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Corso di Laurea in Fisica

Tesi di Laurea

Oscillazioni e sincronizzazione neuronale nella epilepsia: un approccio basato sulla teoria di oscillazioni e la meccanica statistica.
Oscillations and neuronal synchronization in epilepsy: an approach based on oscillation theory and statistical mechanics.

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Abstract in italiano

In questo lavoro si propone di studiare i processi di sincronizzazione neuronale dal punto di vista dei sistemi dinamici, in particolare, della teoria delle oscillazioni. Si può dimostrare che esistono oscillazioni macroscopiche nel sistema talamocorticale dei topi epilettici. Questo fatto permette di modellare gli attacchi epilettici come processi di sincronizzazione di uno o due oscillatori auto-sostenuti, i cui parametri vengono ricavati dalle funzioni di risposta di fase ottenute sperimentalmente. Si osservano anche le cosiddette lingue di Arnold e i plateau di sincronizzazione, caratteristici della risposta di fase dei processi con un ciclo limite. Inoltre, utilizzando metodi della fisica statistica e la teoria di informazione, si ricava un rapporto fra la sincronizzazione e la quantità di informazione contenuta nelle rette funzionali del cervello. Si osserva che questa quantità di informazione è massima a livelli intermedi di sincronizzazione, in stati normali di veglia, e molto più bassa durante gli attacchi epilettici

Abstract in inglese

In this work we propose to study the neuronal synchronization processes from the point of view of the dynamical systems, in particular of the oscillations theory. It can be demonstrated that there are macroscopic oscillations in the thalamocortical network in epileptic rats. So we are able to model the epileptic seizures as synchronization processes of one or two self-sustained oscillator, whose parameters are extracted from the phase response functions obtained experimentally. We observe also the Arnold tongues and the synchronization plateau that are typical pf the phase response processes with a limit cycle. Moreover, using statistical physics and information theory methods, we obtain a relation between synchronization and quantity of information contained in the brain functional lines. This quantity of information has a peak at intermediate synchronization levels, as in conscious awareness states, and it is lower during epileptic seizures.

Chapter 1

Introduction

Coordinated cellular activity is a major characteristic of the nervous system functions [1]. Neurons, in fact, can synchronize and exhibit collective behavior that is not intrinsic to any individual neuron [2]. This coordinated neuronal dynamics ensures macroscopic rhythms like pacemaker activity, rhythmic motor pattern generation or alpha, theta and gamma cortical rhythm [3]. But an increased synchrony may result in pathological types of activity, such as epilepsy or Parkinson's disease [3].
So being able to understand the relation between brain function and behavior is very important in order to develop methods to control the brain activity and increase the lifestyle of many people, for example through seizure cancellation [2, 3].

An adequate framework to study the dynamics of coordinated activity in neuronal ensembles is the theory of coupled oscillators that offers a very appropriate level of description to characterize the functional connectivity between brain areas [1]. Namely, in theoretical and computational modeling this collective brain dynamics is frequently considered as a macroscopic endogenous self-sustained oscillation.

In this thesis work we first describe mathematically what is synchronization, introducing the method of description of an oscillator by its phase and describing the method of reduction of coupled oscillators to simple phase models. The main tool used in this theory is the *phase response curve* PRC [2], also called phase resetting curve, that is the difference between the old phase and the new one due to an external stimulus [2].

Afterwards, the focus is on the characterization of the dynamics of epileptiform activity by obtaining experimentally the PRCs in the thalamus and neocortex and incorporating them into a model of two coupled oscillator [3].

Then it is proved that the whole epileptic thalamocortical network is a macroscopic self-sustained oscillator by demonstrating frequency locking to external periodic stimuli and finding the characteristic Arnold tongues [3].

Furthermore, in the end, the aim is to identify features of brain organization that are optimal for sensory processing and that may guide the emergence of cognition and consciousness [4]. In order to do so, the possible configurations of interactions between brain networks, representing entropy values, are studied by analyzing neurophysiological recordings in conscious and unconscious states [4]. The result is quite simple: normal wakeful states are characterized by the greatest number of possible configurations, so by the highest entropy [4]. Therefore the information content is larger in the network associated to conscious states, suggesting that consciousness could be the result of an optimization of information processing [4].

Chapter 2

Methods and results

2.1 Synchronization

Recent years have witnessed a surge of interest in the concept that synchronized activity in brain cellular networks plays a key role in information processing and behavioral responses. Like any other physical, chemical or biological oscillators, neurons can synchronize and exhibit collective behavior that is not intrinsic to any individual neuron [2]. For example, partial synchrony in cortical networks is believed to generate various brain oscillations, such as the alpha and gamma EEG rhythms. Collective coordinated neural dynamics is crucial for macroscopic rhythms like pacemaker activity or rhythmic motor pattern generation, but an increased synchrony may result in pathological types of activity, such as epilepsy [3]. So, depending on the circumstances, synchrony can be good or bad, and it is important to know what factors contribute to synchrony and how to control it.

Physical, chemical and biological oscillators can all be described by a single phase variable θ, called *phase of oscillation* [2]. In the context of tonic spiking, the phase is usually taken to be the time since the last spike and θ=0 corresponds to the peak of the spike, unless stated otherwise. The notion of the phase of oscillation is related to the notion of parametrization of a limit cycle attractor, as shown in the figure below (b).

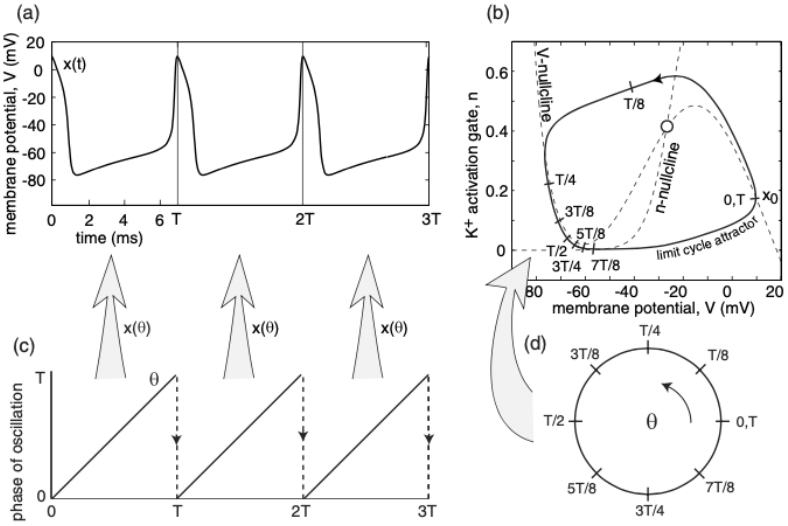

Figure 2.1: Definition of a phase of oscillation. The phase is usually taken to be the time since the last spike (a). The notion of the phase of oscillation is related to the notion of parametrization of a limit cycle attractor (b). Take a point x_0 on the attractor and plot the trajectory x(t) with x(0) = x_0. Then the phase of x(t) is θ=t. As t increases past the period T, then 2T, an so on, the phase variable θ wraps around the interval [0,T], jumping from T to 0 (c,d). (Reproduced from [2])

Considering a periodically spiking neuron, after it receives a single brief current pulse, it changes the timing, therefore the phase, of the following spikes due to this perturbation [2]. The magnitude of the phase shift of the spike train depends on the exact timing of the stimulus relative to the phase of oscillation θ (see fig 2.2). So by stimulating the neuron at different phases, it is possible to measure the *phase response curve* (PRC) defined as the difference between the new phase and the old one [2]

$$\text{PRC}(\theta)=\theta_{new} - \theta$$

Positive/negative values of the function correspond to phase advances/delays in the sense that they advance/delay the timing of the next spike. The only caveat is that to measure the new phase of oscillation perturbed by a stimulus, one must wait long enough for the transients to subside [2].
Phase differences between neurophysiological recordings is an adequate order parameter to describe temporal relations between brain areas and to catch a glimpse of the establishment of their possible function connectivity. Historically, PRCs have been used to analyze synchronization properties of both natural and artificial neural systems.

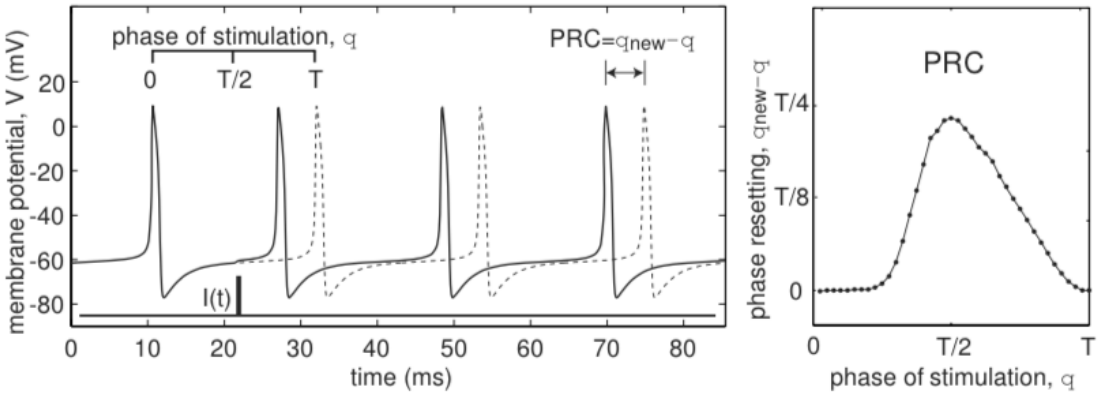

Figure 2.2: PRC: phase response curve (Reproduced from [2])

The PRC describes the response of an oscillator to a single pulse, but it can also be used to study its response to a periodic pulse train using a 'stroboscopic' approach, which will lead to a so called *Poincaré phase map* that describes the phase of oscillation at the time the $(n+1)_{th}$ input pulses arrives [2]. Let θ_n denote the phase of the oscillation when the nth input pulse arrives. The pulse resets the phase by PRC(θ_n). Also the period of the pulsed oscillation T_s must be taken into account. So the phase of the next oscillation is described by

$$\theta_{n+1} = (\theta_n + PRC(\theta_n) + T_s) mod T \tag{2.1}$$

Thus, this stroboscopic mapping of a circle to itself is called *Poincaré phase map* [2]. Knowing the initial phase of oscillation θ_1 at the first pulse, all the others can be determined and the sequence that it is obtained θ_n with n=1,2,.. is called *orbit* of the map.
Given

$$\theta_{n+1} = f(\theta_n) \tag{2.2}$$

its *fixed points* θ are the ones that comply the condition:

$$\theta = f(\theta) \tag{2.3}$$

which are analogues of equilibria of continuous dynamical systems. At such point the orbit θ_{n+1}=f(θ_n) is fixed.

Two periodic pulse trains are synchronous when the pulses occur at the same time or with a constant phase shift [2]. A synchronized state corresponds to a stable fixed point of the Poincaré phase map [2]. The in-phase, anti-phase, or out-of-phase synchronization corresponds to the phase shift θ=0, θ=T/2 or some other value respectively. Usually the in-phase synchronization is simply called synchronization and the other adjectives anti-phase or out-of-phase are used to denote the other types of synchronization (see fig 2.3) [2].
When the period of stimulation, T_s, is near the free-running period of tonic spiking T, the fixed point of the Poincaré phase map satisfies:

$$\mathrm{PRC}(\theta)=T-T_s.$$

Thus synchronization occurs with a phase shift θ that compensates for the input period mismatch $T-T_s$. The maxima and the minima of PRC determine the oscillator's tolerance of mismatch [2].

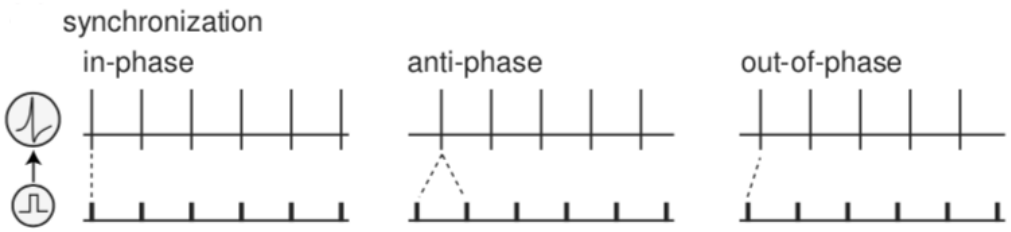

Figure 2.3: Examples of fundamental types of synchronization of spiking activity to periodic pulsed inputs. The in-phase, anti-phase, or out-of-phase synchronization corresponds to the phase shift θ=0, θ= T/2, or some other value, respectively (Reproduced from [2])

The phenomenon of *p:q phase locking* occurs when the oscillator fires p spikes for every q input pulses. Synchronization is 1:1 phase-locking. In general p:1 corresponds to a fixed point of the Poincaré phase map with p fired spikes per single input pulse [2].
Indeed, the map tells the phase of the oscillator at each pulse, but not the number of oscillations between the pulses. Each p:q locked solution corresponds to a stable periodic orbit of the Poincaré phase map with the period q (see fig 2.4) [2]. Since maps can have coexistence of stable fixed points and periodic orbits, various synchronized and phase-locked states can coexist in response to the same input pulse train. The oscillator converges to one of the states, depending on the initial phase of oscillation, but can be switched between states by a transient input [2].

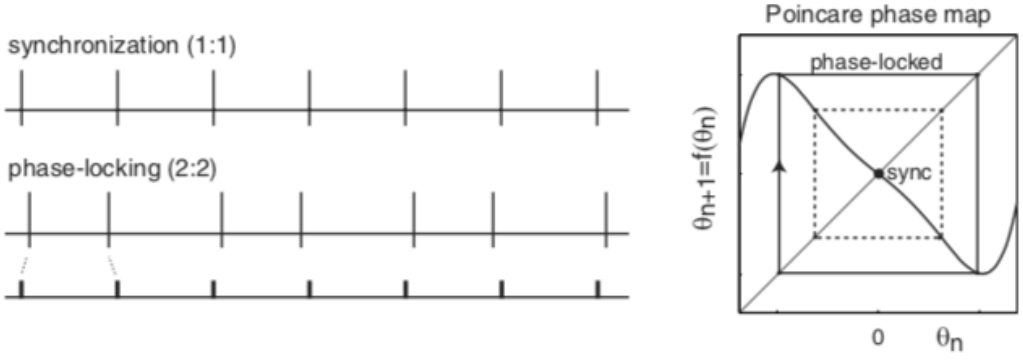

Figure 2.4: Synchronization and phase-locking (Reproduced from [2])

To synchronize an oscillator the input pulse train must have a period T_s sufficiently near the oscillator's free running period T. The amplitude of the function |PRC(θ,A)| decreases as the strength of the pulse A decreases, because weaker pulses produce weaker phase shift. Hence the region of existence of a synchronized state shrinks as A$\rightarrow$ 0 and it looks like a horn or a tongue on the ($T_s - A$)plane. This

region is called *Arnold tongue* (see fig 2.5) [2]. Each p:q-phase-locked state has its own region of existence. The tongues can overlap, leading to the coexistence of phase-locked states [2].

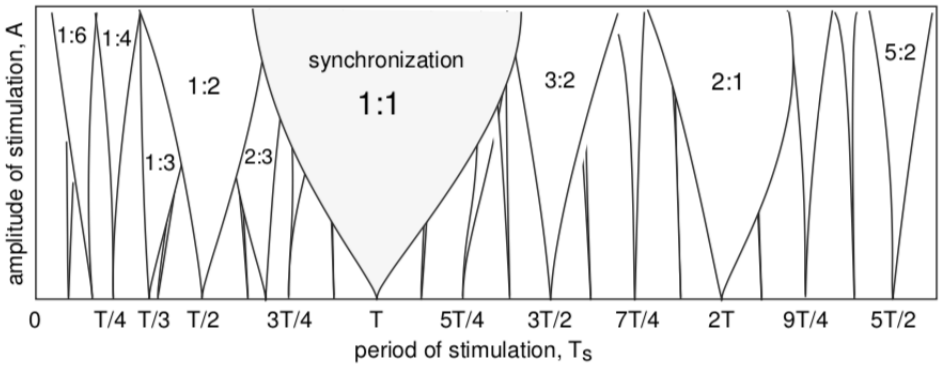

Figure 2.5: Arnold Tongues (Reproduced from [2])

From now on are considered dynamical systems of the form

$$\dot{x} = f(x) + \varepsilon p(t) \tag{2.4}$$

describing periodic oscillators, $\dot{x}$=$f(x)$, forced by a time dependent input $\varepsilon p(t)$ from other oscillator in a network, for instance [2].
This type of connection is called *weak coupling*.
The positive parameter ε measures the overall strength of the input, and it is assumes to be sufficiently small, denoted as $\varepsilon << 1$, but not $\varepsilon \to 0$.
Intending to transform the equation above into the phase model

$$\dot{\vartheta} = 1 + \varepsilon PRC(\theta)p(t) + o(\varepsilon) \tag{2.5}$$

three different, but equivalent, approaches can be used: *Winfree's Approach, Kuramoto's Approach* and *Malkin's Approach* [2]. Let's focus on the second one.
Kuramoto's Approach considers an unperturbed oscillator (ε=0) and let the function $\vartheta(x)$ denote the phases of points near its limit cycle attractor [2]. Differentiating the function yields

$$\frac{d\vartheta(x)}{dt} = grad\vartheta \cdot \frac{dx}{dt} = grad\vartheta \cdot f(x) \tag{2.6}$$

where gradϑ=$\vartheta_{x1}(x), ..., \vartheta_{xn}(x)$ is the gradient of $\vartheta(x)$ with respect to the state vector x=$(x_1, ..., x_n)$ $\in \mathbb{R}$. However it is known that near the limit cycle

$$\frac{d\vartheta(x)}{dt} = 1 \tag{2.7}$$

therefore the following useful equation is obtained

$$grad\vartheta \cdot f(x) = 1. \tag{2.8}$$

Applying the chain rule to the perturbed system, Kuramoto found

$$\frac{d\vartheta(x)}{dt} = grad\vartheta \cdot \frac{dx}{dt} = grad\vartheta \cdot f(x) + \varepsilon p(t) = grad\vartheta \cdot f(x) + \varepsilon grad\vartheta \cdot p(t) \tag{2.9}$$

and using 2.8 obtained the phase model

$$\dot{\vartheta} = 1 + \varepsilon grad\vartheta \cdot p(t) \tag{2.10}$$

Now consider n weakly coupled oscillators of the form

$$\dot{x_i} = f_i(x_i) + \varepsilon \sum_{j=1}^{n} g_{ij}(x_i, x_j) \tag{2.11}$$

with $x_i \in \mathbb{R}^m$ and $p_i(t) = \sum_{j=1}^{n} g_{ij}(x_i, x_j)$ and assume that the oscillators, when uncoupled ($\varepsilon = 0$), have equal free-running periods $T_1 = ... = T_n = T$. Applying any of the three methods above to such a weakly perturbed system, the result is the corresponding phase model

$$\dot{\vartheta_i} = 1 + 1\varepsilon Q_i(\vartheta_i) \cdot \sum_{j=1}^{n} g_{ij}(x_i(\vartheta_i), x_j(\vartheta_j)) \tag{2.12}$$

where $p_i(t) = \sum_{j=1}^{n} g_{ij}(x_i(\vartheta_i), x_j(\vartheta_j))$, $Q(\vartheta) = grad\vartheta(x)$ and where each $x_i(\vartheta_i)$ is the point on the limit cycle having phase ϑ_i [2]. To study collective properties of the network, such as synchronization, it is convenient to represent each $\vartheta_i(t)$ as

$$\vartheta_i(t) = t + \varphi_i \tag{2.13}$$

with the first term capturing the *fast* free-running natural oscillation $\dot{\vartheta_i} = 1$ and the second term capturing the *slow* network induced build-up of *phase deviation* from the natural oscillation [2]. Substituting 2.13 into 2.12 results in

$$\dot{\varphi_i} = 1 + \varepsilon Q_i(t + \varphi_i) \cdot \sum_{j=1}^{n} g_{ij}(x_i(t + \varphi_i), x_j(t + \varphi_j)). \tag{2.14}$$

The classical method of averaging, reviewed by Hoppensteadt and Izhikevich [2], consists in a near-identity change of variables that transforms the system into the form

$$\dot{\varphi_i} = \varepsilon\omega_i + \sum_{j \neq i}^{n} H_{ij}(\varphi_j - \varphi_i) \tag{2.15}$$

where

$$H_{ij}(\varphi_j - \varphi_i) = \frac{1}{T} \int_0^T Q_i(t) \cdot g_{ij}(x_i(t), x_j(t + \varphi_j - \varphi_i))dt \tag{2.16}$$

and each $\omega_i = H_{ii}(\varphi_i - \varphi_i) = H_{ii}(0)$ describes a constant frequency deviation from the free-running oscillation [2].
A special case of 2.15 occurs when H is replaced by its first Fourier term, sine. The resulting system, written in the slow time $\tau = \varepsilon t$

$$\varphi_i' = \omega_i + \sum_{j=1}^{n} c_{ij} sin(\varphi_j - \varphi_i + \psi_{ij}) \tag{2.17}$$

is called the *Kuramoto phase model* [2]. Here the frequency deviations ω_i are interpreted as intrinsic frequencies of oscillators. The strength of connections c_{ij} are often assumed to be equal to K/n for some constant K, so that the model can be studied in the limit $n \to \infty$, the phase deviations ψ_{ij} are often neglected for the sake of simplicity [2].
Consider two coupled phase variable (2.12) in a general form

$$\dot{\vartheta_1} = h_1\ (\vartheta_1, \vartheta_2),$$
$$\dot{\vartheta_2} = h_2\ (\vartheta_1, \vartheta_2),$$

Since each phase variable is defined on the circle $\mathbb{S}^1$, the state space of this system is the 2-torus $\mathbb{T}^2 = \mathbb{S}^1 \times \mathbb{S}^1$ depictated in the figure below, with ϑ_1 and ϑ_2 being the longitude and the latitude, respectively [2]. The torus can be represented as a square with vertical and horizontal sides identified, so that a solution disappearing at the right side of the square appears at the left side (see fig 2.6. The coupled oscillators above are said to be *frequency-locked* when there is a periodic trajectory on the 2-torus, which is called a *torus knot* [2]. It is said to be of type (p, q) if ϑ_1 makes p rotations while ϑ_2 makes q rotations, and p and q are relatively prime integers, that is, they do not have a common divisor greater than 1 [2]. Torus knots of the type (p, q) produced $p : q$ frequency-locking.

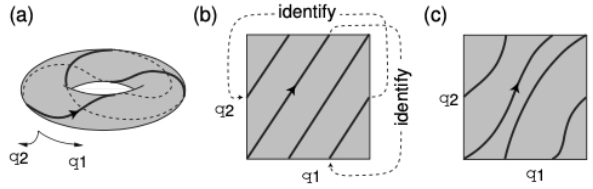

Figure 2.6: Torus knot of type (2,3) (a) and its rapresentation on the square (b). The torus produces frequency-locking and phase-locking. (c) Torus knot that does not produce phase-locking (Reproduced from [2])

A 1:1 frequency-locking is called *entrainment* [2]. Suppose the oscillators are frequency-locked, that is, there is a $p : q$ limit cycle attractor on the torus. Then the two oscillators are *p:q phase-locked* if

$$q\vartheta_1(t) - p\vartheta_2(t) = const \tag{2.18}$$

on the cycle [2]. The value pf the constant determines whether the locking is in-phase (const=0), anti-phase (const= $T/2$, half period) or out-of-phase. Frequency-locking does not necessarily imply phase-locking. Frequency-locking without phase-locking is called *phase trapping*. Finally, *synchronization* is a 1:1 phase locking. The phase difference $\vartheta_2 - \vartheta_1$ is also called *phase lag* or *phase lead* [2].
Frequency-locking, phase-locking, entrainment and synchronization of a network of n 2 oscillators are the same as pairwise locking, entrainment and synchronization of the oscillators comprising the network [2]. Synchronization of oscillators with nearly identical frequencies is described by the phase model (2.15).

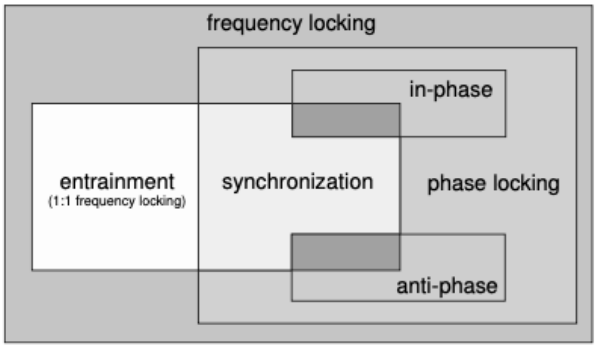

Figure 2.7: Various degrees of locking of oscillators (Reproduced from [2])

2.2 Model of coupled oscillators

In this section the purpose is to show that in certain conditions part of the brain can work as two coupled oscillators [1]. The theory of coupled oscillator offers a very adequate level of description to study the dynamics of coordinated activity in neuronal ensembles [5]. The focus is on the characterization of the dynamics of epileptiform activity, based on some seizures that manifest themselves with very periodic rhythmic activity termed *absence seizures* and, more specifically in this case, *spike and wave discharges* SWDs. This rhythmic paroxysmal activity is restricted to the thalamus and neocortex and it can be thought as a manifestation of the activity of two couples oscillators: the thalamus and the neocortex, precisely [1].
The approach is to obtain experimentally the phase resetting curves (PRCs) in the neocortex and thalamus and incorporate them into a model of coupled oscillators, representing the evolution of the respective phases and of their phase difference to assess stable phase locking patterns in the activity of these two brain areas.

In order to do so bipolar electrodes were implanted into specific brain areas of rats as shown in the picture below.

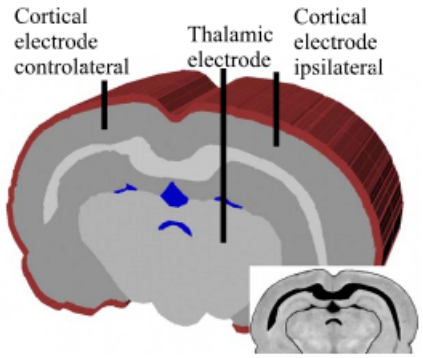

Figure 2.8: Positions of the electrodes (Reproduced from [1])

Very periodic rhythms were observed in two seizure models that are considered to represent human absence epileptiform activity, one chronical and the other not [6, 7]. This property was very useful for calculate the PRCs. Both models were induced by administrating drugs to rats. A single, "weak" stimulus was applied to the thalamus or cortex while recording from the other one, respectively. When stimulating the thalamus, two cortical recordings were simultaneously obtained, from the ipsilateral and contralateral side, in order to see possible differences in the PRC derived from a unilateral thalamic stimulation. The PRCs were qualitatively the same in both cortical hemispheres [1]. The stimulation was done at random time, making sure there were enough seconds between stimuli. As a result of a weak perturbation, the next wave could have been delayed, advanced or unchanged. The phase shift used to estimate the PRCs was calculated using the following formula [8]:

$$\theta = \frac{T_1 - T_2}{T_1} \times 2\pi \tag{2.19}$$

where T_1 and T_2 are the periods of oscillations preceding and just after the pulse, respectively. A positive phase shift ($T_1 > T_2$) indicates an advance of the next spike in the waveform, whereas a negative one a delay. The graph of this function θ is the PRC. This study follows the philosophy of Kuramoto model, since the brain areas that oscillate are described as phase oscillators that are deterministically coupled. This allow to calculate stable phase-locked states and compare them with the values obtained experimentally [1].

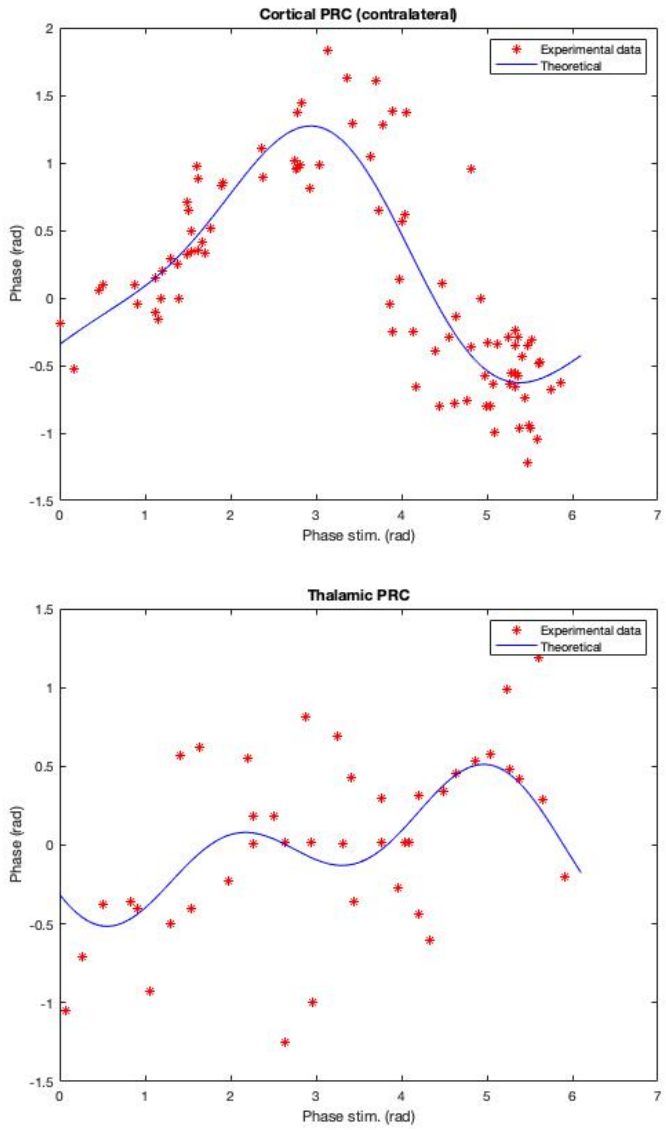

Figure 2.9: Cortical (contralateral) PRC and Thalamic PRC graphs. In red the experimental data from [1] are shown. Blue lines represent the curved fitted from the Kuramoto model

Then the PRCs were approximated with a Fourier series (blu curves, see fig 2.9) and inserted these into the following coupled oscillator model of the Kuramoto type:

$$\frac{d\theta_c}{dt} = \omega_c + K_{tc} H_c(\theta_c - \theta_t) \tag{2.20}$$

$$\frac{d\theta_t}{dt} = \omega_t + K_{ct} H_t(\theta_t - \theta_c) \tag{2.21}$$

where θ_c and θ_t are the phases of the cortex and thalamus respectively, K_{tc} and K_{ct} are the couplings between thalamus and cortex (thalamocortical) and between cortex and thalamus (corticothalamic), H is the interaction function and ω are the "intrinsic frequencies" that were taken as those of the SWD.
In order to calculate the fixed phase differences $\Delta\theta = \theta_t - \theta_c$, that are the stationary states of phase locking, the equations are subtracted:

$$\frac{d\Delta\theta}{dt} = \Delta\omega + K_{ct} H_t(\Delta\theta) - K_{tc} H_c(-\Delta\theta) \tag{2.22}$$

and solved for $\frac{\Delta\theta}{dt}$=0 to reveal stationary states of the phase difference $\Delta\theta$.
The experimentally obtained interaction function $H(\theta)$ was approximated with a Fourier series

$$\sum_{n=0}^{2} a_n cos(n\theta) + \sum_{n=0}^{2} b_n sin(n\theta) \tag{2.23}$$

Four stationary states were found: two stable and two unstable [1]. The stable phase differences were compared with the ones found in the experimental recordings. In general, in rhythmic oscillations, it is not very meaningful to state that one oscillator leads the other , but at least it was possible to determine in which electrode the spike-and-wave discharges starts and, while there is some variability, the first spike is observed in the thalamus 20-30% of the times [1]. With the parameters set to reproduce the experimental data of the phase difference, it is revealed a small lag between the spike in the thalamus and in the cortex. This relatively small phase difference could be due to conduction delays between the cortex and the thalamus, but considering that there is a monosynaptic connection between these two areas and taking into account the distance between electrodes and the axonal conduction velocity, a small conduction delay is conceivable.
Thus, some of the phase lag observed in the recordings and also determined by the linear stability analysis aforementioned can be due to conduction and synaptic delays in the transmission between these two brain areas. It is dutiful to notice that the calculated unstable fixed points are never found in the experimental recording of SWDs, since their nature is unstable [1].
Further analysis was done to determine the relative stability of the phase differences with different oscillating frequencies, by letting $\Delta\omega$ change from 0 to an arbitrary large value. The data suggest that the thalamo-cortical coupling K_{tc} keeps the oscillation more "tightly controlled" because there are small changes to the fixed point when the cortico-thalamic coupling is decreased noticeably relative to the thalamo-cortical.
Neurophysiological data demonstrated that thalamo-cortical coupling is, almost, five times stronger than cortico-cortical one, supporting the concept of a stronger influence of the thalamic input to the cortex in the stabilization of a phase locking pattern [9].
The classical synchronization theory distinguishes between mutual synchronization of self-sustained periodic oscillators and forced synchronization by driving forces [10, 11]. It is more plausible that the second one is the main operant, whilst mutual synchronization in a more rare phenomenon. SWDs can be treated as both mutual synchronization and as forced synchronization for two main reasons. First, the influence of the thalamus on the cortex (and viceversa) can be considered strong in this type of paroxysmal (seizure) activity because there are many cells firing almost synchronously and thus providing a strong synaptic input to the receiver neuronal ensemble. Second, there is an ongoing very periodic oscillation in thalamus and cortex that provides the opportunity for fine adjustment of frequencies characteristic of mutual synchronization [10, 5].
In conclusion these observations supports the notions that multistability in the nervous system function can be delivered from coupled oscillator models [12, 13].

2.3 Macroscopic Oscillator

In the previous section it is demonstrated that thalamus and neocortex behave like two weakly coupled oscillators. In this section the aim is to show that the whole epileptic thalamocortical network is a macroscopic self-sustained oscillator.
Coordination of the activity within and between the brain's cellular networks achieved through synchronization has been invoked as a functional feature of normal and abnormal temporal dynamics [14], the integration and segregation of information [15, 16] and the emergence of neural rhythms [17, 18]. Harmful examples of the rhythmic collective dynamics of large brain cell networks are the pathological activities found in epilepsies and Parkinson's disease [19, 20]. It has been hypothesizes that the origin of these specific phenomena is the coordinated activity of many thousand of neurons. Therefore, this collective brain dynamics is frequently consider as a macroscopic endogenous self-sustained oscillation [21, 22]. Note that this reductionist approach, treating a large neuronal network as a single active unit, stems from numerous studies of non linear dynamics and is also known as mean field approach. In order to prove so, the phase response curves (PRCs) and the entrainment properties of the gamma rhythm under external stimulation are derived. Evidence from *in vitro* experiments in rat hippocampus strongly suggest that a macroscopic oscillator emerges at least on the important case of gamma rhythm [23]. Synchronization theory [24, 5] predicts that if a system can be modeled as a noisy limit cycle or weakly chaotic oscillator, then it should react to a rhythmical perturbation by adjusting its frequency. If the frequency of the oscillator, Ω, is initially close to the one of the external stimulation, ω, then stimulation of sufficient strength leads to frequency locking, that is to say the two frequencies are equal to each other. This frequency locking condition shall be preserved for a range of amplitudes I and external frequencies ω of the forcing. The domain of the locking in the I-ω plane is known as the Arnold tongue. The ability to be synchronized, or entrained, by an external drive is a general property of endogenous oscillators according to the theory, this is also valid for macroscopic oscillations of ensembles consisting of many interacting units, in this case neurons [25, 26]. Hence, if the above formulated approach is valid, the brain rhythm shall exhibit frequency locking to external force. This approach is corroborated for the case of the sustained activity of absence epileptic seizures. It is investigated a specific type of paroxysmal activity, spike and wave discharges SWD, induced in rats using drugs. The rhythmic activity notably appears in the thalamcortical circuit. It is demonstrated that periodic pulse stimulation of this circuit leads to the frequency locking and thus present strong evidence that it can be considered as a macroscopic self-sustained oscillation [3].

At first, the corticl and thalamic responses were investigated at constant amplitude of stimulation, but at different frequencies, and subsequently they were analyzed at various amplitudes so that the Arnold tongues could be generated. The electrodes were implanted as shown in the picture below (fig 2.10). The thalamus was stimulated with a periodic square pulse train (unlike in the previous section where the stimulation was at random times) and simultaneously a cortical electrode recorded the activity in the frontal areas [3].

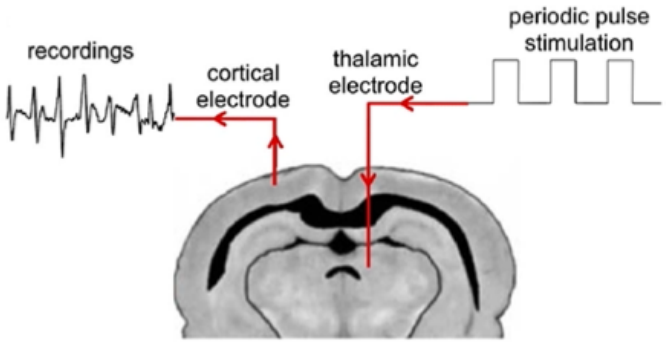

Figure 2.10: Positions of the electrodes in the thalamocortical areas (Reproduced from [3])

The crucial point is that the relative size of the evoked response is proportional to the intensity of the stimulation current. This can be easily understood in terms of the theory of self-sustained oscillators, which predicts two qualitatively different transitions to synchronization for a forced self-sustained oscillator, depending on the strength of the coupling or forcing.
For weak forcing, the transition to synchronization occurs via phase locking: a small external force affects mainly the phase of oscillations (and, hence, also the frequency) but not the amplitude, so that the phase difference between oscillators is constant inside the synchronization region.
A stronger forcing influences both the phase and the amplitude.
As a result, transition to synchrony occurs via suppression of natural oscillation, while the oscillation with the forcing frequency is imposed. Thus, the theory predicts different outcomes for small and large amplitudes of stimulation and, indeed, the experimental observation are in full agreement with these expectations [3] (see fig 2.11).

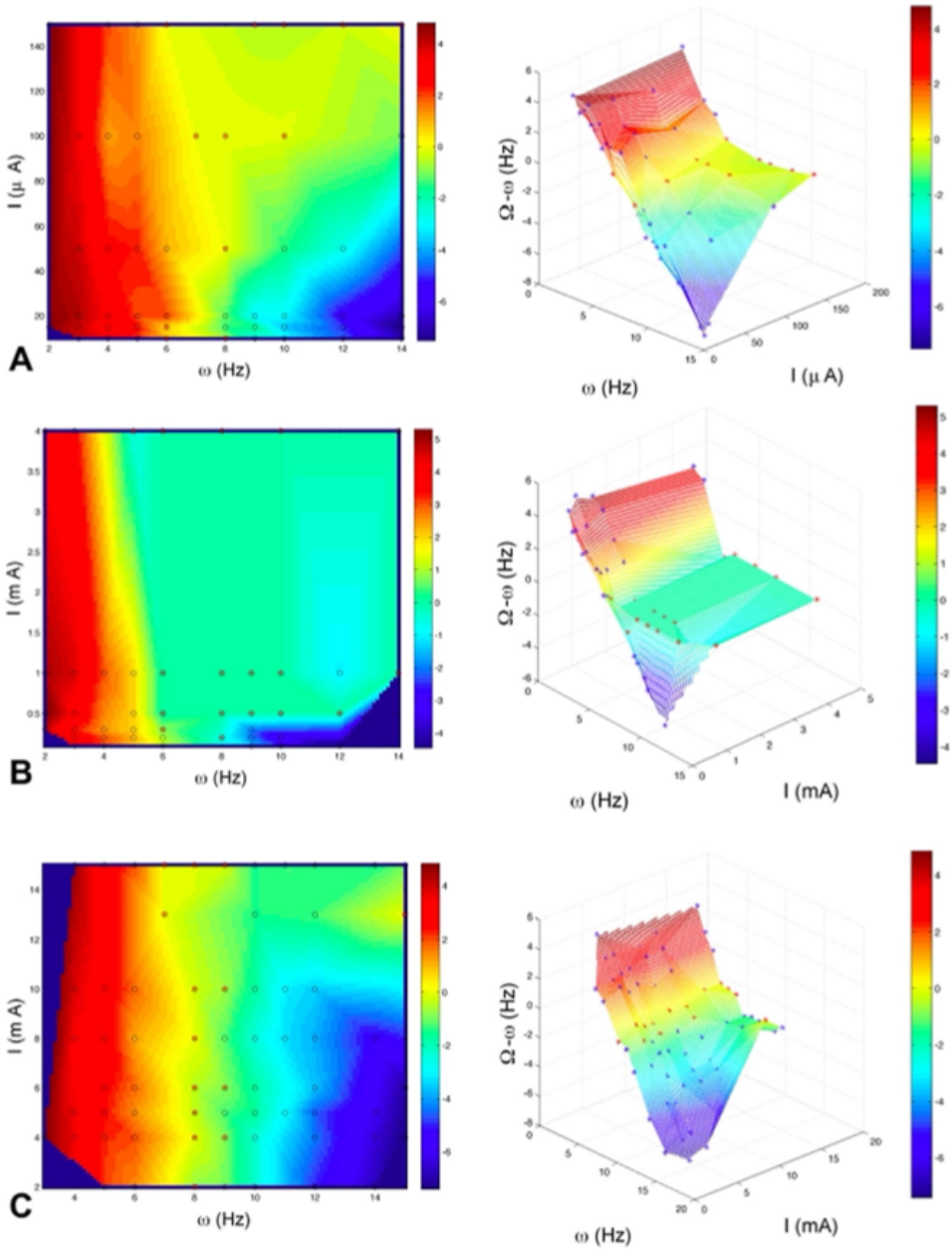

Figure 2.11: Arnold tongues depicted in 2D (left) and in 3D (right). The x-axis I is the intensity of the stimulation current, the y-axis ω is the frequency of periodic stimulation and the z-axis is the difference between the frequency of SWD Ω and the imposed frequency ω (Reproduced from [3])

In fact synchronization at higher frequencies (ω >10 Hz) is achieved by increasing the external forcing (*strong forcing regime*, as compared to synchronization at around the natural frequency (7-8 Hz, *weak forcing regime*). This explains why the shape of the recorded waveforms is also changed at higher frequencies. Notice that, typical for noisy systems, only the main locking region is pronounced, therefore there is 1:1 locking. Interestingly, the Arnold tongues are strongly asymmetrical, in agreement with the prevalence of phase advancement over phase delay in the resetting of cortical oscillations by thalamic stimulation [1]. Because periodic pulse trains were used, unlike in the previous sections, PRCs were not easily computed since PRC requires a wide range of stimulation phases, so the focus was on the reconstruction of the Arnold tongues.
The propensity for advancement of the cortical activity in response to thalamic stimulation is conceivable if the phenomenon known as the *thalamic augmenting response* is considered, that is, the net result of thalamic inputs to cortex is an enhancement of the cortical excitation. On the other hand, because of the recurrent inhibitory activity in the cortical circuits, stimulation that arrives in the late phase of the cycle of SWDs will retard the wave, and thus a delay may be expected [1].
Taken together, the observed results represent clear evidence of frequency locking in the thalamocortical circuit in this rat model of periodic and synchronous paroxysmal discharges, a model that shares many features with human absence seizures.

In conclusion it has been experimentally observed frequency locking and Arnold tongues were obtained in experiments with stimulated brain activity *in vivo*. Specifically, the thalamocortical circuit in rat models of paroxysmal activity shows the phenomenon of frequency-locking when stimulated by periodic electrical pulses, at least in a certain frequency range. So the hypothesis that the epileptic thalamocortical network behaves as a macroscopic self-sustained oscillator is confirmed [3].

2.4 Information content

Previously, it has been shown that during epileptic seizures the thalamocortical network synchronizes and behaves like a self-sustained oscillator. This final section explores the connection between information processing and epileptic seizures and when the maximization of it verifies, during conscious or unconscious states [4]. Hence, the identification of features of brain organization that are optimal for sensory processing and that may guide the emergence of cognition and consciousness has been sought. This leads to a surprisingly simple result: normal wakeful states are characterized by the greatest number of possible configurations of interactions between brain networks, representing highest entropy values. Therefore, the information content is larger in the network associated to conscious states [4].

Starting with the most basic experimental observations, neurophysiological recordings of brain activity demonstrate fluctuating patterns of cellular interactions, a variability that allows for a wide range of states, or configurations of connections of widely distributed networks exchanging information, and support the flexibility needed to process sensory inputs and cognition in general.
Previous studies have revealed values of different indicators of brain coordinated activity, such as synchronization, associated with healthy and pathological states by comparison of baseline values and those in, for instance, unconscious states such as coma and epileptic seizures [27, 28, 29, 30]. These observation prompt the question of what physiological organization underlies the specific values of the synchrony indices found in normal alert states and other conditions. The answer is that there is a certain general organization of brain cell ensembles that will be optimal for conscious awareness and this happens when there is a tendency towards a widespread distribution of energy or, equivalently, a maximal information exchange. The term *information* is used in the intuitive sense that normally permeates neuroscience: cells ensemble that are functionally connected to process and exchange information [4].

In order to seek this optimal brain organization, it was used the classic approach in physics to understand collective behaviors of systems composed of myriads of units. This approach focus on the assessment of the number of possible configurations, or *microstates*, that the system can adopt. Several types of brain recording are used to inspect non only superficial cortical activity, but also that of deeper structures in conscious or unconscious states, evaluating the number of connections between these areas and the associated entropy and complexity. The specific types of neurophysiological recording are: magnetoencephalography (MEG), scalp electroencephalography (EEG) or intracranial EEG (iEEG).
The recordings showed evidence that conscious states result from higher entropy and complexity in the number of configurations of pairwise connections. In other words, the number of pairwise channel combinations is near the maximum of all possible configurations when the individual is processing sensory inputs in a normal manner (e.g. with open eyes). This evidence leads to the interpretation that a greater number of configurations of interactions allows the brain to optimally process sensory information, fostering the necessary variability in brain activity needed to integrate and segregate sensorimotor patterns associated with conscious awareness [4].

The calculation for the phase synchrony index R was done for all possible signal pairs and the mean value thus obtained was then estimated for the desired time length [27, 31, 28].
The total number of possible pairs of channels, given a specific channel montage, is given by the binomial coefficient

$$N = \frac{N_c!}{2!(N_c - 2)!} \tag{2.24}$$

where N_c is the total number of channels in the recording montage. Recordings were analyzed from nine subjects and for each subject the number of connected pairs of signals in the different behavioral states p was calculated and then the number of possible combinations of p pairs, denoted C:

$$C = \frac{N!}{p!(N-p)!} \tag{2.25}$$

where N is the aforementioned valued.
Given a maximum total number of N pairs of connected signals, in how many ways can the experimental observation of p connected pairs be arranged? The crucial result is the number of configurations C, but another useful tool is the computation of *entropy*:

$$S = \ln C \tag{2.26}$$

The entropy estimation does not provide any further information than C, but, since the evaluation of C is not feasible due to large number of sensors, thanks to the Stirling approximation for large number n the entropy is easily calculated. The Stirling approximation is frequently used in statistical mechanics to simplify entropy-related computation and it reads as follows:

$$\ln(n!) = n\ln(n) - n \tag{2.27}$$

Using this approximation, and after some basic algebra, the equation for entropy is:

$$S = N\ln\left(\frac{N}{N-p}\right) - p\ln\left(\frac{p}{N-p}\right) \tag{2.28}$$

where N is the total number of possible pairs of channels and p the number of connected pairs of signals in each experiment. Because this equation is derived from the Shannon entropy, it indicates the information content of the system as well.

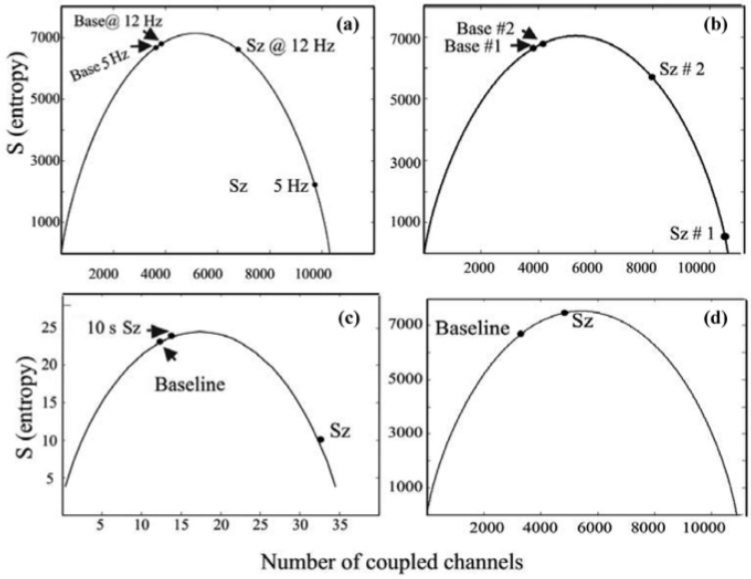

Figure 2.12: Graphs representing the entropy of the number of pairwise configurations of signals in epileptic patients during conscious (baseline) and unconscious states (generalized seizures, labeled Sz) (Reproduced from [4])

Note in figure 2.12 that during conscious states, when patients are not having generalized seizures with loss of awareness, the entropy is close to the maximum, whereas entropy is lower (more distant from the top) for seizure states. The values during the seizures fall on the right-hand side of the graph because, due to higher synchrony during ictal (seizure) events such that the number of coupled channels is larger than during intericatl (between seizures) activity, there are fewer pairwise configurations and

therefore lower entropy. This phenomenon seems associated with the level of consciousness since when the seizures are not generalized (Figs 2.12c and 2.12d) and the patients remain responsive and conscious, the entropy values are similar to those interictal (baseline) activity.
Where in the the data points are located depends of course on the synchrony index. Because seizures had higher synchrony than interictal periods (baseline), the number of coupled signals is greater and the number of combinations is lower.
Similar trends are observed in the case of sleep.

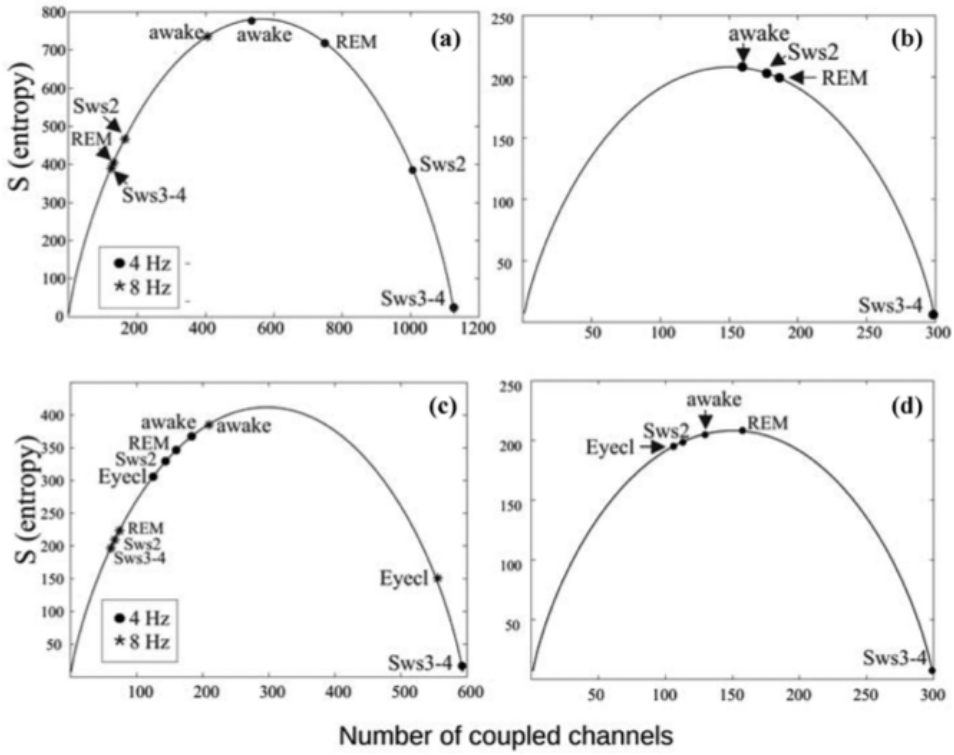

Figure 2.13: Same graph types as in fig 2.12, using sleep recordings. Data samples were taken during wakefulness with eyes open (awake) or with eyes closed (Eyecl) and sleep stages slow wave (Sws2), deepest sleep stages (Sws3-4) and rapid eye movement (REM) (Reproduced from [4])

Note how during wakefulness the entropy is closer to the maximum of the curve, whereas the deeper the sleep stage is, the more distant from the maximum the values are (see fig 2.13). Interestingly, the entropy during REM sleep is very close, in most cases, to the normal alert state. This result may not be as surprising as it sounds if we consider the mental activity during REM episodes that are normally associated with dreams. It is worth noting too that in the recordings taken when the subjects had their eyes closed, the entropy is much lower than during eyes-open condition and sometimes it is as low as during slow wave 3-4 sleep. As depicted in figs 2.13a and 2.13c it is not always the case of high synchrony having lower entropy, sometimes it is lower synchrony that results in fewer channel combinations and thus lower entropy as compared to fully alert states.

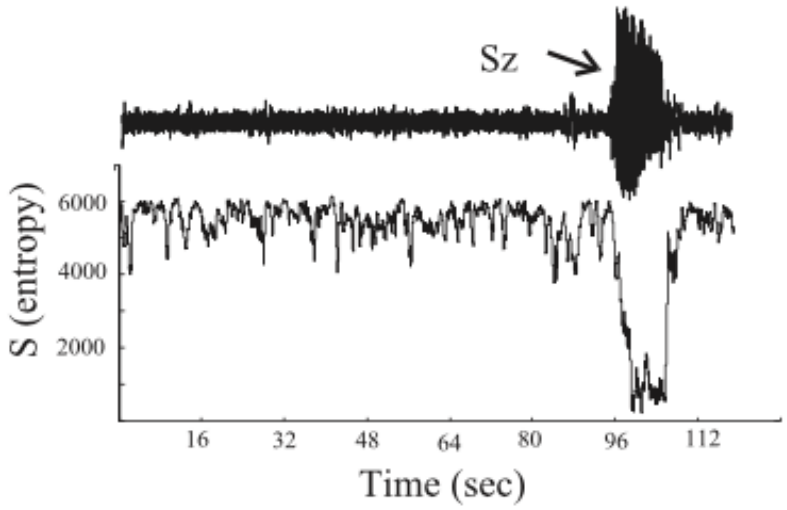

Figure 2.14: Time course of the entropy of the number of configurations of connected MEG signals before, during and after a generalized absence seizure. MEG signal is shown at the top (Reproduced from [4])

Shown in fig 2.14 is an example of the time course of the entropy before and during an ictal event, where the fluctuations in the entropy magnitude can be seen, notice the drop in entropy during the seizure. In particular during a specific state the magnitude remain relatively constant, although some fluctuations are evident.

Hence, as demonstrated, specific values of the synchrony index R in fully alert states represent the largest number of combinations of pairwise signal configurations, whereas lower entropy (and thus fewer combinations of connections) is characteristic of either unconscious states or altered states of alertness (eyes closed). This observation reflects a relatively simple general organizing principle at this collective level of description, which results in the emergence of properties associated with consciousness [4].

A general organizing principle of natural phenomena is the tendency toward a maximal, or more probable, distribution of energy [32] as dictated by the second principle of thermodynamics, which can be encapsulated by the notion of the maximization of information transfer [33]. As well, the notions of information and energy exchange are conceptually related since "the common currency paying for all biological information is energy flow" [4, 34, 35]. In the final analysis, information exchange implies energy exchange, hence information exchange can be interpreted as as energy distribution [32]. Therefore, the number of pairwise channel combinations occurs near the maximum of possible configurations in periods with normal alertness, as the greater number of configurations of interactions represents the most probable distribution of energy and information resulting in conscious awareness [4].

Chapter 3

Discussion

The initial purpose was trying to find a way to describe how the brain works under certain conditions in order to develop methods for the control of brain activity to improve people's life, for example through seizure cancellation. Latest years have seen an increased interest in the idea that synchronization in brain cellular networks plays a crucial role in information processing and behavioral responses [36, 37].

Phase response curves (PRCs) were studied with the aim to characterize the epileptiform activity. At first, PRCs were obtained to study a particular case of dynamics of epileptiform activity, that is, seizures that manifest themselves with very periodic rhythmic activity, termed absence seizure [1]. The obtained results in the cortex and thalamus were incorporated into a model of coupled oscillators. The theory of coupled oscillators [38] offers a very adequate level of description to study the dynamics of coordinated cellular activity in neuronal ensembles and to characterize the functional connectivity between brain areas [1]. The results obtained experimentally were in good agreement with the one extracted from the Kuramoto model and suggest that this simplistic model can be the base for further analysis. Within the framework of coupled oscillators theory, PRCs have been used to analyze synchronization properties of natural [39, 40, 41, 42, 43, 44, 6] and artificial [44] neural systems. In general, coupled oscillator theory [45, 46, 38] rests upon two main characteristics: intrinsic oscillator that are weakly coupled. It is not yet completely clear if these features are common to nervous system, but it is undeniable that some reasonable approximations are useful to unravel the dynamics of neuronal coordinated activity [11, 47].

Up to this point, thalamus and cortex were considered as two coupled oscillators, but it has been proved that the whole epileptic thalamocortical network can be seen as a self-sustained oscillator [3]. Electrophysiological response of the thalamocortical network of rat model of epilepsy were measured during seizure activity [3]. According to the theory, the ability to be synchronized by an external drive is a general property of endogenous oscillators and this is also valid for macroscopic oscillations of ensemble consisting of many interacting units, in this case neurons [25, 26]. The data demonstrated that periodic pulse stimulation of the thalamocortical circuit leads to frequency locking and the formation of Arnold tongues, thus present strong evidence that it can be considered as a macroscopic self-sustained oscillation [3]. This result is very important for understanding the mechanisms of possible control of pathological brain activity [48, 49].

The final aim is to find features of how brain process information and how the synchronization is one indicator of brain coordinated activity associated with healthy and pathological states [3, 1]. In general, the activity of nervous system cells is to a large extent coherent, showing a high degree of temporal correlation and coordination of the activity [50, 51]. These observations prompt the question of what physiological organization underlies the specific values of synchrony indices found in normal alert states and other condition. The task is not simple, but surprisingly the result is: a greater number of possible configurations of interaction between brain networks is associated with alert states, representing high entropy, whereas lower entropy (and thus fewer combinations of connections) is characteristic of either unconscious states or altered states of alertness (e.g. eyes closed) [3]. It has been proposed that aspects of awareness emerge when certain level of complexity are reached [52]. It is then

possible that the organization (complexity) needed for consciousness to arise requires the maximum number of configurations that allow for greater variety of interaction between brain cell assemblies because this structure leads to optimal segregation and integration processing [53]. The maximization of information transfer corresponds to a maximal distribution of energy, as ascertained by the second principle of thermodynamics [33, 32]. Hence, information exchange implies energy exchange and it is correlated with a large number of different configurations of interactions [4, 32].
In conclusion, the results support computational and theoretical studies showing that patterns of organized activity arise from the maximization of fluctuations in synchrony [54] and that cognition and consciousness are not static property, but a dynamic process with constant flux of energy, or information exchange [32].

Bibliography

[1] J.L. Perez Velazquez et al. "Phase response curves in the characterization of epileptiform activity". In: *Physical Review* 76, 061912 (2007).

[2] Eugene M. Izhikevich. *Dynamical Systems in Neuroscience [The Geometry of Excitability and Bursting]*. The MIT Press, 2007, pp. 443–491.

[3] J. L. Perez Velazquez, R. Guevara Erra, and M. Rosenblum. "The Epileptic Thalamocortical Network is a Macroscopic Self-Sustained Oscillator: Evidence from Frequency-Locking Experiments in Rat Brains". In: *Scientific Reports* (2015).

[4] R. Guevara Erra et al. "Statistical mechanics of consciousness: Maximization of information content of network is associated with conscious awareness". In: *Physical Review* 94, 052402 (2016).

[5] A. Pikovsky, M. Rosemblum, and J. Kurths. *Synchronization: A Universal Concept in Nonlinear Sciences*. Cambridge University Press, Cambridge, 2001.

[6] E. Proulx et al. In: *European Journal of Neuroscience* 23, 489 (2006).

[7] O.C. Snead. In: *Epilepsia* 29, 361 (1988).

[8] J. Rinzel and G.B. Ermentrout. *Methods in Neuronal Modeling*. Ed. by c. Koch and I. Segev. MIT,Cambride, 1989.

[9] Z. Gil, B.W. Coonors, and Y. Amitai. In: *Neuron* 23, 385 (1999).

[10] V.S. Anishchenko et al. *Nonlinear Dynamics of Chaotic and Stochastic Systems*. Springer, Berlin, 2002.

[11] J. L. Perez Velazquez. In: *NeuroQuantology* 4, 155 (2006).

[12] M. Majtanik, K. Dolan, and P. Tass. In: *Journal of Biological Physics* 32, 307 (2006).

[13] D. Takeshita, Y. Sato, and S. Bahar. In: *Physics Review* 75, 051925 (2007).

[14] X. J. Wang. "Neurophysiological and computational principles of cortical rhythms in cognition". In: *Physiological Reviews* 90 (2010).

[15] F. Varela et al. "The brain web: phase synchonization and large-scale integration". In: *Nature Reviews Neuroscience* 2, 229-239 (2001).

[16] J. L. Perez Velazquez and R. Wennberg. *Coordinated Activity in the Brain: Measurements and Relevance to Brain Function and Behavior*. Springer, New York, 2009.

[17] G. Buzsaki. *Rhythms of the Brain*. Oxford University Press, Oxford, 2009.

[18] N. Kopell. "We got rhythm: Dynamical systems of the nervous system". In: *Not. AMS* 47 (2000).

[19] A. Destexhe and T. J. Sejnowski. *Thalamocortical Assemblies*. Oxford University Press, Oxford, 2001.

[20] R. Llinas and D. Pare. "Role of intrinsic neuronal oscillations and network ensembles in the genesis of normal and pathological tremors". In: *Neurol. Dis. Ther.* 30, 7-36 (1994).

[21] P. Suffczynski and A. Pikovski. "Dynamics of non-conclusive epileptic phenomena modeled by a bistable neuronal network". In: *Neuroscience* 126, 467-484 (2004).

[22] P.A. Tass. "A model of desynchronizing deep brain stimulation with a demand-controlled coordinated reset of neural subpopolations". In: *Biol. Cybern.* 89, 81-88 (2003).

[23] T. Akam et al. "Oscillatory dynamics in the hippocampus support dentate gyrus-CA3 coupling". In: *Nature Neuroscience* 15, 763-768 (2012).

[24] L. Glass. "synchronization and rhythmic processes in physiology". In: *Nature* 410, 277-284 (2001).

[25] E. Ott and T.M. Antonsen. "Long time evolution of phase oscillator systems". In: *Chaos Interdiscip. J. Nonlinear Sci.* 19, 023117 (2008).
[26] H. Sakaguchi. "Cooperative phenomena in couple oscillator systems under external fields". In: *Progress of Theoretical Physics* 79, 39-46 (1988).
[27] L. Garcia Dominguez et al. In: *Journal of Neuroscience* 25,8077 (2005).
[28] F. Mormann et al. In: *Physica D* 144, 358 (2000).
[29] V. Nenadovic, J.L. Perez Velazquez, and J.S. Hutchison. In: *PLos One* 9, e94942 (2014).
[30] D.C. Shields et al. In: *Surgical Neurology International* 67, 354 (2007).
[31] R. Guevara et al. In: *Neuroinformatics* 3, 301 (2005).
[32] J.L. Perez Velazquez. In: *Journal of Biological Physics* 35,209 (2009).
[33] H. Haken. *Synergetics: Introduction and Advanced Topics*. Springer Science & Business Media, Berlin-Heidelberg, 1998.
[34] H.J. Morowitz. *Energy Flow in Biology*. Academic Press, New York, 1968.
[35] E. Smith. In: *Journal of Theoretical Biology* 252, 185 (2008).
[36] S.L. Bressler and J.A.S. Kelso. In: *Trends in Cognitive Science* 5, 26 (2001).
[37] W. Singer. In: *NeuroQuantology* 4, 134 (2006).
[38] A. Winfree. *The Geometry of Biological Time*. Springer Verlag, Berlin, 1980.
[39] R.F. Galan, G.M. Ermentrout, and N.N. Urban. In: *Physical Review Letters* 94, 158101 (2005).
[40] R.F. Galan, G.M. Ermentrout, and N.N. Urban. In: *Neurocomputing* 69 1112 (2006).
[41] P. Goel and B. Ermentrout. In: *Physica D* 163, 191 (2002).
[42] W. Govaerts and B. Sautois. In: *Neural Computation* 18, 817 (2006).
[43] T. Netoff et al. In: *Journal of Neurophysiology* 93, 1197 (2005).
[44] S. Oprisan and C. Canavier. In: *Neural Computation* 14, 1027 (2002).
[45] F.C. Hoppensteadt and E.M.Izhikevich. *Weakly Connected Neural Networks*. Springer, Berlin, 1997.
[46] Y. Kuramoto. *Chemical Oscillations, Waves and Turbulence*. Springer, New York, 1984.
[47] J.L. Perez Velazquez. In: *Physica D* 212, 161 (2005).
[48] L.B. Good. "Control of synchronization of brain dynamics leads to control of epileptic seizures in rodents". In: *International Journal of Neural System* 19, 173-196 (2009).
[49] L.D. Iasemidis. "Epileptic seizure prediction and control". In: *IEEE Transaction on Biomedical Engineering* 50, 549-558 (2003).
[50] G. Tkacik et al. In: *Proceedings of the National Academy of Science USA* 112, 115 (2015).
[51] F. Varela et al. In: *Nature Review Neuroscience* 2 (2001).
[52] M. Gell-Mann. In: *Annals of the New York Academy of Sciences* 929, 41 (2001).
[53] G. Tononi. In: *BMC Neuroscience* 5, 474 (2004).
[54] V. Vuksanovic and P. Hovel. In: *Chaos* 25, 023116 (2015).