime that leads to chaotic behavior and ictal state generation.

Arnold diffusion

Since electric charges present many degrees of freedom small-amplitude variations can accumulate little by little over time in extended epileptogenic HFO regions. However this accumulation that internally grows can determine *diffusion along the resonance lines.* Both mechanisms can be combined, Arnold diffusion can develop gradually and finally reach a level where resonance overlapping may generate the final transition to ictal state.



Supplementary Figure 10: **a**.The significant difference in ANOVA lies in changes that occur in the average of HFO, 5 min before the seizure compared to all other previous 9 groups.

b, In case of LFO these changes are significant only to other two groups and is mainly related to Neuralynx low pass filtering and difficulty in estimating LFO changes

Appendix 4: The regulatory mechanism can be described in terms of energy or electrical power developed in the epileptogenic region. The firing rate is a good measure of ' electrical power' P_n which for one neuron can be written:

$$P_n = \frac{N * e_{sp}}{T} \qquad (19)$$

where N is the number of spikes that occur during the time T and e_{sp} is the average energy in one single spike which is proportional with the estimated firing rate of the cell. Additionally, the assumption of a proportional increase of the synaptic activity with firing rate leads to:

$$P_n^{total} = k * f_r \qquad (20)$$

where k is a constant and f_r is the firing rate where P_n^{total} includes the entire electrical activity of the neuron. Close time to any seizure (5 to 10 min before in HFO epileptogenic region) strong ripples in low frequency domain occur. The firing rate varies from high firing values to absence of firing or very low firing rate (see Figure 6 a). This change in firing rate that precedes the seizure is a significant marker of dysfunction in regulation of neuronal activity which can be seen simultaneously in the power spectrum alterations in the frequency domain (HFO, Figure 7b). In other words, the regulatory mechanism is present in the frequency domain. Instead of maintaining a regime where main spectrum lies in the FO domain (FO, 1-100 Hz) the preictal state includes strong harmonics of HFO and LFO which reflect the dysfunction of neuronal activity (Figure 11).

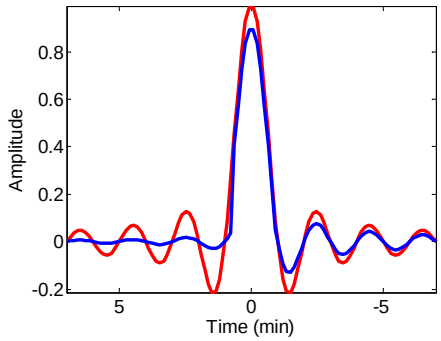


Figure 11: In the epileptogenic region high fluctuations of neuronal activity represented in red color occur and precede the ictal event. These strong fluctuation can be seen in the firing rate (Figure 6 a) and also in the power spectrum (HFO, Figure 7b). If the electrode is far from this focal region then the fluctuations of firing rate (in blue color) or HFO are small and the problem of neuronal regulation cannot be perceived.

Acknowledgement: The author wish to thank especially to Paul Buckmaster for continuous excellent feedback and Izumi Toyoda, Mark Bower and Anatol Bragin for suggestions to improve the manuscript. This work was supported by Epilepsy Foundation Award 161096

References

Adamantidis AR, Zhang F, Aravanis AM, Deisseroth K and de Lecea L (2007) Neural substrates of awakening probed with optogenetic control of hypocretin neurons. Nature 450: 420-4.

Adeli, H., Zhou, Z., Dadmehr, N. 2003 ,Analysis of EEG records in an epileptic patient using wavelet transform,Journal of Neuroscience Methods 123 (1), pp. 69-87 143

Andrzejak RG, Mormann F, Kreuz T, et al. 2003, Testing the null hypothesis of the nonexistence of a preseizure state. Phys Rev E;67:010901.

Arnold , V I ,1963, Proof of a Theorem by A. N. Kolmogorov on the invariance of quasi-periodic motions under small perturbations of the Hamiltonian. Russian Math. Survey 18 : 13-40.

Aur D., and Jog, M, Neuroelectrodynamics- Understanding The Brain Language , IOS Press 2010, http://dx.doi.org/10.3233/978-1-60750-473-3-i

Aur, D., Connolly, C.I., and Jog, M.S, (2005), Computing spike directivity with tetrodes, Journal of Neuroscience Methods, Volume 149, Issue 1, 30, pp. 57-63;

Aur D., Jog, MS, Building Spike Representation in Tetrodes, Journal of Neuroscience Methods Volume 157, Issue 2 , 30 October 2006, Pages 364-373

Aur, Toyoda, I. Bower, M.R. Buckmaster, P.S., 2010, System and Method for Seizure Prediction and Treatment of Epileptic Seizures, S10-419-prov. patent

Babloyantz, A., Destexhe, A.,1986,Low-dimensional chaos in an instance of epilepsy,Proceedings of the National Academy of Sciences of the United States of America 83 (10), pp. 3513-3517.

Bazhenov, M. Timofeev I., Steriade M. and Sejnowski T.J., 2004, Potassium model for slow (2–3 Hz) in vivo neocortical paroxysmal oscillations, J. Neurophysiol. 92, pp. 1116–1132.

Bédard, C., Destexhe, A. 2009 Macroscopic models of local field potentials and the apparent 1/f noise in brain activity, Biophysical Journal 96 (7), pp. 2589-2603

Bentzen, N.C.K., Zhabotinsky, A.M., Laugesen, J.L. 2009, Modeling of glutamate-induced dynamical patterns, International Journal of Neural Systems 19 (6), pp. 395-407

Bragin, A., Engel Jr., J., Wilson, C.L., Fried, I., Buzsáki, G. 1999 High-frequency oscillations in human brain, Hippocampus 9 (2), pp. 137-142

Bragin A., Engel J.Jr.,. Wilson C.L, Fried I.and Mathern G.W., 1999, Hippocampal and entorhinal cortex high-frequency oscillations (100–500 Hz) in human epileptic brain and in kainic acid–treated rats with chronic seizures, Epilepsia 40, pp. 127–137

Bragin, A., Engel, J., Staba, R.J. 2010, High-frequency oscillations in epileptic brain

Current Opinion in Neurology 23 (2), pp. 151-156

Bragin, A., Mody, I., Wilson, C.L., Engel Jr., J. 2002, Local generation of fast ripples in epileptic brain, Journal of Neuroscience 22 (5), pp. 2012-2021

Bonni, A., Sun, Y., Nadal-Vicens, M., Bhatt, A., Frank, D.A., Rozovsky, I., Stahl, N., (...), Greenberg, M.E. , 1997, Regulation of gliogenesis in the central nervous system by the JAK-STAT signaling pathway, Science 278 (5337), pp. 477-483

Bower, M.R. Buckmaster, P.S., 2008, Changes in Granule Cell Firing Rates Precede Locally Recorded Spontaneous Seizures by Minutes in an Animal Model of Temporal Lobe Epilepsy, Vol 99; Nr 5, pages 2431-2442

Buckmaster, P.S., Zhang, G.F., Yamawaki, R. 2002, Axon sprouting in a model of temporal lobe epilepsy creates a predominantly excitatory feedback circuit ,Journal of Neuroscience 22 (15), pp. 6650-6658

Buzsáki, G. 2002 Theta oscillations in the hippocampus, Neuron 33 (3), pp. 325-340

Buzsáki, G., 2006, Rhythms of the Brain, Oxford University Press,

Cartmell, J., Schoepp, D.D. 2000 Regulation of neurotransmitter release by metabotropic glutamate receptors , Journal of Neurochemistry 75 (3), pp. 889-907

Cvitanovic P., 1995, Classical and Quantum Chaos: A Cyclist Treatise. Lecture notes, preprint;.

Chirikov, B.V. 1979, A universal instability of many-dimensional oscillator systems, Physics Reports 52 (5), pp. 263-379

Chu, Y., Jin, X., Parada, I., Pesic, A., Stevens, B., Barres, B., Prince, D.A. 2010 Enhanced synaptic connectivity and epilepsy in C1q knockout mice , Proceedings of the National Academy of Sciences of the United States of America 107 (17), pp. 7975-7980

Claes, L., Del-Favero, J., Ceulemans, B., Lagae, L., Van Broeckhoven, C., De Jonghe, P. 2001, De novo mutations in the sodium-channel gene SCN1A cause severe myoclonic epilepsy of infancy, American Journal of Human Genetics 68 (6), pp. 1327-1332

Crépon, B., Navarro, V., Hasboun, D., Clemenceau, S., Martinerie, J., Baulac, M., Adam, C., Le Van Quyen, M. 2010, Mapping interictal oscillations greater than 200 Hz recorded with intracranial macroelectrodes in human epilepsy, Brain 133 (1), pp. 33-45

Crick, F. and Koch, C., 1990, Towards a neurobiological theory of consciousness. Seminars in the Neurosciences 2: 263-275.

Crick, F., Koch, C. , 2003, A framework for consciousness, Nature Neuroscience 6 (2), pp. 119-126

D'Ambrosio R. (2004), The role of glial membrane ion channels in seizures and epileptogenesis, Pharmacol. Ther. 103 pp. 95–108.

Deans, J.K., Powell, A.D., and Jefferys, J.G. (2007). Sensitivity of coherent oscillations in rat hippocampus to AC electric fields. J. Physiol. 583, 555–565

Escayg, A., Goldin, A.L., 2010, Sodium channel SCN1A and epilepsy: Mutations and mechanisms, Epilepsia 51 (9), pp. 1650-1658

Fagan, K.J., Soo Ik Lee, 1990, Prolonged confusion following convulsions due to generalized nonconvulsive status epilepticus ,Neurology 40 (11), pp. 1689-1694

Feigenbaum, M.J. 1983, Universal behavior in nonlinear systems Physica D: Nonlinear Phenomena 7 (1-3), pp. 16-39.

Fisher R.S., Webber W.R., Lesse R.P.r, Arroyo S. and Uematsu S., (1992) High-frequency EEG activity at the start of seizures, J. Clin. Neurophysiol. 9, pp. 441–448

Feldman, D.P., Crutchfield, J.P. 1998, Measures of statistical complexity: Why? Physics Letters, Section A: General, Atomic and Solid State Physics 238 (4-5), pp. 244

Fries, P., Womelsdorf, T., Oostenveld, R., and Desimone, R. (2008). The effects of visual stimulation and selective visual attention on rhythmic neuronal synchronization in macaque area V4. J. Neurosci. 28, 4823–4835.

Fröhlich, F., Bazhenov, M., Iragui-Madoz, V., Sejnowski, T.J. 2008, Reviews: Potassium dynamics in the epileptic cortex: New insights on an old topic Neuroscientist 14 (5), pp. 422-433

Fröhlich, F., McCormick, D.A. 2010 Endogenous electric fields may guide neocortical network activity, Neuron 67 (1), pp. 129-143.

Fujiwara, T., Sugawara, T., Mazaki-Miyazaki, E., Takahashi, Y., Fukushima, K., Watanabe, M., Hara, K., Inoue, Y. 2003 Mutations of sodium channel α subunit type 1 (SCN1A) in intractable childhood epilepsies with frequent generalized tonic-clonic seizures, Brain 126 (3), pp. 531-546.

Gaspard, P. 1996, Hydrodynamic modes as singular eigenstates of the Liouvillian dynamics: Deterministic diffusion, Physical Review E - Statistical Physics, Plasmas, Fluids, and Related Interdisciplinary Topics 53 (5 SUPPL. A), pp. 4379-4401

Golding, N.L., Staff, N.P., Spruston, N. 2002 Dendritic spikes as a mechanism for cooperative long-term potentiation, Nature 418 (6895), pp. 326-331

Grassberger P. and Procaccia I., 1983 Measuring the strangeness of strange attractors, Physica D 9 (1983), pp. 189–208.

Hausser, M., Spruston, N., Stuart, G.J. 2000 Diversity and dynamics of dendritic signaling, Science 290 (5492), pp. 739-744

Iasemidis, L.D., Sackellares, J.C., Zaveri, H.P., Williams, W.J. 1990, Phase space topography and the lyapunov exponent of electrocorticograms in partial seizures, Brain Topography 2 (3), pp. 187-201

Iasemidis, L.D. 2003, Epileptic seizure prediction and control.IEEE transactions on Bio-medical Engineering 50 (5), pp. 549-558

Jacobs KM, Mogensen M, Warren E, Prince DA. 1999 Experimental microgyri disrupt the barrel field pattern in rat somatosensory cortex. Cereb Cortex. Oct-Nov;9(7):733-44.

Haglund M.M.and. Schwartzkroin P.A, 1990, Role of Na–K pump potassium regulation and Ipsps in seizures and spreading depression in immature rabbit hippocampal slices, J. Neurophysiol. 63, pp. 225–239.

Heinemann U., Konnereth A., Pumain R.and Wadman W., 1986, Extracellular calcium and potassium concentration changes in chronic epileptic brain tissue, J. Adv. Neurol. 44, pp. 641–661.

Huguenard, J.R. 1999, Neuronal circuitry of thalamocortical epilepsy and mechanisms of antiabsence drug action. Adv Neurol 79:991-9.

Jensen M.S and Yaar Y.i, 1997, Role of intrinsic burst firing, potassium accumulation, and electrical coupling in the elevated potassium model of hippocampal epilepsy, J. Neurophysiol. 77, pp. 1224–1233.

Kennel, M.B., Isabelle, S. 1992, Method to distinguish possible chaos from colored noise and to determine embedding parameters ,Physical Review A 46 (6), pp. 3111-3118

Korn S.J., Giacchino J.L., Chamberlin N.L.and R. Dingledine, (1987) Epileptiform burst activity induced by potassium in the hippocampus and its regulation by GABA-mediated inhibition, J. Neurophysiol. 57, pp. 325–340

Koch, C. 2009, The SCP is not specific enough to represent conscious content, Trends in Cognitive Sciences 13 (9), pp. 367.

Kolmogorov, A N.,1954, On the conservation of conditionally periodic motions under small perturbation of the Hamiltonian. Dokl. Akad. Nauk. SSR 98: 527-530.

Lewis, D. 2000, Causation as Influence. The Journal of Philosophy 97: 182-197.

Lerner, R.N., McDonald, J. 2010, Higgs inflation and naturalness ,Journal of Cosmology and Astroparticle Physics 2010 (4)

Lichtenberg AJ, Lieberman MA.,1992, Regular and Chaotic Dynamics, second ed. New York: Springer,

Litt B, Lehnertz K., 2002,Seizure prediction and the preseizure period. Curr Opin Neurol;15:173–7.

Lux, H.D. 1974, The kinetics of extracellular potassium relation to epileptogenesis, Epilepsia 15, pp. 375–393

Moody, W.J. Futamachi K.J.and D.A. Prince, 1974, Extracellular potassium during epileptogenesis, Exp. Neurol. 42, pp. 248–263.

Mateos, J.L. 2000, Chaotic Transport and Current Reversal in Deterministic Ratchets

Physical Review Letters 84 (2), pp. 258-261.

Moller, A.R. 1988, Use of zero-phase digital filters to enhance brain-stem auditory evoked potentials (BAEPs) ,Electroencephalography and Clinical Neurophysiology 71 (3), pp. 226-232.

Mormann F, Andrzejak RG, Elger CE, Lehnertz K. 2007,Seizure prediction: the long

and winding road. Brain;130:314–33.

Moritani, T., Smoker, W.R.K., Sato, Y., Numaguchi, Y., Westesson, P.-L.A. 2005 Diffusion-weighted imaging of acute excitotoxic brain injury, American Journal of Neuroradiology 26 (2), pp. 216-228.

Mormann, F. Kreuz, Th. Rieke Ch.,. Andrzejak R.G, Kraskov A., David P., Elgerh.E and K. Lehnertz, 2005, On the predictability of epileptic seizures, Clin Neurophysiol 116, pp. 569–597.

Moser , J K, 1967, Convergent series expansions for quasi-periodic motions. Math. Ann. 169 : 136-176.

Møller, Chr., Plesset, M.S. 1934, Note on an approximation treatment for many-electron systems,Physical Review 46 (7), pp. 618-62

Newman, E.A. 2003 New roles for astrocytes: Regulation of synaptic transmission, Trends in Neurosciences 26 (10), pp. 536-542

Niedermeyer E., 2005, Epileptic Seizure Disorders. In: E. Niedermeyer and F. Lopes Da Silva, Editors, Electroencephalography: Basic Principles, Clinical Applications, And Related Fields (Fifth Edition), Lippincott Williams and Wilkins, Philadelphia, pp. 505–621.

Park E.H. and Durand D.M., 2006, Role of potassium lateral diffusion in non-synaptic epilepsy: a computational study, J. Theor. Biol. 238 pp. 666–682.

Palus M., 1996, Coarse-grained entropy rates for characterization of complex time series, Physica D 93 (1996), pp. 64–77

Petrov, V., Ouyang, Q., Swinney, H.L. 1997, Resonant pattern formation in a chemical system, Nature 388 (6643), pp. 655-657

Turing, A. M. (1952). The chemical basis of morphogenesis. Phil. Trans. R. Soc. Lond. B 237, 37–72.

Penfield W., Jaspers H. and McNaughton F., 1954, Epilepsy and the Functional Anatomy of the Human Brain, Little Brown, Boston

Pezard L., Lachaux J-Ph., andrinoJ-L. Adam N, C., Garnero L., Renault B., Varela F. and Martinerie J., 1997 Local and global entropy quantification in neural systems, J Tech Phys 38 , pp. 319–322.

Pritchard, W.S., Duke, D.W. 1992, Measuring chaos in the brain: a tutorial review of nonlinear dynamical EEG analysis. International Journal of Neuroscience 67 (1-4), pp. 31-80 103

Pincus S.M., Gladstine I.M. and Ehrenkranz R.A., 1991,A regularity statistic for medical data analysis, J Clin Monit 7 (1991), pp. 335–345.

Qingchao, Y., Shuyong, L., Shijian, Z., Aimin, D. 2010, Development of experimental chaos identification analysis system , Proceedings of the ASME International Design Engineering Technical Conferences and Computers and Information in Engineering Conference 2009, DETC2009 1 (PART A), pp. 591-596

Reichl L. E. 2004, The transition to chaos: conservative classical systems and quantum manifestations, Springer Verlag

Rosenstein,M.T. Collins J.J. and De Luca C.J., 1993 A practical method for calculating largest Lyapunov exponents from small data sets, Physica D 65 (1993), pp. 117–134

Sackellares JC, Shiau DS, Principe JC, et al. 2006,Predictability analysis for an automated seizure prediction algorithm. J Clin Neurophysiol;23:509–20.

Staba, R.J., Wilson, C.L., Bragin, A., Fried, I. 2002, Quantitative analysis of high-frequency oscillations (80-500 Hz) recorded in human epileptic hippocampus and entorhinal cortex, Journal of Neurophysiology 88 (4), pp. 1743-1752

Small, M. 2005, Applied nonlinear time series analysis : applications in physics and physiology, World Scientific,

Schad A., Schindler K., Schelter B., Maiwald T., Brandt A., Timmer J., Schulze-Bonhage A. (2008)
Application of a multivariate seizure detection and prediction method to non-invasive and intracranial long-term EEG recordings Clinical Neurophysiology, 119 (1), pp. 197-211.

Seifert, G., Schilling, K., Steinhäuser, C. 2006, Astrocyte dysfunction in neurological disorders: A molecular perspective , Nature Reviews Neuroscience 7 (3), pp. 194-206

Torres M.E., Anino M.M., Gamero L.G. and Gemignani M.A., 2001,Automatic detection of slight changes in nonlinear dynamical systems using multiresolution entropy tools, Int J Bifurcation Chaos 11, pp. 967–981.

Turnbull, J., Lohi, H., Kearney, J.A., Rouleau, G.A., Delgado-Escueta, A.V., Meisler, M.H., Cossette, P., Minassian, B.A. 2005 Sacred disease secrets revealed: The genetics of human epilepsy , Human Molecular Genetics 14 (17), pp. 2491-2500

Tani, H., Bandrowski, A.E., Parada, I., Wynn, M., Huguenard, J.R., Prince, D.A., Reimer, R.J. 2007 Modulation of epileptiform activity by glutamine and system A transport in a model of post-traumatic epilepsy, Neurobiology of Disease 25 (2), pp. 230-238

Tauck, D.L., Nadler, J.V.,1985, Evidence of functional mossy fiber sprouting in hippocampal formation of kainic acid-treated rats,Journal of Neuroscience 5 (4), pp. 1016-1022

Tribolet, Jose M. 1977, New Phase Unwrapping Algorithm, IEEE Transactions on Acoustics, Speech, and Signal Processing ASSP-25 (2), pp. 170-177

Urbach, D., Pratt, H. 1986, Application of finite impulse response digital filters to auditory brain-stem evoked potentials , Electroencephalography and Clinical Neurophysiology 64 (3), pp. 269-273 .

Vitányi, P.M.B., Li, M. 2000, Minimum description length induction, Bayesianism, and Kolmogorov complexity,IEEE Transactions on Information Theory 46 (2), pp. 446-464

Wallace, R.H., Wang, D.W., Singh, R., Scheffer, I.E., George Jr., A.L., Phillips, H.A., Saar, K., Mulley, J.C. 1998, Febrile seizures and generalized epilepsy associated with a mutation in the Na+-channel β1 subunit gene SCN1B ,Nature Genetics 19 (4), pp. 366-370

Worrell GA, Parish L, Cranstoun SD, Jonas R, Baltuch G, Litt B. High-frequencyoscillations and seizure generation in neocortical epilepsy. Brain 2004;127:1496–506.

Van Le Quyen Khalilov M, I, Ben-Ari Y. 2006 The dark side of high-frequency oscillations in the developing brain. Trends Neurosci;29:419–27.

Zhao, C., Deng, W., Gage, F.H. 2008 Mechanisms and Functional Implications of Adult Neurogenesis, Cell 132 (4), pp. 645-660